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Review

Impact of Molecular Symmetry/Asymmetry on Insulin-Sensitizing Treatments for Type 2 Diabetes

Jessica Georgina Filisola-Villaseñor [1], María E. Aranda-Barradas [2], Susana Patricia Miranda-Castro [2], Jessica Elena Mendieta-Wejebe [3], Amaranta Sarai Valdez Guerrero [4], Selene Amasis Guillen Castro [4], Macario Martínez Castillo [5], Feliciano Tamay-Cach [4,*] and Samuel Álvarez-Almazán [2,4,*]

1 Laboratorio 2, Departamento de Bioquímica, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Av. Instituto Politécnico Nacional 2508, San Pedro Zacatenco, Mexico City 07360, Mexico; jessica.filisola@cinvestav.mx
2 Laboratorio de Biotecnología, Unidad de Posgrado, Facultad de Estudios Superiores Cuautitlán Campus 1, Universidad Nacional Autónoma de México, Av. 1º. De Mayo S/N Sta. María Las Torres, Cuautitlán Izcalli 54740, Mexico; mariaeugeniaarandab@comunidad.unam.mx (M.E.A.-B.); mircas@unam.mx (S.P.M.-C.)
3 Laboratorio de Biofísica y Biocatálisis, Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional, Plan de San Luis y Salvador Díaz Mirón s/n, Casco de Santo Tomás, Miguel Hidalgo, Mexico City 11340, Mexico; jesmenwej@yahoo.com
4 Laboratorio de Investigación en Bioquímica Aplicada, Sección de Estudios de Posgrado e Investigación, Departamento de Formación Básica Disciplinaria, Escuela Superior de Medicina, Instituto Politécnico Nacional, Plan de San Luis y Salvador Díaz Mirón s/n, Casco de Santo Tomás, Miguel Hidalgo, Mexico City 11340, Mexico; amvaldezg@ipn.mx (A.S.V.G.); sguillenc@ipn.mx (S.A.G.C.)
5 Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional, Plan de San Luis y Salvador Díaz Mirón s/n, Casco de Santo Tomás, Miguel Hidalgo, Mexico City 11340, Mexico; mmartinezcas@ipn.mx
* Correspondence: ftamay@ipn.mx (F.T.-C.); samuel.alvarez@cuautitlan.unam.mx (S.Á.-A.); Tel.: +52-55-57296300 (ext. 62755) (F.T.-C. & S.A.-A.)

Abstract: Although the advantages and disadvantages of asymmetrical thiazolidinediones as insulin-sensitizers have been well-studied, the relevance of symmetry and asymmetry for thiazolidinediones and biguanides has scarcely been explored. Regarding symmetrical molecules, only one thiazolidinedione and no biguanides have been evaluated and proposed as an antihyperglycemic agent for treating type 2 diabetes. Since molecular structure defines physicochemical, pharmacological, and toxicological properties, it is important to gain greater insights into poorly investigated patterns. For example, compounds with intrinsic antioxidant properties commonly have low toxicity. Additionally, the molecular symmetry and asymmetry of ligands are each associated with affinity for certain types of receptors. An advantageous response obtained in one therapeutic application may imply a poor or even adverse effect in another. Within the context of general patterns, each compound must be assessed individually. The current review aimed to summarize the available evidence for the advantages and disadvantages of utilizing symmetrical and asymmetrical thiazolidinediones and biguanides as insulin sensitizers in patients with type 2 diabetes. Other applications of these same compounds are also examined as well as the various uses of additional symmetrical molecules. More research is needed to exploit the potential of symmetrical molecules as insulin sensitizers.

Keywords: symmetrical molecule; asymmetrical molecule; type 2 diabetes; insulin resistance; thiazolidinediones; biguanides

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1. Introduction

Type 2 diabetes is a complex disease that involves damage to multiple signaling pathways [1–4]. Through various pathways, chronic high blood glucose generates or aggravates insulin resistance. The drugs most widely used to decrease insulin resistance without

producing hypoglycemia are biguanides (e.g., metformin) and thiazolidinediones (TZDs, such as pioglitazone) [3–6]. Among the compounds evaluated as insulin sensitizers are many asymmetrical TZDs [1], but only a few asymmetrical biguanides and one symmetrical molecule (a TZD). Furthermore, the impact of molecular symmetry itself on therapeutic success has not been thoroughly examined.

Symmetry and asymmetry are manifested in nature, each having a particular impact on the structure and properties of molecules [7,8]. The aim of the current review was to analyze and summarize the relevant reports on the advantages and disadvantages of administering symmetrical and asymmetrical TZDs and biguanides as insulin sensitizers to patients with type 2 diabetes. The main findings discussed presently focus on theoretical, in vitro, and in vivo studies. Clinical tests have only been carried out with asymmetrical compounds, making the comparison with symmetrical compounds impossible for this type of study. Finally, other possible therapeutic effects of symmetrical and asymmetrical TZDs and biguanides are also scrutinized.

2. Use of Symmetrical Compounds

In recent years, symmetrical molecules have been a focus of research due to their unique structural characteristics, including stability and internal balance. Their design and synthesis have aimed to achieve atom economy, which has been confirmed by their characterization. The most desirable process of synthesis is staggered and scalable within an ecological and sustainable green chemistry approach [8].

The testing of symmetrical molecules on distinct biological tissues has provided very encouraging results [8,9]. By applying the fields of chemistry, biochemistry, and medical pharmacology, new compounds have been proposed for treating diabetes, cancer, malaria, fungal and bacterial infections, and metabolic syndrome (the latter with cardioprotective agents) [10–12]. However, symmetrical molecules have not yet been extensively appraised as insulin-sensitizers for treating diabetes. They have rarely been synthesized and evaluated as a way of lowering glucose levels and avoiding the serious repercussions of this disease [1].

2.1. Advantages of Molecular Symmetry

The harmonious structure of symmetrical molecules, which is identical on both sides of its axis (Figure 1), furnishes them with internal balance and stability [8]. Given these qualities, it is important to examine their conformation, since it defines their biochemical and biophysical characteristics. Hence, the interaction of symmetrical molecules with receptors is herein analyzed with docking studies in order to compare the different responses of new molecular designs with respect to the desired biological activity [13]. An appropriate chemical structure depends on the particular physicochemical processes of the organism being targeted. A characteristic that is advantageous for a compound in one treatment could be a disadvantage in another.

2.1.1. Low Toxicity and Good Antioxidant Activity

Some symmetrical molecules can serve as antioxidants because they have oxidation-reduction properties and are safe and non-cytotoxic [1,9,11,12]. Intrinsic antioxidant capacity has been related to a chemical structure with conjugated double bonds, amino groups, and/or hydrogen atoms available for donation [2,11]. For example, 1G [(5*Z*,5′*Z*)-5,5′-((oxy*bis*(4,1-phenylene))*bis*-(methanylylidene))*bis*(thiazolidine-2,4-dione)] has a series of conjugated double bonds that run throughout the molecule, which may give it greater antioxidant capacity than symmetrical tetradentate Schiff base complexes of oxovanadium(IV) [9] or *bis*ferrocenyl *bis*thiourea analogs [11]. For the last two types of compounds, conjugated double bonds do not extend throughout the molecule.

Among molecules with similar structures capable of inhibiting oxidation, those with symmetry (versus asymmetry) will have a greater antioxidant capacity [11], since both regions contribute to the same property. On the other hand, this could be a disadvantage

because the high oxidative stress in diabetes [3] might limit recognition of these compounds by the corresponding receptor, and thus, decrease the intended pharmacological effect. Additionally, symmetrical molecules possibly trigger signaling pathways for the activation of endogenous antioxidant molecules. It has been hypothesized that the binding of **1G** to its receptor induces the expression of glutathione peroxidase (GSHpx), superoxide dismutase (SOD), and catalase (CAT) [1], but further research is required to confirm this notion.

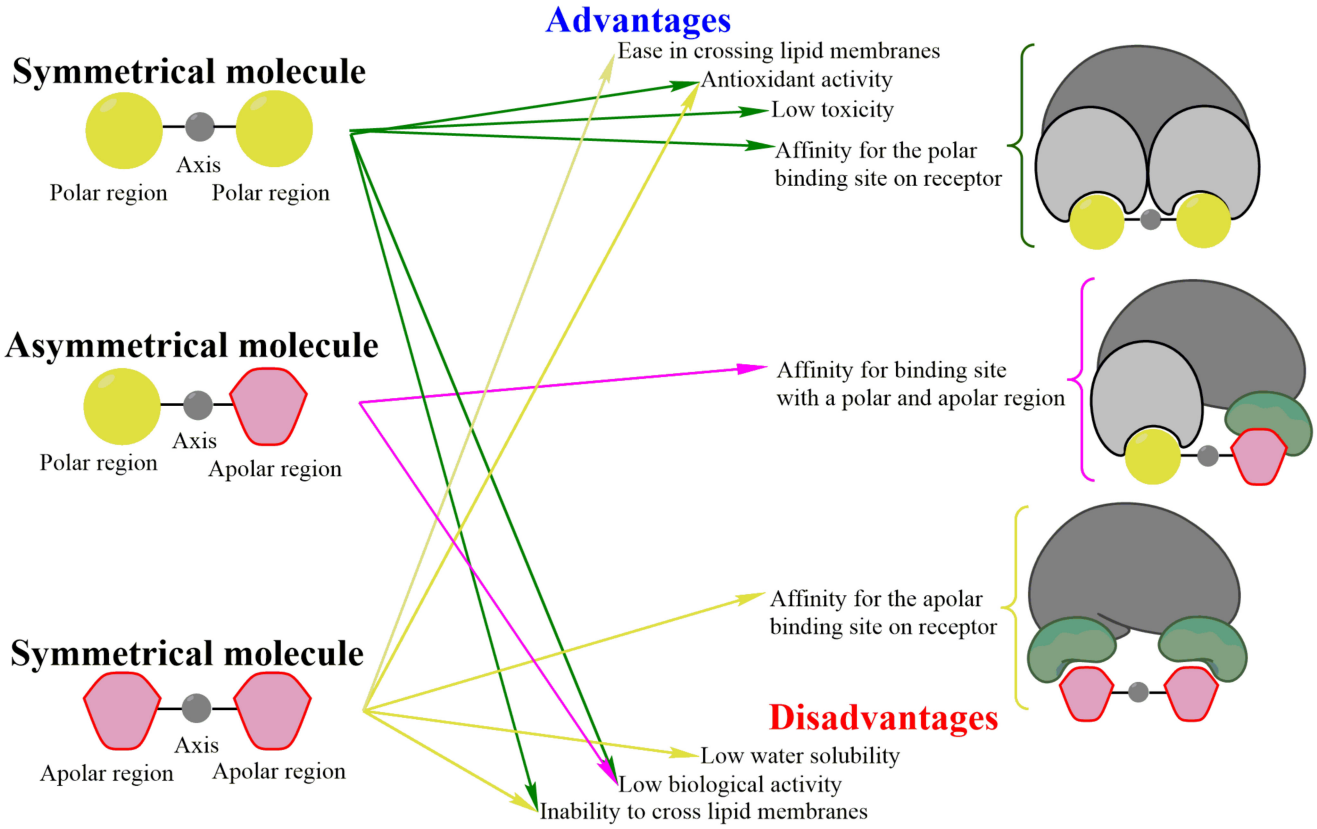


Figure 1. General scheme of the advantages and disadvantages of molecules with or without symmetry. Symmetrical molecules have two equal regions joined by an axis of symmetry (**left**). Their advantages include low toxicity, antioxidant capacity, and the possibility (for non-polar symmetrical molecules) of crossing lipid membranes. Polar symmetrical molecules bind with high affinity (**right**) at the polar site of their receptors, whereas nonpolar symmetrical compounds show high affinity for the apolar region. If a receptor contains a polar and a non-polar region in the binding site, greater affinity will exist for asymmetrical molecules with a polar and a non-polar region compared to symmetrical polar and non-polar molecules. Among the disadvantages of symmetrical molecules are low biological activity, the inability to cross cell membranes, and low water solubility (the latter applies to nonpolar molecules).

2.1.2. Affinity of Ligands for Their Receptors

The affinity of a ligand depends largely on its polarity and the nature of the target receptor. Whereas polar molecules are more suitable for kidney therapy, nonpolar compounds tend to be able to cross the blood-brain barrier (BBB) and reach the brain [14,15].

Adequately designed symmetrical molecules can bind to a given receptor and cause the desired response. If the binding site of a receptor has enough space and the proper electrostatic characteristics, it will accept a symmetrical molecule with either ionizable groups or hydrophobic ligands. In contrast, asymmetrical molecules require a relatively large binding site or one with a combination of polar and nonpolar characteristics [16]. Polar symmetrical molecules interact with polar binding sites [1] but not nonpolar ones (or only with low affinity). Likewise, nonpolar symmetrical molecules interact with nonpolar

sites [17]. In all cases, a molecule with adequate affinity interacts with amino acids crucial for receptor activation [3,9,11,18]. The peroxisome proliferator-activated receptor gamma (PPARγ) has a wide ligand binding pocket (LBP) with polar and non-polar properties. Consequently, it can interact with symmetrical polar molecules, such as 1G, and asymmetrical ones, such as pioglitazone (PIO), rosiglitazone (ROSI), and other recently designed ligands, including lobeglitazone [18].

The reason why a particular compound has multiple types of activity (e.g., anticancer, antibiotic, antifungal, antidiabetic, etc.) may be due to its ability to bind to multiple receptors [17]. Whether a ligand is polar or nonpolar and symmetrical or asymmetrical might determine the nature of its activity as an inhibitor, partial agonist, or total agonist. Selectivity is stablished by the receptor, with PPARs being highly non-selective, interacting with a variety of fatty acids and exogenous ligands [3,9,11,16,18]. In contrast, enzymes are much more specific and therefore bind to a specific substrate, or at least, a very limited number of them [19].

Insulin-sensitizing agents have additional applications (summarized in Section 7) based on their affinity for other receptors. One example of the multiple-receptor hypothesis is the symmetrical compound presently denominated **1G**. The structure of this compound, with an acidic head and tail region, perhaps decreases its affinity for PPARγ but favors binding to other proteins, which would account for its antioxidant, lipid-lowering, and anti-inflammatory effects. In contrast, multiple activity has not been found for PIO [1]. PIO and ROSI may have other activities dependent on their affinity for distinct proteins. In a docking and a half-maximal inhibitory concentration (IC_{50}) study, ROSI displayed a higher affinity for the nutrient-deprivation autophagy factor-1 (NAF-1) protein. NAF-1 has been shown to participate in aging, cell proliferation, deafness, blindness, and diabetes [20], which confirms that the binding site of each protein has specific characteristics (size, polarity, etc.) capable of determining its affinity for a certain ligand.

2.2. Disadvantages of Molecular Symmetry

Symmetrical molecules have certain disadvantages that must be considered when designing and synthesizing new compounds. For instance, molecules bearing ionizable groups have low lipophilicity and consequently cannot cross biological membranes, which lends itself to adverse effects or even tissue damage [3,8,11]. However, low lipophilicity could be considered suitable for avoiding the accumulation of these compounds in adipose tissue or passage through the BBB [14,15]. Asymmetrical molecules with a polar and nonpolar region (e.g., metformin) do not have the ability to cross the BBB, but perhaps their mimetic amino acid structure favors transport across this barrier, which could explain their association with neuroprotective effects [21].

Elaborating facile synthetic strategies for symmetrical molecules is a challenge [8]. In some cases, they turn out to be very toxic, causing mutagenic, teratogenic, or irritant effects [19]. Regarding the relationship of the antioxidant capacity of symmetrical molecules with low toxicity (mentioned in the previous section), it is necessary to carry out further studies to achieve greater congruency in the findings. Moreover, the response produced by symmetrical molecules is not always the desired one [9,12], possibly due to the formation of homo-oligomers [13]. This might explain the low solubility of symmetrical molecules, a subject in need of further research.

2.3. Symmetry: An Advantage or Disadvantage for Ligand-Receptor Interactions?

As aforementioned (Section 2.1.2), symmetrical molecules may have the advantage of high affinity for receptors containing an LBP with similar polarity [1] or the disadvantage of low affinity for an LBP with distinct polarity. In the case of PPARγ, the LBP is Y-shaped or T-shaped and relatively large in size [16,18]. The main region (branch I) of LBP is polar, another region (branch II) is nonpolar, and the last one (branch III) is polar and nonpolar [22], which allows a symmetrical molecule like **1G** to bind to PPARγ between

branches I and III and act as a partial agonist. This could be advantageous given that partial agonists tend to have fewer side effects [18].

The affinity for a receptor is determined by the polarity, length, and number of rotatable bonds of the ligand. Compound **1G** has four rotatable bonds and a binding affinity of −12.19 kcal/mol. PIO and ROSI have seven rotatable bonds and lower binding affinities (−10.164 kcal/mol and −10.106 kcal/mol, respectively). All three compounds contain five H-bonds [1]. The clear differences are the polarity and symmetry of **1G** and the smaller number of rotatable bonds due to the double bond at carbon 5 (Figure 2). The probable greater stability of **1G** favors its interaction with the receptor. Hence, **1G** would be expected to have greater pharmacological activity than PIO. However, both treatments were found to have similar effects in a rat model of diabetes, evidencing partial agonist activity [1].

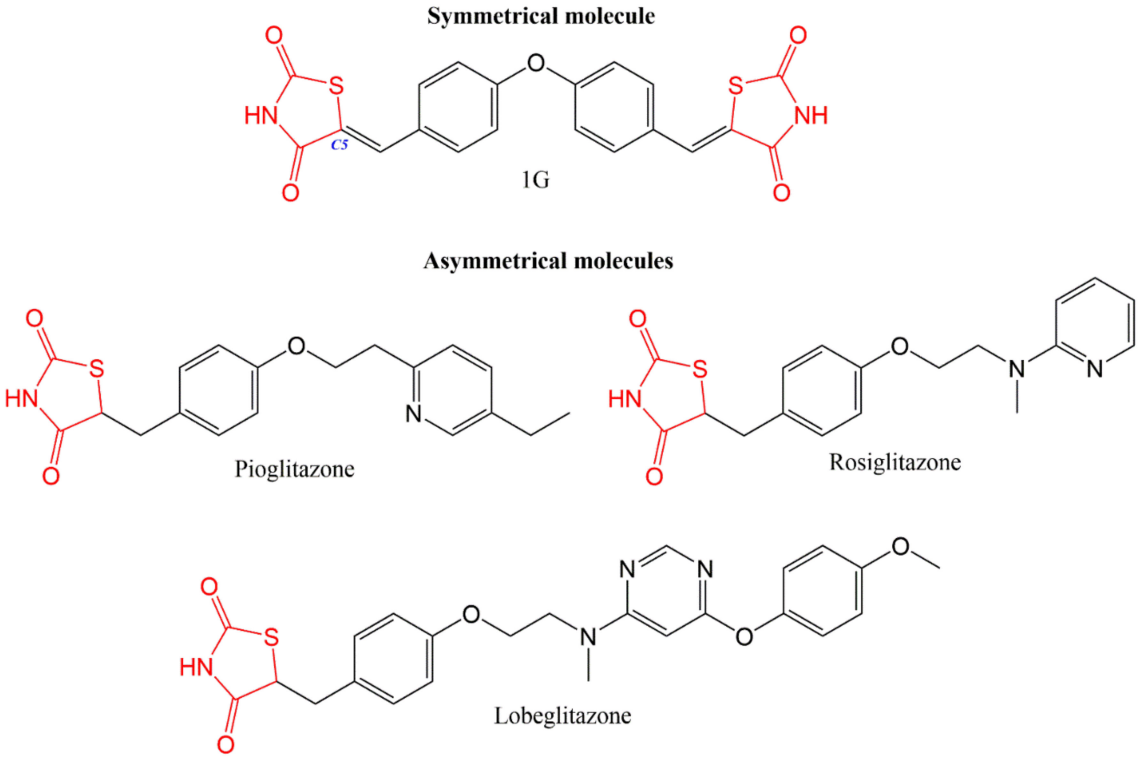


Figure 2. The chemical structure of symmetrical and asymmetrical thiazolidinediones. **1G**, PIO, and ROSI are similar in length. The symmetrical regions of **1G** have high polarity due to the thiazolidinedione ring (marked in red) that is unsaturated at carbon 5 (marked in blue), resulting in rigidity and fewer rotatable bonds. PIO and ROSI are asymmetrical molecules with more rotatable bonds than **1G**. Lobeglitazone is an asymmetrical molecule that is longer and has more rotatable bonds than **1G**, PIO, and ROSI.

Another possible explanation for the observed behavior is that **1G** interacts with the receptor for a shorter time than PIO, owing to subsequent dissociation from the receptor resulting from the solubility of the ligand in the cytoplasm (polar medium). PIO has less polarity because it is an asymmetrical molecule with one polar region and another region with less polarity, which may favor a longer interaction with the receptor. In this case, molecular symmetry turns out to be a disadvantage for PPARγ binding. Perhaps a receptor exists with the necessary characteristics to bind **1G** with high affinity (leading to favorable therapeutic activity). More research needed on plausible receptors for **1G**.

The way a ligand binds to a receptor can mediate its interaction with other proteins. The capacity of cyclin-dependent kinase 5 (Cdk5) to inhibit PPARγ phosphorylation at Ser245 has been suggested to somehow enhance the pharmacological ability of compounds to lower blood glucose. Asymmetrical molecules might favor this inhibition. Lobeglitazone

is a relatively long asymmetrical molecule capable of binding to the wide LBP of PPARγ. The binding site may be located in branch I and branch II of the receptor, allowing the ligand to act as a selective PPARγ modulator (SPPARγM) [18]. The ligand-dependent activating function (AF-2) of the receptor is in branch I, whereas Ser245 is located in beta sheet 1 of branch II (polar and non-polar region). Since this pattern of interaction is able to cause conformational changes, lobeglitazone has been suggested to block Cdk5-mediated phosphorylation of PPARγ. The polar head of this ligand generates the same interaction network with AF-2 as ROSI, thought weaker. Nevertheless, lobeglitazone binds with higher affinity to PPARγ than ROSI (−11.4 versus −9.6 kcal/mol, respectively). This might be explained by the hydrophobic interactions produced by the nonpolar region of the ligand, and the conformational change favored by interaction of the ether group of the *p*-methoxyphenol moiety with Arg280. These ligand-induced molecular changes in the receptor could be related to its efficacy for lowering hyperglycemia by means of blocking Ser245 phosphorylation [18].

3. Use of Asymmetrical Molecules: Analogs and Derivatives

There are a greater number of asymmetrical than symmetrical molecules. Computer-assisted structure–activity relationship (SAR) studies culminate in asymmetrical molecules, perhaps being the main reason for the scarcity of lead molecules that are symmetrical. The advantages or disadvantages of a ligand depend on the characteristics of the therapeutic target site or pocket, which define the resulting ligand-receptor interactions [3,18].

3.1. Advantages of Molecular Asymmetry

The higher water solubility of asymmetrical molecules allows them to be distributed in the intra- and extracellular medium and to cross biological membranes, thus increasing the likelihood of their interaction with multiple therapeutic targets [23–25]. The low solubility of symmetrical compound **1G** (<18 mg/mL) [1] and other purified symmetric compounds in most solvents can be affected by intra- and intermolecular interactions as well as the formation of homo-oligomers (other disadvantages are described in Section 2.2). In contrast, asymmetrical compound **C40** has fewer solubility problems [26] (Table 1), possibly because of a lower number of intermolecular interactions. Accordingly, asymmetrical molecules might have better bioavailability [27], representing an interesting question for future research.

Table 1. Solubility of compounds synthesized as insulin sensitizers.

Molecule Name	Solubility (mg/mL)						Reference
	DMSO	Ethanol	dH_2O	Methanol	Acetone	Ethyl Acetate	
Symmetrical compound							
1G	18.0	3.6	2.7	NR	NR	NR	[1]
Asymmetrical compound							
C40	Good	NR	NR	Good	Good	Good	[26]

Abbreviations: DMSO, dimethyl sulfoxide; dH_2O, distilled water; NR, not reported.

It should be kept in mind that water molecules form solvation spheres around compounds (even non-polar compounds [14]), which are capable of interacting with ions and molecules in the intra- and extracellular medium. The solvation spheres of asymmetrical molecules (with a polar and nonpolar region) allow them to pass through cells and interstices, giving them an advantage in achieving good biodistribution [25]. Nonpolar molecules could have more problems in relation to distribution, but they can easily cross membranes [14]. Hence, the difficulties and facilities of polar and nonpolar symmetrical molecules may lead to a similar biodistribution.

3.2. Disadvantages of Molecular Asymmetry

A molecule with multiple therapeutic targets has a greater probability of adverse effects [22,28,29]. However, the secondary effects might be more related to the diversity of proteins present in the organism and their location than any particular structural characteristic of the compounds. Even though hydrophobic molecules may undergo hydrophobic hydration [14], high hydrophobicity is still a limiting factor for the adequate biodistribution of ligands, even if they have plasma transporters (e.g., albumin) and intracellular lipid-binding lipoproteins (iLBPs) [1,25,30]. The ligands able to bind to PPARγ exhibit highly variable results depending on their size and the interactions at the binding site. According to one hypothesis, ligands with a longer tail region, and thus greater hydrophobicity, exhibit better activity [1,31]. In such a case, it is advantageous for the head region to be acidic (hydrophilic) and the tail to have a lipophilic portion [16,18,32].

4. Theoretical Studies (In Silico) of Symmetrical and Asymmetrical Insulin Sensitizers

Whereas there are abundant in silico analyses of asymmetrical TZD molecules, scant studies exist for symmetrical TZD molecules or any type of biguanide derivative. Perhaps the reason is that rational drug design tends to identify asymmetrical lead molecules. Furthermore, metformin does not have a well-defined receptor [6,33,34]. Most computational predictions focus on molecular docking analyses, and fewer examine physicochemical or biological properties such as toxicity, pharmacokinetics, and drug metabolism (Table 2). The aim of docking studies is to map the predicted ligand-receptor interactions, which allows for more rational drug design, and consequently, lower drug development costs [31,35,36]. In recent years, computer-assisted studies have become faster and more accurate [1,37,38] because the prediction software has integrated a larger quantity of structure-based experimental results (in two and/or three dimensions) [29]. Docking studies (Table 2) have focused on the canonical receptor PPARγ, but activity has also been found for the inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-β) [39], aldose reductase (ALR2) [17], PPARα [31], α-amylase [40], α-glucosidase [41,42], and protein tyrosine phosphatase 1B (PTP1B) [37,38,43,44], thus confirming the capacity of a molecule to have multiple therapeutic activities by interacting with more than one therapeutic target.

Table 2. Program/software used to predict the properties of symmetrical and asymmetrical compounds.

Molecule	Receptors Involved in Docking	Docking Program/Hydrogen Bonds	Physico-Chemical Properties	Target Predictions	Toxico-Logical Predictions	Pharmaco-Kinetic Predictions	Reference
Symmetrical compound							
1G	PPARγ (2PRG)	AutoDock 4.2/5 H-bonds	Molinspiration and Osiris Property Explorer	SwissTarget-Prediction	ACD/Tox Suite and Osiris Property Explorer	NR	[1]
Asymmetrical compounds							
1	PPARα (1I7G) and PPARγ (1I7I)	AutoDock 4.2/3 H-bonds for PPARα and 4 for PPARγ	NR	NR	ACD/Tox Suite	NR	[31]
5	PPARγ (2PRG)	Molecular Operating Environment (MOE)/3 H-bonds	MOE and ADME-T	NR	ADME-T	ADME-T	[27]
ChEMBL:259883, 1563849, 1599789, 1523092, 259883, 405972, and 1599789	PPARγ (3K8S) and ALR2 (3RX3)	Glide Maestro 9.0 Schrödinger Suite and GOLD/5 H-bonds for PPARγ and 3 for ALR2	QikProp 3.2	TarFisDock, DRAR-CPI, and Pharm-Mapper, BindingDB, ChEMBL, and Specs	DEREK	QikProp 3.2	[17]
Lobeglitazone	PPARγ (1PRG)	AutoDock 4.0/ 4 H-bonds	NR	NR	NR	NR	[18]

Table 2. *Cont.*

Molecule	Receptors Involved in Docking	Docking Program/Hydrogen Bonds	Physico-Chemical Properties	Target Predictions	Toxico-Logical Predictions	Pharmaco-Kinetic Predictions	Reference
24 and **26**	PPARγ (4A4W and 2XKW)	GOLD 5.2/5 H-bonds for **24** and **26**	NR	SEA, PASS, and Pharm-Mapper	NR	NR	[28]
13 and **16**	PTP1B (2NT7)	Glide 5.8 Schrödinger 2012/6 H-bonds for **13** and **16**	QikProp 3.5	PASS	NR	QikProp 3.5	[37]
C40	PPARγ (2PRG)	AutoDock 4.0/ 5 H-bonds	Molinspiration and Osiris Property Explorer	NR	Osiris Property Explorer	NR	[26]
46	PTP1B (2NT7)	Glide 5.8, Schrödinger 2012/5 H-bonds	QikProp 3.5	NR	NR	QikProp 3.5	[43]
4b	PPARγ (P37231)	VLife MDS 4.3/2 H-bonds	NR	NR	NR	NR	[45]
1	PTP1B (1c83)	AutoDock 4.2/4 H-bonds	admetSAR	NR	admetSAR	admetSAR	[38]
Tz21, **Tz7**, and **Tz10**	PPARγ (1FM9) and α-glucosidase (2QMJ)	Maestro 9.0 Schrödinger suite /Regarding PPARγ, 4 H-bonds for Tz21 and 3 for Tz17 and Tz10	Molins-piration	NR	NR	NR	[42]
11n, 11o, and **22a**	α-glucosidase (homology modeling)	MOE 2016.0208/ 2 H-bonds for **11o** and 4 for **22a**	NR	NR	NR	NR	[41]
7m	IKK-β (3QA8)	Glide Maestro Schrödinger suite/ 3 H-bonds	NR	NR	NR	NR	[39]
17	PTP1B (2QB5)	AutoDock 4.2/ 6 H-bonds	pkCSM	NR	ProTox	pkCSM	[44]
5 and **9**	PPARγ (2PRG) and α-amy-lase (2QV4)	MOE 2019/ Regarding PPARγ, 1 H-bond for **5** and **9**; Regarding α-amylase, 1 H-bond for **5** and 4 for **9**	admetSAR	NR	admetSAR ADME-Tox	admetSAR ADME-Tox	[40]
4 and **5**	PPARγ (2PRG) and α-amylase (2QV4)	MOE 2019/ Regarding α-amylase, 1 H-bond for **4** and 2 for **5**	NR	NR	NR	NR	[46]

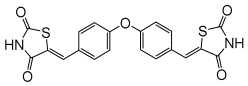
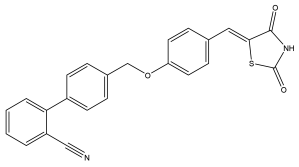
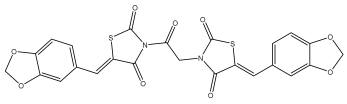
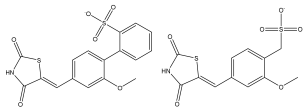
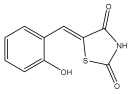
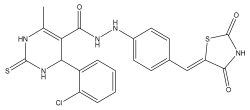
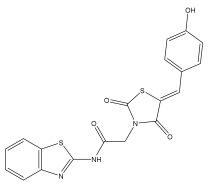
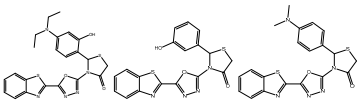
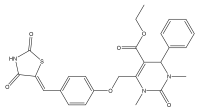
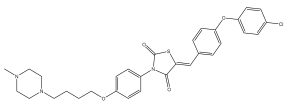
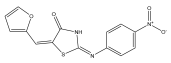
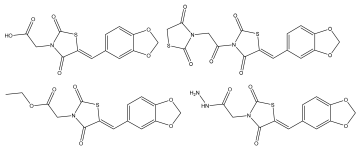
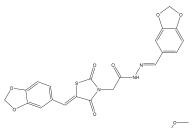
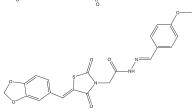
Abbreviations: ADME-T, absorption, distribution, metabolism, elimination, and toxicity; ALR2, aldose reductase; H-bonds, hydrogen bonds; IKK-β, inhibitor of nuclear factor kappa-B kinase subunit beta; MOE, molecular operating environment; PPARα, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; PTP1B, protein tyrosine phosphatase 1B; NR, not reported.

4.1. Design and Synthesis of Symmetrical and Asymmetrical Molecules

Drug design based on SAR studies most commonly gives rise to asymmetrical rather than symmetrical lead molecules. On the other hand, the design of symmetrical molecules with a pharmacophore is not very complex. The main challenge is to achieve the synthesis of such molecules [1].

Generally, the synthesis of TZD derivatives involves a Knoevenagel condensation reaction with long reaction times and yields over 45% (Table 3). The raw material is usually an aldehyde condensed with a TZD ring [1,26,31]. In most cases, TZD derivatives are obtained very quickly due to the simplicity of the Knoevenagel reaction [38]. However, the pharmacophore attached to the 2,4-thiazolidinedione ring affects the number of reactions carried out, the time required to deliver the final product, and of course, the yield. According to the molecules reviewed, a bulky compound generally needs a longer reaction time and/or more chemical reactions, which entails a loss of time and economic resources, as well as in the mass of reaction intermediates, even if good reaction yields are afforded.

Table 3. Structure of symmetrical and asymmetrical compounds and the corresponding results of synthesis.

Structure	Number of Reactions	Total Synthesis Time	Yield (%)	Reference
Symmetrical compound				
	1	3 h	83.0	[1]
Asymmetrical compounds				
	2	3–4 h	80.0	[31]
	5	6 h	70.0	[27]
	3	48.2 h	58.4 for **13** and 68.4 for **16**	[37]
	1	2 h	90.6	[26]
	4	15.45 h	67.6	[45]
	5	104.15 h	56.0	[38]
	5	58.5 h	69.0 for Tz21 and Tz7, and 67.0 for Tz10	[42]
	4	24 h	59.9	[41]
	7	50.5	52.0	[39]
	3	25 h	45.0	[44]
	5	8 h	71.0 for **6** and 73.0 for **11**	[40]
	5	9 h	74.0 for **4**, 65.0 for **5**, 61.0 for **6**, and 58.0 for **7**	[46]
				

4.2. Structure-Related Physicochemical Properties and Pharmacokinetics

The capacity of efficacious medicinal drugs to dissolve, cross membranes, and bind to their therapeutic target is vital for their oral bioavailability [25]. These properties are determined by the physicochemical characteristics [25,40] resulting from particular atoms in the molecule and their connectivity. For new chemical entities in general and antidiabetic agents in particular, the acceptable ranges for the parameters of oral bioavailability are typically represented by Lipinski's rule of five [25,42]. However, it should not be overlooked that not all effective commercial drugs completely comply with Lipinski's rules [47].

According to Lipinski's rules, the molecular weight of new chemical entities should be less than 500 Da as an indicator of their ease of movement as well as good diffusion and absorption. Molecular hydrophobicity is described by the octanol-water partition coefficient (LogP), and should not exceed 5. The topological polar surface area (TPSA) is a very useful parameter for predicting the efficient transport of drugs. It is defined in Lipinski's rules as no more than five hydrogen bond donors and no more than ten hydrogen bond acceptors [25,42], which may allow molecules to be biodistributed without being involved in a multitude of interactions that prevents them from moving from their site of administration to their receptor binding site.

TZD derivatives contain a heteroatomic ring attached to an aromatic nucleus bearing other substituents. The nitrogen and sulfur atoms of the heteroatomic ring and the ketone groups are responsible for its acidic property. Due to the presence of the aromatic nucleus, its substituents directly affect the acidity of the 2,4-thiazolidinedione ring, which could account for the different patterns of interaction with PPARγ, and consequently, distinct therapeutic effects. The choice of substituents has various implications for the activity of the compounds. For example, electron donating substituents such as hydroxyl in the *ortho*, *meta*, and *para* positions favor hypoglycemic activity [26]. As some SAR studies have confirmed, there is a much more pronounced antidiabetic effect generated by compounds with electron donating versus electron withdrawing groups as substituents on the phenyl ring of 2,4-thiazolidinedione [42]. This is the basis of the theory that the acidity of the heteroatomic ring depends on the substituents in the aromatic ring and influences the binding of the ligand to its receptor. The selectivity of other molecules for a given receptor is also determined by the kind of substituents on the aromatic ring [19].

Toxicity predictions help avoid the use of potentially harmful or even dangerous compounds in clinical trials. The acute toxicity of a molecule is defined as the dose lethal for 50% of the treated animals (LD_{50}). It is a marker for evaluating the progressive potential to produce various acute effects [14].

Another factor is indirect toxicity stemming from the inhibitory activity of a compound on cytochrome P450 (CYP450) [31]. In cases of the co-administration of drugs, the inhibition of some CYP450 isoforms might bring about drug-drug interactions, which can substantially reduce their metabolism and lead to increased accumulation, possibly reaching toxic levels. CYP3A4 is the main enzyme responsible for the metabolism of xenobiotics in humans. Hence, its inhibition by a clinically relevant concentration can trigger drug-drug interactions and adverse effects. Moreover, the cardiotoxicity of drug-like compounds associated with the inhibition of the human ether-a-go-go (hERG) channel is becoming a more common cause for the failure of drug candidates. This type of channel regulates heart rate by allowing potassium to be released from the cytoplasm for repolarization of the myocyte membrane [48].

Overall, these parameters serve to test the probability of toxicity of a molecule. The toxicity predictors shown in Table 2 have helped identify the aforementioned factors known to be involved in some cases of toxic effects. Although the predictions are highly reliable, it is of course important to assess compounds experimentally to ensure the absence of toxic effects. This strategy avoids the withdrawal of drugs after clinical trials or approval by the Food and Drug Administration (FDA) due to their toxic effects, as happened with troglitazone, a TZD withdrawn from the market for triggering hepatotoxicity [16,49].

4.3. Prediction of Drug Targets

Each protein has characteristics that determine the type of ligand capable of binding to it. Thus, the proteins for which symmetrical ligands have higher affinity could be distinct from those preferred by asymmetrical ligands (Figure 1), a phenomenon that is known to occur even between isoforms [31].

Since many proteins are homologous across species, target prediction tools are a first step in scaling from one species to another. Consequently, a treatment proven to be effective in rats or mice is considered a promising candidate for humans [1]. However, the many subtle differences between homeostasis in each species likely explains why positive results in a murine model do not automatically translate into a successful treatment for human patients.

The conventional docking technique explores the binding of a set of small molecules to a single protein. There are also servers designed for the prediction of drug targets based on the inverse/reverse method, where a small molecule is docked to a large number of proteins. Some servers predict therapeutic indications and adverse reactions of drugs in accordance with an interaction profile of the structure of a molecule and its target. The pharmacophore mapping approach seeks to identify putative binding targets for small molecules [17,29].

The prediction of plausible targets facilitates the investigation of the bioactivity of a molecule in applications other than the one for which it was created. For example, molecules with the predicted ability to reduce hyperglycemia and insulin resistance may also be beneficial for targeting proteins in adipose tissue or those involved in cell growth and differentiation, inflammation, arthritis, heart disease, and cancer. Moreover, these molecules might also participate in the pharmacokinetics and metabolism of xenobiotics [1], providing an explanation for the unexplored link between predictions and the additional therapeutic uses of some drugs (discussed in Section 7).

5. In Vitro Studies of Symmetrical and Asymmetrical Molecules

To our knowledge, few in vitro studies have focused on cell models of insulin sensitizers (Table 4). Perhaps the very complex nature of diabetes [3,4] makes it preferrable to analyze pharmacological effects with animal models. In vitro studies are normally utilized to test feasible mechanisms of action for new insulin sensitizers. In this sense, reports in the literature mostly focus on the inhibitory activity of molecules on protein tyrosine phosphatase (PTP1B) [37,38] and α-glucosidase [42], whereas a few have examined their antioxidant potential [27]. The research on the mechanism of action of TZDs and biguanides has helped to explain the various effects observed in vivo. One example is the ability of lobeglitazone to block PPARγ phosphorylation at residue Ser245, which is associated with its capacity to produce a better glucose-lowering effect than ROSI [18].

5.1. Activity of Thiazolidinediones on Different Cells

Two TZDs, ROSI and PIO, are currently approved by the FDA for monotherapy or administration in combination with metformin or sulfonylureas to manage type 2 diabetes [50]. Since both these TZDs have high affinity for PPARγ, they trigger its transactivation and increased gene expression in human embryonic kidney cells and mature adipocytes, respectively [51–53]. As a consequence, docking studies (see Section 4.1) use PPARγ for the design of new derivatives.

In the mouse 3T3-L1 cell line, TZDs favor the accumulation of lipids and the elevated expression of *RESISTIN*, *ADIPONECTIN*, and *FABP4* genes, all markers of mature adipocytes [54]. Additionally, ROSI promotes high protein levels of PPARγ and PR domain zinc finger protein 16 (PRMD16) in adipocytes. Such proteins are positively associated with insulin sensitivity and the expression of the markers for white adipose tissue, including adipogenic genes (*PPARG*, *ADIPOQ*, *PLIN1*), insulin signaling-related genes (*IRS1*, *GLUT4*), and lipogenic genes (*FASN*, *ACACA*) [54,55]. PIO enhances expression of glucose trans-

porter type 4 (*GLUT4*) in adipocytes, which is linked to glucose uptake and the reduction of insulin resistance [56].

Table 4. In vitro results of asymmetrical TZDs employed in insulin-sensitizing treatments.

Compound	Duration of Treatment	Cells or Assays	Control Treatment	Aim	Effectiveness	Reference
1	24 h	3T3-L1 fibroblasts	Cells without treatment	Relative expression of mRNA	mRNA of PPARγ (5-fold), PPARα (6-fold), and LUT-4 (3-fold)	[31]
Lobeglitazone	Assay	Kinase assay	ROSI	Comparison of blocking phosphorylation	Better inhibition of phosphorylation.	[18]
1	Assay	Inhibition assay	NR	Inhibition of PTP1B	85% inhibition at 20 μM	[38]
Tz21	Assay	Inhibition assay	Acarbose	Inhibition of α-glucosidase	0.21 μM	[42]
5	Assay	DPPH assay	Ascorbic acid	Antioxidant activity	∼10% decrease	[27]
13 and **16**	Assay	Inhibition assay	Suramin at 9.76 μM	Inhibition of PTP1B	7.31 and 8.13 μM	[37]

Abbreviations: GLUT-4, type 4 glucose transporter; NR, not reported; PPARα, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; PTP1B, protein tyrosine phosphatase; ROSI, rosiglitazone.

TZDs also improve insulin sensitivity by boosting free fatty acid (FFA) uptake by stimulating the expression of fatty acid transport protein (FATP) and acyl-CoA synthetase (ACS), and inhibiting lipolysis and the release of FFA by adipocytes. As a possible mechanism, the reduced expression of adipose triglyceride lipase (ATGL) or Akt-signaling would lead to a decrease in the level of cyclic adenosine monophosphate (cAMP), and thus, in lipase activity [57–59]. TZDs can activate the phosphatidylinositol-3 kinase (PI3K)-Akt pathway through specific mechanisms. For instance, PIO elicits the phosphorylation of Ser473 in Akt, high protein levels of the p110 catalytic subunit, and the phosphorylation of the p85 regulatory subunit of PI3K in primary adipocytes [59].

TZDs are thought to sensitize cells to insulin, primarily by effects on insulin-sensitizing tissues such as adipocytes, and secondarily by diminishing pancreatic cell apoptosis. Accelerated pancreatic cell apoptosis is set in motion by elevated glucose and the corresponding increase in glucose-stimulated insulin secretion (GSIS) [60]. Mechanistically, PIO may protect rat and human pancreatic cells under hyperglycemic conditions by triggering AMP-activated protein kinase (AMPK), resulting in the stabilization of glutaminase-1 by mitochondrial chaperone heat shock protein (HSP75/TRAP1). The latter activates the glutathione antioxidant system, which reduces the formation of reactive oxygen species (ROS) and prevents the loss of mitochondrial membrane potential and the activation of cleaved caspase-3 [61].

PIO suppresses glucose production and affects mitochondrial metabolism in primary hepatocytes because it generates a PPARγ-dependent rise in PDK4 gene expression and protein levels, a critical negative regulator of pyruvate dehydrogenase [62]. Furthermore, in a mouse atrial cardiomyocyte cell line under oxidative stress conditions, PIO gives rise to the expression of PGC-1α, a transcription coactivator of PPARγ that acts as a key regulator of mitochondrial biogenesis [63].

5.2. Effect of Biguanides on Different Cells

Among biguanides, metformin is the only compound approved as a drug by the FDA [64]. It decreases circulating glucose levels by several molecular mechanisms, including an increase in glucose transport [34,65–68]. Additionally, by activating insulin receptor (IR) signaling, metformin enhances insulin-induced tyrosine phosphorylation of the IR and insulin receptor substrate-1 (IRS-1), as detected in an insulin-resistant muscle cell line (C2C12), leading to restored PI3K activity [34,69]. The activation of signaling by the IR also promotes its kinase activity and IRS-2 phosphorylation in primary human hepatocytes and hepatoma cells (HepG2) [68,70]. Therapeutic concentrations of metformin (0.01–0.1 mmol/L) have consistently reversed the low levels of phosphorylation of the IR,

IRS-1, and IRS-2, as well as the reduced association of these proteins with PI3K, fomented by chronic insulin treatment of HepG2 cells [71]. Downstream from the IR, metformin is able to upregulate MAPK and PI3K activity in hepatoma cells [70] and p38 MAPK activity in skeletal muscle cells [34].

Mechanistically, it has been proposed that metformin regulates glucose uptake by increasing the translocation of glucose transporters (GLUT-1) to the plasma membrane of smooth muscle cells, hepatoma cells, and myotube cells [66,68,72], as well as GLUT-4 to the plasma membrane of human adipocytes [67]. Moreover, metformin reverses the delayed endocytosis rate of GLUT-4 observed in rat adipocytes chronically treated with insulin [73].

Another possible molecular mechanism of metformin for regulating circulating glucose levels is the enhancement of glycogenesis and lipogenesis, as found in insulin-treated rat hepatocytes and hepatoma cells under basal conditions [70,74]. An additional reported mechanism is the inhibition of gluconeogenesis, as detected in rat hepatocytes [75–78] and adipocytes [79]. The latter effect might result from the capacity of metformin to activate pyruvate kinase (thus favoring lactate/pyruvate formation instead of glucose flux in hepatocytes) [76], inhibit glucagon-stimulated glucose production in primary hepatocytes [77], and inhibit complex I and complex IV of the respiratory chain in liver mitochondria [80,81].

In the assay with H4IIE cells, furthermore, metformin downregulated gene expression for key enzymes of gluconeogenesis in primary hepatocytes and hepatoma cells, including glucose 6-phosphatase (G6Pc), phosphoenolpyruvate carboxykinase (PEPCK), protein phosphatase 1, and regulatory subunit 3C (Ppp1r3c) [78,82–84]. Finally, metformin activates AMPK, which participates in the regulation of transcription factors or coactivators, such as PPARγ coactivator 1α (PGC-1α), forkhead box protein (FOXO1), hepatocyte NF 4α (HNF4α), and p160 steroid receptor coactivator 2 (SRC-2). These are important for the transcriptional activation or repression of hepatic gluconeogenic enzymes in hepatocyte cell models [85,86].

6. In Vivo Studies of Symmetrical and Asymmetrical Molecules

The administration of newly designed and synthesized molecules in standardized animal models provides the closest approximation, short of clinical trials, of the effects that may be produced in humans. Hence, in vivo and ex vivo studies are carried out with drug candidates to choose the best options for clinical trials. Regarding diabetes, treatments aim to control the underlying mechanisms of the disease and/or inhibit the progression of complications. Thus, it is worthwhile analyzing symmetrical and asymmetrical molecules within this framework [87].

Streptozotocin (STZ) and alloxan, both employed as diabetes-inducing agents, exhibit some differences in the generation of hyperglycemic states (Table 5). However, both are known to cause similar symptoms in animal models of diabetes [37]. PIO, glibenclamide, and metformin are the most common control treatments for such models. STZ-induced hyperglycemia in rodents is most commonly used for assessing antidiabetic compounds, with PIO generally serving as the reference drug [1,2,26].

6.1. Symmetrical Compounds

The evaluation of symmetrical molecules with in vivo models has been limited. The symmetrical molecule **1G** (Table 5) shows a tendency to reduce the typical signs of diabetes, such as polydipsia, polyphagia, inflammation, and systemic oxidation. In addition, the compound may have characteristics favorable for therapies targeting arthritis, inflammation, heart disease, and cancer [1]. Although the findings are promising, they must be more conclusive.

6.2. Asymmetrical Compounds

Since more asymmetrical molecules (obtained from SAR studies) have been assessed in vivo, more are used clinically. Most research on insulin sensitizers has focused on TZD derivatives [2,27], with less known about biguanides. TZDs designed in recent years with a

great variety in length and polarity have displayed good activity (Table 5), perhaps related to the large size of the LBP of PPARγ and the diverse polarity of its regions (discussed in Section 2.3).

Table 5. In vivo results of evaluating symmetrical and asymmetrical compounds.

Molecule Name/Dosage	Duration of Treatment	Model/Dosage	Control Treatment/ Dosage	Higher Effectiveness?	Reference
Symmetrical compound					
1G at 35.7 mg/kg/day	2 w	STZ rat model at 45 mg/kg	PIO (Agopar®) at 30 mg/kg/day	Yes	[1]
Asymmetrical compounds					
1 at 50 mg/kg/ single dose	-	STZ (at 65 mg/kg) and NIC (at 110 mg/kg) rat model	Glibenclamide at 5 mg/kg	Yes	[31]
Tz21 at 36 mg/kg	4 h	STZ (60 mg/kg) rat model	PIO at 36 mg/kg	Yes	[42]
C40 and **C81** at 18 and 21 mg/kg/day, respectively	3 w	STZ (at 45 mg/kg) rat model	PIO (Agopar®) at 30 mg/kg/day	Yes	[2]
5 at 50 mg/kg	4 d	Alloxan (100 mg/kg) rat model	Metformin at 500 mg/kg	Yes	[27]
4b (NR)	8 d	Alloxan (120 mg/kg) rat model	PIO at 40 mg/kg	Similar	[45]
16 (NR)	1 w	Alloxan (185 mg/kg) albino mouse model	PIO (NR)	Similar	[37]

Abbreviations: d, days; h, hours; w, weeks; NIC, nicotinamide; NR, not reported; PIO, pioglitazone; PPARα, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; PTP1B, protein tyrosine phosphatase 1B; STZ, streptozotocin.

6.3. Toxicity

As previously mentioned, toxicity tests should explore potential damage to CYP450 [31] as well as any general toxic effect on the organism under study. By subjecting TZD derivatives to an oral toxicity test, evidence was provided of adipogenicity with the risk of body weight gain [1,26]. To our knowledge, the other proposed antidiabetic compounds have not been submitted to any toxicity test. However, their beneficial effects are substantial, apparently outweighing any possible toxicity [2]. Therefore, it is crucial to consider reports on their pharmacokinetic parameters, which govern the ability of a molecule to reach the active site of its target.

6.4. Ex Vivo Studies of Symmetrical and Asymmetrical Molecules

Most of the compounds evaluated in vivo have also been examined ex vivo. Symmetrical compound **1G** [1] and asymmetrical compound **1** [31] (Table 6) showed a similar capacity to lower blood glucose. The asymmetrical compound **C40** produces a better hypoglycemic effect than the commercial drug PIO [2]. As a plausible explanation, the first two compounds have a longer structure that may facilitate stabilization of the receptor in branches II and III to function as partial or total agonists. **C40** for its part, might act mainly by stabilizing helix H12, where AF2 is found. These findings suggest the need for further investigation into the possible impact of molecular symmetry on lowering the level of blood glucose.

Asymmetrical molecules can trigger the activation or synthesis of endogenous antioxidant molecules. For instance, **C40** decreases the level of reduced glutathione (GSH) and superoxide dismutase (SOD) [2]. Moreover, some molecules have demonstrated an antioxidant capability based on tests with 2,2-diphenyl-1-picryl-hydrazyl radical (DPPH) [27] and 2,2′-azino-*bis*(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) (see Section 3.1). DPPH provides a measure of the capacity of a compound to chemically react with free radicals, and ABTS measures its ability to react with positively charged radicals (causing their stabilization).

Table 6. Ex vivo results from the evaluation of insulin-sensitizing treatments.

Study	Molecule Name/Control Treatment	Effectiveness	Reference
Symmetrical compound			
Blood glucose and triacylglyceride levels	**1G**/PIO (Agopar®)	Similar effect	[1]
Asymmetrical compounds			
Blood glucose level	**1**/glibenclamide	Similar effect	[31]
Blood glucose level	**5**/metformin	Lesser effect	[27]
Serum glucose, cholesterol, TAG, LDL level	**4b**/PIO	Similar effects (only a minor effect for TAG)	[45]
Levels of blood glucose, TAG, cholesterol, and antioxidant molecules (SOD and GSH)	**C40**/PIO (Agopar®)	Greater effect	[2]

Abbreviations: GSH, reduced glutathione; LDL, low-density proteins; PIO, pioglitazone; PPARα, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; SOD, superoxide dismutase; TAG, triacylglycerides.

7. Other Uses of Symmetrical and Asymmetrical Molecules

In the last few years, a variety of new applications have been described for different molecules in the TZD and biguanide groups. Some of them have proven to be efficient in various contexts not related to diabetes (Table 7), which could result from interaction with receptors other than PPARγ or the activation of signaling pathways in a specific manner that controls the expression of certain types of genes. The new findings include the following effects: cardioprotective, antioxidant, α-amylase inhibitor, antihyperlipidemic, anti-inflammatory, anticonvulsant, antidepressant, and anticancer. These effects have at least two explanations, one being the ability of the compounds to bind to more than one protein [6,88–90], and the other the important participation of PPARγ in cellular homeostasis [4,5,91,92]. The new approaches to multitarget therapies have described something that was not considered at the beginning of pharmacology, yet they have existed since drugs were first used.

Table 7. Other applications for thiazolidinediones and biguanides.

Application	Findings	Model	Reference
Thiazolidinediones			
Insulin sensitizer	A dose of <45 mg per day lowered the level of edema as well as the rate of weight gain and heart failure. However, it was not possible to reduce the risk of fractures.	Insulin resistance intervention after a stroke (IRIS) trial in humans	[93]
Cardioprotective agent PIO	The cardioprotective activity of PIO may owe itself to the depleted level of collagenase III in plasma.	Clinical trials	[94]
Anticancer, antiaging	PIO and ROSI presented good affinity for NAF-1 and could be linked to anticancer and anti-aging activity. Additionally, ROSI moderately inhibit complex I of the mitochondrial chain.	Human hepatocellular carcinoma (HepG2) cells overexpressing NAF-1 and complex I.	[20]

Table 7. *Cont.*

Application	Findings	Model	Reference
	Thiazolidinediones		
Antihyperglycemic, α-amylase inhibitors, antioxidants, and antihyperlipidemic agents	Some TZD derivatives were able to inhibit α-amylase more effectively than acarbose. They showed a great capacity for scavenging free radicals (better than vitamin C), leading to a decrease in blood glucose and an antihyperlipidemic effect.	Alloxan-induced diabetes in male Wistar rats. The inhibition of α-amylase was measured in vitro. The DPPH assay revealed antioxidant capacity.	[40]
Anti-inflammatory agents, anticonvulsants and antidepressants	TZDs reduced the expression of microglial and inflammatory cytokines and chemokines in the brain. Likewise, they lowered the level of proinflammatory transcription factors in the CNS. TZDs were capable of inhibiting COX-2, an essential enzyme in the inflammatory cascade. They also activated PPARγ, causing a decline in the amount of TNFα and iNOS. This diminished inflammatory damage and improved the cognitive abilities of patients with Alzheimer's. The antidepressant and anticonvulsant effects were better than the standard drug.	Parkinson's produced by 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) in mice, in other animal models, and in cells.	[95]
Antimalarial	TZDs displayed moderate activity against the growth of *P. falciparum* and weakly inhibited FP-2. Although addition of halogen or electron-withdrawing groups significantly increased the inhibition of the FP-2 enzyme, there was no decrease in whole-cell activity. Hence, the compounds were evaluated with liver microsomes, resulting in rapid degradation, which suggests their metabolic instability.	In vitro inhibition of cysteine protease falcipain-2 (FP-2), whole cells of *Plasmodium falciparum* and hepatic microsomes from human, rat, and mouse liver.	[96]
Anticancer	In some cell lines, TZDs induced apoptosis by inter-nucleosomal DNA fragmentation. Similarly, they inhibited the growth of some adenocarcinomas. TZDs also lowered the level of endotrophin, a vital substance in cancer cells. Additionally, cytotoxic and cytostatic effects have been detected, perhaps due to the repression of human telomerase reverse transcriptase (hTERT).	HL-60 and U937 human myeloid leukemia cells; human alveolar basal epithelial adenocarcinoma A549; human chronic myelogenous leukemia K562; MCF-7 human breast adenocarcinoma; human acute lymphoblastic leukemia MOLT-4; and H1299 cells.	[97]

Table 7. *Cont.*

Application	Findings	Model	Reference
	Thiazolidinediones		
Antioxidant and antigout	TZDs inhibited xanthine oxidase, a metallo-flavoprotein overexpressed in gout, and produced greater levels of reactive oxygen species.	For in vitro tests, the enzyme xanthine oxidase was obtained from rat liver. The antioxidant capacity was measured by the DPPH radical assay.	[98]
Antimicrobial	TZDs with methoxy, fluoro, chloro, and bromo groups helped improve antimicrobial activity by increasing specificity, evidenced by the lack of cytotoxicity for cell lines.	The minimum inhibitory concentration was quantified in vitro with gram-positive bacteria (*Staphylococcus aureus*, *Bacillus cereus*, *Bacillus subtilis*, *Listeria monocytogenes*, and *Micrococcus luteus)* and Gram-negative bacteria (*Pseudomonas fluorescens*, *aeruginosa*, *Escherichia coli*, *Salmonella typhi*, and *Flavobacterium devorans)*. Cytotoxicity was assessed in HeLa and MCF-7 cells.	[99,100]
	Biguanides		
Several types of cancer treatment	Activation of LKB1 and AMPK and inhibition of mTOR activity, inhibition of protein synthesis, cell cycle arrest, triggering of apoptosis and autophagy by p53 and p21, respectively, lowering of blood insulin levels, inhibition of UPR, activation of the immune system, destruction of cancer stem cells, prevention of angiogenesis, and decreased hyperlipidemia.	Clinical trials in non-diabetic patients	[90,101]
Neurodegenerative diseases	AMPK activation via metformin was neuroprotective against Aβ. According to other in vitro studies, metformin reduced phosphorylation through signaling by mTOR/PP2A (protein phosphates 2A) and produced a lesser degree of molecular pathologies associated with Alzheimer's disease. In rodent Parkinson's disease models, dietary metformin diminished oxidative phosphorylation by inhibiting complex I in mitochondria and by inhibiting gluconeogenesis, which further aided neurons to decrease their oxidative burden by minimizing the utilization of NADH. The mTOR pathway links several biological pathways underlying neurodegenerative diseases, and metformin inhibited this signaling cascade.	In vitro studies, mouse models, and clinical trials with diabetic and non-diabetic patients	[21]

Table 7. *Cont.*

Application	Findings	Model	Reference
	Thiazolidinediones		
Acute kidney diseases	Metformin protected renal tubular cells from inflammation, apoptosis, ROS, endoplasmic reticulum stress, and epithelial mesenchymal transition via AMPK activation. Additionally, it inhibited cystic fibrosis transmembrane conductance regulator (CFTR)-mediated fluid secretion and the mTOR-induced cyst formation negatively regulated by AMPK in autosomal dominant polycystic kidney disease. For diabetic patients with kidney diseases, however, clinical investigations have shown an insignificant, even detrimental, effect of metformin.	In vitro studies, animal models, and clinical trials	[102]
Obesity-induced inflammation	Short-term metformin treatment led to greater cytokine levels in hepatocytes, including IL-1 , TNF-α, IL-6, MCP-1, and IFN-α, as well as a higher concentration of IL-1 and IL-6 in a hepatocyte culture medium. Metformin decreased the phosphorylation of c-JNK-1 and the level of fat deposition. In hepatocytes, it diminished the level of pro-inflammatory cytokines, increased AMPK phosphorylation, and reduced fat deposition after long-term treatment.	Obese mice	[6]
Non-alcoholic fatty liver disease (NAFLD)	Metformin lowered hepatocyte triglyceride accumulation triggered by hyperglycemia and hyperinsulinemia. It reduced ApoA5 expression. Metformin-induced down-regulation of ApoA5 was associated with enhanced phosphorylation of cellular AMPK, a metabolite-sensing protein kinase, and LXR. Metformin also decreased the expression of stearyl-coenzyme A desaturase 1 (SCD1), which participates in lipid de novo synthesis and catalyzes saturated fatty acids to form monounsaturated fatty acids. Animal and in vitro models were used.	HepG2 cell line and hepatocytes from obese mice	[6]

Table 7. *Cont.*

Application	Findings	Model	Reference
	Thiazolidinediones		
Polycystic ovary syndrome (PCOS)	Metformin elicited ovulation. It diminished hyperandrogenism through its effect on both the ovary and adrenal gland by suppressing androgen production. This in turn lowered the level of the pituitary luteinizing hormone and increased the generation of sex hormones and their binding with globulin in the liver. There was a decline in ovarian cytochrome P450c17-α activity.	Non-diabetic and diabetic patients, both obese and lean	[103,104]
Dyslipidemia	Metformin decreased the mRNA expression of sterol regulatory element-binding protein 1, ACC1, and ApoA-IV (involved in the secretion of chylomicrons).	Diabetic patients	[6]
Modulation of gut microbiota	A 30-day treatment with metformin significantly modified the expression of 46 gut microbes. After the diversity of the gut microbiota was significantly reduced in mice with diet-induced obesity, and *Akkermansia* spp. was introduced into their gut, glucose homeostasis improved.	Healthy and obese mice	[6]
Antihypertensive effects	Metformin inhibited angiotensin II-induced ER stress by means of AMPK activation.	Diabetic patients	[6]
Cardiovascular Protective Effects	Metformin protected against cardiac ischemia reperfusion injury by activating AMPK, which promoted glycolysis and protected myocyte viability through the closure of the mitochondrial permeability transition pore (PTP), preventing it from opening and rupturing. This effect was mediated by greater phosphorylation of eNOS, resulting in nitric oxide production. Metformin has also been observed to reduce post-ischemia myocardial injury by restoring depleted PGC-1 levels and enhancing in mitochondrial biogenesis.	Clinical trials	[6]

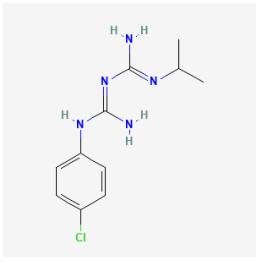
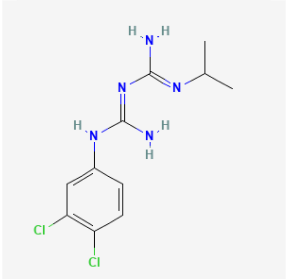
Table 7. *Cont.*

Application	Findings	Model	Reference
	Thiazolidinediones		
Anti-aging	Metformin is involved in the activation of AMPK and the inhibition of signaling through the mTOR pathway. Signaling via mTOR is associated with accelerated aging. AMPK is a key regulator of many cellular pathways linked to both health and lifespan, including the beneficial effects of calorie restriction.	In vitro studies, animal models, and clinical trials	[105]

Abbreviations: ACC1, acetyl coenzyme A carboxylase; AMPK, monophosphate activated kinase; ApoA-IV, apolipoprotein A-IV; ApoA5, apolipoprotein-5; APP, amyloid precursor protein; BACE1, beta-site amyloid precursor protein cleaving enzyme 1; c-JNK-1, c-Jun kinase; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; IFN-α, interferon-α; IL-1, interleukin-1; IL-6, interleukin–6; LKB1, liver kinase B1; LXR, liver X receptor; MCP-1, monocyte chemoattractant protein-1; mTOR, mammalian target of rifampicin; PIO, pioglitazone; PGC-1, peroxisome proliferator-activated receptor gamma coactivator; NADH, nicotinamide adenine dinucleotide; PIKE-L, phosphatidylinositol 3-kinase enhancers; TNF-α, tumoral necrosis factor-α; UPR, unfolded protein response.

Two other biguanides, phenformin and buformin, have been withdrawn from the market in most countries due to toxic effects. These two drugs improved glycemic control of diabetes by increasing insulin sensitivity. Phenformin was generally associated with an unacceptably high incidence of lactic acidosis, which was caused by a decrease in mitochondrial Ca^{+2}, and inversely correlated with elevated blood lactate concentrations [106]. Buformin displayed severe toxicity in cells cultured in galactose, and like phenformin, it diminished ATP (by ~19%) in cells cultured in glucose [107]. Some biguanides (mainly proguanil and chlorproguanil) have been successful for the treatment of malaria, acting against key enzymes in the malaria parasites *Plasmodium falciparum* and *Plasmodium vivax* (Table 8).

Table 8. Other asymmetrical biguanides with therapeutic applications.

Molecule	Structure	Application	Findings	Reference
Proguanil		Prophylactic antimalarial drug	Both drugs inhibit dihydrofolate reductase, an enzyme involved in the reproduction of the malaria parasites *Plasmodium falciparum* and *Plasmodium vivax* in red blood cells.	[108]
Chlorproguanil		Clinical trials for the treatment of malaria		

Symmetrical molecules, as aforementioned, are less common than asymmetrical molecules. The former is mainly found in natural products [8], although some of them have been designed for a wide variety of therapeutical purposes (Table 9). Like dendrimers,

symmetrical molecules can be used for treating diabetes, either through the delivery of genes encoding key proteins in insulin-sensitizing pathways or by loading molecules in these pathways. They have been designed for treating diabetes-related complications as well.

Table 9. Natural and synthetic symmetrical molecules with several therapeutic applications.

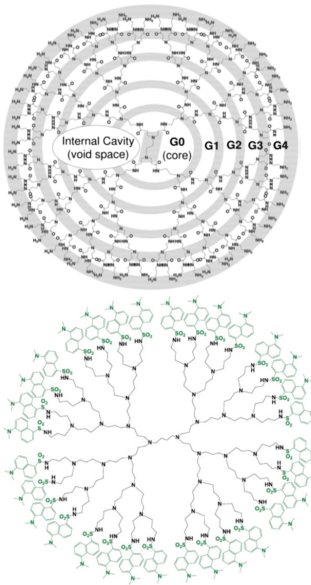
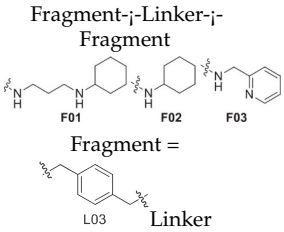
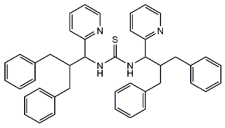
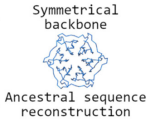
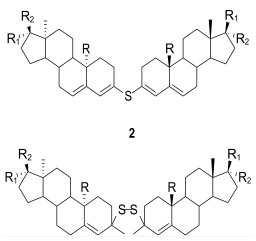
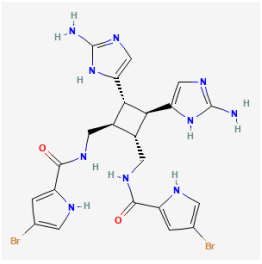
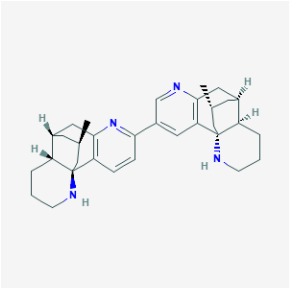
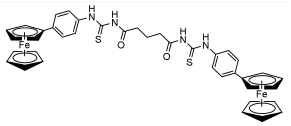
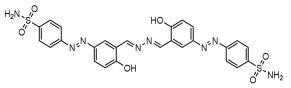
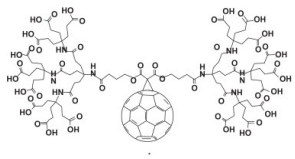
Molecule	Structure	Origin	Findings	Reference
Dendrimers (Polypropylene amine, PAMAM, pseudorotaxane, ethylene diamine, etc.)		Synthetic	Analogous to proteins, enzymes and viruses. Delivers anticancer drugs. Delivers genes. Forms part of contrast agents in magnetic resonance imaging. Serves as a sensor. Enhances solubility. Participates in photodynamic therapy. Dendrimers and other molecules can either be attached to the periphery or encapsulated in their interior voids. Modern medicine uses a variety of these molecules as artificial blood substitutes (e.g., PAMAM dendrimers). Drug–dendrimer conjugates show high solubility, reduced systemic toxicity, and selective accumulation in solid tumors.	[109]
Polyamines synthesized as potential small molecule CXCR4 antagonists		Synthetic	Antagonist that blocks the entry of human immunodeficiency virus type 1 (HIV-1).	[110]
Thioureas		Synthetic	Antioxidant activity that scavenges ABTS, and antibacterial activity against *Agrobacterium tumefaction*.	[12]
Proteins		Synthetic	The redesign of existing proteins may result in enhanced functions. Energy minimization is achieved by symmetrical assemblies.	[111]
Steroid dimers		Synthetic	Improvement of biological potential leads to antiproliferative activity in human cell lines of cervical cancer (HeLa), breast cancers (MDA-MB-453 and MDA-MB-361), and leukemia (K562), with values ranging from 14.9 to 27.1 µM (values for cisplatin ranged from 2.1 to 17.1 µM). Dimeric compounds exhibited antifungal activity against *Saccharomyces cerevisiae*.	[112]

Table 9. *Cont.*

Molecule	Structure	Origin	Findings	Reference
Sceptrin		Natural product	Antibacterial, antiviral, antihistaminic, and antimuscarinic agent, and possibly beneficial in treating coronavirus disease (COVID).	[8,113,114]
Complanadine A		Natural product	Treatment for Alzheimer's disease or spinal cord injury.	[8,115]
G_{3F}		Synthetic	Antifungal and antidiabetic activity. Docking results show that the lowest energy value is for α-amylase and α-glucosidase. In vitro studies with these two enzymes yielded IC_{50} values of 22.8 and 21 µg/mL, respectively.	[11]
5g		Synthetic	α-Glucosidase and α-amylase inhibitors. Electron attracting substituents on the aromatic ring favor inhibition.	[19]
Dendro fullerenes		Synthetic	Antiviral. Fullerene is able to fit inside the hydrophobic cavity of HIV proteases, inhibiting the access of substrates to the catalytic site of the enzyme. If exposed to light, fullerene produces singlet oxygen with high quantum yields. This activity, together with direct electron transfer from the excited state of fullerene and DNA bases, can be used to cleave DNA.	[30]

Abbreviations: ABTS, 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid); COVID, coronavirus disease; HIV, human immunodeficiency virus; IC_{50}, mean inhibitory concentration; PAMAM, polyaminoamine.

8. Conclusions

The very limited study of symmetrical molecules as antidiabetic agents has restricted their clinical evaluation and use. Contrarily, there has been much attention given to asymmetrical TZD molecules. Research on symmetrical insulin-sensitizing drugs should be broadened, emphasizing the structural regions of molecules theoretically capable of favoring interaction with the target receptor and those experimentally proven to be effective in vivo. Perhaps it would be appropriate to avoid the antioxidant capacity of the pharmacophore so as not to interfere with the ligand-receptor interaction. It may also be advantageous to increase the length of the molecule in order to stabilize the beta 1 sheet of the LBP of PPARγ. Solubility is another characteristic that should be considered since symmetry might not favor bioavailability. According to the findings, moreover, asymmetrical molecules are currently the best option for insulin sensitizers. Their effectiveness increases with a longer hydrophobic region, which can cause stabilization of PPARγ by inhibiting phosphorylation at Ser245. Just as asymmetry has its advantages and disadvantages in drug design, so does symmetry. It is important to expand the investigation of symmetrical

molecules in relation to diabetes and other diseases (e.g., cancer and infections) to take advantage of their potential and broaden the available options for treatment.

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