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RESEARCH ARTICLE

Synthesis and Characterization of Pyrimidine Containing Thiazolidinedione derivatives

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ABSTRACT

The synthesis and characterization of tweleve Pyrimidine Containing Thiazolidinedione derivatives has been studied. The yield of all the synthesised compounds is found to be significant. The purity was checked by TLC. The characterizations of the synthesized compounds were carried out by determining their melting points, UV absorption maxima, IR spectra, Mass spectra and NMR spectra.

Key Words: Pyrimidine, Thiazolidinedione, UV, I.R.

Introduction:

Non- insulin dependent diabetes mellitus (NIDDM, type-II diabetes) is a chronic metabolic disease characterized by insulin resistance, hyperglycemia and hyperinsulimia. It represents 80-90% of the human population with diabetes and approximately 215 million will be affected worldwide by 2010. The disease is often associated with obesity, dyslipidemia and hypertension leading to cardiovascular risk. Primary therapy for the type-II diabetes is caloric restriction and aerobic exercise but only a small percentage of patients adopt them with sufficient rigor to achieve a significant improvement in hyperglycemic condition. Current therapies for type-II diabetes have inherent problems including non-compliance, ineffectiveness and hypoglycemic episodes with insulin and sulphonylureas. Glitazone type therapeutic agents are in market but some of them have been reported to have hepatotoxicity. Therefore, here still remains a great need for more effective orally administered agents.

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.[1] TZDs are a group of pharmacological agents that enhance insulin action (insulin sensitizes) and promote glucose utilization in peripheral tissues.[2]

It has been demonstrated that TZDs elicit their pharmacological actions by binding and activating nuclear receptor PPARγ.[3-4] 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.[5-6] 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.[7-9]

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[10-11] structure of the substituted moiety were derived from recently reported a novel pyridine and purine TZD derivatives.[12-20] 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.

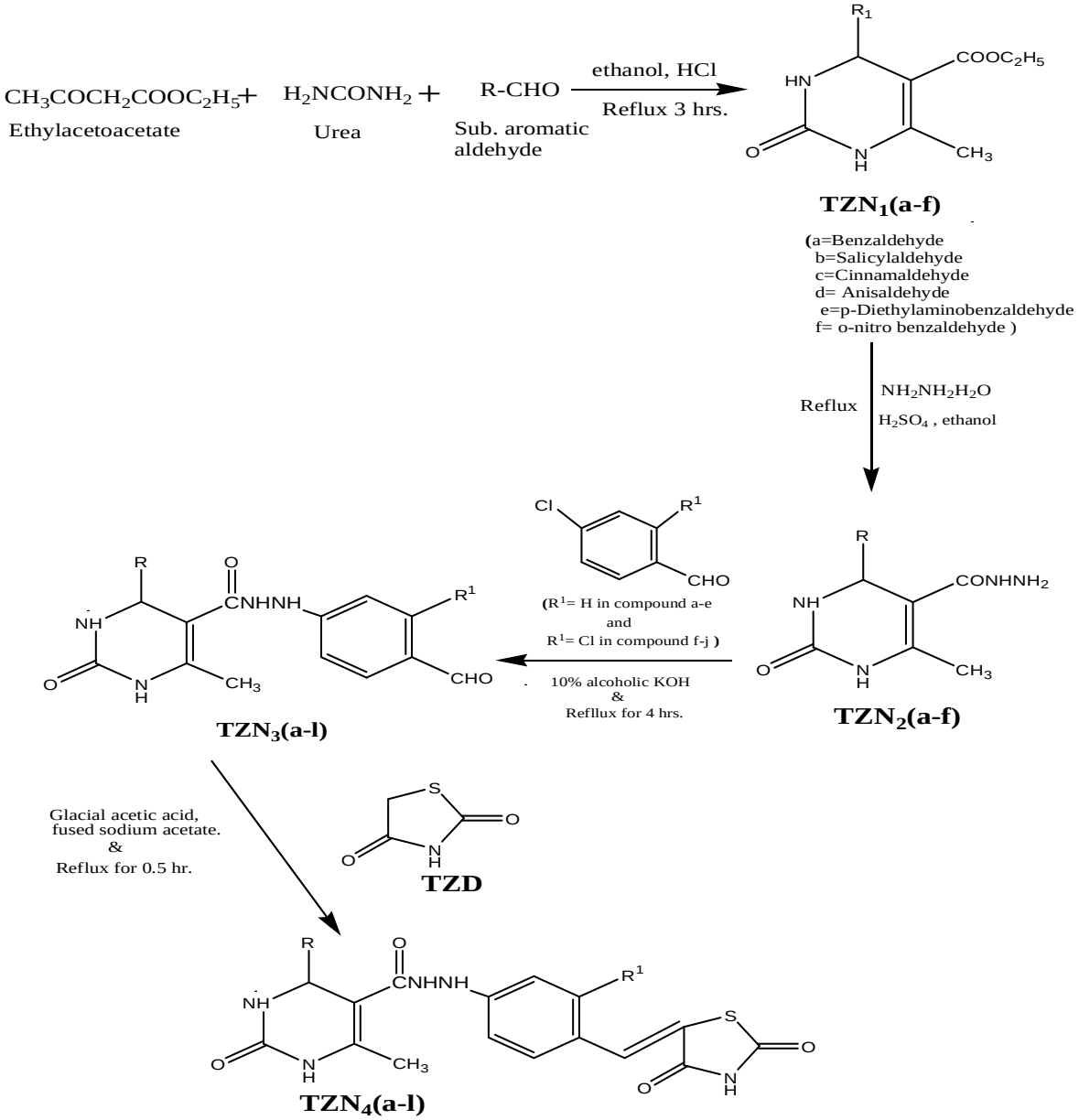
Chemistry

The synthesis of 3, 4-dihydropyrimidine was performed by using substituted aromatic aldehyde, urea and ethylacetoacetate by **Biginelli condensation**.

The hydrazide derivative of the dihydropyrimidine- 2-one was synthesized by the product of TZN_1 by hydrazine hydrate in presence of ethanol with catalytic amount of concentrated sulfuric acid.The reaction proceeds by the way of ammonolysis of esters. The mechanism involves nucleophilic attack on the electron deficient carbon atom of the ethoxy group, $-OC_2H_5$, by hydrazine hydrate. The alkoxy group gets replaced by $–NHNH_2$ to yield the product, hydrazide derivative. By using two different type of rectant like chloro-benzaldehyde and di-chloro-benzaldehyde hydrazide derivatives are formed. Hydrazide derivative are formed by condensation process.

Synthesis and Characterization of Pyrimidine Containing Thiazolidinedione derivatives

The thiazolidinedione was synthesized by the condensation of chloroacetic acid and thiourea in the presence of water. The thiazolidinedione derivatives of pyrimidine derivatives were synthesized by the condensation of the product $TZN_{3(a-l)}$ derivatives and thiazolidinedione in the presence of glacial acetic acid and fused sodium acetate.



Experiment

Procedure for step-1

1. Synthesis of 4-phenyl-5-carboethoxy-6-methyl-3,4-dihydropyrimidine-2-one[21]

0.5 moles of urea, 0.75 moles of ethylacetoacetate and 0.5 moles of substituted aromatic benzaldehyde were mixed in 25 ml of ethanol. Catalytic amount of concentrated hydrochloric acid (5 drops) was added to the mixture and the mixture was refluxed until the completion of the reaction (approximately 3 hours). On cooling, a solid separated which was filtered and recrystallised using ethanol to give the product $TZN_{1(a-f)}$. Completion of the reaction was monitored by TLC.

Procedure for step-2

Synthesis of 4-phenyl-5-carboxyhydrazide-6-methyl-3, 4-dihydroprimidinedione 2-one[22]

To 0.1 mole of the product TZN $_{1(a-f)}$ in 20 ml ethanol, 0.1 mole of hydrazine hydrate was added. To the mixture, catalytic amount of concentrated sulfuric acid was added. The mixture was refluxed until the completion of the reaction (approximately 2 hours). On cooling, a solid separated, which was recrystallized from ethanol to give the product TZN $_{2(a-f)}$.

Procedure for step-3

Synthesis of 4-subsituted-carboxyhydrzide-N-benzaldehyde-6-methyl-3,4-Dihydro

-pyrimidine-2-one derivatives[23]

(a) To 1 mole of product TZN $_{2(a-f)}$ in 15 ml of 10% alcoholic potassium hydroxide, was added of 1 mole of para-chlorobenzaldehyde. The reaction mixture was refluxed until the completion of the reaction (approximately 4 hours). On cooling, a solid separated, which was recrystallized from chloroform: ether (1:1) to give the product TZN $_{3(a-f)}$.

(b) To 1 mole of product TZN $_{2(a-f)}$ in 15 ml of 10% alcoholic potassium hydroxide, was added of 1 mole of para-chlorobenzaldehyde. The reaction mixture was refluxed until the completion of the reaction (approximately 4 hours). On cooling, a solid separated, which was recrystallized from chloroform: ether (1:1) to give the product TZN $_{3(g-l)}$.

Procedure for step-4

Synthesis of thiazolidinedione[24]

To 0.6 mole of chloroacetic acid in 60 ml of water, was added of 0.6 mole of thiourea. The reaction mixture was stirred until white ppt was formed, (approximately 15 min.) and refluxed

until the completion of the reaction (approximately 40 hours). On cooling, a solid separated, which was recrystallized from ethyl alcohol to give the product TZD.

Procedure for step-5

Synthesis of thiazolidinedione derivatives of pyrimidine[25]

To 0.25 mole of product $TZN_{3(a-l)}$ in 50 ml of hot glacial acetic acid, 0.25 mole of thiazolidinedione (TZD) and 1.8 gm of fused sodium acetate were added. The reaction mixture was refluxed until the completion of the reaction (approximately 1 hour) with occasional shaking. Mixture was poured in water (500 ml). Product was filtered and washed with water, alcohol and ether. On cooling, a solid separated, which was recrystallized from glacial acetic acid to give the product $TZN_{4(a-l)}$.

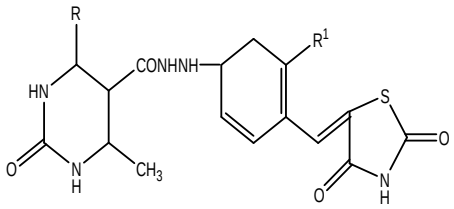
CHEMICAL CHARACTERIZATION [26] **OF THE SYNTHESIZED COMPOUNDS**

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.

RESULTS

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

Structure Elucidation

Compound code - $TZN_{4(a)}$

^{1}H-NMR ($CDCl_3$, 300MHZ) - δ=7.25(C-H, Benzene); 7.31(C-H, Benzene); 7.41(C=CH, Methene); 2.35(N-H, Amine); 1.58(CH_3, Methyl); 8.6(N-H, 2^0Amide); 1.25(C-H, Benzene); 7.44(C-H, Benzene); 7.46(C-H, Benzene).

Mass (m/e) - 480.56; (m+1) 481.0.

IR (KBr) - C=O (1680-1630) 1653.50; C-H (3150-3020) 3107.54; C=C (1675-1600) 1614.34; N-H (3500-3100) 3554.99; C=C (1600-1450) 1584.79, 1477.79; C-H (2960-2850) 2933.06; C-H (3100-3010) 3039.13.

Compound code - $TZN_{4(b)}$

^{1}H-NMR ($CDCl_3$, 300MHZ) - δ=7.26(C-H, Benzene); 7.39(C-H, Benzene); 7.42(C=CH, Methene); 2.07(N-H, Amine); 1.51(CH_3, Methyl); 8.7(N-H, 2^0Amide); 1.25(C-H, Benzene); 7.44(C-H, Benzene); 7.46(C-H, Benzene); 6.94(N-H, Benzene); 7.26(O-H, Phenol).

Mass (m/e) - 496.54; (m+19) 515.2.

IR (KBr)- C=O (1680-1630) 1676.80; C-H (3150-3020) 3042.73; N-H (3500-3100) 3397.17, 3297.55; C=C (1600-1450) 1584.79,1477.79; O-H (3400-3200) 3297.55, 3202.53.

Compound code -$TZN_{4(c)}$

^{1}H-NMR ($CDCl_3$, 300MHZ)- δ=7.27(C-H, Benzene); 7.30(C-H, Benzene); 7.41(C=CH, Methene); 2.3(N-H, Amine); 1.58(CH_3, Methyl); 8.6(N-H, 2^0Amide); 1.25(C-H, Benzene); 7.44(C-H, Benzene); 7.26(C-H, Benzene); 6.17(N-H, Benzene); 4.23(CH=CH, ethene); 7.32(H, Benzene).

Mass (m/e) - 506.60; (m+1) 507.2.

IR (KBr) - C=O (1680-1630) 1652; C-H (3150-3020) 3045.31; C=C (1675-1600) 1613.27; N-H (3500-3100) 3112.55; C=C (1600-1450) 1585, 1481; C-H (3100-3010) 3045.31.

Compound code -$TZN_{4(d)}$

^{1}H-NMR ($CDCl_3$, 300MHZ)- δ=7.22(C-H, Benzene); 7.26 (C-H, Benzene); 7.41(C=CH, Methene); 2.3(N-H, Amine); 1.59(CH_3, Methyl); 8.6(N-H, 2^0Amide); 1.25(C-H, Benzene); 7.44(C-H, Benzene); 7.6(C-H, Benzene); 7.96(H, Benzene); 6.82(N-H, Benzene).

Mass (m/e) - 510; (m+1) 511.0.

IR (KBr) - C=O (1680-1630) 1651.13; C-H (3150-3020) 3112.47; C=C (1675-1600) 1613.97; N-H (3500-3100) 3232, 3112; C-H (2960-2850) 2933.32; C=O (1725-1700) 1703.85; C=C (1675-1600) 1613.97.

Compound code - $TZN_{4(e)}$

^{1}H-NMR ($CDCl_3$, 300MHZ)- δ=7.2(C-H, Benzene); 1.5(CH_3, Methyl); 1.25(C-H, Benzene);.

Mass (m/e) - 523.21; (m+1) 524.0.

IR (KBr) - C=O (1680-1630) 1687; N-H (3500-3100) 3099; C=C (1600-1450) 1613; C-H (3000-2850) 2992.19; C-N (1360-1180) 1339.01, 1299.77, 1233.37, 1188.71; C-N (1360-1180).

Compound code - $TZN_{4(f)}$

^{1}H-NMR ($CDCl_3$, 300MHZ) - δ=7.2(C-H, Benzene); 7.44(C-H, Benzene); 7.4(C=CH, Methene); 5.82(N-H, Amine); 1.2(CH_3, Methyl); 8.4(N-H, 2^0Amide); 9.1(N-H, imide); 7.44(C-H, Benzene); 7.62(C-H, Benzene); 7.5(H, Benzene); 8.6(N-H, Benzene).

Mass (m/e) - 525; (m+1) 526.

IR (KBr) - C=O (1680-1630) 1646.30; C-H (3150-3020) 3108.54; N-H (3500-3100) 3230.63; C=C (1600-1450) 1475.17; C-H (3150-3050) 3108.54; Ar. NO_2 (1570-1500 and 1370-1300) 1519.35, 1349.64.

Compound code - $TZN_{4(g)}$

^{1}H-NMR ($CDCl_3$, 300MHZ)- δ=7.26(C-H, Benzene); 7.28(C-H, Benzene); 7.46(C=CH, Methene); 1.5(CH_3, Methyl); 8.18(N-H, 2^0Amide); 7.47(C-H, Benzene); 8.15(C-H, Benzene); 8.1(H, Benzene); 6.9(N-H, Benzene); 9.1(N-H, imide).

Mass (m/e) - 515; (m+1) 516.

IR (KBr) - C=O (1680-1630) 1650.77; N-H (3500-3100) 3230; C-H (2960-2850) 2935.24; C-Cl (800-600) 780.86.

Compound code - $TZN_{4(h)}$

^{1}H-NMR ($CDCl_3$, 300MHZ)- δ=7.26(C-H, Benzene); 7.34(C-H, Benzene); 7.46(C=CH, Methene); 1.56(CH_3, Methyl); 8.18(N-H, 2^0Amide); 1.25(C-H, Benzene); 8.15(N-H, Benzene); 9.10(N-H, imide).

Mass (m/e) - 531; (m+1) 533.

IR (KBr) - C=C (1600-1450) 1462.57; C-Cl (800-600) 776.49

Compound code -$TZN_{4\ (i)}$

^{1}H-NMR ($CDCl_3$, 300MHZ))- δ=7.26(C-H, Benzene); 7.31(C-H, Benzene); 7.47(C=CH, Methene); 1.45(CH_3, Methyl); 8.17(N-H, 2^0Amide); 7.46(C-H, Benzene); 6.7(N-H, Benzene); 9.0(N-H, imide); 4.11(CH=CH, ethene).

Mass (m/e) - 521.04; (m+1) 522.

IR (KBr) - C=O (1680-1630) 1646.36; C=C (1675-1600) 1610.00; N-H (3500-3100) 3233.04; C=C (1600-1450) 1577.11,1460.67; C-Cl (800-600) 776.49; C-H (3150-3050) 3083.41.

Compound code - $TZN_{4(j)}$

^{1}H-NMR ($CDCl_3$, 300MHZ))- δ=7.22(C-H, Benzene); 7.32(C-H, Benzene); 7.35(C=CH, Methene); 1.57(CH_3, Methyl); 8.15(N-H, 2^0Amide); 1.5(C-H, Benzene); 6.7(N-H, Benzene); 9.0(N-H, imide); 4.11(CH=CH, ethene).

Mass (m/e) - 545; (m+1) 546.

IR (KBr) - C=O (1680-1630) 1649.25; C=O (1725-1700) 1704.83; C-H (3150-3050) 3085.50; C=C (1675-1600) 1610.76; N-H (3500-3100) 3232.12; C=C (1600-1450) 1578.63, 1548.45, 1512.34; C-H (2960-2850) 2948.45; C-Cl (800-600) 666.88, 781.34.

Compound code - $TZN_{4(k)}$

^{1}H-NMR ($CDCl_3$, 300MHZ) - δ=7.26(C-H, Benzene); 7.32(C-H, Benzene); 7.44(C=CH, Methene); 2.33(N-H, Amine); 1.58(CH_3, Methyl); 8.15(N-H, 2^0Amide); 7.34(C-H, Benzene); 6.64(C-H, Benzene); 6.5(N-H, Benzene); 9.0(N-H, imide); 4.11(CH=CH, ethene).

Mass (m/e) - 558; (m+1) 559.

IR (KBr) - C=O (1680-1630) 1686.41; C=C (1675-1600) 1612.93; N-H (3500-3100) 3551.84; C=C (1600-1450) 1581.46; C-Cl (800-600) 744.98, 680,93; C-H (3000-2850) 2978.99; C-N (1360-1180) 1311.86; C-N (1230- 1030) 1228.27.

Compound code - $TZN_{4(l)}$

^{1}H-NMR ($CDCl_3$, 300MHZ)- δ=7.2(C-H, Benzene); 7.32(C-H, Benzene); 7.43(C=CH, Methene); 1.59(CH_3, Methyl); 8.08(N-H, 2^0Amide); 7.445(C-H, Benzene); 7.38(C-H, Benzene), 6.09(N-H, Benzene); 9.11(N-H, imide); 3.9(CH=CH, ethene).

Mass (m/e) - 560; (m+1) 561.

IR (KBr) - C=O (1680-1630) 1644.55; N-H (3500-3100) 3222.59; C=C (1600-1450) 1578.05; C-Cl (800-600) 744.81, 610.80; C=C (1600-1450) 1578.05; Ar. NO_2 (1570-1500 and 1370-1300) 1519.89, 13.43.15; -O-N=O (1625-1605) 1613.60.

Discussion

With an orientation to utilize the information produced by the work of Hong Woo Lee et al, the synthesis of the novel pyrimidine derivatives having thiazolidinedione were carried out and the synthesized compounds were evaluated for their hypoglycaemic and hypolipidimic activities.[27]

Characterizations of the synthesized compounds were carried out by determining their melting points, UV absorption maxima, IR spectra, Mass spectra, NMR spectra. The purity was checked by TLC.

The yield of all the synthesised compounds is found to be significant. The structural confirmation of the compounds is done by IR spectra, Mass spectra and NMR spectra.

The compounds were evaluated for acute toxicity and their antidiabetic activity by using alloxan-induced diabetes model. All the synthesised compounds possessed antidiabetic activity at a dose of 100mg/kg.

The results obtained may be helpful in designing a new potent molecule for treatment of diabetes. A detailed structure activity relationship study would be helpful in obtaining better antidiabetic pyrimidine derivatives.

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