Design, Molecular Docking, Synthesis, Anticancer and Anti-Hyperglycemic Assessments of Thiazolidine-2,4-diones Bearing Sulfonylthiourea Moieties as Potent VEGFR-2 Inhibitors and PPARγ Agonists

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Abstract: Newly designed thiazolidine-2,4-diones 3–7a–c were synthesized, and their anticancer activities were screened against three cancer lines. They showed potent activities against HepG2 compared to the other HCT116 and MCF-7 tumor cell lines. Compounds 7c and 6c were detected as highly effective derivatives against MCF-7 (IC50 = 7.78 and 8.15 μM), HCT116 (IC50 = 5.77 and 7.11 μM) and HepG2 (IC50 = 8.82 and 8.99 μM). The highly effective derivatives 6a–c and 7a–c were tested against VERO normal cell lines. All derivatives were evaluated for their VEGFR-2 inhibitory actions and demonstrated high to low activities, with IC50 values varying from 0.08 to 0.93 μM. Moreover, derivatives 5a–c, 6a–c and 7a–c were assessed to verify their in vitro binding affinities to PPARγ and insulin-secreting activities. Finally, docking studies were performed to explore their affinities and binding modes toward both VEGFR-2 and PPARγ receptors.

Keywords: anti-hyperglycemic; VEGFR-2 inhibitors; docking; PPARγ; sulfonylthiourea; thiazolidine-2,4-dione

1. Introduction

Thiazolidinediones are widely found throughout nature in various forms. Thiazolidinedione nucleus is present in numerous biological compounds, e.g., antidiabetic [1], anticancer [2], anti-malarial, antimicrobial, anti-mycobacterium [3], anticonvulsant [4], antiviral, anti-HIV (human immunodeficiency virus) [5], anti-inflammatory [6] and antioxidant agents [7].
Thiazolidine-2,4-diones (TZDs) have been described to have anticancer effects in a broad range of cancers [8–10]. TZDs are PPARγ (PPAR-gamma) activators used for type-2 diabetes treatment. Recently, PPAR gamma ligands (TZDs) were proved to exhibit anticancer effects by disturbing cell differentiation, proliferation, and cycle and apoptosis, and were also proven to hinder tumor angiogenesis. The antiangiogenic activity of TZDs is attributed to its inhibition of endothelial cell proliferation and reduction of the production of vascular endothelial growth factors. As it is assumed that the anticancer activity of TZDs is mediated through PPARγ activation, they have been clinically tested against human cancers that express high levels of PPARγ [11,12].

The well-known PPAR-γ agonist rosiglitazone (RGZ) (I) has been widely clinically used because of its significant function lipid, glucose metabolism and energy homeostasis regulation. PPAR-γ is broadly spread in HepG2 cells. RGZ was confirmed to present a transcription factors activity regulator that is critical for apoptosis. In addition, RGZ was used in leukemia and lung cancer cells to induce apoptosis [13].

PPAR-γ is expressed in both malignant and normal mammary epithelial cells. Breast carcinoma proliferation was suppressed by TZDs in vitro and in experimental animals. In addition, the conjugated linoleic acid activation of PPAR-γ has an antiproliferative effect in MCF7 breast cancer. Moreover, the preponderance of evidence among studies investigating the effects of TZDs against breast cancer suggests that both in vivo and in vitro apoptosis induction and inhibition of angiogenesis, proliferation, and invasion are performed by PPAR-γ ligands. In colon cancer, the TZD, pioglitazone (II), inhibited the cell proliferation in a dose-dependent manner [14].

Rosiglitazone (I) and pioglitazone (II) suppress the expression of VEGF via a responsive element for PPAR-γ in the VEGF gene promoter [15]. However, several TZD derivatives, e.g., ciglitazone III and compound (IV), have also been reported to be effective as antiangiogenic and antineoplastic agents through VEGFR-2 targeting [16–24] by reducing the in vitro model of VEGF production [20]. The VEGFR-2 receptor is the most important antiangiogenic target due to its crucial role in cancer angiogenesis. Several effective inhibitors of VEGFR-2 have been developed and approved as antiangiogenic agents for different cancer medicines, for example, pazopanib (V) [25,26] and sorafenib (Nexavar)® (VI) [27–29] (Figure 1).

![Approved inhibitors of VEGFR-2](image)

**Figure 1.** Approved inhibitors of VEGFR-2.

Pancreatic β-cells contain sulfonylurea receptors, which are the second receptor involved in diabetes management. The binding of Sulfonylureas (SUs) and sulfonylthioureas with sulfonylurea receptors stimulates insulin secretion [30,31]. Glipizide (VII) and glimepiride (VIII) (Figure 2) are sulfonylureas containing an amidic group which interacts with SURs B site [32]. Moreover, some second- and third-generation sulfonylureas have been reported to act through SURs and PPARγ to exert their clinical efficacy [33–35].
According to the abovementioned facts, and to obtain novel multi-target anti-cancer drugs, a new series of thiazolidinediones-sulfonylthiourea hybrid was synthesized as potent PPARγ agonists and VEGFR-2 inhibitors. Moreover, the same hybrids were designed as dual SURs and PPARγ agonists for antihyperglycemic activity.

1.1. Structure-Based Design Rationale

1.1.1. As Anticancer Agents

In continuance of our earlier works in the scope of the design and syntheses of novel anticancer medicines [36–44], particularly VEGFR-2 inhibitors [45–54], thiazolidine-2,4-diones bearing sulfonylthiourea moieties were synthesized to obtain the four keys of VEGFR-2 inhibitors pharmacophoric features (Figure 3) [55–57]. The focus of the current study was to utilize the lead modification approach for sorafenib, a potent VEGFR-2 inhibitor, to obtain
novel potent inhibitors. Modification was selected to cover the four main parts of sorafenib, with the aim of obtaining strongly active derivatives. The first site of modification was the “hinge-binding” head, in which the sorafenib pyridine ring was modified to a thiazolidine-2,4-dione one. Regarding the “Linker” part, an N-phenylacetamide moiety was the central aryl linker ring used in our design. With respect to the “hydrogen-bonding moiety,” the urea moiety of sorafenib was herein extended to be a sulfonylthiourea target to enhance VEGFR-2 binding affinities. Lastly, the hydrophobic tail of sorafenib was substituted by other different hydrophobic groups, including ethyl, phenyl and/or cyclohexyl groups.

Figure 3. Pharmacophoric requirements and structural similarities of VEGFR-2 inhibitors and our derivatives.
Finally, examining several inhibitors bound to VEGFR-2, X-ray analysis proved the presence of an additional available space for various substituents around the terminal hetero aromatic ring [58,59]. This finding encourages us to design extra phenyl and/or 4-methylphenyl groups to occupy this space, aiming to increase the binding activities with the receptor as in compounds 6a–c and 7a–c, respectively.

1.1.2. As Antidiabetic Agents

The basic structural requirements of PPARγ are similar to that of SUR agonists, which drove us to design new thiazolidine-2,4-diones bearing sulfonylthiourea comprising both requirements (Figure 2). The thiazolidine-2,4-diones head is required for PPARγ agonistic activity. Sulfonylthiourea moieties were introduced to our derivatives, providing both SUR and PPARγ agonistic actions [60]. Aliphatic and aromatic substituents on sulfonylthiourea moieties act as lipophilic centers essential for agonistic action on SUR. Furthermore, the sulfamoyl NH group is completely ionized at physiological pH due to its acidity (pKa = 4.9–6.5) [61]. This ionization provides the anionic linker that is markedly required for SUR agonists [62]. Different linkers between the aromatic moieties (spacer groups) and lipophilic tails were prepared to study their effects on SAR of the new derivatives. These linkers are also important for the agonistic action of PPARγ. On the other hand, they contain the amide(-CONH-) group necessary for interaction with the SURs B site [56].

Based on previous findings, new thiazolidine-2,4-diones-sulfonylthiourea hybrids were designed and synthesized to obtain new multi-target antihyperglycemic agents (Figure 2).

2. Results and Discussion

2.1. Chemistry

In Schemes 1 and 2, the reactions sequence for the preparation of our target compounds is demonstrated. The sequence starts with chloroacetic acid and thiourea cyclocondensation to obtain thiazolidine-2,4-dione (1) [16–18], which undergoes Knoevenagel condensation [16–18] to provide the corresponding derivatives (2a,b). The heating of (1) and/or 2a,b with 2-chloro-N-(4-sulfamoylphenyl)acetamide under reflux provided the corresponding acetamide derivatives 3 and/or 4a,b, respectively (Scheme 1). On the other hand, 2-chloro-N-(4-sulfamoylphenyl)acetamide was synthesized according to the directions of Jacobs and Heidelberger [63]. Subsequent heating of 3 and/or 4a,b with the appropriate isothiocyanate under reflux provided the corresponding sulfonylthiourea derivatives 5a–c, 6a–c and/or 7a–c, respectively (Scheme 2).

2.2. Docking Studies

Molsoft software was applied for the molecular docking studies. All experiments utilized VEGFR-2 and PPARγ (PDB ID 4ASD) [64], and (PDB ID 3CS8) [65], respectively.

2.2.1. Docking Studies as VEGFR-2 Inhibitors

The achieved results showed that all studied congeners showed similar orientations and positions inside the identified VEGFR-2 active site (Figure 4). Calculating the binding free energies of (ΔG) of the docked members explained their high binding affinities to the receptor, and the total trend was indicated by the calculated values (Table 1).
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#### Scheme 1. The target compounds 3–4a,b synthetic pathway.

#### Table 1. The ligands binding free energy (calculated) (ΔG in Kcal/mole).

| Compound | ΔG [kcal mol⁻¹] | Compound | ΔG [kcal mol⁻¹] |
|----------|----------------|----------|----------------|
| 3        | −90.00         | 6b       | −126.72        |
| 4a       | −92.62         | 6c       | −130.36        |
| 4b       | −98.37         | 7a       | −125.48        |
| 5a       | −115.75        | 7b       | −129.68        |
| 5b       | −121.80        | 7c       | −138.79        |
| 5c       | −125.96        | Sorafenib | −110.12       |
| 6a       | −118.64        |          |                |

The suggested binding mode of sorafenib showed an affinity value of −110.12 kcal/mol and formed five H-bonds. It formed two H-bonding interactions with Cysteine919 (2.51 Å and 2.10 Å), two H-bonds with Glutamate885 (1.77 Å and 2.75 Å) and one H-bonding interaction with Aspartate1046 (1.50 Å). The N-methylpicolinamide group occupied the pocket produced by Leucine1035, Lysine920, Cysteine919, Phenylalanine918, Glutamate917, Valine848 and Leucine840. Furthermore, the central phenyl linker occupied the hydrophobic groove produced by Cysteine1045, Leucine1035, Threonine916, Lysine868 and Valine848. In addition, the terminal 3-trifluromethyl-4-chlorophenyl group occupied the hydrophobic channel formed by Aspartate1046, Cysteine1045, Histidine1026, Isoleucine892, Isoleucine888 and Glutamate885 (Figure 5). The urea linker had a significant function in the binding with VEGFR-2 enzyme. However, the linker was responsible for the high binding affinity of sorafenib. These conclusions led us to use the sulfonylthiourea linker to obtain effective VEGFR-2 inhibitors.
Scheme 2. The target compounds 5–7a–c synthetic pathway.

Compound 7c and sorafenib had virtually the same binding mode, which showed seven H-bonds and an affinity value of $-138.79$ kcal/mol. The sulfone moiety of the sulfonylethiourea linker was stabilized by the construction of one H-bond with Aspartate1046 (1.82 Å) and four H-bonds with Lysine868 (0.83 Å, 1.50 Å, 2.21 Å and 2.66 Å), but its NH group formed another H-bond with Glutamate885 (2.38 Å). Moreover, the C=O group at position-2 of the thiazolidine-2,4-dione moiety established one H-bond with Cysteine919 (1.59 Å). The 4-methylphenyl group occupied the hydrophobic space around the terminal thiazolidine-2,4-dione ring formed by Lysine920, Leucine840 and Lysine838. Furthermore, the thiazolidine-2,4-dione group inhabited the hydrophobic ATP binding pocket produced by Leucine1035, Cysteine919, Phenylalanine918 and Leucine840. The central hydrophobic phenyl resides in the hydrophobic pocket produced by Aspartate1046, Cysteine1045, Leucine1035, Valine916, Lysine868 and Valine865. Moreover, the distal cyclohexyl cycle inhabited the hydrophobic groove produced by Cysteine1045, Histidine1026, Isoleucine892, Isoleucine888 and Glutamate885 (Figure 6). Compound 7c interactions may clarify its greatest anticancer action.
Figure 4. Superimposition of compounds 4b, 6b, 6c, 7b and 7c inside the active site of 4ASD.

Figure 5. Sorafenib with the 4ASD predicted binding mode. H-bonded atoms are designated by dotted lines.
Figure 6. 7c with the 4ASD predicted binding mode.

The suggested 6c binding mode was similar to 7c, with −130.36 kcal/mol. 6c formed six H-bonds with Lysine868 (1.84 Å and 2.52 Å), Aspartate1046 (2.17 Å and 2.92 Å), Glutamate885 (2.73 Å) and Cysteine919 (1.81 Å) (Figure 7).

Figure 7. 6c with the 4ASD predicted bind mode.

The obtained docking results (Table 1) revealed that the sulfonylthiourea linkers played an essential role in the greater affinities for the VEGFR-2 enzyme. The affinities toward the VEGFR-2 enzyme were increased as result of the benzylidene hydrophobic interactions. The thiazolidine-2,4-dione facilitated the novel targets to form H-bonds with Cysteine919. Structure extension was an essential factor in the inhibitory action to VEGFR-2.
2.2.2. Docking Studies as PPARγ Agonists

The achieved results revealed that all studied compounds exhibited similar orientations and positions within the identified binding site of PPARγ (Figure 8). The results of the binding free energy (\(\Delta G\)) showed that the majority of these compounds showed high receptor binding affinities, and the computed values indicated a global trend (Table 2).

![Figure 8. Rosiglitazone, 6c, 7b and 7c docked compounds superimposition in the active site of 3CS8.](image)

| Compound | \(\Delta G\) [kcal mol\(^{-1}\)] | Compound | \(\Delta G\) [kcal mol\(^{-1}\)] |
|----------|----------------------------------|----------|----------------------------------|
| 3        | −84.12                           | 6b       | −118.03                          |
| 4a       | −92.97                           | 6c       | −128.20                          |
| 4b       | −91.92                           | 7a       | −125.77                          |
| 5a       | −108.58                          | 7b       | −125.42                          |
| 5b       | −111.97                          | 7c       | −132.78                          |
| 5c       | −119.97                          | Rosiglitazone | −94.38                           |
| 6a       | −115.47                          |          |                                  |

The suggested binding manner of rosiglitazone showed an affinity value of \(-94.38\) kcal/mol and five H-bonds. The thiazolidine-2,4-dione established three H-bonds with Serine289 (2.83 Å, 2.91 Å and 2.97 Å) and one H-bond with Arginine288 (2.44 Å). The linker oxygen atom formed one H-bond with Cysteine285 (2.96 Å). The central phenyl inhabited the hydrophobic channel produced by Arginine288, Cysteine285, Phenylalanine363, Phenylalanine282 and Isoleucine341. Moreover, the aminoethoxy linker inhabited the hydrophobic pocket produced by Phenylalanine282, Isoleucine281 and Isoleucine341. In addition, the cyclic pyridine tail inhabited the hydrophobic pocket produced by Isoleucine281, Isoleucine341, Lysine261 and Isoleucine249 (Figure 9).
Compound 7c represented nearly a similar binding mode as rosiglitazone, which showed an affinity value of $-132.78$ kcal/mol and five H-bonds. It formed two H-bonding interactions with Serine289 (2.09 Å and 2.96 Å), one H-bond with Cysteine285 (2.47 Å) and two H-bonds with Isoleucine281 (1.92 Å and 2.49 Å). The 4-methylphenyl moiety was placed in the hydrophobic space around the terminal thiazolidine-2,4-dione ring formed by Phenylalanine363, Histidine449 and Phenylalanine282. The central hydrophobic phenyl ring was located in the formed hydrophobic pocket by Arginine288, Cysteine285, Phenylalanine363, Phenylalanine282 and Isoleucine341. Furthermore, the cyclohexyl tail was positioned in the hydrophobic furrow formed by Isoleucine281, Isoleucine341, Lysine261 and Isoleucine249 (Figure 10).
Compound 6c had virtually the same binding mode as 7c, with −128.20 kcal/mol. Compounds 6c and 7c and formed four H-bonds with Serine289 (2.78 Å and 2.98 Å) and one H-bond with Cysteine285 (2.66 Å, 2.96 Å) (Figure 11).

From the achieved results of docking (Table 2), we assumed that the sulfonylthiourea linkers displayed an essential role for higher affinities toward the PPARγ enzyme. In addition, the benzylidene moieties enhanced hydrophobic interactions and, accordingly, affinities for the PPARγ enzyme.

2.3. In Vitro Cytotoxic Activity

The novel prepared thiazolidine-2,4-diones 3–7a–c, antiproliferative activity was inspected against three human tumor cell lines—MCF-7, HepG2 and HCT-116—by means of MTT colorimetric assay, as defined by Mosmann [66]. Doxorubicin and sorafenib were included in the experiments as standards. In Table 3, the results are presented as IC50 values (50% inhibitory concentration). The achieved findings clarified that the majority of the synthesized congeners exhibited modest to excellent growth inhibitory activity toward the checked tumor cell lines. Generally, observing the cytotoxic activity showed that HepG2 was the most susceptible cell line to the impact of the novel compounds. Compounds 7c and 6c were the most effective compounds against the MCF-7 (IC50 = 7.78 and 8.15 µM), HCT116 (IC50 = 5.77 and 7.11 µM) and HepG2 (IC50 = 8.82 and 8.99 µM) tumor cell lines. Compounds 7c and 6c exhibited lower activities than sorafenib (IC50 = 7.26, 5.47 and 9.18 µM) against MCF-7 and HCT116 but higher activities against HepG2, respectively. However, these compounds demonstrated lower actions than doxorubicin (IC50 = 6.75, 8.07 and 7.94 µM) against the three cell lines, respectively. Regarding HepG2, compounds 7b, 6b, 7a and 6a exhibited the greatest anticancer effects, with IC50 = 9.65, 10.67, 12.05 and 14.16 µM, respectively. Derivatives 5c, 5b and 5a, with IC50 = 20.75, 21.99 and 24.49 µM, respectively, showed potent cytotoxicity. Derivatives 4b, 4a and 3, with IC50 = 48.56, 52.87 and 58.55 µM, respectively, exhibited moderate cytotoxicity.
Table 3. Novel prepared derivatives in vitro cytotoxicity against HepG2, HCT-116, MCF-7 and VERO cell lines, and VEGFR-2 kinase assay.

| Compound | HepG2 (µM) | HCT116 (µM) | MCF-7 (µM) | VERO (µM) | VEGFR-2 (µM) |
|----------|------------|-------------|------------|-----------|--------------|
| 3        | 58.55 ± 5.1| 61.48 ± 5.1 | 60.18 ± 5.1| b NT      | 0.93± 0.06   |
| 4a       | 52.87 ± 5.1| 55.12 ± 5.1 | 54.99 ± 5.1| b NT      | 0.92 ± 0.06  |
| 4b       | 48.56 ± 5.1| 57.87 ± 5.1 | 62.43 ± 5.1| b NT      | 0.89 ± 0.06  |
| 5a       | 24.49 ± 2.2| 40.11 ± 2.2 | 28.79 ± 2.2| b NT      | 0.46 ± 0.05  |
| 5b       | 21.99 ± 2.0| 25.68 ± 2.0 | 23.24 ± 2.0| b NT      | 0.44 ± 0.05  |
| 5c       | 20.75 ± 2.6| 23.56 ± 2.6 | 24.59 ± 2.6| b NT      | 0.44 ± 0.05  |
| 6a       | 14.16 ± 2.3| 17.65 ± 2.3 | 16.47 ± 2.3| 48.31 ± 0.22| 0.17 ± 0.02 |
| 6b       | 10.67 ± 1.6| 13.78 ± 1.2 | 12.95 ± 1.2| 40.88 ± 0.22| 0.15 ± 0.02 |
| 6c       | 8.99 ± 1.2 | 7.11 ± 1.7  | 8.15 ± 1.6 | 49.26 ± 0.22| 0.08 ± 0.02 |
| 7a       | 12.05 ± 1.5| 16.79 ± 1.5 | 16.66 ± 1.5| 60.12 ± 0.18| 0.14 ± 0.02 |
| 7b       | 9.65 ± 1.7  | 13.48 ± 1.6 | 12.89 ± 1.7| 52.61 ± 0.22| 0.11 ± 0.02 |
| 7c       | 8.82 ± 1.9  | 5.77 ± 1.9  | 7.78 ± 1.9 | 68.25 ± 0.21| 0.08 ± 0.02 |
| Sorafenib| 9.18 ± 0.6  | 5.47 ± 0.3  | 7.26 ± 0.3 | b NT      | 0.10 ± 0.02 |
| Doxorubicin| 7.94 ± 0.6  | 8.07 ± 0.8  | 6.75 ± 0.4 | b NT      | b NT         |

a IC₅₀ = mean ± S.D. of triplet separate experiments. b NT: Derivatives not assessed as VEGFR-2 inhibitors.

Derivatives 7b, 6b, 7a and 6a exhibited the greatest anticancer effects, with IC₅₀ = 13.48, 13.78, 16.79 and 17.65 µM, respectively, against HCT-116. Moreover, derivatives 5c and 5b, with IC₅₀ = 23.56 and 25.68 µM, respectively, showed potent cytotoxic effects. Derivatives 5a, 4a and 4b, with IC₅₀ = 40.11, 55.12 and 57.87 µM, respectively, demonstrated moderate cytotoxic action. Derivative 3, with IC₅₀ = 61.48 µM, showed the lowest cytotoxic activity.

Derivatives 7b, 6b, 6a and 7a exhibited the greatest anticancer effects, with IC₅₀ = 12.89, 12.95, 16.47 and 16.66 µM, respectively, upon assessment against MCF-7. Derivatives 5b, 5c and 5a, with IC₅₀ = 23.24, 24.59 and 28.79 µM respectively, showed great cytotoxic effects. Derivative 4a, with IC₅₀ = 54.99 µM, showed mild cytotoxicity. Derivatives 3 and 4b, with IC₅₀ = 60.18 and 62.43 µM, demonstrated mild cytotoxic action.

In the end, the highly effective candidates, 6a–c and 7a–c, were assessed against VERO normal cell lines to evaluate their cytotoxic effects. The outcomes showed that the assessed candidates possessed weak toxicity against normal VERO cells, with IC₅₀ values ranging from 40.88 to 68.25 µM. The cytotoxic effects of the prepared derivatives against the malignant cell lines ranged from 5.77 to 17.65 µM. Derivatives 6a–c and 7a–c were, respectively, 3.41-, 3.83-, 6.93-, 4.99-, 5.45- and 7.74-fold times more toxic against HepG2 than normal VERO cells. Similarly, derivatives 6a–c and 7a–c were, respectively, 2.74-, 2.97-, 6.04-, 3.58-, 3.90- and 11.83-fold more toxic in HCT-116 than in normal VERO cells. Moreover, compounds 6a–c and 7a–c were, respectively, 2.93-, 3.16-, 4.85-, 3.61-, 4.08- and 8.77-fold times higher toxicity in MCF-7 than in normal VERO cells.

2.4. In Vitro Assay of VEGFR-2 Kinase

In addition, our compounds were assessed for their VEGFR-2 inhibitory effects by applying an anti-phosphotyrosine antibody with the Alpha Screen system (PerkinElmer, Waltham, MA, USA) [67,68]. The results are described as IC₅₀ (50% inhibition concentration value) in Table 3. In this assessment, sorafenib was applied as a positive standard. The assessed derivatives demonstrated high to low inhibitory effects, with IC₅₀ values varying from 0.08 to 0.93 µM. Derivatives 7c and 6c were observed to be the highest effective derivatives that inhibited VEGFR-2 at the same IC₅₀ = 0.08 µM. Compound 7b displayed great activity with IC₅₀ = 0.11 µM. Moreover, compounds 7a, 6b and 6a possessed high VEGFR-2 inhibition, with IC₅₀ = 0.14, 0.15 and 0.17 µM, respectively. Derivatives 5a–c displayed moderate VEGFR-2 inhibitory effects, with IC₅₀ = 0.46, 0.44 and 0.44 µM, respectively. Candidates 3, 4a and 4b showed lower VEGFR-2 inhibitory effects, with IC₅₀ = 0.93, 0.92 and 0.89 µM, respectively.
2.5. In Vitro Binding Assay of PPARγ Ligand

Derivatives with effective cytotoxic activities (5a–c, 6a–c and 7a–c) were additionally assessed to evaluate their PPARγ in vitro binding affinities. The binding capabilities of our new target compounds with PPARγ were evaluated using the Fluorescence Polarization Assessment technique [69]. Rosiglitazone was applied as standard with IC\text{50} = 0.292. Table 4 shows a comparison of the IC\text{50} values of the tested derivatives. Candidates 7c and 6c substantially bound to PPARγ, with IC\text{50} = 0.296 and 0.300 \mu M, respectively. Moreover, compounds 6a, 6b, 7a and 7b exhibited strong binding affinities toward PPARγ, with IC\text{50} = 0.323, 0.308, 0.320 and 0.305 \mu M, respectively. Alternatively, compounds 5a, 5b and 5c moderately demonstrated PPARγ binding affinities, with IC\text{50} = 0.393, 0.377 and 0.360 \mu M, respectively.

Table 4. In vitro PPARγ binding affinities and insulin-secreting activities of the new derivatives and standard drugs.

| Comp. | IC\text{50} (\mu M) | PPAR\gamma Binding Affinity | EC\text{50} (\mu M) | Insulin Secreting Activity |
|-------|---------------------|------------------------------|---------------------|---------------------------|
| 5a    | 0.393               | 1.20                         |                     |                           |
| 5b    | 0.377               | 1.13                         |                     |                           |
| 5c    | 0.360               | 1.00                         |                     |                           |
| 6a    | 0.323               | 0.87                         |                     |                           |
| 6b    | 0.308               | 0.78                         |                     |                           |
| 6c    | 0.300               | 0.70                         |                     |                           |
| 7a    | 0.320               | 0.81                         |                     |                           |
| 7b    | 0.305               | 0.75                         |                     |                           |
| 7c    | 0.296               | 0.70                         |                     |                           |
| Rosiglitazone | 0.292              | NT d                         |                     |                           |
| Glimiperide  | NT d               | 0.73                         |                     |                           |

\textsuperscript{a} All results are within 10\% (n = 3). \textsuperscript{b} Concentration of the tested derivatives required to displace 50\% of the titrated ligand. \textsuperscript{c} Concentration needed to make 50\% of the maximum action.

2.6. In Vitro Insulin Assay

Compounds 5a–c, 6a–c and 7a–c were also assessed to establish their insulin-secretion activities in vitro against isolated pancreatic islets of rats through the quantitative sandwich technique of enzyme immunoassay [70]. Glimiperide was applied as the standard. The findings are described as the EC\text{50} values (Table 4).

The assessed derivatives showed high to moderate insulin-secreting activities within a range of EC\text{50} values from 0.70 to 1.20 \mu M. Glimiperide demonstrated EC\text{50} = 0.73 \mu M. Derivatives 7c and 6c displayed effective insulin-secretion activities with the same EC\text{50} = 0.70 \mu M. In addition, compounds 6a, 6b, 7a and 7b showed good activities, with EC\text{50} = 0.87, 0.78, 0.81 and 0.75 \mu M, respectively. Conversely, derivatives 5a, 5b and 5c showed moderate activities, with EC\text{50} = 1.20, 1.13 and 1.00 \mu M, respectively.

2.7. SAR (Structure Activity Relationship)

The primary SAR analysis concerned the influence of the substitution of sorafenib urea linker by sulfonethylurea linkers, which acted as H-bond acceptors and H-bond donors. These linkers interacted with Aspartate1044 and Glutamate883. Similarly, hydrophobic interactions occurred via the hydrophobic distal moieties. The impact of the substitution of sorafenib azine moiety by the thiazolidine-2,4-dione scaffold of the prepared derivatives on the anticancer actions was also observed. These thiazolidine-2,4-dione moieties inhabited the hydrophobic ATP binding pocket, which was inhabited by the azine moiety of sorafenib and formed H bonding interactions with Cysteine919. Alternatively, various phenyl and aliphatic moieties were established to replace the reference phenyl tail with various electronic and lipophilic natures to examine their action on the antitumor activity. The existence of cyclohexyl tails connected to the sulfonethylurea linkers and distal benzylidene moieties attached to thiazolidine-2,4-diones, as in derivatives 7c and 6c,
increased affinities toward the active position, respectively (Figure 12). In addition, the 4-methylbenzylidene derivatives 7a–c displayed greater actions than the unsubstituted derivatives 6a–c and thiazolidine 2,4-diones without benzylidene distal moieties 5a–c, respectively. The obtained results showed that the examined derivatives demonstrated various levels of antitumor effects and had a distinguished selectivity model against the HepG2 cell lines. Commonly, the linkers (HBD-HBA), of an electronic and lipophilic nature, displayed a vital role in antitumor activity. From the structure of our compounds and the results presented in Table 3, we can allocate these checked derivatives into three groups. In the first group, containing 5a–c, the thiazolidine 2,4-dione nucleus did not bind to any hydrophobic distal benzylidene moieties. Derivative 5c and 5b with a cyclohexyl and phenyl tail, respectively, showed greater actions than derivative 5a with ethyl ones against the three cell lines (HepG2, HCT116 and MCF-7). In the second group, containing 6a–c, derivative 6c with a cyclohexyl tail showed greater effects than derivatives 6b and 6a with phenyl and ethyl tails against both HCT116 and MCF-7. Moreover, in the third group, containing 7a–c, candidate 7c with a cyclohexyl tail demonstrated higher activities than candidates 7b and 7a with phenyl and ethyl tails against both HCT116 and MCF-7.

Figure 12. Graphical summary of the SAR study.

2.8. ADMET, in Silico Studies Profile

An in silico report of the highly active derivatives 6c, 7b and 7c was conducted to evaluate their physicochemical characters and calculate their proposed ADMET profiles. The report was predicted using SwissADME and pkCSM descriptors algorithm procedures [71] and matched to rule of five described by Lipinski [72]. Good absorption properties were expected for the molecules that accomplished at least three rules: (i) hydrogen bond donors are not more than five; (ii) partition coefficient (logP) is not more than 5, (iii) molecular weight less than 500, (iv) hydrogen bond acceptors are not more than 10. In the current work, the standard anticancer agent sorafenib and our new compounds 6c, 7b and 7c violate only one rule. In addition, the ADMET profiles of the three new compounds were initially calculated for their potential evaluation as good drugs.

Considering the obtained data (Table 5), we can assume that these three compounds have good GIT absorption in humans (74.229–76.168), which indicates that they can easily cross different biological membranes [73]. Therefore, they may show a significant high bioavailability through GIT. Concerning CNS penetrability, our prepared compounds have the capability to reach CNS (CNS permeability values −2.254 to −2.529). The CNS permeability values were lower than sorafenib (CNS permeability −2.007) but higher than rosiglitazone (CNS permeability −2.72).
It well known that CYP3A4, the major drug-metabolizing enzyme, can be inhibited by sorafenib and 7b but 6c, 7c and rosiglitazone cannot be. This can be attributed to the superior lipophilicity of sorafenib and 7b. Elimination was expected depending on the total clearance, which is a considerable factor in deciding dose intervals. The data showed that rosiglitazone confirmed higher clearance rates compared to sorafenib and our new compounds, which demonstrated very low clearance values. Thus, rosiglitazone could be eliminated more quickly. As a result, rosiglitazone is supposed to have shorter dosing intervals. Unlike rosiglitazone, the prepared compounds exhibited a slow clearance rate, which signifies a longer duration of action and extended dosing intervals. Toxicity is the final studied ADMET profile factor. As presented in Table 5, sorafenib, rosiglitazone and the novel compounds shared the drawback of unwanted hepatotoxic actions. Rosiglitazone, 6c and 7b demonstrated the lowest maximum tolerated doses. In contrast, sorafenib and 7b demonstrated the highest maximum tolerated doses, which involve the advantage of the broad therapeutic index of sorafenib and 7b, respectively. The oral acute toxic dose (LD50) of the novel compound is the least one (2.306), while 6c and 7c showed higher oral acute toxic doses than sorafenib but lower than rosiglitazone. Lastly, compared to rosiglitazone,
the low-down Minnow toxicity results of the new compounds 6c, 7c and sorafenib indicate their excellent selectivity toward tumor cells over normal cells.

3. Materials and Methods
3.1. Chemistry
3.1.1. General

The starting and intermediate derivatives, thiazolidine-2,4-dione (1), 5-benzylidenethiazolidine-2,4-dione (2a,b) [22,24] and 2-chloro-N-(4-sulfamoylphenyl)acetamide [63], were synthesized according to the reported procedures. All compounds were crystallized from ethanol, and their NMR spectra were obtained in DMSO-d6 solvent at 400 MHz for 1HNMR and 100 MHz for 13CNMR. NMR and mass data are provided in the Supplementary Materials.

3.1.2. General Procedure for Synthesis of 2-(2,4-Dioxothiazolidin-3-yl)-N-(4-Sulfamoylphenyl)Acetamide (3)

Equimolar quantities of thiazolidine-2,4-dione 1 (1.17 g, 0.01 mol), 2-chloro-N-(4-sulfamoylphenyl)acetamide (2.34 g, 0.01 mol) and potassium carbonate (1.5 g, 0.011 mol) in acetone (50 mL) were heated under reflux for 15 h. The reaction mixture was filtered while hot. The filtrate was allowed to cool to room temperature to obtain compound 3. Yield, 82%; m.p. 217–9°C; IRνmax (cm⁻¹): 3402, 3294 (NH & NH2), 3062 (CH aromatic), 2958 (CH aliphatic), 1701, 1666 (3C = O amide), 1311, 1161 (SO₂); 1HNMR δ (ppm): 4.22 (s, 2H, NCH₂), 4.72 (s, 2H, SCH₂), 7.29 (s, 2H, NH₂) (D₂O exchangeable), 7.41–7.93 (m, 4H, aromatic ring) and 10.94 (s, 1H, NH) (D₂O exchangeable); 13CNMR: 23.12, 46.27, 120.98 (2), 130.35 (2), 130.72, 153.44, 154.80, 156.38, 168.06; MS (m/z): 330 (M⁺ + 1, 15.18%), 329 (M⁺, 9.41%), 271 (26.92%), 131 (100%, base beak), 129 (55.67); Anal. Calcd. for C11H11N3O5S2 (329.0): C, 40.12; H, 3.37; N, 12.76. Found: C, 40.11; H, 3.25; N, 12.90.

3.1.3. General Procedure for Synthesis of Compounds (4a,b)

A mixture of 5-benzylidenethiazolidine-2,4-dione 2a,b (0.01 mol), 2-chloro-N-(4-sulfamoylphenyl)acetamide (2.34 g, 0.01 mol) and potassium carbonate (1.5 g, 0.011 mol) in acetone (50 mL) was heated under reflux for 15 h. Then, it was filtered while hot. The filtrate was allowed to cool to room temperature to obtain the target compound 4a,b, respectively.

2-(5-Benzylidene-2,4-dioxothiazolidin-3-yl)-N-(4-sulfamoylphenyl)Acetamide (4a)

Yield, 85%; m.p. 226–8°C; IRνmax (cm⁻¹): 3418, 3332 (NH & NH2), 3036 (CH aromatic), 2958 (CH aliphatic), 1701, 1666 (3C = O amide); 1H NMR δ (ppm): 3.98 (s, 2H, CH₂), 7.25 (s, 2H, NH₂) (D₂O exchangeable), 7.62–7.65 (m, 5H, aromatic ring), 7.71–7.74 (m, 4H, aromatic ring), 7.93 (s, 1H, CH=C) and 10.40 (s, 1H, NH) (D₂O exchangeable); Anal. Calcd. for C18H15N3O5S2 (417.0): C, 51.79; H, 3.62; N, 10.07. Found: C, 51.85; H, 3.74; N, 10.26.

2-(5-(4-Methylbenzylidene)-2,4-dioxothiazolidin-3-yl)-N-(4-sulfamoylphenyl)Acetamide (4b)

Yield, 85%; m.p. 240–2°C; IRνmax (cm⁻¹): 3425, 3232 (NH & NH₂), 3055 (CH aromatic), 2962 (CH aliphatic), 1685, 1670, 1651 (3C=O amide), 1307, 1149 (SO₂); 1H NMR (400 MHz, DMSO-d6) δ (ppm): 2.36 (s, 3H, CH₃), 7.25 (s, 2H, NH₂) (D₂O exchangeable), 7.61–7.65 (m, 5H, aromatic ring), 7.71–7.74 (m, 4H, aromatic ring), 9.37 (s, 1H, CH=CO) and 10.40 (s, 1H, NH) (D₂O exchangeable); Anal. Calcd. for C19H17N3O5S2 (431.1): C, 52.82; H, 3.97; N, 9.74. Found: C, 53.12; H, 4.15; N, 9.94.

3.1.4. General Procedure for Syntheses of Compounds (5a–c)

Equimolar quantities of the benzenesulfonamide 3 (3.29 g, 0.01 mol), the appropriate isothiocyanate, namely ethylisothiocyanate, phenylisothiocyanate and/or cyclohexylisothiocyanate (0.01 mol) and potassium carbonate (2.5 g, 0.018 mol) in acetone (50 mL) were heated for 24 h under reflux. The reaction mixture was filtered to obtain the target sulfonylthioureas 5a–c, respectively.
2-(2,4-Dioxothiazolidin-3-yl)-N-(4-(N-(ethylcarbamothioyl)sulfamoyl)phenyl)acetamide (5a)
Yield, 78%; m.p. 251–3 °C; IR \( \nu_{\text{max}} \) (cm\(^{-1}\)) = 3348, 3313, 3232 (NH), 3059 (CH aromatic), 2962 (CH aliphatic), 1701, 1660, 1643 (3C=O), 1315, 1149 (SO\(_2\)); \(^1\)H NMR δ (ppm): 1.20–1.24 (t, 3H, CH\(_3\)CH\(_2\), J = 7.6 Hz), 3.35 (s, 2H, N-CH\(_2\)), 4.15–4.20 (q, 2H, CH\(_2\)CH\(_3\), J = 7.6 Hz), 4.49 (s, 2H, S-CH\(_2\)), 6.65 (s, 2H, 2NH) (D\(_2\)O exchangeable), 7.33–7.35 (d, 2H, aromatic ring, J = 8 Hz), 7.50–7.52 (d, 2H, aromatic ring, J = 8 Hz), and 10.43 (s, 1H, NH) (D\(_2\)O exchangeable); \(^{13}\)CNMR: 14.33, 21.75 (2), 56.59, 114.56 (2), 116.61, 118.78, 121.76, 123.99, 124.33, 125.58, 128.90, 129.26, 129.32 (2), 129.50 (2), 148.60, 158.33, 171.26; MS (m/z): 505 (+, 30.11 %), 455 (32.58 %), 335 (76.18 %), 292 (100 %, base peak), 259 (82.11 %), 160 (48.17 %); Anal. Calcd. for C\(_{18}\)H\(_{16}\)N\(_4\)O\(_5\)S\(_3\) (546.4): C, 46.54; H, 3.47; N, 12.06. Found: C, 46.73, H, 3.55; N, 12.12.

N-(4-(N-(Cyclohexylcarbamothioyl)sulfamoyl)phenyl)-2-(2,4-dioxothiazolidin-3-yl)acetamide (5c)
Yield, 84%; m.p. 267–9 °C; IR \( \nu_{\text{max}} \) (cm\(^{-1}\)) = 3317, 3244 (NH), 3043 (CH aromatic), 2951 (CH aliphatic), 1708, 1662 (3C=O), 1307, 1149 (SO\(_2\)); \(^1\)H NMR δ (ppm): 0.87–0.91 (t, 3H, CH\(_3\)), 4.02 (s, 4H, 2CH\(_2\)), 6.47–7.90 (m, 11H, 9 aromatic ring & 2NH (D\(_2\)O exchangeable)), and 10.81 (s, 1H, NH) (D\(_2\)O exchangeable); Anal. Calcd. for C\(_{18}\)H\(_{16}\)N\(_4\)O\(_5\)S\(_3\) (464.0): C, 47.63; H, 3.55; N, 11.91. Found: C, 46.73; H, 3.47; N, 11.91.

3.1.4.4. General Procedure for Syntheses of Compounds (6a–c)
Equimolar quantities of the benzyldenesulfonamide 4a (4.17 g, 0.01 mol), the appropriate isothiocyanate, namely ethylisothiocyanate, phenylisothiocyanate and/or cyclohexylisothiocyanate (0.01 mol) and potassium carbonate (0.018 mol) in acetone (50 mL), were heated for 24 h under reflux. The reaction mixture was filtered to obtain the target sulfonothioureas 6a–c, respectively.

2-(5-Benzylidene-2,4-dioxothiazolidin-3-yl)-N-(4-(N-(ethylcarbamothioyl)sulfamoyl)phenyl)acetamide (6a)
Yield, 85%; m.p. 282–4 °C; IR \( \nu_{\text{max}} \) (cm\(^{-1}\)) = 3329, 3259 (NH), 3047 (CH aromatic), 2951 (CH aliphatic), 1708, 1666 (3C=O), 1346, 1145 (SO\(_2\)); \(^1\)H NMR δ (ppm): 0.87–0.91 (t, 3H, CH\(_3\)), 3.18–3.23 (q, 2H, CH\(_2\)), 4.56 (s, 2H, N-CH\(_2\)), 7.36–8.39 (m, 11H, 9 aromatic ring & 2NH (D\(_2\)O exchangeable)), 8.56 (s, 1H, CH = C) and 10.68 (s, 1H, NH) (D\(_2\)O exchangeable); \(^{13}\)CNMR: 14.33, 21.51, 42.56, 62.21, 119.61, 130.30, 130.48 (2), 130.75 (2), 134.65, 141.92, 165.44, 167.19, 167.41; MS (m/z): 554 (M\(^+\), 20.05 %), 552 (18.04 %), 338 (100 %, base peak), 294 (86.01 %), 130 (57.67 %); Anal. Calcd. for C\(_{21}\)H\(_{20}\)N\(_4\)O\(_5\)S\(_3\) (504.6): C, 49.85; H, 4.03; N, 11.05. Found: C, 49.85; H, 4.03; N, 11.05.
2-(5-Benzylidene-2,4-dioxothiazolidin-3-yl)-N-(4-(Cyclohexylcarbamothioyl)sulfamoyl)phenyl)acetamide (6c)

Yield, 75%; m.p. 294–6 °C; IR νmax (cm⁻¹): 3398, 3332, 3275 (3NH), 3059 (CH aromatic), 2924 (CH aliphatic), 1693 (3 C=O), 1315, 1149 (SO₂); ¹H NMR δ (ppm): 1.24–1.93 (m, 10H, cyclohexyl), 4.09 (s, 2H, CH₂), 6.02 (s, 2H, 2NH) (D₂O exchangeable), 7.24–7.99 (m, 9H, aromatic ring), 8.42 (s, 1H, CH=C) and 10.43 (s, 1H, NH) (D₂O exchangeable); ¹³C NMR: 22.87, 24.86, 31.35, 32.78 (2), 46.55 (2), 55.43, 126.4 (4), 127.42 (5), 135.45, 143.09, 156.60 (2), 171.60 (2), 195.20; Anal. Calcd. for C₁₉H₁₈N₂O₅S₃ (558.1): C, 53.75; H, 4.69; N, 10.03.

3.1.4.8. General Procedure for Synthesis of Compounds (7a–c)

Equimolar quantities of the 4-methylbenzylidene sulfonamide 4b (0.01 mol) and potassium carbonate (0.018 mol) in acetone (50 mL), were heated for 24 h under reflux. The reaction mixture was filtered to obtain sulfonylthiourea derivatives 7a–c, respectively.

N-(4-(4-(Ethylcarbamothioyl)sulfamoyl)phenyl)-2-(5-(4-methylbenzylidene)-2,4-dioxothiazolidin-3-yl)acetamide (7a)

Yield, 85%; m.p. 285–7 °C; IR νmax (cm⁻¹): 3336, 3201 (3NH), 3066 (CH aromatic), 2931 (CH aliphatic), 1697 (3C=O), 1315, 1176 (SO₂); ¹H NMR δ (ppm): 0.87–0.93 (t, 3H, CH₃-CH₂), 1.71 (s, 3H, CH₃-phenyl), 3.09 (q, 2H, CH₂-CH₂, J = 5.6 Hz), 3.87 (s, 2H, N-CH₂), 6.26, 6.62 (s, 2H, 2NH) (D₂O exchangeable), 7.41–7.71 (m, 8H, aromatic ring), 7.79 (s, 1H, CH=C) and 10.26 (s, 1H, NH) (D₂O exchangeable); MS (m/z): 519 (M⁺, 36.00%), 517 (2.25%), 445 (100%, base beak), 420 (76.07%), 250 (72.49%), 191 (45.90%); Anal. Calcd. for C₂₅H₂₀N₄O₅S₃ (558.1): C, 53.75; H, 4.69; N, 10.03.

N-(4-(4-(N-(Phenylcarbamothioyl)sulfamoyl)phenyl)-2-(5-(4-methylbenzylidene)-2,4-dioxothiazolidin-3-yl)acetamide (7b)

Yield, 73%; m.p. 290–2 °C; IR νmax (cm⁻¹): 3298, 3190 (3NH), 3070 (CH aromatic), 2920 (CH aliphatic), 1690, 1681, 1647 (3C=O), 1323, 1153 (SO₂); ¹H NMR δ (ppm): 2.34 (s, 3H, CH₃), 3.97 (s, 2H, CH₂), 6.47–7.93 (m, 15H, 13 aromatic ring & CH=C & NH (D₂O exchangeable)), 10.00 (s, 1H, 1NH) (D₂O exchangeable) and 10.76 (s, 1H, NH) (D₂O exchangeable); ¹³C NMR: 13.38, 56.59, 114.69 (4), 116.80 (2), 121.78 (2), 122.41, 123.56, 124.03, 124.47, 125.9, 128.93 (4), 129.35 (4), 129.50, 148.48, 169.41; MS (m/z): 567 (M⁺, 11.57%), 493 (92.95%), 332 (100%, base beak), 282 (46.61%), 176 (45.13%), 79 (54.01%); Anal. Calcd. for C₁₉H₁₈N₂O₅S₃ (566.7): C, 55.11; H, 3.91; N, 9.89. Found: C, 55.17; H, 3.98; N, 9.78.

N-(4-(4-(N-(Cyclohexylcarbamothioyl)sulfamoyl)phenyl)-2-(5-(4-methylbenzylidene)-2,4-dioxothiazolidin-3-yl)acetamide (7c)

Yield, 83%; m.p. 300–2 °C; IR νmax (cm⁻¹): 3414, 3232,3116 (3NH), 3078 (CH aromatic), 2927 (CH aliphatic), 1710, 1697, 1640 (3C=O), 1315, 1149 (SO₂); ¹H NMR δ (ppm): 1.06–1.84 (m, 10H, cyclohexyl), 2.52 (s, 3H, CH₃), 3.69 (m, 1H, cyclohexyl), 4.30 (s, 2H, CH₂), 5.95 (s, 2H, 2NH) (D₂O exchangeable), 7.28–8.04 (m, 8H, aromatic ring), 8.39 (s, 1H, CH=C) and 10.68 (s, 1H, NH) (D₂O exchangeable); ¹³C NMR: 22.70, 32.75 (2), 43.66 (2), 43.70, 55.42, 61.90, 113.69, 119.53, 119.81, 119.97, 121.14, 126.77, 127.31, 128.79, 129.92, 130.57, 132.98, 134.52, 138.97, 141.50, 141.62, 165.87, 166.18, 168.00; MS (m/z): 573 (M⁺, 24.94%), 555 (29.22%), 532 (59.00%), 483 (100%, base beak), 419 (93.22%), 304 (43.73%), 134 (40.81%); Anal. Calcd. for C₂₉H₂₈N₂O₅S₃ (572.7): C, 54.53; H, 4.93; N, 9.78. Found: C, 54.60; H, 4.90; N, 9.75.
4. Conclusions

In summary, 12 novel thiazolidine-2,4-dione-based compounds were designed and synthesized, and their anticancer activities were evaluated against HepG2-, HCT-116- and MCF-7-inhibiting VEGFR-2 enzymes. They showed potent activity against the HepG2 cell line compared to the other HCT116 and MCF-7 cell lines. Compounds 7c and 6c were highly effective derivatives against the MCF-7 (IC\(_{50}\) = 7.78 and 8.15 µM), HCT116 (IC\(_{50}\) = 5.77 and 7.11 µM) and HepG2 (IC\(_{50}\) = 8.82 and 8.99 µM) tumor cell lines. Their activities were lower than sorafenib (IC\(_{50}\) = 7.26, 5.47 and 9.18 µM) against MCF-7 and HCT116 but higher against HepG2, respectively. In addition, the anticancer activities of these compounds were lower than doxorubicin (IC\(_{50}\) = 6.75, 8.07 and 7.94 µM) against the three cell lines, respectively. The highly effective derivatives 6a–c and 7a–c were tested against VERO normal cell lines. The results showed that the assessed derivatives showed low toxicity against normal VERO cells, with IC\(_{50}\) values ranging from 40.88 to 68.25 µM. All derivatives were evaluated for their VEGFR-2 inhibitory actions and demonstrated high to low activities, with IC\(_{50}\) values varying from 0.08 to 0.93 µM. Derivatives 7c and 6c were observed to be the most effective compounds, with IC\(_{50}\) = 0.08 µM against VEGFR-2. Moreover, derivatives 5a–c, 6a–c and 7a–c were assessed to verify their in vitro binding affinities to PPAR\(\gamma\) and insulin-secreting activities. Compounds 7c and 6c notably bound to PPAR\(\gamma\), with IC\(_{50}\) = 0.296 and 0.300 µM, respectively. In addition, derivatives 7c and 6c showed powerful insulin-secreting activities with the same EC\(_{50}\) value of 0.70 µM. Moreover, docking studies were performed for binding mode and affinities investigation toward both VEGFR-2 and PPAR\(\gamma\) receptors. The docking data were highly associated with that of the biological screening. Furthermore, our compounds represented good in silico ADMET calculations.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ph15020226/s1. Supplementary Material is the NMR and mass data of the compounds.

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