RESEARCH PAPER

Design, Synthesis, Molecular Docking and QSAR-Driven Optimization of Thiazolidinedione Scaffolds as Emerging Multi-Target Anticancer Agents:

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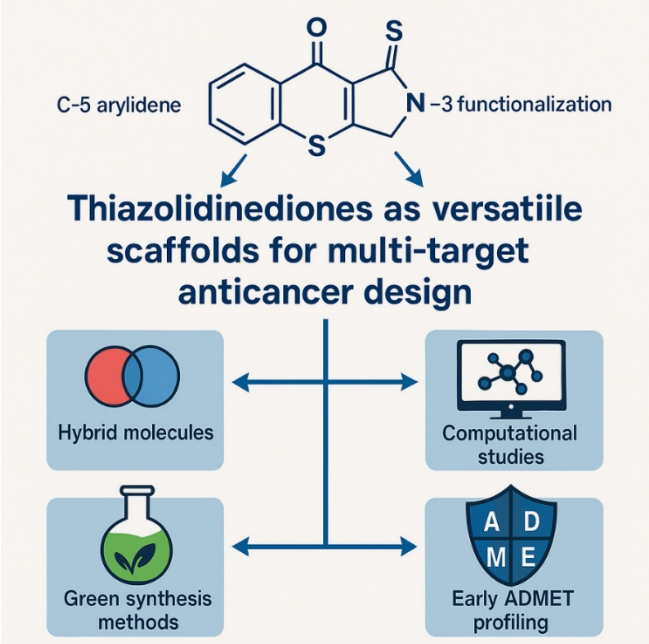
Graphical Abstract



Abstract

Thiazolidinediones (TZDs), originally introduced as antidiabetic agents, have over time emerged as one of the most adaptable and pharmacologically rich heterocyclic cores for anticancer drug discovery. Beyond their classical role as PPARγ agonists, the TZD ring offers a compact yet highly tunable framework: the C-5 and N-3 positions can be modified with relative synthetic ease, and this flexibility has been exploited to generate compounds that interact with a wide range of cancer-relevant targets, including VEGFR-2, EGFR, histone deacetylases (HDACs), PIM-1 kinase, glucose transporters (GLUTs) and PPARγ itself. In this review, we survey and critically discuss recent developments in the medicinal chemistry of TZD derivatives, with particular emphasis on structure–activity relationships, hybrid pharmacophore design, and the use of modern, greener synthetic approaches such as PEG-300-based media, microwave irradiation and ultrasound-assisted protocols, alongside other late-stage diversification strategies. Computational methods now play a central role in these efforts. Docking studies have helped to rationalise binding at kinase and epigenetic targets, clarifying, for example, how TZD carbonyl groups engage hinge residues and how sulfonyl or urea linkers orient within the active site and hydrophobic pockets. QSAR and 3D-QSAR models have further contributed by suggesting which steric and electronic features are most favourable for activity. Nevertheless, many published models still suffer from familiar weaknesses, notably small and chemically narrow datasets, limited external validation and an overreliance on rigid-receptor docking protocols, all of which call for more stringent and transparent computational workflows. On the biological side, numerous TZD-based molecules show promising in vitro cytotoxicity

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Keywords: Thiazolidinediones (TZDs), Anticancer drug discovery, PPARγ agonists, Structure–activity relationship (SAR), Hybrid pharmacophores, VEGFR-2/EGFR/HDAC targeting, Green synthetic methods, Molecular docking, QSAR and 3D-QSAR, In vitro cytotoxicity

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1. Introduction

Cancer continues to rank among the most significant global health challenges, contributing heavily to both morbidity and mortality. Even though the last decade has seen remarkable growth in targeted therapeutics, immuno-oncology, and precision-medicine approaches, several limitations still restrict their long-term success. Issues such as dose-dependent systemic toxicity, rapid emergence of drug resistance, inadequate tumor selectivity, and the inherent complexity and redundancy of oncogenic signaling pathways frequently compromise treatment outcomes (Debnath, Paul, & Pahari, 2025; Latambale & Juvale, 2025). Consequently, there is a sustained need for new chemical frameworks capable of engaging multiple cancer-associated targets while retaining acceptable pharmacokinetic and toxicity profiles. In this regard, heterocyclic scaffolds hold a particularly strong position. Many approved anticancer drugs incorporate heterocycles because these structures allow fine control over electronic properties, molecular shape, lipophilicity, and hydrogen-bonding behavior, all of which are crucial in modern drug design.

Within this category, thiazolidine-2,4-diones (TZDs) have attracted increasing attention. Initially, TZDs became widely known through antidiabetic "glitazone" drugs such as pioglitazone and rosiglitazone, which act mainly as agonists of the nuclear receptor PPARγ, improving insulin sensitivity and glycemic regulation (Nazreen et al., 2014; Salahuddin et al., 2025). Over the past two decades, however, preclinical studies have consistently shown that TZDs possess a much broader pharmacological portfolio, including anticancer, antioxidant, and anti-inflammatory activities. Importantly, several of these effects occur independently of PPARγ modulation (Blanquicett, Roman, & Hart, 2008; Malik & Singh, 2025). This broader activity profile opened the door to repositioning TZDs as versatile scaffolds for oncology-focused medicinal chemistry.

The rationale for their use as anticancer agents is supported by multiple independent findings. Numerous TZD derivatives influence fundamental hallmarks of cancer biology, including uncontrolled proliferation, resistance to apoptosis, angiogenic signaling, cell-cycle progression, and metabolic shifts favoring tumor growth. Mechanistic studies have shown that different TZD analogues can engage a range of molecular targets, including kinases such as VEGFR-2, EGFR, and PIM-1; epigenetic enzymes such as HDACs; glucose transporters like GLUT1 and GLUT4; carbonic anhydrases IX and XII; and proteins regulating apoptosis, notably the Bcl-2 family (Latambale & Juvale, 2025; Malik & Singh, 2025; Debnath et al., 2025). Hybrid molecules containing TZDs linked to other pharmacophores have also been designed to simultaneously modulate two or more of these targets, demonstrating improved activity profiles and, in some cases, better selectivity toward malignant cells (Tilekar et al., 2021; Abdelgawad et al., 2022). These observations align with biological screening data showing that several TZD derivatives exhibit nanomolar to low-micromolar in vitro potency, and a limited number even demonstrate meaningful tumor inhibition in animal models (Abdelgawad et al., 2022; Corigliano et al., 2018).

From a structural viewpoint, the TZD ring is a compact five-membered heterocycle containing sulfur at position 1 and nitrogen at position 3, flanked by carbonyl groups at the 2- and 4-positions. The electron withdrawal from the two carbonyls renders the N-3 proton more acidic and enhances the nucleophilicity of the C-5 methylene group. These features give rise to two practical "exit vectors" for derivatization: N-3 functionalization and C-5 substitution through Knoevenagel condensation with aldehydes. This dual functionalization potential allows medicinal chemists to introduce steric or electronic variation and to fine-tune hydrogen-bonding, lipophilicity, or conformational behavior (Kumar et al., 2012; Zhang et al., 2012; Lončarić et al., 2022). The consistent observation that electron-withdrawing arylidene substituents on C-5 enhance antiproliferative potency—especially toward VEGFR-2 and HDACs—has further reinforced the importance of targeted C-5 modification (Abdelgawad et al., 2022; Malik & Singh, 2025).

In parallel with developments in medicinal chemistry, synthetic strategies for TZDs have also evolved. Although conventional condensation reactions remain common, newer methods based on principles of green chemistry—such as PEG-300 as a reaction medium, ionic liquids, ultrasound assistance, and microwave irradiation—have gained traction due to their reduced reaction times, better yields, and lower environmental impact (Mane, 2008; Sandhu et al., 2013; Yang et al., 2011; Drawanz et al., 2014). These advances are especially useful for programs that depend on rapid compound generation and iterative design–make–test–analyze cycles.

Computational techniques now form an integral part of TZD-based drug discovery efforts. Molecular docking has been extensively used to predict binding modes, interpret SAR, and prioritize analogues for synthesis. Docking studies on VEGFR-2 provide a clear example, where predicted pose patterns and key hydrogen-bonding interactions have shown good correlation with measured enzyme inhibition (Abdelgawad et al., 2022; Ikram et al., 2019). Similarly, QSAR and 3D-QSAR

models have been developed for various TZD series, often reporting strong statistical fits (Asati, Bharti, & Budhwani, 2017; Asati, Bharti, & Mahapatra, 2016). Nonetheless, many published computational models face familiar challenges: small datasets, insufficient chemical diversity, limited external validation, and a tendency to rely heavily on rigid-receptor assumptions. These shortcomings restrict the true predictive value of such models in prospective design.

Despite promising in vitro data and substantial progress in synthetic and computational methodologies, a significant divide remains between discovery-phase research and translational development. As multiple recent reviews emphasize (Malik & Singh, 2025; Latambale & Juvale, 2025; Debnath et al., 2025), most TZD derivatives have never advanced beyond cell-line studies. Only a handful have been evaluated in animal models, and none have progressed to clinical trials for oncology indications. This translational gap is further exacerbated by known liabilities of the glitazone class, including risks of hepatotoxicity, cardiotoxicity, fluid retention, and in some cases carcinogenicity (Blanquicett et al., 2008; Toth et al., 2013). These concerns underline the need for comprehensive ADMET assessment early in development.

In view of these opportunities and challenges, there is a clear need for an updated, integrative review that examines TZDs from both chemical and biological angles. Existing reviews tend to focus on their antidiabetic or anti-inflammatory activities, or provide broad summaries of anticancer work without dissecting synthetic strategies, SAR logic, computational methods, and translational hurdles in detail (Nazreen et al., 2014; Latambale & Juvale, 2025; Debnath et al., 2025; Malik & Singh, 2025). The present review attempts to fill this gap by offering a medicinal-chemistry-centered synthesis of the field. Specifically, the goals are to:

1. outline key chemical and pharmacological attributes of the TZD scaffold;
2. analyze SAR trends, including C-5 and N-3 diversification and hybridization strategies;
3. review classical and green synthetic approaches enabling rapid scaffold expansion;
4. summarize anticancer biological data, with emphasis on integrating in vitro and in vivo findings;
5. evaluate docking and QSAR/3D-QSAR studies, identifying strengths and methodological weaknesses;
6. discuss mechanistic insights related to apoptosis, angiogenesis, metabolic regulation and cell-cycle control; and
7. highlight future priorities, including early ADMET screening, rational safety-by-design strategies, and the integration of AI/ML tools for compound generation and optimization.

Through this combined analysis, the review aims to establish a coherent framework to support the development of next-generation TZD-based anticancer agents that are not only potent but also synthetically viable, mechanistically rational, and translationally realistic.

2. Chemistry and Pharmacology of the Thiazolidinedione Core

The thiazolidine-2,4-dione ring system is structurally simple yet chemically rich. The nitrogen at position 3 is flanked by two carbonyl groups, which enhance the acidity of the N–H proton and allow the formation of salts and strong hydrogen bonds in protein environments. The C-5 methylene is activated by conjugation with the carbonyls and the ring sulfur, enabling efficient Knoevenagel condensations with aldehydes to generate exocyclic C=C bonds that expand the π-system and optimize interactions with hydrophobic regions of targets such as kinase ATP-binding sites (Malik & Singh, 2025; Paul et al., 2022).

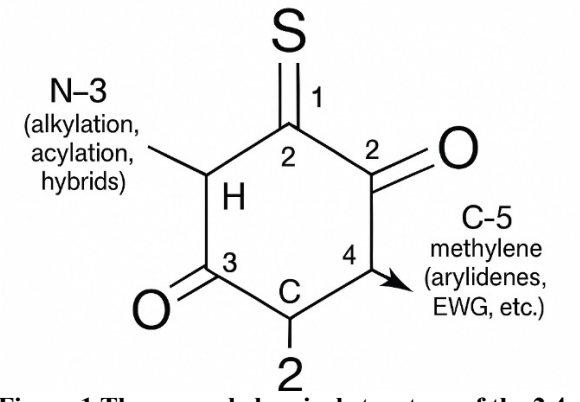

Figure 1 The general chemical structure of the 2,4-thiazolidinedione (TZD) scaffold.

Historically, the pharmacology of TZDs has been dominated by their role as PPARγ agonists. Pioglitazone and rosiglitazone improve insulin sensitivity by modulating gene expression programs related to glucose transport, adipogenesis, and lipid metabolism (Nazreen et al., 2014). However, PPARγ activation is a double-edged sword: while it can exert antiproliferative and pro-differentiation effects in certain cancer cell types, it is also associated with adverse metabolic events, including weight gain and fluid retention, that limit chronic use. This has led to the pursuit of TZD derivatives that either exhibit PPARγ-independent anticancer mechanisms or carefully balanced dual profiles.

Over the past decade, multiple studies have demonstrated that TZDs can act as potent inhibitors of HDACs, VEGFR-2, EGFR, PIM-1, and other kinases, often in a PPARγ-independent manner (Blanquicett et al., 2008; Abdelgawad et al., 2022; Asati et al., 2017; Latambale & Juvale, 2025). In colorectal and breast cancer models, TZD derivatives have been shown to induce apoptosis, promote cell cycle arrest, and inhibit angiogenesis, frequently correlating with downregulation of PI3K/Akt and MAPK signaling pathways (Ikram et al., 2019; Yoon et al., 2020). These pleiotropic effects support the concept of TZDs as multi-target anticancer agents with the capacity to blunt multiple oncogenic pathways simultaneously.

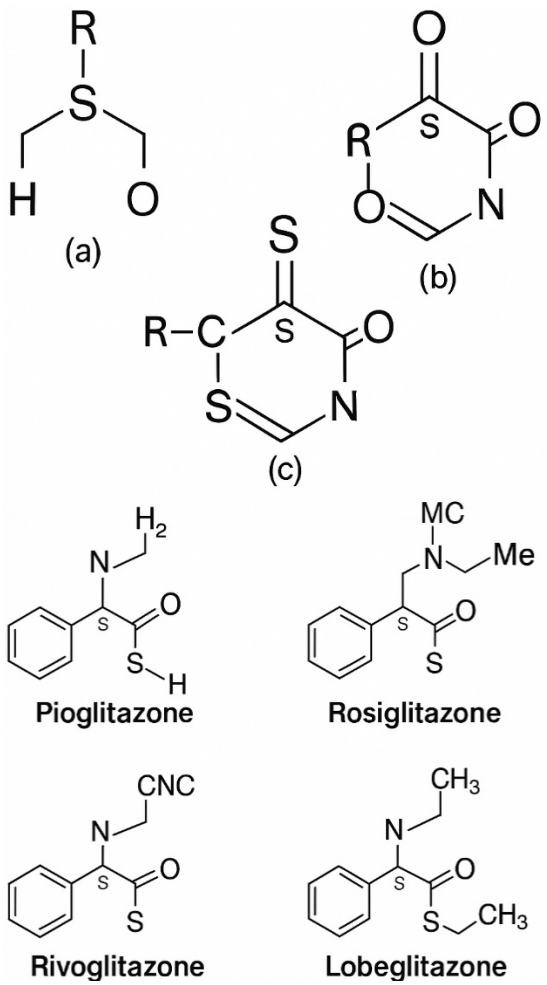

Figure 2. Conceptual representation of the TZD scaffold as a "privileged structure

3. Rational Design Strategies: Hybridization, SAR and Multi-Target Profiles

In recent years, the design of TZD-based anticancer agents has shifted strongly towards multi-target and hybrid strategies, rather than simple single-target optimization. A common approach is to fuse the TZD core with a second pharmacophore so that a single molecule can modulate more than one cancer-relevant pathway. For instance, naphthalene–TZD hybrids have been developed as dual HDAC/PPARγ modulators, where judicious variation of aryl substituents is used to balance activity between the epigenetic and metabolic targets (Tilekar et al., 2021; Debnath et al., 2025). Indole–TZD conjugates provide another illustration; these compounds can act as HDAC inhibitors while also interacting with DNA, and have been shown to trigger pronounced apoptotic responses in breast cancer models (Corigliano et al., 2018). Hybrids incorporating benzothiazole, quinoline or chromone motifs similarly exploit the intrinsic tumour selectivity and DNA-binding or intercalating features of these scaffolds, with the TZD ring contributing additional engagement of kinase or epigenetic targets (Taghour et al., 2022; Kamboj et al., 2024).

Several structure–activity relationship features recur across these hybrid series. The C-5 benzylidene fragment is frequently essential for maintaining high potency; the exocyclic double bond and attached aromatic ring enhance hydrophobic contacts and can participate in π–π stacking within ATP-binding regions of kinases or aromatic pockets in HDACs (Malik & Singh, 2025; Abdelgawad et al., 2022). Electron-withdrawing groups such as chloro, fluoro or nitro substituents, particularly at ortho or para positions on the C-5 arylidene ring, often lead to improved inhibition of VEGFR-2 and related kinases, an effect that is commonly attributed to a better complementarity with hydrophobic cavities and favourable modulation of dipole and acidity (Abdelgawad et al., 2022; Debnath et al., 2025). The linker region between the TZD core and the second pharmacophore is also critical: sulfonylthiourea linkers, for example, have been shown to promote VEGFR-2 binding through multiple hydrogen bonds to hinge and catalytic residues, whereas amide or ether linkers primarily influence overall flexibility and aqueous solubility (Abdelgawad et al., 2022; Ikram et al., 2019). Conversely, excessive bulk or poorly positioned substituents can create steric clashes or misalign key interaction motifs, leading to a loss of activity even when standard physicochemical parameters appear acceptable.

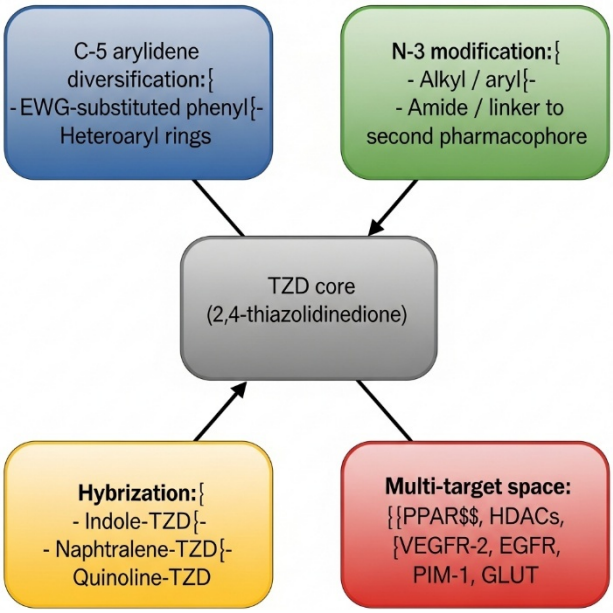

Figure 3. Schematic depiction of core design strategies for TZD-based anticancer agents

4. Synthetic Toolbox for TZD-Based Anticancer Libraries

The TZD scaffold is relatively easy to access synthetically, and a variety of established methods are available for both its construction and subsequent functionalisation. For modification at the C-5 position, the Knoevenagel condensation between 2,4-thiazolidinedione and aromatic or heteroaromatic aldehydes remains the workhorse reaction. Classical procedures typically use a basic catalyst such as piperidine in protic or aprotic media and afford 5-arylidene-2,4-TZD derivatives in moderate to excellent yields (Mane, 2008; Yang et al., 2011). In line with broader trends in synthetic chemistry, there has been a noticeable move towards greener and more

operationally simple variants of this transformation. Polyethylene glycol-300 (PEG-300), for example, has been employed as a recyclable, non-volatile reaction medium, with the added benefits of straightforward work-up and consistently high yields (Mane, 2008). Other groups have explored ionic-liquid-based systems, such as hydroxylammonium- and imidazolium-derived salts, which enable solvent-free or aqueous condensations with recyclable catalysts and a more favourable environmental footprint (Zhang et al., 2014; Lončarić et al., 2022). Ultrasound and microwave irradiation have also been applied successfully, typically reducing reaction times from hours to minutes and in many cases improving yields through enhanced mass transfer and localized heating (Sandhu et al., 2013; Drawanz et al., 2014; JoAC, 2020).

Functionalisation at the N-3 position is most commonly achieved by straightforward alkylation or acylation using suitable alkyl halides or acid chlorides under basic conditions. More complex N-3 elaborations, particularly those aimed at building hybrid molecules or large pharmacophore conjugates, often rely on stepwise amide coupling, click-type cycloadditions, or one-pot multi-component protocols (Taghour et al., 2022; Kamboj et al., 2024; Gharge et al., 2024). Although these N-3 transformations can be more capricious, sometimes giving lower yields or displaying sensitivity to steric and electronic factors, they are central to fine-tuning lipophilicity, solubility, and target engagement by introducing secondary binding motifs or linkers that connect the TZD core to additional pharmacophores.

Table 1. Representative synthetic methodologies for 5-arylidene-2,4-thiazolidinedione derivatives and key advantages.

Method / Catalyst / Medium	Typical conditions	Yield range (%)	Key advantages	Limitations
Classical base-catalyzed Knoevenagel (piperidine, EtOH or DMF) (Mane, 2008)	Reflux, 2–8 h	70–90	Simple, robust, broad aldehyde scope	Organic solvents, longer reaction times
PEG-300 mediated condensation (Mane, 2008)	Moderate temperature, PEG-300	80–95	Green solvent, easy work-up	Viscous medium, scale-up considerations
Ionic liquid catalysis (Zhang et al., 2014)	[bmim]H_2PO_4, 70 °C, solvent-free	80–95	Recyclable catalyst, high efficiency	Cost and handling of ionic liquids
Ultrasound-assisted (Drawanz et al., 2014)	Aqueous / mixed media, sonication	85–95	Short times, mild conditions	Equipment dependence
Microwave-assisted TiO_2 (JoAC, 2020)	Solvent-free, 3–5 min	>90	Very fast, eco-friendly, high yield	Hot-spot control, microwave reactor needed
Ionic liquid / aqueous hybrid protocols (Lončarić et al., 2022)	Aqueous IL, mild temperature	80–92	Green, recyclable, scalable potential	Optimisation of IL composition required

5. Biological Activity Landscape: In Vitro and In Vivo Evidence

A broad spectrum of TZD-based derivatives has been tested across multiple human and murine cancer cell lines, including breast (MCF-7, 4T1), colon (HCT116, HT-29), liver (HepG2), lung (A549), and hematological malignancies such as K562 and CEM, among others. In many of these studies, the most active compounds display IC_{50} values in the nanomolar to low-micromolar range, frequently matching or even surpassing the performance of established reference drugs like sorafenib, erlotinib, and the HDAC inhibitor SAHA (Abdelgawad et al., 2022; Debnath et al., 2025; Taghour et al., 2022; Kamboj et al., 2024). In a recent survey of work published between 2020 and 2024, Malik and Singh (2025) highlighted several such high-potency series, including VEGFR-2-directed inhibitors that also exhibit pronounced antiangiogenic activity, as well as HDAC-focused hybrids capable of modulating epigenetic markers.

In contrast to the extensive in vitro dataset, in vivo evaluation remains comparatively limited. A particularly illustrative case is an ergosterol peroxide–TZD hybrid that achieved over 80% inhibition of tumour growth in a syngeneic 4T1 mouse mammary carcinoma model at a dose of 30 mg/kg, with no severe toxicity reported at the tested regimen (Malik & Singh, 2025). Other reports describe moderate tumour growth suppression in xenograft models, most often in breast or colon cancer settings, but detailed pharmacokinetic parameters and comprehensive toxicity assessments are seldom provided (Latambale & Juvale, 2025; Debnath et al., 2025). To clarify the landscape and avoid overgeneralisation from isolated examples, a selection of representative studies is summarised in tabular form in the following section.

Table 2. Selected literature on TZD-based anticancer agents: materials, methods, and main findings.

Author (Year)	Materials / Scaffold Focus	Methodology (core aspects)	Outcomes (potency, targets)	Key findings / conclusions
Blanquicett et al. (2008)	Glitazone TZDs (pioglitazone, troglitazone)	Review of preclinical/clinical data on TZDs in cancer	PPARγ-mediated antiproliferative effects in multiple cancers	TZDs are promising but limited by metabolic side effects
Corigliano et al. (2018)	Indole–TZD conjugates	Synthesis, cytotoxicity in MCF-7, docking, mechanistic studies	Low-micromolar cytotoxicity; apoptosis and HDAC-related mechanisms	Indole–TZD hybrids are potent, multi-mechanistic anticancer leads
Abdelgawad et al. (2022)	Sulfonylthiourea-linked TZDs targeting VEGFR-2	Synthesis, VEGFR-2 enzymatic assays, cell assays, docking (PDB 4ASD)	Potent VEGFR-2 inhibition ($IC_{50} \approx 0.08$ μM); strong cellular activity	Docking correlates well with SAR; sulfonylthiourea linkers crucial
Ikram et al. (2019)	Kinase-inhibiting TZD hybrids	In vitro kinase profiling, docking, selectivity assessments	Multi-kinase inhibition and antiproliferative activity	TZD hybrids can be tailored as multi-kinase panels
Latambale & Juvale (2025)	Broad TZD anticancer review	Comprehensive literature analysis	Summarizes multi-target roles (PPARγ, HDACs, kinases, CAIX)	TZDs emerge as multi-functional anticancer chemotypes
Debnath et al. (2025)	TZD derivatives: synthetic strategies & SAR	Review of chemistry, SAR, biological data	Highlights potent series against VEGFR-2, EGFR, HDACs	Emphasizes C-5 arylidene and hybridization strategies
Taghour et al. (2022)	Heterocyclic TZD hybrids	Synthesis, antiproliferative assays, docking	Sub-micromolar IC_{50} values vs MCF-7; kinase and HDAC interactions	Substituent pattern and linker architecture strongly affect potency
Kamboj et al. (2024)	Imidazothiazole–TZD hybrids	Synthesis, anticancer and anti-inflammatory evaluation, modeling	Micromolar cytotoxicity; dual anticancer/anti-inflammatory profile	Supports hybridization for polypharmacology
Asati et al. (2017)	TZDs as PIM-1 kinase inhibitors	3D-QSAR, docking, virtual screening, model validation	QSAR model $R^2 \approx 0.97$; identifies key steric/electrostatic features	Good internal fit, but limited external validation
Malik & Singh (2025)	2,4-TZDs in 2020–2024	Medicinal chemistry review, summary of in vitro/in vivo data	Several nanomolar series; few in vivo studies	Identifies "in vivo data desert" as key translational bottleneck
Lončarić et al. (2022)	Green TZD synthesis and bioactivity	Ionic liquid-mediated synthesis, preliminary bioassays	Efficient green routes; moderate bioactivity reported	Demonstrates feasibility of green synthetic pipelines
Salahuddin et al. (2025)	Glitazone derivatives across indications	Data mapping (antidiabetic, anticancer, antioxidant, antimicrobial)	Identifies multiple anticancer-active glitazone derivatives	Supports TZDs as privileged scaffolds

6. Molecular Docking: Insights, Strengths, and Pitfalls

Molecular docking has been widely employed to interpret the structure–activity relationships of TZD-based inhibitors and to assist in the design of new analogues. Among the various targets explored, VEGFR-2 remains the most thoroughly characterized example. Docking studies performed using high-resolution crystal structures such as PDB 4ASD consistently show that the most active TZD derivatives adopt binding orientations similar to sorafenib, engaging both the hinge region and adjacent hydrophobic pockets (Abdelgawad et al., 2022). A recurring feature in these models is the involvement of the C-2 carbonyl of the TZD ring, which typically forms a crucial hydrogen bond with hinge residues like Cys919. Linker groups, particularly sulfone and sulfonylthiourea moieties, often establish additional interactions with residues including Asp1046 and Lys868, while the arylidene fragment occupies hydrophobic regions lined by Leu840, Val848 and Phe918, anchoring the ligand firmly within the active site.

In several cases, docking results show a reasonable qualitative correlation with biological potency, especially within chemically coherent compound series.

Abdelgawad and co-workers (2022), for instance, observed that compounds 6c and 7c, which were the most potent VEGFR-2 inhibitors in their series, also had the highest docking affinity and the largest number of stabilizing noncovalent interactions. Comparable trends have been noted for PIM-1 kinase, where steric and electrostatic contour maps from CoMFA/CoMSIA models align well with binding orientations predicted from docking, offering insight into substituent patterns that enhance ATP-site occupancy (Asati et al., 2017; Xia et al., 2009).

Despite these strengths, excessive confidence in docking poses or raw scores can be misleading. Most docking protocols still treat the protein largely as a rigid structure, an approach that struggles with targets requiring notable induced-fit adjustments or in cases where water networks play a central role in ligand stabilization. Additionally, commonly used scoring functions, although robust on average, may fail to capture the delicate enthalpic and entropic balance, solvent reorganization, or ligand strain penalties specific to the TZD chemotype. A further limitation is the inconsistent methodological rigor across published TZD docking studies—validation steps such as redocking co-crystallized inhibitors, screening against decoy sets, or correlating predicted affinities with experimental IC_{50} values are often absent (Latambale & Juvale, 2025; Debnath et al., 2025). This reduces confidence in the reported predictive power of the docking models. A balanced perspective is therefore essential. Docking is most reliable when used as a hypothesis-generating tool, helping to identify plausible binding modes, rationalize SAR trends, and highlight interactions worth exploring synthetically. When combined with complementary approaches such as molecular dynamics, MM-GBSA, or well-validated homology models, and supported by experimental data, it becomes a powerful component of an integrated medicinal chemistry workflow for guiding next-generation TZD analogue design.

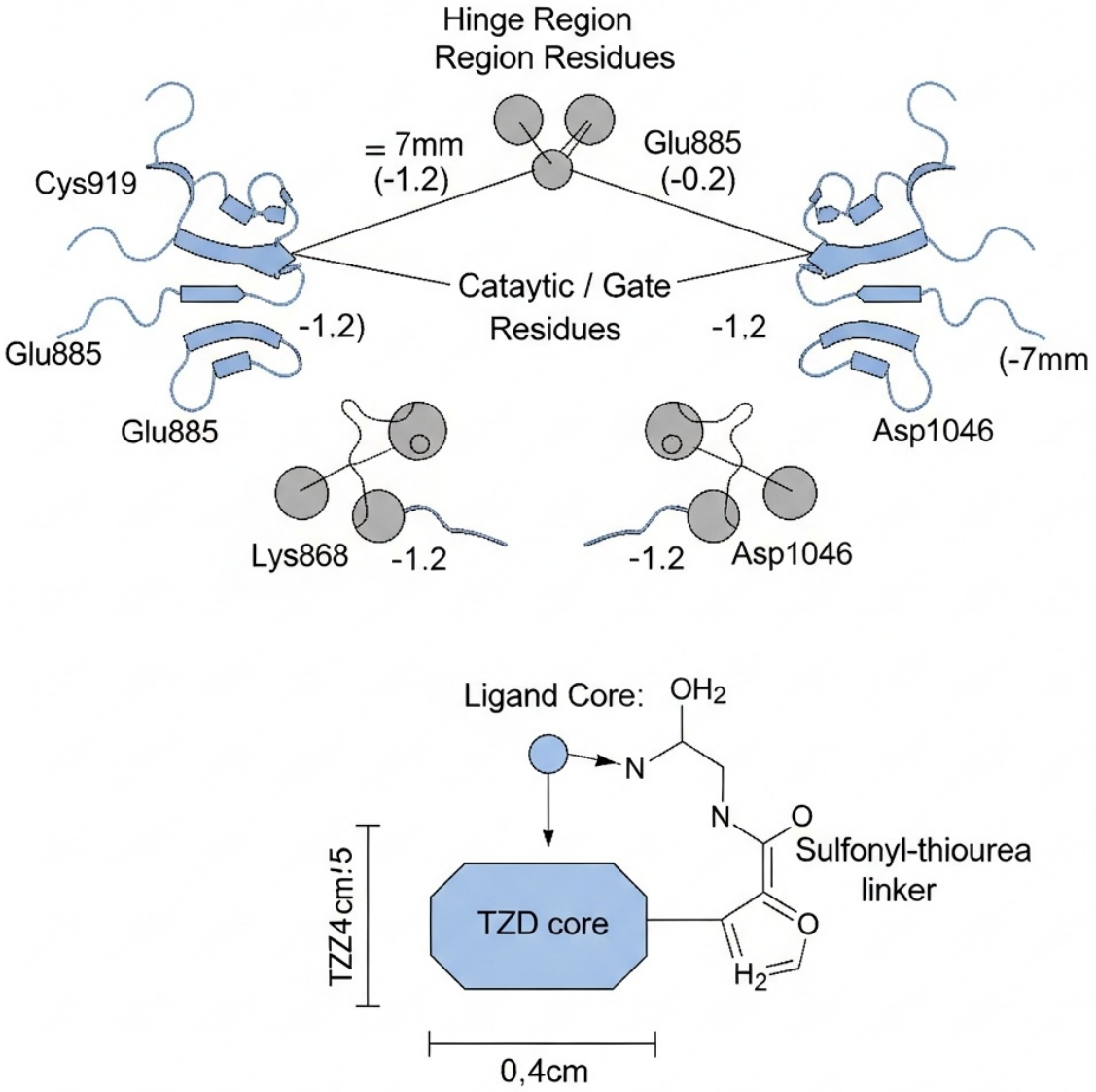

Figure 4. Representative docking pose of a potent sulfonylthiourea–TZD derivative in the VEGFR-2 active site

Table 3. Overview of docking-based studies on TZD anticancer agents and their correlation with biological data.

Study / Target	Docking platform / PDB code	Series / Scaffold focus	Correlation with bioactivity	Key strengths	Main limitations
Abdelgawad et al. (2022)	Glide / AutoDock; PDB 4ASD	Sulfonylthiourea–TZDs	Good qualitative correlation with IC_{50}	Multiple H-bonds, clear SAR linkage	Limited receptor flexibility analysis
Asati et al. (2017)	JMol Struct (QSAR + docking)	PIM-1-directed TZDs	Docking supports 3D-QSAR fields	Combined CoMFA/CoMSIA + docking	Dataset size modest; external test limited
Corigliano et al. (2018)	Glide / MOE	Indole–TZD hybrids	Docking rationalizes HDAC inhibition	Explains orientation in catalytic tunnel	Lacks systematic validation metrics
Ikram et al. (2019)	AutoDock / GOLD	Kinase-inhibiting TZD hybrids	Partial correlation with kinase profile	Good coverage of multiple kinases	Simplified solvent and dynamics treatment

7. QSAR and 3D-QSAR: Predictive Tools or Overfitting Traps?

Quantitative structure–activity relationship (QSAR) analysis has been applied to several TZD series in an effort to relate structural features to biological activity and to guide rational optimization. One of the most detailed examples comes from work on PIM-1 kinase inhibitors, where Asati and co-workers (2017) constructed 3D-QSAR models using Partial Least Squares regression in combination with CoMFA and CoMSIA fields. Their best-performing models exhibited strong internal-fit statistics (R^2 values close to 0.97) and acceptable cross-validated Q^2 values. Interpretation of the steric and electrostatic contour maps indicated that regions near the TZD nucleus and adjacent linker segments favor bulky, hydrophobic substituents, whereas the introduction of highly polar groups in certain spatial locations tended to reduce activity.

QSAR efforts have also been extended to TZD derivatives targeting 15-PGDH and other cancer-associated enzymes (Asati et al., 2016; Jain et al., 2025). These studies generally rely on a combination of 2D descriptors—logP, topological parameters, hydrogen-bonding counts, and polar surface area—paired with modeling techniques such as Multiple Linear Regression, Partial Least Squares, Random Forests, and Support Vector Machines. While many reports highlight strong statistical outcomes, including high R^2 and Q^2 values, external validation using independent datasets is often missing, and in several cases, basic diagnostic controls such as Y-scrambling are not performed.

This recurring pattern contributes to what is effectively a credibility problem in QSAR modeling within the TZD literature. Models developed on small or chemically uniform datasets may simply memorize (rather than generalize) structural information, producing overoptimistic statistics that do not hold up when applied prospectively. To strengthen the reliability of QSAR models for TZD-based anticancer agents, several best practices should be consistently adopted:

(i) use of sufficiently large and structurally diverse datasets; (ii) clear separation between training, validation, and test sets; (iii) reporting of multiple internal metrics such as Q^2, RMSE, and MAE; (iv) demonstration of external predictivity via R^2_pred on previously unseen compounds; and (v) inclusion of mechanistic or chemically interpretable descriptors to avoid purely correlative models. When these principles are followed, QSAR can serve as a powerful tool to complement synthetic and biological studies, offering insight into substituent effects and guiding the design of next-generation TZD analogues.

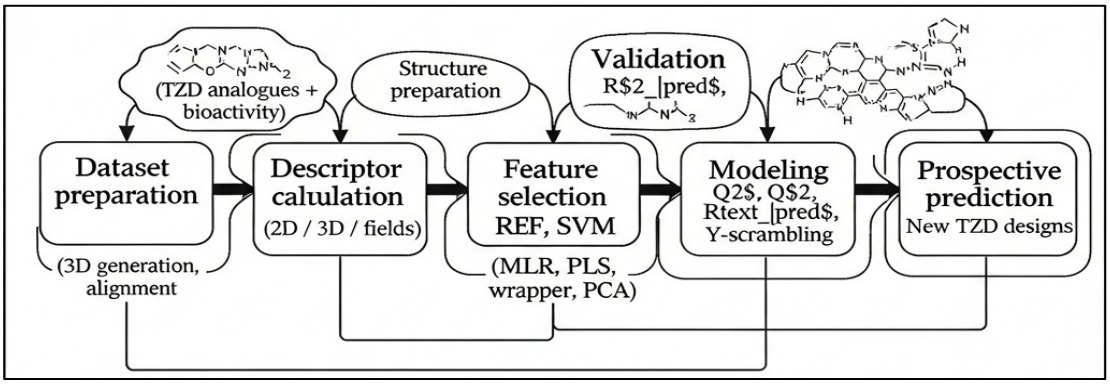

Figure 5. Generalized workflow for QSAR/3D-QSAR modeling of TZD derivatives

Table 4. Typical QSAR practices in TZD-based anticancer studies and suggested improvements.

Aspect	Common practice in TZD QSAR papers	Issues identified	Recommended best practice
Dataset size	20–60 compounds	Risk of overfitting	Aim for ≥50–100 structurally diverse compounds
Validation	Internal only (R^2, Q^2)	Lack of external test sets	Include independent external test set, Y-scrambling
Descriptors	Mixed 2D/3D; often many variables	Risk of collinearity and noise	Use feature selection, domain knowledge-guided descriptors
Algorithms	MLR/PLS predominantly	Linear models may miss non-linear patterns	Consider non-linear methods (RF, SVM, NN) with care
Interpretability	Often limited to statistical metrics	Hard to translate into design hypotheses	Prioritise interpretable descriptors and maps (CoMFA/CoMSIA)

8. Mechanistic Convergence: Apoptosis, Cell Cycle and Signaling

At the mechanistic level, thiazolidinedione derivatives interfere with tumour growth through several interconnected pathways rather than a single dominant mode of action. A consistent observation across multiple studies is the induction of apoptosis, typically documented by activation of caspase-3, cleavage of PARP, dissipation of the mitochondrial membrane potential, and reduced expression of anti-apoptotic proteins such as Bcl-2 and Mcl-1 (Corigliano et al., 2018; Ikram et al., 2019; Yoon et al., 2020). TZDs also frequently impose cell-cycle blockade, with many reports describing arrest at either the G_1/S or G_2/M transition. This is often accompanied by downregulation of cyclins and cyclin-dependent kinases, including cyclin D1, CDK4/6 or cyclin B1, together with upregulation of CDK inhibitors such as p21 and p27 (Yoon et al., 2020; Lyles et al., 2009).

Beyond direct effects on tumour cells, several TZD series designed to target VEGFR-2 exhibit marked antiangiogenic activity, suppressing endothelial cell proliferation, migration and tube formation in vitro, and reducing VEGF-driven signalling and microvessel density in xenograft models (Abdelgawad et al., 2022; Latambale & Juvale, 2025). In parallel, TZDs with activity against histone deacetylases contribute to epigenetic reprogramming, as evidenced by increased histone acetylation, re-expression of silenced tumour suppressor genes and improved responsiveness to co-administered chemotherapeutics (Corigliano et al., 2018; Tilekar et al., 2021).

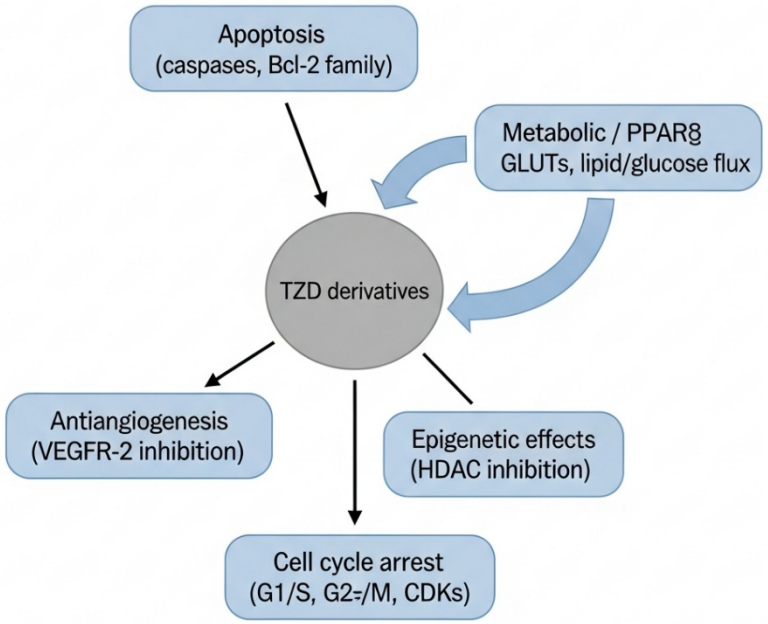

Figure 6. Mechanistic landscape of TZD-based anticancer agents: simultaneous modulation of apoptosis, cell cycle regulation, angiogenesis, epigenetic state (HDACs), and metabolic signaling (PPARγ and GLUTs), across both PPARγ-dependent and independent pathways.

A notable aspect of TZD pharmacology is that many anticancer responses occur independently of PPARγ activation. Although activation of PPARγ can promote differentiation and exert moderate anti-proliferative effects, numerous derivatives intentionally engineered to have weak or negligible PPARγ agonist activity still display potent cytotoxicity and robust effects on apoptosis, cell-cycle control, angiogenesis, and epigenetic regulation (Blanquicett et al., 2008; Malik & Singh, 2025; Debnath et al., 2025). These findings indicate that the TZD framework can be redirected toward alternative oncogenic pathways without relying on classical nuclear-receptor signaling. This has important design implications: by selectively minimizing PPARγ engagement, medicinal chemists can pursue "safety-by-design" TZDs that retain strong anticancer efficacy while reducing the metabolic liabilities typically associated with glitazone-type agonists, such as edema, fluid retention, and weight gain.

9. Integrated Results and Discussion: Comparative Analysis and Future Directions

Although the present review does not report new experimental data, integrating findings across multiple studies allows for a comparative evaluation of how different structural and design strategies have shaped the performance of TZD-based anticancer agents. From a medicinal chemistry standpoint, one of the strongest and most consistent observations is the benefit of C-5 arylidene substitution. Regardless of the target class, analogues bearing a C-5 exocyclic double bond linked to an aromatic ring generally show markedly enhanced anticancer activity. This effect is particularly pronounced when the aryl ring carries electron-withdrawing substituents, which often improve ligand orientation within kinase or HDAC binding pockets and strengthen hydrophobic or π–π contacts. When these substitutions are combined with carefully optimized linkers and additional pharmacophores, such as naphthalene, indole, imidazothiazole, quinoline, or chromone frameworks, the resulting hybrids typically outperform simpler TZD analogues across both enzymatic assays and cellular models (Debnath et al., 2025; Taghour et al., 2022; Kamboj et al., 2024). At the same time, several series demonstrate that the introduction of excessive steric bulk can disrupt ideal alignment within subpockets, providing a reminder that productive structure–activity optimization requires a nuanced balance of electronics, topology, and spatial orientation.

A comparison across independent investigations also highlights the advantages of hybrid and multi-target designs over single-target TZDs. Compounds that simultaneously modulate epigenetic regulators, metabolic pathways, and kinase signaling tend to show broader antiproliferative profiles, activity in multiple cancer cell lines, and—in some cases—greater resilience against resistance mechanisms. For example, naphthalene–TZD hybrids capable of inhibiting both HDAC4 and PPARγ match or exceed the potency of established HDAC inhibitors while offering additional biological leverage through metabolic pathway modulation (Tilekar et al., 2021; Malik & Singh, 2025). Likewise, indole–TZD hybrids, which combine DNA interaction with HDAC inhibition, exhibit robust multi-mechanistic anticancer behavior that is not achievable with monofunctional TZDs (Corigliano et al., 2018).

Synthetic feasibility remains an important dimension of comparative analysis. Green and accelerated methods, including PEG-300-mediated condensations, ionic-liquid catalysis, sonochemistry, and microwave irradiation, have proven highly valuable for medicinal chemistry workflows aimed at rapid DMTA (design–make–test–analyze) cycles. These methods typically deliver improved yields, shorter reaction times, and simpler purification steps, which are critical when exploring broad SAR landscapes. However, from the standpoint of eventual industrial or preclinical translation, more systematic assessments of catalyst recyclability, impurity formation, and process safety will be necessary.

Computational support has played a central role in many TZD optimization campaigns, though with mixed levels of rigor. Docking has been particularly effective for VEGFR-2 and PIM-1 inhibitors, where high-quality crystallographic structures exist and docked poses correspond well with experimentally validated SAR trends. Nevertheless, there remains an overabundance of docking-only studies, many of which lack essential validation steps or rely too heavily on scoring functions without corroborating experimental data. A similar pattern appears in QSAR studies, where models often report impressive statistical metrics but are built on small or structurally narrow datasets, limiting their reliability under prospective testing. These comparative insights are synthesized schematically in the table below.

Table 5. Comparative analysis of key strategic dimensions in TZD-based anticancer drug discovery.

Dimension	Classical single-target TZDs	Hybrid / multi-target TZDs	Current gaps / needs
Main targets	PPARγ, occasionally single kinase	HDAC + PPARγ, VEGFR-2 + EGFR, etc.	Deeper exploration of rational combinations
C-5 substitution	Simple aryl or benzylidene groups	Electron-withdrawing, bulky aryl, extended π-systems	Systematic mapping of substituent space
N-3 functionalization	Simple alkyl/aryl	Amide-linked pharmacophores, polar handles	Better control over solubility and PK

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Potency (in vitro)	Micromolar	Often sub-micromolar	Standardized assay conditions
In vivo data	Limited, mostly glitazones	Very rare (few hybrids tested)	Systematic PK/PD and toxicity programs
Synthetic methods	Classical solvents, longer times	Increasing use of green/microwave/ultrasound	Scale-up of green protocols
Docking & QSAR support	Mixed quality, often retrospective	Useful for pose rationalization and SAR maps	Prospective, AI/ML-integrated pipelines
Safety profile	PPARγ-related metabolic side effects	Largely unknown	Early ADMET profiling and safety-by-design

Looking ahead, several concrete priorities can be identified if TZD-based anticancer agents are to move closer to clinical application. A first and non-negotiable requirement is the early integration of ADMET profiling into discovery workflows. Basic properties such as solubility, permeability, and metabolic stability should be evaluated alongside cytochrome P450 inhibition, cardiotoxic liability (for example, hERG inhibition), and off-target receptor binding. These in vitro studies must be complemented by toxicity assays in non-malignant cell lines and carefully designed in vivo models. In light of the historical safety concerns associated with TZDs, particular attention should be given to signals of hepatotoxicity, cardiotoxicity and potential carcinogenicity (Blanquicett et al., 2008; Toth et al., 2013).

A second, closely related, priority is the deliberate pursuit of safety-by-design. Instead of treating PPARγ activity as an unavoidable property of TZD-based molecules, future design should actively modulate or dampen PPARγ agonism where appropriate. This can be approached by incorporating structural features that steer binding toward cancer-relevant kinases or epigenetic targets, or by creating balanced dual modulators that achieve their therapeutic effect at exposure levels below those associated with metabolic side effects.

Third, there is considerable scope to make more systematic use of artificial intelligence and machine learning. Generative models such as variational autoencoders, generative adversarial networks and diffusion architectures, coupled with active-learning strategies, can help explore the chemical space around the TZD scaffold in a targeted way, proposing analogues that are not only predicted to be potent but also display favourable ADMET profiles and realistic synthetic accessibility (Almukadi et al., 2023). When these tools are integrated with robust QSAR models, structure-based design, and green synthetic methods, they have the potential to shorten design–make–test cycles significantly.

Finally, combination strategies deserve more attention, both at the molecular design level and at the therapeutic regimen level. On the one hand, multi-target hybrid molecules built around the TZD core can be engineered to act on complementary pathways within the same chemical entity. On the other hand, TZDs may prove particularly useful in combination with immunotherapies, targeted kinase inhibitors, or DNA-damaging agents. Their ability to modulate metabolic and inflammatory signalling suggests that they could help to remodel the tumour microenvironment or sensitize tumours to other treatment modalities, thereby extending their utility beyond direct cytotoxic action.

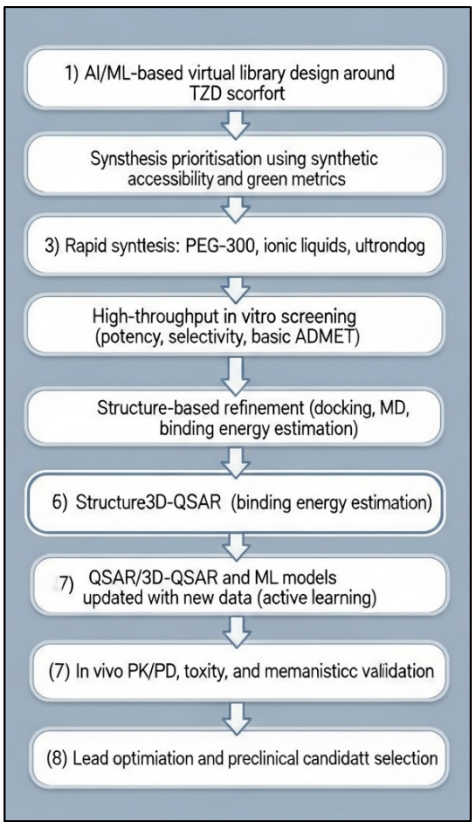

Figure 7. Flowchart of an integrated TZD-based anticancer discovery pipeline

10. Conclusion

Thiazolidinediones have evolved far beyond their origins as insulin-sensitizing agents and now represent one of the most adaptable heterocyclic platforms in contemporary anticancer drug design. The inherent structural flexibility of the 2,4-thiazolidinedione nucleus, particularly the tunable C-5 and N-3 positions, enables the development of molecules that can engage a variety of cancer-relevant targets, ranging from kinases and epigenetic enzymes to metabolic regulators and membrane transporters. A wealth of medicinal chemistry data shows that C-5 arylidene substitution,

especially with π-extended or electron-withdrawing aromatic groups, consistently enhances potency. Meanwhile, hybridization strategies incorporating pharmacophores such as indole, naphthalene, quinoline, or imidazothiazole frequently provide multi-target engagement and improved antiproliferative profiles compared with classical TZD analogues.

The synthetic landscape supporting these discoveries has also advanced considerably. PEG-mediated protocols, ionic-liquid catalysis, and energy-efficient ultrasound or microwave methods now offer rapid, cleaner, and more sustainable routes for generating structurally diverse TZD libraries, an advantage that aligns well with accelerated design–make–test–analyze cycles. Parallel progress in computational chemistry has clarified binding interactions within VEGFR-2, PIM-1, HDACs, and related targets. Docking and 3D-QSAR studies have provided valuable structural hypotheses and, in favourable cases, have closely paralleled observed SAR trends. Yet, despite these successes, computational reliability remains inconsistent, largely owing to small datasets, insufficient external validation, and the continued use of rigid-receptor docking protocols.

A more pressing issue is the stark contrast between the abundance of in vitro cytotoxicity data and the limited in vivo and ADMET evidence. The historic safety liabilities of PPARγ agonists, including hepatotoxicity, cardiotoxicity, and fluid retention, underscore the importance of early pharmacokinetic and toxicity assessment. Without systematic evaluation of metabolic stability, CYP interactions, and organ-specific toxicities, promising TZD leads risk stalling before reaching preclinical validation. Thus, while the molecular potential of TZDs is clear, real translation will rely on a more coordinated, data-driven strategy that balances potency with pharmacological realism.

Overall, thiazolidinediones stand as genuinely privileged, highly tunable scaffolds for the design of multi-target anticancer agents. Their future impact will depend not only on continued creativity in structural design but also on the adoption of integrated workflows combining green synthesis, validated computational modeling, AI-supported exploration of chemical space, and rigorous early-stage safety profiling. Only through such an interdisciplinary and translationally focused approach can TZD-based chemotypes progress from potent in vitro hits to credible preclinical candidates and, ultimately, to clinically meaningful anticancer agents.

1. A Privileged Polypharmacology Scaffold: TZDs now function as versatile multi-target frameworks capable of modulating kinases, HDACs, CA IX/XII, GLUT transporters, and PPARγ, making them well-suited for modern polypharmacology.
2. C-5/N-3 Functionalization Drives SAR: Electron-withdrawing arylidene groups at C-5 and strategic N-3 modifications (alkyl, amide, heterocyclic linkers) constitute the main medicinal chemistry levers. Hybrid TZD–pharmacophore designs consistently outperform simple analogues.
3. Green & Accelerated Synthesis is Transformational: PEG-based media, ionic liquids, microwave irradiation, and sonochemistry provide rapid, scalable, and environmentally improved routes, supporting efficient DMTA cycles.
4. Computational Methods Help, but Require Rigor: Docking and QSAR/3D-QSAR have clarified SAR for targets like VEGFR-2 and PIM-1, yet many published models rely on small datasets, minimal validation, or rigid receptor assumptions, limiting predictive value.
5. The Major Bottleneck is ADMET, Not Potency: Despite hundreds of TZD derivatives showing sub-micromolar potency, only a few possess meaningful in vivo, PK, or toxicity data. PPARγ-related risks demand early ADMET screening and "safety-by-design" strategies.
6. An Integrated, Translational Pipeline is Essential: Progress will depend on combining multi-target design, sustainable synthesis, validated computational workflows, AI/ML-guided analog generation, and early ADMET de-risking into a single iterative development loop.

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