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A Series Of Novel Triazole Derivatives And Their Impact On Diabetes Management

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Abstract
Diabetes mellitus represents a group of chronic metabolic disorders characterized by persistent hyperglycemia due to defects in insulin secretion, action, or both. If left unmanaged, chronic hyperglycemia can lead to severe complications, including cardiovascular diseases, nephropathy, and neuropathy. Current therapeutic approaches focus on lowering blood glucose levels, often employing α-glucosidase and α-amylase inhibitors to control postprandial glucose absorption. In recent years, considerable attention has been directed toward the development of novel nitrogen-containing heterocyclic compounds, particularly triazoles, as promising α-glucosidase inhibitors. Notably, quinazolinone-1,2,3-triazole hybrids and triazine-triazole derivatives have demonstrated significantly lower IC50 values than the standard drug acarbose, highlighting their potential as effective antidiabetic agents. These findings underscore the importance of ongoing efforts to design and optimize new inhibitors and to explore their structure-activity relationships, aiming to improve therapeutic options for diabetes management.
Keywords: *Diabetes mellitus, hyperglycemia, α-glucosidase, α-amylase, triazoles*

INTRODUCTION:

Diabetes refers to a group of long-term metabolic disorders marked by persistent high blood glucose (hyperglycemia) caused by impaired insulin production, action, or both [1]. Among its various forms, type I and type II diabetes are the most prevalent. Type I diabetes is caused by the immune system attacking and destroying pancreatic cells that produce insulin, whereas type II diabetes is characterized by the body's resistance to insulin or an inability to produce enough insulin to regulate blood sugar properly. Overall, diabetes involves complex and chronic conditions defined by glucose intolerance resulting from absolute or relative disruptions in insulin secretion or effectiveness [2].

In 2006, the World Health Organization (WHO) projected that by 2030, type 2 diabetes mellitus (T2DM) would affect approximately 366 million individuals, representing nearly 9.9% of adults worldwide. Several lifestyle factors, including obesity, sedentary behavior, smoking, poor dietary habits (low fiber, high glycemic index foods), and psychological conditions like depression, are recognized contributors to T2DM development [3,4]. If left uncontrolled, persistent high blood sugar (hyperglycemia) can severely damage vital organs, such as the kidneys, heart, and nervous system [5,6]. Therefore, the primary therapeutic approach in diabetes focuses on regulating blood glucose levels and managing related complications.

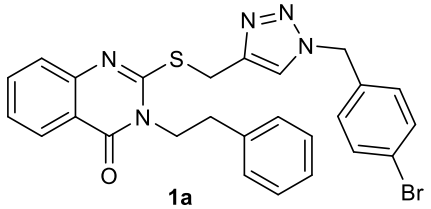
One of the key enzymes involved in carbohydrate metabolism is α-glucosidase, present in the lining of the small intestine, responsible for breaking down complex carbohydrates into simple sugars that are easily absorbed [7]. Inhibiting α-glucosidase is an effective strategy to prevent post-meal spikes in blood sugar, making this enzyme an important target in diabetes treatment [8,9]. Similarly, α-amylase (EC 3.2.1.1) facilitates the breakdown of starch into smaller sugar units, including maltose, dextrins, and glucose [10–12]. By simultaneously inhibiting α-amylase and α-glucosidase, it is possible to slow carbohydrate digestion, thus reducing the rate of glucose absorption and minimizing postprandial blood sugar increases [13,14]. However, while drugs such as acarbose, metformin, and miglitol are used to inhibit these enzymes, they often produce side effects, including gastrointestinal issues, weight gain, and liver dysfunction [5,6,15]. This has motivated the search for new and safer α-glucosidase and α-amylase inhibitors [16].

Nitrogen-containing heterocyclic compounds form the core structure of many pharmaceuticals, due to their strong affinity for biological targets and favorable pharmacokinetic profiles [17,18]. These heterocycles are present in various bioactive substances like vitamins, nucleic acids, drugs, and agrochemicals, making them crucial in drug discovery and medicinal chemistry [19–25]. Among these, 1,2,3-triazoles are five-membered nitrogen-rich rings ($C_2N_3H_3$) known for interacting with enzymes,

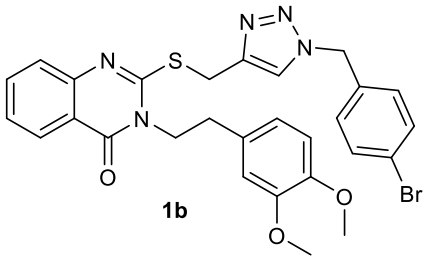
proteins, and nucleic acids through hydrogen bonding, dipole interactions, and Van der Waals forces [26,27].

Moreover, triazole derivatives play an essential role in modulating the conformation and activity of enzymes such as glycosidases and glycosyltransferases, affecting important biological processes like glycosylation and glycoside hydrolysis [28]. The presence of oxygen and other heteroatoms in their structures enhances their enzyme inhibitory activity [29]. Structure-activity relationship (SAR) studies have been instrumental in designing improved triazole-based molecules with enhanced therapeutic properties [30]. Notably, azole derivatives, including 1,2,4-triazoles, are recognized as well-tolerated antidiabetic agents with additional urease inhibitory activity [31–35]. Furthermore, conjugating triazoles with amino acids has shown promise for developing novel therapeutics and diagnostic agents.

In recent studies, a series of quinazolinone-1,2,3-triazole hybrid molecules were synthesized and evaluated for their α-glucosidase inhibitory potential, demonstrating significant anti-diabetic effects. These compounds exhibited IC_{50} values ranging from 181.0 to 474.5 μM, outperforming acarbose (IC_{50} = 750.0 μM). Notably, derivatives containing a 4-bromobenzyl substituent on the triazole ring showed the strongest inhibition. Among them, compounds **1a** and **1b** achieved the most potent effects, with IC50 values of 181.0 ± 1.4 μM and 192.3 ± 1.8 μM, respectively [36].

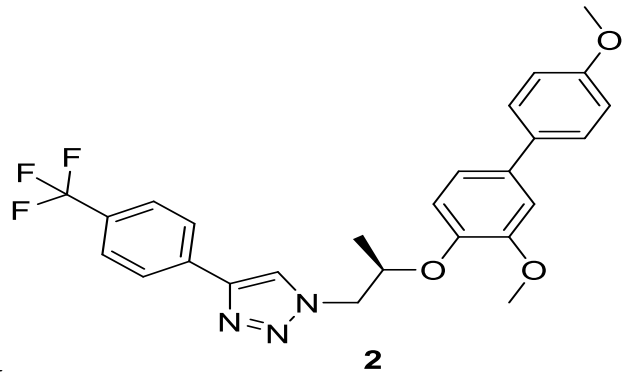


1a



1b

A well-recognized approach to managing postprandial blood glucose levels in diabetes is through the inhibition of α-glucosidase. In pursuit of new inhibitors, a series of (R)-1-(2-(4-bromo-2-methoxyphenoxy)propyl)-4-(4-(trifluoromethyl)-1H-1,2,3-triazole) derivatives **2** was synthesized and evaluated for their α-glucosidase inhibitory activity, showing IC_{50} values ranging from 14.2 to 218.1 μM. Among these, compound **2** demonstrated the most potent activity (IC_{50} = 14.2 μM), outperforming the standard reference drug. Furthermore, structure-activity relationship (SAR) analysis indicated that the 1H-1,2,3-triazole ring is crucial for the observed activity, highlighting these compounds as promising antidiabetic candidates [37].



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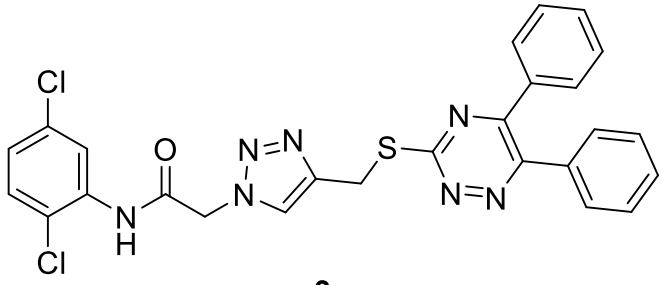
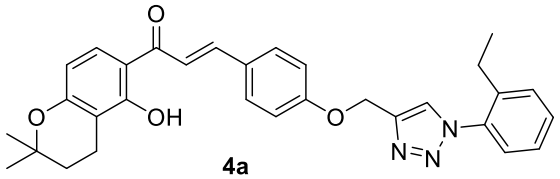
2

A series of triazine-triazole derivatives **3** was synthesized and evaluated for their antidiabetic potential as α-glucosidase inhibitors. All synthesized compounds demonstrated potent inhibitory activity, with IC_{50} values ranging from 11.63 ± 0.15 to 37.44 ± 0.35 μM, significantly outperforming the standard drug acarbose (IC_{50} = 817.38 ± 6.27 μM). Among them, compound **3**, containing a 2,5-dichloro substitution on the phenyl ring, was identified as the most potent inhibitor (IC_{50} = 11.63 ± 0.15 μM). Additionally, molecular docking studies with a homology-modeled α-glucosidase enzyme were performed to investigate possible inhibitory mechanisms. Overall, triazine-triazole derivatives represent a novel class of α-glucosidase inhibitors, offering promising leads for future antidiabetic drug development [38].

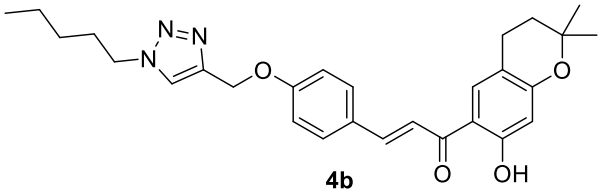


3

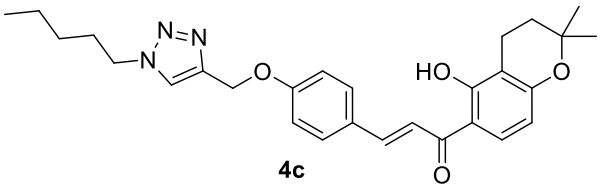
A novel series of chromano chalcone–1,2,3-triazole hybrid compounds was synthesized and evaluated for their α-glucosidase inhibitory and antidiabetic activities. Among these, **4a**, **4b**, and **4c** exhibited notable α-glucosidase inhibition, with IC_{50} values of 67.77 μM, 74.94 μM, and 102.10 μM, respectively. In addition, molecular docking studies demonstrated that these compounds effectively interact with the α-glucosidase enzyme, showing binding energies in the range of 100.37 to 107.78, supporting their potential inhibitory mechanism. These results indicate that chromano chalcone–triazole hybrids may serve as promising candidates for the development of new antidiabetic drugs [39].



4a

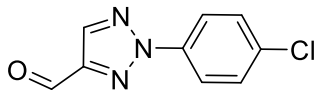


4b



4c

1-phenyl-1H- and 2-phenyl-2H-1,2,3-triazol derivatives were synthesized and tested for their inhibitory effects on baker's yeast α-glucosidase (MAL12) and porcine pancreatic α-amylase (PPA). Compound **5** being the most active compound exhibited notable α-glucosidase inhibition, with IC_{50} values 322.8± 40.1[40].



5

A series of cyanoacetohydrazides linked to 1,2,3-triazoles was synthesized and evaluated for their antidiabetic potential. Several of these compounds demonstrated potent α-glucosidase inhibitory activity, with IC_{50} values ranging from 1.00 ± 0.01 to 271.17 ± 0.30 μM, showing superior activity compared to acarbose (IC_{50} = 754.1 ± 0.5 μM) [42]. Notably, compound **6a**, containing a para-chlorobenzyl group (IC_{50} = 1.00 ± 0.01 μM), and compound **6b**, bearing an ortho-fluorobenzyl moiety (IC_{50} = 1.50 ± 0.01 μM), were the most effective. Both acted as uncompetitive α-glucosidase inhibitors with Ki values of 0.24 and 0.43 μM, respectively [41].

In addition, inhibitors targeting dipeptidyl peptidase-4 (DPP-4), an enzyme that enhances insulin secretion and inhibits glucagon release, have been recognized as promising candidates for treating type 2 diabetes mellitus [43]. A novel series of 1,2,3-triazole-5-carboximidamide derivatives was synthesized and assessed for DPP-4 inhibition, where compound **7** exhibited significant activity with an IC_{50} of 14.75 μM, outperforming sitagliptin in vitro [42].

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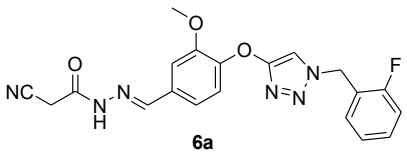
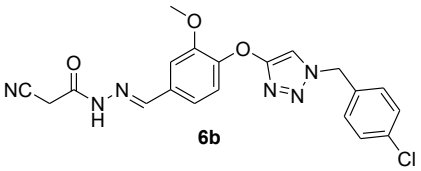
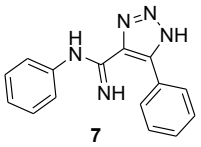


6a

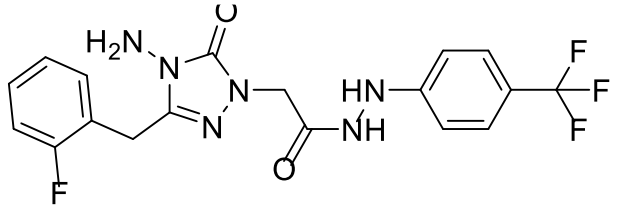


6b



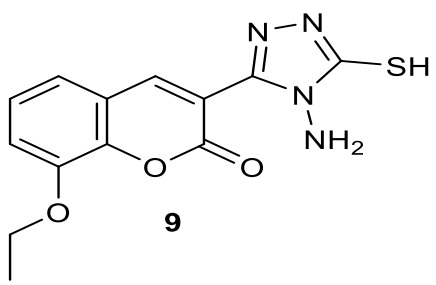
7

A set of ten triazole derivatives was synthesized and tested in vitro to evaluate their inhibitory effects on α-amylase and α-glucosidase enzymes, along with their corresponding IC_{50} values [44]. All compounds exhibited notable inhibitory activity against α-amylase, with IC_{50} values ranging from 185.2 ± 3.4 to 535.6 ± 5.5 μM, showing better or comparable results to the standard drug acarbose (IC_{50} = 411.3 ± 6.4 μM). Similarly, for α-glucosidase, IC50 values were observed between 202.1 ± 3.8 and 803.2 ± 10.3 μM, relative to acarbose (IC_{50} = 252.0 ± 4.8 μM). Among these, eight compounds demonstrated excellent dual inhibitory activity against both α-amylase and α-glucosidase, as indicated by their IC_{50} values [45–47].
The inhibitory efficiency of these triazole derivatives was found to be highly dependent on their chemical structures, as different substituents influenced their binding properties. Some derivatives are likely to interact directly with the active site of the enzymes, while others may bind to substrate recognition sites, leading to diverse inhibition mechanisms. These structure-dependent effects underscore the importance of substituent type and position in modulating enzyme inhibition. Notably, compound **8**, decorated with 2-fluoro (2-F) and 4-trifluoromethyl (4-CF3) substituents on the benzene rings, demonstrated outstanding dual inhibition, making it the most promising molecule in the series. Given its potent activity, compound **8** may serve as a valuable lead compound for further optimization and development of effective therapeutic agents targeting type 2 diabetes mellitus [45–47].

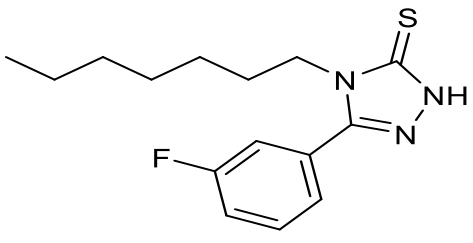


8

A series of novel coumarin-linked 1,2,4-triazole-3-thiol derivatives was synthesized and evaluated for their antidiabetic activity by investigating their α-amylase inhibitory potential [48]. The evaluation revealed that compound **9** and compound **10** exhibited the most significant inhibition of the α-amylase enzyme, showing percentage inhibition values of 86.05 ± 0.27% and 79.67 ± 0.58%, respectively. These results were further supported by their low IC_{50} values, with compound **9** having an IC_{50} of 5.43 μM and compound **10** showing an IC_{50} of 5.98 μM. The high inhibitory activity of these compounds indicates their strong potential as α-amylase inhibitors, suggesting that coumarin-triazole hybrids could serve as promising lead structures for developing new antidiabetic agents targeting postprandial hyperglycemia.



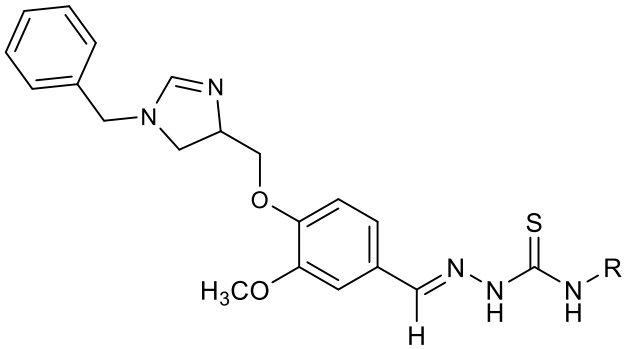
9



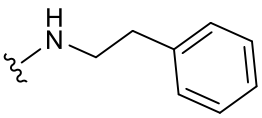
10

Thiosemicarbazone derivatives have been recently recognized for their antidiabetic potential [49]. In addition, hybrid molecules combining thiosemicarbazone and triazole scaffolds were synthesized and examined for their biological activities against malaria, obesity, and diabetes [50–51]. Among these, compounds **11a** and **11b** demonstrated significant effects in stimulating glucose uptake, as confirmed by increased expression levels of Glut-4, Mef2a, and Nrf-1, indicating a potential mechanism for enhancing glucose absorption [52].

Compounds **11a** and **11b** exhibited a good α-glucosidase inhibitory activity, with IC50 values 5.3 and 5.8 µg/ml respectively relative to acarbose (IC_{50} = 4.2 µg/ml). Moreover, both **11a** and **11b** exhibited notable antioxidant activity, suggesting their role in scavenging free radicals and reducing oxidative stress, which is often associated with diabetic complications. These dual effects on glucose metabolism and oxidative stress reduction highlight **11a** and **11b** as promising therapeutic candidates for the treatment of diabetes mellitus [52].



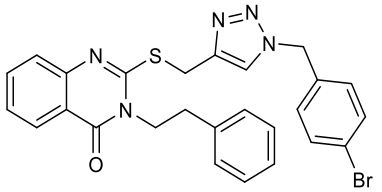
11a: R =



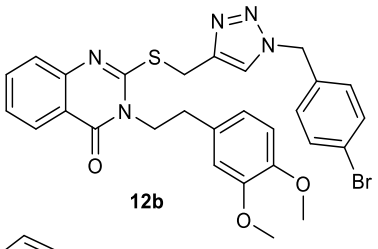
11a: R =

A series of benzimidazole-linked 1,2,3-triazole derivatives was synthesized through a click reaction between 2-substituted 1-(prop-2-yn-1-yl)-1H-benzo[d]imidazole and azides generated in situ [52]. The chemical structures of the synthesized compounds were confirmed using a combination of spectroscopic techniques, including 1D and 2D NMR, FT-IR, and high-resolution mass spectrometry [52].

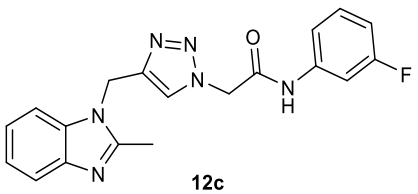
These compounds were further examined for their antidiabetic activity by evaluating their ability to inhibit α-amylase and α-glucosidase enzymes. The results revealed that all compounds possessed moderate to strong inhibitory activity, with IC_{50} values ranging from 16.24 to 31.74 µg/ml against α-amylase and 5.3 to 29.3 µg/ml against α-glucosidase. Notably, **12a, 12b,** and **12c** emerged as the most potent inhibitors. Additionally, molecular docking studies provided insight into the binding interactions and conformations of these active compounds within the enzyme active sites [52].



12a



12b

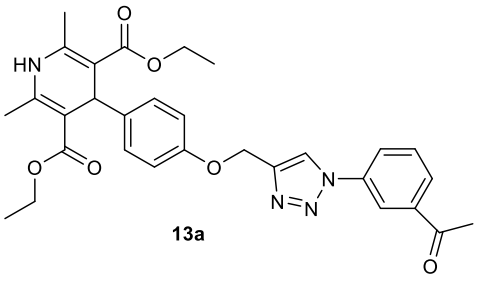


12c

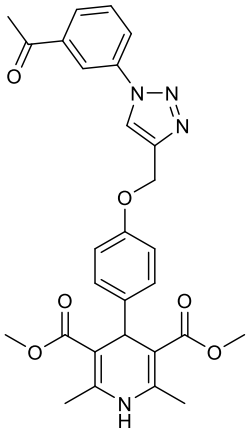
11-Beta-Hydroxysteroid dehydrogenase-1 (11β-HSD1) inhibitors represent a novel class of compounds with potential to prevent diabetic complications such as insulin resistance and obesity [54]. In this context, a new series of 4-(1-substituted-1H-1,2,3-triazol-4-yl)-1,4-dihydropyridine derivatives was synthesized and

evaluated for their antidiabetic activity. Among these, compounds **13a** and **13b** exhibited significant antidiabetic effects with IC50 values 72.71 ± 1.09, 73.83 ± 1.17 μM respectively when compared with acarbose standard (IC50 = 395.17 μM).[54]

To explore their mechanism of action, **13a** and **13b** were further assessed for 11β-HSD1 inhibitory activity through in vitro enzymatic assays, where both compounds showed high inhibitory potency and stability [54]. Additionally, molecular docking studies revealed that compound **13a** and compound **13b** possess stable binding interactions with human 11β-HSD1, displaying docking scores of -9.758 and -8.495, respectively, supporting their potential as effective 11β-HSD1 inhibitors for diabetes management [54].

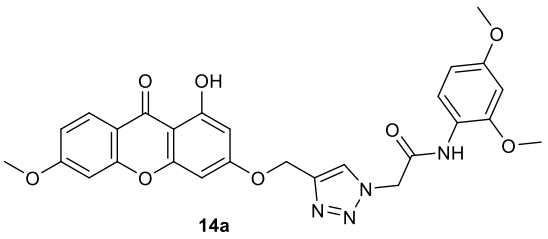


13a

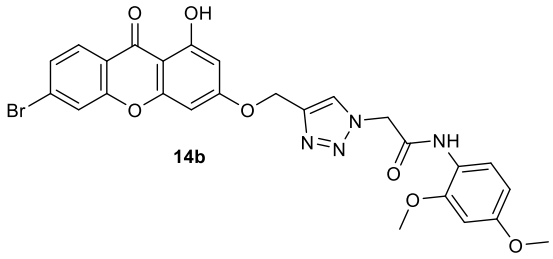


13b

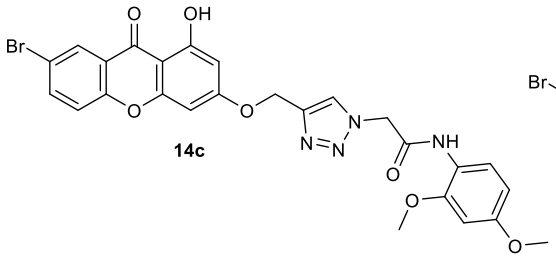
A series of novel xanthone-triazole derivatives was synthesized and evaluated for their antidiabetic potential [55]. The compounds were tested for α-glucosidase inhibitory activity as well as their ability to enhance glucose uptake in HepG2 cells. Among the synthesized derivatives, compounds **14a, 14b, 14c,** and **14d** exhibited notable biological activity, demonstrating both effective glucosidase inhibition (with IC50 values 2.06 ± 0.16, 2.78 ± 0.22, 3.07 ± 0.56 , 3.17 ± 0.61 μM respectively when compared with 1-deoxynojirimycin is 59.50 ± 4.7 as positive control) and improved glucose absorption, suggesting their potential as promising candidates for diabetes treatment [55].



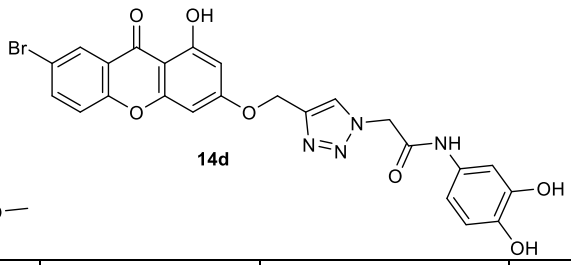
14a



14b



14c



14d

Compound Class	Key Derivatives	Target Enzyme	IC50 Values	Comparison to Standard (IC50)	Notable Findings

Coumarin-linked 1,2,4-triazole-3-thiol	1,2,3-Triazole-5-carboximidamide	Cyanoacetohydrazides linked to triazoles		Chromano chalcone–triazole hybrids	Triazine-triazole derivatives	(R)-1-(2-(4-bromo-2-methoxyphenoxy)propyl)-4-(4-(trifluoromethyl)-1H-1,2,3-	Quinazolinone-1,2,3-triazole hybrids
9, 10	7	6a, 6b	5	4a, 4b, 4c	3	2	1a, 1b
α-Amylase	DPP-4	α-Glucosidase	α-Glucosidase	α-Glucosidase	α-Glucosidase	α-Glucosidase	α-Glucosidase
5.43, 5.98	14.75	1.00 ± 0.01, 1.50 ± 0.01	322.8±40.1	67.77, 74.94, 102.10	11.63 ± 0.15	14.2	181.0 ± 1.4, 192.3 ± 1.8
Acarbose: 411.3 ± 6.4	Sitagliptin :16.39	Acarbose: 754.1 ± 0.5	Acarbose: 177 ± 11.9	Acarbose: 750.0	Acarbose: 817.38 ± 6.27	Acarbose: 750.0	Acarbose: 750.0
High inhibition (86.05% and 79.67%).	Outperformed sitagliptin in DPP-4 inhibition.	Uncompetitive inhibitors with Ki values of 0.24 and 0.43 μM.		Demonstrated binding energies of 100.37–107.78 in docking	Most potent inhibitor; supported by molecular	1H-1,2,3-triazole ring crucial for activity.	4-bromo benzyl substit

Thiosemicarbazone derivatives	11a ,11b	α-glucosidase	5.3 and 5.8 µg/ml	Acarbose :4.2 µg/ml	
Benzimidazole-linked triazoles	12a, 12b, 12c	α-Amylase, α-Glucosidase	16.24 to 31.74 (amylase), 5.3 to 29.3 (glucosidase)	Acarbose: 15.31(amylase), Acarbose: 4.12 (glucosidase)	Potent dual inhibitors; docking studies confirmed
4-(1-substituted-1H-1,2,3-triazol-4-yl)-1,4-dihydropyridine	13a, 13b	α-Glucosidase	72.71 ± 1.09, 73.83 ± 1.17	Acarbose: 395.17	High inhibitory potency; docking scores of -9.758 and -8.495.
Xanthone-triazole derivatives	14a-d	α-Glucosidase	2.06 ± 0.16, 2.78 ± 0.22, 3.07 ± 0.56 , 3.17 ± 0.61	1-Deoxynojirimycin : 59.50 ± 4.7	Enhanced glucose uptake and glucosidase inhibition.

Table 1: Summarized table of the key findings from the research on novel triazole derivatives and their antidiabetic potential.

CONCLUSION

Diabetes mellitus continues to be a major global health challenge, with type II diabetes presenting particular concerns due to its rising prevalence associated with lifestyle factors. Effective management of hyperglycemia is crucial to minimize the risk of severe complications such as cardiovascular diseases and nephropathy. Current therapeutic strategies, including α-glucosidase and α-amylase inhibitors like acarbose, are limited by side effects, necessitating the development of safer and more efficacious alternatives.

Recent advancements in medicinal chemistry have highlighted the potential of nitrogen-containing heterocycles, particularly triazole derivatives, as potent antidiabetic agents. Studies demonstrate that novel triazole-based compounds—such as quinazolinone-1,2,3-triazole hybrids, triazine-triazole conjugates, and chromano chalcone-triazole hybrids—exhibit superior enzyme inhibitory activity compared to conventional drugs, with significantly lower IC50 values. These compounds leverage structural diversity to enhance binding affinity and selectivity, as evidenced by molecular docking and structure-activity relationship (SAR) studies. Additionally, derivatives targeting DPP-4 and 11β-HSD1 enzymes show promise in addressing insulin resistance and glucose metabolism. These findings highlight the importance of ongoing research into structure-activity relationships to further optimize these molecules for clinical application. As scientific knowledge in diabetes pharmacotherapy expands, the development of safe and effective enzyme inhibitors holds significant potential to enhance patient outcomes and improve diabetes management.

The integration of computational modeling with synthetic approaches has accelerated the design of triazole-based inhibitors, offering insights into their mechanisms of action and optimizing therapeutic profiles. Future research should focus on in vivo validation, pharmacokinetic studies, and clinical trials to translate these findings into viable treatments. By bridging chemical innovation with biological efficacy,

triazole derivatives represent a frontier in diabetes therapy, paving the way for next-generation antidiabetic drugs that combine potency, safety, and multifunctional activity.

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