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Synthesis and Evaluation of 1, 3-Thiazolidin-4-One Derivatives as Antihyperglycemic Agent

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Abstract

Thiazolidinedione (TZD) class of drugs which were approved for the management of type 2 diabetes mellitus exemplified by rosiglitazone and pioglitazone (PG), act by modulation of PPARγ receptors. Rosiglitazone was found to induce heart failure due to fluid retention and hence it has been withdrawn from market. Concerns were also raised recently on the apparent risk of bladder cancer with the use of Pioglitazone. Based on the advances and better understanding of antidiabetic agents, rational approaches have been applied for further development of the newer antidiabetic agents. The dual agonists of PPAR-α/γ, PPAR-α/δ, PPAR-δ\α, PPAR pan agonists and selective PPARC modulators and partial agonists are cardinal attractive targets for medicinal chemists in this sojourn. Attempts were reported to develop such agents several modifications on thiazolidinedione ring and the substituents were made. This research paper presents the design of new series of thiazolidinones with pyridine/ pyrimidine tail and cyclopropyl\alkyl and aryl substituent with an ethoxy linker and their evaluation for antihyperglycemic activity. Some of the new thiazolidin-4-one derivatives were found to be equipotent to pioglitazone in lowering blood glucose in streptozotocin induced diabetic rats.

Keywords
Thiazolidinedione; Type2 Diabetes mellitus; synthesis; antihyperglycemic

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1.0 INTRODUCTION:

Diabetes has become a leading killer disease in recent years. The statistical report of 2021 on diabetes indicated that a whopping 537 million people were suffering with this disease which is estimated to reach 643 million by 2030. Astounding 6.7 million people which is one death in every five seconds. High incidences of diabetes have been reported from low- and middle-income countries which account for 3 in 4 people. The currently available drugs for the treatment of diabetes were associated with several untoward effects.[1] 1, 3-Thiazolidin-4-ones have gained importance due to their wide spectrum of biological and pharmacological activities such as anti-microbial, antitubercular, anti-inflammatory, analgesic, antihistaminic, anti-parkinsonism, antitumor, hypolipidemic, antioxidant and antihyperglycemic activities. Numerous TZDs have been employed in clinical management of DM and are associated with various untoward effects including weight gain, fluid retention and heart failure. Further modifications of 1,3-thiazolidin-4-ones were reported as a new class of agents associated with partial agonistic activity, a new class osf antihyperglycemic agents. Hence, the attention of researchers is focused on the development of novel agents which are devoid of such side effects associated with TZD. Thus, 1,3-

thiazolidin-4-ones are expected to be potent antidiabetic agents without associated potential untoward effects.[2] There is an urgent need to develop novel antidiabetic agents, without the development and progression of complications or compromising on safety. Modification on the TZD were attempted in order to develop agents with reduced or no toxic effects.[3-7]Hence, in the present work, it is proposed to synthesize and screen the molecules shown in general structure, obtained by the incorporation of pyrimidine in place of pyridine (tail) with modifications in the head with R (cyclopropyl, alkyl, phenyl and substituted phenyl etc.). Thus replacement of thiazolidindione (head group) with thiazolidine-4-one resulted in new series of compounds as shown in **Figure 1**.

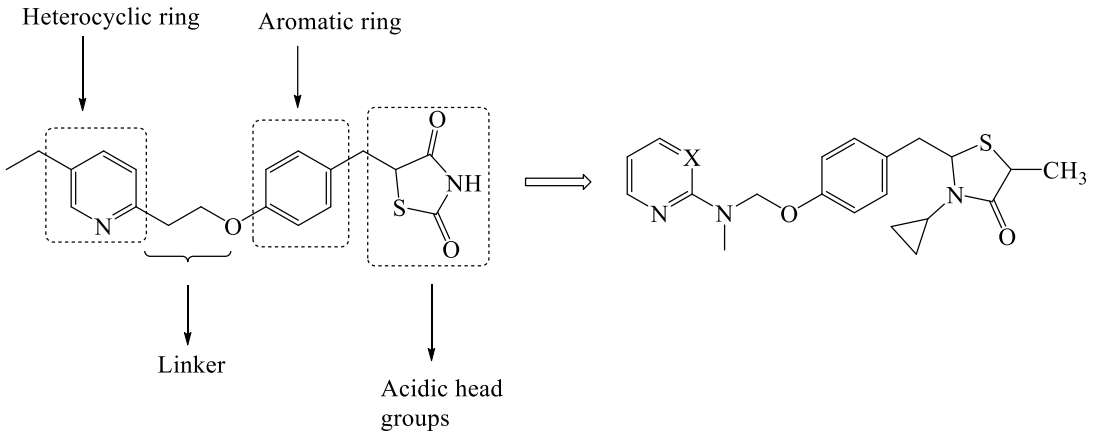


Fig.1. Synthesize and screen the molecules shown in General Structure.

2.0 MATERIALS AND METHODS:

Melting points were determined by open capillary tubes using VEEGO VMP-D Digital melting point. FTIR spectra of the powdered compounds were recorded using KBr on a JASCO FTIR 4100 series and are reported in cm^{-1} and 1H NMR spectra were recorded on a Varian Mercury YH300 (300 MHz FT NMR) spectrophotometer using TMS as an internal reference (Chemical shift represented in ppm). The purity of the compounds was checked on TLC plates using silica gel G as stationary phase and iodine vapors and UV chamber as the visualizing agent.

2.1. General procedure for 2-(Methyl-pyrimidin/pyridin-2-yl-amino)-ethanol (3a-b):

A mixture of 2-chloropyridine **1a**/ 2-chloropyrimidine**1b** (300 mmol) and N-methyl amino ethanol **2**(16.0mL, 200 mmol) was heated under nitrogen at 160°C while stirring for 15 hours. The reaction mixture was cooled to room temperature, poured into water and the solution was extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The crude product was purified by passing over silica gel using a mixture of methanol-chloroform as eluent to afford the **3a-b.**

2.2. General procedure for 4-[2-(Methyl- pyridin / pyrimidin-2-yl-amino)-ethoxy]-benzaldehyde (5a-b): To a stirred suspension of sodium hydride (4.7g) in DMF (20mL) was added 2-(methylpyridin-2-yl-amino)-ethanol **(3a)** 2-(methylpyrimdin-2-yl-amino)-ethanol and **(3b)** (12 g, 78.95mmol) in dry DMF (250mL) under nitrogen and the mixture was stirred for 30 min. A solution of 4-fluorobenzaldehyde **4** (12.2mL, 118.43mmol) in dry DMF (100mL) was added and stirred for 15-18 hours at 80°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 corresponding benzaldehyde derivatives (**5a-b**).

2.3. General method of preparation of thiazolidin-4-ones (8a-d and 9a-c):

The appropriate aldehydes**5a-b** (4.0 mmol) were stirred in dry THF under ice cold conditions for 10 min, followed by addition of mercaptoacetic acid **6**(6.0 mmol) / marcaptolactic acid **7**. 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. DCC was removed by filtration and the filtrate was concentrated under reduced pressure and the resulting residue was dissolved 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 crude products which were purified by column chromatography on silica gel using ethyl acetate-hexane mixture as eluent to afford pure **8a-d** and **9a-c**.

2.4 Antihyperglycemic activity:

Diabetes was induced in rats by the administration of streptozotocin in ice cold normal saline, as 45 mg/kg body weight intraperitoneally.[8-10]After 72 hours, sample was collected from rats by orbital puncture of all surviving animals and the serum was analyzed for glucose levels. Rats with blood glucose levels of 300mg/dl and above were considered as diabetic and selected for the study.

Following an overnight fasting, rats were divided into 4 groups (n = 6).

1. Normal control group
2. Diabetic control group
3. Standard group: Animals received pioglitazone p.o (30mg/kg)
4. Test groups consist of seven compounds (**8a-d and9a-c**) administered to animals p.o (30mg/kg).

Blood samples were collected from orbital puncture Riley *et al*[11]at time intervals between 0, 1, 2, 4, 6, 8, 10 and12 hrs using heparinized capillaries. Serum was separated by centrifugation using Biofuge-13 (Heraeus Instruments, Germany). And blood glucose levels were determined using GOD-POD method and remaining serum was stored in vials at −70°C until further analysis.

Procedure for estimating blood glucose:

In the present study, the enzymatic, glucose-oxidase-peroxidase (GOD-POD) method was employed, [12-16]Glucose kit constitutes following reagents.

1) Glucose reagent → glucose oxidase, peroxidase
2) Glucose standard → dextrose (100mg/dl).

The solutions were mixed well, incubated at 37 °C for 10min at room temperature and the absorbance of test and standard was read against blank at 520 nm.From the absorbance, mean blood glucose levels (mg/dL) and percentage reduction in blood glucose levels in diabetic rats were calculated.

2.5 Spectral and Analytical data:

2.5.1.3-cyclopropyl-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl) thiazolidin-4-one (8a):IR spectrum(KBr, cm^{-1}): 3025.01 (C-H Aromatic (str)), 2923.09 (C-H Aliphatic (str)), 1660.82 (C=O (str)), 1616.39 (C=N (str)), 1515.06 (C=C Aromatic(str)), 635.22 (S-CH(str),1101.76(C-O (str)), 1360.26(C-N (str)), ^{1}H NMR (400MHz $CDCl_3$, δ ppm):0.82-0.86(m, 4H, cyclopropyl), 2.32-2.36-2.38(m, 1H, cyclopropyl), 3.21(s, 3H, N-CH3), 3.95(s, 1H, CH), 4.14-4.18(m, 4H), 5.92(s, 1H, CH-S), 7.20-7.24(m, 6H, Aromatic), 7.32-7.34(d, 2H,Aromatic).^{13}C NMR(100MHz,$CDCl_3$) 5.1, 5.3, 29.5, 34.2, 35.8, 61.3, 62.3, 66.1, 106.2, 114.3, 115.2, 117.6, 129.3, 129.5, 135.2, 138.4, 148.2, 154.2, 157.6, 170.2. MASS spectrum of this compound showed [M+H] $^+$peak atm/z: 369.15 (100.0%), 370.15 (23.5%), Anal. Calc for Elemental Analysis: C, 65.01; H, 6.27; N, 11.37; O, 8.66; S, 8.68: found C, 65.05; H, 6.20; N, 11.31; S, 8.61.

2.5.23-methyl-2-(4-(2-(methyl (pyridin-2-yl) amino) ethoxy) phenyl) thiazolidin-4-one (8b):IR spectrum(KBr, cm^{-1})3080.01 (C-H Aromatic (str)), 2950.09 (C-H Aliphatic (str)), 1680.82 (C=O (str)), 1650.39 (C=N (str)), 1529.06 (C=C Aromatic(str)), 1358.26(C-N (str)), 1120.76(C-O (str)), 658.22 (S-CH(str)), ^{1}H NMR (400MHz $CDCl_3$, δ ppm):3.21(s, 3H, N-CH_3), 3.47(s, 3H), 3.98(s, 2H), 4.14(t, 2H), 4.24(t, 2H), 5.97(s, 1H), 6.98-7.02(m, 4H, Aromatic), 7.68-7.70 (m, 4H, Aromatic):^{13}C NMR(100MHz,$CDCl_3$): 31.7, 33.6, 35.8, 61.3, 66.1, 67.3, 106.3, 114.3, 114.7, 117.9, 129.4, 129.6,135.4, 148.1, 154.1, 157.2, 171.2.MASS spectrum of this compound showed $[M+H]^+$peak atm/z: 343.14 (100.0%), 344.14 (19.8%), 345.13 (4.5%): Anal. Calcd for Elemental Analysis: C, 62.95; H, 6.16; N, 12.23;S, 9.34 found C, 62.89; H, 6.25; N, 12.18; S, 9.90.

2.5.3.5-methyl-2-(4-(2-(methyl(pyridin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one(8c): IR spectrum(KBr, cm^{-1})3025.01 (C-H Aromatic (str)), 2923.09 (C-H Aliphatic (str)), 1660.82 (C=O (str)), 1616.39 (C=N (str)), 1515.06(C=C Aromatic(str)), 635.22 (S-CH(str)),1101.76(C-O (str)), 1360.26(C-N (str)), ^{1}H NMR (400MHz $CDCl_3$, δ ppm):1.40(d, 3H), 3.21(s, 3H, N-CH_3), 3.65-3.68(m, 1H), 4.14 - 4.16 (t, 2H), 4.24- 4.27(t, 2H), 5.90(s, 1H), 7.05-7.08(m, 4H, aromatic), 7.85-7.89(m, 4H, aromatic), 8.02(s,1H, amide): ^{13}C NMR(100MHz,$CDCl_3$): 20.0, 35.8,45.0, 53.2, 61.3, 66.3, 106.2, 114.3, 114.3, 117.9, 129.3, 129.3, 130.5, 138.3, 148.1, 154.3, 157.8, 175.7: MASS spectrum of this compound showed $[M+H]^+$peak atm/z: 343.14 (100.0%), 344.14 (19.8%), 345.13 (4.5%): Anal. Calcd for Elemental Analysis: C, 62.95; H, 6.16; N, 12.23; S, 9.34: found C, 62.75; H, 6.26; N, 12.13; S, 9.38:

2.5.4.3-cyclopropyl-5-methyl-2-(4-(2-(methyl(pyridin-2yl)amino)ethoxy)phenyl)thiazolidin-4-one(8d):IR spectrum(KBr, cm^{-1})3063.01 (C-H Aromatic (str)), 2950.09 (C-H Aliphatic (str)).1685.82 (C=O (str)), 1620.39 (C=N (str)), 1530.06 (C=C Aromatic(str)), 675.22 (S-CH(str)),1108.76C-O (str)), 1365.26(C-N (str)), ^{1}H NMR (400MHz $CDCl_3$, δ ppm):0.82-0.84(m, 4H, Cyclopropyl), 1.40-142(d, 3H), 2.32-2.36(m, 1H), 3.21(s, 3H, NCH_3), 3.65-3.67 (m, 1H), 4.14-4.16(t, 3H), 4.24-4.26(m, 3H), 5.92(s, 1H), 7.54-7.58(m, 4H, aromatic), 7.98-8.02(m, 4H, aromatic). ^{13}C NMR (100MHz, $CDCl_3$): 5.1, 5.1, 20.3, 29.8, 35.8, 43.2, 59.8, 61.3, 66.3, 106.2, 114.3, 114.3, 117.3, 129.3, 135.4,

138.2, 148.1, 154.2, 157.2, 173.2: MASS spectrum of this compound showed [M+H] $^{+}$peak atm/z: 383.17 (100.0%), 384.17 (23.9%), 385.16 (4.5%). Anal. Calcd for Elemental Analysis: C, 65.77; H, 6.57; N, 10.96; O, 8.34; S, 8.36: found C, 65.75; H, 8.26; N, 10.93; S, 8.38.

2.5.5.3-cyclopropyl-2-(4-(2-(methyl(pyrimidin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one(9a):IR spectrum(KBr, cm^{-1}) 3025.01 (C-H Aromatic (str)), 2923.09 (C-H Aliphatic (str)), 1660.82 (C=O (str)), 1616.39 (C=N (str)), 1515.06 (C=C Aromatic(str)), 635.22 (S-CH(str),1101.76(C-O (str)), 1360.26(C-N (str)), ^{1}H NMR (400MHz $CDCl_3$, δ ppm):0.82-0.86(m, 4H, cyclopropyl), 2.32-2.36(m, 1H, cyclopropyl), 3.21(s, 3H, NCH_3), 3.95(s, 1H, CH), 4.14-4.18(m, 4H), 5.92(s, 1H, CH-S), 7.20-7.24(m, 5H, Aromatic), 7.32-7.34(d, 2H,Aromatic).^{13}C NMR(100MHz,$CDCl_3$) 5.1, 5.3, 29.5, 34.2, 35.8, 61.3, 62.3, 66.1, 106.2, 114.3, 115.2, 117.6, 129.5, 135.2, 138.4, 148.2, 154.2, 157.6,170.2. MASS spectrum of this compound showed [M+H]$^{+}$peak atm/z: 370.15 (100.0%), 371.15 (21.7%), 372.14 (4.5%), 372.15 (2.9%): Anal. Calcd for Elemental Analysis: C, 61.60; H, 5.99; N, 15.12; S, 8.66found C, 61.48; H, 5.59; N, 15.37; S, 8.14:

2.5.6.5-methyl-2-(4-(2-(methyl(pyrimidin-2-yl)amino)ethoxy)phenyl)thiazolidin-4-one(9b): IR spectrum(KBr, cm^{-1})3065.01 (C-H Aromatic (str)), 2980.09 (C-H Aliphatic (str)), 1680.82 (C=O (str)), 1620.39 (C=N (str)), 1520.06 (C=C Aromatic(str)), 645.22 (S-CH(str),1120.76C-O (str)), 1355.26(C-N (str)), ^{1}H NMR (400MHz $CDCl_3$, δ ppm): 1.40-1.42 (d, 3H), 3.21(s, 3H, N-CH3), 3.65-3.68(m, 1H), 4.130-4.16 (t, 2H), 4.24- 4.27(t, 2H), 5.90(s, 1H), 7.05-7.08(m, 4H, aromatic), 7.85-7.89(m, 3H, aromatic), 8.02(s,1H, amide): ^{13}C NMR(100MHz,$CDCl_3$): 20.0, 35.8,45.0, 53.2, 61.3, 66.3, 106.2, 114.3, 114.3, 117.9, 129.3, 129.3, 130.5, 138.3, 148.1, 154.3, 157.8, 175.7:MASS spectrum of this compound showed [M+H]$^{+}$peak atm/z: 344.13 (100.0%), 345.13 (20.7%), 346.13 (5.4%), 346.14 (1.6%): Anal. Calc for Elemental Analysis: C, 59.28; H, 5.85; N, 16.27; S, 9.31: found C, 59.75; H, 5.26; N, 16.13; S, 9.38:

2.5.7.3-cyclopropyl- 5- methyl- 2- (4- (2- (methyl (pyrimidin- 2- yl) amino) ethoxy) phenyl) thiazolidin- 4- one (9c):IR spectrum(KBr, cm^{-1}), 3054.01 (C-H Aromatic (str)), 2940.09 (C-H Aliphatic (str)).1675.82 (C=O (str)), 1650.39 (C=N (str)), 1540.06 (C=C Aromatic(str)), 675.22 (S-CH(str),1120.76 (C-O (str)), 1375.26 (C-N (str)), ^{1}H NMR (400MHz $CDCl_3$, δ ppm):0.82-0.84(m, 4H, Cyclopropyl), 1.42-144 (d, 3H), 2.32-2.36(m, 1H), 3.21(s, 3H, N-CH_3), 3.65-3.67 (m, 1H), 4.14-4.16(t, 3H), 4.24-4.26(m, 3H), 5.92(s, 1H), 7.54-7.58(m, 4H, aromatic), 7.98-8.02(m, 3H, aromatic). ^{13}C NMR (100MHz, $CDCl_3$): 5.1, 5.1, 20.3, 35.8, 43.2, 59.8, 61.3, 66.3, 106.2, 114.3, 114.3, 117.3, 129.3, 135.4, 138.2, 148.1, 154.2, 157.2, 173.2: MASS spectrum of this compound showed [M+H] $^{+}$ peak atm/z: 384.16 (100.0%), 385.17 (22.0%), 386.16 (5.0%), 386.17 (2.7%). Anal. Calc for Elemental Analysis: C, 62.48; H, 6.29; N, 14.57; S, 8.34: found C, 62.75; H, 6.26; N, 14.93; S, 8.38.

3.0 RESULTS AND DISCUSSIONS:

Chemistry:

The synthetic protocol of 1,3-thiazolidine-4-one derivatives is presented in **Scheme-1**. Synthesis of the 1,3-thiazolidin-4-one derivatives (**8a-d and 9a-c**) containing an acidic head group, a central phenyl group and a hydrophobic tail group joined by an alkyl linker is carried out in a three-step procedure. In the first step, the alcoholic derivatives of pyridine and pyridimine (**1a-b**) were synthesized using N-methyl amino ethanol**2**. In the second step the alcoholic derivative (**3a-b**) was reacted with 4-fluorobenzaldehyde **4** in presence of NaH, to afford benzaldehyde derivative (**5a-b**). In the third step benzaldehyde derivative (**5a-b**) ware reacted with appropriate amines and mercapto carboxylic acids (thioglycolicacid **6**\thiolactic acid**7**) in the presence of DCC at room temperature to afford thiazolidin-4-one derivatives (**8a-d** and **9a-c**) by three component condensation method in one pot reaction. The synthesized compounds were purified and characterized by IR, NMR and Mass spectral and elemental (C, H, N) analysis data.

The structure of the compounds was as assigned based on spectral analysis. The IR spectrum of 3-cyclopropyl-2-(4-(2-methyl (pyridine-2-yl) amino) ethoxyl phenyl) thiazolidine-4-one (**8d**) showed C-H aromatic str. band at 1660, and C=N Str at 1616 cm^{-1}.^{1}H-NMR (ppm) spectrum showed a multiplet between 0.82-0.86 for four protons corresponding to cyclopropyl ring, a multiplet for one proton between 2.32-2.36 assignable to CH of cyclopropyl ring. Three protons of methyl groupon nitrogen appeared as a singlet at 3.21. Four protons of ethyl linker (-CH_2-CH_2-) appeared as a multiplet between 4.14-4.18 ppm, one proton of thiazolidine ring on carbon atom adjacent to sulfur (CH-S) appeared as a singlet at 5.92. Eight aromatic protons appeared as two multiplets between 7.20-7.24& 7.32-7.34 for six and two protons respectively. Mass spectrum of the compound also showed [M+1] Peak at 369.15 (100%). C, H, N analysis data was also found to be in agreement the molecular remaining formula of the compound. Similarly, other compounds were analyzed and characterized.

Glucose standard graph:

Table 1: Physical data of Title compounds pyridine series 8a-dand pyrimidine series 9a-c:

Comp.	Comp.	R^1	X	R	Mol. Formula	Mol. wt	Melting point (°C)	% Yield
IIIa	8a	-H	CH	Cyclopropyl	$C_{20}H_{23}N_3O_2S$	369.48	80-82	52.23
IIId	8b	-H	CH	Methyl	$C_{18}H_{21}N_3O_2S$	343.44	100-102	41.59
IIIf	8c	$-CH_3$	CH	-H	$C_{18}H_{21}N_3O_2S$	343.44	102-104	40.12
IIIg	8d	$-CH_3$	CH	Cyclopropyl	$C_{21}H_{25}N_3O_2S$	383.51	85-87	62.83
IVa	9a	-H	N	Cyclopropyl	$C_{19}H_{22}N_4O_2S$	370.47	106-108	40.13
IVf	9b	$-CH_3$	N	H	$C_{17}H_{20}N_4O_2S$	344.43	102-104	73.93
IVg	9c	$-CH_3$	N	Cyclopropyl	$C_{20}H_{24}N_4O_2S$	384.50	106-108	52.18

Table 2: Absorbance Vs Concentration:

Concentration (mg/dl)	Optical density (OD)
0	0
50	0.15
100	0.27
200	0.49
300	0.76
400	0.98

Table 3: Mean blood glucose levels (mg/dL) in diabetic rats:

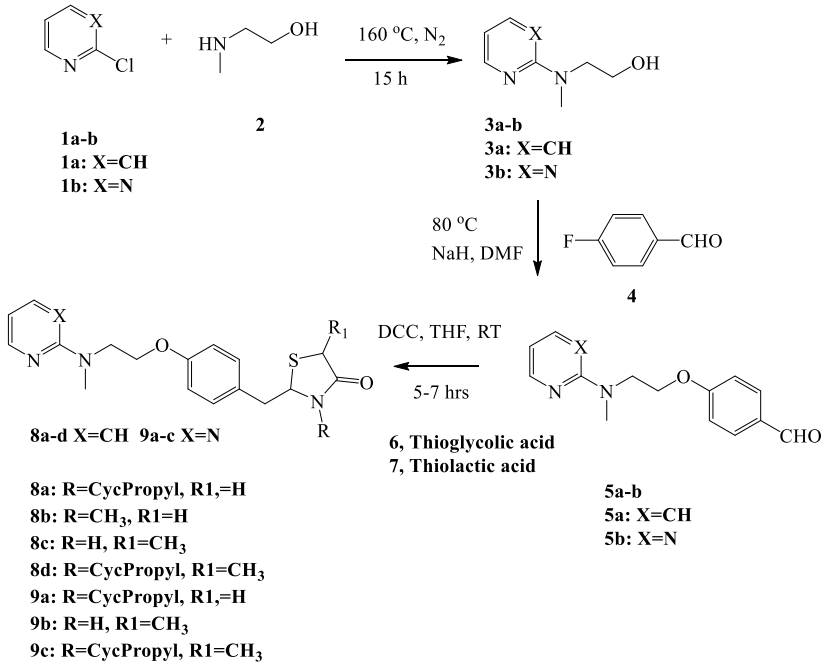
S. No		Time (hr)							
		0	1	2	4	6	8	10	12
IIIa	8a	234.15± 1.38	226.12± 4.30	218.30± 7.26	208.14± 1.26	196.18± 5.60	206.12± 7.26	218.03± 1.30	226.23± 6.30
IIId	8b	246.51± 4.32	209.30± 6.46	206.97± 6.80	162.79± 6.97	137.20± 9.30	213.95± 8.84	230.23± 5.81	320.93± 2.63
IIIf	8c	226.93± 7.31	218.43± 4.61	203.81± 7.26	191.43± 6.31	186.39± 5.20	209.86± 1.30	216.43± 7.86	218.93± 2.63
IIIg	8d	265.11± 3.30	213.17± 1.85	163.56± 1.38	151.16± 6.98	224.02± 7.75	227.12± 3.87	239.53± 2.33	247.27± 3.09
IVa	9a	254.89± 1.96	248.47± 1.03	236.34± 1.14	212.14± 1.28	200.74± 4.32	198.63± 6.96	189.38± 6.14	213.24± 5.86
IVf	9b	242.34± 3.20	230.18± 4.30	212.16± 1.26	200.12± 4.12	196.38± 1.32	226.63± 1.58	230.57± 6.96	232.83± 1.43
IVg	9c	292.24± 4.57	213.95± 3.90	203.87± 1.85	178.29± 8.53	131.00± 1.93	116.27± 1.86	100.07± 2.40	106.19± 5.28
PG		292.24± 6.2	222.48± 1.78	217.82± 1.28	149.61± 7.75	121.70± 1.08	141.85± 2.32	191.47± 1.47	280.61± 1.31

Values of this data was mentioned in the Mean ±SD, n=6

Table 4: Percentage reduction in blood glucose levels in diabetic rats:

	0	1	2	4	6	8	10	12
8a	0	3.42± 0.03	6.76± 0.06	11.1± 0.01	16.21± 0.35	11.97± 0.04	6.88± 0.13	3.38± 0.01
8b	0	15.09± 0.01	16.03±0.37	33.96±0.10	44.34±0.018	13.2± 0.67	6.6± 0.02	3.18± 0.02
8c	0	3.74± 0.03	10.18±0.18	15.64± 0.54	17.86± 0.02	7.52± 0.01	4.62±0.01	3.52±0.01
8d	0	19.6± 0.01	38.31± 0.01	42.99± 0.23	15.49± 0.62	14.32± 0.14	9.64± 0.001	6.72± 0.08
9a	0	2.51± 0.03	12.45± 0.08	16.77± 0.86	21.24± 0.12	22.07± 0.01	25.7± 0.12	16.34± 0.23
9b	0	26.78± 0.06	22.45±0.12	17.38± 0.93	18.96± 0.01	6.48± 0.01	4.85± 0.06	3.92± 0.45
9c	0	26.79± 0.15	30.23± 0.01	38.99±0.01	55.17±0.07	60.21± 0.02	65.75± 0.02	63.66± 0.01
PG	0	23.87± 0.01	25.46± 0.01	48.8± 0.29	58.35± 0.14	51.46± 0.01	34.48± 0.01	3.97± 0.01

Data were analyzed by two-way ANOVA followed by Dunnett's multiple comparison test, n = 6.



Scheme-1, Synthesis of compounds 8a-d and 9a-c

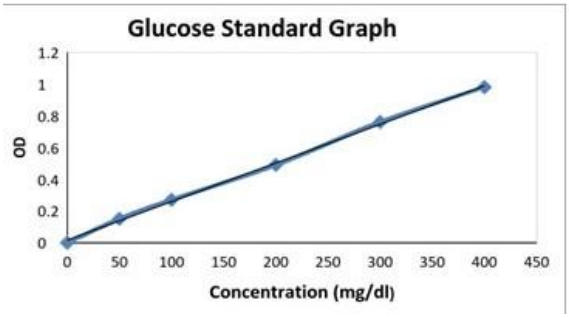


Fig.3. Absorbance Vs Concentration (for glucose standard graph)

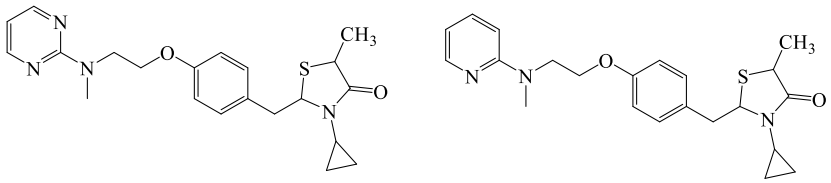


Fig.4. Synthetic Potent active compounds 8d and 9c structures.

All the seven compounds tested showed the significant reduction in blood glucose levels in the streptozotocin induced diabetic rats at 4th and 6thhrs after administration of test compounds. Among the compounds tested, the compound **9c** in pyrimidine series with cyclopropyl and a methyl group (R^1=CH_3)on nitrogen exhibited highest potency with 55.17% reduction in blood glucose levels at 6thhr when compared to 58.35% reduction shown by the standard (PG). Activity increased with time with % reduction in blood glucose levels reaching 65.75 at 10th hr whereas the standard showed only 3.97% reduction at similar time interval (10thhr), indicating the prolonged activity of compound **9c**.The pyridine analog with cyclopropyl substitution (R^1=CH_3) **8d** was found to be the next in the order of potency with 42.99% reduction in blood glucose levels when compared to 48.8% and 38.9% reduction at 4thhr shown by standard and compound **9c**. However, the activity decreased from 6thhr onwards with 15.49% reduction in blood glucose levels. The cyclopropyl analogue**(8a)** without a methyl substitution (R^1=H) showed 11.1% reduction in blood glucose levels at 4th hr of administration. The cyclopropyl derivative of pyrimidine series, **9a** (R^1=H) showed greater potency with 21.2 and 22% reduction in blood glucose levels at 6th and 8thhr respectively than that of the pyridine series, **8a** (R^1=H) with 16.2 and 11.7% reduction in blood glucose levels at similar time intervals. Replacement of cyclopropyl group with methyl in

pyridine series as in case of **8b** resulted in increase in potency with 33.7 and 44.3% reduction in blood glucose levels at 4th and 6thhr respectively.**Fig.4. 8d and 9c potent active Compounds.**

Statistical analysis:

The values were expressed as mean ± SEM. Statistical analysis was done by using two-way ANOVA followed by Dunnett's multiple comparison test. P<0.01 was considered significant when compared with control.

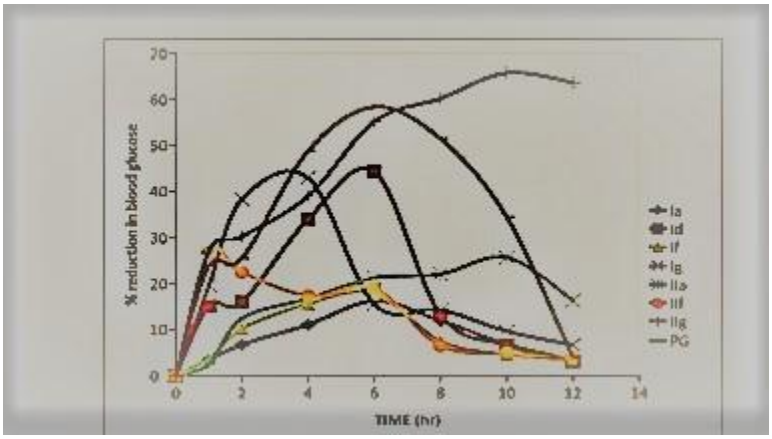


Fig.5. Statistical analysis was done by using two-way ANOVA followed by Dennett's multiple comparison test.

CONCLUSION:

All the twenty 1, 3-thiazolidin-4-one derivatives were characterized by spectral methods. Seven compounds were screened for antihyperglycemic activity by using streptozotocine induced diabetic Wister rats with the help of GOD-POD kit. The results were compared with standard drug Pioglitazone. All the compounds in Table **2** showed significant antihyperglycemic activity. Among them compound **9c** exhibited prolonged duration of action and found to be most active among all the tested compounds. The compound (**9c**) with pyrimidine substitution is 3 1/2 times more active than pyridine substitution (**8d**) in the head group of 1,3-thiazolidin-4-one derivatives.

REFERENCES:

1. Nguyen Q, Nguyen L, Felicetta J. Evaluation and management of diabetes mellitus. Am Health Drug Benefits 2008; 1(8):39-48. PMID: 25126259; PMCID: PMC4106505.
2. Sucheta, Tahlan S, Verma PK. Biological potential of thiazolidinedione derivatives of synthetic origin. Chem Cent J 2017; 8;11(1):130. doi: 10.1186/s13065-017-0357-2. PMID: 29222671; PMCID: PMC5722786.
3. SaiHarika M, Naga Sudha B, Raghavendra HG. Synergistic Activity of Thiadiazole and Thiazolidinone Derivatives Against Alloxan Induced Diabetes In Rats.Sch. Acad. J. Pharm 2014;3(10); 301-305.
4. Ahmed O, Salahuddin Md, Vinutha K, Sharma P, Design, Synthesis and Biological Evaluation of Some Novel Substituted Thiazolidinone Derivatives as Potent Antihyperglycemic Agents.IJPRS2013;1(3); 166-173.
5. Flefel EM, Sayed HH, Hashem AI, Saleh DO, Sofany WE,Abdel-Megeid FME. Hyperglycedemia and hypertriglyceridemia activities of newly synthesized compounds derived from 3´-(4-halophenyl)-5´-aryldiene spiro(cyclohexane-(1,2´)-thiazolidin)-4´-one. DerPharmaChemica2013; 4(5);142-157
6. Sen S, De B, Easwari TS. Synthesized 2-Substituted-3-Phenylthiazolidine-4-ones as Potent Antioxidants and Antidiabetic Agents.TJPR2014; 16:1445-1454.
7. Shukla R, Kalra S. Pioglitazone Indian perspective, Ind J Endocrin Metab. 2011; 4(15): 294-297.
8. Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi S, Farhangi A, Verdi AA, Mofidian SMA, Rad BL. Induction of diabetes by Streptozotocin in rats. Indian J Clin Biochem. 2007;22(2):60-4. doi: 10.1007/BF02913315. PMID: 23105684; PMCID: PMC3453807.
9. Isloor AM, Dhanya S, Shetty P, Malladi S,Pai KSR, Naseer M. Synthesis, characterization, anticancer, and antioxidant activity of some new thiazolidin-4-ones. Med Chem Res 2013;1(22):758–767.
10. RosenCJ.The rosiglitazone story-lessons learned, N Eng J Med 2010;5(12): 803-806.
11. Riley Dave MP, Langalia NA. J. Ind. Chem. Soc. 1985;3(11);254-255.
12. Trinder M. Synthesis and Oral Hypoglycemic Activity of 3-[5'-Methyl-2'-aryl-3'-(thiazol-2'' -ylamino) thiazolidin-4'-one] coumarin Derivatives. E-Jour Chem. 2011;1(6);386-390.
13. Gale EA. Lessons from the glitazones: a story of drug development. Lancet. 2001; 9;357(9271):1870-5. doi: 10.1016/S0140-6736(00)04960-6. PMID: 11410214.
14. Diurno MV, Mazzoni O, Correale G, Gomez Monterrey I, Calignano A, La Rana G, Bolognese A. Synthesis and structure-activity relationships of 2-(substituted phenyl) -3- [3-(N, N-dimethylamino)

propyl]-1,3-thiazolidin-4-ones acting as H1-histamine antagonists. Farmaco. 1999; 30;54(9):579-83.
doi: 10.1016 /s0014-827 x (99) 00064-6. PMID: 10555258.

15. Banerji MA, Lebovitz HE. Insulin action in black Americans with NIDDM. Diabetes Care. 1992;15(10):1295-302.
doi: 10.2337/diacare.15.10.1295. PMID: 1425092.
16. Molyneux P, The use of the stable free radical diphenyl picrylhydrazyl (DPPH) for estimating antioxidant activity. Songklanakarin J. Sci. Technol. 2004; 2(12); 211-219.