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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Benzoxazolyl linked benzylidene based rhodanine and analogs as novel antidiabetic agents: synthesis, molecular docking, and in vitro studies

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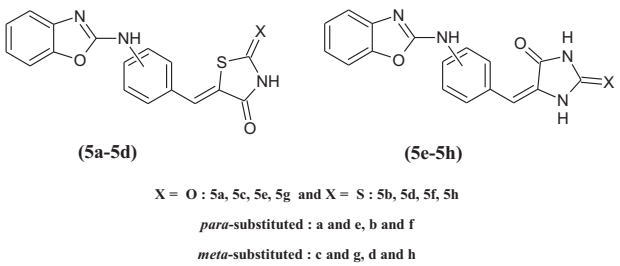
Abstract

Benzoxazolyl linked *meta*- and *para*-substituted new chemical entities (**5a**–**5h**) featuring thiazolidinedione, rhodanine, hydantoin, and thiohydantoin moieties were synthesized and characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, and HRMS spectral studies. In addition, all compounds were screened for α-glucosidase inhibitory activity and further supported by molecular docking studies carried out at the active site of α-glucosidase (PDB code: 3TOP) in comparison to acarbose used as a standard drug. Out of eight tested compounds, **5d** was found as the most active inhibitor of α-glucosidase ($IC_{50} = 9.48 \pm 0.36\ \mu M$), having rhodanine moiety substituted at *meta*-position of the phenyl ring.

Graphical Abstract



Keywords Benzoxazole · Molecular docking · α-Glucosidase · Antidiabetic

Introduction

Diabetes mellitus is the most common metabolic disorder growing at alarming rates in developed as well as developing countries. According to the International Diabetes Federation, the number of patients suffering from the disease is expected to increase up to 693 million by 2045 [1]. Increased blood glucose level characterized by hyperglycemia is either because sufficient insulin is not produced by the pancreas or the insulin receptor does not act in response to the secreted insulin [2]. Diabetes is also the primary cause of morbidity and mortality associated with many complications such as heart disease, neuropathy, nephropathy, stroke, and vascular diseases [3]. Therefore, there is an urgent need to develop newer therapeutic approaches for the prevention and management of diabetes. Various

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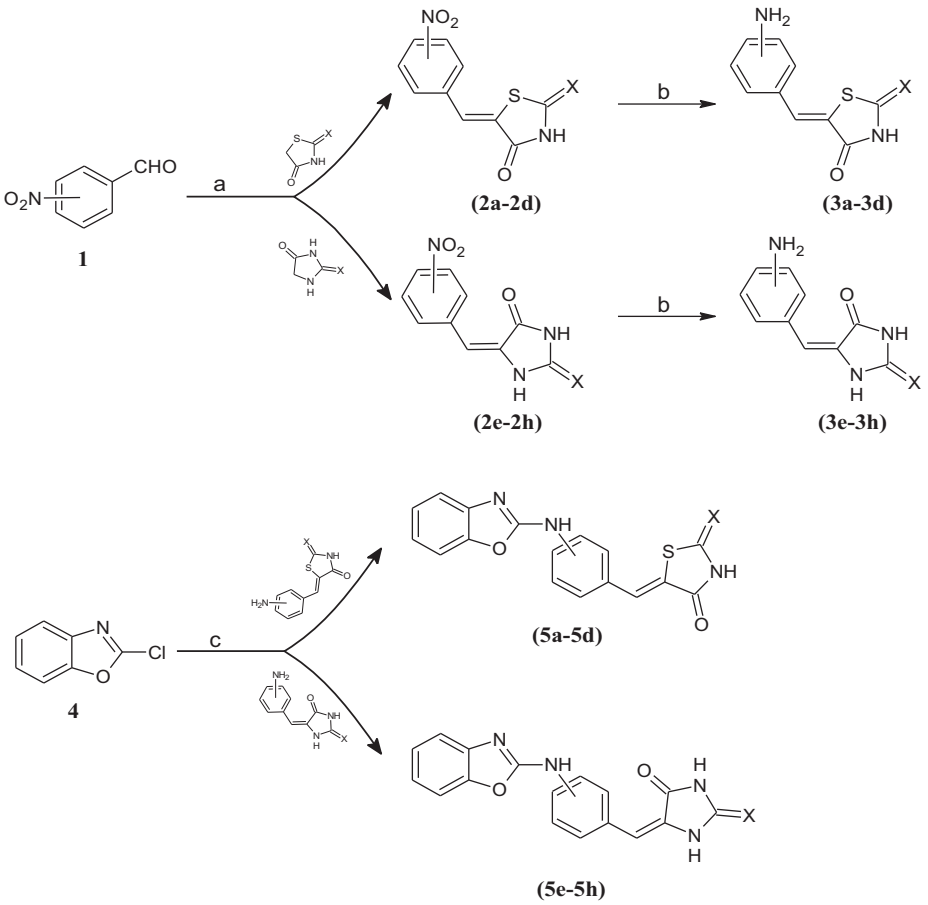

Scheme 1 (a) CH_3COONH_4, CH_3COOH, reflux 15 h. (b) $SnCl_2.H_2O$, EtOH, reflux 4 h. (c) EtOH, MW, 15 min

X = O : 2a, 2c, 2e, 2g and X = S : 2b, 2d, 2f, 2h

X = O : 3a, 3c, 3e, 3g and X = S : 3b, 3d, 3f, 3h

X = O : 5a, 5c, 5e, 5g and X = S : 5b, 5d, 5f, 5h

***para*-substituted : a and e, b and f**

***meta*-substituted : c and g, d and h**

therapeutic strategies to treat diabetes include increasing insulin secretion from pancreatic β cells, intensification of insulin action, reduction in the production of hepatic glucose, or inhibition of glucosidase digestive enzyme [4]. Increased blood glucose levels in the body can be controlled by inhibiting the enzymes α-amylase and α-glucosidase, which are involved in hydrolyzing carbohydrates [5]. The α-amylase enzyme firstly breakdown the long chains present in the polysaccharides, and the enzyme α-glucosidase finally helps to convert the disaccharides and starch to glucose. Thus, inhibition of enzymes α-amylase and α-glucosidase is a favorable therapeutic measure to treat diabetes mellitus, which helps to delay the absorption process of glucose after taking meals. Presently, a few inhibitors of these enzymes, such as voglibose, acarbose, and miglitol, are being used clinically for the treatment of type II diabetes [6, 7]. Furthermore, inhibitors of α-glucosidase are also used as anti-HIV, anticancer, and antihepatitis agents [8–10]. Therefore, the development of new inhibitors of α-glucosidase enzymes is emerging as a thrust area of research in medicinal chemistry. Thaizolidine-2,4-diones, rhodanine, and their derivatives are recently studied as a new class of α-glucosidase inhibitors in the field of medicinal chemistry [11, 12]. On the other hand, the literature revealed that compounds with a benzoxazole heterocyclic system are promising pharmacophores that exhibited antidiabetic activities [13]. In continuation of our interest in designing and synthesizing new chemical entities [14–16], we are reporting, the synthesis of novel benzoxazole derivatives (**5a**–**5h**) featuring thiazolidinedione rhodanine, hydantoin, and thiohydantoin moieties as antidiabetic agents for the management of type II diabetes, in the present

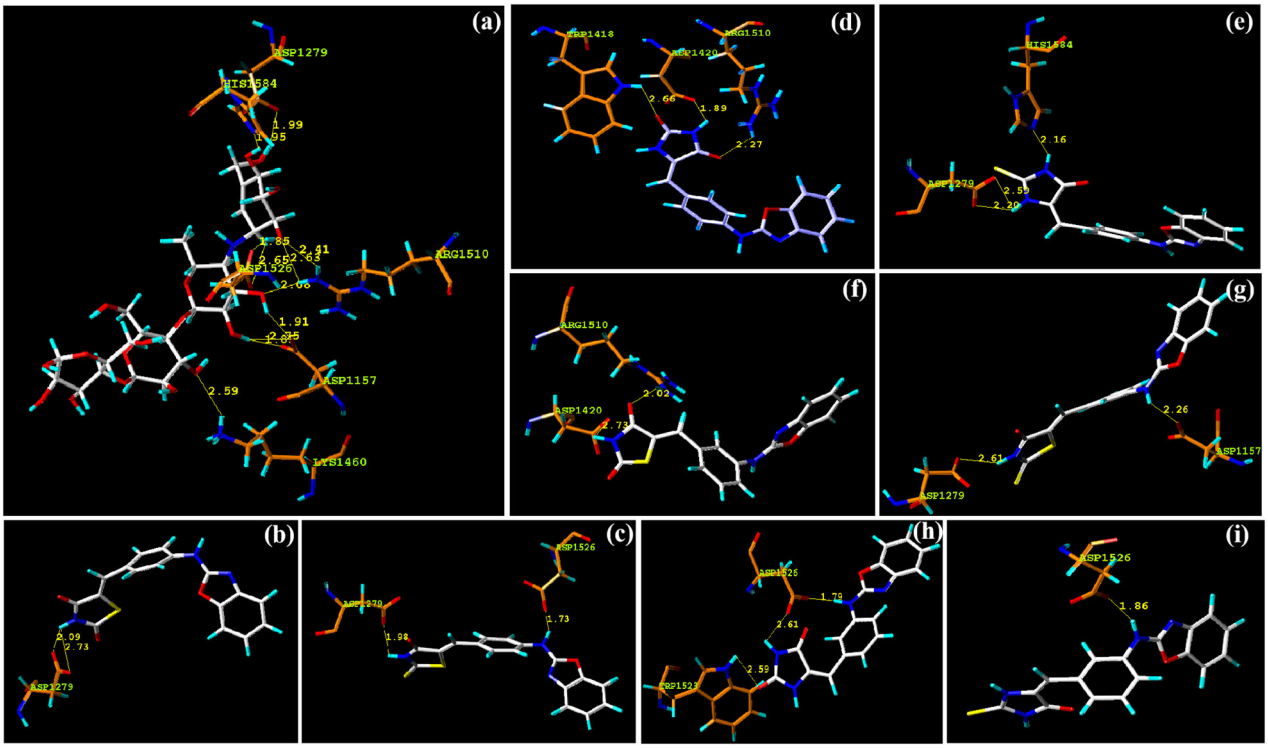

Fig. 1 Hydrogen bond interactions and distances of the standard drug acarbose and benzoxazole derivatives with the amino acid residues of the active site of α-glucosidase (PDB code: 3TOP). **a** Acarbose. **b 5a. c 5b**. **d 5e**. **e 5f. f 5c. g 5d. h 5g**. **i 5h**

study. The targeted molecules thus synthesized were screened for their in vitro α-glucosidase inhibitory activity and which is further supported, with the help of molecular docking studies using SYBYL 7.3 at the active site of the crystal structure of the α-glucosidase (PDB: 3TOP), to predict binding affinities in terms of Gold score (G score) and hydrogen-bonding interactions.

Result and discussion

Chemistry

The synthetic strategy designed begins with the preparation of nitrobenzylidene-based compounds (**2a**–**2h**) through "Knoevenagel condensation" of 4-nitrobenzaldehyde/3-nitrobenzaldehyde with active methylene containing moieties such as thiazolidinedione, rhodamine, hydantoin, and thiohydantoin using ammonium acetate in acetic acid under reflux (Scheme 1). Z isomer was found the only isomer in compounds **2a**–**2d**, whereas compounds **2e**–**2h** formed as single isomers with E configuration. The configuration thus assigned was established through the presence of one proton singlet for the methine proton in the ^{1}H NMR spectrum of compounds **2a**–**2d** and **2e**–**2h**. The downfield one proton singlet at δ 7.92–7.70 ppm in thiazolidinedione- and rhodanine-based compounds **2a**–**2d** predicted Z configuration, whereas hydantoin- and thiohydantoin-based compounds **2e**–**2h** were assigned E configuration [17]. The methine proton appeared as one proton singlet at δ 6.52–6.45 ppm. The downfield shift of methine protons in isomers (**2a**–**2d**) with Z configuration has been reported due to the deshielding effect of the adjacent carbonyl group [18, 19].

Reduction of nitrobenzylidene-based compounds (**2a**–**2h**) with tin(II) chloride dihydrate in ethanol as solvent under reflux gave corresponding aminobenzylidene-based compounds (**3a**–**3h**). The completion of reduction of the nitro group to amino was evident from the presence of two proton broad singlet of NH_2 protons at δ 4.06–6.17 ppm in ^{1}H NMR spectrum along with the broad band in the range 3471–3414 cm^{-1} characteristic of bonded N–H stretch of –NH_2 group in their IR Spectra. The presence of a molecular ion peak in the GC-MS spectra of all these compounds further confirmed the structure assigned. The 2-chlorobenzoxazole (4) required in the synthetic sequence was prepared by chlorination of the corresponding 2-mercaptobenzoxazole according to the literature procedure via displacement of thiol group present in 2-mercaptobenzoxazole by the chloro group substituent using $POCl_3$/PCl_5 reagent [20].

Targeted compounds (**5a**–**5h**) were finally synthesized by the coupling of aminobenzylidenes (**3a**–**3h**) with 2-chlorobenzoxazole (4) in ethanol under microwave irradiations (340 W) as shown in Scheme 1. A characteristic

singlet signal corresponding to NH of linker at δ 11.07–10.33 ppm was found in the respective ^{1}H NMR spectrum of compounds **5a**–**5h**, whereas the absence of broad singlets for NH_2 at δ 4.06–6.17 ppm which appeared in corresponding aminobenzylidenes (**3a**–**3h**) strongly indicated the formation of **5a**–**5h** via coupling reaction.^{13}C peaks in the ^{13}C NMR spectrum were found at their expected chemical shift positions corresponding to all intermediates and final targeted compounds. Further, the presence of $[M + H]^+$ as a base peak in their respective HRMS spectrum of **5a**–**5h** provides additional support to the structures assigned.

Molecular docking studies in the active site of α-glucosidase (PDB code: 3TOP)

Docking studies were performed to explore the G score values, binding conformations and affinities, and various hydrogen-bonding interactions with different amino acid residues in the active site of α-glucosidase. The hydrogen bond interactions and distances for compounds (**5a**–**5h**) with the amino acid residues of α-glucosidase protein compared to the standard drug acarbose are shown in Fig. 1. All the targeted compounds were docked using SYBYL 7.3 (Tripose Inc. software available in our in silico Drug Design Lab) by using the C-terminal domain of protein α-glucosidase PDB: 3TOP [14–16]. Acarbose was found to have binding affinity in terms of its G score value −160.51. It binds α-glucosidase by making hydrogen bonds with ASP1526, ASP1279, ASP1157, HIS1584, ARG1510, and LYS1460 amino acids in the active site of α-glucosidase (Table 1). It was observed from the comparison of the results of the docking studies that *meta*-substituted compound **5d** (−185.75) and a *para*-substituted compound **5b** (−167.64) having rhodanine as the polar head group showed higher binding affinities in comparison to acarbose and form hydrogen bonds with ASP1157, ASP1279, and ASP1526, ASP1279 amino acid residues, respectively, through –NH of the linker and –NH of rhodanine moiety. Thiazolidinedione-based *meta*-substituted compound **5c** (−155.39) and *para*-substituted compound **5a** (−142.03) showed comparable binding affinities but less than that of acarbose (−160.51) and are found to interact with ARG1510, ASP1420, and ASP1279 through the –NH and CO group of thiazolidinedione ring. Hydantoin-based compound **5e** (−112.16) and **5g** (−133.07) along with thiohydantoin-based compound **5f** (−128.51) and **5h** (−94.18) were showing much lesser binding affinities compared to acarbose while interacting with ASP1526, TRP1523 ARG1510, TRP1418, ASP1420, HIS1584, and ASP1279.

In general, it was found that *meta*-substituted compounds (**5c**, **5d**, and **5g**) showed higher binding affinities compared to their *para*-substituted counterparts (**5a**, **5b**, and **5e**), except compounds (**5f** and **5h**) featuring thiohydantoin moiety. Acarbose forms eleven hydrogen bonds with α-glucosidase, whereas numbers of hydrogen bonds were found lesser in synthesized ligands. It was also observed that all compounds are interacting within the same region of the active site (Fig. 1) with similar amino acid residues as that of acarbose. The Hydrogen bond distances in Å between the ligands and amino acid residues found in the range. In most cases, distances are shorter than the distances observed in the case of acarbose. Generally, the carbonyl group, –NH group of the polar heads, and –NH of the linker of the ligands are found to involve in the formation of hydrogen bonds. It was further observed and analyzed that the docking and in vitro studies results showed a good correlation.

In vitro studies

All the synthesized compounds (**5a**–**5h**) were subjected to in vitro analysis to evaluate their potential as inhibitors of the α-glucosidase enzyme using acarbose as a standard drug ($IC_{50} = 15.01 \pm 1.90$ μM, Table 2). All these compounds (**5a**–**5h**) have shown good potential toward inhibition of α-glucosidase activity having IC_{50} values ranging from 9.48 ± 0.36 to 28.47 ± 0.52 μM. The rhodanine-based *meta*-substituted compound **5d** ($IC_{50} = 9.48 \pm 0.36$ μM) showed the best α-glucosidase inhibition potential among all the synthesized compounds in the series (**5a**–**5h**). The corresponding rhodanine-based *para*-substituted compound **5b** ($IC_{50} = 16.17 \pm 0.60$) and thiazolidinedione-based compounds **5a** ($IC_{50} = (18.40 \pm 0.20$ μM) and **5c** ($IC_{50} = 17.50 \pm 0.50$ μM) were found with less but comparable inhibition potential to that of the standard drug acarbose ($IC_{50} = 15.01 \pm 1.90$ μM) as shown in Table 2. It has been found that the hydantoin and thiohydantoin-based compounds **5e**, **5f**, **5g**, and **5h** with IC_{50} values 20.07 ± 0.28, 21.03 ± 0.24, 20.93 ± 0.66, and 28.47 ± 0.52 μM, respectively, (Table 2) exhibited much lesser inhibitory potential in comparison to acarbose (15.01 ± 1.90 μM). The results of α-glucosidase inhibition studies have also been additionally supported by the results of molecular docking studies in terms of G scores and various binding interactions in the active site of the α-glucosidase in comparison to acarbose. The overall analysis of the results depicted a good correlation between the in vitro α-glucosidase inhibition and the molecular docking studies of the final compounds while displaying a good correlation coefficient ($R^2 = 0.883$) between the IC_{50} values and G scores values (Fig. 2).

The analysis thus demonstrated that hydrogen-bonding parts (thiazolidinedione, rhodanine, hydantoin, and thiohydantoin) and the position of the hydrogen-bonding parts of the benzoxazole derivatives played an important role in the

Table 1 Docking results of the compounds (**5a**–**5h**) as compared to acarbose (standard drug) at the active site of α-glucosidase protein (PDB: 3TOP)

Compound	G score	H-bonding interactions between the ligands and the active site amino acid (AA) residues			
		Atoms of ligands[a]	AA residues	Bond distance (Å)	No. of hydrogen bonds
Acarbose	−160.51	O**H**	ASP1279	1.99	11
		O**H**	HIS1584	1.95	
		O**H**	ASP1526	2.65	
		O**H**	ASP1526	1.85	
		OH	ARG1510	2.41	
		OH	ARG1510	2.63	
		OH	ARG1510	2.08	
		O**H**	ASP1157	1.91	
		O**H**	ASP1157	1.85	
		O**H**	ASP1157	2.75	
		OH	LYS1460	2.59	
5a	−142.03	N**H** of thiazolidinedione	ASP1279	2.73	2
		N**H** of thiazolidinedione	ASP1279	2.09	
5b	−167.64	N**H** of linker	ASP1526	1.73	2
		N**H** of rhodanine	ASP1279	1.98	
5e	−112.16	3-N**H** of hydantoin	ASP1420	1.89	3
		4-C**O** of hydantoin	ARG1510	2.27	
		2-C**O** of hydantoin	TRP1418	2.66	
5f	−128.51	1-N**H** of thiohydantoin	ASP1279	2.20	3
		1-N**H** of thiohydantoin	ASP1279	2.59	
		3-N**H** of thiohydantoin	HIS1584	2.16	
5c	−155.39	4-C**O** of thiazolidinedione	ARG1510	2.02	2
		N**H** of thiazolidinedione	ASP1420	2.73	
5d	−185.75	N**H** of linker	ASP1157	2.26	2
		N**H** of rhodanine	ASP1279	2.61	
5g	−133.07	3-N**H** of hydantoin	ASP1526	2.61	3
		N**H** of linker	ASP1526	1.79	
		2-C**O** of hydantoin	TRP1523	2.59	
5h	−94.18	N**H** of linker	ASP1526	1.86	1

[a]The particular atom of the ligands involved in H-bonding has been indicated by boldface

Table 2 α-glucosidase inhibitory activity of the synthesized compounds

Compounds	IC_{50} (μM)
5a	18.40 ± 0.20
5b	16.17 ± 0.60
5e	20.07 ± 0.28
5f	21.03 ± 0.24
5c	17.50 ± 0.50
5d	9.48 ± 0.36
5g	20.93 ± 0.66
5h	28.47 ± 0.52
Acarbose	15.01 ± 1.09

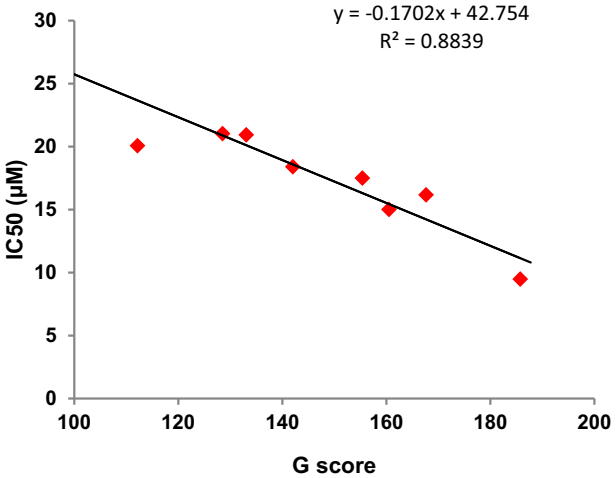

Fig. 2 Correlation graph between the G score values and IC_{50} values

α-glucosidase inhibition potential. It was observed that compound **5d** having rhodanine group substituted at the *meta*-position to the phenyl moiety displayed the best inhibitory potential among all the other benzoxazole derivatives. Replacing the position of the rhodanine moiety from *meta* to *para* decreased the inhibitory activity, whereas replacement of the rhodanine moiety with other cyclic analogs such as thiazolidinedione, hydantoin, and

thiohydantoin drastically decreased the inhibitory potential. The information thus obtained from this structure–activity relationship will provide a better tool and be helpful for the future scope of structural optimization.

Conclusions

All the reported compounds **5a**–**5h** prepared in excellent yield via microwave-assisted synthetic strategy. The results of comparative in vitro α-glucosidase inhibition studies demonstrated that compound **5d** ($IC_{50} = 9.48 \pm 0.36$ μM) displayed the best α-glucosidase inhibition potential in comparison to acarbose ($IC_{50} = 15.01 \pm 1.90$ μM) among all the compounds of this series. Compounds **5b**, **5c**, and **5a** have also shown IC_{50} values very close to that of acarbose. The results of the docking/scoring study of the targeted compounds in the active site of α-glucosidase (PDB code: 3TOP) and those of the in vitro analysis also showed a good correlation ($R^2 = 0.883$).

The pharmacophoric features incorporated in the designed new chemical entities rendered this scaffold to inhibit α-glucosidase enzyme—responsible for prolonged hyperglycemia leading to oxidative stress and subsequent cardiac artery disease. The information thus obtained through structure–activity relationship will provide a better tool for the future scope in structural optimization and may direct in the design and future studies with this and similar scaffolds to be developed for the management of T2D.

Material and methods

Chemistry

All the chemicals used in the reported work were purchased from Sigma-Aldrich and SD Fine Chemicals without further purification. The melting/boiling points reported here were recorded using an open concentrated sulfuric acid bath and are uncorrected. TLC analysis was carried out on glass plates coated with silica gel-GF254 (Loba Chemie), and spots were visualized using a UV cabinet (Perfit India). Column chromatography was performed using silica gel 60–120 mesh (Loba Chemie). The Infrared spectra were recorded on Perkin Elmer Spectrum RX FT-IR Spectrophotometer, USA. ^{1}H, ^{13}C, NMR spectra were recorded on a Bruker AVANCE II 400 (400.13, 100.62 MHz) NMR spectrometer, Bruker BioSpin, Switzerland. Chemical shifts were reported in ppm (δ) with reference to the internal standard TMS. The signals were designated as: br broad, s singlet, d doublet, t triplet, and m multiplet. The GC-MS spectra of intermediates and HRMS of final compounds were recorded on Shimadzu GCMS-QP2010 Plus mass spectrometer and XEVO G2-XS Q-TOF, respectively. The spectral data of all intermediates and final compounds are provided in Supplementary Data.

General procedure for the synthesis of compounds (2a–2h)

To the stirred suspension of 4-nitrobenzaldehyde/3-nitrobenzaldehyde (13.24 mmol) and active methylene compound, thiazolidinedione/rhodanine/hydantoin/thiohydantoin (19.87 mmol) in 20 mL glacial acetic acid, ammonium acetate (26.49 mmol) was added, and the reaction mixture refluxed for 15 h. Then, the solution was cooled and the residue filtered off, washed with warm water, and dried.

(5Z)-5-(4-nitrobenzylidene)-1,3-thiazolidine-2,4-dione (2a)

Yield: 81%; mp: 275–277 °C; FT-IR (KBr, cm^{-1}): 3424, 3195 (NH), 1752(C=O), 1714(C=O); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.80$ (1H, br s, NH), 8.36 (2H, dt, $J =$ 2.44 Hz and 8.84 Hz, Ar-H), 7.91 (1H, s, benylidene), 7.87 (2H, dt, $J = 2.40$ Hz and 8.80 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.35$(C=O), 167.01(C=O), 147.38, 139.31, 130.86(2C), 129.01, 127.99, 124.19(2C); GC-MS (*m*/*z*): 250 $[M]^+$.

(5Z)-5-(4-nitrobenzylidene)-2-thioxo-1,3-thiazolidin-4-one (2b)

Yield: 92%; mp: 255–257 °C; FT-IR (KBr, cm^{-1}): 3427, 3050 (NH), 1717(C=O), 1318, 1191 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 13.86$ (1H, br s, NH), 8.32 (2H, d, $J = 8.76$ Hz, Ar-H), 7.79 (2H, d, $J = 8.84$ Hz, Ar-H), 7.70 (1H, s, benylidene); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 194.45$ (C=S) 168.98(C=O), 147.36, 139.13, 130.93 (2C), 129.94, 128.23, 123.99(2C); GC-MS (*m*/*z*): 266 $[M]^+$.

(5E)-5-(4-nitrobenzylidene)imidazolidine-2,4-dione (2e)

Yield: 72%; mp: 311–313 °C; FT-IR (KBr, cm^{-1}): 3333, 3196 (NH), 1779(C=O), 1744(C=O); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 11.38$ (1H, br s, NH), 10.96 (1H, br s, NH), 8.20 (2H, d, $J = 8.88$ Hz, Ar-H), 7.85 (2H, d, $J = 8.84$ Hz, Ar-H), 6.49 (1H, s, benylidene); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 165.22$(C=O), 155.74(C=O), 146.15, 139.97, 130.81, 130.09(2C), 123.68(2C), 105.12; GC-MS (*m*/*z*): 233 $[M]^+$.

(5E)-5-(4-nitrobenzylidene)-2-thioxoimidazolidin-4-one (2f)

Yield: 80%; mp: 284–286 °C; FT-IR (KBr, cm^{-1}): 3300, 3209 (NH), 1743 (C=O), 1175 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.40$ (1H, br s, NH), 12.25 (1H, br s, NH), 8.15 (2H, d, $J = 8.84$ Hz, Ar-H), 7.85 (2H, d, $J = 8.84$ Hz, Ar-H), 6.46 (1H, s, benylidene); ^{13}C NMR (100 MHz,

DMSO-d_6): $\delta = 179.93$(C=S), 165.48(C=O), 146.49, 139.05, 130.54(2C), 130.12, 123.39(2C), 107.70 GC-MS (*m/z*): 249 $[M]^+$.

(5Z)-5-(3-nitrobenzylidene)-1,3-thiazolidine-2,4-dione (2c)

Yield: 83%; mp: 260–262 °C; FT-IR (KBr, cm^{-1}): 3418, 3164 (NH), 1746(C=O), 1693 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.70$ (1H, br s, NH), 8.41 (1H, t, $J =$ 1.88 Hz, Ar-H), 8.28–8.26 (1H, m, Ar-H), 7.97(1H, d, $J =$ 7.96 Hz), 7.92 (1H, s, benylidene), 7.78 (1H, t, $J = 8.04$ Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 166.87$ (C=O), 166.79(C=O), 148.11, 135.30, 134.75, 130.47, 129.20, 126.59, 124.10, 124.03; GC-MS (*m/z*): 250$[M]^+$.

(5Z)-5-(3-nitrobenzylidene)-2-thioxo-1,3-thiazolidin-4-one (2d)

Yield: 95%; mp: 235–237 °C; FT-IR (KBr, cm^{-1}): 3430, 3248 (NH), 1693 (C=O), 1172 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 13.90$ (1H, br s, NH), 8.42 (1H, t, $J =$ 1.84 Hz, Ar-H), 8.30–8.28 (1H, m, Ar-H), 7.98 (1H, d, $J =$ 7.84 Hz), 7.80 (1H, t, $J = 7.80$ Hz, Ar-H), 7.77 (1H, s, benylidene); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 194.70$ (C=S), 169.16(C=O), 148.20, 135.63, 134.68, 130.69, 128.66, 124.47, 124.34; GC-MS (*m/z*): 266 $[M]^+$.

(5E)-5-(3-nitrobenzylidene)imidazolidine-2,4-dione (2 g)

Yield: 78%; mp: 265–267 °C; FT-IR (KBr, cm^{-1}): 3491, 3204 (NH), 1779(C=O), 1737 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.94$ (2H, br s, NH), 8.29 (1H, t, $J =$ 1.80 Hz, Ar-H), 8.06–8.03 (1H, m, Ar-H), 7.90 (1H, d, $J =$ 7.88 Hz), 7.57 (1H, t, $J = 8.00$ Hz, Ar-H), 6.45 (1H, s, benylidene); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 165.08$ (C=O), 155.70(C=O), 148.08, 134.86, 134.78, 130.04, 129.55, 123.39, 122.09, 105.34; GC-MS (*m/z*): 233 $[M]^+$.

(5E)-5-(3-nitrobenzylidene)-2-thioxoimidazolidin-4-one (2h)

Yield: 85%; mp: 278–280 °C; FT-IR (KBr, cm^{-1}): 3168,3079 (NH), 1717 (C=O), 1314, 1193 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.17$ (2H, br s, NH), 8.46 (1H, t, $J = 1.60$ Hz, Ar-H), 8.14–8.12 (1H, m, Ar-H), 8.05 (1H, d, $J = 7.80$ Hz), 7.62 (1H, t, $J = 8.00$ Hz, Ar-H), 6.52 (1H, s, benylidene); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 179.97$ (C=S), 165.67(C=O), 148.08, 135.56, 134.25, 130.34, 129.49, 123.98, 122.64, 107.92; GC-MS (*m/z*): 249 $[M]^+$.

General procedure for the synthesis of compounds (3a–3h)

To the stirred suspension of compound **2a/2b/2c/2d/2e/2f/2g/2h** (8 mmol) in 25 mL ethanol, Tin(II) chloride dihydrate (32 mmol) was added and the reaction mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure and the residue obtained was dissolved in 100 mL saturated aqueous $NaHCO_3$ solution. The product was extracted with hot ethyl acetate (5 × 50 mL) and combined organic extract washed with brine (2 × 50 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain **3a**–**3h**.

(5Z)-5-(4-aminobenzylidene)-1,3-thiazolidine-2,4-dione (3a)

Yield: 77%; mp: 246–248 °C; FT-IR (KBr, cm^{-1}): 3471, 3373 (NH_2), 3241 (NH), 1708(C=O), 1669 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.36$ (1H, br s, NH), 7.65 (1H, s, benylidene), 7.34 (2H, d, $J = 8.64$ Hz, Ar-H), 6.71 (2H, d, $J = 8.64$ Hz, Ar-H), 6.16 (2H, s, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 168.08$(C=O), 167.54 (C=O), 151.09, 133.13, 132.15(2C), 120.23, 115.28, 113.97(2C); GC-MS: 220 $[M]^+$.

(5Z)-5-(4-aminobenzylidene)-2-thioxo-1,3-thiazolidin-4-one (3b)

Yield: 88%; mp: 250–252 °C; FT-IR (KBr, cm^{-1}): 3460, 3364 (NH_2), 3036 (NH), 1676 (C=O), 1198 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 13.21$ (1H, br s, NH), 7.44 (1H, s, benylidene), 7.26 (2H, d, $J = 8.72$ Hz, Ar-H), 6.67 (2H, d, $J = 7.00$ Hz, Ar-H), 6.17 (2H, br s, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 194.95$(C=S), 169.46 (C=O), 152.28, 133.48, 133.19(2C), 119.83, 116.70, 114.02(2C); GC-MS: 236 $[M]^+$.

(5E)-5-(4-aminobenzylidene)imidazolidine-2,4-dione (3e)

Yield: 90%; mp: 236–238 °C; FT-IR (KBr, cm^{-1}): 3414, 3337 (NH_2), 3243, 3051 (NH), 1746(C=O), 1705 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.89$ (1H, s, NH), 10.08 (1H, s, NH), 7.30 (2H, d, $J = 8.56$ Hz, Ar-H), 6.60 (2H, d, $J = 8.52$ Hz, Ar-H), 6.30 (1H, s, benylidene), 5.54 (2H, br s, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta =$ 165.65(C=O), 155.40 (C=O), 149.13, 130.92(2C), 123.46, 120.46, 113.90(2C), 110.67; GC-MS: 203 $[M]^+$.

(5E)-5-(4-aminobenzylidene)-2-thioxoimidazolidin-4-one (3f)

Yield: 87%; mp: 225–227 °C; FT-IR (KBr, cm^{-1}): 3440, 3341 (NH_2), 3218 (NH), 1715 (C=O), 1379, 1178(C=S); ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.94$ (1H, br s, NH), 10.11 (1H, br s, NH) 7.30 (2H, d, $J = 8.56$ Hz, Ar-H), 6.57 (2H, d, $J = 8.56$ Hz, Ar-H), 6.28 (1H, s, benylidene), 5.63 (2H, s, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 165.63$ (C=S), 155.39(C=O), 149.53, 131.02(2C), 123.28, 120.10, 113.71(2C), 110.72; GC-MS: 219 $[M]^+$.

(5Z)-5-(3-aminobenzylidene)-1,3-thiazolidine-2,4-dione (3c)

Yield: 83%; mp: 204–206 °C; FT-IR (KBr, cm^{-1}): 3461, 3375 (NH_2), 3159 (NH), 1739(C=O), 1678 (C=MR (400 MHz, DMSO-d_6): $\delta = 12.05$ (1H, br s, NH), 7.59 (1H, s, benylidene), 7.14 (1H, t, $J = 7.80$ Hz, Ar-H), 6.77 (1H, t, $J = 1.80$ Hz, Ar-H), 6.73–6.69 (2H, m, Ar-H), 5.31(2H, br s, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.93$ (C=O), 167.26(C=O), 148.66, 133.38, 132.74, 129.40, 122.28, 118.29, 116.36, 114.58; GC-MS: 220 $[M]^+$.

(5Z)-5-(3-aminobenzylidene)-2-thioxo-1,3-thiazolidin-4-one (3d)

Yield: 92%; mp:185–187 °C; FT-IR (KBr, cm^{-1}): 3450, 3346 (NH_2), 3140 (NH), 1689 (C=O), 1176 (C=S); ^1H NMR (400 MHz, DMSO-d_6): $\delta = 12.54$ (1H, br s, NH), 7.65 (1H, s, benylidene), 7.21 (1H, t, $J = 7.92$ Hz, Ar-H), 6.78 (2H, d, $J = 7.52$ Hz, Ar-H), 6.74–6.71 (1H, m, Ar-H), 5.46 (2H, br s, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta =$ 195.84(C=S), 169.35(C=O), 149.29, 133.34, 132.65, 129.67, 124.29, 119.01, 116.68, 114.17; GC-MS: 236 $[M]^+$.

(5E)-5-(3-aminobenzylidene)imidazolidine-2,4-dione (3g)

Yield: 95%; mp: 173–175 °C; FT-IR (KBr, cm^{-1}): 3414, 3337 (NH_2), 3242, 3051 (NH), 1747 (C=O), 1707 (C=O); ^1H NMR (400 MHz, DMSO-d_6): $\delta = 10.27$ (1H, s, NH), 9.36 (1H, s, NH), 6.18 (1H, t, $J = 7.80$ Hz, Ar-H), 5.94 (1H, t, $J = 1.80$ Hz, Ar-H),5.89 (1H, d, $J = 7.76$ Hz, Ar-H) 5.72–5.69 (1H, m, Ar-H), 5.39 (1H, s, benylidene), 4.06 (2H, br s, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta =$ 164.65(C=O), 154.67(C=O), 147.71, 132.43, 128.27, 126.49, 116.69, 113.62, 108.50; GC-MS: 203 $[M]^+$.

(5E)-5-(3-aminobenzylidene)-2-thioxoimidazolidin-4-one (3h)

Yield: 91%; mp: 210–212 °C; FT-IR (KBr, cm^{-1}): 3419, 3160 (NH_2), 3039 (NH), 1719 (C=O), 1334, 1183 (C=S); ^1H NMR (400 MHz, DMSO δ ppm): 12.23 (1H, br s, NH),11.75 (1H, br s, NH) 7.07 (1H, t, $J = 7.80$ Hz, Ar-H), 6.96 (1H, s, Ar-H), 6.85(1H, d, $J = 8.16$ Hz), 6.66–6.63 (1H, m, Ar-H) 6.34 (1H, s, benylidene), 4.89 (2H, s, NH_2); ^{13}C NMR (100 MHz, DMSO):178.78(C=S), 165.67(C=O), 148.40, 132.63, 129.09, 127.21, 118.70, 115.40, 114.81, 112.55; GC-MS: 219 $[M]^+$.

General procedure for the synthesis of compounds (5a–5h)

A solution of 2-chlorobenzoxazole (1.63 mmol) and amine **3a/3b/3c/3d/3e/3f/3g/3h**(1.63 mmol) in 10 mL ethanol was irradiated in microwave (320 W) for 15 min. The reaction mixture was cooled and the precipitates obtained were filtered and washed with 5 mL of ethanol to get the targeted compound (**5a**–**5h**).

(5Z)-5-[4-(1,3-benzoxazol-2-ylamino)benzylidene]-1,3-thiazolidine-2,4-dione (5a)

Yield: 89%; mp: 257–259 °C; FT-IR (KBr, cm^{-1}): 3355, 3312 (NH), 1723 (C=O), 1686 (C=O);^1H NMR (400 MHz, DMSO-d_6): $\delta = 12.44$ (1H, s, NH), 10.99 (1H, s, NH of linker), 7.94 (2H, d, $J = 8.76$ Hz), 7.74 (1H, s, benzylidene), 7.58 (2H, d, $J = 8.76$ Hz), 7.47–7.44 (2H, m, Ar-H), 7.25–7.21 (1H, m, Ar-H), 7.17–7.13 (1H, m, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 167.96$ (C=O), 167.39 (C=O), 157.28, 146.99, 142.02, 140.69, 131.65, 131.46(2C), 126.50, 124.17, 122.17, 120.62, 117.79(2C), 116.94, 109.16; HRMS (*m/z*): 338.0594 (calcd. for $C_{17}H_{12}N_3O_3S$ 338.0599).

(5Z)-5-[4-(1,3-benzoxazol-2-ylamino)benzylidene]-2-thioxo-1,3-thiazolidin-4-one (5b)

Yield: 91%; mp: 261–263 °C; FT-IR (KBr, cm^{-1}): 3307, 3249 (NH), 1684 (C=O), 1180 (C=S);^1H NMR (400 MHz, DMSO-d_6): $\delta = 13.68$ (1H, s, NH), 11.07 (1H, s, NH of linker), 7.95 (2H, d, $J = 8.80$ Hz), 7.59 (2H, d, $J =$ 8.76 Hz), 7.59 (1H, s, benzylidene), 7.48–7.44 (2H, m, Ar-H), 7.28–7.22 (1H, m, Ar-H), 7.18–7.14 (1H, m, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 195.48$ (C=S), 169.41 (C=O), 157.19, 146.99, 141.98, 141.08, 132.07(2C), 131.74, 126.42, 124.21, 122.50, 122.24, 117.91(2C), 117.00, 109.20; HRMS (*m/z*): 354.0370 (calcd. for $C_{17}H_{12}N_3O_2S_2$ 354.0371).

(5E)-5-[4-(1,3-benzoxazol-2-ylamino)benzylidene] imidazolidine-2,4-dione (5e)

Yield: 90%; mp: 242–244 °C; FT-IR (KBr, cm^{-1}): 3275, 3198 (NH), 1774 (C=O), 1725 (C=O);^1H NMR (400 MHz, DMSO-d_6): $\delta = 11.11$ (1H, s, NH), 10.77 (1H, s, NH), 10.39 (1H, s, NH of linker), 7.81 (2H, d, $J = 8.68$ Hz), 7.60 (2H, d, $J = 8.72$ Hz), 7.46–7.41 (2H, m, Ar-H), 7.24–7.20 (1H, m, Ar-H), 7.14–7.10 (1H, m, Ar-H), 6.41 (1H, s, benzylidene); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 165.50$ (C=O), 157.49 (C=O),155.55, 146.97, 142.24, 138.79, 130.18(2C), 126.63, 126.32, 123.80, 121.61, 117.53, 116.63, 108.71(2C), 108.60; $[M + H]^+$; HRMS (*m/z*): 321.0980 (calcd. for $C_{17}H_{13}N_4O_3$ 321.0988).

(5E)-5-[4-(1,3-benzoxazol-2-ylamino)benzylidene]-2-thioxoimidazolidin-4-one (5f)

Yield: 92%; mp: 214–216 °C; FT-IR (KBr, cm^{-1}): 3160 (NH), 1719 (C=O), 1185 (C=S);^1H NMR (400 MHz, DMSO-d_6): $\delta = 11.22$ (1H, s, NH), 10.88 (1H, s, NH),

10.47 (1H, s, NH of linker), 7.78 (2H, d, $J = 5.84$ Hz), 7.65 (2H, d, $J = 8.80$ Hz), 7.49 (2H, d, $J = 7.60$ Hz), 7.26–7.24 (1H, m, Ar-H), 7.17–7.15 (1H, m, Ar-H), 6.40 (1H, s, benzylidene);^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 179.57$ (C=S), 165.73(C=O), 161.74, 150.24, 141.52, 135.75, 130.79(2C), 128.93, 127.39, 126.16, 125.78, 125.02, 119.90, 111.00(2C), 109.76; HRMS (*m/z*): 337.0754(calcd. for $C_{17}H_{13}N_4O_2S$ 337.0759).

(5Z)-5-[3-(1,3-benzoxazol-2-ylamino)benzylidene]-1,3-thiazolidine-2,4-dione (5c)

Yield: 88%; mp: 198–200 °C; FT-IR (KBr, cm^{-1}): 3314, 3184 (NH), 1737 (C=O), 1692 (C=O);^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.63$ (1H, br s, NH), 10.94 (1H, s, NH of linker), 8.14 (1H, s, Ar-H), 7.87–7.84 (1H, m, Ar-H), 7.80 (1H, s, benzylidene), 7.58–7.50 (3H, m, Ar-H), 7.33–7.27 (2H, m, Ar-H), 7.22–7.18 (1H, m, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 168.09$ (C=O), 167.34 (C=O), 157.65, 146.94, 142.12, 139.52, 133.58, 131.66, 129.94, 124.38, 124.11, 123.93, 121.94, 119.38, 117.53, 116.72, 109.06; HRMS (*m/z*): 338.0597 (calcd. for $C_{17}H_{12}N_3O_3S$ 338.0599).

(5Z)-5-[3-(1,3-benzoxazol-2-ylamino)benzylidene]-2-thioxo-1,3-thiazolidin-4-one (5d)

Yield: 95%; mp: 180–182 °C; FT-IR (KBr, cm^{-1}): 3309, 3189 (NH), 1690 (C=O), 1187 (C=S);^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 13.64$ (1H, br s, NH), 10.83 (1H, s, NH of linker), 8.01 (1H, s, Ar-H), 7.75–7.73 (1H, m, Ar-H), 7.51 (1H, s, benzylidene), 7.45–7.41 (2H, m, Ar-H), 7.39–7.37 (1H, m, Ar-H), 7.22–7.15 (2H, m, Ar-H), 7.10–7.06 (1H, m, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 195.99$ (C=S), 169.41 (C=O), 157.62, 146.94, 142.11, 139.63, 133.46, 131.42, 130.03, 125.93, 125.14, 124.11, 121.95, 119.62, 117.57, 116.66, 109.08; HRMS (*m/z*): 354.0379 (calcd. for $C_{17}H_{12}N_3O_2S_2$ 354.0371).

(5Z)-5-[3-(1,3-benzoxazol-2-ylamino)benzylidene] imidazolidine-2,4-dione (5g)

Yield: 93%; mp: 179.181 °C; FT-IR (KBr, cm^{-1}): 3275, 3197 (NH), 1775 (C=O), 1727 (C=O);^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 11.20$ (1H, s, NH), 10.98 (1H, br s, NH), 10.33 (1H, s, NH of linker), 7.84 (1H, s, Ar-H), 7.77–7.53 (1H, m, Ar-H), 7.45 (d, 1H, $J = 7.40$ Hz), 7.41–7.36 (2H, m, Ar-H),7.29, (d, 1H, $J = 7.80$ Hz) 7.22–7.18 (1H, m, Ar-H), 7.13–7.09 (1H, m, Ar-H), 6.41 (1H, s, benzylidene); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 165.41$ (C=O), 165.35 (C=O), 157.93, 155.61, 147.02, 142.27, 139.04, 134.20, 133.58, 129.41, 128.56, 124.01, 121.73, 118.95, 117.72, 116.68, 108.99; HRMS (*m/z*): 321.0996 (calcd. for $C_{17}H_{13}N_4O_3$ 321.0988).

(5Z)-5-[3-(1,3-benzoxazol-2-ylamino)benzylidene]-2-thioxoimidazolidin-4-one(5h)

Yield: 87%; mp: 208–210 °C; FT-IR (KBr, cm^{-1}): 3403, 3251 (NH), 1728 (C=O), 1178(C=S);^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 12.42$ (1H, s, NH), 12.05 (1H, s, NH), 10.65 (1H, s, NH of linker), 7.89 (1H, s, Ar-H), 7.83–7.80 (1H, m, Ar-H), 7.51 (2H, m, Ar-H), 7.45–7.42 (2H, m, Ar-H),7.25–7.21 (1H, m, Ar-H) 7.16–7.12 (1H, m, Ar-H), 6.46 (1H, s, benzylidene); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta =$ 179.30 (C=S), 165.66 (C=O), 157.89, 147.01, 142.27, 139.04, 132.95, 129.44, 128.36, 124.04, 123.42, 121.75, 119.39, 118.48, 116.74, 111.33, 109.00; HRMS (*m/z*): 337.0769 (calcd. for $C_{17}H_{13}N_4O_2S$ 337.0759).

Molecular docking methods

The crystal structure of the C-terminal domain of human intestinal α-glucosidase (PDB code: 3TOP) was used as a molecular target. The crystal structure complexed with acarbose (original ligand) was downloaded from RCSB Protein Data Bank (PDB). Hydrogen atoms were added, whereas water molecules were removed from the structure of the enzyme and energy was minimized using Gasteiger–Huckel charges and tripos force field in the Sybyl software suit. Benzoxazole-based compounds were assigned Gasteiger–Huckel charges and subsequently minimized via Powel method using SYBYL 7.3 software. The energy-optimized sketched compounds were subjected to docking run at the ligand-binding site of α-glucosidase by the Surflex dock in SYBYL 7.3 [21]. Docking analysis was conducted using the Surflex dock module to predict and examine the binding modes of the synthesized derivatives at the active site of α-glucosidase. The hydrogen-bonding interactions (amino acid residues and bond distances) of the synthesized molecules at the respective active sites were also compared to standard inhibitor acarbose (Table 1 and Fig. 1).

In vitro enzymatic starch digestion assay

in vitro enzymatic starch digestion method with some modifications was followed [22]. One hundred milligrams of corn starch was gelatinized in 3 mL distilled water with or without test compound or acarbose (a standard drug used). To this solution, 4 µg α-amylase was added, vortexed, and then the mixture was incubated at 80 °C for 20 min. After 20 min incubation, 3 mL of the mixture was diluted to 10 mL by adding distilled water. Then, 1 mL of the above solution was taken and added to 2 mL of 0.1 M sodium acetate buffer (pH = 4.75). To this 3 mL mixture,

30 µg of α-glucosidase was added, and the mixture was again incubated at 60 °C for 30 min. Control samples were having neither acarbose nor test compound. Following equation was used to calculate the rate of inhibition of the test compounds on enzymatic starch digestion:

(%) inhibition of enzymatic starch digestion $= [A_o - A_i/A_o] \times 100$, where $A_o =$ absorbance of the control sample and $A_i =$ Absorbance given by test compound.

IC_{50} values (in µM) were determined by plotting the graph between percentage inhibition of starch digestion versus different concentrations of test compounds.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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