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New tetrazoloquinolinyl methoxyphenyl-4-thiazolidinones: synthesis and antihyperglycemic evaluation

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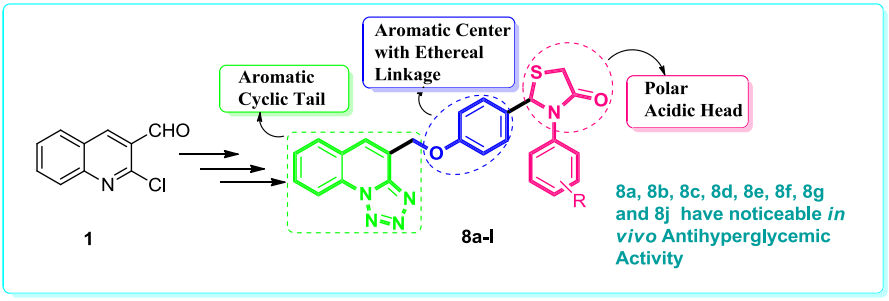
Abstract We report synthesis and in vivo antihyperglycemic evaluation of new 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones (**8a–l**). The title 4-thiazolidinones were synthesized by one-pot cyclocondensation of new 4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)benzaldehyde (**5**), anilines, and mercaptoacetic acid in PEG-400. The required aldehyde (**5**) was also synthesized, starting from 2-chloroquinoline-3-carbaldehyde via a successive multistep route. The newly synthesized products were thoroughly characterized based on their spectral data. Amongst them, compounds **8a–g**, **j** exhibited notable in vivo antihyperglycemic activity. Compounds **8f**, **g** showed percentage improvement in oral glucose tolerance of 18.9 and 20.7, respectively, compared with 28.3 for the reference metformin.

Graphical Abstract



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Introduction

Diabetes mellitus is a major metabolic disorder, being considered to be one of the greatest health catastrophes in the world. Approximately 415 million people are affected by diabetes, and this number is predicted to increase to 642 million by 2040 [1]. Non-insulin-dependent diabetes mellitus (NIDDM/type 2) is the most predominant form of diabetes; it is a complex metabolic disorder with multiple heterogeneous etiologies, characterized by insulin resistance and impaired insulin secretion. These metabolic disorders cause hyperglycemia, which is significantly responsible for diabetic complications [2–4]. Microangiopathic complications of untreated or inadequately treated diabetes include neuropathy, nephropathy, retinopathy, obesity, dyslipidemia, hypertension, and other cardiovascular diseases. These are believed to be triggered by excessive protein glycation due to the higher level of circulating glucose, i.e., hyperglycemia [5–9]. Hence, in recent years, several researchers have focused their attention on development of dual-acting (blood glucose and lipid lowering) drugs [10–16].

Most oral hyperglycemic drugs currently used for treatment of type 2 diabetes mellitus (T2DM) are peroxisome proliferator-activated receptor γ (PPARγ) agonists, i.e., thiazolidinediones (TZDs), sulfonylureas, biguanides, α-glucosidase inhibitors, and dipeptidyl peptidase (DPP) IV inhibitors [17–19]. They have beneficial effects in patients with T2DM, effectively enhancing insulin secretion and/or decreasing glucose absorption. Enormous numbers of drugs on the market have shown attractive profiles, but none of them fully address the problems of T2DM treatment, and these agents are often associated with undesired side-effects, including hyperglycemia, weight gain, gastrointestinal disorders, and lactic acidosis [20]. Therefore, there is a continuing quest to develop therapeutics with higher efficacy and lower toxicity for diabetes mellitus.

Rosiglitazone (**1**) [21] and pioglitazone (**2**) [22] (Fig. 2) are TZDs used clinically to treat and control diabetes mellitus. However, their use is accompanied by undesirable effects such as cardiovascular risk and bladder tumors [23–25]. TZDs act mainly by improving peripheral insulin sensitivity through eliciting pharmacological actions by binding the receptor (PPARγ) at its active sites. The exact mode of action of clinically used TZDs was reported recently [26, 27]: TZDs were found to be typical PPARγ agonists, with all of them having typical structural features including acidic head (2,4-TZDs) and cyclic tail (pyridine and other heterocyclic rings) with alkoxy linker and hydrophobic spacer ring (Fig. 1). Efforts are underway

Fig. 1 Representation of peroxisome proliferator-activated receptor γ (PPARγ) agonist

to modify these sites of clinical TZDs to generate a library of molecules with various degrees of activity [28–31]. In this regard, over the last decade, we have also been actively engaged in developing new TZDs to identify potential antidiabetic agents [32–37].

4-Thiazolidinones with different biodynamic heteryl substituents are found to serve as privileged scaffolds and are gaining importance due to their chemotherapeutical value [38–40]. Recently, new analogues of rosiglitazone (**3**) in which the structural sequence of the skeleton in Fig. 1 is modified to the general skeleton shown in Fig. 2, bearing 4-thiazolidinones as acidic head, a central phenyl ring, and a hydrophobic tail group joined by ethereal linker, have been synthesized and their antidiabetic activity evaluated [41]. 4-Thiazolidinones with 2-mercaptobenzimidazolyl (**4**) [42], coumarinyl (**5**) [43], and pyrazolyl (**6**) [44] scaffolds have been reported, and some of them have displayed potential antidiabetic activity (Fig. 2).

Quinoline motifs are well explored as bioactive agents [45, 46]. Recently, reported quinoline carboxyguanidines were found to possess antihyperglycemic activity [47]. Yohei Ikuma et al. reported a novel series of 3*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-ones as DPP IV inhibitors [48, 49]. To enhance the bioavailability of imidazoloquinolines, their carboxylate prodrugs have also been prepared, being found to display notable antidiabetic activity [50]. Recently, novel 4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazones and their evaluation as in vitro α-glucosidase inhibitors were reported [51]. Molecules/compounds with tetrazolo[1,5-*a*]quinolinyl scaffold have shown various bioactivities [52–59]. The aryloxy linker is a necessary component in the molecular framework of the TZD class of antidiabetic agents [21, 22, 60, 61].

In continuation of our antidiabetic drug discovery program [32–37, 62, 63] and to generate a library of new TZDs, we replaced the acidic head and cyclic tail of

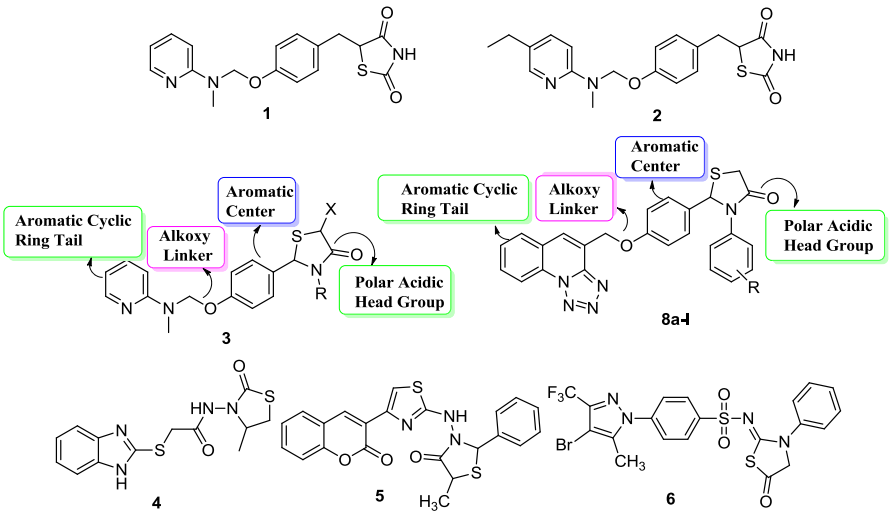
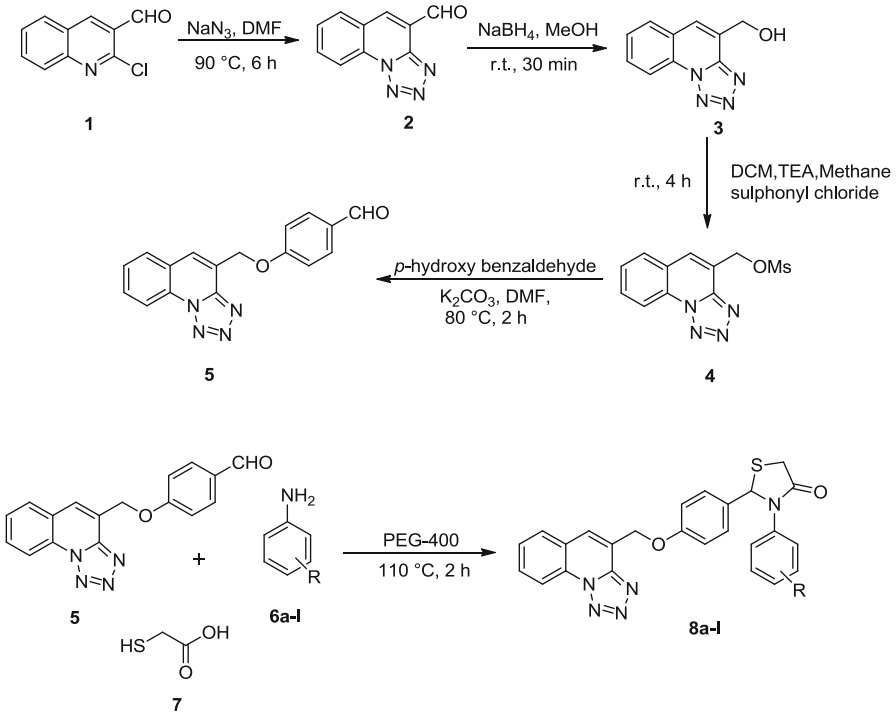


Fig. 2 Antidiabetic agents containing 2,4-thiazolidinediones and 4-thiazolidinones with representative structure of target compound

classical TZDs with 4-thiazolidinone and quinolinotetrazole scaffolds (Fig. 2), respectively, in the hope of obtaining molecules with enhanced antihyperglycemic activity. Here, we considered it worthwhile to adopt the strategy of coupling three chemically different but pharmacologically compatible moieties, viz. 4-thiazolidinones, tetrazolo[1,5-*a*]quinoline, and phenyl ring, in a molecular frame using alkoxy linker to create new TZD analogues with potential antihyperglycemic activity.

Results and discussion

We report herein synthesis of new tetrazoloquinolinyl methoxyphenyl-4-thiazolidinones using PEG-400 as green reaction catalyst and medium. New 4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)benzaldehyde (**5**), a key intermediate required for synthesis of the target compounds, was prepared by following the reaction sequences outlined in Scheme 1. It was prepared from known 2-chloroquinoline-3-carbaldehyde (**1**) [64]. Compound **1**, when condensed with sodium azide in dimethylformamide (DMF), gave tetrazolo[1,5-*a*]quinoline-4-carbaldehyde (**2**) [65]. In the next step, the tetrazoloquinolinyl aldehyde **2** was reduced by sodium borohydride to obtain tetrazolo[1,5-*a*]quinolin-4-yl methanol (**3**) by following a reported procedure [66]. The quinolinyl methanol (**3**), when allowed to react with methane sulfonyl chloride



Scheme 1 Synthesis of new 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl) thiazolidin-4-ones

in presence of triethylamine (TEA) in DCM at 0 °C, yielded the corresponding mesylate, tetrazolo[1,5-*a*]quinolin-4-ylmethyl methanesulfonate (**4**). The sulfonate **4**, on condensation with *p*-hydroxybenzaldehyde in DMF in presence of K_2CO_3, then afforded the required precursor 4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)benzaldehyde (**5**) with better yield. One-pot cyclocondensation of the aldehyde **5**, anilines **6a–l**, and mercaptoacetic acid was carried out in PEG-400 at 110 °C to obtain 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones **8a–l** in moderate to good yield (Scheme 1).

All synthesized intermediates and title products were characterized using their ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and high-resolution mass spectroscopy (HRMS) spectral data. The ^{1}H NMR spectrum of compound **8g** displayed characteristic peaks for a pair of doublets at δ 3.91 and 3.99 ppm, due to geminal coupling between two hydrogens of S–CH_2–C=O, a sharp singlet at δ 5.98 ppm, corresponding to proton of N–CH–S, and a singlet at δ 5.55 ppm due to methylene proton. Three characteristic carbon signals were observed at δ 33.5, 64.6, and 171.1 ppm in the ^{13}C NMR spectrum of compound **8g** owing to carbons of S–CH_2–CO, N–CH–S, and C=O group, respectively, confirming presence of 4-thiazolidinone ring in **8g**. The HRMS spectrum of compound **8g** further confirmed the structure, as it displayed an $[M+H]^+$ ion peak at *m/z* 484.1444, consistent with the molecular formula $C_{26}H_{21}N_5O_3S$.

Antihyperglycemic activity

Improvement of oral glucose tolerance in Sucrose-loaded rats

Table 1 presents the effects of compounds **8a–l** on improvement of oral glucose tolerance in a sucrose-loaded rat model. The standard antidiabetic drug metformin was taken as positive standard. It is evident from the results that compounds **8a–g**, **j** showed significant improvement of oral glucose tolerance of sucrose-loaded rats. In sucrose-loaded normoglycemic rats, at dose of 100 mg/kg, compounds **8a–g**, **j** showed improvement of oral glucose tolerance of 14.5 ($p < 0.05$), 13.1 ($p < 0.05$), 12.9 ($p < 0.05$), 16.6 ($p < 0.05$), 16.9 ($p < 0.05$), 18.9 ($p < 0.01$), 20.7 ($p < 0.01$), and 17.8 % ($p < 0.05$), respectively, during 0–120 min. The standard drug metformin showed around 28.3 % ($p < 0.01$) improvement of oral glucose tolerance in the sucrose-loaded rat model at the tested dose of 100 mg/kg p.o. (Fig. 3).

The title compounds are analogues of existing TZDs. The mode of action as PPARγ agonists of the existing TZDs was described in the "Introduction." Here, the acidic head is formed from *N*-aryl-substituted thiazolidinones, and it seems that aryl moiety with substituents such as methoxy, bromo, nitro, and chloro might enhance the acidic behavior of the 4-thiazolidinone through either conjugation/mesomeric or inductive effect, resulting in binding with active sites of PPARγ and notable antihyperglycemic activity.

Table 1 Effect of samples, i.e., **8a–l**, and standard drug metformin on improvement of oral glucose tolerance in sucrose-loaded rats

Compound	R	Dose (mg/kg)	% Improvement in oral glucose tolerance (0–120 min)
8a	H	100	14.5*
8b	4-Cl	100	13.1*
8c	4-OC_2H_5	100	12.9*
8d	4-CH_3	100	16.6*
8e	4-NO_2	100	16.9*
8f	4-Br	100	18.9**
8g	4-OCH_3	100	20.7**
8h	2,4-Difluoro	100	9.66
8i	2,5-Dichloro	100	6.72
8j	2-Cl	100	17.8*
8k	2-Br	100	11.1
8l	3-OCH_3	100	6.30
Metformin	–	100	28.3**

Compound no. (significance): **8a** ($p < 0.05$), **8b** ($p < 0.05$), **8c** ($p < 0.05$), **8d** ($p < 0.05$), **8e** ($p < 0.05$), **8f** ($p < 0.01$), **8g** ($p < 0.01$), **8j** ($p < 0.05$)

p-Value (statistically significance difference) was set at the following levels: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

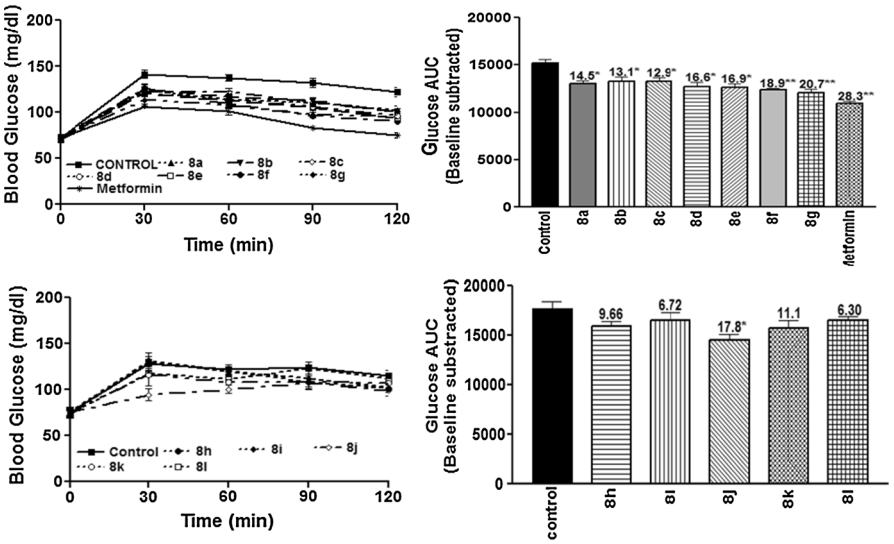


Fig. 3 Effect of samples, i.e., **8a–l**, and standard drug metformin on improvement of oral glucose tolerance of sucrose-loaded rats

Conclusions

We report a novel, more convenient, multistep route for synthesis of new 3-substituted phenyl-2-(4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-ones from freshly prepared 2-chloroquinoline-3-carbaldehyde. Amongst

the synthesized 4-thiazolidinones, compounds **8a**–**g**, **j** displayed notable in vivo antihyperglycemic activity. This work can therefore inspire the preparation of a library of analogues of this series to obtain better leads for treating type 2 diabetic mellitus.

Experimental

Chemicals and solvents required were procured from Merck, Spectrochem, and S.D. Fine-Chem. Melting points were determined in open capillary and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Fourier-transform infrared (FTIR) attenuated total reflection (ATR) instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300–500 (FT-NMR) and Bruker DRX-300 instrument, respectively, using $CDCl_3$/dimethyl sulfoxide (DMSO)-d_6 as solvents and tetramethylsilane (TMS) as internal standard. Chemical shifts are expressed in δ (ppm). High-resolution mass spectroscopy (HRMS) was carried out on an Agilent 6520 quadrupole time-of-flight (QTOF) electrospray ionization (ESI) HRMS instrument, and mass spectra on a JEOL-Accu TOF DART-MS-T 100Lc. The purity of the synthesized compounds was checked by thin-layer chromatography (TLC) using Merck silica gel $60F_{254}$ aluminum sheet with hexane:ethyl acetate as eluent. Metformin and STZ were purchased from Sigma Aldrich Co., USA. One-touch glucometer and glucostrips were purchased from Roche Diagnostics India Ltd.

*General procedure for synthesis of tetrazolo[1,5-a]quinolin-4-ylmethyl methanesulfonate (**4**)* Tetrazolo[1,5-*a*]quinolin-4-yl methanol (**3**) (7 g, 0.035 mol) was dissolved in dichloromethane (DCM) (70 ml). To this solution triethylamine (TEA) (7.39 ml, 0.053 mol) was added, and the solution was stirred for 30 min. To this stirred solution, methane sulfonyl chloride (3.1 ml, 0.039 mol) was added in portions at 0–5 °C, followed by stirring for 4 h. Reaction progress was monitored by thin-layer chromatography (TLC). After 4 h of reaction, solvent was removed from the reaction mass under reduced pressure. The residue was poured onto crushed ice. The thus-obtained solid was filtered, washed with water, and dried. It was crystallized and used for further reaction.

*Tetrazolo[1,5-a]quinolin-4-ylmethyl methanesulfonate (**4**)* Compound **4** was obtained as off-white solid in 82 % yield. M.p. 169–171 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.05 (s, 3H, methyl), 5.12 (s, 2H, methylene), and 7.75–8.71 (m, 5H, quinoline-H).

*General procedure for synthesis of 4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)benzaldehyde (**5**)* A mixture of 4-hydroxybenzaldehyde (1.89 g, 0.015 mol) and potassium carbonate (2.90 g, 0.021 mol) was stirred in DMF (30 ml) for 30 min at 90 °C. To this, tetrazolo[1,5-*a*]quinolin-4-ylmethyl 4-methylbenzenesulfonate (**4**) (5 g, 0.014 mol) was added, and the reaction mass was further stirred at 90 °C. Reaction progress was monitored by thin-layer chromatography (TLC). After 2 h, the reaction mass was allowed to cool and poured onto crushed ice. The obtained solid was filtered, washed with water, dried, and crystallized using ethanol.

*4-(Tetrazolo[1,5-a]quinolin-4-ylmethoxy)benzaldehyde (**5**)* Compound **5** was obtained as off-white solid in 76 % yield. M.p. 159–161 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.70 (s, 2H), 7.21–8.72 (m, 9H, Ar-H and quinoline-H, merged peaks), and 9.93 (s, 1H, aldehydic); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 64.7 (CH_2), 115.2, 117, 121.9, 123.8, 128.3, 129.1, 129.9, 130.2, 130.8, 131.2, 132.1, 146, 162.7, 190.1 (C=O); HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{12}N_4NaO_2$ 327.0858, found 327.0875 and $[M+K]^+$ calculated for $C_{17}H_{12}N_4KO_2$ 343.0597, found 343.0615.

*General procedure for synthesis of 3-phenyl-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8a**)* A mixture of 4-(tetrazolo[1,5-*a*]quinolin-4-ylmethoxy)benzaldehyde (**5**) (1 g, 0.0032 mol), anilines (**6a–l**) (0.30 g, 0.0032 mol), and mercaptoacetic acid (**7**) (0.90 g, 0.0098 mol) was heated in PEG-400 (5 ml) at 110 °C. Reaction progress was monitored by thin-layer chromatography (TLC). After 2 h of heating at 110 °C, the reaction mass was allowed to cool at room temperature and poured into ice-cold water and neutralized with $NaHCO_3$. The thus-obtained crude product was then filtered and crystallized from ethanol. Similarly other compounds (**8b–l**) were synthesized using different substituted anilines.

*3-Phenyl-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8a**)* Compound **8a** was obtained as off-white solid via cyclocondensation reaction between aldehyde **5**, aniline, and mercaptoacetic acid in 2 h in 84 % yield. M.p. 121–123 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.92 (d, $J = 16$ Hz, 1H, methylene), 3.99 (d, $J = 16$ Hz, 1H methylene), 5.55 (s, 2H, methylene), 6.09 (s, 1H, methine), and 7.12–8.71 (m, 14H, Ar-H and quinoline-H, merged peaks); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 33.6 (CH_2), 64.6 (CH_2), 65.3 (CH), 115.1, 116.9, 120.1, 122.4, 123.9, 124.8, 125.9, 127.6, 128.2, 128.8, 129.1, 129.2, 129.7, 131.1, 132.4, 137.4, 134.6, 146.1, 158.3, 167, 171 (C=O); HRMS (ESI) $[M+H]^+$ calculated for $C_{25}H_{20}N_5O_2S$ 454.1338, found 454.1329.

*3-(4-Chlorophenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8b**)* Compound **8b** was obtained as off-white solid via cyclocondensation reaction between aldehyde **5**, 4-chloroaniline, and mercaptoacetic acid in 2 h in 87 % yield. M.p. 110–112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 3.88 (d, $J = 16$ Hz, 1H, methylene), 3.90 (d, $J = 16$ Hz, 1H, methylene), 5.56 (s, 2H, methylene), 5.98 (s, 1H, methine), and 6.96–8.72 (m, 13H, Ar-H and quinoline-H, merged peaks); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 32.8 (CH_2), 63.0 (CH_2), 64.7 (CH), 115, 116.1, 120.8, 121.8, 123.8, 127.3, 128.2, 128.6, 128.2, 128.8, 129.5, 130.6, 131.1, 131.3, 132.1, 136.6, 137.7, 146.2, 158, 166.8, 170.4 (C=O); HRMS (ESI) $[M+H]^+$ calculated for $C_{25}H_{19}ClN_5O_2S$ 488.0948, found 488.1123.

*3-(4-Ethoxyphenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8c**)* Compound **8c** was obtained as off-white solid via cyclocondensation reaction between aldehyde **5**, 4-ethoxyaniline, and mercaptoacetic acid in 2 h in 81 % yield. M.p. 113–115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (*t*, $J = 8$ Hz, 3H, $OCH_2\mathbf{CH_3}$), 3.87 (*q*, $J = 8$ Hz, 2H, $O\mathbf{CH}_2CH_3$), 3.96 (d, $J = 16$ Hz, 1H, methylene), 4.00 (d, $J = 16$ Hz, 1H, methylene), 5.48 (s, 2H, methylene), 6.34 (s,

1H, methine), and 7.03–8.57 (m, 13H, Ar-H and quinoline-H, merged peaks); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.6 (CH_3), 32.6 (CH_2), 63.1 (CH_2), 63.5 (CH_2), 64.7 (CH), 114.3, 114.9, 116.1, 120.8, 121.8, 123.6, 127.4, 128.2, 128.8, 129.5, 129.6, 130.2, 131.1, 131.3, 132.8, 132.7, 146.2, 154.7, 156.8, 157.9, 166.1, 170.3 (C=O); HRMS (ESI) $[M+H]^+$ calculated for $C_{27}H_{24}N_5O_3S$ 498.1600, found 498.1591.

*2-(4-(Tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)-3-(p-tolyl)thiazolidin-4-one (**8d**)* Compound **8d** was obtained as off-white solid via cyclocondensation reaction between aldehyde **5**, 4-methylaniline, and mercaptoacetic acid in 2 h in 80 % yield. M.p. 109–111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H, methyl), 3.87 (d, $J = 16$ Hz, 1H, methylene), 3.96 (d, $J = 16$ Hz, 1H, methylene), 5.55 (s, 2H, methylene), 6.04 (s, 1H, methine), and 6.98–8.72 (m, 13H, Ar-H and quinoline-H, merged peaks); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.1 (CH_3), 32.6 (CH_2), 63.4 (CH_2), 64.8 (CH), 113.8, 113.9, 114.9, 116.1, 120.8, 121.8, 123.6, 127.4, 128.2, 128.8, 129.5, 129.6, 130.3, 132.3, 131.9, 136.7, 146.2, 155.4, 157.5, 157.9, 166.1, 170.3 (C=O); HRMS (ESI) $[M+H]^+$ calculated for $C_{26}H_{22}N_5O_2S$ 468.1494, found 468.1371.

*3-(4-Nitrophenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8e**)* Compound **8e** was obtained as off-white solid via cyclocondensation reaction between aldehyde **5**, 4-nitroaniline, and mercaptoacetic acid in 2 h in 83 % yield. M.p. 151–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.87 (d, $J = 16$ Hz, 1H, methylene), 3.99 (d, $J = 16$ Hz, 1H, methylene), 5.56 (s, 2H, methylene), 5.98 (s, 1H, methine), and 6.78–8.71 (m, 13H, Ar-H and quinoline-H, merged peaks); DART MS (ESI^+, *m/z*): 499 (M^+); Anal. calcd. for $C_{25}H_{18}N_6O_4S$: C, 60.23; H, 3.64; N, 16.86; S, 6.43; found: C, 60.35; H, 3.79; N, 16.98; S, 6.35.

*3-(4-Bromophenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8f**)* Compound **8f** was obtained as pale-yellow solid via cyclocondensation reaction between aldehyde **5**, 4-bromoaniline, and mercaptoacetic acid in 2 h in 90 % yield. M.p. 105–107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.85 (d, $J = 16$ Hz, 1H, methylene), 3.92 (d, $J = 16$ Hz, 1H, methylene), 5.57 (s, 2H, methylene), 6.07 (s, 1H, methine), and 6.99–8.73 (m, 13H, Ar-H and quinoline-H, merged peaks); DART MS (ESI^+, *m/z*): 532 (M^+); Anal. calcd. for $C_{25}H_{18}BrN_5O_2S$: C, 56.40; H, 3.41; N, 13.15; S, 6.02; found: C, 56.35; H, 3.52; N, 13.22; S, 6.06.

*3-(4-Methoxyphenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8g**)* Compound **8g** was obtained as yellow solid via cyclocondensation reaction between aldehyde **5**, 4-methoxyaniline, and mercaptoacetic acid in 2 h in 79 % yield. M.p. 118–120 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.72 (s, 3H, methoxy), 3.91 (d, $J = 16$ Hz, 1H, methylene), 3.99 (d, $J = 16$ Hz, 1H, methylene), 5.55 (s, 2H, methylene), 5.98 (s, 1H, methine), and 6.77–8.78 (m, 13H, Ar-H and quinoline-H, merged peaks); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 33.5 (CH_2), 55.6 (CH_3), 64.6 (CH_2), 65.6 (CH), 114.1, 114.5, 115.1, 116.8, 121.7, 122.3, 123.9, 127.7, 128.3, 129, 129.1, 129.8, 130, 130.2, 131.1, 132.5, 146.1, 156.6, 158.3, 158.5, 166.9, 171.1 (C=O); HRMS (ESI) $[M+H]^+$ calculated for $C_{26}H_{22}N_5O_3S$ 484.1443, found 484.1444.

*3-(2,4-Difluorophenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8h**)* Compound **8h** was obtained as off-white solid via cyclocondensation reaction between aldehyde **5**, 2,4-difluoroaniline, and mercaptoacetic acid in 2 h in 78 % yield. M.p. 119–121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.87 (d, $J = 16$ Hz, 1H, methylene), 3.95 (d, $J = 16$ Hz, 1H, methylene), 5.48 (s, 2H, methylene), 6.35 (s, 1H, methine), and 7.02–8.27 (m, 12H, Ar-H and quinoline-H, merged peaks); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 32.7 (CH_2), 55.6 (CH_2), 63.1 (CH), 114.5, 116.1, 119.3, 121.6, 123.5, 124.2, 125.3, 125.6, 128.6, 128.8, 129.1, 129.3, 131.5, 132.3, 132.5, 135.9, 136.2, 145.9, 152.6, 157, 166.4, 170.3 (C=O); HRMS (ESI) $[M+H]^+$ calculated for $C_{25}H_{18}F_2N_5O_2S$ 490.1149, found 490.1095.

*3-(2,5-Dichlorophenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8i**)* Compound **8i** was obtained as pale-yellow solid via cyclocondensation reaction between aldehyde **5**, 2,5-dichloroaniline, and mercaptoacetic acid in 2 h in 77 % yield. M.p. 144–146 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (d, $J = 16$ Hz, 1H, methylene), 3.98 (d, $J = 16$ Hz, 1H, methylene), 5.58 (s, 2H, methylene), 6.14 (s, 1H, methine), and 7.22–8.10 (m, 12H, Ar-H and quinoline-H, merged peaks); DART MS (ESI^+, *m/z*): 522 (M^+); Anal. calcd. for $C_{25}H_{17}Cl_2N_5O_2S$: C, 57.48; H, 3.28; N, 13.41; S, 6.14; found: C, 57.40; H, 3.32; N, 13.21; S, 6.34.

*3-(2-Chlorophenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8j**)* Compound **8j** was obtained as off-white solid via cyclocondensation reaction between aldehyde **5**, 2-chloroaniline, and mercaptoacetic acid in 2 h in 74 % yield. M.p. 108–110 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (d, $J = 16$ Hz, 1H, methylene), 3.99 (d, $J = 16$ Hz, 1H, methylene), 5.47 (s, 2H, methylene), 5.88 (s, 1H, methine), and 7.01–8.72 (m, 13H, Ar-H and quinoline-H, merged peaks); DART MS (ESI^+, *m/z*): 488 (M^+); Anal. calcd. for $C_{25}H_{18}ClN_5O_2S$: C, 61.54; H, 3.72; N, 14.35; S, 6.57; found: C, 61.71; H, 3.69; N, 14.23; S, 6.67.

*3-(2-Bromophenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8k**)* Compound **8k** was obtained as pale-yellow solid via cyclocondensation reaction between aldehyde **5**, 2-bromoaniline, and mercaptoacetic acid in 2 h in 80 % yield. M.p. 117–119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84 (d, $J = 16$ Hz, 1H, methylene), 4.01 (d, $J = 16$ Hz, 1H, methylene), 5.58 (s, 2H, methylene), 6.22 (s, 1H, methine), and 6.94–8.60 (m, 13H, Ar-H and quinoline-H, merged peaks); DART MS (ESI^+, *m/z*): 532 (M^+); Anal. calcd. for $C_{25}H_{18}BrN_5O_2S$: C, 56.40; H, 3.41; N, 13.15; S, 6.02; found: C, 56.52; H, 3.49; N, 13.10; S, 6.10.

*3-(3-Methoxyphenyl)-2-(4-(tetrazolo[1,5-a]quinolin-4-ylmethoxy)phenyl)thiazolidin-4-one (**8l**)* Compound **8l** was obtained as yellow solid via cyclocondensation reaction between aldehyde **5**, 3-methoxyaniline, and mercaptoacetic acid in 2 h in 78 % yield. M.p. 136–138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.41 (s, 3H, methoxy), 3.90 (d, $J = 16$ Hz, 1H, methylene), 4.00 (d, $J = 16$ Hz, 1H, methylene), 5.51 (s, 2H, methylene), 5.99 (s, 1H, methine), and 7.12–8.71 (m, 13H, Ar-H and quinoline-H, merged peaks); DART MS (ESI^+, *m/z*): 484 (M^+); Anal. calcd. for $C_{26}H_{21}N_5O_3S$: C, 64.58; H, 4.38; N, 14.48; S, 6.63; found: C, 64.76; H, 4.42; N, 14.56; S, 6.52.

Experimental protocol for biological activity

Antihyperglycemic activity evaluation

Compounds **8a–l** were evaluated for their antihyperglycemic activity in a sucrose-loaded Sprague–Dawley-strain male albino rat model.

Procurement and selection of animals

Male albino rats of Sprague–Dawley strain (8–10 weeks of age, body weight 150 ± 20 g) were procured from the animal colony of the Central Drug Research Institute. Research on animals was conducted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) formed by the Government of India in 1964. Rats were always placed in groups of five in polypropylene cages and provided standard environmental conditions. The animals had free access to pellet diet and tap water unless otherwise stated.

Statistical analysis

Analysis of statistical significance of differences in measurements between samples was done by using Dunnett's test (Prism software), denoted by p values. Statistically significance difference was set at the following levels: * represents $p < 0.05$, ** represents $p < 0.01$, and *** represents $p < 0.001$.

Effect in sucrose-loaded rat model

Male albino rats of Sprague–Dawley strain were selected for this study. The fasting blood glucose level of each animal was checked by glucometer using glucostrips (ACCU-CHEK) after 16-h starvation. Animals showing blood glucose level between 60 and 80 mg/dl at 0 min were finally selected and divided into groups of five animals in each. Rats of experimental group were administered suspension of the test sample orally, prepared in 1.0 % gum acacia (vehicle) at desired dose level, i.e., 100 mg/kg body weight of compounds or standard antidiabetic drug metformin. This dose of 100 mg/kg in the rat was selected on the basis of the response to the standard antidiabetic drug metformin: Metformin shows response at this dose. Animals of control group were given an equal amount of 1.0 % gum acacia and termed "sham control." An oral sucrose load of 10 g/kg body weight was always given to each animal exactly 30 min after administration of the test sample/vehicle. The blood glucose profile of each rat was again determined at 30, 60, 90, and 120 min post administration of sucrose by glucostrips and the area under the curve (AUC) determined. Food but not water was withheld from the cages during the course of experimentation. Comparison of the AUC of experimental versus control group determined the overall improvement of oral glucose tolerance by each

compound. Statistical analysis was carried out by using Dunnett's test (Prism software) [67].

The dose of test compound was kept at 100 mg/kg, as the effective dose of metformin was found to be 100 mg/kg in the sucrose-loaded rat model. The improvement in AUC for test compounds **8a–g**, **j** was found to lie in the range of 12.9–20.7 %, being significant. The gold-standard antidiabetic drug, i.e. metformin, showed around 28.3 % improvement. The sucrose dose was found to be maximum at 10 g/kg, so this dose of sucrose was used in all experiments. The significance in AUC even for the 12.9 % result for compound **8c** shows the potency of the compound. Compounds **8a–g**, **j** were found to be potent in the sucrose-loaded rat model.

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