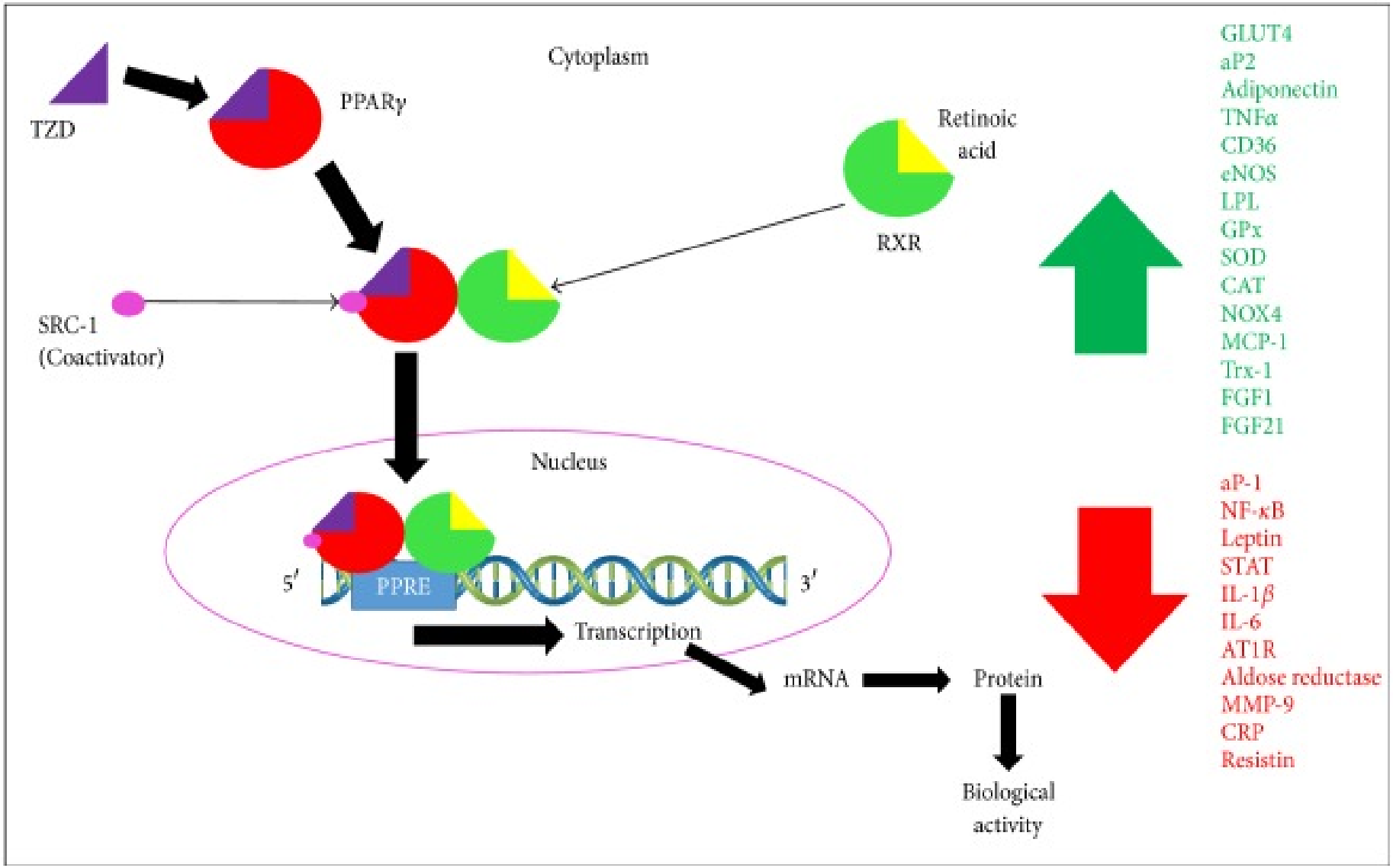
Thiazolidinediones

- Bioorg Chem. 2018 Apr;77:548-567. doi: 10.1016/j.bioorg.2018.02.009. Epub 2018 Feb 12.
- **Thiazolidinediones as antidiabetic agents: A critical review.**
- Nanjan M, Mohammed M, Prashantha Kumar BR, Chandrasekar MJN

- **Abstract**

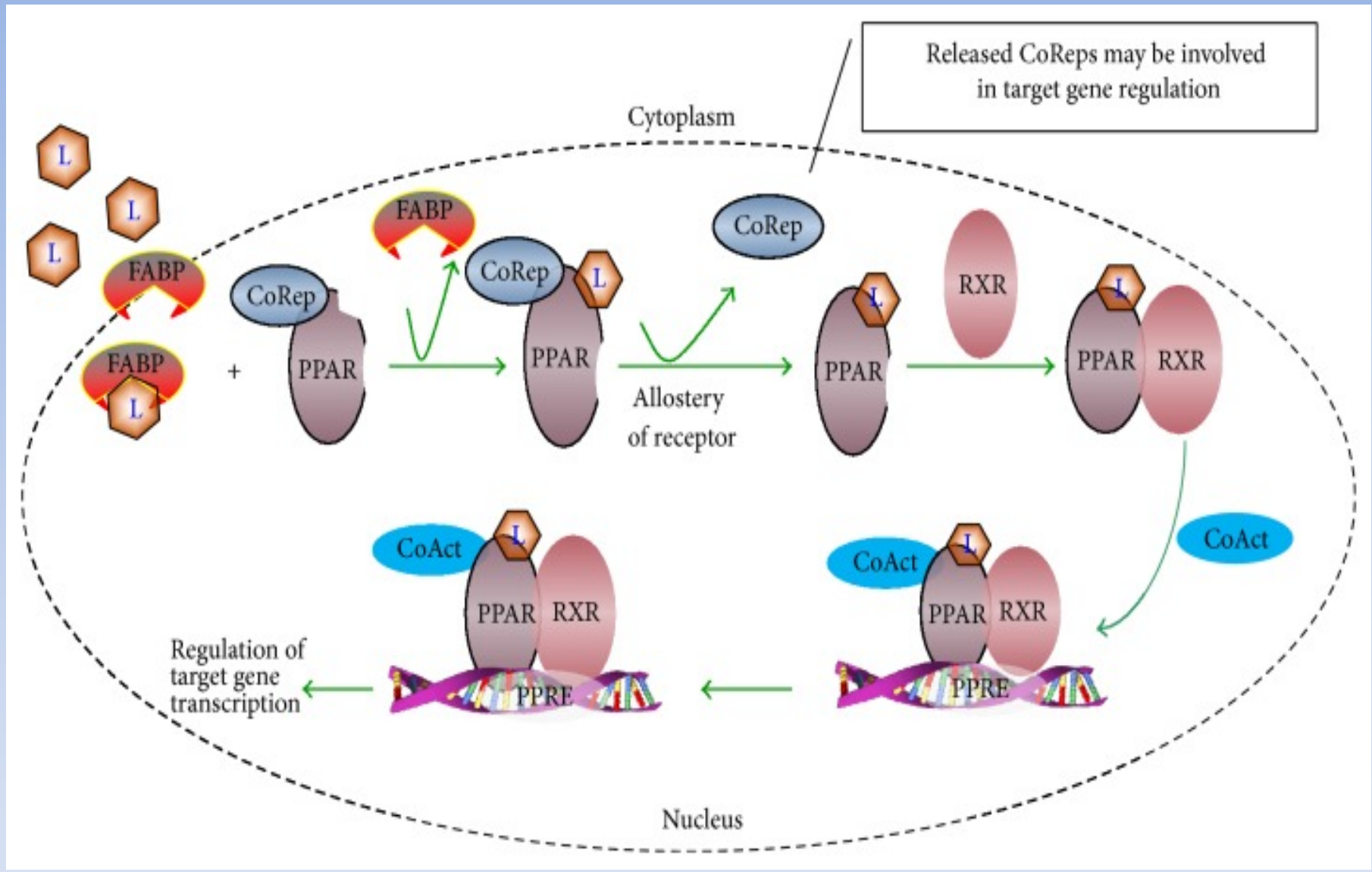
- **Thiazolidinediones (TZDs) or Glitazones are an important class of insulin sensitizers used in the treatment of Type 2 diabetes mellitus (T2DM). TZDs were reported for their antidiabetic effect through antihyperglycemic, hypoglycemic and hypolipidemic agents. In time, these drugs were known to act by increasing the transactivation activity of Peroxisome Proliferators Activated Receptors (PPARs). The clinically used TZDs that suffered from several serious side effects and hence withdrawn/updated later, were full agonists of PPAR-γ and potent insulin sensitizers. These drugs were developed at a time when limited data were available on the structure and mechanism of PPARs. In recent years, however, PPAR-α/γ, PPAR-α/δ and PPAR-δ/γ dual agonists, PPAR pan agonists, selective PPAR-γ modulators and partial agonists have been investigated. In addition to these, several non PPAR protein alternatives of TZDs such as FFAR1 agonism, GPR40 agonism and ALR2, PTP1B and α-glucosidase inhibition have been investigated to address the problems associated with the TZDs. Using these rationalized approaches, several investigations have been carried out in recent years to develop newer TZDs devoid of side effects. This report critically reviews TZDs, their history, chemistry, mechanism mediated through PPAR, recent advances and future prospects.**

- PPAR Res. 2016;2016:7614270. doi: 10.1155/2016/7614270. Epub 2016 May 23.
- **Current Advances in the Biochemical and Physiological Aspects of the Treatment of Type 2 Diabetes Mellitus with Thiazolidinediones.**
- Alemán-González-Duhart D, Tamay-Cach F, Álvarez-Almazán S, Mendieta-Wejebe JE.
- **Abstract**
- **The present review summarizes the current advances in the biochemical and physiological aspects in the treatment of type 2 diabetes mellitus (DM2) with thiazolidinediones (TZDs). DM2 is a metabolic disorder characterized by hyperglycemia, triggering the abnormal activation of physiological pathways such as glucose autooxidation, polyol's pathway, formation of advance glycation end (AGE) products, and glycolysis, leading to the overproduction of reactive oxygen species (ROS) and proinflammatory cytokines, which are responsible for the micro- and macrovascular complications of the disease. The treatment of DM2 has been directed toward the reduction of hyperglycemia using different drugs such as insulin sensitizers, as the case of TZDs, which are able to lower blood glucose levels and circulating triglycerides by binding to the nuclear peroxisome proliferator-activated receptor gamma (PPARγ) as full agonists. When TZDs interact with PPARγ, the receptor regulates the transcription of different genes involved in glucose homeostasis, insulin resistance, and adipogenesis. However, TZDs exhibit some adverse effects such as fluid retention, weight gain, hepatotoxicity, plasma-volume expansion, hemodilution, edema, bone fractures, and congestive heart failure, which limits their use in DM2 patients.**



Mechanism of action of PPARγ when it is activated by its exogenous ligands TZDs.

Current Advances in the Biochemical and Physiological Aspects of the Treatment of Type 2 Diabetes Mellitus with Thiazolidinediones.
Alemán-González-Duhart D et al.



Schematic representation of the mechanism of PPARγ agonist signaling

PPAR Res. 2017;2017:8360919. doi: 10.1155/2017/8360919. Epub 2017 Jun 4.
Discovery of Novel Insulin Sensitizers: Promising Approaches and Targets. Chen Y et al.

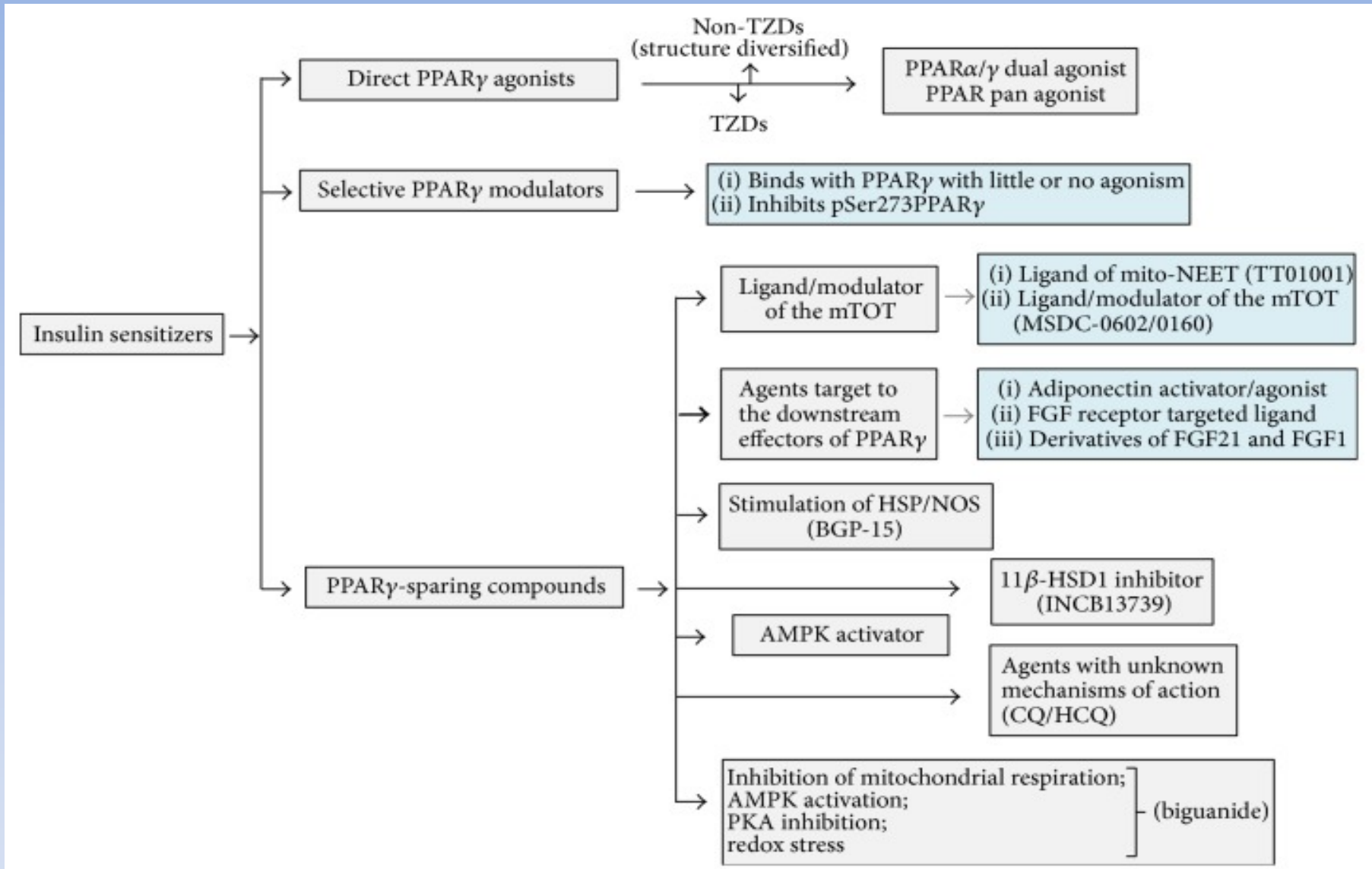
PPAR Res. 2017;2017:8360919. doi: 10.1155/2017/8360919. Epub 2017 Jun 4.

Discovery of Novel Insulin Sensitizers: Promising Approaches and Targets.

Chen Y et al.

Abstract

Insulin resistance is the undisputed root cause of type 2 diabetes mellitus (T2DM). There is currently an unmet demand for safe and effective insulin sensitizers, owing to the restricted prescription or removal from market of certain approved insulin sensitizers, such as thiazolidinediones (TZDs), because of safety concerns. Effective insulin sensitizers without TZD-like side effects will therefore be invaluable to diabetic patients. The specific focus on peroxisome proliferator-activated receptor *γ*- (PPAR*γ*-) based agents in the past decades may have impeded the search for novel and safer insulin sensitizers. This review discusses possible directions and promising strategies for future research and development of novel insulin sensitizers and describes the potential targets of these agents. Direct PPAR*γ* agonists, selective PPAR*γ* modulators (sPPAR*γ*Ms), PPAR*γ*-sparing compounds (including ligands of the mitochondrial target of TZDs), agents that target the downstream effectors of PPAR*γ*, along with agents, such as heat shock protein (HSP) inducers, 5'-adenosine monophosphate-activated protein kinase (AMPK) activators, 11*β*-hydroxysteroid dehydrogenase type 1 (11*β*-HSD1) selective inhibitors, biguanides, and chloroquines, which may be safer than traditional TZDs, have been described. This minireview thus aims to provide fresh perspectives for the development of a new generation of safe insulin sensitizers.



Classification of new-generation insulin sensitizers based on their mechanisms or targets.

PPAR Res. 2017;2017:8360919. doi: 10.1155/2017/8360919. Epub 2017 Jun 4. **Discovery of Novel Insulin Sensitizers: Promising Approaches and Targets.** Chen Y et al.

Drug	Prescribing considerations
Pioglitazone	Not recommended in renal replacement therapy, no dose adjustment required if creatinine clearance >4 ml/min Contraindicated in hepatic impairment Contraindicated with history of cardiac failure Contraindicated with history of bladder cancer or uninvestigated microscopic or macroscopic haematuria Increased risk of fractures, including hip fractures[2]
Rosiglitazone	Licensing authorisation withdrawn by EMA 2010 due to cardiovascular safety concerns
Troglitazone	Licensing authorisation withdrawn by EMA 2000 due to hepatotoxicity

Key: EMA = European Medicines Agency