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Towards the Synthesis of Polycyclic N Heterocyclic Compounds from Malic Acid as an Acyclic Bio-renewable Source

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Towards the Synthesis of Polycyclic *N*-Heterocyclic Compounds from Malic Acid as an Acyclic Bio-renewable Source

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Co-Supervisor: Prof Amanda Rousseau

A dissertation submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Science.

DECLARATION

I declare that the work presented in this dissertation was carried out by myself under the supervision of Dr S. Ntsimango and Professor Amanda Rousseau. It is being submitted for the degree of Master of Science at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Luthfiyyah Essop

[05 August 2025]

ABSTRACT

Bio-renewable levulinic and malic acid, derived from hemicellulose/cellulose and glucose respectively, were utilized in the production of *N*-heterocyclic compounds. The planned synthesis of 4-azipinone derivatives **65** involved three steps: lactamization of levulinic acid **12** with a nitrogen source in the presence of a reducing reagent to form 5-methylpyrrolidin-2-one **69**. Followed by reaction with commercially available aldehydes to obtain *N*-vinyl 2-pyrrolidones **71** that are predisposed to participate in photochemical ring expansion to furnish the target 4-azipinone derivatives **65**. The synthesis of 5-methylpyrrolidin-2-one **69** directly from the reaction of levulinic acid **12** and ammonium formate failed to yield the anticipated product **69**. Further attempts to synthesize **69** by a two-step synthesis from levulinic acid **12** under various reaction conditions proved futile. For example, the reaction between **12** and benzylamine **74** gives 1-benzyl-5-methylpyrrolidin-2-one **75** in 60% yield. All attempted debenzylations did not lead to the isolation of **69**. We later discovered that 5-methylpyrrolidin-2-one **69** is thermally unstable. Therefore, the synthesis of 4-azipinone derivatives **65** was not successful.

The second part of the work involved the use of malic acid **20** to develop a synthetic route to alternative *N*-heterocyclic derivatives bearing an imidazo[1,2-*a*]pyridine or benzo[*c*][1,8]naphthyridine cores. The attempted synthesis of benzo[*c*][1,8]naphthyridine core relied on methyl 6-amino-5-iodonicotinate **77**, while that of imidazo[1,2-*a*]pyridine analogues was based on methyl 6-aminonicotinate **66** starting material. The synthesis of the precursors was achieved from malic acid **20** as a bio-renewable raw material. Thus, the requisite methyl 6-aminonicotinate **66** and methyl 6-amino-5-iodonicotinate **77** were obtained in 29 and 20% overall yields, respectively, from malic acid. We hoped to achieve the synthesis of benzo[*c*][1,8]naphthyridine derivatives **67** in a single step on reacting methyl nicotinate derivative **77** and 2-formylphenyl boronic acid derivatives **82**, in a Suzuki-coupling/imine formation cascade. This however, was not successful. It was decided to separate the steps, thus **77** and (4-methoxyphenyl)boronic acid **84** underwent a Suzuki-coupling reaction to afford the novel compound methyl 6-amino-5-(4-methoxyphenyl)nicotinate **85** with a yield of 30%. The Suzuki-adduct **85** did not undergo the intended intermolecular cyclization with 4-

chlorobenzaldehyde **91** to form methyl 6-(4-chlorophenyl)-8-methoxybenzo[*c*][1,8]naphthyridine-2-carboxylate **87** under the reaction conditions tested. The synthesis of imidazo[1,2-*a*]pyridine derivatives was conducted also using a methyl 6-aminonicotinate **66** . This resulted in the successful production of five imidazo[1,2-*a*]pyridine derivatives **93** in 30 – 95% yields. One of the imidazo[1.2.a]pyridine derivatives, methyl 2-(2,5-dimethoxyphenyl)imidazo[1,2-*a*]pyridine-6-carboxylate **93f**, a novel compound was achieved with a yield of 61%. The compounds were sent for testing against cancer cell lines at the University of Leeds, UK.

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LIST OF ABBREVIATIONS

APIs	Active Pharmaceutical Ingredients
ATP	adenosine triphosphate
CAN	ceric ammonium nitrate
Cat.	catalyst
CNSL	cashew nut shell liquid
DBU	1.8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N,N*-diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNP	dinitrophenylhydrazine
EtOH	ethanol
FDCA	2,5-furandicarboxylic acid
FT-IR	Fourier transform infrared
HMDS	hexamethyldisilazane
HMF	5-hydroxymethylfurfural
IEDDA	Inverse Electron Demand Diels-Alder
IP	imidazo[1,2-*a*]pyridine
IUPAC	The International Union of Pure and Applied Chemistry
JohnPhos	(2-Biphenyl)di-tert-butylphosphine
KHMDS	potassium bis(trimethylsilyl)amide
KO^{t}Bu	potassium tert-butoxide

LA	levulinic acid
MA	malic acid
MeCN	acetonitrile
MeOH	methanol
MS	Mass Spectrometry
NaOtBu	sodium tert-butoxide
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
PARP-1	ADP-ribose polymerase-1
Pd	palladium
PIDA	phenyliodine(III) diacetate
SM	starting material
S-Phos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TFA	trifluoracetic acid
TfOH	triflic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TPPO	triphenylphosphine oxide
UV	Ultraviolet

Chapter 1

1. Introduction

1.1 General introduction to green chemistry

"Green Chemistry" is the design of chemical procedures and products to minimize or eliminate the use and production of hazardous substances.[1] Its origination is associated with the relatively recent recognition of the environmental damage caused by the spread of damaging man-made products and the pollution created in the process of generating them.[2] Therefore, the search for more environmentally friendly resources and mild, simple, non-polluting synthetic techniques is motivated primarily by the moral need to minimize irreparable environmental damage. Furthermore, there is a financial incentive to avoid the expense of restoring contaminated air and water.[2]

This subject has attracted a lot of attention in the last decade for its capacity to use chemical innovation to achieve both environmental and economic goals at the same time.[1] Green chemistry aims to achieve sustainability at a molecular level and revolves around designing environmentally friendly syntheses and processes, and the use of sustainably sourced chemical compounds to reduce the risks posed to human health and the environment.[1,3]

The aims and framework of Green Chemistry can be better understood through comprehensive illustration of its twelve principles established by Paul Anastas and John Warner in 1998.[1,3,4] These principles establish guidelines for the long-term development of safer chemicals and chemical transformations.[1] 'PRODUCTIVELY' is an acronym that attempts to encapsulate the essence of each of the twelve Green Chemistry principles (Figure 1).[4]

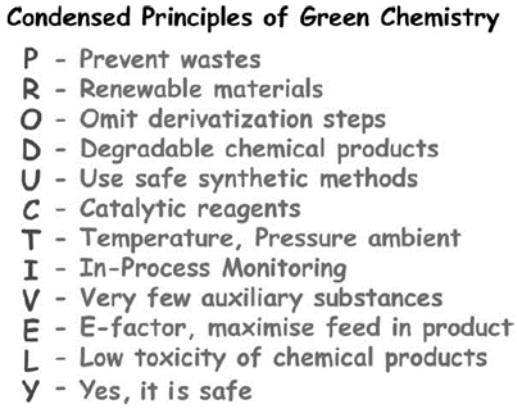


Figure 1. The twelve principles of Green Chemistry are represented by the acronym 'PRODUCTIVELY'.[4]

Pollution avoidance is the core idea of Green Chemistry, and it is expressed in the first principle.[3] Concerns like atom economy, toxicity, solvents, energy consumption, using raw materials from renewable resources and, ecologically acceptable molecules are all covered by the other principles.[3]

In summary, some of the key take away points from Green Chemistry are as follows:

1. Green Chemistry encompasses all phases of the chemical life cycle.[1]
2. Green Chemistry aims to redesign the fundamental character of chemical processes and products to lessen their inherent danger.[1]
3. Green Chemistry functions as a unified set of guidelines or design criteria.[1]

1.2 Bio-renewable resources in synthesis

Currently, chemical synthesis heavily depends on fossil resources such as petroleum, coal, and natural gas. The increasing awareness of sustainability, coupled with the known risks associated with using fossil resources, points to the need for alternative sources. Renewable biomass can be utilized to replace fossil fuels in the production of chemicals.[5] Using biomass in chemical synthesis may have numerous advantages. For example, the number of steps necessary to transform bio-renewable materials into target synthetic compounds may be less than that required for their fossil fuel equivalents.[6] In general, biomass-derived products are endowed with functional groups or congeners that may be present on the target compounds, thus shortening reaction

steps that are necessary to introduce the functionalities that are mostly missing from precursors that are derived from fossil-based resources. Shortening the number of steps helps to improve atom economy, and there is plenty of room for that in the chemical synthesis industry.[6] In addition, the unique functional groups of biomass-derived products allow for the insertion of heteroatoms (e.g., N, S, P) and even the building of heterocycles *via* regulated carbon-heteroatom bond formation.[6]

Organic synthesis mostly involves the construction of carbon skeletons of complex molecules, the origin and destination of these carbon atoms have a substantial impact on the sustainability of an organic product.[6] Biomass is distinct in that it is the only renewable source of fixed carbon.[7] Biomass is a cheap sustainable option that is accessible on a global scale and can store carbon.[8] Consequently, several industrial sectors have started to shift to biomass as feedstock to boost sustainability and minimize overall environmental impact.[8]

1.2.1 Cashew nut shell liquid (CNSL) as a bio-renewable resource

In keeping with the demands of green and sustainable chemistry, de Koning and co-workers[9] employed xylochemical synthesis of several kinds of aromatic UV absorbers using either cardanols **1** or anacardic acids **2** as starting materials (Figure 2a). These components are important as bio-renewable and non-edible carbon sources from cashew nut shell liquid (CNSL). They were used to synthesize UV-absorbing compounds such as xanthones **3**, flavones **4**, triazines **5,** and hydroxybenzophenones **6** (Figure 2b).[9]

The economic value of CNSL is low but it holds tremendous technological promise due to its abundance and the easily extractable phenolic compounds as well as the constituents' biological activity.[9] Through extraction, these phenolic platform chemicals may be easily separated from CNSL. It is an active topic of study to convert them into useful functional chemicals and materials. Several of the synthesized substances shown in Figure 2b demonstrated good UVA and UVB absorption properties.[9] Since CNSL-derived starting materials include phenolic functional groups, they are often favourable for benzoid compounds.

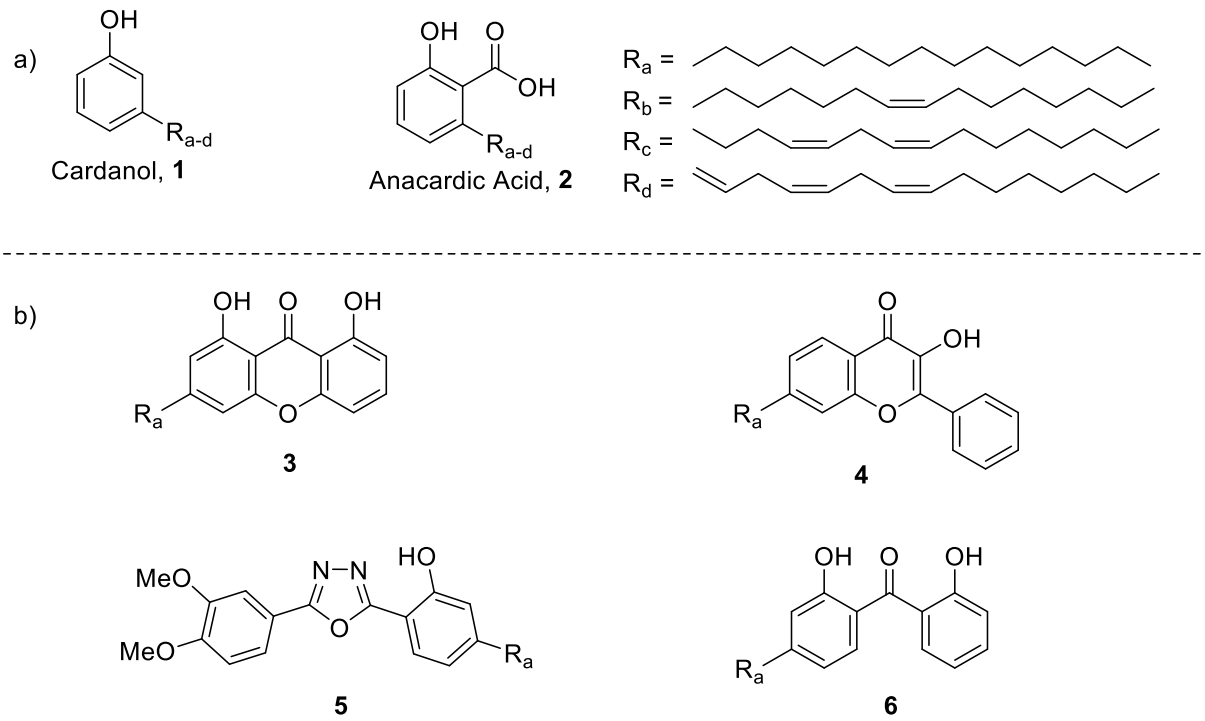


Figure 2. a) Cardanols **1** and anacardic acids **2**, components of the bio-renewable source cashew nut shell liquid (CNSL), b) some of the value-added aromatic compounds that were synthesized from cardanol **1a** and anacardic acid **2a**.[9]

1.2.2 Lignocellulosic biomass as a bio-renewable resource

An alternate bio-renewable source is lignocellulosic biomass. Given its abundant availability, lignocellulosic biomass, a renewable and carbon-neutral substance, is regarded as an appealing raw material.[10,11] It is composed mostly of three different types of polymers, namely lignin, cellulose, and hemicellulose.[12] Cellulose and hemicellulose are the most prevalent polymers in nature, followed by lignin.[12]

The use of lignocellulosic biomass as a raw material has already been achieved on an industrial scale. For example, it has been utilized to produce biofuels and other platform chemicals.[11] These involve the chemical conversion of lignocellulose to biogas, ethanol, methanol, and hydrogen gas.[12]

A wide range of aromatic chemicals can be produced from lignin by depolymerization and it has been employed in industry to synthesize benzene-derived compounds,[10,11]

showing promise as a replacement for petroleum-based products such as styrene and terephthalic acid.[11]

Hemicellulose and cellulose are carbohydrate polymers which may be turned into bio-gasoline and aviation fuel.[13] Some of the compounds that are derived from hemicellulose and cellulose are shown in Figure 3. Furans like furfural **7** and 5-hydroxymethylfurfural (HMF) **8** can also be obtained.[11] 2,5-Furandicarboxylic acid (FDCA) **9**, an HMF derivative, sorbitol **10** and xylitol **11** are representative of some of the compounds that can be produced from hemicellulose and cellulose.[11] While useful as raw materials in the synthesis of value-added molecules, these compounds can also be converted to other important starting materials. A case in point is the conversion of HMF **8** to levulinic acid (LA) **12**, which is a versatile feedstock that can be transformed to a variety of other important molecules.[11,14]

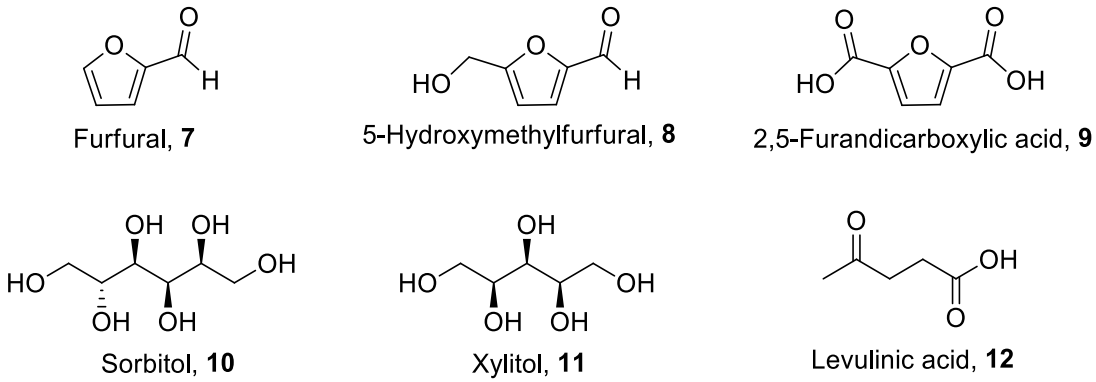


Figure 3. Some compounds that are derived from hemicellulose and cellulose.

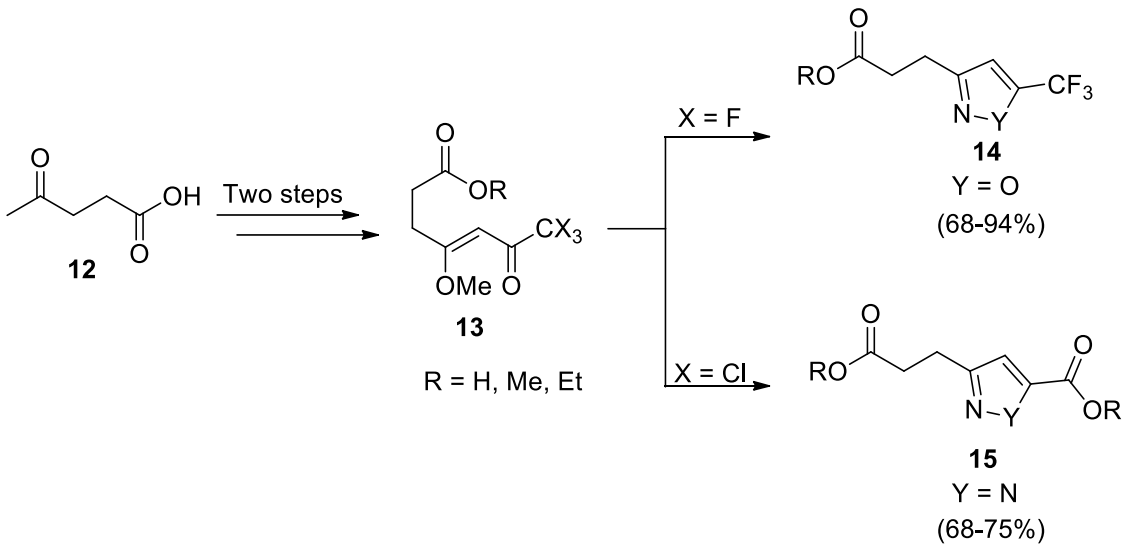
1.2.3 Synthesis of *N*-heterocyclic compounds from lignocellulosic biomass

N-heterocyclic compounds have received little attention, despite the fact that several oxygen-containing aromatic compounds and products derived from benzene have been produced from biomass. If chemical synthesis is to depend on bio-renewable feedstocks to satisfy the societal demands of functional molecules, there is a need to develop processes for the synthesis of *N*-heterocyclic compounds and their building blocks. This is because there is a significant demand for *N*-heterocyclic compounds in most applications that depend on organic compounds, such as medications, agrochemicals,

dyes, corrosion inhibitors, polymers and much more. This project makes progress in addressing this need.

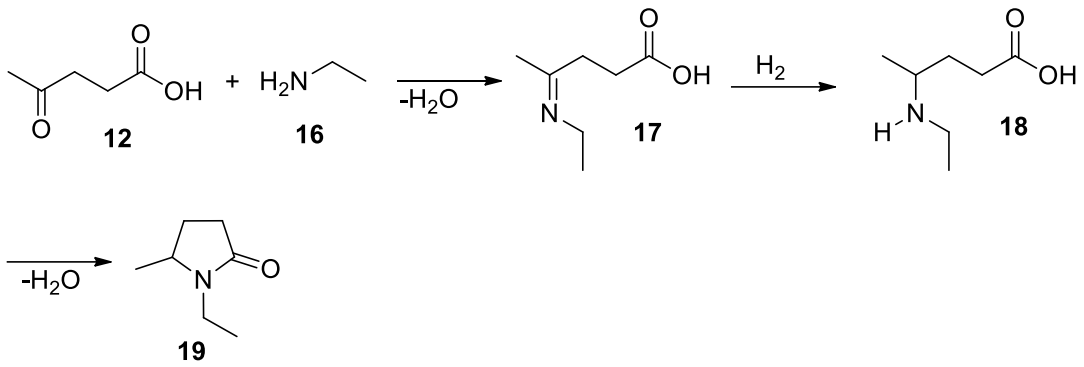
*1.2.3.1 Synthesis of N-heterocycles from levulinic acid **12***

We are by no means the first nor the only group working in this area. Levulinic acid **12** has featured as an acyclic bio-renewable starting material in the synthesis of various *N*-heterocyclic frameworks. [15,16,17,18] For example, Flores and co-workers[16] described a three step synthesis of isoxazole and pyrazole-containing compounds **13** and **14** from levulinic acid **12** through methyl 7,7,7-trihalo-4-methoxy-6-oxohept-4-enoate **15** as the common intermediate (Scheme 1). These novel glutamate-like 3-(azolyl)propanoates compounds **14** and **15** were shown to possess some activity against cerebral ischemia or epilepsy.[16]



Scheme 1. Isoxazole and pyrazole derivatives synthesized from the bio-renewable precursor levulinic acid **12** by Flores and co-workers.[16]

Furthermore, synthesis of the 2-pyrrolidinone core has been reported by Rodriguez-Padron *et al.*[17] In a continuous flow reactor, levulinic acid **12** was reacted with ethylamine **16**, which was produced through *in situ* hydrogenation of acetonitrile. This reaction gave imino acid **17**, followed by reduction into the secondary γ-amino acid **18**, which cyclized to give 1-ethyl-5-methylpyrrolidin-2-one **19** (Scheme 2).

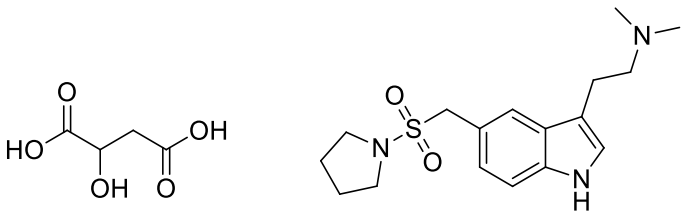


Scheme 2. The synthesis of 2-pyrridones from LA **12** as reported by Rodriguez-Padron *et al*.[17]

A more detailed discussion on the use of LA **12** has been reviewed in three recent review articles.[5,15,18] As discussed in the reviews, LA **12** is widely used to synthesize valuable *N*-substituted pyrrolidones *via* catalytic reductive amination followed by cyclization.[17] In this study, we wish to employ LA **12** as a bio-renewable starting material in the photochemical-based synthesis of 3-substituted 6,7-dihydro-azepin-4-ones (*vide infra*).

*1.2.3.2 Synthesis of N-heterocycles from malic acid **20** via methyl coumalate **23***

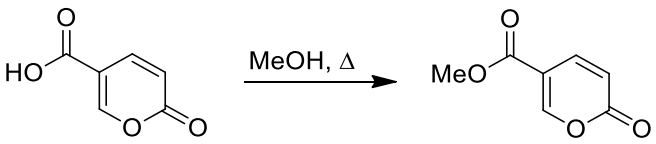
Fermentation of sugars like fructose and glucose present an attractive alternative source of bio-renewable precursors.[19] One such fermentation product is malic acid (MA) **20** (Figure 4), which is a cost-effective, biorenewable feedstock with potential to become a significant platform chemical in the post-fossil fuel future.[20,21] MA **20** may be naturally collected by a variety of microbes and plants, for example, in fruits like apples, plums, litchis and bananas.[21] As a result, its primary use currently is in the food and beverage industry. Other applications include the pharmaceutical industry, such as, as a component of the migraine medication almotriptan malate **21** (Figure 4).[21] However, cellulose is an abundant source of glucose, which could be fermented to produce MA **20**.[22]



Malic acid, **20** Almotriptan malate, **21**

Figure 4. Malic acid **20** and almotriptan malate **21**.

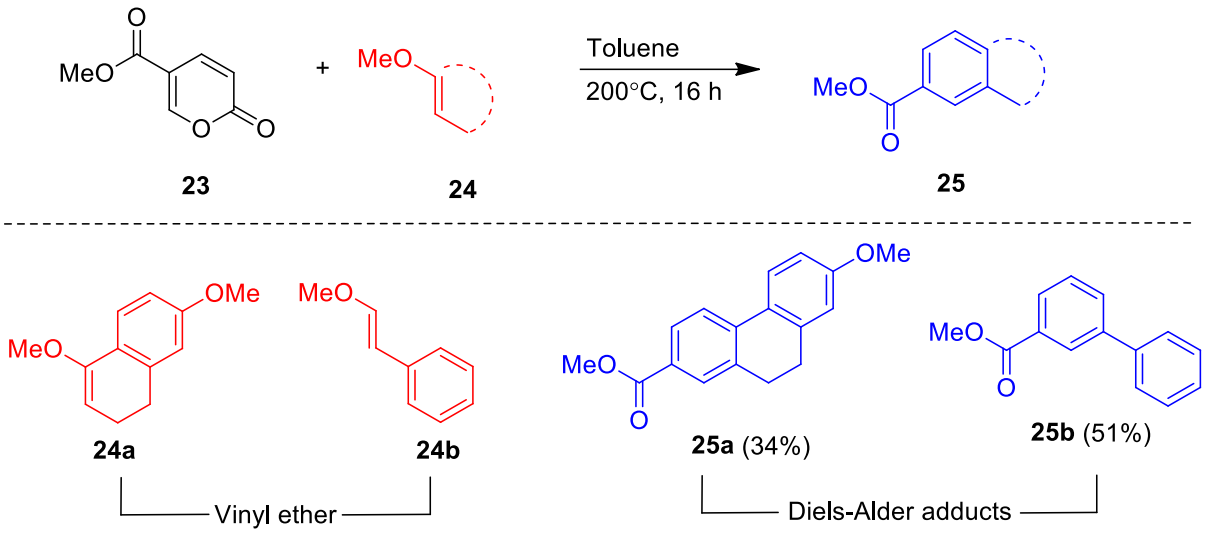
MA **20** has the capability to substitute maleic anhydride, which has a wide range of applications including in the production of industrial chemicals and in the polymer and pharmaceutical industry and is traditionally prepared from fossil fuels.[21] The use of MA **20** as a precursor in the synthesis of *N*-heterocyclic compounds is often via coumalic acid **22**. However, owing to the poor solubility of coumalic acid **22**, its methyl ester **23** is normally used.[20] The esterification of coumalic acid **22** is easily affected as shown in Scheme 3.[20] A recent review details alternative syntheses of 2-pyrone derivatives similar to **23**, from various bio-renewable feedstocks.[23]



22 **23**

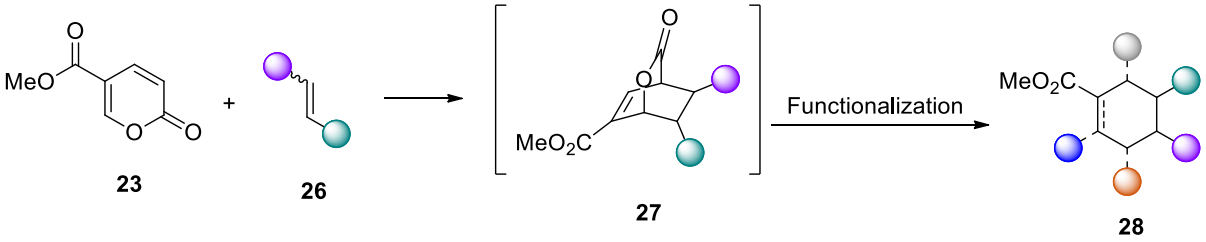
Scheme 3. Esterification of coumalic acid **22** to methyl coumalate **23**.[20]

The application of methyl coumalate **23** in the synthesis of value-added compounds is dominated by its use as a diene in inverse electron demand Diels–Alder (IEDDA) reactions to access oxygenated benzenoid compounds. For example, methyl coumalate **23** was reacted with vinyl ethers **24a** and **24b** in a Diels-Alder reaction, to produce fused tricyclic molecule **25a** and biaryl system **25b**, respectively, as shown in Scheme 4.[19] Molecule **25a** contains a complex backbone that might be used to make anthracene analogues, following an oxidation step, while further derivatization of molecule **25b** reveals promising organic compounds and psychotic illness therapies.[19]



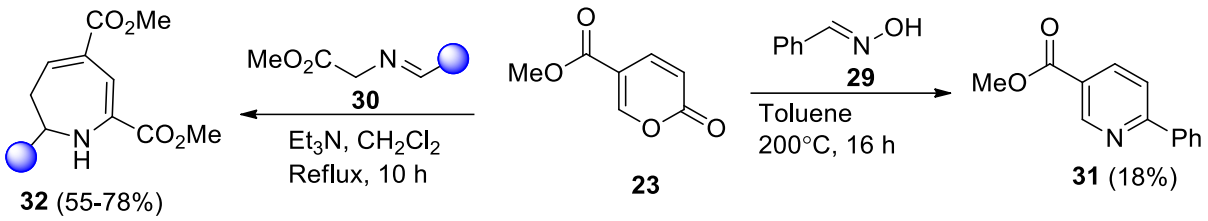
Scheme 4. Formation of fused tricyclic molecule **25a** and biaryl system **25b**.[19]

The use of methyl coumalate **23** is not limited to the synthesis of aromatic benzenoid compounds but has also been used to construct cyclohexane and cyclohexene **28** frameworks. This is achieved through a clever functionalization of the 2-oxabicyclo[2.2.2]oct-5-en-3-one-derivede intermediates **27** (Scheme 5) that result from the IEDDA reaction of **23** with various dienophiles **26**. For specific examples of this kind, the reader is directed to the review by Zheng *et al*.[24]



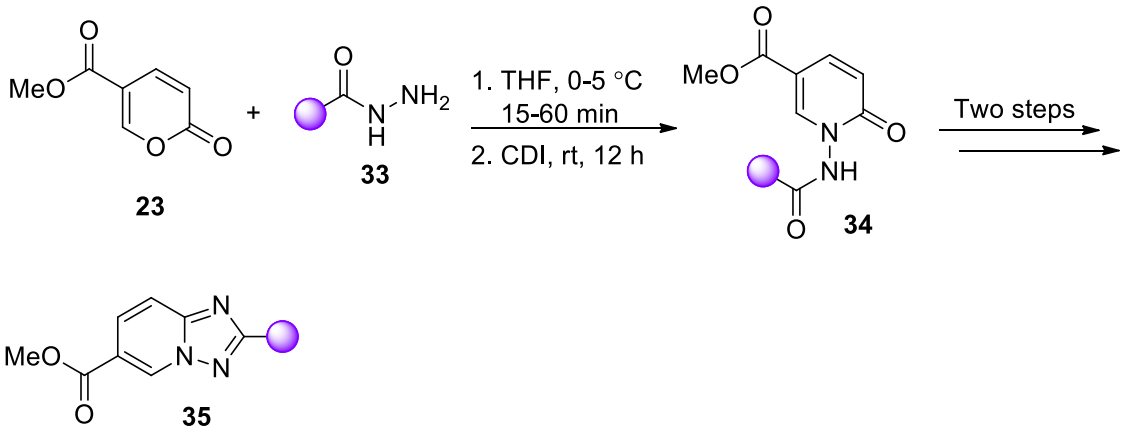
Scheme 5. General scheme depicting IEDDA of **23** and various olefins and the functionalization of the intermediate 2-oxabicyclo[2.2.2]oct-5-en-3-one derivatives.

Synthetic efforts demonstrating the utility of **23** extend to other classes of compounds and types of reactions. The reaction of methyl coumalate **23** with benzaldehyde oxime **29** and imine ester **30**, to produce 6-phenylnicotinate **31** and 2,3-dihydro-azepine derivatives **32**, respectively, serve as examples (Scheme 6).[25]



Scheme 6. Synthesis of pyridine **31** and 2,3-dihydro-azepine derivatives **32** from methyl coumalate **23**.

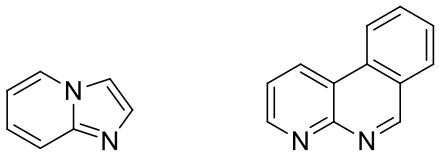
Lactamization of 2-pyridone and its derivatives like coumalate **23** offer an easy access to the 2-pyridone core, which is ubiquitous in nature, and is also an important entry into the pyridine nucleus and related *N*-heterocyclic frameworks. For example, the synthesis of the [1,2,4]triazolo[1,5-*a*]pyridine motif was achieved in three steps through lactamization of **23** with hydrazides **33**, to yield dihydrazide intermediates **34**, which were converted to the target triazolo-pyridine derivatives **35** (Scheme 7).[26]



Scheme 7. Synthesis of triazolo-pyridine core through lactamization of methyl coumalate **23**.

The triazolo-pyridine nucleus is known for its diverse biological activities; hence it is found embedded in several drug candidates, mostly in patent literature.[26] This pyridine-based framework is not unique in its renowned biological activity. Indeed, its methine congener imidazo[1,2-*a*]pyridine (IP) **36** (Figure 5) also possesses such activity. In this project, we set out to synthesize this privileged scaffold. In addition, we also sought to establish a synthetic process for the synthesis of benzo[*c*][1,8]naphthyridine **37** (Figure 5), another promising scaffold that appeared in a single patent literature.[27]

In this study, we wish to employ bio-renewable MA **20** in the synthesis of suitably functionalized 2-aminopyridines, a common starting material, to synthesize imidazo[1,2-*a*]pyridines **36** and benzo[*c*][1,8]naphthyridine **37** frameworks.



36 **37**

Figure 5. Chemical structure of imidazo[1,2-*a*]pyridine **36** and benzo[*c*][1,8]naphthyridine **37** frameworks.

1.3 Pyridine and polycyclic *N*-heterocyclic compounds

Pyridine is a six-membered aromatic ring that contains a single nitrogen atom. Pyridine and its derivatives are commonly found in natural products and biologically active synthetic compounds. This family of compounds also plays an important role in heterocyclic chemistry.[28] Pyridine **38** (Figure 6) and its derivatives are significant chemical compounds that have a wide range of applications.



Pyridine, **38**

Figure 6. Chemical structure of pyridine **38**.

Not surprisingly, pyridine compounds have always been important in pharmaceutical applications, and this trend has not changed.[28,29] A variety of chemical compounds with heterocyclic structural frameworks, containing favoured six-membered *N*-containing pyridine rings, have been found and are connected to a wide spectrum of bioactivity.[29] Figure 7 depicts isoniazid **39**, which is used in the treatment of tuberculosis, and tacrine **40**, which is used to treat Alzheimer's disease. There are also many pyridine-containing medicines employed in cancer therapy such as axitinib **41** (Figure 7), a tyrosine kinase inhibitor.[29]

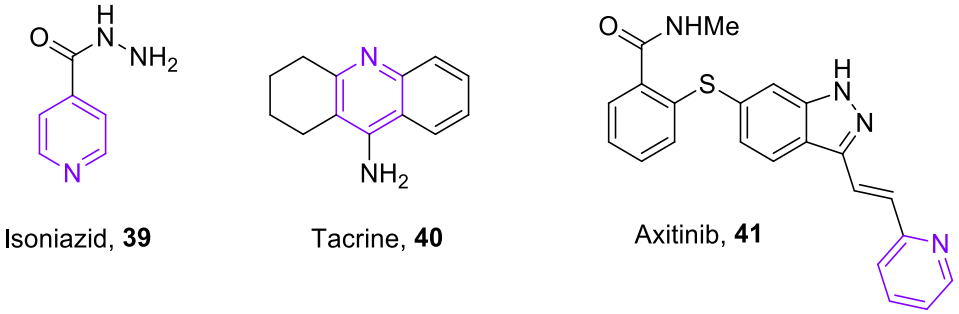
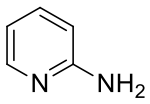


Figure 7. Structure of isoniazid **39**, tacrine **40** and axitinib **41**.[29]

Due to the pyridine core's significance in both biological and chemical domains, scientists have been developing methods for pyridine synthesis for a long time, and it is doubtful that interest in the topic will decline.[30] In the past, pyridine was distilled from coal tar, as a byproduct of coal gasification.[31] This method of producing pyridines was unable to keep up with the market's growing demand.[31] Currently, pyridines are industrially produced using formaldehyde, acetaldehyde, and acrolein which are, however, derived from non-renewable fossil fuels. Acrolein and formaldehyde are extremely harmful and carcinogenic. Therefore, finding a sustainable and environmentally acceptable feedstock to generate pyridines on a wide scale would be ideal.[31] 2-Aminopyridine **42** is a useful starting material for the synthesis of heterocyclic compounds with pharmacological activity, despite having a simple skeleton and little structural complexity.[32] It is made of an amine group at the C-2 position of a pyridine ring, see Figure 8. The substitution pattern of 2-aminopyridine allows for the synthesis of numerous heterocyclic moieties.[32]



42

Figure 8. Chemical structure of 2-aminopyridine **42**.

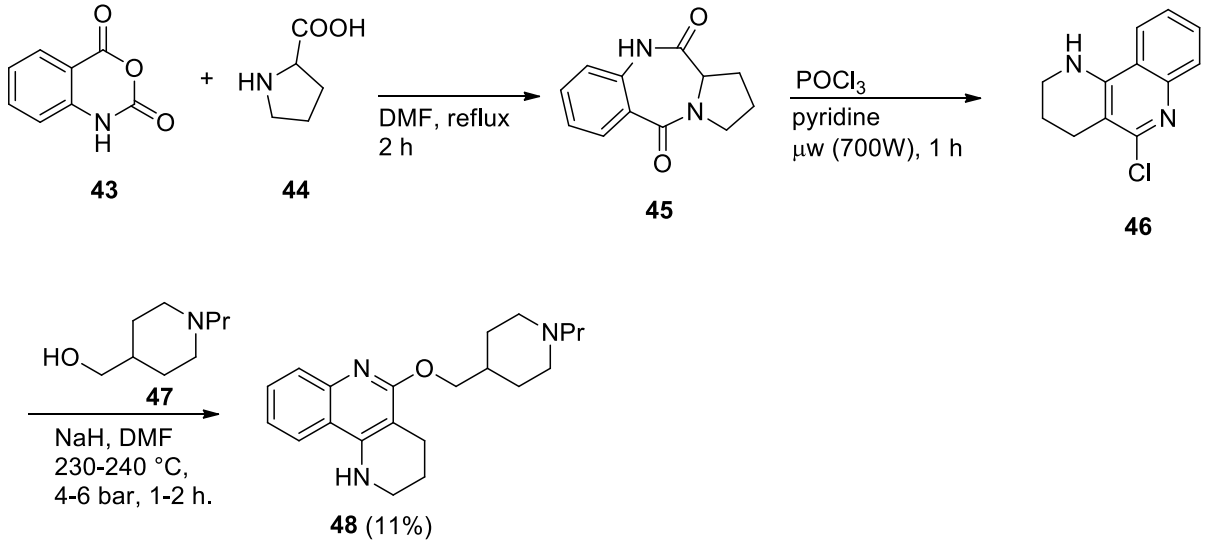
1.4 Synthesis and bioactivities of pyridine-derived *N*-heterocyclic compounds

2-Aminopyridine **42** is the key ingredient in the production of medicines, specifically piroxican and antihistamines.[33] Due to its importance in heterocyclic chemistry, synthetic chemists have devised ways to form 2-aminopyridine. The Chichibabin reaction is the best-known method for the synthesis of 2-aminopyridine **42**. This method is based on the reaction between sodium amide and pyridine.[34] However this reaction

does have some draw backs like the use of extremely basic conditions and high temperatures, along with a narrow range, production in adequate yields and poor functional group tolerance.[35] Furthermore, this reaction is performed on an already formed pyridine ring, which is typically derived from fossil fuels.

1.4.1 Synthesis and bioactivities of benzonaphthyridinones

The most significant scaffolds in medicinal chemistry are substituted nitrogen heterocycles. As a result, the development of novel efficient and diverse techniques for the synthesis of nitrogen heterocycles is a hot subject in organic synthesis. Thus, medicinal and synthetic chemists are involved in finding novel scaffolds or inventing new reactions to access known motifs. For example, derivatives of tricyclic benzo[*h*][1,6]naphthyridine, azepino[3,2-*c*]quinoline and tetracyclodibenzo[*b*,*h*][1,6]naphthyridine were synthesized and evaluated as analgesic agents.[36] To ascertain structure and reactivity patterns on these tricyclic skeletons, the different substitutions were made to identify the structural requirements for excellent affinity and selectivity. The authors discovered compound **48** (Scheme 8) was of particular interest because of its high affinity and selectivity, as well as its powerful analgesic activity *in vivo*.[36]



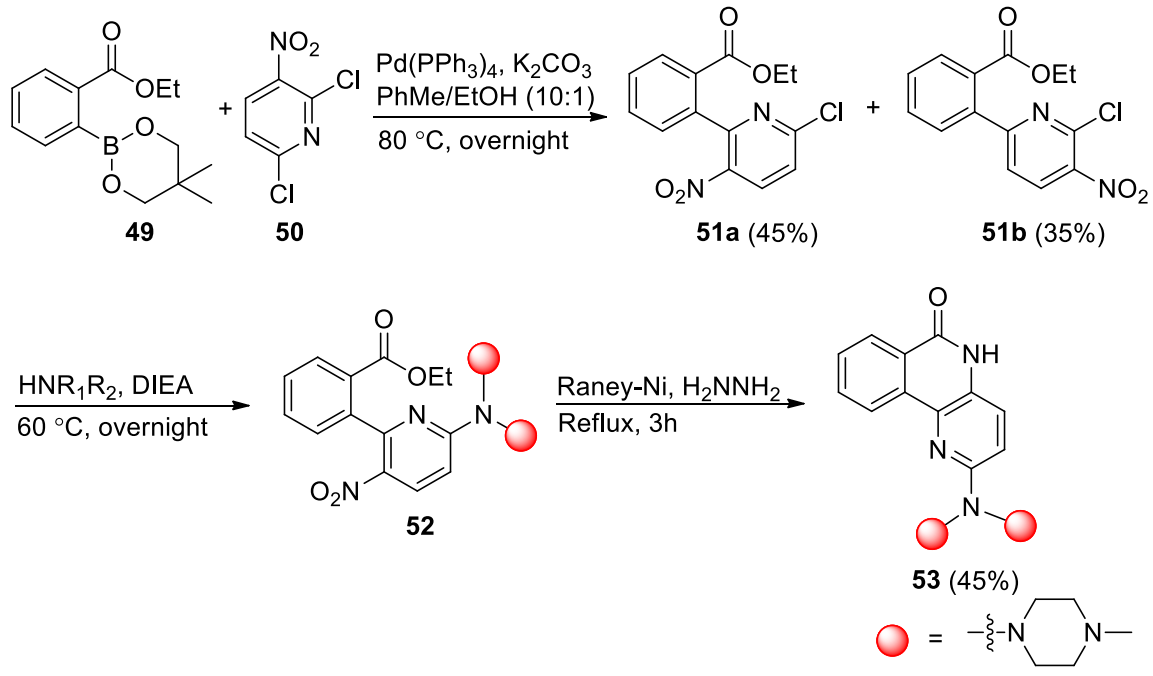
Scheme 8. The synthesis of tricyclic compound **48**.[36]

Compound **48** was synthesized in three steps, beginning with the condensation of isatoic anhydride **43** and 1-proline **44** to yield pyrrolo[2,1-*c*][1,4]benzodiazepine **45**. Compound

45 was rearranged to 5-chloro-1,2,3,4-tetrahydrobenzo[*h*][1,6]-naphthyridine **46**, on boiling with phosphorus oxychloride in a microwave, and a catalytic quantity of pyridine. Compound **46** underwent nucleophilic substitution with (1-propylpiperidin-4-yl)methanol **47** in anhydrous DMF at high temperatures resulting in the displacement of the chlorine atom , giving **48** with a yield of 11% for this step.[36]

The synthesis of an oxidized form of the 1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine **48**, i.e. benzo[*h*][1,6]naphthyridin-5(6*H*)-one **53** was reported by Ferraris and co-workers.[37] A series of benzo[*h*][1,6]naphthyridin-5(6*H*)-one derivatives **53** were synthesized and tested against poly ADP-ribose polymerase-1 (PARP-1) inhibitors. PARP-1 is involved in the cellular life cycle by initiating DNA repair. Its inhibition can prevent cancer cells with damaged DNA from repairing and reproducing. PARP-1 has also been identified as a therapeutically significant target for ischemia injuries.[37]

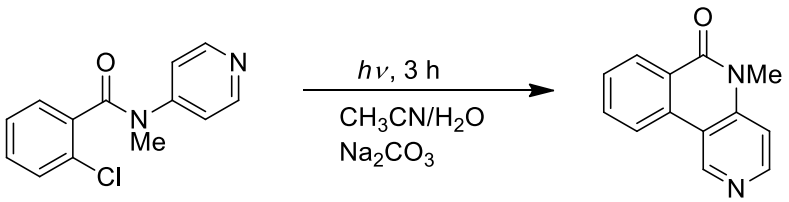
The efficacy of benzonaphthyridones was discovered to be affected by the location of the nitrogen atom inside the core structure. The authors produced variations of the 1-aza-5[*H*]-phenanthridin-6-one core **53**, three of these substrates were shown to possess inhibitory activity against PARP-1, with notable effects in rat models of stroke and cardiac ischemia (Scheme 9).[37]



Scheme 9. The synthesis PARP-1 inhibitor **53**.[37]

The synthesis of 2-amino-1-aza-5[*H*]-phenanhridin-6-one **53** commenced with the Suzuki reaction between boronic ester **49** and 2,6-dicholoro-3-nitropyridine **50** to produce a mixture of the desired isomer **51a**, and undesirable compound **51b**. After separation by column chromatography, compound **51a** was transformed into the nitro ester **52** by nucleophilic aromatic substitution with *N*-methylpiperazine. The nitro group was then reduced, producing an amino ester that immediately cyclized yielding 2-amino-1-aza-5[*H*]-phenanhridin-6-one **53**.[37]

The synthesis of benzo[*c*][1,6]naphthyridin-6(5*H*)-one analogue **55**, which is isomeric to the benzo[*c*][1,5]naphthyridin-6(5*H*)-one derivatives **53** discussed above, was described by Park and colleagues.[38] Their synthesis relied on the photocyclization of 2-chloro-*N*-methyl-*N*-(pyridin-4-yl)benzamide **54** (Scheme 10). Despite this reaction's fantastic yield and step economy, it appears to have a limited substrate scope. Nevertheless, the authors[38] realized the significance of establishing synthetic techniques for heterocyclic molecules like benzonaphthyridinones and their derivatives.

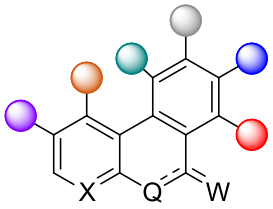


54 **55** (85%)

Scheme 10. Photochemical reaction of 2-chloro-*N*-methyl-*N*-pyridinylbenzaminde **54** to produce photocyclized product 5-(methyl)-benzo[c][1,6]naphthyridine-6(5H)-one **55**.[38]

A related series of benzo[*c*][1,8]naphthyridin-6(5*H*)-ones **56** and their oxygenated congeners were reported in patent literature.[27] The inventors of a patent developed these compounds as potential protein kinase inhibitors like that of Aurora protein kinase. This was conducted to investigate treating diseases connected with these protein kinases, particularly those associated with Aurora A and Aurora B, such as cancer. Protein kinases are a vast class of proteins that play an important role in the regulation of many cellular processes. Aurora kinases are overexpressed in several malignancies, and the study suggested techniques for cancer metastasis.[27] As a result, inhibiting such kinases has emerged as a significant therapeutic target.[27]

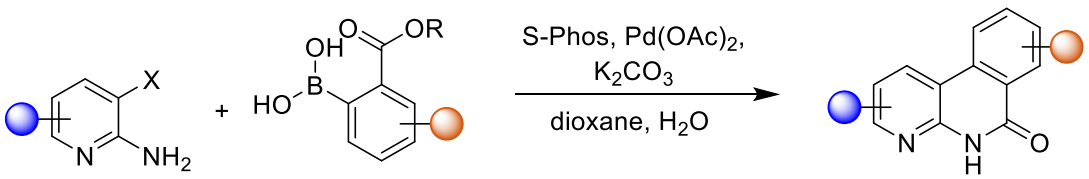
The patent disclosed novel, and selective compounds that showed activity against adenosine triphosphate (ATP) competitive inhibitors of Aurora kinases (A, B and C). The structure of the compounds that were investigated in the study can be generalized in accordance with framework **56** in Figure 9.



56

Figure 9. Framework **56** for compounds synthesized and studied for its effect as a protein kinase inhibitor.[27]

The benzonaphthyridinone scaffold was produced in two steps. This first step was a Suzuki reaction between 2-aminopyridine **57** and boronic acid **58**, this was followed by a ring-closing transamidation to give **59**, as indicated in Scheme 11. A broad range of 2-amino-3-halo pyridines **57** were coupled with 2-substituted boronic acids **58** to yield a collection of substituted benzonaphthyridinones **59**.[27]



57 **58** **59**

Scheme 11. Reaction sequence for the synthesis of substituted benzonaphthyridinones.[27]

1.4.2 Synthesis and bioactivities of benzonaphthyridinones

2-Aminopyridines also grant access to derivatives bearing the imidazo[1,2-*a*]pyridine core **36**, which have many uses in medicinal chemistry containing the preferred pyridine structural motif.[39,40] The core structure is found in several well-known medications (Figure 10) like zolimidine (anti-ulcer),[41] zolpidem for treating insomnia,[42] alpiodem as an anxiolytic,[43] and many other medicinal properties.[44]

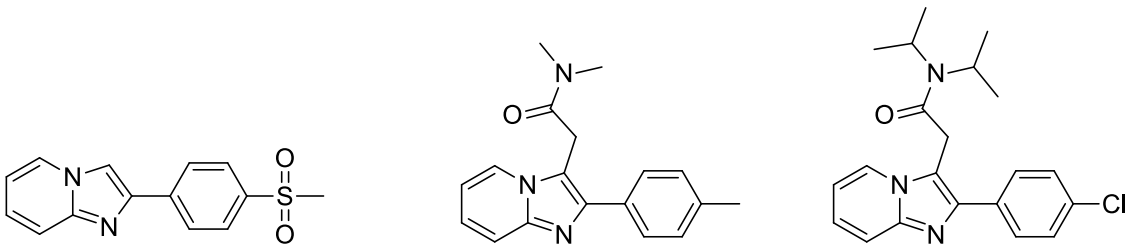
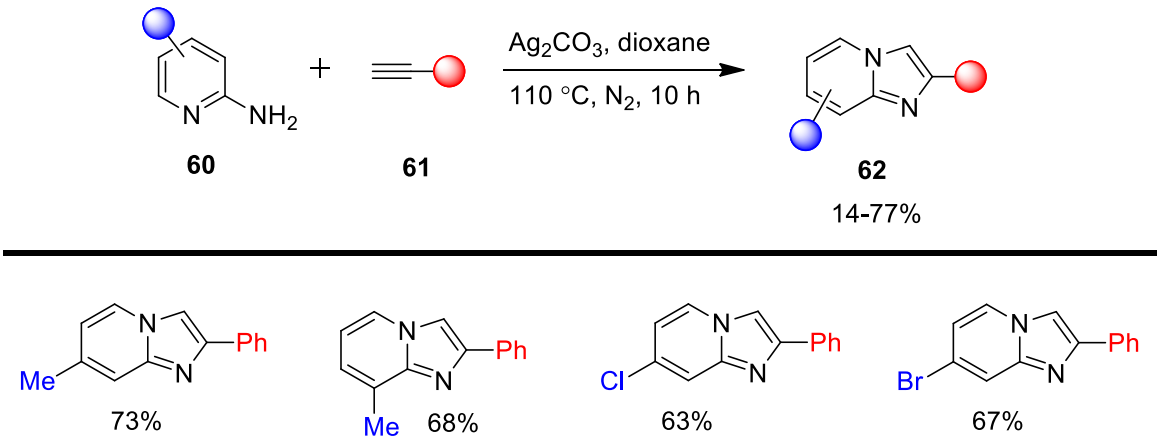


Figure 10. Drugs containing the imidazo[1,2-*a*]pyridine core.

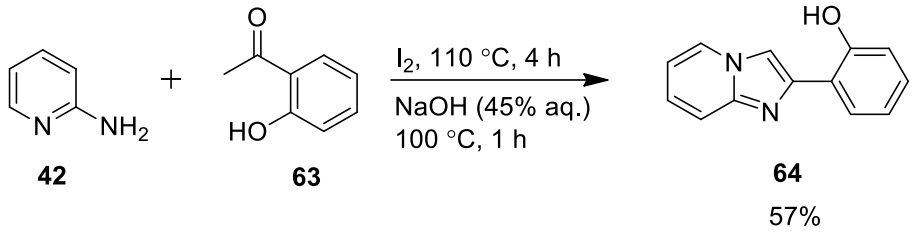
A number of synthetic methods for imidazo[1,2-*a*]pyridines have been established due to their use in many sectors. These methods include several intriguing strategies like multicomponent reactions, tandem sequences and transition-metal-catalyzed C-H functionalizations.[39] He *et al.*[45] have demonstrated that 2-aminopyridines and terminal alkynes may undergo a new, highly selective C-H/C-N oxidative cross-coupling/cyclization mediated by silver. This involves the reaction of the amine group of substituted 2-aminopyridines **60** with substituted alkynes **61** catalyzed by Ag_2CO_3 to give functionalized imidazo[1,2-*a*]pyridines **62** in satisfactory yields[45] as shown in Scheme 12. Generally, with this type of reaction, challenges such as selectivity and the homocoupling of the terminal alkyne were found. However, the Authors[45] successfully developed a selective and by-product free route for this reaction mediated by silver carbonate.



Scheme 12. Reaction of 2-aminopyridines with alkynes for the formation of imidazo[1,2-*a*]pyridines.

Most of the preparations use readily available 2-aminopyridine that is obtained through the Chichibabin reaction between pyridines and sodium amide.[46] For example, Stasyuk *et al.*[47] formulated a process for the synthesis of [1,2-*a*]pyridines derivatives **67** through

the reaction of 2-aminopyridines, acetophenones, and iodine in a one-pot process utilizing the Ortovela-King reaction. In optimization studies, 2-aminopyridine **42** and 2-hydroxy acetophenone **63** were reacted and tested under various optimization parameters to give the IP product **64** in 57% yield, Scheme 13.



Scheme 13. Synthesis of imidazo[1,2-*a*]pyridine **64** using acetophenones.

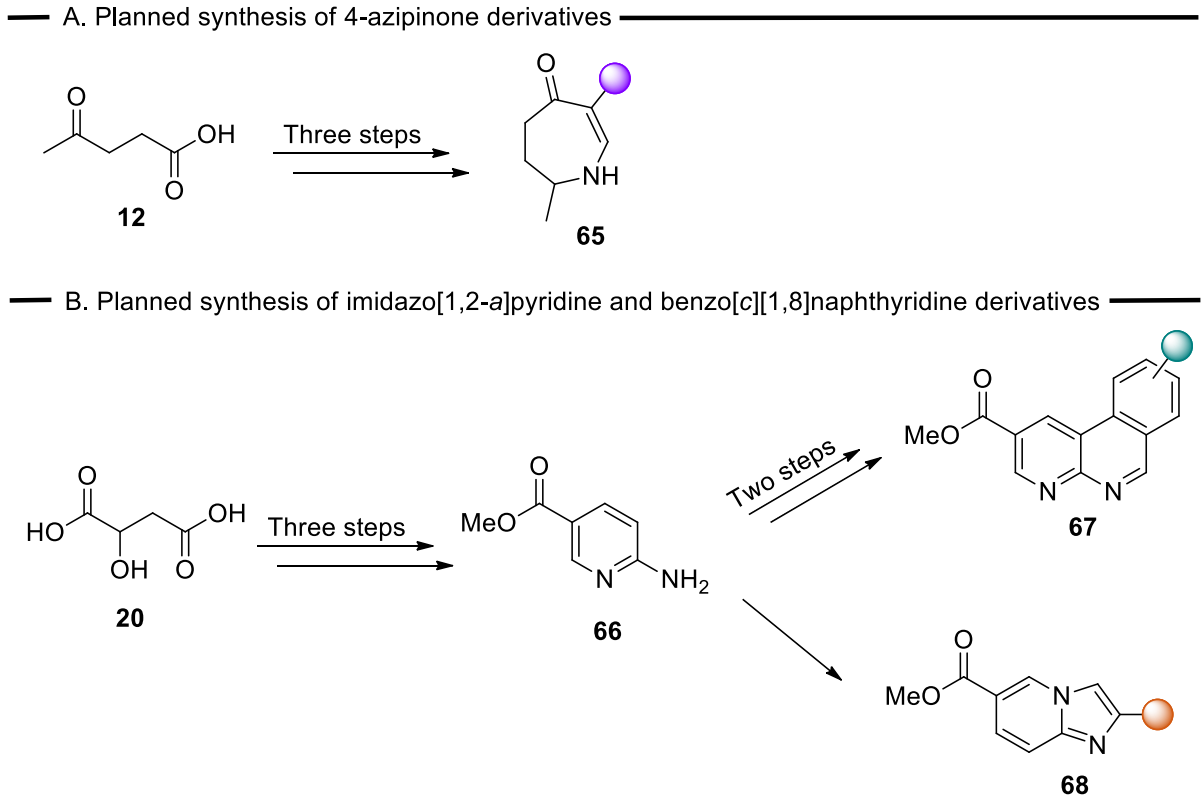
The extensive impact of pyridines and their derivatives on pharmacological activity, as well as their remarkable therapeutic applications, has prompted researchers to produce numerous biologically active compounds containing pyridine, broadening the possibility of developing a cure for other illnesses.[28] However, an overwhelming number of the compounds that have been synthesized depend on depleting, carbon non-neutral fossil fuel starting materials. We propose that these pyridine-based polycyclic compounds can be obtained from biorenewable raw materials.

The synthesis of a functionalised 2-aminopyridine from biorenewable resources offers a substantial chance to promote sustainability and green chemistry. In addition to increasing the accessibility to such 2-aminopyridines, a greener synthesis process would also help in lowering the dependency on non-sustainable resources and provide a method for its conversion into a variety of other useful heterocycles, which is demonstrated in this work.

1.5 Aims and objectives

The aim of this work is to synthesise *N*-heterocyclic compounds from bio-renewable starting materials. We aimed to synthesize 4-azipinone derivatives **65** from levulinic acid **12** (Scheme 14a). Furthermore, we aimed to develop the synthesis of derivatives bearing either an imidazo[1,2-*a*]pyridine **67** or benzo[*c*][1,8]naphthyridine **68** core from a suitably substituted methyl nicotinate derivative **66** (Scheme 14b). The requisite methyl

nicotinate derivative **65** in turn will be obtained from malic acid **20** in three isolable steps. In addition to employing bio-renewable malic acid **20**, we seek to incorporate more principles of green and sustainable chemistry in our synthetic route. Consequently, catalytic manifolds will feature in the synthetic route of all the targeted compounds. We envision that palladium catalysed reactions such as the Suzuki coupling and Sonogashira coupling reactions which will be utilized in our planned synthesis of the desired tricyclic compounds.



Scheme 14. Proposed synthesis of a) 4-azipinone derivatives **65** from levulinic acid **12**; b) imidazo[1,2-*a*]pyridine 67 or benzo[*c*][1,8]naphthyridine **68** derivatives from malic acid **20**, via 2-aminopyridine derivative **66**.

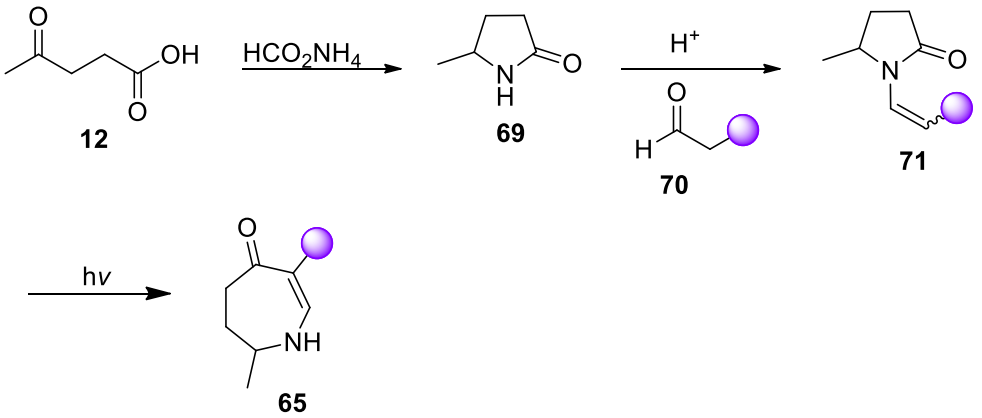
Chapter 2

2. Results and Discussion

As stated in the preceding chapter, we sought to utilize acyclic acids, products of fermentation of naturally occurring sugars, as starting materials for more complex scaffolds.[48] The ensuing chapter will detail the efforts towards the synthesis of 4-azepinone derivatives from levulinic acid **12** and pyridine derivatives from malic acid **20** and subsequent elaboration to polycyclic *N*-heterocyclic compounds.

2.1 Synthesis of 4-azepinone derivatives from levulinic acid

The first part of this chapter deals with the attempted synthesis of the 4-azepinone framework **65**, via the synthetic route shown in Scheme 15. The planned synthesis relied on a photochemical skeletal editing operation of *N*-vinyl 2-pyrrolidones **71**, which should deliver the target 4-azipinone derivatives **65**. The *N*-vinyl 2-pyrrolidones **71**, would, in turn, be obtained from the condensation of 5-methylpyrrolid-2-one **69** and various enolizable aldehydes **70**. Conversely, 5-methylpyrrolidin-2-one **69** is obtainable from the bio-renewable levulinic acid **12**, as proposed in Scheme 1.

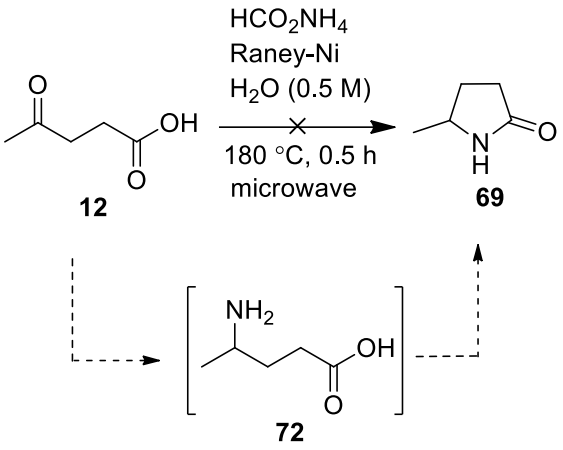


Scheme 15. The original plan for the synthesis of 4-azepinone derivatives.

2.1.1 Attempted synthesis of *N*-vinyl 2-pyrrolidone

The synthesis of the requisite *N*-vinyl 2-pyrrolidones **71** necessitated the construction of 5-methyl-2-pyrrolidinone **69** from levulinic acid **12**. The aim here was to obtain the amine group from a renewable nitrogen source. Ammonium formate was identified as

a suitable nitrogen source since it is produced from the reaction of ammonia and formic acid, both renewable molecules. Thus, following a literature report,[49] a mixture of levulinic acid **12**, ammonium formate and Raney-Nickel in water was irradiated in a microwave reactor (Scheme 16). This reaction between levulinic acid **12** and ammonium formate was expected to lead to a reductive amination product γ-amino acid **72** (Scheme 2). Amino acid **72** is expected to cyclise spontaneously to give the 5-methyl-2-pyrrolidinone **69**. TLC analysis showed the consumption of the starting material (SM), however, the ^{1}H NMR spectrum obtained for the sample after the work-up did not show the expected chemical shifts for compound **69**.



Scheme 16. First attempted synthesis of 5-methlypyrrolidin-2-one **69** with Raney-Nickel as a reductant.

Since the NMR spectroscopic data was inconclusive, we suspected two possibilities: Firstly, it was likely that γ-amino acid **72** could have formed, but instead of cyclizing, it formed the stable zwitterion **72a** (Figure 11). Alternatively, the reduction step could have failed, leading to intermediate **72b**.

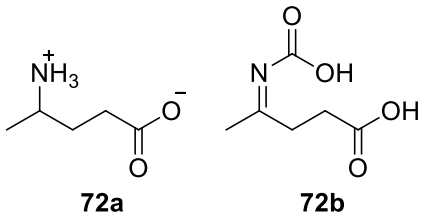
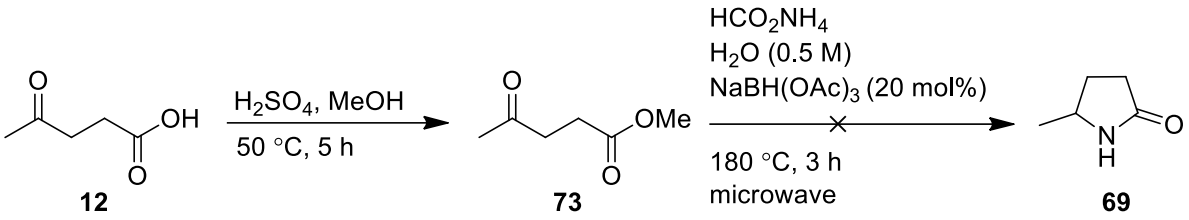


Figure 11. Possible intermediates of the reaction between levulinic acid **12** and ammonium formate.

At the time, the results obtained when Raney-Ni was used as a reductant appeared to enforce the assumption that intermediate **72a** could be formed in the course of the reaction. To circumvent the suspected acid-base reaction leading to the zwitterion **72a**, it was necessary to protect the carboxylic acid group. Thus, levulinic acid **12** was protected as a methyl ester using methanol in the presence of sulfuric acid, to form methyl levulinate **73** in a fair yield of 67% (Scheme 17). The obtained yield is significantly lower than the reported yield of 99%.[50] The yield could possibly be increased if the ratio of levulinic acid **12** increased, since this an equilibrium reaction. However, no such effort was made to improve the yield, since the product obtained was enough to test out the reaction. Both the ^{1}H and ^{13}C NMR spectroscopic data obtained for **73** matched the data reported in literature.[50]

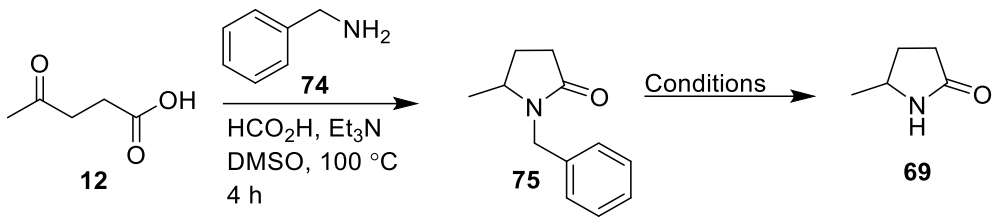


Scheme 17. Esterification of levulinic acid **12** and the subsequent attempted synthesis of 5-methly-2-pyrrolidinone **69**.

Reacting compound **73** under reaction conditions given in Scheme 17 using sodium triacetoxy borohydride as a reducing agent, once again, failed to give the desired 5-methly-2-pyrrolidinone **69**. This reaction also gave a messy ^{1}H NMR spectrum.

Undeterred, it was decided to change the nitrogen source from ammonium formate to benzylamine **74**. Benzylamine **74** was selected because once the 5-methyl-2-pyrrolidone moiety is formed, the benzyl fragment can be removed using the known *N*-benzyl deprotection conditions. This approach would introduce an extra step; the deprotection step, however, at this point, we were keen to establish the synthesis of 5-methyl-2-pyrrolidinone **69** and improving the route could be considered at a later stage. Therefore, following a literature report,[51] levulinic acid **12** was reacted with benzylamine **74** resulting in *N*-benzyl-5-methyl-2-pyrrolidinone **75** in a moderate yield of 60% (Scheme 18). The reported yield of 87%[51] was higher than the obtained yield for this reaction. Loss of product occurred during purification where the product could

have co-eluted with other impurities. The NMR spectroscopic data matched the literature report.[51]



Scheme 18. Synthesis of *N*-benzyl-5-methyl-2-pyrrolidinone **75**.

The next step was the removal of the benzyl protecting group. Frustratingly, none of the literature procedures for the removal of the benzyl group we tried led to the isolation of the target compound **69**. Some of the reaction conditions we attempted are enumerated in Table 1 below.

Table 1. Reaction conditions for the attempted debenzylation of *N*-benzyl-5-methyl-2-pyrrolidinone **75**.

Entry	Reagents	Temperature (°C)	Time (h)	Outcome
1	CAN, H_2O, MeCN	Room temperature	24	Starting material recovered
2	CAN, H_2O, MeCN	0	4	Starting material recovered
3	KO^{t}Bu, DMSO, THF	Room temperature	0.4	Starting material recovered
4	H_2O/MeCN (1:2, v:v), PIDA	Room temperature	24	Starting material recovered
5	10% Pd/C, MeOH, H_2	30	24	Starting material recovered
	10% Pd/C, MeOH, H_2 (5 – 7 bar)	Room temperature	24	Starting material recovered

6	TfOH, toluene, dowex	150 – 210 (Microwave)	0.4 – 0.5	Sarting material consumed, unidentifiable compounds recovered
	TfOH, toluene			
	TfOH, DMSO			
	TfOH, benzene			

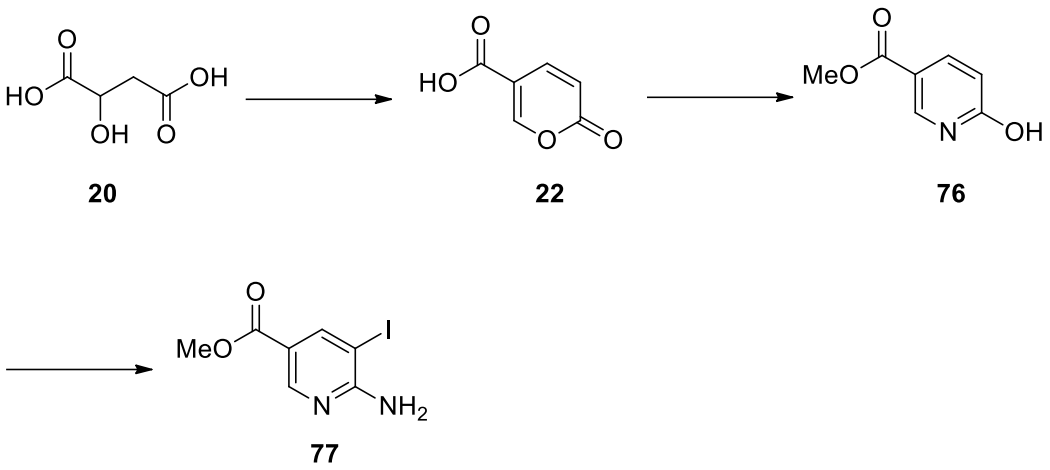
Starting material = *N*-benzyl-5-methyl-2-pyrrolidinone **75**

At this juncture, we speculated that the product may have been decomposing in the reaction and decided to purchase a sample of 5-methyl-2-pyrrolidone **69** from Merck to assess its behaviour. Our suspicions were confirmed when it was delivered wrapped in ice bricks! In retrospect, it is possible that some, if not all, of the reactions above leading to compound **69** were successful, but could not be isolated due to its thermal instability.

Such is the nature of synthesis; it looks straightforward on paper, and it is almost impossible to foretell the stability of an important intermediate from a hand-drawn structure. A foretaste of what awaited us in the future (more on this later). By the time we confirmed the thermal instability of 5-methyl-2-pyrrolidone **69**, precious time had been lost and promising results were being obtained in the second project of interest to this report, the synthesis of pyridine derivatives from bio-renewable malic acid **20**. These efforts are still within the focus of the synthesis of *N*-heterocyclic compounds from bio-renewable resources. We decided to completely abandon the synthesis of 5-methly-2-pyrrolidinone **69** and ultimately 4-azipinone derivatives **65**, to focus fully on the synthesis of pyridine derivatives and the subsequent elaboration to other *N*-heterocyclic compounds.

2.2 Synthesis of 2-aminopyridine derivatives

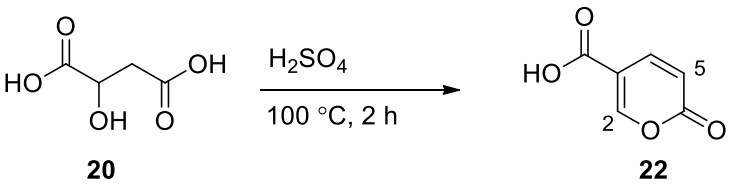
The overview of the planned synthetic route for the preparation of 2-aminopyridine derivatives is delineated in Scheme 19. Dimerization of malic acid **20** to afford coumalic acid **22**, followed by esterification and aminolysis will give methyl 6-hydroxynicotinate **76**. Methyl 6-hydroxynicotinate **76** could then be functionalized into methyl 6-amino-5-iodonicotinate **77**, among other 2-aminopyridine analogues.



Scheme 19. Proposed synthetic route to methyl 6-amino-5-iodonicotinate **77**.

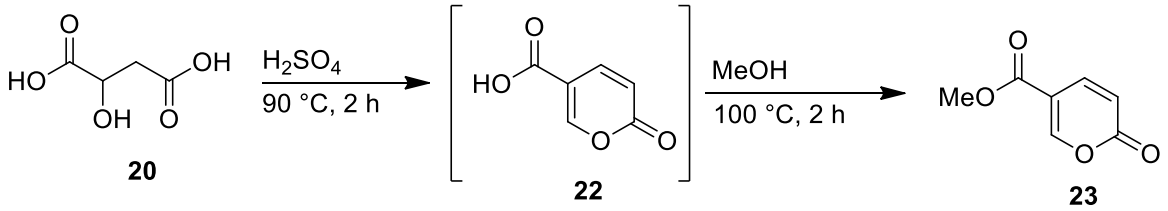
2.2.1 Synthesis of coumalic acid and methyl coumalate

The planned synthesis of pyridine derivatives commenced with the synthesis of coumalic acid **22** through acid-catalyzed dehydration of malic acid (Scheme 20). Coumalic acid **22** was obtained as a brown and sticky substance that was difficult to handle. The ^{1}H NMR spectroscopic data showed three doublet of doublets signals at 8.31, 7.80, and 6.35 ppm, corresponding to the three ring protons. The long-range coupling between protons at positions 2 and 5 is unusual for the ring protons. (*Note: the numbering here does not follow the IUPAC system, because this would lead to confusion in the latter parts of this Dissertation where direct comparison is made between the coumalate and the 6-hydroxynicotinate motifs, whose numbering goes in opposite directions*). In the ^{13}C NMR spectrum, the four signals in the region 142.3 – 112.4 ppm and the two carbonyl carbon peaks at 164.4 and 158.4 ppm, further confirmed the assignment of the coumalic acid **22** as the product. Unfortunately, though, the reaction gave a disappointingly low 8% yield, which is not acceptable for the first step in a multi-step synthesis.



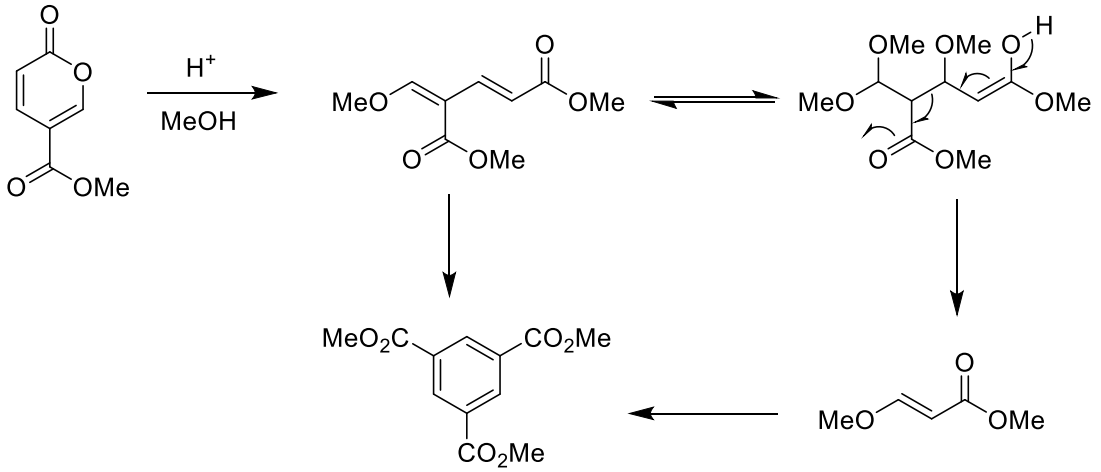
Scheme 20. Synthesis of coumalic acid **22**.

The synthesis of coumalic acid **22** was found to reduce yields at larger scales.[20] Moreover, coumalic acid's poor solubility limits its utilization, even though it's a desirable starting material for numerous synthetic applications. The methyl ester of coumalic acid **22** is more frequently utilized as a more suitable starting material. With this in mind, it was decided to treat coumalic acid **22** as an intermediate in the one-pot two-step synthesis of methyl coumalate **23** from malic acid **20**, following the procedure outlined in the literature (Scheme 21).[20]



Scheme 21. One-pot synthesis of methyl coumalate **23**.

Methyl coumalate **23** was formed with an improved yield of 30 – 60% yield. These inconsistent yields are due to the methyl coumalate **23** being unstable under the reaction conditions and that it breaks down and reorganizes into the other ring species, as in Scheme 22.[20]



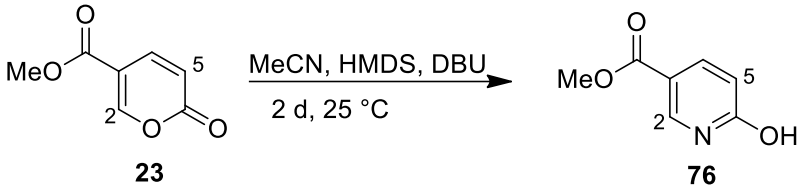
Scheme 22. Production of by-product when coumalic acid **22** is methylated.[20]

The identity of the compound **23** was confirmed by NMR spectroscopy. The appearance of the methoxy peak at 3.89 ppm in the ^{1}H NMR spectrum of **23** was observed, along with the corresponding peaks at 8.30 - 8.21, 8.07, and 6.65 ppm. The ^{13}C NMR spectrum also showed peaks at 165.1 and 164.3 ppm, corresponding to the two ester carbonyl carbon peaks, and the ring carbon peaks at 141.6, 139.7, 119.3 and

112.0 ppm. The melting point for methyl coumalate **23** was recorded at 66 – 68 °C which aligns to literature reports.[20]

2.2.2 Synthesis of methyl 6-hydroxynicotinate

Satisfied with the synthesis of methyl coumalate **23**, we shifted our focus to the synthesis of methyl 6-hydroxynicotinate **76**. To achieve the synthesis of methyl 6-hydroxynicotinate **76**, methyl coumalate **23** was subjected to an aminolysis reaction using HMDS as a nitrogen source to form the desired compound **76** as shown below in Scheme 23.



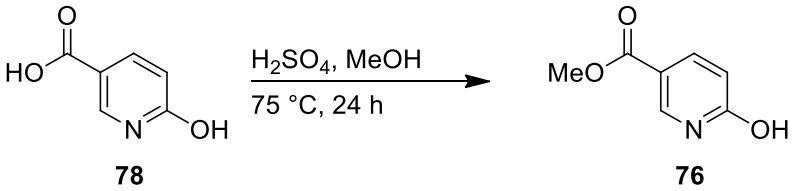
23 **76**

Scheme 23. Synthetic route for the aminolysis of methyl coumalate **23** to methyl 6-hydroxynicotinate **76**.

When we first attempted the aminolysis reaction, we used 16 equivalents of DBU. This proved challenging with product isolation, leading to poorer yield of 14%. However, a literature search revealed that the aminolysis reaction rate is affected by the substituent on the 3-position of the ring.[52] The electron-donating groups have a detrimental effect on the rate of the reaction, while the electron-withdrawing substituents increase the rate of the reaction. We reasoned that, since the substituent is a methyl ester in our case, less DBU would be required. After much experimentation with the amount of DBU added, we found that 5 mol% gave the best yield of 72%. In addition, the increased yield could also be attributed to the use of DBU in catalytic amounts, which aided in the isolation challenges that were brought about by using copious volumes of this base. The formation of the product was confirmed by the downfield shift of the ring peaks, for example the protons in positions 4 and 5 from 7.80 and 6.35 ppm on compound **23** to 8.07 and 6.65 ppm on compound **76**. The downfield shift is consistent with the formation of the 2-pyridinone ring. In addition, the presence of the C-OH group was indicated by a broad singlet at 12.5 ppm in the proton NMR spectrum and a downfield shift from 159.8 to 164.3 ppm in the carbon NMR spectrum.

A similar, smaller shift was observed for protons in the 2-position of these compounds. The ^{13}C NMR spectrum presents carbon peaks in alignment with the above-described shifts, additionally a significant upfield shift of the C-2 peak from 158.2 ppm to 141.6 ppm is due to the amide group resonance. These agree with the reported literature.[52]

The methyl 6-hydroxynicotinate **76** obtained from malic acid **20** was used to synthesize methyl 6-amino-5-iodonicotinate **77**, as described in the ensuing discussion. However, the inconsistent yields obtained of 30 – 60%, in the formation of methyl coumalate **23**, could not be improved in our hands, despite numerous attempts to improve them. We recognize that for the synthesis of pyridine-based *N*-heterocyclic compounds from malic acid **20**, using our process, it is important to improve the yield of the first step. However, for the purposes of establishing synthetic routes to pyridine-based polycyclic compounds, we sought a different method to access methyl 6-hydroxynicotinate **76** to enable this. The commercially available 6-hydroxynicotinic acid **78** was an obvious choice, because a single esterification operation would lead to the desired methyl 6-hydroxynicotinic acid **76**. Thus, 6-hydroxynicotinic acid **78** was treated with methanol and catalytic amounts of sulfuric acid at ambient temperature provided **76** in higher yields (75%) (Scheme 24). This method had an added advantage of effortless isolation of methyl 6-hydroxynicotinate **78** without the need for an additional purification step.



78 **76**

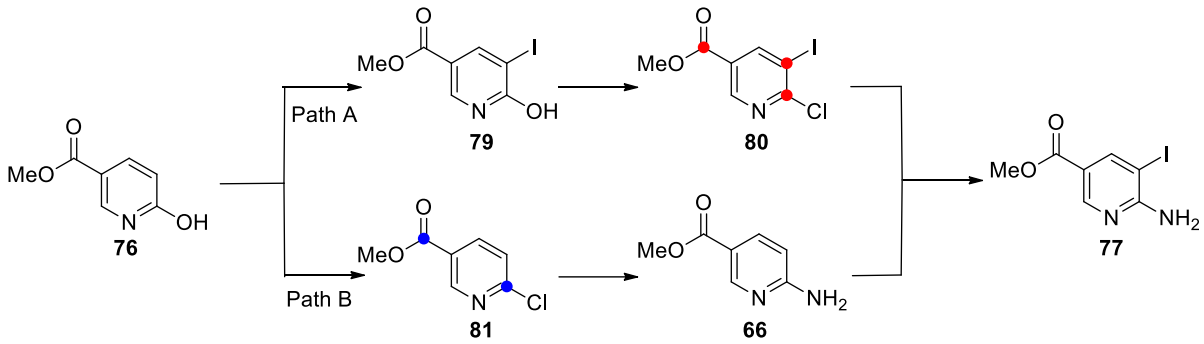
Scheme 24. Esterification of 6-hydroxynicotinic acid **78**.

The expected methoxy peak was observed in the proton NMR spectrum at 3.89 ppm confirming formation of the ester. In addition to the expected six signals from 6-hydroxynicotinic acid **78**, the ^{13}C NMR spectrum of compound **76** shows an additional peak at 52.3 ppm. Both the ^{1}H and ^{13}C NMR spectra matched the data obtained from our other synthetic route (Scheme 23). Desired compound **76** was obtained in yields as high as 75% with a melting point of 162 – 163 °C which is aligned to that recorded in literature of 163 – 164 °C.[53] The methyl 6-hydroxynicotinic acid **76** isolated from the

first method had a recorded melting point of 157 – 160 °C. This lower melting point could be attributed to impurities as the second method produced a product of much higher purity (as per NMR spectrum). Thus, the melting point for the second method was much closer to the literature melting point.

2.2.3 Synthesis of methyl 6-amino-5-iodonicotinate

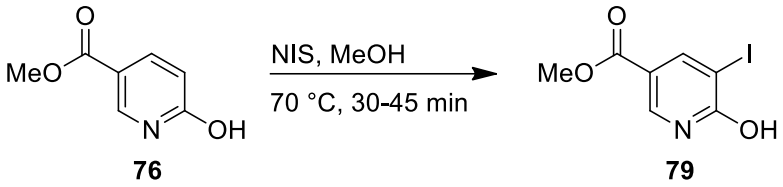
With large enough quantities of methyl 6-hydroxynicotinate **76** in hand, our focus turned to its functionalization to form the intermediates that are suitably substituted for the synthesis of *N*-heterocyclic frameworks. We envisaged that methyl 6-amino-5-iodonicotinate **77** could be achieved in one of the two paths, aptly named path A and B (Scheme 25). These proposed routes involved the same transformations, albeit, in a different order. Path A involved iodination of **76** to form **79**, followed by chlorination at the 6-position to give **80,** and finally the aminolysis to furnish **77**. Path B began with the chlorination-aminolysis sequence to yield **81** and **66**, respectively. Iodination of **66** fashioned **77**. We decided to undertake both paths, to determine which of the two is favourable operationally and better yielding.



Scheme 25. Possible synthetic routes to methyl 6-amino-5-iodonicotinate **77**.

It was visible from the outset that path A posed a greater risk than B. This assessment is based on the fact that intermediate **80** has three electrophilic sites (marked in red dots), which should be susceptible to nucleophilic substitution during the planned aminolysis. By comparison, intermediate **81**, destined to partake in nucleophilic substitution in path B contains only two electrophilic sites (represented by the blue dots). We were also aware of the possibility of transamination on the ester group. Despite this, we reasoned that aminolysis on both paths should proceed favouring substitution on position 6, when considering the electronics of the pyridine ring.

Notwithstanding these reservations, the work on the synthesis of methyl 6-amino-5-iodonicotinate **77** continued.



76 **79**

Scheme 26. Iodination of methyl 6-hydroxynicotinate **76**.

This began with the functionalization of methyl 6-hydroxynicotinate **76** at the 5-position via iodination to give methyl 6-hydroxy-5-iodonicotinate **79** in 96% yield (Scheme 26). The success of this reaction was confirmed by comparing the ^{1}H NMR spectrum of the product with that of the starting material. The spectrum of the product had one less aromatic proton; the proton signal at 6.65 ppm had disappeared. The signal due to the hydroxyl/amide proton of the product was still observed at 12.3 ppm, as seen in compound **76** as well, suggesting that compound **79** forms hydrogen bonded dimers. There are three possible dimers that could form from this compound, and they are shown in Figure 12. The true identity of the dimer is most likely the combination of all these structures. Furthermore, the observed splitting of the remaining two proton signals changed, where the signal due to the proton at the 4-position in compound **76** was previously a doublet of doublets at 8.07 ppm, after iodination, this now became just a doublet at 8.26 ppm with the lack of the adjacent proton. Likewise, the signal due to the proton at the 2-position of the starting material appeared as a multiplet at 8.30 – 8.21 ppm, whereas this same proton in compound **79** now gave rise to a doublet at 8.63 ppm. Furthermore, the ^{13}C NMR spectrum for compound **79** showed a peak at 89.1 ppm which is within the expected C-I region, the peak due to C-5 was at 112.0 ppm in compound **76**. Additionally, a sharp peak around 500 cm^{-1} is observed in the IR spectrum, which is characteristic of the C-I bond.

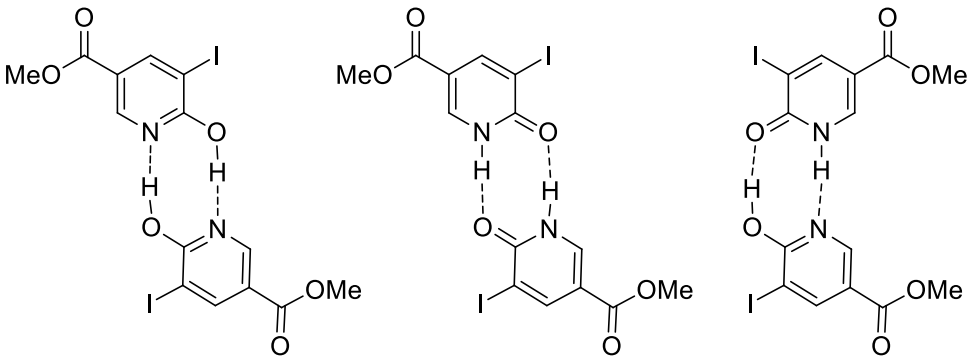
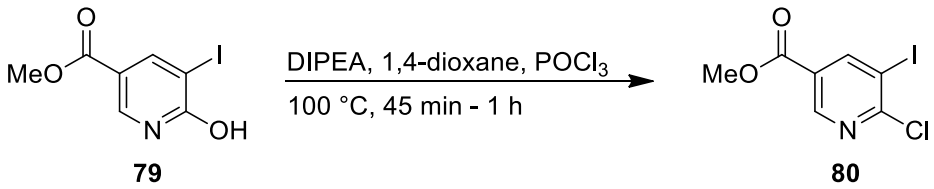


Figure 12. Possible H-bonded dimers of methyl 6-hydroxy-5-iodonicotinate **79**.

2.2.4 Synthesis of methyl 6-chloro-5-iodonicotinate

Encouraged by the yield and the ease with which the iodination worked, we proceeded to chlorinate compound **79** as illustrated in Scheme 27. The reaction gave poor yields when $POCl_3$ was not freshly distilled. The best yield we could obtain for methyl 6-chloro-5-iodonicotinate **80** was 80%. The ^{1}H NMR spectrum of **80** had two signals due to aromatic protons at 8.93 and 8.72 ppm. In addition, the broad singlet at 12.3 ppm was absent, indicating that the hydroxyl group was no longer present. Furthermore, in the ^{13}C NMR spectrum, we observed an upfield shift of the signal due to C-6 from 161.8 ppm to 158.7 ppm, as expected of the C-Cl bond.



79 **80**

Scheme 27. Chlorination reaction of methyl 6-hydroxy-5-iodonicotinate **79** to produce methyl 6-chloro-5-iodonicotinate **80**.

The methods for both the iodination and chlorination steps followed a literature report, where a comprehensive solvent screening was conducted, particularly for the chlorination step.[54] The study revealed that, of the solvents they tested, 1,4-dioxane was the best solvent for these reactions. It is noted that 1,4-dioxane may not be the preferred choice of solvent due to toxicity reasons, however, the research showed better conversion and satisfied scale-up needs as opposed to other greener solvents.[54] $POCl_3$ has also been stated as hazardous,[55] even so, the priority of the research was to demonstrate the conversion of a bio-renewable resource into useful

intermediates and compounds. Thereafter, the focus may be placed on optimizing reaction conditions and finding greener solvents and reagents as alternatives.

2.2.5 First synthesis of methyl 6-amino-5-iodonicotinate

The final step to achieving the anticipated intermediate **77** was carried out through the displacement of the chloro group in compound **80** with a nitrogen source. To achieve this, we experimented with amines and *in situ* generated ammonia. This effort led to inseparable mixtures of products. In particular, benzylamine led mostly to transamidation. Some of the reaction conditions tried and tested but resulted in no positive outcome are listed in Table 2 below. The outcome of each of these reactions was recovered starting material **80** in yields >60%).

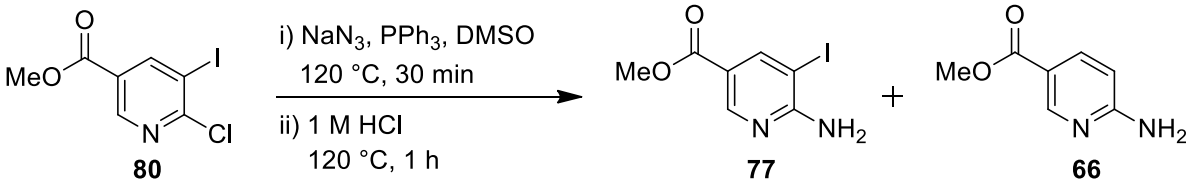
Table 2. Reaction conditions for the attempted synthesis of methyl 6-amino-5-iodonicotinate **77**.

Entry	Reagents	Base + Solvent	Temperature (°C)	Time (h)
1	Benzylamine	Toluene	120	24
2	$Pd(dba)_2$ JohnPhos KHMDS	THF	65	4.5
3	$Pd(dba)_2$ JohnPhos $NaNH_2$	NaO*t*Bu Dioxane	100	1.5

After doing a literature search, we came upon an article by Kandalkar *et al.*[56] that used azide to achieve a similar aminolysis, after Staudinger decomposition.

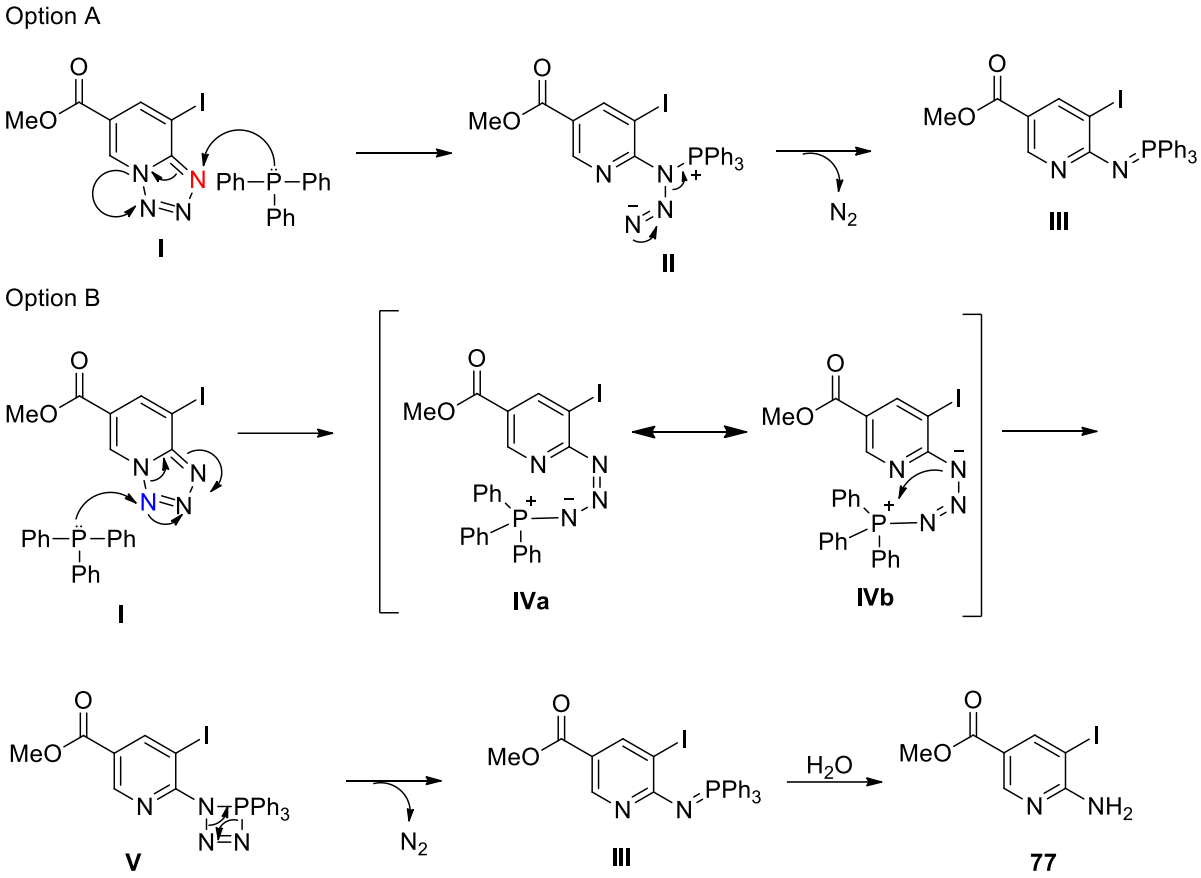
On following the two-step, one-pot method reported by Kandalkar *et al.*[56], we obtained a mixture of methyl 6-amino-5-iodonicotinate **77** and methyl 6-aminonicotinate **66** in 14% and 9% yields respectively, determined through the NMR spectrum (Scheme 28). No starting material **80** was observed in the NMR spectra. The crude proton NMR spectra revealed two broad singlets at 4.93 ppm and 5.41 ppm,

integrating for 2H each, representing the NH_2 groups of compounds **66** and **77** respectively. There are also two methoxy groups, one for each compound present along with five aromatic protons. The reappearance of a signal due to the proton adjacent to the amine at 6.48 ppm confirms the presence of compound **66**. The formation of the two products was further supported by the ^{13}C NMR spectrum of the mixture, which showed the presence of methoxy groups as signals at 52.0 and 51.8 ppm.



Scheme 28. Aminolysis of reactant **80** to produce functionalized 2-aminopyridine **77** and side product **66**.

A proposed mechanism for the reaction between sodium azide and **79** (Scheme 29) begins with the formation of the aromatic tetrazolo[1,5-*a*]pyridine intermediate **I**. This intermediate is then decomposed to the 2-aminopyridine derivative **77** using triphenylphosphine (PPh_3) in a Staudinger reaction. Mechanistically, intermediate **I** could decompose via one or both of the two paths (named option A and B) displayed in Scheme 29. Option A entails a nucleophilic attack on the nitrogen atom in 1-position (red) of tetrazolo[1,5-*a*]pyridine derivative **I** by PPh_3 forming zwitterion **II**, which releases nitrogen gas yielding iminophosphorane intermediate **III**. Alternatively, the nucleophilic attack can take place in the 3-position (blue) leading to resonance forms **IVa** and **IVb**, which participate in an intermolecular reaction to give the stabilized intermediate **V**. Expulsion of nitrogen gas leads to iminophosphorane intermediate **III** – a common intermediate between the two paths. Water hydrolysis of intermediate **III** gives **77**.[56] The formation of **66** should follow the same mechanistic steps, however, it is not clear whether the iodine atom is cleaved, after or during the decomposition.



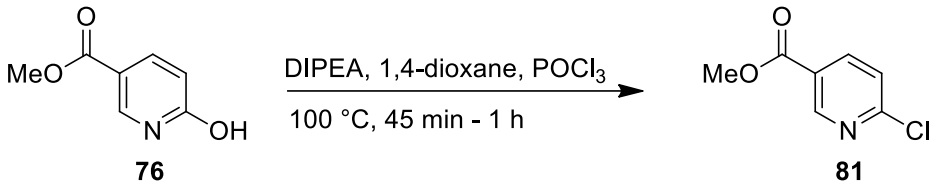
Scheme 29. Possible proposed mechanisms for the formation of methyl 6-amino-5-iodonicotinate **77**.[56]

Despite the low yield obtained in this reaction, it established a protocol to achieve the amination. Given the formation of **66** we hoped the change in the sequence of the reactions as suggested for path B (Scheme 25) would improve the yield for this step.

2.2.6 Synthesis of methyl 6-chloronicotinate

In attempt to improve the yield of **77**, the formation of 2-aminopyridine derivative **66** was considered before conducting the iodination step. Thus, methyl 6-hydroxynicotinate **76** was chlorinated under the same reaction conditions reported for the formation of **80**, resulting in the formation of methyl 6-chloronicotinate **81** with a good yield of 87% (Scheme 30). The proton NMR spectrum revealed that the aromatic protons had shifted more downfield due to the presence of the more electronegative chlorine atom, as expected. The signal due to the proton ortho to the chloro-substituent (at position 5) shifted from 6.65 ppm in the starting material to 7.43 ppm in the product. Similarly, in the ^{13}C NMR spectrum, the signal due to C-6 shifted

downfield to 153.3 ppm for compound **81**, from 143.3 ppm in the starting material, indicating successful synthesis of methyl 6-chloronicotinate **81**. A melting point of 85 – 86 °C was recorded for compound **81** which is similar to the reported melting point of 86 – 87 °C.[57]

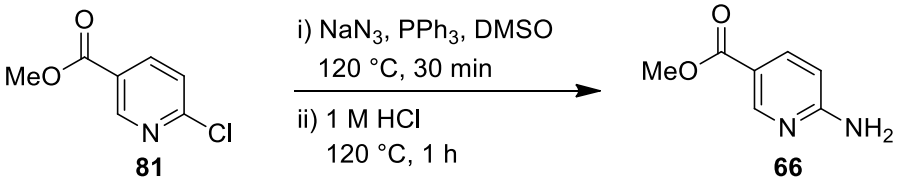


76 **81**

Scheme 30. Synthesis of methyl 6-choloronicotinate **81** from hydroxypyridine **76**.

2.2.7 Synthesis of methyl 6-aminonicotinate

Conducting the same aminolysis reaction as reported for the synthesis of **77**, compound **81** successfully underwent nucleophilic substitution upon reaction with NaN_3, followed by the Staudinger reaction, to produce methyl 6-aminonicotinate **66** with 75% yield, see Scheme 31. This aminolysis reaction was more successful than what we observed for the synthesis of **77**, with the 2-aminopyridine derivative **66** being isolated in a much higher yield. Similar to the NMR spectrum observed for compound **66**, a broad singlet integrating for 2H was observed at 4.68 ppm, indicating the presence of the NH_2. Additionally, an upfield shift in the peaks was seen due to nitrogen being less electronegative than the chlorine atom in compound **81**.



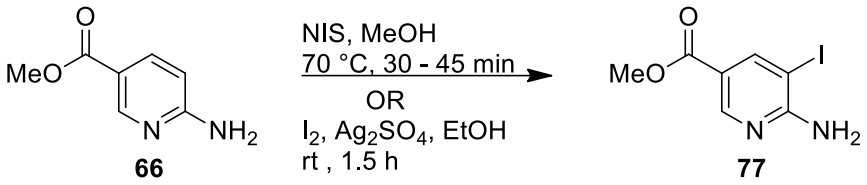
81 **66**

Scheme 31. Aminolysis reaction to produce methyl 6-aminonicotinate **66**.

2.2.8 Second synthesis of methyl 6-amino-5-iodonicotinate

Satisfied with the outcome of the aminolysis reaction, compound **66** was then subjected to the same iodination conditions described for compound **76** in Scheme 26 above. Disappointingly, under these conditions, compound **77** was obtained in a low yield of 4% determined from the NMR spectrum (Scheme 32). The ^{1}H NMR spectrum

of the crude product indicated traces of the desired product, however, conversion was very poor and mostly SM was recovered.



Scheme 32. Iodination of methyl 6-amino-5-iodonicotinate **66**.

To achieve higher yields, alternative reaction conditions were sought for the iodination of 2-aminopyridine **66**. After searching through several reported literature procedures, we tried a method that involved dissolving **66** in ethanol in the presence of iodine and Ag_2SO_4 gave the desired product **77** in a yield of 65% (Scheme 32). This reaction proved to be much more efficient than the original conditions that employ NIS in MeOH, resulting in higher yield and cleaner reaction, with no presence of any side products or starting material. Overall, the synthetic sequence shown in Path B of Scheme 25 was found to be superior to that of Path A, affording the desired aminopyridine **77** in an overall yield of 42%, when compared with the yield of 14% of Path A.

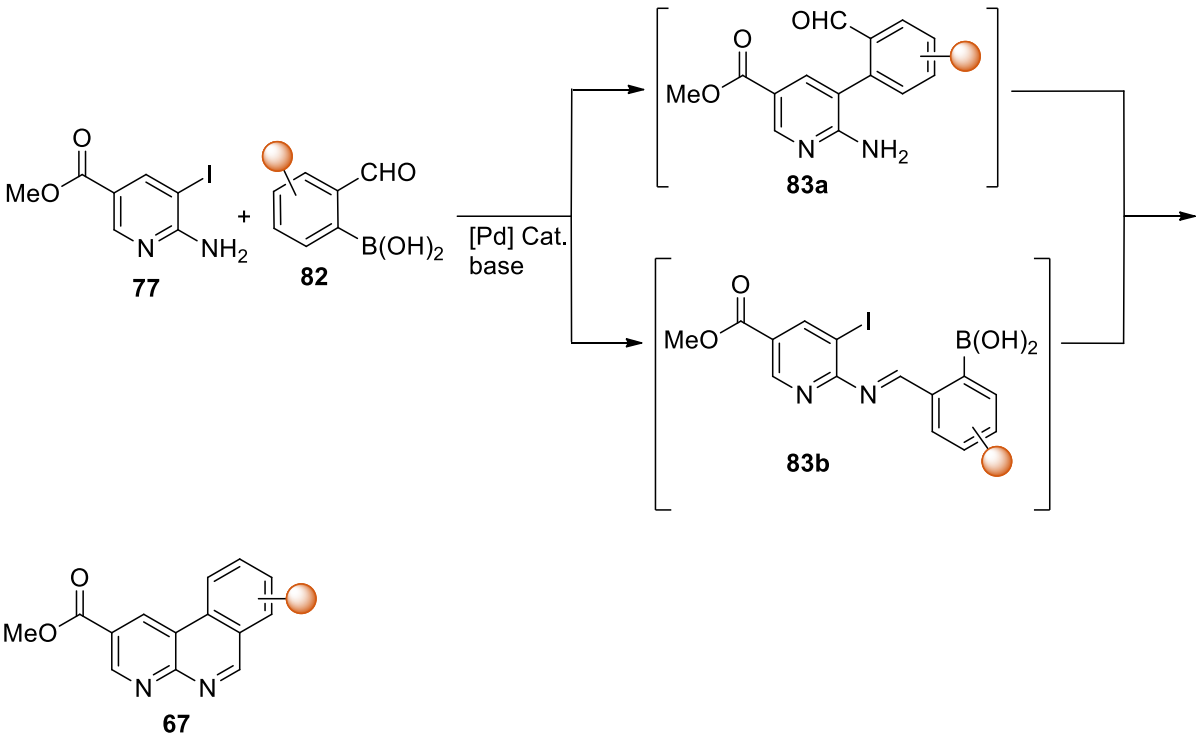
Altogether, the intended functionalized 2-aminopyridine, methyl 5-iodo-6-amionicotinate **77** was successfully synthesized from bio-renewable malic acid **20**. Methyl 5-iodo-6-amionicotinate **77** and other compounds that were formed in this synthetic route, such as **80**, **81**, and **66** could serve as key intermediates in the synthesis of polycyclic *N*-heterocyclic compounds. In this work, methyl 5-iodo-6-amionicotinate **77** was utilized for exploration into the synthesis of benzo[*c*][1,8]naphthyridine derivates, while methyl 6-aminonicotinate **66** was used for the formation of imidazo[1,2-*a*]pyridine analogues.

2.3 Synthesis of benzo[*c*][1,8]naphthyridine core from 6-amino-5-iodo-nicotinate 77

Three functionalities, namely, ester-, amino-, and iodo-groups are appended on the pyridine core in methyl 6-amino-5-iodo-nicotinate **77**. Each of these groups could be used as a linchpin to access diverse structural motifs. For example, the methyl ester fragment could be transformed into other carboxylic acid derivatives or other reduced forms such as aldehyde and alcohol groups, which are also useful functionalities. The

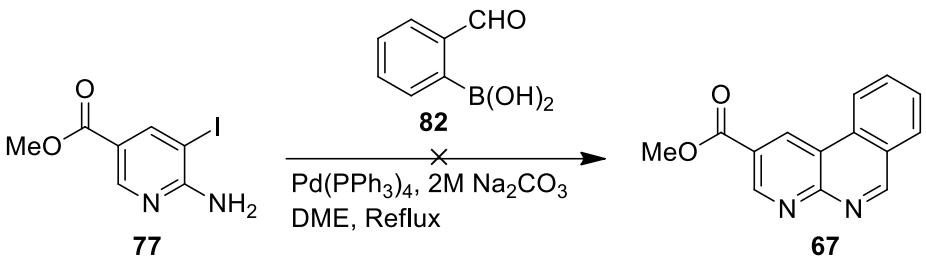
iodo-substituent is also versatile in that is it can be used as a handle to introduce a variety of groups in cross-coupling reactions. The amino group could be transformed into amides on reaction with carboxylic acids or imines upon reacting with aldehydes and amines.

Owing to our commitment to the biomass-based synthesis of polycyclic *N*-heterocyclic compounds of biological relevance, methyl 6-amino-5-iodo-nicotinate **77** presented an opportunity to access the seldom encountered, but biologically active benzo[*c*][1,8]naphthyridine framework. Compound **77** is suitably functionalized to partake in Suzuki coupling reaction via the iodo-group, and imine formation on reaction with an aldehyde through the amino substituent. We hypothesized that subjecting methyl 6-amino-5-iodo-nicotinate **77** to Suzuki coupling reaction conditions with 2-formylphenyl boronic acid derivatives **82**, would lead to the formation of benzo[*c*][1,8]naphthyridine derivatives **67**, in a single operation (Scheme 33). We envisaged that the reaction between the two substrates could involve the Suzuki cross-coupling to form biaryl intermediate **83a**, which should undergo an intramolecular imination reaction forging benzo[*c*][1,8]naphthyridine derivatives **67**. Alternatively, the C–N bond forming event could occur first, to yield imine **83b**, followed by an intramolecular C–C bond formation via the Suzuki reaction. We appreciated that the basic conditions that the reaction is carried out in could slow down the imine formation, thus the initial formation of the intermediate, **83a** was the most probable path. Aromatization of biaryl intermediate **83a** was perceived as a potential driving force for this process.



Scheme 33. Proposed synthesis of benzo[*c*][1,8]naphthyridine derivatives **67**.

Thus, using the standard Suzuki coupling reaction conditions,[58] methyl 6-amino-5-iodo-nicotinate **77** was reacted with simple 2-formylphenyl boronic acid **82** in the presence of *tetrakis* triphenylphosphine palladium(0) ($Pd(PPh_3)_4$) as the catalyst and 2 M Na_2CO_3 as the base, Scheme 34. Unfortunately, this reaction did not give the desired product **67**.



Scheme 34. Attempted synthesis of methyl benzo[*c*][1,8]naphthyridine-2-carboxylate **67**.

Considering the versatility and success of Suzuki coupling reactions, even for sterically crowded substrates, it was not anticipated that this step in the reaction process would prove to be difficult. Starting material **77** for this reaction was consumed as observed by TLC analysis. TLC was used to assess whether the aldehyde was present using a dinitrophenylhydrazine (DNP) stain, however there was no sign of

the formation of biaryl intermediate **83**. After purification, the NMR spectroscopic results did not give any indication that the desired product or intermediate was formed. We could not identify what was present in the mixture.

Disappointed, we varied the reaction conditions in an attempt to improve the results of the reaction. Unfortunately, the outcome for all the reactions was one of two things: either the resulting mixture formed showed consumption of the starting material **77** but no sign of the formation of the product **67** or intermediate **83a** or **83b** and the compounds in the NMR spectrum could not be identified; or the reaction simply did not proceed and both starting materials were recovered. Some of the reaction conditions we attempted are presented in Table 3 below, along with the outcome.

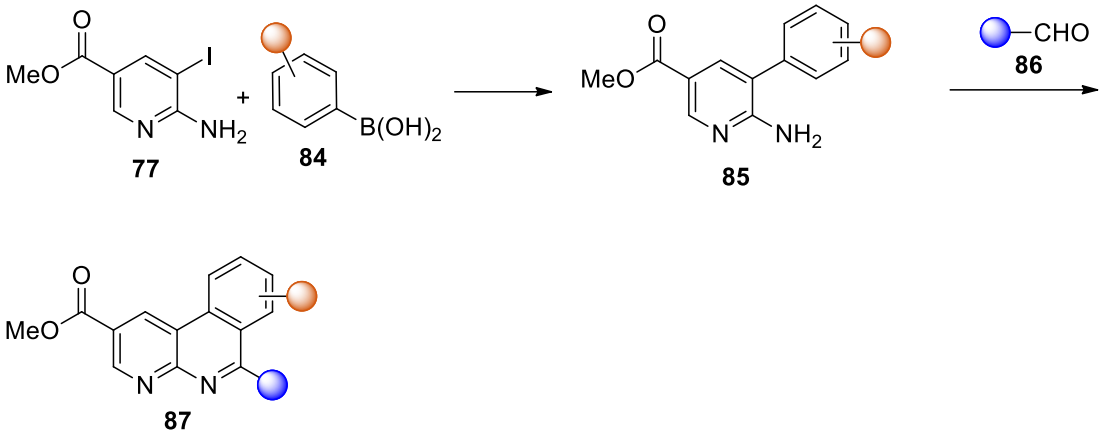
Table 3. Reaction conditions for the attempted synthesis of methyl benzo[*c*][1,8]naphthyridine-2-carboxylate **67**.

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Outcome
1	$Pd(PPh_3)_4$	DME	85	24	Unidentifiable mixture of products
2	$Pd(PPh_3)_4$	DME	85	24	No reaction
3	$Pd(PPh_3)_4$	EtOH:PhMe (1:10)	85	24	Unidentifiable mixture of products
4	$Pd(PPh_3)_4$	EtOH:PhMe (1:10)	85	3 in mw*	Unidentifiable mixture of products
5	$Pd(OAc)_2$/ S-Phos	EtOH:PhMe (1:10)	85	3 in mw*	No reaction
6	$Pd(PPh_3)Cl_2$	Dioxane:H_2O (5:1)	110	24	No reaction
7	$Pd(dppf)Cl_2$	DME	90	24	No reaction

*Microwave

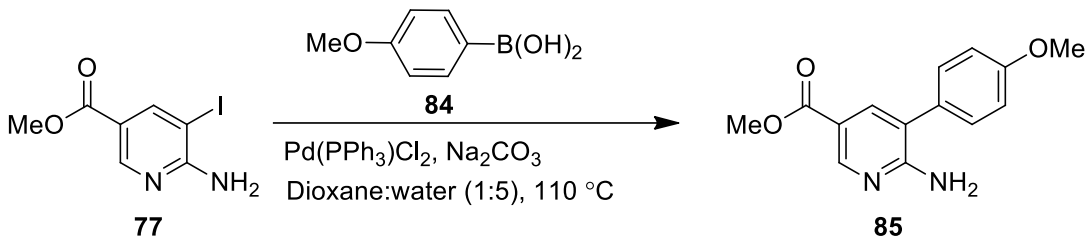
In some cases, the TLC had shown the presence of an aldehyde when stained with dinitrophenylhydrazine which we then suspected could be the intermediate **83a**. However, isolation of this compound through column chromatography did not give any compound that resembled **83a**. Another challenge contributing to the difficulty in identifying what had formed in the NMR spectra, was the presence of triphenylphosphine oxide (TPPO) as a side product that formed when $Pd(PPh_3)_4$ was used as the catalyst. Crystallization, column chromatography, the addition of hexane, and liquid-liquid extraction were all methods used to try and separate the TPPO from the mixture, all of which were not completely successful. Thus, the presence of TPPO complicated the aromatic region of the NMR spectra, resulting in the inability to differentiate the peaks in the aromatic region.

After much experimentation to get positive results from the cascade Suzuki coupling, we attempted to break up the reaction into two steps, to first conduct a Suzuki coupling using the intended intermediate **77** and reacting it with phenyl boronic acid derivative **84** to give the intermediate structure **85** (Scheme 35). This would then be followed by the intramolecular cyclization on reacting **85** with an aldehyde **86** to give the sought-after benzo[*c*][1,8]naphthyridine derivatives **87**. This approach will result in substituents in the 6-position of compound **87**. Simpler boronic acids, phenyl boronic acid derivatives **84**, were considered for use instead of 2-formylphenyl boronic acid derivatives. Steric factors affect the boronic acid's characteristics when substituents are in the *ortho* position.[59] Despite the reported tolerance of the Suzuki coupling reaction to steric factors, steric hindrance could have been a reason for the synthetic challenges experienced. Alternatively, the presence of the reactive formyl group could have interfered in the reaction. Thus, a shift to a simpler boronic acid was considered, to eliminate these concerns.



Scheme 35. Synthetic method proposed and attempted for the synthesis of benzo[*c*][1,8]naphthyridine derivatives **87**.

Following another literature report,[60] methyl 6-amino-5-iodonicotinate **77** underwent a Suzuki coupling reaction with 4-methoxy phenylboronic acid **84** using $Pd(PPh_3)_2Cl_2$ as a catalyst (Scheme 36). This operation proved a success, which led to the formation of methyl 6-amino-5-(4-methoxyphenyl)nicotinate **85** in 30% yield. A simple reaction, yet we were happy with the result, as this confirmed our suspicions that the 2-formyl substituent of boronic acid **82** was playing a role in preventing the Suzuki coupling reaction from taking place.



Scheme 36. Suzuki coupling for the formation of methyl 6-amino-5-(4-methoxyphenyl)nicotinate **85**.

The formation of compound **85** was established with ^{1}H and ^{13}C NMR spectroscopy. The proton NMR spectrum showed two methoxy peaks at 3.89 and 3.86 ppm (OMe), furthermore, additional multiplets at 7.40 – 7.33 and 7.04 – 6.97 ppm integrating for 4H protons appeared in the aromatic region of the spectrum. The two protons of the pyridine ring gave rise to signals at 8.71 and 7.93 ppm, and the singlet due to the NH_2 group still remained. The new methoxy group appeared as a signal at 55.4 ppm in the ^{13}C NMR spectrum, and the signal due to the C-I of the starting material at 73.6 ppm was replaced with a signal at 129.0 ppm in compound **85**. This identification of the

product as structure **85** is further corroborated by the mass spectrometry data, which was found to be 259.1076 and the calculated value was 259.1077. The identity of compound **85** was unequivocally confirmed with single crystal X-ray crystallography (Figure 13).

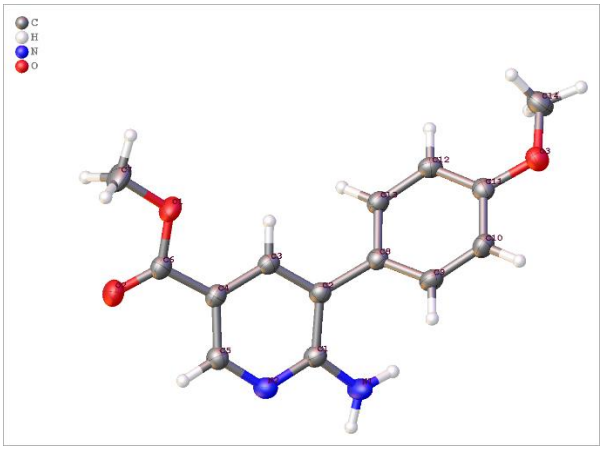
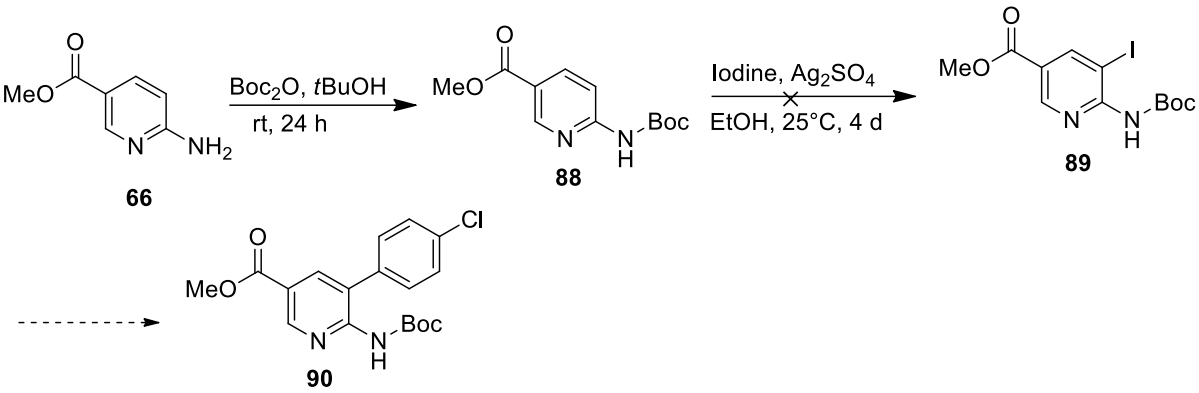


Figure 13. The crystal structure of methyl 6-amino-5-(4-methoxyphenyl)nicotinate **85**.

During experimentation, we constantly recovered both the starting materials and the conversion was low, even with extended reaction times and changing the quantities of catalyst. A brief literature search reveals that the cause for the low yields could be due to the coordination of the amino group to the catalysts, poisoning it.[61] With this in mind, it was decided to first Boc-protect the amino group of methyl 6-aminonicotinate **66** to give compound **88**, then proceed with iodination to form **89** and subsequent Suzuki reaction to yield adduct **90** (Scheme 37). Thus, using a method reported for a similar substrate in literature,[62] methyl 6-aminonicotinate **66** was reacted with Boc_2O in *tert*-butanol to fashion carbamate **88** as depicted in Scheme 37. The protection was successful, giving methyl 6-((*tert*-butoxycarbonyl)amino)nicotinate **88** in 30% yield, which is far below the literature yield of 82%[62]. The nitrogen of the pyridine ring is quite nucleophilic and could have reacted with the Boc_2O to either give protection at the pyridine nitrogen or it could have reacted at both nitrogen sites, lowering the yield of the desired compound **88**.[63] The proton NMR spectrum showed an additional singlet at 1.55 ppm integrating for 9 protons, while the carbon NMR spectrum contained the corresponding C–O and C–Me peaks of the Boc protecting group at 81.4 and 27.8 ppm respectively.

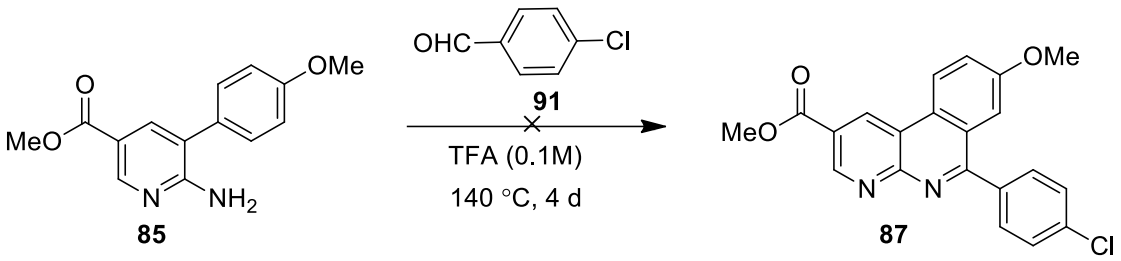
Notwithstanding the low yield, compound **88** was subjected to the same iodination conditions successfully used previously in the synthesis of **66** in attempts to make iodocarbamate **89** (Scheme 37). Unfortunately, this reaction did not proceed and the starting material was recovered.



Scheme 37. The attempted synthesis of methyl 6-((*tert*-butoxycarbonyl)amino)-5-(4-chlorophenyl)nicotinate **90**.

Alternative iodination conditions, such as using NIS in previous reactions, were sought. We considered protecting methyl 6-amino-5-iodonicotinate **77** directly, but at this time we did not have Boc_2O available in our research laboratory. We could not acquire this reagent in time to continue with this line of enquiry, owing to the tardy supply chain that plagues the chemical community in South Africa. Thus, a decision was made to proceed with using the limited amount of biaryl **85** to construct the benzo[*c*][1,8]naphthyridine core.

With biaryl compound **85** in hand, the last step of the reaction sequence was to perform the ring closure between methyl 6-amino-5-(4-methoxyphenyl)nicotinate **85** and an aldehyde, using an acid to facilitate the reaction. To test this reaction, we chose the commercially available 4-chlorobenzaldehyde **91** for two reasons. Firstly, aldehyde **91** is substituted with an electron-withdrawing group, which should increase the electrophilicity of the carbonyl carbon of the aldehyde. Secondly, the *para*-substituted benzene derivative would render interpreting the NMR spectroscopic data easier. Therefore, in efforts to synthesize benzo[*c*][1,8]naphthyridine derivative **87**, methyl 6-amino-5-(4-methoxyphenyl)nicotinate **85** was reacted with 4-chlorobenzaldehyde **91** with trifluoracetic acid (TFA) as a catalyst (Scheme 38).



Scheme 38. Attempted synthesis of methyl 6-(4-chlorophenyl)-8-methoxybenzo[c][1,8]naphthyridine-2-carboxylate **87**.

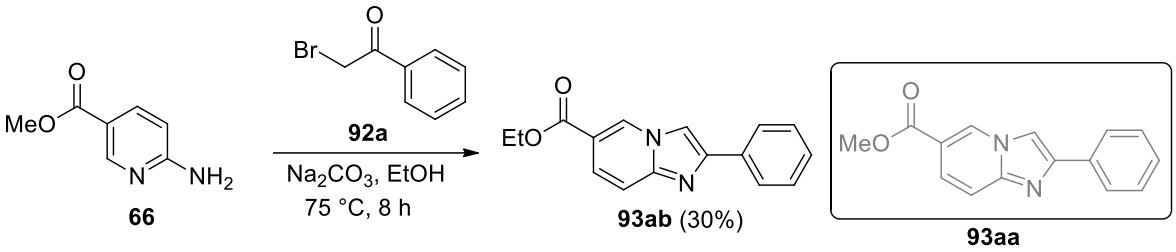
The reaction did not proceed and only starting material was recovered. We tried increasing the number of equivalents of TFA from 1.0 mol equiv. to 1.4 mol equiv. under microwave heating, but the outcome remained unchanged. The reaction could have been hindered by the type of acid chosen; the reason may be related to the acidity of the acid catalyst or due to poor rearrangement under the chosen reaction conditions. Repeating the reaction using a different acid could help promote the cyclization.

Even though the benzo[*c*][1,8]naphthyridine structure is an intriguing target, we had to stop the study at this point since we had depleted our supply of compound **85** and did not have time to prepare more methyl 6-aminonicotinate **66**. In research, it is common for some people to lay the foundation before others take over and see the project through to completion. Although the target benzo[*c*][1,8]naphthyridine derivatives we set out to synthesize were not prepared, we have set the stage for future research in this field. I have gained a great deal of practical knowledge in synthetic organic chemistry from this effort. Thus, our efforts were shifted towards the synthesis of imidazo[1,2-*a*]pyridine derivatives from methyl 6-aminonicotinate **66**.

2.4 Synthesis of imidazo[1,2-*a*]pyridine scaffold from methyl 6-aminonicotinate 66

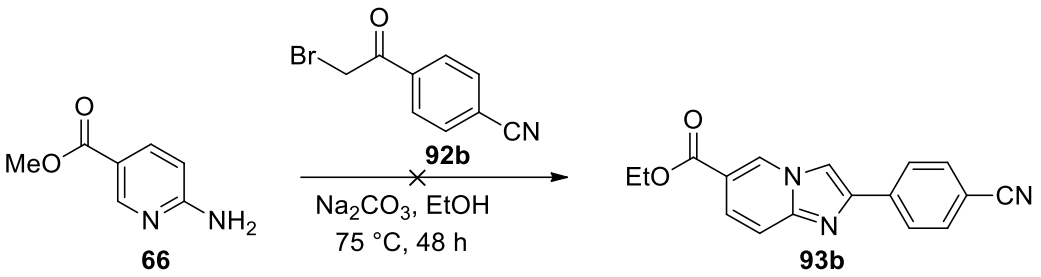
Imidazo[1,2-*a*]pyridine (IP) scaffold is one of a number of privileged families of *N*-heterocyclic compounds that display vast medicinal properties. The 2-aminopyridine derivatives are often utilized in the synthesis of these compounds. This work adds to the body of literature in the synthesis of IPs by starting from bio-renewable resources. The aim here was to use a well-established method for the synthesis of IPs, employing 2-aminopyridine derivatives we have synthesised from malic acid **20**. The IP synthesis that involves the reaction of 2-aminopyridine derivatives (such as **66**) and α-bromoketone analogues was selected due to ease of operation and the mild

conditions.[64] Thus, methyl 6-aminonicotinate **66** was reacted with the commercially available 2-bromoacetophenone **92a** in an attempt to prepare the desired imidazo[1,2-*a*]pyridine. Although not entirely unexpectedly, we isolated ethyl 2-phenylimidazo[1,2-*a*]pyridine-6-carboxylate **93ab** in a low yield of 30% (Scheme 39), with none of the methyl ester **93aa** isolated. This compound is clearly a transesterification product because the reaction was done in ethanol as solvent. In the proton NMR spectrum, we observe a quartet at 4.42 ppm integrating for 2H and a triplet at 1.43 ppm integrating for 3H, confirming the transesterification product formed. This reaction should be repeated in methanol to determine whether the transesterification could be avoided. The broad singlet at 4.86 ppm corresponding to the NH_2 was absent while a new doublet at 7.93 ppm represents H-3, with a correlating peak at 108.7 ppm in the ^{13}C NMR spectrum. Additionally, the signals due to the four aromatic protons of the benzene moiety were observed at 7.97 – 7.37 ppm, with their respective peaks in the region 128.8 – 126.2 ppm in the ^{13}C NMR spectrum.



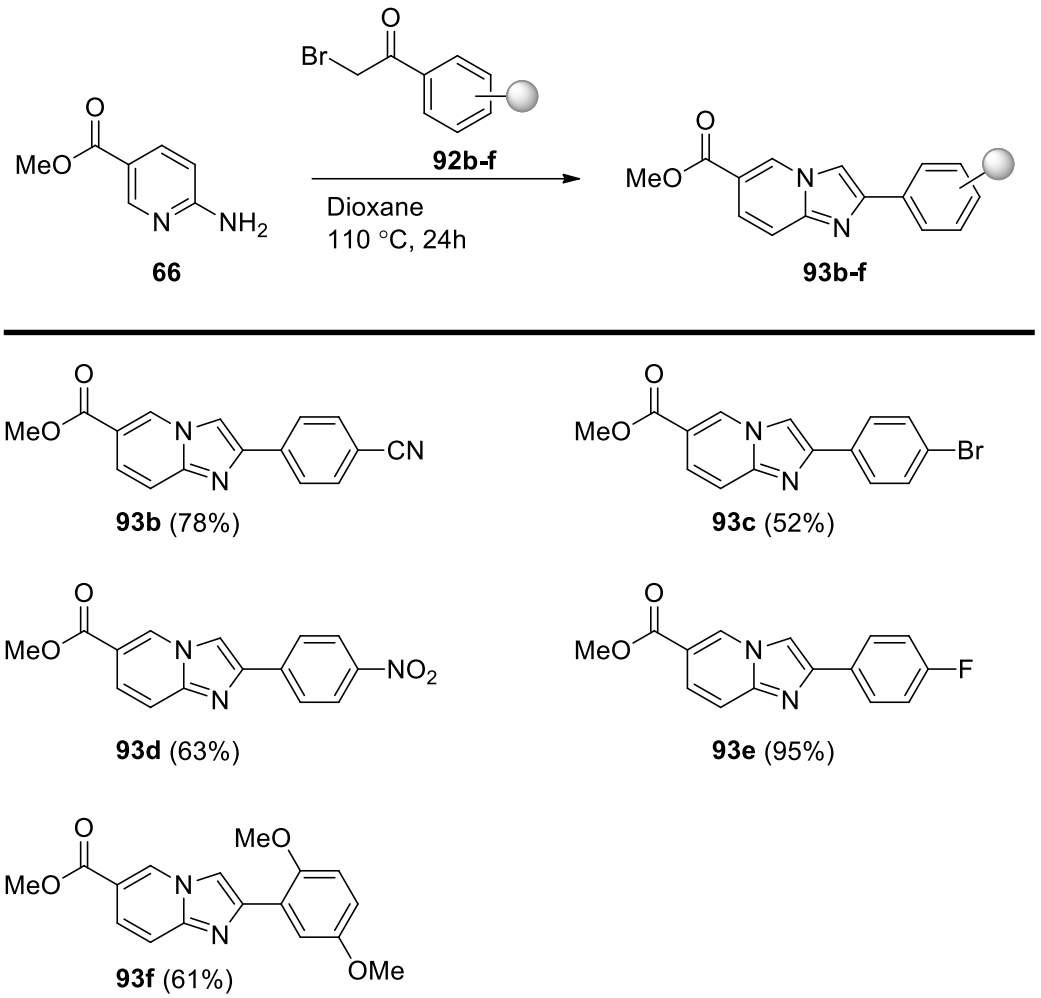
Scheme 39. Synthesis of imidazo[1,2-*a*]pyridine nucleus through the annulation of methyl 6-aminonicotinate **66** with bromoketone **92a**.

Considering the success of the above reaction conditions, we decided to expand the synthesis to other IPs by changing the α-bromoketone reaction partner. Sticking to the above reaction conditions, we reacted methyl 6-aminonicotinate **66** with 4-(2-bromoacetyl)benzonitrile **92b** as in Scheme 40. We expected the same positive outcome resulting in the synthesis of IP **93b**, however, the reaction rate seemed slow, and the reaction was left for an extra 40 h to proceed. TLC analysis still showed the presence of the methyl 6-aminonicotinate **66,** and an additional spot which was thought to be the product. Upon isolation and NMR spectroscopic analysis, this was not the case. The new "product" could not be identified and appeared as a complex mixture.



Scheme 40. Attempted synthesis of methyl 2-(4-cyanophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate **93b**.

The situation was remedied through a procedure reported in patent literature.[65] While the first procedure utilized a base at a lower temperature with ethanol as a solvent, this procedure did not require a base and was conducted at a higher temperature. The procedure used 1,4-dioxane as a solvent to help circumvent the transesterification (although not detrimental) and required a much shorter reaction time with little to no purification. Methyl 6-aminonicotinate **66** and 4-(2-bromoacetyl)benzonitrile **92b** were reacted again under the new conditions to form the desired IP **93b** in 78% yield (Scheme 41). Other commercially available 2-bromoacetophenone derivatives were also used in this reaction to obtain IPs **93c-f** in yields ranging from 52 – 95% (Scheme 41).



Scheme 41. Conversion of methyl 6-aminonicotinate **66** to imidazo[1,2-*a*]pyridines **93**.

The yield was reported in literature[65] for methyl 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate **93d** at 91% while the observed yield in our hands was lower at 63%. However, the reaction was carried out once and was not optimised further. By comparison, the isolated yield of methyl 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate **93e** (95%), closely matched the reported yield for this compound (96%). The remaining IP analogues, except for **93f** which is novel, had no reported yields. The formation of the above IP derivatives was confirmed by NMR spectroscopy and crystallography. Like ethyl 2-phenylimidazo[1,2-*a*]pyridine-6-carboxylate **93ab**, the resulting IPs **93b-f** showed the expected number of proton and carbon signals in their respective spectra. This was further confirmed by the crystal structures, one of which is represented below in Figure 14. The IP compounds showed higher melting points, in the range 210 – 245 °C. Compound **93f** was also characterized by mass spectrum in

which the $[M+H]^+$ value was found to be 313.1175 which is aligned to the calculated value of 313.1183.

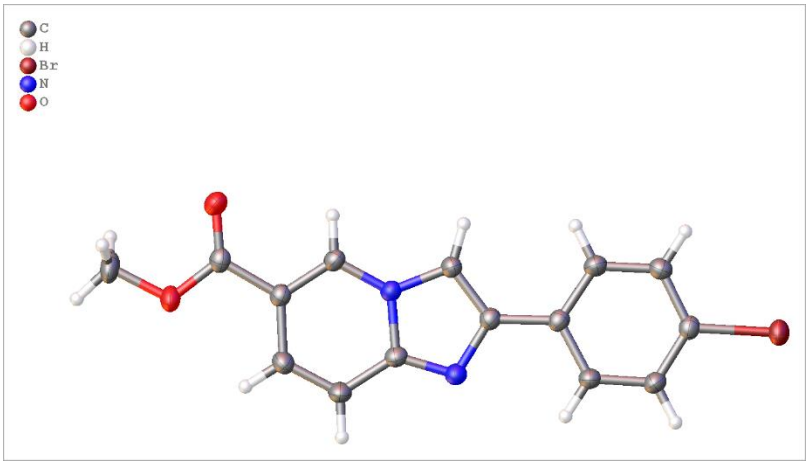


Figure 14. Crystal structure of methyl 2-(4-bromophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate **102c**.

In summary, bio-renewable malic acid **20** was successfully used in the production of heterocyclic compounds which prove useful in industries like in pharmaceutics. Malic acid **20** was converted into a versatile intermediate like methyl 6-aminonicotinate **66** and methyl 6-amino-5-iodonicotinate **77**. In turn, these intermediates were used in the attempted synthesis of benzo[*c*][1,8]naphthyridine derivatives **67** and **87** and the successful synthesis of imidazo[1,2-*a*]pyridine derivatives. These heterocyclic compounds will go on to be tested against cancer lines for biological activity. Since the partner who first consented to do the tests at the beginning of the investigations has retired and is no longer engaged in academic research, the compounds were recently sent to a different collaborator to test for bioactivity against cancer cell lines.

Chapter 3

3. Conclusion and Future Work

3.1 Conclusions

In summary, our efforts to synthesize 4-azepinone derivatives **65** were thwarted by the thermal instability of 5-methylpyrrolidin-2-one **69**, a key intermediate in the synthesis. We established that the *N*-benzylated derivative **75** of this compound is stable enough at room temperature, but decomposed on debenzylation. Additionally, we have demonstrated the utility of malic acid **20** as a suitable bio-renewable raw material for the synthesis of *N*-heterocyclic compounds. In this work malic acid **20** was converted to methyl 6-aminonicotinate **66** and methyl 6-amino-5-iodonicotinate **77** in four and five steps, respectively. The process we developed was able to deliver **66** in a decent 29% overall yield, while **77** was also obtained in a reasonable overall yield of 20% over the five steps. Compound **77** was used in the unsuccessful attempted synthesis of benzo[*c*][1,8]naphthyridine derivatives. However, we managed to obtain the key intermediate methyl 6-amino-5-(4-methoxyphenyl)nicotinate **85**, albeit in a modest yield of 30%. On the other hand, we successfully synthesized a series of imidazo[1,2-*a*]pyridine derivatives with yields ranging from 30 – 95% from bio-renewable derived methyl 6-aminonicotinate **66**. These compounds are currently investigated for their anticancer activities.

Furthermore, this study stresses the utilisation of green chemistry principles. It demonstrates how useful it may be to use renewable ingredients from biomass, such cellulose and glucose, as starting materials in development of pharmacologically relevant compounds that are good for the environment. Despite obstacles faced in some synthetic pathways, the overall methodology illustrates a transition towards more sustainable chemical techniques. The successful synthesis of imidazo[1,2-a]pyridine derivatives in good yields from malic acid demonstrates a viable path forward for greener heterocycle synthesis.

3.2 Future work

The synthetic route we developed to access methyl 6-aminonicotinate **66** and methyl 6-amino-5-iodonicotinate **77** from malic acid **20** could be translated into an industrial process. However, for this to be possible, the following issues would need to be addressed. Firstly, more reliable reaction conditions for the synthesis of methyl coumalate **23** or a related alkyl coumalate would have to be devised. Secondly, the steps that employ non-green reagents and solvents should be re-investigated with more environmentally benign reagents and solvents. In particular, an alternative nitrogen atom source will need to be investigated for HMDS which is used in the conversion of methyl coumalate **23** into methyl 6-hydroxynicotinate **76**.

Once the synthesis of the methyl nicotinate intermediates has been improved, they can further provide a pathway for the synthesis of pyridine-containing active pharmaceutical ingredients (APIs). The report by Marshall *et al*.[66] disclosed that the percentage of FDA approved drugs with at least one nitrogen heterocycle has increased from 59% in earlier decades to 82% in the 2010 – 2023 period, with pyridine being the most common high-frequency nitrogen heterocycle. Some examples of APIs that can be synthesized from the methyl nicotinate intermediates are represented below in Figure 15. Therefore, the project could benefit immensely if it can focus on the synthesis of these APIs.

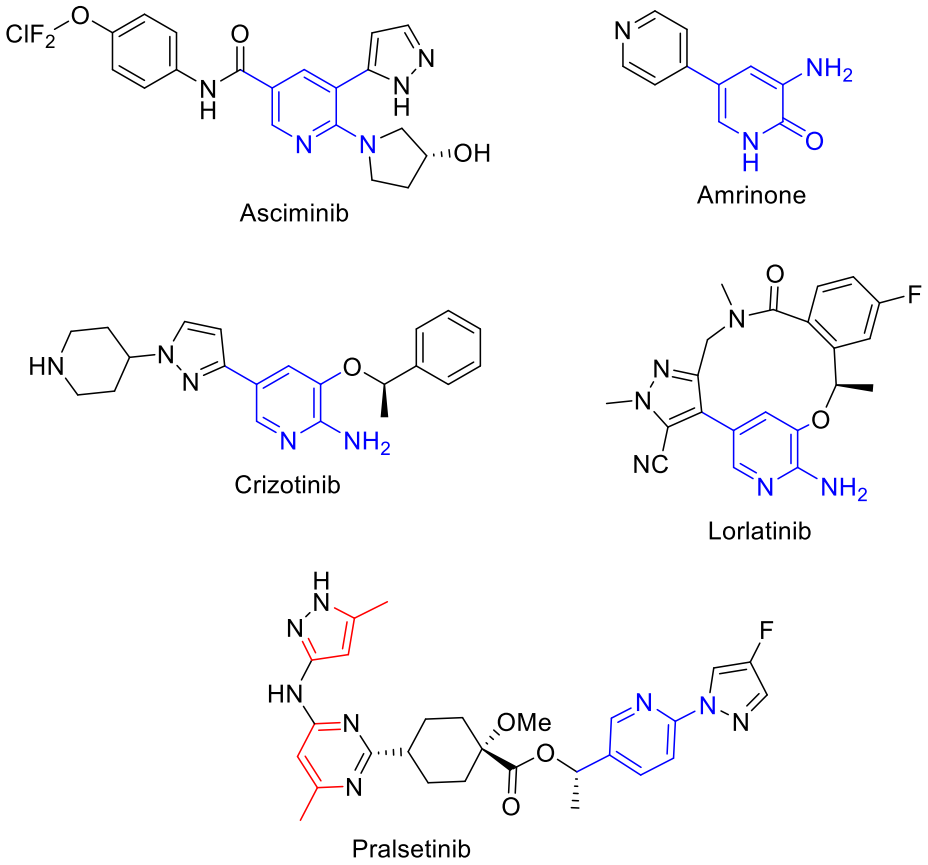


Figure 15. Examples of APIs that can be synthesized from methyl nicotinate derivatives.

Chapter 4

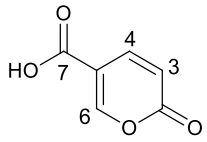
4. Experimental Methods

4.1 General experimental procedures:

All reagents and solvents used were purchased from commercial suppliers and used without further purification. Reactions were monitored using TLC (thin layer chromatography) on aluminium-backed Merck silica gel 60 F254 plates; a UV lamp was using as a means of detection. Organic layers were dried over anhydrous $MgSO_4$ prior to evaporation using a rotary evaporator. Purification of compounds was carried out by means of column chromatography using flash silica gel (particle size 0.04-0.063 mm) purchased from Merck. NMR Spectroscopy was carried out using the Bruker Avance 400 MHz and Bruker Avance 300 MHz instruments to record ^{1}H NMR and ^{13}C NMR spectra. Spectra were recorded in deuterated chloroform and water. The reported chemical shift data are reported in parts per million and coupling constants are reported in Hertz. Fourier transform infrared (FT-IR) spectra were recorded on a Bruker Tensor 27 single channel infrared spectrometer. Mass Spectrometry was carried out using the Bruker Compass Data Analysis 4.3. Melting points were determined on a Stuart SMP10 melting point apparatus.

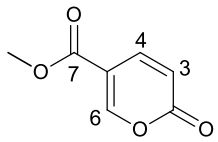
4.2 Synthetic procedures:

2-Oxo-2*H*-pyran-5-carboxylic acid 22



To a 250 mL round-bottom flask containing malic acid (5.0 g, 40 mmol, 1.0 equiv.), was added 95–99% concentrated sulfuric acid (10 mL, 190 mmol, 5.0 equiv.) in one portion, while stirring. The mixture was heated to 90 °C for 1 h before the temperature was raised to 100 °C for another 1 h. The mixture was cooled to room temperature, poured over crushed ice, and stirred for 30 min. The mixture was filtered and washed with ice-cold water and recrystallized from methanol to obtain the title compound as a sticky tan solid (0.2 g, 8% yield). **M.p.** = 195 – 198 °C. **FTIR:** ṽ (cm^{-1}) = 3063 (C-H, aromatic), 2957 (C-OH), 2798 (C-H, aliphatic), 1703 (C=O). **^{1}H NMR** (400 MHz, MeOD): δ (ppm) = 8.46 (dd, *J* = 2.6, 1.1, Hz, 1H, H-6), 7.89 (dd, *J* = 9.8, 2.6 Hz, 1H, H-4), 6.39 (dd, *J* = 9.8, 1.2 Hz, 1H, H-3).**^{13}C NMR** (100 MHz, $CDCl_3$): δ = 164.4 (C-7), 158.4 (C-2), 142.3 (C-4), 114.4 (C-3), 112.4 (C-5).[20]

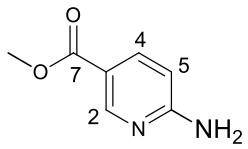
Methyl 2-oxo-2*H*-pyran-5-carboxylate 23



The title compound **23** was prepared *via* a two-step, one-pot synthesis. To a 250 mL round-bottom flask equipped with a magnetic stirrer bar was added malic acid (5.0 g, 40 mmol, 1.0 equiv.), followed by the addition of 95-99% concentrated sulfuric acid (10 mL, 190 mmol, 5.0 equiv.) in one portion, while stirring at room temperature. The mixture was heated to 90 °C for 1 h or until the reaction went to completion. The solution was cooled to room temperature before placing it in an ice bath. Methanol (7 mL) was added dropwise over 15 min, and the mixture was heated to 95 °C until completion (that was about 1 h). The contents of the flask were allowed to cool to room temperature before pouring over ice and stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine

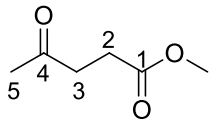
(10 mL). The solution was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from 2-propanol resulted in a pale yellow solid (3.1 g, 54% yield). **M.p.** = 68-70 °C. **FTIR:** ṽ (cm^{-1}) = 3039 (C-H, aromatic, 2957 (C-H, aliphatic), 1743 (C=O), 1701 (COOMe). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.31 (dd, *J* = 2.6, 1.2 Hz, 1H, H-6), 7.80 (dd, *J* = 9.8, 2.6 Hz, 1H, H-4), 6.35 (dd, *J* = 9.8, 1.2 Hz, 1H, H-3), 3.89 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 163.4 (C-7), 159.8 (C-2), 158.2 (C-6), 141.6 (C-4), 115.3 (C-3), 112.0 (C-5), 52.5 (COOMe).[20]

Methyl 6-aminonicotinate 66



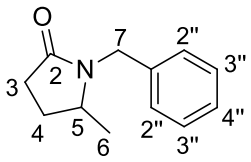
A 100 mL round-bottom flask equipped with a stirrer bar was charged, successively, with methyl 6-choloronicotinate **81** (50 mg, 0.3 mmol, 1.0 equiv.), sodium azide (40 mg, 0.6 mmol, 2.0 equiv.), triphenylphosphine (160 mg, 0.6 mmol, 2.0 equiv.) and DMSO (2.5 mL). The resulting slurry was heated to 120 °C for 30 min while stirring vigorously. 1M HCl (0.5 mL) was then added, and the solution was allowed to stir for an additional 30 min while maintaining temperature at 120 °C. The mixture was cooled to room temperature before being diluted with additional 1M HCl (0.5 mL). The mixture was poured into distilled water (6.5 mL) and washed with EtOAc (3 × 3 mL). The aqueous layer was then neutralized using saturated aq. $NaHCO_3$ before extracting with EtOAc (3 × 5 mL) followed by drying over $MgSO_4$, filtered and concentrated to give an off-white solid (33 mg, 75% yield). **M.p. =** 128 °C. **FTIR:** ṽ (cm^{-1}) = 3384 (N-H),3145 (C-H, aromatic), 2946 (C-H, aliphatic), 1657 (C=O), 1272 (C-NH_2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.74 (d, *J* = 2.3 Hz, 1H, H-2), 8.02 (dd, *J* = 8.7, 2.3 Hz, 1H, H-4), 6.48 (d, *J* = 8.7 Hz, 1H, H-5), 4.86 (s, 2H, NH_2), 3.88 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 166.2 (C-7), 160.9 (C-NH_2), 151.5 (C-2), 139.0 (C-4), 116.5 (C-3), 107.4 (C-5), 51.8 (COOMe).[56]

Methyl 4-oxopentanoate 73



Methyl 4-oxopentanoate **73** was prepared by adding 95-99% concentrated sulfuric acid (0.1 mL, 2.1 mmol, 0.3 equiv.) to a solution of levulinic acid (0.8 g, 7.0 mmol, 1.0 equiv.) in methanol (10 mL) and heating to 50 °C for 5 h. The solution was evaporated under reduced pressure and the residue was diluted with EtOAc (20 mL) before adding saturated $NaHCO_3$ (10 mL). The organic layer was extracted and dried over $MgSO_4$, filtered, and evaporated to give a pale-yellow oil of sufficient purity, thus it was used in subsequent reaction without further purification (0.61 g, 67% yield). **FTIR:** ṽ (cm^{-1}) = 3032 (C-H, aromatic), 2876 (C-H, aliphatic), 2929 (-CH_2-), 1662 (C=O). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 3.67 (s, 3H, COOMe), 2.78 (t, *J* = 6.8 Hz, 2H, H-3), 2.57 (t, *J* = 6.7 Hz, 2H, H-2), 2.20 (s, 3H, H-5). **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 206.4 (C-4), 173.0 (C-1), 51.5 (COOMe), 37.7 (C-3), 29.6 (C-5), 27.5 (C-2).[50]

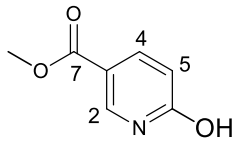
1-Benzyl-5-methylpyrrolidin-2-one 75



To a sealed tube containing a mixture of levulinic acid **12** (1.0 g, 8.61 mmol, 1.0 equiv.), formic acid (1.63 mL, 43.1 mmol, 5.0 equiv.) and benzylamine (1.89 mL, 17.2 mmol, 2.0 equiv.) in DMSO (30 mL) was added Et_3N (1.18 mL, 8.61 mmol, 1.0 equiv.) The reaction was heated to 100 °C for 4 h. The reaction mixture was cooled to room temperature followed by adding water (300 mL) and extracted with EtOAc (3 × 20 mL). This was followed by drying over $MgSO_4$, filtered, concentrated *in vacuo* and purified using silica gel chromatography (20% EtOAc: Hex) to give a light-yellow oil (0.98 g, 60% yield). **FTIR:** ṽ (cm^{-1}) = 3062 (C-H, aromatic), 2870 (C-H, aliphatic), 1772 (C=O), 1203 (C-N). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 7.22 (d, *J* = 6.1 Hz, 2H, H-3''), 7.16 (t, *J* = 9.4 Hz, 3H, H-2'', H-4''), 4.88 (d, *J* = 15.0 Hz, 1H, H-7), 3.90 (d, *J* = 15.0 Hz, 1H, H-7'), 3.43 (h, *J* = 6.6 Hz, 1H, H-5), 2.26 – 2.45 (m, 2H, H-3), 2.05 (ddt, *J* = 15.0, 12.7, 4.8 Hz, 1H, H-4), 1.57 – 1.43 (m, 1H, H-4'), 1.10 – 1.03 (m, 3H, H-6). **^{13}C NMR** (100 MHz, $CDCl_3$): δ =

174.9 (C-2), 136.8 (C-1''), 128.6 (C-3''), 127.9 (C-2''), 127.4 (C-4''), 52.8 (C-5), 43.8 (C-7), 30.3 (C-3), 26.6 (C-4), 19.6 (C-6).[51]

Methyl 6-hydroxynicotinate 76



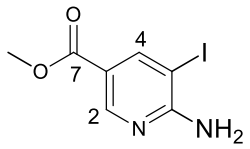
Method A

Methyl 6-hydroxynicotinate **76** was prepared by adding HMDS (2 mL, 10 mmol, 1.5 equiv.) to a solution of methyl 2-oxo-2*H*-pyran-5-carboxylate **23** (1.0 g, 6.5 mmol, 1.0 equiv.) in MeCN (3.5 mL), followed by the addition of DBU (0.04 mL, 0.3 mmol, 5% mol equiv.). The reaction mixture was allowed to stir at room temperature for 48 h. The mixture was then diluted with ethyl acetate (10 mL) and was washed successively with HCl (5 mL), Na_2HCO_3 (5 mL) and brine (5 mL). The solution was dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from 2-propanol resulted in a brown-tan solid (0.7 g, 72% yield). **M.p.** = 157 – 160 °C.

Method B

A suspension of 6-hydroxynicotinic acid **78** (10g, 70 mmol, 1.0 equiv.) in methanol (50 mL) was treated with H_2SO_4 (4.2 mL, 76 mmol, 1.05 equiv.). The mixture was heated to reflux and left to stir for 24 h. The solution was cooled to room temperature before the solvent was evaporated. To the formed suspension was added distilled water, keeping the same volume and stirred at room temperature for 15 min. The solution was refrigerated overnight before filtering and washing with water (50 mL) to give brown crystals (8.3 g, 75% yield). **M.p. =** 162 - 163 °C. **FTIR:** ṽ (cm^{-1}) = 3058 (C-H, aromatic), 2863 (C-H, aliphatic), 1643 (C=N), 1608 (C=O amide). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.30 – 8.21 (m, 1H, H-2), 8.07 (dd, *J* = 9.5, 2.5 Hz, 1H, H-4), 6.65 (dd, *J* = 9.5, 0.7 Hz, 1H, H-5), 3.89 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 165.1 (C-7), 164.3 (C-6), 141.6 (C-2), 139.7 (C-4), 119.3 (C-3), 112.0 (C-5), 52.3 (COOMe).[52]

Methyl 6-amino-5-iodonicotinate 77



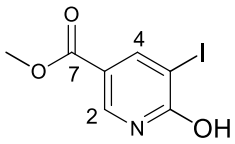
Method A

Methyl 6-aminonicotinate **66** (3.0 g, 20 mmol, 1.0 equiv.) and Ag_2SO_4 (8.7 g, 28 mmol, 1.4 equiv.) were added to a solution of iodine (7.0 g, 28 mmol, 1.4 equiv.) in ethanol (200 mL). The mixture was stirred at room temperature 48 h or until the consumption of the starting material. The resulting mixture was filtered and the tan precipitate was heated with 20% MeOH/$CHCl_3$ and filtered. The combined filtrates were evaporated and the resulting solid was recrystallized in MeOH to give an off-white solid (3.36 g, 65% yield).

Method B

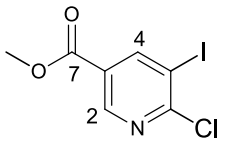
Methyl 6-choloro-5-iodonicotinate **80** (100 mg, 0.34 mmol, 1.0 equiv.), sodium azide (44 mg, 0.68 mmol, 2.0 equiv.) and triphenyl phosphine (262 mg, 0.68 mmol, 2.0 equiv.) were dissolved in DMSO (2.7 mL). The mixture was stirred and heated to 120 °C for 30 min. 1M HCl (0.5 mL) was then added and stirred for an additional 30 min at 120 °C. The mixture was cooled to room temperature before being diluted with additional 1M HCl (0.5 mL). The mixture was poured into distilled water (6.5 mL) and washed with EtOAc (3 × 3 mL). The aqueous layer was then neutralized using saturated aq. $NaHCO_3$ before extracting with EtOAc (3 x 5 mL) followed by drying over $MgSO_4$, filtered and concentrated to give an off-white solid (12 mg, 14% yield). **M.p.** = 128 °C. **FTIR:** ṽ (cm^{-1}) =3068 (C-H, aromatic), 2924 (C-H, aliphatic), 1707 (C=O), 1579 (C=N), 3420 (N-H). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.67 (d, *J* = 2.0 Hz, 1H, H-2), 8.46 (d, *J* = 2.0 Hz, 1H, H-4), 5.39 (s, 2H, NH_2), 3.88 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 162.6 (C-7), 157.8 (C-6), 148.5 (C-2), 145.8 (C-4), 115.8 (C-3), 73.6 (C-5), 49.8 (COOMe).[67]

Methyl 6-hydroxy-5-iodonicotinate 79



To a stirring warm (55-60 °C) solution of methyl 6-hydroxynicotinate **76** (0.1 g, 0.7 mmol, 1.0 equiv.) in methanol (3 mL) was added NIS (0.19 g, 0.84 mmol, 1.2 equiv.) and rinsing with methanol. The mixture was then heated to 70 °C and stirred until completion (that was about 30 min). The mixture was cooled to 10 °C and 10% aq. Na_2SO_3 (0.4 mL) solution was added to the reaction. The mixture was then concentrated to about half the original volume under vacuum at 40 °C followed by the addition of water (2 mL) at the same temperature. The resulting mixture was then cooled with stirring to 10 °C over 45 min and stirred for additional 1.5 h, while maintaining the same temperature. The mixture was centrifuged and the organic layer extracted and concentrated to give a pale yellow solid (0.15 g, 96% yield, based on recovered SM). **M.p.** = 190 - 193 °C. **FTIR:** $\tilde{\nu}$ (cm^{-1}) = 3058 (C-H, aromatic), 2854 (C-H, aliphatic), 1723 (C=O ester), 1639 (C=N), 1611 (C-OH amide), 2916 (C-H). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 12.3 (s, 1H, OH), 8.63 (d, *J* = 2.3 Hz, 1H, H-2), 8.26 (d, *J* = 2.3 Hz, 1H, H-4), 3.88 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 175.5 (C-7), 161.8 (C-OH), 148.1 (C-4), 138.0 (C-2), 111.2 (C-3), 89.1 (C-I), 50.9 (COOMe).[54]

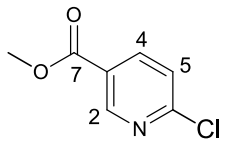
Methyl 6-choloro-5-iodonicotinate 80



To a mixture of methyl 6-hydroxy-5-iodonicotinate **80** (0.2 g, 0.7 mmol, 1.0 equiv.) and DIPEA (0.1 mL, 0.7 mmol, 1.0 equiv.) was added 1,4-dioxane (1 mL) and $POCl_3$ (0.01 mL, 0.14 mmol, 0.2 equiv.) and the mixture was stirred and heated to 95 °C. At 95 °C, was added additional $POCl_3$ (0.1 mL, 1.3 mmol, 1.85 equiv.) and continued stir for another 45 min to 1 h while maintaining the same temperature. On consumption of methyl 6-hydroxy-5-iodonicotinate **80** (based of the TLC of the reaction mixture), the heating stirrer was removed to cool the reaction to room temperature. The reaction

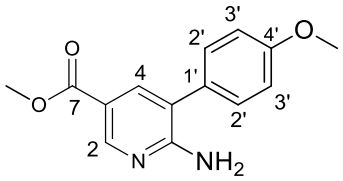
mixture was then added dropwise over 20 min to a second flask containing water with a temperature of 10-15°C, with agitation. The resulting precipitate was filtered off and rinsed with water to give an off-white solid (0.12 g, 80% yield, based on recovered SM). **M.p.** = 85 - 86 °C. **FTIR:** ṽ (cm^{-1}) = 3052 (C-H, aromatic), 2853 (C-H, aliphatic), 1712 (C=O), 1569 (C=N). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.93 (d, *J* = 2.1 Hz, 1H, H-2), 8.72 (d, *J* = 2.1 Hz, 1H, H-4), 3.97 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 163.7 (C-7), 158.7 (C-Cl), 149.8 (C-2), 149.6 (C-6), 125.7 (C-3), 94.4 (C-I), 52.9 (COOMe).[54]

Methyl 6-choloronicotinate 81



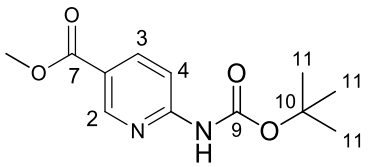
To a stirring solution of methyl 6-hydroxynicotinate **76** (0.1 g, 0.7 mmol, 1.0 equiv.) in DIPEA (0.1 mL, 0.7 mmol, 1.0 equiv.) was added 1,4-dioxane (1.0 mL) and $POCl_3$ (0.01 mL, 0.1 mmol, 0.2 equiv.) and the temperature was raised to 95°C. (NB: it was necessary to follow this sequence of addition of reagents to minimize caking). At 95°C, the remaining $POCl_3$ (1.85 equiv.) was added and continued to heat and stir for another 45 min to 1 h, at which the reaction reached completion, judging from TLC. The reaction mixture was cooled to room temperature and was added dropwise over 20 min to a second flask containing 10-15 °C cold water with agitation. The resulting precipitate was filtered off and rinsed with water to give a light brown solid (0.2 g, 83% yield). **M.p. =** 85 - 86 °C. **FTIR:** ṽ (cm^{-1}) = 3072 (C-H, aromatic), 2962 (C-H, aliphatic), 1717 (C=O), 1583 (C=N). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.00 (dd, *J* = 2.4, 0.8 Hz, 1H, H-2), 8.25 (dd, *J* = 8.3, 2.4 Hz, 1H, H-4), 7.43 (dd, *J* = 8.3, 0.8 Hz, 1H, H-5), 3.96 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 162.5 (C-7), 153.3 (C-Cl), 148.8 (C-2), 137.2 (C-4), 122.6 (C-3), 121.8 (C-5), 50.2 (COOMe).[57]

Methyl 6-amino-5-(4-methoxyphenyl)nicotinate 85



To a solution of methyl 6-amino-5-iodonicotinate **77** (300 mg, 1.08 mmol, 1.0 equiv) in dioxane-water (5:1) (15 mL) was added 4-methoxyphenyl boronic acid (1.29 mmol, 1.2 equiv.), anhydrous Na_2CO_3 (2.16 mmol, 2.0 equiv.) and $Pd(PPh_3)Cl_2$ (0.21 mmol, 0.2 equiv.). The mixture stirred at room temperature under N_2 before heating to 110 °C for 24 h. The solution was cooled to room temperature before quenching with water and extracting with EtOAc (3 x 15 mL). This was followed by drying over $MgSO_4$, filtered, concentrated *in vacuo* and purified using silica gel chromatography to give dark brown crystals (76 mg, 30% yield). **FTIR:** $\tilde{\nu}$ (cm^{-1}) = 3203 (C-H, aromatic), 2933 (C-H, aliphatic), 1695 (C=O), 1243 (C-O ether). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.71 (s, 1H, H-2), 7.93 (d, *J* = 2.2 Hz, 1H, H-4), 7.40 – 7.33 (m, 2H, H-2'), 7.04 – 6.97 (m, 2H, H-3'), 5.01 (s, 2H, NH_2), 3.89 (s, 3H, COOMe), 3.86 (s, 3H, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 166.4 (C-7), 159.6 (C-4'), 159.0 (C-6), 150.0 (C-2), 139.9 (C-4), 138.5 (C-1'), 129.8 (C-2'), 129.0 (C-5), 117.0 (C-3) 114.7 (C-3'), 55.4 (OMe), 51.8 (COOMe). **XRD:** $C_{14}H_{14}N_2O_3$ (M = 258.27 g/mol): monoclinic, space group $P2_1/c$, a = 10.3826(4) Å, b = 14.4886(5) Å, c = 8.3546(4) Å, β = 97.501(2)°, V = 1246.02(9) Å3, Z = 4, T = 173.00 K, μ(MoKα) = 0.098 mm^{-1}, Dcalc = 1.377 g/cm^3, 26893 reflections measured (3.956° ≤ 2Θ ≤ 56.952°), (R_{int} = 0.0599, R_{sigma} = 0.0341) which were used in all calculations. The final R_1 was 0.0408 (I > 2σ(I)) and wR_2 was 0.1168 (all data); **HRMS:** (m/z) calcd. for $C_{14}H_{15}N_2O_3$ $[M+H]^+$ 259.1077; found $[M+H]^+$ 259.1076.

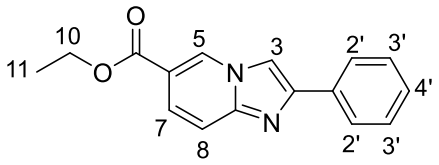
Methyl 6-((tert-butoxycarbonyl)amino)nicotinate 88



To a solution of Boc_2o (0.63 mL, 0.66 mmol, 1.0 equiv.) in *tert*-butanol (2 mL) was slowly added methyl 6-aminonicotinate **66** (107 mg, 0.66 mmol, 1.0 equiv.). The solution was

stirred at room temperature to give a white solid (51 mg, 31% yield). **M.p.** = 169 -172 °C. **FTIR:** ṽ (cm^{-1}) = 3178 (C-H, aromatic), 2947 (C-H, aliphatic), 1712 (C=O), 1586 (C=N), 1270 (C-O). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.89 (d, *J* = 2.3 Hz, 1H, H-2), 8.26 (dd, *J* = 8.9, 2.3 Hz, 1H, H-3), 8.04 (d, *J* = 8.8 Hz, 1H, H-4), 7.97 (s, 1H, NH), 3.92 (s, 3H, COOMe), 1.55 (s, 9H, H-11). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 165.2 (C-7), 154.7 (C-9), 151.5 (C-5), 149.8 (C-2), 139.1 (C-3), 120.4 (C-6), 110.7 (C-4), 81.4 (C-10), 51.7 (COOMe), 27.8 (C-11).

Ethyl 2-phenylimidazo[1,2-*a*]pyridine-6-carboxylate 93ab

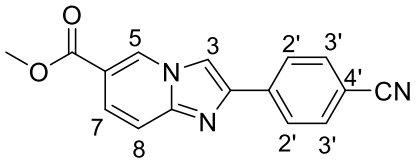


Methyl 6-aminonicotinate **66** (800 mg, 4.98 mmol, 1.0 equiv.) was dissolved in 2-bromoacetophenone 7 (900 mg, 4.98 mmol, 1.0 equiv.) and ethanol (10 mL, 0.5 M). Na_2CO_3 (0.5 g, 4.53 mmol, 0.9 equiv.) was then added. The mixture was stirred at 75 °C for 72 h. The product was extracted using ethyl acetate (3 × 20 mL) and water. The extracted layers were combined, washed with brine, and then dried using $MgSO_4$. Column chromatography was then used to purify the product **93ab** which resulted in an orange solid (0.4 g, 30% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 8.91 (dd, 1H, H-5), 7.97 (m, 1H, 2'), 7.95 (m, 1H, 2'), 7.93 (m, 1H, H-3), 7.74 (dd, 1H, H-7), 7.62 (dt, 1H, H-8), 7.46 (m, 2H, 3'), 7.37 (m, 1H, 4'), 4.42 (q, *J* = 7.2 Hz, 2H, H-10), 1.43 (t, *J* = 7.1 Hz, 3H, H-11). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 164.9 (C=O), 147.6 (C-2), 146.2 (C-9), 133.1 (C-1'), 129.7 (C-5), 128.8 (C-3'), 128.5 (C-4'), 126.2 (C-2'), 124.4 (C-7), 116.8 (C-6), 116.7 (C-8), 108.9 (C-3), 61.5 (C-10), 14.3 (C-11).

General procedure for the synthesis of IPs 93b-f

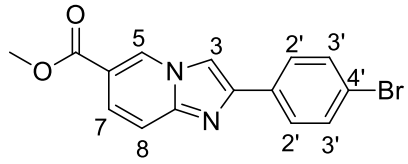
In a 250 mL flask was added the substituted acetophenone (0.66 mmol, 1.0 equiv.) and methyl 6-aminonicotinate **66** (0.66 mmol, 1.0 equiv.) in 1,4-dioxane (6.3 mL). The mixture was heated to reflux for 24 h before cooling and filtering to obtain the desired compounds in good yield.

Methyl 2-(4-cyanophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93b



Synthesized from 4-(2-bromoacetyl)benzonitrile (104 mg, 0.66 mmol, 1.0 equiv.) and methyl 6-aminonicotinate **66** (100 mg, 0.66 mmol, 1.0 equiv.) in 1,4-dioxane (6.3 mL). The desired compound **93b** was an off-white solid (143 mg, 78%). **FTIR:** ṽ (cm^{-1}) = 3024 (C-H, aromatic), 2847 (C-H, aliphatic), 1725 (C=O), 1650 (C=N), 2226 (C≡N). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) = 9.29 (s, 1H, H-3), 8.50 (s, 1H, H-5), 8.29 (s, 2H, H-7, H-8), 8.19 (dd, *J* = 8.4, 2.0 Hz, 2H, H-2'), 7.88 – 7.80 (m, 2H, H-3'), 4.05 (d, *J* = 1.9 Hz, 3H, COOMe). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) = 161.2 (C=O), 143.8 (C-2), 140.0 (C-9), 134.6 (C-1'), 133.2 (C-3'), 131.9 (C-5), 128.0 (C-7), 126.7 (C-2'), 118.6 (CN), 117.7 (C-6), 114.8(C-8), 113.2 (C-'4), 111.4 (C-3), 52.8 (C-COOMe).[65]

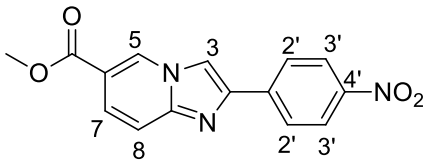
Methyl 2-(4-bromophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93c



Synthesized from 2-bromo-1-(4-bromophenyl)ethanone (131 mg, 0.66 mmol, 1.0 equiv.) and methyl 6-aminonicotinate **66** (101 g, 0.66 mmol, 1.0 equiv.) in 1,4-dioxane (6.3 mL). The resulting compound **93c** was an off-white solid (120 mg, 52%). **FTIR:** ṽ (cm^{-1}) =3071 (C-H, aromatic), 2840 (C-H, aliphatic), 1716 (C=O), 1652 (C=N). **^{1}H NMR** (400 MHz, MeOD): δ (ppm) = 9.50 (s, 1H, H-3), 8.68 (s, 1H, H-5), 8.41 (dd, *J* = 9.4, 1.7 Hz, 1H, H-), 7.98 (d, *J* = 9.5 Hz, 1H, H-8), 7.88 – 7.78 (m, 4H, H-2', H-3'), 4.05 (s, 3H-COOMe). **^{13}C NMR** (100 MHz, MeOD): δ (ppm) = 163.4 (C=O), 142.0 (C-2), 137.1 (C-9), 132.6 (C-2'), 132.5 (C-7), 132.1 (C-3), 127.9 (C-3'), 125.4 (C-1'), 124.8 (C-4'), 121.2 (C-6), 112.2 (C-5), 111.7 (C-8), 52.2 (COO<u>Me</u>). **XRD:** $C_{15}H_{11}BrN_2O_2$ (M = 331.17 g/mol): triclinic, space group P-1, a = 7.6788(3) Å, b = 9.3292(3) Å, c = 10.7461(4) Å, β = 101.2360(10)°, V = 648.40(4) Å3, Z = 2, T = 173.00 K, μ(MoKα) = 3.172 mm^{-1}, Dcalc = 1.696 g/cm^3, 28017 reflections measured (4.108° ≤ 2Θ ≤ 56.942°), (R_{int} = 0.0502, R_{sigma}

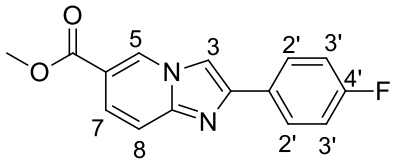
= 0.0284) which were used in all calculations. The final R_1 was 0.0219 ($I > 2\sigma(I)$) and wR_2 was 0.0567 (all data). [65]

Methyl 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93d



Synthesized from 2-bromo-1-(4-nitrophenyl)ethanone (161 mg, 0.66 mmol, 1.0 equiv.) and methyl 6-aminonicotinate **66** (108 mg, 0.66 mmol, 1.0 equiv.) in 1,4-dioxane (6.3 mL). Compound **93d** was an off-white solid (123 mg, 63%). **FTIR:** ṽ (cm^{-1}) = 3048 (C-H, aromatic), 2722 (C-H, aliphatic), 1732 (C=O), 1346 (N-O). **^{1}H NMR** (400 MHz, MeOD): δ (ppm) = 9.46 (t, *J* = 1.3 Hz, 1H, H-3), 8.78 (s, 1H, H-5), 8.39 (dd, *J* = 9.2, 1.8 Hz, 3H, H-7, H-3'), 8.12 – 8.04 (m, 2H, H-2'), 7.95 (d, *J* = 9.4 Hz, 1H, H-8), 3.95 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, MeOD): δ (ppm) = 163.3 (C=O), 149.1 (C-2), 142.2 (C-4'), 135.5 (C-9), 133.4 (C-7), 132.4 (C-3), 132.0 (C-1'), 127.4 (C-2'), 124.4 (C-3'), 121.6 (C-6), 114.0 (C-5), 111.8 (C-8), 52.3 (COO<u>Me</u>). [65]

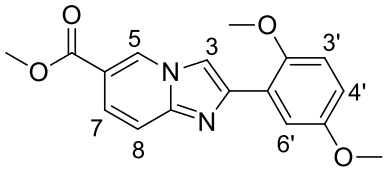
Methyl 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93e



Synthesized from 2-bromo-1-(4-fluorophenyl)ethanone (143 mg, 0.66 mmol, 1.0 equiv.) and methyl 6-aminonicotinate **66** (98 mg, 0.66 mmol, 1.0 equiv.) in 1,4-dioxane (6.3 mL). The desired compound **93e** was an off-white solid (169.2 mg, 95%). **FTIR:** ṽ (cm^{-1}) = 3062 (C-H, aromatic), 2857 (C-H, aliphatic), 1721 (C=O), 1505 (C=N). **^{1}H NMR** (400 MHz, MeOD): δ (ppm) = 9.49 (d, *J* = 1.6 Hz, 1H, H-3), 8.62 (s, 1H, H-5), 8.40 (d, *J* = 9.5 Hz, 1H, H-7), 7.98 (dd, *J* = 8.7, 5.5 Hz, 3H, H-8, H-2', H-2'), 7.39 (t, *J* = 8.6 Hz, 2H, H-3' H-3'), 4.05 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, MeOD): δ (ppm) = 163.5 (C=O), 141.8 (C-2), 137.2 (C-9), 132.5 (C-7), 132.0 (C-3), 128.7 (C-2'), 122.7 (C-1'), 121.2 (C-6), 116.6 (C-3'), 111.8 (C-5), 111.6 (C-8), 52.2 (COO<u>Me</u>). **XRD:** $C_{15}H_{11}FN_2O_2$ (M = 270.26 g/mol): triclinic, space group P-1, a = 8.9081(3) Å, b = 9.3111(3) Å, c = 10.8844(6) Å, β =

111.432(2)°, V = 740.45(6) Å3, Z = 2, T = 173.00 K, μ(MoKα) = 2.801 mm^{-1}, Dcalc = 1.656 g/cm^3, 36380 reflections measured (4.55° ≤ 2Θ ≤ 56.606°), (R_{int} = 0.0492, R_{sigma} = 0.0270) which were used in all calculations. The final R_1 was 0.02190 (I > 2σ(I)) and wR_2 was 0.0575 (all data). [65]

Methyl 2-(2,5-dimethoxyphenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93f



Synthesized from 2-bromo-1-(2,5-dimethoxyphenyl)ethanone (171 mg, 0.66 mmol, 1.0 equiv.) and methyl 6-aminonicotinate **66** (104 mg, 0.66 mmol, 1.0 equiv.) in 1,4-dioxane (6.3 mL). The resulting compound **93f** was an off-white solid (125 mg, 61%). **FTIR:** ṽ (cm^{-1}) = 3061 (C-H, aromatic), 2840 (C-H, aliphatic), 1726 (C=O), 1652 (C=N). **^{1}H NMR** (400 MHz, MeOD): δ (ppm) = 9.41 (t, *J* = 1.3 Hz, 1H, H-3), 8.66 (s, 1H, H-5), 8.31 (dd, *J* = 9.4, 1.6 Hz, 1H, H-7), 7.89 (d, *J* = 9.4 Hz, 1H, H-8), 7.36 (d, *J* = 2.9 Hz, 1H, H-6'), 7.13 (d, *J* = 9.1 Hz, 1H, H-3'), 7.05 (dd, *J* = 9.1, 2.9 Hz, 1H, H-4'), 3.93 (s, 6H, OMe), 3.77 (s, 3H, COOMe). **^{13}C NMR** (100 MHz, MeOD): δ (ppm) = 163.5 (C=O), 154.2 (C-5'), 151.5 (C-2'), 134.0 (C-9), 132.4 (C-7), 131.9 (C-3), 121.2 (C-6), 117.2 (C-4'), 114.4 (C-5), 113.0 (C-3'), 112.9 (C-6'), 111.3 (C-8), 55.3 (OMe), 55.0 (O<u>Me</u>), 52.2 (COO<u>Me</u>). **Mass spectrum:** HRMS, m/s calcd. for $C_{17}H_{17}N_2O_4$ $[M+H]^+$ 313.1183; found $[M+H]^+$ 313.1175.

References

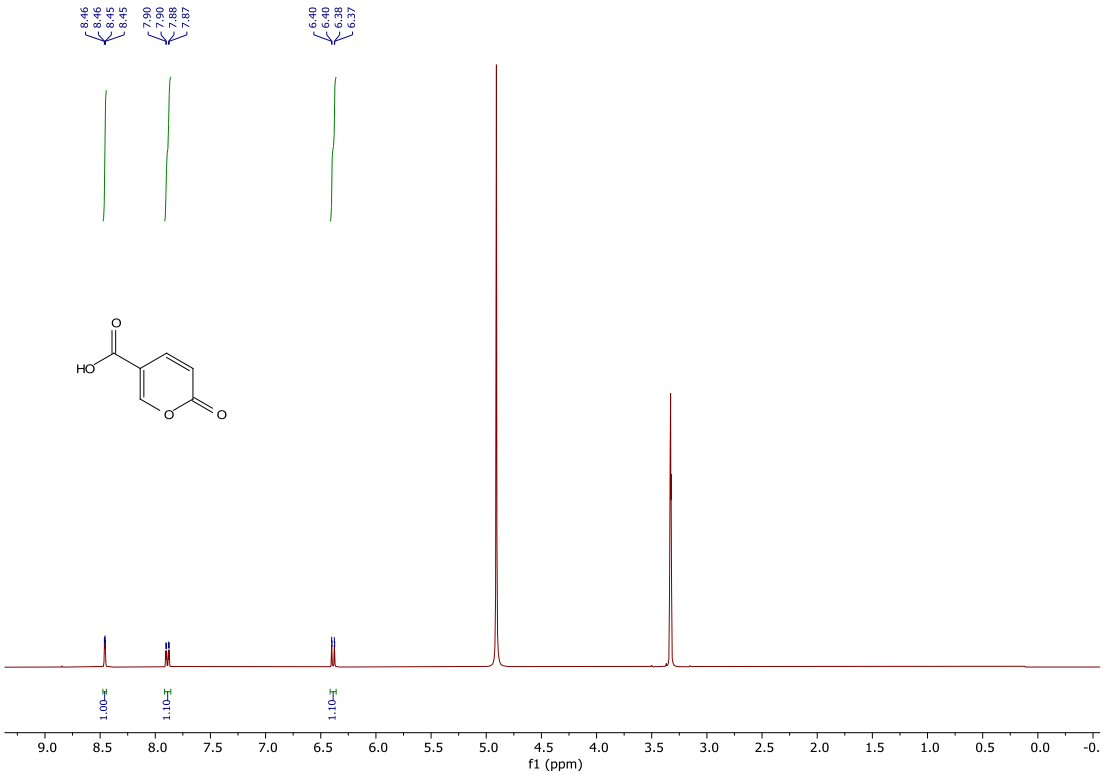
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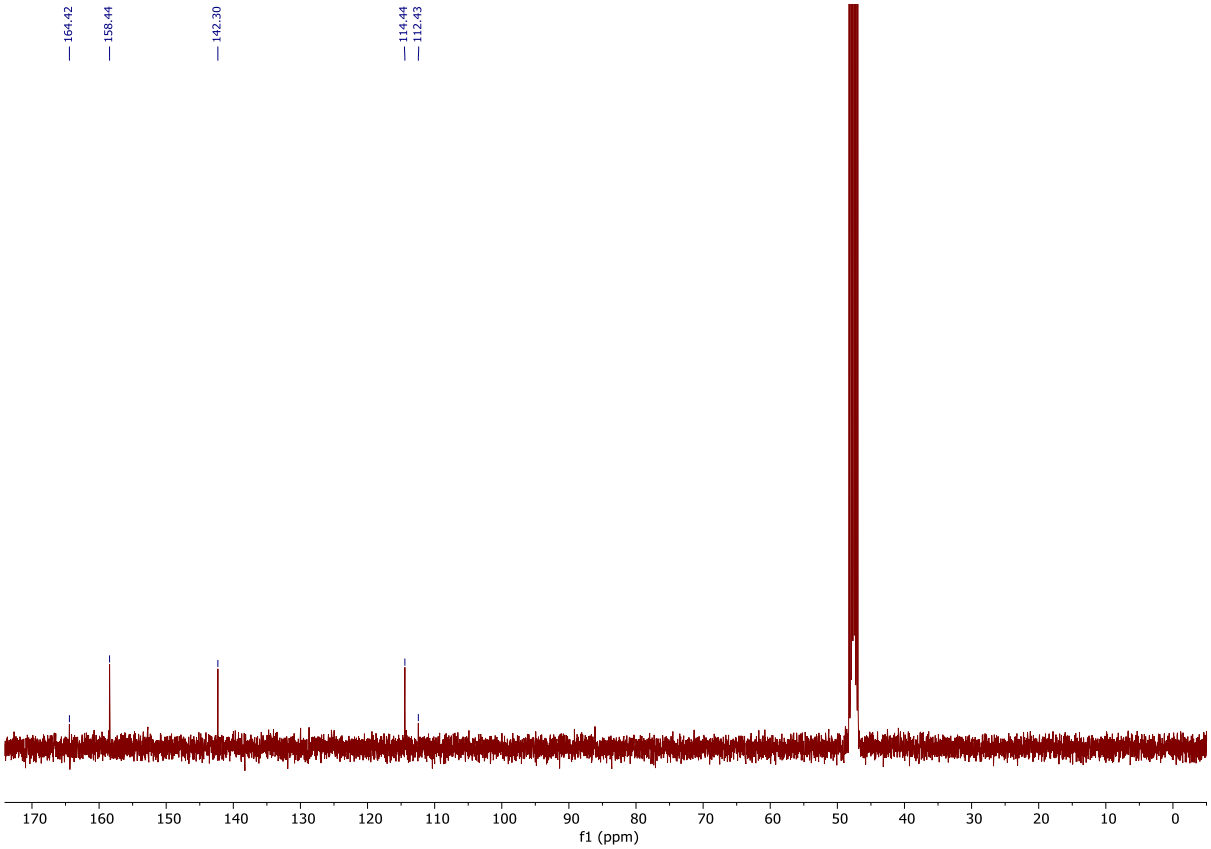
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Appendix

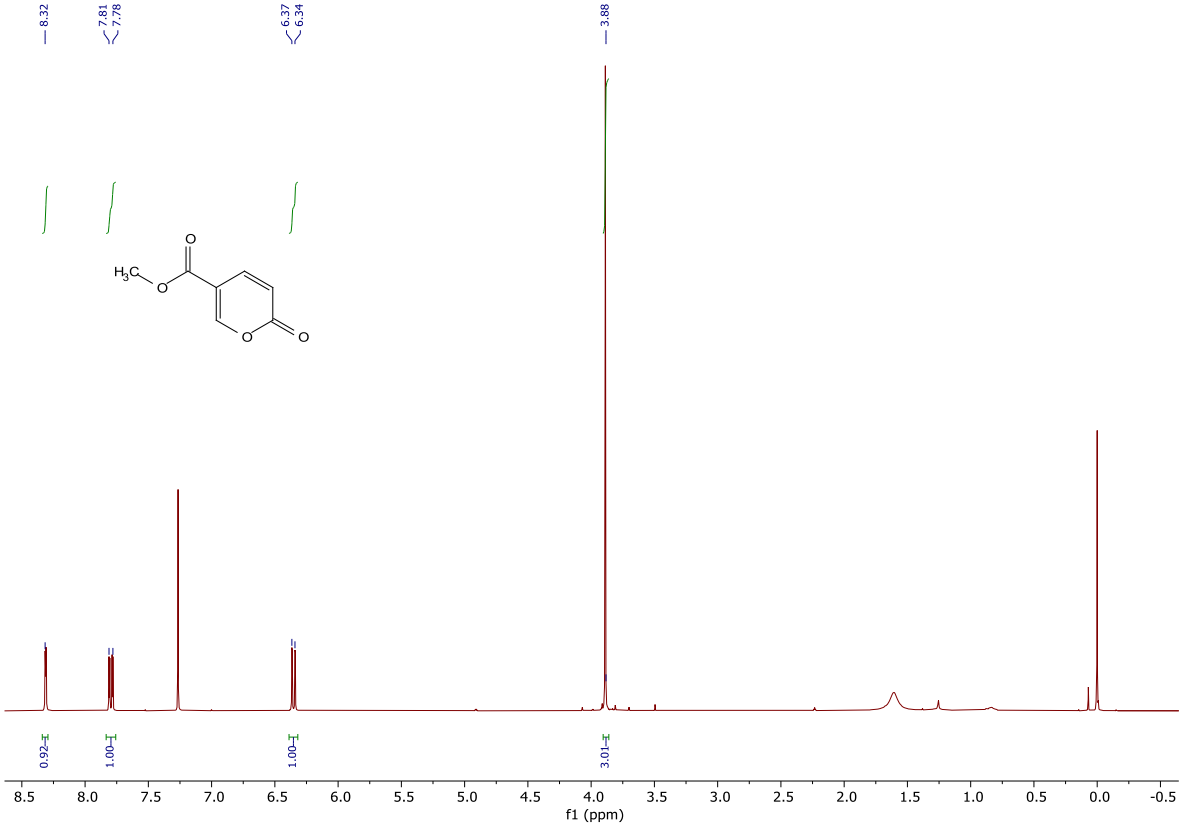
^{1}H NMR spectrum of 2-oxo-2*H*-pyran-5-carboxylic acid 22



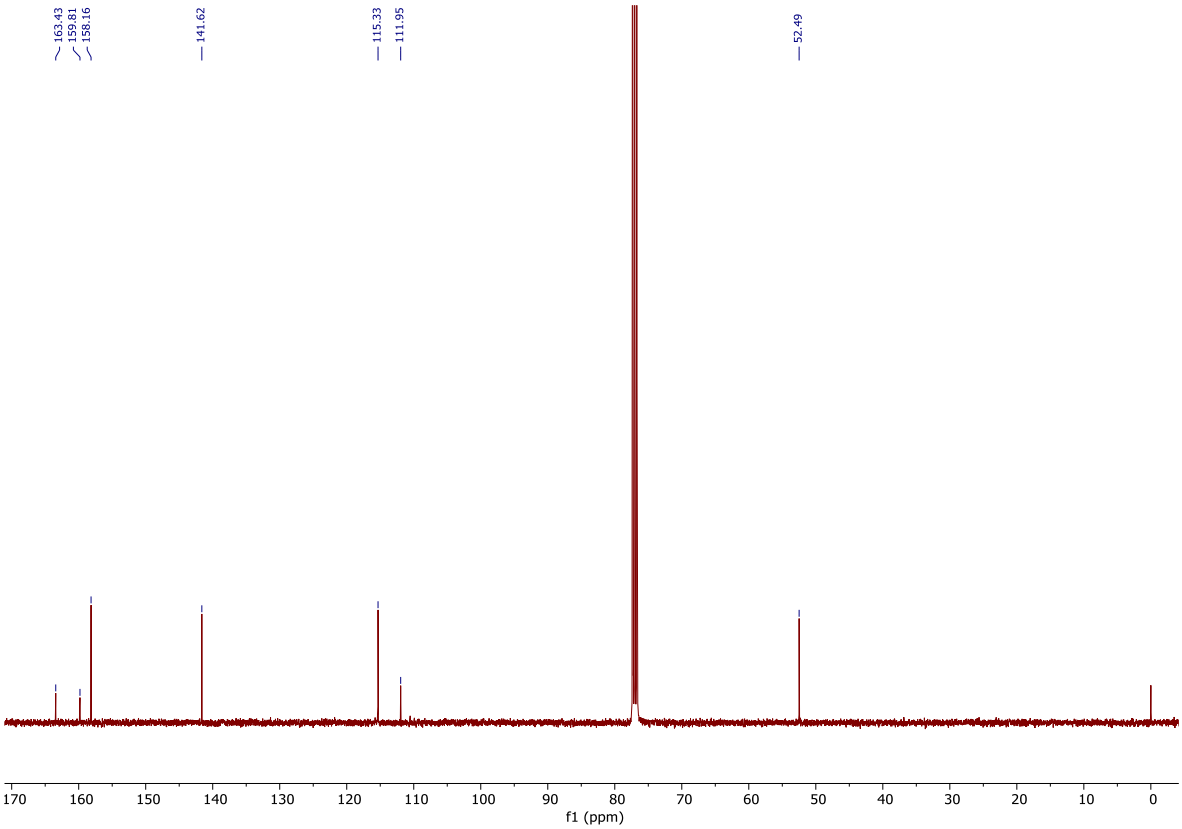
^{13}C NMR spectrum of 2-oxo-2*H*-pyran-5-carboxylic acid 22



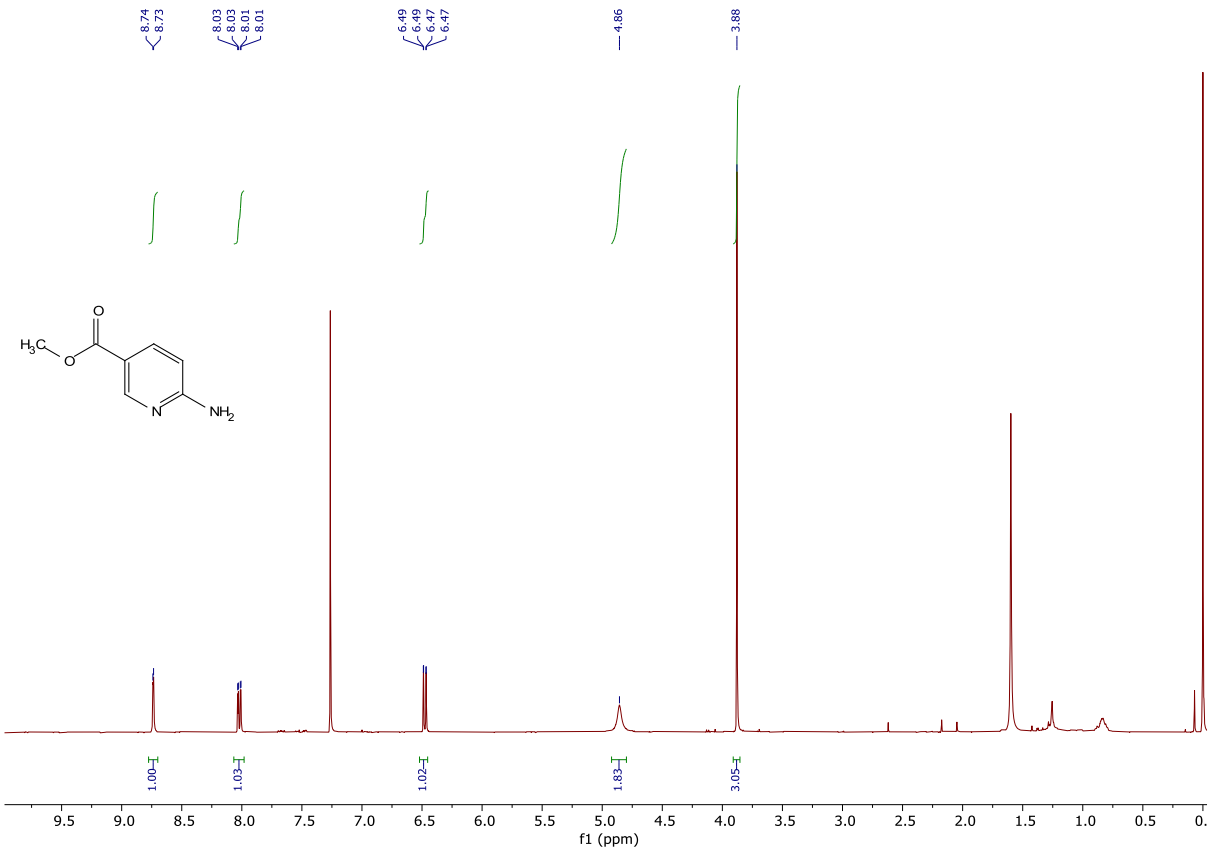
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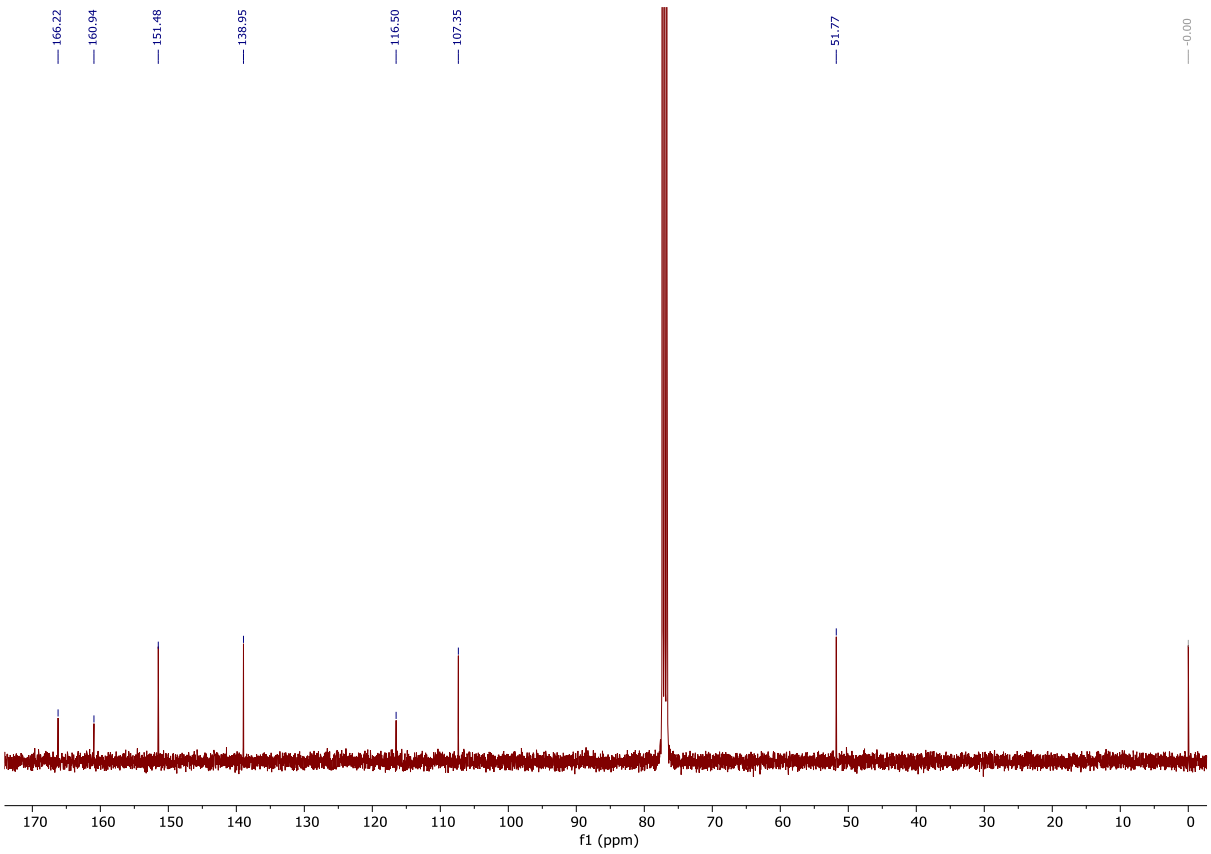
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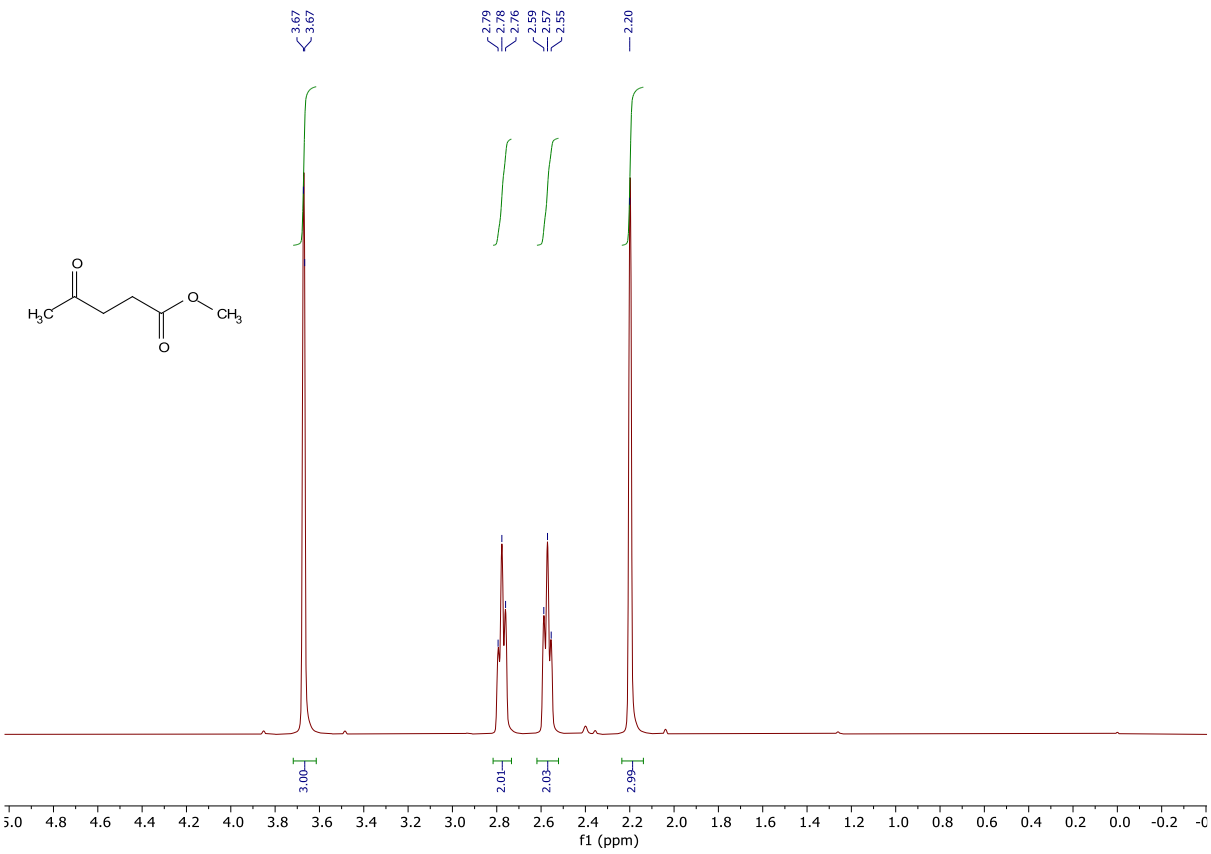
^{1}H NMR spectrum of Methyl 6-aminonicotinate 66



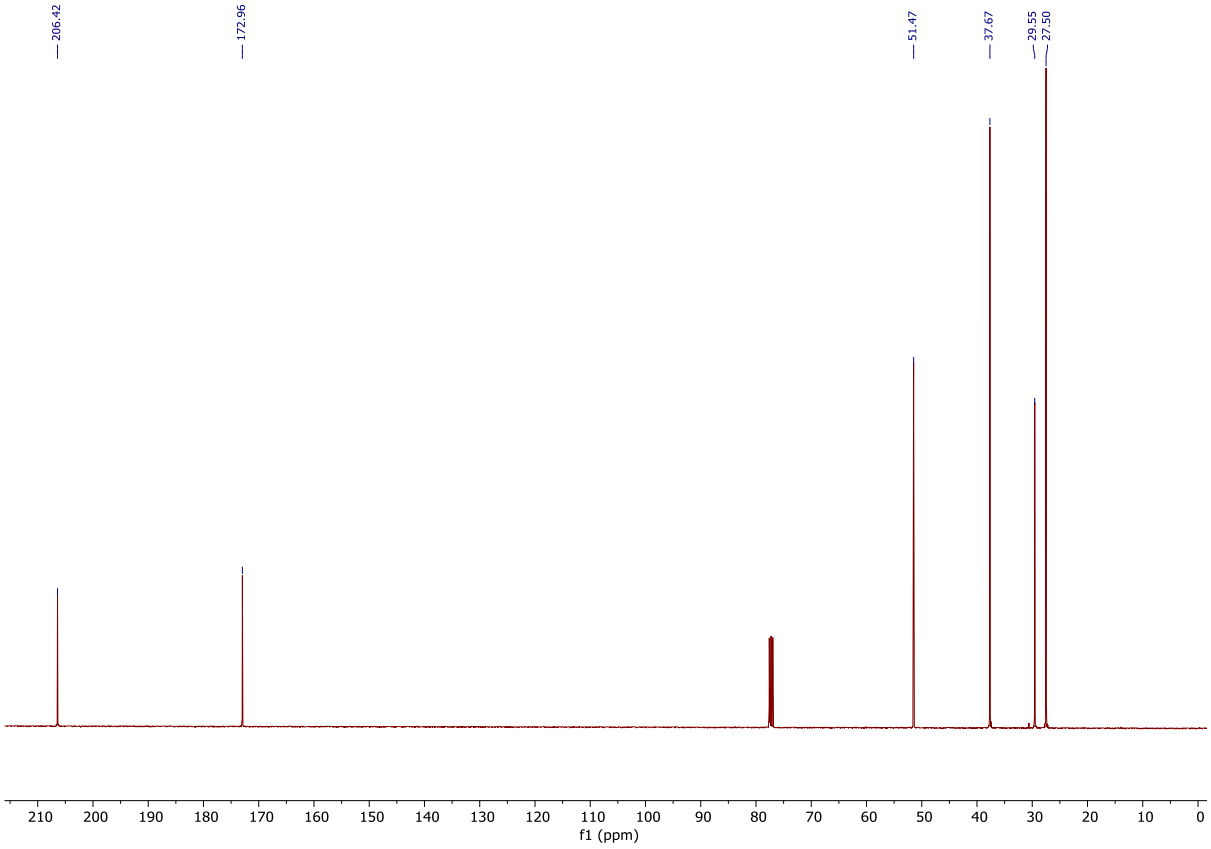
^{13}C NMR spectrum of Methyl 6-aminonicotinate 66



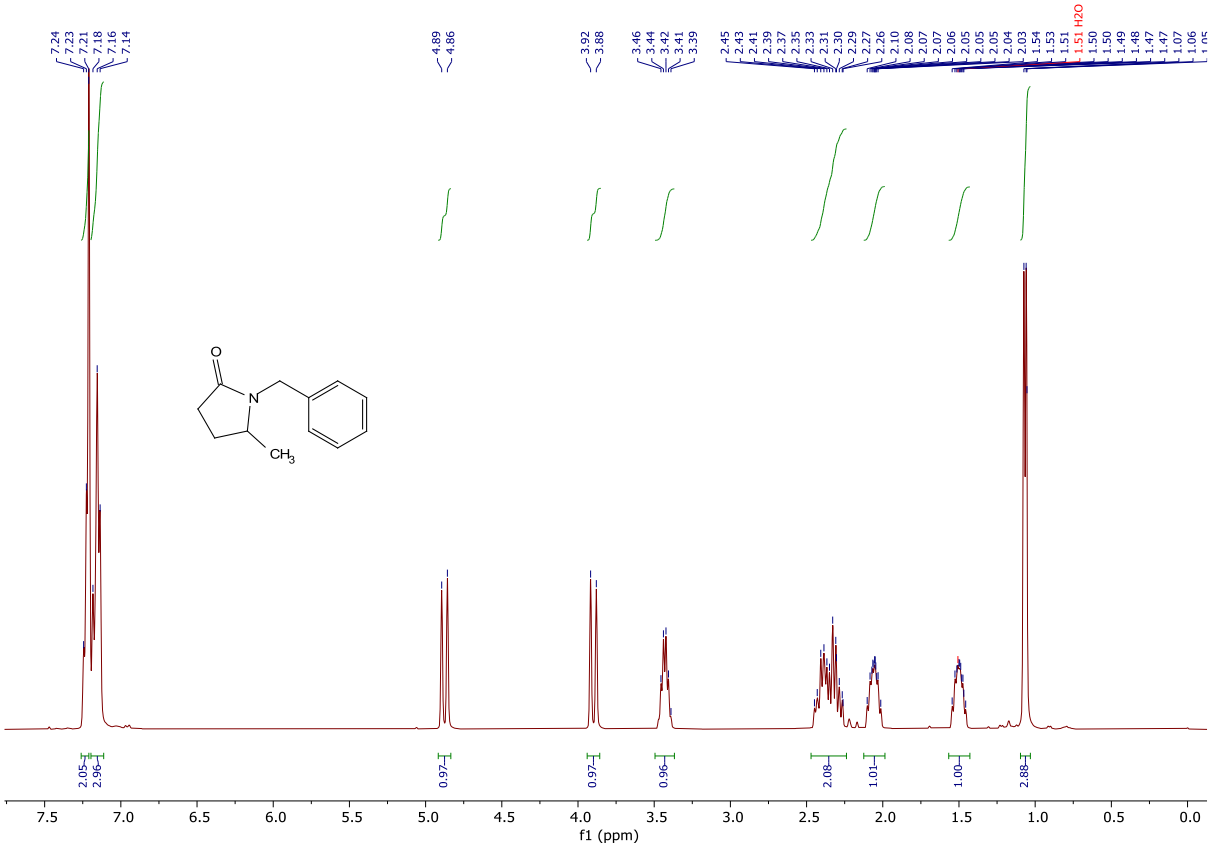
^{1}H NMR spectrum of Methyl 4-oxopentanoate 73



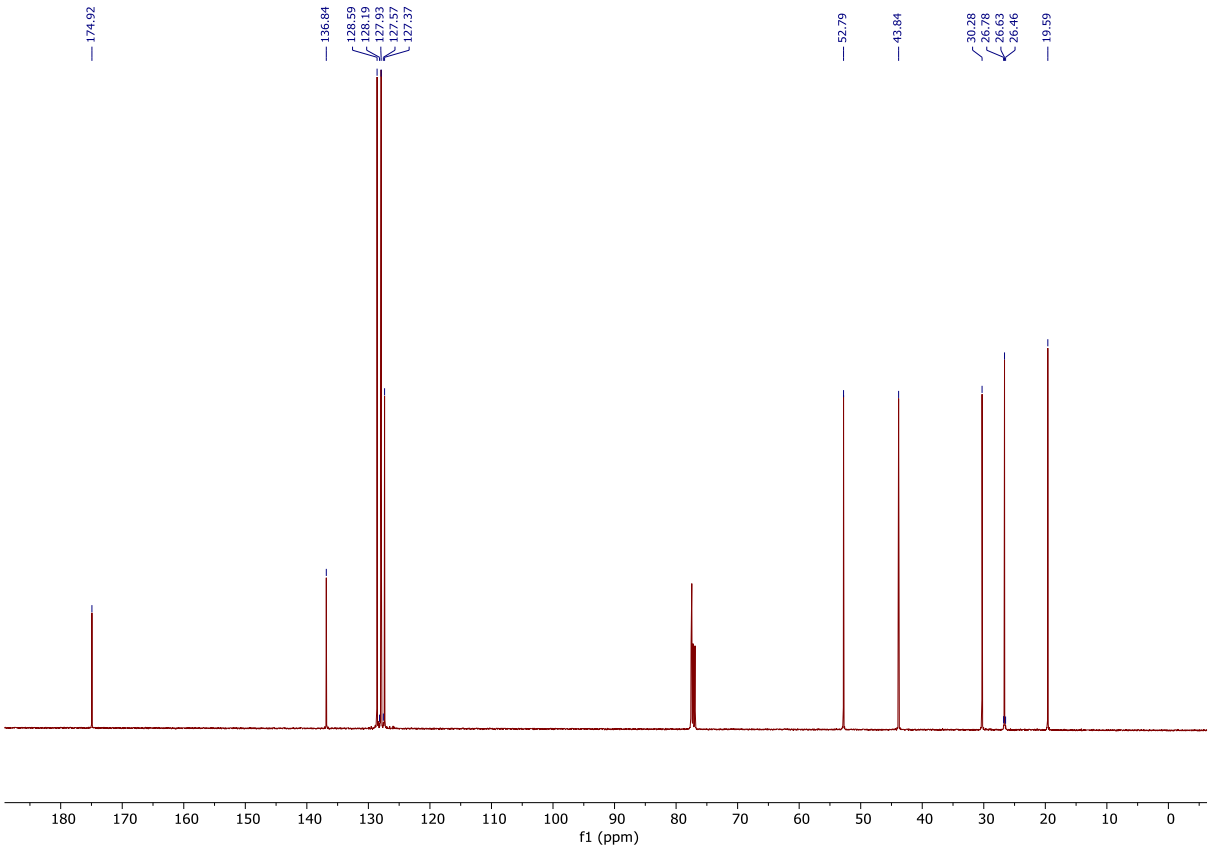
^{13}C NMR spectrum of Methyl 4-oxopentanoate 73



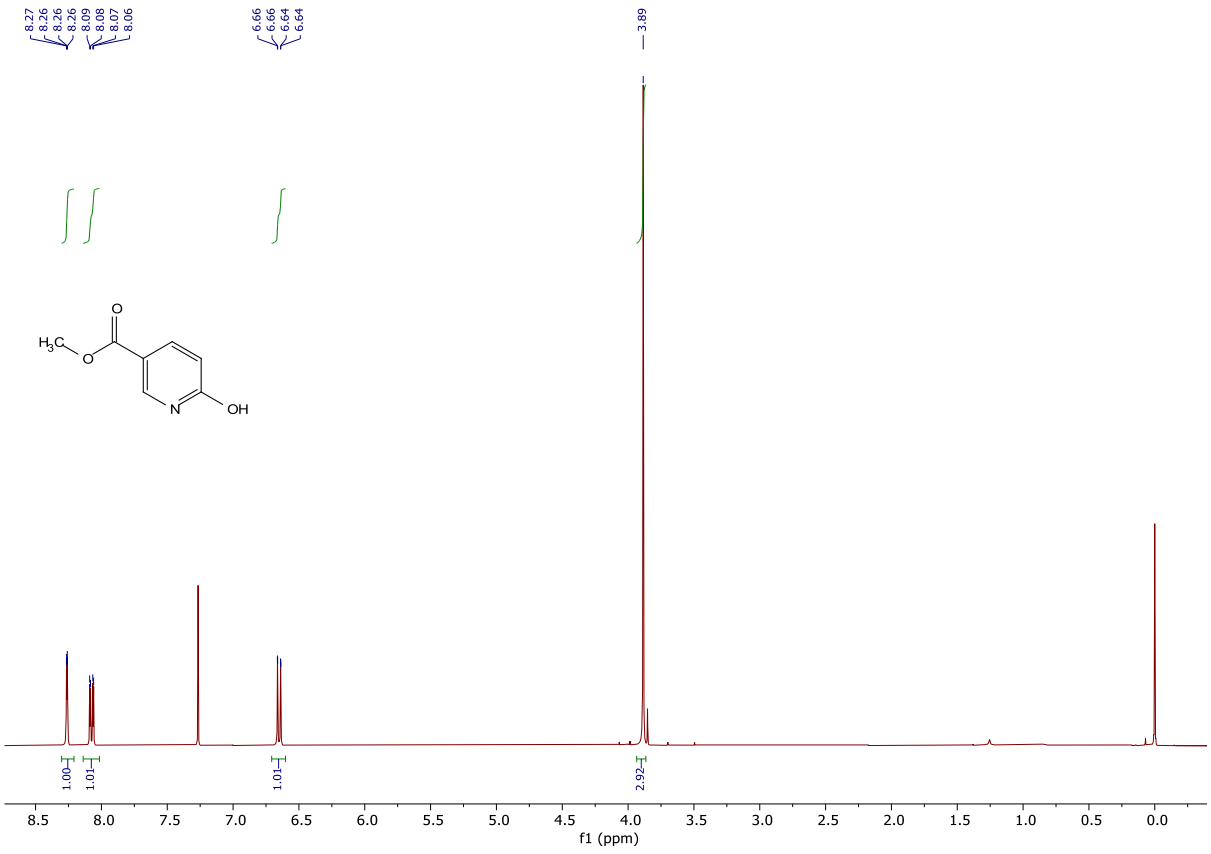
^{1}H NMR spectrum of 1-benzyl-5-methylpyrrolidin-2-one 75



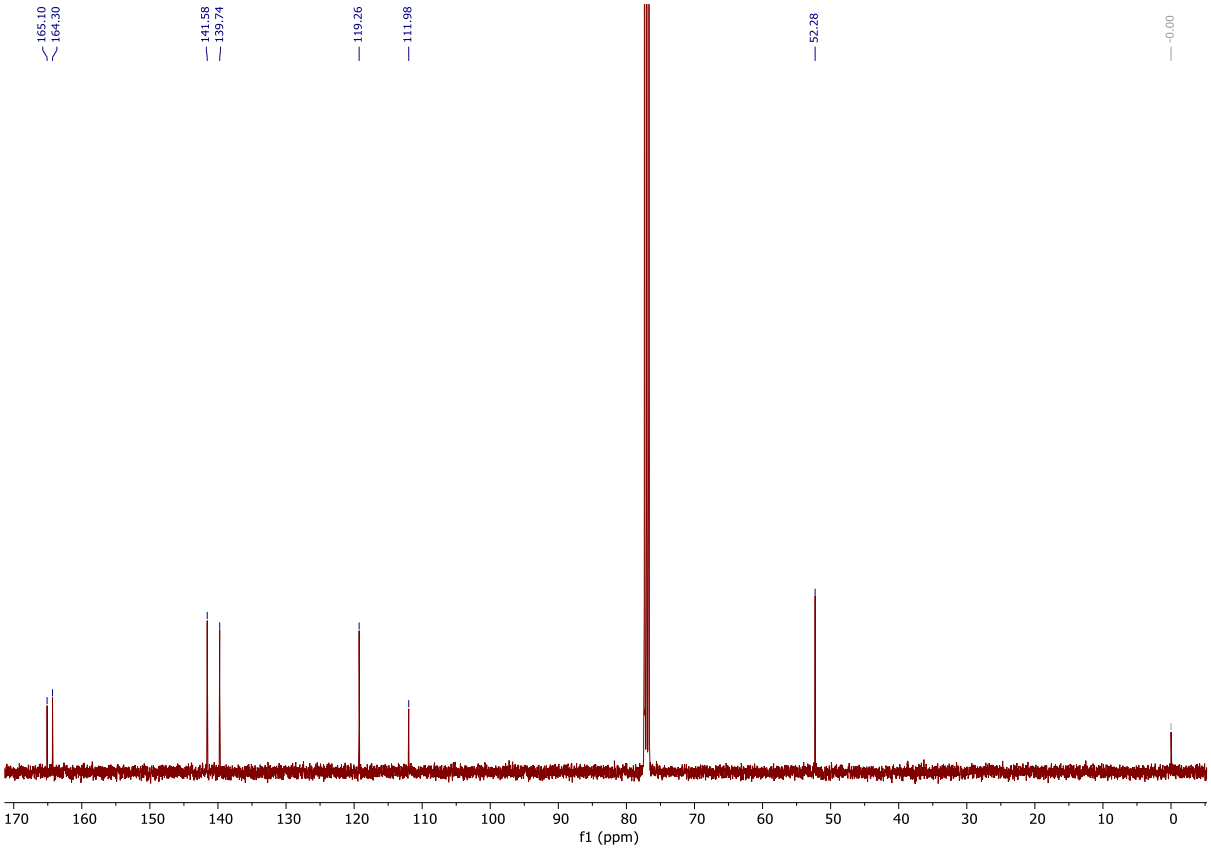
^{13}C NMR spectrum of 1-benzyl-5-methylpyrrolidin-2-one 75



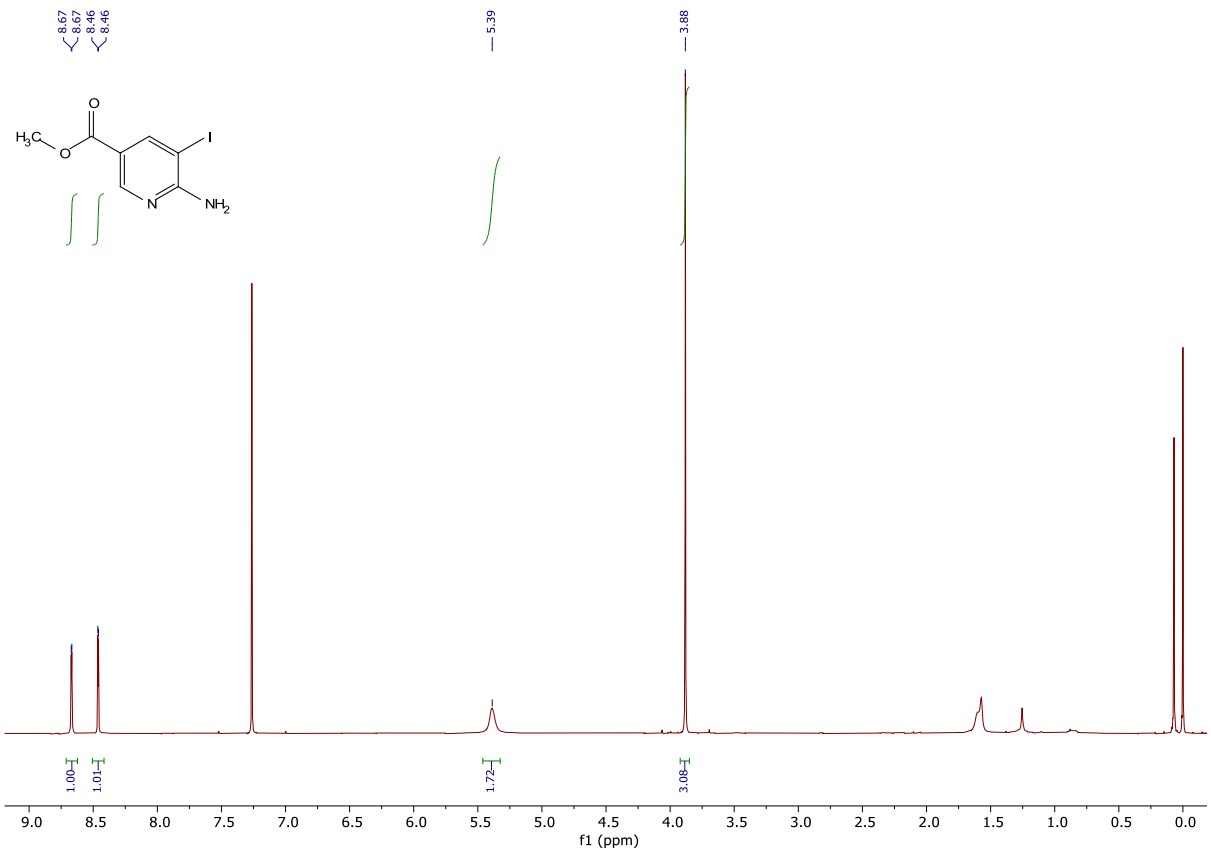
^{1}H NMR spectrum of Methyl 6-hydroxynicotinate 76



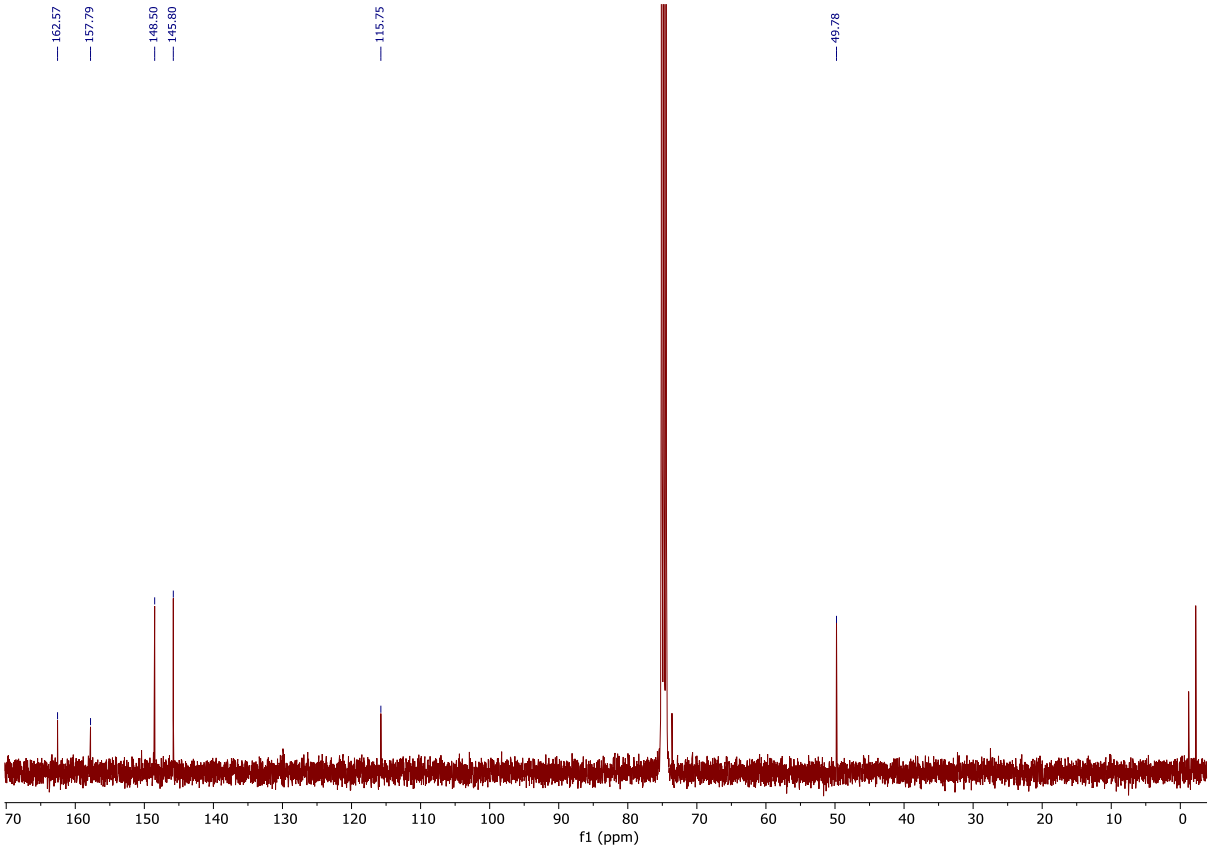
^{13}C NMR spectrum of Methyl 6-hydroxynicotinate 76



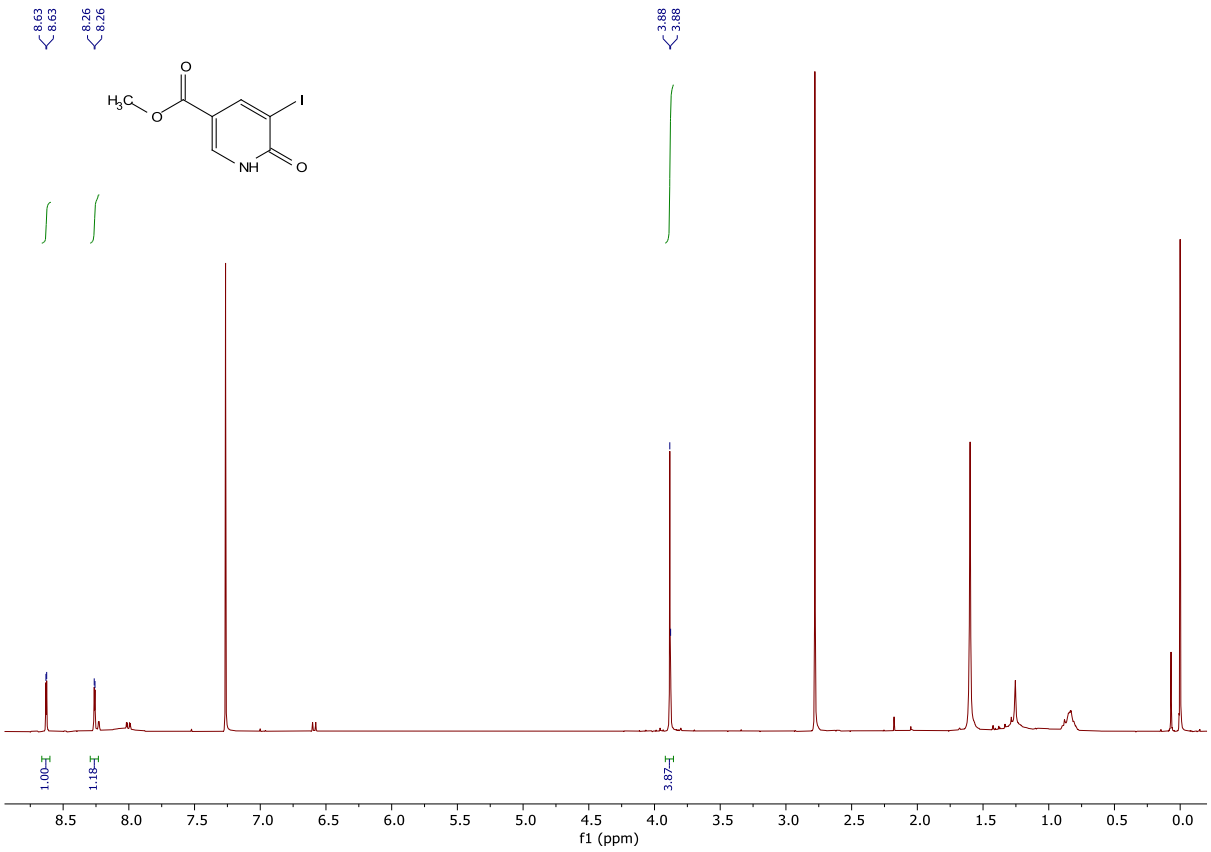
^{1}H NMR spectrum of Methyl 6-amino-5-iodonicotinate 77



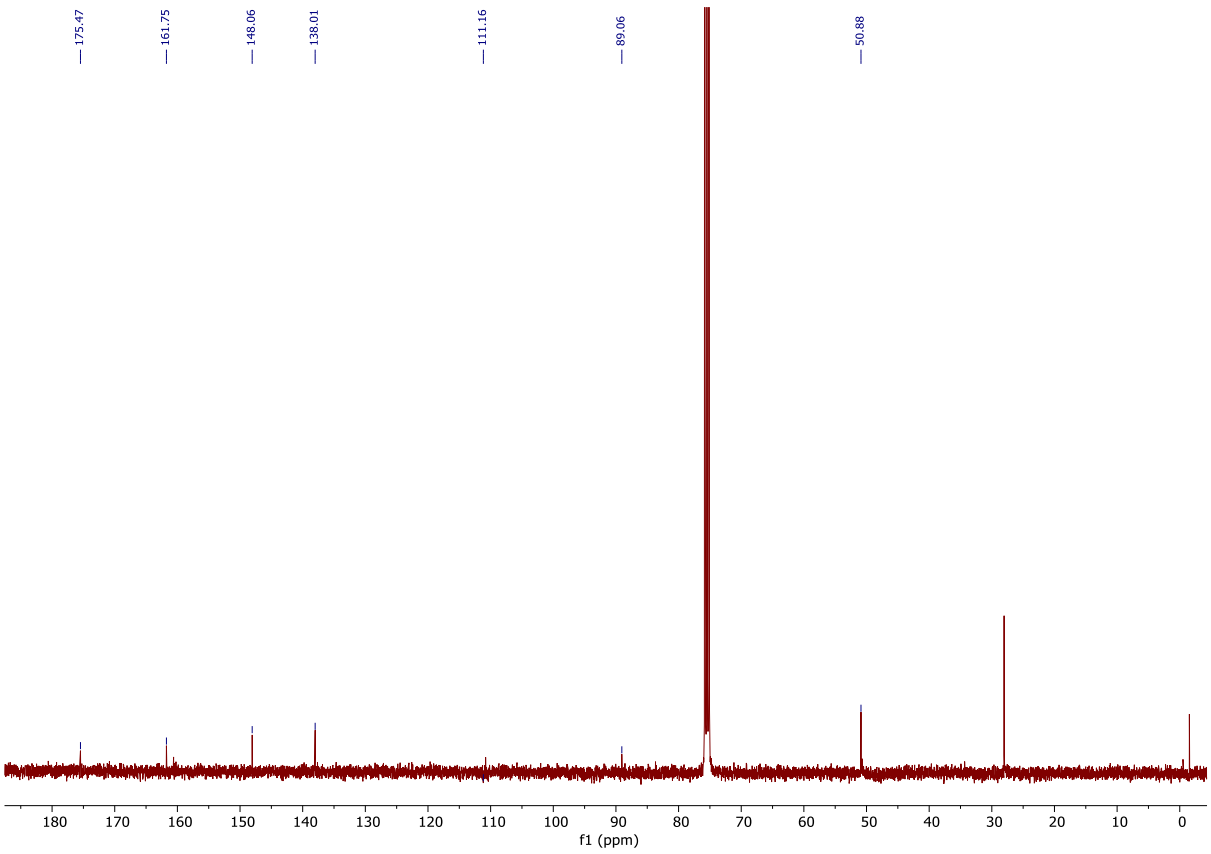
^{13}C NMR spectrum of Methyl 6-amino-5-iodonicotinate 77



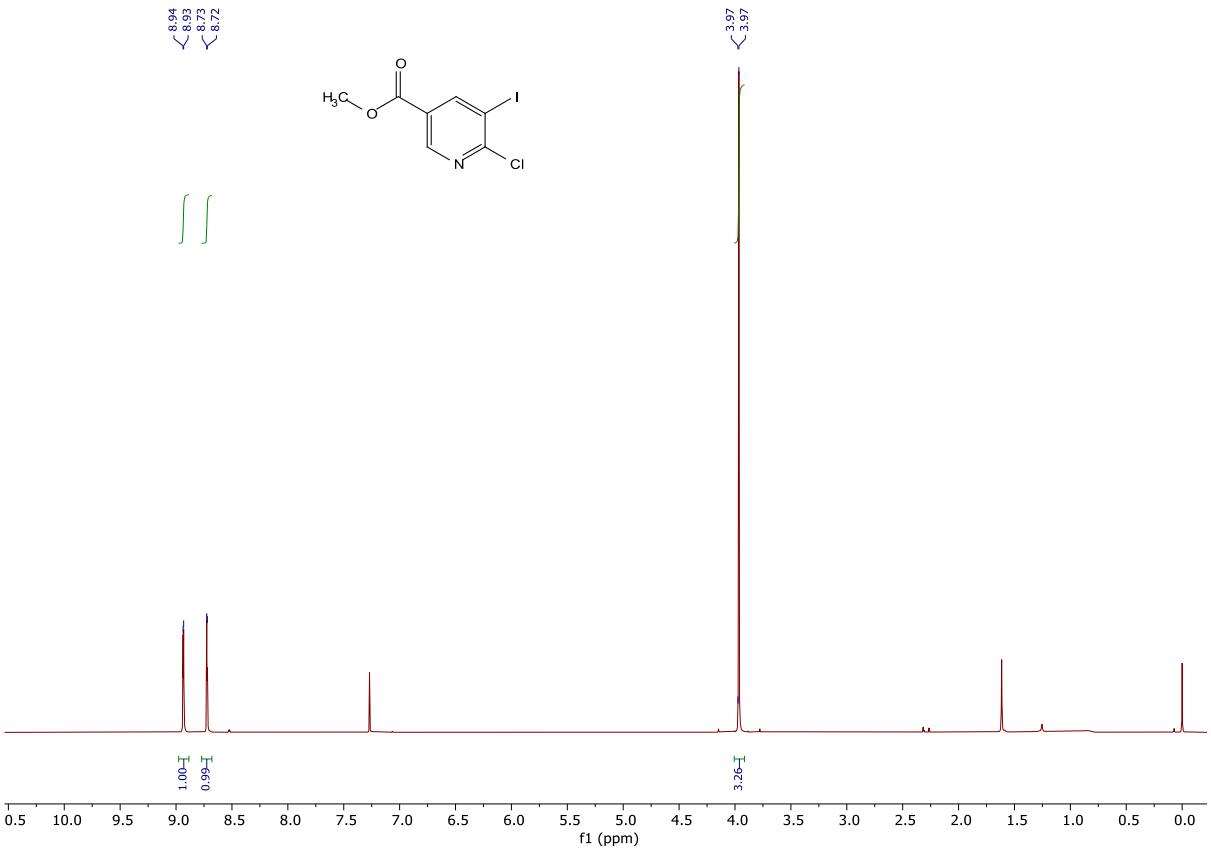
^{1}H NMR spectrum of Methyl 6-hydroxy-5-iodonicotinate 79



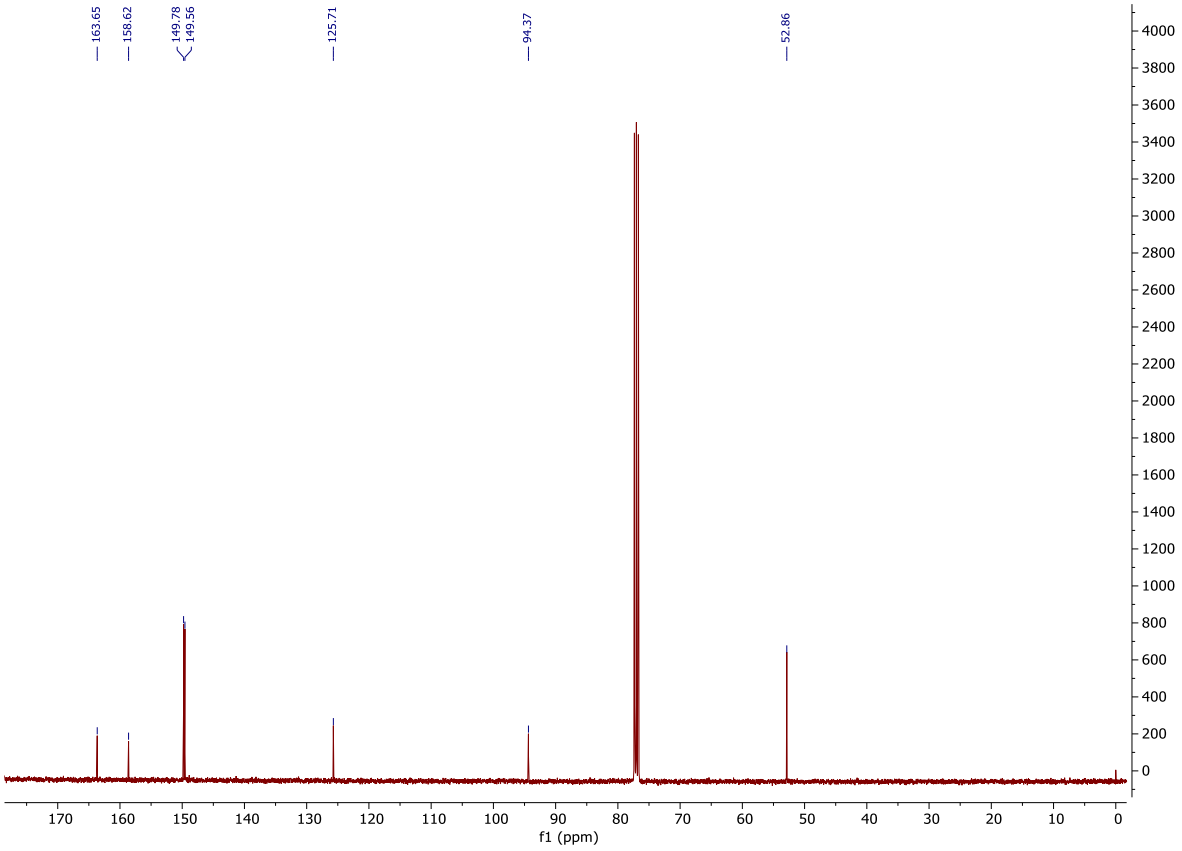
^{13}C NMR spectrum of Methyl 6-hydroxy-5-iodonicotinate 79



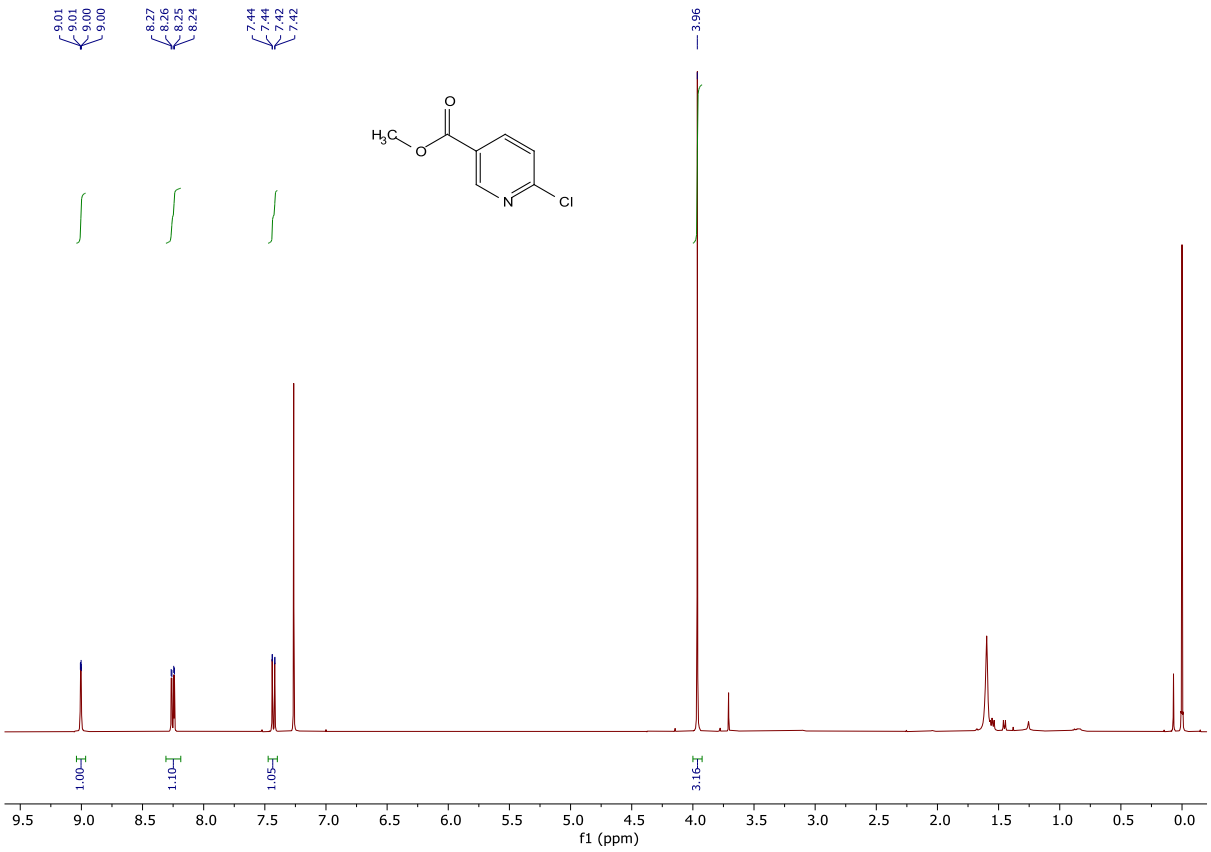
^{1}H NMR spectrum of Methyl 6-choloro-5-iodonicotinate 80



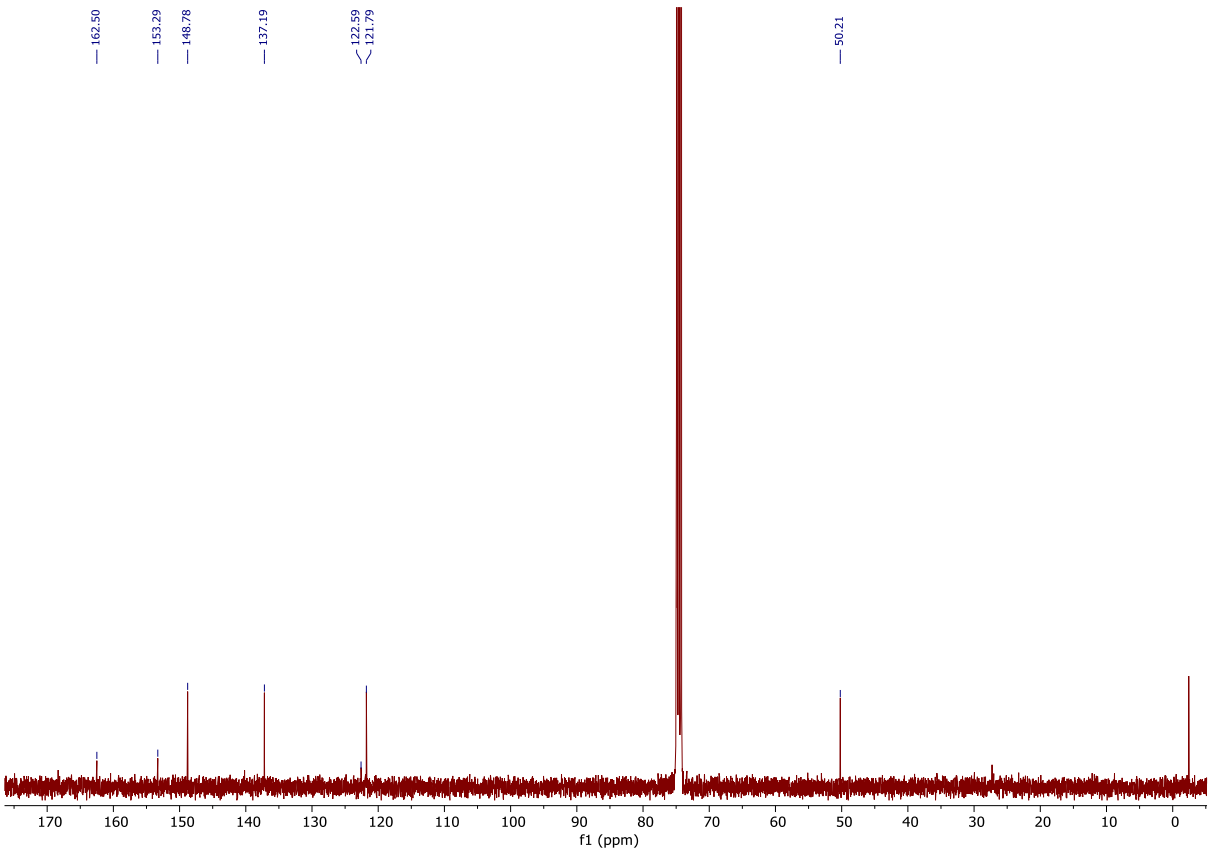
^{13}C NMR spectrum of Methyl 6-choloro-5-iodonicotinate 80



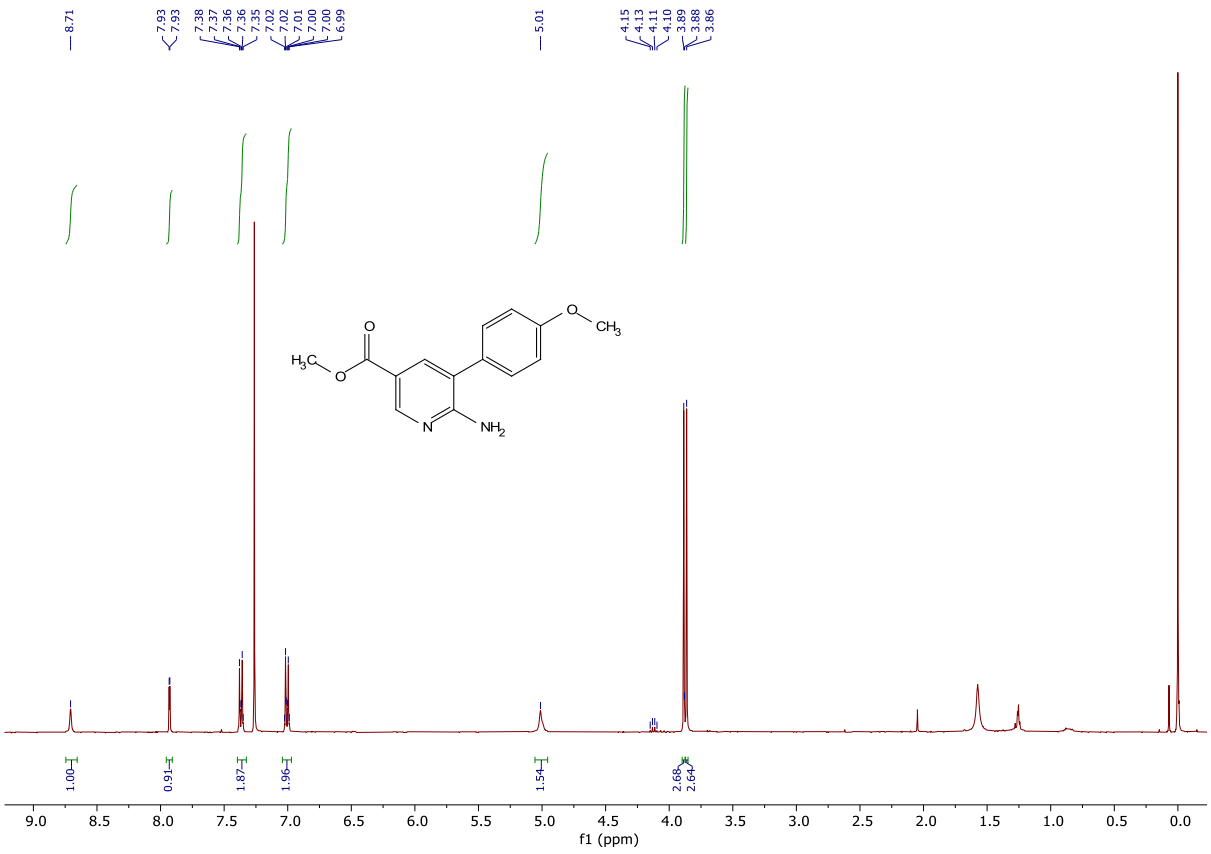
^{1}H NMR spectrum of Methyl 6-choloronicotinate 81



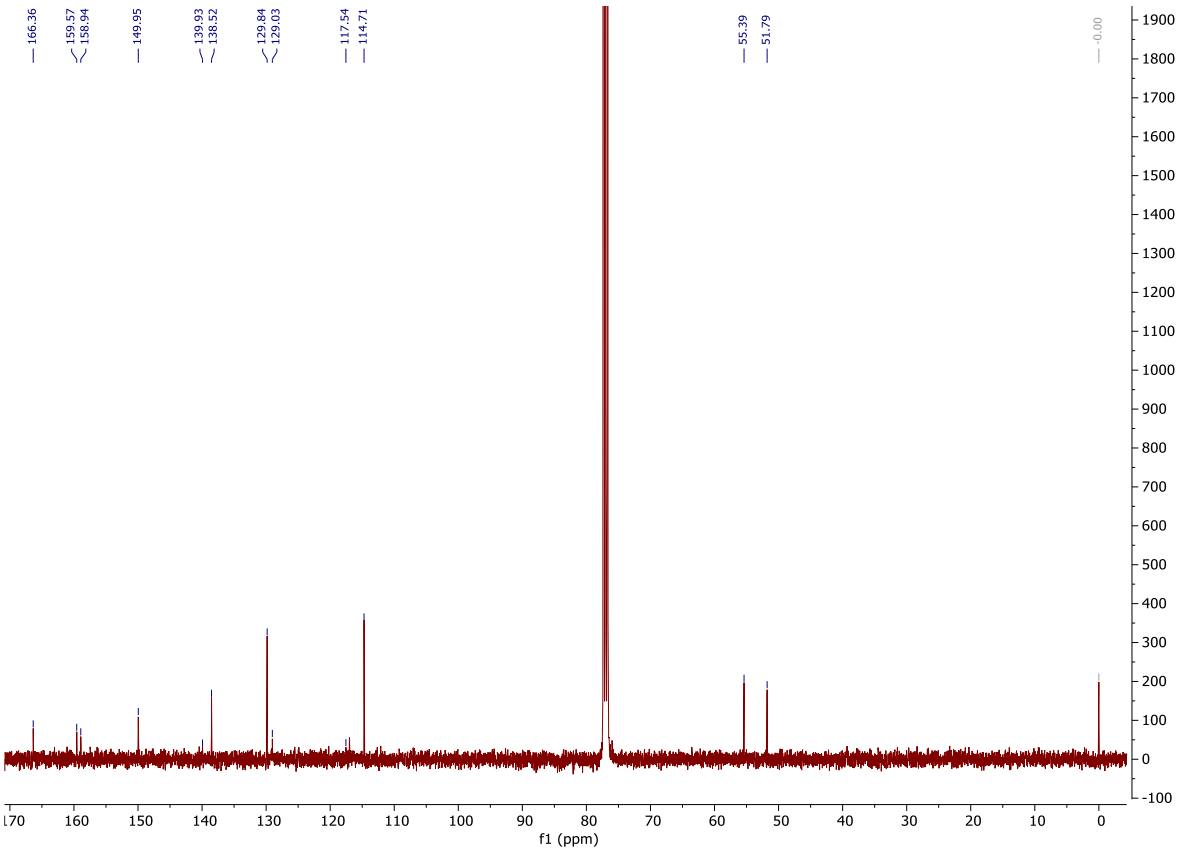
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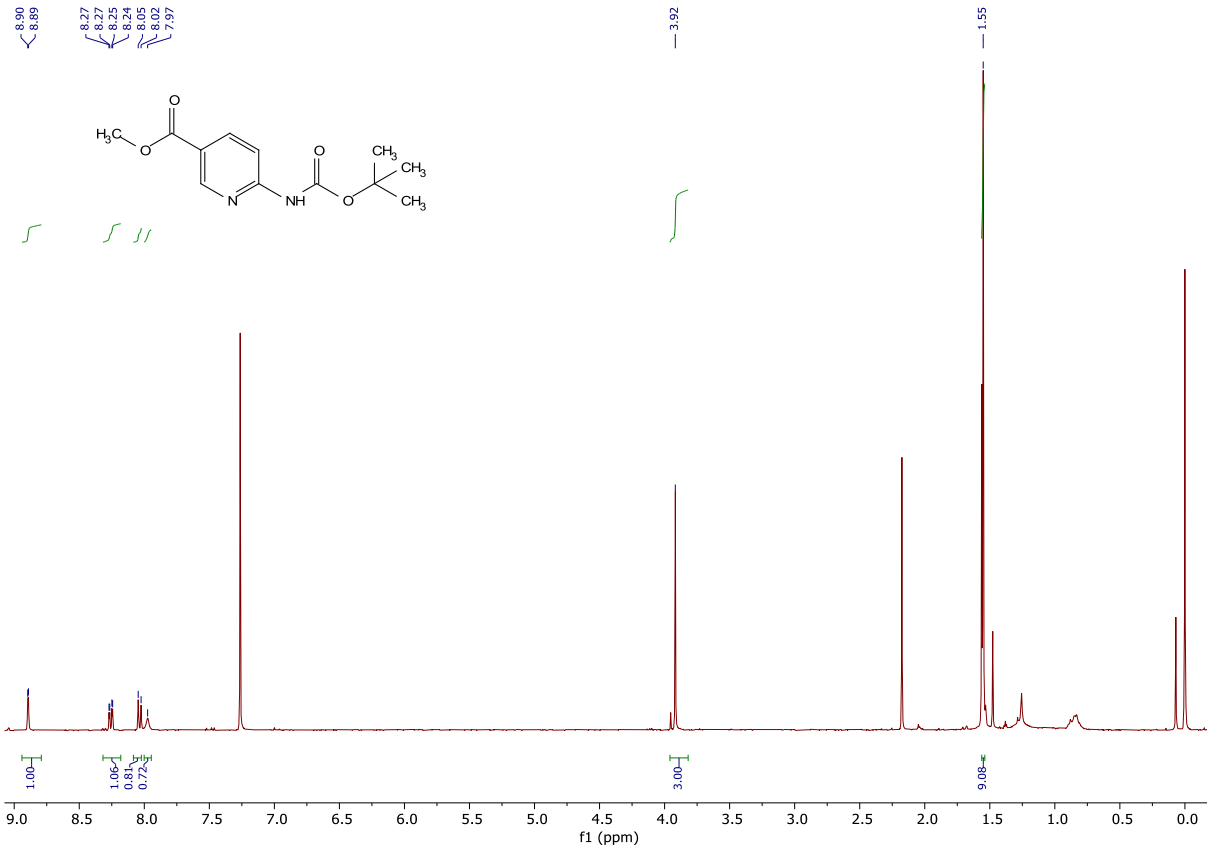
^{1}H NMR spectrum of Methyl 6-amino-5-(4-methoxyphenyl)nicotinate 85



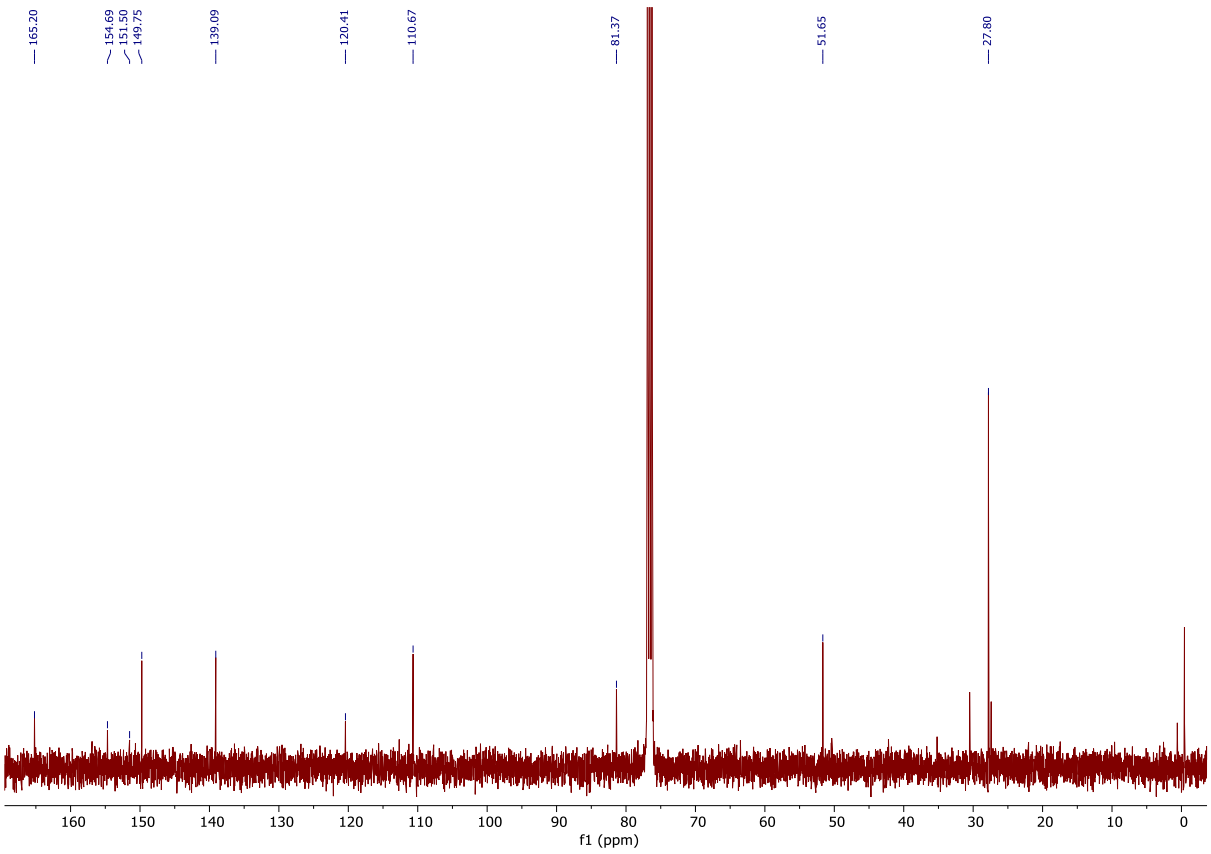
^{13}C NMR spectrum of Methyl 6-amino-5-(4-methoxyphenyl)nicotinate 85



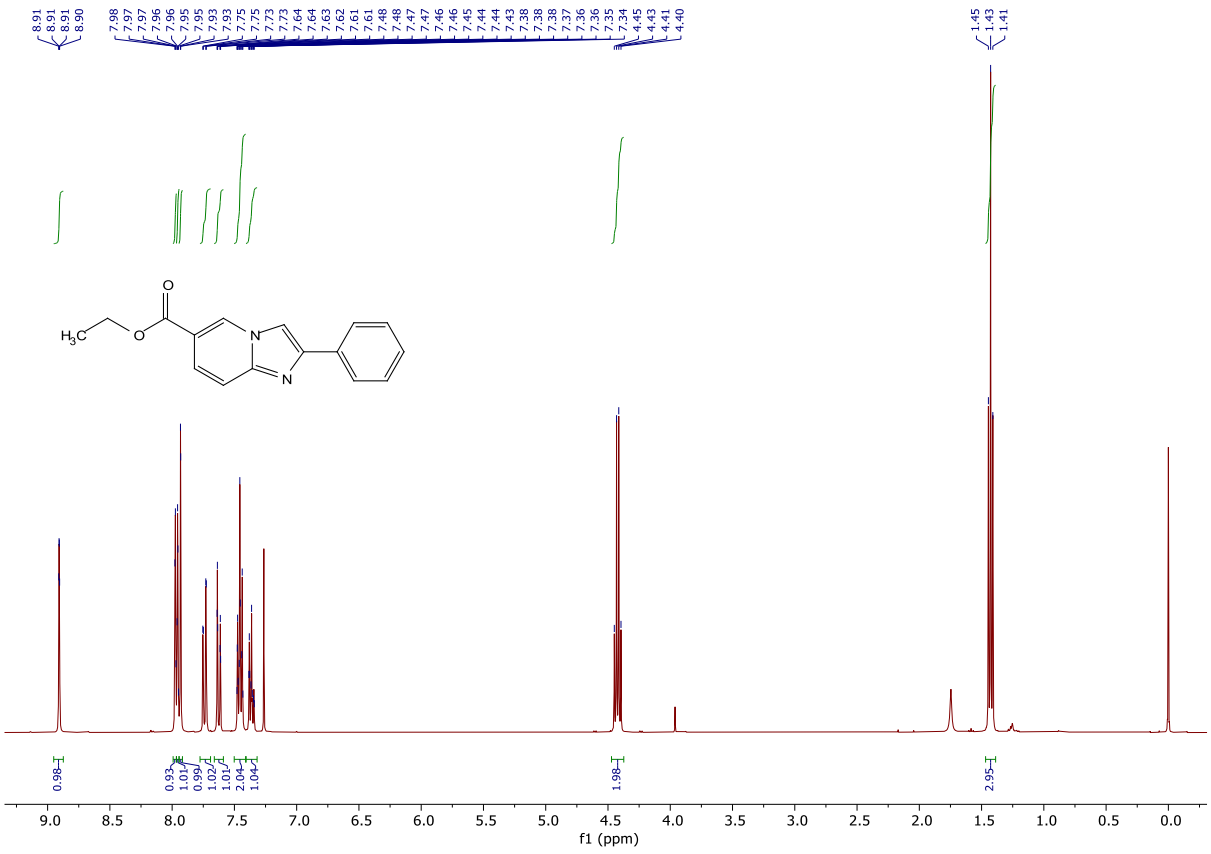
^{1}H NMR spectrum of Methyl 6-((tert-butoxycarbonyl)amino)nicotinate 88



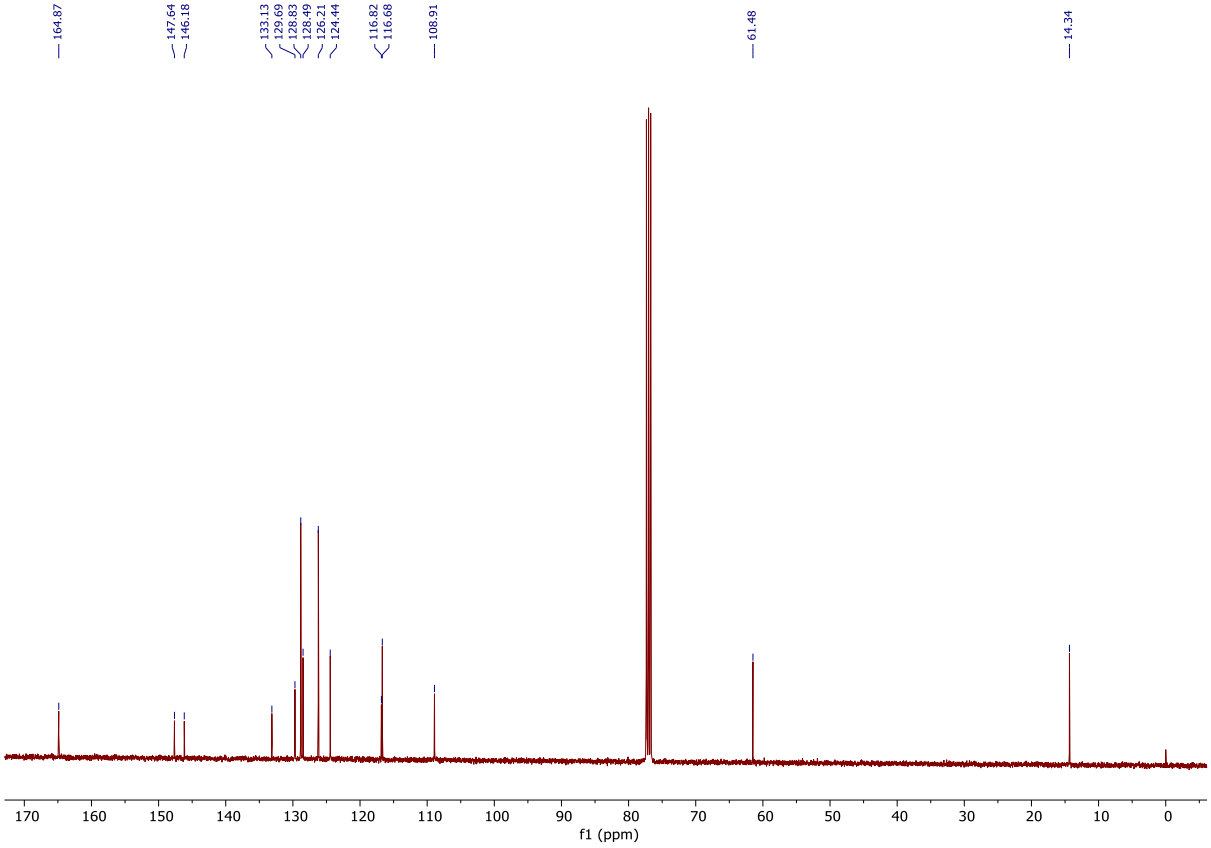
^{13}C NMR spectrum of Methyl 6-((tert-butoxycarbonyl)amino)nicotinate 88



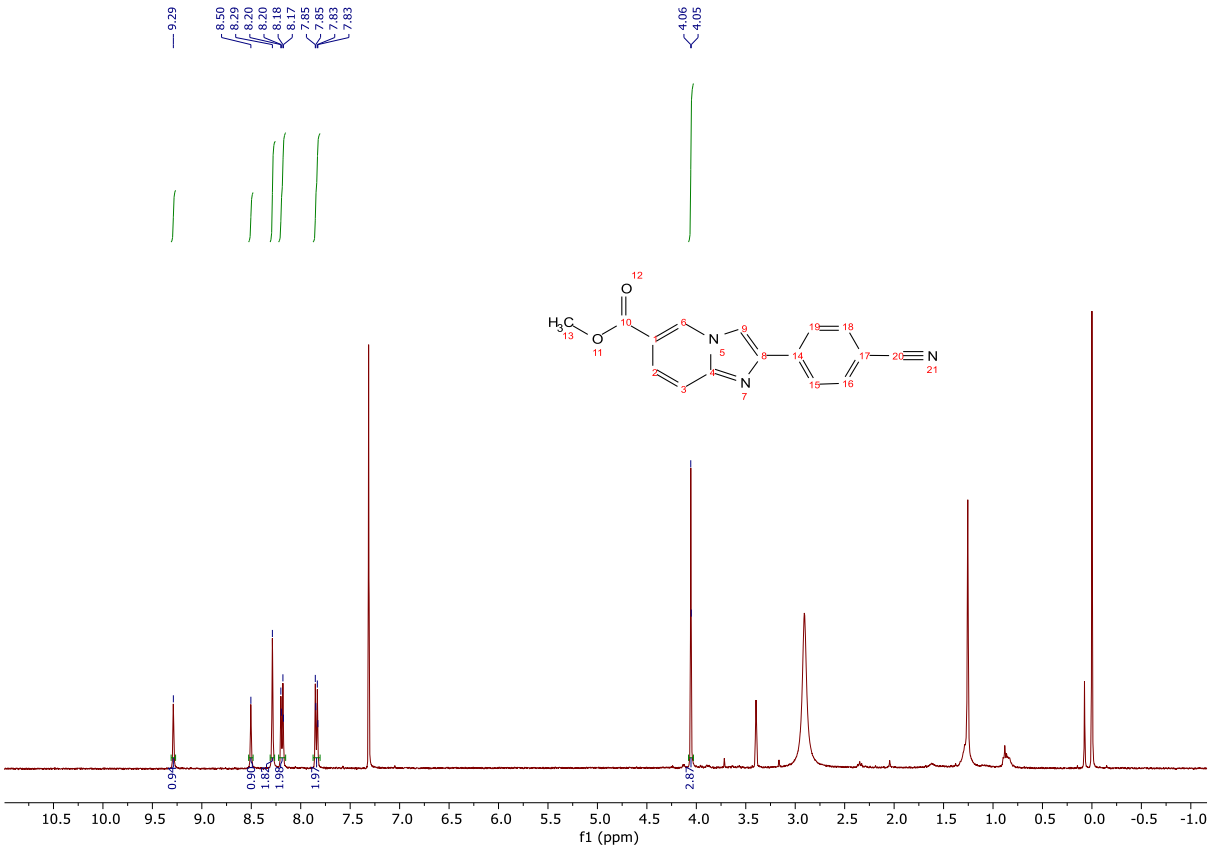
^{1}H NMR spectrum of Ethyl 2-phenylimidazo[1,2-α]pyridine-6-carboxylate 93ab



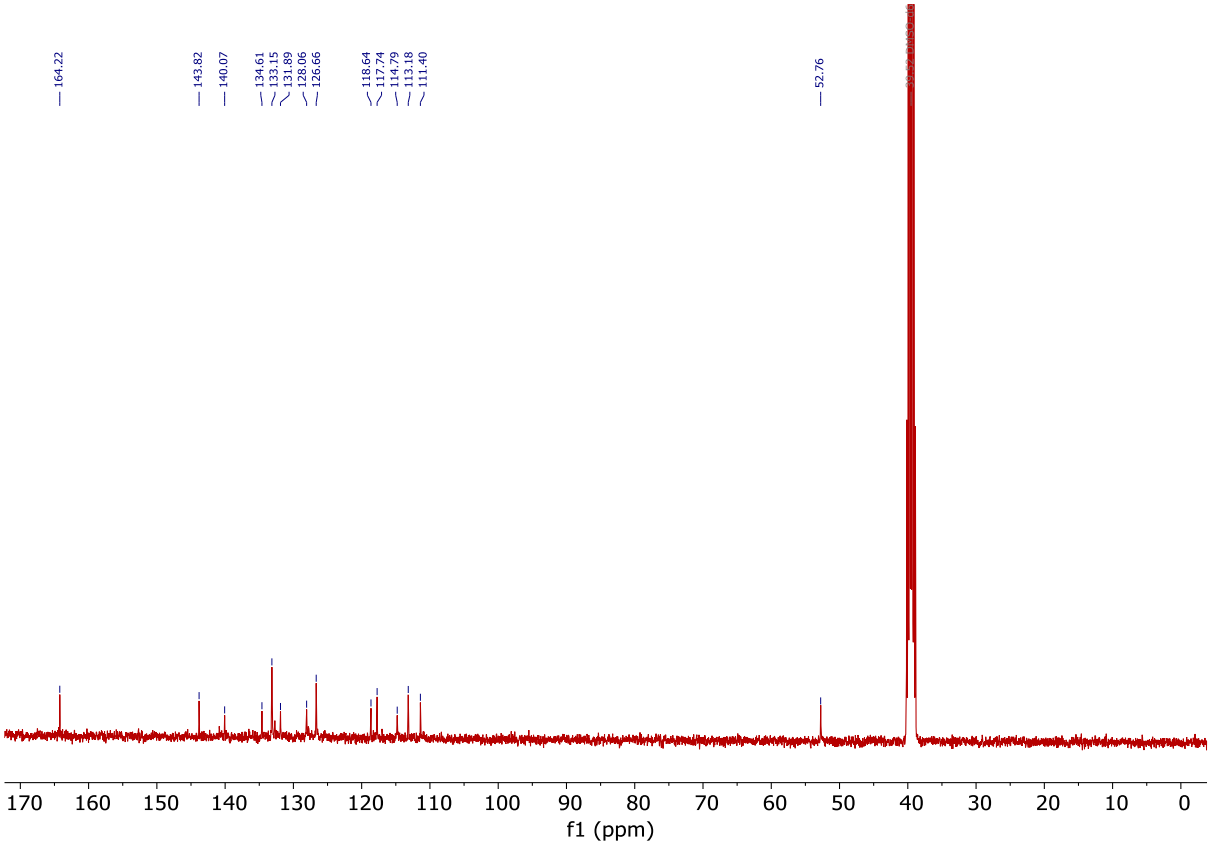
^{13}C NMR spectrum of Ethyl 2-phenylimidazo[1,2-*α*]pyridine-6-carboxylate 93ab



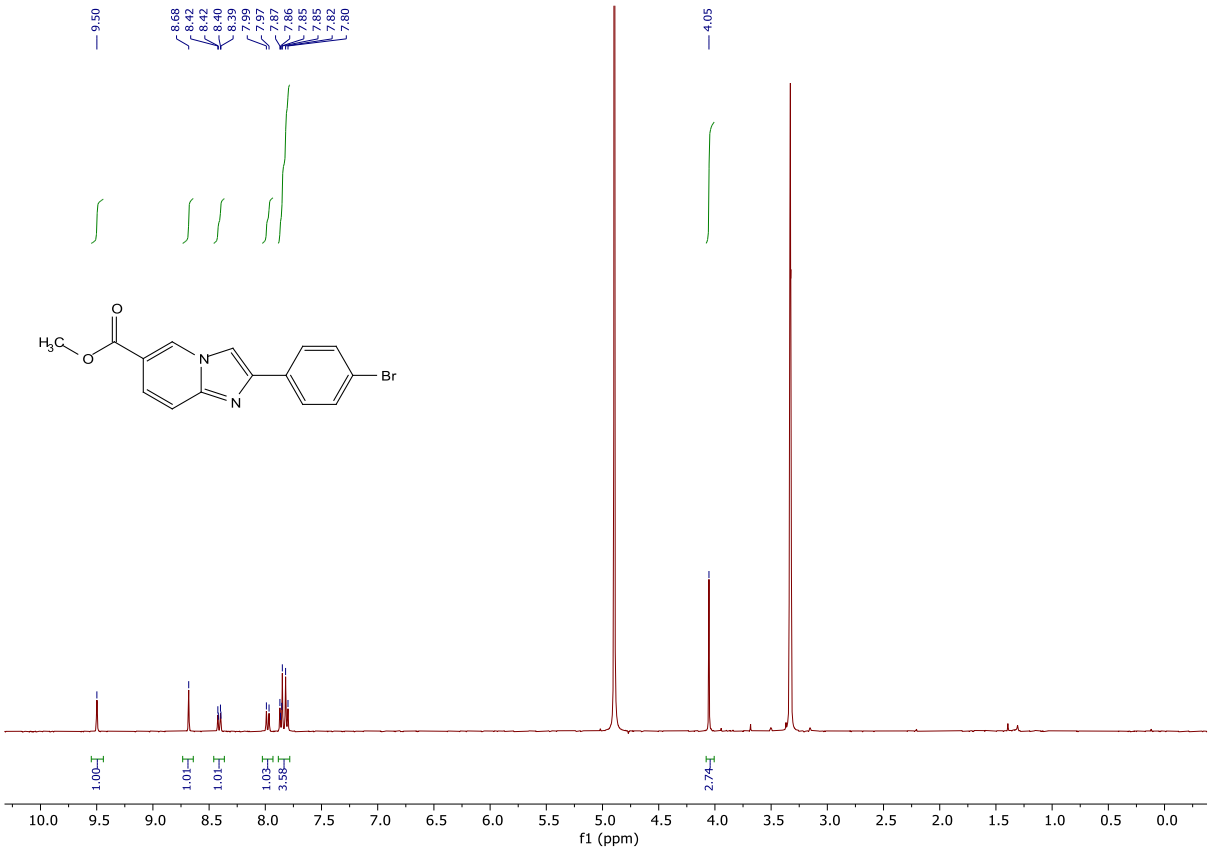
^{1}H NMR spectrum of Methyl 2-(4-cyanophenyl)imidazo[1,2-*α*]pyridine-6-carboxylate 93b



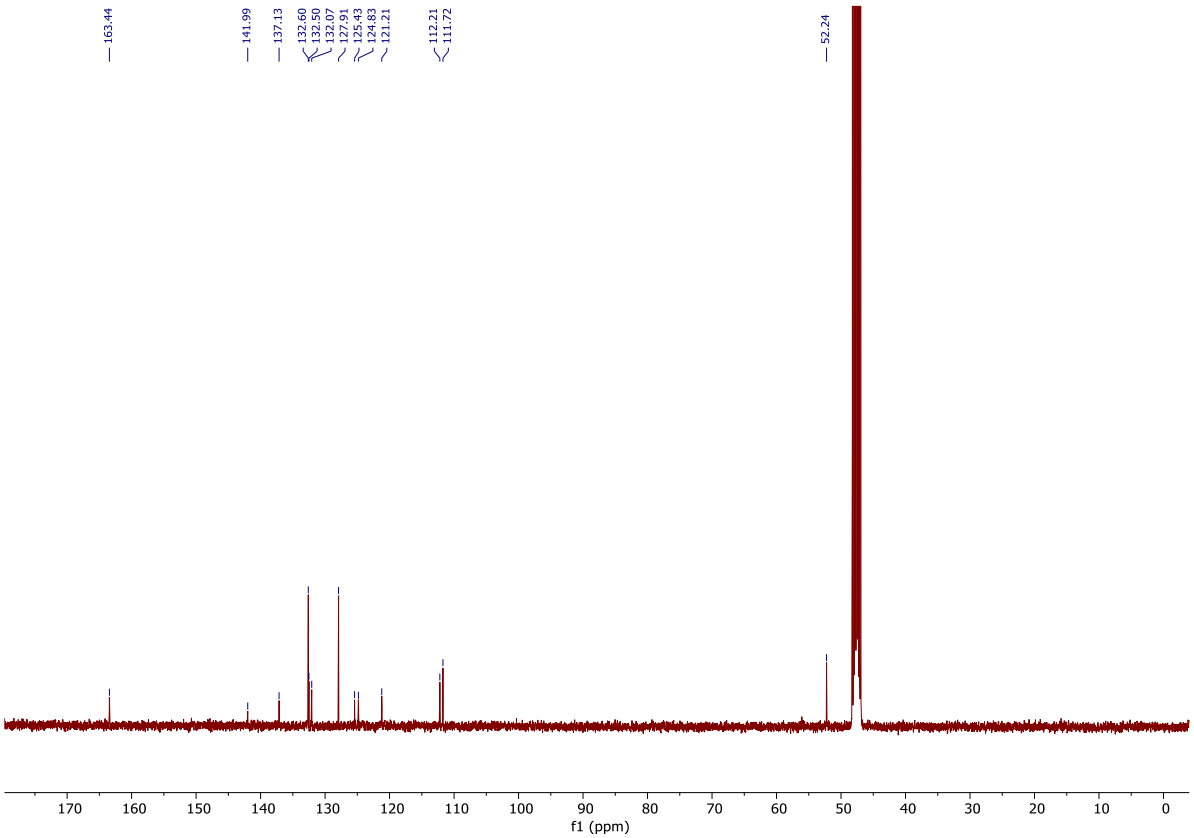
^{13}C NMR spectrum of Methyl 2-(4-cyanophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93b



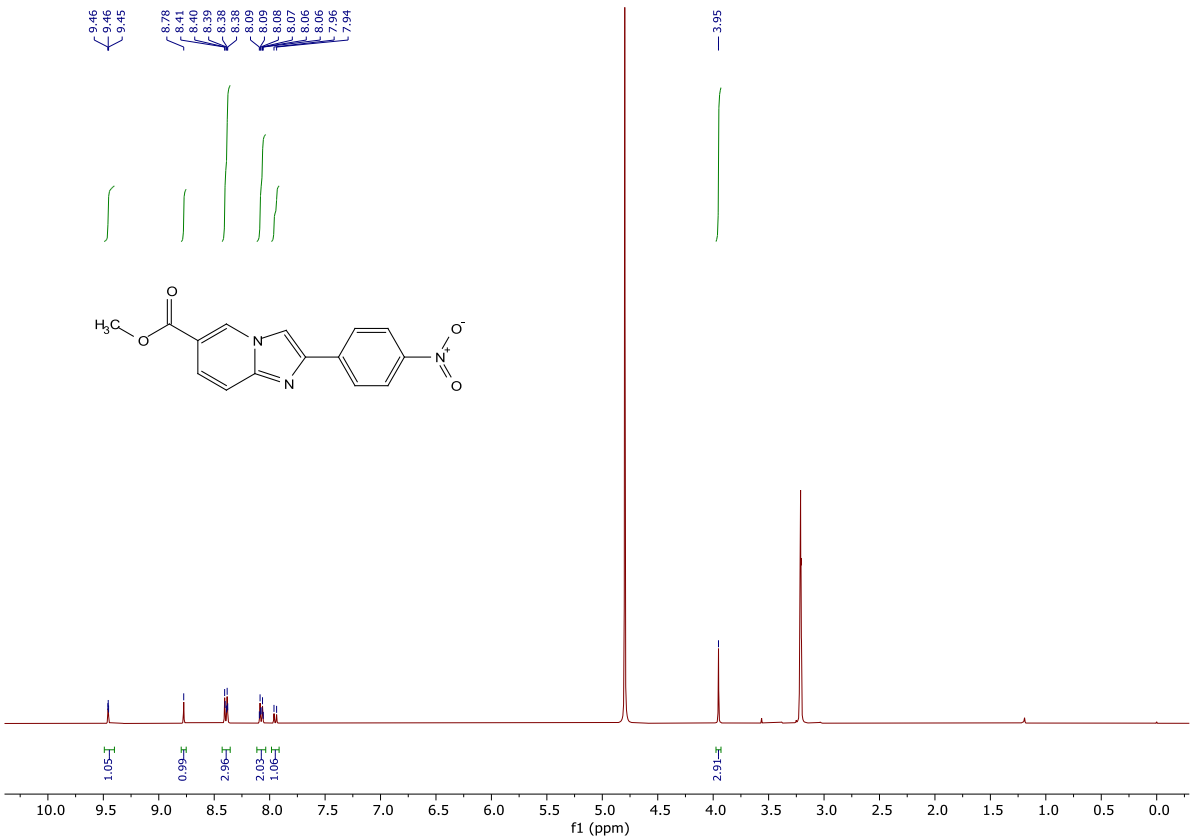
^{1}H NMR spectrum of Methyl 2-(4-bromophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93c



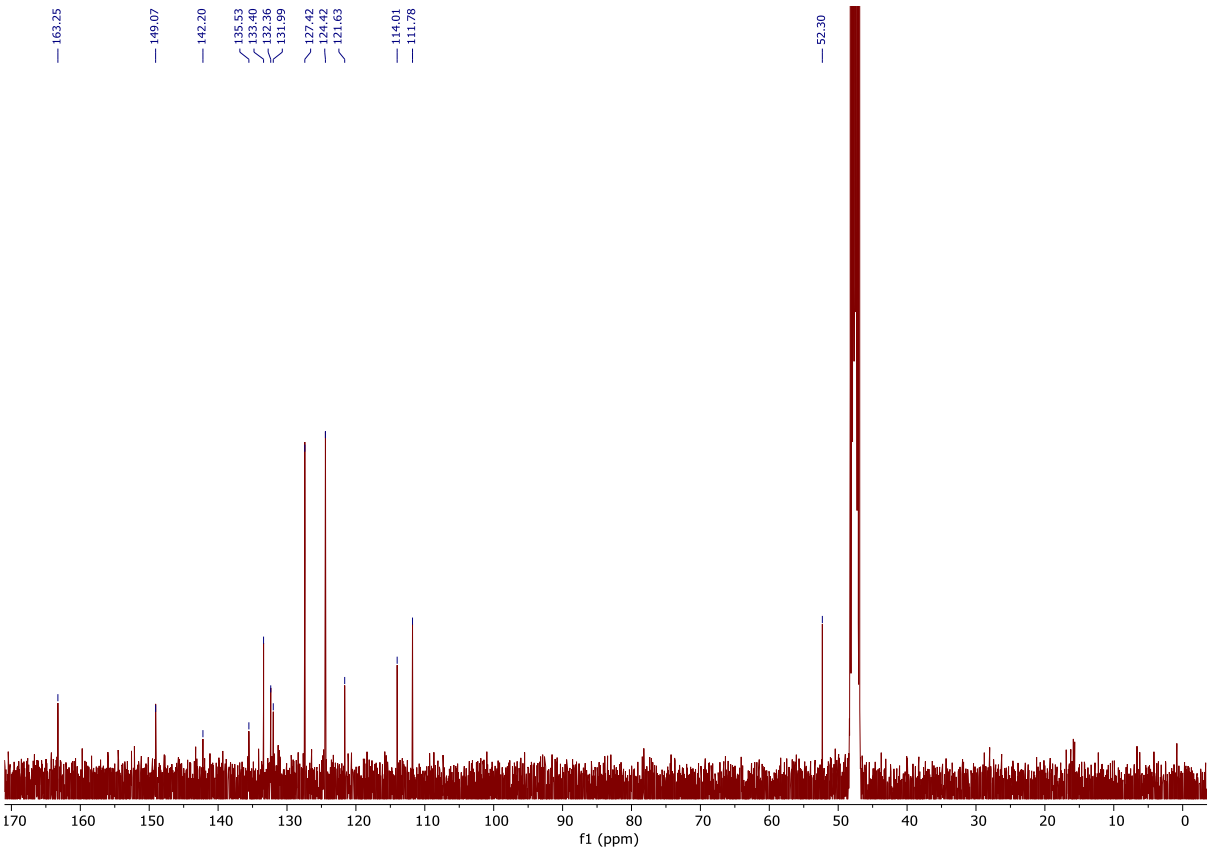
^{13}C NMR spectrum of Methyl 2-(4-bromophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93c



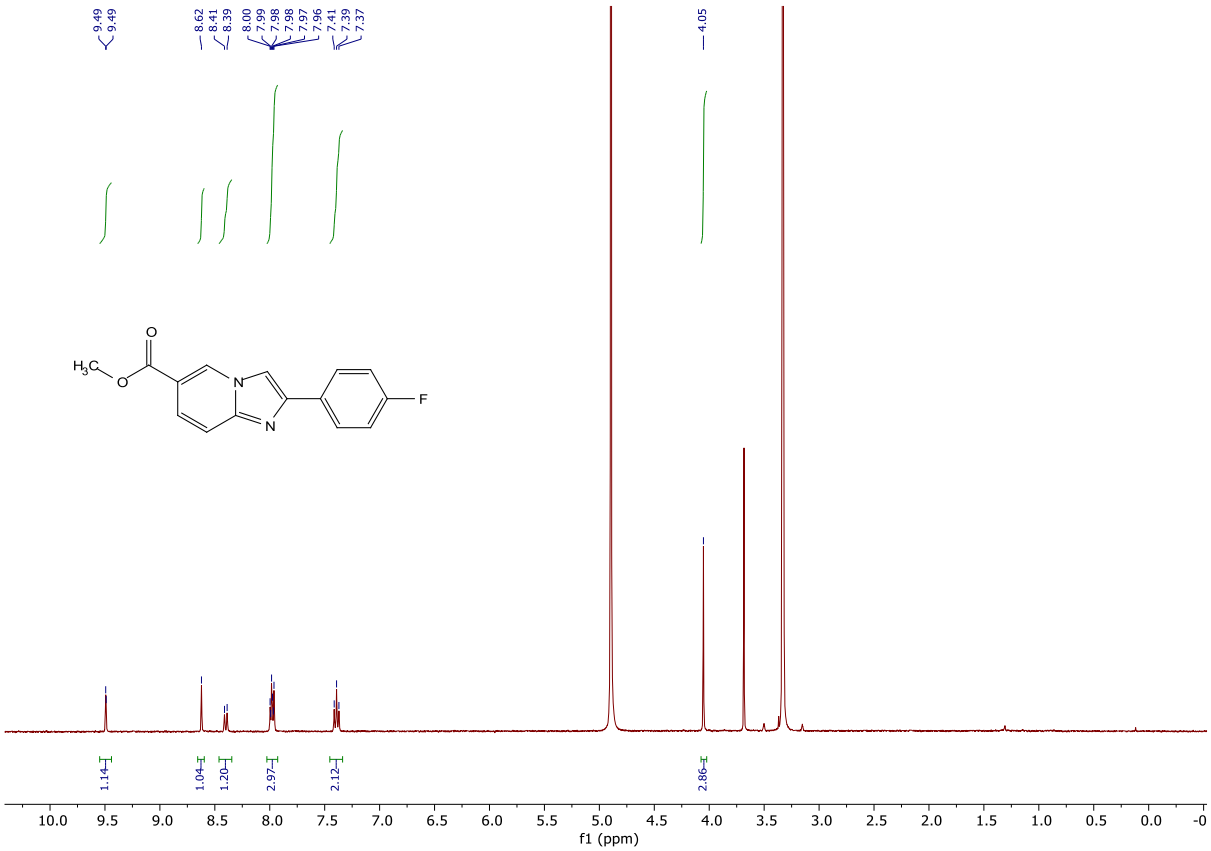
^{1}H NMR spectrum of Methyl 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93d



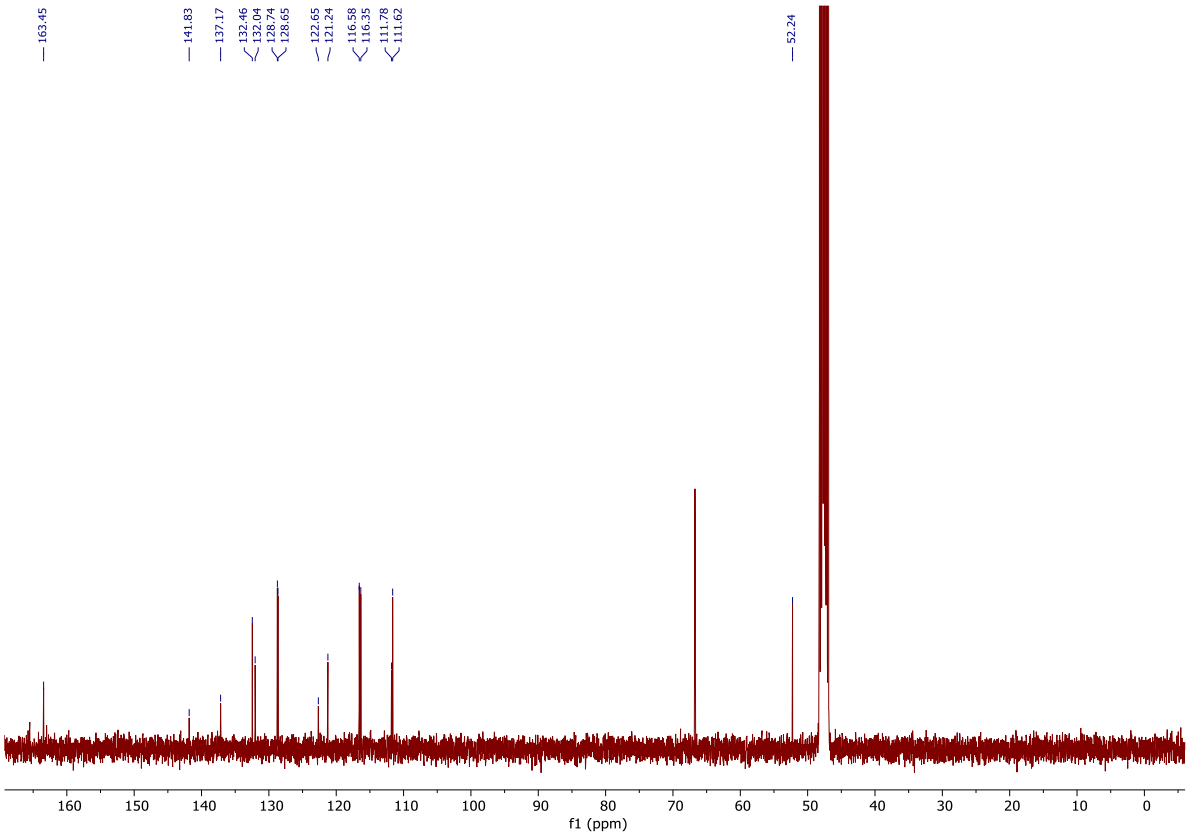
^{13}C NMR spectrum of Methyl 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93d



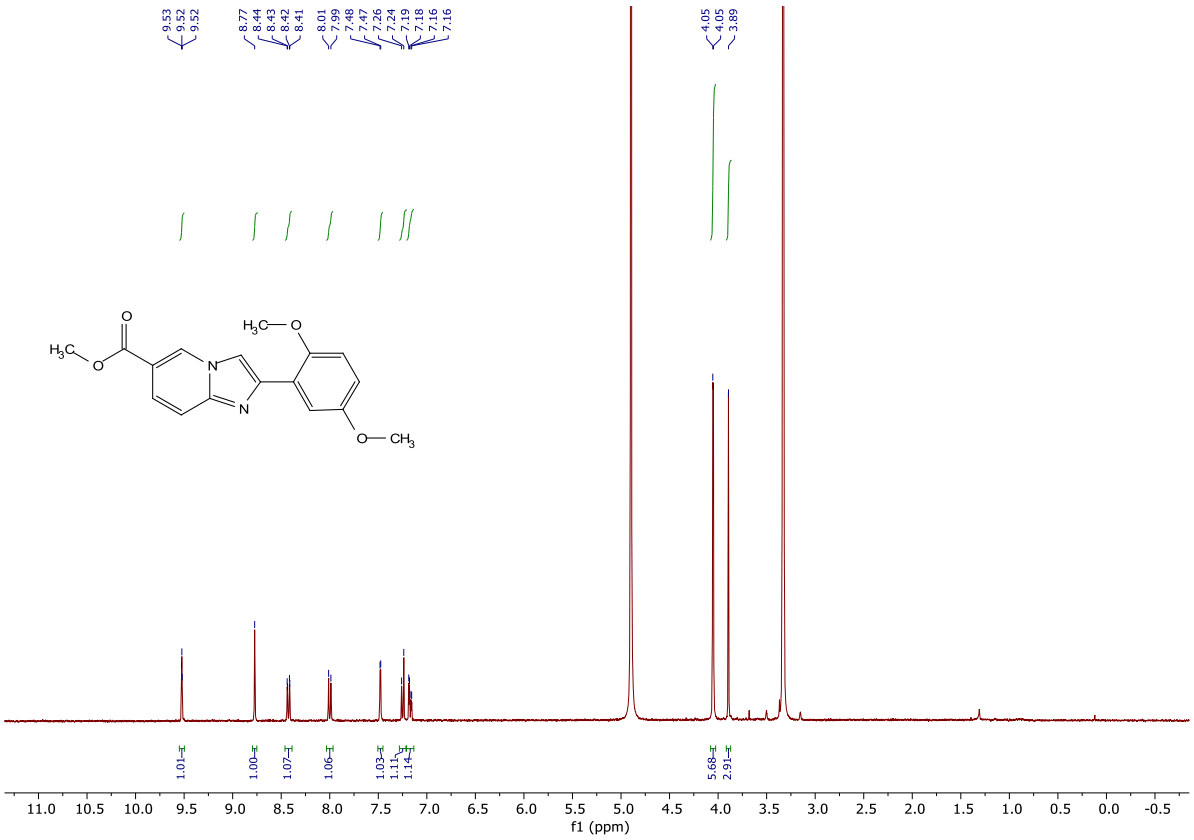
^{1}H NMR spectrum of Methyl 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93e



^{13}C NMR spectrum of Methyl 2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93e



^{1}H NMR spectrum of Methyl 2-(2,5-dimethoxyphenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93f



^{13}C NMR spectrum of Methyl 2-(2,5-dimethoxyphenyl)imidazo[1,2-*a*]pyridine-6-carboxylate 93f

