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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL METHYLPYRIMIDINE DERIVATIVES AS AN ANTIDIABETIC AND ANTIHYPERLIPIDEMIC AGENTS

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Keywords:

Methylpyrimidine derivatives, Antidiabetic activity, Antihyperlipidemic activity

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ABSTRACT: Diabetes and hyperlipidemia become a major risk factor for cardiovascular diseases in the world. Hyperlipidemia is a relatively common problem in patients with poorly controlled diabetes. In searching for a new class of antidiabetic and antihyperlipidemic agents, many compounds with pyridine moiety have been found to possess good activity against diabetes and hyperlipidemia. The present study was carried out to synthesize, characterize, and screening of methyl pyrimidine derivatives for antidiabetic and antihyperlipidemic activity. A novel series of 2-amino-4-(substituted phenylamino)-6-methylpyrimidine derivatives have been synthesized from Guanidine hydrochloride. Synthesized compounds were characterized by IR, MASS, ^{1}H-NMR, and C NMR spectroscopy. Synthesized compounds were screened for antidiabetic and antihyperlipidemic activity in Swiss albino mice. The blood sample was collected and used to determine serum glucose, triglyceride, LDL (low-density lipoprotein), HDL (high-density lipoprotein), and total cholesterol level in mice. Among the synthesized derivatives, 2-amino-4-(4-methoxyphenylamino)-6-methylpyrimidine and 2-amino-4-(4-bromophenylamino)-6-methylpyrimidine shows good antidiabetic and antihyperlipidemic activity which was comparable to the standard drug, and it can be useful for the further clinical studies.

INTRODUCTION: Diabetes mellitus is a chronic metabolic disorder characterized by a high level of blood glucose due to insufficient action of insulin [1]. Diabetes mellitus affects a population of approximately 425 million peoples worldwide in year 2018 [2]. Hyperglycemia, hyperlipidemia, and oxidative stress are the most common factors of diabetes mellitus [3-4]. Hyperlipidemia is a cardinal sign of atherosclerosis and other cardiovascular diseases, such as coronary heart diseases, ischemic cerebrovascular diseases and peripheral vascular diseases. Cardiovascular diseases are one of the leading causes of morbidity and mortality among India and worldwide population.

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It contributes to nearly one-fourth of the deaths in the working-age group of 25-65 years in the country [5]. According to the Indian Council of Medical Research (ICMR), a survey conducted in different Indian states showed that the urban population has a higher prevalence of hyper-cholesterolemia than the rural population [6]. In hyperlipidemia, high levels of lipids (fat, cholesterol, and triglycerides) circulating in the bloodstream [7-8]. Epidemiological studies demonstrate that hyperlipidemia is the most prevalent indicator of susceptibility to atherosclerosis and heart diseases [9-10].

Thus, decreasing plasma lipid levels play a major role in the treatment and prevention of coronary heart diseases. For this reason, many studies have been conducted to evaluate the potential for the lipid-lowering activity of synthetic, semisynthetic, and naturally occurring compounds. Abnormalities in lipid profiles are one of the most common complications in diabetes mellitus [11].

Diabetes induction causes an increase in cholesterol, triglycerides, LDL, and VLDL. The level of serum lipids is usually elevated in diabetes mellitus, and such an elevation represents the risk factor for coronary heart diseases [12]. In 1984, it was demonstrated for the first time that there exists a link between serum cholesterol level and risk to coronary heart diseases (CHD) [13]. A 1% drop in serum cholesterol reduces the risk for CHD by 2%. The agents in current use are, however, insufficiently active or are accompanied by unacceptable side effects. A reduction in LDL cholesterol concentration remains the principal desired action, although an elevation in HDL may also be beneficial in CHD. In the last decade, many studies have shown that pyrimidine derivatives have promising potentials as lipid lowering agents [14-17]. A logical strategy to prevent or to treat atherosclerosis and to reduce the incidence of cardiovascular disease events is to target hyperlipidemia by drugs and/or dietary intervention. With this aim, efforts were made to develop effective and better antihyperlipidemic agents. In this perspective, the current study was carried out to develop potent antihyperlipidemic agents. The pyrimidine derivatives 5a-e have been synthesized, characterized, and evaluated for the antihyperlipidemic and antidiabetic activity to check the efficacy of compounds.

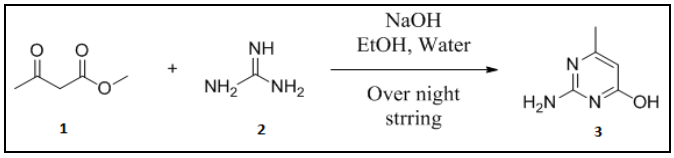
MATERIALS AND METHODS:

Chemicals and Instruments: The melting point of all compounds was determined in open glass capillaries and was uncorrected. Thin-layer chromatography of synthesized compounds was performed on microscopic slides coated with Silica Gel-GF, and spots were visualized by UV light and exposure to iodine vapor. UV spectra of all the compounds were recorded using Shimadzu UV-Visible spectrophotometer UV-160A. IR spectra of compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer, using KBr as an internal reference. Mass spectra of compounds were recorded on LCMS 2010EV Shimadzu Mass Spectrometer. ^{1}H NMR spectra were obtained in $CDCl_3$ on Bruker Advance-II 400 MHz instrument, and chemical shifts were measured as parts per million (δ ppm) downfield from tetramethylsilane as an internal standard. ^{13}C NMR spectra of all synthesized compounds were taken in DMSO using Bruker Advance-II 400 MHz instrument, and chemical shifts were measured as parts per million (δ ppm).

Synthesis and Scheme: The methyl acetoacetate [1] was treated with guanidine hydrochloride [2] which was previously neutralized with sodium hydroxide to afford 2-amino-4-hydroxy-6-methylpyrimidine [3]. Compound [3] was refluxed with phosphorous oxychloride to yield 2-amino-4-chloro-6-methyl-pyrimidine [4]. Refluxing of compound [4] with different reagents like p-anisidine, p-toluene, *p*-chloroaniline, p-bromoaniline, o-anisidine in presence of hydrochloric acid and ethanol to afford 2-amino-4-(substituted phenylamino)- 6- methyl- pyrimidine derivatives like 2-amino-4-(4-methoxyphenylamino)-6-methylpyrimidine 5A, 2-amino - 4 - (4 - methyl phenylamino)-6-methyl-pyrimidine 5B, 2-amino-4-(4-chlorophenylamino)-6- methylpyrimidine 5C, 2 - amino - 4 - (4 –bromo phenylamino)-6-methylpyrimidine 5D, 2-amino - 4 - (2 - methoxyphenylamino) - 6 -methylpyrimidine 5E respectively. The structures of all the synthesized compounds were confirmed by spectral analysis. The scheme of synthesis was presented in **Scheme 1**.

Scheme 1: Synthetic Scheme for the Methyl-pyrimidine Derivatives:

Step 1:



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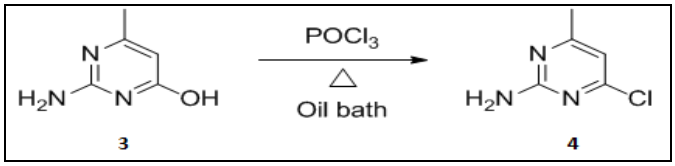

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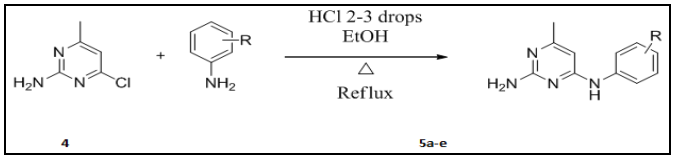

Where, R = p-OCH3, p-CH3, p-Cl, p-Br, o- OCH3

Animals: The experiments were performed as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animal

(CPCSEA), Minister of Social Justice and Empowerment, Government of India. Adult Swiss albino mice, either sex having the weight of 20-30 g will be selected for experiment purpose. All animals will be housed at ambient temperature (22 ± 1 °C), relative humidity (55 ± 1 %), and 12 h light-dark cycles. Animals will have free access to a standard pellet diet and water *ad libitum*.

Antihyperlipidemic and Antidiabetic Activity: To induce diabetes, mice were fed with a high-fat diet except normal control group. At the end of the second week of dietary manipulation, a single dose of intraperitoneal injection of streptozotocin 35 mg/kg (STZ in citrate buffer, pH 4) will be administered and the high-fat diet feeding was continued. After the elevation of blood glucose level, treatment was started with a synthesized compound at the dose of 10 mg/kg of body weight. General parameters like body weight, food intake, and water intake were monitored at regular intervals up to five weeks. The blood was collected from tail vein of each animal, and the serum was separated and used for the estimation of glucose, triglyceride, LDL, HDL, and total cholesterol.

Statistical Analysis: For the determination of change in glucose, triglyceride, LDL, HDL, and total cholesterol levels, individual mice were considered as an experimental unit. All the results were expressed as mean values and standard deviations. The data were analyzed by one way ANOVA method.

RESULTS AND DISCUSSION:

Synthesis and Characterization of Methyl-pyrimidine Derivatives:

Synthesis of 2 - amino - 4 - hydroxyl - 6 - methylpyrimidine (Compound 3): Guanidine hydrochloride (0.018 mol) was neutralized using (0.022 mol) sodium hydroxide solution in ethanol. The mixture was stirred for 15 min at room temperature and filtered. Methyl acetoacetate (0.022 mol) was added dropwise to the above filtrate and stirred overnight. A crude 2-amino-4-hydroxy- 6- methylpyrimidine was filtered, separated, and recrystallized using hot water. Colorless solid; Yield 80 %; m.p. 292-295 °C (298-300 °C); R_f value 0.53 (Dichloromethane: methanol: 90:10); Mol. formula: $C_5H_7N_3O$; Mol. Wt.: 125.13 g/mol.

Synthesis of 2 - amino - 4 - chloro - 6 - methyl - pyrimidine (Compound 4): A mixture of 2-amino-4-hydroxy-6-methylpyrimidine (3.0 gm, 0.024 mol) and phosphorous oxychloride (7.0 mL, 0.78 mol) was refluxed for 30 min. The excess phosphorous oxychloride was distilled off to give gummy residue, which was poured into ice cold water and neutralized with a saturated solution of sodium bicarbonate. A crude yellow solid of 2-amino-4-chloro-6-methylpyrimidine was filtered, separated, and recrystallized using methanol. Yellow solid; Yield 54 %; m.p. 176-180 °C (182-184 °C); R_f value 0.92 (Dichloro-methane: methanol: 90:10); Mol. formula: $C_5H_6C_lN_3$; Mol. Wt.: 143.57 g/mol.

Synthesis of 2 - amino - 4 - (4 - methoxyphenylamino) - 6 - methylpyrimidine (Compound 5A): To a solution of 2-amino-4-chloro-6-methylpyrimidine (1.0 gm, 0.007 mol), p-anisidine (1.0 gm, 0.0084 mol) in ethanol (10 mL), hydrochloric acid (0.3 mL) was added. The reaction mixture was refluxed till it gets completed. The reaction progress was monitored by TLC. The crude solid was filtered and recrystallized by methanol to give the 2 – amino - 4 - (4 -methoxy-phenylamino)-6-methylpyrimidine. Yellow solid; Yield 50%; m.p. 215-218 °C (218-220 °C); R_f value 0.72 (n-hexane:ethyl acetate::80:20); Mol. formula: $C_{12}H_{14}N_4O$; Mol. Wt.: 230.27 g/mol. IR: 3321, 3286(-NH_2), 1230, 1037 (-O-) cm^{-1}; Mass (m/e): 231(M+1); ^{1}H NMR (DMSO-d6, 400 MHz, δ ppm): 2.51(s, 3H, CH_3); 3.58(s, 3H, OCH_3); 7.2-7.3(m, ^{1}H, Ar-NH); 7.66-7.72(m, ^{2}H, Ar-H); 8.30 (s, ^{1}H, Ar-NH); 10.36(s, ^{2}H, Ar- NH_2). ^{13}C NMR (DMSO-d6, 100 MHz, δ ppm): 23; 55.05; 62.50; 99.66; 115.1; 120.9; 132.7; 154.7; 161; 164.9; 167.5.

Synthesis of 2-amino-4-(4-methyl phenylamino)-6-methylpyrimidine (Compound 5B): To a solution of 2-amino-4-chloro-6-methylpyrimidine (1.0 gm, 0.007 mol), p-toluene (1.0 gm, 0.0084 mol) in ethanol (10 mL), hydrochloric acid (0.3 mL) was added. The reaction mixture was refluxed till it gets completed. The reaction progress was monitored by TLC. The crude solid was filtered and recrystallized by methanol to give the 2-amino-4- (4-methyl phenylamino)-6-methylpyrimidine. Yellow solid; Yield 42 %; m.p. 198-203 °C; R_f value 0.67 (n-hexane: ethyl acetate::80:20); Mol.

formula: $C_{12}H_{14}N_4$; Mol. Wt.: 214.27 g/mol. IR: 3301, 3226(-NH_2), 3087(-NH-) cm^{-1}; Mass (m/e): 215(M+1); ^{1}H NMR (DMSO-d6, 400 MHz, δ ppm): 2.51(s, ^{3}H, CH3); 2.4(s ^{3}H, CH3); 5.8(s, ^{1}H, Ar-h); 7.24-7.3(d, ^{2}H, Ar-H); 7.43-7.62(d, ^{2}H, Ar-H); 8.6(s, ^{1}H, Ar-NH), 10.56(s, ^{2}H, Ar-NH_2); ^{13}C NMR (DMSO-d6,100 MHz, δ ppm): 21.3; 24.2; 93.8; 121.3; 130.8, 137.9; 163.1; 164.7

Synthesis of 2-amino-4-(4-chlorophenylamino)-6-methylpyrimidine (Compound 5C): To a solution of 2-amino-4-chloro-6-methylpyrimidine (1.0 gm, 0.007 mol), p-chloroaniline (1.0 gm, 0.0084 mol) in ethanol (10 mL), hydrochloric acid (0.3 mL) was added. The reaction mixture was refluxed till it gets completed. The reaction progress was monitored by TLC. The crude solid was filtered and recrystallized by methanol to give 2 - amino - 4 - (4 - chlorophenylamino) – 6 - methylpyrimidine. Yellow solid; Yield 69 %; m.p. 210-215 °C; R_f value 0.73 (n-hexane: ethyl acetate::80:20); Mol. formula: $C_{11}H_{11}C_lN_4$; Mol. Wt.: 234.68 g/mol. IR: 3487, 3294(NH^2), 3126(-NH-) cm^{-1}; Mass (m/e): 235(M+1), 236(M+2); 1H NMR (DMSO-d6, 400 MHz, δ ppm): δ2.6(s, 3H, CH_3); 7.24-7.3(m, ^{1}H, Ar-H); 7.66-7.62(d, ^{2}H, Ar-H); 8.50(s, ^{1}H, Ar-NH), 10.6(s, ^{2}H, Ar-NH^2); ^{13}C NMR (DMSO-d6,100 MHz, δ ppm): 23.9; 93.9; 122.3; 127.7; 129.6; 163.3; 164.6; 170.3.

Synthesis of 2-amino-4-(4-bromophenylamino)-6-methylpyrimidine (Compound 5D): To a solution of 2-amino-4-chloro-6-methylpyrimidine (1.0 gm, 0.007 mol), p-bromoaniline (1.0 gm, 0.0084 mol) in ethanol (10 mL), hydrochloric acid (0.3 mL) was added. The reaction mixture was refluxed till it gets completed. The reaction progress was monitored by TLC. The crude solid was filtered and recrystallized by methanol to give 2 - amino - 4 - (4-bromophenylamino) - 6 - methylpyrimidine. Yellow solid; Yield 72 %; m.p. 225-228 °C; Rf value 0.69 (n-hexane: ethyl acetate::80:20); Mol. formula: $C_{11}H_{11}BrN_4$; Mol. Wt.: 279.14 g/mol. IR: 3475, 3296(NH2), 3126(-NH-) cm-1; Mass (m/e): 279(M+1), 280(M+2); 1H NMR (DMSO-d6, 400 MHz, δ ppm): 2.45(s, 3H, CH_3); 7.01(d, ^{2}H, Ar-H); 7.36-7.42(d, 2H, Ar-H); 8.30(s,^{1}H, Ar-NH); 10.36(s, ^{2}H, Ar-NH_2); ^{13}C NMR (DMSO-d6,100 MHz, δ ppm): 22.5; 93.9; 116.9; 118.8; 132.5; 139.9; 163.3; 164.6; 170.5.

Synthesis of 2 - amino - 4 - (2 –methoxy-phenylamino)-6-methylpyrimidine (Compound 5E): To a solution of 2-amino-4-chloro-6-methylpyrimidine (1.0 gm, 0.007 mol), o-anisidine (1.0 gm, 0.0084 mol) in ethanol (10 mL), hydrochloric acid (0.3 mL) was added. The reaction mixture was refluxed till it gets completed. The reaction progress was monitored by TLC. The crude solid was filtered and recrystallized by methanol to give 2 - amino - 4-(2-methoxy-phenyl-amino) - 6 - methylpyrimidine. Yellow solid; Yield 45 %; m.p. 232-235 °C; R_f value 0.74 (n-hexane: ethyl acetate::80:20); Mol. formula: $C_{12}H_{14}N_4O$; Mol. Wt.: 230.27 g/mol. IR: 3454,3288(-NH_2) 3134(-NH-) cm^{-1}; Mass (m/e): 231(M+1); ^{1}H NMR (DMSO-d6, 400 MHz, δ ppm): δ2.33(s, ^{3}H, CH3); 3.83(s ^{3}H, OCH_3); 7.25-7.35(m, ^{2}H, Ar-H); 7.66-7.62(m, ^{2}H, Ar-H); 8.50(s, ^{1}H, Ar-NH), 10.6(s, ^{2}H, Ar-NH_2)*; 13C NMR (DMSO-d6,100 MHz, δ ppm): 23.9; 55.7; 93.8; 112.3; 113.4; 121.8; 122.8; 132.6; 147.4; 163.5; 164.5; 170.3.

Antidiabetic and Antihyperlipidemic Activity: All the synthesized compounds were screened for antidiabetic and antihyperlipidemic activity by using adult Swiss albino mice. The synthesized compounds exhibit both antidiabetic and antihyperlipidemic activity. The serum level of glucose, triglyceride, LDL, HDL, and total cholesterol of all the treated groups were measured, and results are shown in **Table 1** and **Fig. 1** to **5**. In comparison with the normal control, streptozotocin (disease control) caused a significant increase in glucose, triglyceride, LDL, and total cholesterol level. Streptozotocin caused a significant decrease in HDL level in the diabetic and hyperlipidemic control in comparison with the normal control.

Effect of Synthesized Compounds (5A-E) on Serum Level of Glucose, Triglyceride, LDL, HDL and Total Cholesterol: The oral administration of synthesized methylpyrimidine derivatives (compound 5A and 5D) to mice significantly decreases the serum level of glucose, triglyceride, LDL, and total cholesterol in comparison to the disease control. The serum level of HDL significantly increased in mice treated with compound 5A and 5D in comparison to the disease control. The results were shown in **Table 1**.

TABLE 1: EFFECT OF DIFFERENT DERIVATIVES OF METHYLPYRIMIDINE ON SERUM GLUCOSE, TRIGLYCERIDE, LDL, HDL AND TOTAL CHOLESTEROL LEVEL IN STREPTOZOTOCIN INDUCED DIABETIC AND HYPERLIPIDEMIC MICE

Groups	Treatment Dose (mg/kg)	Glucose (mg/dl)	TG (mg/dL)	LDL (mg/dl)	HDL (mg/dl)	TC (mg/dla)
Normal Control	Vehicle	82.31±1.23	99.83±2.47	35.38±3.01	49.19±n5.23	92.68± 4.02
Disease Control (STZ)	150	306.43±2.28	142.43±1.98	112.25±3.26	42.52± 4.58	367.11±2.84
Saroglitazar	3	156.09±3.25	43.69±1.88	34.98±5.80	45.96± 1.79	223.63±3.54
Comp 5a	10	166.34±2.58	56.03±1.29	48.53±5.08	41.64± 3.44	241.21±1.09
Comp 5b	10	279.81±2.84	102.35±3.84	106.24±4.83	33.53± 4.61	359.14±1.77
Comp 5c	10	221.65±2.58	136.48±6.78	99.57± 1.28	34.97±4.98	334.04±6.87
Comp 5d	10	186.72±4.85	86.48±4.81	66.82± 3.26	42.35±2.07	284.57±4.95
Comp 5e	10	202.87±3.39	88.54±4.02	90.14±n1.85	30.19±1.98	311.89±6.57

Results are expressed in mean ± SEM (n=6), STZ = streptozotocin, TG = triglyceride, LDL = low density lipoprotein, HDL = high density lipoprotein, TC = total cholesterol. The data were analyzed by one-way ANOVA followed by Dunnett test, and difference *P<0.05 were considered statistically significant as compared with Saroglitazar 3 mg/kg.

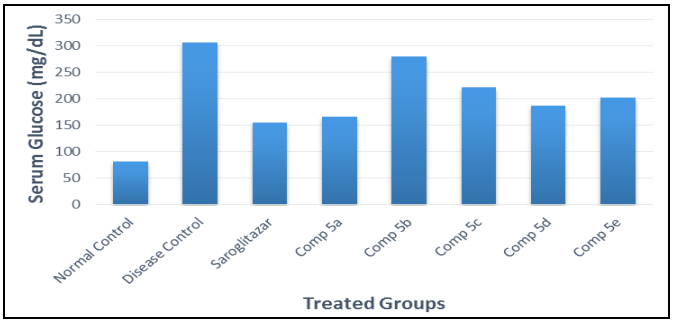

FIG. 1: EFFECT OF DIFFERENT DERIVATIVES OF METHYLPYRIMIDINE ON SERUM GLUCOSE IN STREPTOZOTOCIN INDUCED DIABETIC AND HYPERLIPIDEMIC MICE

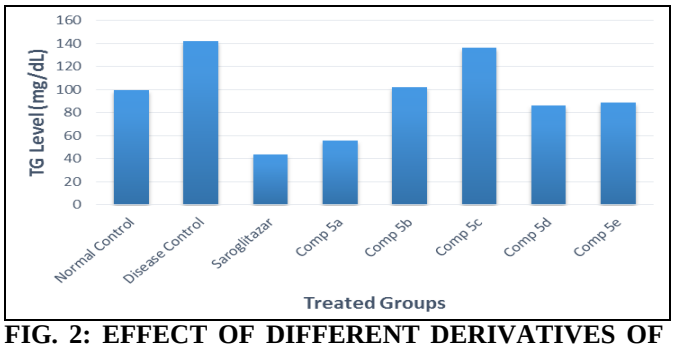

FIG. 2: EFFECT OF DIFFERENT DERIVATIVES OF METHYLPYRIMIDINE ON SERUM TRIGLYCERIDE IN STREPTOZOTOCIN INDUCED DIABETIC AND HYPERLIPIDEMIC MICE

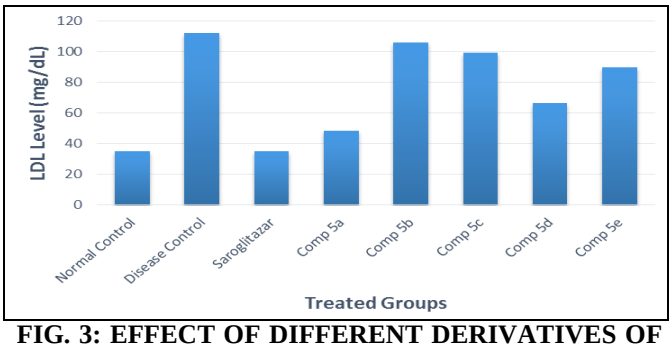

FIG. 3: EFFECT OF DIFFERENT DERIVATIVES OF METHYLPYRIMIDINE ON SERUM LDL IN STREPTOZOTOCIN INDUCED DIABETIC AND HYPERLIPIDEMIC MICE

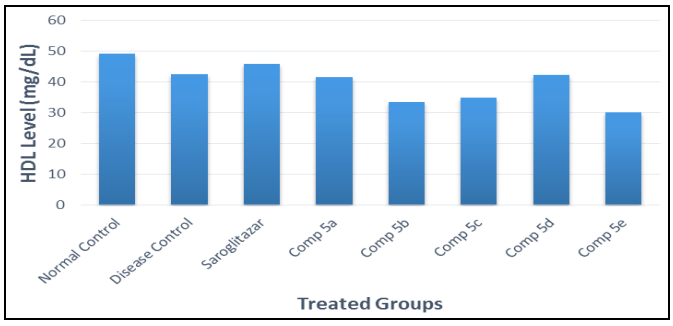

FIG. 4: EFFECT OF DIFFERENT DERIVATIVES OF METHYLPYRIMIDINE ON SERUM HDL IN STREPTOZOTOCIN INDUCED DIABETIC AND HYPERLIPIDEMIC MICE

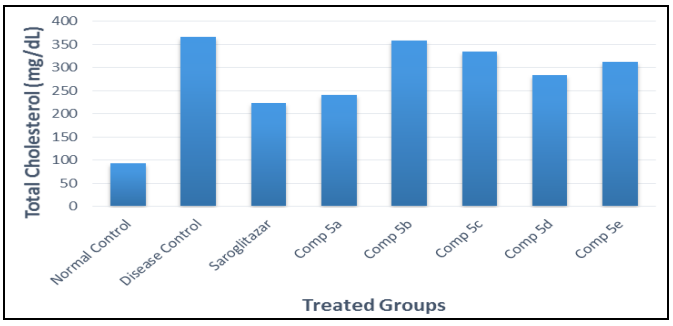

FIG. 5: EFFECT OF DIFFERENT DERIVATIVES OF METHYLPYRIMIDINE ON SERUM TOTAL CHOLESTEROL IN STREPTOZOTOCIN INDUCED DIABETIC AND HYPERLIPIDEMIC MICE

DISCUSSION: The present investigation discusses the antidiabetic and antihyperlipidemic potential of methylpyrimidine derivatives in STZ-induced diabetic mice. The use of STZ to induce diabetes in rodent models is widely accepted, and STZ-induced diabetes is reported to resemble human diabetes mellitus [18]. Saroglitazar is often used as a standard antidiabetic drug in STZ-induced diabetes to compare the antidiabetic effects of various compounds [19]. In the present work, administration of the methylpyrimidine derivatives (Compound 5A and 5D) at the dose of 10 mg/kg significantly reduces the serum glucose level in STZ-induced hyperglycemia in mice.

In diabetes, the occurrence of marked hyperlipidemia may be a consequence of the uninhibited action of lipolytic hormones on the fat depots and increase in mobilization of fatty acids from fatty tissues [20]. Diabetic hyperlipidemia is associated with enhanced glucose, triglyceride, low-density lipoproteins, and total cholesterol and decreased high-density lipoproteins level. These changes result in an increased risk of coronary heart diseases in patients with diabetes mellitus.

An increase in LDL and a decrease in HDL are directly associated with the risk of cardiovascular diseases [20-21]. The present investigation shows the lowering of lipid parameters such as TG, TC, and LDL and an increase in HDL cholesterol levels in STZ-induced diabetes by the administration of methylpyrimidine derivatives (Compound 5A and 5D). HDL cholesterol plays a crucial role in preventing cardiovascular diseases because of its role in the transportation of excess cholesterol out of the body.

CONCLUSION: In conclusion, the present findings demonstrated that the newly synthesized methylpyrimidine derivatives are exhibiting significant antidiabetic and antihyperlipidemic activities against STZ-induced diabetic mice. Further studies to find out the mechanism of these compounds may use for further clinical study.

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CONFLICTS OF INTEREST: The authors declare that they have no conflicts of interest.

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