SYNTHESIS OF TRIDENTATE LIGANDS BASED ON THEORETICAL DESIGN TO MIMIC HPCD ENZYME

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

MUZAFFER GÖKÇE

IN PARTIAL FULFILLMENT OF THE REQUIREMENS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

JANUARY 2018

Approval of the thesis

SYNTHESIS OF TRIDENTATE LIGANDS BASED ON THEORETICAL DESIGN TO MIMIC HPCD ENZYME

submitted by **MUZAFFER GÖKÇE** in partial fulfillment of the requirements for the degree of **Master of Science in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Gülbin Dural Ünver
Dean, Graduate School of **Natural and Applied Sciences** _____

Prof. Dr. Cihangir Tanyeli
Head of Department, **Chemistry** _____

Assist. Prof. Dr. Salih Özçubukçu
Supervisor, **Department of Chemistry, METU** _____

Examining Committee Members:

Prof. Dr. Özdemir Doğan _____
Department of Chemistry, METU

Assist. Prof. Dr. Salih Özçubukçu _____
Department of Chemistry, METU

Assoc. Prof. Dr. Akın Akdağ _____
Department of Chemistry, METU

Assoc. Prof. Dr. Emrullah Görkem Günbaş _____
Department of Chemistry, METU

Assist. Prof. Dr. Yunus Emre Türkmen _____
Department of Chemistry, Bilkent University

Date: 11.01.2018

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name: Muzaffer Gökçe

Signature:

ABSTRACT

SYNTHESIS OF TRIDENTATE LIGANDS BASED ON THERORETICAL DESIGN TO MIMIC HPCD ENZYME

Gökçe, Muzaffer

M.Sc., Department of Chemistry
Supervisor: Assist. Prof. Dr. Salih Özçubukçu

January 2018, 103 pages

There is an increasing interest on the aromatic oxidative ring opening reactions due to their challenging features. Among these reactions, the ones using molecular oxygen attract even more attention. In one of these aromatic ring opening reactions, homoprotocatechuate dioxygenase (HPCD) enzyme is used as a catalyst. The active site of this enzyme consists of either iron or manganese ions. In this work, two tridentate ligands have been designed theoretically in order to mimic the active site of this enzyme to perform the same reaction using smaller organic molecules instead of enzyme. These ligands are composed of adenine, imidazole and carboxylic acid moieties. Based on calculations, -NH_2 group on adenine would be acting as a base which is involved in the hydrogen transfer from –OH group of catechol to dioxygen on the metal center. This transfer is found to be lowering the activation barrier of one intermediate. These designed ligands are attempted to be synthesized using different strategies. Tremendous efforts have been spent however, the synthesis of these designed ligands could not be succeeded so far. There is still ongoing work to complete the synthesis of these ligands.

Keywords: artificial enzymes, computational chemistry, ligands, adenine, imidazole.

ÖZ

TEORİK TASARIM İLE HPCD ENZİMİNİ TAKLİT EDEN ÜÇ DİŞLİ LİGANT SENTEZİ

Gökçe, Muzaffer

Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Yrd. Doç. Dr. Salih Özçubukçu

Ocak 2018, 103 sayfa

Aromatik oksidatif halka açılması tepkimeleri zor gerçekleşen tepkimeler olduğundan dolayı büyük ilgi görmüştür. Bu tepkimeler arasında moleküler oksijen kullanan halka açılma tepkimeleri daha da ilgi çekmektedir. Bu aromatik halka açılmalarından birinde Homoprotokatekolat dioksijenaz enzimi katalizör olarak kullanılmaktadır. Bu enzimin aktif bölgesinde ise demir veya mangan iyonları bulunmaktadır. Bu çalışmada, bu enzimin aktif bölgesini taklit edip daha küçük organik moleküllerle aynı tepkimeyi yapmak için üç dişli iki ligant tasarlanmıştır. Bu ligantlar adenin, imidazol ve karboksilik asit gruplarını içermektedir. Teorik hesaplamalara göre, adenin üzerindeki -NH_2 grubunun, katekol üzerindeki –OH grubu ile metal merkezi üzerindeki dioksijen arasında hidrojen alışverişinde baz olarak davranabileceği görülmüştür. Bu alışverişin bir ara ürünün aktivasyon enerjisini düşürdüğü bulunmuştur. Bu tasarlanan ligantlar farklı yöntemler kullanılarak sentezlenmeye çalışılmıştır. Büyük çaba gösterilmesine rağmen tasarlanan ligantların sentezi şimdiye kadar gerçekleştirilememiştir. Bu ligantların sentezlenmesi için çalışmalar hala devam etmektedir.

Anahtar Kelimeler: Yapay enzim, hesaplamalı kimya, ligantlar, adenin, imidazol.

To my family

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my supervisor Assist. Prof. Dr. Salih Özçubukçu for his valuable guidance, understanding and most importantly, his friendship. It would have been impossible for me to accomplish this work without his endless patience and encouragement. It has been great honor for me to be a part of his research group as a graduate student.

I also would like to thank every single member of Özçubukçu Reseach group, Volkan Dolgun, Mehmet Seçkin Kesici, Orkun Evran, Dr. Melek Parlak Khalili, Güzide Aykent, Tuğçe Yılmaz, Burcu Okyar and Medine Soydan for their friendship, advices and helps.

I would also like to thank Dr. Aytül Saylam for her precious guidance in this thesis also her friendship and her motivational support.

I also would like to thank Muhammed Büyüktemiz and Assoc. Prof. Dr. Yavuz Dede for the computational work of designing artificial enzymes.

I wish to thank NMR specialist Betül Eymur for NMR analysis in our department

I wish to express my gratitude to the academic stuff of Department of Chemistry at METU for their supports and guidance throughout my whole undergraduate and graduate years.

A special thanks to my friends Ertuğrul Eryiğit and Aslı Eda Aydemir for their priceless friendships.

I would like to thank my wife Sevtap for her support, encouragement, patience and unwavering love.

Finally, I would thank my family for their endless love.

TABLE OF CONTENT

LIST OF FIGURES

FIGURES

LIST OF TABLES

TABLES

LIST OF SCHEMES

SCHEMES

LIST OF ABBREVIATIONS

CDI: Carbonyldiimidazole

DCM: Dichloromethane

DIEA: *N*,*N*-Diisopropylethylamine

DMF: *N*,*N*-Dimethylformamide

DMSO: Dimethyl sulfoxide

GC-MS: Gas Chromatography-Mass Spectroscopy

HPCD: Homoprotocatechuate dioxygenase

LDA: Lithium diisopropylamide

NBS: *N*-Bromo succinimide

NMR: Nuclear Magnetic Resonance Spectroscopy

THF: Tetrahydrofuran

TMS: Tetramethylsilane

CHAPTER 1

INTRODUCTION

1.1. Enzymes

All living organisms have to keep their metabolic activities in a certain rate, but the rate of these chemical reactions is not enough to sustain the life. To increase the rate of reactions, temperature can be increased but increasing temperature can be fatal for the organism because at high temperatures, essential proteins may be denatured. Another method for increasing the rate of reaction is decreasing the activation energy to start the chemical reaction. The way to lower the activation energy is using catalysts in chemical reactions [1]. Enzymes are produced in living cells which act as catalysts in biological reactions. They all have the protein structure which made up in living cells. Enzymes reduce the activation energy and increase the rate of reaction enough up to 10^{10} to 10^{15} fold [2]. They can be seen in almost every transformation which takes place in vivo [3]. Their capability of catalyzing reactions is enormous.

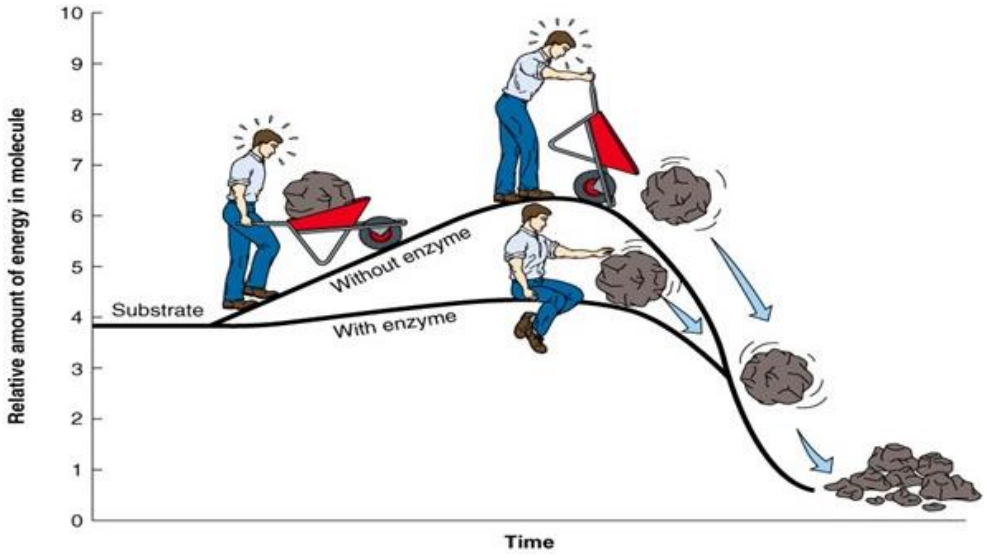


Figure 1. Effect of enzyme on activation energy [1].

1.1.1. Cofactors

Most of the enzymes are composed of proteins, which consist of amino acids. Side chains of enzymes are limited because amino acids are limited in nature. That is why, enzyme catalytic groups do not have efficient electron acceptors. To eliminate this situation enzymes are evolved to use some metal ions which named as cofactors. For instance, zinc ions are common as cofactors in many proteases [4].

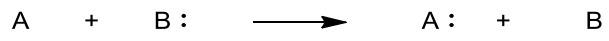
1.1.2. Classification of Enzymes

Enzymes are classified into six categories based on the reactions that they catalyze [5].

-*Oxidoreductases*

Oxidoreductase enzymes include electron shift (either one electron or two electron in one step) one molecule to another molecule and changes oxidation

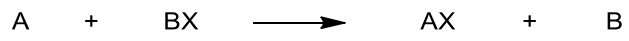
states of molecules.



Lactate dehydrogenase is an example of this type of enzymes. Lactate dehydrogenase enzyme catalyzes the reversible reduction of pyruvate to lactate via oxidation of NADH to NAD^+ [6].

-Transferases

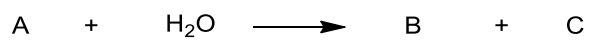
Transferases type of enzymes remove a group from a compound and attach to another molecule.



Peptidyltransferase can be given as an example of transferases. Peptidyltransferase is a part of ribosome which catalyzes relocation of aminoacids from tRNA to proteins [7].

-Hydrolases

This kind of enzymes can catalyze the hydrolysis of compound.



Serine hydrolase is one of the most known hydrolases. Serine hydrolases catalyzes reaction of hydrolytic cleavage of ester, thioester and amide bonds in their substrates [8].

-Lyases

Lyases dissociates a molecule into two molecules without using water and without doing any oxidation or reduction.

Argininogosuccinate lyase is an example of lyases. Argininogosuccinate lyase enzyme catalyzes the reversible dissociation of argininosuccinate to arginine and fumerate in urea cycle [9].

-Isomerases

In biochemistry, isomerase is an enzyme that allows the structural rearrangement of isomers.

Glucose isomerase can be given an example of isomerases. Glucose isomerase

enzyme catalyzes the isomerization reaction of glucose into fructose which is the hydrolysis product of granular starch [10].

-Ligases

In biochemistry, ligase is an enzyme that combines two large molecules by forming a chemical bond between them; usually a small chemical group of one of these large molecules is hydrolyzed during the reaction.

DNA Ligase is one of the most common ligases. DNA ligase catalyzes the formation of phosphodiester bond while binding the DNA strands together [11].

1.1.3. Advantages of Using Enzymes in Chemical Reactions

Enzymes are not only used in biological reactions, they also have remarkable applications in synthetic organic chemistry as catalyst. Using enzymes in chemical reactions has several advantages. First of all, they are more environmentally friendly than non-enzymatic catalysis which commonly requires transition or heavy metals. Besides, using enzymes in aqueous media also adds to their environmental value because they have excellent activity in aqueous media. However, it is also a limitation for catalyzing substrates which are soluble in another solvent rather than water. Their selectivity is also very good by means of both regioselectivity and chemoselectivity. Since enzymes have the chiral active sites, products of enzymes are enantiopure [12].

1.1.4. Disadvantages of Using Enzymes in Chemical Reactions

Despite all those advantages, there are also some disadvantages of using enzymes in chemical reactions. First, enzymes are very delicate for pH changes. Also, at high temperatures they may be decomposed. Enzymes can be found in nature in only one

enantiomeric form which reduces the variety of reactions that can be catalyzed by them. Solvent for enzymatic reactions is usually water which is an advantage for environmental considerations, but it is also a limitation since not all substrates are water soluble. In addition to that, removing of the water is too difficult because of its high boiling point and high heat of vaporization. Another disadvantage is that enzymes are very sensitive for even little contaminations. Therefore, even little amount of impurity in the substrate highly affects the reaction. The most critical disadvantage is the high cost of extraction and purification of enzymes and they require co-factors or co-substrates which raises the cost of production. This reason discourages the uses of enzymes as catalysts in chemical reactions particularly in fields that already have a viable and feasible procedures [12][3].

1.2. Artificial Enzyme

Mankind have been using enzymes since ancient times in making wine, beer, bread and vinegar with fermentation via microorganisms. After pioneer works of Eduard Buchner [4], it was revealed that enzymes do not require a living organism for being active. Scientists started to isolate enzymes from bacteria and used them for the same purposes. Recently, in order to imitate the functions of enzymes, artificial enzymes (also known as enzyme mimic) are developed as catalysts for many reactions. They have some advantages because of their adjustable structures and catalytic performances, remarkable resistance to harsh media, lower cost and requirement only synthetic ways for their preparation. For this reason, there are many ongoing research in order to develop new artificial enzymes. There is already a number of artificial enzymes that are currently used as catalysts, but these enzymes increase the reaction rate up to 10^3-fold. However, for natural enzymes this value is about 10^6 [13].

1.3. Reactions of Molecular Oxygen

Molecular oxygen is a very substantial oxidant both in industry and in natural reactions. An example for industrial importance of molecular oxygen is the synthesis of phenol and acetone from cumene using molecular oxygen as an oxidant [8]. Reactions of molecular oxygen in nature have great importance. Other than the respiration of aerobic metabolisms, these reactions are crucial for biodegradation of nitroaromatics in soil, converting the heavy aromatic oils into lighter products and sustaining energy for the organisms in soil [15,16].

1.4. Catechol

Catechol is the ortho isomer of the three isomers of benzenediol. Catechol is a product of lignin which is the second most abundant natural polymer on earth. For this reason, the chemicals which were produced from the lignin play an important role because of economic considerations. Research for obtaining more effective lignin depolymerization methods to get catechol still require significant effort. Nevertheless, the studies published up to this time showed that presence of 2-methoxyphenol (guaiacol) in lignin derived bio-oils is high. Because of high volatility of 2-methoxyphenol, it can be separated and converted into catechol and then catechol can be separated by using its acidic properties [17].

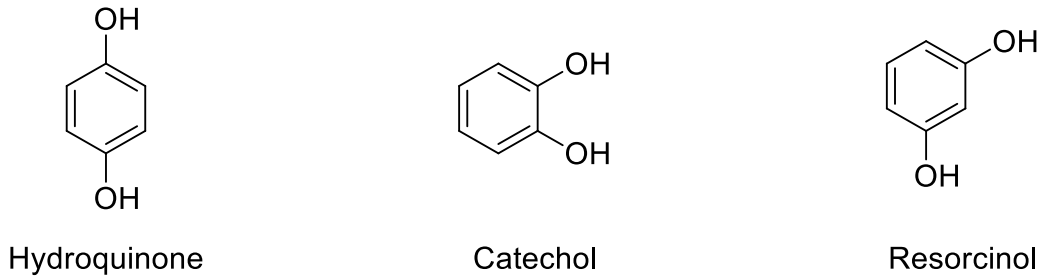


Figure 2. Isomers and names of benzenediols.

1.5. Homoprotocathecuate 2, 3 Dioxygenese Enzyme

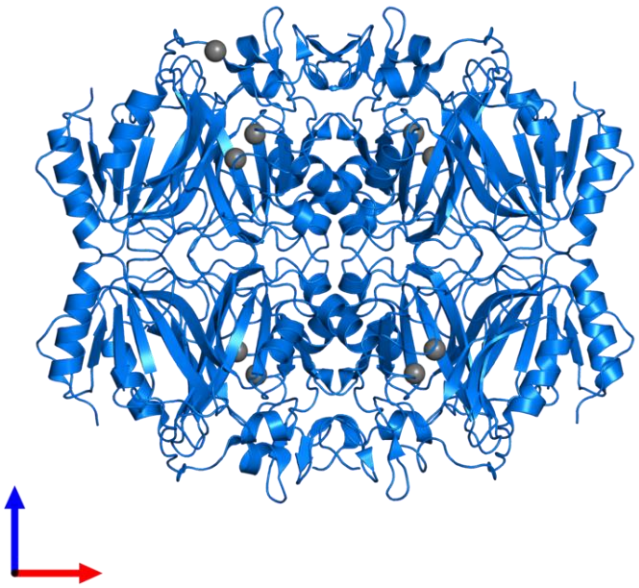


Figure 3. Homoprotocatechuate dioxygenase enzyme.

Homoprotocathecuate enzyme is extracted from Brevibacterium fuscum, Bacillus macerans and Arthobacter globiformis microorganisms. These microorganisms play an important role in extradiol oxidative cleavage for catechol derivatives in nature by using the homoprotocathecuate dioxygenese enzyme as catalyst. This enzyme catalyzes extradiol aromatic ring opening reaction with association of O_2 [18].

1.6. Oxidative Aromatic Ring Cleavage an Enzymatic Reaction

Oxidative aromatic ring opening reactions are challenging reactions. That's why,

there is an increasing interest for these reactions.

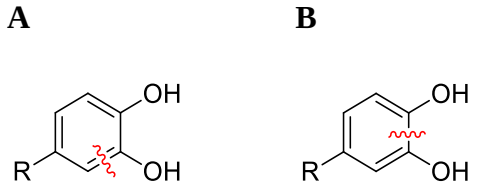


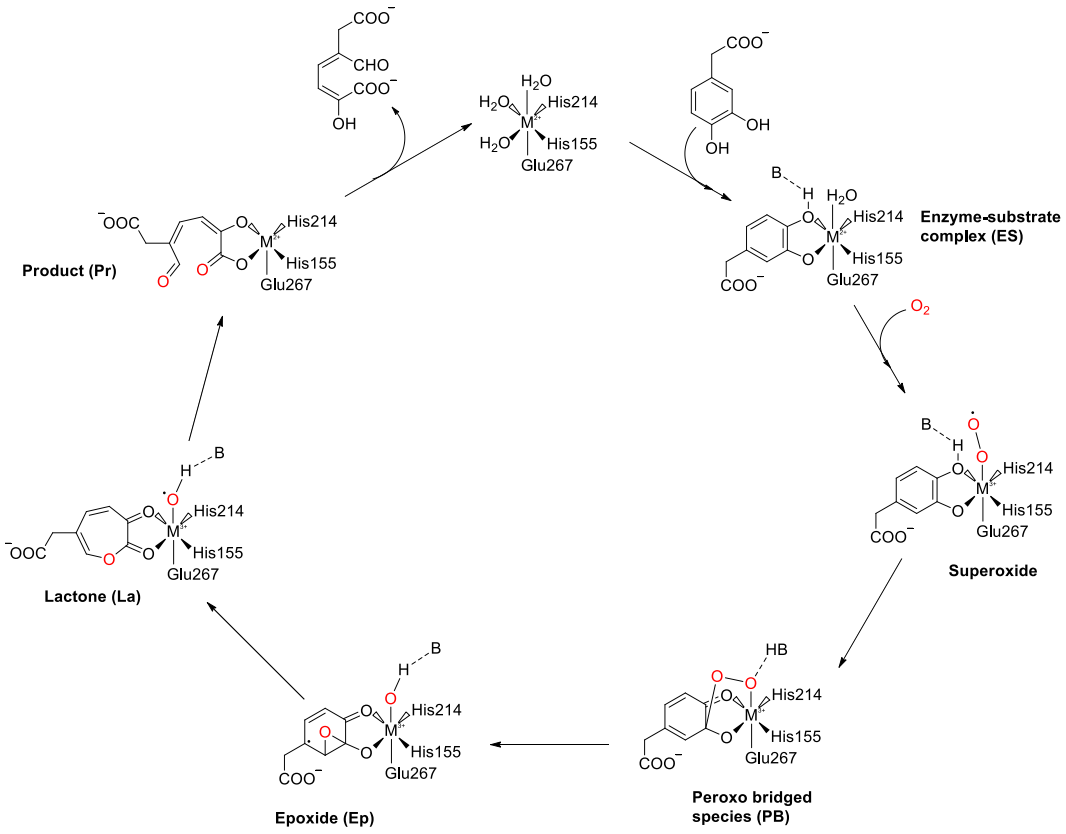
Figure 4. (A) Extradiol cleavage of catechol. (B) Intradiol cleavage of catechol.

These reactions can occur in two different ways. The first one is the extradiol and the other one is the intradiol cleavage. In the case of intradiol opening, cleavage of C-C bond is between the two hydroxyl groups whereas in extradiol case, bond cleavage is adjacent to hydroxyl group. Natural enzymes' active sites are different for intradiol and extradiol cases. For intradiol aromatic ring opening reaction, active site of enzyme contains two histidine, two tyrosine residues and iron(III) ion as a cofactor. However in the case of extradiol aromatic ring opening reaction, active site of enzyme contains two histidine, one glutamic acid residues and iron(II) ion as a cofactor [19-21].

1.6.1. Catalytic cycle of extradiol aromatic ring opening reaction of catechol

In the proposed mechanism, the first step of the reaction begins with the addition of the substrate to the metal center, while the two water molecule is removed at the same time. Then, molecular oxygen exchanges with the third water ligand from the sixth coordination site. Afterwards, reduction of oxygen to the superoxide occurs upon coordination of molecular oxygen to the metal center. Then with the help of the external base, acidic hydrogen of catechol is captured and this superoxide makes the peroxide bridge between substrate and metal center. Then the bond between the two oxygens breaks while oxygen on the metal center abstract hydrogen from

external base. Afterwards, lactone formation occurs with Criegee rearrangement. Eventually, OH radical attacks to the substrate and C-O bond cleavage occurs which gives the final ring opening product [22].



Scheme 1. Consensus mechanism for catalytic cycle of HPCD enzyme.

1.7. Computational Chemistry

Computational chemistry is a field which can be employed by all fields of chemistry. In computational chemistry, there is a systematization of chemical laws, standards and principles, their refinement and detailing, building in hierarchical

order. Computational chemists also use numerical and physical techniques to clarify the structures and dynamics of chemical systems and to associate, comprehend, and foresee their thermodynamic and kinetic properties. A computational chemist can plan synthesis of new molecules using various computer programs. For this reason, it is possible to consider the next step in synthetic chemistry by using computational chemistry [23].

1.8. Aim of the Study

In this study, two tridentate ligands were designed theoretically in order to mimic the active site of HPCD enzyme to perform the extradiol aromatic ring opening reactions. These ligands are composed of adenine, imidazole and carboxylic acid moiety. Based on calculations, -NH_2 group on adenine would be acting as a base which is involved in the hydrogen transfer from –OH group of catechol to dioxygen on the metal center. This transfer is found to be lowering the activation barrier of one intermediate. These designed ligands are tried to be synthesized using different strategies. After the synthesis, their catalytic activity on catechol derivatives will be investigated for the aromatic oxidative ring opening reaction.

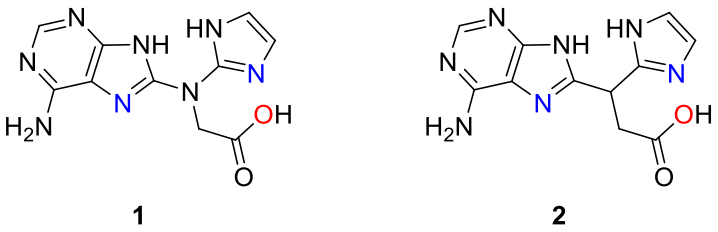


Figure 5. Theoretically designed molecules.

CHAPTER 2

RESULTS AND DISCUSSION

2.1. A Theoretical Study towards a Functional Model of Homoprotocatechuate Dioxygenase Enzyme

General purpose of designing enzymes is to build up a new catalyst having desired selectivity and activity. A promising approach of designing new molecules is to use computational methods. Dede *et al.* showed that better mimicry of homoprotocathecuate dioxygenese is possible by using an amine functional group which mimics the external base in the second coordination sphere inside the artificial enzyme [24].

In Figure 6, there are two molecules designed by using computational methods which described previously by Dede *et al.* [24].

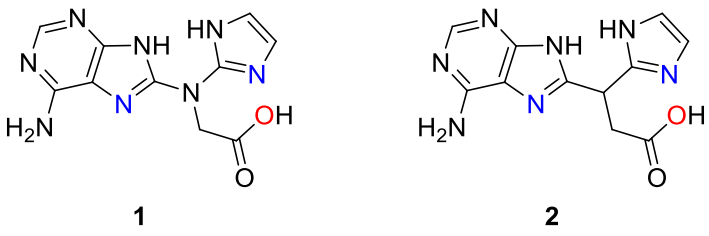


Figure 6. Theoretically designed molecules.

Structural studies also showed that the external base of homoprotocathecuate dioxygenase enzyme simultaneously takes one proton from hydroxy of catechol and gives one proton to the dioxygen during the oxidative cleavage of cathechol [22].

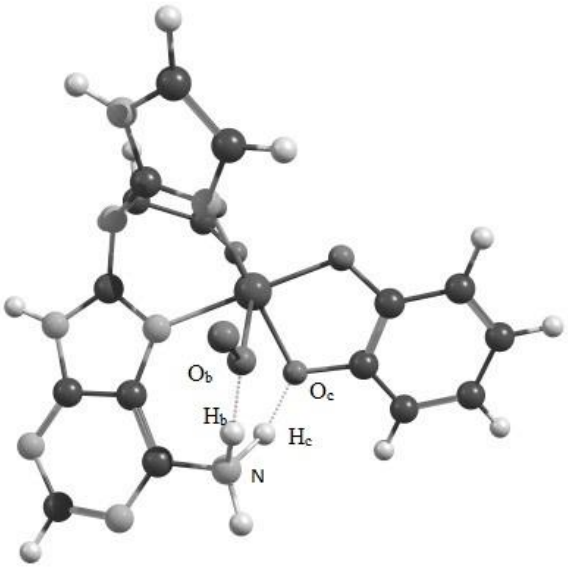


Figure 7. Molecular representation of linearity between N-H_b-O_b and O_c-H_c-N atoms.

Theoretical studies also showed that linearity of N-H_b-O_b and O_c-H_c-N reduces the activation energy [24].

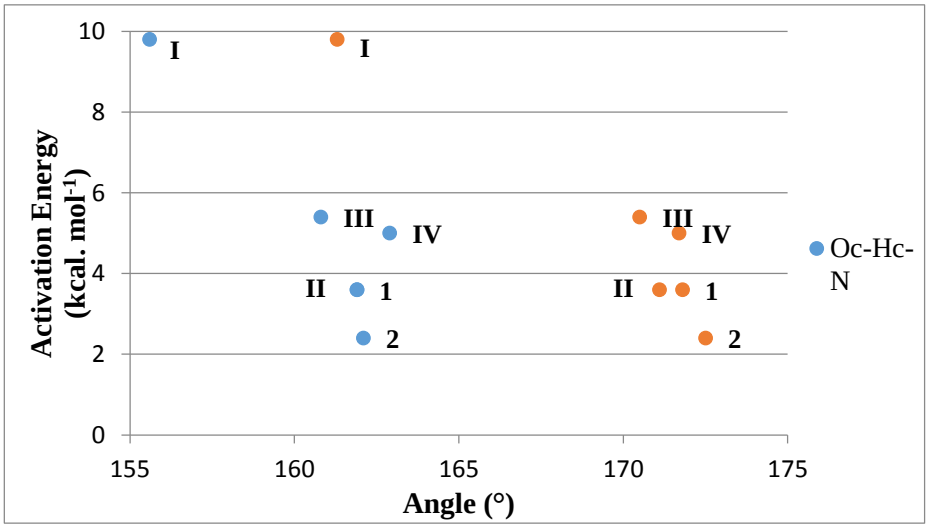


Figure 8. Activation energy versus angle graphics of theoretically designed ligands.

Theoretical studies of some molecules with internal base are shown in Figure 9.

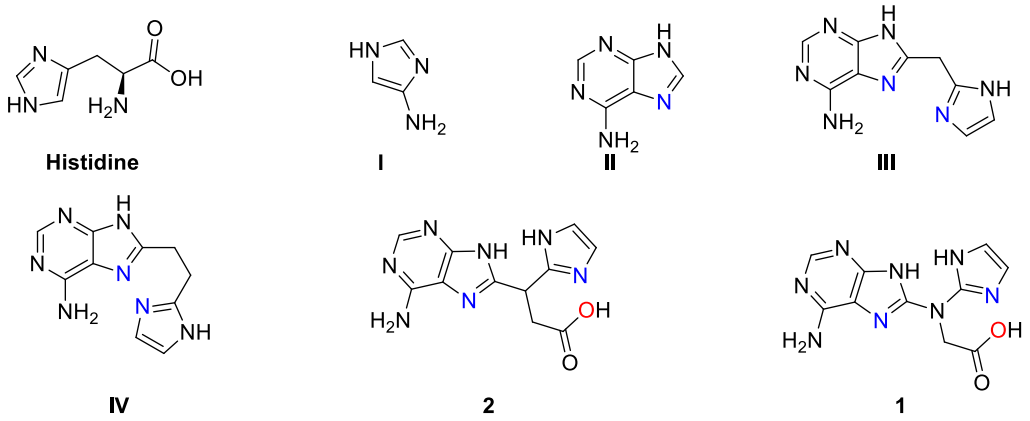


Figure 9. Mono, bi- and tri-dentate ligands studied in theoretical calculations by Dede [24].

Table 1. Effect of linearity on angle between NH_bO_b and O_cH_cN on activation energy.

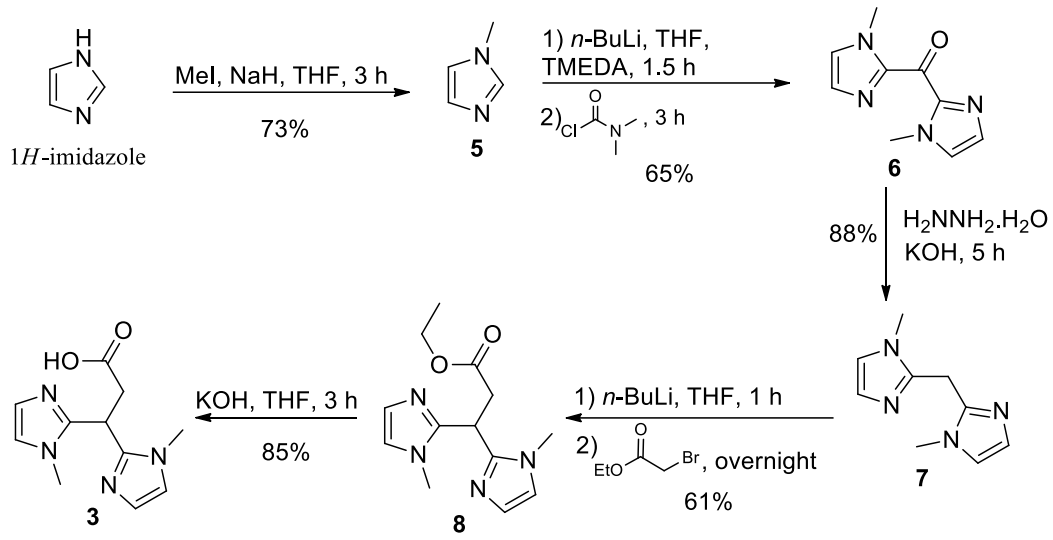
Ligand system	ΔE	∠ O_c-H_c-N	∠ N-H_b-O_b	R O_b-H_b	R N-H_c
1	9.8	155.6	161.3	1.514	1.313
2	3.6	161.9	171.1	1.423	1.246
3	5.4	160.8	170.5	1.403	1.247
4	5.0	162.9	171.7	1.322	1.262
5	2.4	162.1	172.5	1.350	1.210
6	3.6	161.9	171.8	1.394	1.207

In the Table 1, the effect of linearity between O_c-H_c-N and N-H_b-O_b on the activation energy of intermediate is shown and when bidentate and tridentate ligands are considered, it can be seen that as the angle of O_c-H_c-N and N-H_b-O_b approaches to linearity, the activation energy decreases.

2.2 Synthesis of compound 3

From literature [25, 21], it is known that compound **3** mimics the homoprotocathecuate dioxygenase enzyme by catalyzing aromatic oxidative ring opening reaction. It is considered that our target molecules can be more effective than compound **3,** because it has no free amino group to mimic the external base which involves in proton exchange between the dioxygen and catechol derivative. Compound **3** was synthesized according to the literature procedure to see the effects of this free amino group.

For the synthesis of compound **3**, commercially available imidazole was converted to 1-methyl-1*H*-imidazole (**5**) with using methyl iodide and sodium hydride. Compound **5** was deprotonated with *n*-BuLi, then coupled with *N*,*N*-dimethylcarbamoyl chloride in dry THF with presence of TMEDA as base to give bis(1-methyl-1*H*-imidazol-2-yl)methanone (**6**) in 65% yield. Wolff Kischner reduction of compound **6** using hydrazine hydrate with KOH produced bis(1-methyl-1*H*-imidazol-2-yl)methane (**7**) in 88% yield. Methylene proton of compound **7** was then removed with *n*-BuLi and the anion was treated with ethyl bromoacetate to obtain ethyl-bis(1-methyl-1*H*-imidazole) propiolate (**8**) in 61% yields. Basic hydrolysis was yielded to **8** with KOH to obtain the compound **3** with overall yield 30% from 1-methyl-1*H*-imidazole. ^{1}H NMR data of compound **3** is consistent with literature [43].



Scheme 2. Synthesis of compound **3**.

2.3 Studies towards synthesis of compound 1

Compound **1** is one of the target ligands which will be used as catalyst for the reaction of aromatic oxidative ring opening. As shown in retrosynthetic analysis of **1** in Figure 10, it is combination of three moieties: imidazole, adenine and glycine. The synthesis was started with coupling of imidazole and glycine derivatives. For this purpose, glycine was first protected with benzyl groups which can be easily removed by catalytic hydrogenation.

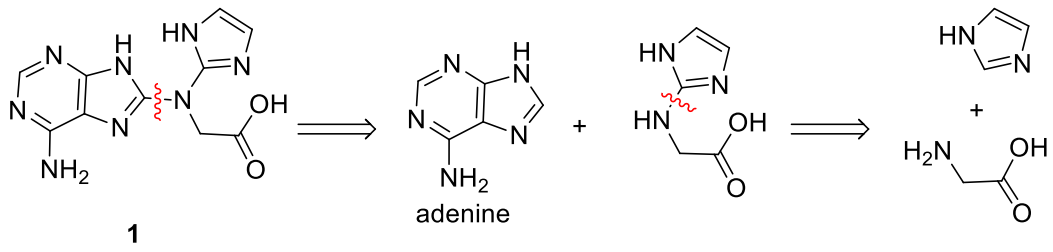
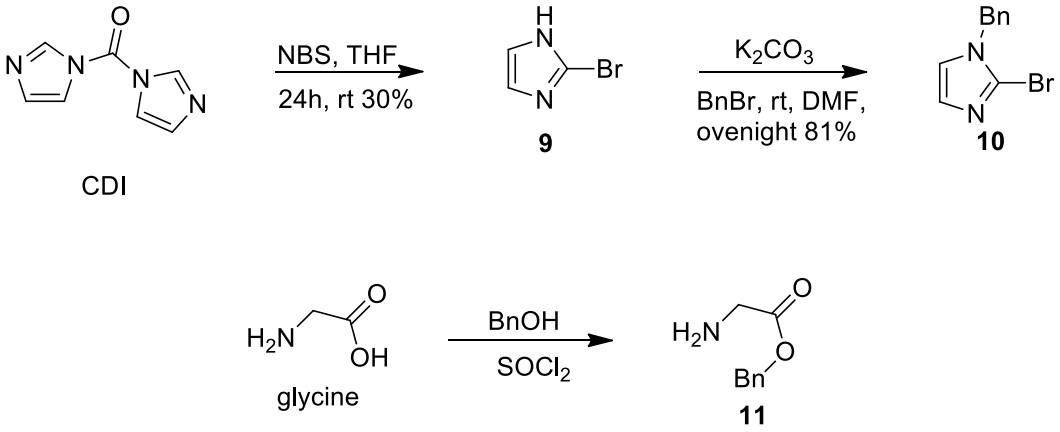


Figure 10. Retrosynthetic analysis of compound **1**.

Glycine was reacted with benzyl alcohol in $SOCl_2$ to give corresponding glycine benzyl ester in good yield (51%). In order to generate a reactive coupling site on imidazole, bromination of carbonyldiimidazole (CDI) with NBS was performed to yield 2-bromo-1*H*-imidazole (**9**) [26]. To protect NH group on imidazole, it was reacted with benzyl bromide in the presence of K_2CO_3 in DMF. After stirring at room temperature overnight, 1-benzyl-2-bromo-1*H*-imidazole (**10**) was obtained in 81% yield. Meanwhile, iodo derivative of 1-benzylimidazole was also synthesized. But in this case, first imidazole is deprotonated by NaH in DMF, then reacted by benzyl bromide. Afterwards, it was deprotonated by *n*-BuLi in THF from 2-positions and further reacted by I_2 to give 1-benzyl-2-iodo-1*H*-imidazole in 37% overall yield.



Scheme 3. Synthesis of starting materials **10** and **11**.

After synthesis of compound **10** and compound **11**, their coupling reactions were tested under varying conditions which is summarized in Table 2 and 3. Different bases, solvents, reaction durations were tested. Microwave heating was also tried (Table 2, entries 5-6). However, no desired product was obtained. Then, copper catalyzed coupling was also attempted but unfortunately it failed (Table 3).

Moreover, instead of using benzyl protected glycine, benzyl amine was tried as a simple model amine (Table 2, entries 13, 14; Table 3, entries 1, 2 and 5.). However, they also did not give any desired product. Detailed screening of base, copper sources, ligands, temperature and solvents might be necessary in order to obtain desired products. However, at this stage, instead of performing intensive screening, it is thought to continue with the synthesis of target molecule **2** instead of **1**.

Table 2. Coupling reactions with different parameters.

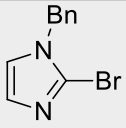
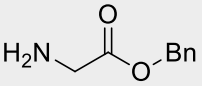
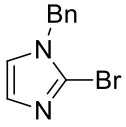
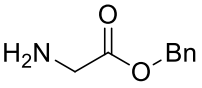
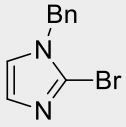
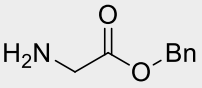
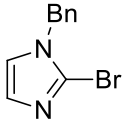
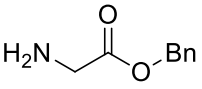
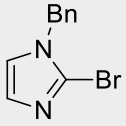
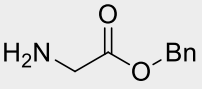
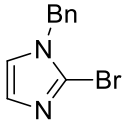
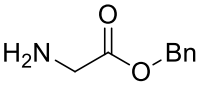
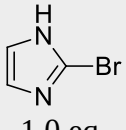
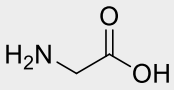
Entry	Reagent 2	Reagent 2	Base	Solvent	Temp.	Time
1	 1.0 eq.	 0.5 eq.	Et_3N 0.5 eq.	MeOH	r.t	Overnight
2	 1.0 eq.	 0.5 eq.	Et_3N 1.0 eq.	MeOH	50 °C	5h
3	 1.0 eq.	 0.5 eq.	DIEA 2.0 eq.	1-Methyl-2-pyrrolidinone	150 °C	5 h
4	 1.0 eq.	 0.5 eq.	DIEA 0.8 eq.	DMF	140 °C	14 h
5	 1.0 eq.	 0.5 eq.	DIEA 0.8 eq.	MeCN	150 °C	MW 850 W 2 h
6	 1.0 eq.	 0.5 eq.	DIEA 0.8 eq.	MeOH	65 °C	MW 850 W 3 h
7	 1.0 eq.	 1.0 eq.	K_2CO_3 1.5 eq.	H_2O	r.t.	Overnight

Table 2. Continued.

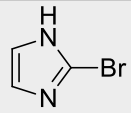
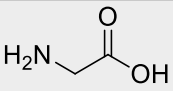
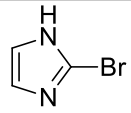
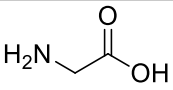
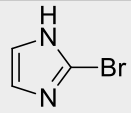
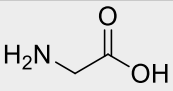
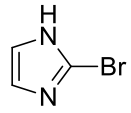
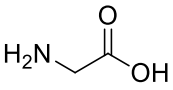
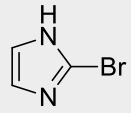
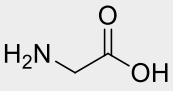
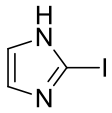
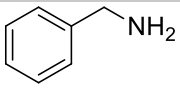
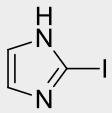
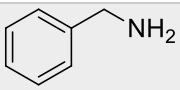
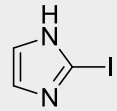
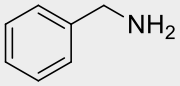
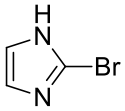
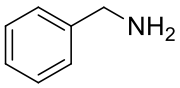
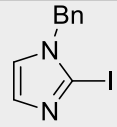
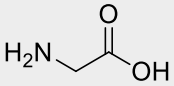
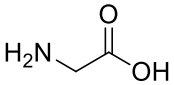
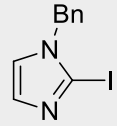
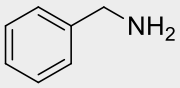
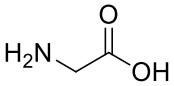
8	 1.0 eq.	 0.5 eq.	K_2CO_3 2.0 eq.	DMSO	r.t.	overnight
9	 1.0 eq.	 1.0 eq.	K_2CO_3 2.5 eq.	DMSO	r.t.	Overnight
10	 1.0 eq.	 1.0 eq.	Et_3N 10 eq.	H_2O	r.t.	Overnight
11	 1.0 eq.	 2.0 eq.	-	Phenol 6.0 eq.	120 °C	18 h
12	 1.0 eq.	 2.0 eq.	-	Phenol 12 eq.	120 °C	18 h
13	 1.0 eq.	 1.0 eq.	K_2CO_3 1.0 eq.	EtOH	r.t.	14 h
14	 1.0 eq.	 2.0 eq.	NaH 10.0 eq.	DMF	r.t.	2 h

Table 3. Coupling reactions using CuI with different parameters.

Entry	Reagent 2	Reagent 2	Base	Solvent	Temp.	Time
1	 1.0 eq.	 0.5 eq.	Cs_2CO_3 1.0 eq. CuI 0.5 eq. Trans-1,2-cyclohexadiamine 0.5 eq.	Dioxane	90 °C	1.5 h
2	 1.0 eq.	 0.84 eq.	Cs_2CO_3 1.0 eq. CuI 0.5 eq. Trans-1,2-cyclohexadiamine 0.5 eq.	Dioxane	90 °C	1.5 h
3	 1.0 eq.	 1.0 eq.	K_2CO_3 2.0 eq. CuI 0.1 eq. glycine 0.2 eq.	Dioxane	90 °C	1.5 h
4	 1.0 eq.	 1.0 eq.	K_2CO_3 2.0 eq. CuI 0.1 eq. glycine 0.2 eq.	Dioxane	90 °C	4 h
5	 1.0 eq.	 1.3 eq.	K_2CO_3 4.3 eq. CuI 0.1 eq. glycine 0.15 eq.	Dioxane	reflux	24 h
6	 1.0 eq.	 1.2 eq.	K_2CO_3 2.0 eq. CuI 0.1 eq. Gly 0.25 eq.	Dioxane	Reflux	24 h

2.4 Studies towards synthesis of compound 2

After failing the coupling of imidazole and glycine derivative, second target compound **2** was tried to be synthesized. The difference between compound **2** from **1** is having carbon atom in the conjunction point of each group instead of nitrogen. Therefore, the retrosynthetic analysis was slightly changed as shown in Figure 11.

In this retrosynthesis, imidazole and adenine moieties were used as nucleophiles where in the previous target molecular **1**, they were acting as electrophile.

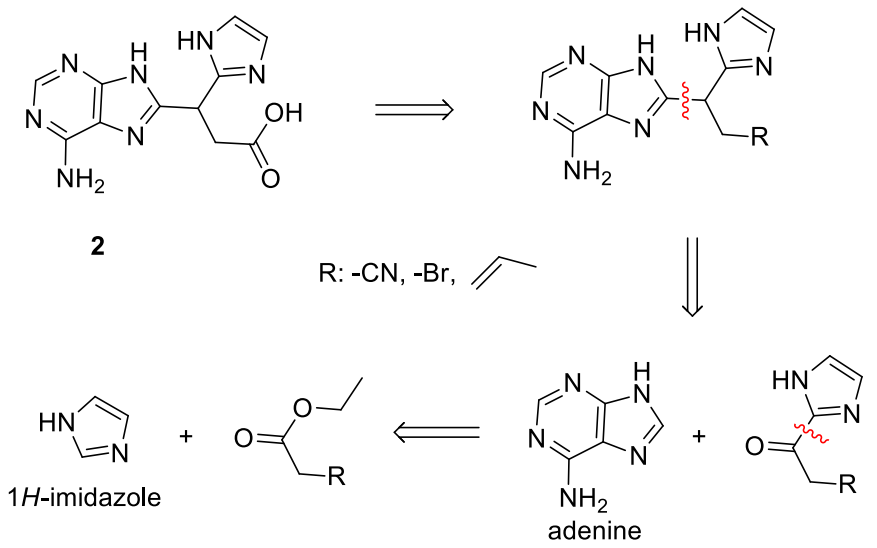
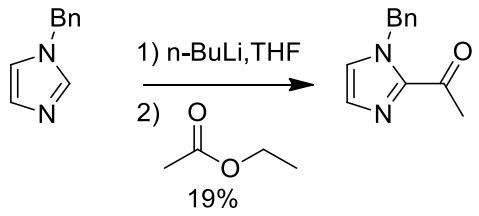


Figure 11. Retrosynthetic analysis of compound **2**.

The synthesis was started with imidazole and ester derivatives. Imidazole was protected by benzyl group as discussed above. 2-position of imidazole was deprotonated by *n*-BuLi in dry THF and reacted with ethyl acetate to test this reaction. The desired product was obtained in low yield (19%).



Scheme 4. Test reaction with EtOAc.

When ethyl bromoacetate was used as ester group, lithiated imidazole derivative captured bromine atom to give 1-benzyl-2-bromo-1*H*-imidazole, instead of attacking ester group. Furthermore, ethyl cyanoacetate were used as ester but no

desired product was observed although different reaction conditions were tried as shown in Table 4 (entries 1-8). This might be because of quenching of lithiated imidazole with the acidic hydrogen of ethyl cyanoacetate, instead of reacting with the carbonyl group. Therefore, ethyl acrylate was chosen as an alternative ester since it does not contain any acidic alpha hydrogen. Unfortunately, it also did not give the corresponding product (Table 4, entries 9-10).

Table 4. Coupling reactions with different parameters.

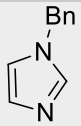
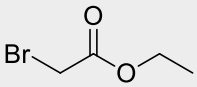
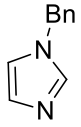
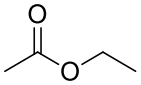
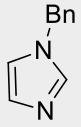
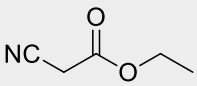
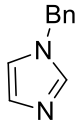
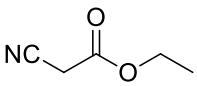
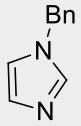
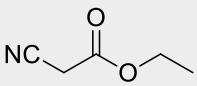
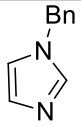
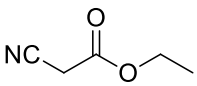
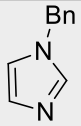
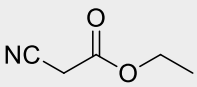
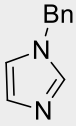
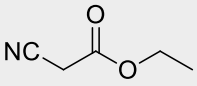
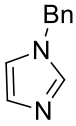
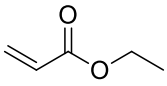
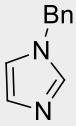
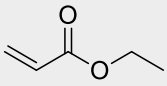
Entry	Reagent-1	Reagent-2	Base	Solvent	Time	Yield
1	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	THF	0.75 h+3 h	-
2	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	THF	0.75 h+3 h	19%
3	 1.0 eq.	 3.0 eq.	*n*-BuLi 1.0 eq.	THF	0.75 h+3 h	-
4	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	THF	3h+3h	-
5	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	THF	0.75 h+ overnight	-
6	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	THF	3h+overnight	-
7	 1.0 eq.	 0.5 eq	*n*-BuLi 1.0 eq.	THF	0.75 h+3 h	-

Table 4. Continued.

8	 1.0 eq.	 0.5 eq.	*n*-BuLi 1.0 eq.	THF	3h+3h	-
9	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	THF	0.75 h+3 h	-
10	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	THF	2h+3h	-

2.5. Studies towards synthesis of Compound 4

In literature, when there are simple alkyl groups such as methyl or ethyl on the *N*-9 position of adenine and 1-position of imidazole, they give similar reactions that was tried previously in this work. Benzyl group is sterically bulkier than methyl and ethyl group. Therefore, it is thought that the reason of unsuccessful reactions for the synthesis of compound **1** and **2** might be due to the bulkiness of alkyl group that was used on imidazole which was benzyl group. Compound **3** which was used as a catalyst to mimic of HPCD enzyme has methyl groups on 1-position of imidazoles. Since there is no contribution of that positions on binding metal ion, it is thought that a small alkyl groups like methyl or ethyl can be used instead of benzyl group which was originally planned to be removed at the end of the synthesis to have free NH groups. Therefore, a modified target molecule **4** with methyl and ethyl groups on nitrogen was selected (Figure 12).

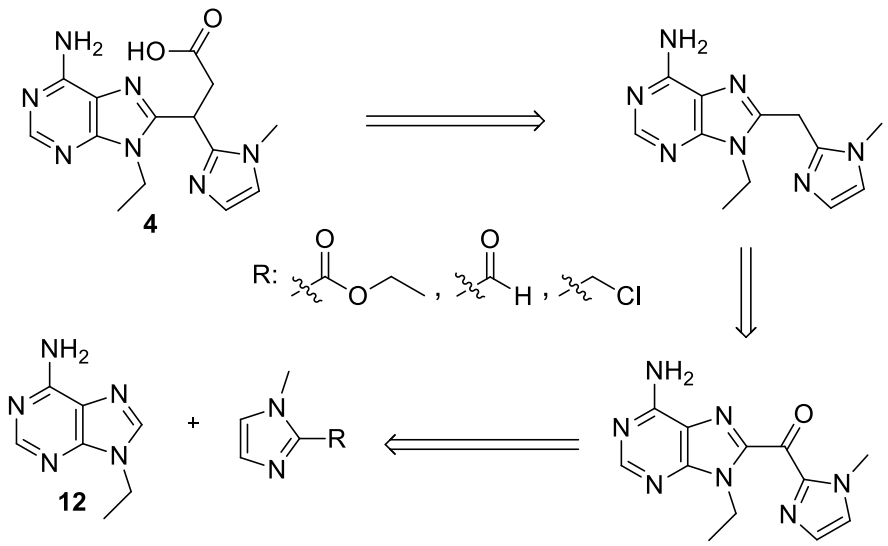
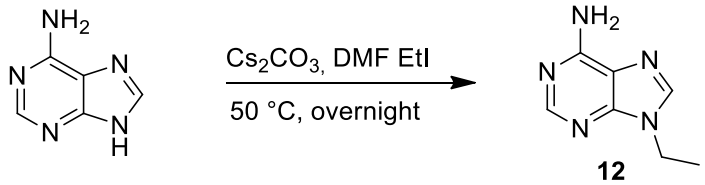
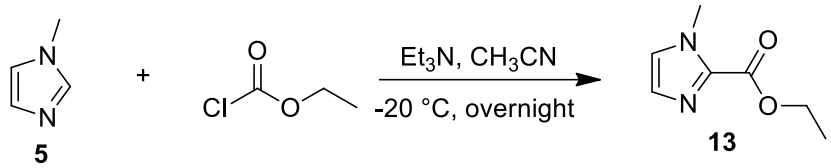


Figure 12. Retrosynthetic analysis of compound **4**.

First of all, *N*-9-ethyl adenine (**12**) was synthesized by following literature procedure starting from commercially available adenine with ethyl iodide in the presence of Cs_2CO_3 in DMF (Scheme 5). Ethyl-1-methyl-1*H*-imidazole-2-carboxylate (**13**) was synthesized from imidazole in two steps. In the first step, imidazole was methylated by methyl iodide after deprotonation with NaH in THF. In the second step, 1-methyl-*1H*-imidazole was treated with ethylchloroformate in the presence of Et_3N as base in acetonitrile to give compound **13** in 61% yield (Scheme 6).

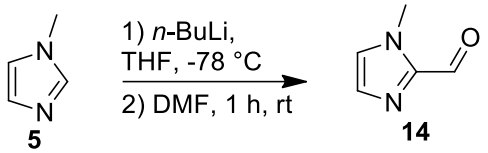


Scheme 5. Synthesis of compound **12**.



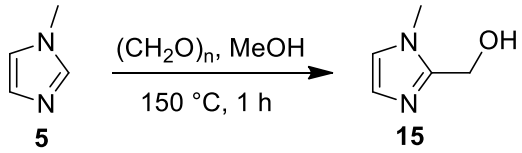
Scheme 6. Synthesis of compound **13**.

1-Methyl-1*H*-imidazole-2-carbaldeyde (**14**) was synthesized starting from 1-methyl-*1H*-imidazole by deprotonating with *n*-BuLi, then treated with DMF as carbaldehyde source in THF (79% yield) (Scheme 7).

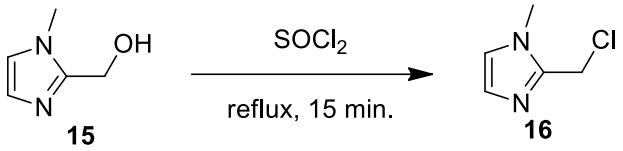


Scheme 7. Synthesis of compound **14**.

(1-Methyl-1*H*-imidazole-2yl)-methylene chloride was synthesized in two steps starting from 1-methyl-1*H*-imidazole. In the first step, it was treated with paraformaldehyde to give the alcohol **15** in methanol with 42% yield (Scheme 8). Then, it was converted to chloride derivative in neat $SOCl_2$ as chlorinating agent **16** (Scheme 9).



Scheme 8. Synthesis of compound **15**.



Scheme 9. Synthesis of compound **16**.

After the synthesis of imidazole ester **13**, aldehyde **14**, the reaction with lithiated adenine derivatives were tested. The results are summarized in Table 5. Deprotonation of ethyl adenine was performed by *n*-BuLi. Surprisingly, instead of addition of lithiated adenine to **13** and **14**, *n*-BuLi itself was reacted to **13** and **14** to to give addition products which were determined by GC-MS. This might be because of the unsuccessful deprotonation of ethyl adenine by *n*-BuLi under reaction conditions. When *n*-BuLi could not act as a base, then it was reacting as a nucleophile to give addition products.

Therefore, excess amount of LDA was used as a bulky base to deprotonate ethyl adenine to avoid addition products. However, under several reaction conditions summarized in Table 6, LDA again acted as nucleophile instead of base and gave addition products on **13**, **14** and **16** which were determined by GC-MS.

Table 5. Lithiation of ethyl adenine and reactions with various imidazole derivatives under different reaction conditions.

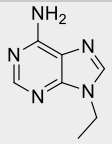
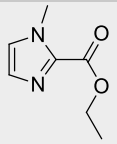
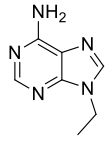
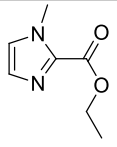
Entry	Reagent 1	Reagent 2	Base	Temp.	Solvent	Time
1	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	-78 °C	THF	0.75 h + 3 h
2	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.5 eq.	-78 °C	THF	2 h + 3 h

Table5. Continued.

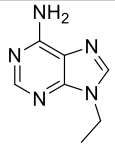
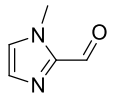
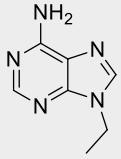
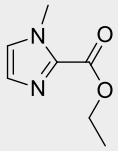
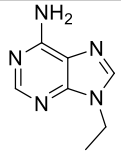
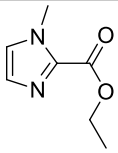
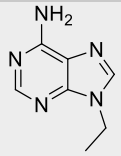
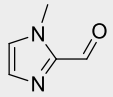
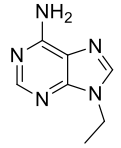
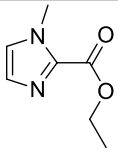
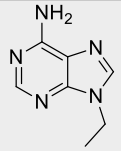
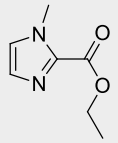
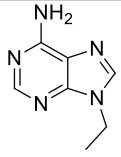
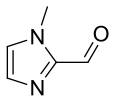
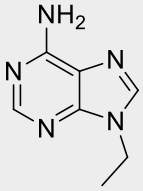
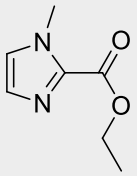
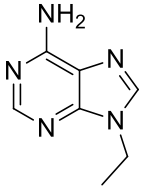
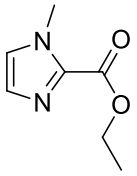
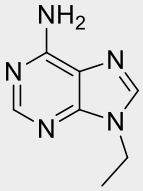
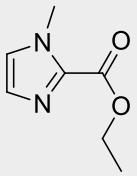
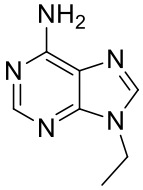
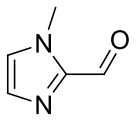
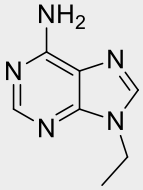
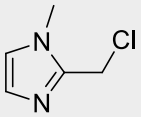
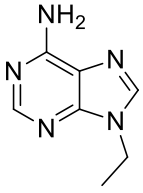
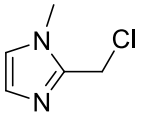
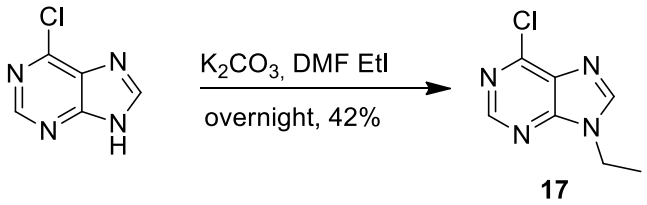
3	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	-78 °C	THF	0.75 h + 3 h
4	 1.0 eq.	 1.0 eq.	*n*-BuLi 1.0 eq.	-78 °C	THF	3 h + 3 h
5	 1.0 eq.	 1.0 eq.	*n*-BuLi 0.9 eq.	-78 °C	THF	0.75 h + 3 h
6	 1.0 eq.	 1.0 eq.	*n*-BuLi 0.9 eq.	-78 °C	THF	0.75 h + 3 h
7	 1.0 eq.	 1.0 eq.	*n*-BuLi 0.9 eq.	-78 °C, -30 °C, -78 °C	THF	rt overnight
8	 1.0 eq.	 1.0 eq.	*n*-BuLi 0.9 eq.	-78 °C, 0 °C, -78 °C	THF	rt overnight
9	 1.0 eq.	 1.0 eq.	*n*-BuLi 0.9 eq.	-78 °C, 0 °C, -78 °C	THF	rt overnight

Table 6. Lithiation of ethyl adenine by LDA and reactions with various imidazole derivative under different reaction conditions.

Entry	Reagent 1	Reagent 2	Base	Temperature	Solvent	Time
1	 1.0 eq.	 1.6 eq.	LDA 5.1 eq.	-78 °C	THF	1 h + 2 h
2	 1.0 eq.	 1.6 eq.	LDA 5.1 eq.	-78 °C	THF	1 h + 2 h
3	 1.0 eq.	 1.6 eq.	LDA 1.0 eq.	-78 °C	THF	1 h + 2 h
4	 1.0 eq.	 1.6 eq.	LDA 5.1 eq.	-78 °C	THF	1 h + 2h
6	 1.0 eq.	 1.6 eq.	LDA 5.1 eq.	-78 °C	THF	1 h + 2 h
7	 1.0 eq.	 1.6 eq.	LDA 1.0 eq.	-78 °C	THF	1 h + 2 h

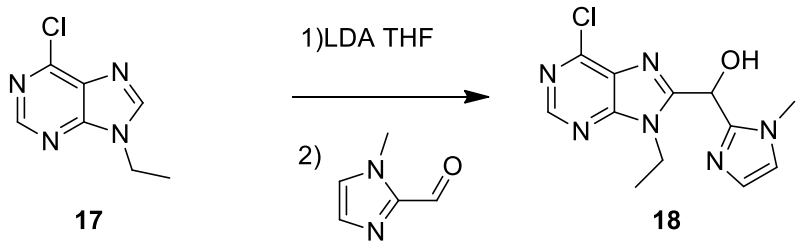
In the literature, it is known that chloropurine derivatives are easier to deprotonate from C-8 position than adenine derivatives. Chloropurines can be also converted into adenine by reacting with ammonia solution at high temperature in sealed tube. Since adenine derivatives were all failed to react with ester **13**, aldehyde **14** and chloride **16**, it is decided to use chloropurine derivatives as an adenine precursor.

For this purpose, 6-chloropurine was converted into ethyl derivative by using K_2CO_3 and ethyl iodide in DMF in 42% yield following literature procedure [54].



Scheme 10. Synthesis of 9-ethyl-6-chloropurine.

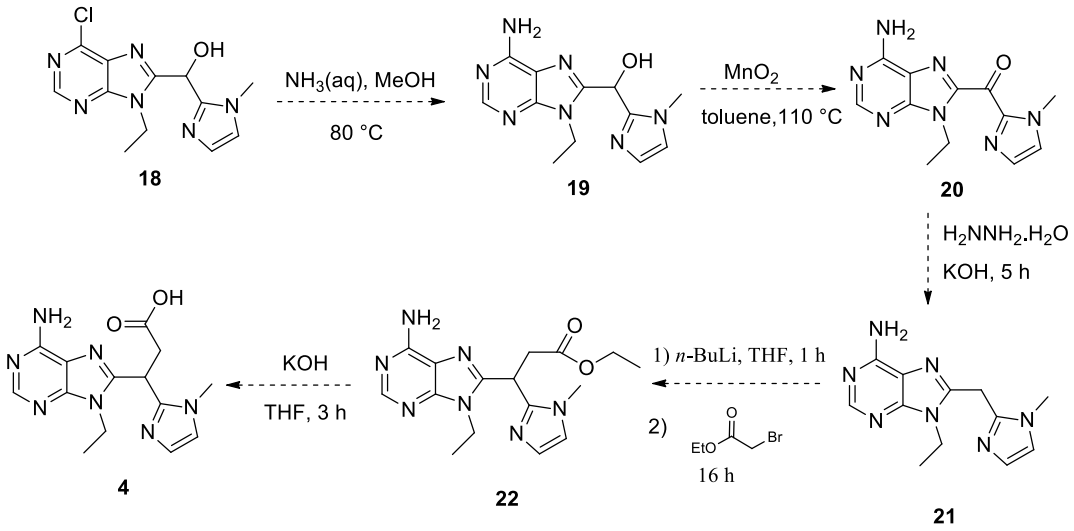
After lithiation of compound **17** using LDA at -78 °C, it was treated with aldehyde **14** to give corresponding alcohol **18** in poor yield (30%).



Scheme 11. Synthesis of compound **18**.

After successful coupling of purine and imidazole derivatives, adenine moiety will be obtained by treating with ammonia following literature procedures [52, 53, 42, 43]. The rest of the synthesis will be performed as in the synthesis of compound **3**.

The planned synthetic scheme for compound **4** from compound **18** is shown in Scheme 12.



Scheme 12. The planned synthetic scheme for compound **4** from compound **18**.

2.6. Conclusion

In this work, the synthesis of two ligands based on theoretical design was tried with various reaction conditions starting from adenine and imidazole. None of these reactions were successful to get the desired products. Only some unexpected side products were observed.

However, starting from 6-chloropurine instead of adenine derivatives gave successful coupling product of purine and imidazole derivative which was the key part of the synthesis of these ligands.

After converting chloropurine derivative into adenine, the synthesis of target molecule **4** will be performed as planned.

The test ligand (compound **3**) was successfully synthesized following literature procedures.

After completing the synthesis of compound **4**, all the ligands will be tested in the aromatic oxidative ring cleavage reaction of cathecol derivatives by Karadaş Research Group from Bilkent University.

CHAPTER 3

EXPERIMENTAL

3.1. Materials and Methods

HPLC grade solvents were supplied from Sigma Aldrich, Germany.

6-Chloropurine was supplied from Chem Impex, IL, USA.

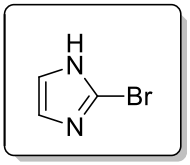
Other solvents are technical grade. They were purified, when necessary, using distillation method.

The mass spectra were recorded on Agilent 7890 A 5975C VL MSD GC/MS.

Nuclear magnetic spectra were read in $CDCl_3$ and CD_3OD on Bruker Spectrospin Advance DPX 400 spectrometer. Chemical shifts were received in parts per million (ppm) with TMS as internal reference. NMR spectra of the compounds are given in Appendix A.

Adenine and imidazole were supplied from Sigma Aldrich, Germany.

3.2. Synthesis of 2-bromo-1*H*-imidazole

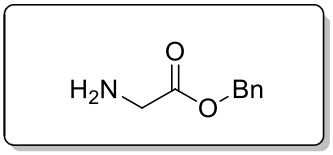


Based on the literature [26], 1,1'-carbonyldiimidazole (2.05 g, 12.6 mmol) was dissolved in 50 mL of THF. To this solution, of NBS (4.49 g, 25.2

mmol) was added at 0 °C and the mixture was warmed to room temperature. Reaction mixture was stirred at room temperature for 24 h then the solvent was removed under reduced pressure. 30 ml of water added to the solid and stirred for 30 minutes at 0 °C again. Precipitate was filtered and washed with water twice and dried in a fume hood. Yellow solid (0.55 g, 3.80 mmol), was obtained as product. Yield is 30%.

^{1}H NMR (400 MHz, DMSO) δ: 7.06 (s, 1H)

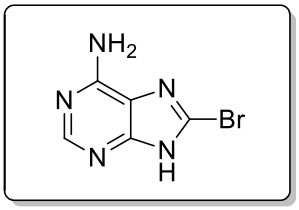
3.3 Synthesis of glycine-benzyl ester



A mixture of glycine (0.38 g, 5.0 mmol) in benzyl alcohol (26 mL, 0.25 mmol) was stirred at 0 °C. $SOCl_2$ (1.8 mL, 25 mmol) was added drop wise to this mixture while temperature was kept constant at 0 °C. Then the reaction temperature was increased to 90 °C and stirred at this temperature for 5 h. Reaction mixture was then placed in an ice bath and diethyl ether was added drop wise until the color of the mixture turned to the cloudy. The resultant mixture was filtered and the crude product was recrystallized from ethanol and diethyl ether. White solid product was obtained with a yield of 51%.

^{1}H NMR (400 MHz, DMSO) δ: 8.46 (s, 2H), 7.51-7.29 (m, 5H), 5.23 (s, 2H), 3.86 (s, 2H)

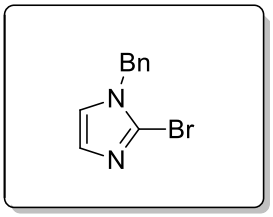
3.4. Synthesis of 8-bromo-adenine



Based on the literature [27], bromine (0.10 mL, 1.96 mmol) was added to 15 mL of water and adenine (140 mg, 1.0 mmol) was added to this mixture. Then the mixture was stirred for 24 h at room temperature. Reaction mixture was then extracted with DCM three times. Solvent was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated using rotary evaporator to give a white solid. The solid was then purified with flash column chromatography (DCM:MeOH = 1:1) on silica gel and the target compound obtained (60 mg, 0.28 mmol) as a white solid. Yield is 28%.

^{1}H NMR (400 MHz, DMSO) δ: 13.61 (s, 1H), 8.11 (s, 1H), 7.43 (s, 2H)

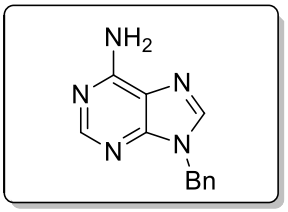
3.5. Synthesis of 1-benzyl-2-bromo-1*H*-imidazole



Based on the literature [28], K_2CO_3 (0.78 g, 5.7 mmol) was added to a stirred solution of 2-bromo-1*H*-imidazole (0.78 g, 0.57 mmol) and DMF (10 mL). To this solution, benzyl bromide (0.11 g, 0.63 mmol) was added at once and the reaction mixture was stirred at room temperature overnight. The mixture was then filtered to remove excess potassium carbonate. The solid was washed with DMF and the solvent was removed by using rotary evaporator. Resultant mixture was extracted with ethyl acetate and 1 M NaOH solution three times. The organic

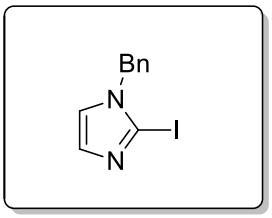
phase was then dried over anhydrous $MgSO_4$ filtered and the solvent was evaporated using rotary evaporator. Obtained mixture was purified with flash column chromatography (EtOAc:Hexane = 1:1) on silica gel and obtained colorless oil (109 mg, 0.46 mmol). Yield 81%.

3.6. Synthesis of *N*-9-benzyladenine



Based on the literature [29], adenine (1.0 g, 7.41 mmol) was dissolved in 20 mL of DMF. To the mixture NaH (0.178 g, 7.41 mmol) was added slowly at 0 °C. Reaction mixture was stirred for 1 h at 25 °C. After an hour, of benzyl chloride (1.70 mL, 14.8 mmol) was added slowly then the reaction mixture was stirred overnight. The solvent was evaporated with using rotary evaporator. Obtained solid was separately washed with diethyl ether and water. Crude product which is *N*-7-benzyladenine and *N*-9-benzyladenine was purified by short column chromatography on silica gel eluted with (EtOAc:Hexane=1:3) to give a white solid (400 mg, 1.78 mmol). Yield is 24%.

3.7. Synthesis of 1-benzyl-2-Iodo-1*H*-imidazole

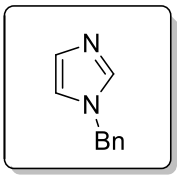


Based on the literature [30], to a mixture of dry tetrahydro

furan (5.0 mL) and benzyl imidazole (0.48 g, 3.0 mmol) *n*-BuLi (1.9 mL, 3.0 mmol) from a 1.6 M solution in hexane were added slowly at -78 °C and stirred for 45 minutes. Then iodine (760 mg, 3.0 mmol) was added and stirred for 3 more hours at 25 °C. The mixture was extracted with DCM and water. Organic phase was dried with anhydrous Na_2SO_4 filtered and the solvent was evaporated using rotary evaporator. Residue was then purified by flash column chromatography (EtOAc:Hexane = 3:1) on silica gel to obtain yellow solid (310 mg, 1.1 mmol). Yield is 37%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.02 (s, 2H), 6.94 (s, 1H), 7.09-7.04 (m, 2H), 7.33-7.21 (m, 3H)

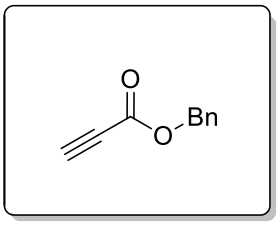
3.8. Synthesis of 1-benzylimidazole



Based on the literature [31], imidazole (1.42 g, 20.8 mmol) was dissolved in 20 mL of 1,4-dioxane. This solution was mixed with a sodium hydride (0.500 g, 20.8 mmol) and stirred for 1 h at 90 °C. In to the mixture, benzyl bromide (3.24 g, 19 mmol) in 20 mL of 1,4-dioxane solution was added drop wise. The resultant solution was stirred for 22 h at 90 °C. Solvent of resultant mixture was then dried in vacuo and extracted with DCM adding 50 mL of water. Organic phase was then dried with anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure using rotary evaporator then purified by flash column chromatography (EtOAc:Hexane = 1:3) and obtained brown solid (1.1 g, 6.96 mmol) with yield 34%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (s, 1H), 7.33-7.21 (m, 3H), 7.10-7.04 (m, 2H), 7.01 (s, 1H), 6.82 (s, 1H), 5.04 (s, 2H).

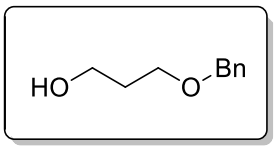
3.9. Synthesis of benzyl propiolate



Based on the literature [32], potassium carbonate (4.47 g, 32.3 mmol) was dissolved in DMF (15 mL). In to this mixture, propiolic acid (2.00 mL, 23.3 mmol) in DMF (8 ml) was added and stirred at 0°C. After stirred for 10 minutes, benzyl bromide (3.2 mL, 26.9 mmol) was added and the reaction mixture was allowed to warm to 25 °C. Reaction mixture was then stirred for 2 h and extracted with adding 45 mL of water and EtOAc-Hexane 1:1. Organic phases were mixed and extracted again with brine then the solvent was dried with anhydrous sodium sulfate then solvent was evaporated with using rotary evaporator to obtain brown liquid (2.5 g, 15.6 mmol). Yield is 67%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.09 (s, 1H), 7.26 (s, 1H), 2.79 (s, 1H).

3.10. Synthesis of 3-benzyloxypropanol

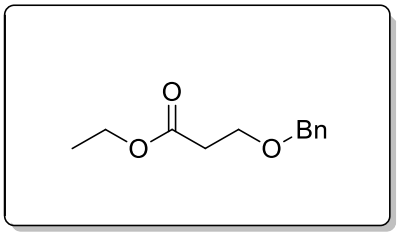


Based on the literature [33], to a solution of 1,3-propanediol (0.420 ml, 6.0 mmol) in THF (2.0 ml) oil free sodium hydride (0.072 g, 3.0 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h and benzyl bromide (0.720 ml, 6.0 mmol) was then added. The reaction mixture was slowly warmed to room temperature, stirred overnight, and saturated ammonium chloride solution was added. Then the mixture was extracted with ethyl acetate three times and the solvent was dried with anhydrous sodium sulfate and evaporated with using rotary

evaporator to yield mono-benzyl ether (0.50 g, 50%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58-7.08 (m, 5H), 4.51 (s, 2H), 3.74 (t, *J*=5.83 Hz, 2H), 3.64 (t, *J*=5.95 Hz, 3H), 1.86 (p, *J* = 6.0 Hz, 2H).

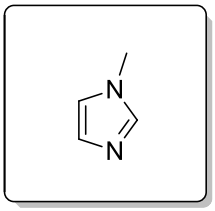
3.11. Synthesis of propanoic acid, 3-(phenylmethoxy)-, ethyl ester



Based on the literature [34], to a solution of 3-benzyloxypropanol (300 mg, 1.80 mmol) and acetone (6 mL), Jones reagent (0.8 g chromium trioxide, 0.69 mL concentrated sulfuric acid, diluted with water to 3 mL) was added dropwise at 0 °C. The temperature was increased to room temperature and stirred for 2 h. The resultant mixture was filtered on silica gel and washed with acetone. The solvent was removed and extracted with ethyl acetate and water three times. Organic phase was combined and dried with anhydrous magnesium sulfate and solvent was evaporated under high vacuum. Then ethanol (3 mL) and concentrated H_2SO_4 (0.1 mL) solution were added and the mixture was refluxed for 12 h. Solvent was evaporated and extracted with ethyl acetate and water then combined organic phase was dried with anhydrous sodium sulfate. Solvent was removed by using rotary evaporator to give colorless oil (0.169 g). Yield is 52%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36-7.28 (m, 5H), 4.54 (s, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.75 (t, *J* = 6.2 Hz, 2H), 2.61 (t, *J* = 6.2 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H).

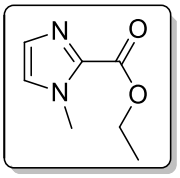
3.12. Synthesis of 1-methyl-imidazole



Based on the literature [35], imidazole (1.0 g, 15 mmol) was dissolved in 25 mL of THF. Into this mixture, oil-free NaH (700 mg, 29 mmol) was added. Then methyl iodide (2.5 g, 18 mmol) was added to the reaction mixture and stirred for 3 h. Solvent was evaporated by using rotary evaporator. The mixture was extracted with DCM and water then organic phases was dried with anhydrous sodium sulfate. Colorless liquid (0.9 g, 10.9 mmol) was obtained as product with yield 73%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (s, 1H), 6.95 (s, 1H), 6.80 (s, 1H), 3.59 (s, 3H).

3.13. Synthesis of 1-methyl-1*H*-imidazole-2-carboxylate

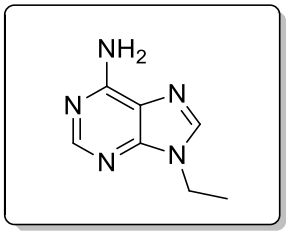


Based on the literature [36] *N*-methylimidazole (0.32 g, 3.9 mmol) was dissolved in 2 mL of dry acetonitrile. To this mixture, triethylamine (1.0 mL, 7.17 mmol) was added at -20 °C. Then ethylchloroformate (1.0 g, 9.2 mmol) was added slowly while the temperature was about -20 °C and the reaction mixture was stirred at room temperature for 18 h. The mixture was filtered to remove formed triethylamine hydrochloride from reaction mixture. Solvent was removed under high vacuum and the mixture was extracted with DCM and water. Organic phase was dried with anhydrous Na_2SO_4 filtered and the solvent was evaporated using

rotary evaporator. Residue was then purified by flash column chromatography (EtOAc:Hexane = 3:1) on silica gel to obtain 370 mg colorless liquid (370 mg, 2.35 mmol). Yield is 61%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (s, 1H), 6.73 (s, 1H), 3.77 (q, *J* =7.3, 2H), 2.26 (s, 1H), 1.25 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.9, 126.7, 118.2, 40.6, 15.8, 12.7.

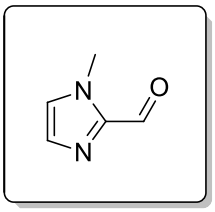
3.14. Synthesis of 9-ethyladenine.



Based on the literature procedure [37] Adenine (0.7 g, 5.2 mmol) and cesium carbonate (2.0 g, 6.3 mmol) was dissolved in dry DMF under nitrogen atmosphere at room temperature. To this mixture iodoethane (0.50 mL, 6.3 mmol) was added and the temperature was increased to 50 °C for 16 h. White precipitate was removed by filtration then solvent was quenched with 5 mL of water then solvents was evaporated using rotary evaporator. Yellow methanol and chloroform (1:1) was added and mixture was partially soluble, insoluble materials was filtered off. Obtained mixture was purified with flash column chromatography (DCM:MeOH = 20:1) on silica gel and obtained white solid (420 mg, 2.58 mmol). Yield 50%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (s, 1H), 7.77 (s, 1H), 6.11 (s, 2H), 4.20 (q, *J* = 7.3 Hz, 2H), 1.48 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.4, 152.7, 140.0, 38.9, 15.5.

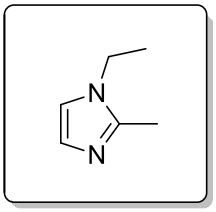
3.15. Synthesis of 1-methyl-1*H*-imidazole-2-carbaldehyde



Based on the literature [38]1-Methyl-imidazole (0.82 mL, 10 mol) was dissolved in 10 mL of dry THF, under nitrogen atmosphere, the mixture was cooled to -78 °C and was stirred for 15 min, to this mixture *n*-BuLi (6.2 mL, 10 mmol) from a commercial 1.6 M solution in hexane was added dropwise then DMF (1.5 mL, 20 mmol) was added to the mixture and the solution was stirred at -78 °C for 1 h then the mixture was allowed to warm to the room temperature and stirred for 1 h more. Then 8 mL 2M HCl was added and stirred for 1 h more at room temperature. The mixture was neutralized to pH 10 with using 40% NaOH and extracted with DCM for three times and al organic phases were combined and solvent was dried with anhydrous sodium sulfate then the solvent was evaporated under high vacuum and obtained yellowish liquid. The resultant liquid was purified with using flash column chromatography (Hexane:EtOAc =1:3) and obtained colorless liquid (0.87 g, 7.9 mmol. Yield is 79%.

(400 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 7.22 (s, 1H), 7.06 (s, 1H), 3.96 (s, 1H)

3.16. Synthesis of 1-Ethyl-2-methyl-1*H*-imidazole

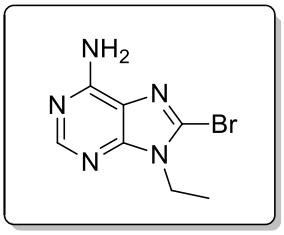


Based on the literature [39], 2-methyl-1H-imidazole (0.82 g, 0.01

mol), ethyl iodide (0.87 mL, 0.011 mol) and aqueous solution of 50% sodium hydroxide (3 mL) were put together in a flask and was stirred for 10 min at room temperature. The reaction temperature was increased to 30-40 °C after the solidification to obtain liquid form of the solution. The solution was extracted with 30 ml of chloroform in three times. After washing with water, anhydrous sodium sulfate was added to remove water residue. Finally, the solution was evaporated and the obtained product was purified using the flash column chromatography (DCM:MeOH = 10:1) on silica gel and obtained yellowish liquid (165 mg, 1.5 mmol). Yield is 15 %.

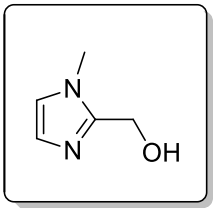
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.81 (s, 1H), 6.76 (s, 1H), 3.80 (q, *J* = 7.3, 2H), 2.29 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 1H).

3.17. Synthesis of 8-bromo-9-ethyl-9*H*-purin-6-amine



Based on the literature [40], bromine (0.24 mL, 4.65 mmol) was added a solution of ethyl adenine (0.1 g, 0.6 mmol) in 20 mL of chloroform and stirred for 18 hours at room temperature. After that, an aqueous saturated solution of $Na_2S_2O_3$ was introduced to the resultant mixture. The obtained precipitate was washed with water and dichloromethane after filtration. Product obtained but couldn't have been isolated.

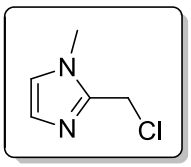
3.19. Synthesis of (1-methyl-1*H*-imidazol-2yl)methanol



Based on the procedure [41] *N*-methylimidazole (2.5 g, 30 mmol) was mixed with paraformaldehyde (2.5 g, 82.5 mmol) then mixture was refluxed at 160 °C for 1 h. mixture was dissolved in MeOH and cooled to -18 °C and triturated then precipitate was filtered. Resultant product was recrystallized in methanol/petroleum ether to give 2-hydroxymethyl-1-methylimidazole as white crystals (1.4 g, 12.5 mmol). Yield is 42%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.81 (s, 1H), 6.75 (s, 1H), 4.58 (s, 2H), 3.66 (s, 2H).

3.21 Synthesis of 1-methyl-2-(chloromethyl)imidazole hydrochloride



Based on the literature [45], 1-methyl-2-hydroxymethyl imidazole (250 mg, 2.32 mmol) was added dropwise to $SOCl_2$ (0.42 mL, 4.26 mmol) and refluxed at 75 °C for 15 min. Then resultant mixture was recrystallized in ethanol and dried in high vacuum to give 1-Methyl-2-(chloromethyl)imidazole hydrochloride (154 mg, 0.92 mmol). Yield is 40%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (s, 1H), 7.10 (s, 1H), 5.11 (s, 2H), 3.91 (s, 3H)

3.20. General Procedure 1

A similar literature procedure is followed [46]. To a solution of glycine in a solvent, base was added and then halogenated imidazole derivative was added to this solution and stirred at various temperature for a certain period of time. Sometimes under microwave assisted conditions were tried.

Entry 1:

1-Benzyl-2-bromo-1*H*-imidazole (0.237 g, 1.0 mmol) and glycine benzyl ester (100 mg, 0.5 mmol) is reacted in methanol using Et_3N (70 µL, 0.5 mmol) as base following general procedure 1. After 14 h reaction duration, no product was observed.

Entry 2:

1-Benzyl-2-bromo-1*H*-imidazole (0.237 g, 1.0 mmol) and glycine benzyl ester (100 mg, 0.5 mmol) is reacted in methanol using Et_3N (70 µL, 1.0 mmol) as base following general procedure 1. After 5 h reaction duration at 50 °C, no product was observed.

Entry 3:

1-Benzyl-2-bromo-1*H*-imidazole (0.117 g, 0.5 mmol) and glycine benzyl ester (50 mg, 0.25 mmol) is reacted in 1-Methyl-2-pyrrolidinone using DIEA (68 µL, 1.0 mmol) as base following general procedure 1. After 5 h reaction duration at 150 °C, no product was observed.

Entry 4:

1-Benzyl-2-bromo-1*H*-imidazole (0.117 g, 0.5 mmol) and glycine benzyl ester (50 mg, 0.25 mmol) is reacted in DMF using DIEA (34 µL, 0.4 mmol) as base following general procedure 1. After 14 h reaction duration at 140 °C, no product was observed.

Entry 5:

A similar literature procedure is followed [47]. 1-Benzyl-2-bromo-1*H*-imidazole (0.117 g, 0.5 mmol) and glycine benzyl ester (50 mg, 0.25 mmol) is reacted in acetonitrile using DIEA (34 μL, 0.4 mmol) as base under microwave condition (850 W) following general procedure 1. After 2 h reaction duration at 150 °C, no product was observed.

Entry 6:

A similar literature procedure is followed [47]. 1-Benzyl-2-bromo-1H-imidazole (0.117 g, 0.500 mmol) and glycine benzyl ester (50 mg, 0.25 mmol) is reacted in methanol using DIEA (34 μL, 0.40 mmol) as base under microwave condition (850 W) following general procedure 1. After 3 h reaction duration at 65 °C, no product was observed.

Entry 7:

2-Bromo-1*H*-imidazole (0.292 g, 2.0 mmol) and glycine benzyl ester (250 mg, 2.0 mmol) is reacted in water using K_2CO_3 (414 mg, 3.0 mmol) as base following general procedure 1. After 14 h reaction duration at room temperature, no product was observed.

Entry 8:

2-Bromo-1*H*-imidazole (0.292 g, 2.0 mmol) and glycine (75 mg, 1.0 mmol) is reacted in DMSO using K_2CO_3 (552 mg, 4.0 mmol) as base following general procedure 1. After 14 h reaction duration at room temperature, no product was observed.

Entry 9:

2-Bromo-1*H*-imidazole (0.292 g, 2.00 mmol) and glycine (150 mg, 2.0 mmol) is reacted in DMSO using K_2CO_3 (690 mg, 5.0 mmol) as base following general procedure 1. After 14 h reaction duration at room temperature, no product was

observed.

Entry 10:

2-Bromo-1*H*-imidazole (0.045 g, 0.30 mmol) and glycine (23 mg, 0.30 mmol) is reacted in water using Et_3N (300 mg, 3.00 mmol) as base following general procedure 1. After 14 h reaction duration at room temperature, no product was observed.

Entry 11:

1-Benzyl-2-iodo-1*H*-imidazole (0.310 g, 1.10 mmol) and benzylamine (240 µL, 2.2 mmol) is reacted in ethanol using K_2CO_3 (304 mg, 2.20 mmol) as base following general procedure 1. After 14 h reaction duration at room temperature, no product was observed.

Entry 12:

1-Benzyl-2-iodo-1*H*-imidazole (0.284 g, 1.00 mmol) and benzylamine (105 µL, 1.00 mmol) is reacted in DMF using sodium hydride (240 mg, 10 mmol) as base following general procedure 1. After 2 h reaction duration at room temperature, no product was observed.

Entry 13:

A similar literature procedure is followed [50]. 2-Bromo-1*H*-imidazole (0.44 g, 3mmol) glycine (0.225 g, 3.00 mmol), and phenol (1.7 g, 18 mmol) were placed in a flask and heated to 150 °C for 15 h. Then further glycine (0.225 g, 3.00 mmol) was added to resultant mixture then heated 3 h more. Then the mixture was cooled to room temperature and EtOAc was added for dilution and brown precipitates was formed. The precipitates was filtered off but no product was observed.

Entry 14:

A similar literature procedure is followed [50]. 2-Bromo-1*H*-imidazole (0.095 g, 0.65 mmol) glycine (0.048 g, 0.65 mmol), and phenol (0.74 g, 7.8 mmol) were

placed in a flask and heated to 150 °C for 21 h. Then further glycine (0.048 g, 0.65 mmol) was added to resultant mixture then heated 3 h more. Then the mixture was cooled to room temperature and EtOAc was added for dilution and brown precipitates was formed. The precipitates was filtered off but no product was observed.

3.21. General procedure 2

A similar literature procedure is followed [44]. To a solution of primary amine in dioxane, copper(I) iodide, base and ligand was added to this solution and stirred at various temperature for a certain period of time.

Entry 1:

2-Bromo-1*H*-imidazole (0.147 g, 1.00 mmol) and benzylamine (54 mg, 0.50 mmol) is reacted in dioxane using Cs_2CO_3 (325 mg, 1.00 mmol) as base, CuI (95 mg, 0.50 mmol) and trans-1,2-cyclohexadiamine (23 mg 0.2 mmol) as ligand following general procedure 2. After 1.5 h reaction duration at 90 °C, no product was observed.

Entry 2:

2-Bromo-1*H*-imidazole (0.147 g, 1.00 mmol) and benzylamine (92 μL, 0.84 mmol) is reacted in dioxane using Cs_2CO_3 (325 mg, 1.00 mmol) as base, CuI (95 mg, 0.5 mmol) and trans-1,2-cyclohexadiamine (58 μL 0.50 mmol) as ligand following general procedure 2. After 1.5 h reaction duration at 90 °C, no product was observed.

Entry 3:

A similar literature procedure is followed [48]. 1-Benzyl-2-iodo-1*H*-imidazole

(0.284 g, 1.10 mmol) and glycine (83 mg, 1.1 mmol) is reacted in dioxane using K_2CO_3 (0.276 g, 2.00 mmol) as base, CuI (19 mg, 0.10 mmol) and glycine (15 mg, 0.20 mmol) as ligand following general procedure 2. After 1.5 h reaction duration, no product was observed.

Entry 4:

A similar literature procedure is followed [48]. 1-Benzyl-2-iodo-1*H*-imidazole (0.39 g, 1.1 mmol) and glycine (83 mg, 1.1 mmol) is reacted in dioxane using K_2CO_3 (0.276 g, 2.00 mmol) as base, CuI (19 mg, 0.10 mmol) and glycine (15 mg, 0.20 mmol) as ligand following general procedure 2. After 4 h reaction duration at 90 °C, no product was observed.

Entry 5:

A similar literature procedure is followed [48]. 1-Benzyl-2-iodo-1*H*-imidazole (0.39 g, 1.4 mmol) and benzylamine (193 mg, 1.80 mmol) is reacted in dioxane using K_2CO_3 (0.828 g, 6.00 mmol) as base, CuI (29 mg, 0.15 mmol) and glycine (15 mg, 0.20 mmol) as ligand following general procedure 2. After 24 h reaction duration at 110 °C, no product was observed.

Entry 6:

A similar literature procedure is followed [49]. 1-Benzyl-2-iodo-1*H*-imidazole (0.34 g, 1.2 mmol) and glycine (110 mg, 1.45 mmol) is reacted in dioxane using K_2CO_3 (0.330 g, 2.4 mmol) as base, CuI (23 mg, 0.12 mmol) and glycine (22 mg, 0.3 mmol) as ligand following general procedure 2. After 24 h reaction duration at 110 °C, no product was observed.

Entry 7:

Magnesium turnings (120 mg, 5.00 mmol) and a small crystal of iodine was heated in reflux and vigorously stirred in THF. *tert*-Butyl chloride (0.625 mL, 5.50 mmol) was added to this solution and heated for 2 h to obtain *tert*-butylmagnesium

chloride. Resultant mixture was added to benzyl imidazole solution in dry THF under nitrogen atmosphere. Reaction mixture was stirred for 1 h at 0 °C. Then benzyl propiolate (0.8 g, 5.0 mmol) was added to this mixture and stirred for 2 h at 0 °C. Resultant mixture was extracted with DCM three times. Organic phase was then dried with anhydrous Na_2SO_4 salt and solvent was removed under reduced pressure. No desired product was observed.

3.22. General Procedure 3

A similar literature procedure is followed [30]. 1-Benzyl-1*H*-imidazole was dissolved in 5.0 mL of dry THF, and *n*-BuLi was added to this mixture at -78 °C and stirred for a certain period of time under nitrogen atmosphere. Then, ester derivative was added to the mixture and stirred at room temperature for a certain period of time. The solvent was then evaporated by using rotary evaporator. Crude mixture was extracted with DCM and water three times for each. Combined organic phases were dried with anhydrous sodium sulfate and filtered. After extraction part, solvent was evaporated by using rotary evaporator.

Entry 1:

1-Benzyl-1*H*-imidazole (0.475 g, 3.00 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then ethyl bromoacetate (0.334 mL, 3.00 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 2:

1-Benzyl-1*H*-imidazole (0.475 g, 3.00 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then ethylacetate (0.293 mL, 3.00 mmol) was added and reaction mixture was allowed to stir to the room

temperature and continued stirring for 3 h and obtained 1-(1-benzyl-1*H*-imidazol-2-yl)ethanone as colorless liquid with 19% yield.

Entry 3:

1-Benzyl-1*H*-imidazole (0.475 g, 3.00 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then ethyl cyanoacetate (0.95 mL, 9.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 4:

1-Benzyl-1*H*-imidazole (0.475 g, 3.00 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 3 h. Then ethyl cyanoacetate (0.318 mL, 3.00 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 5:

1-Benzyl-1*H*-imidazole (0.475 g, 3.0 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then ethyl cyanoacetate (0.318 mL, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 14 h. No product was observed.

Entry 6:

Following a similar literature procedure,[30] 1-benzyl-1H-imidazole (0.475 g, 3.0 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 3 h. Then ethyl cyanoacetate (0.318 mL, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 14 h. No product was observed.

Entry 7:

1-Benzyl-1*H*-imidazole (0.475 g, 3.00 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then ethyl cyanoacetate

(0.160 mL, 1.50 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 8:

1-Benzyl-1*H*-imidazole (0.475 g, 3.00 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 3h. Then ethyl cyanoacetate (0.160 mL, 1.50 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 9:

1-Benzyl-1*H*-imidazole (0.475 g, 3.00 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then ethylacrylate (0.32 mL, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 10:

1-Benzyl-1*H*-imidazole (0.475 g, 3.00 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 2 h. Then ethylacrylate (0.32 mL, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

3.23. General Procedure 4

To a mixture of 1.0 eq. of adenine and 5 mL of dry THF *n*-BuLi was added under nitrogen atmosphere at -78 °C. Solution was stirred for certain period of time. Then ester derivative of imidazole or aldehyde derivative of imidazole was added to this mixture then mixture was allowed to warm to room temperature for certain period of time. Solvent of mixture was removed under high vacuum. Residue was extracted with DCM and water four times then organic solvent was dried with

anhydrous sodium sulfate and was filtered then solvent was evaporated using rotary evaporator.

Entry 1:

A similar literature procedure is followed [30]. Ethyladenine (0.49 g, 3.0 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then, ethyl-1-methyl-1*H*-imidazolecarboxylate (0.46 mg, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 2:

A similar literature procedure is followed [30]. Ethyladenine (0.33 g, 2.0 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 2 h. Then, ethyl-1-methyl-1*H*-imidazole-carboxylate (0.308 mg, 2.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 3:

A similar literature procedure is followed [30]. Ethyladenine (0.49 g, 3.0 mmol) and *n*-BuLi (1.9 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then 1-methyl-1H-imidazolecarbaldehyde (0.33 g, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 4:

A similar literature procedure is followed [30]. Ethyladenine (0.77 g, 4.7 mmol) and *n*-BuLi (2.9 mL, 4.7 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 3h. Then, ethyl-1-methyl-1*H*-imidazole-carboxylate (0.72 mg, 4.7 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 5:

A similar literature procedure is followed [30]. Ethyladenine (0.70 g, 4.3 mmol) and *n*-BuLi (2.4 mL, 3.9 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then, ethyl-1-methyl-1*H*-imidazole-carboxylate (0.66 mg, 4.3 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 6:

A similar literature procedure is followed [30]. Ethyladenine (0.70 g, 4.3 mmol) and n-BuLi (2.4 mL, 3.9 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then, 1-methyl-1*H*-imidazole-carbaldehyde (0.473 mg, 4.3 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 7:

A similar literature procedure is followed [30]. Ethyladenine (0.49 g, 3.0 mmol) and n-BuLi (1.7 mL, 2.7 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min then reaction mixture was allowed to -30 °C and stirred for 30 min at this temperature then again cooled to -78 °C. Then, ethyl-1-methyl-1*H*-imidazole-carboxylate (0.46 mg, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 14 h. No product was observed.

Entry 8:

A similar literature procedure is followed [30]. Ethyladenine (0.49 g, 3.0 mmol) and *n*-BuLi (1.7 mL, 2.7 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min then reaction mixture was allowed to 0 °C and stirred for 30 min at this temperature then again cooled to -78 °C. Then, ethyl-1-methyl-1*H*-imidazole-carboxylate (0.46 mg, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 14 h. No product was

observed.

Entry 9:

A similar literature procedure is followed [30]. Ethyladenine (0.49 g, 3.0 mmol) and *n*-BuLi (1.7 mL, 2.7 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min then reaction mixture was allowed to 0 °C and stirred for 30 min at this temperature then again cooled to -78 °C. Then, 1-methyl-1*H*-imidazole-carbaldehyde (0.330 mg, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 14 h. No product was observed.

Entry 10:

A similar literature procedure is followed [30]. 1-Methyl-1*H*-imidazole (0.20 g, 2.4 mmol) and *n*-BuLi (1.5 mL, 2.4 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then, ethyl-1-methyl-1*H*-imidazole-carboxylate (0.37 g, 2.4 mmol) 1-methyl-1H-imidazole (0.197 mg, 2.4 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

Entry 11:

A similar literature procedure is followed [30]. 1-Methyl-1*H*-imidazole (0.25 g, 3.0 mmol) and *n*-BuLi (1.88 mL, 3.0 mmol) in 1.6 M in hexane is stirred in THF at -78 °C for 45 min. Then, ethyl-1-methyl-1*H*-imidazole-carboxylate (0.46 g, 3.0 mmol) was added and reaction mixture was allowed to stir to the room temperature and continued stirring for 3 h. No product was observed.

3.24. General Procedure 5

Following a similar literature procedure [50] to a mixture of LDA, in dry THF and ethyl adenine in dry THF was added drop wise under nitrogen atmosphere at -78 °C. After 1 h a mixture of imidazole derivative in dry THF was added drop wise and continued for stirring for 1 h. then solvent was evaporated.

Entry 1:

Following a similar literature procedure [50], LDA was prepared with using freshly distilled diisopropylamine (0.88 mL, 6.28 mmol) in dry THF (5 mL) and *n*-BuLi (3.9 mL, 6.3 mmol) in a 1.6 M hexane solution under nitrogen atmosphere at -78 °C. To this mixture ethyladenine (200 mg, 1.23 mmol) was added drop wise at -78 °C, after 1 h mixture of ethyl-1-methyl-1*H*-imidazole-carboxylate (302 mg, 1.96 mmol) was added drop wise. Then it was stirred for 1 h more at this temperature then was allowed to warm to room temperature after 1 h, solvent was evaporated and was extracted by DCM three times and organic phase was then dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under high vacuum. No product was observed.

Entry 2:

Following a similar literature procedure [50], commercial LDA (3.05 mL, 3.05 mmol) in a 1 M solution in THF was added drop wise in a mixture of ethyladenine (100 mg, 0.60 mmol) in dry THF and stirred for 1 h at -78 °C. Then ethyl-1-methyl-1*H*-imidazole-carboxylate (150 mg, 0.98 mmol) was added dropwise. Then was stirred at 1 h more at this temperature then was allowed to warm to the room temperature after 1 h solvent was evaporated and was extracted with using DCM three times and organic phase was then dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under high vacuum. No product was observed.

Entry 3:

Following a similar literature procedure [50] commercial LDA (0.62 mL, 0.62 mmol) in a 1 M solution in THF was added drop wise in a mixture of ethyladenine (100 mg, 0.6 mmol) in dry THF and stirred for 1 h at -78 °C. Then, ethyl-1-methyl-1*H*-imidazole-carboxylate (150 mg, 0.98 mmol) was added drop wise. Then was stirred at 1 h more at this temperature then was allowed to warm to the room temperature after 1 h solvent was evaporated and was extracted with using DCM three times and organic phase was then dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under high vacuum. No product was observed.

Entry 4:

Following a similar literature procedure [50] commercial LDA (3.05 mL, 3.05 mmol) in a 1 M solution in THF was added drop wise in a mixture of ethyladenine (100 mg, 0.60 mmol) in dry THF and stirred for 1 h at -78 °C. Then, 1-methyl-1*H*-imidazole-carbaldehyde (108 mg, 0.98 mmol) was added drop wise. Then was stirred at 1 h more at this temperature then was allowed to warm to the room temperature after 1 h solvent was evaporated and was extracted with using DCM three times and organic phase was then dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under high vacuum. No product was observed.

Entry 5:

Based on the procedure, [50] commercial LDA (3.05 mL, 3.05 mmol) in a 1 M solution in THF was added drop wise in a mixture of ethyladenine (100 mg, 0.60 mmol) in dry THF and stirred for 1 h at -78 °C. Then iodine (108 mg, 0.98 mmol) was added drop wise. Then was stirred at 1 h more at this temperature then was allowed to warm to the room temperature after 1 h solvent was evaporated and was extracted with using DCM three times and organic phase was then dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under high vacuum. Resultant mixture was purified with flash column chromatography (DCM:MeOH = 20:1) on silica gel and obtained yellow solid (98 mg, 0.34 mmol). Yield is 56%.

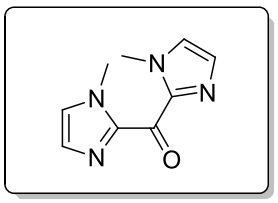
Entry 6:

Following a similar literature procedure [50] commercial LDA (1.22 mL, 1.22 mmol) in a 1 M solution in THF was added drop wise in a mixture of ethyladenine (40 mg, 0.25 mmol) in dry THF and stirred for 1 h at -78 °C. Then 2-(chloromethyl)-1-methyl-1H-imidazole (49 mg, 0.38 mmol) was added drop wise. Then was stirred at 1 h more at this temperature then was allowed to warm to the room temperature after 1 h solvent was evaporated and was extracted with using DCM three times and organic phase was then dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under high vacuum. No product was observed.

Entry 7:

Following a similar literature procedure [50] commercial LDA (0.46 mL, 0.46 mmol) in a 1 M solution in THF was added drop wise in a mixture of ethyladenine (47 mg, 0.29 mmol) in dry THF and stirred for 1 h at -78 °C. Then 2-(chloromethyl)-1-methyl-1H-imidazole (76 mg, 0.58 mmol) was added drop wise. Then was stirred at 1 h more at this temperature then was allowed to warm to the room temperature after 1 h solvent was evaporated and was extracted with using DCM three times and organic phase was then dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under high vacuum. No product was observed.

3.25. Synthesis of bis (1-methyl-imidazoyl)methanone



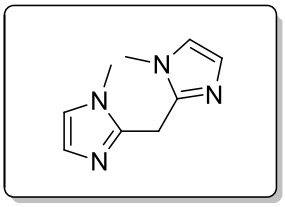
Based on literature procedure [42], to a mixture of 1-methyl-1H-imidazole (1.43 g, 16.0 mmol) and dry THF (21 mL) TMEDA (2.4 mL, 16

mmol) was added at -78 °C. Then *n*-BuLi (10.8 mL, 17.4 mmol) from a 1.6 M commercial solution in hexane was added drop wise then the solution was stirred for 1.5 h at 55 °C. Then *N*,*N*-dimethylcarbomylchloride (0.74 mL, 8.0 mmol) was added drop wise at -78 °C. Reaction mixture was heated to the room temperature and was stirred for 14 h. then a saturated solution of NH_4Cl (8.0 mL) was added. Solvent was removed in high vacuum, then aqueous layer was extracted with DCM three times and organic phases were combined and was dried with using anhydrous sodium sulfate, filtered and the solvent was evaporated with using rotary evaporator and obtained yellowish oil. Resultant mixture was crystallized with acetone/hexane to give 928 mg white solid. Yield is 65%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (s, 2H), 7.02 (s, 2H), 3.95 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.1, 143.0, 130.4, 126.7, 35.9.

2.26. Synthesis of bis(1-methylimidazoyl)methane

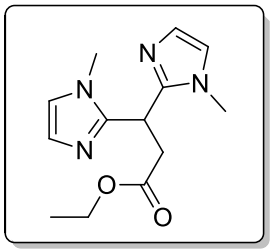


Based on the literature [42], hydrazinemonohydrate (2.25 mL, 46.5 mmol) and KOH (0.39 g, 7.0 mmol) were mixed with bis(1-methyl-1*H*-imidazoyl)methanone (0.37 g, 19 mmol) and this mixture was heated to 120 °C under nitrogen atmosphere for 2 h. Then reaction mixture was heated to 150 °C and was stirred for 3 h more under reflux condenser. The mixture was cooled to room temperature then the white solid was precipitated. DCM (3 mL) was added to this mixture and separated. The remaining light brown liquid was extracted with DCM three times and organic phases was dried with anhydrous magnesium sulfate and

filtered and solvent was removed with using rotary evaporator to obtain cream solid (304 mg). Yield is 88%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.83 (s, 1H), 6.71 (s, 1H), 4.16 (s, 1H), 3.59 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.5, 127.2, 121.5, 33.1, 26.9.

3.27. Synthesis of ethyl-bis(methylimidazol-2yl)propionate

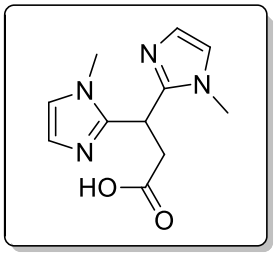


Based on the literature [43] To the solution of bis (1-methylimidazoyl)methane (0.176 g, 1.0 mmol) in THF, *n*-BuLi (0.63 mL, 1.01 mmol) from a 1.6 M commercial solution in hexane was added drop wise at -78 °C under nitrogen atmosphere. The mixture was stirred for 1 h at this temperature. Then ethyl bromo acetate (170 mg, 1.018 mmol) was added drop wise and the temperature was allowed to increase to the room temperature and stirred for 14 h resulted a yellowish white suspension. Water was added to this solution for quenching and solvents were removed under high vacuum. Then resulted mixture was extracted with ethyl acetate and water three times then organic phases dried with anhydrous sodium sulfate filtered and solvents were removed with using rotary evaporator resultant product was purified with flash column chromatography (EtOAc:MeOH = 9:1) on silica gel to give ethyl-bis(1-methyl1H-imidazol-2yl) propionate (159 mg).Yield is 61%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.89 (s, 2H), 6.70 (s, 2H), 5.07 (t, *J* =7.8 Hz. 1H), 4.08-4.03 (q, *J* =7.1 Hz. 2H), 3.44 (s, 6H), 3.30-3.21 (d, 2H), 1.12 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 144.9, 126.6, 122.2, 60.9, 33.0, 14.0, 36.1, 34.0.

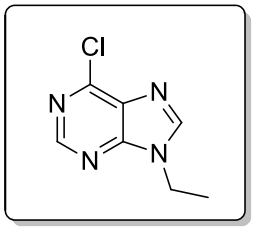
3.28. Synthesis of bis(methylimidazol-2-yl)propiolic acid



Based on the literature Procedure [43], to a mixture of ethyl-bis (methylimidazol-2-yl)propionate (157 mg, 0.597 mmol) and THF (1.5 mL) NaOH (22.7 mg, 0.57 mmol) solution in water (1.5 mL) was added then the mixture was stirred at room temperature for 3 h. Afterwards aqueous solution of HCl was added to this mixture. Solvents was evaporated under high vacuum and obtained a mixture of product and KCl as white solid. The mixture was dissolved in water and washed with DCM (5x2.5 mL). The aqueous phase was dried in vacuo and the residue was recrystallized with MeOH/Et_2O to obtain bis(methylimidazol-2-yl)propiolic acid hydrochloride as white solid. Yield is 85%.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.46 (s, 3H), 7.51-7.29 (m, 5H), 5.23 (s, 2H), 3.86 (s, 2H)

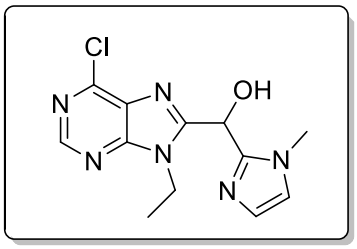
3.29. Synthesis of 9-ethyl-6-chloro-purine



Based on the literature procedure[54] 6-chloropurine (6.0 g, 0.039 mol) and potassium carbonate (5.4 g, 0.039 mmol) was mixed in DMF (90 mL) and then ethyl iodide (3.1 mL, 0.039 mmol) was added and stirred for 24 h at room temperature. The solvent was removed with using rotary evaporator. The resultant mixture was extracted with DCM and water three times and combined organic layers was dried with anhydrous magnesium sulfate filtered and solvent was evaporated under high vacuum to obtain yellow solid. The yellow solid was further purified by flash column chromatography (EtOAc:Hexane:MeOH =3:1:0.05) on silica gel and obtained white solid (3.0 g, 0.016 mol). Yield is 43%.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (s, 1H), 8.10 (s, 1H), 4.31 (q, *J* = 7.3 Hz, 2H), 1.53 (t, *J* = 7.3 Hz, 3H).

2.30. Synthesis of compound 18



Following a similar literature procedure [55], LDA (2.2 mL, 2.2 mmol) from a commercial 1 M solution in THF were added in 5 mL of dry THF at -78 ºC. 9-ethyl-6-chloropurin (0.364 g, 2.00 mmol) was added at this temperature and the mixture was stirred for 5 min. 1-methyl-1*H*-imidazole-2-

carbaldehyde (0.275 g, 2.00 mmol) was added to this mixture and stirred for 1 h at -78 ºC. Reaction mixture was warmed to 0 ºC and stirred for an additional 1 h. The mixture was then quenched with saturated NH_4Cl solution and extracted with DCM three times. Combined organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Product was the purified with column chromatography (EtOAc:Hexane:MeOH= 3:1:0.05) of yellowish white solid was obtained with a yield of 30%.

^{1}H NMR (400 MHz, D_2O) δ: 8.49 (s, 1H), 7.29-7.26 (m, 2H), 6.53 (s, 1H), 4.25 (q, *J* = 7.3 Hz, 2H), 3.42 (s, 3H), 1.19 (t, *J* = 7.3 Hz, 3H).

REFERENCES

1) Enger, E. D.; Kormelink, J. R.; Ross, F. C.;Smith, J. R. *Concepts in Biology.* **1994,** Wm. C. Brown Publishers,IA.
2) Kuah, E.; Toh, S.; Yee, J.; Ma, Q.; Gao, Z. Enzyme mimics: advances and applications. *Chem. Eur. J.* **2016,** *22*, 8404-8430.
3) Whitesides, G. M. Enzymes as Catalysts in Organic. *Aldrichimica Acta*, **1983** *16*, 627
4) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*.**1995**, VCH, Weinheim
5) Thompson, R. H. S. Classification and nomenclature of enzymes. *Science*, **1962,** *137*, 405-408.
6) Seo, M.; Blake, R. C.; Lee, Y. H. Cancer Drug Design and Discovery. **2014,** Academic Press is an imprint of Elsevier, London.
7) Polacek, N.; Mankin, A. S. The ribosomal peptidyl transferase center: structure, function, evolution, inhibition. *Crit. Rev. Biochem. Mol. Biol.*, **2005,** *40*, 285-311.
8) Sieber, S. A.; Böttcher, T.; Staub, I.; Orth, R. 9.17-Small Molecules as Versatile Tools for Activity-Based Protein Profiling Experiments. *Elsevier* **2010,** *9*, 629-674.
9) Walker, V. Ammonia Metabolism and Hyperammonemic Disorders. Advances in clinical chemistry. *Elsevier*, **2014,** *67*, 73-150.
10) Tomasik, P., & Horton, D. (2012). Enzymatic conversions of starch. *Adv. Carbohydr. Chem. Biochem.*, **2012,** *68*, 59-436.
11) Doherty, A. J., & Suh, S. W. Structural and mechanistic conservation in DNA ligases. *Nucleic Acids Res*. **2000,** *28*, 4051-4058.
12) Johannes, T.; Simurdiak, M. R.; Zhao H. *Encyclopedia of Chemical Processing.* **2006,** Taylor & Francis, New York.
13) Singla, R. K. Artificial Enzymes. *WebmedCentral* Pharmaceutical Sciences **2012,** *3* WMC003666.

14) Schmidt, R. J. Industrial catalytic processes-phenol production. *Elsevier* **2005,** *285,* 89-103.

15) Chatterjee, S.; Paine, K. T. Oxygenative Aromatic Ring Cleavage of 2-Aminophenol with Dioxygen Catalyzed by a Nonheme Iron Complex: Catalytic Functional Model of 2-Aminophenol Dioxygenases. *Inorg. Chem.* **2015,** *54,* 1720-1727.

16) Lin, G.; Reid, G.; Bugg, T. D. H. Extradiol Oxidative Cleavage of Catechols by Ferrous and Ferric Complexes of 1,4,7-Triazacyclononane: Insight into the Mechanism of the Extradiol Catechol Dioxygenases. *J. Am. Chem. Soc.* **2001,** *123,* 5030-5039

17) Stuart, M. L.; Gavin, J. H.; Matthew, L. C. Catalytic constructive deoxygenation of lignin-derived phenols: new C C bond formation processes from imidazole-sulfonates and ether cleavage reactions. *Chem comm*. **2014,** *50*, 11511-11513.

18) Wolgel, S. A.; Dege J. E.; Perkins-Olson, P. E.; Jaurez-Garcia, C. H.; Crawford, R. L.; Münck, E.; Lipscomb, J. D. Purification and Characterization of Protocatechuate 2,3-Dioxygenase from Bacillus macerans: a New Extradiol Catecholic Dioxygenase. *J. Bacteriol*., **1993,** *175*, 4414-4426.

19) Bruijnincx,P. C. A.; Lutz, M.; Spek, L. A.; Hagen, R. W.; Weckhuysen, M. B.; Koten, G.; Gebbink, K. M. J. R. Modeling the 2-His-1-Carboxylate Facial Triad: Iron-Catecholato Complexes as Structural and Functional Models of the Extradiol Cleaving Dioxygenases. *J. Am. Chem. Soc.* **2006,** *129*, 2275-2286.

20) Folkertsma, E.; Waard, E. F.; Korpershoek, G.; Arnoldus Schaik, J. A.; Mirón, S. N.; Borrmann, M.; Nijsse, S.; Moelands, M. A. H.; Lutz, M.; Otte, M.; Moret, M. E.; Gebbink, K. M. J. R. Mimicry of the 2-His-1-Carboxylate Facial Triad Using Bulky N,N,O-Ligands: Non-Heme Iron Complexes Featuring a Single Facial Ligand and Easily Exchangeable Co-Ligands. *Eur. J. Inorg. Chem.* **2016,** 1319–1332.

21) Bugg, D. H. T.; Lin, G. Solving the riddle of the intradiol and extradiol catechol dioxygenases: how do enzymes control hydroperoxide rearrangements? *Chem. Comm*. **2001,** 941–952.

22) Christian, G. J.; Ye, S.; Neese, F. Oxygen activation in extradiol catecholate dioxygenases–a density functional study. *Chem. Sci*. **2012**, *3*, 1600-1611.

23) Feller, D.; Davidson, E. R., Basis sets for ab initio molecular orbital calculations and intermolecular interactions. **1990,** *Reviews in Computational Chemistry, Volume 1*, 1-43.

24) Büyüktemiz, M.; Dede, Y. Mimicking the Secondary Sphere of Homoprotocatechuate Dioxygenase (HPCD) Enzyme Active Site; A Theoretical Study. *J. Turk. Chem. Soc.* **2015,** *2*, 105-108.

25) Bruijnincx,P. C. A.; Lutz, M.; Spek, L. A.; Hagen, R. W.;Koten, G.;Gebbink, K. J. M. R. Iron(III)-Catecholato Complexes as Structural and Functional Models of the Intradiol-Cleaving Catechol Dioxygenases. *Inorg. Chem.* **2007,** *46*, 8391-8402.

26) Takeshi, S.; Yuichi, I.; "Preperation of 2-haloimidazoles from 1.1'-carbonyldiimidazoles" JP **2008**/037801

27) Laxer, A.; Major, D. T.; Gottlieb, H. E.; Fischer, B. ($^{15}N_5$)-Labeled adenine derivatives: synthesis and studies of tautomerism by ^{15}N NMR spectroscopy and theoretical calculations. *J. Org. Chem.,* **2001,** *66*, 5463-5481.

28) Serpell, C. J.; Kilah, N. L.; Costa, P. J.; Félix, V.; Beer, P. D. Halogen bond anion templated assembly of an imidazolium pseudorotaxane. *Angew. Chem. Int. Ed.*, **2010,** *122*, 5450-5454.

29) Koeneman, M.; Guthman, H.; Bach, T. "Macrocyclic nitrogen compounds and their use in optical storage media and org. semiconductors." WO **2008**/052814.

30) Figueiredo, R. M.; Thoret, S.; Dubois, J. H. C. Palladium-Catalyzed Intramolecular Arylation of N-Benzyl-2-iodoimidazoles: A Facile and Rapid Access to 5*H*-Imidazo[2,1-a]isoindoles. *Synthesis,* **2007,** *4*, 0529-0540.

31) Zang, Y.; Wu, X. M.; Zheng, Z. Y.; Song, H. B.; Liu, Q. X. 1-Benzylimidazolium hexafluorophosphate–1-benzylimidazole. *Acta. Cryst.*, **2008,** *64*, o478-o478.

32) Baker, A. E.; Marchal, E.; Lund, K. L. A.; Thompson, A. (2014). The use of tin (IV) chloride to selectively cleave benzyl esters over benzyl ethers and benzyl amines. *Canadian Journal of Chemistry*, **2014,** *92*, 1175-1185.

33) Nakano, A.; Hayashi, D.; Hirama, M.; Yamashita, S.; Hayashi, Y. Total synthesis of avermectin B 1a revisited. *J. Antibiot.*, **2016,** *69*, 31.

34) Pei, J.; Lei, Dou, J. "Compound with branching alkyl-chains, method for preparing the same, and use thereof in photoelectric device**."** EP **2013**/2698835 A1.

35) Cuerva, M. J. C.; Justica, J. G. L.; Oltra, E. J. F. "Deuterated tapazole and derivatives, preparation method therefor and use of same." WO **2009**/074703 A1

36) Dervan, B. P.; Gottesfeld, J. M. "Complex formation between dsDNA and oligomer of cyclic heterocycles." US **1996**/5998140A.

37) Redwan, N. I.; Bliman, D.; Tokugawa M.; Lawson, C.; Grøtli, M. Synthesis and photophysical characterization of 1- and 4-(purinyl) triazoles. *Tetrahedron*, **2013,** *69*, 8857-8864.

38) Villar, O. N.;Saldivar, U. V. M.; Pérez, F. B.; Alamo, F. M.; Real, J. A.; Esparza, M. R. A new N 6 hexadentate ligand and a novel heptacoordinated N_6O-type Fe (III) compounds: Synthesis, characterization and structure of [Fe (dimpyen)(OH)]$(A)_2$ (A= PF_6^- or ClO_4^-). *Inorganica Chim. Acta* **2011,** *375*,213-219.

39) Pilarski, B. A New Method for *N*-Alkylation of Imidazoles and Benzimidazoles. *Liebigs. Ann. Chem.* **1983,** 1078-1080.

40) Vernejoul, F.; Debin, A.; Drocourt, D.; Perouzel, E.; Tiraby, G.; Lioux, T. "Conjugated tlr7 and/or tlr8 and tlr2 agonists." US **2014**/0141033 A1.

41) Wang, Q. J; Cheng, W. G.; Sun, J.; Shi, T. Y.; Zhanga, P. X.; Zhang, S. J. Efficient fixation of CO_2 into organic carbonates catalyzed by 2-hydroxymethyl-functionalized ionic liquids. *RSC Adv.* **2014,** 4, 2360-2367.

42) Elgafi, S.; Field, L. D.; Messerle, B. A.; Hambley, T. W.; Turner, P. (1997). Synthesis of novel ruthenium complexes containing bidentate imidazole-based ligands. *J. Chem. Soc., Dalton Trans.,* **1997,** 2341-2346.

43) Bruijnincx, P. C.; Lutz, M.; Spek, A. L.; Faassen, E. E.; Weckhuysen, B. M.; Koten, G.; Gebbink, R. J. Bis (1-methylimidazol-2-yl) propionates and Bis (1-methylbenzimidazol-2-yl)-propionates: A New Family of Biomimetic N, N, O Ligands–Synthesis, Structures and Cu (II) Coordination Complexes. *Eur. J. Inorg. Chem.,* **2005**, 779-787.

44) Brain, T. C.; Thoma, G.; Sung, J. M. "Pyrrolopyrimidine compounds and their uses." WO **2007,** 140222 A2.

45) Liao, C.; Zhu, X.; Sun, X. G.; Dai, S. Investigation of carbon-2 substituted imidazoles and their corresponding ionic liquids. *Tetrahedron Lett.* **2011,** 52, 5308-5310.

46) Neeb, M.; Hohn, C.; Ehrmann, F. R.; Härtsch, A.; Heine, A.; Diederich, F.; Klebe, G. Occupying a flat subpocket in a tRNA-modifying enzyme with ordered or disordered side chains: Favorable or unfavorable for binding?. **2016,** Bioorganic & medicinal chemistry. *Bioorganic Med. Chem., 24,* 4900-4910.

47) Zhu, J.; Wu, C. F.; Li, X.; Wu, G. S.; Xie, S.; Hu, Q. N.; Deng, Z.; Zhu,X. M.; Luo, H. R.; Hong, X. Synthesis, biological evaluation and molecular modeling of substituted 2-aminobenzimidazoles as novel inhibitors of acetylcholinesterase and butyrylcholinesterase. *Bioorganic Med. Chem.,* **2013,** *21, 4218-4224.*

48) Wang, M.; Zhang, Z.; Xie, F.; Zhang, W. Cu-catalyzed amidation of halogenated imidazoles. *Chem. Comm.* **2014,** *50,* 3163-3165.

49) Kendall, A. J.; Salazar, C. A.; Martino, P. F.; Tyler, D. R; Direct Conversion of Phosphonates to Phosphine Oxides: An Improved Synthetic Route to Phosphines Including the First Synthesis of Methyl JohnPhos. *Organometallics*, **2014,** *33*, 6171-6178.

50) Gao, C.; Li, B;, Zhang, B.; Sun, Q.; Li, L.; Li, X.; Chen, C.; Tan, C.; Liu, H.; Jiang, Y. Synthesis and biological evaluation of benzimidazole acridine

derivatives as potential DNA-binding and apoptosis-inducing agents. *Bioorg. Med. Chem.*, **2015,** *23*, 1800-1807.

51) Volpini, R.; Costanzi, S.; Lambertucci, C.; Vittori, S.; Martini, C.; Trincavelli, M. L.; Cristalli, G. 2-and 8-alkynyl-9-ethyladenines: Synthesis and biological activity at human and rat adenosine receptors. *Purinergic Signal.*, **2005,** *1*, 173.

52) Röttger, K.; Marroux, H. J.; Chemin, A. F.; Elsdon, E.; Oliver, T. A.; Street, S. T.; Roberts, G. M. (2017). Is UV-Induced Electron-Driven Proton Transfer Active in a Chemically Modified A· T DNA Base Pair? *J. Phys. Chem. B* **2017,** *121*, 4448-4455.

53) Kamimura, A.; Komatsu, H.; Moriyama, T.; Nozaki, Y. Sub-stoichiometric oxidation of benzylic alcohols with commercially available activated MnO 2 under oxygen atmosphere: a green modification of the benzylic oxidation. *Tetrahedron*, **2013,** *69*, 5968-5972.

54) Celik, G. D.; Disli, A.; Oner, Y.; Acik, L. Synthesis of some novel amino and thiotetrazole purine derivatives and investigation of their antimicrobial activity and DNA interactions. *Med. Chem. Res.* **2013,** *22*, 1470-1479.

55) Tobrmanová, M.; Tobrman, T.; Dvořák, D. Pd-catalyzed allylic substitution of purin-8-yl (allyl) acetate: Route to (E)-alkenylpurines. *Collect Czechoslov Chem Commun.* **2011,** *76*, 311-326.

APPENDIX A

NMR DATA

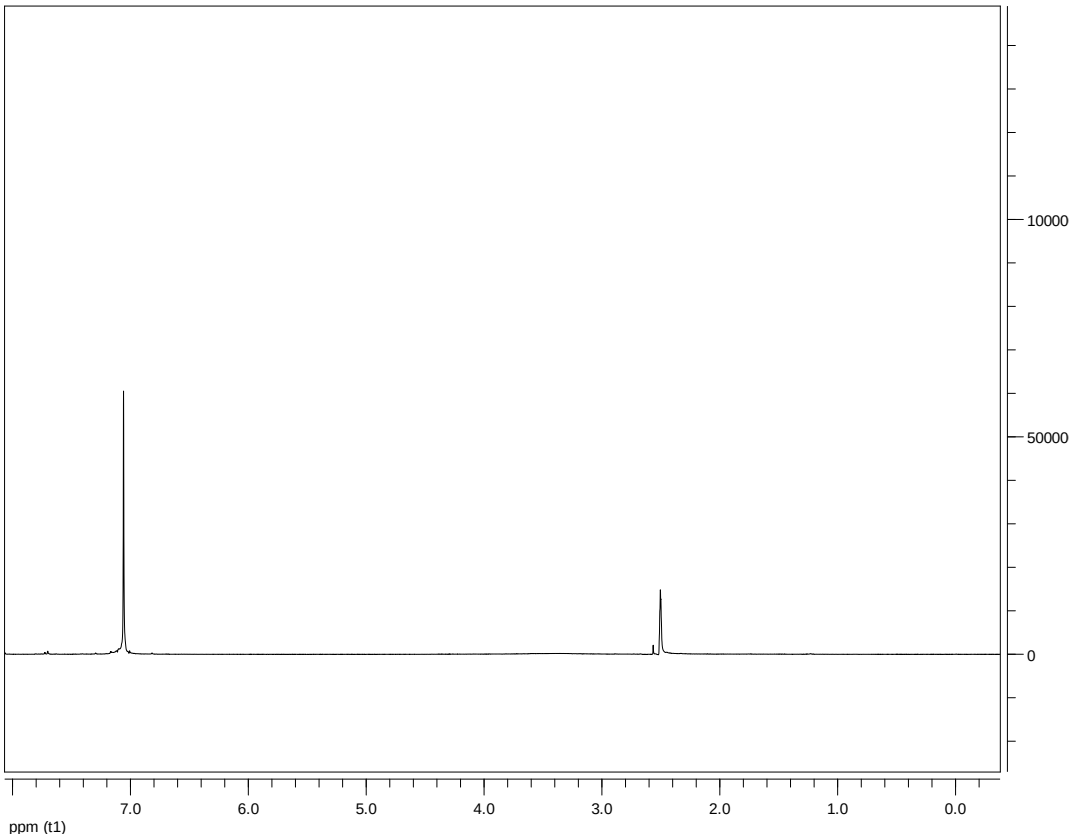


Figure A 1. ^{1}H NMR spectrum of 2-bromo-1H-imidazole in DMSO.

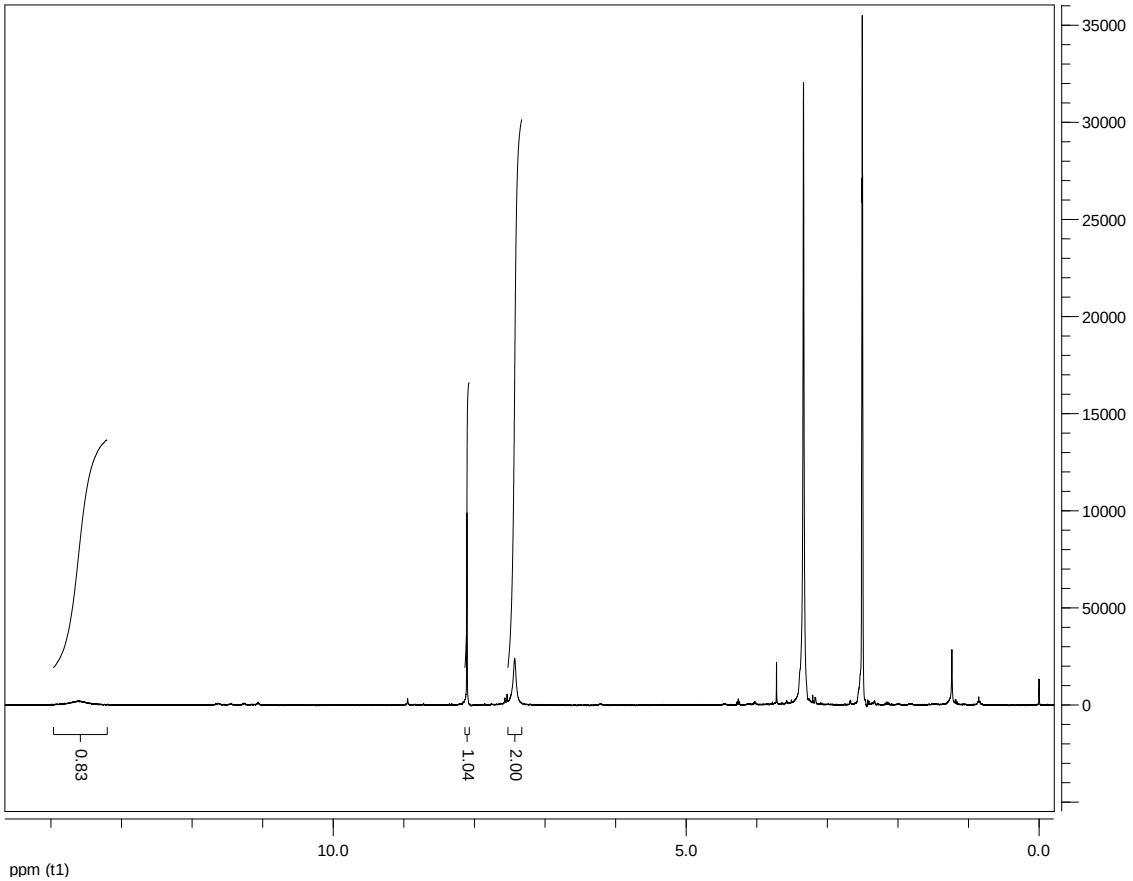


Figure A 2. ^{1}H NMR spectrum of 8-bromo-adenine in DMSO.

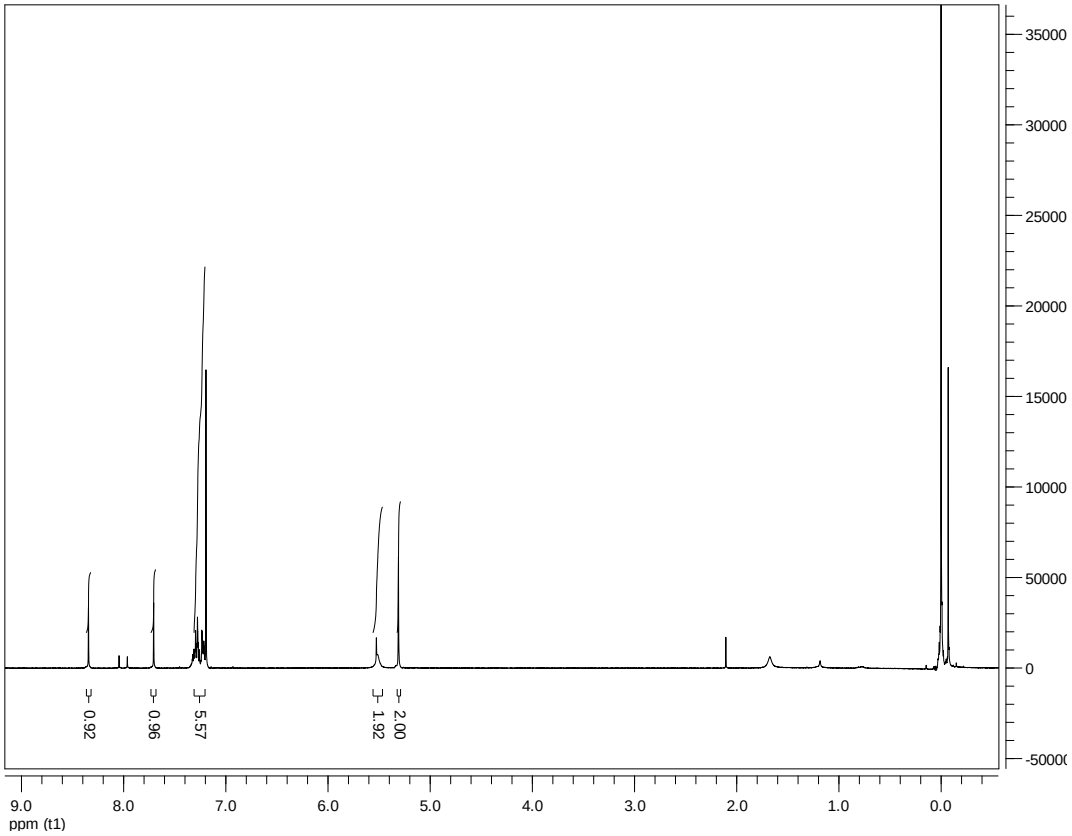


Figure A 3. ^{1}H NMR spectrum of *N*-9-benzyl-adenine in $CDCl_3$.

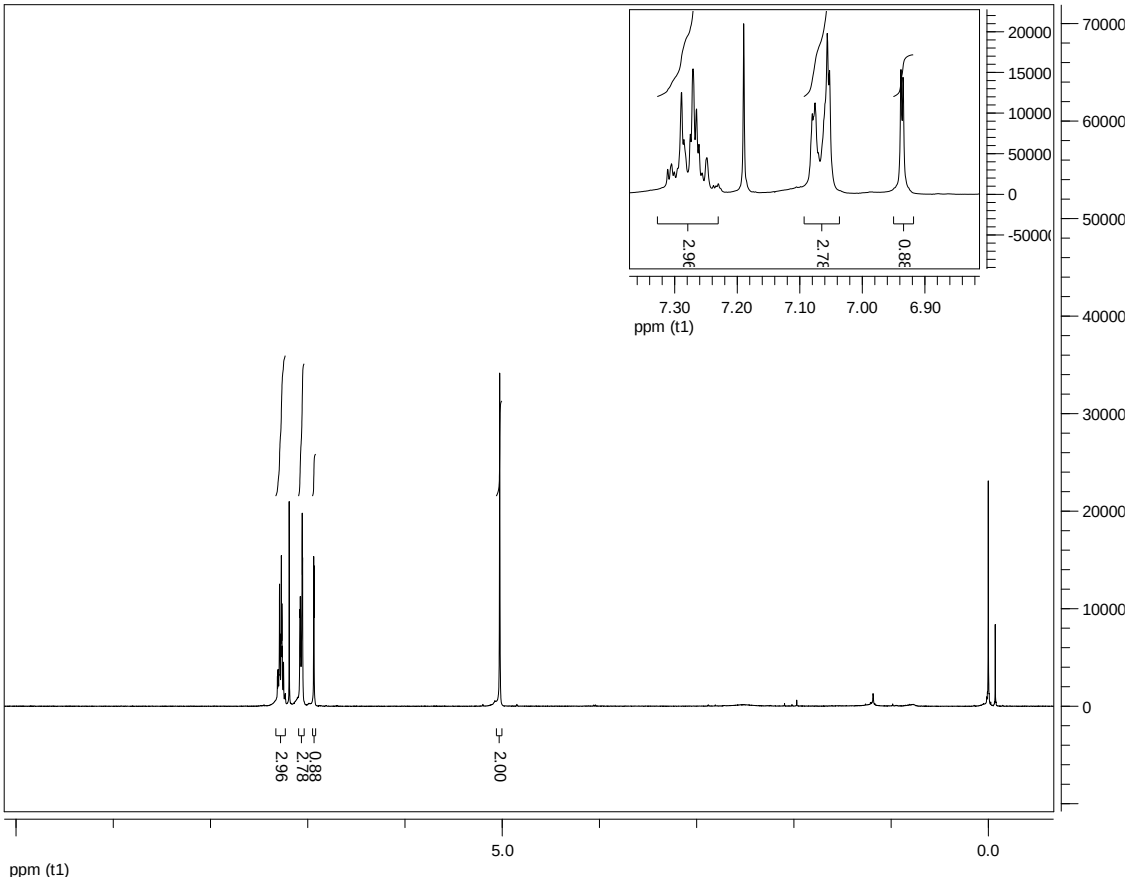


Figure A 4. ^{1}H NMR spectrum of 1-benzyl-2-Iodo-1*H*-imidazole in $CDCl_3$.

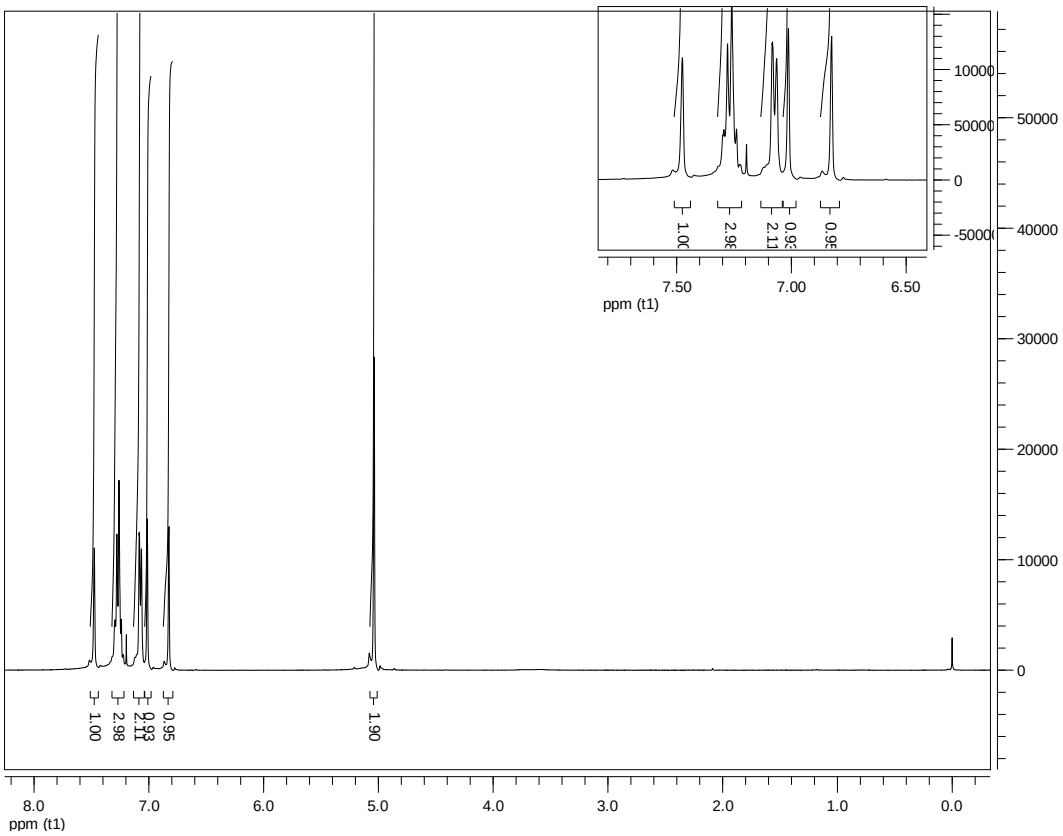


Figure A 5. ^{1}H NMR spectrum of 1-benzylimidazole in $CDCl_3$.

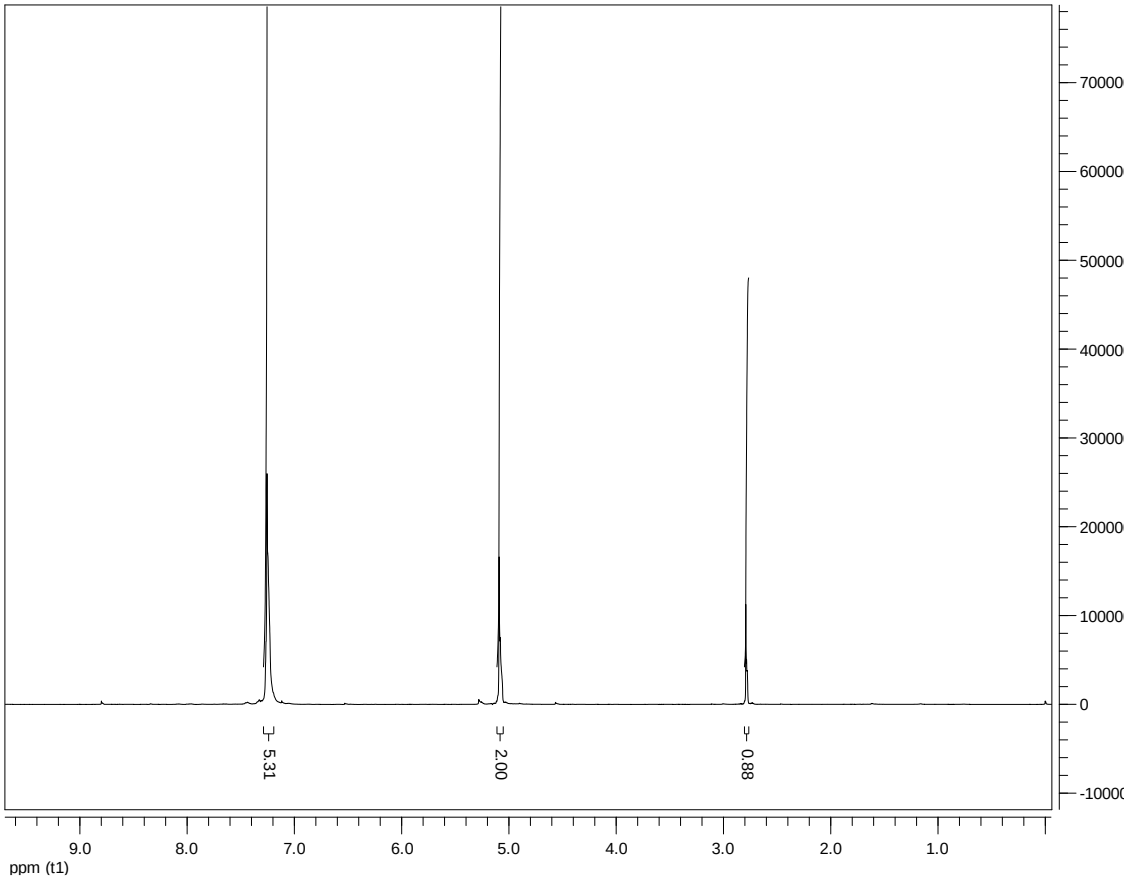


Figure A 6. ^{1}H NMR spectrum of benzyl propiolate in $CDCl_3$.

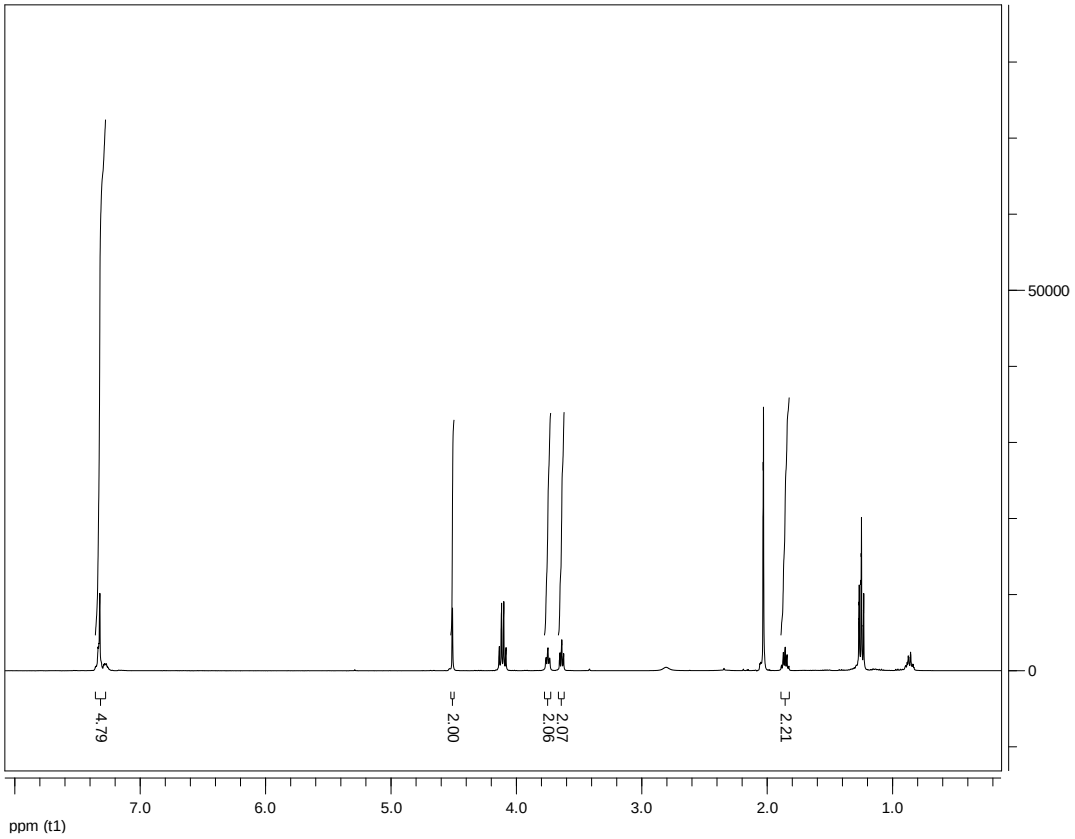


Figure A 7. ^{1}H NMR spectrum of 3-benzyloxypropanol in $CDCl_3$.

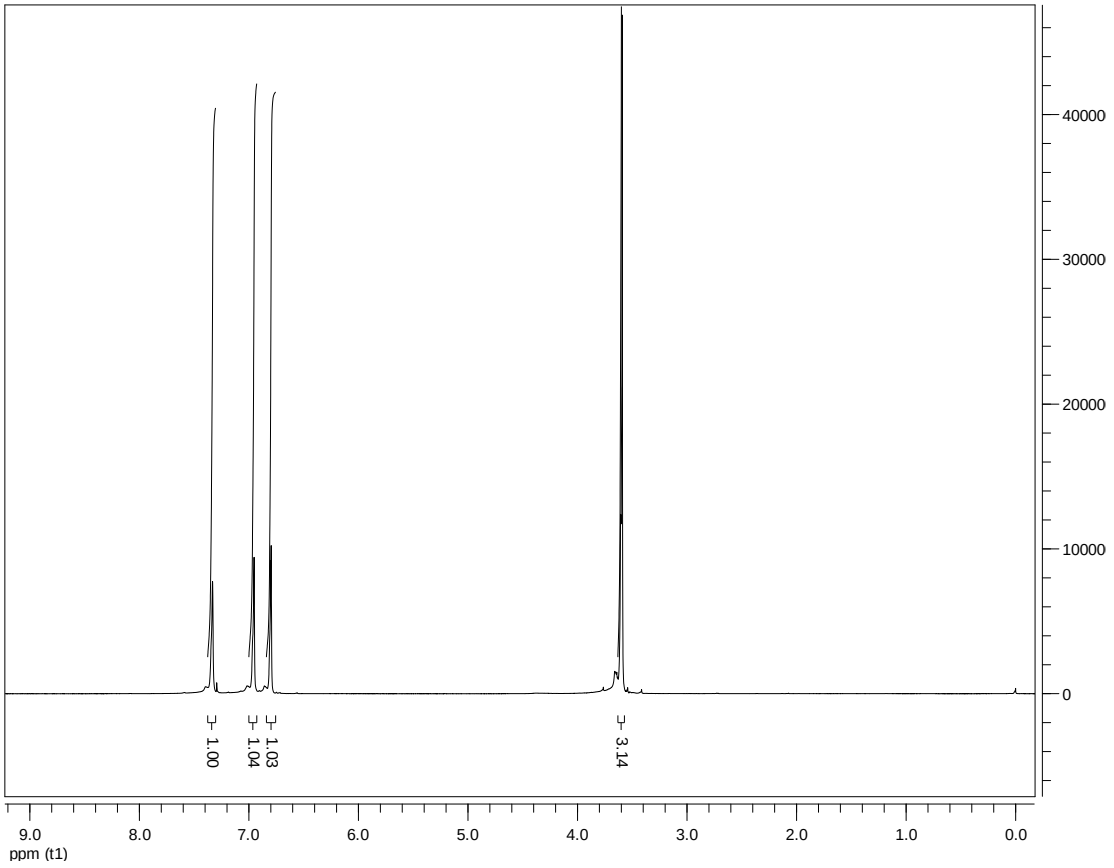


Figure A 8. ^{1}H NMR spectrum of 1-methylimidazole in $CDCl_3$.

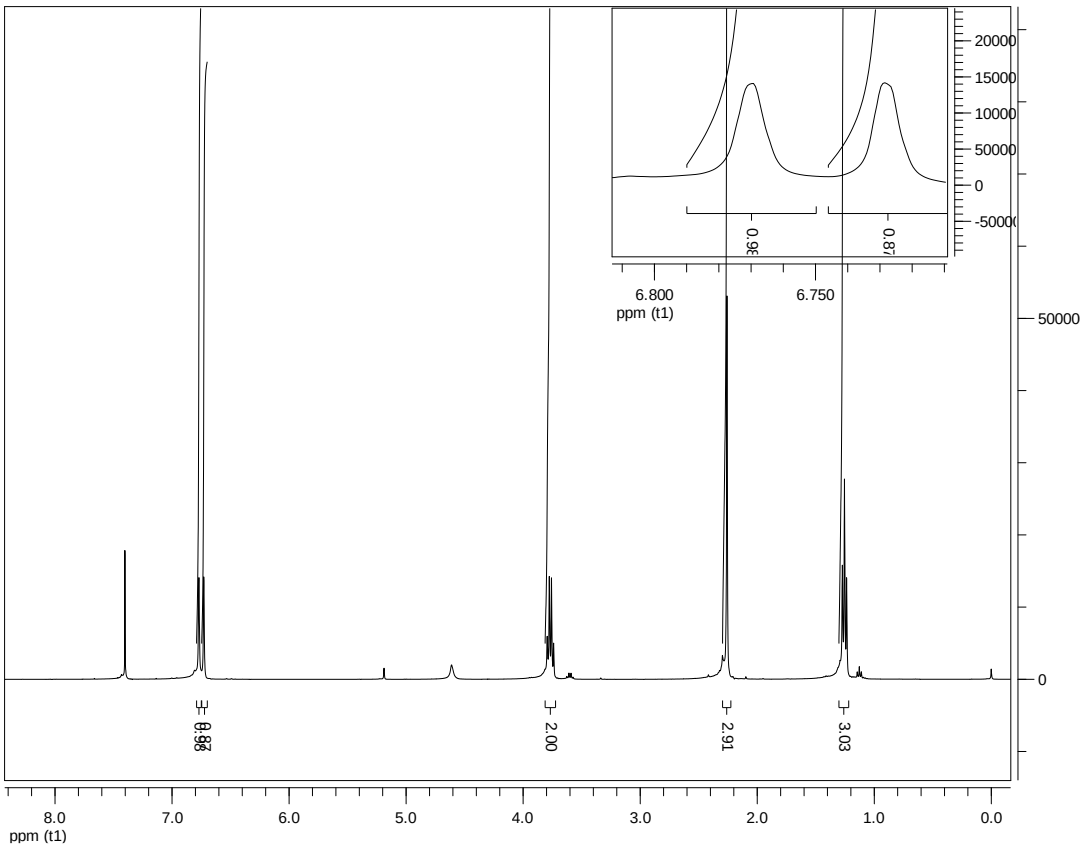


Figure A 9. ^{1}H NMR spectrum of ethyl 1-methyl-1*H*-imidazole-2-carboxylate in $CDCl_3$.

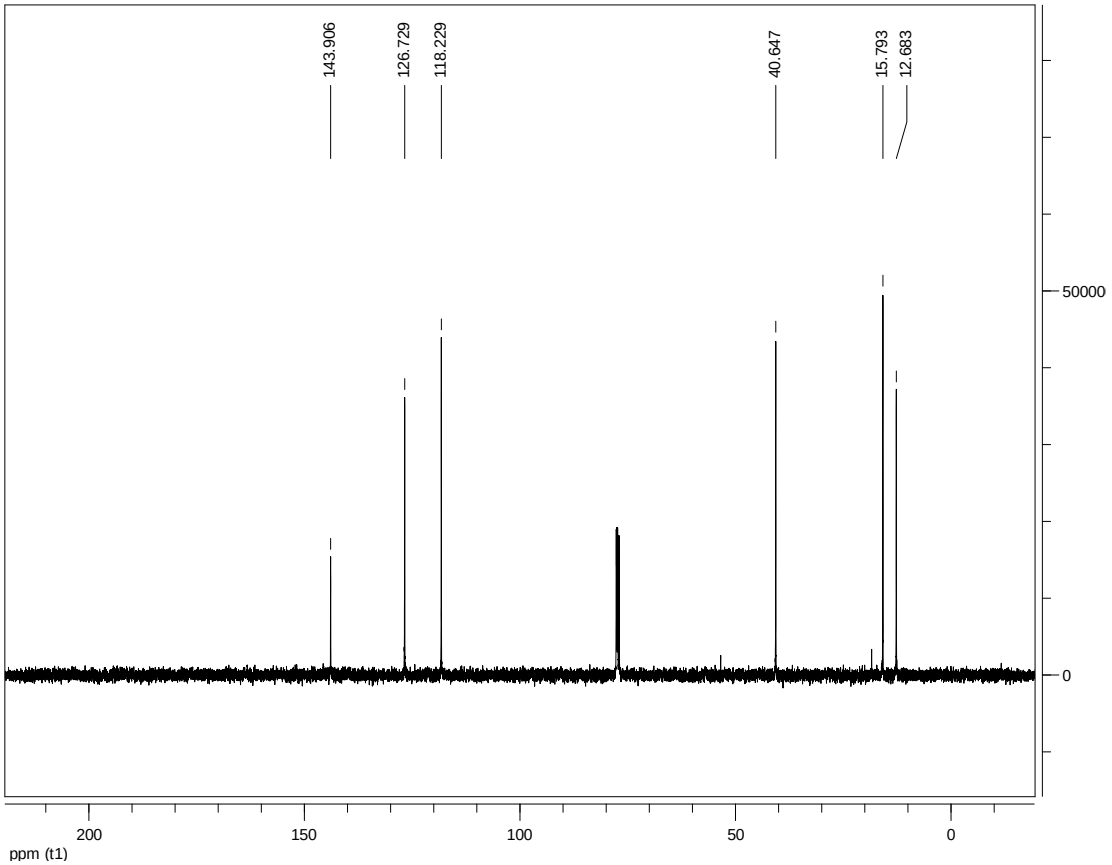


Figure A 10. ^{13}C NMR spectrum of ethyl 1-methyl-1*H*-imidazole-2-carboxylate in $CDCl_3$.

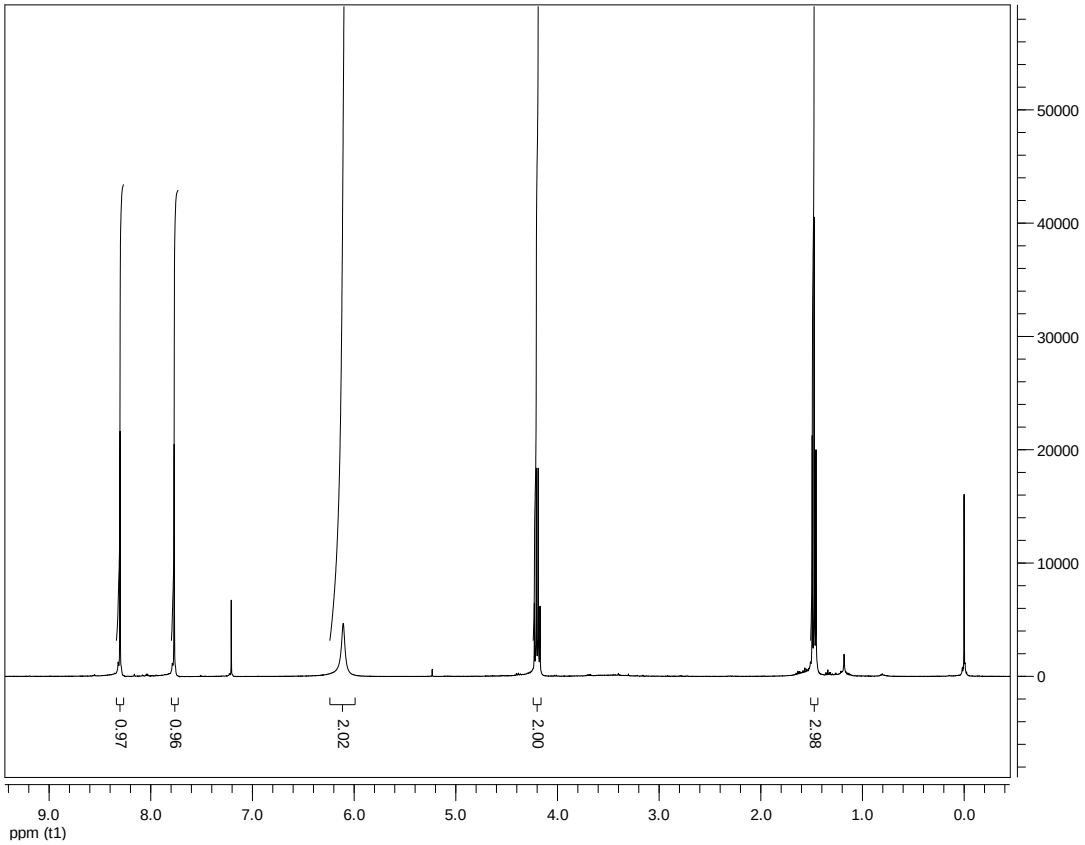


Figure A 11. ^{1}H NMR spectrum of 9-ethyladenine in $CDCl_3$.

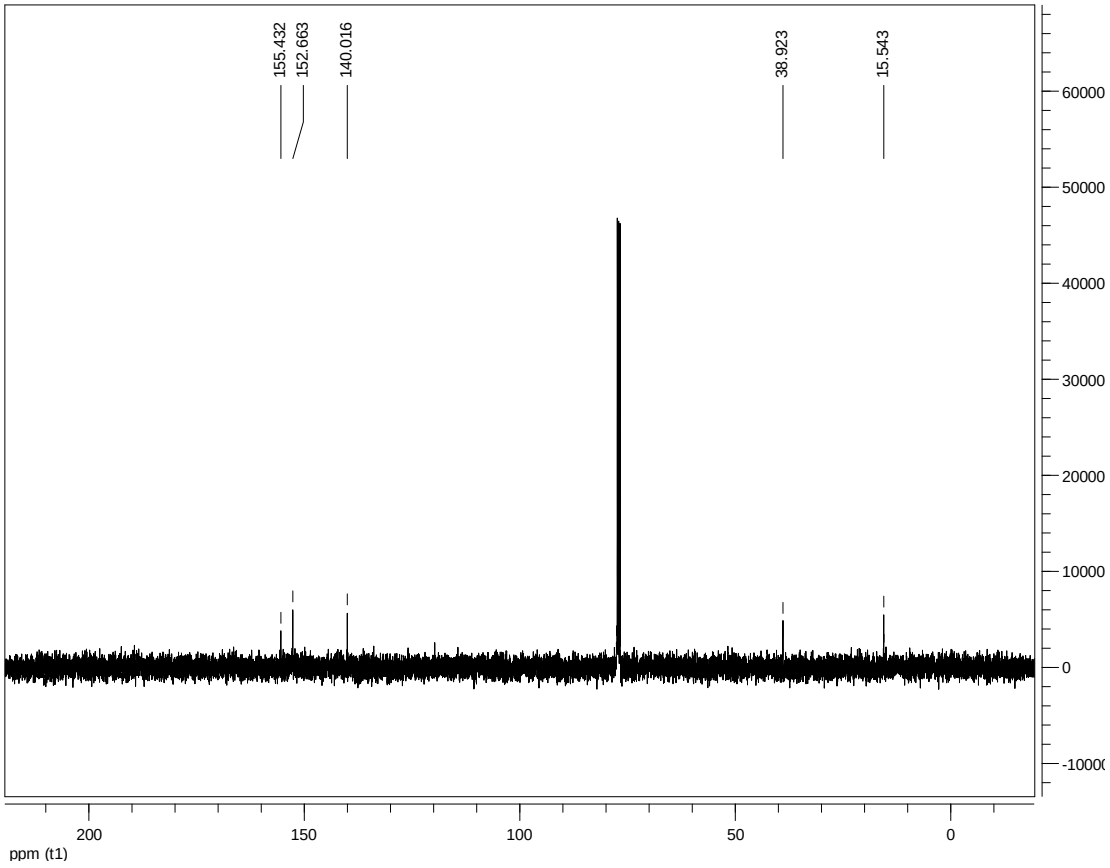


Figure A 12. ^{13}C NMR spectrum of 9-ethyladenine in $CDCl_3$.

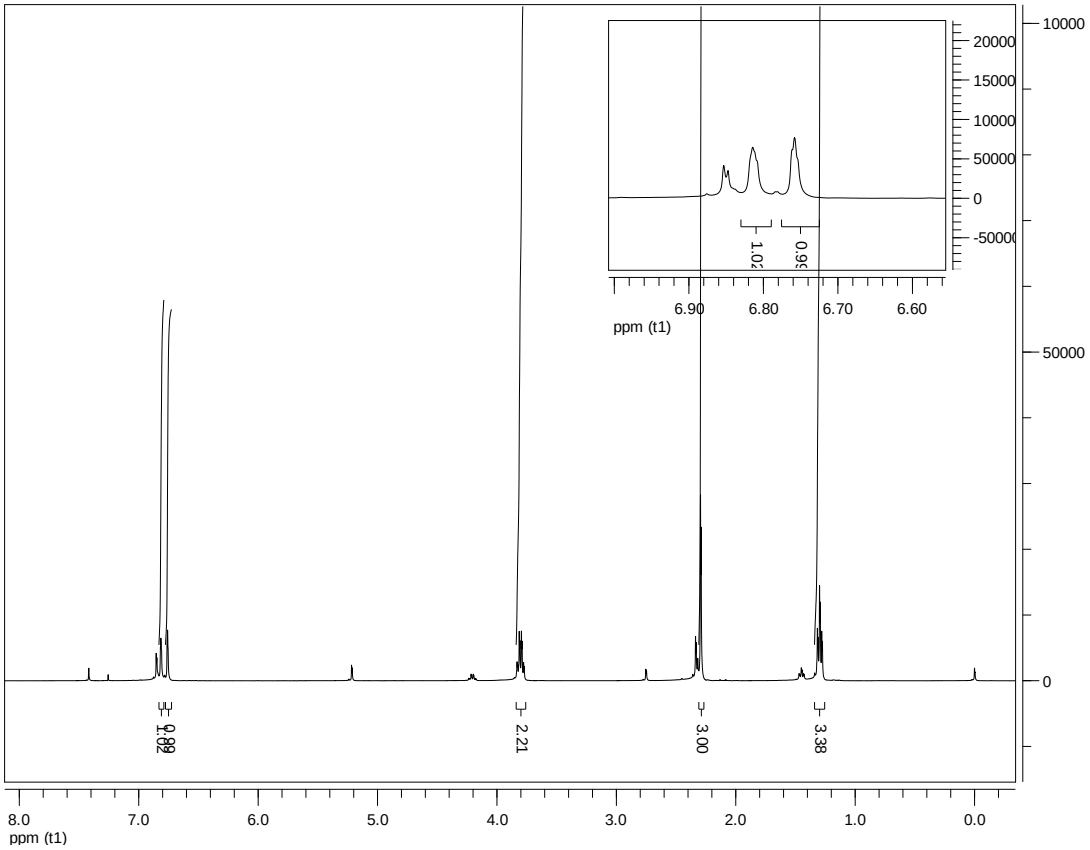


Figure A 13. ^{1}H NMR spectrum of 1-ethyl-2-methyl-1*H*-imidazole in $CDCl_3$.

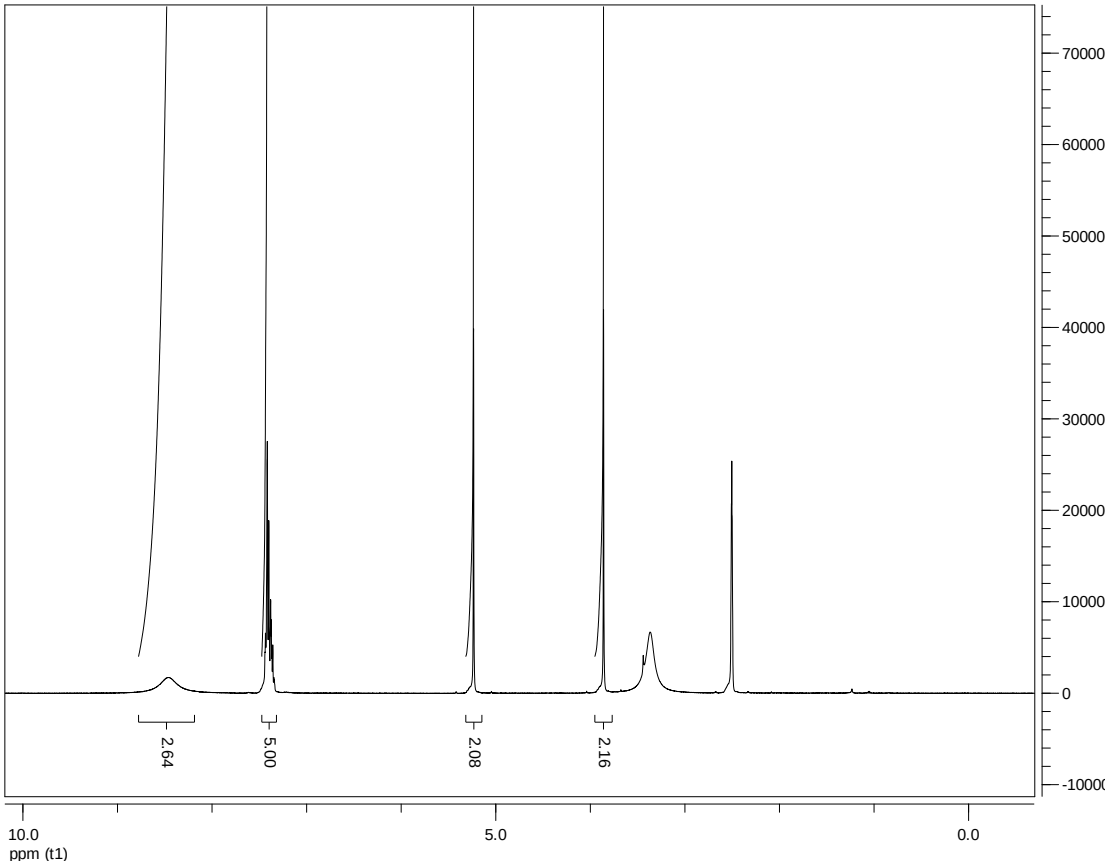


Figure A 14. ^{1}H NMR spectrum of glycine benzyl ester in DMSO.

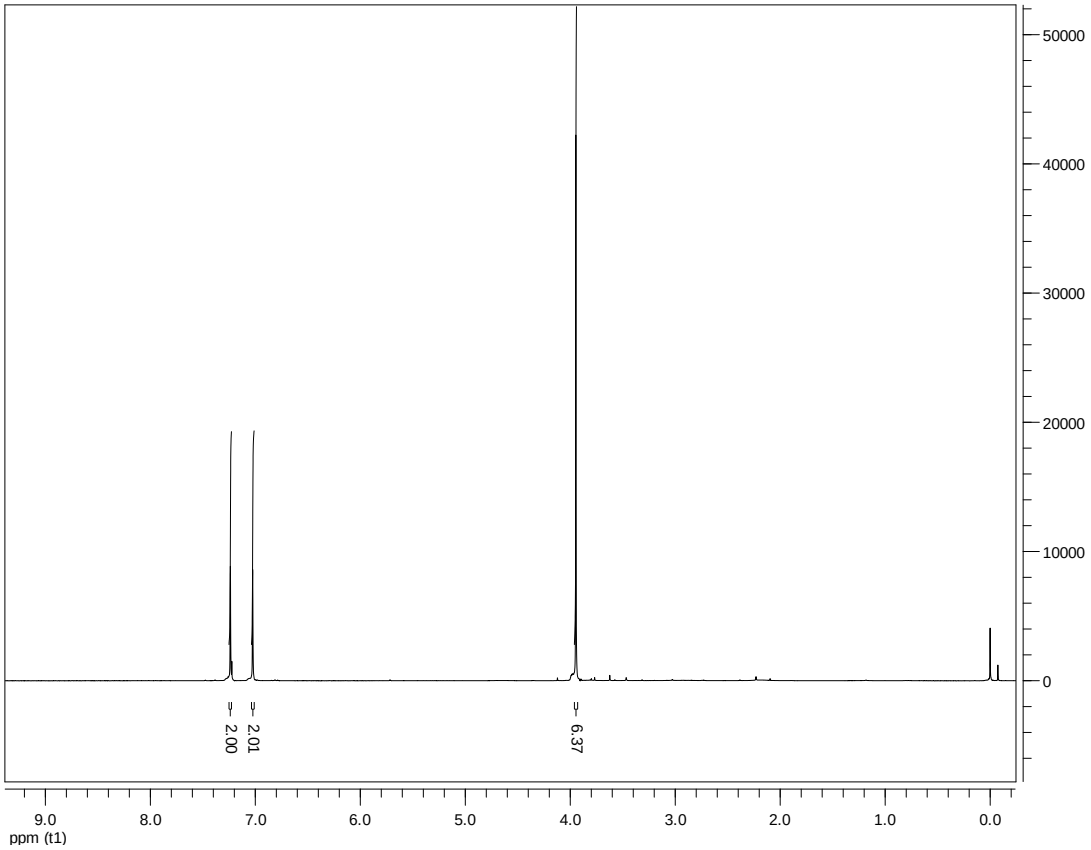


Figure A 15. ^{1}H NMR spectrum of bis (1-methyl-imidazoyl)methanone in $CDCl_3$.

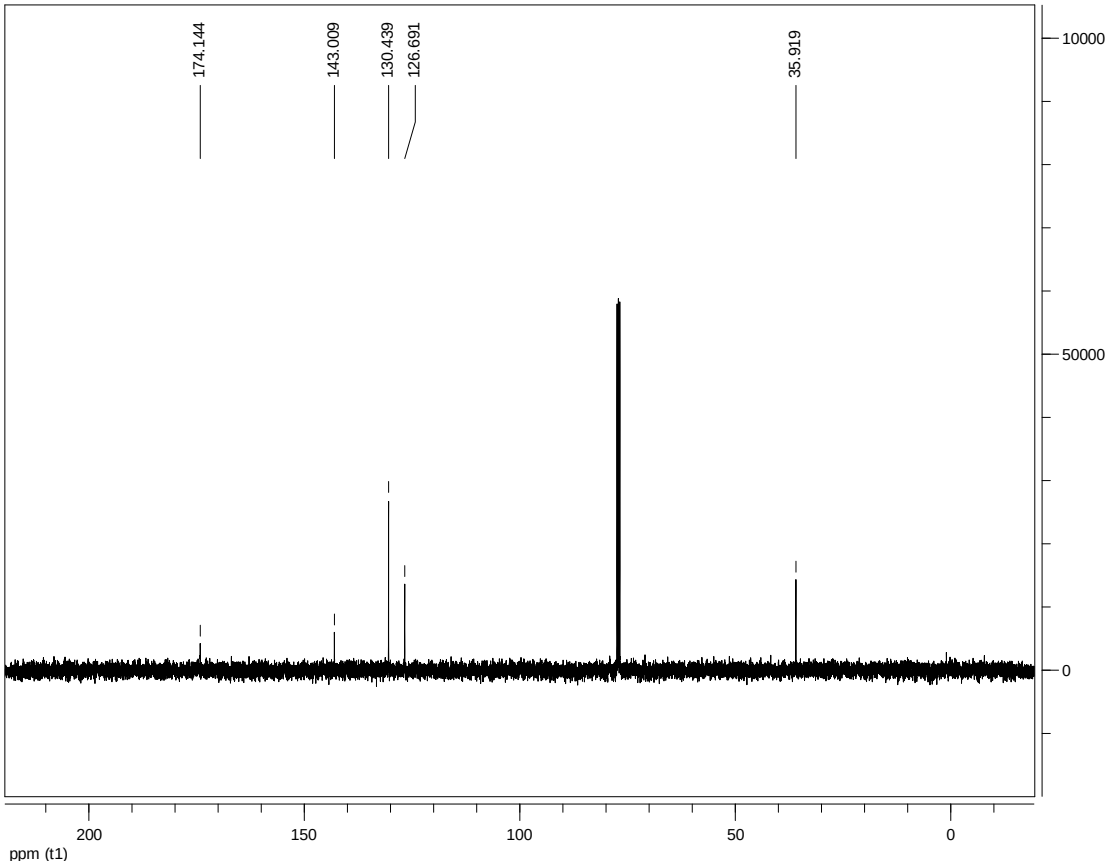


Figure A 16. ^{13}C NMR spectrum of bis (1-methyl-imidazoyl)methanone in $CDCl_3$.

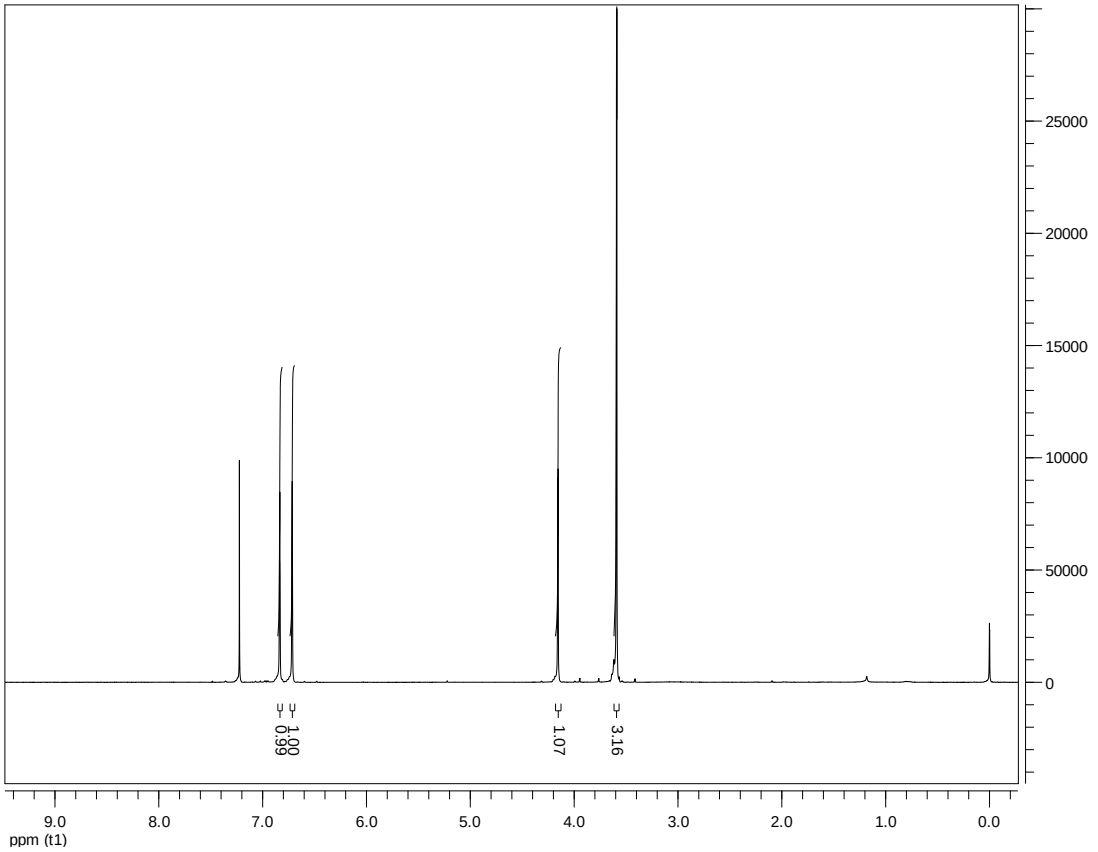


Figure A 17. ^{1}H NMR spectrum of bis(1-methylimidazoyl)methane in $CDCl_3$.

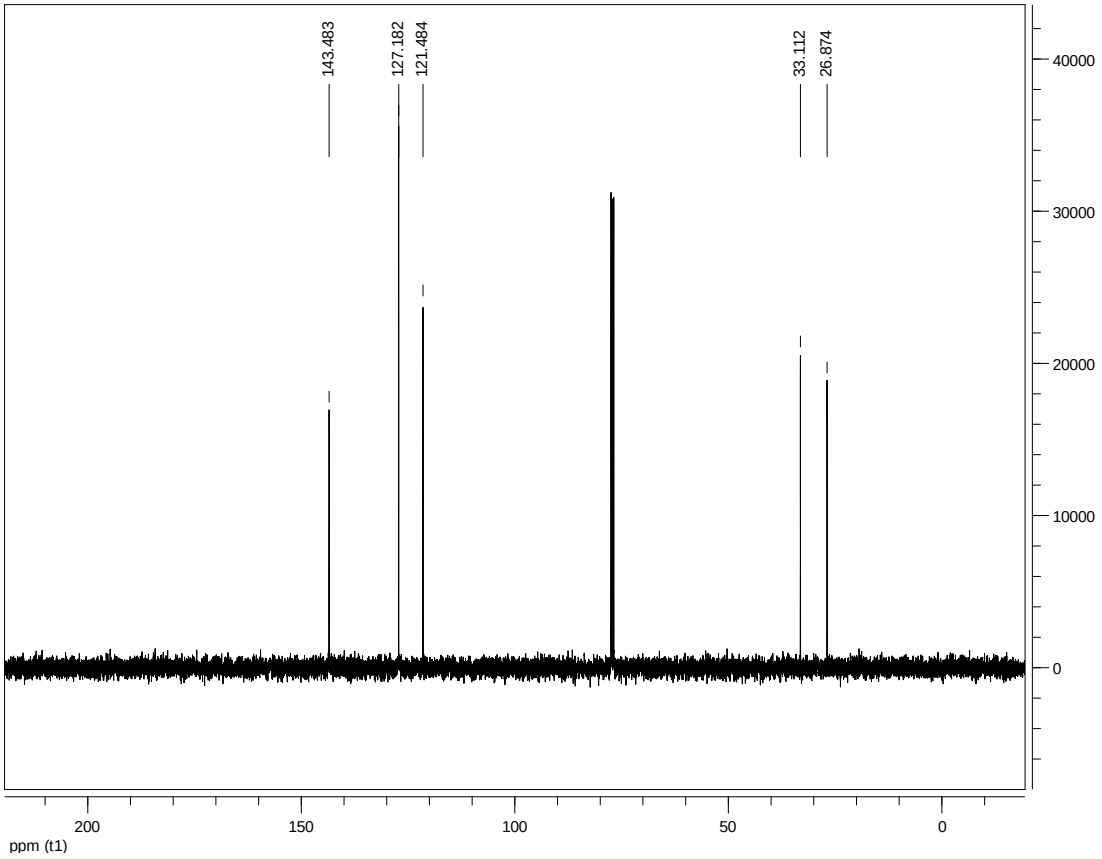


Figure A 18. ^{13}C NMR spectrum of bis(1-methylimidazoyl)methane in $CDCl_3$.

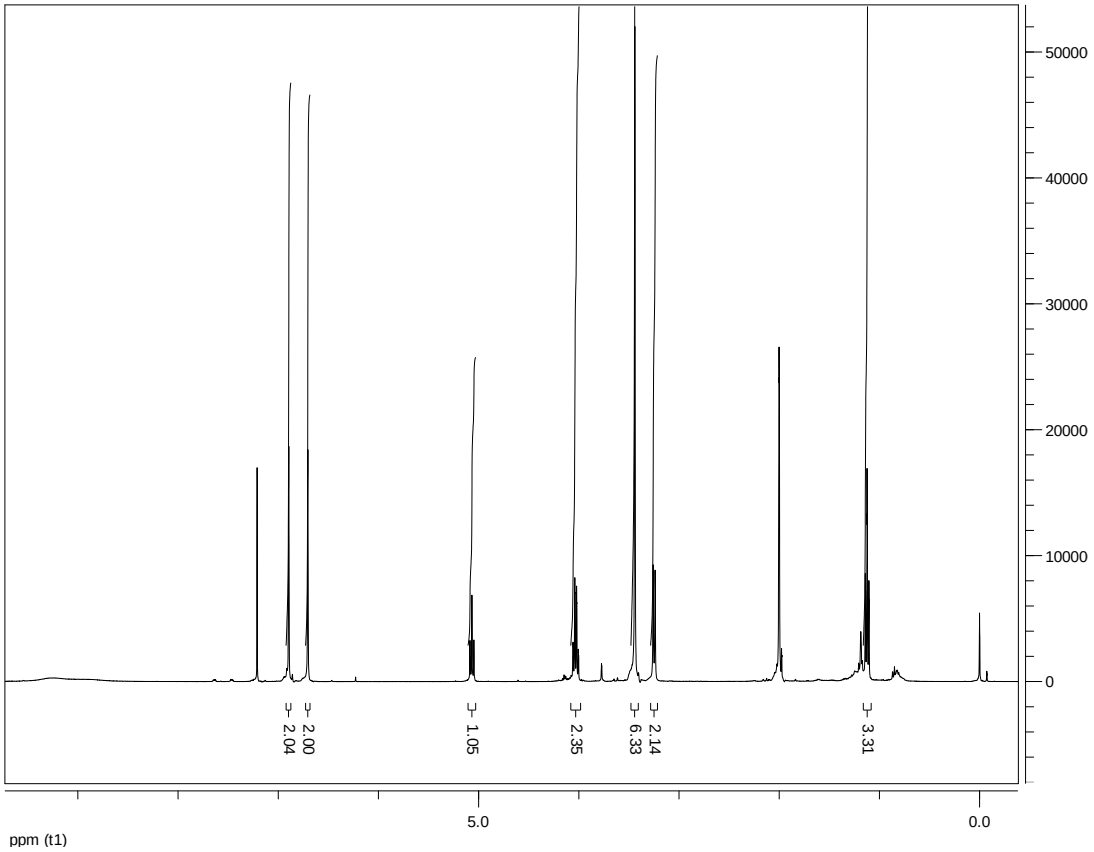


Figure A 19. ^{1}H NMR spectrum of ethyl-bis(methylimidazol-2yl)propionate in $CDCl_3$.

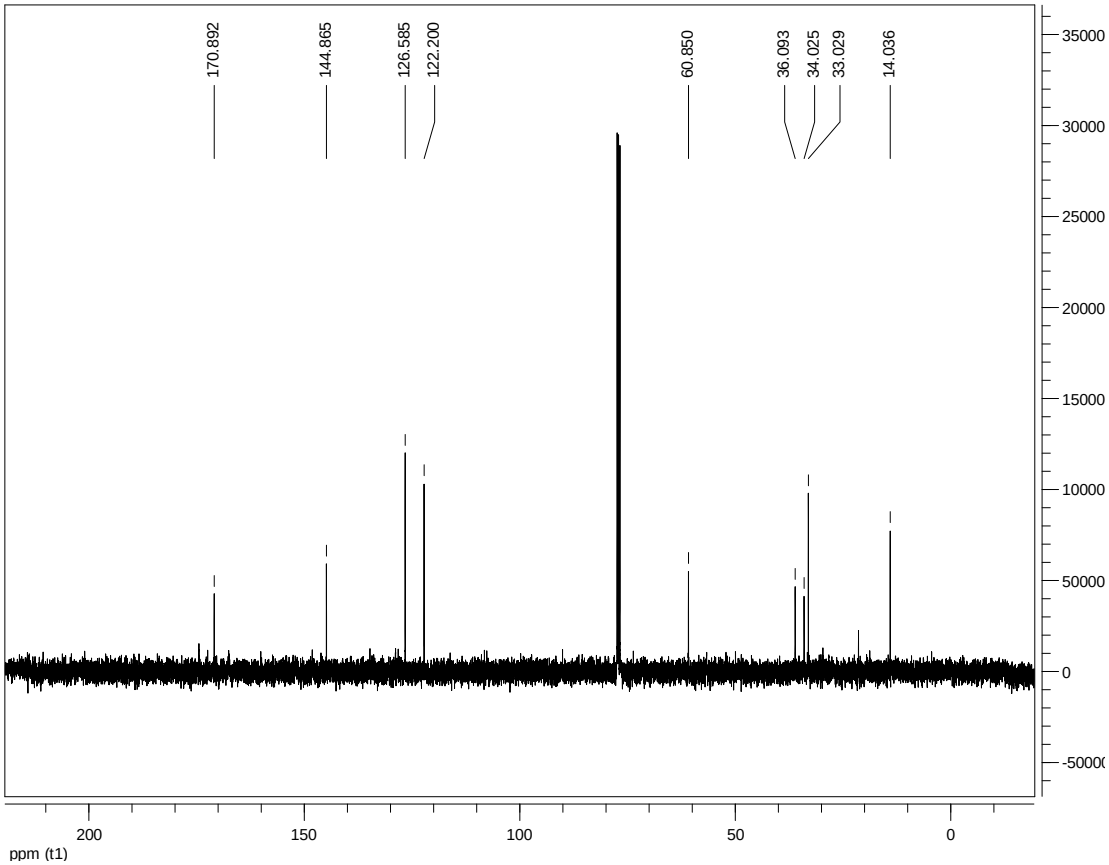


Figure A 20. ^{13}C NMR spectrum of ethyl-bis(methylimidazol-2yl)propionate in $CDCl_3$.

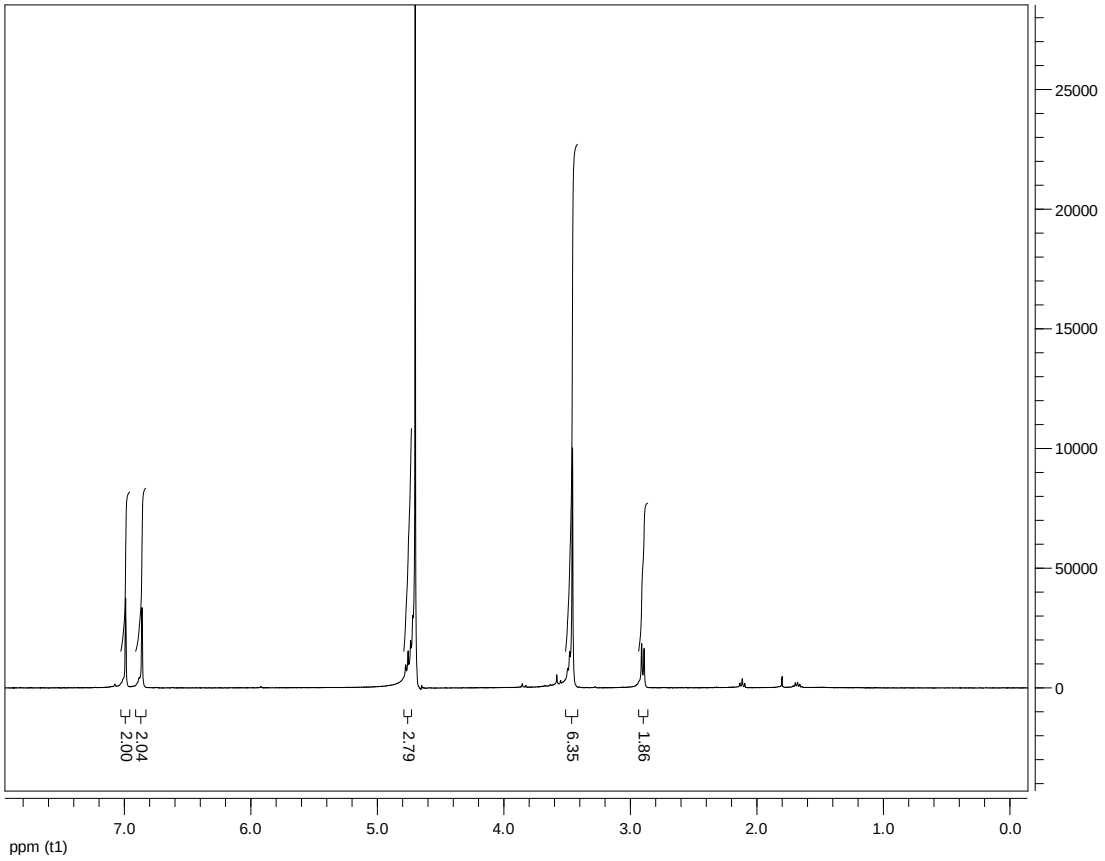


Figure A 21. ^{1}H NMR spectrum of bis(methylimidazol-2yl)propionic acid in $CDCl_3$.

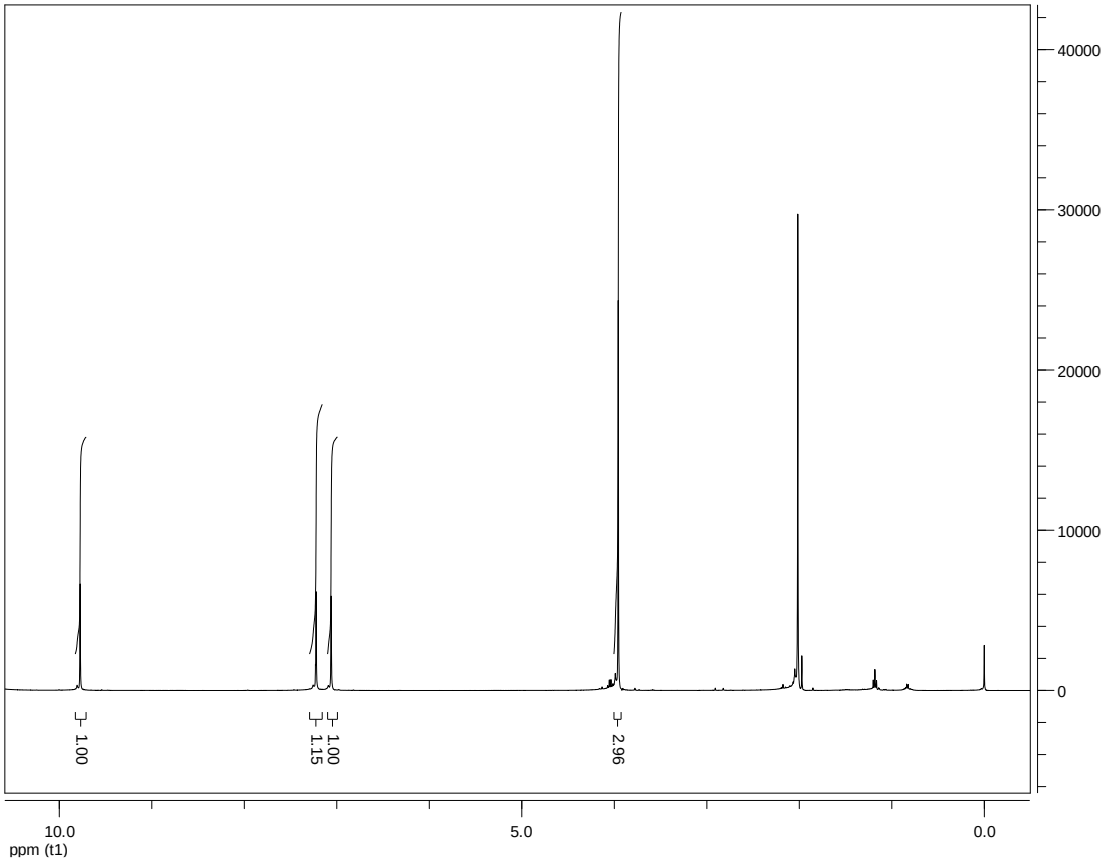


Figure A 22. ^{1}H NMR spectrum of 1-methyl-1*H*-imidazole-2-carbaldehyde in $CDCl_3$.

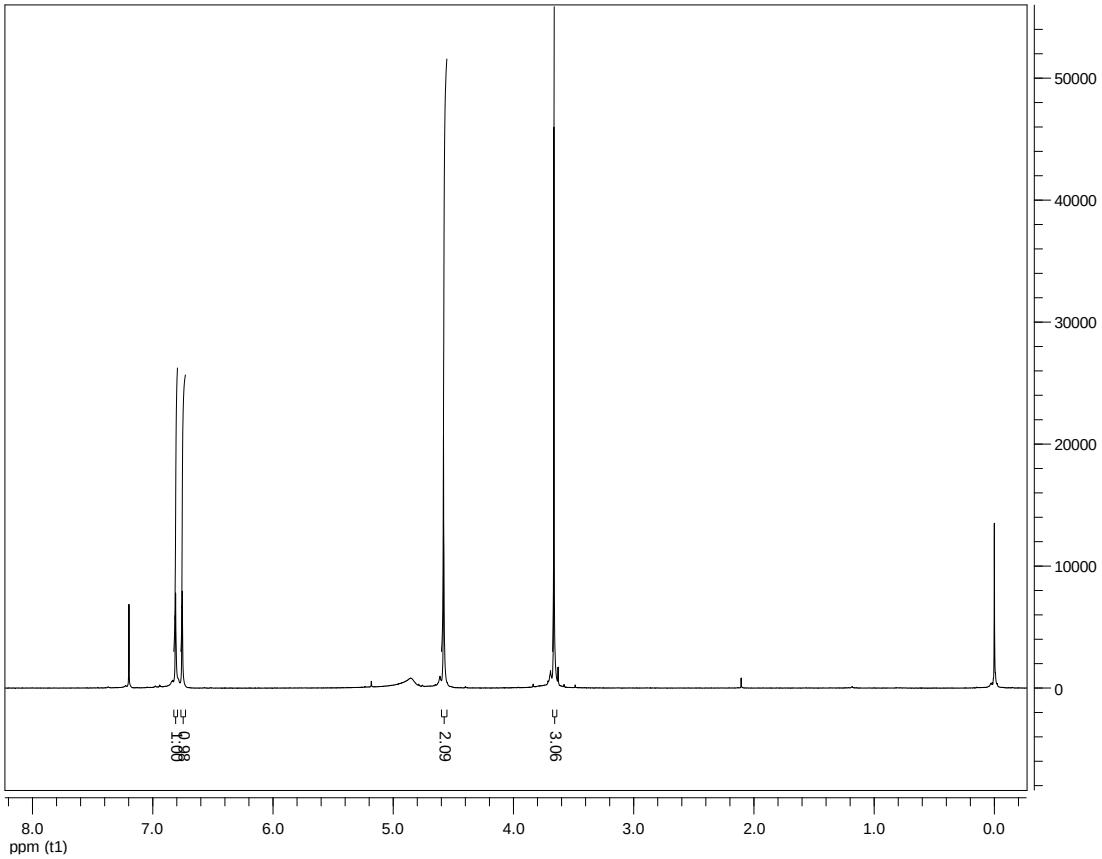


Figure A 23. ^{1}H NMR spectrum of (1-methyl-1*H*-imidazol-2yl)methanol in $CDCl_3$.

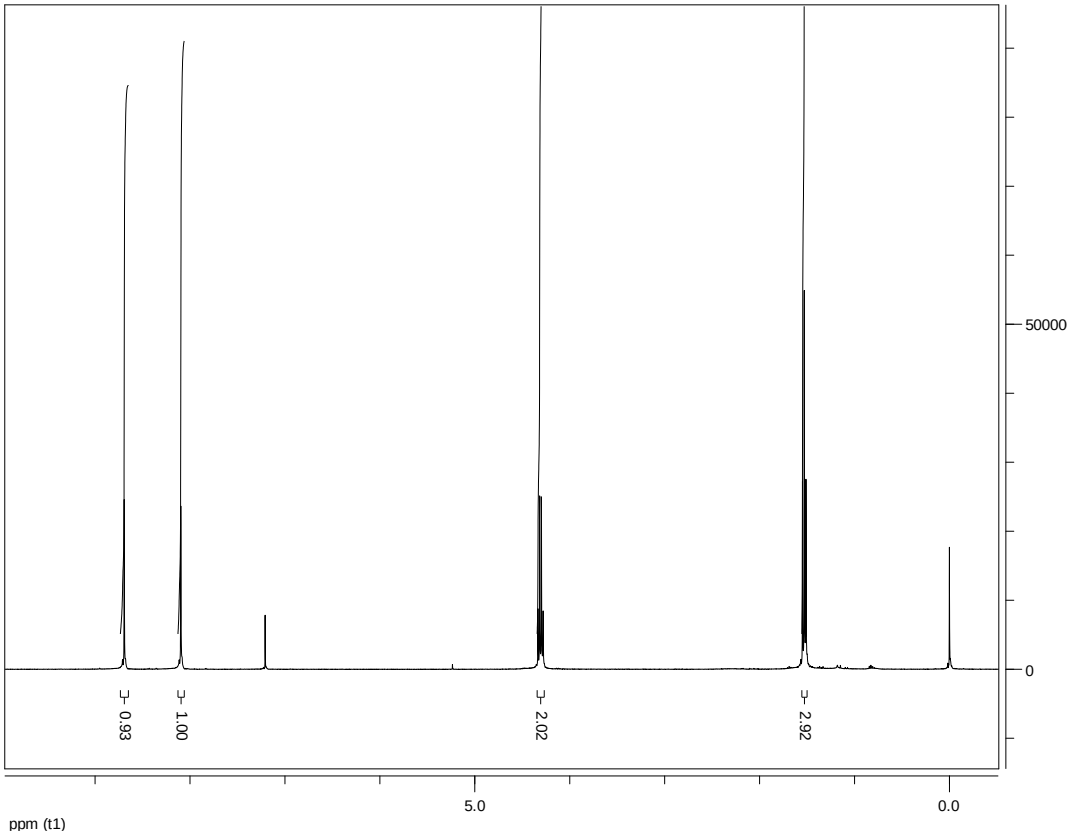


Figure A 24. ^{1}H NMR spectrum of 9-ethyl-6-chloro-purine in $CDCl_3$.

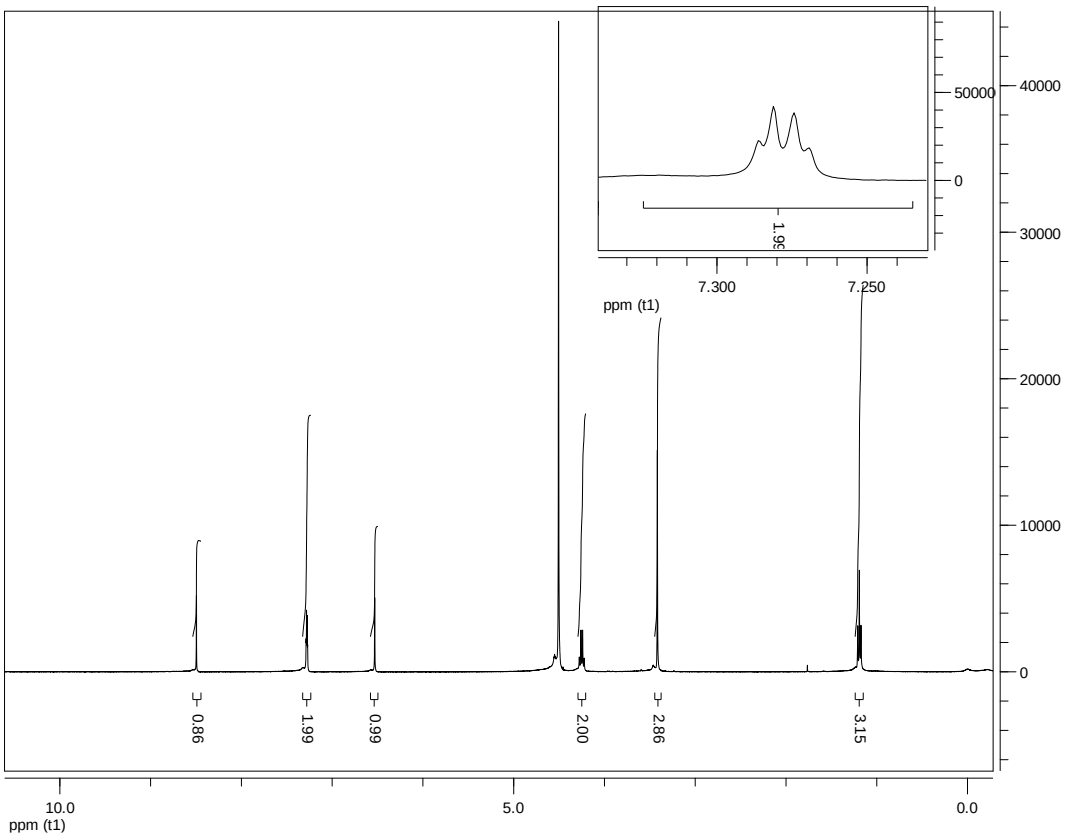


Figure A 25. ^{1}H NMR spectrum of compound **18** in D_2O.

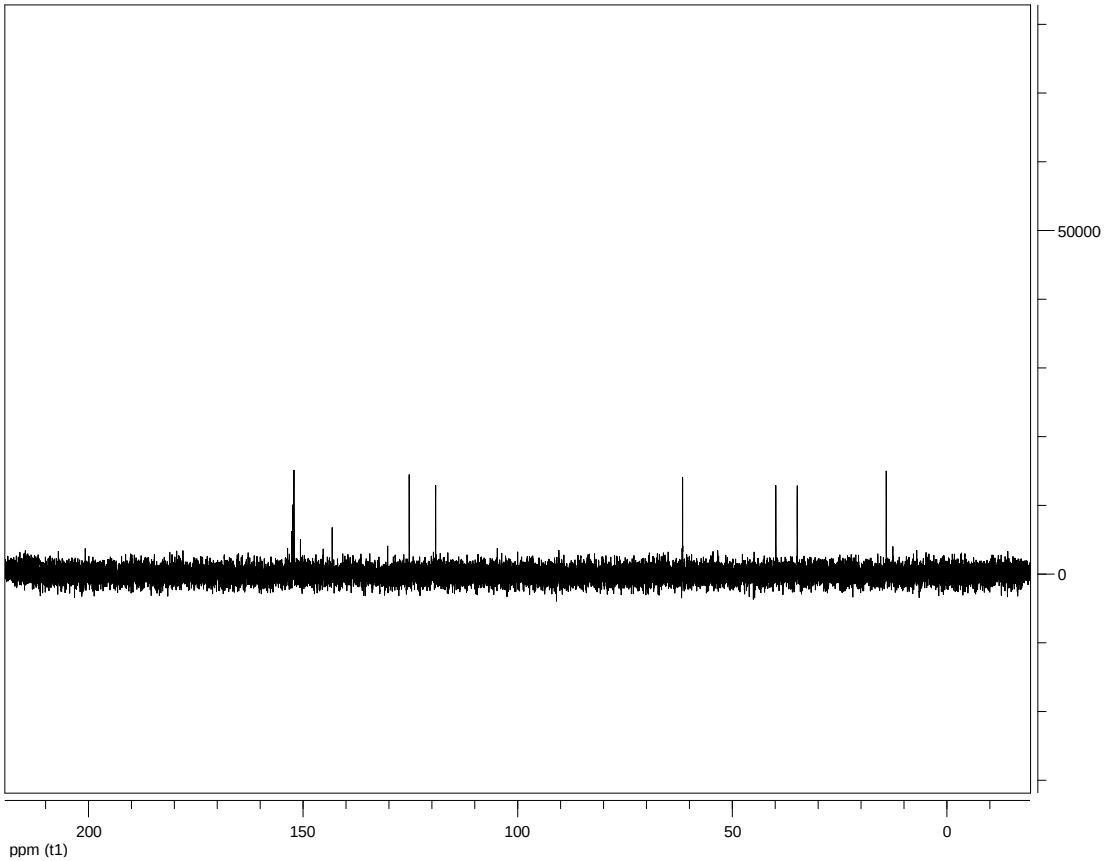


Figure A 26. ^{13}C NMR spectrum of compound **18** in D_2O.

APPENDIX B

GC-MS RESULTS

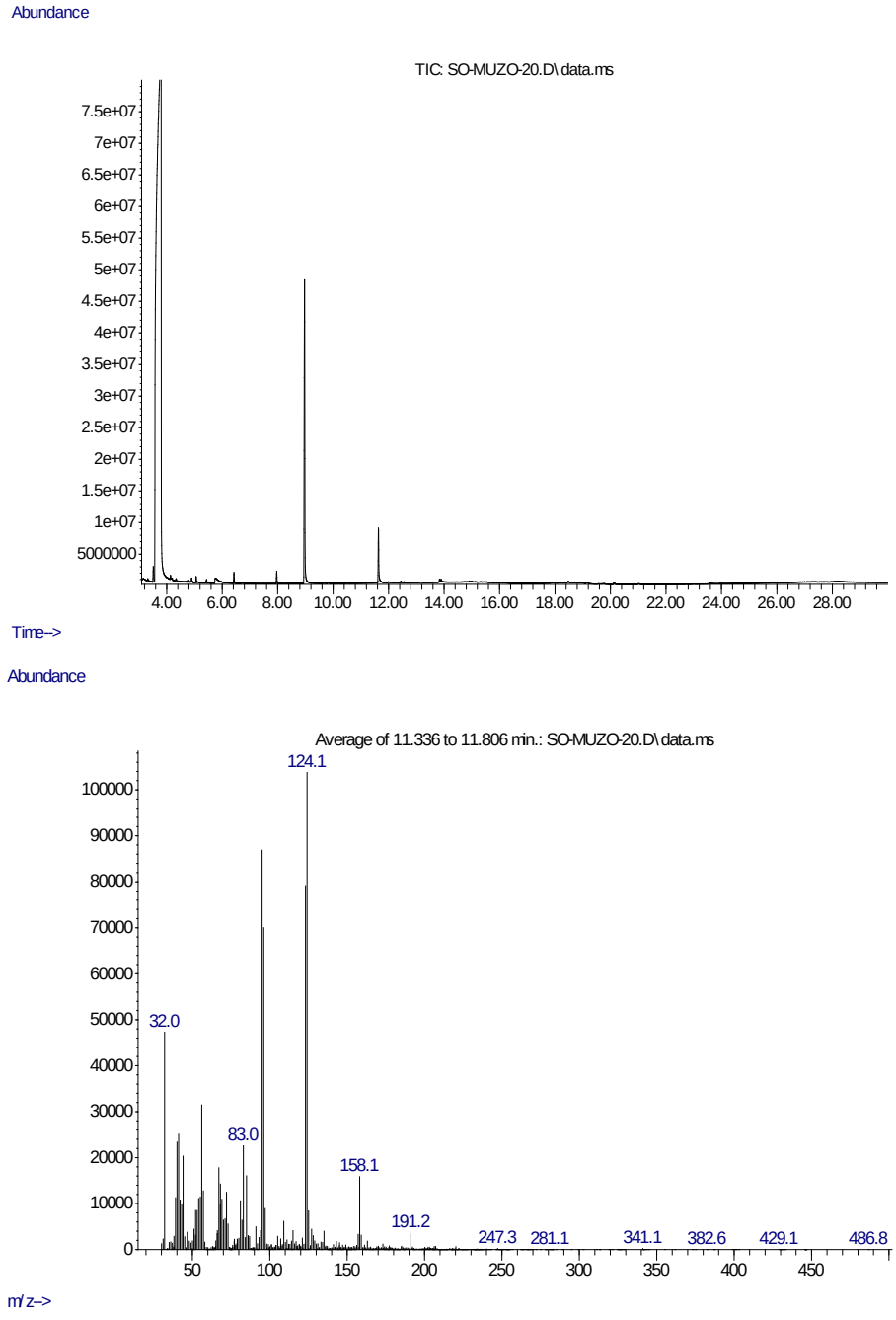


Figure B 1. GC-MS spectrum for1-ethyl-1*H*-imidazole-2-carboxaldehyde.

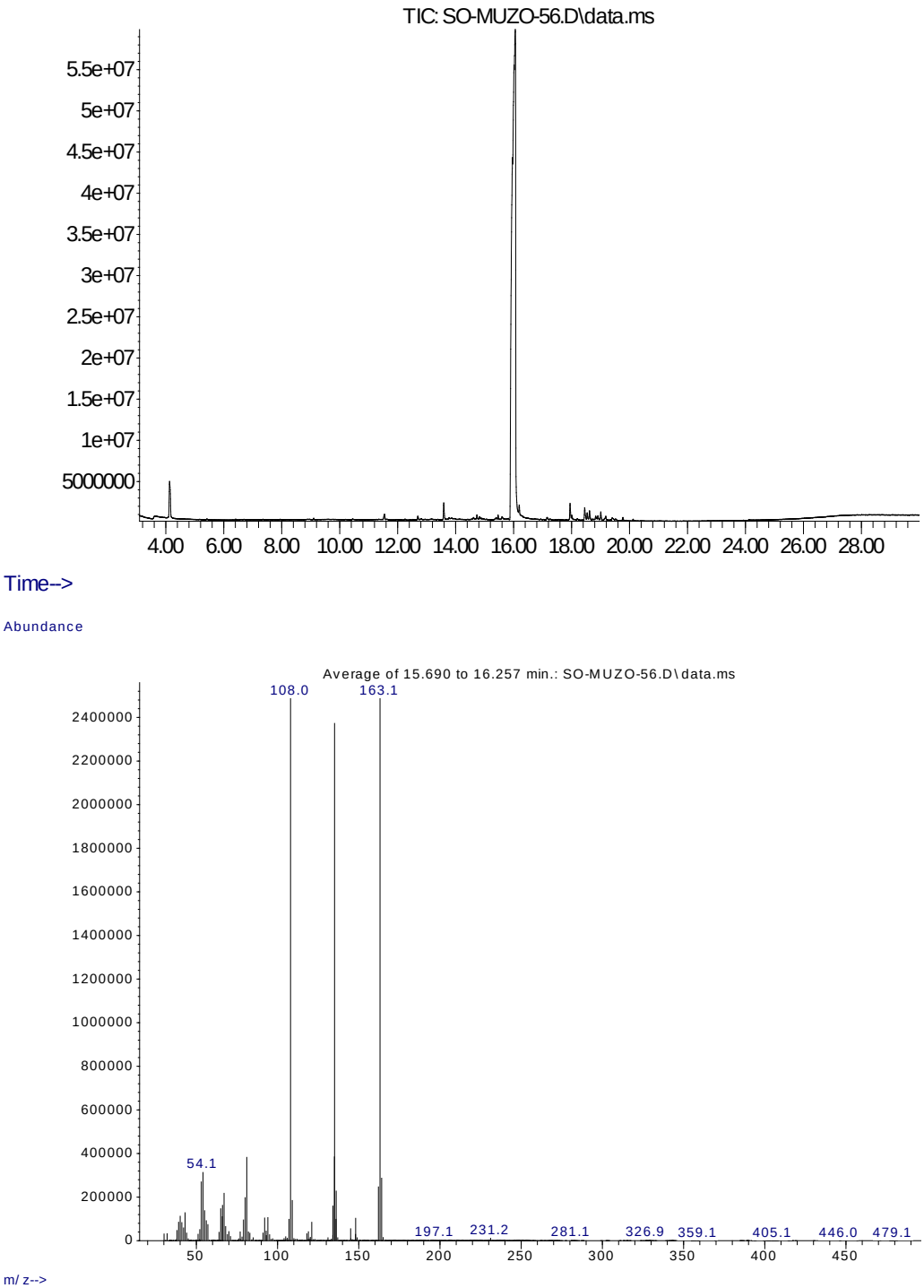


Figure B 2. GC-MS spectrum for 9-ethyladenine.

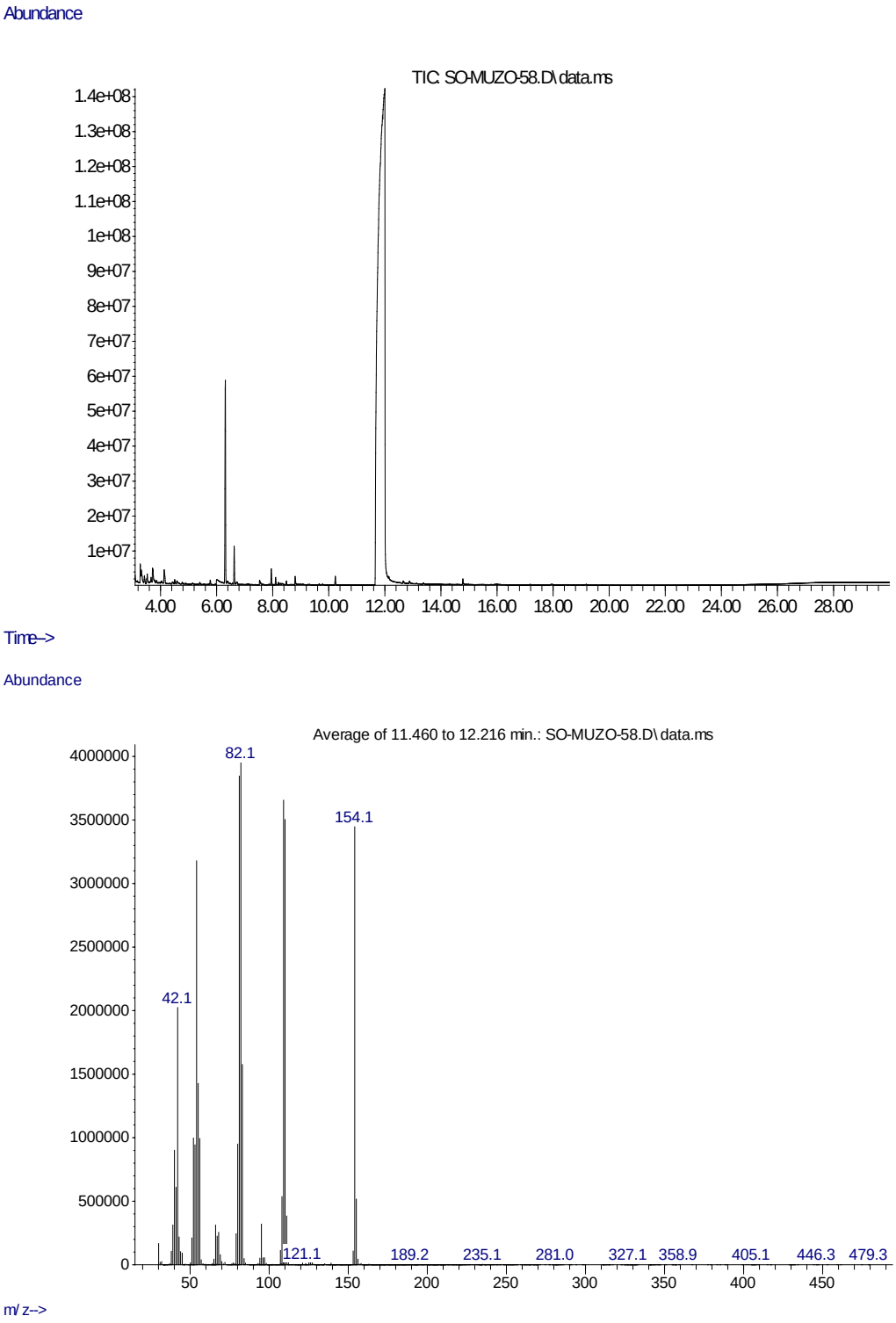


Figure B 3. GC-MS spectrum for ethyl 1-methylimidazole-2-carboxylate.

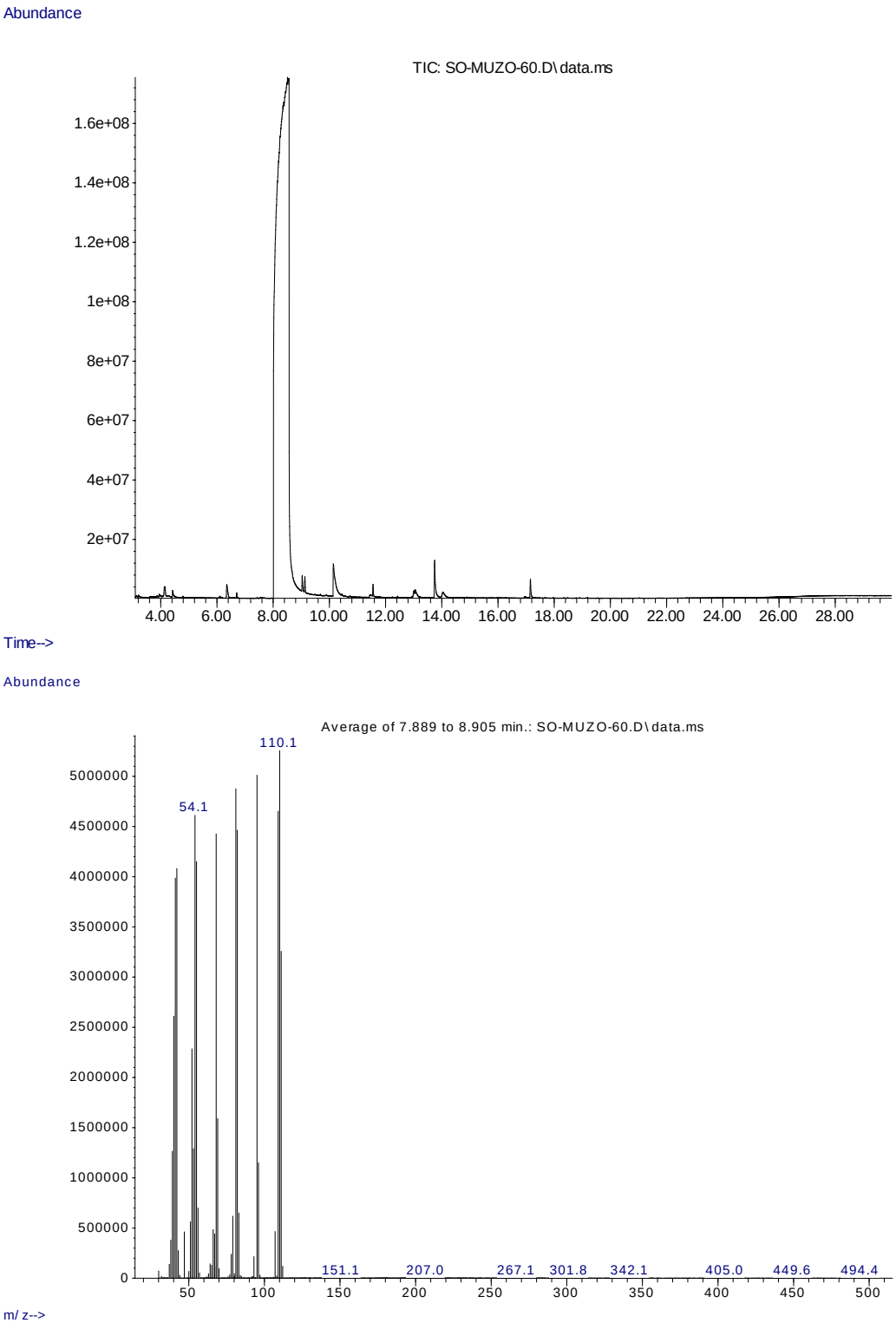


Figure B 4. GC-MS spectrum for 1-ethyl-2-methyl-1*H*-imidazol.

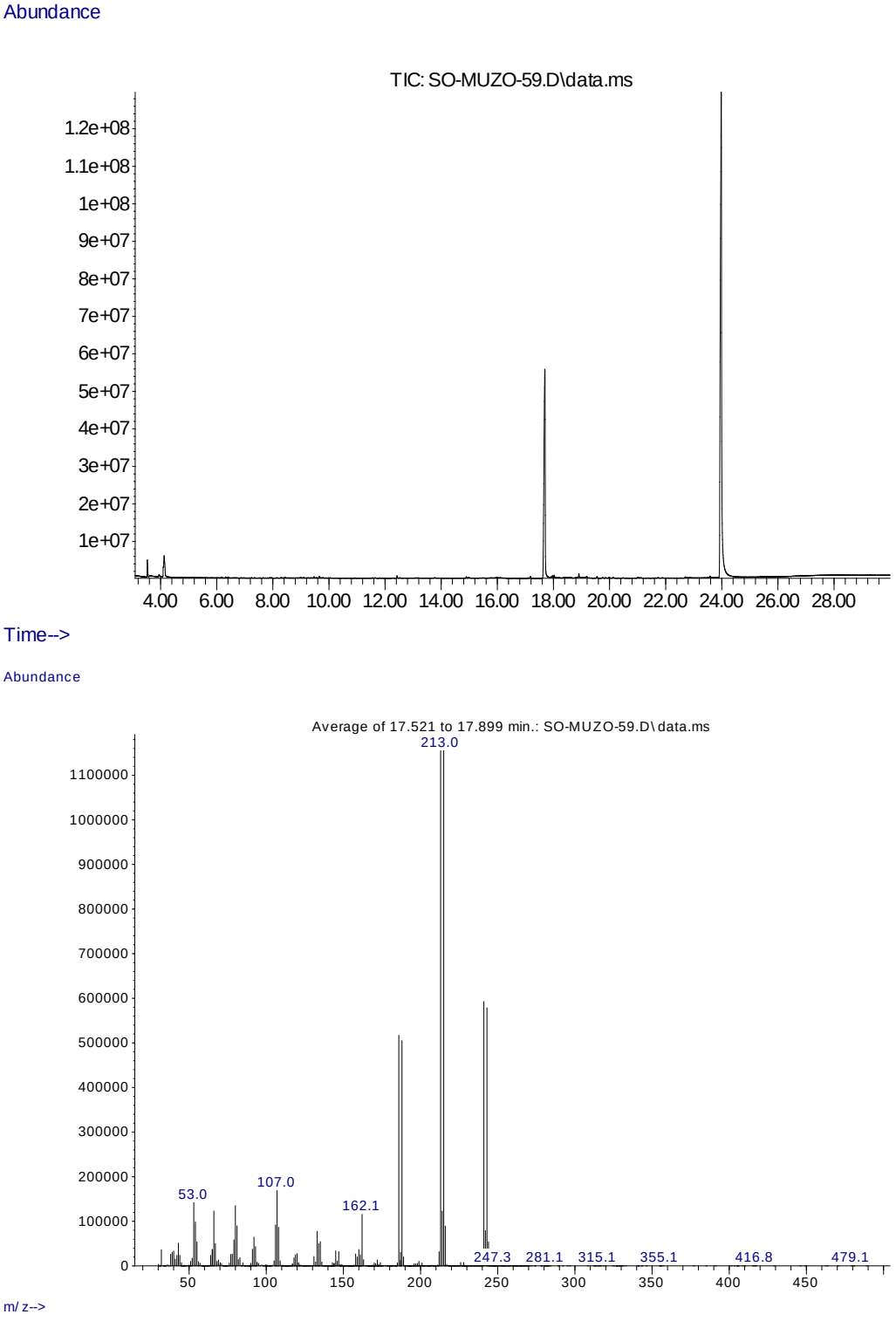


Figure B 5. GC-MS spectrum for 8-bromo-9-ethyladenine

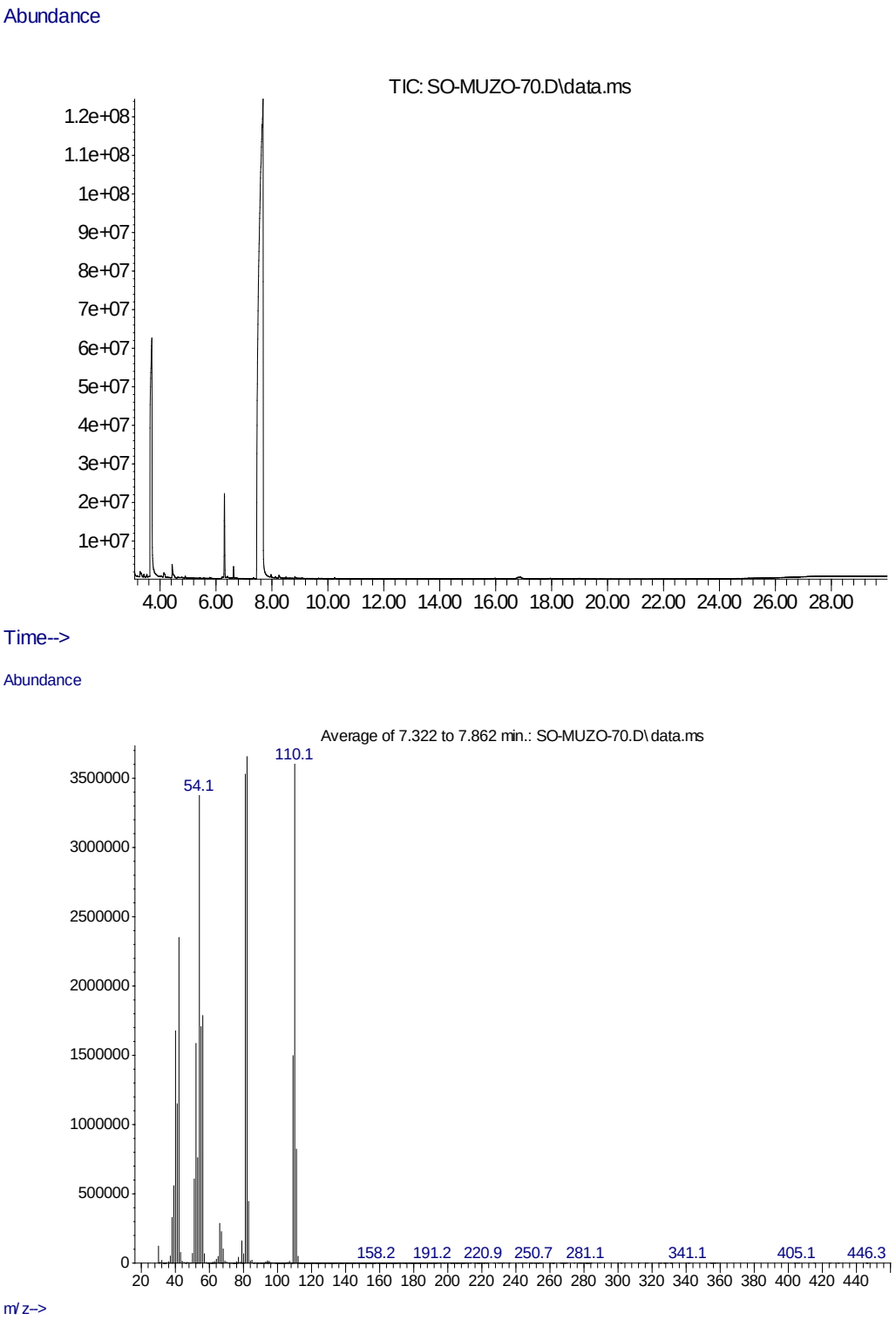


Figure B 6. GC-MS spectrum for 1-methyl-1*H*-imidazole-2-carbaldehyde.

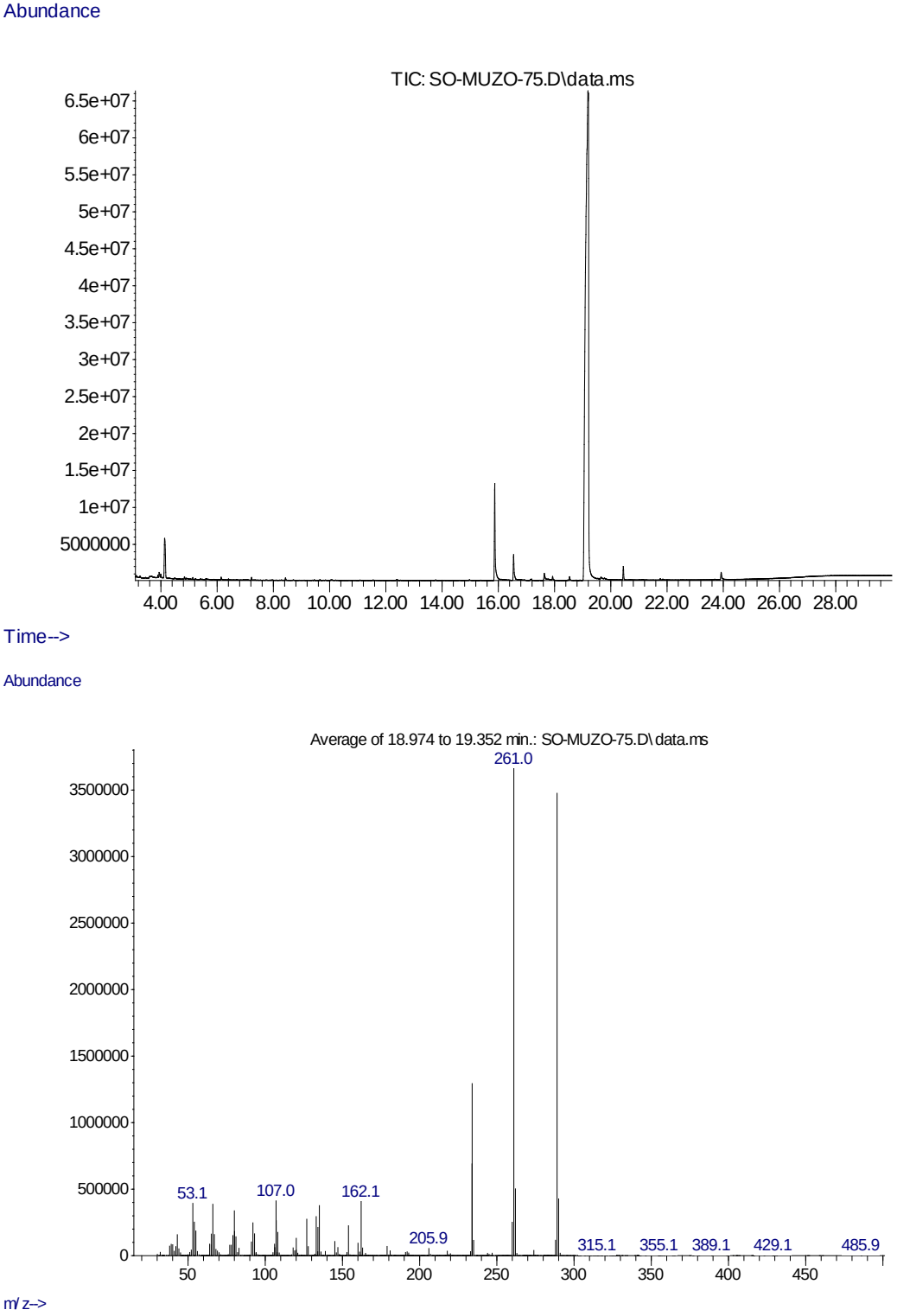


Figure B 7. GC-MS spectrum for 8-bromo-9-ethyladenine.

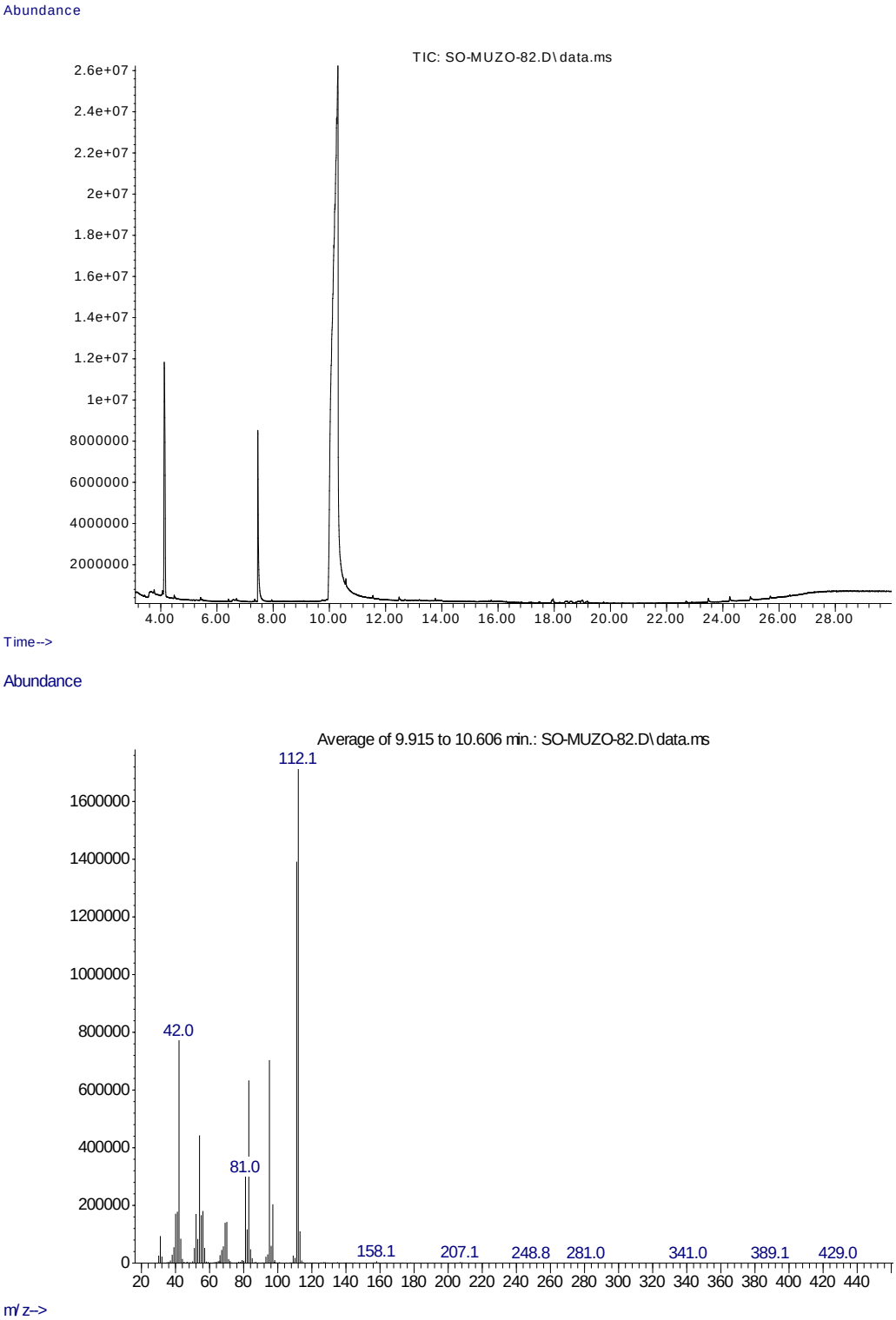


Figure B 8. GC-MS spectrum for 1-methyl-1*H*-imidazole-2-methanol.

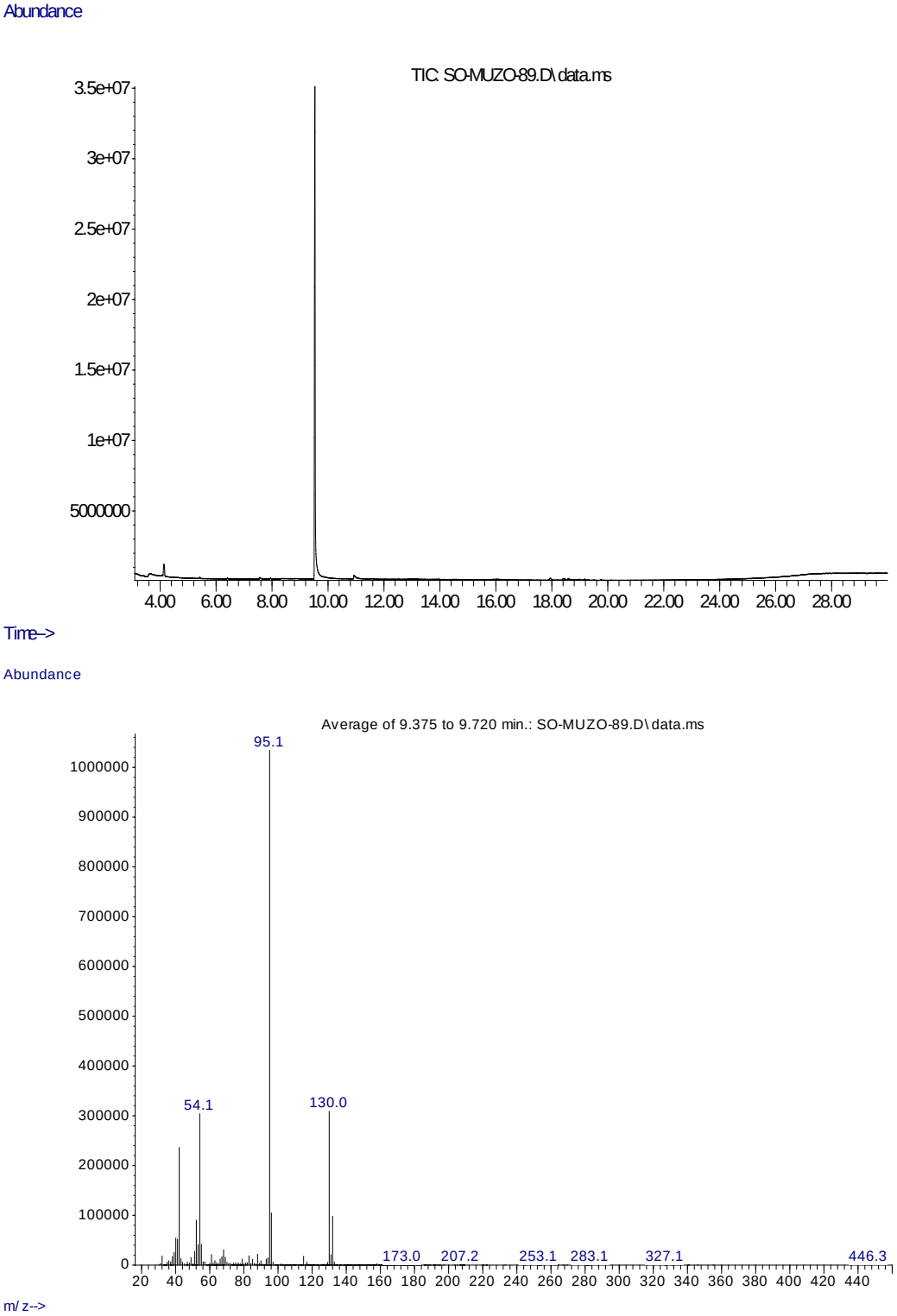


Figure B 9. GC-MS spectrum for 2-(chloromethyl)-1-methyl-1*H*-imidazole.