Microwave assisted synthesis, docking studies and anti-hyperlipidemic activity of some novel heterocyclics-fibrate hybrids

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Abstract

A new series of compounds containing fibrates, thiazolidin-2,4-dione and its structural analog barbituric acid in a single molecular framework were synthesized (J- 1.1.1 to J-1.1.3 and J-3.1 to J-3.3) in a two-step process employing conventional and microwave aided techniques. Initially, aromatic aldehydes (2-hydroxy-1- naphthaldehyde, 4-hydroxy benzaldehyde and vanillin) reacted with thiazolidine-2,4- dione/ or barbituric acid to give 5-arylidine- thiazolidin-2,4-dione derivatives (J-1.1 toJ-1.3) and 6-arylidine-barbituric acid derivatives ((J-3.1to J-3.3), respectively. Finally, these intermediates (J-1.1 to J- 1.3) reacted with ethyl-a-bromoisobutyrate in the presence of K2CO3, to give the title compounds. Thin layer chromatography (TLC) was used to monitor the progress ofthe reaction, using methanol: chloroform (2:1) and ethyl acetate:n- hexane as solvents. For detection, the spot was exposed to UV light as well as iodine vapors. Various physicochemical methods like solubility studies, melting point, Rf value, and mass spectra was used to characterize intermediates however, physicochemical and spectral methods such as UV, IR, 1H-NMR and mass.

Keywords: thiazolidine, bromoisobutyrate, and naphthaldehyde.

INTRODUCTION

Hyperlipidemia is a medical condition where there are abnormally high levels of lipids, or fats, in the blood. This includes cholesterol and triglycerides. Hyperlipidemia can be inherited or caused by lifestyle factors like diet and physical activity. It's very common, especially in developed countries, and is increasing globally. The most common type of hyperlipidemia is high cholesterol. Other types include hypertriglyceridemia and mixed hyperlipidemia, where both cholesterol and triglyceride levels are high.

Hyperlipidemia is usually manageable with early diagnosis and treatment. People with untreated hyperlipidemia are twice as likely to develop coronary artery disease (CAD) than those with normal cholesterol levels. CAD can lead to clogged arteries and serious problems like heart attack or stroke.

Hyperlipidemia is an imbalance of cholesterol in your blood caused by a combination of having too much LDL cholesterol and not enough HDL cholesterol to clear it up.There are two main classifications of hyperlipidemia: familial and acquired. The familial type stems from genes you inherit from your parents. The acquired type is the result of, underlying health conditions, medications you take, lifestyle choices. Familial combined hyperlipidemia (or mixed hyperlipidemia) is a type that you can inherit from your parents or grandparents. It causes high cholesterol and high triglyceride levels. People with familial combined hyperlipidemia often develop high cholesterol or high triglyceride levels in their teens and receive a diagnosis in their 20s or 30s. This condition increases chances of early coronary artery disease and heart attack. Unlike people with typical hyperlipidemia, people with familial combined hyperlipidemia may experience symptoms of cardiovascular disease early in life, such as chest pain at a young age, heart attack at a young age, cramping in the calves while walking, sores on the toes that don't heal properly.

Hyperlipidemia usually does not show symptoms until it has advanced to the state where people have emergency complications, such as a heart attack or stroke. These can occur when high cholesterol has led to plaque buildup in your arteries that limits or blocks the flow of blood. A simple blood test will let you and your doctor know your blood cholesterol levels.

The 2018 guidelines Trusted Source published in the Journal of the American College of Cardiology (JACC) propose that a total blood cholesterol level above 240 milligrams per deciliter (mg/dL) is considered high, while levels above 200 mg/dl are considered elevated. This can vary based on many factors, however. The CDCTrusted Source recommends that generally, you should get a cholesterol test starting at the age of 20, then, every 5 years if you are at low risk for cardiovascular disease, more frequently than every 5 years if you have cardiovascular disease risk factors

Sometimes, tests are appropriate for children and adolescents. The CDC points out that 1 in 5Trusted Source adolescents have high cholesterol in the United States. Check with your doctor about a cholesterol test for your child if, your family has a history of early heart attacks or heart disease, your child has excess weight or obesity, your child has diabetes.

MATERIALAND MERHORD

All chemicals, reagents, and solvents were obtained from commercial suppliers
such as Spectrochem Pvt. Ltd. A new series of compounds containing fibrates, thiazolidin-2,4-dione and its structural analog barbituric acid in a single molecular framework were synthesized **(J-1.1.1**to **J-1.1.3** and **J-3.1** to **J-3.3)** in a two-step process employing conventional and microwave aided techniques. Initially, aromatic aldehydes (2-hydroxy-1-naphthaldehyde, 4-hydroxy benzaldehyde and vanillin) reacted with thiazolidine-2,4-dione/ or barbituric acid to give 5-arylidine-thiazolidin-2,4-dione derivatives **(J-1.1 to J-1.3)** and 6-arylidine-barbituric acid derivatives **((J-3.1 to J-3.3),** respectively.

Finally, these intermediates **(J-1.1 to J-1.3)** reacted with ethyl-α-bromoisobutyrate in the presence of K 2 CO 3 ,to give the title compounds.Thin layer chromatography (TLC) was used to monitor the progress of the reaction, using methanol: chloroform (2:1) and ethyl acetate: n-hexane as solvents. For detection, the spot was exposed to UV light as well as iodine vapors. Various physicochemical methods like solubility studies, melting point, Rf value, and mass spectra was used to characterize intermediates however, physicochemical and spectral methods such as UV, IR, 1H-NMR and mass spectrometry was used to characterize the final derivatives **(J-1.1.1 to J-1.1.3 and J-3.1**
to **J-3.3).**

SYNTHESIS

Synthesis of (Z)-5-(2-hydroxynapthalen-1-yl)methylene)thiazolidine-2,4-dione (J-1.1)

In a round bottom flask, 2-hydroxy-1-naphthaldehyde (4mmol) and thiazolidine-2,4-dione (4mmol) were combined with few drops of piperidine and CH 3 COOH at room temperature. The resultant mixture was microwaved for 30 minutes at 140-350 W power. After washing the reaction mixture with H 2 O (5ml), the crude product was refined by recrystallization from EtOH. TLC was used to monitor the reaction using the solvent system CHCl3 : MeOH: (9.8:0.2). Yang et al. [6]

Synthesis of(Z)-ethyl-2-((2,4-dioxothiazolidin-5-ylidene)methyl)napthalen-2-yl)oxy)-2methylpropanoate(J-1.1.1)

In a round bottom flask appropriately taken intermediate J-1.1 (0.108gm), ethyl-α-bromoisobutyrate (0.099gm, 0.075ml), potassium carbonate (0.118gm), and methylisobutyl ketone (2.5 ml) and irradiated for 35 min. in a microwave synthesizer at 450-560 W.The reaction mixture was cooled to room temperature, and the inorganic salts were removed. The solvent was then evaporated under reduced pressure, and the solid residue was recovered and recrystallized from ethanol to produce the title compound**J-1.1.1**. TLC was used to monitor the reaction, taking ethylacetate:n-hexane (7:3) as solvent. Singh et al. [4]

Synthesis of (E)-5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (J-1.2)

In a round bottom flask, 4-hydroxy-benzaldehyde (4mmol) and thiazolidine-2,4-dione (4mmol) were combined with few drops of piperidine and CH 3 COOH at roomtemperature. The resultant mixture was microwaved for 30 minutes at 140-350 W power. After washing the reaction mixture with H 2 O (5ml), the crude product was refined by recrystallization from EtOH. TLC was used to monitor the reaction using the solvent system CHCl 3 : MeOH: (9.8:0.2). Yang et al. [6]

Synthesis of ethyl-2-(-4-(2,4-dioxothiazolidin-5-yl)phenoxy)-2-methyl-propanoate(J-1.1.2)

In a round bottom flask appropriately taken intermediate J-1.2 (0.108gm), ethyl-α-bromoisobutyrate (0.099gm, 0.075ml), potassium carbonate (0.118gm), and methyl isobutyl ketone (2.5 ml) and irradiated for 35.3 min. in a microwave synthesizer at 450-560 W. The reaction mixture was cooled to room temperature, and the inorganic salts were removed.The solvent was then evaporated under reduced pressure, and the solid residue was recovered and recrystallized from ethanol to produce the title compound**J-1.1.2.** TLC was used to monitor the reaction, taking ethylacetate:n-hexane (7:3) as solvent. Singh et al. [4]

Synthesis of (E)-5-(4-hydroxy-3-methoxybenzylidene)thiazolidine-2,4-dione (J-1.3)

In a round bottom flask, 4-hydroxy-3-methoxybenzaldehyde (4mmol) and thiazolidine-2,4-dione (4mmol) were combined with few drops of piperidine and CH 3 COOH at room temperature. The resultant mixture was microwaved for 30 minutes at 140-350 W power. After washing the reaction mixture with H 2 O (5ml), the crude product was refined by recrystallization from EtOH. TLC was used to monitor the reaction using the solvent system CHCl 3 : MeOH: (9.8:0.2). Yang et al. [6]

Synthesis of (E)-ethyl 2-(4-((2,4-dioxothiazolidin-5-ylidene)-2-methoxyphenoxy)2-methylpropanoate(J-1.1.3)

In a round bottom flask appropriately taken intermediate J-1.3 (0.108gm), ethyl-α-bromoisobutyrate (0.099gm, 0.075ml), potassium carbonate (0.118gm), and methyl isobutyl ketone (2.5 ml) and irradiated for 35 min. in a microwave synthesizer at 450-560 W. The reaction mixture was cooled to room temperature, and the inorganic salts were removed.The solvent was then evaporated under reduced pressure, and the solid residue was recovered and recrystallized from ethanol to produce the title compound**J-1.1.3.** TLC was used to monitor the reaction, taking ethylacetate:n-hexane (7:3) as solvent. Singh et al. [4]

Synthesis of 5-((2-hydroxynaphthalen-1-yl)methylene)pyrimidine-2,4,6-(1H,3H,5H)-trione(J-3.1)

In a round bottom flask, 2-hydroxy-1-naphthaldehyde(4mmol) and barbituric acid (4mmol) were combined with few drops of piperidine and CH 3 COOH at room temperature. The resultant mixture was microwaved for 30 minutes at 140-350 W power. After washing the reaction mixture with H 2 O (5ml), the crude product was refined by recrystallization from EtOH. TLC was used to monitor the reaction using the solvent system CHCl 3 : MeOH: (9.8:0.2). Yang et al. [6]

Molecular docking

Docking studies were performed to better appreciate the binding affinity and binding mode of the synthesized derivatives (J-1.1.1 to J-1.1.3 and J-3.1 to J-3.3) to the biologicaltarget. In the present study, PPARα-receptor (PDB-ID: 2P54) was identified as molecular target for the prepared derivatives to embrace anti-hyperlipidemic activity. The crystallographic structure of the protein was downloaded from PDB database. Every step of the docking procedure, which included protein selection, protein preparation, ligand preparation and docking, was executed in the Maestro interface of the Schrodinger software. The PDB protein crystal structure was prepared using “Protein Preparation Wizard”. The arranged proteins with co-crystal ligands were split into proteins, ligand, and others, Simultaneously, the ligands were prepared using “LigPrep” wizardThe protein crystal structure's corresponding binding sites were docked with ligands. Slip and slide docking procedure “extra precision (XP) mode” was applied for this purpose, keeping the remaining parameters at the defaults setting. The associated energy minima for the 3D conformers of the ligands were provided by the OPLS- 2005 energypasture, which was utilized to simulate. The capacity of the approach to precisely predict the binding conformation was demonstrated by GLIDE’s flawless replication of the ligand’s experimental position. Furthermore, Glide score along with binding complementarity of the protein-ligand complexes were considered as the main criteria to select the most active derivatives among the synthesized series.Sundriyal et al.,Singh et al.[39],[4]

In silico prediction of pharmacokinetic properties

Initially, Corwin Hansch and other researchers worked on this in the 1960s and continued in the 1970s Their models utilized small sets of in-vivo ADME data. Computational approaches involving prediction of various physicochemical and pharmacokinetics properties of potential drug candidates are used in the drug development process to save time, effort,and money. The term “drug-likeness” denoted the consistency of the relationship between the structural characteristics and various molecular properties that determine drug discovery and improvement. The pharmacokinetics profile of the synthesized compounds, i.e., absorption distribution metabolism and excretion (ADME) were predicted with the help of QikProp module of Schrodinger and online servers such as Swiss-ADME and pkCSM.

There are many computer programs available that can predict the potentialtoxicity of a compound using in-silico methods. These include QikProp, LAZAR, and pkCSM tools. LAZAR and pkCSM tools predict complex toxicological endpoint, such as reproductive toxicity, carcinogenicity, long-term toxicity and AMES toxicity. The open-source pkCSM-pharmacokinetics online tool uses experimental data and graph-based signature to predict and optimize the ADME/Tox characteristics of small molecules.Singh etal.[4]

Biological Activity

Male Wistar rats weighing between 150 and 200 g were obtained from the Hygia Institute of Pharmaceutical Education and Research's Lucknow facility in Lucknow, Uttar Pradesh, India, and used in the experiment after Institutional Animal Ethical Committee approval (IAEC No:HIPER/IAEC/110/03/2023).In a typical biological condition (22±6°C, 40% humidity, and 12-hour light/dark cycle), all animals were maintain in separate polypropylene cages with unlimited access to running water. They were fed commercial pellet meals and unlimited amounts of water after being divided into groups. The standards of the Committee for Control and Supervision of studies with Animals (CCSEA) were followed during the experiments.The Institutional Animal Ethical Committee (IAEC) authorized all research.

RESULTS

The recent study was aimed at synthesis, characterization and evaluation of anti-hyperlipidemic properties of six new derivatives (J-1,1,1 to J-3,3) The synthesis of derivatives **(J-1,1,1 to J-3,3)** was achieved through a two-step process using standard technique (microwave assisted synthesis) First of all, (J-1,1,1 to J-3,3) wassynthesized using reported procedure. Then it was reaction of (J-1.1) with aldehyde and thiazolidine -4-one nucleus in the presence of potassium carbonate and ethyl alpha bromoisobutyrate and methyl isobutyl ketone finally, the (J-1,1,1 to J-3,3) were obtained by (J-1.1) with relevant aldehyde in glacial aceticacid.Analysis of results concluded that compounds J-1,1,3 and J-3,3are themost effective derivatives in the synthesized series when compared to the others in terms of docking (Glidegscore) results at the binding site of PPAR-alpha/gama (2P54) target Proteins. 2D and 3D Ligand- receptor interaction diagrams of compounds J-1,1,3 and J-3,3 are presented in Fig3.1 Showing complementary and binding interactions with the target protein associated with the antihyperlipidemic activity.

Table 3.1. Docking Results of Synthesized Derivatives (J-1,1,3 to J-3,3) using Glide Tool

Compounds			
	Docking score	Glide gscore	Glide emodel
J-1,1,1	-5.768	-7.205	-37.282
J-1,1,2	-5.592	-5.907	-59.978
J-1,1,3	-6.104	-7.46	-63.731
J-3,1	-4.554	-6.746	-39.274
J-3,2	-4.427	-5.449	-36.475
J-3,3	-2.198	-3.221	-46.697

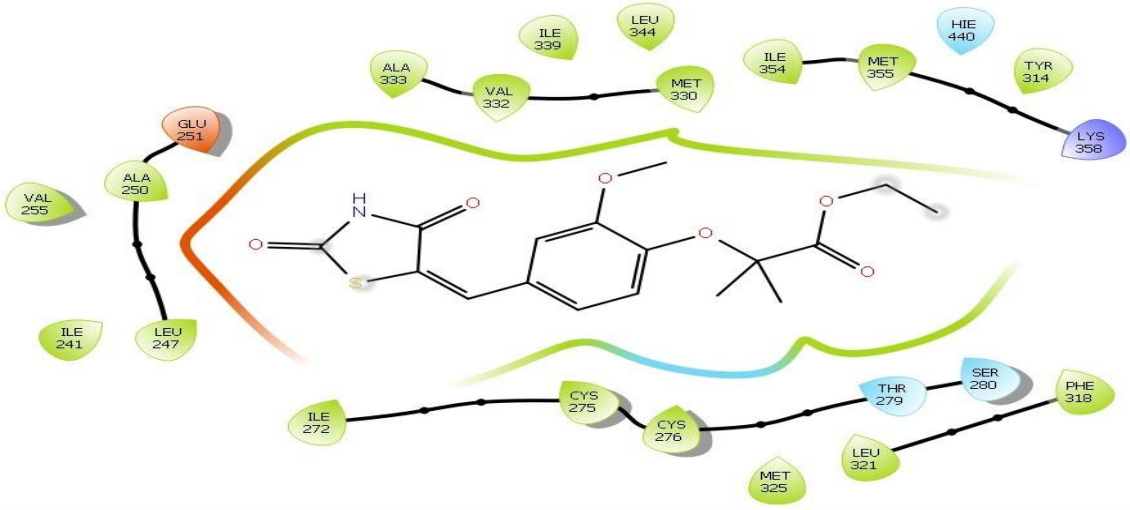

Fig. 3.1.2D Ligand-receptor interaction diagram of a compound **J-1.1.3 a t** the protein (2P54) binding site.

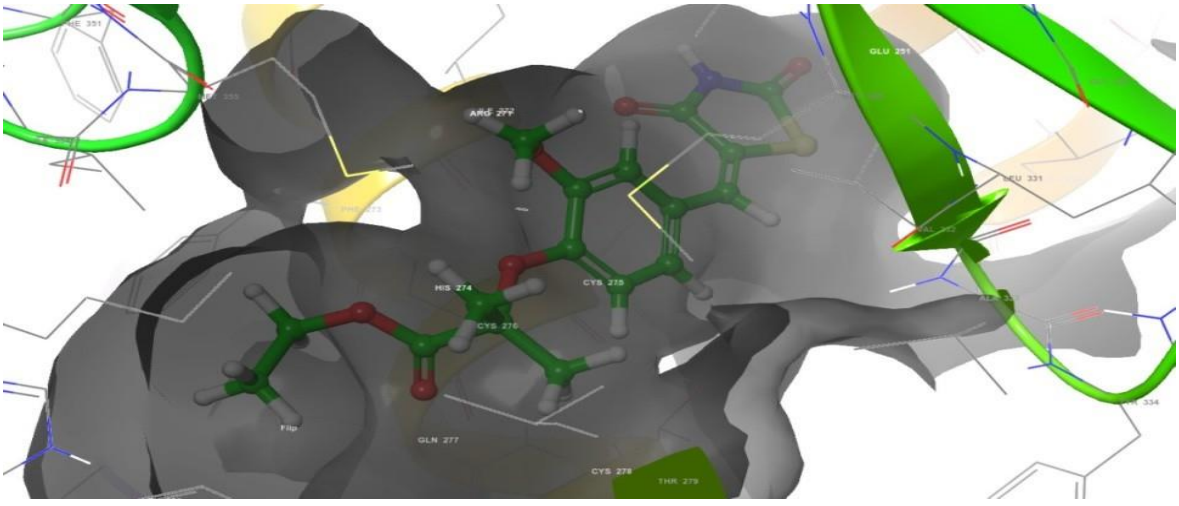

Fig. 3.2. 3D Orientation of compound **J-1.1.3** at the protein (2P54) binding site.

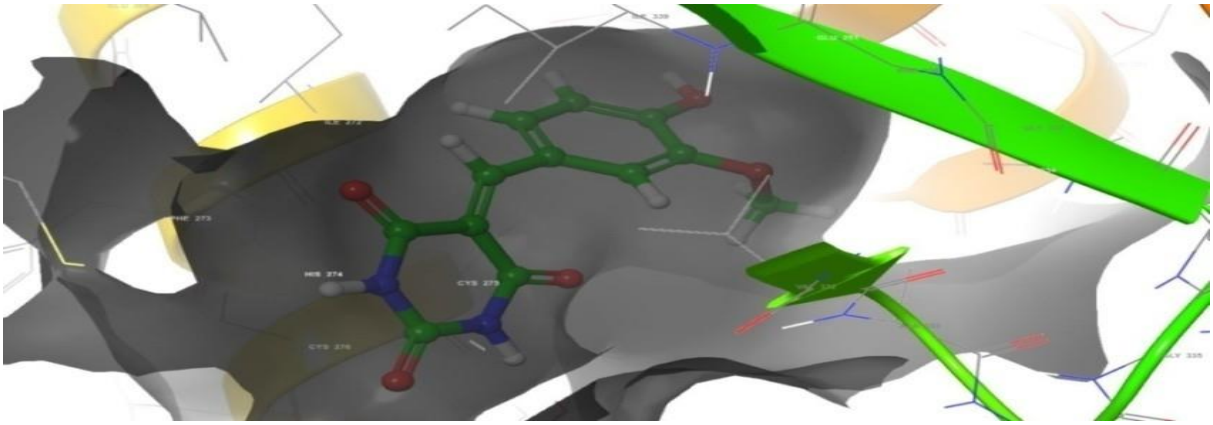

Fig. 3.4. 3D Orientation of compound **J-3.3** at the protein (2P54) binding site.

In-silico prediction of pharmacokinetic properties of the synthesized compounds **(J-1.1.1** to **J-3.3)** was done with the help of the Swiss-ADME and pkCSM online servers and results were summarized in **Table 3.2.** Also, LAZAR and pkCSM tools accurately predicted complex toxicologic endpoints, such as reproductive toxicity, carcinogenicity, continuing toxicity, AMES toxicity, and hepatotoxicity.

Table 3.2. ADMET Prediction of Synthesized Derivatives **(J-1.1.1** to **J-3.3)** using QikProp Tools

Descriptors	**Reference Value**	**Predicted Value of Derivatives**					
		J-1,1,1	**J-1,1,2**	**J-1,1,3**	**J-3,1**	**J-3,1**	**J-3,3**
# Stars	0-5	0	0	0	0	0	0
#rtvFG	0 – 2	0	0	0	0	0	0
CNS	–2 to +2	-2	-1	-2	-2	-2	-2
mol_MW	130.0 – 725.0	385.434	323.363	365.400	282.255	232.195	262.221
Dipole	1.0 – 12.5	0	0	0	0	0	0
SASA	300.0 – 1000.0	587.198	555.211	629.293	455.789	398.558	431.639
FOSA	0.0 – 750.0	237.219	273.314	369.158	15.158	14.042	101.043
FISA	7.0 – 330.0	150.462	144.915	146.341	208.811	226.481	218.154
Volume	500.0 – 2000	1127.180	994.893	1114.653	793.129	666.624	741.424
DonorHB	0.0 – 6.0	1	1	1	3	3	3
AccptHB	2.0 – 20.0	5.750	5.750	6.500	4.750	4.750	5.500
QPlogPo/w	–2.0 – 6.5	3.175	2.679	2.805	0.884	0.134	0.610
QPlogS	–6.5 – 0.5	-3.934	-3.966	-4.436	-2.478	-1.695	-2.273
QPlogHERG	Concern below –5	-4.231	-4.119	-4.662	-4.108	-3484	-3.398
QPPCaco	<25 poor, >500 great	370.739	418.478	405.645	103.693	70.498	84.557
QPlogBB	–3.0 – 1.2	-1.059	-0.856	-1.393	-1.302	-1.404	-1.404
QPPMDCK	<25 poor, >500 great	169.264	328.026	338.399	42.706	596.192	34.255

Glob		0.8920225	0.8680756	0.8261748	0.9091396	0.9259648	0.9178160
#NandO		6	6	7	6	6	7
	Maximum is 4	0	0	0	0	0	0

RuleofFive							
QPlogPC16		11.506	9.733	10.620	9.605	8.093	8.389
#rotor		6	4	7	3	34	
#ringatoms		15	11	11	16	12	12
SA amideO		0.000	0.000	0.000	0.000	0.000	0.000
#nonHatm		27	22	25	21	17	19
EA (ev)		0.000	0.000	0.000	0.000	0.000	0.000
#amine		0	0	0	0	0	0
Percent Human Oral Absorption	80% is high, 25% is poor	91.519	89.554	90.051	68.197	60.809	65.008
#amidine		0	0	0	0	0	0
QPlogKhsa	-1.5-1.5	0.337	0.063	0.081	-0.249	-0.504	-0.468
QPlogPw		9.318	8.947	9.021	12.224	11.705	11.935
Dip^2/V		0.0000000	0.0000000	0.0000000	0.0000000	0.0000000	0.0000000
RuleofThree	Maximum is 3	0	0	0	0	0	0
#in34		0	0	0	0	0	0
#in56		15	11	11	16	12	12
Jm		0.043	0.014	0.007	0.051	0.073	0.062
#noncon		0	1	0	0	0	0
PSA	7.0-200.0	107.914	108.673	114.735	129.656	131.645	138.82
ACxDN .5/SA		0.0097923	0.0103564	0.0103291	0.0180506	0.0206425	0.0220070
QPpolrz		37.009	32.000	34.595	25.875	20.107	22.023
SAflurine		0.000	0.000	0.000	0.000	0.000	0.000
#metab		1	2	2	1	1	2
RuleofFive							
QPlogPC16		11.506	9.733	10.620	9.605	8.093	8.389
#rotor		6	4	7	3	34	
#ringatoms		15	11	11	16	12	12
SA amideO		0.000	0.000	0.000	0.000	0.000	0.000
#nonHatm		27	22	25	21	17	19

The Antihyperlipidemic activity of six newely synthesized substituted thiazolidin-4-on derivatives **(J-1.1.1** to **J-3.3)** was evaluated by Triton induce in Albino wistar rats. Finofibrate was used as a standard drug. The details results were expressed in the form of mean±SEM and summarized in **Table 3.3** and **Fig**. **3.5-3.8** ANOVA Followed by tukey test was used for statistical significance.

Effect of 4-thiazolidinone derivatives on total cholesterol

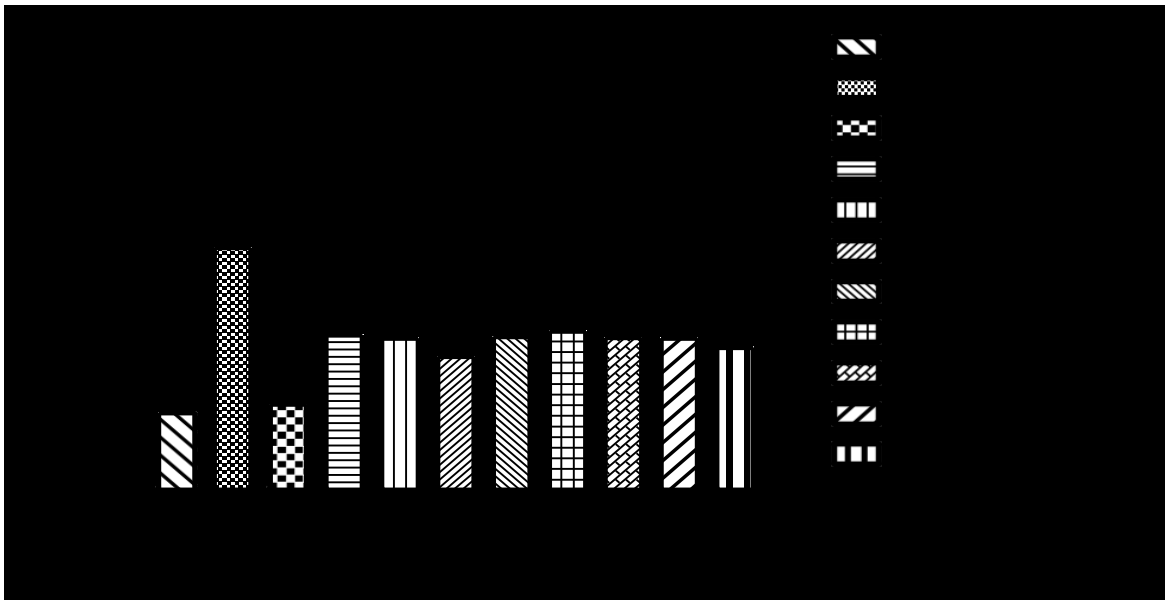

Fig. 3.5 Anti-hyperlipidemic effect of the synthesized derivatives **(J-1.1.1** to **J-1.1.3**and **J-3.1** to **J-3.3).** on the total cholesterol on triton induce model.

Effect of 4-thiazolidinone derivatives on triglycerides

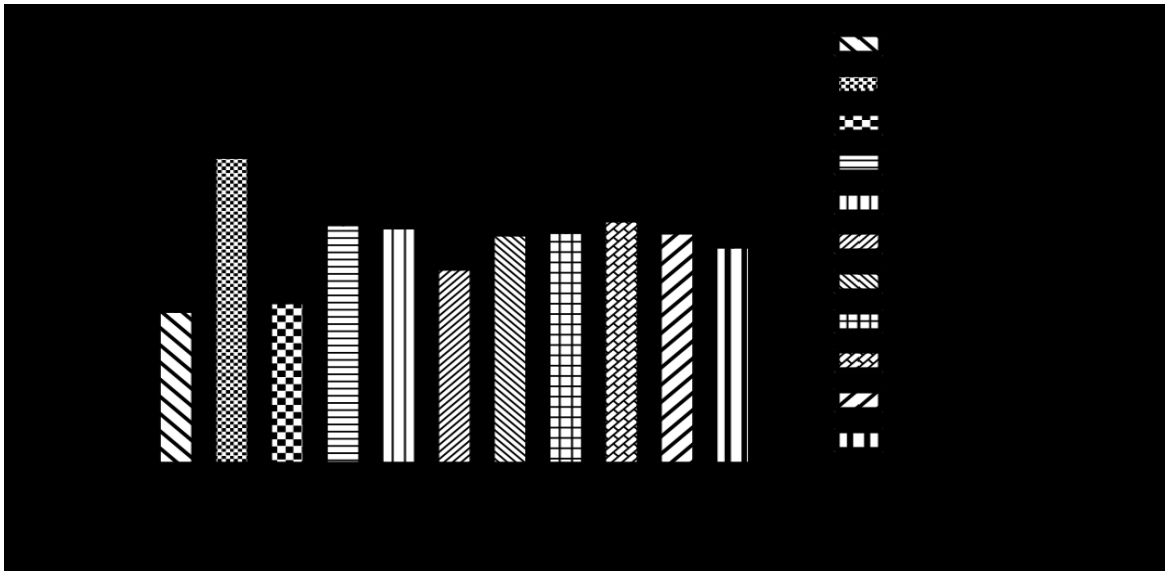

Fig. 3.6 Anti-hyperlipidemic effect of the synthesized derivatives **(J-1.1.1** to **J-1.1.3** and **J-3.1** to **J-3.3).** on the triglycerides on triton induce model

Effect of 4-thiazolidinone derivatives on HDL

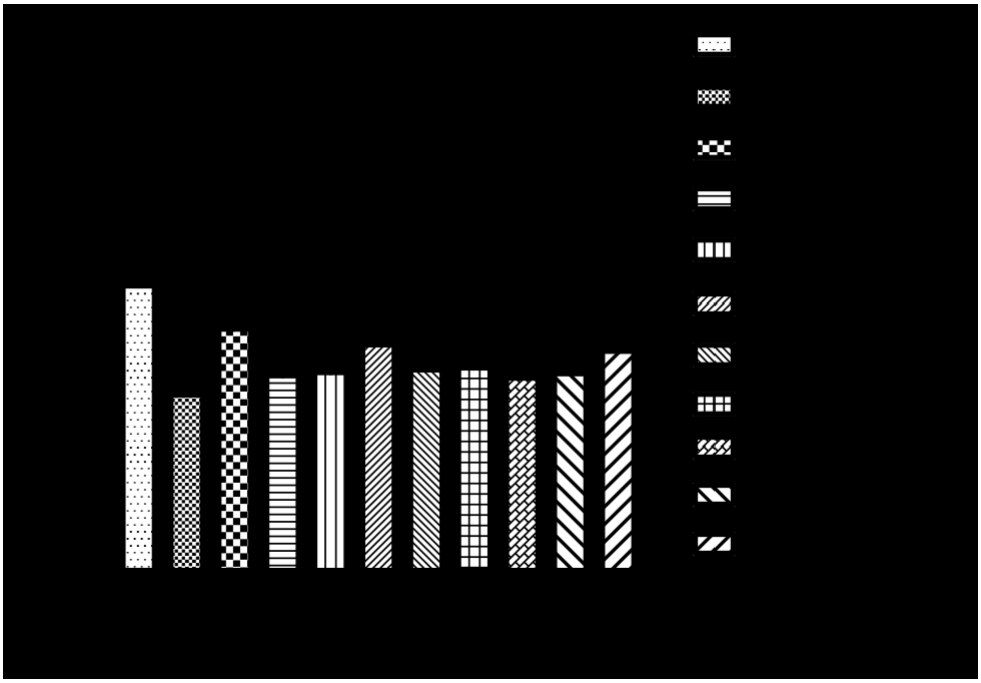

Fig.3.7 Anti-hyperlipidemic effect of the synthesized derivatives **(J-1.1.1** to **J-1.1.3** and **J-3.1** to **J-3.3).** on the HDL on triton induce model

Effect of 4-thiazolidinone derivatives on LDL

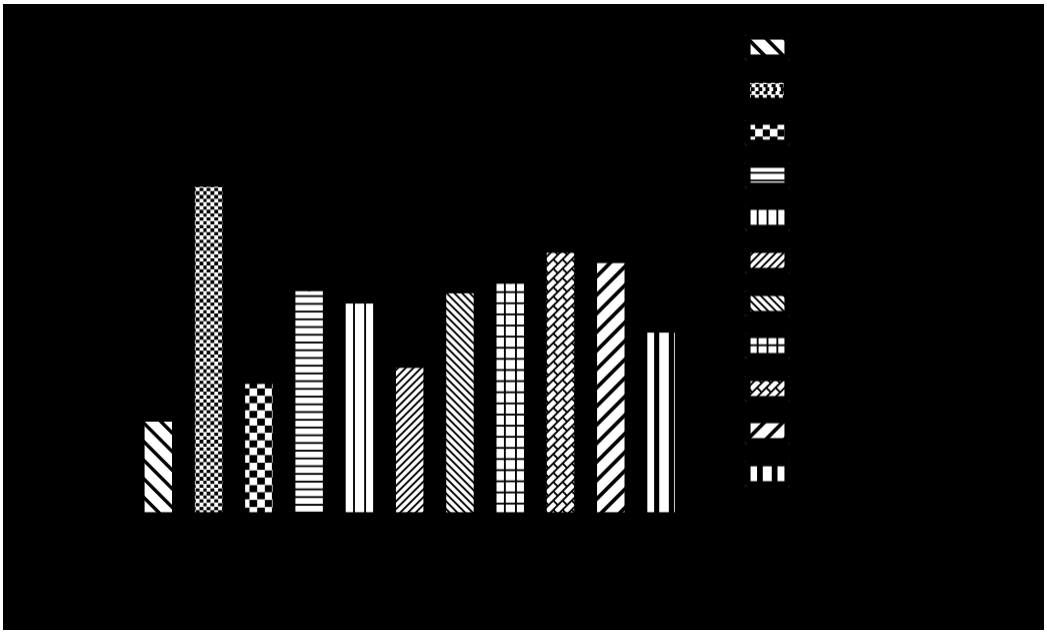

Fig. 3.8 Anti-hyperlipidemic effect of the synthesized derivatives **(J-1.1.1** to **J-1.1.3** and **J-3.1** to **J-3.3).** on the LDL on triton induce mode

S.No	**Group**	**Treatment**	**TC**(mg/dl)	**TG**(mg/dl)	**HDL**(mg/dl)	**LDL**(mg/dl
1	Normal Control	CMC 0.5% Soln. (1ml/kg p.o)	86.60±1.44	89.16±4.76	24.32±0.44	38.52±3.56
2	Disease Control	Triton (300mg/kg i.p)	272.80±17.11	178.60±10.19	14.96±0.40	133.50±6.34
3	Standard Drug	Fenofibrate (65mg/kg p.o)	96.20±7.19	94.00±5.76	20.60±0.49	53.80±3.85
4	T1	Triton + J-1,1,1 (30mg/kg)	174.60±11.50	139.40±6.96	16.60±0.67	91.28±6.81
5	T2	Triton +J-1,1,2 (30mg/kg)	170.80±10.04	137.60±5.73	16.90±0.19	86.32±8.91
6	**T3**	**Triton + J-1,1,3**(30mg/kg)	**150.00±14.53**	**113.60±4.84**	**19.26±0.57**	**60.28±3.88**
7	T4	Triton + J-1,1,3 (30mg/kg)	172.60±10.36	133.40±7.41	17.10±0.60	90.44±6.96
8	T5	Triton + J-3,1 (30mg/kg)	178.88±10.38	134.92±6.67	17.30±0.41	94.36±6.28
9	T6	Triton + J-3,2 (30mg/kg)	171.48±9.39	141.54±8.40	16.42±0.15	106.84±7.39
10	T7	Triton + J-3,3 (30mg/kg)	170.86±10.96	134.56±6.34	16.80±0.41	102.72±6.46
11	**T8**	**Triton + J-3,3**(30mg/kg)	**160.00±11.31**	**126.40±6.94**	**18.70±1.03**	**74.56±4.78**

Table: 3.3.*In vivo* Anti- hyperlipidemic activity of Synthesized Compounds **(J-1.1.1 to J-3.3)** against Triton induce Model

Conclusion

In the current investigation, a versatile synthetic approach was used to prepare **(J-1.1.1** to **J-3.3)** in two step reaction. The synthesis of proposed derivatives was ascertained by various physiochemical and spectral methods. Furthermore, the anti-hyperlipidemic efficacy of novel thiazolidine-4-one derivatives was assessed. In- vivo anti-hyperlipidemic screening studies identified good to moderate activity of tested compounds against Triton induce which was comparable to the standard drug, Finofibrate, A close analysis of results obtained from in vivo studies was complemented by docking studies (Glide gscore) of the prepared derivatives at the binding site of PPAR- alpha/gama (2P54) Ligand-receptor interaction studies showed excellent complementarity and binding energies of the prepared compounds with the target receptors.

The in-silico, in-vivo screening results of synthesized compounds against different biological targets for anti-hyperlipidemic activity allowed us to identify two most potent derivatives **(J-1.1.3)** and **(J-3.3)** among the synthesized series.

Both of the above compound were found to passes hyperlipidemia inhibition ofter 72 hr triton induce model for anti- hyperlipidemic activity. The result of computational studies were also found to be consistent with the results from wet lab experiments, demonstrating remarkable receptor fit and binding energies (Glide gscore) of **-7.46** and **-3.221** against 2P54 Target for anti-hyperlipidemic effect. Additionally, it was discovered that the majority of the synthesized compounds, notably above two, had impressive BBB penetration, human oral absorption and oral bioavailability characteristics, as well as optimal to exceptional in silico ADME capabilities without violating Lipinski's rule of five. Additionally, it was discovered that these compounds posed no toxicological issues at all. As a result, it can be said that the majority of projected ADMET attributes were within the range that was acceptable for drug candidacy, minimizing the danger of failure for such compounds in later stages of drug discovery and development. This work also enable a hyperlipidemia directions and provide imminent into the design and mechanistic study of some novel entities with promising potential in hyperlipidemia as future endeavours.

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