Review Article

Recent Pharmacological Developments on Rhodanines and 2,4-Thiazolidinediones

Ravinder Singh Bhatti,¹ Sakshi Shah,² Suresh,² Pawan Krishan,¹ and Jagir S. Sandhu²

¹ Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147 002, India

² Department of Chemistry, Punjabi University, Punjab, Patiala 147 002, India

Correspondence should be addressed to Suresh; jind.suresh7@rediffmail.com

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Thiazolidines are five-member heterocyclic having sulfur, nitrogen, and oxygen atoms in their ring structure and exhibiting potent as well as wide range of pharmacological activities. In this minireview, recent updates on synthesis and pharmacological evaluations of molecules based on 2,4-thiazolidine and rhodanine are discussed.

1. Introduction

Five-membered heterocyclic molecules containing thiazole nucleus with carbonyl group on fourth carbon such as rhodanine and 2,4-thiazolidinedione derivatives have broad spectrum of pharmacological activities. In past two decades, rhodanines and 2,4-thiazolidinediones have emerged as potent antidiabetic agents. Some of them are clinically used such as ciglitazone, englitazone, pioglitazone, glitazones, epalrestat, and troglitazone for the treatment of type 2 diabetes mellitus and related complications. This is the reason why investigation/molecular modification and pharmacological evaluation of these molecules have attracted special attention of synthetic chemists and pharmacologists, respectively.

Rhodanine

2, 4-Thiazolidinedione

In recent years, a number of synthetic/pharmacological protocols based on these molecules have been emerged extensively and in witness available in the literature. These multifaceted molecules exhibit varied type of biological activities. Some recent developments in synthesis and pharmacology of these molecules are discussed in this section.

2. Recent Developments in Rhodanine Pharmacology

In 1997, Boyd carried out a study based on rhodanine-containing molecules of pharmaceutical interest and found pharmacological importance of these molecules is limited because of poor solubility of rhodanine derivatives in water (exception of rhodanine-3-acetic acids). However, these compounds exhibit a broad range of significant biological activities [1]. Rhodanine-3-acetic acid (RAA) **1** was prepared by Korner [2] in 1908, and Knoevenagel condensation products of the acid with various aldehydes, namely, [(5*Z*)-(5-benzylidene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl)]acetic acids **2** were reported in the same year [3]. From 1960 onwards, studies revealed that such type of molecule exhibit potential antimycobacterial [4, 5], antifungal [6–15], pesticidal [16–18], antihypertensive [19], and antineoplastic [20, 21] activities. Their NMR characterization performed in 1982 [22]. In 2006, similar derivatives have been prepared under microwave irradiation [23]. Further, the Knoevenagel products of rhodanine-3-acetic acid with pyridinecarbaldehydes were prepared in 1961 and they possess potential antibacterial and antifungal activities [8]. {(5*Z*)-[4-Oxo-5-(pyridin-2-ylmethylidene)-2-thioxo-1,3-thiazolidin-3-yl]}acetic acid **3** were patented as a potential drug for the treatment of metabolic bone diseases [24, 25]. Later, it was found out

that they stimulate parathyroid hormone receptor-mediated cAMP formation and could be useful for the local and systemic treatment of rheumatoid arthritis, osteoarthritis, and degenerative arthrosis [24, 25].

Trypanocidal activity of substituted rhodanine-3-acetic acids has been reported recently [26]. The only rhodanine acetic acid derivative that has been used clinically is the aldose reductase inhibitor epalrestat **4**. It was marketed in Japan and used to slow eye damage associated with diabetes and to prevent diabetic peripheral neuropathy [1, 22, 27–29]. Aldose reductase is not the only enzyme inhibited by rhodanine carboxylic acids. It was found that many other enzymes are also inhibited by the derivatives of this structural class and may be responsible for their various biological effects [30]. Other rhodanine-based molecules have also been popular as small molecule inhibitors of numerous targets such as hepatitis C viral (HCV) NS3 protease [31], antidiabetic mechanism [32], aldose reductase [33], β -lactamase [34, 35], histidine decarboxylase [36], and JNK Stimulatory Phosphatase-1 (JSP-1) [37]. This section is a brief account on synthesis and biological effects and recent developments of newly prepared potential drugs based on nitrogen-sulphur containing heterocycles having rhodanine nucleus.

2.1. Rhodanine as Antidiabetic Agent. Murugana et al. synthesized [38] a series of dispiropyrrrolidines **5** (16-compounds) by 1,3-dipolar cycloaddition reaction of azomethine ylides (*in situ* generated by the reaction of sarcosine with isatin) with 5-arylidene-1,3-thiazolidine-2,4-dione and 5-arylidene-4-thioxo-1,3-thiazolidine-2-one derivatives as dipolarophiles. They performed molecular docking studies on 1FM9 protein and screened synthesized compounds for their antidiabetic activity on male Wistar rats (after alloxan treatment). The synthesized compounds exhibited attractive antidiabetic properties and are more effective than rosiglitazone in ameliorating stress conditions.

2.2. Rhodanine as Antiapoptotic Agent. Xing and his co-worker synthesized, a series of BH3I-1 based dimeric modulators of **6**. The overexpression of antiapoptotic Bcl-2 proteins which protects cells from apoptosis is one mechanism for tumours to acquire drug resistance. In this study they found dimeric modulators **7–8** have enhanced binding activity against antiapoptotic Bcl-2 proteins and proved dimerization of monomeric modulators is one practical approach to enhance the bioactivity of Bcl-2 antagonists [39].

Moorthy and his group [40] designed and synthesized 5-isopropylidene derivatives of 5-benzilidene-3-ethyl rhodanine (BTR-1) **9**, 3-dimethyl-2-thio-hydantoin (ITH-1) **10**, and 3-ethyl-2-thio-2,4-oxazolidinedione (ITO-1) **11** and tested their chemotherapeutic properties. They found all the compounds induced cytotoxicity in a time- and concentration-dependent manner on leukemic cell line, CEM. Among these compounds, BTR-1 **9** was found to be manifold more potent in inducing cytotoxicity than ITH-1 **10** and ITO-1 **11** with an IC50 value of $<10 \mu\text{M}$ and affected cell division by inducing a block at S phase, which finally led to the activation of apoptosis.

The same research group reported [41] the synthesis of 5-isopropylidene-3-ethyl rhodanine **12** by conventional and microwave-assisted method, and they found that rhodanine ITR **12** treatment led to cytotoxicity in leukemic cell line, CEM, by inducing apoptosis.

2.3. Rhodanine as Antimicrobial Agent. Habib et al. reacted [42] thiazolo[4,5-d]pyrimidines with rhodanines and investigated the obtained products (7 compounds with 60–80% yields) **13** for antimicrobial screening and they found antifungal activity against *Aspergillus niger* and *Penicillium* sp. with IZ 20–38 mm and MIC <50 – $<25 \mu\text{g/mL}$. They claimed compound **14** is the most active against *Aspergillus niger* while compound **15** is the most active against *Penicillium* sp.; and 5-fold less active than the standard antibiotic clotrimazole. They concluded that the presence of an alkyl group at position 3 of the thiazolopyrimidine ring **14** is superior to that of other aromatic substituents; also the introduction of an arylideneamino group at position 6 of **15** enhanced the antifungal activity.

Opperman and his group disclosed [43] that aryl rhodanines **16–19** did not exhibit antibacterial activity against any of the bacterial strains tested and are not cytotoxic against HeLa cells. Their study revealed that the aryl rhodanines **16–19** specifically inhibit the early stages of biofilm development by preventing attachment of the bacteria (specifically inhibit biofilm formation of *S. aureus*, *S. epidermidis*, *Enterococcus faecalis*, *E. faecium*, and *E. gallinarum* but not the Gram-negative species *Pseudomonas aeruginosa* or *Escherichia coli*.) to surfaces.

MBX-1246

17

MBX-1384

18

MBX-1427

19

Sim and his associates reported [44] benzyldiene rhodanines **20–22** as novel inhibitors of uridine diphospho-N-acetylmuramate/L-alanine ligase. They observed that compounds **20–22** exhibit selective whole-cell activity against the Gram-positive methicillin resistant *Staphylococcus aureus* (MRSA) but not against the Gram-negative *Escherichia coli*. They also evaluated their cytotoxic effect on mammalian Chinese hamster ovary (CHO) cells.

20

21

22

Hardej et al. synthesized [45] a series of glycine and phenylalanine-derived rhodanine analogs and evaluated their anti-MRSA activity. The antibacterial activity of compounds **23** and **24** against a panel of MRSA strains was significantly greater than that of the reference antibiotics penicillin G and ciprofloxacin. They claimed compound **24** exhibited only a 2–4-fold higher MIC value than that of vancomycin. They concluded from their study that the phenylalanine-derived compounds **23** and **24** are promising templates for the development of new drugs to treat MRSA infections.

23

24

Chen and his group synthesized [46] several hybrid compounds (19 compounds with 31–58% yields) **25** having

chalcone and rhodanine-3-acetic acid units and tested these compounds for their antibacterial activity. They found some compounds presented great antimicrobial activities against Gram-positive bacteria (including the multidrug-resistant clinical isolates) as active as the standard drug (norfloxacin) and less active than oxacillin.

31–58%, 19 compounds

R = 4-CH₃, 2, 4-(CH₃)₂, 3-OCH₃, 4-OCH₃,
H, 2-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 2, 4-(Cl)₂,
2-Br, 3-Br, 4-Br, 3-F, 4-NO₂, 3-OCH₂OCH₃,
4-OCH₂OCH₃, 4-NHCOCH₃.

25

Tomasic et al. reported [47] the synthesis and antibacterial activity for a series of rhodanine-, rhodanine-N-acetic acid-, thiazolidine-2,4-dione-, barbituric-, and thiobarbituric acid-based compounds bearing an ylidene substituent at position 5. The most potent compound of the series, (Z)-5-(2,3,4-trifluorobenzylidene)rhodanine **26**, inhibited the growth of *S. aureus* at 0.5 mg/mL and MRSA at 32 mg/mL.

89%
26

Orchard and his group [48] synthesized rhodanine-3-acetic acid-based compounds **27–28** and described as inhibitors of fungal protein: mannosyl transferase 1 (PMT1). They observed 5-[[3-(1-phenylethoxy)-4-(2-phenylethoxy)phenyl]methylene]-4-oxo-2-thioxo-3-thiazolidineacetic acid **29** inhibit *Candida albicans* PMT1 with IC₅₀s in the range 0.2–0.5 μ M. Members of the series are effective in inducing changes in morphology of *C. albicans* *in vitro* that have previously been associated with loss of the transferase activity. According to them, these compounds **27–28** could serve as useful tools for studying the effects of protein O-mannosylation and its relevance in the search for novel antifungal agents.

R = Me, Et, i-Pr, CH₂OH,
CONH₂, CON(*n*-Pr)₂.

7 compounds
27

10 compounds
28

29

Sortino et al. reported [49] benzylidene-rhodanines **30** which act as antifungal agents. They evaluated that compounds **31** and **32** showed fungicidal activity and are the most active against *Candida* genus and *C. neoformans* including clinical isolates. Other compounds of this series showed a very good activity against dermatophytes.

30

R = H, 4-Cl, 4-Br, 4-F, 4-CF₃,
2-F, 2-CF₃, 4-CH₃, 4-OCH₃,
3, 4-OCH₂O-, 3, 4, 5-tri-CH₃O,
2-pyridyl, 3-pyridyl, 4-pyridyl.

31

32

2.4. Rhodanine as Antihepatitis C Virus (HCV) Agent. Sing et al. disclosed [50] arylalkylidene rhodanines **33–34** inhibit HCV NS3 protease at moderate concentrations. They claimed these rhodanine derivatives are better inhibitors of serine proteases such as chymotrypsin and plasmin. They concluded that selectivity of arylmethylidene rhodanines **33–34** with bulkier and more hydrophobic functional groups increases by 13- and 25-fold towards HCV NS3 protease, respectively.

2.5. Rhodanine as HIV-1 Integrase Inhibitors. Rajamaki and his associate synthesized [51] and biologically evaluated rhodanine-based compounds **35** and identified these exhibiting anti-HIV-1 integrase activity and moderate inhibition of HIV-1 cell replication.

35

2.6. Rhodanine as Anti-Inflammatory Agent. Cutshall et al. reported [52] synthesis and evaluation of rhodanine-based compounds **36** as inhibitors of JSP-1. On SAR studies they demonstrated that stronger electron-withdrawing functional groups appended to the aryl-benzylidene position provided analogs with the greatest potencies as illustrated by compound **37**. Compound **37** has also reversible and competitive bind with substrate and showed a high degree of enzyme selectivity against other phosphatases.

36

Irvine et al. identified [53] a series of rhodanine derivatives as novel inhibitors of phosphodiesterase type 4 (PDE4). Structures **39** and **40** displayed the most significant activity of the compounds synthesized, being some 20- and 24-fold more potent than lead compound **38**.

2.7. Rhodanines for Sleeping Sickness. Smith et al. developed [26] the first small molecular inhibitors of dolicholphosphate mannose synthase (DPMS), a mannosyltransferase critically involved in glycoconjugate biosynthesis in *T. brucei*. They claimed thiazolidinones **41**, **42**, and **43** in particular are promising candidates for further development because of their respective activities against trypanosomal DPMS and GPI anchor biosynthesis. They reported that these DPMS inhibitors prevent the biosynthesis of glycosylphosphatidylinositol (GPI) anchors and possess trypanocidal activity against live trypanosomes. Drug-like molecules **41–43** with activity against *Trypanosoma brucei* are urgently required as potential therapeutics for the treatment of African sleeping sickness.

2.8. Rhodanines as Tyrosinase Inhibitors. Liu et al. synthesized [54] a series of dihydropyrimidin-(2H)-one analogues and rhodanine derivatives and evaluated their inhibitory effects on the diphenolase activity of mushroom tyrosinase. In results they found that some of the synthesized compounds exhibited significant inhibitory activities. Particularly, compound **44** bearing a hydroxyethoxyl group at position-4 of phenyl ring exhibited the most potent tyrosinase inhibitory activity with IC₅₀ value of 0.56 mM. The inhibition mechanism analysis of compound **44** demonstrated that the inhibitory effect of the compound on the tyrosinase was irreversible. These results suggested that such compounds might be served as lead compounds for further designing new potential tyrosinase inhibitors.

2.9. Rhodanines as PRL-3 Inhibitors. Ahn et al. synthesized [55] and evaluated a series of rhodanine derivatives **45** for their ability to inhibit oncolytic phosphatase (PRL-3). Benzylidene rhodanine derivative **45** showed good biological activity, while compound **46** is found to be the most active in this series exhibiting IC₅₀ value of 0.9 Lm *in vitro* and showed a reduced invasion in cell-based assay.

R = H, Benzyl, CH₃SO₂, Pyridin-3-yl-methyl,
2-Chlorobenzyl, 2-Bromobenzyl, 4-Bromobenzyl.
X = Br, H, Phenyl, Benzofuran-3-yl.

45

3. Pharmacological Developments in 2,4-Thiazolidinediones

The most commonly used antidiabetic agents have been sulfonylureas, metformin, and certain α -glucosidase inhibitors and meglitinides. These agents increase insulin secretion from pancreatic β -cells but sometimes induce severe hypoglycemia and weight gain [56], and hyperinsulinemia is known to be a risk factor for ischemic heart disease [57]. In addition, high rates of both primary and secondary failure have been observed with these drugs [58–61]. Therefore, drugs that ameliorate the insulin resistance without stimulating insulin release from β -cells have been developed for the treatment of type 2 diabetes. Type 2 diabetes is a multifactorial disease defined by a high plasma glucose level and is characterized by both insulin resistance and impaired insulin secretion by pancreatic β -cells [62]. The prototypical 2,4-thiazolidinedione, ciglitazone **47** was discovered [63] by Takeda Chemical Industries, Ltd., Japan, and has antihyperglycemic activity in insulin-resistant animal models, KK_{Ay} mice [64], and Wistar fatty rats [65] but no effect in insulin-deficient animal models of diabetes [66, 67]. During structure-activity relationship studies on 2,4-thiazolidinediones and related compounds, they discovered highly potent compounds, such as pioglitazone **48** [68] and AD-5061 **49** [69]. Since the discovery of ciglitazone **47**, a number of pharmaceutical companies have been evaluating new 2,4-thiazolidinedione analogs as agents for improving insulin resistance. Troglitazone **50** [70] was launched first in the market but had been withdrawn because of liver toxicity and related deaths associated with the drug. Nowadays, two 2,4-thiazolidinedione class agents, pioglitazone **48** and rosiglitazone **51** [71], have been clinically used. Furthermore, many companies are still endeavoring to find a new glucose-lowering agent [72–84].

Although the precise mechanism of action of these drugs remains unknown, a recent study suggests that antidiabetic thiazolidinediones interact with a family of nuclear receptors known as peroxisome proliferator-activated receptor (PPAR)- γ [85]. PPAR γ is one of a subfamily of PPARs encoded by independent genes. Three human PPARs, designated PPAR α , PPAR γ , and PPAR δ , have been identified to date [86–88]. It was also observed that the potency for the activation of PPAR γ *in vitro* mirrored the *in vivo* glucose-lowering activity in diabetic *ob/ob* mice [89]. This would indicate that the major mechanisms of action of 2,4-thiazolidinediones involve PPAR γ . In case of those 2,4-thiazolidinediones already on the market, several side effects, such as anaemia, edema, and body weight gain, have been reported [90]. Therefore, search for new compounds with fewer side effects and a more advanced profile than existing drug molecules is the main focus of attention for chemists as well as for pharmacologists. Recent developments in the synthesis and evaluations of thiazolidinedione-based compounds for a variety of biological activities along with antidiabetes is discussed in the ongoing pages.

3.1. Thiazolidinedione as Antidiabetic Agent. Rakowitz et al. synthesised [91] and tested several 5-benzyl-2,4-thiazolidinediones **52–53** as *in vitro* aldose reductase inhibitors (ARIs). Their evaluation shows N-unsubstituted 5-benzyl-2,4-thiazolidinediones **52** and (5-benzyl-2,4-dioxothiazolidin-3-yl)acetic acids **53** displayed moderate-to-high inhibitory activity levels. The insertion of an acetic chain on N-3 significantly enhanced AR inhibitory potency, leading to acids **53** which proved to be the most effective among the tested compounds. In addition, in N-unsubstituted derivatives **52** the presence of an additional aromatic ring on the 5-benzyl moiety was generally beneficial.

Madhavan et al. synthesized [92] and evaluated 2,4-thiazolidinedione derivatives of 1,3-benzoxazinone for their PPAR- α and - γ dual activation. They obtained that a compound DRF-2519 (**54**), through SAR of TZD derivatives of benzoxazinone, has shown potent dual PPAR activation. In *ob/ob* mice, it showed better efficacy than the comparator molecules. In fat fed rat model, it showed significant improvement in lipid parameters, which was better than fibrates.

Bozdağ-Dündar et al. prepared [93] a new series of chromonyl-2,4-thiazolidinediones **55** aiming to reduce diabetic complications especially which have effect on the cataract formation. The synthesized compounds were tested for their ability to inhibit rat kidney AR by an *in vitro* spectrophotometric assay. Compound **56** showed the highest inhibitory activity. They concluded that the increasing inhibitory effect of compounds **55** might depend on the acetic acid side chain of 2,4-thiazolidinedione, and these compounds especially **56** could display therapeutic potential

in the prevention and the treatment of diabetic complications as promising ARIs.

55

56

Maccari et al. reported [94] new ARIs via *in vitro* evaluation of a series of 5-arylidene-3-(3,3,3-trifluoro-2-oxopropyl)-2,4-thiazolidinediones **57** as ARIs allowed the identification of two new noncarboxylic acid containing 5-arylidene-2,4-thiazolidinedione derivatives (**58** and **59**) that found active at low-micromolar doses.

57

58

59

3.2. Thiazolidinedione as Anticancer Agent. Patil et al. synthesized [95] and evaluated ten derivatives of 5-benzylidene-2,4-thiazolidinediones **60** for their antiproliferative activity in a panel of 7 cancer cell lines using four concentrations at 10-fold dilutions. Sulforhodamine B (SRB) protein assay used to estimate cell stability or growth. These compounds showed varying degrees of cytotoxicity in the tested cell lines, most marked effect observed by compound **60** in MCF7 (breast

cancer), K562 (leukemia), and GURAV (nasopharyngeal cancer) cell lines with log₁₀ GI₅₀ values of -6.7, -6.72, and -6.73, respectively.

60

3.3. Thiazolidinedione as Anti-Inflammatory Agent. Barros et al. synthesized [96] 5-arylidene-3-benzyl-thiazolidine-2,4-diones **61** with halide groups on their benzyl rings (8 compounds) and assayed *in vivo* to investigate their anti-inflammatory activities, and 3-(2-bromo-benzyl)-5-(4-methanesulfonyl-benzylidene)-thiazolidine-2,4-dione, compound **62**, showed higher anti-inflammatory activity than the rosiglitazone reference drug as it bound PPAR γ with 200-fold lower affinity than the reference ligand.

8 compounds

R = 3-Cl; 2-Br; 2Cl, 6-F.
R₁ = 5-Br, 2-OCH₃; 4-SO₂CH₃;
4-C₆H₅; 3-Br, 4-OCH₃; 2-Fluorene;
4-OCH₃; 2, 4-Cl₂.

61

62

Alagawadi and Alegaon described [97] the synthesis and antimicrobial activity of 5-substituted-2,4-thiazolidinedione derivatives. They evaluated all compounds for their preliminary *in vitro* antibacterial and antifungal activity. The investigation of antimicrobial screening revealed that some of the tested compounds showed moderate to good bacterial and fungal inhibition. Particularly, compounds **63–66** have shown good activity against *S. aureus* and *E. faecalis* with minimum inhibitory concentration (MIC) values between 4 and 32 μ g/mL. They found all compounds active against

tested fungal strains at 1–64 $\mu\text{g/mL}$ concentration. Compounds **63–66** also showed good antifungal activity against *C. albicans* at 1–4 $\mu\text{g/mL}$ and *C. neoformans*, *A. flavus*, *A. niger* at 2–8 $\mu\text{g/mL}$ concentration.

63 **64** **65** **66**

Liu et al. synthesized [98] a series of chalcone derivatives bearing the 2,4-thiazolidinedione and benzoic acid moieties **67** and evaluated for their antibacterial activity. In tested compounds, the most effective results obtained with MIC value in the range of 0.5–4 mg/mL against six Gram-positive bacteria (including multidrug-resistant clinical isolates).

31–58%, 19 compounds
R = H, 2-Cl, 2-Br, 2- OCH_3 , 2-OH

67

3.4. Thiazolidinedione as Antioxidant. Jeong et al. synthesized [99] multisubstituted benzylidenethiazolidine-2,4-diones **68** by Knoevenagel condensation of di- or trisubstituted 4-hydroxybenzaldehydes with thiazolidine-2,4-dione and evaluated the antioxidant activities of Cu^{2+} -induced oxidation of human low-density lipoproteins (LDLs). Among compounds, **69** was found to be superior to probucol in LDL-antioxidant activities and found to be 9-fold more active than probucol.

R = H, Me.
R₁ = H, Me
R₂ = t-BU, i-Pr, Me, OH, F, OMe.
R₃ = t-BU, i-Pr, Me, H, F, OMe.

73–98%, 8 compounds

68 **69**

Hossain and Bhattacharya synthesized [100] a series of 5-arylidene-2,4-thiazolidinediones and its geranyloxy or prenyloxy derivative and studied their radical scavenging activity using 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. They expressed comparable scavenging activities as IC₅₀ value. Compounds **70–72** showed appreciable radical scavenging activities. The vanillin-based thiazolidinedione compound **70** displayed the highest activity comparable to that of α -tocopherol. But in vivo, compound **72** showed better results in inducing phase II detoxifying/antioxidative enzyme. The compounds **70–72** found to be effective in enhancing the host antioxidant defence system such as superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), and reduced Glutathione (GSH) and at the same time lowering the serum ALT and AST level at the preliminary screening dose of 3 mg/kg in normal Swiss albino mice given orally for 20 days as compared to the control animals. The hepatic lipid-peroxidation level (LPO) remained unchanged.

70

Ottanà et al. explored [101] 5-arylidene-4-thiazolidinones as antioxidant agents and aldose reductase inhibitors. They found that compounds **73** and **74** proved to be interesting inhibitors of the enzyme as well as excellent antioxidant agents that are potentially able to counteract the oxidative stress associated with both diabetic complications as well as other pathologies.

3.5. Thiazolidinedione as Antiobesity. Hu et al. disclosed [102] synthesis of methylsulfonamide-substituted 2,4-thiazolidinedione (6 compounds) **75** and found **76** to be a potent ($EC_{50} = 0.01$ mM, $IA = 1.19$) and selective (more than 110-fold over β_1 and β_2 agonist activity) β_3 agonist. This compound has also been proven to be active and selective in an *in vivo* mode.

Bhattacharjee et al. synthesized [103] benzylidene-2,4-thiazolidinedione derivatives (9 compounds) with substitutions on the phenyl ring at the ortho or para positions of the thiazolidinedione group **77** as protein tyrosine phosphatase (PTP1B) inhibitors with IC₅₀ values in a low-micromolar range. Compound **78**, the lowest, bore an IC₅₀ of 5.0 μM. In vivo efficacy of **78** as an antiobesity and hypoglycemic agent evaluated in a mouse model system. This compound also significantly suppressed weight gain and significantly improved blood parameters such as TG, total cholesterol, and NEFA. Compound **78** also was found to activate peroxisome proliferator-activated receptors (PPARs) indicating multiple mechanisms of action.

Same research group [104] synthesized benzylidene-2,4-thiazolidinedione derivatives (12 compounds) **79** as PTP1B inhibitors with IC₅₀ values in a low-micromolar range. Compound **80**, the lowest, bores an IC₅₀ of 1.3 μ M. In a peroxisome proliferator-activated receptor- γ (PPAR- γ) promoter reporter gene assay, **80** was found to activate the transcription of the reporter gene with potencies comparable to those of troglitazone, rosiglitazone, and pioglitazone. In vivo efficacy of **80** as an antiobesity and hypoglycemic agent was evaluated in a mouse model system. Compound **80** significantly suppressed weight gain and significantly improved blood parameters such as TG, total cholesterol, and NEFA without overt toxic effects.

3.6. Thiazolidinedione as Antiprostaglandins. Ying et al. synthesized [105] a range of benzylidene thiazolidinedione derivatives (27 compounds with 75–88% yields) with

different substituents on the phenyl ring and evaluated their inhibitory 15-hydroxyprostaglandin dehydrogenase (15-PGDH) activity. Based on the structures of the thiazolidinediones analogues and inhibitory activity, replacement of the cyclohexylethyl group of **81** with the hetero five-member ring increased the inhibitory potency. However, replacement of the cyclohexylethyl group with a hetero six-member ring decreased the inhibitory potency significantly. They found that compound **82** (5-(4-(2-(thiophen-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione) is the most potent inhibitor and effective in the nanomolar range.

3.7. Thiazolidinedione as Thyroid Hormone Receptor Antagonists. Komatsu et al. designed and synthesized [106] diphenylamine derivatives **83** with a thiazolidinedione moiety as the terminal polar group as thyroid hormone receptor (TR) antagonists. Thiazolidinedione derivatives **83** with N-alkyl group showed antagonistic activities towards both the hTR α 1 and hTR β 1 subtypes.

4. Conclusion

In recent past, a variety of molecules based on rhodanine and thiazolidinedione have been synthesized and evaluated with improved pharmacological activities. Due to wide range of pharmacological activities and clinically used 2,4-thiazolidines, these molecules have attracted much attention and encouraged the chemists and biologists to be extensive investigations or molecular manipulations, and as a result further improved protocol with better observation is still under progress.

References

- [1] D. B. J. Boyd, "On the rhodanines and their presence in biologically active ligands," *Journal of Molecular Structure*, vol. 401, no. 3, pp. 227–234, 1997.
- [2] H. Korner, "Über einige derivate der dithiocarbamino-essais ure," *Berichte der Deutschen Chemischen Gesellschaft*, vol. 41, no. 2, pp. 1901–1905, 1908.
- [3] R. Andreasch, "Über substituierte Rhodaninsäuren und deren Aldehydkondensationsprodukte," *Monatshefte für Chemie und verwandte Teile anderer Wissenschaften*, vol. 29, no. 5, pp. 399–419, 1908.
- [4] H. Taniyama, B. Yasui, N. Takehara, and H. Uchida, "Chemotherapeutics for mycobacterium tuberculosis. XIX. Synthesis and antibacterial activity of some 3-substituted rhodanines," *Yakugaku Zasshi*, vol. 79, pp. 1465–1468, 1959.
- [5] J. Singh, C. F. Nathan, R. Bryk, R. Samy, K. Pupek, and M. Gurney, "Cyclic carboxylic acid rhodanine derivatives for the treatment and prevention of tuberculosis," WO Pat 2008005651, 2008.
- [6] F. J. Allan, G. G. Allan, G. Crank, and J. Jack, "The condensation of rhodanine and derivatives with benzaldehyde sulphonic acids," *Recueil des Travaux Chimiques des Pays-Bas*, vol. 79, pp. 247–254, 1960.
- [7] F. J. Allan and G. G. Allan, "The condensation of rhodanine and derivatives with 4-antipyrinaldehyde," *Canadian Journal of Chemistry*, vol. 39, no. 6, pp. 1397–1399, 1961.
- [8] F. J. Allan, G. G. Allan, and J. Thompson, "The condensation of rhodanine and derivatives with pyridine and quinoline aldehydes," *Recueil des Travaux Chimiques des Pays-Bas*, vol. 80, pp. 403–408, 1961.
- [9] F. J. Allan and G. G. Allan, "The condensation of rhodanine and derivatives with some indole aldehydes," *Monatshefte für Chemie*, vol. 94, pp. 1434–1447, 1963.
- [10] F. J. Allan and G. G. Allan, "The condensation of rhodanine and derivatives with aromatic aldehydes containing iodine," *Recueil des Travaux Chimiques des Pays-Bas*, vol. 82, pp. 177–181, 1962.
- [11] F. J. Allan and G. G. Allan, "Izoxazolylmethylenerhodanines," *Recueil des Travaux Chimiques des Pays-Bas*, vol. 83, pp. 1299–1300, 1964.
- [12] M. G. Orchard, J. C. Neuss, and C. M. S. Galley, "Benzylidene thiazolidinediones and their use as antimycotic agents," WO Pat 02017915, 2002.
- [13] M. G. Orchard and J. D. Neuss, "Preparation of thiazolidines as antifungal agents," WO Pat 0222612, 2002.
- [14] M. G. Orchard, "Preparation of 5-benzylidene-4-thiazolidinone-2-thione antifungal agents," WO Pat 03070238, 2003.
- [15] M. G. Orchard, J. C. Neuss, C. M. S. Galley et al., "Rhodanine-3-acetic acid derivatives as inhibitors of fungal protein mannosyl transferase 1 (PMT1)," *Bioorganic and Medicinal Chemistry Letters*, vol. 14, no. 15, pp. 3975–3978, 2004.
- [16] V. V. Dovlatyan and F. V. Avetisyan, "2-Thioxo-4-imino(oxo)-1,3-thiazolidin-3-ylacetic acid and its alkyl esters," *Armianskii Khimicheskii Zhurnal*, vol. 26, pp. 494–498, 1973.
- [17] Y. Inamori, C. Muro, R. Tanaka, A. Adachi, K. Miyamoto, and H. Tsujibo, "Phytogrowth-inhibitory activity of sulphur-containing compounds. I. Inhibitory activities of thiazolidine derivatives on plant growth," *Chemical and Pharmaceutical Bulletin*, vol. 40, no. 10, pp. 2854–2856, 1992.
- [18] C. Muro, M. Yasuda, Y. Sakagami et al., "Inhibitory activities of rhodanine derivatives on plant growth," *Bioscience, Biotechnology and Biochemistry*, vol. 60, no. 8, pp. 1368–1371, 1996.
- [19] I. A. Frankov, M. V. Kirillov, T. N. Sokolova, R. Skupskaya, A. N. Kharitonovich, and I. I. Chizhevskaya, *Khimiko-Farmatsevticheskii Zhurnal*, vol. 19, pp. 943–946, 1985.
- [20] W. G. Friebe, H. W. Krell, S. Woelle, and H. P. Wolff, "Thiazolidine carboxylic acid derivatives and their use in the treatment of cancer," WO Pat 0157006, 2001.
- [21] R. Singh, U. V. Ramesh, D. Goff et al., "Rhodanine derivatives and pharmaceutical compositions containing them," WO Pat 2004043955, 2004.
- [22] T. Tanaouchi, M. Kawamura, A. Ajima et al., "Rhodanine derivatives, process for their preparation, and aldose reductase inhibitor containing the rhodanine derivatives as active ingredient," European Patent 0047109, 1982.
- [23] J. F. Zhou, Y. Z. Song, F. X. Zhu, and Y. L. Zhu, "Facile synthesis of 5-benzylidene rhodamine derivatives under microwave irradiation," *Synthetic Communications*, vol. 36, no. 22, pp. 3297–3303, 2006.
- [24] A. Esswein, W. Schaefer, C. Tsaklakidis, K. Honold, and K. Kaluza, "Rhodanine carboxylic acid derivatives for the treatment and prevention of metabolic bone disorders," US Patent Application 2003032813, 2003.
- [25] A. Esswein, W. Schaefer, C. Tsaklakidis, K. Honold, and K. Kaluza, "Rhodanine carboxylic acid derivatives for the treatment and prevention of metabolic bone disorders," US Patent Application 6673816, 2004.
- [26] T. K. Smith, B. L. Young, H. Denton, D. L. Hughes, and G. K. Wagner, "First small molecular inhibitors of T. brucei dolicholphosphate mannosyl synthase (DPMS), a validated drug target in African sleeping sickness," *Bioorganic and Medicinal Chemistry Letters*, vol. 19, no. 6, pp. 1749–1752, 2009.
- [27] D. Ziegler, "Treatment of diabetic neuropathy and neuropathic pain: how far have we come?" *Diabetes care*, vol. 31, supplement 2, pp. S255–S261, 2008.
- [28] M. A. Ramirez and N. L. Borja, "Epalrestat: an aldose reductase inhibitor for the treatment of diabetic neuropathy," *Pharmacotherapy*, vol. 28, no. 5, pp. 646–655, 2008.
- [29] T. Tanaouchi, M. Kawamura, A. Ajima et al., "Rhodanine derivatives, process for their preparation, and aldose reductase inhibitor containing the rhodanine derivatives as active ingredient," US Patent 4464382, 1984.
- [30] T. Tomasic and L. P. Masic, "Rhodanine as a privileged scaffold in drug discovery," *Current Medicinal Chemistry*, vol. 16, no. 13, pp. 1596–1629, 2009.
- [31] W. T. Sing, C. L. Lee, S. L. Yeo, S. P. Lim, and M. M. Sim, "Arylalkylidene rhodanine with bulky and hydrophobic functional group as selective HCV NS3 protease inhibitor," *Bioorganic and Medicinal Chemistry Letters*, vol. 11, no. 2, pp. 91–94, 2001.

- [32] Y. Momose, K. Meguro, H. Ikeda, C. Hatanaka, S. Oi, and T. Sohda, "Studies on antidiabetic agents. X. Synthesis and biological activities of pioglitazone and related compounds," *Chemical & Pharmaceutical Bulletin*, vol. 39, no. 6, pp. 1440–1445, 1991.
- [33] H. Fujishima and K. Tuboto, "Improvement of corneal fluorescein staining in post cataract surgery of diabetic patients by an oral aldose reductase inhibitor, ONO-2235," *British Journal of Ophthalmology*, vol. 86, no. 8, pp. 860–865, 2002.
- [34] E. B. Grant, D. Guiadeen, E. Z. Baum et al., "The synthesis and SAR of rhodanines as novel class C β -lactamase inhibitors," *Bioorganic & Medicinal Chemistry Letters*, vol. 10, no. 19, pp. 2179–2181, 2000.
- [35] A. Zervosen, W. P. Lu, Z. Chen, R. E. White, T. P. Demuth Jr., and J. M. Frere, "Interactions between penicillin-binding proteins (PBPs) and two novel classes of PBP inhibitors, arylalkylidene rhodanines and arylalkylidene iminothiazolidin-4-ones," *Antimicrobial Agents and Chemotherapy*, vol. 48, no. 3, pp. 961–969, 2004.
- [36] C. A. Free, E. Majchrowich, and S. M. Hess, "Mechanism of inhibition of histidine decarboxylase by rhodanines," *Biochemical Pharmacology*, vol. 20, no. 7, pp. 1421–1428, 1971.
- [37] N. S. Cutshall, C. O'Day, and M. Prezhdo, "Rhodanine derivatives as inhibitors of JSP-1," *Bioorganic & Medicinal Chemistry Letters*, vol. 15, no. 14, pp. 3374–3379, 2005.
- [38] R. Murugana, S. Anbazhagan, and S. S. Narayanan, "Synthesis and in vivo antidiabetic activity of novel dispiropyrrolidines through [3 + 2] cycloaddition reactions with thiazolidinedione and rhodanine derivatives," *European Journal of Medicinal Chemistry*, vol. 44, no. 8, pp. 3272–3279, 2009.
- [39] L. Wang, F. Kong, C. L. Kokoski, D. W. Andrews, and C. Xing, "Development of dimeric modulators for anti-apoptotic Bcl-2 proteins," *Bioorganic & Medicinal Chemistry Letters*, vol. 18, no. 1, pp. 236–240, 2008.
- [40] B. T. Moorthy, S. Ravi, M. Srivastava et al., "Novel rhodanine derivatives induce growth inhibition followed by apoptosis," *Bioorganic & Medicinal Chemistry Letters*, vol. 20, no. 21, pp. 6297–6301, 2010.
- [41] S. Ravi, K. K. Chiruvella, K. Rajesh, V. Prabhu, and S. C. Raghavan, "5-Isopropylidene-3-ethyl rhodanine induce growth inhibition followed by apoptosis in leukemia cells," *European Journal of Medicinal Chemistry*, vol. 45, no. 7, pp. 2748–2752, 2010.
- [42] N. S. Habib, S. M. Ridal, E. A. M. Badaweyl, H. T. Y. Fahmyl, and H. A. Ghozlan, "Synthesis and antimicrobial activity of rhodanine derivatives," *European Journal of Medicinal Chemistry*, vol. 32, no. 9, pp. 759–762, 1997.
- [43] T. J. Opperman, S. M. Kwasny, J. D. Williams et al., "Aryl rhodanines specifically inhibit staphylococcal and enterococcal biofilm formation," *Antimicrobial Agents and Chemotherapy*, vol. 53, no. 10, pp. 4357–4367, 2009.
- [44] M. M. Sim, S. B. Ng, A. D. Buss, S. C. Crasta, K. L. Goh, and S. K. Lee, "Benzylidene rhodanines as novel inhibitors of UDP-N-acetylmuramate/l-alanine ligase," *Bioorganic & Medicinal Chemistry Letters*, vol. 12, no. 4, pp. 697–699, 2002.
- [45] D. Hardej, C. R. Ashby Jr., N. S. Khadtare, S. S. Kulkarni, S. Singh, and T. T. Talele, "The synthesis of phenylalanine-derived C5-substituted rhodanines and their activity against selected methicillin-resistant *Staphylococcus aureus* (MRSA) strains," *European Journal of Medicinal Chemistry*, vol. 45, no. 12, pp. 5827–5832, 2010.
- [46] Z. H. Chen, C. J. Zheng, L. P. Sun, and H. R. Piao, "Synthesis of new chalcone derivatives containing a rhodanine-3-acetic acid moiety with potential anti-bacterial activity," *European Journal of Medicinal Chemistry*, vol. 45, no. 12, pp. 5739–5743, 2010.
- [47] T. Tomasic, N. Zidar, M. M. Premru, D. Kikelj, and L. P. Masic, "Synthesis and antibacterial activity of 5-ylidenethiazolidin-4-ones and 5-benzylidene-4,6-pyrimidinediones," *European Journal of Medicinal Chemistry*, vol. 45, no. 4, pp. 1667–1672, 2010.
- [48] M. G. Orchard, J. C. Neuss, C. M. S. Galley et al., "Rhodanine-3-acetic acid derivatives as inhibitors of fungal protein mannosyl transferase 1 (PMT1)," *Bioorganic and Medicinal Chemistry Letters*, vol. 14, no. 15, pp. 3975–3978, 2004.
- [49] M. Sortino, P. Delgado, S. Juárez et al., "Synthesis and antifungal activity of (Z)-5-arylidenerrhodanines," *Bioorganic and Medicinal Chemistry*, vol. 15, no. 1, pp. 484–494, 2007.
- [50] W. T. Sing, C. L. Lee, S. L. Yeo, S. P. Lim, and M. M. Sim, "Arylalkylidene rhodanine with bulky and hydrophobic functional group as selective HCV NS3 protease inhibitor," *Bioorganic & Medicinal Chemistry Letters*, vol. 11, no. 2, pp. 91–94, 2001.
- [51] S. Rajamaki, A. Innitzer, C. Falciani et al., "Exploration of novel thiobarbituric acid-, rhodanine- and thiohydantoin-based HIV-1 integrase inhibitors," *Bioorganic and Medicinal Chemistry Letters*, vol. 19, no. 13, pp. 3615–3618, 2009.
- [52] N. S. Cutshall, C. O'Day, and M. Prezhdo, "Rhodanine derivatives as inhibitors of JSP-1," *Bioorganic & Medicinal Chemistry Letters*, vol. 15, no. 14, pp. 3374–3379, 2005.
- [53] M. W. Irvine, G. L. Patrick, J. Kewney, S. F. Hastings, and S. J. MacKenzie, "Rhodanine derivatives as novel inhibitors of PDE4," *Bioorganic & Medicinal Chemistry Letters*, vol. 18, no. 6, pp. 2032–2037, 2008.
- [54] J. Liu, F. Wu, L. Chen et al., "Evaluation of dihydropyrimidin-(2H)-one analogues and rhodanine derivatives as tyrosinase inhibitors," *Bioorganic & Medicinal Chemistry Letters*, vol. 21, no. 8, pp. 2376–2379, 2011.
- [55] J. H. Ahn, S. J. Kim, W. S. Park et al., "Synthesis and biological evaluation of rhodanine derivatives as PRL-3 inhibitors," *Bioorganic & Medicinal Chemistry Letters*, vol. 16, no. 11, pp. 2996–2999, 2006.
- [56] R. R. Holman and R. C. Turner, in *Textbook of Diabetes*, J. C. Pickup and G. Williams, Eds., pp. 462–476, Blackwell Scientific Publications, London, UK, 1991.
- [57] J. P. Depres, B. Lamarcha, P. Mauriege et al., "Hyperinsulinemia as an independent risk factor for ischemic heart disease," *The New England Journal of Medicine*, vol. 334, pp. 952–957, 1996.
- [58] The Diabetes Control and Complications Trials (DCCT), "Lymphocytic Infundibuloneurohypophysitis as a Cause of Central Diabetes Insipidus," *The New England Journal of Medicine*, vol. 329, supplement 2, pp. 683–689, 1993.
- [59] American Diabetic Association, "Implications of the diabetes control and complications trial," *Diabetes*, vol. 43, pp. 1555–1558, 1993.
- [60] A. D. B. Harrower, "Comparison of efficacy, secondary failure rate, and complications of sulfonylureas," *Journal of Diabetes and its Complications*, vol. 8, no. 4, pp. 201–203, 1994.
- [61] UK Prospective Diabetes Study Group, "U.K. prospective diabetes study 16: overview of 6 years' therapy of type II diabetes: a progressive disease," *Diabetes*, vol. 44, pp. 1249–1258, 1995.
- [62] R. A. DeFronzo, *Diabetes*, vol. 37, pp. 255–297, 1998.
- [63] T. Sohda, K. Mizuno, E. Imamiya, Y. Sugiyama, T. Fujita, and Y. Kawamatsu, "Studies on antidiabetic agents. II. Synthesis of

- 5-[4-(1-Methylcyclohexylmethoxy)-benzyl] thiazolidine-2, 4-dione (ADD-3878) and its derivatives," *Chemical & Pharmaceutical Bulletin*, vol. 30, no. 10, pp. 3580–3600, 1982.
- [64] H. Iwatsuka, A. Shino, and Z. Suzuoki, "General survey of diabetic features of yellow KK mice," *Endocrinologia Japonica*, vol. 17, no. 1, pp. 23–35, 1970.
- [65] H. Ikeda, A. Shino, T. Matsuo, H. Iwatsuka, and Z. Suzuoki, "A new genetically obese-hyperglycemic rat (Wistar fatty)," *Diabetes*, vol. 30, no. 12, pp. 1045–1050, 1981.
- [66] T. Fujita, Y. Sugiyama, S. Taketomi et al., "Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-Methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4-dione (ADD-3878, U-63,287, Ciglitazone), a new antidiabetic agent," *Diabetes*, vol. 32, no. 9, pp. 804–810, 1983.
- [67] A. Y. Chang, B. M. Wyse, and B. J. Gilchrist, "Ciglitazone, a new hypoglycemic agent. I. Studies in ob/ob and db/db mice, diabetic Chinese hamsters, and normal and streptozotocin-diabetic rats," *Diabetes*, vol. 32, no. 9, pp. 830–838, 1983.
- [68] T. Sohda, Y. Momose, K. Meguro, Y. Kawamatsu, Y. Sugiyama, and H. Ikeda, "Studies on antidiabetic agents. Synthesis and hypoglycemic activity of 5-[4-(pyridylalkoxy)benzyl]-2,4-thiazolidinediones," *Arzneimittel-Forschung*, vol. 40, no. 1, pp. 37–42, 1990.
- [69] T. Sohda, K. Mizuno, Y. Momose, H. Ikeda, T. Fujita, and K. J. Meguro, "Studies on antidiabetic agents. II. Novel thiazolidinedione derivatives as potent hypoglycemic and hypolipidemic agents," *Journal of Medicinal Chemistry*, vol. 35, no. 14, pp. 2617–2626, 1992.
- [70] T. Yoshioka, T. Fujita, T. Kanai et al., "Studies on hindered phenols and analogs. I. Hypolipidemic and hypoglycemic agents with ability to inhibit lipid peroxidation," *Journal of Medicinal Chemistry*, vol. 32, no. 2, pp. 421–428, 1989.
- [71] B. C. C. Cantello, M. A. Cawthorne, G. P. Cottam et al., "[ω -(Heterocyclamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents," *Journal of Medicinal Chemistry*, vol. 37, no. 23, pp. 3977–3985, 1994.
- [72] H. K. Rami and S. A. Smith, "Synthetic ligands for PPAR γ -review of patent literature 1994–1999," *Expert Opinion on Therapeutic Patents*, vol. 10, no. 5, pp. 623–634, 2000.
- [73] B. B. Lohray, V. Bhushan, B. P. Rao et al., "Novel euglycemic and hypolipidemic agents," *Journal of Medicinal Chemistry*, vol. 41, no. 10, pp. 1619–1630, 1998.
- [74] B. B. Lohray, V. B. Lohray, A. C. Bajji et al., "(-)-3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid [(-)DRF 2725]: a dual PPAR agonist with potent antihyperglycemic and lipid modulating activity," *Journal of Medicinal Chemistry*, vol. 44, no. 16, pp. 2675–2678, 2001.
- [75] M. Oguchi, K. Wada, H. Honma et al., "Molecular design, synthesis, and hypoglycemic activity of a series of thiazolidine-2,4-diones," *Journal of Medicinal Chemistry*, vol. 43, no. 16, pp. 3052–3066, 2000.
- [76] M. Nomura, S. Kinoshita, H. Satoh et al., "(3-Substituted benzyl)thiazolidine-2,4-diones as structurally new antihyperglycemic agents," *Bioorganic & Medicinal Chemistry Letters*, vol. 9, no. 4, pp. 533–538, 1999.
- [77] B. R. Henke, S. G. Blanchard, M. F. Brackeen et al., "N-(2-benzoylphenyl)-L-tyrosine PPAR γ agonists. 1. Discovery of a novel series of potent antihyperglycemic and antihyperlipidemic agents," *Journal of Medicinal Chemistry*, vol. 41, no. 25, pp. 5020–5036, 1998.
- [78] J. L. Collins, S. G. Blanchard, G. E. Boswell et al., "N-(2-benzoylphenyl)-L-tyrosine PPAR γ agonists. 2. Structure-activity relationship and optimization of the phenyl alkyl ether moiety," *Journal of Medicinal Chemistry*, vol. 41, no. 25, pp. 5037–5054, 1998.
- [79] J. E. Cobb, S. G. Blanchard, E. G. Boswell et al., "N-(2-benzoylphenyl)-L-tyrosine PPAR γ agonists. 3. Structure-activity relationship and optimization of the N-aryl substituent," *Journal of Medicinal Chemistry*, vol. 41, no. 25, pp. 5055–5069, 1998.
- [80] H. Shinkai, S. Onogi, M. Tanaka et al., "Isoxazolidine-3,5-dione and Noncyclic 1,3-Dicarbonyl Compounds as Hypoglycemic Agents," *Journal of Medicinal Chemistry*, vol. 41, no. 11, pp. 1927–1933, 1998.
- [81] M. J. Reginato, S. T. Bailey, S. L. Krakow et al., "A potent antidiabetic thiazolidinedione with unique peroxisome proliferator-activated receptor γ -activating properties," *The Journal of Biological Chemistry*, vol. 273, pp. 32679–32684, 1998.
- [82] B. Hulin, L. S. Newton, D. M. Lewis, P. E. Genereux, E. M. Gibbs, and D. A. Clark, "Hypoglycemic activity of a series of α -alkylthio and α -alkoxy carboxylic acids related to ciglitazone," *Journal of Medicinal Chemistry*, vol. 39, no. 20, pp. 3897–3907, 1996.
- [83] D. A. Clark, S. W. Goldstein, R. A. Volkmann et al., "Substituted dihydrobenzopyran and dihydrobenzofuran thiazolidine-2,4-diones as hypoglycemic agents," *Journal of Medicinal Chemistry*, vol. 34, no. 1, pp. 319–325, 1991.
- [84] Y. Momose, K. Meguro, H. Ikeda, C. Hatanaka, S. Oi, and T. Sohda, "Studies on antidiabetic agents. X. Synthesis and biological activities of pioglitazone and related compounds," *Chemical & Pharmaceutical Bulletin*, vol. 39, no. 6, pp. 1440–1445, 1991.
- [85] J. M. Lehmann, L. B. Moore, T. A. Smith-Oliver, W. O. Wilkison, T. M. Willson, and S. A. Kliewer, "Sulfated glycans stimulate endocytosis of the cellular isoform of the prion protein, PrP, in cultured cells," *Journal of Biological Chemistry*, vol. 270, pp. 12953–12956, 1995.
- [86] I. Isseman and S. Green, "Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators," *Nature*, vol. 347, pp. 645–650, 1990.
- [87] A. Schmidt, N. Endo, S. J. Rutledge, R. Vogel, D. Shinar, and G. A. Rodan, "Identification of a new member of the steroid hormone receptor superfamily that is activated by a peroxisome proliferator and fatty acids," *Molecular Endocrinology*, vol. 6, no. 10, pp. 1634–1641, 1992.
- [88] S. A. Kliewer, B. M. Forman, B. Blumberg et al., "Differential expression and activation of a family of murine peroxisome proliferator-activated receptors," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 91, no. 15, pp. 7355–7359, 1994.
- [89] T. M. Willson, J. E. Cobb, D. J. Cowan et al., "The structure-activity relationship between peroxisome proliferator-activated receptor γ agonism and the antihyperglycemic activity of thiazolidinediones," *Journal of Medicinal Chemistry*, vol. 39, no. 3, pp. 665–668, 1996.
- [90] Y. Iwamoto, K. Kosaka, T. Kuzuya, Y. Akanuma, Y. Shigeta, and T. Kaneko, "Effects of troglitazone: a new hypoglycemic agent in patients with NIDDM poorly controlled by diet therapy," *Diabetes Care*, vol. 19, no. 2, pp. 151–156, 1996.

- [91] D. Rakowitz, R. Maccari, R. Ottana, and M. G. Vigorita, "In vitro aldose reductase inhibitory activity of 5-benzyl-2,4-thiazolidinediones," *Bioorganic & Medicinal Chemistry*, vol. 14, no. 2, pp. 567–574, 2006.
- [92] G. R. Madhavan, R. Chakrabarti, K. A. Reddy et al., "Dual PPAR- α and - γ activators derived from novel benzoxazinone containing thiazolidinediones having antidiabetic and hypolipidemic potential," *Bioorganic & Medicinal Chemistry*, vol. 14, no. 2, pp. 584–591, 2006.
- [93] O. Bozdağ-Dündar, B. Evranos, N. Daş-Evcimen, M. Sarikaya, and R. Ertan, "Synthesis and aldose reductase inhibitory activity of some new chromonyl-2,4-thiazolidinediones," *European Journal of Medicinal Chemistry*, vol. 43, no. 11, pp. 2412–2417, 2008.
- [94] R. Maccari, R. Ciurleo, M. Giglio et al., "Identification of new non-carboxylic acid containing inhibitors of aldose reductase," *Bioorganic & Medicinal Chemistry*, vol. 18, no. 11, pp. 4049–4055, 2010.
- [95] V. Patil, K. Tilekar, S. Mehendale-Munj, R. Mohan, and C. S. Ramaa, "Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2,4-thiazolidinedione derivatives," *European Journal of Medicinal Chemistry*, vol. 45, no. 10, pp. 4539–4544, 2010.
- [96] C. D. Barros, A. A. Amato, T. B. D. Oliveira et al., "Synthesis and anti-inflammatory activity of new arylidene-thiazolidine-2,4-diones as PPAR γ ligands," *Bioorganic and Medicinal Chemistry*, vol. 18, no. 11, pp. 3805–3811, 2010.
- [97] K. R. Alagawadi and S. G. Alegaon, "Synthesis, characterization and antimicrobial activity evaluation of new 2,4-Thiazolidinediones bearing imidazo[2,1-*b*][1,3,4]thiadiazole moiety," *Arabian Journal of Chemistry*, vol. 4, no. 4, pp. 465–472, 2011.
- [98] X.-F. Liu, C.-J. Zheng, L.-P. Sun, X.-K. Liu, and H.-R. Piao, "Synthesis of new chalcone derivatives bearing 2,4-thiazolidinedione and benzoic acid moieties as potential antibacterial agents," *European Journal of Medicinal Chemistry*, vol. 46, no. 8, pp. 3469–3473, 2011.
- [99] T.-S. Jeong, J.-R. Kim, K. S. Kim, K.-H. Cho, K.-H. Bae, and W. S. Lee, "Inhibitory effects of multi-substituted benzylidenethiazolidine-2,4-diones on LDL oxidation," *Bioorganic & Medicinal Chemistry*, vol. 12, no. 15, pp. 4017–4023, 2004.
- [100] S. U. Hossain and S. Bhattacharya, "Synthesis of O-prenylated and O-geranylated derivatives of 5-benzylidene-2,4-thiazolidinediones and evaluation of their free radical scavenging activity as well as effect on some phase II antioxidant/detoxifying enzymes," *Bioorganic & Medicinal Chemistry Letters*, vol. 17, no. 5, pp. 1149–1154, 2007.
- [101] R. Ottanà, R. MacCari, M. Giglio et al., "Identification of 5-arylidene-4-thiazolidinone derivatives endowed with dual activity as aldose reductase inhibitors and antioxidant agents for the treatment of diabetic complications," *European Journal of Medicinal Chemistry*, vol. 46, no. 7, pp. 2797–2806, 2011.
- [102] B. Hu, J. Ellingboe, I. Gunawan et al., "2,4-Thiazolidinediones as potent and selective human β_3 agonists," *Bioorganic and Medicinal Chemistry Letters*, vol. 11, no. 6, pp. 757–760, 2001.
- [103] B. R. Bhattarai, B. Kafle, J.-S. Hwang et al., "Thiazolidinedione derivatives as PTP1B inhibitors with antihyperglycemic and antiobesity effects," *Bioorganic & Medicinal Chemistry Letters*, vol. 19, no. 21, pp. 6161–6165, 2009.
- [104] B. R. Bhattarai, B. Kafle, J.-S. Hwang et al., "Novel thiazolidinedione derivatives with anti-obesity effects: dual action as PTP1B inhibitors and PPAR- γ activators," *Bioorganic & Medicinal Chemistry Letters*, vol. 20, no. 22, pp. 6758–6763, 2010.
- [105] W. Ying, H.-H. Tai, and H. Cho, "Synthesis and SAR of thiazolidinedione derivatives as 15-PGDH inhibitors," *Bioorganic & Medicinal Chemistry*, vol. 18, no. 4, pp. 1428–1433, 2010.
- [106] T. Komatsu, T. Hirano, C. Songkram, E. Kawachi, and H. Kagechika, "Novel thyroid hormone receptor antagonists with an *N*-alkylated diphenylamine skeleton," *Bioorganic & Medicinal Chemistry*, vol. 15, no. 9, pp. 3115–3126, 2007.