RECENT ADVANCES ON SYNTHESIS AND ANTI-CANCER ACTIVITIES OF FIVE MEMBER HETEROCYCLIC THIAZOLIDINE ANALOGUE: AN OVERVIEW

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Abstract:
The potential of thiazolidin-4-ones as a versatile and promising compound for anti-cancer drug discovery. Thiazolidin-4-ones possess a unique five-membered heterocyclic ring structure with a sulfur heteroatom and a cyclic amide bond, making them attractive for various biological activities. While thiazolidine-2,4-dione has been more extensively studied, there's growing interest in thiazolidin-4-ones, especially in the context of anti-cancer drug development. Researchers have been exploring their structural diversity, substitution patterns, and potential enzymatic targets for drug discovery. This comprehensive review aims to shed light on the anti-cancer potential of thiazolidin-4-ones, including their structure-activity relationship (SAR), selectivity for cancerous tissues over healthy cells, and future directions for translational research. Further studies, such as pharmacokinetic and metabolic stability assessments, are crucial for identifying potential lead candidates with promising translational outcomes.
Keywords: Anti-Cancer Activity, Apoptosis, Breast Cancer, Drug discovery, Thiazolidin-4-ones

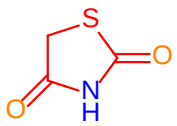
Introduction:

All cancer is an unwelcome growth of cells that affects people's health globally and is the primary cause of death [1]. As per the 2022 World Cancer Report, the disease has claimed approximately 20 million lives and resulted in 9.7 million deaths, making it the leading cause of mortality in the last few decades. Approximately half of all cancer fatalities globally are attributable to lung, breast, liver, stomach, pancreatic, blood, colorectal, and bowl cancers. Men were found to have been diagnosed with lung, prostate, colorectal, stomach, and liver cancer, which are the most prevalent cancer kinds [2]. Breast cancer ranks second among the many forms of malignant tumors that have been reported thus far in terms of female fatalities, after stomach, lung, and cervix cancer. Third among causes of death is pancreatic cancer [3]. Huge efforts were made to deploy novel treatment approaches in the quest for possible anticancer drugs, which led to the development of scaffolds with heterocyclic structure as a significant structural feature. Heterocyclic compounds are crucial to the treatment of cancer. One significant favored motif in pharmaceutical chemistry that has arisen is thiazolidine. Because thiazolidine offers high affinity ligands for multiple types of receptors, it is becoming more and more popular among researchers in the field of medicinal chemistry [4]. Thiazolidionones, frequently referred to as glitaziness, are heterocyclic rings with five members that include two heteroatoms (sulfur and nitrogen) and three carbons. The heterocyclic molecule is called a Thiazolidine-2,4-dione [5] because it contains two carbonyl groups in the thiazide,

one at position 4 and another at position 2. Because of its broad profile, thiazolidinedione is still being researched for more effective, safer, and potentially useful pharmacological agents. The biological activities demonstrated by TZD include antihyperglycemic [6], antimicrobial [7], antiviral [8], antioxidant [9], anticancer [10], anti-inflammatory [11], anti-plasmodia, alpha glycosidase inhibitory, xanthine oxidase inhibitory activity, etc.When coupled with various other heterocyclic rings, TZDs constitute one of the primary heterocyclic ring systems that have medicinal significance. In modern medicinal chemistry, the integration of two pharmacophores into a single molecule is an attractive, useful, and frequently employed opportunities for the research of novel and highly active therapeutic molecules.Certain Thyroid-Suppressing Drugs (TZDs) are intended to treat human cancers that exhibit elevated levels of Peroxisome Proliferator-Activated receptor gamma (PPAR-γ). This protein is expressed in a variety of human tumors, such as cancers of the bladder, colon, prostate, and breast. It is thought that their anticancer action is mediated via PPAR-γ activation. Troglitazone's toxicity has not been linked to the TZD ring, according to published reports, which has led to the development of this unique class of anticancer medicines using the TZD ring as a scaffold [12]. In order to mitigate their adverse effects, the TZD moiety has been linked directly to an N-heterocyclic ring [13, 14]. Type II nuclear receptor PPAR-γ, or Peroxisome Proliferator-activated receptor gamma, additionally referred to as the glitazóne receptor or NRl C3, has been encoded by the PPARG gene in humans. The main regulator of fatness, PPAR-γ, is the pharmacological target of insulin sensitizers in the TZD class. PPARs function as metabolic repulsors, regulating the expression of genes linked to adipocyte development, lipid and glucose metabolism, immune cell proliferation, and inflammation. In addition to its established physiological functions, PPAR-γ has also been shown to be overexpressed. malignant tumors of the breast, bladder, prostate, colon, and thyroid in humans. PPAR-γ agonists demonstrate antitumor effects. It was additionally suggested to cause some cancerous cell lines to engage in apoptosis. PPAR-γagonists had been shown in both in vitro and in vivo experiments to demonstrate antiproliferative and proapoptotic properties, suggesting that PPAR may be a suitable therapeutic target for treating malignancies [15].

Thiazolidinone as an Anticancer Agent:

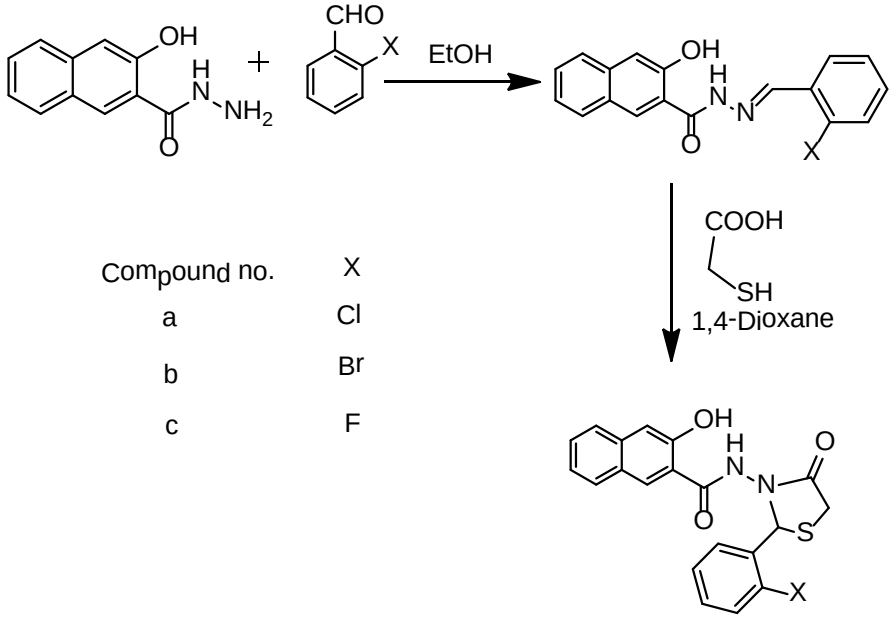
Principal bioactive saturated heterocyclic scaffold



1,3-Thiazolidine-2,4-dione

Popioleka and colleagues synthesized and investigated novel derivatives of 1,3-thiazlidine-4-one (a–c). New 1,3-thiazolidine-4-one derivatives are produced when 3-hydroxy-2-napthanoic acid hydrazide, which is synthesized by reacting with different aldehydes, is cyclized with thioglycolic acid in a solvent of 1,4-dioxane (**Scheme 1**). The in vitro cytotoxicity of the derived thiazolidine motifs was evaluated against Hep G2 and human renal cell adenocarcinoma (769-P) cells. Derivatives were tested against the adult Swiss mice's central nervous system in vivo. According to the study's findings, compound (C) and its derivatives were the most effective against renal adenocarcinoma cells (769-P) at IC25 concentration. An in vivo investigation on mice's central nervous systems demonstrates the examined substances N-[2-(2-chlorophenyl)-4-oxo-1, 3-thiazolidine-3-yl] N-[2-(2-Flurophenyl)-4-oxo-1, 3-thiazolidine-3-yl] & 3-hydroxynapthalene-2-carboxamideIn terms of biological activity, 3-hydroxynapthalene-2-carboxamide was most active. Because compound (c) blocked the G2/M cell cycle, it exhibited strong anodyne effects. Optimum level of biological activity. Because compound (c) stimulated apoptosis and blocked the G2/M phase cell cycle, it exhibited strong anodyne activity. The highest and most selective antiproliferative activity against the reference cell lines, rat cardiac myoblast (HgC2) and GMK, was demonstrated by compound (c), according to the authors. These findings verified compound (c)'s strong anticancer efficacy among TZD synthetic derivatives. [16]

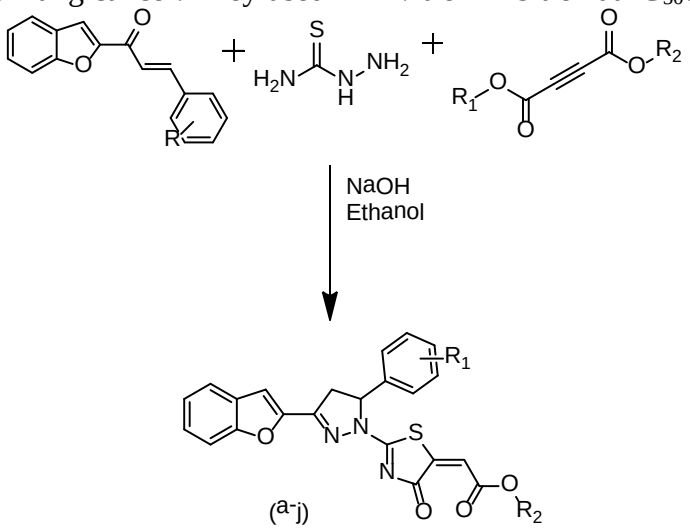
ISSN (PRINT): 2393-8374, (ONLINE): 2394-0697, VOLUME-11, ISSUE-9, 2024
DOI: 10.21276/ijcesr.2024.11.9.47



Compound no.	X
a	Cl
b	Br
c	F

Scheme-1

Yakaiah and Coworkers synthesized new type of compound called Pyrazolo-oxothiazolidine derivatives. These compounds were synthesized using a method that combines multiple components in a single step. Beside that author focused on the yields of the compounds by optimizing reaction condition it reveals that at 20 mol % of NaOH catalyst and ethanol at 80^0C was the effective condition for high yield (91%) of the product (**Scheme 2**). The synthesized compound further tested for their effectiveness against A549 cell lines, which is associated with lung cancer. They used specific receptors called EGFR 14 and VEGFR 2 to evaluate the compounds ability to inhibit cell growth. The obtained results tested with standard drug called sorafenib (IC_{50}, 3.779 µg/ml). The study found that one of the compound labelled as (j), showed encouraging results with an IC50 value of 2.445 µg/ml. This indicates that it has the potential to inhibit cell growth effectively. Following the compound (a) (0.930 µg/ml), compound (e) (1.207 µg/ml), compound (g) (1.078 µg/ml), compound (h) (0.967 µg/ml), and compound (f) (0.808 µg/ml) in vitro inhibition at IC_{50}. [17].



Scheme -2

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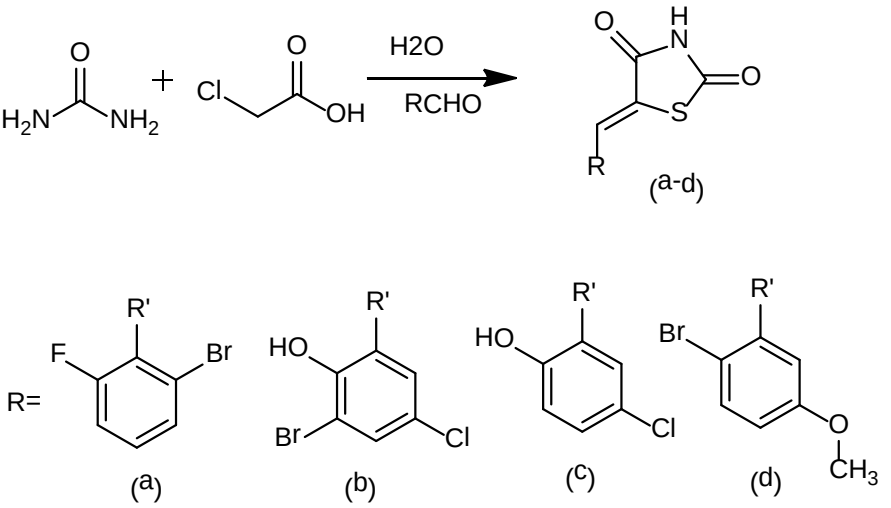
Product	R1	R2	Time (Hr)	Yield %
a	p-Flouro	-ethyl	3.5	83%
b	p-chloro	-ethyl	3.5	81
c	3,4-dimethoxy	-ethyl	3.5	93
d	m-bromo	-ethyl	4	89
e	p-methoxy	-ethyl	4	83
f	p-flouro	-methyl	3.5	82
g	p-chloro	-methyl	3.0	89
h	3,4-dimethoxy	-methyl	3.5	91
i	m-bromo	-methyl	3.5	81
j	p-methoxy	-methyl	4	80

Rodrigues et al. Conducted a study were the synthesized benzylidene-2,4-thiazolidinedione derivatives. The synthesized compound labelled as (a-d), further these compounds tested for their selective cytotoxic and genotoxic activity. To evaluated their effectiveness, the derivatives were tested on various cancer cell lines including NCI-H292 (human lung carcinoma), MCF-7 (breast adenocarcinoma), HEp-2 (Cervix Carcinoma), K562 (leukemia) and HT29 (Colon Adenocarcinoma). The authors used MTT assay to assess cytotoxicity and the alamarBlue assay to evaluate non-tumor cells (human peripheral blood mononuclear cells, PBMC).The synthesis of benzylidene-2,4-thiazolidinedione derivatives involved reacting aldehydes with thiourea and alpha-chloroacetic acid in an aqueous medium, resulting in the formation of various thiazolidine-2,4-dione derivatives (Scheme 3)[18]. Among the compound tested the highest genotoxicity and cytotoxicity were observed in compound 5-(2-bromo-5-methoxybenzylidene)-thiazolidine-2,4-dione (d). It exhibited the lowest IC_{50} value of 1.26 µg/ml for NCI-H292 Cells while not affecting normal cells.



Scheme-3

Ansari et al. conducted a study on the synthesis, cytotoxicity and antitumor activity of Pyridine thiazolidinones. Authers aimed to develop unique human CAIX inhibitors by supporting a mixture of3-(furan-2-ylmethyl)-2-(phenylimino)-1,3-thiazolidine-4-one, aldehydes and hexahydropyridine using ethanol as a solvent (**scheme-3**). To evaluate the cytotoxicity of compounds a standard MTT assay was performed for molecular docking studies, CAIX (PDB ID:3IAI) was used. The derivatives of compounds showed varying level of inhibition against CAIX. Specifically, compounds 89c, d, f, g, j, m, n and q exhibited low inhibitory activity with IC50 values ranging from 38.40 µM to 63.11 µM. These compounds contained alkoxy and chloro groups. On the other hand, compound 89i, o,r and s showed good inhibitory effects with IC50 values of 6.64 µM, 10.04 µM, 16.68 µM and 20.92 µM respectively. These compounds had a disubstituted methoxy groups or heterocyclic

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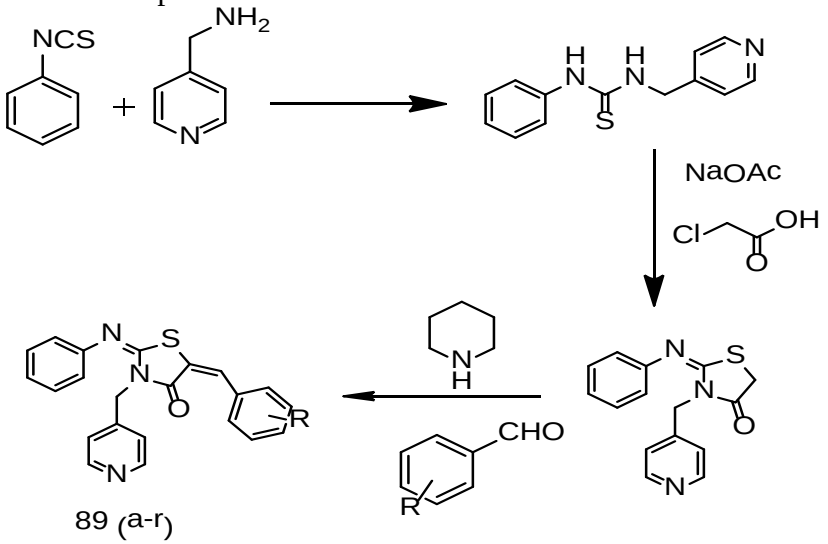
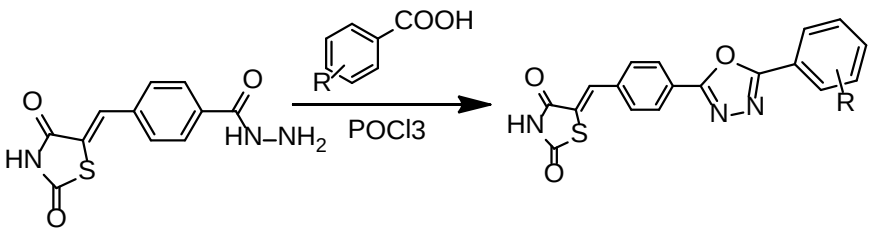
substitution, Compounds 89 (e,h,k & r) which contained a nitro or hydroxyl group exhibited outstanding inhibitory activity with IC50 values of 1.61 µM, 1.84 µM and 6.64 µMRespectively. Authors concluded that both the substituents and the molecular skeleton play a role in the inhibition of CAIX. The cytotoxicity of the compounds was evaluated using HEK lines as a reference and all compounds showed satisfactory activity against MCF-7 and HePG2 cell lines. Notably, Compounds 89h and 89k demonstrated the most promising activity for cancer treatment.Overall, this study provides valuable insights into the, synthesis, cytotoxicity and anticancer activity of pyridine-thiazolidinone and their potential as CAIX inhibitor [19].



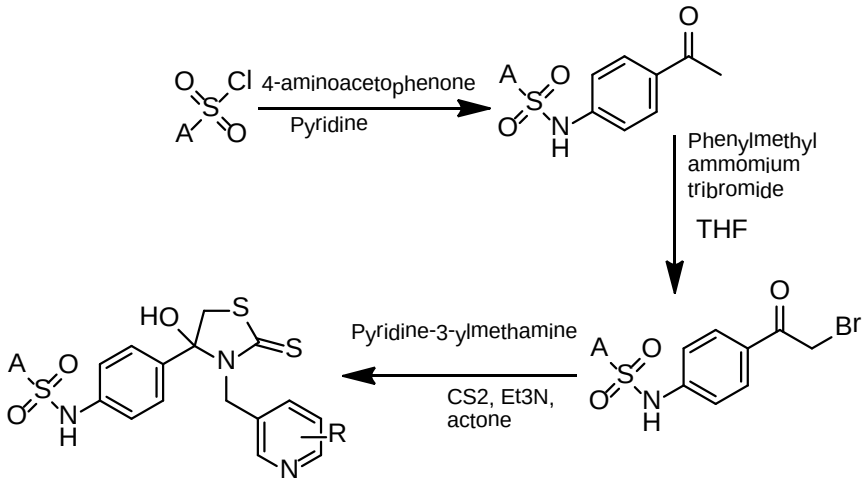
Asati and Coworkers conducted a study on the synthesis and anticancer activity of thiazolidinone-2,4-dione derivatives. The derivatives were obtained by reacting with 4-((2,4-dioxothiazolidine-5ylidene) methyl) benzohydrazide with aliphatic or aromatic acids in the presence of POCl3 (Scheme4). The anticancer activity of thiazolidine derivatives was evaluated against MCF-7 cells using the SRB method. The authors also found that the H-bonding interaction of the oxygen atoms at the second and fourth positions of the thiazolidinonederivatives with ASP186 and LYS67, respectively played a crucial role in their activity. The nature and presence of substituent also influenced the activity.Among the tested compounds, compound 90x exhibited the most remarkable effect on MCF-7 cell lines with a GI50 value of 0.004 µM. It also showed a docking score of -6.688 against PIM-1 kinase. Compound 90c, 90d, 90e, 90f, 90h, 90i, 90o and 90t exhibited potent activity with GI50 values ranging from 0.012 µM to 0.097 µM. compounds 90g, 90i-k, 90m, 90q, 90r, 90s, 90u and 90v showed intermediate inhibition effects. The study further authors reveals that the introduction of electron withdrawing effect such as Cl, Be and I increased the activity, while the presence of EDG like 2-methyl decreased the activity. SAR studies find presence of phenyl ring crucial for the observed anticancer activity. Finally, authors highlight the compound 90 demonstrating the most marked effect on the MCF-7 cell lines. The findings provide valuable insights into the SAR and importance of specific substituents in these derivatives for the future drug development[20].



Scheme-4

ISSN (PRINT): 2393-8374, (ONLINE): 2394-0697, VOLUME-11, ISSUE-9, 2024
DOI: 10.21276/ijcesr.2024.11.9.47

Study conducted on the synthesis and antiproliferative activity of 4-hydroxy-thiazolidine-2-thione derivatives done by Li and coworkers. The synthesized derivatives labelled as 91a-91z, further they were screened for their biological activity. The study aimed to explore the potential of the 4-hydroxy-2-thione moiety as a drug and focused on two structural subunits: subunit A (phenyl group) and subunit B (pyridine-3-ylmethyl) moiety. The modification of subunit A involved the reaction the reaction of substituted sulfonyl chlorides and 4-aminoacetophenone to form intermediates, further it will react with phenyl trimethylammonium tribromide, pyridine-3-ylmethenamine and carbon disulphide (scheme5). The resulting compounds were found to be potent activators of pyruvate kinase M2 isoform (PKM2). Furthermore, authors explore the SAR using a fluorescent PK-LDH coupled assay. It was observed that the electronic and steric effects of substituents on the benzene ring influenced the activation activity of PKM2. Compounds 91t and 91y exhibited higher potency with IC50 values of 0.52 µM and 0.74 µM respectively. The presence of EWG (91h-91m), multi-substituent (91d and 91e), and large group causing steric hindrance (91n-91p) on the benzene ring deactivates PKM2. Conversely, the introduction of a methyl group in the ortho position at nanomolar concentration enhanced the activity. Methoxy and methyl group at meta and para position decreased the activity. Compound 91h exhibited the most potent antitumor activity against HCT116, Hela; H1299 and PC3 cell lines, with IC50 values of 0.46 µM to 0.81 µM. Finally, 4-hydroxy-thiazolidine-2-thione framework and the pyridine framework shows potent antiproliferative activity by affecting PKM2 activity due to hydrogen bonding [21].



Scheme-5

N. Finiuk& coworkers synthesized a series of novel Pyrrolinedione-thiazolidines & evaluate their physicochemical characteristics. The synthesis of the novel Thiazolidinone procedure involved mixing 2-(4-oxo-2 thioxathiazlidine-3-yl) succinic acid an appropriate aromatic amine in glacial acetic acid, followed by refluxing the mixture (scheme). The obtained series of product (1a-c) further screen for various cancer cell lines, normal human keratynocytes and lymphocytes of peripheral human blood. Hit compounds 2a & 2b have emerged as promising candidates with sub-micromolar cytotoxic activity against a diverse range of cancer cell line, inducing leukemia colon cancer, CNS, and ovarian cancer cells. Notably author's reveals that these compounds exhibit a remarkable ability to selectivity inhibit T-leukemia cells of the jurkat line while demonstrating low toxicity towards normal human keratinocytes and nitrogen activated lymphocytes from healthy donors. Compound 2a and 2b induce apoptosis in T-leukemia cells via modulation of mitochondrial apoptosis associated proteins accompanied by pro-apoptotic morphological changes. Intriguingly although these compounds induce DNA damage, they do not directly bind to DNA molecule. Finally, authors conclude the compound 2a and 2b target cancer therapy but also highlight avenue for further exploration into their clinical efficacy & safety profiles [22].

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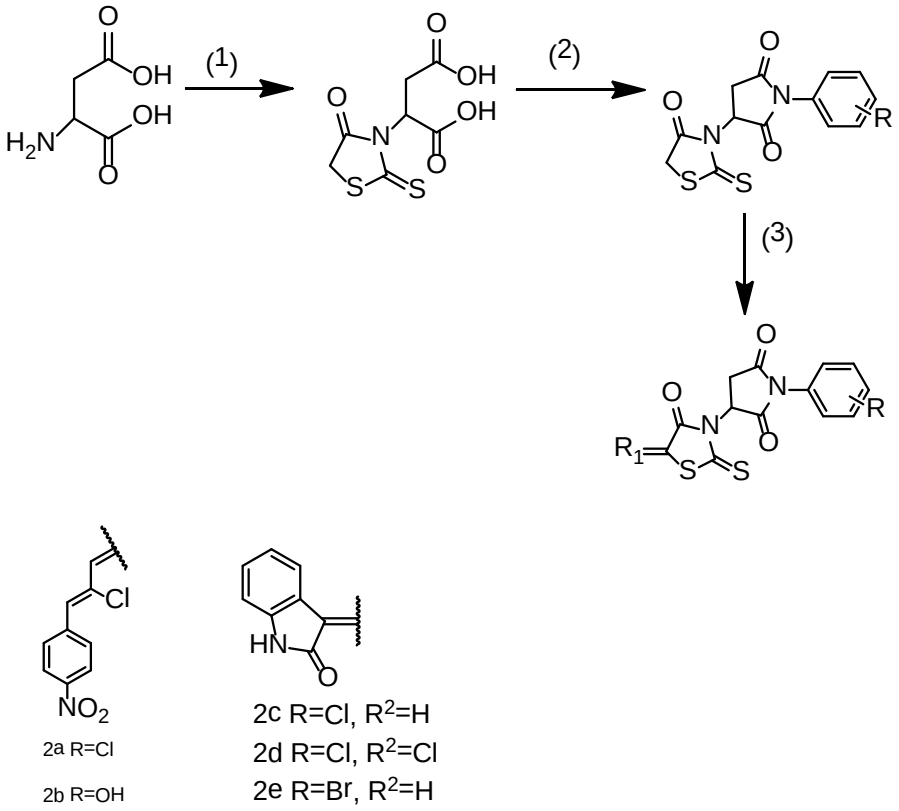
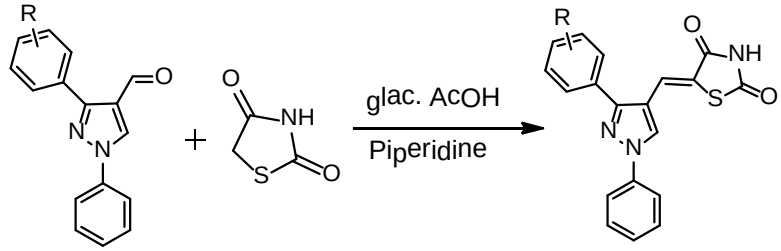


The study conducted by Kumar and colleagues involved the synthesis and evaluation of novel hybrid compounds consisting of 2, 4-thiazolidinedione and pyrazole moieties for their anticancer activity. These compounds were designated as 3-(substituted aryl)-1-phenyl-1H-pyrazolyl-2,4-thiazolidinediones (102a–h). The synthesis of these compounds involved the cyclization of substituted phenyl hydrazones via the Vilsmeier–Hack reaction, followed by condensation with 2,4-thiazolidinedione using piperidine as a catalyst in glacial acetic acid, as illustrated in Scheme 80. After synthesizing the compounds, they were subjected to evaluation for their anticancer properties. against three different cancer cell lines: A549, MCF-7, and DU145. The evaluation was performed using MTT-based cytotoxic assay, with Doxil serving as the reference drug. Among all the synthesized hybrid compounds, compound 102b exhibited notable cytotoxic activity against all three cancer cell lines, A549, MCF-7, and DU145, with IC50 values of 4.63, 1.32, and 5.25 μg, respectively. Additionally, compounds 102c and 102h also demonstrated significant activity against A549 and MCF-7, with IC50 values ranging from 4.44 to 9.16 μg. This study highlights the potential of these novel hybrid compounds, particularly compound 102b, as promising candidates for further development as anticancer drugs [23].



Akshaya & Coworkers synthesized 5-(4-substituted)-3-{[(4-substituted) amino] methyl}-1,3-thiazolidine-2,4-diones through reflux of 5-arylidene thiazolidine-2,4-diones, formaldehyde, and aromatic amines in methanol. The reaction involved Knoevenagel condensation catalyzed by l-tyrosine, followed by Mannich reaction, yielding Mannich bases (Scheme 81). All derivatives exhibited cytotoxic effects against both PPAR-γ and MCF-7 cell

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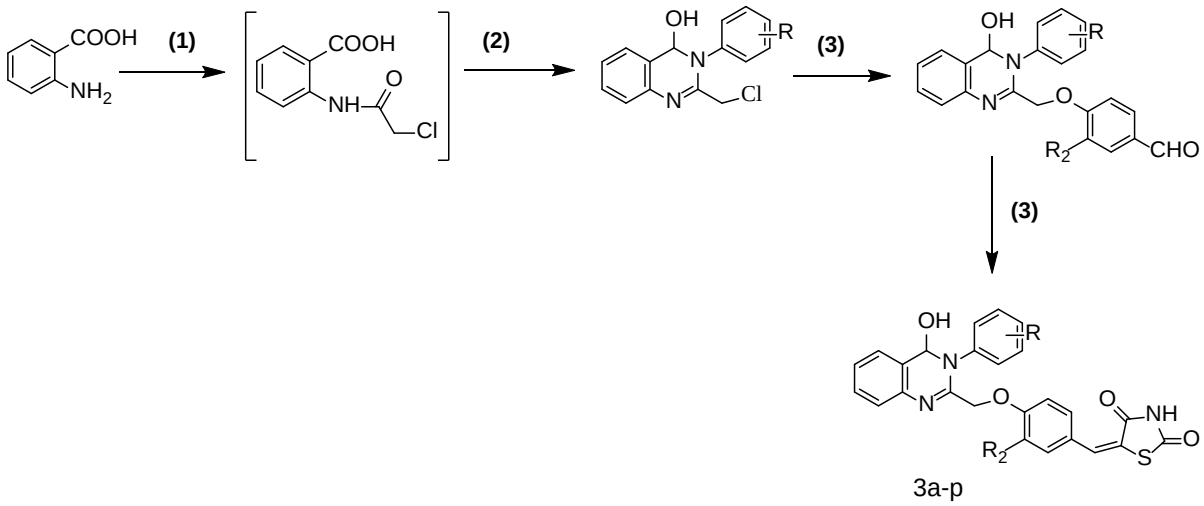
lines, as determined by MTT assay. SAR analysis highlighted the potency enhancement with electron-withdrawing groups (bromine, chlorine, fluorine). Compounds 103a and 103b demonstrated high activity against MCF-7 due to electronegative substituents and non-bonding valence electrons, while electron-releasing groups reduced activity against MCF-7.9 [24]. Metwally & Coworkers introduced an innovative class of quinazoline linked 2,4-thiazoidinedione. The synthetic route for the A-series and B-series of target TZD are described in (scheme10). For the A-series and B-series chloromethyl quinazolinones (1a-j) synthesis followed by cyclization with anilines to obtain intermediates, aldehydes (2s-p) were then produced and subjected to Knoevenagel condensation with2,4-thiazolidinoe to yield the desired TZD target (3a-p). For B-series analogue synthesis involves the condensation of appropriate aldehydes with 2,4-Thiazolidinedione form intermediate chalcone (4a-c) which were then alkylated with chloromethyl quinazolinones (1a,1f, 1k & 1l) to yield the target TZD (5a-p). Obtained resultant product screening against panel human cancer cell line which includes PC-3, MDA-MB-231 and HT-1080 cell lines by taking toglitazone as a standard reference drug. Compound 3c, 3i, 5c and 5d displayed notable in vitro cytotoxic activity at low concentration. Further author's reveals the position of TZD ring in the molecule didn't affects their effective mechanistic investigations revealed that the most potent compounds induce apoptosis with specific signaling pathways varying depending on the cancer cell type [25].



Scheme-10

In the recent study conducted by, Bataille and collaborators commence on the synthesis of innovative 4-thiazolidinone derivatives, focusing on their potential as anticancer agents specifically targeting cancers in blood and lymph tissues. The assessment of anticancer activity centred on inhibiting the PIM kinase family,facilitated by the application of the differential scanning fluorimetry (DSF) technique. Two distinct methodologies were predominantly employed.A fused tricyclic series was synthesized through hydrolysis followed by conjugate addition. This approach yielded compounds exhibiting notable improvements in both solubility and metabolic stability, crucial factors in their potential therapeutic applications.An alternative approach involved enhancing metabolic activity by incorporating pseudothiohydantoin in lieu of the rhodanine head group. This modification contributed to improved metabolic stability, expanding the potential utility of the synthesized compounds.Compound 96, a member of the synthesized series, was formed through Knoevenagel condensation of carbonyl compounds and rhodanine using piperidine in EtOH (Scheme 11).

This method demonstrated versatility in compound formation. Other derivatives were synthesized through Suzuki–Miyaura coupling, utilizing RB(OH)2 and Pd(PPh3)4 in Na2CO3. Subsequent Knoevenagel condensation with rhodanine, catalyzed by piperidine, resulted in the formation of tricyclic compounds. The

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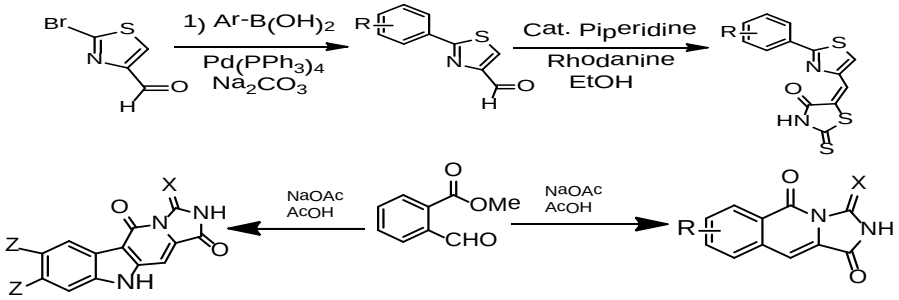
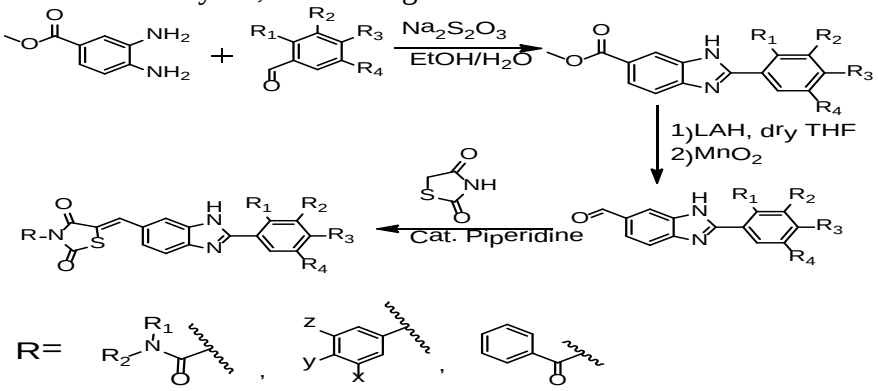
DOI: 10.21276/ijcesr.2024.11.9.47

compounds were categorized into 11 classes based on their structural characteristics.The synthesized series exhibited superior selectivity for pan-PIM kinases compared to other kinases. Notably, all tested compounds displayed commendable activity, with derivative 98b standing out for its high efficacy against the K562 cell line, boasting an IC50 value of 0.75 μM.Compound 97a, featuring a phenyl group, exhibited a remarkable 90-fold increase in activity with an IC50 value of 6.7 ± 3.1 nM. In silico studies uncovered a crucial interaction between the rhodanine head group and water, linked to the Lys67 residue, resembling a sandwich-like interaction within the lipophilic area of the PIM binding pocket. The Structure-Activity Relationship (SAR) study indicated that electronic effects played a minimal role in inhibition activity. Compound 98a, incorporating a sulfonamide group, emerged as an excellent PIM1 inhibitor (IC50 25 ± 4 nM) while exhibiting superior activity. This multifaceted investigation underscores the potential of these 4-thiazolidinone derivatives as promising candidates for anticancer therapies, with a focus on PIM kinase inhibition and enhanced structural characteristics for improved efficacy and specificity in kinetic solubility compared to other compounds [26].



Scheme-11

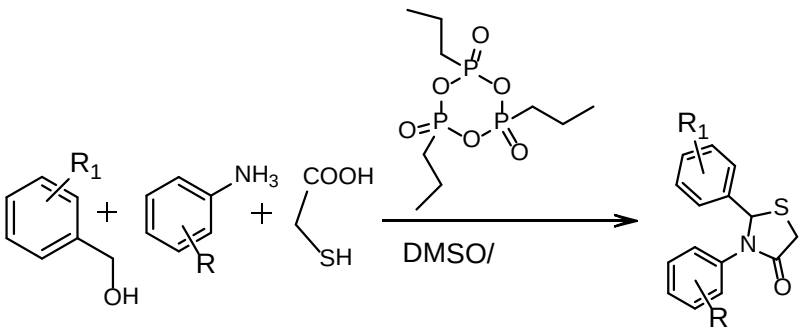
In a study conducted by Sharma and colleagues, a novel class of compounds featuring benzimidazole nucleus-linked thiazolidinedione hybrids was synthesized and evaluated for their potential as cytotoxic and apoptosis-inducing agents against various human cancer cell lines, including prostate (PC-3 and DU-145), breast (MDA-MB-231), A549, and MCF10A. The MTT assay was employed for screening, with 5-FU serving as the standard drug for comparison.The synthesis of these benzimidazole-thiazolidinedione hybrids involved Knoevenagel condensation between substituted thiazolidinedione and 1-alkyl-1H-benzo[d]imidazole-2-carbaldehydes, resulting in moderate to high yields. The reaction pathway is detailed in **Scheme 12**. Among compound were screened against A549 cell lines compound 99j, 99p & 99r obtained as the most potent with IC50 value of ≥15μM. Without affecting MCF10A cell line which indicate a degree of selectivity for cancer cells reveals arrest at the G2/M phase. Various assay was studied by authors for apoptosis induction by compound 99a in A549 cells. Structure-activity relationship (SAR) studies indicated that substitutions on the head position led to compounds with higher bioactivity compared to tail substitution.



Scheme-12

ISSN (PRINT): 2393-8374, (ONLINE): 2394-0697, VOLUME-11, ISSUE-9, 2024
DOI: 10.21276/ijcesr.2024.11.9.47

In a study led by Kumar and coworkers, a straightforward and efficient synthesis of 4-thiazolidinone derivatives was developed using propylphosphonic anhydride (T_3P)-DMSO media as a cyclodehydrating0 agent. These derivatives were subsequently evaluated for their cytotoxicity both in vitro and in vivo, particularly against leukemic cell lines (Reh and Nalm6).The synthesis of 4-thiazolidinone derivatives (designated as 100(a–j)) involved a one-pot process using T3P-DMSO media. This method proved effective for converting primary and secondary alcohols, as well as aryl amines, into the desired thiazolidine derivatives. High yields were achieved, as illustrated in Scheme13. The series of products were screened for in vitro and in vivo studies against leukemic cell lines (Reh and Nalm6) shows superior result against Reh cell lines compared to Nalm6 cell lines. Prominently, compound 3-(4-bromophenyl)-2-(4-(dimethylamino) phenyl) thiazolidin-4-one (100e) demonstrated potent activity against both Reh cells and Nalm6 cells, with IC50 values of 11.9 µM & 13.5 µM. Also, compound 100e induced cell aggregation in the SubG1 phase, indicating its impact on cell cycle progression. Cytotoxic effects indicates decreased in mitochondrial membrane potential and increased cell death through apoptotic pathways in tested cell lines. In vivo result shows significant reduction in tumour cell volume.Finally, study highlights the successful development of a direct synthesis method for 4-thiazolidinone derivatives using T3P-DMSO media and their promising cytotoxic effects, particularly against leukemic cell lines[28].



Scheme-13

N. Subhashini & Colleague synthesized a novel series of pyrazole and triazole linked TZD & screened against human breast cancer cell lines. The synthesis if titled compound novel compound implicates in consecutive four steps. The first step involves the condensation between acetophenone and phenyl hydrazine form phenyl hydrazine, subsequently it was undergoing cyclization by using POCl3/DMF forms compound 4. Compound 4 undergoes Knoevenagel condensation by using 2,4-Thiazolidinedione got compound 5 which then N-alkylation with propargylic bromide to yield intermediate 6, finally compound 6 underwent click reaction with various substituted phenyl azides (7a-n) in DMF with sodium ascorbate and copper sulfate catalysts, resulting in final derivatives (8a-n) (Scheme14).The synthesized derivatives screened for in vitro cell viability assay against human breast cancer cell line (MCF-7) by taking Cisplatin as a standard reference drug. Author's reveals that most of the synthesized derivatives exhibited moderate to excellent cytotoxic activity. Notably, derivatives containing EDG demonstrated significant cytotoxicity. Lead analogue 8j (with R1 = OMe and R3 = NO2) and 8e (with R3 = CF3) exhibited excellent cytotoxic activity with IC50 values of 0.426 µM ± 0.455 and 0.608 µM ± 0.408 respectively. Surpassing the standard drug cisplatin (IC50 = 0.636 µM ± 0.455). However, compounds with various halo substituents at different positions on the triazole phenyl ring demonstrated lower cytotoxic activity. Finally, authors suggest that the synthesized hybrid possess promising cytotoxic potential of novel analogue[29].

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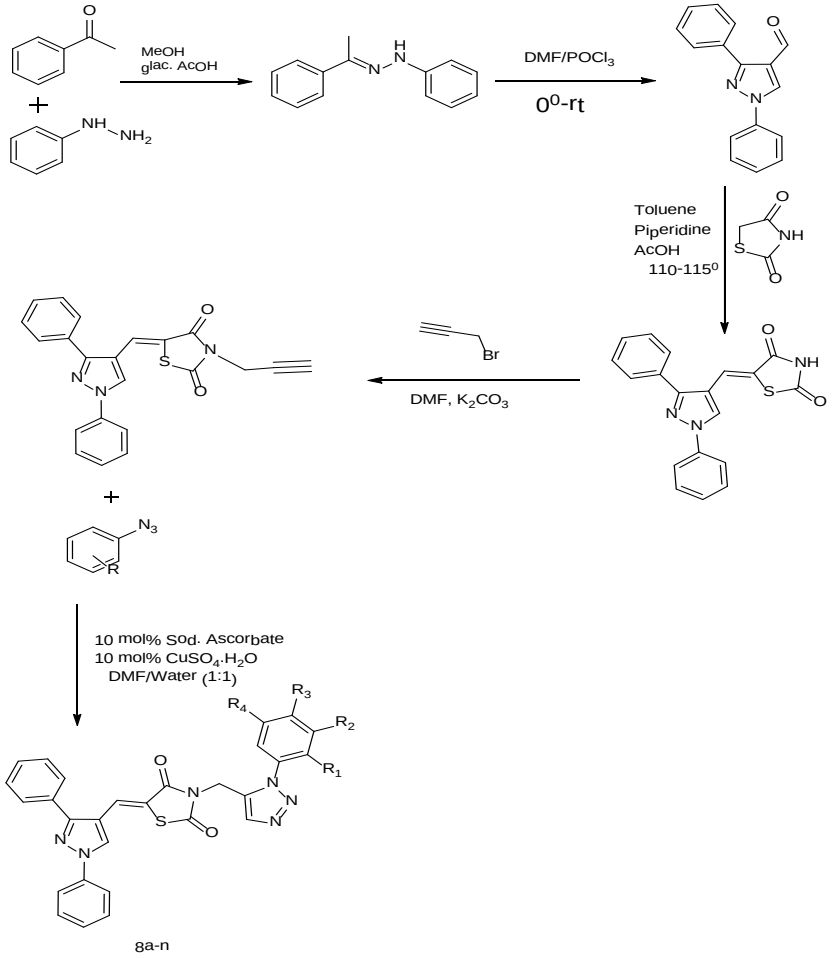
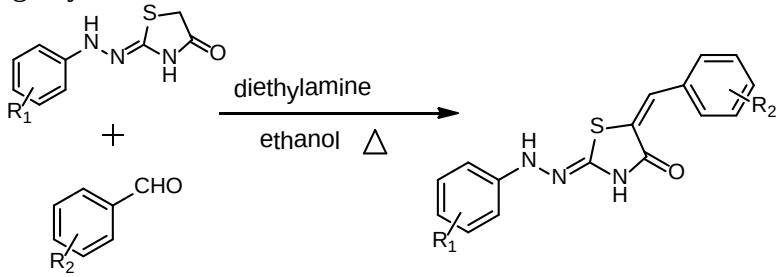


Scheme-14

K. Gokhale & Coworkers develop a novel series of 5-arylidene-1,3-thiazolidin-4-one analogue by serving diethyl amine as a catalyst. Synthesis of compound was conducted using simple and efficient protocol in the literature as depicted in **scheme-15**. Furthermore, the synthesized derivatives screened against MCF-7 cell lines which exhibits GI50 values of <10µg/ml by taking Adriamycin as a standard reference. Authors reveals that among synthesized derivatives compound 9b exhibits excellent inhibition of the HoP62 cell lines as represented by its GI50 value of <10µg/ml. Except 9b none of the derivatives ineffective against inhibition of HeP G2 cell lines. This concludes that compound possess cytotoxic potential specifically against human cancer cell lines recommends that their anticancer activity is solely based on their structure with no observed systemic toxicity [30].



Scheme-15

Novel hybrid molecule containing 5-Benzylidene Thiazolidine-2,4-dione synthesized by Romagnali& Coworkers. The synthesis of 5-(nitrobenzylidene)-Thiazolidine-2,4-dione derivatives were prepared by the Knoevenagel Condensation of the 2,4-TZD with 4 or 3-nitrobenzaldehyde, subsequently the product of reaction with alkyl, benzyl or phenyl ethyl halide in DMF in the presence of sodium hydride, furnished the corresponding N-3-substituted Thiazolidine-2,4-dione derivatives. The reduction of nitro derivatives with Fe and

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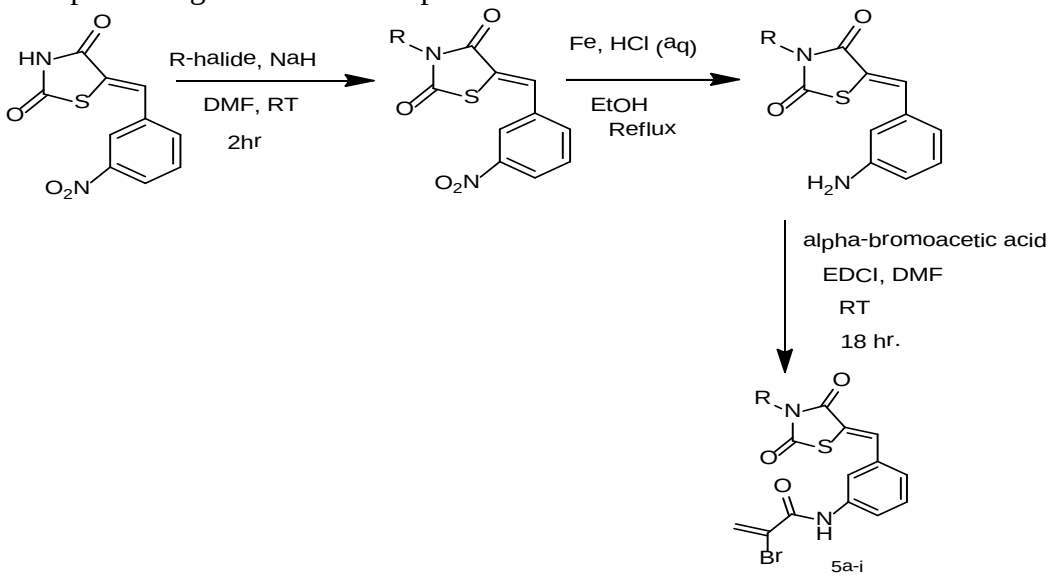
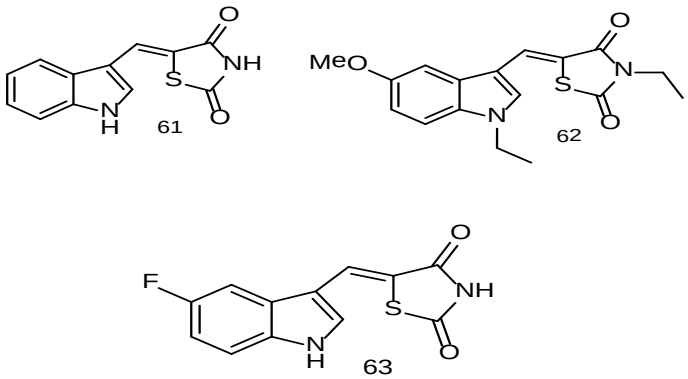
mixture of 37% HCl in water and ethanol under reflux, furnished the Corresponding hybrid compound (scheme16). The synthesized product screened with HL-60 and U937 cell lines. The compound 4a exhibited the greatest antiproliferative activity with IC50 value of 0.19-0.87 µM. Among the 5a, 5c, & 5g (3 µM, 6h), the compound 5g is the most potent apoptotic inducer when tested with U937 cells. The percentage of apoptotic cells increased 6-fold, 4-fold & 16-fold. The experimental findings revealed a notable increase in the proportion of cells entering the sub G0-G1 peak upon exposure to the investigated molecules suggested the apoptotic induction[31].



Scheme-16

Corigliano K.W. et al. synthesized indole and 2,4-thiazolidinedione conjugates in 2018 and performed their structural analysis (SAR) (Scheme 17). Using MTT assays and wound healing assays, compounds 61, 62, and 63 (IC50: 5µM) were shown to be the most potent when compared against the standard medicine rosiglitazone and evaluated against PC3 (prostate cancer) and MCF-7 (breast cancer). The docking data (PDB ID: 2PRG: Schrodinger, LLC, New York, NY. 2017) unambiguously shows that ligands were well-accommodated into the PPARγ active site by creating an H-bond between their thiazolidine moiety's carbonyl group and the residues H343, Y473, and H449[32].



Scheme-17

Sulforhodamine B assay was used by Ozen C. et al. (2017) to investigate the anticancer activity of thiazolyl-2,4-thiazolidinedione/rhodanine against two hepatocellular carcinoma (HCC) cell lines, Huh7 and Plc/Prf/5 (Plc) (compound 18). Doxorubicin is the conventional medication,

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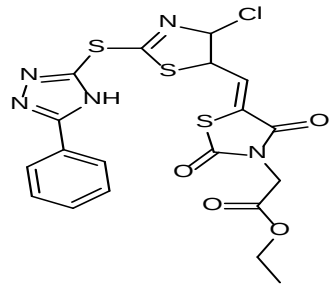
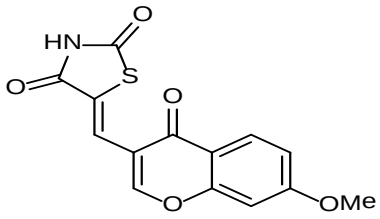
and compound 58 (IC50: 2 to 16 μM) shows the most potent activity [33].



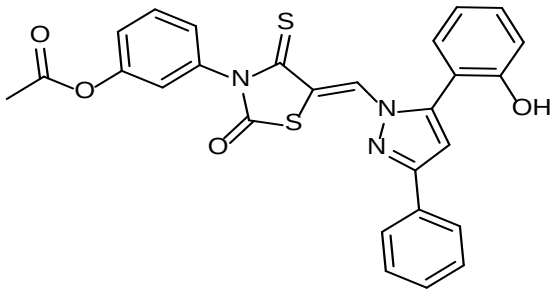
Compound-18

In 2015, Hoang Le T.A. and colleagues synthesized novel chromonelthiazolidine derivatives and investigated their effectiveness as anticancer agents against human epidermoid carcinoma (IC50: 44.1 ± 3.6 μg/ml) and breast cancer (IC50: 32.8 ± 1.4 μg/ml) (compound 18). When compared to other derivatives, compound 38 is thought to be the most potent, with an IC50 of 32.8 ± 1.4 μg/ml, and typical dosages of MCF-7 and elipticine.Different sections of plants and vegetables include derivatives of chromomes. These compounds demonstrated selective cytotoxicity towards cancer cell lines and low mammalian toxicity with a broad spectrum of biological activities. Medicinal chemists are interested in the TZD moiety because of its broad range of biological action and capacity to inhibit a variety of enzymes [34].



Compound-19

Senkiv J. et al. (2016) developed and synthesized new derivatives of 5-ene-4-thiazolidinone and assessed their anticancer and selective antileukemic properties. The MTT assay was used to assess the cytotoxicity (compound 20). Doxorubicin is the regular medication, and compound 57 was the most active derivative against HL-60 and HL-60/ADR cell lines (IC50: 118 nM/HL-60) with minimal toxicity towards pseudo-normal cells. Intense research is being done on 4-TZD and related heterocycles in an attempt to create a new, more potent medicinal molecule. The molecule becomes electrophilic and perhaps reactive upon conjugation of the 5-ene fragment to the carbonyl group at the C-4 position of the thiazolidine core. This is because nucleophilic protein residues may Michael add to the exocyclic double bond. 5-ene-4-TZD inhibits cancer growth by reversibly inhibiting [35].



Compound-20

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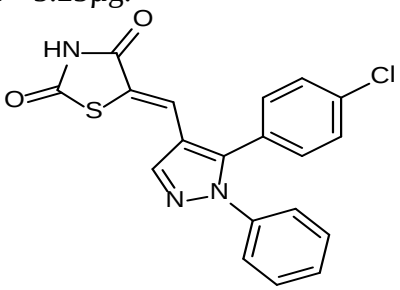
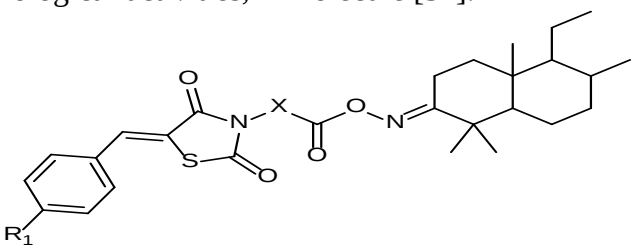
In 2014, Sudheer K. et al. developed a novel pyrazolyl thiazolidinedione derivative using the Vilsmeier-Haack reaction. They then used the MTT assay to test the derivatives' cytotoxic potential against human cancer cell lines A549, MCF-7, and DU145 (compound 21). Using Doxil as a positive control, compound 53 was shown to be the most potent, with IC50s of 4.63, 1.32, and 5.25µg. According to recent findings, TZDs have tumor suppressor properties in addition to their ability to sensitize insulin. Conversely, pyrazole has garnered interest over time because of its wide range of biological activity. Motivated by the distinct biological characteristics of pyrazole and the TZD moiety, an attempt has been made to employ a hybridization technique [36].



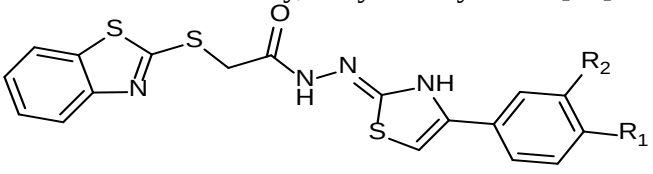
Compound-21

A group of novel acylated oxime derivatives of oleanolic acid containing 3-(5)-carboxylic acid moieties and 4-thiazolidinone were reported by Kaminsky D. et al. (2011) (compound 22). Testing Compound 52 against 60 human cancer cell lines revealed that it exhibited a broad range of biological activities, as evidenced by the dose-dependent metrics pGI50 = 5.51/5.57, pTGI = 5.09/5.13, and pLC50 = 4.62/4.64 for 4-azolidinone-3(5) carboxylic acid. This study aims to create double drugs by combining oleanane scaffold and 4-TZD carboxylic acid into a single molecule [37].



Compound-22

Novel2-(benzothiazol-2-ylthio)-N-(3-substituted-4-(3,4-substitutedphenyl) thiazol-2(3H)-ylidene) acetohydrazides were synthesized by D. Osmaniye and colleagues (compound 23), subsequently studied their anticancer efficacy against A549 and C6 cells. The produced benzothiazoles' cytotoxic effects on NIH3T3 cell lines in a healthy state were further investigated. During investigation authors conclude Compounds 4a and 4d were found equally cytotoxic when combined with cisplatin against the C6 cell line. Additionally, compound 4a inhibited the C6 cell line more selectively than compound 4d. Examining the anticancer activity results, it is evident that compounds having cyclohexyl substitutions (4a–4h) are more effective than those with phenyl substitutions.4i–4p in opposition to the C6 cell line. Compound 4a exhibited the anticancer activity screening of new benzothiazole-thiazoline derivatives. The novel derivatives has a higher capacity to induce apoptosis than cisplatin according to flow cytometry result [38].



Compound-23

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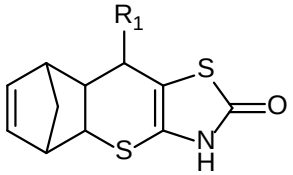
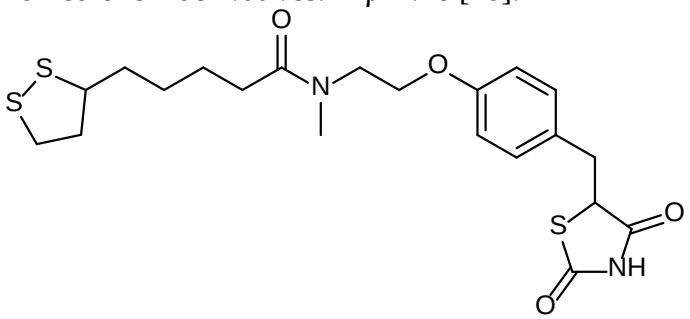
By using a stereoselective hetero-Diel's alder reaction to combine a 5-ylidene-4-thioxo-2-thiazolidone derivative with norbornene, Lesyk R. et al. succeeded to create a novel technique for thiopyrano [2, 3-d] thiazol-2-ones with norbornane moiety (compound 24). The synthesized compounds have in vitro anticancer activity against a variety of human tumor cell lines, notably SF-268 (cancer of the central nervous system), MCF7 (breast cancer), and NCI-H460 (non-small cell lung cancer). Compound 1 demonstrates strong anticancer properties. Docking study results (PDB ID: 1FM6 and INYX, Glide, Schrodinger LLC and Fred, Open eye Inc.) showed that a collection of QSAR models had acceptable predictive power and significance [39].



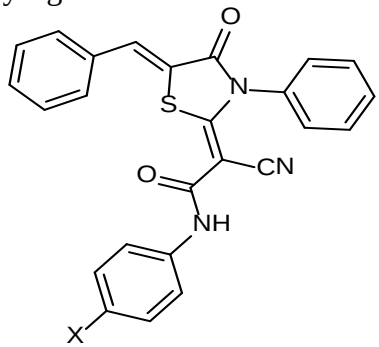
Compound-24

In order to test their anticancer potential against normal and malignant human cell types, Amar G.C. et al. developed a novel class of hybrid lipoic thiazolidinedione derivatives. Pioglitazone and Rosiglitazone were used as standards, and compound 25 showed the strongest action with an EC50 value of 0.015 µM.76 [40].



Compound-25

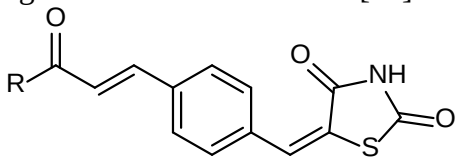
In order to create 5-arylidene-4-thiazolidinones and 5-arylhydrazone analogs, Riham F. George et al. developed a novel method. After the successful synthesis they subsequently utilized the SRB assay to test the compounds' in-vitro anticancer activity against the colon cancer cell line HCT-116, the breast cancer cell line MCF-7, and the liver cancer cell line HEPG2. IC50 for Compound 26 is 7.89 µM. Doxorubicin is utilized as standard and is discovered to be the most active (Discovery Studio 2.5 software) [41].



Compound-26

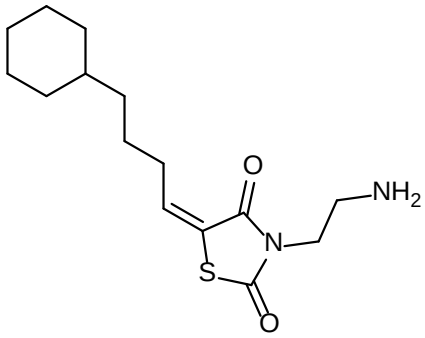
An in vitro studies Brine shrimp mortality experiment was carried out to assess the cytotoxicity activity of a variety of newly synthesized 2, 4-thiazolidinediones by Avupati V.R. et al. Podophyllotoxin was utilized as the reference medication, and Compound 27 (ED50: 4.00±0.25 µg) shown strong effects. The thiazolidinedione ring exhibited a particular

interaction with adjacent amino acid residues of LBD, according to a molecular docking investigation (PDB id: 3CS8: Molegro Virtual Docker v 4.0). H-bonding with amino acids Cys 285, His 449, and Tyr 473 is one of these interactions [42].



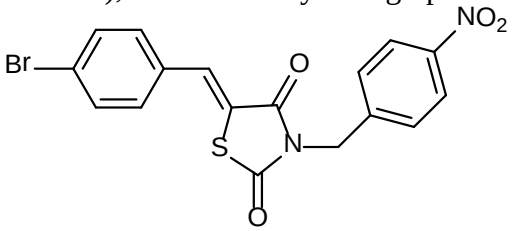
Compound-27

Employing the [3-H]-thymidine uptake test, Liu K. et al. constructed a novel series of 2,5-disubstituted-thiazolidine-2,4-dione and investigated their cytotoxic potential on U937, M12, and DU145 cancer cell lines. With GI50 values ranging from 1.40 μM to 5.10 μM, compound 26 exhibited strong anticancer activity. Based on Gold Software ver. 3.0's docking data (PDB ID: 1s9j for MEK-1 and PDB ID: 3hhm for PI3Kα), compound 5 likely to fit well into the ATP binding pocket of the MEK1 and PI3K signaling pathways [43].



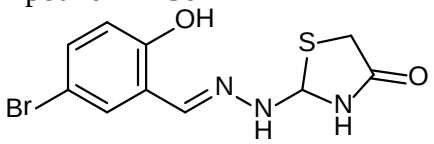
Compound-28

Melo R. et al. constructed a number of novel di-substituted thiazolidinedione derivatives and tested their cytotoxicity against six tumour cell lines: Raji (Burkitt's lymphoma), Jukart (T cell leukemia), MIA PaCa (pancreatic adenocarcinoma), NG97 (glioblastoma), and HepG2 (hepatocarcinoma). Using amsacrine as a standard medication, compound 29 showed the most potent activity with an IC50 of >100 μM (PDB ID: 2HWQ, Gold software version 5.1, Cambridge crystallographic data centre) [44].



Compound-29

Lv P.C. et al. created novel thiazolidinedione compounds and used a solid-phase ELISA technique to test them for anticancer activity. Using erlotinib as a reference medication, compound 30 demonstrated noteworthy efficacy against MCF-7 cancer cell lines, with IC50 values of 0.09 μM for EGFR and 0.42 μM for HER-2 [45].



Compound-30

Solid-phase ELISA assay technique was used by Qiu KM. et al. to assess the anticancer activity of pyrazolyl-thiazolidinone derivatives against MCF-7, B-16-F10, and HCT-116 cancer cell lines. Compound 31 demonstrated the highest level of potency, with an IC50 of 1.07 μM for HER-2 and 0.24 μM for EGFR [46].

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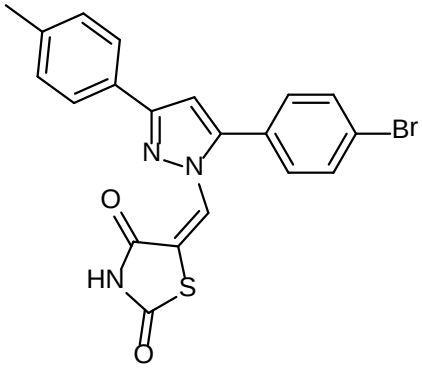
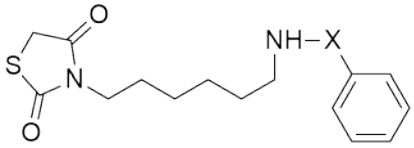


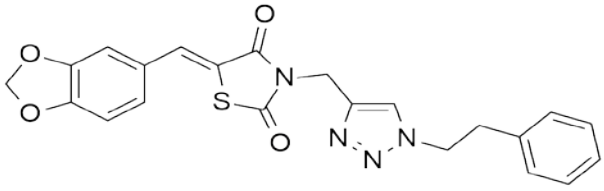
Compound-31

In order to assess the anticancer potential of their newly created 2,4-thiazolidinedione derivatives as zinc chelating agents, Mohan R. & Coworkers used the HDAC enzyme assay and the cell proliferation assay against human liver cell lines, transformed (HepG2) and untransformed embryonic (WRL68) cell lines. Using SAHA as the positive control and compound 32 (100 μM) as the active ingredient, it was discovered to be the most potent (PDB ID: 1c3s: MOE 2006.08) [47].



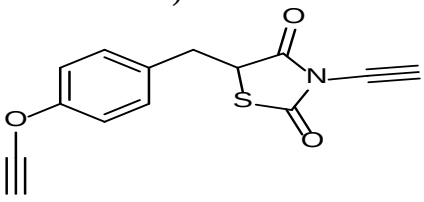
Compound-32

Hep G2 (human hematoma), MCF-7 (breast adenocarcinoma), and IMR 32 (neuroblastoma) were the three cancer types against which Chinthala Y. et al. developed a novel series of thiazolidinedione using the Knoevenagel condensation method. Doxorubicin was used as the standard medication in this process. Compound 33 was determined to be the most effective, with an IC50 value of 30 μg/ml for MCF-7 and 31 μg/ml for Hep G2 [48].



Compound-33

According to Tahseen A. et al. (2014), benzylidene thiazolidine 2,4-thiazolidone derivative was synthesized and tested for anticancer activity using the SRB assay against the colon cancer cell lines DLD-1 and SW 620, the breast cancer cell lines MCF-7 and MDAMB-231. Compound 34 exhibits the strongest anticancer activity, with IC50 values of 10.8 μM (SW620), 8.4 μM (MCF-7) 7.5 μM (DLD-1), and 50.8 μM (MDAMB-231). Treating obesity, diabetes, and cancer with a PTP1B inhibitor is an innovative approach. In the endoplasmic reticulum, there is an enzyme called protein tyrosine phosphatase 1B that is not transmembrane (Compound-34). Tyrosine kinase JAK 2 (Janus kinase 2) is caused to lose a phosphate group when PTPB1 is present. Certain types of cancer might be stopped by its suppression [49].



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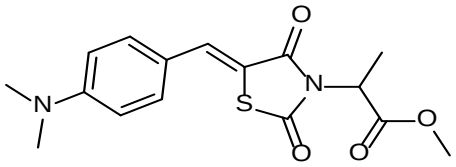
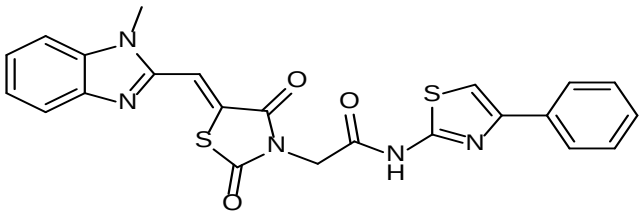
Compound-34

Six unique 2-(5-arylidene-2,4-dioxo tetrahydro thiazole-3-yl) propanoic acids and six corresponding methyl had been synthesized by Bozic B, Rogan J, Poleti D, Rancic M, Trisovic N, Bozic B, Uscumlic G et al. Melting points, elemental analysis, FT-IR, 1H, and 13C NMR spectroscopy were used to describe compound 15. X-ray analysis was used to confirm the crystal structure of methyl-2-(5-(4-methoxy benzylidene)-2,4--dioxo tetrahydro thiazole-3-yl) propionate. It was determined whether the synthesized compounds had any antiproliferative effect on the human colon cancer, breast cancer, and myelogenous leukemia cell lines, HCT-116, MDA-231, and K562, respectively. The outcomes show that the synthetic esters' antiproliferative effectiveness outperforms that of the equivalent acids. Against HCT116 cells, synthesized compound 35 significantly inhibited ant proliferation at all tested concentrations (0.01–100 μM)[50].



Compound 35

New benzimidazole-thiazolidinedione hybrid molecules were constructed by Sharma P. et al., and their cytotoxic potential was assessed using the MTT assay against specific four human cancer cell lines from the prostate (PC-3 and DU-145), breast (MDA-MB-231), lung (A549), and normal breast epithelial cell (MCF10A). IC50:11.46±1.46μM for Compound 36 was determined to be the most powerful derivative when 5-FU was administered as the standard medication [51].



Compound 36

Conclusion:

The numerous actions of thiazolidinedione, including its antidiabetic, anti-inflammatory, wound-healing, antifungal, antiviral, antitubercular, antibacterial, anticancer, and anticonvulsant properties, show how potent this dynamic nucleus is. The type and location of the substituents linked to the thiazolidinedione nucleus affect the synthetic derivatives' effectiveness. The in-silico prediction also revealed that the human body's thiazolidinedione nucleus has approximately 100 potential targets. It is possible to think that the nucleus of thiazolidinedione may be crucial in the creation of a novel medicinal agent. Therefore, greater focus should be placed on changing and replacing this nucleus in order to study better and innovative biological activities that may result in the creation of a novel biologically important drug candidate.

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