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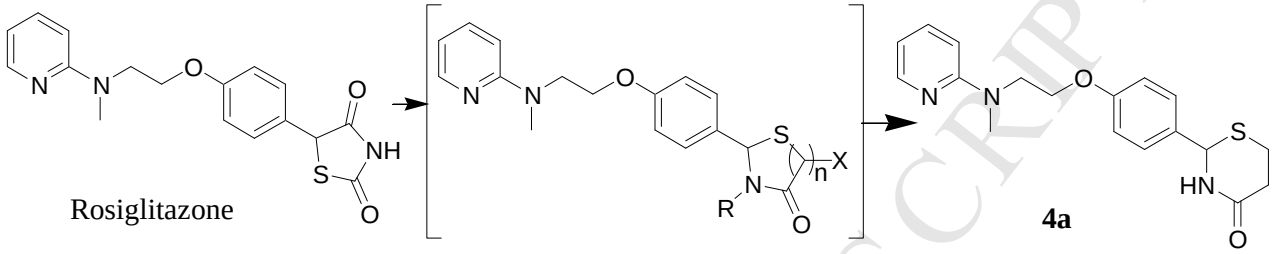
Graphical Abstract

A series of thiazolidin-2,4-dione and thiazinan-4-one are reported with promising anti-hyperglycemic activity both *in vitro* and *in vivo* models. The thiazinan-4-one derivative 4a showed maximal (45%) improvement in oral glucose tolerance test in db/db mice at 30 mg/kg oral dose.



Rosiglitazone derivatives **3**-**7**

R = H, alkyl, aryl etc; X = H, CH_3; n = 1, 2

Highlights

- A convenient synthesis of thiazolidinones and thiazenans are described
- Structural analogs of rosiglitazone as novel insulin sensitizers
- The compounds exhibited promising anti hyperglycaemic and lipid lowering activity
- In vitro and in vivo assay results are described

Thiazolidin-4-one and Thiazinan-4-one Derivatives Analogous to Rosiglitazone as Potential Antihyperglycaemic and Antidyslipidemic Agents

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Abstract

A number of thiazolidin-4-one and Thiazinan-4-one derivatives were prepared by three component condensation in one pot reaction method. These compounds were evaluated for anti-hyperglycemic activity by in vitro and in vivo assay systems. The compounds with thiazolidin-4-one and thiazinan-4-one moieties exhibited significant anti-hyperglycemic activity. A few compounds (**3a**, **3b**, **4a** and **4b**) have exhibited both anti-hyperglycemic and anti-dyslipidemic activities. Among them the thiazinan-4-one derivative **4a** showed maximal (45%) improvement in oral glucose tolerance test in db/db mice at 30 mg/kg oral dose.

Key words: Thiazolidin-4-ones, antihyperglycemic, antidyslipidemic, insulin resistance reversal, Rosiglitazone, Metformin

1. Introduction

Type 2 diabetes is a chronic metabolic disorder characterized by abnormal insulin secretion and insulin resistance [1]. Current therapeutic approaches include combination of regulated diet with concomitant medication. The available antidiabetic drugs for control of type 2 diabetes include sulfonylurea, biguanides, α-glucosidase inhibitors, thiazolidin-2,4-diones (TZDs), DPP IV inhibitors [2]. Among these TZDs is an important class that enhances insulin sensitivity of the target cells via activation of Peroxisome Proliferator-Activated Receptor-gamma (PPAR-γ), a nuclear receptor involved primarily in glucose homeostasis, adipogenesis, inflammatory diseases and certain types of cancers [3]. Despite clinical usage this class of drugs induces adverse effects namely, weight increase, edema, and myocardial infarction and bone loss [4,5]. Detailed biochemical studies have led to identification of receptor sub-types namely alpha, gamma and delta. Furthermore, it has been established that selective activation of PPAR gamma sub-type is primarily responsible for the observed undesirable effects. Therefore, partial agonists are considered a safer alternative to currently used thiazolidinediones (TZDs) [6-9].

The thiazolidindione analogs explored so far may be visualized as having essentially an acidic head group, a central phenyl ring and a hydrophobic tail group joined by alkyl linker. Several modifications have been attempted in the tail and head groups towards developing more potent and safer antihyperglycaemic agents [10-13]. The structural modifications carried out in the head and tail portions include structures like indole, [14,15] indinone, [16] indolyl acetic acid, [17] thiazole and oxazoles, [18], oxazolidinedione and isoxazolidinedione moieties [19, 20]. Many of these compounds have displayed interesting antihyperglycaemic activity thereby showing that modifications at either site could modulate the biological activity. Compounds like balaglitazone, which has successfully completed phase III clinical trials and rivoglitazone, which is currently under clinical trials are two such compounds which display better pharmacological profile than the existing TZD drugs [21-23]. More recently, it has been reported that replacement of sulphur with oxygen in the head group has been found beneficial for anti-hyperglycemic activity. The resulting oxazolidinone derivatives were found to exhibit better glucose lowering potential compared to thiazolidinediones but could not be developed further due to certain undesirable side effects observed during clinical trials [24].

Based on the SAR data reported in the literature it appears that the acidic head group may be one of the factors responsible for side effects of this class of compounds. We have designed compounds where the acidic thiazolidinedione head group is replaced with structurally related and neutral groups like the thiazolidin-4-one and thiazinan-4-one moieties as shown in **figure 1**. For the present study we have designed and synthesized a series of head group modified thiazolidinone derivatives. The present manuscript describes synthesis and biological activity of thiazolidin-4ones as a new class of antihyperglycemic agents.

2. Matetrials and Methods

2.1. Chemistry

The synthetic protocol comprises the formation of an aldehyde **2** and its subsequent conversion into the thiazolidin-4-one and thiazinan-4-one derivatives. Preparation of common intermediate **2** is a two step process. In the first step pyridyl alcohol **1** was prepared by refluxing 2-chloropyridine with N-methyl amino ethanol. In the second step alcohol **1** was reacted with 4-fluorobenzaldehyde in the presence of NaH, to afford the aldehyde **2** as in **Scheme 1**.

The thiazolidin-4-one derivatives reported in the present study were prepared by three component condensation method in one pot reaction as reported earlier from this laboratory [25]. In this protocol, N,N-dicyclohexylcarbodiimide (DCC) is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and improved yields. The benzaldehyde derivative **2** was reacted with appropriate amines and mercaptocarboxylic acids in the presence of DCC at room temperature. After completion of the reaction, the desired products were obtained in moderate to excellent yields and purity. Reaction with mercaptoacetic acid gave the thiazolidin-4-ones **3a-3h**, while reaction with 3-mercaptopropionic acid gave the thiazinan-4-ones **4a-4f**. The 5-methyl substituted thiazolidin-4-ones derivatives **5a-5b** were obtained by reaction of the aldehyde **2** with 2-thiolactic acid. Compounds **3d** and **3f** were subjected to selective oxidation with oxone to get the corresponding sulfoxides **6a-6b** and sulfones **7a-7b** [26]. The synthetic route for preparation of the title compounds is shown in **Scheme 1.**

2.2. Biological activity

All synthesized compounds were evaluated for their effect on glucose uptake by skeletal muscle cells *in vitro*. Compounds showed increased glucose utilization were further studied for anti-hyperglycemic, antidyslipidemic and insulin resistance reversal activities in the in vivo models. Adipocyte differentiation assay was performed to probe the mode of action. The evaluation protocols employed for these biological activities are presented below.

2.2.1. Glucose utilization by skeletal muscle cells

Stock cultures of skeletal muscle cells (L6 myoblasts) were maintained in DMEM supplemented with 10% (v/v) FBS, streptomycin (200 µg/ml), penicillin G (100 µg/ml) under an atmosphere of 5% CO_2/95% humidified air at 37 ºC. For differentiation into myotubes, cells were reseeded in 24-well plate containing DMEM media (10% FBS) for overnight culture. When cells were nearly confluent, 10% FBS containing DMEM media were replaced with 2% FBS containing DMEM media for differentiation into myotubes as reported earlier [27]. Differentiated L6 mature myotubes cultured on 24-well plates were treated with the test compounds or standard drugs for 18 hours. The test compounds were taken at 10 µM concentration whereas metformin and rosiglitazone were taken at 500 µM and 50 µM concentration respectively. Cells were then washed 3-times with Krebs–Ringer N-(2-hydroxyethyl) piperazine-N-2-ethanesulfonic acid (HEPES) buffer saline. For glucose uptake measurement, cells were incubated in HEPES buffer saline (HBS) containing 3µCi radio-labelled 2-deoxy-[3H] D-glucose and 20µM unlabelled 2-deoxyglucose for 15 min. The reaction was terminated by three washes with ice-cold HEPES buffer saline. Cells were lysed in 0.1 N NaOH and cell-associated radioactivity was determined by liquid scintillation counter. The results are expressed as % increase in glucose uptake by L-6 myotubes as compared to control.

2.2.2. Antihyperglycaemic, antidyslipidemic and insulin resistance reversal activities on db/db mice

The anti-hyperglycemic, antidyslipidemic and insulin resistance reversal activities of the desired test compounds on db/db mice was carried out according to the previously published

protocols [28-30]. 10 to 12 weeks old male db/db mice weighing over 40 g were chosen for this study. Prior to start of the test sample feeding, a vehicle training period was followed from day -3 to day 0 during which all the animals were given vehicle 1% gum acacia. At day 0 the animals having blood glucose level between 180 to 300 mg/dl were finally selected and divided into four groups consisted of six animals in each. One group was considered as sham treated control while the other two groups were test substances treated groups. The test substance treated groups were given suspension of the desired compounds at 30 mg/kg standard antidiabetic drugs i.e. rosiglitazone at 30 mg/kg and metformin at 100 mg/kg (suspensions prepared in vehicle 1% gum acacia) once daily from day 1 to day 15. The sham treated control group was given an equal amount of vehicle. All the animals had free access to fresh water and normal diet. Blood glucose of each animal was measured everyday whereas, on day 10 and day 15 post treatment an oral glucose tolerance test (OGTT) of each animal was performed after keeping the animals on an overnight fast. On the following day their blood glucose profiles were measured at -30 min and 0 min (baseline) and then at 30, 60, 90 and 120 min post an oral glucose load of 3.0 g/kg body weight. At the end of the experiment blood was withdrawn from the retro-orbital plexus of the eye for the estimation of insulin, triglycerides, cholesterol and HDL-C content in plasma using ELISA and colorimetric diagnostic kits as supplied by Merck and Roche diagnostics, respectively. Quantitative glucose tolerance of each animal was calculated by area under curve (AUC) method (Prism software). Comparing the AUC of experimental and control groups determined the % antihyperglycemic activity. Lowering in plasma total cholesterol (T-Chol), triglycerides (TGs) and elevation in HDL-cholesterol (HDL-C) expressed antidyslipidemic activity and lowering in plasma insulin content expressed the insulin resistance reversal activities. The statistical comparisons between groups were made by Dunnett's test.

2.2.3. Cell culture and adipocyte differentiation

3T3L1 pre-adipocytes (obtained from ATCC, USA) were cultured in DMEM with 10% fetal bovine serum (FBS) supplemented with antibiotics (100 U/ml penicillin and 100 µg/ml streptomycin (Gibco BRL, NY, USA) at 37 °C under a humidified 5% CO_2 atmosphere. For differentiation 3T3L1 preadipocytes were grown in 24 well plates for 2 days post-confluence and the cells were induced by the differentiation medium (combination of 0.5 mM/l of IBMX, 0.25 µM/l of dexamethasone and 5 mg/l of insulin in DMEM medium with 10% FBS) to differentiate

into adipocytes. Three days after induction, the differentiation medium was replaced with medium containing 5 mg/ml insulin alone. The medium was subsequently replaced again with fresh culture medium (DMEM with 10% FBS) after 2 days the extent of differentiation was measured by monitoring the formation of multinucleation in cells.

Oil Red O Staining

Differentiated 3T3-L1 were rinsed in phosphate buffered saline (pH 7.4), and stained with Oil Red O (0.36 % in 60 % Isopropanol) for 30 min, Finally the cells were rinsed twice with phosphate buffer saline and observed under microscope. Lipid and Oil Red O were extracted using isopropanol, and absorbance was measured using a spectrophotometer at a wavelength of 490 nm.

3. Results

3.1. In vitro antihyperglycaemic activity

The effect of compounds **3a-7b** on glucose utilization by L-6 myotubes is presented in Table-1. The metformin and rosiglitazone were used as reference compounds. Out of the 20 compounds tested six compounds (**3a**, **3b**, **4a**, **4b**, **6b** and **7a**) displayed increased glucose utilization, whereas, four compounds (**3f**, **4c**, **4d** and **4f**) showed moderate increasing effect. As shown in Table 1, both thiazolidin-4-one (5 membered ring) derivatives (**3a**, **3b** and **3f**) and thiazinan-4-one (6 membered ring) derivatives (**4a**, **4b**, **4c**, **4d** and **4f**) showed increased glucose utilization by L-6 myotubes. However, substituted thiazolidin-4-one derivatives (**5a** and **5b)** having a methyl substituent at 5 position of the thiazolidin-4-one ring did not show similar effect. Among the thiazolidin-4-ones as well as thiazinan-4-ones, the N-unsubstituted and N-cyclopropyl- substituted compounds displayed better effect at 10 µM concentration than other derivatives. The butyl and benzyl substituted thiazinan-4-ones were also found better as compared to thiazolidie-4-ones. The octyl-, 4-chlorophenyl- and 2-(1H-indol-3yl) ethyl-analogs were inactive at 10 µM. The substituents on the N of thiazolidin-4-one have impact on the biological activity. The anti-hyperglycemic activity of smaller substituents such as isopropyl was

found mild while butyl and benzyl showed moderate activity. The presence of sulfoxide and sulfone groups appears to enhance the glucose uptake as compounds **6b** and **7a which** showed nearly 45.5 and 51.3 % increase, respectively in glucose utilization at 10µM concentration. Whereas, rosiglitazone exhibited 61.6 % increase in glucose utilization by L-6 myotubes at 50µM.

3.2. Anti-hyperglycemic, antidyslipidemic and insulin resistance reversal activities

(i) Antihyperglycemic activity

The antihyperglycemic activity profile of the selected compounds in *db/db* mice is presented in Figure -3. The graphs 1, 2, 3, 4, 5, 6, 7, 8 and 9 depict an overall glucose lowering effect of **3a**, **3b**, **3d**, **3f**, **4a**, **4b**, **4f**, **6a**, **6b** and **7a** at 30 mg/kg dose. As evident from the figures, these compounds caused significant decline in the hyperglycemia by 18.5, 25.6, 22.1, 15.4, 30.4, 22.4, 19.1, 25.9, 22.1 and 30.2%, respectively as compared to vehicle treated control *db*/*db* mice. Rosiglitazone at 30 mg/kg and metformin at 100 mg/kg caused around 53.7% ($p<.01$), and 23.7 % ($p<.05$) decline in hyperglycemia, respectively. Among the test compounds **3f** and **7a** showed maximum decline on hyperglycemia and are better than rosiglitazone at the same dose level, whereas the other compounds have comparable effect. Table 2 represents the improvement on oral glucose tolerance (OGTT) by compounds **3a**, **3b**, **3d**, **3f**, **4a**, **4b**, **4f**, **6a**, **6b** and **7a,** respectively at 30 mg/kg dose. The fasting baseline blood glucose values at 0 min were found lower in all the treated groups compared to vehicle treated control group at the corresponding time because of antihyperglycemic effect. The treatment with these compounds also inhibited the rise in postprandial blood glucose levels post glucose load. The improvement in OGTT by these compounds were calculated around 25.9, 26.6, 20.2, 4.30, 40.8, 20.4, 29.4, 12.9, 6.40 and 26.8%, respectively on day 10^{th} and around 36.6, 40.9, 25.4, 16.4, 44.9, 27.9, 42.6, 27.2, 20.2 and 30.9%, respectively on day 15^{th}. The standard antidiabetic drugs i.e. rosiglitazone and metformin showed improvement on OGTT by around 33.3 % ($p<0.01$) and 29.1% ($p<.05$), respectively on day 10^{th} and around 40.7% ($p<.01$), and 29.7% ($p<.05$), respectively on day 15^{th} .

II. Antidyslipidemic activity

Table 3 represents the antidyslipidemic activity profile of selected compounds i.e. **3a**, **3b**, **3d**, **3f**, **4a**, **4b**, **4f**, **6a**, **6b** and **7a**) at 30 mg/kg dose. Oral administrations of these test compounds for 15 consecutive days lowered the plasma triglycerides (TG) by nearly 14.0, 15.6, 31.8, 9.83, 13.2, 29.9, 25.6, 19.2, 18.4 and 14.7%, respectively/ Plasma total cholesterol (T-Chol) level was found lowered by 19.3, 12.6, 4.80, 10.2, 15.1, 29.5, 9.88, 10.8, 0.57 and 7.20 %, respectively. The plasma HDL-cholesterol levels were found elevated by 0.65, 8.80, 10.1, 22.2, 1.46, 3.38, 6.47, 39.6, 20.0 and 25.7%, respectively. The standard antidiabetic drugs i.e. rosiglitazone and metformin lowered the plasma triglycerides (TG) by 32.5 % and 12.1 %, respectively and total cholesterol (T-Chol) level by 26.4% and 14.6%, respectively, and enhanced plasma HDL-cholesterol level by 22.2% and 6.80%, respectively, at 30 and 100 mg/kg doses.

III. Insulin resistance reversal activity

The effect of test compounds (**3a**, **3b**, **3d**, **3f**, **4a**, **4b**, **4f**, **6a**, **6b** and **7a**) on plasma insulin levels in *db*/*db* mice is presented in Table-3. Repeated oral gavages of these test samples to db/db mice at an oral dose of 30 mg/kg body weight for 15 consecutive days caused significant decrease in their plasma insulin levels by 27.4, 31.8, 17.6, 22.4, 28.8, 26.6, 21.5, 24.6, 20.4 and 28.8%, respectively compared to vehicle treated control group. The decrease in plasma insulin levels by rosiglitazone and metformin treatment in db/db mice was calculated to around 44.8% and 37.0 %, respectively.

3.3 Effect of compounds 3a and 3b on the adipocyte differentiation

The effect of compounds **3a** and **3b** on adipocyte differentiation was studied as follows; 3T3-L1 pre-adipocytes were treated with differentiation media in the presence of these compounds. On day 9 post initiation of differentiation, accumulated lipid droplets were detected by staining with Oil Red O. Treatment of 3T3-L1 pre-adipocytes with 10 μM concentrations of **3a** and **3b** promoted adipocyte differentiation (Figure 3a). The OD values of the Oil Red O eluted solutions were slightly increased by 5.53 % and 3.87 % respectively (Fig.3b). Whereas, the reference compound rosiglitazone at a concentration of 10μM, significantly promoted

adipocyte differentiation in 3T3L1 adipocytes with 24.0 % increase in O.D. was recorded. These results suggest that compounds **3a** and **3b** slightly enhance adipocyte differentiation.

Discussion

Replacement of the head group present in rosiglitazone from thiazolidindione to thiazolidin-4-one and thiazinan-4-one resulted in the identification of new compounds with potential anti-hyperglycemic activity in both *in vitro* and *in vivo* assays. All the compounds prepared for this study were subjected to anti-hyperglycemic assay *in vitro* using L-6 muscle cells. It was observed that several compounds showed promising activity, namely compounds **3a**, **3b**, **4b**, **6b** and **7a** exhibited activity at 10 μM comparable to similar activity exhibited by rosiglitazone at 50 μM concentration rosiglitazone which was used as positive control. Remaining compounds showed mixed response. However, 5-substituted thiazolodin-4-one derivatives **5a** and **5b** were found to be the least active in this series. It may be inferred that a methyl group at 5-position of thiazolodin-4-one moiety is unfavorable for receptor binding. Based on these results and structural features we have selected ten compounds **(3a**, **3b**, **3d**, **3f**, **4a**, **4b**, **4f**, **6a**, **6b** and **7a)** for *in vivo* activities.

Assessment of anti-hyperglycemic activity of the test compounds was carried out *in vivo* using *db/db* mice by observing overall glucose lowering effect and also the improvement on oral glucose tolerance at 30 mg/kg for a period of 15 days (single dose daily). Rosiglitazone was taken as positive control. The test compounds showed significant anti-hyperglycemic effect in the range of 15- 30% decline in random blood glucose levels as shown in figure 2. However, a few among these compounds could not show decline in random blood glucose levels comparable to rosiglitazone, which was around 53% at the same dose level (data not shown). Compounds **4a** and **7a** were found to exhibit highest activity among the tested compounds and showed nearly 30 % decreases in random blood glucose levels. The effect of compounds **3a**-**7b** on the improvement of oral glucose tolerance was found to be very encouraging. OGTT was performed on day 10 as well as on day 15 post treatment to observe the effectiveness of the duration of the treatment. All these compounds showed better improvement on oral glucose tolerance on day 15 compared to day 10, indicating the therapeutic potential of this series of compounds. Compounds **3b**, **4a** and **4f** showed activity comparable to rosiglitazone at both check points, whereas

compound **4a** with un-substituted thiazinan-4-one head group was found to have superior activity compared to rosiglitazone. The lipid profiles and insulin levels of these compounds were also quite encouraging as this series of compounds exhibited reduction of lipid levels, further enhancing their therapeutic potential.

These findings suggest that thiazolidinedione moiety in TZDs skeleton may be replaced with thiazolidin-4-one and thiazinan-4-one for the development of novel therapeutic agents for the treatment of type-2 diabetes. The compounds with free NH in the head group are more effective as compared to N-substituted compounds. Both thiazolidin-4-one and thiazinan-4-one moieties are well tolerated and compounds with thiazinan-4-one moiety are relatively better. On the other hand 5-substituted thiazolidin-4-one moiety results in loss of activity. Incorporation of lipophilicity at position 3 (N-substitution) results in compounds with reduced activity. It is interesting to note that oxidation of sulphur to sulphone and sulphoxide is also well tolerated and results in retention of activity (Compounds **6a**, **6b** and **7a**).

The interesting feature of this series of compounds is that in addition to significant *in vivo* efficacy as anti-hyperglycemic agents, these compounds also elevate HDL-C level, improving the diabetic dyslipidemia in db/db mice. The *db*/*db* mice exhibit an initial phase of hyperglycemia, hyperinsulinemia, hyperphagia and obesity. Interestingly, the test compounds were found to lower the postprandial hyperglycemia as well as improve the glucose tolerance of *db*/*db* mice. The level of plasma lipids are usually raised in diabetic conditions and the results of the present study have demonstrated that these anti-hyperglycemic lead molecules produce a significant decrease in plasma triglycerides and total cholesterol as well as significant increase the level of cardio protective plasma HDL-cholesterol, which is a desirable effect. The plasma insulin decreased in *db*/*db* mice as a result of treatment with these compounds; it is reasonable to infer that the effect of the treatment on hyperglycemia is not through an increase in insulin concentration but improvement in the insulin sensitivity. Further studies are required to explore the exact mechanism(s) of antihyperglycemic, antidyslipidemic and insulin resistance reversal activities in these interesting compounds.

Effect of two active compounds **3a** and **3b** on adipogenesis was assessed in 3T3L1 adipocytes. Adipogenesis, the process of preadipocyte differentiation into adipocytes is

controlled by various positive and negative regulators such as hormones, adipogenic genes, adipokines and growth factors [31]. PPARγ, CCAAT/enhancer binding protein and sterol regulatory element binding protein (SREBP) families are well documented primary adipogenic transcription factors involved in adipocyte differentiation, and among these PPARγ is the most extensively studied and clinically validated adipogenic gene for therapeutic utility in type 2 diabetes [32]. Upregulation of PPARγ gene by thiazolidinediones in skeletal muscle has been reported to improve insulin sensitivity and glucose uptake [33]. Although relatively beneficial for their anti-diabetic action, thiazolidinediones have been reported to cause abnormalities in lipid metabolism and cardiac side-effects [34]. In the present study, 3T3L1 adipocytes incubated with compounds **3a** and **3b** revealed that the effect of compounds **3a** and **3b** led to increase in lipid droplets formation.

3. Conclusions

In conclusion, we have synthesized a series of the thiazolidin-4-one and thiazinan-4-one derivatives and evaluated for their effect on glucose utilization in vitro and antihyperglycemic, antidyslipidemic and insulin reversal activities in vivo in *db/db* mice. Some of the compounds of in the series (**3a**, **3b**, **4a** and **4b**) have exhibited potent anti-hyperglycemic activity comparable to standard antidiabetic drugs namely rosiglitazone and metformin and have anti-dyslipidemic and insulin resistance reversal activities. Thus, thiazolidin-4-one and thiazinan-4-one derivatives of TZDs have remarkable promise for further exploration as anti-diabetic drug candidates.

4. Experimental

4.1. Chemistry

Thin-layer chromatography was performed on readymade silica gel plates (Merck, UV active, λ_{254} nm). Chromatography was performed on silica gel (230-400 mesh). Melting points (mp) were recorded in open capillaries on Complab melting point apparatus and are uncorrected. The ^{1}H spectra were obtained with Bruker DPX-200 or DRX-300 MHz FT-NMR spectrometers. The chemical shifts are reported as parts per million (δ ppm) taking tetramethylsilane (TMS) as an internal standard. The ^{13}C-NMR spectra were recorded on Bruker DRX-300 FT-NMR spectrometer (75 MHz). Infrared (IR) spectra were recorded as neat samples or in KBr on an FT-

IR Perkin–Elmer spectrometer and reported in wave number (cm^{-1}). Mass spectra were obtained on Micromass Quattro II Spectrometer using Electro spray ionization mass spectrometry (ESI MS positive) and on JMS-T100LC Acuu. TOF Mass Spectrometer for High resolution mass spectrometry (HRMS). The C, H, N analyses were carried out on CARLO-ERBA EA1108 elemental analyzer.

4.1.1. 2-(Methyl-pyridin-2-yl-amino)-ethanol (1). A mixture of 2-chloropyridine (28.2mL, 300mmol) and N-methyl amino ethanol (16.0mL, 200mmol) was heated under nitrogen at 160 °C with stirring for 15 hours. The mixture was cooled to room temperature and poured into water, and the solution was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The crude product was chromatographed over silica gel using methanol-chloroform as eluent to afford the title compound 1. Yield 66% syrupy liquid; ESI-MS *m/z* 153 $[M+H]^+$; IR (Neat) γ_{max} 3418 cm^{-1}, ^1H NMR ($CDCl_3$, 200MHz) δ 3.07 (s, 3H), 3.71 (t, *J* =4.9 Hz, 2H), 3.86 (t, *J* =4.5Hz, 2H), 5.30 (s, 1H), 6.52-6.61 (m, 2H), 7.44-7.52 (m, 1H), 8.04-8.06 (m, 1H).

4.1.2. 4-[2-(Methyl-pyridin-2-yl-amino)-ethoxy]-benzaldehyde (2). To a stirred suspension of sodium hydride (4.7 g, 60% w/w dispersion in oil) in DMF (20mL) was added 2-(Methyl-pyridin-2-yl-amino)-ethanol **(1)** (12 g, 78.95mmol) in dry DMF (250mL), under nitrogen, and the mixture was stirred for 30 min. A solution of 4-fluorobenzaldehyde (12.2mL, 118.43mmol) in dry DMF (100mL) was added and stirred for 15-18 hours at 80^{o}C. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography over silica gel using a mixture of ethyl acetate-hexane as eluting solvent to get the title compound 2. Yield 44% gummy solid; ESI-MS *m/z* 257 $[M+H]^+$;IR (Neat) γ_{max} 1695 cm^{-1}, ^1H NMR ($CDCl_3$, 200MHz) δ 3.15 (s, 3H), 4.03 (t, *J* =5.6 Hz, 2H), 4.29 (t, *J* =5.5 Hz , 2H), 6.50-6.61 (m, 2H), 7.01 (d, *J*=8.6 Hz, 2H), 7.44-7.52 (m, 1H), 7.81 (d, *J*=8.6 Hz, 2H), 8.15-8.17 (m, 1H), 9.87 (s, 1H);.

4.1.3. General method of preparation of thiazolidin-4-ones and thiazinan-4-ones (3a-3h, 4a-4f, 5a-5b). The appropriate amine (2.0 mmol) and aldehyde **2** (4.0 mmol) were stirred in dry

THF under ice cold conditions for 10 min, followed by addition of mercaptocarboxylic acid (6.0 mmol). After 10 min DCC (2.4mmol) was added to the reaction mixture at 0°C and the reaction mixture stirred for an additional 5-6 hours at room temp. DCU was removed by filtration and the filtrate was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was successively washed with 5% aq. citric acid, water, 5% aq. sodium bicarbonate and then finally with brine. The organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using ethyl acetate-hexane mixture.

4.1.3.1. 2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one (3a). This compound was prepared by the general procedure using saturated methanolic-ammonia (1.0 ml). Yield 20.7 % gummy solid; ESI-MS *m/z* 330 $[M+H]^+$; IR (Neat) γ_{max} 1654.5 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 3.16 (s, 3H), 3.69 (d, *J* =1.3 Hz, 2H), 4.01 (t, *J* 5.7 Hz, 2H), 4.21 (t, *J* 5.7 Hz, 2H), 5.76 (s, 1H), 6.25 (s,1H), 6.53-6.60 (m, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 7.33 (d, *J*=8.6 Hz, 2H), 7.45-7.51 (m, 1H), 8.16-8.18 (m, 1H); HRMS calcd for $C_{17}H_{19}N_3O_2S$ $[M^+]$ 329.1198, found 329.1157.

4.1.3.2. 3-cyclopropyl-2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one (3b). Yield 49.8 %, gummy solid. ESI-MS *m/z* 370 $[M+H]^+$; IR γ_{max} (Neat)1675.1 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.52-0.60 (m, 2H), 0.87-0.94 (m, 2H), 3.17 (s, 3H), 3.65 (d, *J*=15.5 Hz, 1H), 3.80-3.85 (m, 2H), 4.01 (t, *J* =5.6 Hz, 2H), 4.21 (t, *J* 5.6 Hz, 2H), 5.47 (s, 1H), 6.53-6.60 (m, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=8.8 Hz, 2H), 7.45-7.51 (m, 1H), 8.16-8.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 5.04, 7.53, 26.00, 33.30, 37.91, 49.49, 64.31, 66.49, 105.82, 111.82, 114.89(2C), 127.98(2C), 132.37, 137.38, 147.79, 158.23, 159.29, 172.20.

4.1.3.3. 3-isopropyl-2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one (3c). Yield 42.1 %, gummy solid. ESI-MS *m/z* 372$[M+H]^+$; IR (Neat) γ_{max} 1658.2 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.97 (d, *J* =7.0 Hz, 3H), 1.27 (d, *J*= 8.6 Hz, 3H), 3.18 (s, 3H), 3.81-3.92 (m, 3H), 4.02 (t, *J* =5.6 Hz, 2H), 4.22 (t, *J*= 5.6 Hz, 2H), 5.64 (s, 1H), 6.54-6.61 (m, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 7.26 (d, *J*=8.6 Hz, 2H), 7.46-7.50 (m, 1H), 8.17-8.19 (m, 1H); ^{13}C NMR

($CDCl_3$, 75MHz) δ 19.51, 20.39, 33.33, 37.83, 47.79, 49.40, 66.36, 66.36, 105.78, 111.76, 114.59, 115.07, 128.01, 129.29, 132.37, 137.36, 147.83, 158.24, 159.25, 171.28.

4.1.3.4. 3-butyl-2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one (3d). Yield 84.0 %, gummy solid. ESI-MS *m/z* 386 $[M+H]^+$; IR (Neat) γ_{max} 1665.8 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.87 (t, *J*= 7.2 Hz, 3H), 1.22-1.27 (m, 2H), 1.38-1.42 (m, 2H), 2.60-2.69 (m, 1H), 3.16 (s, 3H), 3.60-3.70 (m, 1H), 3.70 (d, *J*=15.4 Hz, 1H), 3.81 (d, *J*=15.4 Hz, 1H), 4.00 (t, *J* =5.6 Hz, 2H), 4.21 (t, *J*= 5.6 Hz, 2H), 5.60 (s, 1H), 6.52-6.60 (m, 2H), 6.91 (d, *J*=8.5 Hz, 2H), 7.23 (d, *J*=8.7 Hz, 2H), 7.44-7.50 (m, 1H), 8.16-8.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.69, 19.97, 28.79, 33.12, 37.92, 42.52, 49.46, 63.33, 66.47, 105.80, 111.82, 114.90(2C), 128.45(2C), 131.21, 137.39, 147.79, 158.21, 159.49, 171.02.

4.1.3.5. 3-octyl 2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl) thiazolidin-4-one (3e). Yield 72.1% gummy solid. ESI-MS *m/z* 442 $[M+H]^+$; IR (Neat) γ_{max} 1667.6 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.87 (t, *J* =6. 7Hz, 3H), 1.22-1.27 (m, 10H), 1.40-1.44 (m, 2H), 2.61-2.67 (m, 1H), 3.17 (s, 3H), 3.59-3.67 (m, 1H), 3.71 (d, *J*=15.4 Hz, 1H), 3.81 (d, *J*=15.5 Hz, 1H), 4.01 (t, *J*= 5.5 Hz, 2H), 4.21 (t, *J*= 5.6 Hz, 2H), 5.60 (s, 1H), 6.53-6.60 (m, 2H), 6.91 (d, *J*=8.6 Hz, 2H), 7.22 (d, *J*=8.6Hz, 2H), 7.45-7.51 (m, 1H), 8.17-8.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.06, 22.60,26.69, 26.73, 29.08, 29.11, 31.72, 33.10, 37.86, 42.79, 49.42, 63.32, 66.48, 105.70, 111.80, 114.90(2C), 128.44(2C), 131.27, 137.30, 147.86, 158.26, 159.51, 170.90.

4.1.3.6. 3-benzyl-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl) thiazolidin-4-one (3f). Yield 82.0% gummy solid. ESI-MS *m/z* 420 $[M+H]^+$; IR (Neat) γ_{max} 1670.7cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 3.18 (s, 3H), 3.53 (d, *J*= 14.7 Hz, 1H), 3.76 (d, *J*=15.7 Hz, 1H), 3.89 (d, *J*=15.7 Hz, 1H), 4.02 (t, *J*= 5.6 Hz, 2H), 4.23 (t, *J*= 5.6 Hz, 2H), 5.13 (d, *J* =14.7 Hz, 1H), 5.37 (s, 1H), 6.54-6.60 (m, 2H), 6.91 (d, *J*=8.6 Hz, 2H), 7.08-7.11 (m, 2H), 7.14 (d, *J*=8.7 Hz, 2H), 7.28-7.31 (m, 3H), 7.45-7.51 (m, 1H), 8.17-8.19 (m, 1H); Anal. Calcd for $C_{24}H_{25}N_3O_2S$: C, 68.71; H, 6.01; N, 10.02; Found: C, 69.71; H, 6.31; N, 9.99.

4.1.3.7. 3-(4-chlorophenyl)-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl) thiazolidin-4-one (3g). Yield 56.3 %, gummy solid. ESI-MS *m/z* 440 $[M+H]^+$; IR (Neat) γ_{max} 1652.4 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 3.13 (s, 3H), 3.85-3.99 (m, 4H), 4.15 (t, J=5.5 Hz, 2H), 6.03 (s, 1H), 6.50-6.60 (m, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 7.08 (d, *J*=8.6 Hz, 2H), 7.18-7.26 (m, 4H), 7.44-7.50 (m, 1H), 8.15-8.16 (m, 1H) ; HRMS calcd for $C_{23}H_{22}ClN_3O_2S$ $[M^+]$ 439.1121, found 439.1129.

4.1.3.8. 3-(2-(1H-indol-3-yl) ethyl)-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl) thiazolidin-4-one (3h). Yield 76.0%, gummy solid. ESI-MS *m/z* 473$[M+H]^+$; IR (Neat) γ_{max} 1663.1 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 3.53 (m, 1H), 3.00-3.09 (m, 2H), 3.17 (s, 3H), 3.70 (d, *J*=15.2 Hz, 1H), 3.80 (d, *J*=15.4 Hz, 1H), 3.82-3.91 (m, 1H), 4.01 (t, J =5.6 Hz, 2H), 4.21 (t, *J*=5.6 Hz, 2H), 5.32 (s, 1H), 6.53-6.60 (m, 2H), 6.81-7.51 (m, 10H), 8.08 (s, 1H), 8.17-8.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 30.96, 33.12, 37.92, 43.47, 49.46, 63.95, 66.48, 105.84, 111.24, 111.84, 112.50, 114.82(2C), 118.61, 119.39, 122.13(2C), 127.16, 128.86(2C), 130.86, 136.26, 137.42, 147.80, 158.24, 159.55, 171.17.

4.1.3.9. 2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl)-1, 3-thiazinan-4-one (4a).

This compound was prepared by the general procedure using methanolic ammonia. Yield 24.9 %, white solid. M.p. 115-118 ºC; ESI-MS *m/z* 344 $[M+H]^+$; IR (Neat) γ_{max} 1650.5 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 2.76-2.80 (m, 2H),2.86-3.11 (m, 2H), 3.16 (s, 3H), 4.00 (t, *J*= 5.6 Hz, 2H), 4.21 (t, *J* 5.6 Hz, 2H), 5.62 (s, 1H), 6.33 (s,1H), 6.52-6.59 (m, 2H), 6.91 (d, *J*=8.6 Hz, 2H), 7.34 (d, *J*=8.8 Hz, 2H), 7.44-7.50 (m, 1H), 8.16-8.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 25.51, 33.32, 37.83, 49.40, 59.36, 66.47, 105.72, 111.81, 114.89(2C), 128.27(2C), 130.10, 137.31, 147.86, 158.27, 159.55, 171.19;.

4.1.3.10. 3-cyclopropyl-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl)-1, 3-thiazinan-4-one (4b). Yield 48.9 %, gummy solid. ESI-MS *m/z* 384 $[M+H]^+$; IR (Neat) γ_{max} 1656.1 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.58-0.68(m, 2H), 0.71-0.78 (m, 1H), 0.89-0.97 (m, 1H), 2.56-2.67 (m, 2H), 2.70-2.81 (m, 3H), 3.16 (s, 3H), 4.00 (t, *J*= 5.6 Hz, 2H), 4.20 (t, *J* =5.6 Hz, 2H), 5.55 (s, 1H), 6.52-6.59 (m, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 7.14 (d, *J*=8.6 Hz, 2H), 7.44-7.47 (m, 1H), 8.15-8.17(m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 6.57, 8.85, 23.52, 31.28, 35.10,

37.92, 49.46, 62.74, 66.47, 105.75, 111.79, 114.47(2C), 127.48(2C), 132.04, 137.39, 147.84, 158.22, 158.53, 171.54.

4.1.3.11. 3-isopropyl-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl)-1, 3-thiazinan-4-one (4c). Yield 38.8 %, gummy solid. ESI-MS *m/z* 386 $[M+H]^+$; IR (Neat) γ_{max} 1650.6 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.97 (d, *J* =7.0 Hz, 3H), 1.27 (d, *J* 6.8 Hz, 3H), 2.66-2.75 (m, 2H), 2.78-2.87 (m, 2H), 3.17 (s, 3H), 4.01(t, *J*= 5.6 Hz, 2H), 4.20 (t, *J*= 5.6 Hz, 2H), 4.89-4.98 (m, 1H), 5.56(s, 1H), 6.52-6.59 (m, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 7.21 (d, *J*=8.7 Hz, 2H), 7.44-7.50 (m, 1H), 8.16-8.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 19.74, 20.09, 23.54, 34.02, 37.90, 47.17, 49.48, 57.00, 66.45, 105.74, 111.79, 114.21(2C), 127.59(2C), 133.34, 137.32, 147.88, 157.75, 158.27, 169.59.

4.1.3.12. 3-butyl-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl)-1, 3-thiazinan-4-one (4d). Yield 54.0 %, gummy solid. ESI-MS *m/z* 400 $[M+H]^+$; IR (Neat) γ_{max} 1626.0 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.90 (t, *J*= 7.5 Hz, 3H), 1.26-1.33 (m, 2H), 1.54-1.59 (m, 2H), 2.53-2.64 (m, 2H), 2.72-2.83 (m, 3H), 3.17 (s, 3H), 4.01 (t, *J*= 5.5 Hz, 2H), 4.06-4.15 (m, 1H), 4.20 (t, *J* =5.5 Hz, 2H), 5.48 (s, 1H), 6.53-6.60 (m, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 7.14 (d, *J*=8.7 Hz, 2H), 7.45-7.51 (m, 1H), 8.16-8.17(m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.87, 20.20, 21.86, 29.60, 34.40, 37.99, 47.64, 49.53, 61.55, 66.45, 105.91, 111.79, 114.45(2C), 127.74(2C), 131.42, 137.54, 147.51, 158.01, 158.61, 169.17.

4.1.3.13. 3-octyl 2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl)-1, 3-thiazinan-4-one (4e). Yield 52.3 %, gummy solid. ESI-MS *m/z* 456 $[M+H]^+$; IR (Neat) γ_{max} 1610.7 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88 (t, *J* =6. 2Hz, 3H), 1.26-1.27 (m, 10H), 1.38-1.40 (m, 2H), 2.52-2.65 (m, 2H), 2.73-2.84 (m, 3H), 3.18 (s, 3H), 4.02 (t, *J*= 5.4 Hz, 2H), 4.07-4.15 (m, 1H), 4.21 (t, *J*= 5.5 Hz, 2H), 5.49 (s, 1H), 6.54-6.59 (m, 2H), 6.90 (d, *J*=8.7 Hz, 2H), 7.15 (d, *J*=8.7 Hz, 2H), 7.47-7.52 (m, 1H), 8.17-8.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 14.07, 22.61, 26.95, 27.47, 29.16, 29.29, 31.76, 34.41, 37.99, 42.18, 47.90, 49.59, 61.59, 66.45, 106.04, 111.80, 114.47(2C), 127.76(2C), 131.47, 137.66, 147.30, 157.98, 158.61, 169.18.

4.1.3.14. 3-benzyl-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl)-1, 3-thiazinan-4-one (4f). Yield 53.1 %, gummy solid. ESI-MS *m/z* 434 $[M+H]^+$; IR (Neat) γ_{max} 1605.7 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 2.62-2.89(m, 2H), 2.20-2.99(m, 2H), 3.18(s, 3H), 3.55(d, *J*= 14.7 Hz, 1H), 4.02(t, *J* =5.6 Hz, 2H), 4.22(t, *J* =5.6 Hz, 2H), 5.38(s, 1H), 5.75(d, *J* 14.7 Hz, 1H), 6.53-6.60 (m, 2H), 6.92 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.7 Hz, 2H), 7.20-7.36 (m, 5H), 7.45-7.51 (m, 1H), 8.17-8.19(m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 23.49, 34.60, 37.97, 49.36, 49.57, 60.56, 66.52, 105.94, 111.81, 114.63(2C), 127.53, 127.76(2C), 127.88(2C), 128.71(2C), 136.34, 137.56, 147.48, 158.75, 160.05, 169.52.

4.1.3.15. 3-butyl-5-methyl-2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one (5a). Yield 62.0 %, gummy solid. ESI-MS *m/z* 400 $[M+H]^+$; IR (Neat) γ_{max} 1666.1 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.88 (t, *J*= 7.4 Hz, 3H), 1.23-1.27 (m, 2H), 1.37-1.44 (m, 2H), 1.60 (d, *J* =6.9, 3H), 2.60-2.69 (m, 1H), 3.17 (s, 3H), 3.63-3.73 (m, 2H), 3.96-4.06 (m, 1H), 4.00 (t, *J*= 5.5 Hz, 2H), 4.20 (t, *J* =5.5 Hz, 2H), 5.55 (s, 1H), 6.53-6.60 (m, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 7.19 (d, *J*=8.6 Hz, 2H), 7.45-7.51 (m, 1H), 8.16-8.17 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.70, 19.90, 20.23, 28.84, 37.89, 41.87, 42.62, 49.47, 61.27, 66.49, 105.79, 111.82, 114.92(2C), 128.18(2C), 131.56, 137.37, 147.80, 158.24, 159.35, 174.01.

4.1.3.16. 3-benzyl-5-methyl-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl) thiazolidin-4-one (5b). Yield 52.5 %, gummy solid. ESI-MS *m/z* 434 $[M+H]^+$; IR (Neat) γ_{max} 1671.7 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.64(d, *J* =7.1, 3H), 3.18 (s, 3H), 3.51 (d, *J* =14.7 Hz, 1H), 4.02 (t, *J* =5.6 Hz, 2H), 4.11-4.18 (m, 1H), 4.22 (t, *J*= 5.6Hz, 2H), 5.15 (d, *J*= 14.7 Hz, 1H), 5.30 (s, 1H), 6.54-6.61 (m, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 7.05-7.34 (m, 5H), 7.12 (d, *J*=8.8 Hz, 2H), 7.45-7.51 (m, 1H), 8.17-8.19 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 75MHz) δ 20.30, 29.71, 37.93, 46.17, 49.50, 60.48, 66.50, 105.80, 111.81, 114.94(2C), 127.82, 128.17(2C), 128.48(2C), 128.77(2C), 130.97, 135.56, 137.37, 147.84, 158.23, 159.41, 174.12.

4.1.4. General method of preparation of sulfoxide (6a-6b)

The compounds **3d** and **3f** (300 mg) was dissolved in 10 mL methanol: water (1:1) solution. The reaction mixture was cooled to -5^o to -10^o C and Oxone (0.8 equiv.) was added.

The reaction mixture was stirred for 30-40 minutes. The solvent was then evaporated under vacuum and the residue was taken up in ethyl acetate. The organic layer was successively washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using mixture of 10% methanol in chloroform.

4.1.4.1. 3-butyl-2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one sulfoxide (6a). Yield 67.4 %, gummy solid. ESI-MS *m/z* 402 $[M+H]^+$; IR (Neat) γ_{max} 1685.8 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.91 (t, *J*= 7.3 Hz, 3H), 1.30-1.42 (m, 2H), 1.54-1.59 (m, 2H), 2.89-2.98 (m, 1H), 3.16 (s, 3H), 3.42 (d, *J*=17.1 Hz, 1H), 3.73 (d, *J*=17.1 Hz, 1H), 3.88-3.96 (m, 1H), 4.01 (t, *J*= 5.5 Hz, 2H), 4.22 (t, *J*= 5.6 Hz, 2H), 5.47 (s, 1H), 6.54-6.61 (m, 2H), 6.97 (d, *J*=8.6 Hz, 2H), 7.13 (d, *J*=8.6 Hz, 2H), 7.47-7.52 (m, 1H), 8.16-8.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.64, 19.73, 23.47, 38.00, 43.27, 49.49, 51.99, 66.58, 84.55, 106.03, 111.91, 115.73(2C), 122.14, 127.68(2C), 137.71, 147.30, 157.85, 160.08, 168.46.

4.1.4.2. 3-benzyl-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl) thiazolidin-4-one sulfoxide (6b). Yield 56.8 %, gummy solid. ESI-MS *m/z* 436$[M+H]^+$; IR (Neat) γ_{max} 1692.6 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 3.16 (s, 3H), 3.54 (d, *J*=17.0 Hz, 1H), 3.82 (d, *J*=16.7 Hz, 1H), 3.86 (d, *J*= 14.9 Hz,1H), 4.02 (t, *J* =5.7 Hz, 2H), 4.23 (t, *J* =5.6 Hz, 2H), 5.28 (s, 1H), 5.38 (d, *J*= 14.9 Hz, 1H), 6.52-6.61 (m, 2H), 6.97 (d, *J*=8.7 Hz, 2H), 7.08 (d, *J*=8.7 Hz, 2H), 7.23-7.35 (m, 5H), 7.46-7.51 (m, 1H), 8.16-8.18 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 75MHz) δ 37.95,46.52, 49.41, 52.15, 66.62, 83.49, 105.82, 111.90, 115.78(2C), 121.62, 127.77(2C), 128.10(2C), 128.17, 128.98(2C), 134.23, 137.48, 147.66, 158.09, 160.14, 168.60.

4.1.5. General method of preparation of Sulfone (7a-7b)

The thiazolidinone (300 mg) was dissolved in 10 ml methanol: water (1:1) solution. The reaction mixture was cooled to -5^o to -10^o C and oxone (3 equiv.) was added. The reaction mixture was stirred for 30-40 minutes at -5^o to -10^o C and then for 2 hours at room temperature. It was then evaporated to dryness under vacuum and the residue was taken up in ethyl acetate. The organic layer was successively washed with water and brine. The organic layer was dried

over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using 10% methanol-chloroform as eluent.

4.1.5.1. 3-butyl-2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one sulfone (7a). Yield 70.3 %, gummy solid. ESI-MS *m/z* 418 $[M+H]^+$; IR (Neat) γ_{max} 1696.7 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 0.90 (t, *J*= 7.4 Hz, 3H), 1.28-1.35 (m, 2H), 1.59-1.54 (m, 2H), 2.75-2.84 (m, 1H), 3.16 (s, 3H), 3.84 (s, 2H), 4.05-4.09 (m, 1H), 4.02 (t, *J* =5.4 Hz, 2H), 4.25 (t, *J*= 5.4 Hz, 2H), 5.50 (s, 1H), 6.52-6.60 (m, 2H), 7.02 (d, *J*=8.6 Hz, 2H), 7.22 (d, *J*=8.5 Hz, 2H), 7.45-7.50 (m, 1H), 8.16-8.18 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 75MHz) δ 13.60, 19.80, 28.82, 37.02,42.26, 49.38, 50.19, 66.61, 81.56, 105.73, 111.90, 114.71, 115.49, 119.85, 129.48(2C), 137.36, 147.90, 158.25, 160.90, 162.62.

4.1.5.2. 3-benzyl-2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one sulfone (7b). Yield 63.3 %, gummy solid. ESI-MS *m/z* 452 $[M+H]^+$; IR(Neat) γ_{max} 1700.1 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 3.18 (s, 3H), 3.67 (d, *J* =14.7 Hz, 1H), 3.93 (s, 2H), 4.03 (t, *J* =5.6 Hz, 2H), 4.26 (t, *J* =5.6 Hz, 2H), 5.28 (s, 1H), 5.53 (d, *J* =14.7 Hz, 1H), 6.53-6.61 (m, 2H), 7.09-7.12 (m, 2H), 7.02 (d, *J*=8.7 Hz, 2H), 7.17 (d, *J*=8.7 Hz, 2H), 7.33-7.35 (m, 3H), 7.46-7.52 (m, 1H), 8.17-8.19 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 75MHz) δ 37.99, 45.42, 49.40, 50.43, 66.60, 80.59, 105.79, 111.90, 115.51(2C), 119.08, 128.52(3C), 129.11(2C), 129.82(2C), 133.72, 137.43, 147.83, 158.18, 160.90, 162.68.

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References and Notes

[1] S. E. Khan, The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes, Diabetologia 46, (2003), 3-19

[2] (a) J. S. Skyler, Diabetes Mellitus: Pathogenesis and Treatment Strategies, J. Med. Chem. 47, (2004) 4113-4117. (b) B. Ahréna B. GLP-1 for type 2 diabetes, *Experimental Cell Research.* 317 (2011) 1239-1245.

[3] G. J. Murphy, J. C. Holder, PPAR-γ agonists: therapeutic role in diabetes, inflammation and cancer, Trends Pharmacol Sci. 21 (2000) 469-474.

[4] Y. Momose, et al., Studies on Antidiabetic Agents. X. Synthesis and Biological Activities of Pioglitazone and Related Compounds, Chem. Pharm. Bull. 39 (1991) 1440-1445.

[5] B. C. C. Cantello, et al., The synthesis of BRL 49653 - a novel and potent antihyperglycaemic agent, Bioorg. Med. Chem. Lett. 4 (1994) 1181-1184.

[6] C. Knouff, J. Auwerx, J., Peroxisome Proliferator-Activated Receptor-γ Calls for Activation in Moderation: Lessons from Genetics and Pharmacology, *Endocr. Rev*. 25 (2004) 899-918.

[7] S. Singh, Y. K. Loke, C. D. Furberg, Long-term Risk of Cardiovascular Events With Rosiglitazone-A Meta-analysis, JAMA 298 (2007) 1189-1195.

[8] A. K. McDonough, et al., The effect of thiazolidinediones on BMD and osteoporosis, Nat. Clin. Pract. Endocrinol. Meta. 4 (2008) 507-513.

[9] S. E. Nissen, K. Wolski, E. J. Topol, Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus, JAMA 294 (2005) 2581-2586.

[10] P. J. Larsen, et al,. Dissociation of antihyperglycaemic and adverse effects of partial perioxisome proliferator-activated receptor (PPAR-γ) agonist balaglitazone , Eur. J. Pharmacol. 596 (2008) 173-179.

[11] V. D. Pratik, et al., Design and Synthesis of N-[(4-Methoxyphenoxy)carbonyl]-N-[[4-[2-(5- methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]glycine [Muraglitazar/BMS-298585], a Novel Peroxisome Proliferator-Activated Receptor α/γ Dual Agonist with Efficacious Glucose and Lipid-Lowering Activities, J. Med. Chem. 48 (2005) 2248-2250.

[12] J. Li, et al., Discovery of an Oxybenzylglycine Based Peroxisome Proliferator Activated Receptor α Selective Agonist 2-((3-((2-(4-Chlorophenyl)-5-methyloxazol-4-yl)methoxy)benzyl)(methoxycarbonyl)amino)acetic Acid (BMS-687453J. A. J. Med. Chem. 53 (2010) 2854-2864.

[13] N. Masahiro, et al., (3-Substituted benzyl)thiazolidine-2,4-diones as structurally new antihyperglycemic agents, Bioorg. Med. Chem. Lett. 9, (1999) 533-538.

[14] N. Mahindroo, et al., Novel Indole-Based Peroxisome Proliferator-Activated Receptor Agonists: Design, SAR, Structural Biology, and Biological Activities J. Med. Chem. 48 (2005) 8194-8208.

[15] N. Mahindroo, et al., Structural Basis for the Structure−Activity Relationships of Peroxisome Proliferator-Activated Receptor Agonists J. Med. Chem.49 (2006) 6421-6424.

[16] J. H. Ahn, et al., Indenone Derivatives: A Novel Template for Peroxisome Proliferator-Activated Receptor γ (PPARγ) Agonists J. Med. Chem. 49 (2006) 4781-4784.

[17] N. Mahindroo, et al., Indol-1-yl Acetic Acids as Peroxisome Proliferator-Activated Receptor Agonists: Design, Synthesis, Structural Biology, and Molecular Docking Studies, J. Med. Chem. 49 (2006) 1212-1216.

[18] R. Epple, et al., Novel Bisaryl Substituted Thiazoles and Oxazoles as Highly Potent and Selective Peroxisome Proliferator-Activated Receptor δ Agonists, J. Med. Chem.53 (2010) 77-105.

[19] R. L. Dow, et al., Benzyloxazolidine-2,4-diones as potent hypoglycemic agents, J. Med. Chem. 34 (1991) 1538-1544.

[20] H. Shinkai, et al., Isoxazolidine-3,5-dione and Noncyclic 1,3-Dicarbonyl Compounds as Hypoglycemic Agents, J. Med. Chem. 41 (1998) 1927-1933.

[21] K. Henriksen, et al., A comparison of glycemic control, water retention, and musculoskeletal effects of balaglitazone and pioglitazone in diet-induced obese rats, Eur. J. Pharmacol. 616 (2009) 340-345.

[22] http://www.news-medical.net/news/20100104/Headline-results-from-first-phase-III-study-of-Balaglitazone-announced.aspx

[23] S. Kanda, et al., Potent Antidiabetic Effects of Rivoglitazone, a Novel Peroxisome Proliferator–Activated Receptor-γ Agonist, in Obese Diabetic Rodent Models, J. Pharmacol. Sci. 111 (2009) 155-166.

[24] B. B. Lohray, et al., Novel Euglycemic and Hypolipidemic Agents, J. Med. Chem. 41 (1998) 1619-1630.

[25] T. Srivastava, W. Haq, S. B. Katti, Tetrahedron 58 (2002) 7619-7624.

[26] B. M. Trost, D. P. Curran, Chemoselective oxidation of sulfides to sulfones with potassium hydrogen persulfate, Tett. Lett .22 (1981) 1287-1290.

[27] A. K. Tamarkar, et al., Stimulatory effect of Ceriops tagal on hexose uptake in L6 muscle cells in culture, Nat Prod Res.22, (2008) 592-599.

[28] L. Herberg, D.L. Coleman. Laboratory animals exhibiting obesity and diabetes syndromes. Metab. Clin. Exp., 26 (1977) 59–100

[29] E. H. Leiter, The genetics of diabetes susceptibility in mice, FASEB J. 3 (**1989)** 2231-2241.

[30] M. J. Orland, M. A. Permutt, Quantitative analysis of pancreatic proinsulin mRNA in genetically diabetic (db/db) mice, Diabetes 36 (1987) 341-347.

[31] O. A. MacDougald, and S. Mandrup, Adipogenesis: forces that tip the scales. Trends Endocrinol.Metab. 13 (2002) 5–11

[32] X. Sheng, Y. Zhang, Z. Gong, C. Huang, and Y. Q. Zang, Improved insulin resistance and lipid metabolism by cinnamon extract through activation of peroxisome proliferator-activated receptors. PPAR Res. (2008) 581348. Published online 2008 December 11. doi: 10.1155/2008/581348.

[33] S. Yonemitsu, H. Nishimura, M. Shintani et al. Troglitazone induces GLUT4 translocation in L6 myotubes. Diabetes 50 (2001) 1093–1101.

[34] S. Pastromas and S. Koulouris. Thiazolidinediones: antidiabetic drugs with cardiovascular effects. Hellenic J. Cardiol. 47 (2006) 352–360.

Captions for figures, tables and shemes:

Figure 1.

New Rosiglitazone derivatives

Figure 2.

Panels 1-9 showing the blood glucose lowering effect of 3a, 3b, 3d, 3f, 4a, 4b, 4f, 6a, 6b and 7a on db/db mice

Figure 3. Effects of compound 3a and 3b on adipocyte differentiation in 3T3-L1 pre-adipocytes. (Photographs 3a). and change in O.D. (Fig. 3b)

Table 1.

Effect of compounds 3a-7b on glucose utilization by L-6 myotubes

Table 2.

Effect of test compounds on oral glucose tolerance test post glucose load (OGTT) on db/db mice on day 10^{th} and day 15^{th} post treatment.

Table 3.

Effect of test compounds on lipid profiles and insulin level on db/db mice on day 16^{th}

Scheme 1

Synthesis of compounds 3-7

Table 1:

S. No.	Compd.[a]	R	Effect on glucose uptake %
1.	**3a**	H	+51.9
2.	**3b**	Cyclopropyl	+67.2
3.	**3c**	Isopropyl	NS
4.	**3d**	Butyl	NS
5.	**3e**	Octyl	NS
6.	**3f**	Benzyl	NS
7.	**3g**	4- chlorophenyl	NS
8.	**3h**	2-(1H-indol-3 yl)ethyl	NS
9.	**4a**	H	+53.5
10.	**4b**	Cyclopropyl	+69.5
11.	**4c**	Isopropyl	+14.8
12.	**4d**	Butyl	+35.4
13.	**4e**	Octyl	NS
14.	**4f**	Benzyl	+33.0
15.	**5a**	Butyl	NS
16.	**5b**	Benzyl	NS
17.	**6a**	Butyl	NS
18.	**6b**	Benzyl	+45.5
19.	**7a**	Butyl	+51.3
20.	**7b**	Benzyl	NS
21.	**Rosiglitazone**[b]		+61.6

NS= Not significant; a: conc. 10µM; b: conc. 50µM

Table 2.

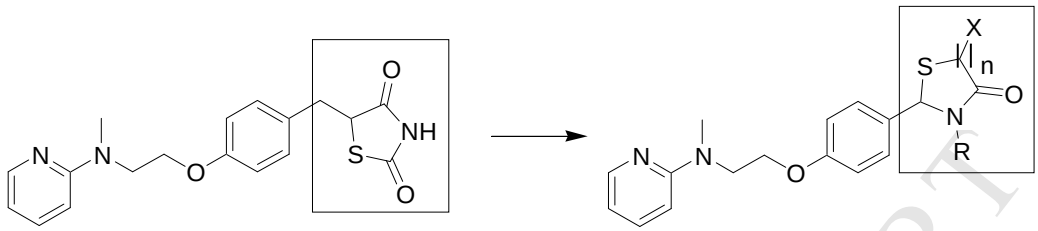
Group	% improvement in OGTT	
	Day 10th	Day 15th
3a	-25.9*	-36.6**
3b	-26.6*	-40.9*
3d	-20.2*	-25.4*
3f	-4.30	-16.4
4a	-40.8*	-44.9**
4b	-20.4*	-27.9*
4f	-29.4*	-42.6**
6a	-12.9	-27.2*
6b	-6.40	-20.2*
7b	-26.8*	-30.9*
Rosiglitazone	-33.3**	-40.7**

Values are % change as compare to control, Statistical significance * $P<0.05$, ** $P<0.01$

Table 3.

Group	% change in serum profile			
	TG	**Chol**	**HDL-c**	**Insulin**
3a	-14.0	-19.3	-	-27.4
3b	-15.6	-12.6	+8.80	-31.8
3d	-31.8	-4.80	+10.1	-17.6
3f	-9.83	-10.2	+22.2	-22.4
4a	-13.2	-15.1	+1.46	-28.8
4b	-29.9	-29.5	+3.38	-26.6
4f	-25.6	-9.88	+6.47	-21.5
6a	-19.2	-10.8	+39.6	-24.6
6b	-18.4	-	+20.0	-20.4
7a	-14.7	-7.20	+25.7	-28.8
Rosiglitazone	-32.5	-26.4	-22.8	-44.8

Values are % change as compare to control, the minus (-) sign denotes decrease in value whereas the plus (+) sign denotes the increase in the value



Rosiglitazone

Rosiglitazone derivatives **3-7**
R = H, alkyl, aryl etc; X = H, CH_3; n = 1, 2

Figure 1.

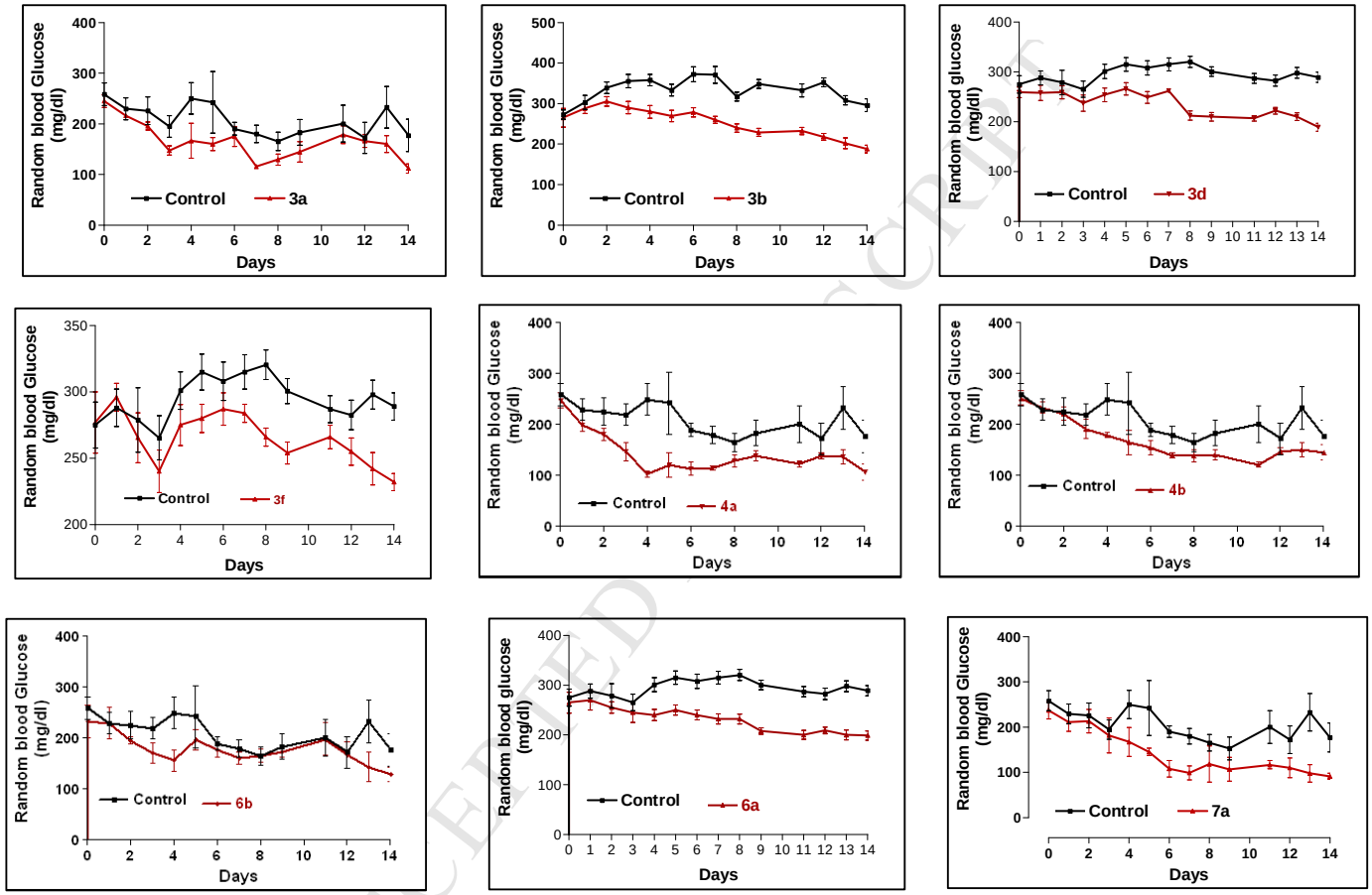
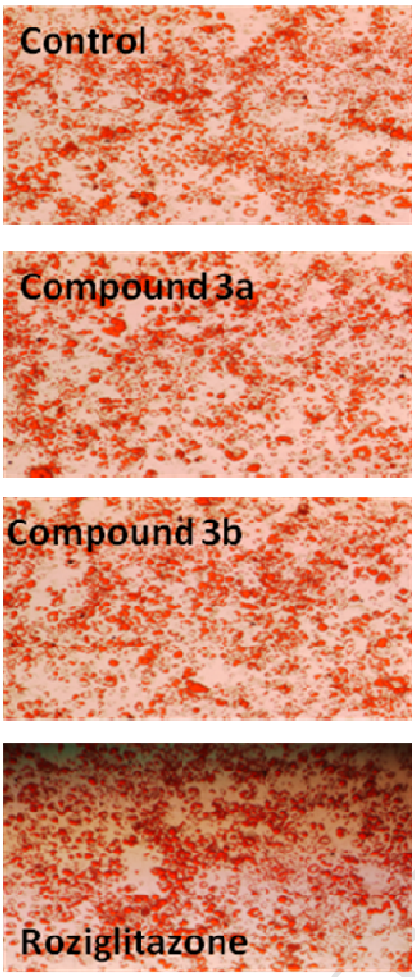


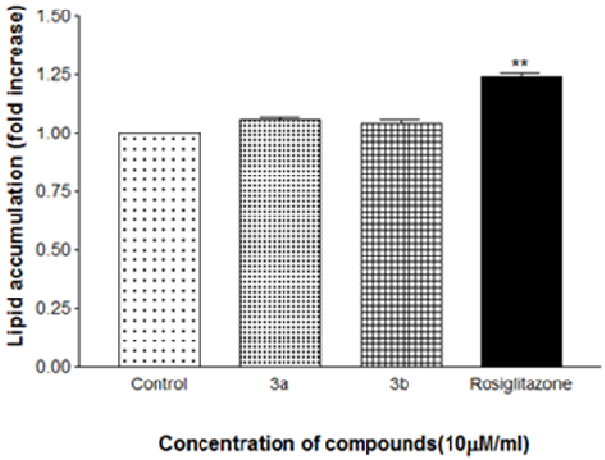
Figure 2: Panels 1-9 showing the blood glucose lowering of **3a**, **3b**, **3d**, **3f**, **4a**, **4b**, **4f**, **6a**, **6b** and **7a** in db/db mice

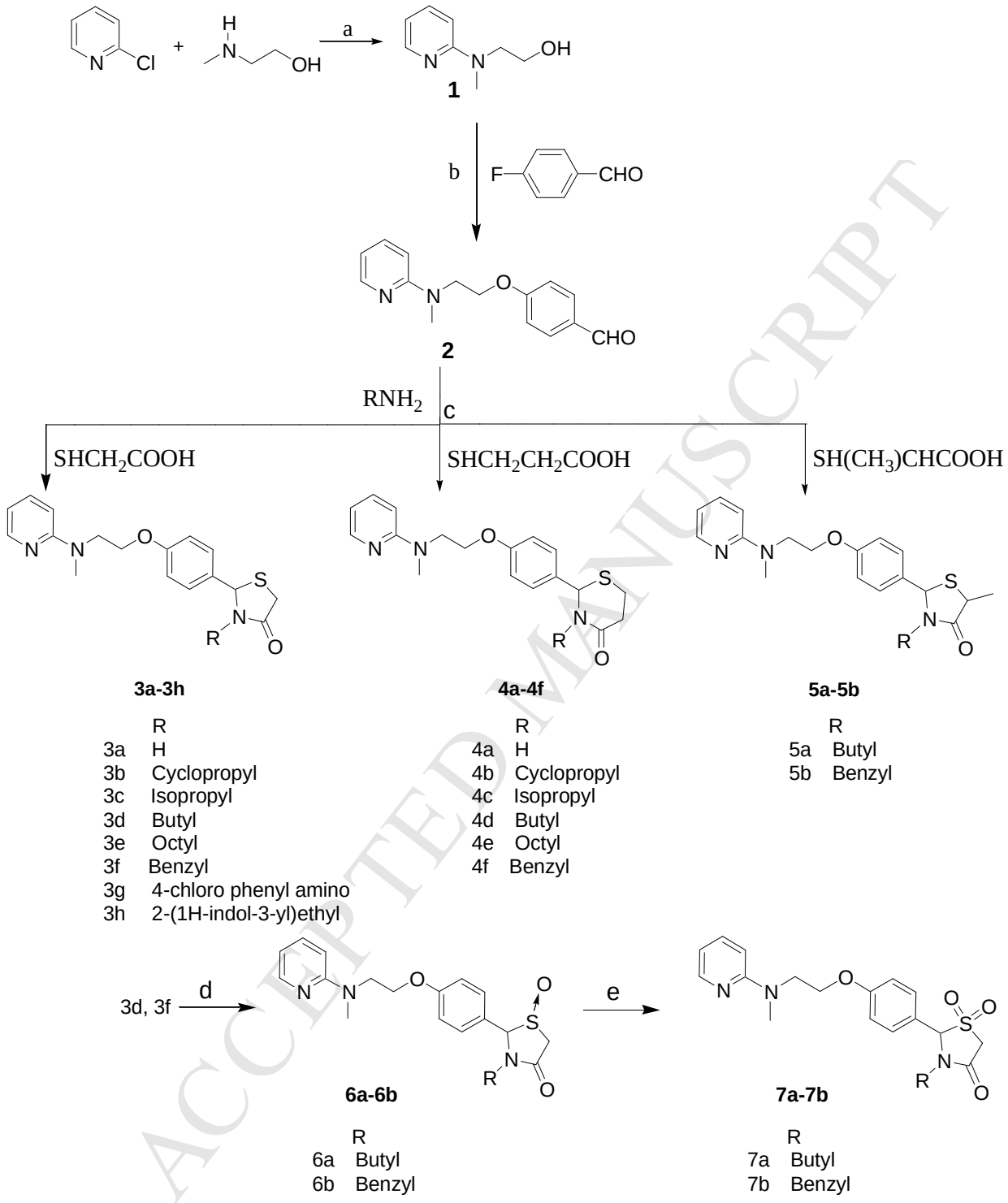
Figure 3



3(a)

3(b)





Scheme-1

Reagents and conditions: (a) neat, 150-160°C, 15hrs; (b) NaH, DMF, 80°C, 15-18 hrs. (c) DCC, THF, 5-7 hrs; (d) oxone, MeOH-H_2O, -10° to -5°C, 30-40 mins; (e) excess oxone, rt, 2 hrs.