Hindawi
Journal of Chemistry
Volume 2023, Article ID 9462176, 11 pages
https://doi.org/10.1155/2023/9462176

Research Article

Synthesis, Characterization, and Pharmacokinetic Studies of Thiazolidine-2,4-Dione Derivatives

Bushra Ansari,[1] Haroon Khan ,[1] Muhammad Saeed Jan,[2] Khalaf F. Alsharif,[3] Khalid J. Alzahrani,[3] Umer Rashid ,[4] and Abdul Saboor Pirzada[1]

[1]*Department of Pharmacy, Abdul Wali Khan University Mardan, Mardan, Pakistan*
[2]*Department of Pharmacy, Bacha Khan University, KP, Charsadda 24420, Pakistan*
[3]*Department of Clinical Laboratory, College of Applied Medical Science, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia*
[4]*Department of Chemistry, COMSATS University Islamabad, Abbottabad 22060, Pakistan*

Correspondence should be addressed to Haroon Khan; haroonkhan@awkum.edu.pk and Umer Rashid; umerrashid@cuiatd.edu.pk

Received 20 September 2022; Revised 16 December 2022; Accepted 4 January 2023; Published 16 January 2023

Academic Editor: Vinod Kumar Tiwari

Various derivatives of thiazolidine-2,4-dione (C1–C5) were designed and synthesized by chemical reaction with 4-nitrobenzaldehyde using Knoevenagel reaction conditions which results in the reduction of nitro group to amine and further modification results in target compounds. The chemical structures of all the 2,4-thiazolidinedione derivatives have been elucidated by ^{1}H and ^{13}C NMR spectroscopy. These compounds were further characterized by *in silico* ADME (absorption, distribution, metabolism, and excretion) studies. The pharmacokinetic properties were assessed by SwissADME software. The *in silico* ADME (absorption, distribution, metabolism, and excretion) assessment reveals that all derivatives (C1 to C5) have 5 to 7 rotatable bonds. Lipophilicity and water solubility showed that C1, C2, and C4 are water soluble except for C3 and C5 which are moderately soluble. All the compounds have high GI absorption except C3. None of the derivatives are blood-brain barrier permeant. Drug metabolism of TZDs derivatives showed that C3 was identified as an inhibitor of CYP2C9 and C5 as an inhibitor of CYP1A2 and CYP2C19. Drug likeness properties indicate that C1 has only one violation of the Ghose rule while C3 has violations in the Ghose and Egan rules. The *in silico* pharmacokinetic studies revealed high GI absorption and the inability to pass blood-brain barrier which can be further assessed by *in vitro* and *in vivo* antihyperglycemic activity. This study will contribute to providing TZDs derivatives with an improved pharmacokinetic profile and decreased toxicity.

1. Introduction

Thiazolidine-2,4-dione (TZDs) or glitazones are a class of heterocyclic compounds containing a five-membered thiazolidine group and carbonyl groups at positions 2 and 4. Only the 3 and 5 positions enable various substitutions; however, the substitution at position 2 results in the most significant modification to the structure and characteristics of TZDs. These heterocyclic moieties having nitrogen and sulfur known as thiazoles such as 1,3-thiazolidine-2,4-diones, The application of 4-(4-benzoylaminophenoxy)phenol analogues in a wide variety of pharmacological activities has sparked significant interest in several fields of medicinal chemistry [1, 2]. TZDs are now approved for use in the treatment of type 2 diabetes patients with poor glycemic control despite receiving the maximum tolerable dose of oral monotherapy with either metformin or sulphonylurea. TZDs should only be administered with metformin in individuals who are obese, according to general recommendations [3]. TZDs such as ciglitazone, pioglitazone, troglitazone, rosiglitazone, and a new agent, lobeglitazone [4], are widely used as effective antidiabetic drugs, etc. Through the stimulation of the peroxisome proliferator-activated receptor gamma (PPARγ), these drugs make fat

cells more sensitive to insulin [1]. It has been proposed that PPARγ activates endothelial nitric oxide synthase, which is crucial for cardioprotection [5, 6]. Human kidneys and target tissues for insulin action, such as adipose, skeletal muscles, and liver tissues, are the organs where PPAR receptors are produced. The transcription of insulin-responsive genes involved in the regulation, synthesis, transport, and use of glucose is controlled by the activation of PPAR nuclear receptors [7]. It has been demonstrated that TZDs increase the insulin sensitivity of adipose, muscle, and liver tissue. TZDs reduce both fasting and postprandial hyperglycemia by reducing insulin resistance and enhancing the efficiency of endogenous insulin. TZDs outperform other antihyperglycemic medications in terms of their ability to reduce hyperglycemia over time [8]. Since TZDs are the only medications that primarily target insulin resistance and recent literature has linked them to side effects like weight gain, edoema, heart failure, anaemia, hepatotoxicity, and bone fractures in women [9], the use of these relatively inexpensive medications justifies a re-evaluation of their clinical use[10]. This grabbed the curiosity of scientists who had developed a variety of TZD derivatives and evaluated them for a range of biological activities. TZDs showed no of pharmacological activities such as hypoglycemic and anti-hyperlipidemic [11], cardioprotective effect [12], antioxidant activity, MAO inhibitor [13], antimicrobial activity [14], anti-inflammatory activity [15], antituberculosis activity [16], anticancer [17]. *In silico* ADME studies are anticipated to minimise the risk of late-stage attrition in drug development and increase the testing and screening of the most promising compounds [18]. The present research is designed to synthesize new derivatives of TZDs with improved pharmacokinetic properties and fewer adverse effects.

2. Materials and Methods

2.1. Chemical. The chemicals used were dimethyl sulfoxide (DMSO), methanol, chloroform, ethanol, acetone, sodium bicarbonate, phosphate buffer saline, toluene and piperidine, chloride dehydrate, bromoacetyl bromide, K_2CO_3, and tetrahydrofuran.

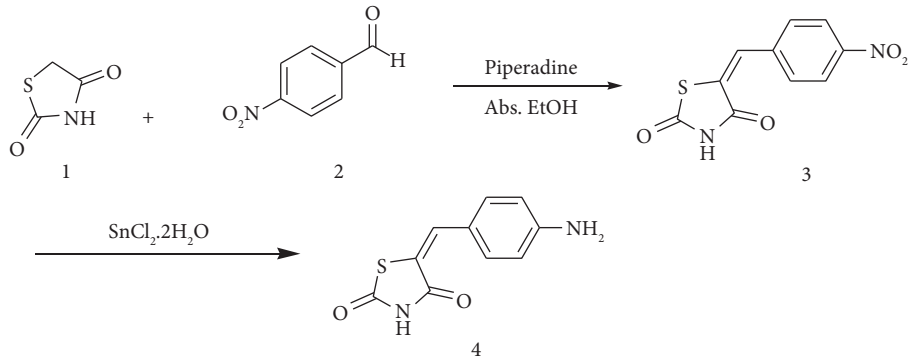
2.2. General Method for the Synthesis of (C1–C5) Thiazolidine-2,4-Dione Derivatives. Thiazolidine-2,4-dione derivatives were obtained via a double-step protocol, as shown in synthetic Schemes 1 and 2 4-nitrobenzaldehyde undergoes Knoevenagel condensation by thiazolidine-2,4-dione in absolute ethanol with piperidine as the base/condensing agent to yield compound 3. Nitro derivative was reduced to amine (**4**) by using tin (II) chloride dehydrate. In the second step, amino derivative 4 reacted with bromoacetyl bromide in tetrahydrofuran at 0°C using K_2CO_3 as the base to form mono-bromo derivatives. The synthesized derivative was further reacted with primary or secondary amines to form target derivatives.

2.3. (Z)-N-(4-((2, -Dioxothiazolidin-5-ylidene)Methyl)Phenyl)-2-(Piperazin-1-yl)Acetamide (C1). Yellow color solid, Yield = 59%, m.p. 197–199°C; $R_f = 0.51$; (DCM/MeOH; 2 : 1); ^{1}HNMR (400 MHz, DMSO-d_6) (ppm); 12.11 (brs, 1H, TZD-NH), 8.54 (brs, 1H, NH-CO), 7.74 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.60 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.52 (s, 1H, =CH), 3.19 (s, 2H, CH_2), 2.85–2.81 (m, 4H, pip-CH_2), 2.61–2.56 (m, 4H, pip-CH_2), 2.02–1.98 (m, 1H, pip-NH); ^{13}CNMR (100 MHz, DMSO-d_6); δ 173.2, 165.7, 162.9, 141.7, 130.3, 127.8, 127.0 (2 carbon), 125.7, 120.4 (2 carbon). 57.6, 53.9 (2 carbon), 47.3 (2 carbon); LCMS: $m/z = 347.4$ $[M + H]^+$. Analysis calculated for $C_{16}H_{18}N_4O_3S$. C, 55.48; H, 5.24; N, 16.17. Observed value: C, 55.56; H, 5.22; N, 16.15. The 1H, 13C NMR and CHN of the compound **C1** is presented in supplementary material as Figures S1–S3.

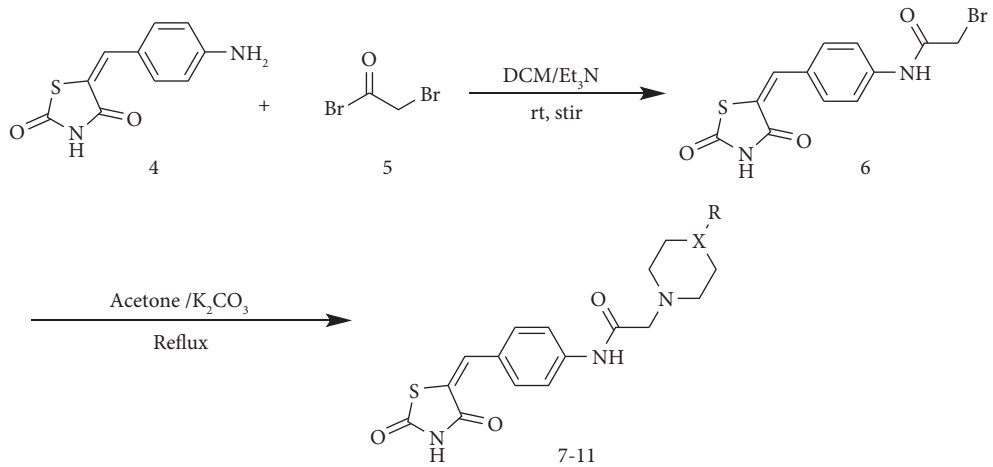
2.4. (Z)-N-(4-((2,4-Dioxothiazolidin-5-ylidene)Methyl)Phenyl)-2-(4-Methylpiperazin-1-yl)Acetamide (C2). Pale yellow color solid, Yield = 64%, m.p. 183–185°C; $R_f = 0.54$; (DCM/MeOH; 2 : 1); ^{1}HNMR (400 MHz, DMSO-d_6) (ppm); 12.13 (brs, 1H, TZD-NH), 8.54 (brs, 1H, NH-CO), 7.78 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.62 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.51 (s, 1H, =CH), 3.18 (s, 2H, CH_2), 2.74 (s, 3H, N-CH_3), 2.23–2.19 (m, 4H, pip-CH_2), 2.02–1.97 (m, 4H, pip-CH2), ^{13}CNMR (100 MHz, DMSO-d_6); δ 173.1, 165.6, 162.8, 141.6, 130.2, 127.7, 127.0 (2 carbon), 125.7, 120.4 (2 carbon), 63.0, 52.4 (2 carbon), 51.5 (2 carbon), 44.2; LCMS: $m/z = 361.2$ $[M + H]^+$. Analysis calculated for $C_{17}H_{20}N_4O_3S$ C, 56.65; H, 5.59; N, 15.54; observed value: C, 56.76; H, 5.57; N, 15.55. The 1H, 13C NMR and CHN of the compound C2 is presented in the supplementary material as Figures S4–S6.

2.5. (Z)-N-(4-((2,4-Dioxothiazolidin-5-ylidene)Methyl)Phenyl)-2-(4-(Phenylsulfonyl)Piperazin-1-yl)Acetamide (C3). Dark yellow color solid, Yield = 54%, m.p. 221–223°C; $R_f = 0.50$; (DCM/MeOH; 4 : 1); ^{1}HNMR (400 MHz, DMSO-d_6) (ppm); 12.11 (brs, 1H, TZD-NH), 8.52 (brs, 1H, NH-CO), 7.89 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.74 (d, 2H, $J = 8.0$ Hz, Ar-H), 7.64 (m, 5H, Ar-H), 7.52 (s, 1H, =CH), 3.18 (s, 2H, CH_2), 3.29 (t, 4H, $J = 5.64$ Hz, pip-CH_2), 2.58 (t, 4H, $J = 5.64$ Hz, pip-CH_2), ^{13}CNMR (100 MHz, DMSO-d_6); δ 172.9, 166.0, 162.7, 141.6, 136.2, 130.8, 129.0 (2 carbon), 128.1, 127.0 (2 carbon), 126.6, 126.0 (2 carbon), 121.3 (2 carbon), 60.8, 52.6 (2 carbon), 47.3 (2 carbon); LCMS: $m/z = 487.7$ $[M + H]^+$. Analysis calculated for $C_{22}H_{22}N_4O_5S_2$, C, 54.31; H, 4.56; N, 11.51; O, 16.44; S, 13.18; observed value: C, 54.39; H, 4.58; N, 11.52.

2.6. (Z)-N-(4-((2,4-Dioxothiazolidin-5-ylidene)Methyl)Phenyl)-2-Morpholinoacetamide (C4). Yellow color solid, Yield = 73%, m.p. 203–205°C; $R_f = 0.48$; (DCM/MeOH; 2 : 1); ^{1}HNMR (400 MHz, DMSO-d_6) (ppm); 12.11 (brs, 1H, TZD-NH), 8.55 (brs, 1H, NH-CO), 7.74 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.60 (d, 2H, $J = 8.4$ Hz, Ar-H),7.53 (s, 1H, =CH), 3.73 (t, 2H, $J = 6.72$ Hz, CH_2), 3.19 (s, 2H, CH_2), 2.67 (t, 2H, $J = 6.72$ Hz, CH_2); ^{13}CNMR (100 MHz, DMSO-d_6); δ 172.6, 165.8, 163.1, 141.8, 130.5, 128.0, 127.4 (2 carbon), 125.9, 120.3 (2 carbon), 65.4 (2 carbon), 62.9, 53.8 (2 carbon). LCMS: $m/z = 348.8$ $[M + H]^+$. The 1H, 13C NMR, and CHN of the compound C4 is presented in supplementary material as Figures S7–S9.



Scheme 1: Synthesis of amine derivative.



Scheme 2: Synthesis of targeted compounds C1–C5.

2.7. (Z)-N-(4-((2,4-Dioxothiazolidin-5-ylidene)Methyl)Phenyl)-2-(Piperidin-1-yl)Acetamide (C5). Light yellow color solid, Yield = 71%, m.p. 181–183°C; R_f = 0.56; (DCM/MeOH; 2 : 1); ^{1}HNMR (400 MHz, DMSO-d_6) (ppm); 12.13 (brs, 1H, TZD-NH), 8.57 (brs, 1H, NH-CO), 7.76 (d, 2H, J = 8.4 Hz, Ar-H), 7.60 (d, 2H, J = 8.4 Hz, Ar-H),7.53 (s, 1H, =CH), 3.17 (s, 2H, CH_2), 2.61 (t, 4H, J = 5.8 Hz, CH_2), 1.74 (t, 4H, J = 5.4 Hz, CH_2), 1.33 (p, 2H, J = 5.4 Hz, CH_2); ^{13}CNMR (100 MHz, DMSO-d_6); δ 172.4, 165.8, 164.2, 141.8, 130.2, 128.0, 127.4, 125.9, 120.3, 64.0, 61.3, 51.6.

2.8. Characterization. The physical appearance of the compounds, R_f values and isolated yields of the pure synthesized compounds were noted separately. Nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR) was used for structure elucidation of the synthesized compounds.

2.9. Pharmacokinetic Studies. In the development and choice of drug candidates, the idea of drug-like chemical spaces is frequently employed. Compounds with pharmacokinetic characteristics that enable them to endure the end of human phase I clinical trials are referred to as drug-like chemical space [19]. The SwissADMET database was used to estimate the physicochemical qualities, such as lipophilicity and water solubility, pharmacokinetic profile, drug likeness, and medicinal chemistry of the compounds [20, 21]. The 2D structures were drawn in the database which also allowed for a string-based search (Table 1).

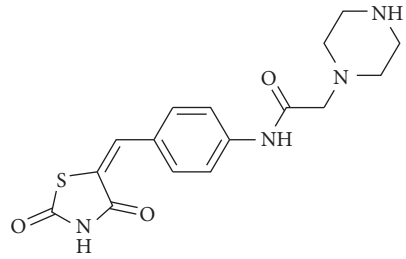
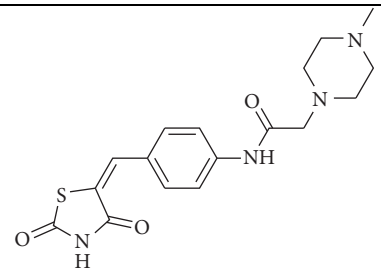
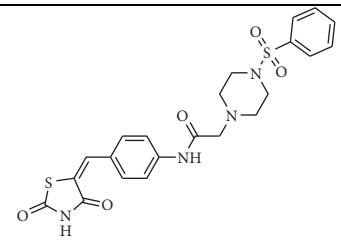
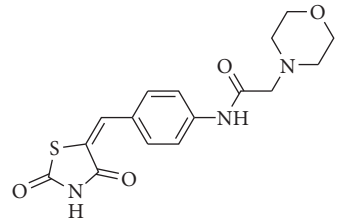
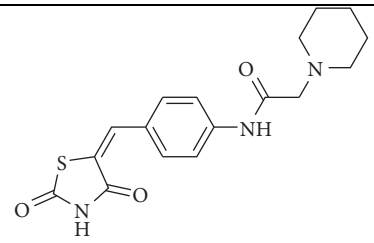
3. Results

3.1. Chemistry. In Scheme 1, nitro derivative 3 was synthesized by reacting 4-nitrobenzaldehyde (2) with thiazolidinedione (1) in the presence of acetic acid and piperidine in ethanol under reflux condition. The synthesized nitro intermediate was then reduced to amine 4 by using tin (II) chloride dihydrate under reflux conditions in ethanol.

Compound **4** was further reacted with bromo-acetyl bromide in dimethylformamide in the presence of potassium carbonate to obtain monobromo derivative **compound 6** which was finally reacted with secondary amines to yield final compounds (C1–C5).

3.2. Analysis of Physicochemical Properties. Out of the five TZDs derivatives, none of them violate Lipinski's rule of five except C3 which has TPSA of 149.57 Å^2. This implies their suitability for oral drugs-like molecular nature (Table 2).

Table 1: IUPAC name and structure of TZDs (C1–C5) derivatives.

Ligand	IUPAC name	Structure
C1	(**Z**)-N-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenyl)-2-(piperaszin-1-yl)acetamide	
C2	(**Z**)-N-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenyl)-2-(4-methylpiperazin-1-yl)acetamide	
C3	(**Z**)-N-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenyl)-2-(4-(phenylsulfonyl)piperazin-1-yl)acetamide	
C4	(**Z**)-N-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenyl)-2-morpholinoacetamide	
C5	(**Z**)-N-(4-((2,4-Dioxothiazolidin-5-ylidene)methyl)phenyl)-2-(piperidin-1-yl)acetamide	

Molecular weight (MW), No of H-bond donors (nHBD), topological polar surface area (TPSA), Log*P*, and number of hydrogen bond acceptors (NHBAs) of all TZDs derivatives are within the recognized limits of ≤500, ≤5, ≤140 A^2 and ≤10, respectively (Table 2). The F. Csp^3 values for TZDs derivatives range from 0.23 to 0.35 (Table 2). From C1 to C5 all derivatives have 5 to 7 rotatable bonds. The molar refractivity ranges from 98.45 to 136.79 (Figure 1).

3.3. Lipophilicity and Water Solubility. Log $P_{o/w}$ values of all derivatives ranged from 0.68 to 1.82 which reflects its partition preferably into water compartment. Except for C3 and C5 which are predicted as moderately soluble, all other derivatives are water soluble. Log *S* is aqueous solubility with a defined range of −4~0.5 log mol/L as shown (Table 3).

3.4. Pharmacokinetics Profile. Pharmacokinetics (PK) of a drug molecule is important to achieve the desired pharmacological goal. This implies that every pharmacokinetic parameter of a compound can eventually affect the pharmacological profile of a drug. The SwissADME database revealed high GI absorption for all derivatives except C3. The boiled-egg graph of C1–C5 is shown in Figures 2–6, respectively. All TZDs derivatives (C1, C2, C4, C5) showed good GI

Table 2: The physicochemical property of TZDs derivatives calculated with swissADME database.

Ligands	Molecular formula	MW (g/mol)	nHA	nAHA	F. Csp^3	nRB	nHBA	nHBD	MR	TPSA (A^2)
C1	$C_{16}H_{18}N_4O_3S$	346.40	24	6	0.31	5	5	3	104.08	115.84
C2	$C_{17}H_{20}N_4O_3S$	360.43	25	6	0.35	5	5	2	108.99	107.05
C3	$C_{22}H_{22}N_4O_5S_2$	486.56	33	12	0.23	7	7	2	136.79	149.57
C4	$C_{16}H_{17}N_3O_4S$	347.39	24	6	0.31	5	5	2	98.45	113.04
C5	$C_{17}H_{19}N_3O_3S$	345.42	24	6	0.35	5	4	2	102.17	103.81

Molecular weight: M. W, No. heavy atom: nHA, No. arom. heavy atom: nAHA, No. of sp^3 hybridized carbon out of total carbon count: F. Csp^3, No. rotatable bonds: nRB, No. H-bond acceptors: nHBA, No. H-bond donors: nHBD, Molar refractivity: MR, topological polar surface area: TPSA.

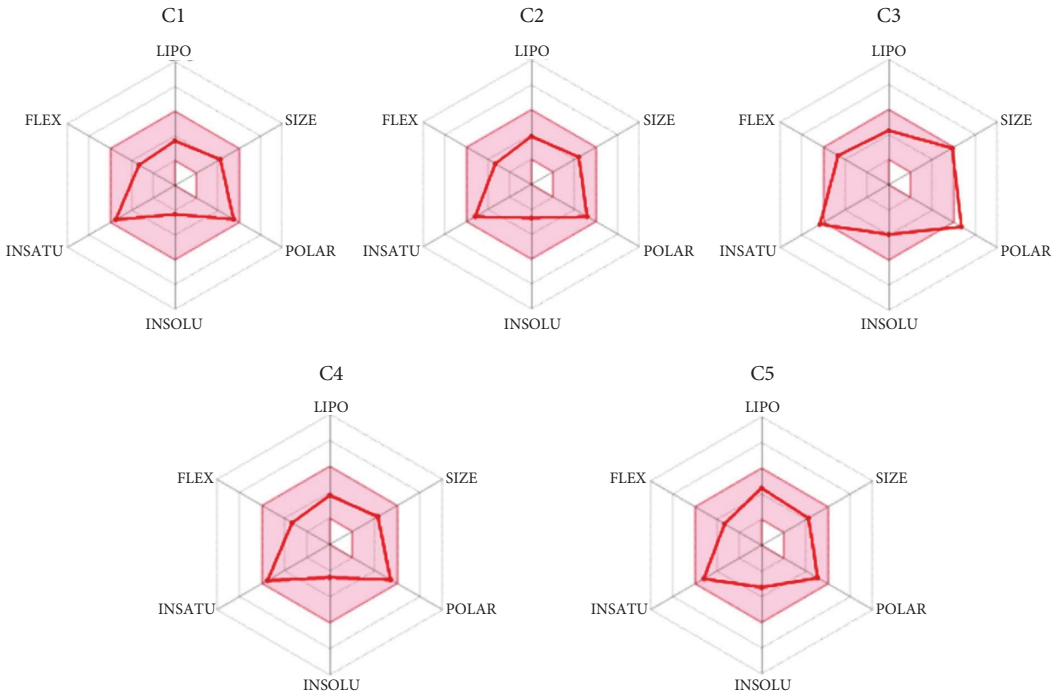


Figure 1: Physicochemical properties radar chart of **C1**–**C5**.

Table 3: Lipophilicity and water solubility of TZDs (**C1**–**C5**) derivatives.

Ligands	Lipophilicity	Water solubility					
	Consensus log $P_{o/w}$	Log *S* (ESOL)	Solubility class	Log *S* (all)	Solubility class	Log *S* (SILICOS-IT)	Solubility class
C1	0.68	−2.33	Soluble	−2.79	Soluble	−4.06	Moderately soluble
C2	0.93	−2.71	Soluble	−3.10	Soluble	−3.73	Soluble
C3	1.57	−3.96	Soluble	−4.83	Moderately soluble	−5.66	Moderately soluble
C4	0.97	−2.52	Soluble	−3.04	Soluble	−3.75	Soluble
C5	1.82	−3.28	Soluble	−4.11	Moderately soluble	−4.29	Moderately soluble

absorption except C3 which is not fit for intestinal absorption. All derivatives from C1–C5 were not able to cross the blood brain barrier. All derivatives are *P*-glycoprotein substrates.

In the case of drug metabolism C3 was identified as an inhibitor of CYP2C9 and C5 as an inhibitor of CYP1A2 and CYP2C19. All other derivatives have no effect on CYP3A4, CYP1A2, CYP2C19, CYP2C9, and CYP2D6. All derivatives have a similar Table 4 bioavailability Table 5 score of 0.55.

3.5. Drug Likeness. C2, C4, and C5 do not violate any of the five drug likeness parameters, i.e., Lipinski, Muegge, Ghose, Veber, and Egan rules of drug likeness. However, C1 has only one violation of the Ghose rule (WLOGP < −0.4). C3 has violations in Ghose (MW > 480, MR > 130), Veber (TPSA > 140), and Egan rules (TPSA > 131.6).

3.6. Medicinal Chemistry. TZDs (C1–C5) derivatives have no PAINSalert; free from α-screen artifacts, frequent hitters, and reactive compounds. Brenk structural alert has identified two reactive groups in TZDs derivatives, i.e., a thioester group and Michael acceptor. C1, C4, and C5 has molecular weight <350, so they have lead likeness capability. C2 and C3 cannot serve as leads as their MW is >350. The SwissADME database has assigned TZDs derivatives scores of 3.16 to 3.84 which represent easy step reactions of synthesis.

4. Discussion

Chemically, thiazolidinediones are heterocyclic rings containing two carbonyl groups at the second and fourth positions that may be modified structurally to create a variety of derivatives [22]. Ciglitazone was the first member of the thiazolidinedione group to be synthesised, and it was followed by the production of additional derivatives including Englitazone, Pioglitazone, and Troglitazone. All of them have a similar thiazolidine-2,4-dione structure, a characteristic that provides them most of their pharmacological effects [23]. Troglitazone, which has the ability to reduce blood sugar levels, was discovered by the Sankyo Company in 1988. In the year 1997, the FDA gave approval for this product for treatment in T2DM. Troglitazone was withdrawn from the UK market six weeks after Glaxo Wellcome launched it due to a rare but potentially deadly idiosyncratic hepatotoxicity, and the FDA removed completely it in March 2000. The first TZD, Ciglitazone, was found in 1982 after intensive research on the structure-activity connection. Animal models showed Ciglitazone to have potential lipid- and glucose-lowering effects. However, this chemical was eventually stopped due to severe liver damage [24, 25]. In the present study, thiazolidine-2,4-dione intermediates were synthesized by using Knoevenagel reaction conditions. Knoevenagel condensation is considered as a variant of the Aldol condensation, and it is a classical method for the synthesis of C-C bond formation. A key step in the synthesis of the medicinally important antidiabetic Glitazone family involves Knoevenagel condensation. 5-arylidene-2,4-thiazolidinediones core is synthesized by the condensation reaction of thiazolidine-2,4-dione with aldehydes. Only *Z*-configuration was obtained by adding an arylidene moiety to thiazolidine-2,4-dione, according to published data from X-ray diffraction and NMR investigations. TZDs are

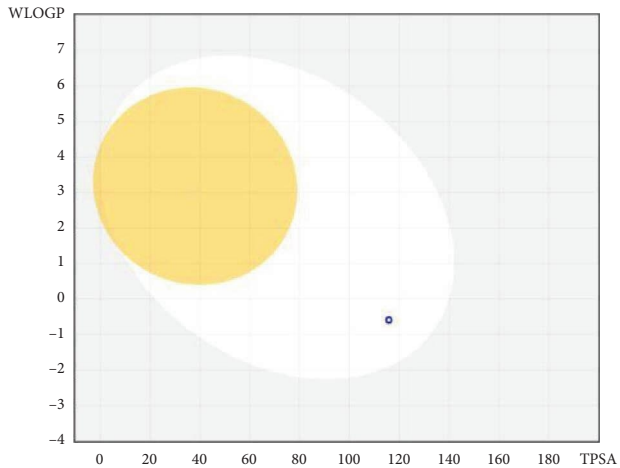


Figure 2: Boiled graph representation of C1.

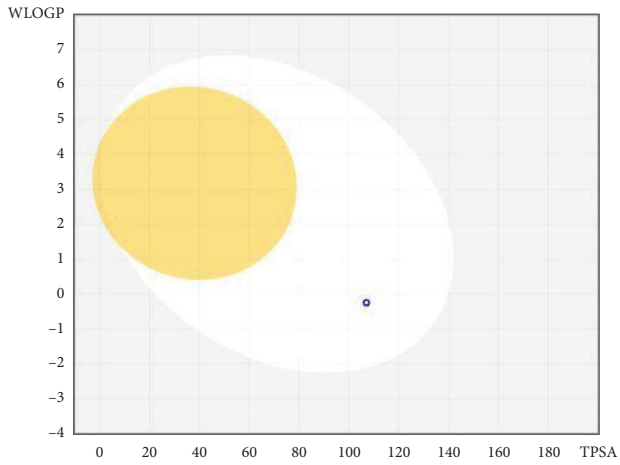


Figure 3: Boiled graph representation of C2.

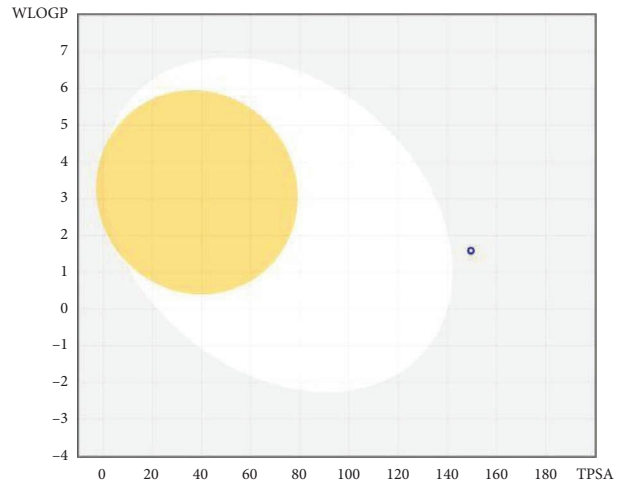


Figure 4: Boiled graph representation of C3.

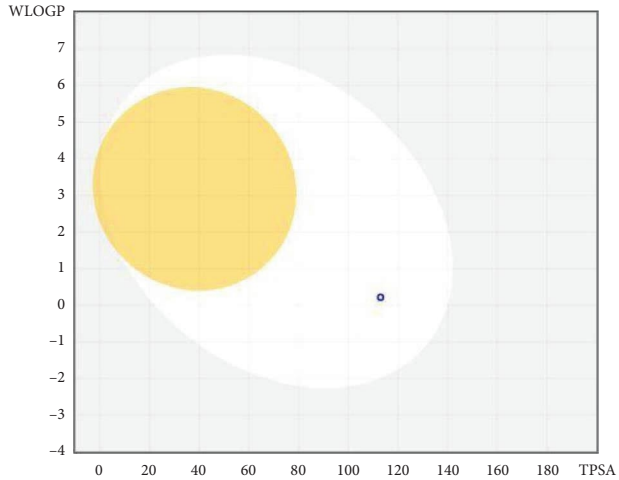


Figure 5: Boiled graph representation of C4.

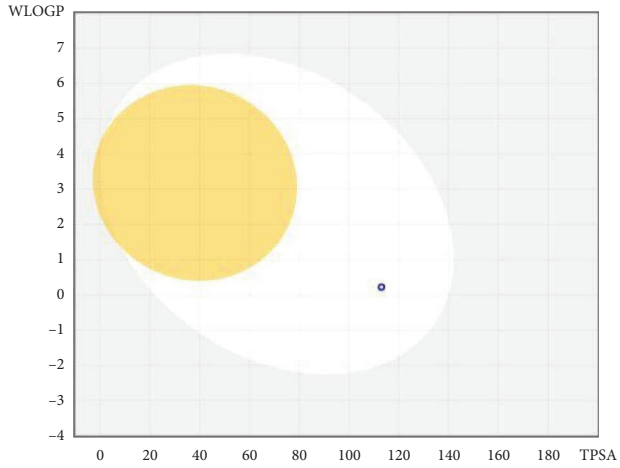


Figure 6: Boiled graph representation of C5.

Table 4: Pharmacokinetics of TZDs (C1–C5) derivatives calculated with SwissADME database.

Ligands	GI absorption	Bioavailability score	BBB permeant	*P*-gp substrate	CYP1A2 inhibitors	CYP2C19 inhibitors	CYP2C9 inhibitors	CYP2D6 inhibitors	CYP3A4 inhibitors
C1	High	0.55	No	Yes	No	No	No	No	No
C2	High	0.55	No	Yes	No	No	No	No	No
C3	Low	0.55	No	Yes	No	No	Yes	No	No
C4	High	0.55	No	Yes	No	No	No	No	No
C5	High	0.55	No	Yes	Yes	Yes	No	No	No

a significant class of medications that work by enhancing the transactivation activity of PPARs. As a result, they decrease hepatic glucose production while increasing peripheral glucose utilization and lipid metabolism. The preload and afterload on b-cells and lipid homeostasis are thus decreased as a result of these effects.he impact of endogenous insulin improves in order to maintain blood glucose levels. Rationalized techniques have been employed to continue expanding antidiabetic TZDs group in light of current developments and a better knowledge of the structure and operations of other antidiabetic targets. More recent approaches are based on the structural considerations of the ligands and receptors and the interactions between ligands and receptors [26, 27].

The pharmacokinetic analysis of TZDs C1–C5 showed that Lipinski's rule of five is necessary for rational drug development. Any drug molecule violating even one of the rules may have low permeability or poor absorption [28]. Fsp^3 is the fraction of sp^3 carbon atoms out of the total carbon count. This reflects the carbon saturation and characterizes complexity of the molecular spatial structure. A suitable value considered optimum for Fsp^3 is ≥0.42, as about 84% of commercial drugs meet this criterion [29]. However, sp^3 content needs to be increased within a range

because a higher Fsp^3 score is not a guarantee of higher performance and can increase the difficulty of chemical synthesis [30]. Synthetic products usually have a lower fraction of sp^3 than natural molecules, and so natural products are a rich source of drugs [31]. Rotatable bond count is employed as "drug filter" which is correlated with reduced rat oral bioavailability if the number of rotatable bonds is greater than 10 [32]. Mechanistically utilizing "rotatable bond filter" is still unclear, as its count does not correlate with the *in vivo* clearance rate in rats. However, the filter is justified from an in vitro screening prospect because ligand affinity decreases at an average of 0.5 kcal for each two rotatable bonds [33]. The H-bond acceptor and donor are within accurately strict limit, except C3 being within limit but a little higher nRB and nHBA (Table 2). Oral drugs have fewer H-bond acceptors, donors, and rotatable bonds [20]. These three parameters favor oral route of administration as being flexible, convenient, and simple one.

The molecules with a TPSA of $\geq 140\ Å^2$ would be poorly absorbed with less than 10% fractional absorption, while those with a TPSA of $60\ Å^2$ would be well absorbed with greater than 90% fractional absorption [34]. C1, C2, C4, and C5 are predicted to have better absorption as reflected from TPSA, however, C3 has a TPSA of $149.57\ Å^2$ suggestive of poor oral absorption.

The Log $P_{o/w}$ calculated by SwissADME is an average of iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT, referred to as the consensus Log $P_{o/w}$. Log $P_{o/w}$ is the Log of the octanol/water partition coefficient. A higher log $P_{o/w}$ value indicates higher lipophilicity, and it depends upon polarity, molecular size, and hydrogen bonding. Log $P_{o/w}$ values of all derivatives ranged from 0.68 to 1.82 which reflects their partition preferably into the water compartment. However, the values of log $P_{o/w}$ exhibit optimal lipophilicity (Optimal: $0 < \text{Log } P < 3$) [35]. These values are somewhat congruent with log S values. The SwissADME database revealed high GI absorption for all derivatives except C3 [21].

None of TZDs derivatives are predicted to cross blood-brain barrier. This will minimize or eradicate the chances of CNS toxicity. All TZDs derivatives are substrates of *p*-glycoprotein. This may associate them in interactions with different endogenous or exogenous chemicals, especially drugs. *P*-glycoprotein interactions may ultimately affect the pharmacological profile of other drugs [36]. CYP3A4 is one of the most important isoforms of the CYP P450 system metabolizing majority of drugs and endogenous chemicals. All derivatives are predicted to have no effect on CYP3A4, indicating a diminished number of interactions. In a similar pattern all the derivatives do not affect other important isoforms like CYP1A2, CYP2C19, CYP2C9, and CYP2D6, except that C3 is an inhibitor of CYP2C9 and C5 is an inhibitor of CYP1A2 and CYP2C19. This may involve C3 and C5 in pharmacokinetic drug interactions. The bioavailability score indicates a good enough plasma concentration. The calculation of bioavailability and permeability is important before proceeding for the synthesis or any advanced testing. Therefore, a probability-based score is given to a drug candidate to have $F > 10\%$ in rat [37]. C2, C4, and C5 are compliant with many widely acceptable drug likeness rules, i.e., Lipinski, Muegge, Ghose, Veber, and Egan. However, C1 has a single violation of solubility, while C3 has a high TPSA value, MR, and molecular weight. This is a violation of Ghose, Veber, and Egan rules. However, there was no problem identified in the absorption of four derivatives as defined by the boiled-egg graphical representation. The yellowish region on the boiled-egg graph represents CNS penetration; the white region represents human intestinal absorption. If the drug absorption is other than oral, it will be represented in the gray area of the graph [21].

All TZDs derivatives (C1, C2, C4, and C5) showed good GI absorption except C3 which is not fit for intestinal absorption. None of the derivatives are blood brain barrier permeant, indicating a positive gesture of being free of CNS toxicity. All derivatives are *P*-glycoprotein substrates. TZDs derivatives have "zero" PAINS (Pan Assay interference compounds) alert, and so excluded from the list of α-screen artifacts, frequent hitters, and reactive compounds. PAINS have an unrestrained behavior of producing false positive hits during HTS. The mechanism is poorly understood; however, it is associated with protein reactivity and non-covalent interactions [38]. In SwissADME a structural alert is created for 105 fragments identified by Brenk et al. which are chemically reactive, toxic, metabolically unstable, or likely to have poor pharmacokinetics. This can identify a problematic fragment found in a given molecule [39]. This structural alert has identified two reactive groups, i.e., a thioester group and Michael acceptor. A thioester group is present in these five TZD derivatives, and MedChem rules consider a thioester fragment as potentially reactive or promiscuous [40]. Considering this observation, these compounds can be considered for structural optimization. Thioesters are acylating agents which give rise to hydrolysis products that interfere with assays [41]. In the same manner, Michael acceptor can prove to be reactive and contribute to side effects [42]. However, this can be correlated with the preclinical studies carried out which are available at this stage. Lead likeness parameter represents the ability of a molecule to serve as "lead" in the drug discovery process. C1, C4, and C5 have a molecular weight <350, so they have lead-likeness capability. On the basis of SAR, their pharmacophores can be modified further to achieve better pharmacological results. C2 and C3 have violated one of the lead-likeness rules as their MW is >350. Therefore, these two molecules are unable to become lead molecules. TZDs (C1–C5) derivatives have been synthesized in the lab. However, the SwissADME database prediction of its synthetic accessibility is congruent to the actual situation. The SwissADME database has assigned to TZDs derivatives the scores of 3.16 to 3.84 which suggest easy step reactions of synthesis. The difficult synthetic approaches for those molecules having a score of 10 [20].

Table 5: Drug likeness and medicinal chemistry of TZDs derivatives.

Ligands	Drug likeness rules						Medicinal chemistry		
	Lipinski	Ghose	Veber	Egan	Muegge	PAINS	Brenk	Lead likeness	Synthetic accessibility
C1	Yes	No; 1 violation WLOGP <−0.4	Yes	Yes	Yes	0 alert	2 alerts: michael_1, thioester	Yes	3.29
C2	Yes	Yes	Yes	Yes	Yes	0 alert	2 alerts: michael_acceptor_1, thioester	No; 1 violation: MW > 350	3.40
C3	Yes	No; 2 violations: MW > 480, MR > 130	No; 1 violation: TPSA >140	No; 1 violation: TPSA >131.6	Yes	0 alert	2 alerts: michael_acceptor_1, thioester	No; 1 violation: MW > 350	3.84
C4	Yes	Yes	Yes	Yes	Yes	0 alert	2 alerts: michael_acceptor_1, thioester	Yes	3.21
C5	Yes	Yes	Yes	Yes	Yes	0 alert	2 alerts: michael_acceptor_1, thioester	Yes	3.16

5. Conclusion

In the present research, we have successfully synthesized 2,4-thiazolidinedione derivatives (C1–C5) under Knoevenagel reaction conditions. Most of the derivatives of TZD display higher GI absorption and have good water solubility. In the present study it is concluded that most of derivatives of thiazolidinedione (C1, C2, C4, and C5) has improved pharmacokinetic properties. These targeted agents may contribute to newer antihyperglycemic drugs with higher PK properties. Furthermore, in our lab, we were working on these compounds for their *in vitro*, *in vivo* studies and docking studies which will confirm their antihyperglycemic activity.

Data Availability

The required data can be provided upon reasonable request to the corresponding author..

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Figure S1: ^{1}H NMR of compound C1; Figure S2: ^{13}C NMR of compound C1; Figure S3: CHN of compound C1; Figure S4: ^{1}HNMR of compound C2; Figure S5: ^{13}C NMR of compound C2; Figure S6: CHN of compound C2; Figure S7: ^{1}HNMR of compound C4; Figure S8: ^{13}C NMR of compound C4; and Figure S9: CHN of compound C4. (*Supplementary Materials*)

References

[1] U. Vanitha, R. Elancheran, K. Senthamaraikannan, and S. Kabilan, "Screening of 1, 3, 4-Thiadiazole Derivatives by in Silico Molecular Docking to Target Estrogen Receptor for Breast Cancer," *Biointerface Research in Applied Chemistry*, vol. 13, no. 2, pp. 1–10, 2022.

[2] A. Ahmad, F. Ullah, A. Sadiq et al., "Pharmacological evaluation of aldehydic-pyrrolidinedione against HCT-116, MDA-mb231, NIH/3T3, MCF-7 cancer cell lines, antioxidant and enzyme inhibition studies," *Drug Design, Development and Therapy*, vol. 13, pp. 4185–4194, 2019.

[3] T. Fujita, Y. Sugiyama, S. Taketomi et al., "Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-methylcyclohexylmethoxy) benzyl]-thiazolidine-2, 4-dione (ADD-3878, U-63, 287, ciglitazone), a new antidiabetic agent," *Diabetes*, vol. 32, no. 9, pp. 804–810, 1983.

[4] J. Bae, T. Park, H. Kim, M. Lee, and B. S. Cha, "Lobeglitazone: a novel thiazolidinedione for the management of type 2 diabetes mellitus," *Diabetes & metabolism journal*, vol. 45, no. 3, pp. 326–336, 2021.

[5] M. S. Jan, S. Ahmad, F. Hussain et al., "Design, synthesis, in-vitro, in-vivo and in-silico studies of pyrrolidine-2, 5-dione derivatives as multitarget anti-inflammatory agents," *European Journal of Medicinal Chemistry*, vol. 186, Article ID 111863, 2020.

[6] F. Iftikhar, F. Yaqoob, N. Tabassum et al., "Design, synthesis, in-vitro thymidine phosphorylase inhibition, in-vivo antiangiogenic and in-silico studies of C-6 substituted dihydropyrimidines," *Bioorganic Chemistry*, vol. 80, pp. 99–111, 2018.

[7] S. Pattan and C. Suresh, "Synthesis and antidiabetic activity of 2-amino [5'(4-sulphonylbenzylidine)-2, 4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole," *ChemInform*, vol. 37, 2006.

[8] S. E. Kahn, S. M. Haffner, M. A. Heise et al., "Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy," *New England Journal of Medicine*, vol. 355, no. 23, pp. 2427–2443, 2006.

[9] A. P. Wang, X. Li, Y. Zheng et al., "Thiazolidinediones protect mouse pancreatic β-cells directly from cytokine-induced cytotoxicity through PPARγ-dependent mechanisms," *Acta Diabetologica*, vol. 50, no. 2, pp. 163–173, 2013.

[10] H. E. Lebovitz, "Thiazolidinediones: the forgotten diabetes medications," *Current Diabetes Reports*, vol. 19, no. 12, pp. 151–213, 2019.

[11] F. Hussain, Z. Khan, M. S. Jan et al., "Synthesis, in-vitroα-glucosidase inhibition, antioxidant, in-vivo antidiabetic and molecular docking studies of pyrrolidine-2, 5-dione and thiazolidine-2, 4-dione derivatives," *Bioorganic Chemistry*, vol. 91, Article ID 103128, 2019.

[12] J. A. Dormandy, B. Charbonnel, D. J. Eckland et al., "Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial," *The Lancet*, vol. 366, no. 9493, pp. 1279–1289, 2005.

[13] R. Jadoon, M. Aamir Javed, M. Saeed Jan et al., "Design, synthesis, in-vitro, in-vivo and ex-vivo pharmacology of thiazolidine-2, 4-dione derivatives as selective and reversible monoamine oxidase-B inhibitors," *Bioorganic & Medicinal Chemistry Letters*, vol. 76, Article ID 128994, 2022.

[14] K. R. Alagawadi and S. G. Alegaon, "Synthesis, characterization and antimicrobial activity evaluation of new 2, 4-Thiazolidinediones bearing imidazo [2, 1-b] [1, 3, 4] thiadiazole moiety," *Arabian Journal of Chemistry*, vol. 4, no. 4, pp. 465–472, 2011.

[15] A. M. Youssef, M. Sydney White, E. B. Villanueva, I. M. El-Ashmawy, and A. Klegeris, "Synthesis and biological evaluation of novel pyrazolyl-2, 4-thiazolidinediones as anti-inflammatory and neuroprotective agents," *Bioorganic & Medicinal Chemistry*, vol. 18, no. 5, pp. 2019–2028, 2010.

[16] N. B. Chilamakuru, "Synthesis, characterisation and anti-tubercular activity of some new 3, 5-disubstituted-2, 4-thiazolidinediones," *Asian Journal of Pharmaceutical and Clinical Research*, vol. 6, pp. 29–33, 2013.

[17] H. L. T. Anh, N. Cuc, B. Tai et al., "Synthesis of chromonylthiazolidines and their cytotoxicity to human cancer cell lines," *Molecules*, vol. 20, no. 1, pp. 1151–1160, 2015.

[18] R. Elancheran, K. Saravanan, S. Divakar et al., "Design, synthesis and biological evaluation of novel 1, 3-thiazolidine-2, 4-diones as anti-prostate cancer agents," *Anti-Cancer Agents in Medicinal Chemistry*, vol. 17, no. 13, pp. 1756–1768, 2017.

[19] R. Bade, H. F. Chan, and J. Reynisson, "Characteristics of known drug space. Natural products, their derivatives and synthetic drugs," *European Journal of Medicinal Chemistry*, vol. 45, no. 12, pp. 5646–5652, 2010.

[20] I. Ahmad, H. Khan, M. Usman Amin, S. Khalid, T. Behl, and N. Ur Rahman, "An overview on the anticancer potential of punarnavine: prediction of drug-like properties," *Oncologie*, vol. 23, no. 3, pp. 321–333, 2021.

[21] A. Daina, O. Michielin, and V. Zoete, "SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules," *Scientific Reports*, vol. 7, no. 1, pp. 42717–42813, 2017.

[22] N. Chadha, M. S. Bahia, M. Kaur, and O. Silakari, "Thiazolidine-2, 4-dione derivatives: programmed chemical weapons for key protein targets of various pathological conditions," *Bioorganic & Medicinal Chemistry*, vol. 23, no. 13, pp. 2953–2974, 2015.

[23] S. Malik, P. K. Upadhyaya, and S. Miglani, "Thiazolidinediones: a plethro of biological load," *International Journal of PharmTech Research*, vol. 3, no. 1, pp. 62–75, 2011.

[24] F. Lalloyer and B. Staels, "Fibrates, glitazones, and peroxisome proliferator–activated receptors," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 30, no. 5, pp. 894–899, 2010.

[25] R. Zafar, M. Zubair, S. Ali et al., "Zinc metal carboxylates as potential anti-Alzheimer's candidate: in vitro anticholinesterase, antioxidant and molecular docking studies," *Journal of Biomolecular Structure and Dynamics*, vol. 39, no. 3, pp. 1044–1054, 2021.

[26] M. Nanjan, M. Mohammed, B. Prashantha Kumar, and M. Chandrasekar, "Thiazolidinediones as antidiabetic agents: a critical review," *Bioorganic Chemistry*, vol. 77, pp. 548–567, 2018.

[27] F. Mahmood, J. A. Khan, M. H. Mahnashi et al., "Anti-inflammatory, analgesic and antioxidant potential of new (2 S, 3 S)-2-(4-isopropylbenzyl)-2-methyl-4-nitro-3-phenylbutanals and their Corresponding carboxylic acids through in vitro, in silico and in vivo studies," *Molecules*, vol. 27, no. 13, p. 4068, 2022.

[28] M. Pathak, H. Ojha, A. K. Tiwari, D. Sharma, M. Saini, and R. Kakkar, "Design, synthesis and biological evaluation of antimalarial activity of new derivatives of 2, 4, 6-s-triazine," *Chemistry Central Journal*, vol. 11, no. 1, pp. 132–211, 2017.

[29] D. C. Kombo, K. Tallapragada, R. Jain et al., "3D molecular descriptors important for clinical success," *Journal of Chemical Information and Modeling*, vol. 53, no. 2, pp. 327–342, 2013.

[30] E. M. Gerlach, M. A. Korkmaz, I. Pavlinov, Q. Gao, and L. N. Aldrich, "Systematic diversity-oriented synthesis of reduced flavones from γ-pyrones to probe biological performance diversity," *ACS Chemical Biology*, vol. 14, no. 7, pp. 1536–1545, 2019.

[31] C. Y. Jia, J. Y. Li, G. F. Hao, and G. F. Yang, "A drug-likeness toolbox facilitates ADMET study in drug discovery," *Drug Discovery Today*, vol. 25, no. 1, pp. 248–258, 2020.

[32] D. F. Veber, S. R. Johnson, H. Y. Cheng, B. R. Smith, K. W. Ward, and K. D. Kopple, "Molecular properties that influence the oral bioavailability of drug candidates," *Journal of Medicinal Chemistry*, vol. 45, no. 12, pp. 2615–2623, 2002.

[33] P. R. Andrews, D. J. Craik, and J. L. Martin, "Functional group contributions to drug-receptor interactions," *Journal of Medicinal Chemistry*, vol. 27, no. 12, pp. 1648–1657, 1984.

[34] D. E. Clark, "Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. 1. Prediction of intestinal absorption," *Journal of Pharmaceutical Sciences*, vol. 88, no. 8, pp. 807–814, 1999.

[35] M. Bitew, T. Desalegn, T. B. Demissie, A. Belayneh, M. Endale, and R. Eswaramoorthy, "Pharmacokinetics and drug-likeness of antidiabetic flavonoids: molecular docking and DFT study," *PLoS One*, vol. 16, no. 12, Article ID e0260853, 2021.

[36] H. Zhang, H. Xu, C. R. Ashby, Y. G. Assaraf, Z. Chen, and H. Liu, "Chemical molecular-based approach to overcome multidrug resistance in cancer by targeting P-glycoprotein (P-gp)," *Medicinal Research Reviews*, vol. 41, no. 1, pp. 525–555, 2021.

[37] Y. C. Martin, "A bioavailability score," *Journal of Medicinal Chemistry*, vol. 48, no. 9, pp. 3164–3170, 2005.

[38] S. N. Bolz, M. F. Adasme, and M. Schroeder, "Toward an understanding of pan-assay interference compounds and promiscuity: a structural perspective on binding modes," *Journal of Chemical Information and Modeling*, vol. 61, no. 5, pp. 2248–2262, 2021.

[39] R. Brenk, A. Schipani, D. James et al., "Lessons learnt from assembling screening libraries for drug discovery for neglected diseases," *ChemMedChem*, vol. 3, no. 3, pp. 435–444, 2008.

[40] C. Nastasă, R. Tamaian, O. Oniga, and B. Tiperciuc, "5-Arylidene (chromenyl-methylene)-thiazolidinediones: potential new agents against mutant oncoproteins K-Ras, N-Ras and B-Raf in colorectal cancer and melanoma," *Medicina*, vol. 55, no. 4, p. 85, 2019.

[41] R. F. Bruns and I. A. Watson, "Rules for identifying potentially reactive or promiscuous compounds," *Journal of Medicinal Chemistry*, vol. 55, no. 22, pp. 9763–9772, 2012.

[42] A. K. Singh, M. Bilal, D. Barcelo, and H. M. Iqbal, "A predictive toolset for the identification of degradation pattern and toxic hazard estimation of multimeric hazardous compounds persists in water bodies," *Science of the Total Environment*, vol. 824, Article ID 153979, 2022.