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Letter

Indole–thiazolidinedione–triazole hybrids: synthesis, molecular docking, absorption, distribution, metabolism and excretion (ADME) profiling, and biological evaluation as α-amylase inhibitors

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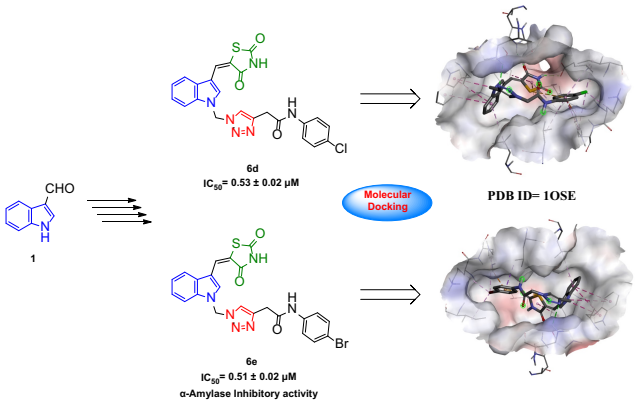
Abstract

A novel series of hybrid indole–thiazolidinedione–triazole derivatives (**6a-l**) were synthesized and assessed for their in vitro inhibitory activity against porcine pancreatic α-amylase. The synthetic procedure consists of 3 steps. A crucial step in this process involves the generation of novel target molecules using a Cu(I)-catalyzed azide–alkyne cycloaddition reaction. The α-amylase inhibition IC_{50} value of the targeted compounds ranged from 0.51 ± 0.02 to 7.99 ± 0.28 μM as compared with 0.68 ± 0.02 μM with acarbose as the standard drug. Using the Autodock technique, all the derivatives **6a-l** were subjected to molecular docking investigations against porcine pancreatic α-amylase (PDB ID: 1OSE). Moreover, it was discovered that the docked compounds had excellent binding affinities that ranged from −10.1 to −10.8 kcal/mol as compared with the standard −7.9 kcal/mol. Additionally, a comprehensive analysis of the physicochemical and pharmacokinetic properties associated with absorption, distribution, metabolism and excretion (ADME) was conducted for all the synthesized compounds.

Keywords: 1,2,3-Triazole, α-amylase, antidiabetic activity, indole, molecular docking, thiazolidinedione.

Graphical Abstract



Diabetes mellitus (DM), which is commonly known as hyperglycemia, refers to a group of metabolic disorders that are associated with the reduced function of the pancreas gland, which is responsible for producing the digestive hormone insulin.[1,2] Prolonged high blood sugar can damage tissues such as eyes, heart, blood vessels, kidneys, and nerves.[3,4] DM is categorized by insulin production levels or blood sugar regulation.[5] Type 2 diabetes (DM2) results from insufficient insulin secretion or insulin resistance, often due to a high carbohydrate intake and obesity.[6,7] In 2022, the International Diabetes Federation reported 464 million people with diabetes globally, with over 90% having DM2.[8] Current α-amylase inhibitors such as acarbose, miglitol, and metformin cause side effects including diarrhea and liver disorders, highlighting the need for new drug discovery approaches to improve efficacy and reduce side effects.[9–11]

In medicinal chemistry, thiazolidine-2,4-dione is a unique novel class of heterocyclic moiety that demonstrates noteworthy biological properties such as antibacterial,[12,13] anticancer,[14–16] antithyroid,[17] antimycobacterial,[18] and antidiabetic activities,[19] and serves as a versatile scaffold with multi-targeted properties.

Drugs such as pioglitazone, rosiglitazone, lobeglitazone, and epalrestat treat DM2, while ponesimod is approved for multiple sclerosis and psoriasis. Indole, an aromatic heterocyclic compound, is notable for its diverse pharmacological effects, including anticancer,[20,21] anti-inflammatory,[22,23]

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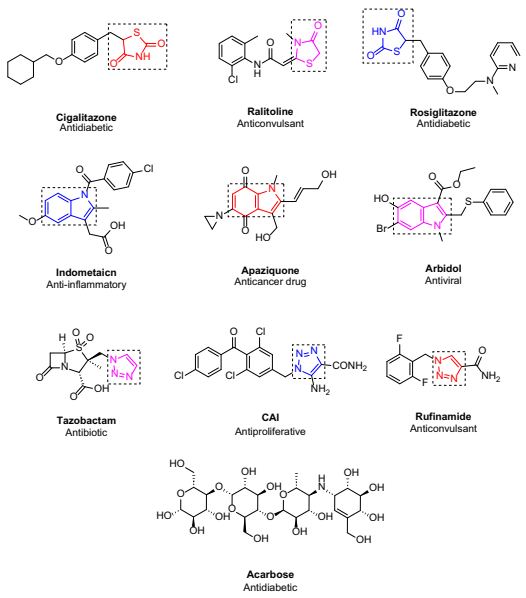


Fig. 1. Commercially available drugs containing indole, thiazolidinedione, triazole motif, and acarbose.

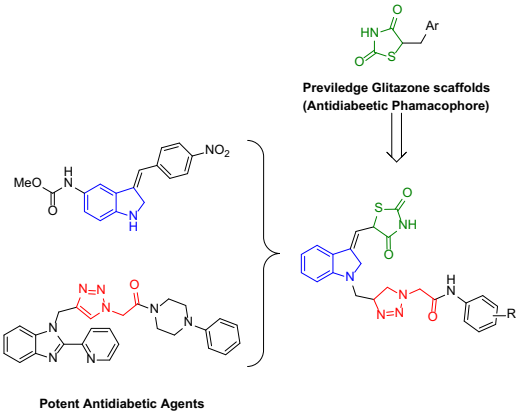
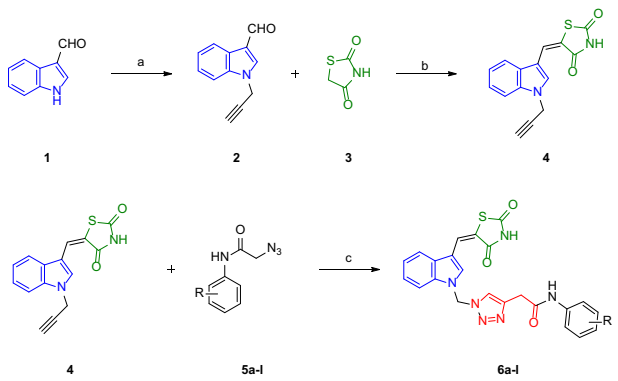


Fig. 2. Design of indole–thiazolidinedione–triazole hybrids.

analgesic,[24,25] anticonvulsant,[26,27] antitubercular,[28] antidiabetic,[29–31] and antimicrobial[32] properties. Similarly, 1,2,3-triazole is a stable moiety with various biological properties and industrial applications such as antitubercular,[33,34] anticancer,[35,36] antidiabetic,[37,38] antimalarial,[39] anti-inflammatory,[40,41] anti-HIV,[42] and antimicrobial[43] activities. Figure 1 presents compounds with thiazolidine-2,4-dione, triazole, and indole moieties, emphasizing their significance in medicinal chemistry. Moreover, hybrids containing indole, thiazolidinedione, and triazole moieties have shown promising potential as anticancer,[44] antimalarial, and antibacterial agents.[45] However, their potential as α-amylase inhibitors has not yet been explored.

Therefore, to further our research interest in developing potent α-amylase inhibitors,[46–48] we synthesized indole–thiazolidinedione–triazole hybrids using a hybrid drug design strategy to evaluate their α-amylase inhibition activities (Fig. 2).

We discovered a novel antidiabetic compound and synthesized 12 heterocyclic molecules featuring thiazolidine-2,4-dione and indole-linked 1,2,3-triazole, as depicted in Scheme 1. *N*-propargylation of the indole ring using propargyl bromide and K_2CO_3 in Dimethylformamide (DMF) at ambient temperature yielded terminal alkyne **2** in 92% yield. Compounds **2** and **3** underwent Knoevenagel condensation using piperidine as the base and ethanol as the solvent at reflux.[49] After synthesizing alkyne **4**, organic azides **5a-l** were prepared.[50] Compounds **6a-l** were then formed by reacting alkyne **4** with azides **5a-l** in DMF at 70 °C using $CuSO_4{\cdot}5H_2O$ and sodium ascorbate, in yields of 82% to 88%. Final purification was done by recrystallization in DMF.



Scheme 1. Synthesis of Indole clubbed 2,4-thiazolidinedione linked 1,2,3-triazole **6a-l** via click chemistry. Reaction conditions: (a) propargyl bromide, K_2CO_3, DMF; (b) piperidine, MeOH, reflux; (c) $CuSO_4$, sodium ascorbate, DMF:H_2O, microwave irradiation.

Various solvents (Tetrahydrofuran [THF], tert-butanol, DMF) and catalysts (CuI, $CuSO_4$, $Cu(OAc)_2$ with sodium ascorbate) were tested for synthesizing compounds **6a-l**. Microwave irradiation significantly improved yields compared with conventional methods. According to Table 1, microwave irradiation increased yields to 50% (THF, $CuSO_4$, H_2O) from 24%, to 69% (tert-butanol, $Cu(OAc)_2$, H_2O) from 28%, and to 73% (DMF, $Cu(OAc)_2$, H_2O) from 62%. The optimal condition was DMF/H_2O (2:1) with $CuSO_4$ and sodium ascorbate, yielding up to 88% in 12 min.

Compounds **6a-l** were evaluated for in vitro α-amylase activity using acarbose as a positive control at concentrations of 25, 50, 100, 200, and 400 μg/mL, and the results are shown in Table 2. Compounds **6a-l** showed promising α-amylase inhibition, with effectiveness increasing linearly with concentration, suggesting potential for antidiabetic drug development.

The comparative study of percentage inhibition exhibited that the targeted drugs **6a-l** effectively and dose-dependently inhibited α-amylase. Among all the synthesized compounds, particularly halogen containing compounds 4-chloro substituted **6d** and 4-bromo substituted **6e**, were identified to be potent inhibitors with 83.22 ± 0.33 and $82.12 \pm 0.62\%$ inhibition having $IC_{50} = 0.53 \pm 0.02$ and 0.51 ± 0.02 μM, respectively. However, 4-flouro substituted **6i** led to a significant decrease in potency with IC_{50} of 6.43 ± 0.26 μM. Furthermore, when comparing the acarbose with an IC_{50} value of 0.55 ± 0.04 μM, derivatives **6d** and **6e** show excellent inhibitory activity, while 4-methyl substituted **6c** ($IC_{50} = 0.9 \pm 0.05$ μM) and 2,6 dichloro substituted **6l** ($IC_{50} = 0.68 \pm 0.02$ μM) showed good inhibitory activity, and derivatives **6a**, **6b**, **6f**, **6g**, **6h**, **6j**, and **6k** showed moderate activity with IC_{50} values ranging from 1.28 to 7.99 μM.

We used Autodock Vina 1.5.7 for docking α-amylase (PDB ID: 1OSE).[51–53] Potent compounds are tabulated in Table 3

Table 1. Optimization of the reaction conditions for (E)-2-(4-((3-((2,4-dioxothiazolidin-5-ylidene)methyl)-1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-*N*-(p-tolyl) acetamide.

			Conventional method		Microwave method	
Sr no.	Solvent	Catalyst	Time (h)	Yield (%)[a]	Time (min)	Yield (%)[a]
1	THF:H_2O (2:1)	$CuSO_4$, sodium ascorbate	28	24	45	50
2	t-BuOH:H_2O (2:1)	$Cu(OAc)_2$, sodium ascorbate	13	28	29	69
3	DMF:H_2O (2:1)	$Cu(OAc)_2$, sodium ascorbate	10	62	22	73
4	t-BuOH:H_2O (2:1)	CuI	11	57	20	71
5	DMF:H_2O (2:1)	CuI	9	66	17	79
6	t-BuOH:H_2O (2:1)	$CuSO_4$, sodium ascorbate	8	64	14	78
7	DMF:H_2O (2:1)	$CuSO_4$, sodium ascorbate	7	73	12	88

[a]Isolated yield after crystallization from DMF.

Table 2. In vitro α-amylase inhibitory activity of the synthesized compounds (**6a-l**).

	Sample concentration (μg/mL) ± SD Inhibition of α-amylase (%)[a]					
Compound no.	25	50	100	200	400	IC_{50} (μM)
6a	38.08 ± 1.04	45.59 ± 0.52	51.65 ± 1.00	55.74 ± 0.65	59.49 ± 0.10	1.76 ± 0.08
6b	42.50 ± 1.07	48.24 ± 0.94	54.08 ± 0.84	57.62 ± 0.75	61.48 ± 0.71	1.28 ± 0.05
6c	45.92 ± 0.57	52.98 ± 0.51	58.72 ± 0.43	66.44 ± 0.59	68.88 ± 0.49	0.9 ± 0.05
6d	48.24 ± 0.53	60.82 ± 0.60	66.89 ± 0.40	72.29 ± 0.92	83.22 ± 0.33	0.53 ± 0.02
6e	48.01 ± 0.44	59.38 ± 0.27	64.90 ± 0.45	71.41 ± 0.47	82.12 ± 0.62	0.51 ± 0.02
6f	36.20 ± 1.10	40.95 ± 0.76	51.21 ± 0.81	54.08 ± 0.59	58.83 ± 0.88	1.95 ± 0.10
6g	27.37 ± 0.69	29.25 ± 0.77	35.21 ± 0.67	43.38 ± 0.77	51.43 ± 1.13	6.83 ± 0.81
6h	27.04 ± 0.39	31.35 ± 0.59	37.97 ± 0.71	45.25 ± 0.10	51.54 ± 0.99	6.70 ± 0.44
6i	30.91 ± 0.77	35.87 ± 0.49	41.06 ± 0.86	46.14 ± 0.54	53.53 ± 0.10	6.43 ± 0.26
6j	20.64 ± 0.49	28.26 ± 0.41	38.41 ± 0.78	44.48 ± 0.59	51.10 ± 0.85	6.98 ± 0.47
6k	22.18 ± 1.38	27.81 ± 0.90	35.32 ± 0.90	42.83 ± 0.24	50.33 ± 0.44	7.99 ± 0.28
6l	45.36 ± 0.51	56.07 ± 0.27	63.13 ± 0.59	69.65 ± 0.45	79.47 ± 0.30	0.68 ± 0.02
Acarbose	46.69 ± 0.71	55.30 ± 0.60	60.60 ± 0.41	68.21 ± 0.72	76.05 ± 1.79	0.55 ± 0.04

[a]Each value is the mean ± SD, standard deviation.

Table 3. The docking scores for the potent compounds and acarbose with porcine pancreatic α-amylase (PDB: 1OSE).

Ligand name	Binding energy (kcal/mol)	No. of H-bonds	Key residues interacted with ligand
6d	−10.6	3	His299, Asp300, Asp197, Gly306, His201, Tyr62, Trp59, Val163, Lys200, Leu162, Ile235, Leu165
6e	−10.3	3	Asp197, His299, Gly306, Asp300, His201, Tyr62, Trp59, Val163, Lys200, Leu165, Leu162, Ile235
Acarbose	−7.9	5	His299, Arg195, Gly306, Lys200, Trp69, Tyr151, Asp300

and additional compounds are presented in the supplementary information. Molecular docking shows that all compounds bind efficiently to α-amylase with scores of more than −7.9 kcal/mol. Compounds **6d** and **6e**, with binding energies of −10.6 and −10.3 kcal/mol, respectively, both form similar hydrogen bonds with Asp197, His299, and Gly306 (Figs. 3 and 4). Thiazolidinedione protonation in docking is influenced by the MMFF94 force field, which may not reflect the deprotonated state expected under physiological conditions. Docking studies showed that 2,4–thiazolidinedione–indole-1,2,3–triazole derivatives bind effectively to α-amylase, with favorable interactions. Re-docking and superimposing the co-crystallized ligand with the extracted ligand yielded an root mean square deviation (RMSD) of 0.963 Å, confirming the docking procedure (Fig. 5).

The structural activity relationship analysis of the inhibitors, based on their molecular docking studies and antidiabetic activity assays, reveals significant insights into their efficacy. Compound **6a** with aniline substitution exhibited a moderate IC_{50} value of 1.76 ± 0.08 μM and a binding energy of −10.2 kcal/mol, forming 4 hydrogen bonds. Electron-donating groups, such as methoxy (**6b**, 4-OCH_3) and methyl (**6c**,

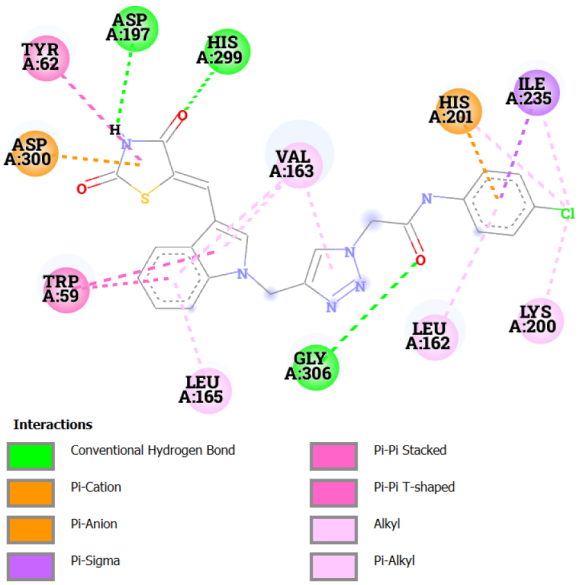


Fig. 3. 2D binding interactions of compound **6d** with α-amylase.

4-CH_3), showed varying effects. Compound **6b** displayed an improved IC_{50} of 1.28 ± 0.05 μM and a binding energy of −10.1 kcal/mol, while **6c** showed an even better IC_{50} of 0.9 ± 0.05 μM with a binding energy of −10.6 kcal/mol, indicating enhanced activity with 4-position methyl substitution. However, disubstituted compound **6h** (2,6-CH_3) exhibited decreased activity (IC_{50} of 6.70 ± 0.44 μM), likely due to steric hindrance. Electron-withdrawing groups generally enhanced antidiabetic activity. Notably, **6d** (4-Cl) and **6e** (4-Br) showed significantly low IC_{50} values of 0.53 ± 0.02 and 0.51 ± 0.02 μM, respectively, with binding energies of −10.6 and −10.3 kcal/mol, forming 3 hydrogen bonds. Conversely, the difluoro-substituted compound **6k** (2,6-F) displayed the weakest activity (IC_{50} of 7.99 ± 0.28 μM), possibly due to steric effects. Compounds with multiple substituents, such as **6j** (3-Cl, 4-F), showed moderate activity (IC_{50} of 6.98 ± 0.47 μM), suggesting steric constraints from combined substituents. Compounds **6d** and **6e**, with binding energies of −10.6 and −10.3 kcal/mol, showed stronger interactions than acarbose (−7.9 kcal/mol) and had a lower IC_{50} value of 0.55 ± 0.04 μM.

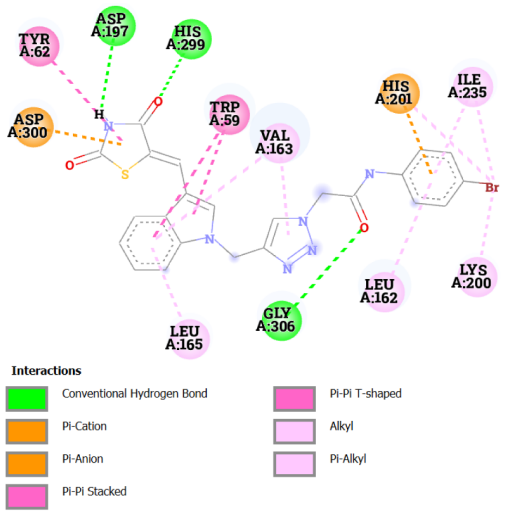


Fig. 4. 2D binding interactions of compound **6e** with α-amylase.

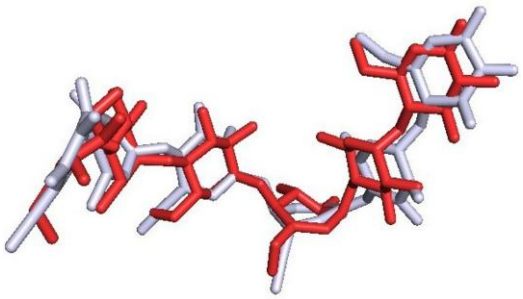


Fig. 5. Superimposed image of native ligand (red) and re-docked ligand (gray), RMSD = 0.963 Å.

The drug-like characteristics of compounds **6a-l** was evaluated using the Swiss Institute of Bioinformatics ADME tool[54] and the results are tabulated in Table 4. The analysis in silico prediction of physicochemical properties is provided in the supplementary information.

In conclusion, a series of rationally designed indole–thiazolidinedione–triazole hybrids were synthesized using a scaffold combination approach and evaluated for antidiabetic activity as potential α-amylase inhibitors through Cu(I)-catalyzed azide–alkyne cycloaddition under microwave irradiation. Compounds **6d** and **6e** demonstrated potent α-amylase inhibition, with IC_{50} values of 0.53 ± 0.02 and 0.51 ± 0.02 μM, respectively, outperforming the standard drug acarbose. Molecular docking studies further validated these findings, with binding energies of the stable ligand–enzyme complexes ranging from −10.1 to −10.8 kcal/mol.

Supplementary data

Supplementary material is available at *Chemistry Letters* online.

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Conflict of interest statement. None declared.

Table 4. Physicochemical, pharmacokinetic, and medicinal chemistry properties of the synthesized compounds (**6a-l**).

	Physicochemical properties						Pharmacokinetics		Medicinal chemistry	
Compound	RB (range ≤10)	HBA (range ≤10)	HBD (range ≤5)	TPSA (Å^2) (range ≤140)	Log $P_{O/W}$ (range ≤5)	Log S	GIA	Log K_P	RoF (V)	SA
6a	7	5	2	136.21	2.21	−4.36	High	−7.19	Yes	3.78
6b	8	6	2	145.44	2.2	−4.43	Low	−7.4	Yes	3.88
6c	7	5	2	136.21	2.5	−4.66	Low	−7.02	Yes	3.9
6d	7	5	2	136.21	2.68	−4.95	Low	−6.96	Yes	3.77
6e	7	5	2	136.21	2.77	−5.27	Low	−7.19	Yes	3.8
6f	7	5	2	136.21	2.86	−4.96	Low	−6.85	Yes	4
6g	7	5	2	136.21	2.72	−4.95	Low	−6.96	Yes	3.77
6h	7	5	2	136.21	2.84	−4.96	Low	−6.85	Yes	4
6i	7	6	2	136.21	2.46	−4.52	Low	−7.23	Yes	3.76
6j	7	6	2	136.21	3.05	−5.11	Low	−7	Yes	3.77
6k	7	7	2	136.21	2.82	−4.68	Low	−7.27	Yes	3.78
6l	7	5	2	136.21	3.2	−5.55	Low	−6.73	Yes	3.81
Acarbose	9	19	14	321.17	−6.24	2.56	Low	−16.29	No	7.34

RB, rotatable bonds; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; TPSA, topological polar surface area; Log $P_{O/W}$, octanol/water partition coefficient; Log S, aqueous solubility (log mol/L); GIA, gastrointestinal absorption; Log K_P, skin permeation; RoF (V), Lipinski's rule of five; SA, synthetic accessibility.

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