SYNTHESIS AND SAR STRATEGY OF THIAZOLIDINEDIONE: A NOVEL APPROACH FOR CANCER TREATMENT

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ABSTRACT

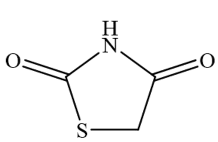
In current review, authors aim to inspire the researcher through structure activity relationship strategy for the finding of safe and effective anticancer molecules. Nowadays cancer is measured as one of the major health problems in human beings in the world from decades. A classes of heterocyclic compounds have been recognized through molecular biology, empirical screening and rational drug development for the evaluation of anticancer molecules however regrettably, till now we could not find a medicine to be entirely active and nontoxic for the treatment of cancer patients. In pointed view, it might be measured that Thiazolidinedione (TZD) heterocyclic compounds are prodigious standing in the synthetic and pharmacological approach of medicinal chemistry. Thiazolidinedione (TZD) nucleus upon the substitution of various functional groups is provides a wide spectrum of biological activity by the use of different mechanism on different target sites. Recently, some of the substituted thiazolidinedione molecules are designed for the treatment of human cancers cell line through different molecular mechanism such as EGFR & Mushroom Tyrosine kinase inhibitor, COX enzyme inhibitors, Histone deacetylase inhibitors, Alpha glucosidase inhibitor, DNA intercalation and Protein tyrosine phosphatase 1B (PTP1B) inhibitor, basically in which PPAR gamma express are in high levels. Peroxisome proliferator-activated receptor (PPAR) gamma ligands effect on apoptosis, cell proliferation and cell differentiation on different types of cell. The most commonly cascades in human cancers cell are Raf/MEK/ERK, Wnt and PI3/Akt. This article highlights and embraces a concise overview of recent approaches for the synthesis of new thiazolidinedione molecules with its structure activity relationship strategy and effects on various signaling pathways, which is responsible for the expresses of cancer cell line activity.

Keywords: TZD, SAR, PPARγ, HDAC inhibitors, AGIs, PTP1B inhibitor, EGFR and Mushroom Tyrosine kinase inhibitor, COX enzyme inhibitors and DNA intercalation.

1. INTRODUCTION

Cancer is a malignant disease of cell cycle in which abnormal cells divide mitosis without control and being one of the major health problems in the world from decades. Globally, it affect a large population of world, if not treated properly, leading to invasion of surrounding tissue and often spreading to other parts of the body and become a serious health issue [1-2]. Every year more than 11 million cases are diagnosed with cancer and by the end of 2020 there may be 16 million new cases [3-4]. According to 2019 Cancer statistics given by American cancer society 1,762,450 new cancer cases and 606,880 cancer deaths occurred in U.S. Both increased national investment in cancer research and demand of existing cancer control knowledge across all segments of population necessary for developing progress against cancer [5].

Among all the types of cancer, breast cancer is the second most prominent cause of death among women [6]. Many traditional cytotoxic drugs and new rationally designed drugs are being used for cancer treatment now days, but the high cost and risk associated with these drugs will recommended us to find another alternative approach [7]. In cancer chemotherapy, heterocyclic compounds play an important role. Thiazole is a class of heterocyclic compound derived from five member ring system which comprises of three carbon atoms, one nitrogen atom and one sulfur atom with two double bonded oxygen on 2 and 4 position. Thiazole ring is found in many natural product and synthetic medicine with a wide range of activities such as anticancer, antiviral, antifungal, antibacterial, anti-inflammatory and antiparkinsonism [8-9]. According to the literature survey Thiazolidinedione (TZD) is one of the most important novel heterocyclic ring system of Thiazole and having a wide range of therapeutic action and when combined with other heterocyclic compound to produce various biological activities (Figure 1) [10].



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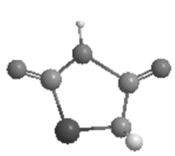

1b

Figure 1. Chemical structure of Thiazolidinedione (**1a**) and 3D view, ball and stick model (**1b**).

2. PPAR GAMMA RECEPTOR ACTIVATOR

Thiazolidinediones (TZDs) are activators of peroxisome proliferator-activated receptors (PPARs) a group of nuclear receptors, particular for PPARγ (PPAR-gamma) and widely used for the treatment of type 2 diabetes [11]. Recently, PPAR gamma ligands (TZDs) are found to show anticancer activity in a wide-ranging of cancer models by disturbing to cell cycle, cell proliferation, cell differentiation and apoptosis in addition to stopping tumour angiogenesis.

These anticancer effects are mediated by the activation of PPAR-γ which is based on the concentration and types of tumour cell [12]. The Angiogenesis activity of TZDs are mediated through the inhibition of endothelial cell proliferation and movement in addition to decrease tumour cell vascular endothelial growth factor production. Currently, TZDs are being tested in clinical trials for the treatment of human cancers expressing high levels of PPARγ because it is assumed that activation of PPARγ mediates their anticancer activity.

Poly (ADP-ribose) polymerase 1 (PARP1) have been shown various biological functions such as DNA repair, synthetic lethality, necrosis, apoptosis and histone binding. DNA repair will be prevented if PARP1 is inhibited, which leads to cell death [13]. In a wide variety of cancer models; TZDs have antitumor activity by affecting the cell cycle, induction of cell differentiation and apoptosis [14]. Thiazolidinedione, also known as glitazones was initially discovered by Takeda Pharmaceuticals, Japan in 1975 [15]. The use of thiazolidinedione's are associated with some side effects, however thiazolidinediones are well tolerated by people.

Troglitazone is the first TZD available in the market which was withdrawn due to it's sever hepatotoxicity. Edema, macular edema, heart failure and weight gain are the other common side effects associated with this drug (Figure 2) [16].

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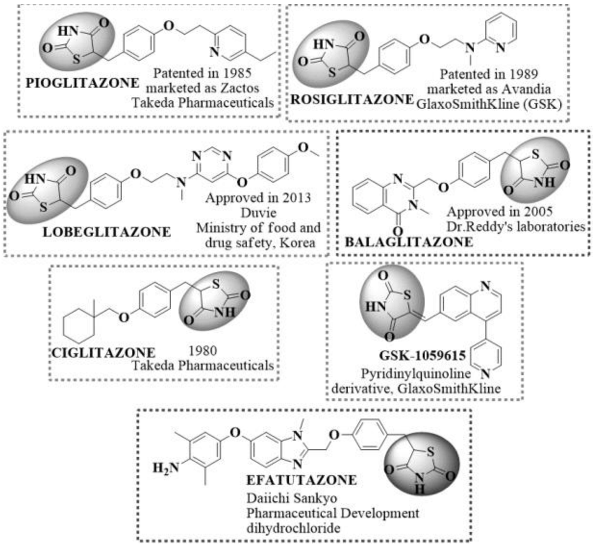


Figure 2. Thiazolidinediones moiety containing marketed drugs.

PPAR-γ is a ligand activated transcription factor which belongs to steroid hormone receptor superfamily. Heterodimerization of PPAR with retinoid X receptor (RXR) takes place and it binds with specific DNA sequences, which are known as PPAR –γ response element (Figure 3) [17].

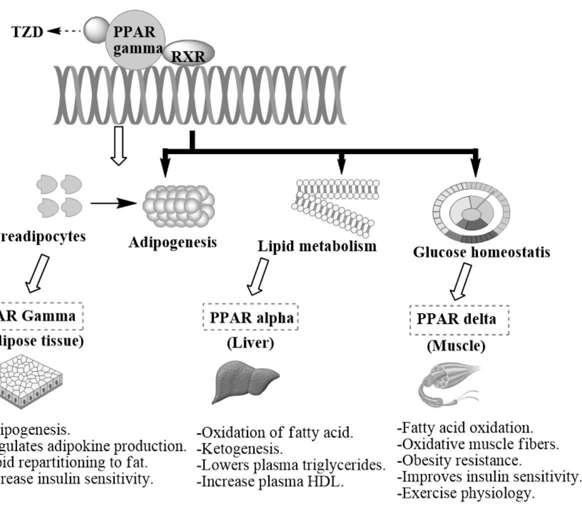


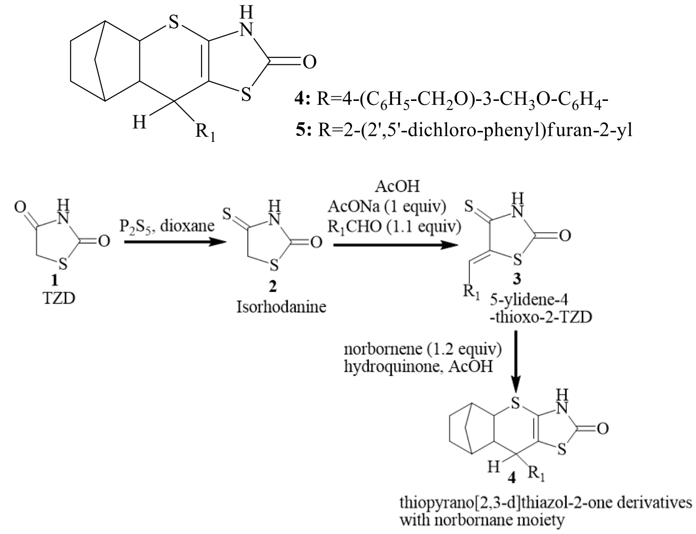
Figure 3. Metabolic function regulated by PPARs.

In economically developed countries, cancer is the leading cause of death. Cancer is increasing day by day due to population aging, growth and cancer-associated habits such as smoking, physical inactivity and more consumption of fast food. For oncology, thiazolidinedione research area became interesting and promising [18-19]. PPAR-γ is a peroxisome proliferator-activated receptors which come under the family of nuclear receptor. Induction of differentiation of adipocytes, are the basic function performed by PPARγ. [20]. It functions mainly occurred by the heterodimerization with retinoid X receptor, later on this RXR complex gets bound to DNA sequence elements known as peroxisome proliferator response elements (PPREs) [21-23].

Synthesis and Structure Activity Relationship

Lesyk R. et al. in 2006 was described a new method for the synthesis of thiopyrano [2, 3-d][1,3] thiazol-2-ones with norbornane moiety by stereo selective hetro-diels alder reaction of 5-ylidene-4-thioxo-2-thiazolidone derivative with norbornene-2 (Scheme 1).

All the synthesized compounds undergo *in-vitro* antitumor activity against human tumor cell lines panel such as NCI-H460 (non-small cell lung cancer), MCF7 (breast cancer) and SF-268 (CNS cancer) cell lines. Compound **4** and **5** exhibit potent anticancer activity. Docking study (PDB ID: 1FM6 and INYX, Glide, Schrodinger LLC and Fred, Open eye Inc. results in a set of QSAR models was found with satisfactory significance and predictive ability [24].



Scheme 1. Synthesis of new thiopyrano [2,3-d]thiazol-2-one derivatives with norbornane moiety.

The following study represents the fusion of thiopyrane cycle with thiazolidine moiety for the improvement of lipophilicity parameters. The thiopyrano [2,3-d] thiazole scaffold are combined with bulky and lipophilic moiety like norbornane (Figure 4).

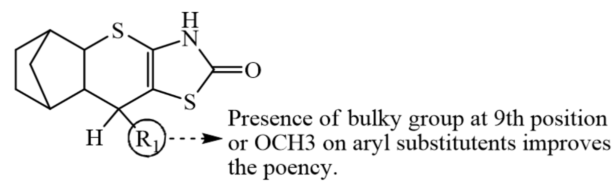
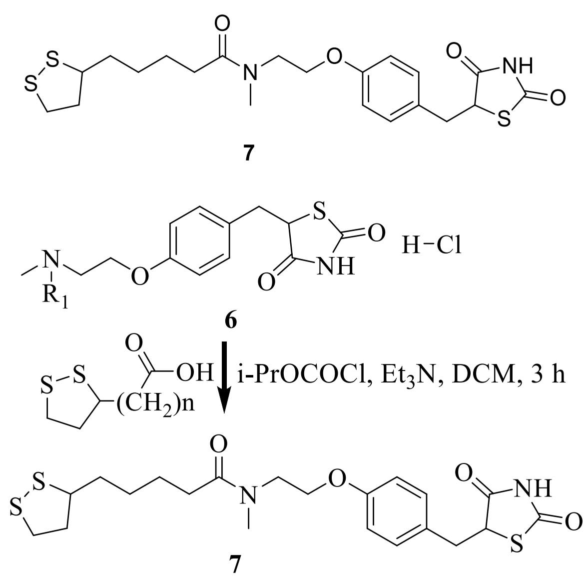


Figure 4. SAR of thiopyrano [2,3-d][1,3]thiazol-2-ones with norbornane moiety.

Amar G.C. et al. in 2006 was carried out the synthesis of unique class of hybrid lipoic-TZD derivative and evaluated them for anticancer activity against normal and neoplastic cultured human cell types (Scheme 2). Compound **7** was exhibit most potent activity with EC_{50} value of 0.015μM, Pioglitazone and Rosiglitazone are taken as standard [25].



Scheme 2. Synthesis of dithiolane thiazolidinedione derivative.

The side effects which is caused by TZD such as systemic edema, exacerbation of congestive heart failure, there is substantial need of TZD and non- TZD insulin sensitizing PPAR-γ agonists which do not have the adverse effects of fluid retention. α-Lipoic acid is combined with TZD moiety, due to its potency and cytoprotective effects (PDB id: 2PRG) (Figure 5).

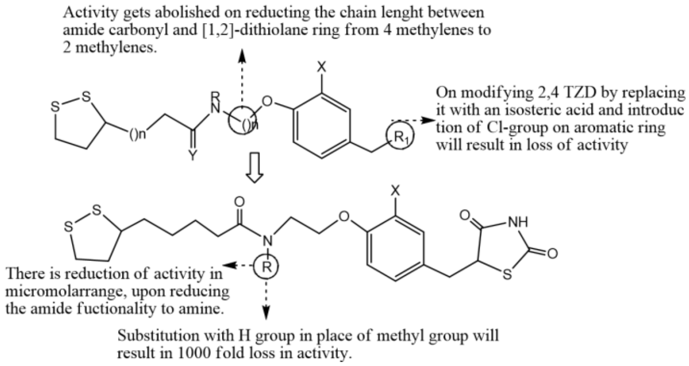
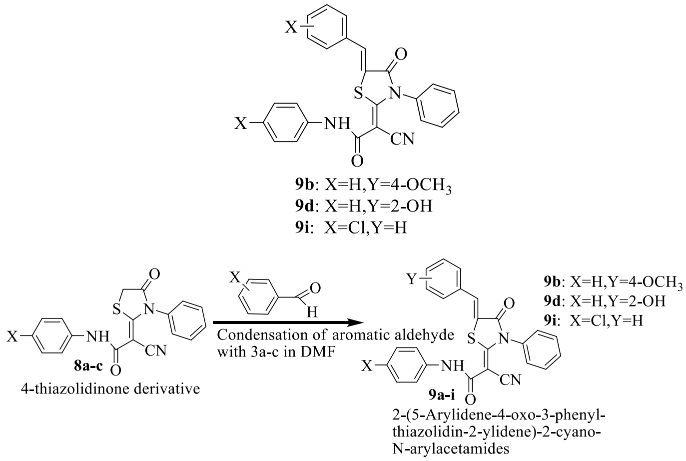


Figure 5. SAR (Structure activity relationship) of dithiolane thiazolidinedione derivatives.

Riham F. George et al. in 2012 was described a new method for the synthesis of 5-arylidene-4-thiazolidinones and 5-arylhydrazono analogs and evaluated them for *in-vitro* anticancer activity by SRB assay against HCT-116 (Colon cancer cell line), MCF-7 (Breast cancer cell line) and HEPG2 (Liver cancer cell line) (Scheme 3). Compound **9b, 9d, 9i** (IC_{50}: 7.89, 8.85, 7.89 μM respectively) is found to be most active (Discovery Studio 2.5 software) and Doxorubicin is used as standard [26].



Scheme 3. SAR of 5-arylidene-4-thiazolidinones and 5-arylhydrazono analogs.

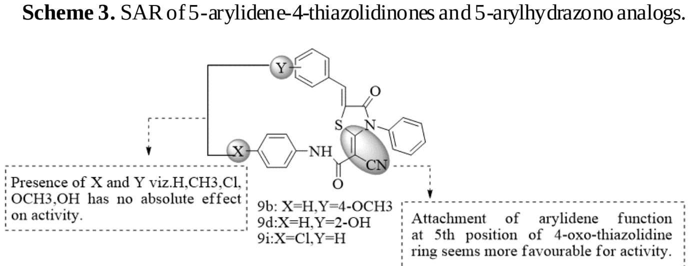
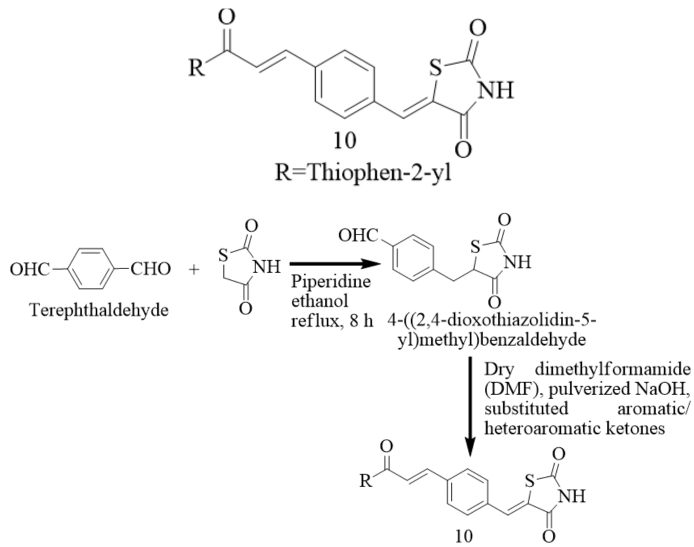


Figure 6. SAR of 5-arylidene-4-thiazolidinones and 5-arylhydrazono analogs.

Avupati V.R. et al. in 2012 was reported a series of novel 2, 4-thiazolidinediones and evaluated for cytotoxicity activity by *in-vitro* Brine shrimp lethality assay (Scheme 4). Compound **10** (ED_{50}: 4.00±0.25μg.mL) showed potent results and Podophyllotoxin is used as standard drug. Study of molecular docking (PDB id: 3CS8: Molegro Virtual Docker v 4.0) revealed that thiazolidinedione ring shows specific interaction with neighboring amino acid residues of LBD. These interactions include H bonding with amino acid Cys 285, His 449, Tyr473 [27].



Scheme 4. Synthesis of novel 2,4- thiazolidinediones.

2,4-thiazolidinediones have wide range of biological studies thereby these molecules have attracted medicinal chemist and consequently many approaches are made to synthesize them (Figure 7).

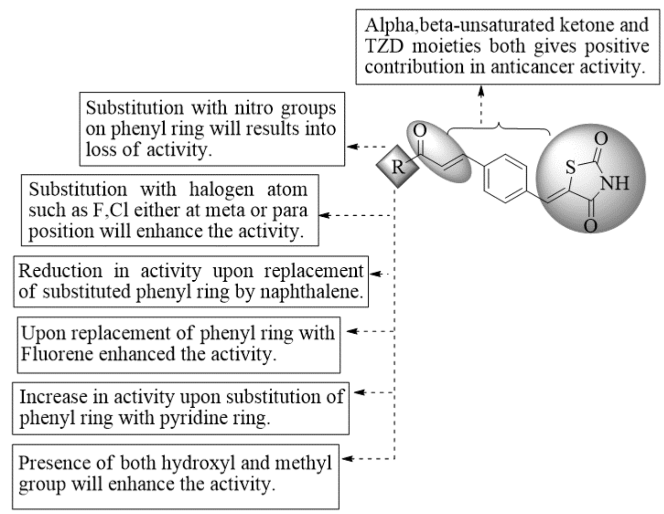
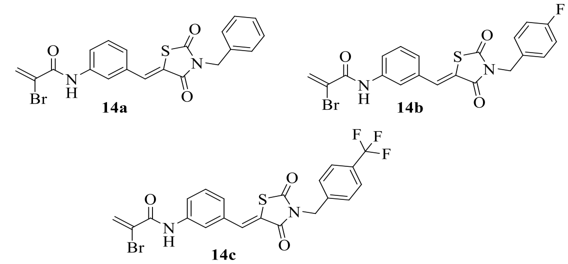
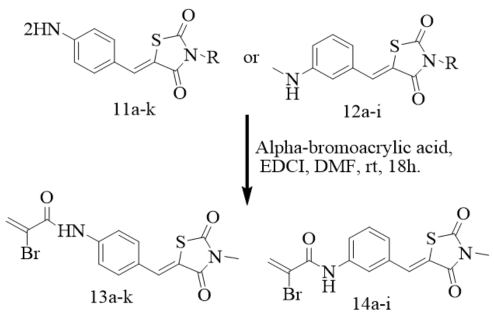


Figure 7. SAR of novel 2,4-thiazolidinediones derivatives.

Romagnoli R. et al. in 2013 was designed and synthesized novel hybrid molecules containing 5-benzylidene thiazolidine-2, 4-dione and evaluated them for anticancer activity against growth of murine leukemia (L1210 cell line), murine mammary carcinoma (FM3A), human T-lymphoblastoid (CEM) and human cervix carcinoma (HeLa) (Scheme 5). Compound **14a, 14b, 14c** was the most potent derivative with IC_{50} for **14a** is 0.38±0.13μM for L1210, 0.81±0.01μM for FM3A, 0.51±0.02μM for CEM and 1.4±1.1μM for HeLa, similarly IC_{50} for **14b** is 0.68±0.02μM for L1210 0.92±0.03μM for FM3A, 0.68±0.15μM for CEM and 0.80±0.19μM for HeLa, similarly IC_{50} for **14c** is 0.72±0.04μM for L1210 0.87 ±0.11μM for FM3A, 0.92 ±0.13μM for CEM and 0.82±0.19μM for HeLa. Melphalan is taken as reference drug for study [28].





Scheme 5. Synthesis of novel molecules.

2,4-TZD moiety is a well-known scaffold in medicinal chemistry, which is used in the formation of new potential anticancer agent. The hybridization of 2 different bioactive molecules into a single molecule is an effective approach to develop more potent anticancer drug (Figure 8).

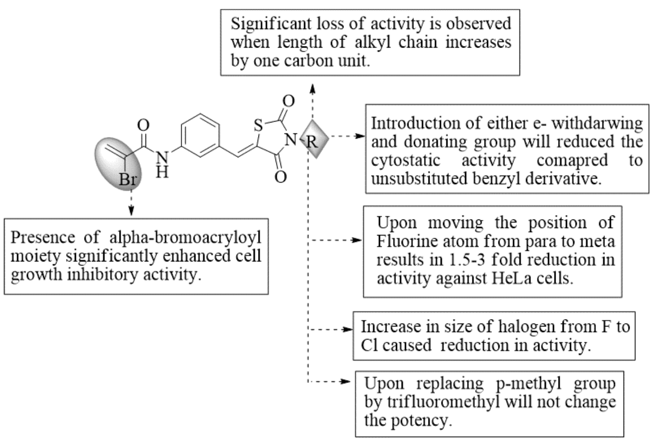


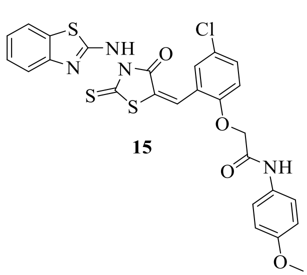
Figure 8. SAR of 5-benzylidene thiazolidine-2,4-dione.

3. RAF KINASE INHIBITOR

The kinase inhibitor protein present in the cell, regulates many signaling pathways and shown to inhibit G protein coupled receptor kinase upon phosphorylated by protein kinase C [30]. A lot of heterocyclic compounds are revealed which inhibit to Raf kinase enzyme, used for proliferation and survival of tumour cells. These inhibitors is stopping the Raf protein expression and delaying Ras-Raf interaction. Currently various Raf kinases inhibitor are available in the market which shown promising anticancer efficacy with a very high safety profile [31]. This inhibitory protein belongs to the family of phosphatidylethanolamine-binding protein family. Raf kinase inhibitor protein is also involved in physiological functions such as neural development, cardiac function, and spermatogenesis as well as pathophysiological processes like Alzheimer's disease and diabetic nephropathy [32].

Synthesis and Structure Activity Relationship

Havrylyuk D. et al. in 2010 was reported benzothiazole-4-thiazolidinediones hybrids by using Knoevenagel condensation procedure and assessed them against leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancer cell lines for their anticancer activity by using SRB protein assay (Scheme 6). Compound **15** emerged as a most promising candidate with log GI_{50} and log TGI values -5.38 and -4.45 respectively [33].



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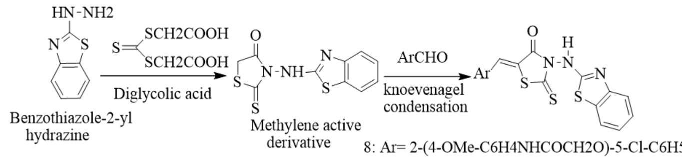


Scheme 6. Synthesis of of benzothiazole substituted 4-thiazolidinediones.

The combination of 4-thiazolidinone template with benzothiazole moiety in one molecule allowed the achievement of 1 log of activity (GI_{50} level) when compared with 2/3-unsubstituted analogues, thereby considered as promising approach in drug design and reported as potential antitumor agent (Figure 9 & 10).

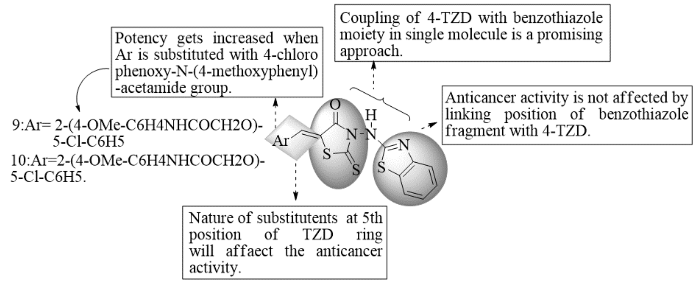


Figure 9. SAR of benzothiazole moiety linked with thiazolidinone moiety.

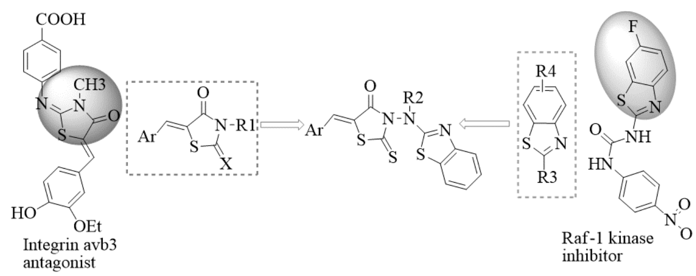
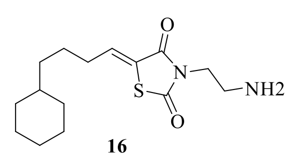


Figure 10. Design strategy for 4-thiazolidinones combined with benzothiazole moiety.

Liu K. et al. in 2012 was reported a new series of 2, 5-disubstituted – thiazolidine-2,4-dione and evaluated their cytotoxic potential on U937,M12 and DU145 cancer cell lines by using [3-H]-thymidine incorporation assay (Scheme 7). Compound **16** was showed good anticancer activity with GI_{50} values of 1.40 µM-5.10µM. Docking (PDB ID: 1s9j for MEK-1 and PDB ID: 3hhm for PI3Kα, Gold Software ver. 3.0) results suggest that compound **15** fits nicely into ATP binding pocket of both MEK1 and PI3K signaling pathways [34].



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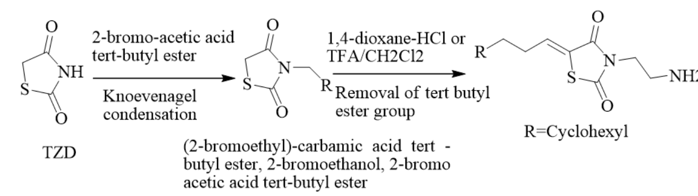


Scheme 7. Synthesis of 2,5-disubstituted thiazolidine-2,4-dione.

With the discovery of many chemotherapeutic strategies for the cancer development and treatment, it remains deadly. Raf/MEK/extracellular signal regulated kinase (ERK) and phosphatidyl inositol-3-kinase (PI3K) are the two signaling pathways, which have synergistic effects in triggering cancer cell death when interrupted by combination regimen. In this study, the synthesis of TZD analog has been, discussed which mainly act by inhibition of Raf/MEK/ERK and PI3/Akt signaling pathways to induce apoptosis (Figure 11 & 12).

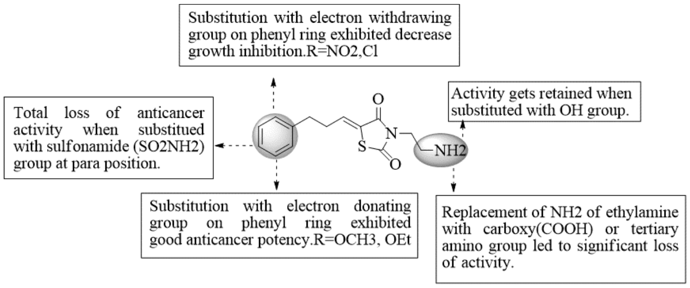


Figure 11. SAR of 2,5-disubstituted -thiazolidine-2,4-dione.

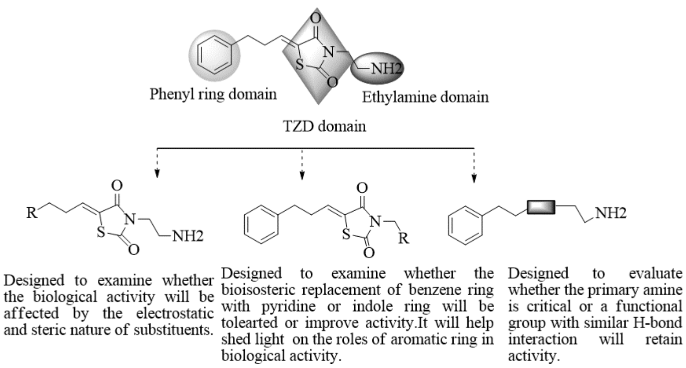
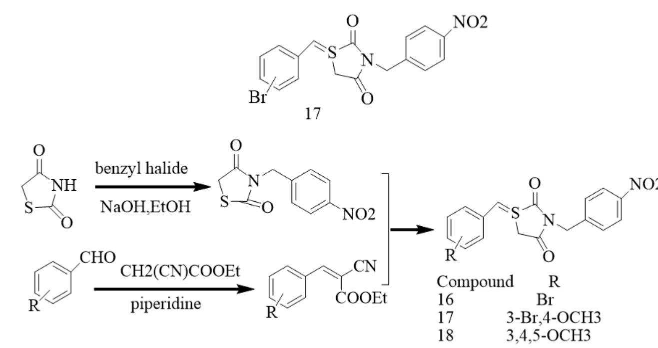


Figure 12. Design strategy for 2,5-disubstituted-thiazolidinone2,4-dione.

Melo R. et al. in 2014 were prepared a series of new disubstituted thiazolidinediones derivative and assayed them for cytotoxicity using MTT assay against 6 tumor cell lines: NG97 (glioblastoma), HepG2 (hepatocarcinoma), MIA PaCa (pancreatic adenocarcinoma), T47D (human breast cancer), Raji (Burkitt's lymphoma) and Jukart (T cell leukemia) (Scheme 8). Compound **28** exhibited most potent activity with IC_{50} : >100μM and Amsacrine is taken as standard drug (PDB ID: 2HWQ, Gold software ver.5.1, Cambridge crystallographic data center) [35].



Scheme 8. Synthesis of new disubstituted TZD derivative.

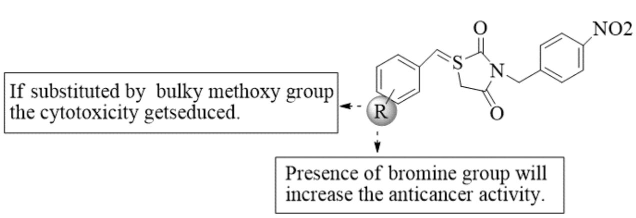
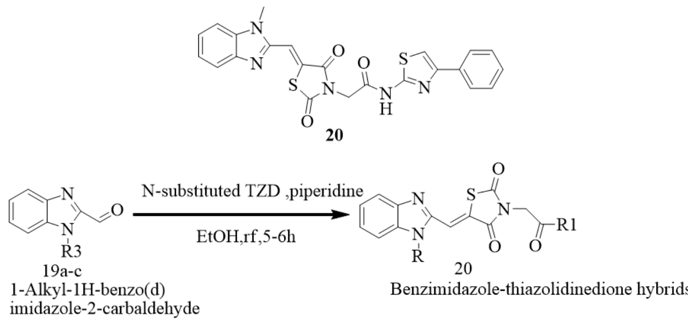


Figure 13. SAR of new TZD derivative.

Sharma P. et al. in 2016 was synthesized new benzimidazole-thiazolidinedione hybrid molecules and evaluated for their cytotoxic potential by using MTT assay against a selected human cancer cell lines of prostate (PC-3 and DU-145), breast (MDA-MB-231), lung (A549) and a normal breast epi|thelial cells (MCF10A) (Scheme 9). Compound **20** was found as the most potent derivative with IC_{50}:11.46±1.46μM and 5-FU used as standard drug [36].



Scheme 9. Synthesis of benzimidazole-thiazolidinedione hybrids.

Instead of availability of anticancer drug, this disease is still deadly, since no effective treatment has been presented yet. In search of potential anticancer drugs, efforts have been focused on development of heterocyclic structure. Thiazolidinediones are among the privileged fragment having broad spectrum of activity (Figure 14). Benzimidazole scaffold have wide spectrum of medicinal application and therefore considered as a master key. The combination of two dissimilar bioactive pharmacophores into single entity is successful and frequently used approach.

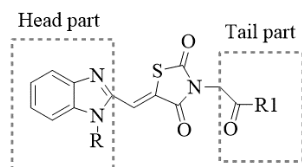
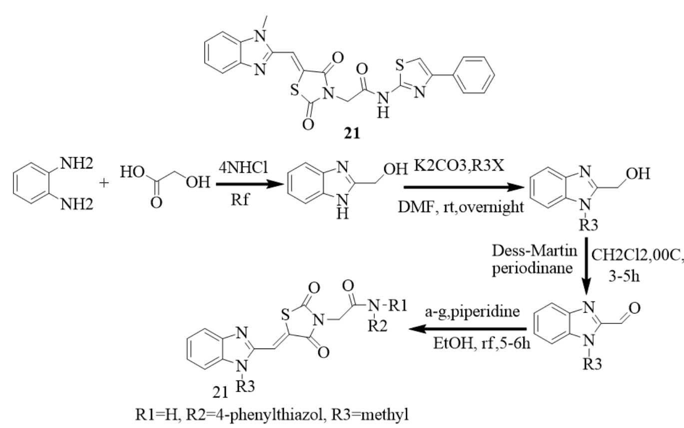


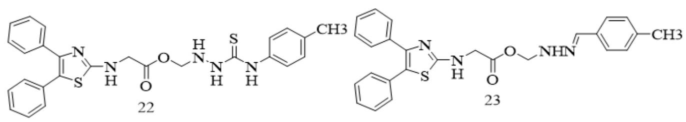
Figure 14. Design strategy of benzimidazole-thiazolidinedione hybrids.

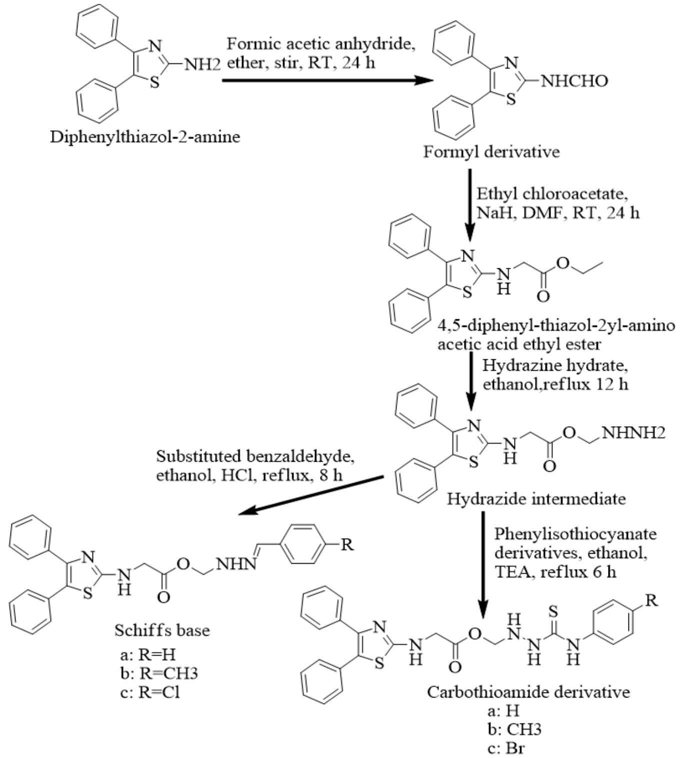
Sharma P. et al. in 2016 was designed and synthesized a series of novel benzimidazole-thiazolidinedione hybrids and evaluated them against human cancer lines prostate (PC-3 and DU-145), breast (MDA-MB-231), lung (A549) and one normal breast epithelial cell (MCF10A) using MTT assay (Scheme 10). For this series, compound **21** shows most promising anticancer activity with IC_{50}: 11.46±1.46 μM on A549 cancer cell line when tested for MCF10A cell line and it did not show any significant toxicity and 5-FU is taken as standard [37].



Scheme 10. Synthesis of benzimidazole-thiazolidinedione hybrids.

Ahmed H. Abdelazeem et al. in 2017 was reported the synthesis of novel diphenylthiazole derivatives having anticancer activity and assayed by MTT assay against target EGFR, Tubulin and BRAF (Scheme 11). Compound **10b** and **17b** exhibited potent cytotoxicity against various cancer cell lines with IC_{50}: EGFR (0.4 and 0.2 μM) and BRAF (1.3 and 1.7 μM) using Doxorubicin as standard drug. Compound **22** and **23** working against EGFR kinase gets fit nicely inside the ATP-active site engaging in one H bond with Asp 831 residue as shown by docking study (PDB ID: EGFR: 1M17 and BRAF: 2FB8, ligand fit embedded in the discovery studio software) [38].





Scheme 11. Synthesis of diphenylthiazole derivative.

To treat the multi drug resistance in patients having low drug resistance, combination therapies is one of the approaches. However it is of high cost, drug-drug resistance and toxicity. Therefore design of multitargeted anticancer agent is a good approach for the treatment of cancer (Figure 15).

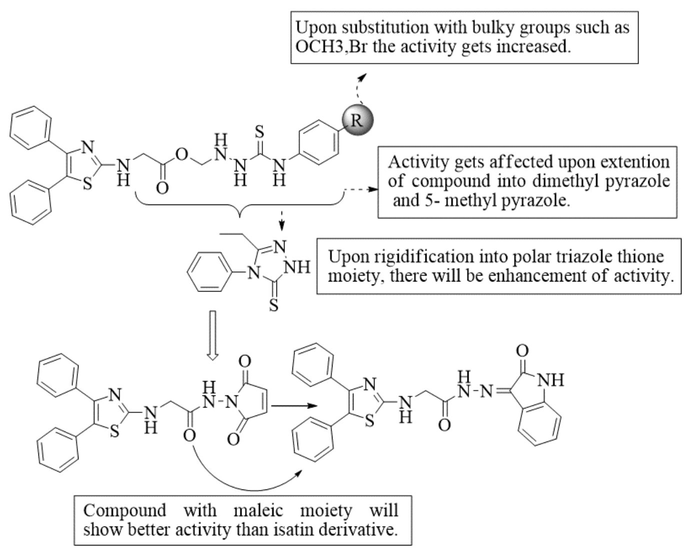
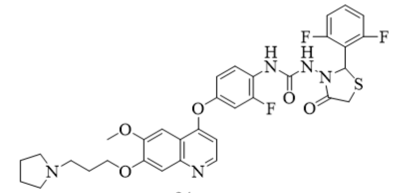


Figure 15. SAR of diphenylthiazole derivatives.

Baohui Q. et al. in 2018 synthesized N1-(2-aryl-1, 3-thiazolidin-4-one)-N3-aryl urea and evaluated them for anticancer activity against a panel of kinases including c-kit, RET, EGFR, Src, IGF-IR and AXL (Scheme 12). Compound **24** (IC_{50}: 1.11μM) exhibited potent activity against A549 cancer cell line and Cabozantinib is taken as standard drug. As per the molecular docking study (MOE, Chemical computing Group Inc., Canada), compound adopt an extend conformation as type 2 kinase inhibitors was buried into the binding pocket of c-MET kinase completely. The ATP-binding sites are occupied completely for the formation of 2 strong H-bonds and one weak H-bonds takes place [39].



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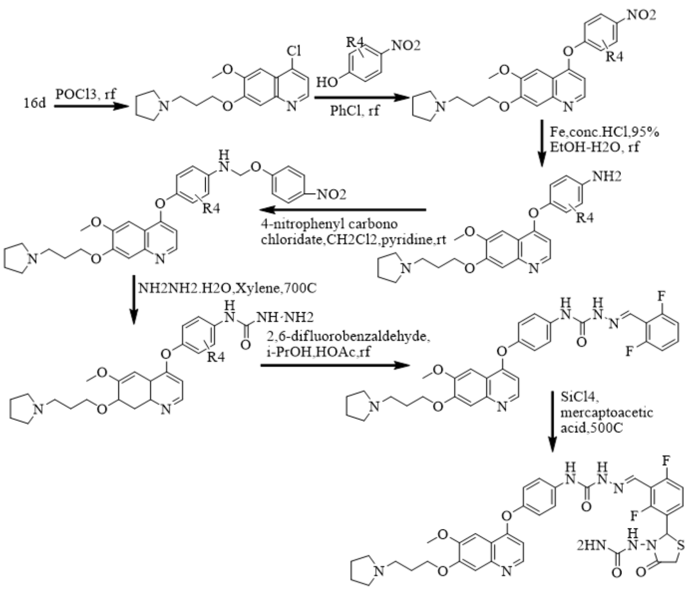


Scheme 12. Synthesis of novel N1(2-aryl-1,3-thiazolidin-4-one)-N3-aryl urea.

1,3-Thiazolidin-4-one and its derivative have been found wide broad-spectrum of pharmacological properties in paper, hybrid compound were designed by linking the main structural unit of 4-phenoxy-6,7-disubstituted quinolines with 1,3-thiazolidin-3-one scaffolds to maximize the anticancer activity (Figure 16 & 17).

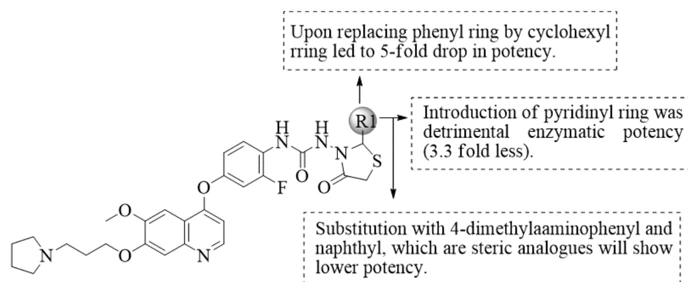


Figure 16. SAR of N1-(2-aryl-1, 3-thiazolidin-4-one)-N3-aryl urea derivatives.

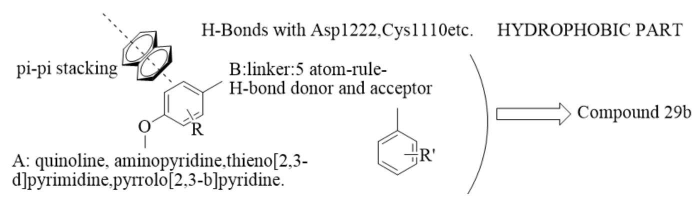
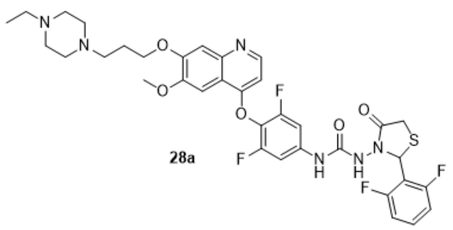
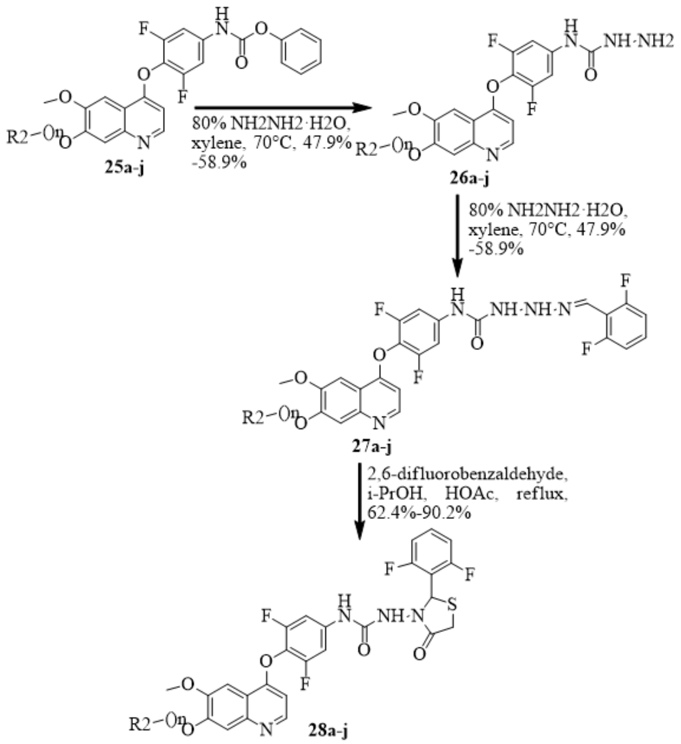


Figure 17. Design strategy of N1-(2-aryl-1, 3-thiazolidin-4-one)-N3-aryl urea derivatives.

Baohui Q. et al. in 2019 was prepared a series of novel *N1*-(2-aryl-1,3-thiazolidin-4-one)-*N3*-aryl urea derivatives and evaluated them as *in-vitro* by MTT assay against A549, HT-29 and MDA-MB-231 cancer cell lines for their c-Met kinase inhibition (Scheme 13). Cabozantinib is taken as standard drug. Compound **28a** (IC_{50}: 0.015µM for c-Met) was shows most potent anticancer activity [40].





Scheme 13. Synthesis of novel N1-(2-aryl-1,3-thiazolidin-4-one)-N3-aryl urea derivatives.

C-Met has prognostic value and is robustly associated with invasiveness, propagation and poor survival in certain cancer. It helps in activation of downstream signal transduction pathways which include Ras/MAPK, PI3K/AKt, c-Src and STAT3/5. Therefore, c-Met is considered to be an attractive target for cancer therapy (Figure 18).

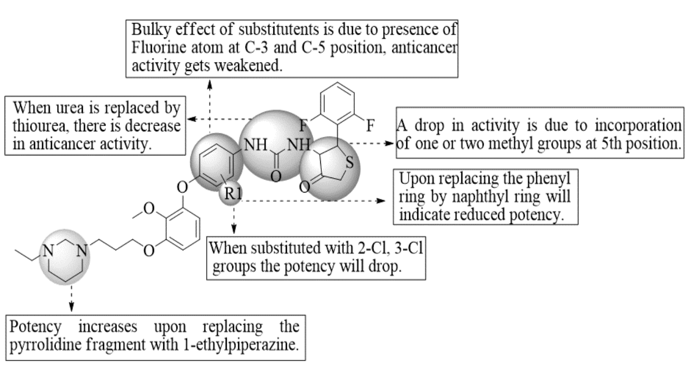


Figure 18. SAR of N1-(2-aryl-1,3-thiazolidin-4-one)-N3-aryl urea derivatives.

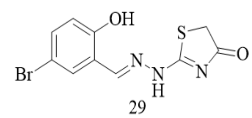
4. EGFR TYROSINE KINASE INHIBITOR

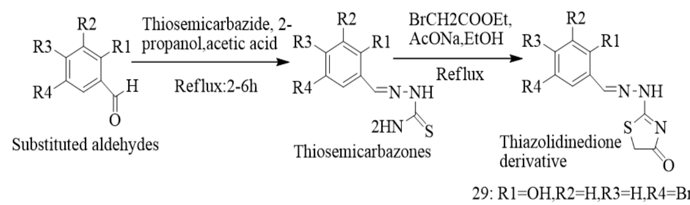
The use of EGFR tyrosine kinase inhibitors also known as epidermal growth factor receptor inhibitor is to treat cancer. Found on the surface of normal cells and helps in growth of cells. The maximum content of EGFR is present in cancerous cells thereby helping cancer cell to grow and divide. So, upon blocking the EGFR the growth of cancer cells will stop [41]. EGFR kinase receptor protein belongs to ErbB receptor family.

EGFR kinase act by forming a heterodimer with another member of ErbB receptor family. This dimerization induce intrinsic protein-tyrosine kinase activity which results in auto phosphorylation of its C-terminal tyrosine residues. This auto phosphorylation results in induction of signaling cascades such as AKT, mitogen-activated protein kinase as well as JNK pathways, which ultimately results into synthesis of DNA, cell cycle progression and proliferation of cell [42-44].

Synthesis and Structure Activity Relationship

Lv P.C. et al. 2010 was reported new derivatives of thiazolidinediones and assayed for anticancer activity by solid phase ELISA assay (Scheme 14). Compound **29** showed significant results against MCF-7 cancer cell lines with IC_{50} of 0.09µM for EGFR and IC_{50} 0.42µM for HER-2 using Erlotinib as reference drug. Compound **12** is nicely bound to the region, with hydroxyl group forming a more optimal H-bond interaction, as suggested by molecular docking studies. Nitrogen of compound **12** also forms H bond with the side chain mercapto group of Cys 751 (PDB ID: 1M17**,** Auto dock version 4.0) [45].





Scheme 14. Synthesis of thiazolidinone derivatives.

Role of Epidermal growth factor receptor (EGFR) and Human epidermal growth factor receptor (HER-2) has shown poor prognosis. The over expression of these two receptors is also seen in lung cancer, ovarian cancer and in hormone–refractory prostate cancer. Hence, the new therapeutic antitumor agent having tendency to inhibit the kinase activity of EGFR and HER-2 after binding of its cognate ligand are required. In view of the facts above mentioned, the synthesis of two series of TZDs derivative is discussed in this study (Figure 19).

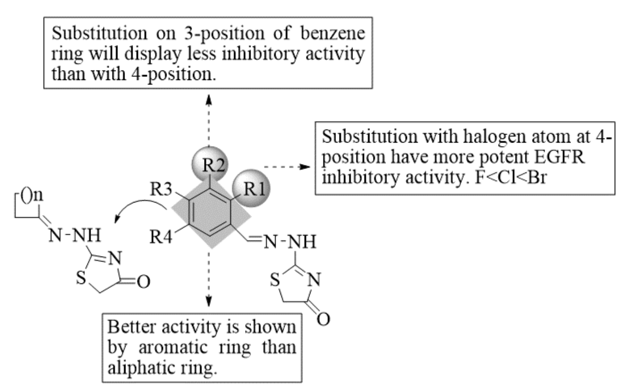
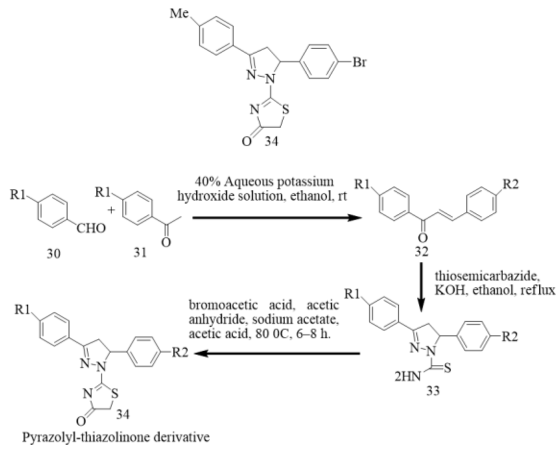


Figure 19. SAR of thiazolidinone derivatives.

Ke-Ming Q. et al. in 2012 was prepared pyrazolyl-thiazolidinone derivative and evaluated them for anticancer activity against MCF-7, B-16-F10 and HCT-116 cancer cell lines using solid phase ELISA assay (Scheme 15). Compound **34** exhibited most potent activity with (IC_{50}: 1.07µM for HER-2 and 0.24µM for EGFR). Erlotinib act as standard. As per docking study (PDB ID: 1M17, Discovery studio version 3.1) compound E28, bounds nicely to the ATP binding site of EGFR by hydrophobic interaction and this binding is stabilized by a H-bond and a pie-cation interaction (Figure 20) [46].



Scheme 15. Synthesis of pyrazolyl-thiazolinone derivatives.

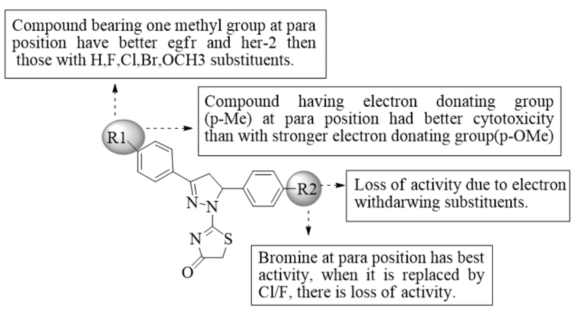


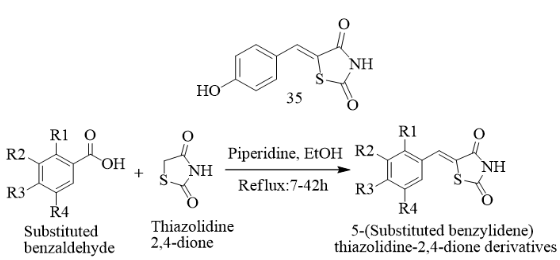
Figure 20. SAR of pyrazolyl-thiazolinone derivatives.

5. MUSHROOM TYROSINE KINASE INHIBITOR

Tyrosinase also called as polyphenol oxidase are the enzyme which copper and found in microorganism, plants and animals. They have many biological applications, its popularity among researchers gets increased due to its availability and less expensive (47). Natural inhibitors of tyrosine kinase are classified into two categories: 1. Polyphenols: Also known as vegetable tannins as they are responsible for the colors of many flower. It consist of complex compounds which are present in bark, roots and leaves of the plant. Flavonoids mostly inhibit the enzyme by chelating copper in the active site. Flavonoids having α-keto group are the potent tyrosine kinase inhibitors. [48-50]. 2. Aldehydes: Anisaldehyde, cumin aldehyde, cumic acid, transcinnamaldehyde are the various aldehydes which act as mushroom tyrosine kinase inhibitors. Aldehydes forms Schiff's base with the primary amino group of enzyme thereby have inhibitory effect. Among all the aldehydes, cumin aldehyde is regarded as most strong inhibitor [51-54].

Synthesis and Structure Activity Relationship

A series of 5-(substituted benzylidene) thiazolidine-2,4-diones have been synthesized by Young Ha Y.M. et al. in 2012 and evaluated them for cytotoxicity activity against B16 melanoma cells (Scheme 16). Compound **2a** was found to be most potent cytotoxic agent with (IC_{50} value of 13.36 µM) when compared with standard drug kojic acid. Compound **35** binds strongly to the potato catechol oxidase active site as per docking simulation (PDB ID: 1M17, Auto dock version 4.0) and found to be a competitive inhibitor of mushroom tyrosine kinase [55].



Scheme 16. Synthesis of 5-(substituted benzylidene) thiazolidine-2,4-dione derivatives.

TZD derivative have been approved by FDA for treating type 2 diabetes. Recently TZD derivative have been reported to be potent inhibitor of PI3Kγ, the pim kinase family, HIV-1, highlighting their versatile role in treatment of inflammation and cancers (Figure 21). However, their effects on tyrosine kinase and skin melanogenesis are unknown. In this study, 5(substituted benzylidene) TZD 2,4-dione analogs are synthesized as potential tyrosine kinase inhibitor (Figure 22).

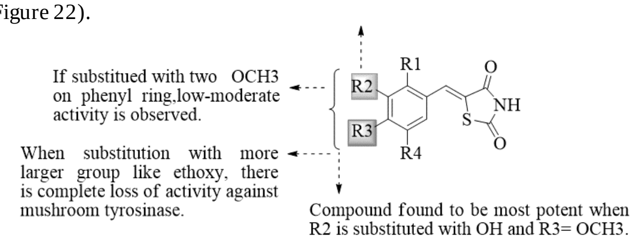


Figure 21. SAR of 5-(substituted benzylidene) thiazolidine-2,4-dione derivatives.

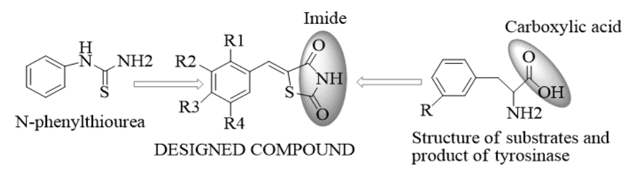


Figure 22. Design strategy for 5-(substituted benzylidene)thiazolidine 2,4-dione.

6. COX ENZYME INHIBITORS

Cyclooxygenase (COX) is also known as prostaglandin-endoperoxide synthase (PTGS) enzyme, specially, a family of isozymes, which is responsible for the production of prostaglandins and prostanoids including thromboxane from arachidonic acid. Drugs which come under NSAIDs are the competitive inhibitor of COX. There are two types of COX enzymes, COX-1 and COX-2.

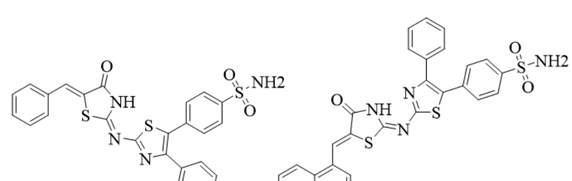
Both enzymes produce prostaglandins that promote inflammation, pain and fever, however only COX-1 produces prostaglandins that activate platelets and protect the stomach and intestinal lining [56]. In different types of cancer, COX-2 is expressed frequently having a role in the formation of genes and promotion of carcinogenesis which is suspected to promote angiogenesis and tissue invasion of tumors and resistance to apoptosis and cancer cell.

Meanwhile, COX-2 contributes to immune evasion and resistance to cancer immunotherapy, which plays a crucial role in the innate and adaptive immune response. Most of the functions of COX-2 are mediated by metabolite prostaglandin E2. The risk of metastasis in cancer patients are reduced upon administration with COX-2 inhibitors. COX-2 and the prostaglandin cascade play important roles in the inflammogenesis of cancer. Inhibitors of COX-2 are reported to reduce the occurrence of cancers growth [57].

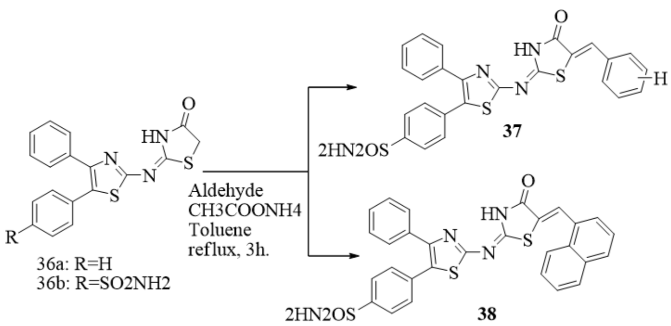
Synthesis and Structure Activity Relationship

Abdelazeem A.H. et al. in 2014 was reported a novel diphenylthiazole-based cyclooxygenase inhibitors and assessed them against five cancer cell lines, HCT-116(human colon cancer), Caco-2 (human colon carcinoma), MCF-7(human breast carcinoma), DU-145(human prostate carcinoma, epithelial-like cell line) and PC-3(human prostate carcinoma) for their cytotoxic potential (Scheme 17).

Compound **37** and **38** were emerged as most promising candidate with IC_{50} value of 8.88 and 19.25µM using doxorubicin as standard drug. Molecular docking studies suggest that ligands bearing a benzylidene moiety have high affinity for COX-2 enzyme [58].



37 **38**



Scheme 17. Synthesis of substituted thiazole compound.

Due to wide variety of existing anticancer agent the treatment of cancer is challenging problem. Therefore, there is an urgent requirement of novel anticancer drug with better therapeutic profile and less side effects. Targeting COX-2 enzyme is an effective approach for the prevention of various cancer types (Figure 23). Thiazolidinone are important heterocyclic compound that possess a variety of biological activities. In the current study, both thiazolidinone skeleton and diphenylthiazole scaffold are combined and studied for anticancer effect (Figure 24).

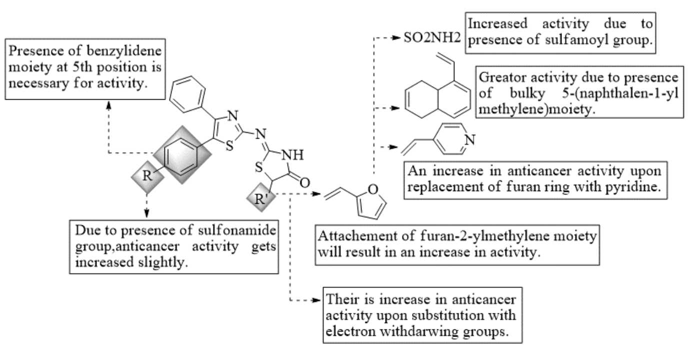


Figure 23. SAR of diphenylthiazole conjugates.

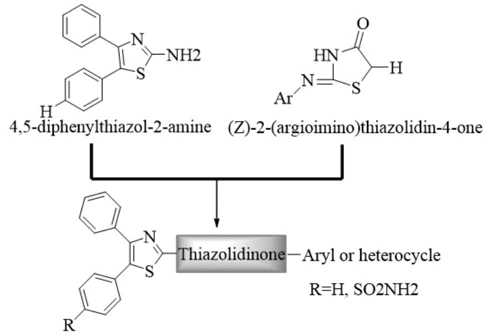
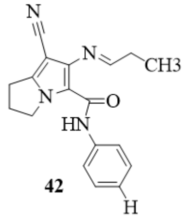


Figure 24. Design strategy of novel diphenylthiazole based COX inhibitors.

Ahmed M. Shawky et al. in 2020 was designed and synthesized novel series of pyrrolizine-5-carboxamide derivative and evaluated them for *in-vitro* anticancer activity against three cancer cell lines MCF-7, A2780 and HT29 (Scheme 18). Compound **42** shows higher activity with IC_{50}: 0.58μM and Lapatinib is taken as standard. Molecular docking studies (PDB ID: CDK2 (3TNW), Aurora (3E5A), BRAF (4RZV), EGFR (1M17) by Auto Dock ver. 4.2) suggest that 2H bonds forms with ILE10 and LYS 89 as compared to 4H bonds for CAN508 [59].



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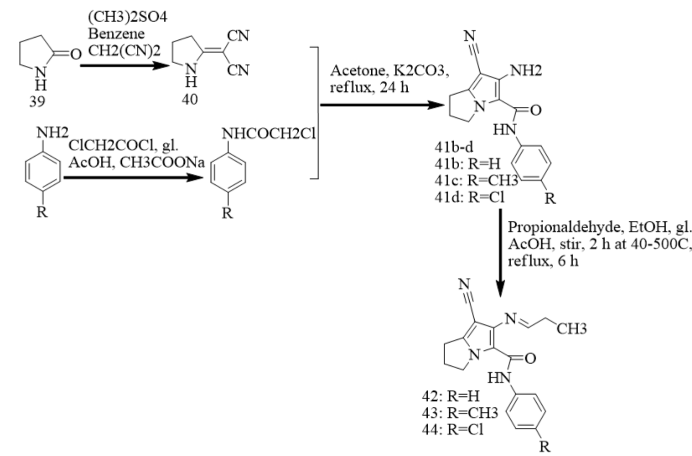


Scheme 18. Synthesis of pyrrolizine-5-carboxamides derivatives.

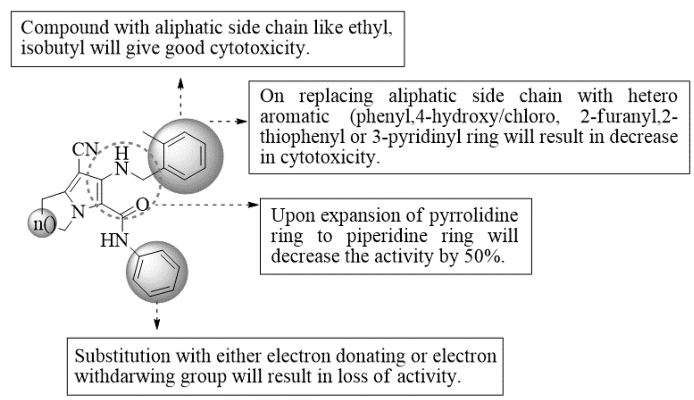


Figure 25. SAR of pyrrolizine-5-carboxamides derivatives.

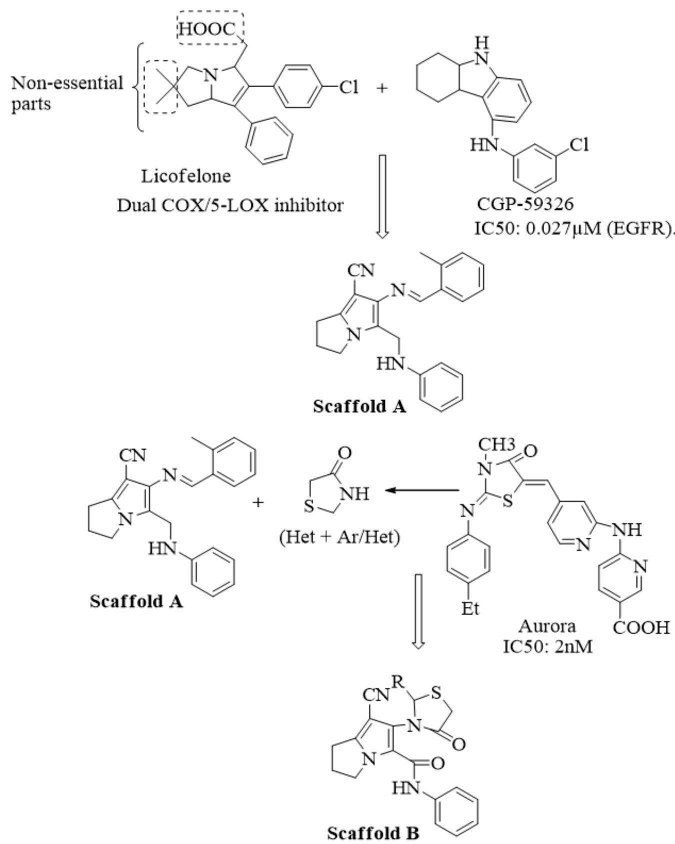


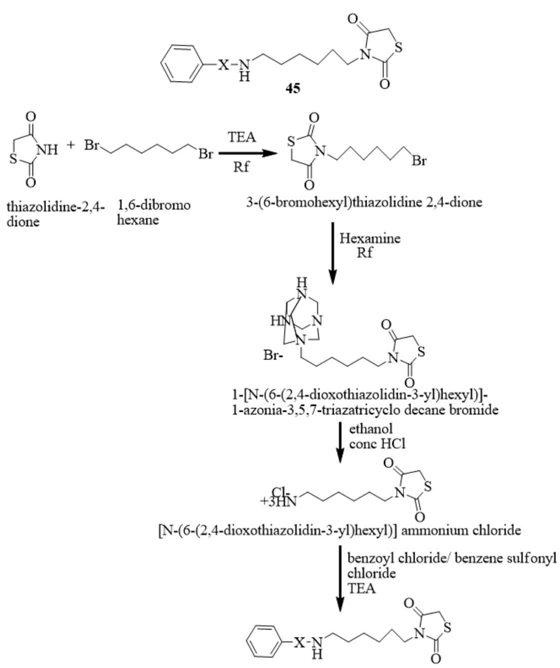
Figure 26. Design strategy of pyrrolizine-carboxamides derivatives.

7. HISTONE DEACETYLASE INHIBITORS

The histone deacetylase inhibitors (HDAC inhibitors, HDACi, HDIs) are a new class of cytostatic agents that inhibit the proliferation of tumor cells in culture and *in-vivo* by inducing cell cycle arrest, differentiation and apoptosis. HDACi have a wide array of biological activities such as in the treated to cancers, psychiatry, neurology, parasitic and inflammatory diseases. HDAC act as a new class of anticancer agent that play important role in inducing death, apoptosis, cell cycle arrest and role in epigenetic or non genetic regulation [60]. HDAC inhibitors are also used to treat hematological cancer. Due to the lesser side effects and tendency to kill cancer cells, these inhibitors are used as targeted cancer therapies [61]. These inhibitors act by altering the gene expression, inhibiting DNA repair and by making post-translational modification of proteins thereby results in inhibition of proliferation of cancer cells, initiation of cell death, and cell cycle arrest. All these actions will ultimately leads to disruption of vital cell function, and stop the ability of cancerous cells to grow and multiply [62].

Synthesis and Structure Activity Relationship

Mohan R. et al. in 2012 described the synthesis of novel 2,4-thiazolidinedione derivatives as zinc chelating agents and evaluated them for anticancer activity by cell proliferation assay and HDAC enzyme assay against on human liver cell lines, transformed (HepG2) and untransformed embryonic (WRL68) cell lines (Scheme 19). Compound **45** (100µM) was found to be most potent in reference to SB and SAHA as positive control (PDB ID: 1c3s: MOE 2006.08) [63].



Scheme 19. Synthesis of novel 2,4-TZD derivatives.

Hepatocellular carcinoma does not treated properly due to its diagnosis at an advanced stage. Only a limited number of pathways are responsible for initiation and maintaining dysregulated cell proliferation (one is epigenetic histone deacetylation pathway). Normal healthy hepatocytes did not express HDAC1, therefore HDAC1 in HCC may be good target for anticancer drugs. 2,4-TZD derivatives as zinc chelating group is used as lead for the development of new antitumor agent (Figure 27).

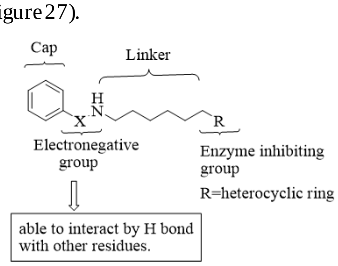


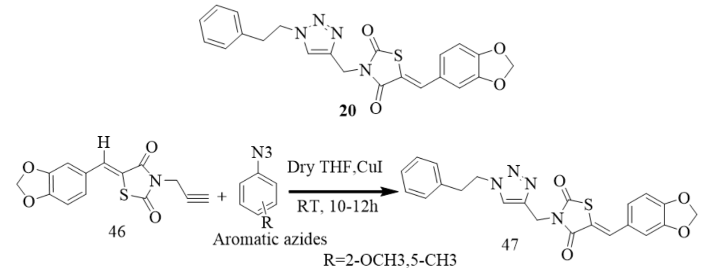
Figure 27. Design strategy of novel 2,4-TZD derivatives.

8. ALPHA GLUCOSIDASE INHIBITOR

Alpha-glucosidase inhibitors (AGIs) are used for diabetes mellitus type 2, as oral anti-diabetic drugs that work by inhibiting the digestion of carbohydrates. Carbohydrates are usually transformed into monosaccharides by alpha-glucosidase enzymes, which present on cells lining the intestine and permitting to absorb through the intestine. Hence, alpha-glucosidase inhibitors reduce the impact of dietary carbohydrates on blood sugar. These are the oral antidiabetic drug which acts by preventing carbohydrate metabolism [64]. Now a days, various alpha GIs inhibitors such as iminosugars, carbasugars, thiosugars and non-sugar derivatives which are used for many diseases such as lysosomal storage disorders, HIV infection and cancer [65].

Synthesis and Structure Activity Relationship

Chinthala Y. et al. in 2013 were synthesized a new series of thiazolidinedione with triazole ring by Knoevenagel condensation and screened them for anticancer activity by MTT assay against IMR 32 (neuroblastoma), Hep G2 (Human Hematoma), MCF-7(Breast adenocarcinoma) using Doxorubicin as the standard drug (Scheme 20). Compound 47 was found to be most potent having IC_{50} value of Hep G2 (31µg/ml) and MCF-7 (30µg/ml). In accordance with molecular docking studies (PDB ID: 3L4Y: Auto dock, Vina software) compound 3j have high binding affinity to alpha-glucosidase because of presence of binding site amino acid residues like LEU-640, ARG-647, ASP-649, ARG-653, PRO-676 thus having high stability [66].



Scheme 20. Synthesis of thiazolidine-2,4-dione-1,2,3- triazole derivatives.

Through the evidence by *in-vitro* and *in-vivo* studies, the TZD have the ability to be used in cancer therapy, the 1,2,3-triazole is an nitrogenous compound having diverse biological potencies (Figure 28). In the following study both the pharmacophores were combined to get a single entity having significant anticancer activity.

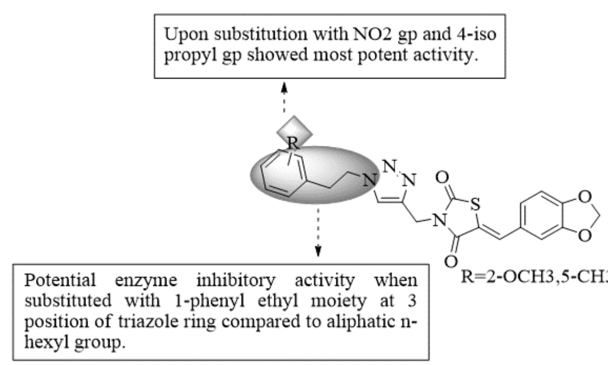


Figure 28. SAR of novel thiazolidinediones -triazole moiety.

9. DNA INTERCALATION

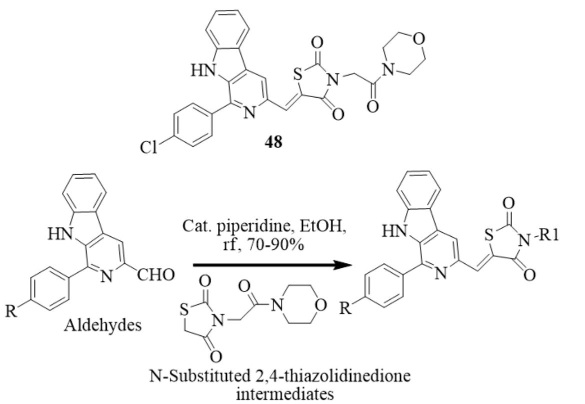
In a wide variety of cellular process, DNA plays a crucial role and act as a target for deadly diseases. In general, intercalating agents are two types: monofunctional and bifunctional. Monofunctional intercalates contain one intercalating unit and bifunctional intercalators (bis-intercalators) contain two intercalating units, normally cationic, separated by a spacer chain that must be long enough to allow double intercalation taking into account the neighbor exclusion principle. Intercalates are the most important group of compounds that interact reversibly with the DNA double helix. The various ways by which molecules interact with DNA is covalently, electrostatic or by intercalation.

Some of them are valuable drugs currently used for the treatment of ovarian and breast cancers and acute leukemia, while many others are in different phases of clinical trials. [67-68].

A number of clinical intercalator molecules are available such as antiparasitic, antimicrobial, anticancer which exert pharmacological action via interacting with double stranded DNA, thereby inhibiting the process of transcription, replication and DNA repair mechanism. The molecules get inserted between the planar base pairs of DNA. In chemotherapeutic treatment, DNA intercalates will inhibit DNA replication in rapidly growing cancer cells. Now a days, metallo intercalators are also available which are the complexes of metal cation with the polycyclic aromatic ligands. Ruthenium, rhodium and iridium are some of the metal ions [69-71].

Synthesis and Structure Activity Relationship

Tokala R. et al. in 2018 was synthesized a new β-carboline-thiazolidinedione hybrids and evaluated them for their *in-vitro* cytotoxicity potential against selected human cancer cell lines such as PC-3, A549, MG-63, HCT-15, MDA-MB-231, A431 and PANC-1 along with a normal human cell line (L-132) (Scheme 21). Compound 48 was the most potent derivative against triple negative breast cancer cell line (MDA-MB-231) with an IC_{50} value of 0.97 ± 0.13 Mm as compared to Harmine and pioglitazone as standard drug. Molecular modeling studies (XP Glide Schrodinger, 2017) revealed that it supports the intercalation of beta-carboline linked TZD hybrids into DNA. [72].



Scheme 21. Synthesis of carboline-thiazolidinedione hybrids.

In cancer therapy there is a need to synthesize novel compound that induce apoptosis and target DNA. β-carbolines are widely distributed in nature and are well known for their multifarious biological activities (Figure 29). Harmine and Harmaline are the natural products of this class which are known to inhibit cancer cell proliferation and leads to apoptosis (Figure 30).

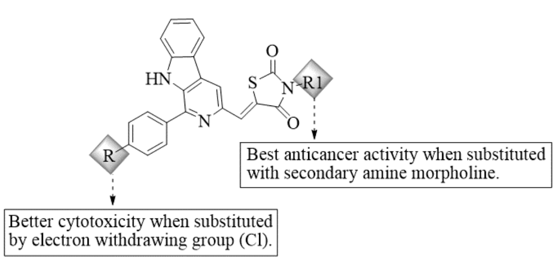


Figure 29. SAR of beta-carboline-thiazolidinedione hybrids.

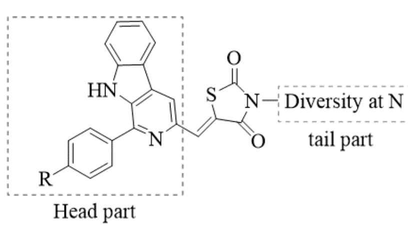


Figure 30. Design strategy of beta-carboline-thiazolidinedione hybrids.

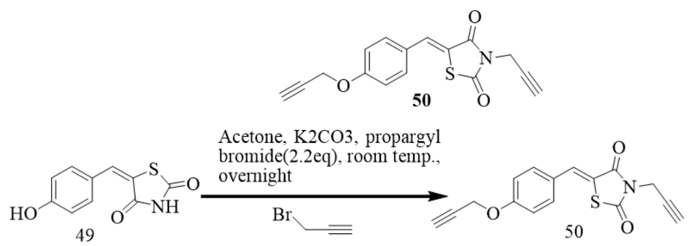
10. PROTEIN TYROSINE PHOSPHATASE 1B (PTP1B) INHIBITOR

PTPB1 is also known as tyrosine-protein phosphatase non-receptor type 1 and it is encoded by PTPN1 gene. PTP1B tyrosine phosphatase is involved in the development of many types of cancers, such as breast cancer or lung cancer. Protein tyrosine phosphatase 1B is a target for obesity and type 2 diabetes. It has a positively charged active site pocket. PTP1B inhibitory agents can be considered as promising target for cancer therapy [73-74].

PTP inhibitor development is in the early discovery phase that specific PTPs are targets for development of novel anticancer drug [75]. BCAR1, vascular endothelial growth factor, epidermal growth factor receptor are the receptors to which PTP1B will interact. For the enzymatic activity of PTP1B, Cys215 residue is essential [76]. The PTP1B shows phosphatase activity in two steps. One is the dephosphorylation of p-Tyr substrate, while in the second step intermediates of enzyme gets broken down [77].

Synthesis and Structure Activity Relationship

Tahseen A. et al. in 2014 were described the synthesis of benzylidene thiazolidine 2,4-thiazolidone derivative and evaluated for anticancer activity by SRB assay against cancer cell lines DLD-1 and SW 620 (colon cancer cell lines), MCF-7 and MDAMB-231 lines (breast cancer cell lines) (Scheme 22). Compound 50 shows highest anticancer activity with IC_{50}: 7.5 μM (DLD-1), 10.8 μM (SW620), 8.4 μM (MCF-7) and 50.8 μM (MDAMB-231) [78].



Scheme 22. Synthesis of benzylidene thiazolidine-2, 4-dione derivative.

PTP1B inhibitor is a novel strategy for the treatment of cancer, diabetes and obesity. Protein tyrosine phosphatase 1B is a non-transmembrane enzyme found in endoplasmic reticulum (Figure 31). The PTPB1 acts by removing a phosphate group from tyrosine kinase, JAK 2 (Janus kinase 2). Its inhibition may lead to stop some forms of cancers (Figure 32).

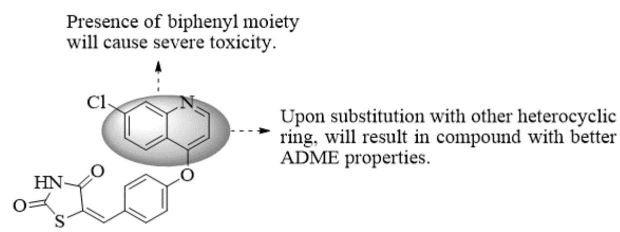


Figure 31. SAR of novel benzylidene thiazolidine-2, 4-dione derivatives.

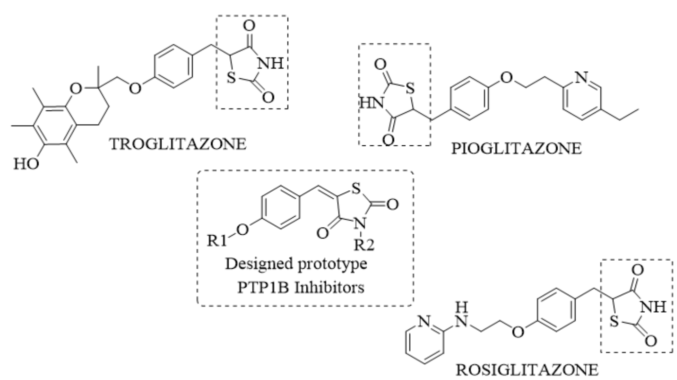
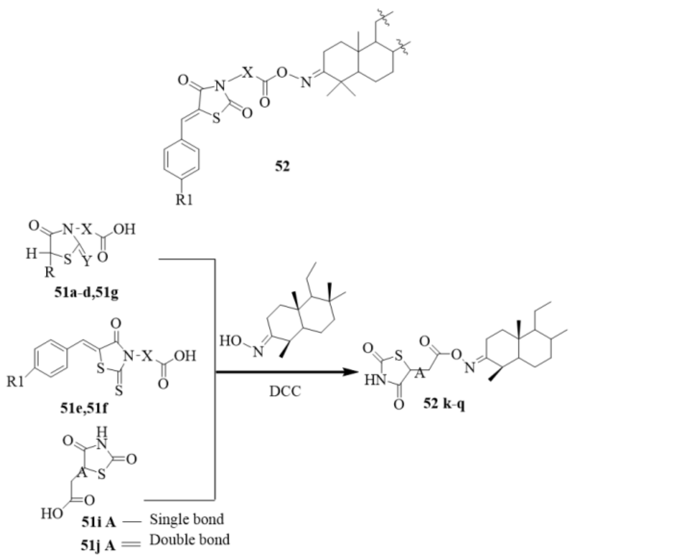


Figure 32. Design strategy of benzylidene thiazolidine 2,4-thiazolidone derivative.

11. MISCELLANEOUS

Synthesis and Structure Activity Relationship

Kaminsky D. et al. in 2011 was described a series of new acylated oximes derivatives of oleanolic acid with 4-thiazolidinone-3(5)-carboxylic acid moieties (Scheme 23). Compound 52 was found to be active when tested against 60 human cancer cell lines, having values of dose depended parameters, pGI50 = 5.51/5.57, pTGI = 5.09/ 5.13, and pLC50 = 4.62/4.64 [79].



Scheme 23. Synthesis of new acylated oximes derivatives.

4-Azolidinone-3(5) carboxylic acid represents wide spectrum of biological activities. In this study, attempts are made to combine both 4-TZD carboxylic acid and oleanane scaffold into one molecule, as part of double drug creation (Figure 33).-

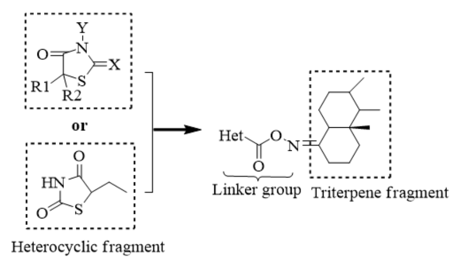
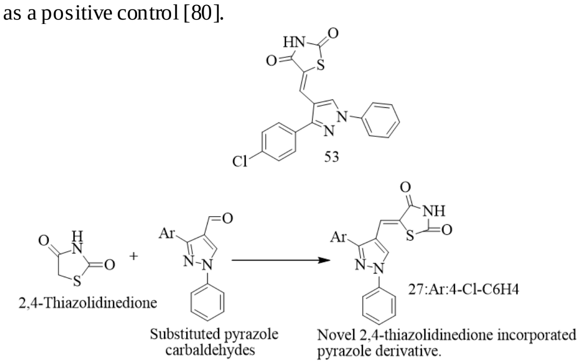


Figure 33. Design strategy of 4-TZD and oleanane scaffold.

Sudheer K. et al. in 2014 was synthesized a novel pyrazolyl thiazolidinediones derivatives by Vilsmeier-Haack reaction and evaluated their cytotoxic potential on human cancer cell line A549, human breast cancer cell line MCF-7 and human prostate cancer cell line DU145 by the use of MTT assay (Scheme 24). Compound 53 was found to be most potent with IC_{50}: 4.63, 1.32 and 5.25µg using Doxil as a positive control [80].



Scheme 24. Hycridization approach for novel 2,4-thiazolidinedione incorporated pyrazole moiety.

Recent reports on TZDs, indicates that besides having insulin sensitization action and also have tumor suppressor action. Pyrazole on the other hand attract attention over the years due to its broad spectrum of biological activities. Inspired by the diverse biological properties of TZD moiety and pyrazole an attempt has been made to use hybridization approach with hope that resulting designed molecule will have better anti-cancer activity with less side effects (Figure 34).

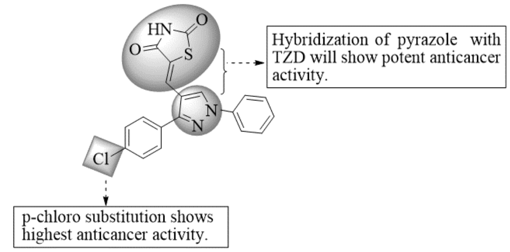
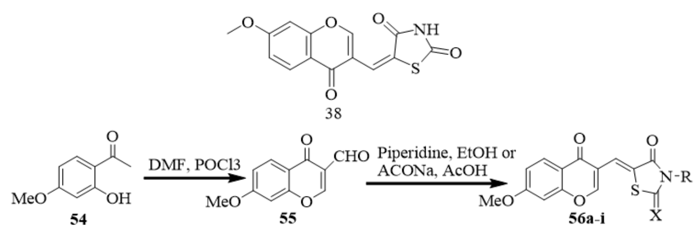


Figure 34. SAR of novel 2,4-thiazolidinedione incoporated pyrazole.

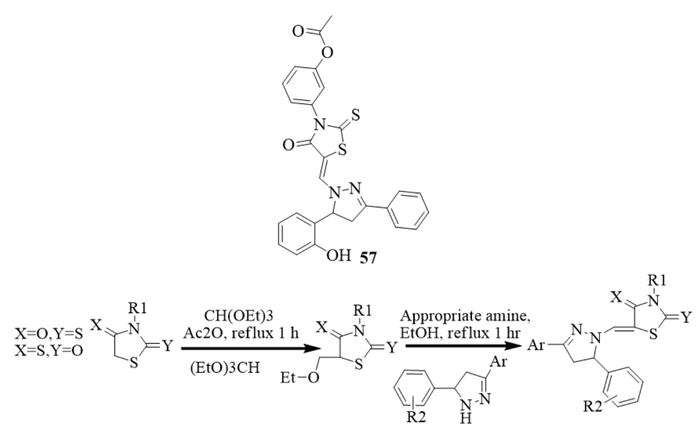
Hoang Le T.A. et al. in 2015 was prepared new derivatives of chromonylthiazolidine and evaluated them for anticancer activity against human epidermoid carcinoma (IC_{50}: 44.1 ± 3.6 µg/ml) and breast cancer (IC_{50}: 32.8 ± 1.4 µg/ml) (Scheme 25). Compound 38 is considered to be most potent having stronger cytotoxicity compared to other derivatives with IC_{50}: 32.8 ± 1.4µg/ml and MCF-7 and Ellipticine is taken as standard [81].



Scheme 25. Synthesis of chromonyl thiazolidines.

Chromone derivatives are found in various parts of plants and vegetables. These derivatives showed low mammalian toxicity with wide range of biological activities as well as selective cytotoxicity towards cancer cell lines. TZD moiety have attracted the attention of medicinal chemist due to wide range of biological activity and ability to inhibit various enzymes.

Senkiv J. et al. in 2016 was designed, synthesized novel 5-ene-4-thiazolidinone derivatives and evaluated them for anticancer activity and selective antileukemic action. The cytotoxicity was determined by MTT assay (Scheme 26). Compound 57 was the most active derivative against HL-60 and HL-60/ADR cell lines (IC_{50}: 118 nM/HL-60) with low toxicity towards pseudo normal cells and Doxorubicin is the standard drug [82].



Scheme 26. Synthesis of 5-ene-4-thiazolidinone derivatives.

For design of new drug molecule having more potency, 4-TZD and related hetero cycle are explored intensively. Upon conjugation of 5-ene fragment to the carbonyl group at C-4 position of thiazolidine core makes the compound to be electrophilic and potentially reactive due to possible Michael addition of nucleophilic protein residues to exocyclic double bond, 5-ene-4-TZD exerts anticancer effect by reversible blocking of cell-cycle progression at G2/M phase border that leads to induction of apoptosis (Figure 35).

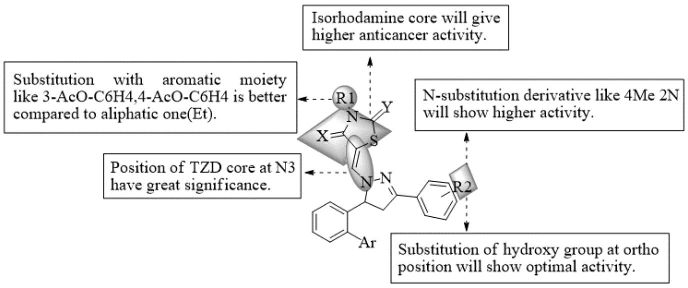
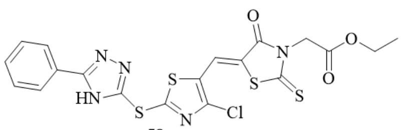
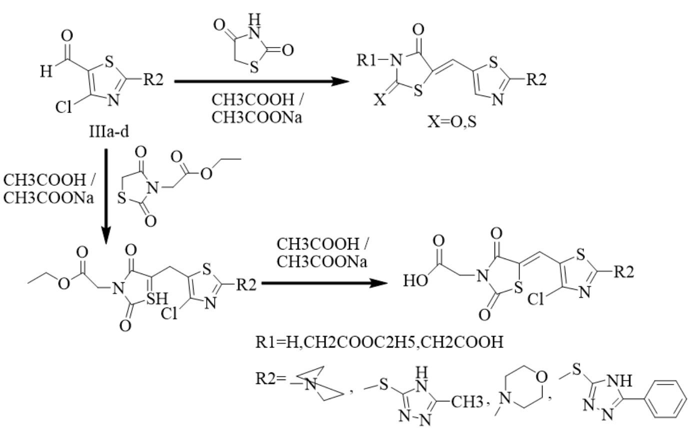


Figure 35. SAR of 5-ene-4-thiazolidinone derivatives.

Ozen C. et al. in 2017 was described the synthesis of thiazolyl-2,4-thiazolidinedione/rhodanine and evaluated them for anticancer activity against two hepatocellular carcinoma (HCC) cell lines, Huh7 and Plc/Prf/5 (Plc) by sulforhodamine B assay (Scheme 27). Compound **58** (IC_{50}: 2 to 16 μM) exhibit most potent activity and Doxorubicin used as standard drug [83].



58



Scheme 27. Synthesis of thiazolyl-2,4-thiazolidinedione/rhodanine compounds.

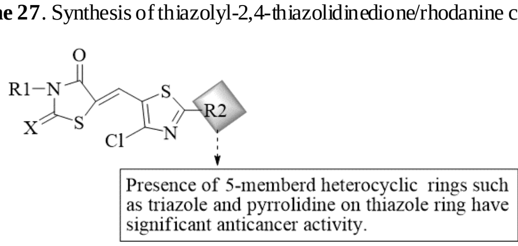
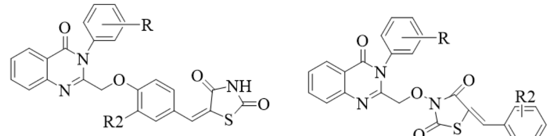


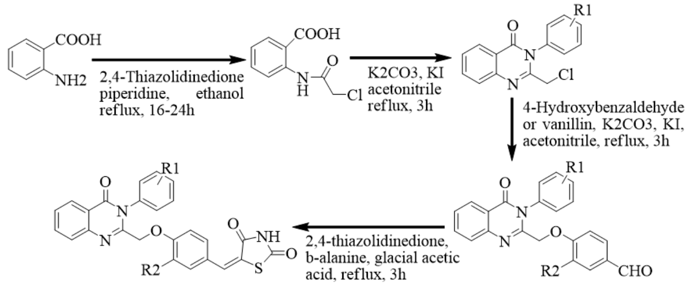
Figure 36. SAR of thiazolyl-2,4-thiazolidinedione/rhodanine compounds.

Metwally K. et al. in 2017 was prepared a new series of 2 TZD scaffold, A-Thiazolidinedione ring in terminal, B-middle of the molecule and tested them against a panel of cancer cell lines prostate cancer cells PC-3, breast carcinoma cells MDA-MB-231 and fibrosarcoma cells HT-1080 (Scheme 28). Compound **59** and **60** was found to be most active with IC_{50} value: μM as mentioned below. Doxorubicin is taken as standard [84].

Compound	PC-3	MDA-MB-231	HT-1080
59	8.7±0.2	4.5±0.7	3.9±0.3
60	19.4±2.8	5.9±0.5	9.0±2.3



59 **60**



Scheme 28. Synthesis of novel 2-TZD scaffold.

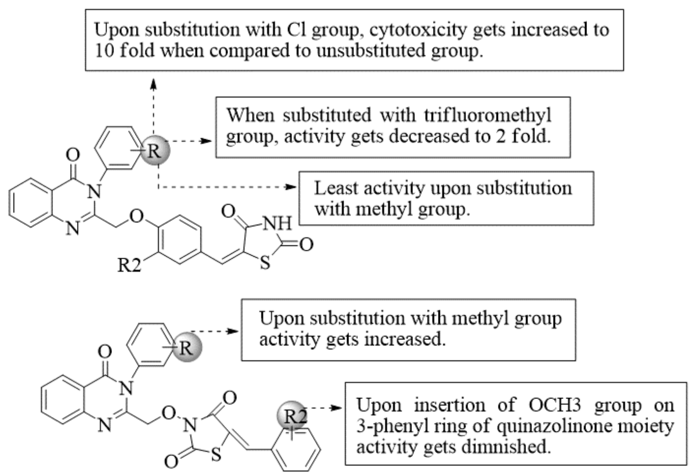
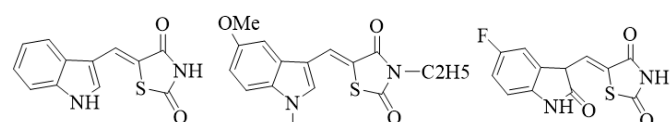
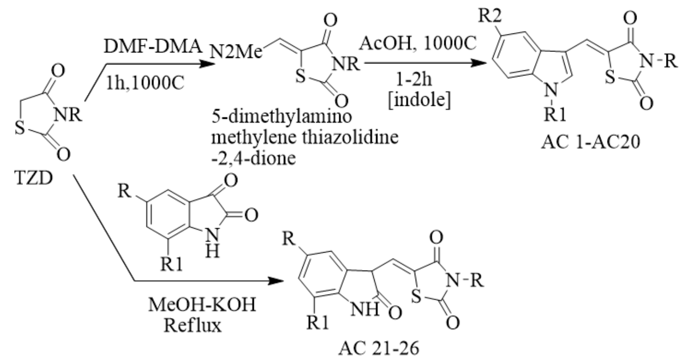


Figure 37. SAR of Thiazolidinedione scaffold.

Indole and 2,4-thiazolidinedione conjugates synthesized and their SAR was done by Corigliano K.W. et al. in 2018 (Scheme 29). Compounds **61**, **62** and **63** (IC_{50}: 5μM) were found to be most potent when compared with standard drug rosiglitazone and evaluated against PC3 (prostate cancer) and MCF-7 (breast cancer) by MTT assay and wound healing assays. The docking (PDB ID: 2PRG: Schrodinger, LLC, New York, NY. 2017) data clearly indicates that ligands were well accommodated into active site of PPARγ by forming H-bond between their carbonyl group of thiazolidine moiety with H343, Y473 and H449 residues [85].



61 **62** **63**



Scheme 29. Synthesis of novel 2-TZD scaffold.

Several studies have suggested that a long term treatment with TZDs, result into increased risk of cardiovascular events, cancer and weight gain, including activation of adipogenesis. The aim of this study is to lessen the side-effects of medicinal products and increases its specificity for specific PPARs. For doing so, N-heterocyclic systems like indolyl and indolinone moieties are attached to side chain of TZD derivative were synthesized (Figure 38).

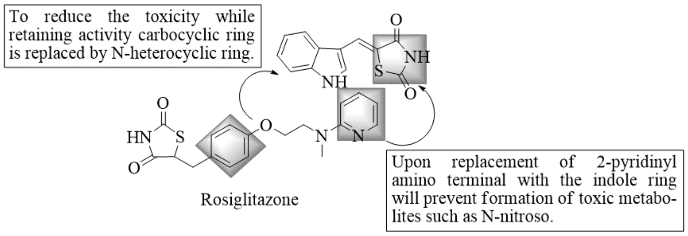


Figure 38. SAR of indole-2,4,-thiazolidinedione conjugates.

CONCLUSION

Due to various biological activities such as antidiabetics, anticancer, anti-inflammatory, antimicrobial, antiviral, antiproliferative, antifungal and anticonvulsant properties etc TZD is chosen as a hot spot compound over the years. Earlier TZD are only known for its antidiabetic properties, but now a days after the research has been extended it is used for many ailments, among which one great way of its use is for cancer. Because of its dramatic antitumor effects and minimal toxicity it is chosen as one of the important scaffold for cancer. This review article highlights the effect of TZD on multiple tumor genesis mechanism. In near future it will be helpful for the biological chemist to design and synthesize TZD derivative with better understanding of their synthetic approaches, SAR, objective of study and design strategy to search effective and shape anticancer molecules.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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