Original Article

Design, synthesis, and characterization of new thiazolidinedione derivatives as potent α-glucosidase inhibitors

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ABSTRACT

In an effort to find new antidiabetic agents, we carried out the design and synthesis of new thiazolidinedione derivatives and evaluated them as α-glucosidase inhibitors. All the synthesized derivatives were evaluated for α-glucosidase inhibitory activity. All the derivatives showed good inhibitory potential against α-glucosidase with IC_{50} values ranging between 35.74 ± 0.134 and 12.29 ± 1.86 μg/mL. Among all the synthesized derivatives, 12d emerged to be the most potential inhibitor of α-glucosidase bearing IC_{50} value of 12.29 ± 1.86 μg/mL. Owing to the results, it can be concluded that the lead identified in the present study can be further explored for the design of potent α-glucosidase inhibitors as antidiabetic agents.

Keywords: Thiazolidinedione, α-glucosidase inhibitors, antidiabetic agents, synthesis, *in vitro* studies

INTRODUCTION

Diabetes mellitus, a chronic metabolic, non-communicable, and unceasing disease, has attained epidemic proportions worldwide.[1] India is one of the epicenters of global diabetes mellitus epidemic and has the second-highest number of people with the disease in the world. A recent study suggested that 49% of the world's diabetes burden is represented by India with an estimated 72 million cases in 2017; a figure is expected to be almost double to 134 million by 2025. As per the recent WHO survey report, over 4.22 billion population around the globe have been affected by diabetes and about 4.18 billion population will be affected by diabetes mellitus in upcoming future.[2] The disease is characterized by elevated levels of glucose levels in blood (or blood sugar), which further leads to serious damage to the heart, blood vessels, eyes, kidneys, and nerves after a period of time. Diabetes mellitus is further classified as type 1, type 2, and gestational diabetes while type 2 diabetes mellitus is the common major form of diabetes which is the consequence of insulin resistance.[3]

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α-glucosidase (EC 3.2.1.20) is a catabolic enzyme which is responsible for the hydrolyzation of complex carbohydrates to simple absorbable sugars in order to produce energy and is essential for the maintenance of healthy functioning and normal physiological functions.[4,5] In contrast, high activity of this enzyme can cause clinically serious problems in patients with type 2 diabetes due to decreased glucose absorption.[6] Numerous reports address the relevance of α-glucosidase inhibition and the regulation of glucose levels in type 2 diabetes mellitus by α-glucosidase inhibitors.[7] Several types of α-glucosidase inhibitors have been clinically applied to inhibit α-glucosidase for medicinal purposes, including acarbose,[8] miglitol,[9] and voglibose.[10]

Thiazolidinedione derivatives have been known to scientific community for over 100 years and are still under exploration due to their extremely interesting biological activity profile. The heterocyclic scaffold thiazolidinedione is regarded as one of the most valuable assets for the development of new drug entities, possessing numerous activities. The structural variability of thiazolidinedione derivatives is endowed primarily at two positions of the scaffold, *i.e.* N-3 and C-5. The introduction of the lipophilic or hydrophilic or aromatic group at one or both of the main positions provides a range of drug design options and physicochemical parameter modifications.[11]

A few reports have been published which described the α-glucosidase inhibitory potential of thiazolidinedione derivatives modified at N-3 and C-5 position. The synthesis and α-glucosidase inhibitory evaluation of pyrrolidine-2,5-dione and thiazolidine-2,4-dione derivatives was carried out by Hussain *et al.*[12] The result of α-glucosidase inhibitory activity revealed that compound 1 was the best compound among the series of synthesized derivatives possessing IC_{50} value of 0.98 ± 0.008 μg/mL. Further, antidiabetic potential of thiazolidinedione derivatives substituted at N-3 and C-5 position was explored by Chinthala *et al.*[13] Moreover, literature reports highlighted the contribution of lipophilic substituent at C-5 position is crucial to obtain high α-glucosidase inhibitory potency.[14] Inspired by the literature reports, we planned to synthesize N-3 and C-5 substituted thiazolidinedione derivatives and evaluated them as possible α-glucosidase inhibitors. The design of proposed molecules is depicted in Figure 1.

RESULTS AND DISCUSSION

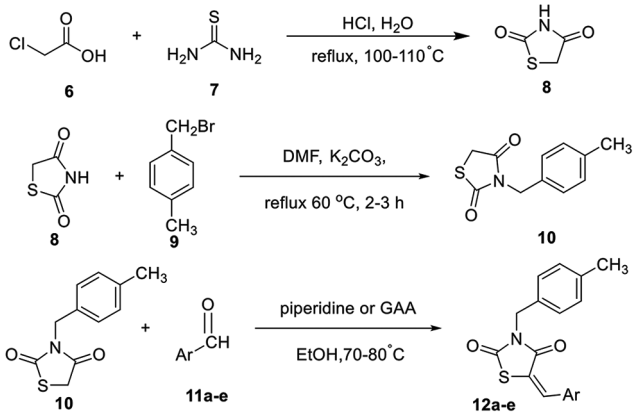
Chemistry

The proposed compounds were synthesized using synthetic strategy as depicted in Scheme 1. 2,4-thiazolidinedione (TZD) was synthesized by cyclization of thiourea (6) with monochloroacetic acid (7) to afford white precipitate of 2-iminothiazolidine-4-one, which upon acidification and refluxing with HCl for 10 h afforded white crystals of TZD using previously reported procedure.[15] The 4-methylbenzyl derivatives of TZD were obtained by N(3)-benzylation of thiazolidinedione (8) with 4-methylbenzyl bromide (9) in the presence of DMF with potassium carbonate, heating at 60°C for 2–3 h, leading to formation of the intermediate (10). Knoevenagel condensation was carried out by treating equimolar ratio of *N*-substituted thiazolidine-2,4-dione with various aromatic aldehydes (11a-e) in ethanol in the presence of catalytic amount of piperidine by refluxing for 3–5 h. The title compounds (12a-q) were obtained as solid in satisfactory yield (61–76%). Further, from the spectral data, it was evidenced that all the title compounds were preferentially obtained as *Z*-isomer, as confirmed from their higher values, and results were in accordance with the literature data.[15] Various physiochemical constants are summarized in Table 1.

α-Glucosidase Inhibitory Activity

We have synthesized thiazolidinedione derivatives and screened them for α-glucosidase inhibitory activity. Acarbose was used as a reference drug for the comparison of α-glucosidase inhibitory potential. IC_{50} values of the synthesized derivatives have been depicted in Table 2. Among the series, all derivatives showed less α-glucosidase inhibitory potential as compared to the standard drug acarbose with IC_{50} values ranging between 35.74 ± 0.134 and 12.29 ± 1.86 μg/mL. Among all the synthesized derivatives, 12d was found to be the most potent derivative possessing IC_{50} value of 12.29 ± 1.86 μg/mL.

The structure–activity relationship (SAR) is shown in Figure 2. The SAR was mainly based upon bringing about different substituents



Scheme 1: Synthesis of title compounds

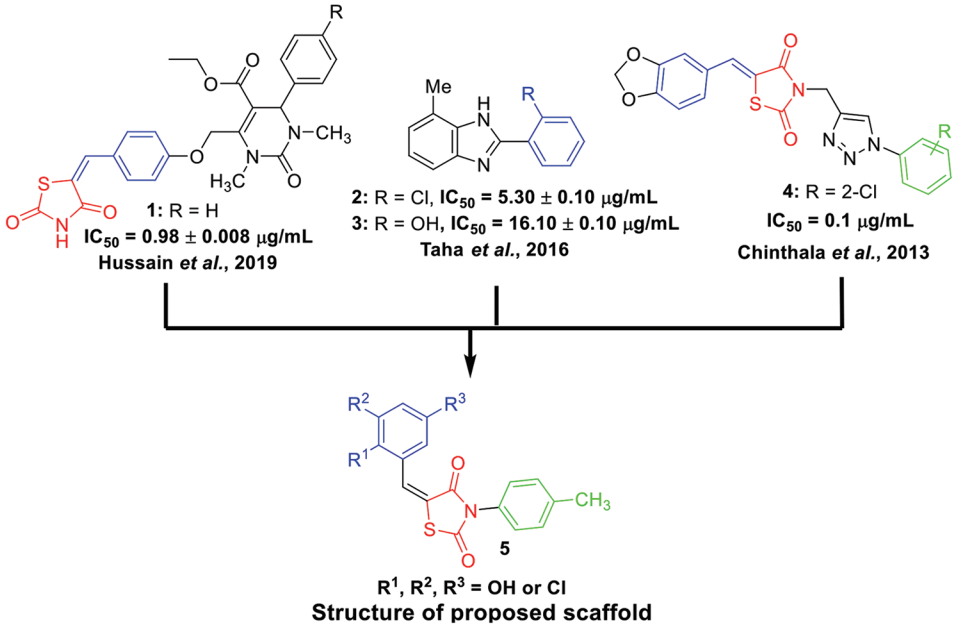


Figure 1: Design of the proposed molecules

Table 1: Physicochemical data of various title compounds (12a–e)

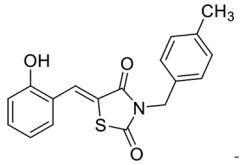
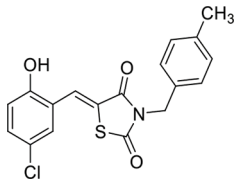
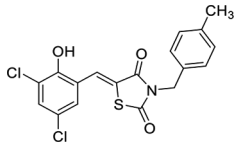
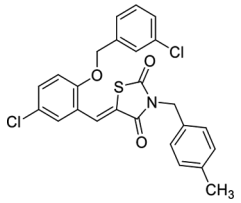
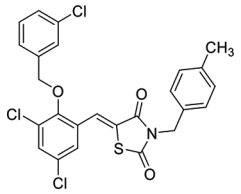
Compound Code	Structure	Chemical Formula	Color	Melting Point (°C)	% Yield
12a		$C_{18}H_{15}NO_3S$	Yellow	203–205	71
12b		$C_{14}H_{14}ClNO_3S$	Pale Yellow	215–217	73
12c		$C_{18}H_{13}Cl_2NO_3S$	Light Yellow	211–213	68
12d		$C_{25}H_{19}Cl_2NO_3S$	White	285–287	70
12e		$C_{25}H_{18}Cl_3NO_3S$	Off-White	267–269	64

Table 2: IC_{50} values of synthesized derivatives (12a-e) against α-glucosidase

Compound	IC_{50} values (μg/mL)
12a	35.74±0.134
12b	20.28±0.247
12c	23.88±0.98
12d	12.29±1.86
12e	18.24±1.786
Acarbose	6.74±1.23

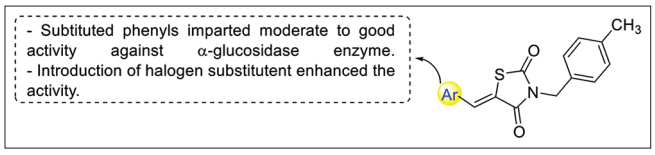


Figure 2: Structure–activity relationship of newly synthesized thiazolidinedione derivatives

on phenyl part. From the *in vitro* α-glucosidase inhibitory studies, it was evident that nature of substituent at arylidene phenyl moiety impacted the activity of compound. Hydroxyl phenyl (12a) was found to possess the least α-glucosidase inhibitory potential. Introduction of dihydroxy phenyl in compound 12b further led to increase in the α-glucosidase inhibitory activity replacement of hydroxy group by benzyl group (12d and 12e) further increased the α-glucosidase inhibitory potential of the compounds.

CONCLUSION

The present work involves the design, synthesis, characterization, and *in vitro* evaluation studies of new thiazolidinedione derivatives as potent antidiabetic agents via α-glucosidase inhibition. Five new N-3 and C-5 substituted thiazolidinedione derivatives were synthesized, structurally elucidated, and evaluated *in vitro* for α-glucosidase inhibitory potential. Results revealed that the synthesized compounds exhibited potent to good α-glucosidase inhibitory profile. In particular, compounds 12d presented the most promising α-glucosidase inhibitory potential. The antidiabetic activity was modulated by the nature of substituent attached to the 5-position of the thiazolidinedione core. The present study identified new thiazolidinedione derivatives as promising α-glucosidase inhibitors, and further studies with the identified lead molecules would be helpful in the design and development of candidates with more potent α-glucosidase inhibitory profile.

EXPERIMENTAL

All the intermediates and title compounds were synthesized using solution-phase chemistry. The progress of reactions was monitored

by thin-layer chromatography (TLC). From the TLC, we ensured to declare the completion of the reaction. The TLC plates were visualized by viewing in ultraviolet (UV) and iodine chamber. The reaction products were purified by different work-up processes to remove unreacted starting material and impurities. Recrystallization or repeated recrystallization was done using suitable solvents to get a pure sample of title compounds. In few cases, intermediate or title compounds were purified by column chromatography. Melting points and R_f values of all the compounds and intermediates were determined. The structure and purity of the anticipated compounds were characterized by physical constants and Fourier-transform infrared spectral studies initially followed by ^{1}H-NMR spectroscopic data, mass, and elemental analysis. The synthetic scheme consists of two steps.

General Procedure for the Synthesis of Thiazolidinedione (Step 1)

To a solution of chloroacetic acid (5 g, 53.19 mmol, 7) in 6 mL of water, added a solution of thiourea (4 g, 52.63 mmol, 6) in 6 mL of water. After stirring for 30 min, 4 mL of concentrated HCl was added to the reaction mixture and the contents were refluxed for 10–12 h. Upon cooling, needle-like crystals of thiazolidinedione (8) precipitated out. The precipitates were filtered under vacuum, washed with water, and recrystallized from ethanol.

IR (KBr) ν_{max} (cm): 3387 (N-H str.), 1681 and 1739 (C=O), 1576 (C=C), 622 (C-S); ^{1}H-NMR (300 MHz, DMSO-d_6): 11.98 (s, NH) and 4.13 (s, CH_2); ^{13}C-NMR (300 MHz, DMSO-d_6): 173.016 and 173.786 (C-N-C), 35.759(CH_2)

General Procedure for the Synthesis of 3-(4-methylbenzyl)thiazolidine-2,4-dione (Step 2)

A mixture of thiazolidine-2,4-dione (8) (500 mg, 4.26 mmol), 4-methylbenzyl bromide (4.3 mmol, 9), potassium carbonate (590 mg, 8.52 mmol), and DMF (6 mL) was taken in a well-dried round-bottom flask. The mixture was then heated at 80°C for 2–3 h. The reaction progress was monitored by TLC. After completion, the reaction mixture was poured over crushed ice. The precipitated solid was then filtered under vacuum, washed with water, dried, and recrystallized from ethanol to afford the *N*-benzylated TZD (10) in good yield.

IR (KBr) ν_{max} (cm): 3110 (aromatic C-H stretching), 2985 (aliphatic C-H stretching), 1669 and 1748 (C=O), 1576 (C=C), 1266 (C-N), 738 (C-H bending), 620 (C-S).

General Procedure for the Synthesis of N-substituted-5-arylidene derivatives of Thiazolidinedione (Step 3)

A mixture of *N*-substituted thiazolidinedione (10, 250 mg) and substituted aromatic aldehyde (11a-e, 1 eq.) was suspended in absolute alcohol, and to this catalytic amount of piperidine and glacial acetic acid was added. The mixture was then allowed to reflux with stirring at 80°C for 3–7 h. The completion of reaction was monitored with the help of TLC. On completion, the precipitate in the reaction mixture was filtered, washed thoroughly with absolute ethanol and with finally with water, and dried. The crude product was recrystallized from ethanol to get the desired pure compounds.

(Z)-5-(2-hydroxybenzylidene)-3-(4-methylbenzyl) thiazolidinedione-2,4-dione (9a)

IR (KBr) ν_{max} (cm^{-1}): 3240 (O-H), 3056 (aromatic C-H stretching), 2856 (aliphatic C-H stretching), 1727 and 1659 (C=O), 1258 (C-O), 1193 (C-N), 682 (C-S), ^{1}H-NMR (300 MHz, $CDCl_3$): 10.27 (s, 1H, -OH), 8.17 (s, 1H, -CH=), 7.40-7.33 (m, 6H, Ar-H), 6.99-6.96 (m, 2H, Ar-H), 4.86 (s, 2H, N-CH_2), 2.19 (s, 1H, -CH_3).

(Z)-5-(5-chloro-2-hydroxybenzylidene)-3-(4-methylbenzyl)thiazolidinedione-2,4-dione (9b)

IR (KBr) ν_{max} (cm^{-1}): 3214 (O-H), 3056 (aromatic C-H stretching), 1720 and 1659 (C=O), 1429 (C=C), 1206 (C-N), 750 (C-Cl), 657 (C-S), ^{1}H-NMR (300 MHz, DMSO-d_6): 10.27 (s, 1H, -OH), 8.12 (s, 1H, -CH=), 7.43-7.37 (m, 5H, Ar-H), 6.99-6.95 (m, 2H, Ar-H), 4.85 (s, 2H, N-CH_2), 2.19 (s, 1H, -CH_3).

(Z)-5-(3,5-dichloro-2-hydroxybenzylidene)-3-(4-methylbenzyl)thiazolidinedione-2,4-dione (9c)

IR (KBr) ν_{max} (cm^{-1}): 3376 (O-H), 3072 (aromatic C-H stretching), 2924 (aliphatic C-H stretching), 1736 and 1685 (C=O), 1607 (C=C), 1331 (C-O), 1261 (C-N), 747 (C-Cl), 684 (C-S), ^{1}H-NMR (500 MHz, DMSO-d_6): 8.03 (s, 1H, -CH=), 7.78 (s, 1H, OH), 7.40-7.39 (m, 3H, Ar-H), 7.33-7.11 (m, 3H, Ar-H), 4.85 (s, 2H, N-CH_2), 2.19 (s, 1H, -CH_3).

(Z)-5-(5-chloro-2-((3-chlorobenzyl)oxy) benzylidene)-3-(4-methylbenzyl)thiazolidinedione-2,4-dione (9d)

IR (KBr) ν_{max} (cm^{-1}): 3050 (aromatic C-H stretching), 2948 (aliphatic C-H stretching), 1683 and 1736 (C=O), 1258 (C-O stretching), 1573 (C=C), 1098 (C-N), 745 (C-Cl), 567 (C-S)

^{1}H-NMR (300 MHz, $CDCl_3$): 7.85 (s, 1H, -CH=), 7.61-7.58 (d, 2H, J = 7.2 Hz, Ar-H), 7.34-7.18 (m, 8H, Ar-H), 4.97 (s, 2H, O-CH_2), 4-86 (s, 2H, N-CH_2), 2.19 (s, 1H, -CH_3).

(Z)-5-(3,5-dichloro-2-((3-chlorobenzyl)oxy) benzylidene)-3-(4-methylbenzyl)thiazolidinedione-2,4-dione (9e)

IR (KBr) ν_{max} (cm^{-1}): 2924 (aromatic C-H stretching), 2854 (aliphatic C-H stretching), 1692 and 1735 (C=O), 1617 and 1527 (C=C), 1342 (C-O stretching), 1259 (C-N), 733 (C-Cl), 683 (C-S).

^{1}H-NMR (300 MHz, $CDCl_3$): 7.85 (s, 1H, -CH=), 7.61-7.58 (d, 2H, J = 7.2 Hz, Ar-H), 7.34-7.18 (m, 8H, Ar-H), 4.97 (s, 2H, O-CH_2), 4-86 (s, 2H, N-CH_2), 2.19 (s, 1H, -CH_3).

A-GLUCOSIDASE INHIBITORY ACTIVITY

The antidiabetic role of synthesized compounds was established by using α-glucosidase inhibition assay.[12] Briefly, the reaction mixture was comprised of 200 µL α-glucosidase solution, 1200 µL phosphate buffer, and 100 µL of various concentrations ranging from 62.5 to 1000 µg/ml of synthesized compounds. 2.5 mM of p-nitrophenyl-α-D-glucopyranoside was added to the mixture and allowed to stand for 20 min at 37°C. Added 800 µL of sodium carbonate solution to the reaction mixture after cooling. Checked absorption of the reaction mixture at 405 nm using UV-visible spectrophotometer. Glucopyranoside was used as standard in the experiment. The given formula was used to find out the percent inhibition of the α-glucosidase enzyme:

$$\% \text{ Inhibition} = \frac{\text{Abs of control} - \text{Abs of sample}}{\text{Abs of control}} \times 100$$

CONCLUSION

Diabetes Mellites is a metabolic disorder associated with high co-morbidities and claiming significant number of lives worldwide. In an effort to identify new molecules as antidiabetic agents, our group design and synthesis of new thiazolidinedione derivatives and evaluated them as α-glucosidase inhibitors. The molecule displayed good α-glucosidase inhibitory activity with IC_{50} between 12.29 to 35 µg/mL. Among them derivative 12d emerged as most potent inhibitor of the enzyme.

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