RESEARCH PAPER

“Design, Synthesis, Characterization, and In Vitro Evaluation of Pyrimidine Derivatives for Anti-Hyperlipidemic Activity.”.

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ABSTRACT

"In this study, a series of N-substituted 2-amino-4-substituted-6-methyl pyrimidine derivatives was synthesized through a three-step process involving various chemical transformations, commencing with benzaldehyde and its substituted derivatives. The chemical structures of the newly synthesized compounds were elucidated using infrared spectroscopy (IR), nuclear magnetic resonance (NMR), and mass spectrometry data analysis. The compounds PM6, N-(2-(1H-imidazol-1-yl)ethyl)-2-(4-chlorophenyl)-6-methylpyrimidin-4-amine, PM8, 6-methyl-N-(2-(piperazin-1-yl)ethyl)-2-(p-tolyl)pyrimidin-4-amine, and PM9: N-(2-(1H-imidazol-1-yl)ethyl)-6-methyl-2-(p-tolyl)pyrimidin-4-amine were among those synthesized. These designated compounds underwent molecular docking studies using ChemDraw and Schrödinger’s Maestro 20 Software

Keywords: Pyrimidine, Hyperlipidemia, Atorvastatin..
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INTRODUCTION

Heterocycles exhibit high efficiency in the one-step synthesis of antibacterial agents. The synthesized compounds demonstrate notable activity against both gram-positive and gram-negative bacteria[1]. The application of a Biginelli multicomponent strategy to 2-methyl sulfonyl pyrimidines leads to the formation of Type C, involving a reactive sulfonly group interacting with nitrogen, oxygen, sulfur, and carbon nucleophiles through microwave irradiation[2]. Further investigations encompass the synthesis and structure-activity relationship studies of 4-amino-2-phenyl pyrimidine derivatives as novel GPR119 agonists[3]. Additionally, the exploration of classical antifolate 2-amino-4-oxo-5-substituted 6-methylpyrrolo[3,2-d] pyrimidines as dual thymidylate synthase inhibitors[4], along with the utilization of pyrimidines in breast cancer cell line studies[5].

The study extends to HSP90 inhibitors, involving computational analysis of cocrystal structural docking studies, with a focus on their interaction with the three N-terminal binding sites[6]. Molecular modeling studies, conducted using Accelrys Insight II and the deposited Aurora-A structures[7], lead to the design of the first series of 6-substituted 6-5 fused ring analogs, showing potential as thymidylate synthase (TS) inhibitors and anti-tumor agents[8]. Targeted compound library generation of biofunctional DHPM and enantio-selective synthesis also contribute to the research[9]. Furthermore, the evaluation of pyrimidines as anti-cancer agents[10] and their role as selective adenosine A1 receptor ligands[11] further enriches this field. The development of New agents with Potent antibacterial activities by microwave mediated synthesis[12], Epidermal Growth Factor Receptor[13]. In-vitro antibacterial and antifungal evaluations[14]

Building upon the provided information, this research seeks to investigate and combine benzaldehyde-substituted derivatives and related compounds. Through the exploration of these derivatives, the aim is to identify substances with enhanced capabilities for combating hyperlipidemia. The resulting synthesized compound exhibits antihyperlipidemic effects comparable to those of Atorvastatin.

Scheme

OH, b – Cl, c- CH_3, d – H, e– NO2

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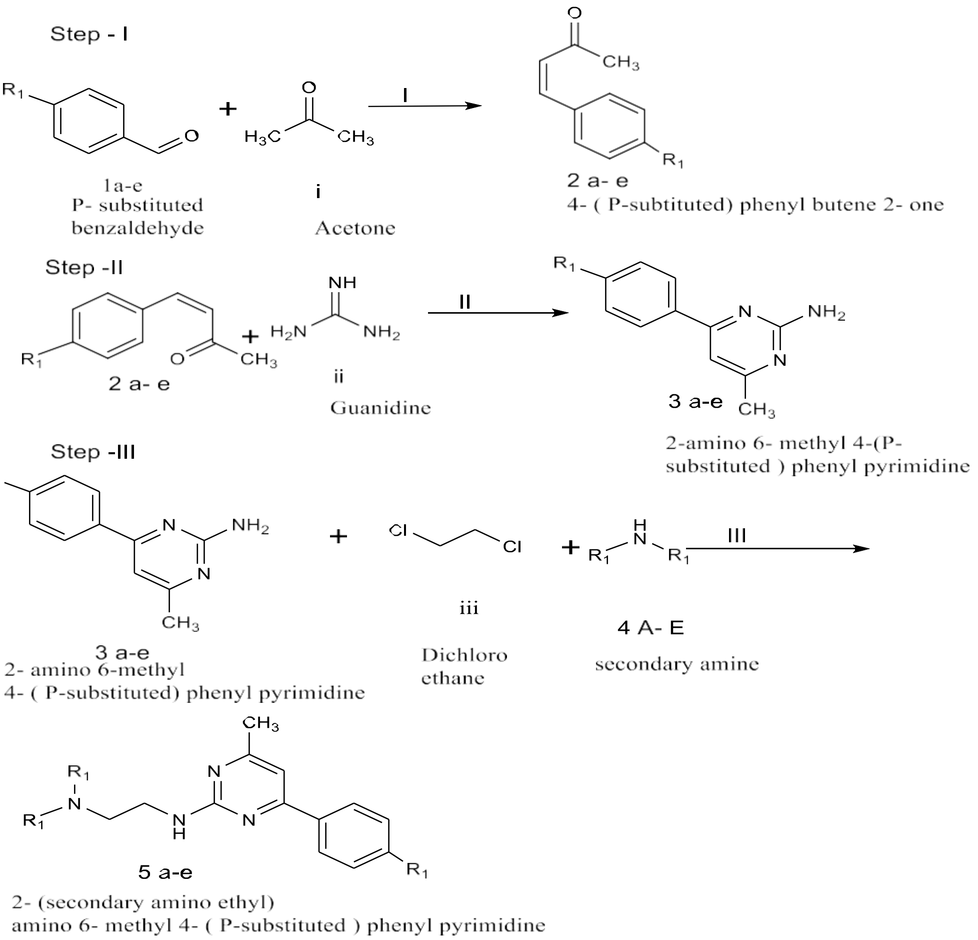


EXPERIMENTAL

MATERIALS AND METHODS

The solvents and reagents employed in this study were procured from Sigma Aldrich, SRL. The melting points of the compounds were determined using a digital melting point apparatus. Glassware used in the research was thoroughly cleaned with dishwashing liquid and subsequently dried in a Digital Hot Air Oven set at 120°C before utilization.

For spectroscopic analysis, an FT IR Perkin Elmer Spectrophotometer was employed. NMR spectra were recorded using a Bruker Avance III 400 MHz NMR Spectrometer, encompassing 1H NMR and 13C NMR analyses. Mass spectral data were acquired through the utilization of a Q-TOF Micromass (LC-MS) Instrument, operating at 70 eV for obtaining mass spectra.

General Procedure for the Synthesis

STEP I

In a 250 ml of Round bottom flask add 5 g of substituted benzaldehyde derivatives, 5ml of acetone 1 g of sodium hydroxide, and 5 ml of ethanol. This reaction mixture condensed on condenser at 80^{0C} for 1 hrs. The hot solution was acidified with conc. HCl and crystallization took place on cooling. Recrystallisation on solvent.

STEP II

In a 250 ml of beaker add 4- substituted benzyl acetone with 3g of guanidine HCl and 1 g sodium hydroxide in 30 ml of ethanol was stirring on magnetic stir at 80 ^{0}C for 1 hrs . This reaction mixture was poured into 50 ml of 10% cold hydrochloric acid solution, and the resultant precipitate was filtered, washed with water until free from acid, dried, and recrystallized from solvent to get desired product.

STEP III

In a 250 ml of Beaker add 2-amino, 6-methyl, 4- (P-substituted) benzene, pyrimidine derivatives with 10 ml di chloro methane, 3 ml of HCl and 5 ml / 5 g of secondary amine 20 ml of DMF (Dimethylformamide) was stirring on magnetic stirrer at 60 ^{0}C for 1-2 hrs. The resultant precipitate was filtered, washed with water until free from acid, dried, and recrystallized from solvent to get desired product. The resulting compounds were purified by recrystallization from ethanol,

2.3 DOCKING STUDIES

On the basis of the chosen Protein's crystal structure, docking studies were conducted on all of the generated Pyrimidine derivatives.investigations of docking and chosen 3DZYis searches from the PDB data store. Chem Draw and Schrodinger's Maestro-20 (Glide) software were used to prepare and inspect the ligands, respectively.

2.3.1 Protein Preparation

Making of proteins the protein must be optimised in every way in order to determine how the ligand and protein interact. The protein was acquired from the PDB and uploaded using Schrodinger's Maestro in this technique. The programme was used to optimise the protein, particularly its hydrogen bond network. A technology called the protein preparation wizard is employed to guarantee structural accuracy.

2.3.2 *Ligands Preparation*

The 2D structures of, ligands were draw on Chem Draw software and it supplied as SD, Mol2, or PDB format.The Schrödinger ligand preparation product LigPrep is designed to prepare high quality, allatom 3D structures for large numbers of drug-like molecules, starting with 2D or 3D structures in SD, Maestro, or SMILES format.

2.3.3 Grid Generation

The Receptor Grid Generation panel enables you to specify the receptor structure by omitting any potential co-crystallized ligand, choose the location and size of the active region as it will be shown by receptor grids, and configure Glide limitations. It is not possible to start a ligand docking job until the receptor grids have been produced.

2.3.4 Molecular Docking Calculations

Molecular docking was to determine the ligand-protein interaction with respect to the binding energy. This allows the interpretation of the characterization of ligands in the active site of receptor

RESULTS AND DISCUSSION

3.1 Docking

Docking studies of the titled compounds pyrimidine derivatives were performed successfully against PPARG (PDB Code 3DZY). **3DZY** was retrieved from Brookhaven Protein Data bank, import the ligands with inside the highest volume cavity of the enzyme and measure the affinity were H-bond score, Whereas 3DZY having two active site . Docking score of the interaction between the two active site of 3DZY and ligand molecules (PM-6,PM-8 and PM-9) has been posted in Table **2**. Among the titled compounds, **PM-6, PM-8 PM-9** showed highest Dock score about 9CR site (PM-6: -8.25, PM-8 : -8.4 and PM-9: -8.25) and BRL site (PM-6: -8.5, and PM-9: -8.5) respectively as compared to the other Pyrimidine derivatives. Among the titled compounds.

Table: 3.1.1

Title	**Docking score**
3DZY - Active site 9CR	**Resolution 3.1**
PM-8	-8.439
PM-6	-8.25
PM-9	-8.25

Table: 3.1.2

3DZY - Active site BRL	**Resolution 3.1**
PM-6	-8.506
PM-9	-8.506
PM-8	-6.688

9cr site

PM-6 ***Figure: 3.1.3 Docking studies on 9CR site with 3D amino acid interaction PM-6***

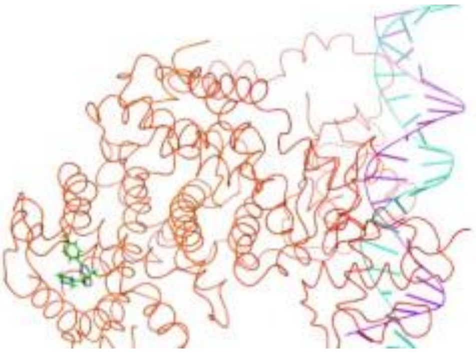


Figure: 3.1.4 Docking studies on 9CR site with 3D amino acid interaction PM-8

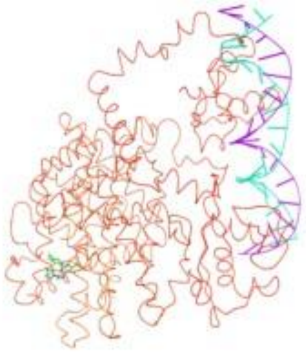


Figure: 3.1.5 Docking studies on 9CR site with 3D amino acid interaction PM-9

BRL site

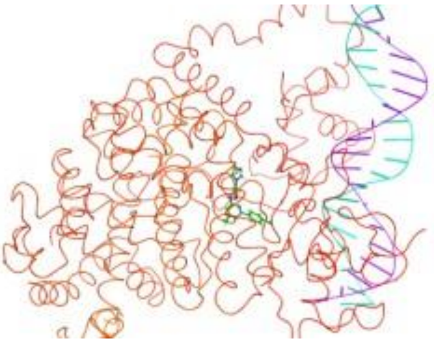


Figure: 3
.1.6 Docking studies on BRL site with 3D amino acid interaction PM-6

Figure: 3.1.7 Docking studies on BRL site with 3D amino acid interaction PM-9

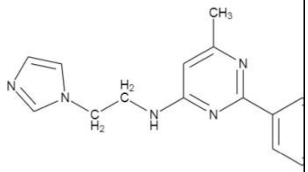
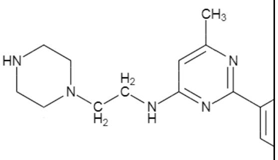
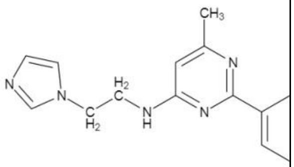
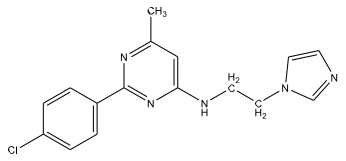
Compound	Structure	IUPAC	Molecular formula	Molecular weight	Melting Point	Yield (%)
PM-6		*N*-(2-(1*H*-imidazol-1-yl) ethyl)-2-(4-chlorophenyl)-6-methylpyrimidin-4-amine	$C_{16}H_{16}ClN_5$	313	125° C	92%
PM-8		6-methyl-*N*-(2-(piperazin-1-yl) ethyl)-2-(*p*-tolyl) pyrimidin-4-amine	$C_{18}H_{25}N_5$	311.21	157° C	89%
PM-9		N-(2-(1H-imidazol-1-yl) ethyl)-6-methyl-2-(p-tolyl) pyrimidin-4-amine	$C_{17}H_{19}N_5$	293.37	151° C	90%

Figure: 3.1.8 Docking studies on BRL site with 3D amino acid interaction PM-8

Table:3.2 Physiochemical parameter

IR SPECTRUM COMPOUND PM-6



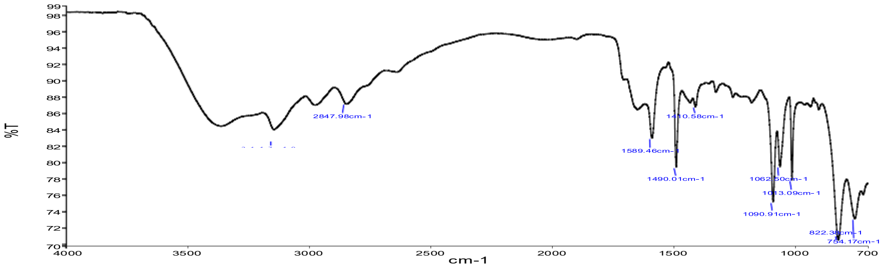


Figure 3.2.1 IR Spectrum of Compound PM-6

MASS SPECTRUM COMPOUND

PM-6

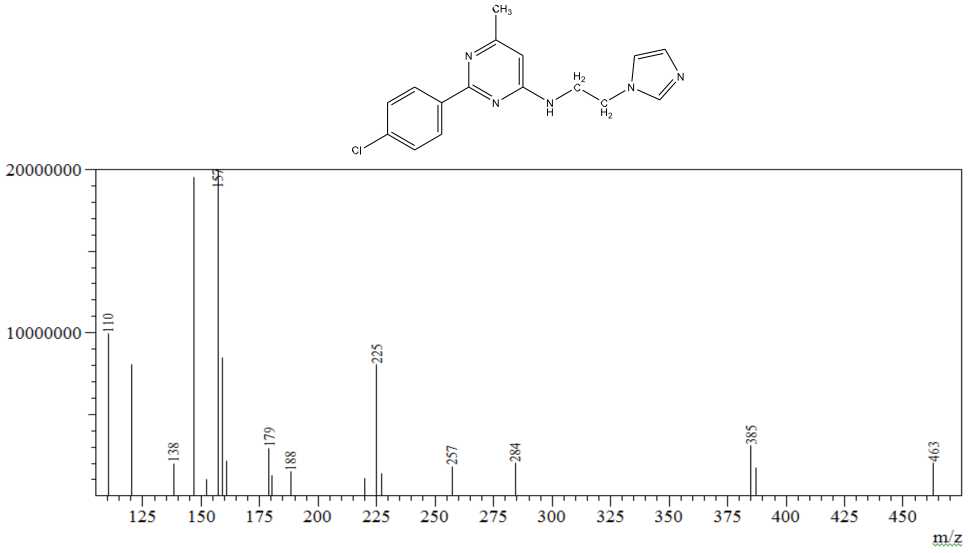


Figure 3.2.2 Mass Spectrum of Compound PM-6

^{1}H NMR SPECTRUM COMPOUND

PM-6

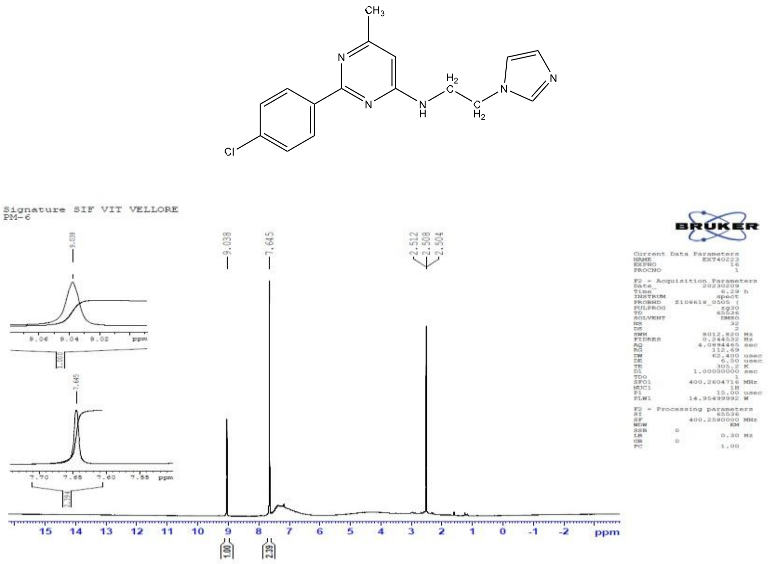
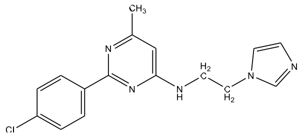


Figure 3.2.3 ^{1}HNMR Spectrum of Compound PM-6

^{13}C NMR SPECTRUM COMPOUND

PM-6



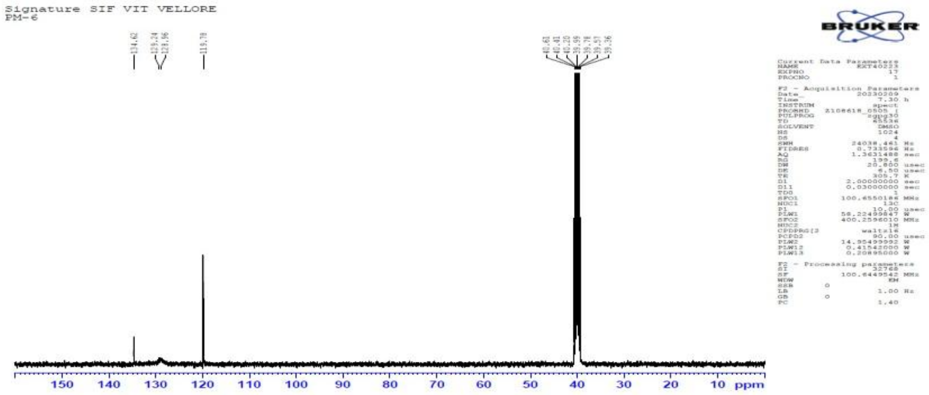
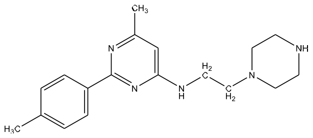


Figure 3.2.4 ^{1}3CNMR Spectrum of Compound PM-6

IR SPECTRA COMPOUND

PM-8



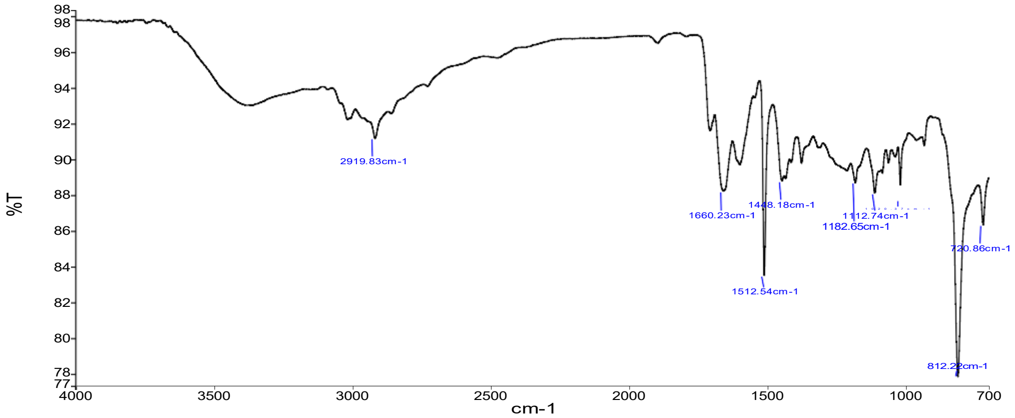
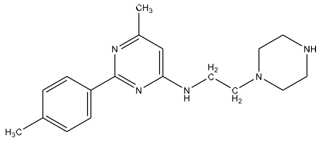


Figure 3.2.5 IR Spectrum of Compound PM-8

MASS SPECTRUM COMPOUND

PM-8



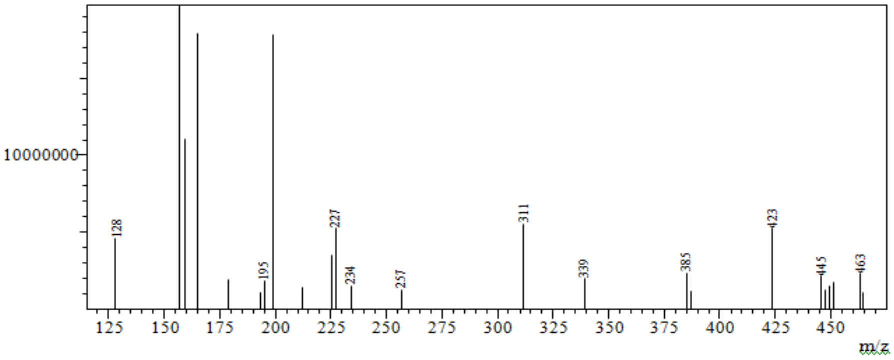
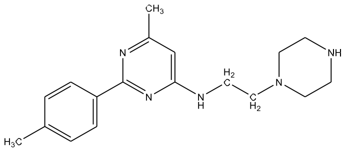


Figure 3.2.6 Mass Spectrum of Compound PM-8

^{1}H NMR SPECTRUM COMPOUND

PM-8



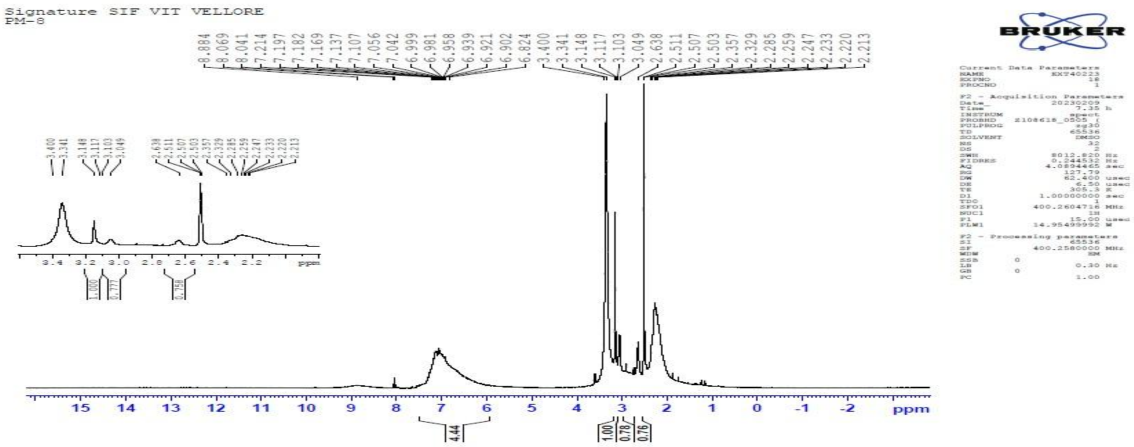
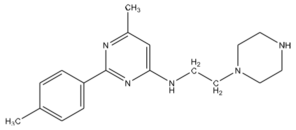


Figure 3.2.7 ^{1}H NMR Spectrum of Compound PM-8

^{13}C NMR SPECTRUM COMPOUND

PM-8



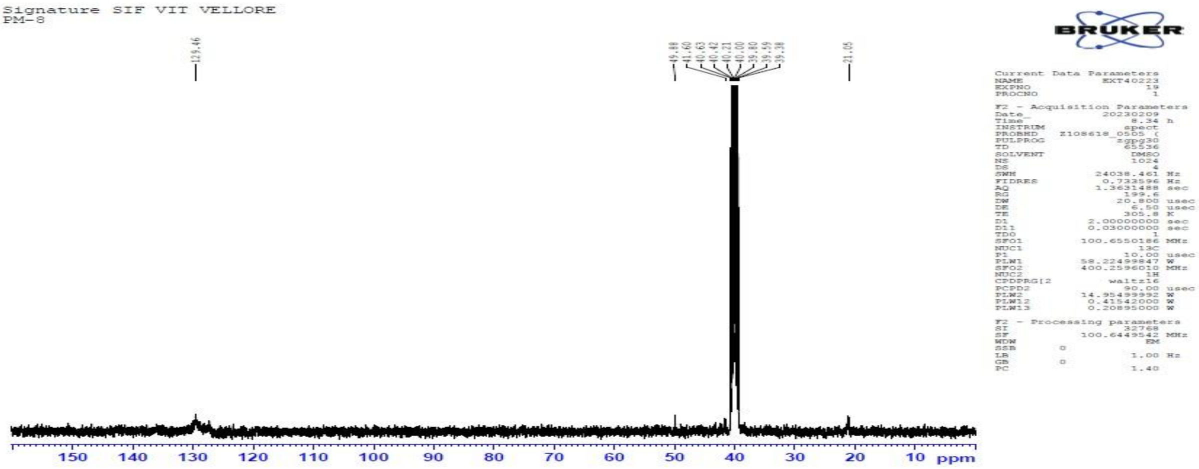


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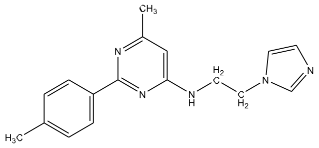
Figure 3.2.8 ^{1}3CNMR Spectrum of Compound PM-8

IR SPECTRA COMPOUND

PM-9



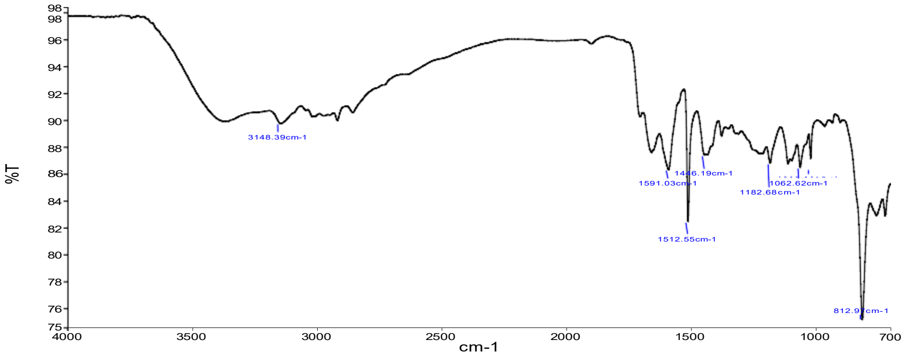
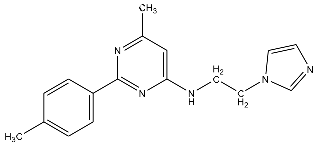


Figure 3.2.9 IR Spectrum of Compound PM-9

MASS SPECTRUM COMPOUND

PM-9



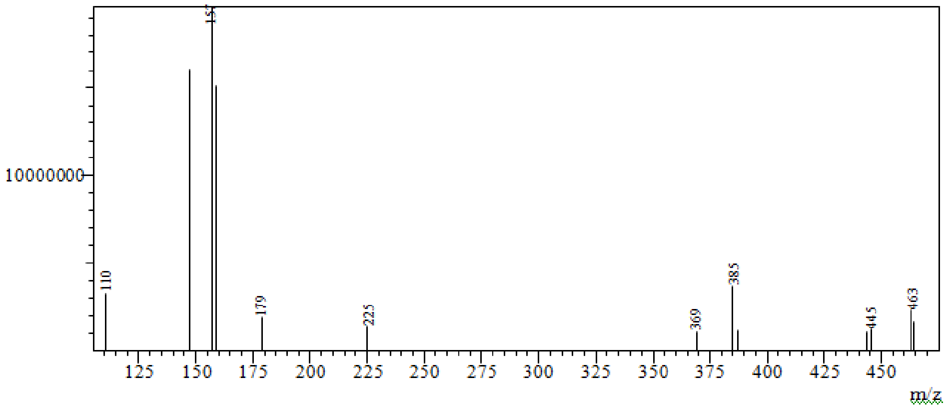
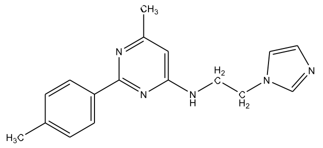


Figure 3.2.10 Mass Spectrum of Compound PM-9

^{1}H NMR SPECTRUM COMPOUND

PM-9



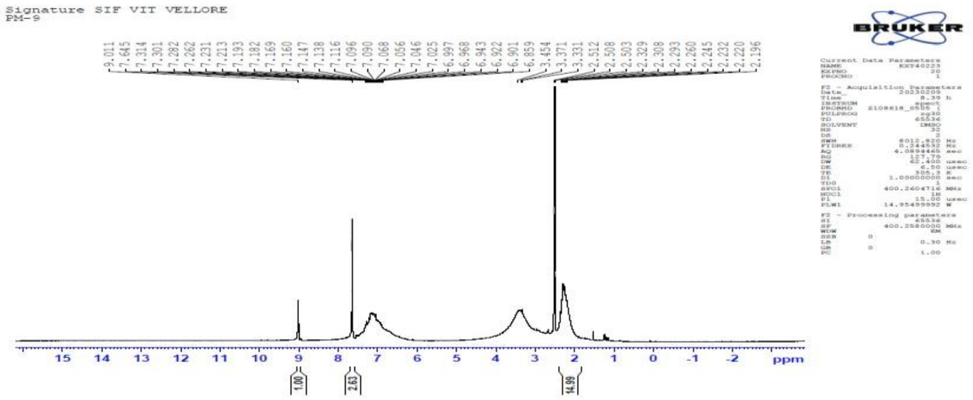
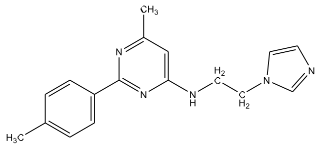


Figure 3.2.11 ^{1}H NMR Spectrum of Compound PM-9

^{13}C NMR SPECTRUM COMPOUND

PM-9



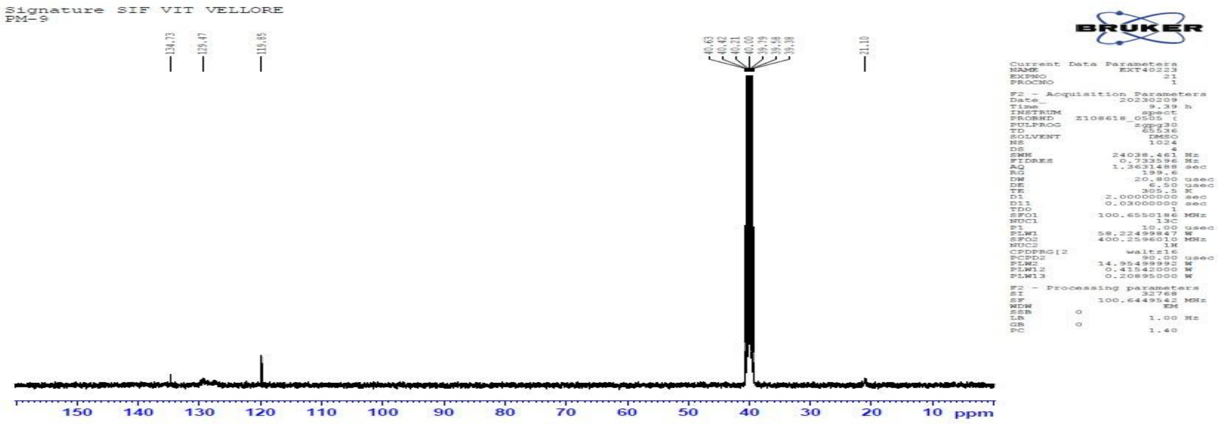


Figure 3.2.12 ^{1}3C NMR Spectrum of Compound PM-9

Interpretation of PM-6

IR spectral analysis: 3147, 2847,1589,1490,1410,1090,1062,1013,822

NMR Spectral analysis: 1H: 6.05 (NH), 7.92 (CH), 7.17 (CH), 4.53(CH2), 3.54 (CH2)

13C NMR: 137.8 (CH), 128(CH) 162(C), 45.9(CH2) , 51.2(CH2), 24.2 (CH3)

Mass Spectrum: molecular ion peak around m/z 463, Strong fragment peaks at m/z 110, 138, 179, and 225

Interpretation of PM-8

IR spectral analysis: 2918, 1660, 1512, 1448, 1182, 1112, 1029, 812

NMR Spectral analysis: NH-1.07, NH-6.05, 2.34 (CH2), 7.45(BENZENE) 8.60 (BENZENE), 2.34(CH3), 3.34(CH2)

13C: 162.9(C), 129(C- BENZENE) 99.3 (CH – PYRIMIDINE) 55.5CH2 (ALIPHATIC)

Mass Spectrum: molecular ion peak around m/z 463, Prominent fragment peaks at m/z 128, 195, 227, and 311.

Interpretation of PM-9

IR Spectral analysis: 3380, 2935, 2776, 2481,1660,1490,1453, 1390, 1159, 1049, 109, 1013

NMR Spectral analysis: 6.05(NH), 7.92(CH), 7.45 (CH-BENZENE), 4.53(CH2-METHYLENE), 3.54(CH2-METHYLENE), 2.42(CH3-METHYL)

13 C NMR Analysis: 162, 128, 99.3 128.5(Benzene), 45.9 (aliphatic) 131.9

Mass Spectrum: molecular ion peak at m/z ~463, Major fragment peaks at m/z 110, 179, and 225

CONCLUSION

The present study deals with designing of some 2, 4-substituted 6- methyl pyrimidine synthesized from P-substituted benzaldehyde and acetone. compound solubility was carried out by using polar and non- polar solvents . The synthesized 2,4- substituted 6-methyl pyrimidine compound uniquely freely soluble in Universal solvent on DMSO , soluble in ethanol, acetone and insoluble in water. The synthesized 2, 4- substituted 6-methyl pyrimidine compound has docking with 3DZY protein. The 3DZY protein obtained from protein data bank. 3DZY Intact PPAR gamma - RXR alpha Nuclear Receptor Complex on DNA bound. PPAR gamma is precursor for lipid metabolism.

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