Biological Potential of Thiazolidinedione Derivatives: A Review

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Abstract:

Background: The authors of the current review aspire to inspire researchers by using the SAR technique to discover a promising and novel therapeutic agent. Currently, we don't have a drug that is both active and non-toxic for the treatment of severe diseases like cancer, diabetes, hypertension, and neurodegenerative diseases. In a summary, thiazolidinedione (TZD) heterocyclic ligands have a spectacular standing in medicinal chemistry's synthetic and pharmacological approaches. Thiazolidinedione (TZD) core upon the replacement of different substitutes, gives a wide range of organic action by the utilization of various components on various objective destinations.

Methods: We looked through the logical data set utilizing relevant keywords. Among the looked through writing, certain research papers were gathered which resolved our inquiries. The vital discoveries of the key findings of these studies were incorporated alongside their significance.

Results: There has been an explosion in the introduction of new classes of pharmacological agents having Thiazolidinedione moieties. Subsequently, new medications with Thiazolidinedione moieties came up with improved compliance and reduced side effects.

Conclusion: The present review describes the significance of the Thiazolidinedione nucleus and its derivatives as a therapeutic agent with an emphasis on the past as well as recent developments.

Keywords: 2,4-Thiazolidinedione derivatives, anti-inflammatory activity, anticancer activity, antidiabetic activity, antimicrobial activity.

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INTRODUCTION

Thiazolidinedione derivatives have occupied a unique place in the field of medicinal chemistry. Thiazolidinedione is an extensively explored heterocyclic derivative that possesses a broad spectrum of pharmacological activities such as antidiabetic, anti-arthritis, anti-inflammatory, antimicrobial, and anticancer activity. [1] An active research field is understanding the molecular processes that support PPAR-induced anti-cancer actions. Due to the anti-neoplastic actions of thiazolidinedione that are independent of PPAR-, the role of PPAR- in carcinogenesis is still debatable. [2] This study will look at recent research on TZDs as anti-tumor agents in lung, breast, and colon carcinoma, the three most frequent cancers in the United States, as well as the potential processes through which Thiazolidinedione exerts its anti-cancer effects. Breast cancer is the most common cancer in women, and after lung cancer, it is the second-largest cause of cancer death in this group. Thiazolidinedione's effects on breast cancer have also been studied in various studies. [3]

A significant class of thiazolidinedione

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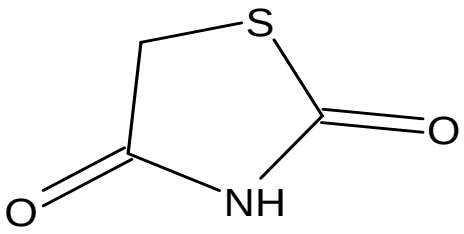
pharmacological activity functional groups. The number of anticancer drugs available in the market is vast, but there is a need to discover novel agents with better pharmacological activity properties with lesser or no side effects. Most of the thiazolidinedione exhibit good anticancer activity. The anticancer activity of thiazolidinedione derivatives is determined by the heterocyclic thiazolidine ring substitution. The current evaluated biological activities of thiazolidinedione can be enhanced by synthe-sizing substituted thiazolidinedione derivatives. This study will be focused on the enhancement of the anticancer activity of novel thiazolidinedione derivatives.[4]

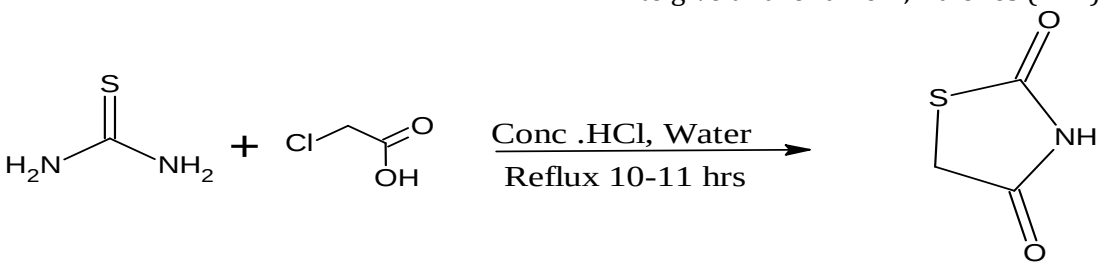


1,3-thiazolidine-2,4-dione

Basic ring of Thiazolidinediones.

Synthesis of thiazolidine-2,4-diones (TZD).

The synthesis of thiazolidine-2,4-dione utilized α-chloroacetic acid and thiourea as the starting material. This method includes the refluxing of α-chloroacetic acid with thiourea for 10- 11 hrs to give thiazolidine-2,4-diones (TZD).



thiourea chloroacetic acid

1,3-thiazolidine-2,4-dione

The biological significance of thiazolidine-ediones.

Thiazolidinediones are the key structure responsible for a wide range of biological activities. This ring has shown a variety of pharmacological activities. The biological research of Thiazolidinediones involves a variety of mechanisms also including enzymatic action and receptor-mediated mechanisms, among many others. The biological study of Thiazolidinediones has revealed that substitution at positions 2, 3, and 5 imparts different activities. As shown in **Fig 1** many commercial drugs containing Thiazolidi-nediones scaffolds exhibit a broad range of biological activities.

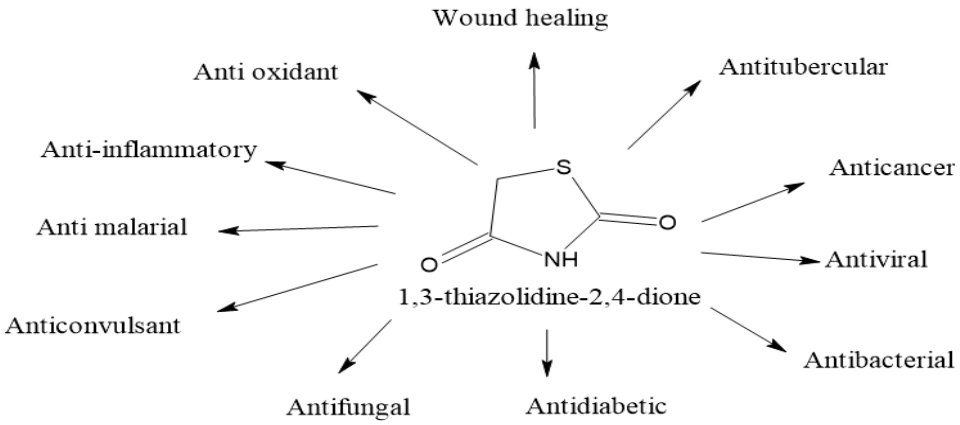
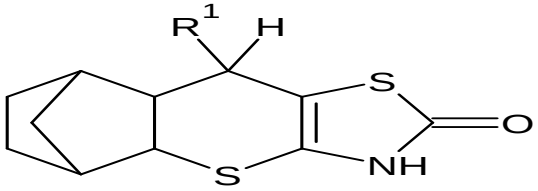


Fig 1 – Biological activities of Thiazolidinedione

Thiazolidinedione as an anti-cancer ligand.

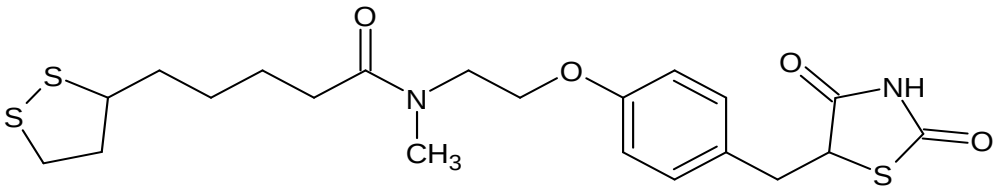
• Lesyk R. *et. al.,* had synthesized a new method for thiopyrano [2, 3-*d*] thiazol-2-ones with norbornane moiety by stereoselective hetero-Diel's alder reaction of 5-ylidene-4-thioxo-2-thiazolidone derivative with nor bornene. The synthesized compounds undergo *in-vitro* antitumor activity against 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 **1** exhibits 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. [1]



O=C1SC=2C([*])C3C4CC(CC4)C3SC=2N1

Compound 1

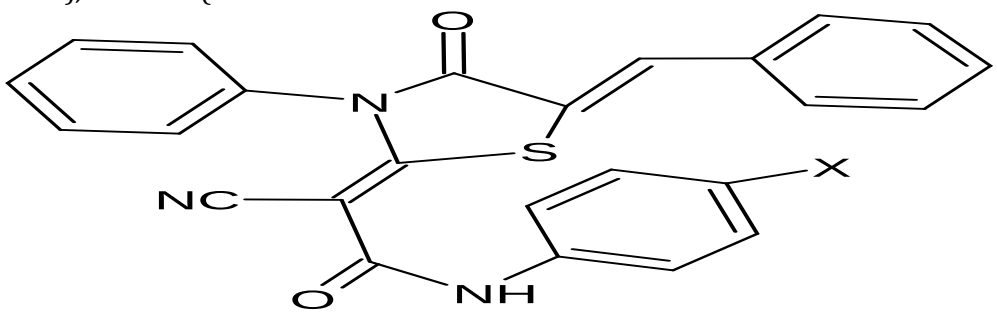
• Amar G.C. *et. al.*, had synthesized a unique class of hybrid lipoic thiazolidinedione derivatives and evaluated them for anticancer activity against normal and neoplastic cultured human cell types. Compound **2** exhibited the most potent activity with an EC50 value of 0.015 µM, Pioglitazone and Rosiglitazone were taken as a standard. [2]



O=C1NC(=O)SC1Cc1ccc(cc1)OCCN(C)C(=O)CCCCC1CCSS1

Compound 2

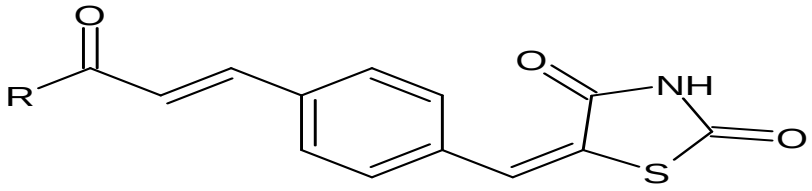
• Riham F. George *et. al.,* had synthesized a new method for the synthesis of 5-arylidene-4-thiazolidinones and 5-arylhydrazone analogs and evaluated them for *in-vitro* anticancer activity by SRB assay against HCT-116 (Colon cancer cell line), MCF-7 (Breast cancer cell line), and HEPG2 (Liver cancer cell line). Compound **3** (IC50: 7.89 µM respectively) is found to be the most active (Discovery Studio 2.5 software) and Doxorubicin is used as standard.[3]



Compound 3

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

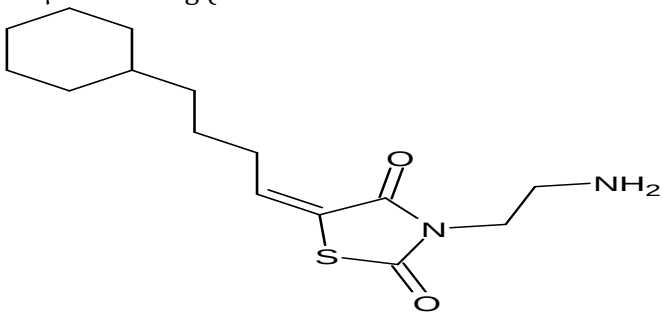
Tyr473. [4]



O=C1NC(=O)S\C1=C\c1ccc(/C=C/C([*])=O)cc1

Compound 4

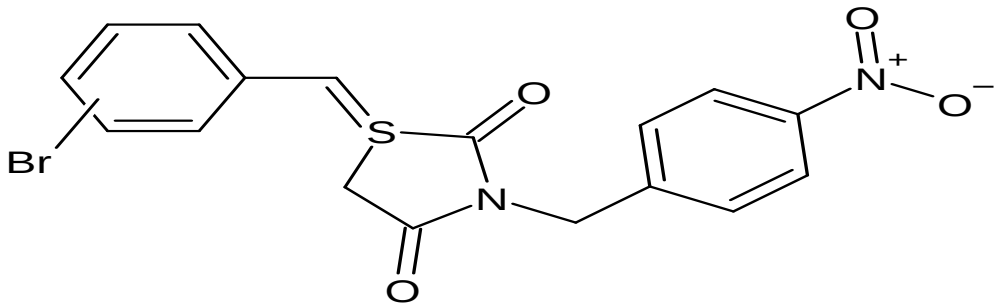
• Liu K. *et. al.,* had synthesized a new series of 2,5-disubstituted-thiazolidine-2,4-dione and evaluated their cytotoxic potential on U937, M12, and DU145 cancer cell lines by using [3-*H*]-thymidine incorporation assay. Compound **5** showed good anticancer activity with GI50 values of 1.40 µM-5.10 µM. Docking (PDB ID: 1s9j for MEK-1 and PDB ID: 3hhm for PI3Kα, Gold Software ver. 3.0) results suggest that compound **5** fits nicely into the ATP binding pocket of both MEK1 and PI3K signaling pathways. [5]



NCCN1C(=O)C(=C\CCCC2CCCCC2)/SC1=O

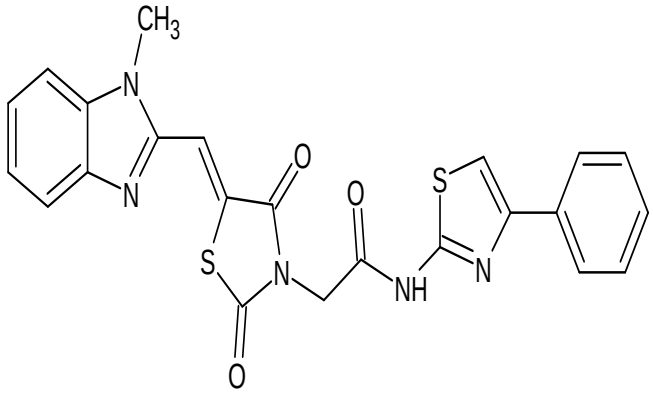
Compound 5

• Melo R. *et.al*., had synthesized a series of new di-substituted thiazolidinedione derivatives 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) Compound **6** exhibited most potent activity with IC50: >100 µM and Amsacrine was taken as a standard drug (PDB ID: 2HWQ, Gold software ver.5.1, Cambridge crystallographic data center). [6]



Compound 6

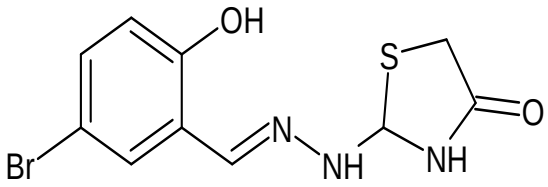
• Sharma P. *et. al.,* had synthesized new benzimidazole-thiazolidinedione hybrid molecules and evaluated for their cytotoxic potential by using MTT assay against selected human cancer cell lines of the prostate (PC-3 and DU-145), breast (MDA-MB-231), lung (A549), and a normal breast epithelial cell (MCF10A). Compound **7** was found the most potent derivative with IC50:11.46±1.46µM and 5-FU used as standard drug. [7]



O=C(Nc1nc(cs1)c1ccccc1)CN1C(=O)C(=C\c2nc3ccccc3n2C)\SC1=O

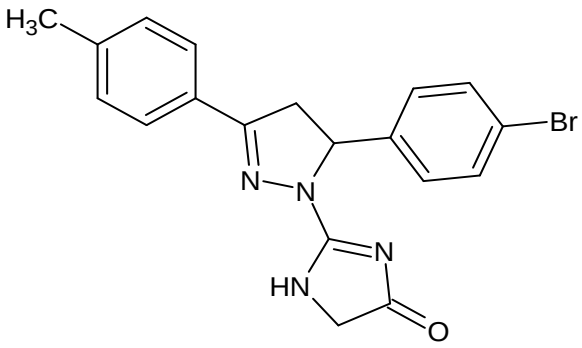
Compound 7

• Lv P.C. *et. al.,* had synthesized new derivatives of a thiazolidinedione and assayed for anticancer activity by solid-phase ELISA assay. Compound **8** showed significant results against MCF-7 cancer cell lines with an IC50 of 0.09 µM for EGFR and IC50, 0.42 µM for HER-2 using Erlotinib as a reference drug. [8]



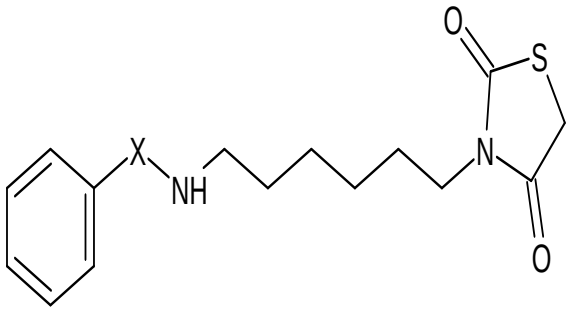
Compound 8

• Ke-Ming Q. *et.al*., had synthesized pyrazolyl-thiazolidinone derivatives and evaluated them for anticancer activity against MCF-7, B-16-F10, and HCT-116 cancer cell lines using solid-phase ELISA assay. Compound **9** exhibited the most potent activity with (IC50: 1.07 µM for HER-2 and 0.24 µM for EGFR). [9]



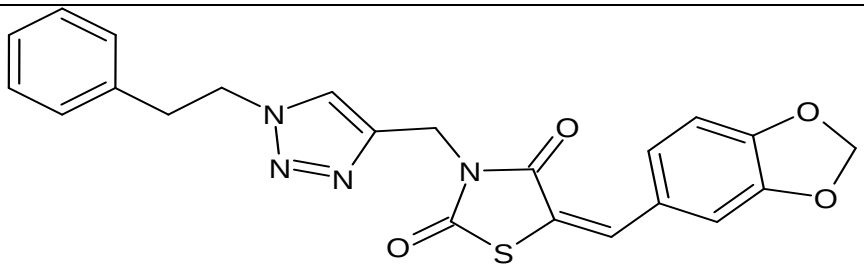
Compound 9

• Mohan R. *et. al*., had synthesized novel 2,4-thiazolidinedione derivatives as zinc chelating agents and evaluated them for anticancer activity by cell proliferation assay and HDAC enzyme assay against human liver cell lines, transformed (HepG2) and untransformed embryonic (WRL68) cell lines. Compound **10** (100 µM) was found to be the most potent about SB and SAHA as the positive control (PDB ID: 1c3s: MOE 2006.08). [10]



Compound 10

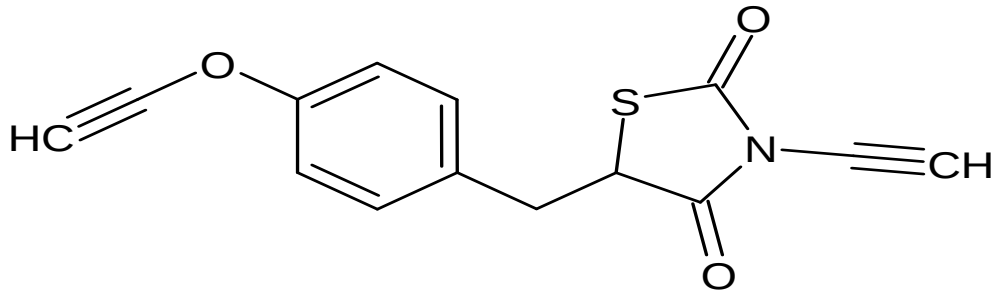
• Chinthala Y. *et. al*., had synthesized a new series of thiazolidinedione with triazole ring by Knoevenagel condensation and screened them for anticancer activity by MTT assay against IMR 32 (neuroblastoma), Hep G2 (Human Hema-toma), MCF-7 (breast adenocarcinoma) using Doxorubicin as the standard drug. Compound **11** was found to be the most potent having an IC50 value of Hep G2 (31µg/ml) and MCF-7 (30 µg/ml).[11]



O=C1S/C(=C/c2ccc3OCOc3c2)C(=O)N1Cc1nnn(CCc2ccccc2)c1

Compound 11

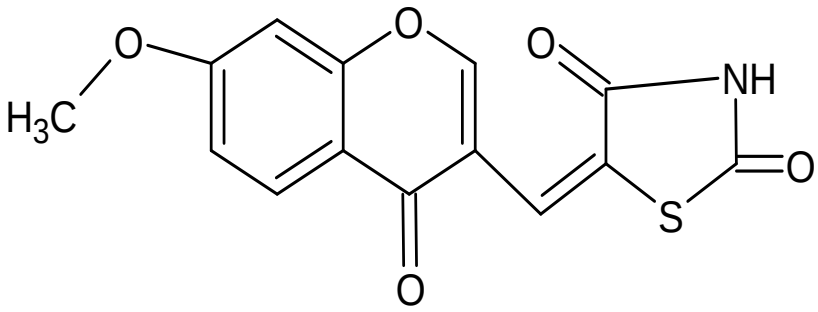
• Tahseen A. *et. al.,* had synthesized benzylidene thiazolidine 2,4-thiazolidone derivative and evaluated for anticancer activity by SRB assay against cancer cell lines DLD-1 and SW 620 (colon cancer cell lines), MCF-7, and MDA-MB-231 lines (breast cancer cell lines) Compound **12** showed the highest anticancer activity with an IC50: 7.5 µM (DLD-1), 10.8 µM (SW620), 8.4 µM (MCF-7) and 50.8 µM (MDA-MB-231). [12]



C#COc1ccc(CC2SC(=O)N(C#C)C2=O)cc1

Compound 12

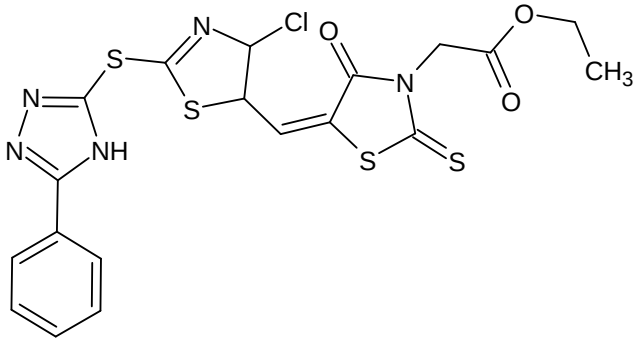
• Hoang Le T.A. *et.al.,* had synthesized new derivatives of chromonyl thiazolidine and evaluated them for anticancer activity against human epidermoid carcinoma (IC50: 44.1 ± 3.6 µg/ml) and breast cancer (IC50: 32.8 ± 1.4 µg/ml). Compound **13** was considered to be the most potent having stronger cytotoxicity compared to other derivatives with an IC50: 32.8 ± 1.4µg/ml and MCF-7 and Ellipticine were taken as standard. [13]



O=C1NC(=O)S\C1=C\C1=COc2cc(OC)ccc2C1=O

Compound 13

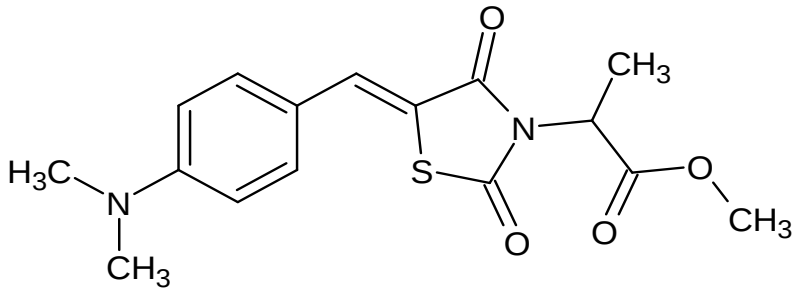
• Ozen C. *et.al.,* had synthesized thiazolyl-2,4-thiazolidinedione/rhodanine and evaluated them for anticancer activity against two hepatocellular carcinomas (HCC) cell lines, Huh7 and Plc/Prf/5 (Plc) by sulforhodamine B assay. Compound **14** (IC50: 2 to 16 µM) exhibits the most potent activity and Doxorubicin is used as a standard drug. [14]



O=C(OCC)CN1C(=S)S/C(=C/C2SC(=NC2Cl)Sc2nnc([NH]2)c2ccccc2)C1=O

Compound 14

• Bozic B, Rogan J, Poleti D, Rancic M, Trisovic N, Bozic B, Uscumlic G *et. al.,* had synthesized a series of six novel 2-(5-arylidene-2,4-dioxo tetrahydro thiazole-3-yl) propanoic acids and six corresponding methyl. Compound **15** was characterized by melting points, elemental analysis, FT-IR, ^{1}H, and ^{13}C NMR spectroscopy. Crystal structure of methyl-2-(5-(4-methoxy benzylidene)-2,4--dioxo tetrahydro thiazole-3-yl) propionate was confirmed by X-ray analysis. The antiproliferative activity of synthesized compounds against human colon cancer, breast cancer, and myelogenous leukemia cell lines, HCT-116, MDA-231, and K562, respectively, was evaluated. The results indicate that the antiproliferative activity of the synthesized esters is better than the activity of the corresponding acids. Synthesized compound **15** showed significant ant proliferative effects against HCT116 cells in all tested concentrations (0.01–100 μM). [15]

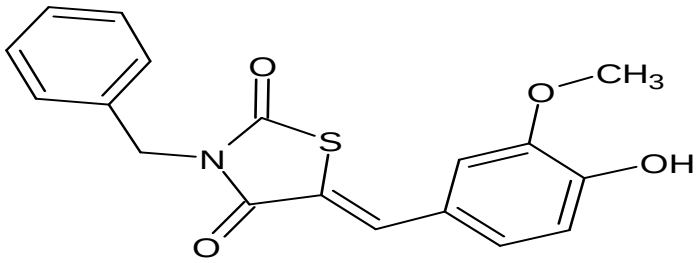


O=C1C(=C/c2ccc(cc2)N(C)C)/SC(=O)N1C(C)C(=O)OC

Compound 15

Thiazolidinedione as an antimicrobial ligand:

• Neeru Malik and D.N. Prasad *et.al.,* had synthesized N-substituted-5-benzylidene-2,4-thiazolidinedione derivatives. Compounds were then evaluated for their antimicrobial activity against the strains *Bacillus subtilis* and *E. coli.* using the cup plate method. The results obtained showed that out of 6 compounds, compound **16** exhibited significant activity. [16]

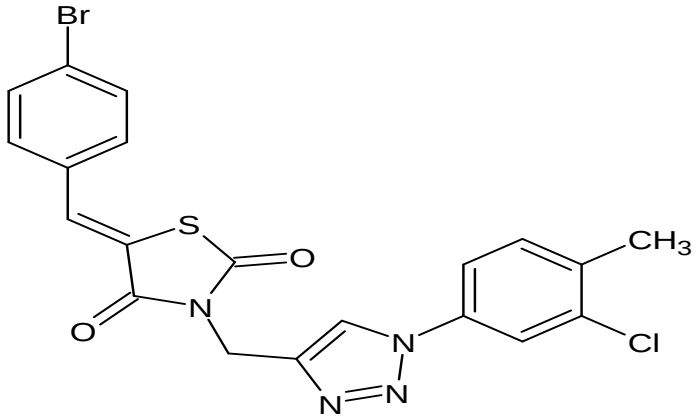


O=C1S\C(=C/c2ccc(O)c(OC)c2)C(=O)N1Cc1ccccc1

Compound 16

Thiazolidinedione as an anti-bacterial ligand:

• Sindhu J, Singh H, Khurana JM, Sharma C, Aneja KR, *et al.* had synthesized a series of novel thiazolidinedione–triazole hybrids by one-pot reaction between thiazolidine-2,4-dione, substi-tuted aryl aldehydes, propargyl bromide and substituted aryl azides using piperidine, $CuSO_4 \cdot 5H_2O$ and sodium ascorbate as catalysts in PEG-400 as a highly efficient and green media. These thiazolidinedione–triazole hybrids were subjected to *in vitro* antibacterial activity against four strains namely, *Staphylococcus aureus*, *Bacillus subtilis*, Escherichia *coli*, *Pseudomonas aeruginosa*, and antifungal activity against two fungal strains namely , *Aspergillus niger* and *Aspergillus flavus.* Compound **17** showed significant antibacterial activity. [17]

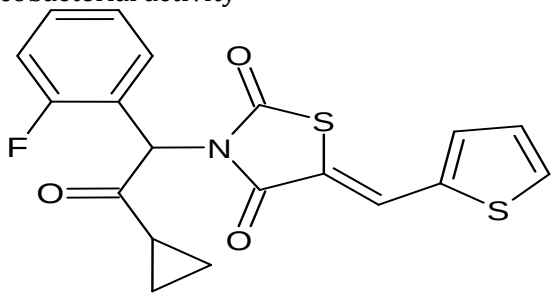


O=C1S\C(=C/c2ccc(Br)cc2)C(=O)N1Cc1nnn(c1)c1ccc(C)c(Cl)c1

Compound 17

Thiazolidinedione as an antimyco-bacterial ligand:

• Ponnuchamy S, Kanchithalaivan S, Kumar RR, Ali MA, Choon TS (2014), *et.al.,* had synthesized a series of novel hybrid heterocycles comprising arylidene thiazolidine-2, 4-dione and 1-cyclopropyl-2-(2-fluorophenyl) ethanone. These compounds were evaluated for their antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv in the High Throughput Screen. Most of the hybrid arylidene thiazolidine-2,4-diones displayed moderate to good activity with MIC of less than 50 µM. Compound **18** exhibited maximum potency being 5.87-fold more active at EC50 and 6.26-fold more active at EC90 than the standard drug pyrimethamine. [18]



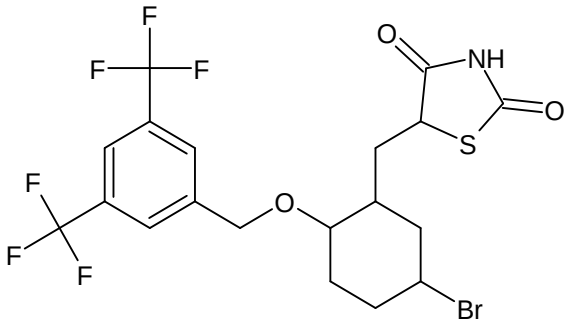
O=C(C(N1C(=O)C(=C/c2cccs2)/SC1=O)c1ccccc1F)C1CC1

Compound 18

Thiazolidinedione as an antihyperglycemic ligand:

• Bhattarai BR, Kafle B, Hwang JS, Khadka D, Lee SM, Kang JS, Ham SW, Han IO, Park H, Cho H *et. al.,* had synthesized Benzylidene-2,4-thiazolid-inedione derivatives with substitutions on the phenyl ring at the *ortho* or *para* positions of the thiazolidinedione (TZD) group as PTP1B inhibitors with IC50 values in a low micromolar range. Compound **19**, the lowest, bore an IC50 of 5.0 µM. *In vivo* efficacy of compound **19** as an anti-obesity nand hypoglycemic agent was evaluated in a mouse model system. Significant improvement in glucose tolerance was

observed. This compound also significantly suppressed weight gain and significantly improved blood parameters such as TG, total cholesterol, and NEFA. Compound **19** was also found to activate peroxisome proliferator-activated receptors (PPARs) indicating multiple mechanisms of action. [19]

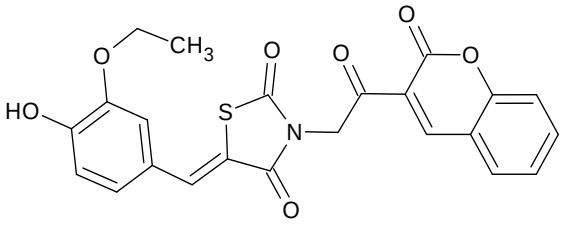


FC(F)(F)c1cc(cc(c1)C(F)(F)F)COC1CCC(Br)CC1CC1SC(=O)NC1=O

Compound 19

Thiazolidinedione as an antioxidant ligand:

- Mishra G, Sachan N, Chawla P *et. al.,* had synthesized benzylidene thiazolidinediones by facile Knoevenagel condensation reaction using various substituted aldehydes, thiourea and chloroacetic acid. Further, 3-Bromo acetyl coumarins were synthesized using salicylaldehyde and ethyl acetoacetate in the presence of piperidine as a catalyst forming 3-acetyl coumarin which was brominated to form 3-Bromo acetyl coumarin. The synthesized compounds were screened for different biological activities. Antioxidant activity was performed *in-vitro* by three different methods namely FRAP (Ferric ion reducing antioxidant power) method, DPPH (1,1-diphenyl-2-picrylhydrazyl) method, and hydrogen peroxide scavenging assay method using ascorbic acid as a standard. Among the synthesized compounds. compound **20** emerged as a breakthrough antioxidant agent. Furthermore, the compounds were checked for their anti-inflammatory and antidiabetic activity in which comp-ound **20** showed promising anti-inflammatory and antidiabetic potential. [20]

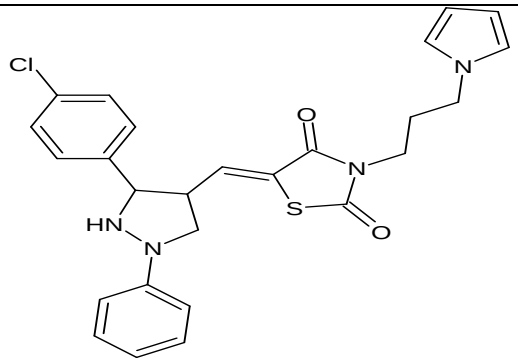


O=C(CN1C(=O)C(=C/c2ccc(O)c(OCC)c2)/SC1=O)C1=Cc2ccccc2OC1=O

Compound 20

Thiazolidinedione as an antifungal ligand:

- Desai NC, Satodiya HM, Rajpara KM, Joshi VV, Bhatt K, Vaghani HV *et.al.,* had synthesized *N*-substituted thiazolidinedione-pyrazole based 3-(3-(1*H*-pyrrole-1-yl) propyl)-5-((3-(substituted phenyl)-1-phenyl-1*H*-pyrazole-4-yl) methylene) thiazolidine-2,4-diones in two successive steps. The initial step involves Knoevenagel type condensation of 3-(substituted phenyl)-1-phenyl-1H-pyrazole-4-carbaldehydes with thiazolidine-2,4-dione to furnish intermediate compounds Finally, target compounds were achieved via a one-pot reaction of compounds 1,3-dibromo propane, and 1*H*-pyrrole. The chemical structures of all the newly synthesized compounds were established based on IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. All the synthesized compounds were evaluated for their *in vitro* antimicrobial activity. compound **21** showed significant anti-fungal activity. [21]

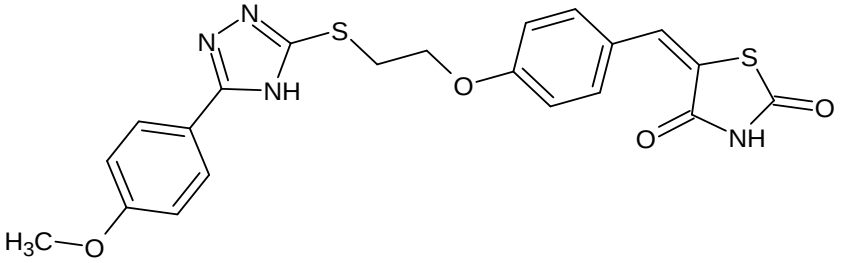


O=C1S\C(=C/C2CN(NC2c2ccc(Cl)cc2)c2ccccc2)C(=O)N1CCCn1cccc1

Compound 21

Thiazolidinedione as a hypoglycemic and hypolipidemic ligand:

• Iqbal AKM, Khan AY, Kalashetti MB, Belavagi NS, Gong YD, Khazi IAM *et. al.,* had synthesized novel thiazolidinedione derivatives by incorporating pharmacologically significant heterocycles viz, substituted thiazole, triazole, and oxadiazole moieties linked to the central phenyl ring *via* heteroatom linkage with one/two carbon spacer as the structural analogs of Pioglitazone by employing multistep synthetic protocols. Structures of all the newly synthesized intermediates and target molecules were established by analytical and spectral data. These newly synthesized compounds were screened for their *in vivo* hypoglycemic and hypolipidemic activities in male Westar rats. Synthesized compound **22** demonstrated good activity. [22]

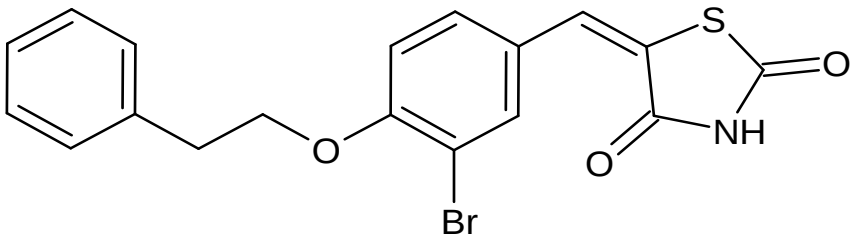


O=C1NC(=O)S\C1=C\c1ccc(OCCSc2nnc([NH]2)c2ccc(OC)cc2)cc1

Compound 22

Thiazolidinedione as a wound healing ligand:

• Piao *et. al.,* had synthesized new potent 15-PGDH inhibitor, 5-(3-bromo-4-phenethoxybenzylidene) thiazolidine-2,4-dione (TD1-91), with an IC_{50} of 4 nm. and tested cell-based wound healing effects. This compound significantly increased the level of PGE_2 (451 pg/mL) in A549 cells, which was about 7-fold higher than that of control. HaCaT cells exposed to TD19. Compound **23** showed significantly improved wound healing after 48 h in scratch wound healing test. [23]

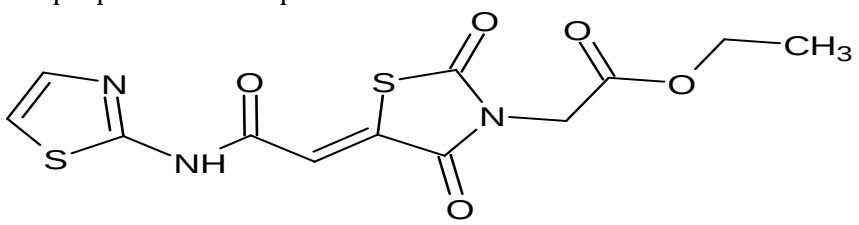


O=C1NC(=O)S\C1=C\c1ccc(OCCc2ccccc2)c(Br)c1

Compound 23

Thiazolidinedione as an anticonvulsant ligand:

• Roman Lesyk *et. al.,* had synthesized new potent(2,4-dioxo-5-(thiazol-2-ylcarbamoylm-ethylene)-thiazolidin-3-yl) acetic acid ethyl ester. Anticonvulsant properties of compounds was evaluated in two different models pentylenetetrazol-induced seizures and maximal electroshock seizure tests. Compound **24** showed excellent anticonvulsant activity in both models. [24]

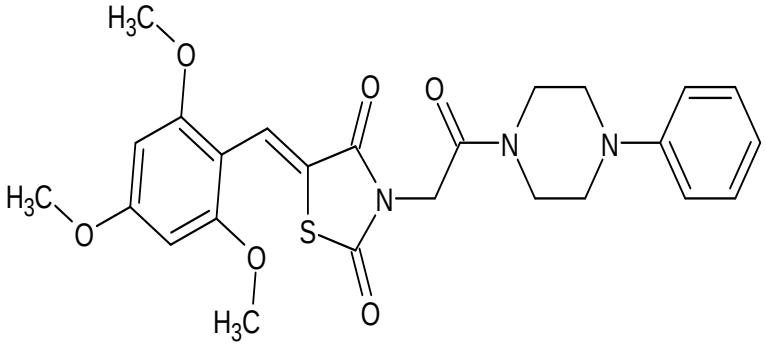


O=C(\C=C1/SC(=O)N(CC(=O)OCC)C1=O)Nc1nccs1

Compound 24

Thiazolidinedione as an anti-malarial ligand:

• Sharma *et al*. synthesized a series of thiazolidinedione as *plasmodium falciparum cysteine protease falcipain-2* inhibitor as well as antiparasitic. Compound **25** showed modest activity due to presence of methyl substituents bore an IC50 of 45.33. [25]



O=C(CN1C(=O)C(=C/c2c(OC)cc(OC)cc2OC)/SC1=O)N1CCN(CC1)c1ccccc1

Compound 25

All the structures mentioned in the article were collected from the chemsketch data base. [26]

In-silico target prediction

The Thiazolidinedione nucleus structure was drawn using Swiss ADME software and it was tested for its possible targets through Swiss Target prediction. Using this software prediction tool, it was found that the thiazolidinedione nucleus can bind with 33.3% of Kinases, 26.7% of Enzymes, 13.3% of Phosphodiesterase, 13.3% of Family A G protein coupled receptor and so on. The results of *in-silico* target prediction are displayed in **Fig 2, 3.a, 3.b, 3.c, 3.d, 3.e, 3.f, 3.g.** The list of targets is displayed according to their probability and affinity towards the Thiazolidinedione nucleus. [27,28]

Swiss target prediction for thiazolidinedione derivatives

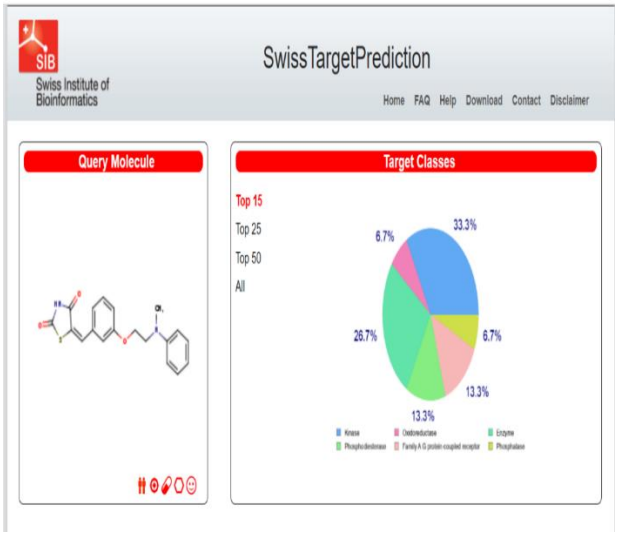


Fig 2 – Target classes of Thiazolidinedione (Using Swiss target prediction)

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Serine/threonine-protein kinase PIM1	PIM1	P11309	CHEMBL2147	Kinase		84 / 39
Cyclooxygenase-2	PTGS2	P35354	CHEMBL230	Oxidoreductase		204 / 4
Serine/threonine-protein kinase PIM2	PIM2	Q9P1W9	CHEMBL4523	Kinase		48 / 37
15-hydroxyprostaglandin dehydrogenase [NAD+]	HPGD	P15428	CHEMBL1293255	Enzyme		105 / 75
Nitric oxide synthase, inducible	NOS2	P35228	CHEMBL4481	Enzyme		29 / 1
Serine/threonine-protein kinase PIM3	PIM3	Q86V86	CHEMBL5407	Kinase		29 / 16
Insulin-like growth factor I receptor	IGF1R	P08069	CHEMBL1957	Kinase		245 / 22
Phosphodiesterase 4B	PDE4B	Q07343	CHEMBL275	Phosphodiesterase		102 / 13
PI3-kinase p110-gamma subunit	PIK3CG	P48736	CHEMBL3267	Enzyme		335 / 54
PI3-kinase p110-alpha subunit	PIK3CA	P42336	CHEMBL4005	Enzyme		973 / 23
G-protein coupled receptor 35	GPR35	Q9HC97	CHEMBL1293267	Family A G protein-coupled receptor		0 / 1
Protein-tyrosine phosphatase 1B	PTPN1	P18031	CHEMBL335	Phosphatase		167 / 57
Serine-protein kinase ATM	ATM	Q13315	CHEMBL3797	Kinase		5 / 0
Phosphodiesterase 4D	PDE4D	Q08499	CHEMBL288	Phosphodiesterase		62 / 0
Dopamine D4 receptor	DRD4	P21917	CHEMBL219	Family A G protein-coupled receptor		121 / 0

Fig: 3.a – List of targets for Thiazolidinedione

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Plasma retinol-binding protein	RBP4	P02753	CHEMBL3100	Secreted protein		7 / 0
Aldose reductase	AKR1B1	P15121	CHEMBL1900	Enzyme		40 / 31
Sodium channel protein type IX alpha subunit	SCN9A	Q15858	CHEMBL4296	Voltage-gated ion channel		1105 / 1
Monoamine oxidase A	MAOA	P21397	CHEMBL1951	Oxidoreductase		50 / 4
Monoamine oxidase B	MAOB	P27338	CHEMBL2039	Oxidoreductase		84 / 7
Prostanoid EP1 receptor	PTGER1	P34995	CHEMBL1811	Family A G protein-coupled receptor		78 / 0
Phosphodiesterase 4A	PDE4A	P27815	CHEMBL254	Phosphodiesterase		78 / 0
Phosphodiesterase 3B	PDE3B	Q13370	CHEMBL290	Phosphodiesterase		34 / 0
Phosphodiesterase 4C	PDE4C	Q08493	CHEMBL291	Phosphodiesterase		8 / 0
Steryl-sulfatase	STS	P08842	CHEMBL3559	Enzyme		13 / 0
Phosphodiesterase 10A	PDE10A	Q9Y233	CHEMBL4409	Phosphodiesterase		882 / 0
Phosphodiesterase 5A	PDE5A	O76074	CHEMBL1827	Phosphodiesterase		96 / 0
GABA receptor alpha-1 subunit	GABRA1	P14867	CHEMBL1962	Ligand-gated ion channel		9 / 0
GABA receptor alpha-5 subunit	GABRA5	P31644	CHEMBL5112	Ligand-gated ion channel		150 / 0
Beta-secretase 1	BACE1	P56817	CHEMBL4822	Protease		418 / 0

Fig: 3.b – List of targets for Thiazolidinedione

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
G protein-coupled receptor 44	PTGDR2	Q9Y5Y4	CHEMBL5071	Family A G protein-coupled receptor		59 / 0
Epoxide hydratase	EPHX2	P34913	CHEMBL2409	Protease		163 / 0
Phosphodiesterase 7A	PDE7A	Q13946	CHEMBL3012	Phosphodiesterase		81 / 0
p53-binding protein Mdm-2	MDM2	Q00987	CHEMBL5023	Other nuclear protein		301 / 0
Serine/threonine-protein kinase mTOR	MTOR	P42345	CHEMBL2842	Kinase		454 / 0
N-acylsphingosine-amidohydrolase	NAAA	Q02083	CHEMBL4349	Enzyme		20 / 0
MAP kinase-interacting serine/threonine-protein kinase MNK1	MKNK1	Q9BUB5	CHEMBL4718	Kinase		23 / 0
Androgen Receptor	AR	P10275	CHEMBL1871	Nuclear receptor		253 / 0
Cannabinoid receptor 1 *(by homology)*	CNR1	P21554	CHEMBL218	Family A G protein-coupled receptor		465 / 0
TGF-beta receptor type I	TGFBR1	P36897	CHEMBL4439	Kinase		35 / 0
Cyclin-dependent kinase 1/cyclin B1	CDK1 CCNB1	P06493 P14635	CHEMBL1907602	Other cytosolic protein		34 / 0
Sodium channel protein type V alpha subunit	SCN5A	Q14524	CHEMBL1980	Voltage-gated ion channel		51 / 0
Dual specificity phosphatase Cdc25A	CDC25A	P30304	CHEMBL3775	Phosphatase		19 / 0
C-C chemokine receptor type 5	CCR5	P51681	CHEMBL274	Family A G protein-coupled receptor		8 / 0
Sigma opioid receptor	SIGMAR1	Q99720	CHEMBL287	Membrane receptor		93 / 0

Fig: 3.c – List of targets for Thiazolidinedione

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Lymphocyte differentiation antigen CD38	CD38	P28907	CHEMBL4660	Enzyme		20 / 0
Solute carrier family 22 member 12	SLC22A12	Q96S37	CHEMBL6120	Electrochemical transporter		162 / 0
Corticotropin releasing factor receptor 1	CRHR1	P34998	CHEMBL1800	Family B G protein-coupled receptor		398 / 0
Cytochrome P450 19A1	CYP19A1	P11511	CHEMBL1978	Cytochrome P450		118 / 0
Prostanoid EP3 receptor	PTGER3	P43115	CHEMBL3710	Family A G protein-coupled receptor		269 / 0
Prostanoid FP receptor	PTGFR	P43088	CHEMBL1987	Family A G protein-coupled receptor		19 / 0
Bradykinin B2 receptor	BDKRB2	P30411	CHEMBL3157	Family A G protein-coupled receptor		13 / 0
Hormone sensitive lipase	LIPE	Q05469	CHEMBL3590	Enzyme		24 / 0
Sodium/glucose cotransporter 1	SLC5A1	P13866	CHEMBL4979	Electrochemical transporter		184 / 0
Melatonin receptor 1A	MTNR1A	P48039	CHEMBL1945	Family A G protein-coupled receptor		161 / 0
Adenosine A1 receptor	ADORA1	P30542	CHEMBL226	Family A G protein-coupled receptor		657 / 0
Adenosine A2a receptor	ADORA2A	P29274	CHEMBL251	Family A G protein-coupled receptor		737 / 0
Adenosine A2b receptor	ADORA2B	P29275	CHEMBL255	Family A G protein-coupled receptor		238 / 0
Adenosine A3 receptor	ADORA3	P0DMS8	CHEMBL256	Family A G protein-coupled receptor		335 / 0
Cholecystokinin B receptor	CCKBR	P32239	CHEMBL298	Family A G protein-coupled receptor		129 / 0

Fig: 3.d – List of targets for Thiazolidinedione

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
P2X purinoceptor 7	P2RX7	Q99572	CHEMBL4805	Ligand-gated ion channel		134 / 0
Bromodomain-containing protein 4	BRD4	O60885	CHEMBL1163125	Reader		173 / 0
HERG	KCNH2	Q12809	CHEMBL240	Voltage-gated ion channel		111 / 0
Phosphodiesterase 8B	PDE8B	O95263	CHEMBL4408	Phosphodiesterase		41 / 0
Tyrosine-protein kinase BTK	BTK	Q06187	CHEMBL5251	Kinase		36 / 0
Acetylcholinesterase	ACHE	P22303	CHEMBL220	Hydrolase		114 / 0
Cathepsin L	CTSL	P07711	CHEMBL3837	Protease		106 / 0
Vanilloid receptor *(by homology)*	TRPV1	Q8NER1	CHEMBL4794	Voltage-gated ion channel		231 / 0
Tissue-type plasminogen activator	PLAT	P00750	CHEMBL1873	Protease		13 / 0
Serotonin 2a (5-HT2a) receptor	HTR2A	P28223	CHEMBL224	Family A G protein-coupled receptor		98 / 0
Serotonin 6 (5-HT6) receptor	HTR6	P50406	CHEMBL3371	Family A G protein-coupled receptor		73 / 0
Muscle glycogen synthase	GYS1	P13807	CHEMBL4000	Enzyme		11 / 0
Cyclin-dependent kinase 2/cyclin E	CCNE2 CDK2 CCNE1	O96020 P24941 P24864	CHEMBL2094126	Other cytosolic protein		70 / 0
Hexokinase type IV	GCK	P35557	CHEMBL3820	Enzyme		107 / 0
Prostanoid EP4 receptor	PTGER4	P35408	CHEMBL1836	Family A G protein-coupled receptor		62 / 0

Fig: 3.e – List of targets for Thiazolidinedione

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Prostanoid EP2 receptor	PTGER2	P43116	CHEMBL1881	Family A G protein-coupled receptor		27 / 0
Type-1 angiotensin II receptor	AGTR1	P30556	CHEMBL227	Family A G protein-coupled receptor		246 / 0
Phosphodiesterase 2A	PDE2A	O00408	CHEMBL2652	Phosphodiesterase		127 / 0
Metabotropic glutamate receptor 5	GRM5	P41594	CHEMBL3227	Family C G protein-coupled receptor		168 / 0
Voltage-gated potassium channel subunit Kv1.3	KCNA3	P22001	CHEMBL4633	Voltage-gated ion channel		44 / 0
Interferon-induced, double-stranded RNA-activated protein kinase	EIF2AK2	P19525	CHEMBL5785	Kinase		8 / 0
Tyrosine-protein kinase receptor FLT3	FLT3	P36888	CHEMBL1974	Kinase		134 / 0
Cyclin-dependent kinase 2/cyclin A	CDK2 CCNA1 CCNA2	P24941 P78396 P20248	CHEMBL2094128	Other cytosolic protein		90 / 0
Cytochrome P450 1A1	CYP1A1	P04798	CHEMBL2231	Cytochrome P450		2 / 0
Cannabinoid receptor 2	CNR2	P34972	CHEMBL253	Family A G protein-coupled receptor		452 / 0
Tyrosine-protein kinase JAK2	JAK2	O60674	CHEMBL2971	Kinase		373 / 0
Cytochrome P450 1A2	CYP1A2	P05177	CHEMBL3356	Cytochrome P450		7 / 0
Cytochrome P450 1B1	CYP1B1	Q16678	CHEMBL4878	Cytochrome P450		5 / 0
Serine/threonine-protein kinase EEF2K	EEF2K	O00418	CHEMBL5026	Kinase		7 / 0
Thromboxane-A synthase	TBXAS1	P24557	CHEMBL1835	Cytochrome P450		14 / 0

Fig: 3.f – List of targets for Thiazolidinedione

Target	Common name	Uniprot ID	ChEMBL ID	Target Class	Probability*	Known actives (3D/2D)
Small ubiquitin-related modifier 1	SUMO1	P63165	CHEMBL2146296	Unclassified protein		1 / 0
Tyrosine-protein kinase JAK1	JAK1	P23458	CHEMBL2835	Kinase		214 / 0
Tyrosine-protein kinase TYK2	TYK2	P29597	CHEMBL3553	Kinase		87 / 0
Group X secretory phospholipase A2	PLA2G10	O15496	CHEMBL4342	Enzyme		9 / 0
C-C chemokine receptor type 9	CCR9	P51686	CHEMBL5815	Family A G protein-coupled receptor		26 / 0
ADAMTS5	ADAMTS5	Q9UNA0	CHEMBL2285	Protease		14 / 18
Histone deacetylase 2	HDAC2	Q92769	CHEMBL1937	Eraser		54 / 0
Serine/threonine-protein kinase Aurora-B	AURKB	Q96GD4	CHEMBL2185	Kinase		225 / 0
Histone deacetylase 1	HDAC1	Q13547	CHEMBL325	Eraser		117 / 0
Bromodomain-containing protein 3	BRD3	Q15059	CHEMBL1795186	Reader		72 / 0

Fig: 3.g – List of targets for Thiazolidinedione

Conclusion:

Thiazolidinedione is a dynamic nucleus, and its potency is demonstrated by its various activities such as antidiabetic, anti-inflammatory, wound healing, antifungal, anti-tubercular, antiviral, antibacterial activity, antitumor activity, and anticonvulsant activity. The potency of the synthesized derivatives is influenced by the nature and position of the substituents attached to the thiazolidinedione nucleus. The *In-silico* prediction also showed that nearly 100 possible targets are available for the Thiazolidinedione nucleus in the human body. This can be taken into consideration that the Thiazolidinedione nucleus can play an important role in the development of a novel therapeutic agent. Hence, more attention should be given during the alteration and newer substitutions of this nucleus to investigate better and newer biological activities which can lead to development of a novel therapeutic molecule /compound for the treatment of severe diseases like cancer, diabetes, hypertension, and neurodegenerative diseases. To improve the design strategy, researchers should focus on structural activity relationship studies as well as its ligand binding studies of the selected nucleus. The writers of the presented article summarized various synthetic routes of thiazolidine as well as their prominent activities. The scientific community will benefit from this review to develop lead compounds or clinical candidates from the selected nucleus in various biological areas.

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