



An-Najah National University
Faculty of Graduate Studies

**3-AMINOIMIDAZO[1,2-a]PYRIDINE DERIVATIVES:
SYNTHESIS AND ANTIMICROBIAL ACTIVITIES**

By
Osama Othman Hamdan Daragmeh

Supervisors
Prof. Nawaf Al-Maharik
Dr. Nisreen Alhaj

**This Thesis is Submitted in Partial Fulfillment of the Requirements for the Degree
of Master of Chemistry, Faculty of Graduate Studies, An-Najah National
University, Nablus, Palestine.**

2024

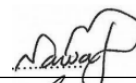
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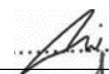
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Prof. Nawaf Al-Maharik
Supervisor



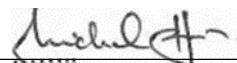
Signature

Dr. Nisreen Alhaj
Co-Supervisor



Signature

Dr. Michel Hanania
External Examiner



Signature

Dr. Derar Al-Smadi
Internal Examiner



Signature

Dedication

This thesis is dedicated to:

My parents for their support and encouragement,

My brother Mohammed for his advice,

My wife for her love and support, patience, and understanding throughout my studying period,

My daughters Zaina and Racel for their kindness.

Acknowledgments

I would like to express my sincerest gratitude to my supervisors, Prof. Nawaf Al-Maharik and Dr. Nisreen Alhaj, for all their valuable and helpful comments, discussions, suggestions, guidance, advice, and support through their knowledge and experience.

A big thank you is extended to Dr. Lubna Abdullah for their assistance in performing the biological assays.

I am eternally grateful to my family for their love, support, and assistance throughout my studies.

I'd also like to express my gratitude to all of my friends for their encouragement and support.

Finally, special thanks to the chemistry department at my university.

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

3-AMINOIMIDAZO[1,2-a]PYRIDINE DERIVATIVES: SYNTHESIS AND ANTIMICROBIAL ACTIVITIES

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: **Osama Othman Hamdan Daragmeh**

Signature: *Osama Daragmeh*

Date: **18/12/2024**

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Abstract

Background: Worldwide, antimicrobial resistance continues to be a major public health issue. Novel antibacterials with improved activity characteristics are therefore in high demand. Antibacterial is one of the many pharmacological actions of imidazo[1,2-a]pyridines. These bioactive substances are the main ingredients of several widely marketed therapeutic medications, such as Alpidem and Zolpidem.

Objectives: Creation of novel 3-amino-6-floroimidazo[1,2-a]pyridine derivatives and evaluation of their effectiveness against five bacterial strains.

Methodology: The one-pot Groebke-Blackburn-Bienayme-Three Component Reaction (GBB-3CR) was used in the compound synthesis. Several spectroscopic methods, including infrared (IR), proton nuclear magnetic resonance (^1H NMR), and carbon-13 nuclear magnetic resonance (^{13}C NMR), were used to confirm the structure. The assessment of purity also makes use of the High-Performance Liquid Chromatography (HPLC) technology. To evaluate the compounds' effectiveness against *S. aureus*, *S. epidermidis*, *K. pneumonia*, *P. aeruginosa*, and *E. coli*, biological experiments were conducted on the produced compounds.

Results: The seven synthetic compounds (85-91) were produced with a purity of 88-100%. These compounds (85-91) have been verified for their structural formula using ^1H NMR, ^{13}C NMR, and IR spectroscopy. These techniques indicate the GBB-3CR normal product. Biologically, compound 91 exhibited the best inhibitory behavior among the others; the lowest MIC value (15.625 $\mu\text{g/ml}$) was recorded for compound 91 against *E. coli*. Moreover, compound 91 works better than Gentamicin against *K. pneumoniae*. The same observation was reported for compounds 85 and 89 against *S. epidermis*. It is worth pointing out that compound 89 in this study kills *E. coli* and *S. epidermis* at lower

concentrations (62.5 $\mu\text{g/mL}$) than Gentamicin antibiotics 125 $\mu\text{g/mL}$ and 250 $\mu\text{g/mL}$, respectively. The same observation was noticed for compound 85 against *S. epidermis* with an MBC value of 62.5 $\mu\text{g/mL}$. Compounds 91, 89, and 85 have good antibacterial effects due to the substitution on C-2 of 3-amino-6-floroimidazo[1,2-a]pyridine scaffolds, which are 1-methylimidazole, p-trifluoromethylphenyl, and 3,5-dimethoxy-4-hydroxyphenyl, respectively.

Conclusions: A straightforward, cost-effective, one-step process was used to create new, promising bioactive chemicals. Additional research on these derivatives might provide more potent compounds that show promise as innovative antibacterial treatment options.

Keywords: 3-Aminoimidazo[1,2-a]pyridines, GBB-3CR, MCR, IMCR, antibacterial.

Chapter One

Introduction

1.1 Background

Medicinal chemistry, is a scientific field that lies at the interface of chemistry and pharmacy. Its primary focus is on the scientific design and development of pharmaceutical medications. A significant part of the field of medicinal chemistry is the process of locating, synthesizing, and developing novel chemical entities that are appropriate for therapeutic application. In addition to this, it encompasses the investigation of current pharmaceuticals, wherein their biological characteristics and quantitative structure-activity relationships (QSAR) are analyzed (1).

Medicines can be organic, inorganic, and organometallic (metallodrug). Lithium carbonate, cisplatin (*cis*-[Pt(NH₃)₂Cl₂]), and gallium nitrate are examples of metallodrugs. Metals are examples of the inorganic medicines that are often known as Metall therapeutics(2). Metals such as Pt,Cu,V,Bi,and Li are used in the study and treatment of diseases and health disorders that are related to the biologicals of cancer, antimicrobials, diabetes, broad-spectrum antibiotics, and bipolar disorder systems(3). However, most medicinal compounds are organic compounds. These compounds are classified into two categories: small organic molecules and biologicals(4). The latter category is typically comprised of medicinal preparations of proteins such as antibodies and hormones. While the small organic molecules encompass synthetic organic chemistry as well as parts of natural products and computational chemistry. Additionally, it works closely with chemical biology, enzymology, and structural biology, all of which work together to discover and develop new therapeutic agents.

Organic chemistry, biological chemistry, computation in chemistry, pharmaceutical science, biology of molecules, statistics, and physical chemistry are all components of medicinal chemistry, which is a highly interconnected area of study that combines organic chemistry with other elements. This interconnected approach allows medicinal chemists to create effective and safe pharmaceuticals (5, 6).

Medicinal chemistry focuses on small organic molecules. This encompasses synthetic organic chemistry as well as parts of natural products and computational chemistry.

Additionally, it works closely with chemical biology, enzymology, and structural biology, all of which work together to discover and develop new therapeutic agents. From a practical standpoint, it entails the identification of chemical features, followed by the methodical and exhaustive modification of novel chemical entities through the process of synthetic modification in order to make them acceptable for therapeutic application (5). To put it another way, it includes the synthetic and computational mechanisms of the investigation of existing medications and agents that are still in the process of being developed in connection to their bioactivities, or the comprehension of their structure-activity correlations (SAR). The concentration of pharmaceutical chemistry is on the quality aspects of medications, with the objective of ensuring that medical products are suitable for their intended use (6).

Hits are novel active chemical compounds discovered through assaying substances for desired biological activity. They can come from observations of natural products, reusing current agents, structural analyses of molecules linked to therapeutic targets, and collective testing of compounds against biological targets. The most successful strategies rely on chemical and biological instincts, formed in team contexts over years of practice. Most successful procedures are based on biological and chemical instincts (7). Additional investigation into synthetic procedures and analyses is necessary to identify compounds that demonstrate suitable SAR and chemical properties. Chemical modifications improve primary and secondary activities, physicochemical properties, and pharmacokinetic/pharmacodynamic profiles, making them suitable for animal and human studies. The modifications can enhance the affinities of the compounds for their targets (8,9). Organic synthesis is not constrained by the limitations placed on synthesis in medicinal chemistry. Protection is essential because of the potential for enhanced preparedness. The potential toxicity of substances affects methodologies (1, 6).

Structured analysis of lead compounds is typically done using computational approaches before synthesizing ligands. Factors such as hydrogen bond donors and acceptors, rotatable bonds, surface area, and lipophilicity are considered. After synthesis, conventional techniques like thin-layer chromatography, nuclear magnetic resonance, and gas chromatography-mass spectrometry are used. Modern organic and medicinal chemistry aims to create novel drugs by constructing molecular complexity and diversity to explore the chemical space (1,6).

1.2 Imidazopyridines overview

A number of bioactive substances contain imidazopyridines as essential structural elements. Similar to indole and azaindole, two of the most prevalent nitrogen-based heterocycles known for their essential biological characteristics, is the two-membered fused ring heterocyclic structure (10, 11). There are four known families of imidazopyridines, which are made up of a pyridine moiety fused to an imidazole ring (Figure 1.1A): imidazo[1,2-a]pyridine a, 1*H*-imidazo[4,5-b]pyridine b, 1*H*-imidazo[4,5-c]pyridine c, and imidazo[1,5-a]pyridine d. These groups are categorized based on the angular nitrogen that connects the two cycles as well as the location of the pyrrolic nitrogen (12).

The imidazopyridine scaffold has become increasingly significant in recent decades. In order to rationally design and develop new synthetic analogs for a variety of therapeutic illnesses, imidazopyridines have been used quickly. In addition to existing chemotherapeutic medicines, a large range of imidazopyridine derivatives have been created as possible anti-cancer, anti-diabetic, anti-tubercular, anti-microbial, anti-viral, anti-inflammatory, and central nervous system (CNS) agents (13). The imidazopyridine heterocyclic system serves as a crucial pharmacophore motif for lead structure optimization and identification, expanding the toolkit of medicinal chemistry. Imidazopyridines' medical significance is highlighted in numerous reviews and research papers, which support their development as lead compounds with enhanced therapeutic efficacies. In order to establish a relationship between the important structural properties and the biological activities, these reviews and studies place additional attention on the SARs of the different developed imidazopyridines (14).

1.3 Imidazo[1,2-a]pyridine synthesis

The scientific community continues to search for new ways to create imidazo[1,2-a]pyridine and pyrimidine derivatives, with the goal of adding various substitutions to these frameworks at positions two and three. As a result of this search, many synthetic methods specifically designed for creating this chemical structure have been developed. A number of categories, including condensation, multicomponent reactions, oxidative coupling, tandem reactions, aminooxygenation, and hydroamination, are used to comprehensively group these approaches (15).

1.3.1 Some of the condensation reactions

Many research teams have developed a wide range of catalytic and non-catalytic techniques throughout the years for the conventional synthesis of pyrimidine derivatives. These methods mostly use condensation reactions between 2-aminopyridines and α -haloketones (15).

1.3.2 Imidazo[1,2-a]pyridine synthesis from α -haloketones via condensation reactions

Tschitschibabin et al. made a major contribution to chemical research in 1925 by introducing a novel technique for the synthesis of pyrimidines (16). Their methodology comprised a sealed tube reaction between 2-aminopyridine e and bromoacetaldehyde f at temperatures between 150 and 200°C. Initially, the yields of imidazo[1,2-a]pyridines g were poor, but this technique produced them. The addition of a base, such as sodium hydrogen carbonate (NaHCO₃), later improved this technique by enabling the reaction under gentler circumstances and greatly increasing its efficiency, as shown in Scheme 1.1A. Ponnala et al. (17) demonstrated the efficiency of neutral alumina as a catalyst for the synthesis of imidazo[1,2-a]pyridine and pyrimidine derivatives g at room temperature. This technology makes it possible to produce a large variety of imidazopyridine derivatives in a simple and effective manner. By reacting α -bromo/chloroketones f with 2-aminopyridine, Dong-Jian Zhu and partners developed a novel technique for creating imidazo[1,2-a]pyridines (18). Surprisingly, this technique works well at a moderate temperature of 60°C and doesn't require a catalyst or solvent. This novel approach works just as well for α -haloketones. The crucial step is the nucleophilic substitution of the pyridine nitrogen found in 2-aminopyridine for the bromide or chloride ion, which is the fundamental mechanism behind these reactions. By removing the need for extra reagents and reducing energy usage, this method not only streamlines the synthesis process but also advances sustainable chemical practices. A major advancement in the synthesis of 6-bromo-2-(3,4-dichlorophenyl)imidazo[1,2-a]pyridine g has been made by Biradar, Bhoi, and their group (19). They developed a technique that makes it easier to prepare the imidazo[1,2-a]pyridine derivative quickly and effectively by using microwave irradiation. By drastically cutting reaction durations and increasing product yields, this novel method simplifies the synthetic process. In addition to quickening the process, microwave radiation helps to provide more consistent heating, which raises the end

product's purity. This technique offers a more effective and sustainable way to create complex compounds, marking a substantial breakthrough in the area of organic synthesis (Scheme 1.1A).

1.4 Tandem reaction

1.4.1 Nitroalkene and 2-aminopyridine Reaction According to Morita-Baylis-Hillman (MBH)

By creating a unique synthesis and functionalization method for imidazo[1,2-a]pyridines **g**, Nair and associates made an important addition to the discipline of organic chemistry (20). As shown in Scheme 1.1B, their methodology is based on the reaction involving Morita-Baylis-Hillman (MBH) nitroalkene acetates **h** with 2-aminopyridines, which is conducted at room temperature in a methanol solvent. By utilizing various 2-aminopyridines and MBH acetates, this method enabled the synthesis of a large range of imidazo[1,2-a]pyridine derivatives **g** in comparatively fast reaction times. The method was shown to be useless with several aminoheterocycles, such as 2-aminopyrimidine, 2-aminopyrazine, and 2-aminothiazole, despite being effective for a wide range of derivatives. This finding highlights the uniqueness of the procedure as well as possible directions for future research and improvement in the formation of intricate heterocyclic molecules.

1.4.2 Nitroolefin and 2-aminopyridine tandem coupling

A novel Fe(II)-catalyzed tandem coupling method was presented by Hao Yan et al. (21) to create 3-methyl-2-arylimidazo[1,2-a]pyridine **g** derived products from 2-aminopyridines and 2-methylnitroolefins. Because Iron(II) chloride (FeCl₂) is more effective than other ferric salts at enabling these intricate conversions, this method, which is explained in Scheme 1.1C, stands out for using it. The researchers produced an extensive set of 3-methyl-2-arylimidazo[1,2-a]pyridine compounds to demonstrate the method's broad range of applications and demonstrate its flexibility. Additionally, 3-ethyl-2-phenylimidazo[1,2-a]pyridine was produced with excellent yields using this innovative technique. The procedure is carried out by a tandem mechanism that utilizes intramolecular cyclization and Michael addition, which represents a major breakthrough in the preparation for imidazo[1,2-a]pyridine variations and broadens the toolkit for building intricate molecular structures with excellent selectivity and efficiency. As shown

in Scheme 1.1C (22), Santra and his group created a simple and effective process for creating 3-unsubstituted imidazo[1,2-a]pyridines by a cascade reaction that joins nitroolefins with 2-aminopyridine. Ferric chloride (FeCl_3) was shown to be the best catalyst after a thorough examination of several Lewis acids used to catalyze this reaction. This FeCl_3 -catalyzed technique is noteworthy for its wide range of applications, as it can efficiently handle a variety of substituted 2-aminopyridine derivatives *g* in addition to aromatic and aliphatic nitroolefins. The effective creation of the intermediate *g* ($\text{R}_2 = \text{C}_6\text{H}_4\text{-SMe}$), a crucial component in the synthesis of the medicinal drug zolimidine 36, utilizing this approach was a noteworthy accomplishment of this study. The production of imidazo[1,2-a]pyridine analogues which substitute for at the 3 position is not covered by this methodology, which is significant because it indicates a particular restriction in the reaction's range. This discovery not only advances the area of heterocyclic chemicals by offering a fresh synthetic pathway to valuable molecules, but it also highlights the possibility of further development and extension of this method to encompass a larger variety of derivatives (22).

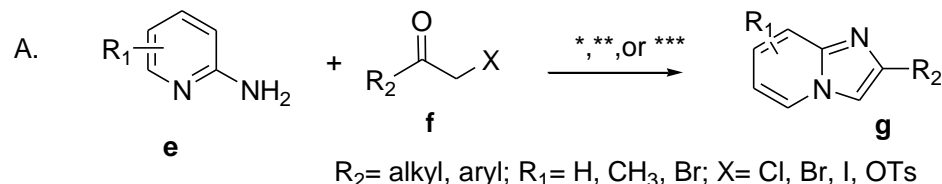
1.4.3 Multicomponent reactions (MCRs)

Multicomponent reactions (MCRs) combine three or more starting materials to produce a single product, where most or all of the atoms from the reactants are incorporated into the final product. They are also beneficial in materials science and natural product synthesis (23). Isocyanide-based multicomponent reactions (IMCRs) are popular due to their exceptional properties, such as resonance between carbon forms with four and two valence electrons. Isocyanides are unique in their ability to function as both nucleophiles and electrophiles, which makes them incredibly versatile in organic synthesis. As Nucleophiles: The carbon atom in the isocyanide group ($-\text{N}\equiv\text{C}$) has a lone pair of electrons, allowing it to attack electrophilic centers. This property is utilized in reactions like the Ugi and Passerini reactions, where the isocyanide attacks a carbonyl compound or an imine. As Electrophiles: The carbon atom in the isocyanide group can also act as an electrophile due to the electron-withdrawing nature of the nitrogen atom. This allows nucleophiles to attack the carbon atom, leading to the formation of various products (24). These reactions are highly efficient, generating structural complexity and having the option to use alternative building blocks or starting materials to achieve structure diversity

in three or more locations in a single step from basic and inexpensive starting materials and catalysts, often under environmentally friendly conditions (23).

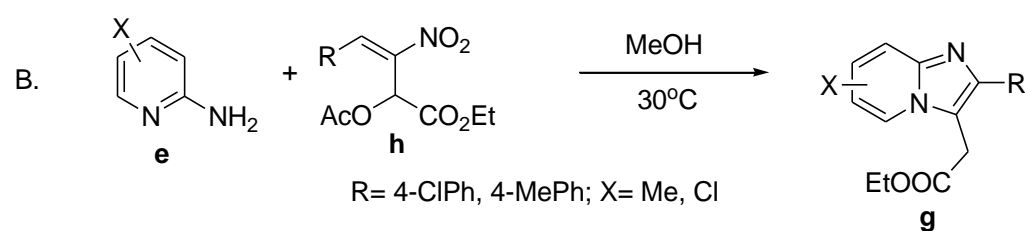
Scheme 1.1

Some of the condensation reactions for Imidazo[1,2-a]pyridine synthesis



* = $\text{NaHCO}_3, \text{EtOH, reflux}$; ** = 10 eq. neutral alumina; *** = 60°C No catalyst, No solvent

A. Using condensation processes to synthesize imidazo[1,2-a] pyridine from α -haloketones.



B. The 2-aminopyridine Reaction and Nitroalkene, According Morita-Baylis-Hillman.

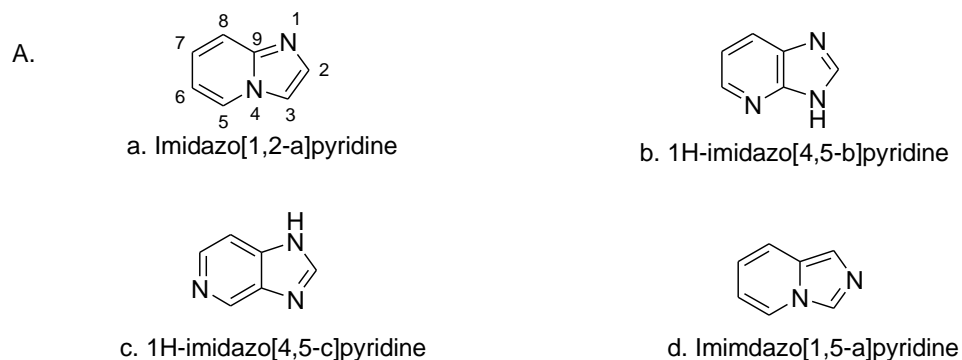


C. Tandem coupling between 2-Aminopyridine and nitroolefin

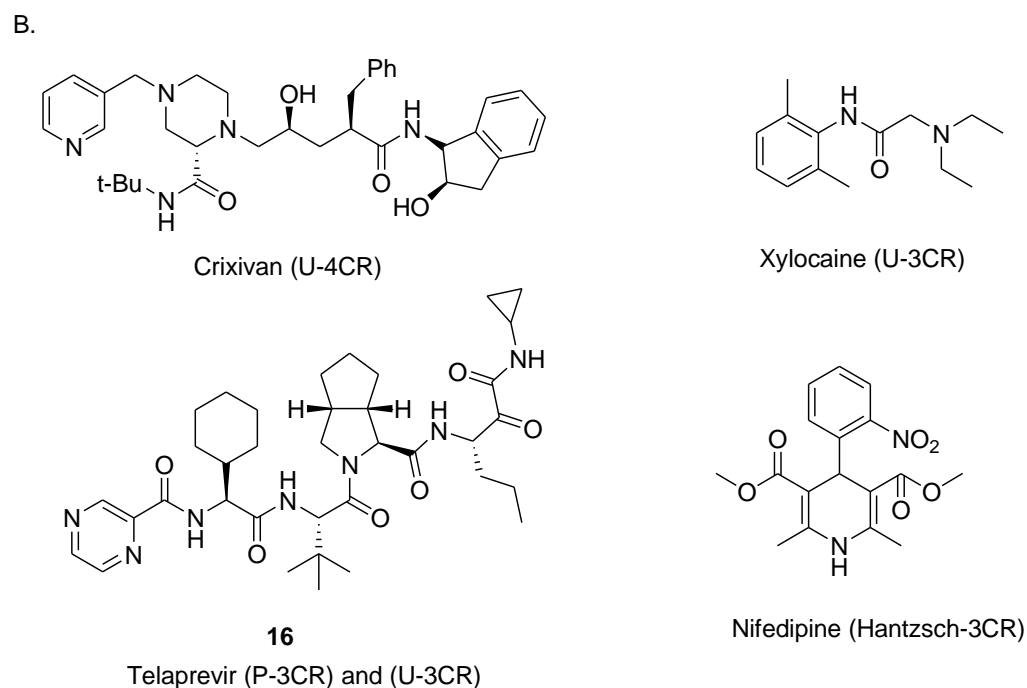
Multicomponent reactions are thought to be able to produce about 5% of the globe's present pharmaceutical supply. Examples of currently available drugs and lead compounds made using the MCR approach include the antiviral Telaprevir (Passerini-3CR) (25), the local anesthetic Xylocaine (Ugi-3CR) (26), the HIV protease inhibitor Crixivan (Ugi-4CR) (27), and cardiovascular blockbuster Nifedipine (Hantzsch-3CR) (Figure 1.1B) (26).

Figure 1.1

Commercial pharmaceuticals produced by MCRs and imidazopyridine structure and nomenclature



A. General structure and nomenclature of imidazopyridine.



B. Commercial drugs synthesized by MCRs

Numerous varieties of MCR reactions exist, including the following examples:

1. The Ugi 4-component reaction (U-4CR)

The Ugi 4-component reaction (U-4CR) is a multi-component reaction in organic chemistry that forms bis-amide⁵ by adding ketone or aldehyde 3, amine 2, isocyanide 4, and carboxylic acid 1 (Scheme 1.1A). Ivar Karl Ugi, the first to record this reaction in 1959, is honored with its name (28). This exothermic reaction yields high chemical yields

when reactants are present in high concentrations, with polar and aprotic solvents like dimethylformamide (DMF) performing well (29).

A probable reaction process is shown in Scheme 1.1B. Here, amine 2 and ketone 3 react to produce imine 6, with the elimination of one equivalent of water. Proton exchange between carboxylic acid and iminium ion 7 enhances the reactivity of the iminium ion, allowing for the nucleophilic addition of isocyanide 4 to the terminal carbon atom of nitrilium ion 9. A second nucleophilic addition occurs at this intermediate with the carboxylic acid anion 8 to form compound 5. The last stage involves a Mumm rearrangement, where the R₄ acyl group is transferred from oxygen to nitrogen. With the exception of the Mumm rearrangement, all reaction stages in the sequence are reversible. However, it is the Mumm rearrangement that propels the entire reaction (30).

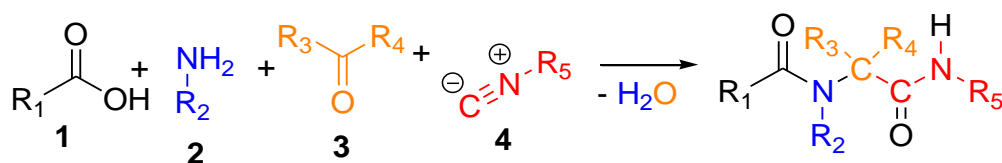
At the beginning of the process of developing chemical libraries, the Ugi reaction was one of the first reactions that was expressly used. This chemical library is a collection of chemicals that have been tested several times. Using the rules of combinatorial chemistry, the Ugi reaction synthesizes dozens of compounds in a single reaction. This is accomplished by the reaction of a variety of its starting materials, aldehydes or ketones, amines, carboxylic acids, and isocyanides. Then, that library tests to discover novel medicinal compounds that are active against their tests (31).

The disadvantage of this method is that the products do not have a diverse chemical composition, but they have the same general structure because they have the same scaffold, but the chemical variety of products that may be produced is expanded. There has been a recent breakthrough in the area of covalent organic frameworks (COFs), where the Ugi reaction is being used to insert various functional handles into the COFs by post-synthetic alteration. This breakthrough brought about a significant advancement in the sector (32). It is expected that a library of COFs that contains helpful functional handles for a variety of significant applications may be produced with the help of this new promising technique.

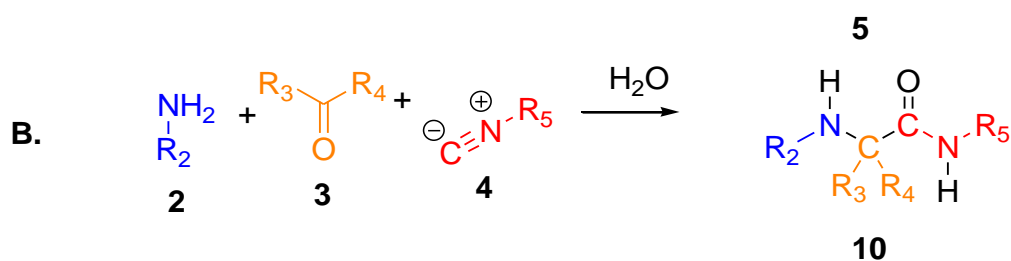
Scheme 1.2

The Ugi 4-component reaction, the Ugi 3-component reaction, and their reaction mechanisms

A.

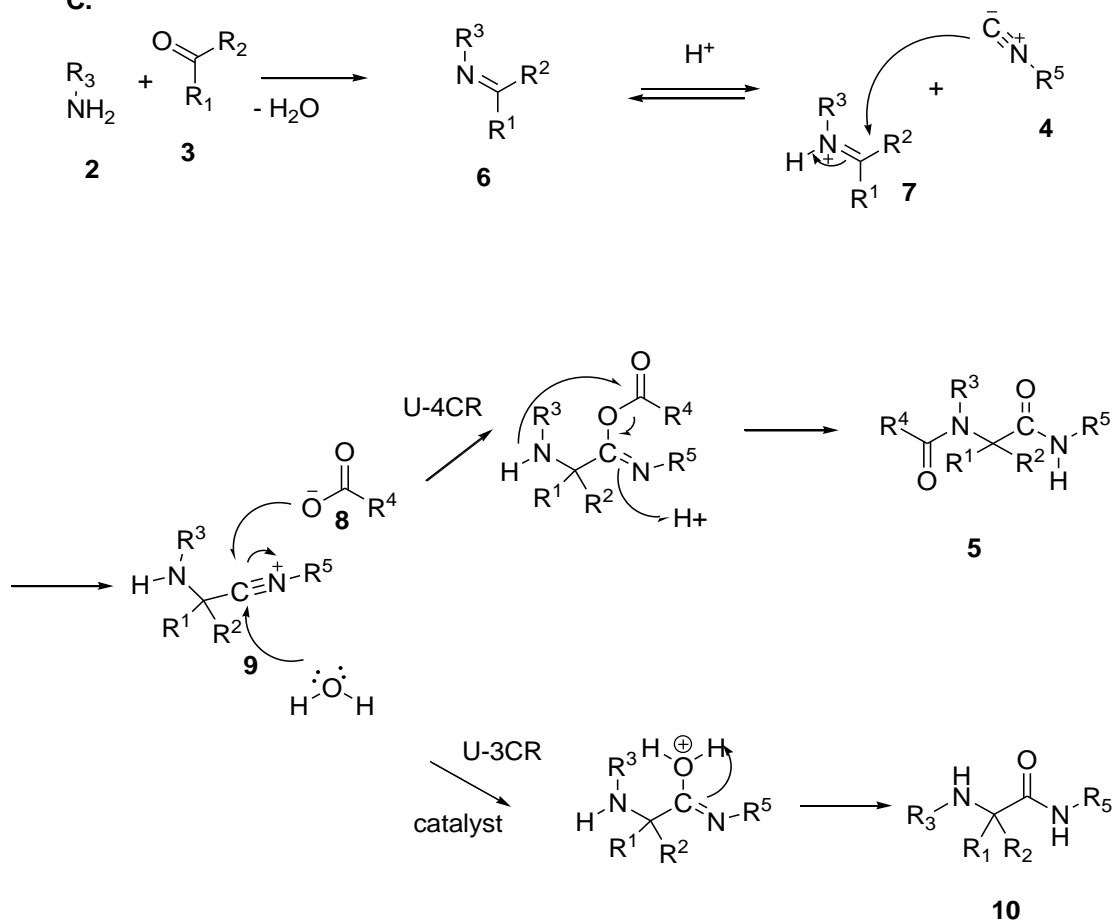


A. The Ugi 4-Component Reaction.



B. Ugi 3-Component Reaction.

C.



C. The reaction mechanism of the Ugi4-component reaction and Ugi 3-Component Reaction

Crixivan can be prepared using the Ugi reaction (33). Crixivan (Figure 1.1B) is a protease inhibitor that is used to treat acquired immunodeficiency syndrome/human immunodeficiency viruses (HIV/AIDS) as part of very effective antiretroviral therapy. It is a white powder that dissolves and is used orally along with other antiviral medications. The medication stops protease from doing its job. HIV viruses are therefore unable to proliferate, which lowers the viral load. Indinavir anhydrous, or indinavir with an extra amine inside the hydroxyethylene backbone, is the form of indinavir that is sold commercially. This improves its oral bioavailability and solubility, which facilitates user intake. It was created artificially with the intention of blocking the HIV virus's protease (34).

2. Ugi 3-Component Reaction (U-3CR)

A typical Ugi 3-Component Reaction (U-3CR) might involve the reaction of benzaldehyde (an aldehyde) 3, aniline (an amine) 2, and tert-butyl isocyanide 4 to form an α -amidoamide product 10. This product can then be further modified or used as a building block in more complex syntheses (35). The mechanism of the U-3CR involves several key steps that lead to the formation of α -amidoamides. Here's a simplified overview of the process: The reaction begins with the condensation of an amine 2 and an aldehyde or ketone 3 to form an imine 6, releasing a molecule of water in the process. The imine 6 then reacts with an isocyanide 4. The nucleophilic carbon of the isocyanide attacks the electrophilic carbon of the imine, forming a nitrilium ion intermediate. The nitrilium ion 9 undergoes a nucleophilic attack by the amine component, leading to the formation of the final α -amidoamide product 10 (Scheme 1.1C)(36).

Since it was first stated in 1960 when Ugi studied water as the nucleophile, U-3CR is a fairly ancient variety (28, 36). It functions similarly to the U-4CR mechanistically, but the primary distinction is that a water molecule attack the electrophilic carbon (U-3CR) when carboxylate is absent (U-4CR), which may be further activated in the presence of a catalyst. As a result, the final and permanent Mumm rearrangement is being removed. As a result, α -amidoamide 10 is synthesized (Scheme 1.1C).

The α -aminoacylamides frequently result in better pharmacokinetic/pharmacodynamic characteristics, such as water solubility and oral bioavailability. Numerous bioactive compounds, natural products, and medications contain them (36, 37). They can also be

found in therapeutic candidates including bradykinin B1 receptor antagonists, HDAC isoform selective inhibitors, NNRTIs⁴, and DPP4 inhibitors, which comprise non-aromatic heterocyclic aminoamides such piperazines and piperazinones (38). It is evident that medications containing aminoacylamides have a high degree of drug-likeness. Furthermore, quite a few of the anesthetics of the caine type are produced via the use of this reaction. Bupivacaine and lidocaine (xylocaine) are two examples of such substances (26, 39).

3. Van Leusen 3-Component Reaction (vL-3CR)

The cycloaddition of tosylmethyl isocyanides (TosMICs) **k** and imines **l** at mild reaction circumstances is one of the three components of the van Leusen imidazole synthesis (Scheme 1.3A). By altering the aldehyde, amine, and TosMIC components, a range of 1,4- and 4,5-disubstituted imidazoles in addition to 1,4,5-trisubstituted imidazoles can be easily produced, which are important in pharmaceuticals and materials science. Additionally, aryl-substituted TosMIC reagents and imines produced in situ can be converted into polysubstituted imidazoles **m** using an effective one-pot procedure that has been documented (40). The functional groups that the van Leusen reaction can tolerate, such as asymmetric amines, aldehydes, and amino acids, make it suitable for complex molecule synthesis. Furthermore, the utilization of adaptable component parts in the van Leusen reaction is made possible by the availability of effective pathways for the synthesis of substituted TosMIC reagents (41).

According to a Van Leusen paper, TosMIC **k**, which has an active methylene group, a leaving group, and an active isocyanide carbon, is what drives the reaction. Under basic conditions, the $-\text{CH}_2\text{N}\equiv\text{C}$ moiety can cycloadditionally add to a polarized $\text{C}=\text{N}$ bond in a stepwise manner. A 1,5-disubstituted imidazole **m** is produced when *p*-toluenesulfonic acid (pTsOH) is removed from the intermediate 4-tosyl-2-imidazoline **n** (Scheme 1.3B). By condensing the amine with an aldehyde, the aldimine **l** can likewise be produced on-site in about 30 minutes. The cycloaddition is unaffected by the water that is produced as a byproduct; therefore drying reagents like MgSO_4 are not required. Nevertheless, because the components react gradually, the vL-3CR is not a real multicomponent reaction, despite its name. Otherwise, oxazoles are produced when aldehydes react with TosMIC without the first imine production (42).

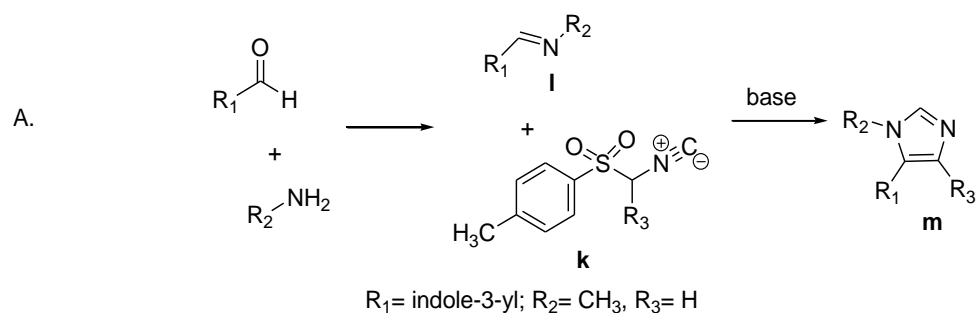
4. Passerini 3-Component Reaction (P-3CR)

An isocyanide 4, an aldehyde 11 (or ketone), and a carboxylic acid 1 are the primary components of the Passerini reaction, which is a chemical process that results in the formation of an α -acyloxy amide 12 (Scheme 1.3C) (43). One of the earliest isocyanide-based multicomponent reactions, this addition reaction was initially published in 1921 by Mario Passerini in Italy. It is thus considered to be one of the oldest reactions (44). Aprotic solvents are the most common medium for carrying out this process; nevertheless, it is also possible to carry it out in ionic liquids like water or in deep eutectic solvents (45). This is a reaction of the third order, with the first order occurring in each of the reactants. When it comes to combinatorial and pharmaceutical chemistry, the Passerini reaction is often used. In recent years, it has also found applications in green chemistry and polymer chemistry (46). As a result of the strong functional group tolerance, chemoselectivity, regioselectivity, and stereoselectivity that isocyanides possess, the Passerini reaction may be used in a broad variety of synthetic applications (31).

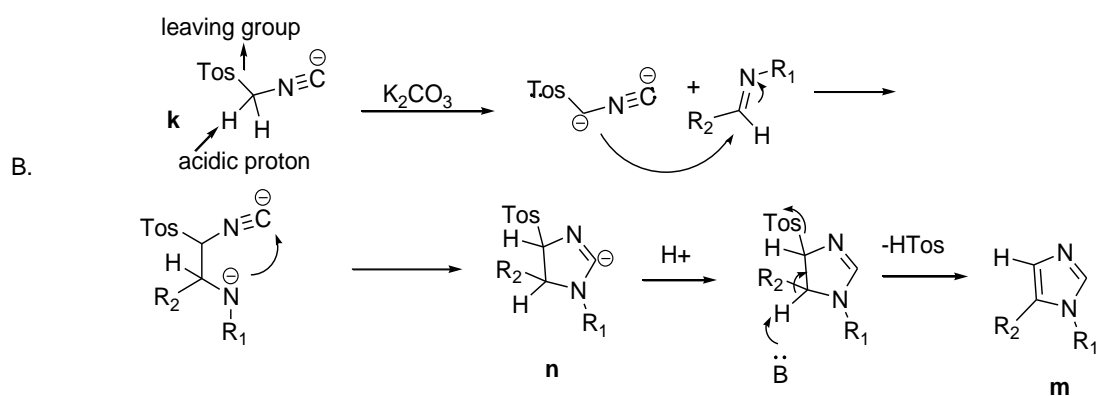
When the Passerini reagents are present in aprotic solvents at large molar concentrations, a concerted process will take place. This mechanism is seen in the S_N2 and Diels-Alder reactions (47). Within this mechanism (Scheme 1.3D), a nucleophilic addition occurs, followed by a reaction between the isocyanide 4, carboxylic acid 1, and carbonyl 13. After going through an imidate intermediate 14, the reaction goes through a Mumm rearrangement, which means an organic rearrangement reaction. It describes a 1,3(O-N) acyl transfer of an acyl imidate or isoimide group to an imide, which ultimately results in the Passerini product 15 (48). The Passerini reaction is considered an organocatalytic reaction due to Mumm rearrangement necessitating the presence of a second carboxylic acid molecule (48). In addition to the formation of α -acyloxy amide compounds, the Passerini reaction has numerous applications, including the formation of heterocycles, polymers, amino acids, and some pharmaceutical products.

Scheme 1.3

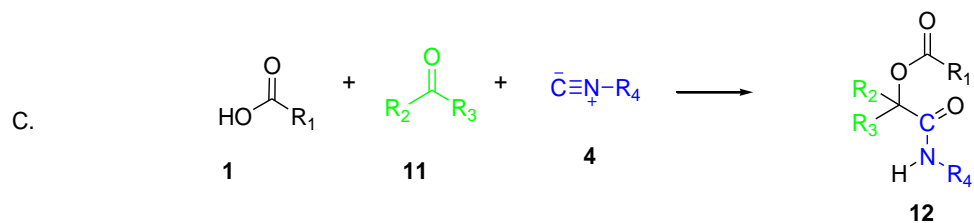
Van Leusen's reaction, the Passerini reaction, and their reaction mechanisms



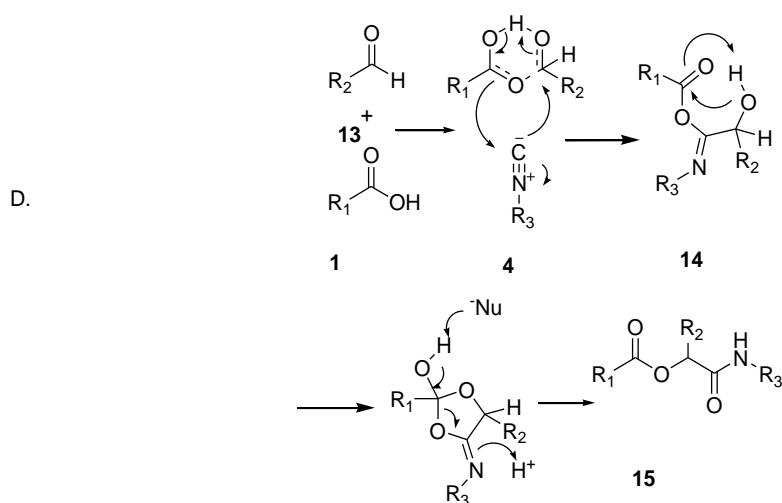
A. Van Leusen imidazole synthesis reaction.



B. Van Leusen imidazole synthesis mechanism.



C. The Passerini reaction.



D. Proposed Passerini reaction mechanism

A post-Passerini cyclization event is responsible for the formation of an isocoumarin structure, which is a heterocycle. Under physiological settings, the initial Passerini reaction results in the production of unstable acyclic depsipeptides. A number of heterocycles, including β -lactams, butenolides, and isocoumarins, have been obtained using post-Passerini cyclization processes. This has been done in order to enhance the stability of the product for use in medical applications. Some reagents, including halogens, azides, and others, are pre-functionalized with reactive groups in order to facilitate these cyclizations. These reagents are then used in conjunction with other processes, such as the Passerini-Knoevenagel and Passerini-Dieckmann reactions, in order to get heterocyclic compounds (49). This reaction has resulted in the production of a number of compounds, including three-, four-, and five-membered oxirane or/and aziridine derivatives, β -lactams, and tetrasubstituted 4,5-dihydropyrazoles, respectively (25). Polymerization, the production of monomers, and post-polymerization modification are all examples of situations in which this process has been used (50). In addition, sequence-defined polymers have been produced by the use of the Passerini reaction (51). It is possible to employ bifunctional substrates for post-polymerization modification or as precursors for polymerization, these applications are possible. Considering that this reaction has a high tolerance for functional groups, the polymers that are produced by utilizing Passerini reaction are quite varied and have characteristics that can be tuned (50). This process has resulted in the production of a four distinguish of different macromolecules, such as macrocyclic depsipeptides, macroamides, and three-armed star branched mesogen core molecules, and three-component dendrimers (31).

The Passerini reaction has been used for the purpose of generating many structures, including α -amino acids, α -hydroxy- β -amino acids, α -ketoamides, β -ketoamides, α -hydroxyketones, and α -aminoxyamides (25). Synthesis of α -Acyloxy carboxamides, which have shown promise as anti-cancer drugs, has been achieved by the Passerini reaction. Additionally, functionalized [C60]-fullerenes, which are used in pharmaceutical and plant chemistry, have also been produced (25). This reaction has also been used as a synthetic step in the process of complete synthesis of medications that are now accessible for commercial use. One example of this is the antiviral medication telaprevir (VX-950) 16 (Figure 1.1B), which is marketed by Vertex medications and Johnson & Johnson (25).

5. Gewald 3-component reaction (G-3CR)

In an environment consisting of elemental sulfur and base, the Gewald 3-component reaction (G-3CR) is a chemical reaction that involves the condensation of a ketone or an aldehyde **3** with an α -cyanoester **17**. This reaction results in the formation of a poly-substituted 2-amino-thiophene **18** (Scheme 1.4A) (52).

The G-3CR, identified three decades prior, entails ketone **3** and α -cyanoester **17**, yielding intermediate **19** via Knoevenagel condensation. The most acidic proton at the δ -C position is removed, leading to a nucleophilic attack by the resulting anion on elemental sulfur, which produces an intermediate. Ring closure occurred through the intramolecular nucleophilic attack of the sulfur atom on the triple bond of the cyano group, as illustrated in Scheme 1.4B (53).

One of the most important scaffolds in heterocyclic chemistry is thiophene and its derivatives. They exhibit a variety of characteristics and can be found in a wide range of intriguing compounds, including pharmacologically active chemicals and dyes. For instance, compounds of substituted 2-aminothiophene were identified as GluR6-antagonists in 2010. While 2-thienylureas have demonstrated strong potency and great selectivity for S6K over a panel of 43 kinases, substituted 2-amidothiophenes were investigated as JNK inhibitors (54).

6. Biginelli 3-component reaction (B-3CR)

An acid-catalyzed, three-component reaction involving an aldehyde **11**, a β -ketoester **22**, and urea **23** in ethanol (EtOH) provides a short and straightforward procedure for synthesizing dihydropyrimidones **24** (Scheme 1.4C), which are intriguing chemicals that have the potential to be used in the pharmaceutical industry (55).

It is hypothesized that the condensation reaction that takes place amid the aldehyde **11** and the urea **23** is the first step in the process. This condensation event has some parallels with that of the Mannich Condensation. The iminium intermediate **25** that is produced serves as an electrophile for a nucleophilic addition of the ketoester enol. The ketone carbonyl of the adduct that is produced as a consequence of this process undergoes condensation with the urea NH_2 to produce the cyclized product **26** (Scheme 1.3D) (56).

Dihydropyrimidinones 26, which are the results from the B-3CR, have been utilized extensively in pharmaceutical manufacturing for the purpose of calcium channel blockers, antihypertensive medicines, and alpha-1-a-antagonists (57).

In more recent times, the outcomes from the Biginelli reaction are being explored for their potential properties as selective antagonists of the Adenosine A2b receptor. In addition, tricyclic compounds that are very selective are included (58).

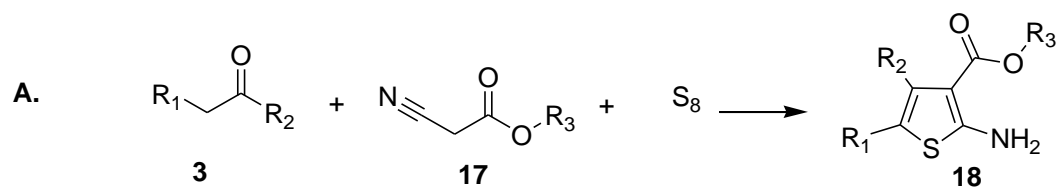
7. Groebke-Blackburn-Bienaymé three-component reaction (GBB-3CR)

The year 1998 witnessed the introduction of a novel iteration of the Ugi MCR by three distinct research teams (Blackburn (59), Bienaymé (60), and Groebke (61)). These groups are commonly denoted as the GBB reaction in scholarly discourse. The process typically entails the combination of heterocyclic amidines, aldehydes, and isocyanides, resulting in the formation of N-bridgehead heterobicyclic compounds using a one-pot methodology.

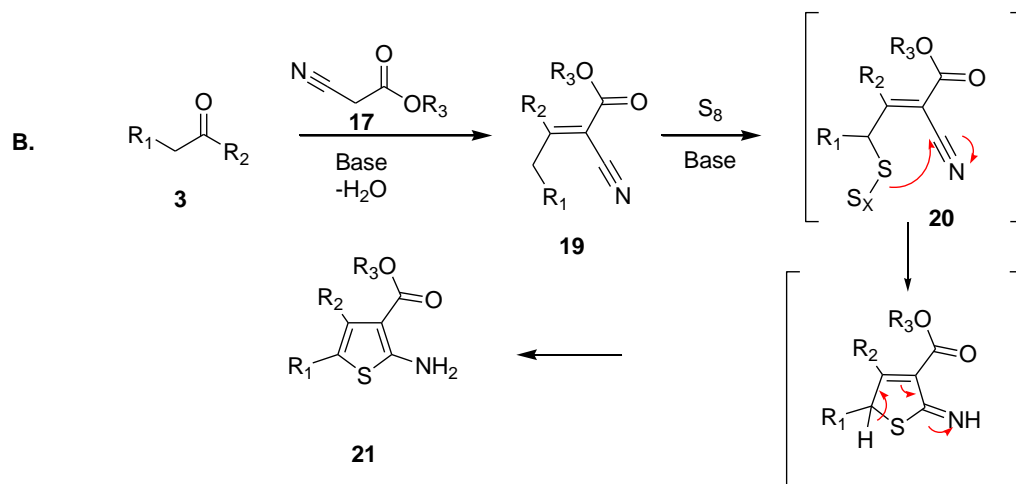
In Katrin Groebke work. In a typical technique, equivalent quantity of each of the three components (isonitriles 4, aldehydes 11, and one of 2-amino-pyridine 27a, 2-amino-pyrazine 27b, or 2-amino-pyrimidine 27c) are combined in methanol (MeOH) and then allowed to react at room temperature (RT) for a whole night. To yield 3-amino-imidazo[1,2-a]pyridines 28, 3-amino-imidazo[1,2-a]pyrazines 29, and 3-amino-imidazo[1,2-a]pyrimidines 30, respectively (Scheme 1.5A). The pace of the reaction is dependent on the pH; the addition of one to two equivalents of acetic acid (AcOH) allows for a significant acceleration of the condensation process. When the crude reaction mixtures were analyzed, it was discovered that the starting ingredients had completely vanished in each and every experiment (61).

Scheme 1.4

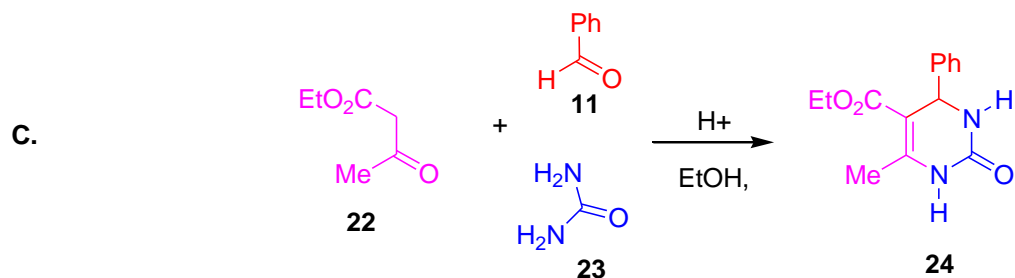
Gewald 3-component reaction, Biginelli 3-component reaction, and their reaction mechanisms



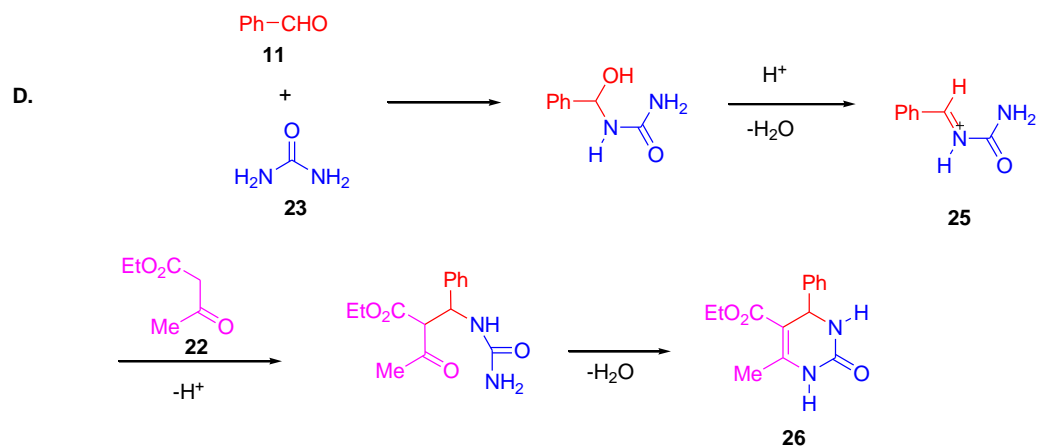
A. The G-3CR.



B. The G-3CR mechanism.



C. B-3CR.



D. The condensation reaction mechanism between aldehyde and urea yielded a cyclized product

In a highly effective novel three-component reaction, Bienayme discovered that heteroaromatic amidines 27c interacted with tert-butylisocyanides 4 plus aldehydes 11 with the help of a catalytic quantity of protic acids to produce 3-amino-imidazo[1,2-a]pyrimidines 30 (Scheme 1.5B). This reaction was carried out in the presence of three components and reported 31 examples by changing one of the starting materials (60).

In Christopher Blackburn research, 2-aminopyridine 27a, an aldehyde 11, and an isocyanide 4 are the three components that are involved in a condensation reaction that is catalyzed by scandium triflate ($\text{Sc}(\text{OTf})_3$). This reaction results in the formation of variations of 3-aminoimidazo[1,2-a]pyridine 28 (Scheme 1.5C). Aminopyrazine also interacts in a similar manner. A library of heterocycles that had been generated in excellent yields by serial synthesis and separation on column chromatography resin was then exposed to further reactions at the amino group (59).

GBB-3CR is used to synthesize various nitrogen-containing heterocycles, which are common scaffolds in many drugs. These heterocycles often exhibit a wide range of biological activities, including anticancer, antimicrobial, and antiviral properties. The reaction is valuable in the early stages of drug discovery for generating diverse libraries of compounds. These libraries can be screened for biological activity, helping identify potential lead compounds for further development. GBB-3CR allows for the rapid modification of lead compounds to improve their pharmacological properties. This includes enhancing potency, selectivity, and metabolic stability. The reaction is widely used in combinatorial chemistry to create large collections of structurally diverse molecules. This diversity is crucial for identifying new drug candidates with unique mechanisms of action. Recent advancements have focused on making GBB-3CR more environmentally friendly by using green catalysts and solvents. This aligns with the growing emphasis on sustainable practices in pharmaceutical research (62, 63).

GBB-3RC mechanism

The mechanism of the GBB-3CR involves several key steps: The reaction begins with the condensation of an aldehyde 11 and an amidine 27a to form an iminium ion 6. This step is typically catalyzed by a Lewis or Brønsted acid. The iminium ion then undergoes a non-concerted [4+1] cycloaddition with an isocyanide. This step forms a new ring system, leading to the creation of a fused imidazole. This concludes with an aromatization

including a 1,3-hydrogen shift to form imidazo[1,2-a]pyridine (Scheme 1.5D). The GBB-3CR can proceed via two separate routes, resulting in the formation of two regioisomers. Route A yields GBB-3CR with a common product of 28, whilst Route B produces the "inverse" GBB-3CR with a value of 39 (62).

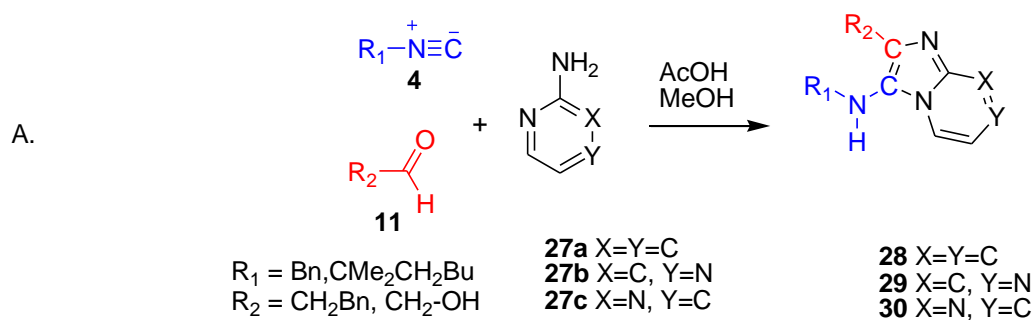
The formation of regioisomers depends on the nature of the substrates and the reaction conditions. For example, the reaction can yield different products depending on whether the endocyclic 38 or exocyclic nitrogen 6 of the amidine participates in the cyclization. The ratio of these regioisomers can be influenced by factors such as the type of catalyst used and the specific reaction conditions (64).

The formation of regioisomers in the GBB-3CR is influenced by the specific substrates and reaction conditions used. Here's a more detailed look at how regioisomers can form: (I) Substrate Influence: The choice of aldehyde can affect the electronic and steric environment, influencing which nitrogen atom of the amidine participates in the cyclization. The structure of the amidine, particularly whether it has an endocyclic or exocyclic nitrogen, plays a crucial role. (II) Reaction Conditions: Different catalysts can favor the formation of one regioisomer over another. For instance, using Sc(OTf)₃ might yield a different ratio of regioisomers compared to using a silver catalyst (62). The choice of solvent and reaction temperature can also impact the regioselectivity. Some solvents might stabilize certain intermediates more than others, leading to a preference for one regioisomer. (III) Mechanistic Pathways: The reaction typically involves the formation of an imine intermediate from the aldehyde and amidine. The isocyanide then attacks this intermediate, leading to cyclization. Depending on whether the endocyclic or exocyclic nitrogen of the amidine is involved in the cyclization, different regioisomers can form (63). For example, when using 2-aminopyridine as the amidine component, the reaction can yield either an imidazo[1,2-a]pyridine or an imidazo[1,5-a]pyridine.

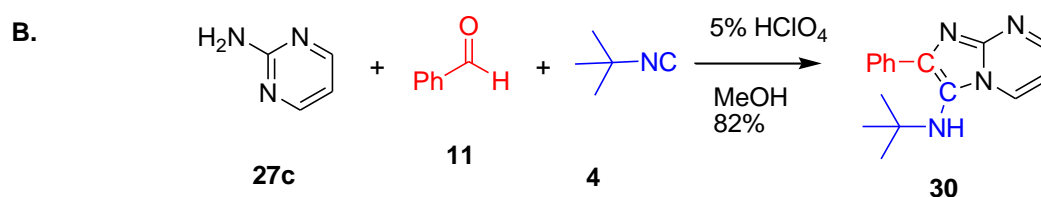
Bradley et al. found two regioisomers in cyclic amidine building blocks. These are the guanidine base Groebke-Blackburn-Bienaymé (GBB) product and the inverse GBB product. X-ray structural analysis revealed the principal product to be the GBB product, making it a valuable synthetic reaction. In most cases, there is no discernible presence of inverse GBB products (65).

Scheme 1.5

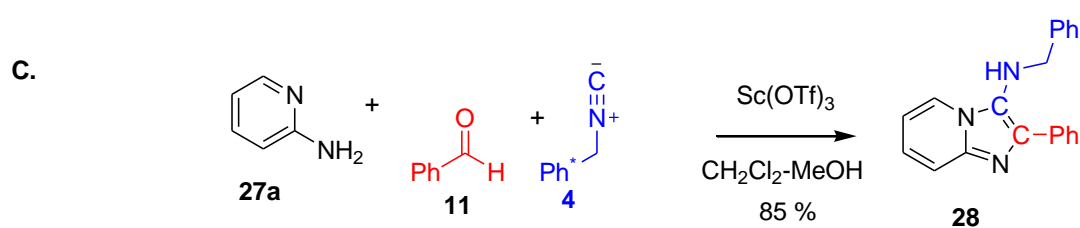
Gtoebke, Bienayme, and Blackburn participate in GBB-3CR and the GBB-3CR mechanism



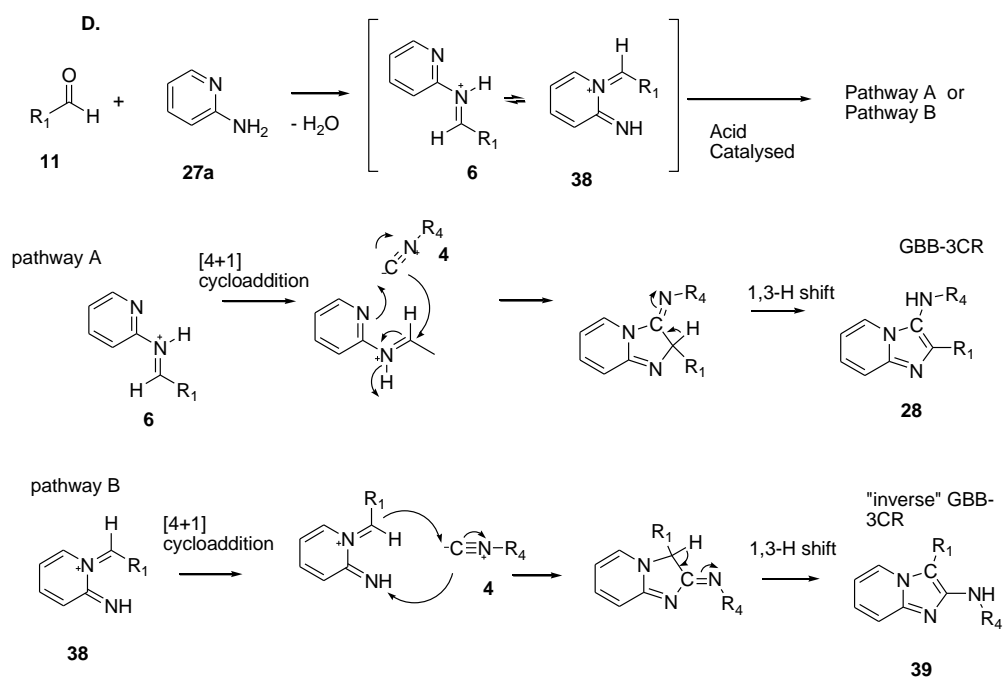
A. The reactions reported by Katrin Gtoebke as contributions to the GBB-3CR discovery.



B. 3-tert-butylamino-2-phenylimidazo[1,2-a]pyrimidine synthesis by Bienayme.



C. The reactions discovered by Christopher Blackburn as contributions to the GBB-3CR discovery.



D. The mechanism of GBB-3CR product formation.

Proceedings in the Development of the GBB-3CR

In the following section, some of the most pertinent studies will be examined, which will demonstrate significant advancements, notable applications, and a number of reaction situations that were used in order to properly appreciate the adaptable nature of the GBB-3CR.

Whittaker et al. demonstrated using the $\text{Sc}(\text{OTf})_3$ as a catalyst of the GBB reaction using a microwave-assisted GBB-3CR in ten minutes to produce high yields. They also used substituted benzaldehydes and primarily aminopyridines (Scheme 1.6A). It is interesting to note that a 5-membered aminothiazole substrate was additionally utilized, which resulted in lower yields. These lower yields were primarily related to the side products that were formed by adding an amount of methanol with the intermediate Schiff base. On the other hand, the creation of the side product 40 might be prevented by using trifluoroethanol as a solvent that is less nucleophilic (66).

Fundamentals of fluorescence: Some compounds with the [1,2-a]pyridine scaffold 42 fluoresced on their own under UV, making the enzymatic fluorescence detection test less reliable in a recent search for hepatitis C virus NS3/4A serine protease inhibitors (9). This led them to employ a GBB-3CR scaffold to search between several hundred microarrays of compounds for fluorophores. Fluorescent imidazo[1,2-a]-pyridine chemicals interact with the peripheral benzodiazepine receptor (translocator protein (TPSO)) and GABAA receptors. The compounds were evaluated with TPSO and as imaging (Scheme 1.6B) (67).

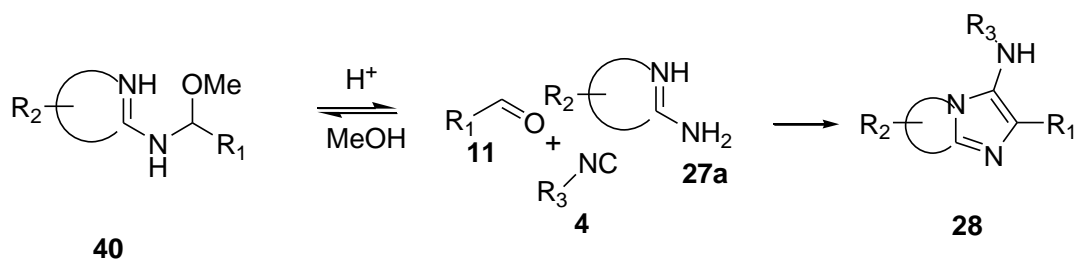
In process chemistry, steps have to be studied in detail to make sure they lead to the best goods. In this way, the study by Mathes et al. is very helpful because it looks into what is driving the GBB-3CR and suggests other ways to clean things up that don't involve labor-intensive chromatography (68). In addition to the standard reagents, a small amount of p-toluenesulfonic acid (pTsOH) or (PTSA) was used to speed up the Schiff base preformation. The next cycloaddition was then sped up by a complex of boron trifluoride and acetonitrile ($\text{BF}_3 \cdot \text{MeCN}$). To speed up the reaction even faster and obtain high yields in less than a day, two equivalents of trimethyl orthoformate (TMOF) were added as a dehydrating agent. The GBB-3CR products' high-purity sulfate salts were created by mixing 1,3 equivalents of sulfuric acid (H_2SO_4) with isopropyl alcohol (i-PrOH). As a

result, the GBB-3CR compounds separated as salts of sulfate. Either a large-scale reaction was performed at a scale of 100 mmol using the improved approach. Or the GBB product 43 was produced at a scale of 1 mmol in yields of 82% and 85%, respectively. It demonstrates that the reaction may be carried out at various sizes (Scheme 1.6C).

Scheme 1.6

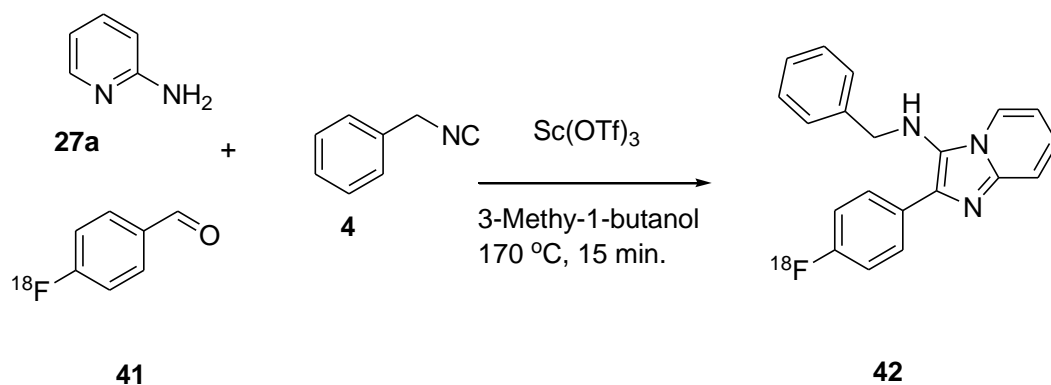
Some proceedings in the development of the GBB-3CR

A.



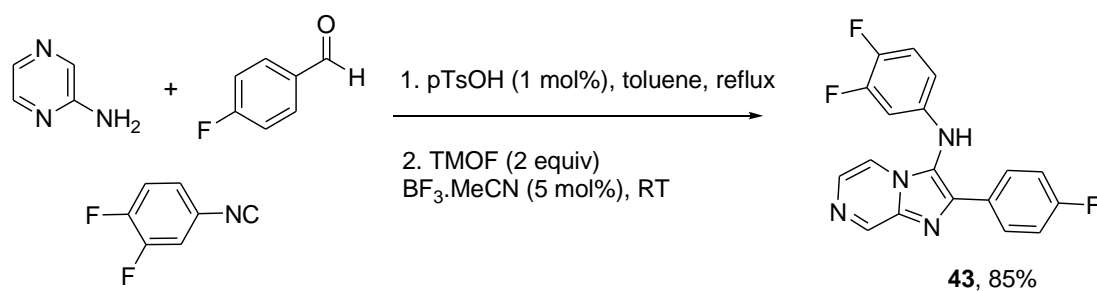
A. The use of electron-deficient cyclic amidines in the GBB-3CR process results in poor conversion rates and undesirable side reactions, such as the addition of MeOH to the Schiff base 6 or 38 intermediate.

B.



B. ¹⁸F has been added to GBB-3CR models.

C.



C. The best way to do a BF₃.MeCN-catalyzed GBB-3CR in one pot and two steps in Mathes et al.'s study

Scope and Limitations of the GBB-3CR

The reaction works best at RT with stoichiometric quantities of arylaldehydes, 2-aminopyridines, and aliphatic isocyanides in MeOH at 0.3–1.0 M and 10 mol% Sc(OTf)₃ as a catalyst. The response of some beginning materials was unpredictable. This couldn't always be blamed on electronic factors, as shown in Figure 1.2A, because steric effects also play a big role (32).

Aliphatic aldehydes and aromatic isocyanides yield well, but a recent study reported a yield drop when aldehydes and isocyanides are both electron-rich. Understanding the GBB-3CR involves examining its extent and limits, including substituent effects on starting materials and their use in future applications (68).

Cyclic 2-aminopyridines in GBB reactions

The amidines are crucial for the imidazo-[1,2-a] heterocyclic form because they act as the nucleophilic component, while the aldehyde and isocyanide components are more dependent and often used for scaffold decoration. The almost 90 amidines in GBB-3CR are five- or six-membered. Which can be categorized by ring size, kind, and additional substituents (60). The GBB-3CR was identified with 2-aminopyridine; Figure 1.2B shows the most common amidine. Commonly used in model reactions to test solvents and catalysts. High-reactivity substituted 2-aminopyridines produce high-quality goods. Functional group compatibility is a hallmark of MCRs. Heteroaromatic amidines are found in all halogens and pseudo halogens, including nitrile ($-\text{C}\equiv\text{N}$), nitro ($-\text{NO}_2$), methoxy ($-\text{O}-\text{CH}_3$), carboxylic acids, esters, amines, phenolic and aliphatic hydroxyls, amides, alkynes, and alkenes. This functional group compatibility is essential for early GBB-3CR product responsiveness and receptor pocket engagement (69).

Aldehydes used in GBB-3CR

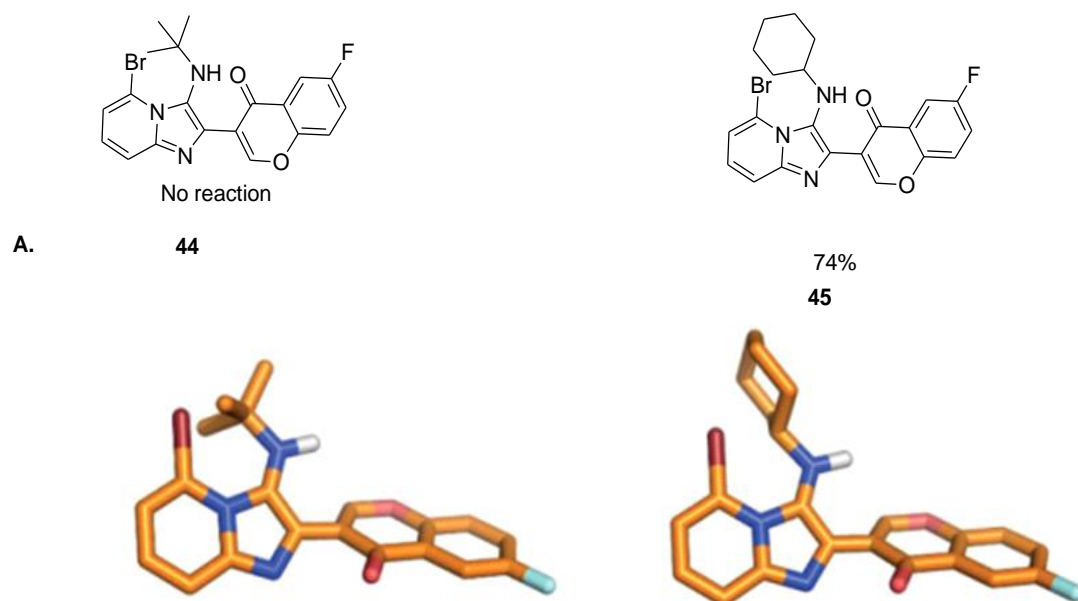
Aldehydes are widely used as the electrophilic component in the GBB-3CR process due to their affordability, commercial availability, and 180 aldehydes reported. Aldehydes range from aromatic to aliphatic, with substituents or not, electron withdrawing (EW) and donating (ED) groups, and reactive to labile protecting groups that can be used for secondary modifications (Figure 1.2C) (62). Aromatic aldehydes form stable Schiff bases, which are a set of chemicals with a double bond that connects carbon and nitrogen atoms with an effective conjugation mechanism. Schiff bases from aliphatic aldehydes

are unstable and can polymerize, resulting in lower yields in this step. Most aldehydes started material use benzaldehyde for process monitoring and good reactivity using thin layer chromatography (TLC) technique. The reactivity of benzaldehydes was affected by their own substitutes. Moreover, ED groups on substituted benzaldehydes typically yield more, while removing substituted decreases yields (43).

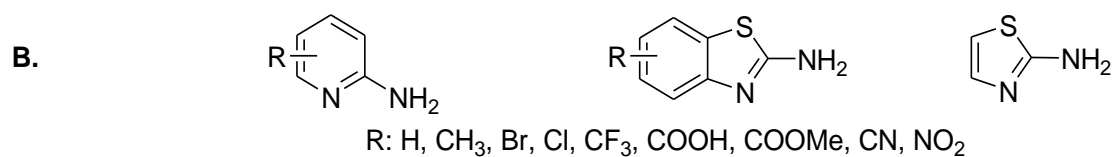
Isocyanides Used in the GBB-3CR

These are crucial for the formation of the imidazo[1,2-a]heterocycle core. Limited commercial availability and high prices of isocyanides stem from their stability, application, and unpleasant smell. Therefore, only a few dozen isocyanides are widely utilized in MCRs. Due to cost and availability, isocyanides are commonly made in-house. Isocyanide is commonly prepared from primary amines using the Hoffman- or Ugi route. Recently, the substrate scope has expanded by converting cheap and widely available oxo-compounds to isocyanides using the repurposed Leuckart-Wallach reaction (45). The GBB-3CR reported over hundred isocyanides, indicating that the variation point is widely used and may not be regarded a limitation in this three-component reaction (Figure 1.2D). Aromatic and aliphatic isocyanides are equally effective in GBB-3CR, however using bulky amidines and aldehydes together can impact yield. As expected, there is strong functional group compatibility. Aliphatic isocyanides, heterocycles, esters, alcohols, and ethers are commonly replaced. A wide range of substituted phenyl isocyanides are compatible with alkyls, halogens, ethers, esters, and thiols at all positions.

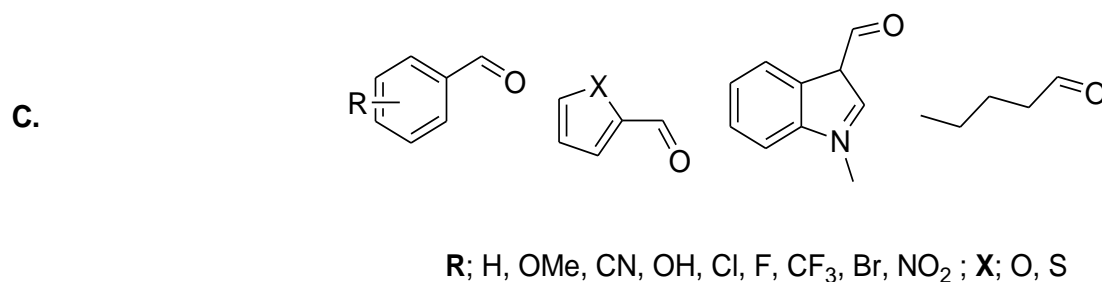
There are some limitations when using specific combinations of starting materials in the GBB-3CR: The electronic properties of the aldehyde and amidine can significantly influence the reaction outcome. For example, electron-rich aldehydes may react more slowly or give lower yields compared to electron-deficient ones. Bulky substituents on the aldehyde, amidine, or isocyanide can hinder the reaction, leading to lower yields or incomplete reactions (64). Not all combinations of aldehydes, amidines, and

Figure 1.2*Steric effects on GBB-3CR and started material of GBB-3CR*

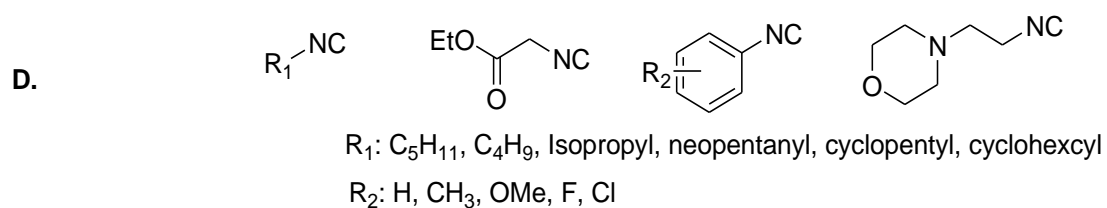
A. Steric GBB-3CR effects. The bulk impact of tert-butyl hinders the process. To increase yield, the optimal geometry for compound 44 was computed by replacing the tert-butyl for a cyclohexyl moiety, and Common



B. 2-aminopyridines.



C. aldehydes.



D. isocyanides used in GBB-3CR.

Isocyanides are equally effective. Some substrates may not form the desired imidazo[1,2-a]heterocycles efficiently due to unfavorable interactions or side reactions. In some cases, the reaction can produce regioisomeric mixtures, especially when using certain amidines or isocyanides. This can complicate product isolation and purification (70).

Variations of the catalyst and solvent in GBB-3CR

Since the publication of the GBB-3CR, numerous methods have been developed to enhance reaction yields, reaction time, and reaction conditions. The mild reaction conditions and the availability of the initial building elements provide exceptionally high levels of diversity and conciseness. The reaction can be conducted either neat (solvent-free) or with various solvents, including MeOH (71), toluene ($C_6H_5CH_3$) (72), acetonitrile (MeCN) (73), dimethyl sulfoxide (DMSO) ($(CH_3)_2SO$) (74), polyethylene glycol (PEG) ($H-(O-CH_2-CH_2)_n-OH$) (75), ionic liquids like 1-Butyl-3-methylimidazolium hexafluorophosphate (BMIM-PF6) (12), and water (76).

Combining methanol (71) and dichloromethane (DCM) as solvents in the GBB-3CR can offer a balance of their individual properties, but also comes with specific considerations: The combination can improve the solubility of a wider range of reactants, leveraging methanol's polar protic nature and DCM's non-polar characteristics. The mixed solvent system can sometimes enhance reaction rates by optimizing the environment for both polar and non-polar intermediates. DCM's volatility aids in easy removal by evaporation, simplifying product isolation and purification. Both solvents are toxic, with DCM being particularly hazardous. This necessitates stringent safety measures and proper ventilation. DCM is a volatile organic compound (VOC) with significant environmental concerns, including ozone depletion. The significant difference in boiling points (methanol: $64.7^\circ C$, DCM: $39.6^\circ C$) can complicate the control of reaction temperatures and solvent removal processes. Methanol can participate in side reactions, especially with reactive intermediates, potentially leading to by-products (77).

In addition, various catalysts have been reported to accelerate the reaction. Among these Bronsted acids were AcOH (61), perchloric acid ($HClO_4$) (60), p-Toluenesulfonic acid (pTsOH or PTSA) is a valuable catalyst in the GBB-3CR, offering a balance of efficiency and versatility, but it requires careful consideration of reaction conditions and substrate compatibility (78), tosylic acid (TsOH) (78), silicasulfuric acid (SSA) ($SiO_2-OSO_3H_2$)

(79), ammonium chloride (NH_4Cl) (73,80), clay (montmorillonite K-10) (81), and pTsOH/N-hydroxysuccinimide (82). In addition, several Lewis acids, including ($\text{Sc}(\text{OTf})_3$) (59,71,83), Zinc chloride (ZnCl_2) (84), trimethylsilyl chloride (TMSCl) (85), and zirconium tetrachloride (ZrCl_4) (86).

1.5 Biological applications

1.5.1 Imidazo[1,2-a]pyridine scaffold in drugs

The imidazo[1,2-a]pyridine a (Figure 1.1A) is a key building block for nitrogen-based heterocycles made through the GBB reaction (87). It has interesting biological properties. This moiety is present in important medications marketed as anxiolytic (Alpidem 32), sedative (Saripidem 33 and Necopidem 34), hypnotic (Zolpidem 35), anti-ulcer (Zolimidine 36), and cardiotoxic (Olprinone 37) (Figure 1.3 in Appendix C) (10).

1.5.2 Antibacterial activity

Globally, bacterial infectious diseases account for a significant number of illnesses and deaths. The rise of multidrug-resistant (MDR) infections caused by pathogenic bacteria presents a worldwide threat to people and other animals. The issue is exacerbated by the availability of over-the-counter antibiotics, the resulting release of antibiotic residues into the environment, inappropriate antibiotic usage, insufficient hygiene, increased international travel, and heightened antibiotic consumption. The World Health Organization (WHO) estimates that antimicrobial resistance (AMR) from bacteria resulted in around 1.27 million global fatalities in 2019 and contributed to an additional 4.95 million deaths (88)

Due to the frequency of infections these Gram-positive bacteria cause in hospitals and their resistance to several antibiotics, MDR bacteria like *Enterococcus faecalis* (*E. faecalis*), *Staphylococcus aureus* (*S. aureus*), and *Staphylococcus epidermidis* (*S. epidermidis*) are causing widespread concern. Many new antibacterial drugs, including quinupristin, daptomycin, tigecycline, ceftobiprole, and Linezolid, have been developed over the past thirty years to treat gram-positive bacterial infections. Nevertheless, the discovery of naturally resistant strains and the severe side effects of some of these medications have spurred the hunt for more potent novel treatments (89).

The biological chemistry of MCRs is extremely rich and offers fantastic prospects for drug seekers and researchers interested in tiny molecules with biological action. There is just one imidazopyridine-based medication on the market as an antibiotic, rifaximin, despite substantial research into bacterial infections (83). Imidazo[1,2-a]pyridine is a crucial scaffold with extensive pharmacological activities against bacterial infections. Its antibacterial properties may lead to the development of antiresistance antibiotics. It targets multiple enzymes involved in cell wall, protein, folic acid, deoxyribonucleic acid (DNA), or ribonucleic acid (RNA) synthesis, and its numerous substituents have significant antibacterial activity.

Al-Tel et al. in 2011 projected indole-based imidazopyridines as antibacterial potential drugs, which were produced using the GBB-3CR and Ugi reactions with a [4+1] cycloaddition procedure involving an 2-aminopyridine, an aldehyde, and an isocyanide with some modifications. In comparison to control antibiotics, these derivatives like 46 and 47 inhibited *S. aureus*, *E. faecalis*, *Bacillus megaterium*, *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Enterococcus aerogenes* with a range of 0.11–23.45 g/mL (Figure 1.4A). They concluded that the type of substituents on the aryl groups illustrated the scope of activity of these compounds. Compared to other substituents, preliminary Structure-Activity Relationship (SAR) analyses demonstrated that bromo-fluoro substituents significantly enhanced antibacterial activity (90).

The new N-benzyl-4-(2-(6-methyl-2-(p-tolyl) imidazo[1,2-a]pyridin-3-yl) acetamido) methyl) benzamide 48 shown in Figure 1.4B was synthesized using the standard procedure described by Budumuru et al. This compound was synthesized and validated by mass, FT-IR, and NMR spectra. The antibacterial efficacy of the produced compound was tested. The greatest concentration evaluated for the synthesized compound exhibited good antibacterial potential when compared to the conventional antibiotic. Common bacterial diseases may benefit in the future from more research into this chemical and its potential usage as a pharmacologically active antibacterial agent (91).

In 2011, Baviskar et al. discovered bicyclic N-fused aminoimidazoles as potential cancer treatments. They created compounds using the GBB-3CR, including previously described topo II inhibitors and medicines with an imidazo[1,2-a] scaffold. Some compounds showed greater efficacy in inhibiting kidney cell cancer than 5-fluorouracil and etoposide.

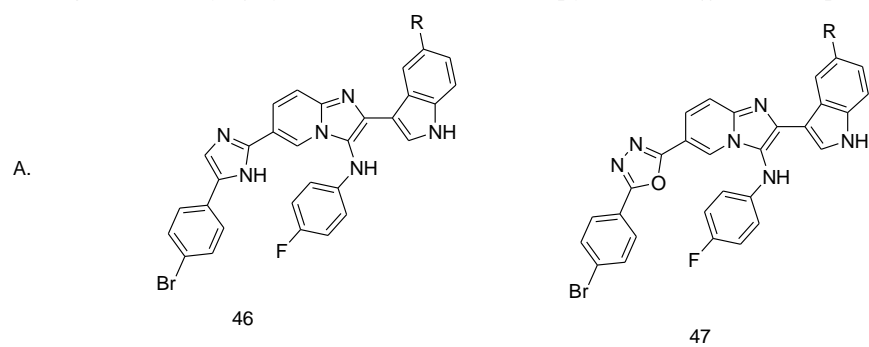
Compound 49 (Figure 1.4C), formed by C2-biaryl and C6-aryl substitutions, exhibited an inhibitory impact on the catalytic cycle of hTopoII α (92, 93).

Chatterjee et al. conducted a screening campaign employing the general population's malaria data to identify new chemical classes capable of inhibiting *Plasmodium falciparum* (*P.falciparum*). Compounds were selected based on characteristics such as high potency, favorable safety index, and ease of production. The imidazolopiperazine molecule was deemed a promising candidate, according to the previously outlined parameters (94). The imidazolopiperazines 50 have been produced by conducting a GBB-3CR under MeOH at RT, initiated by HClO₄, and then reducing them with platinum oxide in a hydrogen-containing environment. The compound 50 shown high potency with half-maximal inhibitory concentration (IC₅₀) values of 3.5 nM against *P.falciparum* (Figure 1.4D) (94).

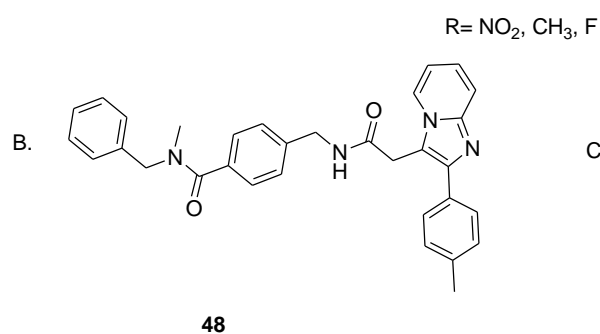
In conclusion, because many diseases presently lack effective treatments, the design and synthesis of physiologically active molecules is an important field in chemistry. Worldwide, antimicrobial resistance and cancer therapy continue to be major public health issues. Novel antibacterial and anticancer drugs with improved activity characteristics are therefore in high demand. These days, IMCRs are thought to be a powerful new synthetic technique that has revolutionized the synthesis of drug-like heterocycles with nitrogen in medicinal chemistry by making the process simple and effective. IMCRs facilitate the synthesis of complex natural products and their analogs. These reactions can mimic the structural complexity of natural molecules, which are often challenging to synthesize using traditional methods. IMCRs are employed in the synthesis of peptides and peptidomimetics, which are crucial in developing new drugs that can modulate protein-protein interaction.

Figure 1.3

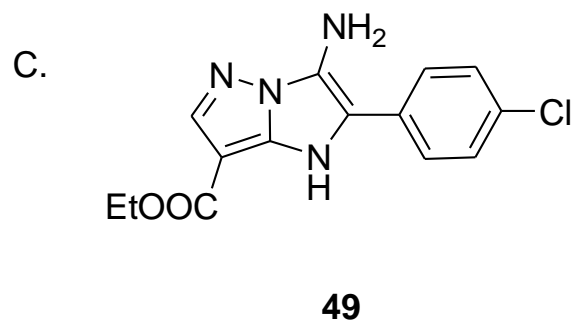
Some of the biological activity of synthetic Imidazo[1,2-a]pyridine scaffold examples



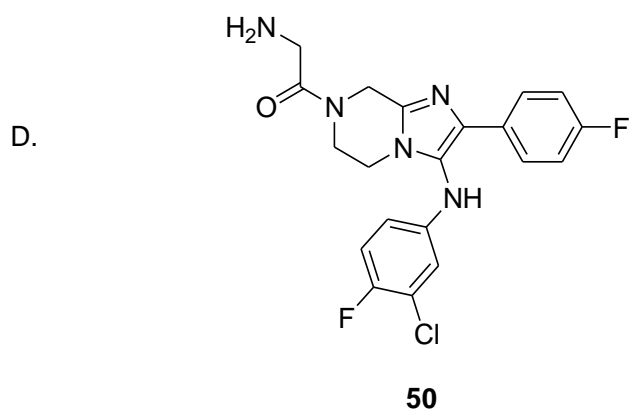
A. synthesizing *new* imidazopyridine derivatives that are effective against various strains of bacteria.



B. Imidazo[1,2-a] derivative as an antimicrobial active molecule.



C. Synthesis, screening, and optimizing of hTopoII α inhibitors.



D. Representative Synthetic Route of Imidazolopiperazines 50.

1.6 Secondary transformations of GBB-3CR products

Secondary transformations of GBB-3CR products can significantly expand the diversity and complexity of the resulting compounds. Here are some common secondary transformations: (I) Intramolecular Cyclization: GBB-3CR products can undergo further cyclization to form additional ring systems, enhancing structural complexity and potentially leading to new biological activities (64). (II) Functional Group Introduction: The imidazo[1,2-a]heterocycle core can be modified through nucleophilic substitution reactions, allowing the introduction of various functional groups at specific positions. (III) Sequential MCRs: GBB-3CR products can serve as intermediates in subsequent multicomponent reactions, enabling the construction of more complex molecular architectures in a single synthetic sequence. (IV) C-C and C-N Bond Formation: Palladium-catalyzed cross-coupling reactions, such as Suzuki or Buchwald-Hartwig couplings, can be used to introduce aryl or alkyl groups, further diversifying the chemical space (62). (V) Functional Group Modifications: Oxidation or reduction reactions can be employed to modify functional groups within the GBB-3CR products, altering their chemical and biological properties (62).

The versatility of GBB-3CR compounds in post-modification processes is indeed remarkable. Here's a deeper dive into the applications on imidazo[1,2-a]pyridine core: Convertible isocyanides are designed to undergo further transformations after the initial GBB-3CR, allowing for the introduction of additional functional groups or structural motifs. This flexibility is particularly useful in creating complex heterocyclic scaffolds that mimic natural products or serve as potential drug candidates. Modifying the main amine site of GBB-3CR products can lead to a wide variety of derivatives, enhancing their chemical diversity and potential biological activities (64). Common derivatization techniques for amine site include acylation, alkylation, and sulfonylation, which can introduce different functional groups and improve pharmacokinetic properties (95). Incorporating a tethered internal leaving group in GBB-3CR products facilitates post-nucleophilic substitution reactions, enabling the formation of more complex molecular structures. This approach can significantly increase molecular complexity and diversity, making it valuable for the synthesis of combinatorial libraries and the discovery of new medicinal compounds. By mimicking the structural complexity of natural products, GBB-3CR derivatives can exhibit similar biological activities, making them attractive for drug

discovery. The ability to easily modify GBB-3CR products allows for the rapid generation of analogs, aiding in the optimization of lead compounds for therapeutic use. The diverse scaffolds accessible through GBB-3CR and subsequent modifications are ideal for creating large libraries of compounds for high-throughput screening. These advancements highlight the power of GBB-3CR in modern synthetic chemistry, providing a robust platform for the development of new and diverse chemical entities (1).

A two-step solution-phase de-tert-butylation of a variety of GBB-3CR products was reported for the first time by Krasavin et al. This was accomplished by using tert-butyl isocyanide as a conversion reagent. After researching, Krasavin et al. found that the removal of the tert-butyl group from GBB-3CR products 51 was not successful utilizing several acids. These acids included hydrochloric acid (HCl) in MeOH, concentrated H₂SO₄, and glacial AcOH. On the other hand, the tert-butyl group can be converted into the trifluoroacetamides 52 easily using neat refluxing in trifluoroacetic acid (TFA) (Scheme 1.7A). This process was carried out in a straightforward and efficient manner. Afterwards, the primary amines 53 that corresponded to the reaction were obtained using alkaline hydrolysis (96).

To add a functional group at the amine group, Lambert also uses the de-tert-butylation approach. Both acylation and sulfonylation of compound 55 were simple processes that resulted in the production of the matching sulfonamide 56 and amide 57 in satisfactory quantities (Scheme 1.7B) (97).

The molecule 6-chloro-2-phenylimidazo[1,2-b]pyridazine 58 is a GBB-3CR compound including a chloro group that serves effectively as a leaving group at position 6. The presence of a chlorine atom promotes the substitution of imidazo[1,2-b]pyridazines. In Scheme 1.7C, the chlorine atom was replaced by a secondary amine, a primary alcohol, or pyrimidine-2-thiol utilizing the appropriate base. The reaction produces the GBB-3CR product, as well as amines 59, alkoxides 60, and thiolates 61, leading to modest yields, each independently (97).

Guasconi et al. (98) described a dual stage process for synthesizing diaminoimidazo[1,2-a]pyrazines. 2-amino-3-chloropyrazine reacts with various aldehydes as well as isocyanides with the aid of TMSCl as a catalyst, resulting in the generation of 3-amino-8-chloroimidazo[1,2-a]pyrazines 62 with a high yield. The chlorine atom at position 8 is

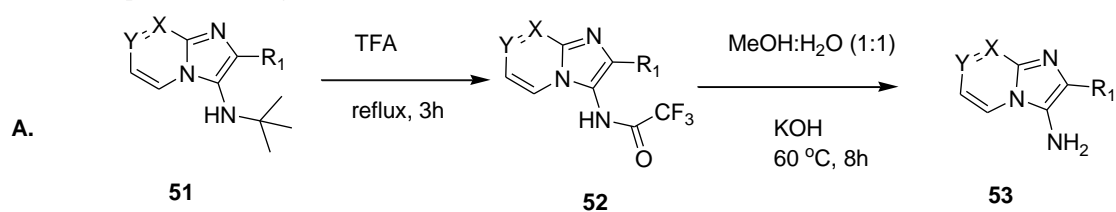
used in aromatic nucleophilic substitution. Heating compound 62 in company of ammonia, primary or secondary amines in dioxane under conventional conditions results in the production of 3,8-diaminoimidazo[1,2-a]pyrazines 63 with good yields (Scheme 1.8 in Appendix C).

Utilizing the aldehyde pyridoxal 64 yields furo[2,3-c]pyridines 67 instead of the imidazo[1,2-a]pyridines product. The outcomes of spectroscopic characterization confirmed this reality. The procedure entails the formation of an iminium species 65, followed by cycloaddition with the isocyanide, culminating in the synthesis of the nitrilium ion 66. The nitrilium ion interacted with the phenolic hydroxyl group of pyridoxal, leading to the synthesis of furo[2,3-c]pyridines 65, as seen in Scheme 1.9 in Appendix C (99).

An innovative synthesizing of fluorous 3-aminoimidazo[1,2-a]pyrazines 69 was described by Lu et al. (100). The use of GBB-3CR, followed by Suzuki coupling post-condensations, is the means by which these two stages may be accomplished. Under microwave (MW) irradiation, the reaction between the started materials of GBB-3CR, including fluorous benzaldehyde 68, was carried out. In order to get the required products like 3-aminoimidazo[1,2-a]pyrazines 71 with reasonable yields, the corresponding GBB products were subjected to the Suzuki coupling process, which included the use of 4-methoxybenzeneboronic acid 70, Pd(1,1-bis(diphenylphosphino)ferrocene)Cl₂ (Pd(dppf)Cl₂), and potassium carbonate (K₂CO₃) under the conditions of MW irradiation (Scheme 1.10 in Appendix C).

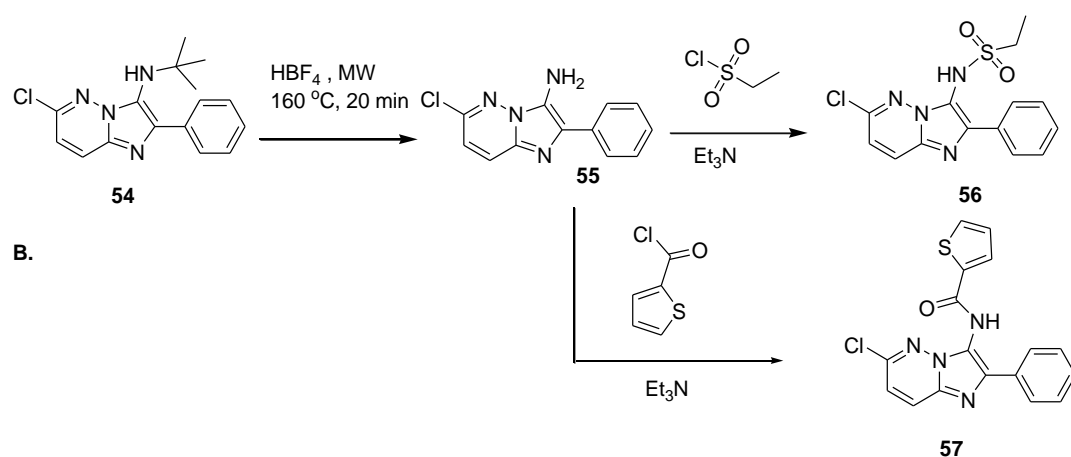
Two-step synthesis of pyrido[2,1:2,3]imidazo[4,5-b]quinoline 76 was described by Arnould et al. (101). This synthesis included the use of propargyl aldehydes 73, which were pioneers in GBB-3CR. Here, firstly, imidazo[1,2-a]pyridines 75 were produced by

Scheme 1.7
GBB-3CR product modifications

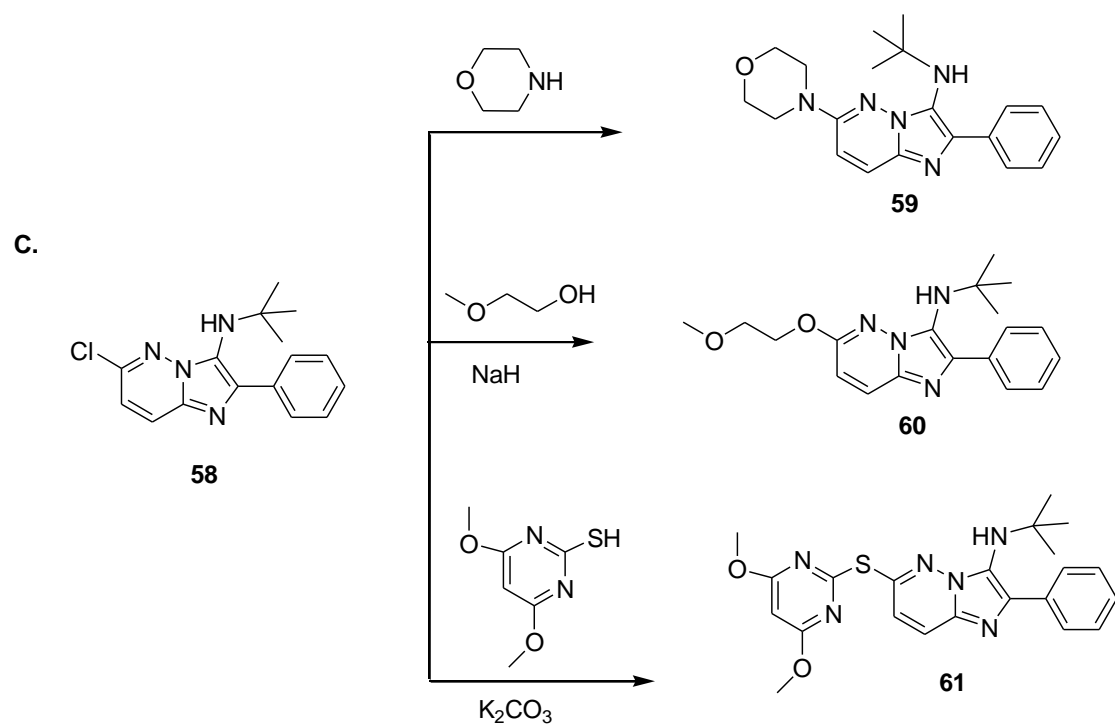


$R_1 = \text{iso-propyl, C}_6\text{H}_5, 4\text{-F-C}_6\text{H}_4$; $X = \text{CH, N}$; $Y = \text{CH, N}$

A. Two-step de-tert-butylation of a number of different GBB-3CR adducts is accomplished using TFA.



B. Modification of GBB-3CR products.



C. Minor aromatic nucleophilic substitution of chlorophenylimidazo[1,2-b]pyridazine

the reaction of 2-amino-5-chloropyridine 74, propargyl aldehydes 73, and different isocyanobenzenes 72; the solvent was MeOH, and also HClO₄ was the catalyst (Scheme 1.11 in Appendix C). The electrophilic cyclization was then enhanced in dioxane using MW irradiation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the catalyst.

The cyclization approach was indifferent to steric hindrance no matter the nature or location of the substituents, and thus, the required products 76 were produced in excellent yields. This is an important point to keep in mind. For post-cyclization to complete, the triple bond component of the propargyl aldehydes 73 was exploited, as shown in the process that was presented (Scheme 1.12 in Appendix C) (101).

GBB-3CR end products may be changed to have handy functionality that is appropriate for many kinds of MCRs directly. Within this particular framework, Semreen and colleagues documented the synthesis of polysubstituted imidazopyridines using GBB-3CR and Ugi reactions (95). This combination facilitated the synthesis of intricate and varied drug-like molecules using a single, cost-effective, and sequential process. This might be accomplished by designing one of the first building pieces to contain appropriate functionality that can be selected and used for additional purposes.

Semreen et al. (95) chose the aldehyde and the amidine components because they have an exposed carboxylic group that is ideal for the Ugi reaction that follows; GBB-3CR adducts with a pendant carboxylic group were successfully synthesized with high yields. This was achieved by using 2-amino-pyridine 77, appropriate isocyanides 78, and 3-or 4-carboxybenzaldehyde 79. The synthesis process included the use of a mixture of MeOH and dichloromethane (DCM) (CH₂Cl₂) solvents, along with the use of Sc(OTf)₃ as a catalyst. The reaction mixture is used without isolating the intermediate, and the attached carboxylic group on 80 serves as a connection for a future Ugi MCR, as seen in Scheme 1.13 in Appendix C.

1.7 Study Objectives

To synthesize a series of imidazo[1,2-*a*]pyridine derivatives needed to evaluate their biological activity by:

- Generating of 3-aminoimidazo[1,2-*a*]pyridine derivatives in a one-pot reaction employing the Groebke-Blackburn-Bienayme-three component reaction (GBB-3CR).
- Characterization of 3-aminoimidazo[1,2-*a*]pyridine derivatives using different chemical techniques, such as HPLC, ¹³C NMR, ¹H NMR, and IR spectroscopy.
- Testing the antimicrobial activity of the synthesized compounds against *Escherichia coli* (*E. coli*) (ATCC 25922), *Klebsiellapneumonia* (*K. pneumonia*) (ATCC 13883), *Pseudomonas aeruginosa* (*P. aeruginosa*) (ATCC 9027), *Staphylococcus aureus* (*S. aureus*) (ATCC 6538P), and *Staphylococcusepidermidis* (*S. epidermidis*) (ATCC 12228).

Chapter Two

Experimental Part

2.1 Chemistry

2.1.1 Material and instruments

Dichloromethane (DCM), ethyl acetate (EtOAc), Potassium bicarbonate (KHCO_3), Methanol (MeOH), Silica gel (100–200 and 200–300 mesh) for flash column chromatography (FCC) and GF254 silica gel for thin-layer chromatography, 2-Amino-5-fluoropyridine (CAS:21717-96-4), 3-morpholinopropionitrile (CAS:4542-47-6), Syringaldehyde 98% (CAS:134-96-3), p-Toluenesulfonic acid (p-TsOH) >98%, 4-dimethylaminobenzaldehyde 98%, Indole-3-carboxaldehyde 97% (CAS:487-89-8), 4-(trifluoromethyl)benzaldehyde 98% (CAS:455-19-6), 4-(methylthio)benzaldehyde 95% (CAS:3446-89-7), and 1-Methyl-2-imidazolecarboxaldehyde 98% (CAS:13750-81-7) were purchased from Sigma Aldrich. 2,3,4-Trimethoxybenzaldehyde 98% (CAS:2103-57-3) was purchased from Alfa Aesar. HPLC-grade methanol was acquired from Sigma-Aldrich and utilized for synthesis processes conducted under inert gas (N_2) conditions. The identification process involved the analysis of infrared spectroscopy (IR) and nuclear magnetic resonance (^1H NMR, ^{13}C NMR). The Chemistry Department of An-Najah National University utilized a Thermo Scientific Nicolet 1s5-Id3 Fourier transform infrared spectrophotometer to capture FT-IR spectra. The Chemistry Department at the University of St Andrews-UK utilized Bruker 500 MHz-Avance III NMR spectrometer equipment to record NMR spectra at frequencies of 300 MHz for ^1H and 75 MHz for ^{13}C . The chemical shift measurements were expressed as δ in parts per million (ppm) relative to deuterated chloroform (CDCl_3), which served as the internal standard. The coupling constants (J) were expressed in units of Hertz (Hz). The advancement of the reaction was seen by employing aluminum-supported Thin Layer Chromatography silica gel sheets (DC-Fertigfolien ALUGRAM® SIL G/UV254), and the spots were made visible using UV fluorescence. In addition, flash column chromatography employed silica gel obtained from Sigma-Aldrich. The silica gel had a pore size of 60 Å, a mesh size of 230-400, and a particle size of 40-63 μm . The column was packed with the silica gel, and compressed air at 5 psi was used. The solvents were evaporated using a Buchner rotary evaporator at the chemical laboratory at An-Najah University.

The purity of the samples was assessed using melting point (MP) and HPLC tests, which were conducted at the chemical laboratory of An-Najah University. The MP points were determined using the Electrothermal Digital Mel-Temp 3.0 Melting Point device. The analysis of the produced compounds was performed using an HPLC Waters Alliance e2695 instrument equipped with a photodiode array detector from Waters Corporation, located in Massachusetts, USA. Table 2.1 displays the composition of the mobile phase and the gradient elution technique employed for the identification of chemicals. In this context, (A) refers to deionized water and (B) represents acetonitrile. The experiment utilized an RP C18 column (Restek Roc, 150 x 4.6 mm, 3 μ m) at a flow rate of 0.8 ml/minute. The wavelength range of the PDA was adjusted to span from 210 to 400 nm, and the column temperature was set at 25°C. The volume of the injection was adjusted to 20 μ l. Every sample was passed through a 0.45 μ l single-use filter.

Table 2.1

The composition of the mobile phase

Time (minutes)	A%	B%
0	70	30
25	0	100
27	0	100
29	70	30
30	70	30

2.1.2 Synthetic procedures

General procedure for the GBB-3CR.

A mixture containing the amino compound (1eq) and the carbonyl compound (1eq) and 20% mmol of p-toluenesulfonic acid was added to a round bottom flask containing 10 ml of MeOH:DCM (2:3), stirred under nitrogen atmosphere for an hour at 50°C. Then, the isocyanide compound (1eq) was added to the mixture and agitated for 72 hours at 50°C. The product was washed with distilled water and 0.3 g KHCO₃, extracted by ethyl acetate (EtOAc), dried over anhydrous magnesium sulfate (MgSO₄), and condensed under reduced pressure. The product was purified by silica gel chromatography (DCM-EtOAc) to afford the desired compound.

Synthesis of compound 2-(3,5-Dimethoxy-4-hydroxyphenyl)-N-(2-morpholinoethyl)-6-fluoroimidazo [1,2-a]pyridin-3-amine (85).

A mixture containing 2-Amino-5-fluoropyridine 82 (300 mg, 2.68 mmol) and Syringaldehyde 83a (478 mg, 2.68 mmol) and 20% mmol of p-toluenesulfonic acid (113 mg) was added to a round bottom flask containing 10 ml of MeOH:DCM (2:3), stirred under nitrogen atmosphere for an hour at 50 °C. Then, 3-morpholinopropionitrile 84 (density = 1.017 g/ml) (368 µl, 2.68 mmol) was added to the mixture and agitated for 72 hours at 50 °C. The product was washed with distilled water and 0.3 g KHCO₃, extracted with ethyl acetate (EtOAc), dried over anhydrous magnesium sulfate (MgSO₄) and condensed under reduced pressure. The product was purified by silica gel chromatography (DCM:EtOAc) to afford the desired compound 85 (Scheme 2.1 in Appendix C).

Orange powder; Chemical Formula: C₂₁H₂₅FN₄O₄; Eluent: (DCM:EtOAc = 9:1, retention factor (R_f) = 0.4); Yield: 167 mg (15%); MP: 163-165 °C; IR (cm⁻¹): 3380 (N-H stretching (str.)), 3100-3600 (O-H str. in alcohol), 2944 (C-H str. in CH₃), 1734 (C=N str.), 1496 (aromatic C=C str.). (Figure 85A in Appendix A); ¹H NMR (300 MHz, CDCl₃) δ ppm: 8.17 (s, 1H), 7.58 (q, J = 4.5 Hz, 1H), 7.30 (s, 2H), 7.05 (t, J = 6.8, 2H), 3.98 (s, 6H), 3.83 (s, 1H), 3.65 (s, 4H), 3.11 (s, 2H), 2.53 (s, 2H), 2.34 (s, 4H). (Figure 85C in Appendix A); ¹³C NMR (75 MHz, CDCl₃) δ ppm: 151.8, 147.3, 138.5, 134.8, 127.6, 117.6, 109.3, 108.7, 104.4, 66.6, 58.7, 56.6, 53.6, 43.9. (Figure 85D in Appendix A).

Synthesis of compound 2-(4-dimethylaminophenyl)-N-(2-morpholin-4-ylethyl)-6-fluoroimidazo[1,2-a]pyridin-3-amine (86).

A mixture containing 2-Amino-5-fluoropyridine 82 (300 mg, 2.68 mmol) and 4-(dimethylamino)benzaldehyde 83a (399 mg, 2.68 mmol) and 20% mmol of p-toluenesulfonic acid (113 mg) was added to a round bottom flask containing 10 ml of MeOH:DCM (2:3), stirred under nitrogen atmosphere for an hour at 50 °C. Then, 3-morpholinopropionitrile 84 (density = 1.017 g/ml) (368 µl, 2.68 mmol) was added to the mixture and agitated for 72 hours at 50 °C. The product was washed with distilled water and 0.3 g KHCO₃, extracted with ethyl acetate (EtOAc), dried over anhydrous magnesium sulfate (MgSO₄) and condensed under reduced pressure. The product was purified by

silica gel chromatography (DCM:EtOAc) to afford the desired compound 86 (Scheme 2.2 in appendix C).

Pale yellow powder; Chemical Formula: $C_{21}H_{26}FN_5O$; Eluent: (DCM:EtOAc = 2:8, Rf = 0.45); Yield: 202 mg (20%); MP: 170-172 °C; IR (cm^{-1}): 3296 (N-H str.), 1612 (C=N str.), 1551 (C=C str.), 1515 (aromatic C=C str.), 1423 (C-H bending in CH₃), 1137 (C-O str.), 1114 (C-F str.). (Figure 86A in Appendix A); ¹H NMR (300 MHz, CDCl₃) δ ppm: 8.10 (t, J = 3.2 Hz, 1H), 7.87 (dt, J = 8.9, 2.1 Hz, 2H), 7.51 (dd, J = 9.7, 4.9 Hz, 1H), 7.02 (dt, J = 8.0, 2.4 Hz, 1H), 6.80 (dt, J = 8.9, 2.8 Hz, 2H), 3.95 (s, 1H), 3.76 (t, J = 4.6, 4H), 3.08 (q, J = 5.4, 2H), 3.01 (s, 6H), 2.55 (t, J = 5.4, 2H), 2.47 (t, J = 4.5, 3H). (Figure 86C in Appendix A); ¹³C NMR (75 MHz, CDCl₃) δ ppm: 150.0, 127.8, 126.1, 116.99, 116.88, 115.7, 112.2, 109.3, 108.8, 66.8, 58.4, 53.6, 43.6, 40.3. (Figure 86D in Appendix A).

Synthesis of compound 2-(Indolyl)-N-(2-morpholin-4-ylethyl)-6-fluoroimidazo[1,2-a]pyridin-3-amine (87).

A mixture containing 2-Amino-5-fluoropyridine 82 (300 mg, 2.68 mmol) and 3-indolcarbaldehyde compound 83c (391 mg, 2.68 mmol) and 20% mmol of p-toluenesulfonic acid (113 mg) was added to a round bottom flask containing 10 ml of MeOH:DCM (2:3), stirred under nitrogen atmosphere for an hour at 50 °C. Then, 3-morpholinopropionitrile 84 (density = 1.017 g/ml) (368 μl, 2.68 mmol) was added to the mixture and agitated for 36 hours at 50 °C. The product was washed with distilled water and 0.3 g KHCO₃, extracted with ethyl acetate (EtOAc), dried over anhydrous magnesium sulfate (MgSO₄) and condensed under reduced pressure. The product was purified by silica gel chromatography (DCM:EtOAc) to afford the desired compound 87 (Scheme 2.3 in Appendix C).

Orange powder; Chemical Formula: $C_{21}H_{22}FN_5O$; Eluent: (DCM:EtOAc = 1:9, Rf=0.2); Yield: 561 mg (55 %); MP: 193-196 °C; IR (cm^{-1}): 3673 (N-H str.), 3269 (aromatic N-H str.), 2971 (C-H str. in CH₃), 1578 (C=N str.), 1446 (C=C str.), 1406 (aromatic C=C str.), 1213 (C-N str.), 1137 (C-O str.), 1066 (C-F str.). (Figure 87A in Appendix A); ¹H NMR (300 MHz, CDCl₃) δ ppm: 8.81 (s, 1H), 8.13 (dd, J = 6.4, 1.9, 2H), 7.66 (d, J = 2.5, Hz, 1H), 7.57 (dd, J = 9.7, 4.97 Hz, 1H), 7.43 (dd, J = 6.3, 2.1 Hz, 1H), 7.23 (dq, J = 5.6, 1.5 Hz, 2H), 7.05 (dt, J = 10.5, 2.4 Hz, 1H), 4.08 (s, 1H), 3.49 (t, J = 4.6 Hz, 4H), 3.01 (q, J = 3.8 Hz, 2H), 2.45 (t, J = 5.5 Hz, 2H), 2.27 (t, J = 4.56 Hz, 4H). (Figure 87C in Appendix

A); ^{13}C NMR (75 MHz, CDCl_3) δ ppm: 150.0, 127.8, 126.1, 116.9, 116.8, 115.7, 112.2, 109.3, 108.8, 66.8, 58.4, 53.6, 43.6, 40.3. (Figure 87D in Appendix A).

Synthesis of compound N-(2-morpholinoethyl) -2-(2,3,4-Trimethoxyphenyl)-6-fluoroimidazo[1,2-a]pyridin-3-amine (88)

A mixture containing 2-Amino-5-fluoropyridine 82 (300 mg, 2.68 mmol) and 2,3,4-trimethoxybenzaldehyde 83d (525 mg, 2.68 mmol) and 20% mmol of p-toluenesulfonic acid (113 mg) was added to a round bottom flask containing 10 ml of MeOH:DCM (2:3), stirred under nitrogen atmosphere for an hour at 50 °C. Then, 3-morpholinopropionitrile compound 84 (density = 1.017 g/ml) (368 μl , 2.68 mmol) was added to the mixture and agitated for 72 hours at 50 °C. The product was washed with distilled water and 0.3 g KHCO_3 , extracted with ethyl acetate (EtOAc), dried over anhydrous magnesium sulfate (MgSO_4) and condensed under reduced pressure. The product was purified by silica gel chromatography (DCM:EtOAc) to afford the desired compound 88 (Scheme 2.4 in Appendix C).

Pale yellow crystal; Chemical Formula: $\text{C}_{22}\text{H}_{27}\text{FN}_4\text{O}_4$; Eluent: (DCM:EtOAc = 2:8, Rf = 0.4); Yield: 660 mg (57 %); MP: 111-114 °C; IR (cm^{-1}): 3680 (N-H str.), 2970 (C-H str. in CH_3), 1736 (C=N str.), 1495 (C=C str.), 1462 (aromatic C=C str.), 1233 (C-N str.), 1137 (C-O str.), 1088 (C-F str.). (Figure 88A in Appendix A); ^1H NMR (300 MHz, CDCl_3) δ ppm: 8.10 (t, J = 3.2 Hz, 1H), 7.54 (dd, J = 9.7, 5.0 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.05 (dt, J = 8.8, 2.4 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 4.72 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 3.68 (s, 3H), 3.58 (t, J = 4.5 Hz, 4H), 2.93 (t, J = 5.3 Hz, 2H), 2.34 (t, J = 5.7 Hz, 2H), 2.25 (t, J = 4.3 Hz, 4H). (Figure 88C in Appendix A); ^{13}C NMR (75 MHz, CDCl_3) δ ppm: 138.7, 136.1, 122.5, 120.8, 120.5, 111.3, 109.1, 77.2, 66.5, 58.1, 53.3, 43.7. (Figure 88D in Appendix A).

Synthesis of compound N-(2-morpholinoethyl) -2-(4-(trifluoromethyl)phenyl)-6-fluoroimidazo[1,2-a]pyridin-3-amine (89).

A mixture containing 2-Amino-5-fluoropyridine 82 (300 mg, 2.68 mmol) and 4-(trifluoromethyl)benzaldehyde compound 83e (393 mg, 2.68 mmol) and 20% mmol of p-toluenesulfonic acid (113 mg) was added to a round bottom flask containing 10 ml of MeOH:DCM (2:3), stirred under nitrogen atmosphere for an hour at 50 °C. Then, 3-

morpholinopropionitrile 84 (density = 1.017 g/ml) (368 μ l, 2.68 mmol) was added to the mixture and agitated for 72 hours at 50 °C. The product was washed with distilled water and 0.3 g KHCO_3 , extracted with ethyl acetate (EtOAc), dried over anhydrous magnesium sulfate (MgSO_4) and condensed under reduced pressure. The product was purified by silica gel chromatography (DCM:EtOAc) to afford the desired compound 89 (Scheme 2.5 in Appendix C).

White powder; Chemical Formula: $\text{C}_{20}\text{H}_{20}\text{F}_4\text{N}_4\text{O}$; Eluent: (DCM:EtOAc = 2:8, R_f = 0.4); Yield: 660 mg (57%); MP: 156-160 °C; IR (cm^{-1}): 3261 (N-H str.), 2973 (C-H str. in SP^3), 1615 (C=N str.), 1580 (C=C str.), 1494 (aromatic C=C str.), 1321 (C-N str.), 1120 (C-O str.), 1158 (C-F str.). (Figure 89A in Appendix A); ^1H NMR (300 MHz, CDCl_3) δ ppm: 8.180 (s, 1H), 8.178 (d, J = 8.0, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.55 (dd, J = 9.78, 4.9 Hz, 1H), 7.10 (dt, J = 8.8, 2.4 Hz, 1H), 4.01 (s, 1H), 3.78 (t, J = 4.43 Hz, 4H), 3.12 (q, J = 5.38, 2H), 2.577 (t, J = 5.37 Hz, 2H), 2.507 (t, J = 4.06 Hz, 4H). (Figure 89C in Appendix A); ^{13}C NMR (75 MHz, CDCl_3) δ ppm: 139.26, 137.64, 127.16, 125.58, 125.53, 118.39, 118.27, 116.74, 116.40, 109.51, 108.96, 66.11, 58.65, 53.55, 43.43. (Figure 89D in Appendix A).

Synthesis of compound 2-(4-(methylthio) phenyl)-N-(2-morpholinoethyl) -6-fluoroimidazo[1,2-a]pyridin-3-amine (90).

A mixture containing 2-Amino-5-fluoropyridine 82 (300 mg, 2.68 mmol) and 4-(methylthio)benzaldehyde 83f (density = 1.44 g/ml) (283 μ l, 2.68 mmol) and 20% mmol of p-toluenesulfonic acid (113 mg) was added to a round bottom flask containing 10 ml of MeOH:DCM (2:3), stirred under nitrogen atmosphere for an hour at 50 °C. Then, 3-morpholinopropionitrile 84 (density = 1.017 g/ml) (368 μ l, 2.68 mmol) was added to the mixture and agitated for 72 hours at 50 °C. The product was washed with distilled water and 0.3 g KHCO_3 , extracted with ethyl acetate (EtOAc), dried over anhydrous magnesium sulfate (MgSO_4) and condensed under reduced pressure. The product was purified by silica gel chromatography (DCM:EtOAc) to afford the desired compound 90 (Scheme 2.6 in Appendix C).

White crystal; Chemical Formula: $\text{C}_{20}\text{H}_{23}\text{FN}_4\text{OS}$; Eluent: (DCM:EtOAc = 2:8, R_f = 0.43); Yield: 670 mg (65%); MP: 160-161 °C; IR (cm^{-1}): 3289 (N-H str.), (C-H str. in SP^3), 1572 (C=N str.), 1531 (C=C str.), 1511 (aromatic C=C str.), 1329 (C-N str.), 1112 (C-O str.),

1159 (C-F str.), 1214 (C-S-C str.). (Figure 90A in Appendix A); ^1H NMR (300 MHz, CDCl_3) δ ppm: 8.12 (t, $J = 3.2$ Hz, 1H), 7.94 (dt, $J = 8.6, 2.0$, 2H), 7.51 (dd, $J = 9.7, 4.9$ Hz, 1H), 7.33 (dt, $J = 8.6, 2.0$ Hz, 2H), 7.05 (dt, $J = 8.8, 2.4$ Hz, 1H), 3.95 (s, 1H), 3.75 (t, $J = 4.6$ Hz, 4H), 3.08 (q, $J = 5.4, 2.0$, 2H), 2.565 (t, $J = 5.6$ Hz, 2H), 2.536 (s, 3H), 2.43 (t, $J = 4.4$ Hz, 4H). (Figure 90C in Appendix A); ^{13}C NMR (75 MHz, CDCl_3) δ ppm: 154.94, 151.80, 138.84, 138.03, 136.32, 130.59, 127.20, 117.82, 117.70, 116.17, 115.83, 109.38, 108.83, 66.53, 58.45, 43.57, 15.68. (Figure 90D in Appendix A).

Synthesis of compound 2-(1-Methyl-2-imidazolephenyl)-N-(2-morpholinoethyl)-6-fluoroimidazo[1,2-a]pyridin-3-amine (91).

A mixture containing 2-Amino-5-fluoropyridine 82 (300 mg, 2.68 mmol) and 1-methyl-2-imidazolecarboxaldehyde 83g (294 mg, 2.68 mmol) and 20% mmol of p-toluenesulfonic acid (113 mg) was added to a round bottom flask containing 10 ml of MeOH:DCM (2:3), stirred under nitrogen atmosphere for an hour at 50 °C. Then, 3-morpholinopropionitrile 84 (density = 1.017 g/ml) (368 μl , 2.68 mmol) was added to the mixture and agitated for 72 hours at 50 °C. The product was washed with distillation water and 0.3 g KHCO_3 , extracted with ethyl acetate (EtOAc), dried over anhydrous magnesium sulfate (MgSO_4) and condensed under reduced pressure. The product was purified by silica gel chromatography (DCM:EtOAc) to afford the desired compound 91 (Scheme 2.7 in Appendix C).

Black paste; Chemical Formula: $\text{C}_{20}\text{H}_{21}\text{FN}_6\text{O}$; Eluent: (DCM:EtOAc = 2:8, $R_f = 0.35$); Yield: 137 mg (15%); MP: 206-210 °C; ^1H NMR (300 MHz, CDCl_3) δ ppm: 8.19 (t, $J = 3.18$ Hz, 1H), 7.52 (dd, $J = 9.8, 4.98$ Hz, 1H), 7.12 (d, $J = 0.8$ Hz, 1H), 7.69 (dt, $J = 8.8, 2.4$ Hz, 1H), 6.96 (d, $J = 0.8$ Hz, 1H), 4.53 (s, 1H), 4.16 (s, 3H), 3.78 (t, $J = 4.6$, 4H), 3.22 (t, $J = 5.87$ Hz, 2H), 2.71 (t, $J = 5.91$ Hz, 2H), 2.59 (s, 4H). (Figure 91C in Appendix A); ^{13}C NMR (75 MHz, CDCl_3) δ ppm: 140.75, 140.47, 138.09, 130.20, 122.8, 122.32, 118.23, 109.98, 109.12, 65.76, 57.82, 53.21, 42.92, 35.50, 20.77. (Figure 91D in Appendix A).

2.2 Biological Evaluation

2.2.1 Antibacterial Activity

2.2.2 Materials and Methods

- Preparation of bacterial cultures

The antibacterial activity of seven compounds was determined using the broth micro-dilution method (NCCLS, 2000). The antibacterial activity of the seven compounds was evaluated against five reference bacterial isolates, which are *E.coli* (ATCC 25922), *K. pneumoniae* (ATCC 13883), *P. aeruginosa* (ATCC 9027), *S. aureus* (ATCC 6538P) and *S. epidermis* (ATCC 12228). All were obtained from the American Type Culture Collection (ATCC). The bacterial strains that were being investigated were left to grow overnight at a temperature of 37 °C on plates containing nutrient agar. The transparency of the liquid culture was adjusted to a turbidity level of 0.5 McFarland, which is equivalent to a bacterial concentration of 1.5×10^8 colony-forming units per milliliter (CFU/mL). Next, a volume of 333 μ l of bacterial culture was mixed with 5 ml of saline solution in order to achieve a concentration of 1.0×10^7 CFU/ml. The culture medium for bacteria was Muller-Hinton broth (MHB) (102).

- Preparation of compounds dilutions

Preparations were made by dissolving the title compounds in 20% DMSO at a concentration of 1 mg/ml. Subsequently, the solution was diluted in the test medium to get a concentration that was twice as high as the intended top concentration in the test. Specifically, it was diluted to 1000 μ g/ml, given that the highest desired concentration was 500 μ g/ml.

- Determination of Minimum inhibitory concentration (MIC) using a 96-well plate

Initially, 100 microliters of MHB medium containing 1 microliter of the bacterial strain being tested (with a concentration of 1.0×10^7 CFU/ml) were distributed into each well of a 96-well plate. Next, 100 μ l of the suitable 2x compound solutions were transferred into the wells in column 1, mixed, and yielded a final concentration of 5×10^4 CFU/ml for the bacterial culture in each well. Subsequently, a serial dilution of compounds was performed by extracting 100 μ l from column 1 and introducing it into column 2, followed by thorough mixing. Subsequently, a volume of 100 μ l from column 2 was sequentially

transferred to column 3 and so forth, resulting in a total of ten concentrations of the compounds under investigation: 500, 250, 125, 62.5, 31.25, 15.625, 7.81, 3.91, 1.95, and 0.98 $\mu\text{g/mL}$. The final two columns were designated for sterility control (negative control) and to evaluate the impact of a 20% DMSO solution on bacterial growth. Additionally, positive control wells were used to examine bacterial growth without the addition of the tested chemicals. Gentamicin, an antibiotic, was employed as the positive control for its antibacterial properties. Ultimately, the cultivated 96-well plates were subjected to incubation at a temperature of 37 °C for a duration of 18 hours. The lowest compound concentration (highest dilution) that inhibited the growth of the tested microorganism was considered the minimum inhibitory concentration (MIC). The minimum bactericidal concentration (MBC) was also determined. In this technique, the contents of the wells resulting from MIC were streaked using sterile cotton swabs on agar plates free of antibacterial agents and incubated at 37°C for 18 hours. The lowest concentration of the compound, which showed no bacterial growth, was considered as MBC (102).

Chapter Three

Results and discussion

3.1 Chemistry

The synthetic procedure for compounds 85-91, as detailed in Table 3.1 and Table 3.2, is outlined in Scheme 3.1 in Appendix C. This scheme involved the synthesis of compounds utilizing 2-morpholinoethyl isocyanide 84, where 2-amino-5-fluoropyridine 82 reacts with various aldehydes 83a-g, resulting in the production of a range of 3-aminoimidazo[1,2-a]pyridines. The yields of these compounds are moderate, varying between 15% and 65%. The compounds were synthesized utilizing the acid-catalyzed GBB-3CR method, with all reactions in this study performed in a nitrogen atmosphere.

3.1.1 Synthesis of 5-floroimidazo[1,2-a]pyridin-3-amine via acid-catalyzed GBB-3CR utilizing 2-morpholinoethyl isocyanide.

Schemes 3.2 in Appendix C depict the condensation reaction between 2-amino-5-fluoropyridine 82 and syringaldehyde 83a at reflux temperature. This reaction is followed by the attack of 2-morpholinoethyl isocyanide 84 and ultimately results in the formation of N-(2-morpholinoethyl)-2-(3,5-Dimethoxy-4-hydroxyphenyl)-5-floroimidazo[1,2-a]pyridin-3-amine 85 through cyclization. pTsOH was utilized as a catalyst in this process, whereas a solvent mixture of MeOH:DCM (2:3) was employed. After allowing the reaction to proceed for 72 hours. Silica gel chromatography was employed to get a product with a purity of 100% according to the HPLC chromatogram (Figure 85B in Appendix A) and a yield of 15%. Scheme 3.2 in Appendix C provides a comprehensive illustration of the proposed mechanism for the synthesis process, using compound 85 as an example. The other reactions in this study exhibited the identical mechanism as the pathway elucidated for the production of compound 85. The organic acid pTsOH initiates the activation of aldehyde 83a. This is followed by the nucleophilic addition of amine 82, resulting in the formation of an iminium compound. Subsequently, a [4+1]-cycloaddition reaction occurs with isocyanide 84. Finally, an aromatization process takes place by a 1,3-H shift, resulting in the formation of imidazo[1,2-a]pyridine(103).

Table 3.1*Reactant and products of GBB-3CR products (85-87) and the % yield*

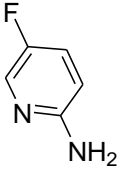
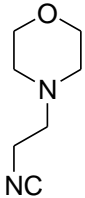
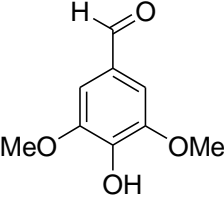
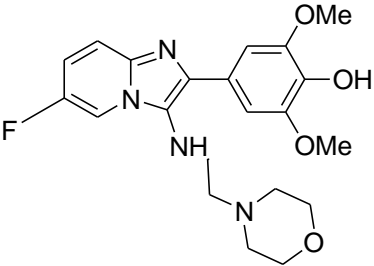
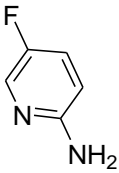
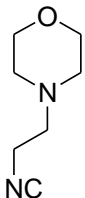
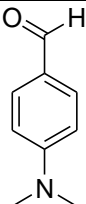
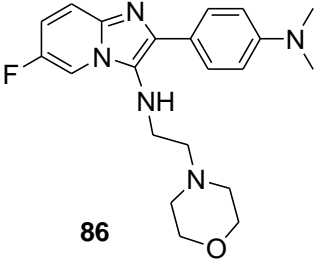
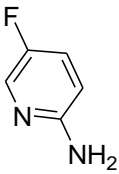
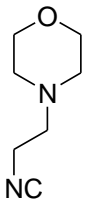
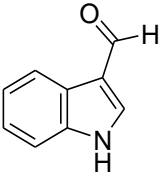
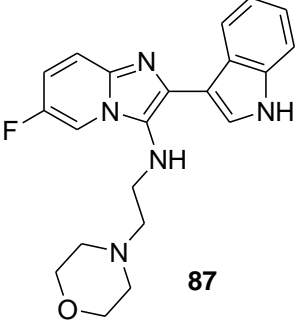
Entry	2-aminopyridene	Isocyanine	Aldehyde	Product	Yield
1	 82	 84	 83a	 85	15%
2	 82	 84	 83b	 86	20%
3	 82	 84	 83c	 87	55%

Table 3.2*Reactant and products of GBB-3CR products (88-91) and the % yield*

Entry	2-aminopyridine	Isocyanide	Aldehyde	Product	Yield
4					57%
5					19%
6					65%
7					15%

Optimization of the synthesis procedure by increasing the pTsOH percentage from 10% to 20% can increase the yield in a significant amount. Moreover, increasing the reaction temperature from room temperature to 50 °C enhances the yield. The use of 2-Morpholinoethyl isocyanide in this work has an impact on the yield. In general, there is a decrease in the yield when 2-morpholinoethyl isocyanide is used, around 25% (67). Tyagi et al. reported that when 2-bromobenzaldehyde and 2-aminopyridine react with isobutyl isocyanide, cyclohexyl isocyanide, and 2-morpholinoethyl isocyanide in the presence of *p*TsOH as a catalyst, the reaction yield drops from 93%, 89%, and 65%, respectively. The reason for this decline in reactivity is due to steric hindrance. Adding a halogen to 2-aminopyridine affects the yield. In fact, when 2-Amino-5-bromopyridine is

used, it also lowers the yield from 93% to 80%. All of these reasons result in the lower yield of compounds 85-91 (84,103).

3-aminoimidazo[1,2-a]pyridines with 3,5-dimethoxy-4-hydroxyphenyl on C-2 substitution in several reactions with other isocyanides gave a yield of 15%–32%; unfortunately, inverse GBB-3CR can be produced alone or in a mixture of both regioisomers (104). In this research compound 85 has a yield of 15%, which is due to firstly using 2-Morpholinoethyl isocyanide. The low yield is also due to the presence of a hydroxyl group, which goes into side reactions or polymerization. Compound 86 is produced in a low yield of 20%; the reasons here are due to the nature of the catalyst and the isocyanide used. In literature, the yield of produced 4-dimethylaminophenylimidazo[1,2-a]pyrimidine is 52% using NH_4Cl as a catalyst and benzyl isonitrile (105). Here, Compound 87 yields 55%, which is higher than compound 92 (Figure 3.1 in Appendix C), which contains a C-2 Indolyl that only yields 50% using the NH_4Cl catalyst (105). Compound 88 yields 57% compared with Akbarzadeh et al.'s yield of 73% for compound 93 (Figure 3.1 in Appendix C), which has 3,4,5-trimethoxyphenyl at C-2 (105). Compound 89 has a yield of 19%, but in literature theyield is higher (106–108). Compound 91 yield is 15%; the closest example in literature has a yield of 74% by using HClO_4 as a catalyst in MeOH (109). Moreover, Baenziger et al. found a decrease in yield when employing simultaneously electron-rich isocyanides and aldehydes in the same combination (68). However, since these compounds had the highest yield values among the others, the presence of electron donating (ED) groups on the benzaldehydes, such as the methyl sulfide group in compound 90, the methoxy groups in compound 88, and the indole hetero cyclic ring in compound 87, increased the yield.

In addition, HPLC analysis confirmed the purity of the synthesized compounds, with purity levels ranging from 88% to 100% (Table 3.3). Furthermore, the retention time (RT) is shown for compounds 85-91 in Table 3.3. The HPLC chromatograms for all synthesized compounds are displayed in Figures(85-91)B in Appendix A. Tests of the MPs for these products confirmed their purity. The lowest mean value recorded was 111-114 °C for compound 88, while the highest was 206-213°C for compound 91.

Table 3.3*Sequential HPLC analysis and MP results of the synthesized compounds*

Compound number	Purity %	RT (min)	Melting point(°C)
85	100%	10.09	163-165
86	100%	11.66	170-172
87	97%	9.76	193-196
88	100%	10.21	111-114
89	97%	12.94	156-160
90	100%	11.74	160-161
91	88%	11.45	206-210

The structures of compounds 85-91 were established using ^1H and ^{13}C NMR spectroscopy, including infrared (IR). To illustrate, consider the IR study of 2-(Indolyl)-N-(2-morpholin-4-ylethyl)-6-fluoroimidazo[1,2-a]pyridin-3-amine 87. Primary absorption bands at 1578 cm^{-1} , 1446 cm^{-1} , and 1323 cm^{-1} corresponded to the stretching vibrations of C=N, C=C, and C-N bonds, respectively. Additionally, a single band was detected at 3269 cm^{-1} , which was attributed to the N-H stretching vibration of compound 87. $\text{Sp}^3\text{-H}$ for compound 87 appears at 2901 cm^{-1} and 2971 cm^{-1} , a strong peak at 1066 cm^{-1} due to the presence of C-O in the ether part, and the 750 cm^{-1} signal indicates N-H wagging. All compounds exhibited a prominent absorption band associated with aromatic C=C stretching, ranging from $1495\text{--}1599\text{ cm}^{-1}$. The characteristic bands for C=N and C-N stretching were observed in the approximate ranges of $1572\text{--}1684\text{ cm}^{-1}$ and $1321\text{--}1365\text{ cm}^{-1}$ for most of the 7 products, respectively (Figure (85-91)A in Appendix A).

For example, ^1H NMR spectra for compound 86 revealed proton resonance around 6.80–8.10 ppm, which was caused by the Imidazo[1,2-a]pyridine heterocyclic aromatic moiety and dimethylamino benzene aromatic rings. Specifically, there are five different protons in the aromatic region; therefore, there are five different peaks. At 3.95 ppm, a proton resonance for the NH group was observed; this broad signal has an integral of 1H and is caused by the NH group on 2-morpholinoethyl isocyanides. Additionally, moving to the upfield section, morpholino in the morpholinoethyl group has also four signals that appear on all synthetic components. Finally, 6H from sp^3 hybridization protons on dimethyl benzene appears at 3.01 ppm as a singlet (Figure 86C in Appendix A). ^{13}C NMR spectrum for compound 86 can be divided into two regions: sp^3 hybridization and aromatic sector; in the up-field area we have five different C's environments, so we have five different signals related to them. In the aromatic region there are 9 signals and 11 different C's environment; to explain this, Chemical shift calculation were done that were

also noticed for all synthetic compounds but in some variation in the chemical shifts (Figure (85-91)D in Appendix A).

3.2 Biology

Every synthetic molecule was tested for its antibacterial properties in vitro against the Gram-negative strains of *K. pneumoniae*, *P. aeruginosa*, and *E. coli*, as well as the Gram-positive strains of *S. aureus* and *S. epidermidis*. The conventional broth micro dilution method was used to determine the MIC for the compounds. MIC values are essential for evaluating the effectiveness of antimicrobial agents. MBC is the lowest concentration of an antimicrobial agent required to kill 99.9% of the initial bacterial inoculums. Disk diffusion method provides a quantitative measure of the bactericidal activity of a compound and is essential for understanding its potential as an antimicrobial agent. The negative control is 20% DMSO used to evaluate the impact the solution on bacterial growth. The positive control is gentamicin was used to examine bacterial growth without the addition of the tested chemicals.

The antimicrobial activity of seven prepared compounds was quantitatively estimated by determining the MIC concentration for each compound against all studied bacteria (Figure 92 in Appendix B). The obtained MIC results revealed that all compounds under study obtained good bacteriostatic activity against the examined bacterial isolates, with some observed variation among them. Moreover, compound 91 exhibited the best inhibitory behavior among the others. It inhibited the growth of all tested bacterial isolates in a concentration range between 15.625 $\mu\text{g/mL}$ and 125 $\mu\text{g/mL}$. Furthermore, the lowest MIC value (15.625 $\mu\text{g/mL}$) was recorded for compound 91 against *E. coli*. However, the other compounds under study displayed noticeable bacteriostatic potential with a concentration range of 62.5-500 $\mu\text{g/mL}$ (Table 3.5). Even more, compound 91 works better than Gentamicin against *K. pneumoniae*. The same observation was reported for compounds 85 (Table 3.4) and 89 against *S. epidermidis* (Table 3.5). In addition to that, the bactericidal effect of all seven compounds that exhibited inhibitory effects was determined by measuring their MBC values. The obtained MBC results provided that all tested compounds had a bactericidal effect in the concentration range (62.5 $\mu\text{g/mL}$ -500 $\mu\text{g/mL}$). It is worth pointing out that compound 89 in this study kills *E. coli* and *S. epidermidis* at lower concentrations (62.5 $\mu\text{g/mL}$) than Gentamicin antibiotics 125 $\mu\text{g/mL}$ and 250 $\mu\text{g/mL}$, respectively. The same observation was noticed for compound 85 against

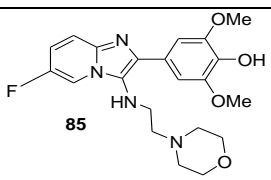
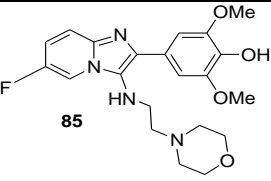
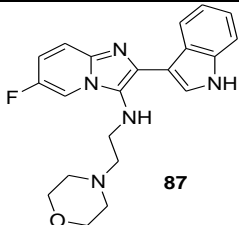
S. epidermidis with an MBC value of 62.5 µg/mL (Figure 92 in Appendix B). However, it's important to consider that these values are determined under controlled laboratory conditions and may not fully reflect the drug's performance in a clinical setting. MIC values are determined in vitro and may not always directly correlate with in vivo efficacy due to factors like drug absorption, distribution, and metabolism.

Initially, it has been determined that 3-amino-imidazo[1,2-a]pyridines constitute a novel class of glutamine synthetase inhibitors for *Mycobacterium tuberculosis*. Furthermore, these substances are the first drug-like inhibitors of this particular enzyme (110). Moreover, as an antibacterial, 3-amino-imidazo[1,2-a]pyridines core can target many enzymes involved in the synthesis of protein, folic acid, cell wall/peptidoglycan, DNA, or RNA. As a result, 3-amino-imidazo[1,2-a]pyridines are bioactivity scaffolds with several targets, which are represented by 1,7-dideaza-5-azapurines (83,104).

All seven synthesized compounds contain ethylmorphine moieties, which are known for their analgesic and antitussive properties. 3-Morpholinopropionitrile compound is used as a chemical intermediate in drug synthesis and is being explored for its potential

Table 3.4

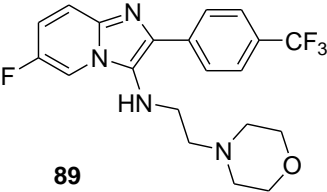
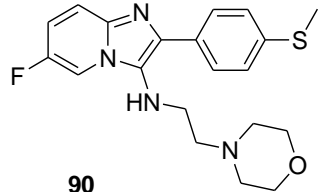
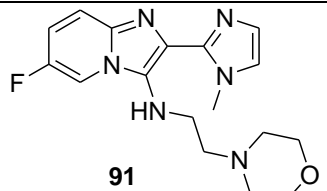
Antibacterial activity of 3-aminoimidazo[1,2-a]pyridine compounds 85-88 has shown MIC and MBC against five bacterial strains

Compound	MIC (µg/mL)					MBC (µg/mL)				
	1*	2*	3*	4*	5*	1*	2*	3*	4*	5*
 85	62.5	62.5	250	125	62.5	250	62.5	500	250	62.5
 86	250	250	250	62.5	250	500	250	500	250	500
 87	62.5	250	500	62.5	125	250	250	500	250	250
Gentamicin (Antibiotic)	62.5	31.2	62.5	31.2	125	125	62.5	62.5	62.5	250

1*: *E. coli* (ATCC 25922), 2*: *K. pneumoniae* (ATCC 13883), 3*: *P. aeruginosa* (ATCC 9027), 4*: *S. aureus* (ATCC 6538P) and 5*: *S. epidermidis* (ATCC 12228).

Table 3.5

Antibacterial activity of 3-aminoimidazo[1,2-a]pyridine compounds 89-91 has shown MIC and MBC against five bacterial strains

Compound	MIC ($\mu\text{g/mL}$)					MBC ($\mu\text{g/mL}$)				
	1*	2*	3*	4*	5*	1*	2*	3*	4*	5*
 89	62.5	250	250	250	62.5	62.5	500	500	500	62.5
 90	125	250	250	250	250	500	250	500	500	500
 91	62.5	15.6	125	31.2	125	250	62.5	500	250	250
Gentamicin (Antibiotic)	62.5	31.2	62.5	31.2	125	125	62.5	62.5	62.5	250

1*: *E. coli*, 2*: *K. pneumoniae*, 3*: *P. aeruginosa*, 4*: *S. aureus* and 5*: *S. epidermidis*.

biological activities, including anti-inflammatory and antiviral effects (111). For example, the 3-(2-morpholinoquinolin-3-yl)acrylonitrile derivatives have been tested in vitro for antimicrobial activity. Most of these compounds showed activity against Gram-positive bacteria (*Bacillus subtilis* and *Clostridium tetani*) and the fungal pathogen *Candida albicans*. These findings suggest that compound 85-91 have promising therapeutic potential, particularly in treating infections and possibly other conditions like inflammation and viral diseases (112).

This research has shown that various substituents on the rings of 3-Amino-imidazo[1,2-a]pyridines exhibit significant antibacterial activity. The antibacterial effects of compounds 85, 89, and 91 are influenced by the substitution at C-2 of 3-Amino-imidazo[1,2-a]pyridines. The variation in antibacterial activity is attributed to the aldehyde fragment. The presence of a hydroxyl group in 85 compounds may significantly influence their pharmaceutical properties, including metabolism, transport, and effects on redox processes and hypoxia in bio membranes and within cells, while also contributing to molecular diversity. Hydroxyphenyl fragments are commonly found in several synthetic and natural antioxidants. The pathogenetic significance of oxygen and organic

free radicals in over 100 diseases has been connected; therefore, it makes sense to assume that the development and screening of hydroxyl-containing 3-Amino-imidazo[1,2-a]pyridine derivatives, such as compound 85, as antioxidants, will go forward swiftly (104).

In deep looking to compound 89, which also has good antibacterial effect. Indeed, the combination of aromatic trifluoromethyl substitutions with 3-Amino-imidazo[1,2-a]pyridine moiety in one compound will increase the biological activity of the final product. The trifluoromethyl group, which is more bulky than the methyl group (Me), is one of the most common lipophilic functional groups. The most well-reported medications with aromatic trifluoromethyl substitution in their chemical structures have this substitution because of how the trifluoromethyl substituents affect the electrical properties of the aromatic rings. For example, Prozac (anti-depressant fluoxetine), Emend (or Aprepitant as an antiemetic drug), Celecoxib (arthritis medication and COX-2 inhibitor) have aromatic trifluoromethyl substitutions. Remarkably, the trifluoromethyl substituent is frequently present and increases efficacy by forming multipolar interactions with the carbonyl groups in the targeted protein (113). The strong electron-withdrawing fluorine atoms of the trifluoromethyl group exhibited hydrogen and/or halogen bonding interactions with multiple residues of the enzyme targets, as demonstrated by the docking studies. These interactions are likely the cause of the observed increased biological activity of these hydrazone derivatives. It has been discovered that the inclusion of a trifluoromethyl group in a molecule increases biological activity because of its improved lipid solubility and metabolic stability, which in turn increases membrane permeability. The carbon atom of the trifluoromethyl group forms a pi-alkyl interaction with the target protein residue. The trifluoromethyl group of this molecule 89 interacts by hydrogen bonds with Tyr133 (AS), Ser203 of the catalytic triad (CAS), and Gly121 (OH residue). It is anticipated that the trifluoromethyl groups of this compound 89 and the protein residues Glu202 (AS) and Gly120 will interact by halogen bonding. The trifluoromethyl group's fluorine atom and the protein residue Gly120 interact through a carbon-hydrogen link (114).

Compound 91 has good antibacterial effects due to the presence of 1-methylimidazole on imidazo[1,2-a]pyridinescaffold. Imidazole is an organic planar azole heterocyclic with two non-adjacent nitrogen atoms that are added in significant amounts to both natural

products and synthetic compounds. Since it is a polar compound, it behaves as a π -deficient ligand, acts as an acid and base at the same time, and has electron-rich nitrogen donors. All of these characters give imidazole derivatives greater affinity to bind with various bioreceptors and enzymes via weak interactions. Moreover, the exceptional structure makes azole-based derivatives not only bind effortlessly through noncovalent interactions like coordination and hydrogen bonds with enzymes and receptors in living organisms but also affect the binding affinity and water solubility of the conjugated system. As a result, it improves the pharmacokinetic properties of the molecules like compound 91 (115,116). The synthesis of two active pharmacophores via a linker bridge by combination of 3-Aminoimidazo[1,2-a]pyridine with imidazole substitution is reported here, and it has promising potential as antibacterial agents in the field of medical chemistry.

3.3 Limitations

Some challenges were encountered, such as the theoretical portion of the research's theoretical limit, which is feeble, and the practical aspect's accurate procurer. For example, the method of purity of synthetic components was confusing and variable from one paper to another. The major limitation is not the availability of chemical instruments; they are using them from other students, waiting for a laboratory technician to operate them, or the absence of them, like mass spectroscopy. The quantity of some material, like 3-morpholinopropionitrile, is limited, so repeating the experiment is not an available choice. Column chromatography is time-consuming and needs eluent like DCM and EtOAc in very large amounts. To finish one reaction, at least 10 days are needed between reaction time and workup and during the organic layer in rotatory evaporation and in the column chromatography process to separate the product, and the list includes IR, HPLC, ^1H NMR, ^{13}C NMR and biological tests.

The reaction nature requires mortaring by TLC in many steps to target the product and separate it from other side products, and unreacted starting materials are challenging, so the better choice is to use HPLC to identify the starting materials from the products. Some attempts to use the crystallization technique are not very successful because of solubility issues. Finally, the time to work in the laboratory is limited to the summer vacation. So two summers were spent in the laboratory; unfortunately, this time is not enough.

3.4 Conclusion

In conclusion, the present study describes the synthesis of a series of 3-amino-6-fluoroimidazo[1,2- a]pyridine derivatives (85-91) utilizing pTsOH as a catalyst using GBB-3CR, followed by characterization of the resulted compounds using different spectroscopic techniques such as IR, ¹H NMR, and ¹³C NMR. All the synthesized compounds were tested for antibacterial activity against some bacterial strains, including *S. aureus*, *K. pneumonia*, *P. aeruginosa*, *S. epidermidis* and *E. coli*. Resulting, compound 91 with imidazole moiety at C-2 and morpholinoethyl at N cite of 6-fluoroimidazo[1,2- a]pyridin-3-amine was found to be promising antibacterial lead compounds against *E. coli*. Recommendations: Additional research on these derivatives might provide more potent compounds that show promise as new antibacterial treatment options or anticancer therapies. Also, using SAR to predict drug structure and using organic chemistry abilities to synthesize it and apply chemical instruments to identify it. Design the chemical procedure by altering the catalyst, reaction time, and reaction temperature to optimize the reaction conditions. Apply purification methods such as crystallization to conserve time and materials. More chemical and biological tests for starting materials are needed to evaluate the degree of altering in chemical and biological properties during the chemical reaction. For example, an HPLC diagram for starting material is helpful for identifying its presence in reaction products.

List of Abbreviations

Abbreviation	Meaning
AcOH	Acetic acid
ATCC	American Type Culture Collection
MDR	Multidrug-Resistant
AMR	Antimicrobial resistance
B-3CR	Biginelli 3-component reaction
BF ₃ .MeCN	Boron Trifluoride Acetonitrile Complex Solution
CNS	Central nervous system
COF	Covalent organic framework
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DNA	Deoxyribonucleic acid
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
CDCl ₃	Deuterated chloroform
ED	Electron donating
EW	Electron withdrawing
<i>E. faecalis</i>	<i>Enterococcus faecalis</i>
<i>E. coli</i>	<i>Escherichia coli</i>
EtOH	Ethanol
EtOAc	Ethyl Acetate
FeCl ₃	Ferric chloride
G-3CR	Gewald 3-component reaction
GBB-3CR	Groebke-Blackburn-Bienaymé-three component reaction
GBB	Groebke-Blackburn-Bienamé
IC ₅₀	Half-maximal inhibitory concentration
HPLC	High-Performance Liquid Chromatography
HCl	Hydrochloric acid
HIV/AIDS	Human immunodeficiency viruses /Immunodeficiency syndrome
IR	Infra-red
FeCl ₂	Iron(II) chloride
IMCRs	Isocyanide-based multicomponent reactions

i-PrOH	Isopropyl alcohol
K. pneumonia	Klebsiella pneumonia
MP	Melting point
MeOH	Methanol
Me	Methyl group
MgSO ₄	Magnesium sulfate
MW	Microwave
MBC	Minimum bactericidal concentration
MIC	Minimum inhibitory concentration
MBH	Morita-Baylis-Hillman
MHB	Muller Hinton broth
MCR	Multicomponent reactions
NMR	Nuclear Magnetic Resonance
NB	Nutrient broth
PTSA or pTsOH	p-toluenesulfonic acid
P-3CR	Passerini 3-component reaction
HClO ₄	Perchloric acid
Pd(dppf)Cl ₂	Pd(1,1-bis(diphenylphosphino)ferrocene)Cl ₂
P.falciparum	Plasmodium falciparum
PEG	Polyethylene glycol
K ₂ CO ₃	Potassium carbonate
P. aeruginosa	Pseudomonas aeruginosa
QSAR	Quantitative structure-activity relationships
R _f	Retention factor
RNA	Ribonucleic acid
RT	Room Temperature
NaHCO ₃	Sodium hydrogen carbonate
SAR	Structure-activity relationship
Sc(OTf) ₃	Scandium triflate
SSA	Silica sulfuric acid
S. aureus	Staphylococcus aureus
S. epidermidis	Staphylococcus epidermidis
Str.	Stretching
H ₂ SO ₄	Sulfuric acid

TLC	Thin Layer Chromatography
TosMIC	Tosylmethyl Isocyanides
TPSO	Translocator Protein
TFA	Trifluoroacetic acid
TMOF	Trimethyl Orthoformate
TMSCl	Trimethylsilyl Chloride
U-3CR	Ugi 4-Component Reaction
U-4CR	Ugi 4-Component Reaction
vL-3CR	Van Leusen Three-Component Reaction
VOC	Volatile Organic Compound
WHO	World Health Organization
ZnCl ₂	Zinc Chloride
ZrCl ₄	Zirconium Tetrachloride

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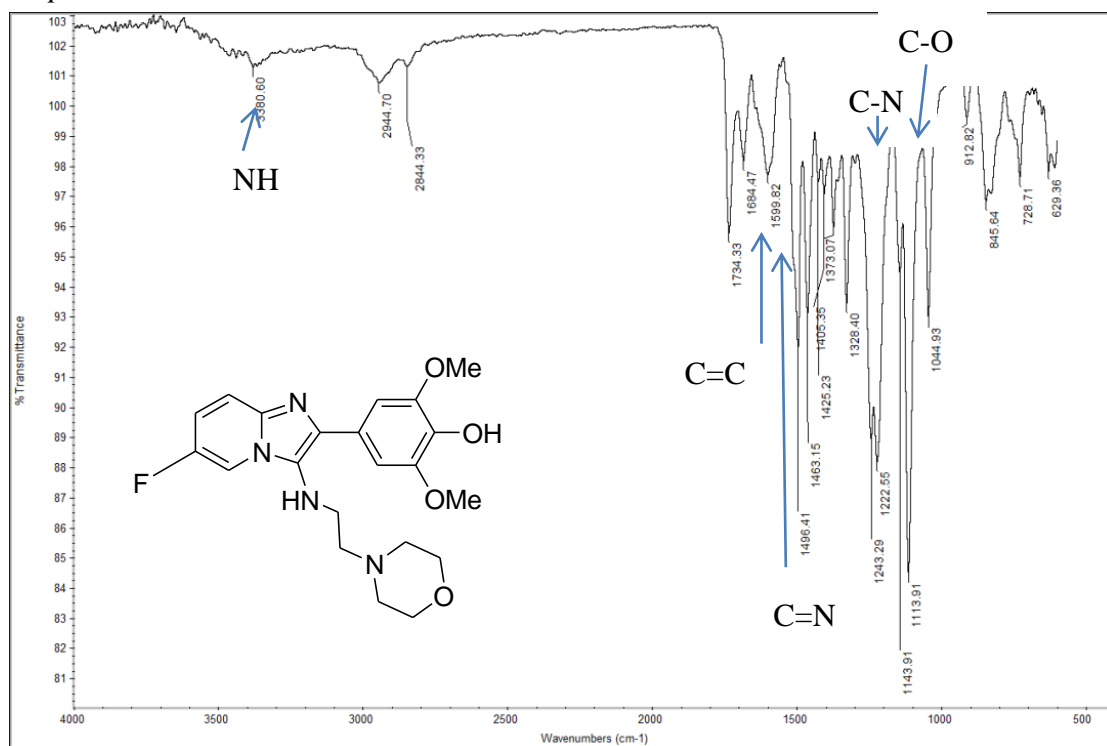
Appendices

Appendix A

IR, ^{13}C NMR, and ^1H NMR spectrum and HPLC diagram

Figure 85

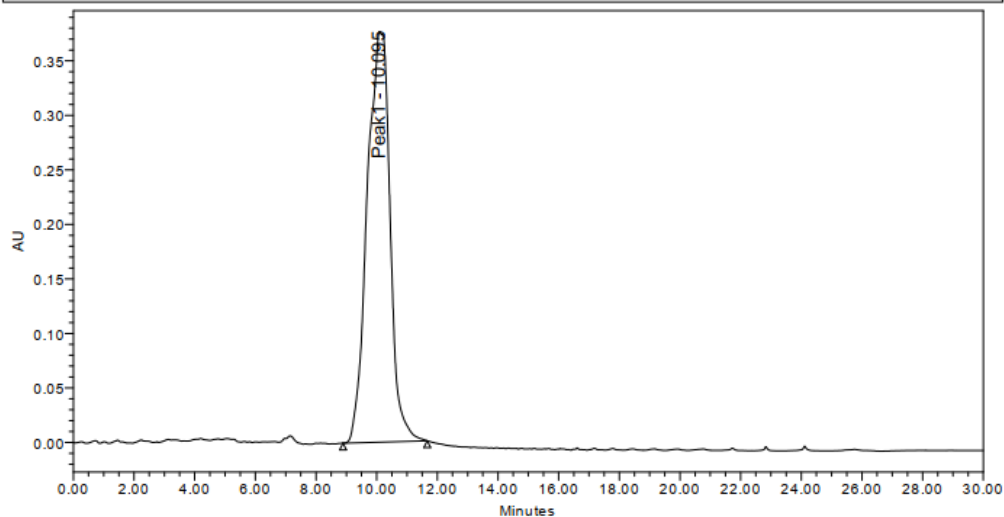
IR spectra, HPLC chromatograms, ^1H NMR spectra, and ^{13}C NMR spectra for compound 85



A. IR spectrum for compound 85

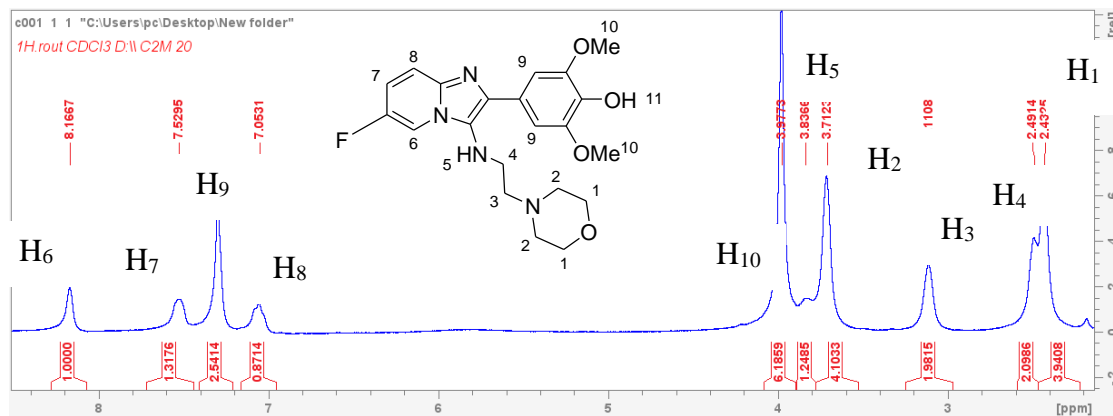
SAMPLE INFORMATION

Sample Name:	osama00001	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	2023-10-02 10:17:45 AM IST
Vial:	1	Acq. Method:	nawaf 1
Injection #:	1	Date Processed:	2023-10-19 3:04:12 PM IST
Injection Volume:	20.00 ul	Channel Name:	2998 Ch1 254nm@1.2nm
Run Time:	30.00 Minutes	Sample Set Name	

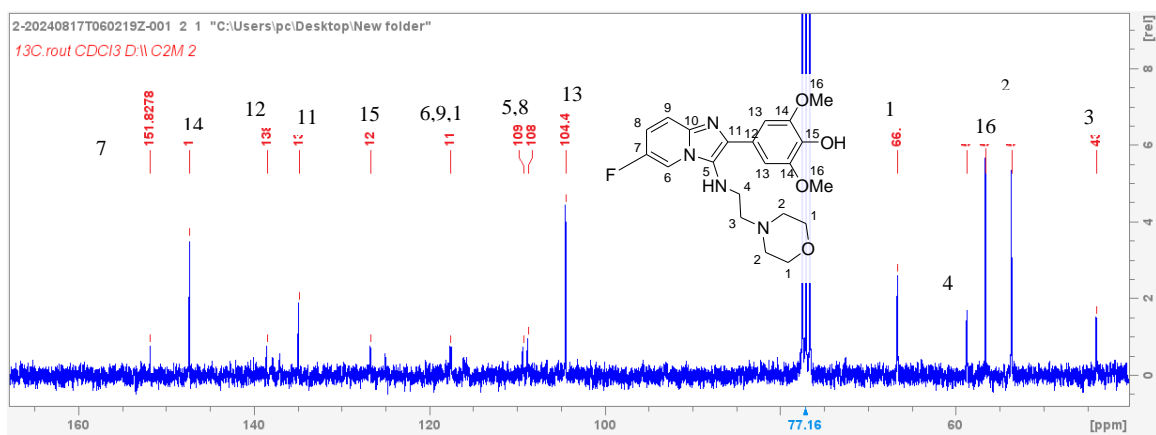
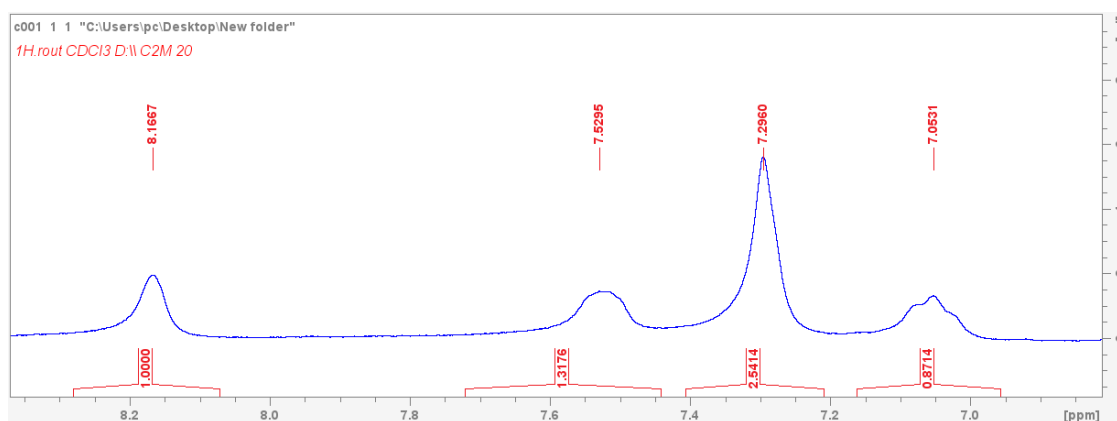
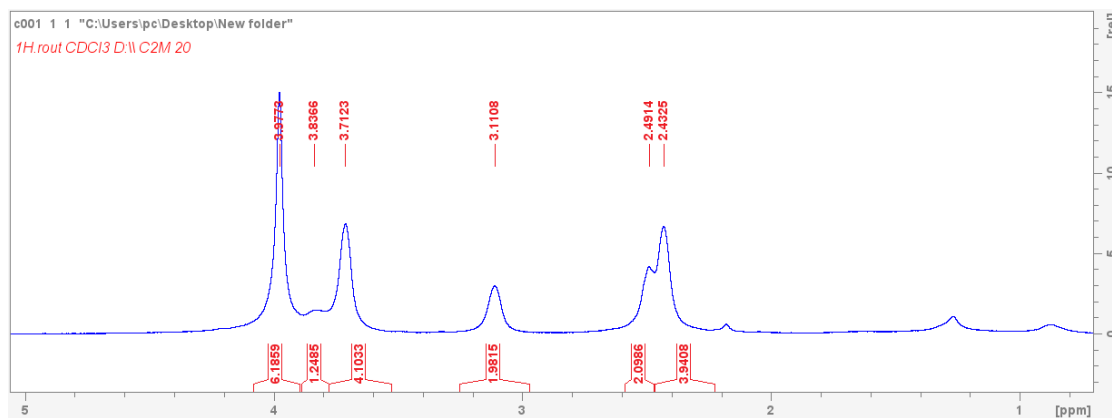


Peak Name	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1 Peak1	10.095	19671593	100.00	376531	100.00

B. HPLC chromatogram of 85



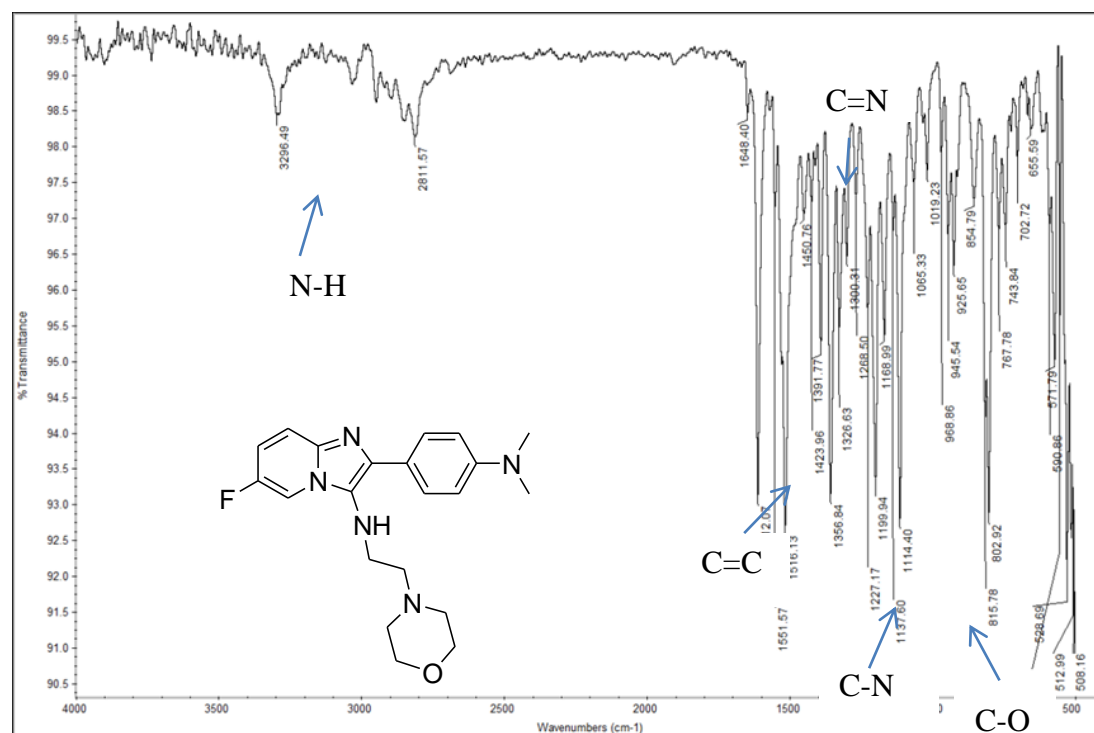
C. ¹H NMR spectrum for compound 85



D. ^{13}C NMR spectrum for compound 85.

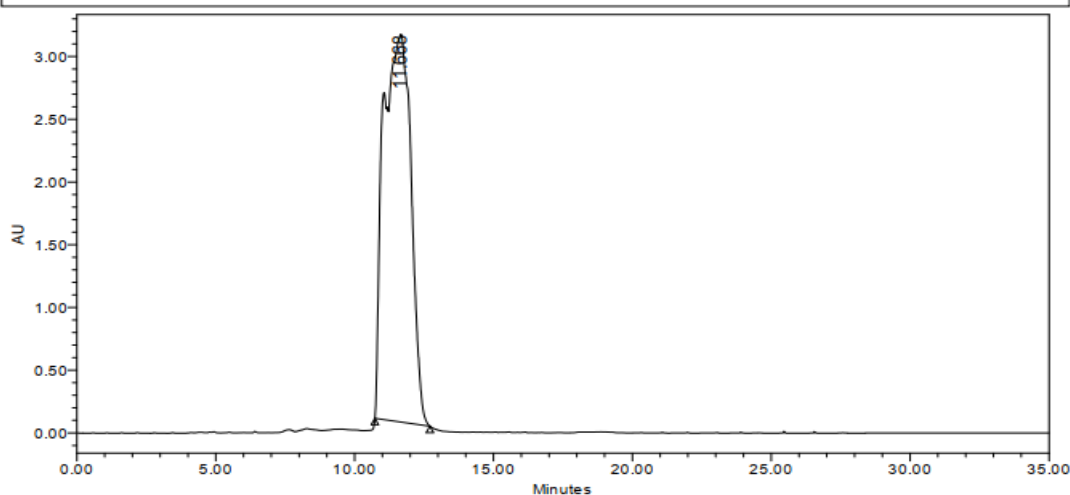
Figure 86.IR

spectra, HPLC chromatograms, ¹H NMR spectra, and ¹³C NMR spectra for compound 86



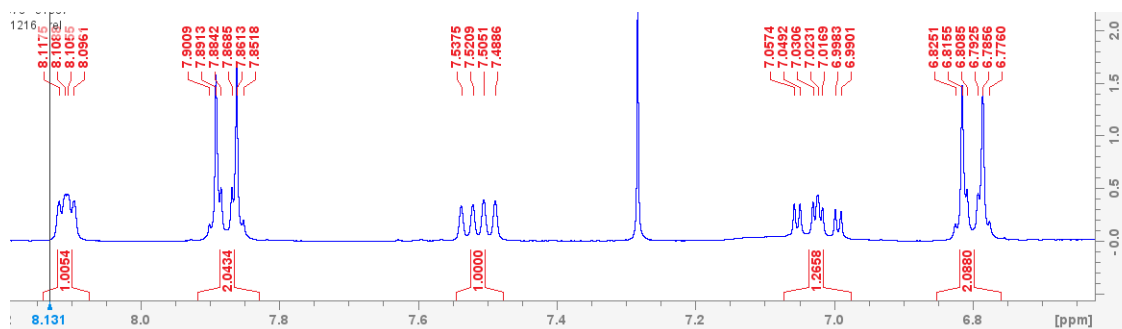
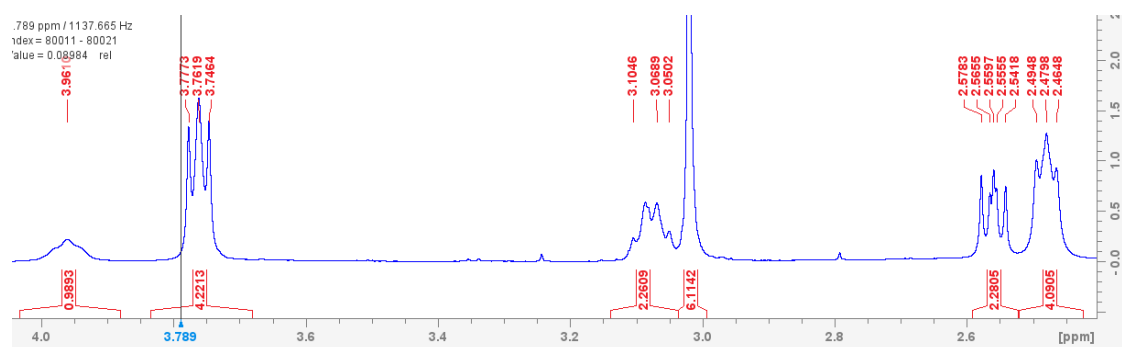
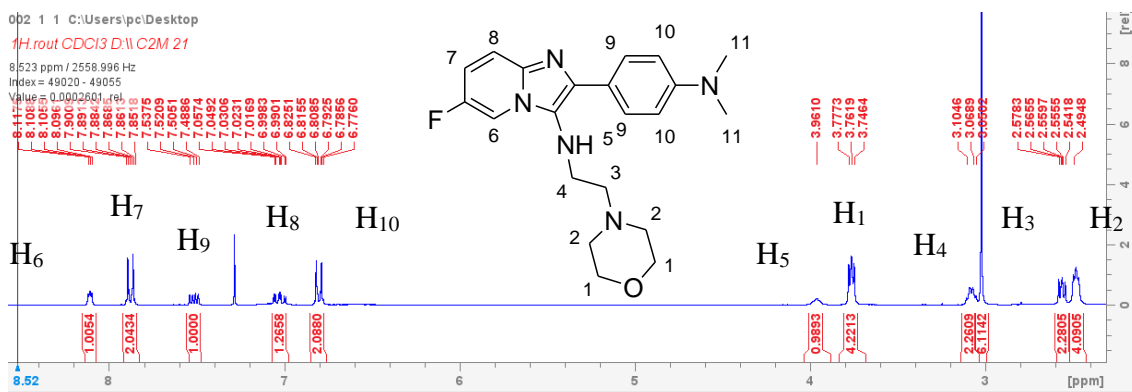
A. IR spectrum for compound 86

SAMPLE INFORMATION			
Sample Name:	osama002	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	2023-09-05 2:49:22 PM IST
Vial:	1	Acq. Method:	nawaf 1
Injection #:	1	Date Processed:	2023-09-05 3:25:16 PM IST
Injection Volume:	20.00 ul	Channel Name:	2998 Ch1 254nm@1.2nm
Run Time:	35.00 Minutes	Sample Set Name:	

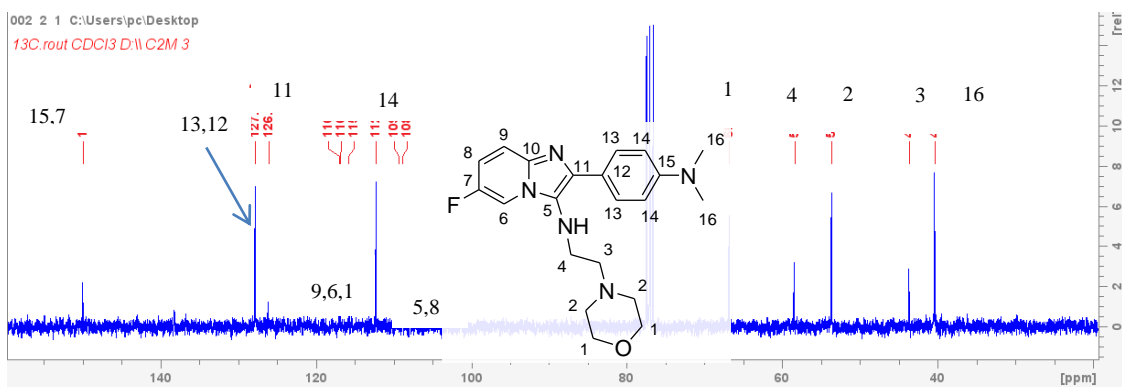


	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	11.668	212447199	100.00	3088955	100.00

B. HPLC chromatogram of 86



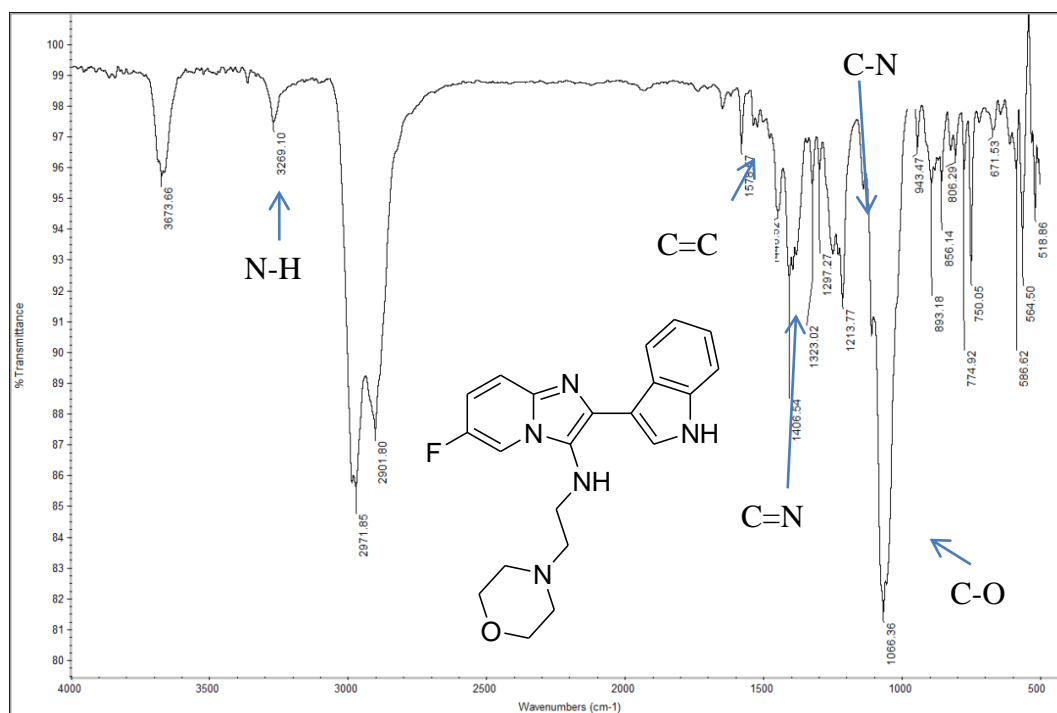
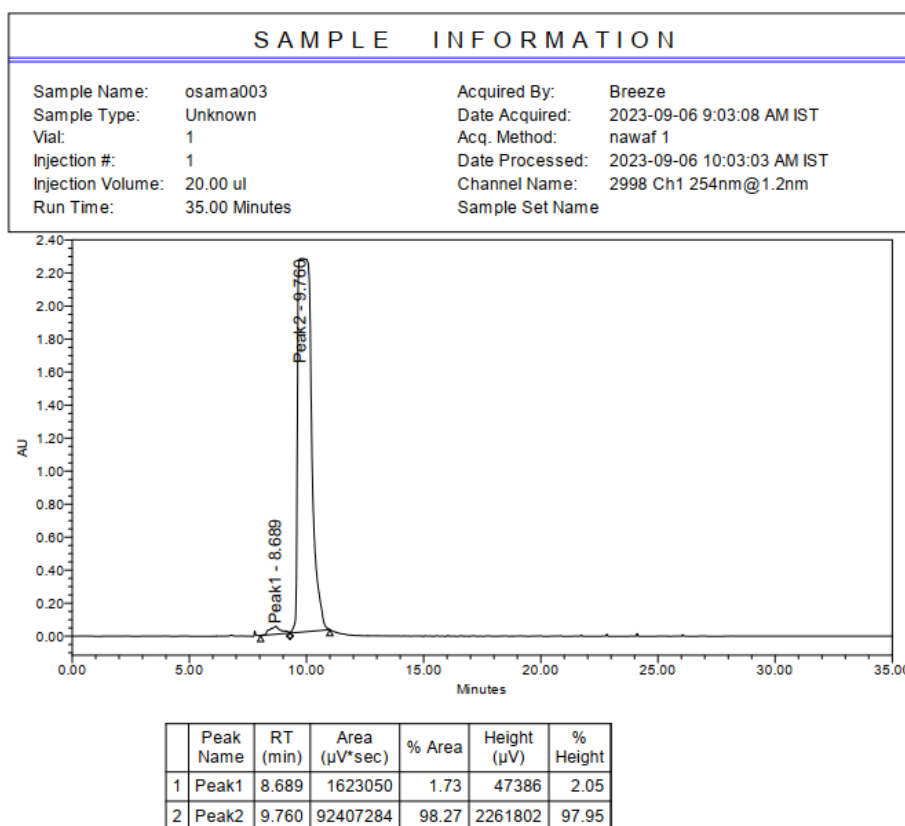
C. ^1H NMR spectrum for compound 86

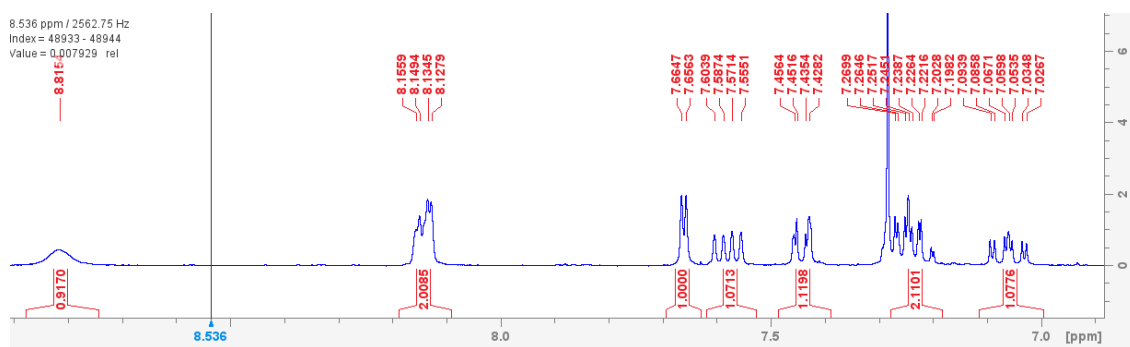
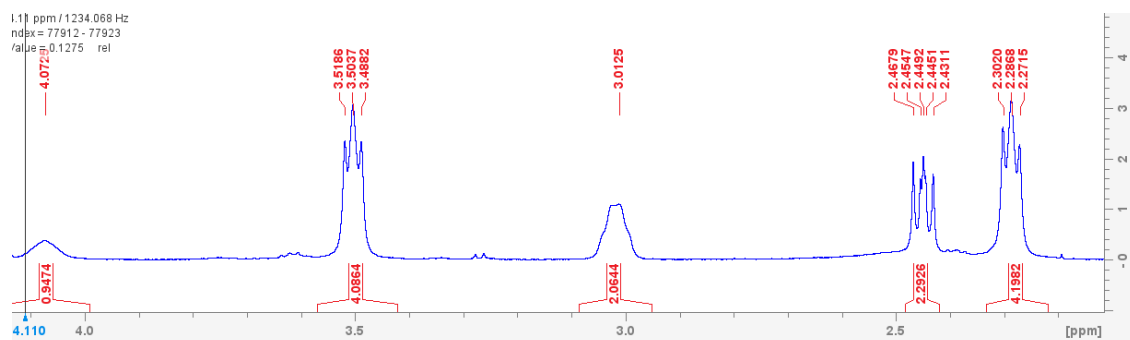
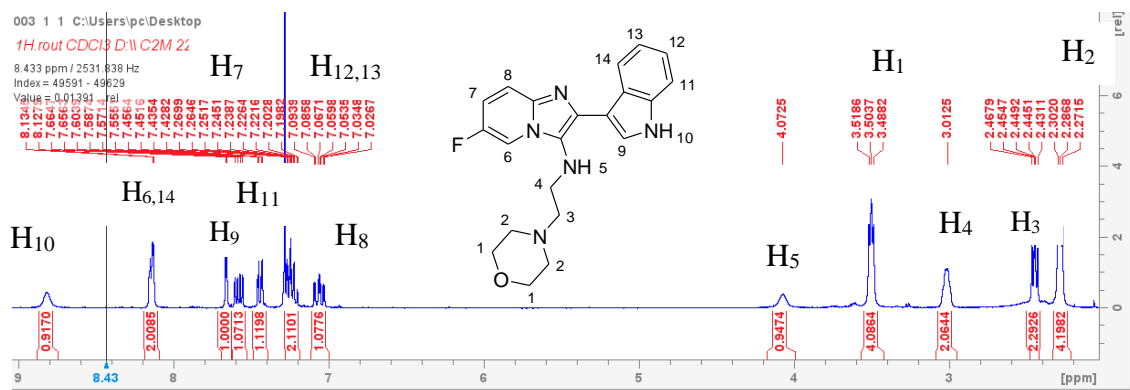


D. ^{13}C NMR spectrum for compound 86

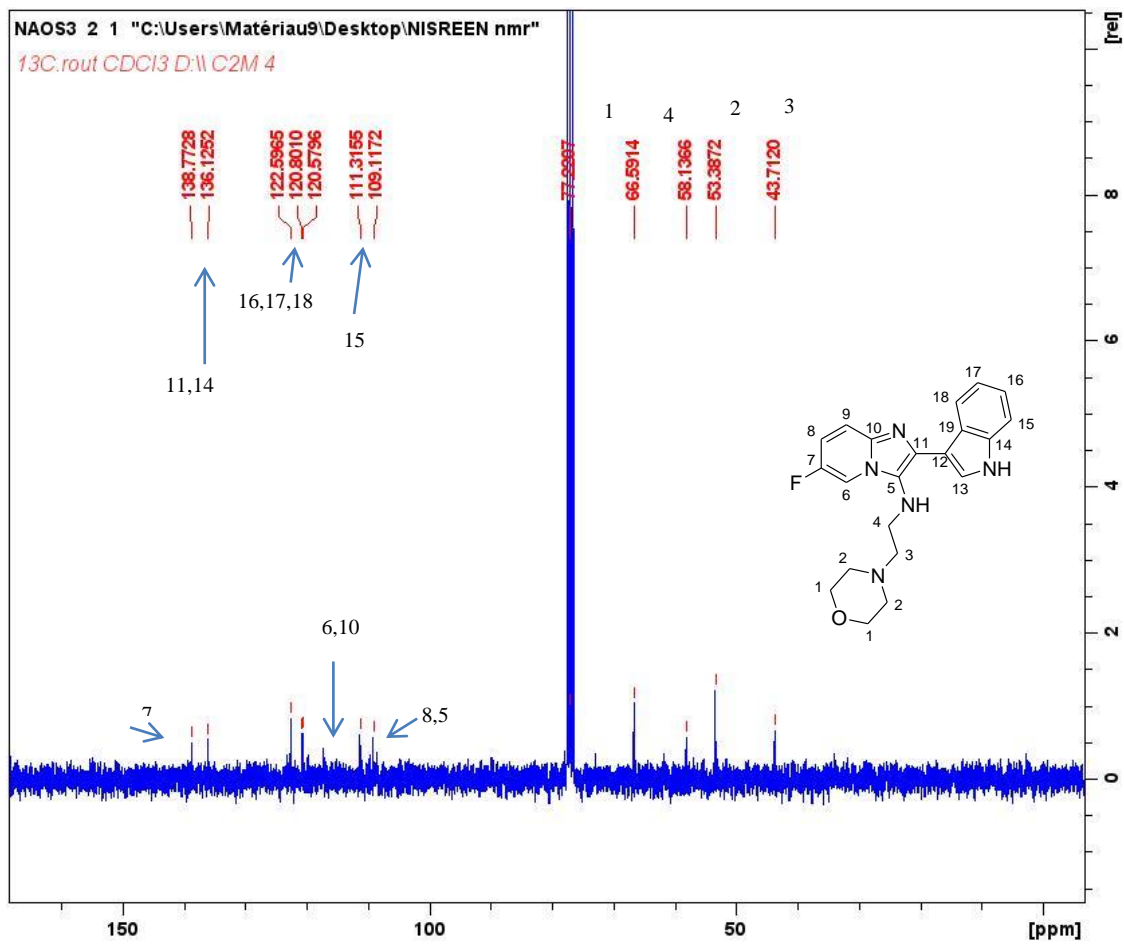
Figure 87

IR spectra, HPLC chromatograms, ^1H NMR spectra, and ^{13}C NMR spectra for compound 87

**A. IR spectrum for compound 87****B. HPLC chromatogram of 87**



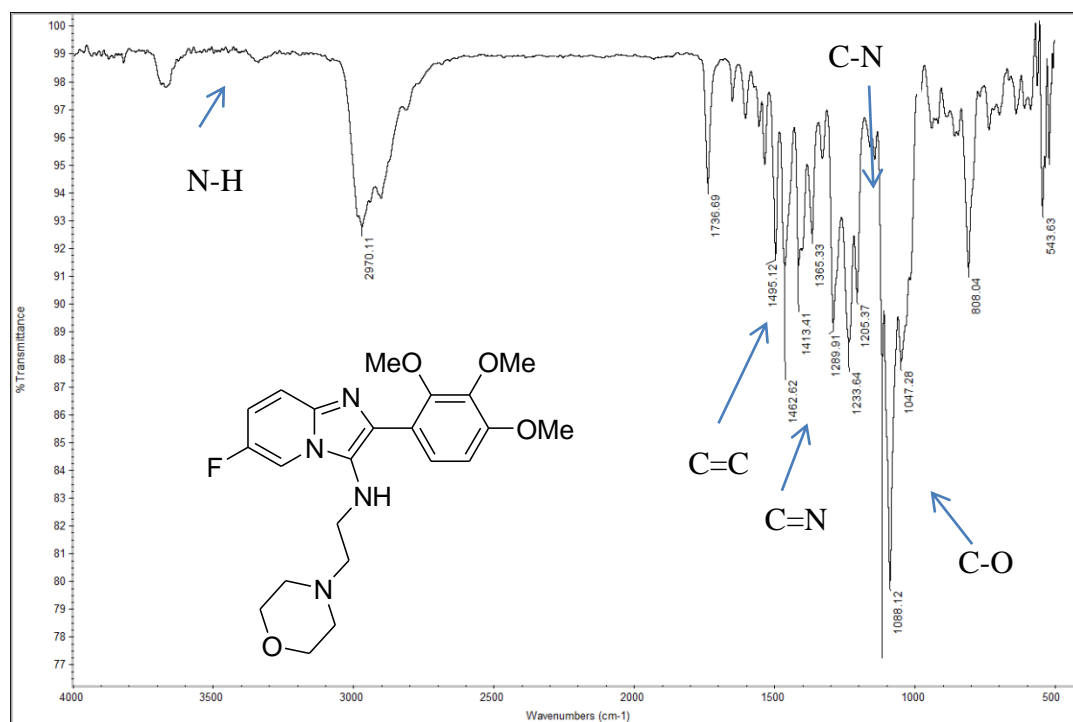
C. ¹H NMR spectrum for compound 87



D. ¹³C NMR spectrum for compound 87

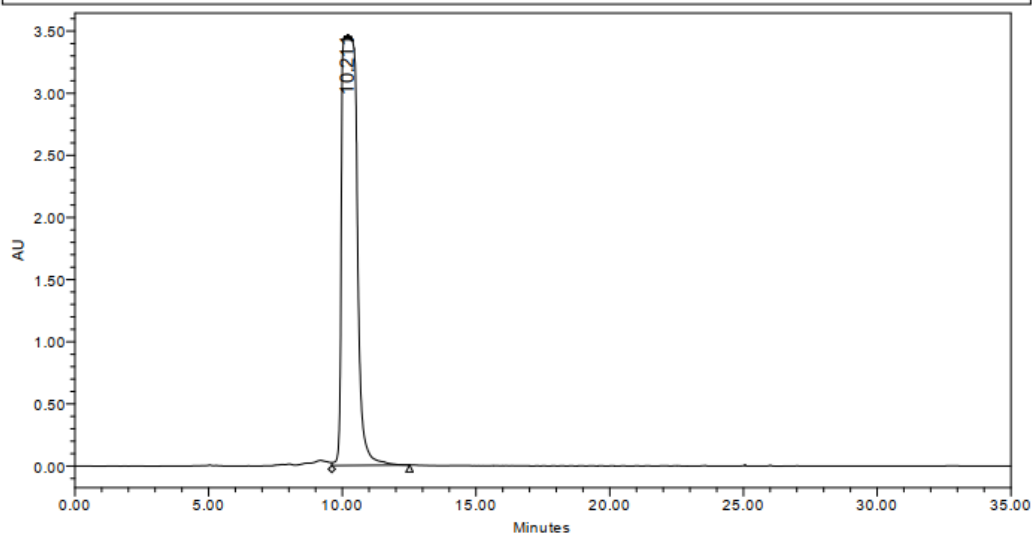
Figure 88

IR spectra, HPLC chromatograms, ^1H NMR spectra, and ^{13}C NMR spectra for compound 88



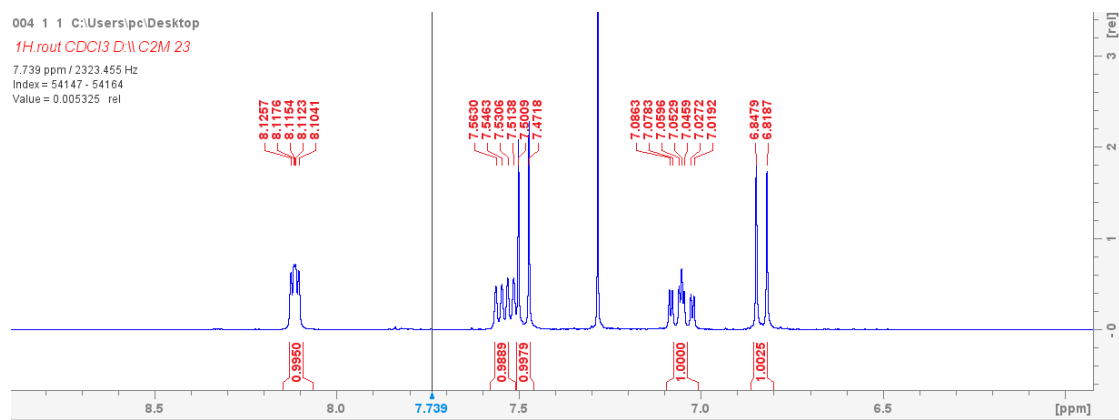
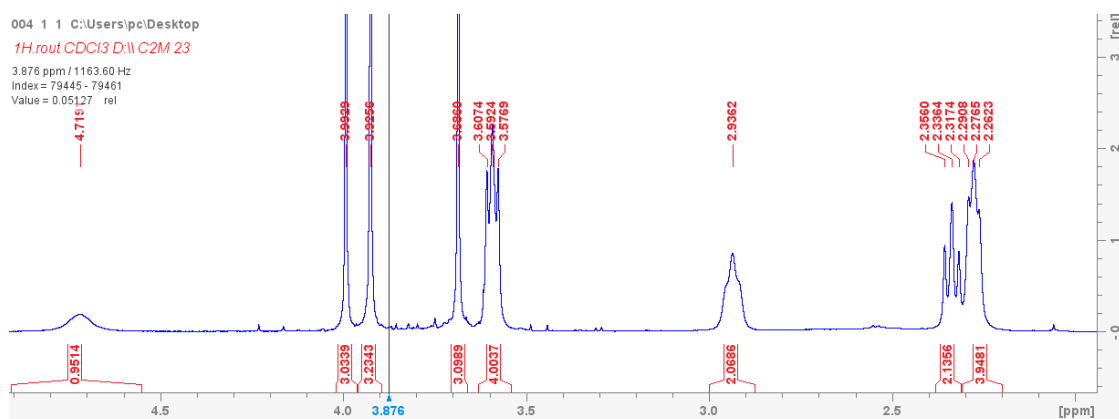
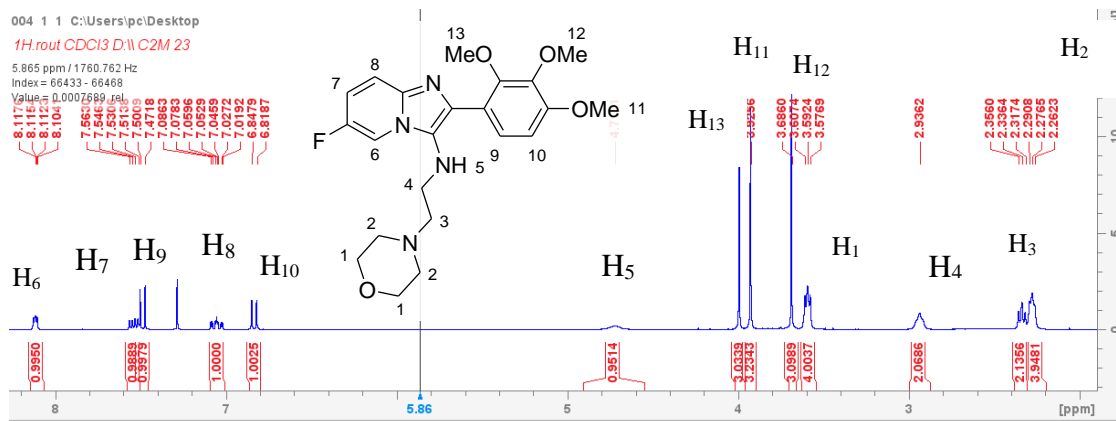
A. IR spectrum for compound 88

Sample Name:	osama004	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	2023-09-06 10:01:47 AM IST
Vial:	1	Acq. Method:	nawaf 1
Injection #:	2	Date Processed:	2023-09-06 10:54:37 AM IST
Injection Volume:	20.00 ul	Channel Name:	2998 Ch1 254nm@1.2nm
Run Time:	35.00 Minutes	Sample Set Name:	

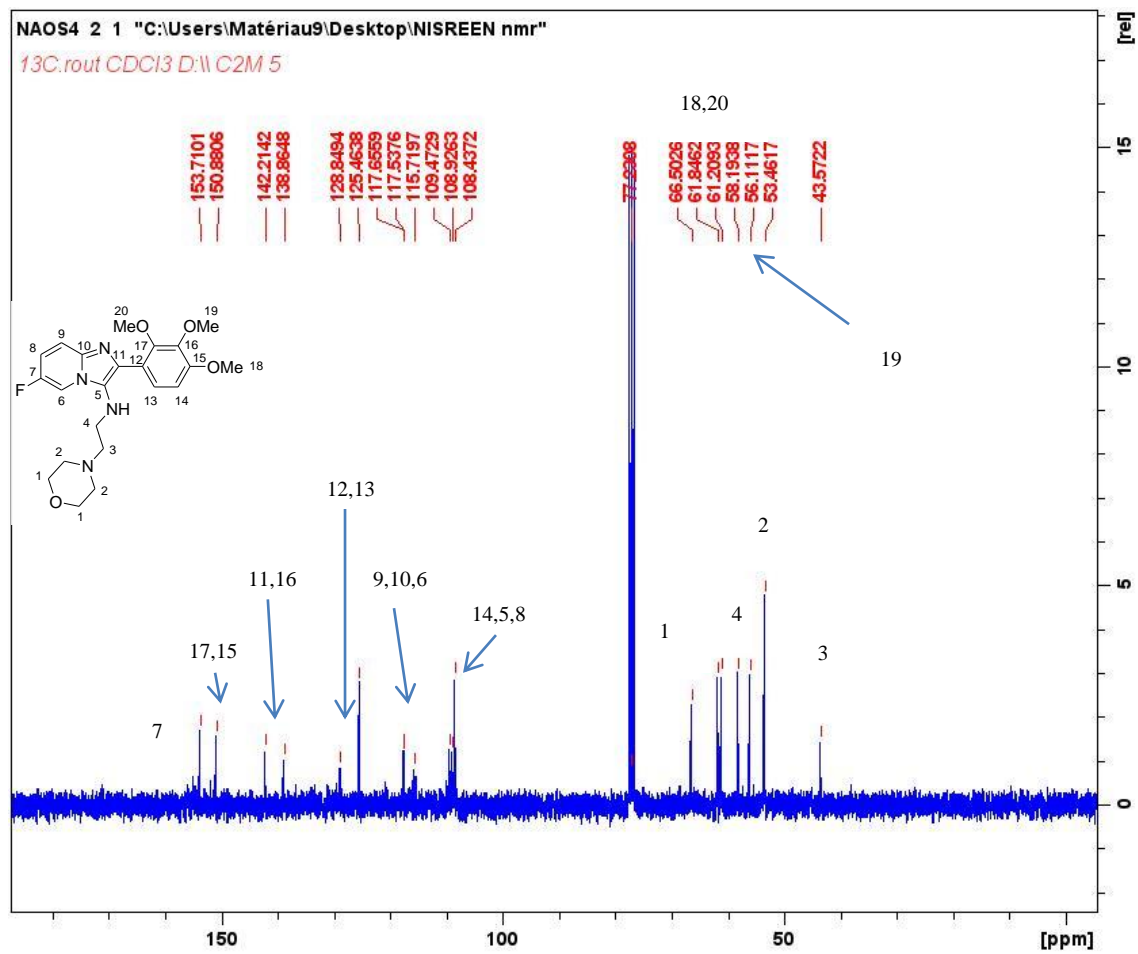


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	10.211	138579982	100.00	3465374	100.00

B. HPLC chromatogram of 88



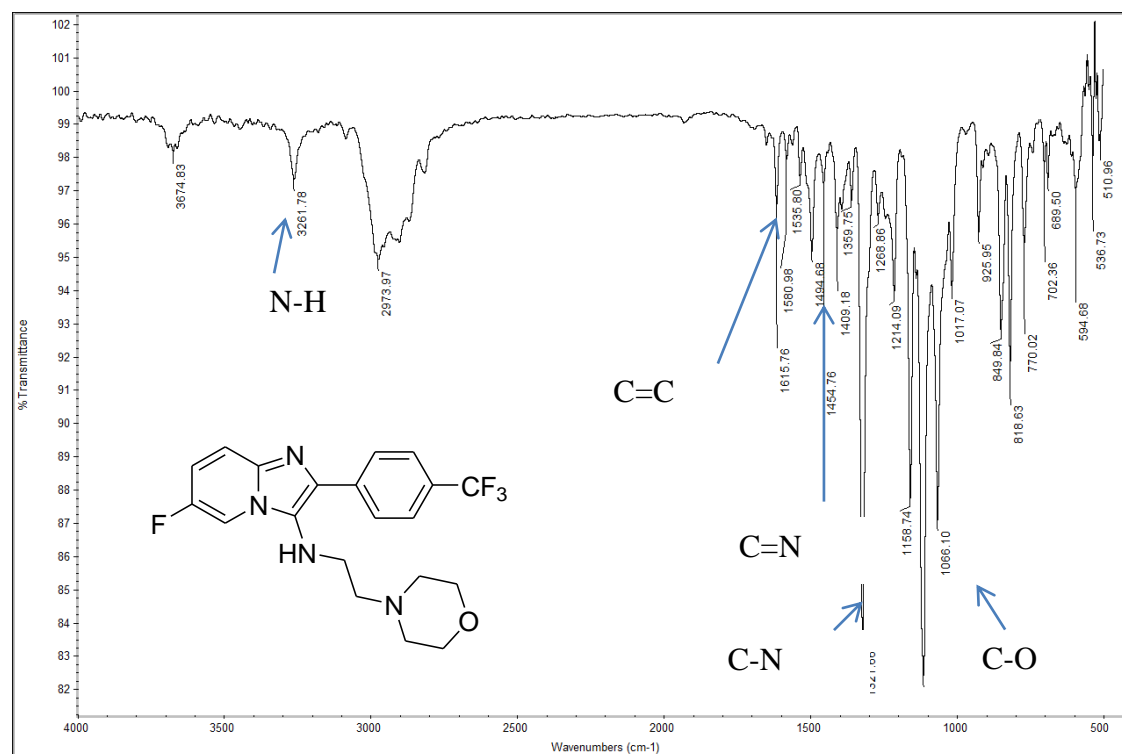
C. ¹H NMR spectrum for compound 88



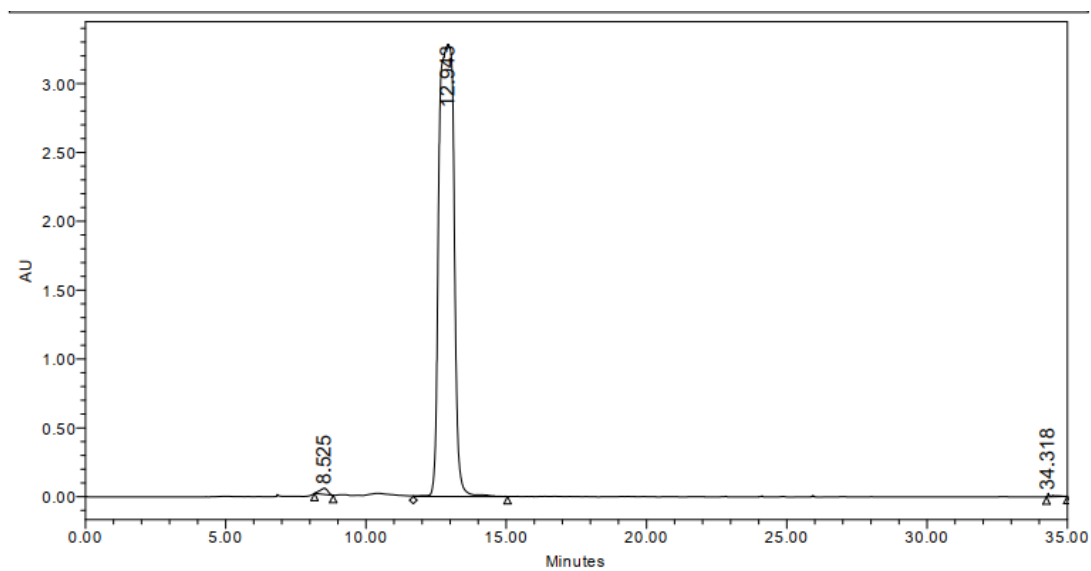
D. ^{13}C NMR spectrum for compound 88

Figure 89

IR spectra, HPLC chromatograms, ^1H NMR spectra, and ^{13}C NMR spectra for compound 89

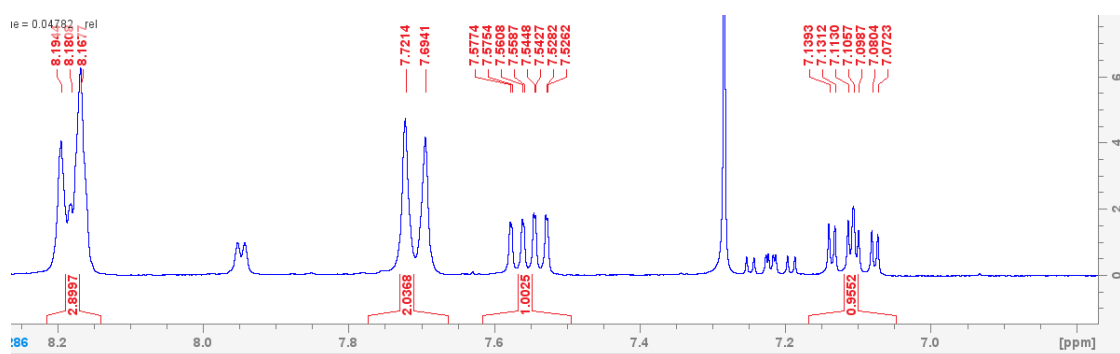
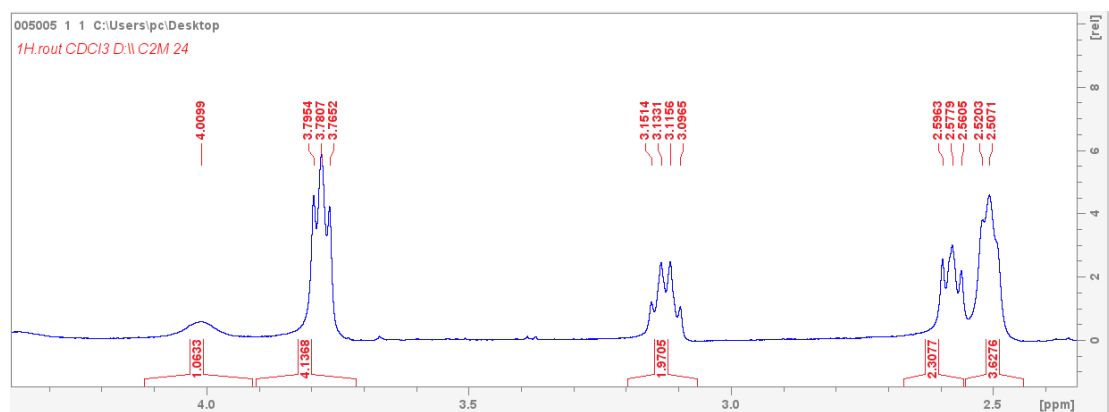
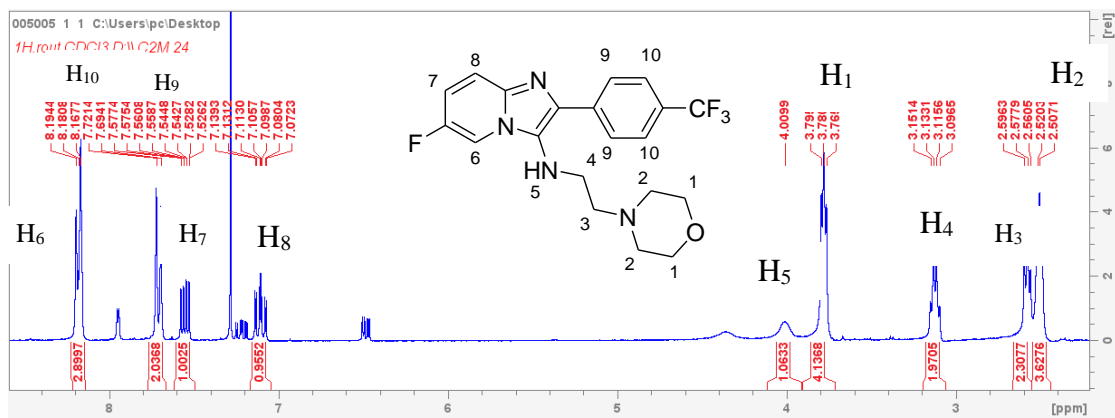


A. IR spectrum for compound 89

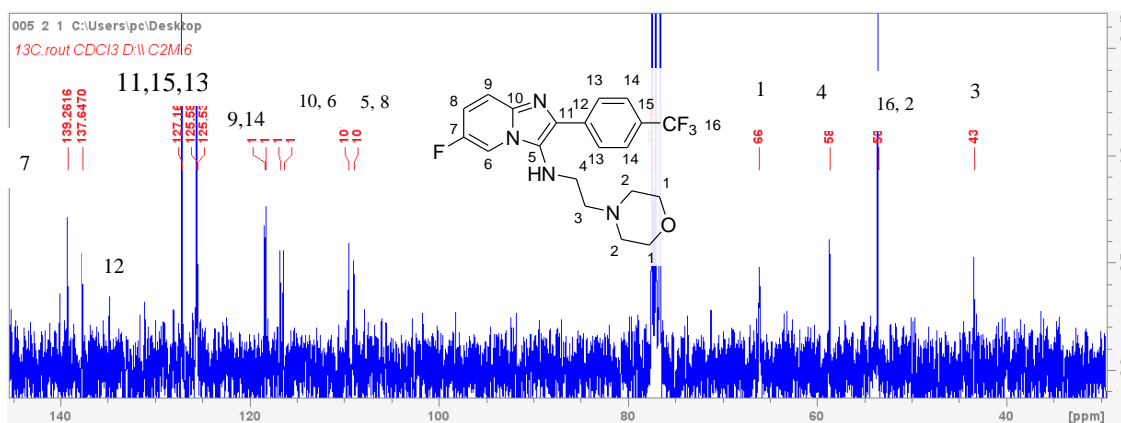


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	8.525	872727	0.70	44332	1.32
2	12.943	123439770	99.12	3282582	97.94
3	34.318	220314	0.18	24594	0.73

B. HPLC chromatogram of 89



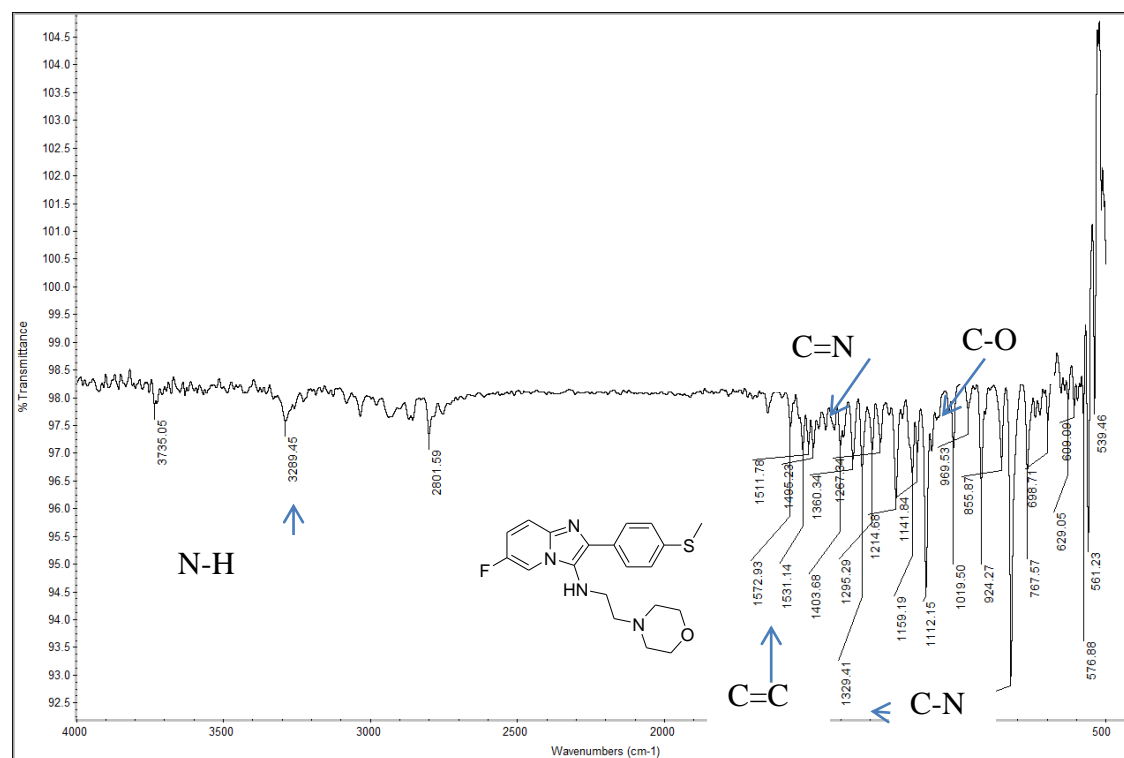
C. ^1H NMR spectrum for compound 89



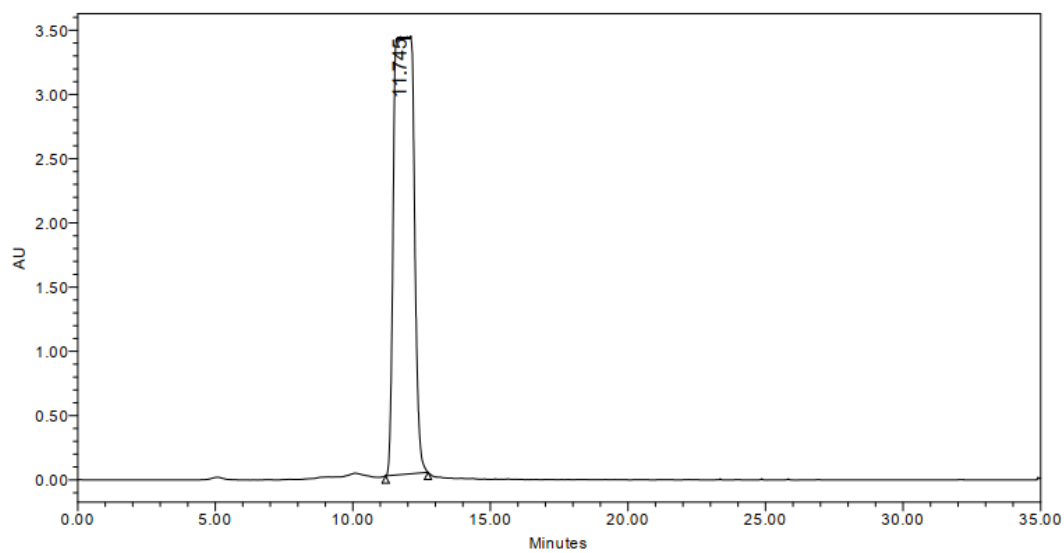
D. ^{13}C NMR spectrum for compound 89

Figure 90

IR spectra, HPLC chromatograms, ^1H NMR spectra, and ^{13}C NMR spectra for compound 90



A. IR spectrum for compound 90

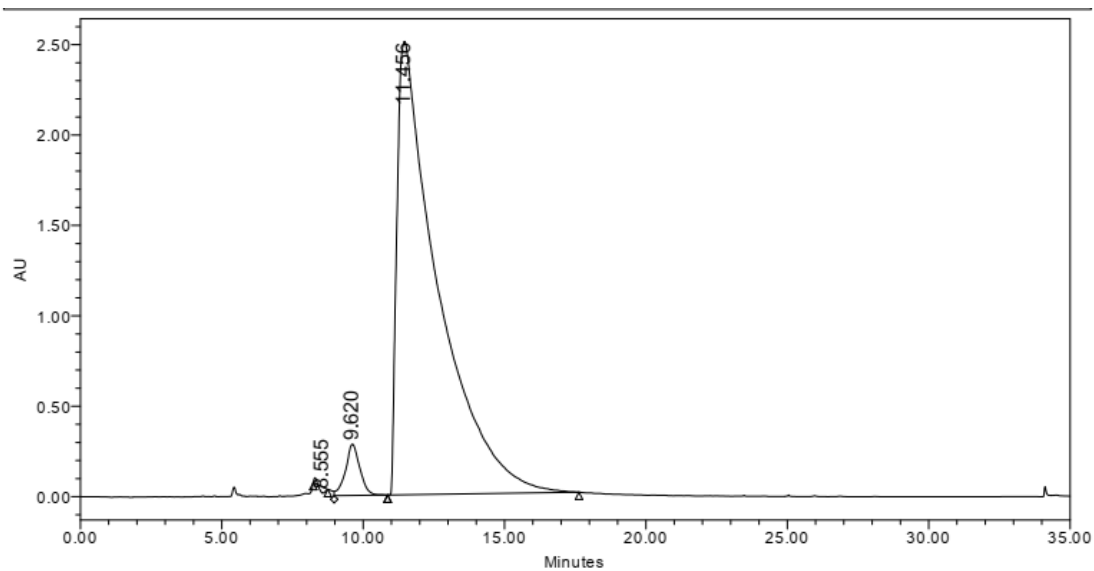


	RT (min)	Area ($\mu\text{V}\cdot\text{sec}$)	% Area	Height (μV)	% Height
1	11.745	171888825	100.00	3408617	100.00

B. HPLC chromatogram of 90

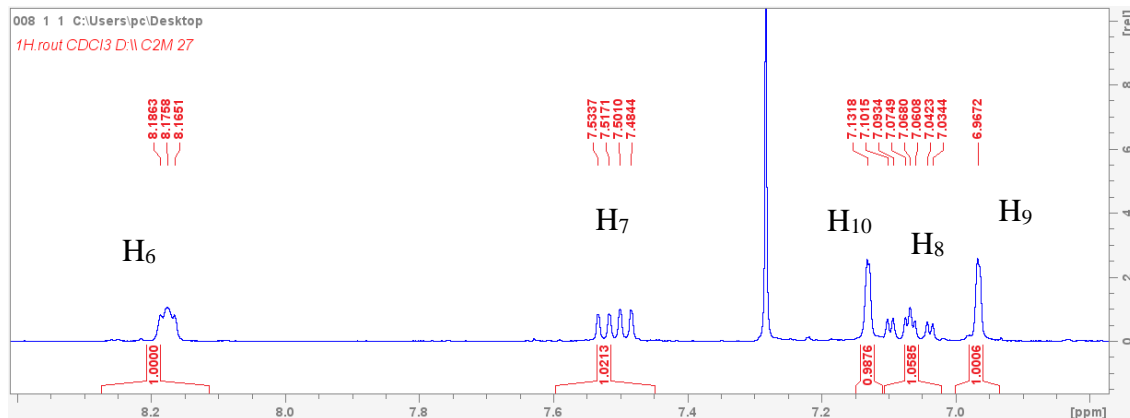
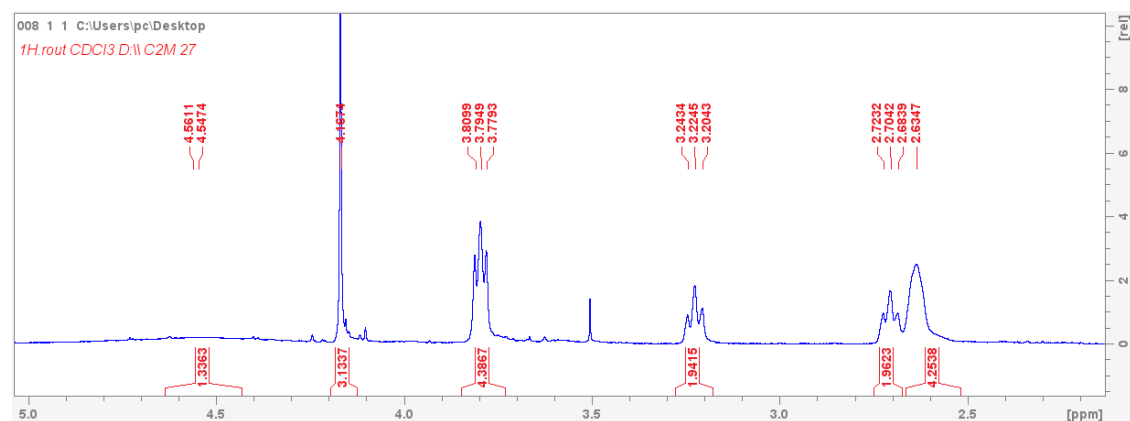
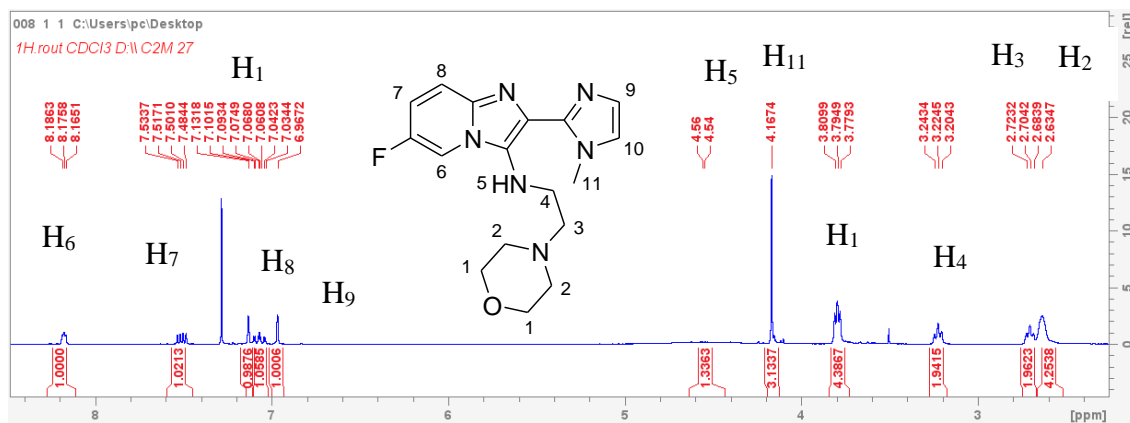
Figure 91

IR spectra, HPLC chromatograms, ¹H NMR spectra, and ¹³C NMR spectra for compound 91

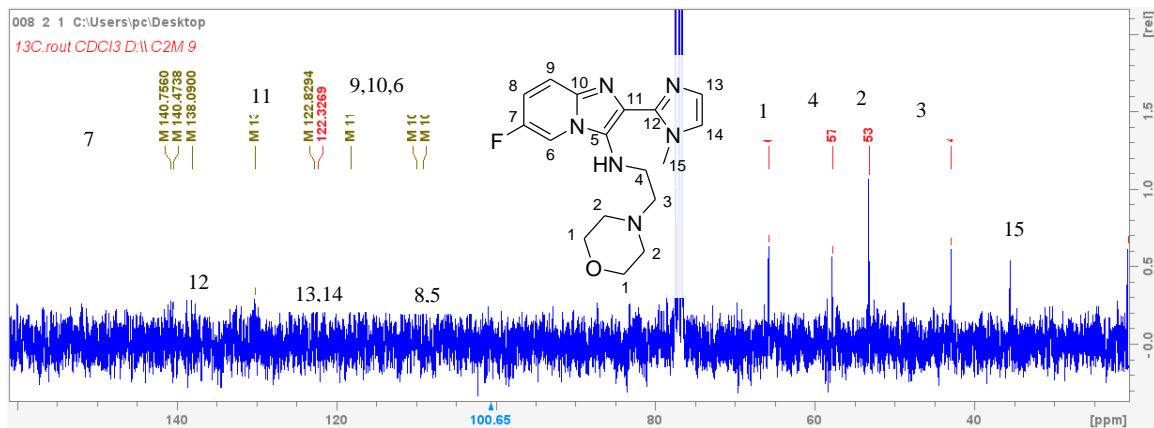
A

	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	8.555	610594	0.23	-33836	1.20
2	9.620	9959269	3.81	282194	10.00
3	11.456	250664129	95.95	2506074	88.80

B. HPLC chromatogram of compound 91



C. ^1H NMR spectrum for compound 91



D. ^{13}C NMR spectrum for compound 91

Appendix B

MIC and MBC for synthetic compounds

Figure 92

Antibacterial activity of the eight tested compounds against five bacterial isolates using the micro-broth dilution method; (MIC) minimum inhibitory concentration ($\mu\text{g/mL}$)

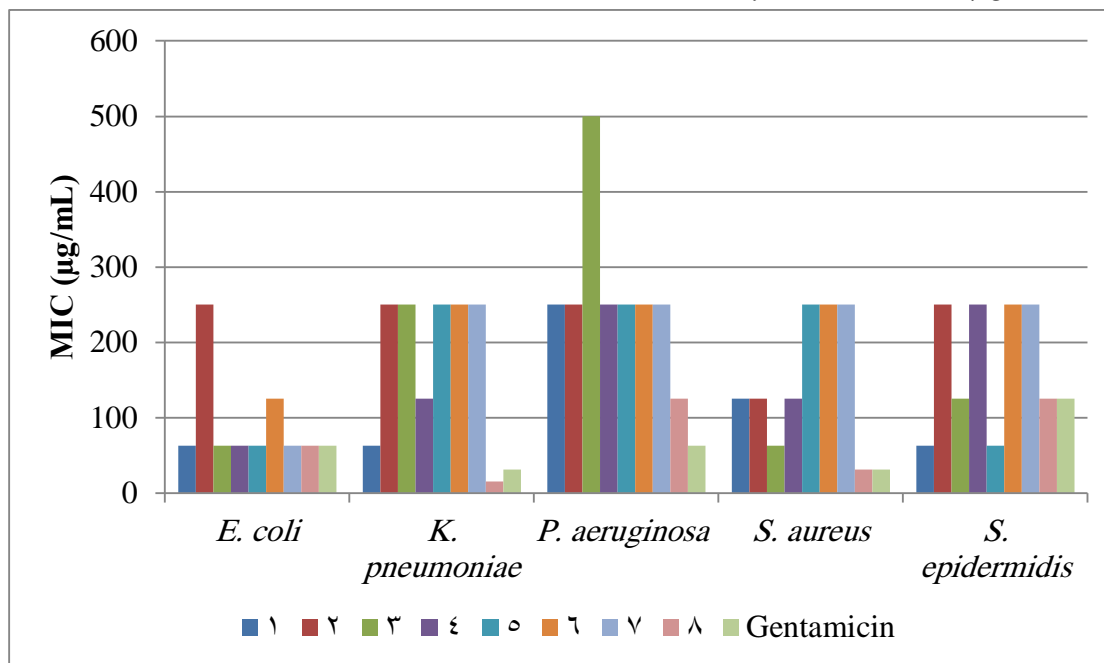
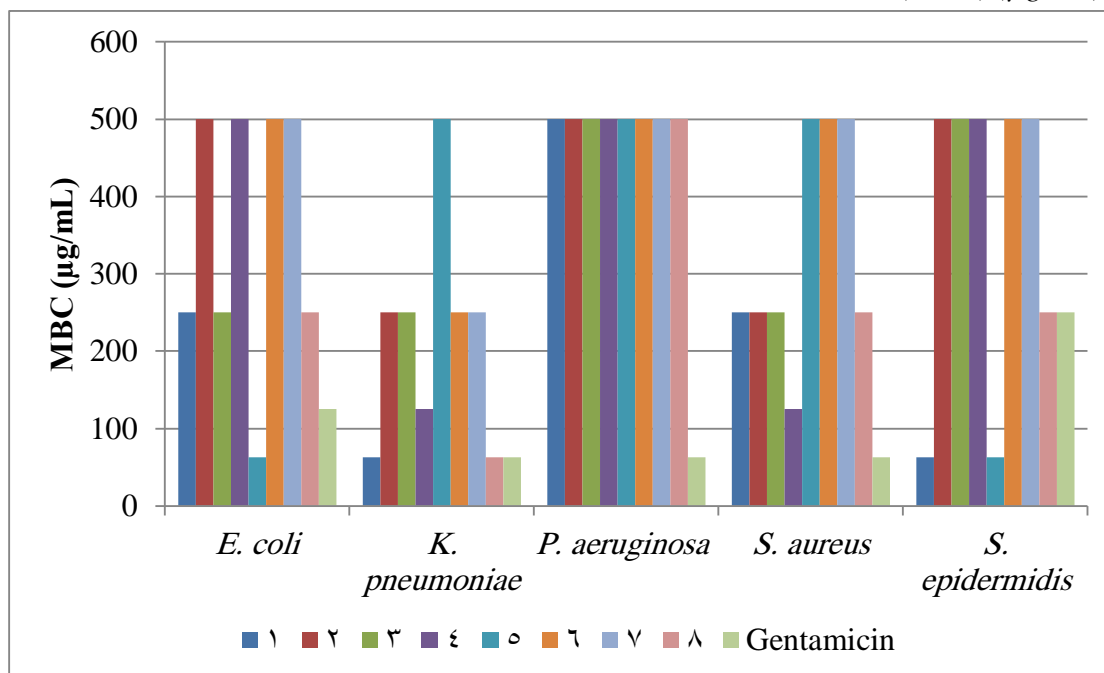


Figure 93

Antibacterial activity of the eight tested compounds against five bacterial isolates using the micro-broth dilution method; minimum bactericidal concentration (MBC) ($\mu\text{g/mL}$)

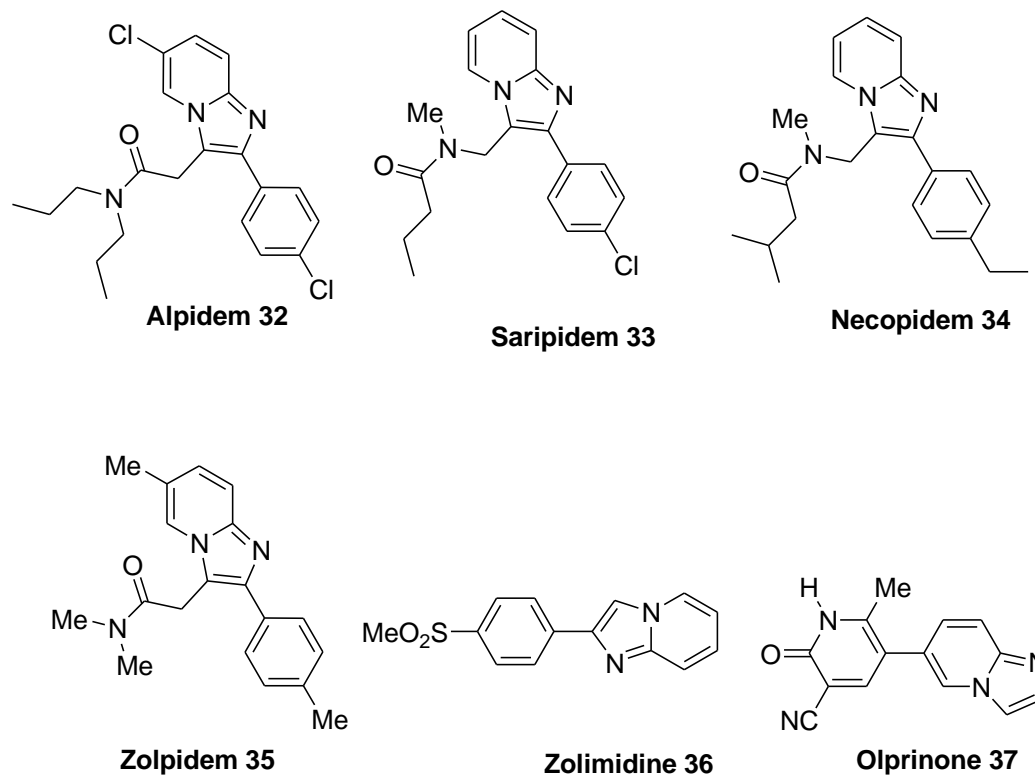


Appendix C

List of Figures and Schemes

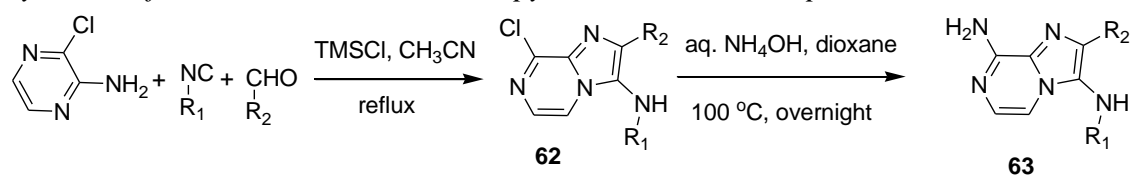
Figure 1.3

Commercially available drug (32-37) of fused imidazo heterocyclic scaffolds



Scheme 1.8

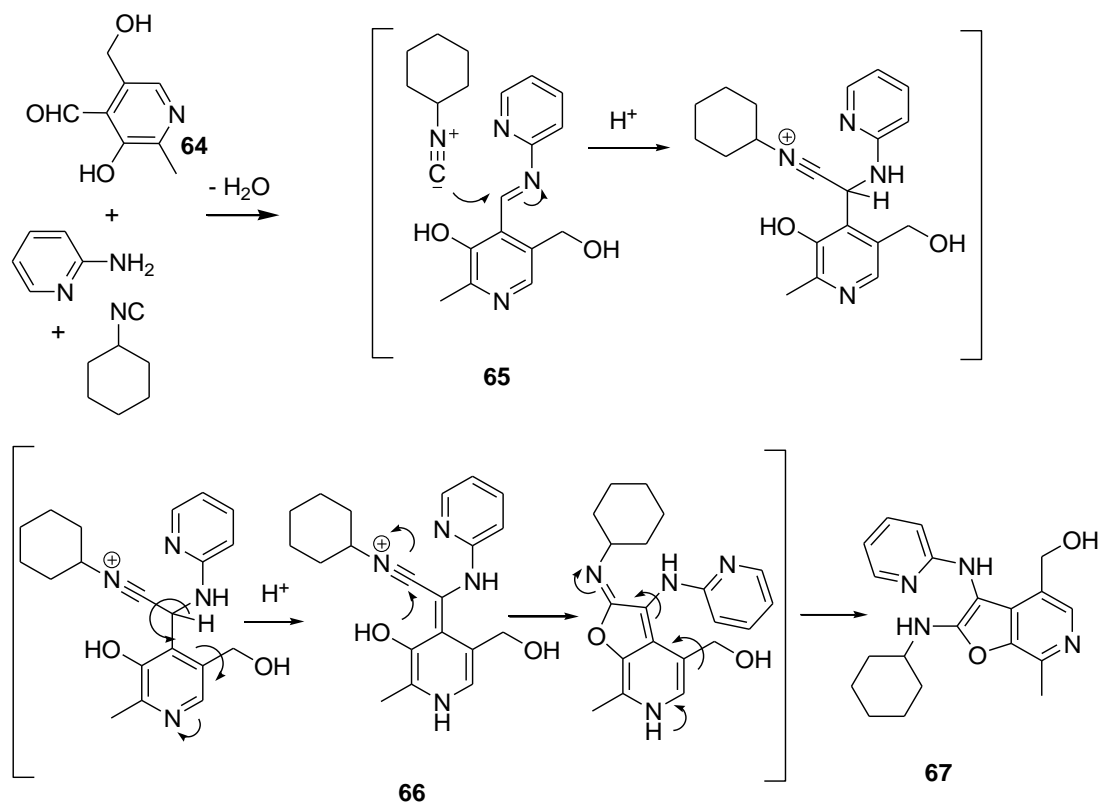
Synthesis of 3,8-diaminoimidazo[1,2-a]pyrazines 63 in two steps



R_1 = tert-butyl, cyclohexyl; R_2 = C_6H_4 , biphenyl, 4-Cl- C_6H_4 , 4- NO_2 - C_6H_4

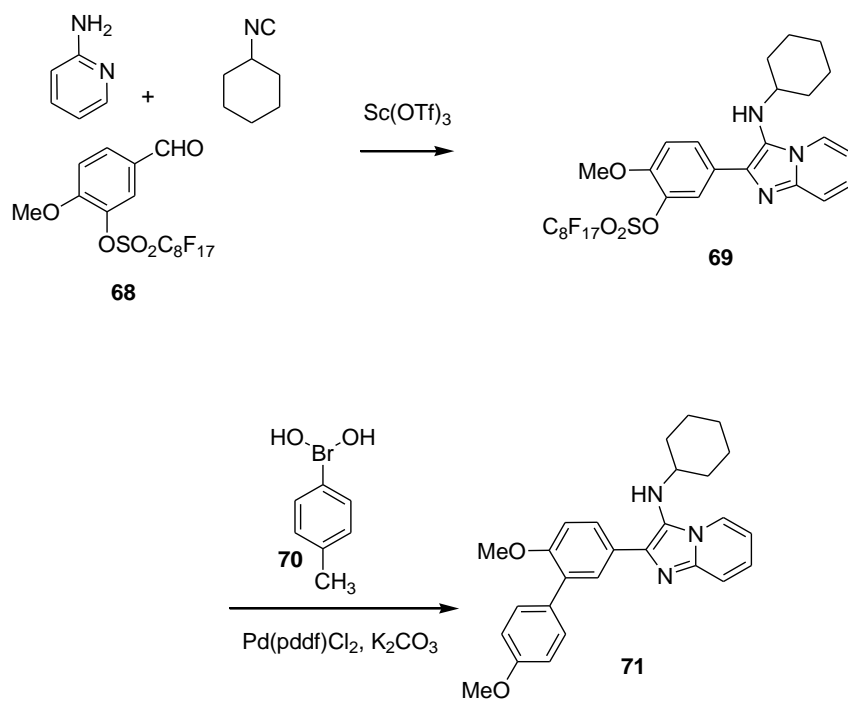
Scheme 1.9

Synthesis mechanism proposed furo[2,3-*c*]pyridines 67



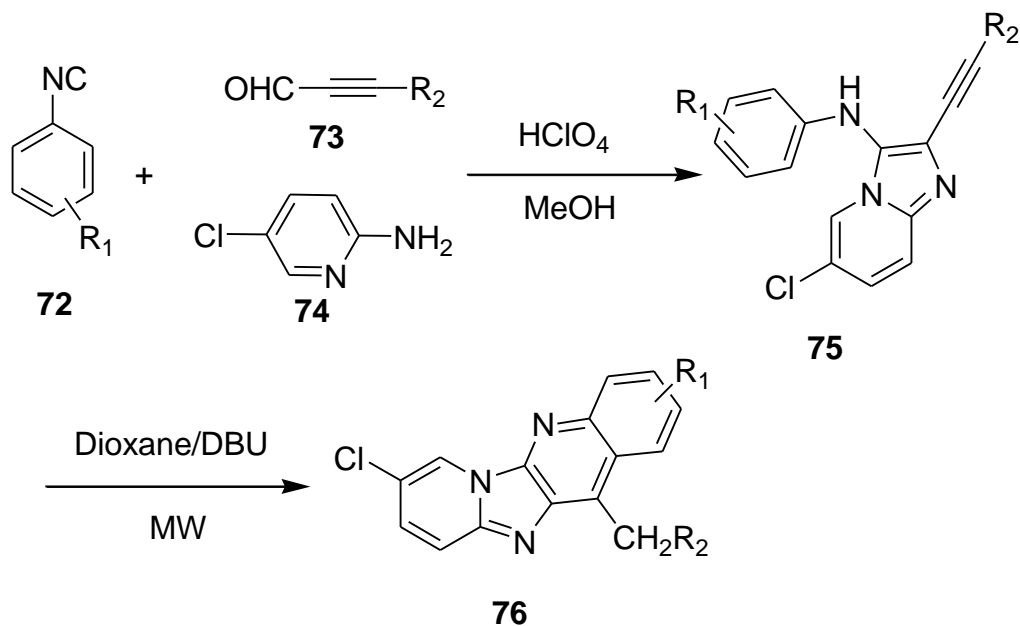
Scheme 1.10

Synthesis of 3-aminoimidazo[1,2-*a*]pyrazines 71



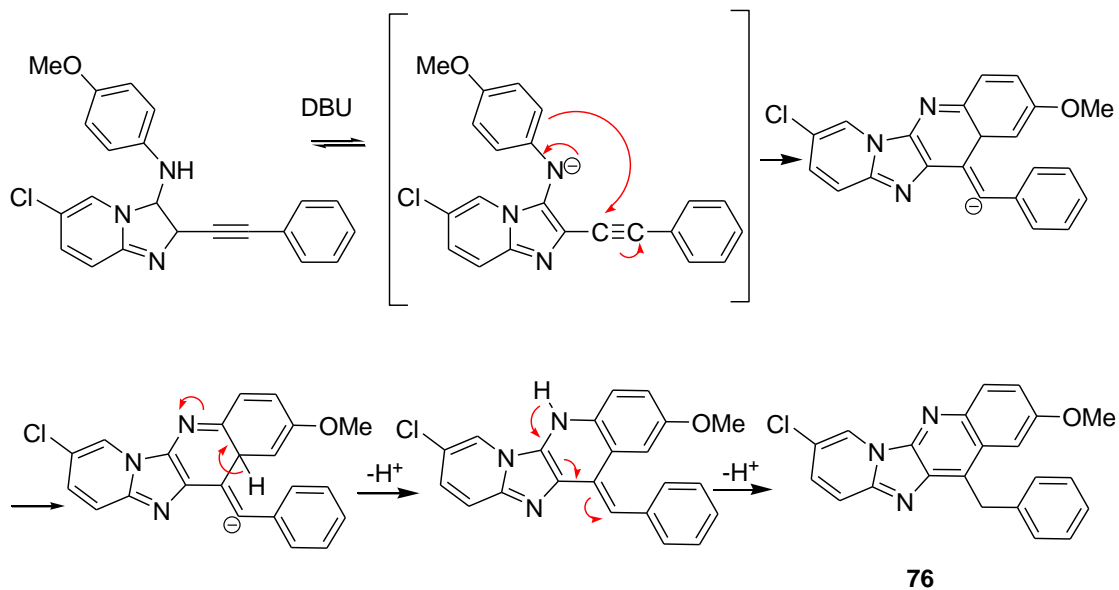
Scheme 1.11

Production of pyrido[2, 1: 2, 3]imidazo[4,5-*b*]quinolones **76** in two steps using various propargyl aldehydes **73**



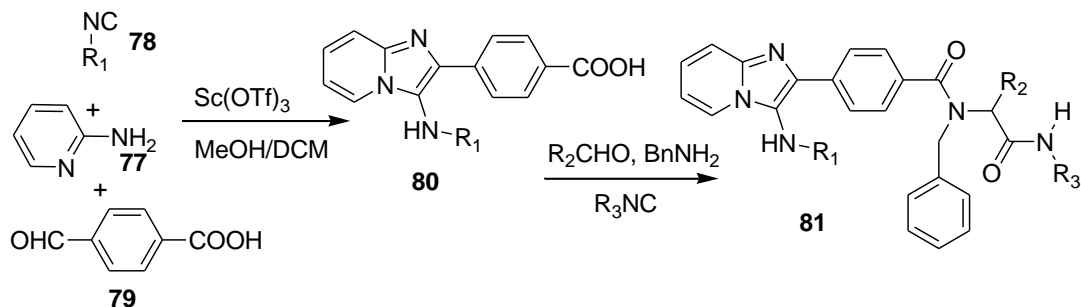
Scheme 1.12

Proposed mechanism for the synthesis of pyrido[2,1:2,3]imidazo[4,5-*b*]quinolones **76**



Scheme 1.13

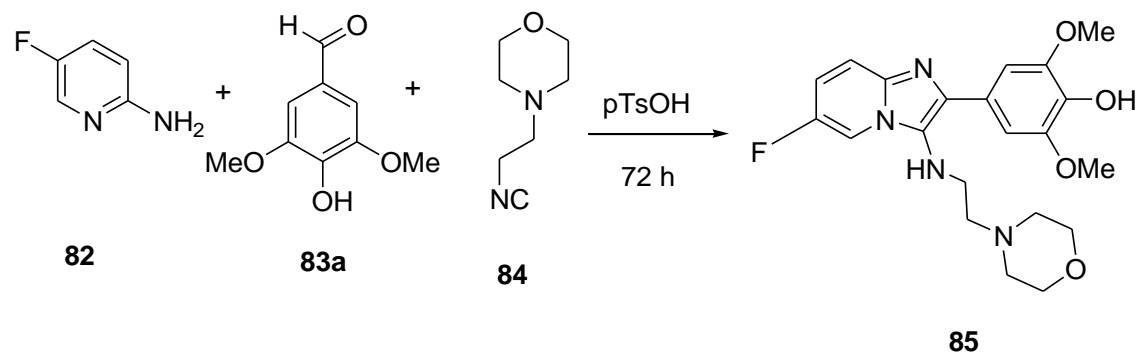
The synthesis of imidazopyridines **81** with several substituents is achieved by the combination of the GBB-3CR and Ugi reactions



$\text{R}_1 = \text{tert-butyl}$, Bn ; $\text{R}_2 = \text{CH}(\text{CH}_3)_2$, $4\text{-F-C}_6\text{H}_4$, Pyridine; $\text{R}_3 = \text{tert-butyl}$, Bn , $\text{CH}_2\text{COOC}_2\text{H}_5$

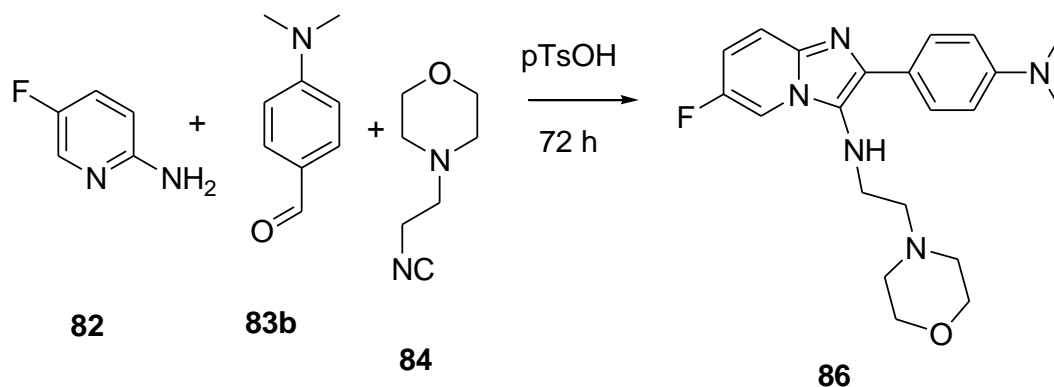
Scheme 2.1

The reaction of 2-amino-5-fluoropyridine **82** with syringaldehyde **83a** and 3-morpholinopropionitrile **84**



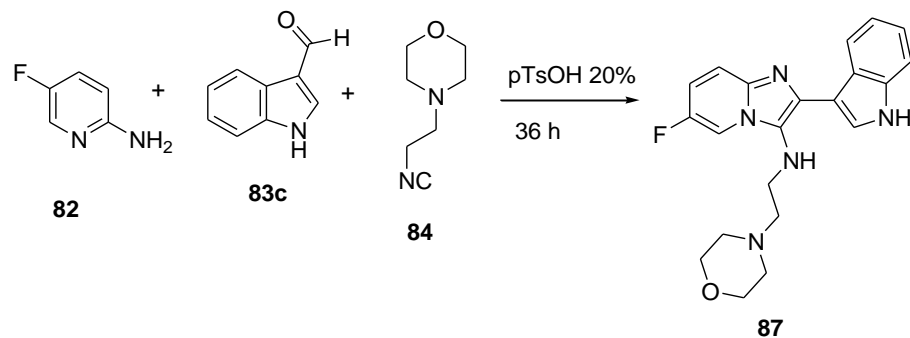
Scheme 2.2

The reaction of 2-amino-5-fluoropyridine **82** with 4-dimethylaminobenzaldehyde **83b** and 3-morpholinopropionitrile **84**



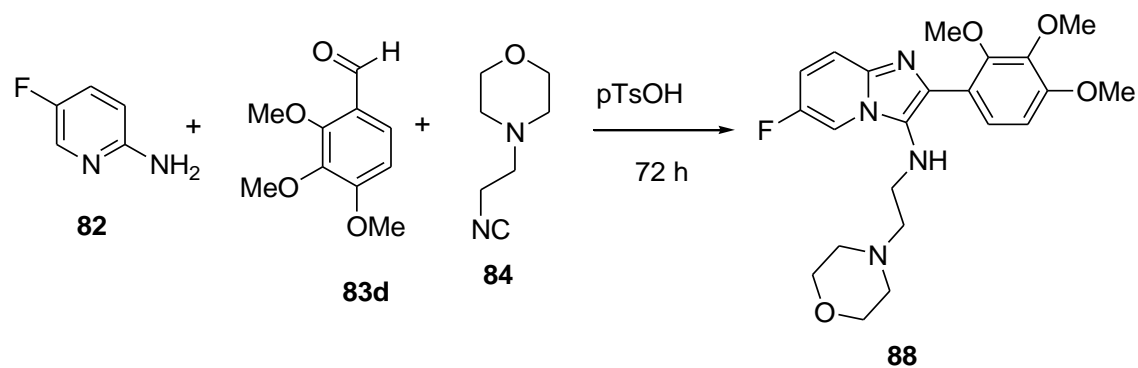
Scheme 2.3

The reaction of 2-amino-5-fluoropyridine **82** with Indole-3-carboxaldehyde **83c** and 3-morpholinopropionitrile **84**



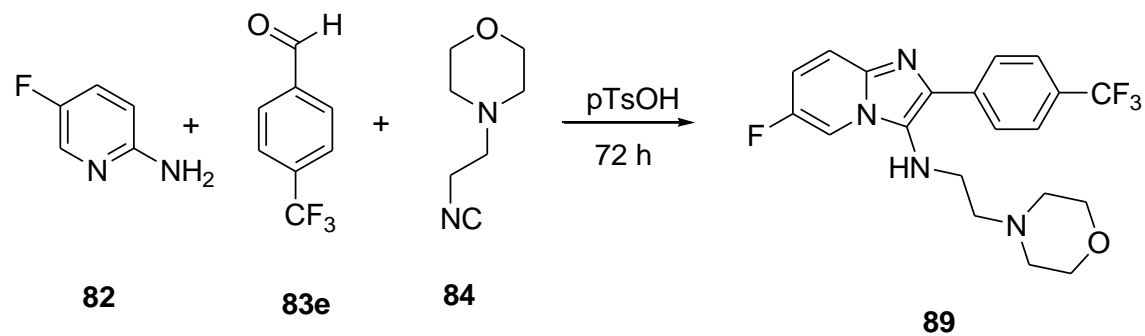
Scheme 2.4

The reaction of 2-amino-5-fluoropyridine **82** with 2,3,4-Trimethoxybenzaldehyde **83d** and 3-morpholinopropionitrile **84**



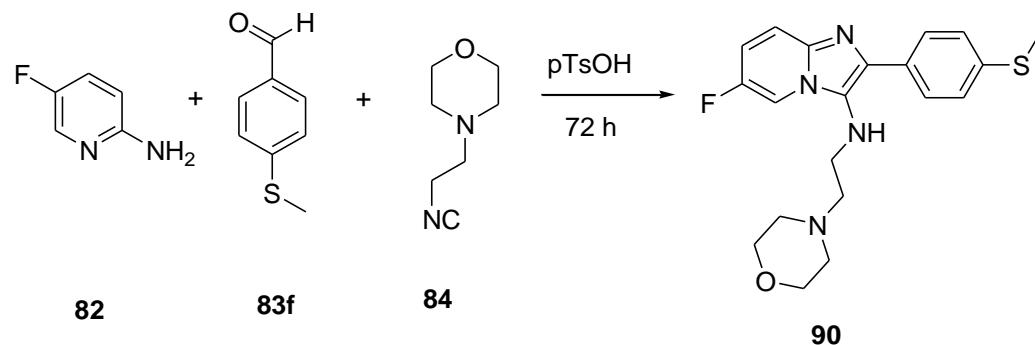
Scheme 2.5

The reaction of 2-amino-5-fluoropyridine **82** with 4-(trifluoromethyl) benzaldehyde **83e** and 3-morpholinopropionitrile **84**



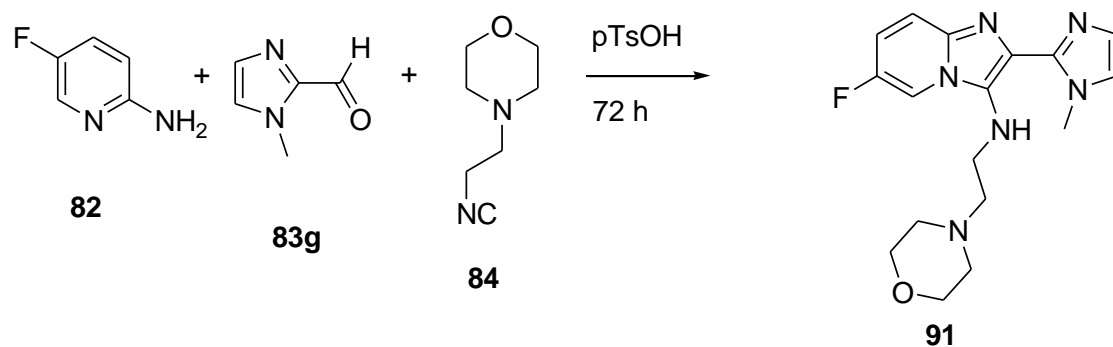
Scheme 2.6

The reaction of 2-amino-5-fluoropyridine **82** with 4-(methylthio) benzaldehyde **83f** and 3-morpholinopropionitrile **84**



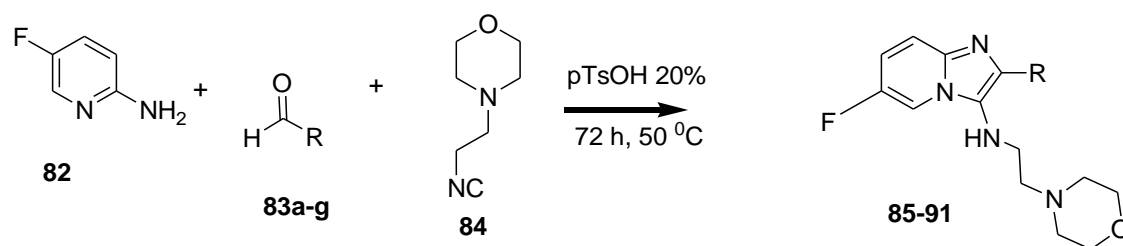
Scheme 2.7

The reaction of 2-amino-5-fluoropyridine **82** with 1-Methyl-2-imidazolecarboxaldehyde **83g** and 3-morpholinopropionitrile **84**



Scheme 3.1

The synthesis of 3-aminoimidazo[1,2-a]pyridines using 2-morpholinoethyl isocyanide **84**, 2-amino-5-fluoropyridine **82**, different aldehydes **83a-g**, and pTsOH (PTSA) as a catalyst in an acid environment by a GBB-3CR reaction is described



83a, R= 3,5-Dimethoxy-4-hydroxyphenyl **83b**, R= 4-(Dimethylamino)phenyl
83c, R= 1H-Indole-3- **83d**, R= 2,3,4-Trimethoxyphenyl **83e**, R= 4-(Trifluoromethyl)phenyl
83f, R= 4-(methylthio)phenyl **83g**, R= 1-methyl-1H-imidazole-2-

Scheme 3.2

A mechanistic rationalization for synthesis of 2-(3,5-Dimethoxy-4-hydroxyphenyl)-N-(2-morpholinoethyl)-6-fluoroimidazo[1,2-a]pyridin-3-amine 85

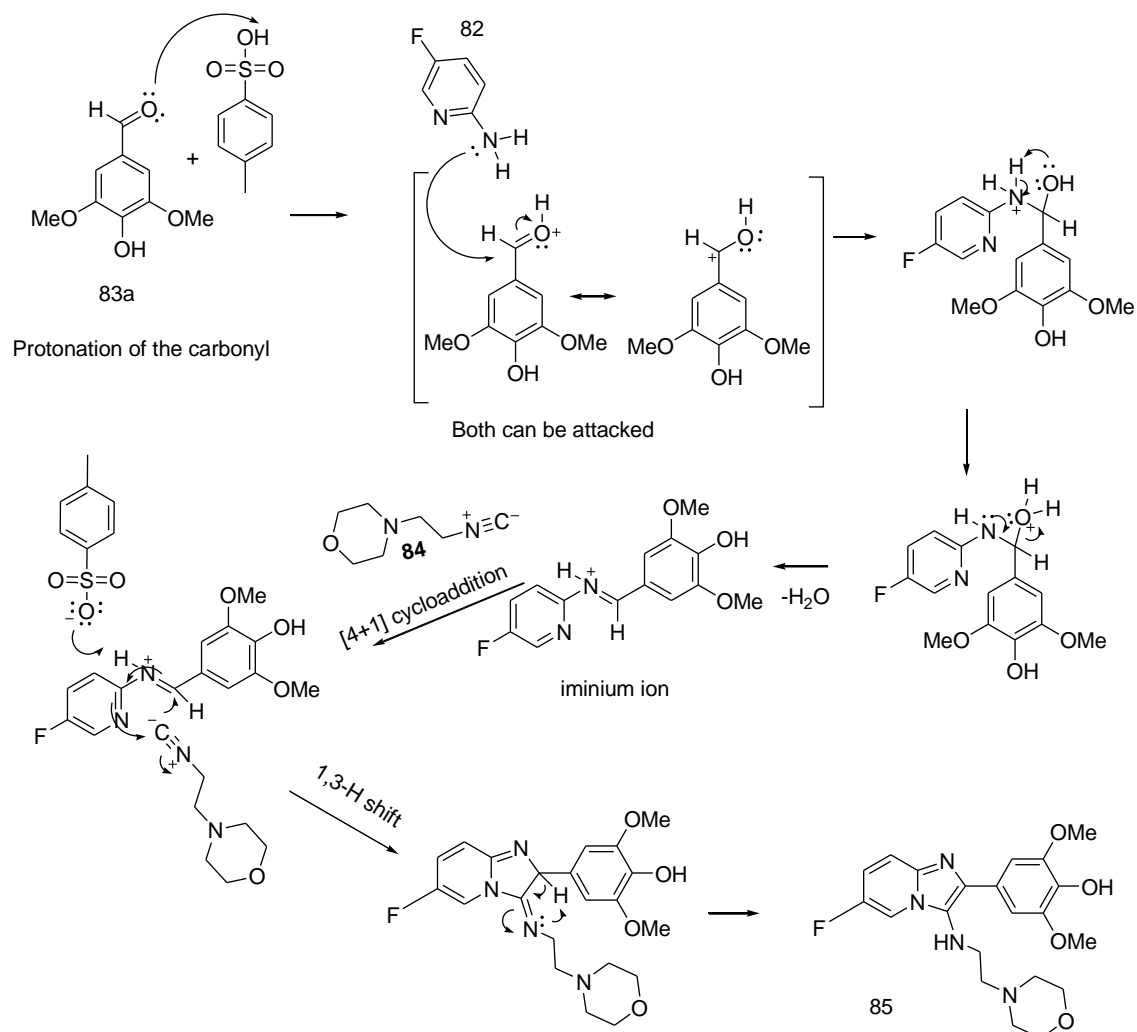
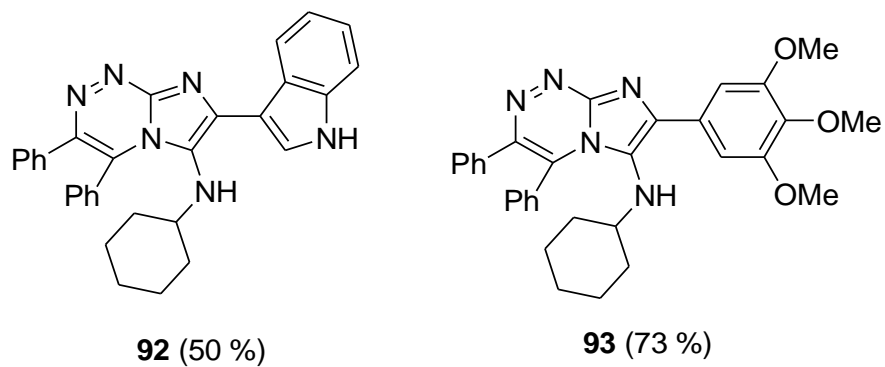


Figure 3.1

Compound 92 contains indole at C-2, and compound 93 contains trimethoxyphenyl at C-2; to compare reactivity with compounds 87 and 88, respectively





جامعة النجاح الوطنية
كلية الدراسات العليا

مشتقات 3-أمينو إيميدازو [1,2-أ] بيريدين: التخليق والأنشطة المضادة للميكروبات

إعداد

اسامة عثمان حمدان دراغمة

إشراف

أ. د. نواف المحاريق

د. نسرين الحج

قدمت هذه الرسالة استكمالاً لمتطلبات الحصول على درجة الماجستير في الكيمياء، من كلية الدراسات العليا، في
جامعة النجاح الوطنية، نابلس - فلسطين.

2024

مشتقات 3-أمينو إيميدازو[1,2-أ]بيريدين: التخليق والأنشطة المضادة للميكروبات

اعداد

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اشراف

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د. نسرين الحاج

الملخص

الخلفية: لا تزال مقاومة مضادات الميكروبات تشكل مشكلة صحية عامة رئيسية على مستوى العالم. وبالتالي، هناك طلب كبير على مضادات الميكروبات الجديدة ذات خصائص النشاط المحسنة. تعد مضادات الميكروبات واحدة من التأثيرات الدوائية العديدة لمركبات لإيميدازو[1,2-أ]بيريدين. هذه المواد النشطة بيولوجياً هي المكونات الرئيسية للعديد من الأدوية العلاجية التي يتم تسويقها على نطاق واسع، مثل الأبيديم وزوليبيديم.

الأهداف: إنشاء مشتقات جديدة من 3-أمينو-6-فلورويميدازو[1,2-أ]بيريدينوتقييم فعاليتها ضد خمس سلالات بكتيرية.

المنهجية: تم استخدام تفاعل جروبي-بلاكبيرن-بيناييم-ثلاثي المكونات (GBB-3CR) أحادي الوعاء في تخليق المركب. تم استخدام العديد من الطرق الطيفية، بما في ذلك الأشعة تحت الحمراء (IR)، والرنين المغناطيسي النووي للبروتون (1H NMR)، والرنين المغناطيسي النووي للكربون-13 (13C NMR)، لتأكيد البنية. كما يستخدم تقييم النقاء تقنية الكروماتوغرافيا السائلة عالية الأداء (HPLC) لتقييم فعالية المركبات ضد *S. aureus* و *S. epidermidis* و *K. pneumonia* و *P. aeruginosa* و *E. coli*، أجريت تجارب بيولوجية على المركبات المنتجة.

النتائج: تم إنتاج المركبات الاصطناعية السبعة (85-91) بنقاء 88-100%. تم التحقق من هذه المركبات (91-85) من حيث صيغتها البنوية باستخدام $^1\text{H NMR}$ و $^{13}\text{C NMR}$ و IR. تشير هذه التقنيات إلى المنتج الطبيعي GBB-3CR. بيولوجيًا، أظهر المركب 91 أفضل سلوك مثبط بين المركبات الأخرى؛ تم تسجيل أقل قيمة MIC (15.625 ميكروجرام / مل) للمركب 91 ضد *E. coli*. علاوة على ذلك، يعمل المركب 91 بشكل أفضل من جنتاميسين ضد *K. pneumoniae*. وقد تم الإبلاغ عن نفس الملاحظة للمركبات 85 و 89 ضد *S. epidermis*. ومن الجدير بالذكر أن المركب 89 في هذه الدراسة يقتل *E. coli* و *S. epidermis* بتركيزات أقل (62.5 ميكروجرام/مل) من المضادات الحيوية جنتاميسين 125 ميكروجرام/مل و 250 ميكروجرام/مل على التوالي. وقد لوحظت نفس الملاحظة للمركب 85 ضد *S. epidermis* بقيمة MBC تبلغ 62.5 ميكروجرام/مل. المركبات 91 و 89 و 85 لها تأثيرات مضادة للبكتيريا جيدة بسبب الاستبدال عند C-2 لـ 3-أمينو-6-فلوروميديازو [1,2-أ] بيريدينات وهي 1-ميثيل إيميدازول، و بارا-تريفلوروميثيل فينيل، و 3،5-ديميثوكسي-4-هيدروكسي فينيل، على التوالي.

الاستنتاجات: تم استخدام عملية بسيطة وفعالة من حيث التكلفة في خطوة واحدة لإنشاء مواد كيميائية حيوية جديدة واعدة. قد توفر الأبحاث الإضافية حول هذه المشتقات مركبات أكثر فعالية تظهر وعدًا كخيارات علاجية مضادة للبكتيريا مبتكرة.

الكلمات الرئيسية: 3-أمينوإيميدازو[1,2-أ]بيريدين، تفاعل جروبيكي-بلاكبيرن-بينياميه ثلاثي المكونات، التفاعلات متعددة المكونات، تفاعلات متعددة المكونات تعتمد على إيزوسيانيد، مضاد للبكتيريا.