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Imidazo[1,2-*a*]pyridin-3-amines as HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

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A dissertation submitted to the Faculty of Science
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Johannesburg

In fulfillment for the requirements of the degree of Master of Science

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WITS
UNIVERSITY

February 2018

Declaration

I **William Katlego Mokone** declare that the work (never been submitted to any other university for any other degree) presented in this dissertation for a Master of Science to the University of the Witwatersrand is my own and was performed under the supervision of Dr Moira Bode and Dr Amanda Rousseau.

…….....

February 2018

Abstract

Imidazo[1,2-*a*]pyridin-3-amine compounds have been reported to exhibit activity against a number of viruses. Their biological activity against the highly mutative HI virus is of specific interest to this research. Reported molecular modelling studies on 2-(2-chlorophenyl)-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine in the allosteric site of HIV reverse transcriptase enzyme revealed that their activity might be improved by increasing the H-bonding ability of these compounds by adding groups with hydrogen bonding abilities to the cyclohexyl group of the molecule. Two approaches on how to access these modified compounds were explored and are described in this dissertation.

In the first approach a cyclohexyl isocyanide possessing a group (acetate) with H-bonding abilities was prepared from 2-hydroxyl-cyclohexylamine in a three step synthetic route; the amine was initially subjected to a formylation reaction which gave 2-hydroxyl-cyclohexylformamide as a product. This was followed by an acetylation reaction (obtaining 2-formamidocyclohexyl acetate) in order to protect the hydroxyl group before the final step, which was the dehydration of the formamide. Both the formylation and acetylation reactions gave products that existed as a mixture of rotamers of different concentrations in solution; with a ratio of 1:2 (minor rotamer: major rotamer) for the formylated product, and 1:3 (minor rotamer: major rotamer) for the acetylated product.

The successful preparation of the isocyanide through dehydration was followed by its use in the GBB multicomponent reaction with an aminopyridine and aldehyde to successfully give a small number of novel 2-(phenyl)-*N*-(2-acetate-cyclohexyl)imidazo[1,2-*a*]pyridin-3-amine derivatives with a H-bonding group on the cyclohexyl ring, and thus possessing improved H-bonding ability. However, the acetate was not the H-bonding group of interest, but rather the hydroxyl group. So we subjected these compounds to a hydrolysis reaction with potassium hydroxide in order to liberate the hydroxyl functional group, and only two compounds from those synthesized were successfully hydrolysed. However, the liberated hydroxyl group was found to participate in an intramolecular nucleophilic displacement of the fluorine atom

to give two 7-membered ring (fused to the imidazo-pyridine scaffold) novel compounds.

The second approach explored for accessing these compounds with increased H-bonding involved the development of an alternative methodology to the first approach. The initial step of the successfully developed methodology involved the use of a convertible isocyanide (*tert*-butyl isocyanide or 1,1,3,3-tetramethylbutyl isocyanide), aminopyridine and aldehyde in the GBB reaction. The use of *tert*-butyl isocyanide led to the successful preparation of a small library of 2-(phenyl)-*N*-(*tert*-butyl)imidazo[1,2-*a*]pyridin-3-amine derivatives, while the use of 1,1,3,3-tetramethylbutyl successfully gave two 2-(phenyl)-*N*-(1,1,3,3-tetramethylbutyl)imidazo[1,2-*a*]pyridin-3-amine derivatives.

These compounds were subsequently used in a dealkylation reaction in which some of them gave their corresponding primary amine derivatives. The primary amine derivatives successfully participated in a reductive amination with cyclohexanone to give the target compounds, 2-(phenyl)-*N*-(cyclohexyl)imidazo[1,2-*a*]pyridin-3-amine derivatives. The versatility of the reductive amination reaction was also briefly investigated, and a number of primary amine derivatives were found to successfully react with 2-chlorobenzaldehyde, thus illustrating that the reductive amination reaction employed might possess some versatility. This successfully developed three step methodology (GBB, dealkylation and reductive amination) could possibly be utilized in the synthesis of 2-(phenyl)-*N*-(cyclohexyl)imidazo[1,2-*a*]pyridin-3-amine derivatives (with improved H-bonding) by using cyclohexanone derivatives functionalized with groups that have H-bonding abilities in the reductive amination reaction.

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To a brother that experienced some of the worst and best moments of this journey with me, a journey that was by no means easy, couldn’t have chosen a better friend. We will meet at our own neon cathedral Thabang Chiya!

Joyful Mdhluli for always encouraging me to keep going and showing up always when it matters. Pakama Mahlumba, the short walks we took went a long way to rejuvenate

the spirit I needed to get the reactions in the lab working. To Tebogo “Nobhala” Mothivhi your ear has never been deaf to me through this journey. Siphiwe Anthony Thwala and Luyanda Mxolisi Sopiseka, in you guys I found brothers that inspired me to be so much more courageous than I could have imagined. The support I received from the both of you in the last days of this work was far more than generous. Brothers not by blood, but by heart. To my friends Katlego “Katz Katz” Modimakoane (you have always been there for me in more ways than you could understand), Lerato Yolanda Moraba, Nonkululeko “Soprano” Ngede, Silindo Mavuso, Zanele Ntile, Goodtime “Papa-G” Moja, Sibusiso Karabo Magxaki, Zinhle Nxumalo, Neo Sambo, Thabo Monyatsi, Mohlominyana Mofokeng, Nozimbali Mthiyane, Odwa Mbanga, Manthako Lethobane, Pandelani Nekhumbe, David Okharedia your encouraging spirits have been a pillar of my strength.

To Angela Bontle Mabunda, I have never had a better friend, no one can ever do friendship better than you. “Where can we lay down the heaviness of our trouble but in a friend’s heart?” – Joseph Conrad

To Ntombizodwa Mabena, a sister who has been with me through this journey and reminded me continuously that in each other, we can find the strength and support to conquer the world.

It would be a great crime if I fail to acknowledge one of the most amazing woman that I have ever met. Florence Chota you have always been able to make sure I keep a level head, and that I maintain discipline, thank you for always being so hard on me, in all the times where I lost my way, I could always trust you to drag me back onto the right path. Thank you for always reminding me that I shouldn’t always be so hard on myself when things were going slow or were not moving at all, and for reminding me always what I am capable of whenever I forget. You had more faith in me than me. We have solved mysteries of the universe together, and I know we will decipher more.

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Last but definitely not least, To Pertunia Thabang Matlala, I can only thank the universe for allowing our paths to cross, and remain intertwined through unbounded love and friendship.

Dedication

This dissertation is dedicated to my brother

ISAAC TAU MOKONE

“There is no worse enemy and no better friend than a brother, for one brother knows another, and in perfect knowledge is strength for good and evil.”

List of abbreviations

2-D- two dimensional

AIDS- Acquired immunodeficiency syndrome

AZT- Azidothymidine

AcOH- Acetic acid

CD4- Cluster of differentiation

C-4- Carbon number 4

cART- Combination antiretroviral therapy

CCl_4- Carbon tetrachloride

$CDCl_3$- Deuterated chloroform

CH_2Cl_2- Dichloromethane

$CHCl_3$- Chloroform

DNA – Deoxyribonucleic acid

dsDNA – Double stranded Deoxyribonucleic acid

DMF- Dimethyl formamide

EtOH- Ethanol

EtOAc- Ethyl Acetate

FLV- Friend leukemia virus

FDA- Food and drug admistration

gp- Glycoprotein

GBB- Groebke-Blackburn-Bienayme

H_2- Hydrogen gas

H/E- Hexane/ethyl acetate

H_2O- Water

HCl- Hydrochloric acid

HAART- Highly active antiretroviral treatment

HTLV- Human T-cell leukemia virus

HIV- Human immunodeficiency virus

IR- Infra red

I_2- Iodine

KZN-Kwa-Zulu Natal

$LaMnO_3$- Lanthanum manganese oxide

MeOH- Methanol

Mol- Mole(s)

mRNA- Messenger Ribonucleic acid

MCRs- Multicomponent reactions

NNRTIs- Non-nucleoside reverse transcriptase inhibitors

NRTIs- Nucleoside reverse transcriptase inhibitors

N_2- Nitrogen gas

NaOMe- Sodium Methoxide

NaCl- Sodium Chloride

Na_2SO_4- Sodium Sulphate

Na_2CO_3- Sodium Carbonate

$NaHCO_3$- Sodium Hydrogen Carbonate

NMR- Nuclear magnetic resonance

PIs- Protease inhibitors

PPh_3- Triphenylphosphine

$Pd(OAc)_2$- Palladium acetate

RNA- Ribonucleic acid

RNase H- Ribonuclease H

RDDP- RNA-dependent DNA polymerase

$RuCl_3$- Ruthenium trichloride

RT- Reverse transcriptase

ssRNA- Single stranded Ribonucleic acid

ssDNA- Single stranded Deoxyribonucleic acid

SA- South Africa

tRNA- transport Ribonucleic acid

TFA- Trifluoro acetic acid

TLC- Thin layer chromatography

TsCl- Toluenesulfonyl chloride

UNAIDS- Joint United Nations Programme on HIV/AIDS

UV- Ultra violet

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Chapter 1: Introduction

1.1 HIV-Human Immunodeficiency Virus

Mankind has found itself faced with different kinds of pandemics, but the AIDS pandemic caused by the Human Immunodeficiency Virus (HIV) is considered to be one of the worst in history as there has been no significant success in obtaining a cure or vaccine, and the mortality rates associated with it are high.[1] UNAIDS estimated that ~ 36.7 million people were living with HIV in the year 2015, however, it reports a decline in the number of new infections from 3.2 million in the year 2000 to an estimated 2.1 million in 2015.[2] The virus also has far reaching implications and adverse effects on economic, social and political stability separate from the direct health effects that are experienced by infected individuals.[1] HIV is a retrovirus, which means that it does not contain deoxyribonucleic acid (DNA), but ribonucleic acid (RNA), and it can only reproduce in the host cell.[3-5] The advanced stages of the viral infection cause the disease acquired immunodeficiency syndrome.[4,5] The importance of combating the HIV/AIDS pandemic in South Africa (SA) is reflected in the 2011 UNAIDS report that placed SA as the country with the highest number of HIV/AIDS sufferers in the world,[6] and the latest reports from UNAIDS estimates that 7 million people were living with the virus in 2015,[2] an increase from an estimated 5.6 million in 2011.[6,7] Furthermore, Thurlow *et al.* predicts that Kwa-Zulu Natal (KZN), the worst affected province, with about 26.4% infections of the working population, will see a 43% decline in its economy by 2025.[8]

1.1.1 A brief history of HIV

HIV was discovered in the early 1980s and isolated in 1983.[1, 9, 10] Its origin is still subject to debate, but one of the most popular and accepted theories is that it was transmitted by other primates,[11] specifically chimpanzees that were infected with the Simian immunodeficiency virus (SIV), which was likely transmitted to humans through the consumption of chimpanzee meat.[12] This transmission is made possible by the close genetic relationship between humans and these primates. HIV was not accepted as the

cause of AIDS until 1984:[1,9-10] it was initially thought to be caused by microbes,[9] chemicals and auto immune diseases.[10] However, cancer-causing virus studies performed by Temin and Baltimore in the same time period led to the discovery of reverse transcriptase (RT), an enzyme present in all retroviruses. Subsequently, the first human retrovirus was then discovered by Robert Gallo who isolated the human T cell leukemia virus type 1 (HTLV-1) and HTLV-2 in 1979 and 1982, respectively. Further studies on the HTLV retrovirus revealed that it could cause an AIDS like syndrome. This led to a consensus amongst scientists that AIDS was caused by a retrovirus that was later identified as HIV.[9-10]

1.1.2 Mode of transmission

HIV has different modes of transmission as a result of its presence in blood, semen, breast milk and other body fluids. Heterosexual transmission is the major route of transmission, at levels greater than 75%, followed by mother to child transmission during childbirth which accounts for 90% of transmission to babies, although the virus can also be transmitted through breastfeeding.[12] Once transmitted, the virus infects the helper T cells, specifically CD4+ T cells. These cells are used to monitor the progression of the virus by using the CD4 count of the infected individual. Over time, the viral load of the HI virus increases due to the high level of replication, leading to immunodeficiency in the infected individual. This is due to the inverse relationship between HIV viral load and CD4 count as shown in **Figure 1**. The immunodeficiency leaves the individual vulnerable and susceptible to opportunistic infections such as tuberculosis.[12-13] When an infected individual begins to show symptoms of opportunistic infections and has fewer than 200 CD4+ T cells per cubic millimeter of blood, then they are diagnosed with AIDS. At that stage, opportunistic infections caused by bacteria, fungi and parasites cannot be fought by the significantly deteriorated immune system.[1, 5]

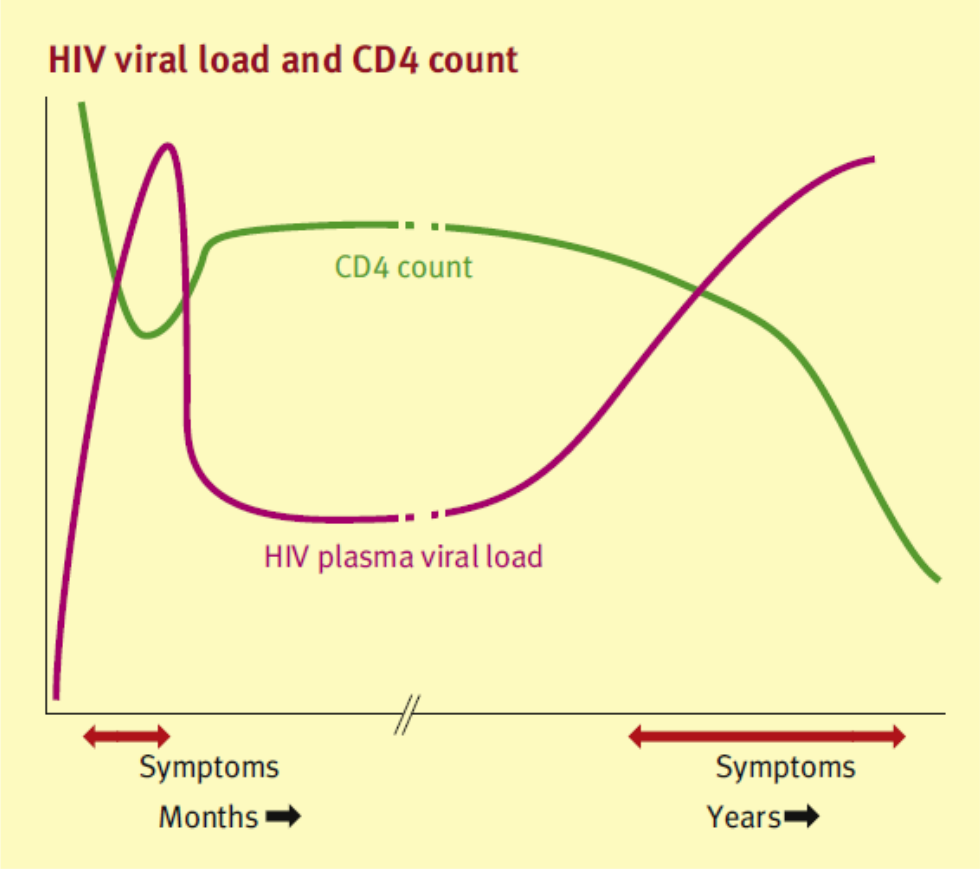


Figure 1: Correlation of HIV viral load and CD4 count over time, after infection[13]

The viral replication is very rapid, and virus particles are present in high levels in the blood immediately after the primary infection. HIV infection progression to AIDS has been found to vary considerably between individuals. After the primary infection, only a small proportion of infected individuals develop AIDS and consequently die within months or a few years. Some individuals (5%) show no sign of AIDS 12 years after primary infection. Individuals infected at an older age (45-54) progress a lot faster to AIDS than individuals infected at an earlier age (15-24).[1, 5, 12]

1.1.3 HIV structure and life cycle

The HI virion is made up of a lipid envelope that encloses a capsid, which in turn encases a single stranded (ss) RNA and three viral enzymes: namely RT, integrase, and protease. These enzymes facilitate and perform different functions in the virus. The lipid envelope is also lined by a matrix protein of the docking glycoprotein (gp120) that protrudes

outwards from the virus particle and is anchored by a trans-membrane glycoprotein (gp41) into the viral envelope. [1, 5, 12-14]

The HI virus life cycle has five major stages as shown in **Figure 2**: (i) Binding and fusion to host cell. This process is facilitated by the matrix proteins in the virus lipid envelope. The gp120 protein attaches itself to the CD4 receptor and co-receptors CCR5 or CXCR4 of the T helper cells (the primary target), any other cells that have these receptors are also susceptible to infection.[1, 5, 12, 15] This binding to the co-receptors results in a conformational change in the gp120 protein that leads to the fusion of the viral envelope and the host cell membrane, thus allowing the gp41 protein to anchor into the host cell membrane and release the viral capsid containing the viral RNA and enzymes into the host cell cytoplasm.[1, 5, 12] (ii) Transcription. The viral capsid envelope is removed by the host cell enzymes once it enters the cytoplasm, thus spilling its contents into the host cell. Transcription of the single stranded RNA to the complementary DNA strand is then catalyzed by the viral enzyme RT to produce a DNA/RNA hybrid, following which the RNA strand is destroyed by the ribonucleic H (RNase H) domain of RT. The ability of the RT enzyme to grow a complementary DNA strand from either the RNA or the DNA template allows it to catalyze the transcription of the double stranded (ds) DNA from the single stranded (ss) DNA produced.[1, 5, 15] (iii) Integration. The viral enzyme integrase directs the newly formed dsDNA to the host cell nucleus and catalyzes the integration of the viral DNA into the host cell chromosomes. At this stage the viral DNA is referred to as a provirus, and its integration into the host cell chromosomes allows it to use the host cell enzymes for the transcription of viral RNA and messenger RNA (mRNA).[1, 5, 15] (iv) Translation. The viral mRNA migrates out of the nucleus onto the host cell ribosomes and undergoes a translation process to produce nonfunctional poly-proteins that are subsequently cleaved by the viral protease enzyme to give functional proteins. [1, 5, 15] (v) Viral assembly. Together with these functional proteins, the viral RNA and enzymes are assembled by the host cell into immature virus particles that bud out of the host cell by using the plasma membrane of the host cell to make a new viral envelope and produce mature, infective virion(s) that go on to repeat the cycle.[1, 5, 15]

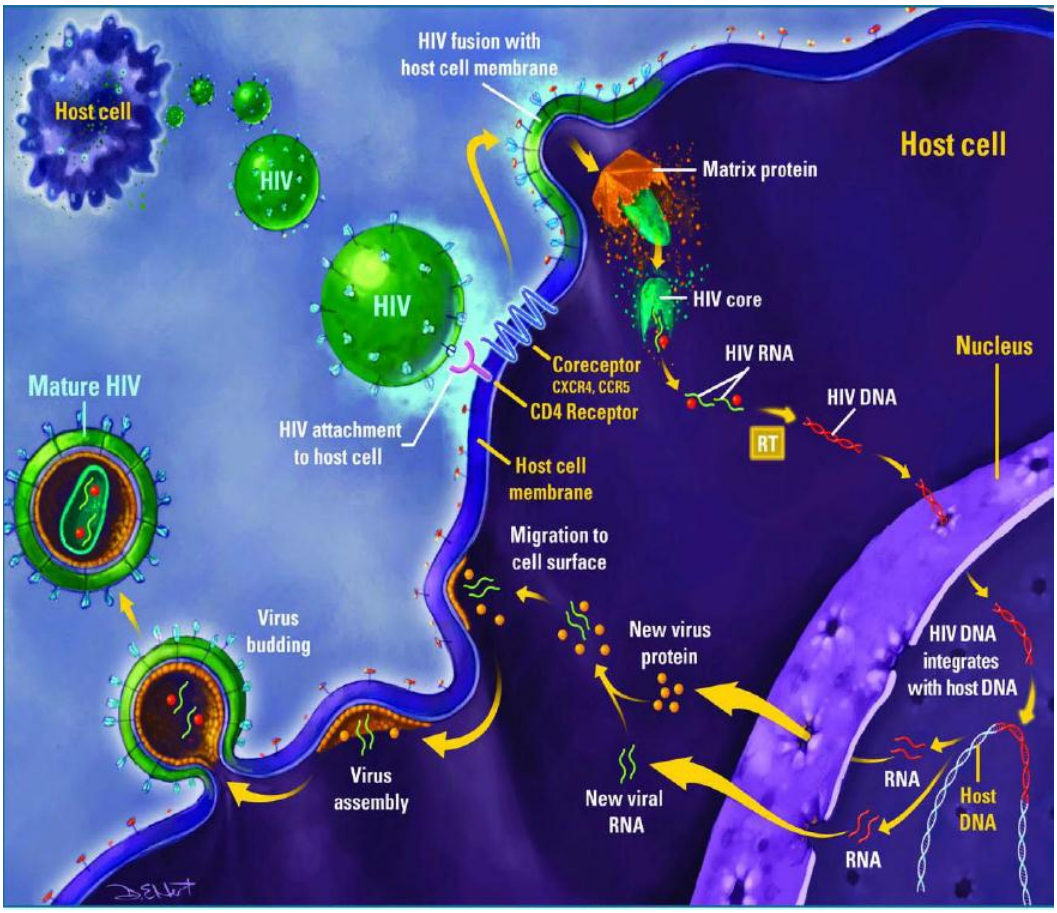
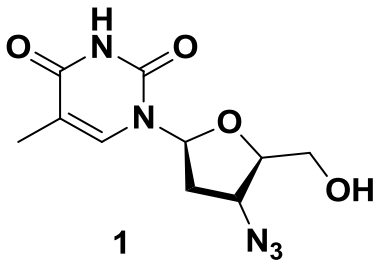


Figure 2: Representation of HIV life cycle[5]

1.1.4 HIV treatment



1

Figure 3: Azidothymidine

The first drug to be approved for HIV/AIDS treatment was azidothymidine (AZT) **1** (**Figure 3**), however, it was first synthesized and tested as an anti-cancer drug in 1964. In 1974 AZT was screened against the retrovirus Friend Leukemia Virus (FLV), and was found to inhibit the virus in a murine cell culture in the cell successfully. In 1984 AZT was found to

show good activity against two retroviruses: FLV and Harvey Sarcoma Virus. This led to AZT being screened againt HIV and it was found to be active against HIV *in vitro*. In 1985, the first person to begin AZT treatment was found to have a significantly increased T cell count after 6 weeks. This led to the expectation that HIV/AIDS would soon be eradicated. However, HIV's rapid mutation rate led to viral resistance against AZT.[1, 5, 15]

Due to a worldwide research effort, different classes of drugs including those active against the viral enzymes have been developed. There are two classes of RT inhibitors, namely nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). In addition, there are integrase inhibitors, protease inhibitors (PIs) and drugs that inhibit viral entry or fusion that have received FDA approval. However, the resistance to drugs used in monotherapy has led to the use of a combination cocktail of three drugs called highly active antiretroviral therapy (HAART),[1, 5, 8] and combination antiretroviral therapy (cART).These therapies comprise of two NRTIs and one NNRTI or one PI boosted with ritonavir at the beginning of treatment, with other classes of drugs being introduced when the virus develops resistance.[16]

The use of HAART is very effective at decreasing viral load and increasing CD4 T cell level. However, HIV still develops resistance to the drugs used in the cocktail. The resistance is due to the extreme inaccuracy of HIV RT, as it has a coding error rate of 1 per 1700 nucleotides incorporated.[1,5] This is a major source of viral diversity that allows the virus to evade pharmacological and immunological defenses, thus making the production of an effective vaccine difficult.[16] This also renders the drug therapies in use ineffective, because the rapidly changing HIV genome leads to HIV mutants that are resistant to the treatment. Hence, blocking of viral replication and effective treatment of HIV infection is hindered.[1, 5, 16]

1.1.4.1 The use of NNRTIs as RT inhibitors

RT plays a very important role in viral replication; it is a major target for antiretroviral drugs. The NRTIs and NNRTIs both target the RT enzyme, but the NNRTIs are of particular interest in this project and will be discussed in more detail. [1, 5, 17]

1.1.4.1.1 Structure of reverse transcriptase enzyme

HIV RT is made up of two subunits, p66 and p51 (**Figure 4**) and is called a heterodimer. The p66 subunit is larger relative to the p51 subunit and has both NRTI and NNRTI binding sites.[18-20] The RNA- and DNA dependent DNA polymerase (RDDP) and RNase H domains are located on the p66 unit, and they are important in the conversion of the single stranded RNA (ssRNA) into dsDNA.[18, 19] To initiate reverse transcription, cellular tRNA is coupled with viral RNA by RDDP, this gives a primer followed by the DNA-RNA hybrid strand that complements the viral RNA.[19] The ssRNA is subsequently hydrolyzed from the DNA-RNA hybrid by RNase H to give a single stranded DNA (ssDNA) that RT uses to make the dsDNA. In addition, the dsDNA migrates to the nucleus of the cell and is incorporated into the chromosal DNA of the host cell.[19]

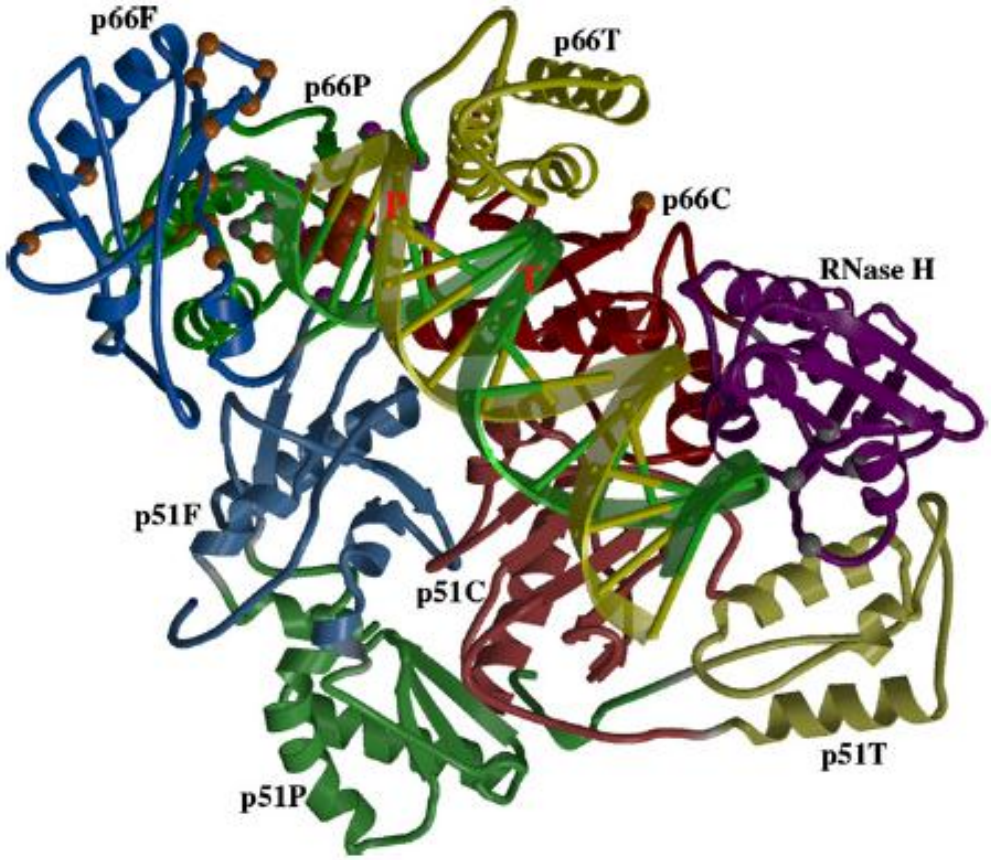


Figure 4: HIV-1 RT heterodimer [18]

1.1.4.1.2 Mode of action of NNRTIs

NNRTIs, unlike NRTIs, are non-competitive inhibitors:[18] they inhibit HIV-1 reverse transcriptase by binding to the allosteric sites of the viral enzyme, which is located 10 Å and 60 Å from the RDDP and RNase H active site, respectively.[18, 19] This results in a conformational change to the substrate-binding site, which then halts DNA synthesis by reducing the rate of incorporation of nucleotides.[1, 5, 17]

1.1.4.1.3 Current regimen of NNRTIs

There are currently five NNRTIs that have FDA approval (**Figure 5**).[21-23] NNRTIs have been reported to possess high selectivity, which makes them the least toxic of the clinically approved antiretrovirals.[24] Furthermore, the low toxicity makes them suitable for preventing mother to child transmission.[17] NNRTIs have high selectivity because they recognize and bind to HIV-1 RT, and not to any other RT or DNA or RNA polymerases.[17]

There are two classes of NNRTIs: the first generation NNRTIs nevirapine (**2**), delavirdine (**3**), and efavirenz (**4**), and the second generation NNRTIs etravirine (**5**) and rilpivirine (**6**) (**Figure 5**). First generation NNRTIs are prone to the development of drug resistance because of viral mutation that occurs as a result of the structural changes that occur at the allosteric binding site of the RT-enzyme.[25-26]

This sensitivity is attributed to their lack of torsional flexibility. However, second generation NNRTIs have the ability to maintain their potency in the presence of viral mutations.[27] This ability can be attributed to the torsional flexibility found in the molecules. The flexibility allows them to adopt multiple binding modes in the allosteric site, and to tolerate changes in the amino acid side chains that result from viral mutations.[28] A lot of effort is spent on the design and synthesis of new and better NNRTIs; for example Brigg *et al.*[29] and Cao *et al.*[30] have recently reported the use of indole sulfides and pyridinones respectively, as potent HIV-1 NNRTIs.

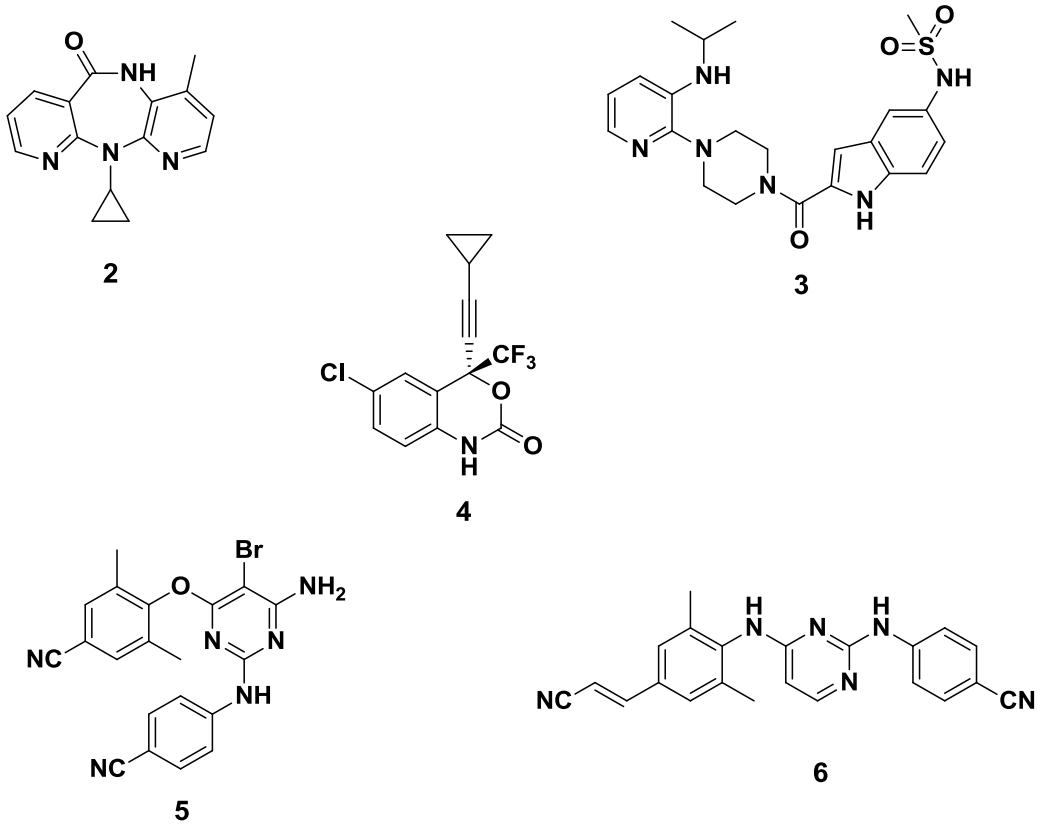
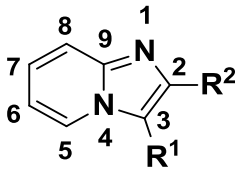


Figure 5: First and second generation FDA approved NNRTIs

1.2 Imidazo[1,2-*a*]pyridines

Heterocyclic compounds have a wide variety of applications and they are essential building blocks in pharmaceutical, veterinary and agricultural products. Imidazo[1,2-*a*]pyridine (**7**) is a fused [5,6] bicyclic heterocycle (**Figure 6**).[31] Imidazo[1,2-*a*]pyridines have been found to be an important class of heterocyclic compounds that have become popular as a result of their widespread biological and pharmaceutical activity.[32-35]

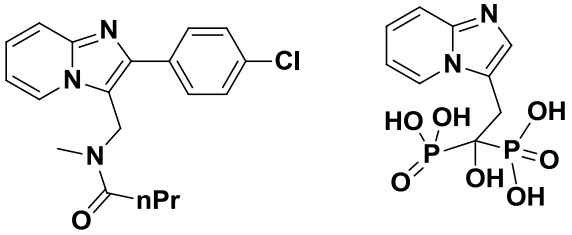


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Figure 6: Imidazo[1,2-*a*]pyridine scaffold with atoms numbered

1.2.1 Biological activity of the imidazo[1,2-*a*]pyridines

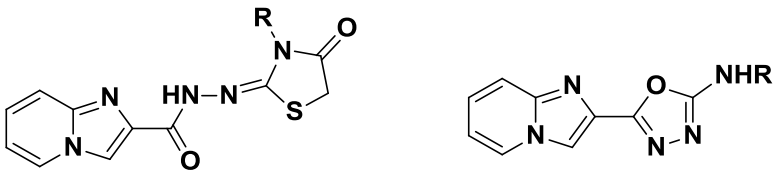
Numerous compounds possessing the imidazo[1,2-*a*]pyridine scaffold have been investigated for the treatment of various conditions, and have been tested in preclinical and clinical trials. A number of these compounds have become commercially available drugs: for example, minodronic acid (**8**) is a drug used to treat anxiety, heart failure and osteoporosis. Sarpidem (**9**) is also a commercially available drug that is used as a sedative (**Figure 7**).[36]



8 **9**

Figure 7: Biologically active imidazo[1,2-*a*]pyridines

Imidazo[1,2-*a*]pyridines have also been reported to have antibacterial activity,[37] and have shown activity in treating heart diseases[35] and gastric diseases.[38] Göktaş *et al.* developed and identified imidazo[1,2-*a*]pyridine derivatives with 1,3-thiazolidine (e.g. **10**) and 1,3-oxadiazole (e.g. **11**) moieties at the 2-position of the imidazo[1,2-*a*]pyridine molecule (**Figure 8**) and these derivatives were found to have antifungal activity.[31]

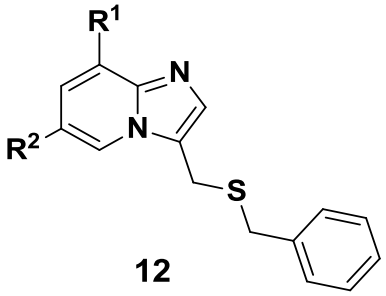


10 **11**

Figure 8: Imidazo[1,2-*a*]pyridine derivatives identified and developed by Göktaş *et a.l*[31]

Imidazo[1,2-*a*]pyridines have also been found to have antiviral activity. Veron *et al.* reported that by varying the groups at the 6-position (R^2) and 8-position (R^1) of the imidazo[1,2-*a*]pyridine nucleus, and by adding a thioether side chain at the 3-position

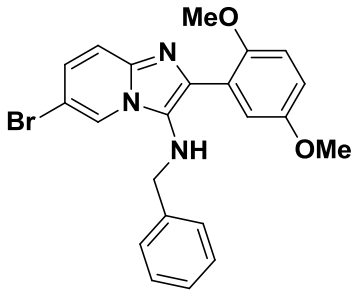
(**Figure 9**), derivatives were obtained with antiviral activity against the cytomegalovirus and varicella-zoster virus.[39]



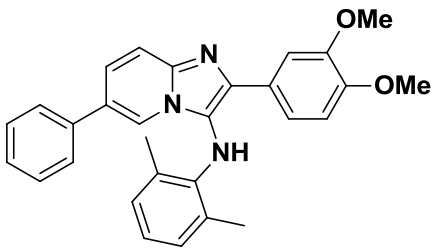
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Figure 9: Imidazo[1,2-*a*]pyridine derivatives identified and developed by Veron *et al.*[39]

The anticancer activity of imidazo[1,2-*a*]pyridines has also been investigated. For example, a study into colon cancer by Dahan-Farkas *et al.* reported the synthesis of 6-substituted-imidazo[1,2-*a*]pyridines and their activity against the HT-29 and Caco-2 cancer cell lines.[40] They were found to induce cell death, i.e. apoptosis, in a time and dose dependent study. Compounds **13** and **14** (**Figure 10**) were reported as the most active drugs, with IC_{50} values of 6.57 μM (HT-29 cell lines) and 6.47 μM (Caco-2 cell lines) for compound **13**, and 8.56 μM (HT-29 cell lines) and 8.73 μM (Caco-2 cell lines) for compound **14**.[40]



13

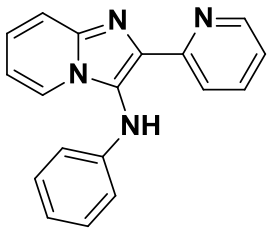


14

Figure 10: Imidazo[1,2-*a*]pyridines that exhibit activity against colon cancer

Lacerda *et al.* described the design and synthesis of novel 3-arylamine-imidazo[1,2-*a*]pyridines and evaluated their anti-inflammatory activity as symbiotic prototypes (inhibition through more than one pathway).[41] They discovered amongst their library of

compounds that compound **15** (**Figure 11**) possessed the highest anti-inflammatory activity, and found it to be a good symbiotic prototype orally active drug.[41]



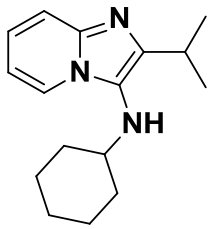
15

Figure 11: Anti-inflammatory imidazo[1,2-*a*]pyridine

These reports suggest that the imidazo[1,2-*a*]pyridine scaffold offers such a wide range of biological activity because there are a number of differing positions to which functional groups can be added and substituted.[31, 37-39]

1.2.1.1 Imidazo[1,2-a]pyridines as NNRTIs against HIV-1 RT

During in-house biological screening, Bode *et al.* found that certain substituted imidazo[1,2-*a*]pyridines exhibited low activity through weak allosteric inhibition of HIV-1 RT.[35] This resulted in the identification of 2-(isopropyl)-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine **16** (**Figure 12**) as weakly active against HIV wild-type RT, but with very poor activity in the whole cell anti-HIV assay.[35]

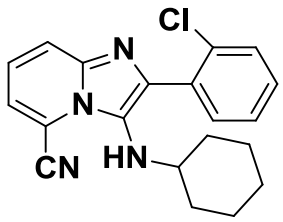


16

Figure 12: 2-(Isopropyl)-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine

Based on the structure of **16** a new library of compounds was designed and synthesized. They were screened for improved activity against the wild-type RT, and those that exhibited the best activity against the wild-type RT were screened in an HIV anti-infective

MAGI whole cell assay. The compound found to have the best activity relative to nevirapine was 2-(2-chlorophenyl)-3-cyclohexylaminoimidazo[1,2-*a*]pyridin-5-carbonitrile **17** (**Figure 13**).[35]



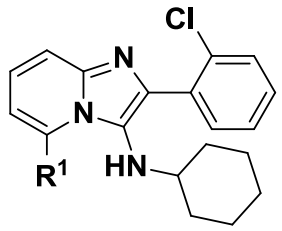
17

IC_{50} = 0.18 μM (MAGI)

Nevirapine
IC_{50} = 0.10 μM (MAGI)

Figure 13: 2-(2-Chlorophenyl)-3-(cyclohexylamino)imidazo[1,2-*a*]pyridine-5-carbonitrile

Four other compounds with comparable activity to nevirapine were identified (**Figure 14**). The activity of compounds **18-20** required rationalization, thus compound **17** was docked into an HIV-1 NNRTI binding site using CDOCKER (Accelrys® Discovery Studio 2.5.5). The compound was simultaneously docked with etravirine **5** and rilpivirine **6** to significantly increase docking robustness.[35]



18 R^1 = H IC_{50} = 0.41 mM
19 R^1 = CH_3 IC_{50} = 0.19 mM
20 R^1 = Cl IC_{50} = 0.24 mM

Figure 14: 2-(2-Chlorophenyl)-3-(cyclohexylamino)imidazo[1,2-*a*]pyridines and their corresponding MAGI whole cell assay IC_{50} values against RT.[35]

A 2-dimensional (2D) map (**Figure 15**) of the docked compound was obtained and it revealed that the imidazo[1,2-*a*]pyridine ring system core fitted into the aromatic rich pocket surrounded by Tyr188, Phe227 and Trp229 amino acids. The chlorophenyl ring gave a second $\pi - \pi$ interaction with Tyr188. The hydrophobic pocket lined by Lys/Arg103

(vulnerable to mutation) was where the cyclohexyl ring lay and they interacted through Van der Waals' forces.[35]

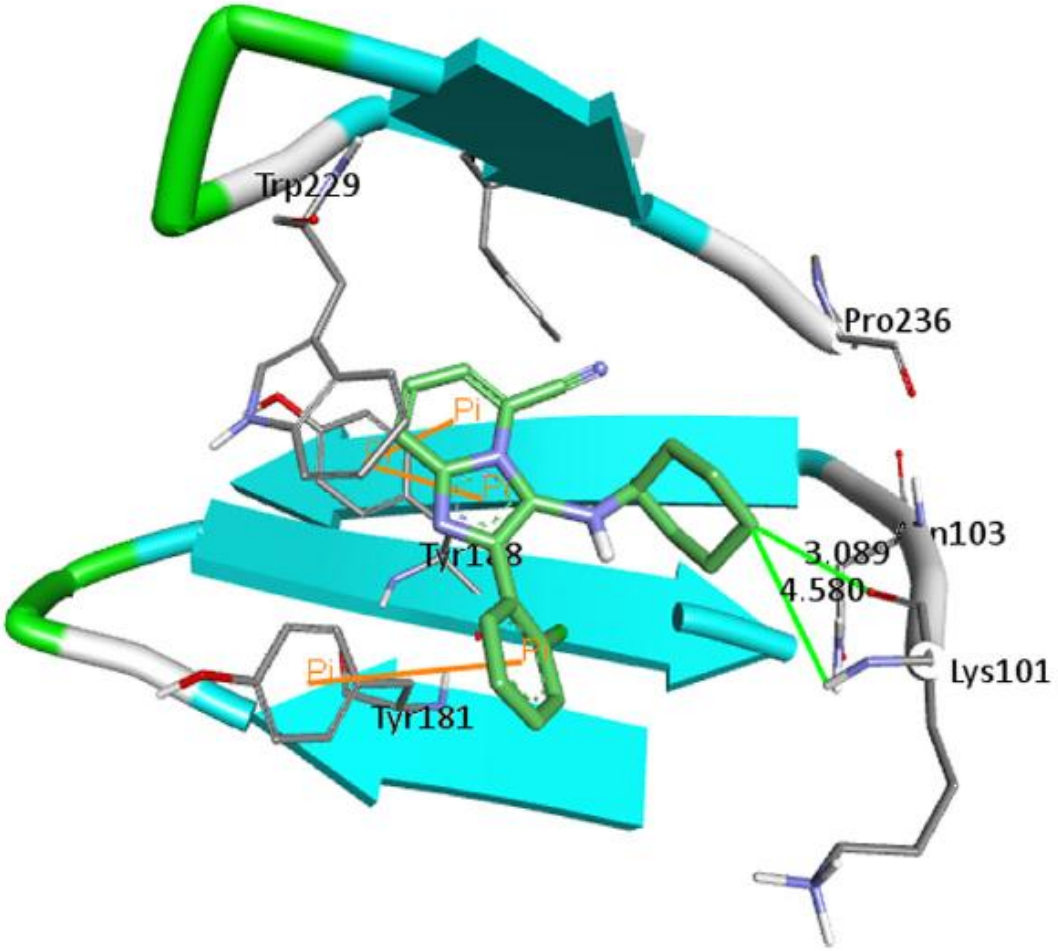


Figure 15: Compound **17** 2-D interaction map in the NNRT binding site and corresponding interactions[35]

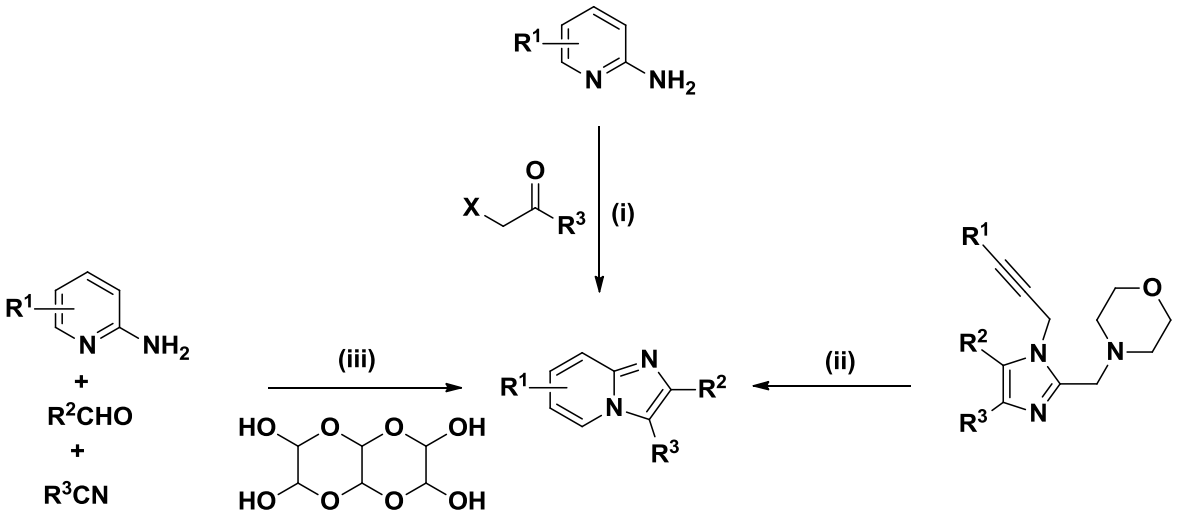
It was also found that an N-H group on Lys101 was located 4.5 Å away from the C-4 position in the cyclohexyl ring. Furthermore, a carbonyl oxygen was found to be 3 Å away from the C-4 position.[35] This suggested that introducing a group able to hydrogen bond to these amino acids may grant an increase in activity comparable to newer NNRTIs.[35, 42]

1.2.2 Synthesis of imidazo[1,2-*a*]pyridines

There are a number of synthetic methods that can be applied to the synthesis of imidazo[1,2-*a*]pyridines, a few of which will be discussed in the following section.

1.2.2.1 General synthetic methods

The essential role that the imidazo[1,2-*a*]pyridine scaffold plays in pharmaceuticals and a wide range of biologically active compounds has led to the development of a variety of synthetic methods for obtaining the scaffold;[36] for example (i) the coupling reactions of α-halocarbonyl compounds with 2-aminopyridine, (ii) the cyclization of 1-(2-alkynyl)-2-aminomethyimidazoles, and (iii) 2-aminopyridine condensation with glyoxal trimer dihydrate (**Scheme 1**).[42]



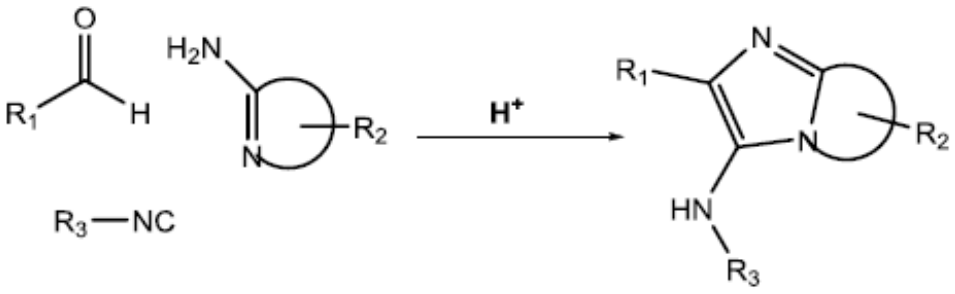
Scheme 1: General synthetic methods for imidazo[1,2-*a*]pyridines

Method (i) is widely used as it can give diverse final products because there are various substituted 2-aminopyridines and α-halocarbonyls that are commercially available or could be easily synthesized. The major disadvantage of this reaction is that it is unable to give 3-amino monosubstituted imidazo[1,2-*a*]pyridines.[43] Knölker *et al.* utilized method (iii) and reported it as a high yielding reaction that gives diverse imidazo1,2-*a*]pyridines. However, the reaction method requires the synthesis of both starting material (i.e. (arylacetyl)imidazoles and acetylene dicarboxylic esters) in order to obtain the diversity in the reaction, thus making this synthetic route a lengthy one.[44] Groziak *et al.* reported method (ii) as a low yielding reaction that does not give diversity in the final product.[45]

1.2.2.2 Multicomponent reactions (MCRs) for the synthesis of imidazo[1,2-*a*]pyridines

MCRs are known as useful and powerful condensation reactions that are performed in a single pot to give products made up of three or more component starting materials.[46] They offer a variety of advantages: (i) the single step synthesis of complex or highly substituted molecules, (ii) a decrease in by-products from the reaction by being significantly more atom economical relative to conventional synthetic methods,[47] and (iii) good MCRs have the ability to diversify products,[48] thus allowing a creation of a large library of compounds for biological screening.[49]

For the synthesis of imidazo[1,2-*a*]pyridines, the Groebke-Blackburn-Bienaymé (GBB) MCR has proven to be indispensable. It is a four centre, three component reaction that was independently discovered by Katrin Groebke, Christopher Blackburn and Hugues Bienayme in 1998 (**Scheme 2**).[50-51] The reaction is versatile as it has been found to have compatibility with a variety of aminoheterocycles such as 2-aminopyridines, 2-aminopyrimidines, 2-aminothiazoles, 2-aminopyrazones, and 2-aminopyrazines.[50, 52] However, for the synthesis of imidazo[1,2-*a*]pyridines the reaction occurs between aldehydes, 2-aminopyridines and isocyanides in the presence of a catalyst. A variety of products can be produced as result of the commercial availability of diverse aldehydes and aminopyridines.[41, 53]



Scheme 2: Groebke-Blackburn-Bienayme reaction[52]

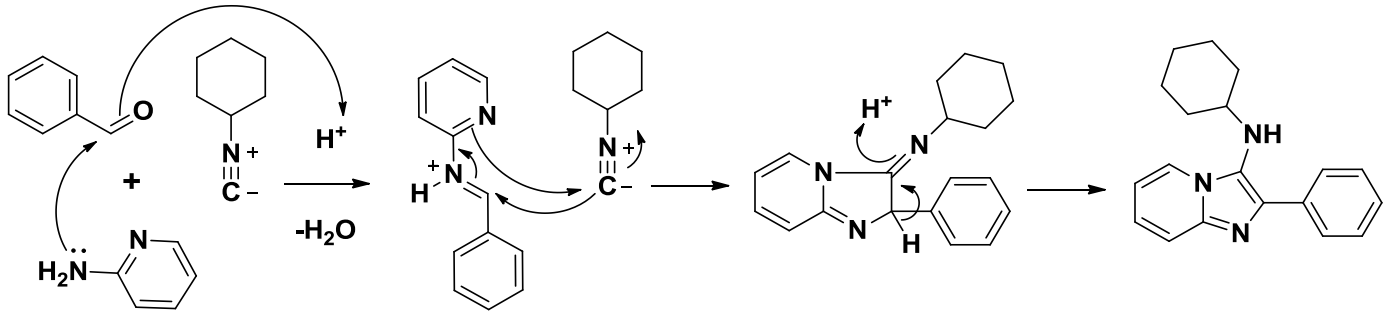
The GBB reaction has a number of additional advantages: it is generally a high yielding reaction, experimentally easy to perform, and it is not sensitive to moisture. [50, 52]

Furthermore, the reaction can be performed at ambient or high temperatures, solvent free and under microwave conditions. For example, Eliedrer and co-workers were able to produce a library of imidazo[1,2-*a*]pyridine compounds in good yields in the presence of $Sc(OTf)_3$, and they were able to replicate this success by producing the same compounds under microwave conditions at 140 °C in the presence of $Sc(OTf)_3$.[50,54] Vidyacharan *et al.* developed a solvent and catalyst free reaction that allowed them to produce a small library of imidazo[1,2-*a*]pyridine derivatives in excellent yields.[50, 55]

The GBB reaction also allows the use of a significant number of different catalysts in the reaction:[50, 52] The reaction can be catalyzed by a Lewis acid/base, for example Puttaraju and coworkers used iodine (20% mol) in the synthesis of *tert*-butyl-imidazo[1,2-*a*]pyridin-3-amines to obtain the product in yields of 81-96%.[56] Rostamnia and Hassankhan used $RuCl_3$ under solvent free conditions to give yields of 89-96% in their production of imidazo[1,2-*a*]pyridine derivatives.[57] Cacerda *et al.* used a Brønsted acid, acetic acid, as a catalyst to produce imidazo[1,2-*a*]pyridine derivatives in yields of 25-85%.[58]

Using the sol-gel method, Tavakkolia and coworkers synthesized a solid acid catalyst, $LaMnO_3$ perovskite particles, and the particles were reported to have excellent catalytic activity in the synthesis of imidazo[1,2-*a*]pyridines.[59] Beifuss *et al.* used montmorillonite clay as a catalyst to produce imidazo[1,2-*a*]pyridines in good yields.[60] Shabbani and coworkers were the first to use ionic liquids (1-butyl-3-methylimidazolium) to produce imidazo[1,2-*a*]pyridines in excellent yields.[61] The ionic liquids are composed of two components: the cationic component that may be acting as a Lewis acid, and the anionic component that may be acting as a Lewis base. This dual catalysis suggests that ionic liquids may enhance the rate of the reaction.[50, 61]

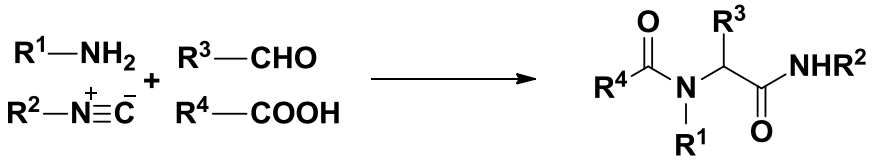
The mechanism of the GBB reaction has been widely discussed (**Scheme 3**); and the reaction is proposed to proceed *via* the initial condensation of aldehydes and amines to give an imine. This is followed by a [4+1] cycloaddition between the protonated imine and the isocyanide to give an intermediate that subsequently undergoes a prototropic shift to give the fused aromatic compound.[50]



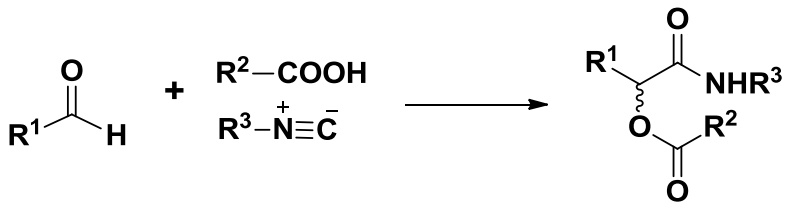
Scheme 3: Proposed mechanism of Groebke-Blackburn-Bienayme reaction

1.2.2.3 Isocyanides: a synthetic and diversity problem?

Isocyanides have proven to be a vital component in various synthetic transformations for the synthesis of heterocycles and in the development of multicomponent condensations.[62] The versatility of isocyanides is attributed to the unique functional group, which plays the role of both the nucleophile and electrophile during the course of a reaction.[63] This has led to their use in a number of MCRs like the Ugi reaction, a four component reaction that requires an aldehyde, amine, carboxylic acid and isocyanide (**Scheme 4**).[64] The Passerini reaction is another essential isocyanide based MCR, it is a three component reaction that requires an aldehyde, carboxylic acid and an isocyanide (**Scheme 5**).[65]



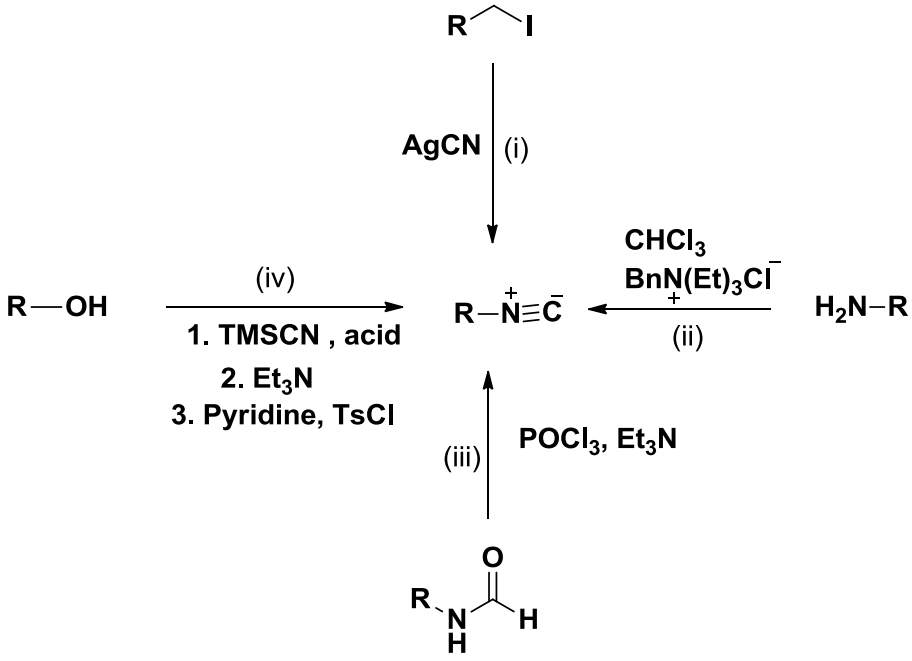
Scheme 4: Representation of the Ugi MCR



Scheme 5: Representation of the Passerini MCR

There has been many applications found for these reactions. For example Gravestock *et al.* reported the successful use of isocyanides in the Passerini-amine deprotection-acyl migration (PADAM) sequence for the synthesis of HIV-1 PIs.[65] Isocyanides were also used by Koopmanichap *et al.* in both the Ugi and Passerini reactions to give cyclic constrained peptidomimetics.[66]

A number of synthetic routes for obtaining isocyanides have been investigated and reported in the literature (**Scheme 6**): (i) treating iodine-substituted compounds with AgCN, (ii) using the Hoffman carbylamine reaction which utilizes a phase transfer catalyst, (iii) dehydration of a formamide using a variety of dehydrating agents (i.e. $POCl_3$ or PPh_3) under different conditions, and (iv) they can also be obtained directly from alcohols. This is the most commonly used route to obtain isocyanides, although it is a non-trivial experimental procedure.[67] The disadvantages associated with the dehydration of the formamide synthetic route are related to the nature, toxicity and scope of the dehydrating agents. For example, despite the wide use of $POCl_3$, it is known to be highly poisonous and sensitive to moisture. TsCl has been used with limited success in the dehydration of *N*-aryl-substituted formamides.[68]



Scheme 6: Various isocyanide synthetic routes

A drawback of the isocyanide based GBB reaction is that only a few different isocyanides are commercially available.[53, 69] The lack of commercially available isocyanides has an additional negative effect in a number of reactions as they usually lead to final products that also lack diversity. However, this challenge can be overcome by using convertible isocyanides.[70] A convertible isocyanide can be defined as a building block in a reaction, and has an isocyanide moiety ($^{+}N\equiv C^{-}$). Reaction of the convertible isocyanide lead to a product with a labile amide functional group that can be converted/removed post reaction.[71] A number of convertible isocyanides (**21, 22, 23, 24**) have been synthesized and reported in literature (**Figure 16**).

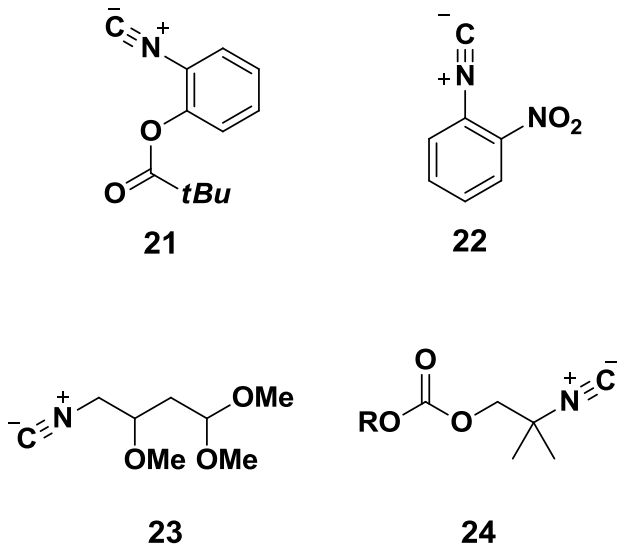
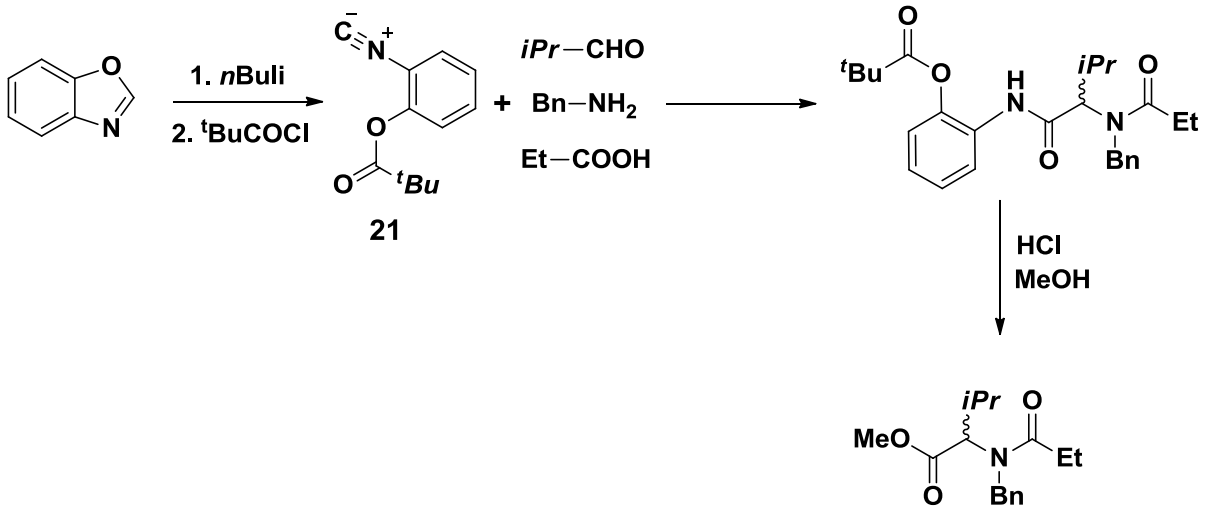


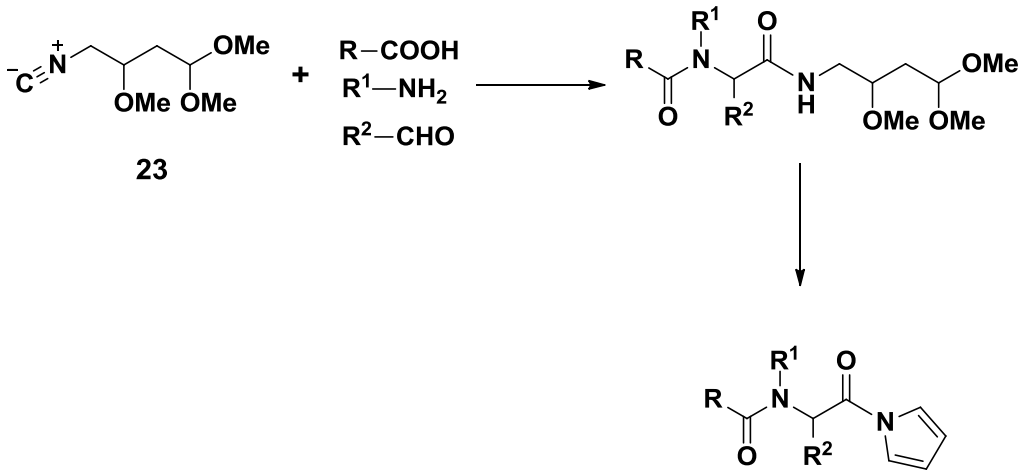
Figure 16: Convertible isocyanides

Ortho-*O*-acyl phenyl isocyanides are reported to be the most practical convertible isocyanides, as they can be easily prepared from benzoxazoles. Pirrung *et al.* successfully synthesized compound **21** and utilized it in a Ugi reaction. The resulting product was treated with hydrochloric acid (HCl) in methanol to successfully convert the resulting amide to the desired ester (**Scheme 7**).[72]



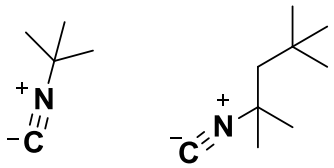
Scheme 7: Synthesis and application of isocaynide **21**

Compound **23** was synthesized and successfully used in Ugi MCRs by Neves-Filho *et al.*, and the compounds obtained from the Ugi MCRs were successfully converted to their corresponding *N*-acylpyrroles (**Scheme 8**).[73]



Scheme 8: Application of isocyanide **23**

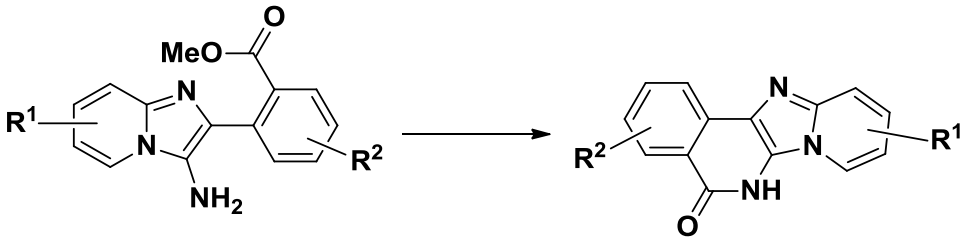
In the GBB reaction for the synthesis of imidazo[1,2-*a*]pyridines, the use of convertible isocyanides *tert*-butyl isocyanide (**25**) and 1,1,3,3 tetramethylbutyl isocyanide (Walborsky reagent) (**26**) are often preferred because of their affordability, commercial availability, stability, ease of storage and their allowance of the liberation of the primary amine in the resulting GBB products.[69]



25 **26**

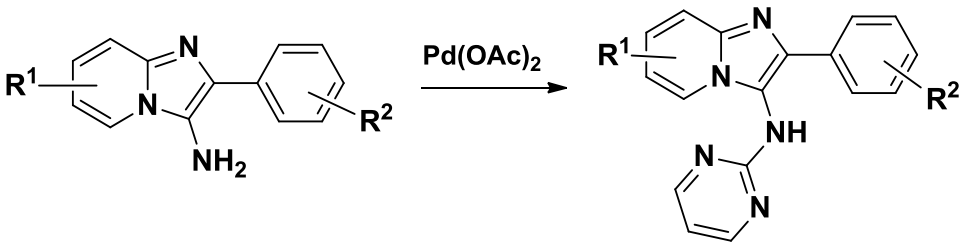
Figure 17: Common convertible isocyanides used in the synthesis of imidazo[1,2-*a*]pyridines.

The resulting primary amines may be reacted further with a variety of functional groups; for example in the arylation of aromatic and heteroaromatic compounds,[74] or the reductive amination of ketones and aldehydes.[69] The use of *tert*-butyl isocyanide as a convertible isocyanide has been investigated and reported by a number of researchers. Guchhait and coworker reported the synthesis of a variety of *tert*-butyl-imidazo[1,2-*a*]pyridin-3-amines and their subsequent treatment with a variety of acids in a de-*tert*-butylation (dealkylation) reaction in order to give their corresponding primary amines. Futhermore, the obtained primary amines underwent an *in situ* cyclization reaction (**Scheme 9**).[69]



Scheme 9: *In situ* cyclization of primary amine

A number of researchers also explored the convertible Walborsky reagent.[69, 74] For example Sadulenko *et al.* reported the synthesis of imidazo[1,2-*a*]pyridin-3-amines using the Walborsky reagent. The products obtained were treated with 4 M HCl in a dealkylation reaction to give the corresponding primary amines in salt form. The amine salts were subsequently reacted with a variety of heteroaromatic compounds in a Pd-catalyzed arylation reaction (**Scheme 10**).[74]



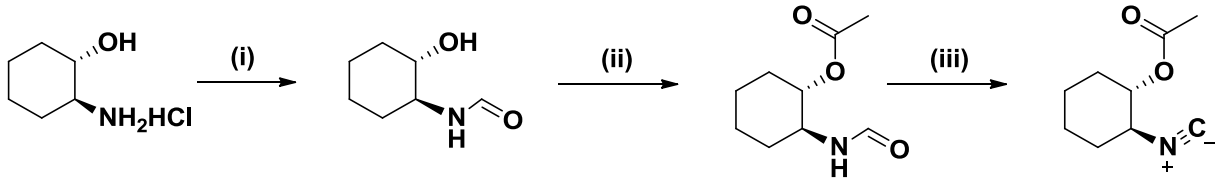
Scheme 10: Pd-catalyzed arylation of primary amine

The primary amines obtained can be reacted further in different reactions such as acylation and carbonylation.[75, 76] The use of convertible isocyanides thus bypasses the "problematic" synthesis of commercially unavailable isocyanides by liberating a functional moiety that could be functionalized further using different types of reactions.

1.3 Project aims and objectives

This chapter illustrates the growing need for NNRTIs with significant potency and activity against HIV-1 RT. It also highlights the shortcomings that are faced in the pursuit of synthesizing these novel NNRTIs. The first aim of this project is to synthesize phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridine-3-amine derivatives that possess increased H-bonding capacity (specifically on the cyclohexyl ring) using the GBB MCR.

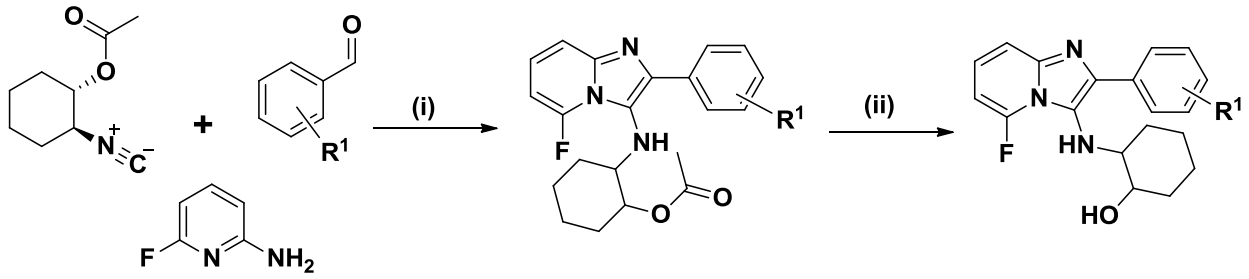
We will begin by exploring the synthesis of the cyclohexyl isocyanide that is functionalized with a moiety that has H-bonding capabilities (**Scheme 11**). The proposed synthetic route begins with the formylation of 2-hydroxy cyclohexylamine hydrochloride, followed by the protection of the hydroxyl group with an acetate in order to prevent its loss in the subsequent dehydration of the formamide that will give the isocyanide.



Scheme 11: Proposed synthetic route: (i) formylation, (ii) acetylation, (iii) dehydration.

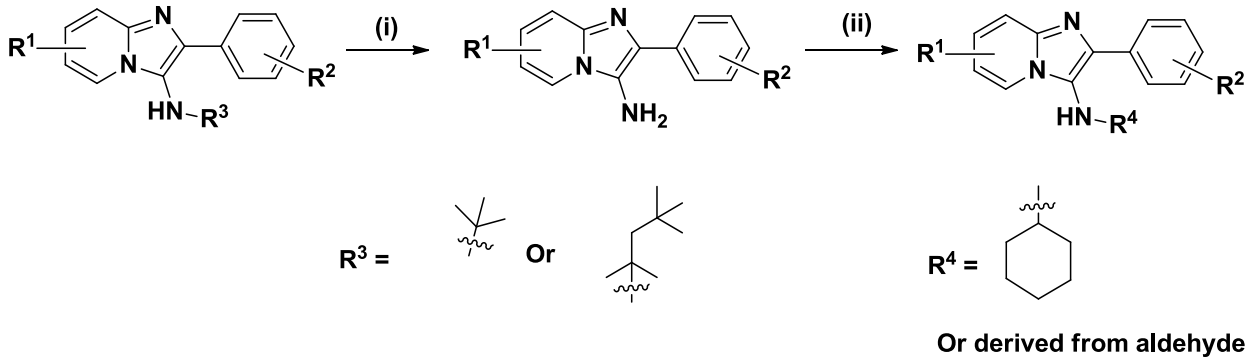
The isocyanide will then be used in the GBB MCR under both conventional and microwave conditions to give different phenyl-*N*-cyclohexlimidazo[1,2-*a*]pyridin-3-amine

derivatives. This will be followed by the hydrolysis of the acetate so as to liberate the hydroxyl functional group (**Scheme 12**).



Scheme 12: (i) GBB MCR. (ii) Hydrolysis of acetate

The aims and objectives of the second part of the project will be to develop a synthetic methodology for obtaining phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine derivatives without the need to synthesize the isocyanide (**Scheme 13**). This will require an initial use of convertible isocyanides **25** and **26** in the GBB reaction. This will be followed by placing the resulting products into a dealkylation reaction to give the corresponding amines, which will subsequently be used in a reductive amination with cyclohexanone in order to test the reaction. The versatility of the amines will be tested by using them together with different electrophiles (i.e. aldehyde) in the reductive amination reaction.



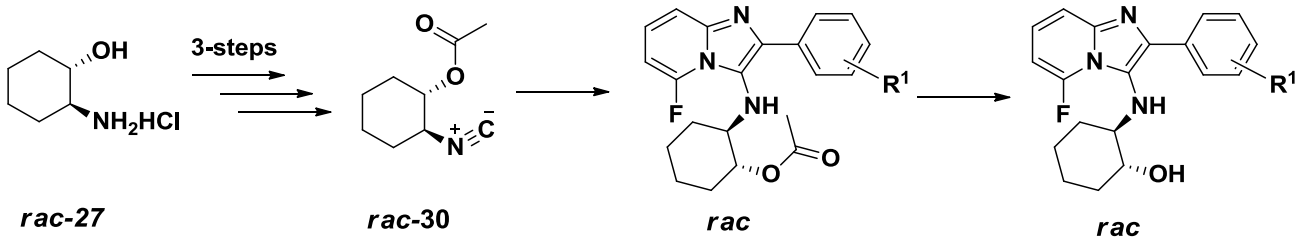
Scheme 13: (i) Dealkylation of imidazo[1,2-*a*]pyridines, (ii) reductive amination of primary amine

We aim to design a method that may later be utilized as an alternative to synthesizing phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridine-3-amine derivatives that possess groups with H-bonding capacity on the cyclohexyl ring.

Chapter 2: Results and Discussion

2.1 Synthesis of 2-((phenyl)-imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate derivatives.

Imidazo[1,2-*a*]pyridines have been widely studied and investigated, from how they are synthesized to their biological activity. One such investigation was carried out by Bode and co-workers, where they reported the synthesis of imidazo[1,2-*a*]pyridine-3-amines with biological activity against the HIV-1 virus, more specifically the RT enzyme of the virus.[35] A small set of 2-(2-chlorophenyl)-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine derivatives (i.e. **Figure 14, Chapter 1**) were identified and reported to possess biological activity comparable to the FDA approved drug nevirapine. Furthermore, a molecular modelling study on these compounds (**Figure 15**) revealed that adding functional groups with H-bonding ability to the cyclohexyl ring of these compounds might significantly improve their biological activity against the RT enzyme, and hence the HI virus.[35] In this chapter we investigate and report on the synthesis of phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine derivatives which are functionalized on the cyclohexyl ring of these derivatives (**Scheme 14**).



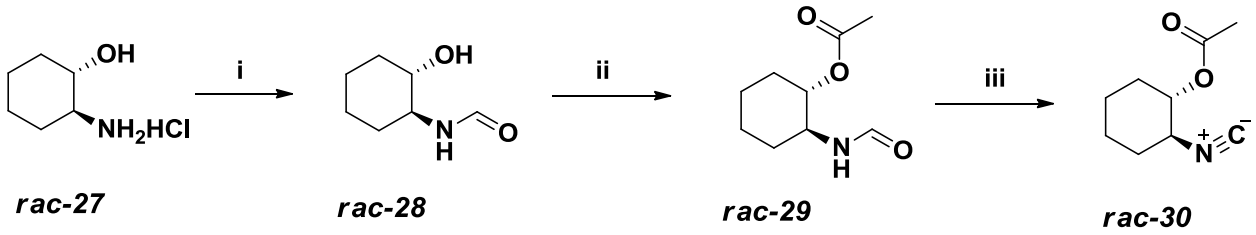
rac-27 *rac-30* *rac* *rac*

Scheme 14: Synthesis of phenyl-*N*-(2-hydroxycyclohexyl)imidazo[1,2-*a*]pyridin-3-amines

We began with a three step synthesis (formylation, acetylation, dehydration) of the functionalized isocyanide from compound **27**. This was followed by the use of the functionalized isocyanide in the GBB reaction to give a small library of phenyl-*N*-(2-hydroxycyclohexyl)imidazo[1,2-*a*]pyridin-3-amines that were to subsequently undergo a hydrolysis reaction in order to liberate the H-bond donating hydroxyl group.

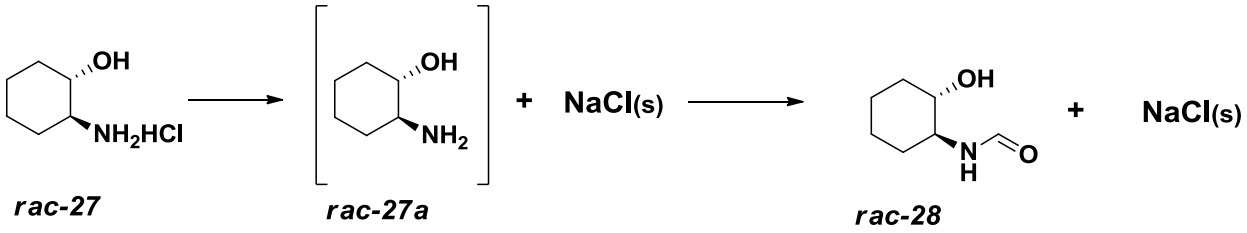
2.1.1 Synthesis of 2-Isocyanocyclohexyl acetate (30)

Isocyanides have been found to be quite versatile compounds that may be used in a variety of essential synthetic transformations that give access to diverse compounds, and they are useful in the development of multicomponent condensation reactions. Despite the various precursors from which isocyanides may be derived, their synthesis has remained a challenge. In our objective to obtain 2-acetylcyclohexyl isocyanide **30**, the dehydration of the formamide ***rac*-29** was the synthetic route of choice (**Scheme 15**).



Scheme 15: Reagents and conditions: (i) NaOMe, methyl formate, MeOH, room temperature, 24 h, 97%.[77] (ii) Acetic anhydride, pyridine, room temperature, 4h, 92%. (iii) *a*) $POCl_3$, triethylamine, 0°C to room temperature, 2 h,[65] or (*b*) Burgess reagent, dry CH_2Cl_2, reflux, 80 min,[62] or (*c*) Triphenylphosphine (Ph_3P), EtN('Pr)$_2$, carbon tetrachloride (CCl_4), CH_2Cl_2, room temperature, 24 h.[65]

A procedure reported by Grenouillat *et al.*[77] (although not specific to the synthesis of **28**) was used to obtain the formamide **28**. Compound **27** was treated with sodium methoxide (NaOMe) to neutralize the acid and give the free amine, which was then treated with methyl formate for 24 h. The solvent was then removed *in vacuo* to give a white residue. However, we had to slightly deviate from the work-up process of the reaction as described by Grenouillat *et al.*, instead of using column chromatography to isolate **28**, the obtained residue was dissolved in methanol and an excess amount of hexane was added to the solution. This was done to allow the NaCl generated alongside the intermediate amine **27a** from the neutralization of the hydrochloride salt **27** to precipitate out of solution (**Scheme 16**). The salt was filtered off, and the collected solvent removed *in vacuo* to give formamide **28** in excellent yield (97%).



Scheme 16

There are a limited number of reports on the synthesis of **28** in the literature, one such rare report by Kukharev *et al.* reported the synthesis of **28** from 2-(vinyloxy)cyclohexanamine by treating it with 2,2,2-trichloroethane-1,1-diol. The reaction successfully gave **28** with a number of by-products and hence a lower yield was obtained compared to the method we employed.[78-79] Before we could transform the formamide into the isocyanide, the hydroxyl group needed to be protected through an *O*-acetylation reaction in order to prevent it from possibly participating in a competing dehydration reaction. The dehydration of a hydroxyl functional groups by a variety of dehydrating agents has been widely investigated, and reported to give alkene products.[80-83]

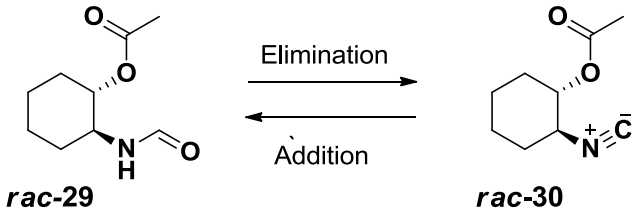
So, in order to acetylate **28**, it was treated with acetic anhydride in the presence of pyridine for 4 h at room temperature. The reaction mixture was quenched with methanol, and the excess methanol and pyridine were removed *in vacuo* as an azeotrope with toluene to give the novel acetylated formamide **29** as a yellow solid in excellent yield of 92% (**Scheme 15**). The next step was to transform **29** into isocyanide **30**, and three different methods and dehydrating reagents were explored in order to obtain compound **30**.

Using the first method compound **29** was treated with $POCl_3$ under an inert atmosphere for 24 h. The resulting black solution was quenched with saturated sodium hydrogen carbonate ($NaHCO_3$) and filtered.The filtrate was extracted with CH_2Cl_2 and the organic layer was concentrated *in vacuo.* The residue obtained was purified by flash silica gel column chromatography to give the novel compound **30** as a yellow oil with the distinct isocyanide smell in good yield (**Scheme 15**, 67%).[65] However, using this method gave these good yields only when 0.1 g of **29** was used; increasing the scale of the reaction (i.e. amount of **29** greater than 0.1 g) while keeping the equivalence of the reagents the same led to a dramatic decrease in yield for compound **30** (Table 1).

Table 1: The effects of scaling up the dehydration reaction of compound **29** on the yields of compound **30**

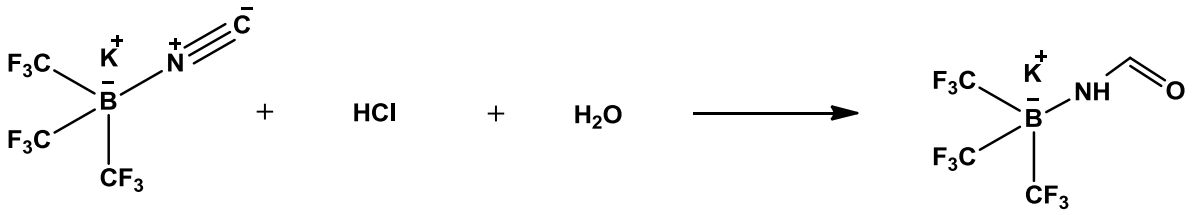
Mass of compound **29** (g)	Compound **30** Yield (%)
0.10	67
0.50	20
1.00	14
5.00	8.0

Possible reasons for this trend are not clear and we could not find similar reports in the literature. However, thin layer chromatography (TLC) did reveal an increase in the number of by-products, and thus revealing the presence of competing reactions as the scale of the reaction was increased. These by-products proved to be a challenge to isolate as a number of them were lost during column chromatography, and those that were isolated had nuclear magnetic resonance (NMR) data that could not be clearly/reliably elucidated. Faced with this challenge we decided to explore a different dehydrating agent, methyl-*N*-(triethylammoniumsulfonyl)carbamate, also known as the Burgess reagent. Compound **29** was treated with the Burgess reagent under reflux for 80 minutes in an inert N_2 gas atmosphere. After work up, CH_2Cl_2 was removed *in vacuo* and the resulting residue was purified using flash silica column chromatography which gave compound **30** as yellow oil in excellent yield (**Scheme 15**, 98%).[64] However, both the use of $POCl_3$ and the Burgess reagent resulted in one common challenge, the isocyanide product obtained from both methods was not stable and reverted back to compound **29** (**Scheme 17**).



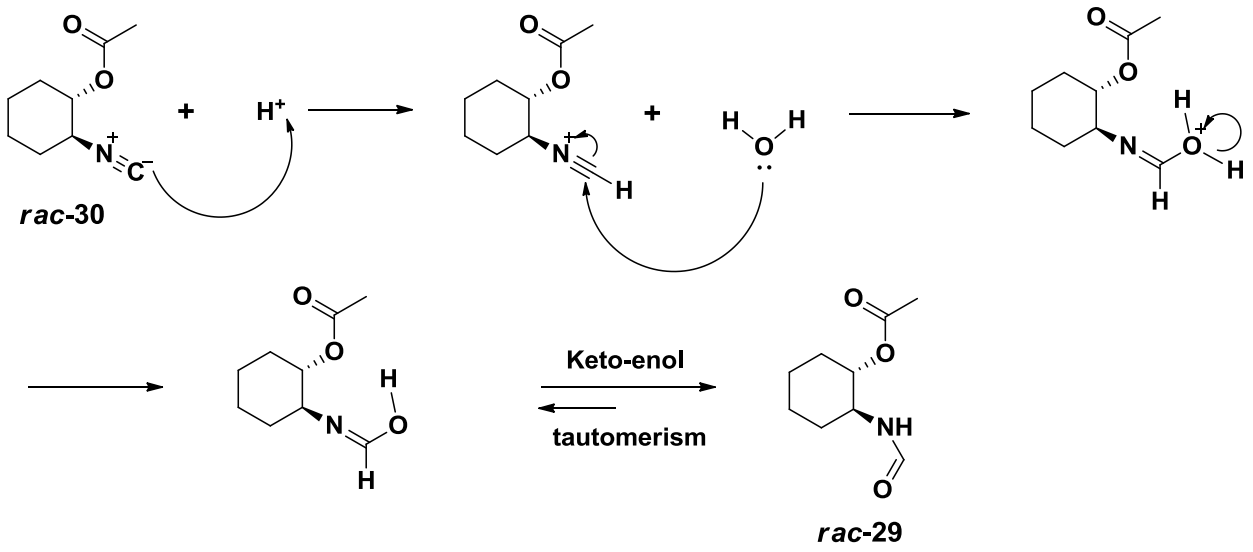
Scheme 17: Reversibility of formamide dehydration reaction

This suggests that in both cases water is being added across the isocyanide bond. We could only locate a single literature report on the addition of water across an isocyanide bond by Finze and co-workers.[84] They dissolved K[$(CF_3)_3$BNC] in water and treated it with hydrochloric acid (HCl), and they obtained the corresponding formamide K[$(CF_3)_3$BNHC(O)H] (**Scheme 18**), but they did not report on the mechanism of the reaction.[84]



Scheme 18: Addition of water across an isocyanide bond.[84]

Coupling this report with the known reaction conditions and work up procedures for the dehydration of **29**, suggests that the addition of water across the isocyanide bond is an acid catalyzed reaction and thus allows us to speculate on the mechanism for this reaction(**Scheme 19**).



Scheme 19: Acid catalyzed addition of water

However, this possible explanation comes under scrutiny because the procedure in which $POCl_3$ is used generates acids that could catalyze this reaction during the addition of

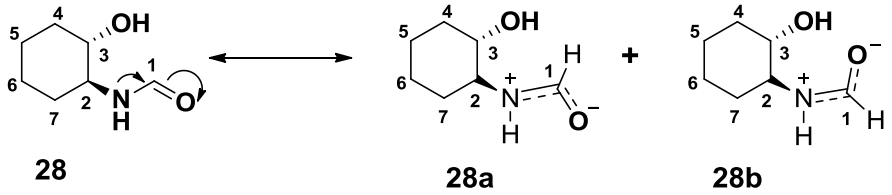
saturated aqueous $NaHCO_3$ but an excess of triethylamine is used in the reaction, and an excess of saturated $NaHCO_3$ is added during the work up of the reaction. These would serve to neutralize any acids generated during the reaction, thus suggesting that the reaction may not be proceeding *via* an acid catalyzed route.

The reaction conditions in which the methyl-*N*-(triethylammoniumsulfonyl)carbamate (Burgess reagent) was used does not have enough information (i.e. lack of reports on the mechanism of the reaction) to corroborate that the addition of water proceeds *via* an acid catalyzed route, but it does suggest that the water introduced during work up of the reaction is key in the reverse reaction. To try and corroborate this we changed the work up process for the dehydration reaction. Upon completion of the reaction, the reaction mixture was diluted with CH_2Cl_2, which was subsequently removed *in vacuo* and the product purified using flash column chromatography. The isolated isocyanide did not revert back to compound **29**.

In light of the complications that arose from using $POCl_3$ and the Burgess reagent, a third method and dehydrating agent were investigated. Compound **29** was treated with Ph_3P in the presence of CCl_4 and $EtN(^iPr)_2$ for 24 h. Solvent was removed *in vacuo*, and the product was purified using flash silica column chromatography to give the isocyanide **30** in good yield (**Scheme 15**, 67%) as a dark yellow oil with the distinct isocyanide smell.[51] The compound isolated did not undergo any conversion back to the starting material, and the yields were not negatively affected by increasing the scale of the reaction.

Infrared spectroscopy, NMR spectroscopy and high resolution mass spectrometry were used to confirm the synthesis of compounds **28**-**30**. ^1H and ^{13}C NMR spectroscopy revealed that in solution compound **28** exists as a mixture of rotamers. Furthermore, these rotamers vary in concentration and the integration of the ^1H NMR spectroscopy signals reveal a 1:2 ratio (minor rotamer: major rotamer) between them. However, it is essential to note that this ratio is dependent on a number of variables such as solvent effects, and consequently H-bonding, anisotropy of solvent molecules and Van de Waals' forces between solute and solvent, so the ratio may change depending on which variable changes.[85] The rotamers may be a result of mesomerism, a phenomenon that has been observed in a number of amides.[85-88] The lone pair of electrons on the nitrogen are

delocalized over the amide bond to give a partial double bond, resulting in a larger barrier of rotation about the CN bond. This leads to a conformational arrangement of either *cis* or *trans* geometry between the N-H and formamide (H-1) protons about the amide bond (**Scheme 20**).



Scheme 20: Mesomerism of compound **28**

It has been observed and reported that in secondary amides, specifically formamides, the coupling constants between the N-H and formamide protons can help differentiate between the two conformational arrangements *cis* and *trans* in ^{1}H NMR spectroscopy. The formamide signal with the largest coupling constant (*J*) has been found to have a *trans* conformation about the amide bond, and that with the smaller coupling constant a *cis* conformation.[85-87] In our case, this allowed us to reasonably determine the conformational arrangement of the major and minor rotamers.

Homonuclear correlation spectroscopy (COSY) NMR of **28** revealed that in both rotamers, the N-H proton couples to the H-1 proton. However, in deuterated chloroform ($CDCl_3$), we could only observe this coupling (*J* = 11.2 Hz) for the minor rotamer, while the signal appeared as a singlet for the major rotamer, and thus we could not compare the coupling constants. We were able to overcome this problem by changing the solvent in which the ^{1}H NMR spectrum for compound **28** was obtained from $CDCl_3$ to deuterated dimethyl sulfoxide (DMSO-d_6). The resulting spectrum gave us the formamide proton signal for the major rotamer as a doublet at 7.98 ppm (*J* = 1.9 Hz), and the minor rotamer was found at 7.90 ppm (*J* = 11.6 Hz). The *J* value for the major rotamer is less than that of the minor rotamer, and this suggest that in the major rotamer the N-H and formamide proton are in a *cis* conformation (compound **28b**), and they are arranged in a *trans* conformation (compound **28a**) in the minor rotamer. The ^{1}H NMR spectrum obtained in $CDCl_3$ revealed the characteristic signal of the formamide proton (H-1) for the major rotamer (**28b**) as a singlet at 8.26 ppm, and as a doublet at 8.06 ppm (*J* = 11.2 Hz) for the minor rotamer

(**28a**) (Table 2). The N-H signals appeared at 6.28 ppm (major rotamer) and 6.61 ppm (minor rotamer) as a broad singlet. The H-2 proton was found at 3.74-3.63 ppm for **28b**, and at 3.07-2.98 ppm or **28a**. The H-3 protons for **28a-b** were found to overlap at 3.42-3.20 ppm (Table 2). For the ^{1}H NMR spectrum obtained in DMSO-(d_6), the signals found at 7.90 ppm and 7.48 were assigned to the N-H protons in **28b** and **28a**, respectively (Table 2).

Table 2: Selected ^{1}H NMR spectroscopy signals for compound **28** and their multiplicity

Compound	H-1	N-**H**	H-2	H-3
28a ($CDCl_3$)	8.06 (d)	6.61 (s, br)	3.07-2.98 (m)	3.42-3.20 (m)
28b ($CDCl_3$)	8.26 (s)	6.28 (s, br)	3.74-3.63 (m)	3.42-3.20 (m)
28a (DMSO)	7.90 (d)	7.48 (t)	2.93-2.82 (m)	3.09-3.01 (m)
28b (DMSO)	7.98 (d)	7.90 (m)	3.49-3.39 (m)	3.24-3.18 (m)

A possible explanation for the non-equivalence of these protons as shown in Table 2 is the anisotropy of the carbonyl oxygen. Similar observations about amides (and various carbonyl containing compounds) have been reported in literature, and it was found that functional groups or protons that are found in the same plane as the carbonyl oxygen experience a deshielding effect ($+\delta$), and those that lie above the plane experience a shielding effect ($-\delta$) (**Figure 18**). As a result, the signals of functional groups or protons that experience a $+\delta$ are likely to be a found at a chemical shift higher than those that experience a $-\delta$ or do not lie in the same plane as the carbonyl oxygen.[85-93]

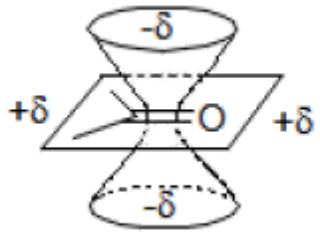
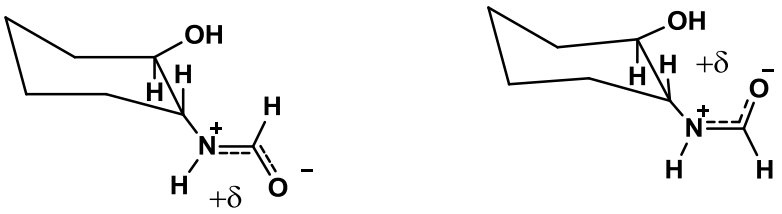


Figure 18: Carbonyl oxygen anisotropy representation[93]

This suggests that the signal for the N-H proton in **28a** is found at a slightly higher chemical shift than the one in **28b** because it might lie in the same plane as the carbonyl oxygen, while the N-H proton in **28b** possibly lies in the same plane but also lies *trans* to the carbonyl oxygen and does not experience the $+\delta$ (**Figure 19**). However, in DMSO-(d_6) the opposite is the case, and although it is not clear why, similar observations were made by Abraham *et al.* in a study that looked into how the NMR spectroscopy data of various amides is affected by the solvents DMSO-(d_6) and $CDCl_3$.[85-86]



28a **28b**

Figure 19

The signal of the H-3 proton in compound **28b** is found at a higher chemical shift than in **28a** as it might lie in the same plane and same side of the N(C)-O partial double bond as the carbonyl oxygen, and thus experiences a $+\delta$ (**Figure 19**). Although the H-3 proton in **28a** lies in the same plane as the carbonyl oxygen, it also lies on the opposite side of the N(C)-O partial double bond as the carbonyl oxygen, and thus does not experience a $+\delta$.

The successful synthesis of compound **28** and its existence as a mixture of rotamers in solution was corroborated further by the ^{13}C NMR spectroscopy data (Table 3). The signals found at 165.14 ppm and 162.54 ppm were assigned to the formamide carbon C-1 for **28a** and **28b** respectively. The C-2 carbon for **28a** was found at 58.69 ppm, and

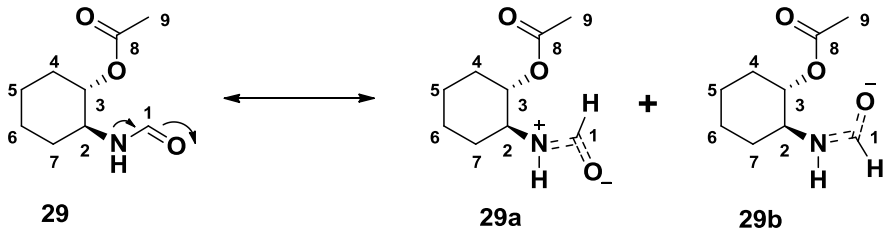
54.60 ppm for **28b**, while the signals for C-3 carbons were observed at 74.41 ppm for **28b** and 73.23 ppm for **28a**.

Table 3: Selected ^{13}C NMR spectroscopy signals for compound **28**

Compound	C-1	C-2	C-3
28a ($CDCl_3$)	165.14	58.69	73.23
28b ($CDCl_3$)	162.54	54.60	74.41

Furthermore, the IR spectrum of **28** revealed the formamide signal as a strong band at 1635 cm^{-1}, and the N-H signal as a weak band at 3341 cm^{-1}. The broad band at 3283 cm^{-1} was assigned to the hydroxyl group. The NMR and IR spectroscopy data for compound **28** was found to be consistent with the one reported in the literature.[78-79]

The analysis of the NMR spectroscopy data for compound **29** in $CDCl_3$ confirmed the success of the acetylation reaction. The ^1H NMR spectrum revealed that, similar to compound **28**, compound **29** exists in solution as a mixture of rotamers, with an approximate ratio of 1:3 (minor rotamer: major rotamer) (**Scheme 21**). The coupling constants of the N-H proton to the formamide proton H-1 may help in differentiating between the two rotamers and which conformational arrangement may belong to the major and minor rotamer. The coupling of the H-1 proton to the N-H proton was observed in the COSY NMR spectrum for both rotamers. However, in the ^1H NMR spectrum obtained from $CDCl_3$ this coupling was only evident for the minor rotamer and not the major rotamer.



Scheme 21: Mesomerism of compound **29**

However, the ^{1}H NMR spectrum of compound **29** obtained in DMSO-(d_6) revealed this coupling. The signal for the formamide proton H-1 in the $CDCl_3$ ^{1}H NMR spectrum was found at 8.14 ppm and 8.06 ppm (J = 11.4 Hz) for the major and minor rotamer, respectively, while in the DMSO-(d_6) ^{1}H NMR spectrum the signal was found at 8.00-7.96 ppm (J = 2.0 Hz) for the major rotamer, and 7.92 ppm (J = 11.5 Hz) for the minor rotamer. Similar to compound **28** we propose that the minor rotamer might have the conformational arrangement of **29a** and the major rotamer that of **29b**.

The chloroform ^{1}H NMR spectrum confirmed the success of the acetylation by revealing the presence of the overlapping acetate signal for both rotamers at 1.98-2.00 ppm. The signals at 6.51 ppm and 6.38 ppm were assigned to the N-H protons for **29a** and **29b** respectively. The successful acetylation is accompanied by a shift in the H-3 proton signals from 3.42-3.20 ppm in **28a-b** to 4.73-4.64 ppm and 4.61-4.54 ppm in **29a** and **29b**, respectively (Table 4).

Table 4: Selected ^{1}H NMR spectroscopy signals for compound **29** and their multiplicity.

Compound	H-1	N-**H**	H-2	H-3	H-9
29a ($CDCl_3$)	8.06 (d)	6.51 (t)	3.33-3.22 (m)	4.61-4.54 (m)	2.05 (s)
29b ($CDCl_3$)	8.14 (s)	6.38 (t)	4.02-3.94 (m)	4.73-4.64 (m)	2.06 (s)
29a (DMSO)	7.92 (d)	7.67 (t)	3.32-3.17 (m)	4.62-4.37 (m)	2.06 (s)
29b (DMSO)	8.00-7.96 (m)	8.00-7.96 (m)	3.83-3.68 (m)	4.62-4.37 (m)	2.05 (s)

As shown in Table 4, the DMSO-(d_6) ^{1}H NMR spectrum for **29** the signals at 7.67 ppm and 8.00-7.96 ppm were assigned to the N-H protons for **29a** and **29b** respectively. The success of the acetate formation is confirmed by the presence of the overlapping acetate

signals at 2.05-2.06 ppm, and the shift of the H-3 proton signal from 3.09-3.01 ppm in **28a** and 3.24-3.18 ppm in **28b** to 4.62-4.37 ppm in **29a-b**, respectively.

The non-equivalence of these protons in both spectra may be explained in a similar fashion to those of compound **28** rotamers, where the anisotropy of the carbonyl oxygen (**Figure 18**) potentially influences the chemical shifts of these protons as shown in **Figure 20**.

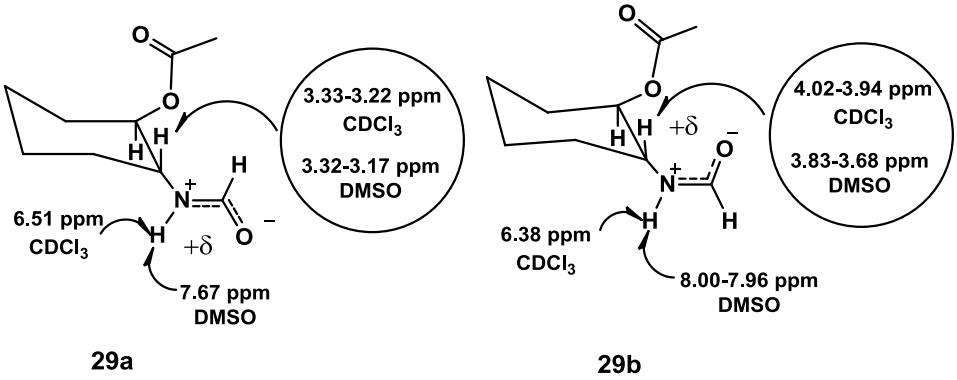


Figure 20: Anisotropy influence of the formamide carbonyl oxygen.

The ^{13}C NMR spectroscopy data summarized in Table 5 also confirmed the success of the acetylation by revealing the presence of the methyl protons at 21.11 ppm for **29b** and 20.96 ppm for **29a**. Furthermore, the signal of the acetate carbonyl carbon atom was found at 171.65 ppm and 170.43 ppm for compounds **29b** and **29a**, respectively. The signals at 161.08 ppm and 164.39 ppm were assigned to the formamide carbonyl carbon atom for **29b** and **29a**, respectively. The C-2 carbon corresponds to the signals at 51.22 ppm for **29b** and 55.04 ppm for **29a**, and the C-3 carbon signal for **29b** was evident at 74.33 ppm, and that of **29a** at 74.88 ppm.

Table 5: Selected ^{13}C NMR spectroscopy signals for compound **29**.

Compound	C-1	C-2	C-3	C-9	C-8
29a ($CDCl_3$)	164.39	55.04	74.88	20.96	170.43
29b ($CDCl_3$)	161.03	51.22	74.33	21.11	171.65

In the IR spectrum for compound **29** the band found at 1726 cm^{-1} was assigned to C=O of the acetate. The C=O stretch band for the formamide carbonyl was present at 1658 cm^{-1}, and that of the N-H moiety was found at 3271 cm^{-1}. The molecular ion peak for compound **29** with a calculated mass of 186.1125 was found to be [M+H] 186.1127 by HRMS.

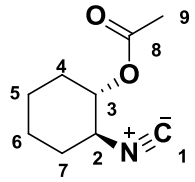


Figure 21 (*rac-30)*

^{1}H and ^{13}C NMR spectroscopy data summarized in Table 6 for compound **30** (**Figure 21**) confirmed that we had obtained the desired product by the absence of the formamide peak, and the presence of the characteristic ^{13}C NMR peak of the $^{+}N{\equiv}\mathbf{C}^{-}$ which appears as a triplet at 155.51 ppm (J = 9.5 Hz). The signal found at 55.11 ppm (J = 13.5 Hz) as a triplet corresponds to the C-2 carbon atom. The multiplicity of both signals ($^{+}N{\equiv}\mathbf{C}^{-}$ and C-2) is due to the nitrogen-carbon (N-C) coupling, since nitrogen has a quadrupole nucleus (meaning it has nuclear spin greater than a half) that is accompanied by quadrupole moment when exposed to a magnetic field. The quadrupole moment amongst other factors such as temperature affects the relaxation time of a nuclear signal in NMR spectroscopy. The faster the relaxation time, the less likely it is to see the signal of a nucleus or its multiplicity (i.e. coupling). One of the factors that governs the quadrupole moment is the electronic symmetry/asymmetry about a nucleus, and this symmetry or asymmetry may result in a slow or fast relaxation time. In the case of the isocyanide functional group, the N-C coupling is observed because the electronic asymmetry of the nitrogen nucleus results in a slow relaxation time.[88, 94-96] The signal at 73.35 ppm was assigned to the C-3 carbon atom, and its corresponding proton (H-3) was assigned to the signal at 4.83 ppm in the ^{1}H NMR spectrum. The signals due to the methyl protons and H-2 proton were found at 2.25-2.01 ppm and 3.55 ppm, respectively.

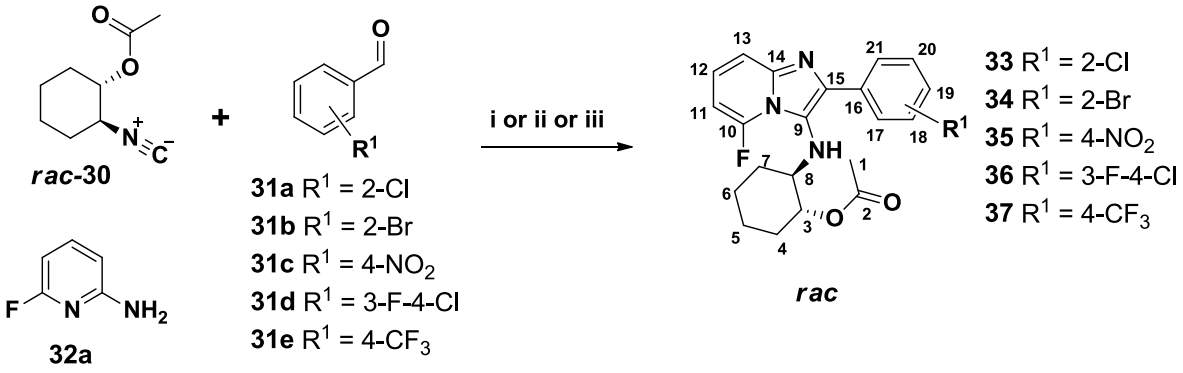
Table 6: Selected ^{1}H NMR and ^{13}C NMR spectroscopy signals for compound **30**

	H-C-N	H-C-O	CH_3	C=O	$^{+}N\equiv C^{-}$
^{1}H NMR	4.83 (td)	3.55 (td)	2.25-2.01	--	--
^{13}C NMR	55.11 (t)	73.35	31.27	169.97	155.51 (t)

The IR spectrum provided further confirmation of the successful synthesis of compound **30**. It revealed the absence of the formamide and N-H bands in the regions of 1630-1700 cm^{-1} and 3100-3400 cm^{-1}, respectively. The $^{+}N\equiv C^{-}$ functional group stretch was found at 2141 cm^{-1} and that of the acetate carbonyl was found at 1736 cm^{-1}. The molecular ion peak for **30** was confirmed by HRMS to be [M+H] 168.1017 and was consistent with the calculated mass for $C_7H_{14}NO_2$ of 168.1019.

2.1.2 Synthesis of amine 2-((phenyl)-imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate derivatives using compound 30

The next aim was to use **30** in the GBB reaction with **32a** and a range of benzaldehydes **31a-e** (**Scheme 22**).



Scheme 22: Reagents and conditions; (i) K-10 montmorillonite clay (250 mg), dioxane, 100°C, 120 Watts, 30 min.[35] (ii) 10 mol % iodine, methanol, room temperature, 24h.[36] (iii) K-10 montmorillonite clay (110 mg), dioxane, 100°C, 120 Watts, 30 min.

Compound **30** was used in the GBB multicomponent reaction using three sets of conditions (**Scheme 22**). The first reaction was performed under microwave irradiation in the presence of K-10 montmorillonite clay (250 mg) in a sealed microwave tube for 30

minutes.[35] The K-10 clay was filtered over celite and washed with ethyl acetate. The ethyl acetate was removed *in vacuo* and the resulting residue was purified by flash silica gel column chromatography and novel compounds **33**-**35** were successfully obtained albeit in poor yields (Table 7).

Table 7: Yields for compounds **33-37** according to method/reaction conditions

Compound	Method: Scheme 22.(i)	Method: Scheme 22.(ii)	Method: Scheme 22.(iii)
33	28%	28%	54%
34	27%	15%	27%
35	6.0%	--	25%
36	--	--	< 25%
37	--	--	< 7.0%

In an attempt to improve the reaction yields, the GBB reaction was then performed at room temperature for 24 h in the presence of catalytic amounts of iodine. The methanol was removed *in vacuo* and the residue purified by flash silica column chromatography.[36] This method was found to be successful only for the synthesis of compounds **33** and **34**, but resulted in no yield improvement for compound **33** and led to a reduction in yield for compound **34**. One of the factors that could have been a major contributor to these reactions being so low yielding was the weak nucleophilicity of the aminopyridine. Fluorine has a high electronegativity, and its presence on the aminopyridine reduces the electron density of the ring and consequently leaves the amine with reduced electron density, making it a weaker nucleophile. Hence its participation in the addition reaction at the carbonyl is reduced, which also provides room for competing reactions, and thus contributes to the reactions being low yielding.

One other factor that we took into account and decided to explore was the amount of catalyst used in method (i), and we thus investigated the effects of K-10 montmorillonite clay on the reaction. The GBB reaction was performed in a sealed tube under microwave irradiation for 30 minutes in the presence of reduced amounts of K-10 montmorillonite, from 250 mg to 110 mg. The K-10 clay was filtered over celite and washed with ethyl

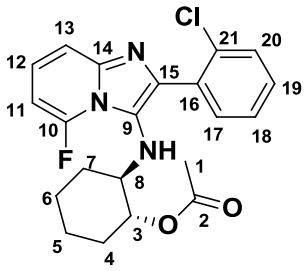
acetate. The solvent was removed *in vacuo* and the resulting residue was purified by flash silica column chromatography. This resulted in a 2-fold increase in the yield for compound **33**. No improvement was observed for compound **34**, but the yield for compound **35** was improved by approximately 5-fold (Table 7).

Upon seeing these improvements, we decided to synthesize **36** and **37** using these reaction conditions. However, isolating these products proved to be a difficult process, as column chromatography failed to successfully separate both novel compounds **36** and **37** from one of the byproducts generated by the reaction. NMR spectroscopy data revealed that this byproduct was the same for both **36** and **37**, but could not be clearly identified or elucidated. Further purification using preparatory thin layer chromatography (prep-TLC) was attempted, but we found that both compounds decomposed during this process. Furthermore, **37** was found to decompose when it was left in solution for at least an hour and a half, and this prevented us from obtaining the ^{13}C NMR spectrum. The decomposition was observed when comparing the ^{1}H NMR spectra obtained immediately after preparing the sample and the one acquired after the sample had been standing for a few hours in solution. As a result of the challenges that arose from attempting to purify compounds **36** and **37**, the NMR data for both desired products is reported as a mixture with their corresponding byproduct (which is the same for both compounds).

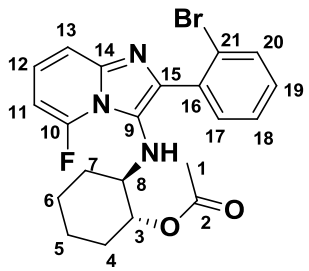
The successful synthesis of the novel compounds **33-37** was confirmed by NMR spectroscopy, and the NMR data obtained revealed a special characteristic of fluorine containing compounds. It was observed that the fluorine nuclei showed coupling (including *long range coupling* in ^{13}C NMR spectra) to hydrogen and carbon nuclei. This phenomenon is due to the fluorine nuclei having a spin half, and fluorine being a monoisotopic element, which means it has a relative abundance of 100%.[97] Key signals from the ^{1}H and ^{13}C NMR spectra for compounds **33**-**37** are shown in Table 8 and 9, respectively.

In the ^{1}H NMR spectra for compounds **33** and **34** (**Figure 22**), the H-11 proton gave rise to a signal at 6.38 ppm in compound **33**, and at 6.39 ppm for compound **34** (Table 8). This assignment was confirmed by the multiplicity of the signals; they appear as a triplet of doublets instead of a doublets of doublets. This is due to the presence of the fluorine

ortho to the H-11 proton, which couples to it the same way a proton would. The coupling constant *J* of the H-11 proton to the fluorine and to H-12 are equal at 7.2 Hz for **33** and 9.7 Hz for **34**, hence they split H-11 signal into a triplet, followed by the H-13 coupling, consequently giving a multiplicity of triplets of doublets. The signals found at 3.54 ppm and 3.52 ppm for **33** and **34**, respectively, were assigned to the N-H proton. The H-3 proton gave rise to signals at 4.58 ppm for compound **33**, and 4.59 ppm for compound **34**.



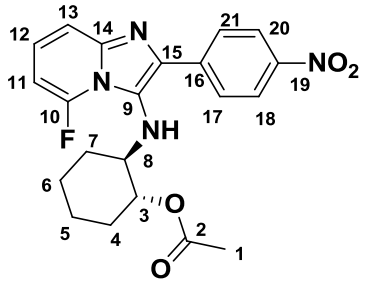
***rac*-33**



***rac*-34**

Figure 22

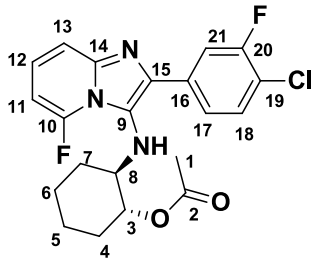
The ^{13}C NMR spectroscopy undoubtedly confirmed the synthesis of both compounds. The C-10 carbon atom gave a doublet signal at 150.55 ppm (*J* = 267.9 Hz) for **33**, and 150.55 ppm (*J* = 267.8 ppm) for **34** (Table 9). Long range carbon-fluorine coupling was also observed in both compounds, with carbon C-11 (*J* = 17.3 Hz for **33** and *J* = 17.4 Hz for **34**), C-12 (*J* = 6.5 Hz), and C-13 (*J* = 5.1 Hz) all appearing as doublets. As expected the coupling constant reducing with the increase in distance (i.e. number of bonds) of the carbon atoms from the fluorine atom. The C-3 carbon atoms gave signals at 76.39 ppm and 76.36 ppm for compound **33** and **34**, respectively, and the signals at 143.67 ppm (*J* = 3.2 Hz) and 143.47 ppm (*J* = 3.3 Hz) were assigned to C-14 for compound **33** and **34**, respectively. The IR spectra confirmed the presence of the N-H and C=N signals at 3352 and 1651 cm^{-1}, respectively, for both compounds. The molecular ion for both compounds were detected using HRMS, they were found to be [M+H] 402.1400 for **33** consistent with the calculated mass for $C_{21}H_{22}ClFN_3O_2$ of 402.1379, and to be [M+H] 446.0898 for **34**, similar to the calculated mass of 446.0874 for $C_{21}H_{22}{}^{79}BrFN_3O_2$.



***rac*-35**

Figure 23

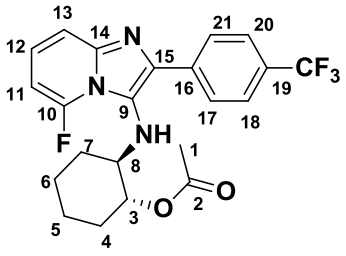
We were able to confirm the formation of compound **35** (**Figure 23**) by ^{1}H and ^{13}C NMR spectroscopy. Proton H-11 with its characteristic multiplicity of triplet of doublets due to the coupling with the fluorine atom was evident at 6.41 ppm (Table 8). The N-H proton was assigned to the signal at 3.66 ppm. The symmetry of the nitro-phenyl component in the molecule was seen by the equivalent signals of H-17 and H-21 at 8.31-8.26 ppm, and those of H-18 and H-20 at 8.53-8.49 ppm. In the ^{13}C NMR spectrum, the C-10 carbon atom which was supposed to have a multiplicity of a doublet as a result of the coupling with fluorine was not detected but its presence was confirmed by the coupling to carbon atoms C-11 at 93.46 ppm with J = 17.6 Hz, C-12 at 125.34 ppm with J = 6.8 Hz, and C-13 at 114.18 ppm with J = 4.9 Hz that all appeared as doublets. The C-14 carbon atom signal was evident at 144.07 ppm, and the C-19 (C-NO_2) carbon atom gave rise to the signal at 146.76 ppm (Table 9). The IR spectrum also supported that **35** was obtained: it revealed a signal corresponding to a C=N stretch at 1652 cm^{-1}, and that of the N-H functional group at 3367 cm^{-1}. The molecular ion peak for **35** was confirmed by HRMS to be [M+H] 413.1650 and was consistent with the calculated mass for $C_{21}H_{22}FN_4O_4$ of 413.1620.



***rac*-36**

Figure 24

The ^{1}H NMR spectrum of **36** (**Figure 24**) clearly confirmed its successful synthesis although the spectrum showed contamination with an unidentified byproduct. For compound **36** the N-H proton signal was observed at 3.51 ppm. Both protons H-11 and H-21 showed coupling to the fluorine atoms *ortho* to them, H-11 was found as a triplet of doublets at 6.37 ppm (*J* = 7.2, 0.9 Hz), and H-21 was found as a doublet of doublets at 8.18 ppm (*J* = 11.0, 1.9 Hz) (Table 8). The ^{13}C NMR spectrum revealed that C-10 and C-20 coupled to the fluorine atoms they were bonded to. Carbon C-10 was matched to the doublet at 150.47 ppm (*J* = 265.3 Hz), and C-21 was assigned to the doublet at 158.35 (*J* = 246.6 Hz). Both fluorine atoms were found to couple to a number of carbon atoms: C-11 at 93.22 ppm (*J* = 11.7 Hz), C-12 at 124.91 ppm (*J* = 6.7 Hz), C-13 at 113.91 (*J* = 5.0 Hz), C-17 at 123.68 ppm (*J* = 3.6 Hz), C-19 at 119.80 ppm (*J* = 17.9 Hz), and C-21 at 115.26 ppm (*J* = 23.2 Hz).The C-14 and C-2 carbon atoms gave rise to signals at 143.82 ppm (*J* = 3.6 Hz) and 170.84 ppm, respectively (Table 9). The IR spectrum also revealed that the bands due to C=N and N-H functional groups were at 1655 cm^{-1} and 3302 cm^{-1}, respectively. The HRMS detected the molecular ion peak for **36** to be [M+H] 420.1314 and this corresponded with the calculated mass for $C_{21}H_{21}F_2N_3O_2$ of 420.1285.



***rac*-37**

Figure 25

Similar to compound **36**, we were unable to completely purify compound **37** (**Figure 25**), but we were able to distinguish between signals of **37** and those corresponding to the impurity. The N-H proton in the ^{1}H NMR spectrum gave rise to a signal at 3.57 ppm, and the signal due to the H-11 proton was found as a triplet of doublets at 6.38 ppm. The H-3 and H-8 proton gave rise to the signals that integrated for one proton each at 4.78 ppm and 3.13-3.05 ppm, respectively (Table 8). We were unable to obtain viable ^{13}C NMR data as some quaternary carbon atoms could not be elucidated, and we also found that the compound did not remain stable long enough to acquire the ^{13}C NMR data. However, we were able to use the COSY NMR spectroscopy data to corroborate the successful synthesis of **37**. The IR spectrum also provided additional evidence: the N-H moiety was found at 3487 cm^{-1} and the C=N functional group gave rise to a peak at 1655 cm^{-1}. The molecular ion peak for compound **37** with a calculated mass of 436.1603 was found to be [M+H] 436.1643 from HRMS.

Table 8: Selected ^{1}H NMR spectroscopy signals for compounds **33-37** and their multiplicity

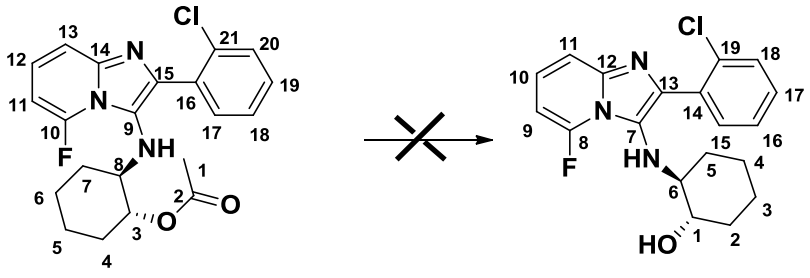
Compound	N-**H**	H-3	H-8	H-1	H-11
33	3.54 (d)	4.58 (td)	2.85-2.84 (m)	1.92 (s)	6.38 (td)
34	3.52 (d)	4.59 (td)	2.86-2.85 (m)	2.01-1.85 (s)	6.39 (td)
35	3.66 (d)	4.79 (td)	3.14-3.03 (m)	1.94 (s)	6.41 (td)
36	3.51 (d)	4.78 (td)	3.17-2.98 (m)	1.95 (s)	6.37 (td)
37	3.57 (d)	4.78 (td)	3.13-3.05 (m)	1.93 (s)	6.38 (td)

Table 9: Selected ^{13}C NMR spectroscopy signals for compounds **33-36**

Compound	C-2	C-3	C-8	C-10	C-14	C-R
33	170.74	76.39	60.83	150.55 (d)	143.67 (d)	126.08 (C-Cl)
34	170.73	76.36	60.78	150.55 (d)	143.47 (d)	123.58 (C-Br)
35	170.71	77.37	61.34	Undetected	144.07 (d)	146.76 ($C-NO_2$)
36	170.84	71.48	61.22	150.47 (d)	143.82 (d)	119.80 (d, C-Cl)

2.1.3 Attempted synthesis of 2-((2-phenyl)-5-fluoroimidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexanol

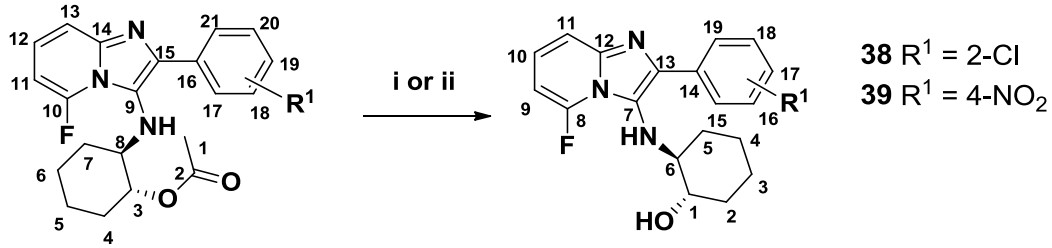
Once compounds **33-37** were successfully synthesized, they had to be subjected to a hydrolysis reaction in order to liberate the hydroxyl functional group. The hydrolysis of **33** had been attempted before in an in-house research project at University of the Witwatersrand. It was found that the treatment of **33** with potassium carbonate (K_2CO_3) in methanol (**Scheme 23**) did not give the corresponding hydroxyl group-containing compound, but led to the isolation of unexpected products.



Scheme 23: Attempted hydrolysis of compound **33**

One of our aims was to investigate and expand on this work, so compounds **33**-**37** were treated with K_2CO_3 in methanol (MeOH) for a 24 h period (**Scheme 24**). The methanol

was then removed i*n vacuo* and the crude material was purified using flash silica gel column chromatography. NMR and IR spectroscopy data revealed that compound **33** appeared to have been successfully hydrolysed, but the hydrolysis of compounds **34-37** was unsuccessful. In the attempted hydrolysis of compounds **34**-**35** only the starting material was retrieved from the reaction, while compounds **36**-**37** appeared to decompose as no starting material or identifiable material was obtained from the reaction. It was evident that K_2CO_3 was not the best choice for hydrolysing these compounds, so we explored the use of a stronger base, KOH. Compounds **33**-**37** were treated with KOH in methanol at room temperature for 24 h, the methanol was removed *in vacuo* and the residue was purified using flash silica gel column chromatography. Compounds **34**, **36** and **37** were not successfully hydrolysed into their corresponding hydroxyl-containing compounds, but similar to when K_2CO_3 was used they appeared to decompose under these conditions because they were not retrieved from the reaction, and no identifiable (v*ia* NMR or IR spectroscopy) compounds were obtained.



38 R^1 = 2-Cl
39 R^1 = 4-NO_2

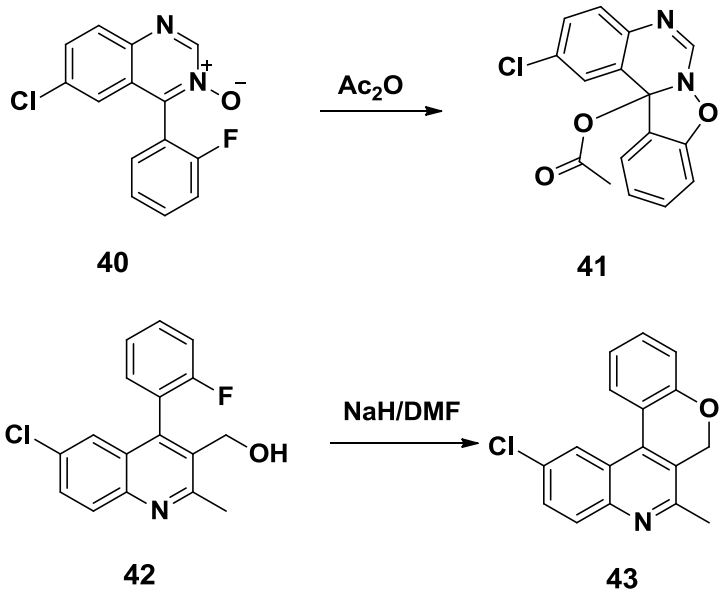
33 R^1 = 2-Cl, successful in both (i) and (ii)
34 R^1 = 2-Br, no reaction in (i), but decomposes in (ii)
35 R^1 = 4-NO_2, no reaction in (i) but successful in (ii)
36 R^1 = 3-Cl, 4-F, decomposes in both (i) and (ii)
37 R^1 = 2-CF_3, decomposes in both (i) and (ii)

Scheme 24: Hydrolysis: (i) K_2CO_3, MeOH, room temperature, 24 h. (ii) potassium hydroxide (KOH), MeOH, room temperature, 24 h.

Although **33** and **35** appeared to successfully undergo the hydrolysis reaction to give compounds **38** and **39**, the IR data for products of both compounds had no evidence of the hydroxyl or acetate functional groups. Furthermore, the ^{1}H NMR spectra for both products revealed that the H-9 protons (i.e *ortho* to fluorine) in each case appeared as a doublet of doublets, instead of a triplet of doublets. The ^{13}C NMR spectra also revealed that there were no carbon atom signals that had any doublet multiplicity as a result of

C-F coupling. This strongly suggested that **33** and **35** were successfully hydrolysed, but not into compounds **38** and **39**, respectively.

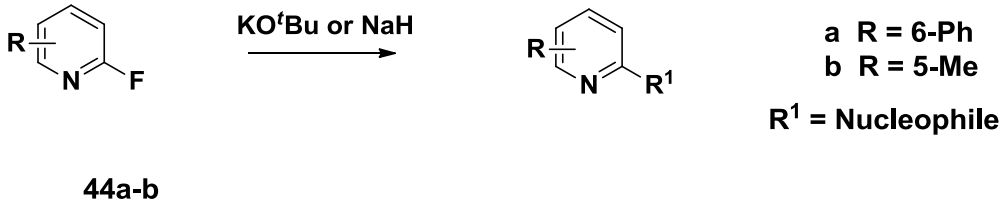
It was clear from the NMR spectroscopy data that the fluorine atom was not present in the products obtained and thus suggested either a nucleophilic substitution/displacement reaction or an elimination reaction had occurred. A nucleophilic substitution was the most likely reaction due to the nature of the C-F bond. The carbon atom C-10 in both compounds is very electrophilic due to the high electronegativity possessed by the fluorine atom. Although no facile displacement of fluorine in imidazo[1 2-*a*]pyridine-3-amines has been specifically reported in literature, it has been reported for other aromatic compounds under various reaction conditions. One such example was reported by Walser *et al.,* where they treated the *N*-oxide **40** with acetic anhydride, and this led to a ring closing reaction (i.e formed a 5-membered ring) that is a consequence of an intramolecular facile displacement of fluorine in order to obtain compounds **41** (**Scheme 25**). [98]



Scheme 25: Intramolecular nucleophilic displacement of fluorine

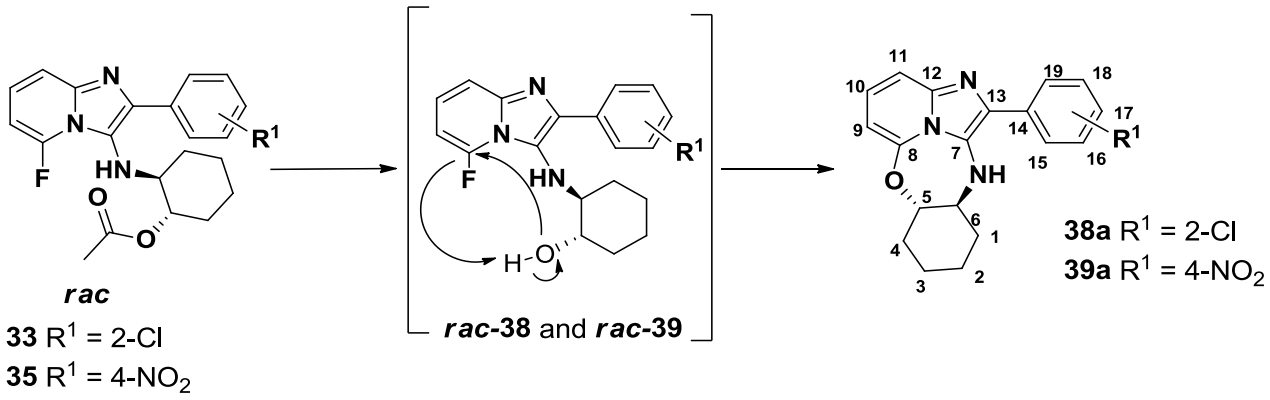
Furthermore, they observed and reported that the treatment of alcohol **42** with sodium hydride (NaH) led to a ring closing (6-membered ring) intramolecular facile displacement reaction of fluorine to give compound **43** (**Scheme 25**).[99] Apart from the intramolecular displacement reactions of fluorine, Fier and co-workers investigated and reported the

successful nucleophilic displacement of fluorine after treating 2-fluoropyridines (**44a-b**) with a series of nucleophiles in the presence of an appropriate base to give a small library of compounds (**Scheme 26**).[100]



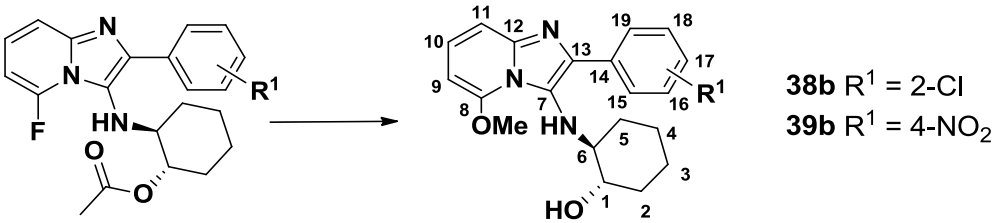
Scheme 26: Nucleophilic displacement of fluorine

So given the "precedence" set by these reactions, and data from the IR and NMR spectra of our compounds, it is essential to identify the nucleophile that displaced the fluorine atom during the hydrolysis reaction. We took into consideration the reaction conditions, and they suggested that there were three possible nucleophiles that could participate in the displacement of the fluorine atom: (i) the carbonate (CO_3^-) ion, but in both the NMR or IR spectra the carbonate ion signals were not observed; (ii) Methanol, if the solvent took part in the reaction, a methoxy signal would be observed in the ^{1}H and ^{13}C NMR spectra, or (iii) the hydroxyl group could participate in the reaction after ester hydrolysis. The absence of the acetate signals in both the IR and ^{1}H NMR spectra of compound **38**-**39** suggested that an intramolecular nucleophilic aromatic substitution reaction with the hydroxyl group acting as a nucleophile had taken place. This meant that **38** and **39** were not the final products but intermediates that underwent an intramolecular reaction to give the 7-membered ring compounds **38a** and **39a** in relatively poor yields (**Scheme 27**).



Scheme 27: Intramolecular substitution reaction

However, **38a** and **39a** were not the only compounds isolated from the hydrolysis reaction. The thin layer chromatography (TLC) of the crude reaction mixtures from the hydrolysis of **33** and **35** using KOH indicated that there were two products generated during the reaction. These second sets of compounds were isolated and their characterization revealed a competing reaction which also involved the hydrolysis of the acetate, and the displacement of the fluorine atom.The presence of the methoxy signal in the ^{1}H NMR spectra suggested that the fluorine atom had undergone a nucleophilic aromatic substitution reaction with methanol as a nucleophile (**Scheme 28**).



33 R^1 = 2-Cl
35 R^1 = 4-NO_2

38b R^1 = 2-Cl
39b R^1 = 4-NO_2

Scheme 28: Competing nucleophilic substitution and hydrolysis reactions

Furthermore, the absence of the acetate signals in the ^{1}H NMR spectra also suggested that the acetate was successfully hydrolyzed. The evidence strongly indicated that we had isolated compounds **38b** and **39b**. However, compound **38b** was found to rapidly decompose, and the proton NMR spectrum was obtained for the crude product, but we cannot report the data. Compound **39b** was found to be stable, and IR spectroscopic analysis on it revealed that the hydroxyl group was present. Compounds **38a-b** and **39a-b** are novel compounds that were isolated in relatively poor yields (Table 10), and KOH proved to be a better choice as a hydrolyzing agent than K_2CO_3.

Table 10: Yields of compounds **38a-b** and **39a-b** according to hydrolyzing agent

Compound	K_2CO_3	KOH
38a	10 %	39 %
38b	~22 %	~46 %
39a	--	28 %
39b	--	41 %

Compound **38a** has not been previously reported in the literature, and its ^{1}H NMR spectroscopy data summarized in Table 11, revealed the N-H proton was at 3.86 ppm. The absence of the fluorine was verified by the multiplicity of the H-9 proton at 6.23 ppm. The multiplicity changed from a triplet of doublets in the presence of fluorine, to a doublet of doublets, confirming the absence of the fluorine (**Figure 26**). The signal for the **H**-C-N (H-6) proton in **38a** was found at a more deshielded position of 3.42 ppm compared to its more shielded position of 2.84 ppm (H-8) in its parent compound **33**. Furthermore, for the **H**-C-O (H-3) proton in the parent compound **33** had a slight change in chemical shift from 4.58 ppm to a lower chemical shift of 4.13 ppm (H-5) in compound **38a** (**Figure 26**).

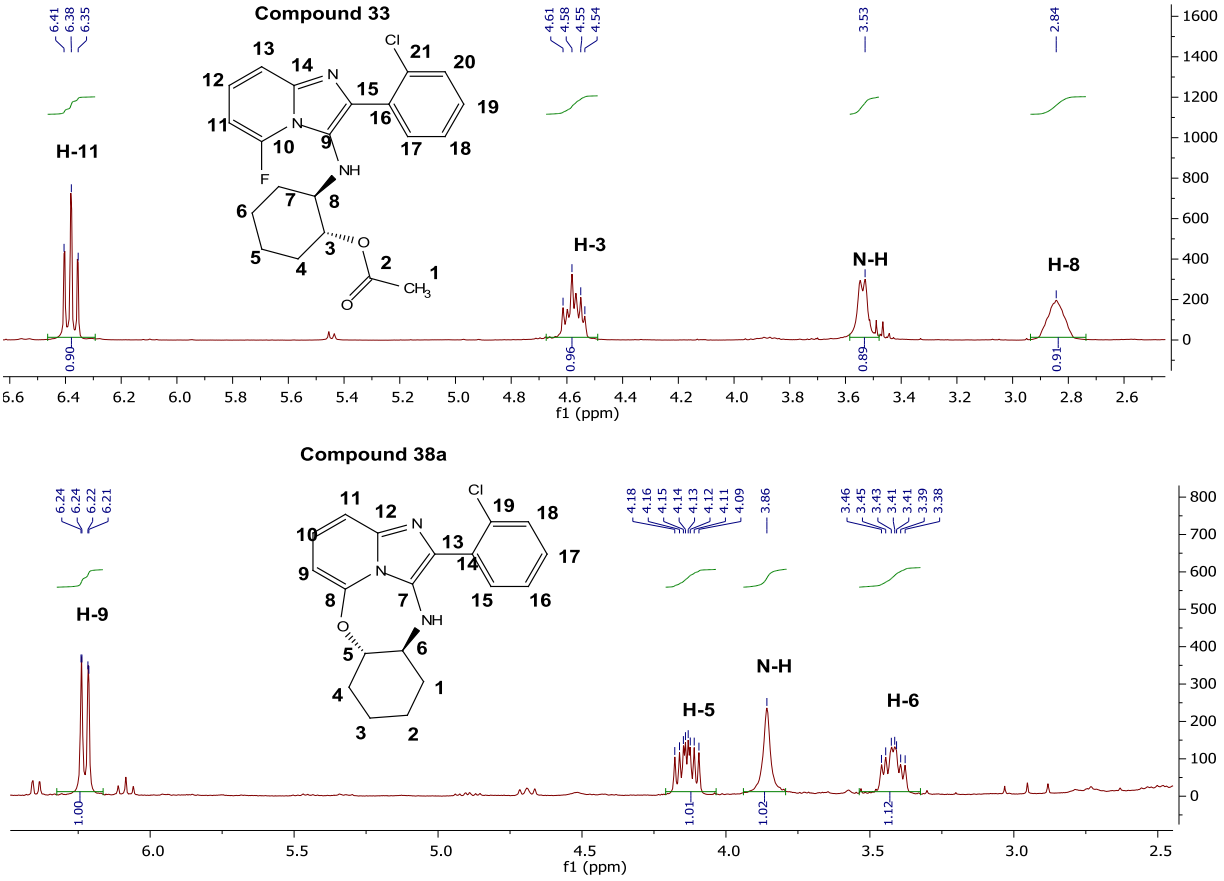


Figure 26: selected regions of ^{1}H NMR spectra of compounds **33** and **38a**

In the ^{13}C NMR spectrum of **38a**, the data of which is summarized in Table 12, the C-8 carbon was found at a much lower than expected chemical shift of 147.57 ppm compared

to a more deshielded position of approximately 149-151 ppm when it is bonded to a highly electronegative fluorine atom (C-10 in **33**). Not only do we expect a higher chemical shift for a C-F carbon atom, but the signal also does not show any evidence of C-F coupling, as it appears as a singlet instead of a doublet (**Figure 27**). The previously observed long range coupling of fluorine to carbon atoms C-9 (C-11 in **33**) at 96.57 ppm, C-10 (C-12 in **33**) at 124.33 ppm, and C-11 (C-13 in **33**) at 111.72 ppm was also absent as their signals appeared as singlets instead of doublets. The spectrum also revealed a change in chemical shift for the H-**C**-O (C-3) in compound **33** from 76.38 ppm to a more deshielded position of 88.40 ppm (C-5) in compound **38a**. The H-**C**-N (C-8) carbon atom in compound **33** experienced a shift from a less shielded position of 60.83 ppm to a slightly less shielded position of 60.37 ppm (C-6) in **38a** (**Figure 27**).

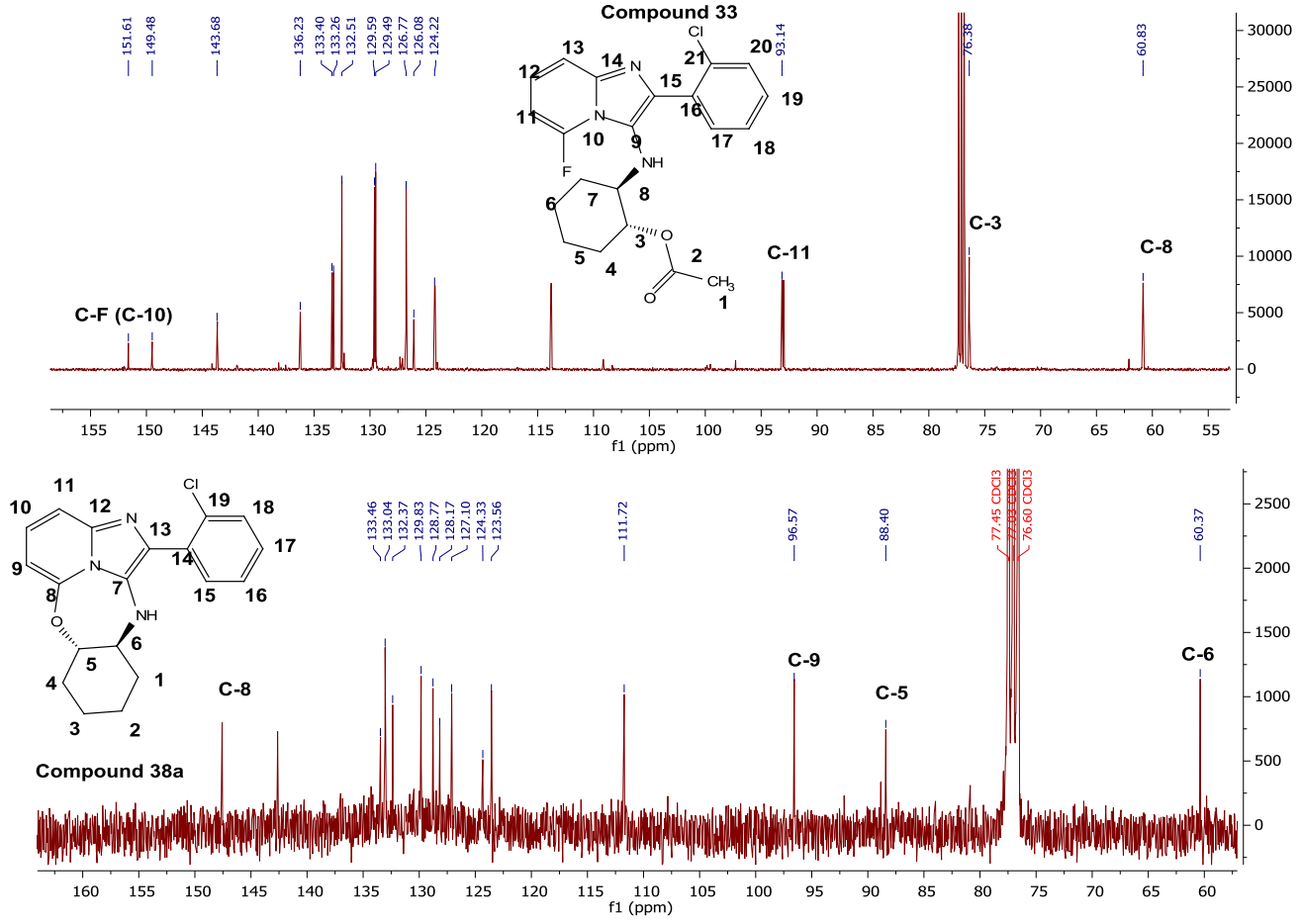


Figure 27: selected regions of ^{13}C NMR spectra of compounds **33** and **38a**

The C=N stretch in the IR spectrum of **38a** was assigned to the signals at 1638 cm^{-1}, and the N-H functional group was found at 3301 cm^{-1}. Formation of **38a** was further confirmed by HRMS, where the molecular ion peak was found to be [M+H] 340.1181 which is in agreement with the calculated mass of 340.1211 for $C_{19}H_{19}ClN_3O$.

Table 11: Selected ^{1}H NMR spectroscopy signals for compounds **38a** and **39a-b**, and their multiplicity

Compound	N-**H**	H-5	H-6	H-9	H-1
38a	3.86 (s)	4.14 (ddd)	3.42 (ddd)	6.23 (dd)	**
39a	2.93 (dt)	4.72 (dd)	2.65 (ddd)	6.40 (dd)	**
39b	3.88-3.65 (m)	1.51-1.46 and 1.05-0.93 (m)	2.88-2.69 (m)	5.97 (dd)	3.52 (dt)

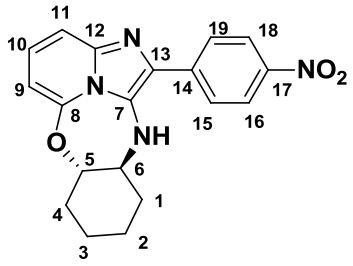
**Cyclohexyl protons that could not be unequivocally determined

Table 12: Selected ^{13}C NMR spectroscopy signals for compounds **38a** and **39b**

Entry	H-**C**-O	C-6	C-8	C-12	**C**-R^1
38a	88.40 (C-5)	60.37	147.57	142.63	128.17 (C-Cl)
39b	75.22 (C-1)	65.52	152.05	144.05	146.30 (C-NO_2)

Compound **39a** (**Figure 28**) was isolated as a yellow oil, but the amount that was isolated was only sufficient to obtain ^{1}H NMR data. The obtained ^{1}H NMR data (Table 11) supports that the isolated compound is **39a**, but it was not sufficient to conclude this without a doubt. Even so, the ^{1}H NMR confirmed the absence of the fluorine atom by revealing that the multiplicity of the H-9 proton at 6.40 ppm was a doublet of doublet, instead of a triplet of doublets that would have been observed in the presence of a fluorine *ortho* to H-9. It also confirmed the absence of the acetate functional group, and the signal for the **H**-C-N (H-6) proton in **39a** was observed at a more shielded position of 2.65 ppm relative to its less shielded position of 3.14-3.03 ppm (H-8) in the parent compound **35**. The **H**-C-O (H-

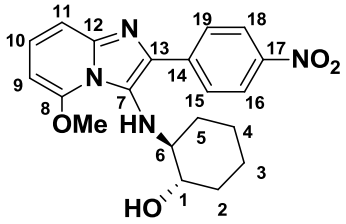
5) proton in compound **39a** had only a slight change in chemical shift from 4.72 ppm to 4.79 ppm (H-3) in compound **35**.



39a

Figure 28

The COSY NMR data also assisted in corroborating the assignment of N-H and the H-6 proton to signals at 2.93 ppm and 2.65 ppm, respectively. Interestingly it also revealed that the H-5 signal found at 4.72 ppm showed no coupling to H-6, although this is a rare phenomenon and it was not observed in compound **39a**. It might be that relative to each other, the two protons may have been arranged at a dihedral angle that prevents them from coupling to each other. This suggests a restricted ring system, and thus it might corroborate that the isolated compound might be **39a**. The IR data was also able to corroborate the absence of the acetate moiety, and it also revealed that the hydroxyl group was absent. Furthermore, it confirmed the presence of the C=N and N-H functional groups at 1676 cm^{-1} and 3348 cm^{-1}, respectively. The molecular ion peak for compound **39a** with a calculated mass of 350.1375 for $C_{19}H_{19}N_4O_3$, was found to be [M+H] 350.1317 in the HRMS. This revelation by the IR data, HRMS, together with data from the ^{1}H NMR spectroscopy about the absence/displacement of the fluorine, and the absence of the acetate group suggests that the hydroxyl group may have participated in an intramolecular reaction to give compound **39a**. However, ^{13}C NMR spectroscopy data is required to definitively prove the structure.



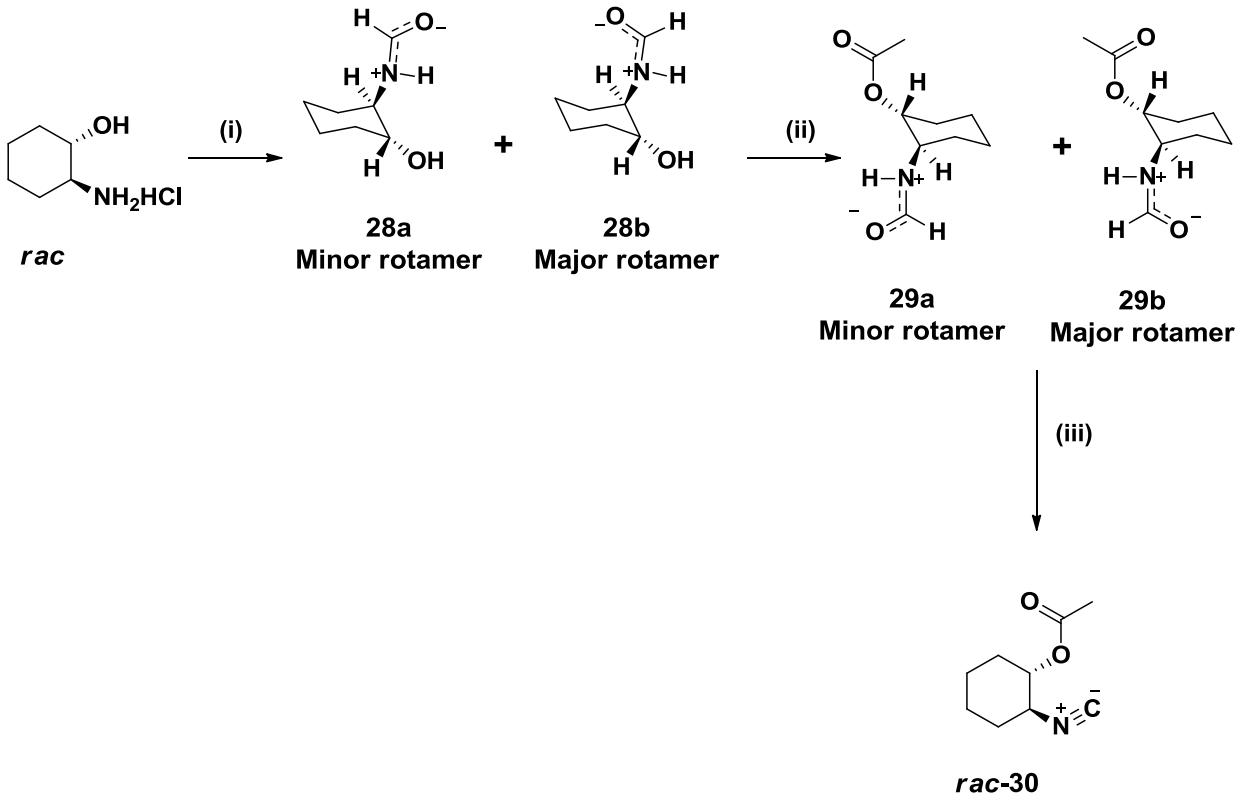
39b

Figure 29

In the case of compound **39b** (**Figure 29**), using ^{1}H NMR spectroscopy data (Table 11) we were able to confirm the displacement of the fluorine atom by the methoxy group (OMe) in the change of the multiplicity in the signal of H-9 at 5.97 ppm from a triplet of doublets to a doublet of doublets (with J = 7.2 Hz and 1.1 Hz). The OMe was identified as a singlet at 4.07 ppm, and both the O-H and N-H protons were found at 3.88-3.65 ppm. The signal at 3.52 ppm was assigned to the H-1 proton which is found at a more shielded position than in its parent compound **35**. The ^{13}C NMR spectrum was also able to provide more evidence for the displacement of the fluorine atom by revealing the C-8 carbon signal at 152.08 ppm as a singlet instead of a doublet which it would be if bonded to a fluorine atom. This absence of the carbon-fluorine coupling was also observed for C-9 at 88.55 ppm, C-10 at 125.92 ppm, and C-11 at 110.74 ppm (Table 12). More evidence for the successful hydrolysis was provided by the IR spectrum in which the absence of the acetate was revealed and the presence of the O-H was found at 3245 cm^{-1}. Furthermore, the N-H and C=N functional groups were found at 3347 cm^{-1} and 1638 cm^{-1} respectively. The molecular ion peak for the novel compound **39b** with a calculated mass of 383.1714 for $C_{20}H_{23}N_4O_4$ was found to be [M+H] 383.1717 by HRMS.

2.1.4 Conclusion

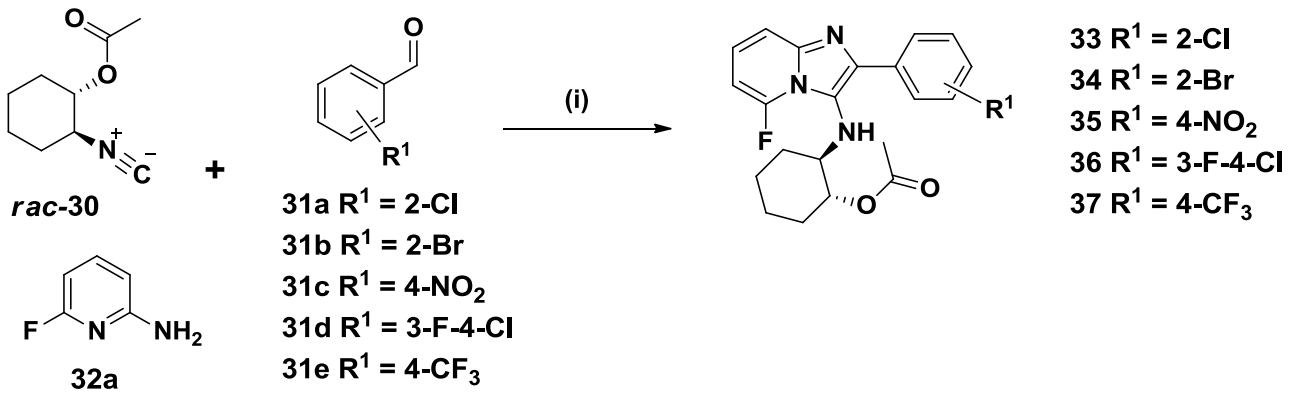
One of the aims of this section of the research was to synthesize a cyclohexyl isocyanide that was functionalized with a group that had H-bonding capabilities. The isocyanide was synthesized successfully in a three step synthetic method, beginning with the formylation of 2-hydroxylcyclohexylamine hydrochloride salt to give compound **28**, which existed as a mixture of rotamers **28a** and **28b** in solution. This was followed by an acetylation in order to protect the hydroxyl group from the subsequent dehydration of the formamide, and this also gave compound **29** that existed in solution as a mixture of rotamers **29a** and **29b** (**Scheme 29**).



Scheme 29: Synthesis of cyclohexyl isocyanide **30**

We were able to identify the structure of the rotamers using ^{1}H NMR spectroscopy, and also identify which rotamer exists as a major and minor rotamer as shown in Scheme **29**. The acetylated formamide **29** was used in a dehydration reaction to give the cyclohexyl isocyanide **30**. Three different dehydrating agents: $POCl_3$, Burgess reagent, and PPh_3 in

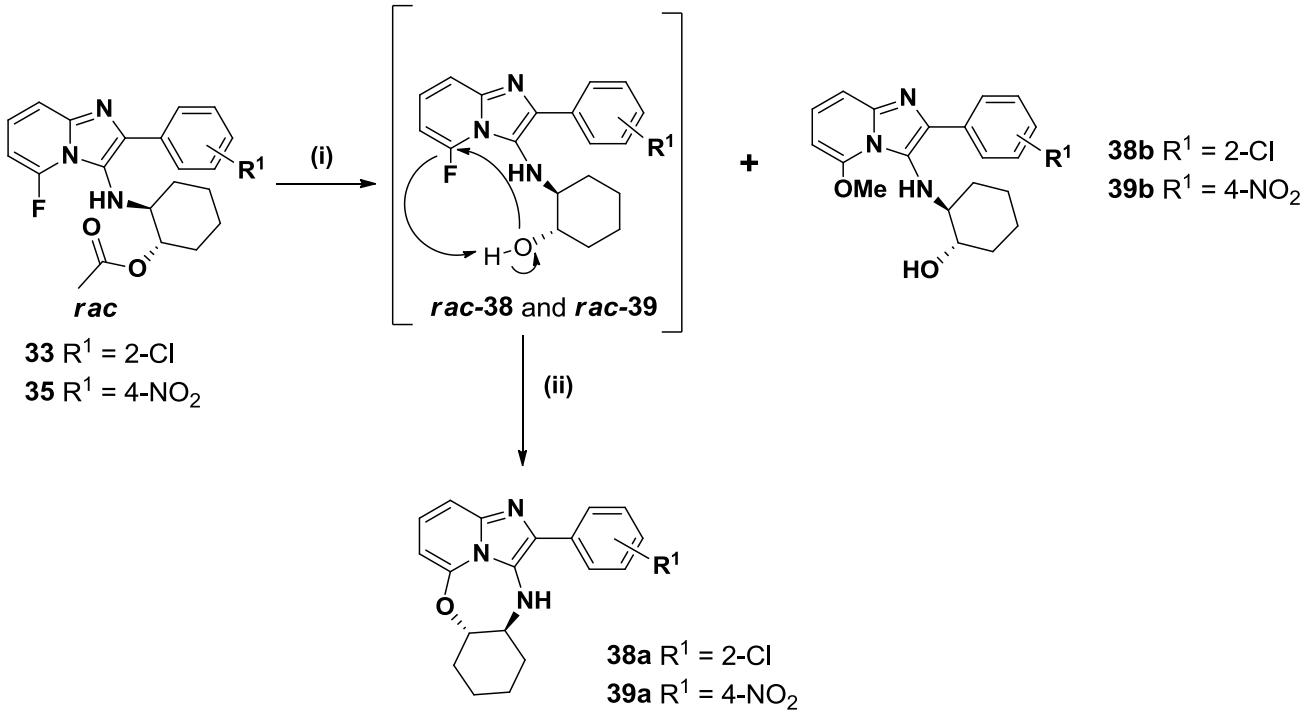
CCl_4 were used successfully for the transformation of compound **29** to compound **30**. The reaction conditions that required the use of $POCl_3$ and the Burgess reagent were found to pose a number of challenges, with the first being that the isocyanide obtained from these methods was not stable as it participated in an acid catalyzed addition of water and reverted to the starting material. The water was introduced during the work up of both reactions: in the $POCl_3$ method it was introduced when saturated $NaHCO_3$ was used to quench the reaction in order to remove the excess $POCl_3$, and the work up for the reaction in which the Burgess reagent was used involved a water wash of the reaction mixture. The method that used the Burgess reagent as a dehydrating agent was altered to remove the use of water in the work up process, and as a result it produced a stable isocyanide that did not participate in the addition reaction. It was also discovered that the method that used $POCl_3$ as a dehydrating agent could not be performed at a scale greater than 0.1 g of **28** without reducing the yield of compound **29** drastically. The use of PPh_3 in CCl_4 as a dehydrating agent gave an isocyanide that was stable in fair yields without having to alter the reaction conditions. However, the high yields ranging from 96-98% observed from using the Burgess reagent method identified it as the best dehydrating agent of choice in this case.



Scheme 30: Synthesis of 2-((phenyl)-imidazo[1,2-a]pyridin-3-yl)amino)cyclohexyl acetate derivatives

The obtained isocyanide was used in the GBB reaction to give 2-phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridine-3-amine derivatives in varying but poor yields. Three methods were explored to obtain these compounds: the first method was performed

under microwave irradiation in the presence of K-10 montmorillonite clay (250 mg) and it only gave **33**-**34** in low yields. The second method of choice was a conventional one, performed at room temperature in the presence of catalytic amounts of iodine for 24 hours, but this was only successful for **33**-**34**. The yields were found to remain the same for **33**, but were reduced by 50 % for **34**. The microwave reaction was revisited and the amount of catalyst K-10 montmorillonite clay used was reduced from 250 mg to 110 mg and the reaction performed under microwave irradiation, and this saw an increase in the yield for **33**, but no improvement for **34**. Compound **36** and **37** were isolated in yields less than 25% and 7% respectively. The yields were reported as approximations as we were unable to completely purify the despite numerous attempts. The yield of compound **35** was found to improve 5-fold from 6% to 25%.



Scheme 31: Hydrolysis reaction of 2-((phenyl)-imidazo[1,2-a]pyridin-3-yl)amino) cyclohexyl acetate derivatives

Once the 2-((phenyl)-imidazo[1,2-a]pyridin-3-yl)amino)cyclohexyl acetate derivatives were obtained they were placed in a hydrolysis reaction in order to liberate the H-bond donating hydroxyl group. Compounds **33**-**37** were treated with KOH in methanol, and out of the five compounds only **33** and **35** were successfully hydrolyzed. However, we

discovered that the liberated hydroxyl group in both compounds went on to participate in an intramolecular substitution reaction to give an 8-membered ring fused to the imidazo[1,2-*a*]pyridine scaffold. We were able to confirm the synthesis of compound **38a**, but we did not have enough data to unequivocally confirm the synthesis of compound **39a**. The hydrolysis reaction also revealed a competing reaction in which methanol, the reaction solvent, participated in a substitution reaction with the hydrolyzed compounds i.e. competing with the hydroxyl group intramolecular reaction to give compounds **38b** and **39b** (**Scheme 31**).

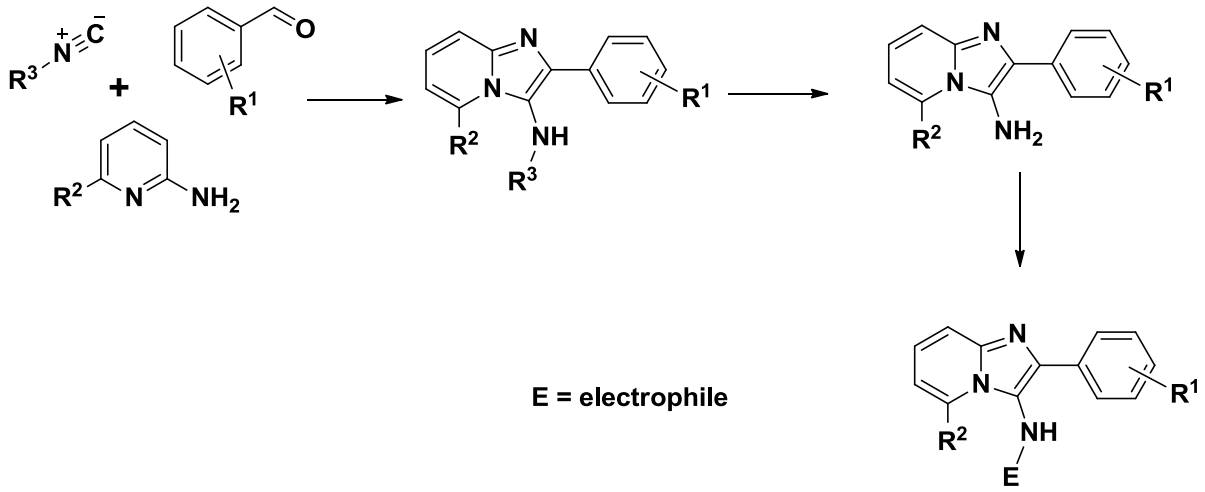
In conclusion, this part of the research revealed that we were able to synthesize a functionalized isocyanide, but it also highlighted some of the challenges with it. The isocyanide was successfully utilized in the GBB to produce 2-((phenyl)-imidazo[1,2-a]pyridin-3-yl)amino)cyclohexyl acetate derivatives, and an attempt to liberate the hydroxyl group for these compounds in a hydrolysis reaction led to a corroboration of the existence of an intramolecular substitution reaction that gave an 7-membered ring fused to the imidazo[1,2-*a*]pyridine scaffold. It also revealed a competing reaction in which the solvent of the reaction participated in a substitution reaction.

2.1.5 Future work

We successfully obtained a functionalized cyclohexyl isocyanide, so future work will include an expansion on the use of the isocyanide in the GBB reaction by producing more diverse products, and also improving the yields of the reaction. Two ways will be explored in an attempt to improve the yields of the reaction, and the initial exploration will include varying the amount of K-10 montmorillonite clay in the microwave GBB reaction, with the second one being the utilization of different catalysts ranging from Brønsted acids to Lewis acids. Furthermore, the hydrolysis reaction will also be investigated and expanded on, and once a 7-membered ring compound can be isolated as a solid it will be recrystallized and crystallographic data will be obtained to provide more evidence for the formation of the 7-membered ring compounds.

2.2 Development of methodology for the synthesis of phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine derivatives using a convertible isocyanide approach.

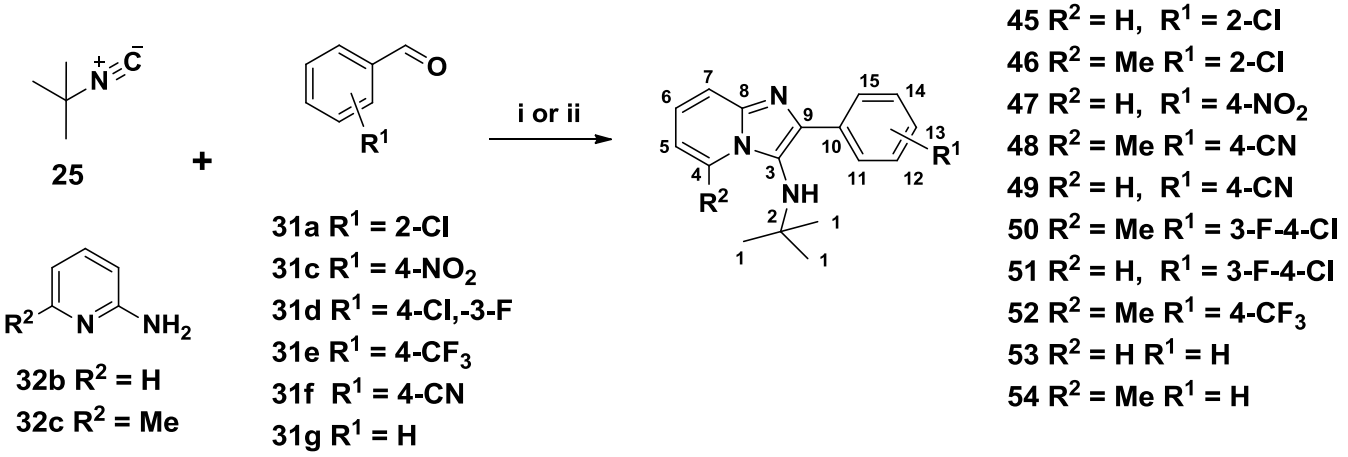
Chapter 1 highlighted the difficulty associated with the synthesis of isocyanides, and this was corroborated by our efforts to obtain **30** as discussed earlier in this chapter. As a result, this called for the development of a new methodology that does not require the synthesis of isocyanides, and more specific to our case, the synthesis of isocyanides functionalized with moieties that have hydrogen donating or acceptor abilities. In this section we will begin with a description of the methodology development where two convertible isocyanides were used in a GBB reaction in order to obtain a small library of imidazo[1,2-*a*]pyridine-3-amine derivatives. This will be followed by discussion of the dealkylation/deamination of the obtained derivatives to liberate the primary amine (NH_2) functional group. The final section details how the successfully dealkylated/deaminated derivatives were subsequently used in a reductive amination reaction with electrophiles to obtain the desired imidazo[1,2-*a*]pyridine-3-amine products (**Scheme 32**).



Scheme 32: Methodology development for the synthesis of imidazo[1,2-*a*]pyridin-3-amine derivatives

2.2.1 Synthesis of 2-(phenyl)-*N*-*tert*-butylimidazo[1,2-*a*]pyridin-3-amine derivatives.

The first step in overcoming the challenges associated with synthesizing functionalized isocyanides was to use convertible isocyanides to obtain the desired imidazo[1,2-*a*]pyridin-3-amine scaffolds using two different convertible isocyanides. The first convertible isocyanide of choice used was *tert*-butyl isocyanide **25**. It was utilized in the GBB reaction with different benzaldehydes **31a** and **31c-g**, and two different 2-aminopyridines **32b-c** (**Scheme 33**). Compounds **32b** and **32c** were used in this reaction because when they were utilized by Bode *et al.* to synthesize two 2-(2-(phenyl)imidazo[1,2-a]pyridin-3-yl)amino)cyclohexyl derivatives (**Figure 14**, **Chapter 1**, compounds **18** and **19**), they were found to have activity against HIV that is comparable to FDA approved nevirapine.[35] This makes them a useful "point of departure" in developing this methodology.



Scheme 33: Reagents and conditions: (i) K-10 montmorillonite clay (250 mg), dioxane, 100°C, 120 Watts, 30 min. (ii) 10 mol % iodine, methanol, room temperature, 24 h.[101]

tert-Butyl isocyanide was utilized in two GBB reaction methods. In the first method the reaction was performed under microwave irradiation in a sealed microwave tube for 30 minutes in the presence of K-10 montmorillonite clay. The resulting solution was filtered over celite to remove the K-10 montmorillonite clay. The solvent was removed *in vacuo* and the resulting residue was purified using column chromatography. Compounds **45**-**54** were successfully synthesized and isolated in good yields, with the exception of **48** and

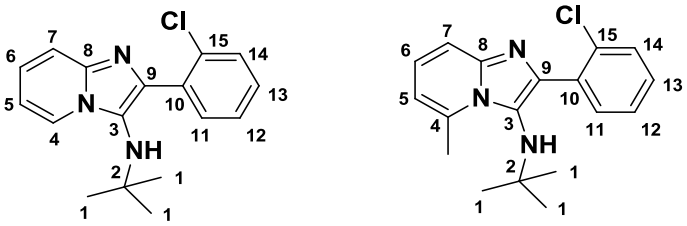
50 (Table 13). However, the general trend of the yields from this methodology corresponds to what is reported in literature.[35]

Table 13: Yields of **45**-**54** according to reaction conditions

Compound	Yield % {method; Scheme 33: (i)}	%Yield {method; Scheme 33: (ii)}
45	88	69
46	76	71
47	53	--
48	27	--
49	70	--
50	33	**
51	58	**
52	91	**
53	86	**
54	90	**

**Method; Scheme 33: (ii) was not used to obtain these compounds

For the second method the GBB reaction was performed in the presence of catalytic amounts of iodine in methanol at room temperature for 24 h for compounds **45**-**46**. The methanol was removed *in vacuo* and the obtained residues were purified using column chromatography. This method gave compounds **45** and **46** in good yields (Table 13). However, the method failed to successfully give compounds **47**-**49**, only starting material was obtained from the reactions. As a result method (i) was seen as a more viable synthetic route, and thus method (ii) was not utilized in the synthesis of compounds **50**-**54**.



45 **46**

Figure 30

^{1}H NMR and ^{13}C NMR spectroscopy data summarized in Table 14 and Table 15, respectively, were used to confirm the formation of **45** and **46** (**Figure 30**). The ^{1}H NMR spectra of both compounds revealed that the N-H functional group gave a signal at 3.20 ppm for **45**, and 2.98 ppm for compound **46**. Furthermore, the signals found at 0.93 ppm and 0.83 ppm were assigned to the *tert*-butyl functional group in compounds **45** and **46**, respectively. In compound **45** the presence of the hydrogen (H-4) *ortho* to the nitrogen atom was evident at 8.32 ppm. The methyl group *ortho* to the nitrogen in compound **46** was assigned to the signal at 2.98 ppm (Table 14). The ^{13}C NMR spectra also corroborated the formation of both compounds, and the C-8 carbon atom gave rise to signals at 142.22 ppm and 143.53 ppm in compound **45** and **46**, respectively. The C-15 carbon atom signals were found at 132.40 ppm for compound **45**, and 135.41 ppm for compound **46**. The C-2 carbon atom gave rise to the signal found at 55.79 ppm in **45**, and found at 55.59 ppm in **46** (Table 15). The differences in chemical shifts observed in both the ^{1}H NMR spectra and ^{13}C NMR spectra of these two compounds may be attributed to the presence of the electron donating methyl group present in compound **46**, which makes it 'electronically' different from compound **45**. The IR spectra for both compounds confirmed the presence of the N-H functional group for compound **45** at 3376 cm^{-1}, and 3361 cm^{-1} for compound **46**. The C=N (C-8) moiety gave rise to the bands at 1627 cm^{-1} for compound **45** and 1635 cm^{-1} for **46**. The NMR and IR data for both compounds **45** and **46** corresponds to data reported in the literature.[102]

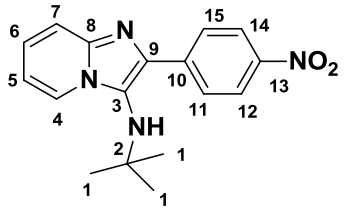
Table 14: Selected ^{1}H NMR spectroscopy signals for compounds **45**-**47** and their multiplicity

Compound	H-1	N-**H**	H-7	H-4	Ar-CH_3
45	0.93 (s)	3.20 (s)	7.54 (dt)	8.32 (dt)	--
46	0.83 (s)	2.98 (s)	7.46-7.40 (m)	--	2.98 (s)
47	1.09 (s)	3.04 (s)	7.55 (dt)	8.19 (dt)	--

Table 15: Selected ^{13}C NMR spectroscopy signals for compounds **45**-**47.**

Compound	C-2	C-1	C-8	C-R^2	C-3
45	55.79	29.89	142.22	132.40 (C-Cl)	137.62
46	55.59	29.53	143.53	135.41 (C-Cl)	139.12
47	56.82	30.51	142.57	146.69 (C-NO_2)	141.99

The ^{1}H NMR spectrum for compound **47** (**Figure 31**) revealed that the N-H functional group gave rise to the signal at 3.03 ppm. We also found that the protons H-11, H-12, H-14 and H-15 had all their signals overlap at 8.30-8.25 ppm. Furthermore, the signal at 1.09 ppm was assigned to the *tert*-butyl moiety, and the presence of the hydrogen *ortho* (H-4) to the nitrogen was evident at 8.19 ppm.

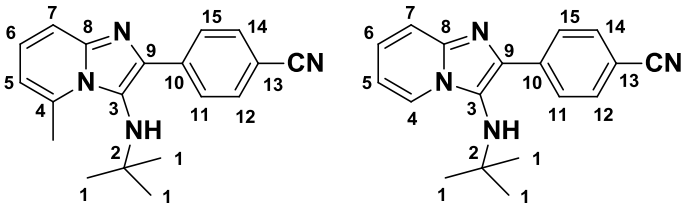


47

Figure 31

The ^{13}C NMR spectrum revealed that the C=N carbon atom gave rise to the signal at 142.57 ppm, and the most deshielded signal found at a chemical shift of 146.69 was assigned to the C-13 (C-NO_2) carbon atom (Table 15). The signal found at 123.57 ppm was assigned to the two equivalent carbon atoms, C-11 and C-15, and the other two equivalent carbon atoms, C-12 and C-14, gave rise to the signal at 128.42 ppm. A look at the IR spectrum revealed that the signal at 1633 cm^{-1} was a result of the C=N functional group, and the signal at 3358 cm^{-1} was assigned to the N-H functional group. Comparison of this data to that reported in literature for compound **47** corroborates its successful preparation.[103]

The ^{1}H NMR spectra (Table 16) confirmed the successful preparation of compounds **48** and **49** (**Figure 32**) by revealing the presence of the N-H functional group that gave rise to the signal that appears as a singlet at 2.95 ppm for **48**, and 3.02 ppm for **49**. The equivalent protons H-12 and H-14 gave rise to the most deshielded signal that appeared at 8.05-7.99 ppm and 8.22-8.13 ppm for **48** and **49**, respectively. The *tert*-butyl (H-1) moiety was clearly visible at 0.89 ppm for **48**, and at 1.07 ppm for **49**.



48 **49**

Figure 32

In the ^{13}C NMR data summarized in Table 17, the signal due to the *tert*-butyl group was evident at 29.67 ppm and 30.47 ppm for compound **48** and **49**, respectively. The C-8 carbon atom gave rise to the most deshielded signal at 143.74 ppm for **48**, and at a slightly lower chemical shift of 142.45 ppm in **49**. The characteristic C≡N carbon atom was evident at 119.11 ppm for compound **48**, and 119.92 ppm for compound **49** (Table 17). The IR stretch due to the C=N functional group was found at 1630 cm^{-1} and 1631 cm^{-1} for compound **48** and **49**, respectively. The N-H moiety gave rise to the signal at 3369 cm^{-1} for compound **48**, and 3280 cm^{-1} for compound **49**, and the C≡N functional group gave rise to a band that was found at 2225 cm^{-1} and 2227 cm^{-1} for **48** and **49**, respectively. The molecular ion peak for both compounds was confirmed by HRMS to be [M+H] 305.1771 for **48**, consistent with the calculated mass for $C_{19}H_{21}N_4$ of 305.1761, and to be [M+H] 291.1617 for **49** similar to the calculated mass of 291.1604 for $C_{18}H_{19}N_4$. Compound **48** is a novel compound, but the spectroscopic data obtained for compound **49** corresponds to the data reported in literature.[104]

Table 16: Selected ^{1}H NMR spectroscopy signals for compounds **48**-**51** and their corresponding multiplicity

Compound	H-1	N-**H**	H-15	H-4	H-14 and/or H-12
48	0.89 (s)	3.04 (s)	7.71-7.69 (m)	--	8.05-7.99 (m)
49	1.07 (s)	3.02 (s)	7.71-7.66 (m)	8.22- 8.13 (m)	8.22-8.13 (m)
50	0.90 (d)	2.98 (s)	7.70 (dd)	--	7.46-7.38 (H-12, m)
51	1.08 (s)	2.95 (s)	7.87 (dd)	8.17 (dd)	7.46-7.38 (H-12, t)

Table 17: Selected ^{13}C NMR spectroscopy signals for compounds **48**-**51**

Compound	C-2	C-1	C-8	C≡N	C-3	C-14
48	56.88	29.67	143.74	119.11	140.55	132.06
49	56.73	30.47	142.45	119.92	139.96	132.02
50	56.77	29.72	143.39	--	139.32	158.02 (d)
51	56.60	30.48	142.19	--	137.44	158.00 (d)

The successful synthesis of novel compounds **50** and **51** (**Figure 33**) was confirmed by their ^{1}H NMR spectra (Table 16). The signals at 2.98 ppm and 2.95 ppm were assigned to the N-H proton in compounds **49** and **50**, respectively. The *tert*-butyl moeity (H-1) appeared at 0.90 ppm for **49** and 1.08 ppm for **50**. The presence of the fluorine atom in both compounds gave rise to hydrogen-fluorine coupling; so the signal with a multiplicity of doublet of doublets found at 7.70 ppm (J = 10.4, 1.9 Hz) was assigned to the H-15 proton in compound **49,** and the signal at 7.87 ppm (J = 10.6, 1.9 Hz) with the same multiplicity was also assigned to the H-15 proton in compound **50.** Both assignments were justified using the COSY NMR spectra, which revealed that both signals coupled to only one proton (H-11) even though they had doublet of doublet multiplicities, thus corroborating that both signals are due to the H-15 proton.

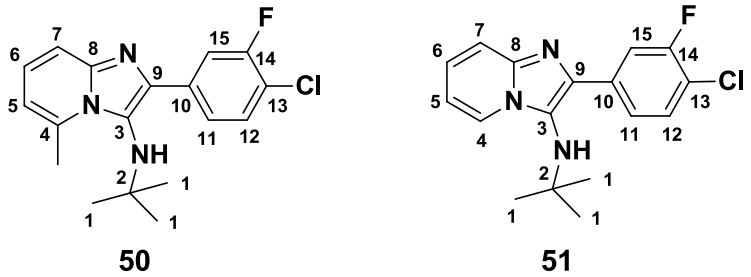
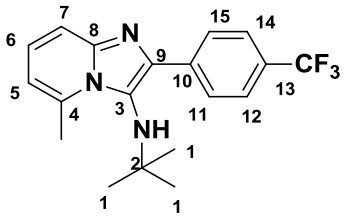


Figure 33

The ^{13}C NMR spectra also provided more evidence for the successful preparation of both compounds; the C-8 carbon atom gave rise to the signal found at 143.39 ppm in compound **50**, and at 142.19 ppm in compound **51**. As expected, the C-14 carbon atom signal appears as a doublet due to the characteristic C-F coupling at 158.02 ppm (J = 247.8 Hz) in compound **50**, and a similar signal is observed at a chemical shift of 158.00 ppm (J = 247.3 Hz) in the spectrum for compound **51** (Table 17). In addition to this, *long range* C-F coupling is observed, and in the spectrum for compound **50** it is observed for carbon atoms C-15 found at 116.62 ppm (J = 22.1 Hz), C-13 at 119.81 (J = 17.9 Hz), C-10 at 136.38 (J = 7.3 Hz), and C-11 at 124.29 (J = 3.4 Hz). Similarly, in compound **51** carbon atoms C-15 found at 115.99 ppm (J = 22.3 Hz), C-13 at 119.58 (J = 17.7 Hz), C-10 at 135.96 (J = 7.5 Hz) and C-11 at 124.28 (J = 3.5 Hz) appeared as doublets as a result of the C-F long range coupling. The infrared spectra of both compounds revealed their C=N stretch at 1632 cm^{-1}. The N-H band for **50** is found at 3280 cm^{-1}, and is found

at 3267 cm^{-1} in compound **51**. The molecular ion peak of **50** with a calculated mass of 332.1324 for $C_{18}H_{20}ClFN_3$ was found to be [M+H] 332.1326. The molecular ion peak for compound **51** was confirmed to be [M+H] 318.1176 for a calculated mass of 318.1168 for $C_{17}H_{18}ClFN_3$.



52

Figure 34

The novel compound **52** (**Figure 34**) was isolated in excellent yields (91 %), and the N-H proton in the ^{1}H NMR spectrum was assigned to the signal at 3.05 ppm. We also found the equivalent protons H-11 and H-15 as a multiplet at 7.73-7.7.61 ppm, and the second set of equivalent protons H-12 and H-14 gave rise to the most deshielded signal as a multiplet at 7.97-7.94 ppm. Furthermore, the *tert*-butyl moiety was evident at 0.87 ppm (Table 18). The ^{13}C NMR data revealed the signals for the C-8 carbon atom at 143.56 ppm. The CF_3 functional group could not be detected, but we attempted to resolve this by increasing the relaxation time, and increasing the time (i.e. number of scans) taken to acquire the ^{13}C NMR spectrum, but the signal due to the CF_3 group was still not observed. However, the presence of the CF_3 functional group is confirmed by the observed C-F long range coupling that led to a multiplicity of a quartet for the signal due to the equivalent carbon atoms C-11 and C-15 found at 125.19 ppm (J = 3.8 Hz). The signal due to the C-2 carbon atom was evident at a chemical shift of 56.72 ppm (Table 19). In the IR spectrum the N-H moeity was found at 3331 cm^{-1} and the C=N functional group gave rise to the band at 1658 cm^{-1}. The HRMS data confirmed the molecular ion peak of **52** to be [M+H] 348.1692 and this was found to be consistent with the calculated mass of 348.1682.

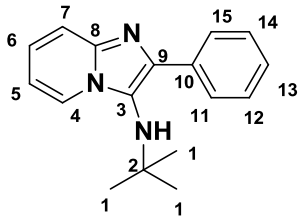
Table 18: Selected ^{1}H NMR spectroscopy signals for compounds **52**-**54** and their corresponding multiplicity

Compound	H-1	N-**H**	H-11 and H-15	H-12 and H-14	Ar-CH_3
52	0.87 (s)	3.05 (s)	7.97-7.94 (m)	7.73-7.61 (m)	2.95 (s)
53	1.04 (s)	3.12 (s)	7.91 (dd)	7.43 (td)	--
54	0.84 (s)	2.98 (s)	7.79 (dd)	7.47-7.35 (m)	2.92 (s)

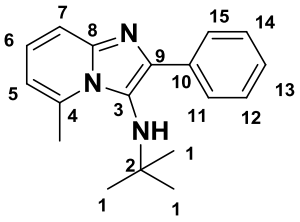
Table 19: Selected ^{13}C NMR spectroscopy signals for compounds **52**-**54**.

Compound	C-2	C-1	C-8	C-11 and C-15	C-2
52	56.72	29.65	143.56	125.19 (q)	140.11
53	56.44	30.30	142.07	128.27	139.07
54	56.41	29.56	143.28	128.69	141.64

The ^{1}H NMR spectroscopy data summarized in Table 18 for compounds **53** and **54** (**Figure 35**) confirmed their successful preparation because as expected, the signal due to the *tert*-butyl group appeared as a singlet at 1.04 ppm and 0.84 ppm for **53** and **54**, respectively. The broad singlet found at 3.12 ppm for compound **53**, and at a slightly lower chemical shift of 2.98 ppm in compound **54** was assigned to the N-H proton. The equivalent protons H-11 and H-15 gave rise to the signal that integrated for two protons at 7.91 ppm in **53**, while they gave rise to the most deshielded signal integrating for two protons at 7.79 ppm in compound **54**.



53



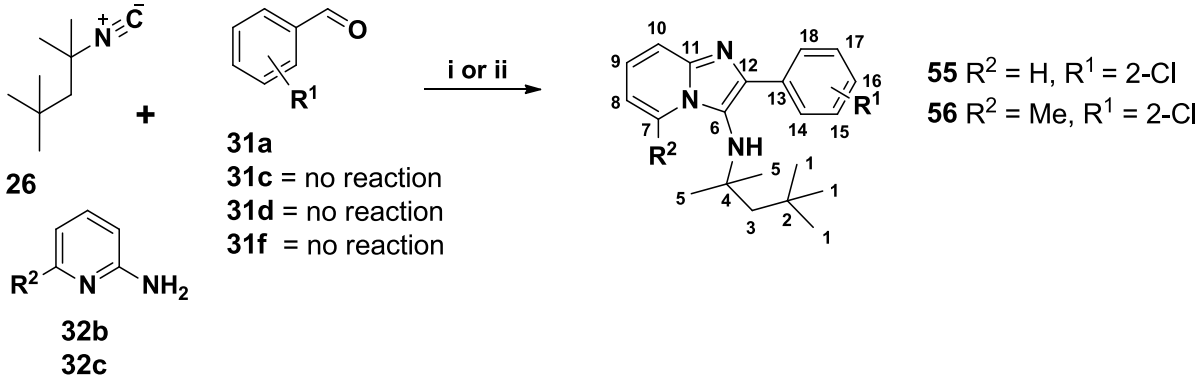
54

Figure 35

The most deshielded signal in the ^{13}C NMR spectra found at 142.07 ppm and 143.28 ppm were assigned to the C-8 carbon atom in **53** and **54**, respectively. The signal due to the equivalent carbon atoms C-11 and C-15 was evident at 128.27 ppm in compound **53**, and at 128.69 ppm in compound **54**. The *tert*-butyl functional group clearly gave rise to the signal that integrated for 9 protons at 30.30 ppm and 29.56 ppm in compound **53** and **54**, respectively. The C-2 carbon atom gave rise to the signal found at 56.44 ppm in compound **53**, and found at 56.41 ppm in compound **54** (Table 19). In the IR spectra, the signals found at 3361 cm^{-1} and 3266 cm^{-1} were assigned to the N-H group in **53** and **54**, respectively. The signal due to the C=N group was found at 1631 cm^{-1} in **53**, and 1633 cm^{-1} in **54**. The observed data is consistent with reports of compound **53** and **54** in literature.[59, 105-106]

2.2.2 Synthesis of 2-(phenyl)-*N*-*(1,1,3,3* tetramethylbutyl)imidazo[1,2-*a*]pyridin-3-amine derivatives.

Upon successfully synthesizing compounds **45**-**54** using *tert*-butyl isocyanide to obtain 2-(pheny)-*N*-*tert*-butylimidazo1,2-*a*]pyridin-3-amine derivatives, we explored the use of the convertible isocyanide 1,1,3,3 tetramethylbutyl isocyanide (**26**, also known as the Walborsky reagent) to obtain 2-(pheny)-*N*-(1,1,3,3-tetramethylbutyl)imidazo[1,2-*a*]pyridin-3-amine derivatives. The reaction conditions employed here in the GBB reaction were the same as those utilized when *tert*-butyl isocyanide was the convertible isocyanide of choice (**Scheme 34**).



Scheme 34: Reagents and conditions: (i) K-10 montmorillonite clay (250 mg), dioxane, 100°C, 120 Watts, 30 min.[35] (ii) 10% mol iodine, methanol, room temperature, 24 h.[36]

When the GBB reaction was performed under microwave irradiation in the presence of K-10 montmorillonite clay at 120 Watts and 100℃, we could not obtain the desired compounds **55**-**56**, only starting material was retrieved in both cases. The reaction was then performed in the presence of catalytic amounts of iodine in methanol at room temperature for 24 h. The methanol was removed *in vacuo* and the resulting residue was purified by column chromatography.[36] Compounds **55** and **56** were prepared successfully in good yields (Table 20), but the attempted preparation of additional compounds derived from **26**, **31c-d**, **31f** and **32b** was unsuccessful and only starting material was retrieved from these reaction. We also found that substituting compound **32b** for compound **32c** also failed to give any additional compounds, the starting material appeared to decompose, and no discernable material (by NMR or IR) was obtained from the reaction.

Table 20: Yields for compounds **55**-**56**

Compound	Yield (%)
55	90
56	80

The characterization of both novel compounds **55** and **56** by ^{1}H NMR spectroscopy revealed that the *tert*-butyl moiety gave rise to the signal at 0.96 ppm for **55**, and the signal at 0.91 ppm for compound **56**. In compound **55** the hydrogen *ortho* (H-7) to the nitrogen gave rise to the most deshielded signal at 8.32 ppm, and the signal due to the methyl group *ortho* to the nitrogen in compound **56** was evident at 2.99 ppm. Furthermore, the signals observed at 3.20 ppm and 3.19 ppm were assigned to the N-H functional group in compounds **55** and **56**, respectively (Table 21). The ^{13}C NMR spectra also confirmed the formation of both compounds with the C-11 carbon atom assigned to signals at 142.21 ppm and 143.57 ppm in compound **55** and **56**, respectively. The C-Cl carbon signal was found at 132.56 ppm for compound **55**, and 135.68 ppm for compound **56**. The C-1 carbon atoms for both compounds had a small difference in their chemical shifts and they were evident at 31.78 ppm and 31.82 ppm in **55** and **56**, respectively (Table 22). The IR spectra provided additional proof: the C=N group gave rise to the bands at 1627 cm^{-1} and 1634 cm^{-1} for **55** and **56**, respectively. The N-H

functional group was found at 3361 cm^{-1} for **55**, and at 3353 cm^{-1} for **56**. The molecular ion peak for **55** with a calculated mass of 356.1888 for $C_{21}H_{27}ClN_3$ was found to be [M+H] 356.1895 by HRMS, and compound **56** with its calculated mass of 370.2045 for $C_{22}H_{29}ClN_3$ was confirmed to be [M+H] 370.2059.

Table 21: Selected ^{1}H NMR spectroscopy signals for compounds **55** and **56** and their corresponding multiplicity

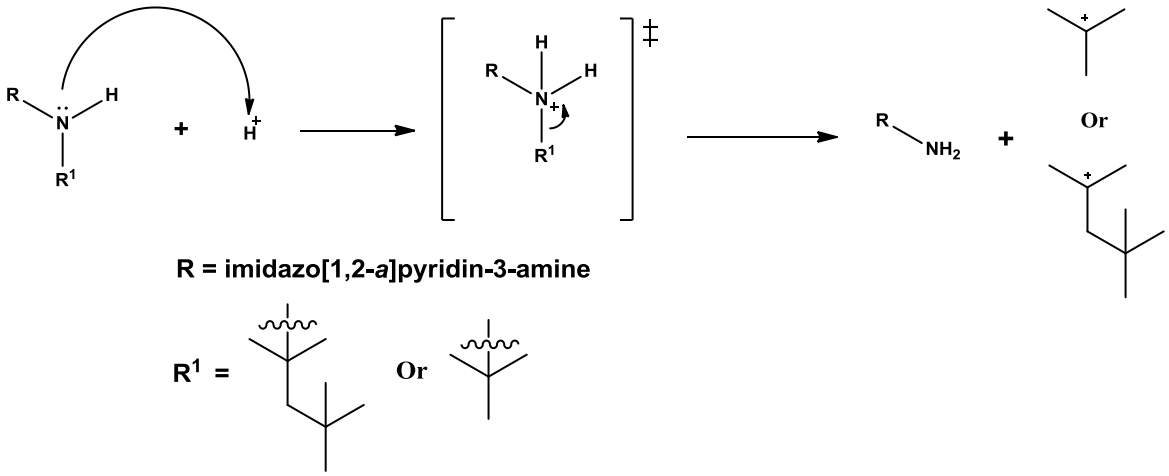
Compound	H-1	N-**H**	H-7	Ar-CH_3
55	0.96 (s)	3.29 (s)	8.32 (dt)	--
56	0.91 (s)	3.20 (s)	--	2.99 (s)

Table 22: Selected ^{13}C NMR spectroscopy signals for compounds **55** and **56**

Compound	C-1	C-11	C-Cl	C-7	Ar-CH_3
55	31.78	142.19	132.56	123.71	--
56	31.82	143.57	135.68	127.04	21.09

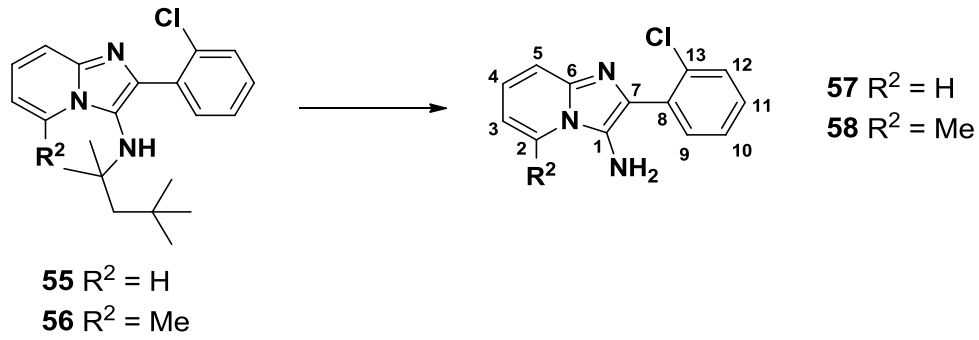
2.2.3 Synthesis of 2-(phenyl)-imidazo[1,2-*a*]pyridin-3-amine derivatives

Upon successfully preparing the small library of imidazo[1,2-*a*]pyridine-3-amine derivatives (**45**-**56**), they were placed in a dealkylation reaction in order to obtain the corresponding primary amines. The mechanism of this reaction is described by Guchhait *et al.* as an acid induced "protonolytic elimination reaction of imidazole-amine" that is contingent on the successful formation of a stable alkyl carbocation. This implies that the reaction proceeds *via* the protonation of the amine, followed by the elimination of the imidazole-amine (**R^1**) (**Scheme 35**).[69]



Scheme 35: Dealkylation/deamination reaction mechanism

The successfully prepared compounds **55** and **56** were placed in a dealkylation reaction reported by Blackburn *et al.* They were treated with trifluoroacetic acid (TFA) in dry CH_2Cl_2 for 5 minutes at room temperature. However, we only retrieved starting material from the reaction despite the reports of yields of 55-58% for similar compounds by Blackburn *et al*.[76] So we looked at what the influence of the reaction time on the success of the reaction could be. As a result, compounds **55** and **56** were treated with TFA in CH_2Cl_2 for 20 minutes at room temperature. This led to a successful conversion of **55** and **56** into compounds **57** (35% yield) and **58** (26% yield), respectively (**Scheme 36**).

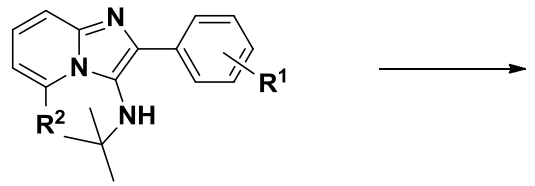


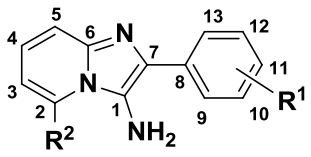
Scheme 36: Reagents and conditions; TFA, Dry CH_2Cl_2, room temperature, 5 min, or 25 min, or 24 h.

The reaction time was increased to 24 h in an attempt to improve the yield of the reaction even further, but the yields were found to be lower; with compound **57** obtained in a low yield of 22% and compound **58** in a poor yield of 26%. Given the poor yields from the

dealkylation of **55**-**56**, an alternative method involving the dealkylation of compounds **45**-**54** had to be explored. A method reported by Guchhait *et al.* was identified, and it involved the preparation of *tert*-butyl isocyanide imidazo[1,2-*a*]pyridin-3-amine derivatives in a GBB reaction catalyzed by $ZrCl_4$, under microwave irradiation in a sealed microwave tube. No work up process was performed, but HBF_4 was added to the reaction mixture and it was irradiated at 120 W and 160°C in a sealed microwave tube for 25 minutes to successfully obtain the primary amine as imidazo[1,2-*a*]pyridin-3-amine products.[69]

In our case, since we had already isolated our imidazo[1,2-*a*]pyridin-3-amine derivatives, our focus was only on the second part of the reaction. However, when we treated these derivatives with HBF_4 under microwave irradiation (120 W, 160°C) for 25 minutes in a microwave sealed tube, it led to pressure building up in the reaction tube and subsequently an explosion of the tube, or the reaction content spilling out of the sealed tube through the cap used to seal it. An attempt to perform the reaction under the exact conditions as described by Guchhait *et al.* still led to the explosion or spillage of the reaction content out of the tube due to pressure build up.





45 R^2 = H, R^1 = 2-Cl
46 R^2 = Me R^1 = 2-Cl
47 R^2 = H, R^1 = 4-NO_2, no reaction
48 R^2 = Me R^1 = 4-CN, no reaction
49 R^2 = H, R^1 = 4-CN
50 R^2 = Me R^1 = 3-F-4-Cl, no reaction
51 R^2 = H, R^1 = 3-F-4-Cl, no reaction
52 R^2 = Me R^1 = 4-CF_3, no reaction
53 R^2 = H R^1 = H
54 R^2 = Me R^1 = H

57 R^2 = H, R^1 = 2-Cl
58 R^2 = Me, R^1 = 2-Cl
59 R^2 = H, R^1 = 4-CN
60 R^2 = H, R^1 = H
61 R^2 = Me, R^1 = H

Scheme 37: Reagents and conditions; HBF_4, *n*-BuOH, reflux 160°C, 120 Watts, 25 min.

As a result, compounds **45**-**54** in *n*-butanol were treated with HBF_4 acid under reflux by microwave irradiation for 25 minutes (**Scheme 37**). Compounds **45**-**46**, **49** and **53**-**54** were successfully transformed into their corresponding primary amine products **57**-**58**, **59** and **60**-**61**, respectively. These products were obtained in yields ranging from 65-70% for compounds **57**-**58**, a very low yield of 22% for **59**, and in yields of 56% and 7.6% for **60** and **61**, respectively (Table 23).

Table 23: Yields (%) for compound **57**-**61**

Compound	Yield (%)
57	67
58	65
59	22
60	56
61	7.6

However, an attempt to transform compounds **50**-**52** into their corresponding primary amines failed, and only led to the decomposition of the starting material and gave no compounds that could be characterized or identified. The attempted transformation of compounds **47**-**48** into their primary amines was also unsuccessful, and only the starting material was retrieved.

This version of the dealkylation reaction revealed an interesting relationship between the amount of acid used in the reaction and the 2-phenyl-*N*-*tert*-butylimidazo[1,2-*a*]pyridin-3-amine derivatives, and the yield of the reaction. This relationship was observed for all the reactions that led to a successful dealkylation. However, we will use only compound **45** to discuss the observation and investigation of this relationship. It was initially observed that the yields of compound **57** (67 %) were only achievable when 0.1 g of compound **45** was used in the reaction, and its mole ratio to HBF_4 was 1:1. However, when the amount of **45** was increased to 0.25 g and the mole ratio to the acid was kept at 1: 1, the reaction was unsuccessful and only starting material was obtained.

This was also observed when the amount of **45** was increased further to 0.5 g and 1.0 g while the mole ratio to the acid was kept constant at 1:1. This led into an enquiry into the mole ratio of 1:1, and we began by altering the mole ratio to 1:3 (**45**:HBF_4) when 0.25 g of **45** was used, and we successfully obtained compound **57**. However, we still found that this new mole ratio was only successful at 0.25 g of **45**, but failed when the amounts were increased by 2 fold to 0.5 g. This prompted another change in the mole ratio. So when 0.5 g of **45** was used, the mole ratio was changed to 1:5 and compound **57** was obtained successfully. We also found that at 1.0 g of **45**, a successful dealkylation required a mole ratio of 1:7. This investigation revealed that for every two fold increase in mass of **45** from 0.1 g, an additional two equivalents of acid was required in order to give the desired product **57** (see **Figure 36**).

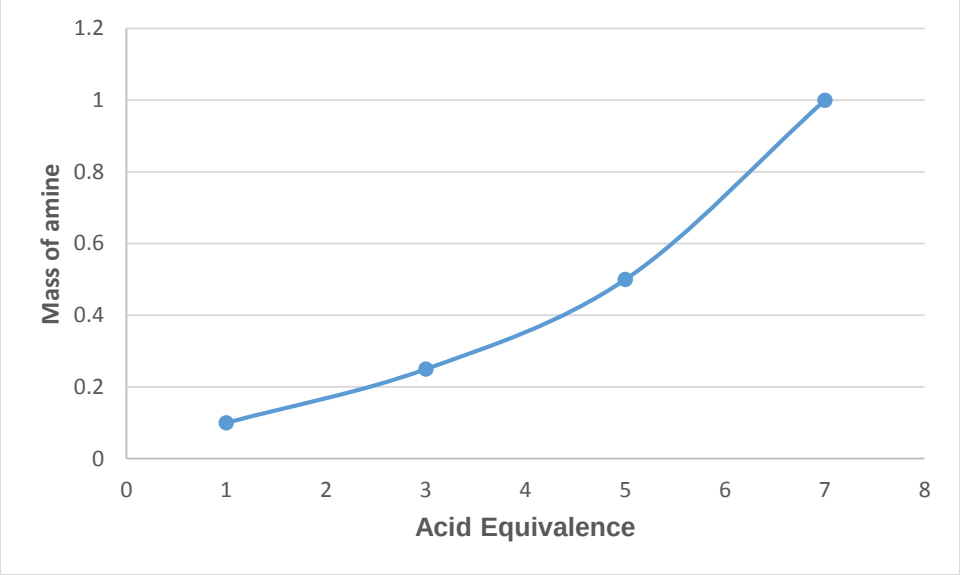
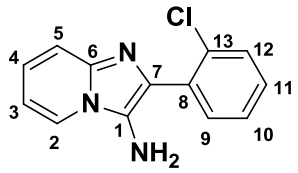


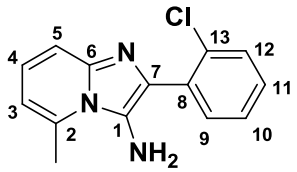
Figure 36: **Relationship between acid equivalence and mass/equivalence of amine**

We also found that the yields for **57** remained in the region of 65-67 % despite the amount of **45** used, and this was observed also in the yields of **58**-**61** (Table 22). We explored this relationship further in an attempt to improve the yields of the reaction. For example, at 0.25 g of **45** the mole ratio used was 1:3, so we looked at how the reaction would be affected if the mole ratio was increased to 1:4, 1: 5 etc. However, it was found that the yields do not improve but remain in the range of 60-70 % for **57**, and this was also true for compounds **58**-**61**. This was attempted at larger reaction scale (i.e. 0.5 g), and it

became clear that the increase in acid equivalence in increments greater than those described in **Figure 36** results in no significant change to the yields of the reaction.



57



58

Figure 37

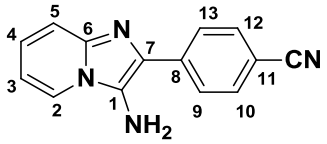
Compounds **57**-**58** (**Figure 37**) were characterized using NMR and IR spectroscopy. The IR spectra revealed the presence of the NH_2 moiety at 3396 cm^{-1} and 3409 cm^{-1} for compound **57** and **58**, respectively. The C=N functional group gave rise to the band at 1638 cm^{-1} for compound **57**, and at 1671 cm^{-1} for compound **58**. The ^{1}H NMR spectra revealed the absence of the *tert*-butyl functional group, and the NH_2 signal was found as a broad singlet accounting for two protons at 3.32 ppm for compound **57**, and at 3.34 ppm for compound **58**. The methyl group in compound **58** was evident at 2.95 ppm, and the hydrogen *ortho* to the nitrogen (H-2) in compound **57** gave rise to the most deshielded signal found at 8.04 ppm (Table 24). The ^{13}C NMR spectra revealed the signal due to the C=N carbon atom at 140.96 ppm and 142.60 ppm for compound **57** and **58**, respectively. The signal found at 131.33 ppm was assigned to the C-Cl carbon atom in compound **57**, and in compound **58** the signal was found at 132.81 ppm (Table 25). The molecular ion peak for the novel compound **58** was confirmed to be [M+H] 258.0791 which was consistent with the calculated mass of 258.0793, and that of **57** was confirmed to be [M+H] 244.0640 which was also consistent with the calculated mass of 244.0636. Literature reports corroborate the data obtained for compounds **57**.[106-107]

Table 24: Selected ^{1}H NMR spectroscopy signals for compounds **57**-**58** and the corresponding multiplicities

Compound	N**H₂**	H-5	H-2	CH_3
57	3.32 (s)	7.55-7.45 (m)	8.04 (dt)	--
58	3.34 (s)	7.37-7.24 (m)	--	2.95 (s)

Table 25: Selected ^{13}C NMR spectroscopy signals for compounds **57**-**58**

Compound	C-6	C-Cl	C-1	CH_3
57	140.96	131.33	133.31	--
58	142.60	132.81	136.09	20.22



59

Figure 38

The successful transformation of compound **49** to compound **59** (**Figure 38**) was also confirmed using NMR spectroscopy which gave data similar to that reported in literature.[107] The broad singlet that integrates for two protons found at 3.43 ppm was assigned to the NH_2 functional group in the ^1H NMR spectrum. The equivalent protons H-9 and H-13 gave rise to the signal integrating for two protons at 7.76-7.67 ppm, and the other two equivalent protons H-10 and H-12 gave rise to the most deshielded signal found at 8.18 ppm. The signal due to the H-2 proton was evident at 8.00 ppm with a multiplicity of doublet of doublets (Table 26). The ^{13}C NMR spectrum gave further evidence, and it revealed that the C-6 carbon atom was found at 141.45 ppm. The signal found at 119.16 ppm was assigned to the characteristic C≡N carbon atom, and the signal due to the equivalent carbon atoms C-9 and C-13 was clearly evident at 127.27 ppm (Table 27). Furthermore, in the IR spectrum the broad band found at 3257 cm^{-1} was assigned to the NH_2 functional group. The signals due to the C≡N and C=N functional groups were found at 2221 cm^{-1} and 1631 cm^{-1}, respectively.

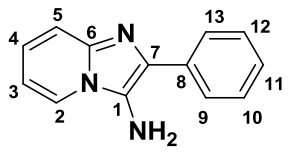
Table 26: Selected ^{1}H NMR spectroscopy signals for compounds **59**-**61**

Compound	N**H₂**	H-9 and H-13	H-10 and H-12	H-2	CH_3
59	3.43 (s)	7.76-7.67 (dd)	8.18 (dd)	8.00 (dd)	--
60	3.45 (s)	7.98-7.95 (m)	7.46 (t)	8.00 (d)	--
61	3.61 (s)	7.87 (d)	7.46-7.39 (m)	--	3.01 (s)

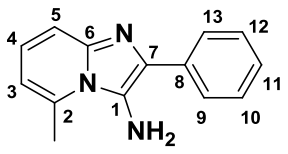
Table 27: Selected ^{13}C NMR spectroscopy signals for compounds **59**-**61**

Compound	C-6	C≡N	C-1	C-9 and C-13
59	141.45	119.16	139.16	127.27
60	140.95	--	138.38	127.17
61	143.05	--	136.32	127.60

The successful preparation of compounds **60** and **61** (**Figure 39**) from compounds **53** and **54** respectively was confirmed by NMR spectroscopy. Compound **61** was not entirely pure, even after it was taken through a series of attempted purification procedures using column chromatography and preparative-TLC, and TLC did not reveal any additional spots or byproducts apart from the product. As a result it is reported as a mixture. The ^{1}H NMR spectrum revealed the most deshielded signal due to the H-2 proton was evident at 8.00 ppm for compound **60**. The signal due to the CH_3 protons was found as a singlet integrating for three protons at 3.01 ppm in the spectrum for compound **61**. In compound **60**, the signal due to the equivalent protons H-9 and H-13 was found at 7.98-7.95 ppm as a multiplet, while in compound **61** it was found at 7.87 ppm as a doublet. The broad singlet that integrated for two protons that appeared at 3.45 ppm and 3.61 ppm was assigned to the NH_2 protons in compound **60** and **61**, respectively (Table 26).



60



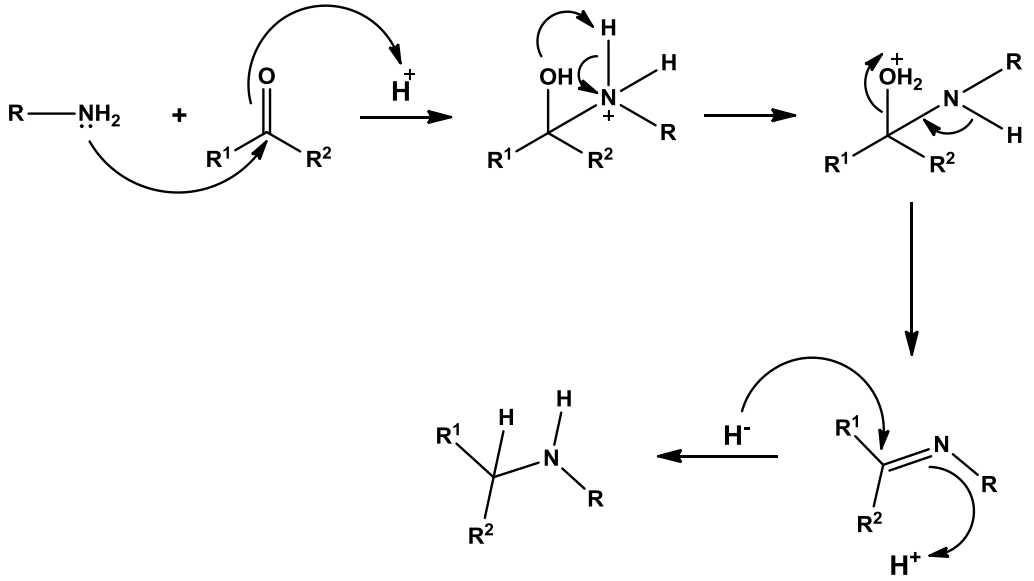
61

Figure 39

In the ^{13}C NMR spectroscopy data (Table 27), as expected, the most deshielded signals found at 140.95 ppm and 143.05 ppm were assigned to the C-6 carbon atom in compounds **60** and **61**, respectively. The equivalent C-9 and C-13 carbon atoms gave rise to the signal found at 127.17 ppm in compound **60**, and at 127.60 ppm in compound **61**. The signals found at chemical shifts of 138.38 ppm and 136.32 ppm were assigned to the C-1 carbon atoms of compounds **60** and **61**, respectively. The IR spectra revealed that the NH_2 groups gave rise to the signal at 3381 cm^{-1} in **60**, and at 3375 cm^{-1} in **61**. The band stretch at 1631 cm^{-1} and 1634 cm^{-1} was assigned to the C=N functional group in **60** and **61**, respectively. Literature reports with similar data also corroborate the successful synthesis of both compounds **60** and **61**.[107, 109]

2.2.4 Reductive amination of ketones and aldehydes with compounds 57-61.

After successfully preparing compounds **57**-**61**, the reactivity of these compounds, and specifically the nucleophilicity of the amine (NH_2) was tested in a reductive amination with cyclohexanone, cyclohexanal and 2-chlorobenzaldehyde.The general mechanism of this reaction involves a nucleophilic attack of the electrophile by the amine functional group to give an imine intermediate, which is treated with a reducing agent that has a source of hydride ions (H^-, i.e $NaBH_4$) in order to give a secondary amine product (**Scheme 38**).[75]



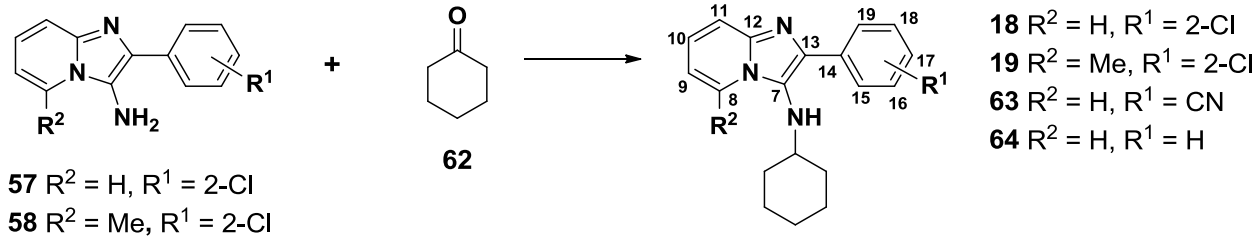
Scheme 38: General reaction mechanism for reductive amination[75]

2.2.4.1 Synthesis of phenyl-*N*-imidazo[1,2-*a*]pyridin-3-amine derivatives in a reductive amination.

Compounds **57** and **58** in dry THF were initially reacted with cyclohexanone in the presence of acetic acid, $MgSO_4$ and zinc powder for 2 h. The resulting reaction mixture was treated with $Na(OAc)_3BH$ at room temperature, under N_2 gas atmosphere for 24 h.[110] This reaction was unsuccessful in transforming compounds **57** and **58**, which were retrieved from the reaction. Given this failed attempt, the reaction was then performed in the absence of $MgSO_4$ and zinc for 2 h. The obtained solution was then treated with $Na(OAc)_3BH$ at room temperature, under N_2 gas atmosphere for 24 h.[110] These reaction conditions still failed to transform compounds **57** and **58** into their corresponding cyclohexyl derivatives, and the primary amines were isolated from the reaction.

A third set of reaction conditions were employed, wherein a mixture of the appropriate primary amine **57** or **58** and cyclohexanone in absolute ethanol, and glacial acetic acid were treated with $NaCNBH_3$ under reflux in a N_2 gas atmosphere for 24 h.[111] This method was also unsuccessful in the preparation of the desired products, and the starting material (**57** or **58**) was obtained from the reaction. Using the same procedure, we substituted the reducing agent $NaCNBH_3$ for the more potent $NaBH_4$, but this change still failed to produce the desired products and only gave the primary amine starting materials. Some of the major factors that govern the reductive amination reaction include: the nucleophilicity of the amine, the electrophilicity of the ketone or aldehyde, the catalyst used, reducing agent, temperature and reaction solvents. Since we could not change the type of nucleophile or electrophile used in our case, another factor we could explore was the catalyst.

One of the catalyst's functions is to improve the electrophilicity of the ketone/aldehyde by coordinating to the carbonyl oxygen atom (see **Scheme 38**). Should the catalyst fail in this function, it will reduce the chances of the reaction proceeding successfully or yielding excellent amounts of the desired product. The catalysts of choice in the first set of reaction conditions investigated are Brønsted acids.



57 R^2 = H, R^1 = 2-Cl
58 R^2 = Me, R^1 = 2-Cl
59 R^2 = H, R^1 = 4-CN
60 R^2 = H, R^1 = H
61 R^2 = Me, R^1 = H, no reaction

62

18 R^2 = H, R^1 = 2-Cl
19 R^2 = Me, R^1 = 2-Cl
63 R^2 = H, R^1 = CN
64 R^2 = H, R^1 = H

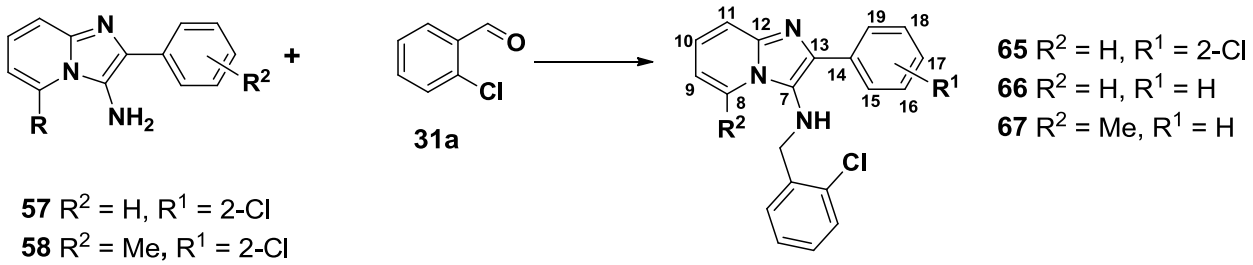
Scheme 39: Reagents and conditions: Aluminium chloride ($AlCl_3$), $NaCNBH_4$, absolute ethanol (EtOH), 70 ℃, 25 h.

In order to investigate the extent of their influence on the reactions, the Brønsted acids were substituted with a Lewis acid, $AlCl_3$. The reaction mixture was heated to 70℃ instead of reflux, and it was performed as an indirect instead of direct reductive amination. The reaction mixture was heated and allowed to stir for 1 h before being treated with $NaCNBH_3$. The resulting mixture was then left to stir for an additional 24 h (**Scheme 39**).This led to the successful transformation of compounds **57-58** and **59**-**60** into compounds **18**-**19** and **63**-**64**, respectively. These compounds were obtained in poor to average yields (Table 28). However, compound **61** failed to participate in the reaction and give the desired product.

Table 28: Yields (%) for compounds **18-19** and **63**-**64**.

Compound	Yield (%)
18	45
19	37
63	25
64	50

Once this was achieved, we looked into exploring the versatility of the reaction by substituting **62** with cyclohexanal and 2-chlorobenzaldehyde (**31a**). Cyclohexanal was used in a reaction with **57** and **58** only, and in both cases we retrieved the primary amines and none of the desired products.



57 R^2 = H, R^1 = 2-Cl
58 R^2 = Me, R^1 = 2-Cl
59 R^2 = H, R^1 = 4-CN
60 R^2 = H, R^1 = H
61 R^2 = Me, R^1 = H

65 R^2 = H, R^1 = 2-Cl
66 R^2 = H, R^1 = H
67 R^2 = Me, R^1 = H

Scheme 40: Reagents and conditions; $AlCl_3$, $NaCNBH_4$, absolute ethanol (EtOH), 70 ℃, 25 h.

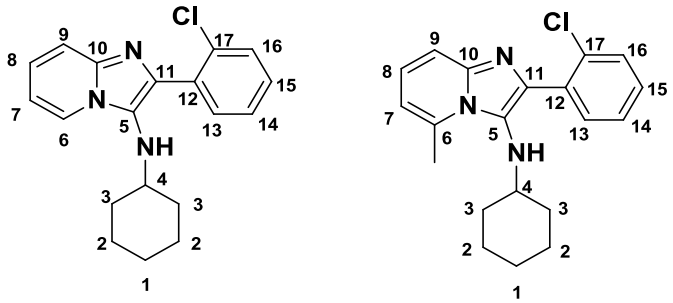
Compound **31a** was then used in the place of cyclohexanal, and this led to the successful preparation of compound **65** from compound **57** (**Scheme 40**). Furthermore, compounds **60**-**61** successfully reacted with **31a** to give the desired products **66**-**67**, respectively. However, the reaction between primary amines **58** and **59** with **31a** was unsuccessful and only led to the isolation of the amines. The successfully synthesized products (**65**-**67**) were obtained in yields varying from excellent to average (Table 29).

Table 29: Yields (%) for compounds **65**-**67**.

Compound	Yield (%)
65	91
66	65
67	42

NMR and IR spectroscopy data provided confirmation for successful preparation of **18**-**19** (**Figure 40**). In the ^{1}H NMR spectra summarized in Table 30, the N-H proton for **18** was found at 3.28 ppm, and at a slightly more shielded position of 3.07 ppm in **19**. The H-6 proton for compound **18** gave rise to the most deshielded signal found at 8.15 ppm, and the methyl protons in compound **19** appeared as a singlet at 2.97 ppm. The signals found at 2.73-2.59 ppm and 2.61-2.54 ppm were assigned to the H-4 proton in

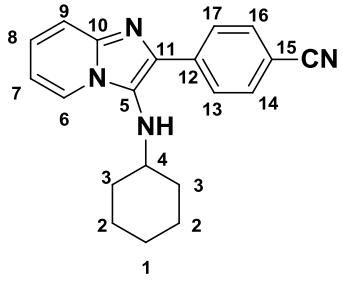
compounds **18** and **19**, respectively. This corresponds to data reported in literature for these two compounds.[35]



18 **19**

Figure 40

The ^{13}C NMR spectroscopy data also provided additional evidence by revealing the C-10 carbon atom (C=N) at chemical shifts of 141.65 ppm for **18**, and at a more deshielded position of 143.34 ppm for **19**. The C-4 carbon atom gave rise to the signal found at 56.39 ppm for **18**, and at 58.87 ppm for **19**. The signals found at 122.86 ppm and 128.23 ppm were assigned to the C-6 carbon atom in compound **18** and **19**, respectively (Table 31). In the IR spectra we were able to identify signals due to the N-H functional groups and they were found at 3362 cm^{-1} and 3352 cm^{-1} for compounds **18** and **19**, respectively. The C=N functional group gave rise to the stretching band found at 1631 cm^{-1} in **18**, and at 1633 cm^{-1} in **19**.



63

Figure 41

The ^{1}H NMR spectrum (data summarized in Table 30) obtained for compound **63** (**Figure 41**) corresponds well with the one reported in literature.[35] The signal integrating for one proton found at 2.99-2.84 as a multiplet was assigned to the H-4 proton, while the

corresponding carbon atom C-4 was evident at 56.96 ppm in the ^{13}C NMR spectrum (data summarized in Table 31). The H-6 proton and its correlating carbon atom C-6 gave rise to the signals found at 8.05 ppm and 117.50 ppm, respectively. The signal that appears as a doublet and integrates for one proton at 3.11 ppm was assigned to the N-H proton. The most deshielded signal in the ^{13}C NMR spectrum was found at 141.84 and it was assigned to the C=N carbon atom C-10, while the signal due to the C≡N carbon atom was evident at 119.20 ppm. The IR spectrum gave additional evidence confirming the successful preparation of **63**; as the C=N and C≡N groups gave rise to the bands found at 1633 cm^{-1} and 2223 cm^{-1}, respectively. The stretching band found at 3308 cm^{-1} was assigned to the N-H functional group.

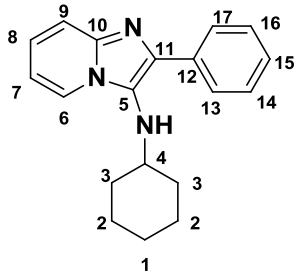
Table 30: Selected ^{1}H NMR spectroscopy signals for compounds **18**-**19** and **63**-**64** and the corresponding multiplicity.

Compound	H-4	N-**H**	H-6	Ar-CH_3
18	2.73-2.59 (m)	3.28 (d)	8.15 (dq)	--
19	2.61-2.54 (m)	3.07 (s)	--	2.97 (s)
63	2.99-2.84 (m)	3.11 (d)	8.05 (dt)	--
64	3.00-2.92 (m)	3.12 (d)	8.10 (dt)	--

Table 31: Selected ^{13}C NMR spectroscopy signals for compounds **18**-**19** and **63**-**64**.

Compound	C-6	C-4	C-10	C≡N
18	122.86	56.39	141.65	--
19	128.23	58.87	143.34	--
63	117.50	56.96	141.84	119.20
64	122.72	56.94	141.61	--

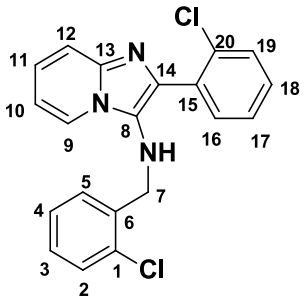
The successful preparation of compound **64** (**Figure 42**) from compound **60** was confirmed by the absence of the NH_2 protons at 3.45 ppm in the ^{1}H NMR spectrum, and the presence of the N-H proton was clearly evident at 3.12 ppm as a doublet (Table 30). The H-6 proton gave rise to the most deshielded signal with a multiplicity of doublet of doublets at 8.10 ppm, and the correlating C-6 carbon atom gave rise to the signal found at 122.72 ppm in the ^{13}C NMR spectrum (Table 31).



64

Figure 42

The H-4 proton and C-4 carbon atom gave rise to signals found at chemical shifts of 3.00-2.92 ppm and 56.94 ppm, respectively. The N-H moiety appeared as a doublet at 3.12 ppm in the proton NMR spectrum, and it gave rise to the stretch band at 3241 cm^{-1} in the IR spectrum. The C=N functional group was clearly evident at 141.61 ppm (C-10) in the ^{13}C NMR spectrum, and at 1631 cm^{-1} in the IR spectrum.

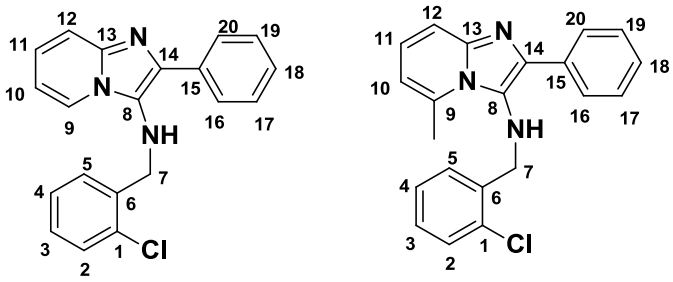


65

Figure 43

The novel compound **65** (**Figure 43**) was successfully obtained from the reductive amination reaction of 2-chlorobenzaldehyde. The ^{1}H NMR spectrum revealed the N-H

moiety and the H-7 protons gave rise to overlapping signals that integrated for three protons at 4.21-3.90 ppm. The most deshielded signal with doublet of doublets multiplicity found at 8.18 ppm was assigned to the H-9 proton (Table 32). In the ^{13}C NMR spectrum, the C-7 carbon atom signal was evident at 49.92 ppm, and the C-13 carbon atom gave rise to the most deshielded signal found at 141.46 ppm (Table 33). The C=N signal in the IR spectrum was found at 1632 cm^{-1} and the N-H functional group gave rise to the band at 3370 cm^{-1}. The molecular ion peak for **65** [M+H] 368.0710 corresponding to the calculated mass of 368.0716 was determined by HRMS.



66 **67**

Figure 44

The identities of **66** and **67** (**Figure 44**) were confirmed by ^{1}H NMR spectroscopy (Table 32). We found that the signal due the N-H proton appeared as a triplet at 3.75 ppm in **66**, and at 3.71 ppm in compound **67**. The signal with a doublet multiplicity and integrating for two protons was found at 4.28 ppm in compound **66**, and at 4.16 ppm in compound in **67** and it was assigned to the H_2C-N protons (H-7). Their corresponding carbon atoms (C-7) gave rise to the signals at 50.19 ppm and 53.15 ppm in compound **66** and **67**, respectively. The C-13 group gave rise to the most deshielded signals found at chemical shifts of 138.22 ppm and 143.17 ppm in the ^{13}C NMR spectra for compounds **66** and **67**, respectively (Table 33). In the IR spectra, the C=N group gave rise to the bands at 1636 cm^{-1} in **66**, and at 1634 cm^{-1} in compound **67**. The bands found at 3350 cm^{-1} and 3332 cm^{-1} were assigned to the N-H moiety of **66** and **67**, respectively.

Table 32: Selected ^{1}H NMR spectroscopy signals for compounds **65**-**67** and their multiplicity.

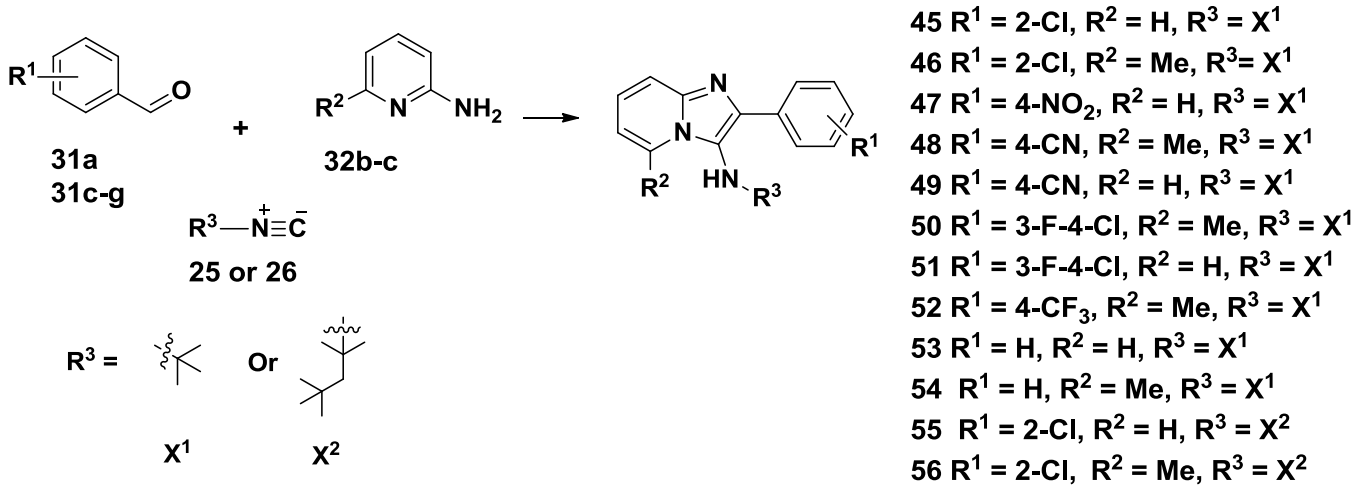
Compound	H-9	N-**H**	C-7	Ar-CH_3
65	8.18 (dq)	4.21-3.90 (m)	4.21-3.90 (m)	--
66	8.00 (d)	3.75 (t)	4.28 (d)	--
67	--	3.71 (t)	4.16 (d)	2.90 (s)

Table 33: Selected ^{13}C NMR spectroscopy signals for compounds **65**-**67**.

Compound	C-7	C-9	C-13	Ar-CH_3
65	49.97	122.53	141.74	--
66	50.19	122.32	138.22	--
67	53.15	130.17	143.17	19.73

2.2.5 Conclusion

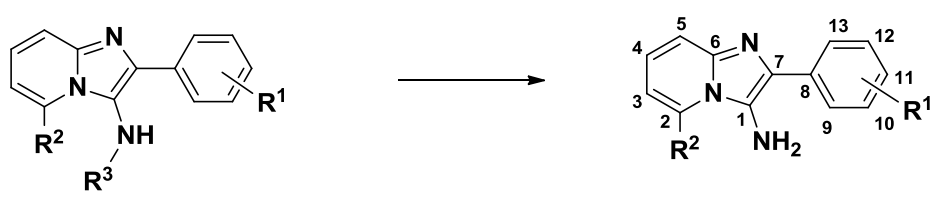
This part of the research was aimed at developing methodology that would allow the synthesis of 2-phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine derivatives without the need to synthesize the required isocyanide component of the reaction. This was essential because the synthesis of isocyanides has been reported in both literature (highlighted in chapter 1), and in the first part of chapter 2 as being accompanied by a number of challenges. The initial step of the methodology development involved the use of inexpensive and readily available convertible isocyanides *tert*-butyl isocyanide and Walborsky reagent in the GBB reaction to obtain 2-phenyl-*N*-*tert*butylimidazo[1,2-*a*]pyridin-3-amine and 2-phenyl-*N*-(1,1,3,3-tetramethylbutyl)imidazo[1,2-*a*]pyridin-3-amine derivatives, respectively (**Scheme 41**).



Scheme 41: Synthesis of 2-phenyl-*N*-t*ert*-butylimidazo[1,2-*a*]pyridin-3-amine and 2-phenyl-*N*-(1,1,3,3-tetramethylbutyl)imidazo[1,2-*a*]pyridin-3-amine derivatives

The 2-phenyl-*N*-*tert*-butylimidazo[1,2-*a*]pyridin-3-amine derivatives were obtained in yields varying from poor to excellent, but we were only able to successfully synthesize two 2-phenyl-*N*-(1,1,3,3-tetramethylbutyl)imidazo[1,2-*a*]pyridin-3-amine derivatives in excellent yields compared to the ten 2-phenyl-*N*-*tert*butylimidazo[1,2-*a*]pyridine-3-amine derivatives obtained. The second step of the methodology development had to do with using both the imidazo[1,2-*a*]pyridin-3-amine derivatives in a deamination/dealkylation

reaction in order to liberate the primary amine in all the compounds to give 2-phenyl-imidazo[1,2-*a*]pyridin-3-amine derivatives (**Scheme 41**).



45 R^1 = 2-Cl, R^2 = H, R^3 = X^1
46 R^1 = 2-Cl, R^2 = Me, R^3= X^1
49 R^1 = 4-CN, R^2 = H, R^3 = X^1
53 R^1 = H, R^2 = H, R^3 = X^1
54 R^1 = H, R^2 = Me, R^3 = X^1
55 R^1 = 2-Cl, R^2 = H, R^3 = X^2
56 R^1 = 2-Cl, R^2 = Me, R^3 = X^2

R³ = X^1 **Or** X^2

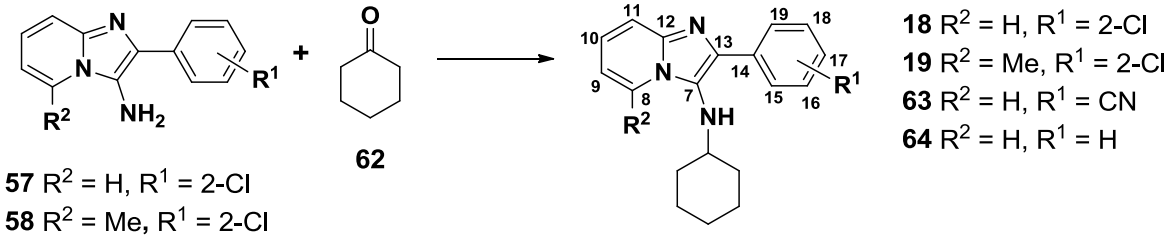
57 R^2 = H, R^1 = 2-Cl
58 R^2 = Me, R^1 = 2-Cl
***59** R^2 = H, R^1 = 4-CN
***60** R^2 = H, R^1 = H
***61** R^2 = Me, R^1 = H

Obtained from $R^3 = X^1$ *only

Scheme 42: Synthesis of 2-phenyl-imidazo[1,2-*a*]pyridine-3-amine derivatives

When the two 2-phenyl-*N*-(1.1.3.3 tetramethylbutyl)imidazo[1,2-*a*]pyridin-3-amine derivatives were treated with acid in the deamination reaction, they were both successfully converted to their corresponding 2-phenyl-imidazo[1,2-*a*]pyridine-3-amine derivatives in poor yields. On the other hand when the eight 2-phenyl-*N*-*tert*butylimidazo[1,2-*a*]pyridin-3-amine derivatives were utilized and treated with acid in the deamination reaction, only five out of the eight were successfully converted to their corresponding phenyl-imidazo[1,2-*a*]pyridin-3-amine derivatives in relatively good yields (**Scheme 42**). An interesting relationship was discovered between the acid and 2-phenyl-imidazo[1,2-*a*]pyridin-3-amine, we found that in order for the deamination reaction to be a success at both low and high scale reactions, the equivalence of 2-phenyl-imidazo[1,2-*a*]pyridin-3-amine to the acid played a significant role. It was established that as the amount of 2-phenyl-imidazo[1,2-*a*]pyridin-3-amine was increased (in approximately 2-fold) from 0.1 g, the amount of acid mole equivalence to the 2-phenyl-imidazo[1,2-*a*]pyridine-3-amine also had to be increased. As the amount of 2-phenyl-imidazo[1,2-*a*]pyridin-3-amine was approximately doubled one was required to add two more mole equivalents of acid to that reaction. We found that 0.1 g required a 1:1 mole equivalence,

however, 0.25 g required 1:3 mole equivalence, and even further than that 0.5 g required 1:5 molar equivalence *etc*.

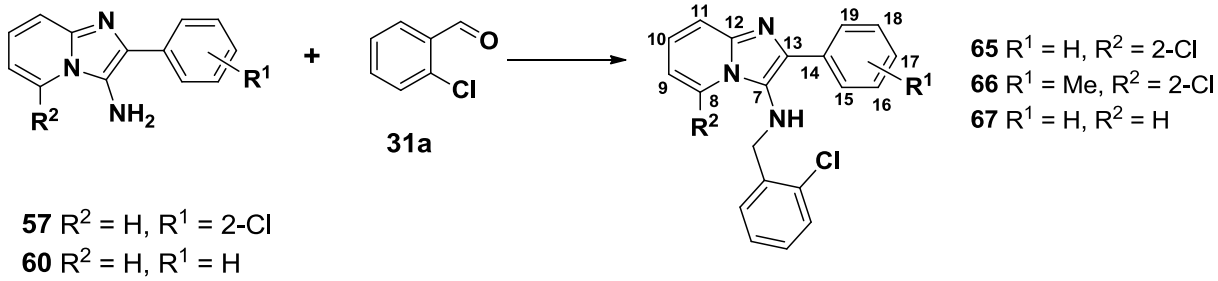


57 R^2 = H, R^1 = 2-Cl
58 R^2 = Me, R^1 = 2-Cl
59 R^2 = H, R^1 = 4-CN
60 R^2 = H, R^1 = H

18 R^2 = H, R^1 = 2-Cl
19 R^2 = Me, R^1 = 2-Cl
63 R^2 = H, R^1 = CN
64 R^2 = H, R^1 = H

Scheme 43: Synthesis of 2-phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridine-3-amine derivatives

Upon obtaining these 2-phenyl-imidazo[1,2-*a*]pyridin-3-amine derivatives they were utilized in the last step of the methodology development. The final step involved the reductive amination of the ketone cyclohexanone in order to obtain the desired 2-phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine derivatives (**Scheme 43**). The 2-phenyl-imidazo[1,2-*a*]pyridin-3-amine **57**-**60** successfully participated in the reductive amination and gave 2-(phenyl)-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine derivatives **18**-**19** and **63**-**64**, respectively.



57 R^2 = H, R^1 = 2-Cl
60 R^2 = H, R^1 = H
61 R^2 = Me, R^1 = H

65 R^1 = H, R^2 = 2-Cl
66 R^1 = Me, R^2 = 2-Cl
67 R^1 = H, R^2 = H

Scheme 44: Synthesis of 2-phenyl-*N*-(2-chlorophenyl)imidazo[1,2-*a*]pyridine-3-amine derivatives and 2-phenyl-*N*-(cyclohexylmethyll)imidazo[1,2-*a*]pyridine-3-amine derivatives

Given the success of the reaction we decided to test the versatility of the 2-phenyl-imidazo[1,2-*a*]pyridin-3-amines in producing a diverse range of compounds (**Scheme 44**). The 2-phenyl-imidazo[1,2-*a*]pyridin-3-amines were used in the reductive amination of

aldehydes cyclohexanal and 2-chlorobenzaldehyde, and it was found that only 2-phenyl-imidazo[1,2-*a*]pyridine-3-amine **57** successfully participated in the reductive amination of 2-chlorobenzaldehyde and gave **65**. Both compounds **60** and **61** successfully participated in the reductive amination of 2-chlorobenzaldehyde, and gave compounds **66** and **67**, respectively.

In conclusion we were able to develop a three step methodology that would give 2-phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine derivatives. The GBB reaction was the first step of the methodology and it revealed the use of the convertible isocyanide *tert*butyl isocyanide as the better synthetic route as it was able to give a greater number of diverse compounds compared to the use of 1,1,3,3-tetramethylbutyl isocaynide. The deamination reaction as a second step of the methodology also revealed that the synthetic route that involved the use of *tert*butyl isocyanide was preferred relative to that of 1,1,3,3-tetramethylbutyl isocyanide because it gave better yields of 2-phenyl-imidazo[1,2-*a*]pyridin-3-amines. The final step of the methodology was the successful reductive amination of the ketone cyclohaxanone which gave the 2-phenyl-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine. The preliminary investigations on how versatile the reductive amination reaction could be suggests that the reaction might possess some versatility.

2.2.6 Future work

This methodology has the potential to be investigated and expanded further; future work will include increasing the number and diversity of 2-phenyl-*N*-*tert*butylimidazo[1,2-*a*]pyridin-3-amine derivatives using the GBB reaction. This will be followed by the deamination reaction of these derivatives, and this part of the method will require further and extensive investigation that will focus on exploring the utilization of different acids in the reaction. The reductive amination will have to be expanded to the use of cyclohexanone derivatives that are substituted with functional groups that possess H-bonding ability. These compounds will then be taken for biological testing in an anti-HIV enzymatic assay.

Chapter 3: Experimental Procedures

3.1 Introduction: general laboratory procedures

3.1.1 Laboratory solvents

Solvents utilized for chromatographic techniques (ethyl acetate and *n*-hexane) were distilled prior to their use by means of conventional distillation processes. The solvents that required drying before being used in reactions were first dried over the suitable drying agent, followed by distillation under an inert atmosphere (argon or nitrogen gas). All the chemicals or reagents were obtained from Sigma-Aldrich or Merck and were used without further purification.

3.1.2 Chromatographic techniques

Thin layer chromatography (TLC) of the compounds was performed on Macherey-Nagel Alugram Sil G/UV254 plates that are pre-coated with 0.25 mm silica gel 60. The TLC plates were viewed under UV light (254 nm and 366 nm), and iodine was also used as a visualizing aid. Normal chromatography was performed with silica gel 60 (Macherey-Nagel, particle size 0.063-0.200 mm) adsorbent. Flash chromatography was performed with Flash silica gel 60 (Macherey-Nagel or Merck, particle size 0.063-0.200 mm) adsorbent.

3.1.3 Spectroscopic Analysis

3.1.3.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

Nuclear magnetic resonance (NMR) spectra were recorded on either a Bruker AVANCE 300 MHz or a Bruker AVANCE III 500 MHz spectrometer. All spectra were recorded in chloroform-*d* or DMSO-d_6. All chemical shift values are reported in parts per million referenced against trimethylsilane which is given an assignment of zero parts per million. Signals that could be unequivocally assigned to protons or carbons are presented in the experimental section, however, those that could not be assigned, are reported as the

number of protons or carbons resulting in that signal. In compounds containing the cyclohexyl ring, the CH_2 protons are differentiated between each other by denoting them with subscript letters *a* and *b* (for example should H-4 represent a CH_2 group in a cyclohexyl ring, each proton would be reported H-4_a and H-4_b), but these do not specify which proton occupies the equatorial or axial positions.

3.1.3.2 Infrared spectroscopy

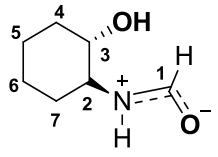
The infra-red spectra were recorded on a Bruker Tensor 27 standard system spectrometer, and the measurements are reported on the wavenumber scale (cm^{-1}).

3.1.4 Melting point determination

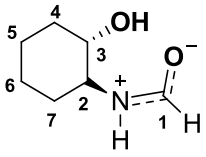
Melting points were determined on a Reichert hot-stage microscope, and remain uncorrected. All crystalline compounds were recrystallized in the appropriate solvents prior to melting point determination. Microwave reactions were conducted in a CEM Discover microwave.

3.2 Synthesis of cyclohexyl isocyanide with increased hydrogen bonding capacity

3.2.1 Synthesis of *N*-(2-hydroxycyclohexyl)formamide 28



***rac*-28a**



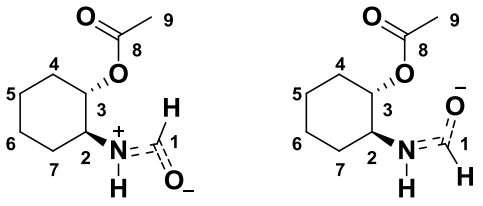
***rac*-28b**

Trans-1-amino-2-hydroxyl cyclohexyl hydrochloride (1 eq., 5.00 g, 3.29 mmol) was dissolved in methanol (40 ml) and treated with NaOMe (1 eq., 3.29 g, 10.0 ml, 3.29 mmol). To this resulting mixture was added methyl formate (4 eq., 8.00 ml, 13.2 mmol), and the reaction was allowed to stir at room temperature for 24 h. A white solid precipitated out of the reaction mixture and was filtered off. An excess of hexane (relative to the volume of methanol) was added to the collected reaction mixture and was allowed to stand

overnight (12 h). The resulting precipitate was removed by filtration and the solvent was removed *in vacuo* to obtain the desired product **28** as a white-light grey solid (4.53 g, 96%). In NMR spectroscopy, product **28** appeared as a mixture of rotamers **28a** and **28b**.

m.p: 136-139 ℃ **; IR** (ν_{max}/cm^{-1}): 3341 (N-H), 3283 (O-H), 2858-2962 (C-H alkyl), 1635 (C=O); **^{1}H NMR (300 MHz, Chloroform-*d*) δ: Compound 28a-b;** 8.26 (0.71H, s, H-1), 8.06 (0.27H, d, *J* = 11.2 Hz, H-1), 6.61 (0.28H, br, s, N-H), 6.28 (0.66H, br, s, N-H), 3.74-3.63 (1H, m, H-2), 3.42-3.20 (1.58H, m, H-3 overlapping with O-H), 3.07-2.98 (0.51H, m, H-2 and O-H), 2.06-1.97 (2H, m, H-4$_a$ and H-7$_a$), 1.90-1.74 (2H, m, H-5$_a$ and H-6$_a$), 1.31-1.25 (4H, m, H-4$_b$, H-5$_b$, H-6$_b$ and H-7$_b$). **δ: Compound 28a-b**: 165.14 (C-1), 162.54 (C-1), 74.41 (C-3), 73.23 (C-3), 58.69 (C-2), 54.60 (C-2), 34.38 (C-4), 33.69 (C-4), 32.31 (C-7), 31.57 (C-7), 24.79 and 24.16 (C-6 and C-5), 24.44 and 24.04 (C-6 and C-5); **^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ: Compound 28a-b;** 7.98 (0.84H, d, *J* = 1.9 Hz, H-1), 7.90 (1H, d, *J* = 11.6 Hz, H-1 overlapping with N-H), 7.48 (0.27H, t, *J* = 10.1 Hz, N-H), 4.79 (0.33H, s, O-H), 4.63 (0.67H, s, O-H), 3.49-3.39 (1H, m, H-2), 3.24-3.18 (0.83H, m, H-3), 3.09-3.01 (0.31H, m, H-3), 2.93-2.82 (0.31H, m, H-2), 1.89-1.75 (2H, m), 1.61-1.54 (2H, m), 1.27-1.03 (4H, m). **HRMS:** (m/*z*), calculated for $C_7H_{14}NO_2$: 144.1019, found $(M + H)^+$: 144.1019.

3.2.2 Synthesis of 2-formamidocyclohexyl acetate 29



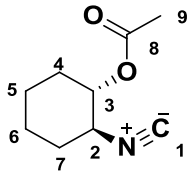
***rac*-29a** ***rac*-29b**

Compound **28** (1 eq., 1.20 g, 8.80 mmol) was dissolved in a solution of acetic anhydride (8 eq., 7.00 ml, 70.4 mmol) and pyridine (6 eq., 4.20 ml, 52.8 mmol) for 4 h at room temperature. The reaction vessel was placed in an ice bath, and excess methanol was added to the resulting solution to quench the excess acetic anhydride. The excess pyridine was removed *in vacuo* as an azeotropic mixture with toluene to give the desired

product **29** as a yellow solid (1.50 g, 92%). In NMR spectroscopy, product **29** appeared as a mixture of rotamers **29a** and **29b**.

m.p: 85-88℃**; IR** (v_{max}/cm^{-1}): 3271 (N-H), 2868-2937 (C-H alkyl), 1726 (C=O ester), 1658 (C=O aldehyde); **^{1}H NMR (300 MHz, Chloroform-*d*) δ: Compound 29a-b**; 8.14 (0.67H, s, H-1), 8.06 (0.22H, d, *J* = 11.4 Hz, H-1), 6.51 (0.27H, br, t, *J*= 10.8 Hz, N-H), 6.38 (0.67H, br, d, *J* = 6.5 Hz, N-H), 4.73-4.64 (0.75H, m, H-3), 4.61-4.54 (0.28H, m, H-3), 4.02-3.94 (0.75H, m, H-2), 3.33-3.22 (0.29H, m, H-2), 2.12-1.92 (5H, m, H-9, H-4$_a$ and H-7$_a$), 1.67-1.84-1.67 (2H, m, H-5$_a$ and H-6$_a$), 1.46-1.18 (4H, m, H-4$_b$, H-5$_b$, H-6$_b$ and H-7$_b$). **^{13}C NMR (75 MHz, $CDCl_3$): Compound 29a-b**: 170.43 (C-8), 171.65 (C-8), 164.39 (C-1), 161.03(C-1), 74.88 (C-3), 74.33 (C-3), 55.04 (C-2), 51.22 (C-2), 32.04 (C-4), 31.74 (C-4), 30.84 (C-7), 30.68 (C-7), 24.15 and 23.64 (C-6 and C-5), 23.95 and 23.35 (C-5 and C-6), 21.11 (C-9), 20.96 (C-9). **^{1}H NMR (300 MHz, DMSO-d_6) δ: Compound 29b**; 8.00-7.96 (1.43H, m, H-1 and N-H), 7.92 (0.28H, d, *J* = 11.5 Hz), 7.67 (0.27H, t, *J* = 10.3 Hz, N-H), 4.62-4.37 (1H, m, H-3) 3.83-3.68 (0.78H, m, H-2), 3.32-3.17 (0.27H, m, H-2), 1.97-2.00-1.75 (5H, m), 1.73-1.53 (2H, m), 1.43-1.13 (4H, m). **HRMS:** (m/*z*), calculated for $C_9H_{16}NO_3$: 186.1125, found $(M + H)^+$: 186.1127.

3.2.3 Synthesis of 2-Isocyanocyclohexyl acetate 30



***rac*-30**

Method A: Compound **29** (1 eq., 0.100 g, 0.652 mmol), triethylamine (20 eq., 1.82 g, 13.0 mol) were mixed in dry dichloromethane (10 ml) and the mixture treated with $POCl_3$ (5 eq., 0.30 ml, 3.260 mmol) at 0 ℃ to room temperature under N_2, and left to stir for 24 h. The resulting mixture was gradually added to ice water over a period of 30 minutes to quench the excess $POCl_3$. The organic layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 ml). The organic layers were combined and washed with sodium hydrogen carbonate solution before being dried over anhydrous sodium sulphate.

The solvent was removed *in vacuo* and the residue purified by column chromatography (flash silica gel, elution 4:1 ethyl acetate/hexane (E/H)) to give the desired product **30** as a light yellow oil with the distinct isocyanide smell (0.073 g, 67%).

Method B: Compound **29** (1 eq., 1.00 g, 5.34 mmol) was dissolved in dry CH_2Cl_2 (30 ml) and treated with the Burgess reagent (1.5 eq., 1.91 g, 8.01 mmol). The resulting mixture was heated to reflux under nitrogen gas atmosphere for 80 minutes. The reaction mixture was diluted with CH_2Cl_2 (25 ml) and washed with distilled water (2 × 20 ml), and dried over magnesium sulphate. The solvent was removed *in vacuo* and the obtained residue was purified using column chromatography (flash silica gel, elution 4:1 ethyl acetate/hexane) to give the desired product **30** as a light yellow oil with the distinct isocyanide smell (0.857 g, 96 %).

Method C: Compound **29** (1 eq., 1.00 g, 5.34 mmol), carbon tetrachloride (1.5 eq., 0.80 ml, 8.10 mmol) and $EtN(^{i}Pr)_2$ (1.5 eq., 1.40 ml, 8.10 mmol) were mixed in dry CH_2Cl_2. The resulting solution was treated with triphenylphosphine (1.5 eq., 2.10 g, 8.10 mmol) at room temperature under nitrogen for 24 h. The solvent was removed *in vacuo* and the residue loaded onto flash silica gel with sufficient CH_2Cl_2 to give the desired product **30** (elution 4:1 ethyl acetate/hexane) as a light yellow oil with the distinct isocyanide smell (0.5803 g, 65%)

R_f = 0.84: **IR** (ν_{max}/cm^{-1}): 1736 (C=O), 2141 ($^{+}N{\equiv}C^{-}$); **^{1}H NMR (300 MHz, Chloroform-*d*) δ:** 4.83 (1H, td, *J* = 9.2, 4.2 Hz, H-3), 3.55 (1H, td, *J* = 9.0, 4.2 Hz, H-2), 2.25-2.01 (5H, m, H-9, H-4_a and H-7_a), 1.84-1.58 (3H, m, H-4_b, H-5_a and H-6_a), 1.52-1.20 (3H, m, H-7_b, H-6_b and H-5_b). **^{13}C NMR (75 MHz, Chloroform-*d*) δ:** 169.97 (C-8), 155.51 (t, *J* = 9.5 Hz, C-1), 73.35 (C-3), 55.11 (t, *J* = 13.5 Hz, C-2), 31.27 (C-4), 29.36 (C-7), 22.83 (C-5), 22.73 (C-6), 20.94 (C-9). **HRMS:** (m/*z*), calculated for $C_9H_{14}NO_2$: 168.1019, found $(M + H)^{+}$: 168.1017.

3.3 Synthesis of imidazo[1,2-*a*]pyridines

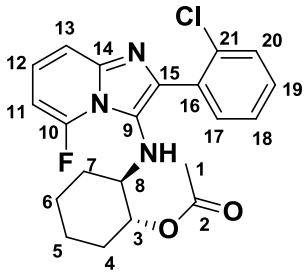
General Procedures

Method A: In the presence of montmorillonite K-10 clay (250 mg) a mixture of 2-amino-6-fluoropyridine (1.00 mmol), benzaldehyde (1.00 mmol), and isocyanide **30** (1.00 mmol) in dioxane (2.0 ml) was irradiated in a sealed tube at 120 Watts and 100℃ for 30 minutes. The reaction was allowed to cool to room temperature, and the K-10 clay was removed by filtering the solution through celite and washing with ethyl acetate. The solvent was removed *in vacuo* and the obtained residue purified by column chromatography (flash silica gel). The column was eluted first with 200 ml hexane followed by 300 ml of 20% E/H and 200 ml of 40% E/H, and the product was collected by eluting with 60% E/H (400-500 ml).

Method B: In the presence of catalytic amounts of iodine (10% mol), a mixture of 2-amino-6-fluoropyridine (1.00 mmol), benzaldehyde (1.00 mmol), and isocyanide **30** (1.00 mmol) in dioxane (5.0 ml) was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the obtained residue purified by column chromatography (flash silica gel). The column was first eluted with 200 ml hexane followed by 400 ml of 20% E/H and 200 ml of 40% E/H, and the product was collected by eluting with 60% E/H (400-500 ml).

Method C: In the presence of montmorillonite K-10 clay (110 mg) a mixture of 2-amino-6-fluoro-pyridine (1.00 mmol), benzaldehyde (1.00 mmol), and isocyanide **30** (1.00 mmol) in dioxane (2.0 ml) was irradiated in a sealed tube at 120 Watts and 100℃ for 30 minutes. For work-up and product purification, the same procedure was used as described for Method A.

3.3.1 Synthesis of 2-((2-(2-chlorophenyl)-5-fluoroimidazo[1,2-*a*]pyridin-3-yl)amino) cyclohexyl acetate 33



***rac*-33**

Method A: In accordance with the general procedure, isocyanide **30** (1 eq., 0.167 g, 1.00 mmol), 2-chlorobenzaldehyde (1 eq., 0.11 ml, 1 mmol), and 2-amino-6-fluoropyridine (1 eq., 0.112 g, 1.00 mmol) in dioxane were heated under microwave irradiation in the presence of K-10 clay (250 mg). The residue obtained from the resulting mixture was purified by flash column chromatography to give the desired product **33** as a black oil (0.112 g, 28% yield).

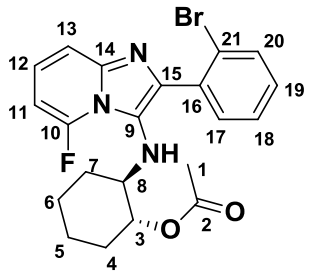
Method B: As per the general procedure; isocyanide **30** (1 eq., 0.167 g, 1.00 mmol), 2-chlorobenzaldehyde (1 eq., 0.11 ml, 1.00 mmol), and 2-amino-6-fluoro-pyridine (1 eq, 0.112 g, 1.00 mmol) in dioxane were stirred in the presence of catalytic amounts of iodine (10 % mol, 0.0258 g, 0.102 mmol). The residue obtained from the resulting mixture was purified by flash column chromatography to give the desired product **31** as a black oil (0.112 g, 28% yield).

Method C: In accordance with the general procedure, **30** (1 eq., 0.167 g, 1.00 mmol), 2-chlorobenzaldehyde (1 eq., 0.11 ml, 1.00 mmol), and 2-amino-6-fluoropyridine (1 eq., 0.112 g, 1.00 mmol) in dioxane were heated under microwave irradiation in the presence of K-10 clay (110 mg). The residue obtained from the resulting mixture was purified by flash column chromatography to give the desired product **33** as a black oil (0.220 g, 54% yield).

R_f = 0.21 (60% E/H): **IR** (ν_{max}/cm^{-1}): 3352 (N-H), 2937 (C-H alkyl), 1730 (C=O), 1651 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.59 (1H, m, H-17), 7.49 (1H, m, H-20), 7.33-

7.37 (3H, m, H-18, H-19 and H-13), 7.09 (1H, ddd, *J* = 9.0, 7.4, 6.0 Hz, H-12), 6.38 (1H, td,*J* = 7.2, 1.0 Hz H-11), 4.58 (1H, td, *J* = 9.5, 4.4 Hz, H-3), 3.54 (1H, d, *J* = 5.4 Hz, N-H), 2.85-2.84 (1H, m, H-8), 1.92 (3H, s, CH_3), 1.90-1.87 (1H, m), 1.70-1.46 (3H, m), 1.26-1.12 (2H, m), 1.02-0.93 (2H, m). **^{13}C NMR (126 MHz, Chloroform-*d*) δ** 170.74 (C-2), 150.55 (d, *J* = 267.9 Hz, C-10), 143.67 (C-14, d, *J* = 3.2 Hz), 136.23 (C-9), 133.40 (C-16), 133.26 (C-15), 132.51 (C-17), 129.59 (C-20), 129.49 (C-18), 126.77 (C-19), 126.08 (C-21), 124.22 (d, *J* = 6.5 Hz, C-12), 113.81 (d, *J* = 5.1 Hz, C-13), 93.10 (d, *J* = 17.3 Hz, C-11), 76.38 (C-3), 60.83 (C-8), 30.89 (C-7), 30.20 (C-4), 23.69 (C-5 and C-6), 21.07 (C-1). **HRMS:** (m/*z*), calculated for $C_{21}H_{22}ClFN_3O_2$: 402.1379, found $(M + H)^+$: 402.1400.

3.3.2 Synthesis of 2-((2-(2-bromophenyl)-5-fluoroimidazo[1,2-*a*]pyridin-3-yl)amino) cyclohexyl acetate 34



***rac*-34**

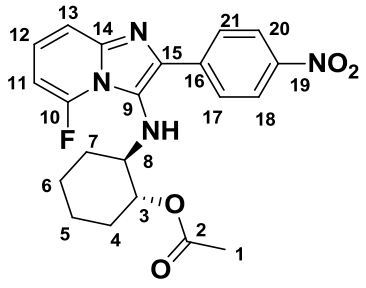
Method A: In accordance with the general procedure, isocyanide **30** (1 eq., 0.167 g, 1.00 mmol), 2-bromobenzaldehyde (1 eq., 0.12 ml, 1.00 mmol), and 2-amino-6-fluoropyridine (1 eq., 0.112 g, 1.00 mmol) were heated under microwave irradiation in the presence of K-10 clay (250 mg). The obtained residue was purified by flash column chromatography to give the desired product **34** as a black oil (0.120 g, 27% yield)

Method B: As per the general procedure; isocyanide **30** (1 eq., 0.167 g, 1.00 mmol), 2-bromobenzaldehyde (1 eq., 0.12 ml, 1.00 mmol), and 2-amino-6-fluoropyridine (1 eq., 0.112 g, 1.00 mmol) in dioxane were reacted together in the presence of catalytic amounts of iodine (10 % mol, 0.0258 g, 0.102 mmol). The obtained residue was purified by flash column chromatography to give the desired product **34** as a black oil (0.067 g, 15% yield).

Method C: In accordance with the general procedure, isocyanide **30** (1 eq., 0.167 g, 1.00 mmol), 2-bromobenzaldehyde (1 eq., 0.12 ml, 1.00 mmol), and 2-amino-6-fluoropyridine (1 eq., 0.112 g, 1.00 mmol) were reacted together in the presence of K-10 clay (110 mg). The obtained residue was purified by flash column chromatography to give the desired product **34** as a black oil (0.120 g, 27% yield)

R_f = 0.2 (60% E/H): **IR** (ν_{max}/cm^{-1}): 3352 (N-H), 2937 (C-H alkyl), 1730 (C=O), 1651 (C=N), **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.69 (1H, dd, *J* = 8.0, 1.2 Hz, H-17), 7.55(1H, dd, *J* = 7.6, 1.8 Hz, H-20), 7.41 (1H, td, *J* = 7.0, 1.4 Hz, H-19), 7.36 (1H, dd, *J* = 9.1, 0.6 Hz, H-13), 7.29 (1H, td, *J* = 9.1, 0.9 Hz, H-18), 7.10 (1H, ddd, *J* = 9.0, 7.4, 6.0 Hz, H-12), 6.39 (1H, td, *J* = 7.3, 0.8 Hz, H-11), 4.59 (1H, td, *J* = 9.6, 4.5 Hz, H-3), 3.52 (1H, d, *J* = 5.0 Hz, N-H), 2.86-2.85 (1H, m, H-8), 2.01-1.85 (4H, m, H-1, H-4$_a$), 1.77-1.43 (3H, m, H-7$_a$, H-6$_a$ and H-5$_a$) 1.26-1.14 (2H, m, H-6$_b$ and H-4$_b$), 1.02-0.95 (2H, m, H-5$_b$ and H-7$_b$). **^{13}C NMR (126 MHz, Chloroform-*d*) δ** 170.73 (C-2), 150.55 (d, *J* = 267.8 Hz, C-10), 143.47 (d, *J* = 3.2 Hz, C-14), 137.73 (C-9), 135.31 (C-16), 132.74 (C-17), 132.62 (C-20), 129.69 (C-18), 127.27 (C-19), 125.72 (C-15), 124.16 (d, *J* = 6.5 Hz, C-12), 123.58 (C-21), 113.80 (d, *J* = 5.1 Hz, C-13), 93.14 (d, *J* = 17.4 Hz, C-11), 76.36 (C-3), 60.78 (C-8), 30.92 (C-7), 30.16 (C-4), 23.66 (C-5 and C-6), 21.10 (C-1). **HRMS:** (m/*z*), calculated for $C_{21}H_{22}BrFN_3O_2$: 446.0874, found (M + H)$^+$: 446.0898.

3.3.3 Synthesis of 2-((5-fluoro-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino) cyclohexyl acetate 35



***rac*-35**

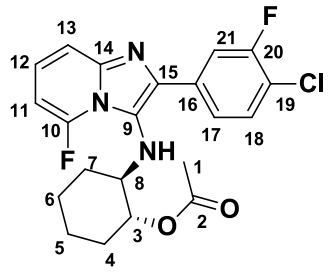
Method A: In accordance with the general procedure, isocyanide **30** (1 eq., 0.167 g, 1.00 mmol), 4-nitrobenzaldehyde (1 eq., 0.151 g, 1.00 mmol), and 2-amino-6-fluoropyridine (1

eq., 0.112 g, 1.00 mmol) were heated under microwave irradiation in the presence of K-10 clay (250 mg). The obtained residue was purified by column chromatography to give the desired product **35** as a black oil (0.025 g, 6% yield)

Method C: In accordance with the general procedure, isocyanide **30** (1 eq., 0.1672 g, 1.00 mmol), 4-nitrobenzaldehyde (1 eq., 0.1511 g, 1.00 mmol), and 2-amino-6-fluoropyridine (1 eq., 0.1121 g, 1.00 mmol) were heated under microwave irradiation in the presence of K-10 clay (110 mg). The obtained residue was purified by column chromatography to give the desired product **35** as a black oil (0.107 g, 26% yield)

Rf = 0.22 (60% E/H): **IR** (ν_{max}/cm^{-1}); 3367 (N-H), 3108 (=C-H), 2961 (C-H), 1732 (C=O), 1652 (C=N), **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.53-8.49 (2H, m, H-18 and H-20), 8.31-8.26 (2H, m, H-17 and H-21), 7.37 (1H, d, *J* = 9.1 Hz, H-13), 7.18-7.11 (1H, m, H-12), 6.41 (1H, td, *J* = 7.3, 0.9 Hz, H-11), 4.79 (1H, td, *J* = 10.0, 4.5 Hz, H-3), 3.66 (1H, d, *J* = 7.1 Hz, N-H), 3.14-3.03 (1H, m, H-8), 2.14-2.00 (1H, m, H-4$_a$), 1.94 (3H, s, H-1), 1.85-1.54 (3H, m, H-5$_a$, H-6$_a$ and H-7$_a$), 1.45-1.18 (3H, m, H-4$_b$, H-5$_b$ and H-7$_b$), 1.18-1.02 (1H, m, H-6$_b$). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 170.71 (C-2), 146.76 (C-19), 144.07 (C-14), 140.51 (C-9), 134.75 (C-16), 127.75 (C-18 and C-20), 126.00 (C-15), 125.34 (d, *J* = 6.8 Hz, C-12), 123.68 (C-17 and C-21), 114.18 (d, *J* = 4.9 Hz, C-13), 93.46 (d, *J* = 17.6 Hz, C-11), 77.37 (C-3), 61.34 (C-8), 31.21 (C-7), 30.74 (C-4), 24.07 (C-5), 23.99 (C-6), 21.05 (C-1). **HRMS**; (m/*z*), calculated for $C_{21}H_{22}FN_4O_4$: 413.1620, found $(M + H)^+$: 413.1650.

3.3.4 Synthesis of 2-((2-(4-chloro-3-fluorophenyl)-5-fluoroimidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate 36

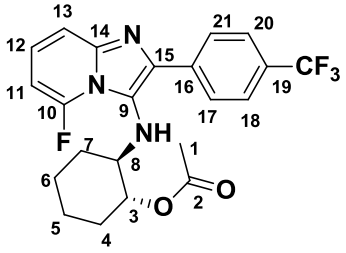


***rac*-36**

Method C: In accordance with the general procedure, isocyanide **30** (1 eq., 0.167 g, 1.00 mmol), 4-chloro-3-fluorobenzaldehyde (1 eq., 0.159 g, 1.00 mmol), and 2-amino-6-fluoropyridine (1 eq., 0.112 g, 1.00 mmol) were heated under microwave irradiation in the presence of K-10 clay (110 mg). The obtained residue was purified by column chromatography and preparative-TLC to give the desired product **36** together with an unidentified byproduct that could not be separated by chromatography as a light brown oil (0.105 g, 25% yield).

Rf = 0.39 (60% E/H): **IR** (ν_{max}/cm^{-1}); 3302 (N-H), 2943 (C-H), 1729 (C=O), 1655 (C=N); **^{1}H NMR (500 MHz, Chloroform-*d*) δ** 8.18 (1H, dd, *J* = 11.0, 1.9 Hz, H-21), 8.06 (1H, ddd, *J* = 8.5, 1.9, 0.8 Hz, H-17), 7.46-7.41 (1H, m, H-18), 7.33 (1H, d, *J* = 9.0, H-13), 7.13-7.08 (1H, m, H-12), 6.37 (1H, td, *J* = 7.2, 0.9 Hz, H-11), 4.78 (1H, td, *J* = 10.0, 4.5 Hz, H-3), 3.51 (1H, d, *J* = 5.7 Hz, N-H), 3.17-2.98 (1H, m, H-8), 2.10-2.03 (1H, m, H-4$_a$), 1.95 (3H, s, H-1), 1.84-1.57 (3H, m, H-6$_a$, H-5$_a$, and H-7$_a$), 1.46-1.20 (4H, m, H-4$_b$, H-5$_b$, H-6$_b$, and H-7$_b$). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 170.84 (C-2), 158.18 (d, *J* = 246.6 Hz, C-20), 150.47 (d, *J* = 265.3 Hz, C-10), 143.82 (d, *J* = 3.6 Hz, C-14), 135.06 (C-9), 134.53 (d, *J* = 7.7 Hz, C-16), 130.35 (C-18), 124.91 (d, *J* = 6.7 Hz, C-12), 124.61 (C-15), 123.68 (d, *J* = 3.6 Hz, C-17), 119.80 (d, *J* = 17.9 Hz, C-19), 115.26 (d, *J* = 23.2 Hz, C-21), 113.91 (d, *J* = 5.0 Hz, C-13), 93.22 (d, *J* = 17.7 Hz, C-11), 71.48 (C-3), 61.22 (C-8), 31.24 (C-7), 30.79 (C-4), 24.09 and 24.05 (C-5 and C-6), 23.81 (C-1). **HRMS**; (m/*z*), calculated for $C_{21}H_{21}ClF_2N_3O_2$: 420.1285, found $(M + H)^+$: 420.1314.

3.3.5 Synthesis of 2-((5-fluoro-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexyl acetate 37

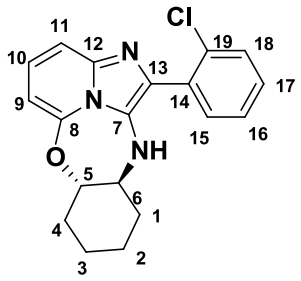


***rac*-37**

Method C: In accordance with the general procedure, isocyanide **30** (1 eq., 0.167 g, 1.00 mmol), 4-trifluromethylbenzaldehyde (1 eq., 0.13 ml, 1.00 mmol), and 2-amino-6-fluoropyridine (1 eq., 0.112 g, 1.00 mmol) were heated under microwave irradiation in the presence of K-10 clay (110 mg). The obtained residue was purified by column chromatography and preparative-TLC to give the desired product **37** together with an unidentified byproduct that could not be separated by chromatography as a light yellow oil (0.030 g, 7.0% yield).

Rf = 0.33 (60% E/H): **IR** (ν_{max}/cm^{-1}); 3487 (N-H), 2985 (C-H), 1731 (C=O), 1655 (C=N); **^{1}H NMR (500 MHz, Chloroform-*d*) δ** 8.43 (2H, d, *J* = 8.1 Hz, H-18 and H-20), 7.68 (2H, d, *J* = 8.2 Hz, H-17 and H-21), 7.37 (1H, d, *J* = 9.0 Hz, H-13), 7.15-7.09 (1H, m, H-12), 6.38 (1H, td, *J* = 7.3, 0.9 Hz, H-11), 4.78 (1H, td, *J* = 10.0, 4.5 Hz, H-3), 3.57 (1H, d, *J* = 5.8 Hz, N-H), 3.13-3.05 (1H, m, H-8), 2.09-2.03 (1H, m, H-4$_a$), 1.93 (3H, s, H-1), 1.83-1.65 (3H, m, H-5$_a$, H-6$_a$, and H-7$_a$), 1.44-1.17 (4H, m, H-4$_b$, H-5$_b$, H-6$_b$, and H-7$_b$). **HRMS**; (m/*z*), calculated for $C_{22}H_{22}F_4N_3O_2$: 436.1643, found $(M + H)^+$: 436.1669.

3.3.6 Synthesis of 1-(2-chlorophenyl)-7,8,9,10,10a,11-hexahydro-6aH-6-oxa-2,2a',11-triazadibenzo[cd,g]azulene 38a



***rac*-38a**

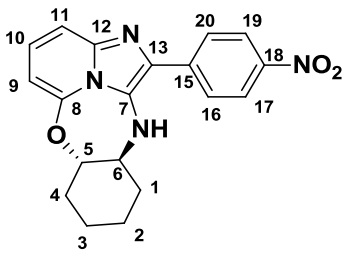
Method A: Compound **33** (1 eq., 0.0983 g, 0.254 mmol) was dissolved in methanol (3.0 ml) and treated with K_2CO_3 (2 eq., 0.070 g, 0.508 mmol) for 4 h at room temperature. The solvent was removed *in vacuo*, and the obtained residue was purified using column chromatography (silica gel, 1.5:1 E/H) to give product **38a** as a black wax (0.69 mg, 10%).

Method B: Compound **33** (1 eq., 0.210 g, 0.542 mmol) was dissolved in methanol (3.0 ml) and treated with KOH (1 eq., 0.303 g, 0.542 mmol) for 24 h at room temperature. The

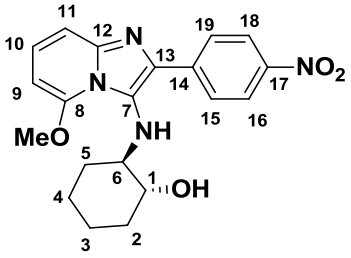
solvent was removed *in vacuo*, and the obtained residue was purified using column chromatography (silica gel, 1.5:1 E/H) to give product **38a** as a black wax (72.0 mg, 39%).

R_f = 0.65 (60% E/H): **IR** (ν_{max}/cm^{-1}): 3301 (N-H), 3067 (=C-H), 2937 (C-H), 1638 (C=N): **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.69 (1H, dd, *J* = 7.8, 1.5 Hz, H-15) , 7.48 (1H, dd, *J* = 7.6, 1.9 Hz, H-18), 7.40-7.24 (3H, m, H-17, H-16, H-11) 6.98 (1H, dd, *J* = 9.0, 7.2 Hz, H-10), 6.23 (1H, dd, *J* = 7.2, 1.0 Hz, H-9), 4.14 (1H, ddd, *J* = 11.2, 9.0, 4.9 Hz, H-5), 3.86 (1H, s, N-H), 3.42 (1H, ddd, *J* = 11.0, 9.0, 5.0 Hz, H-6), 2.39-2.24 (1H, m, H-4$_a$), 2.09-2.01 (3H, m, H-1), 1.89-1.80 (1H, m), 1.80-1.58 (2H, m), 1.49-1.31 (3H, m). **^{13}C NMR (126 MHz, Chloroform-*d*) δ** 147.57 (C-8), 142.63 (C-12), 133.46 (C-7), 133.04 (C-16), 132.37 (C-13), 129.83 (C-18), 128.77 (C-15), 128.17 (C-19), 127.10 (C-17), 124.33 (C-10), 123.56 (C-14), 111.72 (C-11), 96.57 (C-9), 88.40 (C-5), 60.37 (C-6), 32.85 (C-1), 31.62 (C-4), 23.90 and 23.57 (C-3 and C-2). **HRMS**; (m/*z*), calculated for $C_{19}H_{19}ClN_3O$: 340.1211, found $(M + H)^+$: 340.1181.

3.3.7 Synthesis of 1-(4-nitrophenyl)-7,8,9,10,10a,11-hexahydro-6aH-6-oxa-2,2a1,11-triazadibenzo[cd,g]azulene (39a) and 2-((5-methoxy-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)cyclohexanol (39b)



***rac*-39a**



***rac*-39b**

Compound **35** (1 eq., 0.162 g, 0.399 mmol) was dissolved in methanol (3.0 ml) and treated with KOH (10 eq., 0.224 g, 3.99 mmol) for 4 h at room temperature. After this reaction time, the solvent was removed *in vacuo* and the obtained residue purified using column chromatography (silica gel, 1.5:1 E/H) to give compounds **39a** (39.0 mg, 28%) as light yellow oil and **39b** (63.0 mg, 41%) as a dark orange solid.

Compound 39a: Rf = 0.83 (60% E/H), **IR** (ν_{max}/cm^{-1}): 3348 (N-H), 3108 (=C-H), 2938 (C-H), 1676 (C=N); **^{1}H NMR (500 MHz, Chloroform-*d*) δ** 8.66 (2H, d, *J* = 8.8 Hz, H-17 and H-19), 8.36-8.25 (2H, m, H-16 and H-20), 7.35 (1H, d, *J* = 8.9 Hz, H-11), 7.27-7.25 (1H, m, H-10), 6.40 (1H, d, *J* = 7.3 Hz, H-9), 4.72 (1H, dd, *J* = 9.3, 6.3 Hz, H-5), 2.93 (1H, dt, *J* = 15.7, 5.2 Hz, N-H), 2.65 (1H, ddd, *J* = 15.9, 10.6, 5.9 Hz, H-6), 2.50-2.42 (1H, m), 2.11-1.95 (3H, m), 1.81-1.65 (4H, m). **HMRS**; (m/*z*), calculated for $C_{19}H_{18}N_4O_3$: 350.1373, found (M + H)$^+$: 350.1317.

Compound 39b: Rf = 0.20 (60% E/H), **IR** (ν_{max}/cm^{-1}): 3347 (N-H), 3245 (O-H), 2938 (C-H), 1638 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.52-8.44 (2H, m, H-18 and H-20), 8.28-8.20 (2H, m, H-15 and H-19), 7.24-7.01 (2H, m, H-10 and H-11), 5.97 (1H, dd, *J* = 7.2, 1.1 Hz, H-9), 4.07 (3H, s, OMe), 3.88-3.65 (2H, m, N-H and O-H), 3.52 (1H, td, *J* = 9.7, 4.4 Hz, H-1), 2.88-2.69 (1H, m, H-6), 2.05-1.96 (1H, m, H-2), 1.69-1.62 (1H, m, H-3), 1.51-1.46 (2H, m, H-4 and H-5), 1.34-1.16 (2H, m, H-2 and H-3), 1.05-0.93 (2H, m, H-4 and H-5). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 152.05 (C-8), 146.30 (C-17), 144.05 (C-12), 141.56 (C-7), 133.62 (C-14), 128.21 (C-13), 127.83 (C-16 and C-18), 125.92 (C-10), 123.52 (C-15 and C-19), 110.74 (C-11), 88.55 (C-9), 75.22 (C-1), 65.52 (C-6), 56.37 (OMe), 34.22 (C-2), 30.92 (C-4), 30.07 (C-5), 24.35 (C-3). **HMRS**; (m/*z*), calculated for $C_{20}H_{23}N_4O_4$: 383.1714, found (M + H)$^+$: 383.1717.

3.4 Synthesis of imidazo[1,2-*a*]pyridines 45-56 using convertible isocyanides

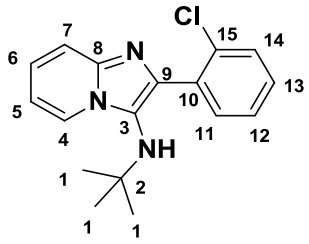
General procedures

Method A: In the presence of montmorillonite K-10 clay (250 mg) a mixture of an appropriate aminopyridine (1.00 mmol), benzaldehyde (1.00 mmol), and isocyanide (1.00 mmol) in *n*-butanol (2.0 ml) was irradiated in a sealed tube at 120 Watts and 140℃ for 25 minutes. The reaction was allowed to cool to room temperature, and the K-10 clay was removed by filtering the solution through celite and washing it with ethyl acetate. The solvent was removed *in vacuo* and the obtained residue purified by column chromatography (silica gel, 60% E/H) to give the desired product.

Method B: In the presence of catalytic amounts of iodine (10% mol), a mixture of 2-amino-aminopyridine (1 eq.), benzaldehyde (1 eq.), and isocyanide (1 eq.) in methanol was

stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the obtained residue purified by column chromatography (silica gel, 60% E/H) to give the desired product.

3.4.1 Synthesis of *N*-(*tert*-butyl)-2-(2-chlorophenyl)imidazo[1,2-*a*]pyridin-3-amine 45



45

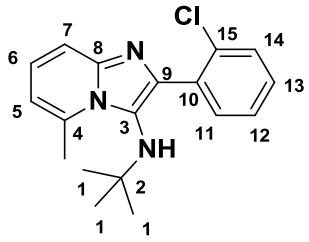
Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), 2-chlorobenzaldehyde (1 eq., 0.11 ml, 1.00 mmol), and 2-aminopyridine (1 eq., 0.090 g, 1 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (1.5:1 E/H) to give the desired product **45** as a yellow solid (0.264 g, 88% yield).

Method B: As per the general procedure; *tert*-butyl isocyanide (1 eq., 2.4 ml, 21.3 mmol), 2-chlorobenzaldehyde (1 eq., 2.4 ml, 21.3 mmol), and 2-aminopyridine (1 eq., 2.00 g, 21.3 mmol) in methanol were reacted together in the presence of catalytic amounts of iodine (10 % mol, 0.67 g, 2.63 mmol). The obtained residue was purified by column chromatography (1.5:1 E/H) to give the desired product **45** as a yellow solid (3.38 g, 69% yield).

R_f = 0.43 (60% E/H): **m.p**: 155-158 °C: **IR** (ν_{max}/cm^{-1}): 3376 (N-H), 3010 (=C-H aromatic), 2969 (C-H alkyl), 1627 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.32 (1H, dt, *J* = 6.9, 1.2 Hz, H-4), 7.72 (1H, dd, *J* = 7.6, 1.8 Hz, H-11), 7.54 (1H, dt, *J* = 9.0, 1.1 Hz, H-7), 7.46 (1H, dd, *J* = 7.9, 1.4 Hz, H-14), 7.37 (1H, td, *J* = 7.5, 1.4 Hz, H-12), 7.31 (1H, td, *J* = 7.5, 1.4 Hz, H-13), 7.16 (1H, ddd, *J* = 9.1, 6.6, 1.3 Hz, H-6), 6.79 (1H, td, *J* = 6.8, 1.1 Hz, H-5), 3.20 (1H, s, N-H), 0.93 (9H, s, H-1).**^{13}C NMR (75 MHz, Chloroform-*d*) δ** 142.22 (C-8), 137.62 (C-3), 134.87 (C-9), 132.79 (C-11), 132.40 (C-15), 129.47 (C-14), 129.11 (C-

13), 127.00 (C-12), 125.07 (C-10), 124.15 (C-6), 123.65 (C-4), 117.39 (C-7), 111.37 (C-5), 55.79 (C-2), 29.89 (C-1). **HRMS**: (m/*z*), calculated for $C_{17}H_{19}ClN_3$: 300.1262, found (M + H)$^+$: 300.1270.

3.4.2 Synthesis of *N*-(*tert*-butyl)-2-(2-chlorophenyl)-5-methylimidazo[1,2-*a*]pyridin-3-amine 46



46

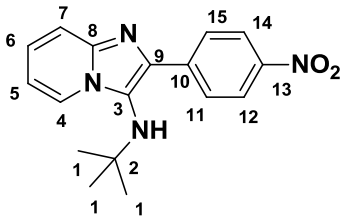
Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), 2-chlorobenzaldehyde (1 eq., 0.11 ml, 1.00 mmol), and 2-amino-6-methylpyridine (1 eq., 0.108 g, 1.00 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (1.5:1 E/H) to give the desired product **46** as a brown solid (0.238 g, 76% yield).

Method B: As per the general procedure; *tert*-butyl isocyanide (1 eq., 2.09 ml, 18.5 mmol), 2-chlorobenzaldehyde (1 eq., 2.1 ml, 18.5 mmol), and 2-amino-6-methylpyridine (1 eq., 2.0 g, 18.5 mmol) in methanol were reacted together in the presence of catalytic amounts of iodine (10 % mol, 0.4692 g, 1.85 mmol). The obtained residue was purified by column chromatography (1.5:1 E/H) to give the desired product **46** as a brown solid (4.12 g, 71% yield).

R_f = 0.49 (60% E/H): **m.p:** 154-157 °C; **IR** (ν_{max}/cm^{-1}): 3361 (N-H), 3062 (=C-H aromatic), 2959 (C-H alkyl), 1635 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.76 (1H, dd, *J* = 7.6, 1.8 Hz, H-11), 7.46-7.40 (2H, m, H-7 and H-14), 7.37 (1H, td, *J* = 7.5, 1.5 Hz, H-12), 7.30 (1H, td, *J* = 7.8, 1.5 Hz, H-13), 7.04 (1H, dd, *J* = 9.0, 6.8 Hz, H-6), 6.46 (1H, dd, *J* = 6.9, 2.1 Hz, H-5), 2.98 (4H, s, N-H and Ar-CH_3), 0.83 (9H, s, H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 143.54 (C-8), 139.12 (C-3), 137.20 (C-9), 135.41 (C-15), 132.82 (C-12), 132.52 (C-4), 129.45 (C-7), 129.04 (C-13), 127.29 (C-11), 126.99 (C-12), 124.29 (C-6),

115.80 (C-14), 113.92 (C-5), 55.59 (C-2), 29.53 (C-1), 20.79 (Ar-CH_3). **HRMS**; (m/*z*), calculated for $C_{18}H_{21}ClN_3$: 314.1419, found $(M + H)^+$: 314.1426.

3.4.3 Synthesis of *N*-(*tert*-butyl)-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridin-3-amine 47

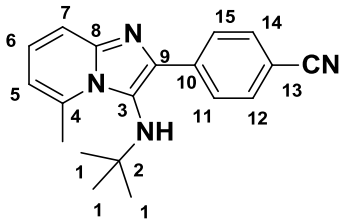


47

Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), 4-nitrobenzaldehyde (1 eq., 0.151 g, 1.00 mmol), and 2-aminopyridine (1 eq., 0.09 g, 1.00 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (40% E/H) to give the desired product **47** as an orange solid (0.165 g, 53% yield).

R_f = 0.21 (40% E/H): **m.p:** 218-220°C; **IR** (ν_{max}/cm^{-1}): 3311 (N-H bend) and 3358 (N-H stretch), 3031 (=C-H), 2959 (C-H alkyl), 1633 (C=N), 1507 (N=O); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.30-8.25 (4H, m, H-11, H-12, H-14, H-15), 8.19 (1H, dt, *J* = 6.9, 1.1 Hz, H-4), 7.55 (1H, dt, *J* = 9.1, 1.0 Hz, H-7), 7.19 (1H, ddd, *J* = 9.1, 6.6, 1.2 Hz, H-6), 6.83 (1H, td, *J* = 6.8, 1.2 Hz, H-5), 3.04 (1H, s, N-H), 1.09 (9H, s, H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 146.69 (C-13), 142.57 (C-8), 141.99 (C-3), 137.17 (C-10), 128.42 (C-12, C-14), 124.97 (C-6), 124.83 (C-9), 123.57 (C-11 and C-15), 123.39 (C-4), 117.77 (C-7), 112.01 (C-5), 56.82 (C-2), 30.51 (C-1). **HRMS**; (m/*z*), calculated for $C_{17}H_{19}N_4O_2$: 311.1503, found $(M + H)^+$: 311.1507.

3.4.4 Synthesis of 4-(3-(*tert*-butylamino)-5-methylimidazo[1,2-*a*]pyridin-2-yl)benzonitrile 48

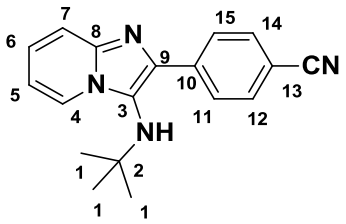


48

Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), 4-cyanobenzaldehyde (1 eq., 0.131 g, 1.00 mmol), and 2-amino-6-methylpyridine (1 eq., 0.108 g, 1.00 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (1:1 E/H) to give the desired product **48** as a brown solid (0.0822 g, 27% yield).

R_f = 0.17 (50% E/H): **m.p:** 154-157°C; **IR** (ν_{max}/cm^{-1}): 3369 (N-H), 3072 (=C-H), 2975 (C-H), 2225 (C≡N) 1630 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.05-7.99 (2H, m, H-12 and H-14), 7.71-7.69 (2H, m, H-11 and H-15), 7.42 (1H, d, *J* = 9.0 Hz, H-7), 7.08 (1H, dd, *J* = 9.0, 6.8 Hz, H-6), 6.50 (1H, d, *J* = 6.9 Hz, H-5), 3.03 (1H, s, N-H), 2.95 (3H, s, Ar-CH_3), 0.89 (9H, s, H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 143.74 (C-8), 140.55 (C-3), 139.54 (C-10), 136.88 (C-9), 132.06 (C-12 and C-14), 129.06 (C-11 and C-15), 126.39 (C-4), 125.25 (C-6), 119.11 (C≡N), 115.94 (C-7), 114.55 (C-5), 110.71 (C-13), 56.88 (C-2), 29.67 (C-1), 20.81 (Ar-CH_3). **HRMS**: (m/*z*), calculated for $C_{19}H_{21}N_4$: 305.1761, found $(M + H)^+$: 305.1771.

3.4.5 Synthesis of 4-(3-(*tert*-butylamino)imidazo[1,2-*a*]pyridin-2-yl)benzonitrile 49

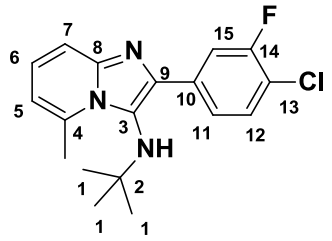


49

Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), 4-cyanobenzaldehyde (1 eq., 0.131 g, 1.00 mmol), and 2-aminopyridine (1 eq., 0.090 g, 1.00 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (40% E/H) to give the desired product **49** as a light yellow solid (0.203 g, 70% yield).

R_f = 0.21 (40% E/H): **m.p:** 157-160℃; **IR** (ν_{max}/cm^{-1}): 3280 (N-H), 3088 (=C-H), 2966 (C-H), 2227 (C≡N), 1631 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.22- 8.13 (3H, m, H-4, H-12 and H-14), 7.71-7.69 (2H, m, H-11 and H-15), 7.53 (1H, d, *J* = 8.3, H-7), 7.18 (1H, ddd, *J* = 9.0, 6.6, 1.3 Hz, H-6), 6.82 (1H, td, *J* = 6.8, 1.1 Hz, H-5), 3.02 (1H, s, N-H), 1.07 (9H, s, H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 142.45 (C-8), 139.96 (C-3), 137.47 (C-10), 132.02 (C-14 and C-12), 128.40 (C-11 and C-15), 124.86 (C-6), 124.47 (C-9), 123.40 (C-4), 119.16 (C≡N), 117.64 (C-7), 111.92 (C-5), 110.55 (C-13), 56.73 (C-2), 30.47 (C-1) **HRMS**: (m/*z*), calculated for $C_{18}H_{19}N_4$: 291.1565, found (M + H)$^+$: 291.1604.

3.4.6 Synthesis of *N*-(*tert*-butyl)-2-(4-chloro-3-fluorophenyl)-5-methylimidazo[1,2-*a*]pyridin-3-amine 50



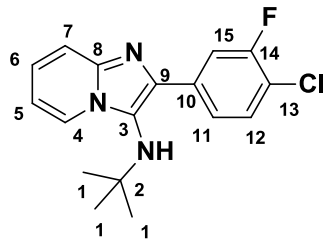
50

Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), 4-chloro-3-fluorobenzaldehyde (1 eq., 0.159 g, 1.00 mmol), and 2-amino-6-methylpyridine (1 eq., 0.108 g, 1.00 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (1:1 E/H) to give the desired product **50** as a yellow solid (0.109 g, 33% yield).

R_f = 0.13 (50% E/H): **m.p:** 164-167℃; **IR** (ν_{max}/cm^{-1}): 3280 (N-H), 3054 (=C-H), 2974 (C-H alkyl), 1632 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.70 (1H, dd, *J* = 10.4, 1.9 Hz, H-15), 7.64-7.57 (1H, m, H-11), 7.46-7.38 (2H, m, H-7 and H-12), 7.06 (1H, dd, *J* = 9.0,

6.8 Hz, H-6), 6.48 (1H, d, *J* = 6.7, H-5), 2.98 (1H, s, N-H), 2.94 (3H, s, Ar-CH_3), 0.90 (9H, s, H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 158.02 (d, *J* = 247.8 Hz, C-14), 143.39 (C-8), 139.32 (C-3), 136.90 (C-9), 136.38 (d, *J* = 7.3 Hz, C-10), 130.35 (C-12), 125.76 (C-4), 125.08 (C-6), 124.94 (d, *J* = 3.4 Hz, C-11), 119.81 (d, *J* = 17.9 Hz, C-13), 116.62 (d, *J* = 22.1 Hz, C-15), 115.77 (C-7), 114.43 (C-5), 56.77 (C-2), 29.72 (C-1), 20.77 (Ar-CH_3). **HRMS**: (m/*z*), calculated for $C_{18}H_{20}ClFN_3$; 332.1324, found $(M + H)^+$: 332.1326.

3.4.7 Synthesis of *N*-(*tert*-butyl)-2-(4-chloro-3-fluorophenyl)imidazo[1,2-*a*]pyridin-3-amine 51



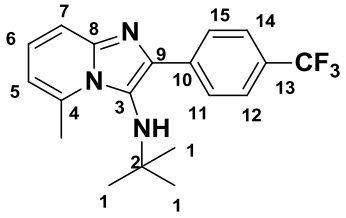
51

Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), 4-chloro-3-fluorobenzaldehyde (1 eq., 0.11 ml, 1.00 mmol), and 2-aminopyridine (1 eq., 0.09 g, 1.00 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (40% E/H) to give the desired product **51** as a yellow solid (0.184 g, 58% yield).

R_f = 0.40 (40% E/H): **m.p:** 176-180℃**; IR** (ν_{max}/cm^{-1}): 3267 (N-H) 3092 (=C-H), 2964 (C-H), 1632 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.17 (1H, dt, *J* = 6.9, 1.2 Hz, H-4), 7.87 (1H, dd, *J* = 10.6, 1.9 Hz, H-15), 7.76 (1H, dd, *J* = 9.6, 1.6 Hz, H-11), 7.51 (1H, d, *J* = 9.0 Hz, H-7), 7.46-7.38 (1H, m, H-12), 7.15 (1H, ddd, *J* = 9.1, 6.6, 1.3 Hz, H-6), 6.79 (1H, td, *J* = 6.8, 1.2 Hz, H-5), 2.95 (1H, s, N-H), 1.08 (9H, s, H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ HRMS:** 158.00 (d, *J* = 247.3 Hz, C-14), 142.19 (C-8), 137.44 (C-3), 135.96 (d, *J* = 7.5 Hz, C-10), 130.26 (C-12), 124.55 (C-6), 124.28 (d, *J* = 3.5 Hz, C-11), 123.68 (C-9), 123.33 (C-4), 119.58 (d, *J* = 17.7 Hz, C-13), 117.49 (C-7), 115.99 (d, *J* =

22.3 Hz, C-15), 111.70 (C-5), 56.60 (C-2), 30.48 (C-1). **HRMS**; (m/*z*), calculated for $C_{17}H_{18}ClFN_3$: 318.1168, found $(M + H)^+$: 318.1176.

3.4.8 Synthesis of *N*-(*tert*-butyl)-5-methyl-2-(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridin-3-amine 52

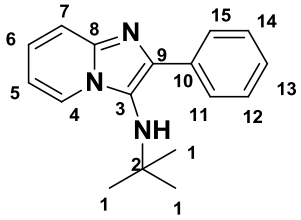


52

Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), 4-trifluoromethylbenzaldehyde (1 eq., 0.174 g, 1.00 mmol), and 2-amino-6-methylpyridine (1 eq., 0.108 g, 1.00 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (1:1 E/H) to give the desired product **52** as a yellow solid (0.316 g, 91% yield).

R_f = 0.13 (50% E/H): **m.p:** 90-93 ℃; **IR** (ν_{max}/cm^{-1}): 3331 (N-H), 3068 (=C-H), 2969 (C-H), 1636 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.97-7.94 (2H, m, H-12 and H-14), 7.73-7.61 (2H, m, H-11 and H-15), 7.40 (1H, d, *J* = 9.3 Hz, H-7), 7.07 (1H, dd, *J* = 9.0, 6.8 Hz, H-6), 6.79 (1H, dt, *J* = 7.3, 1.3 Hz, H-5), 3.05 (1H, s, N-H), 2.95 (3H, s, Ar-CH_3), 0.87 (9H, s, H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 143.56 (C-8), 140.11 (C-3), 139.45 (C-10), 136.97 (C-9), 128.80 (C-14), 126.89 (C-13), 126.12 (C-4), 125.19 (q, *J* = 3.8 Hz, C-11 and C-15), 124.96 (C-6), 115.80 (C-7), 114.36 (C-5), 56.72 (C-2), 29.65 (C-1), 20.79 (Ar-CH_3). **HRMS**: (m/*z*), calculated for $C_{19}H_{21}F_3N_3$: 348.1682, found $(M + H)^+$: 348.1692.

3.4.9 Synthesis of *N*-(*tert*-butyl)-2-phenylimidazo[1,2-*a*]pyridin-3-amine 53

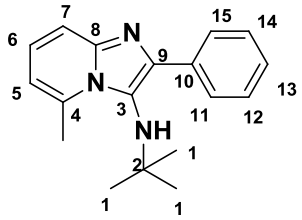


53

Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), benzaldehyde (1 eq., 0.11 ml, 1.00 mmol), and 2-aminopyridine (1 eq., 0.09 g, 1.00 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (1:1 E/H) to give the desired product **53** as a yellow solid (0.228 g, 86% yield).

R_f = 0.54 (50% E/H): **m.p:** 178-182 ℃; **IR** (cm^{-1}): 3316 (N-H), 3031 (=C-H), 2967 (C-H), 1631 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.23 (1H, dd, *J* = 6.9, 1.1 Hz, H-4), 7.91 (2H, dd, *J* = 7.3, 1.4 Hz, H-11 and H-15), 7.54 (1H, dd, *J* = 9.0, 1.1 Hz, H-7), 7.43 (2H, td, *J* = 7.3, 1.0 Hz, H-12 and H-14), 7.35-7.28 (1H, m, H-13), 7.13 (1H, ddd, *J* = 9.0, 6.7, 1.4 Hz, H-6), 6.77 (1H, td, *J* = 6.7, 1.1 Hz, H-5), 3.12 (1H, s, N-H), 1.04 (9H, s, H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 142.07 (C-8), 139.62 (C-3), 135.37 (C-10), 128.27 (C-11 and C-15), 128.18 (C-12 and C-14), 127.35 (C-13), 125.92 (C-9), 123.92 (C-6), 123.48 (C-4), 117.39 (C-7), 111.25 (C-5), 56.44 (C-2), 30.30 (C-1).

3.4.10 Synthesis of *N*-(*tert*-butyl)-5-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine 54



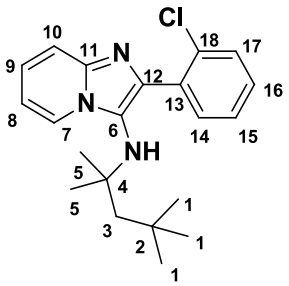
54

Method A: In accordance with the general procedure, *tert*-butyl isocyanide (1 eq., 0.11 ml, 1.00 mmol), benzaldehyde (1 eq., 0.11 ml, 1.00 mmol), and 2-amino-6-methylpyridine (1 eq., 0.108 g, 1.00 mmol) in *n*-butanol were reacted together in the presence of K-10 clay. The obtained residue was purified by column chromatography (50% E/H) to give the desired product **54** as a yellow solid (0.250 g, 90% yield).

R_f = 0.63 (50% E/H): **m.p:** 220-222 ℃; **IR** (ν_{max}/cm^{-1}): 3266 (N-H), 3061 (=C-H), 2932 (C-H), 1633 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.79 (2H, dd, *J* = 7.2, 1.3 Hz, H-11 and H-12), 7.47-7.35 (3H, m, H-12, H-14 and H-7), 7.33-7.26 (1H, m, H-13), 7.01 (1H, dd, *J* = 8.9, 6.8 Hz, H-6), 6.42 (1H, dt, *J* = 6.8, 0.9 Hz, H-5), 2.98 (1H, s, N-H), 2.92 (3H, s,

Ar-CH_3), 0.84 (9H, s, H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 143.23 (C-8), 141.64 (C-3), 136.92 (C-9), 135.88 (C-10), 128.69 (C-11 and C-15), 128.23 (C-12 and C-14), 127.33 (C-13), 125.62 (C-4), 124.23 (C-6), 115.64 (C-7), 113.87 (C-5), 56.41 (C-2), 29.56 (C-1), 20.75 (Ar-CH_3).

3.4.11 Synthesis of 2-(2-chlorophenyl)-N-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyridin-3-amine 55

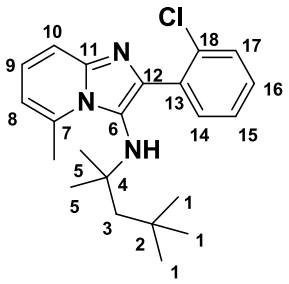


55

Method B: As per the general procedure; 1,1,3,3-tetramethylbutyl isocyanide (1 eq., 4.7 ml, 26.6 mmol), 2-chlorobenzaldehyde (1 eq., 2.9 ml, 26.6 mmol), and 2-aminopyridine (1 eq., 2.50 g, 26.6 mmol) in methanol were reacted together in the presence of catalytic amounts of iodine (10 % mol, 0.670 g, 2.66 mmol). The obtained residue was purified by column chromatography (1:1.5 E/H) to give the desired product **55** as a yellow solid (8.52 g, 90% yield).

R_f = 0.45 (60% E/H): **m.p**: 95-98℃; **IR** (ν_{max}/cm^{-1}): 3361 (N-H), 3067 (C-H aromatic), 2951 (C-H alkyl), 1621 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.32 (1H, dt, *J* = 6.9, 1.1 Hz, H-7), 7.71 (1H, dd, *J* = 7.5, 2.0 Hz, H-14), 7.53 (1H, dt, *J* = 9.0, 1.1 Hz, H-10), 7.45 (1H, dd, *J* = 7.5, 1.8 Hz, H-17), 7.36 (1H, td, *J* = 7.5, 2.0 Hz, H-15), 7.30 (1H, td, *J* = 7.5, 2.0 Hz, H-16), 7.13 (1H, ddd, *J* = 9.1, 6.6, 1.3 Hz, H-9), 6.78 (1H, td, *J* = 6.8, 1.2 Hz, H-8), 3.29 (1H, s, N-H), 1.44 (2H, s, H-3), 0.96 (9H, s, H-1), 0.89 (6H, s, H-5). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 142.19 (C-11), 137.82 (C-6), 135.13 (C-12), 132.79 (C-14), 132.56 (C-18), 129.40 (C-17), 129.09 (C-16), 126.95 (C-15), 124.95 (C-13), 124.01 (C-9), 123.71 (C-7), 117.37 (C-10), 111.29 (C-8), 59.85 (C-4), 56.61 (C-3), 31.78 (C-1), 31.47 (C-2), 28.70 (C-5). **HRMS**; (m/*z*), calculated for $C_{21}H_{27}ClN_3$: 356.1888, found $(M + H)^+$: 356.1895.

3.4.12 Synthesis of 2-(2-chlorophenyl)-5-methyl-N-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyridin-3-amine 56



56

Method B: As per the general procedure 1,1,3,3-tetramethylbutyl isocyanide (1 eq, 1.6 ml, 9.25 mmol), 2-chlorobenzaldehyde (1 eq, 1.0 ml, 9.25 mmol), and 2-amino-6-methylpyridine (1 eq, 1.00 g, 9.25 mmol) in methanol were reacted together in the presence of catalytic amounts of iodine (10 % mol, 0.234 g, 0.925 mmol). The obtained residue was purified by column chromatography (1.5:1 E/H) to give the desired product **56** as a yellow orange wax (2.12 g, 62% yield).

R_f = 0.45 (60% E/H): **IR** (ν_{max}/cm^{-1}): 3353 (N-H), 2950 (C-H alkyl), 1634 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.76 (1H, dd, *J* = 7.5, 2.0 Hz, H-14), 7.48-7.39 (2H, m, H-17 and H-10), 7.39-7.27 (2H, m,H-15 and H-16), 7.04 (1H, dd, *J* = 9.0, 6.8 Hz, H-9), 6.47 (1H, dt, *J* = 6.8, 1.1 Hz, H-8), 3.20 (1H, s, N-H), 2.99 (3H, s, Ar-CH_3), 1.38 (2H, s, H-3), 0.91 (9H, s, H-1), 0.78 (6H, s, H-5).**^{13}C NMR (75 MHz, Chloroform-*d*) δ** 143.57 (C-11), 139.09 (C-6), 137.19 (C-12), 135.68 (C-18), 132.90 (C-13), 132.61 (C-14), 129.48 (C-17), 129.07 (C-16), 127.11 (C-15), 127.04 (C-7), 124.25 (C-9), 115.84 (C-10), 113.97 (C-8), 59.78 (C-4), 56.19 (C-3), 31.82 (C-1), 31.39 (C-2), 28.40 (C-5), 21.09 (Ar-CH_3). **HRMS**; (m/*z*), calculated for $C_{22}H_{29}ClN_3$: 370.2045, found $(M + H)^+$: 370.2059.

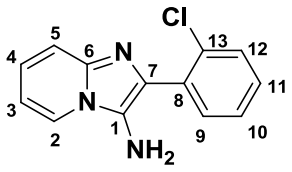
3.5 Synthesis of 2-(2-chlorophenyl)-imidazo[1,2-*a*]pyridin-3-amine derivatives

Method A: The appropriate imidazo[1,2-*a*]pyridine was dissolved in *n*-butanol and treated with hydrofluoroboric acid (HBF_4), and the solution was irradiated to reflux at 120 Watts and 160 ℃ for 25 minutes in a long necked round bottom flask. The solution was basified to pH = 8, extracted with ethyl acetate (3 × 10 ml), and washed with water (3 ×10 ml). The

organic layer was dried using anhydrous sodium sulphate, filtered, and the solvent removed *in vacuo*. The residue obtained was purified by column chromatography to give the desired product (70% ethyl acetate: chloroform).

Method B: The appropriate imidazo[1,2-*a*]pyridine in dichloromethane was treated with TFA for 20 minutes at room temperature. The solution was basified to pH = 8 and extracted with ethyl acetate (3 ×10 ml), and then washed with water (3 ×10 ml). The organic layer was dried over anhydrous sodium sulphate, filtered, and the solvent removed *in vacuo*. The residue obtained was purified by column chromatography to give the desired product (70% ethyl acetate: chloroform).

3.5.1 Synthesis of 2-(2-chlorophenyl)imidazo[1,2-*a*]pyridin-3-amine 57



57

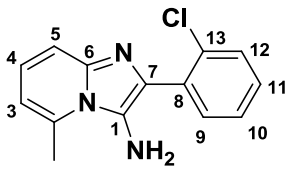
Method A: In accordance with the general procedure, **45** (1 eq., 0.100 g, 0.365 mmol) in *n*-butanol was treated with HBF_4 (1 eq., 0.02 ml, 0.365 mmol) under microwave irradiation. The residue obtained was purified by column chromatography (70% ethyl acetate: chloroform) to give the desired product **57** as a black solid (88.9 mg, 67% yield).

Method A: In accordance with the general procedure, **45** (1 eq., 0.250 g, 0.365 mmol) in *n*-butanol was treated with HBF_4 (3 eq., 0.07 ml, 1.09 mmol) under microwave irridiation. The residue obtained was purified by column chromatography (70% ethyl acetate: chloroform) to give the desired product **57** as a black solid (0.134 g, 66% yield).

Method B: As per the general procedure, **45** (1 eq., 0.50 g, 1.52 mmol) in *n*-butanol was treated with TFA (1 eq., 0.12 ml, 1.52 mmol) at room temperature. The residue obtained was purified by column chromatography (70% ethyl acetate: chloroform) to give the desired product **57** as a black solid (0.189 g, 35 % yield).

R_f = 0.33 (70% ethyl-acetate : chloroform): **m.p:** 130-132℃; **IR** (ν_{max}/cm^{-1}): 3396 (NH_2), 3158 (C-H aromatic), 1638 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.04 (1H, dt, *J* = 6.9, 1.2 Hz, H-2), 7.68-7.63 (1H, m, H-9), 7.55-7.45 (2H, m, H-5 and H-12), 7.39-7.27 (2H, m, H-11 and H-10), 7.11 (1H, ddd, *J* = 9.1, 6.7, 1.3 Hz, H-4), 6.80 (1H, td, *J* = 6.8, 1.1 Hz, H-3), 3.32 (2H, br, s, NH_2).**^{13}C NMR (75 MHz, Chloroform-*d*) δ** 140.96 (C-6), 133.31 (C-1), 132.75 (C-9), 132.65 (C-7), 131.33 (C-13), 129.68 (C-12), 129.19 (C-11), 126.97 (C-10), 124.14 (C-8), 123.22 (C-4), 122.11 (C-2), 117.40 (C-5), 111.75 (C-3). **HRMS**; (m/*z*), calculated for $C_{13}H_{11}ClN_3$: 244.0597, found $(M + H)^+$: 244.0636.

3.5.2 Synthesis of 2-(2-chlorophenyl)-6-methylimidazo[1,2-*a*]pyridin-3-amine 58



58

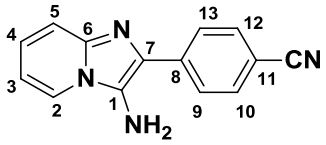
Method A: In accordance with the general procedure, **46** (1 eq., 0.250 g, 0.763 mmol) in *n*-butanol was treated with HBF_4 (3 eq., 0.14 ml, 2.29 mmol) under microwave irradiation. The residue obtained was purified by column chromatography (70% ethyl acetate: chloroform) to give the desired product **58** as an orange yellow oil (0.197 g, 65% yield).

Method B: As per the general procedure, **56** (1 eq., 0.500 g, 1.52 mmol) in *n*-butanol was treated with TFA (1 eq., 0.12 ml, 1.52 mmol) at room temperature. The residue obtained was purified by column chromatography (70% ethyl acetate: chloroform) to give the desired product **58** as an orange yellow oil (0.146 g, 26% yield).

R_f = 0.33 (70% ethyl-acetate : chloroform); **IR** (ν_{max}/cm^{-1}): 3409 (NH_2), 2956 (C-H), 1671 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 7.62-7.56 (1H, m, H-9), 7.48-7.43 (1H, m, H-12), 7.37-7.24 (3H, m, H-5, H-10 and H-11), 6.92 (1H, dd, *J* = 9.1, 6.7 Hz, H-4), 6.38 (1H, dt, *J* = 6.8, 1.1 Hz, H-3), 3.34 (2H, br, s, NH_2), 2.95 (3H, s, Ar-CH_3).**^{13}C NMR (75 MHz, Chloroform-*d*) δ** 142.60 (C-6), 136.09 (C-1), 133.45 (C-7), 132.98 (C-9), 132.81 (C-13), 132.78 (C-8), 129.61 (C-12), 129.20 (C-11), 126.91 (C-10), 126.73 (C-2), 123.60

(C-4), 115.83 (C-5), 112.94 (C-3), 20.22 (Ar-CH_3). **HRMS**: (m/*z*), calculated for $C_{14}H_{13}ClN_3$: 258.0793, found $(M + H)^+$: 258.0791.

3.5.3 Synthesis of 4-(3-aminoimidazo[1,2-*a*]pyridin-2-yl)benzonitrile 59

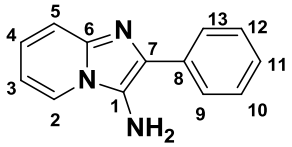


59

Method A: In accordance with the general procedure, **49** (1 eq., 0.158 g, 0.543 mmol) in *n*-butanol was treated with HBF_4 (3 eq., 0.10 ml, 1.63 mmol) under microwave irradiation. The obtained residue was purified by column chromatography (70% ethyl acetate: chloroform) to give the desired product **59** as a green oil (28.0 mg, 22 % yield).

R_f = 0.38 (70% ethyl-acetate : chloroform); **IR** (ν_{max}/cm^{-1}); 3287 (NH_2), 2922 (C-H), 2221 (C≡N), 1631 (C=N), **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.18 (2H, dd, *J* = 8.5, 1.6 Hz, H-10 and H-12), 8.00 (1H, dd, *J* = 6.9, 1.3 Hz, H-2), 7.76-7.67 (2H, m, H-9 and H-13), 7.55 (1H, dd, *J* = 9.1, 1.3 Hz, H-5), 7.22-7.12 (1H, m, H-4), 6.86 (1H, tt, *J* = 6.7, 1.4 Hz, H-3), 3.43 (2H, s, NH_2). **^{13}C NMR (126 MHz, Chloroform-*d*) δ** 141.45 (C-6), 139.16 (C-1), 132.71 (C-7), 132.45 (C-10 and C-12), 131.58 (C-8), 127.27 (C-9 and C-13), 124.15 (C-4), 121.80 (C-2), 119.16 (C≡N), 117.81 (C-5), 112.31 (C-11), 110.25 (C-3). **HRMS**; (m/*z*), calculated for $C_{14}H_{11}N_4$: 235.0978, found $(M + H)^+$: 235.0981.

3.5.4 Synthesis of 2-phenylimidazo[1,2-*a*]pyridin-3-amine 60



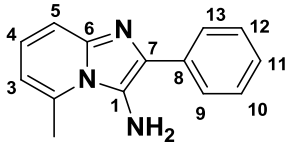
60

Method A: In accordance with the general procedure, **53** (1 eq., 0.402 g, 1.50 mmol) in *n*-butanol was treated with HBF_4 (3 eq., 0.30 ml, 4.50 mmol) under microwave irradiation.

The residue obtained was purified by column chromatography (70% ethyl acetate: chloroform) to give the desired product **60** as a green oil (0.319 g, 56% yield).

Rf = 0.36 (70% ethyl acetate : chloroform): **IR** (v_{max}/cm^{-1}); 3381 (NH_2), 3144 (=C-H), 1631 (C=N); **^{1}H NMR (500 MHz, Chloroform-*d*) δ** 8.00 (1H, d, *J* = 6.9 Hz, H-2), 7.98-7.95 (2H, m, H-9 and H-13), 7.54 (1H, d, *J* = 9.1 Hz, H-5), 7.46 (2H, t, *J* = 8.4 Hz, H-10 and H-12), 7.32 (1H, td, *J* = 7.4, 2.5 Hz, H-11), 7.10 (1H, ddd, *J* = 9.1, 6.6, 1.3 Hz, H-4), 6.80 (1H, td, *J* = 6.7, 1.1 Hz, H-3), 3.45 (2H, m, NH_2); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.95 (C-6), 134.38 (C-1), 133.07 (C-7), 128.72 (C-9 and C-13), 127.20 (C-11), 127.17 (C-10 and C-12), 123.24 (C-4), 122.63 (C-8), 121.84 (C-2), 117.36 (C-5), 111.75 (C-3).

3.5.5 Synthesis of 5-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine 61



61

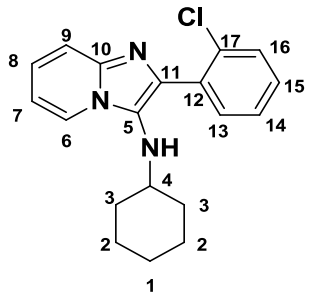
Method A: In accordance with the general procedure, **54** (1 eq., 0.250 g, 0.895 mmol) in *n*-butanol was treated with HBF_4 (3 eq., 0.20 ml, 26.9 mmol) under microwave irradiation. The residue obtained was purified by column chromatography (70% ethyl acetate: chloroform) to give the desired product **61** as a green oil (0.199 g, 7.6% yield).

Rf = 0.52 (70% ethyl acetate : chloroform); **IR** (v_{max}/cm^{-1}); 3375 (NH_2), 3098 (=C-H), 2897 (C-H), 1634 (C=N); **^{1}H NMR (500 MHz, Chloroform-*d*) δ** 7.87 (2H, d, *J* = 7.7 Hz, H-9 and H-13), 7.46-7.39 (3H, m, H-10, H-12 and H-5), 7.31 (1H, t, *J* = 7.4 Hz H-11), 6.96 (1H, dd, *J* = 8.9, 6.8 Hz, H-4), 6.41 (1H, d, *J* = 6.8 Hz, H-3), 3.61 (2H, s, br, NH_2), 3.01 (3H, s, Ar-CH_3). **^{13}C NMR (126 MHz, Chloroform-*d*) δ** 143.05 (C-6), 136.32 (C-1), 135.84 (C-8), 133.77 (C-7), 128.42 (C-10 and C-12), 127.60 (C-9 and C-13), 127.42 (C-11), 126.83 (C-2), 124.55 (C-4), 115.67 (C-5), 113.64 (C-3), 19.77 (Ar-CH_3).

3.6 Reductive amination

General procedure: the appropriate imidazo[1,2-*a*]pyridine primary amine (1 eq.), appropriate electrophile (3 eq., i.e. ketone or benzaldehyde) and $AlCl_3$ (2 eq.) were added to EtOH (5 ml) and stirred at 70 ℃ for 1 h. $NaCNBH_3$ (1.5 eq.) was added to the resulting solution, and the reaction was left to stir at 70 ℃ for 24 h. The reaction was quenched with saturated $NaHCO_3$ solution to give a solution with increased viscosity. The solution was diluted with EtOH (10 ml), extracted with ether (3 × 15 ml) and dried over $NaSO_4$. The organic layer was collected and the solvent removed *in vacuo*. The obtained residue was purified over flash silica to give the desired product.

3.6.1 Synthesis of 2-(2-chlorophenyl)-*N*-cyclohexylimidazo[1,2-*a*]pyridin-3-amine 18



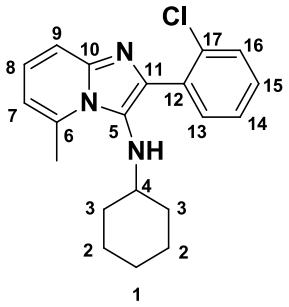
18

In accordance to the general procedure, Compound **57** (1 eq., 68.7 mg, 0.282 mmol), cyclohexanone (3 eq., 0.10 ml, 0.846 mmol) and $AlCl_3$ (2 eq., 75.2 mg, 0.568 mmol) were added to EtOH (5.0 ml). The resulting solution was treated with $NaCNBH_3$ (1.5 eq., 26.6 mg, 0.423 mmol), and the reaction was left to stir for 24 h. The residue obtained was purified over flash silica gel (1.5:1 E/H) to give **18** as yellow oil (41.3 mg, 45% yield).

R_f = 0.70 (60% E/H), **IR** (ν_{max}/cm^{-1}); 3362 (N-H), 3065 (=C-H), 2925 (C-H), 1631 (C=N), **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.15 (1H, dq, *J* = 6.9, 1.1 Hz, H-6), 7.72-7.65 (1H, m, H-13), 7.55 (1H, dd, *J* = 9.0, 1.0 Hz, H-9), 7.47 (1H, dd, *J* = 7.1, 2.1 Hz, H-16), 7.40-7.27 (2H, m, H-14 an H-15), 7.17-7.10 (1H, m, H-8), 6.80 (1H, tt, *J* = 6.8, 1.1 Hz, H-7), 3.28 (1H, d, *J* = 7.2 Hz, N-H), 2.73-2.59 (1H, m, H-4_a), 1.78-1.39 (5H, m, H-3_a, H-1_a and H-2_a), 1.17-0.92 (5H, m, H-3_b, H-1_b and H-2_b). **^{13}C NMR (75 MHz, Chloroform-*d*) δ**

141.65 (C-10), 135.15 (C-5), 134.10 (C-11 and C-17), 132.59 (C-13), 129.46 (C-16), 129.09 (C-15), 126.91 (C-14), 126.36 (C-12), 123.64 (C-8), 122.86 (C-6), 117.57 (C-9), 111.56 (C-7), 56.39 (C-4), 33.86 (C-3), 25.65 (C-1), 24.59 (C-2).

3.6.2 Synthesis of 2-(2-chlorophenyl)-*N*-cyclohexyl-5-methylimidazo[1,2-*a*]pyridin-3-amine 19

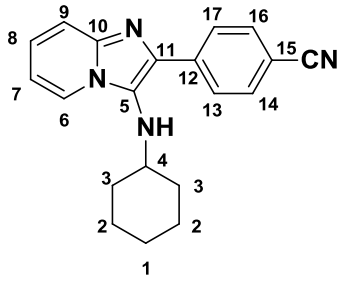


19

In accordance with the general procedure, Compound **58** (1 eq., 0.127 g, 0.442 mmol), cyclohexanone (3 eq., 0.14 ml, 1.33 mmol) and $AlCl_3$ (2 eq., 0.118 g, 0.885 mmol) were added to EtOH (5.0 ml). The resulting solution was treated with $NaCNBH_3$ (1.5 eq., 41.7 mg, 0.664 mmol), and the reaction was left to stir for 24 h. The residue obtained was purified over flash silica gel (1.5:1 E/H) to give **19** as yellow oil (55.6 mg, 37% yield).

R_f = 0.72 (60% E/H), **IR** (ν_{max}/cm^{-1}); 3352 (N-H), 3086 (=C-H), 2927 (C-H), 1633 (C=N), **^{1}H NMR (500 MHz, Chloroform-*d*) δ** 7.65 (1H, dd, *J* = 7.4, 2.0 Hz, H-13), 7.46 (1H, dd, *J* = 7.8, 1.5 Hz, H-16), 7.41 (1H, d, *J* = 9.0 Hz, H-9), 7.38-7.29 (2H, m, H-14 and H-15), 7.01 (1H, dd, *J* = 9.0, 6.8 Hz, H-8), 6.45 (1H, dt, *J* = 6.8, 1.1 Hz, H-7), 3.07 (1H, br, s, N-H), 2.97 (3H, s, Ar-CH_3), 2.61-2.54 (1H, m, H-4), 1.68-1.58 (2H, m, H-3), 1.56-1.36 (3H, m, H-3 and H-2), 1.05-0.97 (3H, m, H-1 and H-2), 0.93-0.82 (2H, m, H-1 and H-2). **^{13}C NMR (126 MHz, Chloroform-*d*) δ** 143.34 (C-10), 137.39 (C-5), 136.83 (C-11), 134.66 (C-12), 132.80 (C-17), 132.66 (C-13), 129.40 (C-16), 129.07 (C-15), 128.23 (C-6), 126.90 (C-14), 124.00 (C-8), 115.90 (C-9), 113.35 (C-7), 58.87 (C-4), 33.17 (C-3), 25.78 (C-2), 24.76 (C-1), 19.97 (Ar-CH_3).

3.6.3 Synthesis of 4-(3-(cyclohexylamino)imidazo[1,2-*a*]pyridin-2-yl)benzonitrile 63

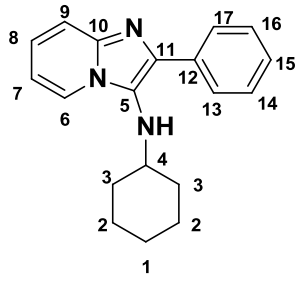


63

As per the general procedure, Compound **59** (1 eq., 0.101 g, 0.431 mmol), cyclohexanone (3 eq., 0.13 ml, 1.29 mmol) and $AlCl_3$ (2 eq., 57.4 mg, 0.862 mmol) were added to EtOH (5.0 ml). The resulting solution was treated with $NaCNBH_3$ (1.5 eq, 40.6 mg, 0.647 mmol), and the reaction was left to stir for 24 h. The residue obtained was purified over flash silica gel (1:1 E/H) to give **63** as green oil (34.0 mg, 25% yield).

R_f = 0.66 (50% E/H), **IR** (ν_{max}/cm^{-1}); 3308 (N-H), 3036 (=C-H), 2931 (C-H), 2223 (C≡N), 1633 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.25-8.19 (2H, m, H-14 and H-16), 8.05 (1H, dt, *J* = 6.9, 1.2 Hz, H-6), 7.73-7.64 (2H, m, H-13 and H-17), 7.60-7.43 (1H, m, H-9), 7.17 (1H, ddd, *J* = 9.1, 6.7, 1.3 Hz, H-8), 6.81 (1H, td, *J* = 6.8, 1.1 Hz, H-6), 3.11 (1H, d, *J* = 5.0 Hz, N-H), 2.99-2.84 (1H, m, H-4), 1.91-1.49 (5H, m, H-3 and H-2), 1.39-1.05 (5H, m, H-2 an H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 141.84 (C-10), 139.00 (C-5), 134.42 (C-11), 132.13 (C-14 and C-16), 127.16 (C-13 and C-17), 126.25 (C-15), 124.87 (C-12), 122.77 (C-8), 119.20 (C≡N), 117.50 (C-6), 112.16 (C-9), 110.15 (C-7), 56.96 (C-4), 34.20 (C-3), 25.61 (C-2), 24.80 (C-1).

3.6.4 Synthesis of *N*-cyclohexyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine 64

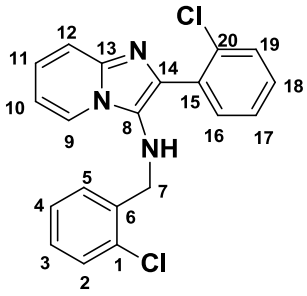


64

As per the general procedure, Compound **60** (1 eq., 70.0 mg, 0.335 mmol), cyclohexanone (3 eq., 0.10 ml, 1.01 mmol) and $AlCl_3$ (2 eq., 89.3 mg, 0.670 mmol) were added to EtOH (5.0 ml). The resulting solution was treated with $NaCNBH_3$ (1.5 eq., 31.6 mg, 0.503 mmol), and the reaction was left to stir for 24 h. The residue obtained was purified over flash silica gel (1:1 E/H) to give **64** as purple oil (48.8 mg, 50% yield).

R_f = 0.53 (50% E/H), **IR** (ν_{max}/cm^{-1}); 3241 (N-H), 3035 (=C-H), 2920 (C-H), 1631 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.10 (1H, dt, *J* = 6.9, 1.2 Hz, H-6), 8.08-7.99 (2H, m, H-13 and H-17), 7.53 (1H, dt, *J* = 9.1, 1.1 Hz, H-9), 7.49-7.40 (2H, m, H-14 and H-16), 7.33 (1H, tt, *J* = 8.1, 1.6 Hz, H-15), 7.12 (1H, ddd, *J* = 9.1, 6.7, 1.3 Hz, H-8), 6.77 (1H, td, *J* = 6.8, 1.2 Hz, H-7), 3.12 (1H, d, *J* = 5.0 Hz, N-H), 3.00-2.92 (1H, m, H-4), 1.91-1.51 (5H, m, H-3 and H-2), 1.32-1.09 (5H, m, H-2 and H-1). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 141.61 (C-10), 136.65 (C-5), 134.61 (C-11), 128.51 (C-14 and C-16), 127.23 (C-15), 127.09 (C-13 andC-17), 124.96 (C-12), 123.74 (C-8), 122.72 (C-6), 117.45 (C-9), 111.47 (C-7), 56.94 (C-4), 34.19 (C-3), 25.74 (C-2), 24.83 (C-1).

3.6.5 Synthesis of *N*-(2-chlorobenzyl)-2-(2-chlorophenyl)imidazo[1,2-*a*]pyridin-3-amine 65

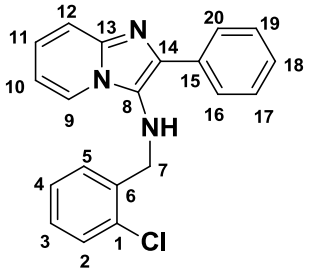


65

As per the general procedure, Compound **59** (1 eq., 70.0 mg, 0.0287 mmol), 2-chlorobenzaldehyde (3 eq., 0.010 ml, 0.086 mmol) and $AlCl_3$ (2 eq., 0.0077 g, 0.0574 mmol) were added to EtOH (5 ml). The resulting solution was treated with $NaCNBH_3$ (1.5 eq., 2.20 mg, 0.0344 mmol), and the reaction was left to stir for 24 h. The residue obtained was purified over flash silica gel (70 % ethyl acetate: chloroform) to give **65** as yellow oil (9.60 mg, 91% yield).

R_f = 0.80 (70 % ethyl acetate: chloroform); **IR** (ν_{max}/cm^{-1}); 3370 (N-H), 3063 (=C-H), 2921 (C-H), 1632 (C=N); **^{1}H NMR (300 MHz, Chloroform-*d*) δ** 8.18 (1H, dq, *J* = 6.8, 1.1 Hz, H-9), 7.56 (1H, dq, *J* = 9.1, 1.1 Hz, H-12), 7.39 (1H, d *J* = 7.2 Hz, H-16), 7.30-7.23 (2H, m, H-17 and H-19), 7.22-7.14 (2H, m, H-11 and H-18), 7.09-6.93 (3H, m, H-2, H-3 and H-5), 6.90-6.80 (2H, m, H-10 and H-4), 4.21-3.90 (3H, m, N-H and H-7). **^{13}C NMR (75 MHz, Chloroform-*d*) δ** 141.74 (C-13), 136.13 (C-8), 135.21 (C-14), 133.87 (C-15), 133.27 (C-1), 132.30 (C-20), 132.28 (C-19), 130.26 (C-6), 129.31 (C-16), 129.23 (C-17), 128.93 (C-2), 128.89 (C-5), 126.69 (C-3), 126.62 (C-18), 126.08 (C-4), 123.82 (C-11), 122.53 (C-9), 117.75 (C-12), 111.86 (C-10), 49.97 (C-7). **HRMS**; (m/*z*), calculated for $C_{20}H_{16}Cl_2N_3$: 368.0716, found $(M + H)^+$: 368.0710.

3.6.6 Synthesis of *N*-(2-chlorobenzyl)-2-phenylimidazo[1,2-*a*]pyridin-3-amine 66

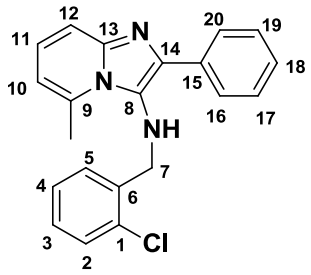


66

In accordance with the general procedure, Compound **60** (1 eq., 11.7 mg, 0.0559 mmol), 2-chlorobenzaldehyde (3 eq., 0.02 ml, 0.168 mmol) and $AlCl_3$ (2 eq., 14.0 mg, 0.112 mmol) were added to EtOH (5.0 ml). The resulting solution was treated $NaCNBH_3$ (1.5 eq., 5.30 mg, 0.0839 mmol), and the reaction was left to stir for 24 h. The residue obtained was purified over flash silica gel (70 % ethyl acetate: chloroform) to give **66** as a white solid (12.1 mg, 65 % yield).

R_f = 0.72 (70 % ethyl acetate: chloroform), **m.p**; 176-179 ℃; **IR** (ν_{max}/cm^{-1}); 3350 (N-H), 3033 (=C-H), 2971 (C-H), 1636 (C=N); **^{1}H NMR (500 MHz, Chloroform-*d*) δ** 8.00 (1H, d, *J* = 6.9 Hz, H-9), 7.94 (2H, d, *J* = 7.7 Hz, H-16 and H-20), 7.56 (1H, d, *J* = 9.0 Hz, H-12), 7.42 (2H, t, *J* = 7.6 Hz, H-17 and H-19), 7.39-7.27 (3H, m, H-2, H-5 and H-18), 7.21-7.10 (3H, m, H-3, H-4 and H-11), 6.75 (1H, t, *J* = 6.8 Hz, H-10), 4.28 (2H, d, *J* = 6.2 Hz, H-7), 3.75 (1H, t, *J* = 7.0 Hz, N-H); **^{13}C NMR (126 MHz, Chloroform-*d*) δ** 138.22 (C-13), 136.39 (C-8), 133.97 (C-15), 132.77 (C-14), 130.48 (C-6), 129.65 (C-2), 129.37 (C-5), 129.20 (C-3), 128.64 (C-16 and C-20), 127.54 (C-18), 127.16 (C-17 and C-19), 127.09 (C-4), 125.16 (C-1), 124.31 (C-11), 122.32 (C-9), 117.36 (C-12), 111.97 (C-10), 50.19 (C-7).

3.6.7 Synthesis of *N*-(2-chlorobenzyl)-5-methyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine 67



67

As per the general procedure, Compound **61** (1 eq., 15.2 mg, 0.0681 mmol), 2-chlorobenzaldehyde (3 eq., 0.023 ml, 0.204 mmol) and $AlCl_3$ (2 eq., 18.2 mg, 0.136 mmol) were added to EtOH (5.0 ml). The resulting solution was treated with $NaCNBH_3$ (1.5 eq., 6.40 mg, 0.102 mmol), and the reaction was left to stir for 24 h. The residue obtained was purified over flash silica gel (70 % ethyl acetate: chloroform) to give **67** as yellow oil (9.90 mg, 42% yield).

R_f = 0.80 (70 % ethyl acetate: chloroform); **m.p**; 176-179 ℃; **IR** (ν_{max}/cm^{-1}); 3332 (N-H), 3013 (=C-H), 2941 (C-H), 1634 (C=N); **^{1}H NMR (500 MHz, Chloroform-*d*) δ** 7.86-7.81 (2H, m, H-16 and H-20), 7.44 (1H, d, *J* = 9.0 Hz, H-12), 7.38 (2H, t, *J* = 7.6 Hz, H-17 and H-19), 7.31-7.24 (2H, m, H-2 and H-18), 7.17-7.06 (3H, m, H-3, H-4 and H-5), 7.02 (1H, t, *J* = 6.9 Hz, H-11), 6.44 (1H, d, *J* = 6.9 Hz, H-10), 4.16 (2H, d, *J* = 6.3 Hz, H-7), 3.71 (1H, t, *J* = 6.7 Hz, N-H), 2.90 (3H, s, Ar-CH_3). **^{13}C NMR (126 MHz, Chloroform-*d*) δ** 143.17 (C-13), 138.56 (C-8), 136.24 (C-14), 135.91 (C-15), 134.18 (C-1), 133.77 (C-6), 130.17 (C-9), 129.46 (C-2), 128.85 (C-5), 128.38 (C-17 and C-19), 127.60 (C-16 and C-20), 127.33 (C-18), 127.30 (C-4), 126.81 (C-3), 124.30 (C-11), 115.79 (C-12), 113.47 (C-10), 53.15 (C-7), 19.73 (Ar-CH_3).

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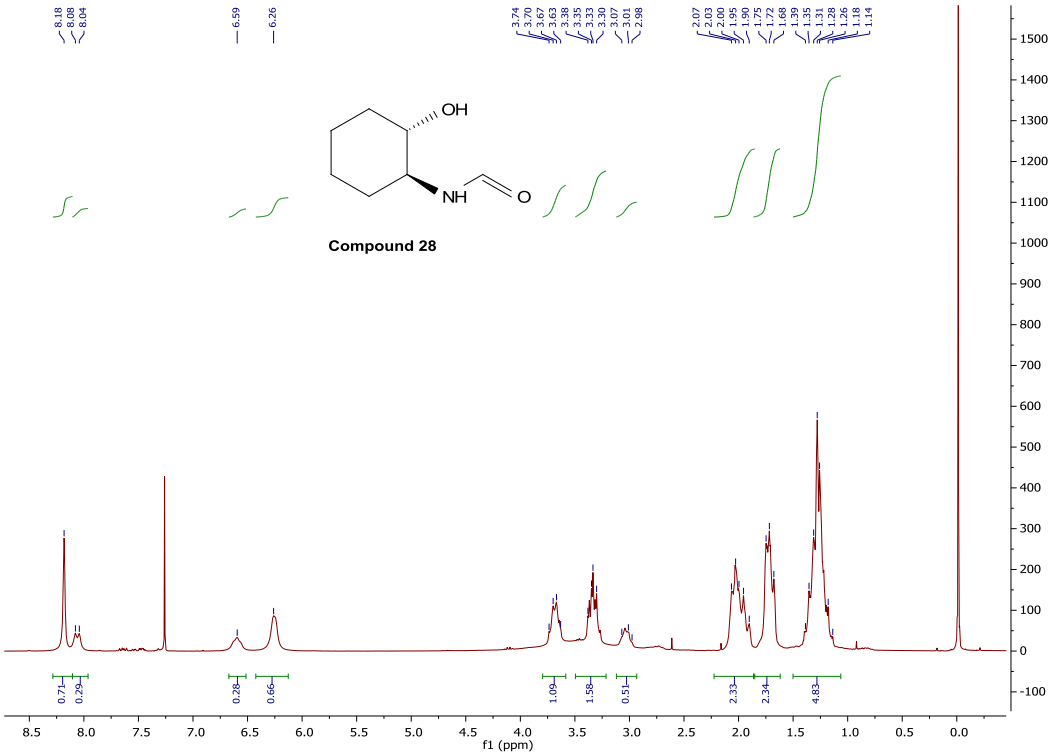
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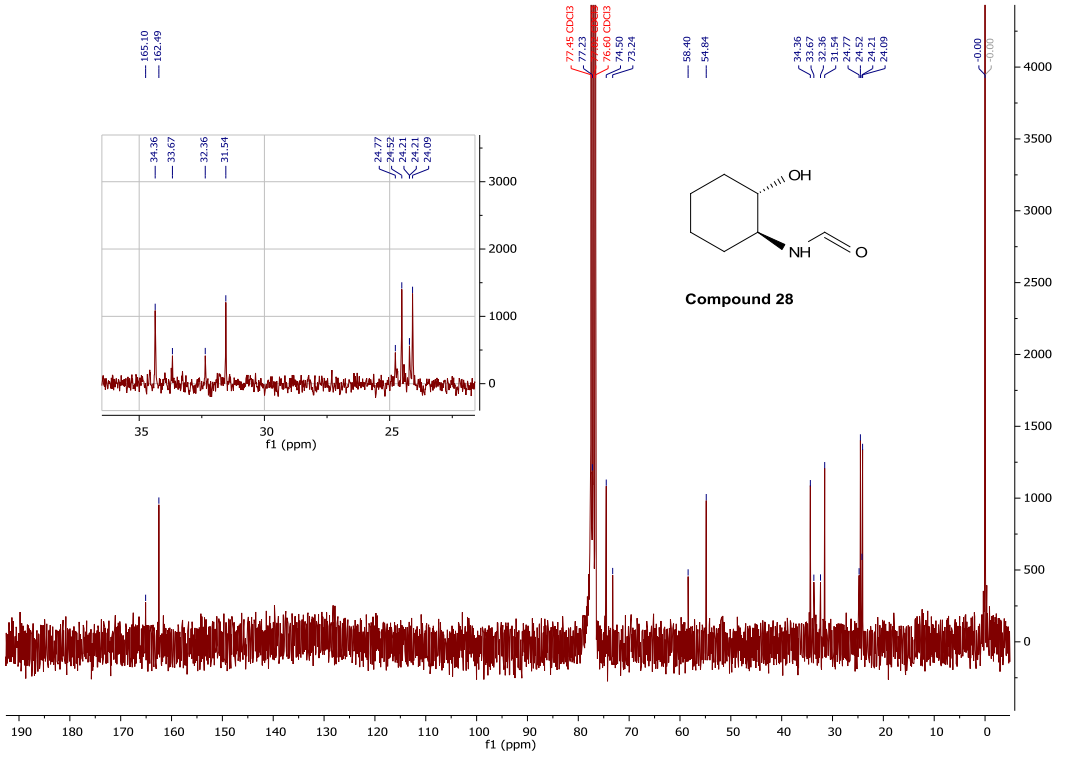
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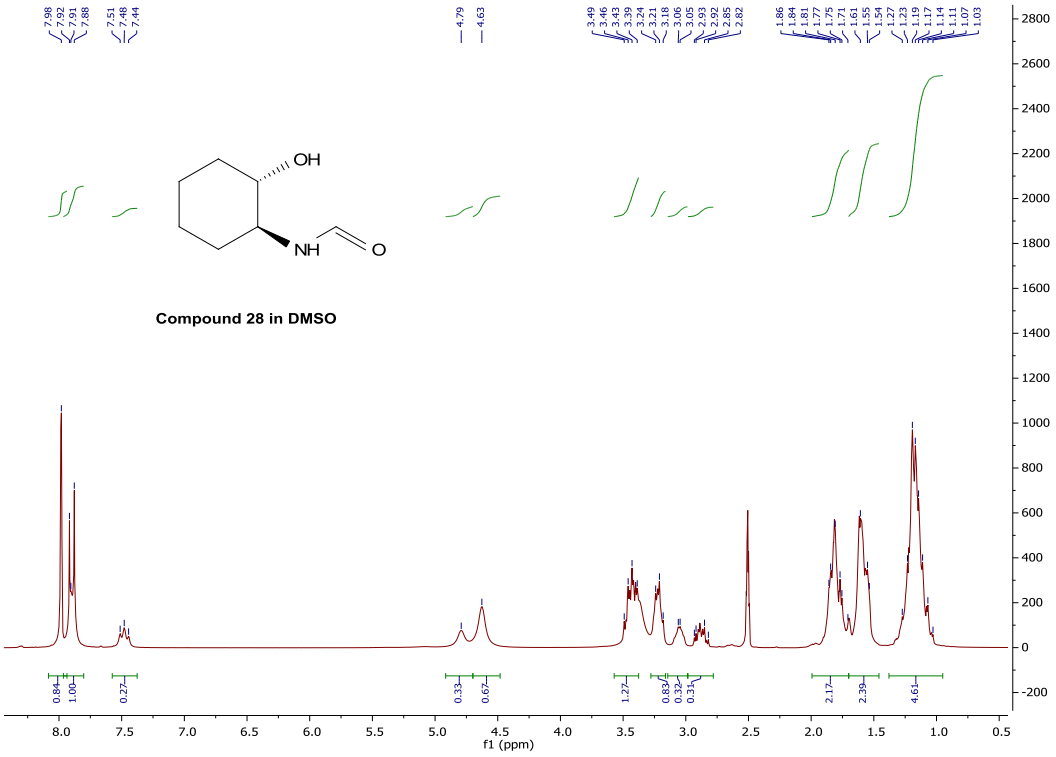
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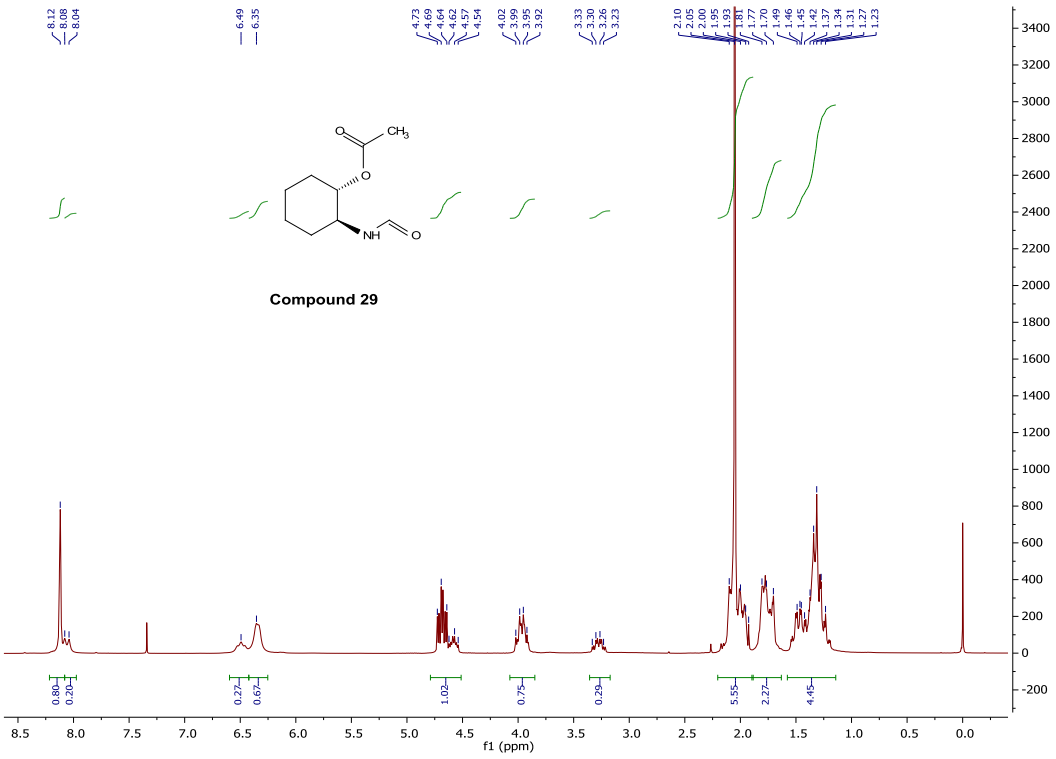
Appendix: Selected ^{1}H and ^{13}C NMR spectra

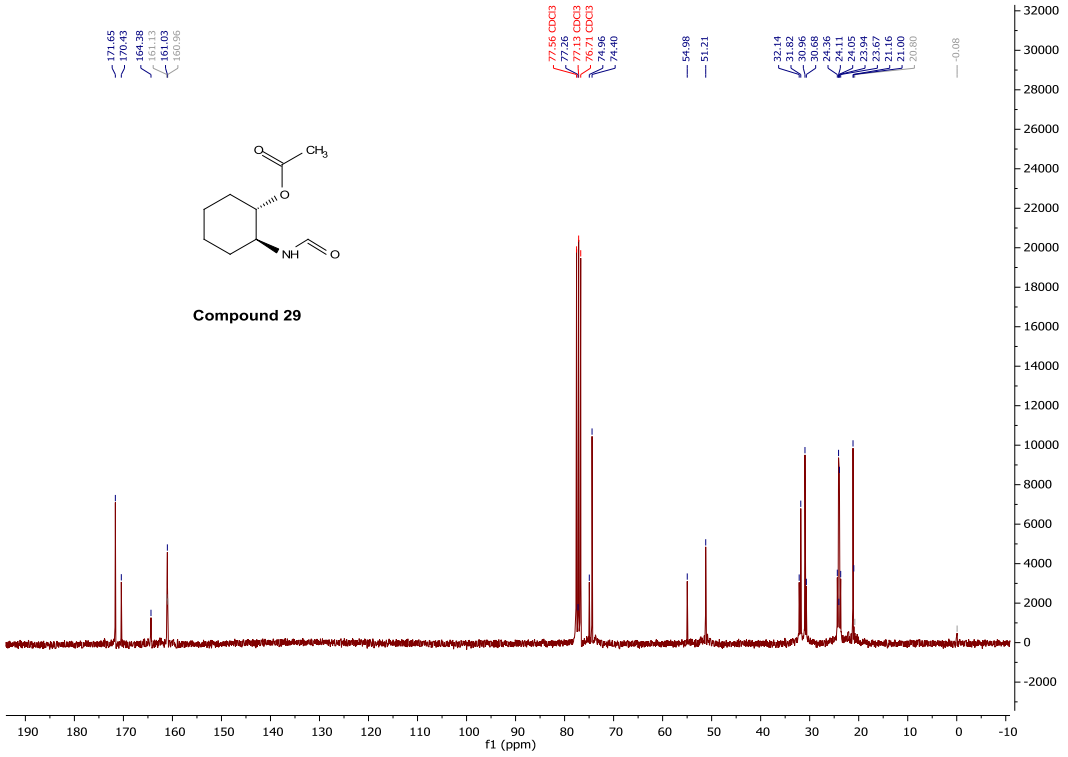


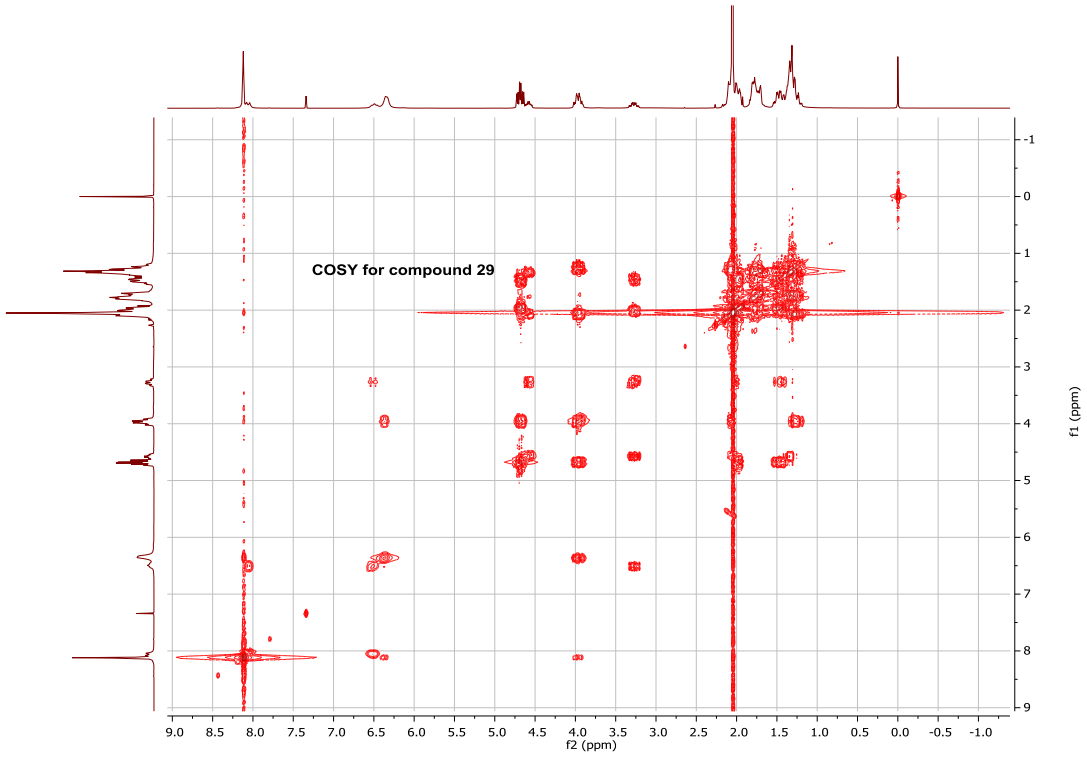

165.10
162.49
77.45 CDCl3
77.23
76.60 CDCl3
74.50
73.24
58.40
54.84
34.36
33.67
32.36
31.54
24.77
24.52
24.21
24.21
24.09
0.00
OH
NH
O
Compound 28
f1 (ppm)

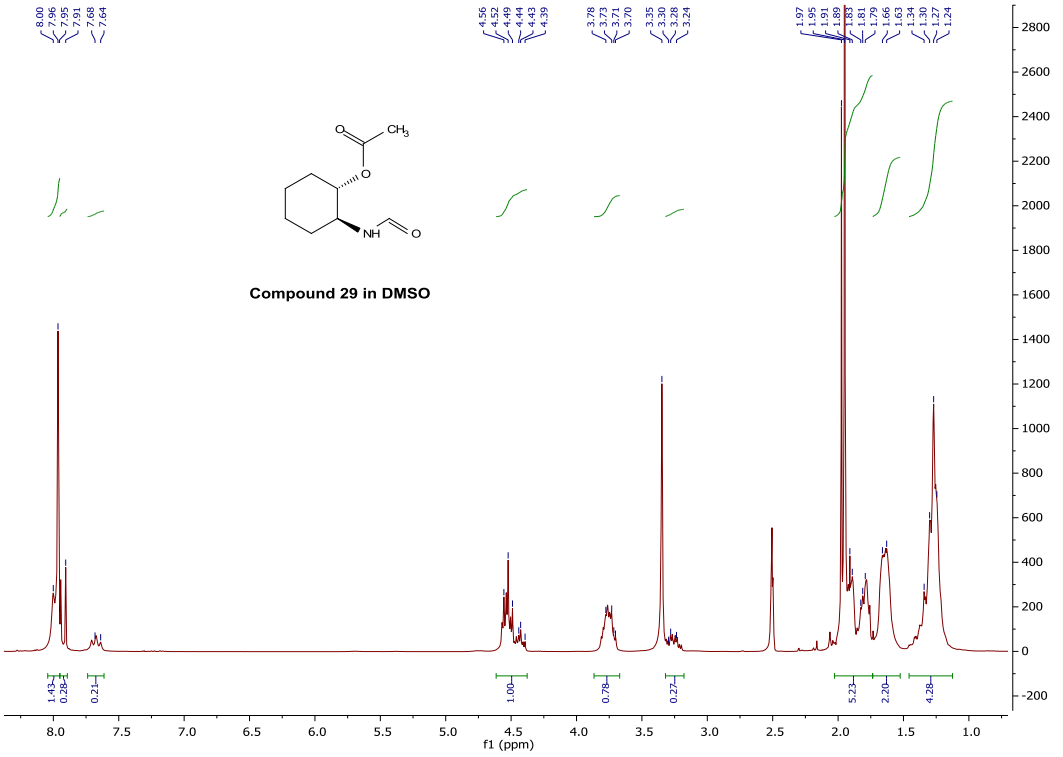

COSY for Compound 28
f2 (ppm)
f1 (ppm)

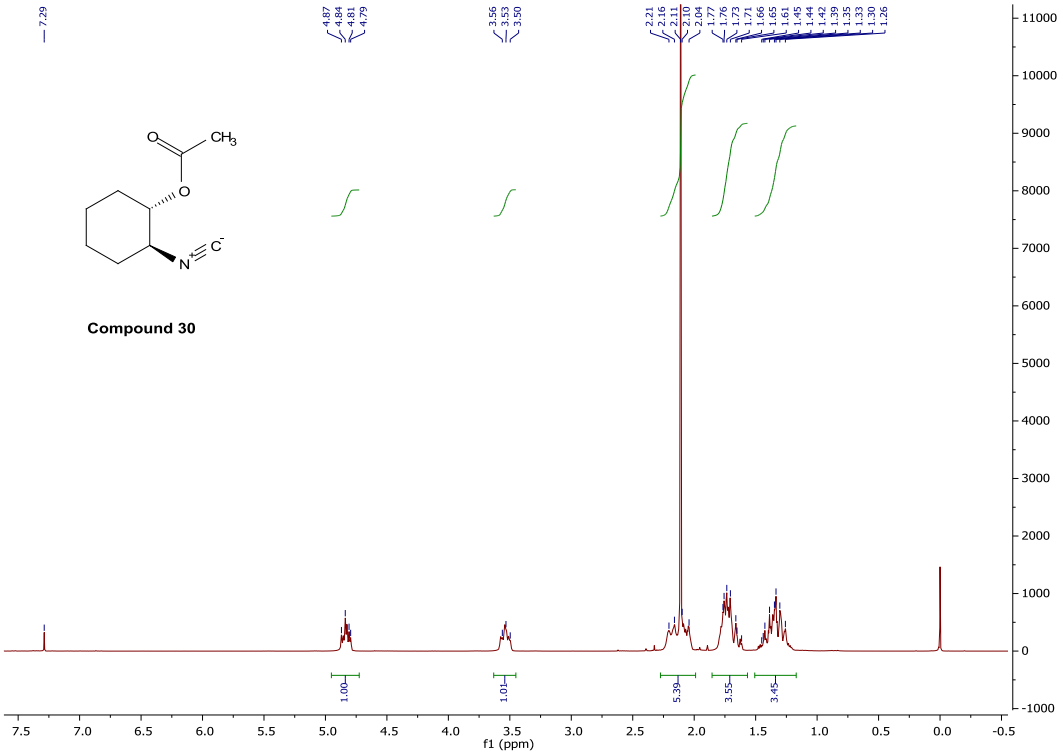

OH
NH
O
Compound 28 in DMSO
f1 (ppm)

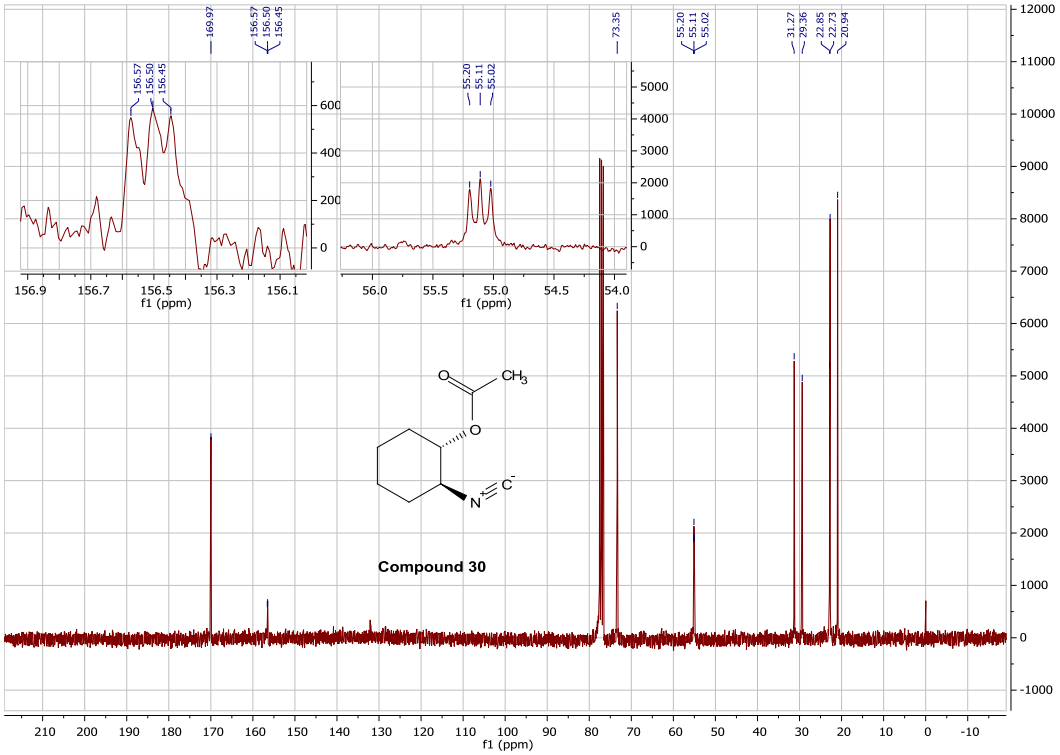

O
CH3
O
NH
O
Compound 29
f1 (ppm)

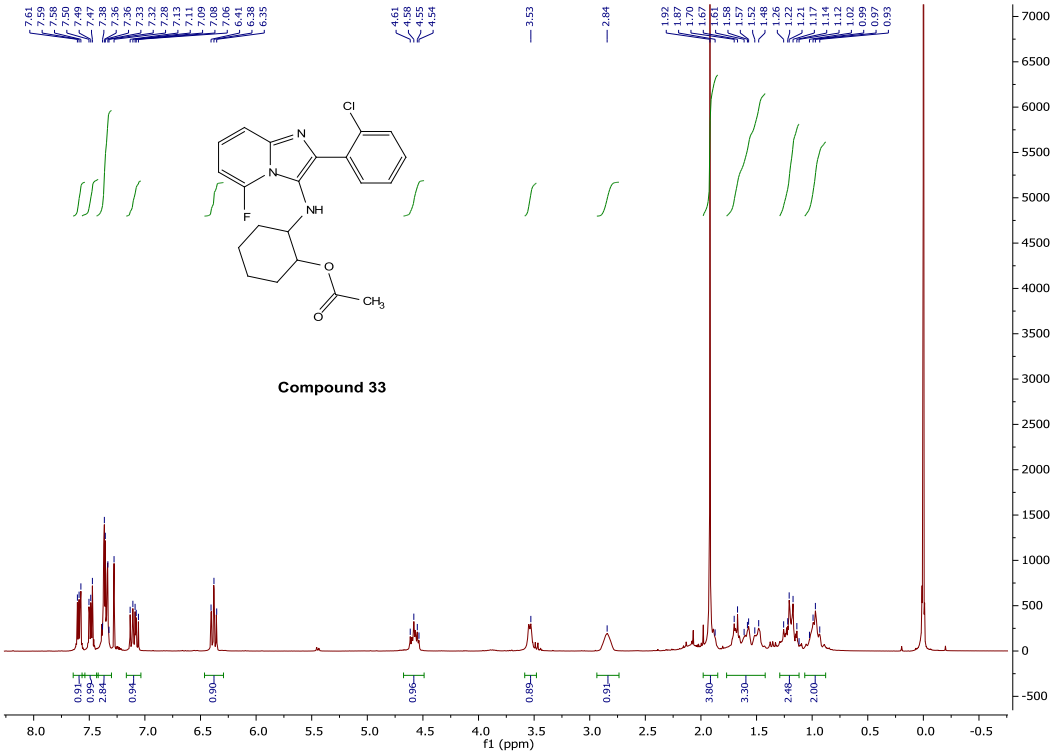

171.65
170.43
164.38
161.13
161.03
160.96
77.56 CDCl3
77.26
77.13 CDCl3
76.71 CDCl3
74.96
74.40
54.98
51.21
32.14
31.82
30.96
30.68
24.36
24.11
24.05
23.94
23.67
21.16
21.00
20.80
-0.08
O
CH3
O
NH
O
Compound 29
f1 (ppm)

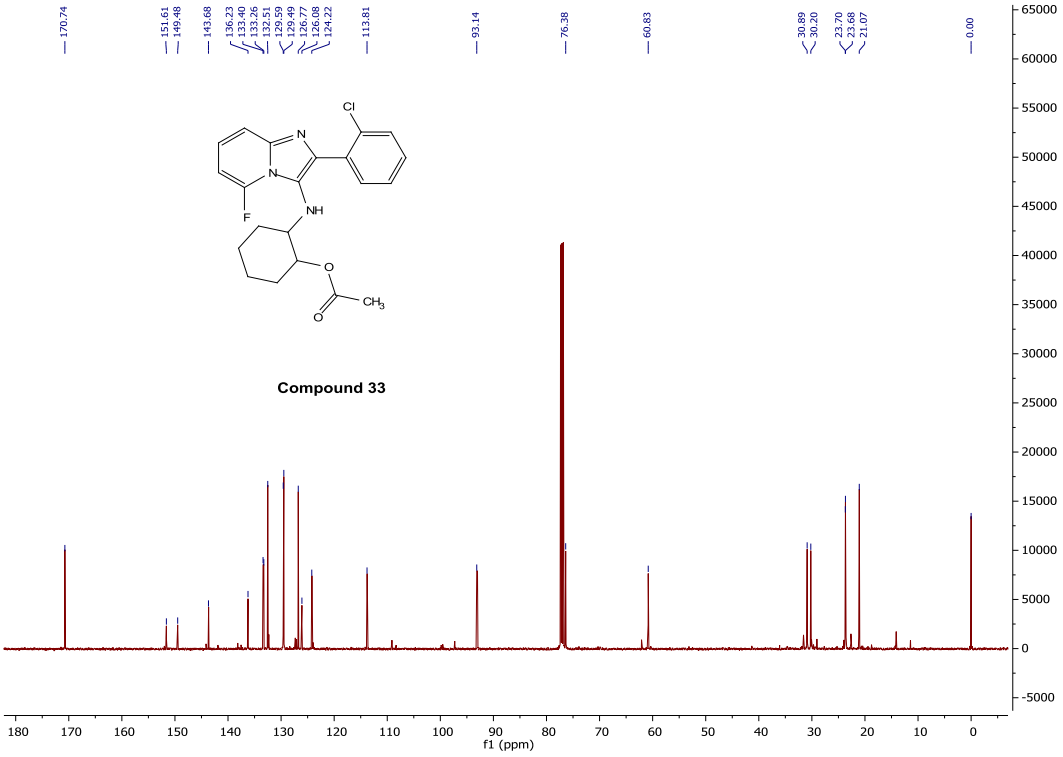

COSY for compound 29
f2 (ppm)
f1 (ppm)


8.00
7.96
7.95
7.91
7.68
7.64
4.56
4.52
4.49
4.44
4.43
4.39
3.78
3.73
3.71
3.70
3.35
3.30
3.28
3.24
1.97
1.95
1.91
1.89
1.83
1.81
1.79
1.66
1.63
1.34
1.30
1.27
1.24
O
CH3
O
NH
O
Compound 29 in DMSO
1.43
0.28
0.21
1.00
0.78
0.27
5.23
2.20
4.28
f1 (ppm)

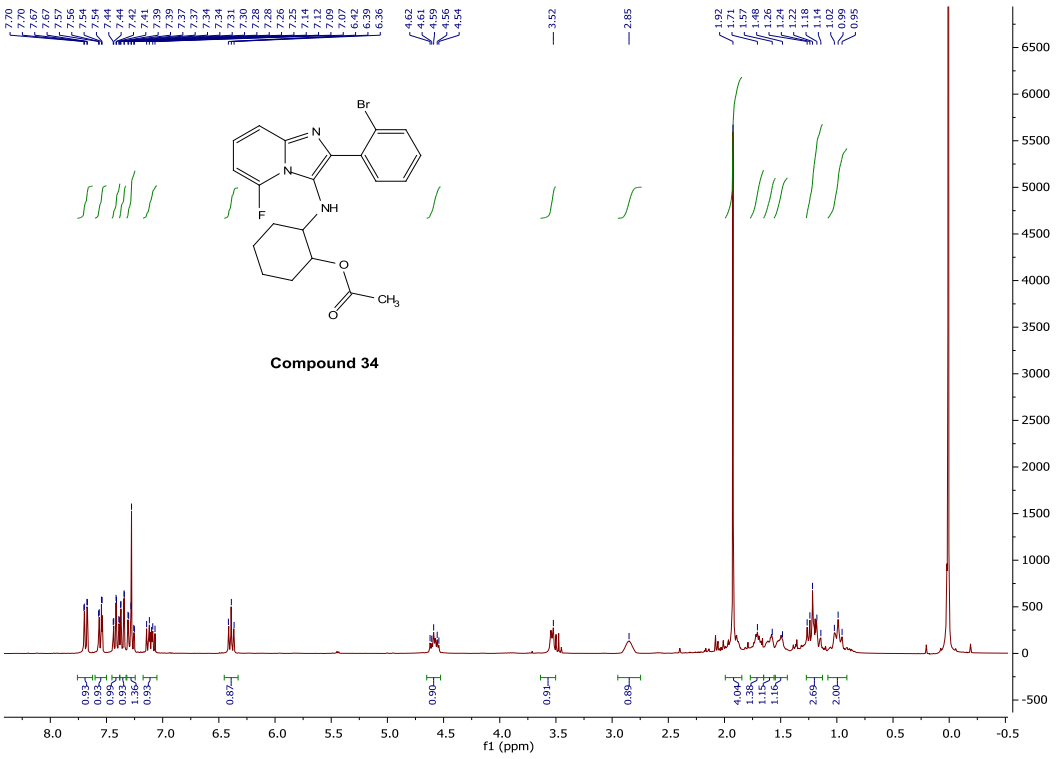

7.29
4.87
4.84
4.81
4.79
3.56
3.53
3.50
2.21
2.16
2.11
2.10
2.04
1.77
1.76
1.73
1.71
1.66
1.65
1.61
1.45
1.44
1.42
1.39
1.35
1.33
1.30
1.26
O
CH3
O
N
C
Compound 30
1.00
1.01
5.39
3.55
3.45
f1 (ppm)


Compound 30
f1 (ppm)

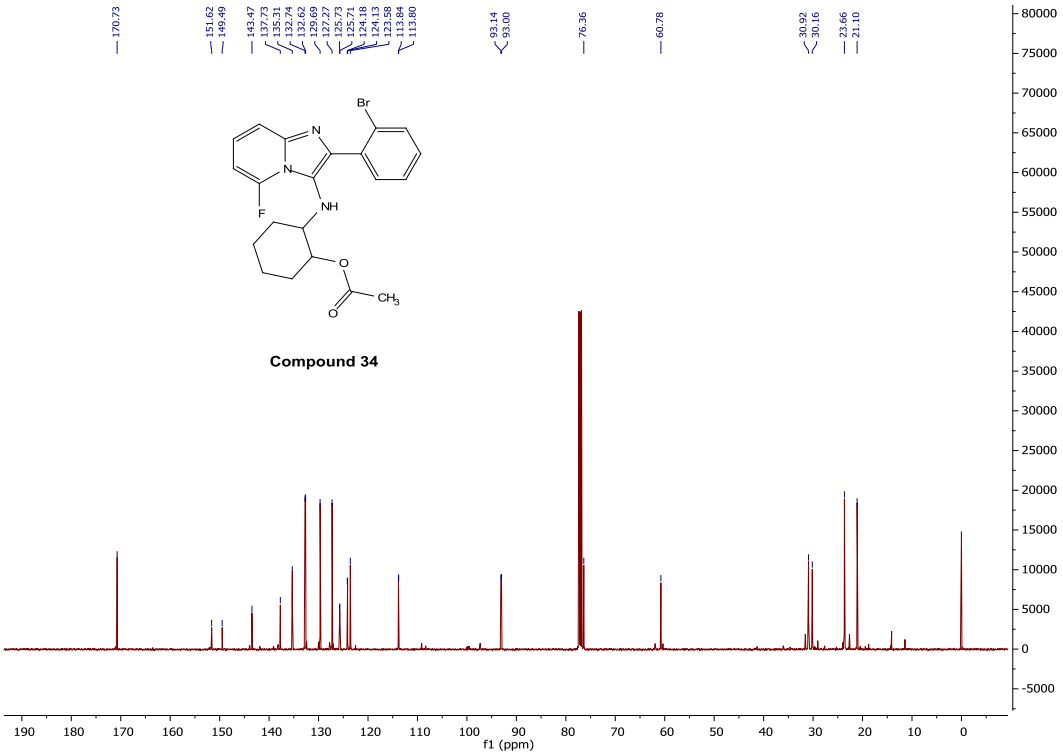

Compound 33
f1 (ppm)



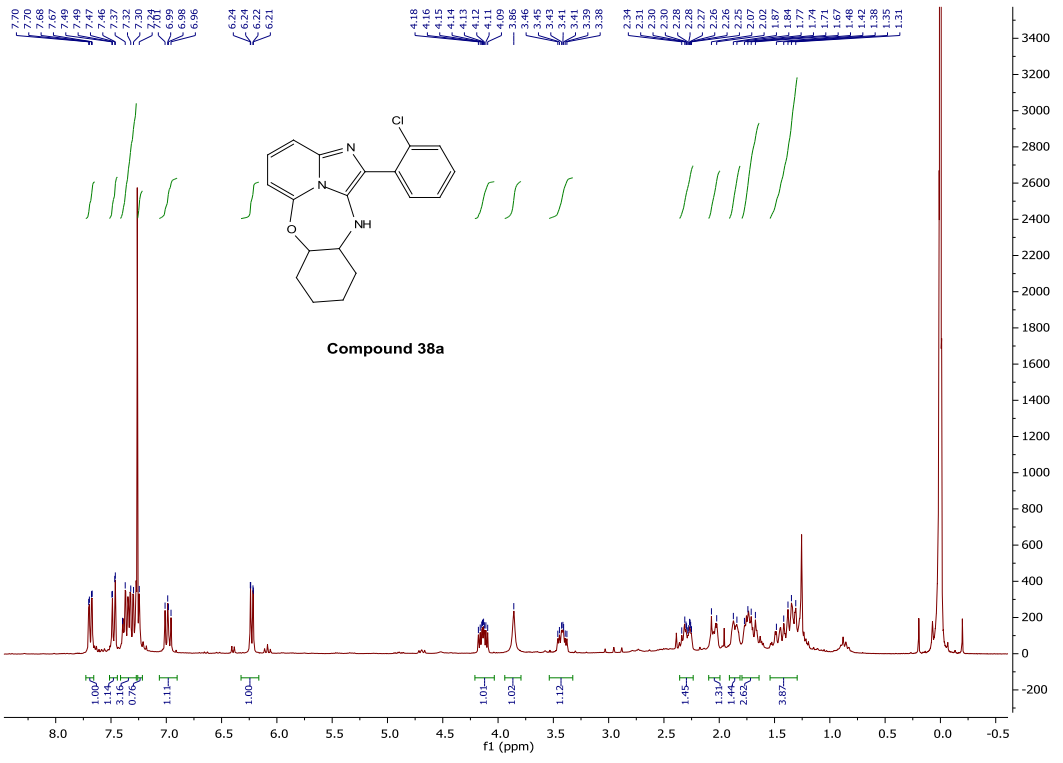
Compound 33



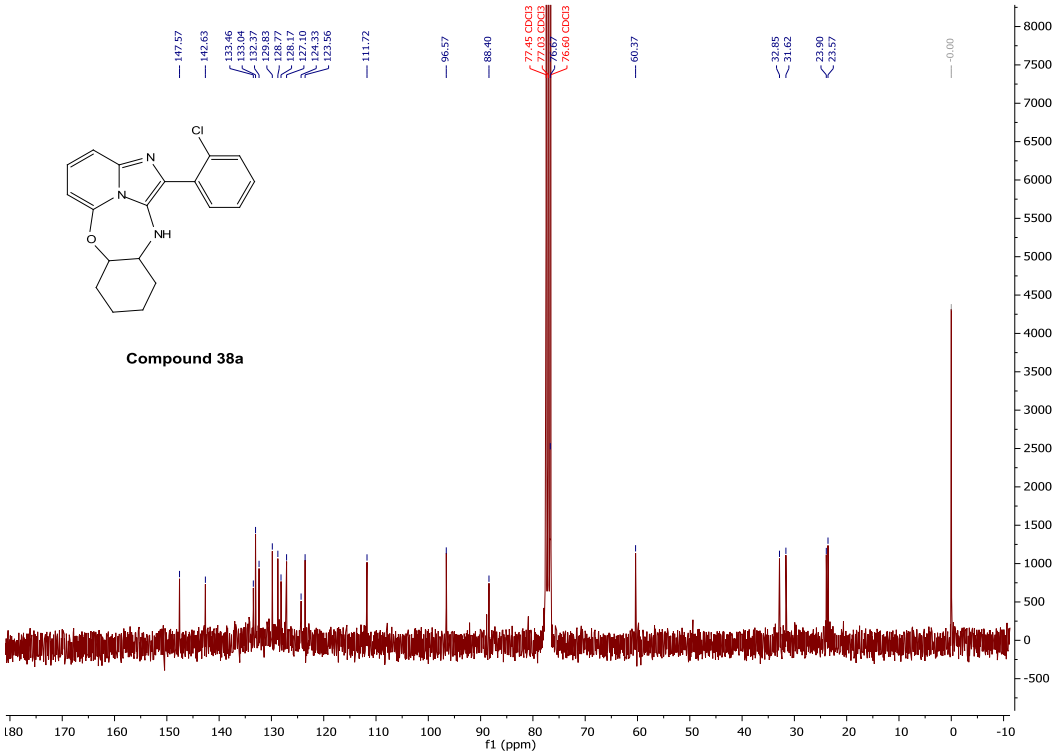
Compound 34



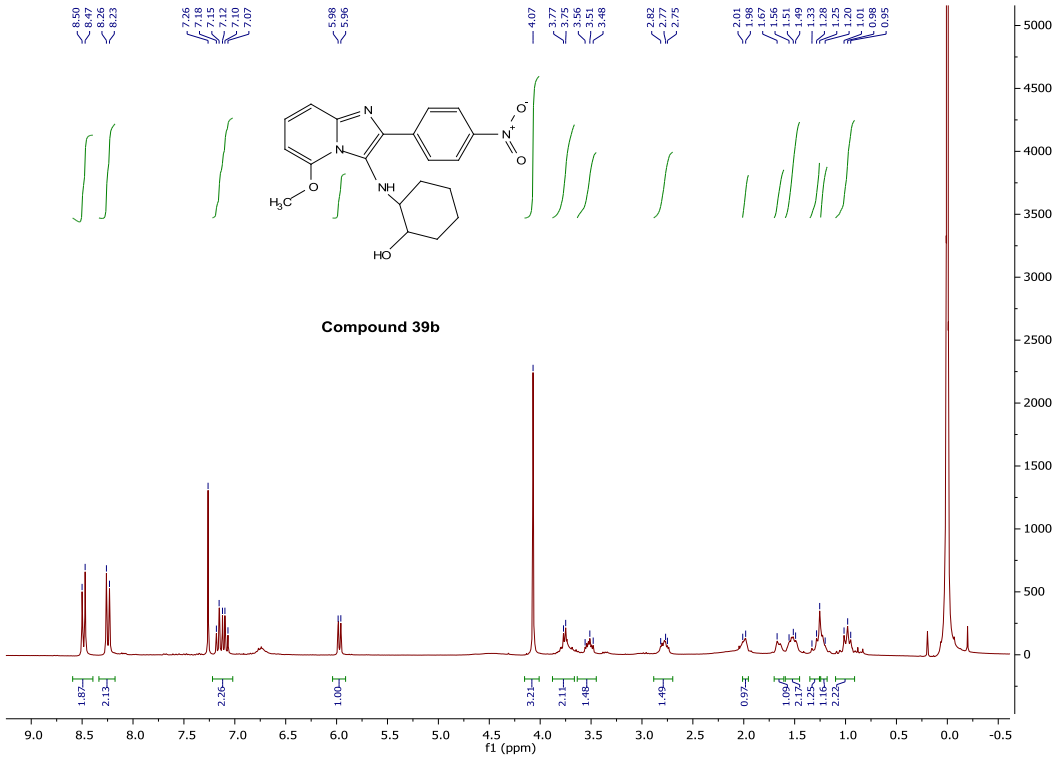
Compound 34



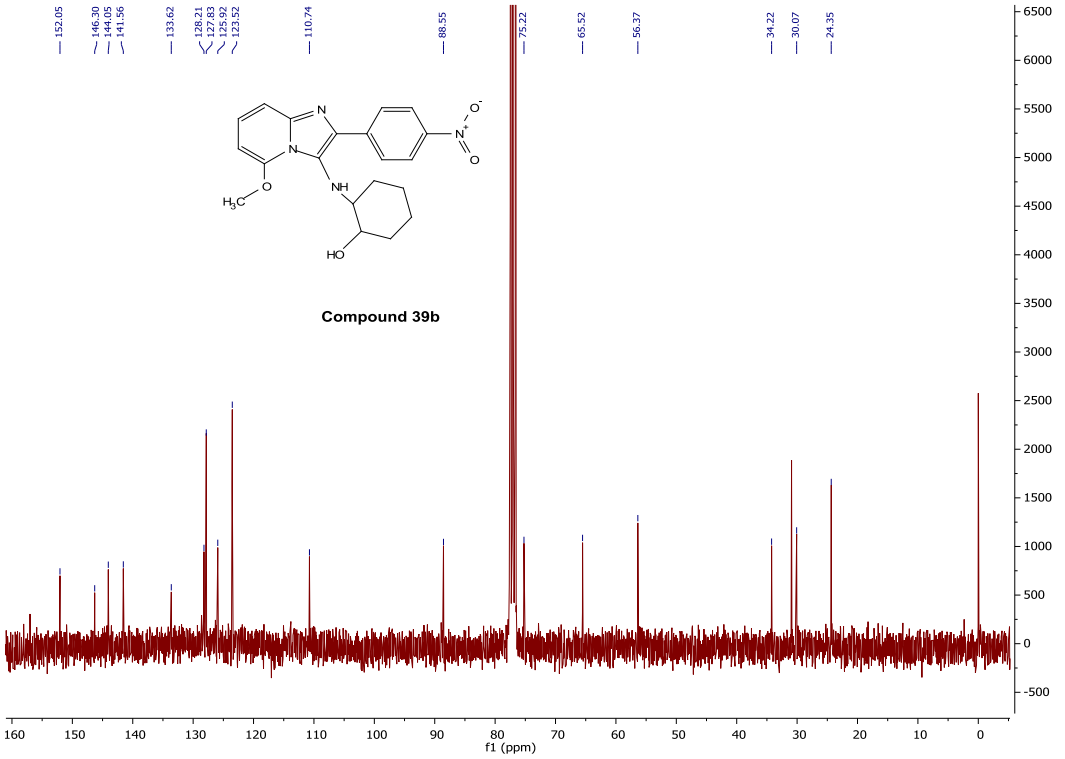
Compound 38a



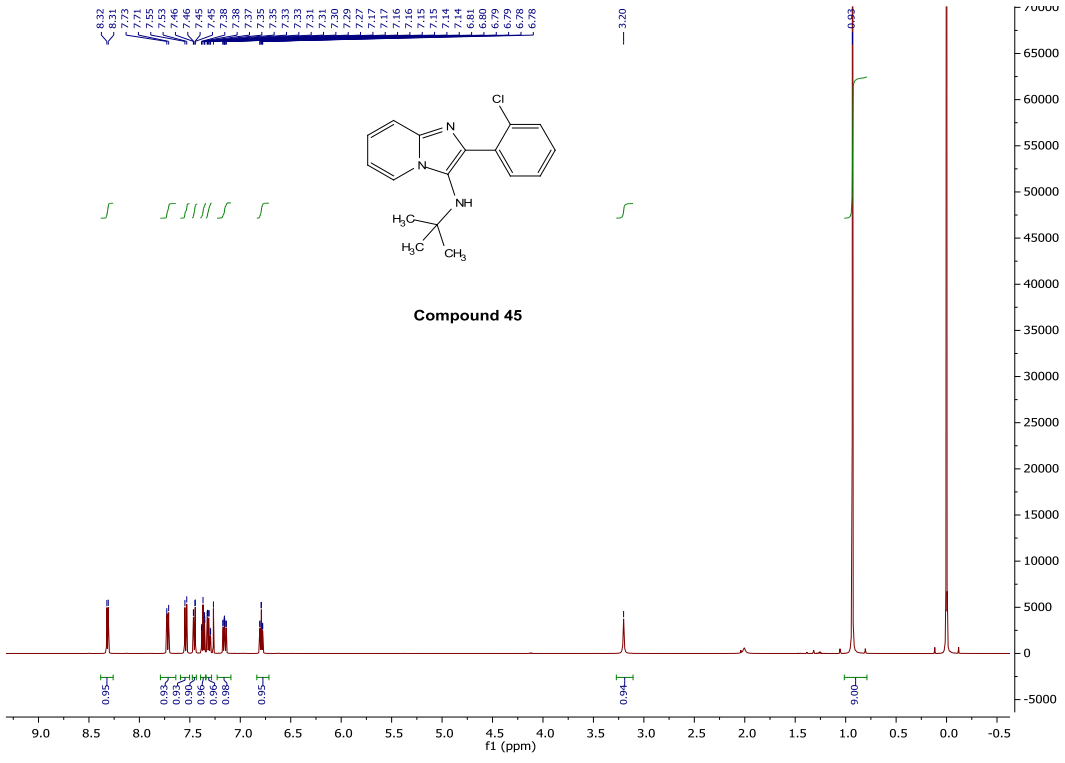
Compound 38a



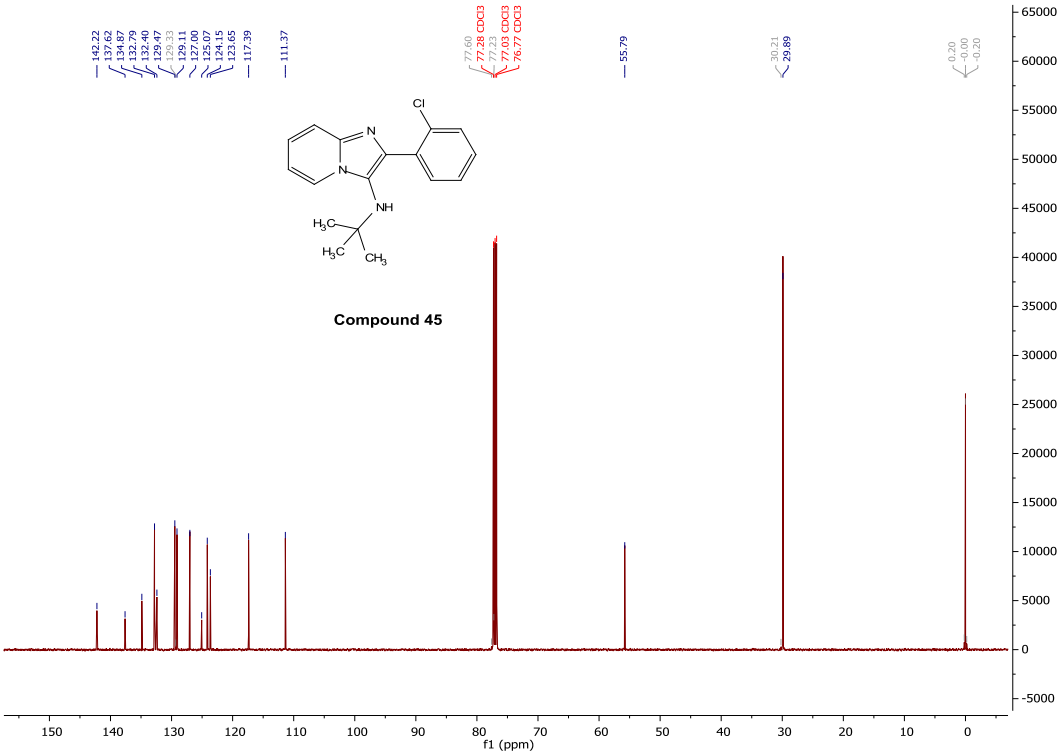
Compound 39b



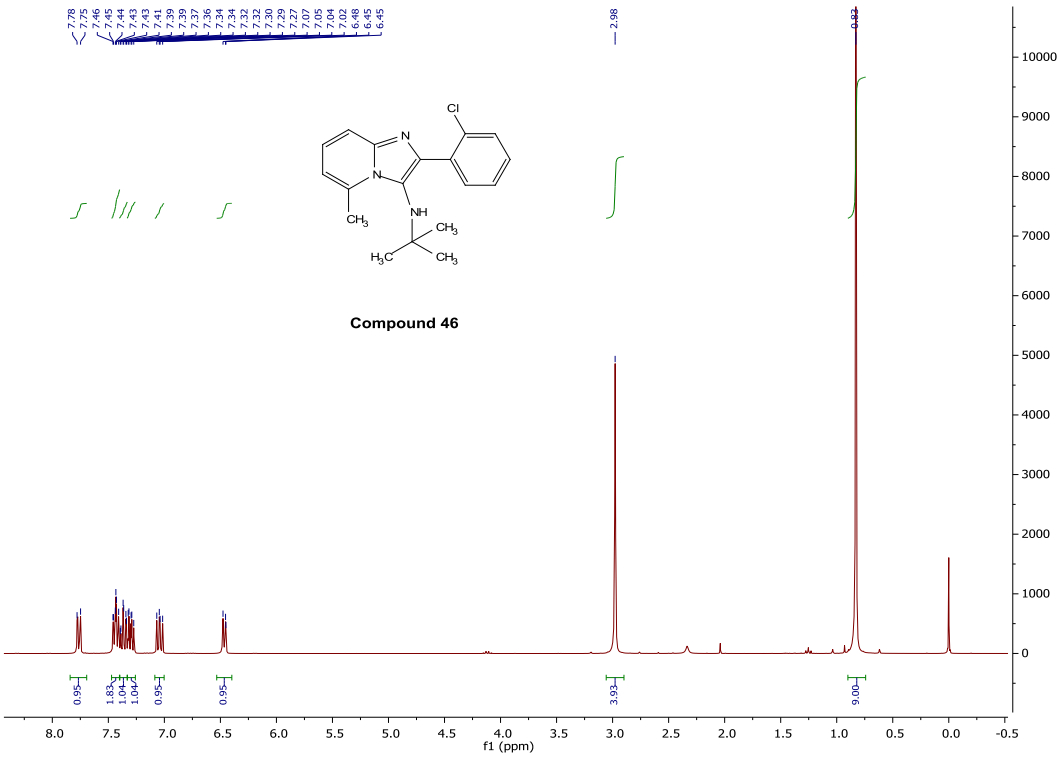
Compound 39b



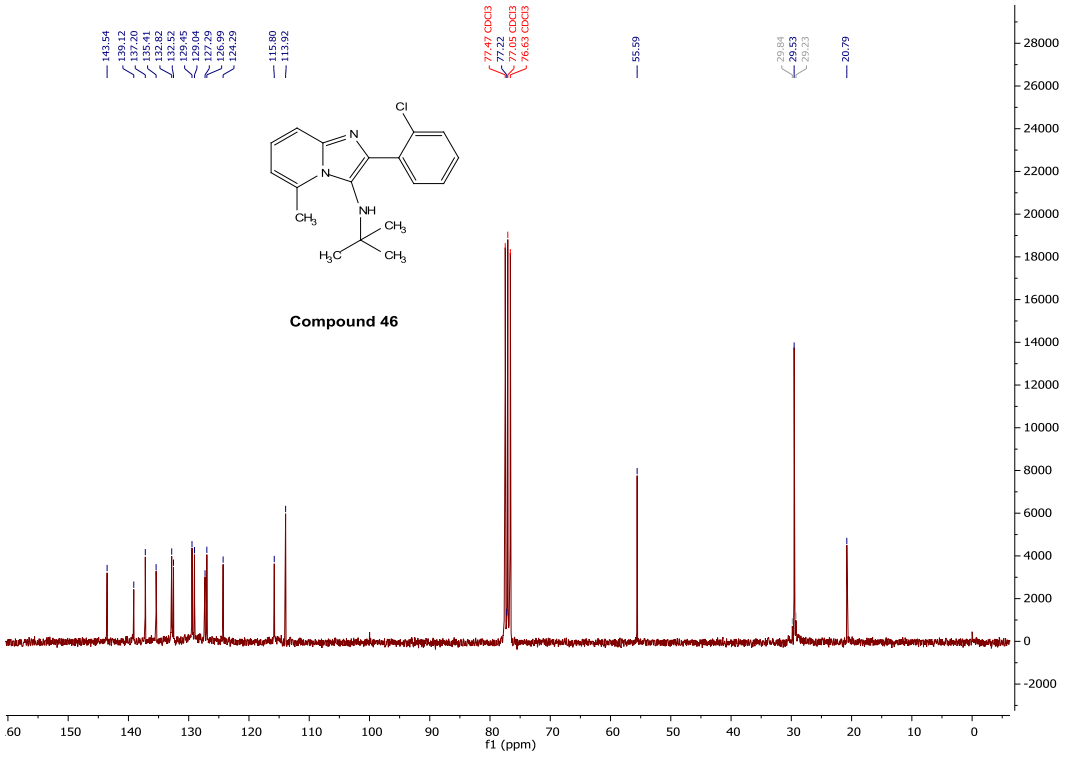
Compound 45



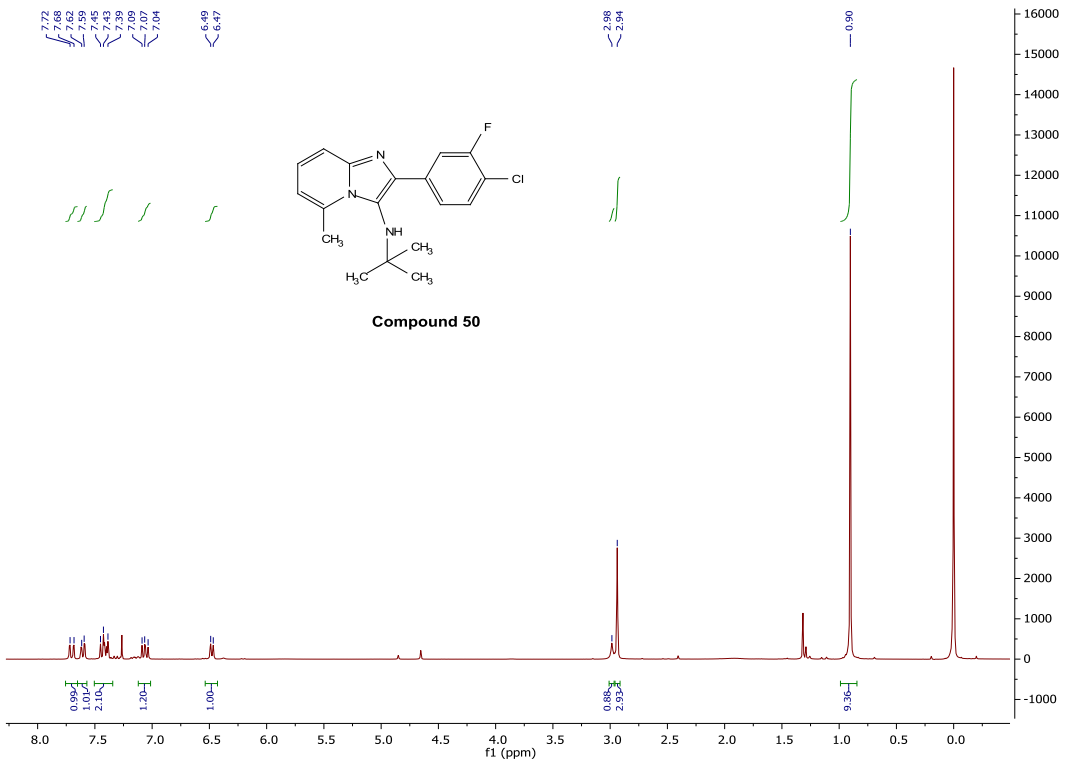
Compound 45



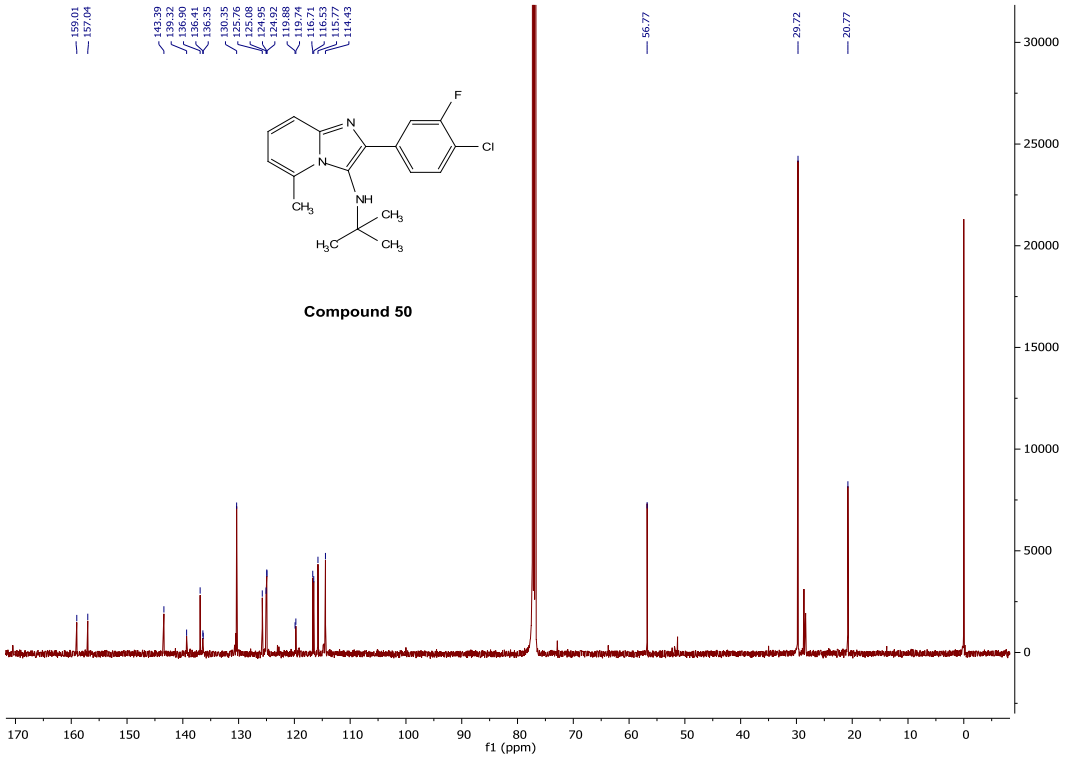
Compound 46



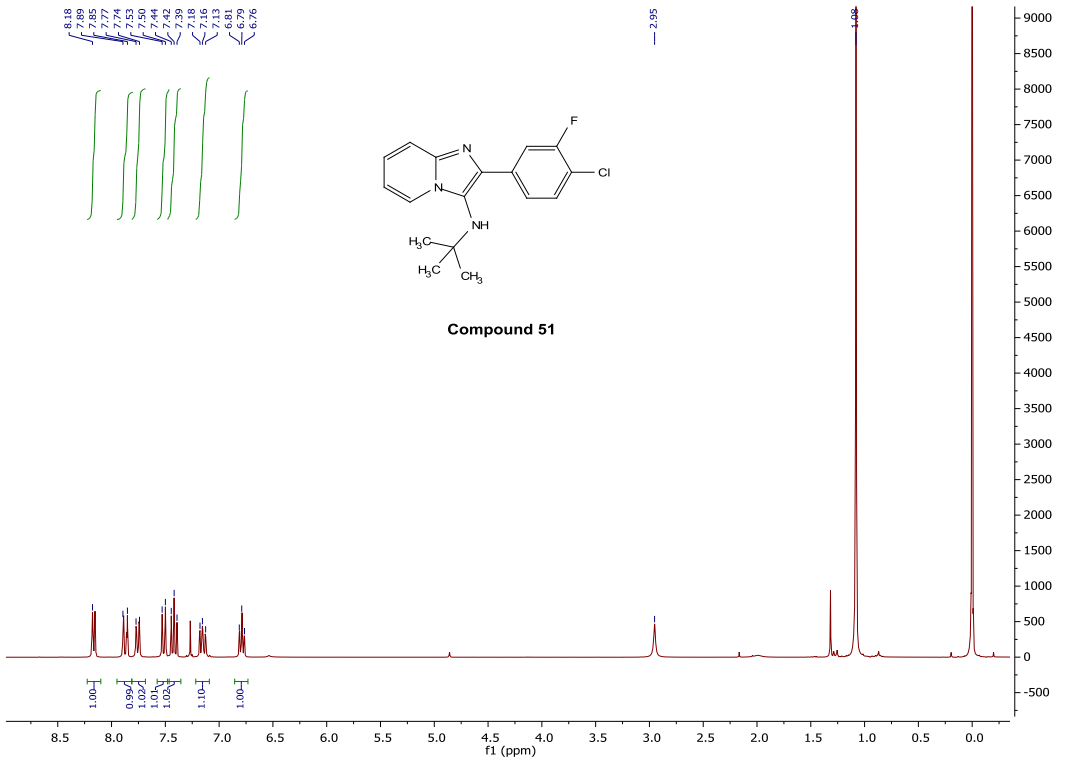
Compound 46



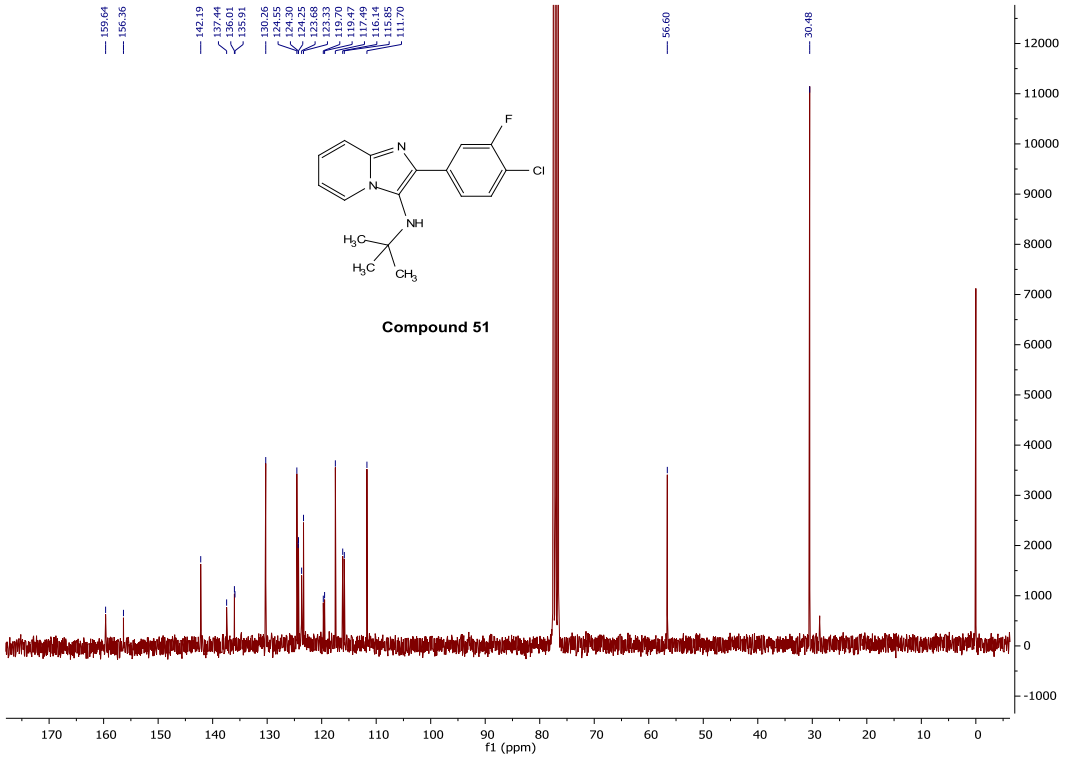
Compound 50



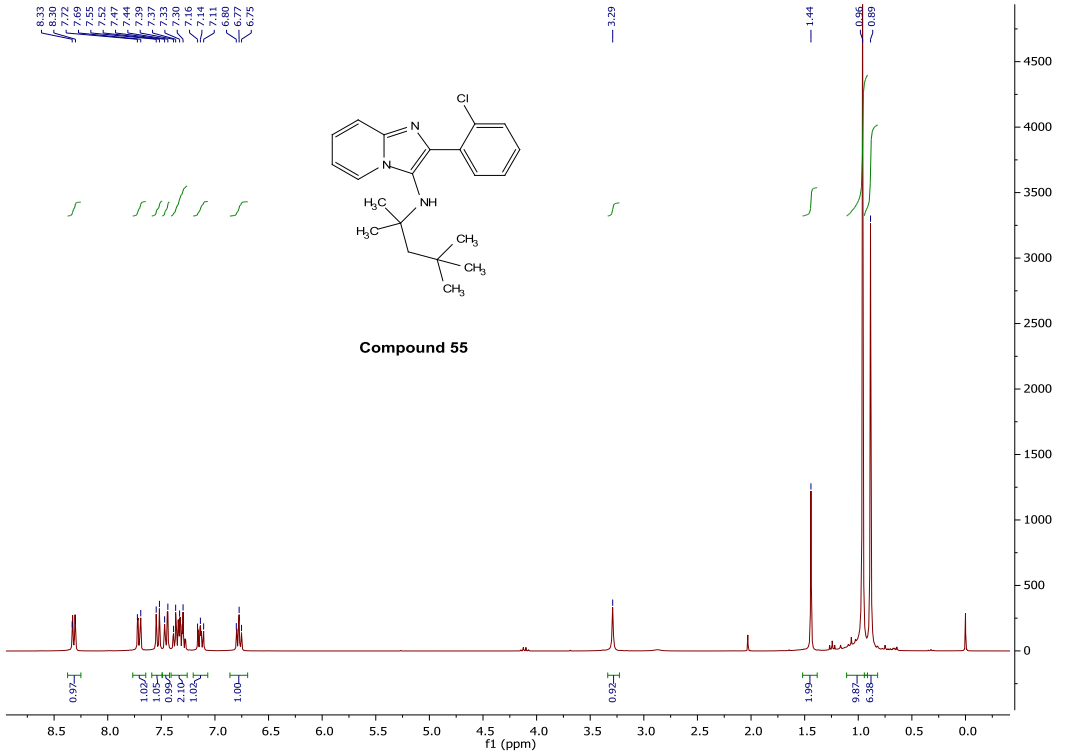
Compound 50



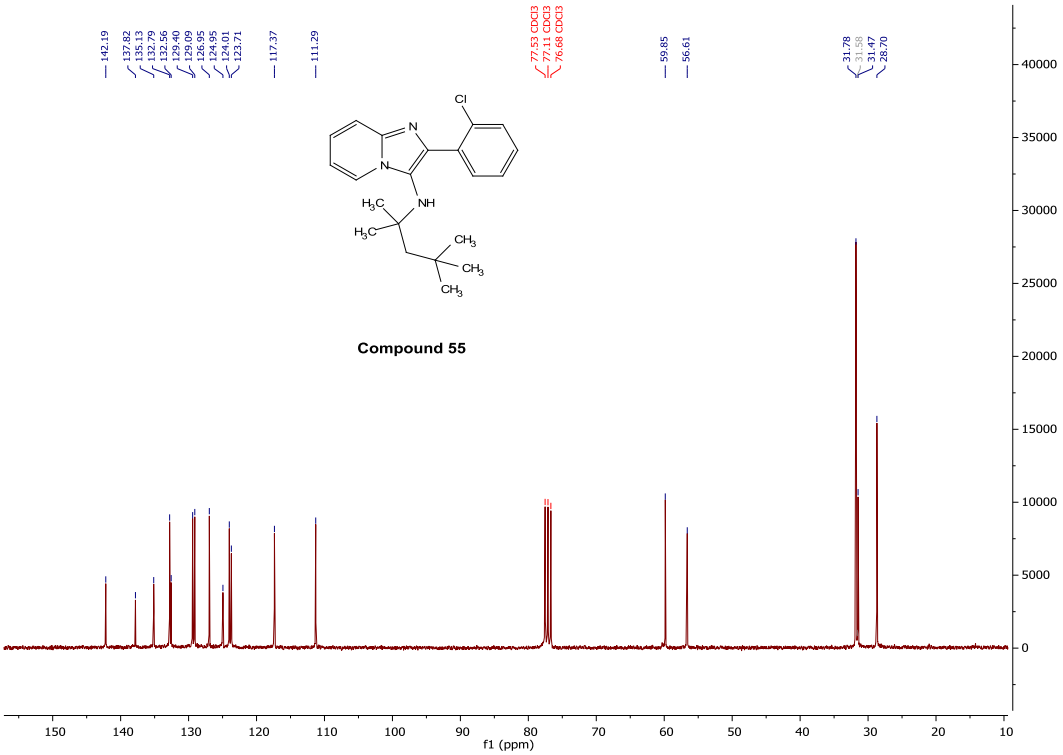
Compound 51



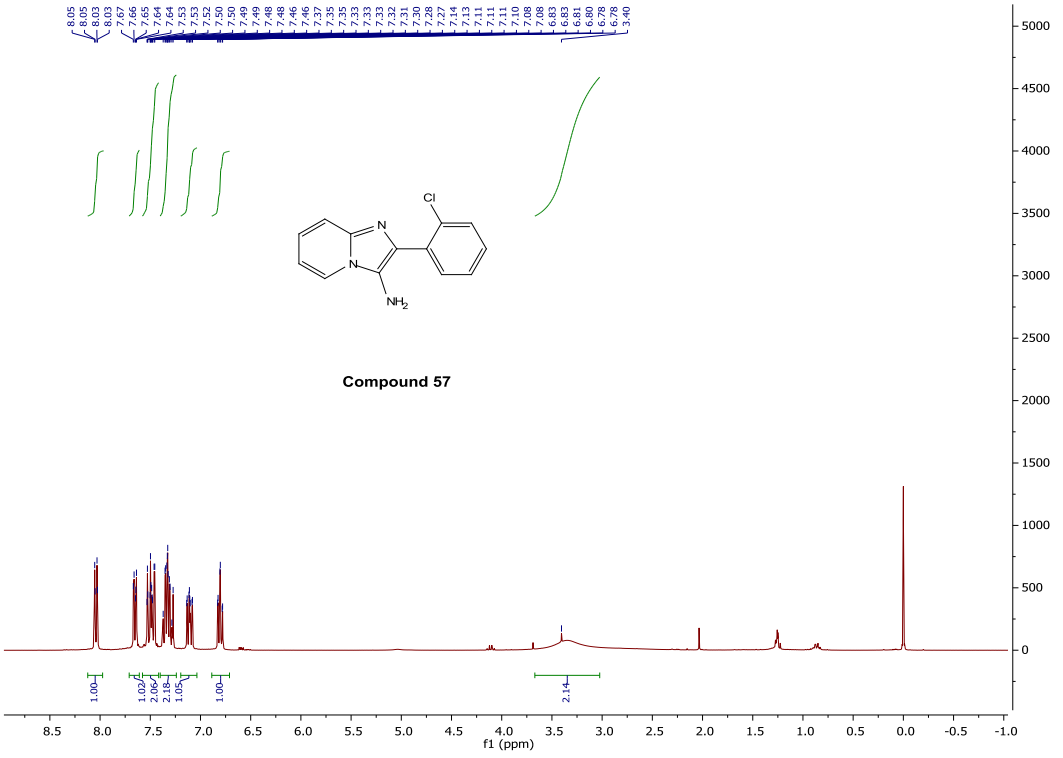
Compound 51



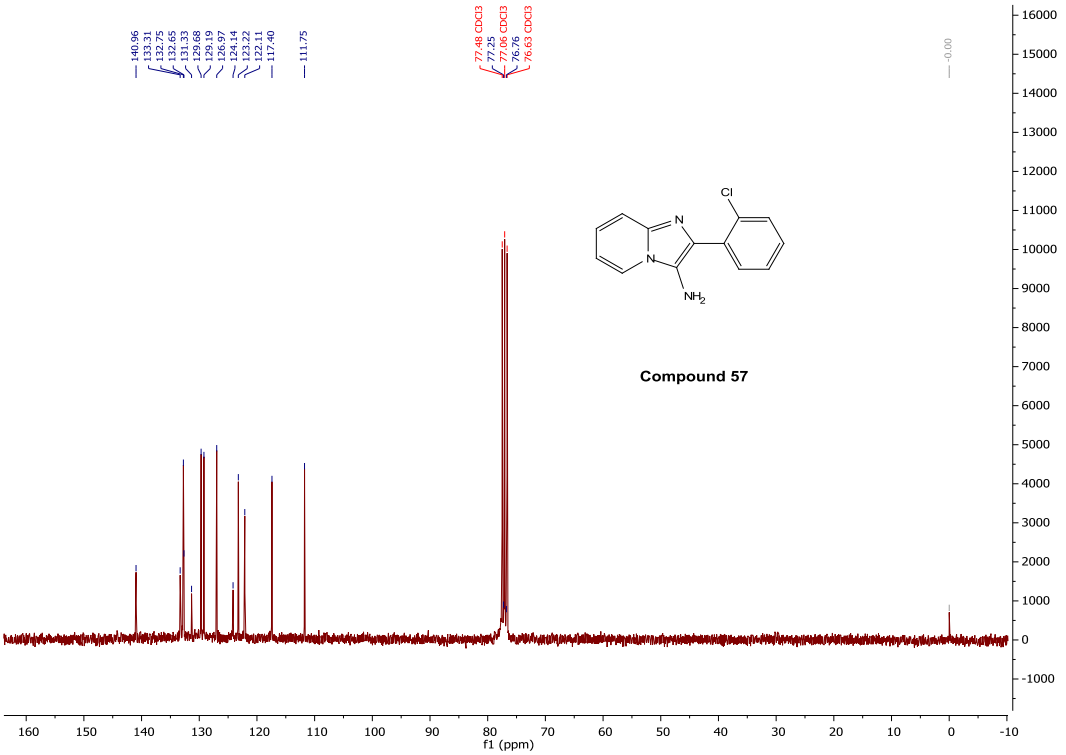
Compound 55

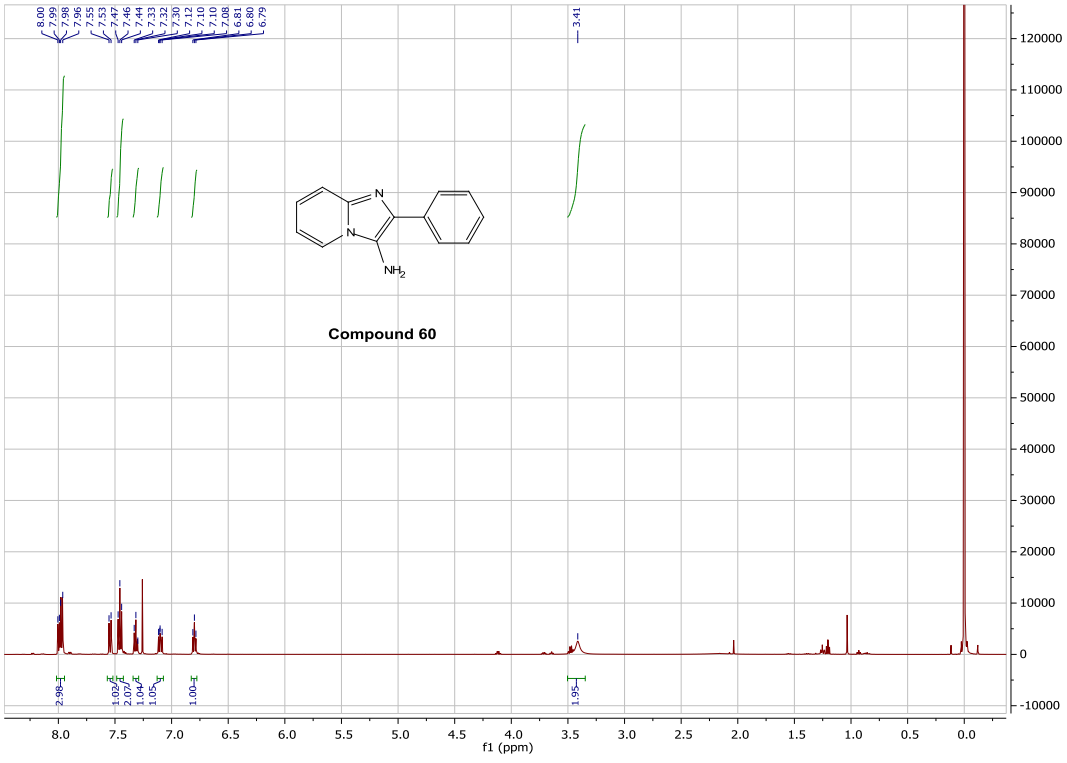


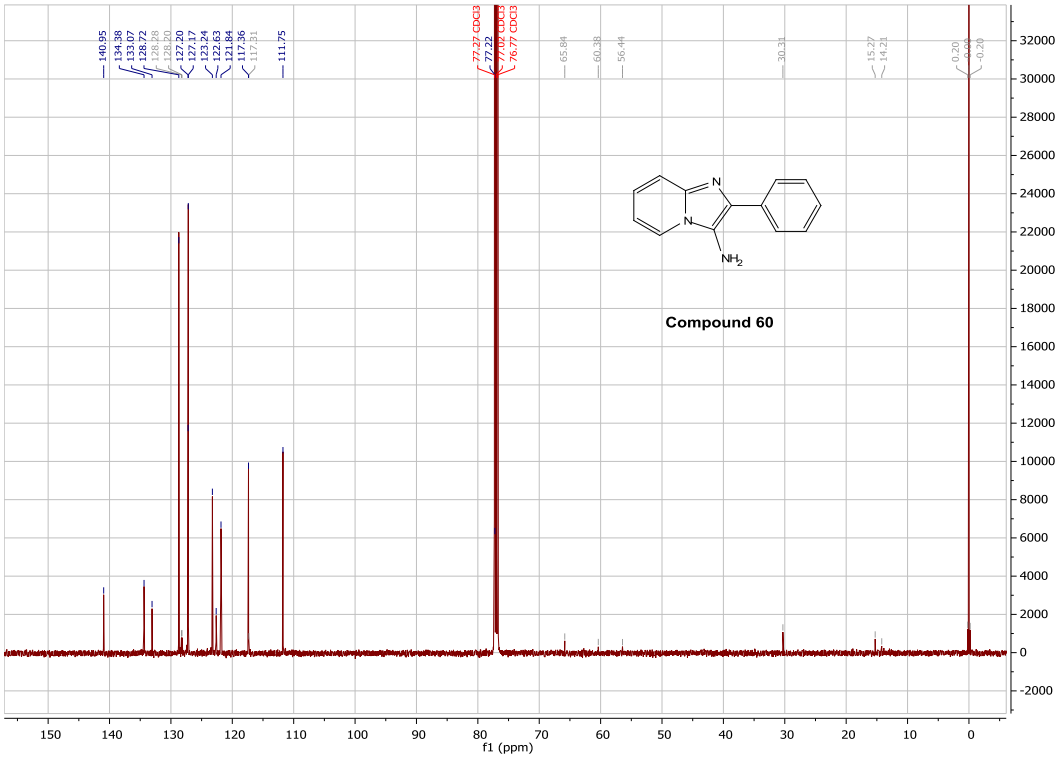
Compound 55



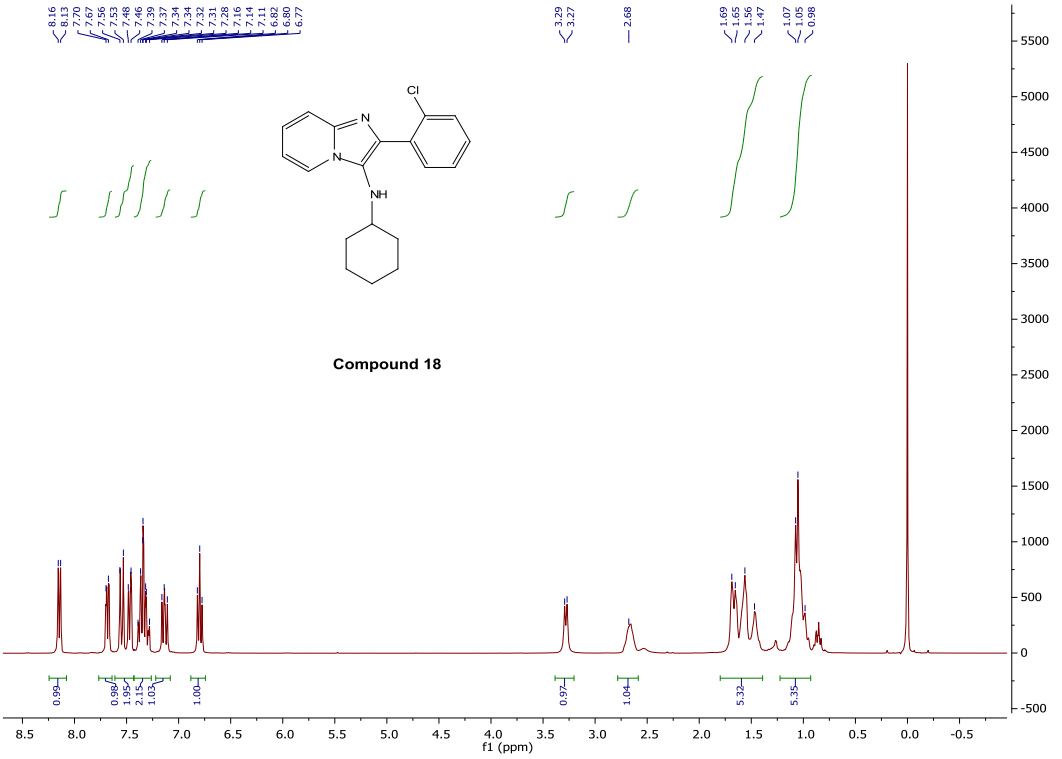
Compound 57


140.96
133.31
132.75
132.65
131.33
129.68
129.19
126.97
124.14
123.22
122.11
117.40
111.75
77.48 CDCl3
77.25
77.06 CDCl3
76.76
76.63 CDCl3
-0.00
Cl
N
N
NH2
Compound 57
f1 (ppm)

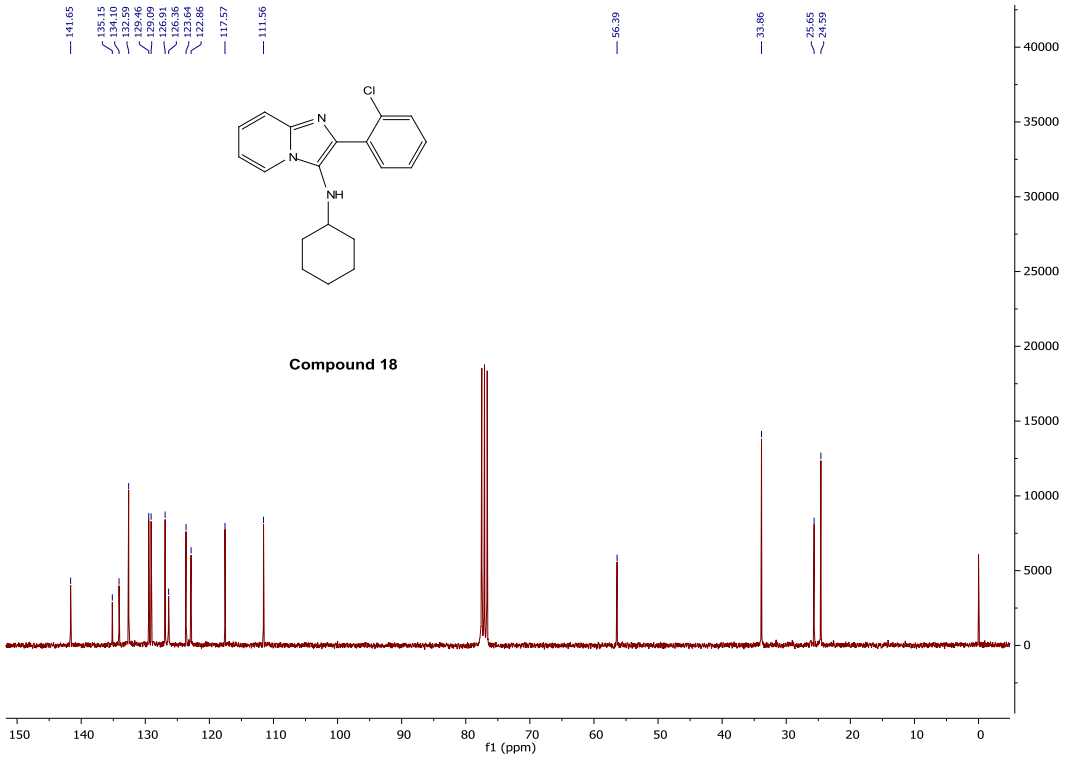

8.00
7.99
7.98
7.96
7.55
7.53
7.47
7.46
7.44
7.33
7.32
7.30
7.12
7.10
7.10
7.08
6.81
6.80
6.79
3.41
2.98
1.02
2.07
1.04
1.05
1.00
1.95
N
N
NH2
Compound 60
f1 (ppm)

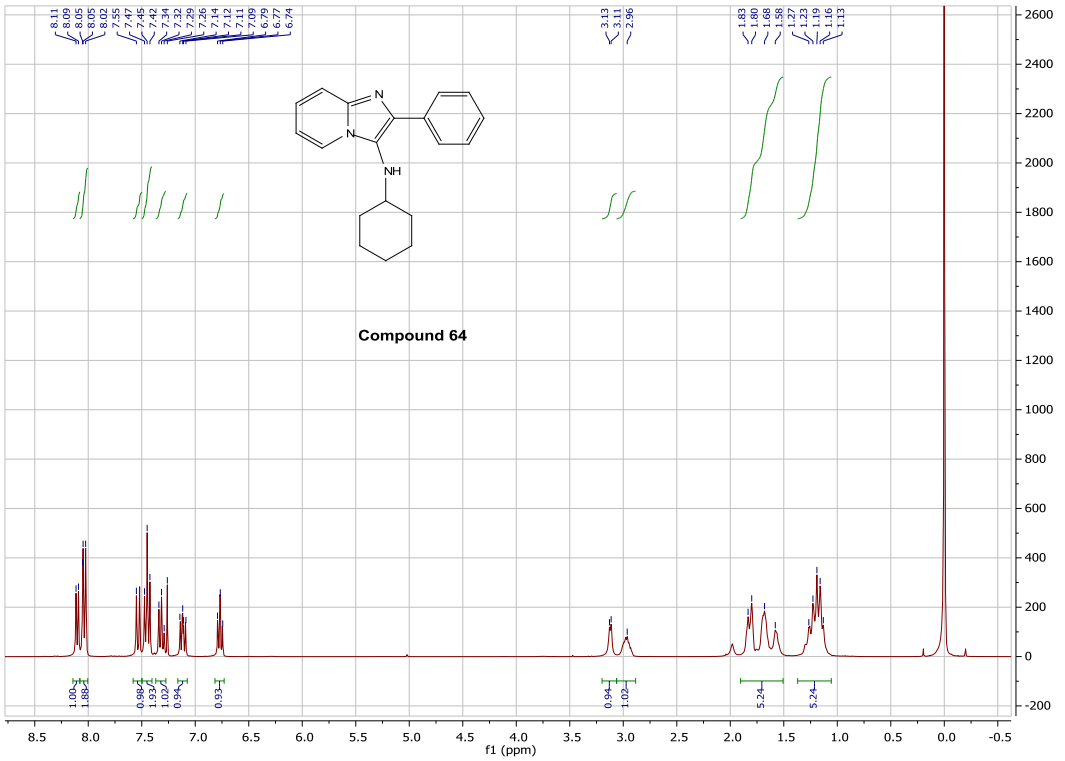


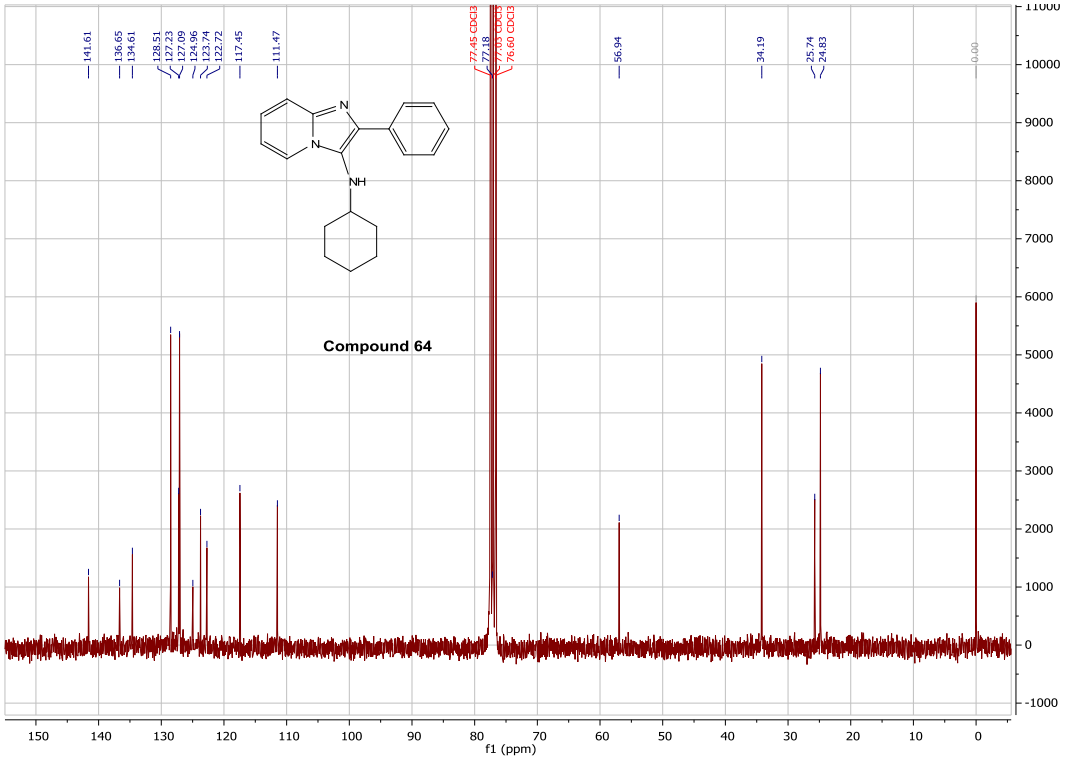
Compound 60

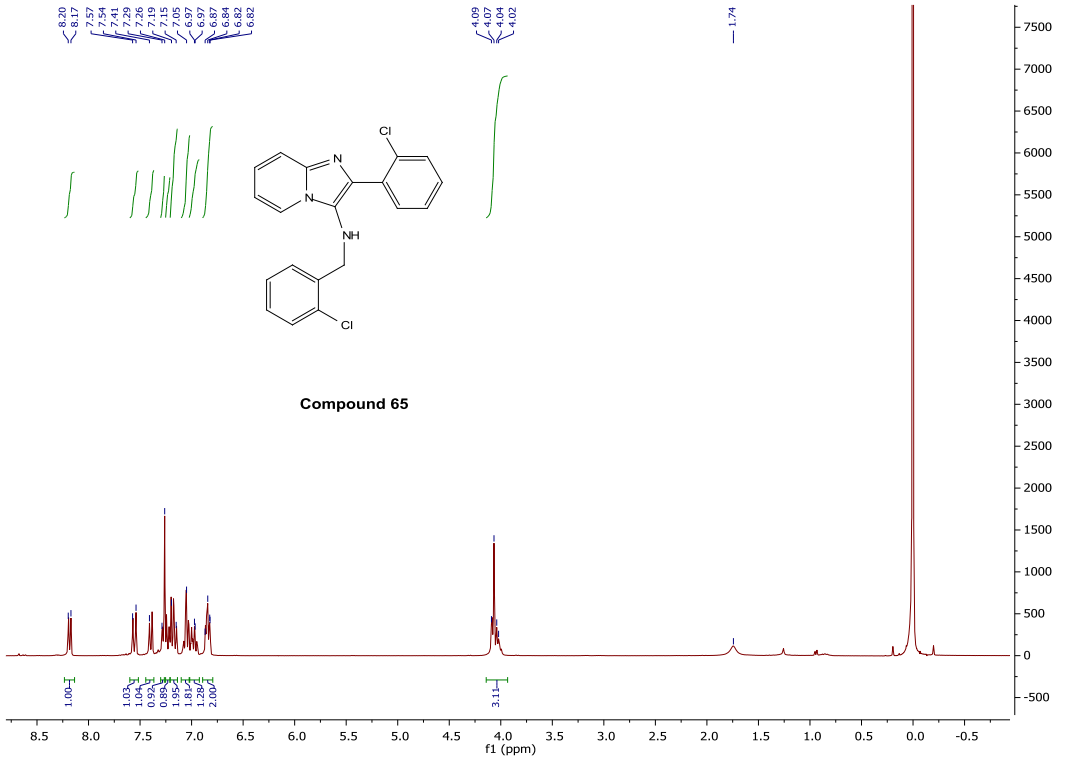


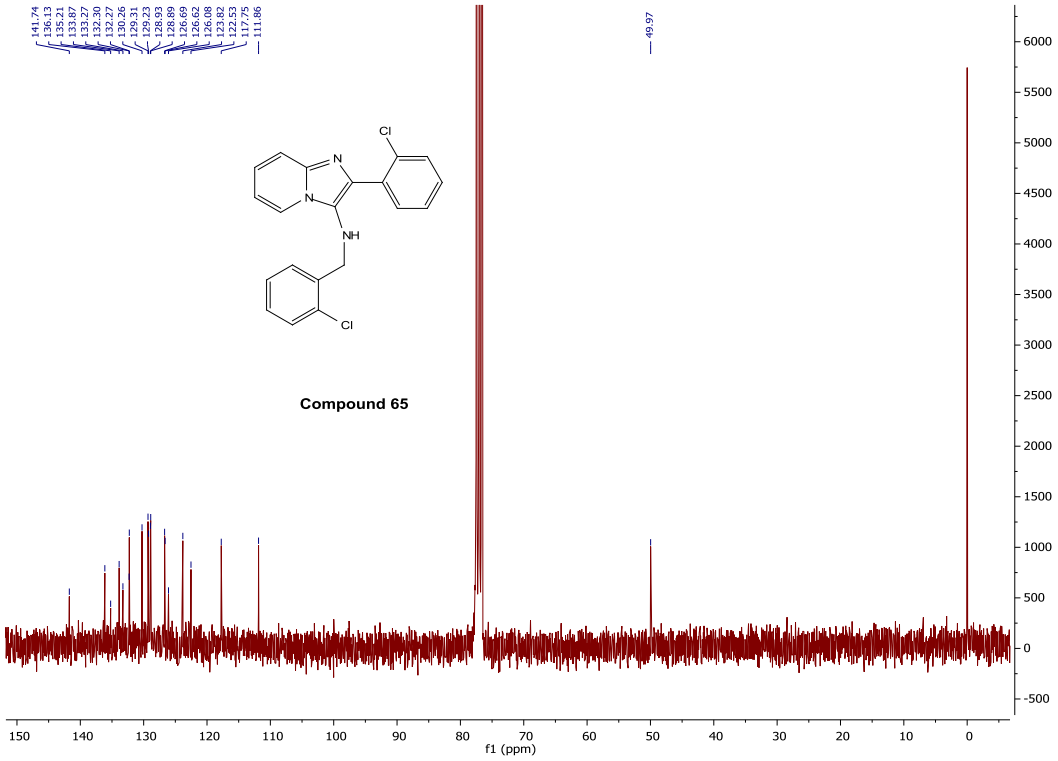
Compound 18


141.65
135.15
134.10
132.59
129.46
129.09
126.91
126.36
123.64
122.86
117.57
111.56
56.39
33.86
25.65
24.59
Cl
N
N
NH
Compound 18
f1 (ppm)


8.11
8.09
8.05
8.05
8.02
7.55
7.47
7.45
7.42
7.34
7.32
7.29
7.26
7.14
7.12
7.11
7.09
6.79
6.77
6.74
3.13
3.11
2.96
1.83
1.80
1.68
1.58
1.27
1.23
1.19
1.16
1.13
N
N
NH
Compound 64
1.00
1.88
0.98
1.93
1.02
0.94
0.93
0.94
1.02
5.24
5.24
f1 (ppm)


141.61
136.65
134.61
128.51
127.23
127.09
124.96
123.74
122.72
117.45
111.47
77.45 CDCl3
77.18
76.90 CDCl3
76.60 CDCl3
56.94
34.19
25.74
24.83
0.00
N
N
NH
Compound 64
f1 (ppm)


8.20
8.17
7.57
7.54
7.41
7.29
7.26
7.19
7.15
7.05
6.97
6.87
6.84
6.82
6.82
4.09
4.07
4.04
4.02
1.74
Cl
N
N
NH
Cl
Compound 65
1.00
1.03
1.04
0.92
0.89
1.96
1.82
1.28
2.00
3.11
f1 (ppm)


141.74
136.13
135.21
133.87
133.27
132.30
132.27
130.26
130.31
129.23
128.93
128.89
126.69
126.62
126.08
123.82
122.53
117.25
111.86
49.97
Cl
N
N
NH
Cl
Compound 65
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)