



Review

Tetrazoles and Related Heterocycles as Promising Synthetic Antidiabetic Agents

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Abstract: Tetrazole heterocycle is a promising scaffold in drug design, and it is incorporated into active pharmaceutical ingredients of medications of various actions: hypotensives, diuretics, anti-histamines, antibiotics, analgesics, and others. This heterocyclic system is metabolically stable and easily participates in various intermolecular interactions with different biological targets through hydrogen bonding, conjugation, or van der Waals forces. In the present review, a systematic analysis of the activity of tetrazole derivatives against type 2 diabetes mellitus (T2DM) has been performed. As it was shown, the tetrazolyl moiety is a key fragment of many antidiabetic agents with different activities, including the following: peroxisome proliferator-activated receptors (PPARs) agonists, protein tyrosine phosphatase 1B (PTP1B) inhibitors, aldose reductase (AR) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists, G protein-coupled receptor (GPCRs) agonists, glycogen phosphorylases (GP) Inhibitors, α -glycosidase (AG) Inhibitors, sodium glucose co-transporter (SGLT) inhibitors, fructose-1,6-bisphosphatase (FBPase) inhibitors, I κ B kinase ϵ (IKK ϵ) and TANK binding kinase 1 (TBK1) inhibitors, and 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1). In many cases, the tetrazole-containing leader compounds markedly exceed the activity of medications already known and used in T2DM therapy, and some of them are undergoing clinical trials. In addition, tetrazole derivatives are very often used to act on diabetes-related targets or to treat post-diabetic disorders.

Keywords: tetrazoles; antidiabetic agents; type 2 diabetes mellitus; peroxisome proliferator-activated receptors (PPARs) agonists; aldose reductase (AR) inhibitors; dipeptidyl peptidase-4 (DPP-4) inhibitors; G protein-coupled receptor (GPCRs) agonists



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1. Introduction

Diabetes mellitus is an incurable disease defined by a metabolic disorder with hyperglycemia, contributing to a number of dangerous diseases: hypertension, thrombosis, neurodegenerative disorders, and so on. Hyperglycemia may be due to poor cellular susceptibility to insulin (insulin resistance) or type 2 diabetes mellitus (T2DM), as well as insufficient secretion of insulin by the pancreas (type 1 diabetes mellitus). Currently, the number of T2DM cases is constantly increasing, and the disease is now considered to be one of the non-transmittable chronic disease epidemics. The problem affects different populations, genders, and ages. Overall, T2DM accounts for about 90% of all cases of diabetes mellitus. To date, there are hundreds of millions of known documented cases of T2DM in the world. Note that not all cases of diabetes are reliably documented. According to International Diabetes Federation (IDF) data, the total number of people living with diabetes is projected to rise to 643 million by 2030 and 783 million by 2045 [1,2]. Type 1 diabetes mellitus can be controlled with the external administration of insulin. In contrast, a direct injection of insulin in the case of T2DM will not significantly reduce blood glucose.

Here, drug therapy is required to target the various biological mechanisms responsible for metabolic processes. A great deal of studies have been dedicated to the development of such drugs, and these studies are being intensively developed [3].

A large number of natural compounds with antihyperglycemic effects are known [4,5], but it is the synthetic drugs that are most widely used in the treatment of diabetes. Dozens of the biological targets of low-molecular antidiabetic agents are well recognized: the incretin hormones Glucagon-like Peptide-1 (GLP-1) and Glucose-Dependent Insulinotropic Polypeptide (GIP) themselves; their regulators such as Dipeptidyl Peptidase-4 (DPP-4); G protein-Coupled Receptors (GPCRs) such as GPR40, GPR120, and GPR119; Glucose Metabolism Pathway-Based Targets, such as Glucose Kinase (GK), Protein Kinase B (AKT/PKB); Insulin-Based Targets like Protein Tyrosine Phosphatase 1B (PTP1B); and other types of targets like Sodium-Glucose Cotransporter Protein-2 (SGLT-2), Peroxisome Proliferator-Activated Receptors (PPARs), etc. [6]. Antidiabetic drugs can have fundamentally different chemical structures, and they can hardly be assigned to a certain type. As can be seen, for example, from Figure 1, the following chemical compounds of different classes can be used as hypoglycemic agents: biguanides, sulfonylureas, thiazolidinediones, pyrimidines, purines, sugars, oligonucleotides, peptides, and many others [7,8]. In addition, other multiple medications are commonly used in combination with antidiabetic drugs to suppress secondary effects associated with T2DM and high blood sugar levels: cardiovascular and neurological agents, immunomodulators, and many others. Thus, medical treatments for T2DM are complex processes, and drug therapy, in combination with proper diet and lifestyle, can significantly improve the patient's condition and reduce the dangerous consequences of hyperglycemia. Nevertheless, to date, there are no universal and highly effective drugs, either of natural or synthetic origin, to cure T2DM. The known drugs have a number of side effects, which has even led to a ban on the use of some of them [7]. Therefore, the development of more effective medications for the treatment of T2DM remains very important.

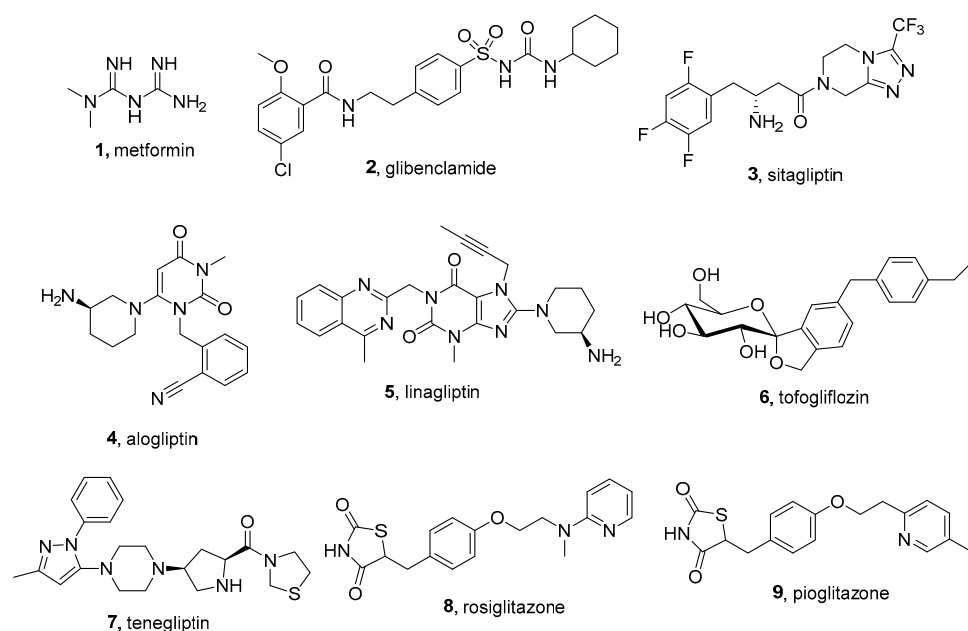


Figure 1. Some low-molecular oral antidiabetic medications: 1—metformin (known since 1922, decreases glucose production in the liver, increases the insulin sensitivity of body tissues), 2—glibenclamide (known since 1960s, stimulates insulin secretion by pancreatic β -cells, increases insulin release), 3—sitagliptin (DPP-4 inhibitor, Merck), 4—alogliptin (DPP-4 inhibitor, Takeda Pharmaceutical Company), 5—linagliptin (DPP-4 inhibitor, Boehringer Ingelheim), 6—tofogliflozin (SGLT-2 inhibitor, Chugai Pharma), 7—teneligliptin (DPP-4 inhibitor, Mitsubishi Tanabe Pharma), 8—rosiglitazone (PPAR agonist, GlaxoSmithKline), 9—pioglitazone (PPAR agonist).

2. Tetrazoles for Biomedicine

It can be seen from Figure 1 and the cited literature sources that most of the known antidiabetic drugs in use include nitrogen heterocyclic moieties: azoles, azines, annelated azoloazines, oxazoles, thiazoles, and some others. The development of novel antidiabetic agents often involves the use of polynitrogen heterocyclic systems with more than two endocyclic heteroatoms (triazoles, tetrazoles, oxadiazoles, or their fused derivatives) as key scaffolds [8–10]. These moieties are very promising in drug design because they are often metabolically stable, easily participate in various intermolecular interactions through hydrogen bonding, conjugation, or van der Waals bonding with biological targets, and many of them are bioisosters of functional groups of endogenous molecules [11].

Among other heterocyclic systems, the tetrazole cycle has a unique structure and unique properties. Despite the fact that the tetrazole cycle contains only one endogenous carbon atom and four nitrogen atoms, it is a very thermally and metabolically stable system. Previously, the synthesis and properties of tetrazoles have been discussed in detail in numerous reviews and monographs, including by the authors of this review [12–16].

Tetrazolyl moiety is present in the top 10 most frequent nitrogen heterocycles in US FDA-approved drugs and in a total of 16 pharmaceuticals [11]. This heterocycle is incorporated into active pharmaceutical ingredients of medications of various actions: hypotensives 10–12, diuretic 13, antihistamines 14–15, antibiotics, analgesics, and some others (Figure 2) [17].

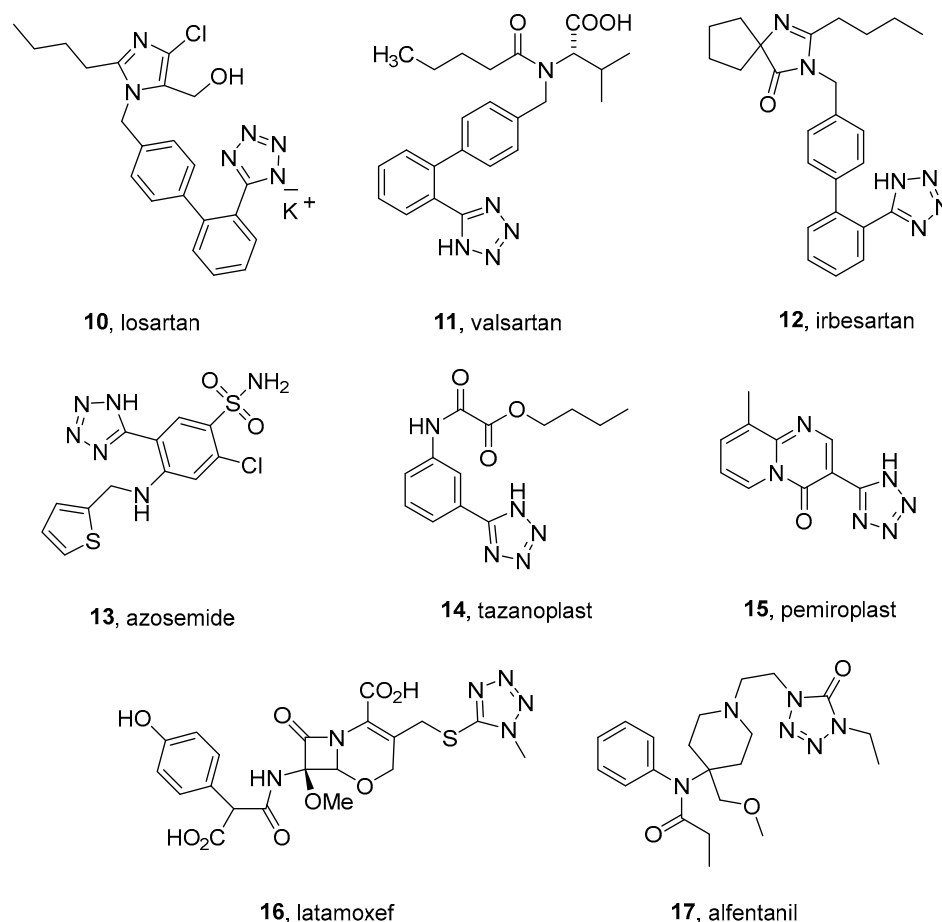


Figure 2. Some examples of tetrazole-containing medications.

Quite a lot of research has been devoted to the medicinal chemistry of tetrazoles, the results of which are summarized in a number of reviews on this topic [16–21]. Significant achievements have been made in the field of drug development for hypotensive, anticancer

drugs, semi-synthetic antibiotics, and agents acting on the central nervous system [17,19]. However, there are few data points, and there is no systematic analysis of the antidiabetic activity of tetrazole derivatives. In view of the above, this review can fill this gap.

Tetrazoles vary greatly in properties depending on their prototropic form and substituent isomerism (Figure 3).

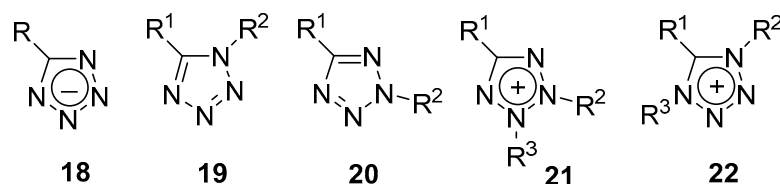
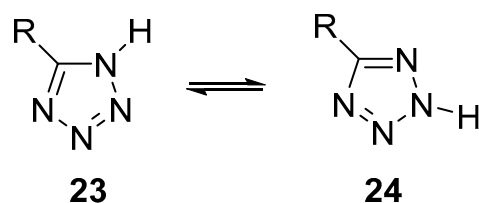


Figure 3. Main isomeric forms of tetrazoles.

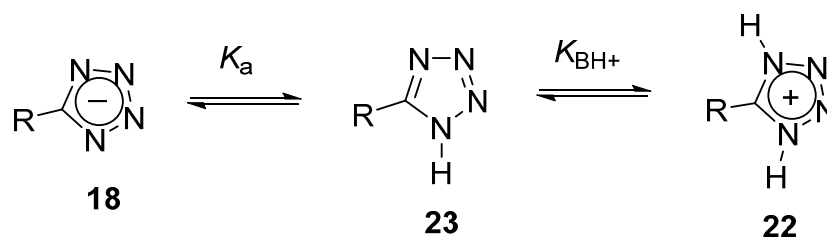
Tetrazolate anions (tetrazolides) **18** are highly nucleophilic particles that are very soluble in water and other polar solvents and easily coordinate with transition metal ions [22]. Neutral *1H*-tetrazoles **19** are usually more polar and thermally stable than *2H*-tetrazoles **20**. Isomeric tetrazolium ions **21**, **22** are also very different in their properties. For example, cycle **21** can easily open under radiolysis, while ion **22** is still stable under these conditions [23]. The high stability of tetrazole forms can be partially explained with the sufficiently high aromaticity of the heterocycle. All the forms are planar and highly conjugated systems. Thus, the structural criteria of aromaticity for *2H*-tetrazoles **20**, especially tetrazolides **18**, are close to those for benzene [24].

NH-Unsubstituted tetrazoles may exist as *1H*- and *2H*-tautomers **23** and **25** (Scheme 1). The most polar form **23** (where R is an electron-donor substituent or hydrogen) is preferred in condensed media (solutions or crystals), whereas the less polar *2H*-form **24** with the same substituents prevails in the gas phase and non-polar solvents [25].



Scheme 1. Tautomerism of *NH*-unsubstituted tetrazoles.

Tetrazoles are relatively strong *NH*-acids and weak bases (Scheme 2). The acidity of *NH*-tetrazoles **23** is comparable to that of aliphatic carboxylic acids. The acidity of parent tetrazole is pK_a 4.9, and depending on the nature of the C^5 -substituent, it can vary from 6 (for 5-aminotetrazole) to -1 (for 5-nitrotetrazole). Tetrazoles are also weak bases that ionize in strong mineral acids (for parent tetrazole, pK_{BH^+} -2.7), and their basicity can vary in the range pK_{BH^+} $-1 \div -9$ [25].



Scheme 2. Ionizations of tetrazoles.

A special mention should be made of the unique ability of the tetrazole cycle to form stable hydrogen bonds simultaneously with several proton donors and acceptors

(Figure 4). Such interactions are often predominant in the binding of active molecules to their biological targets. As we have recently shown, based on theoretical and experimental pK_{HB} values, tetrazoles are sufficiently strong bases for the formation of hydrogen bonding, and the substituent at position 5 of the cycle has a noticeable effect on the basicity [26].

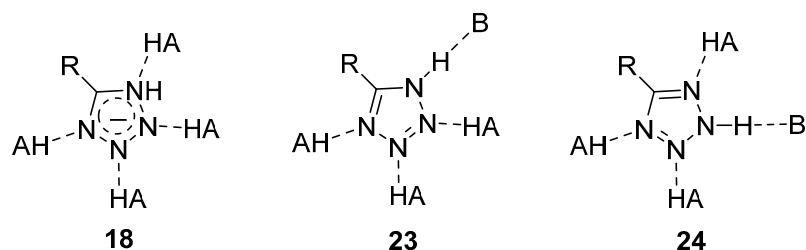


Figure 4. Possible ways of hydrogen bonding for different prototropic forms of 5-R-tetrazoles.

It is now generally accepted that neutral 1*H*-tetrazole forms **19**, **23** are metabolically stable bioisosteric analogs of *cis*-amide and carboxyl groups, and tetrazolide **18** is an analog of carboxylate anion. However, in recent years, this concept of bioisosterism has been refined. As shown by Allen and co-authors, based on the analysis of crystallographic data and the results of theoretical calculations, the nature of hydrogen bond formation in pairs—1*H*-tetrazole-COOH and tetrazolide-carboxylate—is somewhat different [27]. The authors of the cited work also indicated that the functional groups of biomolecules linked by hydrogen bonds to 1*H*-tetrazole or tetrazolate anion are located at a distance greater by approximately 1.2 Å compared to the isosteric fragments of -COOH and -COO⁻. Our recent quantitative studies of the hydrogen bonding basicity of tetrazoles also support the fact that their ability to form hydrogen bonds is unique and significantly different from the carboxylic group [26].

Further, we have tried to analyze and structuralize the known studies, which examined the direct antidiabetic action of tetrazole derivatives towards known established biological targets. The sequence of the materials is presented in accordance with the effectiveness and scope of the results obtained for bioactive tetrazoles, and it is structured according to the targets of action.

We intentionally omit a large number of publications in which biologically active tetrazoles are considered components of the complex therapy of T2DM. For example, sartans **10–12** and angiotensin II receptor (ATR) blockers are very often used in this context, and ATRs are considered diabetes-associated targets. The use of sartans prevents the development of diabetes in hypertensive patients and reduces the progression of cardiovascular and renal diseases [28].

3. Low-Molecular Antidiabetic Agents Containing Tetrazolyl Moiety

3.1. Peroxisome Proliferator-Activated Receptors (PPARs) Agonists

Peroxisome proliferator-activated receptors (PPARs) belong to a large family of ligand-inducible nuclear hormone transcription factors that regulate the expression of genes responsible for the differentiation and function of adipose tissue, lipid metabolism, the severity of the inflammatory response, and the production of cytokines and adhesion factors by cells. Three isoforms have been identified in human PPAR: PPAR α , PPAR γ , and PPAR β/δ [29]. Each isoform is encoded by its specific gene and has its own tissue specificity. PPAR α is expressed mainly in liver, brown fat, kidney, heart, and skeletal muscle cells; PPAR γ is expressed in adipose tissue and small intestine; and PPAR β/δ is expressed in skeletal muscle, heart, adipose tissue, and keratinocytes [30]. PPAR α exerts control in lipoprotein assembly and also influences the rate of cholesterol synthesis in hepatocytes. Two isoforms—PPAR γ 1 and PPAR γ 2 are known. The PPAR γ 2 isoform is found in adipocytes, whereas PPAR γ 1 is common in skeletal muscle. PPAR γ regulates tissue glucose content through changes in insulin receptor sensitivity. The insulin-sensitizing

effect of this receptor isotype has been shown to be based on stimulation of proliferation of white adipose cells, which are highly sensitive to insulin. PPAR δ/β is expressed in many tissues and acts as a sensor of polyunsaturated fatty acids. Its overexpression enhances fatty acid oxidation in mitochondria and also reduces obesity and insulin resistance. PPARs are short-lived proteins whose activity changes rapidly in response to ligands (agonists). Such ligands can be fatty acids, endogenous fatty acid metabolites, or synthetic substances. It should be noted that the development of synthetic drugs acting on PPARs is very promising due to the fact that these proteins are highly conserved [29]. In principle, action on all three PPAR isotypes can be successfully applied in the therapy of T2DM, metabolic syndrome, and related diseases. Synthetic chemical compounds that act as agonists of one, two (PPAR α , PPAR γ), or all isotypes of these receptors are known (Figure 5) [30,31]. Nevertheless, today, the major part of the research in drug design for the treatment of T2DM involves the consideration of PPAR γ as a target [8]. It should be noted that some representatives of these ligands, such as thiazolidenediones, exhibit significant toxicity [30]. The development of new agonists of PPARs, especially PPAR γ agonists, has been a very urgent task for a long time.

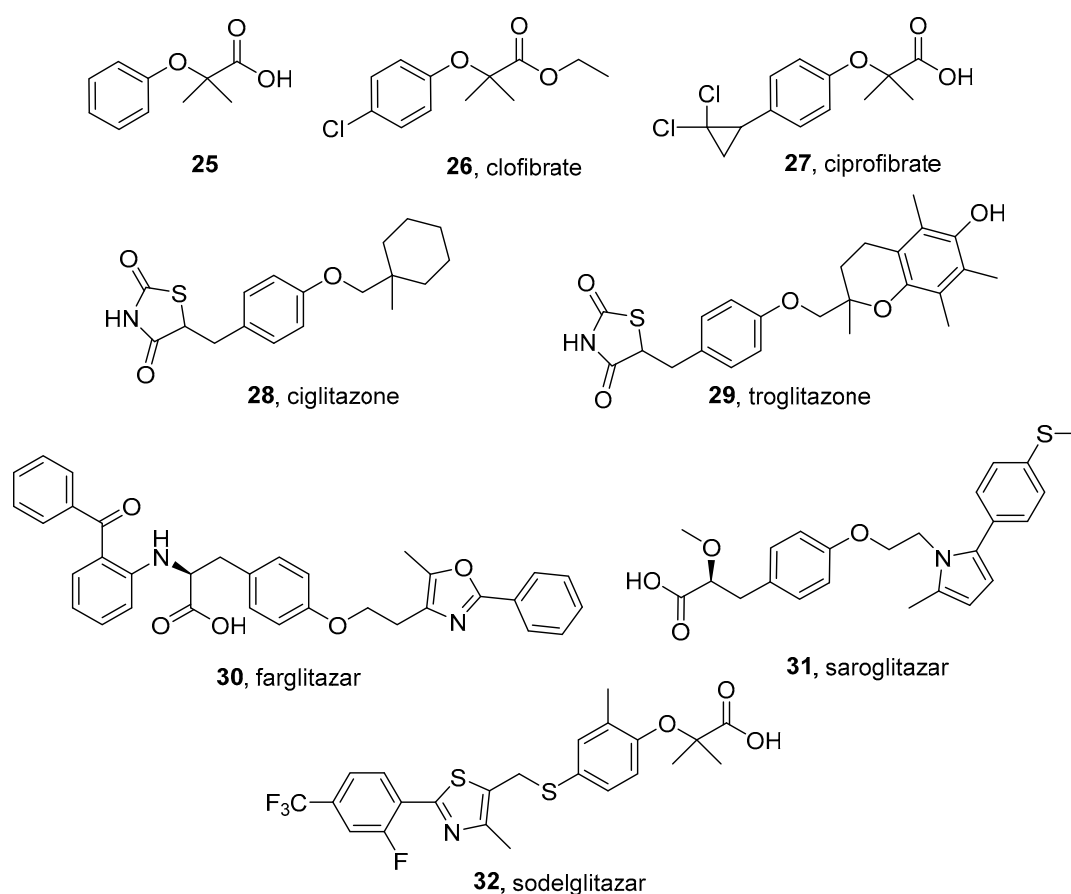


Figure 5. Some low-molecular PPAR agonists: fibric acid **25** and its derivatives **26**, **27** (PPAR- α); thiazolidinediones **28**, **29** (PPAR- γ); glitazars **30** (PPAR- γ), **31** (dual PPAR- α and PPAR- γ), **32** (all PPARs).

Kees et al., in 1989, synthesized and investigated *in vivo* the hypoglycemic activity of a number of tetrazol-5-yl-perfluoro-anilides **33**, **34** on two genetic animal models: obese (ob/ob) and diabetic (db/db) mice (Figure 6). According to the results obtained, perfluorooctanoyl and perfluorononanoyl derivatives showed greater efficacy in normalizing glucose and insulin levels than ciglitazone **28** [32]. Later, these authors somewhat extended the discussed compounds by considering not only perfluoronanilides but also related perfluorocarbon derivatives **35**, **36**, their salts, and so on [33,34]. Whereas the thiazolidine-

diones require the acidic proton on the heterocycle for activity, tetrazolyl derivatives of perfluoro anilides retained antihyperglycemic efficacy in ob/ob mice after alkylation. Although the authors did not specify the biological target for these compounds, tetrazoles **33–36** can be considered structural analogs of typical PPAR γ inhibitors-thiazolidinediones. Significant side effects were also observed for these compounds.

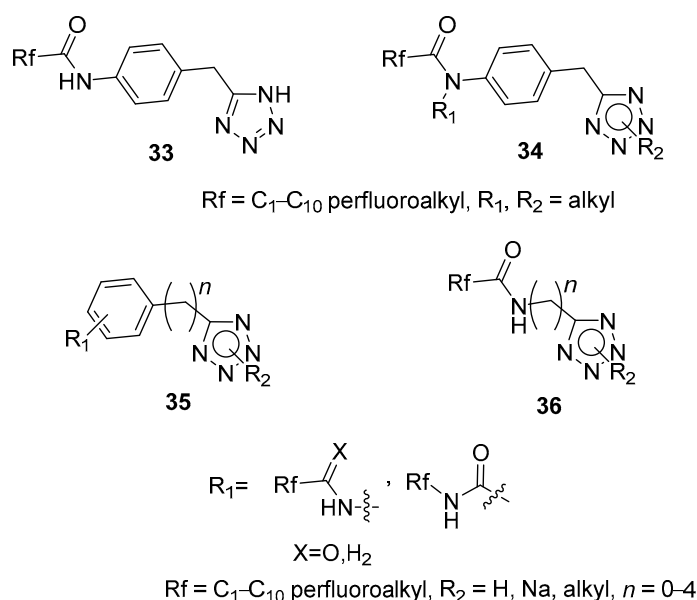


Figure 6. Perfluoroalkyl tetrazoles as antihyperglycemic agents.

It is known that among the derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, effective compounds that are to be PPAR agonists with protein tyrosine phosphatase 1B (PTP1B) inhibition have been found [35]. Morishita et al., in 2019, first synthesized two tetrazolyl derivatives **37**, **38a** based on the related 1,2,3,4-tetrahydroisoquinoline scaffold (Figure 7) [36]. One of these compounds, **38a**, proved to be ten times more active than the well-known drug farglitazar **30** (10^{-7} M) and selective PPAR γ agonist in vitro on COS-1 cells with the human RXR α plasmid and electroporated full-length human PPAR plasmids. At the same time, the effect of **38a** on other PPARs and PTP1B was insignificant. The substitution of an oxygen atom for a sulfur atom in the linker fragment strongly reduced the activity (Figure 7). The significant affinity of **38a** for PPAR γ was also confirmed with theoretical calculations and the interaction of the tetrazolyl fragment with amino acid residues of the protein occurring via salt bridges and hydrogen bonds. Other heterocycles did not show such high activity in this case. Later, the authors extended the series of seven-substituted-2-[(E)-3-(2-furyl)-acryloyl]-6-tetrazolyl-1,2,3,4-tetrahydroisoquinoline derivatives **38a–e** that were synthesized and their PPAR γ partial agonist activity in vitro on COS-1 cells was studied [37]. In this series, a number of compounds turned out to be very active, and the leader was a derivative containing a dihydropyrrole moiety **38e**, which was marked by the authors as KY-903 (Figure 7). The PPAR γ agonist potency of **38e**, based on its EC₅₀ value, was 68-fold stronger than that of pioglitazone **9** [38]. It was once again pointed out that the replacement of tetrazolyl fragments, even with a structure-closed substituent, dramatically affected the activity of the compound. In vivo studies of the compound-leader KY-903 **38e** effects on KK-Ay mice and OVX/HFD rats showed that this compound has weaker adverse effects than pioglitazone **9**, such as increases in body and adipose tissue weights and bone loss are attributed to adipogenesis induced by PPAR γ activation [38].

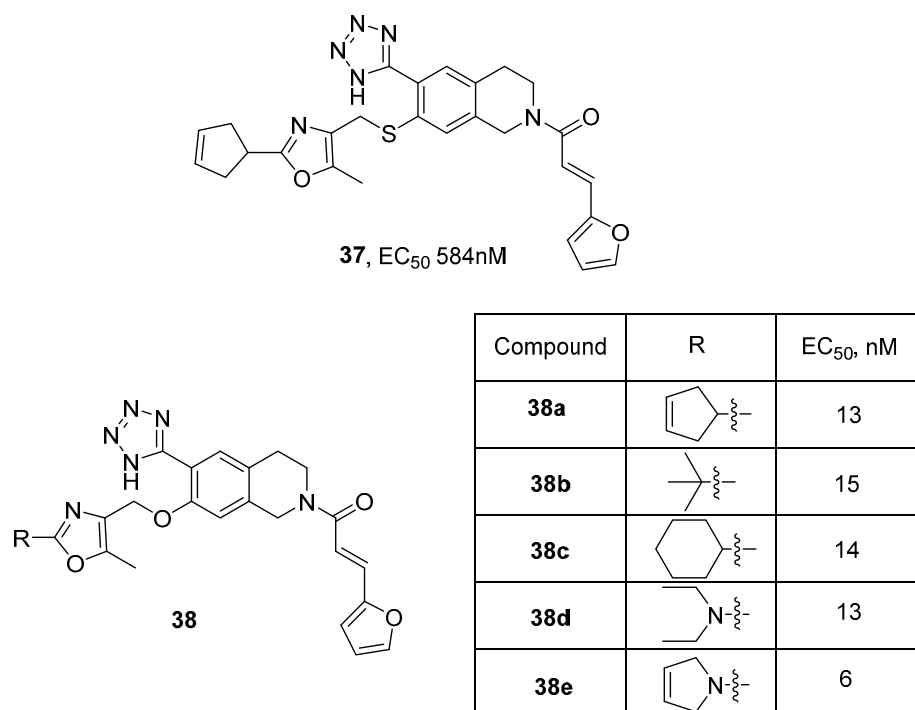


Figure 7. Tetrazol-5-yl-1,2,3,4-tetrahydroisoquinolines as selective PPAR- γ agonists.

A wide series of five-substituted *NH*-tetrazoles, most of which can be described with the general formula **39**, as potential PPAR γ agonists were synthesized by Momose et al. (Figure 8) [39]. Their activity as PPAR γ agonists *in vitro* on PPAR γ :RXR α :PPRE34/CHO K1 cells and lipid-lowering activities *in vivo* on KKAY mice and Wistar fatty rats were studied. These compounds may be considered as glitazone analogs where thiazolidinedione moiety is substituted with the tetrazolyl one. Leader compound, 5-[3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propyl]-1*H*-tetrazole **40**, possessed high antidiabetic effects due to its potent agonistic activity for PPAR γ (EC₅₀ 6.75 nM) and potent glucose-lowering activity (ED₂₅ 0.0839 mg kg⁻¹ day⁻¹), being 72 times more active than pioglitazone hydrochloride **9** (ED₂₅ 6.0 mg kg⁻¹ day⁻¹).

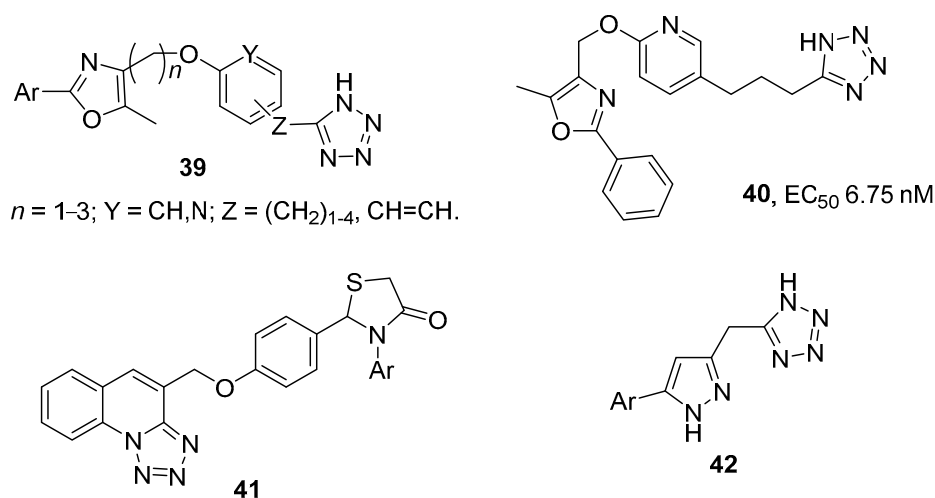


Figure 8. Tetrazole analogs of glitazones as PPAR γ agonists.

A series of three-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones **41** were synthesized, and the effects of these compounds on the improvement of oral glucose tolerance in a sucrose-loaded rat model were investigated

(Figure 8) [40]. Thiazolidinones **41** displayed notable *in vivo* antihyperglycemic activity compared with metformin **1**, and it was proposed that they interact with active sites of PPAR γ . One more analog of glitazones-5-(pyrazol-3-yl)-1*H*-tetrazoles **42** was obtained (Figure 8) [41]. Their agonistic property via PPAR-trans-activation assay was studied but none of them demonstrated any significant activity. According to results of *in vivo* antihyperglycemic activity studies of compounds **42** in sucrose loaded models on Sprague–Dawley rats, only one compound (Ar = 4-CH₃S(CH₂)₂C₆H₄) demonstrated 24.6% of blood glucose lowering activity, which is two times higher than that of metformin **1**.

From the data of the paper [42], the computational analysis suggested that mercapto tetrazole **43** will bind to PPAR γ selectively (Figure 9). However, according to the *in vitro* experiment against this receptor, its activity was lower than for rosiglitazone **8**. In this experiment, hPPAR γ -LBD was cloned into pET28a plasmid and transformed in BL21 DE3 *Escherichia coli* strain. A little later, the same authors investigated three isomeric tetrazole derivatives **44–46**, structurally similar to thiazolidinones, using theoretical and experimental methods (Figure 9) [43]. According to the results obtained, all isomers are able to bind effectively to the PPAR γ ligand binding domain, but the binding energy is still somewhat lower than for rosiglitazone **8**. This is in agreement with the experimental data *in vitro* determined in this assay: rosiglitazone **8** IC₅₀ 160 nM, **44** IC₅₀ 20 μ M, **45** and **46** IC₅₀ 4 μ M. The crystal structure of the PPAR γ /**45** complex was determined, confirming the binding mode.

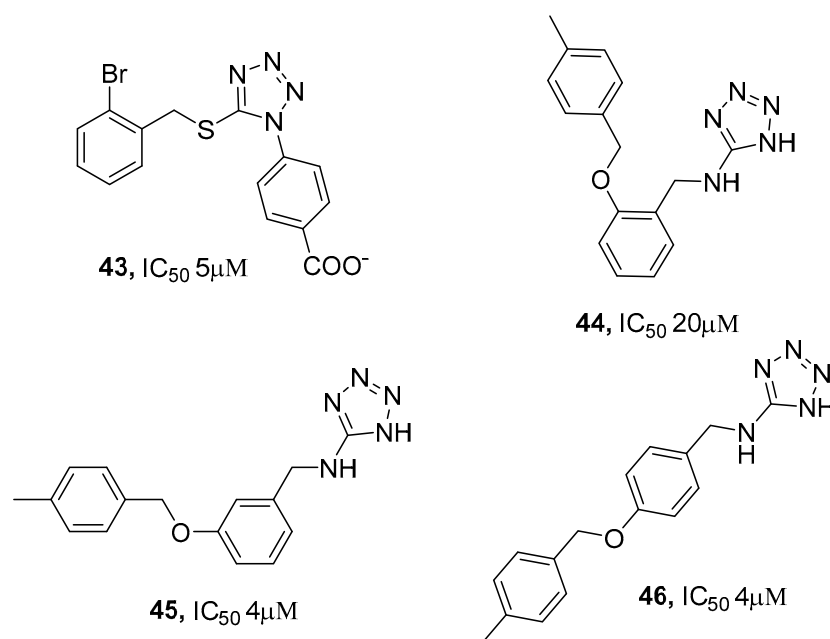


Figure 9. Tetrazole analogs of thiazolidinones as PPAR- γ agonists.

Pattana et al. synthesized sulfamide **47** containing tetrazol-5-yl moiety (Figure 10), and most of them showed good activity compared to glibenclamide **2** [44]. Two series of tetrazolyl derivatives as possible hypoglycemic agents (tetrazolo[1,5-*c*]quinazolin-5(6*H*)-ones **48** and 1-[2-(1*H*-tetrazol-5-yl)aryl]-3-aryl(ethyl)ureas **49**), belonging to ureas or biguanides antidiabetic agent types, were synthesized by Antypenko et al. (Figure 10) [45]. According to the molecular docking calculations, compound **49** (R₁ = H, R₂ = 4-CF₃) demonstrates a good affinity to the PPAR γ receptor with -10.1 kcal mol⁻¹. Dexamethasone diabetes models (glucose tolerance, oral rapid insulin, and adrenalin tests) were used to determine the specific hypoglycemic activity, and compound **48** (R=H) revealed high activity, exceeding the reference drugs metformin **1** and gliclazide on White Wistar rats.

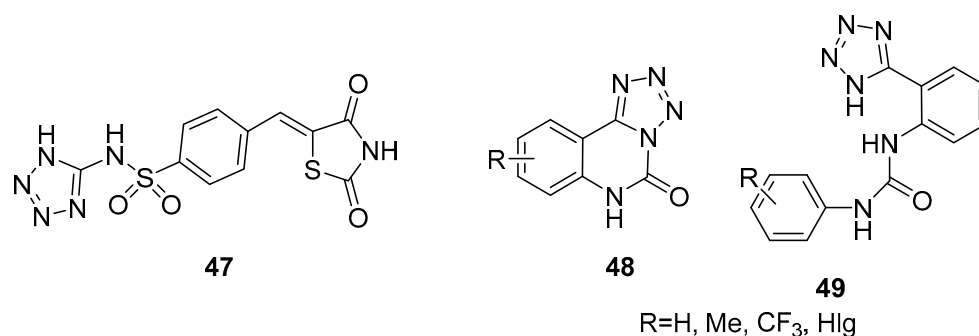
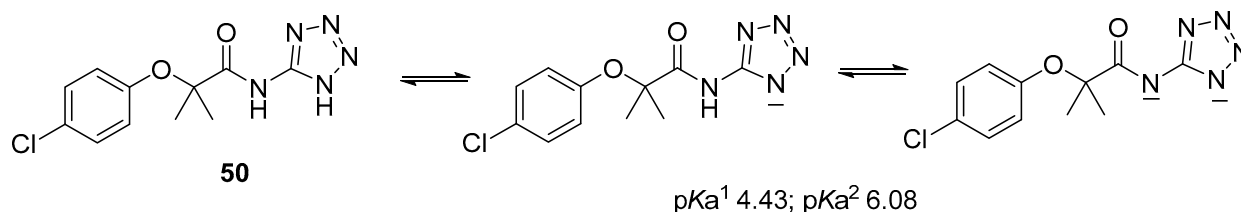
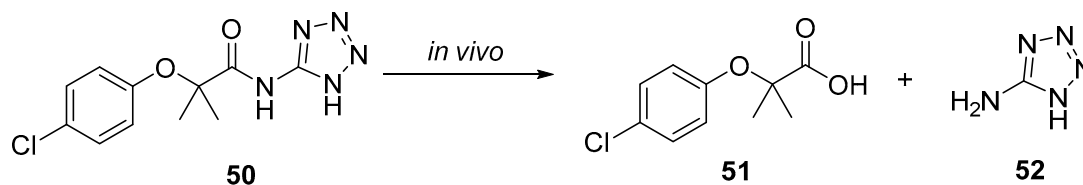


Figure 10. Tetrazolyl sulfamides, ureas and biguanides as PPAR- γ agonists.

The tetrazole analog of clofibric acid **50**-2-(4-chlorophenoxy)-2-methyl-N-(1*H*-tetrazol-5-yl) propanamide, presumed to be a PPAR α agonist, was obtained, and its properties were studied [46,47]. The antidiabetic activity of compound **50** was determined at 50 mg kg⁻¹ single dose using the diabetes mellitus rat model. The results indicated a significant decrease in plasma glucose levels during the 7 h post-administration. This compound may exist in dissociated form (Scheme 3) and should be metabolized *in vivo* with the release of free clofibric acid **51** (Scheme 4). At the same time, the overall toxicity of tetrazole **50** is lower than that of clofibric acid **51**. Thus, compound **50** may be considered a prodrug of **51** as an antidiabetic and anti-dyslipidemic agent.



Scheme 3. Dissociation of tetrazole analog of clofibric acid.



Scheme 4. Hydrolysis of tetrazole analog of clofibric acid *in vivo*.

3.2. Protein Tyrosine Phosphatase 1B (PTP1B) Inhibitors

The insulin and leptin action is controlled through a balance between the phosphorylation and dephosphorylation of insulin and leptin receptors. The action of insulin and leptin is co-directed and results in increasing energy stores in glycogen form in muscle and liver as triglycerides in adipose tissue. The intracellular enzyme protein tyrosine phosphatase 1B (PTP1B) is a negative regulator of the insulin and leptin signaling cascades: its activation leads to the sensitivity-lowering of the corresponding receptors [48,49]. PTP1B can also influence other biological processes and is expressed in multiple tissues, including the skeletal muscle, liver, adipose tissue, and brain [50]. PTP1B inhibitors enhance insulin and leptin signaling and could potentially improve insulin resistance, normalizing plasma glucose and insulin levels without inducing hypoglycemia [51]. Recently, various PTP1B inhibitors have been developed as drug candidates for T2DM therapy (Figure 11) [8,48,51]. These compounds belong to various types of organic or inorganic compounds: aromatics, nitrogen-containing heterocycles, sulfamides, semi-synthetic terpenes, oligonucleotides,

ureas, and vanadium complexes [48,52]. Thiazolidenones and some other typical agonists of PPARs can also act as inhibitors of PTP1B [8]. Thus, a number of the tetrazole PPAR ligands discussed above also weakly inhibit PTP1B; for example, compound **38a** IC₅₀ 1100 nM [36].

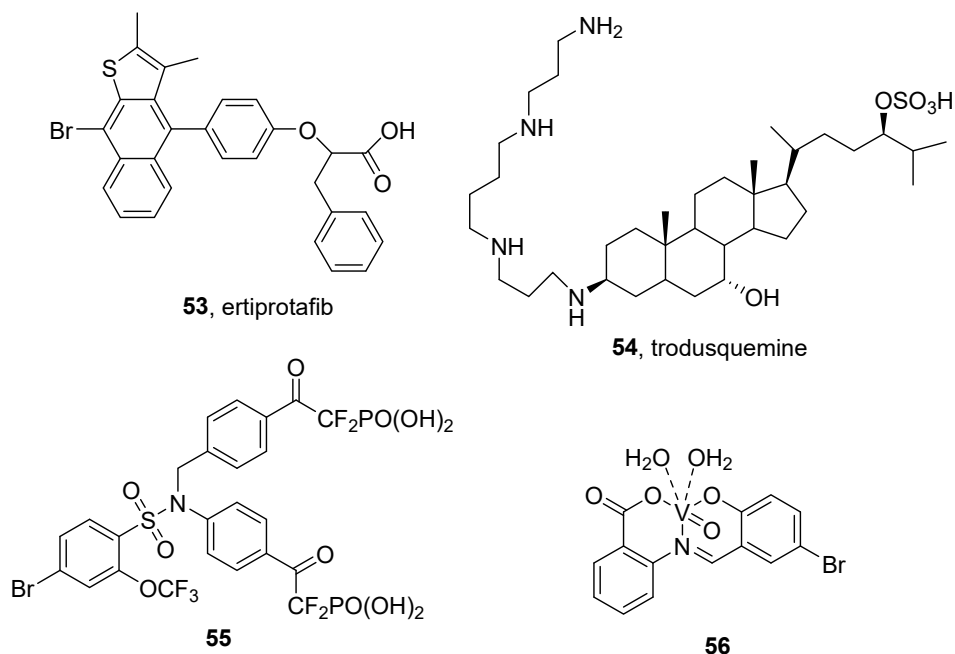


Figure 11. Low-molecular PTP1B inhibitors.

Based on docking and MD modeling, Murthy and Kulkarni suggested that compounds containing tetrazolyl functional groups might exhibit relatively good activity as PTP1B inhibitors. Also, it is possible to incorporate sulfonate or tetrazolyl moieties instead of phosphate ones in the further design of compound-leaders. These results are supported using surface area calculations and are consistent with the inhibitor activity of the compounds [53].

Small molecular-weight peptidomimetics as competitive inhibitors of PTP1B have been synthesized by Liljebris et al. (Figure 12) [54]. Tetrazole **57** showed good PTP1B inhibitory activity (K_i 2.0 μ M), which was equipotent to the dicarboxylic acid analog **58**. The X-ray cocrystal structure of **57** and PTP1B revealed that the tetrazolyl moiety is positioned in the active site and binds similarly to carboxylate analog **58**. It should be noted that isomeric compound **59** did not show such activity.

A series of non-carboxylic inhibitors of PTP1B-N-(3-(1H-tetrazole-5-yl) phenyl) acetamides was synthesized and evaluated in vitro (Figure 12) [55,56]. Two compounds **60a,b** were found to exhibit good inhibitory activity against PTP1B. The active compounds showed the requisite binding interactions with amino acid side chains in the catalytic site of PTP1B, as indicated in molecular docking studies [55]. The leader compound **60b** also showed comparable antidiabetic efficacy to that of standard antidiabetic drugs in two in vivo models [56]. An example of benzene-sulfonamide tetrazole **61** was synthesized using sulfadiazine as a starting material (Figure 12) [57]. The molecular modeling study showed the compounds' high affinity and selectivity to the active site and B-site of PTP1B, holding hydrogen bonding, hydrophobic, and electrostatic interactions. Based on computational design, the structure of tetrazoles **62a–c** as PTP1B inhibitors was proposed. In this case, a good concordance with in vitro results on recombinant 322 amino acids PTP1B was observed (Figure 12) [58].

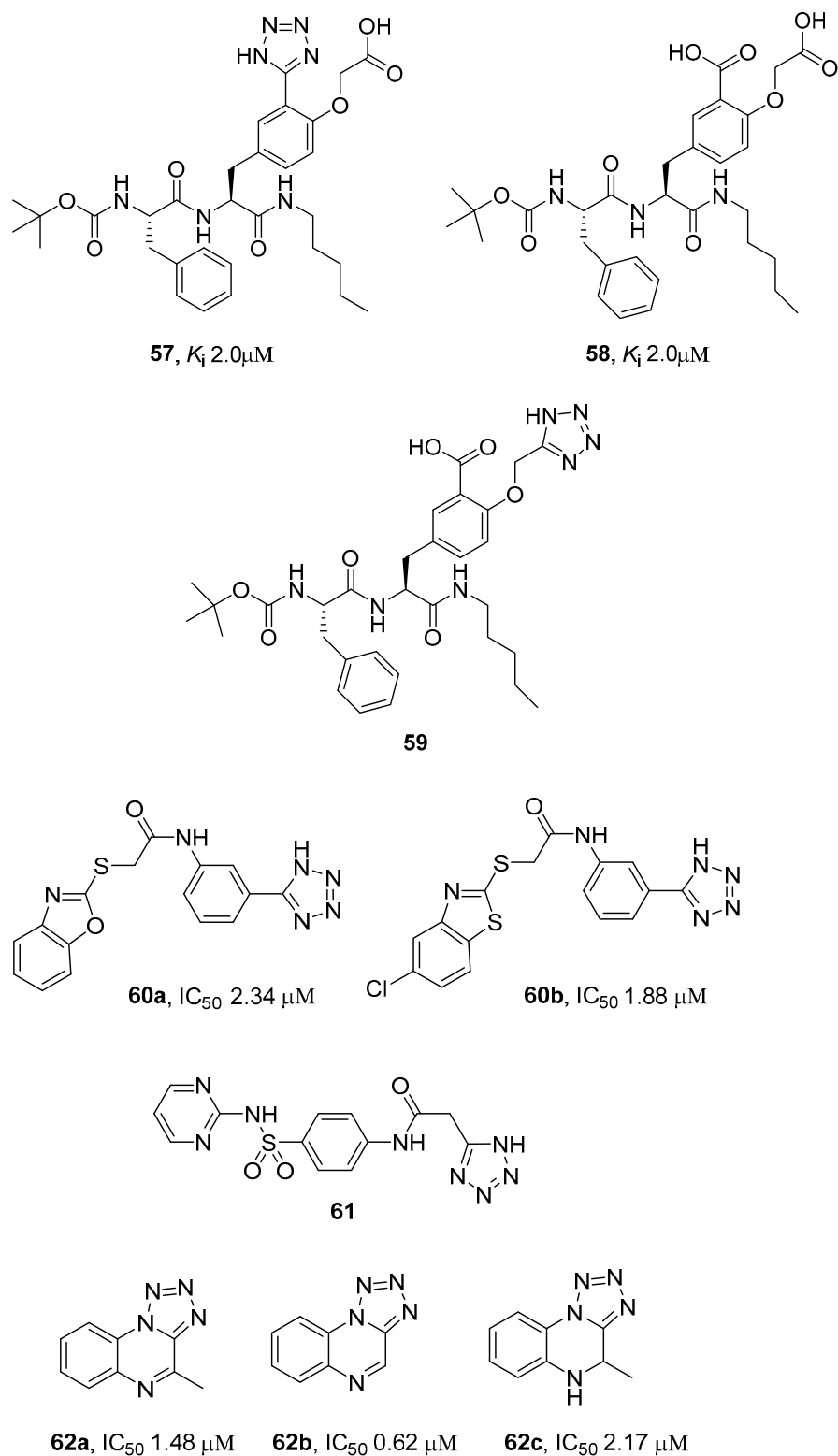


Figure 12. Low-molecular tetrazoles as PTB1B inhibitors.

3.3. Aldose Reductase (AR) Inhibitors

Aldose reductase (AR) is the first enzyme of the so-called polyol pathway, which converts glucose to sorbitol. It forms part of the aldo-keto reductase superfamily and is classified as AKR1B1. Sorbitol is subsequently converted to fructose in the presence of sorbitol dehydrogenase [8,59]. In hyperglycemic conditions with poor sorbitol penetration

and metabolism, an excessive accumulation of sorbitol occurs in tissues, resulting in T2DM-associated complications such as cataracts, glaucoma, nephropathy, and vascular complications. Thus, normally, only less than 3% of glucose is converted to sorbitol, whereas in the case of DM, this amount is about 30%. Hence, inhibition of AKR1B1 has been seen as a plausible therapy for preventing complications arising from T2DM. The development of low-molecular AKR1B1 inhibitors has a rich history and has been ongoing for more than 50 years. To date, dozens of such compounds are known. Most aldose reductase inhibitors can basically be divided into three main classes: cyclic imides **63,64**, carboxylic acids **65,66**, and polyphenols **67,68** (Figure 13) [59].

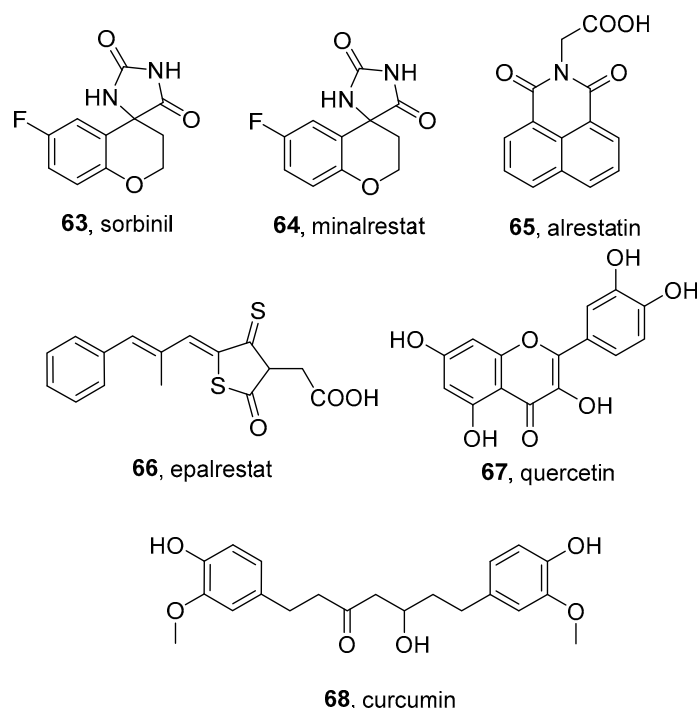


Figure 13. Well-known low-molecular AR inhibitors.

The first example of a tetrazole derivative as an aldose reductase inhibitor was made by Inukai et al. in 1993 [60]. The [5-(3-thienyl)tetrazol-1-yl]acetic acid **69** (Figure 14) demonstrated high inhibition of partially purified AKR1B1 from rat lens (IC_{50} 21 nM), rabbit lens (IC_{50} 23 nM), and human placenta (IC_{50} 28 nM). The oral administration of **69** ($5\text{--}100\text{ mg kg}^{-1}\text{ day}^{-1}$) to (STZ)-induced diabetic rats during a 5-day treatment period decreased the sorbitol content in the sciatic nerve, dose-dependently (ED_{50} $8.8\text{ mg kg}^{-1}\text{ day}^{-1}$ for the prevention and $9.0\text{ mg kg}^{-1}\text{ day}^{-1}$ for the reversal). A little later, Hotta et al. investigated the in vivo properties of tetrazole **69** in more detail. Physiological and biochemical studies were subsequently conducted on rat nerve tissue, and erythrocyte sorbitol content was estimated. Sciatic nerve blood flow was markedly lower (about 43.4%) in untreated diabetic rats than in non-diabetic controls [61]. The results obtained suggest that compound **69** has therapeutic value for diabetic retinopathy [62–64].

Another type of tetrazolyl-containing aldose reductase inhibitors was obtained and studied by Nicolaou et al. [65]. The pyrrolyl-tetrazoles **70–72** have significantly lower activity in vitro, regardless of isomerism and linker chain length (Figure 14). Weakly active were also found to be phenylsulfonamide derivatives **73,74**: 45% and 24% inhibition at $100\text{ }\mu\text{M}$, respectively [66].

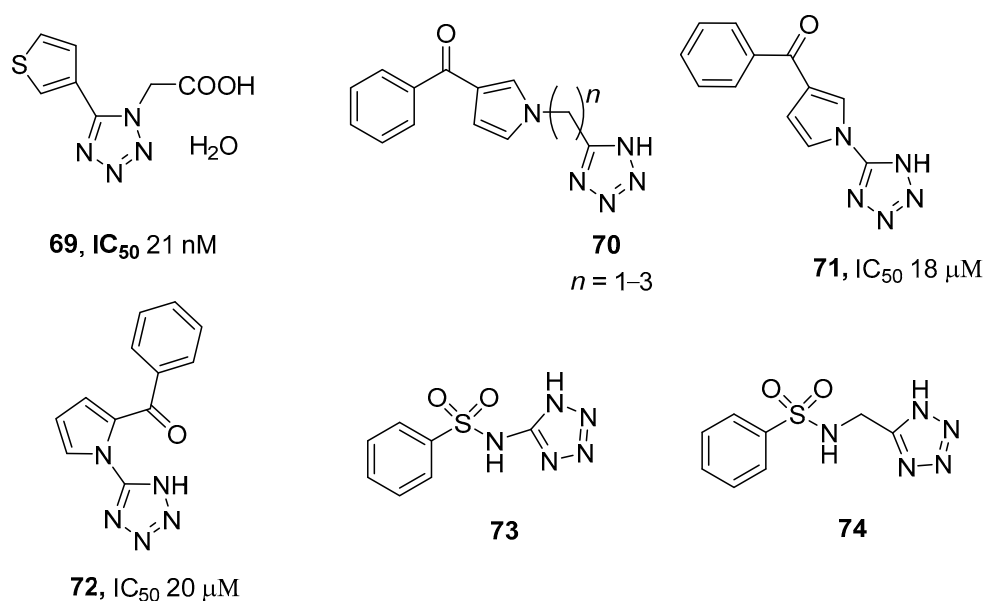


Figure 14. Tetrazoles as AKR1B1 inhibitors.

3.4. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors and Glucagon-like Peptide 1 (GLP-1) Agonists

Incretin hormones—glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)—have a direct influence on glucose homeostasis. They are secreted by L- and K-cells in the intestinal mucosa in response to nutrient intake. These hormones are responsible for the most amount (up to 70%) of insulin secretion whilst suppressing glucagon secretion. However, GLP-1 and GIP are quite unstable, and under the action of enzyme DPP-4, they rapidly cleave within several minutes [8,67]. In type 2 diabetes, the function of incretins is reduced, and insulin secretion is impaired. It should be noted that GLP-1-dependent stimulation of insulin secretion occurs only under conditions of hyperglycemia, and the risk of hypoglycemia is very low. Thus, by inhibiting the action of DPP-4, it is possible to maintain the necessary amount of incretins in the organism. It is now reliably established that DPP-4 is a very convenient target for the action of oral antidiabetic agents, and research on the development of its inhibitors has been very intensively developed in the last two decades. Significant results have been achieved here for the treatment of T2DM. The structures of some known DPP-4 inhibitors, so-called gliptins 3, 4, 5, 7, are shown in Figure 1. More effective compounds are now being developed. It can be noted that practically all such compounds contain polynitrogen heterocyclic moieties [9]. Given this, one would expect that tetrazoles would also be in demand in this context, but there are few such publications.

In the work cited earlier, Antypenko et al., by means of molecular docking calculations, showed a good affinity of 48 and 49 to DPP4 [45]. Gomha et al. synthesized tetrazolo[1,5-a]pyrimidine 75 (Figure 15), which exhibited high activity in vitro examined on DPP4 with the fluorescent method (IC_{50} 14 nM) [68]. The assays in mice demonstrated that the administration of compound 75 at a dose of 200 mg kg^{-1} for 7 days led to a decrease in serum glucose by 41.3%, comparable with sitagliptin (43%).

Acting essentially within the same biological process of the glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion, it is possible to activate the action of GLP-1 through interaction with appropriate ligands-peptides (exendin-4, liraglutide) or some small molecules. Thus, in the UK patent, the preparation and activity as GLP-1 receptor agonists of a series of peptides, containing tetrazol-5-yl and tetrazol-2-yl moieties 76, 77, have been proposed (Figure 15) [69]. Some of these peptides have demonstrated high activity in vitro and in vivo. A synthesis and quite significant biological activity in vitro on HEK293 cell line with 581 fmol mg^{-1} of GLP-1R of the macrocyclic agonist of GLP-1 78 was also described in the WO patent of Eli Lilly Company [70].

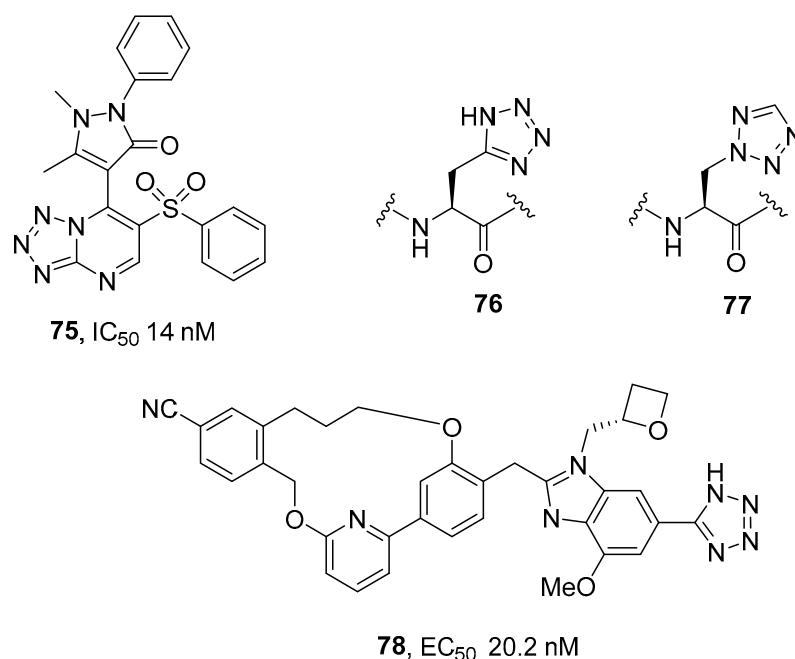


Figure 15. Tetrazoles as DPP-4 inhibitors and GLP-1 agonists.

3.5. G Protein-Coupled Receptor (GPCR) Agonists

Another way that influences the production of incretin hormones GLP-1 and GIP is through the activation of some G protein-coupled receptors (GPCRs) known as cell surface receptors. These receptors mediate internal signal transduction via the detection of molecules on the cell surface, and therefore, they can be activated by low-molecular biological active compounds [8,71]. GPR119, mainly, but also GPR142, GPR120, and GPR40 are representatives of GPCRs, which are considered important targets in T2DM therapy. These receptors are often called potential druggable GPCRs. GPR119 is expressed mainly in pancreatic β -cells and in the endocrine cells of the gastrointestinal tract, and it stimulates insulin secretion. For more than 10 years, this target has been very popular in the development of antidiabetic agents. To date, more than a dozen highly effective agents have been developed, a number of which have already been recommended for use in medical practice and are undergoing clinical trials (Figure 16) [71,72].

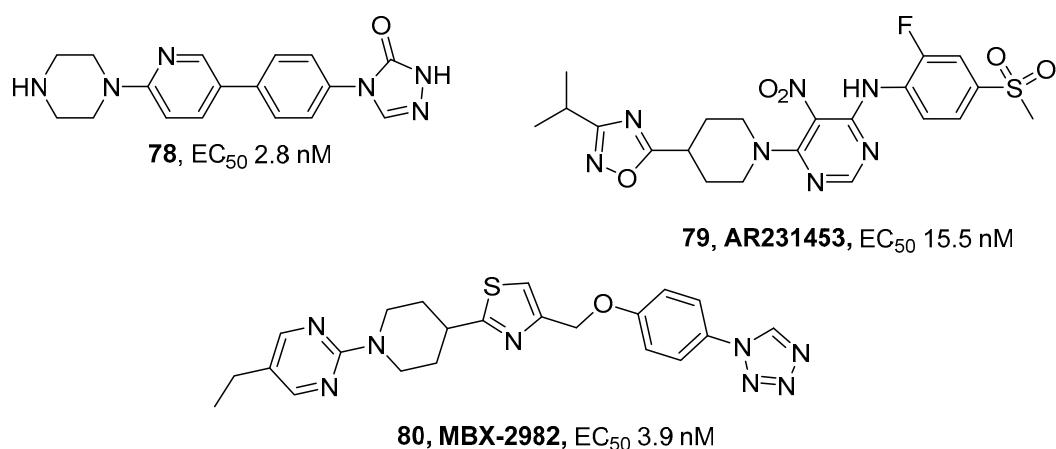


Figure 16. Polynitrogen heterocyclic compounds known as GPR119 agonists.

As can be seen from Figure 16, low-molecular GPR119 ligands usually contain polynitrogen heterocyclic fragments (triazole, oxadiazole, and tetrazole) linked to other aromatic cycles. These fragments effectively participate in the interaction with the active sites of

GPR119, which was confirmed by experimental studies on human GPR119 and theoretical calculations on the structure of ligand-receptor complexes for **79,80** [73]. Compound **80**, developed by Arena Pharmaceuticals, was comprehensively studied in vitro and in vivo assays in numerous studies and was approved for phase II clinical trials [71–74]. However, it has also not been updated for the last clinical status and has not been launched in the drug market. Based on systematic optimization of the general structure MBX-2982, novel tetrazole-tetrahydropyridine derivatives as novel human GPR119 agonists **81a,b** were obtained by Zuo et al. (Figure 17). They showed high GPR119 agonist activity in vitro (**81a** (EC_{50} 4.9 nM) and **81b** (EC_{50} 8.8 nM)), and in vivo compound **81a** showed a hypoglycemic effect and may have an effect on improving basal metabolic rate in DIO mice [75].

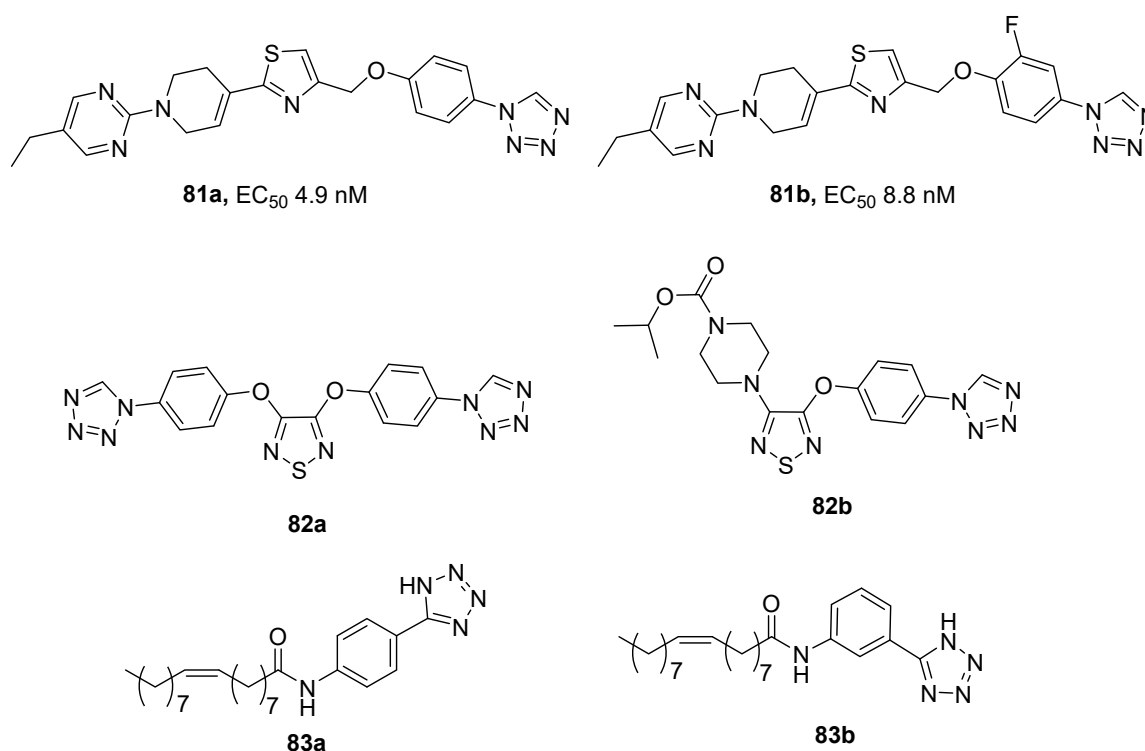


Figure 17. Tetrazole derivatives as promising GPR119 agonists.

Mankind Pharma collaborators have proposed a series of tetrazole-containing compounds that may act as candidates for GPR119 agonists [76]. These compounds, for example, **82a,b**, simultaneously contain 1,2,5-thiadiazole and tetrazole heterocycles. Another type of compound demonstrated that the synthetic derivatives of oleoyl-LPI **83a,b** showed promising GLP-1 secreting capabilities in vivo in an animal model of diabetes. Oleoyl-LPI and its derivatives have been shown to induce the release of GLP-1. Moreover, **83a** and **83b** stimulate the cAMP signaling cascade via GPR119. Oleoyl-LPI and **83a** interact with the GPR119 orthosteric site. Compound **83a** enhances the acute glucose-stimulated GLP-1 secretion in db/db mice. Based on the results of the biological evaluation and molecular modeling, analogies **83a** and **83b** were hypothesized to be the most potent ligands of GPR119, similar to oleoyl-LPI (Figure 17) [77].

Most recently, the recognition of GPR40 as a receptor whose activation enhances glucose-dependent insulin secretion has led to the search for selective agonists for this putative therapeutic target. GPR40, also known as free fatty acid receptor 1 (FFR1), can be endogenously activated by medium-chain saturated and unsaturated fatty acids. The present invention of Janssen Pharmaceutica NV relates to novel compounds **84a,b**, which are very active GPR40 agonists and are useful for the treatment of disorders that are affected by the modulation of the GPR40 receptor (Figure 18) [78–80]. Compounds were tested in a

calcium flux assay using transfected HEK293 cells stably expressing either human GPR40 or male SD rats.

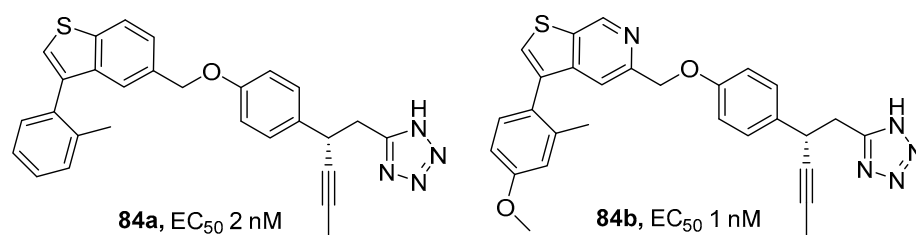


Figure 18. Tetrazole derivatives as promising GPR40 agonists.

3.6. Glycogen Phosphorylases (GP) Inhibitors

The liver is able to store glucose in the form of glycogen and, through a reverse process, produce and release glucose. The liver is one of the main sources of glucose in the blood and in type 2 diabetes; hepatic glucose production is increased, which can lead to hyperglycemia [81]. Glycogenolysis (the breakdown of glycogen) may account for more than 70% of the hepatic glucose production. The main regulatory enzymes of this system are glycogen phosphorylases (GP), which release glucose 1-phosphate from glycogen. GP_a is the phosphorylated isoform, and GP_b is the unphosphorylated isoform, modifying its quaternary homodimeric structure. The inhibition of hepatic GP, the main regulatory enzyme in the liver, might be considered a useful target for the control of blood glucose levels. The structure of these inhibitors often contains functional glucose derivatives or related compounds combined with the nitrogen heterocycle. Thus, in 1996, Mitchell et al. investigated condensed nojirimycin tetrazole **85**; it is a competitive inhibitor with respect to glucose 1-phosphate and an uncompetitive inhibitor with respect to phosphate (Figure 19). Tetrazole **85** has poor affinity for GP, but that phosphate substantially improves its binding ($K_i(\text{GPb}/\text{phosphate})$ 53 μM) [82]. The structure of the complex (GP_b)-**85**-phosphate was demonstrated using calculations and X-ray analysis [83]. Somsák et al., in a series of publications, noted only low activity of 5-(β -D-glucopyranosyl)-1*H*-tetrazole **86**, while some similarly structured triazole, oxadiazole, and imidazole analogs **87** were found to be active at nanomolar concentrations (Figure 19) [84–88]. An in vivo study of isomeric 5-(1-aryl-1*H*-pyrazol-3-yl)-1*H*- and 2*H*-tetrazoles **88a,b** as GP inhibitors showed a maximum fall in the blood glucose levels in streptozotocin-induced diabetic Wistar rats, and a molecular docking study has been performed for the potent molecules with GP as target enzyme corroborated the experimental results [89].

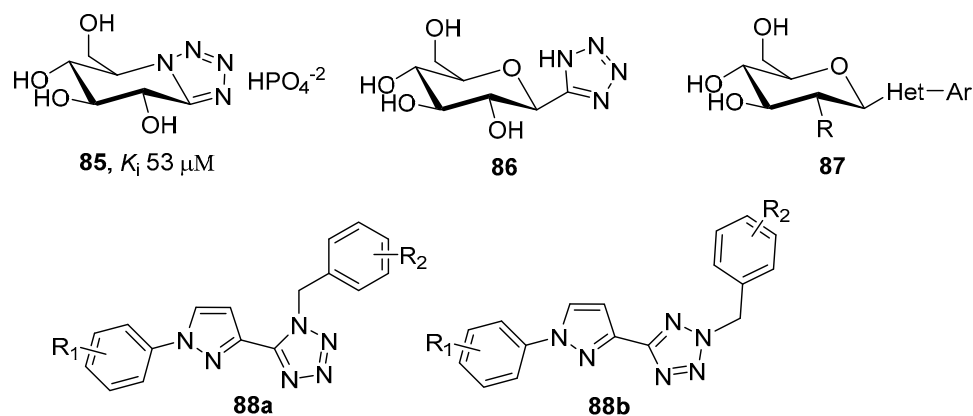


Figure 19. Potential GP inhibitors.

3.7. α -Glucosidase (AG) Inhibitors

α -Glucosidase is one of the carbohydrate hydrolyzing enzymes that catalyzes the liberation of α -glucose by cleaving the glycosidic bond from the non-reducing portion of the oligomeric substrate. α -Glucosidase inhibitors (AGIs) are oral antidiabetic drugs, preferably used in treating type 2 diabetes mellitus, that delay the absorption of carbohydrates from the gastrointestinal system.

A series of fused tetrazolo[1,5-a]pyrimidine **89a,b** derivatives have been synthesized, and their *in vitro* inhibitory activity for α -glucosidase has been screened using yeast maltase (MAL12) as a model enzyme [90]. The IC_{50} values for most active compounds **89a,b** (Figure 20) consist of 49.8 μ M and 85.7 μ M, respectively, which is comparable with acarbose (33.9 μ M). Also, docking studies of the compounds with the active site of the α -glucosidase and *in silico* prediction of their ADMET (absorption, distribution, metabolism, excretion, toxicity) properties were assessed.

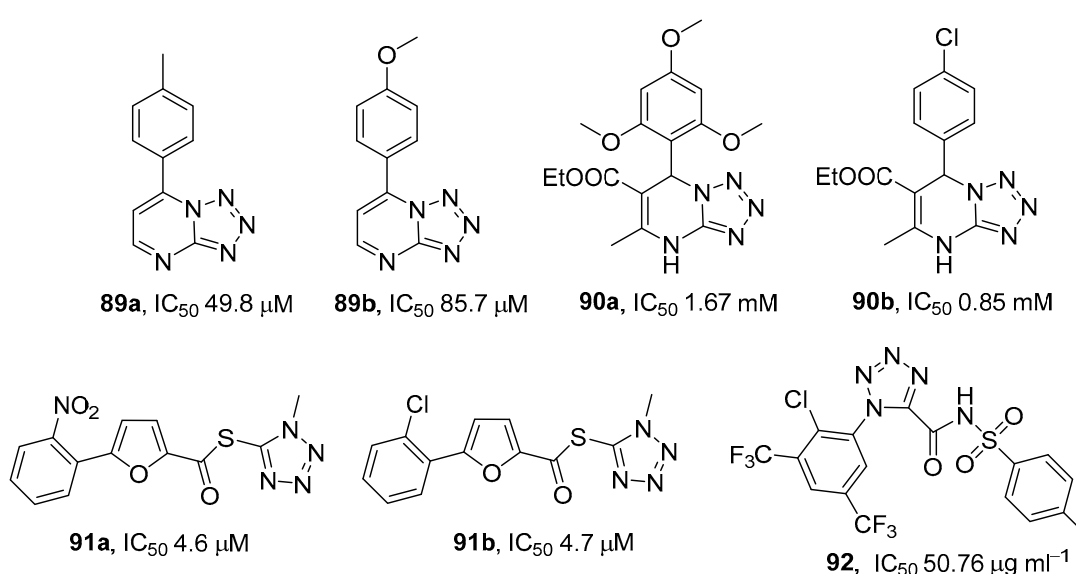


Figure 20. Potential AG inhibitors.

A series of closely related dihydrotetrazolopyrimidines **90a,b** were also designed as AG inhibitors [91]. These compounds exhibited better inhibitory activity against α -glucosidase (against maltase and sucrose) than referenced quercetin. On the basis of the work [92], significantly greater inhibitory activity against α -glucosidase was screened for differences in structure 1*H*-tetrazol-5-yl-2,5-disubstituted furanes **91a,b**. According to the kinetic study, the most promising compound, **91a** (IC_{50} 4.6 μ M), is an uncompetitive inhibitor against α -glucosidase. Molecular docking studies indicated that the existence of theazole group played a critically important role in hydrogen bond interaction with α -glucosidase. Toxicity towards HEK293, RAW264.7, and HepG2 cells suggested that compound **91a** possessed non-toxicity, and it is a good candidate for further investigations. *In vitro* and *in vivo* antidiabetic activities of a series of 1-aryl-*N*-tosyl-1*H*-tetrazole-5-carboxamides were studied [93]. There, compound **92** demonstrated *in vitro* minimum IC_{50} values against AG and α -amylase (50.76 and 59.38 μ g ml⁻¹, respectively). α -Amylase catalyzes the cleavage of α -1,4-glycosidic bonds of starch and other related polysaccharides to generate oligosaccharides. Also, tetrazole **92** exhibited a maximum glucose-lowering effect in diabetic rats.

3.8. Sodium Glucose Co-Transporter (SGLT) Inhibitors

Sodium-dependent glucose cotransporters (SGLT) are a family of glucose transporters found in the intestinal mucosa of the small intestine (SGLT1) and the renal proximal tubules (SGLT2). SGLT2 protein is the main sodium-dependent glucose transporter, and when

SGLT2 protein is inhibited, glucose reabsorption in renal tubules decreases, which leads to glucose excretion in the urine with a subsequent decrease in plasma glucose levels [49]. At the same time, SGLT inhibition can suppress secondary diseases caused by T2DM.

A synthesis and antidiabetic activity (in vitro and in vivo) of a wide series of novel tetrazole-bearing glycosides have been described in several papers and patents (Figure 21) [94–97]. Thus, directly bonded 1*H*- and 2*H*-tetrazoles **93a,b** showed only moderate activity in vitro (IC_{50} 68.9 and 106 nM) in comparison with control selective SGLT2 inhibitor dapagliflozin **94** (EC_{50} 1.1 nM) [95]. Moreover, 5-Arylmethyltetrazoles bearing glycosides were examined in vivo by means of a mouse oral glucose tolerance test [94]. The D-glucose derivatives were found to be more potent inhibitors than their D-galactose counterparts, and usually, the 2-glucosylisomer had higher activity than 1-glucosyltetrazoles. Among these compounds, N-glucosyltetrazoles **95** had better activity in blood glucose level by oral glucose tolerance (R=OEt, 77.0%; R=Ome, 73.9%) compared to reference dapagliflozin **94** (68%).

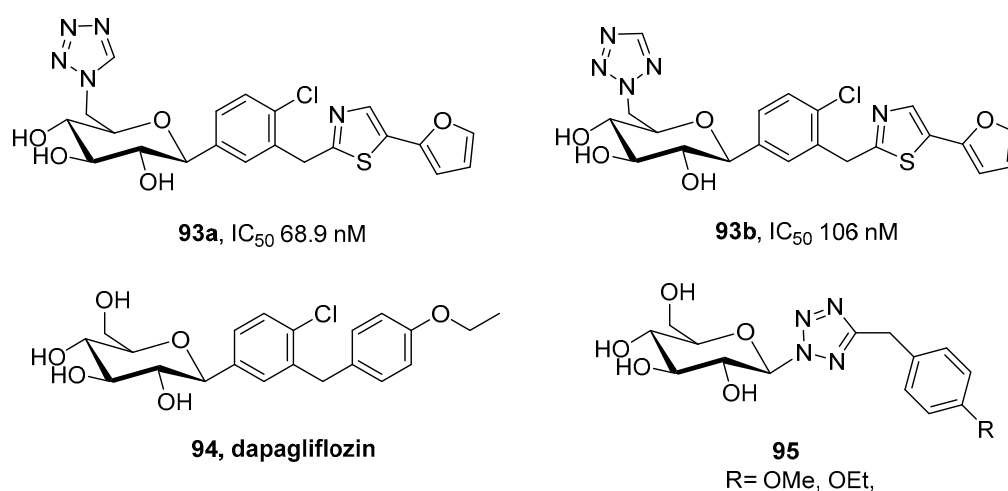


Figure 21. SGLT2 inhibitors.

3.9. Other Types of Activities

In this section, we have discussed those activities that are less discussed above in the context of antidiabetic agents containing tetrazolyl moiety, and the results of such studies are presented in one or two publications. These include, by the way, very important targets for the action of modern antidiabetic agents, which are intensively studied today [49].

Here, first of all, the drug design of fructose-1,6-bisphosphatase (FBPase) inhibitors should be mentioned. FBPase, more precisely the liver form of FBPase (FBP1), is a key enzyme of gluconeogenesis in both the liver and kidneys, which contributes greatly to the development of hyperglycemia in T2DM patients. This target is also of extensive interest because drug therapy does not lead to hypoglycemia, which may be associated with the effects of other antidiabetic agents. A series of 2,5-diphenyl-1,3,4-oxadiazole derivatives were synthesized, and compound **96**, bearing a terminal 1*H*-tetrazole moiety, demonstrated remarkable inhibition of gluconeogenesis by the inhibition of FBPase in vitro (IC_{50} 2.98 μ M) (Figure 22) [98]. In addition, this compound demonstrated an inhibition of glucose output in rat hepatocytes and excellent membrane permeability.

Dysfunctions of hypoxia-inducible factor (HIF-1 α) in diabetes have been indicated to deteriorate wound closure, whereas stabilization of HIF-1 α has been shown to improve wound healing and osteoarthritis. Prolyl hydroxylase 2 (PHD2) is a negative regulator of HIF-1 α , and a deficiency in PHD2 stabilized HIF-1 α . Therefore, PHD2 inhibitors are tools for the treatment of post-diabetic disorders. Based on a virtual screening, compound **97** was identified as a potential PHD2 inhibitor (Figure 22) [99]. It was also shown that tetrazole **97** promotes the migration and capillary tube formation capacity of human umbilical vein endothelial cells through enhancing the stability of HIF-1 α .

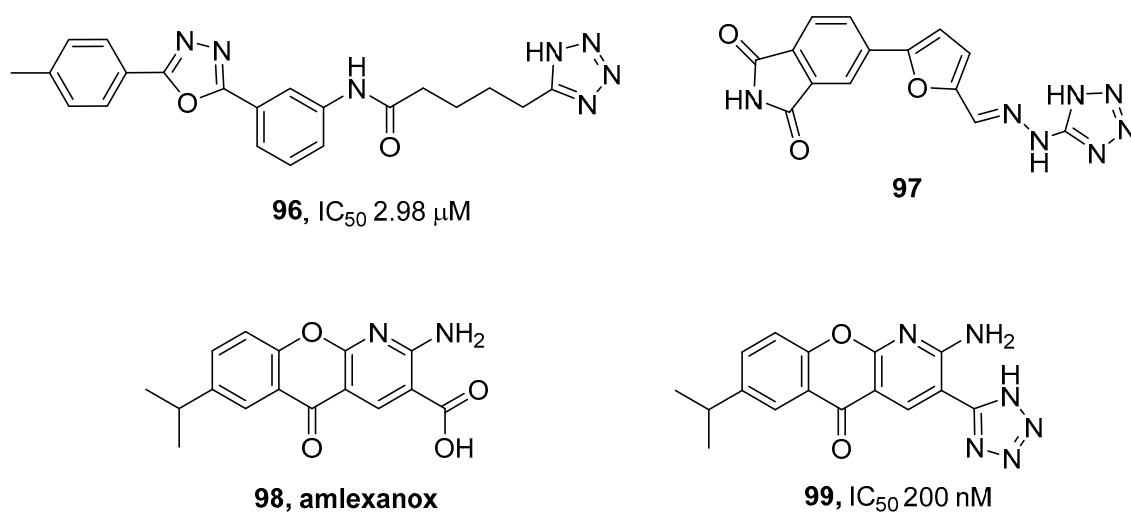


Figure 22. Different types of antidiabetic agents: fructose-1,6-bisphosphatase (FBPase) inhibitor **96**, prolyl hydroxylase 2 inhibitor (PHD2) **97**, IκB kinase ε (IKKε), and TANK binding kinase 1 (TBK1) inhibitors **98**, **99**.

Obesity is a leading risk factor for the development of type 2 diabetes and is accompanied by inflammation of the liver and adipose tissue, leading to impaired metabolism. This leads to increased expression of IκB kinase ε (IKKε) and TANK binding kinase 1 (TBK1), which contributes to additional weight gain and further decreased insulin sensitivity. Amlexanox **98** inhibits IKKε and TBK1 to improve insulin sensitivity (IC_{50} 5800 and 800 nM). Analog **99**, which contained a tetrazole moiety in place of the carboxylic acid, displayed improved potencies: IC_{50} 400 and 200 nM against IKKε and TBK1, respectively [100]. A treatment activity on the diabetic retinopathy of Cu(II)-containing coordination polymer with 5-[3-(1*H*-imidazol-1-yl)phenyl]-1*H*-tetrazolate bifunctional ligand was studied, and the related mechanism was discussed [101].

Inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is another area for the development of new antidiabetic agents that has received considerable attention [49]. This enzyme is mainly found in the liver, adipose tissue, and CNS, where it catalyzes the conversion of physiologically inactive cortisone to the active hormone cortisol. The latter activates the risk of metabolic syndrome, insulin resistance, glucose tolerance, hypertension, and other manifestations of T2DM. Some tetrazoles, discussed above as agents against other targets, exhibit such activity. Thus, compound **50**, according to studies on the cellular line HEK293, is an inhibitor of 11β-HSD1 to a greater extent than clofibrate **26** [46,47]. Also, tetrazolyl ureas and biguanides were tested in vivo on glucocorticoid-induced insulin resistance models, and the most active tetrazolo[1,5-*c*]quinazolin-5(6*H*)-one **48** (R=H) exceeded the reference drugs metformin **1** and gliclazide.

4. Concluding Remarks

The tetrazolyl pharmacophore moiety is widely used in the drug design of novel antidiabetic agents against T2DM and related (associated) diseases. Tetrazole derivatives have been investigated as agents against major biological targets, including the following: peroxisome proliferator-activated receptors (PPARs) agonists, protein tyrosine phosphatase 1B (PTP1B) inhibitors, aldose reductase (AR) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, G protein-coupled receptor (GPCRs) agonists, glycogen phosphorylases (GP) inhibitors, α-glycosidase (AG) inhibitors, sodium glucose co-transporter (SGLT) inhibitors, fructose-1,6-bisphosphatase (FBPase) inhibitors, IκB kinase ε (IKKε) and TANK binding kinase 1 (TBK1) inhibitors, and 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). Impressive advances have been made in the development of antidiabetic agents acting as selective PPARγ agonists, with ex-

amples of tetrazol-5-yl-1,2,3,4-tetrahydroisoquinolines **38** and 5-[3-[6-(5-methyl-2-phenyl-4-oxazolylmethoxy)-3-pyridyl]propyl]-1*H*-tetrazole **40** (EC₅₀ 6–15 nM); aldose reductase (AR) inhibitors on [5-(3-thienyl)tetrazol-1-yl]acetic acid **69** (IC₅₀ 24 nM); DPP-4 inhibitors on tetrazolo[1,5-*a*]pyrimidine **75** (IC₅₀ 14 nM); and high active polycyclic tetrazole-containing systems such as GPR119 agonists **80**, **81**, **84** (EC₅₀ 3.9–8.8 nM) and GPR40 agonists **84** (EC₅₀ 1–2 nM). According to numerous theoretical calculations, the tetrazole heterocycle is actively involved in binding to biological targets. In many cases, the tetrazole-containing leader compounds markedly exceed the activity of medications already known and used in T2DM therapy in vitro and in vivo. Some of them are undergoing clinical trials. In addition, tetrazole derivatives are very often used to act on diabetes-related targets or to treat post-diabetic disorders. Thus, the tetrazole scaffold is promising for further research to develop effective antidiabetic drugs.

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References

1. IDF Diabetes Atlas. *International Diabetes Federation Diabetes Atlas*, 10th ed.; International Diabetes Federation: Brussels, Belgium, 2021.
2. Chatterjee, S.; Khunti, K.; Davies, M.J. Type 2 diabetes. *Lancet* **2017**, *389*, 2239–2251. [[CrossRef](#)] [[PubMed](#)]
3. Salmen, T.; Serbanoiu, L.-I.; Bica, I.-C.; Serafinceanu, C.; Muzurovic, E.; Janez, A.; Busnatu, S.; Banach, M.; Rizvi, A.A.; Rizzo, M.; et al. Review on critical view over newest antidiabetic molecules in light of efficacy. *Int. J. Mol. Sci.* **2023**, *24*, 9760. [[CrossRef](#)]
4. Shi, Y.; Si, D.; Chen, D.; Zhang, X.; Han, Z.; Yu, Q.; Liu, J.; Si, J. Bioactive compounds from Polygonatum genus as anti-diabetic agents with future perspectives. *Food Chem.* **2023**, *408*, 135183. [[CrossRef](#)]
5. Xu, B.; Li, Z.; Zeng, T.; Zhan, J.; Wang, S.; Ho, C.-T.; Li, S. Bioactives of Momordica charantia as Potential Anti-Diabetic/Hypoglycemic Agents. *Molecules* **2022**, *27*, 2175. [[CrossRef](#)]
6. Su, J.; Luo, Y.; Hu, S.; Tang, L.; Ouyang, S. Advances in Research on Type 2 Diabetes Mellitus Targets and Therapeutic Agents. *Int. J. Mol. Sci.* **2023**, *24*, 13381. [[CrossRef](#)]
7. Mahgoub, M.O.; Ali, I.I.; Adeghate, J.O.; Tekes, K.; Kalasz, H.; Adeghate, E.A. An Update on the Molecular and Cellular Basis of Pharmacotherapy in Type 2 Diabetes Mellitus. *Int. J. Mol. Sci.* **2023**, *24*, 9328. [[CrossRef](#)]
8. Kerru, N.; Singh-Pillay, A.; Awolade, P.; Singh, P. Current anti-diabetic agents and their molecular targets: A review. *Eur. J. Med. Chem.* **2018**, *152*, 436–488. [[CrossRef](#)]
9. Rusinov, V.L.; Sapozhnikova, I.M.; Spasov, A.A.; Chupakhin, O.N. Fused azoloazines with antidiabetic activity. *Russ. Chem. Bull.* **2022**, *71*, 2561–2594. [[CrossRef](#)]
10. Mohammad, B.D.; Baig, M.S.; Bhandari, N.; Siddiqui, F.A.; Khan, S.L.; Ahmad, Z.; Khan, F.S.; Tagde, P.; Jeandet, P. Heterocyclic Compounds as Dipeptidyl Peptidase-IV Inhibitors with Special Emphasis on Oxadiazoles as Potent Anti-Diabetic Agents. *Molecules* **2022**, *27*, 6001. [[CrossRef](#)]
11. Vitaku, E.; Smith, D.T.; Njardarson, J.T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274. [[CrossRef](#)]
12. Butler, R.N. Tetrazoles. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A.R., Rees, C.W., Scriven, E.F.V., Eds.; Pergamon: Oxford, UK; New York, NY, USA, 1996; Volume 4, pp. 621–678.
13. Ostrovskii, V.A.; Koldobskii, G.I.; Trifonov, R.E. Tetrazoles. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A.R., Ramsden, C.A., Scriven, E.F.V., Taylor, R.J.K., Zhdankin, V.V., Eds.; Elsevier: Oxford, UK, 2008; Volume 6, pp. 259–423.
14. Ostrovskii, V.A.; Popova, E.A.; Trifonov, R.E. Tetrazoles. In *Comprehensive Heterocyclic Chemistry IV*; Black, D., Cossy, J., Stevens, C., Eds.; Elsevier: Oxford, UK, 2022; Volume 6, pp. 182–232. [[CrossRef](#)]
15. Ostrovskii, V.A.; Popova, E.A.; Trifonov, R.E. Developments in tetrazole chemistry (2009–16). *Adv. Heterocycl. Chem.* **2017**, *123*, 1–62. [[CrossRef](#)]
16. Popova, E.A.; Trifonov, R.E. Synthesis and biological properties of amino acids and peptides containing a tetrazolyl moiety. *Russ. Chem. Rev.* **2015**, *84*, 891–916. [[CrossRef](#)]
17. Popova, E.A.; Trifonov, R.E.; Ostrovskii, V.A. Tetrazoles for biomedicine. *Russ. Chem. Rev.* **2019**, *88*, 644–676. [[CrossRef](#)]

18. Ostrovskii, V.A.; Trifonov, R.E.; Popova, E.A. Medicinal chemistry of tetrazoles. *Russ. Chem. Bull.* **2012**, *61*, 768–780. [[CrossRef](#)]
19. Popova, E.A.; Protas, A.V.; Trifonov, R.E. Tetrazole Derivatives as Promising Anticancer Agents. *Anti-Cancer Agents Med. Chem.* **2017**, *17*, 1856–1868. [[CrossRef](#)]
20. Kaushik, N.; Kumar, N.; Kumar, A.; Singh, U.K. Tetrazoles: Synthesis and Biological Activity. *Immunol. Endocr. Metab. Agents Med. Chem.* **2018**, *18*, 3–21. [[CrossRef](#)]
21. Myznikov, L.V.; Hrabalek, A.; Koldobskii, G.I. Drugs in the tetrazole series. *Chem. Heterocycl. Compd.* **2007**, *43*, 1–9. [[CrossRef](#)]
22. Popova, E.A.; Trifonov, R.E.; Ostrovskii, V.A. Advances in the synthesis of tetrazoles coordinated to metal ions. *ARKIVOC* **2012**, 45–65. [[CrossRef](#)]
23. Pikaev, A.K.; Kriminskaya, Z.K. Radiolysis of tetrazolium salt solutions. *Russ. Chem. Rev.* **1998**, *67*, 745–754. [[CrossRef](#)]
24. Trifonov, R.E.; Alkorta, I.; Ostrovskii, V.A.; Elguero, J. A theoretical study of the tautomerism and ionization of 5-substituted NH-tetrazoles. *J. Mol. Struct. THEOCHEM* **2004**, *668*, 123–132. [[CrossRef](#)]
25. Trifonov, R.E.; Ostrovskii, V.A. Protolytic equilibria in tetrazoles. *Russ. J. Org. Chem.* **2006**, *42*, 1585–1605. [[CrossRef](#)]
26. Kaplanskiy, M.V.; Faizullina, O.E.; Trifonov, R.E. Experimental and Theoretical Quantitative Studies of the Hydrogen Bonding Basicity of 2,5-Disubstituted Tetrazoles and Some Related Heterocycles. *J. Phys. Chem. A* **2023**, *127*, 5572–5579. [[CrossRef](#)] [[PubMed](#)]
27. Allen, F.H.; Groom, C.R.; Liebeschuetz, J.W.; Bardwell, D.A.; Olsson, T.S.G.; Wood, P.A. The Hydrogen Bond Environments of 1 H-Tetrazole and Tetrazolate Rings: The Structural Basis for Tetrazole–Carboxylic Acid Bioisosterism. *J. Chem. Inf. Model.* **2012**, *52*, 857–866. [[CrossRef](#)]
28. Modafferi, S.; Ries, M.; Calabrese, V.; Schmitt, C.P.; Nawroth, P.; Kopf, S.; Peters, V. Clinical Trials on Diabetic Nephropathy: A CrossSectional Analysis. *Diabetes Ther.* **2019**, *10*, 229–243. [[CrossRef](#)] [[PubMed](#)]
29. Brunmeir, R.; Xu, F. Functional Regulation of PPARs through Post-Translational Modifications. *Int. J. Mol. Sci.* **2018**, *19*, 1738. [[CrossRef](#)]
30. Youssef, J.; Badr, M. *Peroxisome Proliferator-Activated Receptors: Discovery and Recent Advances*; Springer: Berlin/Heidelberg, Germany, 2013; pp. 1–137.
31. Dutta, D.; Bhattacharya, S.; Surana, V.; Aggarwal, S.; Singla, R.; Khandelwal, D.; Sharma, M. Efficacy and safety of saroglitazar in managing hypertriglyceridemia in type-2 diabetes: A meta-analysis. *Diabetes Metab. Syndr.* **2020**, *14*, 1759–1768. [[CrossRef](#)] [[PubMed](#)]
32. Kees, K.L.; Cheeseman, R.S.; Prozialeck, D.H.; Steiner, K.E. Perfluoro-N-[4-(1H-tetrazol-5-ylmethyl)phenyl]alkanamides. A new class of oral antidiabetic agents. *J. Med. Chem.* **1989**, *32*, 11–13. [[CrossRef](#)]
33. Kees, K.L.; Smith, T.M.; McCaleb, M.L.; Prozialeck, D.H.; Cheeseman, R.S.; Christos, T.E.; Patt, W.C.; Steiner, K.E. Perfluorocarbon-based antidiabetic agents. *J. Med. Chem.* **1992**, *35*, 944. [[CrossRef](#)]
34. Kees, K.L.; Caggiano, T.J.; Steiner, K.E.; Fitzgerald, J.J., Jr.; Kates, M.J.; Christos, T.E.; Kulishoff, J.M.; Moore, R.D.; McCaleb, M.L. Studies on New Acidic Azoles as Glucose-Lowering Agents in Obese, Diabetic db/db Mice. *J. Med. Chem.* **1995**, *38*, 617. [[CrossRef](#)]
35. Otake, K.; Azukizawa, S.; Takeda, S.; Fukui, M.; Kawahara, A.; Kitao, T.; Shirahase, H. Novel 2,7-Substituted -1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acids: Peroxisome Proliferator-Activated Receptor γ Partial Agonists with Protein-Tyrosine Phosphatase 1B Inhibition. *Chem. Pharm. Bull.* **2015**, *63*, 998–1014. [[CrossRef](#)]
36. Morishita, K.; Miike, T.; Takeda, S.; Fukui, M.; Ito, Y.; Kitao, T.; Ozawa, S.-I.; Hirono, S.; Shirahase, H. (S)-1,2,3,4-tetrahydroisoquinoline derivatives substituted with an acidic group at the 6-position as a selective peroxisome proliferator-activated receptor γ partial agonist. *Chem. Pharm. Bull.* **2019**, *67*, 1211–1224. [[CrossRef](#)] [[PubMed](#)]
37. Morishita, K.; Ito, Y.; Otake, K.; Takahashi, K.; Yamamoto, M.; Kitao, T.; Ozawa, S.-I.; Hirono, S.; Shirahase, H. Synthesis and evaluation of a novel series of 2,7-substituted-6-tetrazolyl-1,2,3,4-tetrahydroisoquinoline derivatives as selective peroxisome proliferator-activated receptor γ partial agonists. *Chem. Pharm. Bull.* **2021**, *69*, 333–351. [[CrossRef](#)] [[PubMed](#)]
38. Ito, Y.; Yamamoto, M.; Furukawa, S.; Fukui, M.; Morishita, K.; Kitao, T.; Shirahase, H. Effects of KY-903, a Novel Tetrazole-Based Peroxisome Proliferator-Activated Receptor γ Modulator, in Male Diabetic Mice and Female Ovariectomized Rats. *Biol. Pharm. Bull.* **2021**, *44*, 659–668. [[CrossRef](#)]
39. Momose, Y.; Maekawa, T.; Odaka, H.; Ikeda, H.; Sohda, T. Novel 5-substituted-1H-tetrazole derivatives as potent glucose and lipid lowering agents. *Chem. Pharm. Bull.* **2002**, *50*, 100–111. [[CrossRef](#)] [[PubMed](#)]
40. Deshmukh, A.R.; Bhosle, M.R.; Khillare, L.D.; Dhumal, S.T.; Mishra, A.; Srivastava, A.K.; Mane, R.A. New tetrazoloquinolinyl methoxyphenyl-4-thiazolidinones: Synthesis and antihyperglycemic evaluation. *Res. Chem. Intermed.* **2017**, *43*, 1107–1120. [[CrossRef](#)]
41. Sharon, A.; Pratap, R.; Tiwari, P.; Srivastava, A.; Maulik, P.R.; Ram, V.J. Synthesis and in vivo antihyperglycemic activity of 5-(1H-pyrazol-3-yl)methyl-1H-tetrazoles. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2115–2117. [[CrossRef](#)]
42. da Silva, F.M.C.; dos Santos, J.C.; Campos, J.L.O.; Mafud, A.C.; Polikarpov, I.; Figueira, A.C.M.; Nascimento, A.S. Structure-based identification of novel PPAR gamma ligands. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5795–5802. [[CrossRef](#)]
43. de Paula, K.; Santos, J.C.; Mafud, A.C.; Nascimento, A.S. Tetrazoles as peroxisome proliferator-activated receptor gamma ligands: A structural and computational investigation. *J. Mol. Graph. Modell.* **2021**, *106*, 107932. [[CrossRef](#)]
44. Pattana, S.R.; Kekareb, P.; Patil, A.; Nikalje, A.; Kittur, B.S. Studies on the synthesis of novel 2,4-thiazolidinedione derivatives with antidiabetic activity. *Iran. J. Pharm. Sci.* **2009**, *5*, 225–230.

45. Antypenko, O.M.; Kovalenko, S.I.; Zhernova, G.O. Search for compounds with hypoglycemic activity in the series of 1-[2-(1H-tetrazol-5-yl)-R1-phenyl]-3-R2-phenyl(ethyl)ureas and R1-tetrazolo[1,5-c]quinazolin-5(6H)-ones. *Sci. Pharm.* **2016**, *84*, 233–254. [[CrossRef](#)]
46. Navarrete-Vazquez, G.; Alaniz-Palacios, A.; Hidalgo-Figueroa, S.; Gonzalez-Acevedo, C.; Avila-Villarreal, G.; Estrada-Soto, S.; Webster, S.P.; Medina-Franco, J.L.; Lopez-Vallejo, F.; Guerrero-Alvarez, J.; et al. Discovery, synthesis and in combo studies of a tetrazole analogue of clofibrilic acid as a potent hypoglycemic agent. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3244–3247. [[CrossRef](#)]
47. Vara-Gama, N.; Valladares-Mendez, A.; Navarrete-Vazquez, G.; Estrada-Soto, S.; Orozco-Castellanos, L.M.; Rivera-Leyva, J.C. Biopharmaceutical characterization and bioavailability study of a tetrazole analog of clofibrilic acid in rat. *Molecules* **2017**, *22*, 282. [[CrossRef](#)] [[PubMed](#)]
48. Cho, H. Protein tyrosine phosphatase 1B (PTP1B) and obesity. *Vitam. Horm.* **2013**, *91*, 405–424. [[CrossRef](#)]
49. Tyurenkov, I.N.; Kurkin, D.V.; Volotova, E.V.; Bakulin, D.A.; Lomkina, E.M. Drug discovery for type 2 diabetes mellitus and metabolic syndrome: Ten novel biological targets. *Diabetes Mellit.* **2015**, *18*, 101–109. [[CrossRef](#)]
50. Olloquequi, J.; Cano, A.; Sanchez-López, E.; Carrasco, M.; Verdaguer, E.; Fortuna, A.; Folch, J.; Bulló, M.O.; Auladell, C.; Camins, A.; et al. Protein tyrosine phosphatase 1B (PTP1B) as a potential therapeutic target for neurological disorders. *Biomed. Pharmacother.* **2022**, *155*, 113709. [[CrossRef](#)]
51. Sun, J.; Qu, C.; Wang, Y.; Huang, H.; Zhang, M.; Zou, W. Type 2 diabetes mellitus and protein-tyrosine phosphatase 1b. *J. Diabetes Metab. Disord. Control* **2016**, *3*, 180–183. [[CrossRef](#)]
52. Deshpande, T.A.; Isshak, M.; Priefer, R. PTP1B Inhibitors as Potential Target for Type II Diabetes. *Curr. Res. Diabetes Obes. J.* **2020**, *14*, 555876. [[CrossRef](#)]
53. Murthy, V.S.; Kulkarni, V.M. Molecular Modeling of Protein Tyrosine Phosphatase 1B (PTP 1B) Inhibitors. *Bioorg. Med. Chem.* **2002**, *10*, 897–906. [[CrossRef](#)]
54. Liljebriis, C.; Larsen, S.D.; Ogg, D.; Palazuk, B.J.; Bleasdale, J.E. Investigation of Potential Bioisosteric Replacements for the Carboxyl Groups of Peptidomimetic Inhibitors of Protein Tyrosine Phosphatase 1B: Identification of a Tetrazole-Containing Inhibitor with Cellular Activity. *J. Med. Chem.* **2002**, *45*, 1785–1798. [[CrossRef](#)]
55. Maheshwari, N.; Karthikeyan, C.; Bhadada, S.V.; Sahi, C.; Verma, A.K.; Hari Narayana Moorthy, N.S.; Trivedi, P. Synthesis and biological evaluation of some N-(3-(1H-tetrazol-5-yl) phenyl)acetamide derivatives as novel non-carboxylic PTP1B inhibitors designed through bioisosteric modulation. *Bioorg. Chem.* **2018**, *80*, 145–150. [[CrossRef](#)]
56. Maheshwari, N.; Karthikeyan, C.; Bhadada, S.V.; Verma, A.K.; Sahi, C.; Moorthy, N.S.H.N.; Trivedi, P. Design, synthesis and biological evaluation of some tetrazole acetamide derivatives as novel non-carboxylic PTP1B inhibitors. *Bioorg. Chem.* **2019**, *92*, 103221. [[CrossRef](#)]
57. Ghareb, N.; El-Sayed, N.M.; Abdelhameed, R.; Yamada, K.; Elgawish, M.S. Toward a treatment of diabetes: Rational design, synthesis and biological evaluation of benzene-sulfonamide derivatives as a new class of PTP-1B inhibitors. *Bioorg. Chem.* **2019**, *86*, 322–338. [[CrossRef](#)]
58. Garcia-Marin, J.; Grier, M.; Alajarin, R.; Rodriguez-Puyol, M.; Rodriguez-Puyol, D.; Vaquero, J.J. A Computer-Driven Scaffold-Hopping Approach Generating New PTP1B Inhibitors from the Pyrrolo[1,2-a]quinoxaline Core. *ChemMedChem* **2021**, *16*, 2895–2906. [[CrossRef](#)]
59. Balestri, F.; Moschini, R.; Mura, U.; Cappiello, M.; Del Corso, A. In Search of Differential Inhibitors of Aldose Reductase. *Biomolecules* **2022**, *12*, 485. [[CrossRef](#)]
60. Inukai, S.; Agata, M.; Sato, M.; Naitou, A.; Matsukawa, H.; Goto, M. Characterization of a novel aldose reductase inhibitor, TAT, and its effects of streptozotocin-induced diabetic neuropathy in rats. *Jpn. J. Pharmacol.* **1993**, *61*, 221. [[CrossRef](#)]
61. Hotta, N.; Kakuta, H.; Fukasawa, H.; Koh, N.; Sakakibara, F.; Nakamura, J.; Hamada, Y.; Wakao, T.; Hara, T.; Mori, K.; et al. Effect of a potent new aldose reductase inhibitor, (5-(3-thienyl)tetrazol-1-yl)acetic acid (TAT), on diabetic neuropathy in rats. *Diabetes Res. Clin. Pract.* **1995**, *27*, 107. [[CrossRef](#)]
62. Hotta, N.; Koh, N.; Sakakibara, F.; Nakamura, J.; Hara, T.; Hamada, Y.; Fukasawa, H.; Kakuta, H.; Sakamoto, N. Effect of an aldose reductase inhibitor on abnormalities of electroretinogram and vascular factors in diabetic rats. *Eur. J. Pharmacol.* **1997**, *326*, 45–51. [[CrossRef](#)]
63. Nakamura, J.; Hamada, Y.; Sakakibara, F.; Hara, T.; Wakao, T.; Mori, K.; Nakashima, E.; Naruse, K.; Kamijo, M.; Koh, N.; et al. Physiological and morphometric analyses of neuropathy in sucrose-fed OLETF rats. *Diabetes Res. Clin. Pract.* **2001**, *51*, 9–20. [[CrossRef](#)]
64. Nakamura, J.; Koh, N.; Sakakibara, F.; Hamada, Y.; Hara, T.; Sasaki, H.; Chaya, S.; Komori, T.; Nakashima, E.; Naruse, K.; et al. Polyol pathway hyperactivity is closely related to carnitine deficiency in the pathogenesis of diabetic neuropathy of streptozotocin-diabetic rats. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 897–902.
65. Pegklidou, K.; Koukoulitsa, C.; Nicolaou, I.; Demopoulos, V.J. Design and synthesis of novel series of pyrrole based chemotypes and their evaluation as selective aldose reductase inhibitors. A case of bioisosterism between a carboxylic acid moiety and that of a tetrazole. *Bioorg. Med. Chem.* **2010**, *18*, 2107–2114. [[CrossRef](#)]
66. Alexiou, P.; Demopoulos, V.J. A Diverse Series of Substituted Benzenesulfonamides as Aldose Reductase Inhibitors with Antioxidant Activity: Design, Synthesis, and in vitro Activity. *J. Med. Chem.* **2010**, *53*, 7756–7766. [[CrossRef](#)] [[PubMed](#)]
67. Gallwitz, B. Clinical Use of DPP-4 Inhibitors. *Front. Endocrinol.* **2019**, *10*, 389. [[CrossRef](#)]

68. Gomha, S.M.; Eldebss, T.M.A.; Badrey, M.G.; Abdulla, M.M.; Mayhoub, A.S. Novel 4-Heteroaryl-Antipyrines as DPP-IV Inhibitors. *Chem. Biol. Drug Des.* **2015**, *86*, 1292–1303. [[CrossRef](#)]
69. Andrews, S.; Congreve, M.S.; Bortolato, A.; Mason, J.S. Preparation of Novel GLP-1 Receptor Agonist Peptides for Treating Diabetes Mellitus and Related Diseases. Patent GB2551945, 10 January 2018.
70. Agejas Chicharro, F.J.; Bauer, R.A.; Bell, M.G.; Chen, Q.; Cumming, G.R.; Fields, T.; Gernert, D.L.; Ho, J.D.; Kaoudi, T.A.; Masquelin, T.J.; et al. Preparation of Macrocyclic Glucagon-like Peptide 1 Receptor Agonists. Patent WO2022246019, 24 November 2022.
71. Li, H.; Fang, Y.; Guo, S.; Yang, Z. GPR119 agonists for the treatment of type 2 diabetes: An updated patent review (2014–present). *Expert Opin. Ther. Pat.* **2021**, *31*, 795–808. [[CrossRef](#)]
72. Jones, R.M.; Leonard, J.N.; Buzard, D.J.; Lehmann, J. GPR119 agonists for the treatment of type 2 diabetes. *Expert Opin. Ther. Pat.* **2009**, *19*, 1339–1359. [[CrossRef](#)]
73. Qian, Y.; Wang, J.; Yang, L.; Liu, Y.; Wang, L.; Liu, W.; Lin, Y.; Yang, H.; Ma, L.; Ye, S.; et al. Activation and signaling mechanism revealed by GPR119-Gs complex structures. *Nat. Commun.* **2022**, *13*, 7033. [[CrossRef](#)]
74. Spasov, A.A.; Kosolapov, V.A.; Babkov, D.A. Effect of GRP119 receptor agonist, compound MBX-2982, on activity of human glucokinase. *Bull. Exp. Biol. Med.* **2017**, *163*, 695–698. [[CrossRef](#)]
75. Zuo, Z.; Chen, M.; Shao, X.; Qian, X.; Liu, X.; Zhou, X.; Xiang, J.; Deng, P.; Li, Y.; Jie, H.; et al. Design and biological evaluation of tetrahydropyridine derivatives as novel human GPR119 agonists. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 126855. [[CrossRef](#)]
76. Patil, R.I.; Gunjal, A.P.; Verma, J.; Kumar, P.; Rai, S.K.; Rai, H.; Kumar, A. Preparation of Heterocyclic Compounds as GPR119 Agonist for Treatment of Metabolic Disorders. Patent WO2017175066, 12 October 2017.
77. Paternoster, S.; Simpson, P.V.; Kokh, E.; Kizilkaya, H.S.; Rosenkilde, M.M.; Mancera, R.L.; Keating, D.J.; Massi, M.; Falasca, M. Pharmacological and structure-activity relationship studies of oleoyl-lysophosphatidylinositol synthetic mimetics. *Pharmacol. Res.* **2021**, *172*, 105822. [[CrossRef](#)]
78. Huang, H.; Lanter, J.C.; Meegalla, S.K.; Player, M.R. Preparation of Cyclohexyl Derivatives as GPR40 Agonists for the Treatment of Type II Diabetes. Patent WO2018081047, 3 May 2018.
79. Huang, H.; Winters, M.P.; Meegalla, S.K.; Arnoult, E.; Lee, S.P.; Zhao, S.; Martin, T.; Rady, B.; Liu, J.; Towers, M.; et al. Discovery of novel benzo[b]thiophene tetrazoles as non-carboxylate GPR40 agonists. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 429–436. [[CrossRef](#)]
80. Meegalla, S.; Player, M.R.; Huang, H.; Winters, M.P. Preparation of Substituted Benzothiophenyl Derivatives as GPR40 Agonists for the Treatment of Type II Diabetes. U.S. Patent US20170291908, 12 October 2017.
81. Staehr, P.; Hother-Nielsen, O.; Beck-Nielsen, H. Hepatic glucose production: Therapeutic target in type 2 diabetes? *Diabetes Obes. Metab.* **2002**, *4*, 215–223. [[CrossRef](#)]
82. Mitchell, E.P.; Withers, S.G.; Ermert, P.; Vasella, A.T.; Garman, E.F.; Oikonomakos, N.G.; Johnson, L.N. Ternary Complex Crystal Structures of Glycogen Phosphorylase with the Transition State Analogue Nojirimycin Tetrazole and Phosphate in the T and R States. *Biochemistry* **1996**, *35*, 7341–7355. [[CrossRef](#)]
83. Heightman, T.D.; Vasella, A.; Tsitsanou, K.E.; Zographos, S.E.; Skamnaki, V.T.; Oikonomakos, N.G. Cooperative Interactions of the Catalytic Nucleophile and the Catalytic Acid in the Inhibition of β -Glycosidases. Calculations and their validation by comparative kinetic and structural studies of the inhibition of glycogen phosphorylase b. *Helv. Chim. Acta* **1998**, *81*, 853–864. [[CrossRef](#)]
84. Bokor, É.; Kyriakis, E.; Solovou, T.G.A.; Koppány, C.; Kantsadi, A.L.; Szabó, K.E.; Szakács, A.; Stravodimos, G.A.; Docsa, T.; Skamnaki, V.T.; et al. Nanomolar Inhibitors of Glycogen Phosphorylase Based on β -d-Glucosaminyl Heterocycles: A Combined Synthetic, Enzyme Kinetic, and Protein Crystallography Study. *J. Med. Chem.* **2017**, *60*, 9251–9262. [[CrossRef](#)]
85. Somsak, L.; Nagy, V.; Hadady, Z.; Docsa, T.; Gergely, P. Glucose analog inhibitors of glycogen phosphorylases as potential antidiabetic agents: Recent developments. *Curr. Pharm. Des.* **2003**, *9*, 1177–1189. [[CrossRef](#)]
86. Toth, M.; Kun, S.; Bokor, E.; Benlifa, M.; Tallec, G.; Vidal, S.; Docsa, T.; Gergely, P.; Somsak, L.; Praly, J.-P. Synthesis and structure-activity relationships of C-glycosylated oxadiazoles as inhibitors of glycogen phosphorylase. *Bioorg. Med. Chem.* **2009**, *17*, 4773–4785. [[CrossRef](#)]
87. Somsak, L.; Bokor, E.; Czifrak, K.; Konya, B.; Kun, S.; Toth, M. Glucose-analog inhibitors of glycogen phosphorylase as potential antidiabetic agents. *Magy. Kem. Foly. Kem. Kozl.* **2010**, *116*, 19–30.
88. Kun, S.; Bokor, E.; Varga, G.; Szocs, B.; Pahi, A.; Czifrak, K.; Toth, M.; Juhasz, L.; Docsa, T.; Gergely, P.; et al. New synthesis of 3-(β -D-glucopyranosyl)-5-substituted-1,2,4-triazoles, nanomolar inhibitors of glycogen phosphorylase. *Eur. J. Med. Chem.* **2014**, *76*, 567–579. [[CrossRef](#)] [[PubMed](#)]
89. Kattimani, P.P.; Somagond, S.M.; Bayannavar, P.K.; Kamble, R.R.; Bijjaragi, S.C.; Hunnur, R.K.; Joshi, S.D. Novel 5-(1-aryl-1H-pyrazol-3-yl)-1H-tetrazoles as glycogen phosphorylase inhibitors: An in vivo antihyperglycemic activity study. *Drug Dev. Res.* **2020**, *81*, 70–84. [[CrossRef](#)] [[PubMed](#)]
90. Suresh, L.; Onkara, P.; Kumar, P.S.V.; Pydisetty, Y.; Chandramouli, G.V.P. Ionic liquid-promoted multicomponent synthesis of fused tetrazolo[1,5-a]pyrimidines as α -glucosidase inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4007–4014. [[CrossRef](#)]
91. Suwito, H.; Kurnyawaty, N.; Haq, K.U.; Ramadhan, R.; Abdulloh, A.; Hardiyanti, H.D.; Phuwapraisirisan, P. Synthesis of dihydrotetrazolopyrimidine derivatives as anticancer agents and inhibitor of α -glucosidase. *Rasayan J. Chem.* **2023**, *16*, 147–158. [[CrossRef](#)]
92. He, M.; Li, Y.-J.; Shao, J.; Fu, C.; Li, Y.-S.; Cui, Z.-N. 2,5-Disubstituted furan derivatives containing imidazole, triazole or tetrazole moiety as potent α -glucosidase inhibitors. *Bioorg. Chem.* **2023**, *131*, 106298. [[CrossRef](#)] [[PubMed](#)]

93. Selvarasu, S.; Srinivasan, P.; Mannathusamy, G.; Maria Susai, B. Synthesis, characterization, in silico molecular modeling, anti-diabetic and antimicrobial screening of novel 1-aryl-N-tosyl-1H-tetrazole-5-carboxamide derivatives. *Chem. Data Collect.* **2021**, *32*, 100648. [[CrossRef](#)]
94. Gao, Y.L.; Zhao, G.L.; Liu, W.; Shao, H.; Wang, Y.L.; Xu, W.R.; Tang, L.D.; Wang, J.W. Design, synthesis and in vivo hypoglycemic activity of tetrazole-bearing N-glycosides as SGLT2 inhibitors. *Indian J. Chem. Sect. B Org. Chem. Incl. Med. Chem.* **2010**, *49B*, 1499–1508. [[CrossRef](#)]
95. Ho, L.T.; Kulkarni, S.S.; Lee, J.C. Development of sodium-dependent glucose co-transporter 2 inhibitors as potential anti-diabetic therapeutics. *Curr. Top. Med. Chem.* **2011**, *11*, 1476–1512. [[CrossRef](#)]
96. Kumari, B.; Chetia, D. In-silico docking studies of selected N-glycoside bearing tetrazole ring in the treatment of hyperglycemia showing inhibitory activity on SGLT. *Int. J. Pharm. Pharm. Sci.* **2013**, *5* (Suppl. 2), 633–638.
97. Reddy, B.P.; Reddy, K.R.; Sharma, V.M.; Reddy, M.M.; Poshala, R. Preparation of Tetrazole Glycosides for Treating Diseases Related SGLT2 Inhibition. Patent WO2010018438, 20 January 2010.
98. Liao, B.-R.; He, H.-B.; Yang, L.-L.; Gao, L.-X.; Chang, L.; Tang, J.; Li, J.-Y.; Li, J.; Yang, F. Synthesis and structure-activity relationship of non-phosphorus-based fructose-1,6-bisphosphatase inhibitors: 2,5-Diphenyl-1,3,4-oxadiazoles. *Eur. J. Med. Chem.* **2014**, *83*, 15–25. [[CrossRef](#)]
99. Zhu, J.; Chen, C.; Dong, J.; Cheng, S.; Li, G.; Wang, C.; Ouyang, D.; Leung, C.-H.; Lin, L. Artificial intelligence-aided discovery of prolyl hydroxylase 2 inhibitors to stabilize hypoxia inducible factor-1 α and promote angiogenesis. *Chin. Chem. Lett.* **2023**, *34*, 107514. [[CrossRef](#)]
100. Beyett, T.S.; Gan, X.; Reilly, S.M.; Chang, L.; Gomez, A.V.; Saltiel, A.R.; Showalter, H.D.; Tesmer, J.J.G. Carboxylic acid derivatives of amlexanox display enhanced potency toward TBK1 and IKKe and reveal mechanisms for selective inhibition. *Mol. Pharmacol.* **2018**, *94*, 1210–1219. [[CrossRef](#)]
101. Wu, A.-D.; Lu, H.-L. A new Cu (II)-coordination polymer: Inhibiting bcl-2 gene expression in retinal cells and exerting treatment activity on diabetic retinopathy. *Inorg. Nano-Met. Chem.* **2021**, *51*, 1453–1458. [[CrossRef](#)]

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