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THIAZOLIDINEDIONE SCAFFOLDS IN MEDICINAL CHEMISTRY: SYNTHETIC ROUTES AND BIOLOGICAL ACTIVITIES

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Abstract

The thiazolidine-2,4-dione ring has been a working scaffold in medicinal chemistry for four decades, first as the pharmacophore of the glitazone insulin sensitisers and later as a starting point for aldose reductase, anticancer, antimicrobial and anti-inflammatory programmes. This narrative review summarises published synthetic routes to the ring and its 5-arylidene, 5-benzyl and N-substituted derivatives, the receptor biology behind the antidiabetic series, and the activities reported for other targets. It also covers the safety experience that shaped clinical use. The literature shows a versatile and synthetically accessible core, but most non-diabetic activity data are in vitro and poorly standardised. This review reports no new experimental data.

1. INTRODUCTION

Few small heterocycles have had as visible a career as thiazolidine-2,4-dione. A five-membered ring carrying sulphur at position 1, nitrogen at position 3 and two carbonyl groups at positions 2 and 4, it is cheap to make, chemically forgiving and easy to decorate. The ring became famous when ciglitazone-type compounds were found to lower glucose in insulin-resistant rodents, and when the clinical members of the class, troglitazone, rosiglitazone and pioglitazone, reached the market in the late 1990s [1, 2, 3].

Their later history, which included a withdrawal and a long cardiovascular argument, has coloured how the scaffold is regarded. Even so, the core continues to

appear in screening libraries and published series [4, 5].

This review follows the scaffold from bench to bedside and back again. It first describes the routes used to build and functionalise the ring, then the receptor pharmacology that explains the antidiabetic series, and then the activities reported against other targets, which are gathered in table 1. Safety experience from trials and surveillance is treated as part of the medicinal chemistry story, because the adverse effects of the glitazones are largely what pushed later work towards partial agonists and non-PPAR mechanisms [6, 7, 8]. No new experimental work is reported; the discussion rests on published reviews, clinical trials and synthetic papers.

A word on terminology helps. Chemists call the parent compound thiazolidine-2,4-dione, often abbreviated TZD, and clinicians use TZD or glitazone for the drugs derived from it. Related rings such as rhodanine, 2-thiohydantoin and 2-imino-4-thiazolidinone share the arylidene chemistry, and they are sometimes grouped with TZDs in screening papers, although their liabilities differ [9, 10]. This review keeps to the 2,4-dione ring unless a comparison is useful. Terminology also differs between chemistry and pharmacology journals: the former tends to number ring positions, whereas the latter refers to the head group, linker and tail, and a reader moving between the two needs to translate [5, 11].

The chemistry literature on the scaffold is large, and it is useful to say what kind of evidence it contains. Early work came from industrial laboratories and was driven by in vivo glucose lowering in obese or diabetic rodents. Academic work of the past two decades is mostly built on the same ring but is guided by docking, cell-line screening and enzyme assays, which are cheaper to run and quicker to publish. The two bodies of work answer different questions. Industrial series asked whether a compound could be a drug; academic series have more often asked whether a ring can be made to show activity at all. Reading them side by side, as this review attempts to do, means weighing a handful of rigorously profiled compounds against hundreds of lightly characterised ones [4, 5, 11].

Table 1: Selected biological activities reported for thiazolidinedione derivatives

Compound class|feature	Reported finding or feature	Ref.
Rosiglitazone PPAR-γ ligand	High-affinity PPAR-γ binding that tracks with antihyperglycaemic potency across analogues.	[1, 3]
Pioglitazone clinical trials	Improved glycaemic control and, in selected patients, fewer strokes and myocardial infarctions.	[12, 13]
Rosiglitazone durability	Slower loss of glycaemic control than metformin or glibenclamide over several years.	[14]
Pioglitazone NASH	Histological improvement in steatohepatitis in randomised trials.	[15, 16, 17]
5-Benzyl-TZDs polyol pathway	Micromolar to submicromolar aldose reductase inhibition in vitro.	[18, 19]
Acetic acid TZDs enzyme pocket	Anion-binding pocket occupied by the acidic group; selectivity tuned by ring substituents.	[4, 19]
5-Benzylidene-TZDs cell lines	Cytotoxicity in breast, colon and leukaemia panels, with apoptosis and cell cycle effects.	[4, 20]
Arylidene scaffolds assay artefacts	Frequent-hitter behaviour complicates interpretation of cell-based activity.	[9, 10]
2-Imino-4-thiazolidinones rat oedema	Reduced paw oedema and cyclo-oxygenase inhibition in vitro.	[21]
Heteroaryl thiazolidinones broth tests	Growth inhibition of Gram-positive bacteria and fungi.	[5, 22]

2. SYNTHETIC ROUTES

The classical entry to the ring is the condensation of chloroacetic acid with thiourea in water under acid, which gives 2-imino-4-thiazolidinone as an intermediate. Prolonged heating with hydrochloric acid then hydrolyses the imine to the 2,4-dione. The method is old, inexpensive and scalable, and it remains the standard way in which academic groups prepare gram quantities of the parent ring [4, 5]. Variants use chloroacetic acid with potassium thiocyanate or with thiosemicarbazones when a substituted nitrogen is wanted at an early

stage. Yields are generally good, but the long reflux and the acidic work-up have prompted milder alternatives, some of which are described below.

Most biologically active derivatives are made by Knoevenagel condensation of the ring with an aromatic aldehyde at the active methylene carbon, C-5 [23]. Piperidine in refluxing ethanol is the textbook catalyst; piperidinium acetate in toluene with azeotropic removal of water, sodium acetate in acetic acid, and ammonium acetate have all been used when the aldehyde is sensitive or poorly soluble. The product is the 5-arylidene derivative, usually obtained as the Z isomer, which is the more stable form and is the geometry reported in most crystal structures [5]. The arylidene is also a Michael acceptor, a property that matters later when assay interference and covalent reactivity are discussed.

The glitazone drugs themselves carry a saturated benzyl group at C-5, so the arylidene must be reduced. Catalytic hydrogenation over palladium is the usual choice in process chemistry, while sodium borohydride in the presence of cobalt salts, and several transfer-hydrogenation systems, have been used on the laboratory scale to avoid pressurised gas [3, 5]. For pioglitazone, a pyridylethoxy side chain is built first onto a nitrophenol, the nitro group is reduced and converted through a diazonium salt to an alpha-halo ester, and cyclisation with thiourea then closes the ring. Rosiglitazone follows a related plan with an N-methyl-N-pyridylaminoethoxy side chain and a late Knoevenagel step [2, 3].

Substitution at nitrogen is the third common operation. The N-3 hydrogen is acidic (pKa near 6.5 for the unsubstituted ring), so mild bases such as potassium carbonate in dimethylformamide, or triethylamine in acetonitrile, give clean N-alkylation with alkyl halides, and Mannich reactions with formaldehyde and secondary amines give aminomethyl derivatives [4, 5]. The consequence for biology is not trivial. The acidic N-H of the ring is a key hydrogen-bond donor in the PPAR-γ ligand-binding domain, and most N-alkylated analogues lose receptor activity, which is one reason they are more often explored as aldose reductase, antimicrobial or anticancer leads than as insulin sensitisers [1, 11].

Hybrid and fused systems form a large fraction of recent synthetic papers. Because the ring offers three modification points (N-3, C-5 and, less often, the carbonyl oxygens or the sulphur), chemists can link it to coumarins, quinolines, indoles, pyrazoles or sugar units through a spacer, usually with the aim of combining two activities in one molecule. Spiro compounds at C-5 and thiazolo-fused heterocycles have also been prepared by cycloaddition or multicomponent reactions. The synthetic effort is often modest, but the resulting molecules can be heavy, lipophilic and poorly soluble, which is not helped when the starting TZD fragment is already a flat conjugated arylidene [4, 5].

Characterisation is less glamorous than synthesis but decides whether a paper can be trusted. Infrared spectra show two carbonyl stretches of the ring near 1700 and 1750 cm^{-1} and a broad N-H band that vanishes on N-alkylation. In the proton NMR spectrum the 5-arylidene derivatives show a singlet for the vinylic proton around 7.5 to 8.0 ppm, whereas the saturated 5-benzyl compounds show a doublet of doublets for H-5 near 4.5 ppm and diastereotopic benzylic protons [5, 23]. Mass spectrometry and elemental analysis complete the usual package. Purity by HPLC is reported less often than it should be, and it matters because residual aldehyde can itself be active in biological tests [9, 10].

Methodological papers have tried to make all of this greener and faster. Microwave heating shortens the Knoevenagel step from hours to minutes and frequently improves yields [24]. Solvent-free grinding, aqueous media, ionic liquids and supported catalysts have been described for the same reaction, and some of the more recent protocols avoid chromatographic purification altogether [4, 5]. How far these gains transfer to the multistep synthesis of a real drug is less clear, since few of the published green protocols have been demonstrated beyond the small-scale arylidene step. Reproducibility data, such as results from repeat batches or from a second operator, are almost never reported. Greener routes also rarely report atom economy.

Scale-up raises a different set of questions from those that dominate the research literature. Piperidine, toluene and chlorinated solvents are routine on the bench but are less welcome in manufacturing, and the Meerwein arylation step in the pioglitazone route generates waste that has to be handled carefully. Process groups have therefore explored alternative sequences that introduce the ring late, and that avoid diazonium intermediates by starting from a pre-formed benzaldehyde [3, 5]. The academic literature rarely addresses these points, though they bear on whether a new analogue could ever be made at a reasonable cost.

3. PPAR-γ AND ANTIDIABETIC ACTIVITY

The molecular target of the glitazones was identified in the mid-1990s, when rosiglitazone was shown to bind peroxisome proliferator-activated receptor gamma (PPAR-γ) with nanomolar affinity and when binding potency tracked with antidiabetic potency across a series of analogues [1, 3]. PPAR-γ is a ligand-activated nuclear receptor that forms a heterodimer with the retinoid X receptor and regulates genes of lipid storage and adipocyte differentiation. On agonist binding, co-repressors are released, co-activators are recruited, and transcription of target genes rises [11, 25]. It is expressed most strongly in adipose tissue, which is why much of the physiology of the drugs is adipocentric.

Structurally, the pharmacophore has three parts: an acidic head group (the TZD ring), a central aromatic spacer, and a lipophilic tail joined by an ether-linked chain. The ring makes hydrogen bonds to residues on helix 12 of the ligand-binding domain, such as Ser289, His323, His449 and Tyr473, which stabilises the active conformation of the activation function-2 surface [11, 25]. Changes in the tail alter potency by orders of magnitude and also change cofactor recruitment, so two full agonists can have different gene-expression profiles. Non-TZD agonists, including the tyrosine-based farglitazar, were developed partly to test whether the ring itself was needed, and they showed that it is not essential for receptor activation [11, 26].

Structure-activity work on the glitazones established several reliable rules. The acidic head is needed for high potency, and replacing the ring with oxazolidinedione or with a carboxylic acid retains some activity but usually at lower affinity [11, 26]. The linker between the central benzene ring and the tail is typically a two- or three-atom ether chain, and shortening it hurts activity. The lipophilic tail, a pyridine in pioglitazone and rosiglitazone, a chromane in troglitazone, contributes much of the potency and also determines which co-activators are recruited [3, 11]. Substitution on the central ring is tolerated only in small amounts, as bulky groups disturb the way the head group sits against helix 12 [11, 25].

How does receptor activation lower glucose? The usual account is that agonists promote storage of free fatty acids in subcutaneous adipose tissue, remodel adipocytes towards smaller and more insulin-sensitive cells, and raise adiponectin, so that muscle and liver are relieved of lipid overload [27, 28]. Clinical studies using pioglitazone found redistribution of fat from visceral to subcutaneous depots alongside improved insulin sensitivity [28]. In the ADOPT trial, rosiglitazone slowed the loss of glycaemic control compared with metformin or glibenclamide in newly diagnosed type 2 diabetes, which is the best-known evidence for durability of effect [14]. The same trial also showed weight gain and a higher fracture rate in women, matters returned to below.

Stereochemistry deserves mention. Carbon-5 of the saturated ring is a stereocentre, so glitazones are sold as racemic mixtures. The two enantiomers interconvert readily under physiological conditions because the C-5 proton is acidic, which means that administering a single enantiomer offers no lasting advantage. In receptor binding, the (S)-enantiomer is the more potent agonist, while the (R)-form has been reported to share some of the non-PPAR actions such as effects on mitochondrial targets [2, 29, 30]. This point is more than a curiosity, because it frames current attempts to design compounds with reduced PPAR-γ activity that still lower glucose, an approach discussed again in the final section.

Not everything about the class can be traced to PPAR-γ. Thiazolidinediones inhibit mitochondrial complex I in cultured cells, much as metformin does, and a mitochondrial outer-membrane protein now called mitoNEET binds pioglitazone in photoaffinity experiments [29, 30]. Whether these off-target actions contribute to glucose lowering in people is uncertain. A different line of work showed that obesity-induced phosphorylation of PPAR-γ at serine 273 by Cdk5 changes the expression of a subset of genes, and that antidiabetic ligands block this phosphorylation even when they are weak classical agonists [8, 31]. That result suggested that a compound might retain insulin-sensitising action while avoiding the fluid retention and weight gain linked to full agonism, an idea that has driven partial agonist design.

Partial agonists and selective modulators represent the clearest attempt to improve on the first generation. Compounds that bind the ligand-binding domain without fully stabilising helix 12 recruit a different set of cofactors, which in rodents produced glucose lowering with less adipogenesis and less fluid retention than full agonists [8, 31]. The clinical record for such molecules is thin. Several candidates have reached early trials, but none has displaced pioglitazone, and the experience of the class suggests that partial activation in a cell assay does not guarantee a favourable balance in people [7, 32]. Researchers working in this area need extended safety follow-up rather than short efficacy studies.

Clinical positioning has shifted over time. Trials such as PROactive reported that pioglitazone did not significantly improve its composite primary endpoint in people with type 2 diabetes and macrovascular disease, although a main secondary endpoint of death, myocardial infarction and stroke was reduced [12]. The IRIS trial later found fewer strokes and myocardial infarctions with pioglitazone in insulin-resistant patients with a recent cerebrovascular event [13]. Clinical practice has long accepted the class where cost matters or hypoglycaemia must be avoided, while steering clear of it in people with heart failure, since fluid retention is the main concern [7, 33].

Albumin binding is worth a line. Both drugs are more than 99 per cent protein bound, which restricts the volume of distribution to roughly the extracellular space and keeps free concentrations low. That is one reason in vitro potencies measured in serum-free medium can overstate what is achievable in patients, a caveat that applies equally to the micromolar cytotoxicity values reported for new analogues [2, 7, 20]. Free-fraction measurements are seldom reported for new analogues, which makes comparisons across laboratories difficult. Binding to serum albumin can also reduce apparent antimicrobial potency in broth containing serum proteins. Such effects are rarely modelled.

4. OTHER BIOLOGICAL ACTIVITIES

Outside diabetes, the best-developed use of the scaffold is aldose reductase inhibition. The enzyme converts glucose to sorbitol in the polyol pathway, and sorbitol accumulation has been linked to diabetic neuropathy, retinopathy and cataract. Acetic acid derivatives of arylidene-TZDs, and 5-benzyl analogues, inhibit the enzyme in vitro at micromolar to submicromolar concentrations, with substituents on the aromatic ring tuning potency and selectivity over the related aldehyde reductase [18, 19]. Molecular modelling places the acidic ring in the anion-binding pocket near the nicotinamide cofactor. No such compound has become a marketed drug, a pattern shared by most aldose reductase inhibitors other than epalrestat, which is used in a few countries.

Anticancer reports are numerous. Series of 5-benzylidene-TZDs have shown cytotoxicity against breast, colon, leukaemia and lung cell lines, often in the low micromolar range, and mechanisms proposed include cell cycle arrest, induction of apoptosis and inhibition of kinases such as PI3K and Pim [4, 20]. Part of the effect may be PPAR-γ dependent, although PPAR-γ ligands also act through receptor-independent routes at the concentrations used in cell culture. The chief problem is interpretation. Many publications report a single cell panel, lack matched normal cells and do not examine reactivity of

the Michael acceptor, so leads are hard to rank against each other [9, 10].

Antimicrobial and anti-inflammatory work follows a similar pattern. Thiazolidinones carrying aryl or heteroaryl groups have inhibited Gram-positive bacteria and fungi in broth dilution tests, and docking studies point to bacterial Mur ligases as plausible targets [5, 22]. In the anti-inflammatory area, 2-imino-4-thiazolidinones with 5-arylidene groups reduced paw oedema in rats and inhibited cyclo-oxygenase in vitro, with some activity comparable to reference non-steroidal drugs in the original tests [21]. Reported activities across these areas are compared in table 1, and their distribution by activity class is shown in fig. 1. Minimum inhibitory concentrations are mostly modest. Reported minimum inhibitory concentrations are mostly modest against reference antibiotics, and few papers include mammalian cell controls.

Enzymes of carbohydrate and lipid metabolism provide a further family of targets. Protein tyrosine phosphatase 1B, a negative regulator of insulin signalling, has been inhibited in vitro by arylidene derivatives bearing carboxylic acid groups, and alpha-glucosidase and alpha-amylase inhibition has been reported for various 5-benzylidene compounds [4, 5]. These activities look attractive on paper because they fit the logic of a diabetes programme. Practical value is limited by modest potency compared with acarbose for the glycosidases and by poor cell permeability for the phosphatase inhibitors, which tend to be highly polar. As with the anticancer work, the number of independent confirmations is small [4].

Ligand-based design has contributed little here compared with the antidiabetic series, because there is no single receptor structure to build on. Docking against whichever protein the authors favour, from PPAR-γ to tubulin to bacterial ligases, is common, but the binding scores seldom correlate with measured activity across the series. Some of the more careful papers combine docking with a small number of enzyme assays and a direct binding measurement, which gives a far firmer basis for later optimisation. Others rely on in silico predictions alone, and their conclusions have to be treated as hypotheses. The better-supported examples remain those linked to a defined enzyme, such as aldose reductase, where co-crystal structures exist for related inhibitors [4, 18, 19].

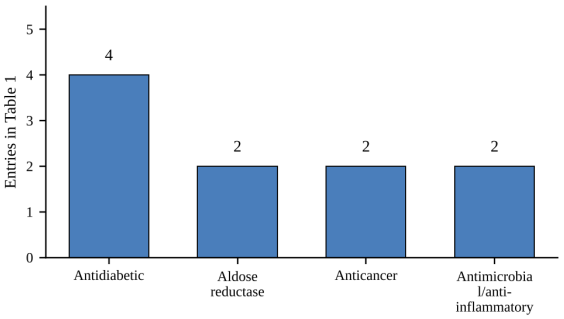


Fig. 1: Number of entries in table 1 by activity class

Why does the same ring appear in so many activity classes? One reason is genuine versatility: it is a compact hydrogen-bonding motif with an acidic proton that fits many anion-binding sites. Another is less flattering. Arylidene rhodanines and related compounds are recognised frequent hitters that can aggregate, absorb light, chelate metals or react with thiols, and published analyses have urged caution when such compounds show activity in many unrelated assays [9, 10]. The 2,4-dione is generally better behaved than rhodanine, but arylidene derivatives deserve counter-screens before claims of selectivity are accepted.

Hybrid molecules deserve a separate comment because they dominate recent literature. A typical paper couples a 5-arylidene TZD to a second pharmacophore, tests the hybrid against a cell line or a microbial panel, and reports that it is more active than either parent. Such statements are sometimes correct. They are also hard to verify when the parent fragments are not tested alongside the hybrid under identical conditions, and when potency is reported relative to a reference drug at a single concentration. Where full dose-response curves and matched controls are given, the claims are much more convincing [4, 9, 20].

5. SAFETY AND CLINICAL EXPERIENCE

The safety history of the glitazones is a case study in how a scaffold can be redeemed or

blamed. Troglitazone, the first in class, was withdrawn from the market in 2000 after idiosyncratic liver injury, an effect that has not been seen at a comparable rate with rosiglitazone or pioglitazone. Fluid retention is the most consistent class effect. Activation of PPAR-γ in the collecting duct increases sodium reabsorption, and the resulting oedema and plasma volume expansion can precipitate heart failure in susceptible people, which led to consensus statements recommending that the drugs be avoided in symptomatic heart failure [2, 32].

Rosiglitazone's cardiovascular reputation was damaged by a 2007 meta-analysis reporting an increased risk of myocardial infarction [6]. Subsequent regulatory restrictions followed in several regions. The RECORD trial, a prospective open-label study, found excess heart failure with rosiglitazone but no clear increase in overall cardiovascular death or myocardial infarction [34], and the episode led to changes in how cardiovascular safety of diabetes drugs is assessed before and after approval [35]. Interpretation remained contested for years, and it is an example of how meta-analysis of small trials can both raise a useful alarm and overstate it.

Bone and cancer concerns arrived later. Observational and trial data indicate that TZDs reduce bone density and raise the risk of fractures, mainly in women, probably through effects on marrow stem cells that favour adipocyte over osteoblast differentiation [14, 36]. For bladder cancer, a cohort study found a modestly increased risk with prolonged and high cumulative pioglitazone exposure, and regulators added a warning, although the picture across studies is not uniform [37]. These findings do not tell us whether the ring or the PPAR-γ mechanism is at fault, which complicates any attempt to engineer a safer successor.

Pharmacokinetics shape how the drugs are used. Both rosiglitazone and pioglitazone are well absorbed orally, highly bound to albumin, and cleared by hepatic metabolism, chiefly through CYP2C8, with CYP3A4 and CYP2C9 contributing to a smaller degree. Inhibitors of CYP2C8 such as gemfibrozil raise exposure to both drugs several-fold, and inducers such as rifampicin lower it, so dose adjustment or avoidance is needed in these combinations [2, 7]. Half-lives are short, yet the pharmacodynamic effect lags behind because transcriptional responses take weeks to build. Patients and prescribers expecting a quick fall in glucose are therefore often disappointed in the first month [2, 14].

Ocular and haematological effects complete the picture. Macular oedema has been reported in a small number of patients taking glitazones and generally resolves after withdrawal. A modest fall in haemoglobin, attributed to haemodilution, is seen in many patients and is rarely of clinical concern. Hypoglycaemia is uncommon when the drugs are used alone, a feature that explains their appeal in older patients and in those with erratic meals, but risk rises when they are combined with insulin or sulphonylureas, at which point oedema and weight gain also become more troublesome [2, 7, 32]. Decisions in individual patients therefore depend on weighing these effects against benefits such as durable glycaemic control and the cardiovascular signals seen in stroke and steatohepatitis populations [13, 14, 16].

Not all of the news from the clinic is negative. Pioglitazone improved histology in patients with non-alcoholic steatohepatitis in randomised trials, with and without diabetes, and practice guidance acknowledges it as an option in biopsy-proven disease [15, 16, 17]. The benefit again raises the question of how to preserve metabolic gains while limiting weight gain and fluid retention. Weight gain of a few kilograms is typical, partly from fluid and partly from subcutaneous fat, and it is among the commonest reasons for stopping treatment in routine practice [2, 7]. Cost and once-daily dosing add to the practical case in many health systems.

6. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations recur across this literature. Structure-activity studies are often carried out on small series made by one group, with one assay and no orthogonal confirmation. Biological testing of arylidene derivatives seldom controls for assay interference. Pharmacokinetic data, including metabolic stability of the ring and the sulphur oxidation

known for pioglitazone, are reported for very few compounds [4, 5]. In the antidiabetic area, in vivo data in diabetic rodents do not always predict the oedema and weight gain seen in humans, so a favourable animal profile has to be treated with restraint [8, 32].

Translational distance is the largest limitation of all. Of the hundreds of derivatives reported in the past twenty years, very few have been tested in a second laboratory, and fewer still in animal models with pharmacokinetic confirmation. The contrast with the PPAR-γ literature, in which crystal structures, knock-out mice and large outcome trials have allowed each hypothesis to be checked, is striking [8, 12, 25]. One reasonable response is for journals and reviewers to expect structural identity data, purity, and at least one orthogonal assay. Another is for authors to concentrate on a small number of chemotypes and do them properly rather than add one more substituent to an already crowded series [4, 5].

There is also a gap between what the field measures and what clinicians need. Most medicinal chemistry papers stop at an IC50 or a cytotoxicity value, whereas the questions that decided the fate of the glitazones were about oedema, fractures, hepatic safety and cardiovascular events observed over years in large populations [6, 12, 36, 37]. Early toxicity flags are possible, for example mitochondrial liability and reactive metabolite formation from the sulphur-containing ring, and they would help to rank candidates before heavy investment. Few academic series include them. A modest set of safety assays added to the usual potency screen would make the published literature much more useful to anyone deciding which scaffold variations are worth taking forward [4, 29, 32].

Future work probably lies in three directions. The first is selective PPAR-γ modulation, in which partial agonists or compounds that block Cdk5-mediated phosphorylation are designed to dissociate insulin sensitisation from adverse effects [8, 31]. The second is dual or pan-PPAR design and hybrid molecules that combine a TZD head group with another pharmacophore, such as an aldose reductase or kinase inhibitor, although polypharmacology brings its own difficulties [19, 20]. The third, which seems the most realistic, is better methodology: standardised cell panels, counter-screens for reactivity, early metabolism data and open reporting of negative results, so that the large body of chemistry already published can be sorted into compounds that deserve follow-up and those that do not [9, 10].

7. CONCLUSION

Thiazolidine-2,4-dione has remained useful because it is easy to make and easy to modify. The three standard operations, ring construction, Knoevenagel condensation and N- or C-5 functionalisation, are well documented, and newer microwave and solvent-free methods make library work quicker [5, 23, 24]. The receptor biology of the antidiabetic series is also well understood: the acidic ring anchors the ligand in PPAR-γ, and potency in animals follows receptor affinity [1, 3, 11]. What is less settled is whether the benefits can be separated from fluid retention, weight gain, fractures and the other effects noted in practice [6, 32, 36].

Activities reported outside diabetes are plentiful but unevenly supported. Aldose reductase inhibition is the most mechanistically coherent, anticancer and antimicrobial reports are mostly cell-based and short on controls, and anti-inflammatory data come largely from older animal tests [18, 20, 21, 22]. For researchers entering the field, the practical lesson is to combine clear synthetic characterisation with counter-screens and early metabolic data, and to measure new compounds against pioglitazone and rosiglitazone as the benchmark [7, 9, 33]. Collaboration between synthetic groups and pharmacology laboratories with access to in vivo models would help move the better leads beyond the screening stage [4, 5].

8. ABBREVIATIONS

TZD-Thiazolidinedione, PPAR-γ-Peroxisome proliferator-activated receptor gamma, NASH-Non-alcoholic steatohepatitis, Cdk5-Cyclin-dependent kinase 5, PI3K-Phosphoinositide 3-kinase, RECORD-Rosiglitazone Evaluated for Cardiovascular Outcomes in oral agent

combination therapy, PROactive-PROspective pioglitAzone Clinical Trial In macroVascular Events, IRIS-Insulin Resistance Intervention after Stroke, ADOPT-A Diabetes Outcome Progression Trial

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Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

1. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ). J Biol Chem 1995;270:12953–6.
2. Yki-Järvinen H. Thiazolidinediones. N Engl J Med 2004;351:1106–18.
3. Cantello BCC, Cawthorne MA, Cottam GP, Duff PT, Haigh D, Hindley RM, *et al.* [[ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiaz olidinediones as potent antihyperglycemic agents. J Med Chem 1994;37:3977–85.
4. Naim MJ, Alam MJ, Ahmad S, Nawaz F, Shrivastava N, Sahu M, *et al.* Therapeutic journey of 2,4-thiazolidinediones as a versatile scaffold: an insight into structure activity relationship. Eur J Med Chem 2017;129:218–50.
5. Jain VS, Vora DK, Ramaa CS. Thiazolidine-2,4-diones: progress towards multifarious applications. Bioorg Med Chem 2013;21:1599–620.
6. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007;356:2457–71.
7. Lebovitz HE. Thiazolidinediones: the forgotten diabetes medications. Curr Diab Rep 2019;19:151.
8. Choi JH, Banks AS, Estall JL, Kajimura S, Boström P, Laznik D, *et al.* Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARγ by Cdk5. Nature 2010;466:451–6.
9. Tomašić T, Peterlin Mašič L. Rhodanine as a privileged scaffold in drug discovery. Curr Med Chem 2009;16:1596–629.
10. Mendgen T, Steuer C, Klein CD. Privileged scaffolds or promiscuous binders: a comparative study on rhodanines and related heterocycles in medicinal chemistry. J Med Chem 2012;55:743–53.
11. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. J Med Chem 2000;43:527–50.
12. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, *et al.* Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study. Lancet 2005;366:1279–89.
13. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, *et al.* Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321–31.
14. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, *et al.* Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–43.
15. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, *et al.* The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328–57.
16. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, *et al.* Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus. Ann Intern Med 2016;165:305–15.
17. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, *et al.* A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–307.
18. Rakowitz D, Maccari R, Ottanà R, Vigorita MG. In vitro aldose reductase inhibitory activity of 5-benzyl-2,4-thiazolidinediones. Bioorg Med Chem 2006;14:567–74.
19. Bruno G, Costantino L, Curinga C, Maccari R, Monforte F, Nicolò F, *et al.* Synthesis and aldose reductase inhibitory activity of 5-arylidene-2,4-thiazolidinediones. Bioorg Med Chem 2002;10:1077–84.
20. Patil V, Tilekar K, Mehendale-Munj S, Mohan R, Ramaa CS. Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2,4-thiazolidinedione

derivatives. Eur J Med Chem 2010;45:4539–44.

21. Ottanà R, Maccari R, Barreca ML, Bruno G, Rotondo A, Rossi A, *et al.* 5-Arylidene-2-imino-4-thiazolidinones: design and synthesis of novel anti-inflammatory agents. Bioorg Med Chem 2005;13:4243–52.
22. Vicini P, Geronikaki A, Anastasia K, Incerti M, Zani F. Synthesis and antimicrobial activity of novel 2-thiazolylimino-5-aryliden e-4-thiazolidinones. Bioorg Med Chem 2006;14:3859–64.
23. Jones G. The Knoevenagel condensation. Org React 1967;15:204–599.
24. Lidström P, Tierney J, Wathey B, Westman J. Microwave assisted organic synthesis: a review. Tetrahedron 2001;57:9225–83.
25. Berger J, Moller DE. The mechanisms of action of PPARs. Annu Rev Med 2002;53:409–35.
26. Henke BR, Blanchard SG, Brackeen MF, Brown KK, Cobb JE, Collins JL, *et al.* N-(2-Benzoylphenyl)-L-tyrosine PPARγ agonists. 1. Discovery of a novel series of potent antihyperglycemic and antihyperlipidemic agents. J Med Chem 1998;41:5020–36.
27. Yamauchi T, Kamon J, Waki H, Murakami K, Motojima K, Komeda K, *et al.* The mechanisms by which both heterozygous peroxisome proliferator-activated receptor γ (PPARγ) deficiency and PPARγ agonist improve insulin resistance. J Biol Chem 2001;276:41245–54.
28. Miyazaki Y, Mahankali A, Matsuda M, Mahankali S, Hardies J, Cusi K, *et al.* Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002;87:2784–91.
29. Brunmair B, Staniek K, Gras F, Scharf N, Althaym A, Clara R, *et al.* Thiazolidinediones, like metformin, inhibit respiratory complex I. Diabetes 2004;53:1052–9.
30. Colca JR, McDonald WG, Waldon DJ, Leone JW, Lull JM, Bannow CA, *et al.* Identification of a novel mitochondrial protein (mitoNEET) cross-linked specifically by a thiazolidinedione photoprobe. Am J Physiol Endocrinol Metab 2004;286:E252–60.
31. Banks AS, McAllister FE, Camporez JPG, Zushin PJH, Jurczak MJ, Laznik-Bogoslavski D, *et al.* An ERK/Cdk5 axis controls the diabetogenic actions of PPARγ. Nature 2015;517:391–5.
32. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, *et al.* Thiazolidinedione use, fluid retention, and congestive heart failure. Circulation 2003;108:2941–8.
33. Erdmann E, Charbonnel B, Wilcox RG, Skene AM, Massi-Benedetti M, Yates J, *et al.* Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). Diabetes Care 2007;30:2773–8.
34. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, *et al.* Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 2009;373:2125–35.
35. Hiatt WR, Kaul S, Smith RJ. The cardiovascular safety of diabetes drugs, insights from the rosiglitazone experience. N Engl J Med 2013;369:1285–7.
36. Schwartz AV, Sellmeyer DE, Vittinghoff E, Palermo L, Lecka-Czernik B, Feingold KR, *et al.* Thiazolidinedione use and bone loss in older diabetic adults. J Clin Endocrinol Metab 2006;91:3349–54.
37. Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP, *et al.* Risk of bladder cancer among diabetic patients treated with pioglitazone. Diabetes Care 2011;34:916–22.