# SYNTHESIS SOME OF HETROCYCLIC ORGANIC MOLECULES AND THEIR BIOLOGICAL ACTIVITIES

**A**
**THESIS**
**SUBMITTED TO**

**GALGOTIAS UNIVERSITY**
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IN FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

**DOCTOR OF PHILOSOPHY**
**IN**
**CHEMISTRY**

**By**

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**JULY-2018**

## CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis, entitled **"Study and Synthesis of some class of Heterocyclic Organic Molecules and for its Biological Activity"** in fulfillment of the requirements for the award of the degree of Doctor of Philosophy in Chemistry and submitted in School of Basic and Applied Sciences Galgotias University, Greater Noida is an authentic record of my own work carried out during a period from JULY, 2015 to JULY, 2018 under the supervision of Prof.(Dr.) ARVIND KUMAR JAIN and Prof.(Dr.) IMRAN ALI

The matter embodied in this thesis has not been submitted by me for the award of any other degree of this or any other University/Institute.

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This is to certify that the above statement made by the candidate is correct to the best of our knowledge.


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# ABSTRACT

The first part of my thesis describes the preparation of Key Starting Materials (KSM) for the synthesis of biologically active heterocyclic molecules and exploration of its activity, Its includes the optimization of reaction conditions such as solvent selection, reagent selection, base selection molar equivalents selection, temperature conditions and purification method of products. Hence we have prepared the following key starting materials for the following compounds to explore to synthesis of our desire molecules and we have developed new, industrially viable, less hazardous, eco-friendly, lower cost one pot process for the preparation of targeted molecules. The entire compounds were characterized by 1H NMR, 13C NMR, Dept. and Mass Spectroscopy.

The Main Key Starting materials are given below.

1. **6-Chloro uracil**
2. **Moc-L-Valine**
3. **6-Chloro-9H-Purine-2-amine**
4. **(1R,3S,4S)-tert-butyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate**

Second part describes the preparation of Uracil based derivative and its biological application

1. Preparation of Uracil based Moc-L-Valine derivatives: We have developed new molecules and new process for the first time to preparation of targeted molecules in one pot synthesis, In general and available literature hazardous chemicals like sodium hydride and DMF has been used for the preparation of targeted molecules and its dangerous to safety, environment and infrastructure, so we have replaced by very cheap easily available and eco-friendly potassium carbonate and whole synthesis was carried out by one pot synthesis (without any isolation steps involved) This leads to single solvent and base has been used for several steps without any isolation of intermediates, without isolation single steps process are more convenient and reduce effluent generation, reduce cycle time and reduced infrastructure requirement, so this process became very much

industrially viable, los cost and eco-friendly and close to green approaches. We have filed Indian patent application for this process and product preparation.

2. Preparation of Uracil based chloroformate derivatives: Synthesis of targeted molecules involves four steps. Benzylation of 6-chlorouracil followed by alkylation, third step involve n-substitution followed by formylation the entire process was involved one pot synthesis, we have been used simple easily available inorganic base and single solvent have been used for the whole target molecule synthesis. We have filed Indian patent application for this process and product preparation.

3. Third Part descries the synthesis of 9H-purine substituted amino acids: Synthesis of 9 developed new protocol for the synthesis of new molecules and its process, in the protocol we have started synthesis from 6-chloro-9H-purine and different kind of amino acids by using water as a solvent and sodium carbonate as a base, this synthesis was very cheap, eco-friendly, industrial viable and green chemistry approach. We have been synthesized 11 molecules by this protocol and reported best synthetic process. Whole protocol not been used any hazardous reagents, solvents and reaction conditions. We have filed Indian patent application for this process and product preparation.

Fourth part describe the synthesis of methyl (S)-1-((1R,3S,4S)-3-(5-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate:

4. synthesis of methyl (S)-1-((1R,3S,4S)-3-(5-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptan-2-yl)-3-methyl-1-oxobutan-2-ylcarbamate are involve five steps, first step involve n-protection from 6-chloro-9H-purine, second step involve the Suzuki coupling, third step involve boc de protection fourth step involve amino acid coupling and fifth step involve de protection to obtained title compounds. We have reported first time the novel molecules and process for their preparations. These molecules are highly complex and have four chiral centers, there are 16 isomers are possible and we have controlled all the isomers during synthesis. We have filled Indian patent application for the novel molecules and their synthesis.

# ACKNOWLEDGEMENT

The Research work presented in this thesis would not been possible without my close association with many peoples. I would like to take this opportunity to extend my sincere thanks and appreciation to all those who made this PhD thesis possible.

First and foremost, praises and thanks to the God, the Almighty, for His showers of blessings throughout my research work to complete the research successfully.

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My sincere gratitude is reserved for **ProfessorRenu Luthra***Vice Chancellor, Galgotias University* for all required permission, support and for this thesis. I would say special thanks to ***Professor (Dr.) Bimal Sarkar***, *Dean School of Basic and Applied Sciences, Galgotias University* for his tremendous support during my PhD and thesis work.

*I would like to express special thanks to my supervisor* ***Prof. (Dr.) Arvind Kumar Jain*** *for his tremendous support and been tremendous mentor for me. I would like to thank you for introducing me to exciting field and always encouraging, motivating, enthusiasm and allowing me to do what I think and continuous support throughout my PhD, your advice and support have been invaluable. I have learned much knowledge from him and those helped me to including how to raise new possibilities, how to regard an old question from a new perspective, how to approach a problem by systematic thinking, data-driven decision making and exploiting serendipity. I owe him lot of gratitude shown me during the way of research. I am very glad to say that such a wonderful person associated with me.*

My special thanks also my research co-guide ***Prof. (Dr.) Imran Ali*** for his continuous support, encouragement, cooperation and facilitating all the requirements always. His constant support, guidance, motivation always pushing me forward. I always feel privileged to be associated with a person like him during my life.

I would like to thanks to my friends Mr. Dnyaneshwar Nighot, Mr. Nadeem Lone, Mr. Suhail and Mr. Rupak Raja for sharing knowledge's, supporting me for the field of work and giving worderful analytical support during my course of PhD.

I feel my deep gratitude my parents who introduced me in the world and I owe my deepest gratitude towards my better half for her eternal support and understanding of my goals and aspirations. Her love and support has always been my strength. Her patience and sacrifice will remain my inspiration throughout my life. Without her help, I would not have been able to complete much of what I have done and become who I am. It would be ungrateful on my part if I thank Anjammal these few words. I am thankful to my son Tarun and Varun for giving me happiness during my studies.

My special thanks to my all teachers because of unexpected teaching at different stages of education has made it possible for me to see this day. Because of their kindness I feel, was able to reach a stage where I could write this thesis.

As impossible always to mention everybody who had an impact to this work even though there are some people those whose spiritual support is even more important.

Thanks God for being with me always and providing all the strength, happiness and good health to carry out this study.

Thank you so much……

VADIVELAN R

## LIST OF PUBLICATIONS

1. Complete **Indian patent**, Application No.201811020947 "NEW PROCESS FOR THE PREPARATION OF NOVEL URACIL ERIVATIVES AND ITS DOCKING STUDY".Date of filing application 05/06/2018, **publication date: 22/06/2018**.
2. Complete **Indian patent**, Application No.201811020953 "HIGHLY EFFICIENT SYNTHESIS FOR THE PREPARATION OF NOVEL 9H-PURIN-2-AMINE DERIVATIVES". Date of filing application 05/06/2018, **publication date: 06/07/2018.**
3. **R.Vadivelan**, Dnyaneshwar Nighot, Arvind Kumar Jain and Imran Ali, one pot synthesis for preparation of highly pure 1-(4-Bromobenzyl)-3-Methyl-6-(Piperidin-1-Y1) Pyrimidine-2,4(1H,3H)-Dione"**International Conference on Advancements in Science & Technology ICAST2017."**
4. Arvind Kumar Jain, Dnyaneshwar Nighot, **R. Vadivelan**, Sunil Jadhav Imran Ali, Di-μ-iodidobis[2,2'-bis(diphenylphosphanyl)-1,1'-bina phthyl,]copper(I) catalyzed Sonoghashira reaction **INROADS** (International Conference **IAET-2016, 5, 1, 215-217**, DOI: 10.5958/2277-4912.2016.00041.2
5. Dnyaneshwar Nighot, Arvind Kumar Jain, **R. Vadivelan** and Imran Ali, Preparation of (Z)-5-((2-mercaptophenylimino)methyl)-2-methoxy phenol Copper complex and its use for Palladium free Coupling of Aryl Iodide and Alkynes "**International Conference on Advancements in Science & Technology ICAST2017."**
6. Arvind Kumar Jain, Dnyaneshwar Nighot, **R. Vadivelan**, Sunil Jadhav Imran Ali, **Green protocol for sp-sp2 coupling of Aryl Iodide and alkynes using Copper Carbonate: Facile synthesis of Aryl alkynesINROADS** (International Conference **IAET-2018,.**
7. **R.Vadivelan**, Nadeem Lone, Arvind Kumar Jain and Imran Ali, High Efficient Inexpensive Synthesis of Uracil Derivatives: Characterization, DNA Binding and Docking Studies **Communicated to Journal of Molecular Structure.**

8. **R.Vadivelan**, Nadeem Lone, Arvind Kumar Jain and Imran Ali, Synthesis of New Uracil based chloroformate Derivatives and it's Characterization, DNA Binding and Docking Studies, to be **communicated.**

9. **R.Vadivelan**, Mohamed Suhail, Arvind Kumar Jain and Imran Ali, An Efficient synthesis for the preparation of novel 9H-purin-2-amine substituted amino acid derivatives, to be **communicated.**

## ABBREVIATIONS

| | |
|---|---|
| CDCl3 | Deuterated chloroform |
| d | Doublet |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| EtOAc | Ethyl acetate |
| CDI | N,N' carbonyldiimidazole |
| KOAc | Potassium acetate |
| hr. | Hour |
| m | Multiplet |
| M | Molar concentration |
| MeOH | Methanol |
| t-BuOH | Tertiary butanol |
| Min. | Minutes |
| NMR | Nuclear magnetic resonance |
| t | Triplet |
| Equi. | Equivalents |
| HATU | 1-[Bis9dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate |
| q | Quartet |
| MDC | Methylene dichloride |
| Temp. | Ttemperature |
| HNMR | Proton Nuclear Magnetic Resonance |
| CNMR | Carbon Nuclear Magnetic Resonance |

## LIST OF CONTENTS

# 1. INTRODUCTION

## 1.1 URACIL BASED DRUG MOLECULES AND ITS ACTIVITIES.

### 1.1.1 GENERAL INFORMATION

In four among the nucleobases uracil is one of the most important nucleobases in the RNA nucleic acid and that are noted by the letters A (adenine), G (guanine), C(cytosine ) and U (Uracil). The new type synthesis of heterocyclic compounds has always been a subject of great interest due to their wide applicability. Heterocyclic compounds occur vary widely in nature and are essential to life. Amongst a large variety of heterocyclic compounds, heterocycles containing uracil moiety are interest because they show some pharmacological and biological activities. Uracil and its derivatives are the important key starting material for the preparation of many organic molecules, drug substances and drug intermediates.Uracil derivatives are an important and useful task in organic chemistry. Tegafur-uracil is a chemotherapy drug used in the treatment of cancer, primarily bowel cancer.

Uracil based derivatives were reported to possess anti-viral[1] [2] [3] [4], anti-diabetics[5][6], anti-tumor [7][8], antibacterial[9], antifungal [10][9], antidepressant [11] and anti-retroviral[12][13][14] activities. Thus, the synthesis of uracil derivatives is an important and useful task in organic chemistry. In recent years, the synthesis of uracil derivatives has been reported. In continuation of our efforts to explore newer reactions for the synthesis of heterocyclic compounds, we wish to report here a facile and one pot synthesis for preparation (S)-methyl 1-(4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate.

### 1.1.2 Antiviral

Virus is very small external organism that is replicate and living in other living organism is called virus, Virus can be divided in to two parts, 1.DNA Virus, 2. RNA=virus. There are several viral infections are happening everyday life. Some examples of viral infections are common cold, poxviruses, herpes,influenza, measles, mumps and etc.

Antiviral is a group of medication which is used for antiviral infection that will help to cure, control or destroy the growth of virual infection.

### 1.1.3 Anticancer

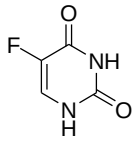
Cancer is nothing but normal cells and abnormal growth, group of disease that involve abnormal cell growth, and it has a potential to spread over the body, cancers are start with tumors and spread over the time period. The symptoms are associated with unexplained weight loss, abnormal bleeding, lumps and prolonged cough.

Anticancer is the medicine which is used to cure or control or destroy the cancer cells. There are several drugs which are in the market for the treatment of cancers.

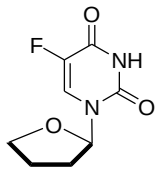
Uracil is one of the most important moieties for drug synthesis because of its has wide range of therapeutic activity, some of them are listed below

### 1.1.4 Uracil based anticancer drugs

**5-Fluorouracil**[15] (5-FU; Fluoroplex, Adrucil, Efudex, Fluorouracil,) is one of the pyrimidine effective metabolite. It used for the treatment of many type of cancer such as colon cancer, breast cancer, stomach cancer, esophageal cancer, pancreatic cancer, and cervical cancer. Gemcitabine (Gemzar) and arabinosylcytosine are other two drugs like 5-Fluorouracil and all are work same mechanism.



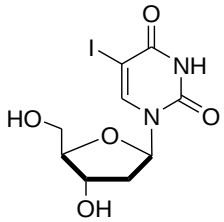

**Tegafur**[16] is a prodrug of 5-fluorouraciland used for treatment of cancers. It is a component of the combination drug tegafur/uracil.




### 1.1.5 Uracil based Herpes simplex virus drugs

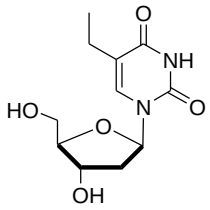
Herpes simplex virus is known as human herpes virus, there are two types of Herpesviras in his family namely HSV-1 and HSV-2. Infected person spread the HSV-1 and HSV-2 virus. The following Uracil based drug molecules are available for the treatment of HSV.

**Idoxuridine**[17]is an anti viral drug especially for anti-herpesvirus. It is became the first antiviral agent in 1962, it is a modified from deoxyuridine, similar enough to be incorporated in to viral DNA replication after adding iodine atom to the Uracil component blocks base pairing.Initially developed as an anticancer drug.



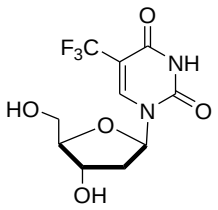

Idoxuridine, IDU, Herplex

**Edoxudine**[18] (or **edoxudin**) is an antiviral drug of thymidine analog, a nucleoside.It has shown effectiveness against herpes simplex virus.




Edoxudine, EDU, Aedurid

**Trifluridine** [19] (**trifluorothymidine** or **TFT**) is an antiviral (anti- herpesvirus) drug, used primarly on theeye. TFT was approved for medical use in 1980.It is also a component of the anti-cancer drug trifluridine/tipracil oral drug.

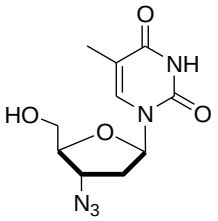



Trifluridine, TFT, Viroptic

### 1.1.6 Uracil based HIV drugs

The human immunodeficiency virus (HIV)[20] is causes HIV infection and it will develop AIDS (Acquired immunodeficiency syndrome) which progressive failure of the immune system allows life-threatening, the following Uracil based drugs are available for the treatment of HIV.

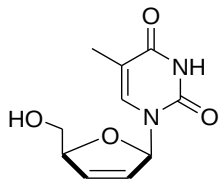
**Zidovudine** [20] also called as **azidothymidine**, is an antiretroviral agent and it can be used for the prevent and treat Human immunodeficiency virus (HIV)/ AIDS. It is used with combination of other antiviral agents. AIDS is prevented by Zidovudine from mother to child during birth or after needle stick injury. Zidovudine used as oral drug or injection with combination of other antiviral agents.




Zidovudine, AZT, Retrovir

**Stavudine** [21] (Zerit),is an antiviral drug. HIV/AIDS can be prevented by using of Stavudine. It cab be used along with other antiviral agents. It is also be used to

prevention needlestick or some other exposure, however, not a first line treatment. It is given by mouth. Stavudine was first described in 1966 and Stavudine is approved drug in USA for treatment of HIV/AIDS.

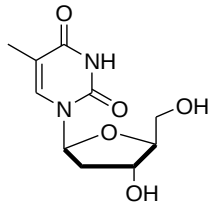



Stavudine, d4T, Zerit

### 1.1.7 Uracil based HCV drugs

Hepatitis C is affects the liver, HCV is caused by infectious diseaseHepatitis C Virus. The following drugs are available for the treatment of HCV infection.

**Telbivudine**[22] Hepatitis B virus can be treated by antiviral drug such as Telbivudine. It is more effective than lamivudine and adefovir. It is used by mouth in 600mg tablet.

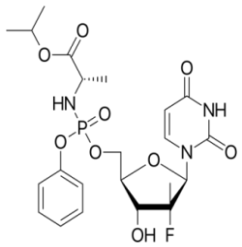



Telbivudine, LdT, Tyzeka

### 1.1.8 Uracil based HBV drugs

Hepatitis B virus is called HBV and it is caused by infection of hepatitis B virus, the following Uralic based drugs are available for the treatment of HBV.

**Sofosbuvir**[23], is used for the treatment of HCV, sold under the brand name **Sovaldi.** It is one of the best selling drugs for HCV infection and the cure rate is 30 to 97% and the drug was discovered by Gilead Science.

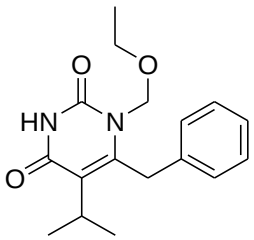


Sofosbuvir, Sovaldi

Uracil has wide varieties of therapeutic activity, so Uralic has been chosen for the molecules development.

### 1.1.9 Uracil based antiviral drugs

**Emivirine** [24] (**MKC-442**) is an antiviral drug used for the treatment of Human immune deficiency virus. It is a non nucleoside reverse transcriptase inhibitor. Promising antiviral activity shown by emivirine in vitro study. In human trails it's failed because it is not show sufficient efficacy. However it is still notable because of more number of antiviral derivatives can be discovered by this concept.



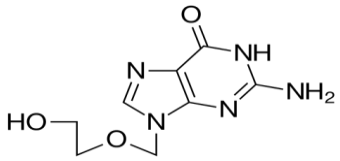
Emivirine

## 1.2 PURINE BASED DRUG MOLECULES AND ITS DERIVATIVES

Purines and substituted puriens is well known for its biological activity purines and substituted purines is the important intermediate for the synthesis of varieties of purine and purine nucleoside molecules, several antiviral drugs are available with purine derivatives such as valaciclovir, femciclovir, acyclovir, valganciclovir, ganciclovir etc.,

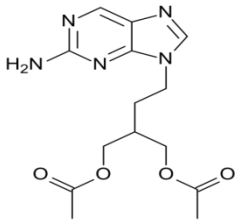
### 1.2.1 Purine based HSV drugs

**Valaciclovir**[25] is a prodrug and it will be converted in to acyclovir in vivo, Herpes simplex, herpes zoster (shingles), and herpes B viruses can be treated by antiviral drug Valaciclovir . It was approved by USFDA for medical use in 1995.



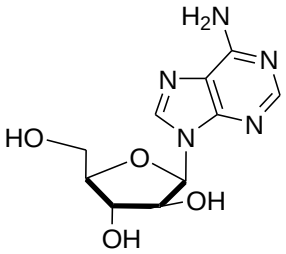
Valaciclovir

**Famciclovir** [26] is a prodrug of penciclovir. In invivo famciclovir converted in to penciclovir. Herpes virus infection, herpes zoster (shingles) are treated by anti viral drug famciclovir. Novartis was discovered famciclovir and it is marketed by the name of **Famvir**.



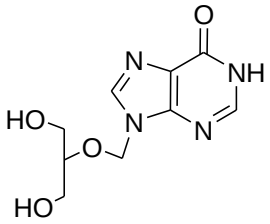
Famciclovir

**Vidarabine**[27] is an antiviral drug which is used for the treatment of herpes simplex and varicella zoster viruses.



Vidarabine, Ara-A, Vira-A

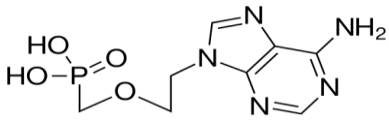
**Ganciclovir** [28][29] is a prodrug of valganciclovir with improved bioavailability, Ganiciclovir an antiviral drug which is used for the treatment of cytomegalovirus (CMV) infections.. Ganciclovir was approved by USFDA for medical use in 1989.




Ganciclovir

### 1.2.2 Purine based HBV drugs

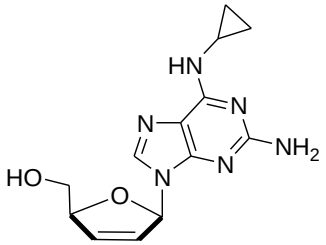
**Adefovir** [30]is a prodrug of adefovir and it is aanti viral drug which is used for the treatment of chronic infection of hepatitis B virus.




Adefovir

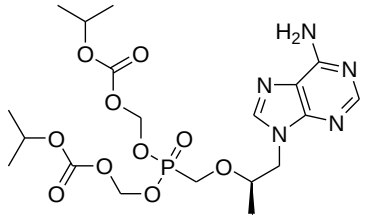
### 1.2.3 Purine based HIV drugs

**Abacavir**[31] is a viral drug and it can be used for the treatment of HIV/AIDS. Abacavir is not recommended alone and it can be used together with other HIV medication. It is oral drug and it is prescribed drug to treat the children over the age of three month. Abacavir was approved by USFDA in 1998 for human use.Other HIV medications, such as abacavir/lamivudine/zidovudine or abacavir/dolutegravir/lamivudine and abacavir/lamivudine are used along with Abacavir.



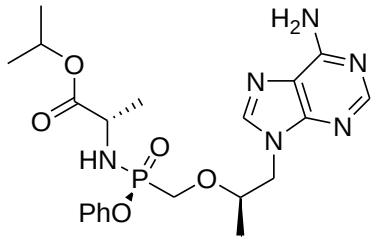

Abacavir

**Tenofovir disoproxil**[32]chronic hepatitis B was treated by tenofovir disoproxil and can be used to prevent and treatment of HIV/AIDS. Tenofovir disproxil is taken by oral along with other antiretrovirals dugs. It is a preventive drug of HIV/AIDS among those at high risk before exposure, and it can be used to prevent infection from mother to baby during birth after needlestick injury or other potential exposure. It is sold both by both single and along with other antiretroviral agents such as emtricitabine/tenofovir and efavirenz/emtricitabine/tenofovir. Tenofovir does not cure hepatitis B inefection of HIV/AIDS. It is available as a oral drus. Tenofovir was approved by USFDA in 2001 for human use.




Tenofovir disoproxil

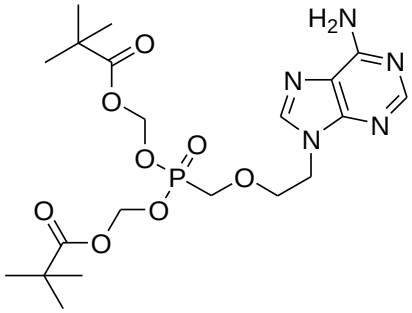
**Tenofovir alafenamide** [33] is a prodrug of tenofovir and HIV infection and chronic hepatitis B infection are treated by tenofovir alafenamide, Tenofovir alafenamidehas greater antiviral activity and better distribution into lymphoid tissues than that agent.USFDA was approved this drug this drug for human use November 2016.



Tenofovir alafenamide

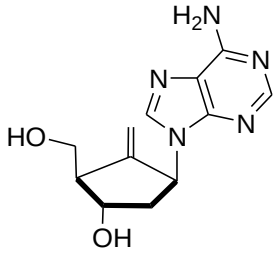
### 1.2.4 Purine based HBV drugs

**Adefovirn** [34] is a prodrug of adefovir and it is used to treat chronic hepatitis B infection, it is oral and prescribed drug. Pivoxil prodrug adefovir dipivoxil was prescribed drug and it was approved by USFDA for human use.



Adefovir

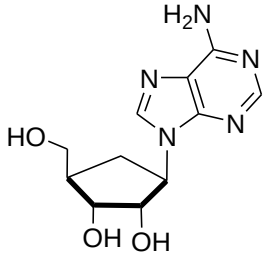
**Entecavir**[35] (**ETV**) is selling under brand name of Baraclude, it is anti-viral drug, it can be used for the treatment of hepatitis B virus (HBV) infection, and also used to treatment of both HIV/AIDS and HBV antiretroviral medication should also be used. Entecavir is oral tablet. Entecavir was approved by USFDA for medical use in 2005.



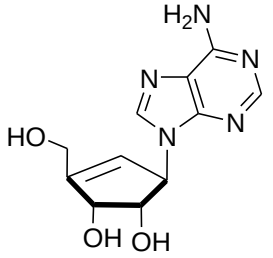

Entecavir, ETV, Baraclude

### 1.2.5 Purine based HBV drugs

Aristeromycin is a 5-membered ring carbocyclic nucleosides , the analog of other drugs are adenosine, and neplanocin A, Aristeromycin cyclopentene analog [36], have been isolated from naturally available sources. Both the molecules are exhibit significant activity towards antiviral and antitumor.

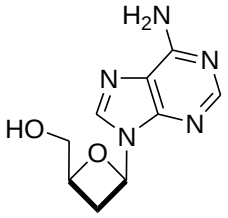



Aristeromycin




Neplanocin A

**Oxetanocin**[37] ia an angent and it was isolated from Bacillus megateriumviral agent.

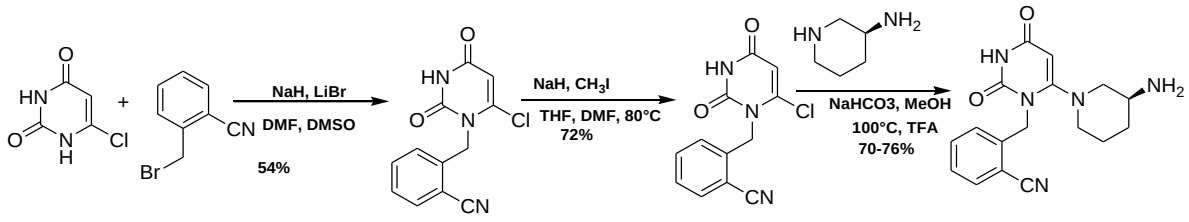


Oxetanocin

## 1.3 BACKROUND ABOUT THE FIELD OF INVENTION OF URACIL MOIETY

Jun Feng, Zhiyuan Zhang etal [38]have been prepared the target compound by 6-chloro uracil reacted with 2-cyano benzyl bromide in the presence of NaH, DMF and DMSO followed by the methylation by using of methyl iodide in the presence of Sodium hydride in THF and DMF, then followed by the coupling of R-2-amino pipridine in the presence of sodium bicarbonate , TFA in Methanol, the over all yield reported by the process is 28.34%.

**Reaction Scheme- 1.1: process for the preparation of alogliptin**



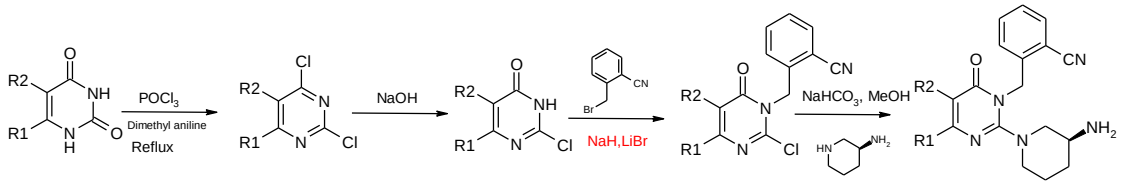

In this total synthesis they have been used potentially hazardous chemicals like NaH and DMF mixture and it is well known for explosion and fire hazard, this can be damage the infrastructure and properties and over all yield has been reported very low.

In another embodiment the following synthesis scheme was reported

Substituted uracil was reacted with $POCl_3$ in dimethyl aniline at reflux temperature to produce chlorinated product then it was reacted with sodium hydroxide to produce mono chloro substituted product and it was further reacted with 2-CN benzyl bromide in

the presence of Sodium hydride and lithium bromide to produce benzylated product further reacted with R-amino piperidine and sodium bicarbonate to produce target compound.

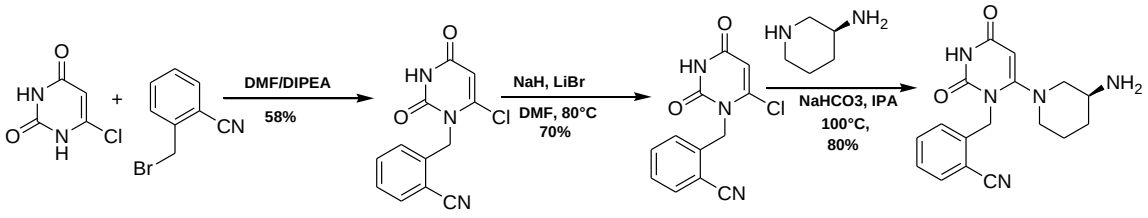
**Reaction Scheme- 1.2: process for the preparation of alogliptin derivatives**




The potentially hazardous sodium hydride was used in this synthesis.

Zeng-WeiLai, Chunhong Li etal[39]have been prepared the compound by 6-chloro uracil reacted with 2-cyano benzyl bromide in the presence of Sodium hydride DMF and DIPEA, overnight followed by the methylation by using of methyl iodide in the presence of Sodium hydride in LiBr and DMF over night at 80°C, followed by the coupling of R-2-amino pipridine in the presence of sodium bicarbonate in IPA, followed by purification by column chromatography, the overall yield reported by the process is 32.48%.

**Reaction Scheme- 1.3: process for the preparation of alogliptin**

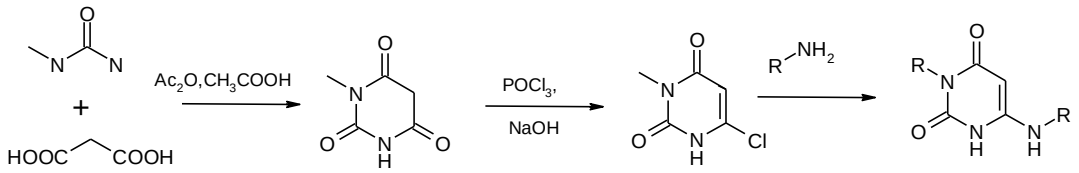



The overall yield was reported very low this leads to higher cost, potentially and environmentally dangerous sodium hydride was used for the preparation of target molecules.

Ajaya R.Shrestha, Takashi Shindo etal [40]have been prepared 6- chloro3-methyl uracil by reacting Methyl urea and the malonic acid in the presence of acetic anhydride and acetic acid followed by chlorination with phosphorous trichloride 6-chloro pyrimidine

2,6-dione was obtained by chlorination of barbituric acid followed by the amine derivatives have been prepared with reaction of amine with higher temperature( 180-200°C ).

**Reaction Scheme- 1.4: process for the preparation of uracil derivatives**




All the above literatures are having drawbacks that, they are using highly hazardous chemical (hazardous to facility, environment and health) such as sodium hydride and DMF mixture has the potential fire hazards and there were several accidents reported in this mixture, so we have proposed to eliminate such as hazardous materials from our synthesis and also planned to prepare our targeted molecules by one pot synthesis.

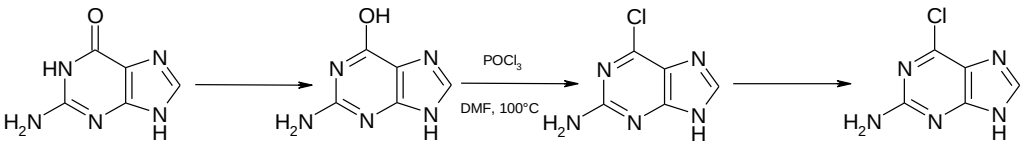
Organic reactions under one pot synthesis are attracted much interest of organic chemists because of particularly one solvent used many steps; it reduces lower cost, environment friendly and higher yield synthesis and view of green chemistry. Green chemistry approaches are much important in organic chemistry due to significant reduction in the industrial waste, byproducts, reduction in use of equipments, energy and cost. The one pot synthesis is nothing but the possibility of conducting multistep reactions under one pot synthesis could enhance their efficiency from an ecological and economic point of view.

## 1.4 BACKROUND ABOUT THE FIELD OF INVENTION OF PURINE

Lei Luo, Guorong and etal,[41] have been syhthesized 2-amino-6-chloro purine , by the following process, Guanine reacted with $POCl_3$ in DMF Was stirred 100°C for 4 hrs followed by addition of water in to it, after stirring 24 hrs, at 25°C, the product was isolated by filtration, solid was Dissolved with 25% ammonia solution insoluble material

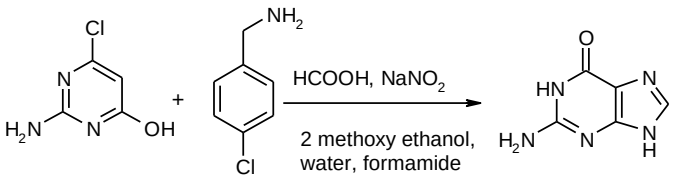
was isolated by filtration insoluble material was removed and MLR was concentrated out the precipitated material was isolated by the filtration with 55% yield.

**Reaction Scheme- 1.5: process for the preparation of Purine derivatives**




Noell and R.K.Robins [42] have been prepared , 2-amino-6-chloro -4- pyrimidinol monohydrate is suspended in methoxy ethanol and 4-chlorobenzene methanamine is added to the suspension, and the solution refluxed for 4-hrs, then poured in to ice water, it was diluted with acetic acid and treated with sodium nitrite in water, then the crude nitrosopyrimidine reduced with sodium dithionate in formamide and formic acid at 70°C then boiled for 15 min, then diluted with water again boiled for 30 min, allow to crystallize in refrigirator, crude n-formyl derivatives collected by filtration and cyclized with formic acid and formamide at 175-180°C for 3hrs, the crude product was poured in to ice water to provide guanine then it was purified with 1N HCl solution at boiling temperature.

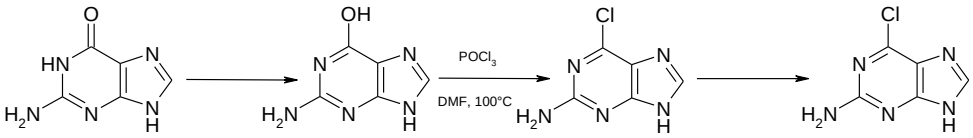
**Reaction Scheme- 1.6: process for the preparation of Purine derivatives**




Ye, Lianbao; Huang, Pengna; Peng, Xuedong; Luo, Yan , has described to prepare 2-amino-6-chloropurine by A one-step synthetic method[43]. 2-Amino-6-chloropurine was synthesized using guanine and phosphorus oxychloride as starting materials under the effect of tetraethylammonium chloride in acetonitrile. The chem. structure of the target compd. was confirmed by IR, MS and 13C NMR etc. The yield of title compd. was

(72.1% and its HPLC purity was not less than 98%). This article can provide a more reasonable route for the production process of 2-amino-6-chloropurine.

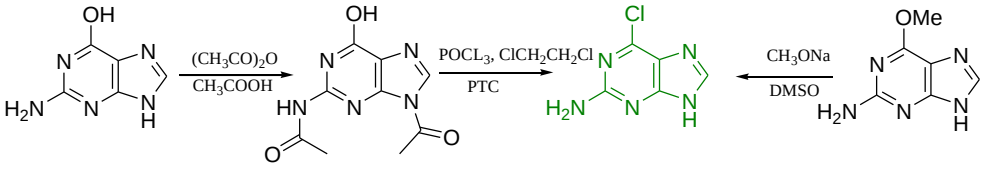
**Reaction Scheme- 1.7: process for the preparation of Purine derivatives**




Yu Lin Hu, Qiang Ge.Ming Lu etal, [44] have been synthesized the above molecules, the mixture of quanine, acetic acid and acetic anhydride wasagitated at 135°C for 7.5 hrs, after the reaction reached end point the solvent and acetic anhydride was removed by distillation under vacuum and the crude product was recrystallized in water to give acylated quanine with 95% yield.

2,9-diacetyl quanine was reacted with phosphorous oxychloride in PEG-2000 and ethylene dichloride at 80°C for 6hrs then reaction completion was judged by TLC then reaction the reaction mass was cooled to 25°C, and the desire compound was isolated by filtration, it was recrystallized by DMSO to produce 2-amino-6-chlorofurine.

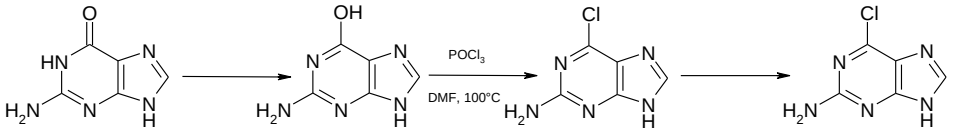
**Reaction Scheme- 1.8: process for the preparation of Purine derivatives**




Ye, Lianbao; Huang, Pengna; Peng, Xuedong; Luo, Yan, A one-step synthetic method of 2-amino-6-chloropurine [44]. 2-Amino-6-chloropurine was synthesized using guanine and phosphorus oxychloride as starting materials under the effect of tetraethylammonium chloride in acetonitrile. The chem. structure of the target compd. was confirmed by IR, MS and 13C NMR etc. The yield of title compd. was (72.1% and its HPLC purity was

not less than 98%). This article can provide a more reasonable route for the prodn. process of 2-amino-6-chloropurine.

**Reaction Scheme- 1.9: process for the preparation of Purine derivatives**

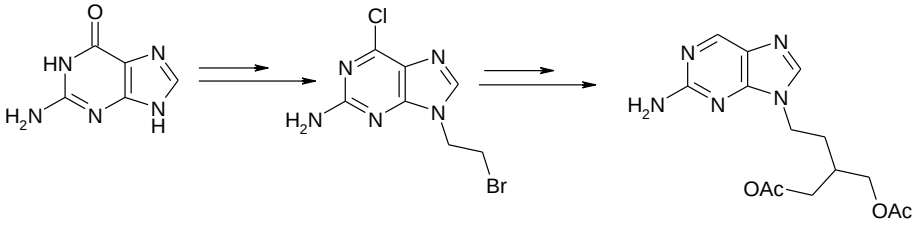



Raghida Bou, Pamela Cohn, Egle, Matthew B. Baker, Maud Voisin, Sarun and Ronald [45] are synthesized 6-Chloro-9H-purine-2-amine was added the solution of $K_2CO_3$ and DMF then agitated 1 hr followed by addition of 2-ethyl hexyl bromide and then it was stirred 16.0 hrs, solvent was removed by distillation, then the crude was purified by column chromatography (56%).

2-Amino-8 bromo-9-(2-ethylhexyl)-1,9-dihydro-6H-purin-6-one , 2-(tributylstannyl)-thiophene, $Pd(PPh_3)_4$ and $Ph_3Bi$ were dissolved in dry xylene 20 ml and heated to reflux and continued reflux for overnight, solvent was concentrated under reduced pressure, the crude was treated with MDC to produce compound with 66% yield.

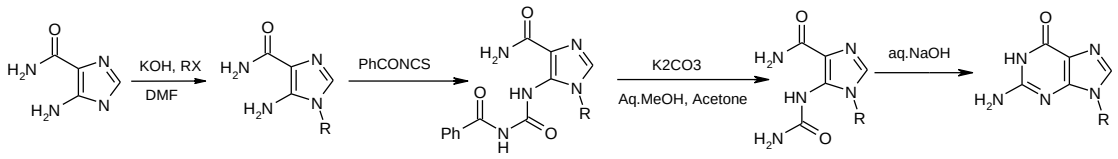
Lei Luo, Guorong Chen and Yuan Chao Li [41] has been reported that a new and eficient method for the synthesis of 2-amino-9-[4-acetoxy-3(acetoxy methyl) butyl-1-yl) purinestarting from guanine, the first step involves chlorination of guanine followed by mitsunobu reaction then coupling with diacetyl malonate then hydrogenation followed by reduction and esterfication, This method does not required any chromatography purification to produce pure femciclovir, industrially viable manufacturing process.

**Reaction Scheme- 1.10: process for the preparation of Purine derivatives**



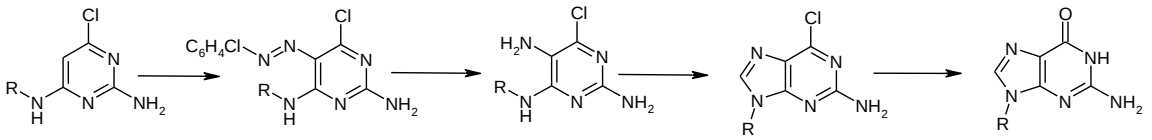
Borge Alhede, Finn Priess Clausen, Jorgen juhi-Christensen, Kalaus K. McCluskey and Herbert F. Preikschat [46] has been prepared by the following process, The precooled suspension of compound 1 and DMF was added with 86% KOH powder after stirred 4 hrs at ice bath, methyl bromide was bubbled after 2 hrs the precipitated solid product was isolated by filtration and washed with DMF and water(yield :55%), Compound 2 was treated with benzoyl isothiocyanate were refluxed in acetone, and drying afford compound as a white solid(yield :95%),Compound 3 in acetone-methanol was added potassium carbonate in water and reflux 6 hrs, cooled and acetic acid was added and the precipitated solid product was isolated by filtration with 96% yield. Compound 4 was treated with 1.0N aq.NaOH solution then Copper (II) acetate, water was added and refluxed for 1.0 hr then cooled to 50°C copper(II) sulfide was removed by filtration, filtrate was acetified with acetic acid to brough th pH 5.0, the precipitated product was filtered and washed with water with 96% yield.

**Reaction Scheme- 1.11: process for the preparation of Purine derivatives**



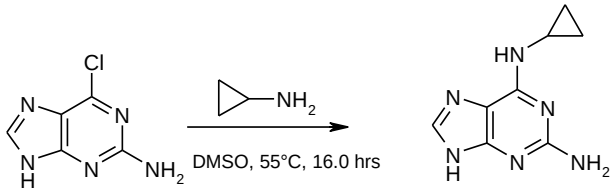

Alan D.Borthwick, Barrie E. Kirk, Keith Biggadike, Anne M.Exall, Suzanne Butt, Stanley M.Roberts, David J.Knight, and D.Michael Ryan[47] has been prepared the title compound by the following process.4-Chlorobenzenediazonium chloride is coupling with compound 1 in aq.acetic acid and with sodium acetate afforded the azo derivatives compound 2, reduction of azo derivative using Zinc, ammonium chloride in methanol compound 3, 2-amino-6-chloro purine were obtained by acid catalyzed reaction with triethylortho formate and then crude produc was treated with 0.6N HCl solution.

**Reaction Scheme- 1.12: process for the preparation of Purine derivatives**



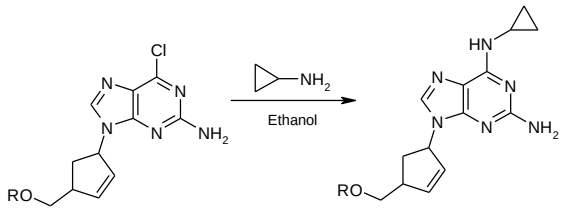
Michael T.Crimmins, Bryan W.King, William J. Znercher and Allision L. Choy [48] have been prepared the title compound Halo compound reacted with cylopropyl amine in DMSO at 55°C for 16.0 hrs after reaction completion solvents was distilled off by rota evaporator and the desire product was purified by column chromatography by using MDC and methanol mobile phase.

**Reaction Scheme- 1.13: process for the preparation of Purine derivatives**




Michael T. Crimmins and Bryan W.King [49]have been synthesized the compound reacted with cyclopropyl amine reacted with halogenated compound to produce desire compound in dry denaturated ethanol at reflux temperature after completion of reaction the solvent was distilled by rotaevaporator and the desire product was purified by column chromatography.

**Reaction Scheme- 1.14: process for the preparation of Purine derivatives**

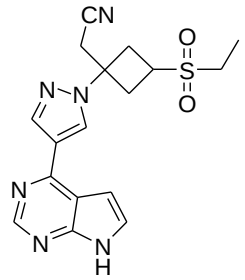


## 1.5 BACKROUND ABOUT THE FIELD OF INVENTION OF 7H-PYRROLO[2,3-d]PYRIMIDINE BASED DRUG INTERMEDIATE

N-heterocyclic compounds are very important in drug design [50][51][52] compare with various heterocyclic compounds, pyrrolopyrimidine functional group containing compounds are structurally deserve class of antibiotic analogs. Both organic and medicinal chemist are attracted by pyrrolo [2,3-d]pyrimidine derivatives because of the presence in naturally occurring products and biologically active compounds[53]. Pyrrolo[2,3-d] pyrimidine derivatives are well known for biologically active compounds like antiviral [54], antibacterial [55], Antimicrobial [56], rheumatoid arthritis [57],Anti microbial [58], antiinflamatory [59],antihypertension[60], antitumor[61], anti-inflammatory[59], Anti-HCV [54][62],antiallergic [63], and antifuncal[58] activities. In organic synthesis pyrrolo[2,3-d]pyrimidines derivatives are interesting intermediate to provide higher access and highly desirable structure. Some of the drugs like Toyocamycin are pyrrolo pyrimidine based drugs which is isolated from Streptomyces speciesand also ability to inhibit with RNA cells.

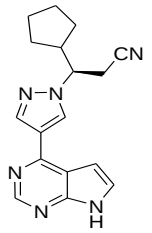
## 1.6 PYRROLOPYRIMIDINE BASED DRUG MOLECULES

**Baricitinib** [57] is a pyrrolopyrimidine based drug molecules for the treatment of rheumatoid arthritis (RA). The drug is approved in European Medical Agency in February 2017 for human use. Baricitinib is a second line approved drug for the treatment of moderate to severe active rheumatoid arthritis in adults.



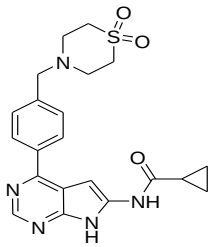

Baracitinib

**Ruxolitinib**[64] is a another drug of pyrrolopyrimidine analog and it is used for the treatment of intermediate or high-risk myelofibrosis, when there is inadequate response to or intolerance of hydroxyurea ruxolitinib can be used and also used to treat a type of myeloproliferative disorder which is affects the bone marrow, and for polycythemia vera (PCV).



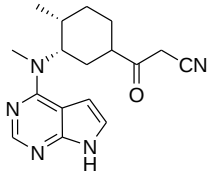

Ruxolitinib

**Filgotinib**[57](cilinical trial code name **GLPG0634**) is a another analog of pyrrolopyrimidine class, which is treatment of rheumatoid arthritis (RA) and Crohn's disease, it is under investigational drug for human use. . It was developed by the Belgianbiotech company Galapagos NV.




Filgotinib

**Tofacitinib** [65] is a medication used to treat rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis.




Tofacitinib

Pyrrolo[2,3-d] pyrimidine has very good activity, so it has been chosen for our synthesis.

## 1.7 SCOPE OF STUDY

Based on through literature survey, it stated that the molecules which are under clinical trial of already in the use of human have some limitation such less solubility, low bio availability and more side effects, Molecules or drugs which are currently using no longer valid because of it resistant of viruses or bacteria's so we urge to new discovery or novel molecules to overcome all these problems.

The current synthesis of drug molecules and drug intermediates has been employed using of hazardous chemicals, raw materials, reagents which will leads to generation of industrial waste, environmental threads, danger in infrastructure and non cost effective, to overcome all these issues need to develop new, eco-friendly, less hazardous, less effluent generated process to be developed moreover one pot synthesis process attract chemist because of one solvent have been used to many synthetic steps it will require less infrastructure and investment, less effluent generation and low cost.

Based on through literature survey we came to conclude that Uracil, Purine and pyrrolo pyrimidine has great interest due to their wide applicability of drug molecules and their activities. So we have been chosen Uracil, Purine and Pyrrolopyrimidine basic moieties has been chosen for the further development of target molecules.

# 2. EXPERIMENTAL

## 2.1 MATERIALS AND INSTRUMENTATION

Reagents and chemicals which was used obtained from highest grade available from Sigma Aldrich, Acros organics, Spectrochem, Loba Chem, Survival Technology and Rankem Laboratories, and were used without purification. TLC was performed on Merck TLC Silica gel 60 F254 plates eluting with specific solvents and samples were made visual with a UV lamp, Silica gel (60-120 mesh) was used for column chromatography. Electrothermal 9100 apparatus were used to measure melting points. High resolution mass spectra were measured were Bruker. The measurement was run in positive ion mode. NMR were obtained using Bruker (for $^{1}H$ NMR in 400 MHz and for $^{13}C$ NMR in 100 MHz) spectrometer in DMSO and $CDCl_3$ with TMS (tetramethylsilane) as an internal standard and PPM (parts per million) is unit used to report chemical shift, tetramethylsilane used as a reference standard to report chemical shift (δ).Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and Coupling constants (J values) are reported in hertz (Hz). All the Mass spectrums were recorded in HRMS: ABSCIEX (4600 Model), QTOF (Quadrupole time of Flight).

## 2.2 THIN LAYER CHROMATOGRAPHY (TLC)

TLC is the chromatography technique [66] can be used to separate mixtures of compounds and also used to monitor the reaction progress too; TLC plates are made in Aluminium foil is coated with thin layer of silica gel or neutral alumina coated and it was dried at higher temperature to remove moisture after plate was dried it is ready to use. All type of chromatography's working in the same principle, Solid phase working as a stationary phase and liquid phase working as a mobile phase.

In TLC Silica gel or Alumina plate is act as a stationary phase and solvents used as a mobile base, the compound to be identified was spotted on the bottom of TLC plate then

it was developed in solvents system and it will give the separation from one another, the picture of TLC are shown below.

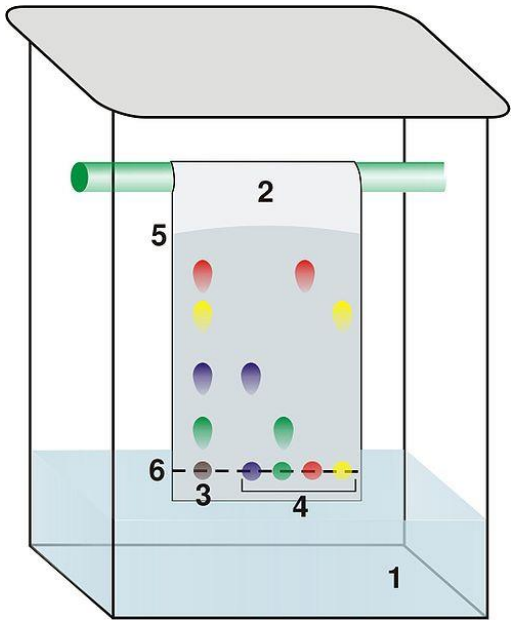



**Fig: 2.1**

## 2.3 NUCLEAR MAGNETIC RESONANCE (NMR)

Nuclear Magnetic Resonance (NMR) is one of the analytical techniques which are used to identify compounds, it is a powerful technique which has application in many discipline.

NMR is the spectroscopic technique which gives the information about the number of protons and its chemical environment. There are two type of NMR can be used to identify the molecules namely $^{1}$HNMR and $^{13}$CNMR.


**Fig: 1.2**

## 2.4 MASS SPECTROSCOPY

Mass Spectroscopy is another one type of powerful technology which can be used to identify the molecular weight of compounds. Mass spectroscopy playing important role in structural identification and it can be used many of the industries like Pharmaceutical, Polymer, agrochemical and etc. Mass spectrometer performs in 3ways.

1. Ion generation: high energy beam of electron when bombard to the target molecules it will generate molecular ions.

2. When they accelerated in electric field they separated based on their mass-to-charge ratio (m/z)
3. Detector will qualify and quantify the separated ions.


**Fig: 1.3**

## 2.5 BIOLOGICAL POTENTIAL OF COMPOUNDS BY PASS PREDICTION:

PASS (*Prediction of Activity Spectra for Substances)* prediction is software which gives Biological *Activity Spectrum* of a chemical compound. This can be used to find out different types of biological activity of the compounds that represented results of the compound's interaction with several biological entities. The “intrinsic" property of chemical compounds that’s depending upon only on its chemical structure and physical-

chemical properties and characteristics. This will give information and combining information's from various sourced in same training set.

PASS is a tool which is used for evaluating biological activity of organic drugs and drug like molecules; many type of organic compounds organic molecules simultaneously biological properties predicted by PASS. This software gives advance information of chemical compounds before synthesis of them. This will help us to save cost and time.

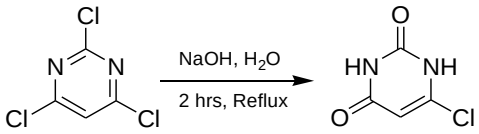
***Pa (probability "to be active")*** this will give active estimation or chance of the organic molecules is belonging to the sub-class of active compounds (similarity to the structures of organic molecules that are the most typical in a sub-set of "actives" in PASS training set).

***Pi (probability "to be inactive")*** this will give estimation of or chance of the organic compound is belonging to the sub-class of inactive compounds (similar to the structures of organic molecules that are the most typical in a sub-set of "inactives" in PASS training set).

## 2.6 PREPARATION OF KEY STARTING MATERIALS (KSM).

### 2.6.1 Synthesis of 6-chloro Uracil

**Reaction Scheme-2.1: process for the preparation of 6-chlorouracil**




### 2.6.2 Experimental procedure:

Sodiumhydroxide ( 27.3 g, 0.682 moles) was added 20 mL water and the solution was stirred for 30 min, 2,4,6 trichloropyrimidine (15.7 mL, 0.136 mol) was added to this solution the reaction mass mas heated to relux and the reaction mass was stirred for 2 hrs, the solution was cooled to 0-5°C and then the solution pH was adjusted to 1.90-2.20 by using 1:1 dilute HCl (100 mL), the precipitated product was isolated by filtration and

washed with hot water, and the product was dried under vacuum at 45-50°C, the title product was isolated as white colored solid 19.5 g. (98.0%, LC-MS m/z: 147.5 [M+H].

## 2.6.3 PROCESS OPTIMIZATION:

### 2.6.4 Solvent Screening

There are several solvents like DMSO, DMF, Toluene, 2-MeTHF, Water, methanol and ethanol have been tried to find the suitable solvents for the reaction, and we found that water giving good reaction conversion and low impurity formation, other solvents are giving less conversion and more impurity formation, so we have been chosen water as a solvent for the reaction.

| Sr.No. | Base | Solvent | Remarks |
|---|---|---|---|
| 1 | NaOH | DMSO | Impurity formation |
| 2 | NaOH | DMF | Impurity formation |
| 3 | NaOH | Toluene | Impurity formation |
| 4 | NaOH | Water | Good conversion |
| 5 | NaOH | 2 Me THF | No reaction |
| 6 | NaOH | Methanol | Impurity formation |
| 7 | NaOH | Ethanol | Impurity formation |

**Table: 2.1**

### 2.6.5 Base Screening

There are several bases like NaOH, $Na_2CO_3$, $K_2CO_3$, KOH and TEA have been tried to find the suitable base for the reaction, and we found that NaOH and KOH giving good reaction conversion and low impurity formation, other bases are giving less conversion and more impurity formation, so we have been chosen NaOH as a base for the reaction.

| Sr.No. | Base | Solvent | Remarks |
|---|---|---|---|
| 1 | NaOH | Water | Good Conversion |
| 2 | Na2CO3 | Water | Less Conversion |
| 3 | K2CO3 | Water | Less Conversion |
| 4 | KOH | Water | Good Conversion |
| 5 | TEA | Water | No Reaction |

**Table: 2.2**

### 2.6.6 Mole equivalents screening

Mole equivalents of Base have been studied to find out optimum condition for the reaction conversion and it was observed that 3.0 mole equivalents of base give very good conversion and it was optimum condition for the reaction.

| Sr.No. | Base | Solvent | Mole Equi. | Remarks |
|---|---|---|---|---|
| 1 | NaOH | Water | 3.00 | Good Conversion |
| 2 | NaOH | Water | 4.00 | Impurity formation |
| 3 | NaOH | Water | 5.00 | Impurty formation |
| 4 | NaOH | Water | 2.00 | Less Conversion |
| 5 | NaOH | Water | 2.50 | Less Reaction |

**Table: 2.3**

### 2.6.7 Temperature Screening

The temperature range from 20°C to 100°C have been studied to find out suitable temperature for the reaction conversion, and it was found that reflux temperature gives

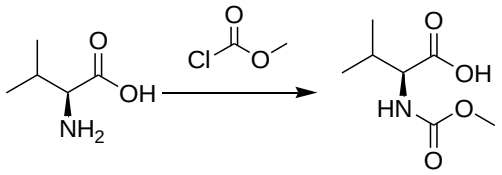
desirable conversion of reaction and yield so reflux temperature have been chosen for the reaction.

| Sr.No. | Base | Solvent | Temp. | Remarks |
|---|---|---|---|---|
| 1 | NaOH | Water | 100°C | Good reaction |
| 2 | NaOH | Water | 90°C | Slow reaction |
| 3 | NaOH | Water | 80°C | Slow reaction |
| 4 | NaOH | Water | 70° | No Reaction |
| 5 | NaOH | Water | 25°C | No Reaction |

**Table: 2.4**

## 2.7 SYNTHESIS OF MOC-L-VALINE

**Reaction Scheme-2.2: process for the preparation of Moc-L-Valine**




### 2.7.1 EXPERIMENTAL PROCEDURE:

Took 645 mL of anhydrous tetrahydrofuran in 4 necked RBF and added L-Valine (0.213 mol) and stirred 20 min. to this obtained clear solution added $NaHCO_3$ (0.640 mol) in water (645 mL) and then added methylchloroformate (0.235 mol) and obtained reaction mass was stirred at room temperature 12 hrs. The reaction mixture was monitored by TLC, and solution pH was acidified to 3.0-3.50 by using with 1N HCl. Ethylacetate was added to the aqueous layer. The organic layers were dried over $Na_2SO_4$, filtered and removed sodium sulphate, solvent was distilled off under reduced pressure to give title compound as a white solid in 98% yield. $^1H$ NMR (DMSO-$d_6$, 400 MHz) δ (ppm) 8.50 (brs, 1H), 5.26 (brs, 1H), 4.33(m, 1H), 3.70 (s, 3H), 2.23 (m, 1H), 1.00 (d, J=7.00 Hz, 3H), 0.93 (d, J=7.00 Hz, 3H) and MS (ESI, EI+) m/z=176 ($MH^+$).

### 2.7.2 Solvent Screening

There were several solvents have been studied for the suitable solvent for the reaction such as Water, DMF, Toluene, Me THF, Methanol and ethanol and we found that water gives good conversion for the reaction, so water have been chosed for the best solvent for the reaction and the results are listed below table.

| Sr.No. | Base | Solvent | Remarks |
|---|---|---|---|
| 1 | $NaHCO_3$ | Water | Good conversion |
| 2 | $NaHCO_3$ | DMF | Impurity formation |
| 3 | $NaHCO_3$ | Toluene | Less Conversion |
| 4 | $NaHCO_3$ | 2 Me THF | Less Conversion |
| 5 | $NaHCO_3$ | Methanol | Impurity formation |
| 6 | $NaHCO_3$ | Ethanol | Impurity formation |

**Table: 2.5**

### 2.7.3 Base Screening

Bases like TEA, DIPEA, K2CO3, Na2CO3, NaOH, KOH, NaHCO3 has been studied for the reaction, when we are using strong bases like NaOH, KOH more impurity formation was observed, when using organic bases less conversion was observed, so we have been chosen weak and inorganic base sodiumbicarbonate have been chosen for the reaction.

| Sr.No. | Base | Solvent | Remarks |
|---|---|---|---|
| 1 | TEA | Water | Less Conversion |
| 2 | DIPEA | Water | Less Conversion |
| 3 | $K_2CO_3$ | Water | Impurity formation |
| 4 | $Na_2CO_3$ | Water | Impurity formation |
| 5 | NaOH | Water | Impurity formation |
| 6 | KOH | Water | Impurity formation |
| 7 | $NaHCO_3$ | Water | Good conversion |

**Table: 2.6**

### 2.7.4 Mole equivalents screening

Methylchloroformate mole equivalents have been studied to find out best mole equivalents for the best reaction condition, when less mole equivalent found that reaction did not completd and mole equivalents range from 1.10-1.25 gives good conversion, more than that not economical, so 1.10 mole equivalents of methylchloroformate was chose for the reaction.

| Sr.No. | Base | Solvent | Mole Equi. | Remarks |
|---|---|---|---|---|
| 1 | $NaHCO_3$ | Water | 1.10 | Good conversion |
| 2 | $NaHCO_3$ | Water | 1.15 | Good conversion |
| 3 | $NaHCO_3$ | Water | 1.25 | Impurity formation |
| 4 | $NaHCO_3$ | Water | 1.50 | Impurity formation |
| 5 | $NaHCO_3$ | Water | 1.00 | Unreacted KSM |
| 6 | $NaHCO_3$ | Water | 0.95 | Unreacted KSM |
| 7 | $NaHCO_3$ | Water | 0.90 | Unreacted KSM |

**Table: 2.7**

### 2.7.5 Temperature Screening

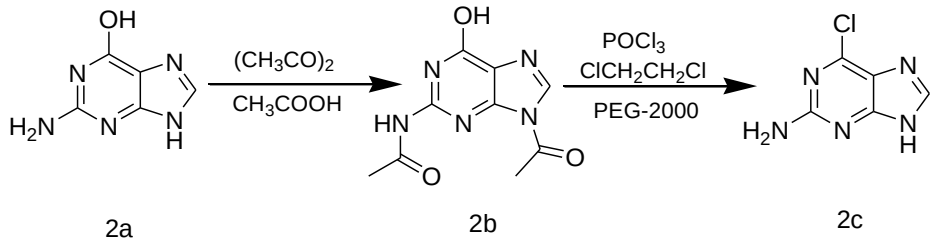
The temperature range from 0°C to 50°C have been studied and found that lower temperature reaction proceeded slow and higher temperature impurity formation was observed and the reaction proceeded well in room temperature (RT), so RT have been chosen for the reaction.

| Sr.No. | Base | Solvent | Temp. | Remarks |
|---|---|---|---|---|
| 1 | $NaHCO_3$ | Water | 20-25°C | Good reaction |
| 2 | $NaHCO_3$ | Water | 0-5°C | Slow reaction |
| 3 | $NaHCO_3$ | Water | 45-50°C | Impurity formation |

**Table: 2.8**

## 2.8 SYNTHESIS OF 6-CHLORO-9H-PURIN-2-AMINE

**Reaction Scheme-2.3: process for the preparation of 6-chloro-9H-purine-2-amine**




2a 2b 2c

## 2.8.1 EXPERIMENTAL PROCEDURE:

### 2.8.2 Preparation of 2,9-diacetylguanine (2b):

Took 1000 mL 4 necks RBF added 60 mL acetic acid followed guanine (2.5 g, 0.0165 moles) and added slowly acetic anhydride (30 mL) then the reaction mixture was stirred at 135° C for 7.5 hrs. The reaction progress was monitored by TLC, after completion of the reaction, distilled off the solvents under reduced pressure to obtained crude product, the obtained crude product was recrystallized from distilled water to give white powder (2-1, 3.7 g, yield 95%). m.p. 251 – 256° C. H NMR (DMSO-d6) δ, 11.56 (s, 1H, OH), 8.15 (s, 1H, NH), 8.11 (s, 1H, CH), 2.16-2.50 (m, 6H, CH3). MS (70 eV) m/z 234.09 (M); MS m/z (%) 234.09 (M, 20), 192.12 (100), 150.08 (23). IR (KBr) 3200, 1680, 1530 cm-1. Analysis Calcd for C9H9N5O3: C, 45.93; H, 3.87; N, 29.76; O, 20.37. Found: C, 45.96; H, 3.86; N, 29.78; O, 20.41.

### 2.8.3 Preparation of 2-amino-6-chloropurine (2c):

Took 100 mL round bottom flask and added 10 mL dichlororethane followed by addition of 2,9-diacetylguanine (2.35 g, 0.010 moles) and PEG-2000 (4 g, 0.002 moles) then the reaction mixture was stirred 20-30 min. at 20-30°C followed by added slowly (dropwise) $POCl_3$ (5.4 g, 0.035 moles) then the reaction mass was stirred 30 min. at 20-30°C, the obtained reaction mixture was heated at 80°C and it was stirred 6hrs at 80°C then reaction progress was monitored by TLC after completion of reaction reaction mass was cooled to room temperature, the precipitated product was filtered off. The solvent was

distilled off under redused pressure and the obtained residue was recrystallized from DMSO to give title compound a white powder (2, 1.42 g, yield 84%). m.p. 298-302°C. 1 H NMR (DMSO-d6), δ, 8.01 (m, 1H, CH), 6.75-6.79 (m, 3H, NH2 and NH). MS (70 eV) m/z 169.13 (M); Mass m/z (%) 169.13 (M), 151.20, 135.13, 116.84, IR Spectra (in KBr) 1636, 1292, 822, 630 $cm^{-1}$. Analysis Calcd for C5H4ClN5: C, 35.37; H, 2.34; Cl, 20.93; N, 41.29. Found: C, 35.41; H, 2.38; Cl, 20.91; N, 41.30.

## 2.8.4 OPTIMIZATION OF REACTION CONDITIONS:

### 2.8.5 Solvent Screening (compound 2c)

There were several solvents have been studied for the suitable solvent for the reaction such as MDC, EDC, Toluene, Me THF, THF, PEG-400, PEG-2000 and EDC: PEG-2000 mixture and we found that EDC: PEG-2000 mixture gives good conversion for the reaction, so mixture of EDC: PEG-2000 have been chosed for the best solvent for the reaction and the results are listed below table.

| Sr.No. | Reagent | Solvent | Remarks |
|---|---|---|---|
| 1 | $POCl_3$ | MDC | Less conversion |
| 2 | $POCl_3$ | EDC | Good conversion |
| 3 | $POCl_3$ | Toluene | Less Conversion |
| 4 | $POCl_3$ | Me THF | Less Conversion |
| 5 | $POCl_3$ | THF | Impurity formation |
| 6 | $POCl_3$ | PEG 400 | Impurity formation |
| 7 | $POCl_3$ | EDC: PEG 2000 | Good conversion |

**Table: 2.9**

### 2.8.6 Reagent Screening

The Chlorinating solvent $POCl_3$ and $PCl_5$ have been explored for the reaction and it was found that POCl3 gives good conversion and low impurity formation, so POCL3 chosed for the reaction.

| Sr.No. | Reagent | Solvent | Remarks |
|---|---|---|---|
| 1 | $POCl_3$ | EDC: PEG 2000 | Good conversion |
| 2 | $PCl_5$ | EDC: PEG 2000 | Impurity formation |

**Table: 2.10**

### 2.8.7 Mole equivalents screening

Mole equivalents of POCl3 range from 1.00 to 3.50 have been studied, Less mole equivalents shows less conversion while 3.00-3.50 mole equivalents gives good conversion and less impurities observed, so 3.00 mole equivalents chosen for the chlorination reaction.

| Sr.No. | Reagent | Solvent | Mole Equi. | Remarks |
|---|---|---|---|---|
| 1 | $POCl_3$ | EDC: PEG 2000 | 3.00 | Good conversion |
| 2 | $POCl_3$ | EDC: PEG 2000 | 3.50 | Good conversion |
| 3 | $POCl_3$ | EDC: PEG 2000 | 4.50 | Impurity formation |
| 4 | $POCl_3$ | EDC: PEG 2000 | 2.50 | Impurity formation |
| 5 | $POCl_3$ | EDC: PEG 2000 | 1.00 | Unreacted KSM |

**Table: 2.11**

### 2.8.8 Temperature Screening

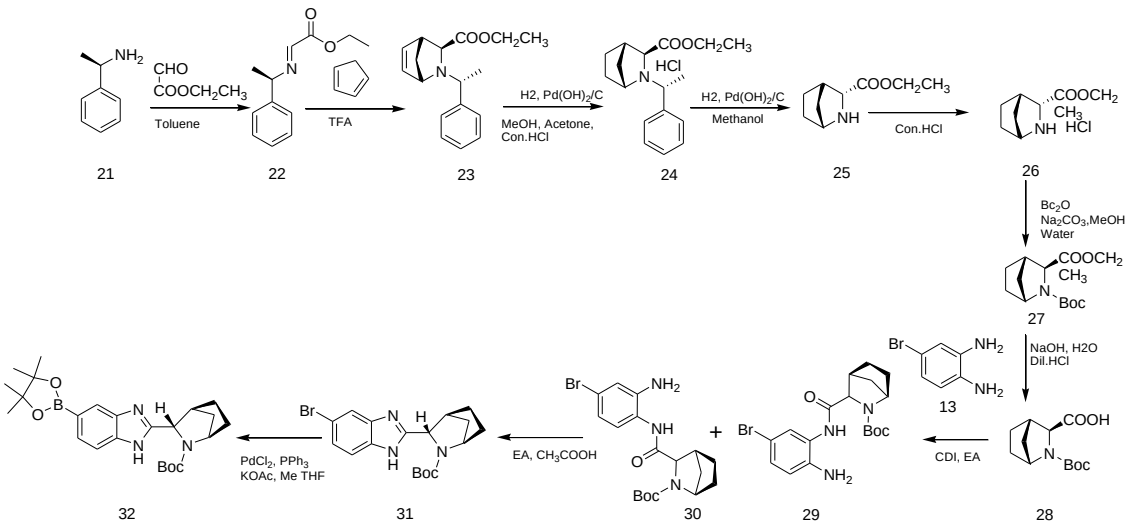
The temperature range from 60°C to 120°C have been studied and found that reaction proceeded well in the temperature range 80-90°C, higher temperature impurity formation was observed and low temperature reaction did not proceed or very slow so 80-90°C is the good temperature for the reaction.

| Sr.No. | Reagent | Solvent | Mole Equi. | Temp. | Remarks |
|---|---|---|---|---|---|
| 1 | $POCl_3$ | EDC: PEG 2000 | 1.10 | 80-85°C | Good conversion |
| 2 | $POCl_3$ | EDC: PEG 2000 | 1.15 | 85-90°C | Good conversion |
| 3 | $POCl_3$ | EDC: PEG 2000 | 1.25 | 100°C | Impurity formation |
| 4 | $POCl_3$ | EDC: PEG 2000 | 1.50 | 120°C | Impurity formation |
| 5 | $POCl_3$ | EDC: PEG 2000 | 1.00 | 60-70°C | Unreacted KSM |

**Table: 2.12**

## 2.9 SYNTHESIS OF (1R,3S,4S)-TERT-BUTYL 3-(5-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2YL)-1H-BENZO[d]IMIDAZOL-2-YL)-2-AZA-BICYCLO[2.2.1]HEPTANE-2-CARBOXYLATE:

**Reaction Scheme-2.4: process for the preparation of (1R,3S,4S)-tert-butyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate**




### 2.9.1 EXPERIMENTAL PROCEDURE:

### 2.9.2 Preparation of (E)-ethyl 2-((R)-1-phenylethylimino) acetate (22):

Charged the 50% solution of ethylglyoxalate in toluene (50.00 gm, 0.4897 moles) in 400 mL MDC, the obtained solution was cooled to 0-5°C followed by added sodium sulphate and R-Phenyl ethyl amine (61.00 gm, 0.5033 moles) the obtained reaction mixture was agitated for 2 hrs at 0-5°C then filtered and removed sodium sulphate then the reaction mass was carry forwarded to next step without isolation.

### 2.9.3 Preparation of (1R, 3S, 4S)-ethyl 2-((R)-1-phenylethyl)-2-aza-bicyclo [2.2.1] hept-5-ene-3-carboxylate (23):

Charged 10.00 gm molecular 3°A sieves to the above reaction mass and cooled to -70 to -80°C and added trifluoroacetic acid (55.78 gm, 0.4892 moles) then the raction mass stirred 15 min at -80 to -70°C, added slowly BF3 etahrate (69.44 gm, 0.4892 moles)

followed by freshly cracked cyclopentadiene (33.30 gm, 0.5037 moles), then the reaction mass was stirred 1-2 hrs at -70 to -80°C, the reaction mass was monitored by TLC then raise reaction temperature to 20-30°C then added saturated sodium carbonate solution to brought pH 8.00-8.50 then the reaction mass was hold to separate layers and layer was separated out then the solvent was distilled off under reduced pressure to produce title compound.

### 2.9.4 Preparation of (1R,3S,4S)-ethyl 2-((R)-1-phenylethyl)-2-aza-bicyclo[2.2.1]heptane-3-carboxylate hydrochloride (24):

1000 mL methanol(10.0 volumes) was charged to the above residue followed by 10 ml (0.20 volumes) water was added followed by 10.00 gm of palladium hydroxide was added in to it (50% wet), the reactor was filled with 1.0 kg hydrogen pressure and reaction mass was stirred 1.0 hr at 25-35°C, after completion of reaction catalyst was separated by filtration, distilled out solvent completely under reduced pressure, then 200 mL acetone was added followed by addition of 35.% Con.HCl solution, the reaction mass was stirred and filtered to produce title compound.

### 2.9.5 Preparation of Ethyl (1R,3S,4S)-2-azabicyclo[2.2.1]heptane-3-carboxylate hydrochloride (26):

1000 mL methanol(10.0 volumes) was charged to the compound 3 followed by 10 ml (0.20 volumes) water was added followed by 10.00 gm of palladium hydroxide was added in to it (50% wet), the reactor was filled with 6-7kg hydrogen pressure and reaction mass was stirred 6 hrs at 25-35°C, after completion of reaction catalyst was separated by filtration, distilled out solvent completely under reduced pressure, then 200 mL acetone was added followed by 35.0% Con.HCl to the reaction mass and the reaction mass was stirred 3.0 hrs and filtered off to produce title compound.

### 2.9.6 Preparation of (1R,3S,4S)-tert-butyl ethyl 2-aza-bicyclo[2.2.1]heptane-2,3-dicarboxylate (27):

Compound 6 was dissolved in 500 mL methanol and 100 mL water followed by addition of Sodium carbonate (62.00 gm, 0.5849 moles) and followed by addition of boc anhydride (36.50 gm, 0.1671 moles) at 10-20°C, the obtained reaction mixture was stirred 12.0 hrs at 20-30°C, reaction progress was monitored by TLC, after completion of reaction methanol was removed by distillation under reduced pressure, the product was partitioned with MDC and successively washed with water and distilled off solvent under reduced pressure to get title compound.

### 2.9.7 Preparation of (1R, 3S, 4S)-2-(tert-butoxycarbonyl)-2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid (28):

Charged water 300 mL and sodium hydroxide (33.00 gm, 0.8250 moles) followed by addition of compound 7 and 300 mL THF, the reaction mixture heated to 50-60°C, the on mass was stirred 6 hrs at 50-60°C, then the THF was distilled off 300 mL MDC was added to the reaction mass followed by addition of dilute HCl solution to bring the pH: 3.50-4.00 then the reaction mass was stirred 40 min at room temperature, then reaction mixture was washed with water separated out organic layer then distilled off the solvent under reduced pressure and 150 mL cyclohexane was added in to it, the mixture was stirred 8 hrs at 20-30°C, the precipitated product was isolated by the filtration to produce title compound 30.0 gm.

### 2.9.8 Preparation of (1R,3S,4S)-tert-butyl 3-(2-amino-5-bromophenylcarbamoyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (9) and (1R,3S,4S)-tert-butyl 3-(2-amino-4-bromophenylcarbamoyl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (30):

50 gm of compound 8 dissolved in 500 mL of ethy acetate carbonyldiimidazole (CDI) (40.33 gm, 0.2486 moles) was added in to it, the reaction mass stirred 1 hrs at 20-30°C

under nitrogen atmosphere, then charged 4-bromobenzene-1,2-diamine ( 40.70 gm, 0.2176 moles) and the reaction mass was stirred 1 hrs at 25-35°C, the reaction progress was monitored by TLC, and water was added in to it, organic layer was separated out then organic layer was washed with water, solvent removed by distillation under reduced pressure to afford title compound 76.52 gm, (90.00% yield).

### 2.9.9 Preparation of (1R,3S,4S)-tert-butyl 3-(5-bromo-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (31) :

Compound 9 and 10 mixture (70.00 gm, 0.1706 moles) was added in 490 mL ethylacetate followed by 105 mL acetic acid the reaction mixture heated in to reflux then continued refflux till reaction completion water added after reaction completed ethylacetate layer was distilled off and the precipitated product was isolated by filtration and affored a white solid (63.57 gm, 95.0%).

### 2.9.10 Preparation of (1R,3S,4S)-tert-butyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (32):

Palladium chloride (1.88 gm, 0.0160 moles) was suspended in 500 ml 2Me THF followed by triphenyl phosphine (6.31 gm, 0.0240 moles) then the reacton mass was stirred under nitrogen atmoshphereandCompound 11 (63 gm, 0.1605 moles) followed by potassium acetate (39.33 gm, 0.4008 moles) followed by addition of Bis(pinacolato)diboron (44.85 gm, 0.1766 moles), this reaction mass was heated into reflux and continued reflux till reaction completion, after reaction completion water was added in to it, organic layer was distilled off and acetonitrile 190 ml was added in to it, desire product was isolated by filtration as a white solid (62.80 gm, 89.5%).

### 2.9.11 OPTIMIZATION OF REACTION CONDITIONS:

### 2.9.12 Solvent Screening for preparation of Compound-22:

There were several solvents have been studied for the suitable solvent for the reaction such as MDC, Ethylacetate, Toluene, Methanol and IPA and we found that MDC and Toluene gives good progress for the reaction, and MDC give little less impurity formation compare with toluene, so MDC have been chosed for the reaction solvent.

| Sr.No. | Solvent | Mole Equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Toulene | 1.03 | 0-5°C | Good conversion |
| 2 | MDC | 1.03 | 0-5°C | Good conversion |
| 3 | Ethylacetate | 1.03 | 0-5°C | Impurity formation |
| 4 | Methanol | 1.03 | 0-5°C | Impurity formation |
| 5 | Isopropyl alcohol | 1.03 | 0-5°C | Impurity formation |

**Table: 2.13**

### 2.9.13 Mole Equivalents Screening of R-Phenylethylamine for preparation of Compound-22:

Mole equivalents of R-phenylethylamine have been studied from range of 0.80 to 1.30 have been studied, Less mole equivalents shows less conversion while 1.03 mole equivalents gives good conversion and less impurities observed, so 1.03 mole equivalents chosen for the reaction.

| Sr.No. | Solvent | Mole Equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | MDC | 1.03 | 0-5°C | Good conversion |
| 2 | MDC | 1.03 | 0-5°C | Reaction did not completed |
| 3 | MDC | 1.03 | 0-5°C | Reaction did not completed |
| 4 | MDC | 1.03 | 0-5°C | Impurity formation |
| 5 | MDC | 1.03 | 0-5°C | Impurity formation |

**Table: 2.14**

### 2.9.14 Temperature screening for preparation of Compound-22:

The temperature range from -10°C to 25°C have been studied and found that reaction proceeded well in the temperature range 0-10°C, higher temperature impurity formation was observed and low temperature reaction very slow so 0-10°C is the optimum temperature for the reaction.

| Sr.No. | Solvent | Mole Equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | MDC | 1.03 | 0-5°C | Good conversion |
| 2 | MDC | 1.03 | -5 to -10°C | Long time |
| 3 | MDC | 1.03 | 5-10°C | Good conversion |
| 4 | MDC | 1.03 | 10-15°C | Impurity formation |
| 5 | MDC | 1.03 | 20-25°C | Impurity formation |

**Table: 2.15**

### 2.9.15 Solvent Screening for preparation of Compound-23:

There were several solvents have been studied for the suitable solvent for the reaction such as MDC, Ethylacetate and Toluene have been studied to find the good solvent for the reaction and it was found that MDC gives good conversion and less impurity formation , so MDC have been chosed for the reaction solvent.

| Sr.No. | Solvent | Mole Equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Toulene | 1.03 | 0-5°C | Impurity formation |
| 2 | MDC | 1.03 | 0-5°C | Reaction proceeded well |
| 3 | Ethylacetate | 1.03 | 0-5°C | Impurity formation |

**Table: 2.16**

### 2.9.16 Mole Equivalents Screening of $BF_3$ etharate for preparation of Compound-23:

Mole equivalents of cyclopentadiene have been studied from range of 0.90 to 1.20 have been studied, Less mole equivalents shows less conversion while 1.00 mole equivalents gives good conversion and less impurities observed, so 1.00 mole equivalents chosen for the diels-alder reaction.

| Sr.No. | Solvent | Mole Equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | MDC | 1.00 | 0-5°C | Good conversion observed |
| 2 | MDC | 0.95 | 0-5°C | Reaction did not completed |
| 3 | MDC | 0.90 | 0-5°C | Reaction did not completed |
| 4 | MDC | 1.10 | 0-5°C | Impurity formation |
| 5 | MDC | 1.20 | 0-5°C | Impurity formation |

**Table: 2.17**

### 2.9.17 Mole Equivalents Screening of Cyclopentadiene for preparation of Compound-23:

Mole equivalents of $BF_3$ have been studied from range of 0.90 to 1.20 have been studied, Less mole equivalents shows less conversion while 1.03 mole equivalents gives good aconversion and less impurities observed, so 1.03 mole equivalents chosen for the reaction.

| Sr.No. | Solvent | Mole Equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | MDC | 1.03 | -70 to -80°C | Good conversion observed |
| 2 | MDC | 0.95 | -70 to -80°C | Reaction did not completed |
| 3 | MDC | 0.90 | -70 to -80°C | Reaction did not completed |
| 4 | MDC | 1.10 | -70 to -80°C | Impurity formation |
| 5 | MDC | 1.20 | -70 to -80°C | Impurity formation |

**Table: 2.18**

### 2.9.18 Temperature screening for preparation of Compound-23:

The temperature range from -80°C to 25°C have been studied and found that reaction proceeded well in the temperature range -70 to -80°C, higher temperature impurity formation was observed and low not studied so -70 to -80°C is the optimum temperature for the reaction.

| Sr.No. | Solvent | Mole Equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | MDC | 1.00 | -70 to -80°C | Good conversion |
| 2 | MDC | 1.00 | -50 to -40°C | Impurity formation |
| 3 | MDC | 1.00 | -5 to-10°C | Impurity formation |
| 4 | MDC | 1.00 | 10-15°C | Impurity formation |
| 5 | MDC | 1.00 | 20-25°C | Impurity formation |

**Table: 2.19**

### 2.9.19 Solvent Screening for preparation of Compound-24:

There were several solvents have been studied for the suitable solvent for the reaction such as Methanol, Ethanol, Acetic acid, water, and Con.HCL have been studied to find the suitable solvent for the hydrogenation reaction and it was found that Methanol gives good conversion and less impurity formation , so Methanol have been chosen for the reaction solvent.

| Sr.No. | Solvent | Cat. w/w $Pd(OH)_2$ | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Methanol | 20% | 25-35°C | Reaction proceeded well |
| 2 | Ethanol | 20% | 25-35°C | Less conversion than MeOH |
| 3 | Water | 20% | 25-35°C | Very few conversion |
| 4 | Acetic acid | 20% | 25-35°C | Impurity formation |
| 5 | Con.HCl | 20% | 25-35°C | Impurity formation |

**Table: 2.20**

**Table: 2.20**

### 2.9.20 Catalyst screening for preparation of Compound-24:

Reduction catalyst such as palladium on carbon, palladium hydroxide and Raney nickel have been studied to find out suitable catalyst for the hydrogenation reaction, palladium hydroxide give very good conversion in readuction reaction followed by debenzylation reaction also, so palladium hydroxide have been chosen for the reaction.

| Sr.No. | Solvent | Cat. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Methanol | Pd/C | 25-35°C | Reaction proceeded well |
| 2 | Methanol | Pd(OH)2 | 25-35°C | Reaction proceeded well |
| 3 | Methanol | Raney Ni | 25-35°C | No conversion |

**Table: 2.21**

### 2.9.21 Temperature screening for preparation of Compound-24:

The temperature range from 10°C to 45°C have been studied and found that reaction proceeded well in the temperature range 30 to 45°C, higher temperature impurity formation was observed and low temperature reaction very very slow, so optimum temperature 25-35°C chosen for the reaction.

| Sr.No. | Solvent | Cat. w/w $Pd(OH)_2$ | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Methanol | 20% | 25-35°C | Reaction proceeded well |
| 2 | Methanol | 20% | 35-45°C | Reaction proceeded |
| 3 | Methanol | 20% | 20-25°C | Reaction takes Long time |
| 4 | Methanol | 20% | 10-15°C | Reation very slow |

**Table: 2.22**

### 2.9.22 Solvent Screening for preparation of Compound-27:

There were several solvents have been studied for the suitable solvent for the reaction such as Methanol, Ethanol, THF, water, and Toluene have been studied to find the suitable solvent for the reaction and it was found that Methanol gives good conversion and less impurity formation , so Methanol have been chosen for the reaction solvent.

| Sr.No. | Solvent | Boc anhydride Mole.equi. | Base | Temp. | Remarks |
|---|---|---|---|---|---|
| 1 | Methanol | 2.0 | $Na_2CO_3$ | 20-30°C | Reaction proceeded well |
| 2 | Ethanol | 2.0 | $Na_2CO_3$ | 20-30°C | Less conversion than MeOH |
| 3 | Water | 2.0 | $Na_2CO_3$ | 20-30°C | Less conversion |
| 4 | THF | 2.0 | $Na_2CO_3$ | 20-30°C | Reaction proceeded well |
| 5 | Toluene | 2.0 | $Na_2CO_3$ | 20-30°C | Reaction not proceeded |

**Table: 2.23**

### 2.9.23 Catalyst screening for preparation of Compound-25:

Reduction catalyst such as palladium on carbon, palladium hydroxide and Raney nickel have been studied to find out suitable catalyst for the hydrogenation reaction, palladium hydroxide give very good conversion in debenzylation reaction followed by debenzylation reaction also, so palladium hydroxide have been chosen for the reaction.

| Sr.No. | Solvent | Cat. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Methanol | Pd/C | 25-35°C | Reaction proceeded well |
| 2 | Methanol | Pd(OH)2 | 25-35°C | Reaction proceeded well |
| 3 | Methanol | Raney Ni | 25-35°C | No conversion |

**Table: 2.24**

### 2.9.24 Temperature screening for preparation of Compound-25:

The temperature range from 10°C to 45°C have been studied and found that reaction proceeded well in the temperature range 30 to 45°C, higher temperature impurity formation was observed and low temperature reaction very very slow, so optimum temperature 25-35°C chosen for the reaction.

| Sr.No. | Solvent | Cat. w/w$Pd(OH)_2$ | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Methanol | 20% | 25-35°C | Reaction proceeded well |
| 2 | Methanol | 20% | 35-45°C | Reaction proceeded |
| 3 | Methanol | 20% | 20-25°C | Reaction takes Long time |
| 4 | Methanol | 20% | 10-15°C | Reation very slow |

**Table: 2.25**

### 2.9.25 Solvent Screening for preparation of Compound-27:

There were several solvents have been studied for the suitable solvent for the reaction such as Methanol, Ethanol, MDC, water, and Ethylacetate have been studied to find the suitable solvent for the reaction and it was found that Methanol gives good conversion and less impurity formation , so Methanol have been chosen for the reaction solvent.

| Sr.No. | Solvent | $Na_2CO_3$ Mol.equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Methanol | 3.0 | 25-30°C | Reaction proceeded well |
| 2 | Ethanol | 3.0 | 25-30°C | Less conversion than MeOH |
| 3 | Water | 3.0 | 25-30°C | Less conversion |
| 4 | MDC | 3.0 | 25-30°C | Less conversion |
| 5 | Ethylacetate | 3.0 | 25-30°C | Less conversion |

**Table: 2.26**

### 2.9.26 Base Screening for preparation of Compound-27:

Bases like Na2CO3, NaOH, KOH, NaHCO3 and TEA has been studied for the reaction, when we are using strong bases like NaOH, KOH more impurity formation was

observed, when using organic bases less conversion was observed, so we have been chosen sodium carbonat for the reaction.

| Sr.No. | Solvent | Base | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Methanol | $Na_2CO_3$ | 25-35°C | Reaction proceeded well |
| 2 | Methanol | $NaHCO_3$ | 25-35°C | Reaction proceeded well but less conversion than $Na_2CO_3$ |
| 3 | Methanol | NaOH | 25-35°C | Impurity formation |
| 4 | Methanol | KOH | 25-35°C | Impurity formation |
| 5 | Methanol | TEA | 25-35°C | Less Conversion |

**Table: 2.27**

### 2.9.27 $Bc_2O$ mole equi. Screening for preparation of Compound-27:

Mole equivalents of cyclopentadiene have been studied from range of 2.50 to 3.50 have been studied, reaction proceeded very well in the range of 3.00 to 3.50 so 3.00 mole equivalents chosen for the diels-alder reaction.

| Sr.No. | Solvent | $Na_2CO_3$Mol.equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Methanol | 3.00 | 25-30°C | Reaction proceeded well |
| 2 | Methanol | 2.75 | 25-30°C | Reaction not complted |
| 3 | Methanol | 2.50 | 25-30°C | Reaction not complted |
| 4 | Methanol | 3.25 | 25-30°C | Reaction proceeded well |
| 5 | Methanol | 3.50 | 25-30°C | Reaction proceeded well |

**Table: 2.28**

### 2.9.28 Temperature screening for preparation of Compound-27:

The temperature range from 10°C to 45°C have been studied and found that reaction proceeded well in the temperature range 30 to 45°C, higher temperature impurity formation was observed and low temperature reaction very slow, so optimum temperature 25-35°C chosen for the reaction.

| Sr.No. | Solvent | $Bc_2O$ | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Methanol | 3.00 | 25-35°C | Reaction proceeded well |
| 2 | Methanol | 3.00 | 35-45°C | Reaction proceeded |
| 3 | Methanol | 3.00 | 20-25°C | Reaction takes Long time |
| 4 | Methanol | 3.00 | 10-15°C | Reation very slow |

**Table: 2.29**

### 2.9.29 Solvent Screening for preparation of Compound-28:

There were several solvents have been studied for the suitable solvent for the reaction such as Methanol, Ethanol, IPA, water, and THF have been studied to find the suitable solvent for the reaction and it was found that Methanol gives good conversion and less impurity formation , so Methanol have been chosen for the reaction solvent.

| Sr.No. | Solvent | NaOH Mol.equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Water | 1.50 | 50-60°C | Reaction proceeded well |
| 2 | THF | 1.50 | 50-60°C | Less conversion than MeOH |
| 3 | Isopropyl alcohol | 1.50 | 50-60°C | Less conversion |
| 4 | Methanol | 1.50 | 50-60°C | Less conversion |
| 5 | Ethanol | 1.50 | 50-60°C | Less conversion |

**Table: 2.30**

### 2.9.30 Base Screening for preparation of Compound-28:

Bases like NaOH, KOH and LiOH have been studied for the reaction, reaction proceeded well in NaOH, so we have been chosen sodium hydroxide for the reaction.

| Sr.No. | Solvent | Base | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Water: THF | NaOH | 50-60°C | Reaction proceeded well |
| 2 | Water: THF | KOH | 50-60°C | Less conversion than MeOH |
| 3 | Water: THF | LiOH | 50-60°C | Less conversion |

**Table: 2.31**

**Table: 2.31**

### 2.9.31 NaOH mole equi. Screening for preparation of Compound-28:

The mole equivalents of NaOH have been studied from the range of 1.00 – 2.50 mole equivalents and the reaction proceeded well and less impurity formation was observed at 1.50-2.00 mole equivalents, so 1.50 equivalents have been chosen for the reaction.

| Sr.No. | Solvent | $Na_2CO_3$Mol.equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Water: THF | 1.50 | 25-30°C | Reaction proceeded well |
| 2 | Water: THF | 2.00 | 25-30°C | Reaction proceeded well |
| 3 | Water: THF | 2.50 | 25-30°C | Impurity formation observed |
| 4 | Water: THF | 1.00 | 25-30°C | Reaction not complted |

**Table: 2.32**

### 2.9.32 Temperature screening for preparation of Compound-28:

The temperature range from 20°C to 70°C have been studied and found that reaction proceeded well in the temperature range 50 to 60°C, higher temperature impurity formation was observed and low temperature reaction very slow, so optimum temperature 50-60°C chosen for the reaction.

| Sr.No. | Solvent | NaOH mole.equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Water: THF | 1.50 | 50-60°C | Reaction proceeded well |
| 2 | Water: THF | 1.50 | 35-45°C | Reaction takes Long time |
| 3 | Water: THF | 1.50 | 65-70°C | Impurity formation |
| 4 | Water: THF | 1.50 | 20-30°C | No Reation |

**Table: 2.33**

### 2.9.33 Solvent Screening for preparation of Compound-29 and 30:

There were several solvents have been studied for the suitable solvent for the reaction such as Ethylacetate, Toluene, MDC, DMF and DMSO have been studied to find the

suitable solvent for the reaction and it was found that ethylacetate gives good conversion and less impurity formation , so Ethylacetate have been chosen for the reaction solvent.

| Sr.No. | Solvent | CDI Mol.equi. | 13 Mol.equi. | Temp. | Remarks |
|---|---|---|---|---|---|
| 1 | Ethylacetate | 1.20 | 1.05 | 20-35°C | Reaction proceeded well |
| 2 | Toluene | 1.20 | 1.05 | 20-35°C | Less conversion |
| 3 | MDC | 1.20 | 1.05 | 20-35°C | Reaction proceeded well |
| 4 | DMF | 1.20 | 1.05 | 20-35°C | Impurity formation observed |
| 5 | DMSO | 1.20 | 1.05 | 20-35°C | Impurity formation observed |

**Table: 2.33**

### 2.9.34 Coupling reagent screening for preparation of Compound-29 and 30:

Amino acid coupling reagents like CDI, EDC,HOBt and DCC have been studied to find out suitable reagent for the aminoacid coupling reaction and it was found that reaction proceeded well in CDI(carbonyl diimidazole), so CDI have been chosen for the reaction.

| Sr.No. | Solvent | Reagent | CDI Mol.equi. | Temp. | Remarks |
|---|---|---|---|---|---|
| 1 | Ethylacetate | CDI | 1.05 | 20-35°C | Reaction proceeded well |
| 2 | Ethylacetate | EDC, HOBt | 1.05 | 20-35°C | Less conversion |
| 3 | Ethylacetate | DCC | 1.05 | 20-35°C | Reaction proceeded |

**Table: 2.34**

### 2.9.35 CDI mole equi. Screening for preparation of Compound-29 and 30:

The mole equivalents of CDI have been studied from the range of 0.90-1.50 mole equivalents and the reaction proceeded well and less impurity formation was observed at 1.20 mole equivalents, so 1.20 equivalents have been chosen for the reaction.

| Sr.No. | Solvent | CDI Mol.equi. | 13 Mol.equi. | Temp. | Remarks |
|---|---|---|---|---|---|
| 1 | Ethylacetate | 1.20 | 1.05 | 25-30°C | Reaction proceeded well |
| 2 | Ethylacetate | 1.10 | 1.05 | 25-30°C | Reaction proceeded well |

| | | | | | |
|---|---|---|---|---|---|
| 3 | Ethylacetate | 0.90 | 1.05 | 25-30°C | Reaction not complted |
| 4 | Ethylacetate | 1.50 | 1.05 | 25-30°C | Impurity formation observed |

**Table: 2.36**

### 2.9.36 13 mole equivalents screening for preparation of Compound-29 and 30:

The mole equivalents of CDI have been studied from the range of 0.95-1.50 mole equivalents and the reaction proceeded well and less impurity formation was observed at 1.05-1.50 mole equivalents, so 1.05 equivalents have been chosen for the reaction.

| Sr.No. | Solvent | 13 mole.equi. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Ethylacetate | 1.05 | 20-35°C | Reaction proceeded well |
| 2 | Ethylacetate | 1.15 | 20-35°C | Reaction proceeded well |
| 3 | Ethylacetate | 1.50 | 20-35°C | Impurity formation |
| 4 | Ethylacetate | 0.95 | 20-35°C | Reaction not completed |

**Table: 2.37**

### 2.9.37 Temperature screening for preparation of Compound-29 and 30:

The temperature range from 20°C to 70°C have been studied and found that reaction proceeded well in the temperature range 50 to 60°C, higher temperature impurity formation was observed and low temperature reaction very very slow, so optimum temperature 50-60°C chosen for the reaction.

| Sr.No. | Solvent | CDI mole.equi. | 13mole.equi. | Temp. | Remarks |
|---|---|---|---|---|---|
| 1 | Ethylacetate | 1.20 | 1.05 | 20-35°C | Reaction proceeded well |
| 2 | Ethylacetate | 1.20 | 1.15 | 20-35°C | Reaction proceeded well |
| 3 | Ethylacetate | 1.20 | 1.50 | 20-35°C | Impurity formation |
| 4 | Ethylacetate | 1.20 | 0.95 | 20-35°C | Reaction not completed |

**Table: 2.38**

### 2.9.38 Solvent Screening for preparation of Compound 31:

There were several solvents have been studied for the suitable solvent for the reaction such as Ethylacetate, Toluene, MDC and Acetic acid have been studied to find the suitable solvent for the reaction and it was found that ethylacetate gives good conversion and less impurity formation , so Ethylacetate have been chosen for the reaction solvent.

| Sr.No. | Solvent | Acetic acid vol. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Ethylacetate | 1.00 | 65-75°C | Reaction proceeded well |
| 2 | Toluene | 1.00 | 65-75°C | Impurity formation |
| 3 | MDC | 1.00 | 30-40°C | Reaction takes long timel |
| 4 | Acetic acid | 1.00 | 65-75°C | Rection proceeded well |

**Table: 2.39**

### 2.9.39 Cyclization reagent screening for preparation of Compound 31:

For the cyclization reaction, reagents like Acetic acid, PTSA and $POCl_3$ have been studied and found that acetic acid is the good solvent for cyclization reaction due to good conversion and easy handling and low cost.

| Sr.No. | Solvent | Reagent | Volumes | Temp. | Remarks |
|---|---|---|---|---|---|
| 1 | Ethylacetate | Acetic acid | 1.00 | 65-75°C | Reaction proceeded well |
| 2 | Ethylacetate | PTSA | 1.50 equi. | 65-75°C | Less conversion |
| 3 | Ethylacetate | $POCl_3$ | 1.50 equi. | 65-75°C | Reaction proceeded |

**Table: 2.40**

### 2.9.40 Acetic acid voume screeningfr preparation of Compound 31:

Volumes of acetic acid have been studied for cyclization reaction and reaction proceeded well from 1.0 volume to 2.0 volumes, so 1.0 volume of acetic acid chosen for the cyclization reaction.

| Sr.No. | Solvent | Acetic acid vol. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Ethylacetate | 1.00 | 65-75°C | Reaction proceeded well |
| 2 | Ethylacetate | 1.50 | 65-75°C | Reaction proceeded well |

| | | | | |
|---|---|---|---|---|
| 3 | Ethylacetate | 2.00 | 65-75°C | Reaction proceeded well |
| 4 | Ethylacetate | 0.50 | 65-75°C | Reaction not completed |

**Table: 2.41**

### 2.9.41 Temperature screening for preparation of Compound 31:

The temperature range from 45°C to reflux have been studied and found that reaction proceeded well in the reflux temperature so reflux temperature chosen for the reaction.

| Sr.No. | Solvent | Acetic acid vol. | Temp. | Remarks |
|---|---|---|---|---|
| 1 | Ethylacetate | 1.00 | 65-75°C | Reaction proceeded well |
| 2 | Ethylacetate | 1.00 | Reflux | Reaction proceeded well |
| 3 | Ethylacetate | 1.00 | 60-70°C | Little slow reation |
| 4 | Ethylacetate | 1.00 | 45-55°C | Very slow reaction |

**Table: 2.42**

### 2.9.42 Solvent Screening for preparation of Compound 32:

There were several solvents have been studied for the suitable solvent for the reaction such as ME THF, THF, Toluene, 1.4 dioxan and 2 methoxy ethane have been studied to find the suitable solvent for the reaction and it was found that Me THF gives good conversion and less impurity formation, so Me THF have been chosen for the reaction solvent.

| Sr. No. | Solvent | $(pinB)_2$ Mole. Equi. | $PdCl_2$ Mole. Equi. | $PPh_3$ Mole. Equi. | Temp. | Remarks |
|---|---|---|---|---|---|---|
| 1 | 2Me THF | 1.20 | 0.03 | 0.06 | Reflux | Reaction proceeded well |
| 2 | THF | 1.20 | 0.03 | 0.06 | Reflux | Reaction proceeded well |
| 3 | Toluene | 1.20 | 0.03 | 0.06 | Reflux | Impurity formation observed |
| 4 | 1,4 Dioxane | 1.20 | 0.03 | 0.06 | Reflux | Impurity formation observed |
| 5 | 2-Methoxyethane | 1.20 | 0.03 | 0.06 | Reflux | Impurity formation observed |

**Table: 2.43**

### 2.9.43 (pin B)$_2$ mole.equivqlents screening for preparation of Compound 32:

The mole equivalents of **(pinB)$_2$** have been studied from the range of 0.90-1.30 mole equivalents and the reaction proceeded well and less impurity formation was observed at 1.20-1.30 mole equivalents, so 1.20 equivalents have been chosen for the reaction.

| **Sr. No.** | **Solvent** | **(pinB)$_2$ Mole. Equi.** | **PdCl$_2$ Mole. Equi.** | **PPh$_3$ Mole. Equi.** | **Temp.** | **Remarks** |
|---|---|---|---|---|---|---|
| 1 | 2Me THF | 1.20 | 0.03 | 0.06 | Reflux | Reaction proceeded well |
| 2 | 2Me THF | 1.30 | 0.03 | 0.06 | Reflux | Reaction proceeded well |
| 3 | 2Me THF | 1.10 | 0.03 | 0.06 | Reflux | Reaction not cmpleted |
| 4 | 2Me THF | 0.95 | 0.03 | 0.06 | Reflux | More unreacted starting material observed |
| 5 | 2Me THF | 0.90 | 0.03 | 0.06 | Reflux | More unreacted starting material observed |

**Table: 2.44**

### 2.9.44 PdCl$_2$ and PPh$_3$ mole equi. Screening for preparation of Compound 32:

The mole equivalents of PdCl$_2$ and PPh$_3$ have been studied from the range of 0.01, 0.02-0.075, 0.15 mole equivalents and the reaction proceeded well and less impurity formation was observed at 0.03, 0.06-0.075, 0.15 mole equivalents, so 0.06 mole equivalents of PdCl$_2$ and 0.06 mole equivalents of PPh$_3$ have been chosen for the reaction.

| **Sr. No.** | **Solvent** | **(pinB)$_2$Mole. Equi.** | **PdCl$_2$Mole. Equi.** | **PPh$_3$Mole. Equi.** | **Temp.** | **Remarks** |
|---|---|---|---|---|---|---|
| 1 | 2Me THF | 1.20 | 0.03 | 0.06 | Reflux | Reaction proceeded well |
| 2 | 2Me THF | 1.30 | 0.05 | 0.10 | Reflux | Reaction proceeded well |
| 3 | 2Me THF | 1.10 | 0.075 | 0.15 | Reflux | Reaction proceeded well |
| 4 | 2Me THF | 0.95 | 0.015 | 0.03 | Reflux | More SM observed |
| 5 | 2Me THF | 0.90 | 0.01 | 0.02 | Reflux | More SM observed |

**Table: 2.45**

### 2.9.45 Base screening for preparation of Compound 32:

The bases like KOAc, NaOH, $Na_2CO_3$, TEA and $NaHCO_3$ have been studied for the reaction and it was found that in KOAc reaction proceeded well, so KOAc have been chosen for the reaction.

| **Sr. No.** | **Solvent** | **$(pinB)_2$Mole Equi.** | **$PdCl_2$Mole Equi.** | **$PPh_3$Mole Equi.** | **Base** | **Temp.** | **Remarks** |
|---|---|---|---|---|---|---|---|
| 1 | 2Me THF | 1.20 | 0.03 | 0.06 | KOAc | Reflux | Proceeded well |
| 2 | 2Me THF | 1.20 | 0.03 | 0.06 | NaOH | Reflux | Impurity formation |
| 3 | 2Me THF | 1.20 | 0.03 | 0.06 | $Na_2CO_3$ | Reflux | Not completed |
| 4 | 2Me THF | 1.20 | 0.03 | 0.06 | TEA | Reflux | Impurity formation |
| 5 | 2Me THF | 1.20 | 0.03 | 0.06 | $NaHCO_3$ | Reflux | Less Conversion |

**Table: 2.46**

### 2.9.46 Temperature screening for preparation of Compound 32:

The temperature range from 35°C to reflux have been studied and found that reaction proceeded well in the reflux, so reflux temperature chosen for the reaction.

| **Sr. No.** | **Solvent** | **$(pinB)_2$ Mole.Equi.** | **$PdCl_2$Mole Equi.** | **$PPh_3$Mole Equi.** | **Base** | **Temp.** | **Remarks** |
|---|---|---|---|---|---|---|---|
| 1 | 2Me THF | 1.20 | 0.03 | 0.06 | KOAc | Reflux | Reaction proceeded well |
| 2 | 2Me THF | 1.20 | 0.03 | 0.06 | KOAc | 65-70°C | Very less conversion |
| 3 | 2Me THF | 1.20 | 0.03 | 0.06 | KOAc | 50-60°C | No reaction |
| 4 | 2Me THF | 1.20 | 0.03 | 0.06 | KOAc | 35-45° | No reaction |

**Table: 2.47**

# 3. PREPARATION OF URACIL BASED MOLECULES

Cancer is abnormal growth of normal cells and it has a potential to spread all over the body, Developed and under developed countries are affected by cancer and it has more leading disease causes of death. Although, there are several anticancer drugs (anti-neoplastic agents or chemotherapeutic agents) are available in the market such as cisplatin, 5-fluorouracil, taxol, procarbazine, carmustine etc, for the treatment of cancer and till we do not have any drugs that can treat cancer effectively at late stages and most of the drugs are having many side effects [67-71]. The presently available anticancer agents in the markets are having serious side effects, low bioavailability and also having poor solubility, narrow therapeutic windows and intensive cytotoxicities to normal tissues [72-76]. Some anticancer drugs are less effective [77-80] due to poor solubility.

Uracil and its derivatives are considered as a one the most important and privileged structures in drug discovery with broad topics of biological activities and synthetic accessibility. Antitumor and Anitiviral are most widely reported activities of uracil derivatives. Even though some other activities were reported such as bactericidal, herbicidal and insecticidal. Their antiviral potential is based on the inhibition of a key step in viral replication pathway resulting in potent activities against HIV, hepatitis B and C, the herpes viruses and so forth. 5-Fluorouracil or 5-chlorouracil was the first pharmacological active uracil derivatives [81-90]. Recently, chemists paid more attention towards uracil analogues, some pharmacologically important analogues are shown in Fig 3.1. In the development of derivatives possessing better pharmacological and pharmacokinetic properties (increased bioactivity, selectivity, metabolic stability, absorption, and lower toxicity) many modifications of uracil have been performed so for to tackle toxicity problems. Researches of new uracil derivatives and fused uracil derivatives as bioactive agents relate to modifications of substituents at different positions of the pyrimidine ring [91]. Besides, some anticancer drugs which are available in the market are having some issues such as higher cost [92] low solubility and low bioavailability these issues are making them less effective [93-95]. Therefore, today we

need new anticancer agents [96] to treat different type of cancers with high solubility and high bioavailability.

Such an important drug molecules are not available affordable cost to the patient and all available literature shows that hazardous chemicals have been used for the preparation of target molecules and it was reported lower yield these drawbacks leads to higher cost and danger to environment and infrastructure.

## 3.1 PREPARATION OF URACIL BASED MOC-L-VALINE DERIVATIVES

To overcome all those drawbacks the effort were made to carry out the reactions with simple and cheaply available raw materials, reagents and less usage of solvents to avoid isolation steps to produced targeted molecules.

To prepare target molecules we have been developed an efficient and simple protocol has been developed in this protocol.

In one pot synthesis organic reactions one solvent have been used in many steps [97], so chemist are attracted by one pot synthesis. Because these reactions are of low cost, environment friendly and produces maximum yield of products and are gives insights into green chemistry .The reduction of by products, waste, energy and cost green chemistry approaches are significant. Due to enhance their efficiency, from an economical and from an ecological consideration, performing multistep reaction under one pot are much important. New heterocyclic compounds synthesis has always been a subject of great interest due to their wide applications in synthetic chemistry as well as in biological world. Because, heterocyclic compounds occur vary widely in nature and are essential to life. Amongst, heterocyclic compounds containing uracil moiety are interesting due to some pharmacological and biological activities. Uracil and its derivatives are the important key starting material for the preparation of many organic molecules, drug substances and drug intermediates [92-94]. Primary bowel cancer [95]and cancers are treated by chemotherapy drug Tegafur-uracil. Thus, the important and useful task in organic chemistry is to preparation new uracil derivatives. In recent

years, the synthesis of uracil derivatives has been reported. In continuation of all the aspects available in literature, the efforts were made to explore new protocol for the development of low cost and one pot synthesis of uracil derivatives. Besides, the experimental and theoretical DNA binding studies were also carried out to find out the binding affinity and modes of various compounds with calf thymus-DNA. The results are given herein.

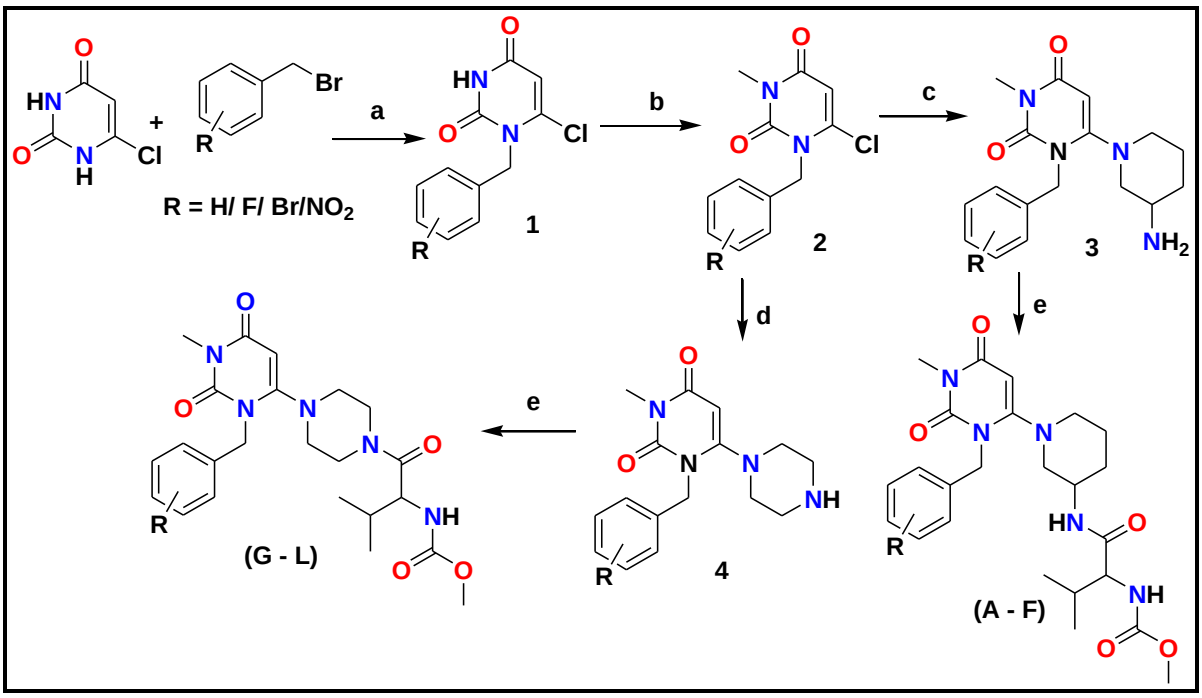
## 3.1 RESULTS AND DISCUSSION:

### 3.1.1 Chemistry

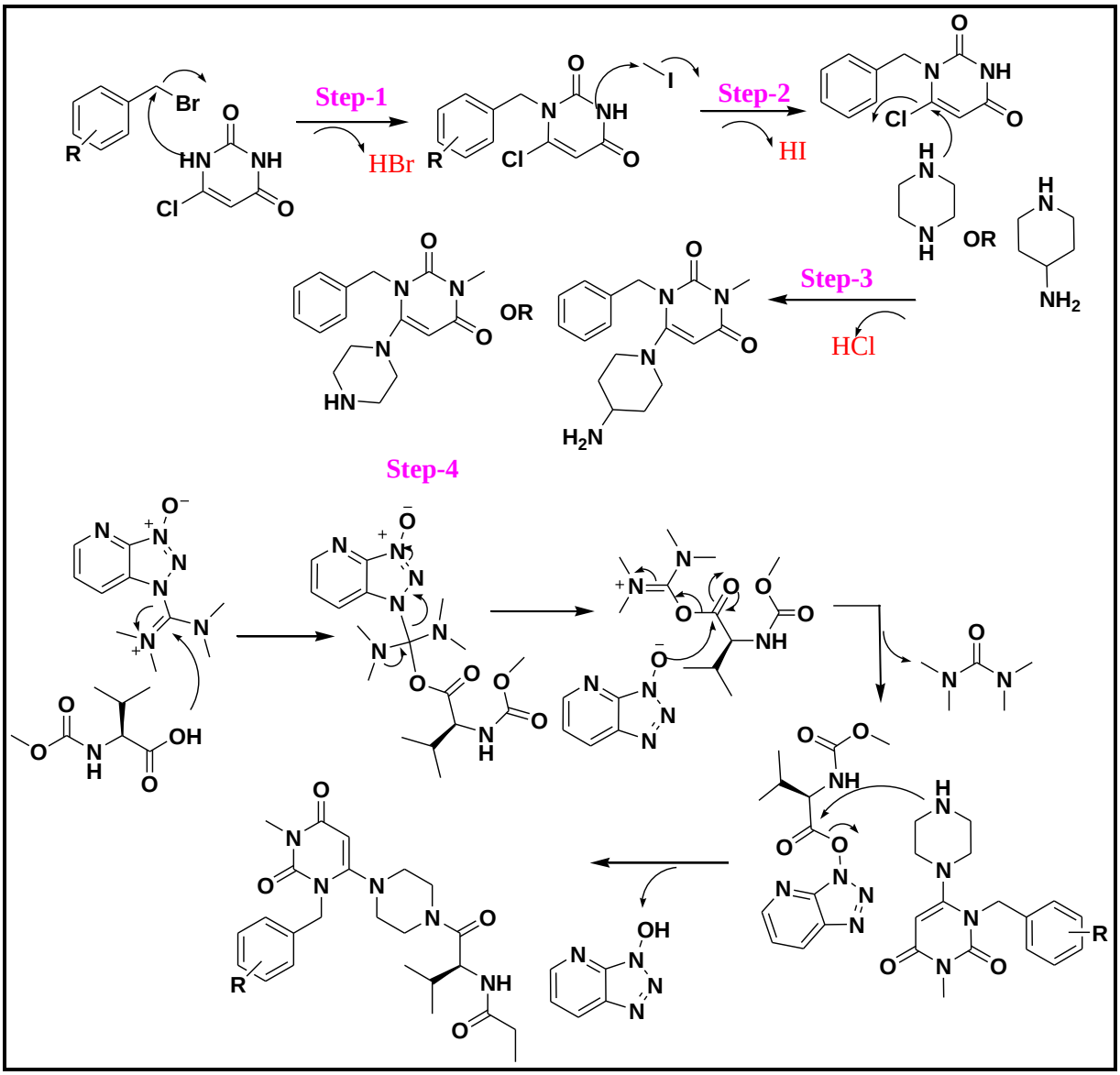
The synthesis of the target uracil derivatives was performed according to **Scheme 3.1**. A simple and successful protocol has been developed for synthesis of uracil derivatives. It should be noted that in the available literature, generally sodium hydride in dimethyl formamide have been used during the alkylation (methylation) reactions which is highly dangerous in the context of safety, environment pollutant and it also results poor yield, impure compounds. In our simple protocol, we used low cost, eco-friendly and safe, inorganic base potassium carbonate in dimethyl formamide solvent in one pot during four steps which is one of the major advantages of our protocol. In addition, we got higher percentage yields of products. Initially, we have synthesized N-substituted uracil analogues in high yields by simple N-alkylation reactions of 4-chlorouracil with different halogenated benzyl halides and methyl iodide respectively, under catalyst free conditions in DMF solvent. Then the chlorine atoms of N-substituted uracil derivatives were substituted with piperazine and 4-aminopiperidine, respectively. In the last step, under similar conditions in same solvent amino acid coupling reactions were done in presence of coupling reagent HATU (1-bis(dimethylamino)methylene-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxid hexafluorophosphate) for the formation of target compounds **A-L**.The whole synthesis has been done in one solvent in one pot that results the reduction of industrial waste, effluent generation and good yields of final products(**49-60**%). A reasonable reaction mechanism for the formation of uracil derivatives is shown in **Scheme 3.1**.

The reaction conditions were optimized using various solvents, bases. The yields ranged from 49 to 60%. A perusal of these indicates that the DMF and inorganic base was the best one; resulting in higher yield and best conversion. During the optimization of organic and inorganic bases were used. It was observed that during organic bases, the reaction was completed at faster rate, but less conversion was observed. The percentage of yield was increased while using inorganic bases under DMF solvent. Hence, throughout the reactions potassium carbonate as base and DMF as solvent were used.

The analytical and spectroscopic data's were well supported for the proposed structures of **A-L.** The compounds **A-L** were found as solids, stable to air, good yields and quite soluble in ethylacetate, methanol, ethanol, chloroform, DMSO, DMF. The characteristic signal from the C**H**$_3$N- group in the $^1$H NMR spectrum was observed as singlet at ~ 2.90-3.10 ppm, alkenic proton of uracil ring C**H**- was observed at 5.00-5.35 ppm, benzylic proton -C**H** at 4.86-5.37 ppm, aromatic protons Ar-**H** appeared in the range of 7.00-8.10 ppm, piperazine protons resonates at 1.50-3.80 ppm, methyl protons appeared in the range of 2.90-3.40 ppm, and methoxy protons -OC**H**$_3$ appeared in the range of 3.40-3.75 ppm. The $^1$H NMR and Mass spectra of target compounds (**A-L**) are shown in **Fig. 3.1**. Elemental analysis data's and ESI-Mass spectroscopic data are well supported for the compositions of the synthesized compounds. The mass spectra of **A-L** showed the peaks at m/z values of 490.24, 490.24, 490.24, 517.23, 472.24, 552.16, 476.23, 476.23, 538.15, 458.23, 503.22 and 476.23 corresponding to**A, B, C, D, E, F, G, H, I, J, K** and **L**. The HR-mass spectra of target compounds **A-L** are given in **Fig. 3.1**. The chemical structures of initial and final coupled products are given in **Table 3.1.**

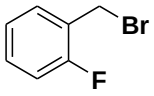
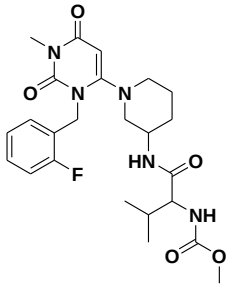
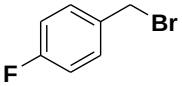
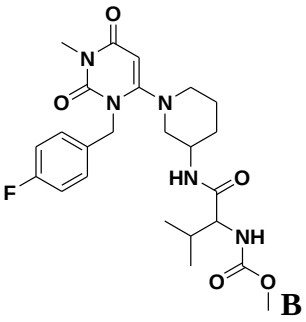
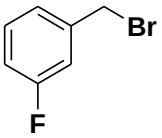
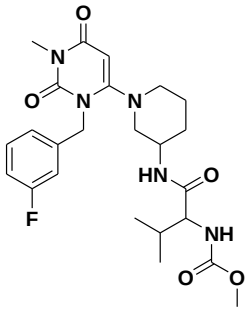
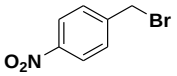
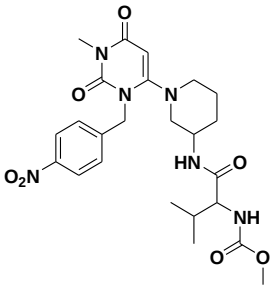
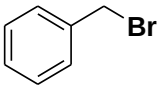
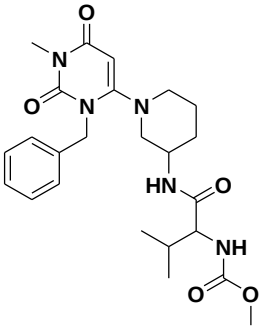
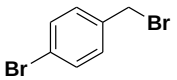
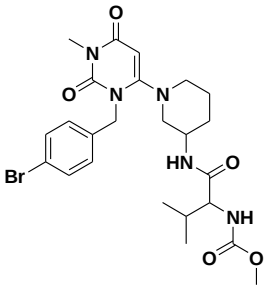


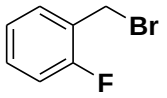
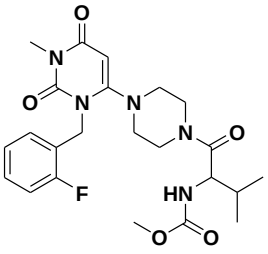
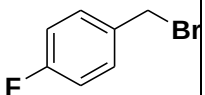
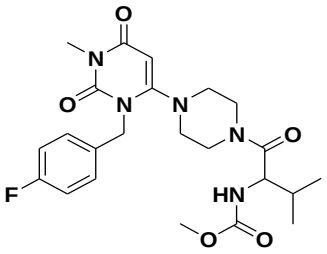
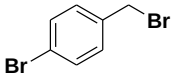
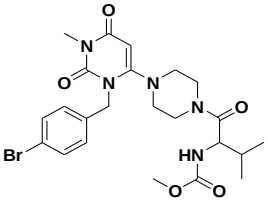
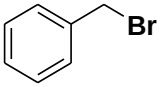
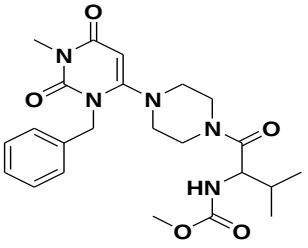
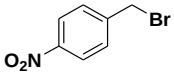
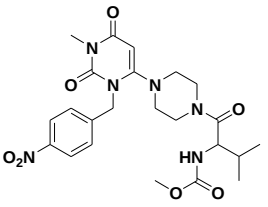
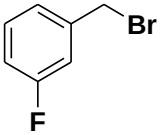
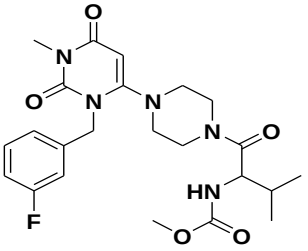
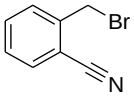
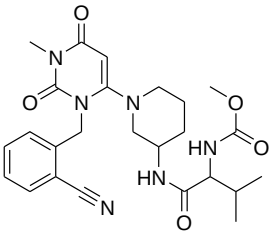
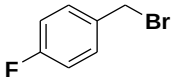
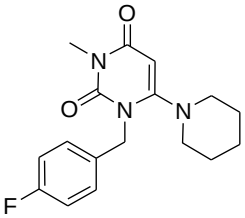

**Scheme 3.1**.A novel synthesis of uracil derivatives. Reagents and conditions: (a) $K_2CO_3$/DMF, Stirring, R.T, 8 hrs(b) $K_2CO_3$/DMF, $CH_3I$, R.T,24 hrs (c) $K_2CO_3$/DMF/3-aminopiperidine,heat, 80 ˚C, 8 hrs (d) $K_2CO_3$/DMF/Piperazine, heat, 80 ˚C, 8 hrs (e) HATU, TEA, Moc-L-Valine/DMF, R.T, 20 min.




**Scheme 3.2.Proposed mechanism for the synthesis of uracil derivatives.**

**Table-3.1:** The chemical structures of initial and final coupled products.

| Halogenated benzyl halides | Product | Yield (%) | Halogenated benzyl halides | Product | Yield (%) |
|---|---|---|---|---|---|
|  |  **A** | **57** |  |  **B** | **52** |
|  |  **C** | **51** |  |  **D** | **59** |
|  |  **E** | **49** |  |  **F** | **56** |

| | | | | | |
|---|---|---|---|---|---|
|  |  **G** | **56** |  |  **H** | **57** |
|  |  **I** | **58** |  |  **J** | **51** |
|  |  **K** | **60** |  |  **L** | **60** |
|  |  **M** | **59** |  |  **N** | **65** |

## 3.2 DNA BINDING

Exposure to radiations, chemicals, endogenous free radicals etc. leads to DNA damage which is ultimately a common cause of premature aging, cancer [97, 98] diabetes mellitus nd other diseases [99,100] and neuropathies [101]. Therefore, the treatment strategies of

these diseases can be aimed at DNA damage prevention and DNA repair enhancement[102,103]. The anticancer drugs which are currently in advance clinical trials or in clinical use are main pharmacological target of many drugs are DNA. This because of interfere the replication or moderating transcription is an important step in the cell growth and division and it is regulate the cell function by DNA. It all seems logical, intuitively appealing, and conceptually straightforward. When inhibition or alteration of DNA the small ligand molecules act as drug and is required to control or cure a disease [104]. Therefore, the study of interaction of the new compounds with DNA is very exciting and significant not only to access their biological potential but also in understanding the mechanism of interaction and for the design of new anticancer and other anti-disease drugs.

The small ligand molecules with DNA and their interactions stability were investigated by simplest and most common method is Ultraviolet and Visible spectroscopy. The changes of absorption properties of DNA and drug molecules [105] are monitored and notified by the uv-vis. spectroscopy study. Besides, the shifting of the position of absorption bands from when the ligand was free in solution to when the ligand was bound with the DNA also indicates interaction between the DNA and the ligand molecules [106-111]. Moreover, the observation of isosbestic points in mixed solutions also indicates the interaction of ligand with DNA molecules. Covalent (i.e. N7 of guanine replaced by the nitrogen atom of DNA base) and non-covalent (i.e. intercalation, electrostatic interaction, and groove binding) interactions are the two possible ways through which a compound can bind with DNA. Normally, in absorption spectra the changes like hypochromism and bathochromism resulted when compound bound to DNA via intercalation and the strength of interaction [112-118] depends upon the extent of hypochromism. Basically, between base pair of DNA [119, 120] and aromatic chromophores stocking interacteraction involved. While, in electrostatic interaction when compound interacted with DNA, no bathochromic [121] shift or hyperchromic shift is observed [122] while lower hypochromicity observed. Upon denaturation in absence of DNA outstanding hyperchromic effect observed. Sometimes, covalent adducts are formed between ligands

and DNA in which generally the result is hyperchromism when compound bound to DNA and when the result is bathochromism when the secondary structure breakage of DNA [123]. On the other hand, the binding of outside groove is normally characterized by minor change or no change in UV-Vis. spectra and sometimes with little hyperchromism. The compounds **(A–N)** absorption spectra in the presence and absence of CT-DNA are shown in **Fig. (3.2-3.4) .**The compounds absorption spectra signals observed in the range of 200-300 nm. The compounds **A-N** showed two absorption bands, first band appeared at 235-260 nm and second band appeared at 269 -296 nm, respectively. When DNA addition the band shifting was observed around 200-300 nm. Due to intra ligand $\pi \rightarrow \pi^*$ transition, small shifting of first band was observed in all the cases, and large shifting of second band was observed because of the $n \rightarrow \pi^*$ transitions of intra ligand of the compounds **A-L** [124]. The bathochromism and hypo-chromicities **Fig. (3.2-3.4)** absorption peaks was observed when different concentration of DNA [0.2 - 1.2 × $10^{-3}$ M] addition, thus, indicating the formation of DNA-compound adducts via intercalative mode (non-covalent) [125]. Moreover, the appearances of isosbestic points in titration experiments also showed that The CT-DNA and the compounds interactions were happened. UV–vis spectra data of compounds **A-L** are listed in **Table 3.2**. For a ready reference, in **Fig. (3.2-3.4)** in the both presence(0.2 –1.4 × $10^{-3}$ M) and absence ofcalf-thymus DNA absorption spectra of compounds (**F, G,** and **H**; 2.0 × $10^{-3}$ M) were given. The compounds DNA binding constants values are varied from 6.0× $10^{5}$ to 9.0 ×$10^{7}$ $M^{-1}$ is representing of very good interaction of these these compounds with DNA. The compounds increasing order of DNA binding constants **A-L** was **G>H>F>B>C>A>L>I>D > J> E.** It can be concluded from these results that the compounds **A-L** intercalated through minor groove with Ct-DNA [126]. Based on literature data it's clearly shows that the stabilized mainly by hydrogen bonds and hydrophobic interaction [127] of the compound form a complex with DNA minor groove. In **Fig. (3.2-3.4)** is shows that the well established fact of DNA titration experiments and docking studies of the compounds were listed.Halogenated compound (containing of fluoro, bromo compounds such as **A, B, C, F, G, H, I** and **L)** are interestingly had high

affinity for DNA (higher $K_b$ values). On the other hand, DNA had better affinity with compounds containing nitro group. The earlier reported work was agreed with these results [128].

**Table 3.2**. UV absorption, wavelength shifts, % hypochromism and binding constants of **A-L**.

| **Compounds** | **$\lambda_{max}$ free (nm)** | **$\lambda_{max}$ bound (nm)** | **$\Delta\lambda_{max}$ (nm)** | **% Hypochromism[a]** | **$K_b$[b] ($M^{-1}$)** |
|---|---|---|---|---|---|
| **A** | 260, 290 | 262,292 | 2 | 1.0 | $6.1 \times 10^7$ |
| **B** | 236, 267 | 238,269 | 2 | 2.3 | $7.1 \times 10^7$ |
| **C** | 235, 294 | 236, 295 | 1 | 5.2 | $6.7 \times 10^7$ |
| **D** | 245, 295 | 246, 296 | 1 | 1.0 | $4.60 \times 10^6$ |
| **E** | 236, 272 | 238, 274 | 2 | 2.3 | $6.0 \times 10^5$ |
| **F** | 235, 267 | 235, 282 | 20 | 6.8 | $7.8 \times 10^7$ |
| **G** | 236, 269 | 236, 279 | 10 | 7.1 | $9.0 \times 10^7$ |
| **H** | 234, 259 | 234, 279 | 20 | 48 | $8.0 \times 10^7$ |
| **I** | 242, 296 | 244, 298 | 2 | 3.1 | $4.9 \times 10^7$ |
| **J** | 257, 291 | 259, 293 | 2 | 2.9 | $8.8 \times 10^5$ |
| **L** | 245, 296 | 246, 297 | 0 | 0.5 | $5.8 \times 10^7$ |

**[a]** % Hypochromicity (H%) = $[A_f\text{-}A_b)/A_f] \times 100$, where $A_f$ and $A_b$ represent the absorbance of free and bound compounds. **[b]** Binding constants.

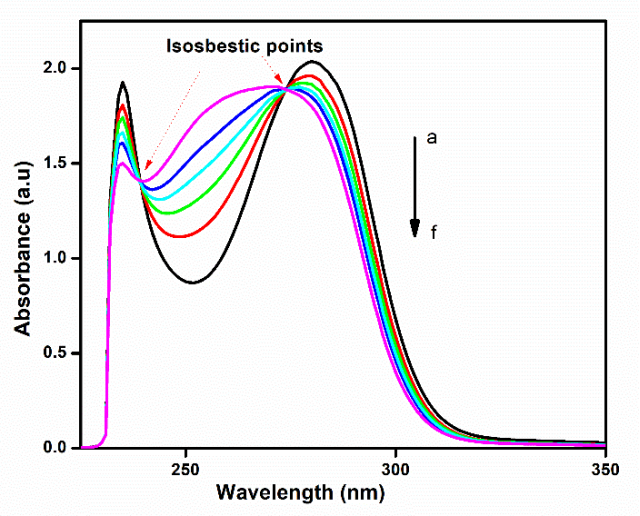



**Fig. 3.1**.Absorption spectra of compound **F**[$2.0 \times 10^{-3}$M**]**, in the absence and presence of DNA**.** The concentration of DNA(a-f)were 0, 0.2, 0.4, 0.6, 0.8, 1.2 and $1.4 \times 10^{-3}$ M.

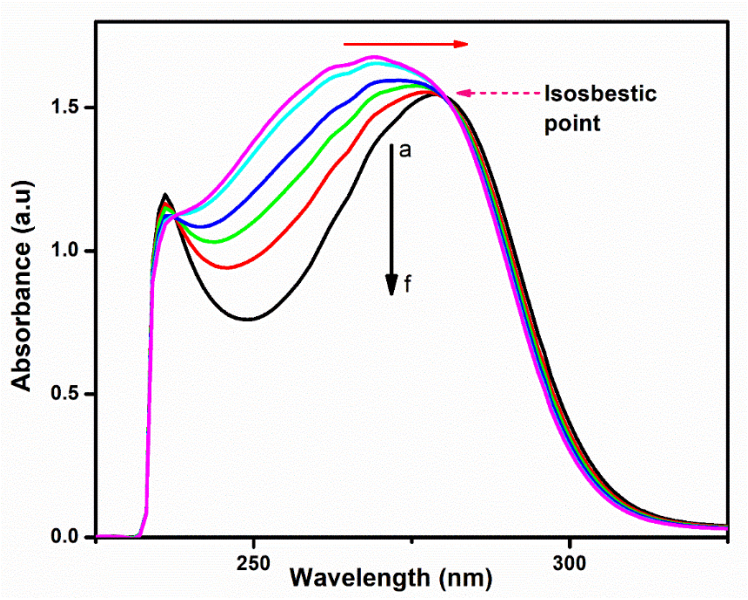



**Fig 3.2:** Absorption spectra of compound **G** [$2.0 \times 10^{-3}$M**]**, in the presence and absence of DNA**.** The concentration of DNA(a-f)were 0, 0.2, 0.4, 0.6, 0.8, 1.2 and $1.4 \times 10^{-3}$ M.

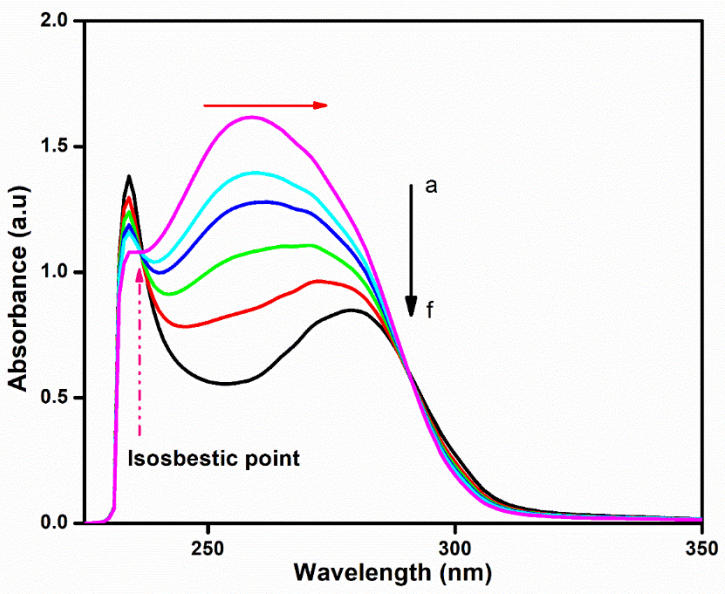



**Fig.3.3:** Absorption spectra of compound **H** [$2.0 \times 10^{-3}$M**]**, in the absence and presence of DNA**.** The concentration of DNA (a-f)were 0, 0.2, 0.4, 0.6, 0.8, 1.2 and $1.4 \times 10^{-3}$ M.

## 3.3 DOCKING STUDY

At supramolecular level, molecular docking is a useful tool for predicting the interactions of drugs with various macromolecules and this section describes interactions of the developed molecules with DNA. To predict the mode of binding with DNA, three target molecules (**F, G** and **H**) were selected for carrying out docking studies due to their high experimental binding affinity with DNA. The long and thin DNA (B-DNA) is the most common form of DNA which has characteristic wide;major deep grooves and narrow; deep minor grooves. The specificity of base pairing between two DNA strands gives distinct hydrogen bond acceptor/donor patterns in major and minor grooves. To find out the possible sites of DNA interactions with the selected compounds reported compounds, Auto Dock (4.2) Vina tool has been used to carry out molecular DNA docking study of the compounds. DNA dodecamers d(CGCGAATTCGCG)2 (PDB ID: 1BNA) were used to study the docking studies of the compounds. The order of binding energies of the selected compounds was **G> H >F.** The 2D and 3D-docked models of **F**, **G** and **H** are shown in **Fig. (3.5-3.9).** It is clear from the docked models that all the compounds preferred DNA minor grooves. The residue involved hydrophobic interaction, residue

involved hydrogen bonding, binding affinity and number of hydrogen bonding formed by compounds **F, G and H** is given in **Table 3.3** .During docking studies, it was observed that the hydrogen bonding between carbonyl oxygen of amide group and ethoxy oxygen group of DNA were the common moieties involved. There are 3 to 4 numbers of hydrogen bonds formation was formed. The common residue of guanine and cytosine of DNA involved in hydrogen bonding. Further more, the hydrophic interactions involved common residues of DNA were dt8, dc9, dg10, dc13, dg14, dc15 and dg16. The various docking of selected compounds are given in **Table 3.3**. During the process of DNA interactions, it had been observed that all the target compounds containing benzene ring are oriented themselves in such a manner that inside minor grooves. Overall, the experimental results of DNA binding were in excellent agreement with those of docking studies.

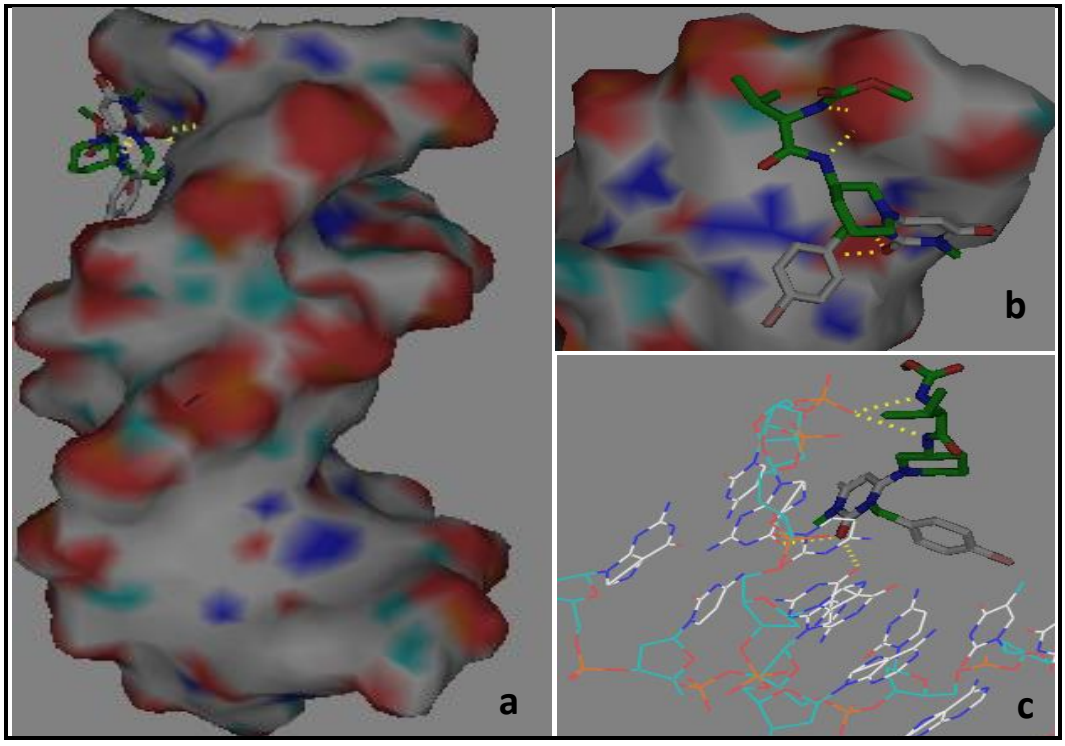



**Fig. 3.4:** 3D-Docking images of compound **F** with CT-DNA. (**a**) shows the interaction via minor groove, (**b**) Closest view within groove and (**c**) indicate polar interactions.

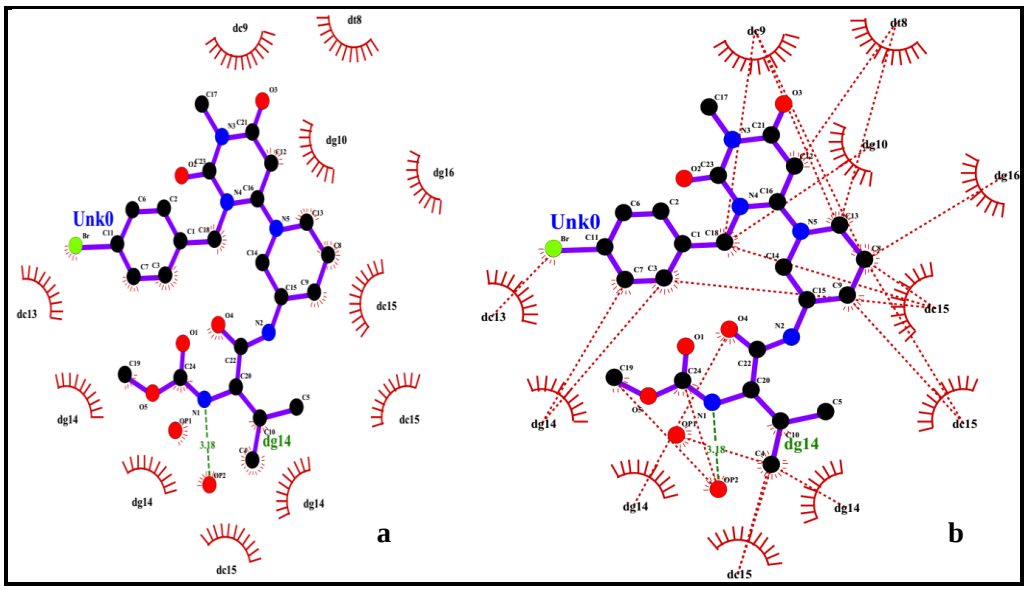



**Fig. 3.5:** 2D-Docking images of compound**F** with CT-DNA. (**a** and **b**) shows the moieties of DNA involved in hydrophobic interactions.

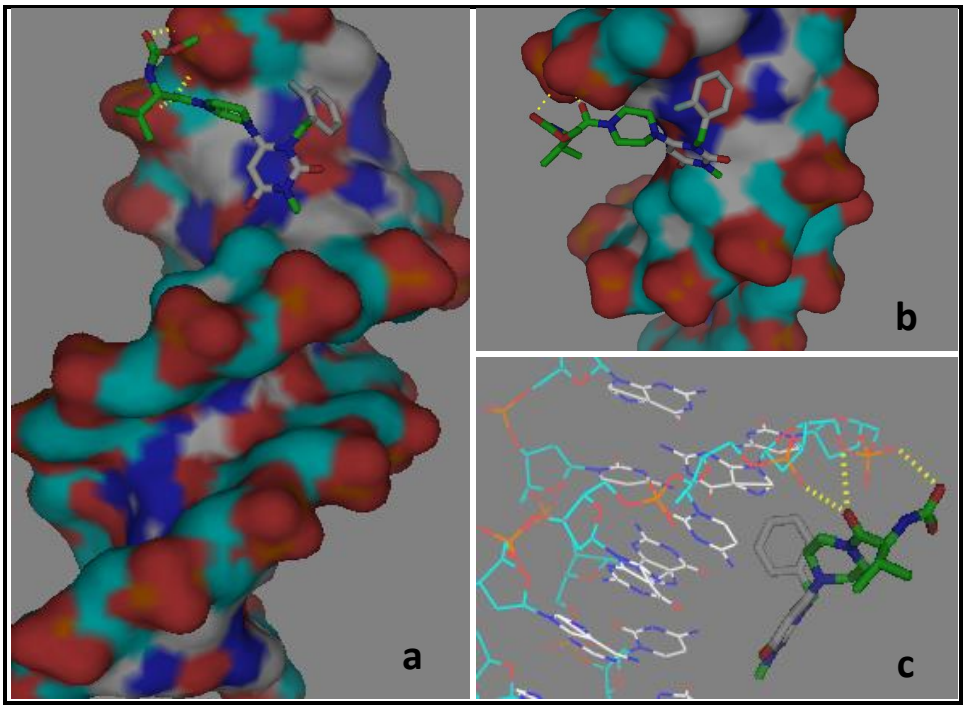



**Fig. 3.6:** 3D-Docking images of compound **G** with CT-DNA. (**a**) shows the interaction via minor groove, (**b**) Closest view within groove and (**c**) indicate polar interactions.

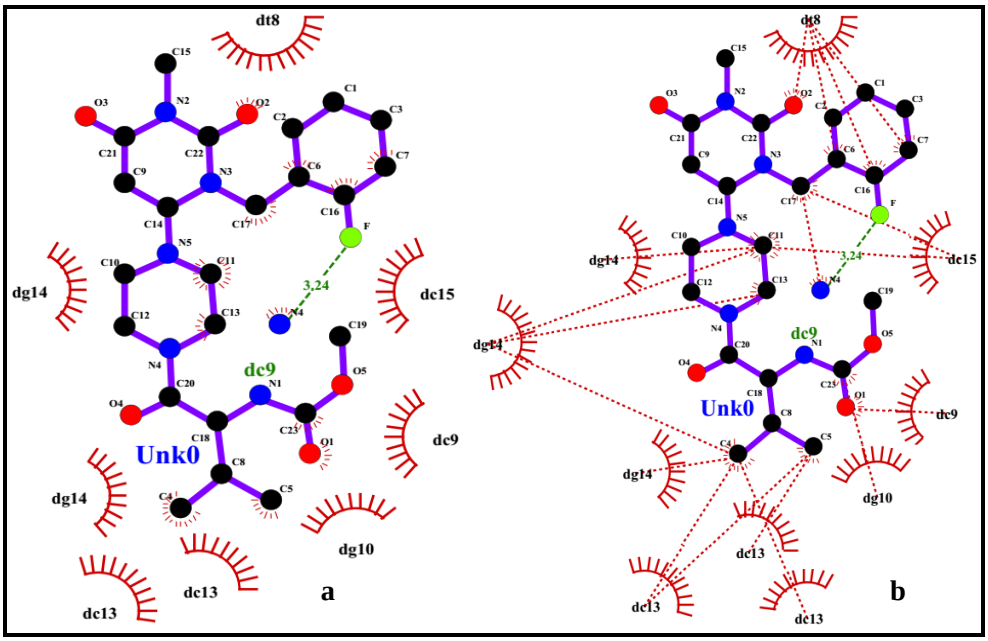



**Fig. 3.7:** 2D-Docking images of compound **G** with CT-DNA. (**a** and **b**) shows the moieties of DNA involved in hydrophobic interactions.

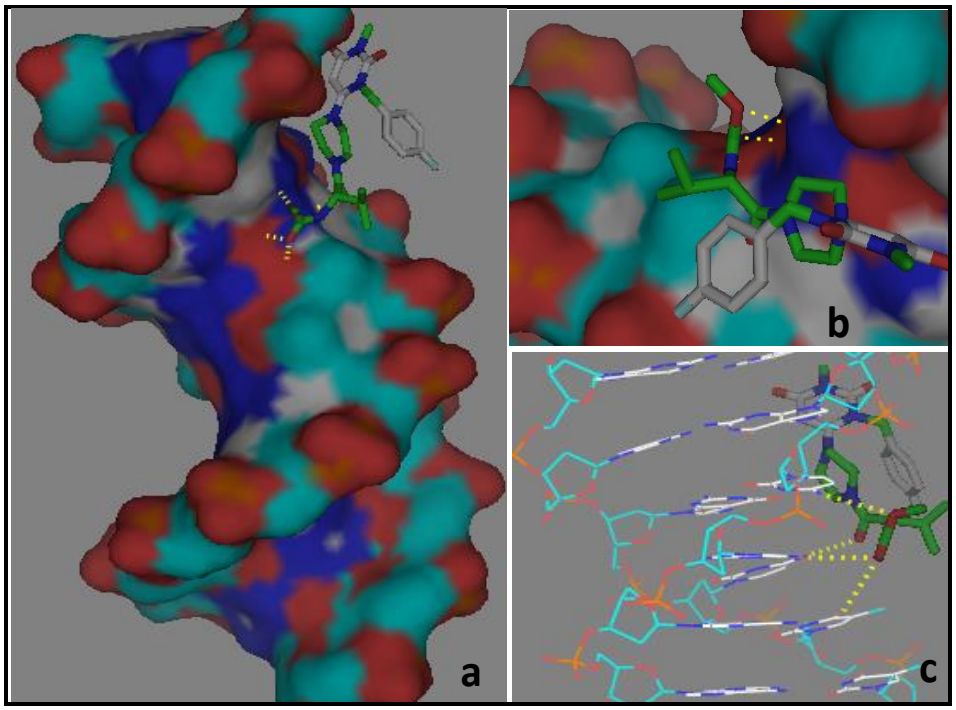



**Fig. 3.8:** 3D-Docking images of compound**H** with CT-DNA. (**a**) shows the interaction via minor groove, (**b**) Closest view within groove and (**c**) indicate polar interactions.

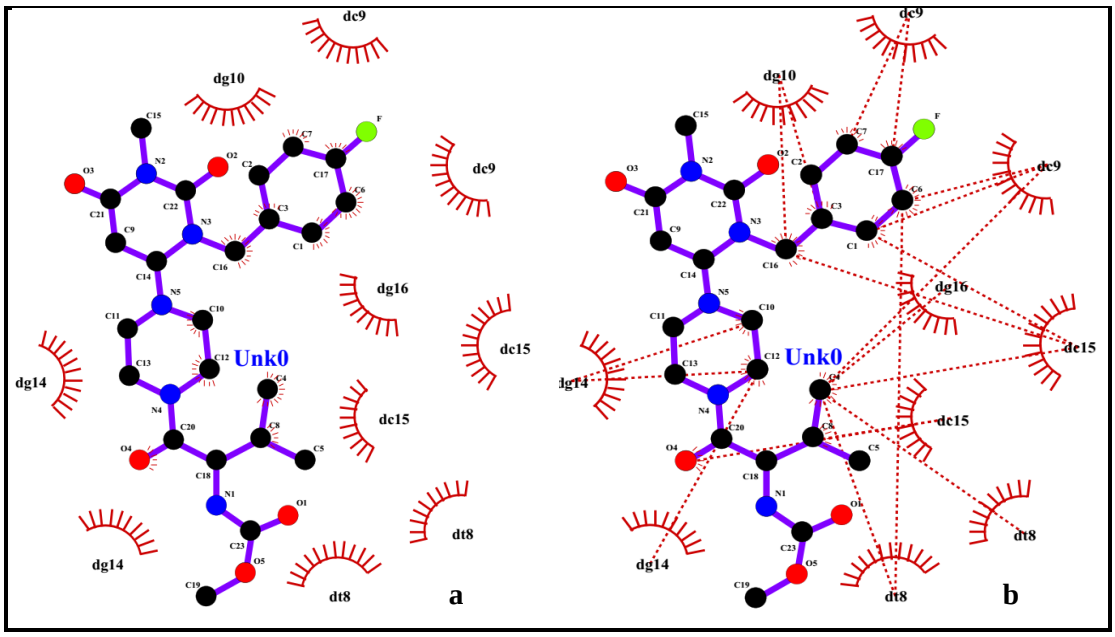



**Fig. 3.9:** 2D-Docking images of compound**H** with CT-DNA. (**a** and **b**) shows the moieties of DNA involved in hydrophobic interactions.

**Table 3.3**.The different docking parameters of selected compounds **F, G** and **H**with DNA**.**

| **Compounds No.** | **Binding affinity (kJ/mol)** | **Number of hydrogen bonds** | **H-bonding involved residues (Bond length)** | **Hydrophobic attraction involved in residues** |
|---|---|---|---|---|
| **F** | -18.8 | 4 | **A:** A/DG:10/H01::O of carbonyl of uracil ring (3.30). **B:** A/DG:14/H06::O Of carbonyl of uracil ring (3.32). **C**:B/DG:14/OP2::NH of 3-aminopiperidine moiety (3.25). | dt8, dc9, dg10, dc13, dg14, dc15 and dg16. |

| | | | | |
|---|---|---|---|---|
| | | | **D**: B/DG:14/PO2::NH of otheramine group (3.39). | |
| **G** | -20.23 | 3 | **A:** B/DG:14/HO2::O of carbonyl of ester group (3.46).<br>**B:** B/DC:15/H01::O of carbonyl linked to piperazine ring (3.38).<br>**C**:B/DG:14/H02::O of carbonyl linked to piperazine ring (3.39). | dt8, dc9, dg10, dc13, dg14 and dc15. |
| **H** | -20.95 | 4 | **A:** B/DG:14/H01::O of carbonyl linked to piperazine ring ((3.48).<br>**B:** B/DG:14/H01:: O of carbonyl linked to piperazine ring(3.52).<br>**C**:B/DG:14/H02::O ofcarbonyl of ester group (3.30).<br>**D**: B/DG:16/HO1::O ofcarbonyl of ester group (3.31). | dt8, dc9, dg10, dc13, dg14, dc15 and dg16. |

## 3.4 EXPERIMENTAL PROCEDURE:

### 3.4.1 One pot synthesis of target compounds (A-L)

Initially, charged 6-chloro uracil (7.75 g, 0.0528M) and potassium carbonate (9.14 g, 0.0661 M) were mixed in 50 mL DMF in 250 mL RBF, followed by halogenated derivatives of 1-(bromomethyl) benzene (10.00 g, 0.0584 moles), the obtained reaction mixture were agitated at least 8 hrs at 20-30°C. Then, with further addition of potassium carbonate (7.31 g, 0.0529 moles) and methyl iodide (15.02 g, 0.10 moles) the reaction

mass were stirred 12-16 hrs at 20-30°C. After that, the charged piperazine (4.52 g, 0.0524 moles) or piperidin-3-amine (9.10 g, 0.0524 moles) was added in to it and mixture of reaction was heated at 80 ˚C for 8hrs. Finally, the Moc-L-Valine (9.22 g, 0.0526 moles) were added to the reaction mass in presence of coupling reagent HATU (40.23 g, 0.1058 moles) and base, triethyl amine (10.71 g, 0.1058 moles) then reaction mixture were stirred for 20 min at 20-30°C. The reaction completion was monitored by TLC, once the reaction was completed water was added and the product was partitioned with organic layer and moisture was removed by treating with sulphate and solvent was removed under vacuum at 40-50°C. The desired products (**A-L**) were purified by column chromatography to get title compounds.

## 3.5 GENERAL PROCEDURE:

### 3.5.1 Synthesis of N-alkylated compounds of 6-chlorouracil (1):

6-chlorouracil (10 g, 0.0682 moles) were dissolved in 50 mL DMF and diisopropylethylamine (18.52 gm, 0.1432 moles) then obtained reaction mixture were stirred for 10 min at 23 to 33°C after that added halogenated 1-(bromomethyl)benzene (12.90 g, 0.0754 moles) then reaction mass stirring was continued for 8 to 10 hrs at 23-33°C. If the reaction were completed add 150 mL water it and the precipitated product (1) was isolated by filtration, dried to obtained 14.37 gm (89.0 %)

### 3.5.2 Synthesis of compounds 2:

Compound **1 (**10.00 g, 0.0422 moles**)** were dissolved in 100 mL acetone followed by potassium carbonate (12.84 g, 0.0929 moles) and the reaction mass were stirred for 15 min at 25-37°C followed by methyl iodide (11.99 g, 0.0844 moles) added in to it and the reaction mass were agitated overnight at 20-30°C reaction progress were monitored by TLC, water added in to it after reaction were judged to complete and the precipitated product (**2**) was isolated by filtration then dried to get 9.74 g (92.0 %).

### 3.5.3 Synthesis of Compounds 3 or 4:

Compound **2** (9.00 g, 0.0359 moles) were dissolved in 45 mL DMF followed by addition of potassium carbonate (9.92 g, 0.0717 moles). Then (3.40 g, 0.0394 moles) of piperazine or piperidin-3-amine (6.83 g, 0.0394 moles) was added, and reaction temperature maintained at 80°C, until reaction completion, the reaction temperature were cooled down after reaction completion water was added in to it and extracted with dichloromethane. The organic layer was separated out and moisture present in organic layer was removed by treating with sodium sulphate. Finally, the dichloromethane distilled off under vacuum at 35-45°C for the formation of compounds **3** (9.16 g, 85.0%) or **4** ( 9.81 g, 87.0%) .

## 3.6 SYNTHESIS OF TARGET COMPOUNDS (A-L):

Compound **3** (9.00 g, 0.0299 moles) or **4** (9.00 g, 0.0286 moles ) were initially dissolved in 90 mL dichloromethane added HATU ( 16.12 gm, 0.0423 moles) followed by Moc-L-Valine (5.20 gm, 0.0296 moles) then TEA (5.72 gm, 0.0565 moles) until reaction completion the mixture was agitated at ambient temperature then added water in to it , the desire product was partitioned with organic layer then moisture in organic layer removed by treating with anhydrous sodium sulphate, dichloromethane was removed under vacumm at 35-40°C to give title compound 12.1 gm (90%).

## 3.7 CHARECTARISATION DETAILS OF COMPOUND (A-L):

### 3.7.1 Methyl (S)-1-((R)-1-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (A):

Yield: 57%, mp; 194-195˚C; White solid powder; Anal. Calcd: C (58.89), H (6.55), N (14.32%), Found: C (58.88),H (6.59), N (14.31%); $^{1}$H-NMR:(DMSO-$d_6$, Bruker 400 MHz), $\delta$ = 0.71-0.75 (dd, 6 H,-$CH_3$), 1.3-1.5 (m; 2 H, -$CH_2$), 1.72-1.77 (m, 3 H, -$CH_2$),

2.3-2.4 (t, 1 H, -$CH_2$), 2.6-2.7 (t, 1 H, -$CH_2$), 2.85-2.95 (d, 1H), 3.05 (s, 3 H, -N-$CH_3$), 3.1-3.2 (d, 1 H, -$CH_2$), 3.47 (s, 3 H, -O-$CH_3$), 3.70-3.74 (t, 2 H, -$CH_2$), 4.99-5.01 (q, 2 H, -$CH_2$), 5.26 ( s, 1 H, -CH), 7.04-7.16 (M, 4 H, Ar-H, -NH), 7.25 (q, 1 H, Ar-H), 7.94-7.96 (d, 1 H, -NH); ES-MS (m/z) Calc. for $C_{24}H_{32}FN_5O_5$: 489.54, found $[M+H]^+$: 490.24.

### 3.7.2 Methyl(S)-1-((R)-1-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (B):

Yield: 52%, mp; 230-231˚C;White solid powder; Anal. Calcd: C (58.87), H (6.57), N (14.29%), Found: C (58.88),H (6.59), N (14.31%); $^1$H-NMR: (DMSO-$d_6$, Bruker 400 MHz), δ = 0.72-0.76 (dd, 6 H,-$CH_3$), 1.29-1.50 (m; 2 H, -$CH_2$), 1.74-1.78 (m, 3 H, -$CH_2$), 2.3-2.4 (m, 1 H, -$CH_2$), 2.46-2.468 (s, 3 H, $CH_2$), 2.59-2.69 (m, 1 H, -$CH_2$), 2.8-2.9 (d, 1 H, -$CH_2$), 3.07-3.15 (s & broad, 4 H, -N-$CH_3$ & -CH), 3.48 (s, 3 H, -O-$CH_3$), 3.71-3.75 (t, 2 H, -$CH_2$), 4.93-4.97 (q, 2 H, -$CH_2$), 5.24 ( s, 1 H, -CH), 7.07-7.11 (m, 3 H, Ar-H & -NH), 7.19-7.22 (m, 2 H, Ar-H), 7.97 (d, 1 H, -NH); ES-MS (m/z) Calc. for $C_{24}H_{32}FN_5O_5$: 489.54, found $[M+H]^+$: 490.24.

### 3.7.3 Methyl (S)-1-((R)-1-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (C):

Yield: 51%, mp; 203-204 ˚C;White solid powder; Anal. Calcd: C (58.89), H (6.58), N (14.33%), Found: C (58.88),H (6.59), N (14.31%); $^1$H-NMR: ($CDCl_3$, Bruker 400 MHz), δ = 0.89- 0.90 (d, 6 H,-$CH_3$), 1.48-2.02 (m; 4 H, -$CH_2$), 2.47-2.86 (m, 3 H, -$CH_2$),3.13-3.49 (m, 4 H, -N-$CH_3$ & -CH), 3.48 (s, 4 H, -O-$CH_3$ &-CH)), 4.04 (broad, 1 H, -CH), 4.99-5.03 (d, 1 H, -CH), 5.11 ( broad , 1 H, -CH), 5.23-5.33 (d, 2H, -Ar-$CH_2$), 5.84 (s, 1H, -CH-), 6.90-7.003 (m, 3 H, Ar-H), 7.26-7.33 (m, 1 H, Ar-H). ES-MS (m/z) Calc. for $C_{24}H_{32}FN_5O_5$: 489.54, found $[M+H]^+$: 490.24.

### 3.7.4 Methyl (S)-1-((R)-1-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (D):

Yield: 59%, mp; 216-217 ˚C;White solid powder; Anal. Calcd: C (55.81), H (6.22), N (16.25%), Found: C (55.80), H (6.24), N (16.27%); $^1$H-NMR: (DMSO-$d_6$, Bruker 400 MHz), δ = 0.65-0.72 (dd, 6 H,-$CH_3$), 1.19-1.15 (t; 1 H, -$CH_2$), 1.29-1.42 (m, 2 H, -$CH_2$), 1.64-1.73 (m, 3 H, -CH), 2.464-2.468 (m, 1 H, -$CH_2$), 2.60-2.65(m, 1 H, -$CH_2$), 2.83-2.86 (m, 1 H, -$CH_2$), 3.02-3.08 (m, 1 H, -$CH_2$), 3.30 (s, 3H, -$CH_3$), 3.47 ( s, 3 H, -$CH_3$), 3.66-3.70(t, 2 H, -$CH_2$), 5.03-5.16(q, 2 H, -Ar-$CH_2$), 5.29 (s, 1 H, -CH), 7.06-7.09 (d, 1 H, -NH), 7.42-7.45 (d, 2H, Ar-H), 7.19-7.93 (d, 1 H, -NH), 8.12-8.15 (d, 2H, Ar-H) ppm; ES-MS (m/z) Calc. for $C_{24}H_{32}N_6O_7$: 516.55, found $[M+H]^+$: 517.23.

### 3.7.5 Methyl (S)-1-((R)-1-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (E):

Yield: 49%, mp; 219-220 ˚C; White solid powder; Anal. Calcd: C (61.15), H (7.01), N (14.84%), Found: C, (61.13), H (7.05), N (14.85); $^1$H-NMR: ($CDCl_3$-d, Bruker 400 MHz), δ = 0.89-0.92 (t, 6 H,-$CH_3$), 1.50-1.64 (m; 2 H, -$CH_2$), 1.77-2.07 (m, 4 H, -CH2), 2.5 (broad, 1 H, -CH), 2.76-2.88 (broad, 2 H, -CH), 3.30-3.34 (s, 4 H, -N-$CH_3$&-CH), 3.69-3.76 (m, 4H, -$OCH_3$& -CH), 4.06-4.08 (m, 1H, -CH-NH), 5.0-5.04 (ss, 1H, -CO-CH-NH), 5.28-5.34 (m, 3H, -Ph-CH2 & =CH-), 7.20-7.22 (d, 2H, Ar-H), 7.27-7.30 (t,1H, Ar-H), 7.34-7.38 (t, 2H, -Ar-H) ppm; ES-MS (m/z) Calc. for $C_{24}H_{33}N_5O_5$: 471.55, found $[M+H]^+$: 472.24.

### 3.7.6 Methyl (S)-1-((R)-1-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (F):

Yield: 56%, mp; 210-212 ˚C; White solid powder; Anal. Calcd: C (52.34), H (5.84), N (12.71%), Found: C (52.37), H (5.86), N (12.72%); $^1$H-NMR: (DMSO-$d_6$, Bruker 400 MHz), δ = 0.70-0.76 (dd, 6 H,-$CH_3$), 1.31-1.44 (m; 2 H, -$CH_2$), 1.75-1.80 (m, 3H, -

$CH_2$), 2.65 (m, 2H, -$CH_2$), 2.83 (t, 1 H, -$CH_2$), 3.30(s, 3 H, -$CH_3$), 3.47 (s, 3H, -$CH_3$), 3.70-3.73 (t, 2H, -$CH_2$), 4.86-5.001( q, 1H, -Ar-$CH_2$), 5.24(s, 1H, -CH), 7.11-7.12 (d, 2H, Ar-H), 7.45-7.47 (d,2H, A-H), 7.95-7.96 (d, 1H,-NH) ppm; ES-MS (m/z) Calc. for $C_{24}H_{32}BrN_5O_5$: 550. 45, found $[M+H]^+$: 552.16.

### 3.7.7 (S)-methyl1-(4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahyd dropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (G):

Yield: 56%, mp; 161-164 ˚C; White solid powder; Anal. Calcd: C (58.07), H (6.33), N (14.71%), Found: C, (58.09), H (6.36), N (14.73%); $^1$H-NMR:(DMSO-$d_6$, Bruker 400 MHz), δ = 0.80-0.95 (d, 3 H, -$CH_3$), 1.12-1.34 (m, 2 H, -$CH_2$), 1.92-1.94 (m, 1 H, -$CH_2$), 2.81-2.88 (m, 4 H, -$CH_2$), 3.12 (s, 3 H, -$CH_3$), 3.36 (m, 4 H, -$CH_2$ ),3.53-3.64 (m, 4H & 2H, -$OCH_3$, -$CH_2$ & -CH), 4.22-4.26 (m, 1H, -CH), 5.10 (s, 2 H, -$CH_2$), 5.39 ( s, 1 H,-CH), 7.17-7.22 (m, 3 H, Ar-H), 7.31-7.33 ( m, 2H, Ar-H); ES-MS (m/z) Calc. for $C_{23}H_{30}FN_5O_5$: 475.22, found $[M+H]^+$: 476.23.

### 3.7.8 (S)-methyl1-(4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahy dropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (H):

Yield: 57%, mp; 217-219 ˚C;White solid powder; Anal. Calcd: C (58.09), H (6.32), N (14.72%), Found: C, (58.09), H (6.36), N (14.73%); $^1$H-NMR: (DMSO-$d_6$, Bruker 400 MHz), δ = 0.85 (d, 6 H,-$CH_3$), 1.92 (m, 1 H, -$CH_2$), 2.65-2.69 (m, 4 H, -$CH_2$), 2.84 (broad, 4 H, $CH_2$), 3.13 (s, 3 H, -N-$CH_3$), 3.35 (broad, 6H, -O-$CH_3$& -$CH_2$), 3.53 (broad, 4 H, -$CH_2$), 3.66 (broad, 2 H, -$CH_2$), 4.22-4.26 ( t, 1 H, -CH), 5.04 (s, 2 H, Ar-CH2), 5.37 (s, 1 H, -CH), 7.14-7.18 (t, 2 H, Ar-H), 7.30-7.34 (m, 3 H, Ar-H, &-NH); ES-MS (m/z) Calc. for $C_{23}H_{30}FN_5O_5$: 475.51, found $[M+H]^+$: 476.23.

### 3.7.9 (S)-methyl 1-(4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (I):

Yield: 58%, mp; 234-233 ˚C; White solid powder; Anal. Calcd: C (51.51), H (5.62), N (13.04%), Found: C (51.50), H (5.64), N (13.06%); $^1$H-NMR:(DMSO-$d_6$, Bruker 400

MHz), δ = 0.83-0.86 (t, 6 H,-$CH_3$), 1.91-1.96 (m; 1 H, -$CH_2$), 2.69 (s, 3H, -$CH_3$), 2.85-2.90 (broad, 4H, -CH), 3.13 (s, 3 H, -$CH_3$), 3.35(s, 4 H), 3.53 (s, 3H), 3.66 (broad, 2H), 4.23-4.27( t, 1H), 5.03 (s, 2H, -Ar-CH2), 5.37(s, 1H, -CH), 7.20-7.22 (d, 2H, Ar-H), 7.28-7.30 (d, 1H, -NH) 7.51-7.53 (d,2H, Ar-H) ppm; ES-MS (m/z) Calc. for $C_{23}H_{30}BrN_5O_5$: 536.42, found $[M+H]^+$: 538.15.

### 3.7.10 (S)-methyl 1-(4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (J):

Yield: 51%, mp; 173-174 ˚C; White solid powder; Elementary Analysis Calculated: C (60.39), H (6.82), N (15.32%), Found: C (60.38), H (6.83), N (15.31%); $^1$H-NMR:(DMSO-$d_6$, Bruker 400 MHz), δ = 0.78-0.81 (t, 6 H,-$CH_3$), 1.84-1.92 (m; 1 H, -$CH_2$), 2.65 (s, 2H, ), 2.79-2.82 (broad, 4 H, -CH), 3.10 (s, 3 H, -$CH_3$), 3.31 (s, 3H, -$OCH_3$ ), 3.60-3.66 (broad, 2H, ) 4.17-4.21(t, 1H), 5.02 (s, 2H, -Ar-CH2), 5.33 (s, 1H, -CH) 7.18-7.23 (m, 3H, Ph), 7.27-7.31 (t,2H, Ph)ppm; ES-MS (m/z) Calc. for $C_{23}H_{31}N_5O_5$: 457.52, found $[M+H]^+$: 458.23.

### 3.7.11 (S)-methyl 1-(4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (K):

Yield: 60%, mp; 205-206 ˚C; White solid powder; Elementary Analysis Calculated: C (54.95), H (6.00), N (16.70%), Found: C (54.97), H (6.02), N (16.72%); $^1$H-NMR:($CDCl_3$, Bruker 400 MHz), δ = 0.93-0.97 (dd, 6 H,-$CH_3$), 1.27-1.30 (d, 1H, -CH), 1.91-1.96 (q, 1 H, -CH), 2.81 (s, 5 H, -N-$CH_3$, $CH_2$), 2.90 (broad, 3H, ) 3.33(s, 3 H, -O-$CH_3$), 4.41-4.45 ( q, 1H, -CH), 5.21 (s, 2H, Ar-$CH_2$), 5.42-5.47 (t, 2 H, ), 7.38-7.40 (d, 2 H, -Ar H), (d, 2 H, -Ar-H), ppm; ES-MS (m/z) Calc. for $C_{23}H_{30}N_6O_7$: 502.52, found $[M+H]^+$: 503.22.

### 3.7.12 (S)-methyl1-(4-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahy dropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (L)

Yield: 60%, mp; 220-222 ˚C; White solid powder; Elementary Analysis Calculated: C (58.09), H (6.34), N (14.73%), Found: C (58.09), H (6.36), N (14.73%); $^{1}$H-NMR:(DMSO-$d_6$, Bruker 400 MHz), δ = 0.71-0.76 (dd, 6 H,-$CH_3$), 1.3-1.5 (m; 2 H, -$CH_2$), 1.74-1.79 (m, 3 H, -$CH_2$), 2.30-2.46 (m, 4 H, -CH), 2.59 (m, 1 H, -$CH_2$), 2.80-2.9(m, 1 H, -$CH_2$), 3.08 (s, 3 H, -N-$CH_3$), 3.48 (s, 3 H, -$CH_3$), 3.74-3.75 (t, 2 H, -$CH_2$), 4.92-5.04 (d, 2 H, -Ar-$CH_2$), 5.25 (s, 1 H, -CH), 6.99-7.05 (m, 3 H, -Ar-H), 7.09-7.11 (d, 1 H, -NH), 7.29-7.34 (q, 1 H, -Ar-H), 7.95-7.96 (d, 1 H, -NH) ppm. ES-MS (m/z) Calc. for $C_{23}H_{30}FN_5O_5$: 475.521, found $[M+H]^+$: 476.23.

### 3.7.13 Methyl(S)-1-((R)-1-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (M):

Yield: 60% , $^{1}$H-NMR:(DMSO-$d_6$, Bruker 400 MHz) δ = 0.74-0.77 (dd, 6 H,-$CH_3$), 1.29-1.32 (m; 1 H, -$CH_2$), 1.46-1.48 (m; 1 H, -$CH_2$), 1.63-1.83 (m, 3 H, -$CH_2$), 2.61-2.65 (m, 1 H, -$CH_2$), 2.93-2.96 (m, 1H, -$CH_2$)3.05 (s, 3 H, -N-$CH_3$), 3.08 (broad, 1H, -CH), 3.48 (s, 3 H, -O-$CH_3$), 3.68-3.72 (t, 2 H, -$CH_2$), 5.11 (q, 2 H, -Ar-$CH_2$), 5.32 ( s, 1 H, -CH), 7.02-7.04 (d, 1 H, Ar-H), 7.21-7.23 (d, 1 H, Ar-H), 7.38-7.42 (t, 1H, ar-H), 7.58-7.62 ( t, 1H, Ar-H), 7.77-7.79 ( d, 1H, -NH), 7.88-7.90 (d, 1 H, -NH). Mass ($C_{25}H_{32}N_6O_5$) m/z= 496.56, M+H= 497.2481.

### 3.7.14 1-(4-fluorobenzyl)-3-methyl-6-(piperidin-1-yl)pyrimidine-2,4(1H,3H)-dione (N):

Charged 1-(4-fluorobenzyl)-6-chloro-3-methylpyrimidine-2,4(1H,3H)-dione (10.00 g, 0.0372 moles) were dissolved in 45 mL DMF followed by addition of potassium carbonate (10.28 g, 0.0743 moles). Then (3.32 g, 0.0390 moles) of piperidine was added, and reaction mixture temperature maintained at 80°C, until reaction completion. Then the reaction mixture temperature was cooled down to 23-33°C and added water in to it and extracted with dichloromethane. The separated organic layer was removed water by

treating with sodium sulphate. Finally, the solvent was removed under reduced pressure for the formation of compounds N(10.75 g, 91.0%).

Yield: 76.0% , $^{1}$H-NMR:($CDCl_3$, Bruker 400 MHz) δ = 1.63-1.67 (m, 6 H,-$CH_2$), 2.86 (broad; 4 H, -$CH_2$), 3.29 (s, 3 H, -N-$CH_3$), 3.08 (broad, 1H, -CH), 5.02 (s, 2 H, -Ar-$CH_2$), 5.32 ( s, 1 H, -CH), 6.98-7.02 (t, 2 H, Ar-H), 7.22-7.28 (qui., 2 H, Ar-H). Mass ($C_{17}H_{20}FN_3O_2$) m/z= 317.15, M+H= 318.08.

## 3.8 DNA BINDING

Absorption titration experiments were performed with fixed concentrations of the compounds. The prepared compounds were made solution with the mixture of 1% DMSO and 99% Tris–HCl buffer ($10^{-2}$ M, pH 7.4). Stock solutions of different compounds and CT-DNA were stored at 4 °C and used after no more than one week Initially, a UV absorption spectrum of CT-DNA in buffer solution was recorded that showing two absorption bands at 230 nm and 260 nm with absorbance ratio = 1.8, which indicated free nature of DNA [129]. UV absorbance at 260 nm after 1: 40 dilutions with known molar absorption coefficient value of 6600 $M^{-1}$ $cm^{-1}$ determined the concentration of DNA. Absorption titration experiments were performed in the absence and presence of different concentrations ($0.2 – 1.4 \times 10^{-3}$) of CT-DNA. The intrinsic binding constant ($K_b$) values were determined with help of Equation 1, which is initially derived by Benessi–Hilderbrand equation and later modified by Wolfe et al [130].

$$[DNA]/(\varepsilon_a - \varepsilon_f) = [DNA]/(\varepsilon_a - \varepsilon_f) + 1/K(\varepsilon_b - \varepsilon_f) \quad \text{..... (1)}$$

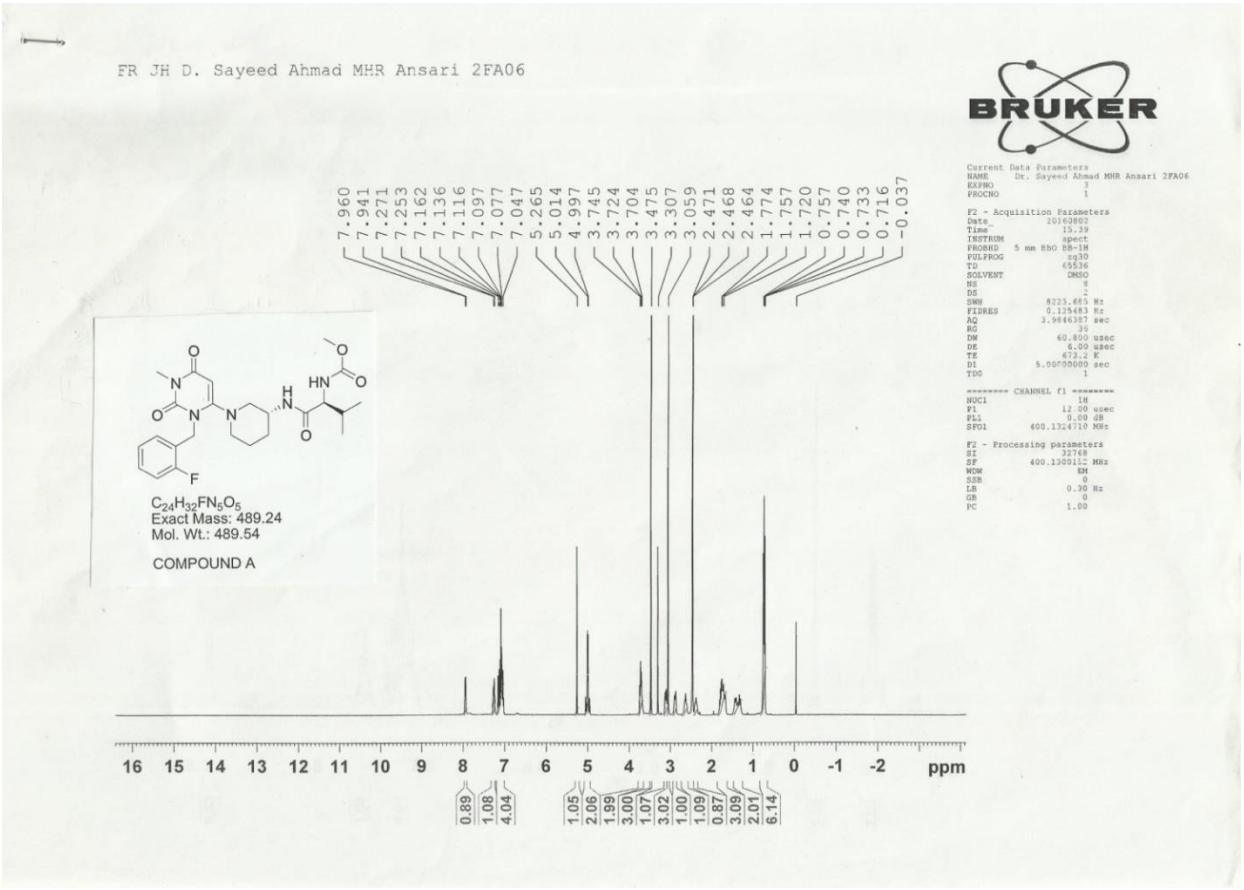
Where, absorption coefficients, $\varepsilon_a, \varepsilon_f$ , and $\varepsilon_b$ correspond to $A_{obs}$/[compound], extinction coefficient for the compound and the extinction coefficient for the compound in the fully bound form, respectively. The binding constants for the different compounds ($K_b$) were determined by the slopes and the intercepts of the plots of $[DNA]/(\varepsilon_a - \varepsilon_f) vs [DNA]$ .

## 3.9 DOCKING STUDY

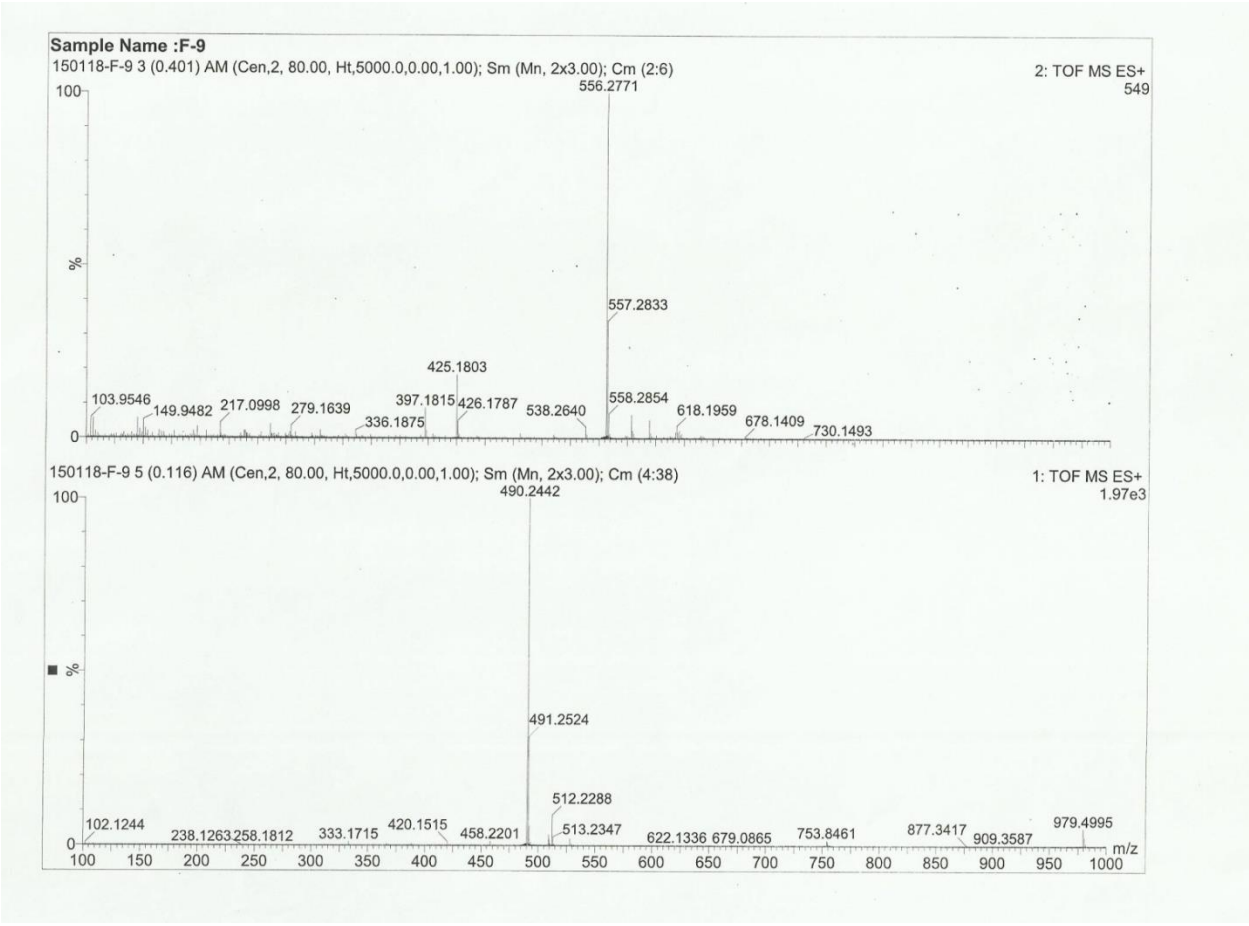
The docking studies of the different compounds (as ligands) were performed by Intel® dual CPU (1.86 GHz) with Windows XP operating system. Marwin sketch software was used to form 3-D structures of the compounds and pdp file format converted from so-obtained 3-D structures. Initially, by assigning Gastegier charges, merging non-polar hydrogens, the ligand was prepared and AutoDock Tools (ADT) 4.2 [131] used to save PDBQT file format of DNA. The DNA X-ray crystal structure were obtained from the Protein Data Bank [132] (PDB ID: 1BNA). By assigning Gastegier charges and removing water molecules of DNA, ADT 4.2 was used to save PDBQT file format of DNA. ADT was used to file grid and docking preparation of parameters. AutoDock 4.2 (Scripps Research Institute, USA) were used to perform docking study. Considered all the receptor as grid and all the rotatable ligand bonds as rotatable. The whole DNA spacing was used 0.372°A and grid box size was 60 × 80 × 110 Å. with 0.375 Å spacing was used that included the whole DNA. PyMOL was used to illustrate virtual screening, and binding site analysis of compounds. AutoDock (4.2) and AutoDock Vina [133] are two popular docking program, the interface between two docking program and PyMOL are represented by plugin. For the docking setup runs [131] and extensive use of a Python script collection (AutoDock Tools), the combined effect of these two software's were used. Moreover, the possibility of hydrophobic interactions of DNA [134] with compounds, Ligplot software was used.

## 3.10 [1]HNMR, MASS SPECTROSCOPY DATA OF URACIL BASED MOC-L-VALINE ERIVATIVES:

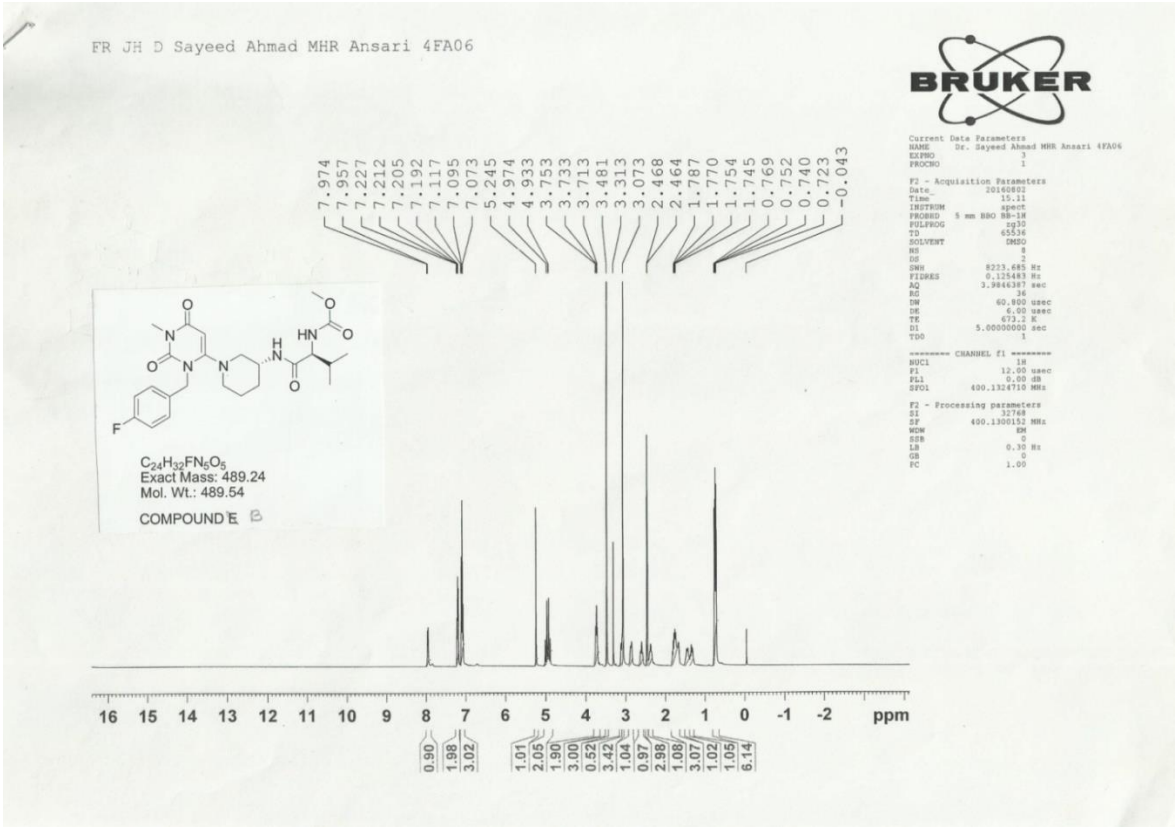
### 3.10.1 [1]HNMR of Methyl (S)-1-((R)-1-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (A)



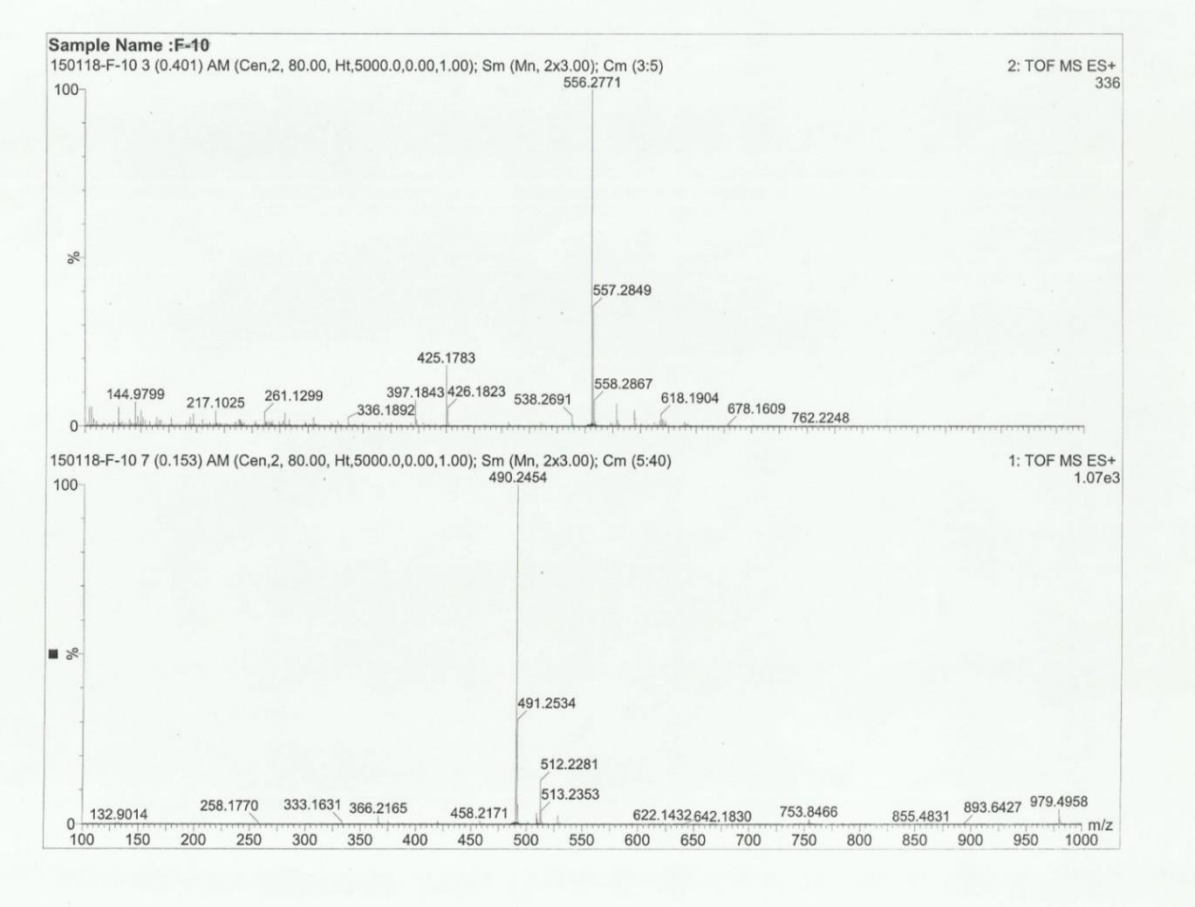
### 3.10.2 HRMS of Methyl (S)-1-((R)-1-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (A)



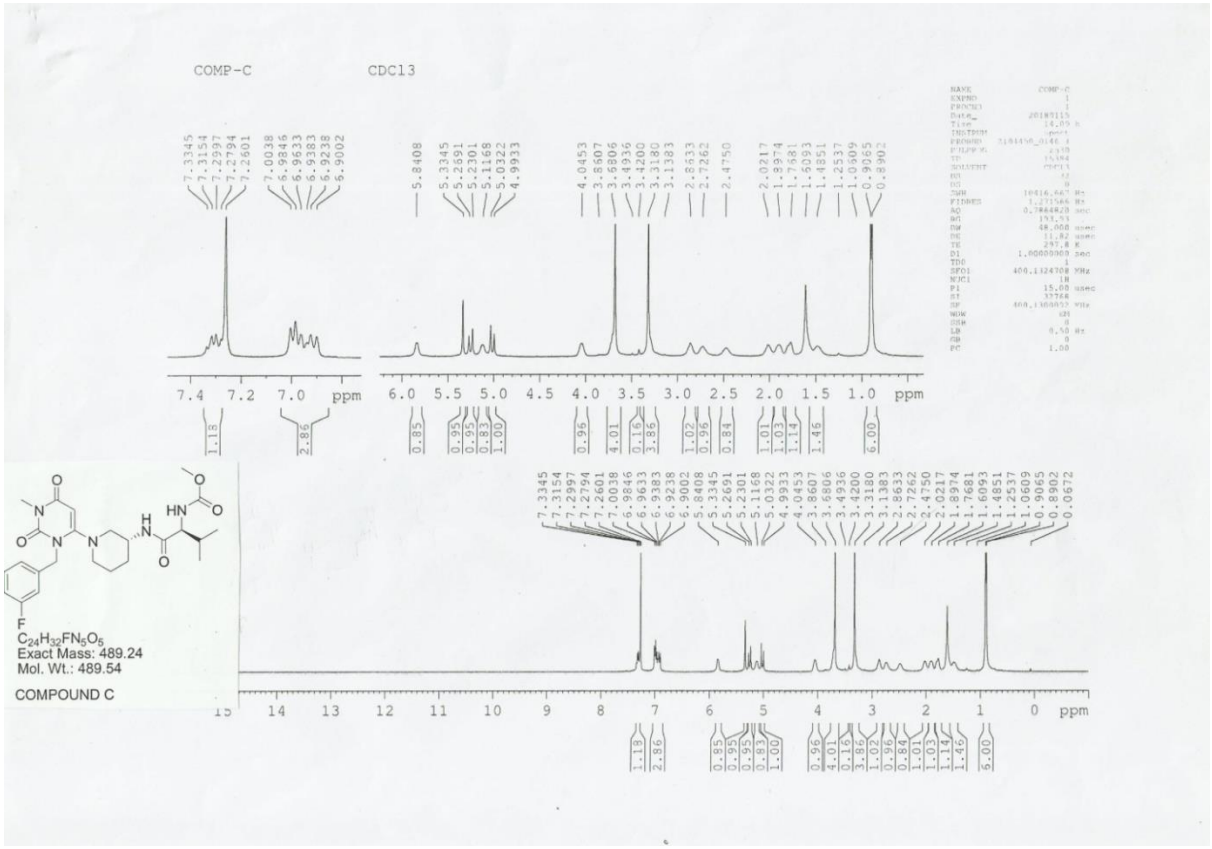
### 3.10.3 $^{1}$H NMR of Methyl (S)-1-((R)-1-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (B)



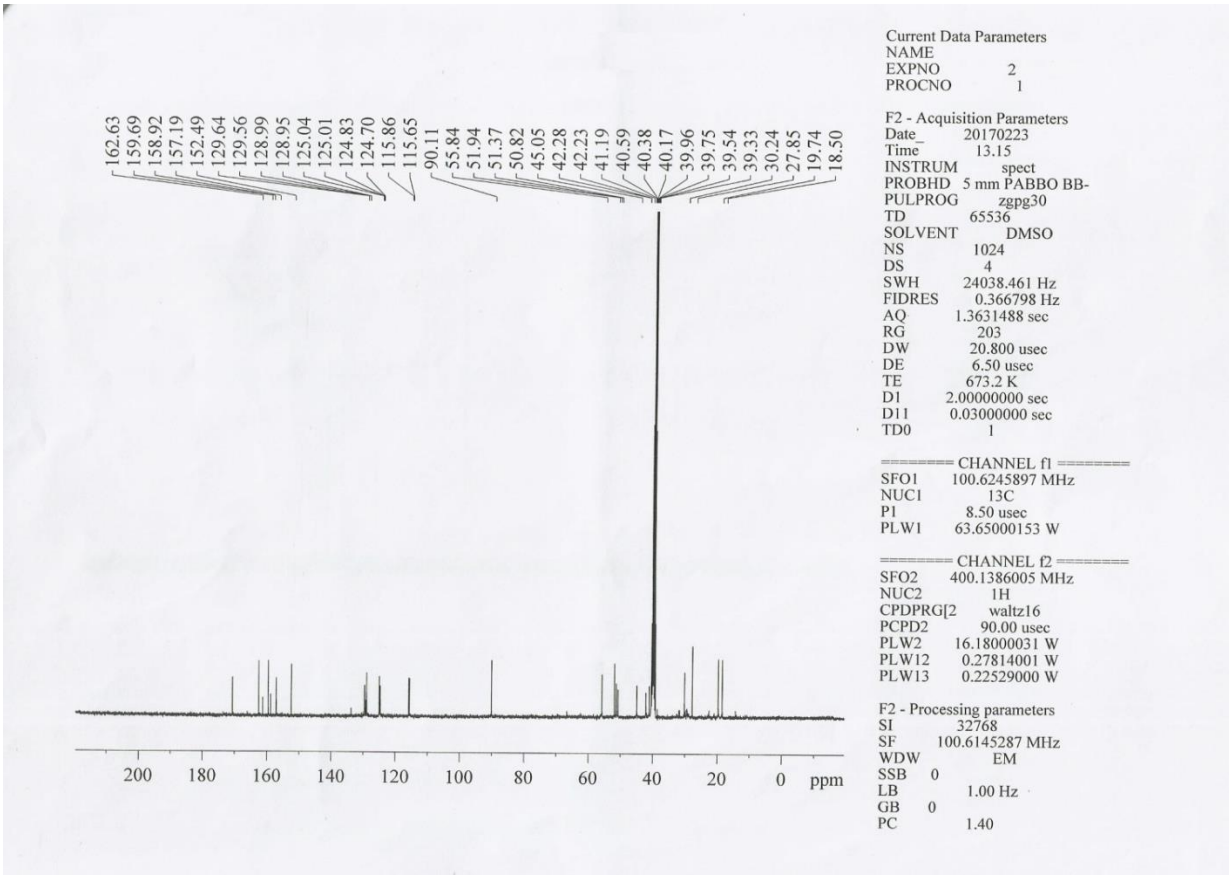
### 3.10.4 HRMS Of Methyl (S)-1-((R)-1-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (B)



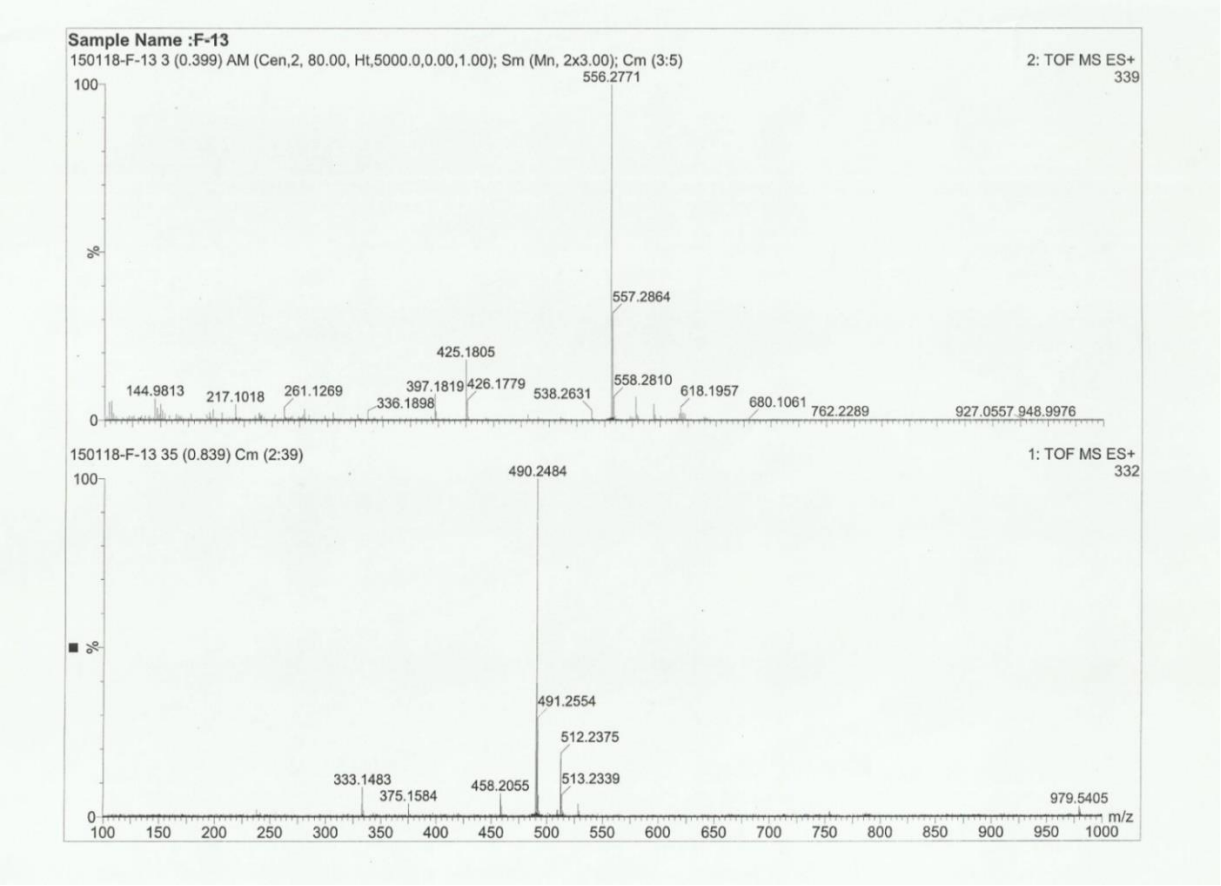
### 3.10.5 $^{1}$H NMR of Methyl (S)-1-((R)-1-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (C)



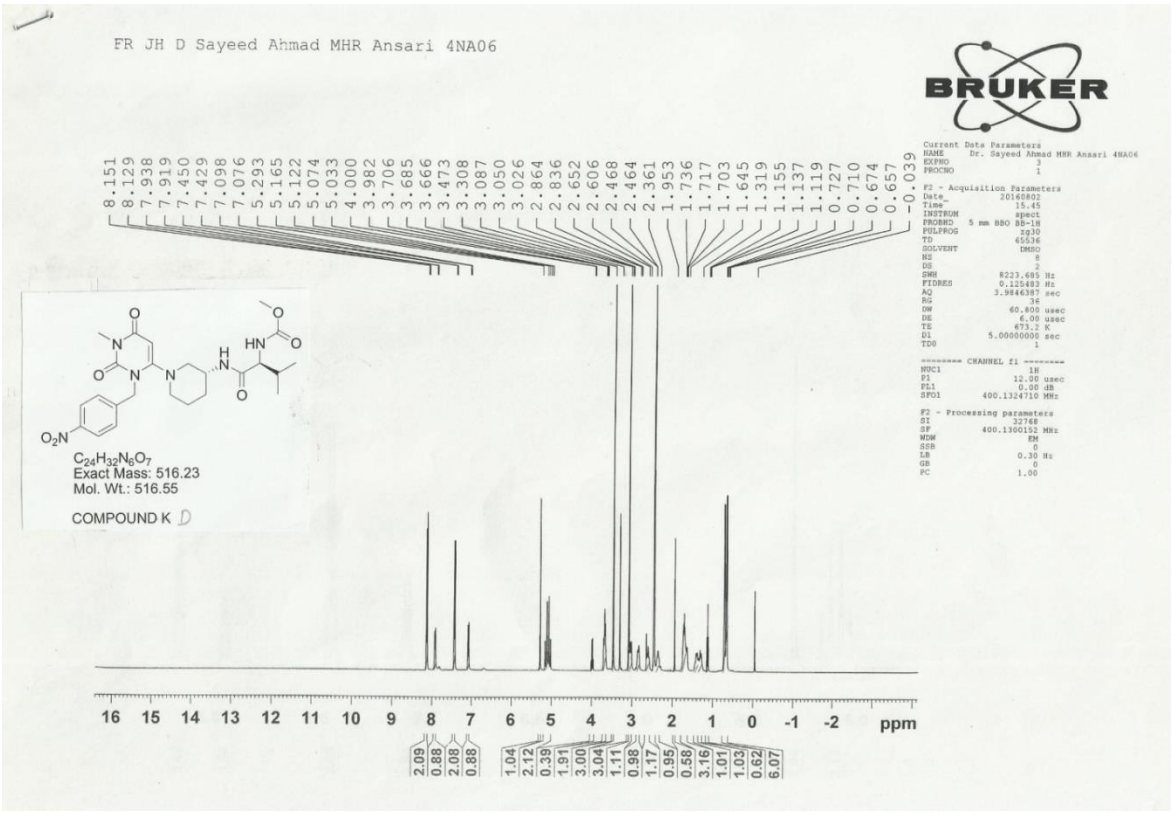
### 3.10.6 $^{13}C$ NMR of Methyl (S)-1-((R)-1-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (C)



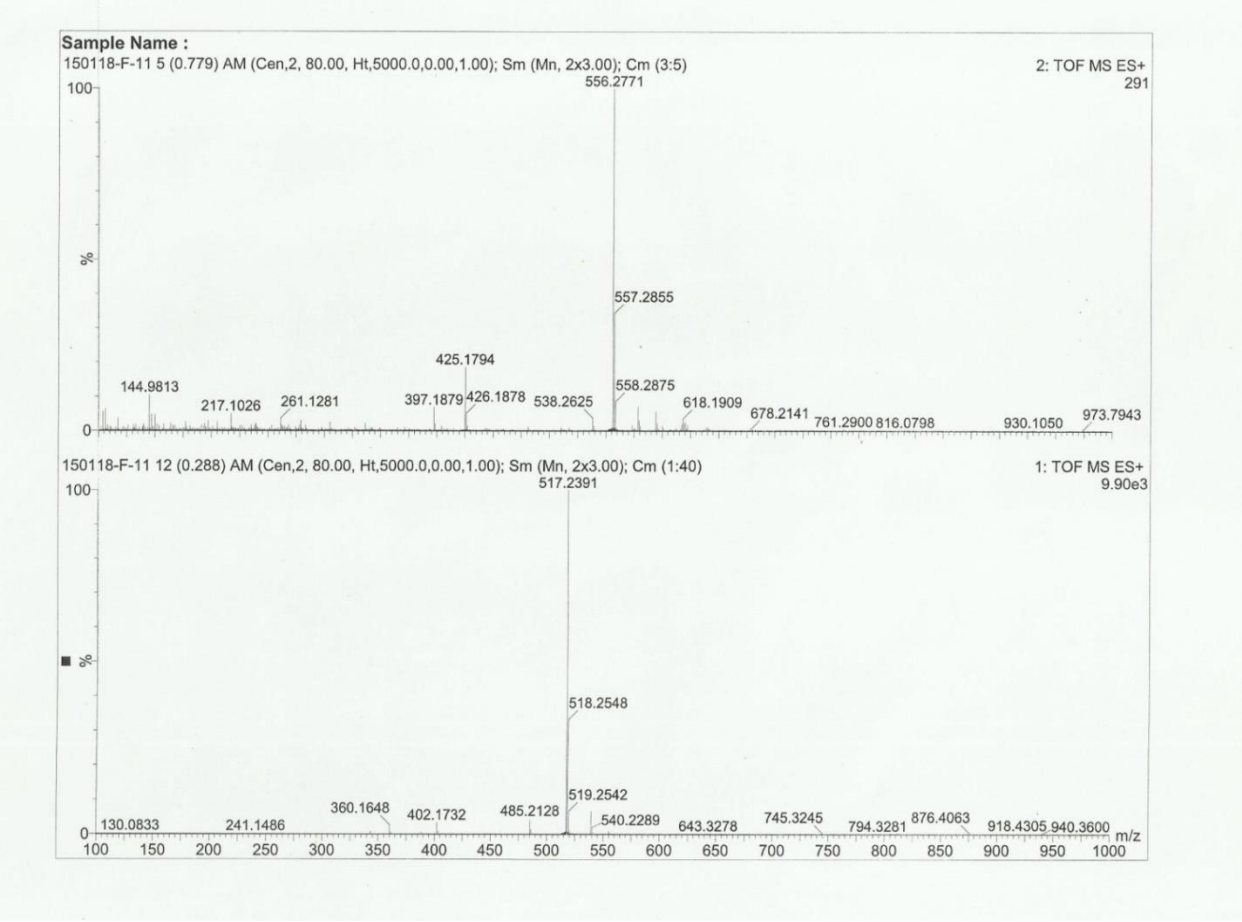
### 3.10.7 HRMS of Methyl (S)-1-((R)-1-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (C)



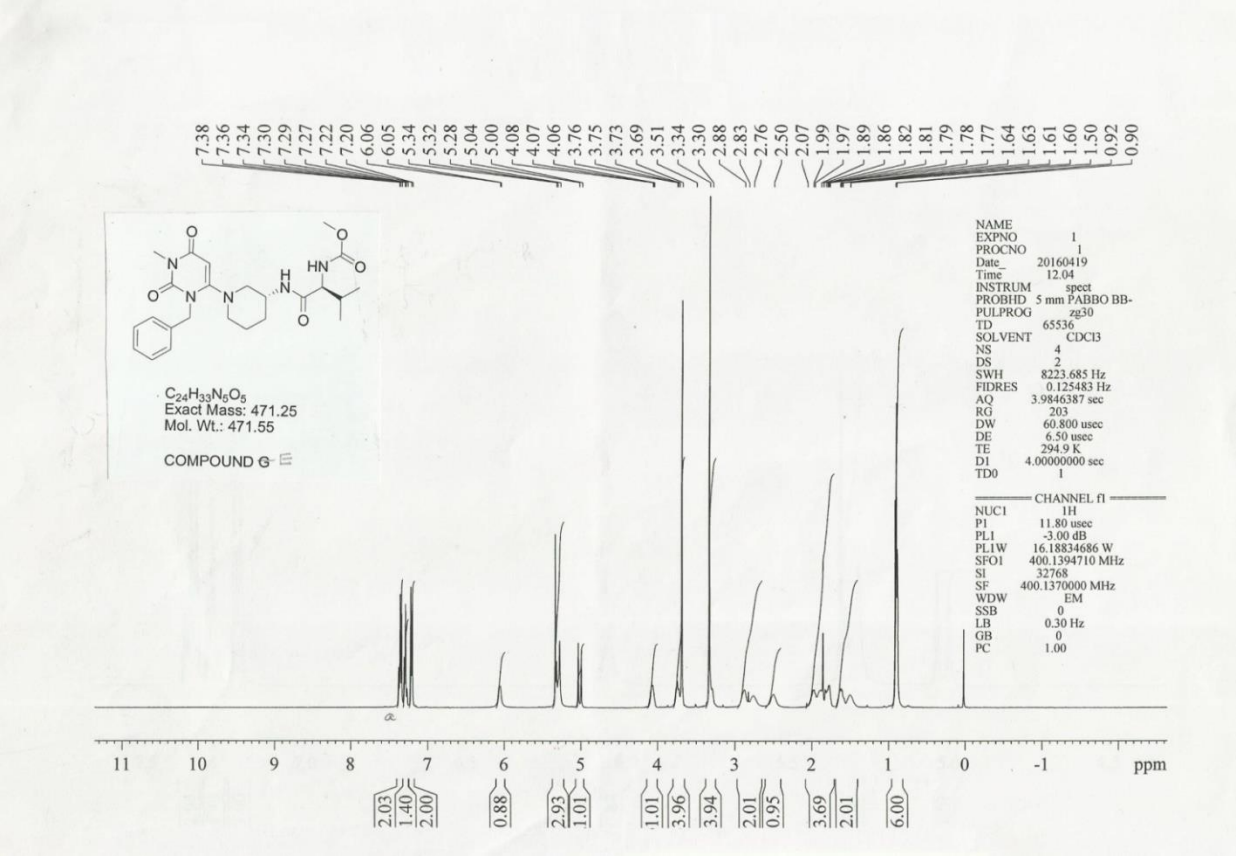
### 3.10.8 $^{1}$H NMR of Methyl (S)-1-((R)-1-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (D)



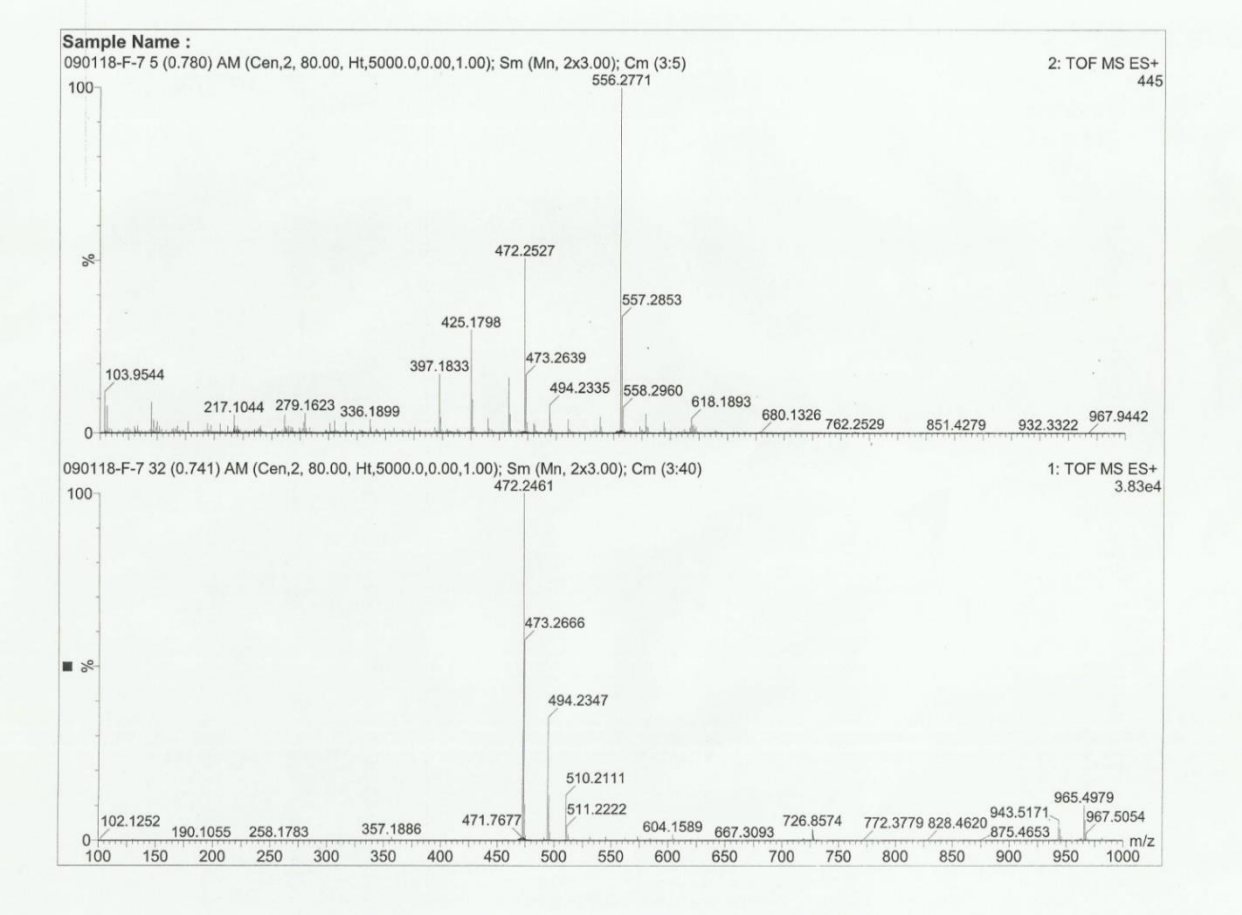
### 3.10.9 HRMS of Methyl (S)-1-((R)-1-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (D)



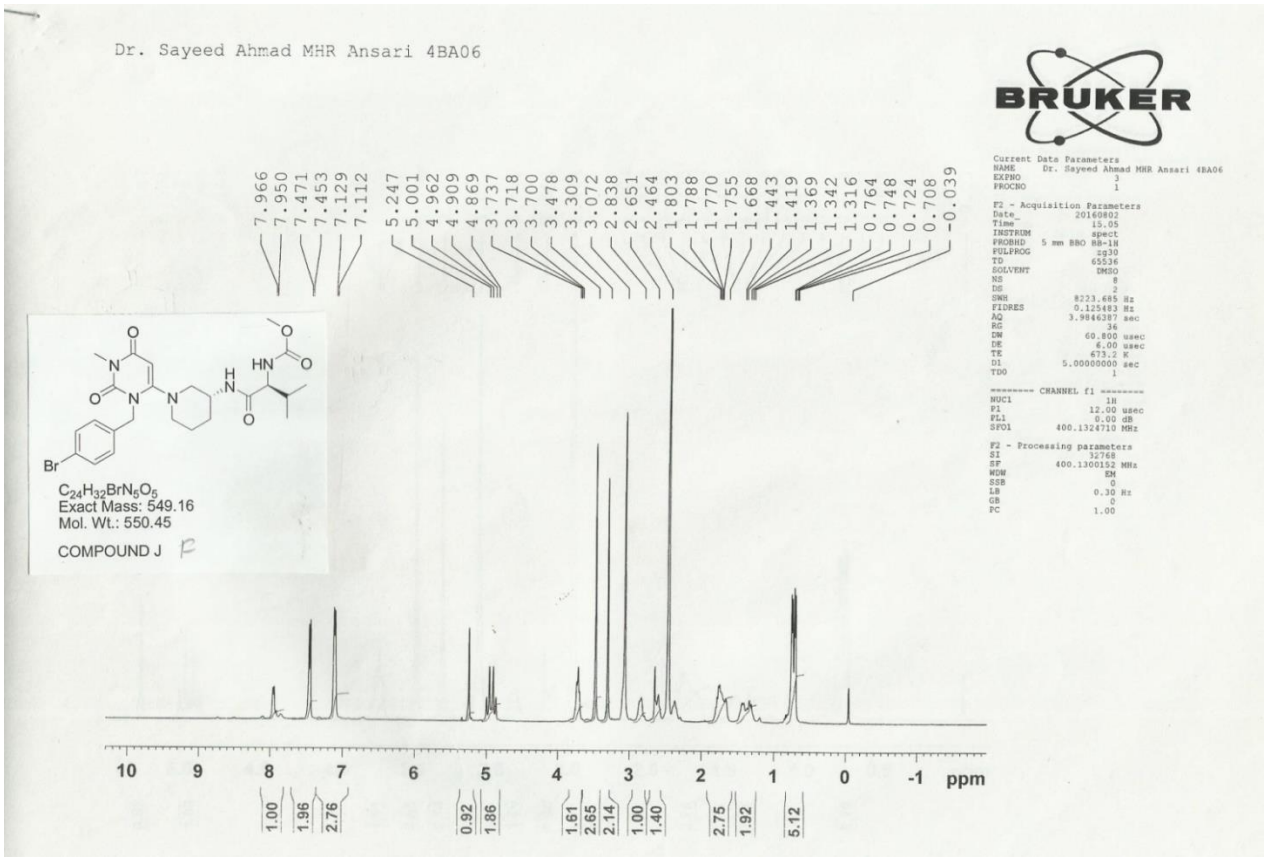
**3.10.10 $^1$H NMR of Methyl (S)-1-((R)-1-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (E)**



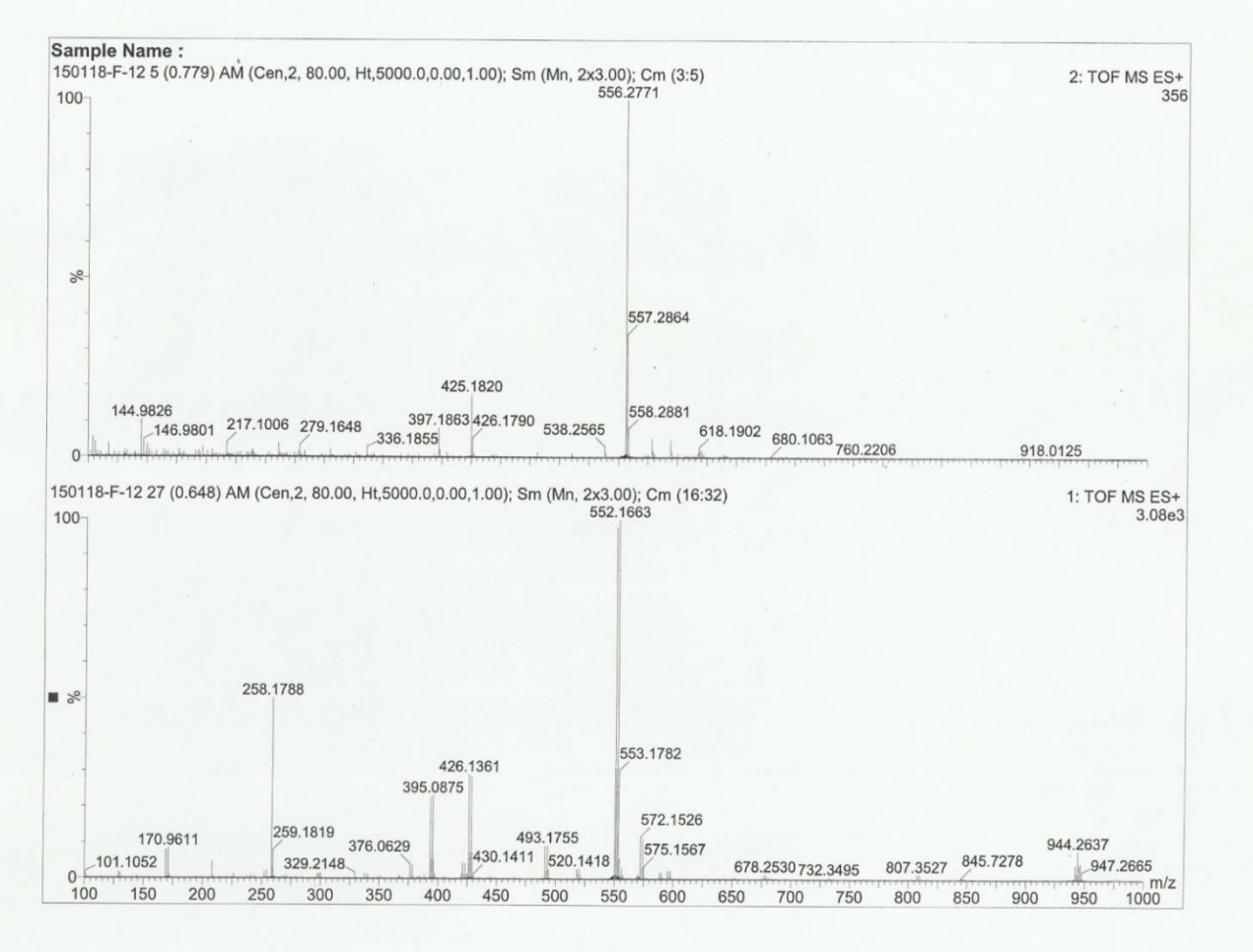
### 3.10.11HRMS of Methyl (S)-1-((R)-1-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (E)



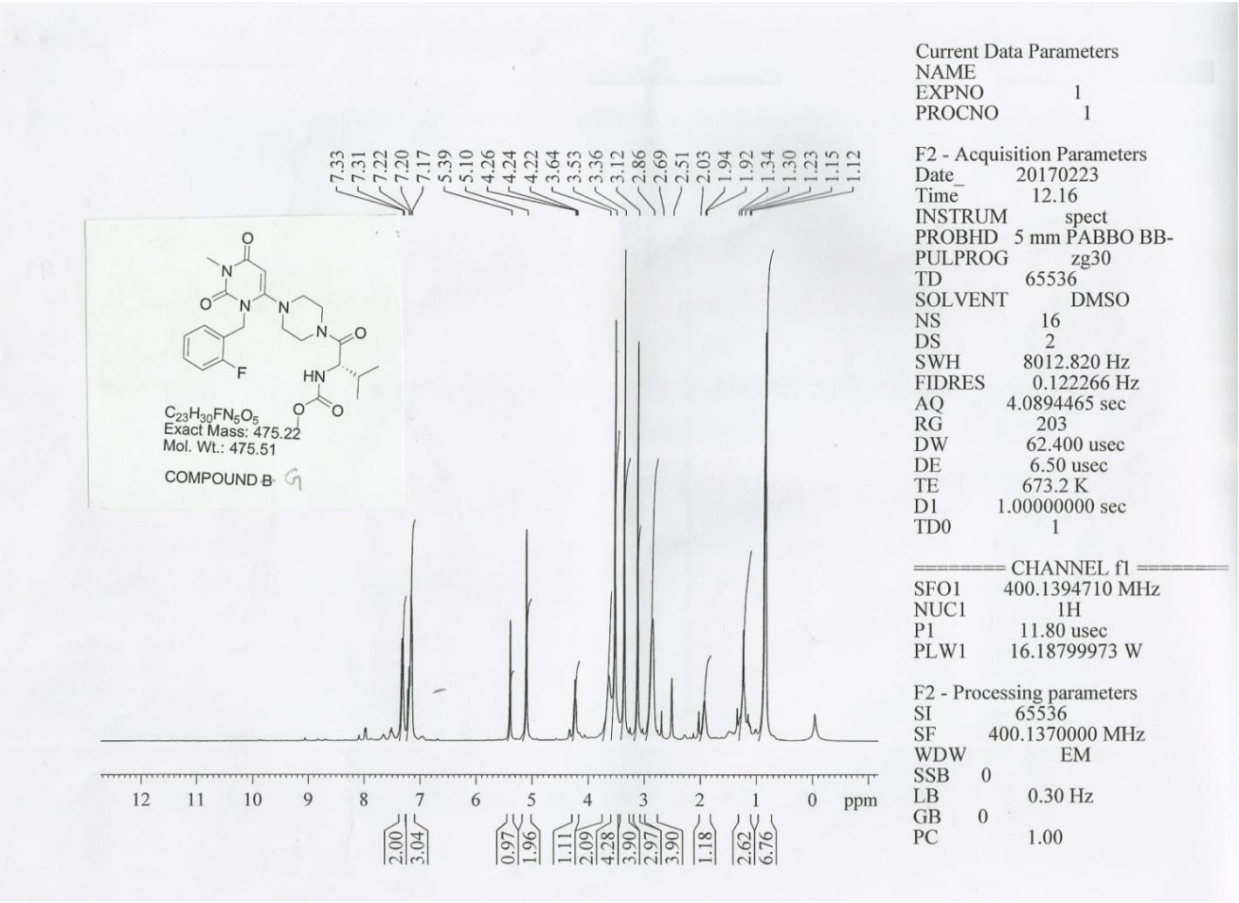
**3.10.12 $^{1}$H NMR of Methyl (S)-1-((R)-1-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (F)**



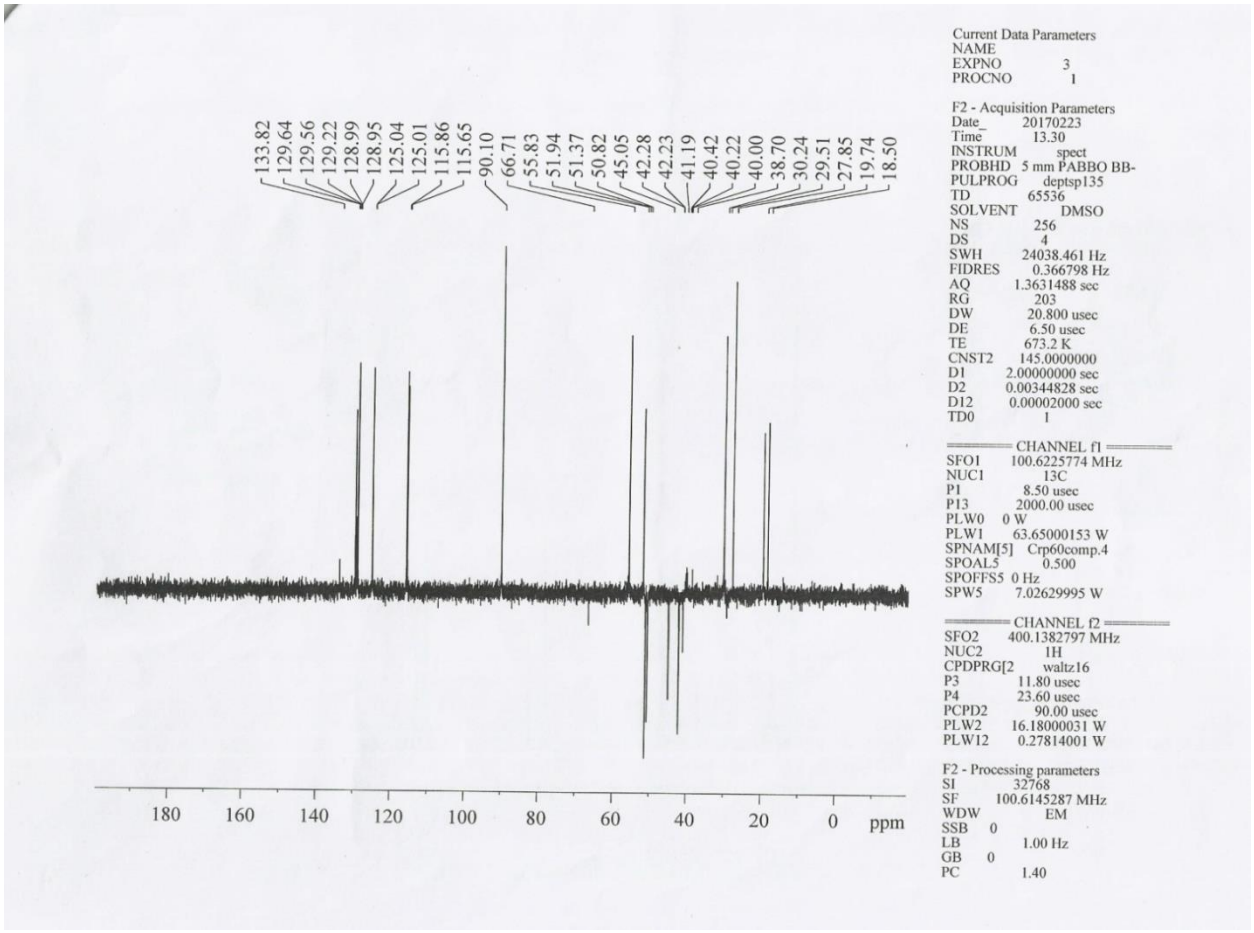
### 3.10.13HRMS of Methyl (S)-1-((R)-1-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (F)



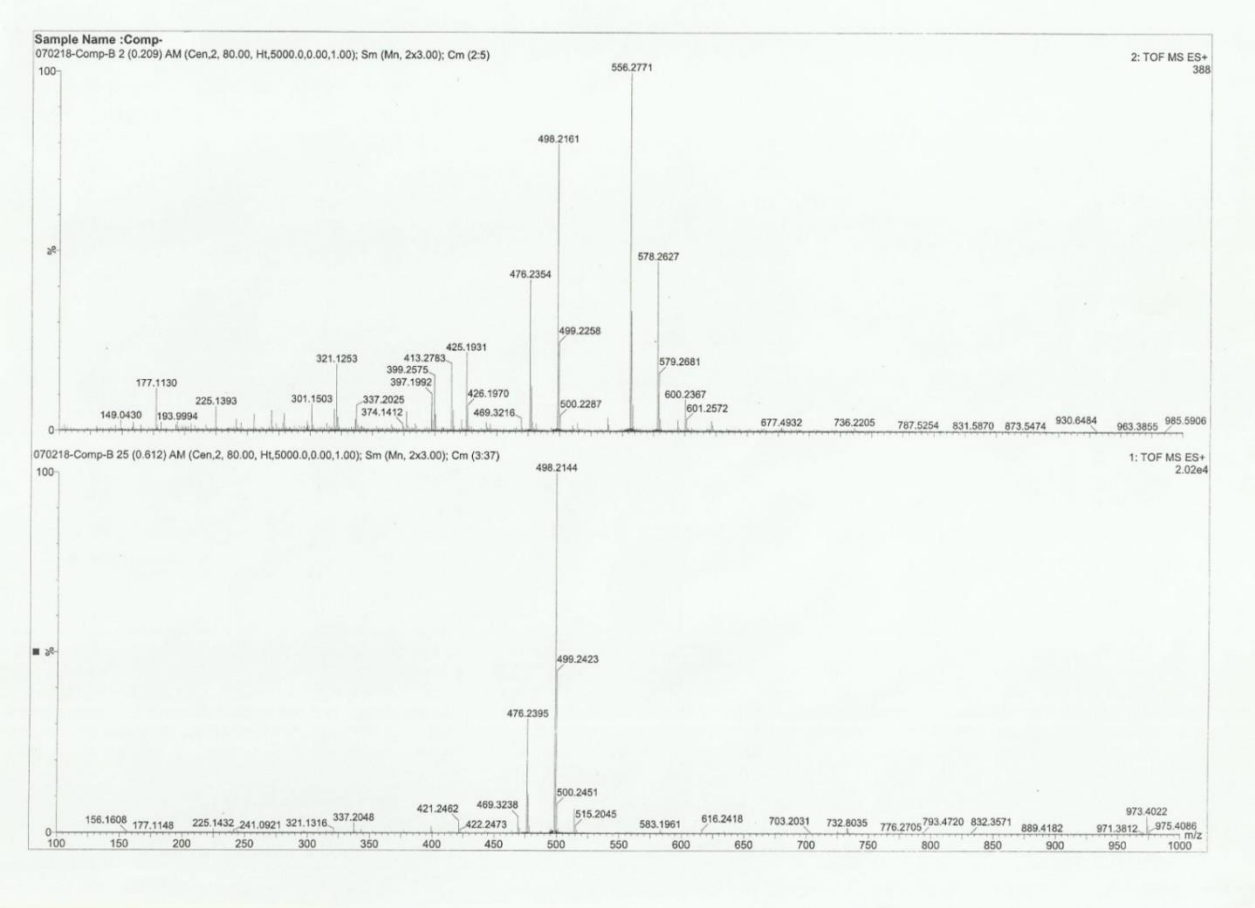
**3.10.14 $^1$H NMR of (S)-methyl 1-(4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (G)**



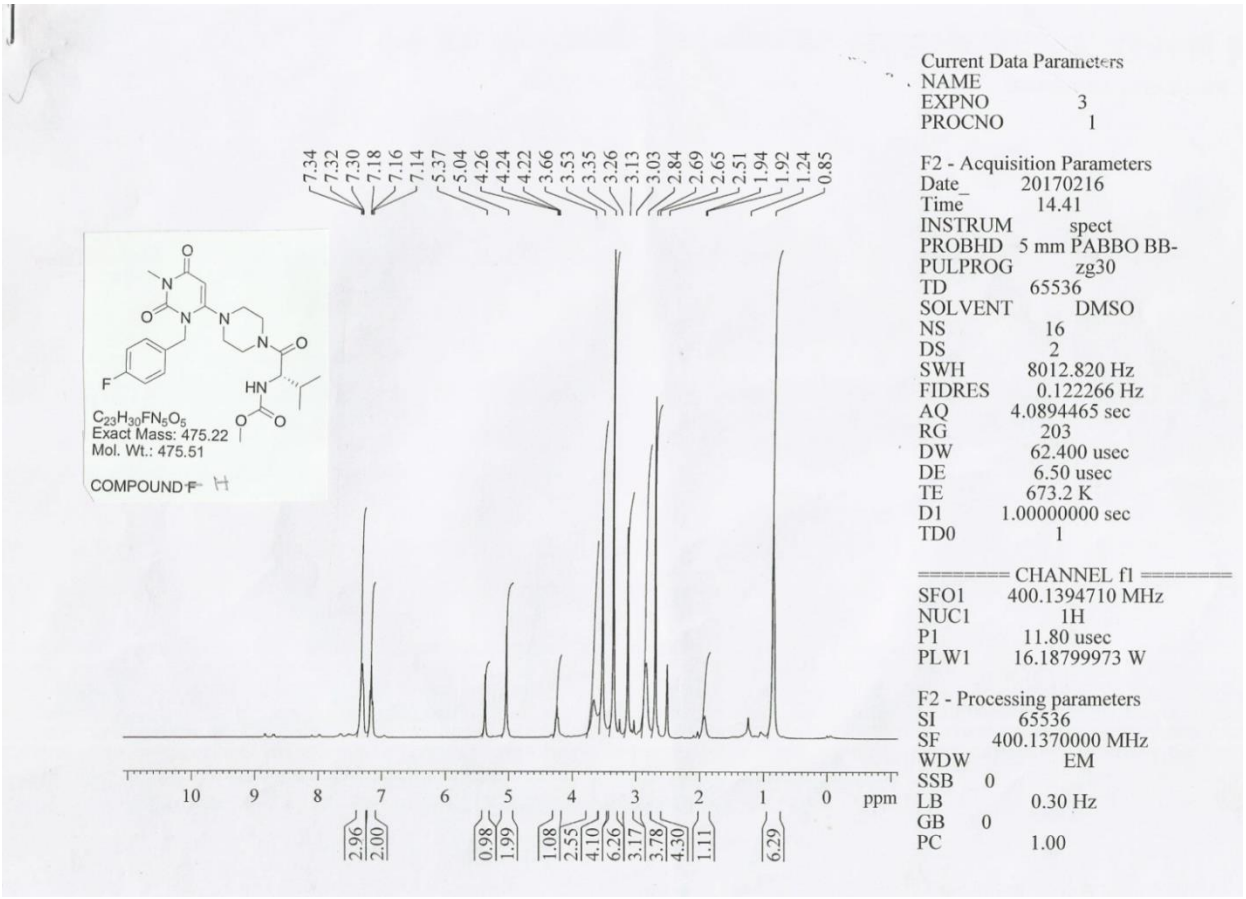
**3.10.15Dept of (S)-methyl 1-(4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (G)**



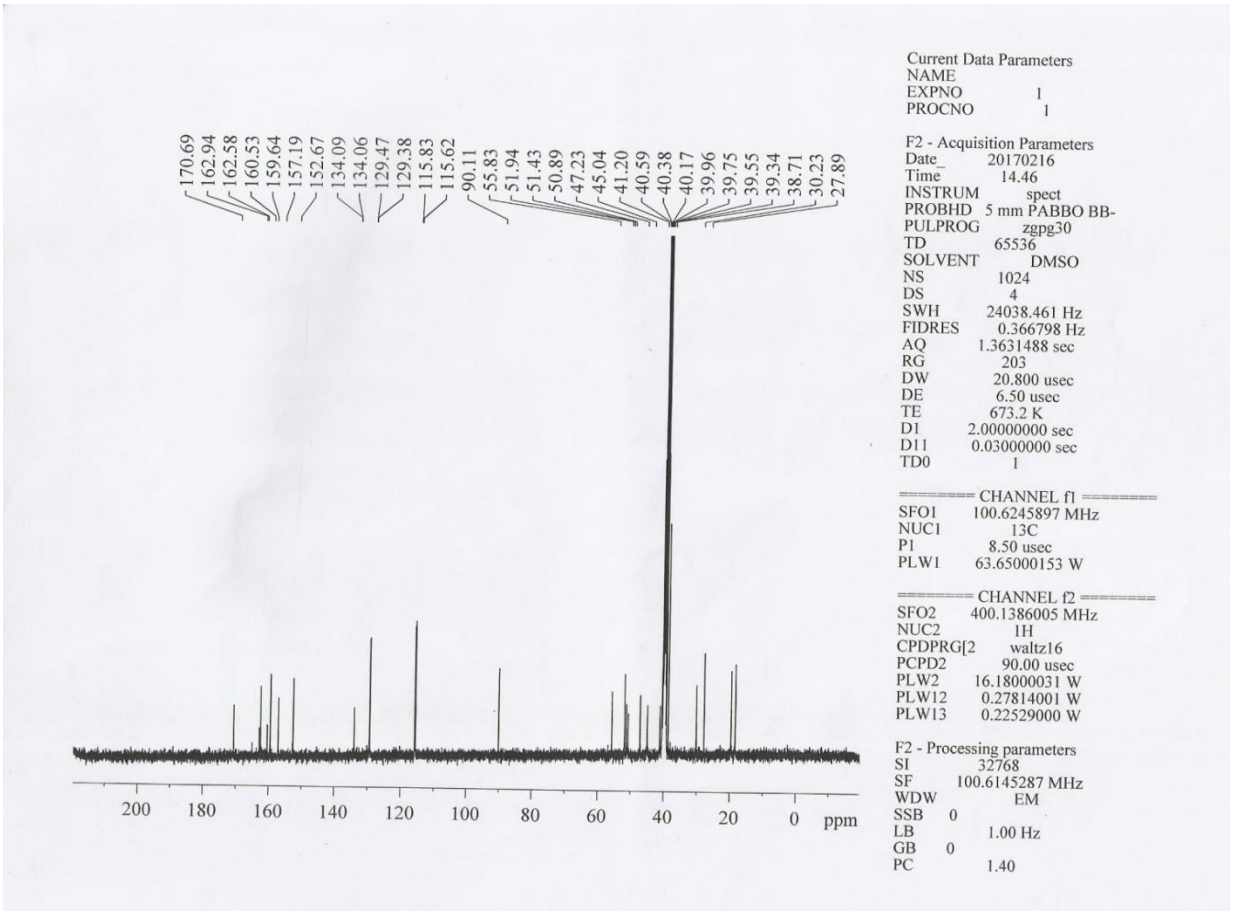
### 3.10.16HRMS of (S)-methyl 1-(4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (G)



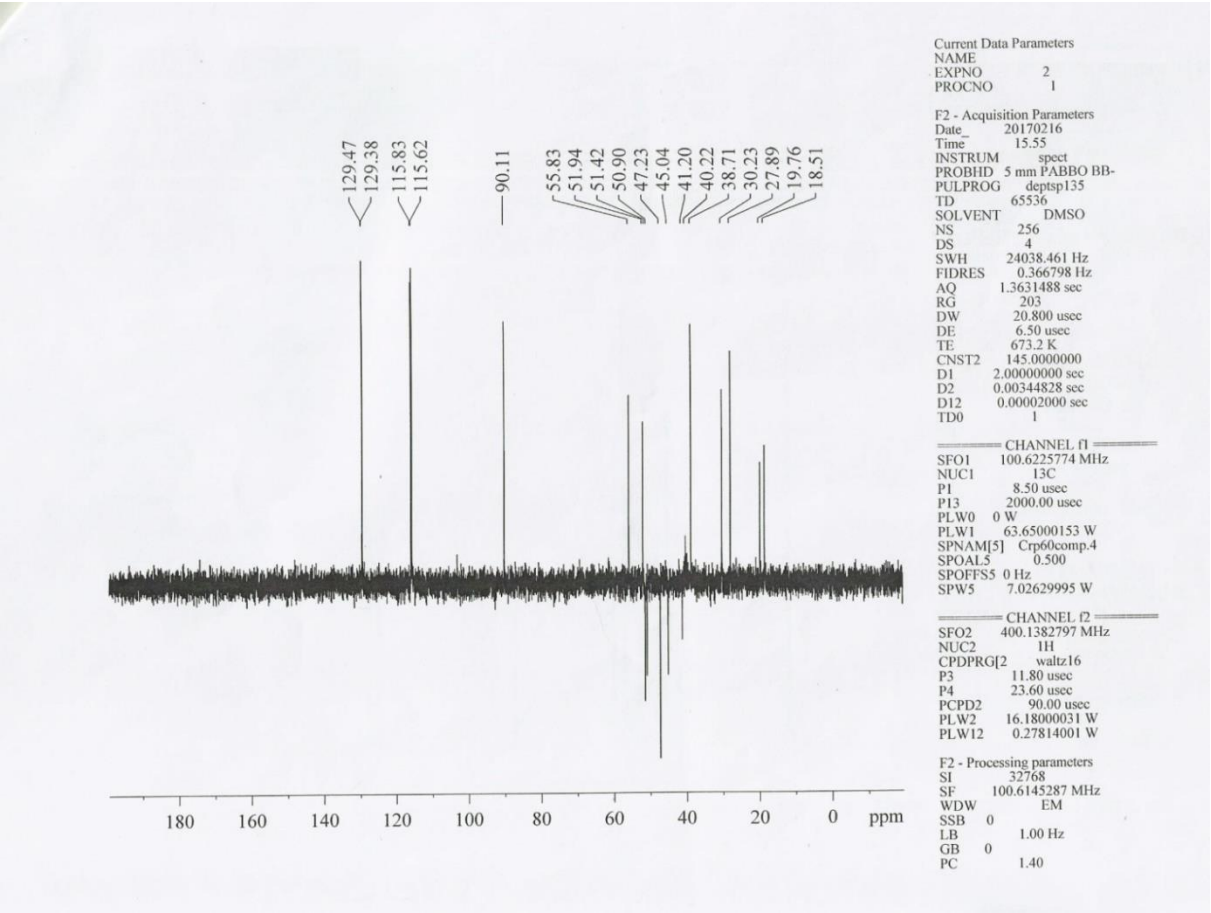
**3.10.17 $^1$H NMR of (S)-methyl 1-(4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (H)**



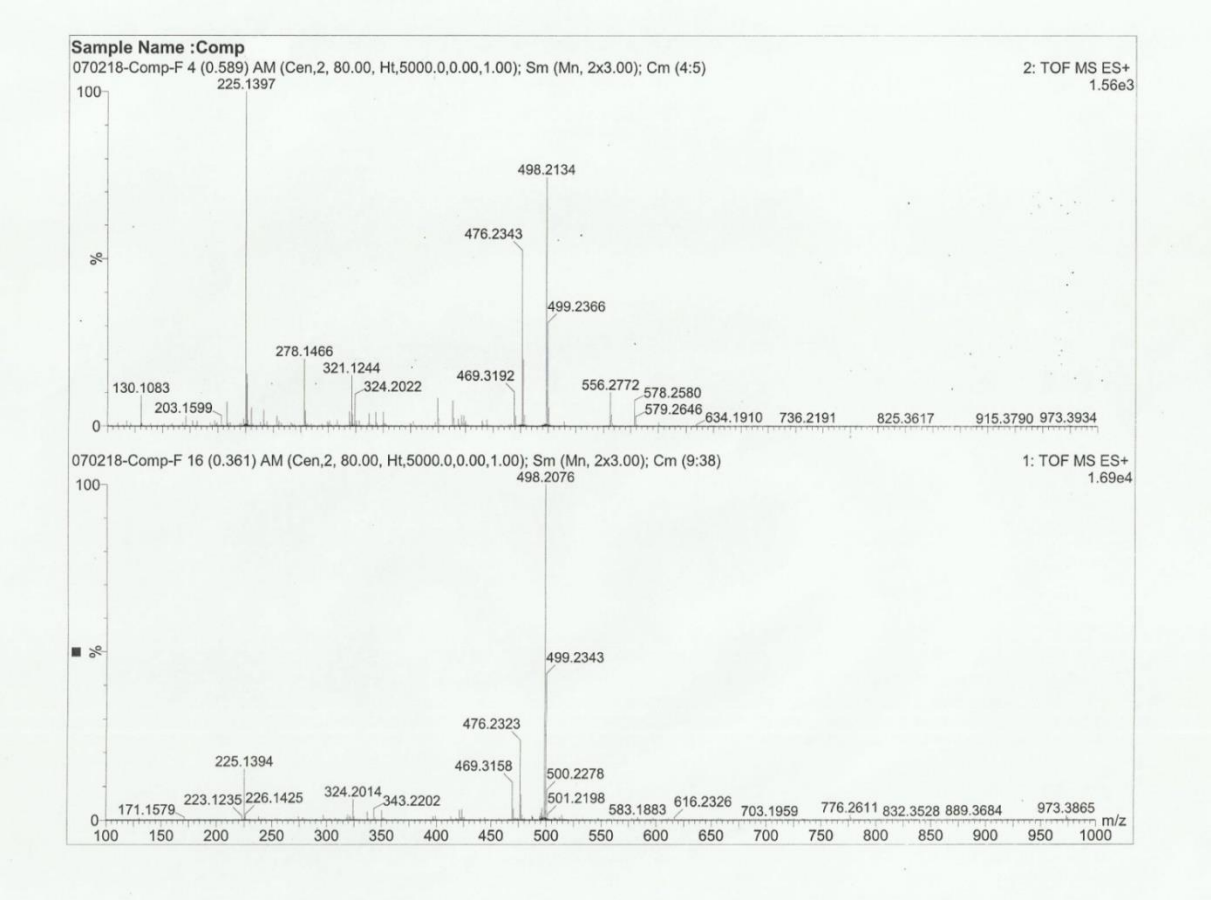
**3.10.18$^{13}$C NMR of (S)-methyl 1-(4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (H)**



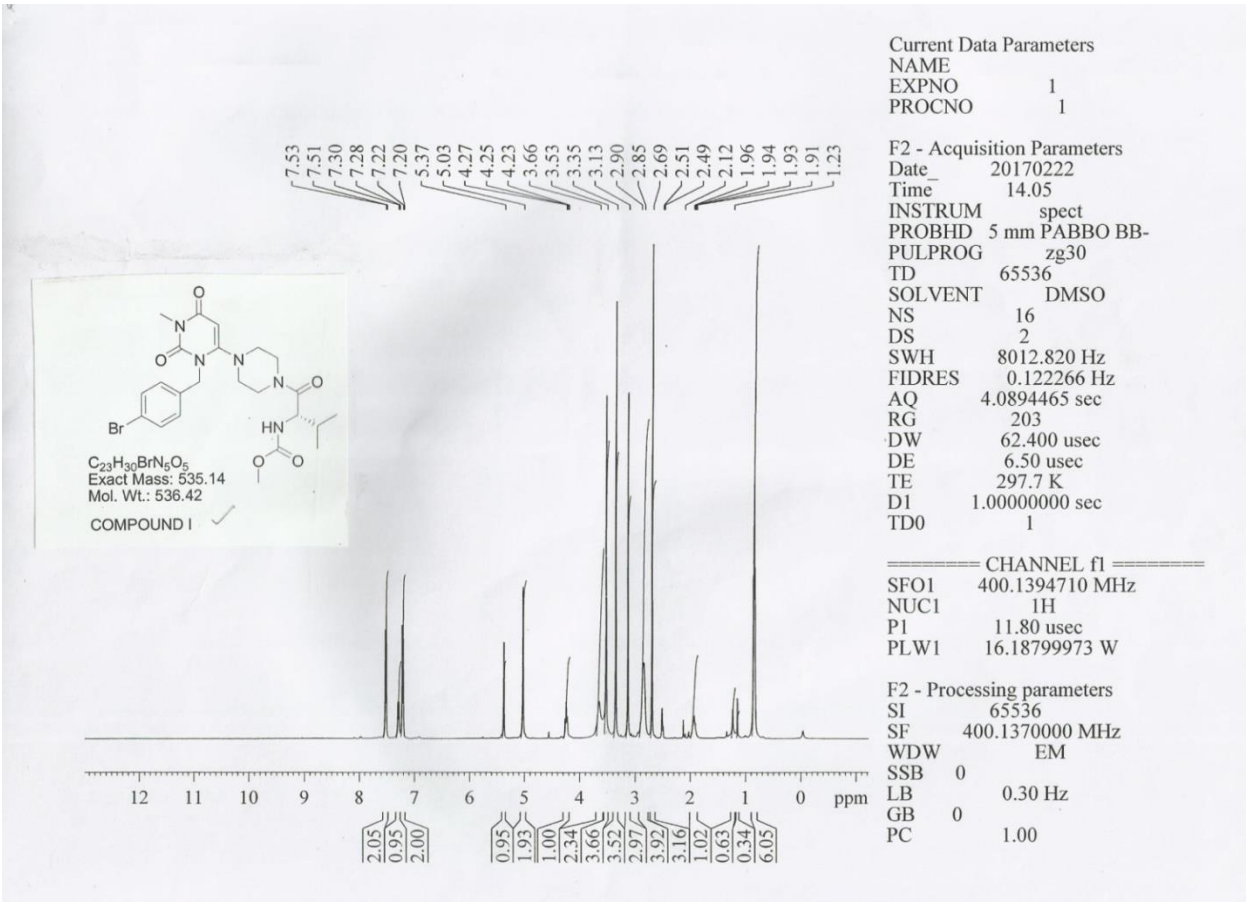
**3.10.19Dept NMR of (S)-methyl 1-(4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (H)**



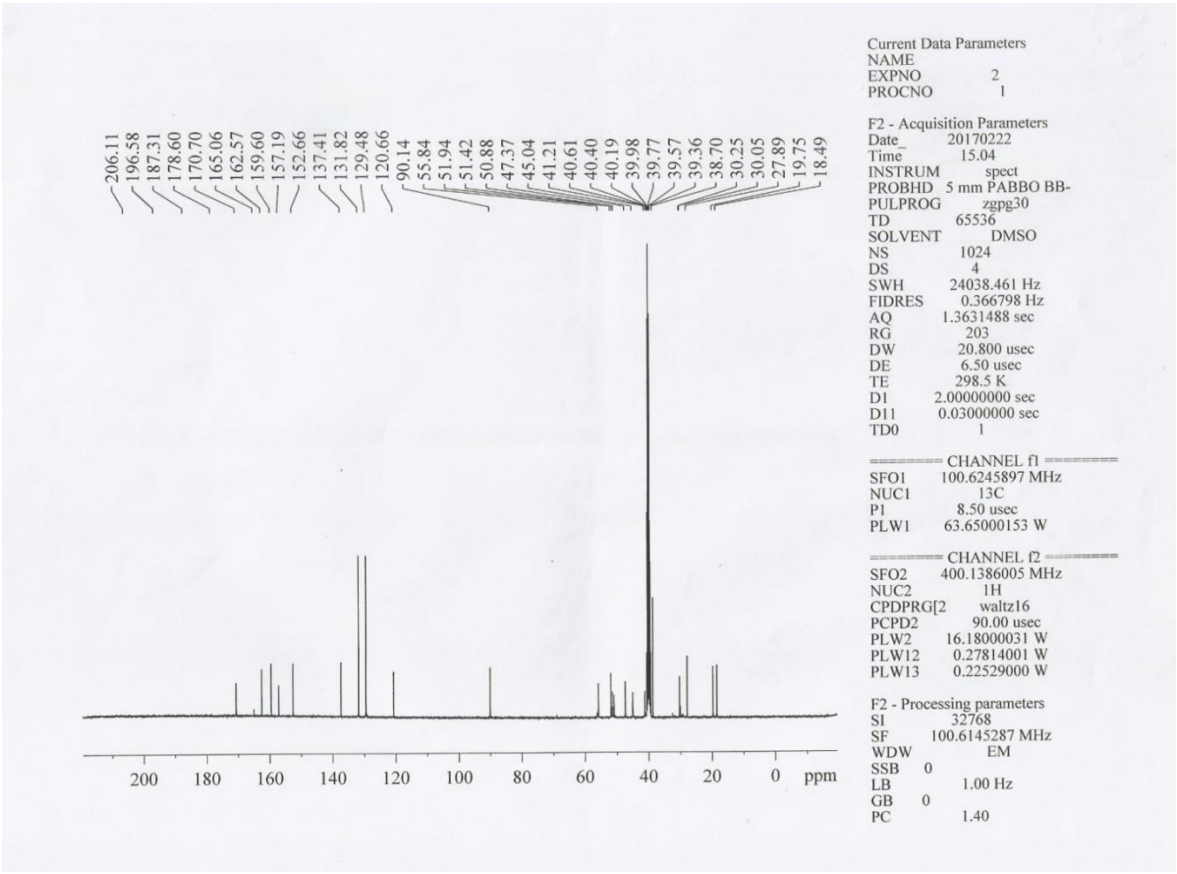
### 3.10.20HRMS of (S)-methyl 1-(4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (H)



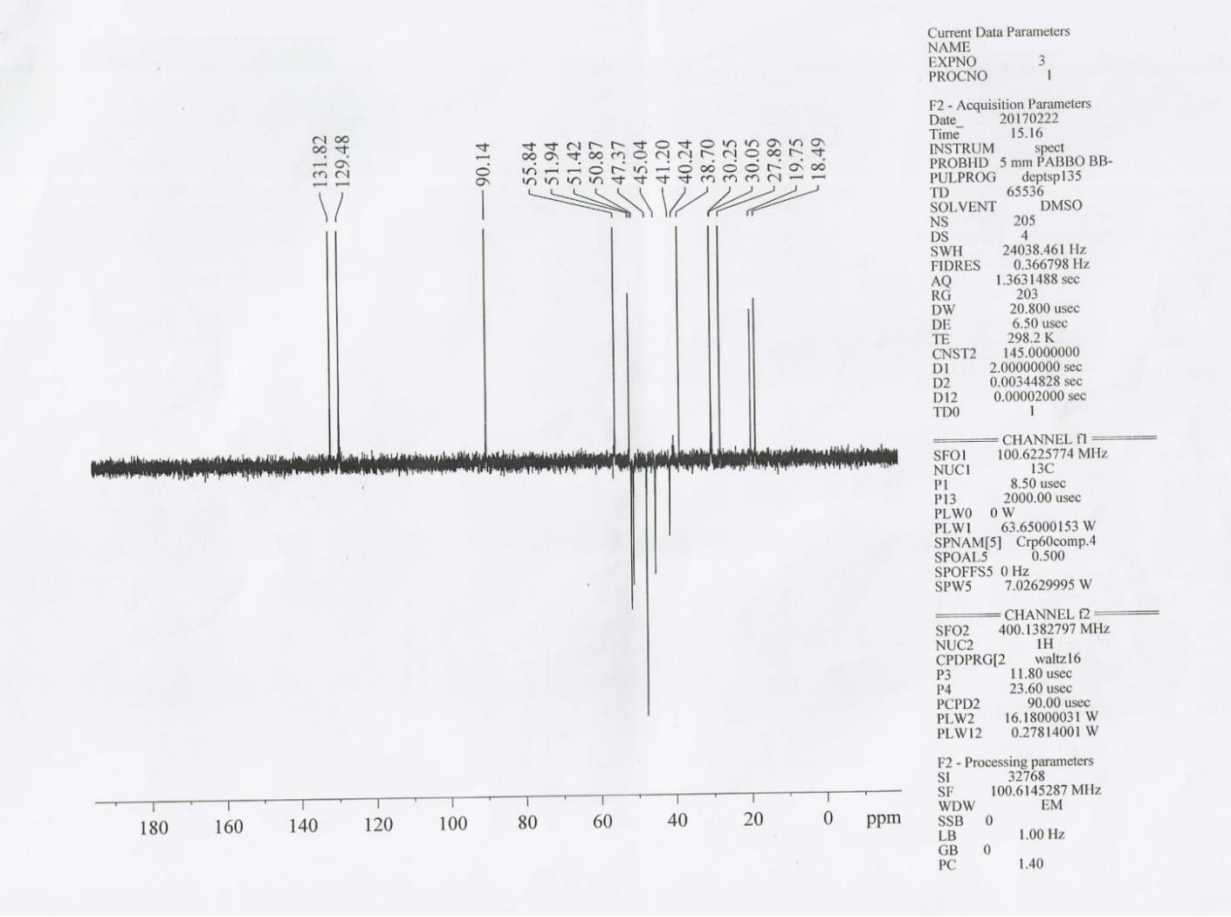
**3.10.21 $^1$H NMR of (S)-methyl 1-(4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (I)**



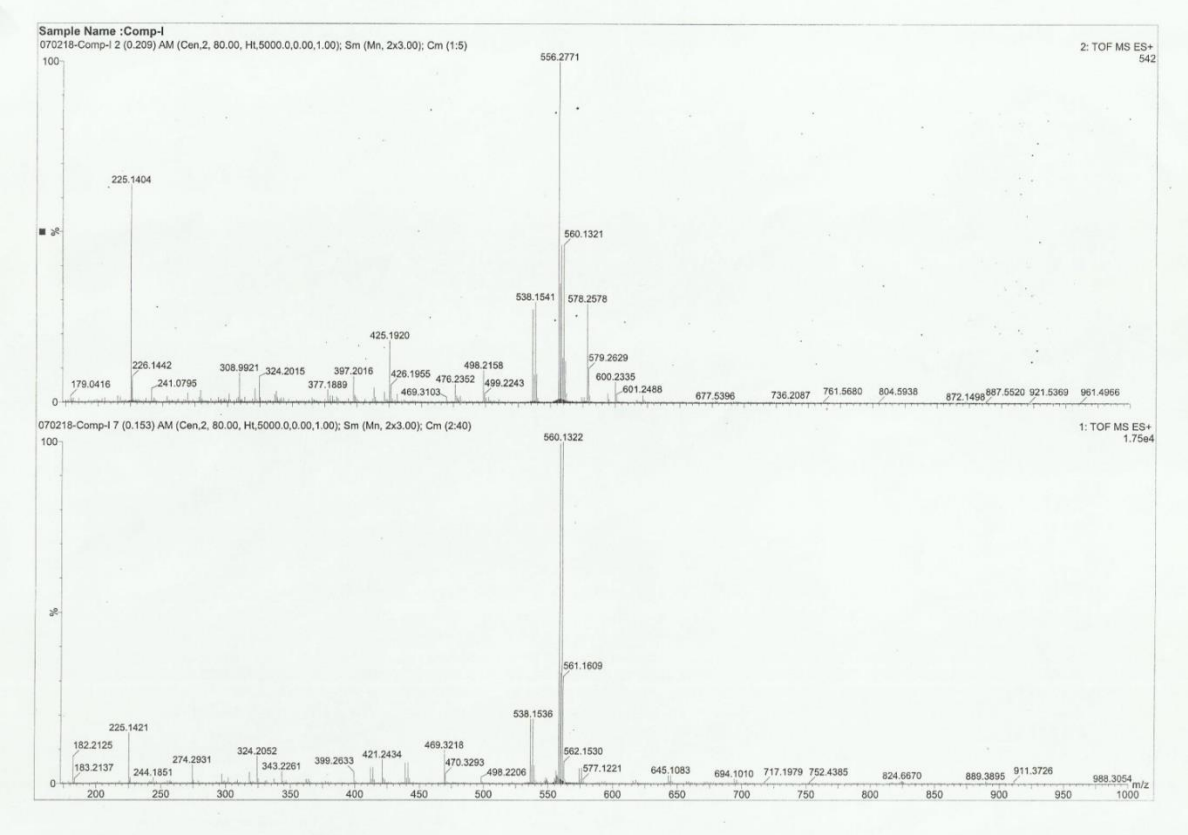
**3.10.22$^{13}$C NMR of (S)-methyl 1-(4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (I)**



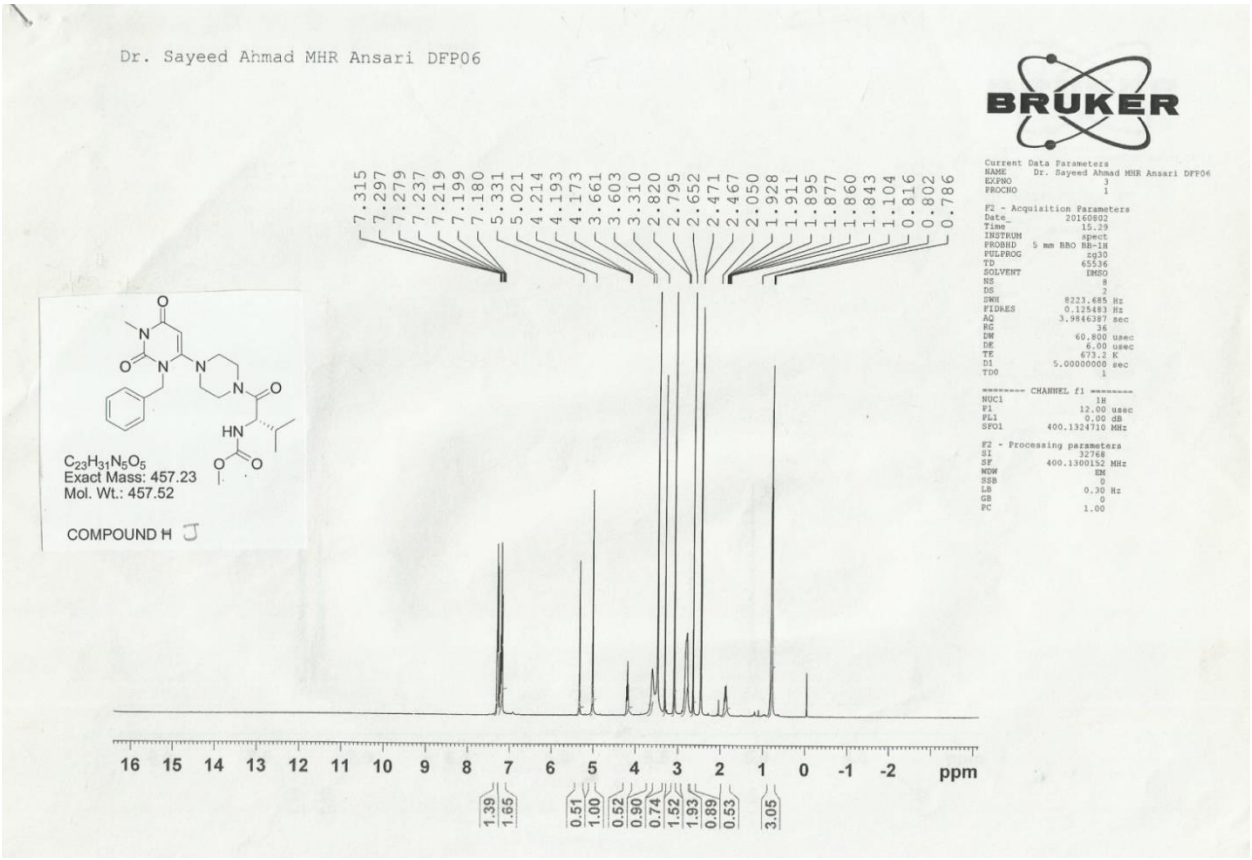
**3.10.23Dept NMR of (S)-methyl 1-(4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (I)**



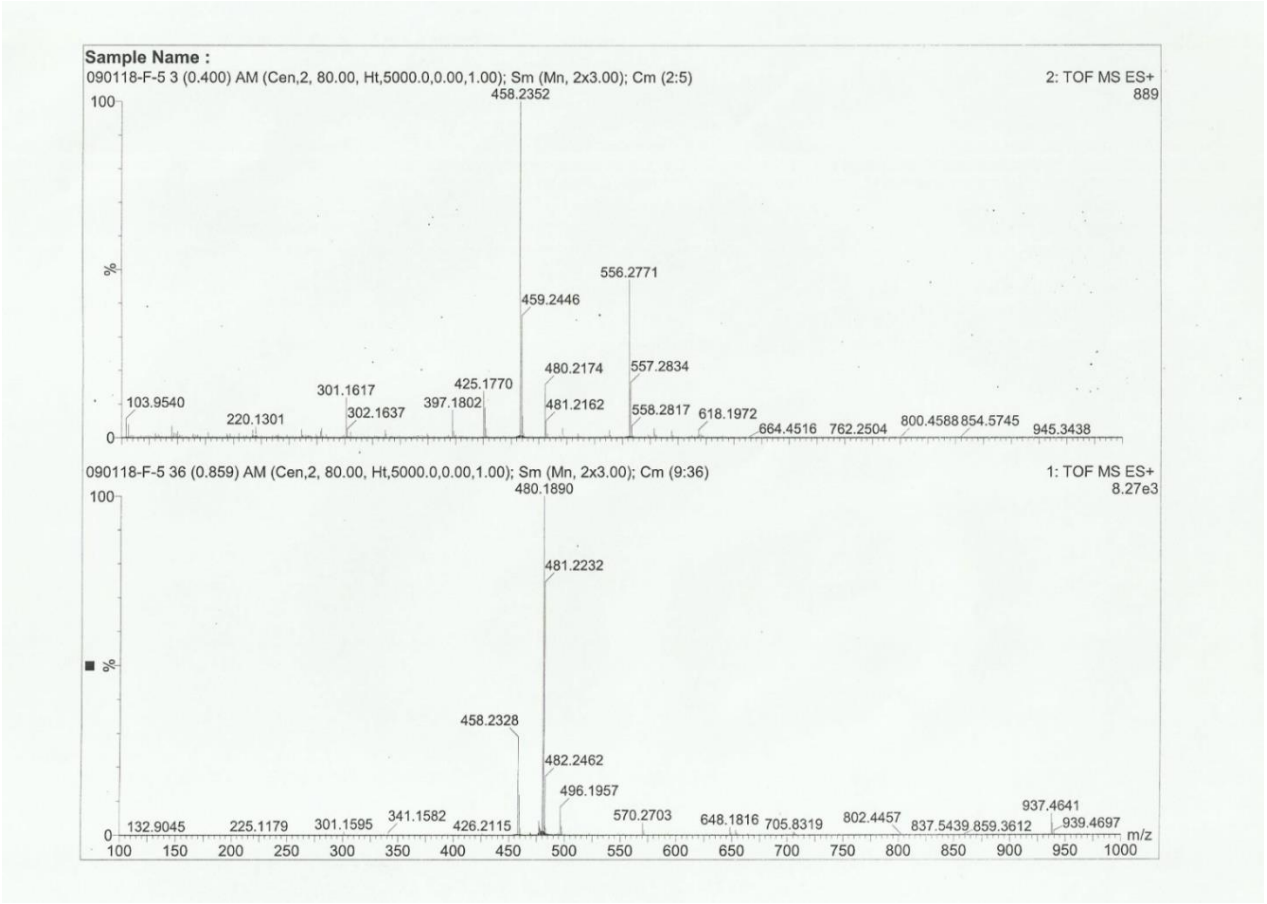
### 3.10.24HRMS of (S)-methyl 1-(4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (I)



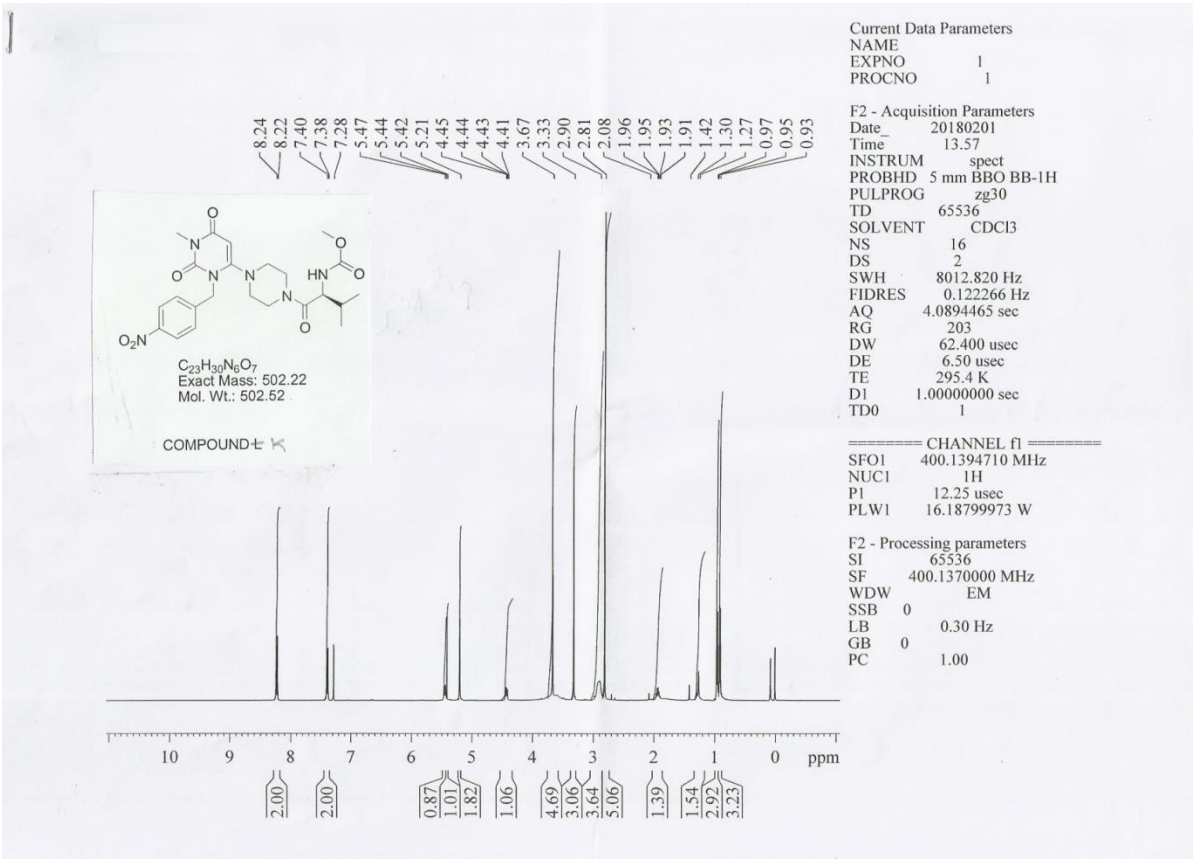
**3.10.25 $^1$H NMR of (S)-methyl 1-(4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (J)**



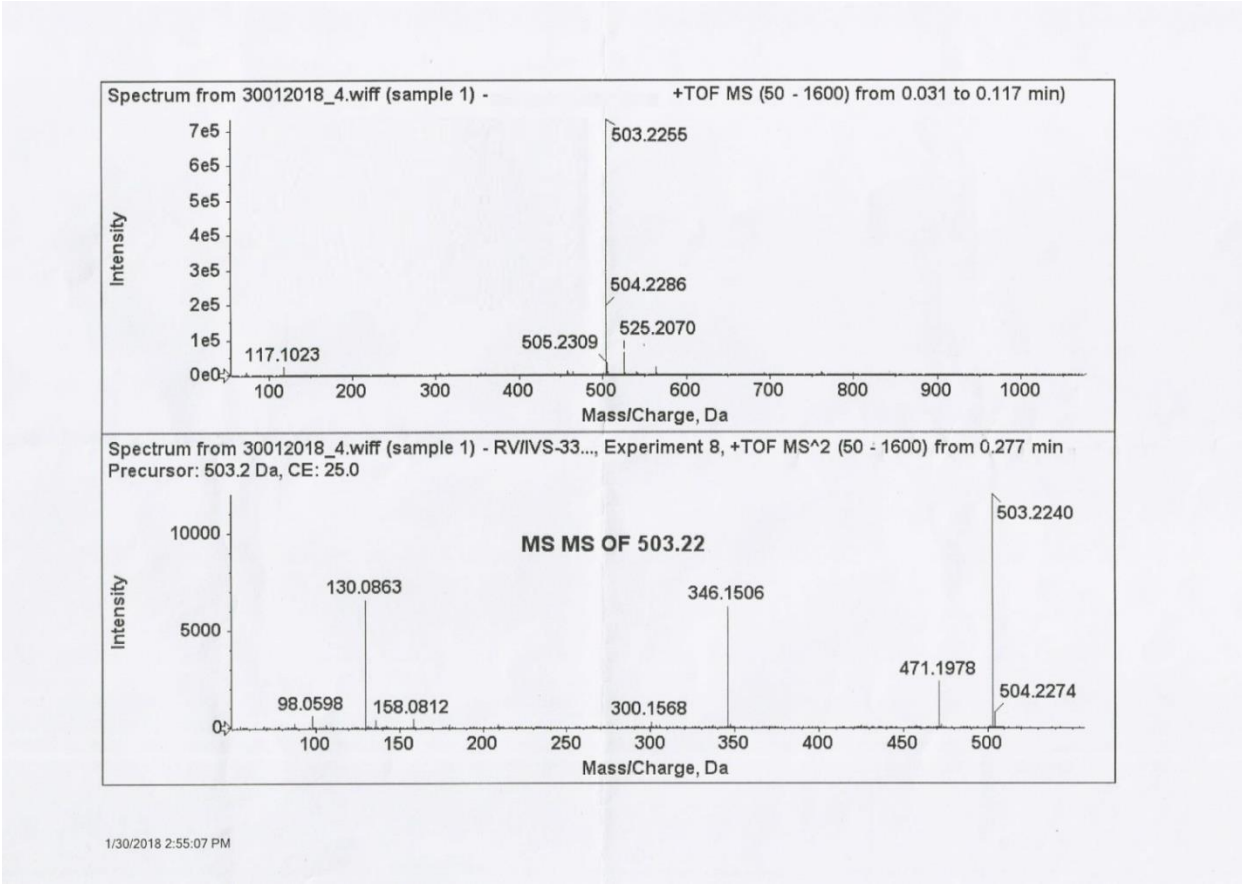
### 3.10.26HRMS of (S)-methyl 1-(4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (J)



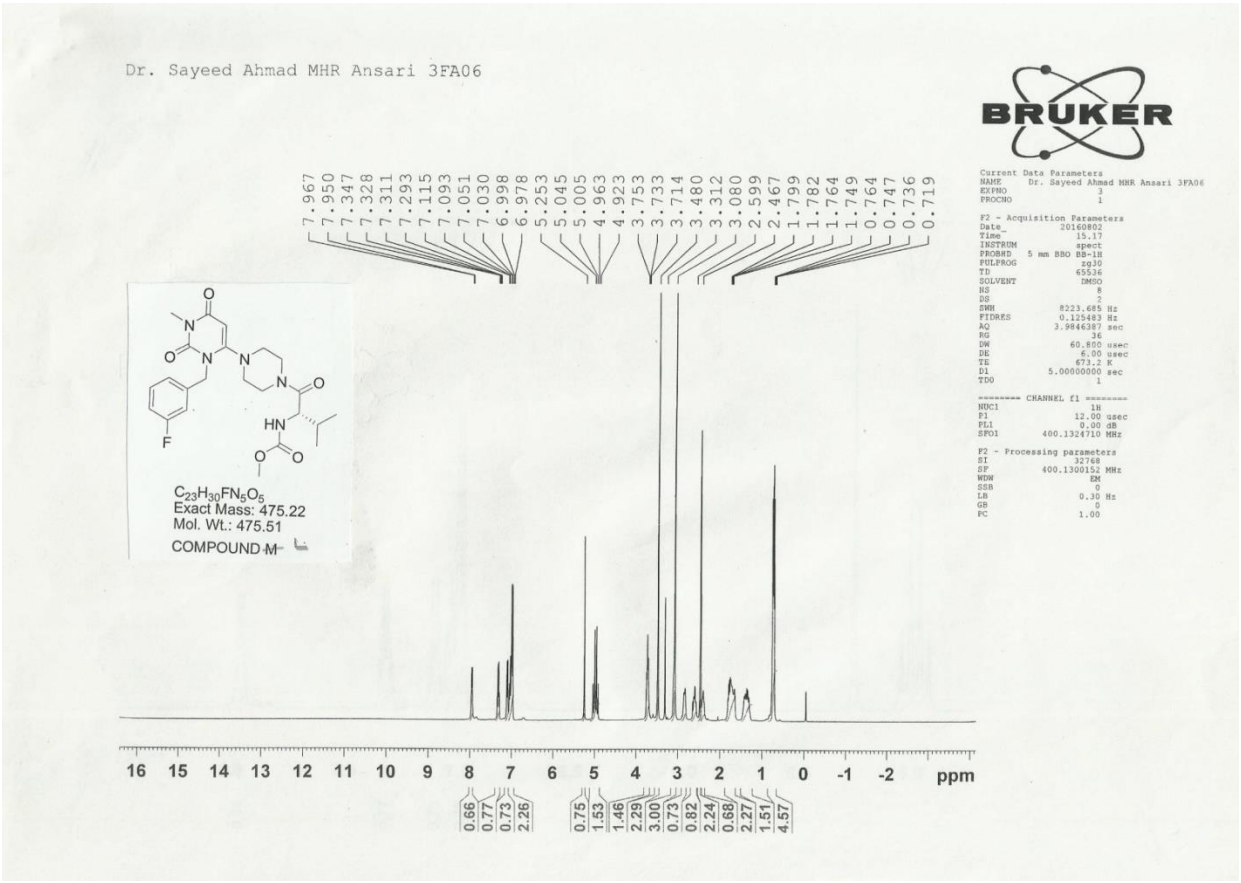
**3.10.27 $^1$H NMR of (S)-methyl 1-(4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (K)**



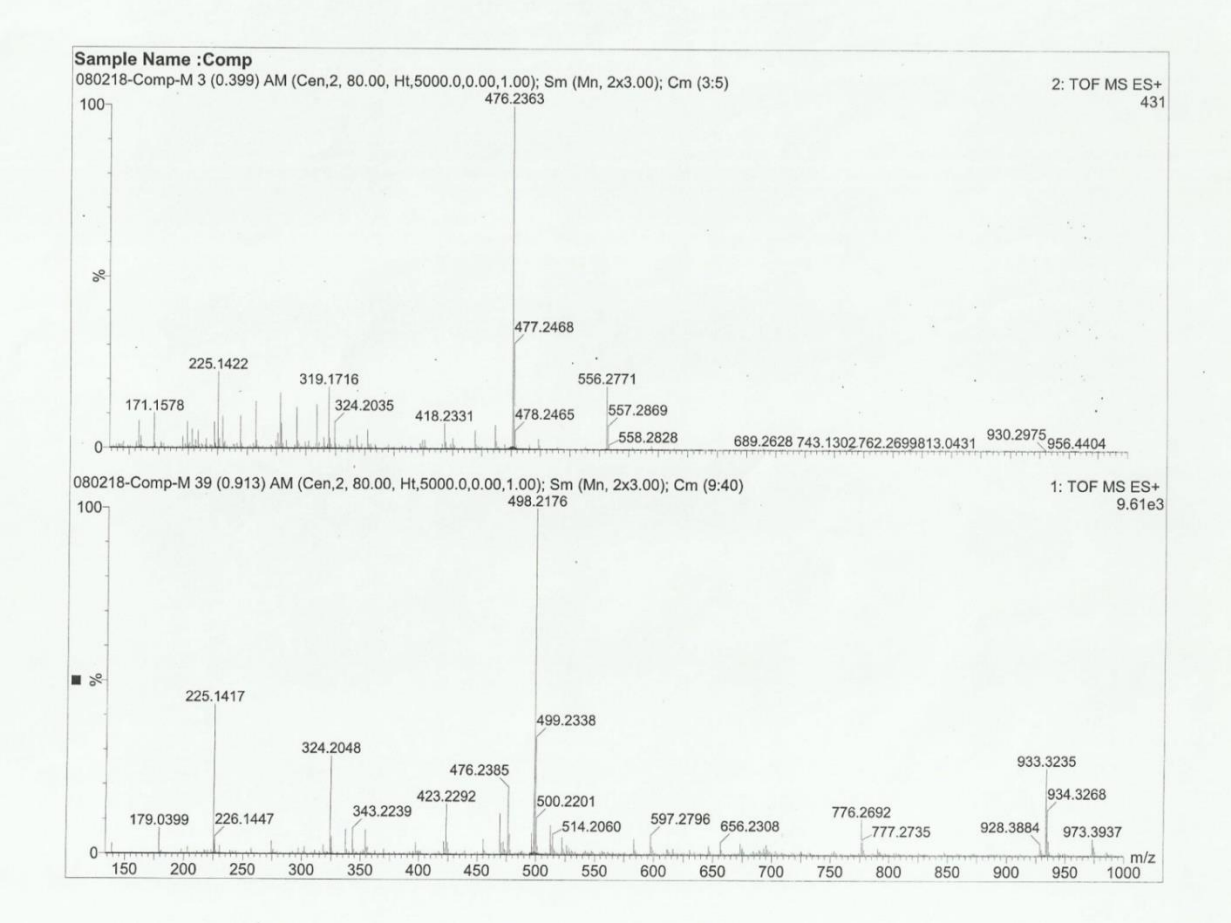
### 3.10.28HRMS of (S)-methyl 1-(4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (K)



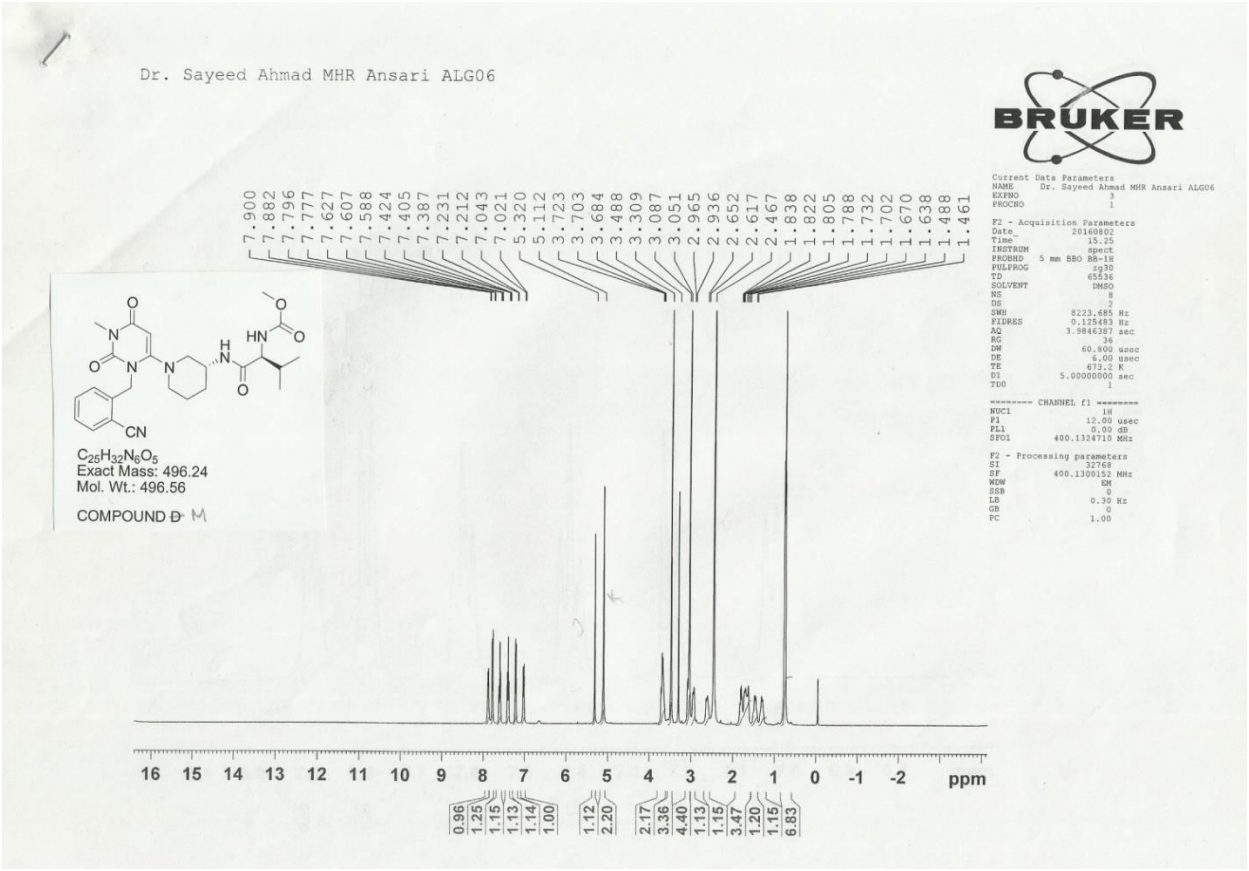
**3.10.29 $^{1}$H NMR of (S)-methyl 1-(4-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (L)**



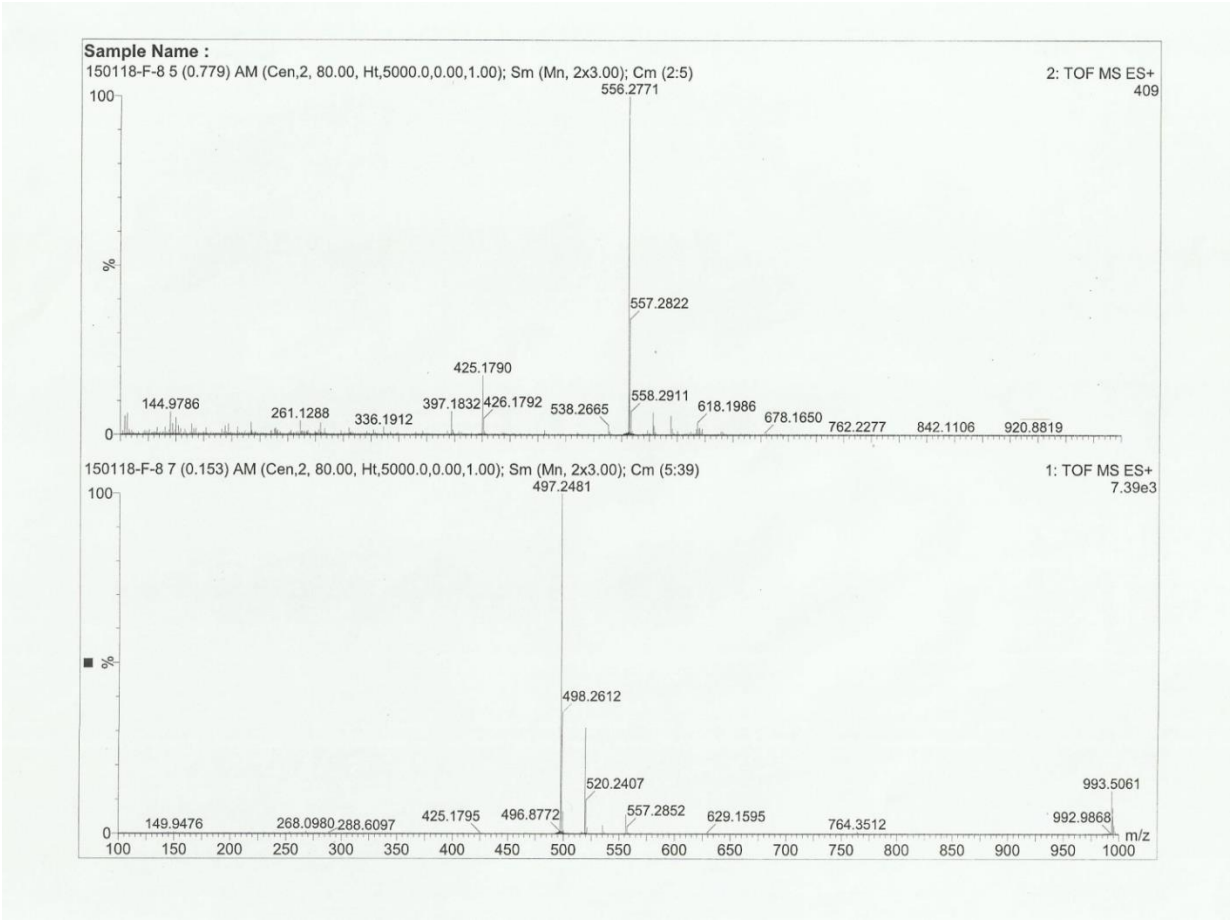
### 3.10.30HRMS of (S)-methyl 1-(4-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (L)



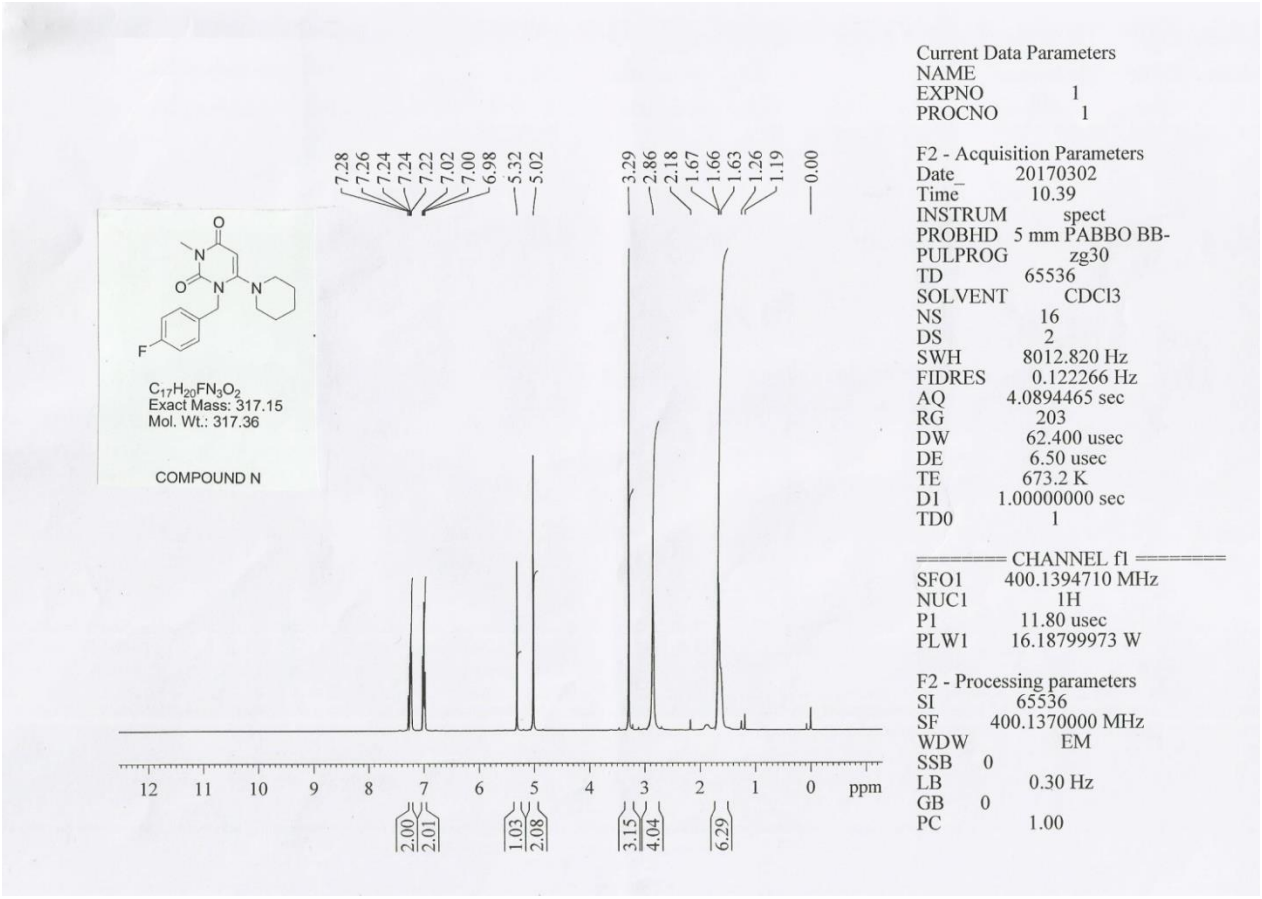
**3.10.31 $^1$H NMR of Methyl(S)-1-((R)-1-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (M)**



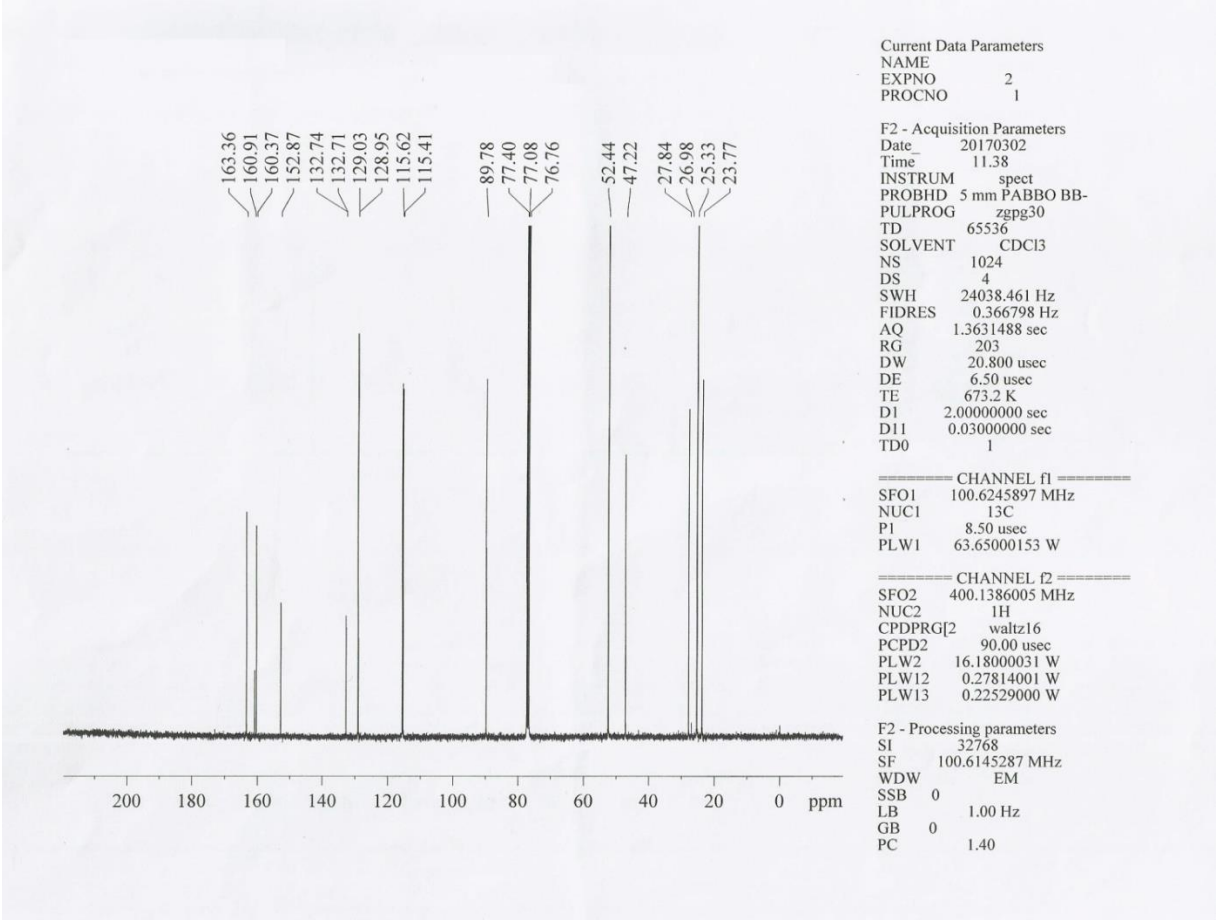
### 3.10.32HRMS of Methyl(S)-1-((R)-1-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (M)



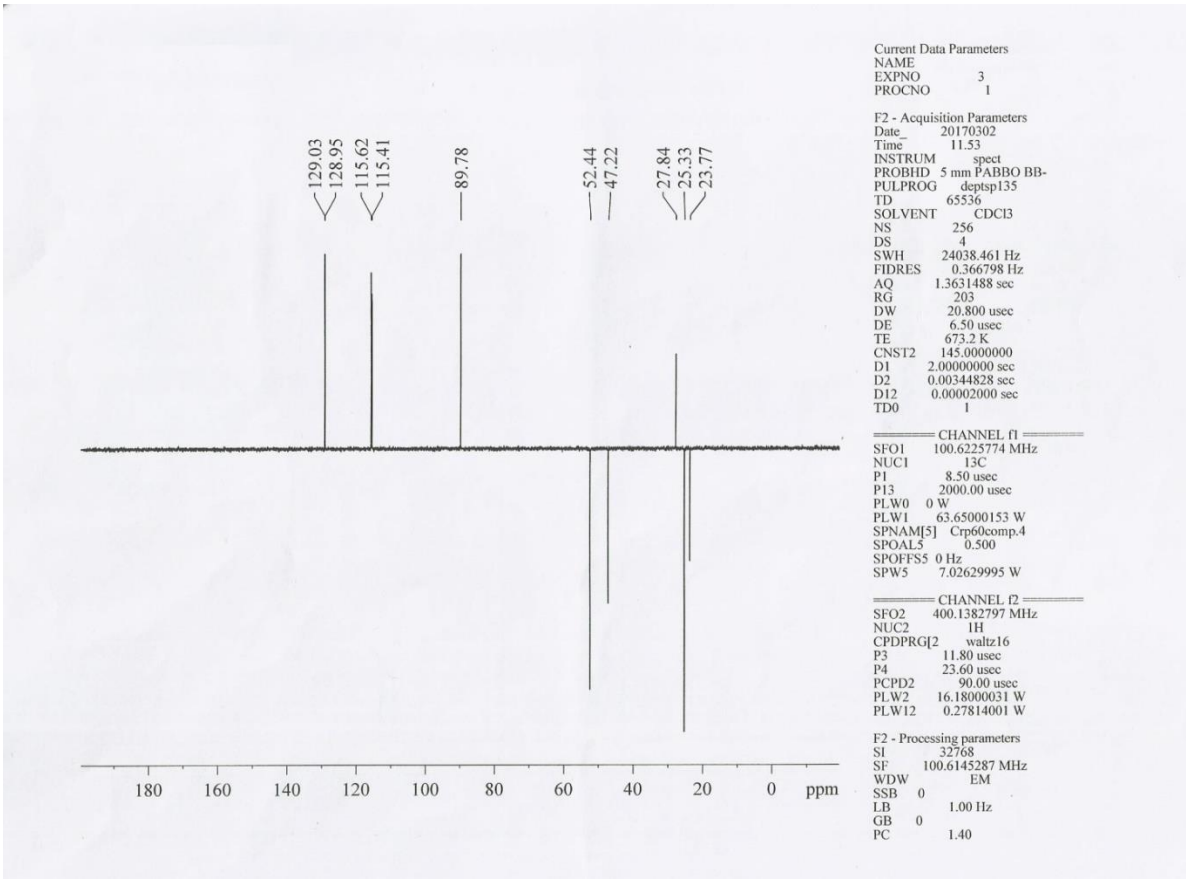
### 3.10.33 $^1$H NMR of 1-(4-fluorobenzyl)-3-methyl-6-(piperidin-1-yl)pyrimidine-2,4(1H,3H)-dione



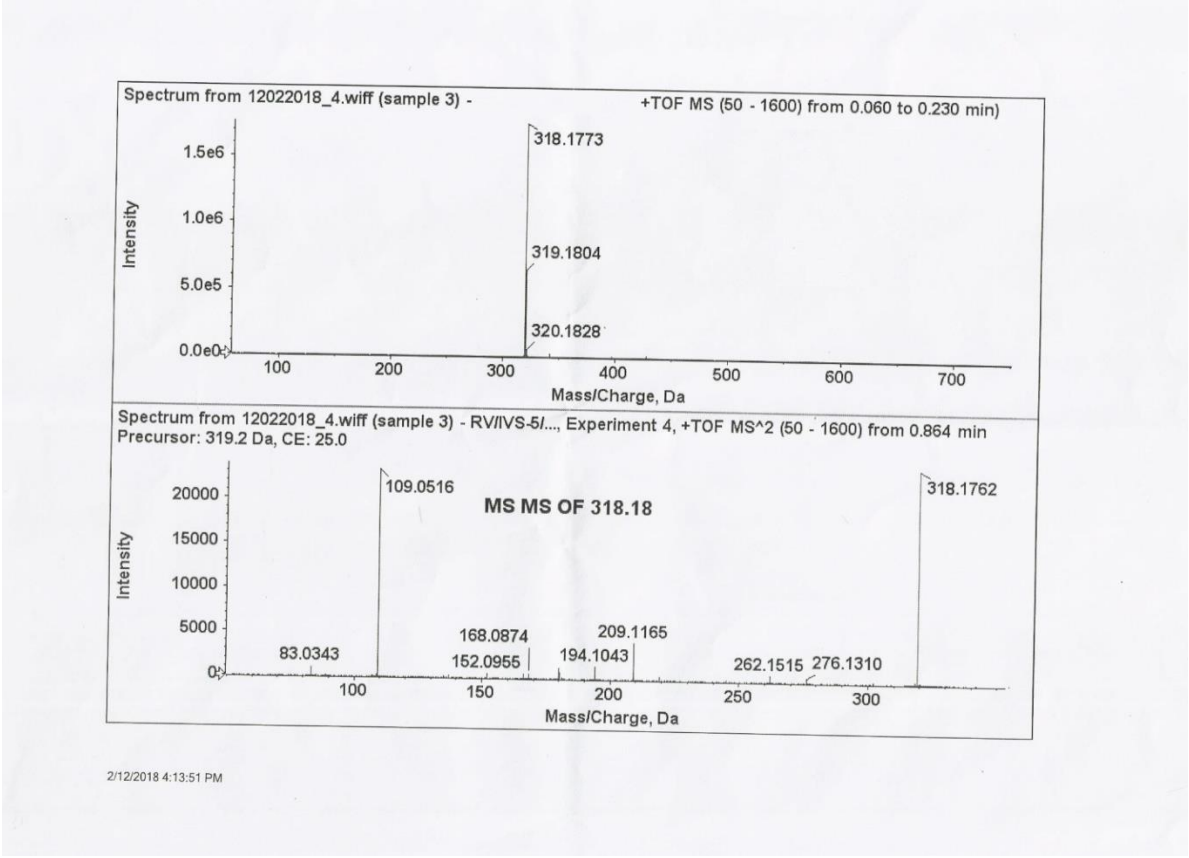
### 3.10.34 $^{13}C$ NMR of 1-(4-fluorobenzyl)-3-methyl-6-(piperidin-1-yl)pyrimidine-2,4(1H,3H)-dione



**3.10.35Dept NMR of (S)-methyl 1-(4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate**



### 3.10.36HRMS of 1-(4-fluorobenzyl)-3-methyl-6-(piperidin-1-yl)pyrimidine-2,4(1H,3H)-dione



## 3.11 BIOLOGICAL POTENTIAL OF COMPOUNDS BY PASS PREDICTION A-L:

Compounds A-L showing tremendous activity in inPASS prediction in various diseases, some of the important activities are listed below tables

### 3.11.1 Methyl (S)-1-((R)-1-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (A)

Compound-A shows some of the important activities like **Antiviral, Antifungal, and Antineoplastic and Anti HIV**

**Table: 3.4 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,458 | 0,020 | CYP2C19 inducer |
| 2 | 0,487 | 0,076 | Proteasome ATPase inhibitor |
| 3 | 0,376 | 0,084 | Muramoyltetrapeptide carboxypeptidase inhibitor |
| 4 | 0,443 | 0,170 | CYP2H substrate inhibitor |
| 5 | 0,293 | 0,046 | Inhibitor Calpain |
| 6 | 0,281 | 0,044 | Antiviral |
| 7 | 0,257 | 0,058 | Antieczematic atopic |
| 8 | 0,229 | 0,062 | Cyclic GMP phosphodiesterase inhibitor |
| 9 | 0,208 | 0,049 | Aldose reductase substrate |
| 10 | 0,335 | 0,176 | Antineoplastic (non-Hodgkin's lymphoma) |
| 11 | 0,160 | 0,004 | Dipeptidyl peptidase inhibitor |
| 12 | 0,264 | 0,113 | H+-transporting two-sector ATPase inhibitor |
| 13 | 0,182 | 0,039 | Antiviral (HIV) |
| 14 | 0,127 | 0,016 | Antifungal enhancer |

### 3.11.2 PASS Prediction of Methyl(S)-1-((R)- 1-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (B):

**Table: 3.5: Pass prediction details of compound B:**

Compound-B shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal** and **Antineoplastic.**

**Table: 3.5 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,538 | 0,054 | Proteasome ATPase inhibitor |
| 2 | 0,473 | 0,017 | CYP2C19 inducer |
| 3 | 0,312 | 0,033 | Antiviral |
| 4 | 0,436 | 0,176 | CYP2H substrate |
| 5 | 0,243 | 0,004 | Leukocyte elastase inhibitor |
| 6 | 0,283 | 0,051 | Calpain inhibitor |
| 7 | 0,254 | 0,035 | Cyclic GMP phosphodiesterase inhibitor |
| 8 | 0,292 | 0,087 | H+-transporting two-sector ATPase inhibitor |
| 9 | 0,233 | 0,034 | Aldose reductase substrate |
| 10 | 0,237 | 0,063 | Respiratory distress syndrome treatment |
| 11 | 0,257 | 0,086 | Antiviral (Influenza A) |
| 12 | 0,183 | 0,018 | Antiviral (Hepatitis) |
| 13 | 0,154 | 0,005 | Antifungal enhancer |
| 14 | 0,159 | 0,014 | Antiviral (Hepatitis C) |
| 15 | 0,172 | 0,052 | Antihistaminic |
| 16 | 0,234 | 0,114 | HIV attachment inhibitor |
| 17 | 0,162 | 0,053 | Antiviral (HIV) |
| 18 | 0,304 | 0,218 | Non-Hodgkin's lymphoma (Antineoplastic) |
| 19 | 0,216 | 0,136 | Antihypertensive |
| 20 | 0,207 | 0,132 | Antineoplastic (bone cancer) |

### 3.11.3 PASS Prediction of Methyl (S)-1-((R)-1-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (C):

**Table: 3.6: Pass prediction details of compound C:**

Compound-C shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal** and **Antineoplastic.**

**Table: 3.6 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,452 | 0,022 | CYP2C19 inducer |
| 2 | 0,476 | 0,081 | Proteasome ATPase inhibitor |
| 3 | 0,266 | 0,051 | Antiviral |
| 4 | 0,328 | 0,185 | Non-Hodgkin's lymphoma (Antineoplastic) |
| 5 | 0,258 | 0,120 | H+-transporting two-sector ATPase inhibitor |
| 6 | 0,173 | 0,045 | Antiviral (HIV) |
| 7 | 0,129 | 0,015 | Antifungal enhancer |
| 8 | 0,126 | 0,024 | Leukocyte elastase inhibitor |
| 9 | 0,189 | 0,088 | Falcipain 3 inhibitor |
| 10 | 0,225 | 0,129 | Immunomodulator |
| 11 | 0,145 | 0,050 | Narcolepsy treatment |
| 12 | 0,222 | 0,159 | Antiviral (Influenza A) |
| 13 | 0,124 | 0,065 | Protease inhibitor |
| 14 | 0,123 | 0,065 | Antiviral (Hepatitis) |
| 15 | 0,106 | 0,052 | Antiviral (Hepatitis C) |
| 16 | 0,176 | 0,124 | Respiratory distress syndrome treatment |
| 17 | 0,032 | 0,005 | HCV NS5A inhibitor |
| 18 | 0,040 | 0,025 | HIV-1 protease inhibitor |

### 3.11.4 PASS Prediction of Methyl (S)-1-((R)-1-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (D):

**Table: 3.7: Pass prediction details of compound D:**

Compound-D shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, Anti hypertension** and **Antineoplastic.**

**Table: 3.7 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,458 | 0,020 | CYP2C19 inducer |
| 2 | 0,487 | 0,076 | Proteasome ATPase inhibitor |
| 3 | 0,377 | 0,048 | Muscular dystrophy treatment |
| 4 | 0,376 | 0,084 | Muramoyltetrapeptide carboxypeptidase inhibitor |
| 5 | 0,359 | 0,149 | Non-Hodgkin's lymphoma (Antineoplastic) |
| 6 | 0,257 | 0,056 | Antiviral |
| 7 | 0,255 | 0,060 | Antieczematic atopic |
| 8 | 0,264 | 0,113 | H+-transporting two-sector ATPase inhibitor |
| 9 | 0,245 | 0,108 | Antiviral (Influenza A) |
| 10 | 0,148 | 0,014 | Leukocyte elastase inhibitor |
| 11 | 0,156 | 0,058 | Antiviral (HIV) |
| 12 | 0,191 | 0,103 | Respiratory distress syndrome treatment |
| 13 | 0,115 | 0,030 | Antifungal enhancer |
| 14 | 0,211 | 0,141 | Antihypertensive |
| 15 | 0,136 | 0,069 | Antiemphysemic |
| 16 | 0,106 | 0,052 | Antiviral (Hepatitis C) |
| 17 | 0,121 | 0,068 | Antiviral (Hepatitis) |
| 18 | 0,039 | 0,029 | HIV-1 protease inhibitor |
| 19 | 0,161 | 0,154 | Antiviral (Hepatitis B) |
| 20 | 0,230 | 0,224 | Fibroblast growth factor agonist |

### 3.11.5 PASS Prediction of Methyl (S)-1-((R)-1-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (E):

**Table: 3.8: Pass prediction details of compound E:**

Compound-E shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Nootropic, Antifungal** and **Antineoplastic.**

**Table: 3.8 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,454 | 0,021 | CYP2C19 inducer |
| 2 | 0,496 | 0,071 | Proteasome ATPase inhibitor |
| 3 | 0,379 | 0,082 | Muramoyltetrapeptide carboxypeptidase inhibitor |
| 4 | 0,287 | 0,049 | Inhibitor Calpain |
| 5 | 0,274 | 0,047 | Antiviral |
| 6 | 0,409 | 0,206 | Nootropic |
| 7 | 0,257 | 0,058 | Antieczematic atopic |
| 8 | 0,348 | 0,162 | Non-Hodgkin's lymphoma (Antineoplastic) |
| 9 | 0,160 | 0,004 | Dipeptidyl peptidase inhibitor |
| 10 | 0,262 | 0,114 | H+-transporting two-sector ATPase inhibitor |
| 11 | 0,176 | 0,043 | Antiviral (HIV) |
| 12 | 0,131 | 0,013 | Antifungal enhancer |
| 13 | 0,151 | 0,034 | Gastrointestinal disorders treatment |
| 14 | 0,130 | 0,021 | Leukocyte elastase inhibitor |
| 15 | 0,227 | 0,145 | Antiviral (Influenza A) |
| 16 | 0,138 | 0,063 | Narcolepsy treatment |
| 17 | 0,183 | 0,114 | Respiratory distress syndrome treatment |
| 18 | 0,125 | 0,062 | Antiviral (Hepatitis) |
| 19 | 0,108 | 0,049 | Antiviral (Hepatitis C) |
| 20 | 0,128 | 0,095 | Antihistaminic |
| 21 | 0,034 | 0,004 | HCV NS5A inhibitor |
| 22 | 0,041 | 0,024 | HIV-1 protease inhibitor |
| 23 | 0,133 | 0,117 | Angiotensin II receptor agonist |

### 3.11.6 PASS Prediction of Methyl (S)-1-((R)-1-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (F):

**Table: 3.9: Pass prediction details of compound F:**

Compound-F shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, Antihistaminic** and **Antineoplastic** (Bone Cancer)**.**

**Table: 3.9 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,547 | 0,050 | Proteasome ATPase inhibitor |
| 2 | 0,304 | 0,035 | Antiviral |
| 3 | 0,217 | 0,005 | Leukocyte elastase inhibitor |
| 4 | 0,292 | 0,088 | H+-transporting two-sector ATPase inhibitor |
| 5 | 0,259 | 0,084 | Antiviral (Influenza A) |
| 6 | 0,251 | 0,089 | HIV attachment inhibitor |
| 7 | 0,158 | 0,004 | Antifungal enhancer |
| 8 | 0,194 | 0,041 | Antihistaminic |
| 9 | 0,174 | 0,021 | Antiviral (Hepatitis) |
| 10 | 0,225 | 0,072 | Respiratory distress syndrome treatment |
| 11 | 0,167 | 0,022 | Histamine H1 receptor antagonist |
| 12 | 0,174 | 0,035 | Histamine antagonist |
| 13 | 0,151 | 0,017 | Antiviral (Hepatitis C) |
| 14 | 0,154 | 0,033 | Gastrointestinal disorders treatment |
| 15 | 0,318 | 0,198 | Non-Hodgkin's lymphoma (Antineoplastic) |
| 16 | 0,215 | 0,105 | Antieczematic atopic |
| 17 | 0,215 | 0,107 | Antineoplastic (bone cancer) |
| 18 | 0,150 | 0,051 | Antiemphysemic |
| 19 | 0,155 | 0,059 | Antiviral (HIV) |
| 20 | 0,118 | 0,025 | Gastroesophageal reflux disease treatment |
| 21 | 0,064 | 0,003 | HCV NS5A inhibitor |
| 22 | 0,175 | 0,123 | Antiviral (Hepatitis B) |
| 23 | 0,199 | 0,153 | Antihypertensive |
| 24 | 0,037 | 0,033 | HIV-1 protease inhibitor |

### 3.11.7 PASS Prediction of (S)-methyl 1-(4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (G):

Compound-G shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, Antineoplastic** and **Gastrointestinal disorders treatment.**

**Table: 3.10 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,536 | 0,054 | Proteasome ATPase inhibitor |
| 2 | 0,490 | 0,014 | CYP2C19 inducer |
| 3 | 0,448 | 0,055 | Muramoyltetrapeptide carboxypeptidase inhibitor |
| 4 | 0,381 | 0,126 | Non-Hodgkin's lymphoma (Antineoplastic) |
| 5 | 0,291 | 0,040 | Antiviral |
| 6 | 0,293 | 0,086 | H+-transporting two-sector ATPase inhibitor |
| 7 | 0,236 | 0,080 | Antieczematic atopic |
| 8 | 0,248 | 0,101 | Antiviral (Influenza A) |
| 9 | 0,184 | 0,038 | Antiviral (HIV) |
| 10 | 0,156 | 0,012 | Leukocyte elastase inhibitor |
| 11 | 0,148 | 0,036 | Gastrointestinal disorders treatment |
| 12 | 0,125 | 0,018 | Antifungal enhancer |
| 13 | 0,130 | 0,055 | Antiviral (Hepatitis) |
| 14 | 0,113 | 0,043 | Antiviral (Hepatitis C) |
| 15 | 0,141 | 0,077 | Antihistaminic |
| 16 | 0,205 | 0,147 | Antihypertensive |
| 17 | 0,034 | 0,004 | HCV NS5A inhibitor |
| 18 | 0,072 | 0,044 | Caspase 9 inhibitor |
| 19 | 0,044 | 0,018 | HIV-1 protease inhibitor |
| 20 | 0,161 | 0,156 | Antiviral (Hepatitis B) |

### 3.11.8 PASS Prediction of (S)-methyl 1-(4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (H):

Compound-H shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, Antihypertensive,Antineoplastic,** Gastrointestinal disorders treatment**.**

**Table: 3.11 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,591 | 0,037 | Proteasome ATPase inhibitor |
| 2 | 0,508 | 0,011 | CYP2C19 inducer |
| 3 | 0,524 | 0,039 | Vasodilator, peripheral |
| 4 | 0,502 | 0,122 | CYP2H substrate |
| 5 | 0,324 | 0,029 | Antiviral |
| 6 | 0,264 | 0,004 | Leukocyte elastase inhibitor |
| 7 | 0,283 | 0,055 | Antiviral (Influenza A) |
| 8 | 0,357 | 0,151 | Antineoplastic (non-Hodgkin's lymphoma) |
| 9 | 0,217 | 0,032 | Antihistaminic |
| 10 | 0,184 | 0,017 | Antiviral (Hepatitis) |
| 11 | 0,231 | 0,068 | Respiratory distress syndrome treatment |
| 12 | 0,154 | 0,005 | Antifungal enhancer |
| 13 | 0,161 | 0,014 | Antiviral (Hepatitis C) |
| 14 | 0,164 | 0,039 | Antiemphysemic |
| 15 | 0,217 | 0,101 | Antineoplastic (bone cancer) |
| 16 | 0,234 | 0,120 | Antihypertensive |
| 17 | 0,230 | 0,120 | HIV attachment inhibitor |
| 18 | 0,162 | 0,053 | Antiviral (HIV) |
| 19 | 0,119 | 0,024 | Gastroesophageal reflux disease treatment |
| 20 | 0,242 | 0,176 | HCV IRES inhibitor |
| 21 | 0,068 | 0,003 | HCV NS5A inhibitor |
| 22 | 0,179 | 0,117 | Antiviral (Hepatitis B) |
| 23 | 0,184 | 0,155 | Antieczematic atopic |
| 24 | 0,041 | 0,024 | HIV-1 protease inhibitor |

### 3.11.9 PASS Prediction of (S)-methyl 1-(4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (I):

Compound-I shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, Antihypertensive,Antineoplastic, Gastroesophageal reflux disease treatment.**

**Table: 3.12 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,547 | 0,050 | Proteasome ATPase inhibitor |
| 2 | 0,470 | 0,017 | CYP2C19 inducer |
| 3 | 0,308 | 0,034 | Antiviral |
| 4 | 0,223 | 0,005 | Leukocyte elastase inhibitor |
| 5 | 0,292 | 0,088 | H+-transporting two-sector ATPase inhibitor |
| 6 | 0,239 | 0,049 | Antineoplastic (bone cancer) |
| 7 | 0,263 | 0,075 | HIV attachment inhibitor |
| 8 | 0,259 | 0,084 | Antiviral (Influenza A) |
| 9 | 0,181 | 0,018 | Antiviral (Hepatitis) |
| 10 | 0,200 | 0,038 | Antihistaminic |
| 11 | 0,159 | 0,014 | Antiviral (Hepatitis C) |
| 12 | 0,145 | 0,007 | Antifungal enhancer |
| 13 | 0,148 | 0,053 | Antiemphysemic |
| 14 | 0,152 | 0,062 | Antiviral (HIV) |
| 15 | 0,114 | 0,026 | Gastroesophageal reflux disease treatment |
| 16 | 0,133 | 0,048 | Bacterial efflux pump inhibitor |
| 17 | 0,202 | 0,147 | Viral entry inhibitor |
| 18 | 0,056 | 0,003 | HCV NS5A inhibitor |
| 19 | 0,184 | 0,153 | Antidiabetic symptomatic |
| 20 | 0,034 | 0,032 | Luteinizing hormone-releasing hormone antagonist |
| 21 | 0,037 | 0,035 | HIV-1 protease inhibitor |
| 22 | 0,026 | 0,026 | Protease 3C (Human rhinovirus) inhibitor |

### 3.11.10PASS Prediction of (S)-methyl 1-(4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (J):

Compound-J shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, and Antihypertensive,Antineoplastic, Fibroblast growth factor agonist** and **Gastroesophageal reflux disease treatment.**

**Table: 3.13 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,454 | 0,021 | CYP2C19 inducer |
| 2 | 0,496 | 0,071 | Proteasome ATPase inhibitor |
| 3 | 0,278 | 0,045 | Antiviral |
| 4 | 0,234 | 0,082 | Antieczematic atopic |
| 5 | 0,262 | 0,114 | H+-transporting two-sector ATPase inhibitor |
| 6 | 0,173 | 0,045 | Antiviral (HIV) |
| 7 | 0,133 | 0,019 | Leukocyte elastase inhibitor |
| 8 | 0,214 | 0,109 | Anti-neoplastic (bone cancer) |
| 9 | 0,116 | 0,029 | Antifungal enhancer |
| 10 | 0,227 | 0,145 | Antiviral (Influenza A) |
| 11 | 0,303 | 0,220 | Non-Hodgkin's lymphoma (Antineoplastic) |
| 12 | 0,131 | 0,054 | Antiviral (Hepatitis) |
| 13 | 0,114 | 0,041 | Antiviral (Hepatitis C) |
| 14 | 0,104 | 0,033 | Gastroesophageal reflux disease treatment |
| 15 | 0,052 | 0,009 | Dipeptidyl peptidase IV inhibitor |
| 16 | 0,198 | 0,156 | Angiogenesis stimulant |
| 17 | 0,131 | 0,090 | Antihistaminic |
| 18 | 0,029 | 0,005 | HCV NS5A inhibitor |
| 19 | 0,040 | 0,026 | HIV-1 protease inhibitor |
| 20 | 0,231 | 0,222 | Fibroblast growth factor agonist |

### 3.11.11PASS Prediction of (S)-methyl 1-(4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (K):

Compound-K shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, and Antihypertensive,Antineoplastic, Fibroblast growth factor agonist** and **Gastroesophageal reflux disease treatment.**

**Table: 3.14 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,447 | 0,023 | CYP2C19 inducer |
| 2 | 0,459 | 0,047 | Polarisation stimulant |
| 3 | 0,476 | 0,081 | Proteasome ATPase inhibitor |
| 4 | 0,333 | 0,074 | Muscular dystrophy treatment |
| 5 | 0,254 | 0,058 | Antiviral |
| 6 | 0,335 | 0,143 | Antianginal |
| 7 | 0,266 | 0,096 | Antihypertensive |
| 8 | 0,256 | 0,088 | Antiviral (Influenza A) |
| 9 | 0,257 | 0,121 | H+-transporting two-sector ATPase inhibitor |
| 10 | 0,324 | 0,190 | Non-Hodgkin's lymphoma (Antineoplastic) |
| 11 | 0,221 | 0,097 | Antieczematic atopic |
| 12 | 0,160 | 0,054 | Antiviral (HIV) |
| 13 | 0,116 | 0,029 | Antifungal enhancer |
| 14 | 0,174 | 0,128 | Respiratory distress syndrome treatment |
| 15 | 0,091 | 0,046 | Gastroesophageal reflux disease treatment |
| 16 | 0,051 | 0,010 | Dipeptidyl peptidase IV inhibitor |
| 17 | 0,098 | 0,066 | Antiviral (Hepatitis C) |
| 18 | 0,111 | 0,083 | Antiviral (Hepatitis) |
| 19 | 0,028 | 0,005 | HCV NS5A inhibitor |
| 20 | 0,039 | 0,029 | HIV-1 protease inhibitor |
| 21 | 0,116 | 0,112 | Antiemphysemic |
| 22 | 0,178 | 0,175 | Fibroblast growth factor 1 agonist |
| 23 | 0,090 | 0,087 | Leukocyte elastase inhibitor |

### 3.11.12PASS Prediction of (S)-methyl 1-(4-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazin-1-yl)-3-methyl-1-oxobutan-2-ylcarbamate (L):

Compound-L shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, and Antihypertensive,Antineoplastic, Fibroblast growth factor agonist** and **Respiratory distress syndrome treatment.**

**Table: 3.15 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,547 | 0,050 | Proteasome ATPase inhibitor |
| 2 | 0,470 | 0,017 | CYP2C19 inducer |
| 3 | 0,336 | 0,061 | Cell adhesion molecule inhibitor |
| 4 | 0,308 | 0,034 | Antiviral |
| 5 | 0,223 | 0,005 | Leukocyte elastase inhibitor |
| 6 | 0,239 | 0,049 | Antineoplastic (bone cancer) |
| 7 | 0,263 | 0,075 | HIV attachment inhibitor |
| 8 | 0,259 | 0,084 | Antiviral (Influenza A) |
| 9 | 0,181 | 0,018 | Antiviral (Hepatitis) |
| 10 | 0,200 | 0,038 | Antihistaminic |
| 11 | 0,187 | 0,031 | Histamine antagonist |
| 12 | 0,159 | 0,014 | Antiviral (Hepatitis C) |
| 13 | 0,145 | 0,007 | Antifungal enhancer |
| 14 | 0,204 | 0,089 | Respiratory distress syndrome treatment |
| 15 | 0,148 | 0,053 | Antiemphysemic |
| 16 | 0,152 | 0,062 | Antiviral (HIV) |
| 17 | 0,222 | 0,157 | Cystic fibrosis treatment |
| 18 | 0,202 | 0,147 | Viral entry inhibitor |
| 19 | 0,056 | 0,003 | HCV NS5A inhibitor |
| 20 | 0,057 | 0,008 | Dipeptidyl peptidase IV inhibitor |
| 21 | 0,185 | 0,153 | Antieczematic atopic |
| 22 | 0,184 | 0,153 | Antidiabetic symptomatic |
| 23 | 0,037 | 0,035 | HIV-1 protease inhibitor |

### 3.11.13PASS Prediction of Methyl(S)-1-((R)-1-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (M):

Compound-M shows some of the important activities like **Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, and Antihypertensive,Antineoplastic** (bone cancer),**Fibroblast growth factor agonist** and **Respiratory distress syndrome treatment.**

**Table: 3.16 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,526 | 0,058 | Proteasome ATPase inhibitor |
| 2 | 0,467 | 0,018 | CYP2C19 inducer |
| 3 | 0,295 | 0,038 | Antiviral |
| 4 | 0,207 | 0,006 | Leukocyte elastase inhibitor |
| 5 | 0,263 | 0,075 | HIV attachment inhibitor |
| 6 | 0,169 | 0,005 | Bacterial efflux pump inhibitor |
| 7 | 0,252 | 0,094 | Antiviral (Influenza A) |
| 8 | 0,155 | 0,005 | Antifungal enhancer |
| 9 | 0,169 | 0,023 | Antiviral (Hepatitis) |
| 10 | 0,214 | 0,081 | Respiratory distress syndrome treatment |
| 11 | 0,147 | 0,018 | Antiviral (Hepatitis C) |
| 12 | 0,173 | 0,051 | Antihistaminic |
| 13 | 0,216 | 0,104 | Antineoplastic (bone cancer) |
| 14 | 0,152 | 0,062 | Antiviral (HIV) |
| 15 | 0,146 | 0,056 | Antiemphysemic |
| 16 | 0,346 | 0,276 | Nootropic |
| 17 | 0,296 | 0,230 | Antineoplastic (non-Hodgkin's lymphoma) |
| 18 | 0,060 | 0,003 | HCV NS5A inhibitor |
| 19 | 0,196 | 0,157 | Antihypertensive |
| 20 | 0,168 | 0,137 | Antiviral (Hepatitis B) |
| 21 | 0,091 | 0,069 | Female sexual dysfunction treatment |
| 22 | 0,037 | 0,035 | HIV-1 protease inhibitor |

### 3.11.14PASS Prediction of 1-(4-fluorobenzyl)-3-methyl-6-(piperidin-1-yl)pyrimidine-2,4(1H,3H)-dione (N):

Compound-M shows some of the important activities like**Muscle relaxant, Dementia treatment, Antiallergic, Antiviral** (influenza A, Hepatitis-C, HIV), **Antifungal, and Antihypertensive,Obsessive-compulsive disorder treatment, Antineoplastic** (bone cancer),**Cystic fibrosis treatment** and **Antipsychotic.**

**Table: 3.17 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,580 | 0,040 | Proteasome ATPase inhibitor |
| 2 | 0,557 | 0,019 | Polarisation stimulant |
| 3 | 0,583 | 0,048 | Kidney function stimulant |
| 4 | 0,400 | 0,006 | Histamine antagonist |
| 5 | 0,354 | 0,041 | Muscle relaxant |
| 6 | 0,375 | 0,075 | Anticonvulsant |
| 7 | 0,369 | 0,079 | Diabetic neuropathy treatment |
| 8 | 0,457 | 0,167 | Nootropic |
| 9 | 0,308 | 0,079 | Antiamyloidogenic |
| 10 | 0,395 | 0,169 | Platelet adhesion inhibitor |
| 11 | 0,235 | 0,010 | Gastrointestinal disorders treatment |
| 12 | 0,328 | 0,109 | Dementia treatment |
| 13 | 0,281 | 0,063 | Antiischemic |
| 14 | 0,169 | 0,020 | Obsessive-compulsive disorder treatment |
| 15 | 0,239 | 0,109 | Antiparkinsonian |
| 16 | 0,222 | 0,152 | Analgesic stimulant |
| 17 | 0,180 | 0,115 | Antiviral (Hepatitis B) |
| 18 | 0,178 | 0,134 | Antidiarrheal |
| 19 | 0,214 | 0,171 | Antiallergic |
| 20 | 0,214 | 0,179 | Cystic fibrosis treatment |
| 21 | 0,150 | 0,122 | Antinaupathic |
| 22 | 0,148 | 0,123 | Antipsychotic |

# 4. PREPARATION OF URACIL BASED CHLOROFORMATE DERIVATIVES

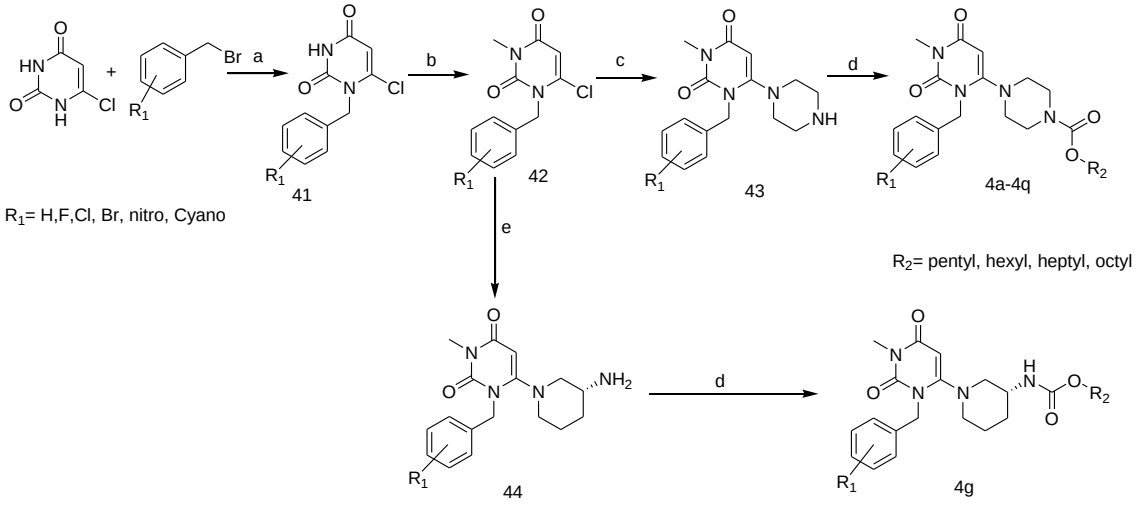
There are another set of seventeen compound synthesized by the Uracil [136][137] and chloroformate series, very simple, high efficient and facile synthesis have been reported. All the synthesized compounds were characterized by proton Nuclear Magnetic resonance and High resonance Mass Spectroscopy.

The synthesis of the target uracil derivatives was performed according to **Scheme 4.1**. A simple and successful protocol has been developed for synthesis of uracil derivatives. It should be noted that in the available literature, generally sodium hydride in dimethyl formamide have been used during the alkylation (methylation) reactions which is highly dangerous in the context of safety, environment pollutant and it also results poor yield, impure compounds. In our simple protocol, we used low cost, eco-friendly and safe, inorganic base potassium carbonate in dimethyl formamide solvent in one pot during four steps which is one of the major advantages of our protocol. In addition, we got higher percentage yields of products. Initially, we have synthesized N-substituted uracil analogues in high yields by simple N-alkylation reactions of 4-chlorouracil with different halogenated benzyl halides and methyl iodide respectively, under catalyst free conditions in DMF solvent. Then the chlorine atoms of N-substituted uracil derivatives were substituted with piperazine and 4-aminopiperidine, respectively. In the last step, Mixture of water and acetone has been used as a solvent, and potassium carbonate used as a base, substituted chloroformates were added in to it after reaction completion judged by TLC water added in to it, product partitioned with ethylacetate and it was purified by coloumn chromatography, to produce title compounds **4a-4q**, with good yield of (40-60%). A reasonable mechanism for the formation of uracil derivatives is shown in **Scheme 3.2**.

The reaction conditions were optimized using various solvents, bases. The yields ranged from 40 to 60%. A perusal of these indicates that the DMF and inorganic base was the best one; resulting in higher yield and best conversion. During the optimization of organic and inorganic bases were used. It was observed that during organic bases, the

reaction was completed at faster rate, but less conversion was observed. The percentage of yield was increased while using inorganic bases under DMF solvent. Hence, throughout the reactions potassium carbonate as base and DMF as solvent were used.

**Scheme- 4.1: Preparation of Uralic based chloroformate derivatives**




## 4.1 EXPERIMENTAL PROCEDURE:

### 4.1.1 One pot synthesis of target compounds (4a-4q):

A suspension of 6-chloro uracil (7.75 g, 0.0528 moles) and potassium carbonate (9.14 g, 0.0661 moles M) were mixed in 50 mL DMF in 250 mL RBF, followed addition of by halogenated benzyl derivatives of 1-(bromomethyl) benzene (10.00 g, 0.0584 moles), the reaction mass 8.0 hrs stirred at 20-30°C, then potassium carbonate (7.31 g, 0.0529 moles) was charged to the reaction mass followed by methyl iodide (15.02 g, 0.10 moles) the reaction mixture was stirred at 20-30°C till reaction completion (16-24 hrs). After that, charged piperazine (4.52 g, 0.0524 moles) or piperidin-3-amine (9.10 g, 0.0524 moles) added during agitation then obtained mass brought temperature to 80 ˚C for 8hrs then the reaction progress monitored by TLC, Ethylacetate and water was used to partition of product, moisture presence in organic layer were removed by sodium sulphate then distilled off solvent completely then 160 mL acetone and 70 mL water was added, followed by potassium carbonate ( 0.1056 moles) and chloroformates ( 0.0633 moles)

added to the above obtained mixture and it was agitated for 2-4 hrs at 23-33°C. Water was added in to it after the completion of reaction and the product was extracted in ethylacetate, organic layer dried over sodium sulphate and solvent was removed by vacuum distillation at elevated temperature. The desired products (4a-4q) were purified by column chromatography to get title compounds.

## 4.2 GENERAL PROCEDURE

### 4.2.1 Synthesis of N-alkylated compounds of 6-chlorouracil (41):

6-chlorouracil (10 g, 0.0682 moles) and diisopropylethylamine (18.52 gm, 0.1432 moles) were soluble in 50 mL DMF and then agitated for 10-20 min at 20-30°C, followed by addition of halogenated 1-(bromomethyl)benzene (12.90 g, 0.0754 moles) then obtained reaction mass were agitated for 8 hrs at 20-30°C, the reaction completion judged using TLC, 150 mL water was added in to it then the precipitated product (**41**) was isolated by filtration, dried to obtained 14.37 gm (89.0 %)

### 4.2.2 Synthesis of compounds (42):

In 100 mL acetone compound **41 (**10.00 g, 0.0422 moles**)** was dissolved then potassium carbonate (12.84 g, 0.0929 moles) and the reaction agitated for 15-25 min. at 20-30°C, followed by methyl iodide (11.99 g, 0.0844 M) added in to it the obtained reaction mass were agitated overnight at 23-33°C, the reaction completion was judged by TLC, during addition of water product were precipitated out and precipitated product were removed by filtration to gives product (**42**) was then dried to get 9.74 g (92.0 %).

### 4.2.3 Synthesis of Compounds 43 or 44:

Compound **2** (9.00 g, 0.0359 moles) were dissolved in 45 mL DMF followed by addition of potassium carbonate (9.92 g, 0.0717 moles) and (3.40 g, 0.0394 moles) of piperazine or piperidin-3-amine (6.83 g, 0.0394 moles), and reaction temperature was maintained at 80°C, until the starting material disappear by TLC, after reaction completion product was extracted by solvent ethyl acetate by addition of water in to it, organic layer was subsequently washed with $H_2O$, distilled out solvent under vacuum at 39-49°C to afford compounds **43** (9.16 g, 85.0%) or **44** ( 9.81 g, 87.0%) .

## 4.3 SYNTHESIS PROCEDURE AND CHARECTERISATION OF TARGET COMPOUNDS (4a-4q):

Compound **43** (9.00 g, 0.0299 moles) or **44** (9.00 g, 0.0286 moles ) was suspended in the mixture of acetone and water mixture (90 mL: 40 mL) followed by addition of potassium carbonate (0.0598 moles) after stirred 10 min. added slowly chloroformates (0.0299 moles) at 20-30°C, the reaction mass agitated at 23-33°C, till starting material disappear and added water added in to it, product was partitioned with water and ethylacetate organic layer successively treated with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compounds (4a-4q) .

### 4.3.1 heptyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4a):

Compound **43** (9.00 g, 0.0285 moles) was suspended in the mixture of acetone 90 mL and $H_2O$ 40 mL followed by addition of potassium carbonate (7.88 g, 0.0570 moles) after stirred 10 min. added slowly chloroformates (4.70 gm, 0.0285 moles) at at 20-30°C, the reaction mass agitated at 23-33°C, till starting disappear from the reaction mass then added water and ethyl acetate to partitioned formed product , successively organic layer treated with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compounds 1. Yield: 12.37 gm, (94.17%).

$^1$H-NMR: δ= 0.87-0.90 (m, 4 H,-$CH_3$), 1.26-1.32 (m, 12 H, -$CH_2$), 1.55-1.65 (3, 3 H, -$CH_2$), 2.85 (broad, 4H, -$CH_2$), 3.31 (s, 3 H, -N-$CH_3$), 3.55 (broad, 2 H, -$CH_2$), 3.61-3.65 (t, 1H, ) 4.05-4.11 (t, 2 H, -O-CH2), 5.07 ( s, 2 H, Ar-$CH_2$-), 5.35 (s, 1 H, -CH), 6.99-7.04 (t, 2 H, ArH) 7.20-7.23 (m, 2 H, ArH) ppm. Mass: ($C_{24}H_{33}FN4O4$) *m/z= 460.25, M+H=461.2840.*

### 4.3.2 octyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4b):

Compound **43** (9.00 g, 0.0285 moles) or **44** (9.00 g, 0.0286 moles ) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.88 gm,

0.0570 moles) after stirred 10 min. added slowly chloroformates (5.49 gm, 0.0285 moles) at room temperature, at 20-30°C, the reaction mass agitated at 23-33°C till starting materials disappear from reaction mass, added water in to it, ethyl acetate were used to extract the product, organic layer successively treated with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title 2. Yield: 12.39 gm, (91.80%).

$^1$H-NMR: δ= 0.88-0.91 ( t, 4 H, -$CH_3$), 1.29-1.32 (m, 14 H, -$CH_2$), 1.56-1.64 (m, 2 H, -$CH_2$), 2.84 (broad, 4H, -$CH_2$), 3.30 (s, 3 H, -N-$CH_3$), 3.57-3.66 (broad, 3 H, -$CH_2$), 4.05-4.12 (t, 2 H, -O-CH2), 5.08 ( s, 2 H, Ar-$CH_2$-), 5.36 (s, 1 H, -CH), 7.01-7.05 (t, 2 H, ArH) 7.21-7.24 (t, 2 H, ArH) ppm. Mass: ($C_{25}H_{35}FN_5O_4$) *m/z= 473.23, M+H=474.2.*

### 4.3.3 hexyl 4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4c):

Compound **43** (9.00 g, 0.0260 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.20 gm, 0.0520 moles) after stirred 10 min. added slowly chloroformates (4.29 gm, 0.0260 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it, ethyl acetate were used to extract product, treated ethylacetate layer with water $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compounds 3. Yield: 11.59 gm, (94.0%).

$^1$H-NMR: δ= 0.80-0.88 ( t, 3 H, -$CH_3$), 1.29 (m, 6 H, -$CH_2$), 1.60-1.61 (d, 3 H, -$CH_2$), 2.84 (broad, 4H, -$CH_2$), 3.31 (s, 3 H, -N-$CH_3$), 3.43-3.52(broad, 4 H, -$CH_2$), 4.06-4.10 (t, 2 H, -O-CH2), 5.18 ( s, 2 H, Ar-$CH_2$-), 5.39 (s, 1 H, -CH), 7.36-7.38 (d, 2 H, ArH) 8.19-8.21 (d, 2 H, ArH) ppm. Mass: ($C_{23}H_{31}N_5O_6$) *m/z= 473.23, M+H=474.2.*

### 4.3.4 Octyl 4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4d):

Compound **43** (9.00 g, 0.0260 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.20 gm, 0.0520 moles) after stirred 10

min. added slowly chloroformates (5.02 gm, 0.0260 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compounds **4d**. Yield: 12.00 gm, (92.0 %).

$^1$H-NMR: δ= 0.85-0.86 ( t, 3 H, -$CH_3$), 1.26-1.29 (m, 10 H, -$CH_2$), 1.59-1.61 (d, 2 H, -$CH_2$), 2.84 (broad, 4H, -$CH_2$), 3.31 (s, 3 H, -N-$CH_3$), 3.43-3.52(broad, 4 H, -$CH_2$), 4.06-4.09 (t, 2 H, -O-CH2), 5.17 ( s, 2 H, Ar-$CH_2$-), 5.39 (s, 1 H, -CH), 7.35-7.38 (d, 2 H, ArH) 8.19-8.21 (d, 2 H, ArH) ppm. Mass: ($C_{25}H_{35}N_5O_6$) *m/z= 501.26, M+H=502.1.*

### 4.3.5 Octyl-4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4e):

Compound **43** (9.00 g, 0.0237 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (6.56 gm, 0.0474 moles) after stirred 10 min. added slowly chloroformates (4.57 gm, 0.0237 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4e**. Yield: 11.31gm, (89.18%).

$^1$H-NMR: δ= 0.86-0.87 ( t, 3 H, -$CH_3$), 1.13-1.41 (m, 12 H, -$CH_2$), 1.62 (t, 3 H, -$CH_2$), 2.83 (broad, 4H, -$CH_2$), 3.31 (s, 3 H, -N-$CH_3$), 3.41-3.53(broad, 4 H, -$CH_2$), 4.06-4.10 (t, 2 H, -O-CH2), 5.04 ( s, 2 H, Ar-$CH_2$-), 5.34 (s, 1 H, -CH), 7.08-7.10 (d, 2 H, ArH) 7.44-7.46 (d, 2 H, ArH) ppm. Mass: ($C_{25}H_{35}BrN_4O_4$) *m/z= 535.47, M+H=537.*

### 4.3.6 Heptyl-4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4f):

Compound **43** (9.00 g, 0.0237 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (6.56 gm, 0.0474 moles) after stirred 10 min. added slowly chloroformates (4.24 gm, 0.0237 moles) at 20-30°C, the reaction mass

agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4f**. Yield: 11.26 gm, (90.27 %).

$^1$H-NMR: δ= 0.86-0.87 ( t, 3 H, -$CH_3$), 1.27-1.31 (m, 9 H, -$CH_2$), 1.62-1.72 (t, 2 H, -$CH_2$), 2.50-2.85 (broad, 4H, -$CH_2$), 3.27-3.28 (s, 4 H, -N-$CH_3$&-CH-), 3.79(broad, 1 H, -CH), 4.01-4.04 (t, 2 H, -O-CH2), 4.62-4.64 ( d, 1 H, -$CH_2$-), 4.92-5.18 (m, 2 H, Ph-$CH_2$), 5.31(s, 1 H, -CH-) 7.05-7.07 (d, 2 H, ArH) 7.42-7.44 (d, 2 H, ArH) ppm. Mass: ($C_{24}H_{33}BrN_4O_4$) *m/z= 520.17, M+H=521*.

### 4.3.7 Octyl 1-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylcarbamate (4g):

Compound **44** (9.00 g, 0.0228 moles ) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (6.33gm, 0.0456 moles) after stirred 10 min. added slowly chloroformates (4.40 gm, 0.0228 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4g**. Yield: 11.78 gm, (93.70%).

$^1$H-NMR: δ= 0.85-0.88 ( t, 3 H, -$CH_3$), 1.26-1.40 (m, 12 H, -$CH_2$), 1.45-1.90 (broad, 6 H, -$CH_2$), 2.68-2.89 (broad, 4H, -$CH_2$), 3.31 (s, 3 H, -N-$CH_3$), 3.39-3.53(broad, 4 H, -$CH_2$), 4.06-4.10 (t, 2 H, -O-$CH_2$), 5.04 ( s, 2 H, Ar-$CH_2$-), 5.34 (s, 1 H, -CH), 7.08-7.10 (d, 2 H, ArH) 7.43-7.46 (d, 2 H, ArH) ppm. Mass: ($C_{26}H_{37}BrN_4O_4$) *m/z= 548.2, M+H=550.9.*

### 4.3.8 Octyl 4-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4h):

Compound **3** (9.00 g, 0.0282 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.81 gm, 0.0564 moles) after stirred 10 min. added slowly chloroformates (5.45 gm, 0.0282 moles) at 20-30°C, the reaction mass

agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4h**. Yield: 11.83 gm, (88.25%).

$^1$H-NMR: δ= 0.85-0.88 ( t, 3 H, -$CH_3$), 1.02-1.40 (m, 12 H, -$CH_2$), 1.59-1.80 (t, 3 H, -$CH_2$), 2.82 (broad, 4H, -$CH_2$), 3.31 (s, 3 H, -N-$CH_3$), 3.42-3.52(broad, 4 H, -$CH_2$), 4.05-4.09 (t, 2 H, -O-$CH_2$), 5.08 ( s, 2 H, Ar-$CH_2$-), 5.34 (s, 1 H, -CH), 6.89-6.94 (q, 1 H, ArH) 6.96-6.98 (d, 2 H, ArH), 7.26-7.31(q, 1 H, ArH) ppm. Mass: ($C_{25}H_{35}FN_4O_4$) *m/z= 474.26, M+H=475.1*.

### 4.3.9 Octyl-4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4i):

Compound **43** (9.00 g, 0.0299 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (8.28 gm, 0.0598 moles) after stirred 10 min. added slowly chloroformates (5.77 gm, 0.0299 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4i**. Yield: 11.63 gm, (85.0 %).

$^1$H-NMR: δ= 0.85-0.88 ( t, 3 H, -$CH_3$), 1.27-1.29 (broad, 12 H, -$CH_2$), 1.53-1.64 (m, 4 H, -$CH_2$), 2.82 (broad, 4H, -$CH_2$), 3.31 (s, 3 H, -N-$CH_3$), 3.51(broad, 4 H, -$CH_2$), 3.60-3.63 (t, 2 H, -$CH_2$), 4.05-4.08 (t, 2 H, -O-$CH_2$), 5.10 ( s, 2 H, Ar-$CH_2$-), 5.33 (s, 1 H, -CH), 7.09-7.27 (m, 2 H, ArH) 7.31- 7.33(t, 2 H, ArH) ppm. Mass: ($C_{25}H_{36}N_4O$) *m/z= 456.27, M+H=457.10*

### 4.3.10 Heptyl-4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4j):

Compound **43** (9.00 g, 0.0299 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (8.28 gm, 0.0598 moles) after stirred 10 min. added slowly chloroformates (5.35 gm, 0.0299 moles) at at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4j**. Yield: 11.49 gm, (86.95%).

$^1$H-NMR: δ= 0.86-0.88 ( t, 3 H, -$CH_3$), 1.28-1.30 (broad, 12 H, -$CH_2$), 1.55-1.72 (m, 3 H, -$CH_2$), 2.83 (broad, 4H, -$CH_2$), 3.32 (s, 3 H, -N-$CH_3$), 3.32-3.51(broad, 4 H, -$CH_2$), 3.62-3.65 (t, 2 H, -$CH_2$), 4.06-4.09 (t, 2 H, -O-$CH_2$), 5.10 ( s, 2 H, Ar-$CH_2$-), 5.34 (s, 1 H, -CH), 7.18-7.20 (d, 2 H, ArH) 7.26- 7.34(m, 3 H, ArH) ppm. Mass: ($C_{24}H_{34}N_4O_4$) *m/z= 442.29, M+H=443.1*.

### 4.3.11 Heptyl 4-(3-(4-nitrobenzyl)-1,2,3,6-tetrahydro-1-methyl-2,6-dioxopyrimidin-4-yl)piperazine-1-carboxylateyl)piperazine-1-carboxylate (4k):

Compound **43** (9.00 g, 0.0260 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.20 gm, 0.0520 moles) after stirred 10 min. added slowly chloroformates (4.66 gm, 0.0260 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4k**. Yield: 11.23 gm, (88.50%).

$^1$H-NMR: δ= 0.86-0.88 ( t, 3 H, -$CH_3$), 1.21-1.24 (broad, 10 H, -$CH_2$), 1.45-1.57 (m, 3 H, -$CH_2$), 2.80 (broad, 4H, -$CH_2$), 3.23 (s, 3 H, -N-$CH_3$), 3.47-3.56 (broad, 4 H, -$CH_2$), 3.99-4.03 (t, 2 H, -O-$CH_2$), 5.13 ( s, 2 H, Ar-$CH_2$-), 5.33 (s, 1 H, -CH), 7.25-7.34 (d, 2 H, ArH) 8.11-8.13(d, 2 H, ArH) ppm. Mass: ($C_{24}H_{33}N_5O_6$) *m/z= 487.24, M+H=488.*

### 4.3.12 Heptyl-4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4l):

Compound **43** (9.00 g, 0.0282 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.81 gm, 0.0564 moles) after stirred 10 min. added slowly chloroformates (5.05 gm, 0.0282 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4l**. Yield: 11.88 gm, (91.70%).

$^1$H-NMR: δ= 0.85-0.88 ( t, 3 H, -$CH_3$), 1.27-1.31 (broad, 8 H, -$CH_2$), 1.55-1.63 (m, 2 H, -$CH_2$), 2.80 (broad, 4H, -$CH_2$), 3.32 (s, 3 H, -N-$CH_3$), 3.49-3.63 (broad, 3 H, -$CH_2$), 4.05-4.08 (t, 2 H, -O-$CH_2$), 5.16 ( s, 2 H, Ar-$CH_2$-), 5.33 (s, 1 H, -CH), 7.02-7.07 (t, 1 H, ArH) 7.09-7.13(m, 2 H, ArH), 7.23-7.28 (m, 1 H, ArH) ppm. Mass: ($C_{24}H_{33}FN_4O_4$) *m/z= 460.25, M+H=461.1*.

### 4.3.13 2-ethylbutyl 4-(3-(2-fluorobenzyl)-1,2,3,6-tetrahydro-1-methyl-2,6-dioxopyrimidin-4-yl)piperazine-1-carboxylate (4m):

Compound **43** (9.00 g, 0.0282 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.81 gm, 0.0564 moles) after stirred 10 min. added slowly chloroformates (4.65 gm, 0.0282 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4m**. Yield: 11.49 gm, (91.20%).

$^1$H-NMR: δ= 0.87-0.91 ( t, 3 H, -$CH_3$), 1.25-1.38 (m, 4 H, -$CH_2$), 1.48-1.56 (m, 1H, -$CH_2$), 2.81-2.90 (broad, 5H, -$CH_2$), 3.33-3.43 (broad, 5 H, -N-$CH_3$, $CH_2$), 3.51 (broad, 4 H, -$CH_2$), 4.01-4.02 (t, 2 H, -O-$CH_2$), 5.16 ( s, 2 H, Ar-$CH_2$-), 5.34 (s, 1 H, -CH), 7.03-7.11 (m, 4 H, ArH) ppm. Mass: ($C_{23}H_{31}FN_4O_4$) *m/z= 446.23, M+H=461.1*

### 4.3.14 Octyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4n):

Compound **43** (9.00 g, 0.0282 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.81 gm, 0.0564 moles) after stirred 10 min. added slowly chloroformates (4.65 gm, 0.0282 moles) at at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4n**. Yield: 12.00 gm (89.50%).

$^1$H-NMR: δ= 0.86- 0.89 ( t, 3 H, -$CH_3$), 1.27-1.30 (broad, 10 H, -$CH_2$), 1.57-1.63 (m, 2 H, -$CH_2$), 2.80 (broad, 4H, -$CH_2$), 3.30 (s, 3 H, -N-$CH_3$), 3.50-3.65 (broad, 4 H, -$CH_2$), 4.06-4.09 (t, 2 H, -O-$CH_2$), 5.16 ( s, 2 H, Ar-$CH_2$-), 5.33 (s, 1 H, -CH), 7.03-7.11 (m, 3 H, Ar H), 7.23-7.26 ( broad, 1 H, ArH) ppm. Mass: ($C_{24}H_{33}FN_4O_4$) *m/z= 460.25, M+H=461.1*

### 4.3.15 Hexyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4o):

Compound **43** (9.00 g, 0.0282 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.81 gm, 0.0564 moles) after stirred 10 min. added slowly chloroformates (4.65 gm, 0.0282 moles) at at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4o**. Yield: 11.21 gm, (89.0%).

$^1$H-NMR: δ= 0.86-0.90 ( t, 3 H, -$CH_3$), 1.30 (broad, 6 H, -$CH_2$), 1.57-1.63 (m, 2 H, -$CH_2$), 2.80 (broad, 4H, -$CH_2$), 3.33 (s, 3 H, -N-$CH_3$), 3.40-3.51 (broad, 4 H, -$CH_2$), 4.06-4.09 (t, 2 H, -O-$CH_2$), 5.16 ( s, 2 H, Ar-$CH_2$-), 5.33 (s, 1 H, -CH), 7.02-7.11 (m, 3 H, ArH) 7.25 (broad , 1 H, ArH) ppm. Mass: ($C_{23}H_{31}FN_4O_4$) *m/z= 460.25, M+H=461.1*

### 4.3.16 4-methylpentyl-4-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4p):

Compound **43** (9.00 g, 0.0276 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.64 gm, 0.0552 moles) after stirred 10 min. added slowly chloroformates (4.55 gm, 0.0276 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4p**. Yield: 11.25 gm (90.0%).

$^1$H-NMR: δ= 0.80-0.88 ( m, 6 H, -$CH_3$), 1.22-1.29 (m, 7 H, -$CH_2$), 1.29-1.31 (m, 1 H, -$CH_2$), 2.80 (broad, 4H, -$CH_2$), 3.10 (s, 3 H, -N-$CH_3$), 3.27-3.30 (t, 2 H, -$CH_2$), 3.51-3.62 (broad, 4 H), 3.92-3.93 (t, 2 H, -O-$CH_2$), 5.07 ( s, 2 H, Ar-$CH_2$-), 5.38 (s, 1 H, -CH), 7.14 (m, 3 H, ArH) 7.15 (m, 1 H, ArH) ppm. Mass: ($C_{24}H_{31}N_5O_4$) *m/z= 453.24, M+H=454.*

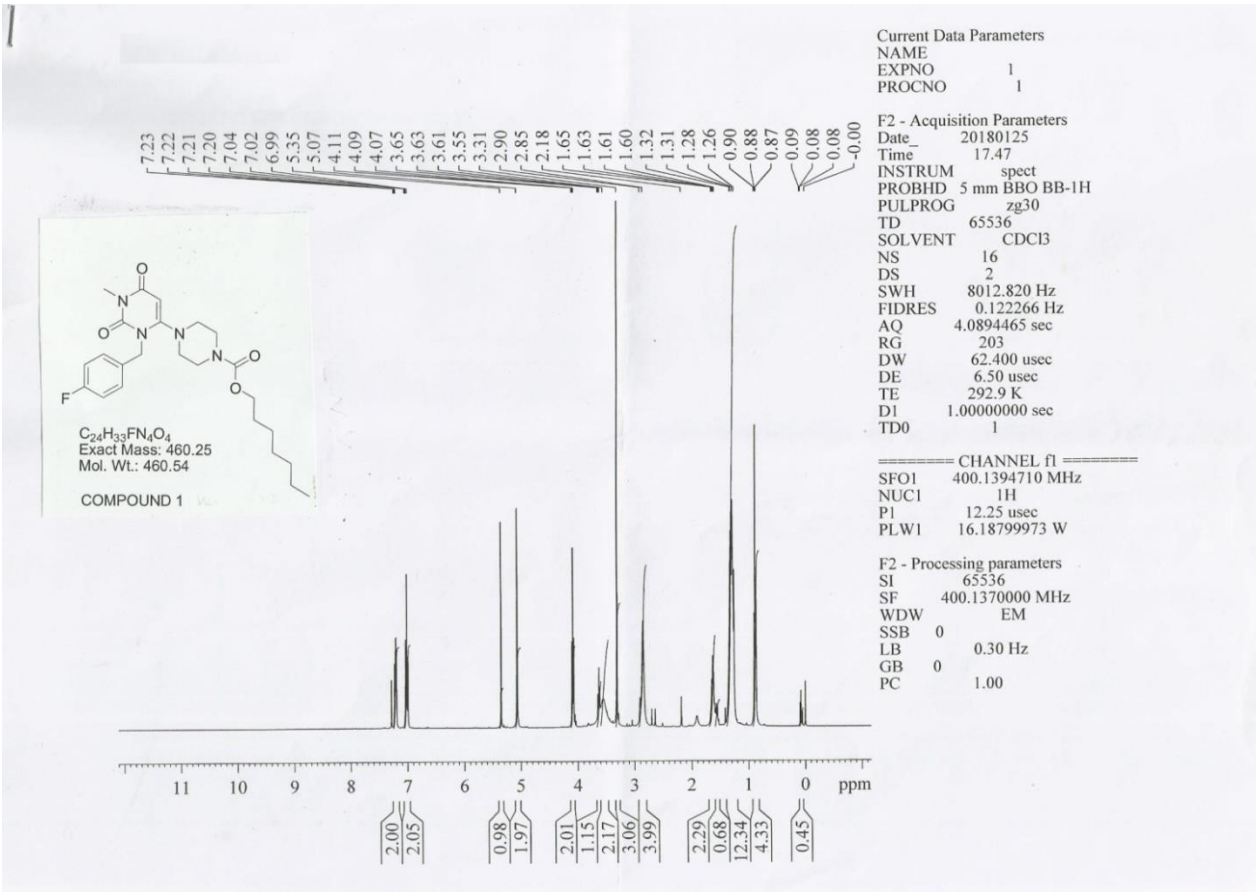
### 4.3.17 Hexyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4q):

Compound **43** (9.00 g, 0.0282 moles) was suspended in acetone 90 mL and water 40 mL followed by addition of potassium carbonate (7.81 gm, 0.0564 moles) after stirred 10 min. added slowly chloroformates (4.65 gm, 0.0282 moles) at 20-30°C, the reaction mass agitated at 23-33°C till starting material disappear from the mass added water in to it ethyl acetate were used to extract product, treated organic layer successively with $H_2O$, followed by dried with sodium sulphate, distilled out ethyl acetate under vacuum at 40-50°C to give title compound **4q**. Yield: 11.59 gm, (92.0%).

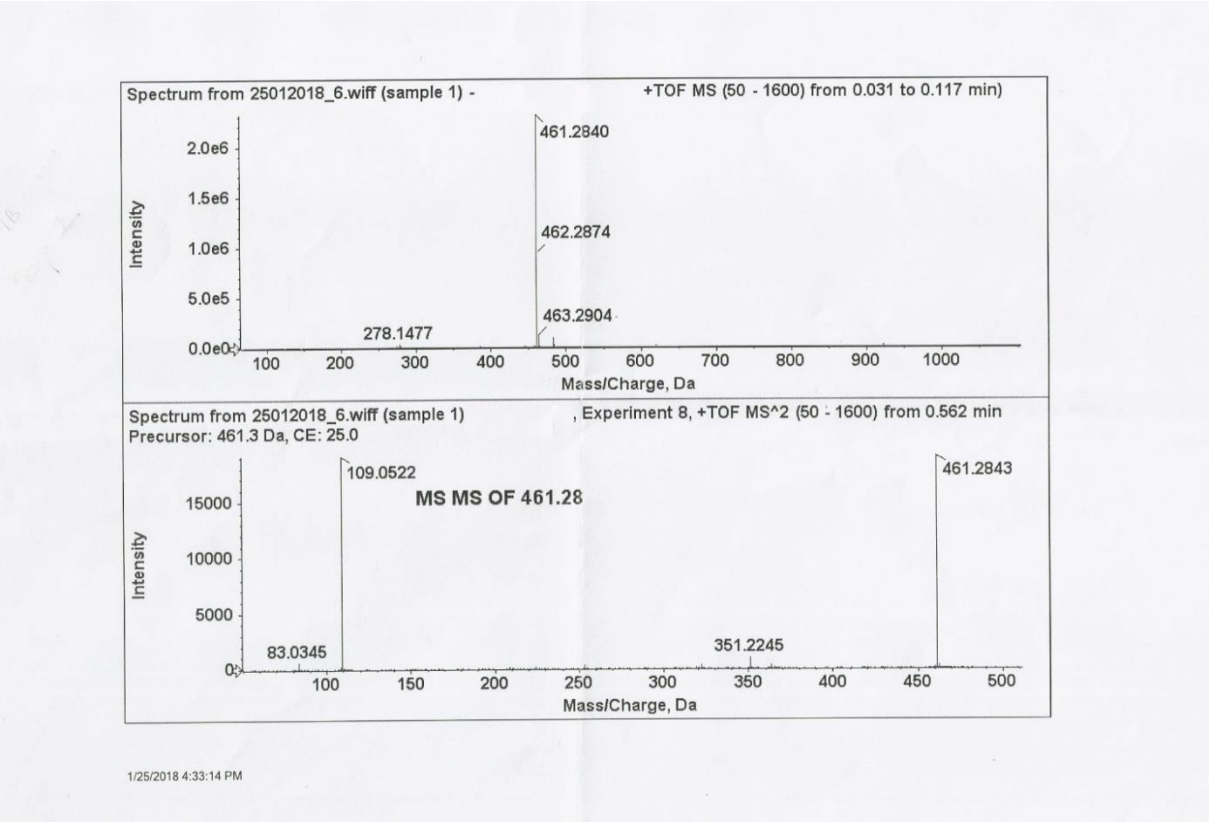
$^1$H-NMR: δ= 0.89-0.91 ( t, 3 H, -$CH_3$), 1.27-1.31 (m, 6 H, -$CH_2$), 1.61-1.70 (m, 3 H, -$CH_2$), 2.86 (broad, 4H, -$CH_2$), 3.33 (s, 3 H, -N-$CH_3$), 3.57 (broad, 3 H, -$CH_2$), 4.09-4.12 (t, 2 H, -O-$CH_2$), 5.08 ( s, 2 H, Ar-$CH_2$-), 5.36 (s, 1 H, -CH), 7.01-7.06 (t, 2 H, ArH) 7.21-7.24(m, 2 H, ArH) ppm. Mass: ($C_{23}H_{31}FN_4O_4$) *m/z= 446.23, M+H=447.2472.*

## 4.4 NMR AND MASS SPECTROSCOPY DATA OF COMPOUNDS (4a-4q):

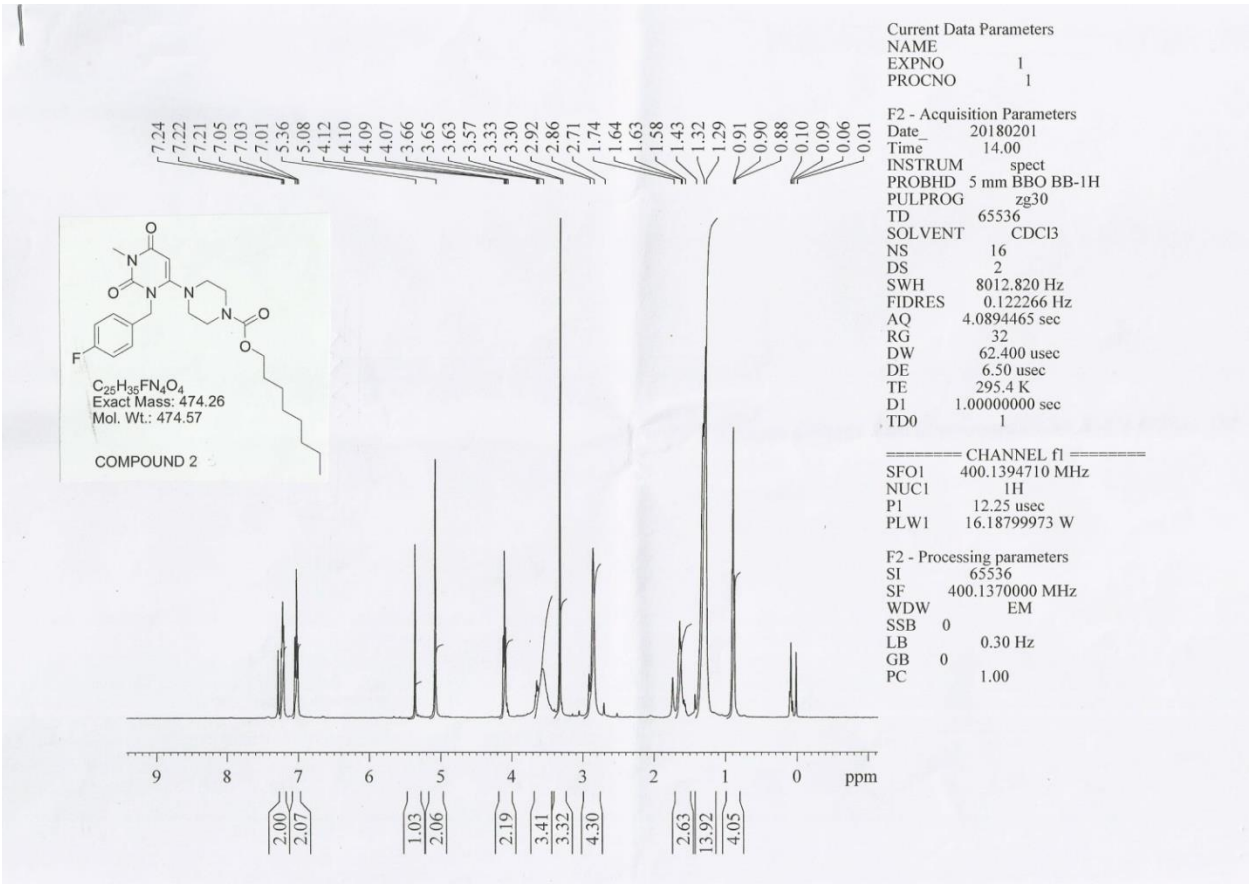
### 4.4.1 $H^1$ NMR Spectra of heptyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4a)



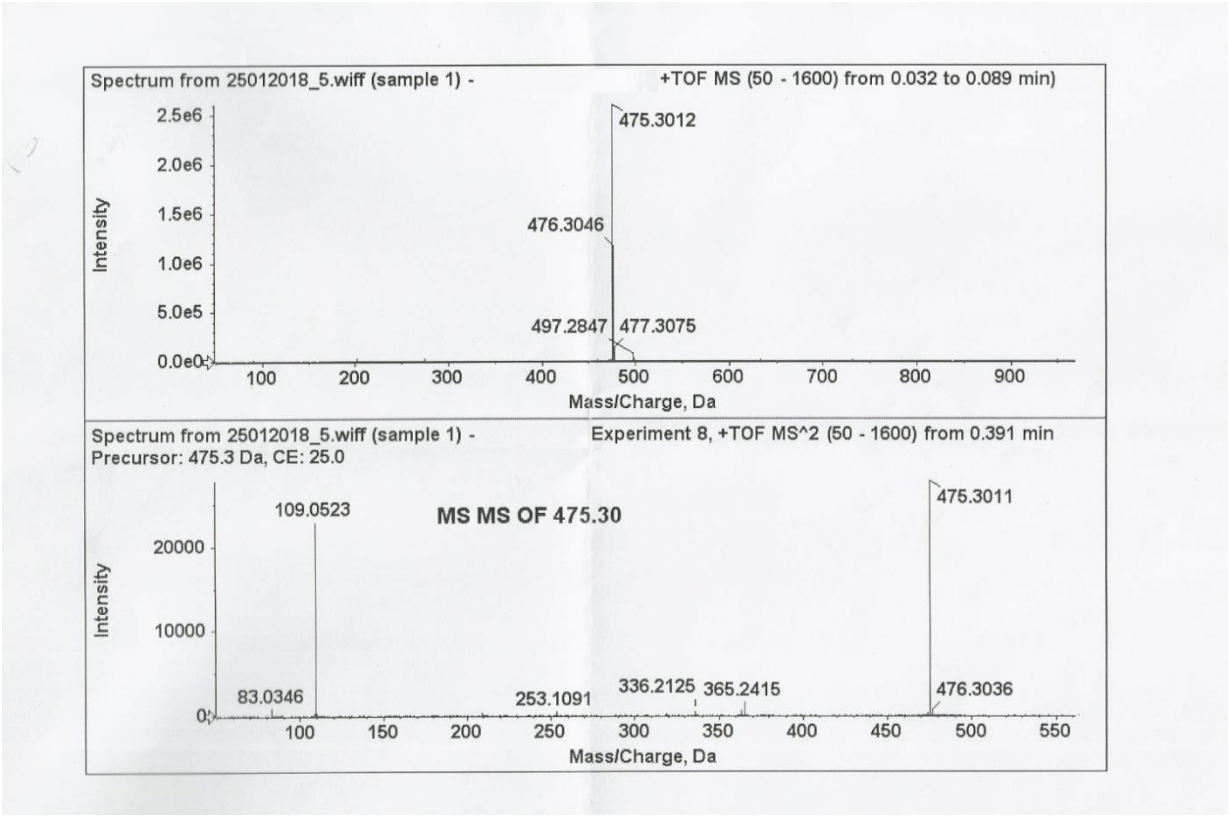
### 4.4.2 HRMS of heptyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4a)



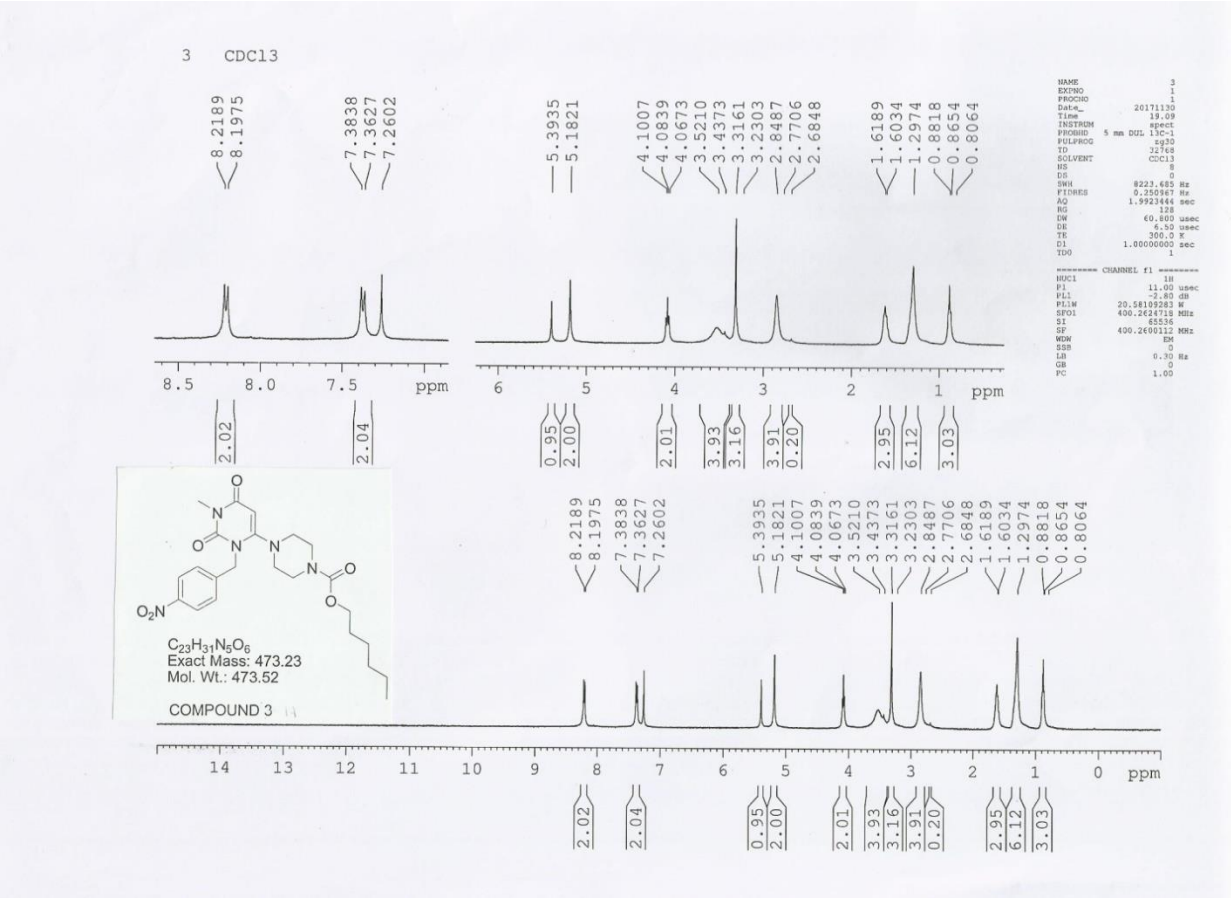
### 4.4.3 $H^1$ NMR Spectra of Octyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4b)



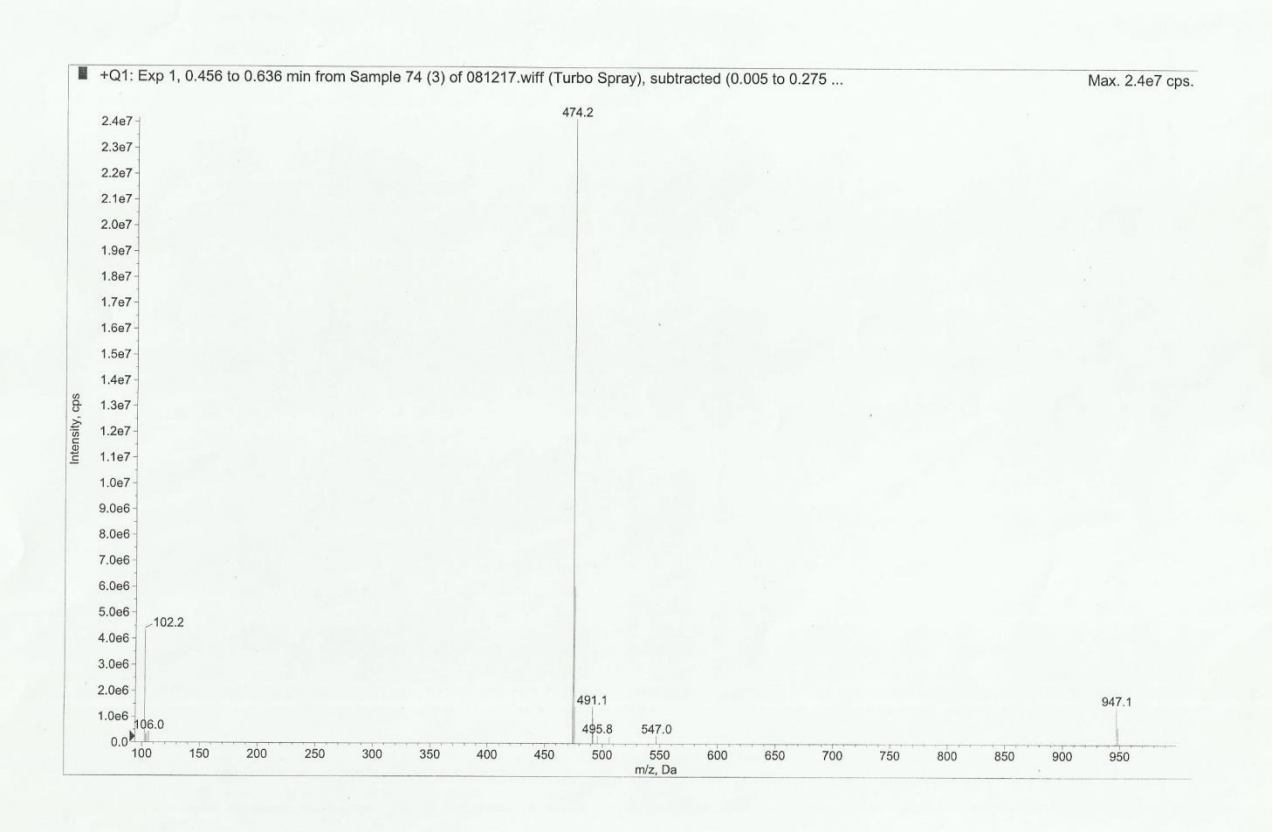
### 4.4.4 HRMS of octyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4b)



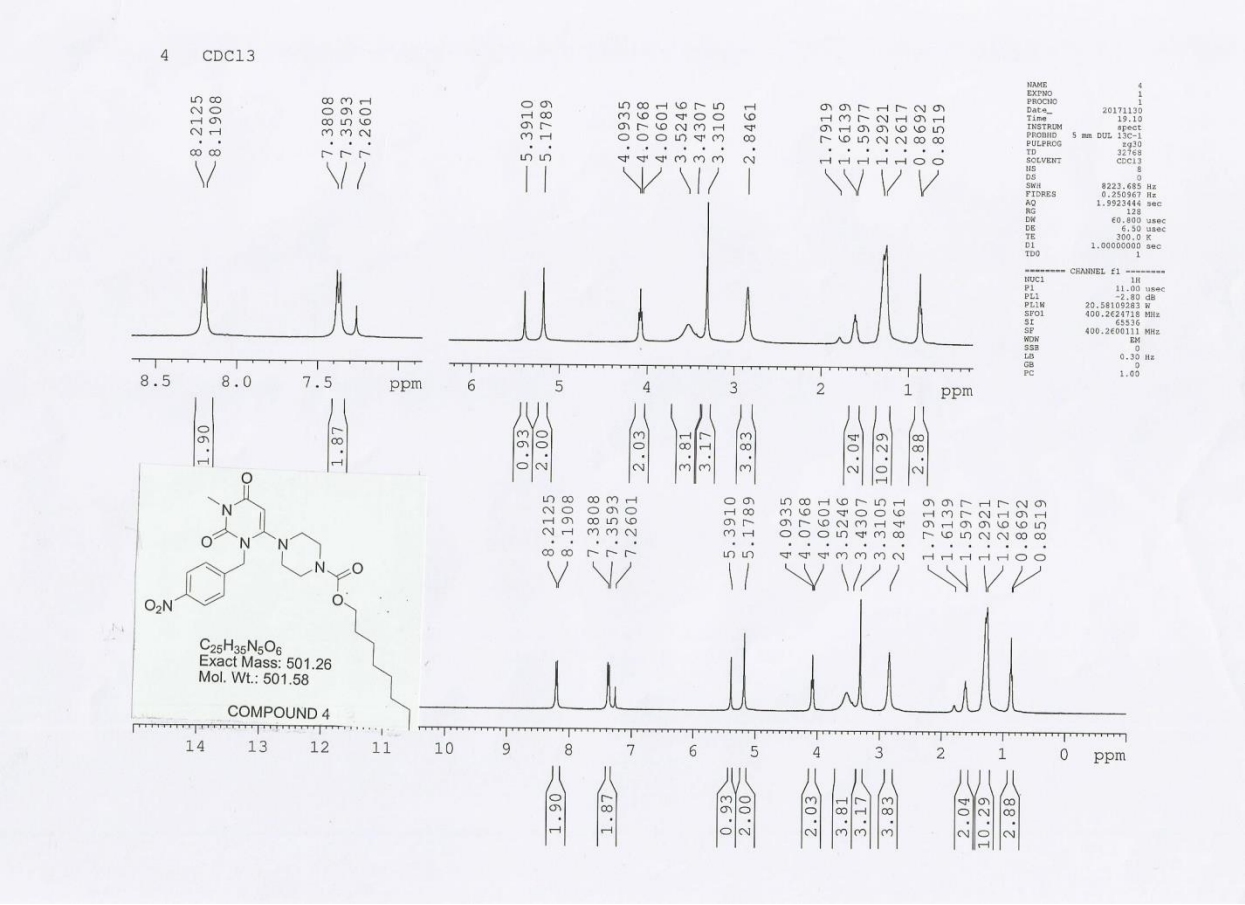
### 4.4.5 $H^1$ NMR Spectra of hexyl 4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4c)



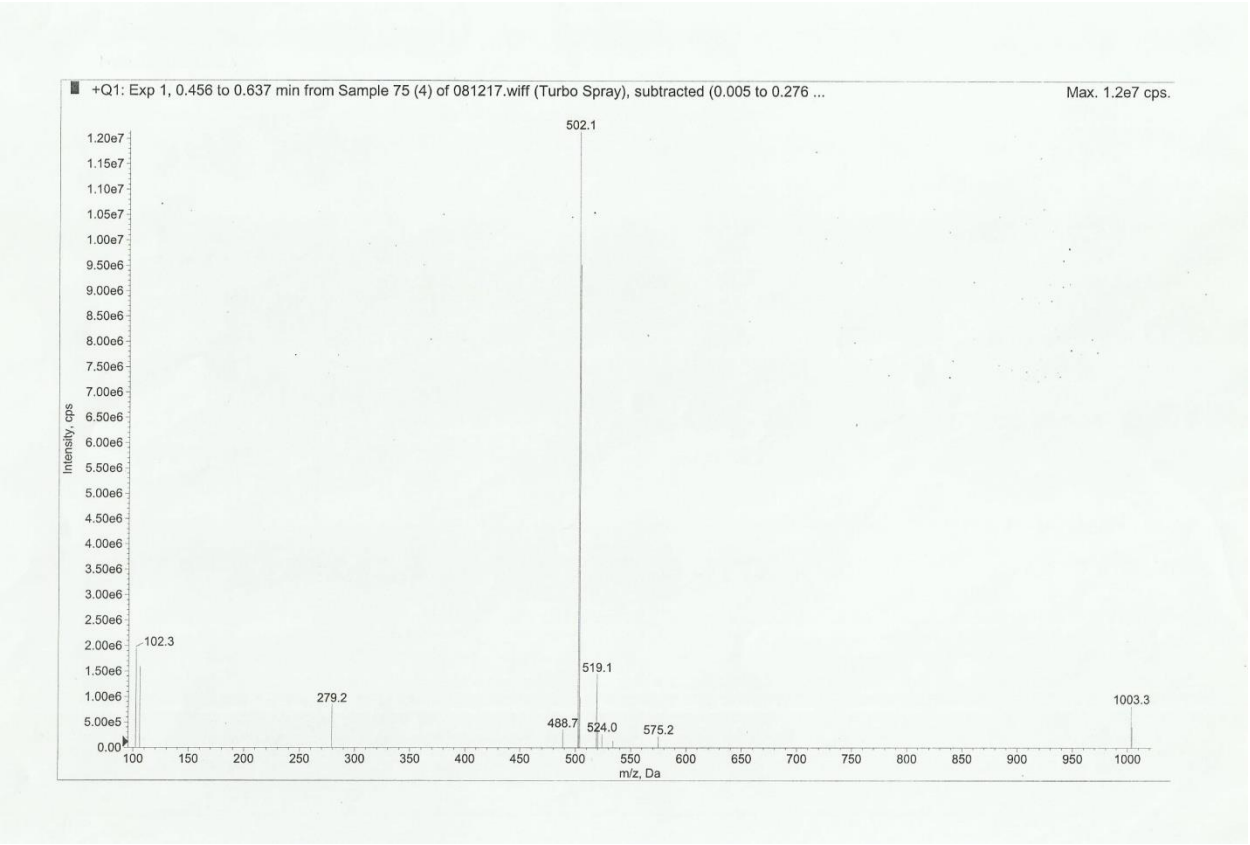
### 4.4.6 HRMS of hexyl 4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4c)



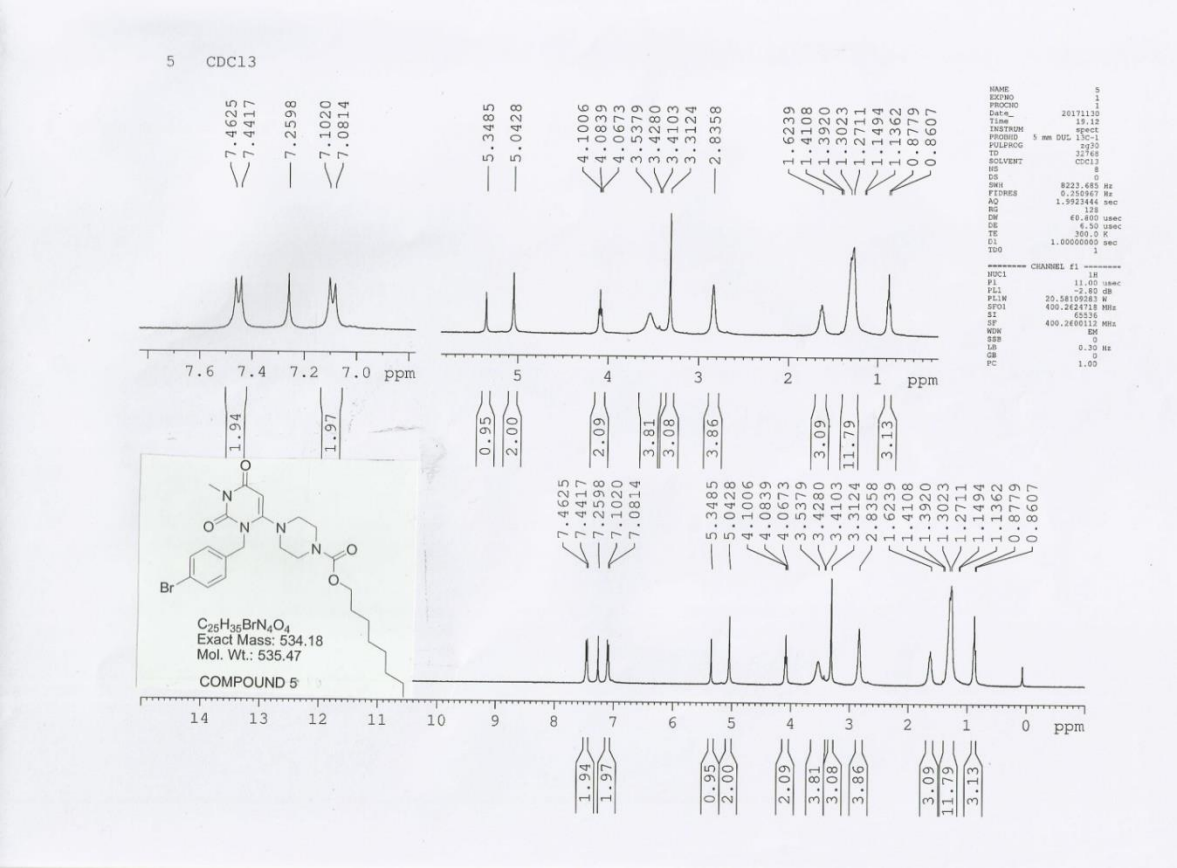
### 4.4.7 $H^1$ NMR Spectra of octyl 4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4d)



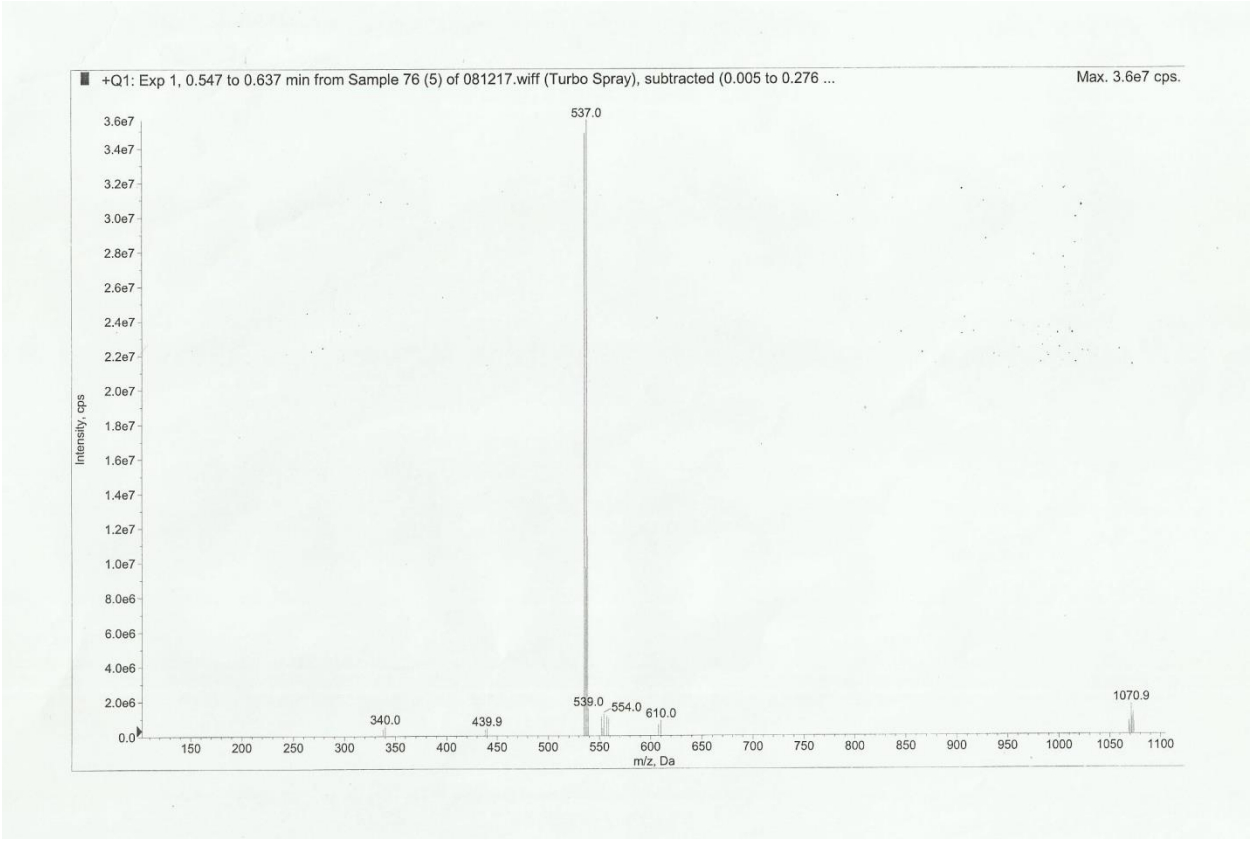
### 4.4.8 HRMS of octyl 4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4d)



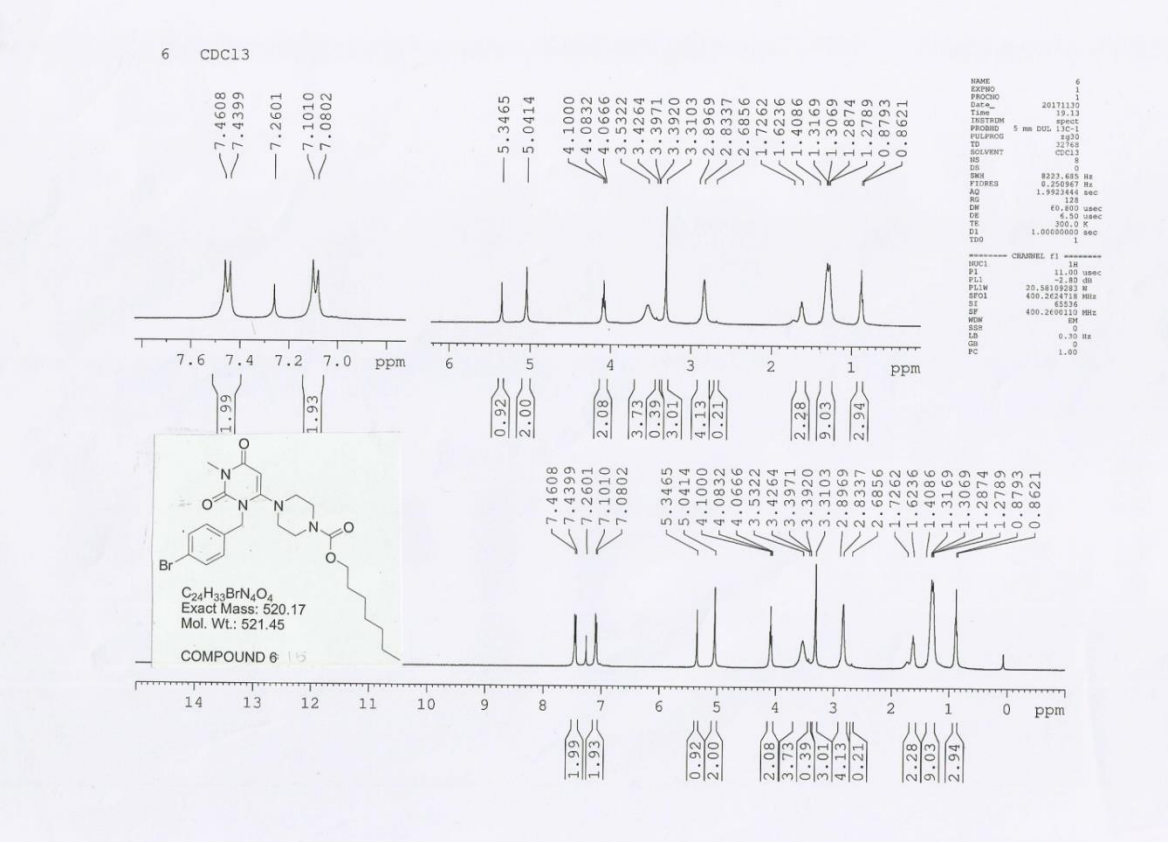
### 4.4.9 $H^1$ NMR Spectra of Octyl-4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4e)



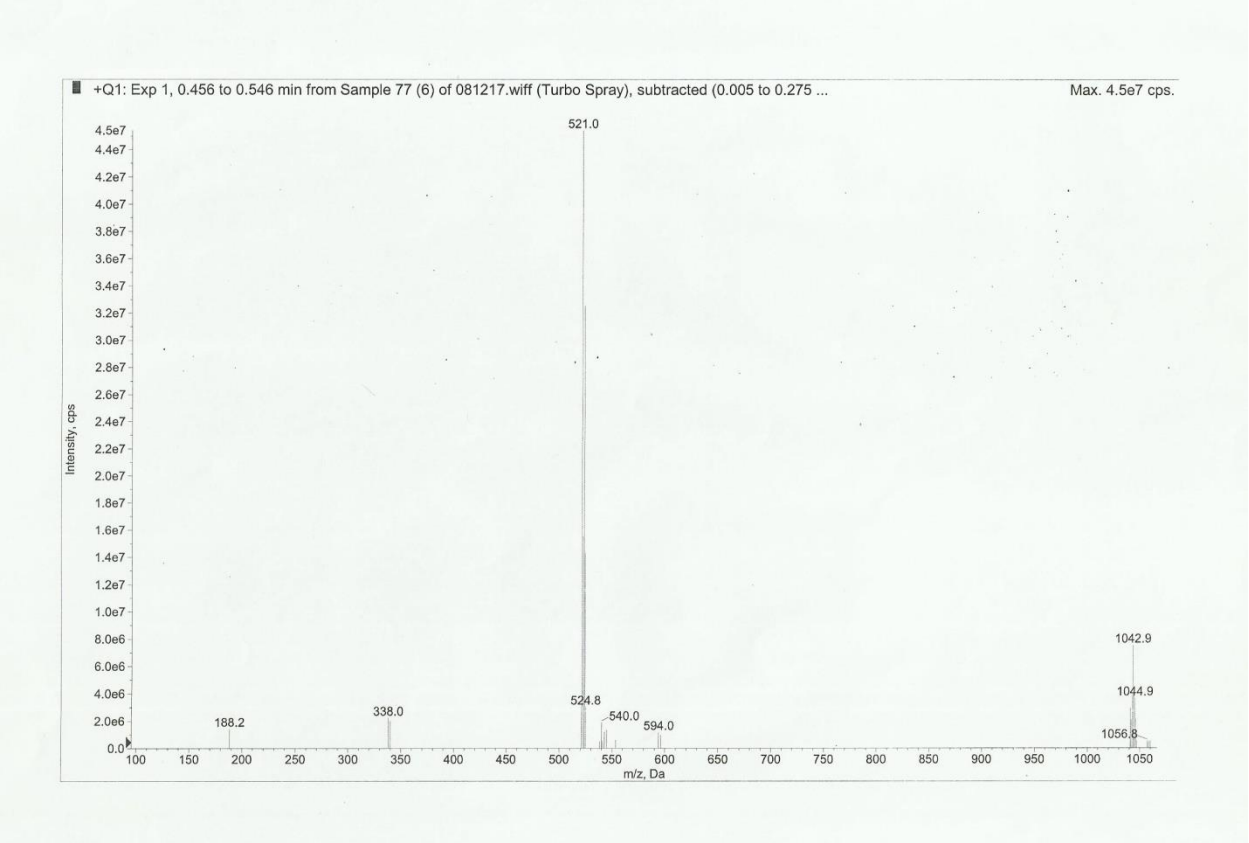
### 4.4.10 HRMS of Octyl-4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4e)



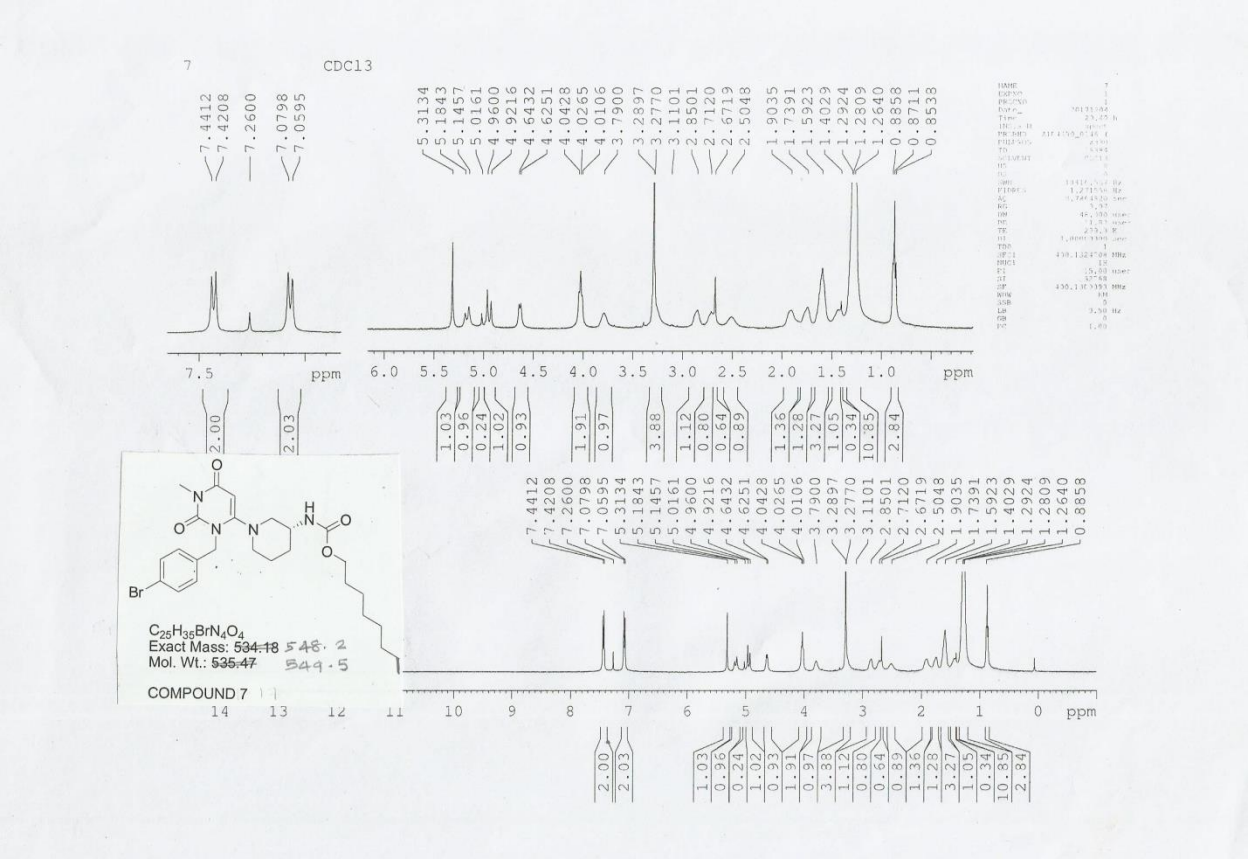
### 4.4.11 $H^1$ NMR Spectra of Heptyl-4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4f)



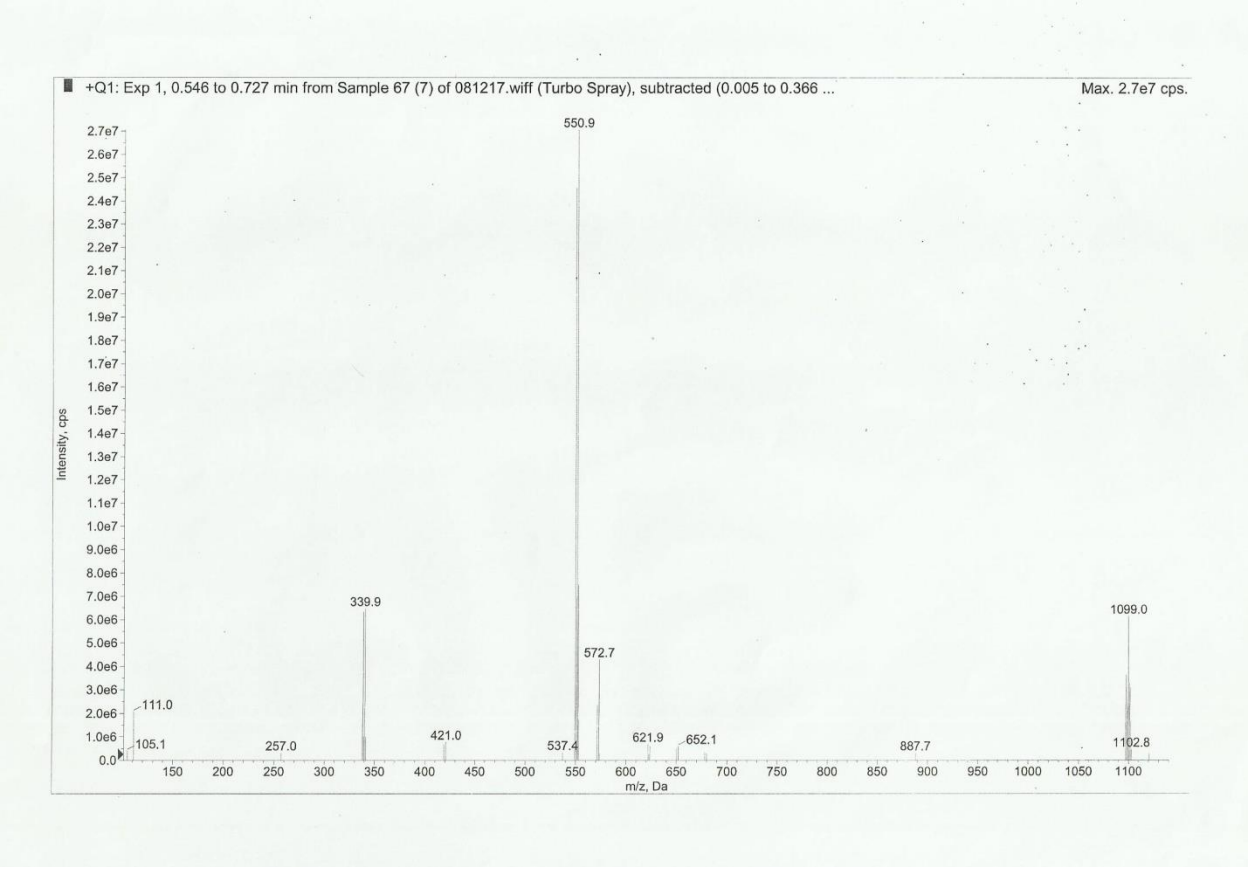
### 4.4.12 HRMS of Heptyl-4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4f)



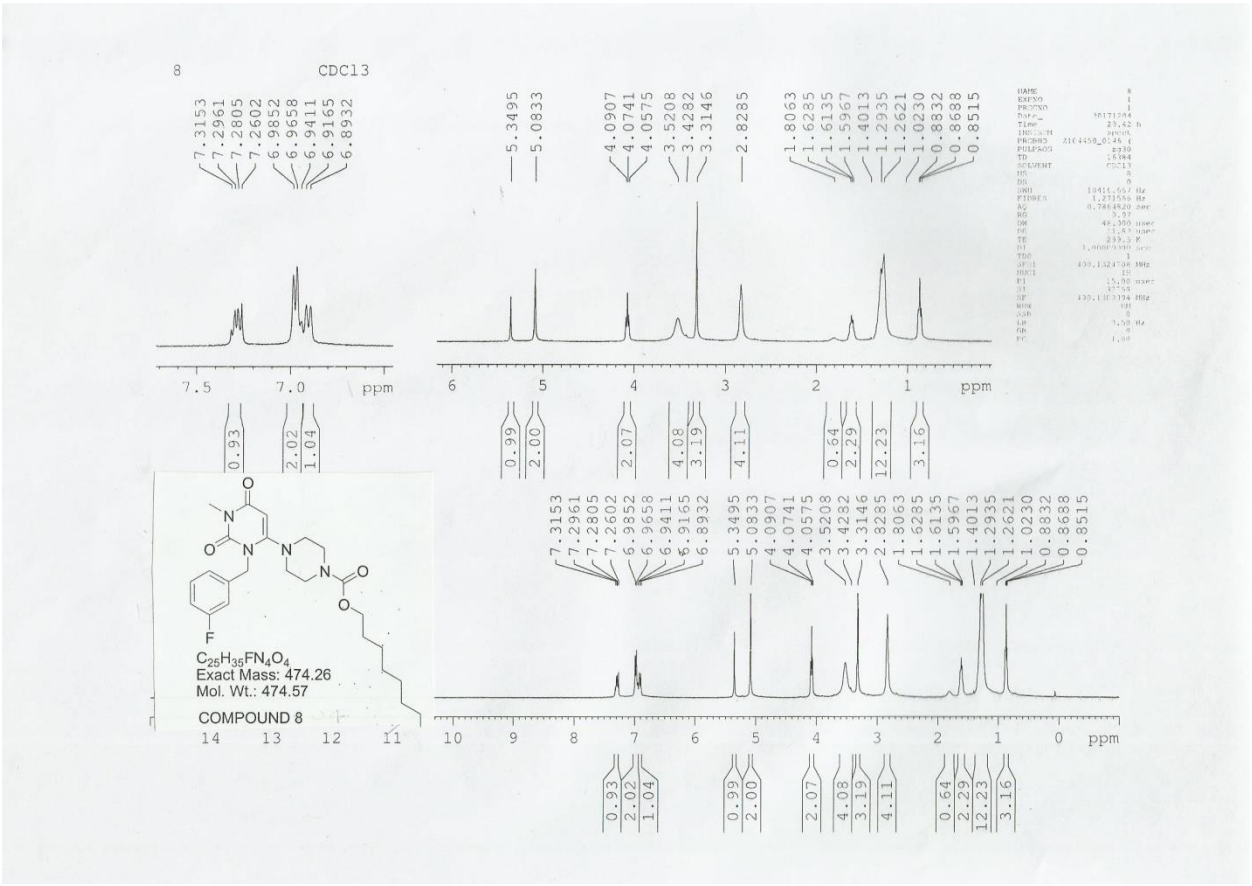
### 4.4.13 $H^1$ NMR Spectra of octyl 1-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylcarbamate (4g)



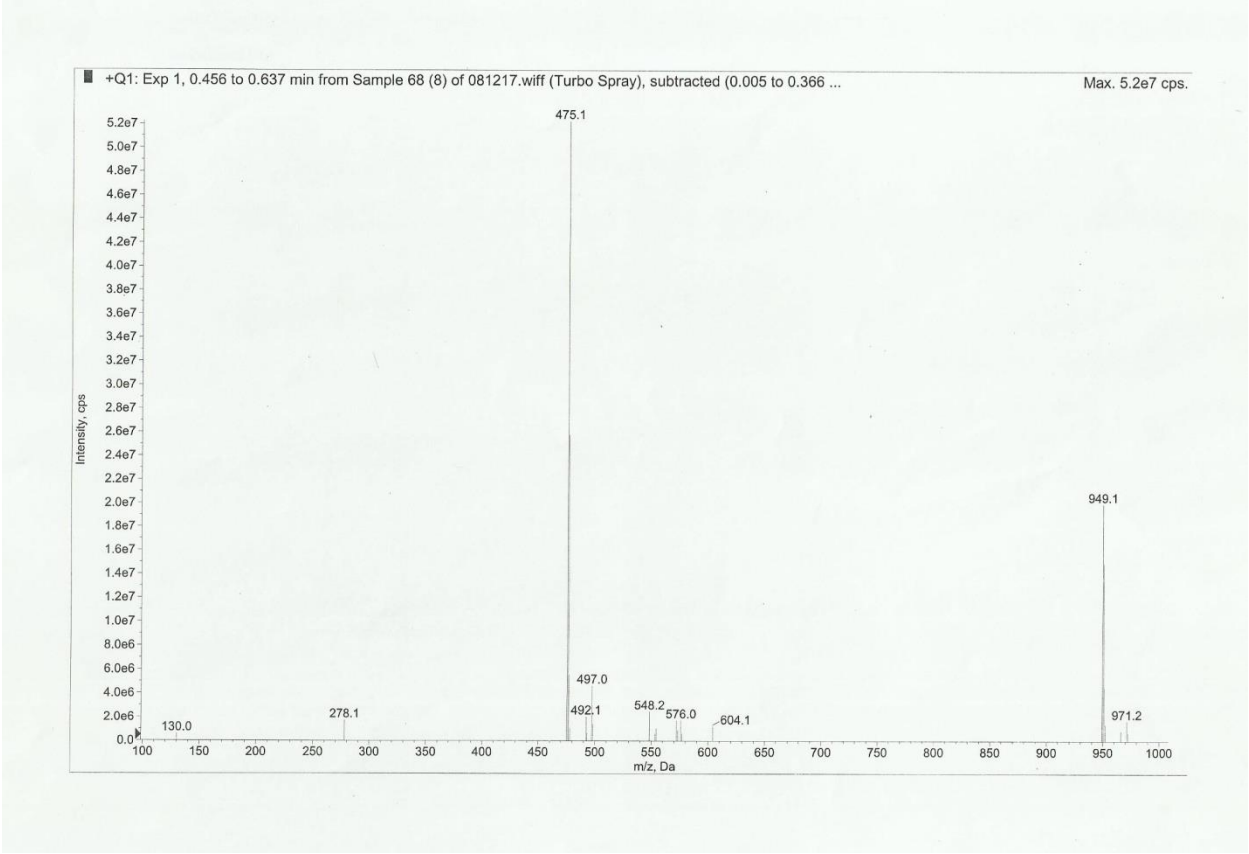
### 4.4.14 HRMS of octyl 1-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylcarbamate (4g)



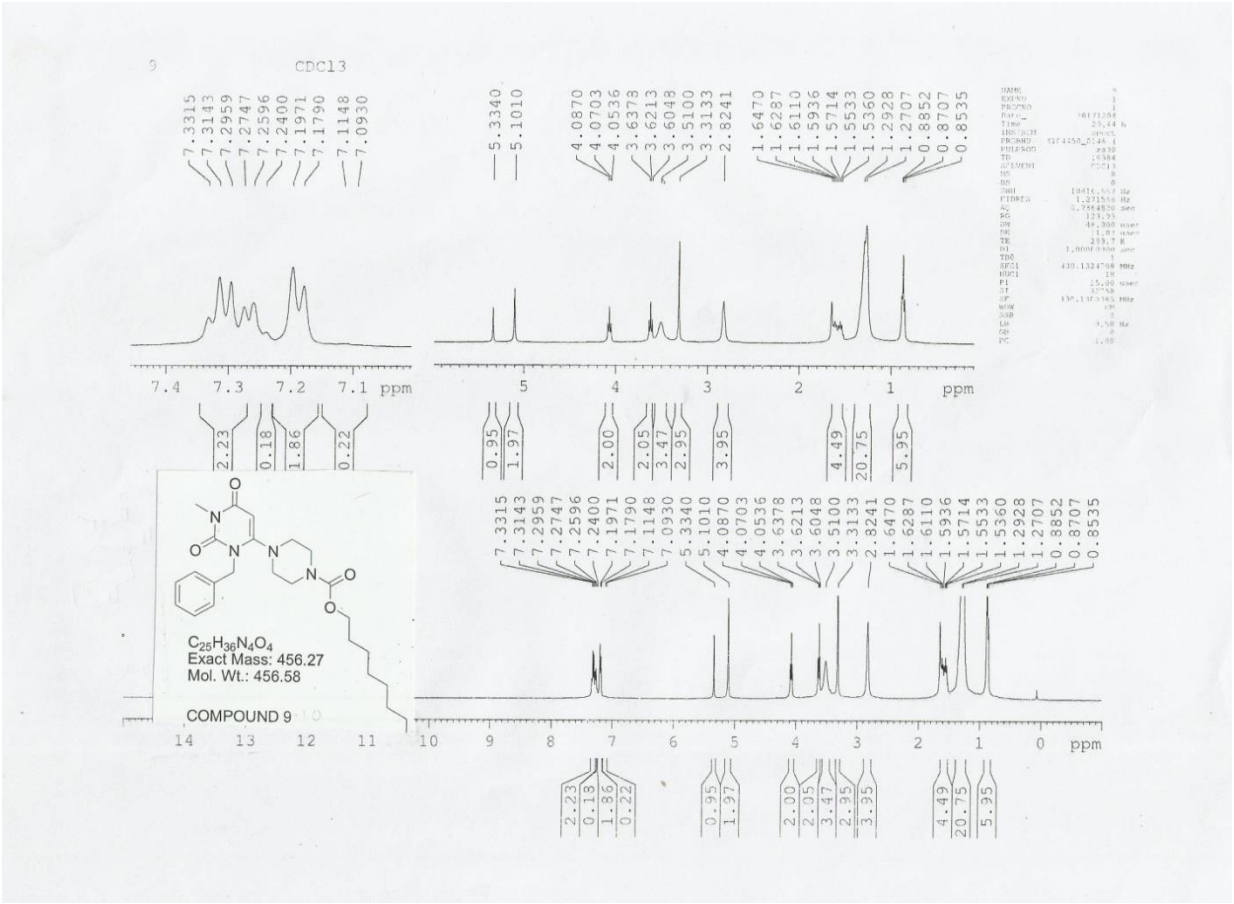
### 4.4.15 H1 NMR Spectra of octyl 4-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4h)



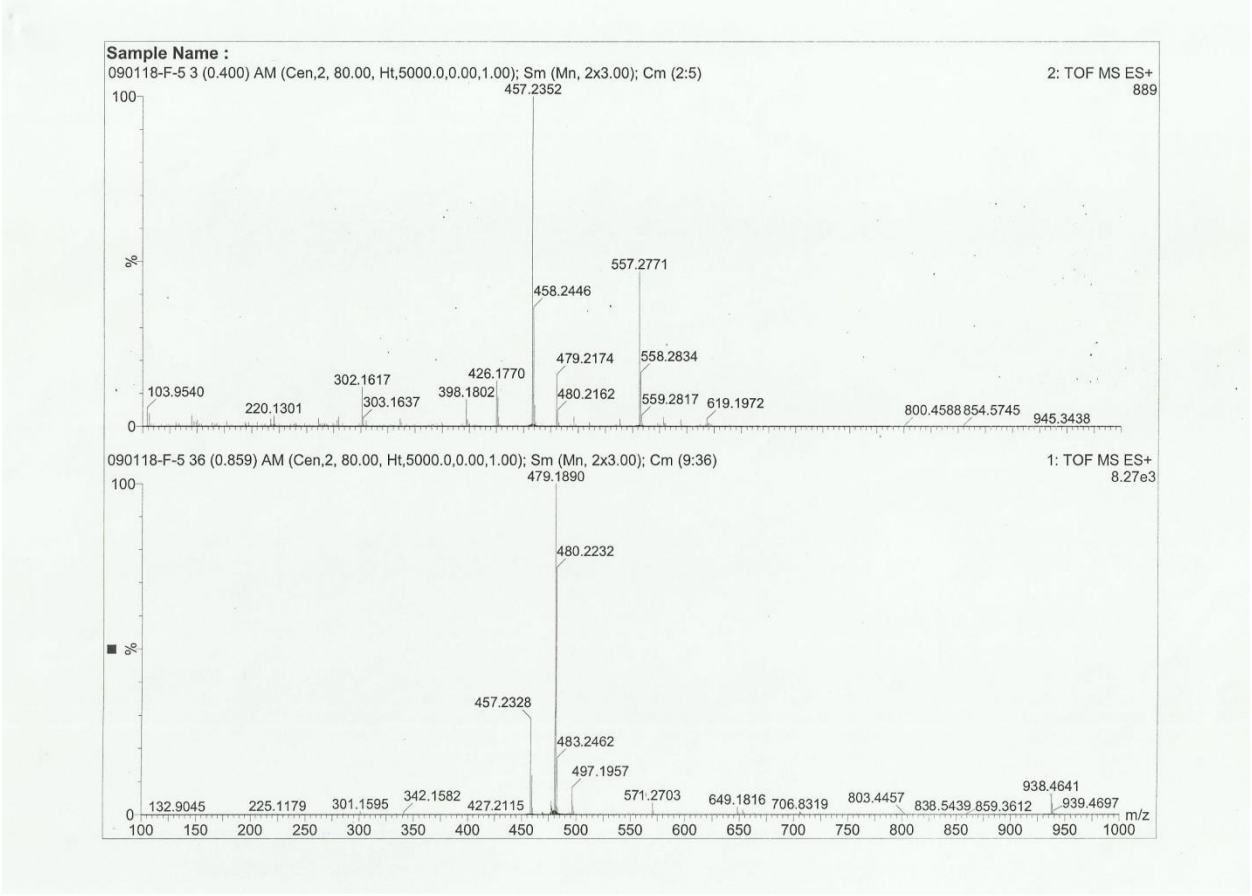
### 4.4.16 HRMS of octyl 4-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4h)



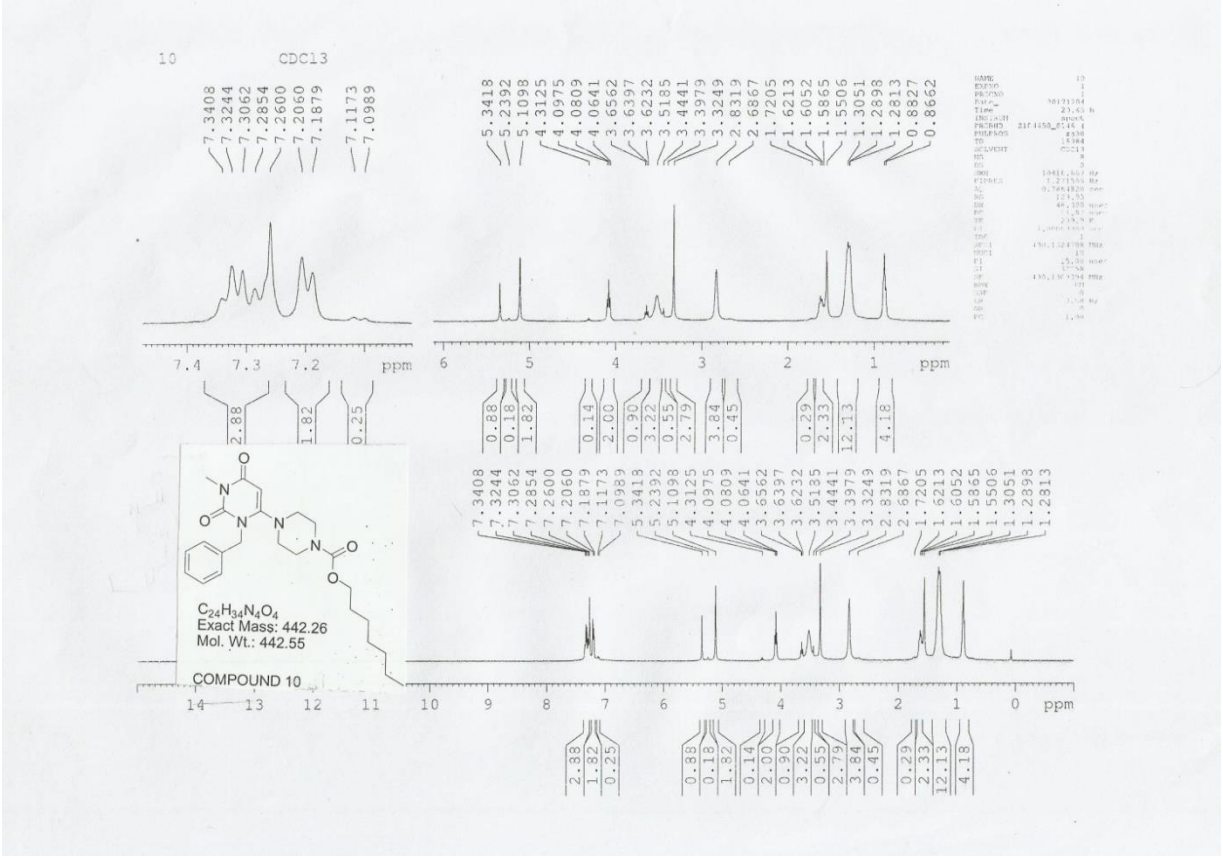
### 4.4.17 $H^1$ NMR Spectra of Octyl-4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4i)



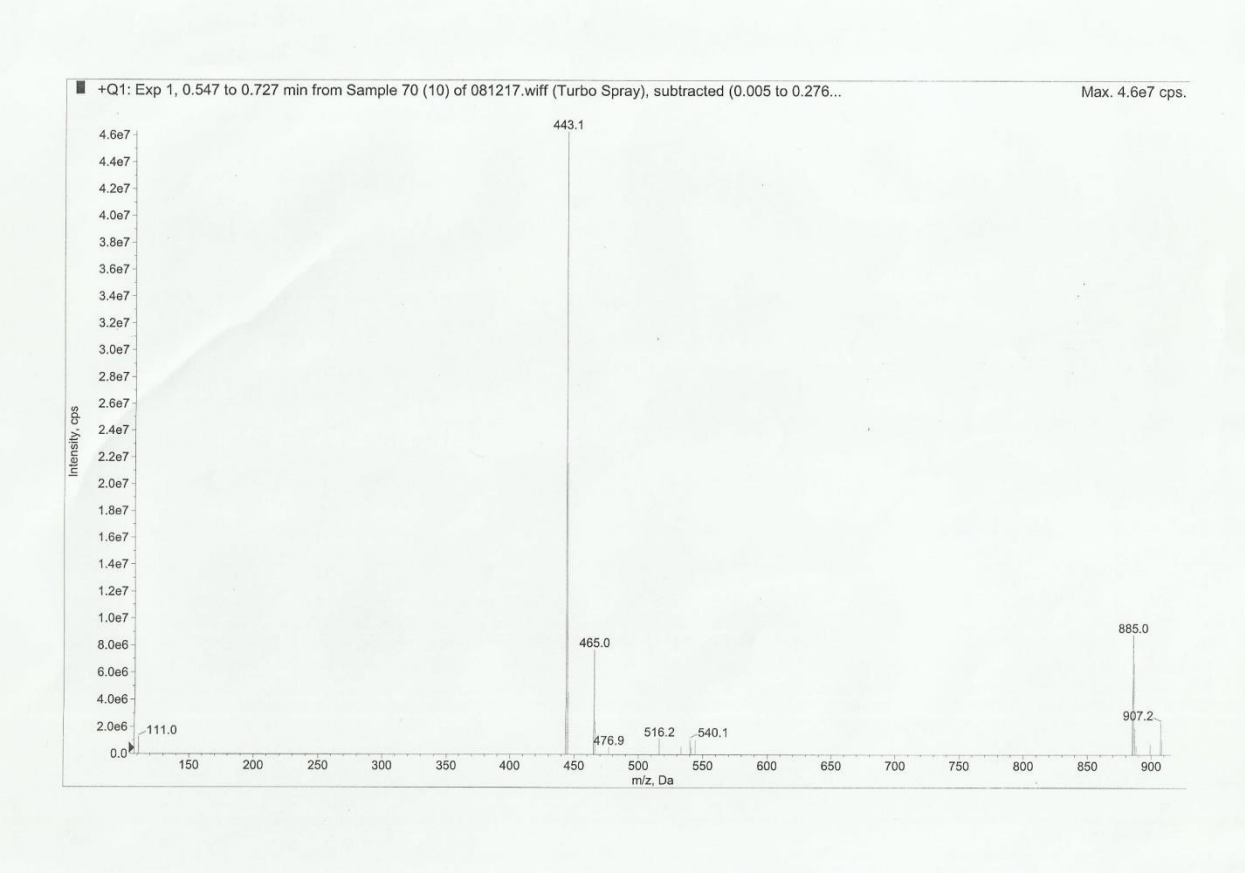
### 4.4.18 HRMS of Octyl-4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4i)



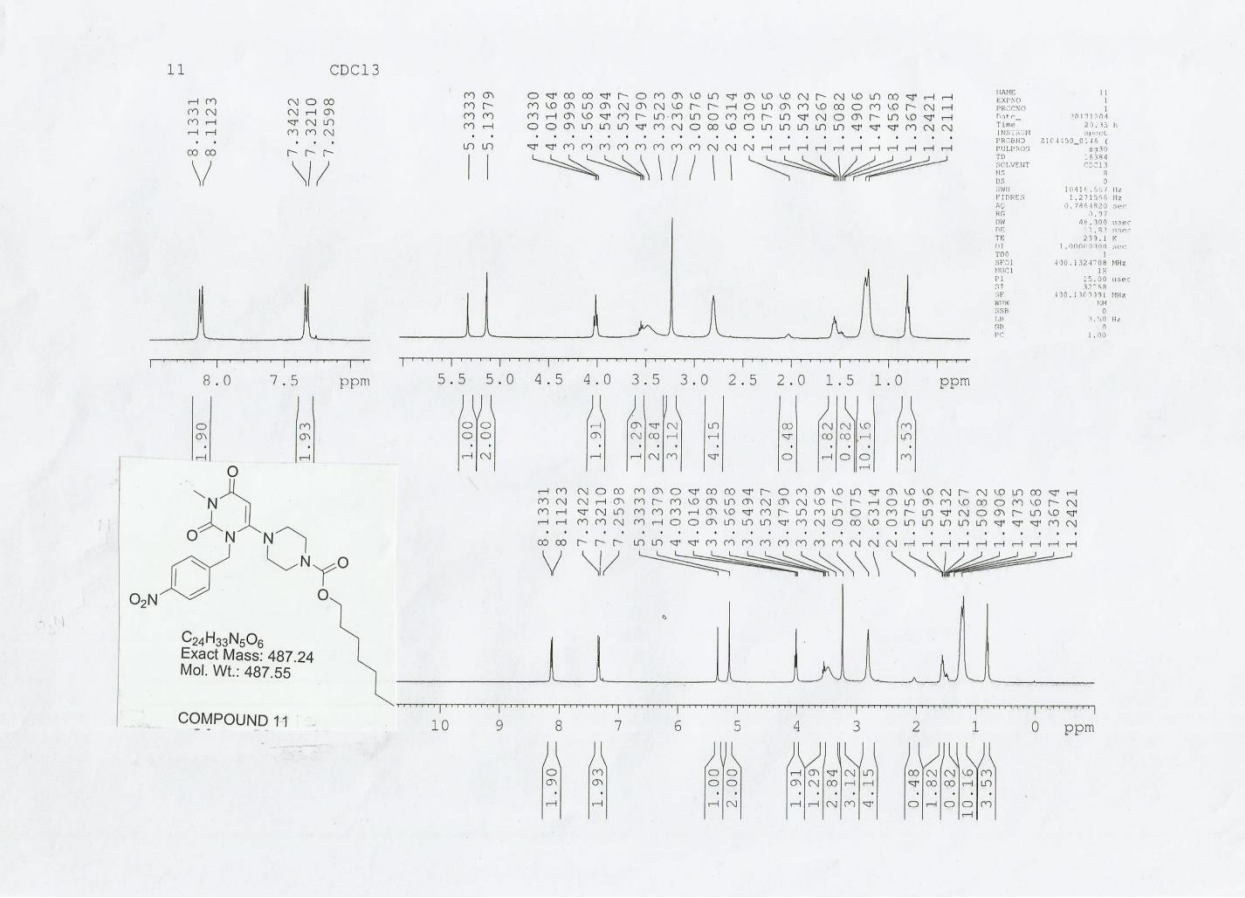
### 4.4.19 $H^1$ NMR Spectra of Heptyl-4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4j)



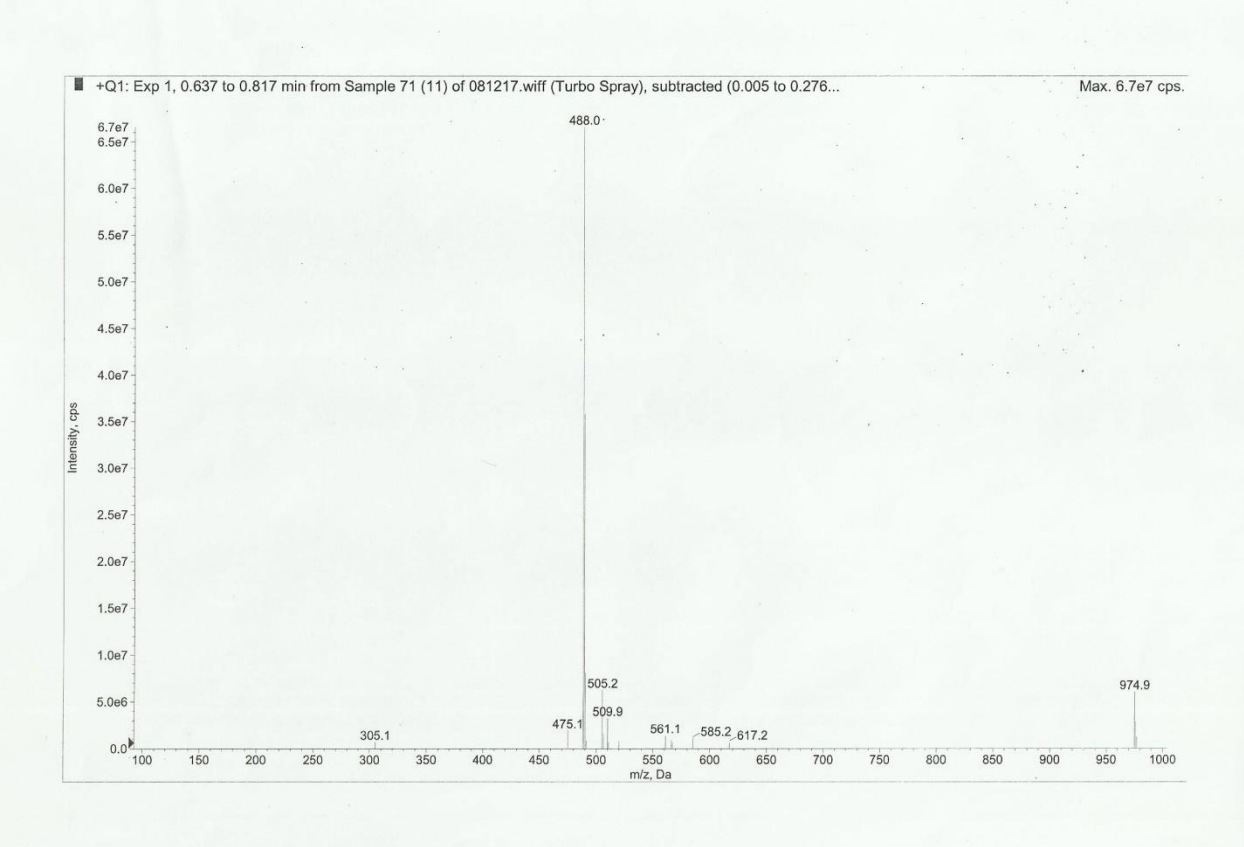
### 4.4.20 HRMS of Heptyl-4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4j)



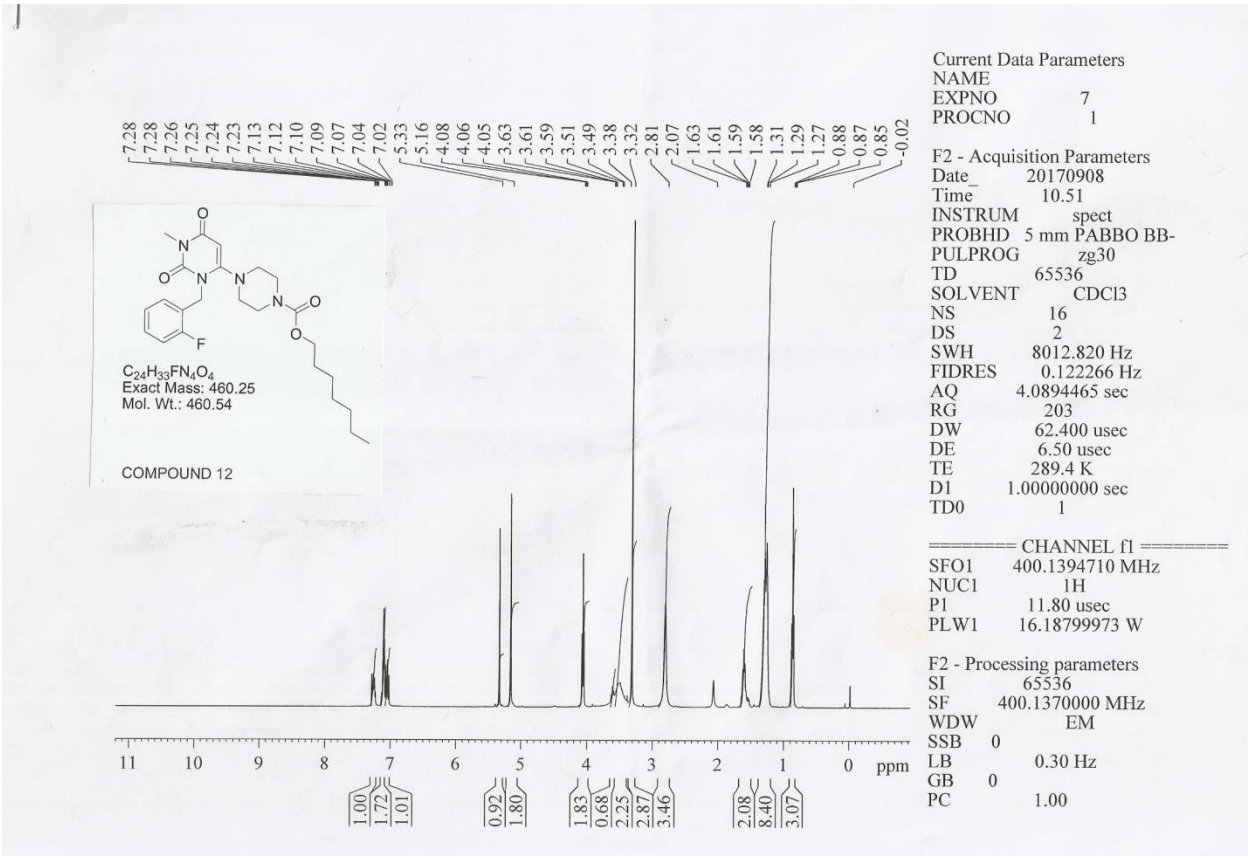
### 4.4.21 $H^1$ NMR Spectra of Heptyl 4-(3-(4-nitrobenzyl)-1,2,3,6-tetrahydro-1-methyl-2,6-dioxopyrimidin-4-yl)piperazine-1-carboxylateyl)piperazine-1-carboxylate (4k)



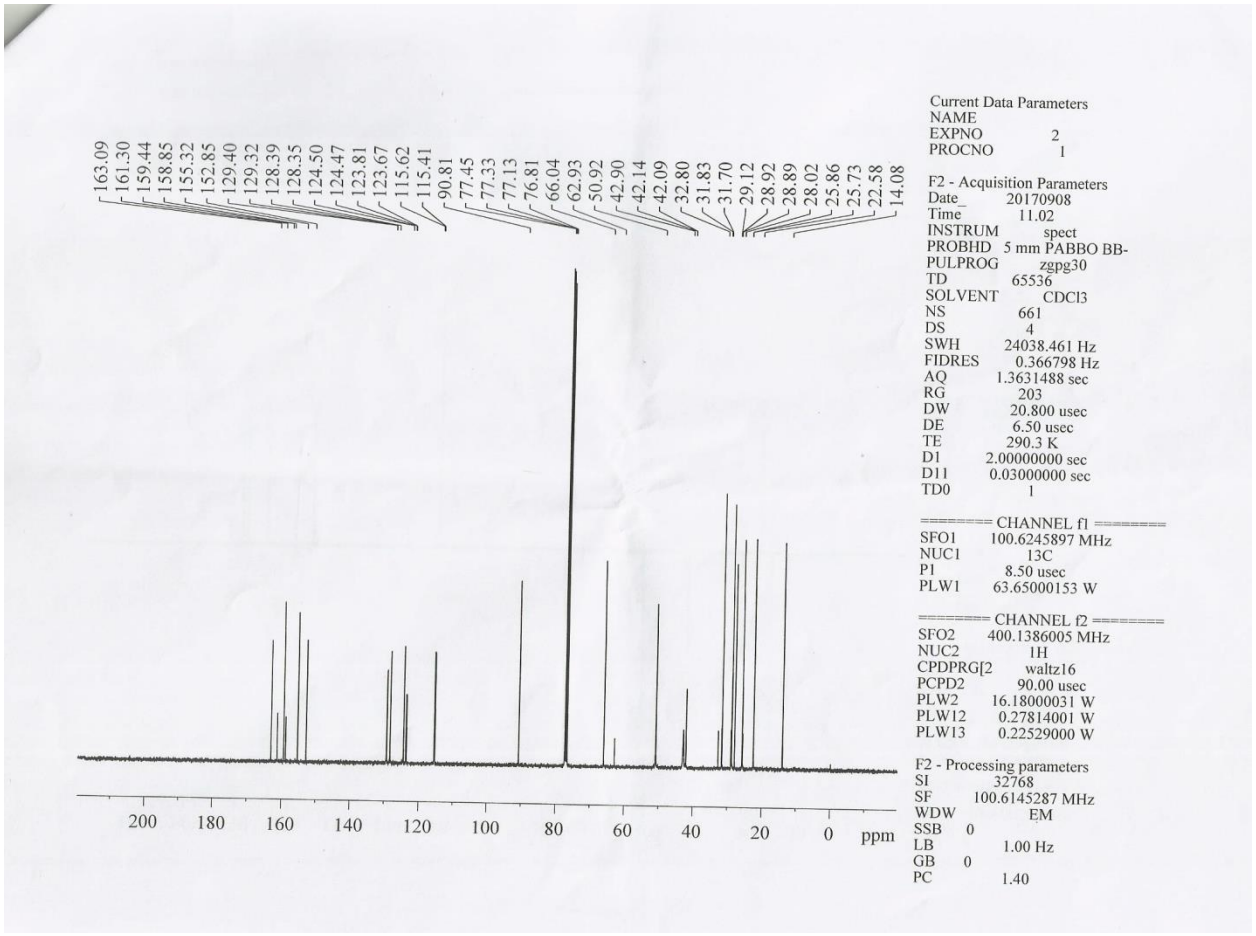
### 4.4.22 HRMS of Heptyl 4-(3-(4-nitrobenzyl)-1,2,3,6-tetrahydro-1-methyl-2,6-dioxopyrimidin-4-yl)piperazine-1-carboxylateyl)piperazine-1-carboxylate (4k)



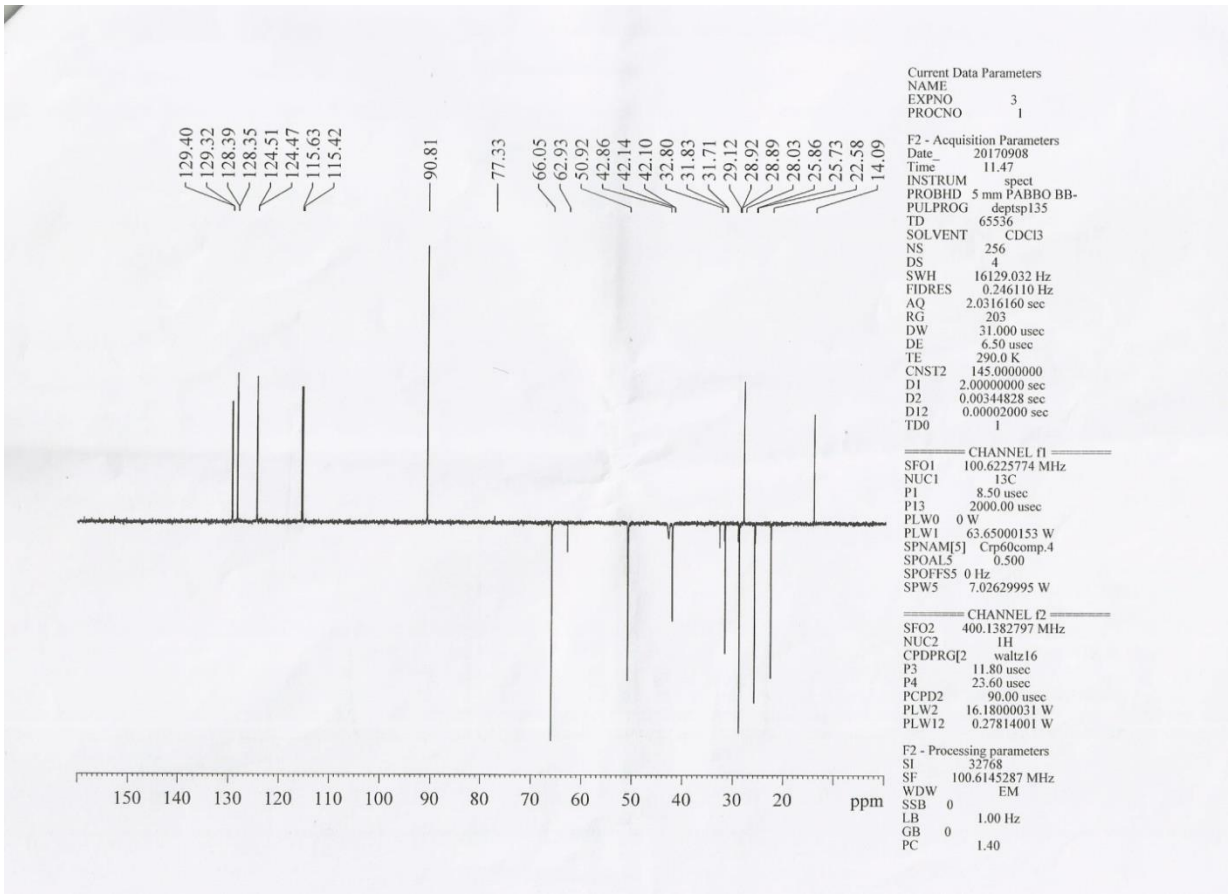
### 4.4.23 $^{1}$HNMR Spectra of Heptyl-4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4l)



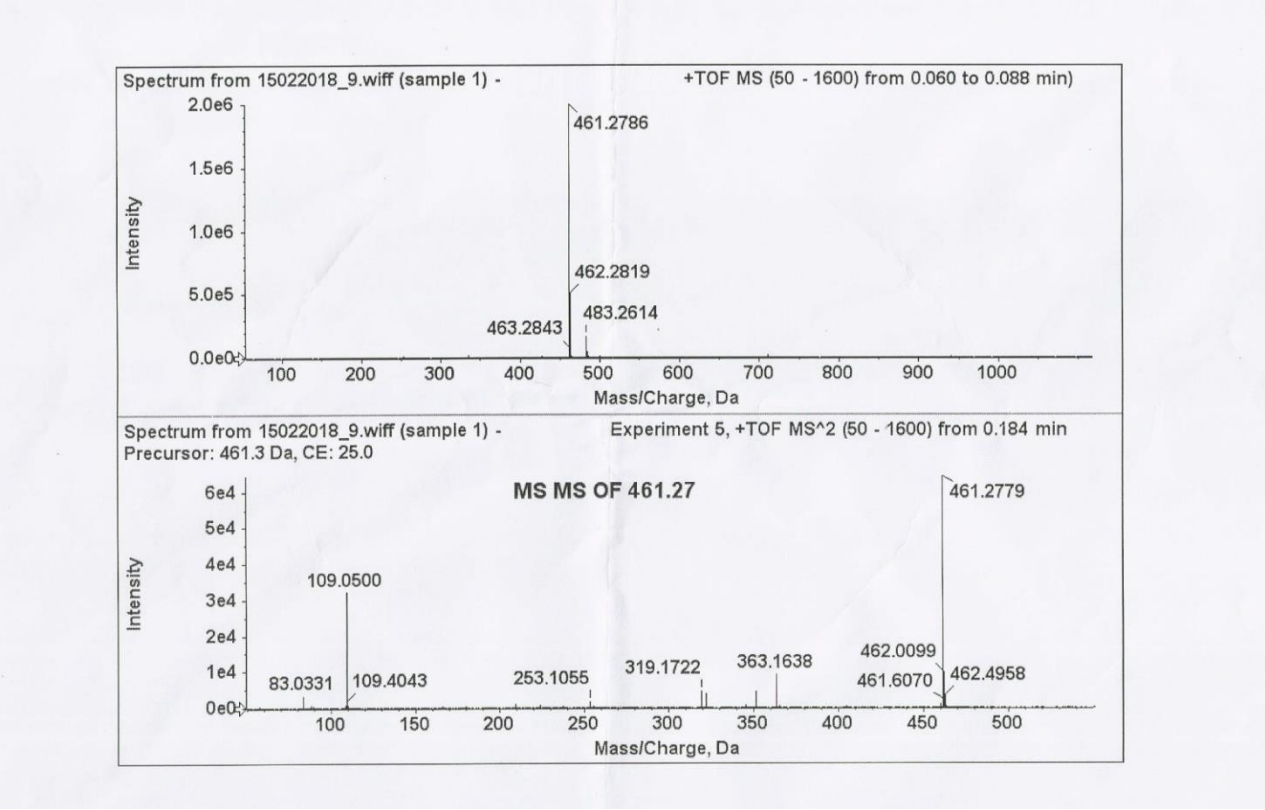
### 4.4.24 $^{13}$CNMR Spectra of Heptyl-4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4l)



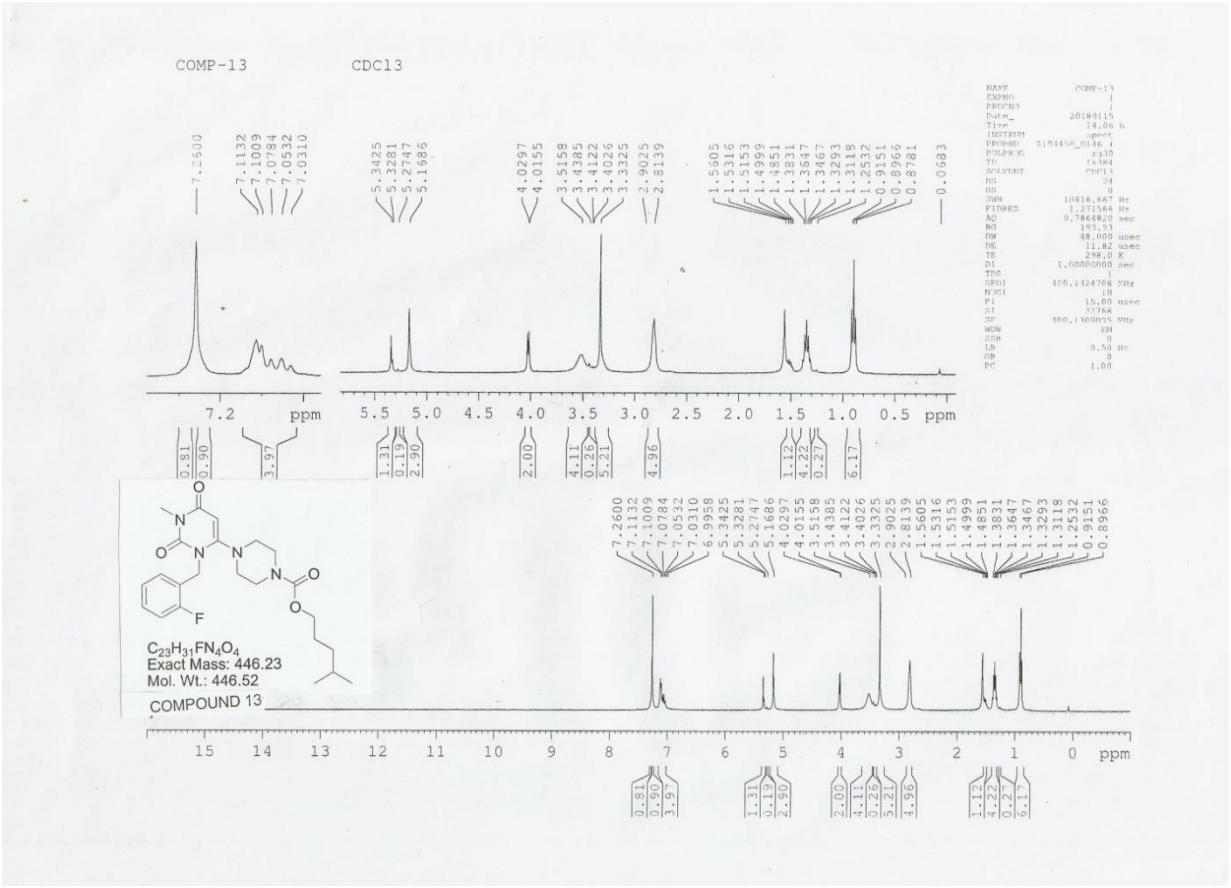
### 4.4.25 Dept NMR Spectra of Heptyl-4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4l)



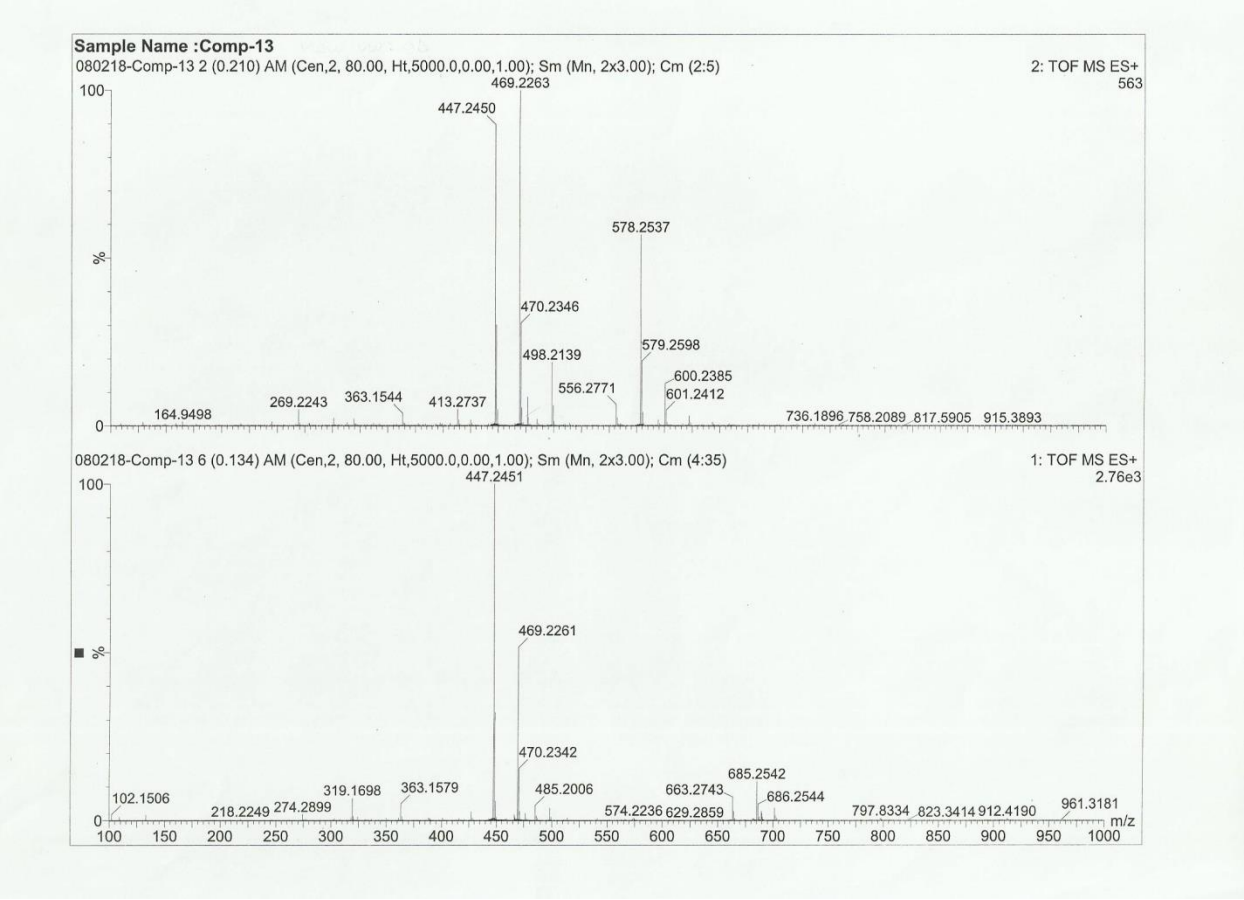
### 4.4.26 HRMS of Heptyl-4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4l)



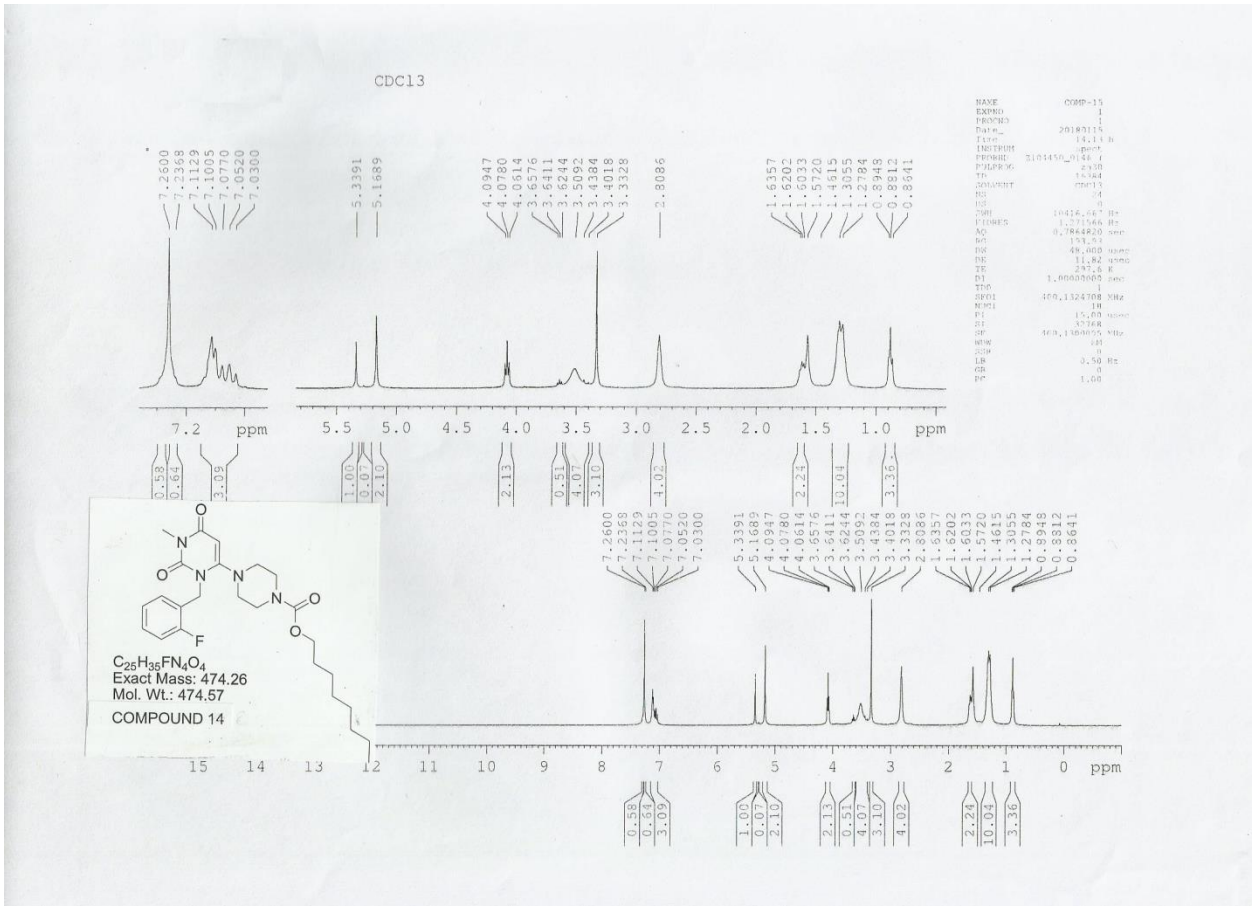
### 4.4.27 $H^1$ NMR Spectra of 2-ethylbutyl 4-(3-(2-fluorobenzyl)-1,2,3,6-tetrahydro-1-methyl-2,6-dioxopyrimidin-4-yl)piperazine-1-carboxylate (4m)



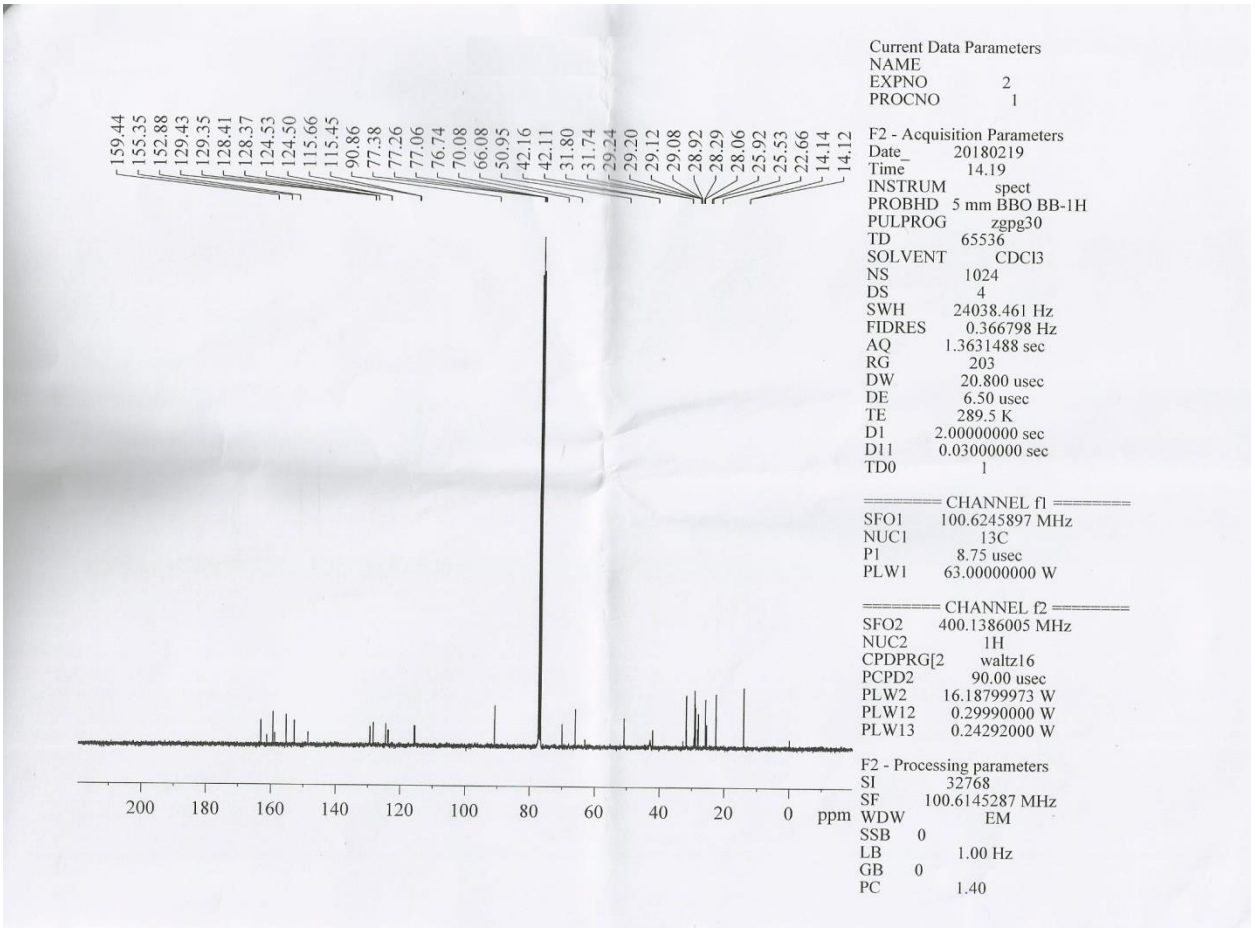
### 4.4.28 HRMS of 2-ethylbutyl 4-(3-(2-fluorobenzyl)-1,2,3,6-tetrahydro-1-methyl-2,6-dioxopyrimidin-4-yl)piperazine-1-carboxylate (4m)



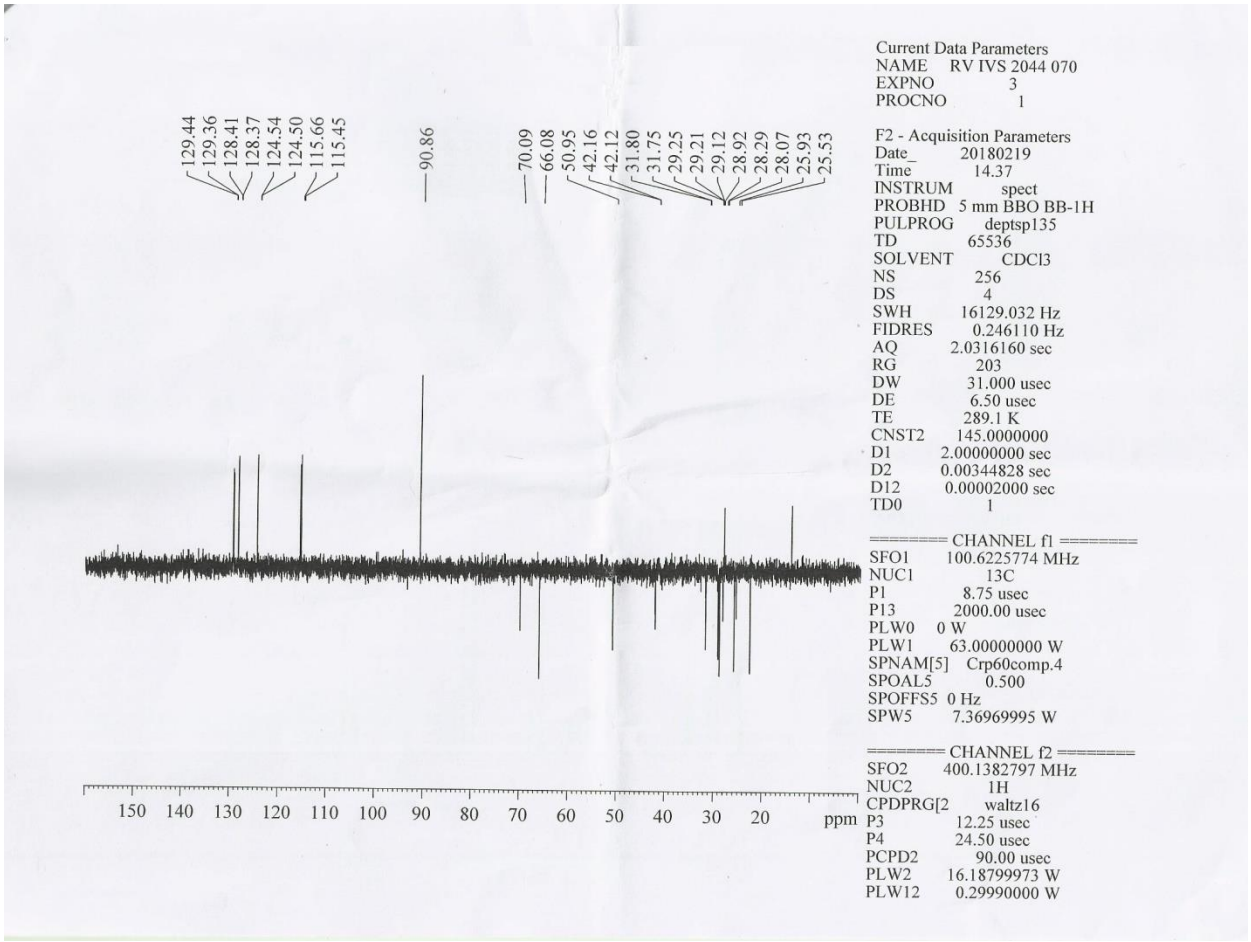
### 4.4.29 $H^1$ NMR Spectra of octyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4n)



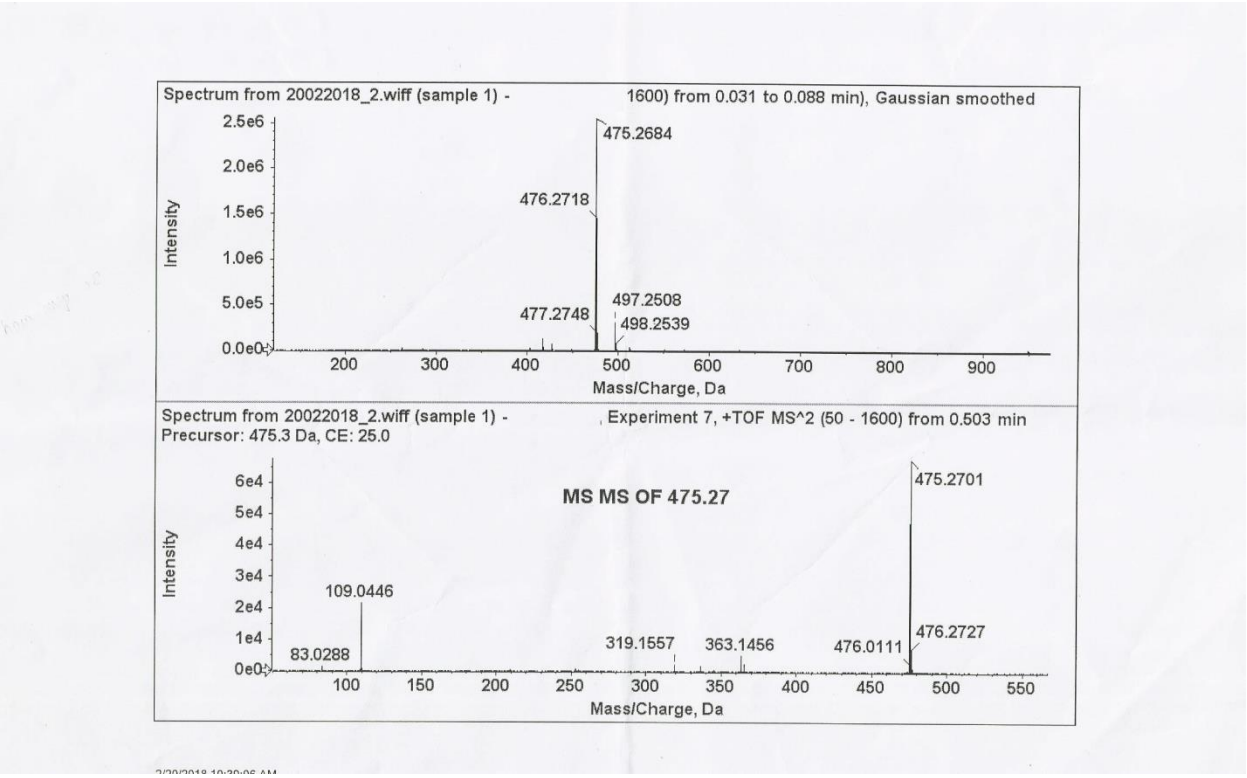
### 4.4.30 $^{13}$CNMR Spectra of octyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4n)



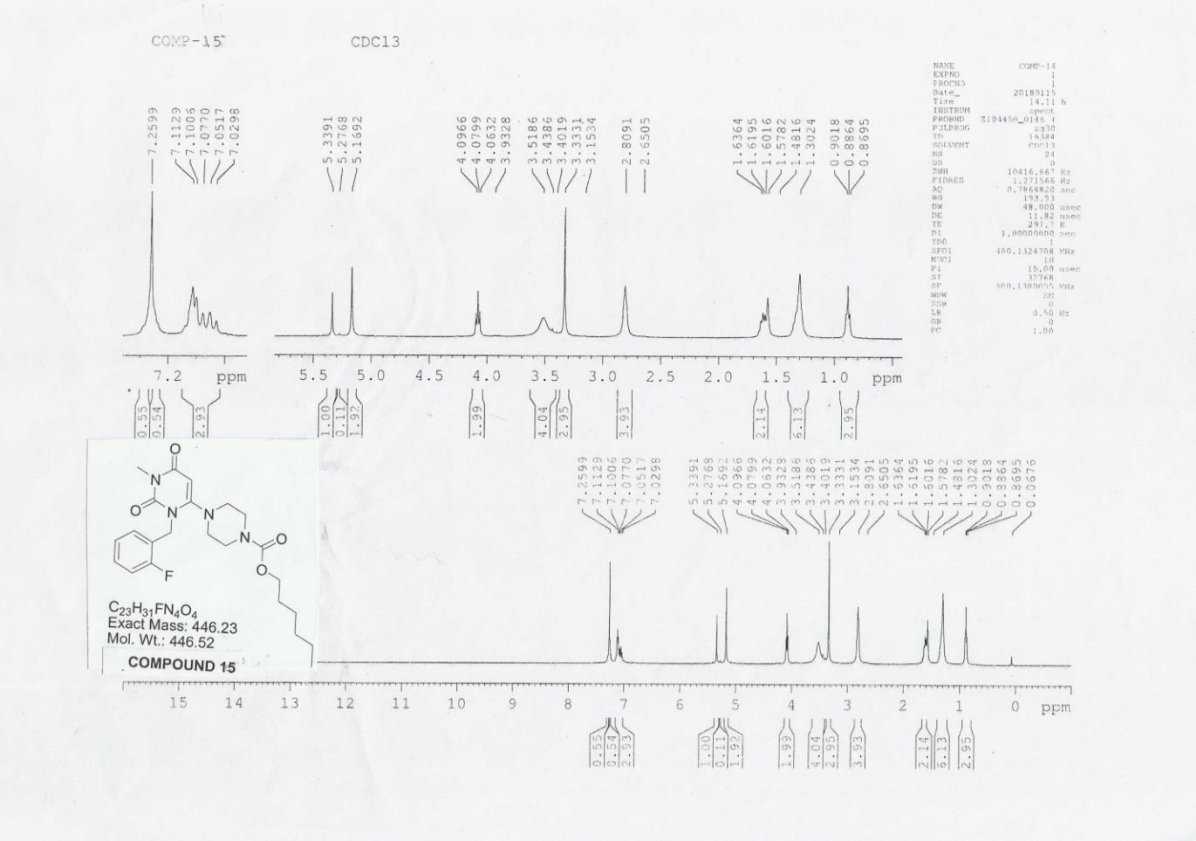
### 4.4.31 DeptNMR Spectra of octyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4n)



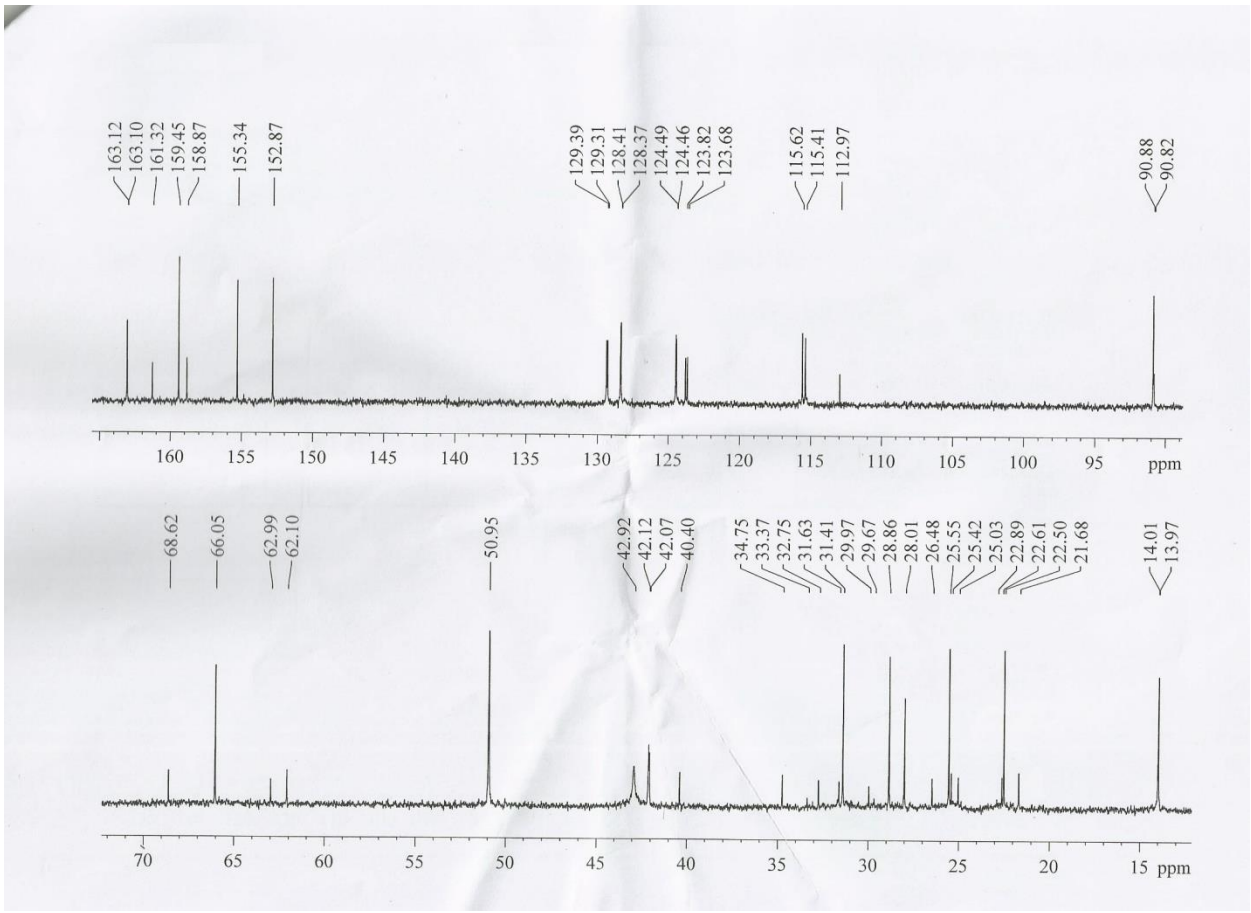
### 4.4.32 HRMS of octyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4n)



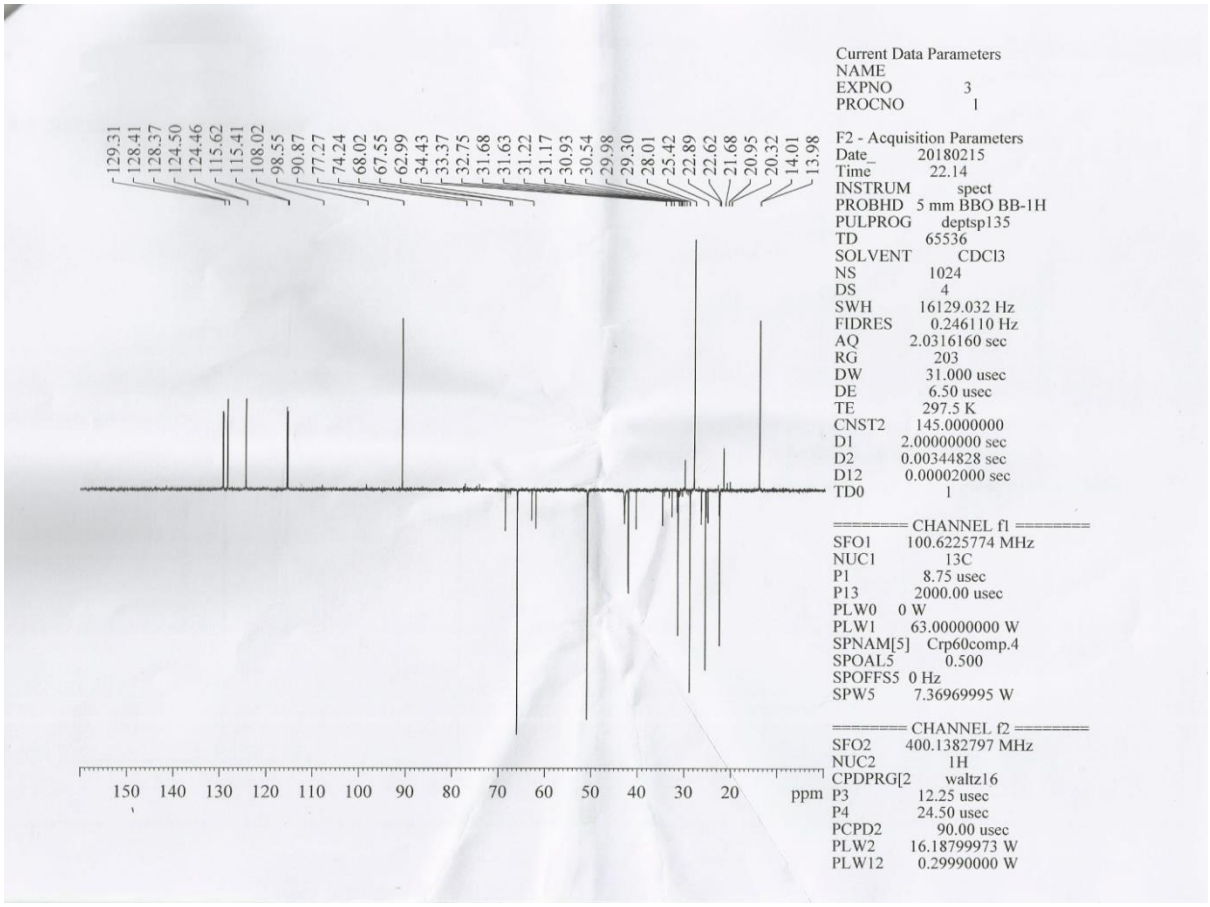
### 4.4.33 $H^1$ NMR Spectra of hexyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4o)



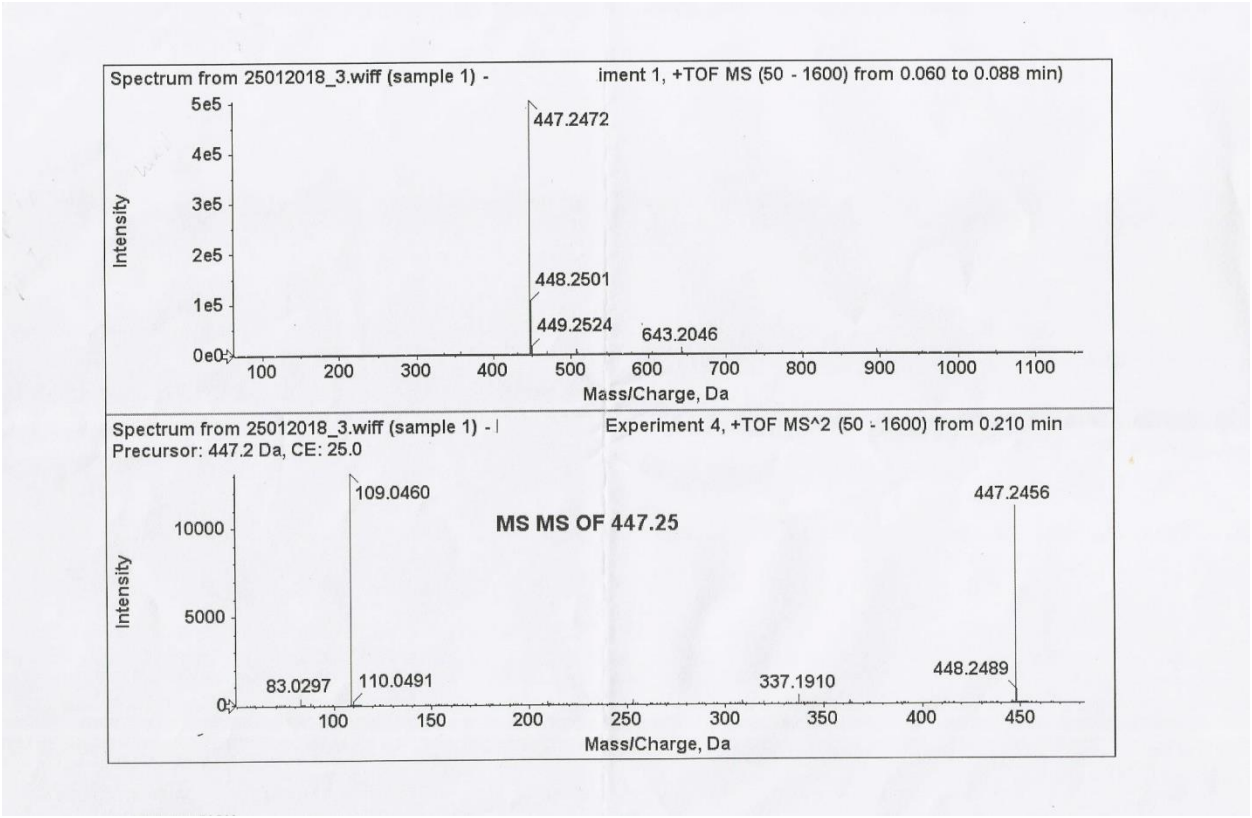
**4.4.34 13C NMR Spectra of hexyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4o)**



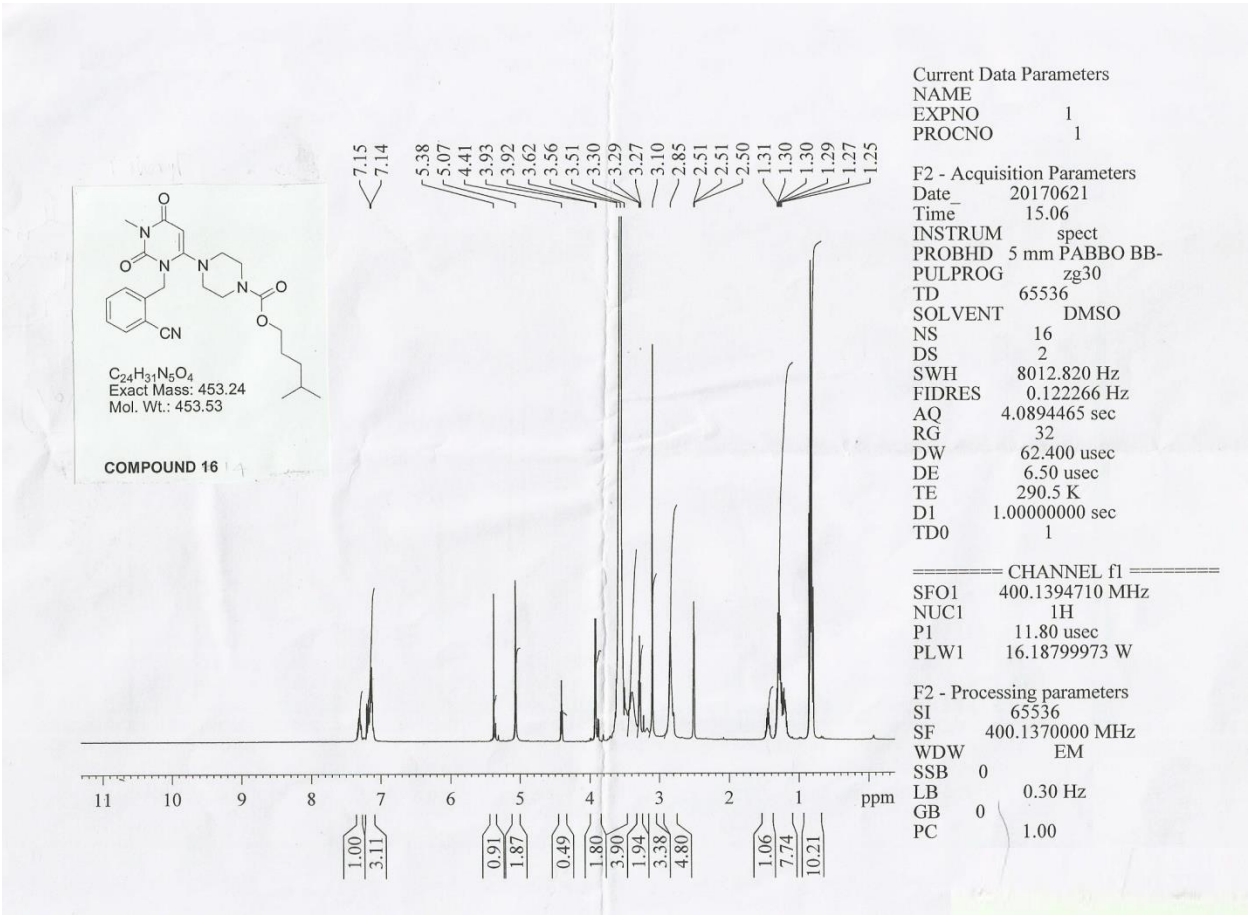
### 4.4.35 DeptNMR Spectra of hexyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4o)



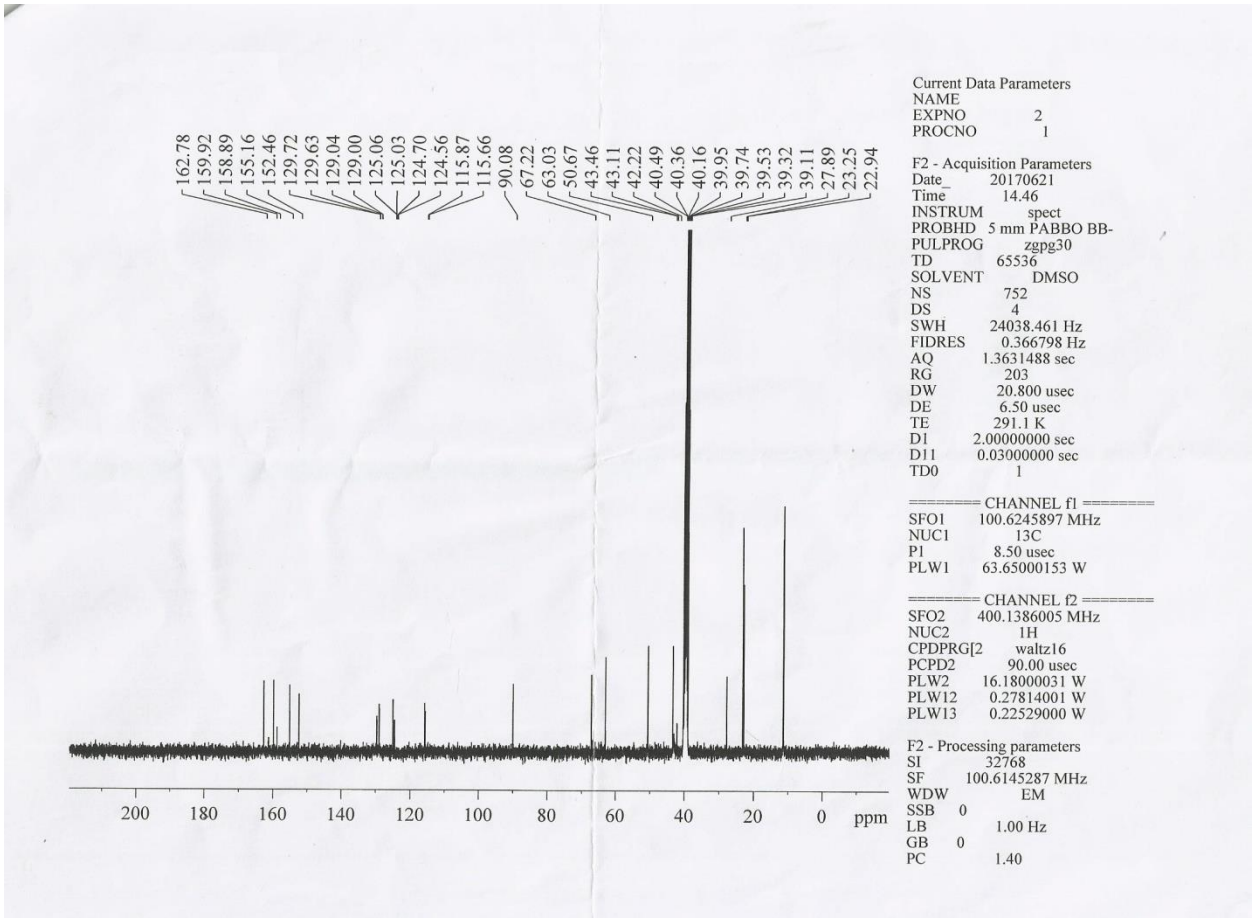
### 4.4.36 HRMS of hexyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4o)



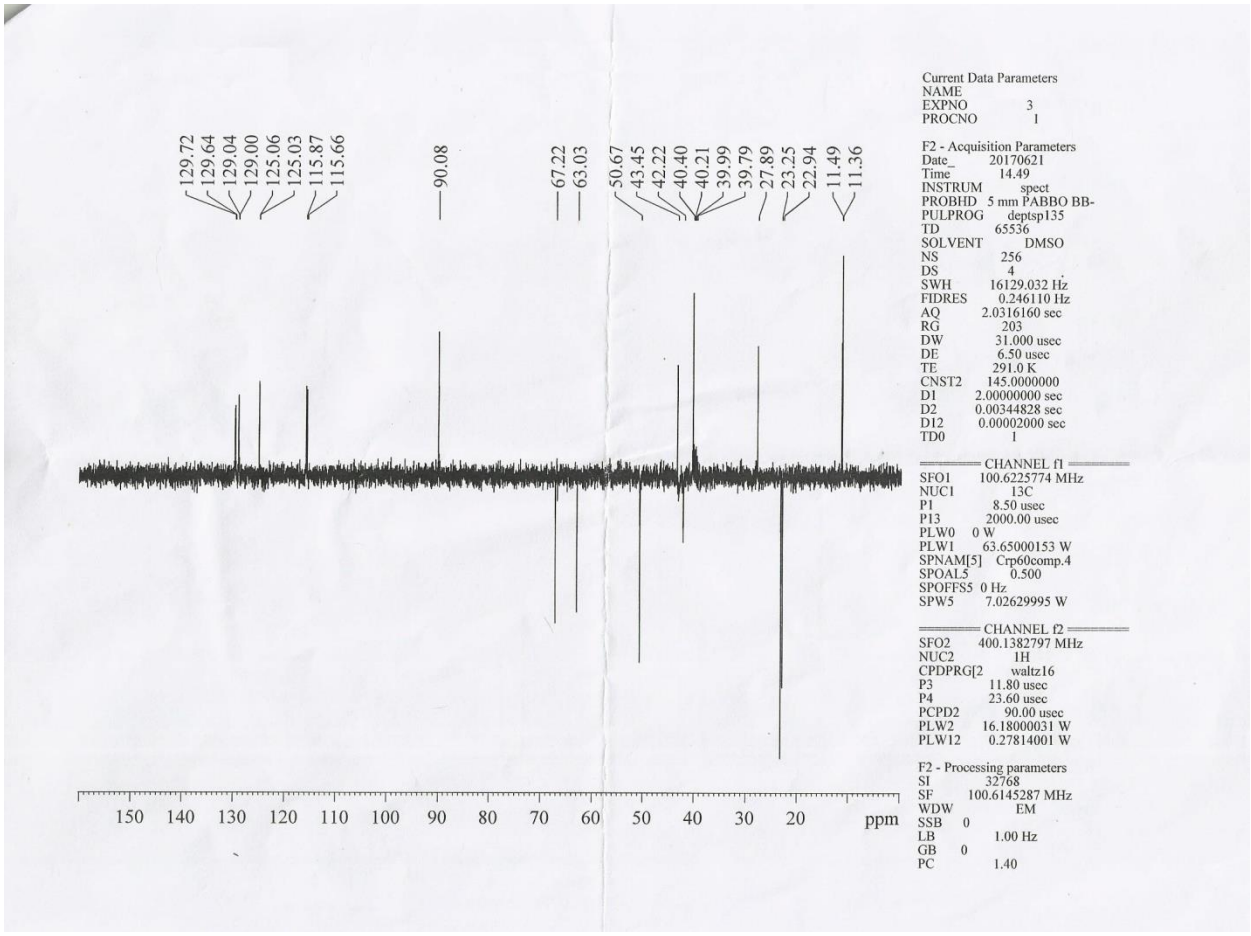
### 4.4.37 $H^1$ NMR Spectra of 4-methylpentyl-4-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4p)



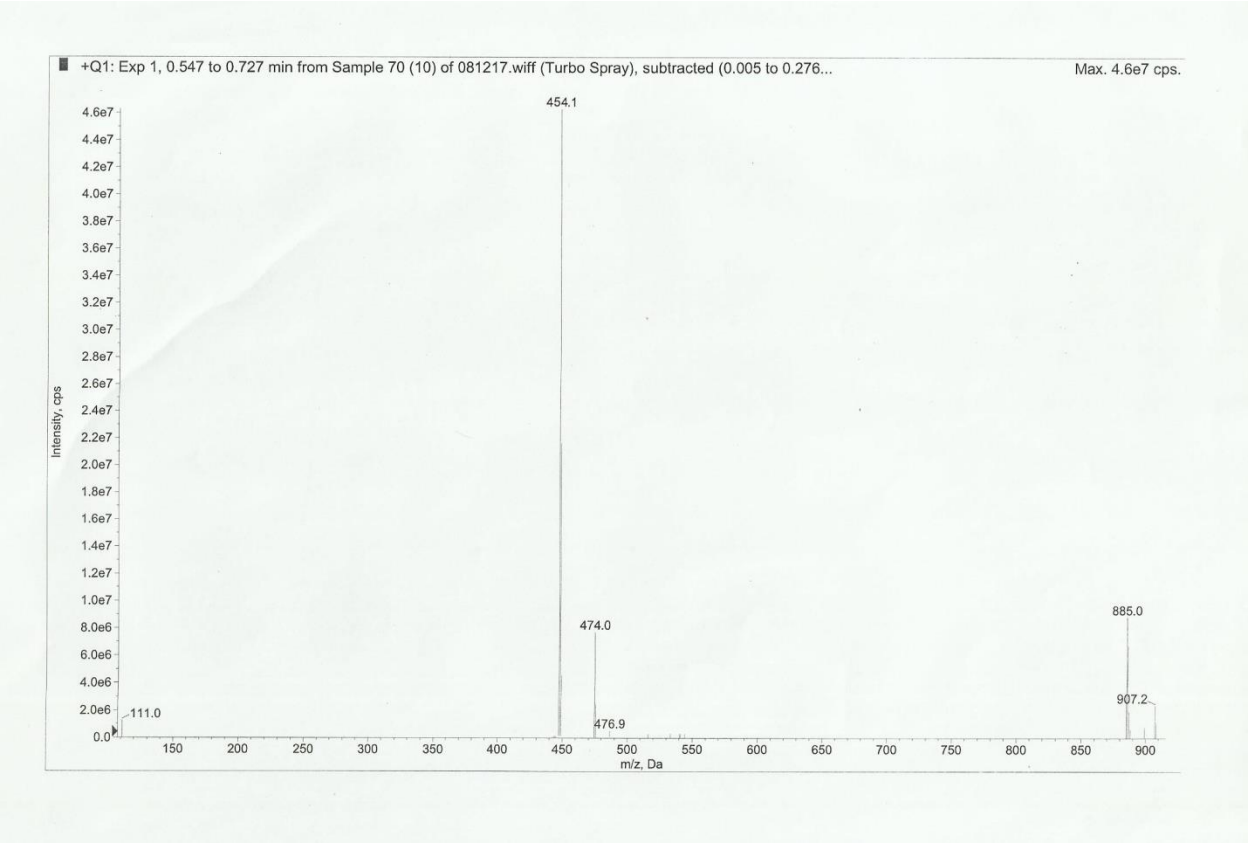
### 4.4.38 $^{13}$CNMR Spectra of 4-methylpentyl-4-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4p)



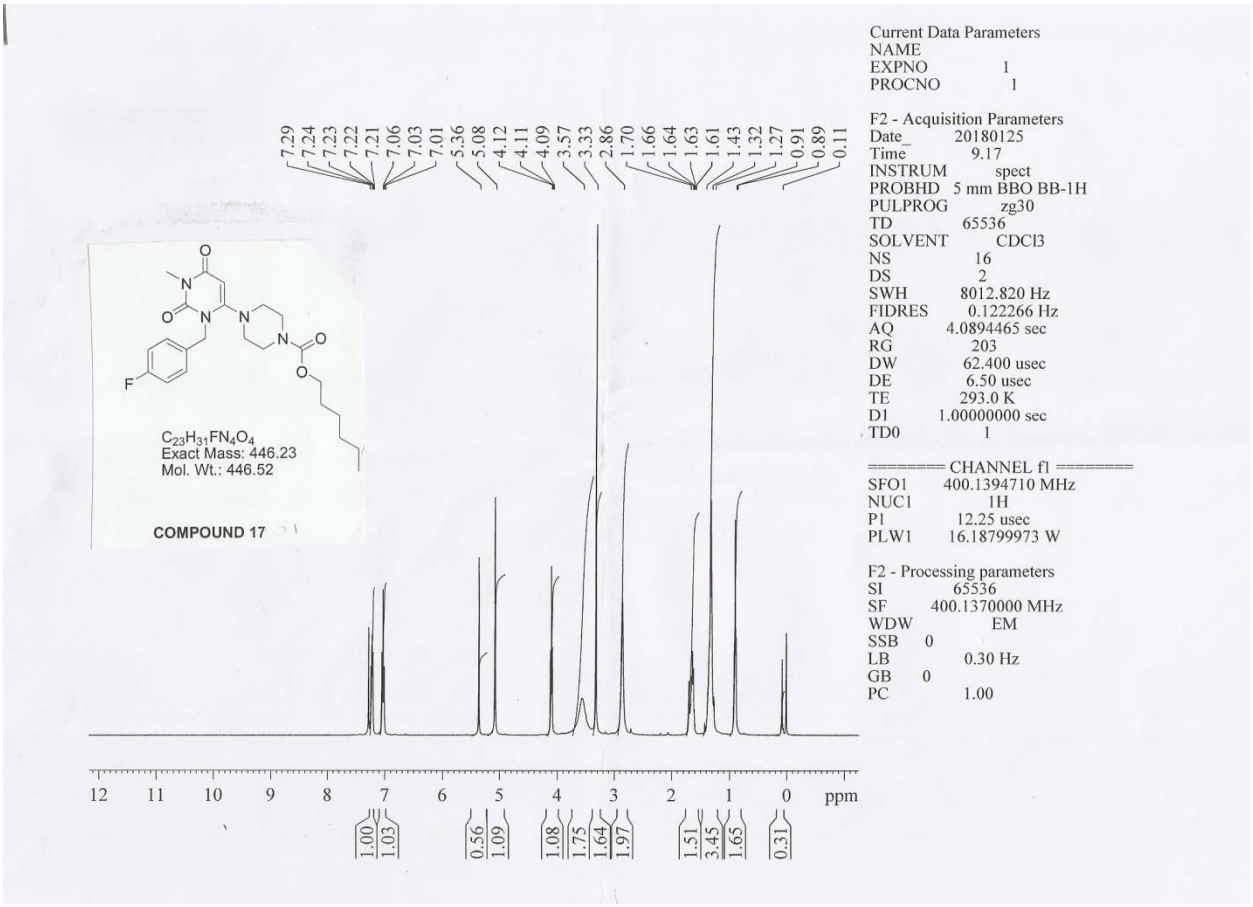
### 4.4.39 DeptNMR Spectra of 4-methylpentyl-4-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4p)



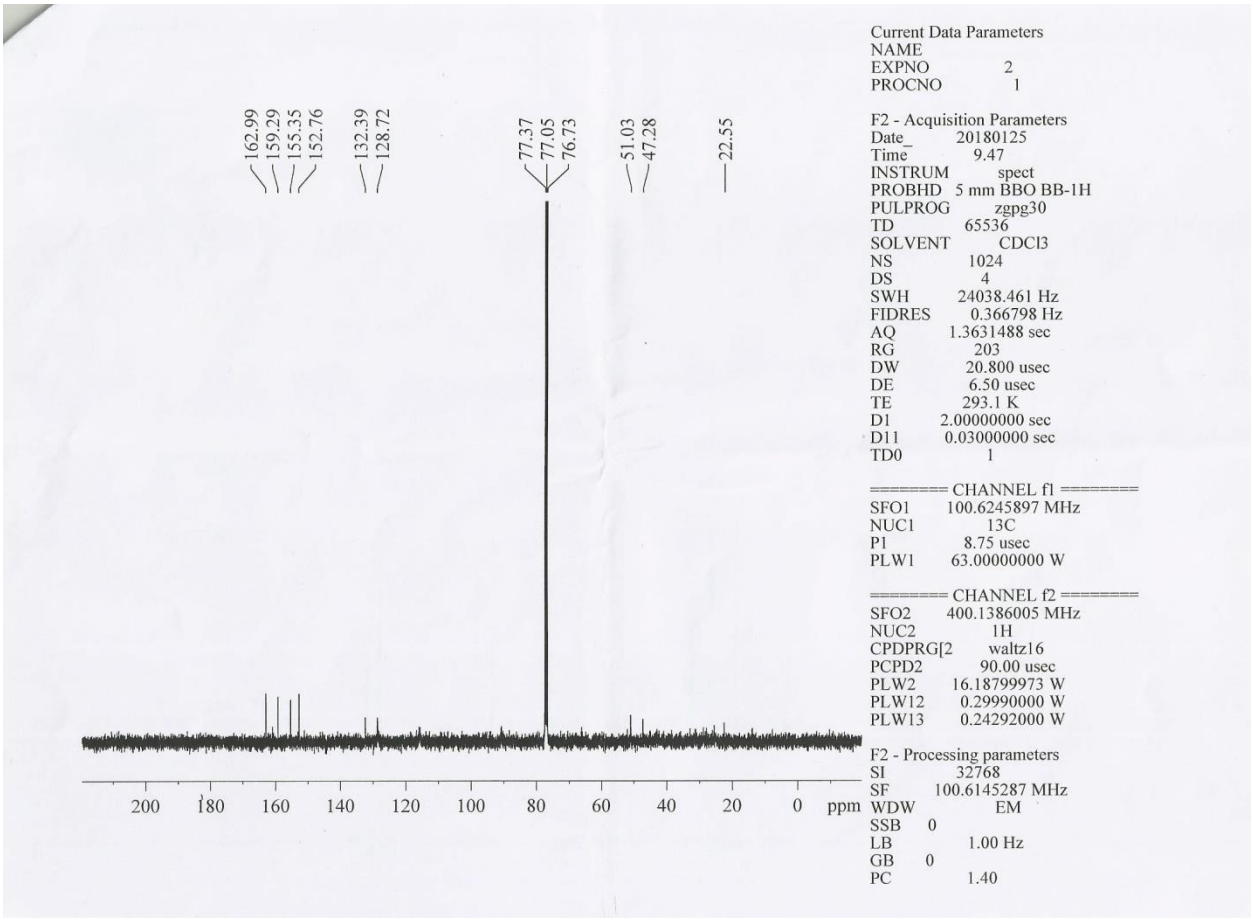
### 4.4.40 HRMS of 4-methylpentyl-4-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4p)



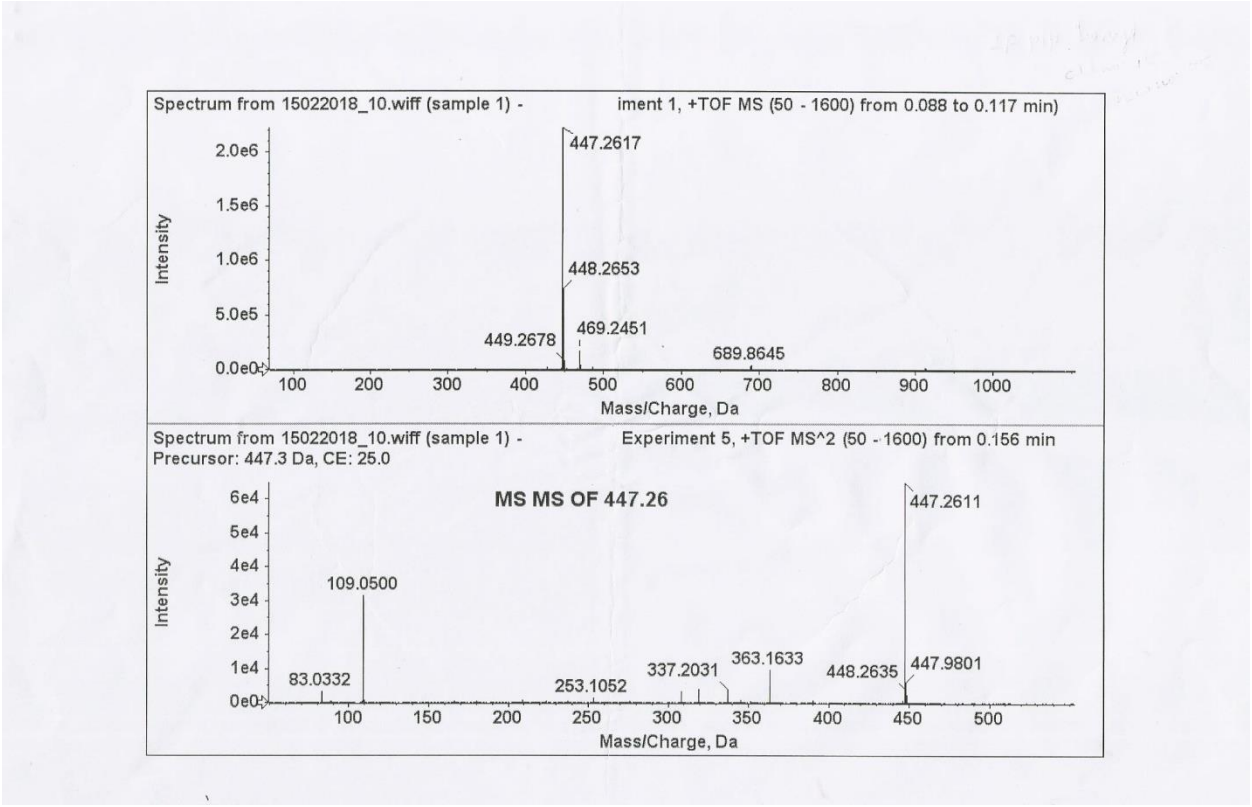
### 4.4.41 $H^1$ NMR Spectra of hexyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4q)



### 4.4.42 $^{13}$C NMR Spectra of hexyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4q)



### 4.4.43 HRMS of hexyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4q)



## 4.5 BIOLOGICAL POTENTIAL OF COMPOUNDS BY PASS PREDICTION:

Compounds 4a-4q shows tremendous activity in PASS prediction in various diseases, some of the important activities are listed below tables

### 4.5.1 heptyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4a):

Compound-**4a** shows some of the important activities like **Anti-infertility (**female), **Ophthalmic drug**, **Atherosclerosis treatment**, **Antidiabeticsymptomatic** and **Gastrointestinal disorders treatment.**

**Table: 4.1 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,779 | 0,003 | Histamine H1 receptor antagonist |
| 2 | 0,719 | 0,004 | Antihistaminic |
| 3 | 0,701 | 0,004 | Histamine antagonist |
| 4 | 0,442 | 0,012 | Antiinfertility, female |
| 5 | 0,501 | 0,130 | Nootropic |
| 6 | 0,418 | 0,057 | Anticonvulsant |
| 7 | 0,338 | 0,037 | Ophthalmic drug |
| 8 | 0,346 | 0,048 | Immunomodulator |
| 9 | 0,291 | 0,016 | Cyclic GMP phosphodiesterase inhibitor |
| 10 | 0,300 | 0,029 | Anti-Helicobacter pylori |
| 11 | 0,297 | 0,028 | Antieczematic atopic |
| 12 | 0,323 | 0,067 | H+-transporting two-sector ATPase inhibitor |
| 13 | 0,318 | 0,099 | Antipruritic |
| 14 | 0,236 | 0,028 | Antiglaucomic |
| 15 | 0,292 | 0,084 | Atherosclerosis treatment |
| 16 | 0,266 | 0,074 | Antiischemic |
| 17 | 0,255 | 0,071 | Antidiabetic symptomatic |
| 18 | 0,197 | 0,018 | Gastrointestinal disorders treatment |

| | | | |
|---|---|---|---|
| 19 | 0,380 | 0,202 | Antiischemic, cerebral |
| 20 | 0,264 | 0,085 | Antiparkinsonian |
| 21 | 0,298 | 0,129 | Analgesic |
| 22 | 0,246 | 0,111 | Antihypertensive |
| 23 | 0,286 | 0,193 | Antianginal |
| 24 | 0,206 | 0,142 | Alzheimer's disease treatment |
| 25 | 0,140 | 0,116 | Antiparkinsonian, tremor relieving |
| 26 | 0,118 | 0,108 | CNS active muscle relaxant |

### 4.5.2 Octyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4b):

Compound-**4b** shows some of the important activities like **Antihistaminic, Anti-infertility (**female), **Ophthalmic drug**, **Antiparkinsonian, Gastrointestinal disorders treatment**, **Antihypertensive** and **Alzheimer's disease treatment.**

**Table: 4.2 PASS Pridiction date**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,779 | 0,003 | Histamine H1 receptor antagonist |
| 2 | 0,719 | 0,004 | Antihistaminic |
| 3 | 0,701 | 0,004 | Histamine antagonist |
| 4 | 0,442 | 0,012 | Antiinfertility, female |
| 5 | 0,338 | 0,037 | Ophthalmic drug |
| 6 | 0,228 | 0,040 | Diabetic nephropathy treatment |
| 7 | 0,255 | 0,071 | Antidiabetic symptomatic |
| 8 | 0,197 | 0,018 | Gastrointestinal disorders treatment |
| 9 | 0,264 | 0,085 | Antiparkinsonian |
| 10 | 0,298 | 0,129 | Analgesic |
| 11 | 0,246 | 0,111 | Antihypertensive |
| 12 | 0,170 | 0,076 | Alkylglycerone-phosphate synthase inhibitor |
| 13 | 0,286 | 0,193 | Antianginal |

| | | | |
|---|---|---|---|
| 14 | 0,277 | 0,209 | Leukopoiesis stimulant |
| 15 | 0,206 | 0,142 | Alzheimer's disease treatment |
| 16 | 0,227 | 0,164 | Analgesic, non-opioid |
| 17 | 0,200 | 0,149 | Angiogenesis stimulant |
| 18 | 0,179 | 0,134 | Muscle relaxant |
| 19 | 0,129 | 0,084 | Narcolepsy treatment |
| 20 | 0,140 | 0,116 | Antiparkinsonian, tremor relieving |
| 21 | 0,019 | 0,009 | Phosphodiesterase 6A inhibitor |

### 4.5.3 hexyl 4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4c):

Compound-**4c** shows some of the important activities like **Antihistaminic, Anti-infertility (**female), **Anticonvulsant**, **Antiparkinsonian, Antineoplastic (pancreatic cancer)** and **Antihypertensive**.

**Table: 4.3 PASS Pridiction date**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,653 | 0,004 | Antihistaminic |
| 2 | 0,639 | 0,004 | Histamine antagonist |
| 3 | 0,424 | 0,014 | Antiinfertility, female |
| 4 | 0,394 | 0,066 | Anticonvulsant |
| 5 | 0,405 | 0,082 | Antianginal |
| 6 | 0,354 | 0,055 | Antihypertensive |
| 7 | 0,307 | 0,048 | Antiischemic |
| 8 | 0,233 | 0,058 | Antiparkinsonian, tremor relieving |
| 9 | 0,234 | 0,088 | Angiogenesis stimulant |
| 10 | 0,222 | 0,078 | Ceramide glucosyltransferase inhibitor |
| 11 | 0,192 | 0,049 | GST M1-1 substrate |
| 12 | 0,230 | 0,094 | Antidiabetic symptomatic |
| 13 | 0,224 | 0,110 | Antiparkinsonian, rigidity relieving |

| | | | |
|---|---|---|---|
| 14 | 0,204 | 0,155 | Antiparkinsonian |
| 15 | 0,230 | 0,204 | DNA polymerase I inhibitor |
| 16 | 0,073 | 0,048 | Phosphodiesterase II inhibitor |
| 17 | 0,123 | 0,098 | Phenylacetate-CoA ligase inhibitor |
| 18 | 0,259 | 0,236 | Leukopoiesis stimulant |
| 19 | 0,198 | 0,175 | D-lactaldehyde dehydrogenase inhibitor |
| 20 | 0,030 | 0,007 | Toll-Like receptor 7 agonist |
| 21 | 0,180 | 0,161 | Skeletal muscle relaxant |
| 22 | 0,023 | 0,005 | DNA polymerase III inhibitor |
| 23 | 0,180 | 0,163 | Macrophage stimulant |
| 24 | 0,053 | 0,038 | Angiotensin antagonist |
| 25 | 0,039 | 0,024 | Dipeptidyl peptidase IV inhibitor |
| 26 | 0,198 | 0,193 | Antineoplastic (pancreatic cancer) |

### 4.5.4 Octyl 4-(3-(4-nitrobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4d):

Compound-**4d** shows some of the important activities like **Antihistaminic, Anti-infertility (**female), **Antiviral (Picornavirus)**, **Analeptic , Antineoplastic (pancreatic cancer)** and **Antidiabetic symptomatic**.

**Table: 4.4 PASS Pridiction date**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,653 | 0,004 | Antihistaminic |
| 2 | 0,639 | 0,004 | Histamine antagonist |
| 3 | 0,424 | 0,014 | Antiinfertility, female |
| 4 | 0,394 | 0,066 | Anticonvulsant |
| 5 | 0,405 | 0,082 | Antianginal |
| 6 | 0,354 | 0,055 | Antihypertensive |
| 7 | 0,389 | 0,119 | Antiviral (Picornavirus) |
| 8 | 0,307 | 0,048 | Antiischemic |

| | | | |
|---|---|---|---|
| 9 | 0,233 | 0,058 | Antiparkinsonian, tremor relieving |
| 10 | 0,230 | 0,094 | Antidiabetic symptomatic |
| 11 | 0,224 | 0,110 | Antiparkinsonian, rigidity relieving |
| 12 | 0,204 | 0,155 | Antiparkinsonian |
| 13 | 0,202 | 0,171 | Analeptic |
| 14 | 0,052 | 0,038 | Angiotensin II receptor antagonist |
| 15 | 0,198 | 0,193 | Antineoplastic (pancreatic cancer) |

### 4.5.5 Octyl-4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4e):

Compound-**4e** shows some of the important activities like **Antihistaminic, Anticonvulsant, Anti-infertility (**female), **Ophthalmic drug, Antineoplastic (bone cancer)**, **Atherosclerosis treatment, Antineoplastic (bone cancer)** and **Antiparkinsonian.**

**Table: 4.5 PASS Pridiction date**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,734 | 0,004 | Antihistaminic |
| 2 | 0,727 | 0,003 | Histamine antagonist |
| 3 | 0,641 | 0,003 | Histamine H1 receptor antagonist |
| 4 | 0,462 | 0,044 | Anticonvulsant |
| 5 | 0,414 | 0,016 | Antiinfertility, female |
| 6 | 0,314 | 0,032 | Antidiabetic symptomatic |
| 7 | 0,323 | 0,042 | Ophthalmic drug |
| 8 | 0,244 | 0,025 | Diabetic nephropathy treatment |
| 9 | 0,221 | 0,099 | HERG 1 channel blocker |
| 10 | 0,221 | 0,117 | Antiischemic |
| 11 | 0,213 | 0,114 | Antineoplastic (bone cancer) |
| 12 | 0,217 | 0,135 | Antihypertensive |
| 13 | 0,215 | 0,139 | Antiparkinsonian |

| | | | |
|---|---|---|---|
| 14 | 0,215 | 0,151 | Atherosclerosis treatment |
| 15 | 0,226 | 0,186 | Antihelmintic (Nematodes) |
| 16 | 0,203 | 0,166 | Cardiotonic |
| 17 | 0,204 | 0,171 | Antiviral (CMV) |
| 18 | 0,053 | 0,031 | Kinesin-like protein 1 inhibitor |
| 19 | 0,232 | 0,211 | Neurodegenerative diseases treatment |
| 20 | 0,025 | 0,004 | DNA polymerase III inhibitor |
| 21 | 0,040 | 0,022 | Dipeptidyl peptidase IV inhibitor |

### 4.5.6 Heptyl-4-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4f):

Compound-**4f** shows some of the important activities like **Antihistaminic, Anticonvulsant, Anti-infertility (**female), **Ophthalmic drug, Kidney function stimulant, Antiviral (CMV), Cardiotonic, Gastroesophageal reflux disease treatment** and **Antiparkinsonian.**

**Table: 4.6 PASS Pridiction date**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,734 | 0,004 | Antihistaminic |
| 2 | 0,727 | 0,003 | Histamine antagonist |
| 3 | 0,641 | 0,003 | Histamine H1 receptor antagonist |
| 4 | 0,462 | 0,044 | Anticonvulsant |
| 5 | 0,414 | 0,016 | Antiinfertility, female |
| 6 | 0,314 | 0,032 | Antidiabetic symptomatic |
| 7 | 0,323 | 0,042 | Ophthalmic drug |
| 8 | 0,380 | 0,184 | Kidney function stimulant |
| 9 | 0,221 | 0,117 | Antiischemic |
| 10 | 0,125 | 0,022 | Gastroesophageal reflux disease treatment |
| 11 | 0,121 | 0,028 | Leukocyte elastase inhibitor |
| 12 | 0,217 | 0,135 | Antihypertensive |

| | | | |
|---|---|---|---|
| 13 | 0,215 | 0,139 | Antiparkinsonian |
| 14 | 0,203 | 0,166 | Cardiotonic |
| 15 | 0,204 | 0,171 | Antiviral (CMV) |
| 16 | 0,232 | 0,211 | Neurodegenerative diseases treatment |
| 17 | 0,165 | 0,151 | Muscle relaxant |

### 4.5.7 Octyl 1-(3-(4-bromobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-3-ylcarbamate (4g):

Compound-**4g** shows some of the important activities like **Antihistaminic, Cardiotonic, Antineoplastic enhancer**, **Cardiotonic, Antineoplastic (bone cancer), Antiviral, Gastrointestinal disorders treatment** and **Antihypertensive.**

**Table: 4.7 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,756 | 0,003 | Histamine antagonist |
| 2 | 0,752 | 0,004 | Antihistaminic |
| 3 | 0,465 | 0,019 | Muscle relaxant |
| 4 | 0,413 | 0,027 | Skeletal muscle relaxant |
| 5 | 0,395 | 0,066 | Anticonvulsant |
| 6 | 0,305 | 0,024 | Antieczematic atopic |
| 7 | 0,216 | 0,014 | Gastrointestinal disorders treatment |
| 8 | 0,159 | 0,034 | Dihydropyrimidine dehydrogenase inhibitor |
| 9 | 0,244 | 0,121 | Cardiotonic |
| 10 | 0,219 | 0,104 | Antidiabetic symptomatic |
| 11 | 0,241 | 0,171 | Antihelmintic (Nematodes) |
| 12 | 0,053 | 0,009 | Dipeptidyl peptidase IV inhibitor |
| 13 | 0,173 | 0,135 | Antineoplastic enhancer |
| 14 | 0,166 | 0,139 | Antiviral |
| 15 | 0,194 | 0,174 | Antineoplastic (bone cancer) |
| 16 | 0,091 | 0,081 | Antiviral (Hepatitis C) |

| | | | |
|---|---|---|---|
| 17 | 0,105 | 0,096 | Antiviral (Hepatitis) |
| 18 | 0,179 | 0,177 | Antihypertensive |

### 4.5.8 Octyl 4-(3-(3-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4h):

Compound-**4h** shows some of the important activities like **Antiinfertility, female, Atherosclerosis treatment, Analgesic, Antiparkinsonian**, **Antihypertensive , Alzheimer's disease treatment, Muscle relaxant** and **Female sexual dysfunction treatment.**

**Table: 4.8 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,765 | 0,003 | Histamine H1 receptor antagonist |
| 2 | 0,665 | 0,004 | Antihistaminic |
| 3 | 0,547 | 0,103 | Nootropic |
| 4 | 0,426 | 0,014 | Antiinfertility, female |
| 5 | 0,444 | 0,049 | Anticonvulsant |
| 6 | 0,329 | 0,040 | Ophthalmic drug |
| 7 | 0,421 | 0,168 | Antiischemic, cerebral |
| 8 | 0,298 | 0,081 | Atherosclerosis treatment |
| 9 | 0,321 | 0,114 | Analgesic |
| 10 | 0,269 | 0,072 | Antiischemic |
| 11 | 0,226 | 0,043 | Diabetic nephropathy treatment |
| 12 | 0,251 | 0,075 | Antidiabetic symptomatic |
| 13 | 0,259 | 0,090 | Antiparkinsonian |
| 14 | 0,186 | 0,020 | Gastrointestinal disorders treatment |
| 15 | 0,240 | 0,115 | Antihypertensive |
| 16 | 0,247 | 0,142 | Analgesic, non-opioid |
| 17 | 0,218 | 0,128 | Alzheimer's disease treatment |
| 18 | 0,115 | 0,035 | Leukocyte elastase inhibitor |

| | | | |
|---|---|---|---|
| 19 | 0,101 | 0,027 | Neuropeptide S antagonist |
| 20 | 0,136 | 0,069 | Narcolepsy treatment |
| 21 | 0,184 | 0,128 | Muscle relaxant |
| 22 | 0,131 | 0,097 | CNS active muscle relaxant |
| 23 | 0,046 | 0,013 | Dipeptidyl peptidase IV inhibitor |
| 24 | 0,195 | 0,170 | Antidiabetic |
| 25 | 0,085 | 0,080 | Female sexual dysfunction treatment |

### 4.5.9 Octyl-4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4i):

Compound-**4i** shows some of the important activities like **Antiinfertility, female, Antiviral (Picornavirus), Kidney function stimulant, Antiparkinsonian**, **Antihypertensive, Alzheimer's disease treatment, Muscle relaxant** and **Antiviral (Rhinovirus).**

**Table: 4.9 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,767 | 0,003 | Antihistaminic |
| 2 | 0,749 | 0,003 | Histamine antagonist |
| 3 | 0,457 | 0,010 | Antiinfertility, female |
| 4 | 0,427 | 0,054 | Anticonvulsant |
| 5 | 0,441 | 0,179 | Nootropic |
| 6 | 0,289 | 0,037 | Antiparkinsonian, tremor relieving |
| 7 | 0,288 | 0,083 | Antihypertensive |
| 8 | 0,256 | 0,070 | Antidiabetic symptomatic |
| 9 | 0,263 | 0,077 | Antiischemic |
| 10 | 0,340 | 0,170 | Antiviral (Picornavirus) |
| 11 | 0,256 | 0,092 | Antiparkinsonian |
| 12 | 0,346 | 0,211 | Kidney function stimulant |
| 13 | 0,247 | 0,116 | Atherosclerosis treatment |

| | | | |
|---|---|---|---|
| 14 | 0,225 | 0,109 | Antiparkinsonian, rigidity relieving |
| 15 | 0,312 | 0,228 | Antiviral (Rhinovirus) |
| 16 | 0,244 | 0,176 | Analgesic |
| 17 | 0,205 | 0,138 | Angiogenesis stimulant |
| 18 | 0,082 | 0,018 | Acetylcholine muscarinic agonist |
| 19 | 0,044 | 0,016 | Dipeptidyl peptidase IV inhibitor |
| 20 | 0,023 | 0,023 | 5. Hydroxytryptamine 4E antagonist |

### 4.5.10 Heptyl-4-(3-benzyl-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4j):

Compound-**4j** shows some of the important activities like **Antiinfertility, female, Ophthalmic drug, Antiviral (Picornavirus), Antiparkinsonian**, **Antidiabetic symptomatic, Atherosclerosis treatment, Muscle relaxant** and **Platelet aggregation inhibitor.**

**Table: 4.10 PASS Pridiction data**

| **Sr.No2** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 3 | 0,767 | 0,003 | Antihistaminic |
| 4 | 0,749 | 0,003 | Histamine antagonist |
| 5 | 0,457 | 0,010 | Antiinfertility, female |
| 6 | 0,416 | 0,009 | Anti-Helicobacter pylori |
| 7 | 0,427 | 0,054 | Anticonvulsant |
| 8 | 0,404 | 0,090 | Leukopoiesis stimulant |
| 9 | 0,338 | 0,037 | Ophthalmic drug |
| 10 | 0,441 | 0,179 | Nootropic |
| 11 | 0,289 | 0,037 | Antiparkinsonian, tremor relieving |
| 12 | 0,280 | 0,038 | Antieczematic atopic |
| 13 | 0,254 | 0,019 | Diabetic nephropathy treatment |
| 14 | 0,288 | 0,083 | Antihypertensive |
| 15 | 0,256 | 0,070 | Antidiabetic symptomatic |

| | | | |
|---|---|---|---|
| 16 | 0,263 | 0,077 | Antiischemic |
| 17 | 0,340 | 0,170 | Antiviral (Picornavirus) |
| 18 | 0,256 | 0,092 | Antiparkinsonian |
| 19 | 0,247 | 0,116 | Atherosclerosis treatment |
| 20 | 0,225 | 0,109 | Antiparkinsonian, rigidity relieving |
| 21 | 0,311 | 0,225 | Platelet aggregation stimulant |
| 22 | 0,312 | 0,228 | Antiviral (Rhinovirus) |
| 23 | 0,202 | 0,125 | Platelet aggregation inhibitor |
| 24 | 0,177 | 0,108 | Antitussive |
| 25 | 0,219 | 0,152 | Antiasthmatic |
| 26 | 0,244 | 0,176 | Analgesic |
| 27 | 0,059 | 0,027 | Angiotensin II receptor antagonist |
| 28 | 0,044 | 0,016 | Dipeptidyl peptidase IV inhibitor |

### 4.5.11 Heptyl 4-(3-(4-nitrobenzyl)-1,2,3,6-tetrahydro-1-methyl-2,6-dioxopyrimidin-4-yl)piperazine-1-carboxylateyl)piperazine-1-carboxylate (4k):

Compound-**4k** shows some of the important activities like **Antiinfertility, female, Ophthalmic drug , Antiviral (Picornavirus), Antiparkinsonian**, **Antidiabetic symptomatic, Antihypertensive, Antineoplastic (pancreatic cancer)** and **Gastroesophageal reflux disease treatment.**

**Table: 4.11 PASS Pridiction data**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,653 | 0,004 | Antihistaminic |
| 2 | 0,639 | 0,004 | Histamine antagonist |
| 3 | 0,424 | 0,014 | Antiinfertility, female |
| 4 | 0,394 | 0,066 | Anticonvulsant |
| 5 | 0,405 | 0,082 | Antianginal |
| 6 | 0,354 | 0,055 | Antihypertensive |
| 7 | 0,389 | 0,119 | Antiviral (Picornavirus) |

| | | | |
|---|---|---|---|
| 8 | 0,291 | 0,059 | Ophthalmic drug |
| 9 | 0,233 | 0,058 | Antiparkinsonian, tremor relieving |
| 10 | 0,230 | 0,094 | Antidiabetic symptomatic |
| 11 | 0,224 | 0,110 | Antiparkinsonian, rigidity relieving |
| 12 | 0,229 | 0,136 | Cardiotonic |
| 13 | 0,103 | 0,033 | Gastroesophageal reflux disease treatment |
| 14 | 0,340 | 0,283 | Nootropic |
| 15 | 0,204 | 0,155 | Antiparkinsonian |
| 16 | 0,232 | 0,188 | Superoxide dismutase inhibitor |
| 17 | 0,202 | 0,171 | Analeptic |
| 18 | 0,259 | 0,236 | Leukopoiesis stimulant |
| 19 | 0,039 | 0,024 | Dipeptidyl peptidase IV inhibitor |
| 20 | 0,198 | 0,193 | Antineoplastic (pancreatic cancer) |

### 4.5.12 Heptyl-4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4l):

Compound-**4l** shows some of the important activities like **Antiinfertility, female, Ophthalmic drug, Atherosclerosis treatment, Antidiabetic symptomatic**, **Analgesic, symptomatic, Antihypertensive, Antineoplastic (pancreatic cancer)** and **Antihypertensive.**

**Table: 4.12 PASS Pridiction data**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,743 | 0,003 | Histamine H1 receptor antagonist |
| 2 | 0,663 | 0,004 | Antihistaminic |
| 3 | 0,490 | 0,038 | Anticonvulsant |
| 4 | 0,430 | 0,013 | Antiinfertility, female |
| 5 | 0,343 | 0,035 | Ophthalmic drug |
| 6 | 0,311 | 0,034 | Antidiabetic symptomatic |
| 7 | 0,314 | 0,071 | Atherosclerosis treatment |

| | | | |
|---|---|---|---|
| 8 | 0,249 | 0,028 | Aldose reductase substrate |
| 9 | 0,416 | 0,199 | Nootropic |
| 10 | 0,317 | 0,116 | Analgesic |
| 11 | 0,317 | 0,122 | Neurodegenerative diseases treatment |
| 12 | 0,269 | 0,081 | Antiparkinsonian |
| 13 | 0,264 | 0,098 | Antihypertensive |
| 14 | 0,130 | 0,021 | Leukocyte elastase inhibitor |
| 15 | 0,245 | 0,145 | Analgesic, non-opioid |
| 16 | 0,235 | 0,136 | Chitinase inhibitor |
| 17 | 0,231 | 0,134 | Cardiotonic |
| 18 | 0,194 | 0,097 | Diabetic nephropathy treatment |
| 19 | 0,119 | 0,036 | Female sexual dysfunction treatment |
| 20 | 0,200 | 0,163 | Antidiabetic |
| 21 | 0,190 | 0,167 | Alzheimer's disease treatment |
| 22 | 0,109 | 0,090 | Myocardial ischemia treatment |
| 23 | 0,118 | 0,110 | Narcolepsy treatment |

### 4.5.13 2-ethylbutyl 4-(3-(2-fluorobenzyl)-1,2,3,6-tetrahydro-1-methyl-2,6-dioxopyrimidin-4-yl)piperazine-1-carboxylate (4m):

Compound-**4m** shows some of the important activities like **Female sexual dysfunction treatment , Antihistaminic , Antiinfertility, female, Ophthalmic drug, Atherosclerosis treatment, Analgesic**, **Analgesic, symptomatic, Antihypertensive, Antineoplastic (pancreatic cancer)** and **Antihypertensive.**

**Table: 4.13 PASS Pridiction data**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,590 | 0,004 | Histamine H1 receptor antagonist |
| 2 | 0,582 | 0,022 | Anticonvulsant |
| 3 | 0,436 | 0,006 | Antihistaminic |

| | | | |
|---|---|---|---|
| 4 | 0,396 | 0,019 | Antiinfertility, female |
| 5 | 0,359 | 0,092 | Analgesic |
| 6 | 0,301 | 0,053 | Ophthalmic drug |
| 7 | 0,251 | 0,075 | Antidiabetic symptomatic |
| 8 | 0,255 | 0,104 | Antihypertensive |
| 9 | 0,249 | 0,114 | Atherosclerosis treatment |
| 10 | 0,261 | 0,128 | Analgesic, non-opioid |
| 11 | 0,181 | 0,067 | Antidiabetic (type 2) |
| 12 | 0,226 | 0,135 | Antidiabetic |
| 13 | 0,110 | 0,029 | Gastroesophageal reflux disease treatment |
| 14 | 0,113 | 0,040 | Female sexual dysfunction treatment |
| 15 | 0,212 | 0,156 | Cardiotonic |
| 16 | 0,206 | 0,152 | Antiparkinsonian |
| 17 | 0,131 | 0,079 | Narcolepsy treatment |
| 18 | 0,334 | 0,291 | Nootropic |
| 19 | 0,169 | 0,136 | Antiviral |
| 20 | 0,116 | 0,100 | Heart failure treatment |
| 21 | 0,105 | 0,095 | Antiviral (Hepatitis) |
| 22 | 0,088 | 0,087 | Antiviral (Hepatitis C) |

### 4.5.14 Octyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4n):

Compound-**4n** shows some of the important activities like **Female sexual dysfunction treatment , Antihistaminic , Antiinfertility, female, Ophthalmic drug, Atherosclerosis treatment, Analgesic**, **Anticonvulsant, Antihypertensive, Antidiabetic (type 2)** and **Antihypertensive.**

**Table: 4.14 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,590 | 0,004 | Histamine H1 receptor antagonist |
| 2 | 0,582 | 0,022 | Anticonvulsant |
| 3 | 0,436 | 0,006 | Antihistaminic |
| 4 | 0,396 | 0,019 | Antiinfertility, female |
| 5 | 0,359 | 0,092 | Analgesic |
| 6 | 0,251 | 0,075 | Antidiabetic symptomatic |
| 7 | 0,255 | 0,104 | Antihypertensive |
| 8 | 0,249 | 0,114 | Atherosclerosis treatment |
| 9 | 0,261 | 0,128 | Analgesic, non-opioid |
| 10 | 0,152 | 0,034 | Gastrointestinal disorders treatment |
| 11 | 0,181 | 0,067 | Antidiabetic (type 2) |
| 12 | 0,226 | 0,135 | Antidiabetic |
| 13 | 0,113 | 0,040 | Female sexual dysfunction treatment |
| 14 | 0,212 | 0,156 | Cardiotonic |
| 15 | 0,206 | 0,152 | Antiparkinsonian |
| 16 | 0,131 | 0,079 | Narcolepsy treatment |
| 17 | 0,245 | 0,197 | Neurodegenerative diseases treatment |
| 18 | 0,169 | 0,136 | Antiviral |
| 19 | 0,105 | 0,095 | Antiviral (Hepatitis) |
| 20 | 0,016 | 0,014 | Phosphodiesterase 6A inhibitor |
| 21 | 0,053 | 0,052 | Lipase inhibitor |
| 22 | 0,088 | 0,087 | Antiviral (Hepatitis C) |

### 4.5.15 Hexyl 4-(3-(2-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4o):

Compound-**4o** shows some of the important activities like **Anticonvulsant, Heart failure treatment, Alzheimer's disease treatment, Female sexual dysfunction treatment, Antihistaminic, Antiinfertility, female, ophthalmic drug, and**

**Atherosclerosis treatment, Analgesic**, **Anticonvulsant, Antihypertensive, Antidiabetic (type 2)** and **Antihypertensive.**

**Table: 4.15 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,743 | 0,003 | Histamine H1 receptor antagonist |
| 2 | 0,663 | 0,004 | Antihistaminic |
| 3 | 0,490 | 0,038 | Anticonvulsant |
| 4 | 0,430 | 0,013 | Antiinfertility, female |
| 5 | 0,343 | 0,035 | Ophthalmic drug |
| 6 | 0,311 | 0,034 | Antidiabetic symptomatic |
| 7 | 0,314 | 0,071 | Atherosclerosis treatment |
| 8 | 0,317 | 0,116 | Analgesic |
| 9 | 0,317 | 0,122 | Neurodegenerative diseases treatment |
| 10 | 0,269 | 0,081 | Antiparkinsonian |
| 11 | 0,220 | 0,034 | Antiglaucomic |
| 12 | 0,201 | 0,017 | Gastrointestinal disorders treatment |
| 13 | 0,328 | 0,150 | Antianginal |
| 14 | 0,264 | 0,098 | Antihypertensive |
| 15 | 0,137 | 0,018 | Gastroesophageal reflux disease treatment |
| 16 | 0,245 | 0,145 | Analgesic, non-opioid |
| 17 | 0,119 | 0,036 | Female sexual dysfunction treatment |
| 18 | 0,129 | 0,079 | Heart failure treatment |
| 19 | 0,200 | 0,163 | Antidiabetic |
| 20 | 0,190 | 0,167 | Alzheimer's disease treatment |
| 21 | 0,118 | 0,110 | Narcolepsy treatment |

### 4.5.16 4-methylpentyl-4-(3-(2-cyanobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4p):

Compound-**4p** shows some of the important activities like **Menstruation disorders treatment, Anticonvulsant, Antidiabetic (type 2), Heart failure treatment , Gastroesophageal reflux disease treatment, Female sexual dysfunction treatment, Alzheimer's disease treatment , ophthalmic drug** and **Atherosclerosis treatment.**

**Table: 4.16 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,433 | 0,005 | Histamine H1 receptor antagonist |
| 2 | 0,359 | 0,010 | Antihistaminic |
| 3 | 0,372 | 0,077 | Anticonvulsant |
| 4 | 0,239 | 0,026 | Menstruation disorders treatment |
| 5 | 0,285 | 0,090 | Antidiabetic |
| 6 | 0,279 | 0,088 | Antihypertensive |
| 7 | 0,231 | 0,048 | Antidiabetic (type 2) |
| 8 | 0,230 | 0,110 | Ophthalmic drug |
| 9 | 0,112 | 0,039 | Leukocyte elastase inhibitor |
| 10 | 0,128 | 0,081 | Heart failure treatment |
| 11 | 0,111 | 0,079 | Gastrointestinal disorders treatment |
| 12 | 0,089 | 0,074 | Female sexual dysfunction treatment |
| 13 | 0,186 | 0,175 | Alzheimer's disease treatment |
| 14 | 0,078 | 0,077 | Gastroesophageal reflux disease treatment |
| 15 | 0,188 | 0,188 | Atherosclerosis treatment |

### 4.5.17 Hexyl 4-(3-(4-fluorobenzyl)-1-methyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperazine-1-carboxylate (4q):

Compound-**4q** shows some of the important activities like **Neurodegenerative diseases treatment, Nootropic, Antidiabetic (type 2), Analgesic, Gastroesophageal reflux**

**disease treatment, Muscle relaxant, Alzheimer's disease treatment , Platelet aggregation inhibitor** and **CNS active muscle relaxant.**

**Table: 4.17 PASS Pridiction data**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,779 | 0,003 | Histamine H1 receptor antagonist |
| 2 | 0,719 | 0,004 | Antihistaminic |
| 3 | 0,442 | 0,012 | Antiinfertility, female |
| 4 | 0,501 | 0,130 | Nootropic |
| 5 | 0,418 | 0,057 | Anticonvulsant |
| 6 | 0,338 | 0,037 | Ophthalmic drug |
| 7 | 0,292 | 0,084 | Atherosclerosis treatment |
| 8 | 0,316 | 0,123 | Neurodegenerative diseases treatment |
| 9 | 0,228 | 0,040 | Diabetic nephropathy treatment |
| 10 | 0,255 | 0,071 | Antidiabetic symptomatic |
| 11 | 0,197 | 0,018 | Gastrointestinal disorders treatment |
| 12 | 0,264 | 0,085 | Antiparkinsonian |
| 13 | 0,298 | 0,129 | Analgesic |
| 14 | 0,246 | 0,111 | Antihypertensive |
| 15 | 0,130 | 0,020 | Gastroesophageal reflux disease treatment |
| 16 | 0,119 | 0,030 | Leukocyte elastase inhibitor |
| 17 | 0,206 | 0,142 | Alzheimer's disease treatment |
| 18 | 0,227 | 0,164 | Analgesic, non-opioid |
| 19 | 0,179 | 0,134 | Muscle relaxant |
| 20 | 0,140 | 0,116 | Antiparkinsonian, tremor relieving |
| 21 | 0,054 | 0,031 | Dipeptidyl peptidase inhibitor |
| 22 | 0,178 | 0,158 | Platelet aggregation inhibitor |
| 23 | 0,118 | 0,108 | CNS active muscle relaxant |

# 5 AN EFFICIENT SYNTHESIS FOR THE PREPARATION OF NOVEL 9H-PURIN-2-AMINE SUBSTITUTED AMINO ACID DERIVATIVES

## 5.1 INTRODUCTION:

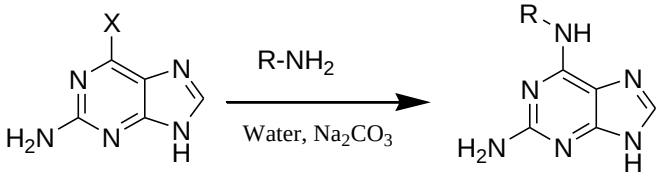
Purines and substituted puriens [138] is well known for its biological activity, the analogues of purine have been showed many kind of biological activity such as antineoplastic [139], antiviral [140], antifuncal [141] agent and some group of agent with similar structures, but it shows some kind of different mechanism of action, indication, pharmacokinetics and adverse effect. In the synthesis of DNA or RNA or both DNA and RNA antimetabolite or competing with triphosphate. In the diseases or infections like Viral, Lymphomas [142] and Leukemia's [143] the analogues of adenine [144] [145], guanine [146] are generally showing excellent activity, Thioguanine, azathiopurine and mercaptopurine which are some substituted thiopurines which are having very much activity against several type Leukemia and also been active against immunosuppressive and immunomodulatory agents in autoimmune condition treatment such as lupus nephritis, Crohn disease, autoimmune hepatitis.

Purine analogues and some other purine derivatives are exclusively showing very good activity against malignant conditions, typically lymphomas and leukemias. The most commonly used and first line treatment of CLL (chronic lymphocytic leukemia) is Fludarabine [147] which is derivative of purine analogue. Fludarabine is also having some other activity against immunosuppressive and also used for the treatment of nonmyeloablative regimen and also for preparation and transplantation of hematopoietic cell. Fludarabine also having very excellent activity against viral infection such as hepatitis B, The adenosine derivatives of Cladribine and Pentostatin [148] are predominantly used for hairy cell leukemia. Cladribine and Pentostatin atleast having hepatotoxic potential so that are used or considered to treat hairy cell leukemia. The

adenine cell has profound immunosuppressive activity and is used in nonmyeloablative regimens in preparation for hematopoietic cell transplantation. Because of its immunosuppressive activity, fludarabine is associated with reactivation of viral infections, including hepatitis B. Cladribine and pentostatin are adenosine derivatives and are used predominantly for hairy cell leukemia. They have minimal hepatotoxic potential, at least at the doses that are used to treat hairy cell leukemia. The adenosine derivatives of Clofarabine is used to treat acute lymphoblastic leukemia which is mostly affected by children who have already failure of other medication,

The guanine derivative of Nelarabine is used to treat in T cell malignancies, generally after failure of prior treatments. During the therapy Nelarabine and Clofarabine are associated with elevated rates of serum aminotransferase and very rare caused liver injury. All the purine derivatives are directly having link with hepatotoxic potential. There are several antineoplastic drugs are available in the market which are Clofarabine, Mercaptopurine, Cladribine, Azathiopine, Fludarabine Thioguanine, Nelarabine and Pentostatin. Purines and substituted purines is the important intermediate for the synthesis of variety of purine and purine nucleoside molecules, several antiviral [149] drugs are available with purine derivatives such as Abacavir, valaciclovir, femciclovir, acyclovir, valganciclovir, ganciclovir etc.,

**Reaction Scheme- 5.1: process for the preparation of purine derivatives**




51 5a-5k

Where X= Halogen, R= Amino acid

## 5.2 GENERAL PROCEDURE:

2-amino-6-Chloropurine **1** (1 mmol), Animo acid **2**(1 mmol) were added Sodium carbonate (2.50 mmol) then heated in to reflux till reaction completed, after reaction was completed reaction mass was cooled to 20-30°C, reaction mass was adjusted the pH 6.5 by adding 1:1 dilute hydrochloric acid, the precipitated product was stirred 2 hrs at RT, then the product was isolated by filtration. Wet product was dried at 45°C to obtained desire product.

### 5.2.1 SYNTHETIC PROCEDURE AND CHARECTERISATION OF COMPOUNDS 22-33

### 5.2.2 Preparation of (R)-2-(2-amino-9H-purin-6-ylamino)-3-(1H-indol-3-yl)propanoic acid (5a):

2-amino-6-chloropurine (10.00 gm, 0.0589 moles) is suspended with 30 mL water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of triptophen ( 12.04 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (R)-2-(2-amino-9H-purin-6-ylamino)-3-(1H-indol-3-yl)propanoic acid as off white solid, Yield: 17.90gm (90.0%); m.p: > 230°C.

$^{1}$H NMR (DMSO)  ppm 3.29-3.33 (d, 4H, -$NH_2$-, -NH-), 4.91 (broad, 1H, -CH), 5.93 (broad, 2H, -$CH_2$), 6.76 (d, 1H, Ar-H), 7.06 ( t, 1H, Ar-H), 7.19 (d, 1H, Ar-H), 7.32-7.34 (d, 1H, Ar-H), 7.54 (d, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 10.88 (s, 1H, -COOH). $^{13}$C NMR  ppm 27.54, 53.87, 110, 111.90, 118.67, 118.93, 121.45, 124.24, 127.65, 136.51, 152.39, 154.09, 159.83, 174.63. HRMS (ESI) m/z calc for $C_{16}H_{15}N_7O_2$, 337.13, Found, [M+ H]: 338.1410.

### 5.2.3 Preparation of (2R)-2-(2-amino-9H-purin-6-ylamino)-3-methylpentanoic acid (5b):

2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 mL water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of isoleucine ( 7.73gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (2R)-2-(2-amino-9H-purin-6-ylamino)-3-methylpentanoic acid as off white solid, Yield: 13.87gm (89.0%); m.p: 228-233°C.

$^{1}$H NMR (DMSO)  ppm 0.87-0.91 (t, 3H, -$CH_3$), 0.93-0.94 (d, 3H, -$CH_3$), 1.23-1.34 (m, 1H, -$CH_2$), 1.43-1.51 (m, 1H, -$CH_2$), 1.94-2.06 (m, 1H, -CH), 2.50-2.51 (d, 1H, -CH), 8.66 ( d, 1H, Ar-H). $^{13}$C NMR  ppm 11.73, 11.92, 15.90, 25.21, 57.90, 105.16, 114.66, 117.56, 120.45, 121.64, 142.59, 148.83152.25, 155.29, 159.44, 159.80, 160.42, 172.66. HRMS (ESI) m/z calc for $C_{11}H_{16}N_6O_2$, 264.13, Found, [M+ H]: 265.1501.

### 5.2.4 Preparation of (R)-2-(2-amino-9H-purin-6-ylamino)-3-phenylpropanoic acid (5c):

To a suspension of 2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 ml water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of phenyl alanine ( 9.74 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (R)-2-(2-amino-9H-purin-6-ylamino)-3-phenylpropanoic acid as off white solid, Yield: 16.0gm (91.0%); m.p:212-217°C.

$^{1}$H NMR (DMSO)  ppm 3.05-3.08(t, 1H, -CH), 3.30-3.33 (d, 2H, -$CH_2$), 4.51 (s, 1H, -CH), 5.72 (s, 2H, -$NH_2$), 7.08-7.14 (m, 5H, Ar-H), 7.66 ( s, 1H, Ar-H). $^{13}$C NMR  ppm 37.87, 56.19, 112.67, 126.21, 128.19, 129.99, 136.49, 139.42, 152.23, 154.03, 158.14,

160.54, 175.10. HRMS (ESI) m/z calc for $C_{14}H_{14}N_6O_2$, 298.12, Found, [M+ H]: 298.1188.

### 5.2.5 (S)-2-(2-amino-9H-purin-6-ylamino)-3-methylbutanoic acid (5d):

To a suspen ion of 2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 ml water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of L-Valine ( 6.908 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (S)-2-(2-amino-9H-purin-6-ylamino)-3-methylbutanoic acid as off white solid, Yield: 13.0gm (88.13%); m.p: > 238°C.

$^1$H NMR (DMSO + TFA)  ppm 0.96-0.98 (t, 3H, -$CH_3$), 2.21-2.29 (m, 1H, -CH), 7.63-8.02 (broad, 4H, -NH2, -NH), 8.60-8.63 ( d, 1H, Ar-H). $^{13}$C NMR  ppm 18.24, 19.28, 30.82, 58.66, 105.16, 111.71, 114.60, 117.49, 120.38, 142.59, 148.54, 152.70, 154.30, 158.82, 172.67. HRMS (ESI) m/z calc for $C_{10}H_{14}N_6O_2$, 250.12, Found, [M+ H]: 251.1529.

### 5.2.6 Preparation of (S)-2-(2-amino-9H-purin-6-ylamino)-4-methylpentanoic acid (5e):

To a suspension of 2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 ml water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of L-Leucine ( 9.73 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (S)-2-(2-amino-9H-purin-6-ylamino)-4-methylpentanoic acid as off white solid, Yield: 13.55gm (87.0%); m.p: > 230°C.

$^1$H NMR (DMSO + TFA)  ppm  0.88-.94 (t, 6H, -$CH_3$), 1.69-1.74 (t, 1H, -$CH_2$, -CH), 4.78-4.81 (t, 1H, -CH),  8.18 ( d, 1H, Ar-H). HRMS (ESI) m/z calc for $C_{11}H_{16}N_6O_2$, 264.13, Found, [M+ H]: 265.1841.

### 5.2.7 Preparation of (S)-2-(2-amino-9H-purin-6-ylamino)propanoic acid (5f):

To a suspension of 2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 ml water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of L-alanine (5.25 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (S)-2-(2-amino-9H-purin-6-ylamino)propanoic acid as off white solid, Yield: 11.35gm (86.64%); m.p: > 230°C.

$^1$H NMR (DMSO + TFA)  ppm 2.62-2.65(t, 3H, -$CH_3$), 3.68-3.71 (t, 1H, -CH), 4.78-4.81 (t, 1H, -CH), 8.11 (d, 1H, Ar-H). HRMS (ESI) m/z calc for $C_8H_{10}N_6O_2$, 222.09, Found, [M+ H]: 223.1307.

### 5.2.8 Preparation of (R)-2-(2-amino-9H-purin-6-ylamino)-3-mercaptopropanoic acid (5g):

To a suspension of 2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 ml water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of L-Cystein (7.14 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (R)-2-(2-amino-9H-purin-6-ylamino)-3-mercaptopropanoic acid (dimer) as off white solid, Yield: 13.27gm (88.50%); m.p: 216-220°C.

$^1$H NMR (DMSO + TFA)  ppm 3.21-3.24(m, 1H, -$CH_2$), 3.38-3.42 (m, 1H, -CH), 5.07-5.10 (t, 1H, -CH), 8.16 (s, 1H, Ar-H), 13.77 (broad, 1H, -COOH). HRMS (ESI) m/z calc for $C_8H_{10}N_6O_2S$, 254.06, Found, [M+ H]: 507.1355.

### 5.2.9 Preparation of (S)-1-(2-amino-9H-purin-6-yl)pyrrolidine-2-carboxylic acid (5h):

To a suspension of 2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 ml water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of L-proline (6.79 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (S)-1-(2-amino-9H-purin-6-yl)pyrrolidine-2-carboxylic acid as off white solid, Yield: 13.46gm (92.0%); m.p: > 238°C.

$^1$H NMR (DMSO + TFA)  ppm 2.04-2.06 (m, 4H, -$CH_2$), 2.26-2.37 (m, 2H, -$CH_2$), 3.68-3.83 (m, 1H, -$CH_2$), 3.98-4.04 (m, 2H, -CH), 4.74-4.76 (d, 1H, -CH), 8.21 (s, 1H, Ar-H), 14.91(broad, 1H, -COOH). HRMS (ESI) m/z calc for $C_{10}H_{12}N_6O_2$, 248.1, Found, [M+ H]: 249.121.

### 5.2.10 Preparation of (R)-2-(2-amino-9H-purin-6-ylamino)-3-hydroxypropanoic acid (5i):

To a suspension of 2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 ml water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of D-Serine (6.20 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (R)-2-(2-amino-9H-purin-6-ylamino)-3-hydroxypropanoic acid as off white solid, Yield: 12.19gm (86.79%); m.p: > 238°C.

$^{1}$H NMR (DMSO + TFA)  ppm 3.79-3.82 (dd, 1H, -$CH_2$), 3.93-3.97 (dd, 2H, -$CH_2$), 4.86-4.88 (t, 1H, -CH), 8.21 (s, 1H, Ar-H), 15.88 (broad, 1H, -COOH). HRMS (ESI) m/z calc for $C_8H_{10}N_6O_3$, 238.08, Found, [M+ H]: 299.0925

### 5.2.11 Preparation of (R)-6-(3-aminopiperidin-1-yl)-9H-purin-2-amine (5j):

To a suspension of 2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 ml water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of R-3-amino piperidine (10.21 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives ((R)-6-(3-aminopiperidin-1-yl)-9H-purin-2-amine as off white solid, Yield: 12.44gm (90.47%); m.p: > 238°C.

$^{1}$H NMR ($D_2O$)  ppm 1.16 (m, 2H, -$CH_2$), 1.53 (broad, 1H, -$CH_2$), 1.73 (broad, 1H, -$CH_2$), 2.06 (broad, 1H, -$CH_2$), 2.58-2.64 ( m, 1H, -$CH_2$), 2.78 (m, 1H, -CH), 4.22-4.37 (m, 2H, _$CH_2$)7.39-7.43 (d, 1H, Ar-H). HRMS (ESI) m/z calc for $C_{10}H_{15}N_7$, 233.14, Found, [M+ H]: 234.1235.

### 5.2.12 Preparation of (R)-2-(2-amino-9H-purin-6-ylamino)-2-phenylacetic acid (5k):

To a suspension of 2-amino-6-chloropurine (10.00 gm, 0.0589 moles) in 30 ml water and added sodium carbonate ( 21.87 gm, 0.2064 moles) followed by addition of L-phenyl glycine (8.91 gm, 0.0589) the reaction mass was refluxed for 8 hrs, reaction completion monitored by TLC, then bring down temperature to 20-30°C, brought the pH 5.0 – 6.0 by addition of acetic acid, precipitated product was stirred for 2 hrs at 20-25°C, the precipitated product isolated by filtration and washed wet product with water and dried at 50-55°C to gives (R)-2-(2-amino-9H-purin-6-ylamino)-2-phenylacetic acid as off white solid, Yield: 15.30gm (91.27%); m.p: 204.2-207.8°C.

$^{1}$H NMR (DMSO)  ppm 5.68 (m, 1H, -CH), 6.37-7.76 (m, 5H, Ar-CH), 8.09 (s, 1H, Ar-H), 12.97 (broad, 1H,-COOH). HRMS (ESI) m/z calc for $C_{13}H_{12}N_6O_2$, 284.27, Found, [M+ H]: 285.1027.

**5.12.13 Preparation of 2,9-diacetylguanine (50):**

In a 2500 mL round bottom flask charged 600 mL acetic acid and guanine (1a, 25.00 g, and 0.1654 moles) stirred for 10 min at RT, added slowly acetic anhydride (300 mL) at RT, then obtained solution heated to 135°C for 7.5 h. Reaction progress was monitored by TLC, if reaction completed, acetic anhydride were distilled under vacuum and the crude product was obtained as solid, then crude product were recrystallized from DI ( de ionized) water to got white powder (1, 36.96 g, yield 95%). m.p. 251 – 256°C. 1 H NMR (DMSO-d6) δ 11.56 (s, 1H, OH), 8.15 (s, 1H, NH), 8.11 (s, 1H, CH), 2.16-2.50 (m, 6H, CH3). IR (KBr) 1530, 1680, 3200 $cm^{-1}$. MS (70 eV) m/z 234.09 (M); MS m/z (%) 234.09 (M, 20), 192.12 (100), 150.08 (23). Analysis Calculated for $C_9H_9N_5O_3$: C, 45.93; H, 3.87; N, 29.76; O, 20.37. Found: C, 45.96; H, 3.86; N, 29.78; O, 20.41.

**5.2.14 Preparation of 2-amino-6-chloropurine (51):**

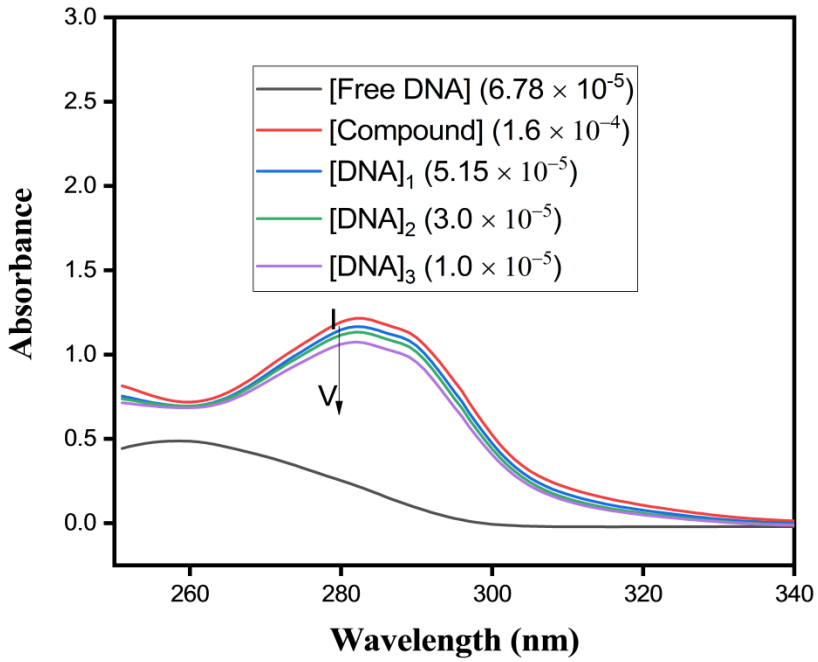
In 1000 mL round bottom flask took 100 mL Dichloroethane and 2, 9-diacetylguanine (23.50 g, 0.1000 moles) and added PEG-2000 (40 g, 0.0200 moles) at 20-30°C. Then added drop wise $POCl_3$ (54.00 g, 0.3500 moles) over the period of 30-40 min. at 20-30°C, raise the temperature slowly to 80° C. The reaction progress was monitored by TLC, after 6.0-7.0 hrs, brings down the temperature to 20-30°C, precipitate solid was removed by filtration. The solvent were distilled out under vacuum at 40-50°C, the obtained residue were recrystallized by using DMSO to produce a white powder (2, 14.20 g, yield 84%). m.p. 298-302°C. $^{1}$H NMR (DMSO-d6) δ 8.01 (m, 1H, CH), 6.75-6.79 (m, 3H, $NH_2$ and NH). IR (KBr) 630, 822, 1292, 1636 $cm^{-1}$. MS (70 eV) m/z 169.13 (M); MS m/z (%) 169.13 (M), 151.20, 135.13, 116.84. Analysis Calculated for C5H4ClN5: C, 35.37; H, 2.34; Cl, 20.93; N, 41.29. Found: C, 35.41; H, 2.38; Cl, 20.91; N, 41.30.

## 5.3 DNA BINDING UV ABSORPTION SPECTRUM OF THE ABOVE MOLECULES ARE LISTED BELOW

The DNA binding studies of said compound were done in UV absorption spectroscopy and are listed below.

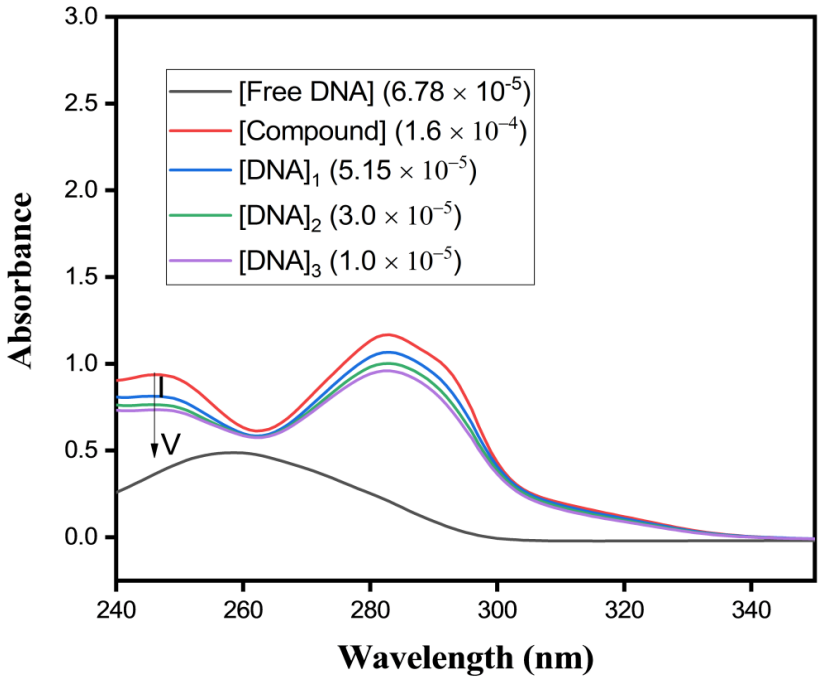
### 5.3.1 UV Spectrum of (R)-2-(2-amino-9H-purin-6-ylamino)-3-(1H-indol-3-yl)propanoic acid (5a):

**Fig: 5.1 : UV Spectrum of Compound 5a**



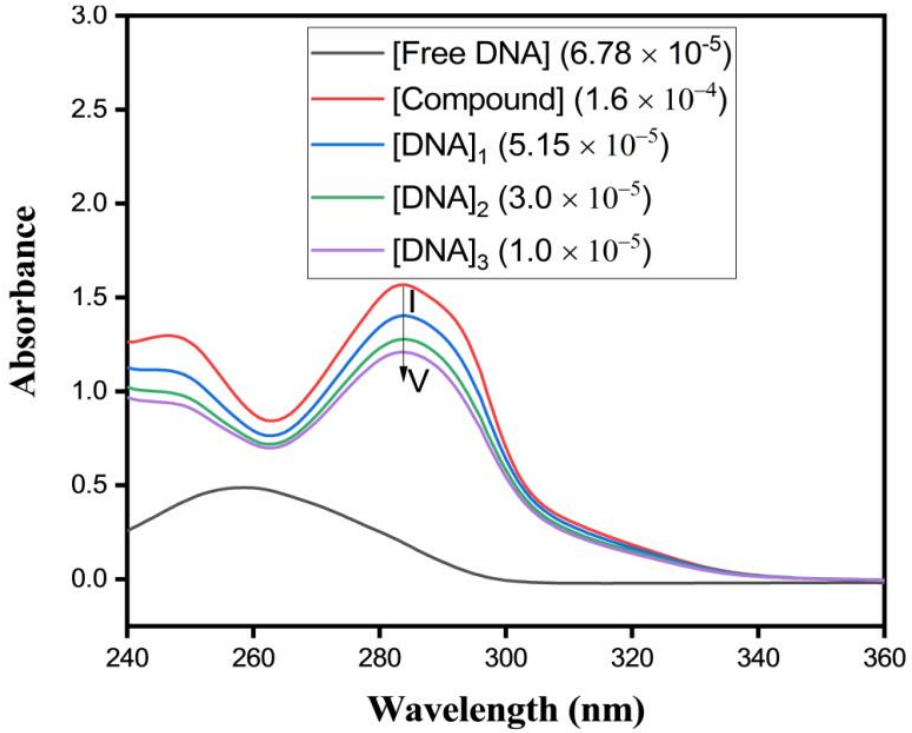
### 5.3.2 Preparation of (2R)-2-(2-amino-9H-purin-6-ylamino)-3-methylpentanoic acid (5b):

**Fig: 5.2 : UV Spectrum of Compound 5b**



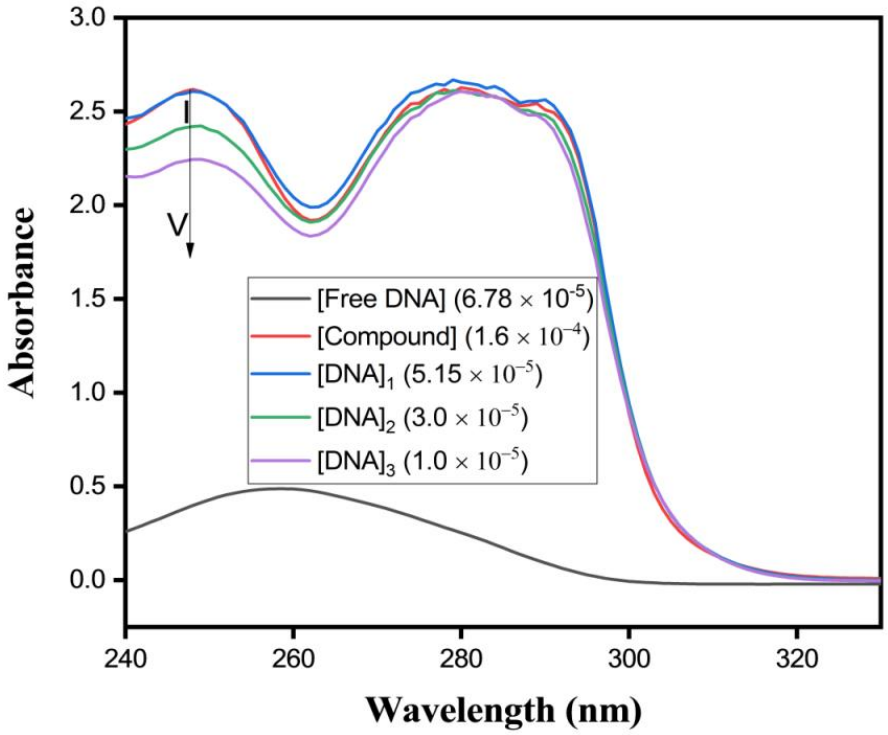
### 5.3.3 Preparation of (R)-2-(2-amino-9H-purin-6-ylamino)-3-phenylpropanoic acid (5c):

**Fig: 5.3 : UV Spectrum of Compound 5c**



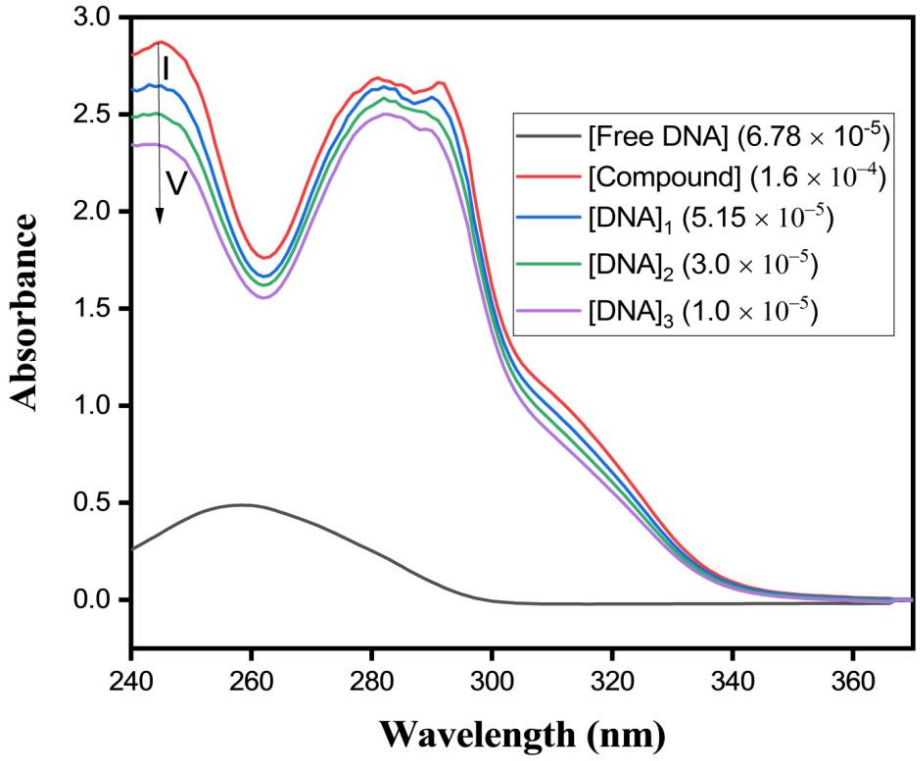
### 5.3.4 (S)-2-(2-amino-9H-purin-6-ylamino)-3-methylbutanoic acid (5d):

**Fig: 5.4 : UV Spectrum of Compound 5d**



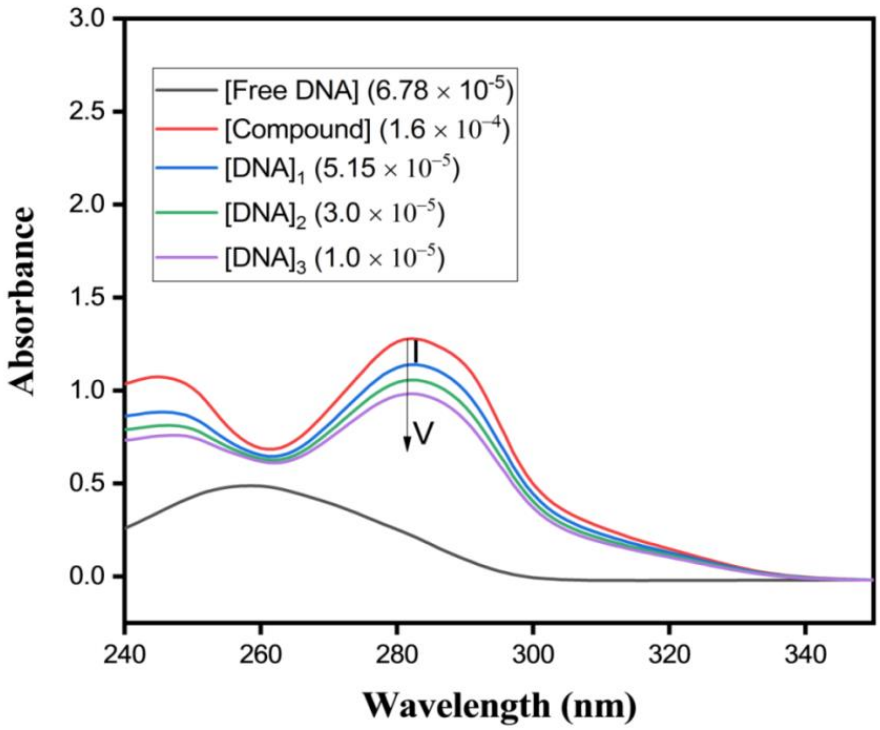
### 5.3.5 Preparation of (S)-2-(2-amino-9H-purin-6-ylamino)-4-methylpentanoic acid (5e):

**Fig: 5.5 : UV Spectrum of Compound 5e**



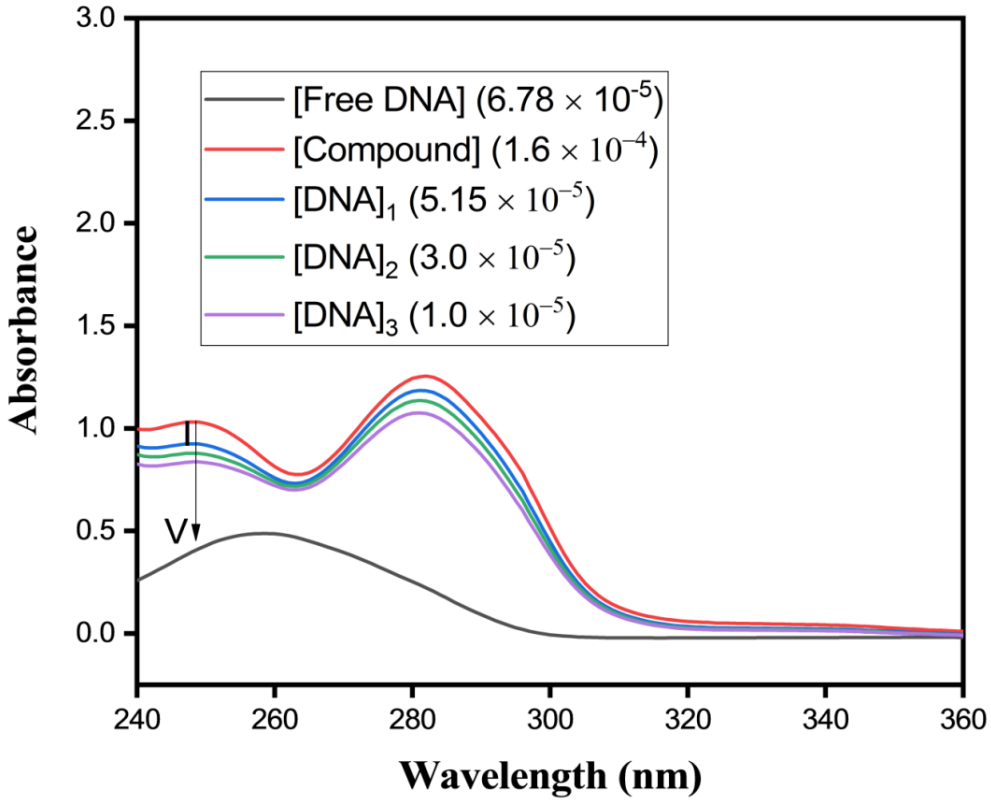
### 5.3.6 Preparation of (S)-2-(2-amino-9H-purin-6-ylamino)propanoic acid (5f):

**Fig: 5.6 : UV Spectrum of Compound 5f**



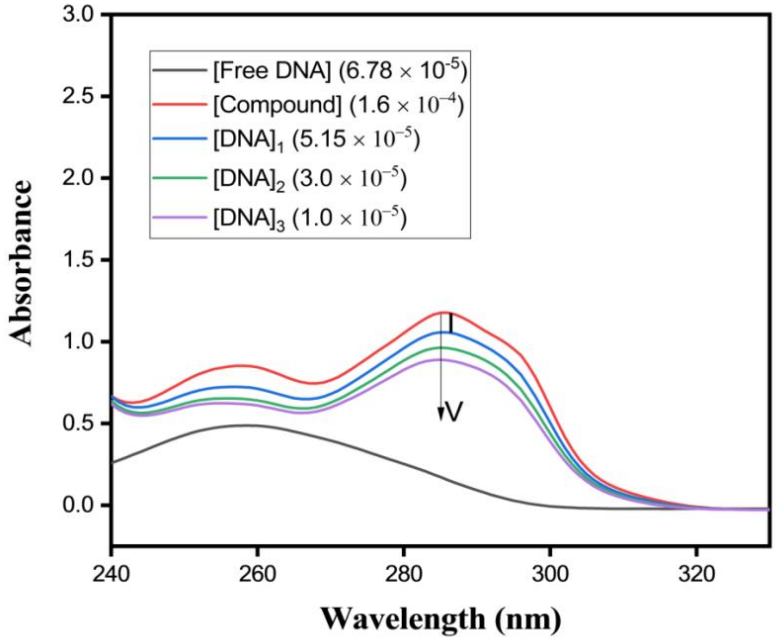
### 5.3.7 Preparation of (R)-2-(2-amino-9H-purin-6-ylamino)-3-mercaptopropanoic acid (5g):

**Fig: 5.7 : UV Spectrum of Compound 5g**



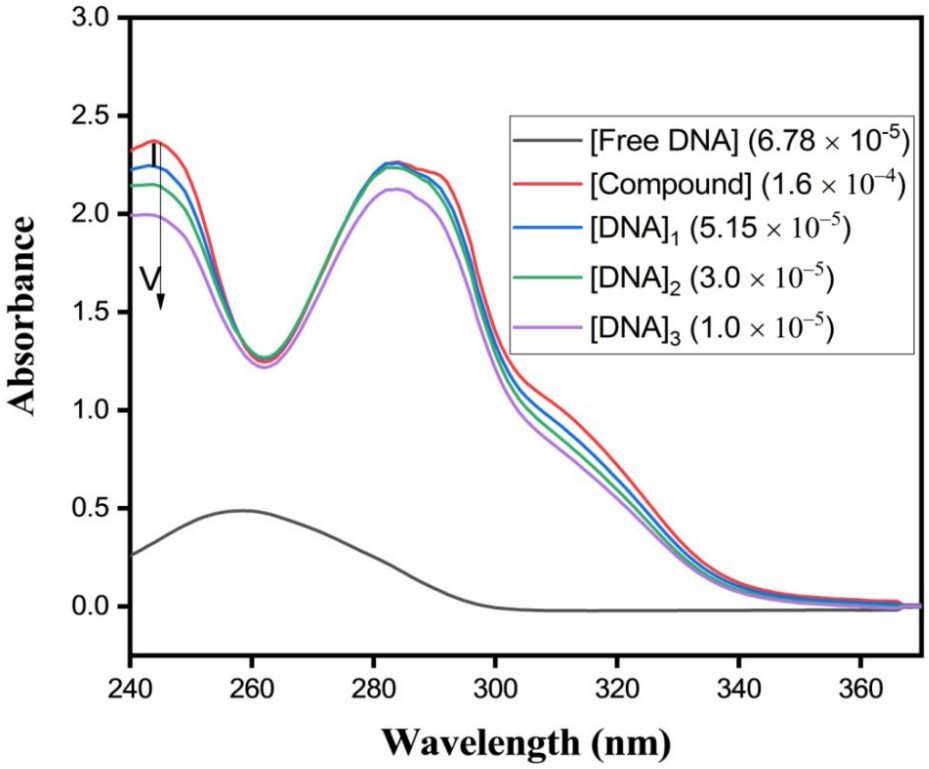
### 5.3.8 Preparation of (S)-1-(2-amino-9H-purin-6-yl)pyrrolidine-2-carboxylic acid (5h):

**Fig: 5.8: UV Spectrum of Compound 5h**



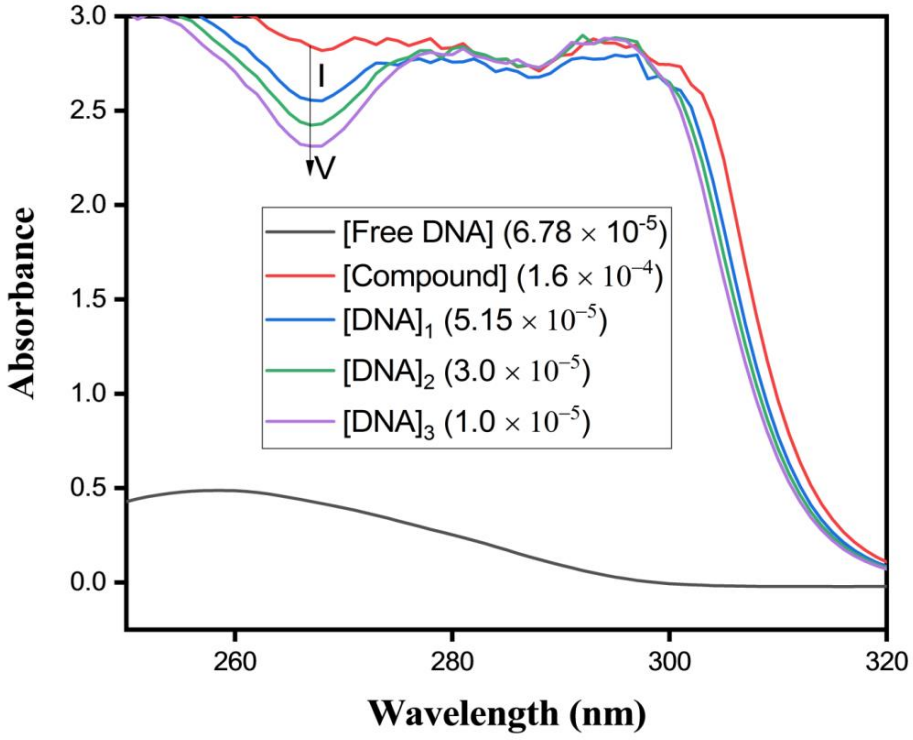
### 5.3.9 Preparation of (R)-2-(2-amino-9H-purin-6-ylamino)-3-hydroxypropanoic acid (5i):

**Fig: 5.9 : UV Spectrum of Compound 5i**



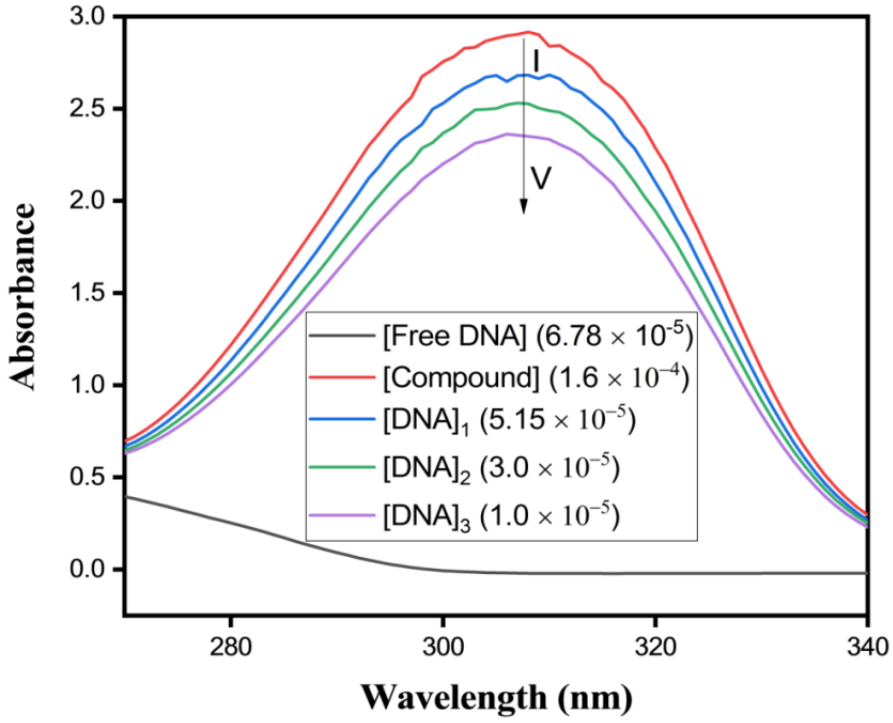
### 5.3.10 Preparation of (R)-6-(3-aminopiperidin-1-yl)-9H-purin-2-amine (5j):

**Fig: 5.10 : UV Spectrum of Compound 5j**



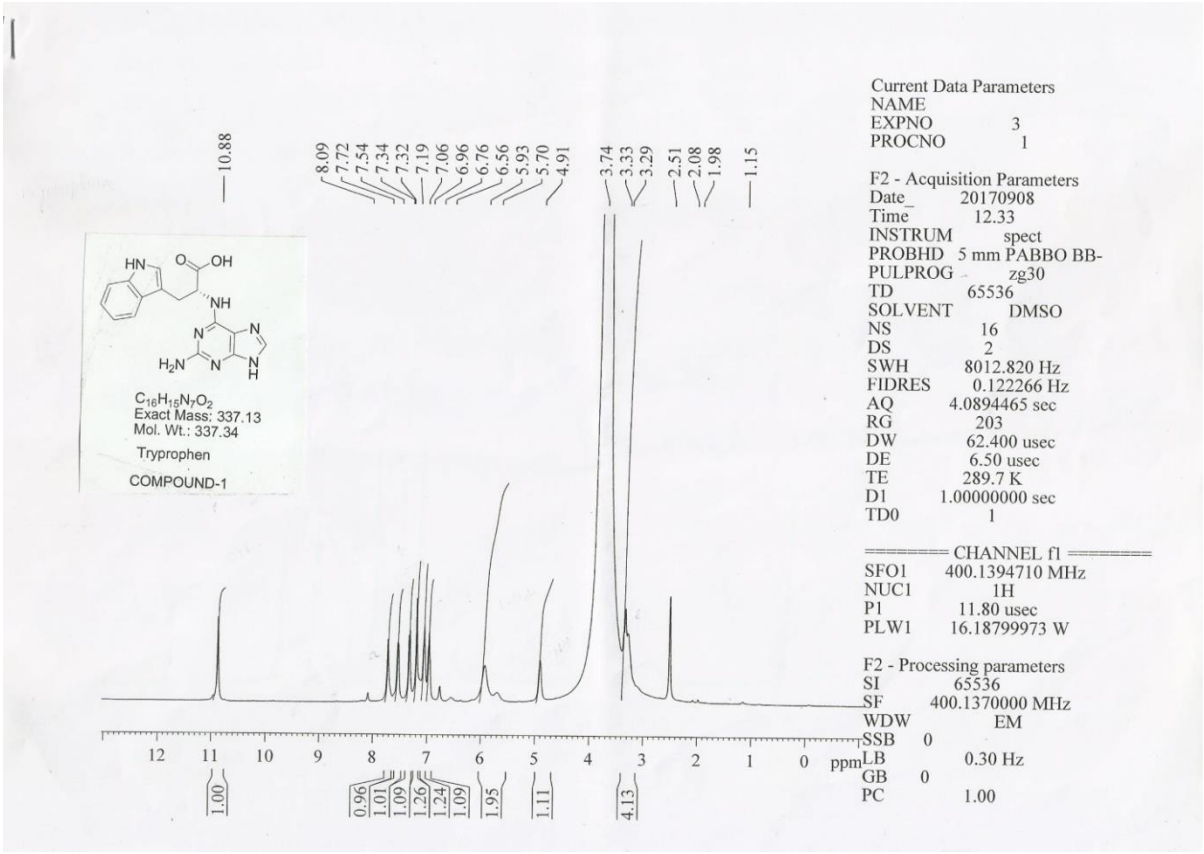
### 5.3.11 Preparation of (R)-2-(2-amino-9H-purin-6-ylamino)-2-phenylacetic acid (5k):

**Fig: 5.11 : UV Spectrum of Compound 5k**

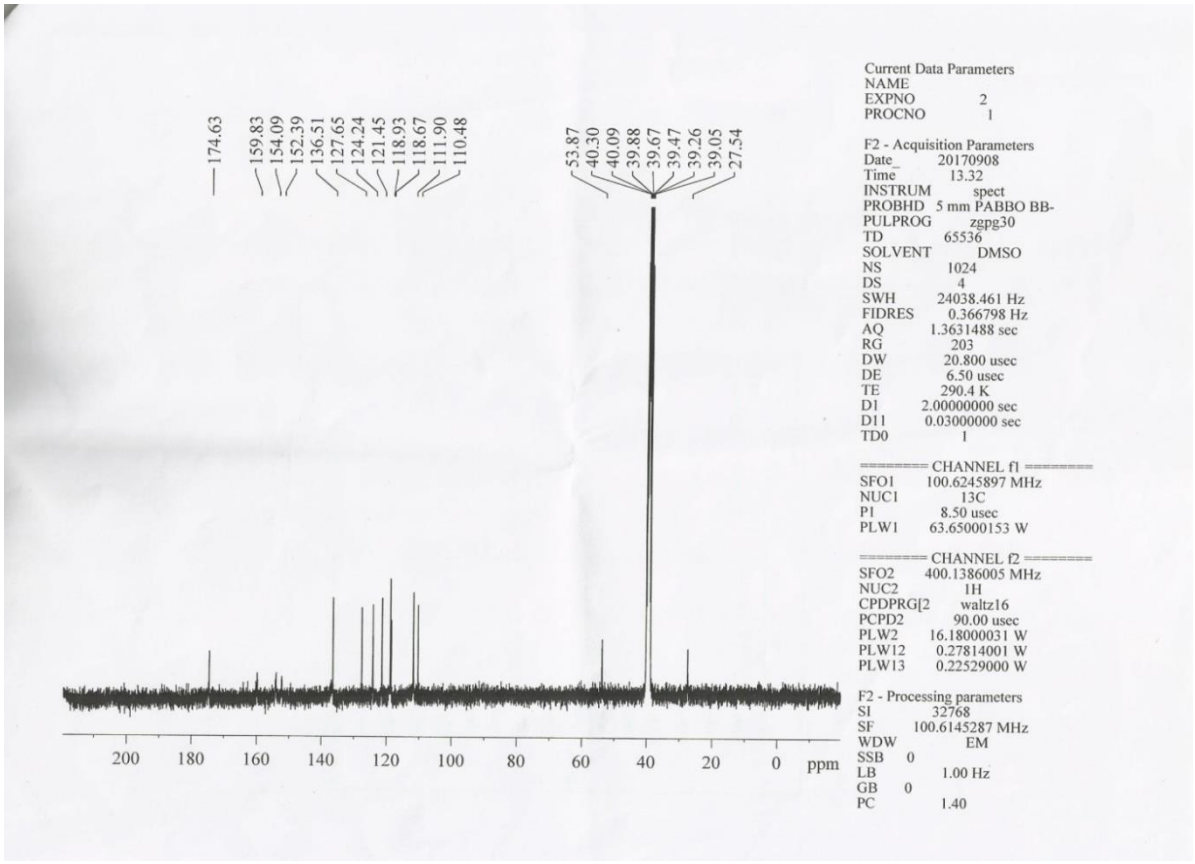


## 5.4 NMR, MASS AND IR SPECTRUM OF COMPOUNDS (5a-5k)

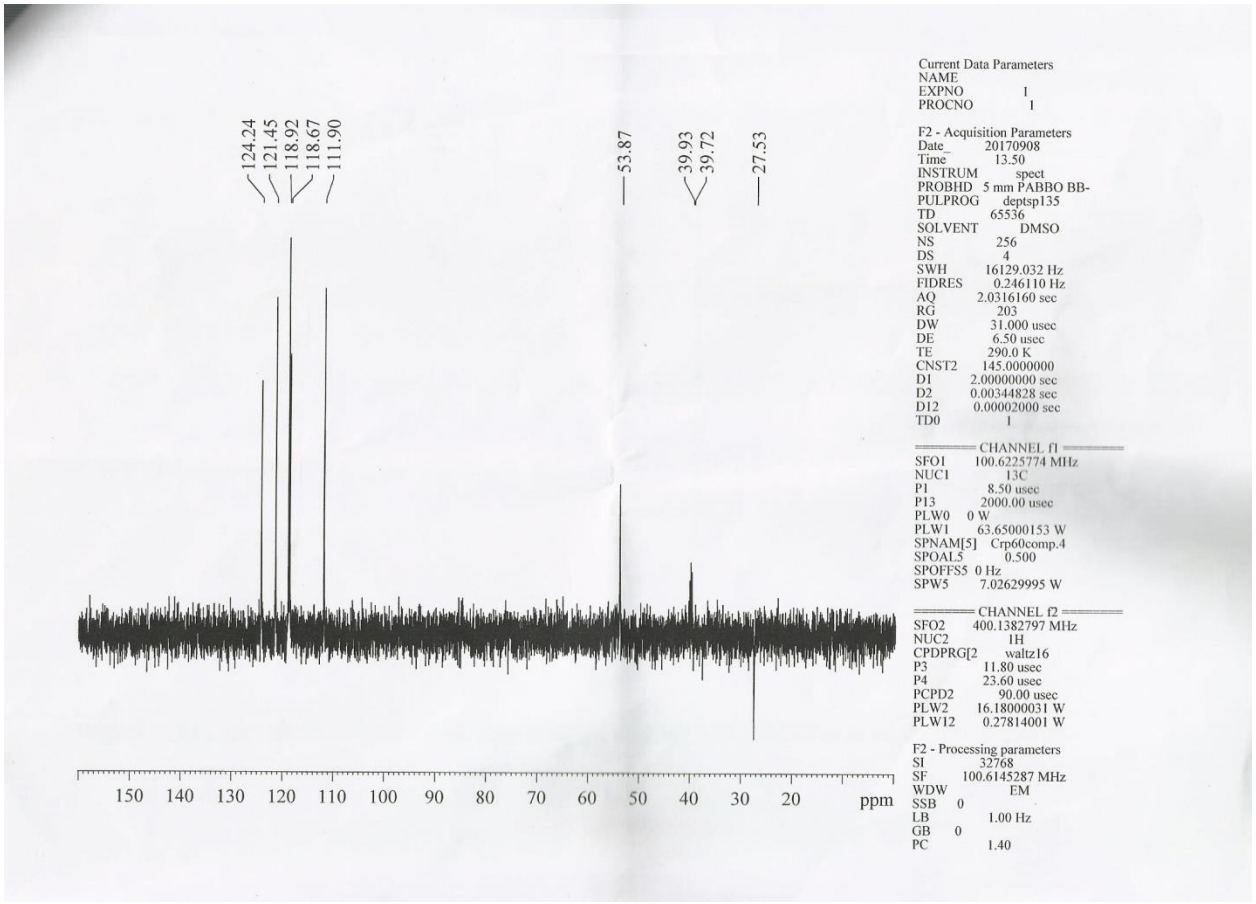
### 5.4.1 $H^1$ NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-3-(1H-indol-3-yl)propanoic acid (5a):



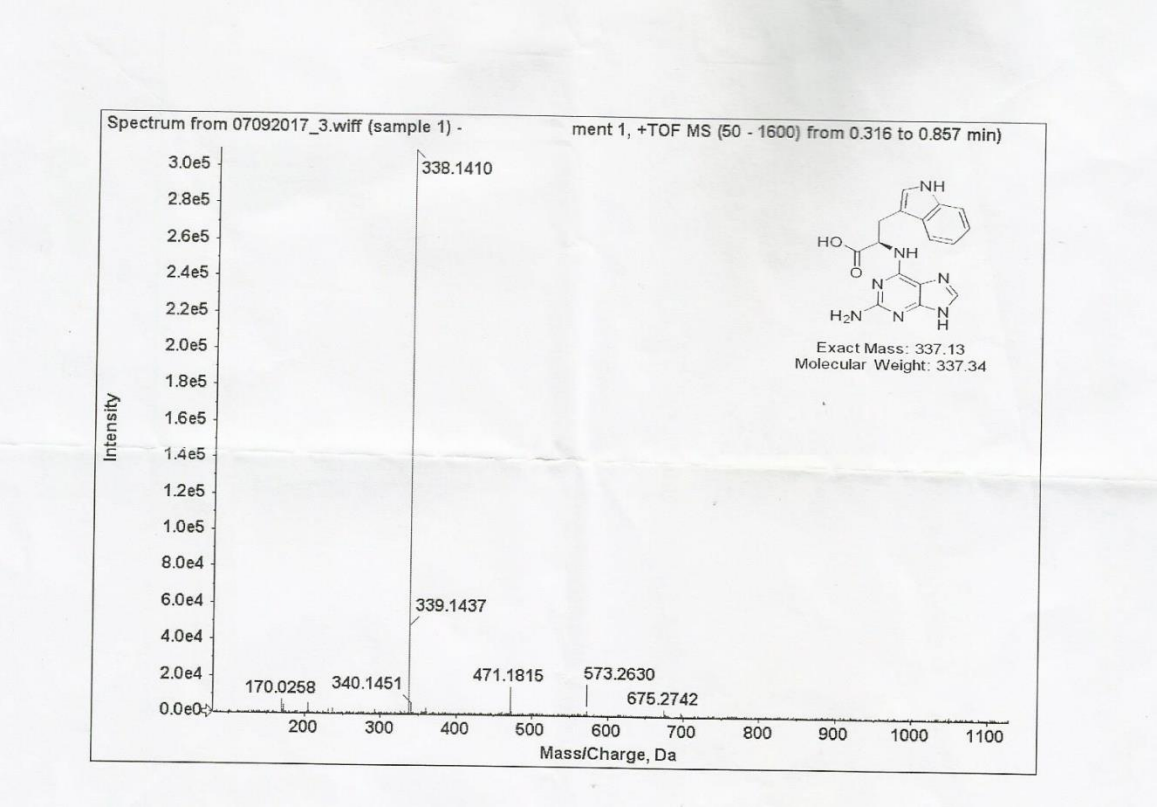
### 5.4.2 $C^{13}$ NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-3-(1H-indol-3-yl)propanoic acid (5a):



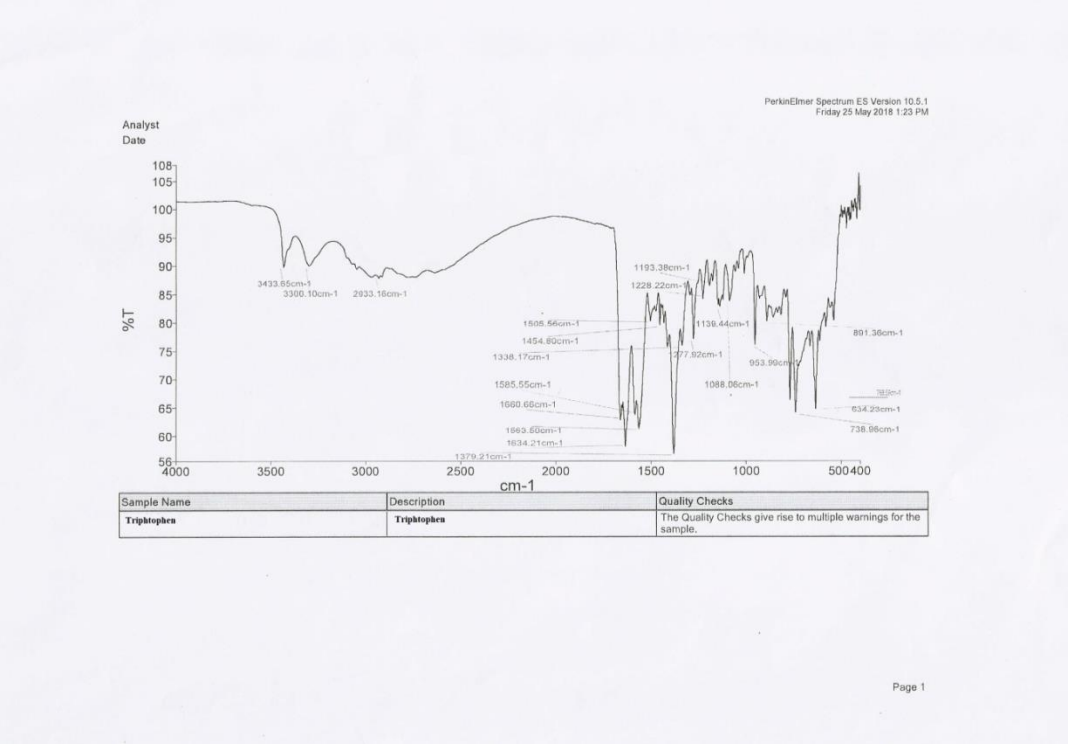
### 5.4.3 Dept NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-3-(1H-indol-3-yl)propanoic acid (5a):



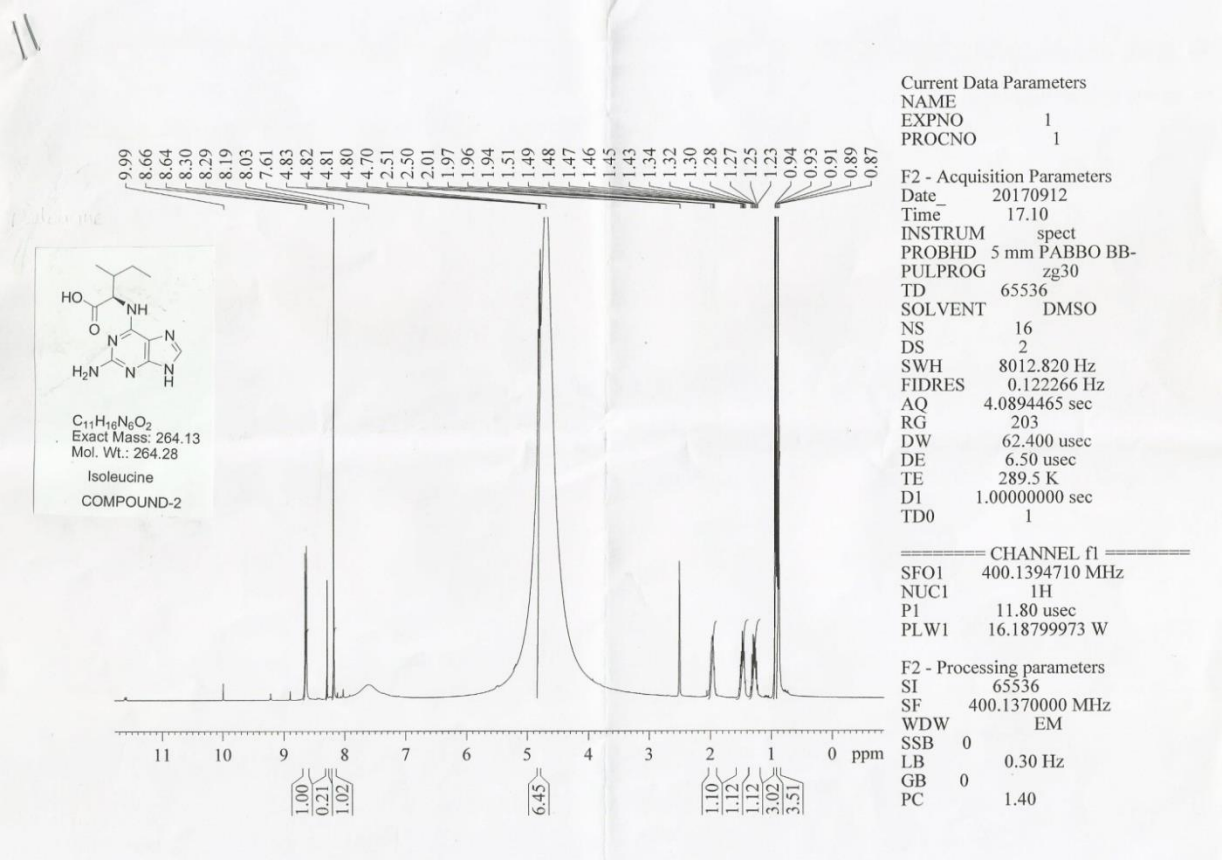
### 5.4.4 HRMS of (R)-2-(2-amino-9H-purin-6-ylamino)-3-(1H-indol-3-yl)propanoic acid (5a):



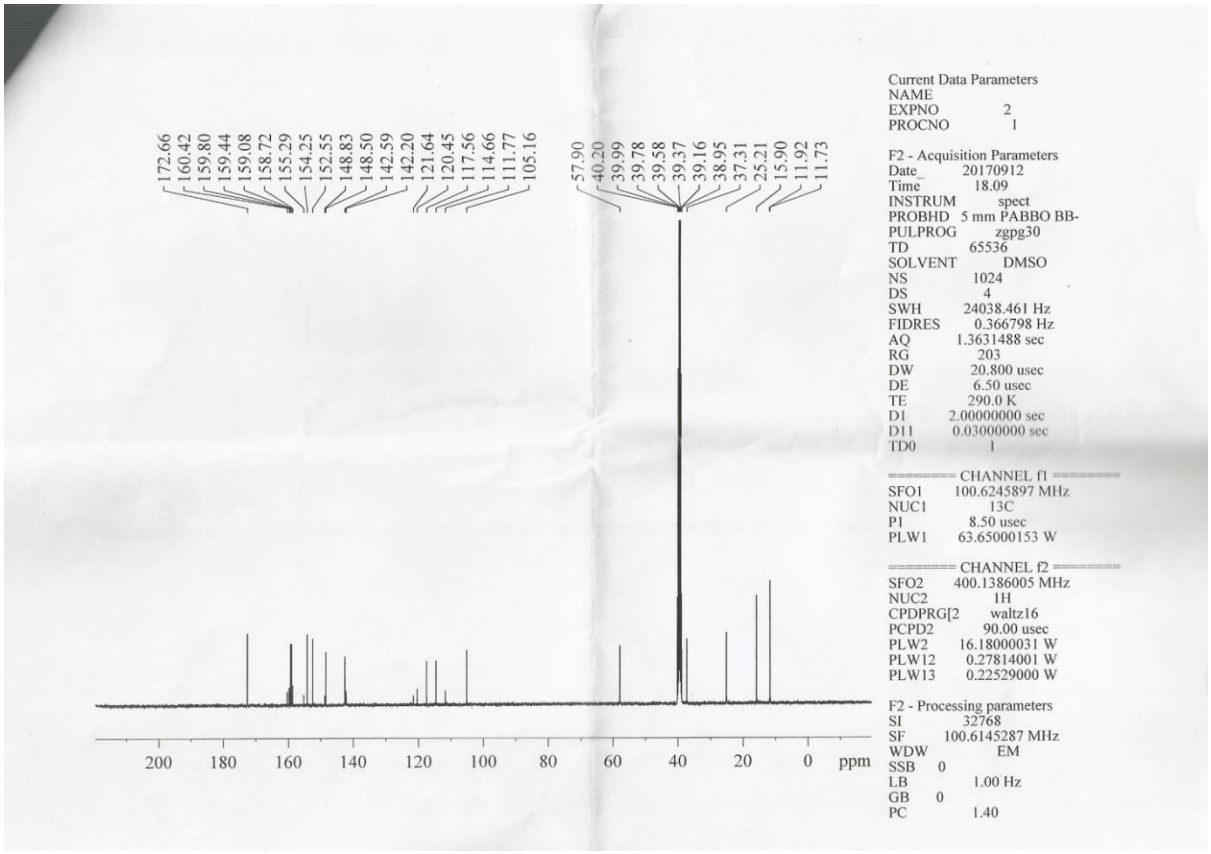
### 5.4.5 IR Spectrum of (R)-2-(2-amino-9H-purin-6-ylamino)-3-(1H-indol-3-yl)propanoic acid (5a):



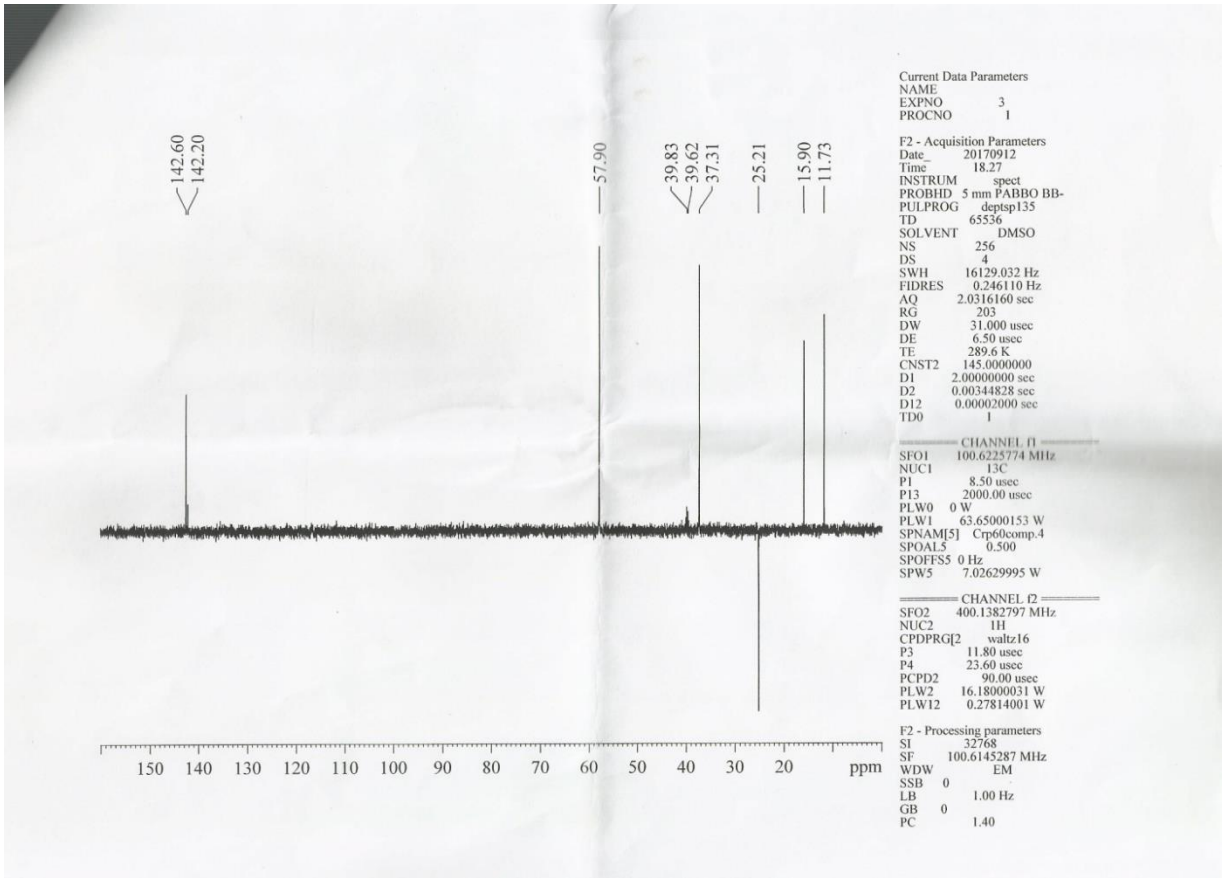
### 5.4.6 $H^1$ NMR of (2R)-2-(2-amino-9H-purin-6-ylamino)-3-methylpentanoic acid (5b):



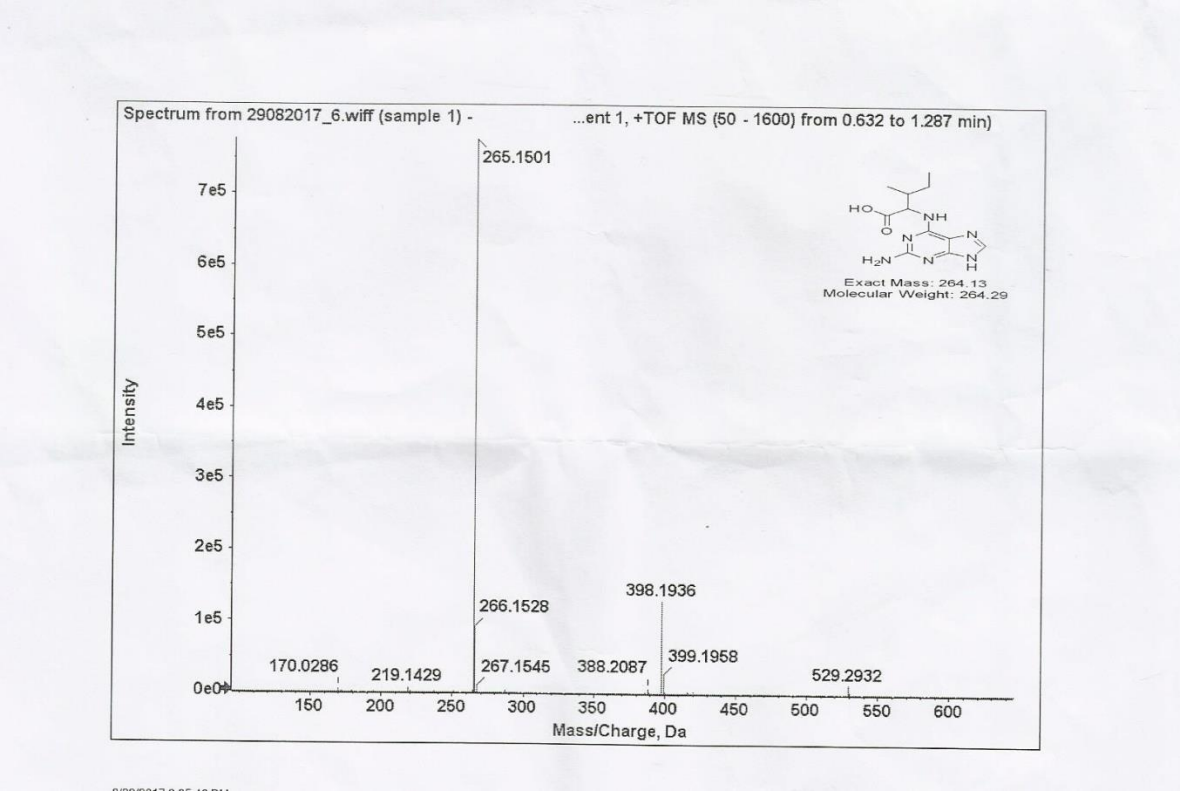
### 5.4.7 $C^{13}$ NMR of (2R)-2-(2-amino-9H-purin-6-ylamino)-3-methylpentanoic acid (5b):



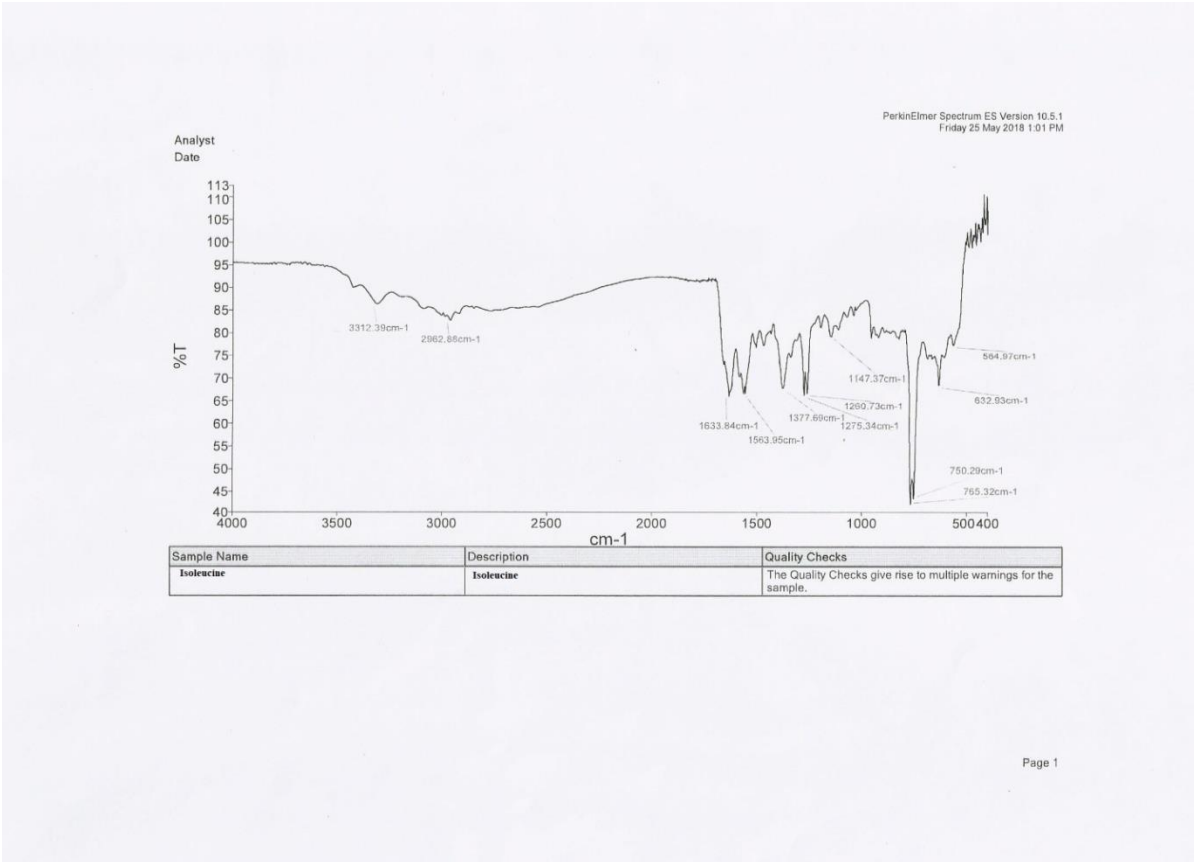
### 5.4.8 Dept NMR of (2R)-2-(2-amino-9H-purin-6-ylamino)-3-methylpentanoic acid (5b):



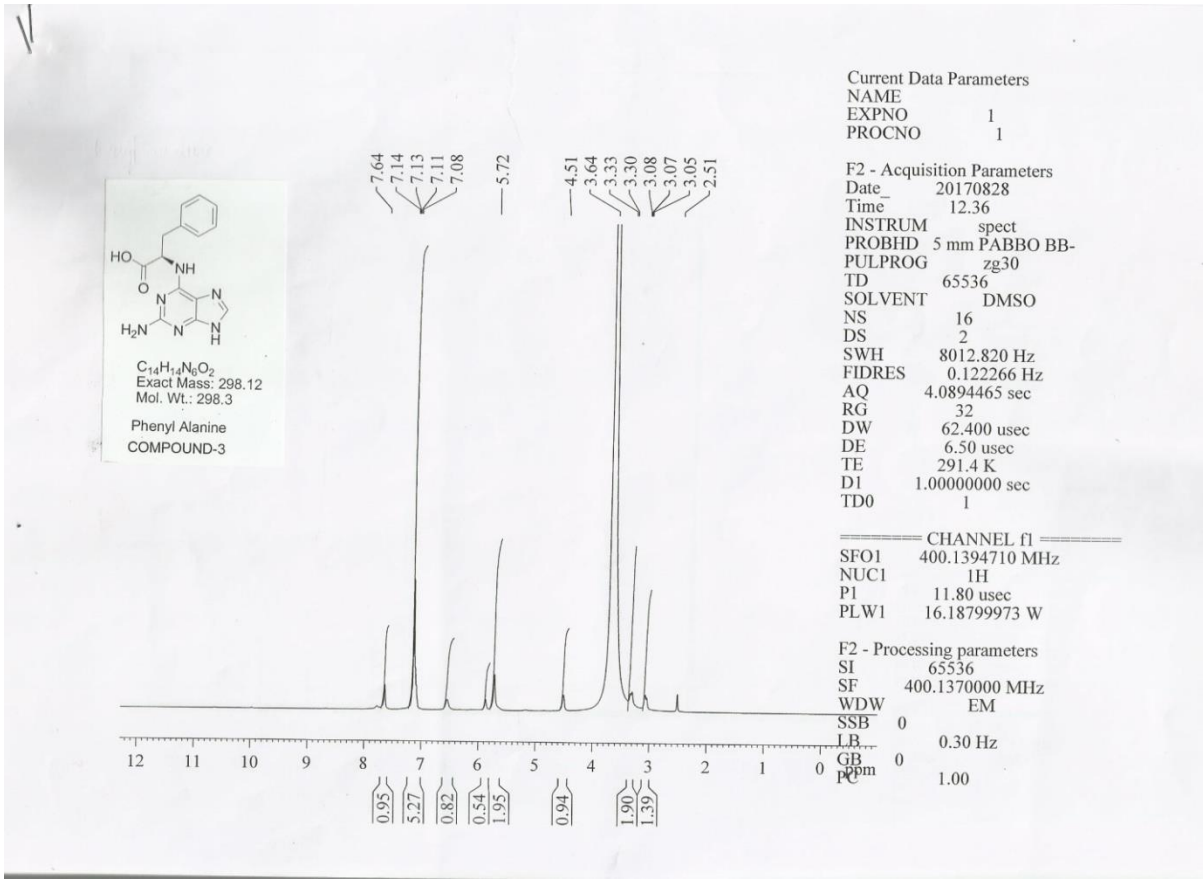
### 5.4.9 HRMS of (2R)-2-(2-amino-9H-purin-6-ylamino)-3-methylpentanoic acid (5b):



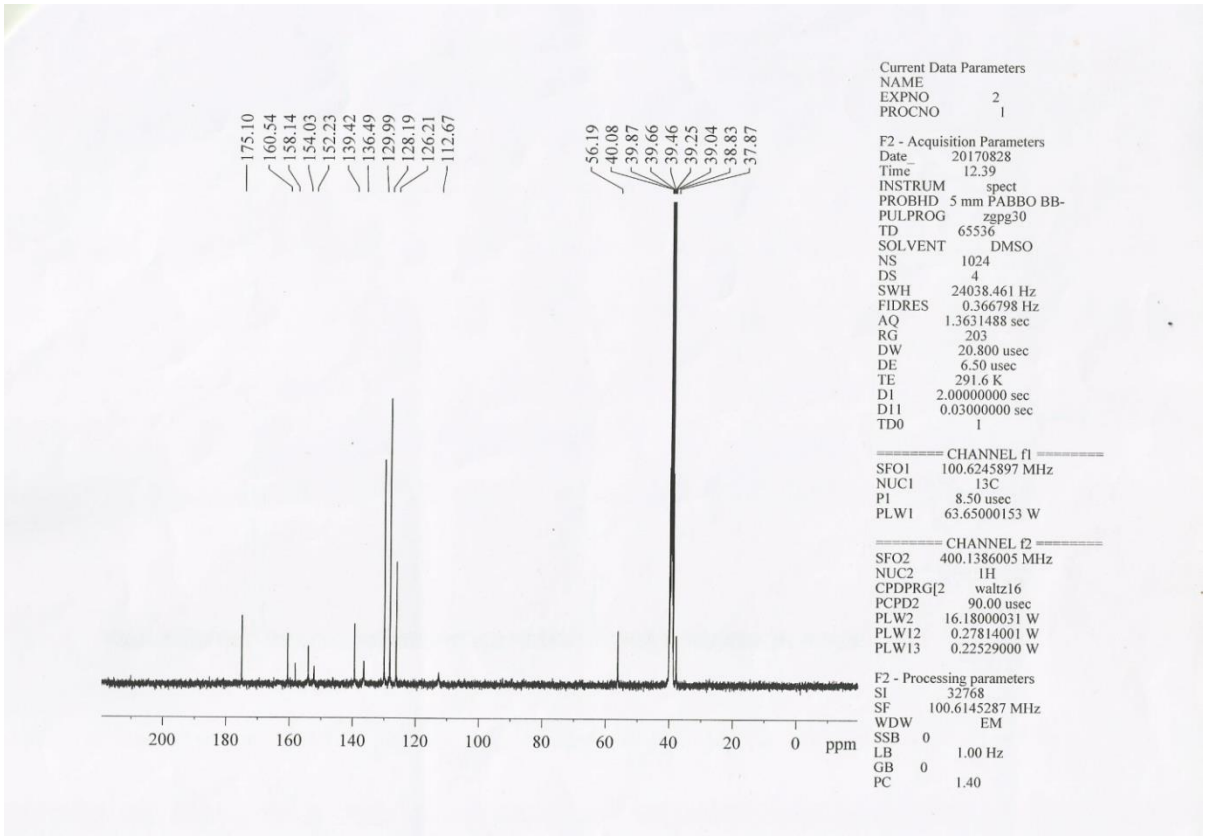
### 5.4.10 IR Spectrum of (2R)-2-(2-amino-9H-purin-6-ylamino)-3-methylpentanoic acid (5b):



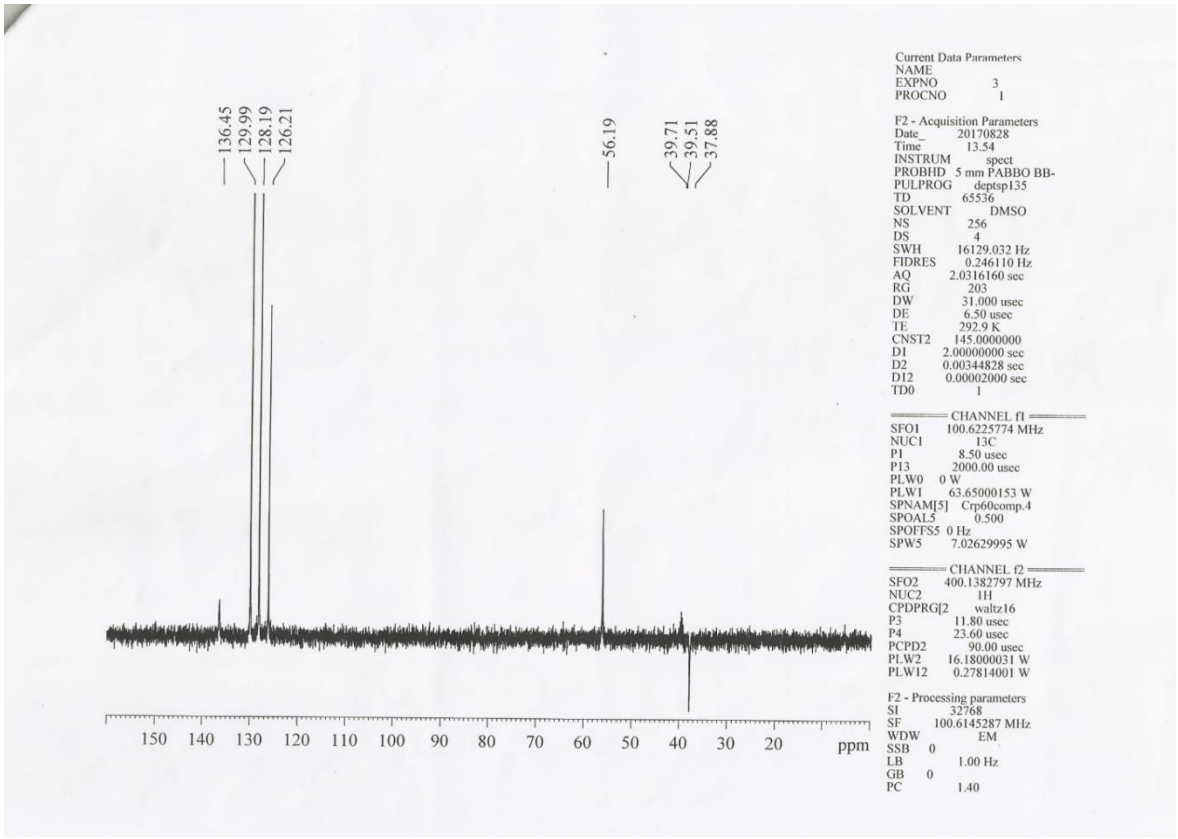
### 5.4.11 $H^1$ NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-3-phenylpropanoic acid (5c):



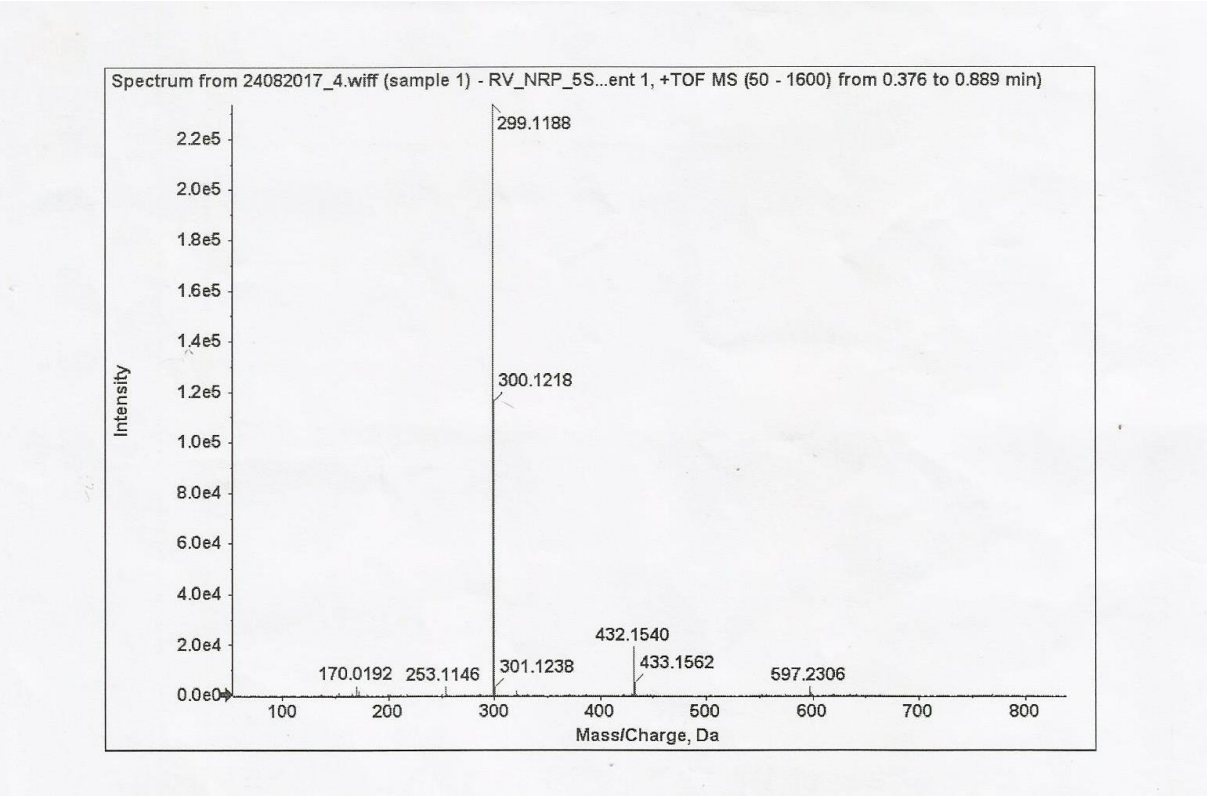
## 5.4.12 $C^{13}$ NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-3-phenylpropanoic acid (5c):



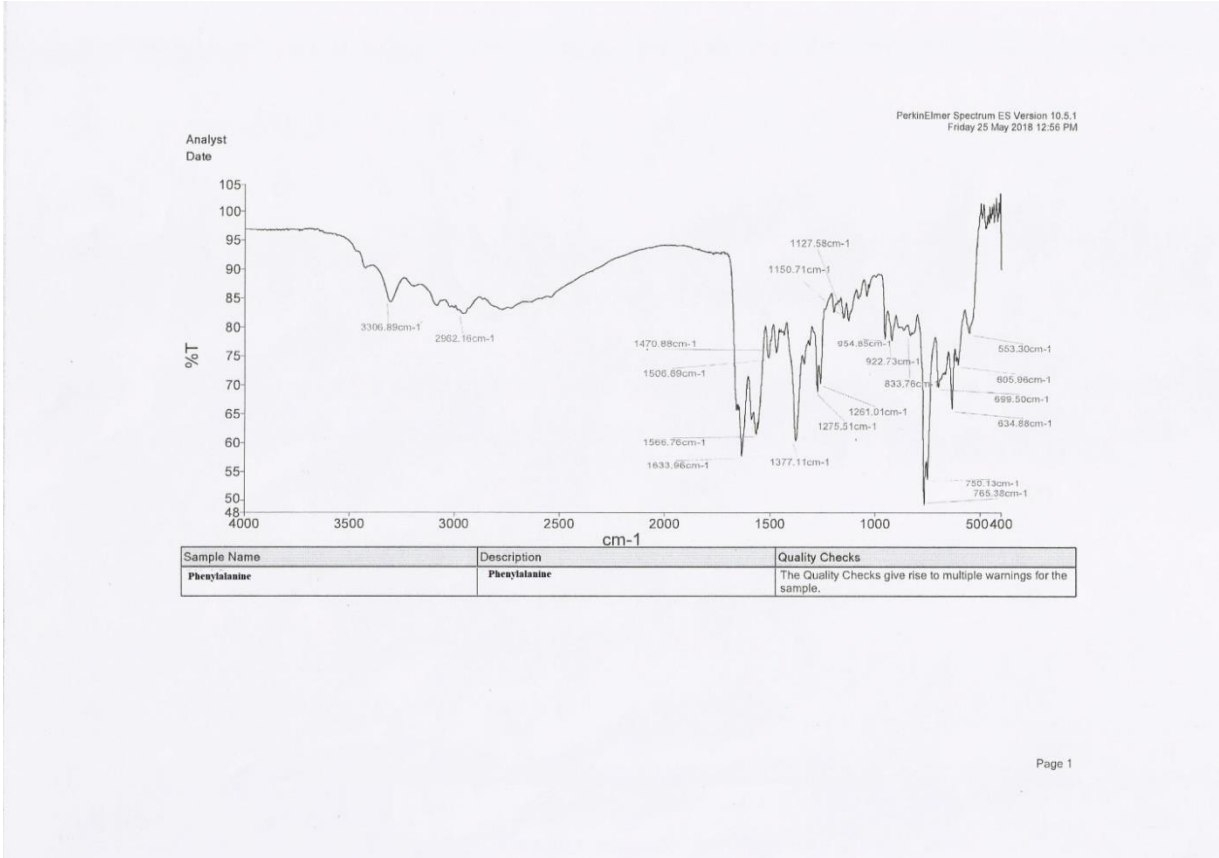
### 5.4.13 Dept NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-3-phenylpropanoic acid (5c):



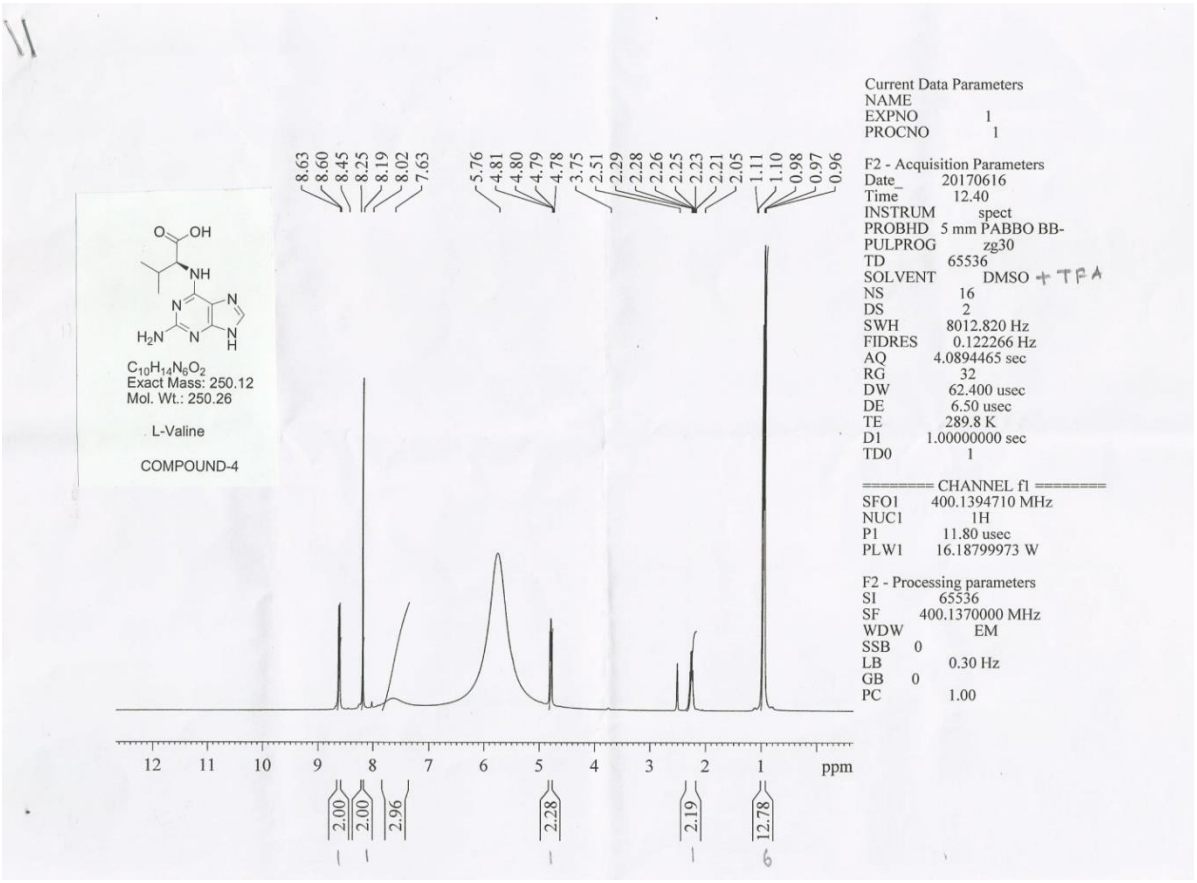
### 5.4.14 HRMS of (R)-2-(2-amino-9H-purin-6-ylamino)-3-phenylpropanoic acid (5c):



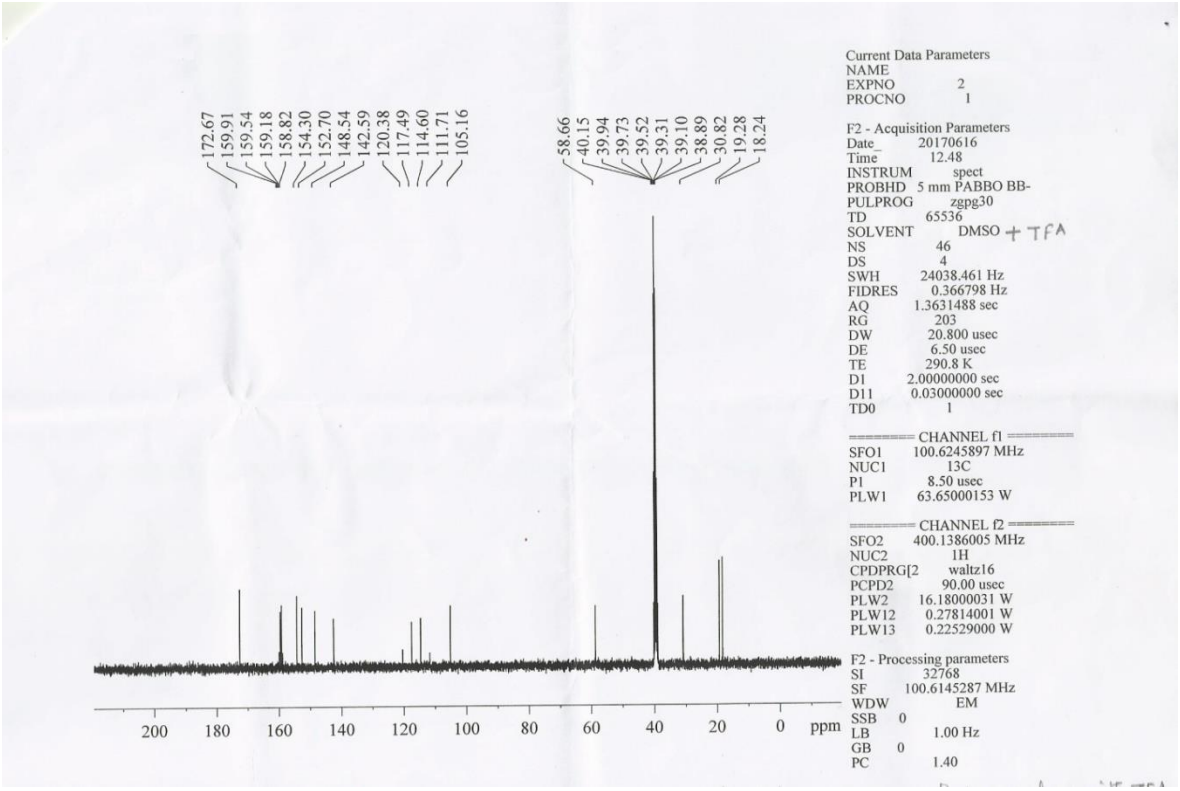
### 5.4.15 HRMS of (R)-2-(2-amino-9H-purin-6-ylamino)-3-phenylpropanoic acid (5c):



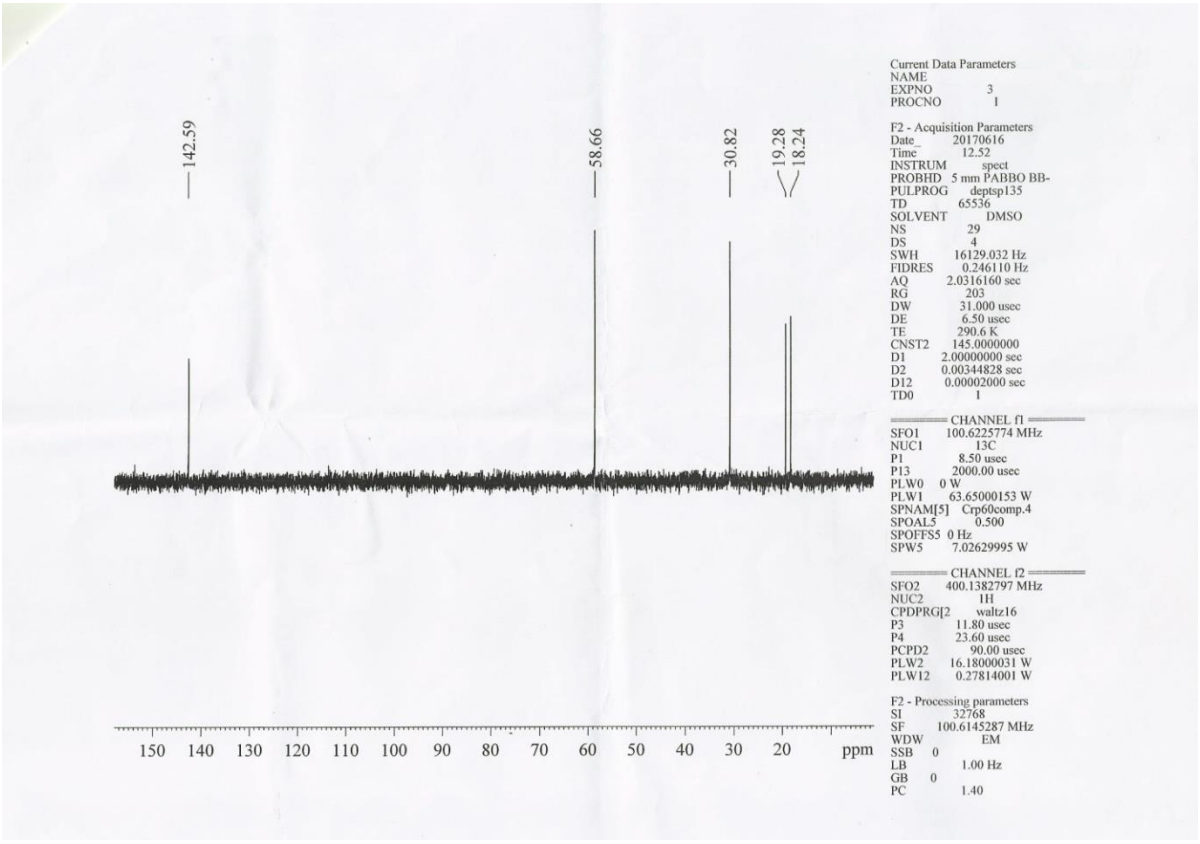
## 5.4.16 $H^1$ NMR of (S)-2-(2-amino-9H-purin-6-ylamino)-3-methylbutanoic acid (5d):



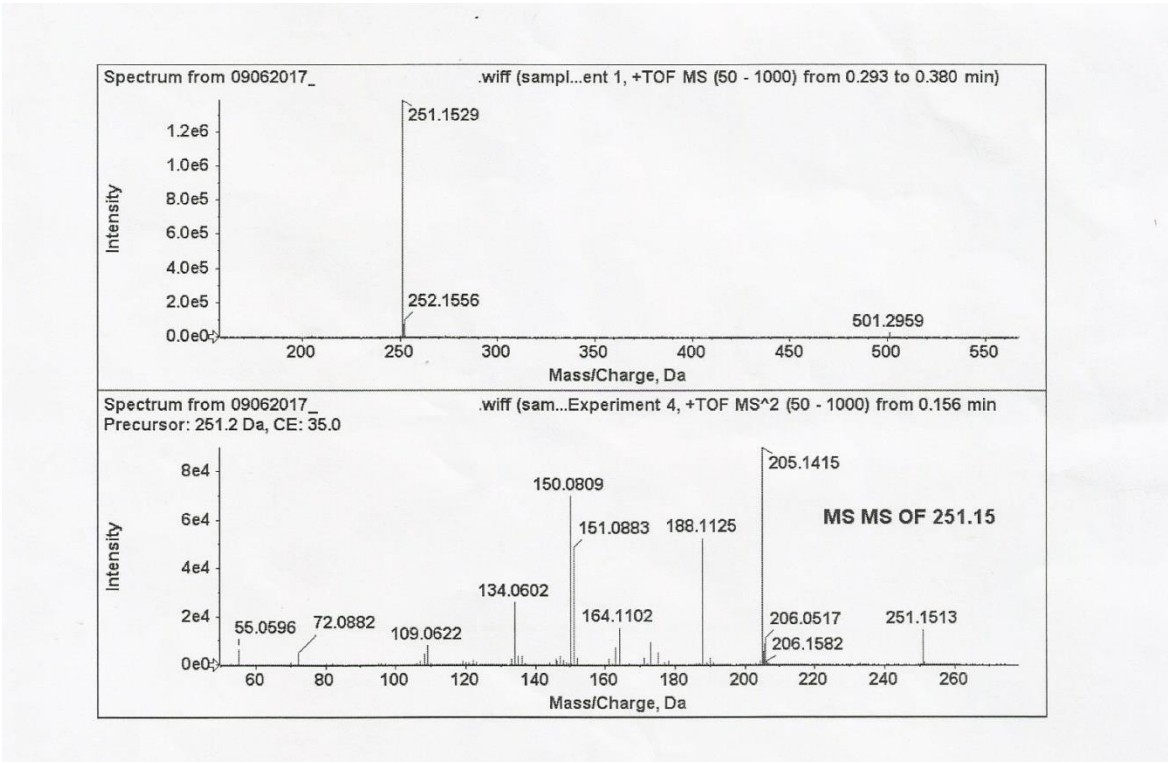
### 5.4.17 $C^{13}$ NMR of (S)-2-(2-amino-9H-purin-6-ylamino)-3-methylbutanoic acid (5d):



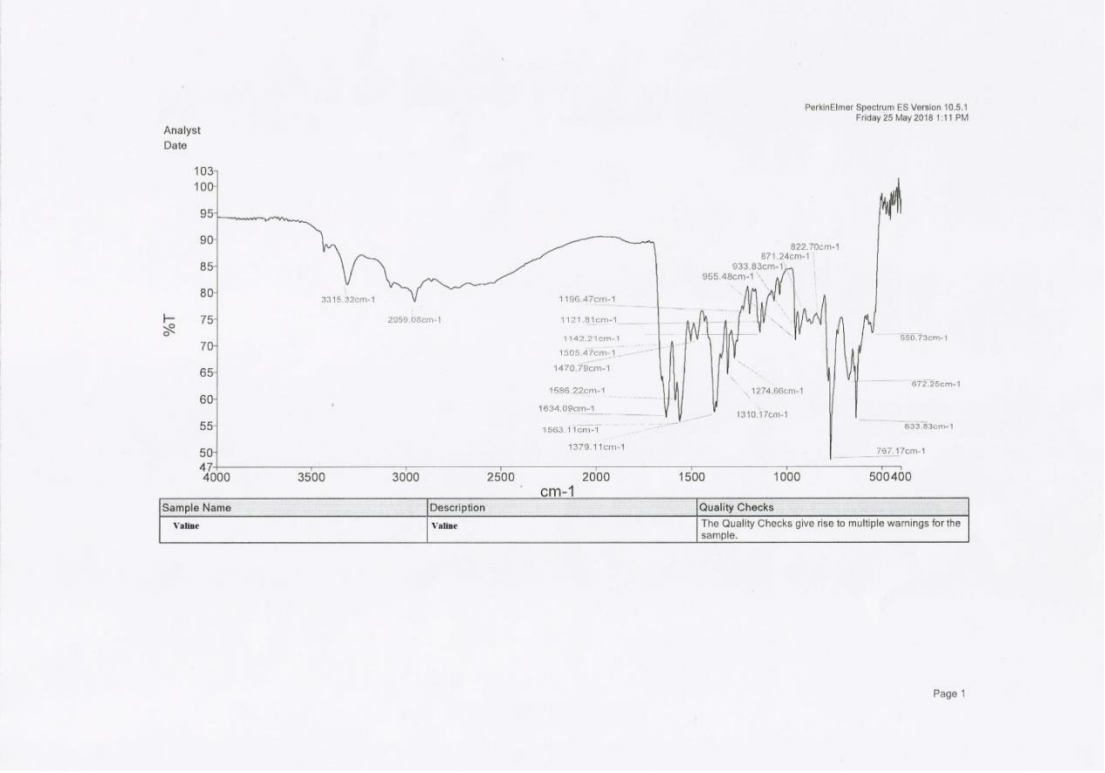
### 5.4.18 Dept NMR of (S)-2-(2-amino-9H-purin-6-ylamino)-3-methylbutanoic acid (5d):



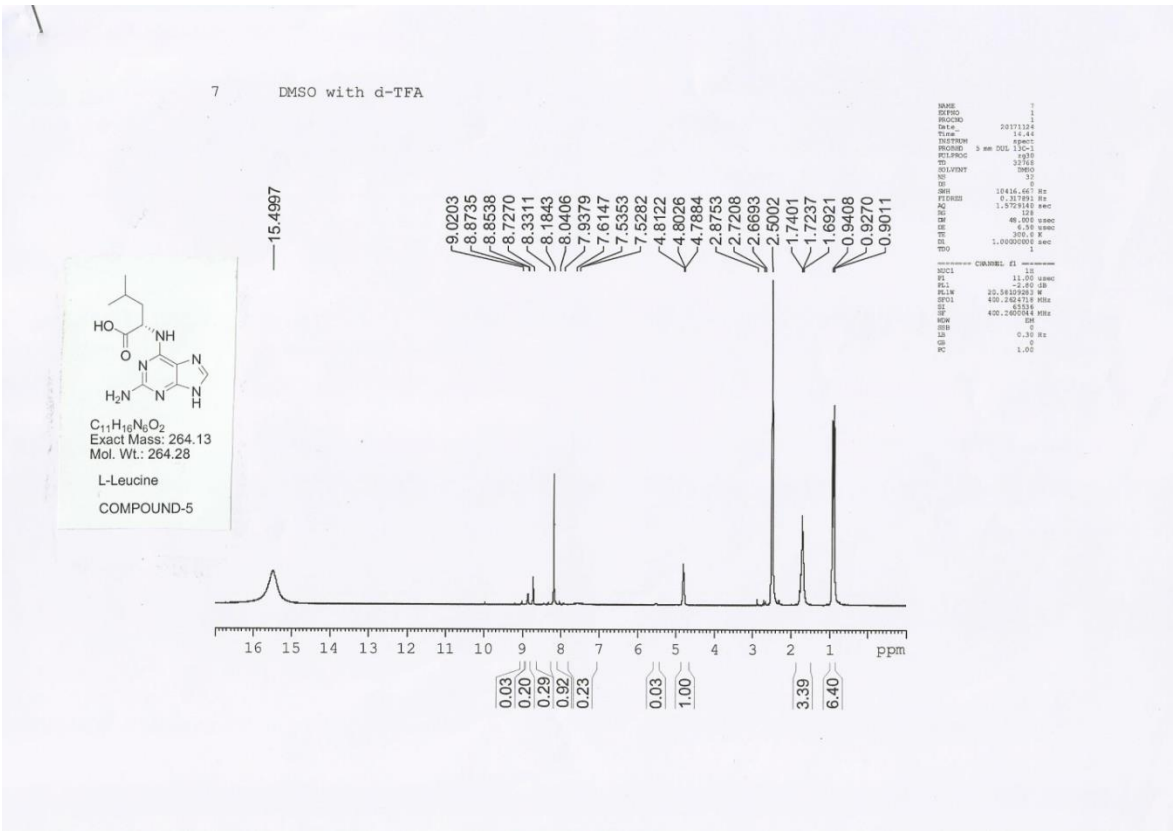
### 5.4.19 HRMS of (S)-2-(2-amino-9H-purin-6-ylamino)-3-methylbutanoic acid (5d):



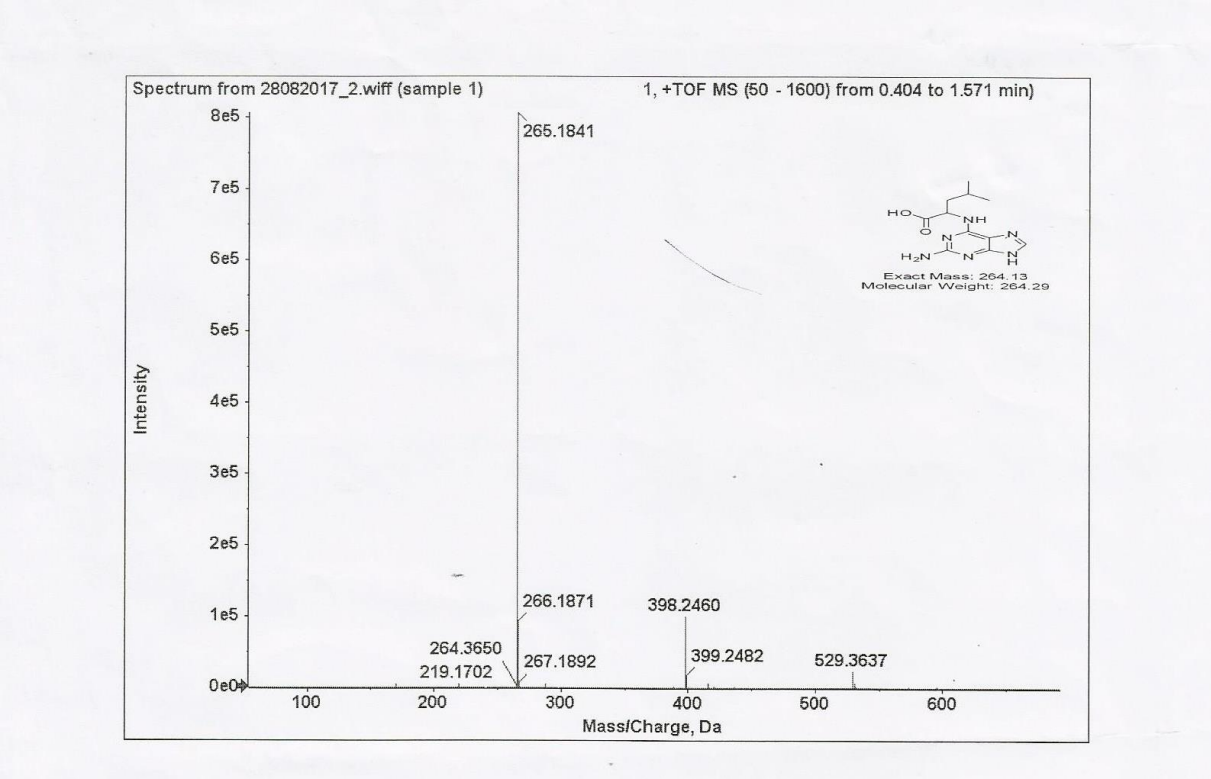
### 5.4.20 IR Spectrum of (S)-2-(2-amino-9H-purin-6-ylamino)-3-methylbutanoic acid (5d):



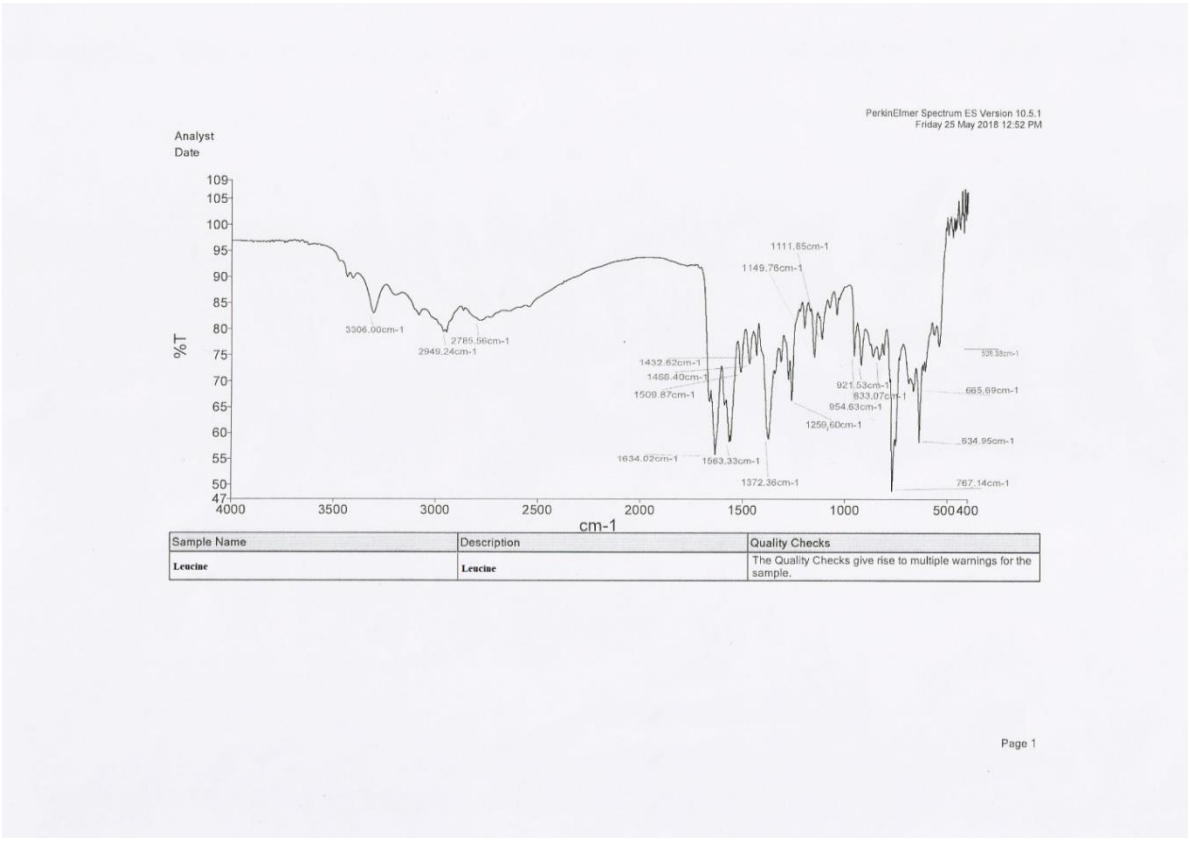
### 5.4.21 $H^1$ NMR of Preparation of (S)-2-(2-amino-9H-purin-6-ylamino)-4-methylpentanoic acid (5e):



### 5.4.22 HRMS NMR of Preparation of (S)-2-(2-amino-9H-purin-6-ylamino)-4-methylpentanoic acid (5e):

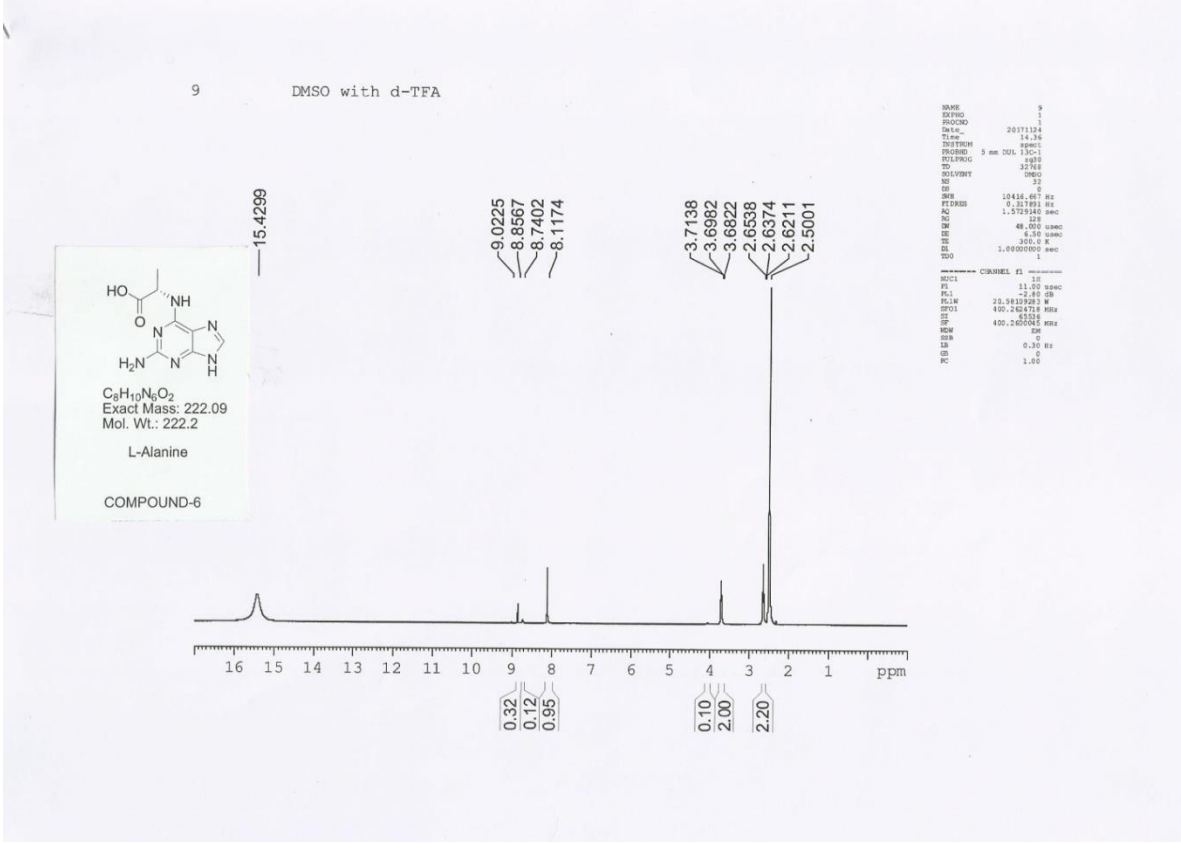


### 5.4.23 IR Spectrum of Preparation of (S)-2-(2-amino-9H-purin-6-ylamino)-4-methylpentanoic acid (5e):

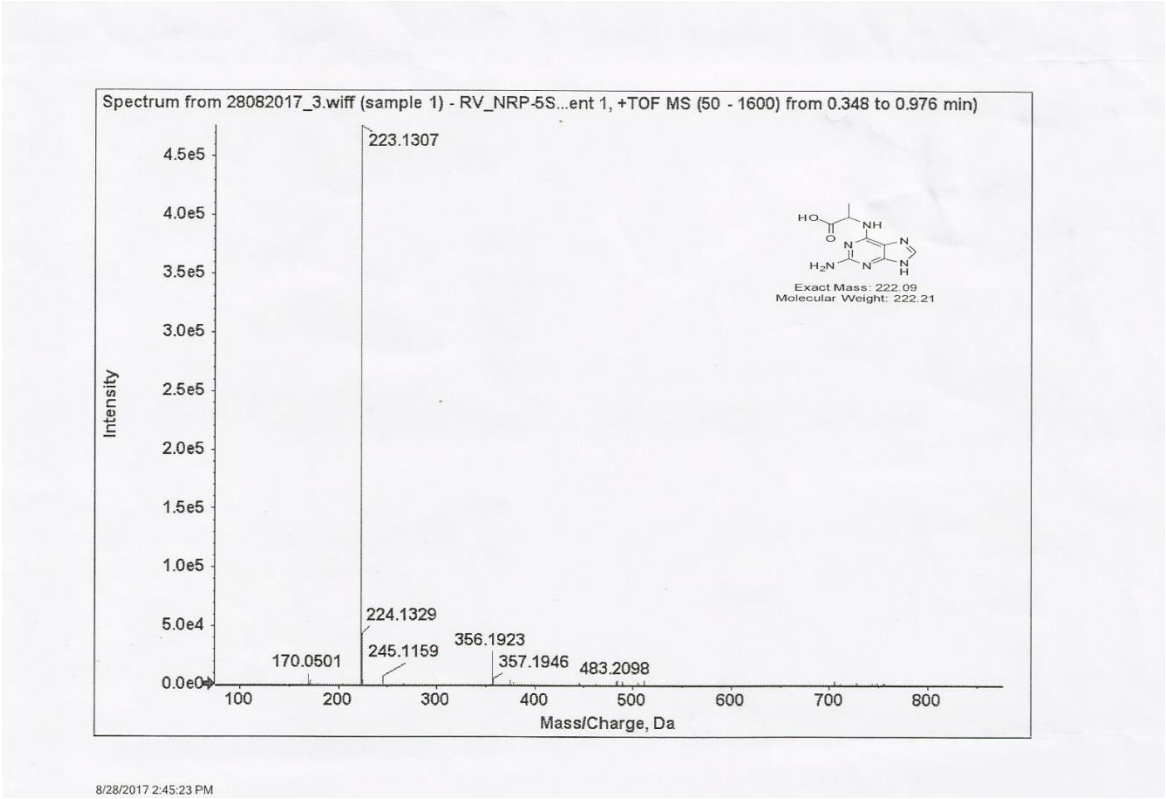



| Sample Name | Description | Quality Checks |
|---|---|---|
| Leucine | Leucine | The Quality Checks give rise to multiple warnings for the sample. |

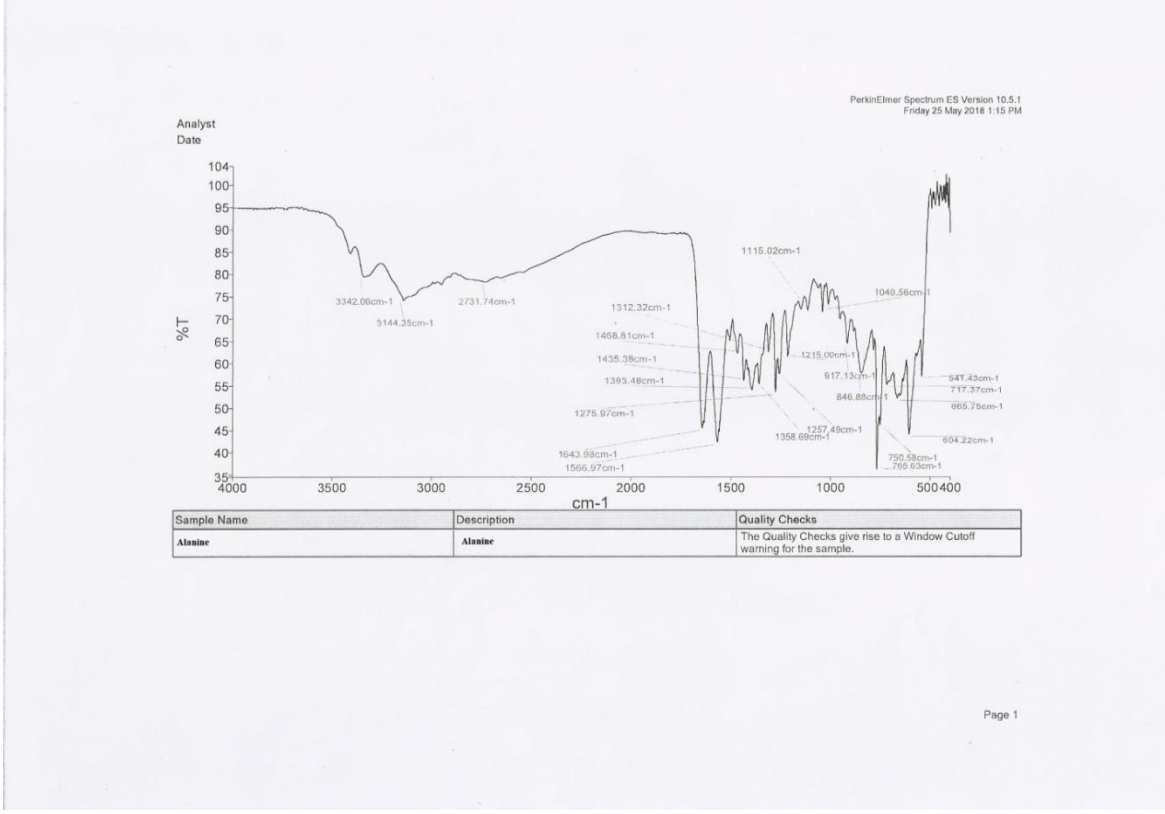
## 5.4.24 $H^1$ NMR of (S)-2-(2-amino-9H-purin-6-ylamino)propanoic acid (5f):



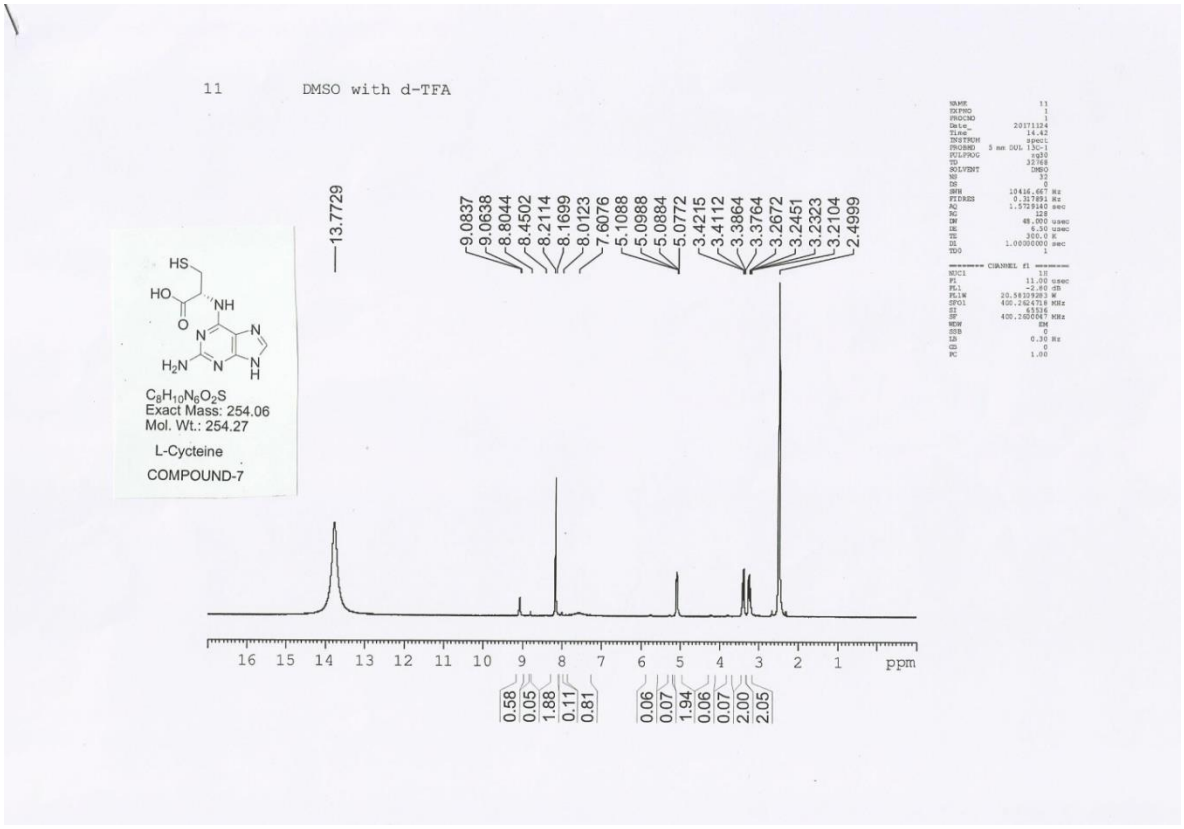
## 5.4.25 HRMS of (S)-2-(2-amino-9H-purin-6-ylamino)propanoic acid (5f):



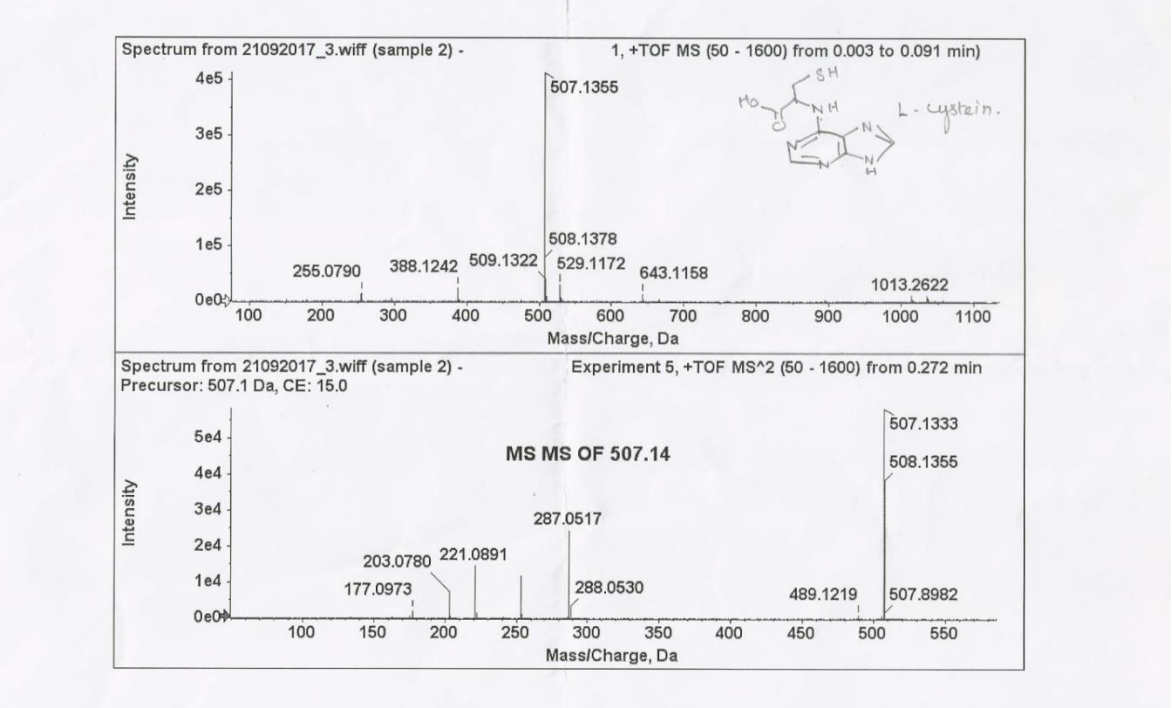
## 5.4.26 IR Spectrum of (S)-2-(2-amino-9H-purin-6-ylamino)propanoic acid (5f):



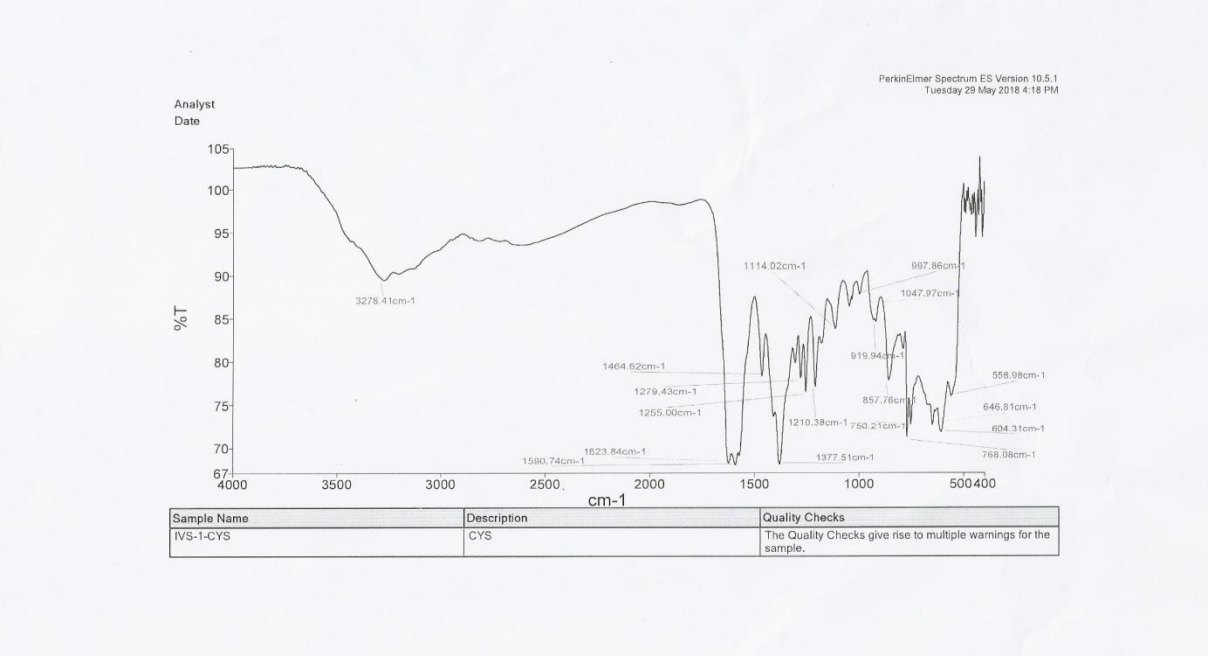
## 5.4.27 $H^1$ NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-3-mercaptopropanoic acid (5g):



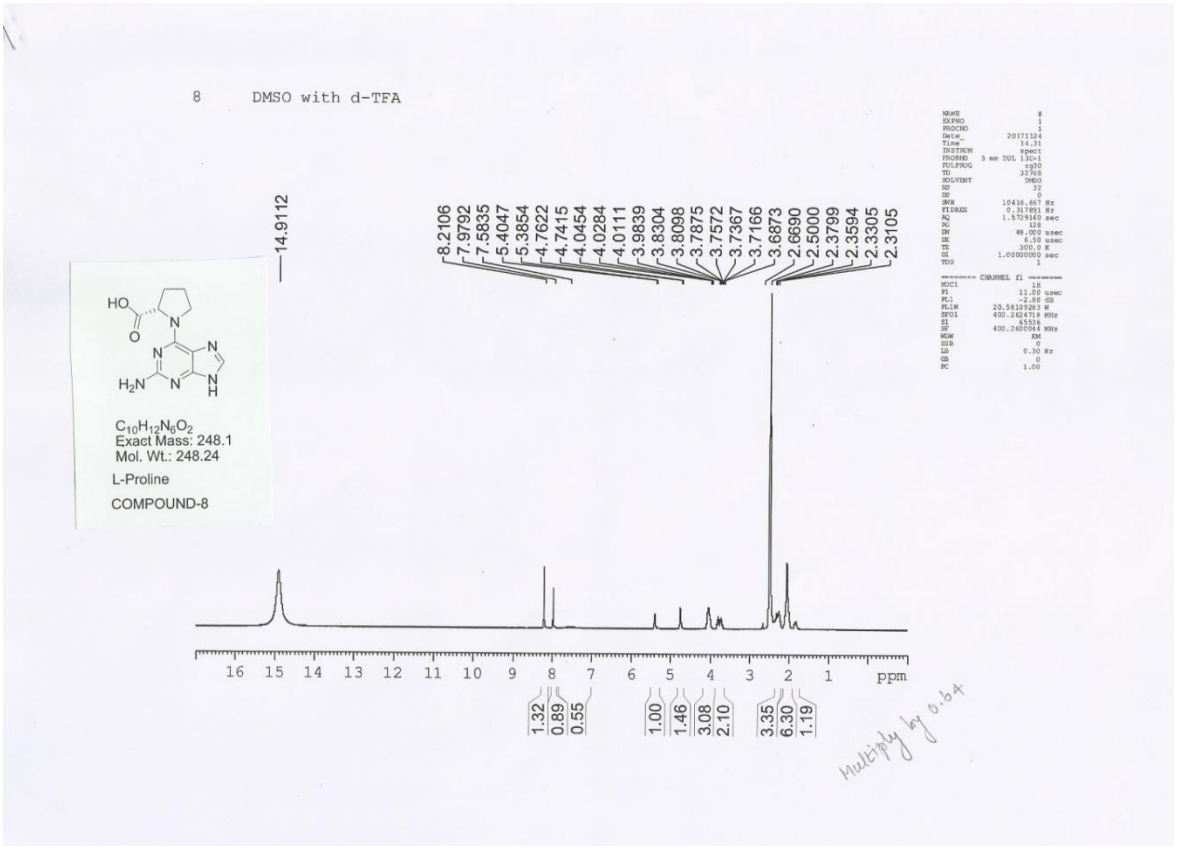
### 5.4.28 HRMS of (R)-2-(2-amino-9H-purin-6-ylamino)-3-mercaptopropanoic acid (5g):



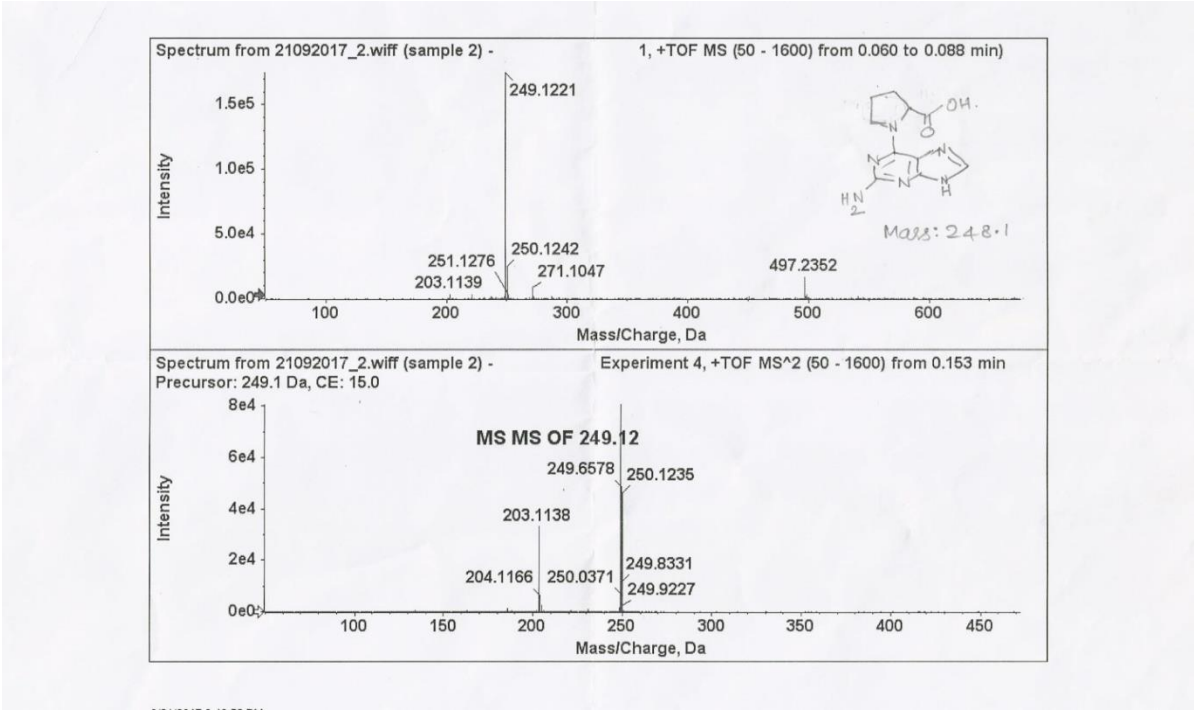
### 5.4.29 HRMS of (R)-2-(2-amino-9H-purin-6-ylamino)-3-mercaptopropanoic acid (5g):



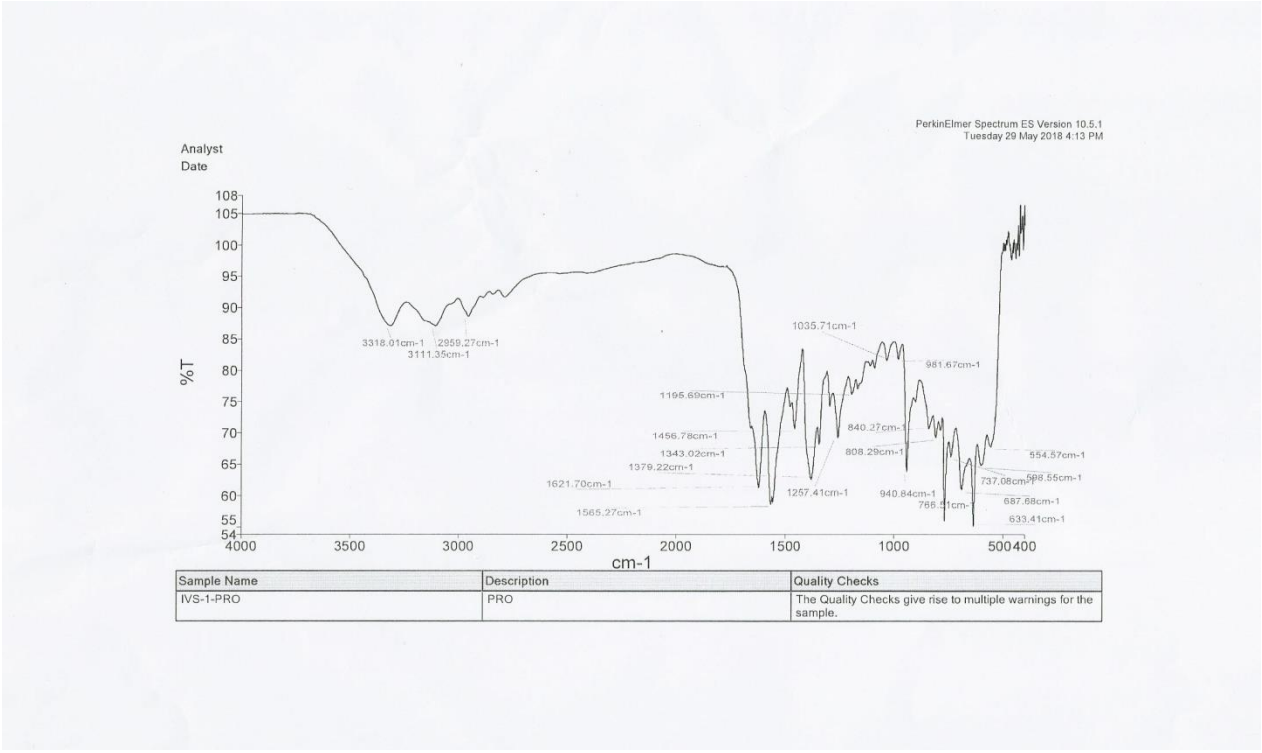
### 5.4.30 $H^1$ NMR of (S)-1-(2-amino-9H-purin-6-yl)pyrrolidine-2-carboxylic acid (5h):



### 5.4.31 HRMS of (S)-1-(2-amino-9H-purin-6-yl)pyrrolidine-2-carboxylic acid (5h):

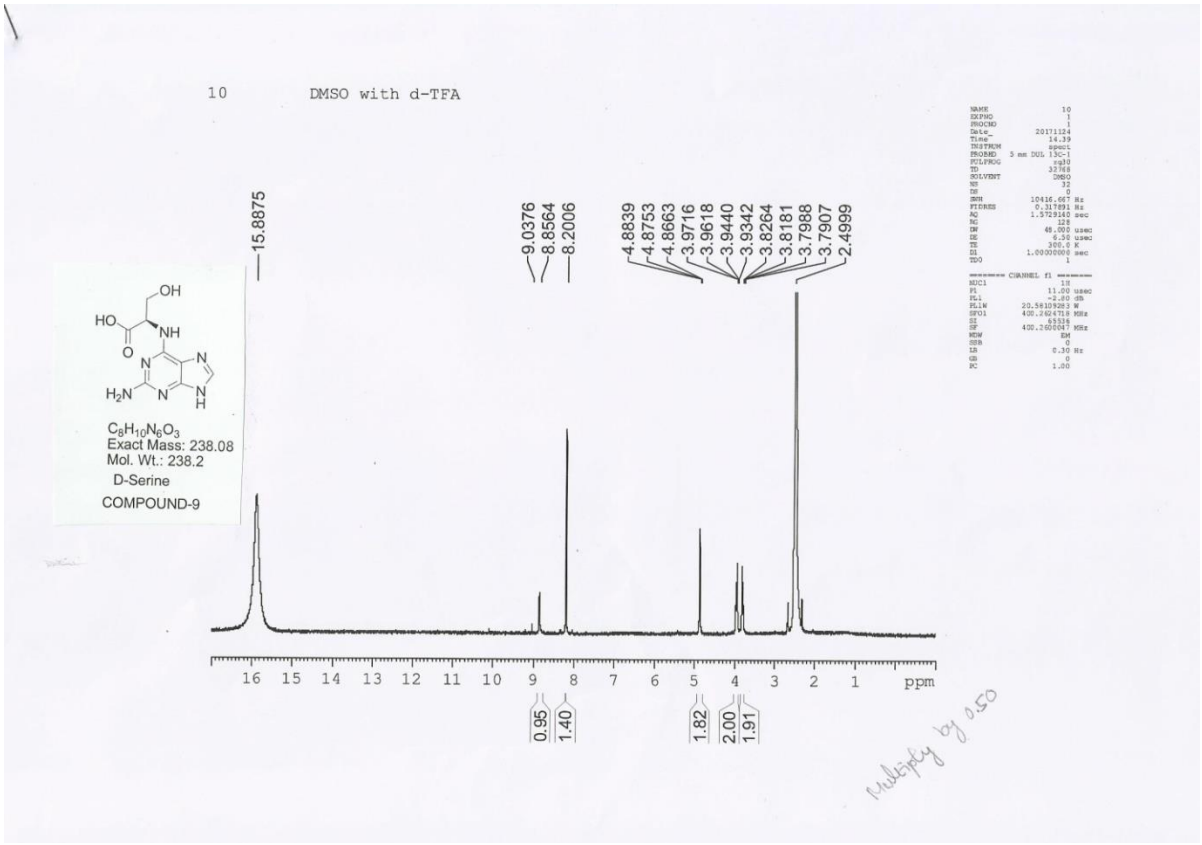


## 5.4.32 HRMS of (S)-1-(2-amino-9H-purin-6-yl)pyrrolidine-2-carboxylic acid (5h):

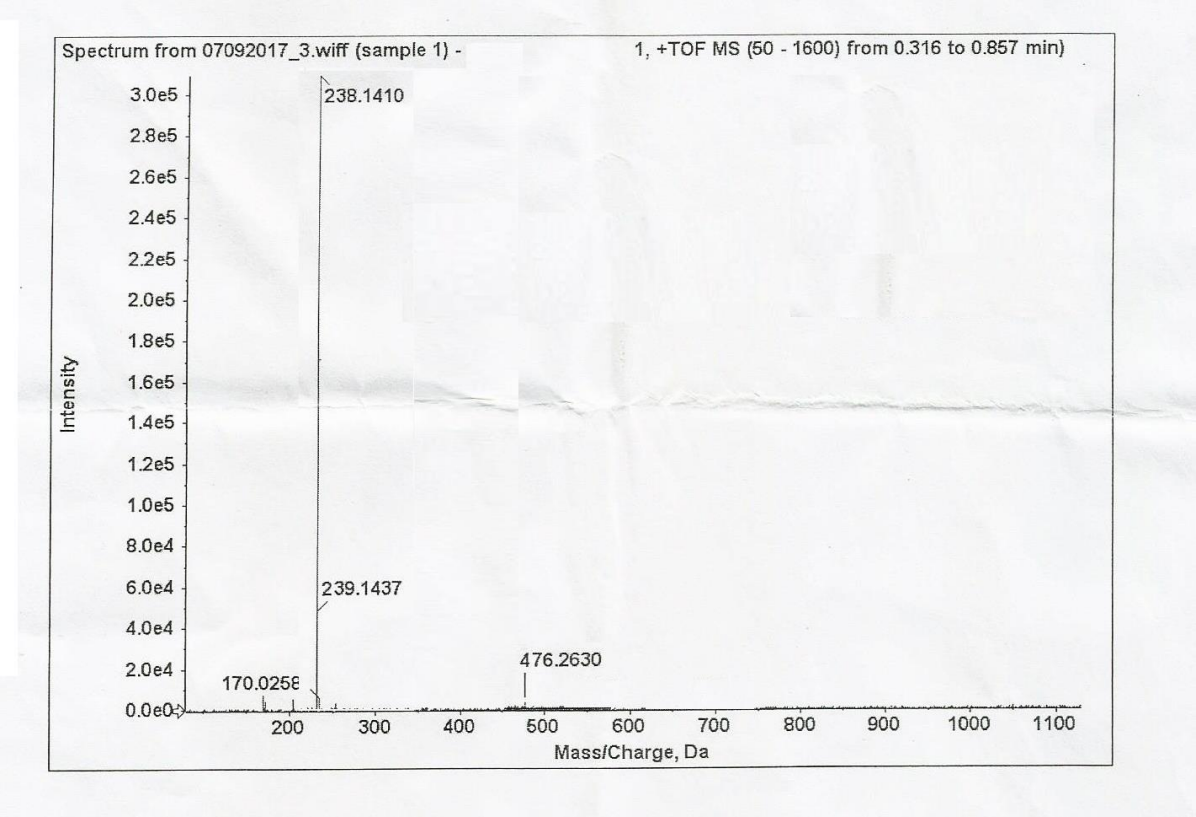



| Sample Name | Description | Quality Checks |
|---|---|---|
| IVS-1-PRO | PRO | The Quality Checks give rise to multiple warnings for the sample. |

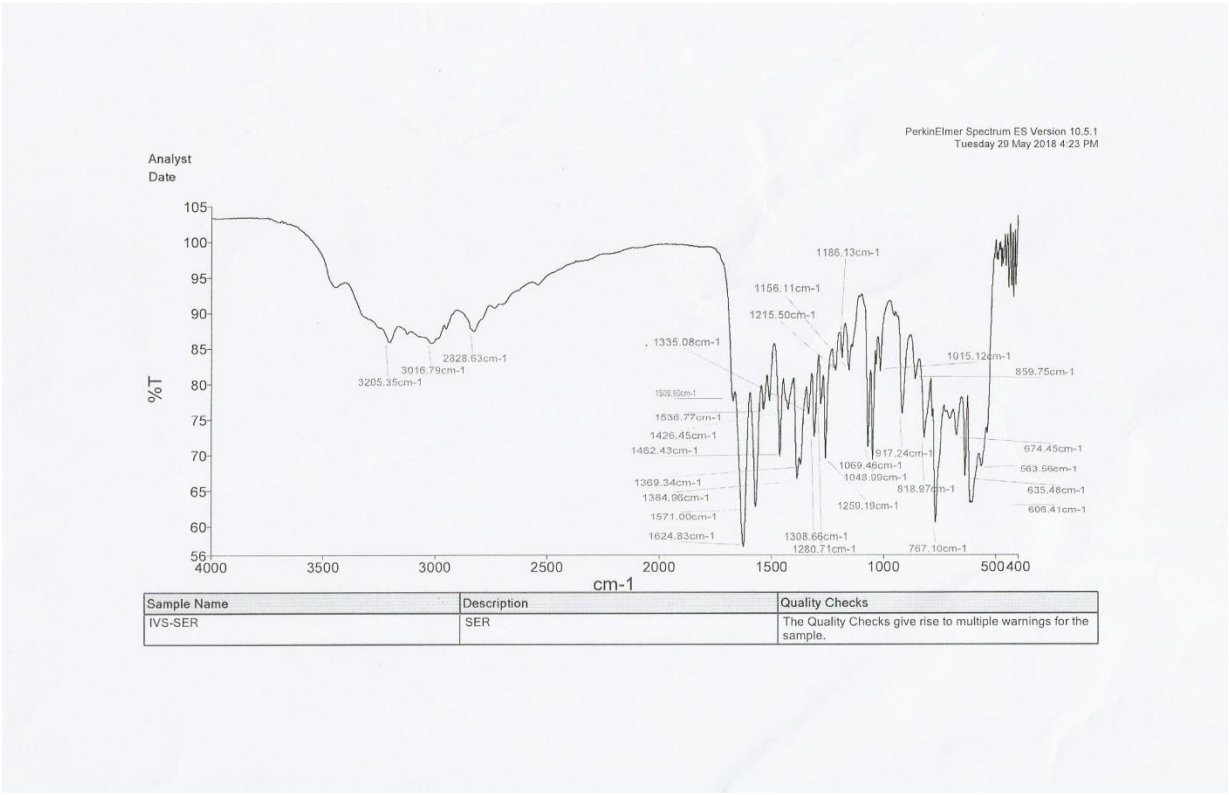
### 5.4.33 $H^1$ NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-3-hydroxypropanoic acid (5i):



### 5.4.34 HRMS of (R)-2-(2-amino-9H-purin-6-ylamino)-3-hydroxypropanoic acid (5i):

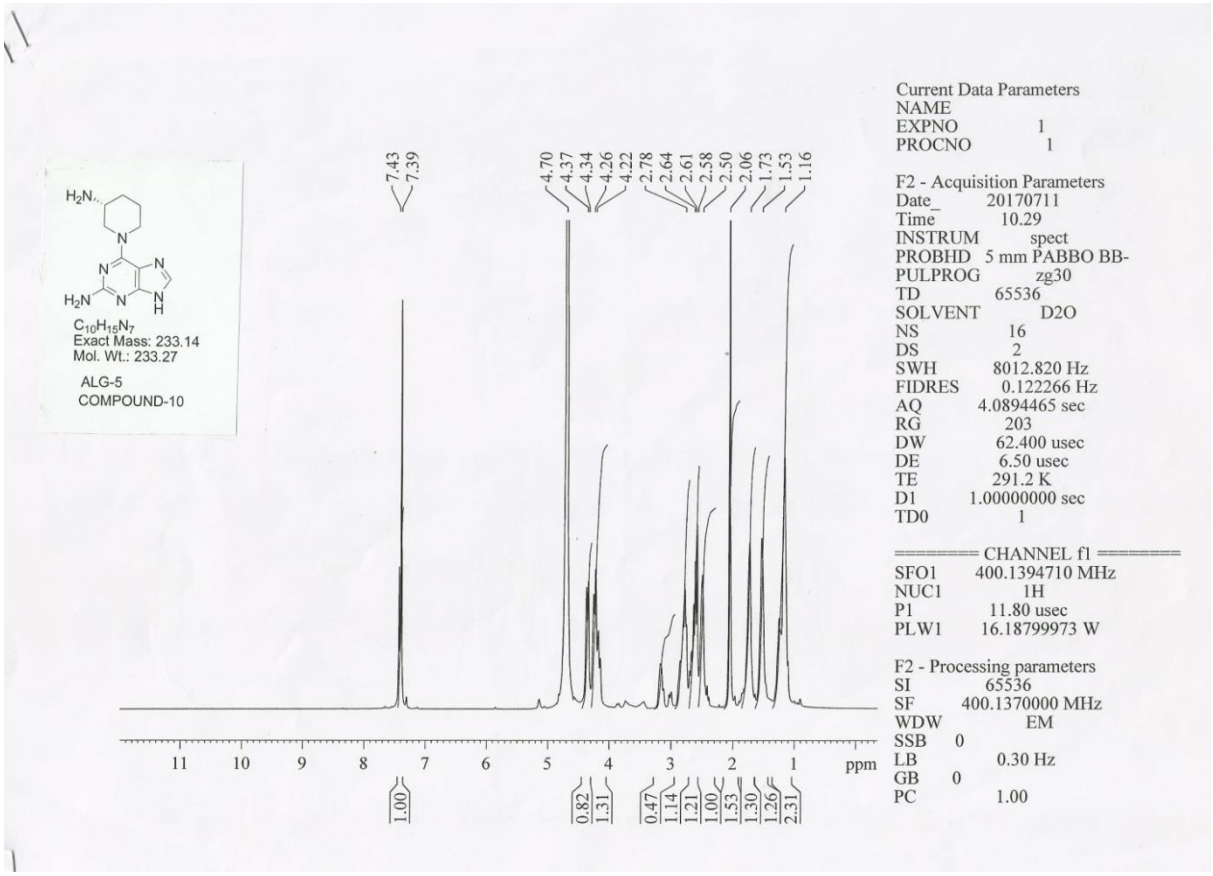


## 5.4.35 HRMS of (R)-2-(2-amino-9H-purin-6-ylamino)-3-hydroxypropanoic acid (5i):

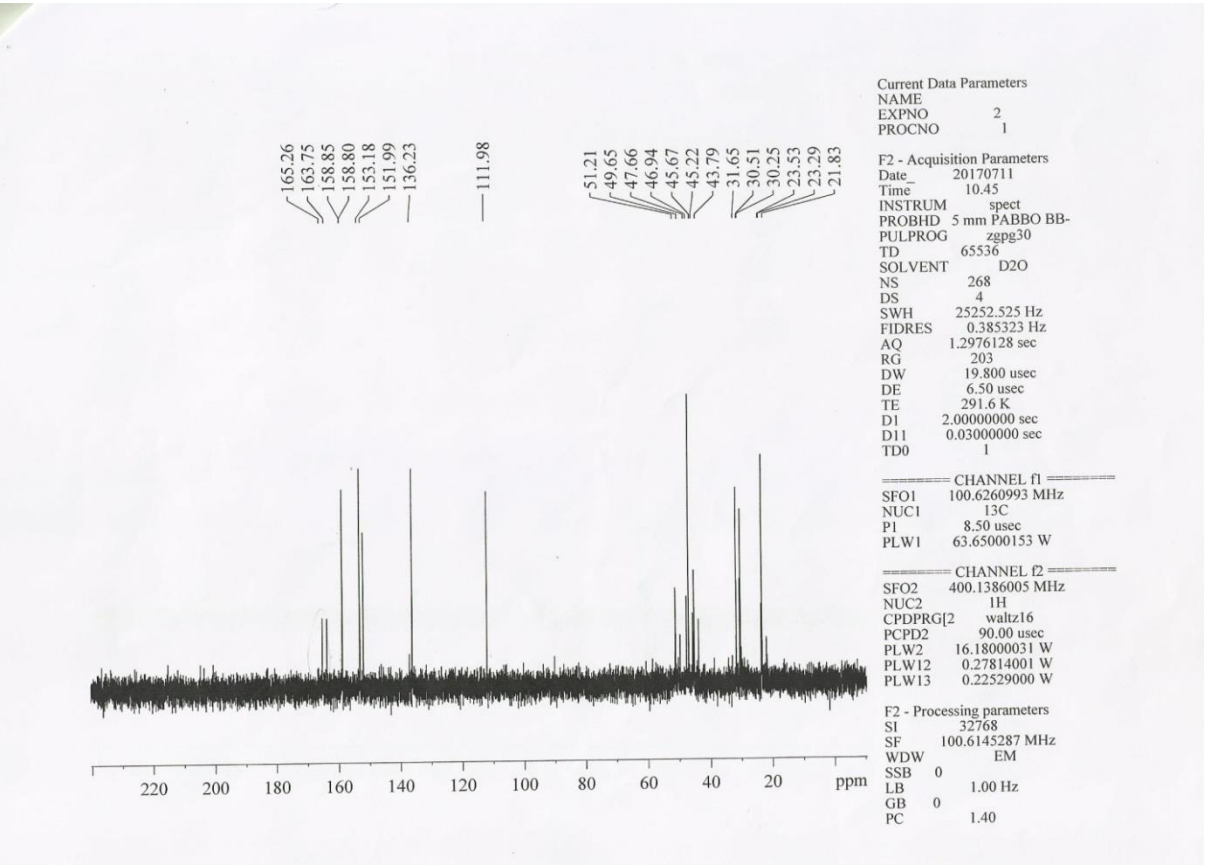



| Sample Name | Description | Quality Checks |
|---|---|---|
| IVS-SER | SER | The Quality Checks give rise to multiple warnings for the sample. |

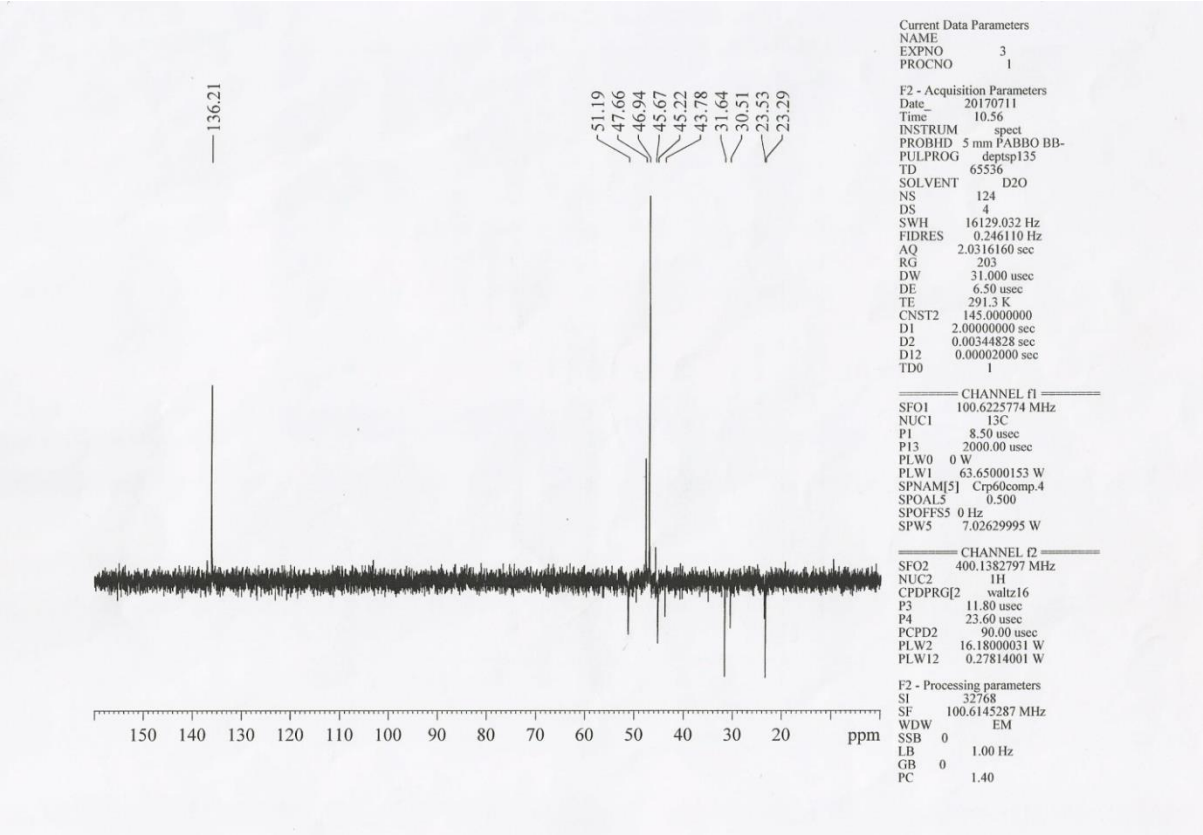
### 5.4.36 $H^1$ NMR of (R)-6-(3-aminopiperidin-1-yl)-9H-purin-2-amine (5j):



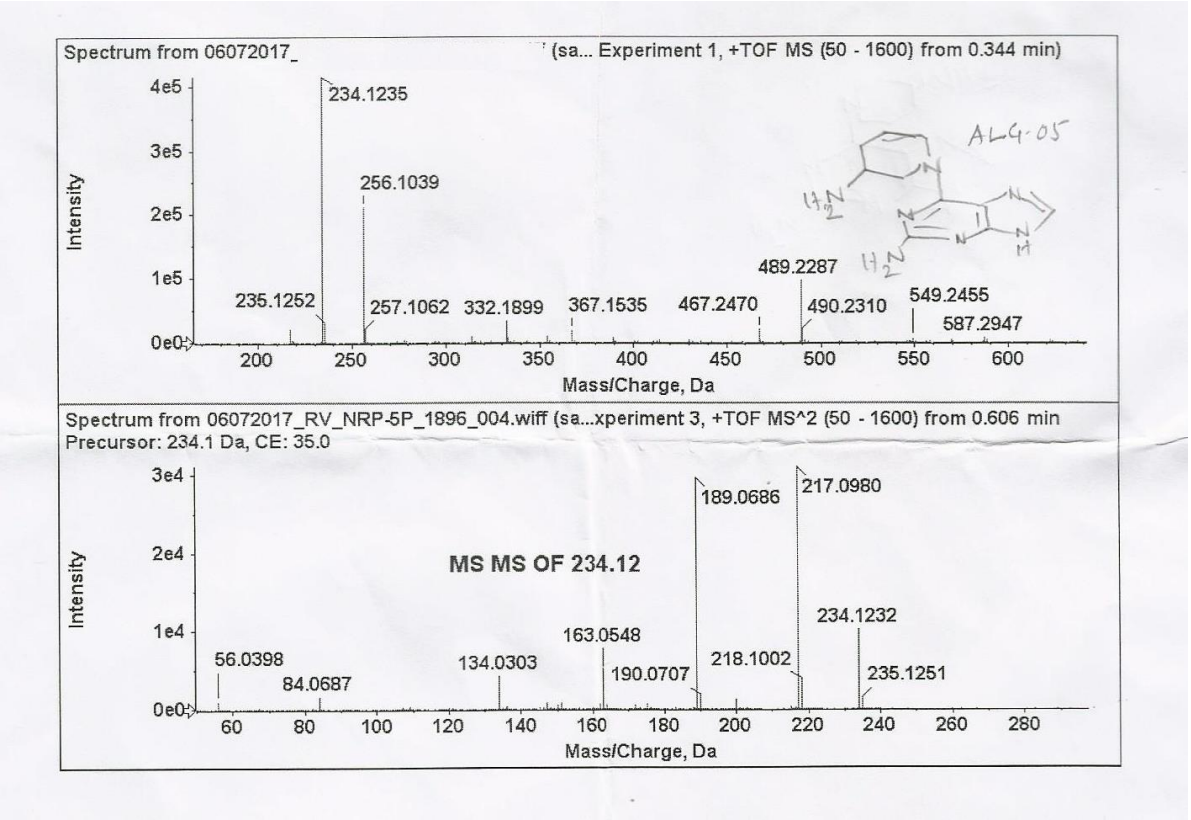
## 5.4.37 $C^{13}$ NMR of (R)-6-(3-aminopiperidin-1-yl)-9H-purin-2-amine (5j):



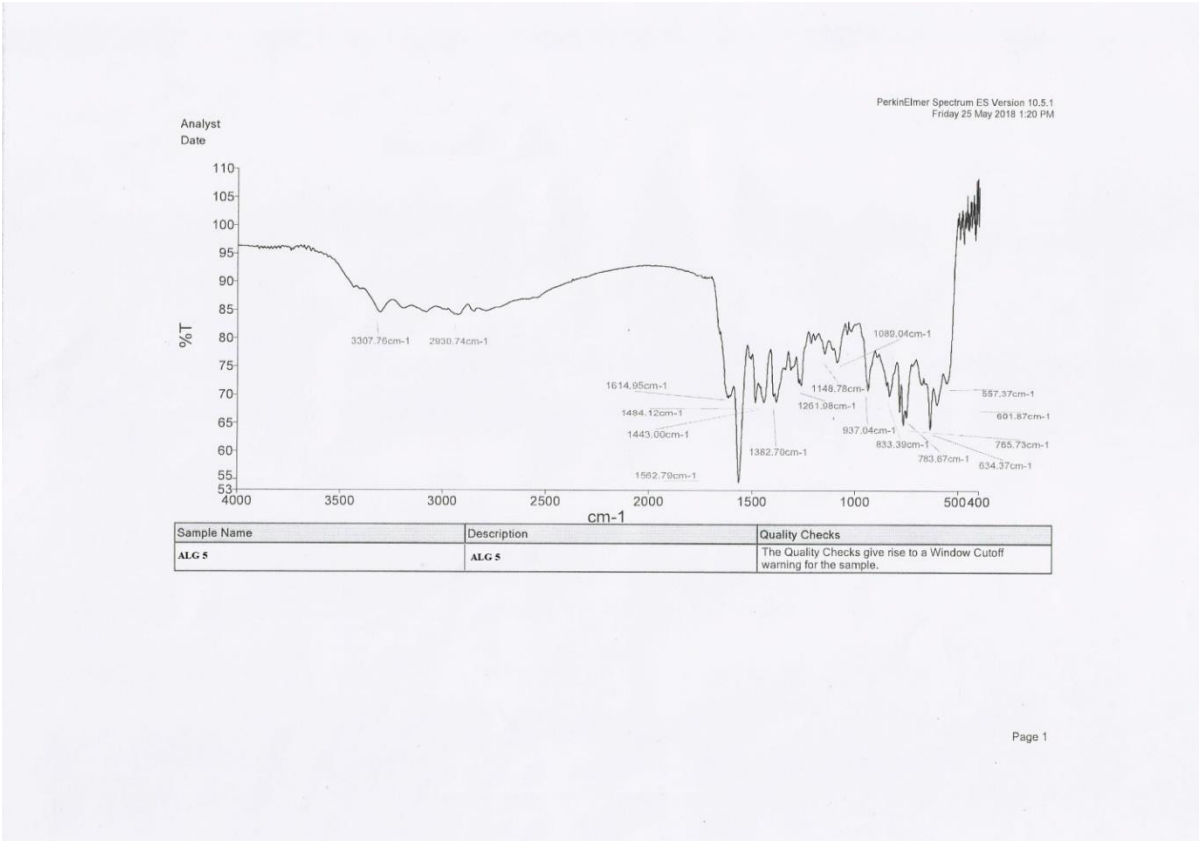
## 5.4.38 Dept NMR of (R)-6-(3-aminopiperidin-1-yl)-9H-purin-2-amine (5j):



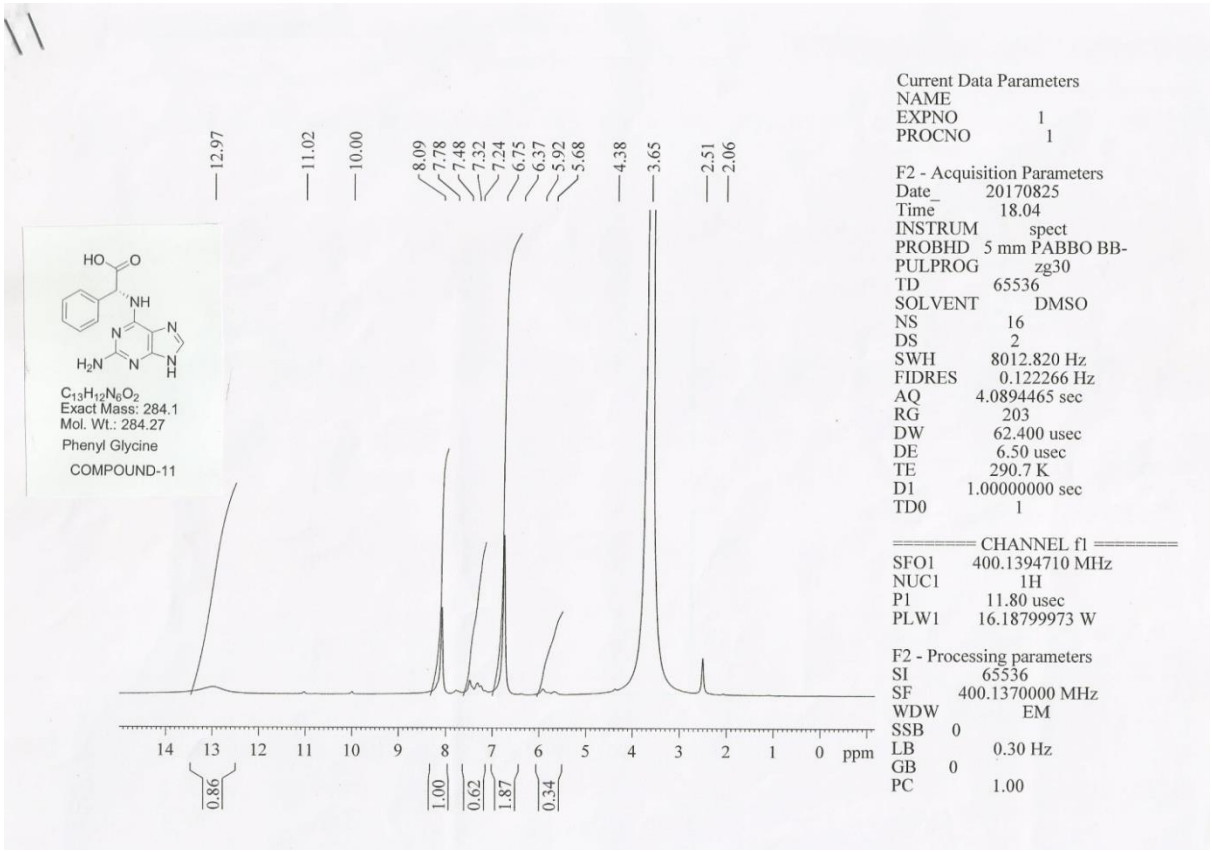
### 5.4.39 HRMS of (R)-6-(3-aminopiperidin-1-yl)-9H-purin-2-amine (5j):



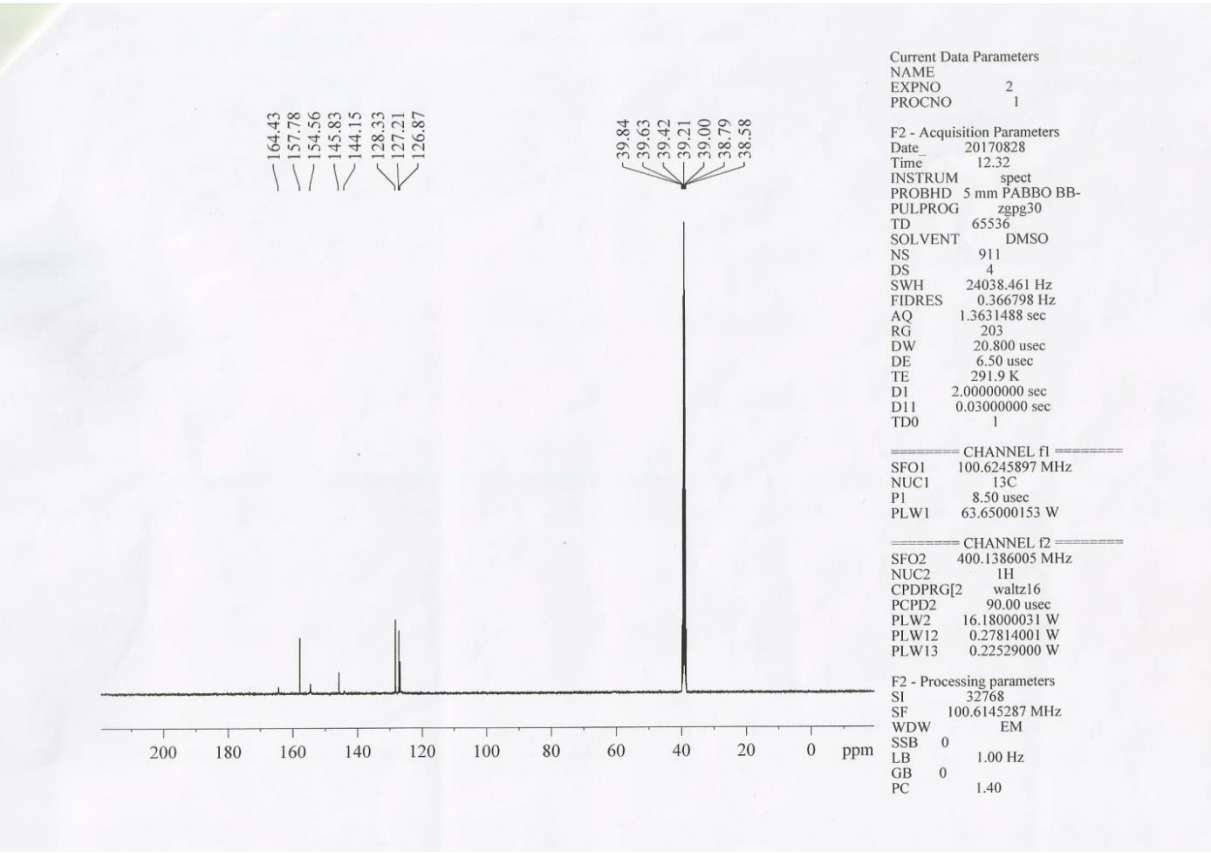
## 5.4.40 HRMS of (R)-6-(3-aminopiperidin-1-yl)-9H-purin-2-amine (5j):



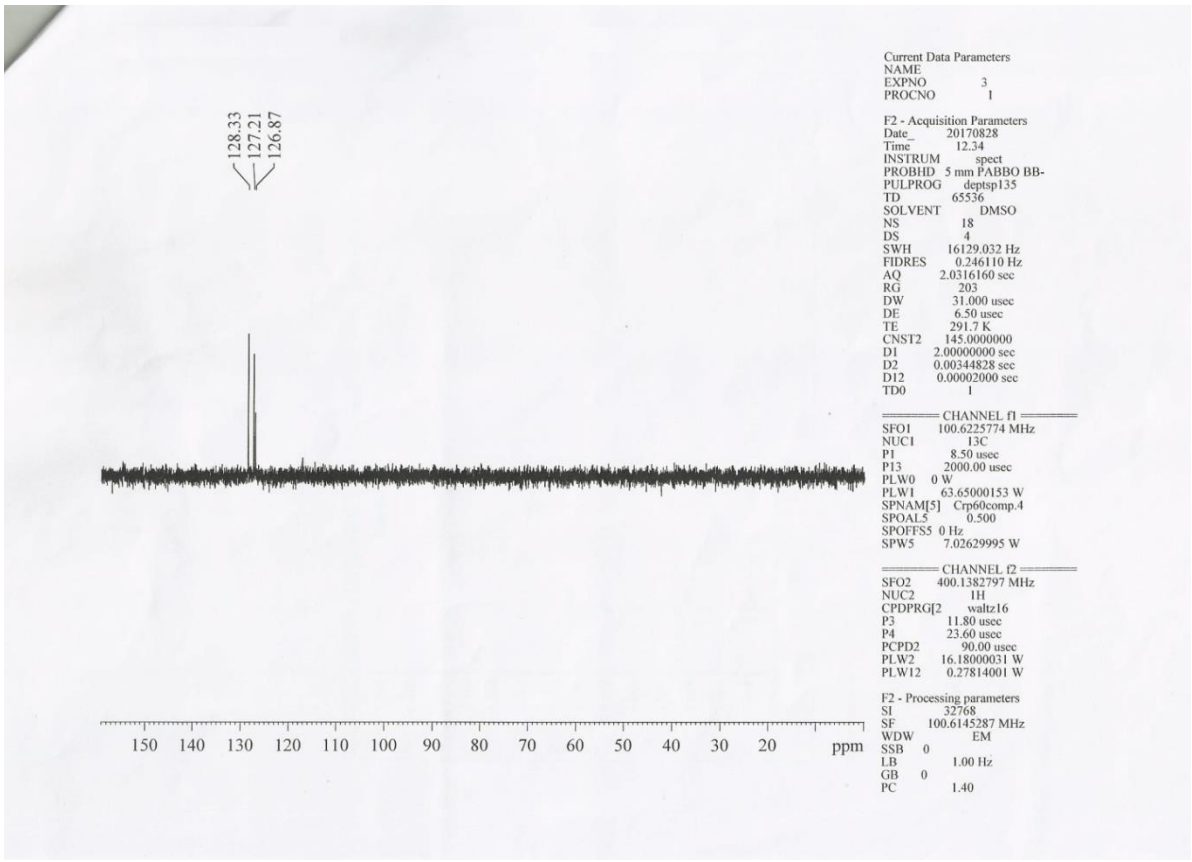
### 5.4.41 $H^1$ NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-2-phenylacetic acid (5k):



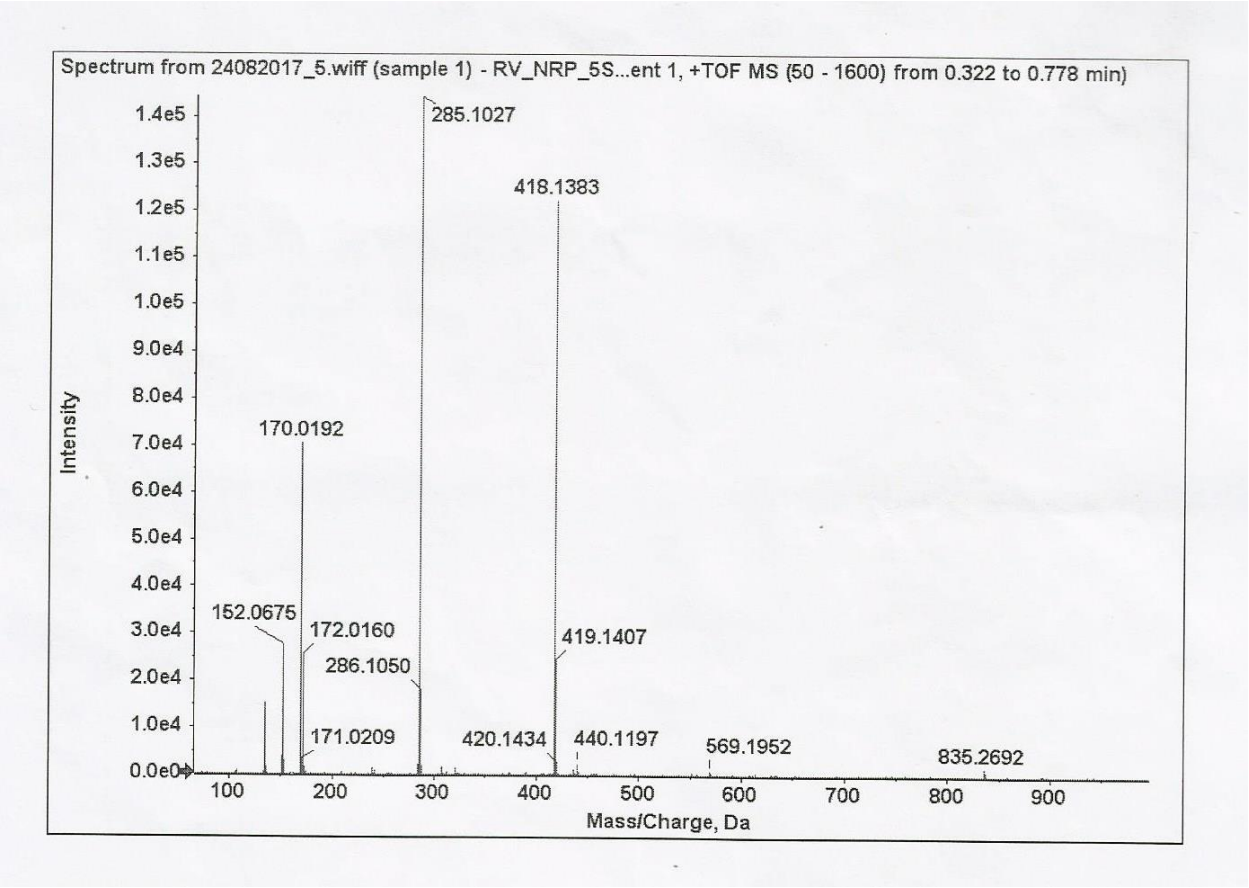
## 5.4.42 $C^{13}$ NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-2-phenylacetic acid (5k):



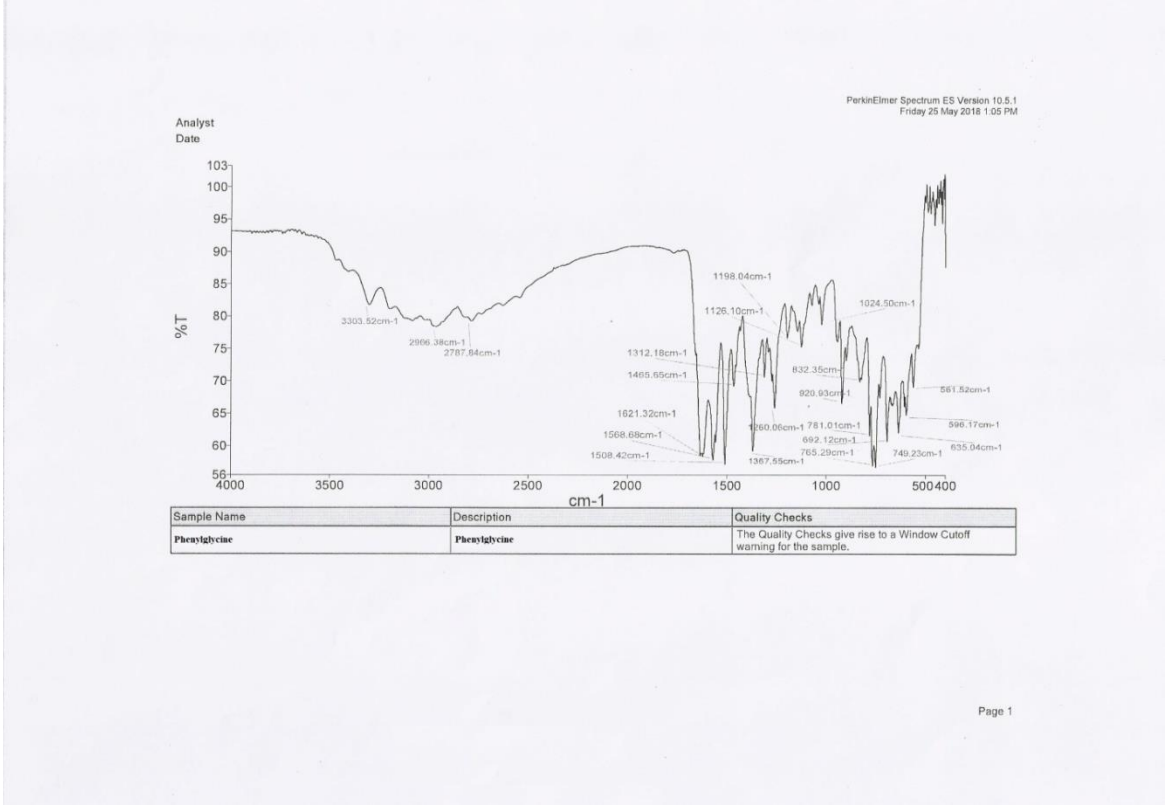
## 5.4.43 Dept NMR of (R)-2-(2-amino-9H-purin-6-ylamino)-2-phenylacetic acid (5k):



### 5.4.44 HRMS of (R)-2-(2-amino-9H-purin-6-ylamino)-2-phenylacetic acid (5k):



### 5.4.45 IR Spectrum of (R)-2-(2-amino-9H-purin-6-ylamino)-2-phenylacetic acid (5k):




| Sample Name | Description | Quality Checks |
|---|---|---|
| **Phenylglycine** | **Phenylglycine** | The Quality Checks give rise to a Window Cutoff warning for the sample. |

## 5.5 BIOLOGICAL POTENTIAL OF COMPOUNDS BY PASS PREDICTION:

Compounds 5a-5k shows tremendous activity in PASS prediction in various diseases, some of the important activities are listed below tables

### 5.5.1 PASS Prediction data of (R)-2-(2-amino-9H-purin-6-ylamino)-3-(1H-indol-3-yl)propanoic acid (5a):

Compound-5a shows some of the important activities like **Antineoplastic antimetabolite, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B), **Cancer associated disorders treatment, Autoimmune disorders treatment, Multiple sclerosis treatment, Growth stimulant** and **Antineoplastic (solid tumors).**

**Table: 5.1 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,795 | 0,005 | Mitochondrial processing peptidase inhibitor |
| 2 | 0,685 | 0,004 | 3'-Demethylstaurosporine O-methyltransferase inhibitor |
| 3 | 0,669 | 0,026 | Pseudolysin inhibitor |
| 4 | 0,424 | 0,015 | Antineoplastic antimetabolite |
| 5 | 0,442 | 0,037 | Antiasthmatic |
| 6 | 0,455 | 0,061 | Antineoplastic (non-Hodgkin's lymphoma) |
| 7 | 0,462 | 0,069 | Antiviral (Picornavirus) |
| 8 | 0,386 | 0,042 | Antiviral (Herpes) |
| 9 | 0,372 | 0,034 | Antiviral (Poxvirus) |
| 10 | 0,365 | 0,029 | Cancer associated disorders treatment |
| 11 | 0,364 | 0,069 | Autoimmune disorders treatment |
| 12 | 0,311 | 0,031 | Analgesic stimulant |
| 13 | 0,316 | 0,048 | Multiple sclerosis treatment |
| 14 | 0,320 | 0,057 | Venom exonuclease inhibitor |
| 15 | 0,337 | 0,076 | Antiallergic |

| | | | |
|---|---|---|---|
| 16 | 0,302 | 0,106 | Rhinitis treatment |
| 17 | 0,269 | 0,076 | Fibroblast growth factor 1 agonist |
| 18 | 0,244 | 0,054 | Antiviral (Hepatitis B) |
| 19 | 0,215 | 0,049 | Growth stimulant |
| 20 | 0,260 | 0,127 | Antineoplastic (solid tumors) |
| 21 | 0,237 | 0,122 | Antiviral (Influenza A) |
| 22 | 0,254 | 0,147 | Antineoplastic (multiple myeloma) |
| 23 | 0,101 | 0,018 | Aralkylamine N-acetyltransferase inhibitor |
| 24 | 0,114 | 0,032 | Histamine N-methyltransferase inhibitor |
| 25 | 0,094 | 0,012 | rRNA (adenosine-2'-O-)-methyltransferase inhibitor |
| 26 | 0,200 | 0,119 | Anticarcinogenic |
| 27 | 0,152 | 0,072 | Antimigraine |
| 28 | 0,233 | 0,160 | Antiviral (Adenovirus) |
| 29 | 0,230 | 0,177 | Antiinfective |
| 30 | 0,204 | 0,172 | Antiviral (CMV) |

### 5.5.2 PASS Prediction data of(2R)-2-(2-amino-9H-purin-6-ylamino)-3-methylpentanoic acid (5b):

Compound-5b shows some of the important activities like **Fibroblast growth factor agonist, Antineoplastic antimetabolite, Kidney function stimulant, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B), **Cancer associated disorders treatment, Autoimmune disorders treatment, Multiple sclerosis treatment, Growth stimulant** and **Antineoplastic (solid tumors).**

**Table: 5.2 PASS Pridiction date**

| **Sr No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,709 | 0,005 | Thiol oxidase inhibitor |
| 2 | 0,572 | 0,026 | Antiviral (Picornavirus) |

| | | | |
|---|---|---|---|
| 3 | 0,523 | 0,029 | Fibroblast growth factor agonist |
| 4 | 0,522 | 0,029 | Antineoplastic (non-Hodgkin's lymphoma) |
| 5 | 0,461 | 0,012 | Antineoplastic antimetabolite |
| 6 | 0,466 | 0,023 | Antiviral (Poxvirus) |
| 7 | 0,418 | 0,028 | Antiviral (Herpes) |
| 8 | 0,483 | 0,109 | Kidney function stimulant |
| 9 | 0,398 | 0,047 | Antiviral (Influenza) |
| 10 | 0,359 | 0,016 | Antiviral (Influenza A) |
| 11 | 0,357 | 0,021 | Antiviral (Hepatitis B) |
| 12 | 0,342 | 0,045 | Fibroblast growth factor 1 agonist |
| 13 | 0,341 | 0,059 | Antiviral (Adenovirus) |
| 14 | 0,324 | 0,064 | HCV IRES inhibitor |
| 15 | 0,332 | 0,079 | Antiinfective |
| 16 | 0,288 | 0,037 | Antiviral (CMV) |
| 17 | 0,363 | 0,119 | Antineoplastic |
| 18 | 0,305 | 0,065 | Venom exonuclease inhibitor |
| 19 | 0,314 | 0,078 | Cancer associated disorders treatment |
| 20 | 0,263 | 0,044 | Hematopoietic |
| 21 | 0,323 | 0,105 | S-formylglutathione hydrolase inhibitor |
| 22 | 0,271 | 0,071 | Anticarcinogenic |
| 23 | 0,196 | 0,039 | Antineoplastic (lymphocytic leukemia) |
| 24 | 0,226 | 0,076 | Antiviral |
| 25 | 0,247 | 0,104 | Analgesic stimulant |
| 26 | 0,253 | 0,134 | Antineoplastic (solid tumors) |
| 27 | 0,225 | 0,145 | Antiasthmatic |
| 28 | 0,132 | 0,053 | Antiviral (Hepatitis) |
| 29 | 0,207 | 0,136 | Antipsoriatic |
| 30 | 0,201 | 0,147 | Angiogenesis stimulant |
| 31 | 0,106 | 0,052 | Antiviral (Hepatitis C) |
| 32 | 0,199 | 0,173 | Analeptic |

### 5.5.3 PASS Prediction data of (R)-2-(2-amino-9H-purin-6-ylamino)-3-phenylpropanoic acid (5c):

Compound-5c shows some of the important activities like **Fibroblast growth factor agonist, Antineoplastic antimetabolite, Antiallergic, Antithyroid, Kidney function stimulant, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B), **Cancer associated disorders treatment, Autoimmune disorders treatment, Multiple sclerosis treatment, Growth stimulant** and **Antineoplastic (solid tumors).**

**Table: 5.3 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,831 | 0,014 | Methylenetetrahydrofolate reductase (NADPH) inhibitor |
| 2 | 0,776 | 0,004 | Thiol oxidase inhibitor |
| 3 | 0,680 | 0,003 | Thiopurine S-methyltransferase inhibitor |
| 4 | 0,660 | 0,014 | Nucleotide metabolism regulator |
| 5 | 0,598 | 0,019 | Antiviral (Picornavirus) |
| 6 | 0,584 | 0,015 | Antiviral (Poxvirus) |
| 7 | 0,584 | 0,017 | Antiasthmatic |
| 8 | 0,550 | 0,013 | Antiprotozoal (Trypanosoma) |
| 9 | 0,523 | 0,029 | Fibroblast growth factor agonist |
| 10 | 0,485 | 0,031 | Antiallergic |
| 11 | 0,458 | 0,013 | Antineoplastic antimetabolite |
| 12 | 0,479 | 0,046 | Antineoplastic (non-Hodgkin's lymphoma) |
| 13 | 0,518 | 0,086 | Kidney function stimulant |
| 14 | 0,434 | 0,005 | Inosine nucleosidase inhibitor |
| 15 | 0,408 | 0,024 | Multiple sclerosis treatment |
| 16 | 0,409 | 0,032 | Antiviral (Herpes) |
| 17 | 0,384 | 0,007 | Antidiarrheal |

| | | | |
|---|---|---|---|
| 18 | 0,402 | 0,029 | Venom exonuclease inhibitor |
| 19 | 0,411 | 0,057 | Pancreatic elastase inhibitor |
| 20 | 0,374 | 0,032 | Inflammatory Bowel disease treatment |
| 21 | 0,346 | 0,043 | Cancer associated disorders treatment |
| 22 | 0,395 | 0,096 | Leukopoiesis stimulant |
| 23 | 0,449 | 0,166 | Antieczematic |
| 24 | 0,306 | 0,032 | Antiviral (Hepatitis B) |
| 25 | 0,307 | 0,034 | Analgesic stimulant |
| 26 | 0,272 | 0,051 | Antiviral (CMV) |
| 27 | 0,279 | 0,059 | Antiviral (Influenza A) |
| 28 | 0,289 | 0,090 | Antineoplastic (multiple myeloma) |
| 29 | 0,279 | 0,108 | Antiviral (Adenovirus) |
| 30 | 0,231 | 0,093 | Anticarcinogenic |
| 31 | 0,159 | 0,043 | Antithyroid |
| 32 | 0,258 | 0,142 | Antiinfective |
| 33 | 0,249 | 0,139 | Antineoplastic (solid tumors) |
| 34 | 0,132 | 0,068 | Antineoplastic (lymphocytic leukemia) |
| 35 | 0,176 | 0,125 | Antiviral |
| 36 | 0,206 | 0,167 | Analeptic |
| 37 | 0,106 | 0,083 | Fibroblast growth factor 2 antagonist |
| 38 | 0,051 | 0,040 | Antifungal (Pneumocystis) |

### 5.5.4 PASS Prediction data of (S)-2-(2-amino-9H-purin-6-ylamino)-3-methylbutanoic acid (5d):

Compound-5d shows some of the important activities like **Fibroblast growth factor agonist, Liver cirrhosis treatment, Antineoplastic , Antiallergic, Antithyroid, Kidney function stimulant, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B), **Cancer associated disorders treatment, Autoimmune disorders treatment, Multiple sclerosis treatment, Growth stimulant** and **Antineoplastic (solid tumors).**

**Table: 5.4 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,796 | 0,003 | Thiol oxidase inhibitor |
| 2 | 0,772 | 0,022 | Methylenetetrahydrofolate reductase (NADPH) inhibitor |
| 3 | 0,609 | 0,016 | Fibroblast growth factor agonist |
| 4 | 0,606 | 0,018 | Antiviral (Picornavirus) |
| 5 | 0,556 | 0,017 | Antiviral (Poxvirus) |
| 6 | 0,521 | 0,030 | Antineoplastic (non-Hodgkin's lymphoma) |
| 7 | 0,495 | 0,011 | Antineoplastic antimetabolite |
| 8 | 0,448 | 0,019 | Antiviral (Herpes) |
| 9 | 0,431 | 00,026 | Fibroblast growth factor 1 agonist |
| 10 | 0,451 | 0,065 | Leukopoiesis stimulant |
| 11 | 0,407 | 0,027 | Venom exonuclease inhibitor |
| 12 | 0,432 | 0,093 | Antineoplastic |
| 13 | 0,338 | 0,011 | Antidiarrheal |
| 14 | 0,343 | 0,024 | Antiviral (Hepatitis B) |
| 15 | 0,364 | 0,046 | Antiviral (Adenovirus) |
| 16 | 0,321 | 0,019 | Antiviral (CMV) |
| 17 | 0,278 | 0,010 | Antimetabolite |
| 18 | 0,350 | 0,093 | Insulin promoter |
| 19 | 0,258 | 0,025 | Antineoplastic (lymphocytic leukemia) |
| 20 | 0,304 | 0,086 | Antiviral (Influenza) |
| 21 | 0,274 | 0,064 | Analgesic stimulant |

| | | | |
|---|---|---|---|
| 22 | 0,278 | 0,104 | Antineoplastic (multiple myeloma) |
| 23 | 0,254 | 0,081 | Anticarcinogenic |
| 24 | 0,286 | 0,114 | Antiinfective |
| 25 | 0,215 | 0,084 | Antiviral |
| 26 | 0,272 | 0,140 | Antinephritic |
| 27 | 0,116 | 0,046 | Liver cirrhosis treatment |
| 28 | 0,239 | 0,182 | HCV IRES inhibitor |
| 29 | 0,115 | 0,088 | Antithyroid |
| 30 | 0,187 | 0,185 | Analeptic |

### 5.5.5 PASS Prediction data of (S)-2-(2-amino-9H-purin-6-ylamino)-4-methylpentanoic acid (5e):

Compound-5e shows some of the important activities like **Fibroblast growth factor agonist, Liver cirrhosis treatment, Antineoplastic , Antiallergic, Immunosuppressant, Insulin promoter, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B), **Antiinfective, Autoimmune disorders treatment, Multiple sclerosis treatment, Growth stimulant** and **Antineoplastic (solid tumors).**

**Table: 5.5 PASS Pridiction date**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,740 | 0,004 | Thiol oxidase inhibitor |
| 2 | 0,726 | 0,027 | Methylenetetrahydrofolate reductase (NADPH) inhibitor |
| 3 | 0,574 | 0,025 | Antiviral (Picornavirus) |
| 4 | 0,502 | 0,010 | Antineoplastic antimetabolite |
| 5 | 0,509 | 0,033 | Antineoplastic (non-Hodgkin's lymphoma) |
| 6 | 0,488 | 0,021 | Antiviral (Poxvirus) |
| 7 | 0,435 | 0,022 | Antiviral (Herpes) |

| | | | |
|---|---|---|---|
| 8 | 0,430 | 0,026 | Fibroblast growth factor 1 agonist |
| 9 | 0,416 | 0,023 | Antiviral (Adenovirus) |
| 10 | 0,465 | 0,121 | Kidney function stimulant |
| 11 | 0,347 | 0,023 | Antiviral (Hepatitis B) |
| 12 | 0,317 | 0,031 | Antiviral (Influenza A) |
| 13 | 0,348 | 0,065 | Antiasthmatic |
| 14 | 0,307 | 0,034 | Analgesic stimulant |
| 15 | 0,290 | 0,020 | Antidiarrheal |
| 16 | 0,284 | 0,040 | Antiviral (CMV) |
| 17 | 0,312 | 0,081 | Cancer associated disorders treatment |
| 18 | 0,304 | 0,075 | Antineoplastic (multiple myeloma) |
| 19 | 0,305 | 0,086 | Antiviral (Influenza) |
| 20 | 0,320 | 0,104 | Immunosuppressant |
| 21 | 0,266 | 0,074 | Anticarcinogenic |
| 22 | 0,277 | 0,108 | Antiallergic |
| 23 | 0,281 | 0,119 | Antiinfective |
| 24 | 0,300 | 0,138 | Insulin promoter |
| 25 | 0,214 | 0,085 | Antiviral |
| 26 | 0,255 | 0,133 | Antineoplastic (solid tumors) |
| 27 | 0,256 | 0,139 | Autoimmune disorders treatment |
| 28 | 0,228 | 0,150 | Analeptic |
| 29 | 0,237 | 0,187 | HCV IRES inhibitor |
| 30 | 0,123 | 0,075 | Antineoplastic (lymphocytic leukemia) |
| 31 | 0,111 | 0,063 | Liver cirrhosis treatment |
| 32 | 0,198 | 0,163 | Antineoplastic (bone cancer) |
| 33 | 0,111 | 0,083 | Antiviral (Hepatitis) |
| 34 | 0,235 | 0,207 | Leukopoiesis inhibitor |

### 5.5.6 PASS Prediction data of (S)-2-(2-amino-9H-purin-6-ylamino)propanoic acid (5f):

Compound-5f shows some of the important activities like **Fibroblast growth factor agonist, Antiasthmatic, Antidiarrheal, Antineoplastic , Antiallergic, Immunosuppressant, Insulin promoter, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B), **Antiinfective, Autoimmune disorders treatment, Multiple sclerosis treatment, Growth stimulant** and **Antileukemic.**

**Table: 5.6 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,863 | 0,002 | Thiol oxidase inhibitor |
| 2 | 0,859 | 0,011 | Methylenetetrahydrofolate reductase (NADPH) inhibitor |
| 3 | 0,747 | 0,011 | ADP-thymidine kinase inhibitor |
| 4 | 0,654 | 0,010 | Antiviral (Picornavirus) |
| 5 | 0,643 | 0,012 | Antiviral (Poxvirus) |
| 6 | 0,562 | 0,019 | Antiasthmatic |
| 7 | 0,559 | 0,023 | Fibroblast growth factor agonist |
| 8 | 0,522 | 0,009 | Antineoplastic antimetabolite |
| 9 | 0,501 | 0,014 | Venom exonuclease inhibitor |
| 10 | 0,551 | 0,066 | Kidney function stimulant |
| 11 | 0,486 | 0,031 | Antiallergic |
| 12 | 0,436 | 0,022 | Antiviral (Herpes) |
| 13 | 0,398 | 0,030 | Antiviral (Adenovirus) |
| 14 | 0,375 | 0,008 | Antidiarrheal |
| 15 | 0,353 | 0,022 | Antiviral (Hepatitis B) |
| 16 | 0,299 | 0,030 | Antiviral (CMV) |
| 17 | 0,295 | 0,045 | Antiviral (Influenza A) |
| 18 | 0,305 | 0,074 | Antineoplastic (multiple myeloma) |

| | | | |
|---|---|---|---|
| 19 | 0,308 | 0,084 | Antiviral (Influenza) |
| 20 | 0,234 | 0,010 | Adenosine receptor antagonist |
| 21 | 0,306 | 0,098 | Antiinfective |
| 22 | 0,322 | 0,140 | Antineoplastic |
| 23 | 0,293 | 0,113 | Analeptic |
| 24 | 0,281 | 0,107 | Antineoplastic (solid tumors) |
| 25 | 0,274 | 0,120 | Autoimmune disorders treatment |
| 26 | 0,125 | 0,075 | Antithyroid |
| 27 | 0,025 | 0,008 | Antibiotic Trimethoprim-like |
| 28 | 0,026 | 0,010 | Adenosine receptor agonist |
| 29 | 0,131 | 0,122 | Antileukemic |

### 5.5.7 PASS Prediction data of (R)-2-(2-amino-9H-purin-6-ylamino)-3-mercaptopropanoic acid (5g):

Compound-5g shows some of the important activities like **Venom exonuclease inhibitor, Cancer associated disorders treatment, Antidiarrheal, Antineoplastic , Bilirubin oxidase inhibitor, Immunosuppressant, Insulin promoter, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B), **Antiinfective, Autoimmune disorders treatment, Multiple sclerosis treatment, Growth stimulant** and **Antileukemic.**

**Table: 5.7 PASS Pridiction date**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,947 | 0,001 | Thiol oxidase inhibitor |
| 2 | 0,911 | 0,003 | NADPH peroxidase inhibitor |
| 3 | 0,885 | 0,002 | Glyoxylate reductase (NADP+) inhibitor |
| 4 | 0,780 | 0,003 | Venom exonuclease inhibitor |
| 5 | 0,768 | 0,004 | Fibroblast growth factor agonist |
| 6 | 0,690 | 0,004 | Bilirubin oxidase inhibitor |

| | | | |
|---|---|---|---|
| 7 | 0,659 | 0,010 | Antiviral (Picornavirus) |
| 8 | 0,564 | 0,017 | Antiviral (Poxvirus) |
| 9 | 0,422 | 0,015 | Antineoplastic antimetabolite |
| 10 | 0,417 | 0,022 | HCV IRES inhibitor |
| 11 | 0,394 | 0,038 | Antiviral (Herpes) |
| 12 | 0,351 | 0,010 | Antidiarrheal |
| 13 | 0,338 | 0,022 | Antiviral (Influenza A) |
| 14 | 0,394 | 0,113 | Antineoplastic (non-Hodgkin's lymphoma) |
| 15 | 0,308 | 0,031 | Antiviral (Hepatitis B) |
| 16 | 0,310 | 0,047 | Antitoxic |
| 17 | 0,286 | 0,099 | Antiviral (Influenza) |
| 18 | 0,255 | 0,070 | Antiviral (CMV) |
| 19 | 0,251 | 0,082 | Anticarcinogenic |
| 20 | 0,196 | 0,099 | Antiviral |
| 21 | 0,261 | 0,178 | Antineoplastic |
| 22 | 0,222 | 0,154 | Analeptic |
| 23 | 0,223 | 0,178 | Antineoplastic (solid tumors) |
| 24 | 0,082 | 0,060 | Aminopeptidase I inhibitor |
| 25 | 0,109 | 0,090 | Antineoplastic (lymphocytic leukemia) |
| 26 | 0,205 | 0,190 | Analgesic stimulant |
| 27 | 0,247 | 0,235 | Pancreatic elastase inhibitor |
| 28 | 0,221 | 0,216 | Cancer associated disorders treatment |
| 29 | 0,019 | 0,014 | Antibiotic Trimethoprim-like |

### 5.5.8 PASS Prediction data of (S)-1-(2-amino-9H-purin-6-yl)pyrrolidine-2-carboxylic acid (5h):

Compound-5h shows some of the important activities like **Antineoplastic (non-Hodgkin's lymphoma), Antieczematic , Stroke treatment, Respiratory analeptic, Antineoplastic (solid tumors) , Bilirubin oxidase inhibitor, Immunosuppressant, Insulin promoter, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C,

hepatitis-B), **Fibroblast growth factor 1 agonist, Antiamyloidogenic** and **Antileukemic.**

**Table: 5.8 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,867 | 0,009 | Glutamate-5-semialdehyde dehydrogenase inhibitor |
| 2 | 0,722 | 0,028 | Methylenetetrahydrofolate reductase (NADPH) inhibitor |
| 3 | 0,704 | 0,011 | Pterin deaminase inhibitor |
| 4 | 0,613 | 0,012 | Antineoplastic (non-Hodgkin's lymphoma) |
| 5 | 0,533 | 0,004 | Glutamate 5-kinase inhibitor |
| 6 | 0,497 | 0,018 | DNA synthesis inhibitor |
| 7 | 0,565 | 0,103 | Antieczematic |
| 8 | 0,446 | 0,078 | Antiviral (Picornavirus) |
| 9 | 0,404 | 0,037 | Antiprotozoal (Trypanosoma) |
| 10 | 0,413 | 0,059 | Fibroblast growth factor agonist |
| 11 | 0,402 | 0,091 | Leukopoiesis stimulant |
| 12 | 0,350 | 0,044 | Antiparkinsonian |
| 13 | 0,336 | 0,044 | Antiviral (Poxvirus) |
| 14 | 0,316 | 0,029 | Antiviral (Hepatitis B) |
| 15 | 0,335 | 0,050 | Venom exonuclease inhibitor |
| 16 | 0,315 | 0,032 | Antiviral (Influenza A) |
| 17 | 0,302 | 0,023 | Antineoplastic antimetabolite |
| 18 | 0,317 | 0,079 | Antiviral (Influenza) |
| 19 | 0,316 | 0,080 | Antiviral (Herpes) |
| 20 | 0,329 | 0,094 | Analeptic |
| 21 | 0,273 | 0,050 | Antiviral (CMV) |
| 22 | 0,297 | 0,092 | Antiviral (Adenovirus) |
| 23 | 0,321 | 0,117 | Antimyopathies |
| 24 | 0,299 | 0,098 | Cancer associated disorders treatment |
| 25 | 0,280 | 0,101 | Antineoplastic (multiple myeloma) |
| 26 | 0,240 | 0,066 | Stroke treatment |

| | | | |
|---|---|---|---|
| 27 | 0,288 | 0,115 | Respiratory analeptic |
| 28 | 0,220 | 0,063 | Antidiarrheal |
| 29 | 0,163 | 0,039 | Antibacterial, ophthalmic |
| 30 | 0,322 | 0,208 | Antiviral (Rhinovirus) |
| 31 | 0,293 | 0,236 | Acute neurologic disorders treatment |
| 32 | 0,120 | 0,063 | Vasculitis treatment |
| 33 | 0,207 | 0,167 | Antiamyloidogenic |
| 34 | 0,187 | 0,160 | Fibroblast growth factor 1 agonist |
| 35 | 0,326 | 0,302 | Nootropic |
| 36 | 0,215 | 0,192 | Antineoplastic (solid tumors) |
| 37 | 0,101 | 0,090 | Constipation treatment |
| 38 | 0,090 | 0,081 | Antineoplastic (squamous cell carcinoma) |
| 39 | 0,018 | 0,011 | Antibiotic Naphthyridine-like |

### 5.5.9 PASS Prediction data of (R)-2-(2-amino-9H-purin-6-ylamino)-3-hydroxypropanoic acid (5i):

Compound-5i shows some of the important activities like **Antineoplastic antimetabolite, Antiallergic, Antieczematic , Venom exonuclease inhibitor, Respiratory analeptic, Cancer associated disorders treatment, Analeptic, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B), **Wound healing agent, Antineoplastic (lymphocytic leukemia), Constipation treatment** and **Antitoxic.**

**Table: 5.9 PASS Pridiction date**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,860 | 0,011 | Methylenetetrahydrofolate reductase (NADPH) inhibitor |
| 2 | 0,811 | 0,011 | NADPH peroxidase inhibitor |
| 3 | 0,794 | 0,003 | Thiol oxidase inhibitor |
| 4 | 0,759 | 0,002 | Thiopurine S-methyltransferase inhibitor |

| | | | |
|---|---|---|---|
| 5 | 0,753 | 0,003 | Interleukin 4 antagonist |
| 6 | 0,755 | 0,020 | Mannotetraose 2-alpha-N-acetylglucosaminyltransferase inhibitor |
| 7 | 0,723 | 0,010 | Nucleotide metabolism regulator |
| 8 | 0,659 | 0,011 | Antiasthmatic |
| 9 | 0,658 | 0,012 | Antiviral (Poxvirus) |
| 10 | 0,593 | 0,016 | Antiallergic |
| 11 | 0,578 | 0,024 | Antiviral (Picornavirus) |
| 12 | 0,504 | 0,010 | Antineoplastic antimetabolite |
| 13 | 0,515 | 0,031 | Antineoplastic (non-Hodgkin's lymphoma) |
| 14 | 0,467 | 0,017 | Venom exonuclease inhibitor |
| 15 | 0,470 | 0,040 | Fibroblast growth factor agonist |
| 16 | 0,439 | 0,021 | Antiviral (Herpes) |
| 17 | 0,386 | 0,017 | Antiviral (Hepatitis B) |
| 18 | 0,368 | 0,008 | Antidiarrheal |
| 19 | 0,389 | 0,034 | Antiviral (Adenovirus) |
| 20 | 0,319 | 0,020 | Antiviral (CMV) |
| 21 | 0,335 | 0,053 | Cancer associated disorders treatment |
| 22 | 0,310 | 0,032 | Analgesic stimulant |
| 23 | 0,332 | 0,059 | HCV IRES inhibitor |
| 24 | 0,328 | 0,057 | Antineoplastic (multiple myeloma) |
| 25 | 0,305 | 0,038 | Antiviral (Influenza A) |
| 26 | 0,323 | 0,073 | Antineoplastic (solid tumors) |
| 27 | 0,321 | 0,086 | Antiinfective |
| 28 | 0,291 | 0,062 | Anticarcinogenic |
| 29 | 0,308 | 0,084 | Antiviral (Influenza) |
| 30 | 0,271 | 0,124 | Analeptic |
| 31 | 0,275 | 0,133 | Antinephritic |
| 32 | 0,225 | 0,094 | Wound healing agent |
| 33 | 0,175 | 0,046 | Antineoplastic (lymphocytic leukemia) |
| 34 | 0,229 | 0,105 | Multiple sclerosis treatment |
| 35 | 0,175 | 0,083 | Antiprotozoal (Plasmodium) |
| 36 | 0,339 | 0,248 | Antieczematic |

| | | | |
|---|---|---|---|
| 37 | 0,113 | 0,051 | Constipation treatment |
| 38 | 0,193 | 0,139 | Antieczematic atopic |
| 39 | 0,104 | 0,054 | Isocitrate dehydrogenase (NAD+) inhibitor |
| 40 | 0,194 | 0,144 | Antitoxic |
| 41 | 0,241 | 0,192 | Antineoplastic |
| 42 | 0,173 | 0,130 | Antiviral |
| 43 | 0,111 | 0,094 | Antithyroid |
| 44 | 0,050 | 0,043 | Antifungal (Pneumocystis) |

### 5.5.10 PASS Prediction data of (R)-6-(3-aminopiperidin-1-yl)-9H-purin-2-amine (5j):

Compound-5j shows some of the important activities like **Antineoplastic antimetabolite, Alopecia treatment, Antineoplastic (multiple myeloma), Immunosuppressant, Antiparkinsonian, Antineoplastic (pancreatic cancer), Antineoplastic (lymphoma), Analeptic, Antiviral** (Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B),and **Antidiarrheal.**

**Table: 5.10 PASS Pridiction date**

| **Sr.No** | **Pa** | **Pi** | **Activity** |
|---|---|---|---|
| 1 | 0,574 | 0,014 | Thiol oxidase inhibitor |
| 2 | 0,566 | 0,006 | Thiopurine S-methyltransferase inhibitor |
| 3 | 0,568 | 0,013 | Na+-transporting two-sector ATPase inhibitor |
| 4 | 0,554 | 0,018 | Cytostatic |
| 5 | 0,560 | 0,029 | Antiviral (Picornavirus) |
| 6 | 0,548 | 0,033 | Alopecia treatment |
| 7 | 0,511 | 0,006 | HCV IRES inhibitor |
| 8 | 0,511 | 0,033 | Antineoplastic (non-Hodgkin's lymphoma) |
| 9 | 0,480 | 0,012 | Antineoplastic (multiple myeloma) |
| 10 | 0,489 | 0,045 | Immunosuppressant |
| 11 | 0,423 | 0,006 | Antiviral (Influenza A) |

| | | | |
|---|---|---|---|
| 12 | 0,352 | 0,039 | Antiviral (Poxvirus) |
| 13 | 0,355 | 0,062 | Antiviral (Influenza) |
| 14 | 0,301 | 0,023 | Antineoplastic antimetabolite |
| 15 | 0,325 | 0,075 | Antiviral (Herpes) |
| 16 | 0,308 | 0,061 | Antiparkinsonian |
| 17 | 0,274 | 0,041 | Antiviral (Hepatitis B) |
| 18 | 0,296 | 0,093 | Antineoplastic (solid tumors) |
| 19 | 0,207 | 0,013 | Antibacterial, ophthalmic |
| 20 | 0,253 | 0,072 | Antiviral (CMV) |
| 21 | 0,281 | 0,106 | Antiviral (Adenovirus) |
| 22 | 0,219 | 0,065 | Antidiarrheal |
| 23 | 0,242 | 0,115 | Antimetastatic |
| 24 | 0,160 | 0,041 | Antiemetic |
| 25 | 0,226 | 0,133 | Venom exonuclease inhibitor |
| 26 | 0,155 | 0,064 | Antihistaminic |
| 27 | 0,139 | 0,051 | Histamine antagonist |
| 28 | 0,116 | 0,043 | Fibroblast growth factor 3 antagonist |
| 29 | 0,220 | 0,156 | Analeptic |
| 30 | 0,215 | 0,176 | Cystic fibrosis treatment |
| 31 | 0,080 | 0,049 | Fibroblast growth factor 1 antagonist |
| 32 | 0,171 | 0,140 | Antineoplastic enhancer |
| 33 | 0,137 | 0,125 | Antineoplastic (lymphoma) |
| 34 | 0,199 | 0,189 | Antineoplastic (pancreatic cancer) |
| 35 | 0,075 | 0,065 | Fibroblast growth factor antagonist |

### 5.5.11 PASS Prediction data of (R)-2-(2-amino-9H-purin-6-ylamino)-2-phenylacetic acid (5k):

Compound-5k shows some of the important activities like **Fibroblast growth factor agonist, Respiratory distress syndrome treatment, Cancer associated disorders treatment, Antineoplastic (multiple myeloma), Growth factor agonist, Antineoplastic (pancreatic cancer), Antineoplastic (lymphoma), Analeptic, Antiviral**

(Picornavirus, hrpes, poxivirus, Influenza A, hepatitis-C, hepatitis-B),and **Antineoplastic (lymphocytic leukemia).**

**Table: 5.11 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,847 | 0,003 | Thiol oxidase inhibitor |
| 2 | 0,790 | 0,020 | Methylenetetrahydrofolate reductase (NADPH) inhibitor |
| 3 | 0,691 | 0,015 | ADP-thymidine kinase inhibitor |
| 4 | 0,650 | 0,004 | Thiopurine S-methyltransferase inhibitor |
| 5 | 0,521 | 0,016 | Antiprotozoal (Trypanosoma) |
| 6 | 0,522 | 0,038 | Leukopoiesis stimulant |
| 7 | 0,491 | 0,021 | Antiviral (Poxvirus) |
| 8 | 0,440 | 0,005 | Respiratory distress syndrome treatment |
| 9 | 0,480 | 0,060 | Antiviral (Picornavirus) |
| 10 | 0,423 | 0,015 | Antineoplastic antimetabolite |
| 11 | 0,463 | 0,056 | Antineoplastic (non-Hodgkin's lymphoma) |
| 12 | 0,422 | 0,055 | Fibroblast growth factor agonist |
| 13 | 0,394 | 0,038 | Antiviral (Herpes) |
| 14 | 0,386 | 0,033 | Venom exonuclease inhibitor |
| 15 | 0,375 | 0,062 | Analgesic, non-opioid |
| 16 | 0,373 | 0,073 | Immunosuppressant |
| 17 | 0,273 | 0,026 | Antidiarrheal |
| 18 | 0,283 | 0,038 | Antiviral (Hepatitis B) |
| 19 | 0,315 | 0,078 | Antiviral (Adenovirus) |
| 20 | 0,312 | 0,081 | Cancer associated disorders treatment |
| 21 | 0,284 | 0,055 | Proliferative diseases treatment |
| 22 | 0,272 | 0,051 | Antiviral (CMV) |
| 23 | 0,291 | 0,087 | Antineoplastic (multiple myeloma) |
| 24 | 0,283 | 0,105 | Antineoplastic (solid tumors) |
| 25 | 0,279 | 0,101 | Antiasthmatic |
| 26 | 0,302 | 0,126 | Analgesic |

| | | | |
|---|---|---|---|
| 27 | 0,256 | 0,089 | Antiviral (Influenza A) |
| 28 | 0,373 | 0,219 | Antieczematic |
| 29 | 0,261 | 0,139 | Antiinfective |
| 30 | 0,227 | 0,107 | Fibroblast growth factor 1 agonist |
| 31 | 0,252 | 0,143 | Autoimmune disorders treatment |
| 32 | 0,204 | 0,101 | Antiprotozoal |
| 33 | 0,184 | 0,084 | Growth factor agonist |
| 34 | 0,195 | 0,100 | Antineoplastic enhancer |
| 35 | 0,230 | 0,155 | Antiviral (Influenza) |
| 36 | 0,222 | 0,152 | Analgesic stimulant |
| 37 | 0,193 | 0,128 | Anticarcinogenic |
| 38 | 0,249 | 0,186 | Antineoplastic |
| 39 | 0,122 | 0,064 | Antihyperammonemic |
| 40 | 0,211 | 0,175 | Antiallergic |
| 41 | 0,116 | 0,083 | Antineoplastic (lymphocytic leukemia) |
| 42 | 0,117 | 0,085 | Antithyroid |
| 43 | 0,052 | 0,039 | Antifungal (Pneumocystis) |

# 6. HIGH FACILE SYNTHESIS OF NOVEL 2,2-DIMETHYL PROPIONIC ACID 4-[2-(2-AZA-BICYCLO[2.2.1]HEPT-3-YL)-1H-BENZOIMIDAZOL-5-YL]-PYRROLO[2,3-d]PYRIMIDIN-7-YLMETHYL ESTER AND ITS DERIVATIVES

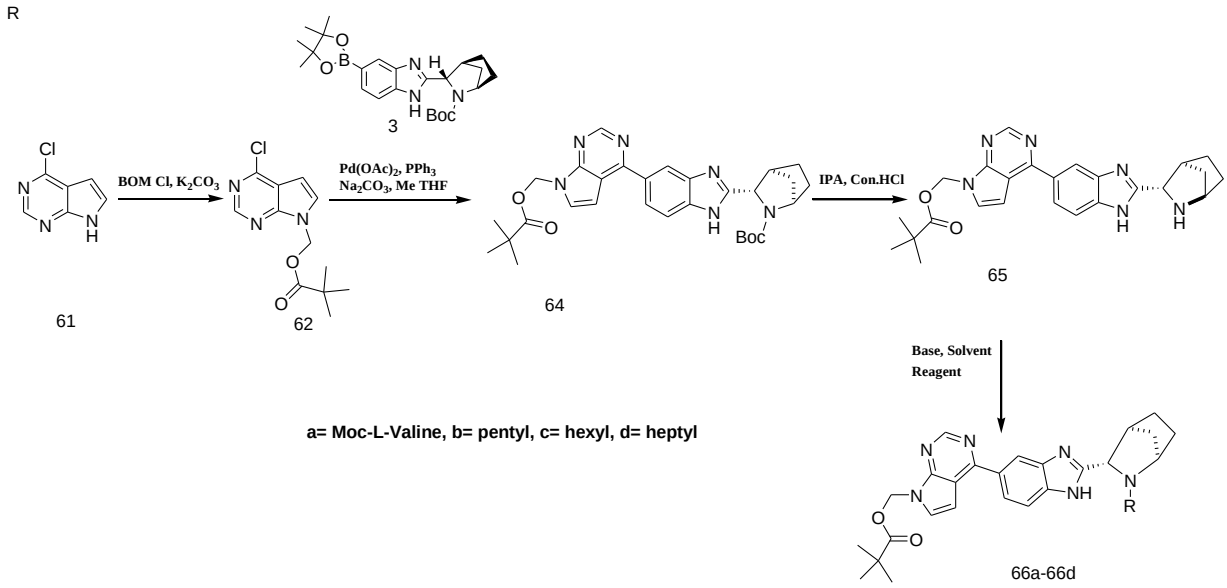
## 6.1 INTRODUCTION:

Compound containing pyrrolopyrimidine ring or pyrrolo[2,3d]pyrimidine derivatives are most important heterocyclic compound in the medicinal chemistry because of this pharmaceutical activity of all areas and also present in naturally occurring products this have been attracted more by the organic and medicinal chemist. Various biological activities of Pyrrolo[2,3-d] pyrimidine derivatives are known such as antitumor, antiviral [150], antibacterial [151] [152] [153], anti-inflammatory [154], antiallergic [155], antifungal, antiocular hypertension [156], cytotoxic [157] and enzyme inhibitor [158].

Access of highly desirable active structure provide by pyrrolo[2,3-d]pyrimidines intermediate and its derivatives, so it is interesting intermediated in organic synthesis. In recent years of organic considerable important received by novel molecules because of their biological activity are mild and good condition to preparing the corresponding products that are high selectivity and excellent yield. There is limited prior art and quite limited of this molecular synthesis are attract us to report novel, simple, efficient, facile, eco-friendly and biologically active compound 2,2-Dimethyl-propionic acid 4-[2-(2-aza-bicyclo[2.2.1]hept-3-yl)-1H-benzoimidazol-5-yl]-pyrrolo[2,3-d]pyrimidin-7-ylmethyl ester derivatives.

## 6.2 REACTION SCHEME:

**Reaction Scheme-6.1: process for the preparation of target molecules**




### 6.2.1 EXPERIMENTAL PROCEDURE CHARACTERIZATION OF COMPOUND 62-66a-66d:

### 6.2.2 Preparation of compound 62:

A suspension of compound 1 (100.00 gm, 0.6511 mole) in 400 mL acetone was stirred 10 min at 20-30°C, followed by addition of potassium carbonate ( 107.99 gm, 0.7814 moles) obtained reaction mixture was stirred 30 min at 20-30°C, then slowly added BOM Chloride ( 107.87 gm, 0.7162 moles) at 20-30°C during time period of 30-40 min., reaction maintained reflux till completion of reaction, reaction progress monitored by TLC then reaction mass cooled to 20-30°C, added slowly 1000 mL water over the period of 2-3 hrs, then stirred reaction mixture for 3-4 hrs at 20-30°C, then isolated the precipitated product and dried at 45°C for 6-8 hrs to obtained (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate ( compound 2) as white solid 158.8 gm (91.0%).

H NMR (DMSO-d $_6$, 400 MHz) δ ppm 8.71 (s, 1H), 7.83 (d, 1H, J = 3.7 Hz), 6.73 (d, 1H, J = 3.8 Hz), 6.23 (s 2H), 1.06 (s, 9H). HRMS (ESI) m/z calc for $C_{12}H_{14}ClN_3O_2$, 267.08, Found, [M+ H]: 268.09.

### 6.2.3 Preparation of compound 64:

Charged 700 mL 2Me THF and passed argon gas for 30 min to removed dissolved oxygen in solvent, then charged $Pd(OAc)_2$ ( 7.31 gm, 0.0325 moes) and triphenyl phosphine ( 12.81 gm, 0.0488 moles) was stirred one hour at 20-30°C, followed by charged compound 2 ( 100.00 gm, 0.3635 moles), compound 3 ( 180.51 gm, 0.4108 moles ) sodium carbonate (76.61 gm, 0.7227 moles) and water 300 ml was heated into reflux, and continued reflux until reaction completion, gradually cool the reaction mass to 30-40°C, the layer was separated out, resulting organic layer was successively washed with 4% N-acetyl-L-Cysteine at 50-60°C, distilled off solvent completely under reduced pressure at 45°C to obtained compound 4 ((1R,3S,4S)-tert-butyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate) as a brown solid.

$^1$H NMR (DMSO)  ppm 1.19 (s, 11H), 1.41 (broad, 2H,), 1.55 (broad, 11H,), 1.77 (broad, 2H), 1.88-190 (broad , 6H), 2.18 (s, 1H), 2.58-2.62 (t, 0.62H ), 3.51(d, 1H ), 4.20 (s, 1H), 4.61(s, 1H), 6.29 (s, 2H), 6.92 (d, 1H), 7.56-7.59 (m, 1H), 7.66-7.70 (m, 1H), 7.88-8.50 (m, 2H) 9.01 (s, 1H. HRMS (ESI) m/z calc for $C_{30}H_{36}N_6O_4$, 544.28, Found, [M+ H]: 545.3395

### 6.2.4 Preparation of compound 65:

Compound 4 dissolved in IPA 1500 mL followed by addition of Con.HCl at 20-30°C and then the reaction mass temperature was maintained at 50-55°C for 3-4 hrs after reaction was completed solvent distilled off completely under reduced pressure to produce compound 5 (2,2-Dimethyl-propionic acid 4-[2-(2-aza-bicyclo[2.2.1]hept-3-yl)-1H-benzoimidazol-5-yl]-pyrrolo[2,3-d]pyrimidin-7-ylmethyl ester) as brown colored solid.

HRMS (ESI) m/z calc for $C_{25}H_{28}N_6O_2$, 444.23, Found, [M+ H]: 445.2342

### 6.2.5 Preparation of compound 66 a:

Compound 5 (10.00 gm, 0.0224 moles) dissolved in DMF in 100 mL followed by addition of Moc-L-Valine (4.21 gm, 0.02040 moles) then HATU (10.26 gm, 0.0269 moles) (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium3-oxidehexa fluorophosphate and triethylamine (5.69 gm, 0.0562 moles) was added in to it at 0-5°C, stirred 2-3 hrs of this reaction mixture at 0-5°C, reaction monitored by TLC after reaction completion water added in to it, the compound was extracted with MDC followed by washed with water, organic layer moisture were removed by sodium sulphate drying, then the compound was purified by column chromatography by MDC and methanol as eluent to obtained compound-6a (2,2-Dimethyl-propionic acid 4-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-1H-enzoimidazol-5-yl}-pyrrolo[2,3-d]pyrimidin-7-ylmethyl ester as pale brown colored solid 10.55 gm, (60.0%).

$^1$H NMR (DMSO)  ppm 0.76-0.96 (m, 6H), 1.11-1.17 (s, 9H), 1.23 (m, 1H), 1.23-1.55(m, 4H)1.78-1.80 (m, 1H), 1.84 ( m, 1H), 1.92 (m, 1H), 1.99 (m, 1H), 2.69 (s,1H), 3.56-3.60 (s, 3H), 4.18-4.20 (m, 1H), 4.56-4.69 (m, 2H), 6.29(s, 2H), 7.02(s,1H), 7.24-7.26 (d, 1H), 7.65-7.71 (m, 1H), 7.79 (s,1H), 7.99-8.04 (m, 1H), 8.30 (d, 1H), 8.93 (s, 1H). HRMS (ESI) m/z calc for $C_{32}H_{39}N_7O_5$, 601.3, Found, [M+ H]: 602.3761.

### 6.2.6 Preparation of compound 66 b:

Compound 5 (10.00 gm, 0.0224 moles) dissolved in acetone 100 mL and water 40 mL mixture followed by addition of potassium carbonate (4.66 gm, 0.0337 moles) followed by addition of pentylchloroformate (3.39 gm, 0.0224 moles) 20-25°C, then obtained reaction mixture were stirred for 2-3 hrs at 20-25°C after, reaction progress monitored by TLC after reaction was judged to completed water added in to it, the compound was partitioned with ethylacetate followed by washed with water, moisture in organic layer

were removed by addition of sodium sulphate, then the title compound were purified by column chromatography by using ethylacetate and hexane as eluent to obtained compound-6b (1R,3S,4S)-pentyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate as pale brown colored solid 6.91 gm, (55.0%).

HRMS (ESI) m/z calc for $C_{31}H_{38}N_6O_4$, 558.3, Found, [M+ H]: 559.2517

### 6.2.7 Preparation of compound 66 c:

Compound 5 (10.00 gm, 0.0224 moles) dissolved in acetone 100 mL and water 40 mL mixture followed by addition of potassium carbonate (4.66 gm, 0.0337 moles) followed by addition of heptylchloroformate (4.02 gm, 0.0225 moles) 20-25°C, then the reaction mixture were stirred for 2-3 hrs at 20-25°C after, reaction progress monitored by TLC after reaction was judged to completed water was added in to it, the compound was extracted with ethylacetate followed by washed with water, organic layer moisture was removed by addition of sodium sulphate, then the title compound were purified by column chromatography by using ethylacetate and hexane as eluent to obtained compound-6d (1R,3S,4S)-heptyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate) as pale brown colored solid 7.96 gm, (60.30%).

$^1$H NMR (DMSO)  ppm 0.86-0.87 (m, 3H), 1.07-1.12 (s, 9H), 1.18-1.24 (m, 3H), 1.24-1.38 (m, 4H)1.38(m, 1H), 1.64-1.79 ( m, 5H), 1.92 (m, 2H), 2.50-2.51 (m, 2H), 4.54-4.64(m, 3H), 6.22(d, 2H), 7.02(m,1H), 7.55-7.57(m, 1H), 7.60-7.65(m, 2H), 7.78-7.79 (m,1H), 8.32 (m, 1H), 8.93-8.97 (d, 1H). HRMS (ESI) m/z calc for $C_{33}H_{42}N_6O_4$, 586.33, Found, [M+ H]: 587.2412

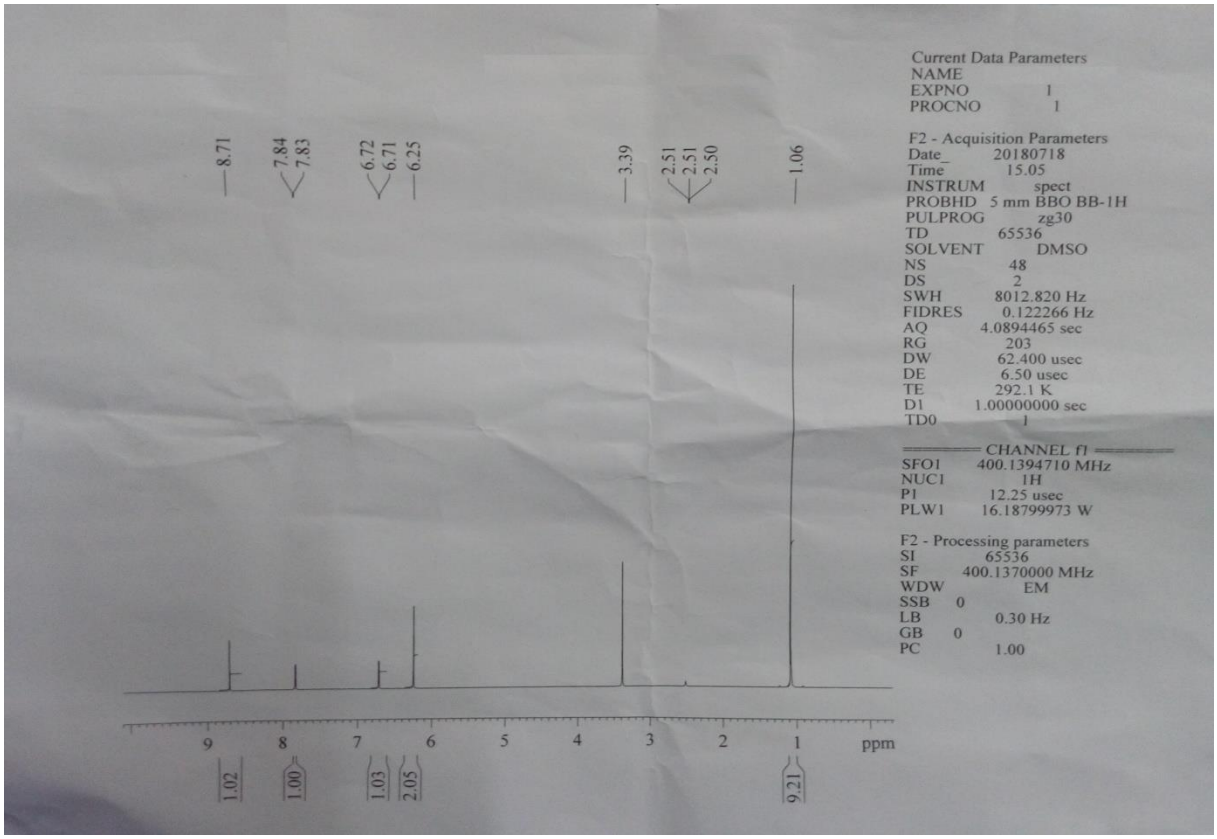
### 6.2.8 Preparation of compound 66 d:

Compound 5 (10.00 gm, 0.0224 moles) dissolved in acetone 100 mL and water 40 mL mixture followed by addition of potassium carbonate (4.66 gm, 0.0337 moles) followed by addition of hexylchloroformate (3.70 gm, 0.0182 moles) 20-25°C, then the reaction mixture were stirred for 2-3 hrs at 20-25°C after, reaction progress monitored by TLC after reaction was judged to completed water added in to it, the compound was partitioned with ethylacetate followed by washed with water, organic layer moisture was removed by addition of sodium sulphate, then the title compound were purified by column chromatography by using ethylacetate and hexane as mobile phase to obtained compound-6c ((1R,3S,4S)-hexyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate) as pale brown colored solid 7.96 gm, (60.30%).

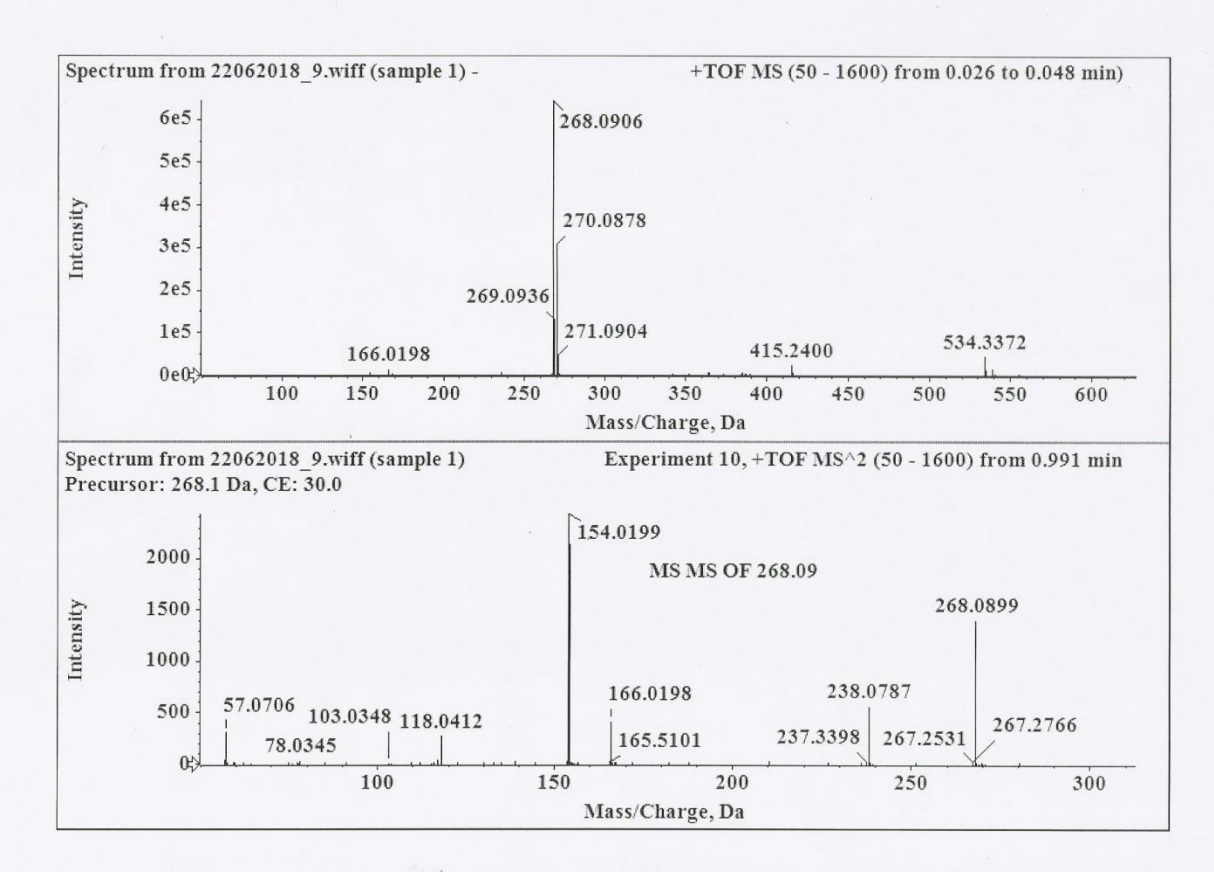
HRMS (ESI) m/z calc for C32H40N6O4, 572.31, Found, [M+ H]: 573.2342

## 6.3 $^{1}$HNMR, $^{13}$C NMR, DEPT AND MASS SPECTROSCOPY OF TARGET COMPOUNDS

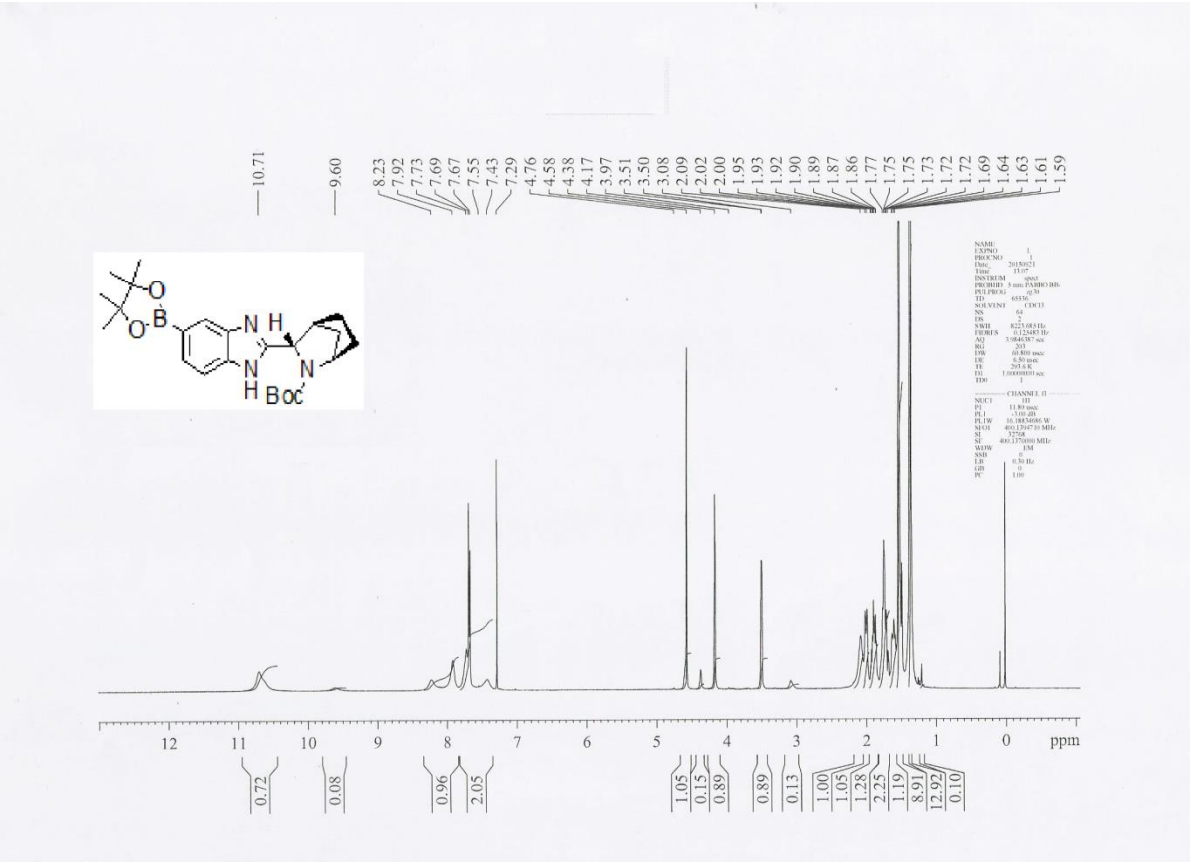
### 6.3.1 $^{1}$HNMR Spectra of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (62)



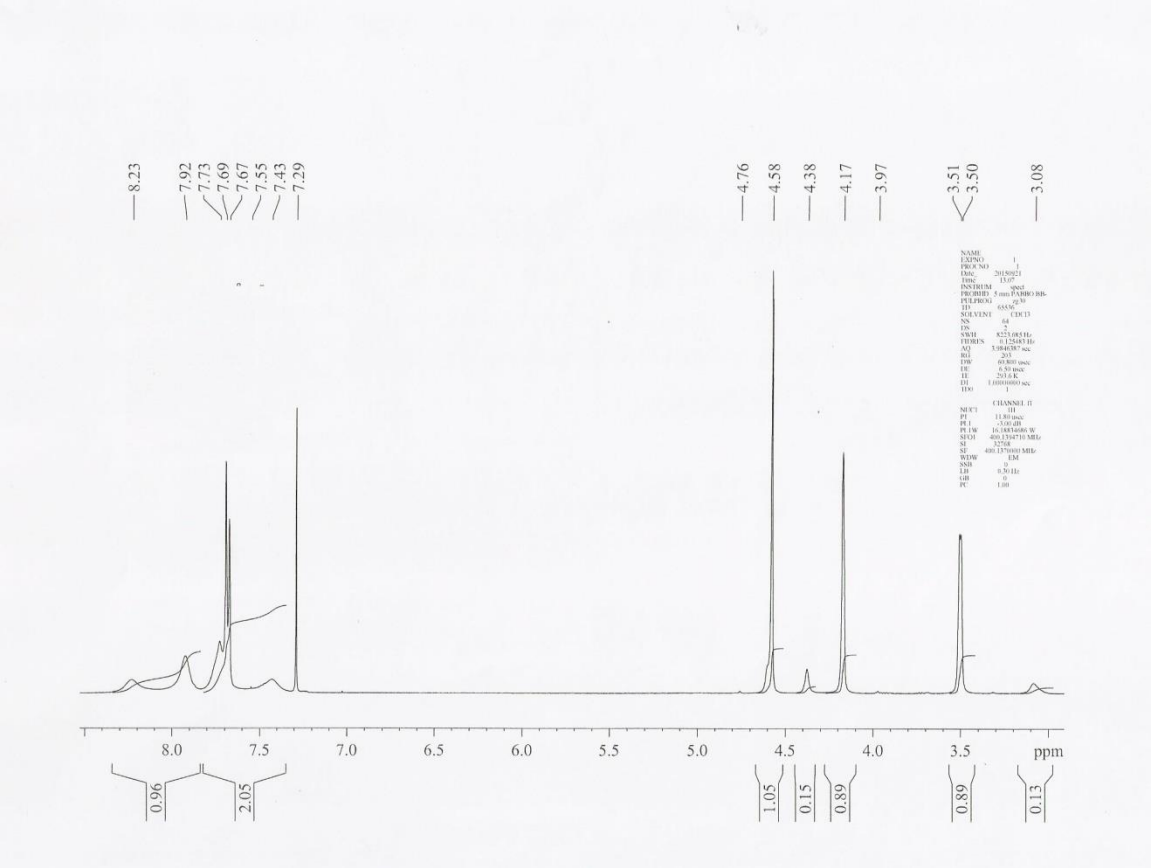
### 6.3.2 Mass Spectra of (4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (62)



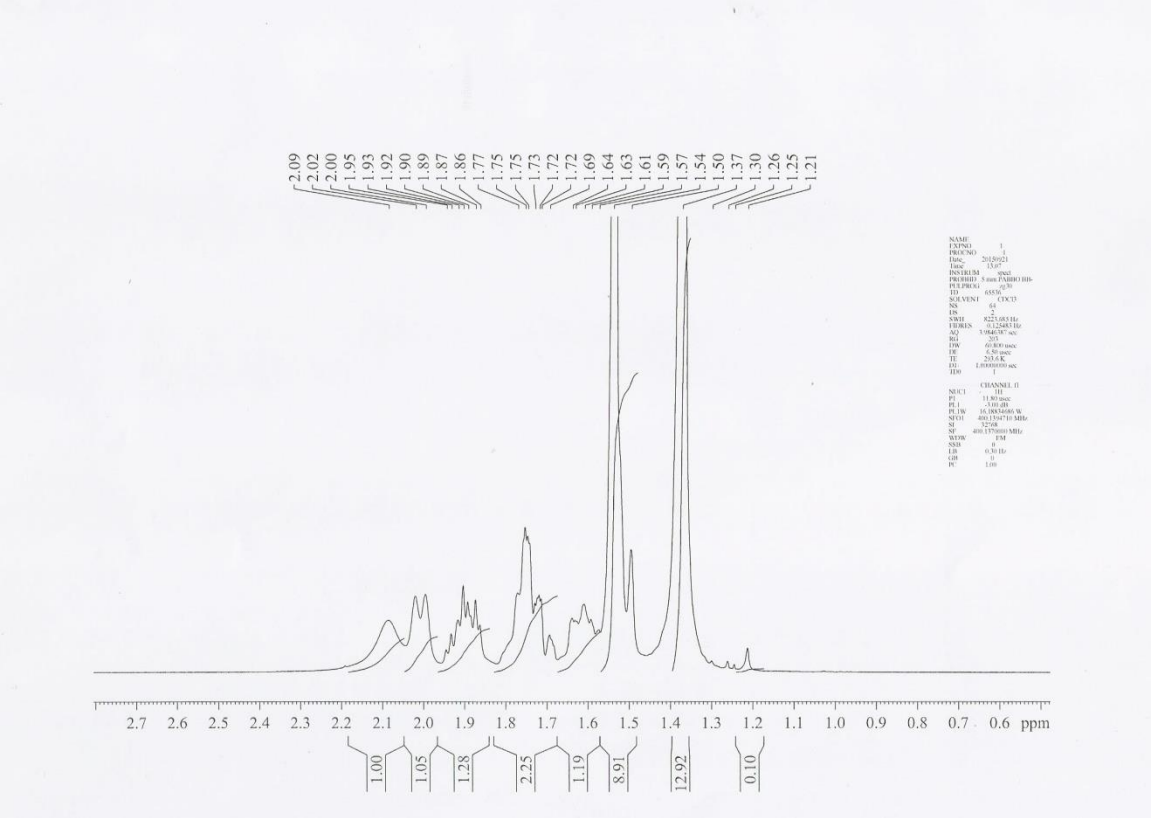
### 6.3.3 [1]HNMR Spectra of (1R,3S,4S)-tert-butyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (3)



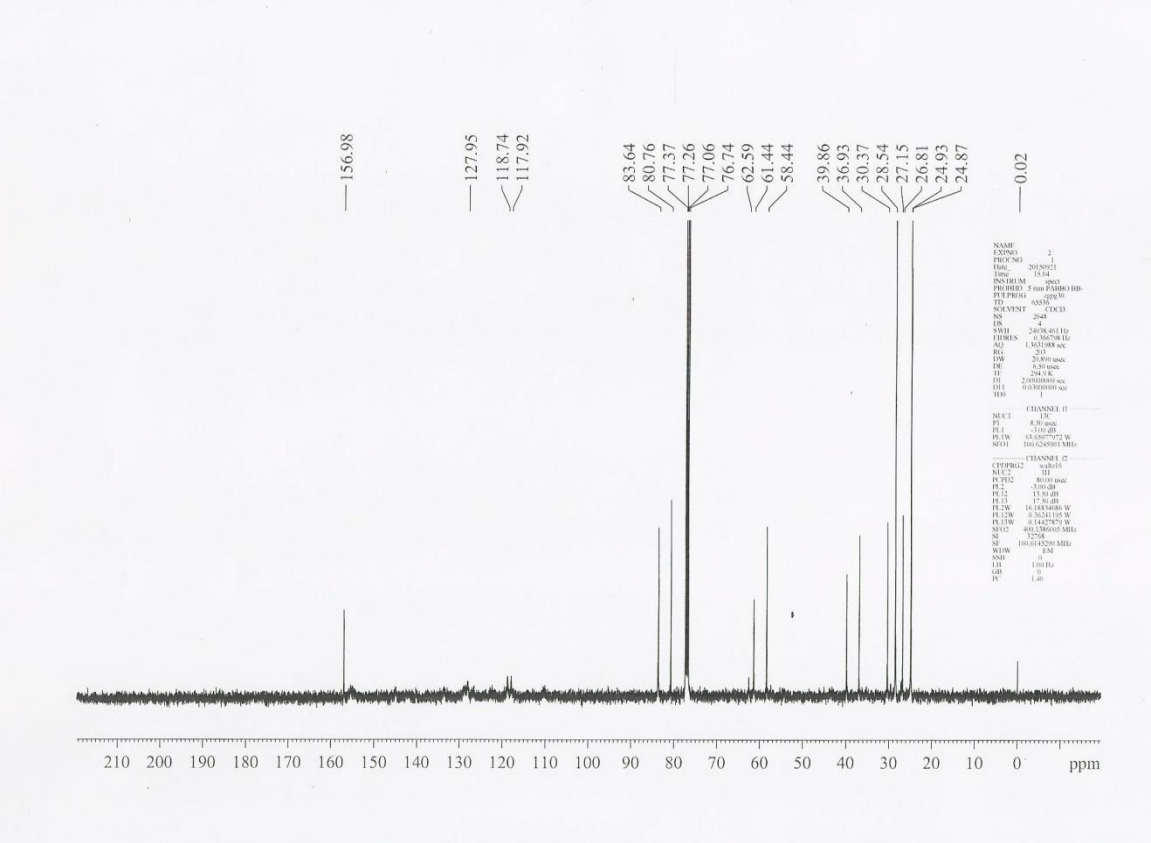
### 6.3.4 [1]HNMR Spectra of (1R,3S,4S)-tert-butyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (3)



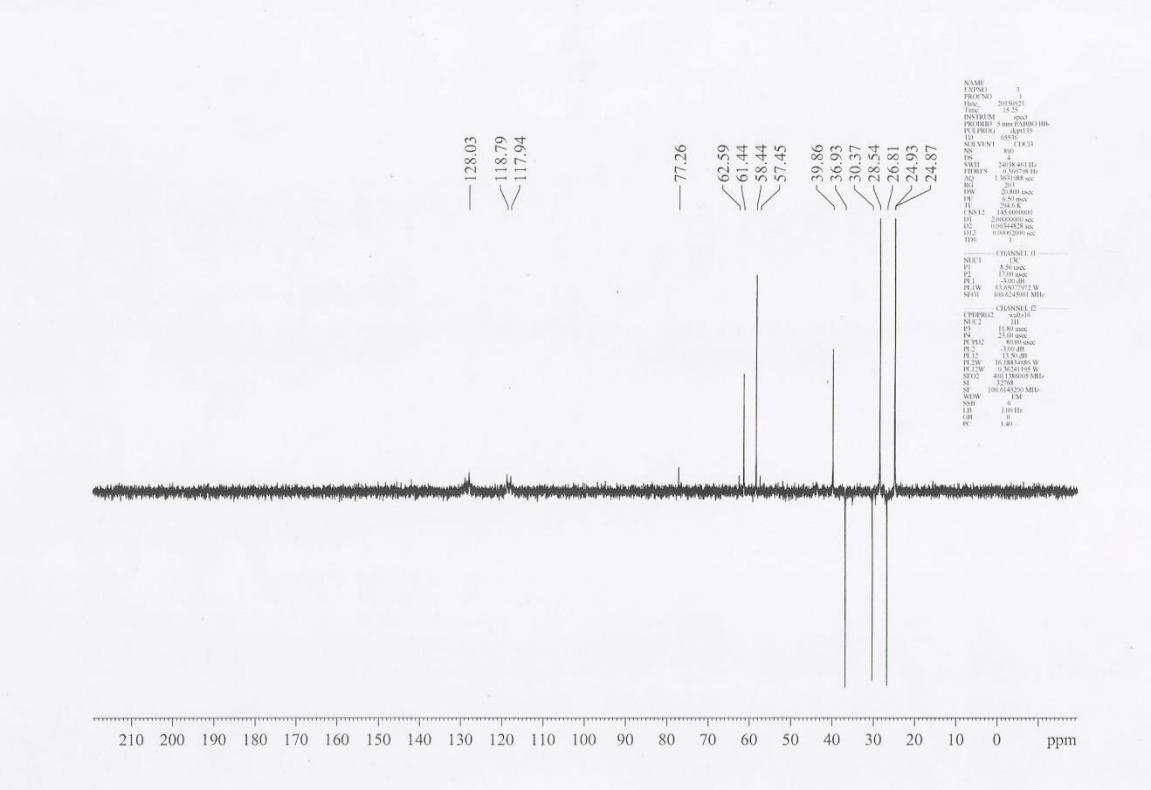
### 6.3.5 $^{1}$HNMR Spectra of (1R,3S,4S)-tert-butyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (3)



### 6.3.6 $^{13}$CNMR Spectra of (1R,3S,4S)-tert-butyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (3)



### 6.3.7 DEPTNMR Spectra of (1R,3S,4S)-tert-butyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (3)



### 6.3.8 MassSpectra of (1R,3S,4S)-tert-butyl 3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (3)

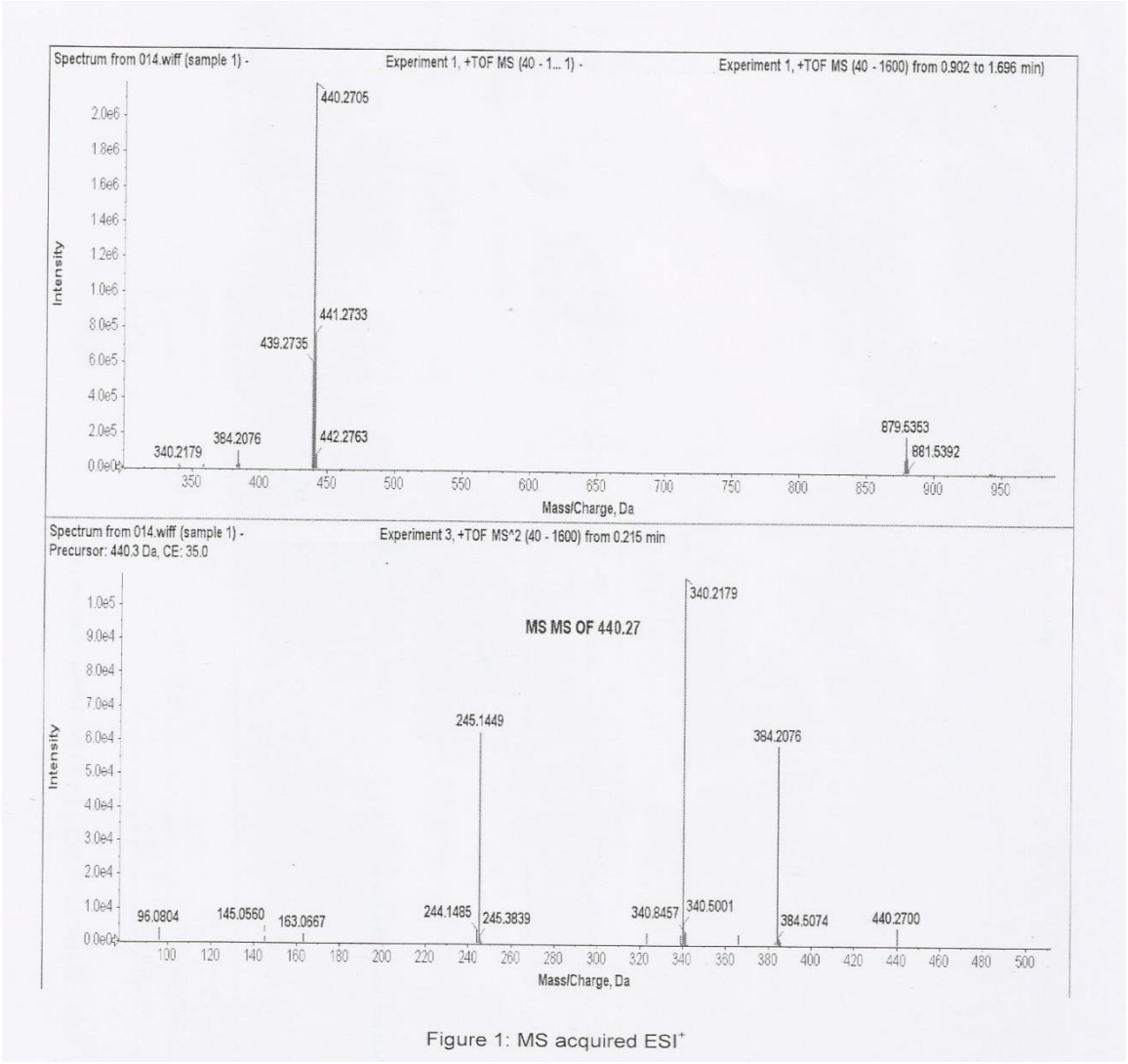
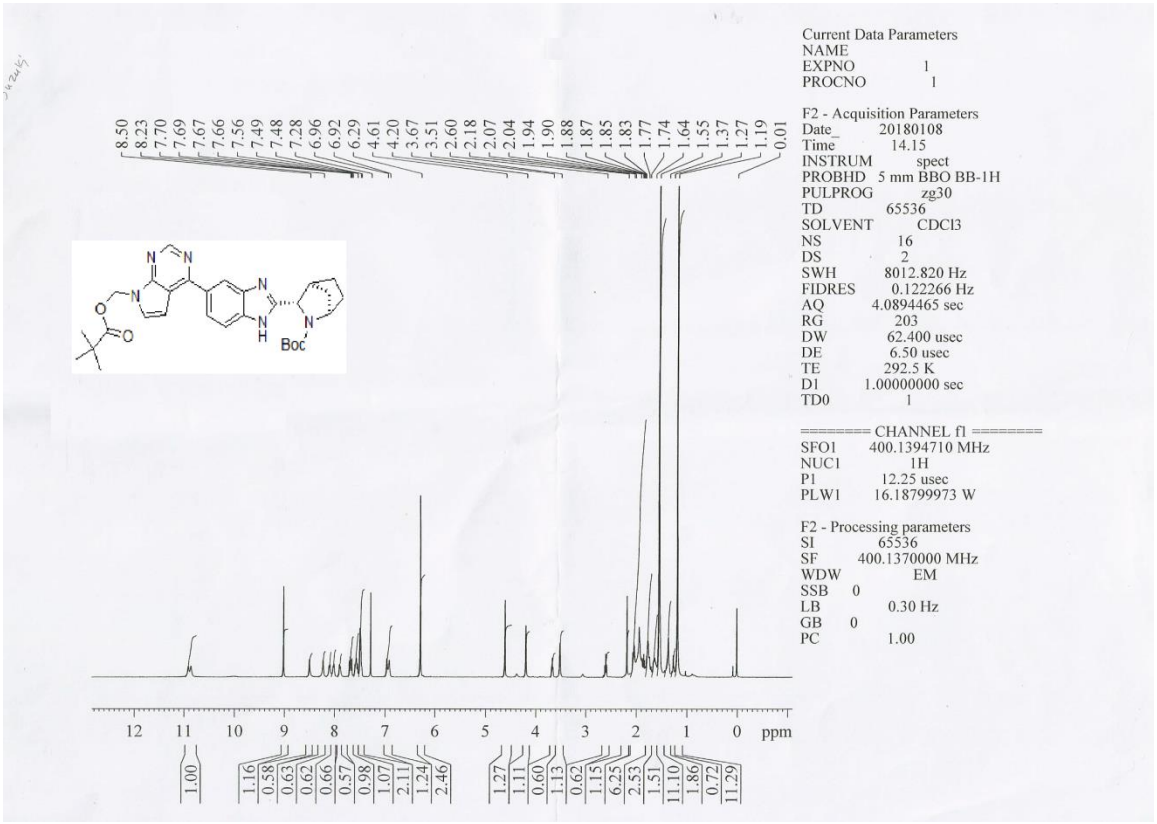
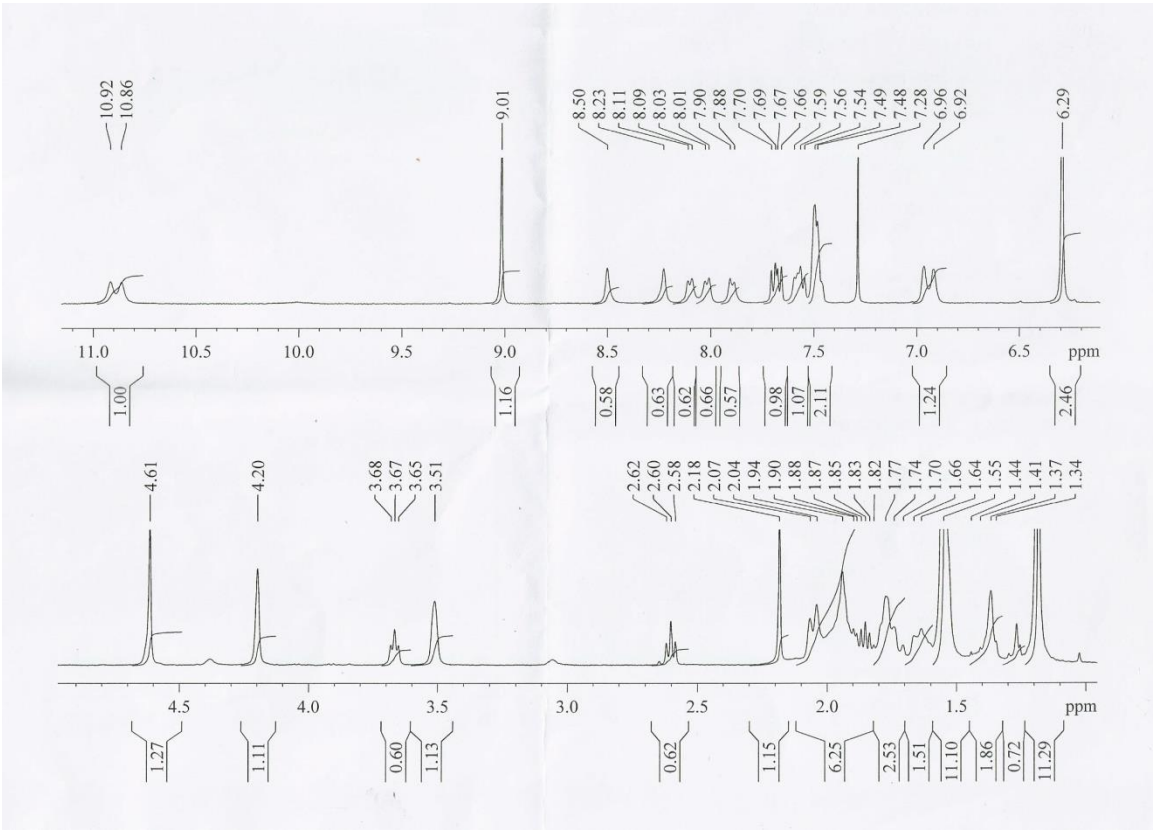



Figure 1: MS acquired ESI$^+$

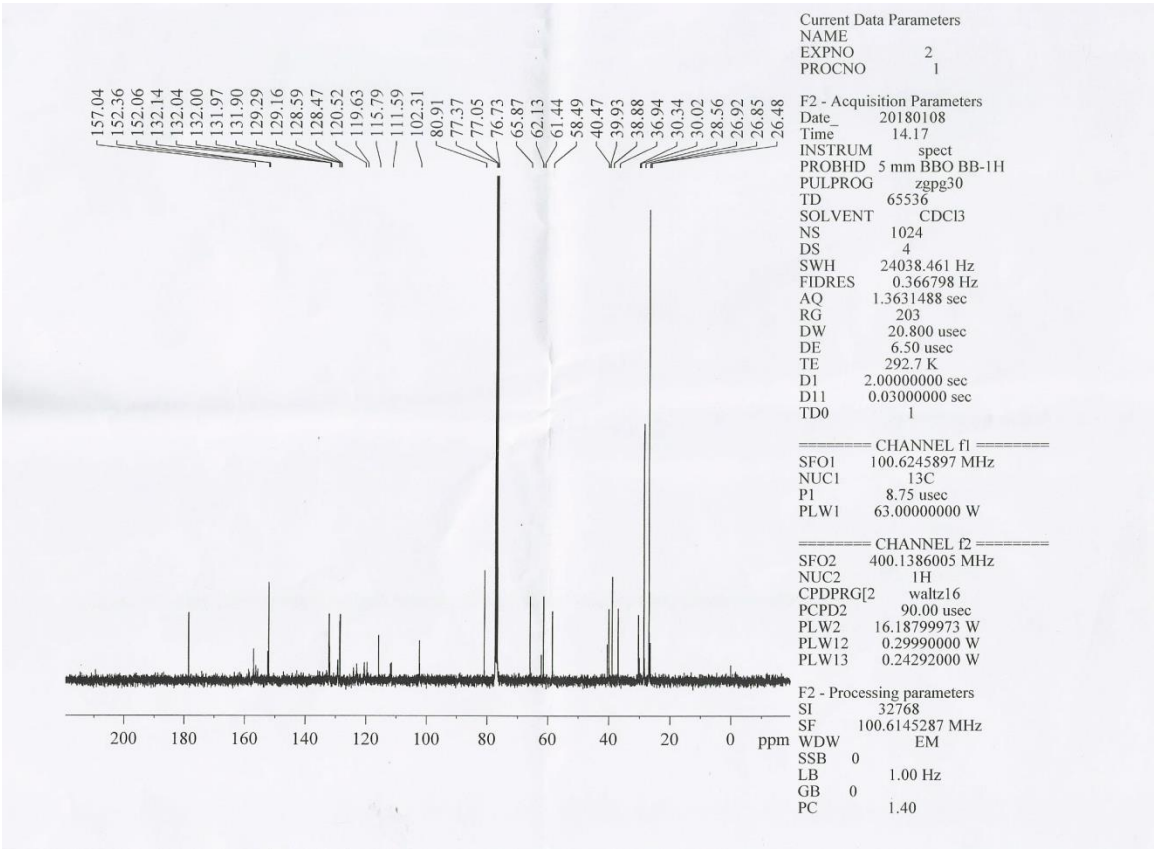
### 6.3.9 [1]HNMR Spectra of (1R,3S,4S)-tert-butyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (64)



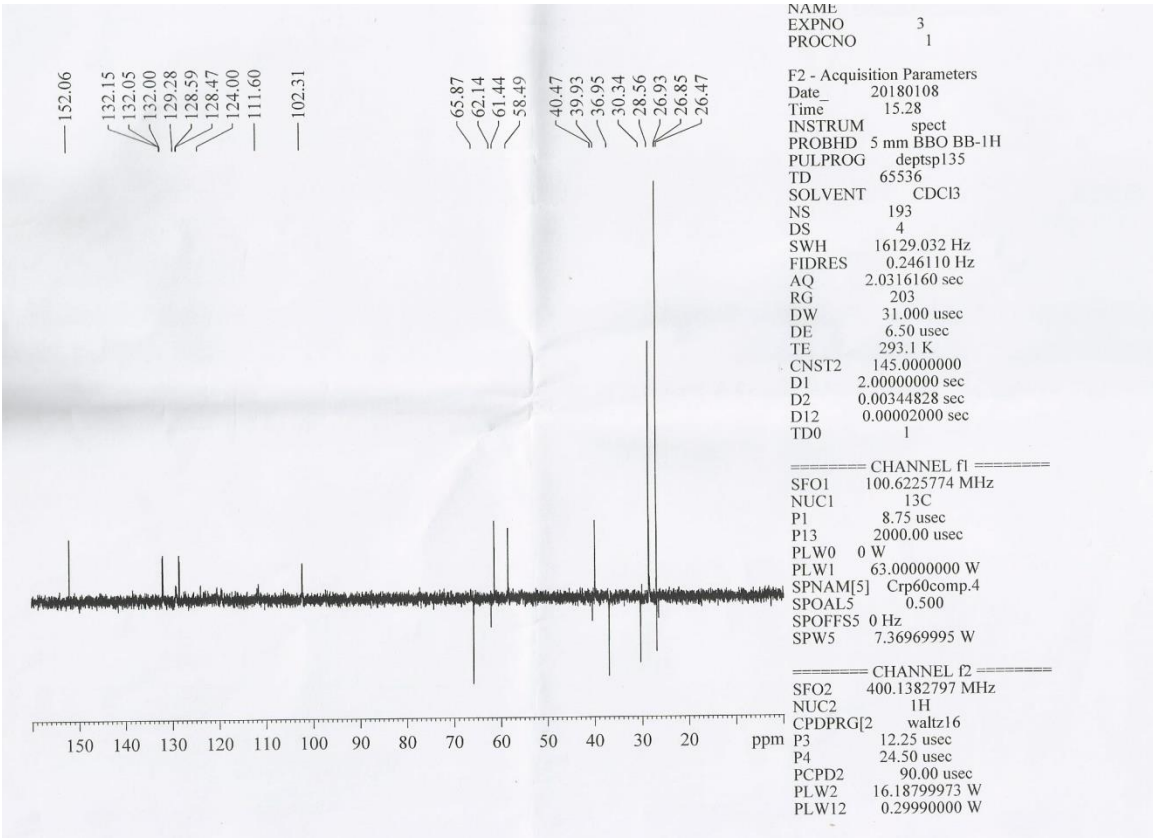
### 6.3.10 $^{1}$HNMR Spectra of (1R,3S,4S)-tert-butyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (64)



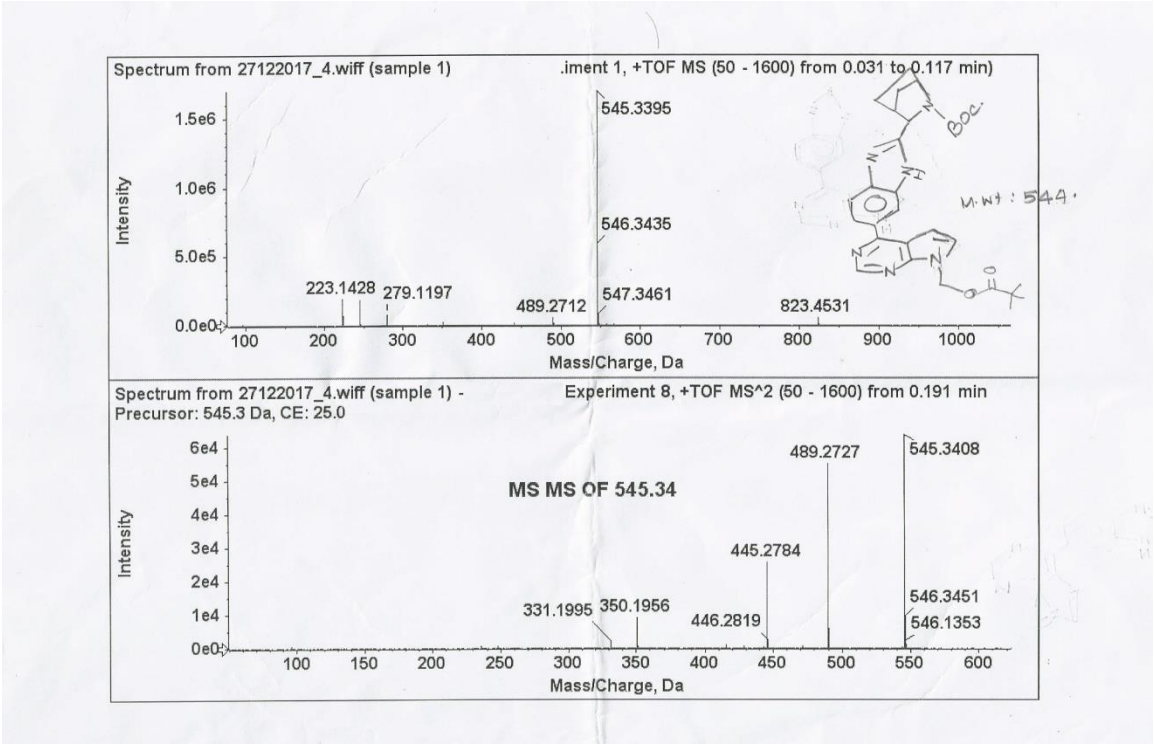
### 6.3.11 $^{13}$CNMR Spectra of (1R,3S,4S)-tert-butyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (64)



### 6.3.12 $^{13}$CNMR Spectra of (1R,3S,4S)-tert-butyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (64)



### 6.3.13 MassSpectra of ((1R,3S,4S)-tert-butyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (64)

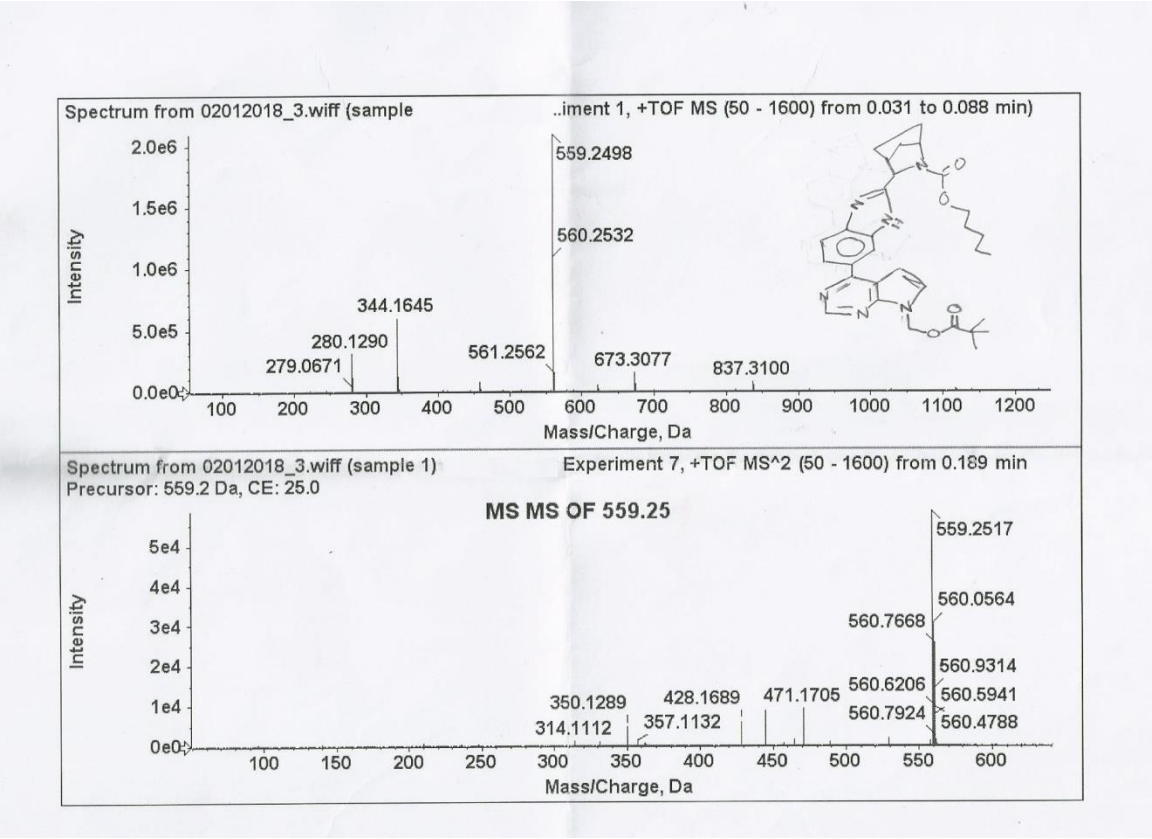


### 6.3.14 HNMR Spectra of 2,2-Dimethy-propionic acid 4-[2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3yl]-1H-benzoinidazol-5-yl]-pyrrolo[2,3-d]pyrimidin-7-ylmethyl ester (64a)

### 6.3.15 Mass Spectra of 2,2-Dimethy-propionic acid 4-[2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3yl]-1H-benzoinidazol-5-yl]-pyrrolo[2,3-d]pyrimidin-7-ylmethyl ester (64a)

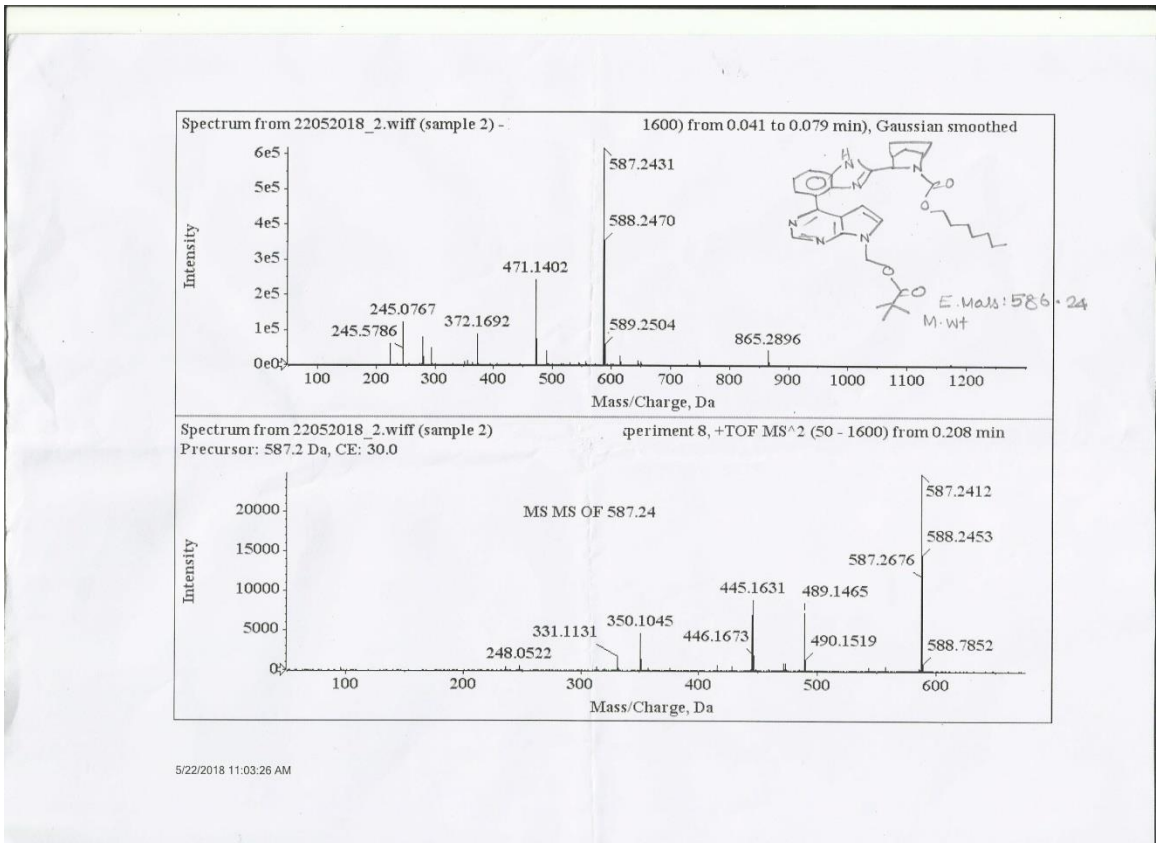
### 6.3.16 HNMR Spectra of (1R, 3S, 4S)-3-{5-[7-(2,2-Dimethy-propionyloxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1H-benzoimidazole-2-yl}-2-aza-bicyclo[2.2.1]heptanes-2-carboxylic acid pentyl ester (64b)

### 6.3.17 HNMR Spectra of (1R, 3S, 4S)-3-{5-[7-(2,2-Dimethy-propionyloxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1H-benzoimidazole-2-yl}-2-aza-bicyclo[2.2.1]heptanes-2-carboxylic acid pentyl ester (64b)



### 6.3.18 HNMR Spectra of (1R, 3S, 4S)-3-{5-[7-(2,2-Dimethy-propionyloxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1H-benzoimidazole-2-yl}-2-aza-bicyclo[2.2.1]heptanes-2-carboxylic acid heptyl ester (64c)

### 6.3.19 HNMR Spectra of (1R, 3S, 4S)-3-{5-[7-(2,2-Dimethy-propionyloxymethyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1H-benzoimidazole-2-yl}-2-aza-bicyclo[2.2.1]heptanes-2-carboxylic acid heptyl ester (64c)



## 6.4 BIOLOGICAL POTENTIAL OF COMPOUNDS BY PASS PREDICTION

Compounds 64, 65, 66a-66c shows tremendous activity in PASS prediction in various diseases, some of the important activities are listed below tables.

### 6.4.1 PASS Prediction data of (1R,3S,4S)-tert-butyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (64)

Compound-64 shows some of the important activities like **Antiparkinsonian, Antiviral, Ophthalmic drug, Antineoplastic enhancer** and **Respiratory distress syndrome treatment.**

**Table: 6.1 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,527 | 0,067 | Nicotinic alpha4beta4 receptor agonist |
| 2 | 0,380 | 0,017 | Antiviral |
| 3 | 0,336 | 0,049 | Antiparkinsonian |
| 4 | 0,321 | 0,043 | Ophthalmic drug |
| 5 | 0,320 | 0,046 | DNA polymerase I inhibitor |
| 6 | 0,288 | 0,034 | RNA directed DNA polymerase inhibitor |
| 7 | 0,250 | 0,054 | Respiratory distress syndrome treatment |
| 8 | 0,262 | 0,073 | Raynaud's phenomenon treatment |
| 9 | 0,270 | 0,096 | Antimetastatic |
| 10 | 0,304 | 0,132 | Neurodegenerative diseases treatment |
| 11 | 0,180 | 0,019 | Antiviral (Hepatitis) |
| 12 | 0,173 | 0,015 | Interleukin 8 antagonist |
| 13 | 0,160 | 0,017 | Xanthine oxidase substrate |
| 14 | 0,257 | 0,127 | CYP17 inhibitor |

| | | | |
|---|---|---|---|
| 15 | 0,177 | 0,052 | DNA directed RNA polymerase inhibitor |
| 16 | 0,147 | 0,038 | Inosine nucleosidase inhibitor |
| 17 | 0,206 | 0,109 | Cyclic GMP phosphodiesterase inhibitor |
| 18 | 0,127 | 0,029 | Antiviral (Hepatitis C) |
| 19 | 0,221 | 0,127 | Interferon alpha agonist |
| 20 | 0,360 | 0,270 | CYP2H substrate |
| 21 | 0,185 | 0,115 | Antineoplastic enhancer |
| 22 | 0,254 | 0,185 | Fibroblast growth factor agonist |
| 23 | 0,147 | 0,079 | Antiglaucomic |
| 24 | 0,114 | 0,048 | Nicotinic alpha3beta4 receptor agonist |
| 25 | 0,048 | 0,003 | HCV NS5A inhibitor |
| 26 | 0,221 | 0,181 | Antineoplastic (solid tumors) |
| 27 | 0,148 | 0,114 | Niemann-Pick C1-like 1 protein antagonist |
| 28 | 0,075 | 0,044 | Phosphodiesterase II inhibitor |
| 29 | 0,034 | 0,018 | Equilibrative nucleoside transport protein 1 inhibitor |
| 30 | 0,030 | 0,014 | Elastase 2 inhibitor |
| 31 | 0,052 | 0,043 | Elastase 1 inhibitor |
| 32 | 0,224 | 0,216 | Transcription factor NF kappa B stimulant |
| 33 | 0,224 | 0,216 | Transcription factor stimulant |
| 34 | 0,175 | 0,170 | Macrophage stimulant |
| 35 | 0,025 | 0,022 | Equilibrative nucleoside transport protein inhibitor |

### 6.4.2 PASS Prediction data of 2,2-Dimethyl-propionic acid 4-{2-[2-(2-methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-1H-benzoimidazol-5-yl}-pyrrolo[2,3-d]pyrimidin-7-ylmethyl ester (65)

Compound-65 shows some of the important activities like **Antineoplastic (solid tumors), Antineoplastic (thyroid cancer), Fibroblast growth factor agonist, Antiviral** (HIV, Influenza-A, hepatitis-C)**, Antineoplastic (melanoma), Antifungal enhancer** and **Respiratory distress Antineoplastic (lymphocytic leukemia).**

**Table: 6.2 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,491 | 0,085 | Nicotinic alpha4beta4 receptor agonist |
| 2 | 0,387 | 0,016 | Antiviral |
| 3 | 0,287 | 0,034 | Respiratory distress syndrome treatment |
| 4 | 0,209 | 0,012 | Antiviral (Hepatitis) |
| 5 | 0,255 | 0,089 | Antiviral (Influenza A) |
| 6 | 0,168 | 0,012 | Antiviral (Hepatitis C) |
| 7 | 0,171 | 0,035 | Antiemphysemic |
| 8 | 0,125 | 0,002 | HCV NS5A inhibitor |
| 9 | 0,374 | 0,250 | CYP2H substrate |
| 10 | 0,160 | 0,054 | Antiviral (HIV) |
| 11 | 0,242 | 0,148 | Antineoplastic (solid tumors) |
| 12 | 0,167 | 0,079 | Antineoplastic (thyroid cancer) |
| 13 | 0,277 | 0,190 | CYP2C19 inducer |
| 14 | 0,254 | 0,185 | Fibroblast growth factor agonist |
| 15 | 0,181 | 0,117 | RNA directed DNA polymerase inhibitor |
| 16 | 0,107 | 0,046 | Antifungal enhancer |
| 17 | 0,068 | 0,016 | Elastase inhibitor |
| 18 | 0,143 | 0,095 | DNA directed RNA polymerase inhibitor |
| 19 | 0,188 | 0,152 | Macrophage stimulant |
| 20 | 0,190 | 0,155 | Cyclic GMP phosphodiesterase inhibitor |
| 21 | 0,098 | 0,073 | Acetylcholine M2 receptor agonist |
| 22 | 0,139 | 0,114 | Antineoplastic (melanoma) |
| 23 | 0,189 | 0,164 | Dolichyl-phosphate beta-glucosyltransferase inhibitor |
| 24 | 0,193 | 0,170 | Antimetastatic |
| 25 | 0,033 | 0,012 | Elastase 2 inhibitor |
| 26 | 0,186 | 0,177 | Interferon alpha agonist |
| 27 | 0,102 | 0,096 | Antineoplastic (lymphocytic leukemia) |

### 6.4.3 PASS Prediction data of 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (66a)

Compound-66a shows some of the important activities like **Antiglaucomic, Antiparkinsonian, Antiparkinsonian, Neurodegenerative diseases treatment, Alzheimer's disease treatment, Ophthalmic drug, Alzheimer's disease treatment, Antineoplastic (solid tumors), Antineoplastic (melanoma), Antiviral (Hepatitis C),** and **Respiratory distress Antiinfertility, female.**

**Table: 6.3 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,489 | 0,086 | Nicotinic alpha4beta4 receptor agonist |
| 2 | 0,383 | 0,027 | Ophthalmic drug |
| 3 | 0,322 | 0,054 | Antiparkinsonian |
| 4 | 0,281 | 0,044 | Antiviral |
| 5 | 0,279 | 0,083 | Immunomodulator |
| 6 | 0,227 | 0,031 | Antiglaucomic |
| 7 | 0,310 | 0,127 | Neurodegenerative diseases treatment |
| 8 | 0,221 | 0,069 | RNA directed DNA polymerase inhibitor |
| 9 | 0,220 | 0,076 | Respiratory distress syndrome treatment |
| 10 | 0,285 | 0,144 | Benzoate-CoA ligase inhibitor |
| 11 | 0,232 | 0,123 | Antimetastatic |
| 12 | 0,224 | 0,122 | Alzheimer's disease treatment |
| 13 | 0,218 | 0,121 | Macrophage stimulant |
| 14 | 0,163 | 0,067 | DNA directed RNA polymerase inhibitor |
| 15 | 0,177 | 0,091 | Prenyl-diphosphatase inhibitor |
| 16 | 0,286 | 0,204 | Glyceryl-ether monooxygenase inhibitor |
| 17 | 0,198 | 0,130 | Cyclic GMP phosphodiesterase inhibitor |
| 18 | 0,326 | 0,260 | Antieczematic |

| | | | |
|---|---|---|---|
| 19 | 0,125 | 0,062 | Antiviral (Hepatitis) |
| 20 | 0,159 | 0,102 | Antineoplastic (thyroid cancer) |
| 21 | 0,132 | 0,075 | Endoglycosylceramidase inhibitor |
| 22 | 0,078 | 0,025 | Purinergic P2T antagonist |
| 23 | 0,223 | 0,177 | Antineoplastic (solid tumors) |
| 24 | 0,103 | 0,058 | Interleukin 8 antagonist |
| 25 | 0,154 | 0,109 | Retinol dehydrogenase inhibitor |
| 26 | 0,217 | 0,176 | Analgesic, non-opioid |
| 27 | 0,144 | 0,109 | Antineoplastic (melanoma) |
| 28 | 0,076 | 0,043 | Phosphodiesterase II inhibitor |
| 29 | 0,036 | 0,004 | HCV NS5A inhibitor |
| 30 | 0,231 | 0,202 | Transcription factor NF kappa B stimulant |
| 31 | 0,231 | 0,202 | Transcription factor stimulant |
| 32 | 0,098 | 0,068 | Nicotinic alpha3beta4 receptor agonist |
| 33 | 0,230 | 0,201 | DNA polymerase I inhibitor |
| 34 | 0,120 | 0,102 | Antiemphysemic |
| 35 | 0,093 | 0,076 | Antiviral (Hepatitis C) |
| 36 | 0,035 | 0,019 | Purinergic P2Y12 antagonist |
| 37 | 0,066 | 0,050 | Purinergic receptor antagonist |
| 38 | 0,091 | 0,075 | Inosine nucleosidase inhibitor |
| 39 | 0,206 | 0,191 | Anticonvulsant |
| 40 | 0,041 | 0,031 | Purinergic P2Y antagonist |
| 41 | 0,146 | 0,138 | Nicotinic alpha4beta2 receptor antagonist |
| 42 | 0,052 | 0,044 | Elastase 1 inhibitor |
| 43 | 0,180 | 0,178 | Undecaprenyl-phosphate mannosyltransferase inhibitor |
| 44 | 0,160 | 0,158 | Antiinfertility, female |
| 45 | 0,024 | 0,022 | Elastase 2 inhibitor |

### 6.4.4 PASS Prediction data of (1R,3S,4S)-pentyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (66b)

Compound-66b shows some of the important activities like **Antiparkinsonian, Antiparkinsonian, Neurodegenerative diseases treatment, Alzheimer's disease treatment, Ophthalmic drug, Alzheimer's disease treatment, Antineoplastic (solid tumors), Antineoplastic (melanoma), Antiviral (Hepatitis C),** and **Respiratory distress Anticonvulsant.**

**Table: 6.4 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,489 | 0,086 | Nicotinic alpha4beta4 receptor agonist |
| 2 | 0,383 | 0,027 | Ophthalmic drug |
| 3 | 0,322 | 0,054 | Antiparkinsonian |
| 4 | 0,281 | 0,044 | Antiviral |
| 5 | 0,279 | 0,083 | Immunomodulator |
| 6 | 0,227 | 0,031 | Antiglaucomic |
| 7 | 0,310 | 0,127 | Neurodegenerative diseases treatment |
| 8 | 0,221 | 0,069 | RNA directed DNA polymerase inhibitor |
| 9 | 0,220 | 0,076 | Respiratory distress syndrome treatment |
| 10 | 0,285 | 0,144 | Benzoate-CoA ligase inhibitor |
| 11 | 0,232 | 0,123 | Antimetastatic |
| 12 | 0,224 | 0,122 | Alzheimer's disease treatment |
| 13 | 0,218 | 0,121 | Macrophage stimulant |
| 14 | 0,163 | 0,067 | DNA directed RNA polymerase inhibitor |
| 15 | 0,177 | 0,091 | Prenyl-diphosphatase inhibitor |
| 16 | 0,286 | 0,204 | Glyceryl-ether monooxygenase inhibitor |
| 17 | 0,198 | 0,130 | Cyclic GMP phosphodiesterase inhibitor |

| | | | |
|---|---|---|---|
| 18 | 0,326 | 0,260 | Antieczematic |
| 19 | 0,125 | 0,062 | Antiviral (Hepatitis) |
| 20 | 0,159 | 0,102 | Antineoplastic (thyroid cancer) |
| 21 | 0,132 | 0,075 | Endoglycosylceramidase inhibitor |
| 22 | 0,078 | 0,025 | Purinergic P2T antagonist |
| 23 | 0,223 | 0,177 | Antineoplastic (solid tumors) |
| 24 | 0,103 | 0,058 | Interleukin 8 antagonist |
| 25 | 0,154 | 0,109 | Retinol dehydrogenase inhibitor |
| 26 | 0,217 | 0,176 | Analgesic, non-opioid |
| 27 | 0,144 | 0,109 | Antineoplastic (melanoma) |
| 28 | 0,076 | 0,043 | Phosphodiesterase II inhibitor |
| 29 | 0,036 | 0,004 | HCV NS5A inhibitor |
| 30 | 0,231 | 0,202 | Transcription factor NF kappa B stimulant |
| 31 | 0,231 | 0,202 | Transcription factor stimulant |
| 32 | 0,098 | 0,068 | Nicotinic alpha3beta4 receptor agonist |
| 33 | 0,230 | 0,201 | DNA polymerase I inhibitor |
| 34 | 0,120 | 0,102 | Antiemphysemic |
| 35 | 0,093 | 0,076 | Antiviral (Hepatitis C) |
| 36 | 0,035 | 0,019 | Purinergic P2Y12 antagonist |
| 37 | 0,066 | 0,050 | Purinergic receptor antagonist |
| 38 | 0,091 | 0,075 | Inosine nucleosidase inhibitor |
| 39 | 0,206 | 0,191 | Anticonvulsant |
| 40 | 0,041 | 0,031 | Purinergic P2Y antagonist |
| 41 | 0,146 | 0,138 | Nicotinic alpha4beta2 receptor antagonist |
| 42 | 0,052 | 0,044 | Elastase 1 inhibitor |
| 43 | 0,180 | 0,178 | Undecaprenyl-phosphate mannosyltransferase inhibitor |
| 44 | 0,160 | 0,158 | Antiinfertility, female |
| 45 | 0,024 | 0,022 | Elastase 2 inhibitor |

### 6.4.5 PASS Prediction data of (1R, 3S, 4S)-hexyl 3-(5-(7-((pivaloyloxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-benzo[d]imidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylate (66 c)

Compound-66c shows some of the important activities like **Antiparkinsonian, Antiparkinsonian, Neurodegenerative diseases treatment, Alzheimer's disease treatment, Ophthalmic drug, Alzheimer's disease treatment, Antineoplastic (solid tumors), Antineoplastic (melanoma), Antiviral (Hepatitis C),** and **Respiratory distress Anticonvulsant.**

**Table: 6.5 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,421 | 0,020 | Ophthalmic drug |
| 2 | 0,473 | 0,095 | Nicotinic alpha4beta4 receptor agonist |
| 3 | 0,366 | 0,038 | Antiparkinsonian |
| 4 | 0,355 | 0,142 | Glyceryl-ether monooxygenase inhibitor |
| 5 | 0,330 | 0,041 | DNA polymerase I inhibitor |
| 6 | 0,329 | 0,028 | Antiviral |
| 7 | 0,326 | 0,260 | Antieczematic |
| 8 | 0,308 | 0,126 | Benzoate-CoA ligase inhibitor |
| 9 | 0,296 | 0,139 | Neurodegenerative diseases treatment |
| 10 | 0,291 | 0,076 | Immunomodulator |
| 11 | 0,286 | 0,076 | Macrophage stimulant |
| 12 | 0,275 | 0,039 | RNA directed DNA polymerase inhibitor |
| 13 | 0,270 | 0,096 | Antimetastatic |
| 14 | 0,259 | 0,179 | Fibroblast growth factor agonist |
| 15 | 0,258 | 0,148 | Anticonvulsant |
| 16 | 0,244 | 0,180 | Transcription factor NF kappa B stimulant |
| 17 | 0,244 | 0,180 | Transcription factor stimulant |

| | | | |
|---|---|---|---|
| 18 | 0,233 | 0,029 | Antiglaucomic |
| 19 | 0,230 | 0,062 | Cyclic GMP phosphodiesterase inhibitor |
| 20 | 0,226 | 0,197 | Alcohol O-acetyltransferase inhibitor |
| 21 | 0,220 | 0,172 | CYP17 inhibitor |
| 22 | 0,217 | 0,187 | Antineoplastic (solid tumors) |
| 23 | 0,192 | 0,079 | Prenyl-diphosphatase inhibitor |
| 24 | 0,192 | 0,153 | Undecaprenyl-phosphate mannosyltransferase inhibitor |
| 25 | 0,175 | 0,126 | Respiratory distress syndrome treatment |
| 26 | 0,166 | 0,151 | Antineoplastic enhancer |
| 27 | 0,166 | 0,143 | Antiviral (Hepatitis B) |
| 28 | 0,165 | 0,064 | DNA directed RNA polymerase inhibitor |
| 29 | 0,165 | 0,096 | Retinol dehydrogenase inhibitor |
| 30 | 0,145 | 0,140 | Nicotinic alpha4beta2 receptor antagonist |
| 31 | 0,144 | 0,039 | Antiviral (Hepatitis) |
| 32 | 0,144 | 0,020 | Xanthine oxidase substrate |
| 33 | 0,141 | 0,066 | Endoglycosylceramidase inhibitor |
| 34 | 0,134 | 0,045 | Inosine nucleosidase inhibitor |
| 35 | 0,131 | 0,068 | Alcohol dehydrogenase substrate |
| 36 | 0,122 | 0,043 | Aldehyde dehydrogenase substrate |
| 37 | 0,121 | 0,099 | Antiemphysemic |
| 38 | 0,108 | 0,050 | Interleukin 8 antagonist |
| 39 | 0,107 | 0,021 | Phosphodiesterase II inhibitor |
| 40 | 0,099 | 0,064 | Antiviral (Hepatitis C) |
| 41 | 0,096 | 0,071 | Nicotinic alpha3beta4 receptor agonist |
| 42 | 0,085 | 0,021 | Purinergic P2T antagonist |
| 43 | 0,055 | 0,038 | Elastase 1 inhibitor |
| 44 | 0,044 | 0,024 | Purinergic P2Y antagonist |
| 45 | 0,041 | 0,004 | HCV NS5A inhibitor |
| 46 | 0,036 | 0,016 | Purinergic P2Y12 antagonist |
| 47 | 0,030 | 0,025 | Equilibrative nucleoside transport protein 1 inhibitor |
| 48 | 0,026 | 0,018 | Elastase 2 inhibitor |

### 6.4.6 PASS Prediction data of 2, 2-Dimethyl-propionic acid 4-[2-(2-aza-bicyclo[2.2.1]hept-3-yl)-1H-benzoimidazol-5-yl]-pyrrolo[2,3-d]pyrimidin-7-ylmethyl ester (65)

Compound-66c shows some of the important activities like **Antiparkinsonian, Platelet aggregation inhibitor, HIV attachment inhibitor, Platelet aggregation inhibitor , Autoimmune disorders treatment, Antidepressant, Anxiolytic** and **Analgesic, non-opioid.**

**Table: 6.6 PASS Pridiction date**

| Sr.No | Pa | Pi | Activity |
|---|---|---|---|
| 1 | 0,574 | 0,049 | Nicotinic alpha4beta4 receptor agonist |
| 2 | 0,467 | 0,030 | HERG 1 channel blocker |
| 3 | 0,434 | 0,003 | TRKB antagonist |
| 4 | 0,404 | 0,009 | Nicotinic alpha4beta2 receptor antagonist |
| 5 | 0,381 | 0,067 | Cyclic AMP phosphodiesterase inhibitor |
| 6 | 0,331 | 0,030 | HIV attachment inhibitor |
| 7 | 0,328 | 0,051 | Antiparkinsonian |
| 8 | 0,164 | 0,019 | Nicotinic alpha3beta4 receptor agonist |
| 9 | 0,221 | 0,105 | Platelet aggregation inhibitor |
| 10 | 0,248 | 0,148 | Autoimmune disorders treatment |
| 11 | 0,203 | 0,106 | Antidepressant |
| 12 | 0,122 | 0,027 | TRKA antagonist |
| 13 | 0,337 | 0,249 | Antieczematic |
| 14 | 0,205 | 0,118 | Anxiolytic |
| 15 | 0,103 | 0,018 | Phosphatidylinositol kinase inhibitor |
| 16 | 0,108 | 0,028 | Protein kinase B gamma inhibitor |
| 17 | 0,116 | 0,037 | Antiacromegalic |
| 18 | 0,092 | 0,021 | Phosphatidylinositol 3-kinase inhibitor |
| 19 | 0,061 | 0,003 | HCV NS5A inhibitor |
| 20 | 0,081 | 0,026 | Adrenaline uptake inhibitor |

| | | | |
|---|---|---|---|
| 21 | 0,113 | 0,067 | Epidermal growth factor receptor kinase inhibitor |
| 22 | 0,062 | 0,016 | Phosphatidylinositol 3-kinase beta inhibitor |
| 23 | 0,126 | 0,088 | Nicotinic alpha6 receptor agonist |
| 24 | 0,331 | 0,296 | Nootropic |
| 25 | 0,108 | 0,084 | Antiemetic |
| 26 | 0,080 | 0,057 | p38 MAP kinase inhibitor |
| 27 | 0,042 | 0,018 | Phosphatidylinositol 3-kinase gamma inhibitor |
| 28 | 0,209 | 0,186 | Analgesic, non-opioid |
| 29 | 0,137 | 0,114 | Protein kinase (CK1) inhibitor |
| 30 | 0,050 | 0,031 | Dopamine transporter inhibitor |
| 31 | 0,068 | 0,049 | Alpha 3 adrenoreceptor agonist |
| 32 | 0,080 | 0,061 | Protein kinase B inhibitor |
| 33 | 0,073 | 0,056 | Insulin like growth factor 1 antagonist |
| 34 | 0,063 | 0,046 | Phosphodiesterase III inhibitor |
| 35 | 0,023 | 0,010 | DNA-dependent protein kinase inhibitor |
| 36 | 0,068 | 0,056 | Platelet activating factor beta antagonist |
| 37 | 0,131 | 0,119 | Protein kinase (CK1) epsilon inhibitor |
| 38 | 0,029 | 0,017 | mTOR inhibitor |
| 39 | 0,109 | 0,097 | Interleukin 1 antagonist |
| 40 | 0,082 | 0,072 | Platelet activating factor antagonist |
| 41 | 0,066 | 0,058 | Threonine-tRNA ligase inhibitor |
| 42 | 0,101 | 0,097 | Protein kinase (CK1) delta inhibitor |
| 43 | 0,045 | 0,040 | Prolactin release inhibitor |
| 44 | 0,058 | 0,055 | Adenosine receptor antagonist |
| 45 | 0,043 | 0,041 | Cholestenol delta-isomerase inhibitor |

# 7. CONCLUSION

1. We have been developed new, highly efficient, environment friendly, less cost novel Uracil based Moc-L-Valine derivatives.
2. We have reported one pot synthesis for preparation of novel 13 compounds of Moc-L-Valine derivatives with higher yield, in one pot synthesis we have been used single solvents in multiple steps this reduce environmental hazards, cost and also reduce effluent waste.
3. We have been eliminated highly hazardous sodium hydride and DMF mixture, and replaced by less hazardous chemicals and reagents when compare with prior art.
4. We have been reported high yield (overall yield) synthesis, this leads to low cost.
5. We have been reported Binding and docking study of target molecules, and we found that some of the molecules showing good binding with DNA.
6. We have been reported Pass prediction analysis of target molecules and all those molecules are showing good activity towards various diseases.
7. Compounds A-L was soluble in Methanol, THF, and DMF. The dockingaffinities varied from 3.3 to 4.6 kcal/mol, and the compounds formed 1-3 hydrogen bonds with the amino acid residues of aspulvinone dimethylallyltransferase enzyme. The reported compounds may be future anti-cizmatics, anti-fobic disorder and inhibition of aspulvinone dimethylallyltransferase properties to control Alzheimer's, Schizophrenia etc. diseases.
8. We have been reported further 17 new compounds with chloroformate series, smooth conversion from starting material to targeted molecules,
9. Developed facile, industrially viable and high efficient synthesis of targeted molecules, where higher yield has been reported by our process.
10. Simple, easily available, less cost, less hazardous and environment friendly raw materials, reagents and solvents have been used throughout the reported process.

11. We have been synthesized new 11 compounds of purine series, since purine has good activity against most of the diseases.
12. We have been developed protocol for the preparation of target molecule by highly efficient synthesis; we have been used simple easily available, lower cost, environmental hazardous free water as a solvent and sodium carbonate as a base.
13. All the compounds in purine series are soluble in acidic and basic solutions only and it does not having solubility solvents like ethanol, methanol, ethyl acetate, MDC etc.
14. The entire target compounds UV absorption spectrum reported along with DNA UV absorption spectrum.
15. We have been isolated entire target compounds with higher yield (87-92%), due to higher yield achievement and water as solvent used, the entire cost of the product are reduce as low as much as possible.
16. We have been prepared novel Pyrrolo[2,3-d] pyrimidine intermediate, because of Pyrrolo[2,3-d] pyrimidine activity towards all kind of diseases.
17. We have been prepared chiral pure and higher yield synthesis of its intermediates, which may have important in drug synthesis.
18. We have been reported PASS prediction details of all the targeted molecules and all the molecules are showing good activity towards various diseases.

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