SYNTHESIS AND MOLECULAR DOCKING OF MULTICOMPONENT REACTION (MCR) BASED HETEROCYCLES AS POTENTIAL KINASE INHIBITORS

BY

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DISSERTATION

Submitted to
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For the award of the degree of
MASTER OF TECHNOLOGY
MAY, 2024

INDIAN INSTITUTE OF TECHNOLOGY (INDIAN SCHOOL OF MINES) DHANBAD

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CONTENTS

CERTIFICATE FROM THE GUIDE ii

DECLARATION iii

CERTIFICATE FOR CLASSIFIED DATA iv

CERTIFICATE REGARDING ENGLISH CHECKING v

COPYRIGHT AND CONSENT FORM 6

ACKNOWLEDGMENTS x

LIST OF TABLES xii

LIST OF FIGURES xii

ABSTRACT xiii

CHAPTER 1: INTRODUCTION 1

CHAPTER 2: LITERATURE REVIEW 3

2.1 DIHYDROPYRIMIDINONE 6

2.2 MOLECULAR DOCKING 7

CHAPTER 3: OBJECTIVE 8

CHAPTER 4: METHODOLOGY 9

4.1 MOLECULAR DOCKING STUDIES 9

4.2. DERIVATISATION OF DIHYDROPYRIMIDINONES 12

4.3. CHARACTERIZATION OF SYNTHESIZED COMPOUNDS 15

CHAPTER 5: RESULTS AND DISCUSSION 20

CHAPTER 6: SUMMARY AND CONCLUSION 29

CHAPTER 7: FUTURE WORK 30

REFERENCES 31

ANNEXURE 34

LIST OF TABLES

Table 1: Binding pocket residues of Aurora Kinase B 5
Table 2: Docking Result Analysis 28

LIST OF FIGURES

Fig. 1: Kinase catalyzed phosphorylation 1
Fig. 2: Tertiary structure of a protein kinase 4
Fig. 3: Probable binding site of DHPM in Aurora B kinase (PDB ID: 4C2V) 5
Fig. 4: Monastrol, an anticancer agent, bearing DHPM scaffold 6
Fig. 5: Ligand Interaction diagram for compound 4c 21
Fig. 6: Molecular Docking based binding pose of compound 4c in 4C2V. 21
Fig. 7: Ligand interaction for compound 3c 22
Fig. 8: Molecular docking predicted pose for compound 3c 22
Fig. 9: Ligand interaction for compound 4a 23
Fig. 10: Molecular docking predicted pose for compound 4a 24
Fig. 11: Ligand interaction diagram for compound 3d 24
Fig. 12: Molecular docking predicted pose of compound 3d 25
Fig. 13: Ligand interaction diagram for compound 3b 25
Fig. 14: Molecular docking predicted binding pose for compound 3b 25
Fig. 15: Ligand interaction diagram for compound 3a 26
Fig. 16: Molecular docking predicted pose for compound 3a 26

ABSTRACT

One of the most difficult challenges in healthcare is devising safer and efficient therapies for diseases of highly complex nature such as cancer. Traditional treatments for cancer include chemotherapy, radiotherapy, surgery which has several side effects like harming the normal cells along with cancer cells. Over the time targeted therapies have been developed like small molecule therapy, monoclonal antibodies which has minimal side effects. Small molecular inhibitors are low molecular weight molecules which can easily penetrate the cell and interrupt the specific protein pathways involved in uncontrolled growth of cancer cells. Long-term use of any drug leads to the development of drug resistance. Over the time genes involved in the disease pathway undergo mutation, which is the main cause of drug resistance. Previously approved anticancer drugs no longer work against the mutated genes, so there is an ever-growing need of developing second line therapies. One of the most essential heterocyclic scaffolds explored in medicinal chemistry is dihydropyrimidinone. They possess a wide range of biological activities like antiviral, antibacterial, anti-inflammatory, antitumoral. However, DHPM derivatives are not explored as targeted therapeutic agents such as kinase inhibitors. Novel derivatives of this scaffold are synthesised employing multicomponent reaction and Suzuki coupling. Molecular Docking is done to study the interactions between ligands synthesised and target protein Aurora Kinase B (PDB ID: 4C2V here).

Keywords *Cancer, Small molecule therapy, Dihydropyrimidinone, Molecular Docking*

CHAPTER 1: INTRODUCTION

Cancer is a group of related diseases rather than a single disease. It is brought on by genetic abnormalities. Since genes regulate how our cells operate, mutations to these genes can make cells behave improperly, leading to aberrant cell growth and division. Tumors are abnormal growths or masses of tissue. Cancer, on the other hand, is the unchecked proliferation and spread of aberrant cells. Several common traits prevail in all types of cancer [1]. They include continuous firing of growth signals, losing the property of contact inhibition, and escaping the normal cellular machinery which keeps a check on the growth of cells. Along with that, cancer cells also possess the property by which it ensures a continuous supply of nutrients to blood vessels, leading to continuous growth of cancer cells, by depriving blood supply to the normal cells [2,3]. The primary methods of treatment include surgery, radiation, biotherapy, and chemotherapy techniques for treating cancer. Chemotherapy, which utilizes chemical agents to either kill or inhibit tumor cell growth and proliferation, was once the sole sort of cancer treatment therapy available which suffered from undesirable side effects. Chemotherapeutic drugs' failure to discriminate between healthy and malignant cells accounts for their cytotoxic and unselective character [4]. Over the last two decades, cancer therapy has progressed from broad-spectrum cytotoxic medications to more tailored and non-invasive treatments. The many forms of targeted therapy include monoclonal antibodies, gene therapy, immunotherapy, and small molecule inhibitor therapy. Targeted treatment has been proven effective for several cancers including leukemia, breast cancer, and lung cancer. It is important to note that most of these treatments target kinases [5].

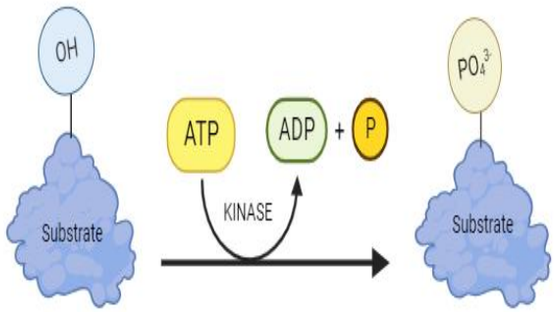


Fig. 1: Kinase catalyzed phosphorylation

Due to their crucial functions in cellular signalling, kinases are widely explored targets in drug discovery and medicinal chemistry research particularly for cancer. The majority of signal transductions are mediated by kinases, which also catalyse the transfer of the gamma-phosphate group of ATP onto a substrate and control a variety of cellular functions like transcription, differentiation, metabolism, and death.2 Kinases are one of the most promising druggable targets since they possess an ATP binding site and an allosteric site [6]. Small molecules competes with ATP for the binding site thereby inhibiting the protein function (phosphorylation) responsible for uncontrolled cell proliferation. Some of the kinases involved in cancer are FLT3, EGFR, BCR-Abl, RET, Auora Kinases [7,8].

MCR (Multicomponent reaction)

A multicomponent reaction is a synthetic process that involves formation of a single product by combining three or more reactants in a single step. The end products of MCRs nearly entirely consist of substrate components, producing virtually no byproducts. One of the wildly explored approaches for a greener synthetic route is employing multicomponent reaction methodology [9]. This simple approach cuts out on cumbersome multiple isolation steps, provides high atom economy, reduces generation of waste products. MCRs are thus extremely efficient and environmentally benign methodology for applications in medicinal chemistry due to facile one pot synthesis of target compounds [10]**.** Ethyl acetoacetate along with aromatic aldehydes and urea in presence of catalytic amount of mineral acid, a three component MCR yields different derivatives of dihydropyrimidinones. The fundamental building block of hereditary material DNA and RNA consists of dihydropyrimidine scaffold. Different therapeutic uses for pyrimidine derivatives may be found in medicinal chemistry. The presence of a pyrimidine base in the fundamental building blocks of nucleic acids, DNA, and RNA, thymine, cytosine, and uracil, is one hypothesized explanation for their activity [11].

CHAPTER 2: LITERATURE REVIEW

Kinases are enzymes which are primarily responsible for phosphorylation of a substrate, such as protein or lipid by facilitating the transfer of a gamma phosphate group from ATP molecule. Phosphorylation, is an important mechanism for controlling cellular signaling pathways, gene expression, metabolism, and other cellular activities. A variety of kinases have been found and categorized based on their structure, function, and substrate selectivity. So far, 538 kinases have been found in the human genome, mostly responsible for protein phosphorylation. Kinases play an important role in several cancer signalling pathways [12,13]. The fundamental architecture of a kinase protein includes of the C-lobe, N-lobe, hinge, activation loop, and ATP and allosteric binding sites. Kinases are druggable targets due to their ATP binding site and allosteric site. Small molecules compete with ATP and interacts with ATP binding site thereby inhibiting the kinase function (phosphorylation) in cancer cells which was responsible for uncontrolled cell proliferation. Despite having different primary amino acid sequences, the three-dimensional (3D) structures of the human kinases are very common, consisting of a N terminus which is predominated by beta sheets, a C-terminus region dominated by alpha helices, the two regions are connected by a hinge, in between there lies an ATP binding pocket. (14) Small molecular inhibitors bind to this pocket in place of ATP which inhibits the function of the protein. A common DFG sequence is observed in the activation loop of all kinases. Small molecule kinase inhibitors play an important role to help understand the functioning of kinases in many pivotal physiological processes [15].

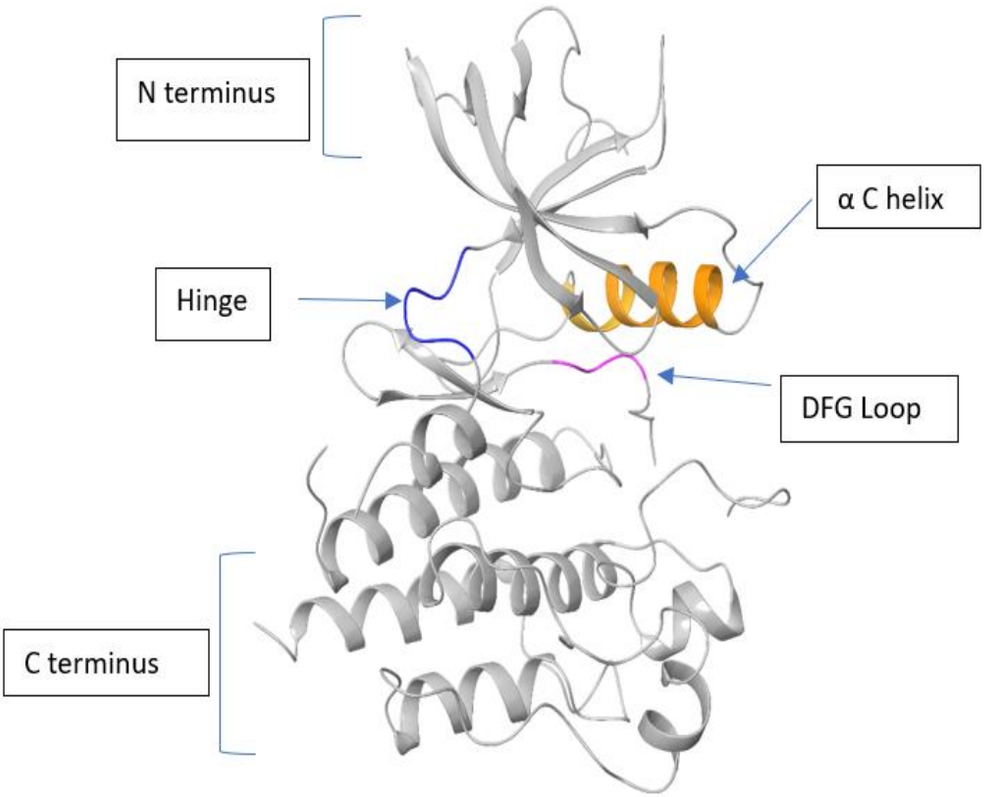


Fig. 2: Tertiary structure of a protein kinase

Aurora Kinase B is a serine-threonine kinase that has a pivotal function in cell division process, mitosis. It primarily functions in the M Phase and is essential for appropriate microtubule-chromosome attachments and cytokinesis. Cancers such as leukaemia, breast cancer, lung cancer shows Aurora B overexpression [16]. Several studies have linked genomic instability to enhanced Aurora B activity, making it a therapeutic target in cancer treatment. Many Aurora Kinase inhibitors have been developed and entered clinical trials but none of them have been approved for marketing. One of the crystal structures of Auorora Kinase B is 4C2V [17]. The binding residues of 4C2V are listed in the table below:

Binding region	Residues
Hinge	Leu 170, Glu 171, Phe 172, Ala 173 Pro 174, Arg175
DFG	Asp 234, Phe 235, Gly 236
α Helix	Glu 141, Gln 145
N-lobe	Leu 154, Lys 122, Leu 168, Ala 120

Table 1: Binding pocket residues of Aurora Kinase B

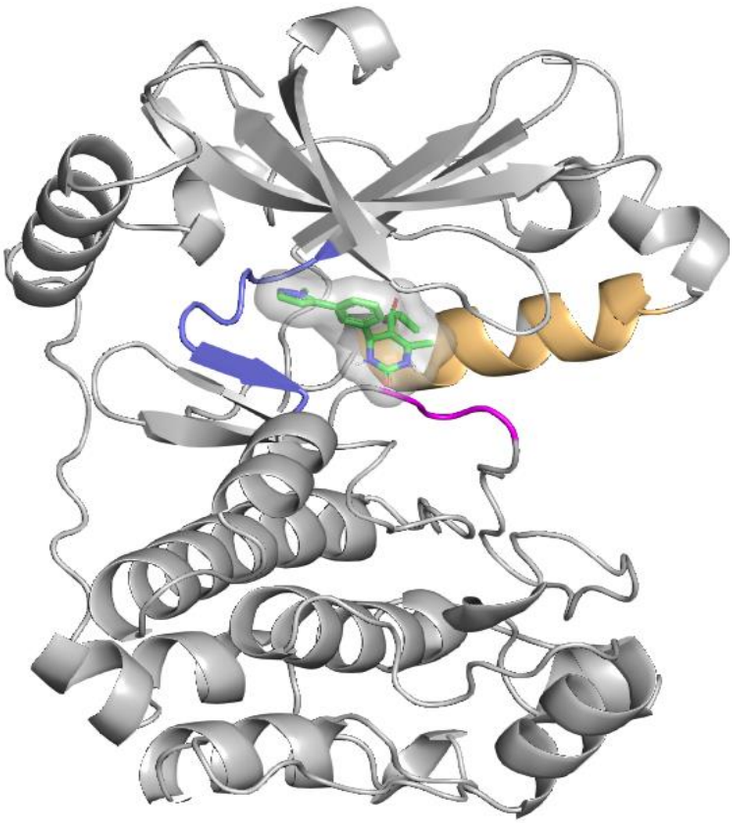


Fig. 3: Probable binding site of DHPM in Aurora B kinase (PDB ID: 4C2V)

2.1 DIHYDROPYRIMIDINONE

Dihydropyrimidinone, being a medicinally important heterocycle core possessing anti-inflammatory, antibacterial, antitumoral properties, have gained significant importance in the field of drug discovery. Since the last two decades, biginelli compounds have drawn attention due to their structural resemblance to the therapeutically effective dihydropyrimidine. exhibiting intriguing pharmacological traits, such as anti-HIV, anti-tubercular, anti-fungal, anti-cancer, and antibacterial [18]. One of the most researched Biginelli adducts is manostrol, whose potential anticancer properties have served as a source of inspiration for the development of novel molecules. causes bipolar mitotic spindle in mammalian cells to become blocked, causing mitotic arrest during G2/M phase and cell death. Since then, monastrol has motivated medicinal chemists to create brand-new anticancer drugs by molecularly altering the DHPM scaffold and changing the substituents' electrical and lipophilic properties [19].

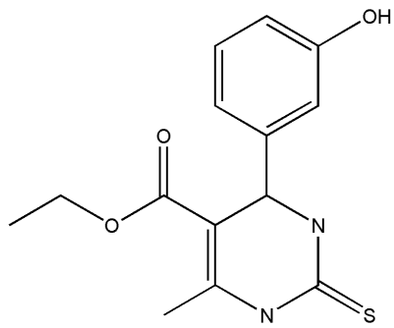


Fig. 4: Monastrol, an anticancer agent, bearing DHPM scaffold

To date 72 FDA-approved therapeutic agents target twenty different kinases.[7] Despite high efficacy and limited toxicity of the drugs, genetic alterations caused by mutations in the protein sequence is mainly responsible for occurrence of drug resistance. Nearly all targeted anticancer drugs show drug resistance over the time. The main cause of development of drug resistance is genetic mutation due to extended use of medication. Similarly, prolonged use of anticancer drugs leads to alterations in protein structures. The existing small molecules used for therapies, are no longer able to inhibit function of mutated proteins.Second line therapies for cancers which are resistant to previously approved drugs are underexplored. Also, there are only a limited types of cancers for which targeted therapies are available [20].

2.2 MOLECULAR DOCKING

Molecular docking is a technique used to predict the overall binding conformation or possible poses a ligand can orient itself around a protein. Molecular docking helps screen potential compounds virtually serving as an alternative for high-throughput screening. Molecular docking is an indispensable tool in fields of medicinal chemistry, biochemistry, biophysics. It predicts guiding intermolecular interactions of ligands with protein residues and conformations of ligands with high levels of accuracy [21]. Molecular Docking predicts the most favourable binding pose of the ligand bound to the receptor and binding energies in kcal/mol. The docking score or binding energy depends on the interactions shown by the ligand bound receptor. Significant interactions include hydrogen bonding, hydrophobic or van der Waals interaction. The most likely conformation in which the ligands bind to the receptor is recognized by adjusting its torsional, translational, and rotational DOF. The estimation of the binding energy of the ligand-receptor complex is calculated by the binding constant (Kd), and Gibbs free energy value ($\Delta G°$) produced using different scoring functions [22].

TOOLS USED:

- Open Babel GUI 2.4.1: Open Babel is a community-driven scientific project that assists users and developers as a cross-platform programme and library meant to facilitate molecular modelling, chemistry, and many other relevant disciplines, including file format and data interconversion.
- BIOVIA Discovery Studio Visualizer (DSV) 2021**:** It lets you view and edit molecular structures, sequences, and Perl scripts created with Discovery Studio. It provides a convenient interface for everyday data analysis tasks, making it ideal for sharing data with collaborators.
- MOLSOFT: Molsoft is a web-based application that calculates molecular attributes such as MolLogP (octanol/water partition coefficient), which tells us the MolLogS (water solubility Log (Mol/L)), MolPSA (Molecular Polar Surface Area (PSA) and volume), and Drug-Likeness Score.
- AutoDock Vina (Trott, 2010): AutoDock is a molecular docking software that can be used for both research and drug discovery. It uses Monte Carlo methods to search for the best binding poses of ligands in complexes with proteins. The program can be used to predict binding modes, estimate the binding affinity in units of Kcal/mole, RMSD values and helps screen potential compounds virtually. The docking software is available for free download on the official website of AutoDock [23].

CHAPTER 3: OBJECTIVE

The aim of the project is to design, and synthesise novel DHPM derivatives targeting Aurora Kinase B. Synthetic steps are achieved by employing facile multicomponent reaction for cyclization step followed by carbon-carbon bond formation via Suzuki coupling reaction. The DHPM core is derivatized by introducing additional nitrogen containing heterocycles which is thought to improve its potency by creating multiple sites for interaction. The ligand is designed in such a way to achieve significant interactions of the designed ligand with the protein residues. Moieties possessing multiple hydrogen bond donor sites as well as hydrogen bond acceptor sites are preferred. Carrying out in-silico studies of the ligands to study its potency against 4C2V kinase is done via Molecular Docking.

A. To design different dihydropyrimidinone based scaffolds.
B. To perform Molecular Docking of the designed compounds with kinase protein structures.
C. To synthesise the novel Biginelli derivatives and characterize them.

CHAPTER 4: METHODOLOGY

4.1 MOLECULAR DOCKING STUDIES

PROTEIN PREPARATION:

Before docking, the protein structure must be prepared by removing co-crystallized ligand, water molecules, other hetero atoms and unwanted chains to understand interaction of our designed ligand with the receptor site of protein. The steps are as follows

1. Firstly, protein structure was downloaded from the open web server RCSB PDB database (https://www.rcsb.org/structure/4C2V) in PDB output file.
2. Autodock Vina was opened, we click on File to Set Preferences. We make sure to copy paste the path of folder in start- up directory. To select the pdb file of protein we click on File→Read Molecule. Unwanted chains are removed by clicking on Select, we select the particular string, then select from the chain list, residues were added and deleted. Next, we need to delete the water molecules to do so Edit → Delete water. Heteroatoms and the co-crystallised ligand if any in the protein structure has to be removed by clicking on select from string, heteroatom was selected, added and deleted.
3. To add polar Hydrogen atoms, for considering H- bonds , Edit → Hydrogens (Polar) → Add. White terminal atoms are shown upon adding polar hydrogens. Now to add charges, Edit → Charges → Add Kollmann Charges. Again, Edit → charges → Compute Gasteiger Charges.
4. To save the protein in PDBQT format, firstly assign AD4 type, Edit → Atoms → Assign AD4 Type. Select → Connect →Remove. To save the file go to File → Save → Write PDBQT.

LIGAND PREPARATION:

1. We need to generate two-dimensional and three-dimensional coordinates to prepare ligands. For that, we need the structure of our ligand, which we can obtain from any of the publically available databases that can be used, such as ZINC-15, ChEMBL, PubChem, etc., if the ligand is known and commercially available. If the ligand we use is novel, we can obtain its SMILES notation from any of the above databases or use ChemDraw.
2. To generate the 2D and 3D coordinates of the ligands we drew the Structure on ChemDraw, select → Edit → Copy as smiles. Paste the smile notation in notepad and save it as “lig.smi”

3. Open Babel GUI 2.4.1 was used to generate PDB structure of the ligand. Open Open Babel GUI 2.4.1 and paste the SMILES notation copied from the ligand database. In INPUT FORMAT, select --SMILES format and select pdb format in OUTPUT FORMAT. Checkboxes for Generate 3D coordinates were clicked. Click on Convert and the file will be saved in pdb format in the location specified.
4. Now to convert the ligand pdb to pdbqt autodock vina was used again. The steps being, Ligand → Input → open the ligand pdb. Next, choose Ligand → Output → Save as pdbqt. (With extension. pdbqt)

GRID GENERATION:

1. AutoDock Vina opened, Select on Grid → Macromolecule then Select the protein pdbqt file.
2. Again, to set Map types we go to the Grid icon and click on Set Map types. Then the ligand was chosen to generate the files
3. Open 42CV.pdb downloaded from RCSB PDB in DSV. Select the ligand (co-crystallised) and click on show 2D Diagram. The interacting residues were noted down. The atoms were labelled to generate a grid box around the interacting residues.
4. Grid→ Grid box. A grid of 25Å×25Å×25Å appears on the screen. We need to make sure that the selected residues are inside the grid. If not, the grid is moved such as all the residues are inside the grid box. Grid Box dimensions chosen here are: 80 x 80 x 60 with x center: 7.603, y center: -26.678, z-center: 5.332. Close saving current option was selected. Then again, Grid→ Output, the Grid Parameter File was saved.
5. Run → run autogrid → path folder of autogrid4 was chosen from the browse option. Parameter file was browsed, gpf file chosen, a grid log (glg) file is created, launch button is clicked.

DOCKING:

1. Protein was selected upon clicking Docking → Macromolecule → Set Rigid filename.
2. Ligand was chosen from Docking →Ligand →Choose. Then launch button pressed after unchecking the two random radiobuttons.
3. To decide the number of runs, we click on Docking then search parameter followed by genetic algorithm option. More the number of runs, better the accuracy of the results predicted. Then we click on Docking →Docking parameter → Use default and accept.

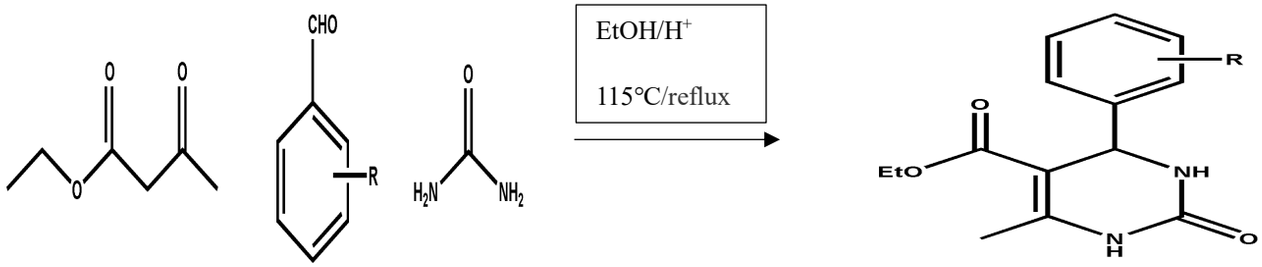
4. To create a docking parameter file (dpf) we again go to Docking → Output → Lamarkian and save the dpf file with extension .dpf
5. Run autodock. Pathname for autodock4 was browsed. Dpf file was browsed, dlg file is created.
6. For docking analysis, we click the Analyse → Docking → Open the dlg, docking log. file
7. Analyse → Macromolecule → choose, selecting the protein.
8. To analyse the different conformations, we choose Analyse → Conformation → Play ranked by energy. The & button is chosen from different play buttons. Energies of all the 10 best poses of the ligands are recorded and can be saved by clicking on the option Write Current. Set play energy option, we click on show info, where binding constant, RMSD and all other parameters are listed. We play the docked file having most negative binding energy and click on Write Current. The file is saved as pdbqt.

Docking results are visualised using Schrodinger Maestro / PyMol. Docking results were generated. Docking results: Binding energy values in the unit of Kcal/mol, root mean square deviation values were calculated. High-quality images were made for Molecular graphics and analyses using Schrodinger Maestro. Images can display significant interactions like hydrogen bonding along with H-bond length (lying in the range 2.7-3.3 Å) hydrophobic interactions, pi-pi stacking interactions etc.

4.2. DERIVATISATION OF DIHYDROPYRIMIDINONES

A series of eight novel dihydropyrimidinones are synthesised employing the below steps:

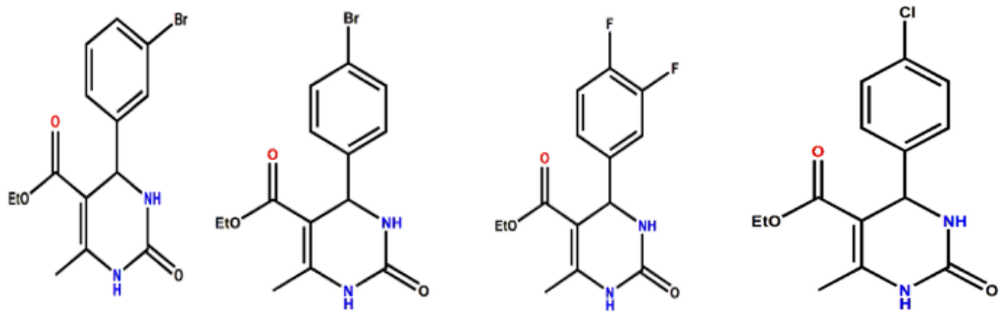
SYNTHESIS VIA BIGINELLI MULTICOMPONENT REACTION:



Yield = ~ 80 %

(1.5 equivalent)

4 examples



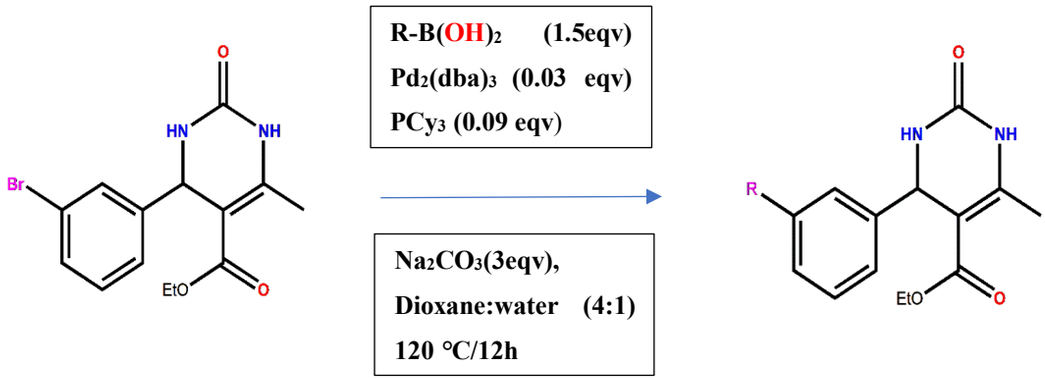
1a **1b** **1c** **1d**

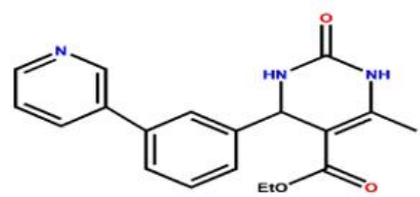
Yield = 85% Yield = 85 % Yield = 80 % Yield = 80 %

A mixture of urea (1eq), ethylacetoacetate (1.5eq), substituted benzaldeyde was taken in a RB with magnetic stirrer, ethanol as a solvent and two to three drops of concentrated HCl was added to it. The reaction mixture was heated in an oil bath set at temperature 115°C. The RB was attached to reflux condenser to avoid loss of solvent as the boiling point of ethanol solvent is lower than that of the set reaction temperature. TLC was checked after half an hour, no spot was formed, the reaction was allowed to progress for another hour, a light spot was observed. The reaction was run for 2-2.5 hours. At the end of the reaction single spot was observed in TLC, no purification was further required.

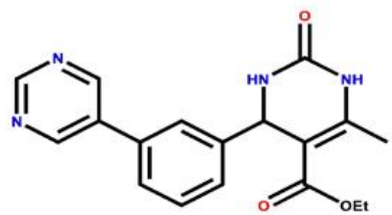
Various substituted benzaldehydes like 3-bromobenzaldehyde, 4-bromobenzaldehyde, 3,4-difluorobenzaldehyde 4-chlorobenzaldehyde was used to obtain 1a-d. Halogen containing benzaldehydes gave us better yields. White-yellow solid crystalline precipitate was observed which was filtered under suction funnel and washed with cold ethanol.

SUZUKI REACTION:

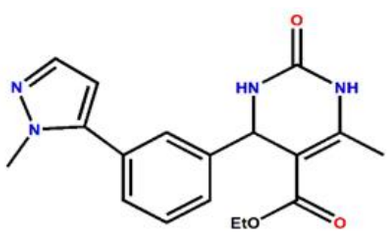




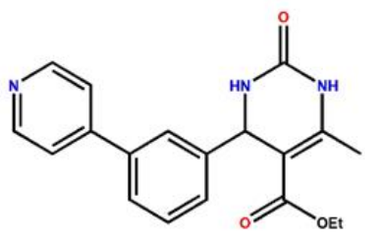
3a ,65 %



3b , 72 %



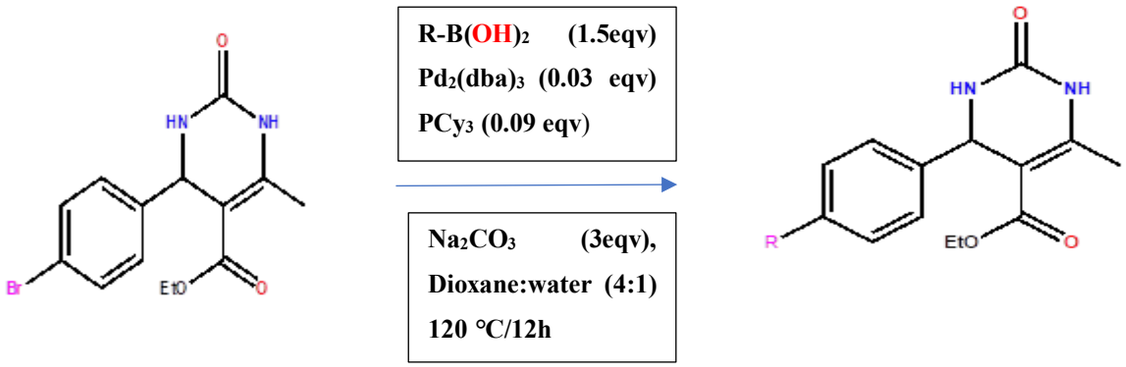
3c 65 %

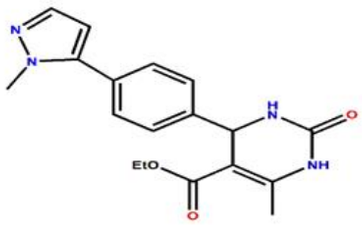


3d. 78 %

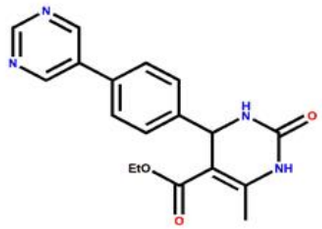
An oven-dried seal tube was taken along with a clean magnetic bead. Boronic acid (1.5 equiv.), 3-bromo Biginelli derivative, Pd(dba)2 (0.03 equiv.), PCy3 as ligand (0.09 equiv.) and Na2CO3 as base (3 equiv.) were stirred in 5mL Dioxane:water solution (4:1)for 12h (overnight) at 120° C. TLC

technique was used to monitor the advancement and consumption of the starting materials. A Celite bed was prepared to filter the reaction mixture to remove palladium catalyst. DCM was used as an eluting solvent. The solvent was evaporated under reduced pressure by a rotary evaporator. The impure product was adsorbed on to the silica gel and purification was performed by column chromatography. The pure product was obtained as a white/yellow solid. Different boronic acids were used (3-pyridinyl boronic acid, 1-Methyl, 1-H pyrazole-5-boronic acid pinacol ester, pyrimidine-5-boronic acid pinacol ester and 4-pyridinyl boronic acid) to yield 3a-d.

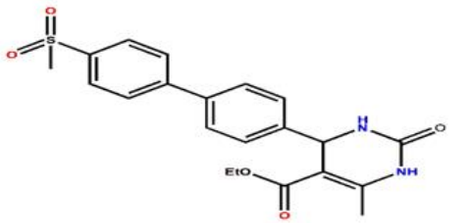




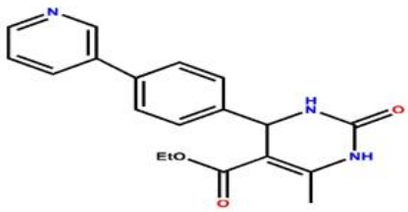
4a , 70 %



4b , 76%



4c , 80 %



4d , 75 %,

An oven-dried seal tube with a cleaned magnetic bead was taken and boronic acid (1.5 equiv.), 4-bromo Biginelli derivative, Pd(dba)2 (0.03 equiv.), PCy3 (0.09 equiv.) and Na2CO¬3 (3 equiv.) were stirred in 5mL Dioxane:water solution (4:1) for 12h (overnight) at 120° C. TLC technique was used to monitor the advancement and consumption of the starting materials. Celite bed filteration of the reaction mixture was done to remove catalyst followed by adsorbing into silica gel the compound was purified by column chromatography. The product was obtained as a white yellowish solid. Different boronic acids were used (3-pyridinyl, 1-Methyl, 1-H pyrazole-5-boronic acid pinacol ester, pyrimidine-5-boronic acid, 4-(Methylsulfonyl) phenyl boronic acid) to yield 4a-d.

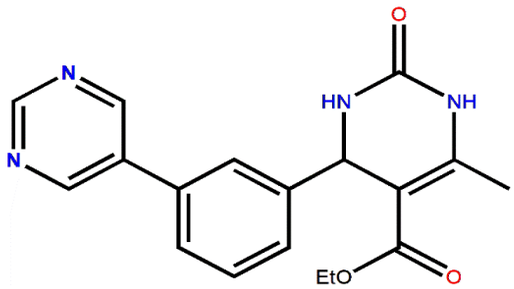
4.3. CHARACTERIZATION OF SYNTHESIZED COMPOUNDS

The characterization of all the synthesized DHPM derivatives and all the intermediates in the 2-step synthesis was carried out using NMR. All the 1H-NMR and 13C-NMR spectra were recorded on Bruker 400 MHz NMR spectrometer in a solution of DMSO using tetramethylsilane as the internal standard, δ values are given in parts per million, and coupling constants (J) in hertz.

SAMPLE PREPARATION:

The completely dried sample is taken into the Eppendorf tube in a 5 to 25mg scale and dissolved in the deuterated DMSO-d6 solution. It is ensured that a minimum amount of solvent is added to the sample to make it soluble, usually 0.6mL addition was enough to make a completely soluble sample. The mixture is then transferred using a micropipette to the thoroughly cleaned and oven-dried NMR tube. Clean the tube using tissue and label the sample.

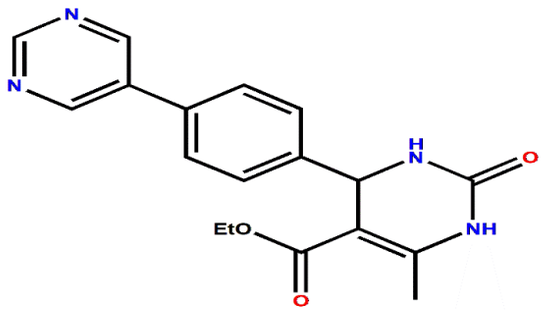
SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDRO-6-METHYL-2-OXO-4-(3-PYRIMIDINE-5-YL) PHENYL) PYRIMIDINE-5-CARBOXYLATE



1H NMR (400 MHz, DMSO) δ 9.21 (d, J = 23.5 Hz, 1H), 9.16 (s, 1H), 9.10 (s, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 5.20 (d, J = 3.3 Hz, 1H), 4.14 (q, 1H), 2.26 (s, 2H), 1.11 (t, J = 7.1 Hz, 2H).

13C NMR (101 MHz, DMSO) δ 165.79 (s), 157.68 (s), 155.13 (s), 152.63 (s), 149.19 (s), 145.94 (s), 133.34 (d, J = 17.8 Hz), 127.59 (d, J = 2.2 Hz), 99.48 (s), 66.82 (s), 59.78 (s), 54.05 (s) 25.41 (s), 18.30 (s), 14.58 (s).

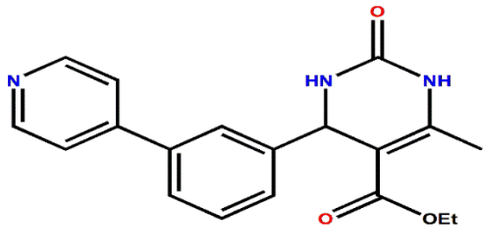
SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDRO-6-METHYL-2-OXO-4-(4-PYRIMIDINE-5-YL) PHENYL) PYRIMIDINE-5-CARBOXYLATE



1H NMR (400 MHz, DMSO) δ 9.21 (d, J = 23.5 Hz, 1H), 9.16 (s, 1H), 9.10 (s, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 5.20 (d, J = 3.3 Hz, 1H), 4.14 – 3.79 (m, 1H), 2.26 (s, 2H), 1.11 (t, J = 7.1 Hz, 2H).

13C NMR (101 MHz, DMSO) δ 165.79 (s), 157.68 (s), 155.13 (s), 152.63 (s), 149.19 (s), 145.94 (s), 133.34 (d, J = 17.8 Hz), 127.59 (d, J = 2.2 Hz), 99.48 (s), 66.82 (s), 59.78 (s), 54.05 (s) 25.41 (s), 18.30 (s), 14.58 (s).

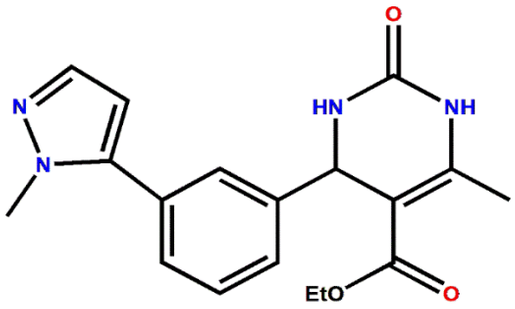
SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDRO-6-METHYL-2-OXO-4-(4-PYRIDINYL) PHENYL) PYRIMIDINE-5-CARBOXYLATE



1H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 8.64 (dd, J = 4.6, 1.4 Hz, 1H), 7.80 (d, J = 3.1 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 5.25 (d, J = 3.1 Hz, 1H), 4.10 – 3.93 (m, 1H), 2.26 (s, 2H), 1.06 (t, J = 7.1 Hz, 2H).

13C NMR (101 MHz, DMSO) δ 165.79 (s), 152.81 – 152.68 (m), 150.81 (s), 149.27 (s), 147.42 (s), 146.37 (s), 137.68 (s), 130.00 (s), 127.36 (s), 126.31 (s), 125.40 (s), 121.59 (s), 99.35 (s), 59.72 (s), 54.44 (s), 18.31 (s), 14.55 (s).

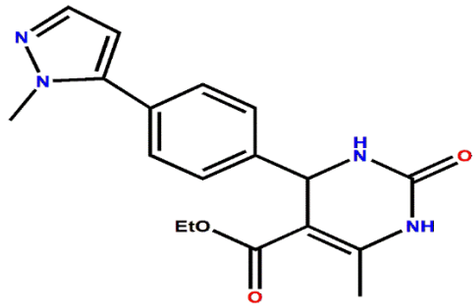
SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDRO-6-METHYL-4-(3-(1-METHYL-1H-PYRAZOLE-5-YL)PHENYL) 2-OXO-PYRIMIDINE-5-CARBOXYLATE;



^{1}H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 7.80 (s, 1H), 7.46 (dd, *J* = 4.6, 2.8 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 15.1 Hz, 1H), 6.33 (d, *J* = 1.8 Hz, 1H), 4.00 – 3.96 (m, 2H), 2.24 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 2H).

^{13}C NMR (101 MHz, DMSO) δ 152.64 (s), 148.09 (s), 134.50 (s), 127.48 (s), 124.32 (s), 99.55 (s), 66.82 (s), 59.76 (s), 54.06 (s), 18.31 (s), 14.59 (s).

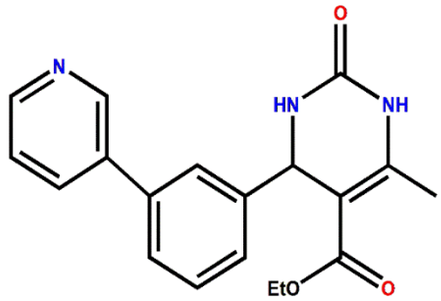
SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDRO-6-METHYL-4-(4-(1-METHYL-1H-PYRAZOLE-5-YL)PHENYL) 2-OXO-PYRIMIDINE-5-CARBOXYLATE



^{1}H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 8.86 (s, 1H), 8.58 (dd, *J* = 29.9, 4.7 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.46 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.19 (d, *J* = 3.2 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 1.14 – 1.05 (m, 3H)

^{13}C NMR (101 MHz, DMSO) δ 155.64 (s), 146.09 (s), 135.50 (s), 126.48 (s), 124.32 (s), 99.55 (s), 66.82 (s), 59.76 (s), 54.06 (s), 18.31 (s), 14.64 (s).

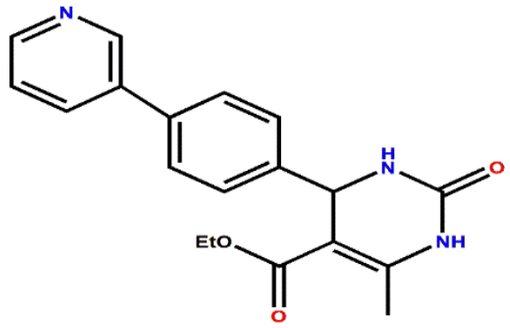
SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDRO-6-METHYL-2-OXO-4-(3-PYRIDINYL)PHENYL) PYRIMIDINE-5-CARBOXYLATE:



^{1}H NMR (400 MHz, DMSO) δ 9.25 (s, 1H), 8.84 (d, *J* = 1.8 Hz, 1H), 8.59 (d, *J* = 3.5 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.55 (s, 1H), 7.52 (d, *J* = 3.0 Hz, 1H), 7.46 (dd, *J* = 12.6, 9.6 Hz, 1H), 5.26 (d, *J* = 3.1 Hz, 1H), 4.08 (m, 2H), 2.27 (s, *J* = 10.3 Hz, 3H), 1.18 (m, 3H).

^{13}C NMR (101 MHz, DMSO) δ 149.16 (d, *J* = 12.8 Hz), 147.99 (s), 134.53 (s), 129.92 (s), 126.32 (d, *J* = 13.6 Hz), 125.48 (s), 124.47 (s), 66.82 (s), 59.73 (s), 54.40 (s), 18.29 (s), 14.56 (s).

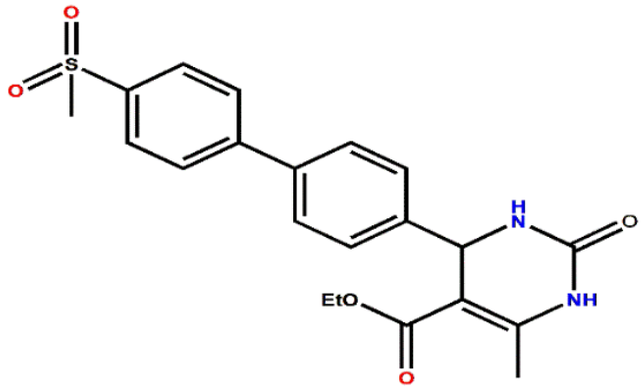
SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDRO-6-METHYL-2-OXO-4-(4-PYRIDINYL)PHENYL) PYRIMIDINE-5-CARBOXYLATE



^{1}H NMR (400 MHz, DMSO) δ 9.24 (s, 1H), 8.86 (s, 1H), 8.58 (dd, *J* = 29.9, 4.7 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.46 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.19 (d, *J* = 3.2 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 1.14 – 1.05 (m, 3H)

^{13}C NMR (101 MHz, DMSO) δ 152.64 (s), 148.09 (s), 134.50 (s), 127.48 (s), 124.32 (s), 99.55 (s), 66.82 (s), 59.76 (s), 54.06 (s), 18.31 (s), 14.59 (s).

SYNTHESIS OF ETHYL 1,2,3,4-TETRAHYDRO-6-METHYL-2-OXO-4-(4-METHYLSULFONYL)PHENYL) PYRIMIDINE-5-CARBOXYLATE



^{1}H NMR (400 MHz, DMSO) δ 9.24 (d, *J* = 1.1 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.79 (s, 1H), 7.70 (dd, *J* = 8.5, 4.6 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 5.20 (d, *J* = 3.3 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.23 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ 165.79 (s), 152.57 (s), 150.81 (s), 149.27 (s), 147.42 (s), 146.37 (s), 137.68 (s), 130.00 (s), 127.36 (s), 126.31 (s), 125.40 (s), 121.59 (s), 99.35 (s), 59.72 (s), 54.44 (s), 18.31 (s), 14.55 (s).

CHAPTER 5: RESULTS AND DISCUSSION

All the eight dihydropyrimidinone derivatives were synthesised and characterised successfully. The corresponding NMR are attached in the appendix. Molecular Docking was performed with AutoDock Vina, where docking scores were obtained. Visualization of the docked poses was carried out with the help of DSV BIOVIA, high-quality images generated are provided below. From the analysis, it was seen that the ligands formed strong interactions with the receptor residues. Strong hydrogen bonding with crucial hinge residue Ala173 was observed along with hydrogen bonding with other residues Lys122, Asp234 and hydrophobic interactions. Hydrogen bond lengths formed were 3-3.2 Å. These significant interactions explain the highly negative docking score. Docking scores and drug-likeness data is given in the table given below. LogP values also fall in the range of < 5 suitable for drug-like property. Compound 4c, bearing the methyl sulfonyl group exhibited highest docking score which can be interpreted from the fact that it bears 5 hydrogen bond acceptor sites, the highest amongst all. Hydrogen bonds were formed with Asp 234, Ala 173 and Lys 103 residues. The pyrimidine bearing scaffolds 4b and 3b also exhibited appreciable binding scores owing to the interactions with Glu 220, Lys 122, Ala 173 residues. Overall, the compounds synthesized have the potential to be viable drug candidates.

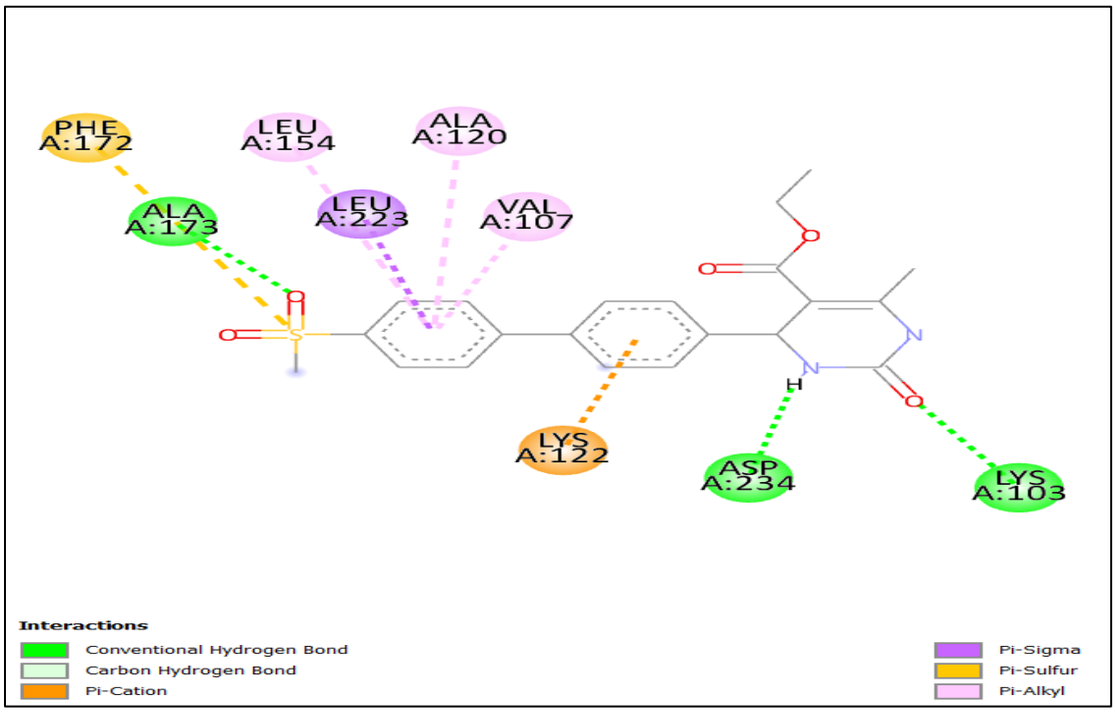


Fig. 5: Ligand Interaction diagram for compound 4c

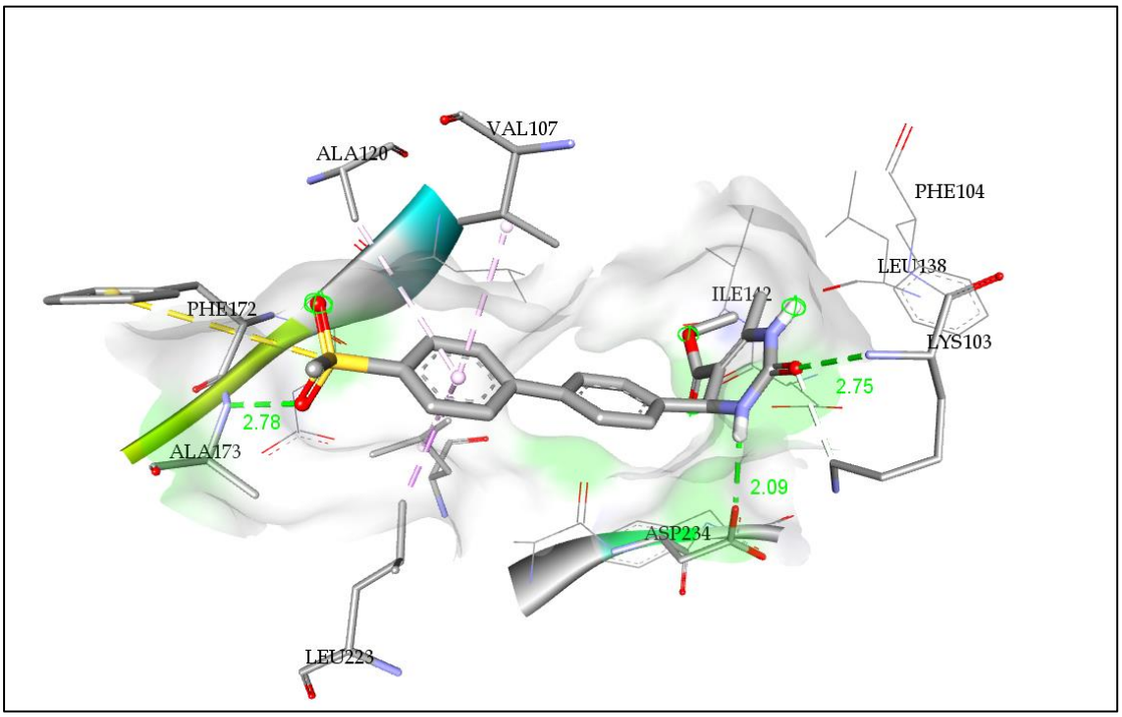


Fig. 6: Molecular Docking based binding pose of compound 4c in 4C2V.

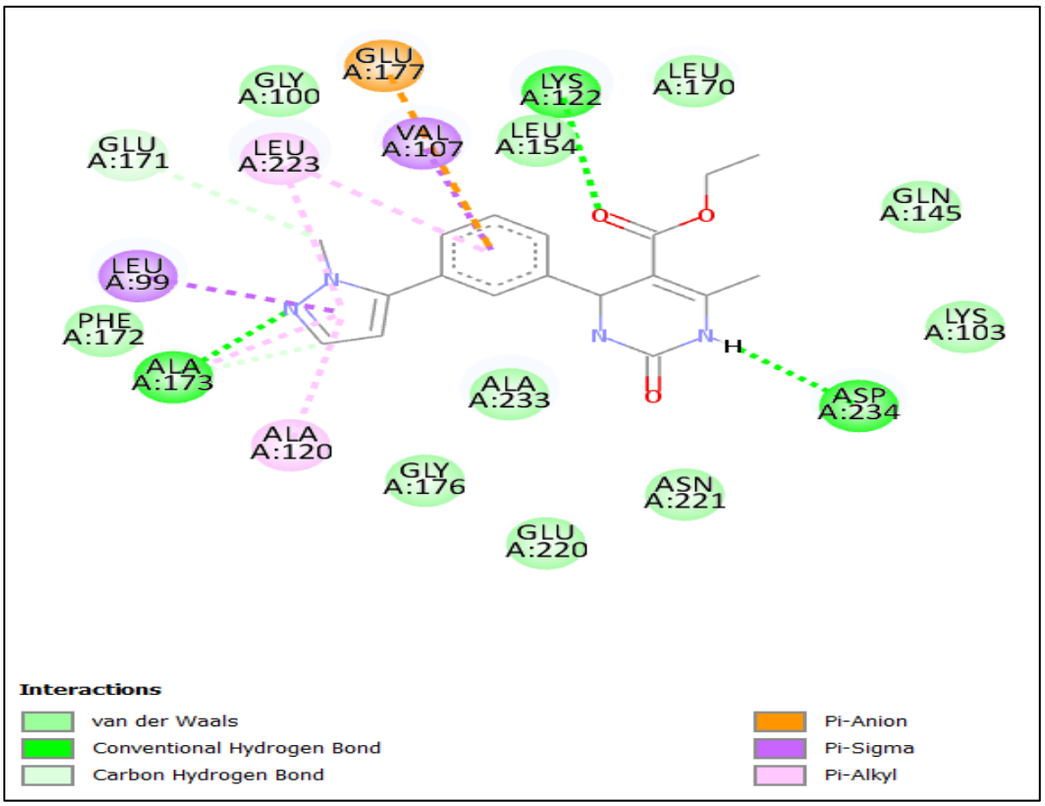


Fig. 7: Ligand interaction for compound 3c

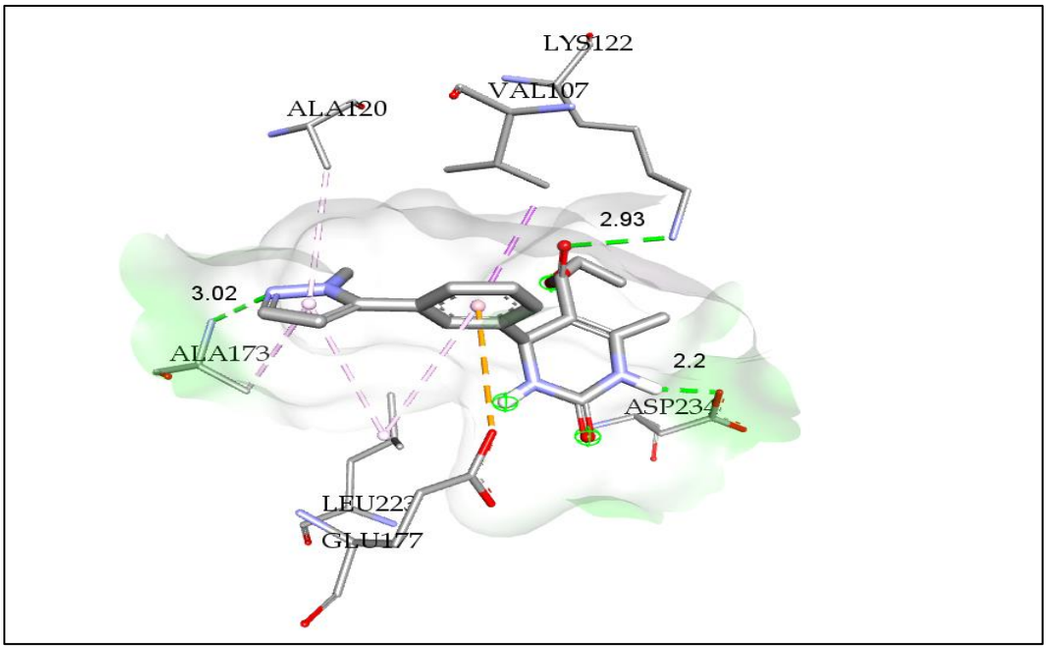


Fig. 8: Molecular docking predicted pose for compound 3c

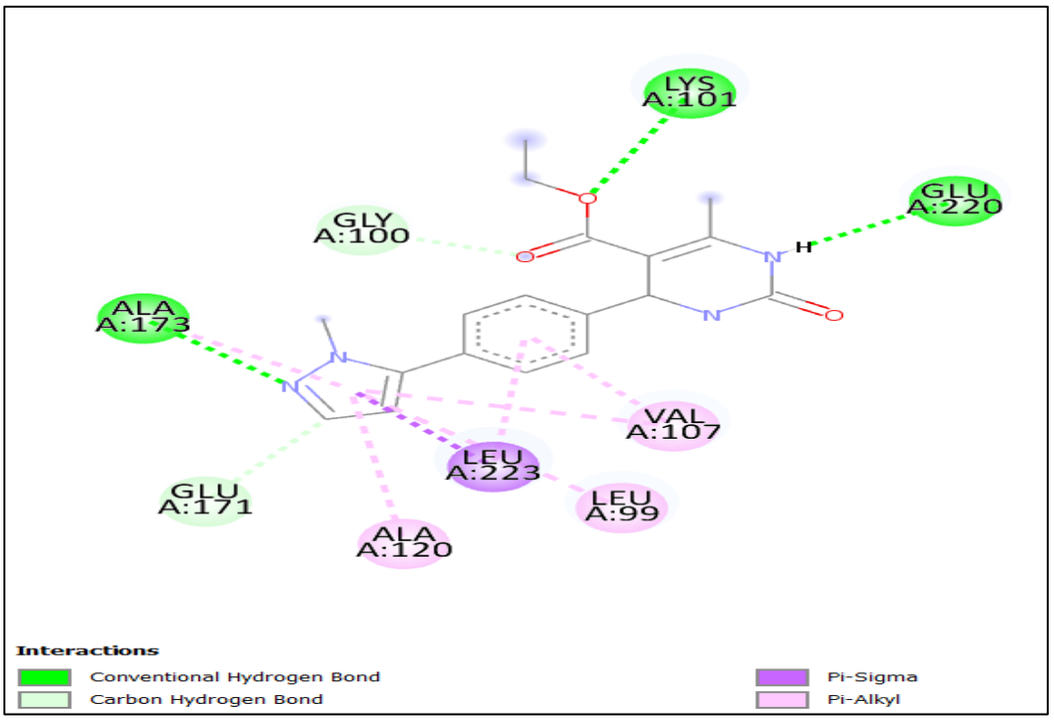


Fig. 9: Ligand interaction for compound 4a

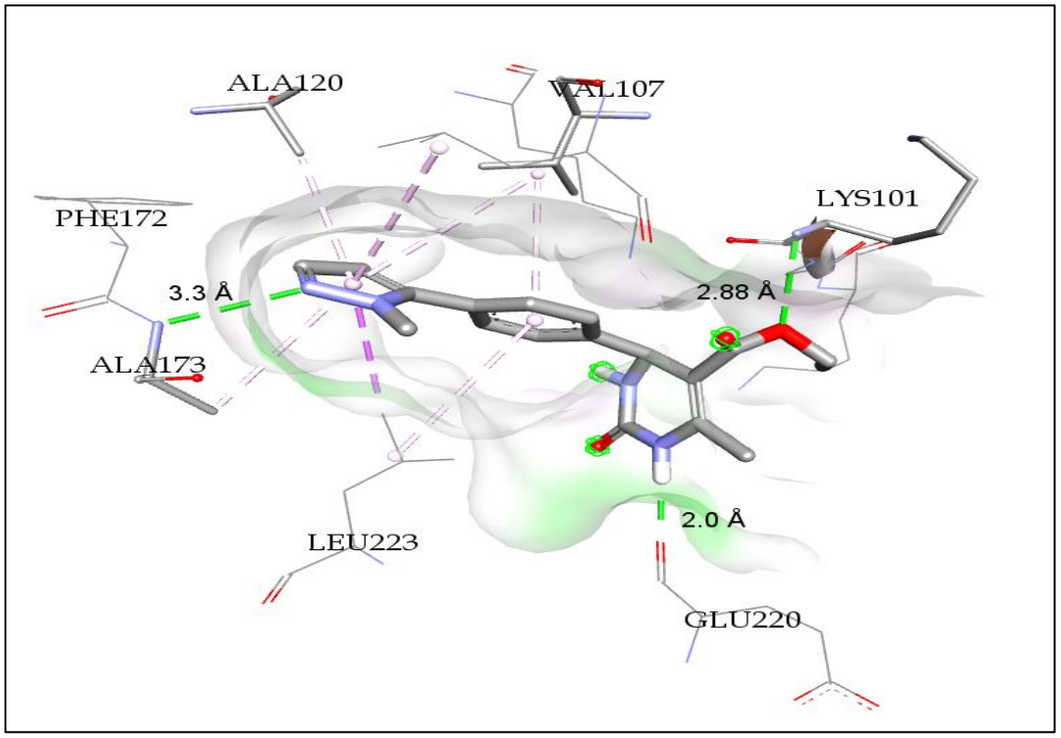


Fig. 10: Molecular docking predicted pose for compound 4a

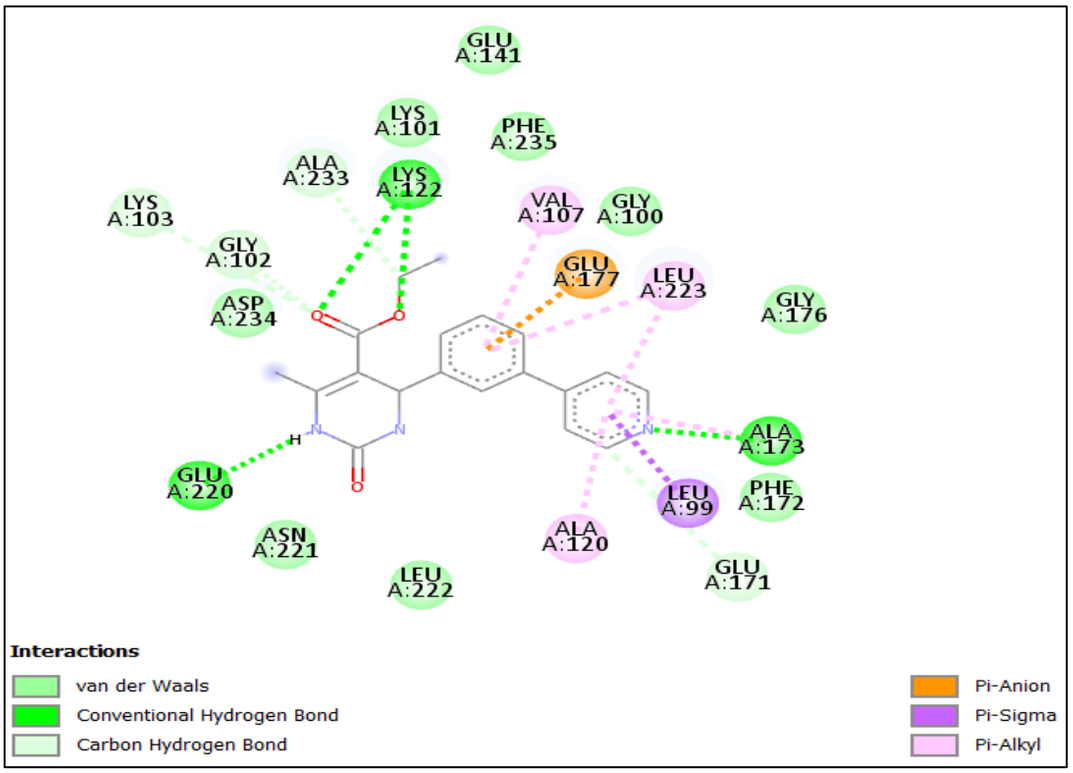


Fig. 11: Ligand interaction diagram for compound 3d

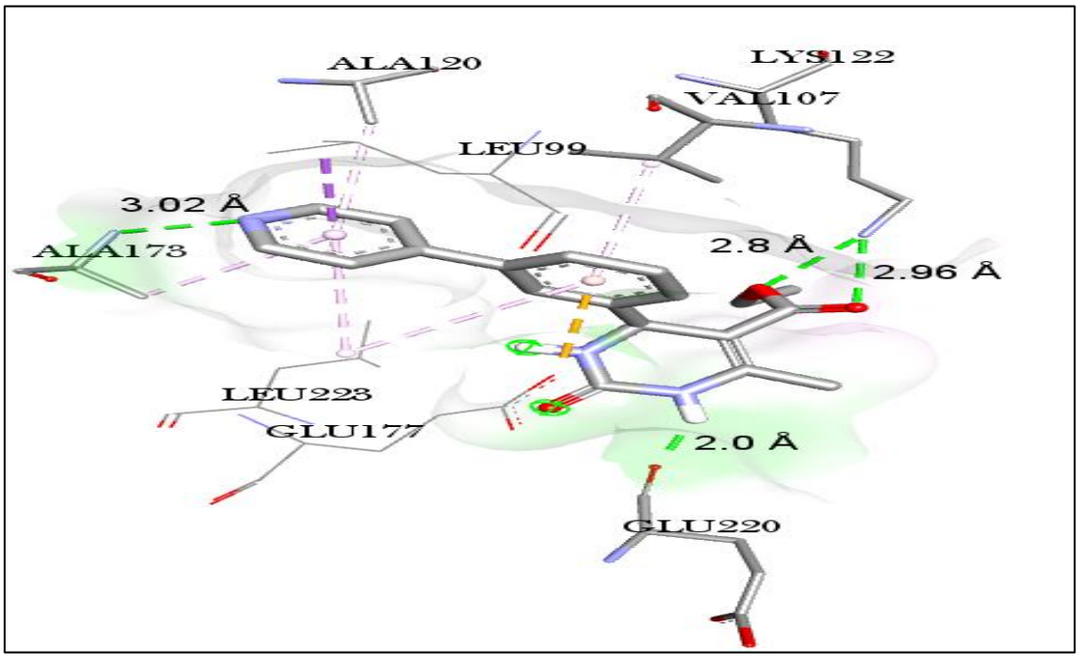


Fig. 12: Molecular docking predicted pose of compound 3d

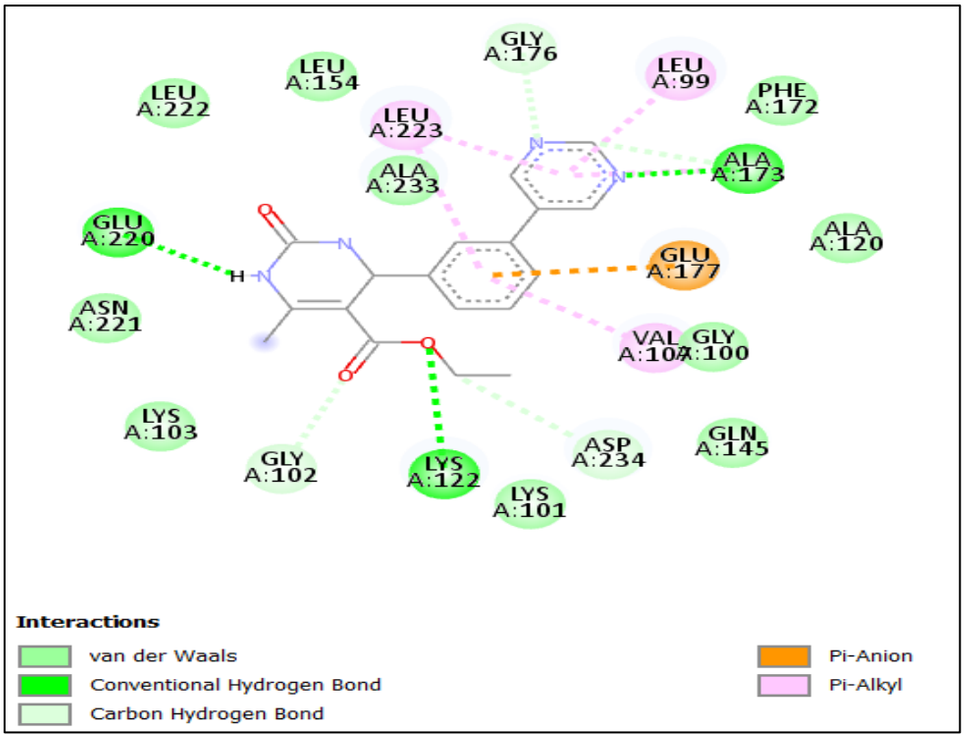


Fig. 13: Ligand interaction diagram for compound 3b

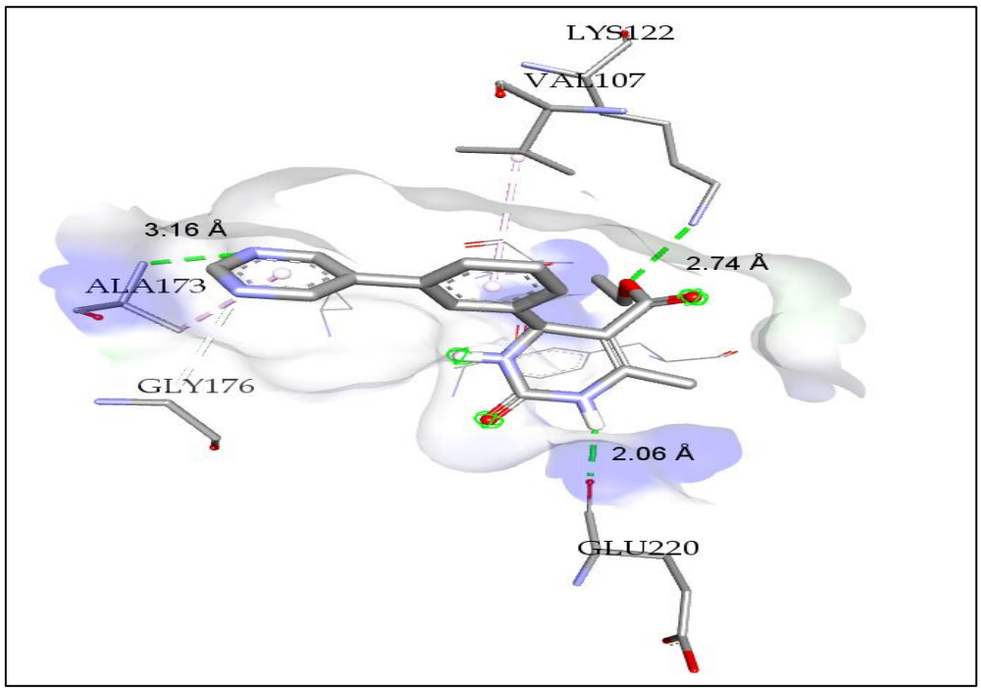


Fig. 14: Molecular docking predicted binding pose for compound 3b

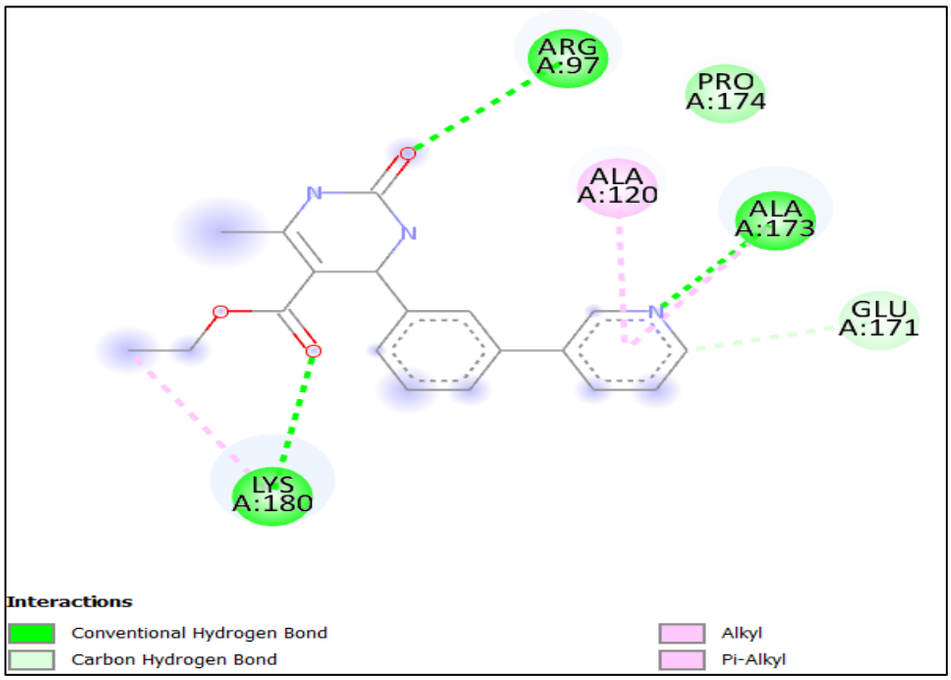


Fig. 15: Ligand interaction diagram for compound 3a

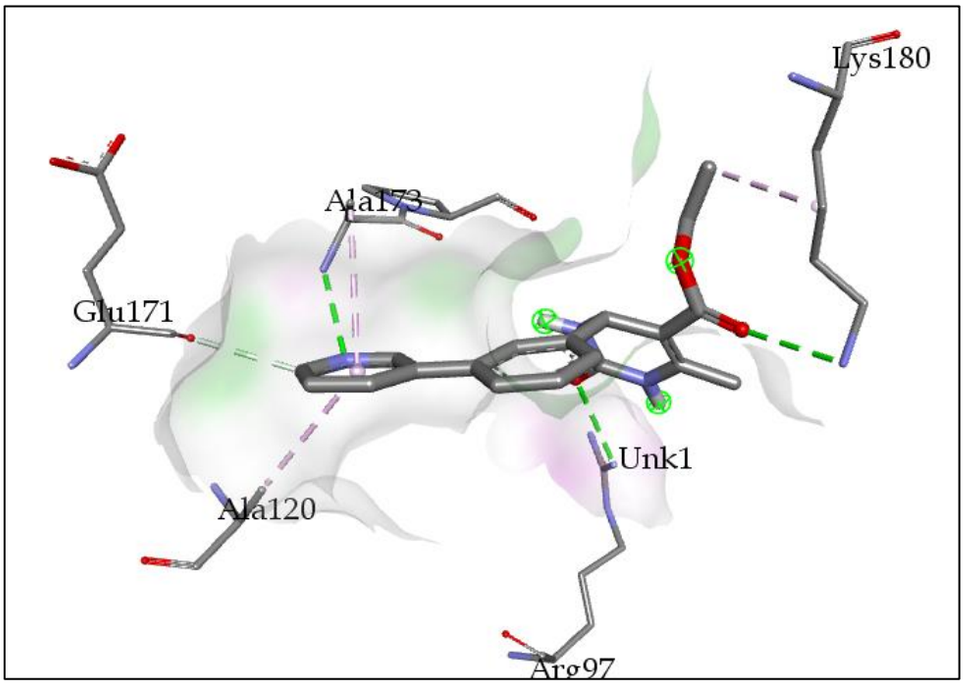
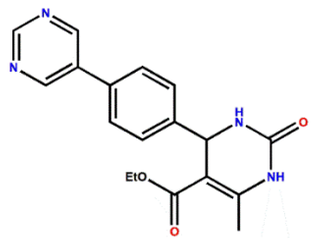
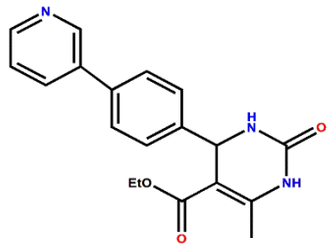
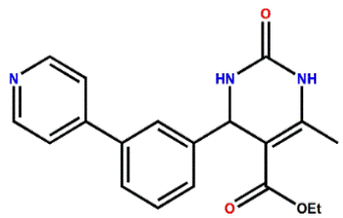
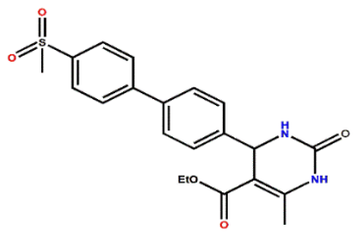


Fig. 16: Molecular docking predicted pose for compound 3a

Sl.No	Structure	Mol wt.	Docking score	HBA	HBD	LogP
1.		338.14	-8.3	5	2	1.07
2.		337.14	-8.2	4	2	2.07
3.		337.14	-8.03	4	2	2.32
4.		414.12	-9.6	5	2	2.30

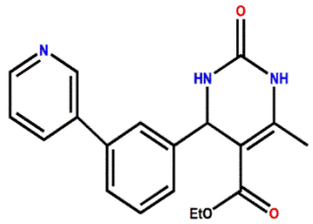
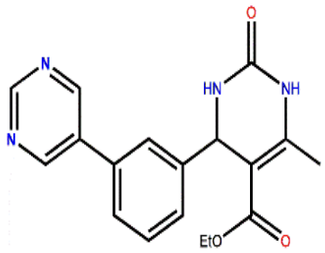
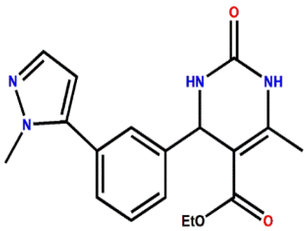
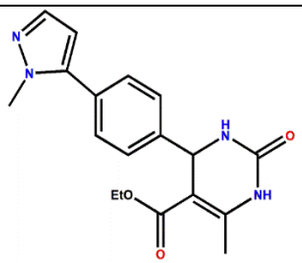
5.		337.14	-8.08	4	2	2.22
6.		338.14	-8.6	5	2	1.22
7.		340.15	-8.09	4	2	1.71
8.		340.15	-8.06	4	2	1.61

Table 2: Docking Result Analysis

CHAPTER 6: SUMMARY AND CONCLUSION

Tackling diseases with inherent complex nature such as cancer remains a big challenge in medical science. Owing to its non-invasiveness, selective nature of targeted therapies in contrast to conventional chemotherapeutic agents, targeted therapeutic drugs have come into focus and are being developed with sparked interest. Small-molecule targeted drugs continues to be the mainstream in cancer treatment because of their unique advantages (small enough to enter cells easily) despite the competition from macromolecule drugs. So, synthesising small molecule scaffolds having anticancer activity will continue to be of interest. Also employing one pot synthesis of the compounds via MCR makes the process easy and efficient, yielding our desired product in reduced number of steps. Prolonged use of a drug causes the genes to mutate which remains as the main cause of drug resistance. So, there is an ever growing need to synthesise new molecules for the mutated targets. Second line therapies for cancers which are resistant to previously approved drugs are underexplored. Dihydropyrimidinones are not much explored as kinase inhibitors although they have reported antitumoral, anti-inflammatory and anticancer activities. Novel Dihydropyrimidinone derivatives are explored here for potential anticancer activity. The heterocyclic core has been derivatised by incorporating pyridinyl, pyrazole, pyrimidine groups. Virtual screening of these dihydropyrimidinones identified them as viable drug candidates against Aurora B kinase. Appreciable docking scores were observed as pyrazole, pyrimidine groups served as hinge binders. Overall, the logP values and drug-likeness scores of these ligands further proves them to be a viable drug candidate.

CHAPTER 7: FUTURE WORK

The potency of the synthesized ligands can be evaluated by enzymatic assay inhibition studies. From a library of novel DHPM derivatives synthesized, compounds giving good binding scores are further advanced into enzymatic assay studies. The enzymatic assay will determine if the selected compounds are blocking Aurora-B kinase driven proliferation. Compounds which can block cell proliferation at nanomolar IC50 level could be certified as hits and can be further used a potential lead candidate.

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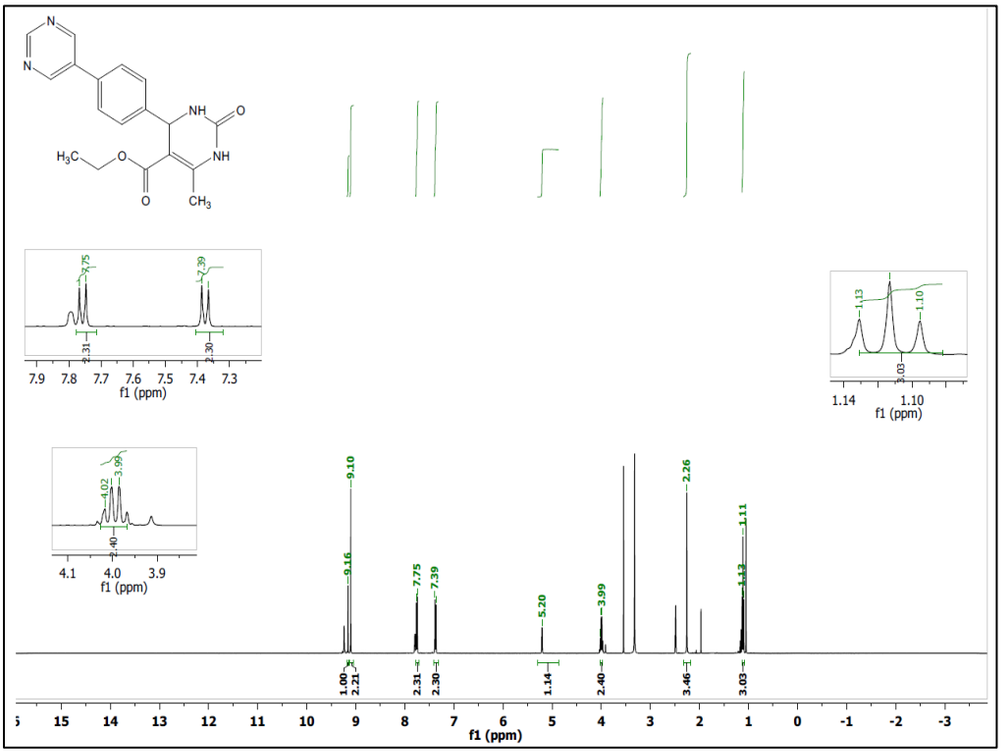
ANNEXURE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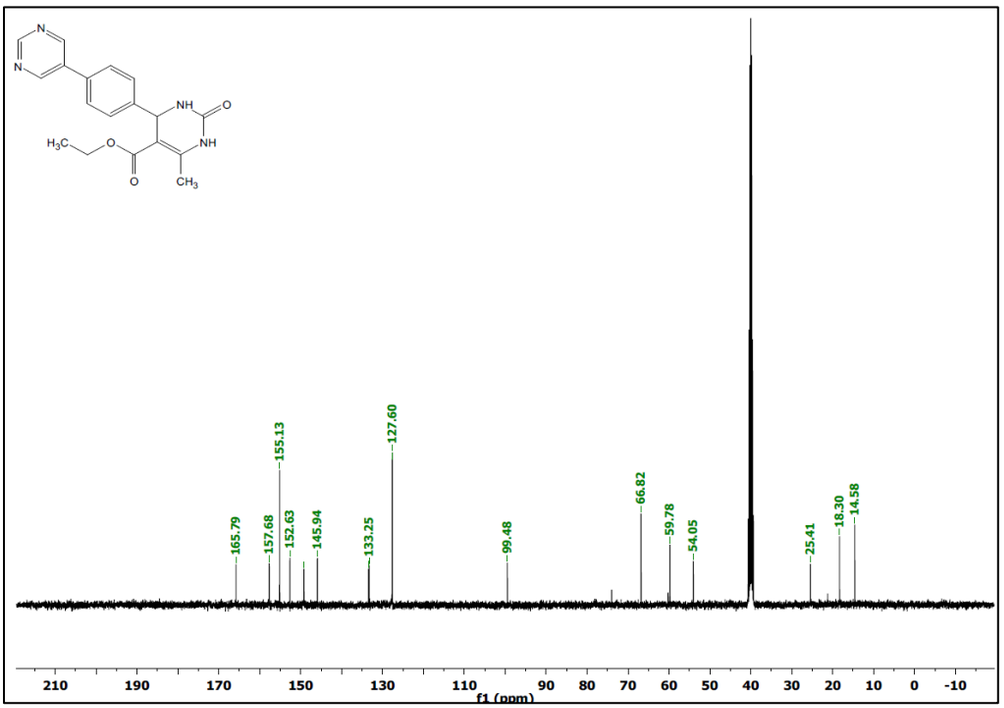
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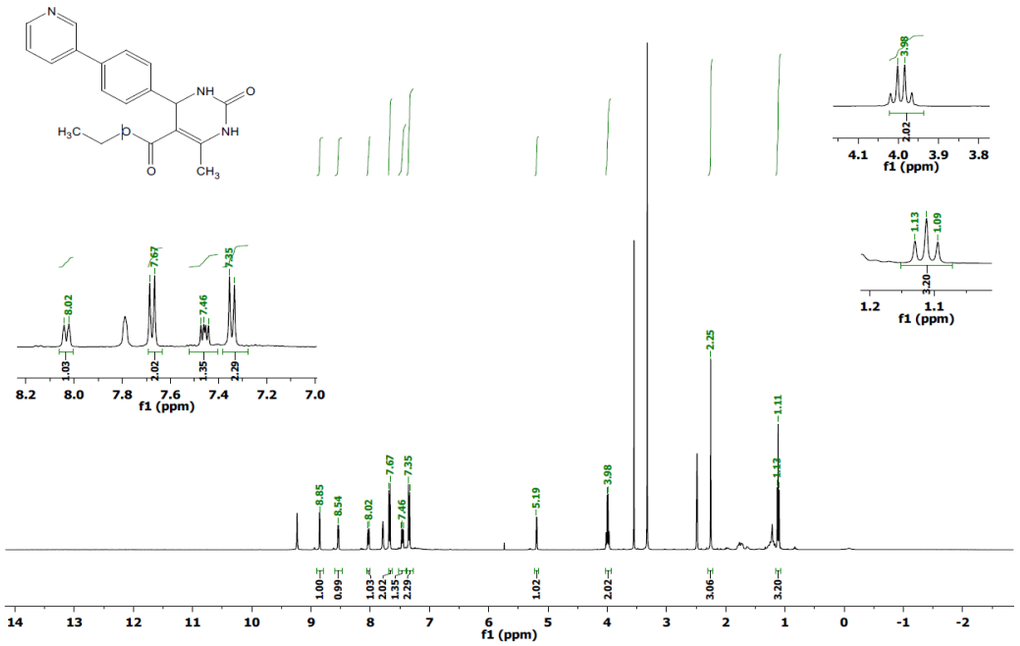
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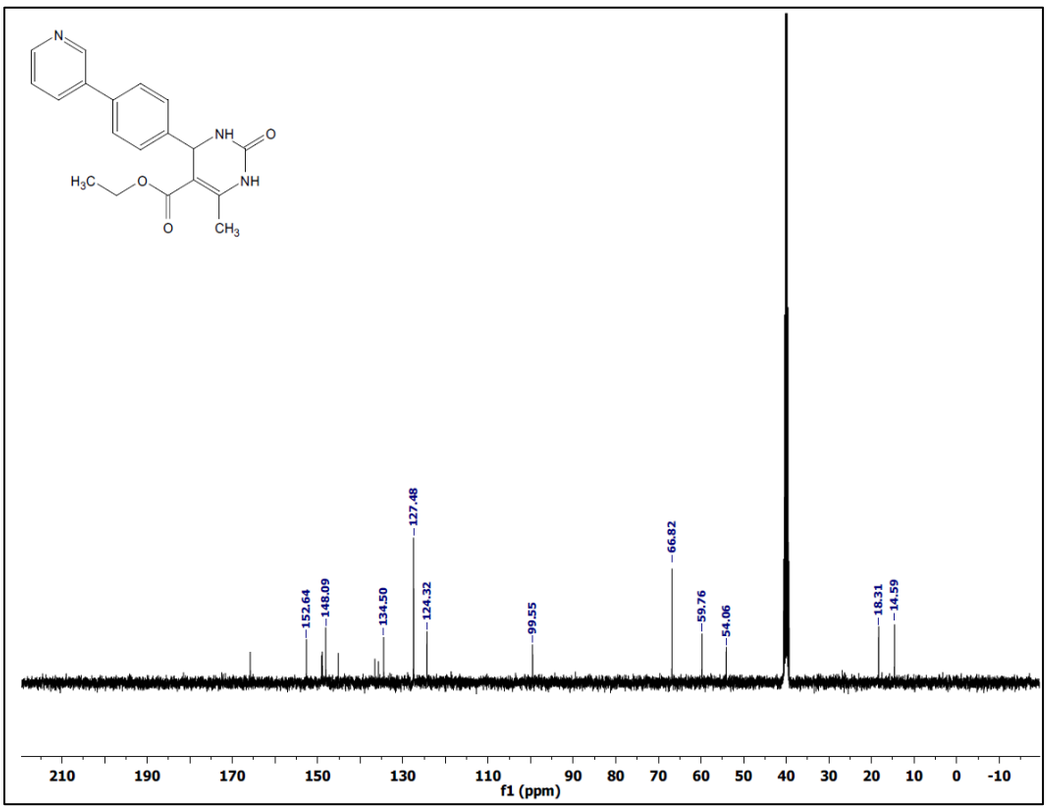
f1 (ppm)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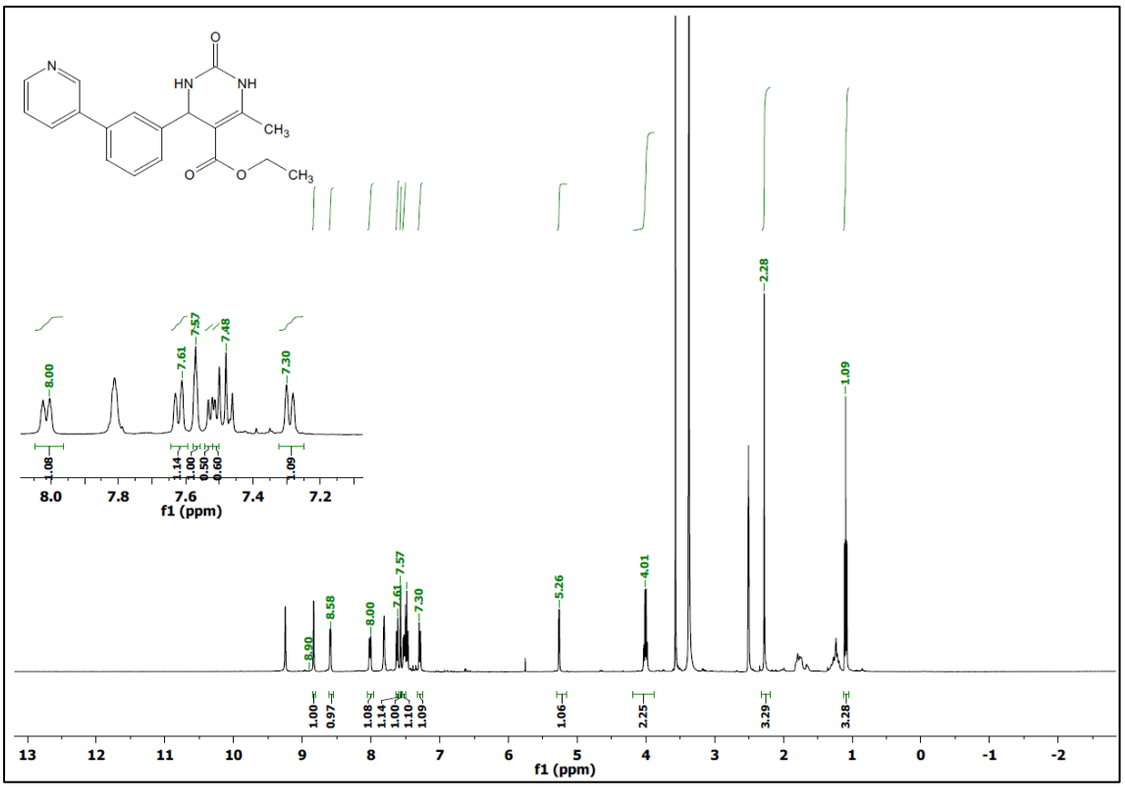
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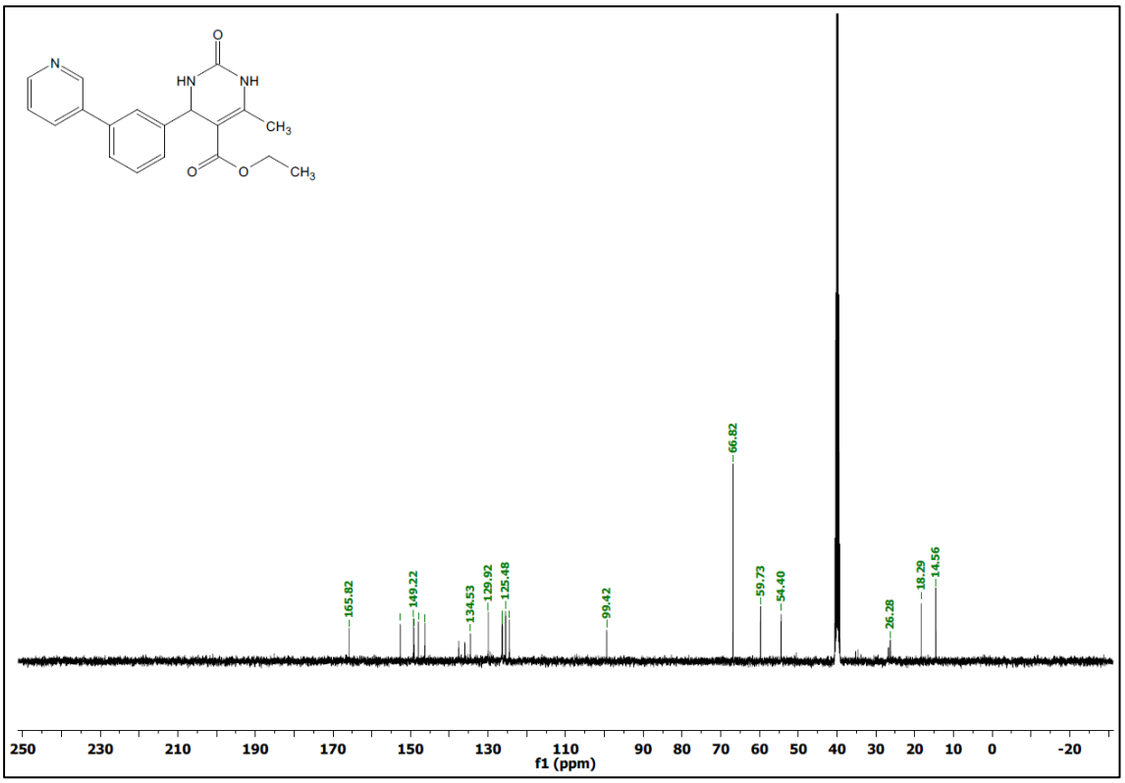
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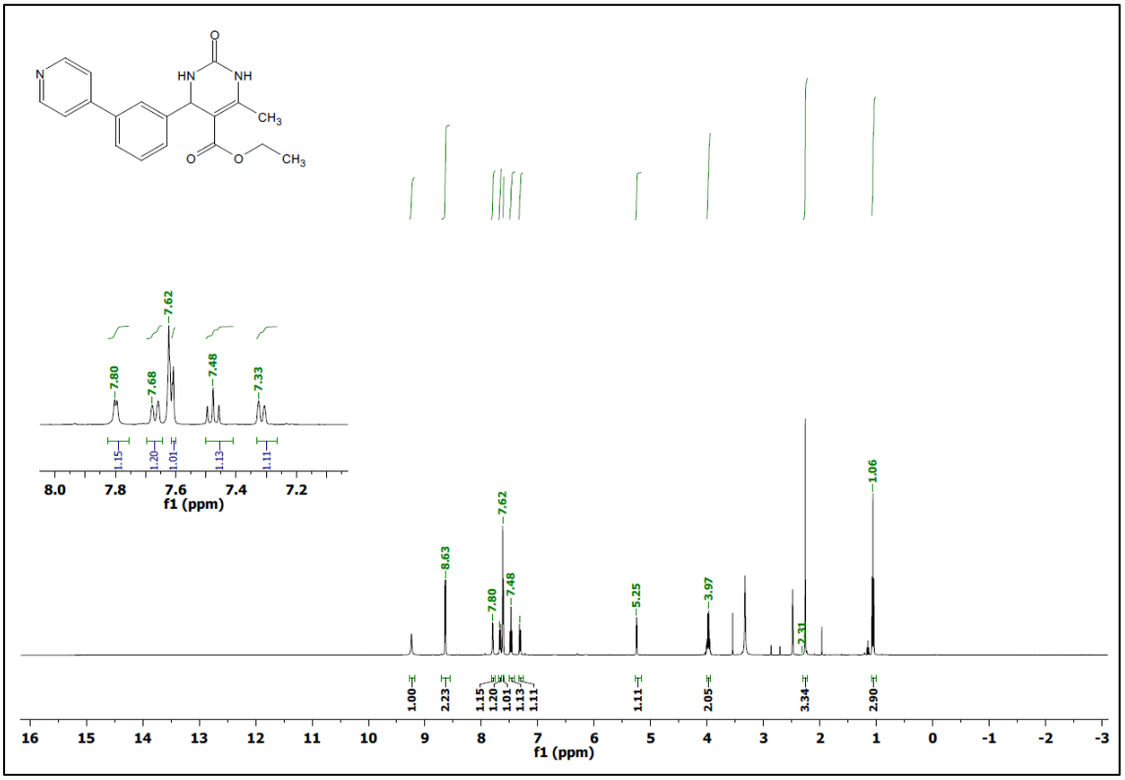
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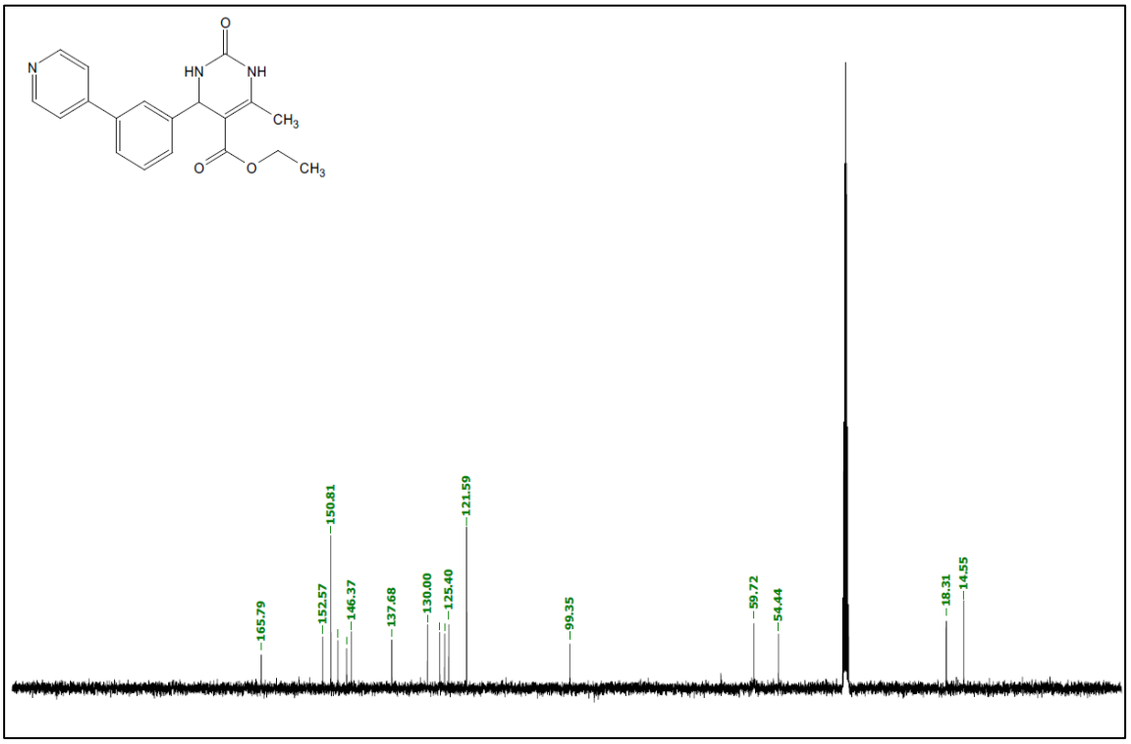
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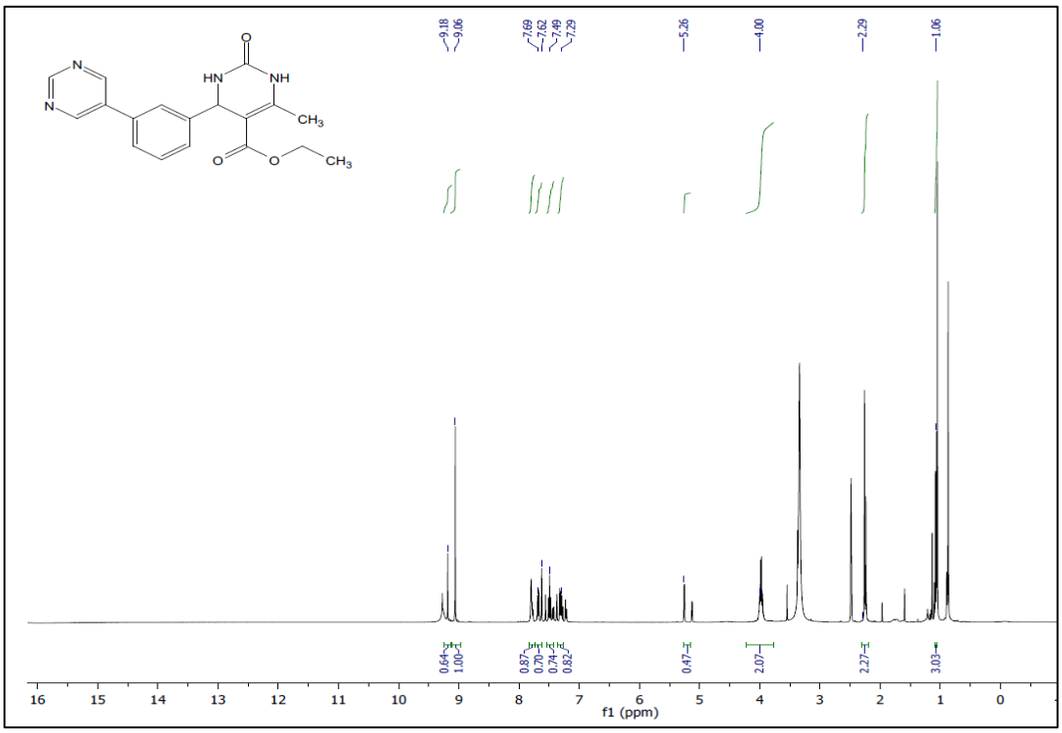
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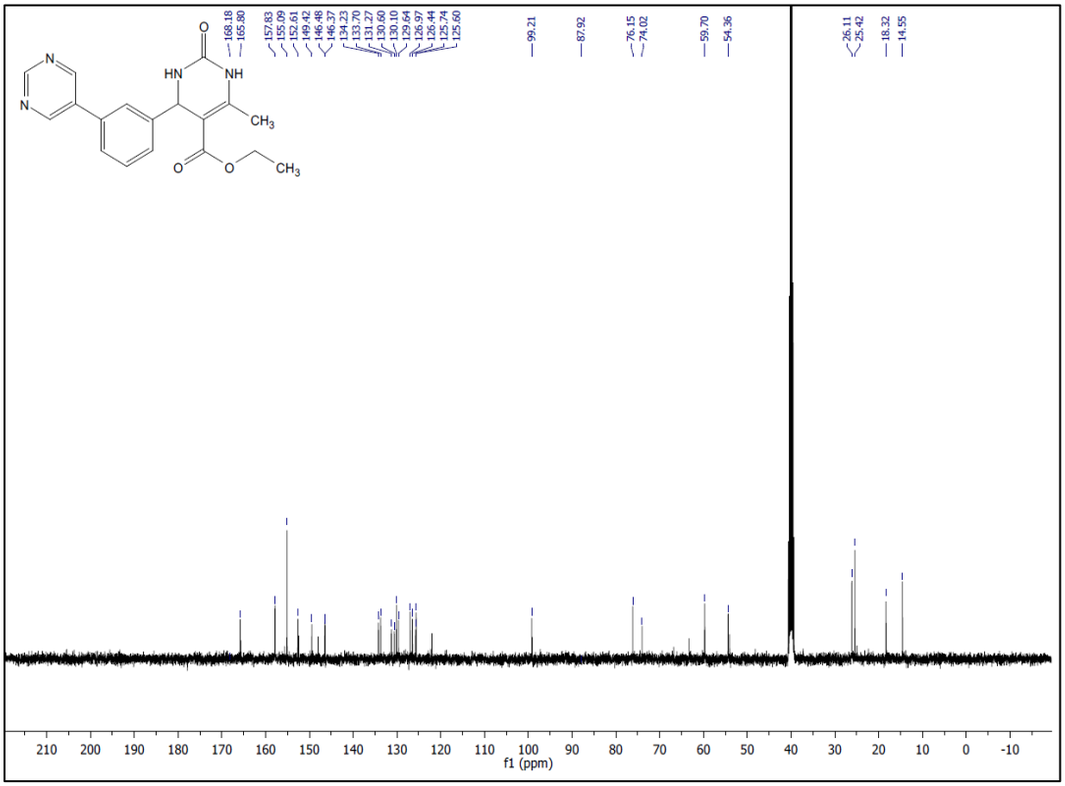
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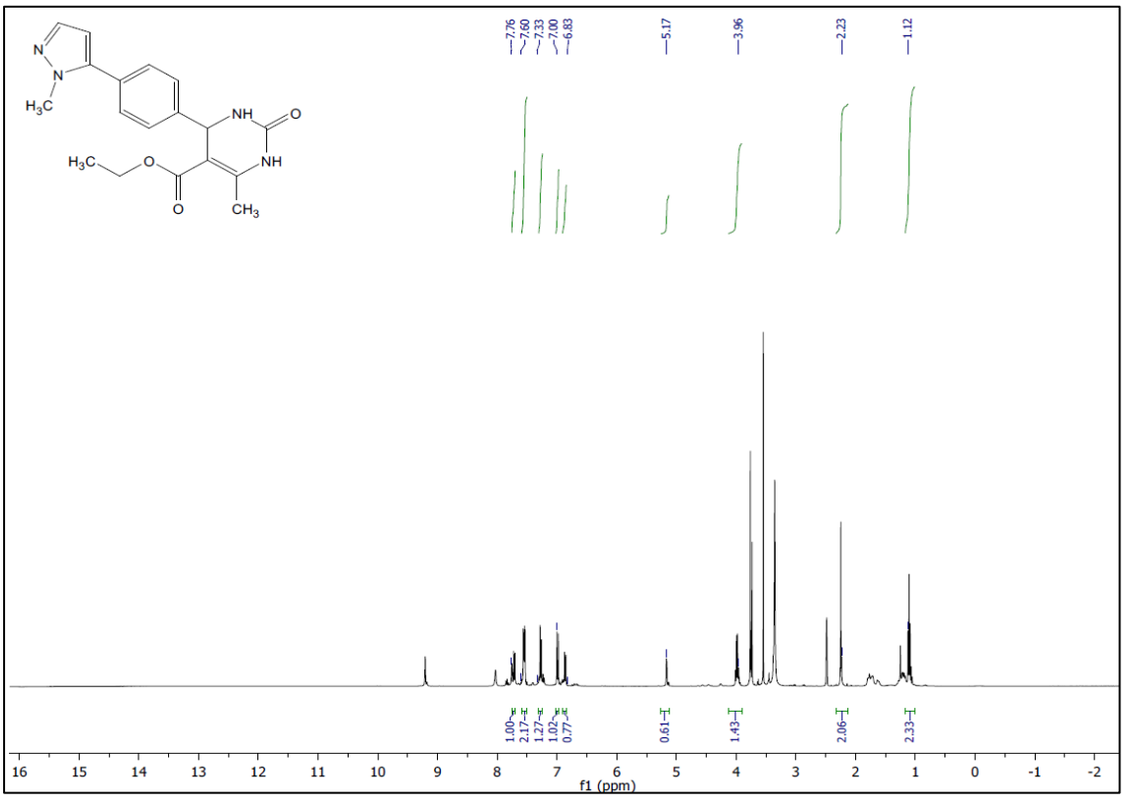
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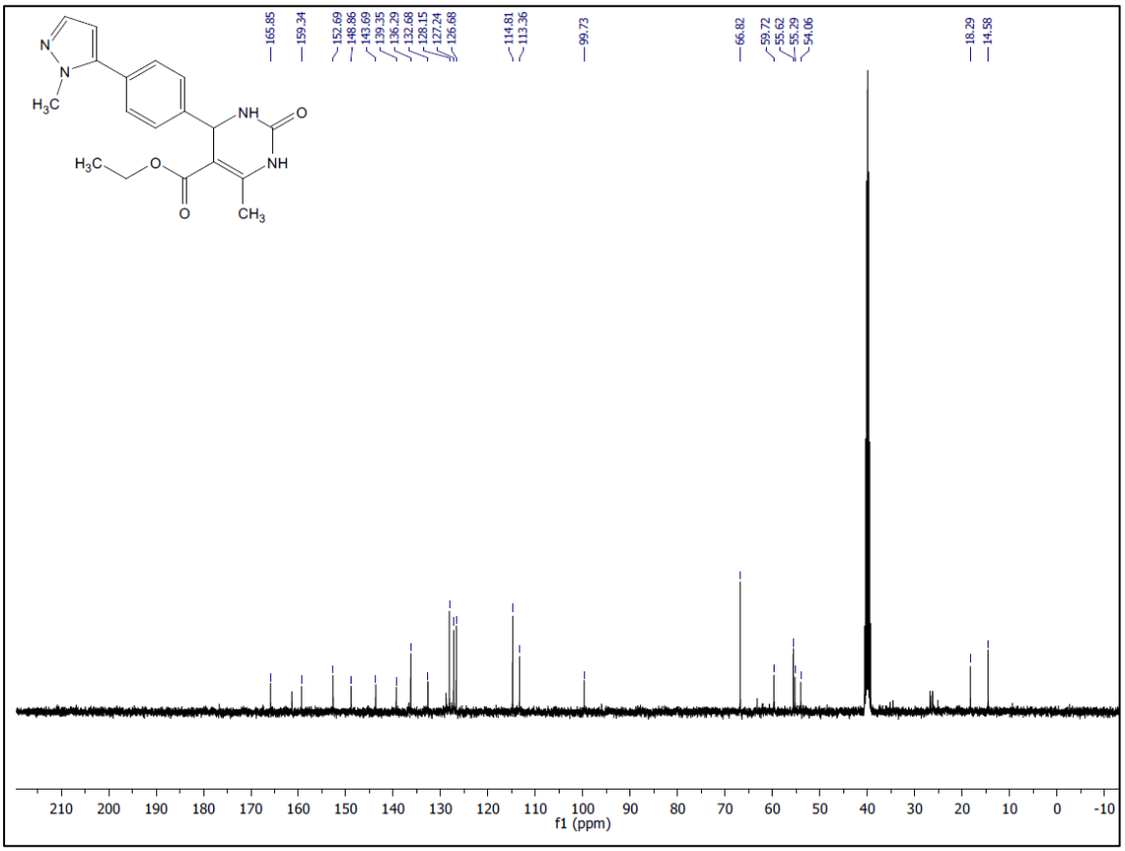
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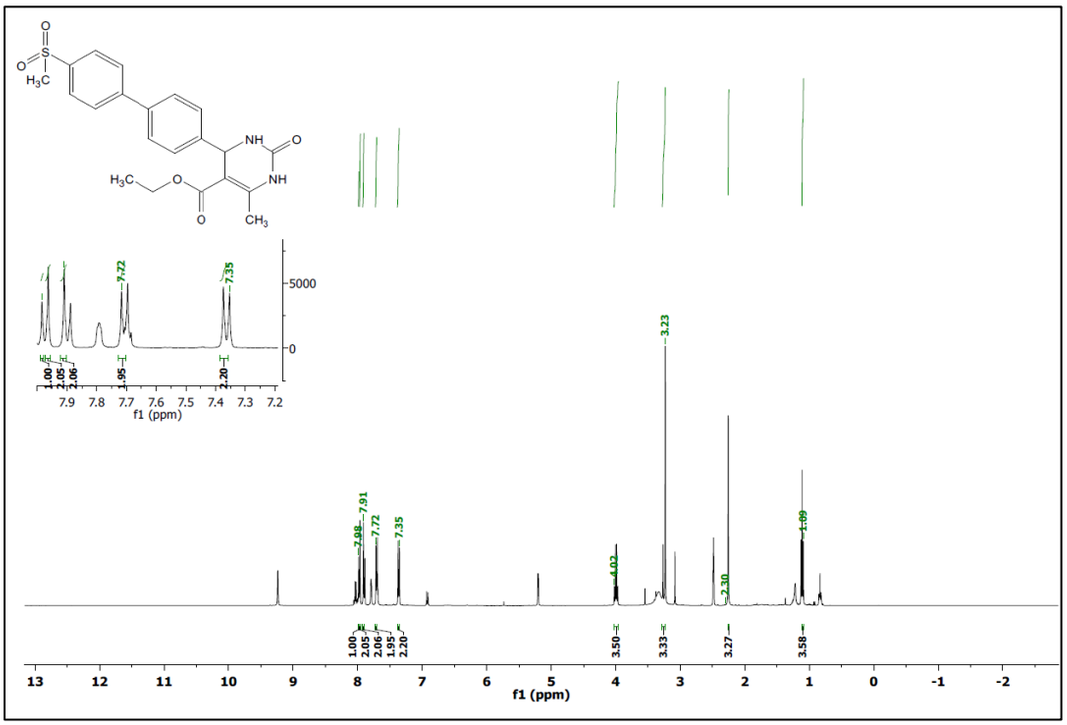
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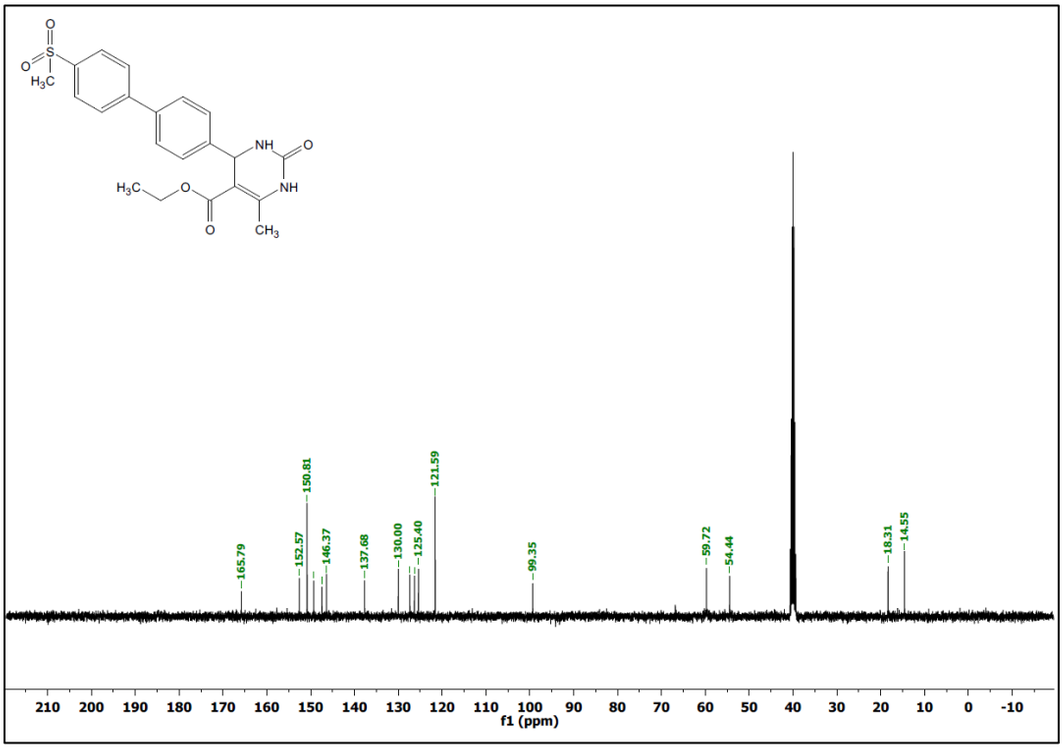
f1 (ppm)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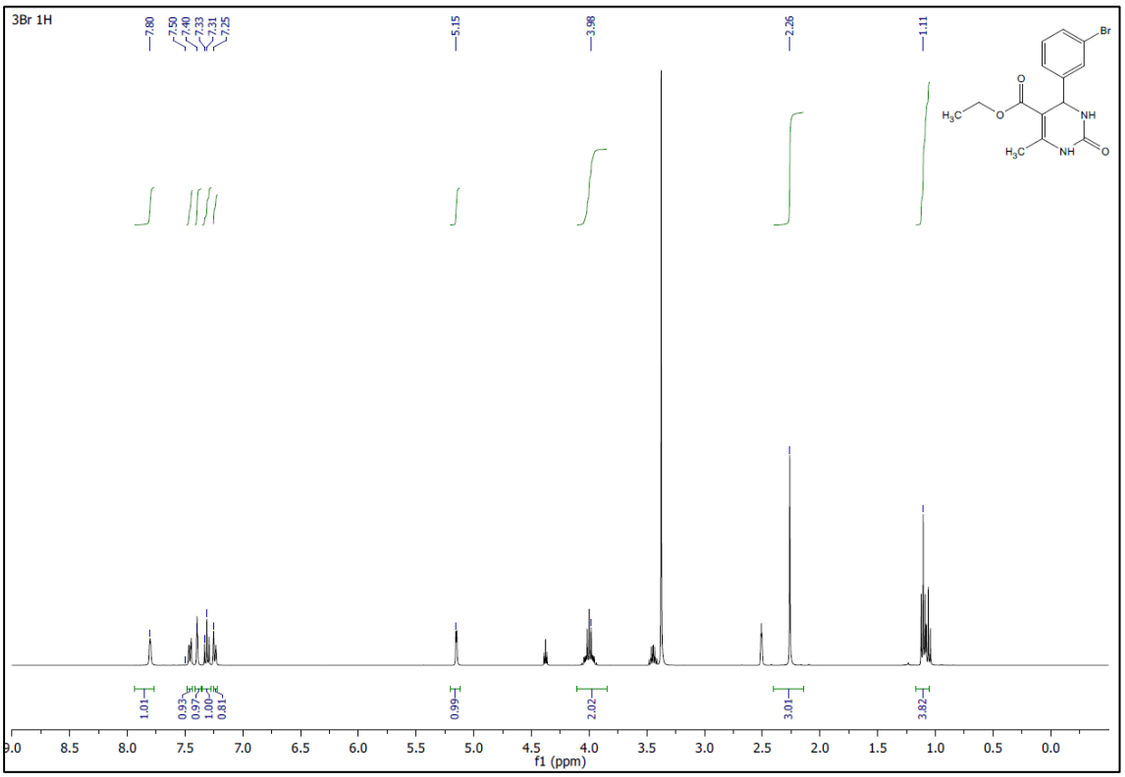
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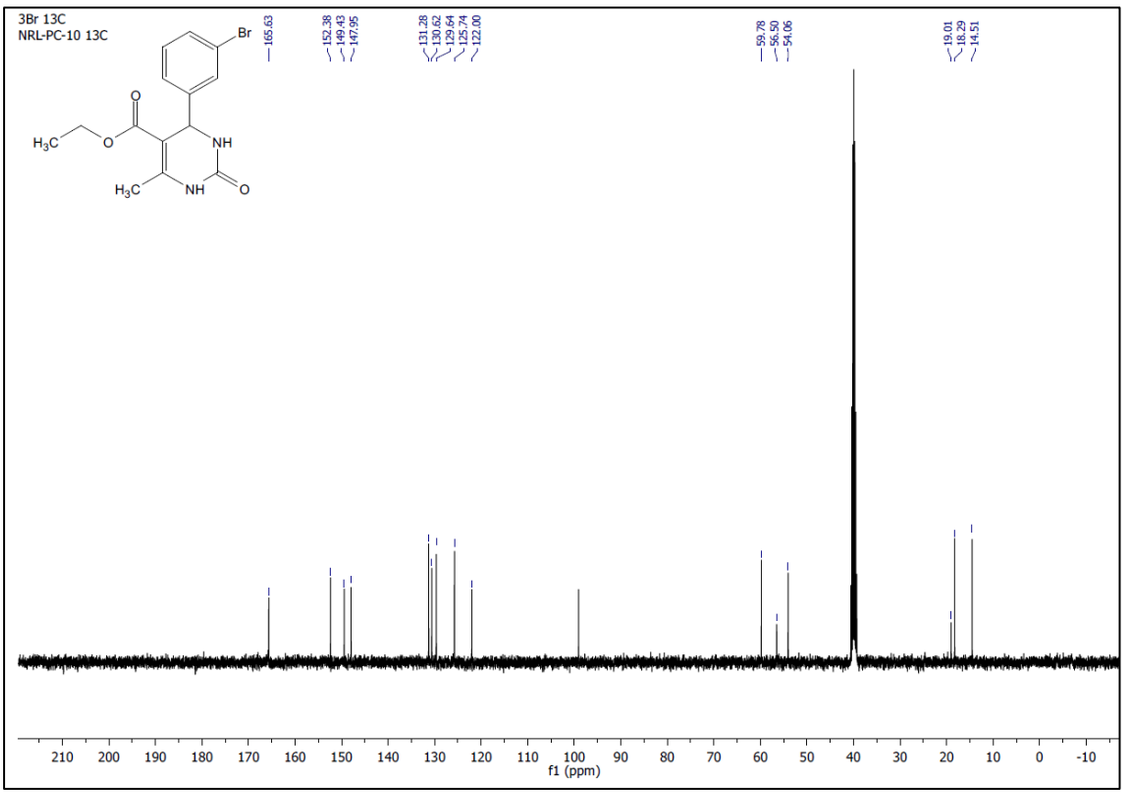
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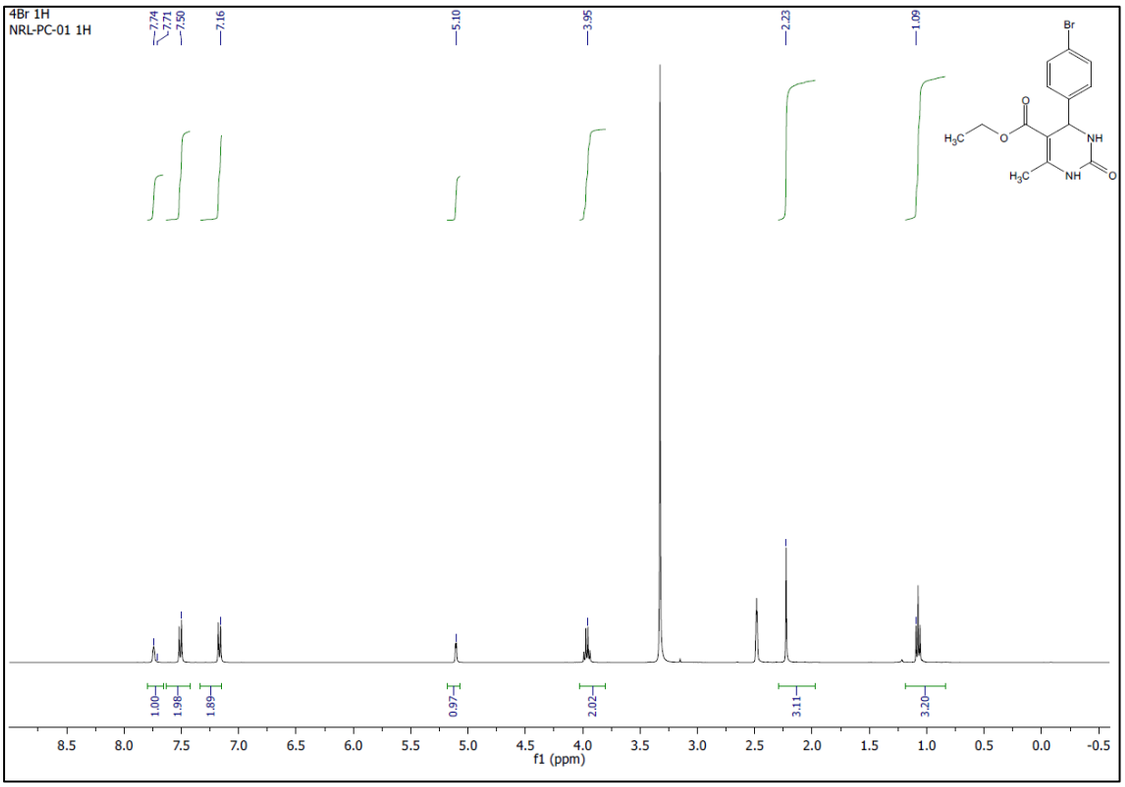
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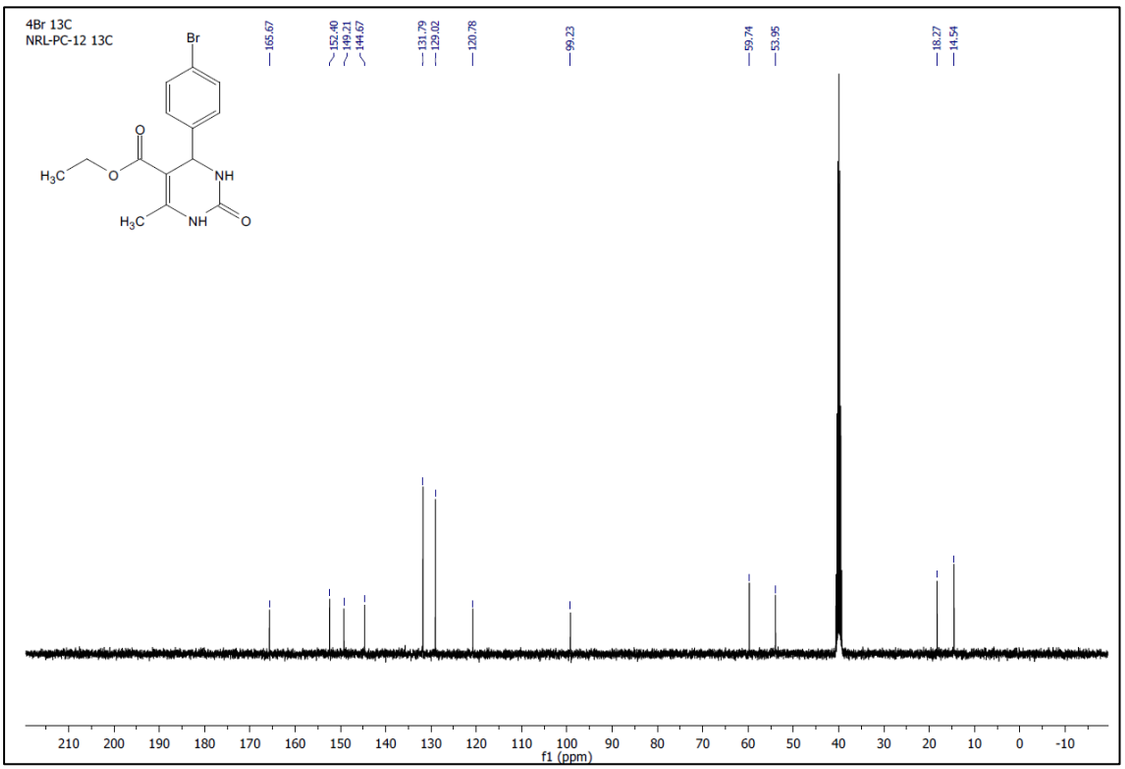
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SYNTHESIS AND MOLECULAR DOCKING OF MULTICOMPONENT REACTION (MCR) BASED HETEROCYCLES AS POTENTIAL KINASE INHIBITORS

BY

PRIYADARSHINI CHAUDHURI
(Admission No. 22MT0252)

DISSERTATION

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