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Design of Novel Quinazoline–Thiadiazolidinedione Hybrids: Synthetic Approach and Comprehensive Spectroscopic Analysis

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ABSTRACT

A recent Research Study on Dipeptidyl Peptidase-4 (DPP-IV) enzyme inhibitors has made it possible to treat type 2 diabetes mellitus (T2DM) with minimal side effects. Dipeptidyl peptidase-4 (DPP-4) is a target for the treatment of type 2 diabetes mellitus. As DPP-4 inhibitors can increase insulin levels and prolong the activity of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), they are effective for glycemic control. Quinazoline-based heterocycles and thiadiazolidinedione scaffolds are widely explored for their diverse pharmacological properties. In the present study, a new series of quinazolinone–thiadiazolidinedione derivatives coded as (S1R1-S1R11) was rationally designed & synthesised to investigate their structural features and potential biological relevance. The target compounds were obtained through a multistep synthetic route involving the formation of the quinazolinone core, followed by its condensation with substituted thiadiazolidinedione moieties under optimised reaction conditions. The synthesised derivatives were purified using chromatographic techniques, and their structures were confirmed through spectral analyses, including FT-IR, MASS, ^{1}H NMR and ^{13}C NMR. The spectral data consistently supported the successful incorporation of both quinazolinone and thiadiazolidinedione rings within the final molecular framework. The study provides a reliable synthetic approach for generating new hybrid heterocycles, which may serve as promising candidates for further pharmacological evaluation.

KEYWORDS: T2DM, DPP-4 inhibitors, Quinazolinone, Thiadiazolidinedione, Synthesis, Structural characterisation..

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterised by elevated blood glucose levels. Persistent hyperglycemia can lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves over time. Three main types of diabetes are well-defined: type 1, type 2, and gestational. According to the World Health Organisation (WHO), about 422 million people worldwide have diabetes, the majority of whom live in low- and middle-income countries. Additionally, 1.6 million deaths are directly attributed to diabetes each year. Type 2 diabetes (T2D) is the most common form, especially in adults. It occurs when the body becomes resistant to insulin or does not produce sufficient insulin. Over the past three decades, the prevalence of T2D has risen dramatically across countries of all income levels. For individuals living with diabetes, access to affordable treatment, including insulin, is critical for survival. A globally agreed target aims to halt the rise in diabetes and obesity by 2025. Currently, a wide range of oral antidiabetic drugs is available, but many of these medications are associated with side effects, including liver problems, diarrhoea, and lactic acidosis. Therefore, the discovery of novel small molecules with potent hypoglycemic activity remains a significant challenge in medicinal chemistry. In this study, the target chosen was the **Dipeptidyl peptidase 4 (DPP-4) enzyme**, a key enzyme in glucose metabolism. DPP-4 inhibitors are antihyperglycemic agents used to manage T2D by acting on incretin hormones, mainly glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP), which help maintain glucose homeostasis. DPP-4 cleaves these incretins, reducing insulin secretion and disrupting glucose regulation. By inhibiting DPP-4, these agents prevent the breakdown of GLP-1 and GIP, restore normal insulin secretion, and improve glycemic control. The design of the study centred on the rational development of quinazolinone –thiazolidinedione hybrids by integrating two pharmacophoric units through a methylene linker to create structurally and electronically diverse derivatives. The strategy involved introducing various aromatic and heteroaryl substituents to modulate steric and electronic effects, thereby influencing molecular planarity, reactivity, and potential biological behaviour. Guided by the structural features of clinically effective DPP-4 inhibitors, the new molecules were conceptualised by hybridising key pharmacophoric elements known to contribute to enzyme inhibition and antidiabetic activity. This design approach aimed to generate novel derivatives with improved structural attributes and enhanced potential for further pharmacological evaluation. In this study, we aim to synthesise a novel series of Quinazolinone –Thiadiazolidinedione heterocyclic derivatives using an efficient multistep synthetic approach and characterise the synthesised compounds through spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry to confirm their structural integrity. Quinazolinone and thiazolidinedione scaffolds are well-recognised in medicinal chemistry due to their diverse pharmacological activities, including antidiabetic, anticancer, anti-inflammatory, and antimicrobial properties. Quinazolinone derivatives are known for their enzyme inhibitory activity and ability to interact with various biological targets through hydrogen bonding and π–π stacking, while thiazolidinediones (TZDs) are clinically established as a class of oral antidiabetic medications that improve insulin sensitivity, enabling the body to utilise insulin more effectively and lower blood glucose levels. TZDs act

primarily by activating peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, widely used for the management of type 2 diabetes mellitus by decreasing hepatic glucose production and increasing glucose uptake by muscle and adipose tissues, thereby improving glycemic control. The fusion of these two bioactive scaffolds into a single hybrid molecule presents an opportunity to generate compounds with enhanced biological potency and selectivity. Previous studies have demonstrated that structural modifications on the Quinazolinone or TZD moieties can significantly influence enzyme binding, receptor selectivity, and pharmacokinetic properties. Despite these advances, there remains a need to design novel hybrids with improved efficacy, stability, and pharmacological profiles. Therefore, the synthesis of quinazolinone–thiazolidinedione hybrids represents a promising strategy to develop multifunctional compounds with potential therapeutic applications, particularly as antidiabetic agents. The structural design of the title compound involved combining crucial features of existing DPP-4 inhibitors to develop a hybrid framework with promising antidiabetic efficacy, as shown in Figure 1.

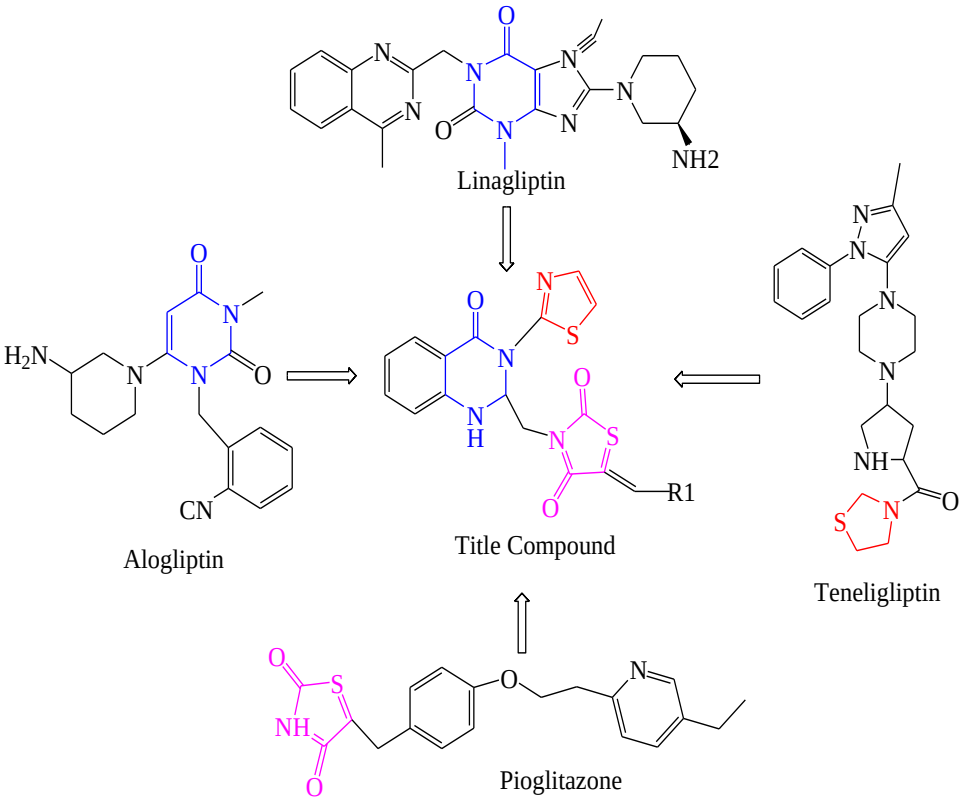


Figure 1. Marketed DPP-4 inhibitors and designed the title compound.

The synthesis of the target compounds was accomplished through a multistep procedure, as illustrated in the Scheme. The specific substituents incorporated in each derivative are summarised in Table 1.

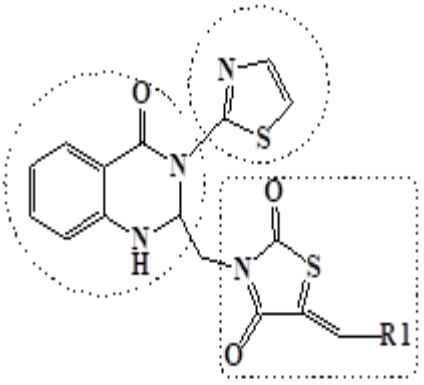
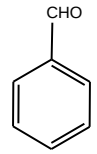
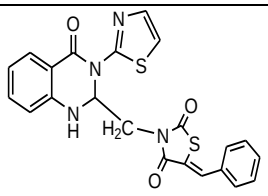
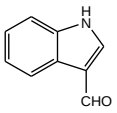
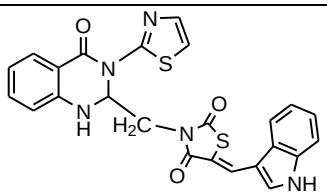
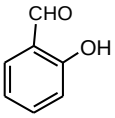
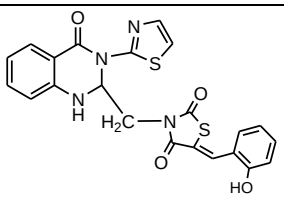
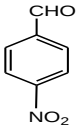
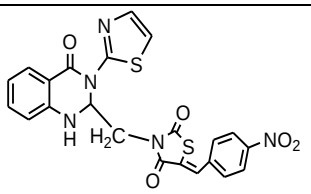
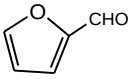
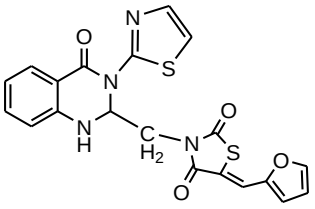
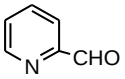
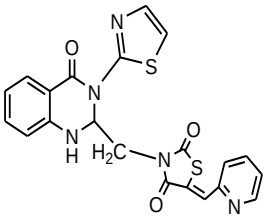
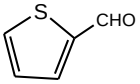
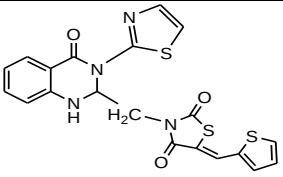
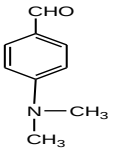
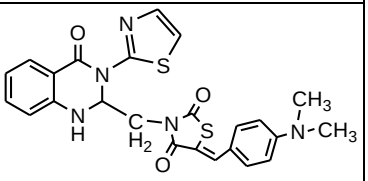
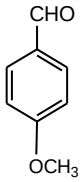
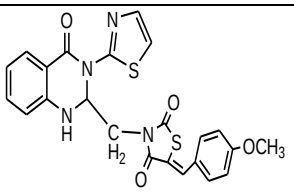
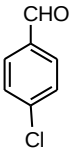
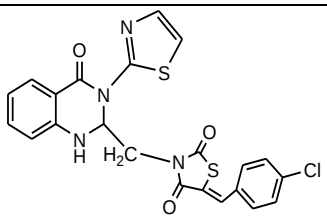
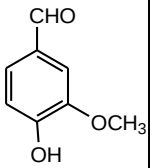
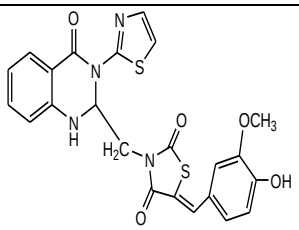


Figure 2. Designed a pharmacophore of Quinazolinone-Thiazolidinedione for DPP-IV activity.

Table 1. The Substituents for the target compounds

Code	R1	Final structure	Code	R1	Final structure
S1R1			S1R7		
S1R2			S1R8		
S1R3			S1R9		
S1R4			S1R10		
S1R5			S1R11		
S1R6					

MATERIALS AND METHOD

2.1. Chemicals and Solvents

All chemicals and solvents were procured from Merck Life Science Pvt. Ltd., Loba Chemie, and Research Lab Fine Chem Industry Pvt. Ltd. All reactions were performed under dry conditions using oven-dried glassware to ensure reproducibility and minimise moisture interference.

2.2. Reaction Monitoring

The progress of the reactions was monitored using high-performance thin-layer chromatography (HPTLC). The solvent system employed was acetone:methanol: acetic acid (4:4:2).

2.3. Spectroscopic Characterisation

Infrared (IR) Spectroscopy: IR spectra were recorded on a JASCO-FTIR 4100 spectrophotometer using KBr pellets. The absorption frequencies are reported as ν_max (cm^{-1}).

Proton Nuclear Magnetic Resonance (^{1}H NMR) Spectroscopy: ^{1}H NMR spectra of the synthesised compounds were recorded in DMSO using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in δ (ppm). Measurements were performed on a Bruker AVANCE NEO 600 MHz spectrometer.

Carbon-13 Nuclear Magnetic Resonance (^{13}C NMR) Spectroscopy: ^{13}C NMR spectra were recorded in **DMSO** with TMS as an internal reference. Spectra were obtained on the Bruker AVANCE NEO 500 MHz spectrometer.

Mass Spectrometry (MS): Mass spectra were obtained to confirm the molecular weights of the synthesised compounds.

1.4. Synthetic Procedures

Step I: Synthesis of Thiazolidine-2,4-dione

Chloroacetic acid (56.4 g, 0.6 mol) and thiourea (45.6 g, 0.6 mol) were dissolved in 60 mL of water in a round-bottom flask and stirred for 15 minutes until a white precipitate formed. The mixture was cooled, and concentrated HCl was added dropwise. The flask was fitted with a reflux condenser, gently heated until complete dissolution, and then refluxed for 8–10 hours at 100–110 °C.

After cooling, the reaction mixture solidified into white needle-like crystals. The solid was collected by filtration, washed with water, and dried to obtain pure thiazolidine-2,4-dione

Step II: Synthesis of Thiazol-2-amine

Thiourea (1 mmol) and 2-chloroacetaldehyde (1 mmol) were dissolved in 30 mL of ethanol and refluxed for 3 hours. The reaction mixture was cooled to room temperature, and the resulting solid was filtered and washed with water to afford thiazol-2-amine

Step III: Synthesis of 2-(Chloromethyl)-2,3-dihydro-3-(thiazol-2-yl)quinazolin-4(1H)-one

A mixture of aldehyde (1 mmol), thiazol-2-amine (1.1 mmol), and isatoic anhydride (1 mmol) was dissolved in 5 mL of acetic acid and refluxed. Reaction progress was monitored by TLC using toluene: ethyl acetate: methanol (7:2:1). After completion, the mixture was poured into 20 mL of ice-cold water. The precipitated solid was filtered, washed with cold water, and recrystallised from ethanol to give 2-(chloromethyl)-2,3-dihydro-3-(thiazol-2-yl)quinazolin-4(1H)-one.

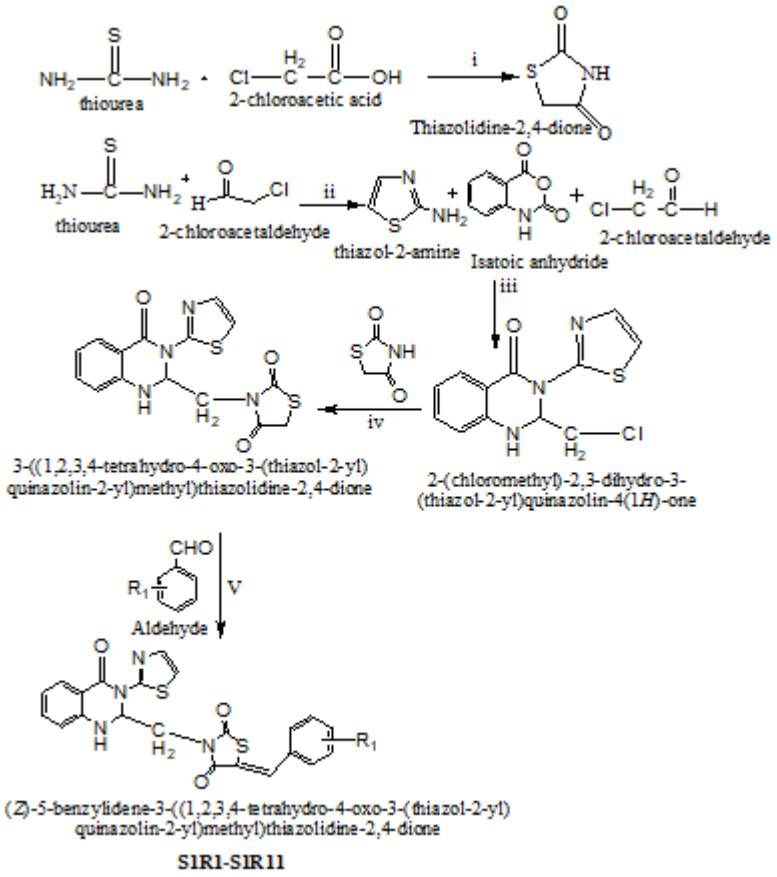
Step IV: Synthesis of 3-((1,2,3,4-Tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione

Thiazolidine-2,4-dione (1 g, 8 mmol) and 2-(chloromethyl)-2,3-dihydro-3-(thiazol-2-yl)quinazolin-4(1H)-one (2.368 g, 8 mmol) were dissolved in 20 mL of absolute ethanol in a round-bottom flask. Potassium carbonate (0.59 g, 4 mmol) was added, and the mixture was refluxed for 12 hours at 65 °C. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (80 mL) and water (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Recrystallisation from ethanol yielded 3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione.

Step V: Synthesis of (Z)-5-Benzylidene-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione

Benzaldehyde derivatives (0.6 mmol) and piperidine (0.3 mmol) were dissolved in 20 mL of absolute ethanol in a round-bottom flask. To this solution, 3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione (0.6 mmol) was added, and the mixture was refluxed for 12 hours at 90 °C. After cooling, the solid product was filtered, washed with anhydrous ethanol, and dried to obtain the final (Z)-benzylidene-substituted quinazoline–thiazolidinedione hybrid.

Scheme I: Synthetic Protocol for the titled compounds (S1R1-S1R11)



Reagents and conditions: (i) Con. HCl/H_2O, reflux for 10 hr. (ii) C_2H_5OH, reflux for 3 hr. (iii) Acetic acid, stirred under reflux, 4h (iv) C_2H_5OH, refluxed for 12 h at 65°C.(v) R_1CHO, refluxed for 12 h at 90°C.

RESULTS

Target molecule S1R1: (Z)-5-benzylidene-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione

Yield: 73%, off white, Fine powder, **Molecular formula:** $C_{22}H_{16}N_4O_3S_2$; calculated: C,58.91; H,3.60; N,12.49; O,10.70; S, 14.30. **Molecular weight**: 448 g/mol, Melting point: 387-389°C, **Rf:** 0.4 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR(KBr) in cm^{-1}**: 3345cm^{-1}(N-H str. Amine), 3099cm^{-1} (C-H str. aromatic), 2985cm^{-1} (C-H str aliphatic), 1701cm^{-1} (C=O str. amide), 1588 (C=C bend. aromatic), 1535cm^{-1} (C=N str), 1301cm^{-1} (C-N str), 766cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm]:** 3.85,4.10 (d, 2H, CH_2), 5.28 (s, 1H, N-H), 5.35 (q, 1H, C-H), 6.75 (t, 1H, Ar-H), 7.0 (d, 1H, Ar-H), 7.33 (t, 1H, Ar-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.56 (q, 2H, Ar-H), 7.65 (t, 2H, Ar-H), 7.67 (d, 1H, Ar-H), 7.85(s, 1H, C-H), 7.86 (d, 1H, C-H).**^{13}C NMR (500 MHz, DMSO δ [ppm]:):** 39.0, 79.2, 115.2, 118.2, 118.85, 119.15, 123.9, 127.4, 128.12, 128.75 (2C), 130.27 (2C), 132.01, 132.30, 132.94, 139.4, 141.95, 160.5, 161.5, 166.9, 169.0. **(M+1):** 448.05

Target molecule S1R2: (Z)-5-(2-hydroxybenzylidene-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione

Yield: 69 %, off white, Fine powder, **Molecular formula:** $C_{22}H_{16}N_4O_4S_2$; Calculated: C,56.66; H,3.47; N,12.06; O,13.78; S, 13.81. **Molecular weight:** 464 g/mol, Melting point: 375-376°C, **Rf:** 0.45 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR(KBr) in cm^{-1}:** 3425cm^{-1}(OH str. Aromatic), 3213cm^{-1}(N-H str. Amine), 3081cm^{-1} (C-H str. aromatic), 2923Cm^{-1} (C-H str aliphatic),1682cm^{-1} (C=O str. amide),1587 (C=C bend. aromatic), 1530 cm^{-1} (C=N str), 1349 cm^{-1} (C-N str), 773 cm^{-1} (C-S str**), ^{1}H NMR (600 MHz, DMSO) δ [ppm]:** 3.85,4.10 (d, 2H, CH_2), 5.28 (s, 1H, N-H), 5.35 (q, 1H, C-H), 6.72(d, 1H, Ar-H), 6.75 (t, 1H, Ar-H), 7.0 (d, 1H, Ar-H), 7.06 (t, 1H, Ar-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.49 (d, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 7.86 (d, 1H C-H), 8.22(s, 1H, C-H), 10.27 (s, 1H, OH).**^{13}C NMR (500 MHz, DMSO) δ [ppm]:** :39.0, 79.2, 111.6, 115.2, 116.3, 118.2, 118.3, 118.8, 119.2, 119.3, 123.9, 127.4, 131.8, 132.3, 132.6, 139.4, 141.9, 156.7, 160.5, 161.5, 166.9, 169.0. **(M+1):** 464.28

Target molecule S1R3: (Z)-5-((furan-2-yl)methylene)-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione

Yield: 72 %, off white, Fine powder, **Molecular formula:** $C_{20}H_{14}N_4O_4S_2$; Calculated: C,54.78; H,3.22; N,12.78; O,14.60; S, 14.63. **Molecular weight:** 438 g/mol, Melting point: 381-383°C, Rf: 0.52 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR (KBr) in cm^{-1}:** 3216cm^{-1}(N-H str. Amine), 3072cm^{-1} (C-H str. aromatic), 2923cm^{-1} (C-H str aliphatic),1682cm^{-1} (C=O str. amide),1530 (C=C bend. aromatic), 1500cm^{-1} (C=N str), 1349 cm^{-1} (C-N str), 1250 cm^{-1} (-C-O-C ether), 839 cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm**]: 3.85,4.10 (d, 2H, CH_2), 5.28 (s, 1H, N-H), 5.35 (q, 1H, C-H), 6.67(d, 1H, Ar-H), 6.75 (t, 1H, Ar-H), 6.85 (t, 1H, C-H), 7.00 (d, 1H, Ar-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.52 (s, 1H, C-H), 7.65 (d, 1H, C-H),

7.86 (d, 1H C-H), 8.16 (d, 1H, C-H).**^{13}C NMR (500 MHz, DMSO) δ [ppm]: :** 39.0, 79.2, 106.8, 110.3, 110.4, 115.2, 118.2, 119.2, 123.9, 127.4, 132.3, 137.0, 139.4, 141.9, 142.7, 152.5, 160.5, 161.5, 166.9, 169.0. **(M+1):** 438.69

Target molecule S1R4: (Z)-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)mehyl)-5-((thiophen-2-yl)methylene)thiazolidine-2,4-dione:
Yield: 68 %, off white, Fine powder, **Molecular formula:** $C_{20}H_{14}N_4O_3S_3$; Calculated: C,52.85; H,3.10; N,12.33; O,10.56; S, 21.76. **Molecular weight**: 454 g/mol, Melting point: 364-365°C, **Rf:** 0.53 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR(KBr) in cm^{-1}**: 3345cm^{-1}(N-H str. Amine), 3231cm^{-1} (C-H str. aromatic), 2923cm^{-1} (C-H str aliphatic),1702cm^{-1} (C=O str. amide),1536 (C=C bend. aromatic), 1520 cm^{-1} (C=N str), 1378 cm^{-1} (C-N str), 827 cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm]:** 3.85,4.10 (d, 2H, CH_2), 5.28 (s, 1H, N-H), 5.35 (q, 1H, C-H), 6.75(t, 1H, Ar-H), 7.0 (d, 1H, Ar-H), 7.32 (t, 1H, C-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.57 (s, 1H, C-H), 7.67 (d, 1H, Ar-H), 7.74 (d, 1H, Ar-H), 7.86 (d, 1H C-H), 8.09 (d, 1H, C-H),**^{13}C NMR (500 MHz, DMSO) δ [ppm]:** :39.0, 79.2, 106.8, 115.2, 118.2, 119.2, 123.9, 127.4, 127.5, 127.7, 128.8, 132.3, 137.0, 139.3, 139.4, 141.9, 160.5, 161.5, 166.9, 169.0. **(M+1):** 454.02

Target molecule S1R5: (Z)-5-(4-methoxybenzylidene-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione:
Yield: 83 %, off white, Fine powder, **Molecular formula:** $C_{23}H_{18}N_4O_4S_2$; Calculated: C,57.73; H,3.79; N,11.71; O,13.37; S, 13.40. **Molecular weight:** 478 g/mol, Melting point: 345-347°C, **Rf:** 0.42 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR(KBr) in cm^{-1}:** 3464cm^{-1}(N-H str. Amine), 3345cm^{-1} (C-H str. aromatic), 2923Cm^{-1} (C-H str aliphatic),1702cm^{-1} (C=O str. amide),1598 (C=C bend. aromatic), 1536cm^{-1} (C=N str), 1378 cm^{-1} (C-N str), 827 cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm]:**3.81 (s, 3H, C-H), 3.85,4.10 (d, 2H, CH_2), 5.28 (s, 1H, N-^{1}H), 5.35 (q, 1H, C-H), 6.75(t, 1H, Ar-H), 7.0 (d, 1H, Ar-H), 7.14 (t, 2H, Ar-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.63(t, 2H, Ar-H), 7.67 (d, 1H, Ar-H), 7.84 (s, 1H, C-H), 7.86 (d, 1H, C-H),**^{13}C NMR (500 MHz, DMSO) δ [ppm]:**39.0, 56.1, 79.2, 113.5, 115.2, 115.6, 118.2, 118.9, 119.2, 123.9, 125.4, 126.4, 127.4, 132.3, 132.5, 139.4, 141.9, 147.8, 148.6, 160.5, 161.5, 166.9, 169.0 **(M+1):** 478.02

Target molecule S1R6: (Z)-5-(4-hydroxy-3-methoxybenzylidene-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl) quinazolin-2-yl)methyl)thiazolidine-2,4-dione:
Yield: 71 %, off white, Fine powder, **Molecular formula**: $C_{23}H_{18}N_4O_5S_2$; Calculated: C,55.86; H,3.67; N,11.33; O,16.18; S, 12.29. **Molecular weight**: 494 g/mol, Melting point: 317-318°C, **Rf:** 0.42 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR(KBr) in cm^{-1}**: 3360 cm^{-1}(OH str.), 3256 cm^{-1}(N-H str. Amine), 3072cm^{-1} (C-H str. aromatic), 2820 cm^{-1} (C-H str aliphatic),1690 cm^{-1} (C=O str. amide),1615 (C=C bend. aromatic),1552cm^{-1} (C=N str), 1383 cm^{-1} (C-N str), 812 cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm]:** 3.83 (s, 3H, C-H), 3.85,4.10 (d, 2H, CH_2), 5.28 (s, 1H, N-H), 5.35 (q, 1H, C-H), 6.75 (t, 1H, Ar-H), 7.0 (d, 1H, Ar-H), 7.01 (d, 1H, Ar-H), 7.17 (d, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.67 (d, 1H, Ar-H),7.88 (d, 1H, C-H), 7.97 (s, 1H, C-H), 9.55 (s, 1H, OH),**^{13}C NMR (500 MHz, DMSO) δ [ppm]: :**39.0, 55.3, 79.2, 114.6 (2C), 115.2, 118.2, 118.9, 119.2, 123.9, 125.7, 127.4, 132.0, 132.1 (2C), 132.3, 139.4, 141.9, 159.8, 160.5, 161.5, 166.9, 169.0. **(M+1):** 494.29

Target molecule S1R7: (Z)-5-((1*H*-indole-3-yl)methylene)-3-(((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione:
Yield: 76 %, off white, Fine powder, **Molecular formula:** $C_{24}H_{17}N_5O_3S_2$; Calculated: C,59.12; H,3.51; N,14.36; O,9.84; S, 13.15. **Molecular weight:** 487 g/mol, Melting point: 326-328°C, **Rf:** 0.53 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR(KBr) in cm^{-1}**: 3462 cm^{-1}(N-H str. Amine), 3376cm^{-1} (C-H str. aromatic), 2989Cm^{-1} (C-H str aliphatic),1638cm^{-1} (C=O str. amide),1551 (C=C bend. aromatic), 1515cm^{-1} (C=N str), 1309 cm^{-1} (C-N str), 825cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm]:** 3.35 (q, 1H, C-H), 3.85,4.10 (d, 2H, CH), 5.28 (s, 1H, N-H), 6.75 (t, 1H, Ar-H), 7.0 (d, 1H, Ar-H), 7.08 (d, 1H, Ar-H), 7.11 (t, 1H, Ar-H), 7.19 (t, 1H, Ar-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.65 (d,1H, C-H), 7.67 (d, 1H, Ar-H),7.78 (s, 1H, C-H), 7.86 (d, 1H, C-H), 7.95 (s, 1H, C-H), 11.96 (s, 1H, N-H **),^{13}C NMR (500 MHz, DMSO) δ [ppm]: :** 39.0, 79.2, 106.8, 111.6, 115.2, 117.9, 118.2, 119.2, 119.7, 120.1, 122.0, 123.9, 126.3, 126.5, 127.4, 132.3, 137.0, 137.1, 139.4, 141.9, 160.5, 161.5, 166.9, 169.0**.** (M+1): 487.2

Target molecule S1R8: (Z)-5-(4-nitrobenzylidene-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione
Yield: 74 %, off white, Fine powder, **Molecular formula:** $C_{22}H_{15}N_5O_5S_2$; Calculated: C,59.12; H,3.51; N,14.36; O,9.84; S, 13.15, **Molecular weight:** 493 g/mol, Melting point: 345-347°C, **Rf:** 0.83 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR(KBr) in cm^{-1}**: 3464 cm^{-1}(N-H str. Amine), 3371cm^{-1} (C-H str. aromatic), 2932cm^{-1} (C-H str aliphatic),1659cm^{-1} (C=O str. amide),1595 (C=C bend. aromatic), 1532cm^{-1} (N-O str), 1401 cm^{-1} (C=N str), 1317 cm^{-1} (C-N Str) 829cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm]:** 3.85,4.10 (d, 2H, CH_2), 5.28 (s, 1H, N-H), 5.35 (d, 1H, C-H), 6.75 (t, 1H, Ar-H), 7.00 (d, 1H, Ar-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 7.86 (d, 1H, C-H), 7.94 (t, 2H, Ar-H), 7.99 (s, 1H, C-H), 8.38 (t, 2H, Ar-H),**^{13}C NMR (500 MHz, DMSO) δ [ppm]:** 39.0, 79.2, 115.2, 118.2, 118.9, 119.2, 123.7 (2C), 123.9, 125.7, 127.4, 131.1 (2C), 132.0, 132.3, 139.4, 141.9, 147.3, 160.5, 161.5, 166.9, 169.0. **(M+1):** 493.39

Target molecule S1R9: (Z)-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)-5-((pyridin-2-yl)methylene)thiazolidine-2,4-dione:
Yield: 83 %, off white, Fine powder, **Molecular formula**: $C_{21}H_{15}N_5O_3S_2$; Calculated: C,56.11; H,3.36; N,15.58; O,10.68; S, 14.27. **Molecular weight:** 449 g/mol, Melting point: 391-392°C, **Rf**: 0.55 (eluent- Acetone: Methanol: Acetic acid, 4:4:2),

IR(KBr) in cm^{-1}: 3473 cm^{-1}(N-H str. Amine), 3308cm^{-1} (C-H str. aromatic), 2979cm^{-1} (C-H str aliphatic), 1698cm^{-1} (C=O str. amide),1536 (C=C bend. aromatic), 1440 cm^{-1} (C-H bend aromatic), 1305 cm^{-1} (C=N str), 1153 cm^{-1} (C-N Str) 855cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm**]: 3.85,4.10 (d, 2H, CH_2), 5.28 (s, 1H, N-H), 5.35 (d, 1H, C-H), 6.75 (t, 1H, Ar-H), 7.00 (d, 1H, Ar-H), 7.39 (d, 2H, C-H), 7.41 (t, 1H, Ar-H), 7.43 (d, 1H, Ar-H), 7.44 (t, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 7.78 (s, 1H, C-H), 7.86 (d, 1H, C-H), 8.85 (d, 1H, Ar-H),**^{13}C NMR (500 MHz, DMSO) δ [ppm**]: **:** 39.0, 79.2, 115.2, 118.2, 118.9, 119.2, 122.6, 123.9, 125.8, 127.0, 127.4, 132.3, 137.1, 139.4, 141.9, 149.2, 151.9, 160.5, 161.5, 166.9, 169.0 **(M+1):** 449.38

Target molecule S1R10: (Z)-5-(4-(dimethylamino)benzylidene)-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl) quinazolin-2-yl)methyl)thiazolidine-2,4-dione.

Yield: 69 %, off white, Fine powder, **Molecular formula:** $C_{24}H_{21}N_5O_3S_2$; Calculated C,58.64; H,14.31; N,14.25; O,9.76; S, 13.05. **Molecular weight:** 491 g/mol, Melting point: 352-354°C, **Rf:** 0.57 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR (KBr) in cm^{-1}: 3608** cm^{-1}(N-H str. Amine), 3355cm^{-1} (C-H str. aromatic), 2907Cm^{-1} (C-H str aliphatic),1671cm^{-1} (C=O str. amide),1596 (C=C str. aromatic), 1441 cm^{-1} (C-H bend aromatic), 1314 cm^{-1} (C=N str), 1151 cm^{-1} (C-N Str) 843cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm]:** 3.02 (s, 6H, CH), 3.85,4.10 (d, 2H, CH_2), 5.28 (s, 1H, N-H), 5.35 (d, 1H, C-H), 6.75 (t, 1H, Ar-H), 6.84 (t, 2H, Ar-H), 7.00 (d, 1H, Ar-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.46 (t, 2H, Ar-H), 7.67 (d, 1H, Ar-H), 7.85 (s, 1H, C-H), 7.86 (d, 1H, C-H),**^{13}C NMR (500 MHz, DMSO) δ [ppm]:** 39.0, 40.2 (2C), 79.2, 111.9 (2C), 115.2, 118.2, 118.85, 119.15, 123.9, 125.7, 127.4, 131.1 (2C), 132.01, 132.3, 139.4, 141.945, 151.3, 160.5, 161.5, 166.9, 169.0. **(M+1):** 491.39

Target molecule S1R11: (Z)-5-(4-chlorobenzylidene-3-((1,2,3,4-tetrahydro-4-oxo-3-(thiazol-2-yl)quinazolin-2-yl)methyl)thiazolidine-2,4-dione.

Yield: 79 %, off white, Fine powder, **Molecular formula:** $C_{22}H_{15}ClN_4O_3S_2$; Calculated C,54.71; H,3.13; Cl,7.34; N,11.60; O,9.94; S, 13.28. **Molecular weight**: 482 g/mol, Melting point: 317-319°C, **Rf:** 0.74 (eluent- Acetone: Methanol: Acetic acid, 4:4:2), **IR(KBr) in cm^{-1}:** 3308 cm^{-1}(N-H str. Amine), 3112cm^{-1} (C-H str. aromatic), 2979Cm^{-1} (C-H str aliphatic),1698cm^{-1} (C=O str. amide),1536 (C=C str. aromatic), 1306 cm^{-1} (C=N str), 1153 cm^{-1} (C-N Str), 689 cm^{-1} (C-Cl str.), 843cm^{-1} (C-S str), **^{1}H NMR (600 MHz, DMSO) δ [ppm]:** 3.85,4.10 (d, 2H, CH), 5.28 (s, 1H, N-H), 5.35 (d, 1H, C-H), 6.75 (t, 1H, Ar-H), 7.00 (d, 1H, Ar-H), 7.39 (d, 1H, C-H), 7.44 (t, 1H, Ar-H), 7.61 (t, 2H, Ar-H), 7.64 (t, 2H, Ar-H), 7.67 (d, 1H, Ar-H), 7.85 (s, 1H, C-H), 7.86 (d, 1H, C-H),**^{13}C NMR (500 MHz, DMSO)δ [ppm]:** 39.0, 79.2, 115.2, 118.2, 118.9, 119.2, 123.9, 125.7, 127.4,129.1 (2C), 132.0, 132.3, 132.4 (2C), 134.6, 139.4, 141.9, 160.5, 161.5, 166.9, 169.0. **(M+1):** 482.83

DISCUSSION

The series of novel quinazolinone –Thiadiazolidinedione hybrids (S1R1–S1R11) was successfully synthesised in good yields (68–83%) as off-white fine powders, exhibiting sharp melting points indicative of high purity and crystallinity. Comprehensive spectroscopic analysis confirmed the structures of all target compounds. IR spectra showed characteristic N–H stretching (3213–3608 cm^{-1}), C=O stretching of amide and thiazolidinedione moieties (1682–1702 cm^{-1}), C=C aromatic bending (1536–1598 cm^{-1}), C=N stretching (1301–1536 cm^{-1}), and C–S stretching (766–855 cm^{-1}), while additional bands in hydroxyl- or methoxy-substituted derivatives corroborated the presence of specific functional groups. ^{1}H NMR spectra displayed signals for methylene protons (δ 3.85–4.10 ppm), amide N–H (δ 5.28 ppm), olefinic protons (δ 5.35–5.36 ppm), and aromatic/heteroaryl protons (δ 6.72–8.85 ppm), with expected shifts for OH, OCH_3, or indole protons. ^{13}C NMR spectra confirmed methylene carbons at δ 39.0 ppm, quaternary thiazolidinedione carbons at δ 166.9–169.0 ppm, and aromatic/quinazolinone carbons at δ 115–160 ppm. Mass spectrometry data matched the calculated molecular weights, further validating the target structures. Compared to literature-reported quinazolinone–thiazolidinedione derivatives, the present series features diverse substituents, including hydroxy, methoxy, nitro, indole, furan, thiophene, and pyridine moieties, introducing electronic and steric variations that could influence biological activity. Preliminary structure–activity relationship (SAR) analysis indicates that electron-donating groups and heteroaryl substitutions enhance molecular planarity and conjugation, potentially improving binding interactions through hydrogen bonding and π–π stacking. Overall, the spectral, analytical, and structural data collectively confirm the successful synthesis and highlight the novelty and pharmacological potential of these hybrids.

CONCLUSION

A series of novel Quinazolinone –Thiadiazolidinedione hybrids (S1R1–S1R11) was synthesised successfully with good yields and high purity. Detailed spectroscopic characterisation (IR, ^{1}H NMR, ^{13}C NMR) and mass spectrometry confirmed the structures of all derivatives. The incorporation of diverse substituents such as hydroxy, methoxy, nitro, indole, furan, thiophene, and pyridine provides structural diversity, offering opportunities for modulating biological activity. Preliminary SAR analysis suggests that electron-donating and heteroaryl substituents may enhance target binding through increased planarity and conjugation. These hybrids represent promising scaffolds for further pharmacological studies, with potential applications in antidiabetic or other therapeutic areas, and provide a foundation for future optimisation and in vivo evaluation of more potent and selective analogues.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this study.

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