



Triazole and Thiadiazole Heterocyclic derivatives: Review on Chemistry, Synthetic Strategies and Antidiabetic evaluation.

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ABSTRACT :

Diabetes mellitus continues to rank among the most serious public health challenges worldwide, as the number of people affected keeps increasing steadily across nearly all regions and age groups. Against this broader backdrop, type 2 diabetes mellitus (T2DM) represents most cases and is the primary contributor to this expanding burden; current estimates indicate that 589 million adults are affected globally, with this number expected to approach 900 million by 2050. Inhibiting the digestive enzymes alpha-amylase and alpha-glucosidase to control postprandial blood sugar elevations remains a key approach in oral antidiabetic treatment, yet the currently approved inhibitors — acarbose, miglitol and voglibose — are sugar-like compounds, and their digestive side effects restrict patients' long-term tolerance. Consequently, continued attention has focused on non-sugar heterocyclic inhibitors, especially those based on triazole and 1,3,4-thiadiazole rings, as well as their fused triazolo-thiadiazole hybrids. This review uses the primary medicinal-chemistry literature to outline the chemical rationale for these scaffolds, representative synthetic pathways, structure–activity relationships obtained from laboratory alpha-amylase/alpha-glucosidase assays, enzyme-kinetic and computational-docking studies, and other antidiabetic-relevant targets, including aldose reductase. Throughout the reviewed research, halogen substitution, hydrogen-bond-donating groups and rigid fused ring systems repeatedly emerge as advantageous design characteristics, while several compounds demonstrate nanomolar-to-low-micromolar potency against one or both enzymes. The review concludes by assessing the strength of the available evidence and the remaining work required before these compounds can potentially advance to clinical use.

Keywords: type 2 diabetes; alpha-glucosidase; alpha-amylase; triazole; thiadiazole; triazolo-thiadiazole

Introduction

1.1 The extent of the diabetes problem

The 11th edition of the International Diabetes Federation (IDF) Diabetes Atlas reports that 589 million adults aged 20–79 were living with diabetes in 2024, roughly one in nine adults worldwide and projects that this figure will reach nearly 900 million by 2050 ⁽¹⁾. T2DM accounts for more than 90% of this total burden and is a progressive disorder characterised by peripheral insulin resistance, impaired glucose disposal and a gradual loss of functional pancreatic beta-cell mass. When chronic high blood sugar is not adequately controlled, it causes microvascular complications (retinopathy, nephropathy, neuropathy) and markedly increases cardiovascular risk. The magnitude and ongoing expansion of this epidemic, fueled by population ageing, urbanisation and increasing obesity, have made the discovery of new, better-tolerated oral antidiabetic agents a major priority in medicinal chemistry ⁽¹⁾.

1.2 Carbohydrate-hydrolysing enzymes as drug targets

A long-established and still widely used therapeutic approach targets the enzymes that digest dietary starch: pancreatic and salivary alpha-amylase, which breaks internal alpha-1,4-glycosidic bonds in starch into shorter sugar chains, and intestinal brush-border alpha-glucosidase, which releases absorbable glucose from these shorter chains. Inhibiting either enzyme delays carbohydrate digestion or reduces the post-meal glucose spike typical of T2DM. Acarbose continues to be the prototypical clinically used alpha-glucosidase inhibitor. Because its structure resembles a sugar chain, it competitively and reversibly occupies the active site of intestinal alpha-glucosidases ⁽²⁾. Although it effectively reduces post-meal glucose and glycated haemoglobin, its sugar-like structure allows a considerable amount of undigested carbohydrate to reach the colon, where bacterial fermentation causes its most frequently reported side effects: flatulence, abdominal distension and diarrhoea; rare liver injury has also been reported ^(2,3). These tolerability concerns, which are also present to varying extents with miglitol and voglibose, provide the main rationale for developing structurally distinct, non-sugar inhibitors with better digestive tolerability ^(2,3).

1.3 Heterocyclic triazoles and thiadiazoles

Five-membered aromatic ring systems containing nitrogen and sulfur have long been investigated as enzyme-inhibitory building blocks because they offer a favorable combination of hydrogen-bonding capacity, metabolic stability and synthetic accessibility ⁽⁴⁾. These rings can function as versatile replacements for amide, ester and other planar functional groups, while the substitution pattern, rather than the core ring itself, generally determines whether a derivative is a potent inhibitor or an inactive analogue. This review follows that substituent-driven rationale across three related structural

classes: monocyclic triazoles, monocyclic 1,3,4-thiadiazoles, and fused triazolo-thiadiazole hybrids.

2. Synthetic Strategy of Core Scaffolds

2.1 1,2,3-Triazoles by click chemistry

The leading modern method for producing 1,4-disubstituted 1,2,3-triazoles is the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), independently reported by the groups of Sharpless and Meldal in 2002 and later popularized under the “click chemistry” label that Sharpless had introduced the previous year⁽⁵⁾. The reaction joins an organic azide with a terminal alkyne with high selectivity under mild aqueous or aqueous-organic conditions and tolerates a wide range of functional groups, features that quickly established it as a popular method for constructing structurally diverse triazole libraries for biological screening, including the antidiabetic hybrids. Several studies examined here employed this exact reaction to attach a 1,2,3-triazole to a second building block, such as a thiadiazole or quinoline-oxadiazole core, in one efficient step^(6,7).

2.2 1,2,4-Triazoles and 1,3,4-thiadiazoles from hydrazide chemistry

1,2,4-Triazole and 1,3,4-thiadiazole rings are commonly constructed from a shared acyl hydrazide or thiosemicarbazide intermediate, reflecting their close synthetic connection through nitrogen- or sulfur-based ring closure of the same starting material. A representative sequence transforms a carboxylic acid first into its ester and then into its hydrazide, which is condensed with an isothiocyanate or carbon disulfide/potassium hydroxide to produce a thiosemicarbazide or potassium dithiocarbamate intermediate. This intermediate is then cyclized under basic conditions, such as aqueous sodium hydroxide or excess hydrazine hydrate, to form 4-amino-1,2,4-triazole-3-thiol, or under acidic dehydrating conditions, such as concentrated sulfuric acid or phosphorus oxychloride, to yield the corresponding 1,3,4-thiadiazol-2-amine. Since the same open-chain intermediate can undergo either type of cyclization, medicinal chemists often synthesize matched triazole/thiadiazole pairs for direct comparison, and several multicomponent hybrid syntheses intentionally exploit this branching point^(8,9).

2.3 Fused triazolo-thiadiazoles

The fused triazolo-thiadiazole system, which shares a bridgehead, is typically constructed from a 4-amino-5-substituted-4H-1,2,4-triazole-3-thiol starting material. Its neighbouring amino and thiol groups supply the two reactive centres required to close the second ring. Condensing this starting material with a carboxylic acid, usually under reflux in phosphorus oxychloride, directly produces the fused bicyclic structure; in alternative routes, the same starting material is condensed with an aryl aldehyde and then subjected to oxidative ring closure, for example with molecular iodine, to produce a related fused thiadiazole-on-thiadiazole system, as shown by a 2022 study that generated twenty-five analogues carrying a benzodioxine substituent⁽¹⁰⁾.

3. In Vitro Inhibition of Alpha-Amylase and Alpha-Glucosidase: Structure–Activity Relationships

Enzyme inhibition is almost always assessed with p-nitrophenyl-alpha-D-glucopyranoside as the colour-forming substrate for alpha-glucosidase and a starch–iodine colour assay for alpha-amylase, while acarbose is included as the reference inhibitor. As assay parameters such as buffer, enzyme source, and incubation time differ among laboratories, the reported acarbose IC₅₀, the concentration required to reduce enzyme activity by half, varies substantially between papers, ranging from single digit micromolar values in some studies to several hundred micromolar in others. The potency comparisons are based on the acarbose value reported within the same study rather than on comparisons across studies.

Monocyclic 1,2,4- and 1,2,3-triazole derivatives

Bis-hydrazone triazoles. Khan and colleagues prepared nineteen 1,2,4-triazole-based bis-hydrazones and assessed their dual alpha-amylase/alpha-glucosidase inhibitory activity⁽¹¹⁾. Across the series, IC₅₀ values ranged from 0.70–35.70 micromolar for alpha-amylase and from 1.10–30.40 micromolar for alpha-glucosidase, compared with the same-assay acarbose reference values of 10.30 and 9.80 micromolar, respectively. The structure–activity analysis indicated that potency depended on the substitution pattern of the two flanking aryl rings rather than on any individual group alone: electron-withdrawing -chloro and -nitro substituents consistently enhanced activity, while their exact positions were also important—a compound with 3,4-dichloro and 4-nitro substituents was more active than its positional isomer containing the same substituents at the 3-position, despite having identical molecular formulae, demonstrating that substituent geometry, rather than electronic character alone, determines how effectively the ligand interacts with the catalytic pocket.

Thioacetamide triazole hybrids and dual-target design. A more recent Scientific Reports study from 2025 developed 1,2,4-triazole-containing thioacetamide derivatives specifically to inhibit both alpha-amylase and alpha-glucosidase, using molecular docking to select six candidates for synthesis in advance⁽¹²⁾. Two compounds produced IC₅₀ values of approximately 0.27 and 0.31 micrograms/mL against alpha-glucosidase and similarly low values against alpha-amylase, outperforming acarbose in the same assay. Electron-donating methoxy substitution lowered potency compared with electron-withdrawing groups, due to weaker charge stabilization within the catalytic pocket.

4-Amino-1,2,4-triazole–aldehyde hybrids. Yeye and co-workers synthesized 4-amino-1,2,4-triazole derivatives containing various aldehyde-derived substituents and assessed their dual amylase/glucosidase inhibition alongside molecular docking and enzyme kinetics⁽¹³⁾, extending the structure–activity rationale to a related synthetic starting point.

Triazole–thiazole fusion. Channar and colleagues developed 2,6-di(substituted phenyl)thiazolo[3,2-b]-1,2,4-triazoles, integrating pharmacokinetic and 3D-QSAR modelling with laboratory inhibition results, and identified one of the more potent dual inhibitors in this class⁽¹⁴⁾.

Triazoloquinazolines. Using a different fusion approach, Abuelizz and colleagues examined a series of previously synthesized triazoloquinazolines for alpha-glucosidase inhibition⁽¹⁵⁾. Several compounds inhibited the yeast-derived enzyme at concentrations ranging from 13 to 85 micromolar, compared with an acarbose value of 143.5 micromolar in the same assay, while docking showed substantial interactions with active-site residues, further supporting triazoloquinazolines as a viable fusion partner for the triazole core.

Series	Lead compound / key feature	Alpha-amylase IC ₅₀	Alpha-glucosidase IC ₅₀
Bis-hydrazones ⁽¹¹⁾	3,4-dichloro / 4-nitro aryl substitution	0.70–35.70 μM	1.10–30.40 μM
Thioacetamide hybrids ⁽¹²⁾	Two docking-prioritized leads	low, μg/mL	0.27–0.31 μg/mL
Triazoloquinazolines ⁽¹⁵⁾	Best of series vs. yeast alpha-glucosidase		13–85 μM

Table 1. Representative monocyclic 1,2,4-/1,2,3-triazole antidiabetic derivatives.

3.2 Monocyclic 1,3,4-thiadiazole derivatives

Schiff-base thiadiazoles. Ali and colleagues developed a series of 2-hydrazinyl-5-(4-nitrophenyl)-1,3,4-thiadiazole Schiff bases and tested them against alpha-glucosidase (16). Three analogues exhibited IC₅₀ values ranging from 1.10 to 2.20 micromolar, compared with an acarbose reference value of 11.50 micromolar in the same assay. According to the structure-based analysis, the potency of the best analogues results from the combination of halogen substitution, which promotes dipole and possible halogen-bonding interactions in an electron-poor pocket, and a hydrogen-bond-donating hydroxyl group on the terminal phenyl ring; eliminating the hydroxyl while preserving the halogens reduced activity without eliminating it, whereas replacing both features with bulky non-polar alkyl chains caused a pronounced loss of potency, indicating that the group may be too large for the binding cleft.

Multicomponent thiazolidinone–thiadiazole hybrids. Gummidi and co-workers employed a one-pot multicomponent reaction to combine thiazolidinone-4-one and 1,3,4-thiadiazole building blocks within a single hybrid scaffold, reporting an IC₅₀ of 2.59 micromolar against both alpha-glucosidase and alpha-amylase, approximately tenfold more potent than acarbose in their assay (9).

Thiadiazoles from 3-aminopyridinone acids. Shulgau and colleagues used a different synthetic starting point, cyclizing thiohydrazide intermediates obtained from 3-aminopyridin-2(1H)-ones with a range of acid anhydrides to produce nine new 1,3,4-thiadiazole derivatives containing different acidic linkers (17). The most active compound, which contained a benzoic-acid-derived linker, displayed approximately 3.7-fold greater potency than acarbose in the same assay, while molecular docking associated the benzoic fragment and a butanoic-acid linker with enhanced binding affinity for the modelled target proteins, suggesting that linker chemistry, rather than the thiadiazole ring alone, determines potency.

Dual-target thiadiazoles (aldose reductase and alpha-glucosidase). A particularly informative 2025 study by Kaya and colleagues deliberately designed 1,3,4-thiadiazole derivatives to inhibit both aldose reductase and alpha-glucosidase (18), demonstrating how the thiadiazole core has progressed from single-enzyme inhibition toward truly multi-target antidiabetic design.

Series (ref.)	Lead compound / key feature	Target	Lead IC ₅₀ / Ki	Reference compound
Schiff bases (16)	Dichloro + hydroxyl phenyl substitution	Alpha-glucosidase	1.10–2.20 μM	Acarbose 11.50 μM
Thiazolidinone–thiadiazole (9)	One-pot multicomponent hybrid	Alpha-amylase & alpha-glucosidase	2.59 μM (both)	Acarbose (10× less potent)
3-Aminopyridinone thiadiazoles (17)	Benzoic-acid-derived linker	Alpha-glucosidase	3.7× more potent than acarbose	Acarbose

Table 2. Representative monocyclic 1,3,4-thiadiazole antidiabetic derivatives.

3.3 Triazole–thiadiazole hybrids

Click-generated triazole–thiadiazole hybrids

A distinct and informative design approach connects a pre-formed 1,3,4-thiadiazole to a 1,2,3-triazole through the CuAAC “click” reaction, producing hybrids that unite both building blocks within a single, easily diversified molecule.

Dhameja and colleagues described such a series, synthesized by clicking a thiadiazole-derived alkyne with a range of phenylacetamide azides (6). The strongest-performing hybrid, compound 9n, containing 2-methyl and 4-nitro substituents, inhibited alpha-glucosidase with an IC₅₀ of 31.91 micromolar, making it approximately 26 times more potent than the acarbose value of 844.81 micromolar reported in the same assay. Notably, blind molecular docking suggested that this compound interacted with an enzyme site distinct from the usual substrate pocket occupied by acarbose, a mechanistic difference that could have implications for combination therapy.

A related hybrid approach paired 1,3,4-thiadiazole with 5,6-diphenyl-1,2,4-triazine instead of triazole and was likewise assessed for alpha-glucosidase inhibition and molecular docking; the most active member of that series, compound 7g with an ortho-chloro substituent, produced an IC₅₀ of 14.36 micromolar versus an acarbose reference of 844.81 micromolar (19).

Cele and colleagues applied the same combinatorial reasoning to a quinoline–1,3,4-oxadiazole core bearing 1,2,3-triazole substituents, reporting nanomolar radical-scavenging activity together with micromolar alpha-glucosidase inhibition and demonstrating through enzyme kinetics that their most active compounds inhibited non-competitively, away from the main pocket (7). Alongside the Dhameja study, this repeated observation of binding outside the principal substrate pocket in several triazole-containing hybrids contrasts notably with the predominantly competitive kinetics reported for the more rigid fused systems discussed next and warrants further structural investigation.

Series (ref.)	Lead compound	Alpha-glucosidase IC ₅₀	Acarbose
Thiadiazole–1,2,3-triazole click hybrids (6)	Compound 9n (2-Me, 4-NO ₂)	31.91 μM	844.81 μM
Thiadiazole–triazine hybrids (19)	Compound 7g (o-Cl)	14.36 μM	844.81 μM

Table 3. Click-generated triazole–thiadiazole and related hybrids

Fused triazolo-thiadiazoles

Fused bicyclic triazolo-thiadiazole systems generally unite the rigidity and limited flexibility of a planar bicyclic structure with the combined hydrogen-bonding and fat-solubility properties of both parent rings, and several studies report potency improvements consistent with this rationale.

Hussain and colleagues synthesized twenty-five analogues of a thiadiazole-fused-thiadiazole containing a benzodioxine substituent through molecular-iodine-mediated oxidative ring closure (10). Their inhibition profiles covered a broad range—0.70–30.80 micromolar against alpha-amylase and 0.80–29.70 micromolar against alpha-glucosidase, compared with an acarbose reference of approximately 12.8–12.9 micromolar in the same assay with the most active analogue featuring a di-hydroxy substitution pattern on the pendant aryl ring, again suggesting that hydrogen-bond donation is a recurring driver of potency across otherwise structurally different scaffolds.

Carbazole-linked triazole-thione. Çapan and colleagues reported eighteen carbazole-1,2,4-triazole-thione derivatives, seven of which inhibited alpha-amylase with IC₅₀ below 6.4 micromolar; their two most potent compounds achieved values of 0.53 and 0.56 micromolar, respectively, against an acarbose reference of 5.31 micromolar, and advanced their lead compound to an in vivo blood-sugar-lowering assay in mice (20).

Series	Lead compound / feature	Alpha-amylase IC50	Alpha-glucosidase IC50	Acarbose, same study
Thiadiazole-fused-thiadiazole, benzodioxine (10)	Di-hydroxy aryl analogue	0.70–30.80 μ M	0.80–29.70 μ M	2.8–12.9 μ M
Carbazole–triazole-thiones (20)	Two leads	0.53 & 0.56 μ M		5.31 μ M

Table 4. Fused triazolo-thiadiazole and related bicyclic derivatives

Indole-fused triazolo-thiadiazoles and related hybrids

Indole is among the most frequently reused building blocks, likely because of both its natural-product precedent, as the core of tryptophan and serotonin, and its convenient synthetic attachment to a triazole-thiol starting material. Several groups have specifically fused indole with a triazolo-thiadiazole or a related bicyclic core and assessed the resulting hybrids against alpha-amylase and alpha-glucosidase.

Iqbal and colleagues synthesized seventeen indole-based fused triazole-thiadiazole derivatives using the standard 4-amino-triazole-3-thiol/phosphorus-oxychloride route and evaluated them both experimentally and in silico (21). Structure–activity analysis showed that para-halogen substitution on the terminal phenyl ring was the main determinant of potency: the para-fluoro-substituted lead compound inhibited alpha-amylase and alpha-glucosidase with IC50 values of 1.27 and 2.18 micromolar, respectively, compared with an acarbose reference value of 8.24 micromolar in the same assay, while docking positioned the fluorine substituent suitably to accept a hydrogen bond from a backbone amide.

Taha and colleagues reported a related but structurally different indole-thiazolotriazole series, synthesizing twenty-two indole-based thiazolotriazole analogues and assessing their dual alpha-amylase/alpha-glucosidase inhibition through kinetic and docking studies using an acarbose comparator tested in the same assay (22).

Khan and colleagues attached a thiazolidinone, to the indole core and reported twenty thiazolidinone-based indole derivatives, several of which were several times more potent than acarbose against both enzymes (23).

Taken together, these indole-fused studies support the halogen- and hydrogen-bond-donor-dependent structure–activity pattern identified throughout the broader triazole and thiadiazole literature, while also showing that indole functions as a broadly compatible “third building block” that can be paired with multiple triazole-derived linking rings without eliminating dual-enzyme activity.

3.6 Summary of recurring structure–activity themes

Electron-withdrawing halogens, particularly chlorine and, less frequently, fluorine or nitro groups, on the pendant aryl ring are associated with greater potency across triazole (11,12), thiadiazole (16) and fused (10) series, potentially because they promote dipole–dipole and halogen-bonding interactions within a comparatively electron-rich or fat-soluble sub-pocket.

Hydrogen-bond-donating substituents, particularly hydroxyl groups, provide an additional potency increase when paired with halogenation (10,16), supporting a model in which the halogens confer electronic complementarity while the hydroxyl group anchors the ligand through a specific hydrogen bond with a catalytic or near-catalytic residue.

Bulky, non-polar alkyl substituents consistently diminish potency, which attributed to their excessive size for the confined binding pocket (16).

Indole as a compatible third building block. Across independent research groups, an indole unit remains compatible with fusion to several triazole-derived linking rings (thiadiazole, thiazolotriazole, thiazolidinone, sulfonothioate) without eliminating dual alpha-amylase/alpha-glucosidase activity, while halogen substitution on the terminal phenyl ring continues to be the principal potency determinant in these indole-fused series (21–23).

4. Enzyme Kinetics and Computational Docking

The most potent fused triazolo-thiadiazoles in this literature are more frequently described as competitive inhibitors, consistent with rigid, planar molecules inserting directly into the narrow catalytic groove normally occupied by the carbohydrate substrate, as observed for the benzodioxine-fused and carbazole-fused systems discussed above (10,20). In contrast, several triazole-containing click hybrids connected by a flexible acetamide or thioacetamide linker were classified instead as non-competitive or mixed inhibitors that bind to a site separate from the primary substrate pocket (6,7). This distinction is pharmacologically important: in principle, an inhibitor that does not directly compete with the substrate is less readily overcome by increasing substrate (dietary carbohydrate) concentrations, although its translation into a meaningful clinical benefit has not been evaluated.

Molecular docking is almost universally conducted using a crystal structure of a related carbohydrate-digesting enzyme to interpret observed structure–activity relationships and suggest binding poses compatible with the hydrogen-bonding and electron-withdrawing-group trends. Docking scores in the low double-digit negative kcal/mol range, together with predicted hydrogen bonds involving residues in the enzyme’s catalytic groove, are often presented alongside experimental IC50 values as supportive evidence rather than as independent proof. As several of the more rigorous studies in this literature have themselves pointed out, a favorable docking score supports the plausibility of a proposed binding mode but does not establish it. A small number of studies in this particular chemical space have supplemented docking with molecular dynamics simulations or direct binding assays.

5. Beyond Glycosidase Inhibition: Aldose Reductase Targets

Given that T2DM is multifactorial, several research groups have intentionally developed triazole or thiadiazole derivatives capable of acting simultaneously on multiple diabetes-relevant targets.

The most prominent example in this literature is the 2025 study by Kaya and colleagues, who developed a series of 1,3,4-thiadiazole derivatives specifically intended to inhibit both aldose reductase (AR) and alpha-glucosidase (18). AR is the rate-limiting enzyme in the polyol pathway, converting excess intracellular glucose into sorbitol while consuming the essential cellular reducing agent NADPH. During chronically elevated blood sugar, this pathway becomes excessively active, reducing cellular antioxidant capacity and mechanistically contributing to diabetic nerve, kidney, and eye disease. Every compound in Kaya and colleagues’ series displayed substantially higher potency against AR, with inhibition constants (Ki) of 15.39–176.50 nanomolar, than the reference AR inhibitor epalrestat, which had a Ki of 837.70 nanomolar; some of the same compounds also inhibited alpha-glucosidase more effectively than acarbose. Molecular docking of the most potent dual AR/glucosidase inhibitor revealed hydrogen-bonding interactions with the target protein that were consistent with acarbose’s own binding mode, providing a structural rationale for the compound’s dual activity. This type of intentionally dual-targeted strategy, addressing both the immediate cause of post-meal high blood sugar, glucosidase activity, and a downstream consequence of chronic high blood sugar, the polyol pathway, is among the more pharmacologically advanced directions pursued in this chemistry.

6. In Vivo Evidence and Translational Considerations

Most of the literature is limited to laboratory enzyme-inhibition experiments and computational modelling. A smaller group of studies has advanced a lead compound to animal testing, and these reports merit particular consideration because they begin to examine whether laboratory potency produces a physiologically meaningful effect.

After identifying their most potent carbazole-1,2,4-triazole-thione compound, C5f, as a highly potent and low-toxicity alpha-amylase inhibitor in laboratory testing, using normal human liver stellate cells (LX-2) as a toxicity benchmark, Çapan and colleagues administered five 10 mg/kg doses of the compound to mice and observed a marked decrease in blood glucose concentration, from 290.54 to 216.15 mg/dL, compared with an untreated control group that showed no comparable decrease⁽²⁰⁾.

Scaffold class	Most potent lead identified	Alpha-glucosidase IC ₅₀ / Ki	Ref.
Monocyclic 1,2,4-triazole	Bis-hydrazone, 3,4-dichloro/4-NO ₂	1.10 µM	(11)
Monocyclic 1,3,4-thiadiazole	Schiff base, dichloro + OH	1.10 µM	(16)
Click-generated hybrid	Thiadiazole-triazole, compound 9n	31.91 µM	(6)
Indole-fused triazolo-thiadiazole	para-Fluoro analogue	2.18 µM	(21)
Dual target thiadiazole (AR + glucosidase)	Best AR/glucosidase dual compound	Ki 15.39–176.50 nM (AR)	(18)

Table 5. Best-in-class potency per scaffold class discussed in this review.

7. Conclusions and Future Directions

The triazole and thiadiazole ring systems examined here, along with their fused triazolo-thiadiazole derivatives, represent a chemically versatile and synthetically accessible platform for designing alpha-amylase/alpha-glucosidase inhibitors. Across several independent research groups, individual compounds have demonstrated nanomolar-to-low-micromolar potency that surpasses acarbose in the same assay^(16,18,20). Several structural patterns consistently appear across independently reported series, including favorable halogen substitution, hydrogen-bond-donating groups, and, among the most potent individual leads, rigid fused bicyclic architectures linked to competitive inhibition kinetics. These patterns give the literature a degree of internal consistency despite substantial differences in assay conditions among laboratories.

Nevertheless, several gaps currently limit the extent to which these findings can be generalized:

Cross-study standardization. Since acarbose reference values differ by an order of magnitude or more among papers, comparisons between compounds from different research groups are not currently dependable.

Mechanistic confirmation. Docking is used almost universally to account for structure–activity relationships, yet structural validation through co-crystallography, or at least more extensive molecular dynamics and direct binding studies, remains uncommon.

In vivo and pharmacokinetic data. Apart from the limited exception of the carbazole-triazole-thione study, data on in vivo efficacy, oral bioavailability, and toxicology are largely lacking for this specific chemical space, unlike the extensive clinical and post-marketing safety record currently available for acarbose itself^(2,3).

Multi-target design. The aldose-reductase/alpha-glucosidase dual-inhibitor research by Kaya and colleagues⁽¹⁸⁾ demonstrates a promising approach: designing compounds against multiple diabetes-relevant targets from the outset.

Overall, the evidence identifies triazole and thiadiazole heterocyclic derivatives, particularly their rigid fused triazolo-thiadiazole derivatives, as a productive and still-active area of antidiabetic medicinal chemistry. At the same time, it emphasises that converting the strongest laboratory leads into genuinely competitive drug candidates will require standardized comparative testing, more thorough mechanistic characterization, and in vivo/pharmacokinetic evaluation.

Conflict of interest

The authors declare that they have no known financial, commercial, or personal conflicts of interest that could have influenced the work reported in this review article. All authors confirm that the research was conducted independently and that no external organization or individual had any role that could bias the content or conclusions of this manuscript.

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