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RESEARCH ARTICLE

Chemical and pharmacological evaluation of Pyrimidine derivatives of Thiazolidinedion

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ABSTRACT

The anti-diabetic activity of pyrimidine derivatives of thiazolidinedione were evaluated in alloxan-induced diabetic mice. Pyrimidine derivatives of thiazolidinedione (100 mg/kg body weight), was administered orally to male Swiss albino mice. Alloxan was used to induce diabetes mellitus. The anti-diabetic potential were assessed by determining oral glucose tolerance, fasting blood glucose. Pyrimidine derivatives of thiazolidinedione were administered to normal and experimental diabetic mice for 7 days. After 7 days of treatment with Pyrimidine derivatives of thiazolidinedione the maximum reduction in fasting blood glucose (101.435 ± 2.14) was observed in diabetic mice treated with $TZN_{4(f)}$ (100 mg/kg). The synthesized compounds exhibited dose dependent glucose lowering potential. At a dose of 50mg/kg body weight, no significant reduction in blood glucose could be achieved. Five out of twelve synthesized compounds, viz. $TZN_{4(b)}$, $TZN_{4(e)}$, $TZN_{4(f)}$, $TZN_{4(k)}$ and $TZN_{4(l)}$ were observed to be capable of significantly reducing the blood glucose levels at a dose of 100mg/kg body weight.

Key Words: Pyrimidine, Thiazolidinedione, anti-diabetic activity.

INTRODUCTION:

Diabetes Mellitus is a complex, chronic, progressive disease which eventually can adversely affect function of the kidney, eyes, and the nervous and vascular systems. Of the estimated 5.8 million individuals diagnosed with diabetes mellitus in United States[1-4], approximately 90% are characterised[5] as non insulin dependent (NIDDM, Type 2) . Most of these patients exhibit hyperglycaemia, peripheral insulin- resistance, and obesity. Besides diet and exercise, current drug therapy for the treatment of diabetes mellitus is aimed at improving glycaemia control.[6] In 1982, Takeda disclosed a novel series of (4-substituted-benzyl) thiazolidine-2, 4-diones that reduce insulin resistance or potentiate insulin action in genetically diabetic or obese animals.[7] Since numerous reports of additional (substituted- benzyl) thiazolidinediones have appeared marketing an effort to identify more potent and better tolerated derivative.[8-13]The thiazolidinediones are the class of oral agents for treatment of type 2 diabetes, improving insulin sensitivity and lowering blood glucose, free fatty acid, and triglyceride levels. The thiazolidinediones are peroxisome proliferators-activated receptors (PPARγ) agonists. The PPARγ receptor is a member of the nuclear hormone receptor family of ligand-activated transcription factors that regulates gene expression of several genes involved in fatty acid and carbohydrate metabolism and adipocyte differentiation.

The treatment of type-II diabetes has been revolutionized with the advent of thiazolidinediones (TZDs) class of molecules that normalize elevated blood glucose level. Unlike sulfonylureas (e.g., glipizide, glyburide), which enhance insulin resistance, and metformin, which reduces hepatic glucose output, TZDs (e.g., troglitazone, rosiglitazon. pioglitazone) improve insulin sensitivity in liver, muscle and fat tissues and thus counteract insulin resistance.[15] TZDs are a group of pharmacological agents that enhance insulin action (insulin sensitizes) and promote glucose utilization in peripheral tissues.[16]

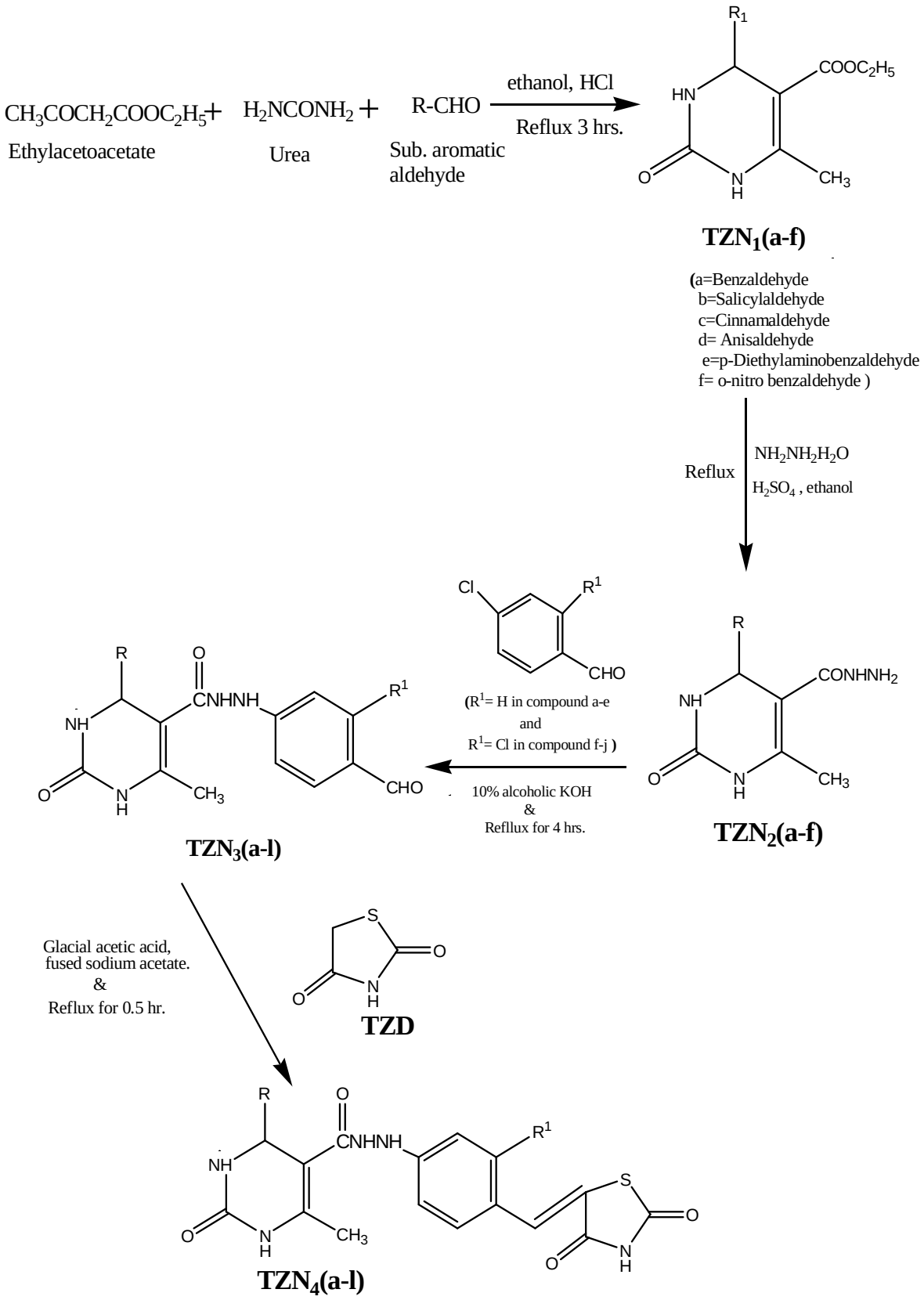
It has been demonstrated that TZDs elicit their pharmacological actions by binding and activating nuclear receptor PPARγ.[17-18] It is hypothesized that their activation by TZDs affect the expression of a number of genes involved in lipid and glucose metabolism and preadipocyte differentiation.[19-20] The peroxisome proliferators activated receptors (PPARs) are a group of nuclear receptor isoforms that play a key role in the regulation of dietary fat storage and are a target for the development of treatments for type-II diabetes, obesity and cardiovascular disease. TZDs at these receptors act as insulin sensitizers, and PPARα and PPARγ receptor subtypes

show different tissue and ligand specifiities, PPARγ agonists improve glycemic control and dyslipidemia in type-II diabetic patients by down regulating cytokines in adipose tissue, while agonists of the PPARα subtype improve the anthrogenic lipoprotein profile of insulin resistance.[21-23]

Herein I describe my efforts to synthesize novel potent glucose lowering compounds. The design of a novel pyrimidine TZD derivatives structure came from the pyrrolidine series that had been studied earlier. Some of the partial[24-25] structure of the substituted moiety were derived from recently reported a novel pyridine and purine TZD derivatives.[26-34] Considering their biological activity and structure of previously reported compounds, I could infer that substituted pyrrolidines and pyridines containing TZD were more efficacious than reference compound, rosiglitazone. Therefore, in order to enhance glucose lowering activities, I focused my attention on the modification of pyrimidine moiety having TZD. I describe the design, synthesis and antidiabetic activities of novel substituted pyrimidine derivatives containing TZD conceptually issued from modification of rosiglitazone.

Material and Method

All the chemicals were of synthetic grade commercially procured. Melting points were determined in open capillary method. Purity of the compound was checked on silica gelG on TLC plate, The compounds were scanned in the region of 200 to 400 nm, using Shimadzu spectrophotometer, Pharmaspec UV-1700. The absorption maximum of the compounds was determined. The I.R. spectra of the synthesized compounds were obtained using FT-IR spectrophotometer, Bruker alpha. NMR and Mass spectra were obtained from SAIF CDRI Lucknow.


CH3COCH2COOC2H5 + H2NCONH2 + R-CHO
Ethylacetoacetate
Urea
Sub. aromatic aldehyde
ethanol, HCl
Reflux 3 hrs.
TZN1(a-f)
(a=Benzaldehyde
b=Salicylaldehyde
c=Cinnamaldehyde
d= Anisaldehyde
e=p-Diethylaminobenzaldehyde
f= o-nitro benzaldehyde)
Reflux
NH2NH2H2O
H2SO4 , ethanol
TZN2(a-f)
(R1= H in compound a-e
and
R1= Cl in compound f-j)
10% alcoholic KOH
&
Refllux for 4 hrs.
TZN3(a-l)
Glacial acetic acid,
fused sodium acetate.
&
Reflux for 0.5 hr.
TZD
TZN4(a-l)

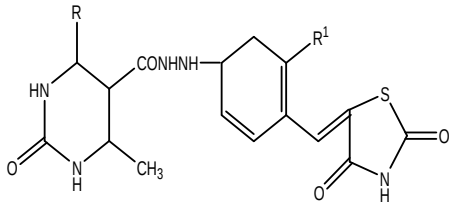
CHEMICAL CHARACTERIZATION [40] OF THE SYNTHESIZED COMPOUNDS

The synthesized compounds $TZN_{4(a)}$, $TZN_{4(b)}$, $TZN_{4(c)}$, $TZN_{4(d)}$, $TZN_{4(e)}$, $TZN_{4(f)}$, $TZN_{4(g)}$, $TZN_{4(h)}$, $TZN_{4(i)}$, $TZN_{4(j)}$, $TZN_{4(k)}$, $TZN_{4(l)}$, are light green to off white crystals, with no characteristic odor. These derivatives are soluble in chloroform, glacial acetic acid, DMSO, slightly soluble in acetone, ethanol, ethyl acetate, benzene, methanol and ether and practicably insoluble in water.

The synthesized compounds TZD are pale yellow to off white crystals, with no characteristic odour. These derivatives are soluble in water, DMSO, slightly soluble in acetone, ethanol, benzene, methanol, ether and glacial acetic acid and practicably insoluble in ethyl acetate, chloroform, hexane, benzene.

Purity of the compound was checked on silica gelG on TLC plate, The compounds were scanned in the region of 200 to 400 nm, using Shimadzu spectrophotometer, Pharmaspec UV-1700. The absorption maximum of the compounds was determined. The I.R. spectra of the synthesized compounds were obtained using FT-IR spectrophotometer, Bruker alpha. NMR and Mass spectra were obtained from SAIF CDRI Lucknow.

Table 1: Calculated molecular weight, percent nitrogen content and the determined λmax of the final synthesized derivatives (physical properties of the synthesized compounds)



Compound Name	R	R^1	Molecular Weight (calculated)	%Nitrogen (calculated)	Absorption Maximum (λ_{max}) Order			
					0	l	ll	Lll
$TZN_{4(a)}$	C_6H_5	H	480.56	14.57	307	283	326	-
$TZN_{4(b)}$	C_6H_4OH	H	496.54	14.10	355	342	207	-
$TZN_{4(c)}$	$CH=CHC_6H_5$	H	506.60	13.82	305	291	206	-
$TZN_{4(d)}$	$C_6H_4OCH_3$	H	510.59	13.72	307	291	206	-
$TZN_{4(e)}$	$C_6H_4NC_2H_6$	H	523.21	16.05	230	285	206	-
$TZN_{4(f)}$	NO_2	H	525.56	15.99	302	297	203	-
$TZN_{4(g)}$	C_6H_5	Cl	515.00	13.60	302	206	204	-
$TZN_{4(h)}$	C_6H_4OH	Cl	531.00	13.19	302	297	-	204
$TZN_{4(i)}$	$CH=CHC_6H_5$	Cl	521.04	12.94	302	288	203	-
$TZN_{4(j)}$	$C_6H_4OCH_3$	Cl	545.03	12.85	303	206	-	204
$TZN_{4(k)}$	$C_6H_4NC_2H_6$	Cl	558.07	15.06	209	298	204	206
$TZN_{4(l)}$	NO_2	Cl	560.00	15.01	302	206	-	205

PHARMACOLOGICAL CHARACTERIZATION

Diabetes can be induced by pharmacologic, surgical or genetic manipulations in several animal species. Most experiments in diabetes are carried out on rodents, although some studies are still performed in larger animals. The classical model employed by Banting and best was pancreatectomy in dogs. It is also described prone strains to diabetes mellitus that have been employed in several researches.

Procurement of experimental animals

Wistar rats (150-200 g) of either sex and of approximately 9-12 week old, used in the present studies were procured from Institute of Animal Health and Veterinary Biologicals, Mhow.

The animals were maintained in clean polypropylene cages with 12 h light and dark cycle at a temperature of 27-29^{O}C and a humidity of 62 to 65%. The animals had access to food and water *ad libitum.* The animals were acclimatized to laboratory condition for one week before starting the experiment. The animals were fasted for at least 12 h before onset of each activity.

The experimental protocol was approved by Institutional animal ethics committee **(Reg no. TIT/IAEC/831/Ph;Chem/2010/03*).***

Acute toxicity studies

Organization for Economic co-operation and Development (OECD) regulates guideline for oral acute toxicity study. It is an international organization which works with the aim of reducing both the number of animals and the level of pain associated with acute toxicity testing.

Following are the main type of guideline followed by OECD

- ✓ Guideline 420, fixed dose procedure. (5 animals used)
- ✓ Guideline 423, acute toxic class. (3 animals used)
- ✓ Guideline 425, Up and Down method. (1animal used)

Preparation of animals

The animals (female) were randomly selected, marked to permit individual identification, and kept in their cages for at least 5 days prior to dosing to allow for acclimatization to the laboratory conditions.

Procedure followed for the starting doses

The animal were kept fasting for overnight and water *ad libitum*, after which the synthesized compound were administered orally 5 mg/kg and then the mortality was observed for 14 days. The same dose was administered again to confirm the toxic dose. Further the synthesized compounds were administered orally at dose level of 50 mg/kg and then the mortality was observed. Further the synthesized compounds were administered orally at dose level of 300 mg/kg and then the mortality was observed. Based on the oral toxicity the synthesized compounds were found to be in GHS category 3 (>50-300mg /kg b.w.) with LD_{50} cutoff of 200 mg/kg b.w. Hence two doses, 50mg/kg and 100mg/kg b.w. were chosen for carrying out the study.

Anti-diabetic activity

Animals were fasted 18 h prior to the administration of freshly prepared alloxan (150 mg/kg i.p.) dissolved in 0.3% CMC solution. After 48 h, the animals were divided in various groups of six rats each (n = 6).

Group I (Normal): treated with 0.3% CMC solution (0.5 ml/100 g), orally single dose up to seven days.

Group II (Diabetic control): treated with alloxan (150 mg/kg, i.p) + 0.3% CMC solution (0.5 ml/100 g), single dose up to seven days.

Group III (Standard): treated with alloxan (150 mg/kg, i.p) + glibenclamide (10 mg/kg p.o.), single dose up to seven days.

Group IV-XV: treated with alloxan (150 mg/kg, i.p) + treated with synthesized compounds $TZN_{4(a)}$, $TZN_{4(b)}$, $TZN_{4(c)}$, $TZN_{4(d)}$, $TZN_{4(e)}$, $TZN_{4(f)}$, $TZN_{4(g)}$, $TZN_{4(h)}$, $TZN_{4(i)}$, $TZN_{4(j)}$, $TZN_{4(k)}$, $TZN_{4(l)}$, (50 and 100 mg/kg, orally), single dose up to seven days.

Blood samples were collected for the measurement of blood glucose level from the tail vein on 0 h, 1 h, 2 h, 4 h, 5 h and 7^{th} day. The blood glucose level was determined by digital glucometer (Gluco check).[41]

RESULTS OF PHARMACOLOGICAL ACTIVITY

Acute toxicity study

The synthesized compounds were screened for oral acute toxicity study by OECD guidelines for the determination of LD_{50} value. The results shows that synthesized compound belonged to GHS category 3 (>50-300). From the results the LD_{50} was found to be 200 mg/kg. Hence doses of 50 and 100 mg/kg were arbitrarily selected for antidiabetic activity.

Table 2: Oral acute toxicity study data

Groups	Total No. of animals screened	Dose (mg/kg)	Result
I	06	5	1 death
II	06	50	No death
III	03	300	3 deaths

Antidiabetic activity

Effect of synthesized compound on blood glucose level

The antidiabetic activity of synthesized compounds was investigated in alloxan induced diabetic rats. The blood glucose levels of normal rats were measured at 0 h, 1 h, 2 h, 4 h, 5 h and 7^{th} day and values were found to be 77.16, 78.26, 76.26, 77.0, 77.5 and 73.66, respectively. The glucose level of alloxan induced diabetic rats were 179.0, 183.83, 187.33, 191.0, 196.16 and 202.33 at 0 h, 1 h, 2 h, 4 h, 5 h and 7^{th} day, respectively. The administration of the synthesized compound (100 mg/kg) significantly reduced the blood glucose level on 7^{th} day, as compared to the standard drug.

Table 3: Effect of synthesized compound on blood glucose level of alloxan induced diabetic rats (100mg/kg).

Groups	Treatment	Blood glucose (mg/dl)					
		0 h	1 h	2 h	4 h	5 h	7th day
I	0.3% CMC solution (0.5 ml/100 g)	77.16 ± 1.53	8.26 ± 1.62	76.26 ± 1.51	77.0 ± 1.52	77.5 ±1.52	73.66 ± 1.56
II	Alloxan (150 mg/kg)	179.0±2.67	183.83±2.72	187.33 ± 2.74	191.0 ±2.47	196.16 ±2.52	202.33 ± 2.27
III	Glibenclamide (10 mg/kg)	186.5±3.19	180.0 ± 3.02**	162.33 ± 2.95**	154.16 ±2.73**	142.33 ± 2.66**	130.66 ± 2.98**
IV	$TZN_{4(a)}$	182.26±1.9	180.3 ± 2.6*	178.3 ± 2.90*	174.6 ±3.1*	172.33±3.21*	162.16 ± 3.0*
V	$TZN_{4(b)}$	184.63 ± 3.2	178.80 ±2.9**	170.66 ± 1.42**	165.33 ± 1.0**	62.33 ± 0.76**	152.36 ± 1.54**
VI	$TZN_{4(c)}$	185.33 ± 2.3	183.33 ± 2.34*	178.66 ± 2.45*	170.83 ± 1.18*	165.33 ± 1.43*	163.16 ± 2.35*
VII	$TZN_{4(d)}$	184.5 ± 2.14	182.0 ± 2.22*	176.51 ± 1.9*	173.66 ± 1.95*	171.33 ± 1.62*	159.66 ± 2.81*
VIII	$TZN_{4(e)}$	188.24± 2.9	185.44± 2.87	178.45± 2.65*	175.43± 2.44*	165.78± 2.38	151.435 ± 2.24
IX	$TZN_{4(f)}$	196.24± 2.6	195.44± 2.81	170.45± 2.45*	165.43± 2.34*	125.78± 2.3	101.435 ± 2.14
X	$TZN_{4(g)}$	192.26 ± 1.53	190.33 ± 2.6*	188.36 ± 2.72	184.66/ ± 3.21*	182.33 ± 3.19	172.16 ± 3.0*
XI	$TZN_{4(h)}$	190.63 ± 3.2	184.80 ± 2.9**	179.66 ± 1.42**	175.33 ± 1.0**	172.33 ± 0.76**	165.36 ± 1.54**
XII	$TZN_{4(i)}$	195.33 ± 2.93	193.33 ± 2.74*	188.66 ± 2.55*	183.83 ± 1.38*	175.33 ± 1.33*	169.16 ± 2.25*
XIII	$TZN_{4(j)}$	188.5 ± 1.24	185.0 ± 1.19*	179.51 ±1.54*	175.66 ± 1.45*	172.33 ± 1.32*	169.66 ± 1.9*
XIV	$TZN_{4(k)}$	180.24± 3.9	177.44± 3.87	173.45± 3.65*	169.43± 3.44*	165.78± 2.38	145.435 ± 2.14
XV	$TZN_{4(l)}$	190.24± 2.6	189.44± 2.81	182.45± 2.45*	175.43± 2.34*	165.78± 2.3	129.435 ± 2.14

Values are mean ±SEM, n = 6. (One way ANOVA Followed by Dunnettes multiple test). *, **, denotes statistically significance of $P<0.05$, $P< 0.001$ compared with control group.

DISCUSSION

The general method known as Biginelli condensation was used to prepare pyrimidine-one derivatives. The carboethoxy group of pyimidine-one was converted to hydrazide & then then this group was converted to an aromatic aldehyde derivative. The methylene group linker between the pyrimidine and 2-4 thiazolidinedione ring was synthesized by knoevenagel condensation of pyrimidine-aromatic aldehyde and 2,4-thiazolidinedione ring. Sodium acetate and glacial acetic acid were used as the reagents in this condensation. The Rf, meiting point, yield, ^{1}H-NMR spectra, IR spectra & mass spectral values are all listed in the previous section. All the spectral data were in accordance with the presumed structure.

In ^{1}H-NMR spectra protons of pyrimidine and benzene ring were observed between 8-7 ppm benzylic proton were observed at 4.8-5.1 ppm & 1.2-3ppm. Other protons were also observed at derived values.

Mass spectra of each compound had a molecular ion peak M^{+} , M+1, & M+2, peaks. Other fragments appeared at expected m/2 values.

IR spectra of the synthesized compound exhibited stretching and bending vibrations for N=H, C=O, C=C, C-C, $CH_{2,}$ C-H confirming the presence of all the desired functional groups in the synthesized compound.

Acute oral toxicity study was performed in accordance with OECD guidelines 423. Toxicity class was assigned according the number of animals that died on oral administration of a particular dose. The animals (all females) were observed for acute toxicity study [immediate as well as delayed (4 hrs. to 14 days respectively)] for mortality.

The alloxan induced diabetes generally occurs due to superoxide radical formation by alloxan and its metabolite, dialuric acid. These radicals cause rapid destruction of pancreatic β-cells thereby causing diabetes in experimental animals.

The synthesized compounds exhibited dose dependent glucose lowering potential. At a dose of 50mg/kg body weight, no significant reduction in blood glucose could be achieved. Five out of twelve synthesized compounds, viz. TZN $_{4(b),}$ TZN $_{4(e),}$ TZN $_{4(f),}$ TZN $_{4(k)}$ and TZN $_{4(l)}$ were observed to be capable of significantly reducing the blood glucose levels at a dose of 100mg/kg body weight.

The significance level of P<0.001 compared to the control group makes these five compounds candidates for development of lead. The presence of an electron withdrawing group at carbon γ to thiazolidinedione ring did not have much influence on the potency.

Presence of a functional group capable of hydrogen bonding at p-position of the aromatic ring at C-4 of pyrimidine was able to increase the antidiabetic potency as evident from the result.

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