REVIEW OF LITERATURE

Review of Literature was carried out through various national and international journals to study various molecules which are already synthesized and tested. This was in order to scope out the key data collection requirements for the primary research to be conducted, and it formed part of the emergent research design process. The approach adopted was in line with current practice in grounded research work.

Diabetes is always associated with degenerative long-term complications that make it one of the leading causes of blindness, renal failure and neuronal pathologies. The increased flux of glucose through the polyol pathway that occurs in hyperglycaemic conditions in tissues possessing insulin-independent glucose transport (nerve, retina, lenses and kidney) is a well-examined factor involved in the onset and progression of such chronic complications. Aldose reductase is the first enzyme of the polyol pathway and catalyses the NADPH-dependent reduction of glucose to sorbitol. Dual agonist of Peroxisomal proliferated activated receptor α/γ represents the novel class of agents having an therapeutic application for the treatment of Type 2 diabetes. PPARγ agonist were reported to exhibit an anti-diabetic effect which enhance the catabolism of glucose while PPARα exhibit an anti-hyperlipidemic effect their by control the increase in body weight by increasing the catabolism of lipid.

Many structurally different compounds have been shown to inhibit Aldose Reductase enzyme with various degrees of efficacy and specificity. But often fail to proceed for clinical trial either because of undesirable side effects or as a result of poor efficacy. Only epalrestat is currently marketed one. Literature revealed that a large number of thiazolidinedione derivatives have been reported as potent inhibitors of Aldose Reductase and PPAR α/γ dual agonist without any side effect. But yet, little work has been carried out on these analogs. Therefore, the review of literature was divided into..

2.1. Aldose Reductase Inhibitors

2.2. Peroxisomal proliferated activated receptor α/γ dual agonist

2.3. Thiazolidinedione derivatives as an anti-diabetic agent.
2.1. Aldose Reductase Inhibitors

1. **Fei Wang et al (2012)**, elucidated the role of Nrf2–anti-oxidant response element (ARE) signal pathway in TGFβ1's regulation of AR expression in human renal mesangial cells (HRMCs). As an in vitro model system, HRMCs were used to investigate AR mRNA by qPCR, protein by Western blot and enzymatic activity by spectrophotometric assay. The ability of TGFβ1 to induce reactive oxygen species (ROS) in cells was measured by electron-spin resonance (ESR) trapping method.

2. **Jae Sue Cho et al (2012)**, predicted the 3D structure of AR in rat and human using a docking algorithm to simulate binding between AR and prenylated flavonoids (1 and 2) and kaempferol (3) and scrutinized the reversible inhibition of AR by these ARIs. Docking simulation results of 1–3 demonstrated negative binding energies and an additional hydrogen bond through Phe122 and Trp219, in addition to the previously proposed interaction of AR and phenolics through Trp20, Tyr48, His110, and Trp111 residues, indicating that the presence of 8-prenyl and 5-methyl groups might potentiate tighter binding to the active site of the enzyme and more effective AR inhibitors. The results suggests that an effective strategy for screening potential ARIs could be established by predicting 3D structural conformation of prenylated flavonoids and the orientation within the enzyme as well as by simultaneously determining the mode of enzyme inhibition.

3. **D.K. Patel et al (2012)**, presented a review summarizing the list of plant material, and their isolated phytoconstituents which have been tested for their AR inhibitory activity. This literature review covers the period to 2011, and a total of 72 plants are listed.

4. **Luciana Marinelli et al (2012)**, reported, starting from the virtual screening-derived ALR2 inhibitor S12728 (1), a rational receptor-based lead optimization.
Carried out efforts to design and synthesized led to the discovery of several new compounds endowed with low micromolar/submicromolar activities.

5. **Yan Liu et al (2011)**\(^5\), synthesized series of pyrido[2,3]-[1,2,4]-thiadiazine 1,1-dioxide acetic acid derivatives and tested for their inhibitory activity against aldose reductase (ALR2). These derivatives were found to be potent aldose reductase inhibitors with \( \text{IC}_{50} \) values ranging from 0.038 \( \mu \text{M} \) to 11.29 \( \mu \text{M} \). Structure–activity relationship studies indicate the requirement of N2-benzyl group with electron-withdrawing substituents and N4-acetic acid group in the pyridothiadiazine scaffold.

6. **Qun Yu et al (2011)**\(^6\), prepared 1,2-benzothiazine 1,1-dioxide acetic acid derivatives and investigated their inhibition activity. Most of these derivatives were found to be active with \( \text{IC}_{50} \) values ranging from 0.11 \( \mu \text{M} \) to 10.42 \( \mu \text{M} \). SAR and docking studies suggest that in comparison with the \( \alpha,\beta \)-unsaturated derivatives, the saturated carboxylic acid derivatives had a greater binding affinity with the enzyme and thus an enhanced inhibition activity. Therefore, development of more powerful ARIs based on benzothiazine 1,1-dioxide by stereo-controlled synthesis could be expected.
7. **Rosaria Ottanà et al (2011)**, explored more effective 5-arylidene-4-thiazolidinones as aldose reductase inhibitors, a new set of suitably substituted compounds. Acetic acids 5, particularly 5a and 5h, 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. Molecular docking experiments supported SAR studies.

8. **Gerhard Klebe et al (2011)**, contribute, the binding of two chemically closely related human aldose reductase inhibitors had been studied by high-resolution X-ray analysis (0.92–1.35 Å) and isothermal titration calorimetry against a series of single-site mutants of the wild-type protein. A crucial threonine thought to be involved in short bromine to oxygen halogen bond to the inhibitors in the wild type has been mutated to the structurally similar residues alanine, cysteine, serine and valine. They also provide deeper insights into how single-site mutations can alter the selectivity profile of closely related ligands against a target protein.
9. **K. V. Ramana et al (2011)**, envisioned that by blocking the molecular signals of ROS that activate redox-sensitive transcription factors, various inflammatory diseases could be ameliorated. Demonstrated that ROS-induced lipid peroxidation-derived lipid aldehydes such as 4-hydroxy-trans-2-nonenal (HNE) and their glutathione-conjugates (e.g. GS-HNE) are efficiently reduced by aldose reductase to corresponding alcohols which mediate the inflammatory signals. Our results showed that inhibition of aldose reductase (AKR1B1) significantly prevented the inflammatory signals induced by cytokines, growth factors, endotoxins, high glucose, allergens and auto-immune reactions in cellular as well as animal models.

10. **Ravichandran Ramasamy et al (2011)**, hypothesized that altered glucose metabolism, in particular, flux of glucose via the polyol pathway (PP) may be responsible, in part, for the enhanced vulnerability of aging myocardium to ischemic injury, even in the absence of superimposed disease processes linked to PP flux, such as diabetes. Results indicate that innate increases in activity of the PP enzymes augment myocardial vulnerability to I/R injury in aging, and that blockers of PP protect the vulnerable aging hearts.

11. **Maria Chatzopoulou et al (2011)**, studied the effect of methoxy-substitution as well as the regioposition of the benzoyl-moiety of 4a [(1-(3,5-difluoro-4-hydroxyphenyl)-1H-pyrrol-3-yl)(phenyl)methanone] and synthesized compounds 4b–c and 5a–c and assayed for aldose and aldehyde reductase inhibitory activity. Compound 5b emerged as the most potent and selective inhibitor.

12. **Gerhard Klebe et al (2011)**, reported the interaction to the mutated residue Thr113 does not directly alter the binding mode of zopolrestat to aldose reductase, a shift of its basic scaffold is induced which affects the interaction with a flexible
loop and introduces disorder. With the related inhibitor IDD393, two distinct binding site conformations result in two different crystal forms: While a backbone flip of the same residues as for zopolrestat is present in both crystal forms, a considerable side-chain movement of a phenylalanine is observed for only one crystal form. The structure of a benzothiazepine reveals a protein conformer, where this phenylalanine is further relocated resulting in the same altered crystal packing.

13. Young Sook Kim et al (2011)\textsuperscript{13}, investigated the inhibitory effects of quercitrin gallate (QG), a polyphenolic compound, on aldose reductase (AR) activity as well as on antioxidant levels and enzyme activity in the lens. QG showed potential inhibitory activity against rat lens AR activity with an IC\textsubscript{50} value of 0.064 µM. These results suggest that QG may provide a potential therapeutic approach for the prevention of diabetic complications, such as cataracts.

14. DK Patel et al (2011)\textsuperscript{14}, reviewed and provided an insight over the pathophysiological and etiological aspects of cataract along with discussing the remedies available for the disorder. Different experimental models with their relevant mechanism and significance such as galactose-induced, naphthalene-induced and selenite-induced cataract models which are mainly used for evaluating
the anticataract activity of a particular drug (mainly of natural origin) also described
Confirmed that the antioxidant property of plants phytoconstituents are basically
responsible for their effective anticataract activity.

15. **Rosanna Maccari et al (2011)**, evaluated 2-Thioxo-4-thiazolidinone derivatives
as aldose reductase inhibitors (ARIs) and most of them exhibited good or excellent
in vitro efficacy. Out of the tested compounds, most N-unsubstituted analogues
were found to possess inhibitory effects at low micromolar doses and two of them
exhibited higher potency than sorbinil, used as a reference drug.

![Chemical Structure](image1)

16. **Rosanna Maccari et al (2010)**, designed non-carboxylic acid containing
bioisosteres of (5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids, as active aldose
reductase (ALR2) inhibitors by replacing the carboxylic group with the
trifluoromethyl ketone moiety. The in vitro evaluation of the ALR2 inhibitory
effects of these trifluoromethyl substituted derivatives led to the identification of
two inhibitors effective at low micromolar doses.

![Chemical Structure](image2)

17. **Sahoo et al (2010)**, reported that The acetic acid derivatives of [1,2,4]triazino[4,3-a]benzimidazole (TBI) were synthesized and tested in vitro and in vivo as selective
aldose reductase (ALR2) inhibitors. Compound PS11(R – CH₂COOC₆H₅) showed
highest inhibitory activity (IC₅₀) 0.32 mM and was found to be effective in
preventing cataract development in severely galactosemic rats when administered as
an eye drop solution.

![Chemical Structure](image3)
18. C. A. Tsoleridis et al (2010), prepared Aryl-diazepinothiophenones from the reaction of o-phenylenediamines 1a–c with phorone. Assignments of structure of new compounds were based on the analysis of their 1H and 13C NMR IR, MS and elemental analysis data. Compounds were evaluated for aldose reductase inhibition and also as antioxidants.

\[
\text{R}_1 \text{N} \quad \text{N} \quad \text{R}_2
\]

19. Satoshi Endo et al (2010), identified human aldose reductase-like protein, AKR1B10 in the aldo-keto reductase (AKR) superfamily, as a therapeutic target in the treatment of several types of cancer. In order to identify potential leads for new inhibitors of AKR1B10, the virtual screening approach we adopted using the automated program ICM, which resulted in the discovery of several chromene-3-carboxamide derivatives as potent competitive inhibitors.

\[
\text{O} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{R}_1 \quad \text{HO} \quad \text{R}_2 \quad \text{R}_3 \quad \text{R}_4 \quad \text{R}_5
\]


\[
\text{S} \quad \text{N} \quad \text{COOH} \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{R} \quad \text{X} \quad \text{N} \quad \text{COOH}
\]
21. **Saito et al (2009)**\(^{21}\), reported that Botryllazine B analogues of diverse substitution patterns have been prepared. Among the 15 compounds 6-(4-aminophenyl)-2-(4-hydroxyphenyl) carbonylpyrazine proved to be the most potent inhibitor, with IC\textsubscript{50} \(\approx 0.91\) mM. Kinetic analyses of botryllazine B revealed that these inhibitors exhibit an unprecedented mixed-type inhibition on h-ALR2 with respect to the substrate D,L-glyceraldehyde, in the presence of NADPH at inhibitor concentrations near the IC\textsubscript{50} values.

![Chemical Structure](image1)

22. **Kyriaki Pegklidou et al (2009)**\(^{22}\), synthesized Pyrrolyl-propionic and butyric-acid derivatives in order to study the effect of the variation of the methylene chain in comparison to the previously reported pyrrolyl-acetic acid compound which was found as potent aldose reductase inhibitor. Result indicate that the presented chemotypes are promising lead compounds for the development of selective aldose reductase inhibitors, aiming to the long-term complications.

![Chemical Structure](image2)

23. **Wanga et al (2009)**\(^{23}\), reported new derivatives of (Z)-5-(4-hydroxybenzylidene)-4-(4-hydroxyphenyl)furan-2(5H)-one as aldose reductase inhibitors.

![Chemical Structure](image3)

24. **Yukinori Shimoshige et al (2009)**\(^{24}\), examined the effect of zenarestat, an aldose reductase inhibitor, on the morphological derangement of the DRG and the sural
nerve of streptozotocin-induced diabetic rats (STZ rats) over a 13-month period. A decrease in fiber size was apparent in the sural nerve of the STZ rats, and the fiber density was greater. The data suggest that, in peripheral sensory diabetic neuropathy, hyperactivation of the polyol pathway induces abnormalities not only in peripheral nerve fiber, but also in the DRG, which is an aggregate of primary sensory afferent cell bodies.

25. **Pablo R. Olmos et al (2009)**\(^{25}\), demonstrated that high glucose mean faster worsening for both diabetic retinopathy and nephropathy and answered, why so many type-2 diabetics develop nephropathy but no retinopathy? They may be due to genetic susceptibility.

26. **Aruni Bhatnagar et al (2009)**\(^{26}\), tested the hypothesis that AR inhibitor protects against ischemic injury by preventing ER stress induced by excessive accumulation of aldehyde-modified proteins in the ischemic heart. Observations support the notion that by removing aldehydic products of lipid peroxidation, AR decreases ischemia–reperfusion injury by diminishing ER stress.

27. **Ossama El-Kabbani et al (2009)**\(^{27}\), used Molecular modelling studies together with binding constant measurements for the four inhibitors Tolrestat, Minalrestat, quercetin and 3,5-dichlorosalicylic acid (DCL) to determine the type of inhibition, and correlate inhibitor potency and binding energies of the complexes with ALR2 and the homologous aldehyde reductase (ALR1), another member of the AKR superfamily. Our results show that the four inhibitors follow either uncompetitive or non-competitive inhibition pattern of substrate reduction for ALR1 and ALR2 while modelling studies suggest that Minalrestat’s binding to ALR1 is accompanied by a conformational change including the side chain of Tyr116 to achieve the selectivity for ALR1 over ALR2.
28. **Ki Hwan Bae et al (2009)**, determined structural composition of methanol extract of Moutan cortex (*Paeonia suffruticosa*) and evaluated for their inhibitory effects against rat lens aldose reductase (RLAR) and advanced glycation end-product (AGEs) formation. Compounds showed the most potent inhibitory activity against RLAR, with IC$_{50}$ values of 11.4 and 28.8 µM, respectively.

29. **Jin Sook Kim et al (2008)**, isolated novel 2,3-dioxygenated flavanone, erigeroflavanone (1), as well as eight known flavonoids and two known γ-pyranone derivatives, from an ethyl acetate-soluble extract of the flowers of *Erigeron annuus*. All of the isolates were subjected to *in Vitro* bioassays to evaluate their inhibitory activity against advanced glycation end products formation and rat lens aldose reductase.

![Chemical Structure](image)

30. **Jae Sue Choi et al (2008)**, evaluated the preventive and therapeutic potency of *Nelumbo nucifera* against oxidative stress and diabetic complications via 1,1-diphenyl-2-picrylhydrazyl (DPPH), Trolox equivalent antioxidant capacity (TEAC), and total reactive oxygen species (ROS) assays, as well as the rat lens aldose reductase (RLAR) and advanced glycation endproducts (AGE) assays. The leaf extract of *N. nucifera* exerted potent antioxidant effects as well as marked inhibitory effects for RLAR and AGE formation, corresponding to high values for total phenolic content (TPC) and total flavonoid content (TFC).

31. **Love K. Soni et al (2008)**, subjected the acetic acid derivatives of 1,2,4-triazino-4,3-a-benzimidazole as aldose reductase inhibitors for QSAR (quantitative structure activity relationship) modeling studies. A total 25 compounds were modelled in MOE and the QSAR model was generated using training set of 17 compounds employing sequential multiple linear regression analysis method. The internal consistency of the training set was confirmed by using leave-one-out (LOO) cross validation method to ensure the robustness of the model. The predictive ability of
model was further confirmed by a test set of eight compounds, so the model can be used to improve the activity of 1,2,4-triazino-4,3-\(a\)-benzimidazole acetic acid derivatives.

![Chemical structures](image1)

32. **Oya Bozdag-Dundar et al (2008)**\(^{32}\), prepared series of chromonyl-2,4-thiazolidinediones by Knoevenagel reaction with substituted 3-formylchromones (3aee) and unsubstituted (1) or substituted 2,4-thiazolidinedione (2). The synthesized compounds were tested for their ability to inhibit rat kidney AR by an in vitro spectrophotometric assay. Compound IIIe showed the highest inhibitory activity.

![Chemical structures](image2)

33. **Andrew G. Mercader et al (2008)**\(^{33}\), performed a predictive analysis based on quantitative structure–activity relationships (QSAR) of an important property of flavonoids, which is the inhibitor of aldose reductase (AR). The importance of AR inhibition is that it prevents cataract formation in diabetic patients. The best linear model constructed from 55 molecular structures incorporated six molecular descriptors, selected from more than a thousand geometrical, topological, quantum-mechanical, and electronic types of descriptors.

34. **Love Kumar Soni et al (2008)**\(^{34}\), performed QSAR study on a series of 5-arylidene-2,4-thiazolidinediones using the Fujita-Ban and the classical Hansch approach and molecular modeling studies employing AM1 calculations to gain structural insight into the binding mode of these molecules to the aldose reductase enzyme. The QSAR models were generated using 18 compounds. The predictive ability of the resulting QSAR models was evaluated employing the leave one-out method of cross validation. Remarkably, the results obtained from the Fujita-Ban...
and Hansch approaches were in agreement with the molecular modeling studies. The QSAR analysis reported herein confirms that the presence of the carboxylic anionic head of the N-3 acetic chain is an important, albeit not essential, structural requisite to produce high levels of enzyme inhibition.

![Chemical structure](image)

35. **David k. Wilson et al (2008)**, reported the refined 1.8 Å x-ray structure of the human holoenzyme complexed with zopolrestat, one of the most potent noncompetitive inhibitors. The zopolrestat fits snugly in the hydrophobic active site pocket and induces a hinge-flap motion of two peptide segments that closes the pocket. The structure is key to understanding the mode of action of this class of inhibitors and for rational design of better therapeutics.

![Chemical structure](image)

36. **Rosanna Maccari et al (2008)**, synthesized and evaluated number of 5-arylidene-2,4-thiazolidinediones containing a hydroxy or a carboxymethoxy group in their 5-benzylidene moiety as in vitro aldose reductase (ALR2) inhibitors. Most of them exhibited strong inhibitory activity, with IC$_{50}$ values in the range between 0.20 and 0.70 μM. Molecular docking simulations into the ALR2 active site highlighted that the phenolic or carboxylic substituents of the 5-benzylidene moiety can favourably interact, in alternative poses, either with amino acid residues lining the lipophilic pocket of the enzyme, such as Leu300, or with the positively charged recognition region of the ALR2 active site.

![Chemical structure](image)
37. **Alexiou et al (2008),** reported that N-(3,5-Difluoro-4-hydroxy phenyl) benzenesulfonamide and its derivatives were prepared as putative bioisosteres. The in vitro aldose reductase inhibitory activity of the prepared compounds is higher than that of the respective glycine derivatives. The parent compound 4 reveals high antioxidant potential.

![Glycine Derivative](image)

38. **Costantino et al (2008),** reported a new series of benzo[h]cinnolinone carboxylic acids, variously substituted at the positions 4, 7–10 and differently modified both at the central ring and at the acidic side chain, were synthesized and tested as inhibitors of ALR2. In addition to the importance of the acidic side chain, their properties are highly influenced by the substituents present on the benzo[h]cinnolinone nucleous, with potency ranging from that of Sorbinil to very weakly active compounds.

![Benzo[h]cinnolinone Carboxylic Acids](image)

39. **Concettina La Motta et al (2008)**, synthesized number of 1,2,4-oxadiazol-5-yl-acetic acids and oxazol-4-yl-acetic acids and tested for their ability to inhibit aldose reductase (ALR2). The lead compound, 2-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]acetic acid, 7c, showed an excellent in vivo activity, proving to prevent cataract development in severely galactosemic rats when administered as an eye-drop solution in the precorneal region of the animals. Computational studies on the ALR2 inhibitors were performed to rationalize the structure-activity relationships observed and to provide the basis for further structure-guided design of novel ALR2 inhibitors.
40. **Stefek et al (2008)**, reported a series of 2-(2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-yl)acetate were synthesized and evaluated. potassium 2-(2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-yl)acetate show high potency and selectivity with IC$_{50}$ value at micromole.

41. **Hans-Jörg Martin et al (2008)**, found that AKR1B10, a cytosolic member of the aldo–keto reductase superfamily, efficiently catalyzes the reduction of 4-hydroxynon-2-enal, 4-oxonon-2-enal and 4-Methylpentanal. AKR1B10 catalyzed 4-MP reduction with a 30-fold increase in activity using NADPH as cofactor compared with NADH. While the best substrates for AKR1B10 are retinals, the high catalytic efficiency together with the protection from inactivation by NADPH suggests a role of AKR1B10 in the detoxification of biogenic aldehydes.

42. **Ossama El-Kabbani et al (2008)**, determined the structure of aldehyde reductase (ALR1) in ternary complex with the coenzyme NADPH and 3,5-dichlorosalicylic acid (DCL), a potent inhibitor of human 20-α-hydroxysteroid dehydrogenase (AKR1C1), at 2.41 Å resolution. The inhibitor formed a network of hydrogen bonds with the active site residues Trp22, Tyr50, His113, Trp114 and Arg312. Molecular modelling calculations together with inhibitory activity measurements indicated that DCL was a less potent inhibitor of ALR1 (256-fold) when compared to AKR1C1. In AKR1C1, the inhibitor formed a 10-fold stronger binding interaction with the catalytic residue (Tyr55), non-conserved hydrogen bonding interaction with His222, and additional van der Waals contacts with the non-conserved C-terminal residues Leu306, Leu308 and Phe311 that contribute to the inhibitor’s selectivity advantage for AKR1C1 over ALR1.

43. **Jin Sook Kim et al (2007)**, evaluated whether KIOM-79, a mixture of extracts obtained from *Puerariae lobata*, *Magnolia officinalis*, *Glycyrrhiza uralensis* and *Euphorbia pekinensis*, could inhibit vascular endothelial growth factor (VEGF) expression in human retinal pigment epithelial (RPE) cells cultured under high glucose (HG, 25 mM) or S100b (a specific ligand of the receptor for advance...
glycation end products (RAGE).

44. **Matthias Zentgraf et al (2007)**, flexibly docked two related inhibitors into different conformers of aldose reductase. Although the overall binding topologies were roughly matched, significant deviations are observed in the subsequently determined crystal structures.

45. **Wang et al (2007)**, reported a series of 3,4 dihydroxyphenyl)acrylic acid were synthesized and evaluated. (Z)-2-benzoyl-3-(3,4-dihydroxyphenyl)acrylic acid shown a high selectivity towards aldose reductase.

46. **Rosanna Maccari et al (2007)**, reported a series of non-carboxylic acid containing 2,4-thiazolidinedione derivatives, analogues of synthesized carboxylic acids which was very active in vitro aldose reductase (ALR2) inhibitors. Although the replacement of the carboxylic group with the carboxamide or N-hydroxycarboxamide one decreased the in vitro ALR2 inhibitory effect which led to the identification of mainly non-ionized derivatives with micromolar ALR2 affinity. The 5-arylidene moiety deeply influenced the activity of these 2,4-thiazolidinediones. Induced-fit docking studies suggested that 5-(4-hydroxybenzylidene)-substituted derivatives may bind the polar recognition region of the ALR2 active site by means of the deprotonated phenol group, while their acetic chain and carbonyl group at position 2 of the thiazolidinedione ring form a tight net of hydrogen bonds with amino acid residues of the lipophilic specificity pocket of the enzyme.
47. **Motta et al (2007)**, reported 2-Phenyl-pyrido[1,2-α]pyrimidin-4-one derivatives bearing a phenol or a catechol moiety in position 2 were tested as aldose reductase (ALR2) inhibitors. Introduction of a hydroxy group in position 6 or 9 (R₁, R₂ – OH) gave an enhancement of the inhibitory potency. All the pyridopyrimidineones displayed significant antioxidant properties, with the best activity shown by the catechol derivatives.

48. **GuanHua Chen et al (2006)**, developed a novel approach that combines neural networks, computer docking and quantum mechanical method to design potent aldose reductase inhibitors (ARIs). Neural network is employed to determine the QSAR among the known ARIs while the physical descriptors of the neural networks, such as electronegativity and molar volume, are evaluated with first-principles quantum mechanical method. Based on the QSAR, new candidates for ARI are predicted, and subsequently screened via computer docking technique.

49. **Love K. Soni et al (2006)**, reported quantitative structure–activity relationship (QSAR) analysis performed by 3D-QSAR analysis, Hansch analysis, and Fujita-Ban analysis on a series of 5-arylidene-2,4-thiazolidinediones as aldose reductase inhibitors. The 2D & 3D-QSAR models were generated using 18 compounds and Fujita-Ban analysis models were obtained using 23 compounds. The predictive ability of the resulting 2D and 3D models was evaluated against a test set of 5
compounds. Analyses of results from the present QSAR study inferred that 3rd position of the phenyl ring and acetic acid substitution at N-position of thiazolidinediones play a key role in the aldose reductase inhibitory activity.

50. David M. Ribnicky et al (2006)\textsuperscript{50}, examined antidiabetic activity of ethanolic extract of Artemisia dracunculus L. as a possible aldose reductase (ALR2) inhibitor, a key enzyme involved in diabetic complications. At 3.75 µg/mL, the total extract inhibited ALR2 activity by 40%, while quercitrin, a known ALR2 inhibitor, inhibited its activity by 54%. These results suggest a use of the extract of A. dracunculus for ameliorating diabetic complications.

51. Hoshik Won et al (2006)\textsuperscript{51}, employed racemate physicochemical descriptors, to probe the quantitative structure activity relationship of spirosuccinimide type aldose reductase inhibitors and the in vivo inhibitory activity of sorbitol accumulation. The in vivo activity data include the percent inhibition and ED\textsubscript{50} assay. The derived QSAR equations show that the hydrophobic character of aldose reductase inhibitor is the major contributing factor to enhance in vivo activity. As the hydrophobicity of compounds is related to both the membrane permeability and the binding affinity to the aldose reductase, its contribution to the pharmacokinetic behavior is further scrutinized by evaluating pKa and the Caco-2 cell permeability.

52. Rakowitz et al (2006),\textsuperscript{52} reported that several substituted benzyloxyphenylacetic acids were prepared. Comparison of their aldose reductase inhibition with the biological activity obtained for recently evaluated benzoic acid analogues revealed
the critical role of a methylene spacer between the aromatic core and the acidic function. Starting from the most potent derivative (i.e. 5d, IC$_{50}$ = 20.9 µM) further structural modifications were performed and their influence on the inhibitory effect was established.

53. Jesus Angel de la Fuente et al (2006)$^{53}$, isolated four different types of marine natural compounds from tunicates found to inhibit human aldose reductase. They all are characterized by a heterocyclic system, and at least two phenolic groups are present in the structure. Two of the compounds tested showed an inhibitory potency 5/6-fold higher than that of the known AR inhibitor sorbinil. One notable structural feature of these active compounds is the lack of either the carboxylic acid or the spiro-hydantoin commonly present in the principal classes of currently used inhibitors.

54. Ossama El-Kabbani et al (2005)$^{54}$, carried out structure determination of porcine aldehyde reductase holoenzyme in complex with the potent aldose reductase inhibitor fidarestat to explain the difference in the potency of the inhibitor for aldose and aldehyde reductases. The hydrogen bonds between the active-site residues Tyr50, His113, and Trp114 and fidarestat are conserved in the two enzymes. In aldose reductase, Leu300 forms a hydrogen bond through its main-chain nitrogen atom with the exocyclic amide group of the inhibitor, which when replaced with a Pro in aldehyde reductase, cannot form a hydrogen bond, thus causing a loss in binding energy. Furthermore, in aldehyde reductase, the side chain of Trp220 occupies a disordered split conformation that is not observed in aldose reductase.
reductase. Molecular modeling and inhibitory activity measurements suggest that the difference in the interaction between the side chain of Trp220 and fidarestat may contribute to the difference in the binding of the inhibitor to the enzymes.

55. Banavara L. Mylari et al (2005), performed high-throughput screening of internal libraries of compounds and identified 6-phenylsulfonylpyridazin-2H-3-one, 8, which showed modest inhibition of AR, both in vitro and in vivo. Initial structure-activity relationships concentrated on phenyl substituents and led to 6-(2,4-dichlorophenylsulfonyl)-2H-pyridazin-3-one, which was more potent both in vitro and in vivo.

56. Settimo et al (2005), reported that The 2,3-dihydrospiro[4H-thiopyrano[2,3-b]pyridin-4,40-imidazolidine]-20,50-dione 3 and its 7-methyl analogue 4 (X-S) were synthesized and tested for their ability to inhibit aldose reductase (ALR2). To expand the structure–activity relationships, the sulfone and the acetic acid derivative were also prepared and tested. Compounds 3 and 4 (R-CH₃) proved to be potent ALR2 inhibitors, with IC₅₀ values in the submicromolar range (0.96 and 0.94µM, respectively) similar to that of sorbinil (0.65µM).
57. **Youngdo Won et al (2005)**\(^{57}\), investigate the quantitative structure activity relationship of spirosuccinimide-fused tetrahydropyrolo[1,2-a]pyrazine-1,3-dione derivatives acting as aldose reductase inhibitors, which contain a chiral center. The resultant QSAR model derived from the racemic descriptors outperforms the original QSAR models. The racemic QSAR model shows that the hydrophobic character of the benzyl moiety is the major contributing factor to the aldose reductase inhibitory activity and the polar surface area descriptors modulate the inhibitory activity.

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_4
\end{align*}
\]

58. **Settimo et al (2005)**\(^{58}\) reported Acetic acid derivatives of naphtho[1,2-d]isothiazole (NiT) were synthesized and tested as novel aldose reductase (ALR2) inhibitors. The parent compound 11 exhibited a fair inhibitory activity (IC\(_{50}\) 10 \(\mu\)M), which was enhanced by 2 orders of magnitude by introducing a second carboxylic group at position 4 (13 and 14: IC\(_{50}\) 0.55 and 0.14 \(\mu\)M, respectively).

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{COOH} & \quad \text{O}
\end{align*}
\]

59. **Van Zandt et al (2005)**\(^{59}\) reported a novel series of highly potent and selective 3-[(benzothiazol-2-yl)methyl]indole- \(N\)-alkanoic acid aldose reductase inhibitors. The lead candidate, 3-[(4,5,7 trifluorobenzothiazol- 2-yl)methyl]indole-\(N\)-acetic acid (lidorestat, 9) inhibits aldose reductase with an IC50 of 5 nM, while being 5400 times less active against aldehyde reductase.

\[
\begin{align*}
\text{N} & \quad \text{S} \\
\text{O} & \quad \text{COOH}
\end{align*}
\]
60. **V.S. Ghole et al (2005)**, studied AR inhibitory activity of Diabecon (an herbal drug used for diabetes) against sugar-induced lens opacity in organ culture. Diabecon aqueous extract (DAE) showed potential inhibitory activity with an IC\textsubscript{50} value of 10µg/ml against rat lens AR. Also demonstrated here that most of these effects are mainly due to *Gymnema sylvestre*, one of the constituent herbs of Diabecon. These results suggest that Diabecon protect the lens against sugar-induced cataract by multiple mechanisms.

61. **Maykel Perez Gonzalez et al (2005)**, modeled inhibitory activity of flavonoid against aldose reductase enzyme using molecular descriptors from Dragon software. In addition, artificial neural networks were trained using charge indices from the linear models but the obtaining networks overfitted the data having low predictive power.

62. **Catherine Koukoulitsa et al (2005)**, investigated five polar constituents of Origanum vulgare L. for their ability to inhibit aldose reductase (ALR2), the first enzyme of the polyol pathway implicated in the secondary complications of diabetes. The most active compound was found to be lithospermic acid B. Docking studies have been undertaken to gain insight into the binding mode of the investigated compounds at the active site of ALR2.

63. **Pau et al (2004)**, reported a novel series of tetrahydrothieno[2,3-\textit{h}]cinnolinone derivatives. Compounds 2e (n- 5, R - H) and 2j (n- 5, R – CH\textsubscript{3}) exert a remarkable inhibitory effect, with IC\textsubscript{50} of 7.6 and 18 µM, respectively. These compounds
incorporate a valid pharmacophore for aldose reductase inhibitory activity represented by a thienocinnolinone template linked through a pentamethylene spacer to a carboxylic function.

64. Nicolaou et al (2004),\(^\text{64}\) had reported that \([1-(3,5-\text{Difluoro-4-hydroxyphenyl})-1H-pyrrol-3-yl]\)phenylmethanone (6) was synthesized as a putative bioisostere of the known aldose reductase (AR) inhibitor (3-benzoylpyrrol-1-yl)acetic acid (I). It was found that 6 is approximately 5 times more potent as an in vitro inhibitor of AR than I, with an IC\(_{50}\) value in the submicromolar range.


66. Van Zandt et al (2004),\(^\text{66}\) reported a series of 2-(2 (benzylcarbamoyl)phenoxy) acetic acid as aldose reductase inhibitors.

Ossama El-Kabbani et al (2004), carried out complexation of human aldose reductase holoenzyme with the $2S4R_-$, $2R4S_-$ and $2R4R_-$-isomers of the potent inhibitor Fidarestat ($2(S,4S)$-6-fluoro-2,5-dioxospiro-[chroman-4,4-imidazoline]-2-carboxamide) in order to elucidate the binding modes responsible for the differences in their inhibitory potencies. The structures of the complexes suggest that the differences in the interactions between the cyclic imide rings and carbamoyl groups of the compounds with residues His110, Trp111, Trp219 and Cys298 account for differences in their inhibitory potencies.

![Chemical Structure](image)


H K. Srivastava et al (2003), demonstrated that treatment with inhibitors of the aldehyde-metabolizing enzyme and aldose reductase (AR) attenuates restenosis of balloon-injured rat carotid arteries. The inhibition of AR also prevents the apoptosis of VECs induced by the tumor necrosis factor-alpha (TNF-$\alpha$). Results suggest that product(s) of AR catalysis may be essential for NF-kB activation. These observations could form the basis of future investigations into the therapeutic utility of AR inhibitors in preserving endothelial function and integrity during atherosclerosis and diabetes.


S.K. Gupta et al (2003), investigated lens AR inhibition activity of four plants to different extent. From dose–response curve, Ocimum sanctum (OS) was found to be the most effective AR inhibitor followed by Curcuma longa (CL), Azadirachta indica (AI) and Withania somnifera (WS). The IC$_{50}$ values of OS, CL, AI and WS were calculated to be 20, 55, 57 and 89µg/ml, respectively. OS possesses a significant anticataract activity in vitro and its anticataract potential could be related with its AR inhibitory effect.

70. **Mylari et al (2003)**

Mylari et al (2003), reported that high-throughput screening of our internal libraries of compounds and identified 6-phenylsulfonylpyridazin-2H-3-one, 8, which showed modest inhibition of AR, both in vitro and in vivo. Initial structure-
activity relationships concentrated on phenyl substituent and led to 6-(2,4-
dichlorophenylsulfonyl)-2\textit{H}-pyridazin-3-one, 8l (2,4-Cl) which was more potent
than 8.

![Chemical Structure](image)

71. **Fuente et al (2003),**\(^71\) reported that study, a polybrominated diphenyl ether (1)
naturally occurring in a marine sponge was found to inhibit recombinant human
ALR2 with an IC\(_{50}\) of 6.4 \(\mu\)M. A series of polyhalogenated analogues that were
synthesized. the most potent synthesized analogue (16) showed a 17-fold increase
in inhibitory activity compared to that of sorbinil (IC\(_{50}\)) 0.24 vs 4 \(\mu\)M

![Chemical Structure](image)

72. **Nicolaou et al (2003),**\(^72\) reported a series of 3-aroyl and 2,4-bis-aroyl derivatives
were synthesized. Important structural features for the potent compounds is the
presence of substituents with relatively low Hammett \(\delta\) values and/ or moieties
which increase their overall aromatic area. The most active derivative was the [2,4-
bis(4 methoxybenzoyl) pyrrol-1-yl]acetic acid, with potency favorably compared to
known ARIs such as tolrestat, epalrestat, zopolrestat, and Fidarestat.

![Chemical Structure](image)

73. **Sun et al (2003),**\(^73\) reported A series of 45 phenethylamine derivatives were
synthesized and evaluated. Their IC\(_{50}\) values ranged from 400 \(\mu\)M to 24 \(\mu\)M. The
binding modes of compounds at the active site of ALR2 were examined using
flexible docking. The results indicated that phenethylamine derivatives nicely fit
into the active pocket of ALR2 by forming various hydrogen bonding and hydrophobic interactions. The best prediction was obtained by CoMSIA combined with hydrophobic and hydrogen bond donor/acceptor field ($q_2$ 0.557, $r_2$ 0.934).

74. **Masayuki Yoshikawa et al (2003)**\(^74\), isolated three new friedelane-type triterpenes from the 80% aqueous methanolic extract of the stems of *Salacia chinensis* collected in Thailand. Their stereostructures were elucidated on the basis of chemical and physicochemical evidence. In addition, six constituents were found to show an inhibitory effect on rat lens aldose reductase.

75. **Federico Da Settimo et al (2003)**\(^75\), synthesized Cyano (2-oxo-2,3-dihydroindol-3-yl)acetic acid derivatives and tested as a novel class of aldose reductase (ALR2) inhibitors. Each compound was evaluated as a diastereomeric mixture, due to tautomeric equilibria in solution. The parent compound 39 exhibited a good inhibitory activity with an IC\(_{50}\) value of 0.85 µM, similar to that of the well-known ARI Sorbinil (IC\(_{50}\) 0.50 µM).

76. **Banavara L. Mylari et al (2002)**\(^76\), report here a novel sorbitol dehydrogenase inhibitor, 16, that shows very high oral potency (50 µg/kg) in normalizing elevated
fructose levels in the sciatic nerve of chronically diabetic rats and sustained duration of action (>24 h). Furthermore, 16 shows attractive pharmaceutical properties, including good solubility in simulated human gastric fluid, excellent Caco-2 Papp, moderate lipophilicity, and metabolic stability for achieving good oral absorption and long duration of action.

\[
\text{Chemical structure of compound 16}
\]

77. **Rakowitz et al (2002)**\(^{77}\) reported new series of acetic acid as aldose reductase inhibitors were synthesized and evaluated.

\[
\text{Chemical structures of compounds 2 and 4c}
\]

78. **R. Maccari et al (2002)**\(^{78}\), synthesized several (Z)-5-arylidene-2,4-thiazolidinediones and tested as aldose reductase inhibitors (ARIs). The most active of the N-unsubstituted derivatives (2) exerted the same inhibitory activity of Sorbinil. The introduction of an acetic side chain on N-3 of the thiazolidinedione moiety led to a marked increase in lending inhibitory activity, conducting to the discovery of a very potent ARI (4c), whose activity level (IC\(_{50}=0.13\) mM) was in the same range of Tolrestat. The substitution pattern on the 5-benzylidene moiety markedly influenced the activity of N-unsubstituted 2,4-thiazolidinediones 2, compounds with substituent at the meta position being generally more effective than the para-substituted one.

\[
\text{Chemical structure of compound 4c}
\]
79. **Tom Solmajer et al (2002)**, performed a thorough investigation of the available experimental data base by using both classical and quantum chemical descriptors in order to develop quantitative structure-activity relationships for these enzyme systems. Relevance of the descriptors to binding properties of both enzyme receptors active site is proposed and the obtained results demonstrate in detail which specific electronic as well as the hydrophobic and steric properties of the substituents play a significant role in their differential binding.

80. **Iwata et al (2001)**, reported structure-based drug design and synthesis in an attempt to find new types of AR inhibitors.

81. **Lewis et al (2001)**, reported that HAR-1 (1H,7H-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran-3-acetic acid) was identified as an ARI with IC$_{50}$ for aldose reductase inhibition at 2 nM. Polyol accumulation in lens epithelial cells was reduced by 80% at 10 µM. HAR-1 is a novel ARI which normalized losses of PKC$_{\gamma}$, changes in Cx46 phosphorylation, and gap junction activity.

82. **Settimo et al (2001)**, reported Acetic acid derivatives of [1,2,4]-triazino-[4,3-a]-benzimidazole(TBI) were synthesized. Compound 3, (10-benzyl[1,2,4]triazino[4,3-a]benzimidazol-3,4(10H)-dion-2-yl)acetic acid, displayed the highest inhibitory activity (IC$_{50}$ ) 0.36 fM) and was found to be effective in preventing cataract development. The activity of 3 was lowered by inserting various substituents on the pendant phenyl ring, by shifting the acetic acid moiety from the 2 to the 3 position of the TBI nucleus, or by cleaving the TBI system to yield benzimidazolylidene-hydrazines as open-chain analogues.
83. **Costantino et al (2001)**, reported a series of $4H$-1-benzopyran-4-one derivatives was synthesized. These compounds possess higher pKa values than carboxylic acids, a characteristic which could make the pharmacokinetics of these compounds very interesting.

![Chemical structure](image)

84. **Yoriko Iwata et al (2001)**, carried out structure-based drug design and synthesis in an attempt to find new types of AR Inhibitors. With the ADAM & EVE program, a three-dimensional database (ACD3D) was searched using the ligand binding site of the AR crystal structure. Out of 179 compounds selected through this search followed by visual inspection, 36 compounds were purchased and subjected to a biological assay. Ten compounds showed more than 40% inhibition of AR at a 15 µg/mL concentration. In a subsequent lead optimization, a series of analogues of the most active compound were synthesized based on the docking mode derived by ADAM&EVE. Furthermore, a hydrophobic subsite was newly inferred, which would be useful for the design of inhibitors with improved affinity for AR.

![Chemical structure](image)

85. **Banavara L. Mylari et al (2001)**, reported efforts to provide a potent sorbitol dehydrogenase inhibitor (SDI) as a tool to probe a recently disclosed hypothesis centered on the role of sorbitol dehydrogenase (SDH) in the second step of the polyol pathway, under conditions of high glucose flux. Described an expedient synthesis of a key building template, 33, for future research in the SDI area that may facilitate the discovery of even more potent SDIs with longer duration of action in vivo.
Chapter 2  
Review of Literature

86. **Rudolf Bauer et al (2000)**\(^86\), isolated two novel prenyl 3-benzoxepin derivatives, perilloxin (1) and dehydroperilloxin (2), from the dichloromethane extract of the stems of *Perilla frutescens* var. *acuta*. They were isolated following bioassay-guided fractionation, using an in vitro cyclooxygenase-1 test. Compounds 1 and 2 possess inhibitory activities, with IC\(_{50}\) values of 23.2 µM and 30.4 µM, respectively.

87. **Oka et al (2000)**\(^87\) reported the crystal structure of human AR complexed with fidarestat was determined. The structure clarified that fidarestat was located in the active site by hydrophilic and hydrophobic interactions and that the carbamoyl group of fidarestat was a very effective substituent for affinity to AR and for selectivity between AR and aldehyde reductase (AHR).

88. **Inoue et al (2000)**\(^88\) reported a novel series of 14 N-nitromethylsulfonanilide derivatives were synthesized and evaluated for their ability to inhibit recombinant aldose reductase. Kinetic analysis of (2-fluoro-5-methyl-N-methyl)-N-nitromethyl sulfonanilide, 11, one of the most potent compounds in this series with an IC\(_{50}\)=0.35 mM, showed uncompetitive inhibition. Subsequent in vitro culture studies of rat lenses with 11 indicated that this series of aldose reductase inhibitors are effective in either preventing or retarding sugar cataract formation associated with diabetes.
89. Murata et al (1999)\textsuperscript{89}, reported a series of 2-(1-((4-oxo-2-thioxothiazolidin-5-ylidene) methyl)naphthalen-2-yloxy)acetic acid were synthesized and evaluated as aldose reductase inhibitors.

90. Costantino et al (1999),\textsuperscript{90} reported 4H-chromen-4-one derivatives as aldose reductase inhibitors.

91. Costantino et al (1999),\textsuperscript{91} reported the isoxazolo-[3,4-d]-pyridazin-7-(6H)-one (2) and its corresponding open derivatives 5-acetyl-4-amino-(4-nitro)-6-substituted 3(2H) pyridazinones.

92. Inoue et al (1999),\textsuperscript{92} reported that a number of dibenzocycloheptanone derivatives, a novel series of aldose reductase inhibitors were synthesized and evaluated. The most active compound in this series was a spirosuccinimide derivative, spiro [2,8-dihydroxy-5h-dibenzo[a,d]-cycloheptene-5,3-prrrolidine] – 2,5’dione, having an \( IC_{50} \) of 3.0 \( \mu \)M.
93. Severi et al (1998),\textsuperscript{93} reported (E)-1-(2,4-dihydroxyphenyl)-3-phenylprop-2-en-1-one identified as potent and selective inhibitors of aldose reductase with IC\textsubscript{50} at micromole.

94. Negoro et al (1998),\textsuperscript{94} reported that a series of novel tetrahydropyrrolo[1,2-a]pyrazine derivatives were synthesized. It was found that AR inhibitory activity resides in the (-)-enantiomer 43 (AS-3201), which was 10 times more potent in inhibition of the AR (IC\textsubscript{50} 1.5-1.8 M) and 500 times more potent in the in vivo activity (ED\textsubscript{50} 0.18 mg/kg/day for 5 days) than the corresponding (+)-enantiomer 44 (SX-3202).

95. Macchia et al (1998),\textsuperscript{95} reported that synthesis and aldose reductase (AR) inhibitory properties of some N-(benzyloxy)glycine derivatives. In compounds 2-5, spacers of different lengths and degrees of rigidity were inserted between the phenyl ring and the carbonyl group of type A derivatives; compound 6 differs from the most active type A derivative (compound 1) in the replacement of the methoxy moiety in the para position of the benzoyl side-chain with a group with different electronic characteristics, such as the trifluoromethyl moiety. Biological results indicated that among compounds 2-5 only derivative 3, which present a CH\textsubscript{2}CH\textsubscript{2}
spacer between the phenyl and the carbonyl moiety, proved to possess AR inhibitory properties.

96. **Benvenuti et al (1998)**,\(^96\) reported 2-benzamidoacetic acid derivatives as aldose reductase inhibitors.

97. **Max Cussac et al (1998)**\(^97\), prepared series of 2,4-dioxo-5-(2-naphthylmethylene)-3-thiazolidineacetic acids and 2-thioxo analogues as aldose reductase inhibitors. In vitro inhibitory activities of bovine lens aldose reductase were determined by a conventional method. 1-Naphthyl-substituted derivatives of the 2-thioxo series were the more potent inhibitors (IC\(_{50}\) = 10 nM) with similar activity to that of Epalrestat. Structural analysis, and molecular modeling comparisons with Zopolrestat were performed provide explanations of the good activity of the inhibitor, the preference for 1-naphthylsubstituted compounds, and the nature of molecular interactions in these systems.

98. **Stefania Benvenuti et al (1998)**\(^98\), synthesized new series of chalcone derivatives and tested in vitro in order to assess their ability to inhibit aldose reductase enzyme (ALR2) and their specificity towards the target enzyme with respect to other oxidoreductases, such as aldehyde reductase, sorbitol dehydrogenase, and glutathione reductase. All the compounds display affinity for ALR2.
99. **Giulio Rasteili et al (1998)**, employed free energy perturbation simulations to rationalize the binding differences between a benzocinnolinone carboxylic acid inhibitor of aldose reductase and its methoxylated analogs in four selected substitution sites. The calculated free energy differences are in qualitative agreement with the experimental results. The balance between the cost for desolvation and the gain in enzyme binding correctly predicts and rationalizes the different inhibitory activities of each methoxylated compound.

100. **Rajeswaran et al (1998)**, reported 5-((1H-indol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives as potent and selective aldose reductase inhibitors were synthesized and evaluated.

101. **Djoubissie et al (1998)**, reported a series of acetic acid derivatives were synthesized and evaluated as aldose reductase inhibitors.

![Chemical structure](image1)

103. **Kotani et al (1997)** reported The uracil or 2,4-dioxoimidazolidine skeleton having the benzothiazolyl or 4-chloro-3-nitrophenyl group as an aryl part indicated not only extremely high AR inhibitory activity but also AR selectivity. The ratio of $IC_{50}(ALR)/IC_{50}(AR)$ of 3-[(5-chlorobenzothiazol-2-yl)methyl]-1,2,3,4-tetrahydro-2,4-dioxopyrimidine-1-acetic acid was more. The uracil skeleton with the benzothiazolyl moiety seemed to be the best combination for selective AR inhibition. Free-Wilson-type neural network analysis of the 5-membered ring compounds indicated that the carbonyl groups at C2 and C5 were important functional groups for AR inhibitory activity.

![Chemical structure](image2)

104. **A Urzhumtsev et al (1997)** suggest the active site of AR to bind tightly to different inhibitors; this happens both upon binding to the inhibitor’s hydrophilic heads, and at the hydrophobic and specificity pockets of AR, which can change their shape through different conformational changes of the same residues. This flexibility could explain the large variety of possible substrates of AR.

![Chemical structure](image3)
105. Costantino et al (1996),\textsuperscript{105} reported Three new series of tricyclic pyridazinones have been synthesized and tested \emph{in vitro} in order to assess (i) their ability to inhibit aldose reductase enzyme (ALR2) and (ii) their specificity toward the target enzyme with respect to other related oxidoreductases.

106. Ishii et al (1996),\textsuperscript{106} reported a series of 3-(arylalkyl)-2,4,5-trioxoimidazolidine-1-acetic acids. 3-(3-nitrobenzyl)-2,4,5-trioxoimidazolidine-1-acetic acid (NZ-314) was selected as the candidate for clinical development.

107. Settimo et al (1996),\textsuperscript{107} reported that Derivatives of [pyrrolo\{3,4-c\}pyridin-1,3(2/-/)dion-2-yl] alkanoic acids were prepared and their \emph{in vitro} aldose reductase inhibitory activity was tested on rat lens enzyme. The acetic derivatives 2, 5 (X-H, Cl, R-H, R\textsubscript{1}-H) and 15a-d proved to be much more potent inhibitors than the propionic derivatives and the iso-propionic derivatives. The presence of a second planar aromatic area in the benzoyl derivatives did not result in any increase in activity.

108. Hiroyuki Haraguchi et al (1996)\textsuperscript{108}, evaluated sulfated flavonoids in \textit{Polygonum hydropiper} as potent inhibition against lens aldose reductase. Among these flavonoids isorhamnetin 3,7-disulfate (5) was most potent. Kinetic analysis showed that 5 exhibited noncompetitive inhibition against both \textit{dl}-glyceraldehyde and NADPH.

110. Hotta et al (1995),\textsuperscript{110} reported a series of series of 2-(5-(thiophen-3-yl)-4,5-dihydrotetrazol-1-yl) acetic acid were synthesized and evaluated as aldose reductase inhibitors.

111. Holger Steuber et al (1993)\textsuperscript{111}, investigated the selectivity-determining features by gradually mapping the residues deviating between the binding pockets of ALR1 and ALR2 into the ALR2 binding pocket. The binding properties of mutants were evaluated using a ligand set of zopolrestat, sorbinil, fidarestat and tolrestat. study revealed induced-fit adaptations within the mutated binding site as an essential prerequisite for ligand accommodation related to the selectivity discrimination of the ligands.

112. Duane D. Miller et al (1992)\textsuperscript{112}, designed 5-bromoacetamide and 5-iodoacetamide analogues which gave irreversible inhibition of aldose reductase while the 5-chloracetamide analogues did not show this type of inhibition. Protection studies indicate that irreversible inhibitions are occurring at the inhibitor binding site. Comparative irreversible inhibition studies with rat lens aldose reductase (RLAR) and rat kidney aldehyde reductase (RKALR) was determined.
113. Mizuno et al (1992),\textsuperscript{113} reported hydantoin derivatives as aldose reductase inhibitors.

114. Ao S. et al (1991),\textsuperscript{114} reported a series of 2-(3-(4-bromo-2-fluorobenzyl)-7-chloro-2,4-dioxo-3,4-dihydroquinazolin-1(2H)-yl)acetic acid as aldose reductase inhibitors.

115. Shizuo Ao et al (1991),\textsuperscript{115} investigated the effect of aldose reductase inhibitor FR74366 on diabetic cataract. Results of streptozocin (STZ)-induced diabetic rats treated with FR74366 for 16 weeks suggested that instillation of FR74366 may be a useful therapeutic agent against diabetic cataract and retinopathy.
116. **Heiner Glombik (1990)**[^116], achieved the stereoselective synthesis of the imidazolidinedione (+)-2, an inhibitor of aldose reductase via heterocyclic bis-lactim ether substitution, acidic cleavage and cyclizationation with urea.

![Imidazolidinedione](image)

117. **Jack De Ruiter et al (1986)**[^117], synthesized number of 2-(arylamino)-4(3H)-quinazolinones (2 a-i) that possess several of the pharmacophore moieties necessary for binding to the inhibitor site of the enzyme aldose reductase and tested for their ability to inhibit crude aldose reductase obtained from rat lens. Only those quinazolinones that possess an acidic moiety on the 2-(arylamino) substituent were found to display significant inhibitory activity, indicating that the pharmacophore moieties present in these compounds may not be positioned optimally relative to one another for maximal interaction with the enzyme.

![Quinazolinone](image)

118. **Allen B. Richon et al (1982)**[^118], evaluated compounds for activity in the rat lens aldose reductase assay. The percent inhibition of aldose reductase prepared from rat lenses was determined for each of the test compounds at a concentration of 50 pM by the procedure of Hayman and Kinoshita.

![Imidazolidinedione](image)
119. **Jurg R. Pfister et al (1980)**, synthesized and assayed series of xanthone-2-carboxylic acids substituted in the 7 position with sulfamoyl and other groups, in vitro for inhibition of aldose reductase isolated from rabbit lenses. At a concentration of 1.4 M, the N-methyl-N-(2-hydroxyethyl) sulfamoyl derivative produced an 83% inhibition of aldose reductase. The structural requirements for this type of activity are discussed.

\[
\begin{align*}
\text{RO}_2\text{S} & \quad \text{O} \\
\text{COOH} & \quad \text{O}
\end{align*}
\]

120. **Rosaria Ottana et al (1988)**, explored more effective 5-arylidene-4-thiazolidinones as aldose reductase inhibitors. Acetic acids 5 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.

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{R} & \quad \text{O}
\end{align*}
\]

121. **Uwe Machon et al (2004)**, identified new class of cysteine protease inhibitors based on fumaric acid derived oligopeptides from high-throughput screening of a solid-phase bound combinatorial library. As target enzymes falcipain and rhodesain were used, which play important roles in the life cycles of the parasites which cause malaria (Plasmodium falciparum) and African sleeping sickness (Trypanosoma brucei rhodesiense) the mechanism of action was also studied and could be shown to be irreversible inhibition.

\[
\begin{align*}
\text{HO} & \quad \text{O}_2\text{S} \\
\text{t-Bu} & \quad \text{O}
\end{align*}
\]
2.2. Thiazolidinone and Rhodanine Nucleus

1. **R. K. Agrawal et al (2012)**\(^{122}\), reviewed on Thiazolidinone and considered it as a biologically important active scaffold that possesses almost all types of biological activities. Successful introduction of ralitoline as a potent anti-convulsant, etozoline as a antihypertensive, pioglitazone as a hypoglycemic agent and thiazolidomycin activity against streptomyces species proved potential of thiazolidinone moiety. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. This review is complementary to earlier reviews and aims to review the work reported on various biological activities of thiazolidinone derivatives from year 2000 to the beginning of 2011. Data are presented for active compounds, some of which have passed the preclinical testing stage.

2. **Ronan Roussel et al (2012)**\(^{123}\), Use of TZD was not associated with increased incidence of major cardiovascular events in patients with diabetes from this large registry. Older patients experienced an increased risk of CHF over the study interval. Limitations of this study include its observational design, and thus unmeasured confounders cannot be excluded.

3. **Shih-Ann Chen et al (2012)**\(^{124}\), demonstrated that TZDs had obvious protective effects on the development of AF in diabetic patients. Drugs acting as ligands to the PPAR-\(\gamma\) may be potential up-stream therapies for AF prevention.

4. **Michael D. Mueller et al (2012)**\(^{125}\), Thiazolidinediones decrease the pro-inflammatory cytokines IL-6 and IL-8 in endometrial stromal cells via a PPAR-\(\gamma\)–independent mechanism. A better understanding of the anti-inflammatory action of this class of drugs may improve their safety and efficacy for endometriosis treatment.

5. **Rosanna Maccari et al (2011)**\(^{126}\), evaluated 2-Thioxo-4-thiazolidinone derivatives were as aldose reductase inhibitors (ARIs) and most of them exhibited good or excellent in vitro efficacy. Out of the tested compounds, most N-unsubstituted analogues were found to possess inhibitory effects at low micromolar doses and two of them exhibited higher potency than sorbinil, used as a reference drug.
6. **Rosaria Ottanà** et al (2011)\(^{127}\), explored a new set of suitably substituted compounds for more effective 5-arylidene-4-thiazolidinones as aldose reductase inhibitors, (4, 5 and 8). Acetic acids 5, particularly 5a and 5h, 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. Molecular docking experiments supported SAR studies.

7. **Changyou Zhou** et al (2010)\(^{128}\), performed Systematic structure–activity relationship (SAR) studies of a screening lead led to the discovery of a series of thiazolidinediones (TZDs) as potent GPR40 agonists. Among them, compound C demonstrated an acute mechanism-based glucose-lowering in an intraperitoneal glucose tolerance test (IPGTT) in lean mice, while no effects were observed in GPR40 knock-out mice.

8. **Ossama El-Kabbani** et al (2010)\(^{129}\), determined the structure of aldehyde reductase (ALR1) in ternary complex with the coenzyme NADPH and [5-(3-carboxymethoxy-4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl] acetic acid (CMD), a potent inhibitor of aldose reductase (ALR2), at 1.99 Å resolution. Molecular modelling calculations and inhibitory activity measurements of CMD and [5-(3-hydroxy-4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]acetic acid (HMD) indicated that p
stacking interactions with several conserved active site tryptophan residues and hydrogen-bonding interactions with the non-conserved C-terminal residue Leu300 in ALR2 (Pro301 in ALR1) contributed to inhibitor selectivity.

9. **M. J. Nanjan et al (2010)**\(^{130}\), designed some novel glitazones based on the structure–activity relationships as possible PPAR-\(\gamma\) agonists. The manually designed glitazones were synthesized by using the appropriate synthetic schemes and screened for their in vitro antihyperglycemic activity by estimating glucose uptake by rat hemi-diaphragm, both in the absence and in the presence of external insulin. Some of the glitazones exhibited good antihyperglycemic activity in presence of insulin.

10. **Rosaria Ottanà et al (2009)**\(^{131}\), identified effective low molecular weight non-phosphorus monoanionic inhibitors of PTPs and synthesized 4-[(5-arylidene-4-oxo-2-phenyliminothiazolidin-3-yl)methyl]- benzoic acids (4) and evaluated their inhibitory activity against human PTP1B and LMW-PTP enzymes. The introduction of a 2-phenylimino moiety onto the 4-thiazolidinone ring was designed to enhance the inhibitor/enzyme affinity by means of further favourable interactions with residues of the active site and the surrounding loops. Molecular modeling experiments inside the binding sites of both enzymes were performed.
11. **Danylo Kaminskyy et al (2009)**\(^{132}\), synthesised and evaluate anticancer activity of 2,4-thia(imida)zolidinedione-3- and 5-acetic acids amides. In vitro anticancer activity of these compounds has been tested in National Cancer Institute (NCI) and discussed relationships between structure and anticancer activity. Among 2,4-azolidinedione-acetic acids derivatives 2-[5 (4-chlorobenzylidene)-2,4-dioxo-imidazolidin-3-yl]-N-(2-trifluoromethyl phenyl) - acetamide(Ic) was superior to other related compounds in terms of high selectivity for the leukemia CCRF cell lines.

![Chemical structure of Ic](image)

12. **Guorong Fana et al (2009)**\(^{133}\), evaluate toxicity and toxicokinetics of MCC-555, a treatment candidate for type 2 diabetes, a novel thiazolidinedione which has comparatively high anti-diabetic efficacy in beagle dogs. During the treatment and recovery periods, the effects of the test agent on mortality, body weight, food consumption, hematology, serum biochemistry, urinalysis, electrocardiogram (ECG), organ weights, bone marrow and histopathology were examined. Metabolites and the metabolic style of MCC-555 are to be approved.

![Chemical structure of MCC-555](image)

13. **Kim Henriksen et al (2009)**\(^{134}\) performed a head-to-head comparison of equipotent glucose lowering concentrations of the partial PPAR\(\gamma\) agonist balaglitazone and the full agonist pioglitazone in male diet-induced obese rats, to investigate effects on bone formation, fluid retention and fat accumulation. MR scans of body fat and water showed that all treatment groups increased their fat mass, whereas only the pioglitazone 30 group accumulated water. Pioglitazone treatment led to reduction of the bone formation marker osteocalcin, whereas balaglitazone treatment did not affect it. Balaglitazone is a novel PPAR\(\gamma\) agonist, which potently lowers glucose levels, while it neither affects fluid retention nor bone formation parameters.
14. **S. Sriman Narayanan et al (2009)**\(^1\) synthesized a series of novel dispiropyrrrolidines by 1,3 dipolar cycloaddition reaction with 5-arylidene-1,3-thiazolidine-2,4-dione and 5-arylidene-4-thioxo-1,3-thiazolidine-2-one derivatives as dipolarophiles. The structure and stereochemistry of the cycloadduct have been established by single crystal X-ray structure and spectroscopic techniques. Molecular docking studies were performed on 1FM9 protein. The synthesized compounds were screened for their antidiabetic activity.

![Image](image_url)

15. **J. P Klopper et al (2009)**\(^2\), Concluded that A375 (DRO) melanoma cell growth is inhibited by rexinoid and TZD treatment, and this response is dependent on RXR and PPAR\(\gamma\) receptor expression. M14 (5–16) melanoma cell growth is inhibited by rexinoid and retinoid treatment, and this response is dependent on RXR expression. These findings may help guide molecular-based treatment strategies in melanoma and provide insight for mechanisms of resistance to nuclear receptor targeted therapies in certain cancers.

16. **Carmelo V. Venero et al (2008)**\(^3\), recognized paradoxical response of HDL-C to some PPAR ligands and suggest that clinicians be aware that rosiglitazone with fenofibrate may reduce HDL-C levels and consider alternative medications should a decrease in HDL-C occur.

17. **Giuseppe Derosa et al (2008)**\(^4\), observed No change BMI, probably because rosiglitazone was added to metformin, that could mitigate the body increase of rosiglitazone. Rosiglitazone improved glycemic control and insulin resistance-correlated parameters when added to intolerant metformin patients. These data suggest that rosiglitazone may be the drug of choice for the treatment of overweight and obese type 2 diabetic patients.
18. **Marcin Baranowski et al (2008)**, investigated the effects of two-week pioglitazone treatment (3 mg/kg/d) on lipid and carbohydrate metabolism in the heart of rats fed on a standard chow or on a high fat diet (HFD) for three weeks. High-fat feeding increased myocardial protein expression of all peroxisome proliferator-activated receptor (PPAR) isoforms. The greatest response was, however, noted in the case of PPARγ. Surprisingly, administration of pioglitazone induced accumulation of free fatty acids (FFA) and diacylglycerol in the heart in both groups, despite concomitant reduction in plasma FFA concentration. Results suggest that thiazolidinediones improve cardiac insulin sensitivity by mechanisms other than reduction in intramyocardial lipid content.

19. **Rosanna Maccari et al (2008)**, reported a series of non-carboxylic acid containing 2,4-thiazolidinedione derivatives, analogues of previously synthesized carboxylic acids which we had found to be very active in vitro aldose reductase (ALR2) inhibitors. Although the replacement of the carboxylic group with the carboxamide or N-hydroxycarboxamide one decreased the in vitro ALR2 inhibitory effect, this led to the identification of mainly non-ionized derivatives with micromolar ALR2 affinity. The 5-arylidene moiety deeply influenced the activity of these 2,4-thiazolidinediones.

20. **Peter J. Harvison et al (2008)**, suggest that Cytochrome P₄₅₀ (CYP)-mediated metabolism in the thiazolidinedione (TZD) ring may contribute to the hepatotoxicity of the insulin-sensitizing agents such as troglitazone. Then administered hepatotoxic doses of DCPT (0.6 or 1.0 mmol/kg, i.p.) to male Fischer 344 rats after pretreatment with vehicle, 1-aminobenzotriazole (ABT, non-selective CYP inhibitor) and troleandomycin (TAO, CYP3A inhibitor). Both hepatotoxic doses of DCPT induced elevations in serum alanine aminotransferase (ALT) levels that were attenuated by ABT or TAO pretreatment. Enzyme activity and Western blotting experiments with rat liver microsomes confirmed the effects of the various pretreatments. Results
suggest that hepatic CYP3A isozymes may be involved in DCPT-induced liver damage in male rats.

![DCPT and Torglitazone structures]

21. Richard T. Carroll et al (2008)\textsuperscript{142} identified a novel protein, mitoNEET, which was later shown to regulate the oxidative capacity of the mitochondria. This identified an alternative target for the glitazones suggesting a possible new drug target for the treatment of neurodegenerative diseases. Molecular docking studies employing the reported crystal structure revealed five possible binding pockets on mitoNEET.

![MitoNEET structure]

22. Carlos A. Alvarez et al (2008)\textsuperscript{143}, demonstrated that a subset of patients with T2DM experienced a paradoxic decrease in HDL-C when taking a fibrate and TZD combination.

23. O. B. Dundar et al (2008)\textsuperscript{144} prepared a series of flavonyl-2,4-thiazolidinediones by Knoevenagel reaction. The synthesized compounds were tested for their ability to inhibit rat kidney aldose reductase (AR) and for their insulinotropic activities in INS-1 cells.

![Flavone structure]

24. Paola Vicini et al (2008)\textsuperscript{145}, synthesized 2-Heteroarylimino-5-benzylidene-4-thiazolidinones, un-substituted or carrying hydroxy, methoxy, nitro and chloro groups on the benzene ring and assayed in vitro for their antimicrobial activity against Gram positive and Gram negative bacteria, yeasts and mould. The structure-activity
relationship of 33 analogues possessing the 2 heteroarylimino-4-thiazolidinone structure is analysed through QSAR models.

![QSAR model](image)

25. **Oya Bozdag-Dundar et al (2008)**\(^{146}\) prepared a new series of chromonyl-2,4-thiazolidinediones by Knoevenagel reaction with substituted 3-formylchromones and unsubstituted (1) or substituted 2,4-thiazolidinedione (2). The synthesized compounds were tested for their ability to inhibit rat kidney AR by an in vitro spectrophotometric assay.

26. **Subho Mozumdar et al (2008)**\(^{147}\), described a simple, efficient, stereoselective, one pot three component condensation reaction between thiazolidine-2,4-dione, aldehyde and amine derivatives using monodispersed, recyclable and inexpensive Cu-nanoparticles for the synthesis of thiazolidine-2,4-dione derivatives in excellent yields and high purity.

![Chemical structure](image)

27. **Ivan da Rocha Pitta et al (2007)**\(^{148}\), synthesized and evaluated new arylidene-thiazolidinediones (ATZDs) in the alloxan-induced hyperglycemia mice model. The molecular target taken into consideration is the nuclear PPAR-\(\gamma\) whose crystallographic structure is available on the PDB database as 2PRG. The hypoglycemic and hypolipidemic activities of compounds were compared with the result of their docking after removal of the co crystallized ligand present in the 2PRG structure. Molecular modeling studies were carried out using the Autodock 3.0.5 and ADT 1.1 programs.
28. **R. Maccari et al (2007)**, synthesized and evaluated number of 5-arylidene-2,4-thiazolidinediones containing a hydroxy or a carboxymethoxy group in their 5-benzylidene moiety as in vitro aldose reductase (ALR2) inhibitors. Most of them exhibited strong inhibitory activity, with IC$_{50}$ values in the range between 0.20 and 0.70 lM. Molecular docking simulations into the ALR2 active site highlighted that the phenolic or carboxylic substituents of the 5-benzylidene moiety can favourably interact, in alternative poses, either with amino acid residues lining the lipophilic pocket of the enzyme, such as Leu300, or with the positively charged recognition region of the ALR2 active site.
29. **Rosanna Maccari et al (2006)**\(^{150}\), synthesised and tested several 5-benzyl-2,4-thiazolidinediones (5–7) as in vitro aldose reductase (ALR2) inhibitors. Most of them, particularly N-unsubstituted 5-benzyl-2,4-thiazolidinediones 5 and (5-benzyl-2,4-dioxothiazolidin-3-yl)acetic acids 7, displayed moderate to high inhibitory activity levels. In detail, the insertion of an acetic chain on N-3 significantly enhanced ALR2 inhibitory potency, leading to acids 7 which proved to be the most effective among the tested compounds.

![Structure of 5-benzyl-2,4-thiazolidinediones](image)

30. **Aurelio Ortiza et al (2005)**\(^{151}\), carried out a novel reaction between oxazolidinethione and bromoacetyl bromide to afford N-substituted 2,4-thiazolidinediones through an intramolecular nucleophilic substitution reaction.

31. **HongWoo Lee et al (2005)**\(^{152}\), reported the synthesis and antidiabetic activity of novel substituted pyrimidines having thiazolidinedione moiety. These compounds (entry No. 5a–i, 10a–d and 16) were evaluated for their glucose and lipid lowering activity in KKAy mice. From the results, novel compounds, 5c and 5g, exhibited considerably more potent biological activity than that of the reference compounds, pioglitazone and Rosiglitazone.

![Structure of novel substituted pyrimidines](image)

32. **Sylvain Berne `s et al (2005)**\(^{153}\), found a novel reaction between oxazolidinethione and bromoacetyl bromide to afford N-substituted 2,4-thiazolidinediones through an intramolecular nucleophilic substitution reaction. Interestingly a step of elimination was carried out in trisubstituted oxazolidinethiones forming a double bond.

33. **I.R. Pitta et al (2005)**\(^{154}\), synthesized a novel set of acridinylidene thiazolidinediones and benzylidene thiazolidinediones by nucleophilic addition of cyanoacrylates. Some of these compounds were evaluated for their glucose lowering capability and their effects on the triglyceride level in alloxan diabetic mice.
34. Jochen Seufert et al (2004)\textsuperscript{155} suggests that the predominant effect of metformin is inhibition of hepatic glucose production, whereas the primary effect of TZDs is reduction of insulin resistance and promotion of peripheral glucose uptake. TZDs appear to have more positive effects on other metabolic processes and to be associated with greater improvements in cardiovascular risk factors compared with metformin.

35. Michael H. Serrano Wu et al (2004)\textsuperscript{156}, Cyclized unsymmetrical thioureas affords 3-(heteroaryl)-iminothiazolidin-4-ones with excellent levels of regiocontrol. In the absence of base, 2-(pyridylmethyl) and 2-(aminomethyl)benzimidazolyl substituents on the thiourea scavenge acid that is generated upon sulfur alkylation with bromoesters. The resulting conjugate acid plays an important role in influencing the regiochemical outcome and overall rate of the reaction.

36. Jieping Zhu et al (2004)\textsuperscript{157}, reported an efficient synthesis of 2-imino-4-thiazolidinones from readily accessible alkyl (aryl) trichloromethylcarbinols and thioureas under mild conditions. A one-pot three-component synthesis of the title compounds from aldehyde, chloroform and thiourea is also developed for the first time.
37. **Devi Prasad Sahu et al (2004)\textsuperscript{158},** synthesized number of thiazolidine-2,4-diones derivatives having carboxylic ester appendage at N-3 and their antihyperglycemic activity was evaluated. Many of these derivatives as well as their corresponding carboxylic acid showed significant improvement on post-prandial hyperglycemia in normal rats, in contrast to their poor agonist activity at PPAR\textsubscript{γ}.

![Thiazolidine-2,4-dione structure](image)

38. **Abdulaziz I et al (2003)\textsuperscript{159},** synthesized a set of new organometallic complexes of lanthanum(III) by direct reaction of lanthanum trichloride with different amines as ligands namely 1,2,4-triazole C\textsubscript{2}H\textsubscript{3}Na, 1,2,4-triazole-3-thiol C\textsubscript{2}HaN\textsubscript{3}S and 2,4-thiazolidindione CaM\textsubscript{3}NS0\textsubscript{2}.

![Trazole structure](image)

39. **Jane E. B. Reusch et al (2003)\textsuperscript{160},** suggested that thiazolidinediones (TZDs) a Insulin-sensitizing agents, improve flow-mediated vasodilation, decrease macrophage and smooth muscle cell activation, proliferation, and migration, and decrease plaque formation. The TZDs exert multifaceted effects on the vasculature by regulating the expression of transcription factors and orchestrating whole-gene programs that restore vascular physiology to the healthy state. Exercise training and increased levels of habitual physical activity have therapeutic benefit in terms of both preventing and treating insulin resistance and diabetes. However, this benefit of exercise training and increased physical activity is complicated by the fact that individuals with insulin resistance or type 2 diabetes have decreased maximal exercise capacity or maximal oxygen consumption and have slower oxygen uptake kinetics at the beginning of exercise. Both of these abnormalities contribute to the decreased levels of habitual physical activity observed in patients with diabetes. Preliminary data suggest that TZDs improve measures of cardiac function and exercise capacity, and investigators
are assessing the impact of treatment with rosiglitazone on exercise capacity in an ongoing clinical trial.

40. **Rahmiye Ertan et al (2003)**\(^{161}\) synthesized series of 3-benzyl (p-substituted benzyl)-5-[4-oxo-1-benzopyran-2-yl]-benzylidene]-2,4- thiazolidinediones. Products were prepared by Knoevenagel reaction and In vitro insulinotropic activity was determined.

\[
\begin{align*}
\text{Ar} & \quad \text{N} \quad \text{O} \\
\text{O} & \quad \text{S} \quad \text{O} \\
\text{O} & \quad \text{R} \quad \text{O} \\
\end{align*}
\]

41. **Partha Neogi et al (2003)**\(^{162}\) synthesized and studied number of 2,4-thiazolidinedione derivatives of -phenyl substituted cinnamic acid for their PPAR agonist activity. Pharmacokinetic, metabolism and permeability studies are consistent with 11 being an active prodrug with an active metabolite, 14, that has similar glucose lowering and PPAR\(\gamma\) agonist properties.

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{R} & \quad \text{O} \\
\text{R} & \quad \text{O} \\
\end{align*}
\]

42. **Vivian Fonseca et al (2003)**\(^{163}\), carried out studies to elucidate the mechanisms behind the apparent paradox of TZDs improving insulin sensitivity while causing weight gain. Data indicate that with TZD treatment, there is a favorable shift in fat distribution from visceral to subcutaneous adipose depots that are associated with improvements in hepatic and peripheral tissue sensitivity to insulin. A weight-management program combining a low-calorie, low-sodium diet with education and behavior modification has been shown to be effective in patients with type 2 diabetes being treated with TZDs. Further research is needed to define the optimal dietary modifications that can be used universally in TZD-treated patients to minimize weight gain while effectively treating insulin resistance and hyperglycemia.
43. **Hans Hauner et al (2002)** suggest that the thiazolidinediones (TZDs) a new class of oral antidiabetic drugs that improve metabolic control in patients with type 2 diabetes through the improvement of insulin sensitivity. TZDs exert their antidiabetic effects through a mechanism that involves activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPARγ), a nuclear receptor. TZD-induced activation of PPARγ alters the transcription of several genes involved in glucose and lipid metabolism and energy balance, including those that code for lipoprotein lipase, fatty acid transporter protein, adipocyte fatty acid binding protein, fatty acyl-CoA synthase, malic enzyme, glucokinase and the GLUT4 glucose transporter. TZDs reduce insulin resistance in adipose tissue, muscle and the liver. However, PPARγ is predominantly expressed in adipose tissue. It is possible that the effect of TZDs on insulin resistance in muscle and liver is promoted via endocrine signalling from adipocytes. Potential signalling factors include free fatty acids (FFA) (well-known mediators of insulin resistance linked to obesity) or adipocyte-derived tumour necrosis factor-a (TNF-a), which is over expressed in obesity and insulin resistance. Although there are still many unknowns about the mechanism of action of TZDs in type 2 diabetes, it is clear that these agents have the potential to benefit the full ‘insulin resistance syndrome’ associated with the disease. Therefore, TZDs may also have potential benefits on the secondary complications of type 2 diabetes, such as cardiovascular disease.

44. **Hsin-Hsiung Tai et al (2002)** synthesized a series of benzylidene thiazolidinediones with varied ring structure and methylene bridge to phenyl ring through ether linkage and assayed for inhibitory activity. It was found that compound CT-8 (5-[4-(cyclohexylethoxy)benzylidene]-2,4-thiazolidinedione) was the most potent inhibitor effective at nanomolar range.

45. **Jens Schmeyers and Gerd Kaupp (2002)** suggest reaction of amines with thiohydantoins as starting materials for various heterocyclic syntheses in one-pot
cascade reactions with excellent atom economy: 2-iminothiazoles (5) are quantitatively formed from 1 and phenacyl bromide in the solid state. Thioparabanic acids (9) are easily accessible from oxalyl dichloride and Benzils react with 1 to afford functionalized 5,5-diaryl-thiohydantoins (14) and dimethylacetylene dicarboxylate gives 2-imino-5- methylene-thiazolidine-4-ones (17) and (18) upon reaction with 1. The one-pot syntheses of imidazo[1,2-c ]pyrimidines (25) and (28) from 1 with benzaldehydes and ethyl cyanoacetate or malodinitrile are benign new accesses to these important heterocycles.

46. **Gurram R. Madhavan et al (2002)**\(^{167}\), synthesized a series of pyrimidinone derivatives of thiazolidinediones. Their biological activity was evaluated in insulin resistant, hyperglycemic and obese db/db mice. In vitro PPAR\(\gamma\) transactivation assay was performed in HEK 293T cells. PMT13 showed the best biological activity in this series. Twenty-eight day oral toxicity study in Wistar rats did not show any treatment-related adverse effects.

47. **R. Maccari et al (2002)**\(^{168}\), synthesized and tested several (Z)-5-arylidene-2,4-thiazolidinediones as aldose reductase inhibitors (ARIs). The most active of the N-unsubstituted derivatives (2) exerted the same inhibitory activity of Sorbinil. The introduction of an acetic side chain on N-3 of the thiazolidinedione moiety led to a marked increase in lending inhibitory activity, conducting to the discovery of a very potent ARI (4c), whose activity level (IC50=0.13 mM) was in the same range of Tolrestat.
48. **Michael W. J. Urquhart et al (2000)**\(^{169}\), accomplished novel regiospecific and general reduction of 5-benzylidene-2,4 thiazolidinediones and 5-benzylidene-4-oxo-2-thiazolidinethiones to the corresponding 5-benzyl derivatives using lithium borohydride in pyridine and tetrahydrofuran. Sodium borohydride and lithium chloride can also be used under these conditions, which represents a cheaper alternative to lithium borohydride.

49. **Hiroyuki Miyachi et al (1999)**\(^{170}\), prepared a series of 3-[(2,4-dioxothiazolidin-5-yl)methyl]benzamide derivatives as part of a search for antidiabetic agents. A structure-activity relationship study of these compounds led to the identification of 5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxy N-[[4-(trifluoromethyl)- phenyl]methyl] benzamide (KRP-297) as a candidate drug for the treatment of diabetes mellitus.

50. **Janine Cossy et al (1999)**\(^{171}\), obtained Troglitazone in 5 steps from 4-bromo-l,l-dimethoxy-3-methylbut-2-ene with an overall yield of 7.5%. The formation of the chromane ring was achieved by condensing an unsaturated acetal with trimethylhydroquinone in the presence of bis(trifluoromethylsulfonyl)imide.

51. **Li Sen Liu et al (1998)**\(^{172}\) suggested that MCC-555 effect was paralleled by a significant dephosphorylation of IRS-1 on Ser/Thr. In conclusion, MCC-555 rapidly sensitizes insulin stimulated cardiac glucose uptake by enhancing insulin signaling resulting from increased intrinsic activity of PI 3-kinase. Acute activation of protein expression leading to a modulation of the Ser/Thr phosphorylation state of signaling proteins such as IRS-1 may be underlying this process. It is may provide a causal therapy of insulin resistance by targeted action on the defective site in the insulin signaling cascade.
52. **Paul J. Hergenrother et al (2012)**\(^{173}\), suggest the poly (ADP-ribose) (PAR) post-translational modification for diverse cellular functions, including regulation of transcription, response to DNA damage, and mitosis. Cellular PAR is predominantly synthesized by the enzyme poly (ADP-ribose) polymerase-1 (PARP-1). Described rhodanine derivatives as PARP-1 inhibitors which (PARP-1) is a critical node in the DNA damage response pathway.

53. **Avadhesha Surolia et al**\(^{174}\), presented the discovery of a rhodanine (2-thioxothiazolidin-4-one) class of compounds as inhibitors of Enoyl acyl carrier protein (ACP) reductase, one of the enzymes of the type II fatty acid biosynthesis pathway, has been established as a promising target for the development of new drugs for malaria. Discussed structure activity relationship of these rhodanine compounds and the most potent inhibitor exhibits an IC\(_{50}\) of 35.6 nM against *Plasmodium falciparum*.

54. **Kikkawa R et al (1983)**\(^{175}\), studied effect of aldose reductase inhibitor, (E)-3-carboxymethyl-5-[(2E-methyl-3-phenylpropenylidene] rhodanine (ONO-2235) on motor nerve conduction velocity of streptozotocin-diabetic rats (60 mg/kg IV) for 14 days. Their results suggest that the compound significantly improved motor nerve conduction velocity and the new aldose reductase inhibitor could be a potential drug for therapy of diabetic neuropathy.

55. **Wolfgang Hanefeld et al (1994)**\(^{176}\), reacted α-Bromoacetylaminorhodanines were with NH\(_4\)SCN yielding 3-(thiazolidin-3-yl)rhodanines, a novel type of rhodanine derivatives bearing a uncommon N-N ring-connection.

56. **Terashima H et al (1984)**\(^{177}\), proposed, ONO-2235 [(E)-3-carboxymethyl-5-[(2E)-methyl-3-phenylpropenylidene] rhodanine], a potent inhibitor of aldose reductase, Sorbitol accumulation in the isolated rat lenses, sciatic nerves and human erythrocytes were all effectively inhibited during incubation with high concentrations of glucose (28-50 mM) by ONO-2235 at a concentration of about 10(-6) M. suggest that ONO-
2235 may prove to be useful in preventing and improving some diabetic complications.

57. Josef Jampiek et al (2009)\textsuperscript{178}, prepared some (5-arylalkyldene-4-oxo-2-thioxo-1,3-thiazolidin-3-yl) acetic acids as potential antifungal compounds.
2.3. Peroxisome Proliferator Activated Receptor (PPAR) α & γ dual agonists

1. **D. R. Dougan, et al (2012)**\(^{179}\), described the design, synthesis and structure activity relationships of novel benzylpyrazole acylsulfonamides as non-thiazolidinedione (TZD), non-carboxylic-acid-based peroxisome proliferator-activated receptor (PPAR) γ agonists. Docking model analysis of in-house weak agonist 2 bound to the reported PPARγ ligand binding domain suggested that modification of the carboxylic acid of 2 would help strengthen the interaction of 2 with the TZD pocket and afford non-carboxylic-acid-based agonists.

2. **Zhiqiang Feng et al (2012)**\(^{180}\), designed and prepared series of novel phenyl-urea derivatives which can simultaneously activate glucokinase (GK) and peroxisome proliferator-activated receptor γ (PPARγ) and their activation of GK and PPARγ was evaluated. The structure activity relationships of these compounds are also described. Three compounds showed potent ability to activate both GK and PPARγ. The possible binding mode of one of these compounds with GK and PPARγ were predicted by molecular docking simulation.
3. **S. Chaudhary et al (2012)**\(^{181}\), characterized the pharmacological profiles of NS-1 chemically known as (5Z)-5-[4-hydroxy-3-methoxy-phenyl)methylene] thiazolidine-2, 4-dione), as a selective partial activator of PPAR\(\gamma\). Studies suggest that NS-1 improves insulin resistance in such animal models through activation of PPAR\(\gamma\)-mediated transcriptional activity and that it would be a new therapeutic candidate with potential for the treatment of type 2 diabetic patients.

\[ \text{Structure of NS-1} \]

4. **P.B. Tirupathi Pichiah et al (2012)**\(^{182}\), investigated the effect of ethanolic extract of seabuckthorn leaves and results indicated that SL is effective in preventing BW gain and fat accumulation in the liver; it also reduced adipose tissue mass, hepatic lipid profile, and serum leptin level in the mouse. Together, these observations suggest that SL is a potential agent to study in the management of obesity and related disorders.

5. **Nabajyoti Deka et al (2012)**\(^{183}\), identified non-TZD PPAR\(\gamma\) agonists which exhibit beneficial effects similar to that of TZDs in animal models, but without the associated adverse effects.

\[ \text{Structure of non-TZD PPAR\(\gamma\) agonist} \]

6. **T. Rosenthal et al (2012)**\(^{184}\), demonstrated the alteration in gene expression associated with the development of hyperglycemia and insulin resistance in Cohen-Rosenthal diabetic hypertensive rat, a unique model of hypertension and type 2 diabetes mellitus comorbidity. Cohen-Rosenthal diabetic hypertensive rats were continuously treated with telmisartan (3 mg/[kg d]) starting at age 6 to 8 weeks before developing hypertension or diabetes.

7. **Han Kiat Ho et al (2012)**\(^{185}\), considered the bioisosteric replacement of the thiazolidinedione ring with a chemically conserved pyrrolidinedione heterocyclic
system. Using pyrrolidinedione analogs of the thiazolidinedione drugs troglitazone (TGZ), rosiglitazone (RGZ), and pioglitazone (PGZ), evaluated their PPAR\(\gamma\) activities, anti-cancer properties as well as toxicological effects.

8. **Christopher A. Luckhurst et al (2011)**\textsuperscript{186}, identified a small molecule isoindoline and tetrahydroisoquinoline derivatives as selective agonists of human peroxisome proliferator-activated receptor \(\delta\). Compound 18 demonstrated efficacy in a biomarker for increased fatty acid oxidation, with upregulation of pyruvate dehydrogenase kinase, isozyme 4 (PDK4) in human primary myotubes.

9. **Shailesh R. Shah et al (2011)**\textsuperscript{187}, reported novel series of thiazole and oxazole containing phenoxy acetic acid derivatives as PPAR agonists. Incorporation of structurally constrained oxime–ether based linker in the chemotype of a potent PPAR\(\delta\) selective agonist GW-501516 was adapted as designing strategy. In vitro, selected test compounds 12a, 12c, 17a and 18a showed PPAR-pan agonists activities and among these four compounds tested, 12a emerged as highly potent and efficacious compound, while 17a exhibited moderate and balanced PPAR pan agonistic activity.

10. **Preeti Raval et al (2011)**\textsuperscript{188}, designed thiophene substituted oxazole containing a-alkoxy-phenylpropanoic acid derivatives as safe and efficacious compounds for the treatment of metabolic disorders as potent PPAR\(\alpha/\gamma\) dual agonists. These compounds were found to be efficacious at picomolar concentrations. Lead compound 18d has emerged as very potent PPAR\(\alpha/\gamma\) dual agonist demonstrating potent antidiabetic and lipid lowering activity at a very low dose and did not exhibit any significant signs of toxicity in rodents.
11. **Wei Wang et al (2011)**\(^{189}\), discovered novel peroxisome proliferator-activated receptor δ agonists with a characteristic benzisoxazole ring. Compound 5 exhibited potent human PPARδ transactivation activity. This indicates that this potential drug may be effective for the treatment of demyelinating disorders such as multiple sclerosis.

12. **Andrew Walding et al (2011)**\(^{190}\), suggest that the triacylglycerol reducing effect of fibrates and thiazolidinediones is partially caused by inhibition of SREBP-1 activation via up-regulation of Insight.

13. **Calin C. Ciocoiu et al (2010)**\(^{191}\), prepared ten 1,4-disubstituted 1,2,3-triazoles and tested for their ability to increase oleic acid oxidation in human myotubes using a high-throughput multi-well assay. Compounds 2e (2-\{4-\{(1- (3-fluoro-4-(trifluoromethyl) phenyl)-1H-1,2,3-triazol-4-yl) methylthio\}-2-methyl phenoxy\} acetic acid) and 2i (2-\{4-\{(1-(3-chloro-4-(trifluoromethoxy)phenyl)-1H-1,2,3-triazol-4-yl)methylthio\}-2-methylphenoxy\} acetic acid) exhibited potent agonist activities. Compounds 2e and 2i also exhibited powerful agonist effects for both PPARα and PPARδ in a luciferase-based assay. Consequently, these triazoles can be categorized as dual PPAR agonists.
14. Ivan da Rocha Pitta et al (2010)\textsuperscript{193}, synthesized and assayed eight new 5-arylidene-3-benzyl-thiazolidine-2,4-diones with halide groups on their benzyl rings in vivo to investigate their anti-inflammatory activities. These compounds showed considerable biological efficacy when compared to rosiglitazone, a potent and well-known agonist of PPAR\(\gamma\), which was used as a reference drug. This suggests that the substituted 5-arylidene and 3-benzylidene groups play important roles in the anti-inflammatory properties of this class of compounds.

![Chemical Structure](image)

15. Marie-Claude Viaud-Massuardn et al (2009)\textsuperscript{193}, interested in designing novel PPAR\(\gamma\) selective agonists and/or dual PPAR\(\alpha/c\) agonists. Based on the typical topology of synthetic PPAR agonists, we focused our design approach on using 4,4-dimethyl-1,2,3,4-tetrahydroquinoline as a novel cyclic scaffold with oxime and acidic head group structural variations.

![Chemical Structure](image)

16. Heiko Zettl et al (2009)\textsuperscript{194} presented novel and robust scaffold for highly active PPAR\(\alpha\) agonists based on the 2 mercaptohexanoic acid substructure. Corroborated the importance of the sulfur atom as well as of the n-butyl chain for PPAR\(\alpha\) activity in the 2-mercaptohexanoic acid head group by preparation of carbon analogs and a-unsubstituted derivatives. Compound 10 represents a low nano molar active PPAR\(\alpha\) activator with excellent selectivity towards PPAR\(\gamma\).
17. **Shin-Yoon Kim et al (2009)**, investigated the effects of a novel peroxisome proliferator-activated receptor γ (PPARγ) agonist, KR62776, on osteoclast differentiation and function, and on the underlying signaling pathways. KR62776 markedly suppressed differentiation into osteoclasts in various osteoclast model systems, including bone marrow mononuclear (BMM) cells and a co-culture of calvarial osteoblasts and BMM cells. Results demonstrate that KR62776 negatively affects osteoclast differentiation and activity by inhibiting the RANKL-induced activation of MAP kinases and NF-jB.

18. **Weiguo Liu et al (2009)**, designed and synthesized a series of 3-acylindole-1-benzylcarboxylic acids while searching for a PPARγ modulator with additional moderate intrinsic PPARR agonistic activity. 2-[3-[(3-(4-Chlorobenzoyl)-2-methyl-6-(trifluoromethoxy)-1H-indol-1-yl)methyl]phenoxy]-2R)-butanoic acid (12d) was identified as such an agent which demonstrated potent efficacy in lowering both glucose and lipids in multiple animal models with significantly attenuated side effects such as fluid retention and heart weight gain associated with PPARγ full agonists.
19. Harold B. Wood et al (2009)\textsuperscript{197}, synthesized compound 6 exhibited comparable efficacy to rosiglitazone and pioglitazone in vivo. However, with regard to the induction of untoward events, 6 displayed no cardiac hypertrophy, attenuated increases in brown adipose tissue, minimal increases in plasma volume, and no increases in extracellular fluid volume in vivo. Investigation of 6 is warranted to determine if the improvement in mechanism-based side effects observed in preclinical species will be recapitulated in humans.

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\text{NOCF}_3
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\text{OCH}_3
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\text{O}
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\text{O}
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\text{20. Jeong-Ho Hong et al (2009)\textsuperscript{198}}, confirmed that KR62980 substantially suppresses rosiglitazone-induced adipocyte differentiation and attenuates adipogenic gene expression via an induced reduction in PPARg activity. KR62980 increased the nuclear localization of TAZ, a PPARg suppressor, and also enhanced the interaction between PPARg and TAZ, thus resulting in the TAZ-mediated suppression of PPARg activity. Furthermore, KR62980 failed to suppress PPARg-mediated adipogenic gene expression and adipocyte differentiation in TAZ knock down 3T3-L1 cells, thus indicating a TAZ-dependent suppressive activity of KR62980 on PPARg-mediated function.

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\text{O}
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\text{O}
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\text{O}
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\text{N}
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\text{KR62980}
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21. Stamatios Theocharis et al (2009)\textsuperscript{199}, reviewed the crucial role of PPAR-\(\gamma\) ligands in arthritis and the underlying mechanisms participating in essential inflammatory signaling pathways are summarized. Taking into consideration the data so far, PPAR-\(\gamma\) ligands seem to represent potential therapeutic agents in the aim to reduce mainly the inflammation implicated in arthritis. However, the precise molecular mechanisms through which PPAR-\(\gamma\) ligands exert their actions are strongly recommended to be
clarified, as both receptor-dependent and -independent actions were shown to be elicited.

22. Sandeep Sundriyal et al (2009)\textsuperscript{200}, developed a ‘sum-model’ to design PPARα/γ/δ agonists by using the sum of activities (EC\textsubscript{50}) of compounds against individual subtypes as a dependent parameter. The generated models were found to be statistically significant with rcv 2 > 0.5 and rncv 2 > 0.9 and the lower values of standard error of estimation (SEE) ranging from 0.097 to 0.160. This approach may find wider applications in the research related to other classes of ‘designed multiple ligands’.

23. Ángel R. de Lera et al (2009)\textsuperscript{201} synthesized series of analogues of the PPARγ ligand 15-deoxy-D12,14-PGJ2 by functionalization of a 5-alkyl-4-hydroxycyclopentenone core structure obtained by Piancatelli rearrangement of precursor furylcarbinol. Transient transactivation assays indicate that analogues 18 and 20 are selective nanomolar agonists of PPARγ. This subtype selectivity is lost in derivatives (23, 24) with an alkynyl (oct-1-yn) chain at the C3 position, although the cyclopentenone derivative with cis relative configuration (23) showed greater affinity for PPARα.

24. Agustin Casimiro-Garcia et al (2009)\textsuperscript{202} presented the synthesis of a new series of phenylpropanoic acid derivatives incorporating an heteroaryl group at the a-position and their evaluation for binding and activation of PPARα and PPARγ. Among the new compounds, (S)-3-{4-[3-(5-methyl-2-phenyl-oxazol-4-yl)-propyl]-phenyl}-2-1,2,3-triazol-2-yl-propionic acid (17j), was identified as a potent human PPARα/γ dual
agonist \( (EC_{50} = 0.013 \text{ and } 0.061 \, \mu\text{M}, \text{ respectively}) \) with demonstrated oral bioavailability in rat and dog. 17j was shown to decrease insulin levels, plasma glucose, and triglycerides in the ZDF female rat model.

![Chemical Structure](image)

25. **Rai Ajit and K. Srivastava (2009)**\(^{203}\), prescribed fenofibrate and rosiglitazone to treat hypertriglyceridemia and diabetes, respectively. Since fenofibrate improves lipid profile in diabetic patients and improves insulin resistance in animal models, examined the mechanism of antidiabetic effects of fenofibrate in KKAy mouse, an animal model of diabetes and dyslipidemia. Results shown that, amelioration of antidiabetic and hyperlipidemic state by fenofibrate in KKAymice occurred via down-regulation of DGAT2, PEPCK and 11\(\beta\)-HSD1 while the undesirable lipogenic effects of T090317 could be dampened by fenofibrate.

![Diagram](image)

26. **Fabio Lannutti et al (2009)**\(^{204}\), synthesized series of 2-heteroarylthioalkanoic acids through systematic structural modifications of clofibric acid and evaluated for human peroxisome proliferator-activated receptor R (PPARR) transactivation activity, with the aim of obtaining new hypolipidemic compounds. Some thiophene and benzothiazole derivatives showing a good activation of the receptor R were screened for activity against the PPAR\(\gamma\) isoform.
27. **Hao Zhang et al (2009)**\(^{205}\), outlined the design, synthesis and structure activity relationships of a novel series of N-phenyl-substituted pyrrole, 1,2-pyrazole and 1,2,3-triazole acid analogs as PPAR ligands. The triazole acid analogs 3f and 4f were identified as potent dual PPAR\(\alpha/\gamma\) agonists both in binding and functional assays in vitro. The 3-oxybenzyl triazole acetic acid analog 3f showed excellent glucose and triglyceride lowering in diabetic db/db mice.

![Chemical Structure](image1)

28. **Paul S. Humphries et al (2009)**\(^{206}\), developed three routes for synthesis of large quantities of an enantiomerically pure novel dual PPAR\(\alpha/\delta\) agonist successfully, with the chosen route utilized to deliver 40 g of material.

![Chemical Structure](image2)

29. **Naoki Miyata et al (2008)**\(^{207}\), modified based on the homology model of GPR120 led to the first GPR120-selective agonist 12. These results provide a basis for constructing new tools for probing the biology of GPR120 and for developing new candidate therapeutic agents.

![Chemical Structure](image3)

30. **Ching-Shih Chen et al (2008)**\(^{208}\), used \(\Delta2CG\), a PPAR\(\gamma\)-inactive analogue of ciglitazone, to conduct lead optimization able to mediate PPAR\(\gamma\)-independent transcriptional repression of androgen receptor (AR) in a tumor cell-specific manner, and to develop a novel class of AR-ablative agents. Structure–activity analysis
indicates a high degree of flexibility in realigning Δ2CG’s structural moieties without compromising potency in AR repression, as evidenced by the higher AR-ablative activity of the permuted isomer 9 whose modification rise to 12 which completely inhibited AR expression at low micromolar concentrations.

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\begin{array}{c}
\text{F}_3\text{C} \\
\text{HO} \\
\text{S}
\end{array}
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31. **Hyun-Ju Park et al (2008)**\(^{209}\), designed and synthesized a series of diaryl R-ethoxy propanoic acid compounds comprising two aryl groups linked by rigid oxime ether or isoxazoline ring in an effort to develop dual PPARR/γ activators with improved therapeutic efficacy. Compound 18, one of the derivatives with an oxime ether linker, was found to selectively transactivate PPARγ (EC\(_{50}\) 0.028 µM) over PPARR (EC\(_{50}\) 7.22 µM) in vitro and lower blood glucose in db/db mice more than muraglitazar.

\[
\begin{array}{c}
\text{HO}_2\text{C} \\
\text{EtO} \\
\text{N}
\end{array}
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32. **Palak Shah et al (2008)**\(^{210}\), employed computational methods successfully in designing dual activators. ‘Additivity of molecular fields’ concept employed to explore the scope and limitations of the concept, with the help of reported PPARα/γ/δ multiple activators. Three individual CoMFA models were first generated, followed by dual and multiple models. Dual PPARα/γ CoMFA model developed successfully.

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\begin{array}{c}
\text{HO} \\
\text{O}
\end{array}
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33. **Antonio Lavecchia et al (2008)**\(^{211}\), present screening results for a series of chiral 2-(4-chloro-phenoxy)-3-phenyl-propanoic acid derivatives, some of which are potent PPARγ agonists as well as PPARα agonists. Investigate the binding modes of the
most interesting derivatives into the PPARα and PPARγ binding clefts and evaluate their agonist activity, docking experiments, molecular dynamics simulations, and MM–PBSA analysis were performed.

34. Roberta Montanari et al (2008)\textsuperscript{212}, reported the crystal structure and activity of the two enantiomeric forms of a clofibric acid analogue, respectively complexed with the ligand-binding domain (LBD) of PPARγ, and provide an explanation on a molecular basis for their different potency and efficacy against PPARγ. The more potent S-enantiomer is a dual PPARR/PPARγ agonist which presents a partial agonism profile against PPARγ. Docking of the S-enantiomer in the PPARR-LBD has been performed to explain its different subtype pharmacological profile.

35. Hong Liu et al (2008)\textsuperscript{213}, designed, synthesized series of 35 novel analogues and evaluated against the agonistic effects exerted by rosiglitazone. These results indicated that most functional groups of 1a were conserved, and six new compounds (1b, 1c, and 9aed) exhibited strong PPARγ antagonistic activities (IC\textsubscript{50} values of 5.2e25.8 mM) against 10 mM rosiglitazone in the promotion of the PPARγeLBDeCBP (ligand-binding domain and cAMP-response-element binding protein) interaction as investigated by yeast two-hybrid technology based assay.
36. **Tetsuo Asaki et al (2008)**\(^{214}\), synthesized series of 1,3-dioxane carboxylic acid derivatives and evaluated for human PPAR transactivation activity. Structure activity relationships on the phenyloxazole moiety of the lead compound 3 revealed that the introduction of small hydrophobic substituents at the 4-position of the terminal phenyl ring increased the PPAR\(\alpha\) agonist activity. This investigation led to the identification of 14d (NS-220) and 14i as highly potent and selective human PPAR\(\alpha\) agonists. Results suggest that highly potent and subtype-selective PPAR\(\alpha\) agonists will be promising drugs for the treatment of metabolic disorders in type 2 diabetes.

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3
\end{array}
\begin{array}{c}
\text{N} \\
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{CO}_2\text{H}
\end{array}
\]

37. **Cassia S. Mizuno et al (2008)**\(^{215}\) synthesized analogs of pterostilbene and investigated their ability to activate PPAR\(\alpha\). Among analogs that was synthesized (E)-4-(3,5-dimethoxystyryl)phenyl dihydrogen phosphate showed activity higher than pterostilbene and control drug ciprofibrate. Docking of the stilbenes inside PPAR\(\alpha\) showed the presence of important hydrogen bond interactions for PPAR\(\alpha\) activation.

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\begin{array}{c}
\text{OH} \\
\text{H}_3\text{CO}
\end{array}
\begin{array}{c}
\text{OH}
\end{array}
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38. **Wei Wang et al (2008)**\(^{216}\), synthesized a novel class of azetidinone acid-derived dual PPAR\(\alpha/\gamma\) agonists for the treatment of diabetes and dyslipidemia. The preferred stereochemistry in this series for binding and functional agonist activity against both PPAR\(\alpha\) and PPAR\(\gamma\) receptors was shown to be 3S,4S. Synthesis, in vitro and in vivo activities of compounds in this series are described. A high-yielding method for N-arylation of azetidinone esters is also described.

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\begin{array}{c}
\text{Ar} \\
\text{N}
\end{array}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{HOOC}
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39. Yushe Yang et al (2008)\textsuperscript{217}, synthesized and evaluated series of benzopyran derivatives for PPAR\(\alpha/\gamma\) agonist activities. Most of the compounds exhibit reasonable PPAR\(\alpha\) and PPAR\(\gamma\) agonist activities. In particular, compounds 7b, 8b, 8e and 8h with remarkable PPAR\(\gamma\) EC\(_{50}\) values of 0.001 mM are excellent full PPAR\(\gamma\) agonists with the functional potency about 130, 20 times stronger than that of leading compound 5 and rosiglitazone, respectively.

\[ \text{Diagram of compound 8h} \]

40. Harikishore Pingali et al (2008)\textsuperscript{218}, designed and synthesized novel 1,3-dioxane carboxylic acid derivatives to aid in the characterization of PPAR\(\alpha/\gamma\) dual agonists. Structural requirements for PPAR\(\alpha/\gamma\) dual agonism of 1,3-dioxane carboxylic acid derivatives included the structural similarity with potent glitazones in fibric acid chemotype. The compounds with this pharmacophore and substituted oxazole as a lipophilic heterocyclic tail were synthesized and evaluated for their in vitro PPAR agonistic potential and in vivo hypoglycemic and hypolipidemic efficacy in animal models.

\[ \text{Diagram of compound 8h} \]

41. Tetsuo Asaki et al (2008),\textsuperscript{219} synthesized and evaluated new series of 1,3-dioxane-2-carboxylic acid derivatives for agonist activity at human peroxisome proliferator-activated receptor (PPAR) subtypes. Structure-activity relationship studies led to the identification of 2- methyl-c-5-[4-(5-methyl-2-phenyl-1,3-oxazol-4-yl)butyl]-1,3-dioxane-r-2-carboxylic acid 4b as a potent PPAR\(\alpha\) agonist with high subtype selectivity at human receptor subtypes.

\[ \text{Diagram of compound 4b} \]

42. Marie-Claude Viaud-Massuardin et al (2008)\textsuperscript{220}, identified Activated Receptors were namely PPAR\(\alpha\), PPAR\(\gamma\) and PPAR\(\delta/(\beta)\) and interested in designing novel
PPARγ selective agonists and/or dual PPARα/γ agonists. Based on the typical topology of synthetic PPAR agonists, focused our design approach on 4,4- dimethyl-1,2,3,4-tetrahydroquinoline as novel cyclic tail.

43. Chun Ho Lee et al (2008)\textsuperscript{221}, prepared Aryl-tetrahydropyridine derivatives and their PPARα/γ dual agonistic activities were evaluated. Among them, compound (S)-5b was identified as a potent PPARα/γ dual agonist with an EC\textsubscript{50} of 1.73 and 0.64 µM in hPPARα and γ, respectively.

44. Gee-Hong Kuo et al (2007)\textsuperscript{222}, Replaced the methylthiazole of 5 (the PPARδ selective agonist) with [1,2,4] thiadiazole gave compound 13, which unexpectedly displayed submicromolar potency as a partial agonist at PPARγ in addition to the high potency at PPARδ which was required to effectively target dyslipidemia to reduce the risk of cardiovascular disease. Optimization of 13 led to the identification of 24 and its close analogs represent a new series of potent and selective PPAR γ/ δ dual agonists.

45. Joachim Rudolph et al (2007)\textsuperscript{223}, reported the synthesis and structure-activity relationship (SAR) studies of novel aryl tail group derivatives that led to a new class of potent PPAR pan agonists. Systematic optimization led to the discovery of 4-thiazolyl-phenyl derivatives with potent PPAR alpha/gamma/delta pan agonistic activity.
46. Nam-Jung Kim et al (2007)\textsuperscript{224}, developed a new class of PPAR\(\alpha/\gamma\) dual agonists, which show excellent agonistic activity in PPAR\(\alpha/\gamma\) transactivation assay. In particular, (R)-9d was identified as a potent PPAR\(\alpha/\gamma\) dual agonist with EC\(_{50}\)s of 0.377 \(\mu\)M in PPAR\(\alpha\) and 0.136 \(\mu\)M in PPAR\(\gamma\), respectively. Interestingly, the structure–activity relationship revealed that the stereochemistry of the identified PPAR\(\alpha/\gamma\) dual agonists significantly affects their agonistic activities in PPAR\(\alpha\) than in PPAR\(\gamma\).

47. Per Sauerberg et al (2007)\textsuperscript{225}, utilized Computational analysis of the ligand binding pocket of the three PPAR receptor subtypes in the design of potent PPAR\(\alpha\) agonists. Optimum PPAR\(\alpha\) potency and selectivity were obtained with substituents having van der Waals volume around 260. Compound 6 had a PPAR\(\alpha\) potency of 0.002 \(\mu\)M and a selectivity ratio to PPAR\(\gamma\) and PPAR\(\delta\) of 410 and 2000, respectively.

48. Jong Sung Koh et al (2007)\textsuperscript{226}, prepared Oxime ethers of \(\alpha\)-acyl-\(\beta\)-phenylpropanoic acids to apply as PPAR\(\alpha\) and \(\gamma\) dual agonists. Among them, compound 11l proved to exhibit potent in vitro activities with EC\(_{50}\) of 19 and 13 nM in PPAR\(\alpha\) and \(\gamma\), respectively. It showed better glucose lowering effects than rosiglitazone 1 and ameliorated the lipid profile like plasma triglyceride in db/db mice model.
49. **Hsing-Pang Hsieh et al (2006)**, reported a structure biology analysis of novel indole-based PPAR agonists to explain the structure-activity relationships and present a critical analysis of reasons for change in selectivity with change in the orientation of the same scaffolds. The results would be helpful in designing novel PPAR agonists.

50. **Yanping Xu et al (2006)**, described the design and synthesis of the dual peroxisome proliferator activated receptor (PPAR) γ/δ agonist (R)-3-{4-[3-(4-chloro-2-phenoxyphenoxy)-butoxy]-2-ethyl-phenyl}-propionic acid (20) for the treatment of type 2 diabetes and associated dyslipidemia. In preclinical models, the compound improves insulin sensitivity and reverses diabetic hyperglycemia with less weight gain at a given level of glucose control relative to rosiglitazone.

51. **Sung Soo Kim et al (2006)**, Agonists of peroxisome proliferator-activated receptor γ (PPAR γ) are of interest as a treatment for diabetes, which prompted the
identification of a new class of non-TZD PPAR γ agonist. Moreover, compound 14c has displayed the most active agonistic activity with an EC50 value of 50 nM, in addition to exhibiting a new binding mode in the X-ray cocrystal structure.

52. Zongru Guo et al (2006)\textsuperscript{230}, synthesized a series of 2-alkoxydihydrocinnamates as PPARγ and PPARα dual agonists. In vitro studies in cell model showed that these compounds were efficacious. Compound 1g was found to be a potent PPARα/γ dual agonist and will be further evaluated for the treatment of type II diabetes.

53. Alan M. Warshawsky et al (2006)\textsuperscript{231}, synthesized PPAR ligands with varied subtype selectivity using an achiral aminomethyl dihydrocinnamate template. Several compounds in this series have demonstrated potent plasma glucose and triglyceride lowering capability in rodent models of type 2 diabetes.

54. Gurram R. Madhavan et al (2006)\textsuperscript{232}, synthesized and evaluated 2,4-Thiazolidinedione derivatives of 1,3-benzoxazinone for their PPARα and γ dual activation. DRF-2519, a compound obtained 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.
55. Zongru Guo et al (2006) synthesized series of azaindole-a-alkyloxyphenylpropionic acid analogues and evaluated for PPAR agonist activities. Structure–activity relationship was developed for PPAR\(\alpha/\gamma\) dual agonism. One of the synthesized compound 7a was identified as a potent, selective PPAR\(\alpha/\gamma\) dual agonist.

56. Guo Q. Shi et al (2005), reported the design and synthesis of a novel class of 2,3-dihydrobenzofuran-2-carboxylic acids as highly potent and subtype-selective PPAR\(\gamma\) agonists. Identified several key structural elements within this class using SAR for maintaining the potency and subtype selectivity. Selected compounds were evaluated in animal models of dyslipidemia using Syrian hamsters and male Beagle dogs, and all these compounds displayed excellent cholesterol and triglyceride lowering activity at dose levels that were much lower than the marketed weak PPAR\(\gamma\) agonist fenofibrate.

57. Matthew J. Ellis et al (2005), developed a novel molecular dynamics (MD) analysis algorithm, DASH, to utilize the sequential nature of MD simulation data. By adjusting a set of parameters, the sensitivity of DASH can be controlled, allowing molecular motions of varying magnitudes to be detected or ignored as desired, with no knowledge of the number of conformations required being prerequisite. MD simulations of three synthetic ligands of the orphan nuclear receptor PPAR\(\gamma\) were generated in vacuo using Tripos’s SYBYL and used as the training set for DASH.
Two X-ray crystal structures of PPAR\(\gamma\) complexed with Rosiglitazone were compared to gain knowledge of the pharmacophoric conformation; this showed that the conformation of the ligand is significantly different between the two structures, indicating that there is no distinct conformation in which rosiglitazone binds to PPAR\(\gamma\) but multiple binding modes. The results show that DASH analysis is as good as Ward analysis in some areas.

58. Kun Liu et al (2005)\textsuperscript{236}, designed, synthesized, and evaluated a series of 2-aryloxy-2-methyl-propionic acid compounds and related analogues for their PPAR agonist activities. 2-{(5,7-Dipropyl-3-trifluoromethyl)benzisoxazol-6-yloxy}-2-methyl propionic acid (4) was identified as a PPARR/\(\gamma\) dual agonist with relative PPARR selectivity and demonstrated potent efficacy in lowering both glucose and lipids in animal models without causing body weight gain.

59. Jose´ A. Martin et al (2005)\textsuperscript{237}, describe a series of potent and selective PPAR\(\gamma\) agonists with moderate PPAR\(\alpha\) affinity and little to no affinity for other nuclear receptors. In vivo studies in a NIDDM animal model (ZDF rat) showed that these compounds are efficacious at low doses in glucose normalization and plasma triglyceride reduction. Compound 1b (LY519818) was selected from our SAR studies to be advanced to clinical evaluation for the treatment of type II diabetes.
60. **John J. Acton et al (2005)**\(^{238}\), yielded compounds 1 and 2 which were sub-micromolar hPPAR\(\gamma\) agonists. Synthetic modifications of these leads led to a series of potent substituted 3-benzyl-2-methyl indoles, a subset of which were noted to be selective PPAR\(\gamma\) modulators (SPPAR\(\gamma\)Ms). SPPAR\(\gamma\)M24 displayed robust anti-diabetic activity with an improved therapeutic window in comparison to a PPAR\(\gamma\) full agonist in a rodent efficacy model.

![Chemical structure of compound 1](image1)

61. **Chenzhong Liao et al (2005)**\(^{239}\), constructed a virtual combinatorial library containing 1226,625 compounds based on the structural characters of PPAR modulators using SMILES strings. Selected ADME filters were employed to compel compounds having poor drug-like properties from this library. This library was converted to sdf and mol2 files by CONCORD 4.0, and was then docked to PPAR\(\gamma\) by DOCK 4.0 to identify new chemical entities that may be potential drug leads against type 2 diabetes and other metabolic diseases. The method to construct virtual combinatorial library using SMILES strings was further visualized by Visual Basic.net that can facilitate the needs of generating other type virtual combinatorial libraries.

62. **Uma Ramachandran et al (2005)**\(^{240}\), synthesized and evaluated series of hydroxycarbazole derivatives for PPAR\(\alpha/\gamma\) dual agonist as well as antioxidant activities. While most compounds showed good antioxidant activity, some compounds were identified as potential PPAR\(\alpha/\gamma\) dual agonists as well.

![Chemical structure of compound 2](image2)
63. **Makoto Takamura et al (2004)**\(^{241}\), reported the synthesis and biological activity of a novel series of oximes and amides having a-substituted-b-phenylpropionic acids as potent PPAR\(\alpha/\gamma\) dual agonist (S)-9d, with which activation of PPAR\(\alpha\) and PPAR\(\gamma\) was considerably more potent than that of the reference compounds GW9578 22 and rosiglitazone 3, respectively.

![Chemical Structure of Oxime and Amide](image1)

64. **Xian Ping Lu et al (2004)**\(^{242}\), reported the design, synthesis, and evaluation of a series of novel PPAR\(\alpha\) selective activators containing 1,3-dicarbonyl moieties. Structure activity relationship studies led to the identification of \(\alpha\) selective activators (compounds 10, 14, 17, 18, and 21) with stronger potency and efficacy to activate PPAR\(\alpha\) over PPAR\(\gamma\) and PPAR\(\delta\). Experiments in vivo showed that compounds 10, 14, and 17 had blood glucose lowering effect in diabetic db/db mouse model after two weeks oral dosing.

![Chemical Structure of Selected Activators](image2)

65. **Brad R. Henke (2004)**\(^{243}\), gives the importance of Peroxisome Proliferator-Activated Receptor \(\alpha/\gamma\) Dual Agonists for the Treatment of Type 2 Diabetes.
66. **Hiroo Koyama et al (2004)**\(^{244}\), synthesized and evaluated a series of chromane-2-carboxylic acid derivatives was for PPAR agonist activities. A structure-activity relationship was developed toward PPAR \(\alpha/\gamma\) dual agonism. As a result, 7-{3-[2-chloro-4-(4-fluorophenoxy) phenoxy] propoxy}-2-ethylchromane-2-carboxylic acid (48) was identified as a potent, structurally novel, selective PPARR/\(\gamma\) dual agonist. 48 exhibited substantial antihyperglycemic and hypolipidemic activities in three different animal models: the db/db mouse type 2 diabetes model, a Syrian hamster lipid model, and a dog lipid model.

![Chemical structure of 48](image)

67. **Nathan B. Mantlo et al (2003)**\(^{245}\), described a new series of hPPARR agonists containing a 2,4- dihydro-3H-1,2,4-triazol-3-one (triazolone) core, leading to the discovery of 5 (LY518674), a highly potent and selective PPARR/\(\gamma\) agonist.

![Chemical structure of 5](image)

68. **Søren Ebdrup et al (2003)**\(^{246}\), developed a new and improved synthesis of the peroxisome proliferator-activated receptor (PPAR) agonist ragaglitazar applicable for large-scale preparation. The convergent synthetic procedure was based on a novel enzymatic kinetic resolution step. The conformation of ragaglitazar bound to the hPPAR\(\gamma\) receptor was quite different compared to the single-crystal structures of the L-arginine salt of ragaglitazar.

![Chemical structure of ragaglitazar](image)
69. Michel Dauca et al (2003)\textsuperscript{247}, present the expression pattern of the PPARα subtype in the adult jerboa Jaculus orientalis, determined by RT-PCR and Western blotting using specific probes and a polyclonal antibody for PPARα, respectively. PPARα is highly expressed in liver and kidney, and to a lesser extent in duodenum and colon. Data indicate that the PP-induced PPARα gene expression is not dependent on the PPARα content in target cells.

70. Hiroo Koyama et al (2003)\textsuperscript{248}, designed, synthesized, and evaluated a series of 5-aryl thiazolidine-2,4-diones containing 4-phenoxyphenyl side chains for PPAR agonist activities. One such compound 28 exhibited comparable levels of glucose correction to rosiglitazone in the db/db mouse type 2 diabetes animal model.
71. Philip J. Rybczynski et al (2003), synthesized a series of benzoxazinones as PPARγ agonists. The compounds were obtained in seven steps, and SAR was developed by variations to the core shown below. The compounds were tested as functional agonists in the induction of the aP2 gene in preadipocytes, and the most potent compound in the series has an EC$_{50}$=0.51 mM.

\[
\text{NO}_2 \text{O} \text{COOH}
\]

72. Per Sauerberg et al (2002), performed Synthesis and structure-activity relationships of tricyclic R-ethoxy-phenylpropionic acid derivatives guided by in vitro PPARR and PPARγ transactivation data and computer modeling led to the identification of the novel carbazole analogue, 3q, with dual PPARα (EC$_{50}$) 0.36 µM) and PPARγ (EC$_{50}$) 0.17 µM) activity in vitro. Investigations of the pharmacokinetics of selected compounds suggested that extended drug exposure improved the in vivo activity of in vitro active compounds.

\[
\text{COOH \ OC}_2\text{H}_5
\]

73. Margaret Y. Chu-Moyer et al (2002), achieved optimization of a previously disclosed sorbitol dehydrogenase inhibitor for potency and duration of action by replacing the metabolically labile N,N-dimethylsulfamoyl group with a variety of heterocycles. Specifically, this effort led to a series of novel, in vitro potent SDIs with longer serum half-lives and acceptable in vivo activity in acutely diabetic rats. Compound 86 was found to be a selective inhibitor of sorbitol dehydrogenase, with excellent pharmacodynamic/pharmacokinetic properties, demonstrating normalization of sciatic nerve fructose in a chronically diabetic rat model.
74. Ramanujam Rajagopalan et al (2001)\textsuperscript{252}, synthesized and evaluated DRF 2725 (6), a phenoxazine analogue of phenyl propanoic acid. Compound 6 showed interesting dual activation of PPAR\textsubscript{α} and PPAR\textsubscript{γ} with good oral bioavailability and impressive pharmacokinetic characteristics. Our study indicates that 6 has great potential as a drug for diabetes and dyslipidemia.

75. Nicolas G. Bazan et al (2000)\textsuperscript{253}, sequenced and described two alternatively spliced variants of rat PPAR\textsubscript{γ}: rPPAR\textsubscript{γ}1\textsubscript{a} and rPPAR\textsubscript{γ}1\textsubscript{b}. Both of these, along with the recently described rPPAR\textsubscript{γ}2 were induced by ROS phagocytosis. PPAR\textsubscript{α} and PPAR\textsubscript{δ} mRNA expression was also detected in RPE cells, but the level of expression did not change during ROS phagocytosis. Selective activation of PPAR\textsubscript{γ} may play an important role in regulating the expression of target genes that are involved in lipid and fatty acid metabolism in the photoreceptor renewal process.