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DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF PROPROTEIN CONVERTASE SUBSTILSIN/KEXIN TYPE 9 INHIBITORS AS POTENT ANTI-HYPERLIPIDEMIC AGENTS

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Keywords:

Benzoxazole, Antihyperlipidemic activity, High fat diet model, Molecular docking, PCSK9

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ABSTRACT: Hyperlipidemia is a systemic disease, which is characterized by elevated lipid levels in blood including total cholesterol (TC), total glyceride (TG), low density lipoprotein cholesterol (LDL-c) and so on. It is one of the major risk factors leading to fatty liver, cardiovascular diseases and atherosclerosis and become the first killer of human health. The present study involves synthesis of some novel heterocycles of benzoxazole derivatives containing Oxadiazole and amino triazole and its evaluation of *in-vivo* and *in-silico* molecular docking for determining antihyperlipidemic activity. The chemical structures of newly synthesized compounds were evaluated by spectrum of IR, ^{1}HNMR, and LC-MS. The molecular docking studies for the synthesized compounds with *PCSK9* showed energy levels ranging from -8 to -10kcal/mol. The compound VD1which shows least binding energy taken for *in-vivo* antihyperlipidemic activity study. The antihyperlipidemic activity was evaluated by high fat diet induced hyperlipidaemia model and the compound VD1 showed significant reduction in serum lipid parameters as that of standard drug Atorvastatin.

INTRODUCTION: Hyperlipidemia is a systemic disease, which is characterized by elevated lipid levels in blood including total cholesterol (TC), total glyceride (TG), low density lipoprotein cholesterol (LDL-c) and so on. It is one of the major risk factors leading to fatty liver, cardiovascular diseases and atherosclerosis (increased plasma level of low-density lipoprotein) and become the first killer of human health [1]. Numerous epidemiological studies shows that pharmacological lowering of LDL significantly reduce the cardiovascular event.

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Currently, many drugs are commercially available for lowering TC and LDL but with serious side effects such as myopathy, muscle pains, and rhadomyolysis [2]. Hence, there is a immediate need to develop new agent with fewer side effects. *Proprotein convertase substilsin/kexin 9 (PCSK9)* plays a crucial role in regulating circulating levels of LDL-c as a consequence of its ability to inhibit LDL receptor recycling in the liver. Loss of functional variants in the *PCSK9* gene results in low LDL-c levels and associated with reduced cardiovascular risk [3-5].

Benzoxazole, Amino Triazole, Oxadiazole possess various pharmacological activities like anti-cancer, anti-hyperlipidemic, anti-inflammatory, hypo-lipidemic activity [6]. This research work reports synthesis, characterization, molecular docking and the *in-vivo* antihyperlipidemic study on HFD induced hyperlipidemia.

Experimental Work: In this study, all chemicals used were of analytical grade and were used as received without further purification. Melting points were determined by open capillary method and are uncorrected. Purity of the synthesized compounds were checked by pre-coated TLC plate-GF254 (Merck), Methanol: Chloroform in the ratio of 9:1 as mobile phase, UV chamber as the detection method. The IR spectra of the synthesized compounds were recorded in the ABB-MB-3000 FTIR Spectrometer. ^{1}H NMR spectra were recorded in a BRUKER Avance 400 MHz instrument using TMS as internal standard and the chemical shifts are reported in ppm. LC-MS spectra of the compounds were recorded using the Agilent technologies 6230B TOF.

General Procedure:

Synthesis of 4-Hydroxy-3-nitro-benzoic Acid Methyl Ester (I): 4- hydroxyl methyl benzoate (10g, 0.74 mol) was placed in a round bottomed flask equipped with reflux condenser and thermometer. A mixture of concentrated sulphuric acid (6.2 ml) and nitric acid (6.2 ml) was added drop wise in p- Hydroxyl methyl benzoate with stirring. Cool the flask in ice bath to 0-10°C. Then the reaction mixture poured into crushed ice. Filtered off the crude product m- nitro-p-hydroxy-methyl benzoate and washed with cold water. Transfer the solids into 500 ml flask and stirred it with ice cold methanol in order to remove a small amount of ortho isomer and other impurities. The mixture was filtered and recrystallized using ethanol as solvent [7]. The purity of product was established by single spot-on TLC. The percentage yield was found to be 83%, M.P.64-66°C.

Synthesis of 3- Amino-4-hydroxy-benzoic Acid Methyl Ester (II): In a 500 ml three necked flask bottom flask equipped with reflux condenser with guard tube, compound I (10g) was dissolved in boiling alcohol (50%, 100 ml) and sodium dithionite was added to this boiling alcohol solution until it becomes almost colourless. Then the alcohol was reduced to one third of its volume by distillation and the residual liquid was triturated with ice cold water. The resulting product was filtered, washed with cold water, dried and recrystallized with ethanol [8]. The purity of product was established by single spot-on TLC. The percentage yield was found to be 77%, M.P. 108-111°C.

Synthesis of 2- methyl Benzoxazole-5-carboxylic Acid Methyl Ester (III): Compound II (0.01 mol) was heated with acetic acid in excess under reflux for 2 hours. The reaction mixture was poured in crushed ice with stirring.

The product thus separated was filtered and washed with cold water. The products were recrystallized by using ethanol as solvent [9]. The purity of product was established by single spot-on TLC. The percentage yield was found to be 75%, M.P.70-73°C.

Synthesis of 2- methyl benzoxazole-5-carboxylic Acid Hydrazide (IV): A mixture of a 2- methyl benzoxazole-5-carboxylic acid methyl ester III (0.001 mol) in alcohol (25 ml) and hydrazine hydrate (99%, 0.015 mol) was heated under reflux on water bath for 4 hours. The alcohol was reduced to half of its volume and cooled.

The product separated was filtered and washed with small portions of cold alcohol and then with cold water repeatedly and dried. The resultant product was recrystallized using ethanol as solvent [10]. The purity of product was established by single spot-on TLC. The percentage yield was found to be 81%, M.P. 143-147°C [7].

Synthesis of 5-(5-phenyl-1,3,4 oxadiazol-2-yl)-benzo(d)oxazole derivatives (V): Compound IV (0.01 mol), aromatic acids (0.01 mol), Phosphorus oxychloride was refluxed for about 5-6 hrs.

Then the mixture was made alkaline with sodium bicarbonate. The product was dried and recrystallized using ethanol [10]. The purity of product was established by single spot-on TLC.

Synthesis of 3-(benzo(d)oxazol-5-yl-)-5-phenyl-4H - 1, 2, 4 - triazole – 4 - amine derivatives (VI): Compound (V) (0.01 mol) was treated with hydrazine hydrate (0.015 mol) and refluxed for about 2 hrs in dry pyridine (15ml).

Then neutralized with hydrochloric acid. The obtained corresponding amino triazoles were filtered, dried and recrystallized with ethanol [10-12].

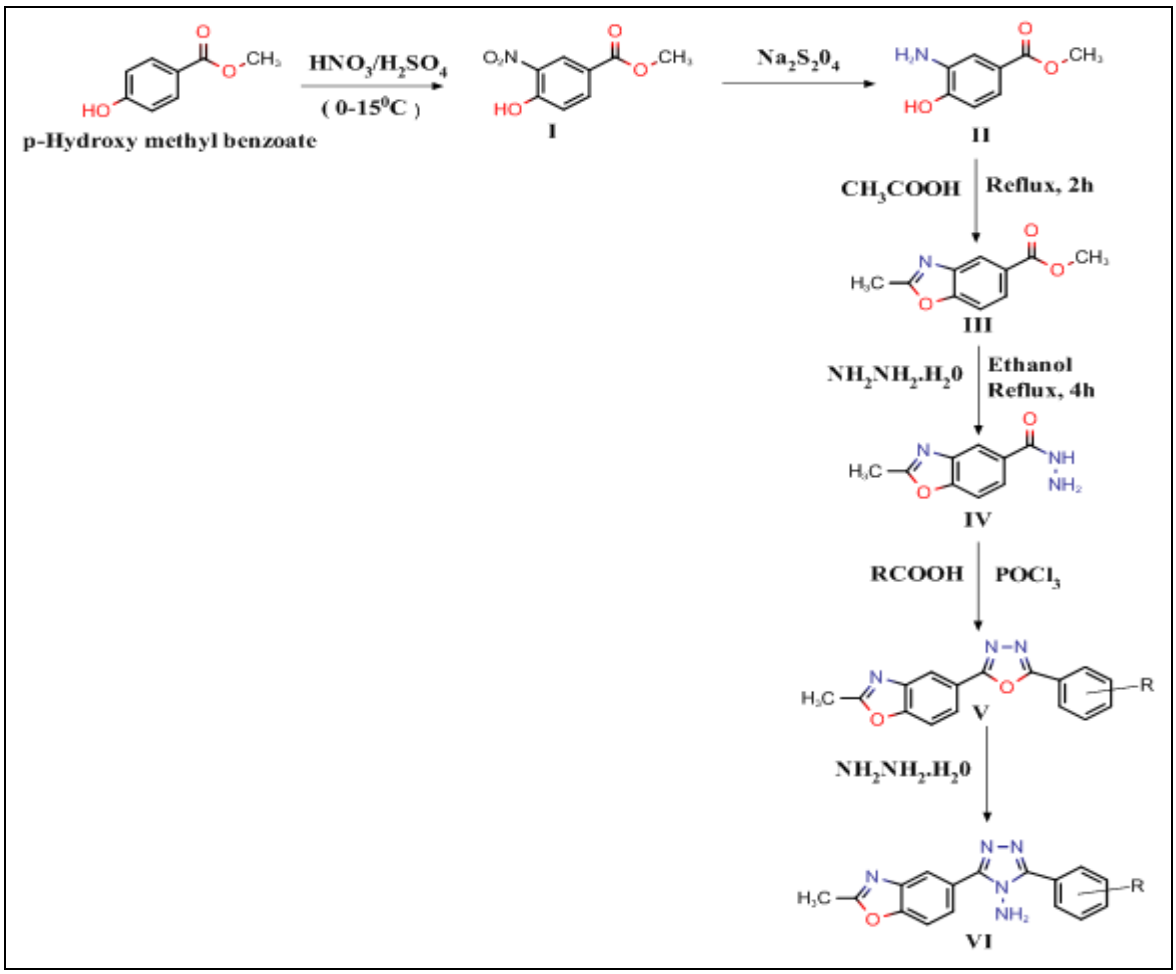


FIG. 1: SCHEME OF THE NEWLY SYNTHESIZED COMPOUNDS

Synthesis of 3-(benzo(d)oxazol-5-yl-)-5-phenyl-4H-1, 2, 4-triazole-4 - amine derivatives (VI): Compound (V) (0.01 mol) was treated with hydrazine hydrate (0.015 mol) and refluxed for about 2 hrs in dry pyridine (15ml). Then neutralized with hydrochloric acid. The obtained corresponding amino triazoles were filtered, dried and recrystallized with ethanol [10-12].

Characterisation:

Compound VD1: 4 - [5 - (2 - methyl - 1, 3 - benzoxazol - 5 - yl) -1,3,4-oxadiazol-2-yl] aniline: **Yield:** 75%, M.P.172-175^{0}C, R_f-0.61**,** IR (KBr) cm^{-1}:3317(NH_2), 1681(C=N), 1234(C-O-C), H^1 NMR (400MHz, DMSO): 2.4(Methyl C-H, s), 7.4-8.5(Aromatic C-H, m), 6.8(NH_2, s), m/z: 292.05.

Compound VD2: 2 - [5 - (2 - methyl - 1, 3 -benzoxazol-5-yl) -1, 3, 4-oxadiazol-2-yl] phenol: **Yield:** 71%, **M.P.**177-179^{0}C, R_f-0.53, IR (KBr) cm^{-1}:3394(OH), 1620(C=N), 1288(C-O-C), H^1 NMR (400MHz, DMSO): 2.5(Methyl C-H, s), 7.2-7.8(Aromatic C-H, m), 5.23(OH, s), m/z: 294.300

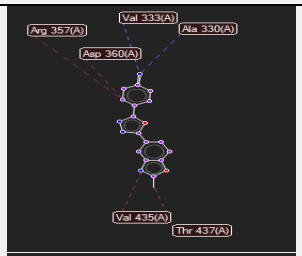
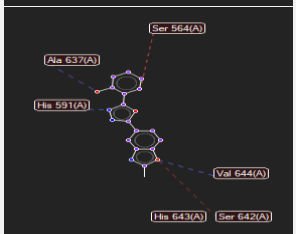
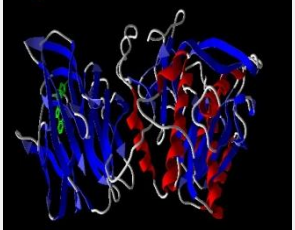
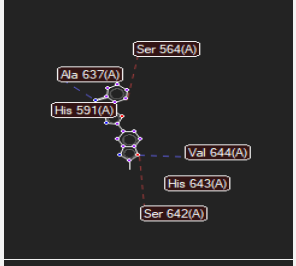
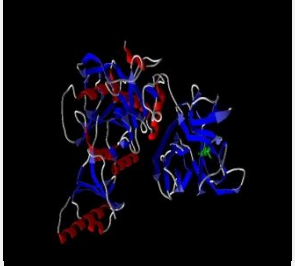
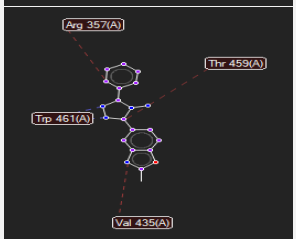
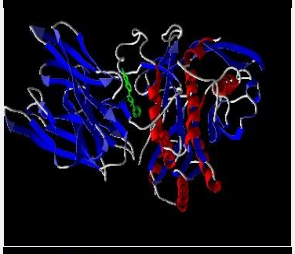
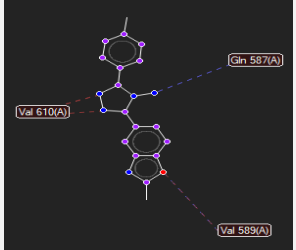
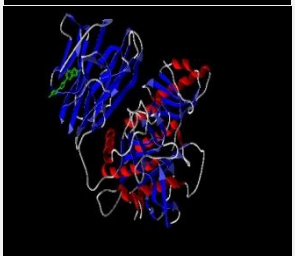
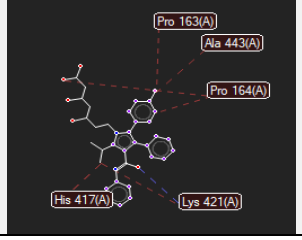
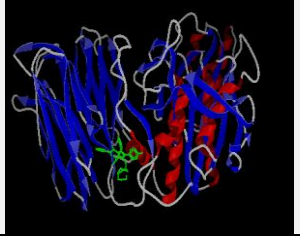
Compound VD3: 2 - [5 -(2 - methyl - 1, 3-benzoxazol-5-yl) -1,3,4-oxadiazol-2-yl] aniline: **Yield:** 73%, M.P.169-172^{0}C, R_f-0.62, IR (KBr) cm^{-1}:3741(NH_2), 1681(C=N), 1280(C-O-C), H^1 NMR (400MHz, DMSO):2.51(Methyl C-H, s), 7.4-8.7(Aromatic C-H, m), 6.8(NH_2, s), m/z: 293.65.

Compound VD4: 3 - (2 - methyl - 1, 3 - benzoxazol - 5 - yl) - 5 - phenyl - 4H - 1, 2, 4-triazol - 4 - amine: **Yield:** 65%, **M.P.**180-182^{0}C, **R_f**-0.57, IR (KBr) cm^{-1}: 3309(NH_2), 1643(C=N), H^1 NMR (400MHz, DMSO): 2.5(Methyl C-H, s), 7.7-8.0(Aromatic C-H, m), 6.6(NH_2, s), m/z: 293.100.

Compound VD5: 3 - (2 - methyl - 1, 3 - benzoxazol - 5-yl) -5-(4-methylphenyl) -4H-1, 2, 4-triazol-4-amine: **Yield:** 67%, M.P.187-189^{0}C, R_f-0.65,IR (KBr) cm^{-1}: 3679(NH_2), 1681(C=N), 1234(C-O-C) H^1 NMR (400MHz, DMSO): 2.4(Methyl C-H, s), 7.80-7.82(Aromatic C-H, m), 6.8(NH_2, s), m/z: 306.25.

Molecular Docking Study of Compounds: Molecular docking is performed to examine the binding orientation of the synthesized compounds with target protein *PCSK9.* The crystal structure *of PCSK9* was retrieved from RCSB Protein Data Bank and *Autodock4.2.6* was employed for molecular docking studies. The 2D structure of the synthesized compounds were sketched were sketched by using *ChemDraw Ultra 12.*0. The energy minimizations of the ligands were carried out with *Chem3D Pro 12.0.*After making the protein file and ligand file, autogrid file were generated and followed by auto dock analysis. The docking results of the ligands with the protein *PCSK9* are tabulated below,

TABLE 1: DOCKING RESULTS OF SYNTHESIZED COMPOUNDS

Sample Code	Docking Score (Kcals/mol)	2D Interactions	3D Interactions
VD1	-10.24		
VD2	-8.53		
VD3	-8.98		
VD4	-8.78		
VD5	-8.01		
Standard Drug (Atorvastatin)	-5.14		

***In-vivo* Evaluation of Anti-hyperlipidaemic Activity:**

Experimental Animals: Healthy Male Wistar rats of (150-180g) were procured from the Animal Experimental Laboratory, Madras Medical College, Chennai-03. Animals were kept in clean and dry polypropylene cages with 12:12 hours light and dark cycle at 25±5°C and 55-58% relative humidity in the animal house. Animals were allowed freely to access standard pellet diet and purified water *ad libitum*. The study was approved by the Institutional Animal Ethical Committee (IAEC) of the Madras Medical College, Chennai which was certified by the Committee for the Purpose of Control and Supervision of Experiments of Animals (CPCSEA), India. (CPCSEA Registration number: 1917/GO/ReBi/2016/CPCSEA). IAEC approval Number: 13/2021-2022.

Acuteoral Toxicity Study: In the present study, the acute toxicity of the synthesized compounds was performed as per the OECD Guidelines- 423. In this method, the toxicity of the synthesized compounds was tested using a stepwise procedure, each step using 3 rats of a single sex. Wistar rats were fasted overnight prior to dosing (food but not water should be withheld). Following the period of fasting the animal should be weighed and the synthesized compounds administered orally at the dose of 2000mg/kg body weight. Animals were observed individually after dosing at least during the first four hours and daily thereafter, for a total of 14 days for sign of toxicity or mortality [13].

***In-vivo* Anti-hyperlipidemic Activity:** The model used to evaluate the antihyperlipidemic activity was High Fat Diet induced hyperlipidemia in rats. Hyperlipidemia in rats was induced by administration of high fat diet (43% carbohydrate, 17% protein and 40% fat, each nutrient per 100g) for 60 days with standard rat chow diet [14-15].

Experimental Design: 30 Male Wistar rats were used in this study. The animals were divided into 5 groups of 6 animals each. The treatment was given for sixty days, orally. The normal control group of animals was given standard rat chow diet and water *ad libitum*. Except the normal group, experimental rats were fed with high fat diet for 60 days. Test substance and standard drug were administered to experimental rats from 31st to 60th day.

TABLE 2: EXPERIMENTAL DESIGN

Group (n=6)	Name of the Group	Treatment Schedule
A	Normal control	Standard rat chow diet for 60 days
B	Disease control	High fat diet for 60 days
C	Low dose	High fat diet for 60 days + Low dose (100mg/kg) of VD1from 31st to 60th day
D	High dose	High fat diet for 60 days + High dose (200mg/kg) of VD1from 31st to 60th day
E	Standard control	High fat diet for 60 days + Atorvastatin (1.2mg/kg) from 31st to 60th day

Biochemical Estimation: At the end of the experiment, the rats were fasted overnight. The rats were weighed and euthanized using light anaesthesia of Isoflurane. Blood samples were collected by cardiac puncture in non-heparinised tubes for serum separation. The clear serum was separated by centrifugation at 2500 rpm for 10 minutes and used for the determination of biochemical parameters such as total cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL and triglycerides.

Histopathological Evaluation: For histopathological analysis the liver and heart were fixed in 10% neutral buffered formalin. The specimen was cleared in xylene and embedded in paraffin, sectioned into 4-6 µm thickness using a rotary microtome. The sections were stained with hematoxylin and eosin and observed under light microscope [16].

Statistical Analysis: Data are presented as Mean ± SEM and the values of $P< 0.01$ were considered statistically significant. Statistical analysis between the control and experimental groups was analyzed using one-way ANOVA followed by Dunnett's multiple comparison tests using *Graph Pad Prism 8.0.2.*

RESULTS AND DISCUSSION: From the acute toxicity studies, it was found that the test compound was safe up to a maximum dose of 2000mg/kg thus, the one tenth and one twentieth doses 100 & 200mg/kg were selected for the further pharmacological evaluation.

Body Weight: A significant increase in body weight was observed in HFD feed rats compared to normal control. The increment in the body weight was reduced considerably (P<0.001) by the administration of Atorvastatin and test compound VD1. Treated group showed significant reduction in the body weight of animals. The results are illustrated in **Table 3.**

TABLE 3: BODY WEIGHT VARIATION IN CONTROL AND EXPERIMENTAL WISTAR RATS

Group	Initial Weight (g)	Final Weight (g)	Weight Gain (g)
A	132.91±1.74	174.06±2.38	35.26±4.39
B	136.84±2.53	254.14±8.58	117.44±6.05
C	150.66±1.26	220.90±7.51	70.33±5.87
D	153.58±2.32	195.78±3.10	42.26±3.34
E	177.83±2.29	218.47±3.78	40.76±3.37

All the values are expressed as Mean ± SEM (n=6). $^{###}$P < 0.001 compared to normal control group, ***P < 0.001 compared to disease control group.

Biochemical Estimation:

TABLE 4: EFFECT OF COMPOUND VD1 ON SERUM LIPID PROFILE

Group	Treatment	TC	TG	HDL	LDL	VLDL
A	Normal Control	111.83±1.137	84.66±1.382	58.66±1.282	37.83±1.740	19.66±1.333
B	Disease control	180.83±1.013	159.83±1.301	25.66±0.954	113.5±1.231	35.16±1.337
C	HFD + Test compound (100mg/kg)	145.51±1.335	115.16±1.424	39.66±1.115	66.33±1.145	29.16±1.301
D	HFD + Test compound (200mg/kg)	120.16±1.137	96.83±1.249	51.5±1.586	46.83±1.249	23.83±1.424
E	HFD + Atorvastatin (1.2mg/kg)	113.5±1.408	92.66±1.406	54.5±1.335	42.16±1.833	21.83±1.137

All the values are expressed as Mean ± SEM (n=6). $^{###}$P < 0.001 compared to normal control group, ***P < 0.001 compared to disease control group.

In HFD induced hyperlipidaemic model, the groups treated with the test compound VD1 and Standard drug Atorvastatin showed a significant reduction in the levels of serum TC, TG, LDL, VLDL particularly treatment with test compound VD1 at the dose of 200mg/kg showed considerable reduction in serum TC, TG, LDL, VLDL as that of Atorvastatin treated group. The levels of serum HDL were significantly decreased in disease Control group in comparison with normal control group. Administration of test compound VD1 at the dose of 100mg/kg and 200mg/kg showed considerable raised serum HDL in comparison with disease control. In comparison of the two doses of test group, the test compound at the dose of 200mg/kg was revealed considerable raise in HDL as that of Atorvastatin treated group.

Histopathological Studies:

Histopathology of Liver: The HFD induced hyperlipidemia and abnormal lipid metabolism all collectively associated with inflammation, congestion, minimal to mild periportal mononuclear cell infiltration. Histopathological studies showed that the liver section was normal in normal control group. The HFD treated group showed marked ballooning, cellular degeneration. These changes were absent in Atorvastatin treated standard group. Test compound VD1 (100mg/kg) treated group showed decrease in cellular degeneration and congestion when compared to normal group. Test compound VD1 (200mg/kg) treated group showed maximum suppression of cellular degeneration and inflammation.

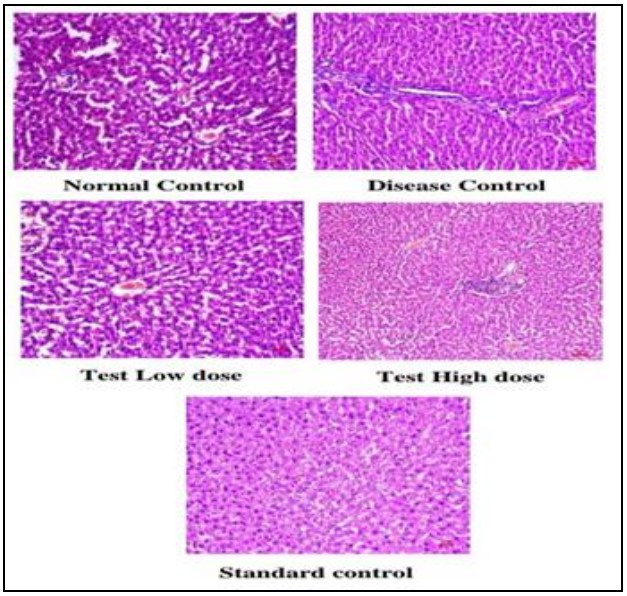


FIG. 2: HISTOPATHOLOGY OF RAT LIVER

Histopathology of Heart: Histopathological section of heart of normal control showed normal cardiac muscle fiber. Section of heart of HFD induced hyperlipidemic group showed excessive fatty infiltration of the myocardium. Heart section of standard group showed cardiac muscle with minimal infiltration. Cross-section of test group (200 mg/kg) showed cardiac muscle with minimal fatty infiltration compared to low dose group.

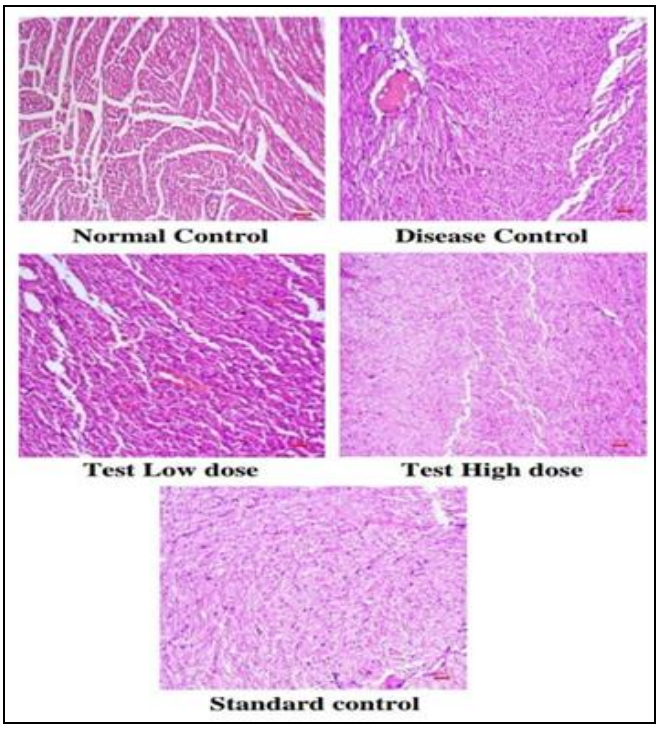


FIG. 3: HISTOPATHOLOGY OF RAT HEART

CONCLUSION: In the current study, a series of benzoxazole derivatives have been synthesized. The structure of the synthesized compounds has been confirmed by spectral analysis. The synthesized compounds on molecular docking studies exhibits significant binding energy levels -8 to -10kcal/mol. The compound (VD1) showing promising docking score was screened for *in-vivo* antihyperlipidemic activity. Treatment of compound VD1 at 100 and 200mg/kg significantly decrease the body weight, it significantly reduced the elevated serum parameters such as TC, TG, LDL, VLDL and augmented HDL level in a dose dependent manner.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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