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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, hyperlipidemia 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

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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 lookout for better, safer and plausible pharmacological agents [20].

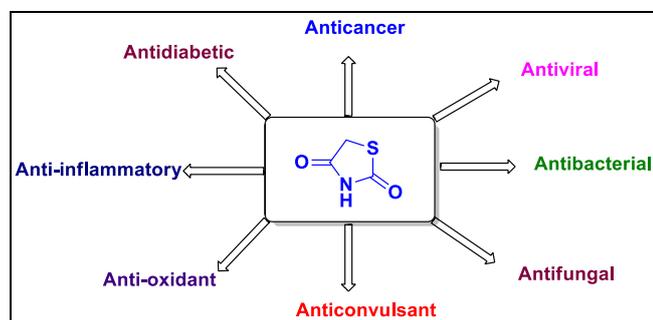


Fig 1: Different biological activities of TZDs

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).

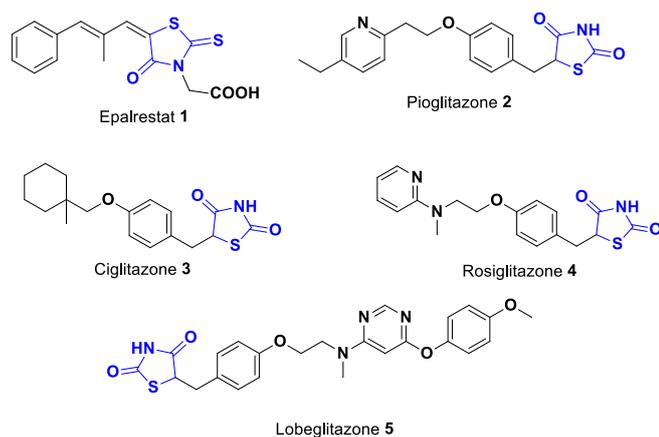


Fig 2: Clinically used molecules having 5-arylidene-2,4-thiazolidinedione derivatives

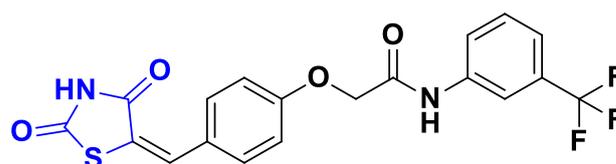
Due to their wide pharmacological profile, in this review, we have made an attempt to collect some of the recent advancement of the anticancer activity of thiazolidinediones and its derivatives of synthetic origin.

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

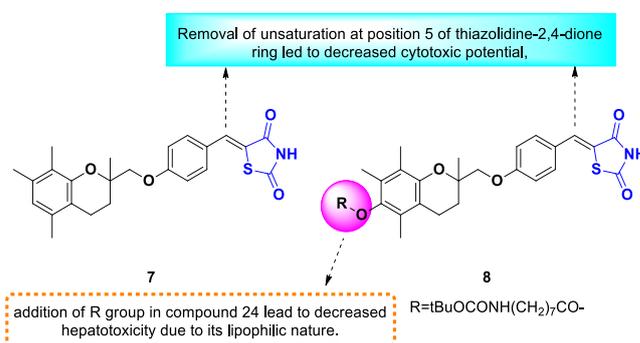
which are induction of apoptosis, cell cycle arrest and differentiation, angiogenesis inhibition by inhibiting endothelial cell proliferation and migration [22]. Some kinds of these molecules also act on activation of peroxisome proliferator-activated receptor-g (PPAR-g), which is expressed in many human 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 GI₅₀ values of 6.7, 5.60, 5.65, 6.72 and 6.73, respectively [17].

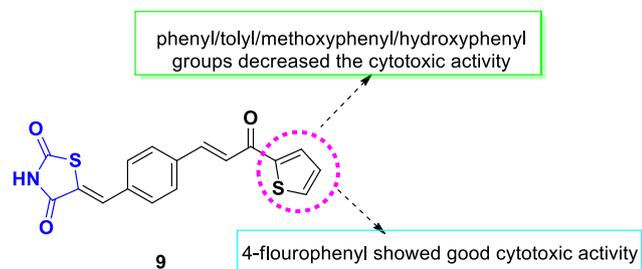


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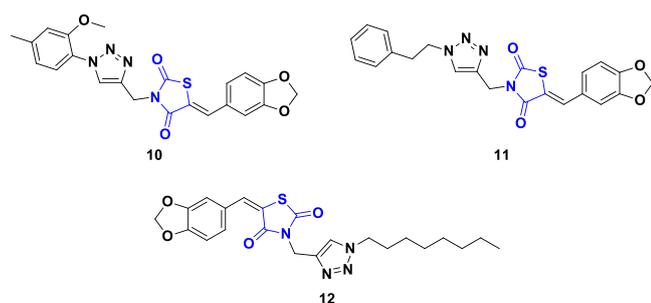
S. Salamone *et al.* in 2012 synthesized new derivatives of troglitazone via a series of chemical reactions, among these derivatives, compound no 7 and 8 were the most potent which show good anti-proliferative activities and low toxicity against hepatocytes, unlike troglitazone. Analysis of the SAR showed 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].



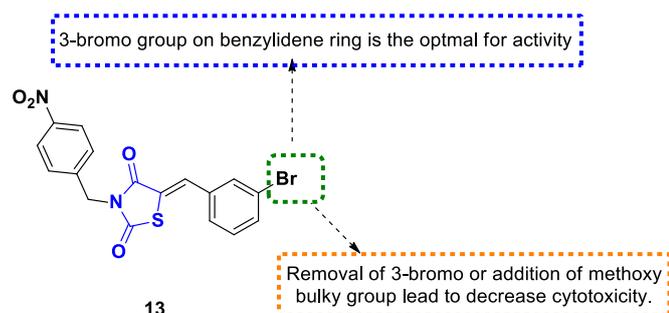
V. R. Avupati *et al.* [25] in 2012 synthesized a series of some novel 2,4-thiazolidinediones (TZDs) via subsequent base catalyzed condensation of the (Z)-4-((2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl)benzaldehyde with appropriate substituted aromatic/heteroaromatic ketones in the presence of pulverized sodium hydroxide in boiling (DMF), among these synthesized compound no 9 was found as the most potent cytotoxic agent with ED₅₀ value 4.00±0.25 µg/mL when compared with the standard drug Podophyllotoxin with ED₅₀ 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-fluorophenyl showed good cytotoxic activity [20].



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].

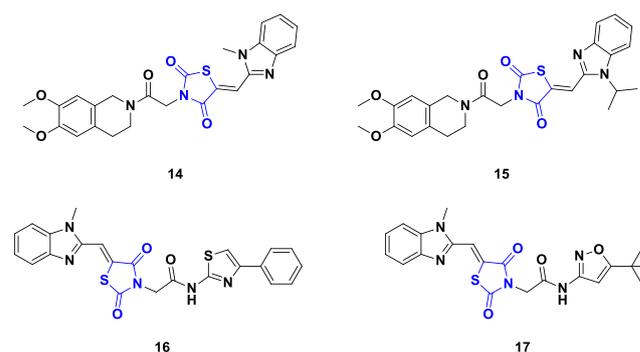


Rego *et al.* in 2013 synthesized 3 new disubstituted thiazolidinediones via refluxed of 3-(4-nitrobenzyl)-thiazolidine-2,4-dione with an appropriately substituted ethyl-2-cyano-3-phenylacrylate in ethanol and piperidine. Derivatives synthesized assayed their cytotoxicity against 6 cancer cell lines, 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].

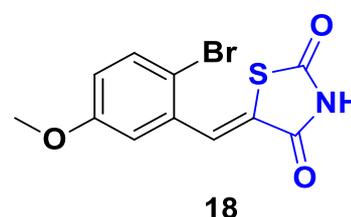


P. Sharma *et al.* [23] in 2016, synthesized Benzimidazole-thiazolidinedione hybrids via the Knoevenagel condensation reaction between *N*-substituted thiazolidinedione and 1-alkyl-1*H*-benzo[d]imidazole-2-carbaldehydes among the hybrids; Compound (no.3) was found to be highest cytotoxic on A549 cancer cell line with IC_{50} of 11.46 ± 1.46

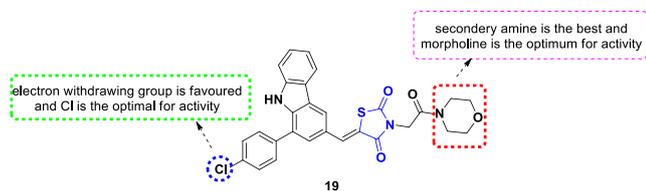
μM . Furthermore, the most active compounds 14, 15, 16 and 17 which exerted $IC_{50} \leq 20 \mu\text{M}$ were tested on normal breast epithelial cell line (MCF10A) to figure out the selectivity to cancer cells [23]. Also, compounds 14, 15 and 16 were found to be selective to cancerous cells since they did not exhibit cytotoxicity ($IC_{50} > 100 \mu\text{M}$) 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-methylbenzimidazole produced more active compounds compared to ethyl and isopropyl groups [23].



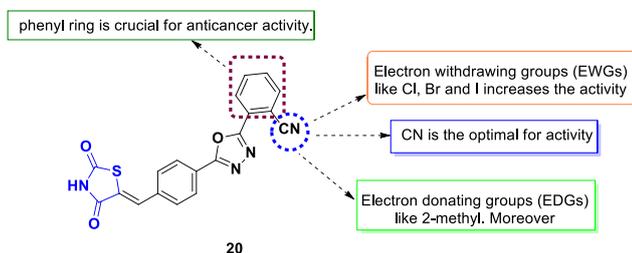
M. Rodrigues, *et al.* [28] in 2017 synthesized series of benzylidene-2,4-thiazolidinedione derivatives via Knoevenagel condensation of thiazolidine-2,4-dione and seven different aromatic aldehydes, among the synthesized compound no 18 was the most potent cytotoxicity, particularly against NCI-H292 lung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



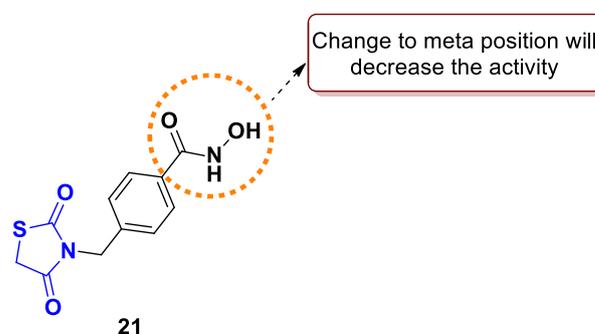
In 2018, Tokala R. and his group [29], have synthesized a new series of β -carboline-thiazolidinedione hybrid derivatives and assessed them for their *in-vitro* anticancer activity against a panel of cancer cell lines such as PC-3, A549, MG-63, HCT-15, MDA-MB-231, A431 and PANC-1 cancer cell lines along 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 $0.97 \pm 0.13 \text{ Mm}$ 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.



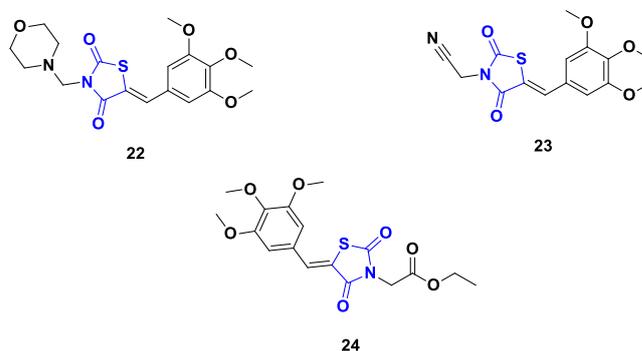
Asati *et al.*, in 2018 ^[30], designed and synthesized a new thiazolidine-2,4-dione derivatives containing 1,3,4-oxadiazole moiety. All the synthesized compounds for their anticancer activity against MCF-7 breast cancer cell lines using the sulforhodamine B (SRB) method. The H-bonding interaction of 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 μ M) 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.



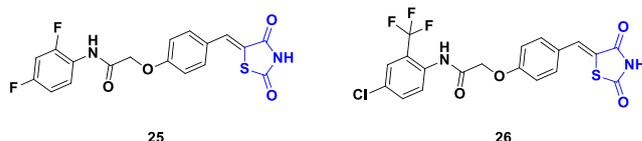
Chiranjeev Sharma *et al.*, in 2019 have designed and synthesized a new series of thiazolidinedione-based HDAC6 inhibitors. Biological evaluation of these derivatives displayed that compound 21 furnished the most potent HDAC6 inhibition activity with an IC_{50} value of 21 nM, which is approximately 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].



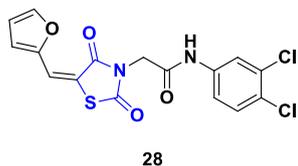
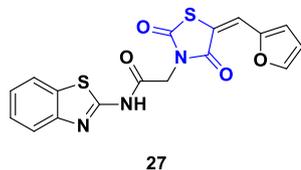
H. El-Kashef, *et al.* in 2020 ^[15] designed and synthesized a novel series of (Z)-3,5-disubstituted thiazolidine-2,4-diones via Knoevenagel reaction and mannich reaction at position 5 and 3 of thiazolidine-2,4-dione, respectively, which incorporate 5-(3,4,5-trimethoxybenzylidene) moiety at position 5 of TZD ring. Among all, compounds 22, 23 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 μ M, respectively ^[15].



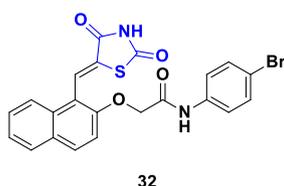
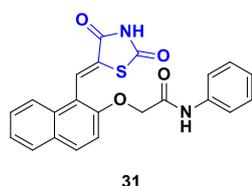
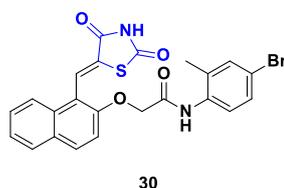
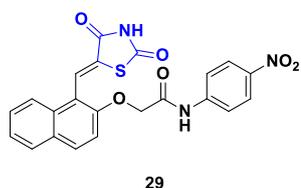
H. Joshi, *et al.* in 2020 ^[18] synthesized 5-benzylidene thiazolidinedione derivatives via the reaction between (Z)-5-(4-hydroxybenzylidene) thiazolidine-2,4-dione and 2-chloro-N-aromaticacetamide, then varying derivatives by keep the amide linkage and benzylidene double bond, but change the aromatic moiety, among the synthesized compounds no 25 and 26 are the most potent against chronic myeloid leukemic cells K562 with GI_{50} value of 0.9 and 0.23 μ M, 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.



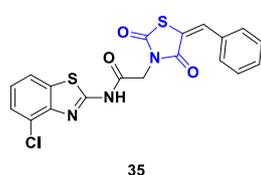
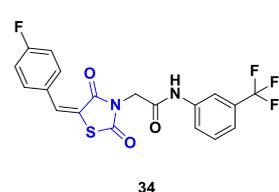
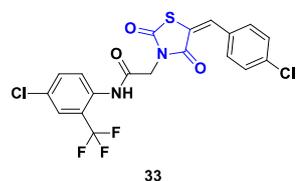
K. Tilekar *et al.* in 2020 ^[32] designed, synthesized, structurally characterized, and biologically evaluated a novel series of furyl-2-methylene thiazolidinediones (TZDs) via the reaction of substituted chloroacetylated amides and potassium (E)-5-(furan-2-ylmethylene)-2,4-dioxothiazolidin-3-ide, among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



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 μ M and 6.3 μ M 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.



K. Tilekar, *et al.* in 2020^[34] designed and synthesized, N-substituted benzylidene thiazolidinedione (TZD) derivatives by refluxed 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 \pm 2.8 μ M, and GLUT5 IC_{50} = 34.5 \pm 2.4 μ M, 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 \pm 1.3, 26.6 \pm 1.8, and 12.6 \pm 1.2 μ M, respectively. Compound no 35 was specific for GLUT1, no 34 inhibited GLUT4 (IC_{50} = 21.6 \pm 4.5 μ M) comparably but did not affect GLUT5.



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

1. kA Bass A, El-Zoghbi MS, Nageeb E-SM, Mohamed MF, Bader M, Abuo-Rahma GE-DA. Comprehensive review for anticancer hybridized multitargeting HDAC inhibitors. *European journal of medicinal chemistry* 2020;11:2904.
2. Mohamed MF, Abuo-Rahma GE-DA. Molecular targets and anticancer activity of quinoline-chalcone hybrids: literature review. *RSC Advances* 2020;10:31139-55.
3. Mohamed MF, Shaykoon MSA, Abdelrahman MH, Elsadek BE, Aboraia AS, Abuo-Rahma GE-DA. Design, synthesis, docking studies and biological evaluation of novel chalcone derivatives as potential histone deacetylase inhibitors. *Bioorganic chemistry* 2017;72:32-41.
4. Clark-Lewis J. 2, 4-Oxazolidinediones. *Chemical reviews* 1958;58:63-99.
5. Hughes SJ, Millan DS, Kilty IC, Lewthwaite RA, Mathias JP, O'Reilly MA, *et al.* Fragment based discovery of a novel and selective PI3 kinase inhibitor. *Bioorganic & medicinal chemistry letters* 2011;21:6586-90.
6. Abd Alhameed R, Almarhoon Z, Bukhari SI, El-Faham A, de la Torre BG, Albericio F. Synthesis and antimicrobial activity of a new Series of thiazolidine-2, 4-diones carboxamide and amino acid derivatives. *Molecules* 25:105.
7. Szychowski KA, Kaminsky DV, Leja ML, Kryshchshyn AP, Lesyk RB, Tobiasz J *et al.* Anticancer properties of 5Z-(4-fluorobenzylidene)-2-(4-hydroxyphenylamino)-thiazol-4-one. *Scientific reports*;9:1-16.
8. Naim MJ, Alam MJ, Ahmad S, Nawaz F, Shrivastava N, Sahu M *et al.* Therapeutic journey of 2, 4-thiazolidinediones as a versatile scaffold: An insight into structure activity relationship. *European journal of medicinal chemistry* 129:218-50.
9. Rosa F, Osorio JS, Trevisi E, Yanqui-Rivera F, Estill CT, Bionaz M. 2, 4-Thiazolidinedione treatment improves the innate immune response in dairy goats with induced subclinical mastitis. *PPAR research* 2017.
10. Mohamed MF, Aziz MA, Abuo-Rahma GE-DA. Ultrasound-assisted green synthesis of 2,4-thiazolidinedione and diaryl substituted pyrazolylthiazolidinediones catalyzed by β -alanine. *International Journal of Pharmaceutical Sciences and Drug Analysis* 2021;1:18-25.
11. Naim MJ, Alam MJ, Nawaz F, Naidu V, Aaghaz S, Sahu M, *et al.* Synthesis, molecular docking and anti-diabetic evaluation of 2, 4-thiazolidinedione based amide derivatives. *Bioorganic chemistry* 2017;73:24-36.

12. Yasmin S, Jayaprakash V. Thiazolidinediones and PPAR orchestra as antidiabetic agents: From past to present. *European journal of medicinal chemistry* 2016;879-93.
13. Nanjan MJ, Mohammed M, Kumar BRP, Chandrasekar MJN. Thiazolidinediones as antidiabetic agents: a critical review. *Bioorganic chemistry* 77:548-67.
14. Nazreen S, Alam MS, Hamid H, Yar MS, Dhulap A, Alam P, et al. Design, Synthesis, and Biological Evaluation of Thiazolidine-2, 4-dione Conjugates as PPAR- γ Agonists. *Archiv der Pharmazie* 2015;348:421-32.
15. El-Kashef H, Badr G, El-Maali NA, Sayed D, Melnyk P, Lebegue N, et al. Synthesis of a novel series of (Z)-3, 5-disubstituted thiazolidine-2, 4-diones as promising anti-breast cancer agents. *Bioorganic chemistry* 2020;96:103569.
16. Rančić MP, Trišović NP, Milčić MK, Ajaj IA, Marinković AD. Experimental and theoretical study of substituent effect on ¹³C NMR chemical shifts of 5-arylidene-2, 4-thiazolidinediones. *Journal of Molecular Structure* 2013;1049:59-68.
17. Patil V, Tilekar K, Mehendale-Munj S, Mohan R, Ramaa C. Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2, 4-thiazolidinedione derivatives. *European journal of medicinal chemistry* 2010;45:4539-44.
18. Joshi H, Patil V, Tilekar K, Upadhyay N, Gota V, Ramaa C. Benzylidene thiazolidinediones: Synthesis, in vitro investigations of antiproliferative mechanisms and in vivo efficacy determination in combination with Imatinib. *Bioorganic & medicinal chemistry letters* 2020;30:127561.
19. Shankar S, Vuppu S. In vitro drug metabolism and pharmacokinetics of a novel thiazolidinedione derivative, a potential anticancer compound. *Journal of pharmaceutical and biomedical analysis* 2020;179:113000.
20. Naim MJ, Alam MJ, Ahmad S, Nawaz F, Shrivastava N, Sahu M *et al.* Therapeutic journey of 2, 4-thiazolidinediones as a versatile scaffold: An insight into structure activity relationship. *European journal of medicinal chemistry* 2017;129:218-50.
21. Asati V, Mahapatra DK, Bharti SK. Thiazolidine-2, 4-diones as multi-targeted scaffold in medicinal chemistry: Potential anticancer agents. *European journal of medicinal chemistry* 2014;87:814-33.
22. Sengottavelan S, Uppal R, Vuppu S. Validation of a sensitive simultaneous LC-MS/MS method for the quantification of novel anti-cancer thiazolidinedione and quinazolin-4-one derivatives in rat plasma and its application in a rat pharmacokinetic study. *Journal of Chromatography B* 2019;1121:18-27.
23. Sharma P, Reddy TS, Thummuri D, Senwar KR, Kumar NP, Naidu V, et al. Synthesis and biological evaluation of new benzimidazole-thiazolidinedione hybrids as potential cytotoxic and apoptosis inducing agents. *European journal of medicinal chemistry* 2016;124:608-21.
24. Salamone S, Colin C, Grillier-Vuissoz I, Kuntz S, Mazerbourg S, Flament S, et al. Synthesis of new troglitazone derivatives: anti-proliferative activity in breast cancer cell lines and preliminary toxicological study. *European journal of medicinal chemistry* 2012;51:206-15.
25. Avupati VR, Yejella RP, Akula A, Guntuku GS, Doddi BR, Vutla VR, et al. Synthesis, characterization and biological evaluation of some novel 2, 4-thiazolidinediones as potential cytotoxic, antimicrobial and antihyperglycemic agents. *Bioorganic & medicinal chemistry letters* 2012;22:6442-50.
26. Chinthala Y, Domatti AK, Sarfaraz A, Singh SP, Arigari NK, Gupta N, et al. Synthesis, biological evaluation and molecular modeling studies of some novel thiazolidinediones with triazole ring. *European journal of medicinal chemistry* 2013;70:308-14.
27. de Melo Rêgo MJB, Galdino-Pitta MR, Pereira DTM, da Silva JC, Rabello MM, de Lima MdCA, et al. Synthesis, in vitro anticancer activity and in silico study of new disubstituted thiazolidinedione derivatives. *Medicinal Chemistry Research* 2014;23:3220-6.
28. Rodrigues MdD, Santiago PB, Marques KM, Pereira VR, de Castro MC, Cantalice JC, et al. Selective cytotoxic and genotoxic activities of 5-(2-bromo-5-methoxybenzylidene)-thiazolidine-2, 4-dione against NCI-H292 human lung carcinoma cells. *Pharmacological Reports* 2018;70:446-54.
29. Tokala R, Thatikonda S, Sana S, Regur P, Godugu C, Shankaraiah N. Synthesis and in vitro cytotoxicity evaluation of β -carboline-linked 2, 4-thiazolidinedione hybrids: potential DNA intercalation and apoptosis-inducing studies. *New Journal of Chemistry* 2018;42:16226-36.
30. Asati V, Bharti SK. Design, synthesis and molecular modeling studies of novel thiazolidine-2, 4-dione derivatives as potential anti-cancer agents. *Journal of Molecular Structure* 2018;1154:406-17.
31. Sharma C, Oh YJ, Park B, Lee S, Jeong C-H, Lee S *et al.* Development of Thiazolidinedione-Based HDAC6 Inhibitors to Overcome Methamphetamine Addiction. *Int J Mol Sci* 2019;20:6213.
32. Tilekar K, Upadhyay N, Hess JD, Macias LH, Mrowka P, Aguilera RJ *et al.* Structure guided design and synthesis of furyl thiazolidinedione derivatives as inhibitors of GLUT 1 and GLUT 4, and evaluation of their anti-leukemic potential. *European journal of medicinal chemistry* 2020;202:112603.
33. Tilekar K, Upadhyay N, Jansch N, Schweipert M, Mrowka P, Meyer-Almes F *et al.* Discovery of 5-naphthylidene-2, 4-thiazolidinedione derivatives as selective HDAC8 inhibitors and evaluation of their cytotoxic effects in leukemic cell lines. *Bioorganic chemistry* 2020;95:103522.
34. Tilekar K, Upadhyay N, Schweipert M, Hess JD, Macias LH, Mrowka P *et al.* Permuted 2, 4-thiazolidinedione (TZD) analogs as GLUT inhibitors and their in-vitro evaluation in leukemic cells. *European Journal of Pharmaceutical Sciences* 2020;154:105512.