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Research Article

Exploring Novel Pyrimidine Derivatives: Design, Synthesis, Characterization, and Pharmacological Evaluation as Antihyperlipidemic Agents

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ABSTRACT

Molecular docking is a computational technique utilized in the field of structural biology and drug discovery. It aims to predict the binding orientation and affinity between two or more molecules, typically a protein and a ligand (small molecule), by simulating their interaction within a defined three-dimensional space. The process involves generating multiple conformations of the ligand and exploring various binding poses within the binding site of the protein. By evaluating intermolecular interactions, such as hydrogen bonds, hydrophobic interactions, and electrostatic forces, docking algorithms estimate the binding energy and thereby predict the strength of the binding interaction. Molecular docking plays a critical role in understanding molecular recognition, deciphering protein-ligand interactions, and aiding in the discovery of potential drug candidates. The technique has wide-ranging applications, including virtual screening of compound libraries, lead optimization, and elucidating the mechanisms of molecular interactions. Through the integration of computational simulations and structural biology data, molecular docking contributes to the acceleration of drug discovery processes and the exploration of molecular interactions that underlie pyrimidine derivatives' significance spans their roles in fundamental cellular processes, such as DNA and RNA synthesis, as well as their utility in drug discovery and development. These derivatives have been extensively studied for their interactions with enzymes, receptors, and other biomolecules, making them crucial components in fields like medicinal chemistry and molecular biology. In drug discovery, pyrimidine derivatives have been exploited as scaffolds for designing drugs targeting a variety of diseases, including cancer, viral infections, inflammation, and metabolic disorders.

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Their versatile nature allows for structural modifications to enhance binding affinities, selectivity, and pharmacokinetic properties, resulting in compounds with improved therapeutic profiles. Furthermore, pyrimidine derivatives have contributed to advancements in personalized medicine, as specific modifications can be tailored to individual genetic variations or disease conditions. The elucidation of their molecular interactions through computational simulations and structural studies has enabled the rational design of novel drug candidates and the optimization of existing ones. various biological phenomena.

INTRODUCTION

Pyrimidines and their derivatives are considered to be important for drugs and agricultural chemicals. Pyrimidine derivatives possess several interesting biologicalactivities such as antimicrobial, anti-tumor and antifungal activities. Many pyrimidine derivatives are used for thyroid drugs and leukemia. The pyrimidine derivatives possess a wide variety of potentially biological properties and are well known to work as herbicides and pesticides. Pyrimidine derivatives have been found to exhibit cytostatic immune modulating and antimicrobial properties. Imatinib is a new anticancer agent, and it is currently marketed by as gleevec. It is a protein tyrosine kinase inhibitor that inhibits the brawl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the philadelphia chromosome abnormality in chronic myeloid leukemia. It has also been found to be effective in the treatment of gastrointestinal stromal tumors is selective inhibition of bcr-abl kinase by imatinib has been a successful therapeutic strategy for cml because of the high efficacy and mild side effects of this compound. Chloranilic acid (ca) and picric acid (pa) form salts with many organic compounds particularly with aromatic and aliphatic amines. The chemistry of heterocyclic compounds is important for the discovery of novel drugs. Various natural compounds such as amino acids, alkaloids, vitamins, hormones, hemoglobin, and many synthetic drugs and dyes contain heterocyclic ring systems. Large numbers of synthetic heterocyclic compounds like pyrimidines, pyrrole, pyrrolidine, furan, thiophene, piperidine, and pyridine and thiazole show significant biological activity. Among these pyrimidines are of great interest. After Scheele isolated uric acid in 1776, fused pyrimidine chemistry started. Pyrimidine is a six membered heterocyclic ring with two nitrogen (N) atoms in their ring. It is a colorless compound, having molecular formula of $C_4H_4N_2$ and molecular weight of 80 dalton having melting point 22.5°c and boiling point 124°c. Pyrimidine is a weaker base than pyridine, imidazole or amidines as addition of a proton does not increase the resonance energy like imidazole and amidines. Understanding the metabolism of pyrimidines is important for drug metabolism of pyrimidine derivatives5. Only one of the nitrogen atom of the pyrimidine can be alkylated by alkylating agents, but with triethyl oxonium borofluoride both nitrogen atoms can be alkylated. Some of the biologically active pyrimidine derivatives are quinethazone, trimethotrexate, prazosin, folic acid and riboflavin. Pyrimidines are always an attraction point for researchers because of its efficiency towards various pharmacological usages. These compounds are known to possess various biological activities. Literature survey shows that various fused pyrimidine derivatives are known to exhibit anti-tubercular, anti-proliferative, anti-HIV, anti-microbial, anti-analgesic, anti- inflammatory and anti-malarial activities. Compounds containing imidazole thiazole derivatives are also of great interest among medicinal chemists as these compounds have also been reported for a wide spectrum of other biological properties. Pyrimidines are the most important member of all the diazines as this ring system occurs widely in living organisms. Pyrimidines have considerable biological importance because of their relation to the nucleic acids and forms the building blocks of DNA and RNA2. Pyrimidine derivatives are used as

anticancer agents, nucleic acid analogues, drugs used for hyperthyroidism, antimalarial agents, antibiotics, antitubercular agents, antihypertensive and diuretic agents. The discovery of potent group of pyrimidines with pronounced antagonistic effect on folic acid in cultures of Lactobacilli led to the development of pyrimethamine and trimethoprim. Pyrimethamine was developed through brilliant feet of organic synthesis guided by biochemical considerations. Additional modifications led to the synthesis of trimethoprim that inhibits bacterial dihydrofolate reductase like other diaminopyrimidines and its consequence selection as antibacterial agent. Trimethoprim is a broad-spectrum antimicrobial and also exhibits antiparasitic activities. Due to intensive use and misuse, resistance has emerged against trimethoprim. Nitrogen containing compounds acquires too much importance in medicinal chemistry becauseof its therapeutic activity. From long back over the years, pyrimidine turned out to be an important pharmacophore, which possess a strong interaction with the synthesis and function of nucleic acid.

Materials and methods:

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.

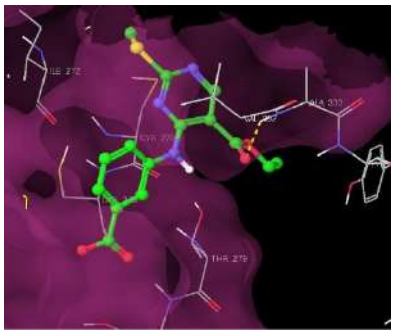


Figure No. 01: Docking of Designed Molecule Interaction ligand; Zinc-11849619

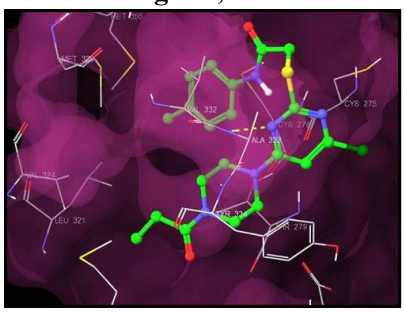
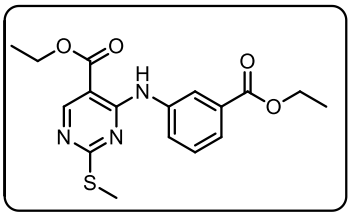


Figure No. 02: Docking of Designed Molecule Interaction ligand; Zinc-16611471

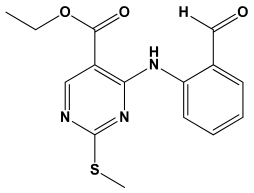
STEP-1

Ethyl 4-(3-(ethoxycarbonyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate: A solution of ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (0.5g, 2.14 mmol) in THF (5 ml) reaction mixture cooled to 0^0C, Ethyl 3-aminobenzoate (0.38ml, 2.36mmol) and DIPEA(2.14ml, mmol) were added stirred at 70^0 C for 16h. TLC shows the completion of starting material.The reaction mixture quenched with icewater extracted with ethyl acetate, dried over sodium sulfate and concentrated under reduced pressure. The obtained crude was triturated with hexane dried under vacuum to get ethyl 4-(3-(ethoxycarbonyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate as solid.Yield (71%). MP-183-85 ºc Yield(91%). TLC was monitored by ethanol: benzene (3:1).



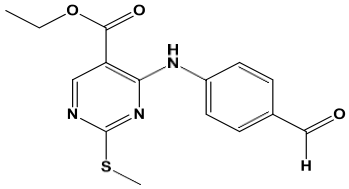
Ethyl 4-((2-formylphenyl)amino)-2-(methylthio)pyrimidine-5-carboxylate:

A solution of ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (0.5g, 2.14 mmol) in THF (5 ml) reaction mixture cooled to 0ºC, 2-aminobenzaldehyde (0.28ml, 2.36mmol) and DIPEA(2.14ml, mmol) were added stirred at 70^0 C for 16h. TLC shows the completion of starting material. The reaction mixture quenched with ice water extracted with ethyl acetate, dried over sodium sulfate and concentrated under reduced pressure. The obtained crude was triturated with hexane dried under vacuum to get Ethyl 4-((2-formylphenyl)amino)-2-(methylthio)pyrimidine-5-carboxylate as solid. Yield (78%). MP-192-94 ºc Yield(84%). TLC was monitored by ethanol: benzene (3:1).



Ethyl 4-((4-formylphenyl)amino)-2-(methylthio)pyrimidine-5-carboxylate:

A solution of ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (0.5g, 2.14 mmol) in THF (5 ml) reaction mixture cooled to 0ºC, 4-aminobenzaldehyde (0.28ml, 2.36mmol) and DIPEA(2.14ml, mmol) were added stirred at 70^0 C for 16h. TLC shows the completion of starting material. The reaction mixture quenched with ice water extracted with ethyl acetate, dried over sodium sulfate and concentrated under reduced pressure. The obtained crude was triturated with hexane dried under vacuum to get Ethyl 4-((4-formylphenyl)amino)-2-(methylthio)pyrimidine-5-carboxylate as solid. Yield (68%). MP-190-92 ºc Yield(80%). TLC was monitored by ethanol: benzene (3:1).



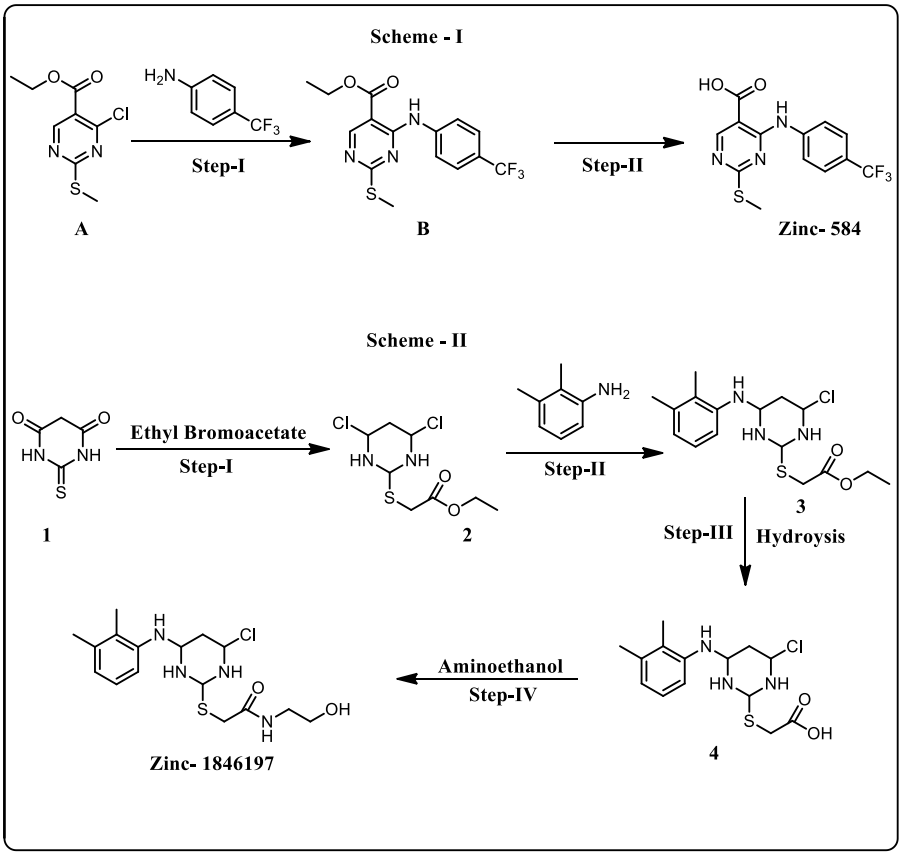
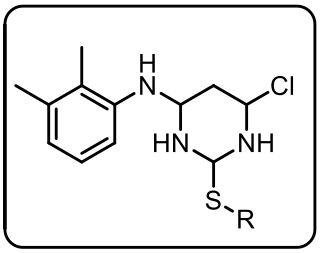


Figure No. 1: Method for the synthesis of PYRIMEDINE derivatives

Table 1: Novel Pyrimidinde different derivatives



Sr. No.	Compound Code	Compound Name
1.	PCC 21	Tert-butyl-4-(2- ((ethoxycarbonyl)methylthio)-6- chloropyrimidin4yl)piperazine-1-carboxylate
2.	PCC 22	2-((4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-chloropyrimidin-2- yl)sulfanyl)acetic acid
3.	PCC 23	Tert-butyl 4-(2-((p- tolylcarbamoyl)methylthio)-6- chloropyrimidin-4-yl)piperazine-1-carboxylate
4.	PCC 24	2-((4-chloro-6-(4-propionylpiperazin-1-yl)pyrimidin-2-yl)sulfanyl)-N-p- tolylacetamide
5.	PCC 25	2-((4-chloro-6-(4-(pivaloyl)piperazin-1-yl)pyrimidin-2-yl)sulfanyl)-N-p- tolylacetamide
6.	PCC 26	2-((4-chloro-6-(4-(pivaloyl)piperazin-1-yl)pyrimidin-2-yl)sulfanyl)-N-p- tolylacetamide
7.	PCC 27	Ethyl-6-((4-ethoxycarbonyl)-2,6- dimethylphenyl)amino)-2- (ethylthio)pyrimidine-4-carboxylate
8.	PCC 28	Ethyl 6-((4-benzoylphenyl)amino)-2-(ethylthio)pyrimidine-4-carboxylate
9.	PCC 29	Ethyl 4-((6-amino-2- (ethylthio)pyrimidine-4-yl)amino)benzoate
10.	PCC 30	Ethyl 4-((6-amino-2- (ethylthio)pyrimidine-4-yl)amino)-3,5-dimethylbenzoate
11.	PCC 31	4-((6-amino-2-(ethylthio)pyrimidine-4-yl)amino)phenyl)(phenyl)methanone
12.	PCC 32	3-((2-(methylthio)-6-phenylpyrimidine-4-yl)amino)benzoic acid
13.	PCC 33	,5 dimethyl-4-((2-(methylthio)-6- phenylpyrimidine-4-yl)amino)benzoicacid
14.	PCC 34	Methyl-4-((2-(methylthio)-6- phenylpyrimidine-4-yl)amino)benzoate
15.	PCC 35	Mthyl-2-((4-phenylamino)quinazoline-2yl)thio)acetate
16.	PCC 36	Methyl-2-((4-((2,4,6-trihydroxyphenyl)amino)quinazoline-2yl)thio)acetate
17.	PCC 37	Mthyl-2-((4-((4-methoxyphenyl)amino)quinazoline-2yl)thio)acetate
18.	PCC 38	Mthyl-2-((4-((2-chlorophenyl)amino)quinazoline-2yl)thio)acetate
19.	PCC 39	Methyl-2-((4-((2,4,6-trichlorophenyl)amino)quinazoline-2yl)thio)acetate
20.	PCC 40	(*S*)-methyl-2-((4-methyl-6- (phenylamino)pyrimidin-2-yl)thio)propanoate

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 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 2arespectively. 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 profile analysis by an enzymatic method with an automated analyzer.

Table No 1: Experimental grouping and prescribed dose

Sr. No	Group	Dose
1	Normal Control (NCG)	0.89 Normal saline
2	Hyperlipidemic Control (HCG)	0.89 Normal saline
3	Compound 2a	100 mg/kg
4	Compound 2a	200 mg/kg
5	Compound 4d	100 mg/kg
6	Compound 4d	200 mg/kg
7	Standard	100 mg/kg
8	Standard	200 mg/kg

Table No 2: Values of lipid profile of experimental rats

Sr. No	Group	TG mg/dl	TC mg/dl	HDL mg/dl	LDL mg/dl	VLDL mg/dl
1	NCG	90	115	52	45	18.0
2	HCG	160	220	26	88	32.0
3	2a 100mg/kg	130*	176*	33*	69*	26.0*
4	2a 200mg/kg	116*	156*	38*	62*	23.2*
5	4d 100mg/kg	128*	190*	32*	73*	25.6*
6	4d 200mg/kg	104*	141*	46*	56*	20.8*
7	Std 100mg/kg	98*	125*	42*	68*	19.6*
8	Std 200mg/kg	92**	120**	50**	50**	18.4**

Statistical data was analysed by one way ANNOVA method.The significant value * represents ($p < 0.001$) ** & represents($p < 0.0001$)

RESULTS AND DISCUSSIONS

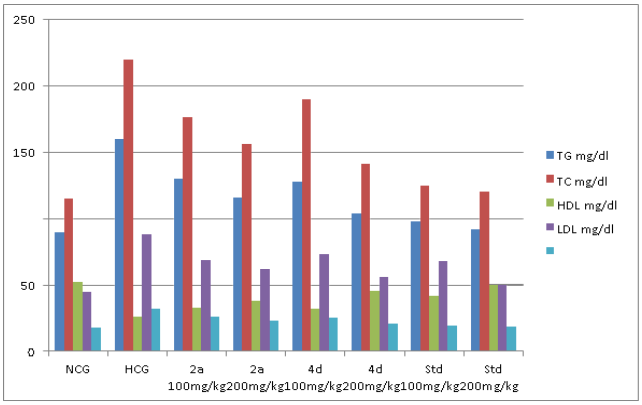


Figure No. 2: Graphical representation of Lipid Profile of experimental rats

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

Spectral Analysis:

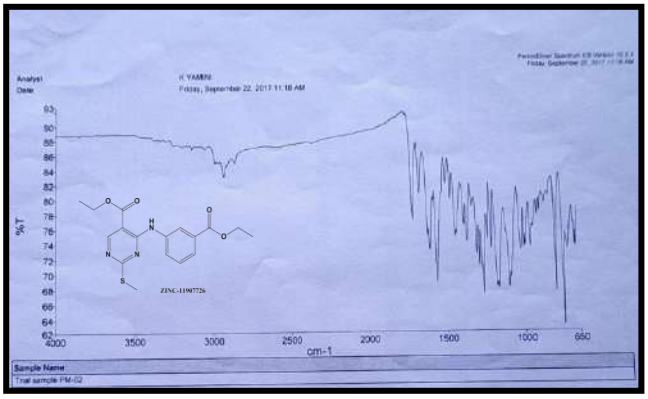


Figure No. 3: FT-IR spectrum of compound Ethyl 4-(3- (ethoxycarbonyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate

IR (KBr,νmax, cm–1): 3450 (N-H), 3150 (C=C-H), 1680 (Ar-COOR), 1560 (C=C), 1430 (C=N), 1230 (C-O-C), 840 (para di substituted compound), 710(ortho di substituted compound)

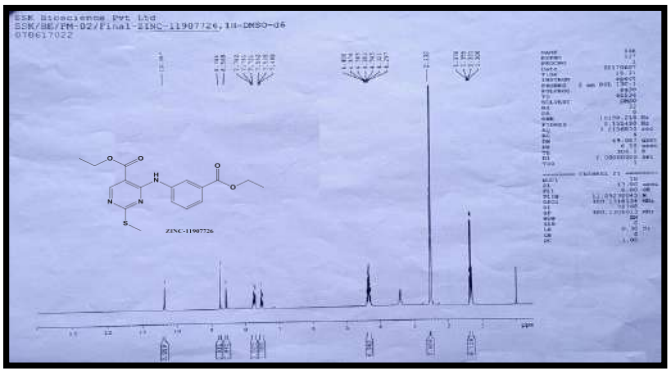


Figure No.4: H1 NMR spectrum of compound Ethyl 4-(3- (ethoxycarbonyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate

1H NMR (300 MHz, DMSO-d6) δ ppm: 1.30-1.37 (t, 6H, (CH3)2), 2.53 (s, 3H, S-CH3), 4.29-4.40 (q, 4H, (CH2)2), 7.49-7.55 (t, 1H, Ar-H), 7.72-7.78 (t, 2H, Ar-H), 8.56 (s, 1H, Ar-H), 8.74 (s, 1H, Ar-H), 10.36 (s, 1H, N-H).

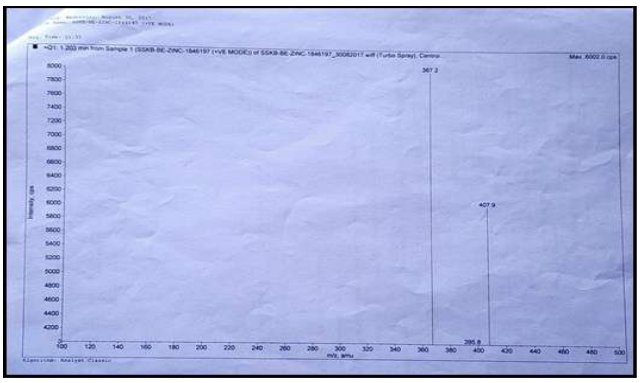


Figure No.5 Mass spectrum of Ethyl 4-(3-(ethoxycarbonyl)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate.

Molecular weight of compound SGSM-46 is 361. CHN Analysis: C17H19N3O4S Cal:C 56.50%, H 5.30%, N 11.63%, Found: C 56.55%, H 5.33%, N 11.66%.

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 accuracy2 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,

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DISCUSSION

The intermediates converted into corresponding derivatives and they were obtained in high purity with good yield. FT-IR spectrum, H1 NMR spectrum, and mass spectra data of synthesized derivatives compounds of pyrimidine Scheme analysis proves that resultant compounds.

The molecular docking study validated the outcome results from the antihyperlipidimic activity and signifies the potential of these derivatives as inhibitors. So, these compounds can be modified further for the development of new antihyperlipidimic agents. The docking study, In-vitro activity results strongly suggest that most of molecules synthesized in this study may indeed be promising drug candidates with interesting pharmacological profile and most of these derivatives could be a fruitful for further development of better antihyperlipidimic activity

CONFLICT OF INTEREST

Authors have no conflict of interest.

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