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Synthesis, characterization and Pharmacological evaluation of Thiazolidinone derivatives as hypoglycaemic agents

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ABSTRACT: Background: Thiazolidinone derivatives having a greater importance to treat the diabetes. This molecule is more potent derivative than the other molecules which is used to treat the diabetes. **Aim:** The present study was aimed to synthesize the thiazolidinone derivatives and to evaluate the synthesized thiazolidinone derivatives for anti-diabetic activity. **Method:** The newer substituted 3-(2-thiazolyl)-4-thiazolidinone derivatives were synthesized by reacting N^4-*p*-tolylthiazole-2,4-diamine in ethanol with substituted aromatic aldehydes and a few drops of glacial acetic acid. The reaction was then proceeded with thioglycolic acid in presence of anhydrous zinc chloride. The synthesis was carried out by the microwave irradiation method. All the synthesized thiazolidinone compounds were characterized for their melting point, retardation factor (R_f), molecular formula and weight by using Chromatographic (TLC and column chromatography) and Spectroscopic analysis (FTIR, MS and ^{1}H NMR). All the synthesized thiazolidinone compounds were tested for antidiabetic activity by streptozicin induced tail tipping method at single dose of 100 mg/kg body weight of Wister rat. The antidiabetic activity of synthesized compounds was compared with the standard drug, Glibenclamide. **Results:** Ten thiazolidinone (TZN-1 to TZN-10) derivative compounds were synthesized. These derivatives also possess significant anti-diabetic activity which was well comparable with the standard antidiabetic drug Glibenclamide. **Conclusion:** All the synthesized compounds through green synthesis technique shows significant anti-diabetic activity. The above green synthesis technique could be a right solution for the medicinal chemistry applications in the future and therapeutic needs.

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INTRODUCTION:

Diabetes mellitus is a heterogeneous group of diseases, characterized by a state of chronic hyperglycaemia [1]. The Diabetes mellitus occur due to environmental, genetic factors. The tissue level causes of diabetes are the defective production or action of insulin. The insulin is a hormone that controls carbohydrates, fats and proteins metabolism. Diabetes mellitus may develop

several complications like hypertension, renal disease, neurological disorder, anxiety, stress and ocular inter current infections [2]. Diabetes mellitus is a condition in which the pancreas no longer produces enough insulin or cells stop responding to insulin that is produced, so that glucose in blood cannot be absorbed into the cells of the body. The symptoms of diabetes are frequent urination, lethargy, excessive thrust and hunger. The treatment for diabetes includes changes in diet, oral medication and in some cases daily injections of insulin. Thiazolidinone derivatives are considered as 'privileged scaffolds' in the design of pharmacological probes. These heterocyclic compounds have high versatility in chemical modifications, allowing the changes to the characteristics of side chains on a rigid platform. A large number thiazolidinones have been reported for various biological activities like antimicrobial [3-6], anti-infective [7], anti-bacterial [8], anti-inflammatory [9,10], analgesic [11,12], anti-pyretic [13], anti-tubercular [14-16], antioxidant [17], anti-malarial [18], anticancer [19], anti-ulcer [20], anti-convulsant [21,22], anti-diabetic [23,24] and anti-HIV [25].

Considering the above observations and in correction to previous publications, the objective of the present study to synthesize the newer thiazolidinone derivatives and screening these synthesize newer thiazolidinone derivatives for their anti-diabetic activity.

MATERIAL AND METHODS:

The Streptozocine was procured from Aldrich, Mumbai. The standard drug Glibenclamide was procured as gift sample from Cadila Pharmaceutical Ltd, Sikkim. The toluidine, glacial acetic acid and ethanol were procured from Merk, Guntur. The thioglycolic acid, zinc chloride, sodium acetate and acetone were purchased from S.D. Fine Chemical, Guntur. The Schiff's base, aromatic aldehyde and thiourea were purchased from Spectrochem, Mumbai. The chloroacetylchloride and methanol were procured form Sisco research laboratories (SRL), Mumbai. All other chemicals, solvents and reagents used in this research study were of analytical grade and procured from authorized dealer.

Synthesis of 2-chloro-N-*p*-tolylacetamide:

The *p*-Toluidene (0.05 mol) was dissolved in glacial acetic acid (25 ml) containing (25 ml) of saturated solution of sodium acetate. In case if the substance did not dissolve completely, the mixture was warmed and then the solution was cooled in ice-bath with constant stirring. To this chloroacetylchloride (0.06 mol) was added drop wise to avoid the vigorous reaction. After half an hour a white colored product was separated and filtered. The product was washed with 50 % aqueous acetic acid and finally it was washed with water. It was recrystallized from aqueous alcohol.

Synthesis of N^4-*p*-tolylthiazole-2, 4-diamine:

A mixture of 2-chloro-N-*p*-tolylacetamide (0.02 mol) and thiourea (0.01 mol) in absolute acetone (90 ml) was refluxed for 45 min in microwave synthesizer. The excess of solvent was distilled off and the solid obtained was poured into ice-cold water, and then the compound was purified by recrystallization from methanol. Now, the solid was washed with 2 % sodium carbonate and then with water to liberate the base completely. The synthesize compound was dried and purified by recrystallization from ethanol/water to furnish compound.

Synthesis of Schiff bases:

To a solution of N^4-*p*-tolylthiazole-2,4-diamine (0.01 mol) in ethanol (60 ml), substituted aromatic aldehydes (0.01 mol) and a few drops of glacial acetic acid were added and the mixture was refluxed for 30 min in microwave synthesizer. It was then cooled, concentrated and poured into crushed ice and filtered. The product thus obtained was purified by recrystallization from methanol to obtain Schiff bases.

Synthesis of 3-(2-thiazolyl)-4-thiazolidinone derivatives:

A solution of Schiff base containing thiazole nucleus derivatives, thioglycolic acid (0.01 mol) and anhydrous zinc chloride (2 g) in absolute ethanol (60 ml) was refluxed for 20 min in microwave synthesizer, which was concentrated, cooled and poured into crushed ice, and then filtered. The product obtained was purified by recrystallization from acetone to get substituted with 3-(2-thiazolyl)-4-thiazolidinone derivatives. All the microwave experiments were performed using RAGA's microwave synthesizer.

Characterization of synthesized thiazolidinone derivatives:

The melting point of synthesized thiazolidinone derivatives was determined by using Digital melting point apparatus (METTLER TOLEDO, India).

The synthesized compounds were characterized with Thin Layer Chromatography (TLC) by using the Merck pre-coated TLC plates. The plates were coated with ACME's silica gel with 13% calcium sulphate ($CaSO_4$) as binder. The components were visualized under Iodine

chamber. The retention factor (R_f) value of all components was determined. The flash column chromatography was performed using Merck silica gel (100 to 200 mesh).

All compounds were purified by recrystallization with suitable organic solvents. IR spectra of synthesized compounds were recorded on BROOKER-ALPHA FT-IR instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique. ^{1}H NMR was determined in $CDCl_3$ solution on a BRUKER Ac 400 MHz spectrometer. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Purity of the synthesized compounds was checked by HPLC AGILENT. The results are in agreements with the structures assigned.

Anti-diabetic activity:

***Testing animals*:**

Adult healthy male Wistar rats weighing 200 to 250 g were housed under standard environmental conditions of temperature (25 ± 2 ^{0}C) and at 12 h light/ dark cycle in animal house of Chalapathi Institute of Pharmaceutical Sciences, Guntur, and Andhra Pradesh. The rats were fed by normal laboratory chow and water.

***Study protocol*:**

During the study period, guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, Institutional Animals Ethical Committee (IAEC) were followed for the maintenance of the animals. The research work was approved by IAEC No: 12/IAEC/CLPT/2017-18.

***Drugs*:**

The Glibenclamide was used as standard drug for antidiabetic study. The diabetes was induced by injecting Streptozocin. The synthesized Thiazolidinone derivatives were used as tested drug for the antidiabetic study.

***Experiment*:**

Acute diabetes was induced by intravenous administration of streptozotocin (40 mg kg^{-1}of each) dissolved in 0.05 M citrate buffer with pH of 4.5 to 24 h fasting rats. Blood glucose changes in blood were measured by using a digital glucometer (DiabaScan TD-4231 Glucometer, India). For the glucose test the blood was collected from rat's tail veins every hour post administration of diabetes. Synthesized compounds were administered at a single dose of 100 mg/kg body weight (b.w.) of rat. Glibencalmide (5 mg/kg b.w.) as the standard was administered orally 48 h post administration of streptozotocin. The basis of comparison was the blood glucose level 2 h post administration of drugs to diabetic rats.

The rats were injected intraperitoneally with streptozotocin dissolved in sterile normal saline at a dose of 60 mg kg^{-1} b.w. The diabetic induced rats with blood glucose level above 250 mg/dl were selected for the antidiabetic study. Hyperglycaemia was confirmed in animals after 72 h of streptozotocin injection. Animals were divided into 12 groups. Each group consists of 6 rats. The groups 1 to 10 were treated with Thiazolidinone derivatives (TZN- 1 to 10) at a dose of 100 mg/kg b.w. The group 11 was treated with normal saline water and 5 % CMC (1 ml). The group 12 was treated with standard drug Glibenclamide at a dose of 5 mg/kg body weight of rat. After administration of drugs to all rats of several groups, the blood sugar level was measured at 0, 1, 3 and 6 h respectively [26].

Statistical analysis:

All data thus obtained in antidiabetic study were analysed statistically by using mean (n = 6), standard deviation and standard error of mean. The probability value (p) <0.01 was considered as statistically significant. Statistical analysis is done with one-way ANOVA followed by Dunnet's't' test [27].

RESULTS AND DISCUSSION:

Thiazolidinone derivatives synthesis:

The *p*-Toluidene, acetic acid, sodium acetate and chloroacetylchloride were used as starting materials to prepare 2-chloro-*N*-*p*-tolylacetamide. To this thiourea was added and refluxed in microwave synthesizer to synthesize the N^4-*p*-tolylthiazole-2,4-diamine. Different aldehyde derivatives were added to this to prepare different Schiff bases. Finally, thioglycolic acid was added and refluxed in microwave synthesizer to get 3-(2-thiazolyl)-4-thiazolidinone derivatives. The formation of compounds has been confirmed by the IR, ^{1}H NMR. These results were also supported by mass spectra. The yield, melting point, molecular formula, molecular weight and Rf value of ten synthesized Thiazolidinone derivatives are given in Table 1.

Characterization of synthesized Thiazolidinone derivatives:

***Spectral data of 2-chloro-N-p-tolylacetamide*:**

IR (KBr, γ_{max} cm^{-1}): 3286.77 (N-H str), 3047.32 (Ar C-H str), 2970.17 (C-H-str), 1692 (C=O str), 1542

(Aromatic C=C str), 1195.75 (C-O str), 756.04 (C-Cl str).[1]HNMR (400 MHz, DMSO) (ppm): 10.32 (1H, s, -NH), 7.18- 7.44 (4H, m, aromatic), 4.3 (2H, s, CH_2Cl), 2.57 (2H, q, -CH_2), 1.12 (3H, -CH_3). MS (m/z): 196 (M^+); Anal. Calcd (found) for $C_{10}H_{12}ClNO$; C, 58.88 (58.86); H, 5.45 (5.43); N, 7.66 (7.65).

***Spectral data of N^4-p-tolylthiazole-2, 4-diamine*:**
IR (KBr, γ_{max} cm^{-1}): 3278.76, 3224.76 (NH_2 str), 3100.18 (Ar C-H str), 2962.46 (alkyl C-H str), 1612.38 (C=N str), 1488.94 (Aromatic C=C str). [1]HNMR (400 MHz, DMSO) (ppm): 7.8-6.8 (m, 4H, Ar-H and 1H, s, CH of thiazole), 5.67 (s, 2H, NH_2), 4.00 (s, 1H, NH), 2.32 (s, 3H, CH_3). MS (m/z): 206 (M^+); Anal. Calcd (found) for $C_{10}H_{11}N_3S$; C, 58.45 (58.43); H, 5.35 (5.32); N, 20.46 (20.46); S, 15.58 (15.56).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-phenylthiazolidin-4-one (TZN-1)*:**
IR (KBr, $\gamma_{max}cm^{-1}$):3400(N-H str), 3015(Ar-CH str), 2997(alkyl C-H str), 1697(C=O str), 1537 (C=C str), 1100 (C-S str). [1]H NMR (400 MHz, DMSO) (ppm): 10.23(1H, s, NH), 6.97-8.32 (9H, m, Ar-H and 1H, s, CH of thiazole), 5.84 (2H, s, CH_2 of thiazolidinone), 5.42 (1H, s, CH of thiazolidinone), 2.32 (3H, s, CH_3). MS (m/z): 368 (M^+); Anal. Calcd (found) for $C_{19}H_{17}N_3OS_2$; C, 62.04 (62.03); H, 4.62 (4.61); N, 11.42 (11.40); S, 17.41 (17.40).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-(naphthalen-1-yl)thiazolidin-4-one(TZN-2)*:**
IR (KBr, γ_{max} cm^{-1}): 3338 (N-H str), 2980 (Ar-CH str), 2963 (alkyl C-H str), 1683 (C=O str), 1525 (C=C str), 1122.00 (C-S str). [1]H NMR (400 MHz, DMSO) (ppm): 11.10(1H, s, NH), 6.55-8.32 (11H, m, Ar-H and 1H, s, CH of thiazole), 6.12 (2H, s, CH_2 of thiazolidinone), 5.38 (1H, s, CH of thiazolidinone), 2.32 (3H, s, CH_3). MS (m/z): 418 (M^+); Anal. Calcd (found) for $C_{23}H_{19}N_3OS_2$; C, 66.10 (66.09); H, 4.55 (4.53); N, 10.05 (10.04); S, 15.32 (15.30).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-(2,4-dichlorophenyl)thiazolidin-4-one(TZN-3)*:**

IR (KBr, γ_{max} cm^{-1}): 3291.61 (N-H str), 3016.46 (Ar C-H str), 2962.46 (alkyl C-H str), 1666.38 (C=O str), 1596.95 (Aromatic C=N str), 1110.92 (C-S str), 756.04 (C-Cl str). [1]HNMR (400 MHz, DMSO) (ppm): 11.8 (s, 1H, NH), 8.5-6.8 (m, 7H, Ar-H and 1H, s, CH of thiazole), 5.8(2H, s, CH_2 of thiazolidinone), 5.6 (1H, s, CH of thiazolidinone), 2.32 (s, 3H, CH_3). MS (m/z): 437 (M^+); Anal. Calcd (found) for $C_{19}H_{15}Cl_2N_3OS_2$; C, 52.24 (52.22); H, 3.43 (3.42); N, 9.62 (9.62); S, 14.66 (14.65).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-(2-hydroxyphenyl)thiazolidin-4-one (TZN-4)*:**
IR (KBr, γ_{max} cm^{-1}): 3371.34 (O-H str), 3291.61 (N-H str), 3016.46 (Ar C-H str), 2962.46 (alkyl C-H str), 1666.38 (C=O str), 1596.95 (Aromatic C=N str), 1087.78 (C-S str), 756.04 (C-Cl str). [1]H NMR (400 MHz, DMSO) (ppm): 11.2 (s, 1H, OH), 8.0-6.8 (m, 8H, Ar-H and 1H, s, CH of thiazole), 5.8 (2H, s, CH_2 of thiazolidinone), 5.4 (1H, s, CH of thiazolidinone), 4.6 (s, 1H, NH), 2.32 (s, 3H, CH_3). MS (m/z): 384 (M^+); Anal. Calcd (found) for $C_{19}H_{17}N_3O_2S_2$; C, 59.45(59.44); H, 4.43(4.41); N, 10.95 (10.93); S, 16.68 (16.66).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-(5-bromo-2-hydroxyphenyl)thiazolidin-4-one(TZN-5)*:**
IR (KBr, γ_{max} cm^{-1}): 3425 (O-H str), 3212 (N-H str), 3066 (Ar-C-H str), 2980 (alkyl CH str), 1681 (C=O str), 1477 (Ar-C=C str), 1110 (C-Sstr). [1]H NMR (400 MHz, DMSO) (ppm): 12.55 (1H, s, OH), 11.10 (1H, s, NH), 6.75-7.77 (8H, m, Ar-H and 1H, s, CH of thiazole), 5.82 (2H, s, CH_2 of thiazolidinone), 5.45 (1H, s, CH of thiazolidinone), 2.33 (3H, s, CH_3). MS (m/z): 463 (M^+); Anal. Calcd (found) for $C_{19}H_{16}BrN_3O_2S_2$; C, 49.31(49.30); H, 3.46 (3.45); N, 9.08 (9.07); S, 13.84 (13.83).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-(4-methoxyphenyl)thiazolidin-4-one (TZN-6)*:**
IR (KBr, γ_{max} cm^{-1}): 3257 (N-H str), 3047 (Ar-C-H str), 2989 (alkyl C-H str), 1701 (C=O str), 1496 (Ar-C=C str), 1110 (C-Sstr). [1]H NMR (400 MHz, DMSO) (ppm): 11.10 (1H, s, NH), 6.85-8.52 (8H, m, Ar-H and 1H, s, CH of thiazole), 5.88 (2H, s, CH_2 of thiazolidinone), 5.41 (1H, s, CH of thiazolidinone), 3.85 (1H, s, OCH_3) 2.33 (3H, s, CH_3). MS (m/z): 398 (M^+); Anal. Calcd (found) for $C_{20}H_{19}N_3O_2S_2$; C, 60.37 (60.36); H, 4.77 (4.76); N, 10.56 (10.55); S, 16.10 (16.09).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-(4-nitrophenyl)thiazolidin-4-one (TZN-7)*:**
IR (KBr, γ_{max} cm^{-1}): 3269 (N-H str), 3013(Ar-C-H str), 2990 (alkyl C-H str), 1697(C=O str), 1503 (Ar-C=C str), 1109 (C-S str). [1]H NMR (400 MHz, DMSO) (ppm): 10.98 (1H, s, NH), 6.85-7.99 (8H, m, Ar-H and 1H, s, CH of thiazole), 5.86 (2H, s, CH_2 of thiazolidinone), 5.48 (1H, s, CH of thiazolidinone), 3.85 (1H, s, OCH_3) 2.33 (3H, s, CH_3). CH of thiazole), 5.86 (2H, s, CH_2 of thiazolidinone), 5.48 (1H, s, CH of thiazolidinone), 3.85

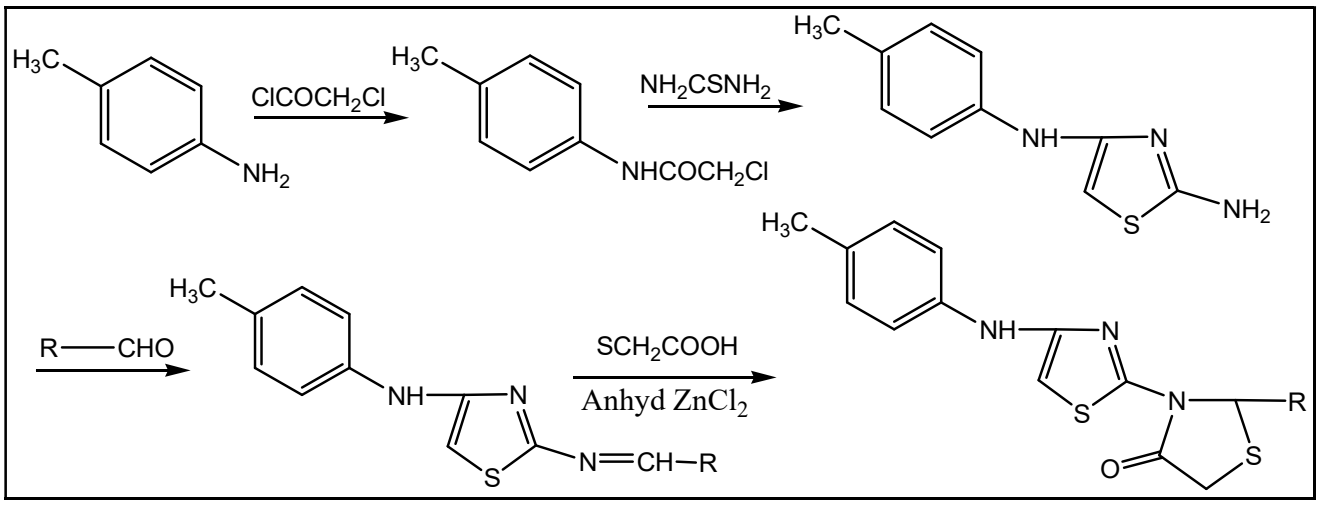

Fig 1. Scheme for synthesis of substituted 3-(2-thiazolyl)-4-thiazolidinone derivatives.

Table 1. Physical data of substituted 3-(2-thiazolyl)-4-thiazolidinone derivatives.

Comp-ounds	R_1	M.F.	M.W.	M.P. (^{0}C)	R_f	Yield (%)
TZN-1	-Phenyl	$C_{19}H_{17}N_3OS_2$	367.49	118-120	0.82	71.85
TZN-2	-Naphthyl	$C_{23}H_{19}N_3OS_2$	417.55	218-220	0.77	82.44
TZN-3	-2,4-Cl	$C_{19}H_{15}Cl_2N_3OS_2$	436.38	160-162	0.92	83.67
TZN-4	-2-OH	$C_{19}H_{17}N_3O_2S_2$	383.49	124-126	0.85	80.15
TZN-5	-5-Br, -2-OH	$C_{19}H_{16}BrN_3O_2S_2$	462.37	218-220	0.72	84.65
TZN-6	-4-OCH_3	$C_{20}H_{19}N_3O_2S_2$	397.52	120-122	0.85	73.35
TZN-7	-4-NO_2	$C_{19}H_{16}N_4O_3S_2$	412.49	210-212	0.81	76.66
TZN-8	-2-Cl	$C_{19}H_{15}ClN_3OS_2$	401.92	186-188	0.74	86.12
TZN-9	-2-NO_2	$C_{19}H_{16}N_4O_3S_2$	412.49	192-194	0.78	78.64
TZN-10	-2-OCH_3	$C_{20}H_{19}N_3O_2S_2$	397.52	132-134	0.73	72.68

M.F. – Molecular formula, M.W. – Molecular weight, M.P. – Melting point and R_f – Retention factor. TZN– Thiazolidinone.

Table 2 Anti-diabetic activity of substituted 3-(2-thiazolyl)-4-thiazolidinone derivatives.

Groups	Drug	Dose (mg/kg)	Blood glucose level in mg/dl (Mean ± SEM, n = 6)			
			0 h	1 h	3 h	6 h
1	TZN-1	100	296.7±4.05	292.7±4.25	187.7±15.6**	148.0±7.8**
2	TZN-2	100	300.5±0.12**	134.5±2.72	123.5±5.23	116.5±5.90**
3	TZN-3	100	320.5±15.81**	145.5±2.26	135.0±3.80	123.5±1.10*
4	TZN-4	100	213.5±8.78	140.7±3.3*	106.3±6.91	95.75±6.06**
5	TZN-5	100	283.5±43.76	205.75±49.7	166.3±38.92	124.5±13.16*
6	TZN-6	100	295.3±7.42*	233.3±23.8	193.0±13.86	159.3±12.12
7	TZN-7	100	289.2±9.98	280.6±9.29*	244.2±9.04**	180.4±1.99**
8	TZN-8	100	203.7±13.79	156.2±13.5	123.3±4.3*	101.5±4.5**
9	TZN-9	100	217.0±3.01	230.0±2.53	164.3±4.74*	146.0±2.19**
10	TZN-10	100	321.5±15.81**	146.5±2.26	136.0±3.80	124.5±1.10*
11	Control	2 ml/kg	123.3±6.00	120.7±5.54	122.3±5.81	123.0±6.4
12	Standard	5	385.8±21.37	230.8±12.35**	156.8±10.87**	93.4±4.98**

****p*<0.01 (considered as significant); Statistical analysis is done one-way ANOVA followed by Dunnet's '*t*' test. Control – Normal saline water, Standard drug - Glibenclamide. S.E.M. – Standard error mean. TZN – Thiazolidinone.**

(1H, s, OCH_3) 2.33 (3H, s, CH_3). MS (m/z): 413 (M^+); Anal. Calcd (found) for $C_{19}H_{16}N_4O_3S_2$; C, 55.27 (55.26); H, 3.87 (3.86); N, 13.57 (13.56); S, 15.51 (15.51).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-(2-chlorophenyl)thiazolidin-4-one(TZN-8)*:**

IR (KBr, γ_{max} cm^{-1}): 3272.61 (N-H str), 3010.56 (Ar C-H str), 2852.46 (alkyl C-H str), 1668.30 (C=O str), 1584.92 (Aromatic C=N str), 1110.90 (C-S str), 750.04(C-Cl str). ^{1}HNMR (400 MHz, DMSO) (ppm): 11.6 (s, 1H, NH), 8.2-6.6 (m, 7H, Ar-H and 1H, s, CH of thiazole), 5.7(2H, s, CH_2 of thiazolidinone), 5.5 (1H, s, CH of thiazolidinone), 2.22 (s, 3H, CH_3). MS (m/z): 402 (M^+); Anal. Calcd (found) for $C_{19}H_{15}ClN_3OS_2$; C, 56.78 (56.72); H, 4.01 (4.00); Cl, 8.82 (8.83); N, 10.45 (10.41); O, 3.98 (3.92); S, 15.96 (15.89).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-(2-nitrophenyl)thiazolidin-4-one (TZN-9)*:**

IR (KBr, γ_{max} cm^{-1}): 3265 (N-H str), 3012 (Ar-C-H str), 2980 (alkyl C-H str), 1692 (C=O str), 1500 (Ar-C=C str), 1100 (C-Sstr). ^{1}H NMR (400 MHz, DMSO) (ppm): 10.91 (1H, s, NH), 6.75-7.89 (8H, m, Ar-H and 1H, s, CH of thiazole), 5.76 (2H, s, CH_2 of thiazolidinone), 5.41 (1H, s, CH of thiazolidinone), 3.80 (1H, s, OCH_3) 2.31 (3H, s, CH_3). MS (m/z): 413 (M^+); Anal. Calcd (found) for $C_{19}H_{16}N_4O_3S_2$; C, 55.32 (55.30); H, 3.91 (3.86); N, 13.58 (13.56); S, 15.55 (15.51); O, 11.64 (11.62).

***Spectral data of 3-(4-(p-toluidino)thiazol-2-yl)-2-(2-methoxyphenyl)thiazolidin-4-one(TZN-10)*:**

IR (KBr, γ_{max} cm^{-1}): 3255 (N-H str), 3042 (Ar-C-H str), 2985 (alkyl C-H str), 1700 (C=O str), 1490 (Ar-C=C str), 1112 (C-S str). ^{1}H NMR (400 MHz, DMSO) (ppm): 11.15(1H, s, NH), 6.82-8.50 (8H, m, Ar-H and 1H, s, CH of thiazole), 5.86 (2H, s, CH_2 of thiazolidinone), 5.42 (1H, s, CH of thiazolidinone), 3.82 (1H, s, OCH_3) 2.31 (3H, s, CH_3). MS (m/z): 398 (M^+); Anal. Calcd (found) for $C_{20}H_{19}N_3O_2S_2$; C, 60.433 (60.36); H, 4.82 (4.78); N, 10.58 (10.56); S, 16.13 (16.10); O, 8.05 (8.01).

Antidiabetic activity:

All the ten synthesized derivatives were screened for their anti-diabetic activity by streptozicin induced tail tipping method. Wistar adult healthy male rats weighing 200 to 250 g were selected. The blood glucose level was induced and the study was carried out in twelve different groups. All the thiazolidinone derivatives exhibited antidiabetic activity. The antidiabetic activity shown by all thiazolidinone derivatives are well comparable with the standard drug Glibenclamide. Out of all ten synthesized compounds (TZN-1 to TZN-10), the compounds TZN-1, TZN-2, TZN-4, TZN-7, TZN-8 and TZN-9 showed significant activity. The compounds TZN-3, TZN-5, TZN-6 and TZN-10 showed moderate activity. The thiazolidinone compounds TZN-4 and TZN-8 showed best antidiabetic activity which was even the greater than the activity shown by the standard drug.

CONCLUSION:

In conclusion, we have reported ten newer substituted 3-(2-thiazolyl)-4-thiazolidinone derivatives which is synthesized the green synthesis techniques like microwave synthesizer. The compounds TZN-1, TZN-2, TZN-4, TZN-7, TZN-8 and TZN-9 showed significant anti-diabetic activity. The compounds TZN-3, TZN-5, TZN-6 and TZN-10 were found to possess moderate anti-diabetic activity. A further of newer substituted 3-(2-thiazolyl)-4-thiazolidinone derivatives in progress to evaluate more potent anti-diabetic agents with minimal side effects.

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