

## A review on thiazolidinediones used as a potent anticancer agent

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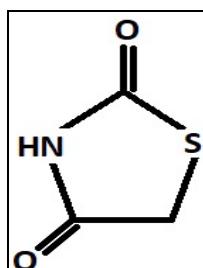
### Abstract

Heterocyclic compounds and their derivative has been an fascinating field in medicinal chemistry because of their biological and pharmacological properties. Heterocyclic compounds are cyclic compounds in which the ring contains carbon, one or more atoms of other elements, commonly called as hetero atoms. Heterocyclic compounds usually contain hetero atoms like nitrogen, sulphur and oxygen. This review reflects the contribution of Thiazolidinedione as a scaffold to develop novel class of anticancer agents through PPAR- $\gamma$  activation mechanism.

**Keywords:** anticancer activity, cancer, PPAR- $\gamma$ , thiazolidinedione

### Introduction

Cancer is nothing but unwanted growth<sup>1</sup> of cells with a large impact on the people's health all over the world, making it the second leading cause of death after cardiovascular diseases<sup>[1]</sup>. According to the<sup>1</sup>World Cancer Report 2014, 1 cancer affected about 8.2 million lives in the year 2012<sup>[2]</sup>, and is 1 believed to be the primary 1cause of death in the coming years.<sup>1</sup> Lung, breast, liver, stomach and bowel cancer are the most common cancer leading to deaths worldwide, accounting for nearly a half of all cancer deaths. The five most common types of disease diagnosed in 2012 were lung, prostate, colorectal, stomach and liver cancer among men<sup>[2]</sup>. Among the various types of malignant tumors reported so far breast cancer is the second most prominent reason for deaths among the women followed by lung, cervix and stomach cancer<sup>[3]</sup>. Colorectal cancer is the third leading cause of death in United States with 50% patients lost their lives in the year 2010<sup>[2]</sup>. In search of potential anticancer agents, enormous efforts aimed at the implementation of new treatment strategies resulting in the development of scaffolds containing heterocyclic structure as their key structural design. Heterocyclic compound play an important role in cancer therapy. Among them Research scholars interest pointed towards thiazolidinedione, a structures that are able to provide high-affinity ligands for more than one type of receptor in modern medicinal chemistry, considering its broad spectrum of biological activities and affinity towards various biological targets<sup>[4]</sup>. Thiazolidinedione (TZDs), also called glitazones is a five-membered carbon ring molecules containing two heteroatoms (nitrogen and sulfur). One carbonyl group in the thiazole at position 4 and another at position 2 makes the heterocyclic compound a thiazolidine-2, 4-dione<sup>[5]</sup>.



**Fig 1:** Thiazolidine-2, 4 - dione

The biological activities exhibited by TZD includes anti-hyperglycaemic<sup>[6]</sup>, antimicrobial<sup>[7]</sup>, antiviral<sup>[8]</sup>, antioxidant<sup>[9]</sup>, anticancer<sup>[10]</sup>, anti-inflammatory<sup>[11]</sup>, anti-plasmodial, alpha glucosidase inhibitory, xanthine oxidase inhibitory activity etc. because of wide profile, thiazolidinediones are still in research for better, safer and potential pharmacological agents.

TZDs are one of the main heterocyclic ring systems having therapeutic importance when combined with other heterocyclic rings. For the investigation of novel and highly active therapeutic compounds the combination of two pharmacophores into a single molecule is an interesting, effective and mostly used direction in modern medicinal chemistry.

There are several mechanisms of anticancer activity of TZDs including

- Induction of apoptosis
- Cell differentiation
- Cell cycle arrest

Some of the TZDs are designed for the treatment of human cancers expressing high levels of Peroxisome Proliferator-activated Receptor gamma (PPAR- $\gamma$ ), which is expressed in many human tumours including lung, breast, colon, prostate and bladder cancer. It is assumed that activation of PPAR- $\gamma$  mediates their anticancer activity

TZD ring has been used as a scaffold to develop this novel class of anticancer agents, encouraged by the literature report that toxicity of troglitazone is not due to TZD ring<sup>[12]</sup>. TZD moiety is directly connected to an N-heterocyclic ring so as to lower their toxic effects<sup>[13]</sup>. PPAR- $\gamma$ , Peroxisome Proliferator-activated Receptor gamma, also known as the glitazone receptor, or NR1C3 is a type II nuclear receptor that in humans is encoded by PPARG gene. PPAR- $\gamma$  is the master regulator of adipogenesis and the pharmacological target of the TZD class of insulin sensitizers. As metabolic regulators PPARs control the expression of genes involved in adipocyte differentiation, lipid and glucose metabolism, and as well as inflammation in immune cells and cell proliferation. Apart from the

known metabolic actions, PPAR- $\gamma$  has also been shown to be over expressed. In numerous human cancers including breast, bladder, prostate, colon and thyroid. PPAR- $\gamma$  agonist exhibit antitumor activities. It was also proposed to induce apoptosis in some malignant cell lineages. *In-vivo* and *in-vitro* studies have revealed anti proliferative and pro apoptotic actions of PPAR- $\gamma$  agonists indicating that PPAR- $\gamma$  could be a promising therapeutic target for the treatment of Cancers<sup>[15]</sup>.

### Antitumor activity of thiazolidinediones

Thiazolidinediones (TZDs), like troglitazone, rosiglitazone, pioglitazone, and ciglitazone are some of the high-affinity ligands for PPAR- $\gamma$  and are clinically being used as oral hypoglycemic agents in type 2 diabetes mellitus patients. TZDs activate the PPAR- $\gamma$  causing transcriptional activation of insulin-sensitive genes in glucose homeostasis in a way which imitates the genomic effects of insulin. In addition, TZDs have been found to decrease colorectal, lung and breast cancer risks in diabetic patients. TZDs mediate their antitumor activities through the induction of cell cycle arrest, apoptosis, and redifferentiation. But the exact anti proliferative mechanisms of TZDs remain unclear; various evidences show that TZDs have both PPAR- $\gamma$  dependent and independent mechanisms. PPAR- $\gamma$  dependent mechanisms include the induction of pro-apoptotic proteins, phosphatase and tensin homolog (PTEN), p53, and BAD; and reducing the level of the anti-apoptotic proteins Bcl-2, Bcl-xL, and survivin, followed by the down-regulation of ERK 1/2, which induce apoptosis via the mitochondrial pathway. The PPAR- $\gamma$  independent action of TZDs, which targets multiple signalling pathways, is mediated through the energy restriction mimetic effect and the induction of starvation-associated cellular responses<sup>[16]</sup>.

### Conclusion

The thiazolidine-2, 4-dione derivatives showing anticancer activity are mainly derivatives modified in the position 5 of the thiazolidine-2, 4-dione derivatives. The fifth position of thiazolidine-2, 4-diones being relatively more reactive, hence most of the modification at this position exhibits a wide spectrum of pharmacological properties. TZD moiety is directly connected to an N-heterocyclic ring in order to improve its anticancer activity. Thus the dose required for anticancer activity of TZD would be significantly lower than that required to bring hypoglycaemic activity.

### References

1. Ahmad S, Alam O, Naim M, Shaquizzaman M, Alam M, Iqbal M. Pyrrole: An insight into recent pharmacological advances with structure activity relationship. *European Journal of Medicinal Chemistry*,2018:157:527-561.
2. Trotsko N, Przekora A, Zalewska J, Ginalska G, Paneth A, Wujec M. Synthesis and *in vitro* antiproliferative and antibacterial activity of new thiazolidine-2,4-dione derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry*,2017:33(1):17-24.
3. Cancer. org. Cancer Facts and Statistics | American Cancer Society, 2020. <http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-036845.pdf>
4. Sharma P, Srinivasa Reddy T, Thummuri D, Senwar K, Praveen Kumar N, 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*,2016:124:608-621.
5. Fröhlich E, Wahl R. Chemotherapy and Chemoprevention by Thiazolidinediones. *BioMed Research International*, 2015, 1-14.
6. Vasincu IM, Apotrosoaei M, Panzariu AT. Synthesis and Biological Evolution of New 1, 3-Thiazolidine-4-one Derivatives of 2-(4-Isobutyl phenyl) Propionic Acid. *Molecules*,2014:19:15005-15025.
7. Chadha N, Bahia MS, Kaur M, Silakari O. Thiazolidine-2, 4-Dione Derivatives: Programmed Chemical Weapons for Key Protein Targets of Various Pathological Conditions. *Bioorganic & Medicinal Chemistry*,2015:23:2953-2974.
8. Sharghia H, Khalifeha R, Moeinia BF, Beyzava MH, Salimi Benic A, Doroodmand MM. Mannich reactions or secondary amines, aldehydes and alkynes in water using cu/c nanoparticles as a heterogenous catalyst. *Journal of the Iranian Chemical Society*,2011:8:S89-S103.
9. Ashwani Kumar, Sahil Kumar. Review on advances in the development of 2, 4-thiazolidinedione derivatives as therapeutic agents. *Critical review in Pharmaceutical Sciences*,2016:5(3):8-34.
10. Panzariu AT, Aprotosoaie M, Profire L. Synthesis and biological evaluation of new 1, 3-thiazolidine-4 -one derivatives of nitro-1-arginine methyl ester. *Chemistry Central Journal*,2016:10:6-10.
11. Singh T, Khobragade D. Synthesis and evaluation of thiazolidine-4-one for their antibacterial activity. *JPSBR*,2014:4:110-113.
12. 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(10):4539-4544.
13. Corigliano D, Syed R, Messineo S, Lupia A, Patel R, Reddy C *et al.* Indole and 2, 4-Thiazolidinedione conjugates as potential anticancer modulators. *Peer J*,2018:6:e5386.
14. Ayyakannu A. Napoleon. Review on recent developments and biological activities of 2, 4-thiazolidinediones. *International Journal of PharmTech Research*,2016:9(3):429-443.
15. Hemanth Gurula, Shila Samuel T, Loganathan. Insilico screening of potent ppargamma agonists among natural anticancer compounds of Indian origin. *Asian J Pharm Clin Res*,2016:9(4):320-324.
16. Omar H, Salama S, Arafa E, Weng J. Antitumor effects of energy restriction-mimetic agents: thiazolidinediones. *Biological Chemistry*,2013:394(7):865-870.