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Recent advancements of anticancer activity and structure-activity relationship of 2,4-thiazolidinedione derivatives

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Abstract
Thiazolidinediones (TZDs) are five-membered heterocyclic having nitrogen, sulfur, and oxygen atoms in their ring structure. Thiazolidinedione, a pharmacophore and a privileged scaffold in medicinal chemistry, is a significant heterocyclic ring system. Their diverse biological activities and therapeutic applications have fascinated the attention of many researchers. Therefore, this review covers some recent anticancer advancements of thiazolidinedione scaffold along with their structure activity relationship so as to afford better correlation among different structures and their biological activities.

Keywords: Thiazolidinedione, Anticancer, SAR, biological activities

1. Introduction

Cancer is a multi-factorial uncontrollable dreadful cell cycle disease characterized by the rapid proliferation of normal cells [1]. It is caused by genetic and/or epigenetic alterations leading to the dysregulation of diverse different pathways through varied molecular mechanisms. In spite of the encouraging continuous clinical progress of chemotherapeutic agents, cancer, with expected 15 million death every year in 2030, has been ranked as the second leading factor of death globally after cardiovascular diseases. Therefore, cancer represents not only a worldwide health problem but also a social and economic dilemma [2]. Moreover, the "single-target single drug" strategy for treatment of cancer using the currently approved chemotherapeutic drugs becomes less effective. This could be attributed to the associated severe side effects of these drugs such as systemic toxicity, their dose-related side effects or lack of selectivity and development of drug-resistance [3]. Therefore, there is an immense medical need for the development of more potent, safe and effective chemotherapeutic agent for such a dreadful disease. In the search for novel anticancer remedies and new strategies for treatment of cancer, 2, 4-thiazolidinediones (TZDs), which known as glitazones, represent one of the most privileged and attractive scaffolds because of its important position in medicinal chemistry, drug design, and drug discovery. Several compounds containing the TZD scaffold displayed numerous biological activities (Fig. 1) such as antihyperglycemic, anticancer, anti-inflammatory, bactericidal, selective PI3 kinase inhibitor, antimicrobial, anti-convulsant, fungicidal, antidiarrheal, pesticidal, insecticidal, anti-HIV, antiarthritic, antihistaminic, 15-hydroxyprostaglandin dehydrogenase inhibitors, anti-ischemic and anti-tubercular activity [4-10].

2. Thiazolidine-2,4-dione (TZD) derivatives as anticancer

Thiazolidine-2,4-dione (TZD), is privileged scaffold of heterocyclic compounds which is particularly explored in the scientific research [15]. Interesting physico-chemical properties and pharmacological effects of TZDs have been the major motivation to begin the recent researches [16]. The drugs containing thiazolidinedione as a core skeleton have a large spectrum of biological activities like antidiabetic, anti-infectious, anti-inflammatory, analgesic, antioxidant, overactive bladder inhibitory and insecticide activities and mores [15]. TZDs also possess inhibitory action towards tyrosinase, hyperlipidimia and acute liver damage [15]. TZDs are a category of insulin sensitizing drugs which consist of ciglitazone, pioglitazone, troglitazone and rosiglitazone, even though troglitazone was eliminated from the market in 2000 due to hepatotoxicity [17]. Apart from their regarded antidiabetic activity, the capability of TZDs to make a contribution to most

cancers remedy has been evidenced through several in vitro and in vivo researches [17]. Researchers carried large efforts on discovering the therapeutic possible of TZDs as anticancer drugs targeting various pathways in cancer [18]. TZDs confirmed anticancer activity in large kinds of cancers which include lung, breast and colon, and also have been used as adjuvant remedy for cancer treatment in some cases [19]. Because of broad pharmacological profile; TZDs are still in lookup for better, safer and plausible pharmacological agents [20].

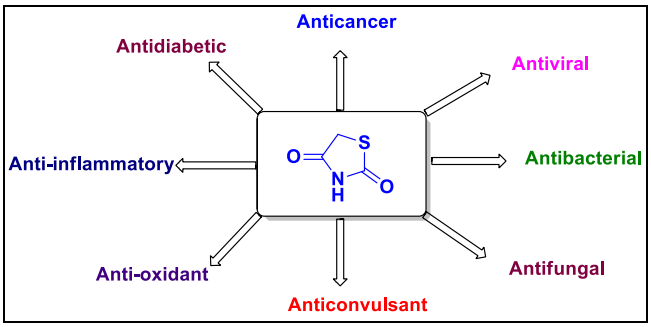


Fig 1: Different biological activities of TZDs

Among these, the anti-diabetic activity is the widely studied effect of TZD derivatives and the position of these molecules seems to be most significant as they constitute a subset of commercially employed insulin-sensitizing and non-insulin-dependent diabetes mellitus agents such as epalrestat 1, pioglitazone 2, ciglitazone 3, rosiglitazone 4, and lobeglitazone 5 [11-14] (Figure 2).

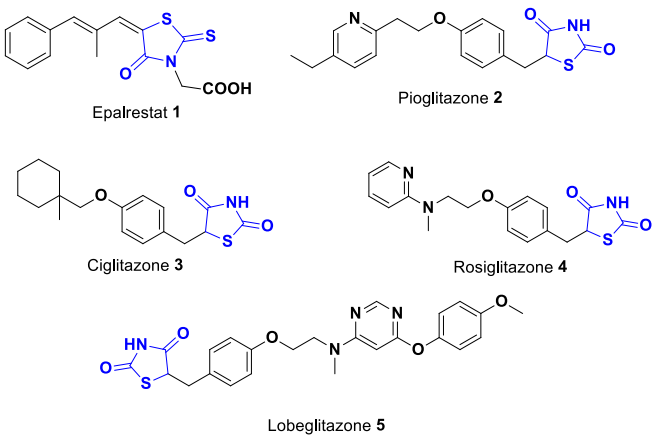


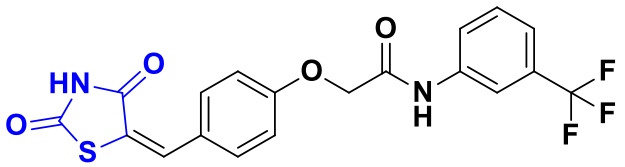
Fig 2: Clinically used molecules having 5-arylidene-2,4 thiazolidinedione derivatives

Due to their wide pharmacological profile, in this review, we have made an attempt to collect some of the recent advancement of the anticancer activity of thiazolidinediones and its derivatives of synthetic origin.

3. Mechanism of action of TZD moiety as anticancer

TZDs are implicated in most cancers development, progression and metastasis, amongst which the Ras/Raf/MEK/extracellular signal regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K)/Akt, Wnt signal transduction pathways and peroxisome proliferator-activated receptors (PPARs) signaling cascades are the most frequently up-regulated in human cancers [21]. The anticancer activity exhibited with the aid of this type of compounds are induced *via* several mechanisms, some of which are induction of apoptosis, cell cycle arrest and differentiation, angiogenesis inhibition by inhibiting endothelial cell proliferation and migration [22]. Some kinds of these molecules also act on activation of peroxisome proliferator-activated receptor-g (PPAR-g), which is expressed in many human tumors, and they modulate the apoptosis and proliferation of these various cancer cell lines, including lung, breast, colon, prostate and bladder [23].

V. Patil *et al*. in 2010 synthesized ten novel 5-benzylidene-2,4-thiazolidinediones derivatives *via* the reaction between (Z)-5-(4-hydroxybenzylidene) thiazolidine-2,4-dione and 2-chloro-N-aromaticacetamide, among synthesized compounds no **6** was the most potent one affect five cell lines MCF7 (breast cancer), PC3 (prostate cancer), KB (Nasopharyngeal cancer), K562 (leukemia) and GURAV (nasopharyngeal cancer) with log10 GI_{50} values of 6.7, 5.60, 5.65, 6.72 and 6.73, respectively [17].



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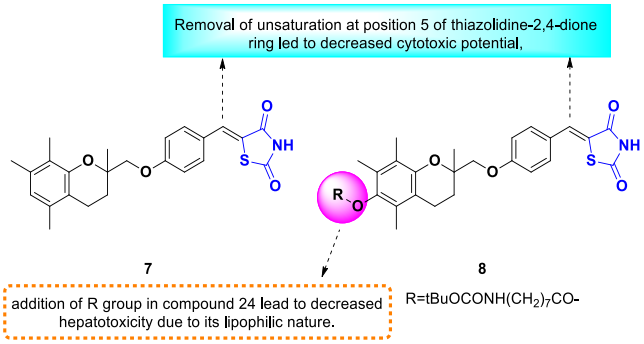
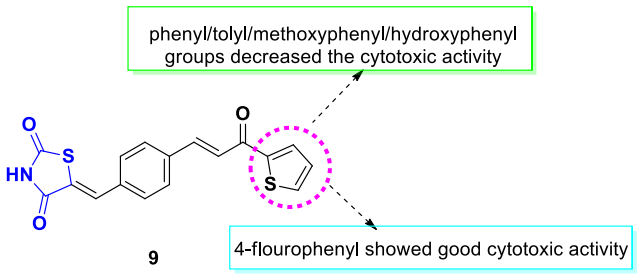
S. Salamone *et al*. in 2012 synthesized new derivatives of troglitazone via a series of chemical reactions, among these derivatives, compound no **7** and **8** were the most potent which show good anti-proliferative activities and low toxicity against hepatocytes, unlike troglitazone. Analysis of the SAR showed that removal of unsaturation at position 5 of thiazolidine-2,4-dione ring led to decreased cytotoxic potential, addition of R group in compound 24 lead to decreased hepatotoxicity due to its lipophilic nature [24].



V. R. Avupati *et al*. [25] in 2012 synthesized a series of some novel 2,4-thiazolidinediones (TZDs) *via* subsequent base catalyzed condensation of the (Z)-4-((2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl)benzaldehyde with appropriate substituted aromatic/heteroaromatic ketones in the presence of pulverized sodium hydroxide in boiling (DMF), among these synthesized compound no **9** was found as the most potent cytotoxic agent with ED_{50} value 4.00±0.25 µg/mL when compared with the standard drug Podophyllotoxin with ED_{50} value of 3.61 µg/mL. The SAR analysis revealed that replacement of thiophene ring by phenyl/tolyl/methoxyphenyl/hydroxyphenyl groups decreased the cytotoxic activity, but when replaced by 4-flourophenyl showed good cytotoxic activity [20].



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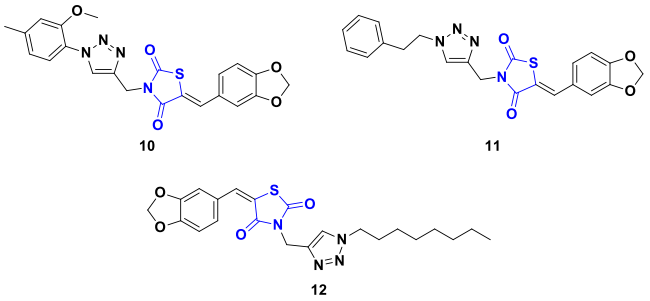
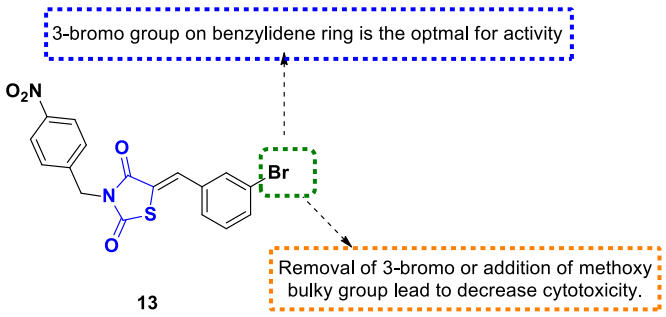
Y. Chinthala *et al*. in 2013 synthesized a new series of thiazolidinedione derivatives via the condensation of 5-(benzo[1,3]dioxol-5-ylmethylene)-3-(prop-2-ynyl) thiazolidine-2,4-dione with various aromatic azides in presence of copper iodide and dry THF, among these synthesized compound no 10, 11 and 12 were the most potent anticancer against IMR-32 (neuroblastoma), Hep-G2 (hepatoma) and MCF-7 (breast) human cancer cell lines [26].



10 11 12

Rego *et al*. in 2013 synthesized 3 new disubstituted thiazolidinediones via refluxed of 3-(4-nitrobenzyl)-thiazolidine-2,4-dione with an appropriately substituted ethyl-2-cyano-3- phenylacrylate in ethanol and piperidine. Derivatives synthesized assayed their cytotoxicity against 6 cancer cell lines, and also against normal cells, among these derivatives compound no 13 was the most one exhibited the highest promising activity; it was selectively cytotoxic against leukemia, lymphoma, glioblastoma, and hepatocarcinoma cell lines without affect normal cells, apoptosis was the main cell death process induced by it [27]. The SAR analysis showed that 3-bromo group on benzylidene ring is the optimal for activity and was contributed to cytotoxicity against HepG2, NG97, Jukart and Raji cell lines. Removal of 3-bromo or addition of methoxy bulky group lead to decrease cytotoxicity [20].



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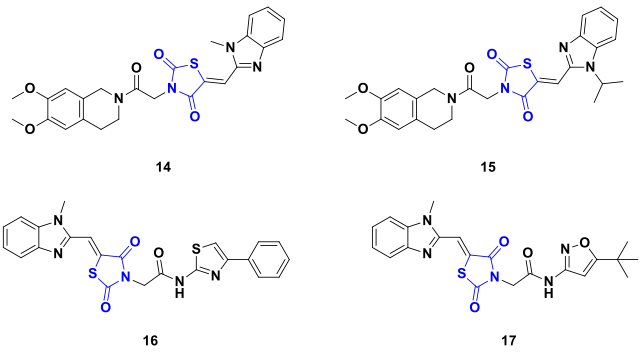
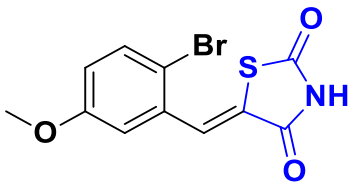
P. Sharma *et al*. [23] in 2016, synthesized Benzimidazole-thiazolidinedione hybrids *via* the Knoevenagel condensation reaction between *N*-substituted thiazolidinedione and 1-alkyl-1*H*-benzo[d]imidazole-2-carbaldehydes among the hybrids; Compound (no.3) was found to be highest cytotoxic on A549 cancer cell line with IC_{50} of 11.46 ± 1.46 µM. Furthermore, the most active compounds 14, 15, 16 and 17 which exerted $IC_{50} \leq 20$ µM were tested on normal breast epithelial cell line (MCF10A) to figure out the selectivity to cancer cells [23]. Also, compounds 14, 15 and 16 were found to be selective to cancerous cells since they did not exhibit cytotoxicity (IC_{50} > 100 µM) on normal MCF10A cells [5]. However, compound 17 showed almost 2.5 times more selectivity for A549 cancerous cells in comparison to normal MCF10A cells. From the SAR study based on the IC_{50} values, it was noted that *N*-substitution on 3rd position of TZD with Oxo ethyl linked morpholine, piperidine, pyrrolidine and 2,6-dimethylmorpholine did not produce the effective compounds. However, most of the compounds containing 6,7-dimethoxy-tetrahydroisoquinoline at the tail side of thiazolidinedione were found to be effective (below 50 µM). On the other side, substitution on position 5 of TZD with 1-methyl-benzimidazole produced more active compounds compared to ethyl and isopropyl groups [23].



14 15 16 17

M. Rodrigues, *et al*. [28] in 2017 synthesized series of benzylidene-2,4-thiazolidinedione derivatives via Knoevenagel condensation of thiazolidine-2,4-dione and seven different aromatic aldehydes, among the synthesized compound no 18 was the most potent cytotoxicity, particularly against NCI-H292 lung cancer, with IC_{50} value of 1.26 µg/mL which did not affect normal cells.



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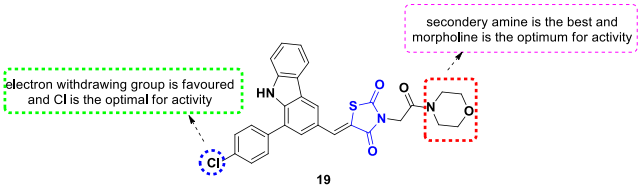
In 2018, Tokala R. and his group [29], have synthesized a new series of β-carboline-thiazolidinedione hybrid derivatives and assessed them for their *in-vitro* anticancer activity against a panel of cancer cell lines such as PC-3, A549, MG-63, HCT-15, MDA-MB-231, A431 and PANC-1 cancer cell lines along with a normal human cell line (L-132). Compound 19 displayed the highest activity against triple negative breast cancer cell line (MDA-MB-231) with an IC_{50} value of 0.97±0.13 Mm compared to Harmine and pioglitazone as standard drugs. Molecular docking studies revealed that it supports the intercalation of β-carboline linked TZD hybrids into DNA. The SAR study revealed that secondary amines are tolerated but morpholine is the optimal for activity. moreover, presence of electron withdrawing group on the phenyl group is favored with Cl atom is the best for activity.



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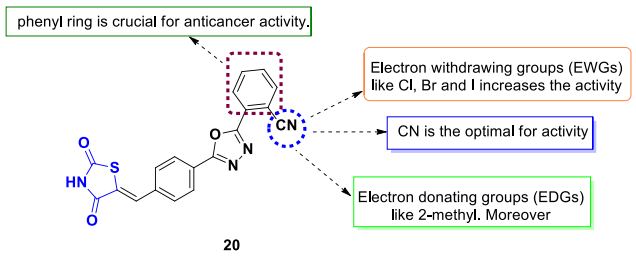
Asati *et al.*, in 2018 [30], designed and synthesized a new thiazolidine-2,4-dione derivatives containing 1,3,4-oxadiazole moiety. All the synthesized compounds for their anticancer activity against MCF-7 breast cancer cell lines using the sulforhodamine B (SRB) method. The H-bonding interaction of the oxygen atom at the second and fourth position of thiazolidinedione derivatives with ASP186 and LYS67, respectively, played a vital role in the activity and nature of the substituents, which was responsible for the activity. Among the tested compounds, compound 20 demonstrated the most marked effect in the MCF-7 cell lines (GI_{50} value 0.004 µM) and displayed a −6.68 docking score against PIM-1 kinase. The Study of SAR showed that presence of electron withdrawing groups (EWGs) like Cl, Br and I increases the activity, and the activity decreased in the presence of electron donating groups (EDGs) like 2-methyl. Moreover, the SAR studies indicated that the presence of a phenyl ring is crucial for anticancer activity.



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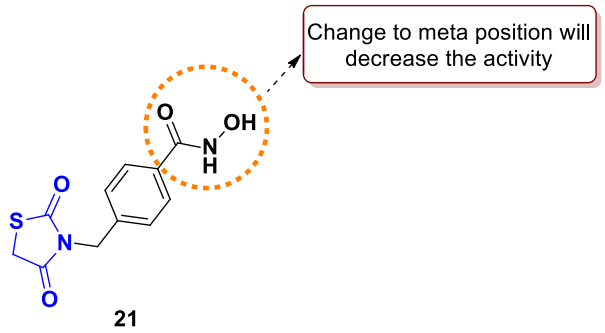
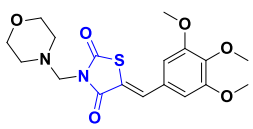
Chiranjeev Sharma *et al.*, in 2019 have designed and synthesized a new series of thiazolidinedione-based HDAC6 inhibitors. Biological evaluation of these derivatives displayed that compound 21 furnished the most potent HDAC6 inhibition activity with an IC_{50} value of 21 nM, which is approximately 10-fold greater than FDA-approved drug, SAHA (HDAC6 IC_{50} = 226 nM). Exposure of SH-SY5Y cells with compound 21 more efficiently promoted the acetylation of *α*-tubulin than Histone H3, indicating that compound 21 suppressed the activity of HDAC6 enzyme more selectively than HDAC1. Moreover, in a dose-dependent manner, compound 22 reversed methamphetamine-induced morphology changes of SH-SY5Y cells. Western blot analysis revealed that biochemical mechanisms underlying methamphetamine-induced morphology changes are associated with disturbance of *α*-tubulin acetylation. These data suggested that compound 21 represents a novel HDAC6-selective inhibitor, demonstrating promising therapeutic potential in methamphetamine addiction [31].



21

H. El-Kashef, *et al.* in 2020 [15] designed and synthesized a novel series of (Z)-3,5-disubstituted thiazolidine-2,4-diones *via* Knoevenagel reaction and mannich reaction at position 5 and 3 of thiazolidine-2,4-dione, respectively, which incorporate 5-(3,4,5- trimethoxybenzylidene) moiety at position 5 of TZD ring. Among all, compounds 22, 234 and 24 were the most potent against breast cancer by inhibiting the proliferation of breast cancer cells without affecting the normal one. Notably, the effect of compounds 22, 23 and 24 on breast cancer cells is a dose dependent with IC_{50} values of 1.27, 1.50 and 1.31 µM, respectively [15].



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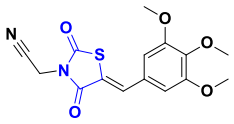

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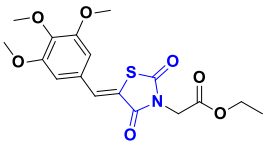

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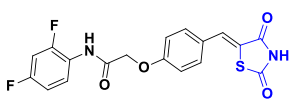
H. Joshi, *et al.* in 2020 [18] synthesized 5- benzylidene thiazolidinedione derivatives *via* the reaction between (Z)-5-(4-hydroxybenzylidene) thiazolidine-2,4-dione and 2-chloro-N-aromaticacetamide, then varying derivatives by keep the amide linkage and benzylidene double bond, but change the aromatic moiety, among the synthesized compounds no 25 and 26 were are the most potent against chronic myeloid leukemic cells K562 with GI_{50} value of 0.9 and 0.23 µM, respectively. Mechanistically, they act by way of inhibit the cell proliferation markers, PCNA and Cyclin D1 and compound 26 up regulated apoptosis markers, cleaved PARP1 and activated caspase three, also founded that combination of compounds 25 and 26 with Imatinib activate the antitumor effects of Imatinib.



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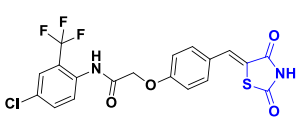
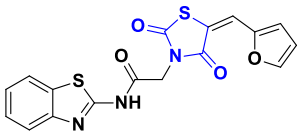


26

K. Tilekar *et al.* in 2020 [32] designed, synthesized, structurally characterized, and biologically evaluated a novel series of furyl-2-methylene thiazolidinediones (TZDs) via the reaction of substituted chloroacetylated amides and potassium (E)-5-(furan-2-ylmethylene)-2,4-dioxothiazolidin -3-ide, among the synthesized compounds, no 27 and 28were the most potent against leukemia by inhibition both GLUT 1 and GLUT 4.



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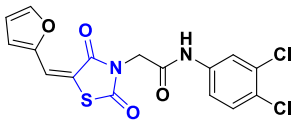
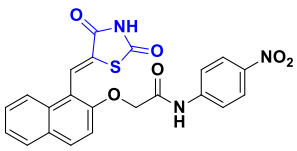


28

K. Tilekar, *et al*. in 2020 [33] designed a series of novel 5-naphthylidene-2,4-thiazolidinedione *via* condensation reaction of (Z)-5-((2-hydroxynaphthalen-1-yl)methylene)thiazolidine-2,4-dione and 2-chloro-N-aromaticacetamide, then varying derivatives by keeping the amide linkage and benzylidene double bond, but changing the aromatic moiety. Among the synthesized compounds, compounds no 29 and 30 were the most potent selective inhibitors of HDAC8 with IC_{50} values of 2.7 µM and 6.3 µM respectively, while 31 and 32 were found to be the most cytotoxic in leukemic cell lines. Also, compounds 30 and 31 were found to induce apoptosis and cause cell cycle arrest in G2/M phase. Docking study correlated properly with the HDAC inhibitory concentrations and carboxylate group used to be located to have interaction with zinc binding group at zinc binding site.



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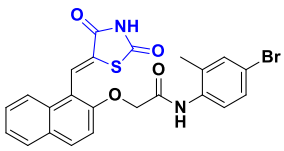

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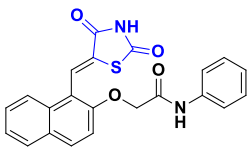

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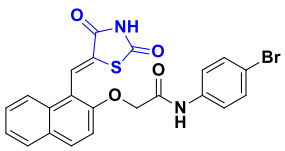
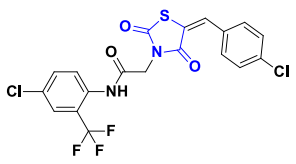


32

K. Tilekar, *et al*. in 2020 [34] designed and synthesized, N-substituted benzylidene thiazolidinedione (TZD) derivatives by refluxed of 2-chloro-N-aromaticacetamide with series of TZD derivatives potassium salt in acetone, change aromatic ring and trisubstitutedbenzylidene with different substituents, among the synthesized compounds no18 was most active and inhibited all three GLUT types, with GLUT4 IC_{50} = 9.5±2.8 µM, and GLUT5 IC_{50} = 34.5±2.4 µM, also discourage the proliferation of leukemia CEM cells while safer for normal blood one. Compounds no 33, 34 and 35 inhibited GLUT1, with IC_{50} values of 5.4±1.3, 26.6±1.8, and 12.6±1.2 µM, respectively. Compound no 35 was specific for GLUT1, no 34 inhibited GLUT4 (IC_{50} = 21.6±4.5 µM) comparably but did not affect GLUT5.



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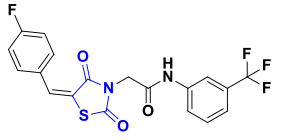

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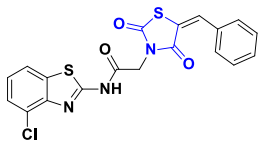

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4. Conclusion

The review focuses especially on the anticancer activities and structure activity relationship (SAR) of thiazolidinedione derivatives which play an important role in medicinal field. These most active thiazolidinediones offer a widespread information to the scientists may be taken as leads to design and develop novel, target oriented and optimized thiazolidinedione agents with potential anticancer activity**.**

5. References

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