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DESIGN, SYNTHESIS, CHARACTERIZATION OF PRIMIDINE DERIVATIVE AS IN MANAGING HYPERLIPIDEMIA AND ASSOCIATED RISK

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ABSTRACT
Hyperlipidemia is a prevalent medical condition characterized by elevated levels of lipids, including cholesterol and triglycerides, in the bloodstream. This condition poses a significant risk factor for cardiovascular diseases due to the accumulation of fatty deposits in arteries. Genetic, lifestyle, and dietary factors contribute to its development. Diagnosis involves measuring lipid levels, and management typically includes lifestyle changes and medications. Pyrimidine derivatives, on the other hand, are essential organic compounds with a six-membered heterocyclic ring structure containing carbon and nitrogen atoms. These derivatives play a vital role in genetics and biochemistry. In DNA and RNA, pyrimidine bases such as cytosine, thymine, and uracil form complementary base pairs with purines, facilitating the storage and transmission of genetic information. They are also involved in metabolic pathways, including de novo pyrimidine biosynthesis and salvage pathways. The importance of pyrimidine derivatives extends beyond genetics. Their structural versatility has led to their use as fundamental scaffolds in pharmaceutical compounds. Several drugs, such as anticancer agents and antiviral medications, are derived from the pyrimidine core structure, demonstrating its significance in medicine and drug development. It highlights the interplay between hyperlipidemia, a condition affecting cardiovascular health, and pyrimidine derivatives, crucial components of genetics and biochemistry. Understanding both aspects contributes to advancing medical knowledge and therapeutic strategies, addressing critical health concerns and enabling pharmaceutical innovation.

KEYWORDS: Pyrimidine, Docking Study, Modeling and Synthesis Method.

INTRODUCTION
Pyrimidine derivatives constitute a diverse and important class of compounds with widespread applications in various fields, including chemistry, biochemistry, and pharmacology. The pyrimidine ring, a six-membered aromatic ring containing two nitrogen atoms at positions 1 and 3, is the core structure from which these derivatives are derived. The introduction of pyrimidine derivatives encompasses a broad range of compounds, each with unique properties and functions.

1. Structure of Pyrimidine
The pyrimidine ring is a heterocyclic structure composed of four carbon atoms and two nitrogen atoms.
It serves as the foundation for the synthesis of a multitude of derivatives with distinct substituents and functionalities.

2. Biological Significance
Pyrimidines are essential components of nucleic acids—DNA and RNA—playing a crucial role in the genetic code.
They are involved in various biological processes, including the synthesis of nucleotides, coenzymes, and energy carriers.

3. Pharmacological Relevance
Pyrimidine derivatives are extensively explored in medicinal chemistry for drug development.
Many pharmaceutical agents, including anticancer drugs and antiviral medications, are derived from or contain pyrimidine structures.

4. Types of Pyrimidine Derivatives
Nucleotide Analogs: Pyrimidine derivatives are often used as analogs in the development of nucleotide-based drugs and antiviral agents.

Anticancer Agents: Certain pyrimidine derivatives exhibit anticancer properties, interfering with DNA replication and cell division.

Antibiotics: Some antibiotics contain pyrimidine moieties in their structures, contributing to their antibacterial effects.

5. Synthetic Chemistry
Chemists utilize various synthetic methodologies to introduce functional groups and modifications to the pyrimidine ring.

These modifications can alter the physicochemical properties and biological activities of pyrimidine derivatives.

6. Industrial Applications
Pyrimidine derivatives find applications in diverse industrial sectors, including agriculture, where they are used in the synthesis of pesticides.

They are also employed in the production of dyes, polymers, and other specialty chemicals.

7. Future Prospects
Ongoing research continues to uncover new pyrimidine derivatives with novel properties and applications.

The versatility of pyrimidine structures provides a fertile ground for innovation in drug discovery and material science.

Pyrimidine derivatives play a significant role in the field of pharmacology, particularly in the context of hyperlipidemia. Hyperlipidemia refers to elevated levels of lipids (fats) in the blood, which can contribute to the development of cardiovascular diseases. Pyrimidine derivatives are a class of compounds that have been explored for their potential therapeutic effects in managing hyperlipidemia. One notable pyrimidine derivative is clofibrate.

Clofibrate is a synthetic derivative of pyrimidine that belongs to the class of fibrates, a group of medications known for their lipid-lowering properties. Here is an introduction to clofibrate and its relevance to hyperlipidemia:

1. Structure and Classification
Clofibrate has a pyrimidine ring in its structure, making it a pyrimidine derivative.
It is classified as a fibric acid derivative and falls under the broader category of fibrates.

2. Mechanism of Action
Clofibrate exerts its effects by activating peroxisome proliferator-activated receptor alpha (PPAR-α). PPAR-α regulates gene expression involved in lipid metabolism.

Activation of PPAR-α leads to increased lipolysis and elimination of triglyceride-rich particles from the plasma.

3. Lipid-Lowering Effects
One of the primary therapeutic effects of clofibrate is its ability to lower plasma triglyceride levels.
It also has a modest impact on increasing high-density lipoprotein cholesterol (HDL-C) levels.

4. Clinical Applications
Clofibrate has been historically used in the management of hyperlipidemia, especially in patients with elevated triglyceride levels.
It may be prescribed as part of a comprehensive approach to reducing cardiovascular risk.

5. Considerations and Side Effects
While clofibrate has lipid-lowering benefits, its use may be associated with certain side effects, including gastrointestinal disturbances.
It is essential for healthcare providers to assess individual patient factors and consider potential drug interactions.

6. Evolving Landscape
The field of hyperlipidemia management continues to evolve, and newer medications are being developed. However, clofibrate remains a notable historical example of a pyrimidine derivative with lipid-lowering properties.

MATERIALS AND METHODS

Molecular docking study

Molecular docking approaches can be used to discover the interaction between a tiny ligand and a target molecule, as well as to see if they could operate as a binding site for two or more constituent molecules with a specific structure Molecular docking is a computational approach that aims to predict the noncovalent interaction of macromolecules or, more commonly, a macromolecule (receptor) and a small molecule (ligand) with a high degree of accuracy[2] When it comes to structure-based drug design, molecular docking has been the most used strategy since the early 1980s. To undertake molecular docking investigations, programmes based on various algorithms have been created, making docking an increasingly significant tool in pharmaceutical research docking of molecules for ligand discovery, chemical database screens are commonly utilised Docking can help with a variety of issues, including protein function prediction and drug lead identification and optimization. The three types of scoring functions are commonly force field, knowledge-based, and empirical the lock-and-key postulation provided by Fischer, which states that both the ligand and the receptor can be considered as rigid entities, was the foundation for the first docking approaches the drug discovery project allows for a SWOT (strengths-weaknesses-opportunity- threat) analysis to determine the program's viability. One of the cornerstones of CADD is molecular docking. It investigates the

interaction of a target protein with tiny compounds to predict how a protein interacts with tiny vitamin-like compounds, molecular docking techniques are applied. This ability controls a large portion of the protein's dynamics, which can help or hurt its biological function An explosion in currently available software tools, as well as an increasing number of chemical and biological databases, are giving a far better foundation for designing ligands and inhibitors with the desired selectivity in drug discovery[10] Molecular docking is a method for analysing the conformation and orientation (together referred to as "position") of molecules in a macromolecular target's binding site. Poses are generated using search algorithms, which are then ranked using scoring methods

Modern medicinal chemistry methodologies, like as molecular modelling, have become increasingly popular in the research-based pharmaceutical business as potent tools for studying structure-activity connections (SAR) Pharmacokinetic parameters, in addition to pharmacodynamic data (e.g., potency, affinity, effectiveness, selectivity), are also important (ADMET: absorption, distribution, metabolism, excretion, and toxicity) have also been studied through the application of these methodologies.

Structure based virtual screening was conducted using a graphical user interface SP- docking mode of program Maestro 9. The protein structure of PPARα was obtained from the RCSB Protein Data Bank (PDB). The protein was optimized for docking from its raw state employing protein preparation wizard with OPLS 2005 force field for minimization Receptor gird generation was accomplished using Glide. Further, we analyzed the compounds for Lipinski's rule of five to evaluate drug likeness using QikProp. The molecular docking tool, GLIDE was used for ligand docking studies into the Acid Pump PPARα pocket. The crystal structure of Acid Pump was obtained from the protein data bank, PDB ID: 1i7g. The protein preparation was carried out using 'protein preparation wizard' in Maestro 8.0 in two steps, preparation and refinement. Grids were generated centering on**co-** crystalized ligand**.** The ligands were developed using maestro build panel and prepared by Ligprep 2.2 module that produces the low energy conformer of ligands using OPLS 2005 force field.

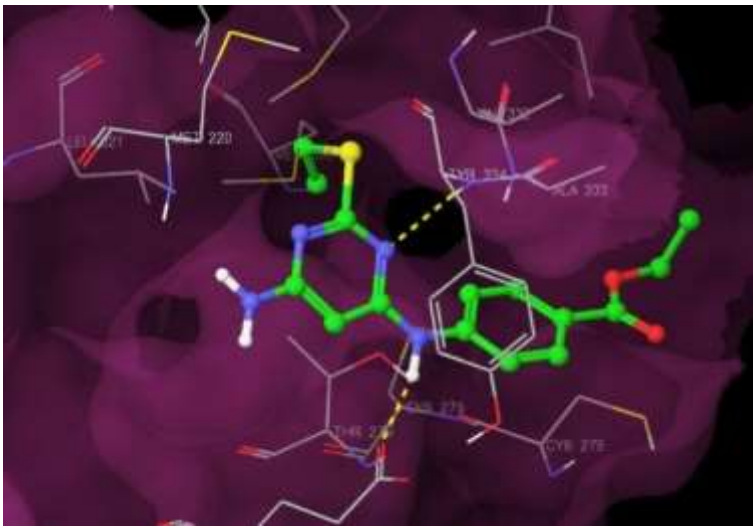


Figure No. 01 Docking of Pyremidine derivative.

STEP-1

Ethyl 4-(4-(trifluoromethyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate

A solution of ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (**1g**, 4.29 mmol), in THF (10 ml), DIPEA (0.55ml,4.29 mmol) and 4-(trifluoromethyl)aniline (0.75ml,4.29 mmol) was added and stirred at 70^0 C for 16 h. TLC shows the completion of starting material. The reaction mixture was quenched with water, extracted with ethyl acetate, dried over sodium sulfate concentrated under reduced pressure. The obtained crude was purified by silica gelchromatography to get Ethyl 4-(4- trifluoromethyl) phenylamino)-2-(methylthio)pyrimidine-5- carboxylate as off white solid. MP-122-24^{o}c, Yield (53%). TLC was monitored by ethanol: benzene (2:1).

Ethyl 2-(methylthio)4-(p-tolylamino)pyrimidine-5-carboxylate

A solution of ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (**1g**, 4.29 mmol), in THF (10 ml), DIPEA (0.55ml,4.29 mmol) and 4-methyl aniline (0.45gm,4.29 mmol) was added and stirred at 70^0C for 16 h. TLC shows the completion of starting material. The reactionmixture was quenched with water, extracted with ethyl acetate, dried over sodium sulfate concentrated under reduced pressure. The obtained crude was purified by silica gel chromatography to get Ethyl 2-(methylthio)4-(p-tolylamino)pyrimidine-5-carboxylate as off white solid. MP-134-36^{o}c,Yield (68%). TLC was monitored by ethanol: benzene (2:1).

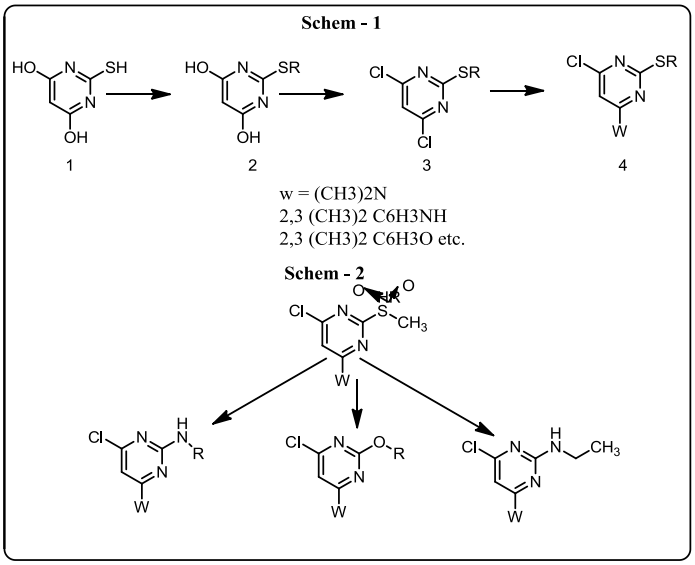
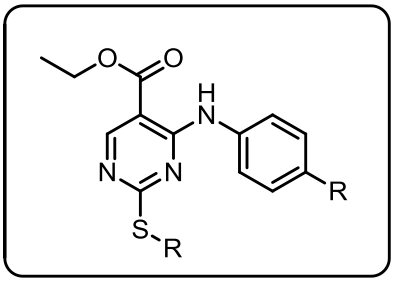


Figure No. 2: Method for the synthesis of PYRIMEDINE derivatives.

Table 1: Novel Pyrimidinde different derivatives.



Sr.No.	Compound Code	Compound Name
1.	PCC 1	Ethyl 4-(4- (trifluoromethyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate
2.	PCC 2	Ethyl 2-(methylthio)4-(p- tolylamino)pyrimidine-5-carboxylate
3.	PCC 3	Ethyl 4-((3,5dimethylphenyl)amino)-2-(methylthio)pyrimidine-5-carboxylate
4.	PCC 4	Ethyl 4-((4-methoxyphenyl)amino)-2-(methylthio)pyrimidine-5-carboxylate
5.	PCC 5	4-(4-(Trifluoromethyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylic acid
6.	PCC 6	2-(methylthio)-4-(p- tolylamino)pyrimidine-5-carboxylic acid
7.	PCC 7	4-((3, 5 dimethylphenyl)amino-2- (methylthio)pyrimidine-5-carboxylic acid
8.	PCC 8	4-((4-methoxyphenyl)amino-2- (methylthio)pyrimidine-5-carboxylic acid
9.	PCC 9	Ethyl 4-(3- (ethoxycarbonyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate

Analysis of the synthesised derivatives

To characterize Pyrimidine derivatives for structure elucidation using CHNS/O elemental analysis and spectroscopic techniques such as IR & ^{1}HNMR, and Mass spectral studies. CHNS/O Elemental Analysis recorded from Sophisticated Analytical Instrument Facility (SAIF), formerly known as the Regional Sophisticated Instrumentation Centre (RSIC), Indian Institute of Technology (IIT) Mumbai. The CHNS(O) Analyzer find utility in determining the percentages of Carbon, Hydrogen, Nitrogen, Sulphur and Oxygen of organic compounds, based on the principle of "Dumas method" which involves the complete and instantaneous oxidation of the sample by "flash combustion". The combustion products are separated by a chromatographic column and detected by the thermal

conductivity detector (T.C.D.), which gives an output signal proportional to the concentration of the individual components of the mixture.

Pharmacological Activity

The animals used in the examination were sheltered in analogy of the Shri B M Patil Medical College and Research Centre and BLDEAs SSM College of Pharmacy and Research Centre Vijayapur animal house, which follows the guidelines and regulation set by the committee for the control and administration of experiments on animals (CPCSEA), Ministry of social justice and empowerment, Government of India. The studies were attempted with previous approval from the Institutional Animal Ethics committee (IAEC) and ultimate care was taken to establish that the animals were handling in the most kind and satisfactory manner. Wister rats and albino mice of either sex, weighing 150-200 gm and 20-25 gm, respectively, were used. Pregnant females were eliminated.

IAEC Permission

The permission of Institutional Animal Ethics Committee (IAEC), duly constituted as per CPCSEA guidelines was obtained from BLDEAs SSM College of Pharmacy and Research Centre Vijayapur for the study. The permission letter is enclosed.

Induction of hyperlipidemia in experimental rats

Triton WR- 1339at a dose of (300 mg/kg body weight) was administered by intraperitoneal route of administration to experimental rats to induced acute hyperlipidemia Triton WR- 1339was dissolved in 0.89% saline, given to all ratsgrouped except the rats of normal control group.

Experimental design

The overnight fasted rats were randomly divided into eight groups each comprising sixrats. Group 1 received an intraperitoneal administration of normal saline and serves as Normal control group (NCG);Group 2 to 8 received triton and 1 hour later was administered with the vehicle or treatment or standard by oral gavage. Group 2 receives vehicle and serves as hyperlipidemic control group (HCG). In the group 3 and 4, hyperlipidemic rats were given intragastrically 100mg/kg body weight and 200mg/kg body weight of compounds **2 a**re spectively. In the group 5 and 6, hyperlipidemic rats were given intragastrically 100mg/kg body weight and 200mg/kg body weight of compounds 4d respectively. In the group 7 and 8, hyperlipidemic rats were given intragastrically 100mg/kg body weight and 200mg/kg body weight of Standard compound respectively. After 24hrs of triton administration blood sample was collected through retro orbital puncture. The blood samples were immediately centrifuged (3000 rpm for 10 min) and the serum was used for lipid profileanalysis by an enzymatic method with an automated analyzer.

RESULTS AND DISCUSSIONS

The plasma total cholesterol (TC), triglyceride (TG), high-density lipoprotein- cholesterol (HDLC), and low-density lipoprotein-cholesterol (LDLC) levels in hyperlipidemic group (HCG) treatedfor 18 h are shown in (Figure 1). Triton WR-1339 caused a significant increase in plasma TC, LDLCand TG ($p < 0.001$), levels, and a significant decrease in HDL-C level ($p < 0.001$) in hyperlipidemic control group (HCG) after 18 h of Triton WR-1339 administration in comparison with the normal control group (NCG). The increase of plasma total cholesterol concentration in the HCG was 191 % after 18 has compared to the NCG. Triglyceride level in the HCG was also elevated by 177 % after 18 h. Atthe same time, LDL-C level in HCG was also elevated by 195 % after 18 h as compared to theNCG. HDL level in HCG was decreased by 50 % after 18 h as compared to NCG.

Effect of compounds 2a, 4d and Standard drug on plasma lipid profile in rats

The effect of compounds **2a, 4d** and **Standard drug**on plasma lipid profile on treated rats after 18 h are shown in Table 2. Interestingly, the elevated plasma TG levels produced bythe acute injection of Triton WR-1339 were significantly ($p < 0.001$) decreased by 27.5, 35% and 42.5% in compounds **2a, 4d**and **Standard drug** respectively ($p < 0.001$) after 18 h, in comparison to Triton treated hyperlipidemic control (HCG). Furthermore, total cholesterol levels were significantly ($p < 0.01$) reduced in **4d**by 36% and in **2a**($p < 0.001$) by 29% after 18 h compared to hyperlipidemic control group (HCG). After 18 h of treatment, LDL- cholesterol levels were lowered by 29.70%, ($p < 0.0001$) in **2a**and 36.36 % ($p< 0.001$) in compound **4d**(Table 1). The HDL-C levels were significantly ($p < 0.001$) increased in compounds **2a** and 4d by 73% and 88% respectively ($p < 0.001$) after 18 h compared toHCG treated rats.

Human PPAR-alpha Transcription Factor Activity AssayAssay FormatSpecificity

The olionucleotide/antibody pair provided in this kit recognizes human PPAR-alpha in whole lysates and nuclear extracts.

Number of Targets Detected: 1
Species Detected: Human
Compatible Sample Types: Cell Lysates, Nuclear Extracts
Design Principle: Sandwich-based
Method of Detection: Colorimetric
Quantitative/Semi-Quantitative: Semi-Quantitative
Solid Support: 96-well Microplate Product Specifications
Size: 1, 2, or 5 x 96-Well Strip Microplate Kit Protein Information
Accession Number: Q07869
Gene ID: 5465
Gene Symbols: NR1C1, PPAR, PPARA

Protein Name & Synonyms
Peroxisome proliferator-activated receptor alpha (PPAR-alpha), nuclear receptor subfamily 1 group C member 1

Target Species
Human Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors of the nuclear hormone receptor superfamily. It includes three subtypes PPAR-alpha, PPAR-gamma, and PPAR-delta. Each one mediates the physiological actions of a large variety of fatty acids (FAs) and FA-derived molecules. The PPARs contain the canonical domain structure common to other nuclear receptor family members, including the amino-terminal AF-1 Trans activation domain, a DNA-binding domain, and a dimerization and ligand-binding domain with a ligand-dependent Tran's activation function AF-2 at the carboxy-terminal region. PPAR-alpha, PPAR-delta, and PPAR-gamma play an essential role in energy metabolism; however, they differ in the spectrum of their activity. PPAR-alpha I highly expressed in hepatocytes, enterocytes, vascular and immune cell types. PPAR-alpha plays a central role in lipid and lipoprotein metabolism, and thereby decreases dyslipidemia associated with metabolic syndrome. PPAR-gamma has been known to regulate adipocyte differentiation, FA storage and glucose metabolism, and is a target of antidIκBetic drugs. PPAR-gamma also enhances the expression of a number of genes involved in glucose and lipid metabolism. PPAR-delta is expressed almost ubiquitously with the highest level of expression found in colon, small intestine, liver and keratinocytes. It is a general regulator of fatty acid oxidation in many tissues, where it promotes FA metabolism and suppresses macrophage derived inflammation. The PPARs form heterodimers with the RXRs in cellular nucleus and can regulate gene expression through binding either PPAR ligands or RXR ligands. The formed heterodimers bind to PPAR-responsive elements (PPREs) that consist of direct repeats (DRs) with the core sequence AGG(A/T)CA separated by one or two base- pairs, designated DR1 and DR2, respectively. In the absence of ligand, the heterodimerretains in the nucleus binding to PPREs in a complex with transcriptional co-repressors. Upon ligand binding to PPARs or RXR, the complex makes conformational transfer that facilitates PPARs/RXR heterodimers binding with co-activator from co-repressors. The activated complex therefore starts transcriptional activation of target genes.

Product Features
Specific transcription factor-DNA binding assay,Perfect alternative to EMSA, Easy to perform in an ELISA format Non-radioactive assay, High throughput (96-well plate format) Assay can be completed within 5 hours Application Notes, Kit Components 96-well Strip Microplate pre-coated with DNA probes DNA Binding Buffer Positive Control Sample Specific Competitor DNA probe Non-specific Competitor DNA probe Assay Reagent, DTT Wash Buffer, Primary Antibody HRP-conjugated Secondary AntibodyAntibody Diluent Buffer TMB One-Step Substrate ReagentStop Solution.

Other Materials Required
Distilled or deionized water, 100 ml and 1 liter graduated cylinders Tubes to prepare sample dilutions Absorbent paper, Precision pipettes to deliver 2 µl to 1 ml volumes Adjustable 1-25 ml pipettes for reagent preparation, Microplate reader capable of measuring absorbance at 450 nm Protocol Outline, Prepare all reagents and samples as instructed in the manual. Add 100 µl of sample or positive control to each well.

Incubate 2 h at RT or O/N at 4 °C., Add 100 µl of prepared primary antibody to each well. Incubate 1 h at RT. Add 100 µl of prepared HRP-secondary antibody to each well. Incubate 1 h at RT., Add 100 µl of TMB One-Step Substrate Reagent to each well. Incubate 30 min at RT. Add 50 µl of Stop Solution to each well. Read at 450 nm immediately.

Total 20 novel Pyrimidine derivatives were designed and used the molecular docking tool; GLIDE was used for ligand docking studies into the Acid Pump PPARα pocket. The crystal structure of Acid Pump was obtained from the protein data bank, PDB ID: 1i7g. The protein preparation was carried out using 'protein preparation wizard' in Maestro 8.0 in two steps, preparation and refinement. Grids were generated centering on**co-**crystalized ligand**.** The ligands were developed using maestro build panel and prepared by Ligprep 2.2 module that produces thelow energy conformer of ligands using OPLS 2005 force field. The low energy conformation of the ligands was selected and docked into the grid generated from protein structures using standard precision (SP) docking mode. We also evaluated the number of violations of Lipinski's rule of five. Compounds that satisfy these rules are considered as drug like. Compounds with fewer (and preferably no) violations of these rules are more likely to be orally available.

Synthesis and characterization of novel derivatives of pyrimidine proves by IR (KBr,νmax, cm–1): 3450 (N-H), 3150 (C=C-H), 1690 (C=O, COOH), 1560 (C=C), 1430 (C=N), 1230 (C-O-C), 840 (para di substituted compound), 710 (ortho di substituted compound) ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm: 1.09(t,3H,C$\underline{H}_3$CH$_2$), 2.45(q,2H,CH$_3$C$\underline{H}_2$), 2.45(t,3H,S-C$\underline{H}_3$), 7.72-7.75(d,2H,Ar $\underline{H}$),7.93-7.95(d,2H, Ar $\underline{H}$),8.74(s,1H Ar $\underline{H}$), 10.35(s,1H, N$\underline{H}$).

Molecular weight of compound Ethyl 4-(4-(trifluoromethyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate is 358.

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The formed heterodimers bind to PPAR-responsive elements (PPREs) that consist of direct repeats (DRs) with the core sequence AGG(A/T)CA separated by one or two base-pairs, designated DR1 and DR2, respectively. In the absence of ligand, the heterodimer retains in the nucleus binding to PPREs in a complex with transcriptional co-repressors. Upon ligand binding to PPARs or RXR, the complex makes conformational transfer that facilitates PPARs/RXR heterodimers binding with co-activator from co-repressors. The activated complex therefore starts transcriptional activation of target genes.

DISCUSSION

Various pyrimidine derivatives were synthesized and characterized by IR, NMR andMass spectrum it shows the formation of novel derivatives of pyrimidine and these derivatives were subjected for molecular docking study and 50 novel designed derivatives were studied for Molecular docking and evaluated for antihyperlipidimic activity some compounds shows satisfied results as antihyperlipidimic agents.

Conflict of interest: Authors have no conflict of interest.

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