Multistep Synthesis of Sulfamoyl Aminopyridine Carboxamides Derivatives as Biologically Active Compounds

A Dissertation

Submitted to the Department of Chemistry, Quaid-I-Azam University, Islamabad, Pakistan in the Partial Fulfilment of the Requirements for the Degree of

Master of Philosophy

in

Organic Chemistry

by

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Islamabad, Pakistan

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In the name of Allah, the most Gracious & the most Merciful

"Your guardian is only Allah, His Prophet, and the faithful who maintain the prayer and give the zakat while bowing down."

(Surah Al-Maidah 5:55)

"I am the city of knowledge and 'Ali is its gate"

(Al-Tirmidhi, Hadith no. 3723)

(Holy Prophet PBUH)

"Innal Hussyn Misbah al Huda wa Safeenat ul Najaah".

- Verily! Hussyn is the light of guidance and the ark of salvation.

DECLARATION

This is to certify that this dissertation entitled **"Synthesis of Sulfamoyl Aminopyridine Carboxamides Derivatives as Biologically Active Compounds"** submitted by **Mr. Agha Danish Mehdi,** is accepted in its present form by the Department of Chemistry, Quaid-i-Azam University, Islamabad, as satisfying the dissertation requirements for the degree of ***Master of Philosophy in Organic Chemistry.***

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Dedication

To my Parents

The reason for what I became today. Thanks Abu & Ami for your great love and support

Acknowledgments

By the grace of **Almighty Allah**, the Most Gracious, the Most Beneficent, and source of ultimate knowledge, Who enabled me to complete this contribution within the due time. All the respect for the **Holy Prophet (PBUH)**, the soul of the universe, the cause of the creation of the universe, and the greatest Educator and Teacher of humanity Who brought the educational revolution to this world.

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Agha Danish Mehdi

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List of Abbrevations

[BMIM][PF_6]	1-Butyl-3-methylimidazolium hexafluorophosphate
[BMIM][BF_4]	1-Butyl-3-methylimidazolium tetrafluoroborate
BOP	(1-Benzo-[1,2,3]-triazol-1-yl)-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate
CDI	Carbonyldiimidazole
DABSO	1,4-Diazabicyclo[2.2. 2]octane bis(sulfur dioxide)
DCC	*N,N'*-Dicyclohexyl carbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIC	*N,N'*-Diisopropyl carbodiimide
DHU	Diisopropylurea
DMAP	*N,N*-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
DSC	*N,N'*-Disuccinimidyl carbonate
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HBTU	2-(Benzo[1,2,3]-triazol-1-yl)-1,1,3,3-tetramethylisouroniumhexafluorophosphate
HCMV	Human cytomegalovirus
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	Hydroxybenzotriazole
HOSu	*N*-Hydroxysuccinimide
HTS	High throughput screening
HMPA	Hexamethylphosphoramide
IC_{50}	Half maximal inhibitory concentration
MIC	Minimal inhibitory concentration
mCPBA	meta-Chloroperbenzoic acid
PAIM [NTf_2]	Piperidine-appended imidazolium-IL
PABA	*p*-Aminobenzoic acid
PNP	*p*-Nitrophenol

PyBOP	(1-Benzo-[1,2,3]-triazol-1-yl)-oxy-tri(pyrrolidinyl) phosphoniumhexafluorophosphate
PyBroP	Bromo-tri(pyrrolidinyl)phosphoniumhexafluorophosphate
SET	Single electron transfer
$SnCl_2$	Tin dichloride
TBHP	*tert*-butyl hydroperoxide
TBAHS	Tetra-butyl-ammonium-hydrogen-sulfate
TBTU	2-(Benzo[1,2,3]-triazol-1-yl)-1,1,3,3-tetramethylisouroniumte trafluoroborate
TCT	2,4,6-Trichloro-1,3,5-triazine
TEA	Triethylamine
THF	Tetrahydrofuran
TMV	Tobbaco mosaic virus
TOTU	*O*-[(Ethoxycarbonyl)cyanomethylenamino]-1,1,3,3-tetramethyluronium

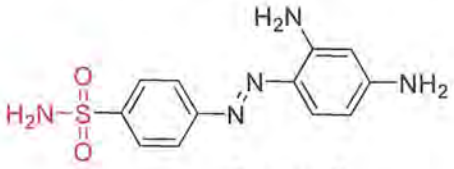
Abstract

Sulfonamides and carboxamide functionalities play a vital role in the pharmaceutical industry, polymer chemistry, and agrochemicals. Sulfonamide and carboxamide along with other groups exhibit excellent anti-bacterial properties. Keeping in view their biological importance, several similar compounds have been designed and synthesized using different methodologies. The aim of this research work is the synthesis of some sulfonamyl-aminopyridine-carboxamide derivatives with a variety of substituents. Sulfonamides were synthesized in the aqueous medium from different chlorosulfonyl benzoic acids by treating with different aliphatic and aromatic amines such as morpholine, pyrrolidine, cyclopropylamine, 4-chloroaniline, aniline, benzylamine etc. While carboxamides were synthesized by treating a variety of aminostilbazoles with carboxyl group-containing sulfonamides using EDC coupling. EDC coupling reagent with DMAP contribute to the activation of carboxylic acids. 4′-Aminostilbazole was synthesized by the Knoevenagel condensation reaction of 4-nitrotoluene with 3-pyridinecarboxaldehyde in the presence of sodium hydroxide as a base followed by the reduction of nitro group to amine using tin dichloride as a reducing agent. Aminopyridine based stilbazoles were synthesized by Heck coupling reaction between different bromo-aminopyridine compounds and differently substituted vinyl pyridines. The synthesized sulfonamide-carboxamide derivatives have different aryl and alkyl substituents including cyclopropyl, morpholine, pyrrolidine substituted anilines, and aminostilbazole moieties. These compounds were obtained in good yields (43-73%) and characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.

CHAPTER 1
INTRODUCTION

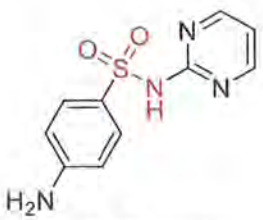
1.1 Sulfonamides

Sulfonamides belongs to class of compounds containing $-SO_2NR_2$ functionality, having general formula RSO_2NR_2 where R is any carbon containing aliphatic or aromatic moiety.[1] Gerhard Domagk discovered first sulfa drug, Prontosil in 1932 which had anti-bacterial activities against blood poisoning bacteria.[2]

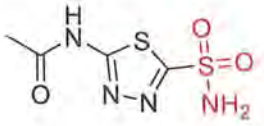


Prontosil

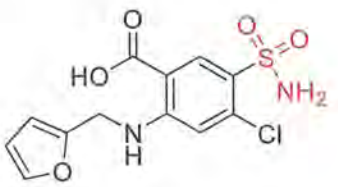
Sulfonamides are belongs to one of the classical family of drugs with indefinite importance in medicinal chemistry. It is quite interesting that the toolbox of medicinal chemists have fairly small privileged building blocks, found in potent drug molecules and sulfonamide moieties are one of them. There is about 22 widely used drugs having sulfonamide moieties. Sulfonamides have diverse biological activities and primary sulfonamide moieties present in various clinical used drugs such as anti-bacterial (Sulfadiazine, Mafenide)[3], carbonic anhydrase inhibitors, such as dichlorophenamide, acetazolamide,[4] diuretics, such as furosemide, thiazides, indapamide,[5] cyclooxygenase inhibitors (COX-2) such as celecoxib and valdecoxib,[6] anti-viral drugs such as amprenavir and fosamprenavir[7] and the anti-psychotic Sulpiride[8] etc.



Sulfadiazine
Anti-bacterial drug



Acetazolamide
Carbonic anhydrase inhibitor



Furosemide
Diuretic

Valdecoxib
Cyclooxygenase inhibitor (COX-2)

Sulpiride
anti-psychotic drug

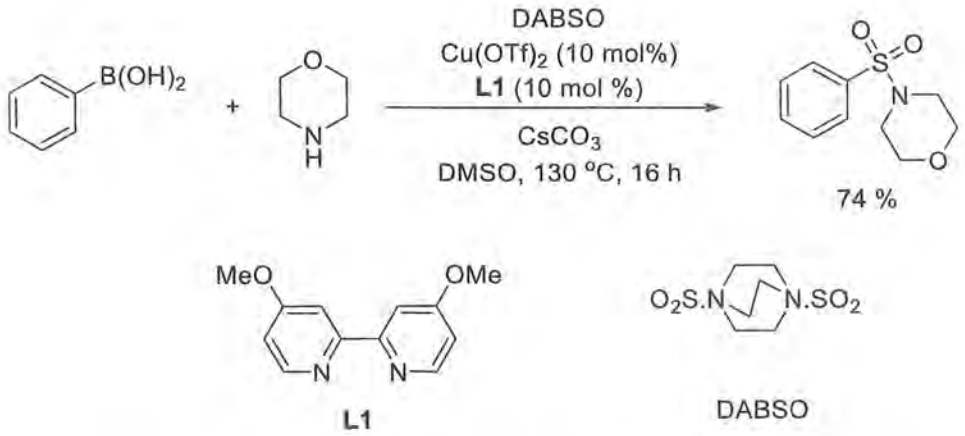
Figure 1.1: Drugs containing Sulfonamide Moiety.

1.2 Synthesis of Sulfonamides

For the first time sulfonamides were synthesized in 1906 and used widely in dye making industry. After the Prontosil discovery which was potent anti-bacterial agent, medicinal chemists incorporated this moiety to synthesize different compounds which are biological important and lead to discovery of different drugs. Here are some common methods to synthesize sulfonamides:

1.2.1 Synthesis of sulfonamides from aryl boronic acid and amine

Chen, Y., *et al.*, reported a three component synthesis of sulfonamides by combining aryl boronic acids with amines, in presence of sulfur dioxide,1,4-Diazabicyclo[2.2.2]octane bis-sulfurdioxide (DABSO) through copper catalysis. DABSO act as a surrogate reagent to deliver sulfur dioxide.[9]

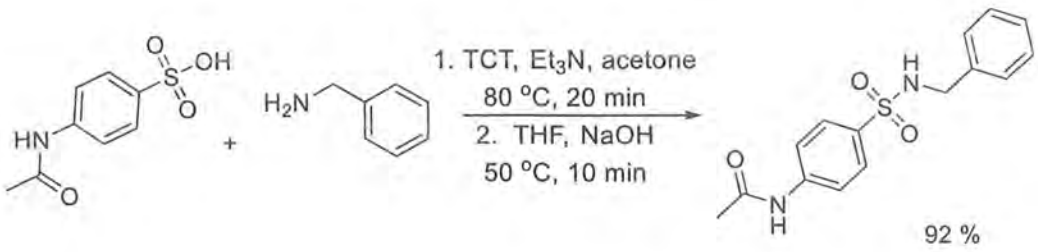


Scheme 1.1: Sulfonamides synthesis *via* Copper catalyzed reaction.

1.2.2 Microwave assisted synthesis of sulfonamides

De Luca *et al.*, reported the sulfonamide synthesis by adding 100 mol% 2,4,6-trichloro-[1,3,5]-triazine (TCT) in a mixture containing 100 mol% sulfonic acid and 100 mol%

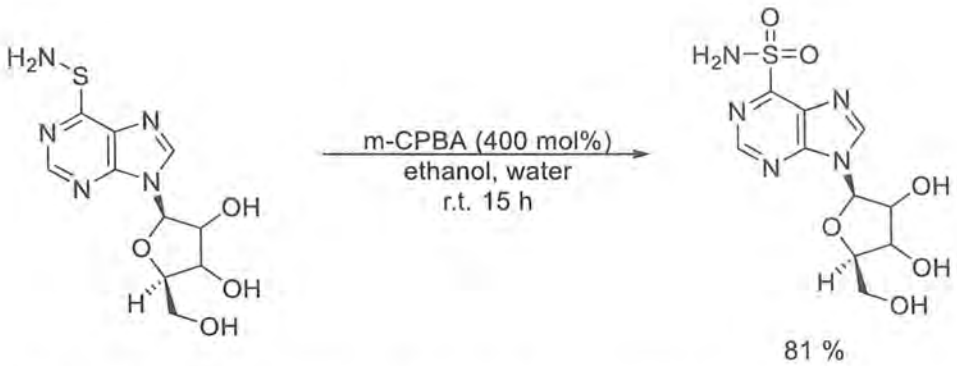
of triethylamine. Reaction was carried in sealed tube stir for 20 min at 80°C and acetone used as solvent.[10]



Scheme 1.2: Sulfonamides synthesis *via* microwave-assisted synthesis.

1.2.3 Oxidation of sulfenamide to give sulfonamides

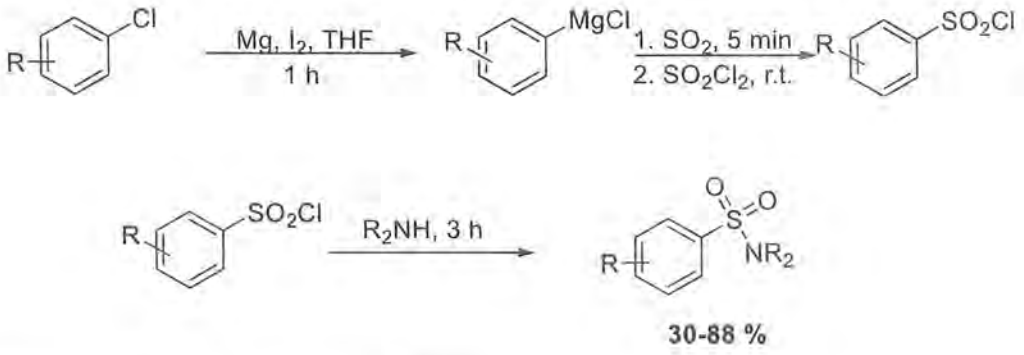
Revankar *et al.* reported that sulfenamide containg purine compound when treated with 4 equivalents of mCPBA , desired sulfonamide was obtained. In this reaction, solution of selfenamde in ethanol and DCM was reacted with mCPBA as oxidizing agent which oxidized the sulfur(II) to sulfone(VI).[11]



Scheme 1.3: Sulfonamides synthesis *via* oxidation of sulfonamide.

1.2.4 Synthesis of sulfonamides from Grignard reagent

Barret *et al.* designed the facile one pot synthesis of sulfonamides by conversion of aryl halides into corresponding Grignard reagent followed by reaction with sulfur dioxide, sulfuryl chloride and desired amine. They carried the synthesis by sulfinylation of corresponding aryl Grignard reagent by using SO_2 to afford sulfinate which on addition of sulfuryl chloride gave corresponding arene sulfonyl chloride which on reaction with amine give sulfonamide.[12]

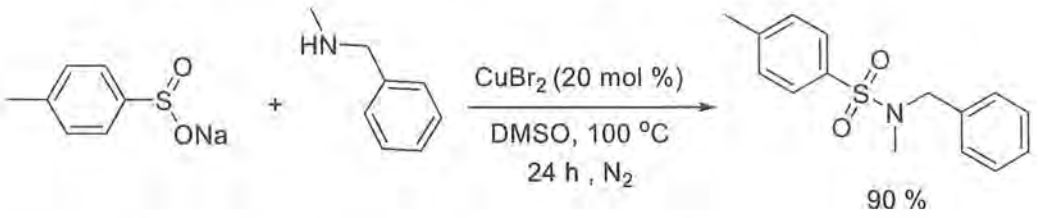


R, R1,R2 are different alkyl or aryl group

Scheme 1.4: Sulfonamides synthesis *via* Grignard reagent.

1.2.5 Copper assisted synthesis of sulfonamides

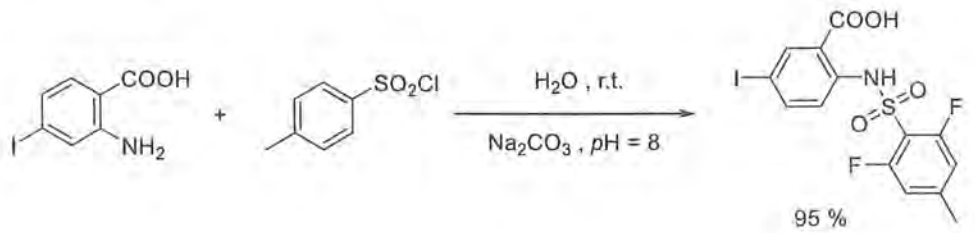
Tang *et al.* developed the method to synthesize sulfonamides by copper assisted oxidative coupling reaction between sodium sulfinate and amine in DMSO which act as solvent as well as an oxidant. Sulfonamides were synthesized in excellent yield with high chemoselectivity. Mechanistic studies of this pathway shows that the reaction occurred by single electron transfer (SET) pathway.[13]



Scheme 1.5: Sulfonamides synthesis *via* Copper catalyzed oxidative coupling.

1.2.6 Green synthesis of sulfonamides in water

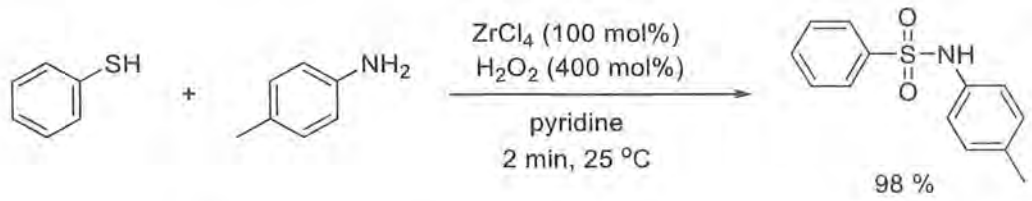
Deng *et al.* reported facile environment friendly synthesis of sulfonamides under *p*H control in aqueous media. Its involves synthesis of sulfonamides which does not needed any further purification and product was isolated on acidification of reaction mixture.[14]



Scheme 1.6: Sulfonamides synthesis in water

1.2.7 Synthesis of sulfonamides from thiols and disulfide

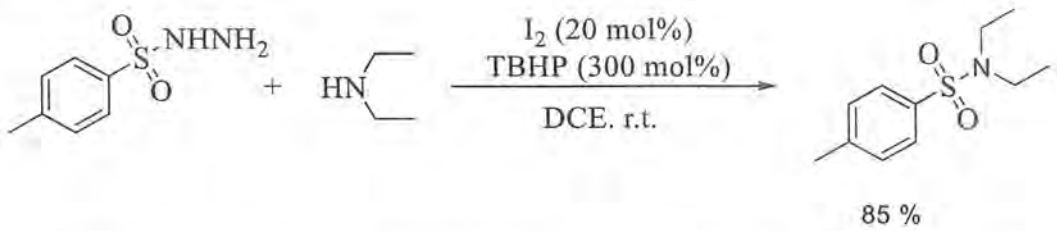
Bahrami *et al.* describes the synthesis of sulfonamides by thiols by *in-situ* oxidation of aromatic thiol by using oxidizing agent followed by chlorinating before the sulfonamide bond formation. [15]



Scheme 1.7: Sulfonamides synthesis from thiols

1.2.8 Iodine-catalyzed sulfonamides synthesis from sulfonyl hydrazides

Yotphan *et al.*, prepared a series of sulphonamides using catalytic amount of iodine with *tert*-butyl hydrogen peroxide (THBP) to give sulfonylation of amines with aryl sulphonyl hydrazides. They used mild reaction conditions and brief reaction time to obtain moderate to excellent yield.[16]



Scheme 1.8: Iodine-catalyzed sulfonamides synthesis form sulfonyl hydrazides

1.3 Pharmacological Activities of Sulfonamides

Sulfonamide compounds are the most effective chemotherapeutic agents having a broad spectrum of pharmacological applications. Numerous sulfonamide based compounds was synthesized which later developed in important drugs which have high therapeutic activities and less toxicity. Sulfonamide based derivatives have numerous biological activities including anti-bacterial,[17] anti-viral,[18] anti-cancer,[19] anti-inflammatory,[20] anti-tuberculosis anti-parasitic, anticonvulsant, and carbonic anhydrase inhibitors.

1.3.1 Anti-bacterial sulfonamides

Sulfonamides are the important motifs in medicinal and pharmaceutical chemistry because of initial disclosure of sulfonamides containing anti-bacterial drugs. Padmaja

et al. prepared the in vitro antibacterial activities of isoxazole containing sulfonamide derivatives which shows the good activities for compounds have 4-Cl group (Compound **1,** Fig 1.2) on benzene [21]. Zhang *et al.* demonstrated the excellent antibacterial activites of benzimidazole-sulfonamides derivatives (Compound **2** and **3,** Fig 1.2). This work shows the electron withdrawing group on phenyl ring increase the antibacterial activities of sulfonamide based scaffolds.[22]

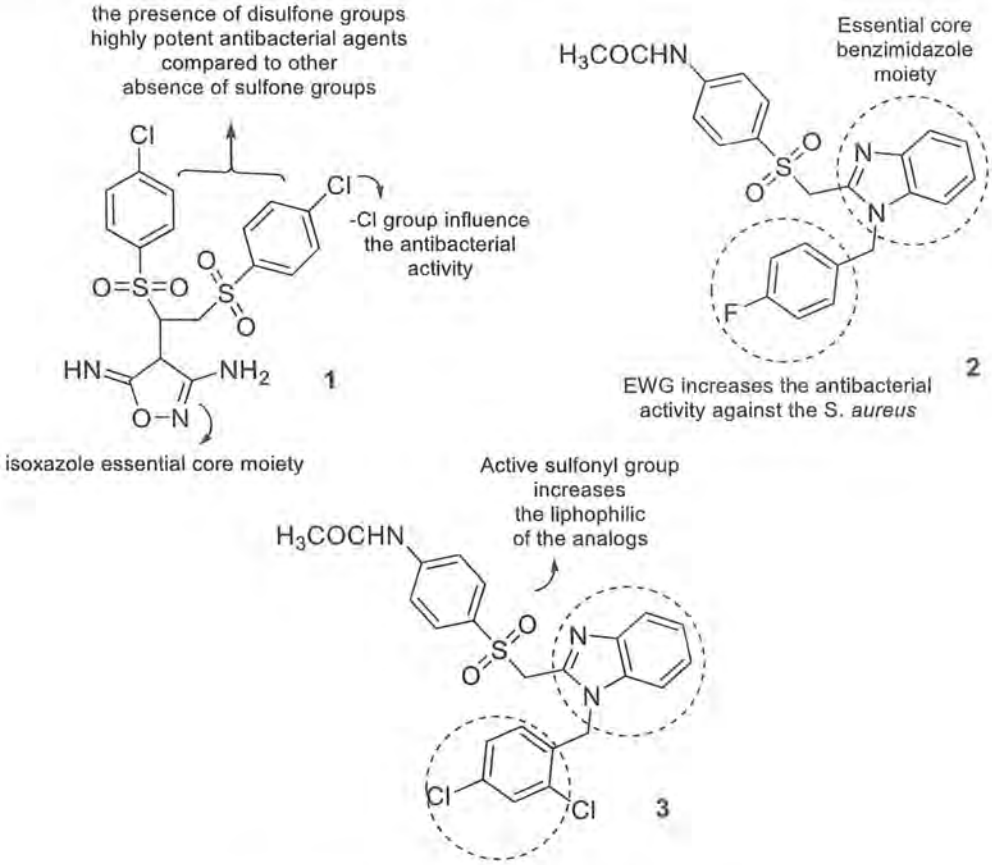


Figure 1.2: Anti-bacterial sulfonamides

1.3.2 Anti-viral sulfonamides

Chen Z. *et al.* reported synthesis of 5-(4-chlorophenyl)-1,3,4-thiadiazole sulfonamides (Compound **4** and **5,** Fig 1.3) which have potential anti-viral activities. These sulfonamide derivatives show activities against tobacco mosaic virus (TMV) in tobacco plants.[23]

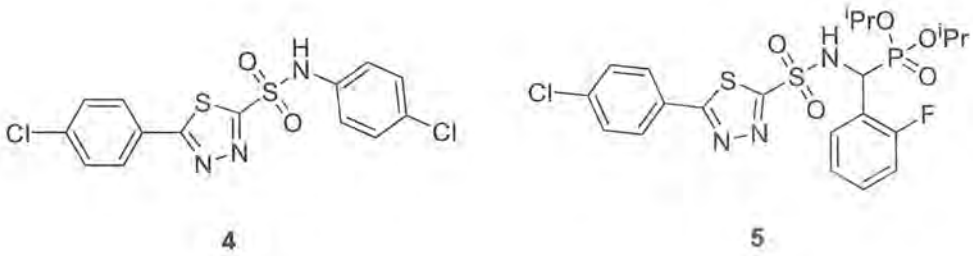


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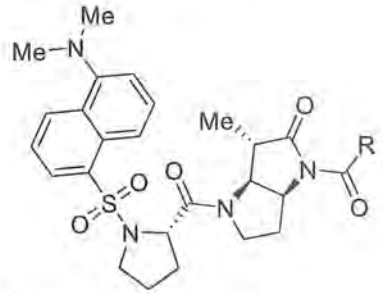
Figure 1.3: Anti-viral sulfonamides active against TMV

Sulfonamide-based antivirals were also recently designed against the human cytomegalovirus (HCMV) protease. Borthwick, A. D. *et al.* reported the synthesis and anti-viral activity against HCMV protease with sulfonamide based inhibitors having dansyl-(*S*)-proline-(*R*)-methyl-5,5-trans-lactam template (Compound **6,** Fig 1.4**)**, which have activity against viral enzyme.[24]



R = CH_3, Cyclopropyl group 6

Figure 1.4: Anti-viral sulfonamides active against HCMV

Stranix, B. *et al.* reported the synthesis of novel scaffold based on lysine sulfonamides which show remarkably high potency against HIV-protease viruses.[25] Kumar k. *et al.* reported that caffeoyl naphthalene sulfonamide derivatives (Compound **7** and **8,** Fig 1.5**)** effective against the HIV integrase and have potency to be an Anti-HIV drug.[26]

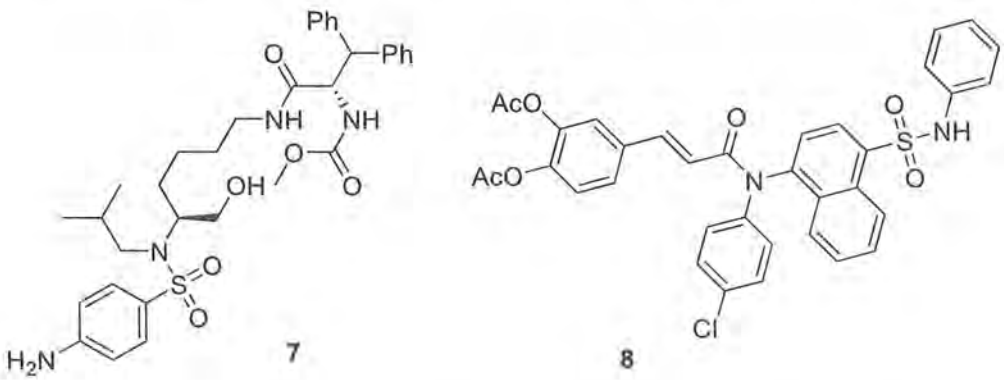


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Figure 1.5: Sulfonamides having anti-HIV activities

1.3.3 Sulfonamides with diuretic activities

Diuretics are the medications which are designed to increase secretion of salts and water in urine. Synthesis of novel quinoxaline sulfonamides derivatives as potential diuretic agents was reported by Husain *et al.* Quinoxaline sulfonamide derivative (Compound **9,** Fig 1.6) containing thiazole moiety showed exceptionally high diuretic activities as compared to urea and acetazolamide as reference drugs.[27]

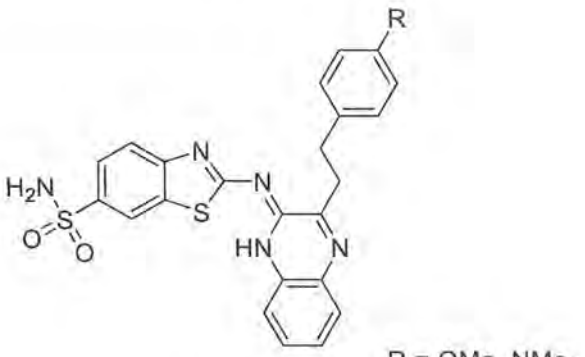

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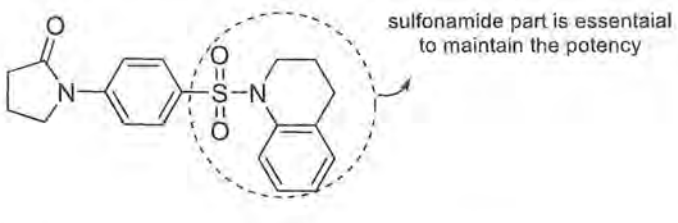
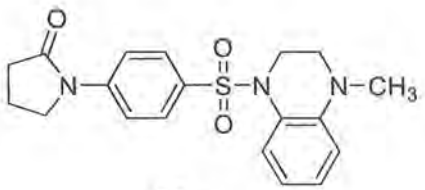
Figure 1.6: Sulfonamides with diuretic activities

1.3.4 Anti-cancer sulfonamides

Okolotowicz J, *et al.* reported the synthesis of novel tertiary sulfonamides (Compound **10** and **11,** Fig 1.7) as potent anti-cancer agents. Results shows that synthesized pyrollidinone based sulfonamides act as anti-proliferation agents against breast cancer cell lines. When different compounds tested by modifying sulfonyl part of compounds, results of study shows that sulfonamide part of compound was essential to maintain the potency.[28]





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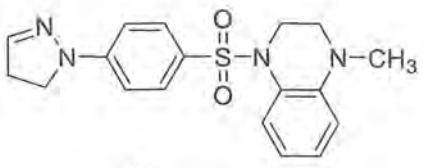

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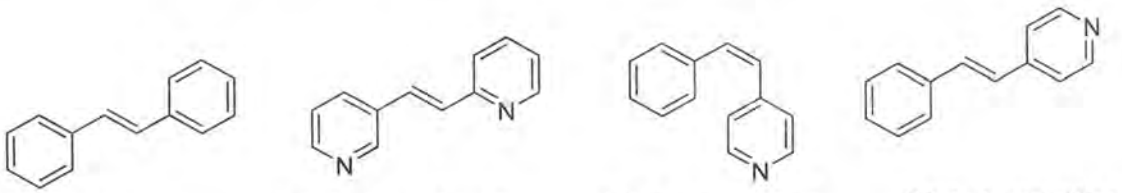
Figure 1.7: Sulfonamides potent against breast cancer

1.4 Stilbazoles

Stilbazoles are compounds, also known as styrlpyridine, have stilbene like structure with one of the carbon of the ring replaced by nitrogen. In stilbazoles, one phenyl and one pyridine ring or both pyridine rings connected through double bond. Stilbazoles can be *cis* or *trans* depending on configuration of double bond.



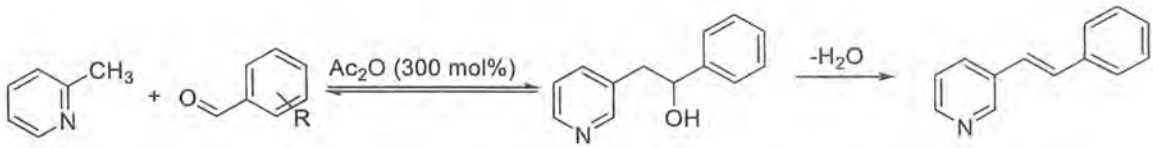
(*E*)-Stilbene (*E*)-vinylpyridylpyridine (*Z*)-4-styrylpyridine (*E*)-4-styrylpyridine

Figure 1.8: Stilbene and Stilbazoles

1.5 Synthesis of Stilbazoles

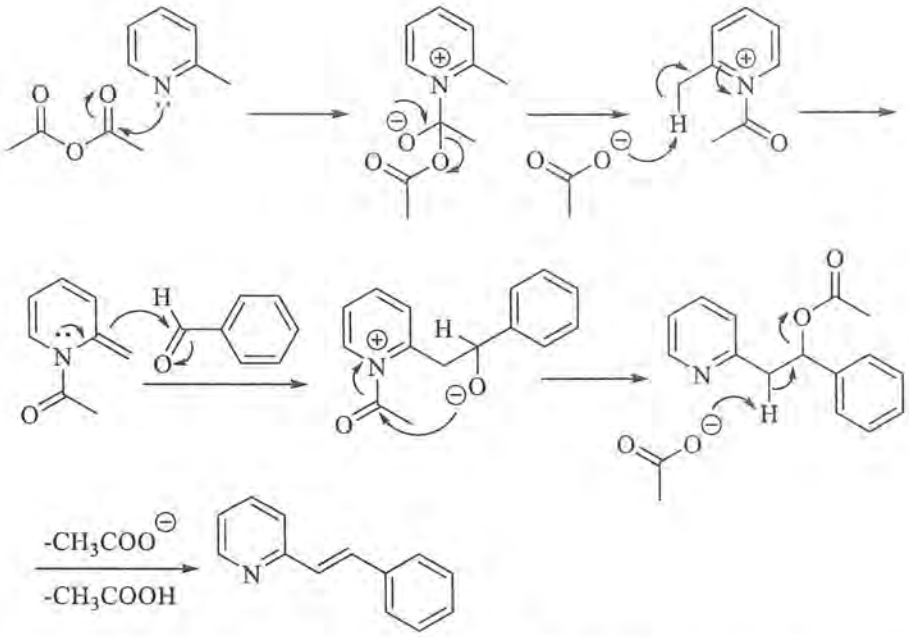
1.5.1 Condensation of picolines with aldehydes

Shaw, B. D. *et al.*, reported stilbazole scaffold can be synthesized by condensation of picoline with different aromatic aldehydes. Reaction was carried by reaction of 2-picoline with aldehyde in presence of concentrated HCl or acetic anhydride as a condensing agent. In this reaction, first step is the reversible formation of stilbazole alkines which on dehydration in second step gives the styrylpyridine product.[29]



Scheme 1.9: Stibazole synthesis by condensation of picoline with aldehydes

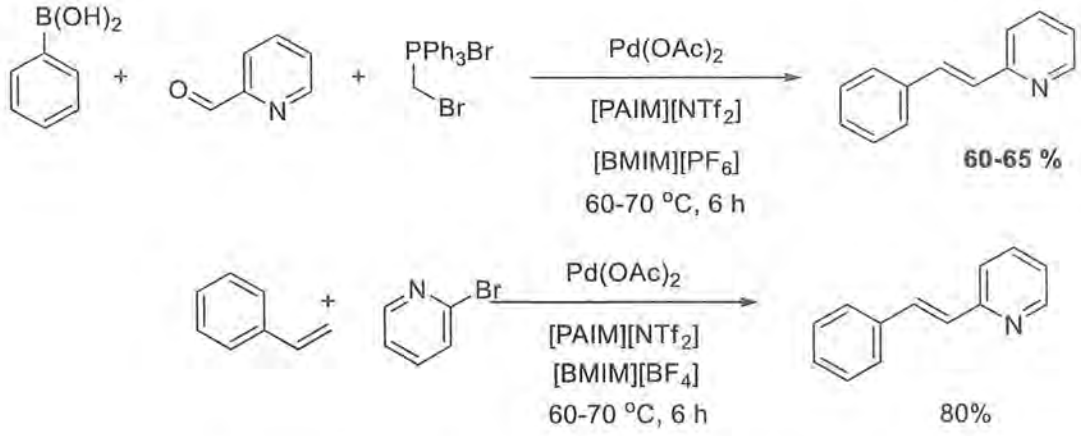
General mechanism proposed for this condensation reaction is given as:[30]



Scheme 1.10: Mechanism of stilbazole synthesis *via* condensation reaction

1.5.2 Synthesis of stilbazole by using ionic liquid

Savanur, H. M., *et al.* reported the synthesis of 2-styrylpridine by Heck coupling reaction and Witting-Suzuki reaction. The important feature of this reaction is that they performed these coupling reaction by using ionic liquids. These transformations involve ionic liquids led stereoselectivity in synthesis of *E*-isomer.[31]

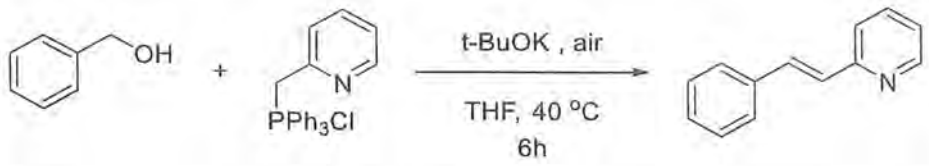


[PAIM][NTf2] = Piperidine-appended imidazolium-IL
[BMIM][PF6} = 1-Butyl-3-methylimidazolium hexafluorophosphate

Scheme 1.11: Stilbazole synthesis by Wittig-Suzuki Reaction using Ionic liquids

1.5.3 Stilbazole synthesis by direct Wittig olefination reaction of alcohols

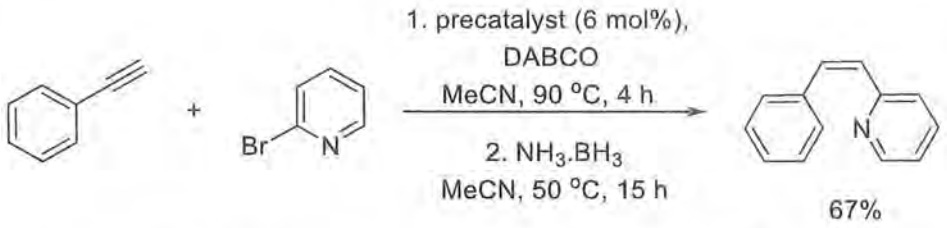
Li, Q. Q., *et al.* reported the base promoted stilbazole synthesis from alcohols under aerobic conditions. In this methodology, air was used as clean and inexpensive oxidizing agent and the (*E*)-Stilbazoles was synthesized predominately .[32]



Scheme 1.12: Stilbazole synthesis by Direct Witting Olefination of Alcohols

1.5.4 Stilbazoles synthesis by Sonogashira coupling

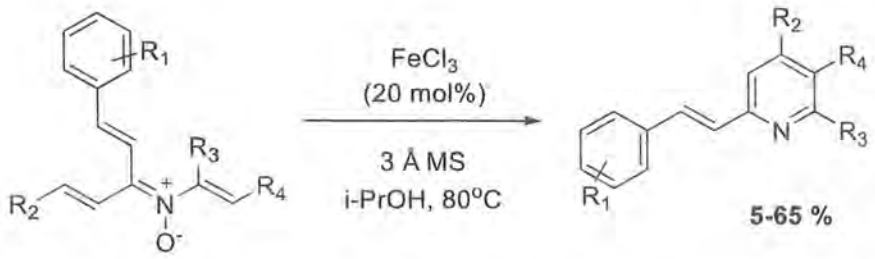
Clauss, R., *et al.*, reported the synthesis of Z-stilbazole by one-pot Sonogashira coupling reaction. Sonogashira coupling was carried by cobalt-palladium precatalyst with 1,4-diazabicyclo[2.2.2]octane (DABCO) and acetonitrile used as a solvent. The reaction was carried at 90°C and semihydrogenation of alkyne done using borazane to afford the desired Z-Isomer.[33]



Scheme 1.13: Stilbazole synthesis by Sonogashira Coupling

1.5.5 Stilbazole synthesis by heterocyclization reaction

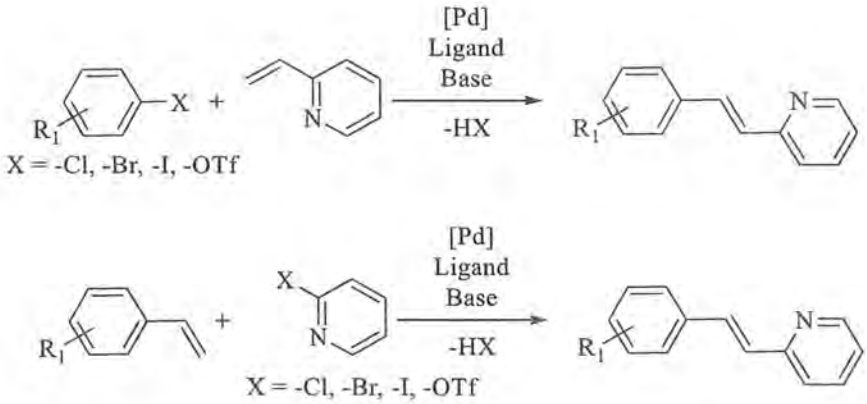
Chen C. *et al.* reported that the synthesis of substituted silbazoles was done by iron catalyzed reaction. In this reaction, Fe(III) controlled cyclization was carried and selective cleavage of N-O bond of *N*-vinyl-α,β-unsaturated nitrones under milder conditions.[34]



Scheme 1.14: Stilbazole synthesis by Iron catalyzed Heterocyclization

1.5.6 Stilbazole synthesis by Heck coupling

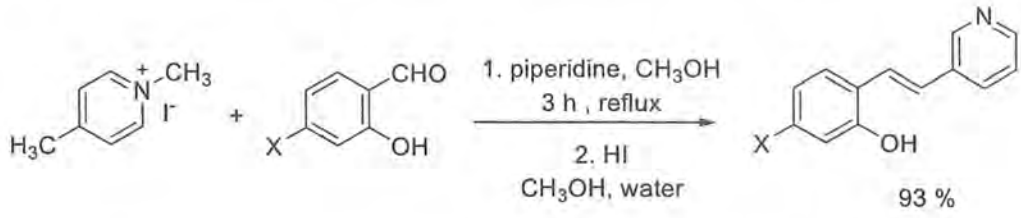
Heck reaction was a most versatile method for synthesis of *trans* stilbenes starting from aryl halides and olefins, named after Richard Heck who discovered this palladium catalyzed coupling reaction. In this reaction aryl halides and triflates are coupled with olefines using catalytic amount of palladium and suitable ligand in presence of base and aprotic solvent. Stilbazoles was also easily synthesized by using Heck coupling reaction.[35,36]



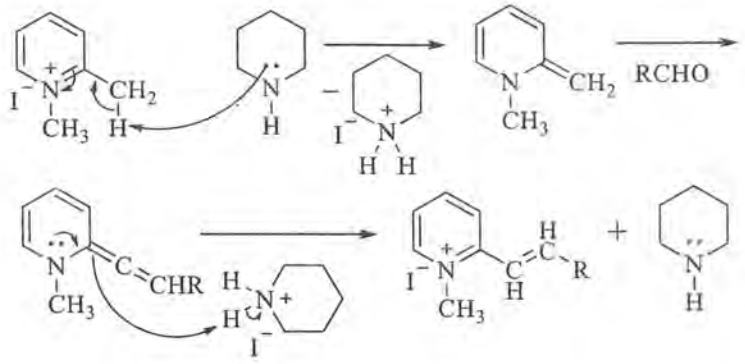
Scheme 1.15: Heck cross Coupling reaction for synthesis of Stilbazole

1.5.7 Synthesis of stilbazole from picoline methiodide

Gibson H.W., *et al.* reported the stilbazole synthesis by reacting picoline methiodide with salicylaldehyde in presence of weak to moderate base to afford stilbazolium methiodide which on treatment with hydrogen iodide afford substituted.[37]



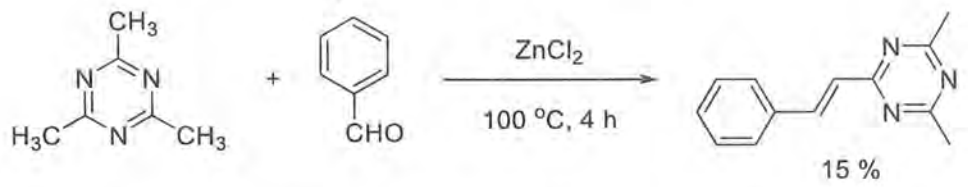
Scheme 1.16: Stilbazoles synthesis from 4-picoline methiodide



Scheme 1.17: Mechanism of condensation of aromatic aldehydes with -picoline methiodide.

1.5.8 Stilbazole synthesis by Claisen condensation of aromatic aldehydes with 2,4,6-trimethylpyrimidine scaffold

Sullivan, H. R., *et al.* reported the synthesis of pyrimidine based Stilbazole by Claisen type condensation of 2,4,6-trimethylpyrimidine with aldehydes by using $ZnCl_2$ as a catalyst for this reaction. Reaction was carried at 100°C by using equimolar of aldehydes and pyrimidines to get selective condensation on only one methyl of pyrimidine.[38]



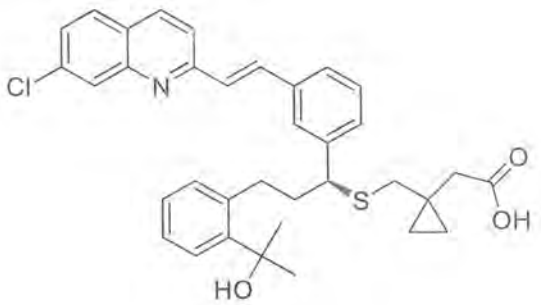
Scheme 1.18: Stilbazole Synthesis by Claisen Condensation

1.6 Pharmacological Importance of Stilbazoles

Compounds containing stilbazole moiety have a wide range of applications. Presence of two aromatic ring joined by olefinic bond give lipophilic character and presence of pyridine nitrogen give special basic properties and its easily converted in salt in acidic medium as nitrogen lone pair available to capture proton in acidic solutions. Stilbazole have certain structural features which make it biological important such as rigidity in structure due to fixed C=C bond but also partial flexibility due to single bond rotation along vinylic and aromatic part that helps it to act as good substrate to interact with enzyme active site like p-stilbazole act as an artificial base pair for photo crosslinking of DNA duplex.[39]

1.6.1 Stilbazole as anti-asthmatic agent

Montelukast is an FDA approved drug which is quite effective against asthma and anti-allergic agent. Montelukast drug contain quinoline based Stilbazole skeleton and act as selective antagonist for the leukotriene receptors and widely used in the treatment of bronchial asthma. Reportedly, Montelukast also effective against other diseases such as obstructive pulmonary disease which have symptoms of restricted air flow in human lungs and also breathing problems and also use to treat sessional allergic reactions.[40 41]

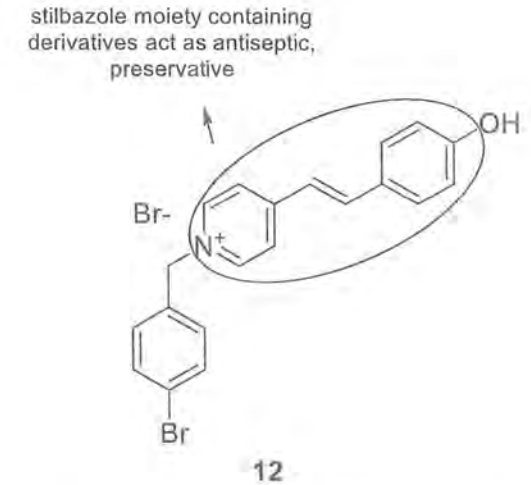


Montelukast

Figure 1.9: Stilbazole derivatives as anti-asthmatic drug

1.6.2 Stilbazoles as anti-microbial agents

Kluska, M., *et al.* studied extraction process and the long term stability of (*E*)-azastilbene derivatives (compound **12**, Fig 1.10) to used them as an anti-septic, preservatives and disinfectant substances. They studied the stability of stilbazole derivatives in surface and waste waters to assure the possible use of these derivatives as anti-septic, aniti-microbial substances.[42]



12

Figure 1.10: Stilbazole derivatives as anti-microbial agents

1.6.3 Stilbazoles as Choline Acetyltransferase Inhibitors

Baker *et al.* reported the inhibition study of choline acetyltransferase enzyme in brain cells of rabbit by using different derivatives of 4-stilbazole (compound **13-16**, Fig 1.11). They reported that the 3',4'-dichloro-4-stilbazole was the most effective acetyltransferase inhibitor which bonded the active site of enzyme 910 times most efficiently than choline substrate.[43]

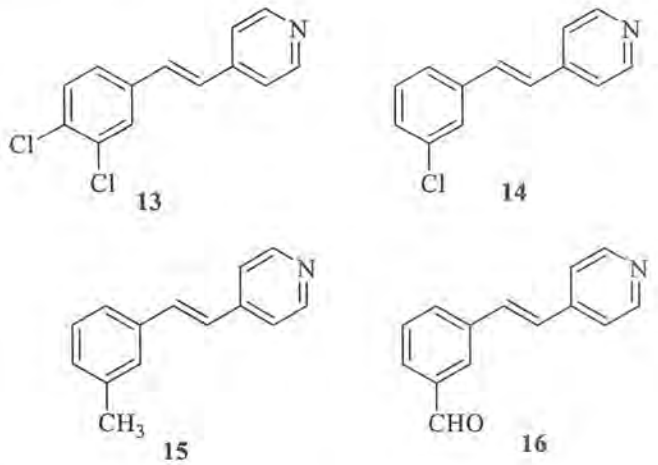
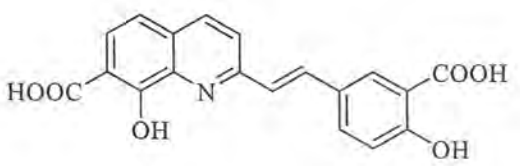


Figure 1.11: Stilbazole derivatives as choline acetyltransferase inhibitors.

1.6.4 Stilbazole derivatives as HIV-1 inhibitors

Acquired immunodeficiency syndrome (AIDS) is a viral disease and for its treatment different anti-retroviral agents were used. These antiretroviral agents effects the replication of HIV-1 strains in acutely infected cells but HIV remains in periphery and affect the infected individual within certain time period.[44,45]

Mekouar *et al.* reported the Stilbazole substrate as effective HIV-1 integrase inhibitor (compound **17**, Fig 1.12) that stops the replicative cycle of HIV strains. The most potent inhibitor was shown below with IC_{50} value of 62 μM and no cytotoxicity.[46]

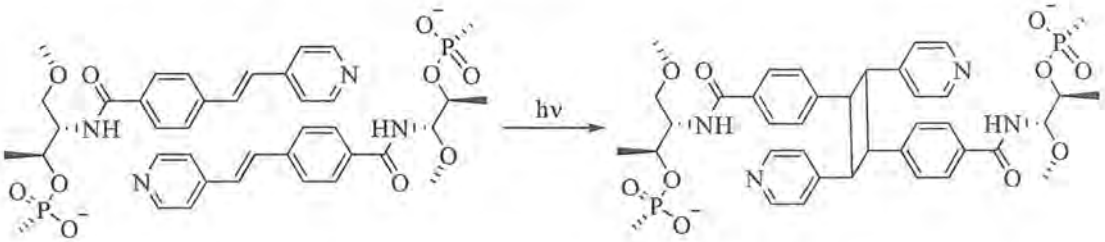


17

Figure 1.12: Styryl quinolines as HIV-1 integrase inhibitors

1.6.5 Stilbazole carboxamides as artifical base pairs in DNA duplex

Kashida *et al.*,reported the use of 4-stilbazole moieties as artificial base pairs into DNA duplex due to high resemblance with natural nucleobases.When it irridated with UV rays, 4-stilbazole react to develop cross linking in DNA duplex as shown below.[39] This photo-cross-linking of 4-stilbazole moieties give thermal stability to DNA duplex.[47]



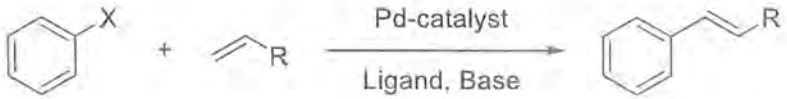
Scheme 1.19: *p*-stilbazole moieties in DNA duplex.

1.7 Palladium-Catalyzed Coupling Reactions

Palladium catalyzed reactions provides facile synthetic routes in organic synthesis for synthesis of C-C, C-N bonds. Palladium act as an effective heterogenous catalyst for synthesis of C-C and C-N coupled products and its synthetic protocols includes versatile methodologies which were extensively applicable protocols in total synthesis of natural products, phrmaceuticals, stereoselective reactions in presence of suitable catalyst, catalyst desigining and material sciences. C-C bond formation through transition metal catalysis possesses an exceptionally broad and contemporary research area in chemistry.

1.7.1 Heck cross coupling reaction

Mizoroki and Heck developed the palladium-catalyzed coupling of aryl halide and olefins, named as the Heck reaction. Its palladium catalyzed C-C bond forming reaction between aryl halides or triflates and activated alkenes in presence of suitable ligand and base at elevated temperatures. It was named after Tsutomu Mizoroki and Richard Heck, who discovered this reaction independently in early 1970s.[35,36] Richard Heck was awarded noble prize in 2010 for its contribution of Pd catalyzed coupling reactions and development of this reaction , which he shared with Ei-ichi Negishi (for Negishi coupling reaction) and Akira Suzuki (for Suzuki reaction). The generalized reaction protocol for Heck reaction utilizing aryl halides, activated alkenes in presence of base, catalyst and suitable ligand as given in Scheme 1.20.[48]



Scheme 1.20: Generalized protocol for Heck Reaction

1.7.2 Mechanistic studies of Heck reaction

Catalytic cycle of Heck reaction consists of three major steps:[49]

- Oxidative addition
- Syn-alkene Insertion
- Reductive Elimination

The catalytic cycle of Heck reaction starts with generation of a homogenous Pd^0 complex as catalytically active species which either form *in situ* by reduction of Pd^{II} salts by suitable ligands [*e.g.* $Pd(OAc)_2$], or by exploiting Pd^0 precatalyst [e.g. $Pd(PPh_3)_4$]. After generation of Pd^0, catalytic cycle involves oxidative insertion of palladium in Ar-X bond of an aryl halide, gives *trans*-complex. The *t*rans-complex then undergoes *syn*-*β*-hydride elimination to release *trans*-product selectively. This process could be reversible leading to the alkene isomerization to originally formed Heck product. The active specie Pd^0 then regenerated by reductive elimination of Pd in last step by base.

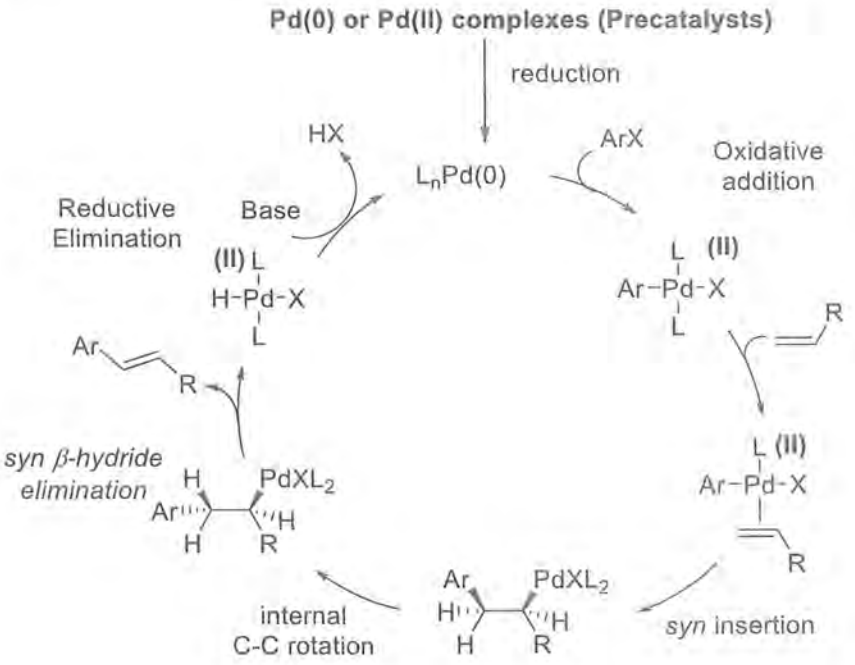


Figure 1.13: Mechanism of Pd-catalyzed Heck Reaction

1.7.3 Ligands employed in Heck reaction

Pd^0 thought to be active specie in Heck reaction catalytic cycle but, on the other hand, the bare Pd^0 is very unstable, less solubility and easily go aggregation which eventually results in deactivation of Pd^0, also called Pd black. High catalyst loading is often required to suppress this problem in catalytic process.[50] Moreover, employing phosphine ligands in this reaction has proved to be an effective and reliable protocol.[35] Previously, few multidentate ligands were used which required very little catalyst loading.[51] Furthermore, the repetitive synthetic pathway of multidentate phosphine ligands restrains their wide applications. π-acidic ligands and few diphosphine ligands containing nitrogen that can easily be prepared, have shown favourable activites for this reaction with exceptional regoselectivites by chelating with palladium. Some monodentate, bidentate phosphine ligands that can be employed in this reaction are given in Figure 1.14.

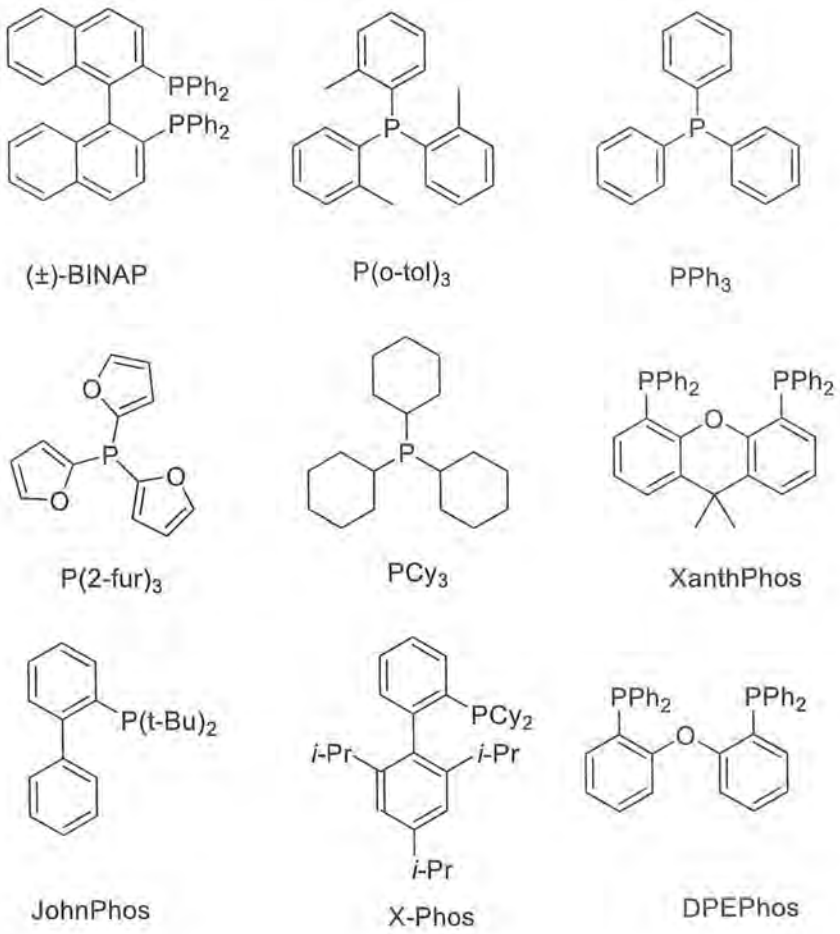


Figure 1.14: Some phosphine ligands employed in Heck reaction

1.7.4 Regioselectivity in Heck reaction

Regio-chemical outcome of Heck reaction can be employed by carbopalladation step in its mechanism which facilitates the synthesis of many desired substrates in organic synthesis. In conventional cross-coupling reaction of aryl iodide with an alkene, it was anticipated that carbopalladation step (migratory insertion step) is irreversible, and hence, regiochemistry of product is governed by this step.

There are many factors which control the region-chemical outcome of the heck reaction. One of them is the electronic aspect of alkene that play a vital role. Usually, C-C bond formation takes place preferentially at the most electron-deficient carbon as indicated by arrow in Fig 1.14.[52]

Steric factors will be more pronounced in alkenes, in which bond polarization is not as drastic, for instance aliphatic alkenes, which provides region-isomeric mixture of products. This type of the reaction conditions and *(pseudo)* halide of the heck substrate used also seems to be crucial, since these affect the identity, in the form of charge and ligands on the Pd atom of active catalyst and by that can influence the regiochemical outcome of the Heck reaction.

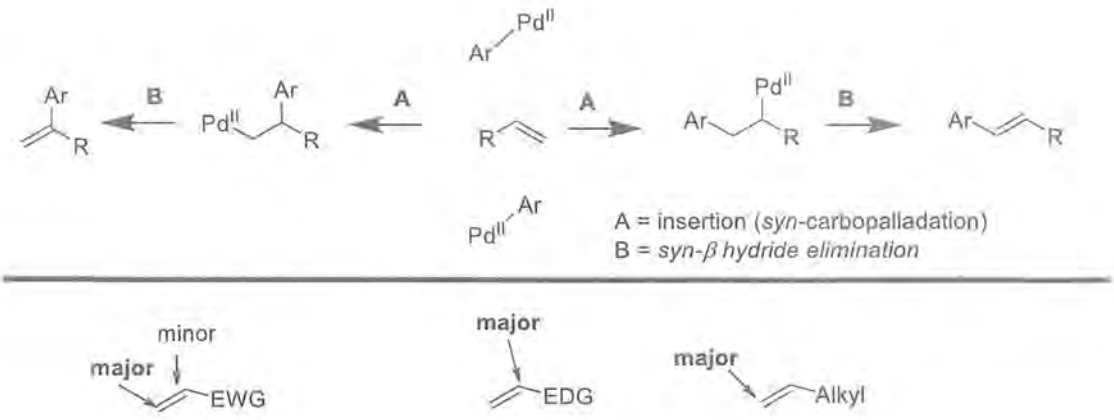


Figure 1.15: Regioselectivity in Heck Reaction

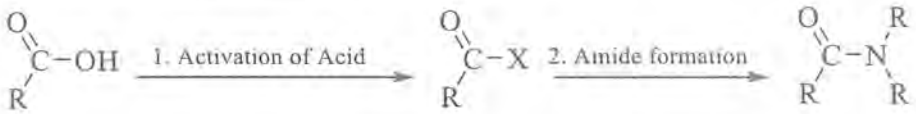
1.8 Carboxamides

Carboxamides are compounds having -$CONH_2$ functional group are important scaffolds in both synthetic as well as natural contents of varying diversity. Most macromolecules of biological importance containing peptides connected through

carboxamide bonds. Amides have many types like carboxamide, polyamide, sulfonamide and acrylamide. Carboxamides are derived from carboxylic acids and amines. Proteins, that are essential for biological processes and perform their role for immune system, storage of chemicals, transport of chemicals, enzymatic catalysis, mechanical support, energy source and growth regulator, mostly have carboxamide type of amides because these are more stable than others. Carboxamides also play a significant role in medicinal chemistry.

1.9 Synthesis of Carboxamides

Intially, carboxamides were synthesized by converting carboxylic acids to most reactive acid halides by using $SOCl_2$, PCl_3, oxalyl chloride etc. In last three decades, various coupling methods and reagents have been developed for carboxamide synthesis under mild reaction conditions which have two main steps namely the activation of acid followed by attack of amine to give amide bond. These methods have the potential to achieve economical synthesis, to improve yield, to facilitate the purification of final product and to avoid racemization if necessary.[53]

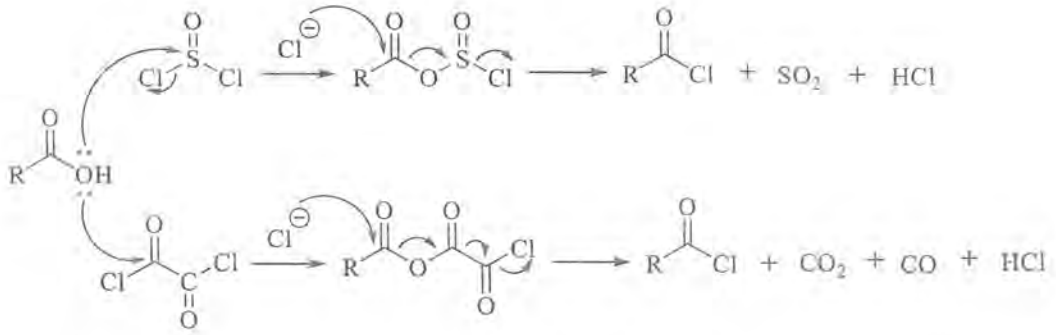


Scheme 1.21: Activation of acid and aminolysis steps for carboxamide synthesis.

1.9.1 Synthesis of carboxamides from acyl halide

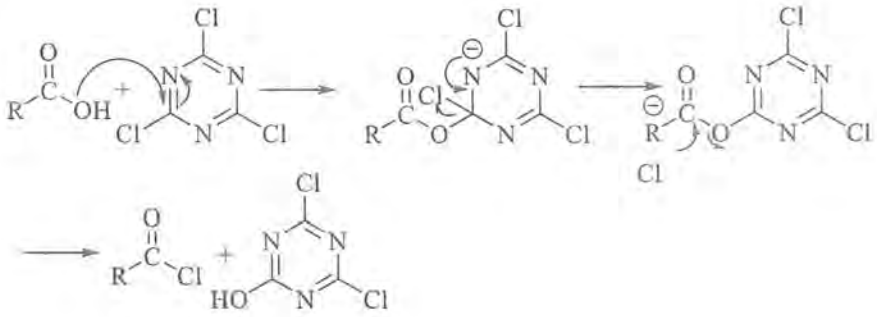
1.9.1.1 Synthesis of Acid Halide

Thionyl chloride ($SOCl_2$) is most versatile and common, inexpensive reagent for synthesis of acid halide.[54] Phosphorous trichloride (PCl_3), phosphorous pentachloride (PCl_5), oxalyl chloride ($COCl_2$), cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) and tetramethyl-α-chloroenamine are also some commonly used chlorinating agents. Acid chlorides are usually synthesized by treatment of thionyl chloride and oxalyl chloride with carboxylic acid in the presence of catalytic amount of *N,N*-dimethylformamide. The main advantage of using thionyl chloride and oxalyl chloride is the formation of gaseous by-products.[55]



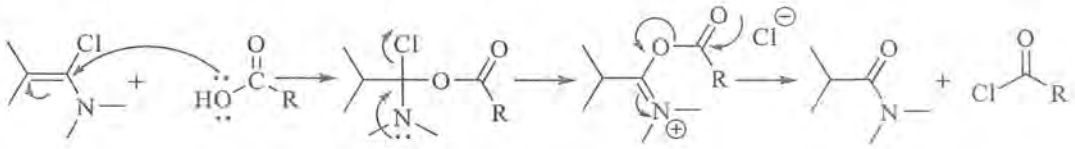
Scheme 1.22: Mechanism of acid chloride formation *via* $SOCl_2$ and $COCl_2$.

Cyanuric chloride is utilized when acid sensitive moieties are present in the substrate and require non-acidic conditions to carry out acyl chloride formation. It is a suitable reagent for the synthesis of amide on large scale. This method decreases the utilization of reagent as well as side product generation because it requires only 1/3 equivalents of reagent.[56]



Scheme 1.23: Mechanism of acid chloride formation *via* cyanuric chloride.

Ghosez *et al.*, described tetramethyl-*α*-chloroenamine as an activating agent and the method is significantly important when acid labile moieties are present in the substrate because it prohibited the formation of hydrochloric acid.[57]

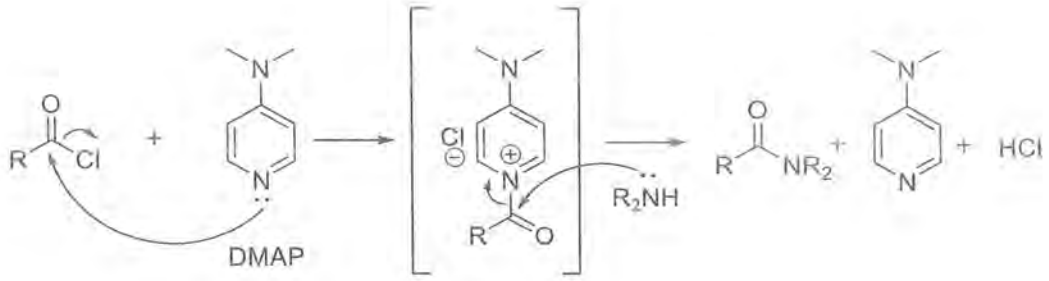


Scheme 1.24: Mechanism of acid chloride formation *via* Ghosez chlorinating agent.

1.9.1.2 Coupling of Acyl Chloride with Amine

When acid chloride is treated with amine, carboxamides are formed. This coupling reaction proceeds in the presence of dry solvents and non-nucleophilic tertiary amines like triethylamine, *N*-methylmorpholine or *N,N*-diisopropylethylamine. Catalytic

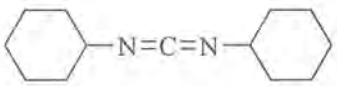
amount of *N,N*-dimethylaminopyridine or simple pyridine is used to speed up the reaction.[58]



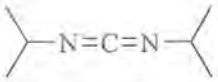
Scheme 1.25: Mechanism of amide formation.

1.9.2 Activation of carboxylic acids using different coupling reagents

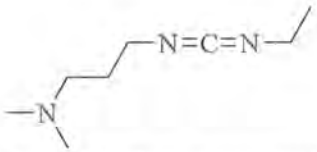
Commonly used activating reagents for carboxylic acids are mentioned in Fig. 1.16. These activating reagents increase the reaction rate and make the reaction easy to handle as well.[59]



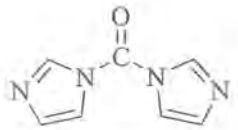
Dicyclohexylcarbodiimide
DCC



Diisopropylcarbodiimide
DIC



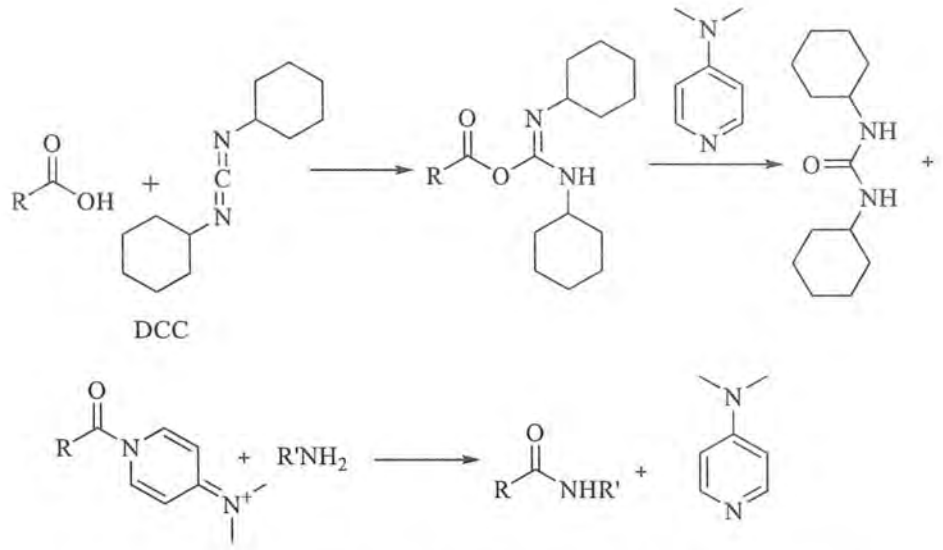
1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide
EDC



Carbonyldiimidazole
CDI

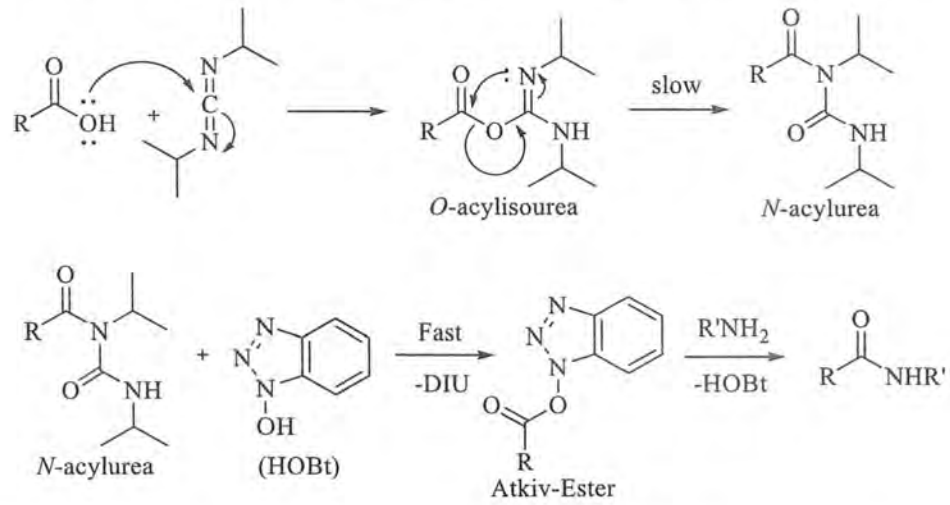
Figure 1.16: Structures of activating reagents for amide formation.

Main advantage of using carbodiimides is that the reaction is carried in mild conditions and products are easily isolated. Activated acyl intermediate is coupled with amine *in-situ* and carboxamide is formed.[60]



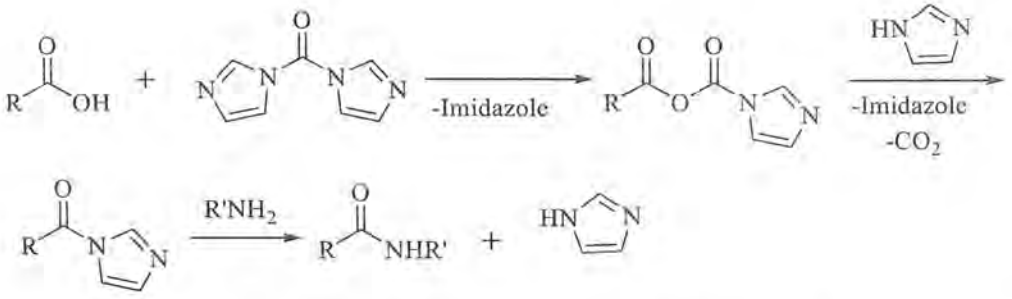
Scheme 1.26: Synthesis of carboxamides *via* DCC activating agent.

The selected nucleophiles such as DMAP and hydroxybenzotriazole (HOBt) are mostly added with carbodiimide for the quick formation of side product urea that is the driving force for this reaction and allow the complete consumption of carboxylic acid.[61]



Scheme 1.27: One-pot carboxamide synthesis *via* DIC-HOBt coupling reagents.

Carbonyldiimidazole (CDI) is useful because it allows one-pot carboxamide synthesis. In this method there is no need of additional base because it itself acts as a base. This activating reagent is commonly useful for large scale peptide synthesis.[62]



Scheme 1.28: One-pot carboxamide synthesis *via* CDI coupling reagent.

1.9.3 Synthesis of Carboxamides from Esters

Activated esters formed from carboxylic acid using activating reagents as mentioned in Fig. 1.17. Compared to alkyl esters, these activating reagents increased the electrophilicity of carbonyl carbon due to electron withdrawing nature of selected alcohols.[63]

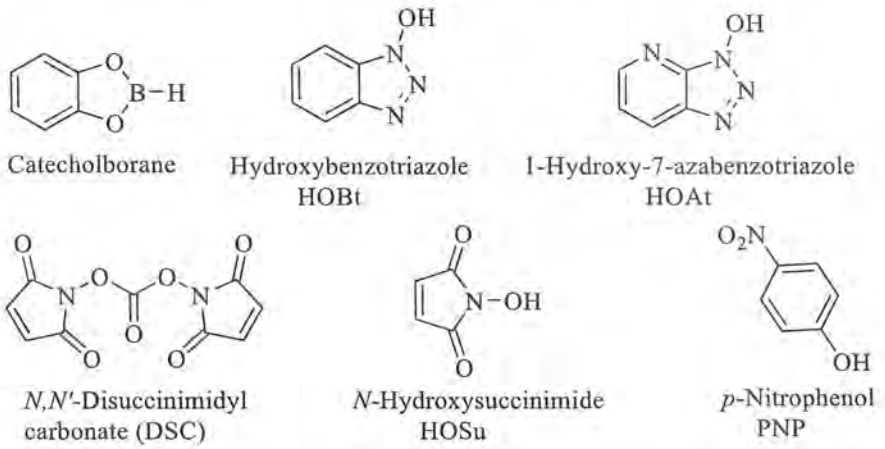
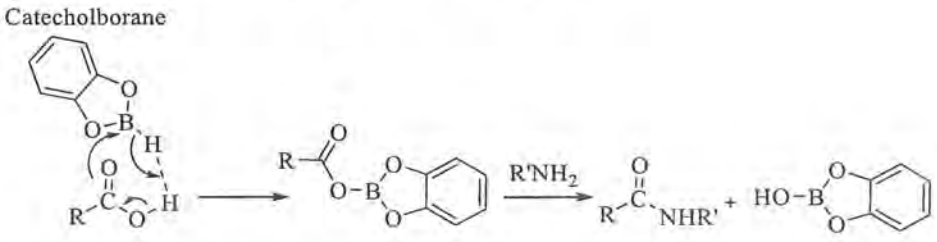


Figure 1.17: Structures of activating reagents for ester formation.

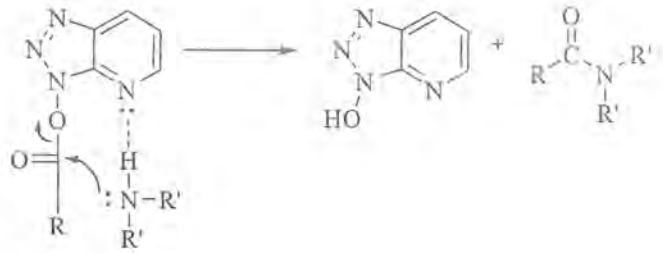
From boron activating reagents, catecholborane is the best choice for the synthesis of carboxamides or lactones due to optimization of yield.[64]



Scheme 1.29: Synthesis of carboxamide *via* catecholborane coupling reagent.

The action mechanism of *N,N'*-disuccinimidyl carbonate (DSC) is like CDI mechanism as depicted in scheme 1.28. 1-Hydroxy-7-azabenzotriazole (HOAt) is more efficient than HOBt during aminolysis step, especially when hindered amine is used for

carboxamide synthesis. This efficacy is due to additional chelation provided by nitrogen atom of pyridine ring.[65]

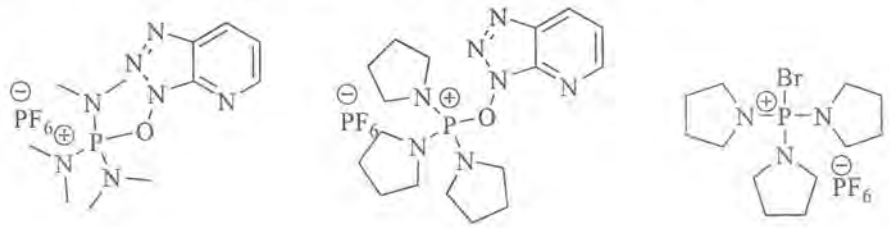


Scheme 1.30: Additional chelation of amine with HOAt during aminolysis step.

1.9.4 Synthesis of Carboxamides from Salts

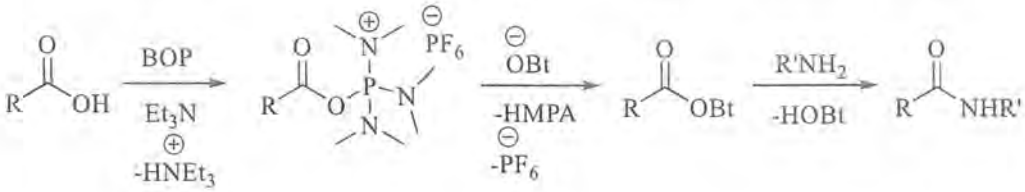
1.9.4.1 From Phosphonium Salts

BOP is also known as Castro's reagent. The generation of hexamethyl phosphoric triamide (HMPA) is driving force for the activation of carboxylic acid but HMPA is highly toxic. PyBrOP and PyBOP are the best alternatives of BOP.[66]



BOP PyBOP PyBrOP

Figure 1.18: Structures of BOP, PyBOP, and PyBrOP activating reagents.



Scheme 1.31: Carboxamide synthesis *via* BOP activating reagent.

1.9.4.2 From Uronium Salts

HBTU,[67] HATU[68] and TOTU are commonly used coupling reagents for carboxamide synthesis. They performed coupling in similar manner as phosphonium salts. The generation of urea is the driving force for the activation of carboxylic acid.[69]

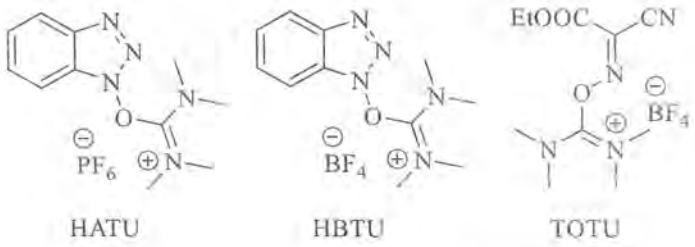
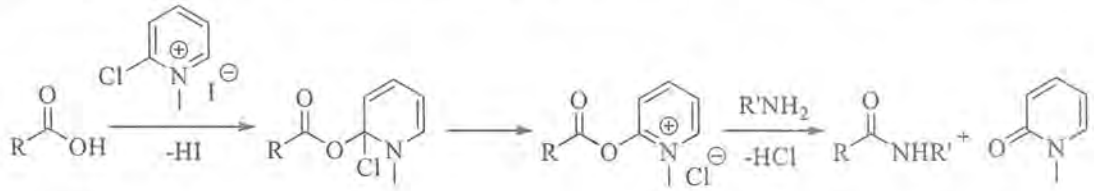


Figure 1.19: Structures of HATU, HBTU, and TOTU activating reagents.

1.9.4.3 From Ammonium Salts

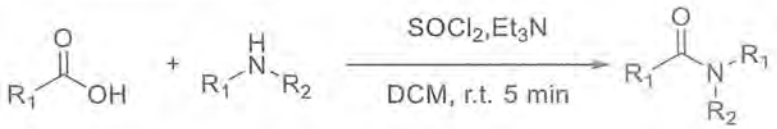
2-Chloro-1-methylpyridinium iodide (Mukaiyama's reagent) reacted with carboxylic acid to give activated pyridinium ester which coupled with numerous nucleophiles.[70]



Scheme 1.32: Carboxamide synthesis *via* Mukaiyama's reagent.

1.9.5 One pot synthesis of amide using $SOCl_2$

Leggio A., *et al.* reported the one pot synthesis of amide bond by converting carboxylic acid to acid chloride using thionyl chloride.They synthesized by taking one equivalent of acid, one equivalent of amine and 3 equivalents of trimethylamine in DCM followed by addition of $SOCl_2$ at room temperature.[71]



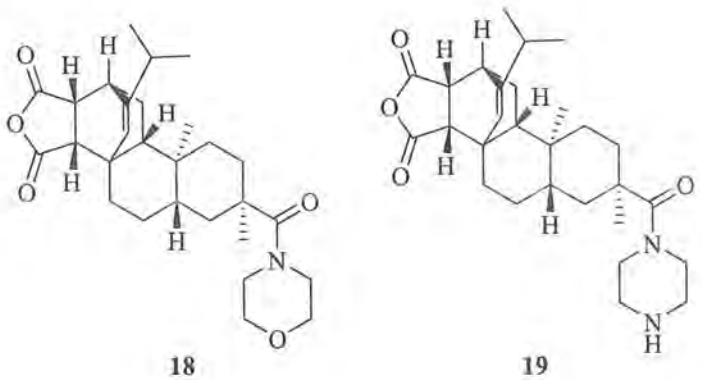
Scheme 1.33: One pot synthesis of amide bond by $SOCl_2$

1.10 Pharmacological Activities of Carboxamides

Carboxamides exhibit a wide range of pharmacological activities and are the most effective chemotherapeutic reagents. They can be used as antifungal, anticonvulsant, antiviral, antitumor, antibacterial, anti-inflammatory insecticidal and analgesic.[72]

1.10.1 Anti-Inflammatory Activity

Kevakoza *et al.*, reported the synthesis of carboxamides of maleopimaric acid with morpholine and piperazine (compound **18** and **19**, Fig 1.20), and the biological assay confirmed their anti-inflammatory activity.[73]

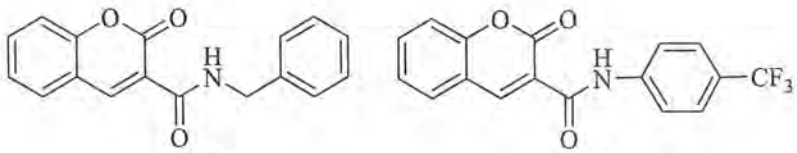


18 19

Figure 1.20: Structures of carboxamides having anti-inflammatory activity.

1.10.2 Analgesic Activity

Bonsignore *et al.,* reported the synthesis of 2-oxo-1-benzopyran carboxamide derivatives (compound **20** and **21**, Fig 1.21), and their biological assay confirmed their analgesic activity.[74]

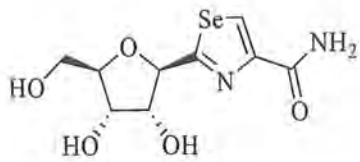


20 21

Figure 1.21: Structures of carboxamides having analgesic activity.

1.10.3 Anti-tumor Activity

Sarivastava *et al.,* reported the synthesis of 2-β-D-ribofuranosylselenazole-4-carboxamide (compound **22**, Fig 1.22). This carboxamide showed significant effectiveness against tumors.[75]

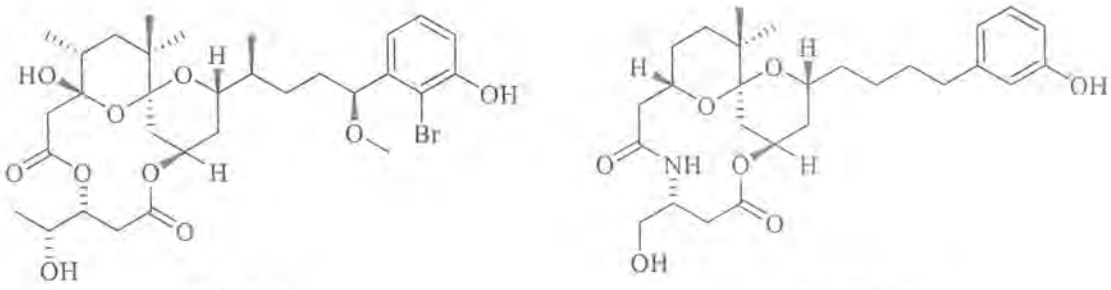


22

Figure 1.22: Structure of carboxamide having antitumor activity.

1.10.4 Anti-Proliferative and Cytotoxic Activity

Hanaki *et al.,* reported the synthesis of aplog-1 and confirmed its effectiveness by cytotoxicity and anti-proliferative activity against human cancer cells. Structure of aplog-1 is like that of aplysiatoxin which is secreted by cyanobacteria as a defense against predators.[76]

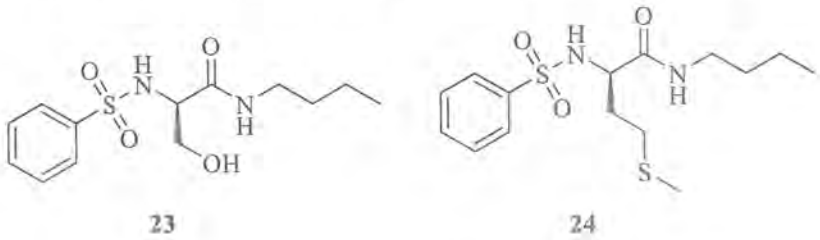


Aplysiatoxin Aplog-1

Figure 1.23: Structures of aplysiatoxin and its analog aplog-1.

1.10.5 Anti-biotic Activity

Eze *et al.*, reported the synthesis of (*R*)-*N*-butyl-3-hydroxy-2-(phenylsulfonamido)-propanamide, and its derivatives (compound **23** and **24**, Fig 1.24) confirmed their effectiveness against two Gram-positive bacteria ((i.e. *B. subtilis* and *S. aureus*) and three Gram-negative bacteria (i.e. *P. aeruginosa, E. coli* and *S. typhi*).[77]

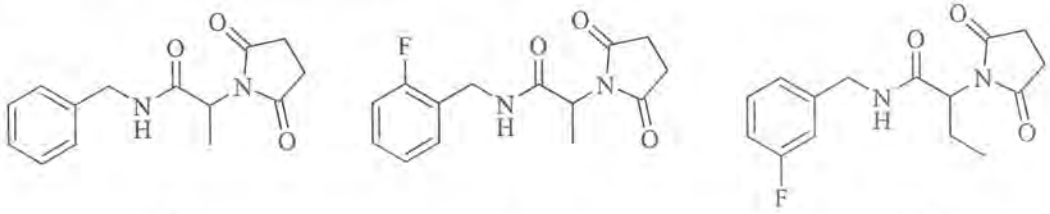


23 **24**

Figure 1.24: Structures of carboxamides having antibiotic activity.

1.10.6 Anticonvulsant Activity

Kaminiski *et al.*, reported the synthesis of *N*-benzyl-2-(2,5-dioxopyrrolidin-1-yl)-propanamide **25**, and its analogs **26-27**, and confirmed their anticonvulsant activity.[78]

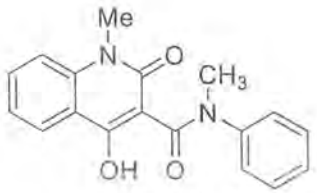


25 **26** **27**

Figure 1.25: Structures of carboxamides having anticonvulsant activity.

1.10.7 Anti-angiogenic Activity

Issacs T. *et al.* reported the synthesis of enol-carboxamide derivatives which are quite effective anti angiogenic agents. Roquinimex is an anti-angiogenic drug that prevents tumor cells from growing its own blood vessels.[79]



Roquinimex

Figure 1.26: Structure of Enol-Carboxamide an effective anti-angiogenic drug

1.11 Plan of Work

Getting an inspiration from biological importance of sulfonamides, stilbazoles and carboxamides, we planned to synthesize sulfamoyl-aminopyridine-carboxamides derivatives

In Part A, we planned to synthesize sulfamoyl benzoic acids starting from three different benzoic acids. Chlorosulfonation of different benzoic acids followed by reaction of sulfonylchloride part with different aromatic and aliphatic amines was planned. In part B, synthesis of different aminostilbazoles having one pyridyl and one phenyl or both pyridyl rings connected through trans alkeneic double bond will be carried. Finally, we planned to couple these sulfamoylbenzoic acids with aminostilbazoles and some simple aminopyridines by carboxamide bond.

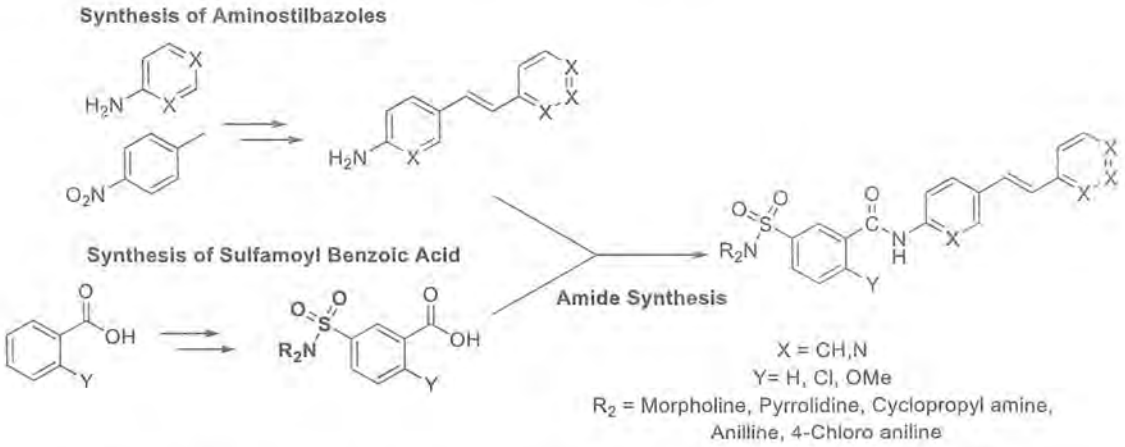


Figure 1.27: General scheme for the synthesis of Sulfamoyl aminopyridine carboxamides derivatives.

CHAPTER 2

EXPERIMENTAL

2.1 General Considerations

All the experiments were performed in clean and dried apparatus. Before setting up the reactions, the solvents were dried and distilled. Nitrogen inert atmosphere was maintained for reactions occurring in non-aqueous solvents. Anhydrous sodium sulphate was used for moisture removal from organic layer after solvent extraction. Thin layer chromatography (TLC) was used to monitor the progress of reaction. For that purpose, Merck plates with pre-coated silica gel-60 F_{254} having 0.2 nm thickness were used. UV visible spots were visualized under UV light at 254 nm wavelength while UV in-active compounds were also spotted by different spraying agents given below:

- **2,4-Dinitrophenylhydrazine (2,4-DNPH) stain:** 3g of 2.4-DNPH in 1:3 100ml solution of water: ethanol
- ***p*-Anisaldehyde stain:** 10 ml of anisaldehyde,7.5 ml of glacial acetic acid and 25 ml of conc.H_2SO_4 added in 250 mL of ethanol as solvent.
- **Ninhydrin stain:** 1.2 g of ninhydrin and 12 mL of glacial acetic acid added in 400 ml of EtOH.

Flash Column Chromatography was performed for purification of most of the products using silica gel (particle size 200-300 mesh).

2.2 Instrumentation

Melting points of synthesized compounds were ascertained by melting point apparatus Gallen Kamp (MP-D). The synthesized compounds were characterized by ^{13}C NMR and ^{1}H NMR spectroscopy using Bruker Avance 75 MHz and 300 MHz spectrophotometer respectively. The chemical shift values were reported in delta (δ) ppm and the value of coupling constant (J) was calculated in Hertz units (Hz). The deuterated solvents used to dissolve the sample of desired compound in NMR probe tube to take NMR spectrum were DMSO-d_6, $CDCl_3$, and acetone-d_6.

2.3 Drying and Distillation of Solvents

Moisture free and dry organic solvents were necessary to accomplish successful reaction. Solvents were dried and distilled using different drying agents and conditions. A brief description of drying and distillation of frequently used organic solvents have been given below which is widely employed in organic synthesis.

2.3.1 Toluene b.p 110.6 °C

Toluene was pre-dried using calcium hydride (CaH_2) and was further dried by reflux with sodium/benzophenone until color of solution turned dark blue. Distilled Toluene was stored over activated 3 Å molecular sieves.

2.3.2 Methanol b.p. 64.7 °C

Analytical grade methanol was used. Combination of Magnesium and iodine was used as a desiccant and refluxed so that color turned milky white. Then this methanol was distilled and stored over 3 Å molecular sieves.

2.3.3 Acetonitrile b.p. 82 °C

Acetonitrile is polar aprotic solvent have high solubility for most of the organic compounds and high affinity for water, therefore, it is difficult to dry. The solvent was distilled after 24 h of static drying with phosphorous pentoxide (P_2O_5) as desiccant. The dry distilled acetonitrile was stored over activated 3 Å molecular sieves.

2.3.4 Tetrahydrofuran b.p. 66 °C

Analytical grade THF was dried by refluxing the it with sodium/benzophenone under inert atmosphere till the solution turned dark blue. For performing moisture sensitive reactions, each time THF freshly distilled.

2.3.5 Dichloromethane b.p. 39.6 °C

DCM has low water content therefore easy to dry. To accomplish its drying, analytical grade DCM was distilled over anhydrous calcium hydride or calcium chloride and stored over activated 3 Å molecular sieves.

2.3.6 N,N-Dimethylformamide b.p. 153 °C

The drying of DMF was accomplished by vacuum distillation as it is polar aprotic solvent having high boiling point and water miscibility. The solvent was stirred

overnight with calcium hydride and then distilled over powdered and activated molecular sieves under reduced pressure. The DMF was stored over activated 3 Å molecular sieves under inert nitrogen.

2.4 Materials

All solvents and chemicals used were of analytical grade, unless otherwise mentioned. The chemicals were purchased from various suppliers such as Sigma-Aldrich, Merck etc. These chemicals include:

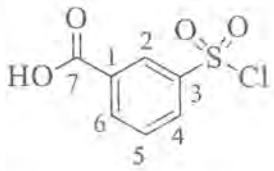
Chemicals	Manufacturer
Pyridinecarboxaldehye (98%) Triethylamine (99%) Sodium Acetate (99%) Pyrrolidine (99%) Dimethylsulfoxide (99.5%) 2-vinylpyridine (97%) 4-vinylpyridine (95%) $Pd(OAc)_2$ (99.9%) Tri(o-tolyl)phosphine (97%)	Sigma-Aldrich
Toluene (99%) Tetrahydrofuran (99.8%) *N,N'*-dimethylformamide (99.5%)	Merck Schuchardt

2.5 Synthesis of Sulfamoyl Benzoic acids

2.5.1 General procedure for the synthesis of chlorosulfonylbenzoic acids (1-2)

Chlorosulfonylbenzoic acids were synthesized according to reported procedure.[80] In an oven dried 25 mL two-neck round bottom flask equipped with magnetic stir bar fitted with condenser, 6 equivalents of chlorosulfonic acid was added and cooled to 0°C using ice bath. One equivalent of benzoic acid was added pinch by pinch and the resultant reaction mixture was heated at 110 °C for 12 hours. After completion of reaction, the reaction mixture was allowed to acquire the room temperature and then it was poured dropwise on the crushed ice. The brown precipitate of chlorosulfonylbenzoic acid **(1&2)** was collected through vacuum filtration.[81]

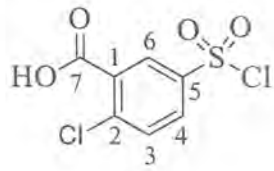
3-(Chlorosulfonyl)benzoic acid (1)



Yield: 85 %; **m.p.** 127-129 °C (Lit. 128 °C)

TLC (SiO_2): R_f = 0.5 ($CHCl_3$: CH_3OH :: 9.5: 0.5)

2-Chloro-5-(chlorosulfonyl)benzoic acid (2)



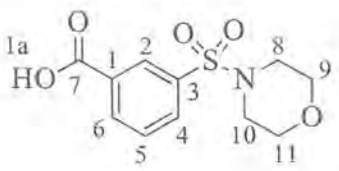
Yield: 76 %; **m.p.** 145-147 °C (Lit. 146 °C)

TLC (SiO_2): R_f = 0.4 ($CHCl_3$: CH_3OH :: 9.5: 0.5)

2.5.2 General procedure for the synthesis of Sulfamoyl benzoic acid (S1-S8)

Different derivatives of Sulfamoyl benzoic acid were synthesized using reported procedure.[14] In oven dried 100 mL 2 neck round bottom flask, one equivalent of chlorosulfonyl benzoic acid and one equivalent of an amine was added in water as a solvent at room temperature which resulted in suspension. The *p*H of suspension was adjusted to 8-9 *p*H by adding aq. Na_2CO_3. After completion of the reaction, concentrated HCl was added dropwise to adjust *p*H to 2-3. The precipitates thus formed were collected by filtration or in some cases the solvent extraction was performed with ethyl acetate to obtain the desired product in organic layer. Differently substituted sulfamoyl benzoic acids **(S1-S8)** were further purified through recrystallization.

3-(Morpholinosulfonyl)benzoic acid (S1)



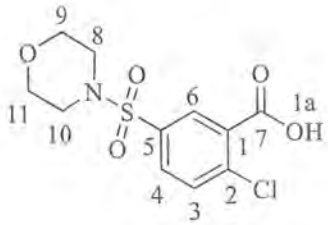
Yield: 89 %; **m.p.** 192-195 °C (Lit. 195 °C)

TLC (SiO_2): R_f= 0.3 ($CHCl_3$: CH_3OH :: 9.5: 0.5)

^1H NMR (300 MHz, Acetone-d_6): δ (ppm) 11.34 (*s*, H-7), 8.38 (*s*, H-2), 8.35-8.36 (*m*, H-4), 8.03-8.06 (*m*, H-6), 7.83-7.88 (*m*, H-5), 3.69-3.72 (*m*, H-9 and H-11), 2.98-3.01 (*m*, H-8 and H-10)

^{13}C NMR (75 MHz, Acetone-d_6): δ (ppm) 165.4 (C-7), 136.1 (C-3), 133.9 (C-1), 131.9 (C-2), 131.7 (C-4), 129.9 (C-6), 128.6 (C-5), 65.7 (C-9 and C-11), 46.1 (C-8 and C-10)

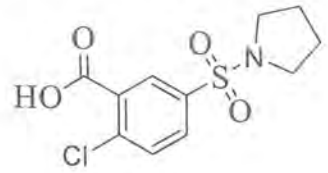
5-(Morpholinosulfamoyl)-2-chlorobenzoic acid (S2)



Yield: 81%, **m.p.** 186-188 °C.

TLC (SiO_2): R_f = 0.43 ($CHCl_3$: CH_3OH :: 8: 2)

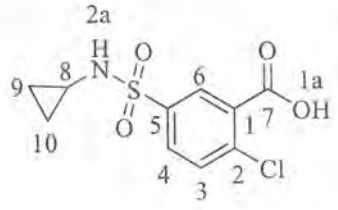
5-(pyrrolidinesulfamoyl)-2-chlorobenzoic acid (S3)



Yield: 83 %; **m.p.** 186-189 °C

TLC (SiO_2): R_f = 0.2 (CHCl3: CH3OH :: 9.5: 0.5)

5-(*N*-Cyclopropylsulfamoyl)-2-chlorobenzoic acid (S4)



Yield: 76%; **m.p.** 195-197 °C.

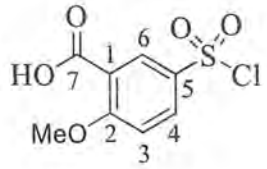
TLC (SiO_2): R_f = 0.29 ($CHCl_3$: CH_3OH :: 8: 2).

2.5.3 Synthesis of 2-methoxy-5-(chlorosulfonyl)benzoic acid

5-(chlorosulfonyl)-2-methoxybenzoic acid was synthesized according to reported procedure.[82] In an oven dried 25 mL two-neck round bottom flask equipped with magnetic stir bar fitted with condenser, 6 equivalents of chlorosulfonic acid was added

and cooled to 0°C using ice bath. One equivalent of 2-methoxybenzoic acid was added pinch by pinch and the resultant reaction mixture was heated at 40°C for 6 hours. After completion of reaction, the reaction mixture was poured on the crushed ice. The off-white precipitate of 5-(chlorosulfonyl)-2-methoxybenzoic acid was collected through vacuum filtration.

2-Methoxy-5-(chlorosulfonyl)benzoic acid (3)

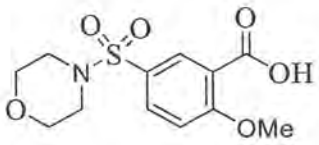


Yield: 76 %; **m.p.** 146-148 °C (Lit. 147-149 °C)

TLC (SiO_2): R_f = 0.3 ($CHCl_3$: CH_3OH :: 9.5: 0.5)

2.5.4 Synthesis of 5-(morpholinesulfamoyl)-2-methoxybenzoic acid (S7)

In oven dried 100 mL 2 neck round bottom flask, 5-(chlorosulfonyl)-2-methoxybenzoic acid (1.5g, 5.98 mmol, 100 mol%) and morpholine (0.52 mL, 5.98 mmol, 100 mol%) was added in water as a solvent at room temperature which gives suspension. The *p*H of suspension was adjusted to 8-9 *p*H by adding aq. Na_2CO_3. After completion of the reaction, concentrated HCl was added dropwise to adjust *p*H to 2-3. The precipitates thus formed were collected by filtration.



Yield: 72 %; **m.p.** 177-179 °C

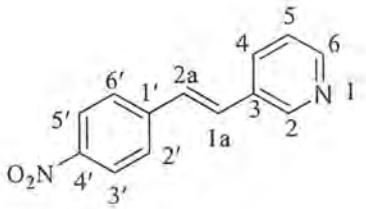
TLC (SiO_2): R_f = 0.2 ($CHCl_3$: CH_3OH :: 9.5: 0.5)

2.6 Synthesis of Aminostilbazoles

2.6.1 Synthesis of 4'-nitrostilbazoles (SNT-1)

Synthesis of 3-(4'-nitro)stilbazole was synthesized according to reported procedure.[83] In oven dried 25 mL 2 neck round bottom flask, 4-nitrotoluene (1.02g , 7.47 mmol, 200 mol%) , pyridine-3-carboxaldehyde (0.35 mL, 3.73 mmol, 100 mol%), Tetrabutyl ammonium hydrogen sulfate (253.6 mg, 0.75 mmol, 20 mol%) and sodium hydroxide

(30 mg, 0.75 mmol, 20 mol%) was added in 7 mL of toluene under inert nitrogen and the reaction mixture was stirred for 36 hours at room temperature. After completion of reaction, first solvent extraction was performed at basic *p*H to remove water soluble by products. Second solvent extraction was performed at *p*H 2. Aqueous layer we get after second extraction was basify by using sodium bicarbonate solution and extracted with ethyl acetate to take the product in organic layer. Organic layer was dried by sodium sulfate and concentrated by rotavap to get yellow precipitates of 3-(4'-nitro)stilbazole product.



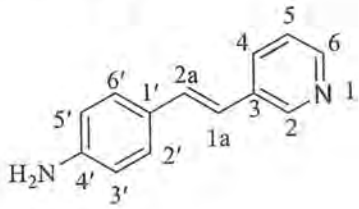
Yield: 51 %; **m.p.** 129-131 °C

TLC (SiO_2): R_f = 0.4 (EtOAc : n-Hex:1: 1)

MS (m/z): 226 ($M^{+\cdot}$), 179, 152,127, 102, 76, 51, 30

2.6.2 Synthesis of 4'-aminostilbazoles (ST-1)

Nitro group of 4'-nitrostilbazoles was reduced to amino group to obtain 4'-aminostilbazoles. In an oven dried 100 mL 2 neck round bottom flask fitted with condenser, 400 mol% of $SnCl_2$ were added slowly at room temperature to the mixture of 800 mol% of hydrochloric acid, methanol/water (1/1) and one equivalent of 4'-nitrostilbazole. After adding $SnCl_2$ slowly to the reaction mixture at room temperature, the temperature of reaction mixture was increased to 70 °C and stir for two hours. After completion of reaction, solvent extraction was performed with ethyl acetate at *pH* 8 to obtain the desired product in organic layer.[84]



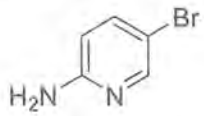
Yield: 77 %; **m.p.** 127-129 °C

TLC (SiO_2): R_f = 0.3 (EtOAc : n-Hex:1: 1)

MS (m/z): 196 ($M^{+\cdot}$), 167, 139,115, 84, 63, 39, 18

2.6.3 Synthesis of 5-bromo-2-aminopyridine

In an oven dried 125 mL three neck round bottom flask fitted with condenser, one equivalent of 2-aminopyridine was dissolved in glacial acetic acid and cooled to 0°C using ice bath. Solution of one equivalent of bromine in glacial acetic acid was prepared and this solution was then added dropwise in the reaction mixture using dropping funnel. As a result, yellow precipitation occured. On further addition of bromine, precipitates disappear and turned to yellow color solution. After complete addition of bromine, reaction was heated at 40°C for 4 hours. After completion of reaction, reaction mixture was extracted with ethyl acetate at *p*H 8-9 and desired product was isolated and purified by column chromatography using EtOAc : n-Hex (1.5-8.5) as eluent.

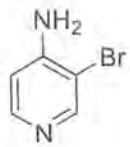


Yield: 60 %; **m.p.** 131-135 °C

TLC (SiO_2): R_f = 0.5 (EtOAc : n-Hex:1: 1)

2.6.4 Synthesis of 3-bromo-4-aminopyridine

In an oven dried 125 mL two neck round bottom flask, 4-aminopyridine (500 mg, 5.31 mmol, 100 mol %) was dissolved in 12 mL acetonitrile and *N*-bromosuccinamide (1.13 g , 6.38 mmol, 120 mol%) was slowly added in reaction flask and the reaction was stirred for 48 hours at room temperature. After completion of reaction, reaction mixture was concentrated and product was isolated by column chromatography (EtOAc: n-hexane:: 2:8).[85]



Yield: 74 %; **m.p.** 131-135 °C (Lit. 133-138°C) [85]

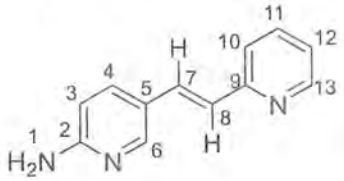
TLC (SiO_2): R_f = 0.4 (EtOAc : n-Hex:1: 1)

MS (m/z): 172 ($M^{+\cdot}$), 118, 93,66, 39,

2.6.5 Synthesis of (*E*)-2-(2-(pyridin-3-yl)vinyl)pyridine by Heck coupling (ST-2)

(*E*)-2-(2-(Pyridin-3-yl)vinyl)pyridine was synthesized by following reported procedure.[86] In an oven dried sealed tube, 5-bromo-2-aminopyridine (150 mg, 0.867 mmol, 100 mol%) , 2-vinylpyridine (0.2 mL, 1.73 mmol, 200 mol%), sodium acetate

(182.31 mg, 1.73 mmol, 200 mol%), $Pd(OAc)_2$ (9.73 mg, 0.043mmol, 5 mol%), *rac*-BINAP (6.75mg, 0.011 mmol, 1 mol%) and $P(o\text{-}tol)_3$ (31.67 mg , 0.104 mmol, 12 mol%) was added in dioxane (1.73 mL, 0.5 M) sealed tube purged with inert nitrogen. The reaction mixture was heated at 120 °C for 48 hours in sealed tube. After completion of reaction, flash column chromatography (EtOAc: n-Hex = 7:3, Et_3N 0.2 mL) was carried out to isolate yellow precipitate of desired product.



Yield: 71 %; **m.p.** 130-132 °C

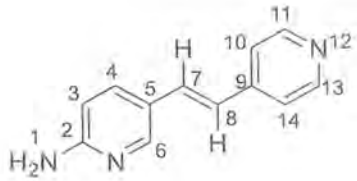
TLC (SiO_2): R_f = 0.2 (EtOAc : n-Hex:8: 2)

^{1}H NMR (300 MHz, acetone-d_6): δ (ppm) 5.74 (*s*, H-1), 6.65 (*d*, H-3, ^3J = 8.7 Hz), 7.43 (*d*, H-4, ^3J = 8.7 Hz), 7.07 (*d*, H-8, ^3J = 16.2 Hz), 7,18 (*dd*, H-10), 7.65 (*d*, H-7 ^3J = 16.2 Hz), 7.73 (*td*, H-11, ^3J = 7.8 Hz; ^4J = 1.8 Hz), 7.84 (*dd*, H-12, ^3J = 8.4 Hz; ^4J = 2.1 Hz), 8.19 (*d*, H-6 ^4J = 2.1 Hz), 8.55 (*d*, H-13, ^3J = 4.5 Hz)

^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 159.7 (C-2), 156.08 (C-9), 149.47 (C-6), 148.62 (C-13), 136.33 (C-7), 134.27 (C-12), 129.7 (C-11), 124.21 (C-4), 121.88 (C-10), 121.55 (C-5), 121.42 (C-8), 108.2 (C-3)

2.6.6 Synthesis of (*E*)-3-(2-(pyridin-4-yl)vinyl)pyridine by Heck coupling (ST-3)

In an oven dried sealed tube, 5-bromo-2-aminopyridine (150 mg, 0.867 mmol, 100 mol%) , 4-vinylpyridine (0.19 mL, 1.73 mmol, 200 mol%), sodium acetate (182.31 mg, 1.73 mmol, 200 mol%), $Pd(OAc)_2$ (9.73 mg, 0.043mmol, 5 mol%), *rac*-BINAP (6.75mg, 0.011 mmol, 1 mol%) and $P(o\text{-}tol)_3$ (31.67 mg , 0.104 mmol, 12 mol%) was added in dioxane (1.73 mL, 0.5 M) sealed tube and purged with inert nitrogen. The reaction was heated at 120 °C for 48 hours in sealed tube. After completion of reaction, Flash column chromatography (EtOAc: n-Hex = 5:5 , Et_3N 0.2 mL) was done to isolate yellow precipitate of desired product.



Yield: 60 %; **m.p.** 135-137 °C

TLC (SiO_2): R_f = 0.28 (EtOAc : n-Hex:8: 2)

MS (m/z): 197 ($M^{+\cdot}$), 169, 142, 115, 87, 51, 28

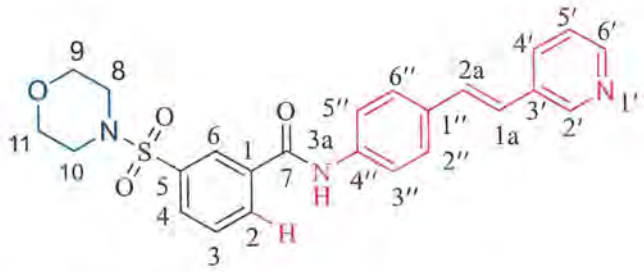
2.7 Synthesis of Carboxamides

2.7.1 Synthesis of *N*-substitutedsulfamoyl benzamide by EDC as coupling reagent (3a-3f)

N-substitutedsulfamoyl benzamide was synthesized by using EDC and DMAP for coupling. 100 mol% of *N*-substituted sulfamoylbenzoic acid was dissolved in 0.5 M DCM and 1.5 M DMF. 10 mol% DMAP, 100 mol% amine and 200 mol% of EDC were added to the reaction mixture and reaction mixture was allowed to stir in inert atmosphere for 24 hours. An undesired product i.e., urea formed from EDC during the reaction. After the completion of reaction, solvent extraction was performed with ethyl acetate at *p*H 2-3 to remove DMAP and by-product urea from the reaction mixture in aqueous layer. Combined organic layers was dried using anhydrous sodium sulfate and concentrated to get the solid product. Product was further purified by washing with acetone.

2.6.1.1 (*E*)-3-(Morpholinosulfonyl)-N-(4-(2-(pyridin-3-yl)vinyl)phenyl)benzamide (3a)

Compound **3a** was synthesized according to the above-mentioned procedure. In oven dried 25 mL two neck round bottom flask, compound 3a was synthesized using (*E*)-3-(4-aminostyryl) pyridine (108.51 mg, 0.553 mmol, 100 mol%), 3-(morpholinosulfamoyl)benzoic acid (150 mg, 0.553 mmol, 100 mol%), DMAP (6.76 mg, 0.055 mmol, 10 mol%) and EDC.HCl (265 mg, 1.38 mmol, 250 mol%). Product was further purified by washing with acetone.



Yield: 61 %; **m.p.** 233-237 °C

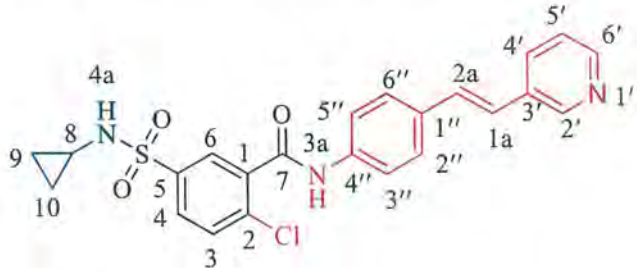
TLC (SiO_2): R_f = 0.2 (EtOAc : n-Hex:: 1: 1)

^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 10.67 (*s*, H-3a), 7.23 (*d*, H-2a, ^3J = 16.5 Hz), 7.36-7.42 (*m*, H-1a and H-4′), 7.65 (*d*, H-5″ and H-3″), 8.77 (*d*, H-2′, ^3J = 1.8 Hz), 8.45 (*dd*, H-5′), 8.33 (*d*, H-2), 8.28 (*m*, H-6′), 8.05 (*dd*, H-3), 8.03 (*m*, H-4), 7.82-7.97(*m*, H-6, H-2″ and H-6″) 2.92 (*t*, 4H, H-8 and H-10), 3.64 (*t*, 4H, H-9 and H-11)

^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 164.7 (C-7), 148.7 (C-2'), 139.1 (C-6'), 136.4 (C-2 and C-5), 135.3 (C-4'), 133.37 (C-4"), 133.0 (C-1"), 132.9 (C-1 and C-4), 130.9 (C-1a), 130.4 (C-3), 130.3 (C-6), 127.5 (C-2a), 127.1 (C-2" and C-6"), 124.4 (C-3'), 124.2 C-5') 121.1 (C-3" and C-5"), 65.7 (C-9 and C-11), 46.3 (C-8 and C-10).

2.6.1.2 (*E*)-2-Chloro-5-(N-cyclopropylsulfamoyl)-*N*-(4-(2-(pyridin-3-yl)vinyl)phenyl)benzamide (3b)

Compound **3b** was synthesized according to the above-mentioned procedure using (*E*)-3-(4-aminostyryl)pyridine (106.7 mg, 0.544 mmol, 100 mol%), 5-(morpholinosulfamoyl)-2-chlorobenzoic acid (150 mg, 0.544 mmol, 100 mol%), DMAP (6.65 mg, 0.054 mmol, 10 mol%) and EDC.HCl (261 mg, 1.36 mmol, 250 mol%). Product was purified by washing with acetone. After purification the amount of product obtained was 128.4 mg with 52% yield.



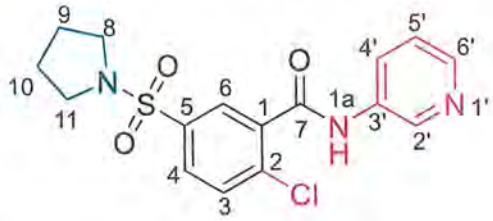
Yield: 52 %; **m.p.** 244-246 °C

TLC (SiO_2): R_f = 0.26 (EtOAc : n-Hex :: 1: 1)

^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 10.84 (*s*, H-3a), 8.77 (*s*, H-4a), 8.45 (s, H-2'), 8.15 (s, H-6), 8.04 (d, H-6'), 7.84-7.95(m, H-3,H-4 and H-5') 7.23 (*d*, H-2a, ^3J = 16.8 Hz), 7.36-7.41 (*m*, H-1a and H-4'), 7.63-7.66 (*m*, H-5'', H-3'', H-2'', H-6''). 2.16 (1H, H-8), 0.44-0.54 (4H, H-9 and H-10)

^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 164.0 (C-7), 148.6 (C-2'), 139.8 (C-6'), 138.8 (C-2 and C-5), 137.8 (C-4'), 134.67 (C-4''), 133.3 (C-1''), 133.0 (C-1 and C-4), 131.3 (C-1a), 130.3 (C-3), 129.7 (C-6), 127.7 (C-2a), 127.4 (C-2'' and C-6''), 124.4 (C-3'), 124.2 (C-5') 120.2 (C-3'' and C-5''), 24.6 (C-9 and C-10), 5.68 (C-8).

2.6.1.3 2-chloro-*N*-(pyridin-3-yl)-5-(pyrrolidin-1-ylsulfonyl)benzamide (3c)



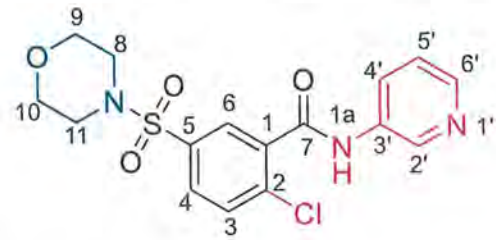
Yield: 71 %; **m.p.** 212-215 °C

TLC (SiO_2): R_f = 0.4 (EtOAc : n-Hex :: 1: 1)

^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 10.91 (*s*, H-1a), 8.5 (*d*, H-2'), 8.35 (*d*, h-6'), 8.15 (*m*, H-5'), 8.03 (*d*, H-6) 7.93 (H-4). 7.84 (H-3) 7.43 (H-4'), 3.23 (*t*, H-8 and H-11), 1.7 (*t*, H-9 and H-10)

^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 164.34 (C-7), 145.5 (C-2'), 141.7 (C-6'), 137.5 (C-2), 136.0 (C-5), 135.7 (C-1), 135.2 (C-3'), 131.5 (C-3), 130.3 (C-4), 128.0 (C-5'), 127.2 (C-6), 124.2 (C-4'), 48.3 (C-8 and C-11), 25.7 (C-9 and C-10)

2.6.1.3 2-chloro-5-(morpholinosulfonyl)-*N*-(pyridin-3-yl)benzamide (3d)



Yield: 62 %; **m.p.** 208-211 °C

TLC (SiO_2): R_f = 0.30 (EtOAc : n-Hex :: 1: 1)

^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 10.92 (*s*, H-1a), 8.85 (*d*, H-2'), 8.35 (*d*, h-6'), 8.15 (*d*, H-5'), 7.97 (*d*, H-6), 7.84 7.97 (H-4 and H-3), 7.43 (H-4'), 3.65 (*t*, H-9 and H-10), 2.95 (*t*, H-8 and H-11)

^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 164.26(C-7), 145.5 (C-2'), 141.7 (C-6'), 137.7 (C-2), 135.7 (C-5 and C-1), 134.1 (C-3'), 131.5 (C-3), 130.3 (C-4), 128.0 (C-5'), 127.2 (C-6), 124.2 (C-4'), 65.7 (C-9 and C-10), 46.3 (C-8 and C-11)

CHAPTER 3
RESULTS AND DISCUSSION

We synthesized sulfamoyl aminopyridine carboxamides derivatives starting from the chlorosulfonation of different benzoic acids followed by treatment with different amines to get *N*-substituted sulfamoyl benzamides that were coupled with 4'-aminostilbaole and aminopyridine based stilbazoles using EDC coupling.

4'-aminostilbazole were synthesized by the knoevenagel condensation of 4-nitrotoluene with 3-pyridinecarboxaldehyde to give 4'-nitrostilbazoles which reduce to 4'-aminostilbazoles using tin chloride and HCl as a reducing agent. Aminopyridine based stilbazole was also synthesized with Heck coupling of different bromo aminopyridine substrates with vinyl pyridine. Various stilbazole based sulfonamide-carboxamides derivatives and also some simple aminopyridne based sulfamoyl carboxamide derivatives were synthesized to develop structure-activity relationship.

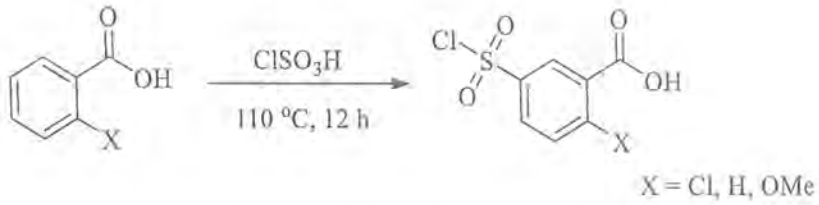
Synthesis of sulfamoyl aminopyridine carboxamides is elaborated below involving the following steps:

3.1 Chlorosulfonation of different benzoic acids

Chlorosulfonic acid is generally electrophilic aromatic substitution reaction used for the chlorosulfonation of aromatic rings. Three different benzoic acids were used with some variation of temperature depending on reactivity of benzoic acid. As chlorosulfonic acid is very strong acid so this electrophilic substitution is quite feasible and gave good yields of sulfamoyl benzoic acids.

3.1.1 Synthesis of Chlorosulfonylbenzoic Acids

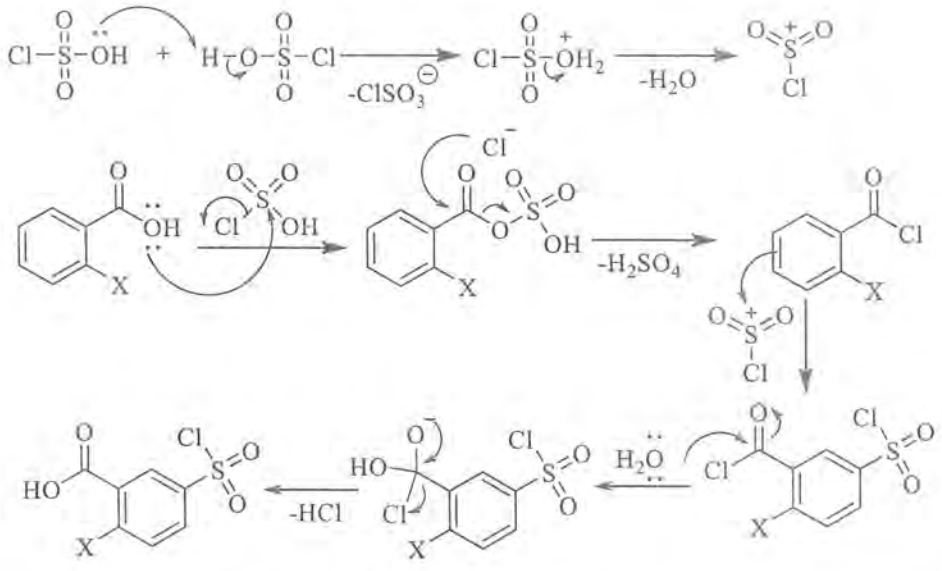
Chlorosulfonylbenzoic Acids was synthesized by reaction with chlorosulfonic acid. Chlorosulfonic acid was cooled to 0°C and benzoic acids was added slowly as heat evolved and then reaction was carried at 110°C for 12 hours. For 2-methoxy benzoic acid, reaction was carried at 40°C for 6 hours. After completion of reaction, reaction mixture poured into ice slowly to afford off white to yellow precipitates. Precipitates formed were filtered, washed with water, and dried in vacuum filtration.



Scheme 3.1: Synthesis of Chlorosulfonylbenzoic acid.

3.1.2 Mechanism for the synthesis of Chlorosulfonylbenzoic acid

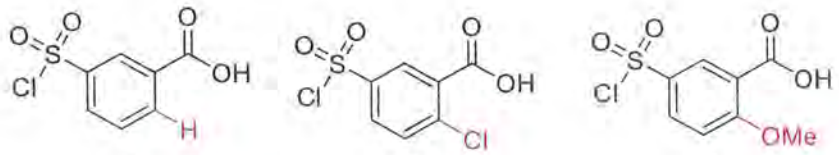
Mechanism of this reaction involves chlorosulfonylium ion formation as electrophile by two molecules of chlorosulfonic acid and one equivalent of chlorosulfonic acid reacts with hydroxyl of carboxyl group of benzoic acid to convert it into benzoylchloride. Then, electrophilic aromatic substitution reaction was done in which chlorosulfonylium ion acts as electrophile and is attacked by the aromatic ring and attached *meta* to -COCl. When reaction mixture is poured onto ice, water hydrolyzed the acid chloride and acid functionality regenerated while chlorosulfonyl remained intact. Mechanism for the synthesis of Chlorosulfonylbenzoic acid is depicted in scheme 3.2.



Scheme 3.2: Mechanism for the synthesis of Chlorosulfonylbenzoic acid.

3.1.3 Characterization by Physical Parameters

Physical data of synthesized derivatives of 5-(chlorosulphonyl)-2-substituted benzoic acid is given in the table 3.1.



1 2 3

Table 3.1: Physical data of derivatives of Chlorosulfonyl benzoic acid

Compd.	Colors	R_f^*	Melting points (ºC)	Yield (%)
1	Light yellow	0.5	127-129 (Lit. 128)	85
2	Light brown	0.4	145-147 (Lit. 146)	76
3	White	0.3	147-150 (lit 147-148)	74

*($CHCl_3$:MeOH::9.5:0.5) on pre coated silica gel plates $60F_{254}$ visualized under UV light at 254 nm

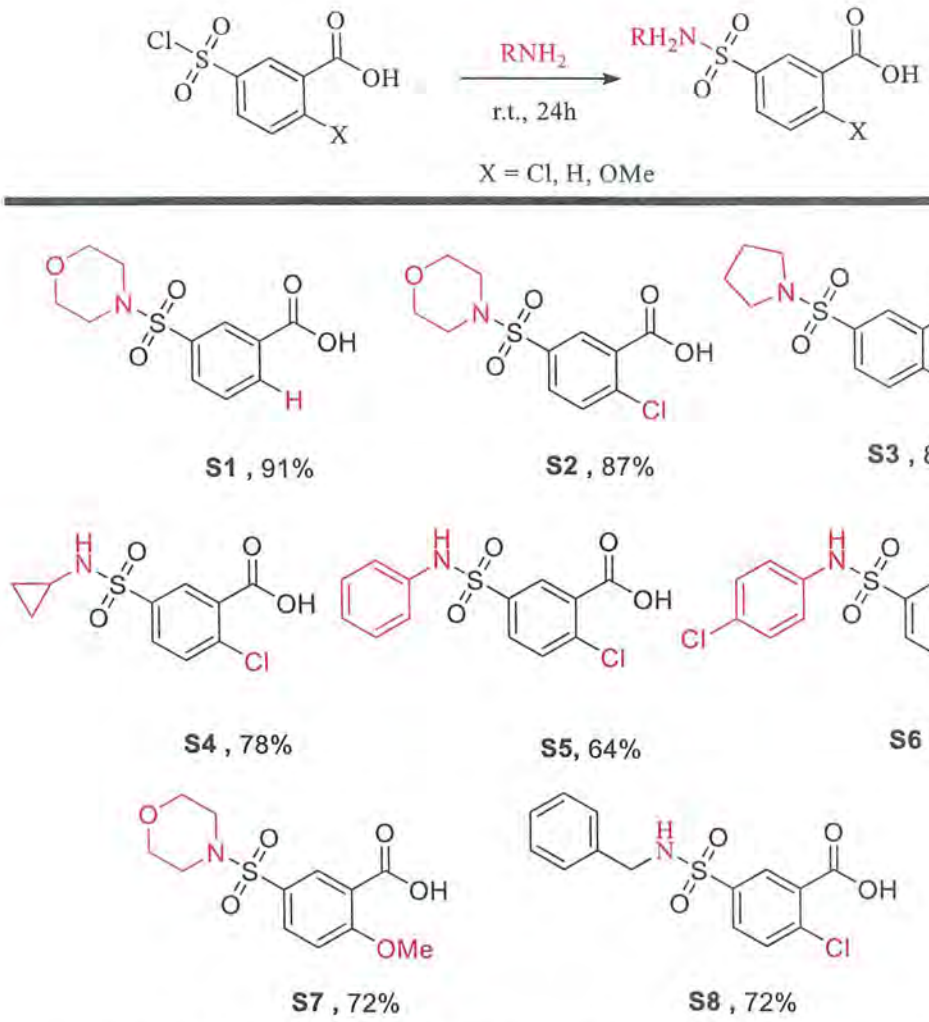
3.2 Synthesis of Sulfamoyl Benzoic acids

The amides of sulfonic acids are commonly known as sulfonamides. This class of compounds comprises $-SO_2NH_2$ functional group. Usually, sulfamoyl benzoic acids can be synthesized from sulfonyl chlorides and primary or secondary amines.

3.2.1 Synthesis of *N*-substitutedsulfamoyl benzoic Acids

N-Substituted sulfamoyl benzoic acids were formed by reacting Chlorosulfonylbenzoic acids with different amines like morpholine, cyclopropylamine, pyrrolidine, aniline, 4-chloroanilline etc. The resulting mixture was allowed to stir at room temperature for 24 hours.

After completion, solvent extraction was performed at *pH* 3 using ethyl acetate to obtain the desired product in organic layer. Product was further purified through recrystallization and column chromatography. Differently substituted sulfamoyl benzoic acids having morpholine, cyclopropylamine, pyrrolidine, aniline, benzylamine, 4-chloroanilline etc. were prepared with good yield.



Scheme 3.3: Synthesis of 5-(substitutedsulfamoyl)-2-chlorobenzoic acids.

3.2.2 Characterization by physical parameters

Physical data of synthesized derivatives of Sulfamoyl benzoic acids is given in table 3.2.

Table 3.2: Physical data of derivatives of Sulfamoyl benzoic acids (**S1-S8**)

Compd.	Colors	R_f^*	Melting points (ºC)	Yield (%)
S1	White	0.2	192-195	91
S2	White	0.3	182-184	87
S3	White	0.2	186-189	83
S4	Light grey	0.6	225-228 (Lit. 229)	78
S5	White	0.3	181-185	64
S6	Grey	0.5	205-207	54

S7	white	0.3	182-184	87
S8	white	0.3	225-228	80

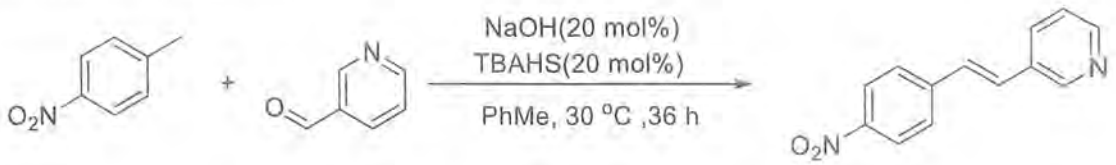
3.3 Synthesis of Amino Stilbazoles

Stilbazoles are compounds, also known as styrlpyridines, having stilbene like structure in which one of the carbon of ring is replaced by nitrogen. In Stilbazoles, one phenyl and one pyridine ring or both pyridine rings connected through double bond. Stilbazoles can be cis or trans depending on configuration of double bond.

Different methodologies have been used to synthesize different stilbazoles like Heck coupling, condensation reaction of picolines and activated $-CH_3$ with aldehydes by Grignard reagent etc. Here, different Stilbazoles were synthesized by Knoevenagel condensation of 4-nitrotoluene with Nicotinaldehyde and Heck reaction using different bromo aminopyridine with differently substituted vinylpyridines.

3.3.1 Synthesis of 4'-nitrostilbazole (SNT-1)

In pre dried and washed 25 mL 2 neck round bottom flask, 4-nitrotoluene (1.02g , 7.47 mmol, 200 mol%) , pyridine-3-carboxaldehyde (0.35 mL, 3.73 mmol, 100 mol%), Tetrabutyl ammonium hydrogen sulfate(253.6 mg, 0.75 mmol, 20 mol%) and sodium hydroxide (30 mg, 0.75 mmol, 20 mol%) was added in 7 mL of toluene under inert nitrogen and the reaction was stirred for 36 hours at 30 °C. After completion of reaction, first solvent extraction was performed at basic *p*H to remove water soluble by products. Second solvent extraction was performed at *p*H 2. Aqueous layer we get after second extraction was basify by using sodium bicarbonate solution as yellow ppt formed which was extracted with ethyl acetate to take the product in organic layer. Organic layer was dried by sodium sulfate and concentrated by rotavap to get yellow precipitates of 3-(4'-Nitro)stilbazole product.



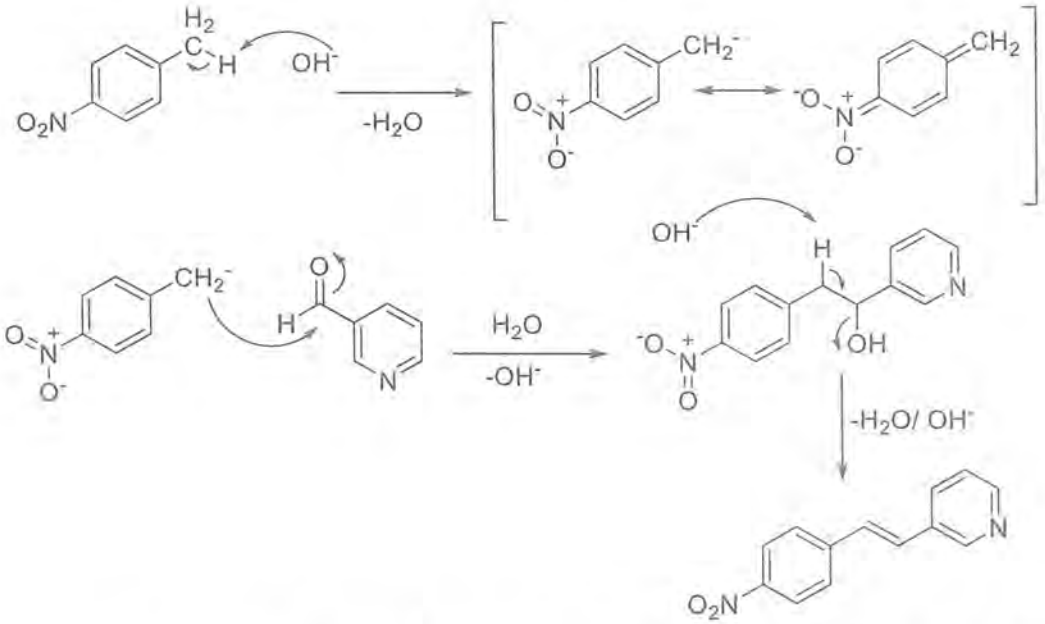
Scheme 3.4: Synthesis of 3-(4'-Nitro)stilbazole

Yield: 51 %; **m.p.** 129-131 °C

TLC (SiO_2): R_f = 0.4 (EtOAc : n-Hex:1: 1)

3.3.1.1 Mechanism of condesnation of 4-nitrotouene with nicotinaldehyde

Mechanism of Knoevenagel condensation of 4-nitrotoluene with 3-pyridinecarboxaldehyde is shown in **scheme 3.5**. 4-nitro toluene having electron withdrawing group at para position makes methyl proton acidic (pka= 20.4). Attack of hydroxide ion on $-CH_3$ group of 4-nitrotoluene generates carbonanion which was stabilized by nitro group present at para to carbonanion. In next step, this carbonanion attacks on carbonyl of 3-pyridinecarboxaldehyde to give alcohol. In last step, base abstract proton adjacent to hydroxide group followed by elimination of –OH group by E1cB mechanism to give desired 4'-nitrostilbazole.



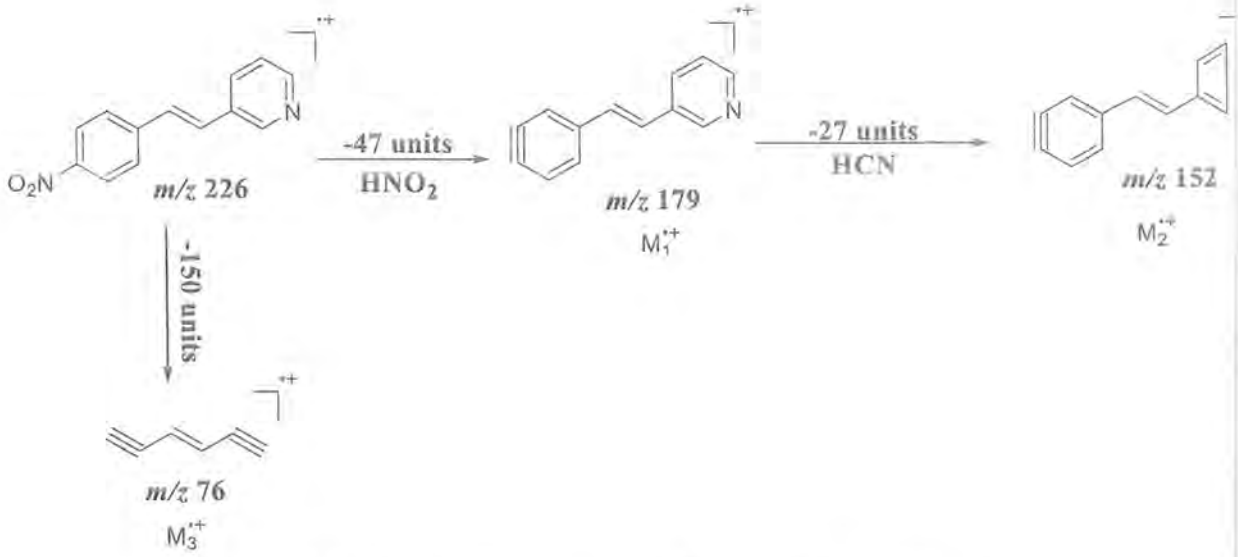
Scheme 3.5: Mechanism of Knoevenagel condensation of 4-nitrotoluene with 3-pyridinecarboxaldehyde

3.3.1.2 Characterization by GC-MS analysis

The major peaks appeared in GC-MS spectrum of 4'-nitrostilbazole are given below:

MS (m/z): 226 ($M^{+\cdot}$), 179, 152,127, 102, 76, 51, 30

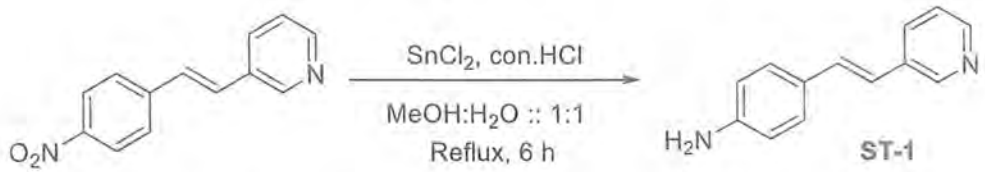
Mass fragmentation pattern for compound **SNT-1** is depicted in the **scheme 3.6.** Molecular ion peak appeared at m/z 226 confirmed the formation of nitrostilbazole. The peak at m/z 179 corresponded to (*E*)-3-(2-(cyclohexa-1,5-dien-3-yn-1-yl)vinyl)pyridine radical cation which appears due to loss of HNO_2 radical from molecular ion. Further loss of 27 mass units from this fragment ion gives peak at m/z 152 is corresponding to radical cation which appears due to loss of HCN from M_1. The peak at m/z 76 corresponds to M_3 radical cation due to loss of 150 mass unit.



Scheme 3.6: Fragmentation pattern of compound (**SNT-1**)

3.3.2 Synthesis of 4'-Aminostilbazoles (ST-1)

Nitro group of 4'-nitrostilbazoles was reduced to amino group to obtain 4'-aminostilbazoles. 4'-nitrostilbazoles dissolved in methanol/water (1/1) and 800 mol% of HCl added followed by addition of 400 mol% of $SnCl_2$ pinch by pinch at room temperature. After adding $SnCl_2$ slowly to the reaction mixture at room temperature, the temperature of reaction mixture was increased to 70 °C for two hours. After completion of reaction, solvent extraction was performed with ethyl acetate at pH 8 to obtain the desired product in organic layer.



Scheme 3.7: Reduction of 3-(4'-Nitro)Stilbazole to 3-(4'-amino)stilbazole

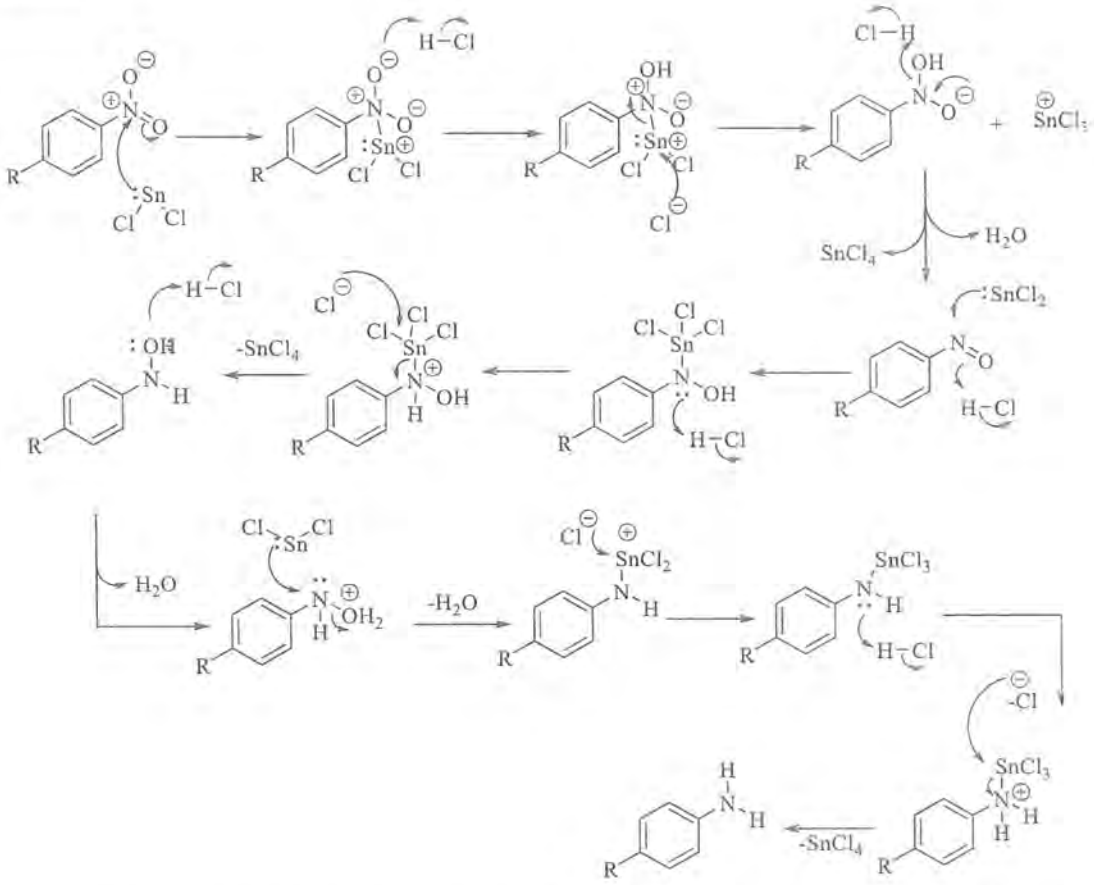
Yield: 77 %; **m.p.** 127-129 °C

TLC (SiO_2): R_f = 0.3 (EtOAc : n-Hex:1: 1)

3.3.2.1 Mechanism of Reduction of -NO_2 to -NH_2 using $SnCl_2$/HCl

Mechanism of reduction for conversion of -NO_2 to -NH2 using $SnCl_2$/HCl is depicted in **scheme 3.8.** Reduction of nitrostilbazole was carried using tin chloride and HCl as reducing agents. One molecule of $SnCl_2$ and two molecules of HCl converts nitro group to nitroso group. Another molecule of $SnCl_2$ and two molecules of HCl converts nitroso group to hydroxylamine. Another molecule of $SnCl_2$ and two molecules of HCl

converts hydroxylamine to amino group. Hence, three molecules of $SnCl_2$ and six molecules of HCl are required for the reduction of one molecule of nitro substrate into amine.



Scheme 3.8: Mechanism of reduction of $-NO_2$ to $-NH_2$ using $SnCl_2$/HCl.

3.3.2.2 Characterization of ST-1 by MS spectrum

GC-MS spectrum for compound **ST-1** was recorded and following major peaks were appeared in MS spectrum as given in **table 3.3**

Table 3.3: Major peaks in MS spectrum of compound **ST-1** is given below:

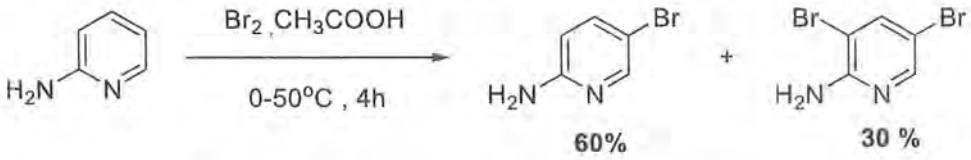
MS(m/z): 196($M^{\cdot+}$), 167,139,115,84,63,39,18

3.3.3 Synthesis of 5-bromo-2-aminopyridine

Bromination of 2-aminopyridine was simply electrophilic aromatic substitution reaction which can be performed due to electron donating group at 2-position which by resonance activate the para-position of ring where bromination occur with high extent. Steric and electronic effects favors formation of 5-bromo-2-aminopyridine.

In oven dried 125 mL three neck round bottom flask fitted with condenser, one equivalent of 2-aminopyridine was dissolved in glacial acetic acid and cooled to 0°C

using ice bath. Solution of one equivalent of bromine in glacial acetic acid was prepared and this solution was then added dropwise in the reaction mixture using dropping funnel so that yellow precipitation occurs. On further addition of bromine, precipitates disappear and turned to yellow color solution. After complete addition of bromine, reaction was heated at 40°C for 4 hours. After completion of reaction, reaction mixture was extracted with ethylacetate at *p*H 8-9 and desired product was isolated and purified by column chromatography using EtOAc : n-Hex (1.5-8.5) as eluent.



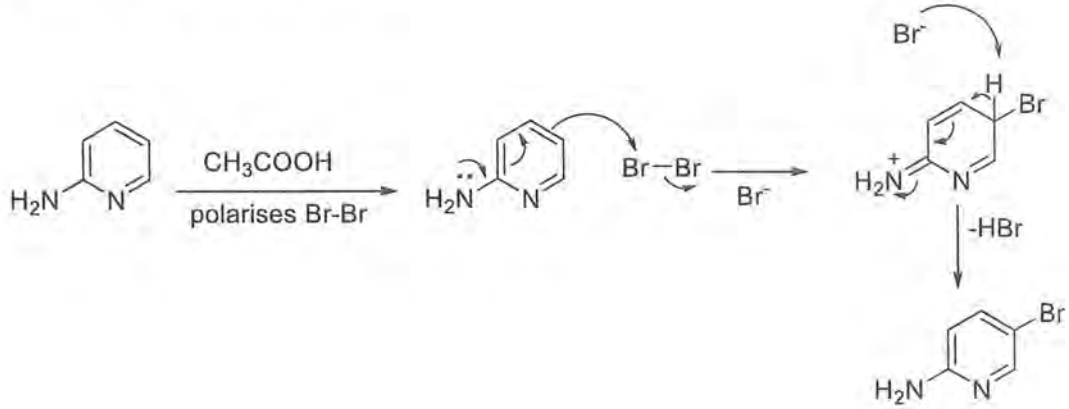
Scheme 3.9: Bromination of 2-aminopyridine

Yield: 60 %; **m.p.** 131-135 °C (Lit. 133-138°C)

TLC (SiO_2): R_f = 0.5 (EtOAc : n-Hex:1: 1)

3.3.3.1 Mechanism of bromination of 2-aminopyridine

Mechanism of bromination of 2-aminopyridine is shown in **scheme 3.10.** Reaction was carried in glacial acetic acid as solvent, 2-aminopyridine was dissolved in glacial acetic acid to and bromine was added slowly by dropping funnel at 0°C. Mechanistic studies show that the acetic acid polarize the non-polar Br-Br bond and generates electrophilic center which electron rich para position of 2-aminopyridine attacks. Slow addition of bromine and low temperature assist the formation of 5-bromo-2-aminopyridine as a major product. Electron rich para position attack the bromine followed by removal for proton to give desired product.

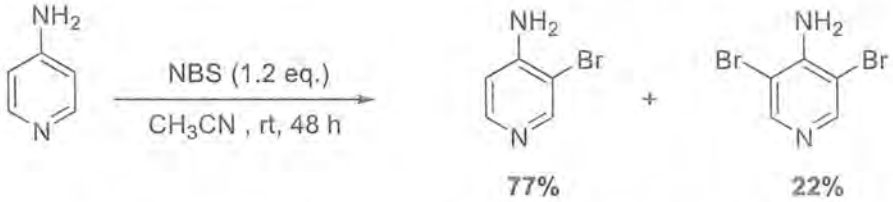


Scheme 3.10: Mechanism of bromination of 2-aminopyridine

3.3.4 Synthesis of 3-bromo-4-aminopyridine

N-Bromosuccinamide is a mild brominating agent and give mono-substituted product as a major product. Synthesis of 3-bromo-4-aminopyridine was carried at room temperature using NBS as for bromination in polar aprotic solvent, acetonitrile.

In oven dried 125 mL two neck round bottom flask, 4-aminopyridine (500 mg, 5.31 mmol, 100 mol %) was dissolved in 12 mL acetonitrile and N-bromosuccinamide (1.13 g , 6.38 mmol, 120 mol%) was slowly added in reaction flask and the reaction was stirred for 48 hours at room temperature. After completion of reaction, reaction mixture was concentrated and product was isolated by column chromatography (EtOAc: n-hexane:: 2:8)



Scheme 3.11: Bromination of 2-aminopyridine by NBS

Yield: 74 %; **m.p.** 131-135 °C (Lit. 133-138°C)

TLC (SiO_2): R_f = 0.4 (EtOAc : n-Hex:1: 1)

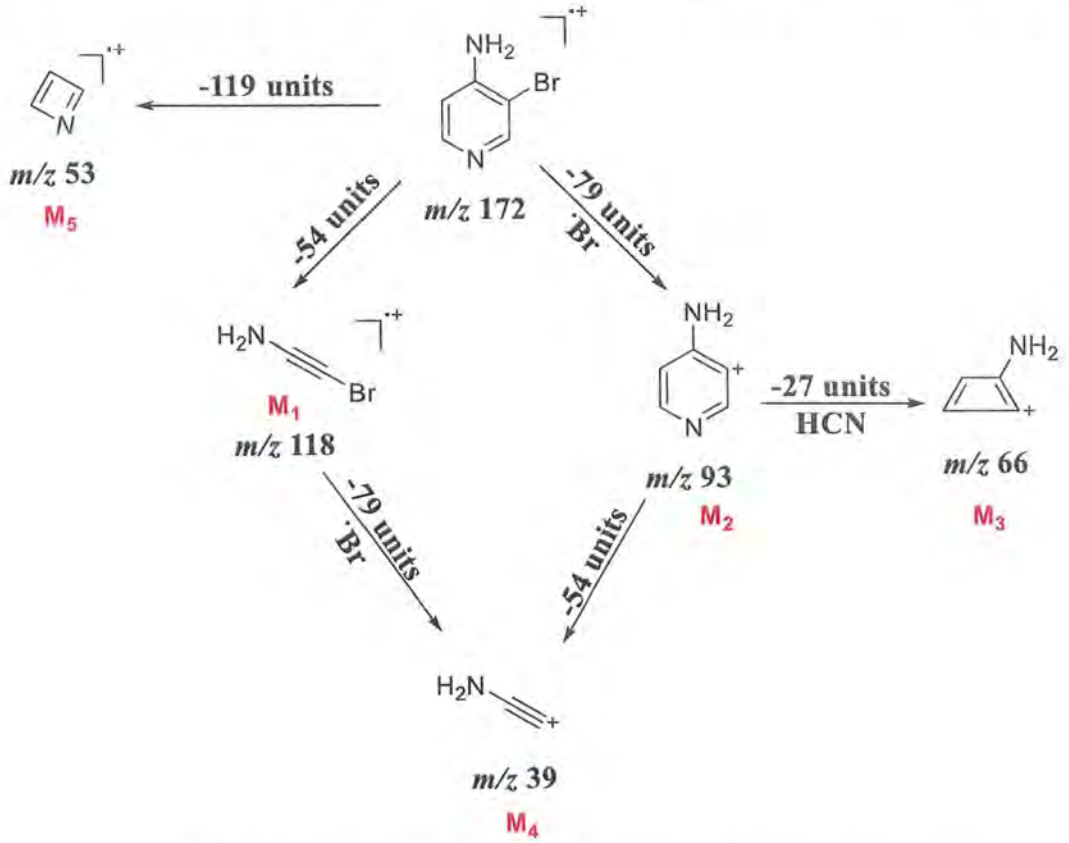
3.3.4.1 Characterization of 3-bromo-4-aminopyridine by MS spectrum

Major peaks in MS-spectrum of 3-bromo-4-aminopyridine is given below:

MS (m/z): 172 ($M^{+\cdot}$), 118, 93,66,53, 39,

Fragmentation pattern of 3-amino-4-aminopyrdine is shown in **scheme 3.12.** Base peak at m/z 172 correspond to molecular ion peak which confirm the formation of product. The peak at m/z 118 corresponds to M_1 radical cation due to loss of 54 mass units. The signal at m/z 93 correspond to M_2 cation which appears due to loss of bromine radical. This M_2 gives daughter fragment M_3 which appears in at m/z 66 due to loss of HCN. M_2 also give rise to fragment M_4 by loss of 54 mass units which appears at m/z 39.

Peak at m/z 53 due to loss of 119 mass units appears for azete radical cation.



Scheme 3.12: Fragmentation pattern of 3-bromo-4-aminopyridine

3.3.5 Heck coupling for synthesis of aminopyridine based stilbazoles

The synthesis of aminopyridine based Stilbazoles having two pyridyl rings connected through *trans* alkenic double bond. General procedure for synthesis of one of stilbazole (**ST-2**) is given below:

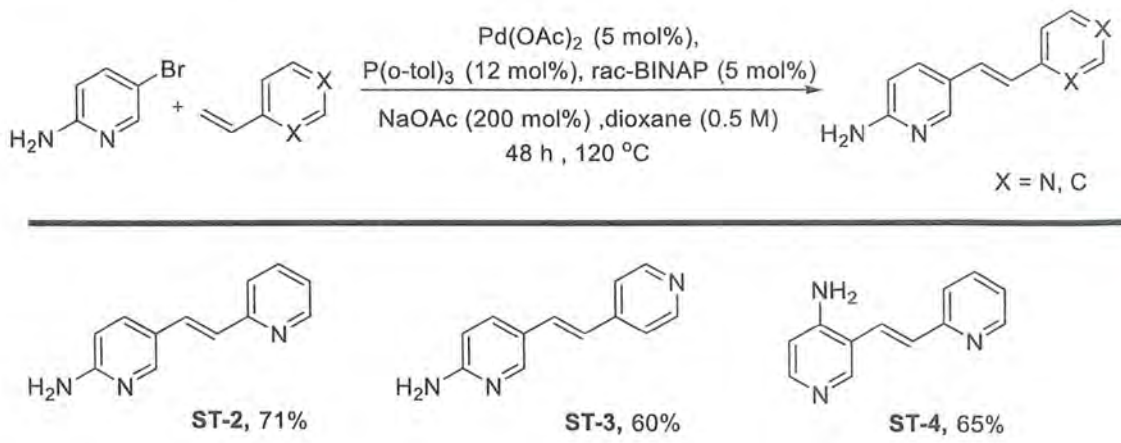
Synthesis of **ST-2** was carried using Heck coupling reaction between 2-amino-5-bromopyridine and 2-vinylpyridine by using palladium as a catalyst. Initially, reaction was carried by taking one equivalent of 2-amino-5-bromopyridine, two equivalents of 2-vinylpyridine, two equivalents of sodium acetate as a base, 5 mol% of $Pd(OAc)_2$ as a catalyst and 12 mol% of triphenylphosphine as a ligand in 0.5 M dioxane as a solvent and reaction was heated at 110°C for 48 hours. The isolated yield of product is only 17 %. This yield is too low to carry this synthesis. Keeping in mind the chemistry of catalytic cycle of Heck reaction, we tried different combinations of catalyst and ligands to optimized the reaction yield as shown in **Table 3.4.**

Table 3.4: Reaction conditions optimization of Heck coupling reaction between 5-bromo-2-aminopyridine and 2-vinylpyridine

ENTRY	**Catalyst (5 mol%)**	**Ligand (12 mol%)**	**Solvent**	**Yield %**
1.	$Pd(OAc)_2$	PPh_3	Dioxane	17 %
2.	$Pd(OAc)_2$	$P(o\text{-}tol)_3$	THF	29 %
3.	$Pd_2(dba)_3$	(±)-BINAP	Dioxane	Traces
4.	$Pd(OAc)_2$	$P(2\text{-}fur)_3$	Dioxane	41 %
5.	Pd-PEPPSI-iPr	-	Dioxane	Traces
6.	$Pd(OAc)_2$	$P(o\text{-}tol)_3$/(±)-BINAP	Dioxane	71%

The best yield was obtained when we used $P(o\text{-}tol)_3$ as ligand in combination with 1 mol% of *rac*-BINAP as an additive.

By following reaction conditions as given in **entry 6** we synthesized different stibazoles (**ST-2,ST-3 and ST-4)** as shown in **scheme 3.13.**



Scheme 3.13: Synthesis of stilbazoles by Heck coupling reaction

3.3.5.1 Characterization by physical parameters

Physical data of synthesized stibazoles is given in **table 3.5**

Table 3.5: Physical data of Stilbazoles

Compd.	Colors	R_f^*	Melting points (ºC)	Yield (%)
ST-1	yellow	0.7	127-129	77
ST-2	Yellow green	0.2	131-134	71
ST-3	Yellow	0.3	124-127	60
ST-4	Light yellow	0.5	118-121	65

Silica gel-60 F_{254} under UV light at 254 nm *EtOAc : n-Hex (8:2)

3.3.5.2 Characterization of Compound ST-2 by NMR Spectroscopy

3.3.5.2.1 Characterization by ^{1}H NMR Spectroscopy

The ^{1}H NMR data of compound **ST-2** is depicted in the table 3.6. The signal at 8.55 ppm with the coupling constant ^3J value of 4.5 Hz appears as a doublet corresponds to the H-13 of pyridinyl ring adjacent to the nitrogen atom, signal at 8.19 ppm with the coupling constant ^4J value of 2.1 Hz appeared as a doublet corresponds to the proton H-6 adjacent of pyridinyl ring nitrogen as smaller coupling constant values and deshielding of proton confirms the proton is adjacent to pyridinyl nitrogen atom of 2-aminopyridinyl ring and there is no ^3J coupling.

The signal at 7.84 ppm with ^3J coupling value 8.4 Hz and ^4J coupling constant of 2.1 Hz correspond to proton labeled as H-12. The smaller coupling value is for the coupling with H-10 proton. The signal at 7.73 ppm with the coupling constant ^3J value of 7.8 Hz and ^4J value of 1.8 Hz appeared as triplet of doublets corresponds to the proton H-11 which have two *ortho* protons.

The signal at 7.65 ppm with coupling value of 16.2 Hz correspond to proton H-7 and signal at 7.07 ppm with same coupling value of 16.2 Hz corresponds to the protons of alkeneic moiety of Stilbazole. Larger coupling value confirms that they are *trans* to each other and the its (*E*)-Stilbazole. The doublet present at 7.43 ppm with ^3J value of 8.7 Hz corresponds to the proton H-4 and the signal at 7.18 Hz which appears as doublet of doublet correspond to proton H-10. The shielded doublet for proton H-3 appears at 6.65 ppm and broad singlet at 5.74 ppm corresponds to exchangeable N-H protons.

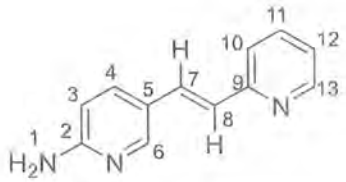


Table 3 6: ^{1}H NMR Data of synthesized compound **ST-2.**

Protons	δ (ppm)	Multiplicity	Integration	*J* (Hz)
H-13	8.55	*d*	1H	4.5
H-6	8.19	*d*	1H	2.1
H-12	7.84	*dd*	1H	8.4, 2.1
H-11	7.73	*td*	1H	7.8, 1.8
H-7	7.65	*d*	1H	16.2
H-4	7.43	*d*	1H	8.7
H-10	7.18	*dd*	1H	--
H-8	7.07	*d*	1H	16.2
H-3	6.65	*d*	1H	8.7
H-1	5.74	*s*	1H	---

3.3.5.2.2 Characterization by ^{13}C NMR Spectroscopy

Structure of compound **ST-2** is further confirmed by ^{13}C NMR spectroscopy. The characteristics signals in ^{13}C NMR data of compound **ST-2** is depicted in the table 3.7. The most deshielded signal appeared at 159.7 ppm corresponds to the *ipso* carbon to amino group of pyridinyl ring adjacent to the nitrogen atom (C-2). The signal appeared at 156.1 ppm corresponds to *ipso* carbon atom (C-9) of second pyridinyl ring. The signal appears at 149.5 ppm corresponds to carbon atom (C-6) of pyridinyl ring containing -NH_2 group and signal at 148.6 ppm corresponds to carbon atom (C-13) adjacent to pyridinyl nitrogen atom of second ring. The most shielded signal appears at 108.2 ppm corresponds to carbon atoms (C-3) *ortho* to amino group and rest of the carbon signals are present in their respective regions.

Table 3 7: ^{13}C NMR data of compound **6a.**

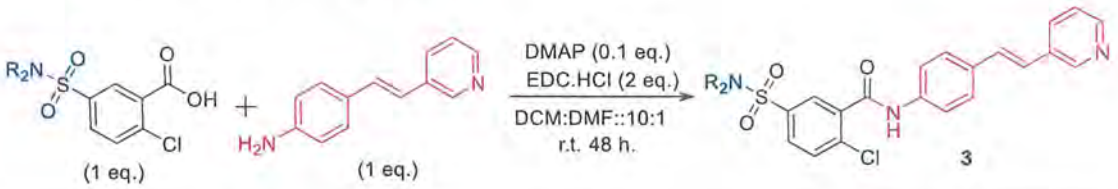
Carbons	C-2	C-9	C-6	C-13	C-3
δ (ppm)	159.7	156.1	149.5	148.6	108.2

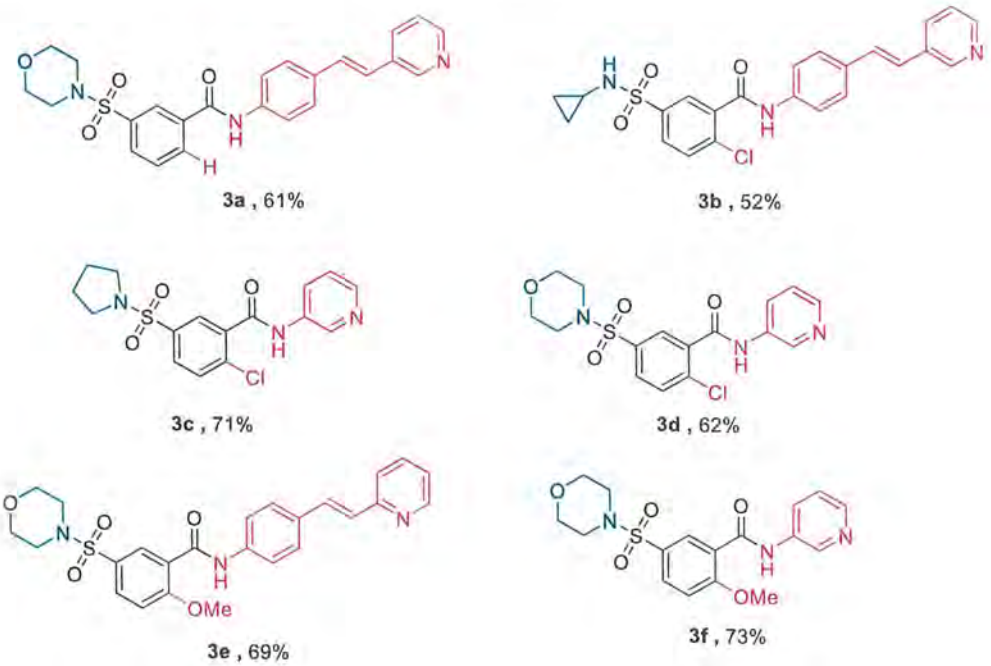
3.4 Carboxamides Synthesis

Carboxamides having $-CONR_2$ can be synthesized through numerous methods but here EDC coupling was used to synthesize carboxamide bond. The important step in amide bond formation is the activation of carboxylic acids.

3.4.1 General procedure for synthesis of *N*-Substitutedsulfamoyl benzamide using EDC as coupling reagent (3a-3f)

N-Substitutedsulfamoyl benzamide was synthesized according to reported procedure by using EDC and DMAP for coupling. *N*-substituted sulfamoylbenzoic acid was dissolved in DCM and DMF, then DMAP, amine and EDC were added to the reaction mixture and reaction mixture was allowed to stir in inert atmosphere for 24 hours. After the completion of reaction, solvent extraction was performed with ethyl acetate at *p*H 2-3 to obtain the product in organic layer. Combined organic layer was dried using anhydrous sodium sulfate and evaporated to get the solid product. Product has been further purified by washing with acetone.

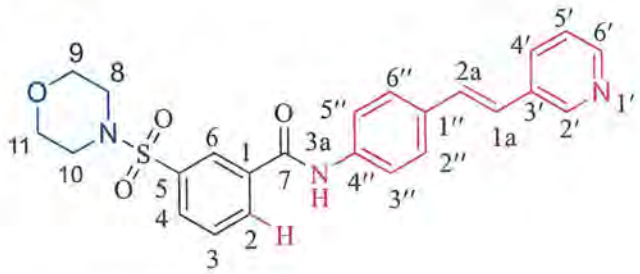




Scheme 3.14: Synthesis of carboxamides using DMAP and EDC coupling.

3.4.1.1 (*E*)-3-(Morpholinosulfonyl)-N-(4-(2-(pyridin-3-yl)vinyl)phenyl)benzamide (3a)

Compound **3a** was synthesized according to the above-mentioned procedure. In oven dried 25 mL two neck round bottom flask, compound 3a was synthesized using (*E*)-3-(4-aminostyryl) pyridine (108.5 mg, 0.553 mmol, 100 mol%), 3-(morpholinosulfamoyl)benzoic acid (150 mg, 0.553 mmol, 100 mol%), DMAP (6.76 mg, 0.055 mmol, 10 mol%) and EDC.HCl (265 mg, 1.38 mmol, 250 mol%). Product was further purified by washing with acetone. After purification the amount of product obtained was 151.6 mg with 61% yield.

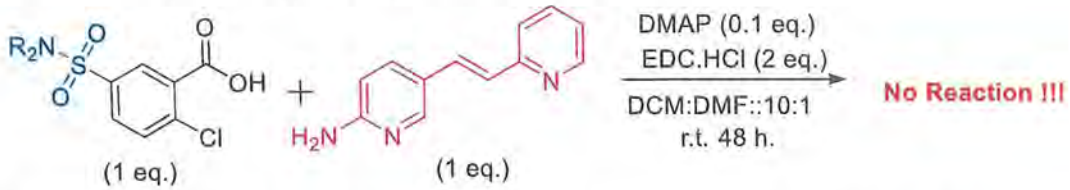


Yield: 61 %; **m.p.** 233-237 °C

TLC (SiO_2): R_f = 0.2 (EtOAc : n-Hex:: 1: 1)

3.4.2 EDC coupling for synthesis of aminopyridinyl based stilbazoles containing Sulfamoyl Carboxamide derivatives

The reaction of synthesized aminopyridinyl based Stilbazoles was carried out with sulfamoyl benzoic acids by EDC coupling procedure as given in **3.4.1.** No reaction was observed. When reaction of 2-aminopyridine was carried with sulfamoyl benzoic acid, no reaction was observed. So we tried to optimize reaction conditions with different coupling reagents as given in **table 3.8.**



Scheme 3.15: Aminopyridinyl based Silbazole reaction with Sulfamoyl benzoic acid by EDC Coupling

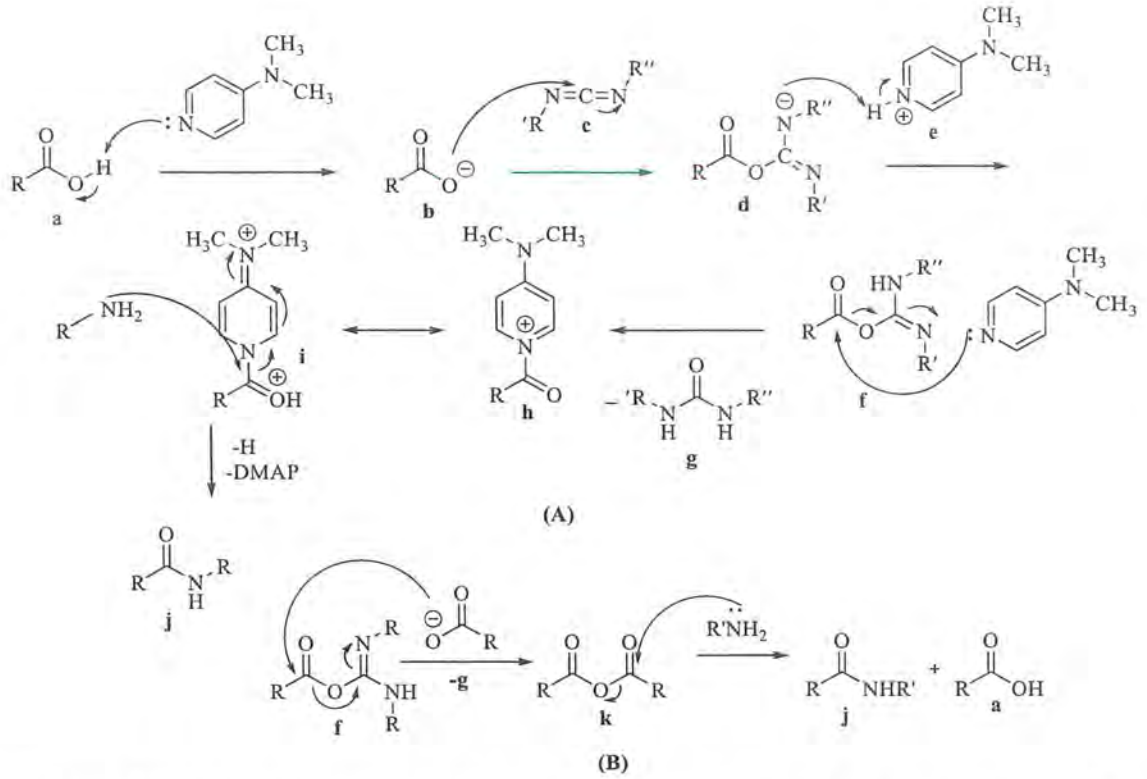
Table 3.8: Reaction optimization for 2-aminopyridine with diferent coupling reagents

ENTRY	COUPLING REAGENT	YIELD (%)
1.	EDC.HCl	No reaction
2.	HOBT + EDC.HCl	-
3.	PyBrop	-
4.	DIC	-

The poor nucleophilic nature of 2-aminopyridine and stability of intermediate formed in coupling reaction was the reason that this reaction not proceed. For synthesis of 2-aminopyridine based sulfamoyl carboxamide derivatives, a good electrophilic center must be produced.

3.4.3 Mechanism for the Synthesis of *N*-Substituted sulfamoyl benzamide

In first step of this reaction, carboxylate ion **(b)** is formed by DMAP which acts as a base and abstracts acidic proton from carboxylic acid **(a)**. This nucleophilic carboxylate ion attacks nucleophilic carbon of carbodiimide **(c)** which results in formation of intermediate **(d)** followed by abstruction of proton from cation of DMAP **(e)** to give *O*-acylisourea. DMAP acts as a nucleophile and attacks on *O*-acylisourea and as a result urea **(g)** is formed as by-product and the desired intermediate **(h)** is also formed which is in resonance with other intermediate **(i)**. Finally, amine attacks on intermediate **(i)** to give desired carboxamide **(j)** and DMAP is regenerated. The fate of coupling reagents is that EDC is consumed in the reaction and DMAP is regenerated (**Scheme. 3.16 A**). There is another possibility of formation of anhydride **(k)** if that carboxylate ion attack on *O*-acylisourea **(f)** instead of DMAP which is further targeted by amine to give carboxamide **(j)** and the residual acid **(a)**. However, we used same equivalents of acid and EDC to minimize the amount of residual acid (**Scheme 3.16 B**).

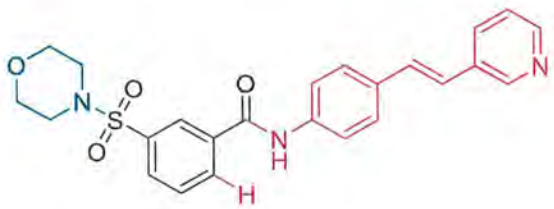
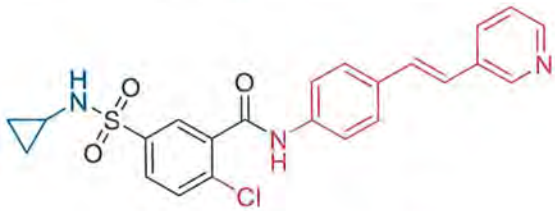
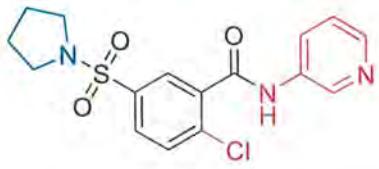


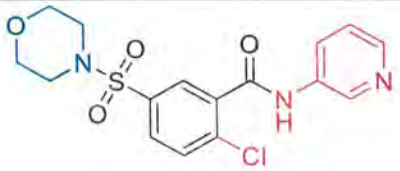
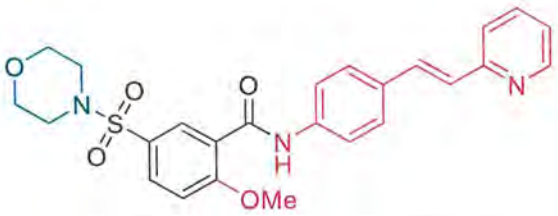
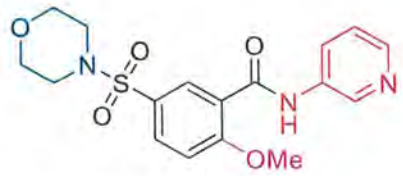
Scheme 3.16: (A) Mechanism for the synthesis of carboxamide *via O*-acylisourea **(B)** Mechanism for the synthesis of carboxamide *via* anhydride

3.4.4. Characterization by Physical Parameters

Physical data of synthesized 4'-nitrostilbazoles **(3a-3f)** is given in table 3.9.

Table 3.9: Physical data of synthesized 4'-nitrostilbazoles **(3a-3f).**

S No	Structure	Color	m.p. (°C)	R_f *
3a		Off-white	233-237	0.20
3b		Light grey	244-246	0.26
3c		White	212-215	0.40

3d		White	208-211	0.30
3e		White	241-243	0.2
3f		Off-white	210-212	0.25

Silica gel-60 F_{254}nder UV light at 254 nm *EtOAc : n-Hex (7:3)

3.4.5 Characterization of Compound (3b) as Representative Example

3.4.5.1 Characterization by ^{1}H NMR Spectroscopy

The ^{1}H NMR data of compound **3b** is depicted in the table 3.10. The most characteristic amide N-H signal appears at 10.84 ppm as a sharp singlet.This confirms the formation of product. The characteristic *trans* olefinic signal of Stilbazole part are appeared at 7.23 ppm with ^3J value of 16.8 Hz. Signal at 8.77 ppm as singlet appeared for N-H proton of cyclopropylamine. The singlet for one proton at 8.45 ppm corresponds to proton H-2' adjacent to pyridinyl nitrogen atom. Signals at 2.16 ppm for one proton and at 0.44-0.54 ppm for 4 protons corresponds to cyclopropyl protons.

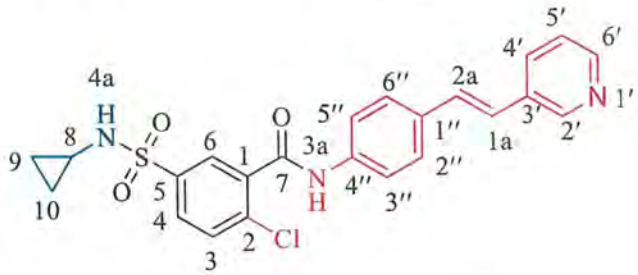


Table 3.10: ^{1}H NMR Data of synthesized compound **3b.**

Protons	δ (ppm)	Multiplicity	Integration	*J* (Hz)
3a	10.84	s	1H	----
4a	8.77	s	1H	----
2'	8.45	s	1H	----

6	8.15	s	1H	----
6'	8.04	d	1H	8.4
3,4, 5'	7.84-7.95	m	3H	----
5'',3'',2'',6''	7.66-7.63	m	4H	----
1a, 4'	7.41-7.36	m	2H	----
2a	7.23	d	1H	16.8
8	2.16	s	1H	----
9,10	0.44-.54	m	4H	----

3.4.5.2 Characterization by ^{13}C NMR Spectroscopy

Structure of compound **3b** is further confirmed by ^{13}C NMR spectroscopy. The characteristics signals in ^{13}C NMR data of compound **3b** is depicted in the table 3.11. The most deshielded signal appeared at 164.0 ppm corresponds to the carbonyl carbon atom (C-7) of amide group gives the evidence for the formation product. The signal at 148.6 ppm corresponds to carbon atom (C-2') of pyridinyl ring adjacent to nitrogen atom. The most shielded signal in aromatic region appeared at 120.2 ppm corresponds to two carbon atoms (C-3" and C-5") of phenyl ring of amine moiety *ortho* to amide group. The signal appeared at 24.6 ppm and 5.68 ppm corresponds to carbon atoms of cyclopropyl carbons of cyclopropyl amine part. Rest of the signals appears in their respective aromatic region.

Table 3.11: ^{13}C NMR data of compound **3b**

Carbons	C-7	C-2'	3", 5"	9,10	8
δ (ppm)	164.0	148.6	120.2	24.6	5.68

CONCLUSION

Sulfonamides and carboxamides functionalities play a versatile role in medicinal chemistry and have wide biological applications. Number of methodologies have been used to synthesize these moieties. Stilbazole based derivatives have been known for number of biological activities from as anti-allergic agents to effective as artificial base pair for DNA duplex. The goal of this research work to utilize the chemistry of these important functionalites and structural moieties to synthesize sulfamoyl carboxamide derivatives with variety of substituents to elobarate structure activity relationship. 4'-Aminostilbazole was synthesized using Knovenagel condensation reaction of 4-nitrotoluene with nicotinaldehyde followed by reduction of nitro group to amine. Aminopyridines based stilbazoles have been synthesized successfully by Heck coupling reaction. Chlorosulfonation reaction of three different benzoic acida was carried out to synthesize sulfamoyl benzoic acid derivatives. Carboxamides were synthesized by using EDC & DMAP as coupling reagents. 2-aminopyridine based stilbazoles and 2-aminopyridine did not work with EDC coupling for amide synthesis. Synthesized sulfamoyl-carboxamide derivatives were characterized using ^{1}H and ^{13}C-NMR spectroscopy.

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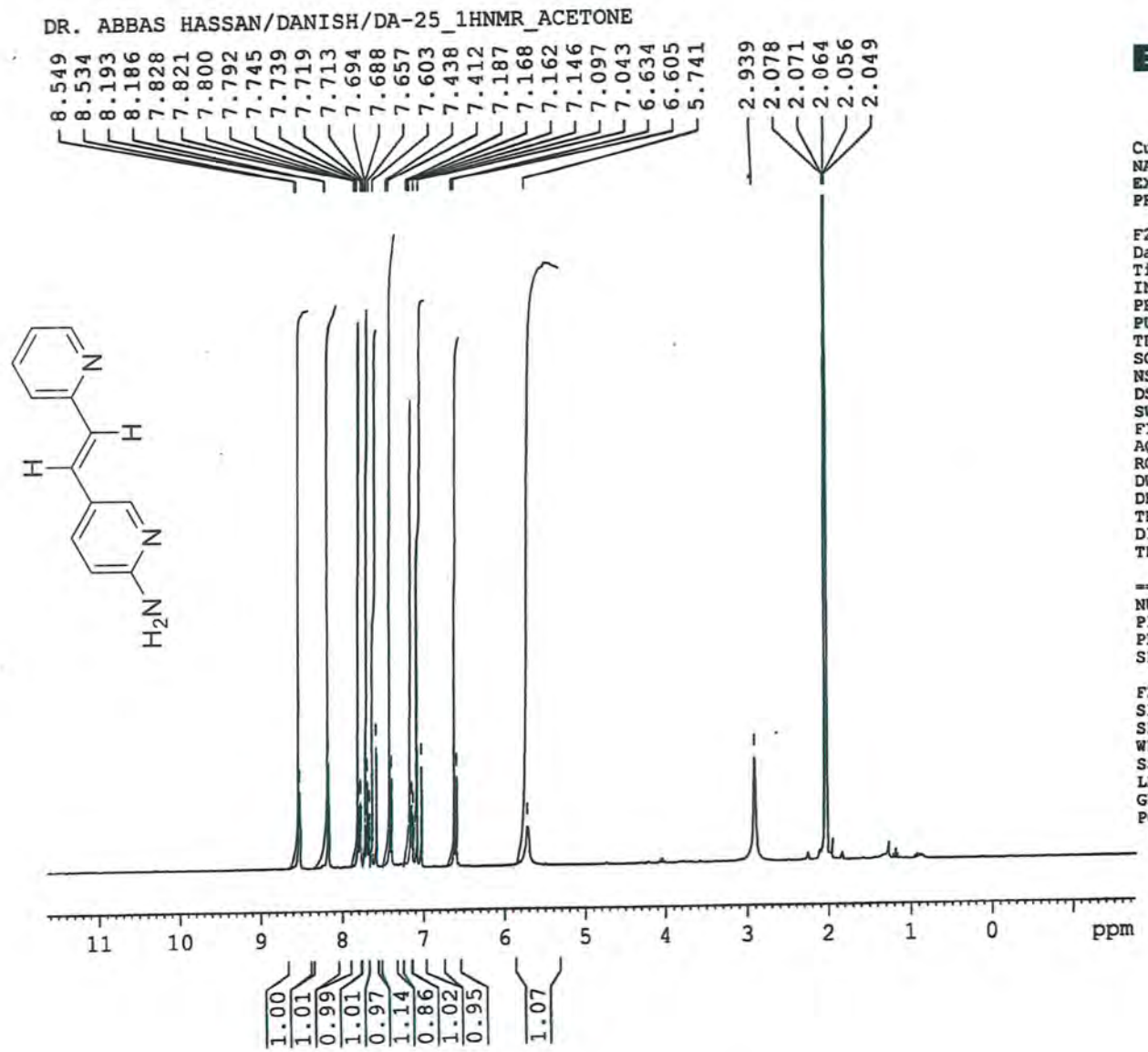
APPENDIX



BRUKER

Current Data Parameters

NAME	DA-25_1HNMR_ACETONE
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	Acetone
NS	8
DS	0
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	406.4
DW	81.000 usec
DE	6.00 usec
TE	290.1 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	9.00 usec
PL1	2.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
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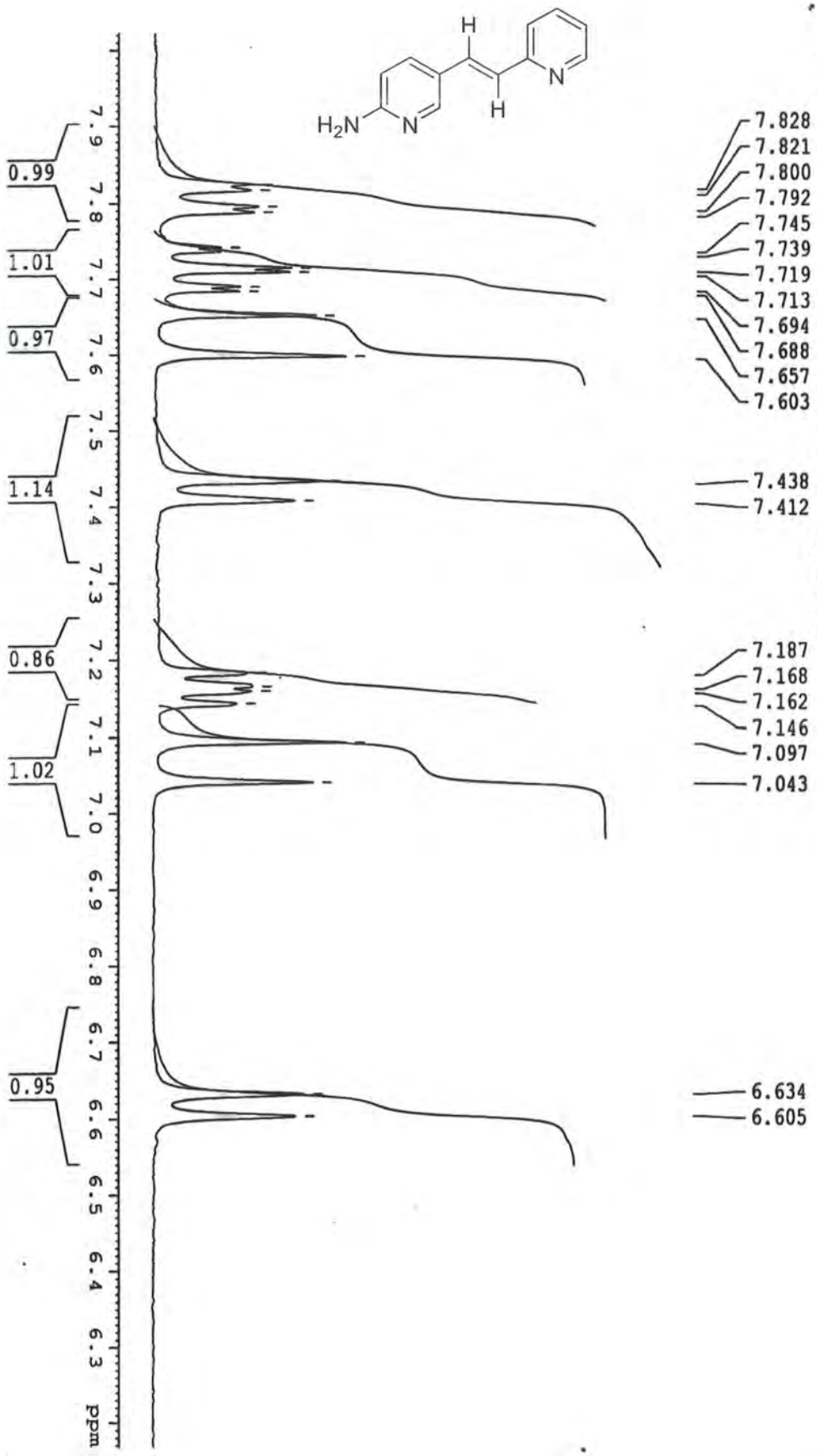
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00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7.713
7.694
7.688
7.657
7.603
7.438
7.412
7.187
7.168
7.162
7.146
7.097
7.043
6.634
6.605
0.99
1.01
0.97
1.14
0.86
1.02
0.95
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
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ppm
H
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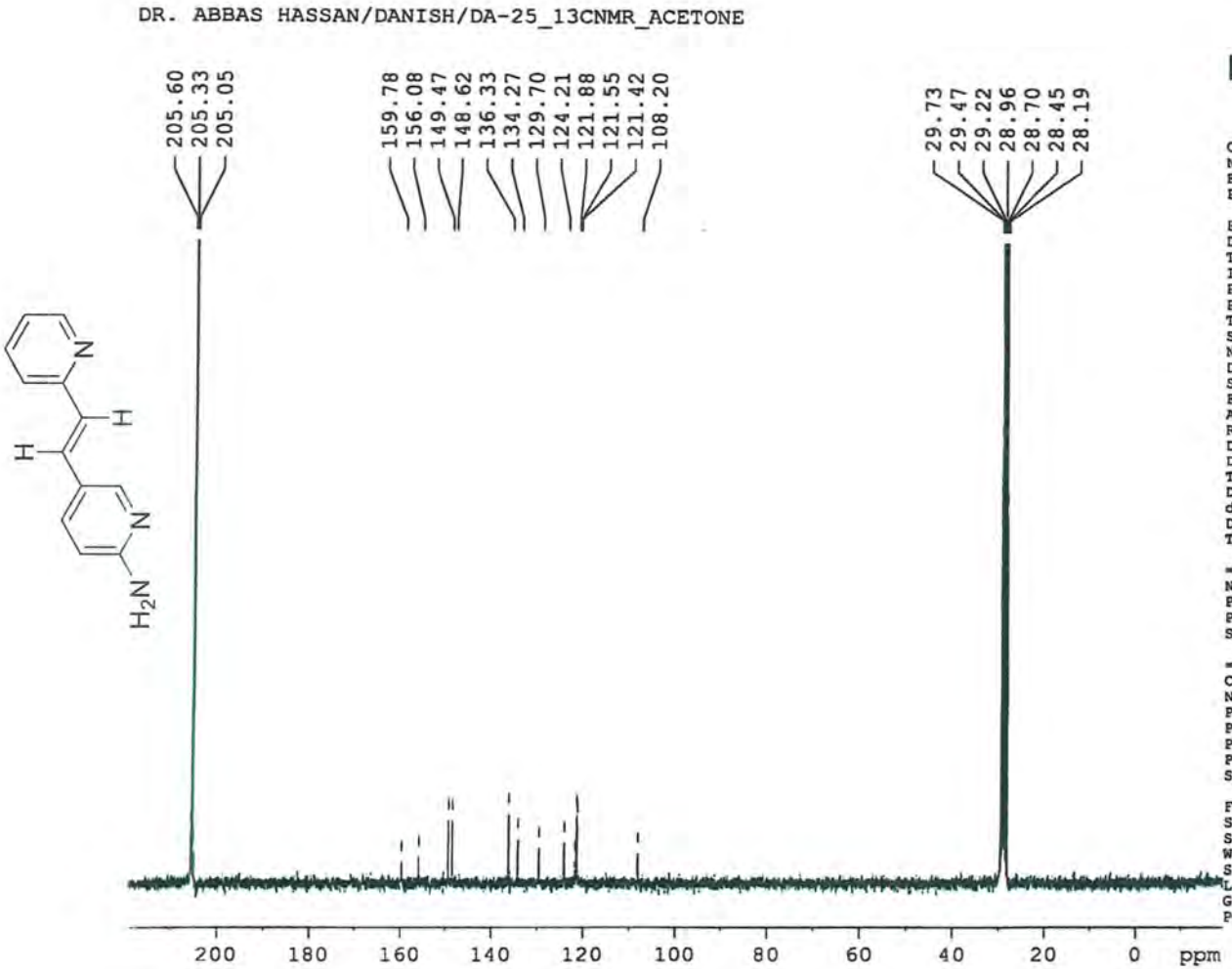
H
H_2N
N

DR. ABBAS HASSAN/DANISH/DA-25_13CNMR_ACETONE



BRUKER

Current Data Parameters
NAME DA-25_13CNMR_ACETONE
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters

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INSTRUM	spect	
PROBHD	5 mm BBO BB-1H	
PULPROG	zgpg30	
TD	35968	
SOLVENT	Acetone	
NS	1024	
DS	0	
SWH	17985.611	Hz
FIDRES	0.500045	Hz
AQ	0.9999604	sec
RG	32768	
DW	27.800	usec
DE	6.00	usec
TE	293.9	K
D1	2.00000000	sec
d11	0.03000000	sec
DELTA	1.89999998	sec
TD0	1	

======== CHANNEL f1 ========

NUC1	13C	
P1	6.00	usec
PL1	-5.00	dB
SFO1	75.4752953	MHz

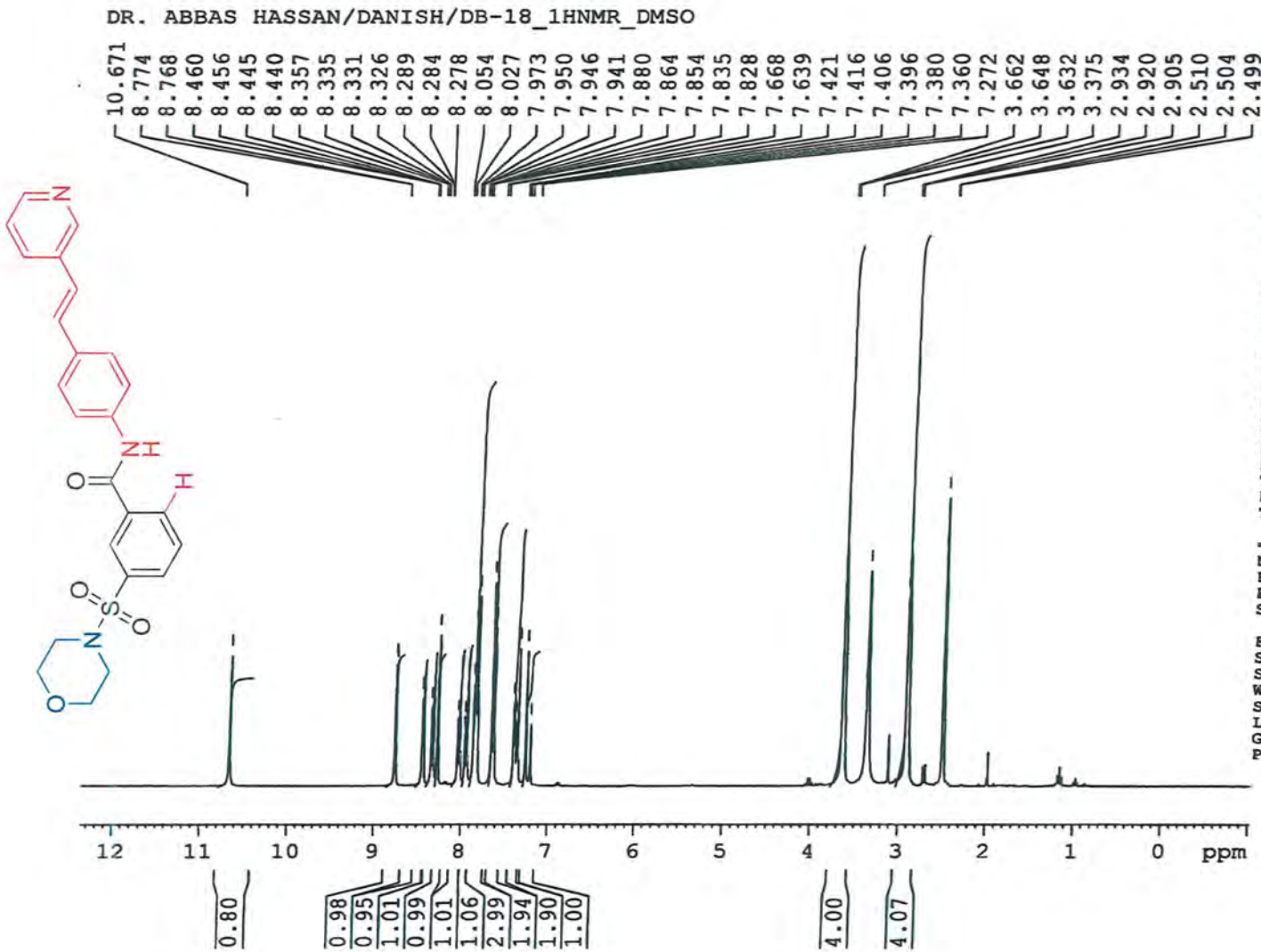
======== CHANNEL f2 ========

CPDPRG2	waltz16	
NUC2	1H	
PCPD2	80.00	usec
PL2	2.00	dB
PL12	20.98	dB
PL13	20.00	dB
SFO2	300.1312005	MHz

F2 - Processing parameters

SI	32768	
SF	75.4677490	MHz
WDW	EM	
SSB	0	
LB	1.00	Hz
GB	0	
PC	1.40	

DR. ABBAS HASSAN/DANISH/DB-18_1HNMR_DMSO



BRUKER

Current Data Parameters

NAME	DB-18_1HNMR_DMSO
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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Time	11.25
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	8
DS	0
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	228.1
DW	81.000 usec
DE	6.00 usec
TE	293.2 K
D1	1.00000000 sec
TD0	1

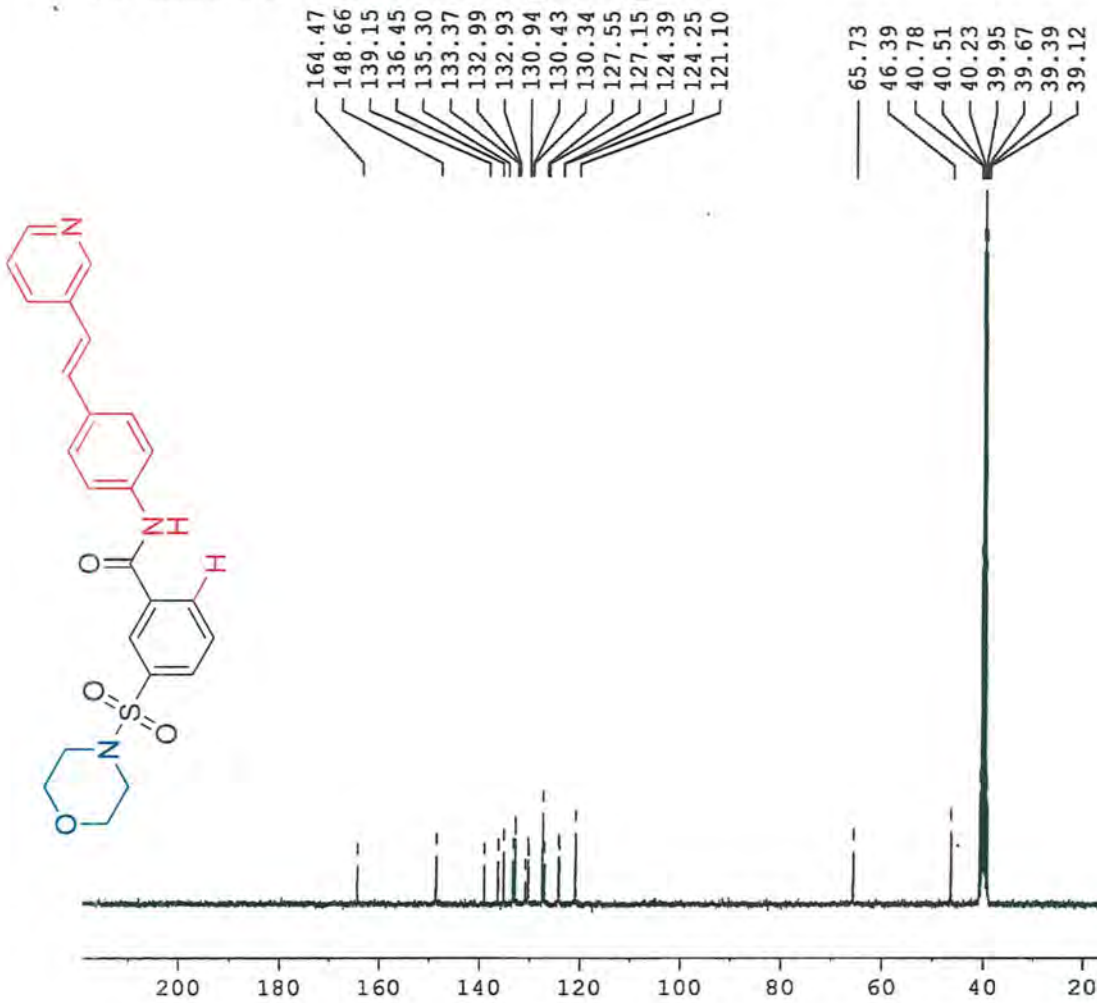
======== CHANNEL f1 ========

NUC1	1H
P1	9.00 usec
PL1	2.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

DR. ABBAS HASSAN/DANISH/DB-18_13CNMR_DMSO



BRUKER

Current Data Parameters
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EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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Time 11.20
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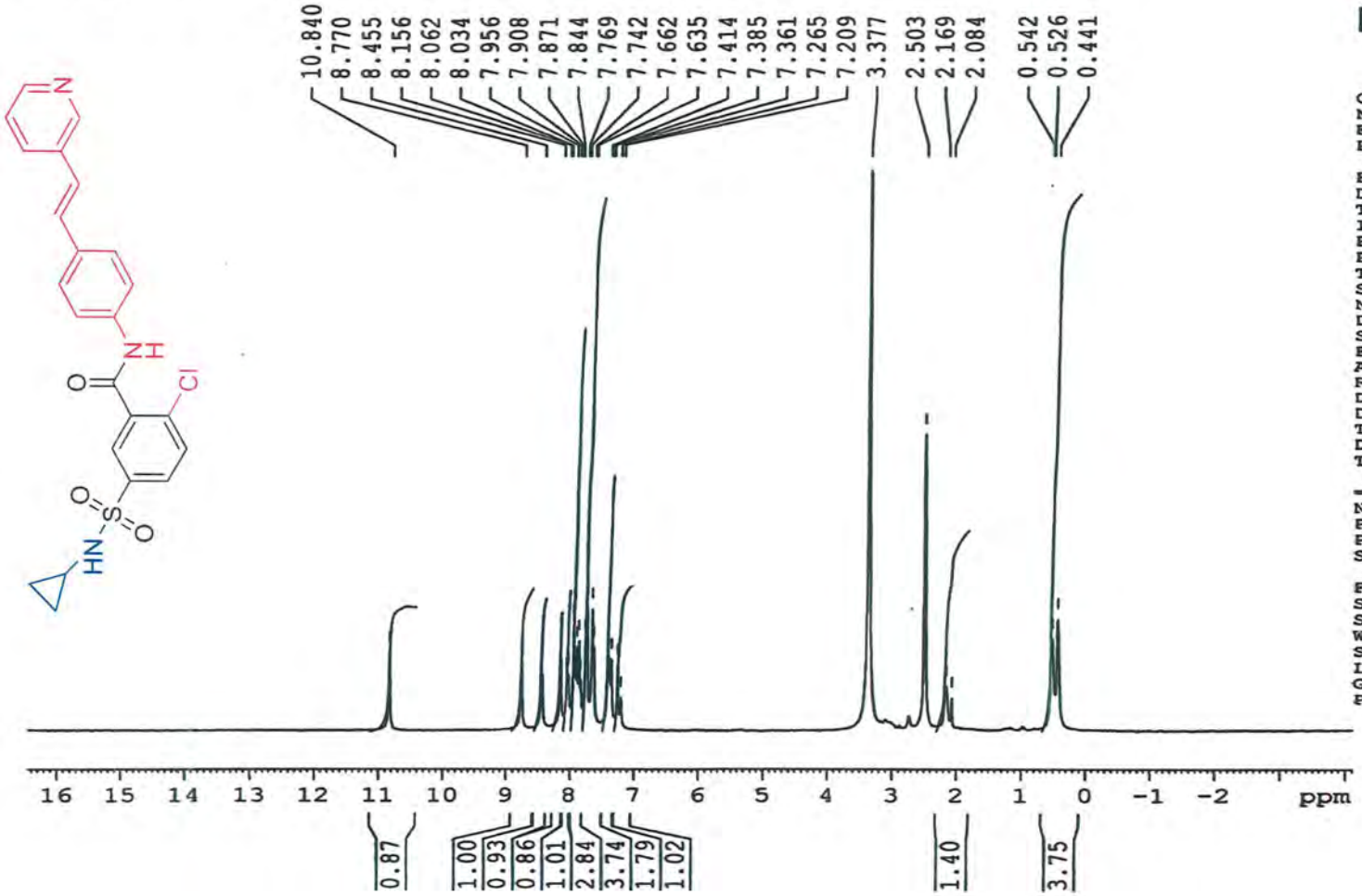
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 35968
SOLVENT DMSO
NS 741
DS 0
SWH 17985.611 Hz
FIDRES 0.500045 Hz
AQ 0.9999604 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 293.7 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

DR. ABBAS HASSAN/DANISH/DA-13_1HNMR_DMSO



BRUKER

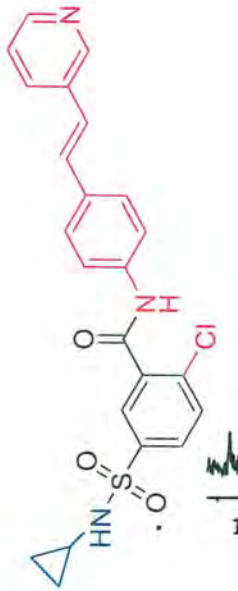
Current Data Parameters
NAME DA-13_1HNMR_DMSO
EXPNO 1
PROCNO 1

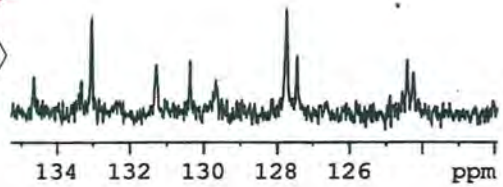
F2 - Acquisition Parameters
Date_ 20230417
Time 11.34
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 0
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 406.4
DW 81.000 usec
DE 6.00 usec
TE 293.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

DR. ABBAS HASSAN/DANISH/DA-13_13CNMR_DMSO





BRUKER

Current Data Parameters
NAME DA-13_13CNMR_DMSO
EXPNO 1
PROCNO 1

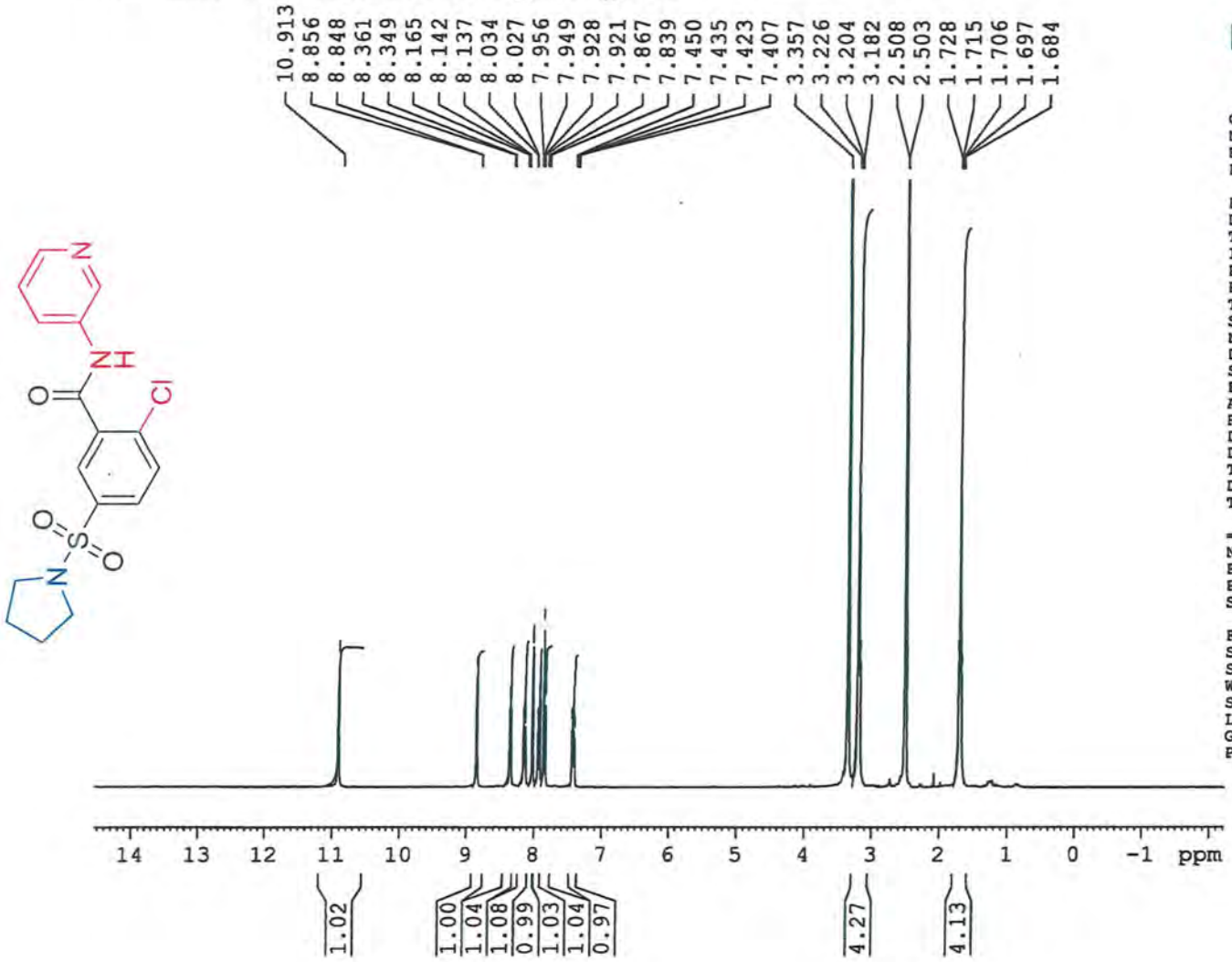
F2 - Acquisition Parameters
Date_ 20230417
Time 11.16
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 35968
SOLVENT DMSO
NS 1024
DS 0
SWH 17985.611 Hz
FIDRES 0.500045 Hz
AQ 0.9999604 sec
RG 32768
DW 27.800 usec
DE 6.00 usec
TE 293.3 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

DR. ABBAS HASSAN/DANISH/DA-40_1HNMR_DMSO



BRUKER

Current Data Parameters

NAME	DA-40_1HNMR_DMSO
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20230603
Time	13.04
INSTRUM	spect
PROBHD	5 mm BBO BB-1H .
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	8
DS	0
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	362
DW	81.000 usec
DE	6.00 usec
TE	294.2 K
D1	1.00000000 sec
TD0	1

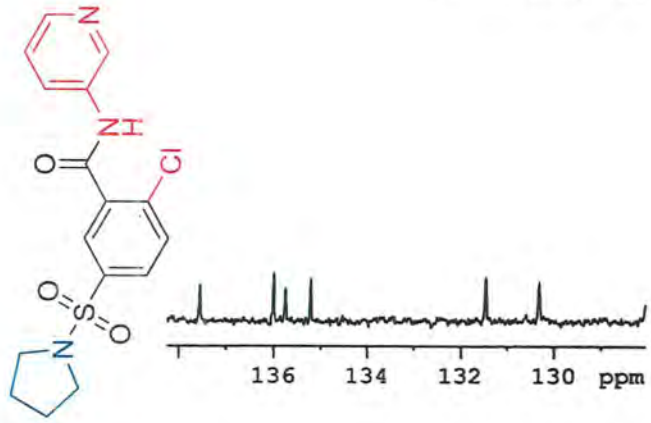
======== CHANNEL f1 ========

NUC1	1H
P1	9.00 usec
PL1	2.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

DR. ABBAS HASSAN/DANISH/DA-40_13CNMR_DMSO



BRUKER

Current Data Parameters
NAME DA-40_13CNMR_DMSO
EXPNO 1
PROCNO 1

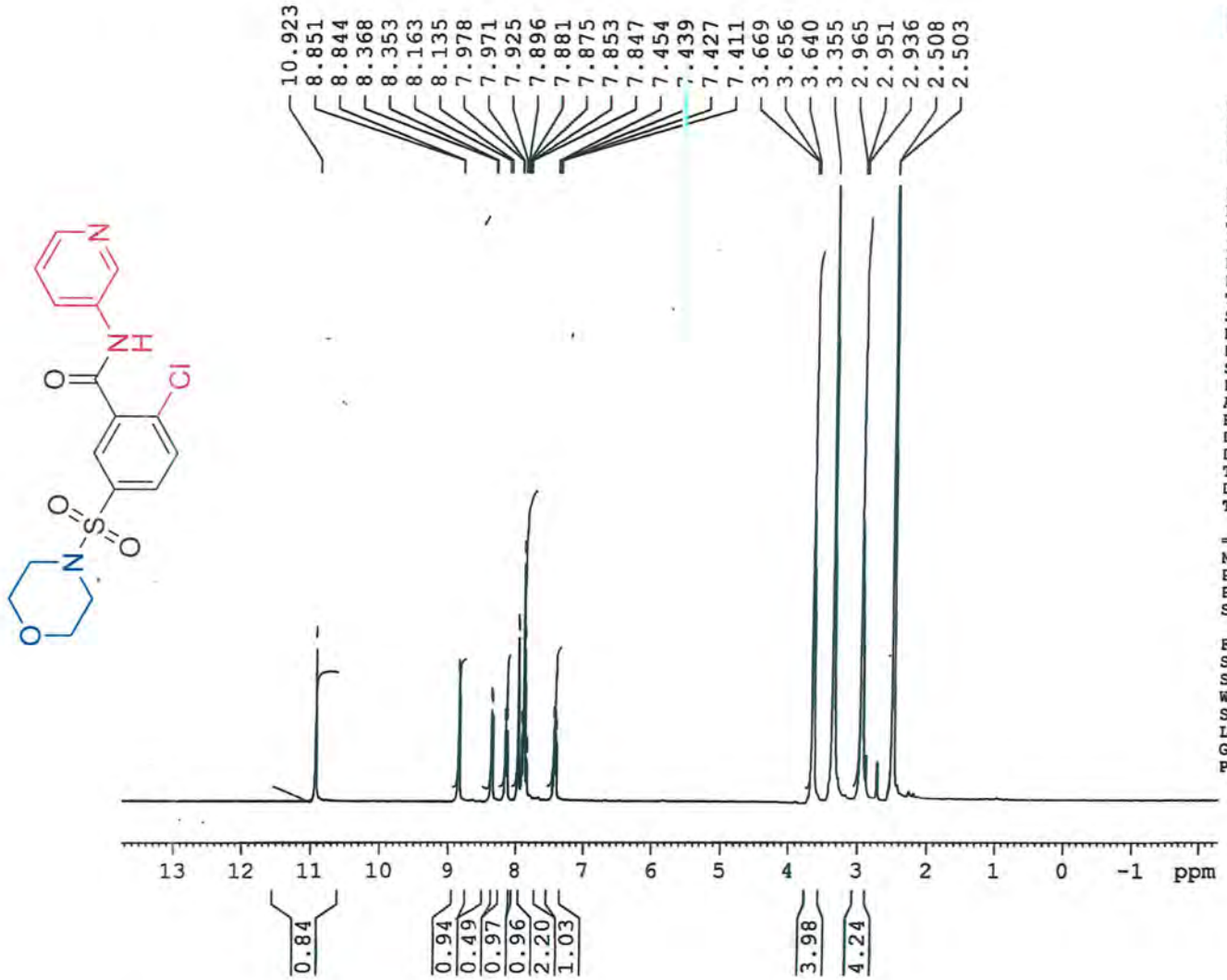
F2 - Acquisition Parameters
Date_ 20230603
Time 13.02
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 35968
SOLVENT DMSO
NS 658
DS 0
SWH 17985.611 Hz
FIDRES 0.500045 Hz
AQ 0.9999604 sec
RG 1290.2
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

DR. ABBAS HASSAN/DANISH/DA-42_1HNMR_DMSO



BRUKER

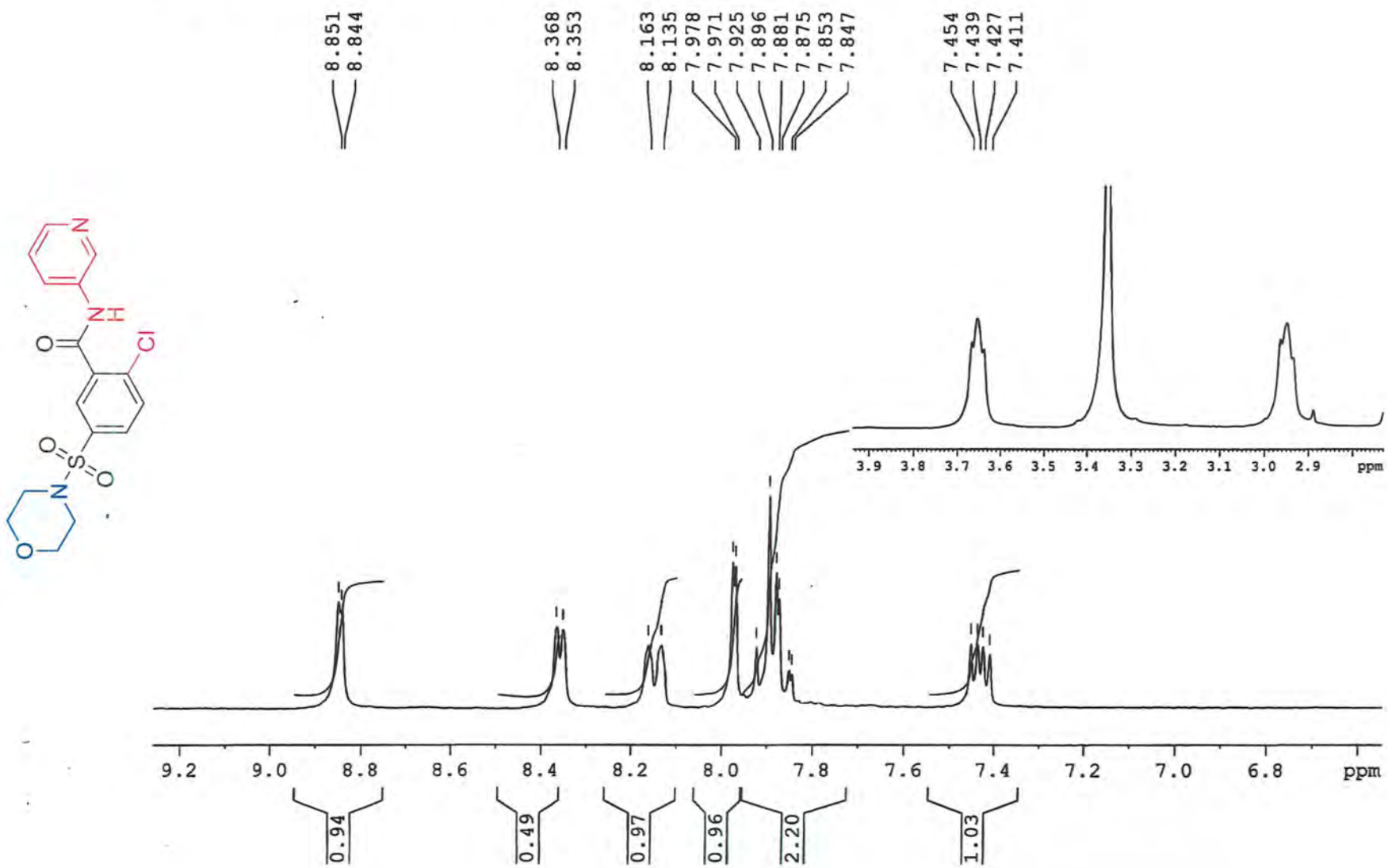
Current Data Parameters
NAME DA-42_1HNMR_DMSO
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20230901
Time 12.00
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 0
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 362
DW 81.000 usec
DE 6.00 usec
TE 295.1 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 9.00 usec
PL1 2.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

DR. ABBAS HASSAN/DANISH/DA-42_1HNMR_DMSO



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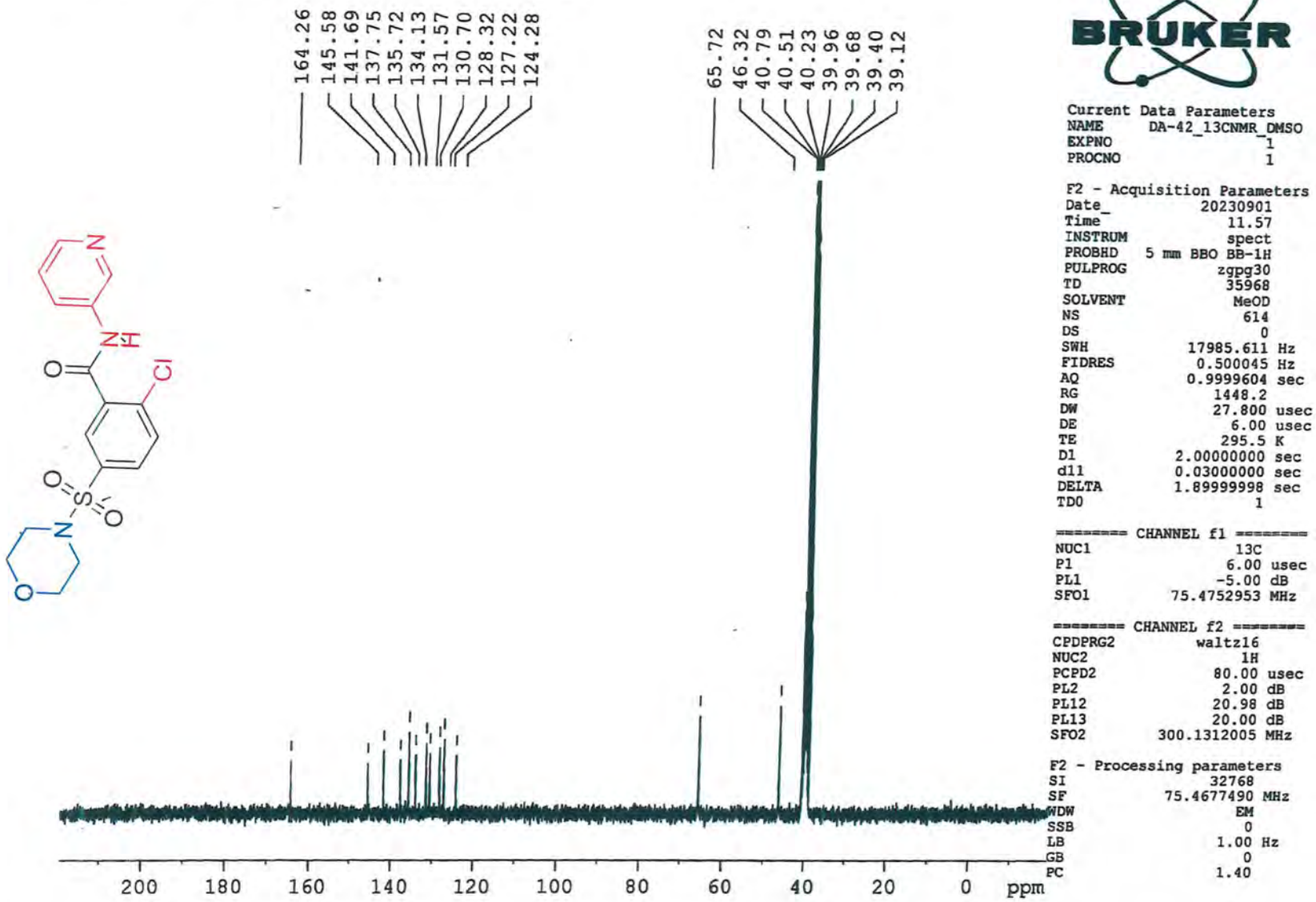


BRUKER

Current Data Parameters

NAME	DA-42_13CNMR_DMSO
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20230901
Time	11.57
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zgpg30
TD	35968
SOLVENT	MeOD
NS	614
DS	0
SWH	17985.611 Hz
FIDRES	0.500045 Hz
AQ	0.9999604 sec
RG	1448.2
DW	27.800 usec
DE	6.00 usec
TE	295.5 K
D1	2.00000000 sec
d11	0.03000000 sec
DELTA	1.89999998 sec
TD0	1

======== CHANNEL f1 ========

NUC1	13C
P1	6.00 usec
PL1	-5.00 dB
SFO1	75.4752953 MHz

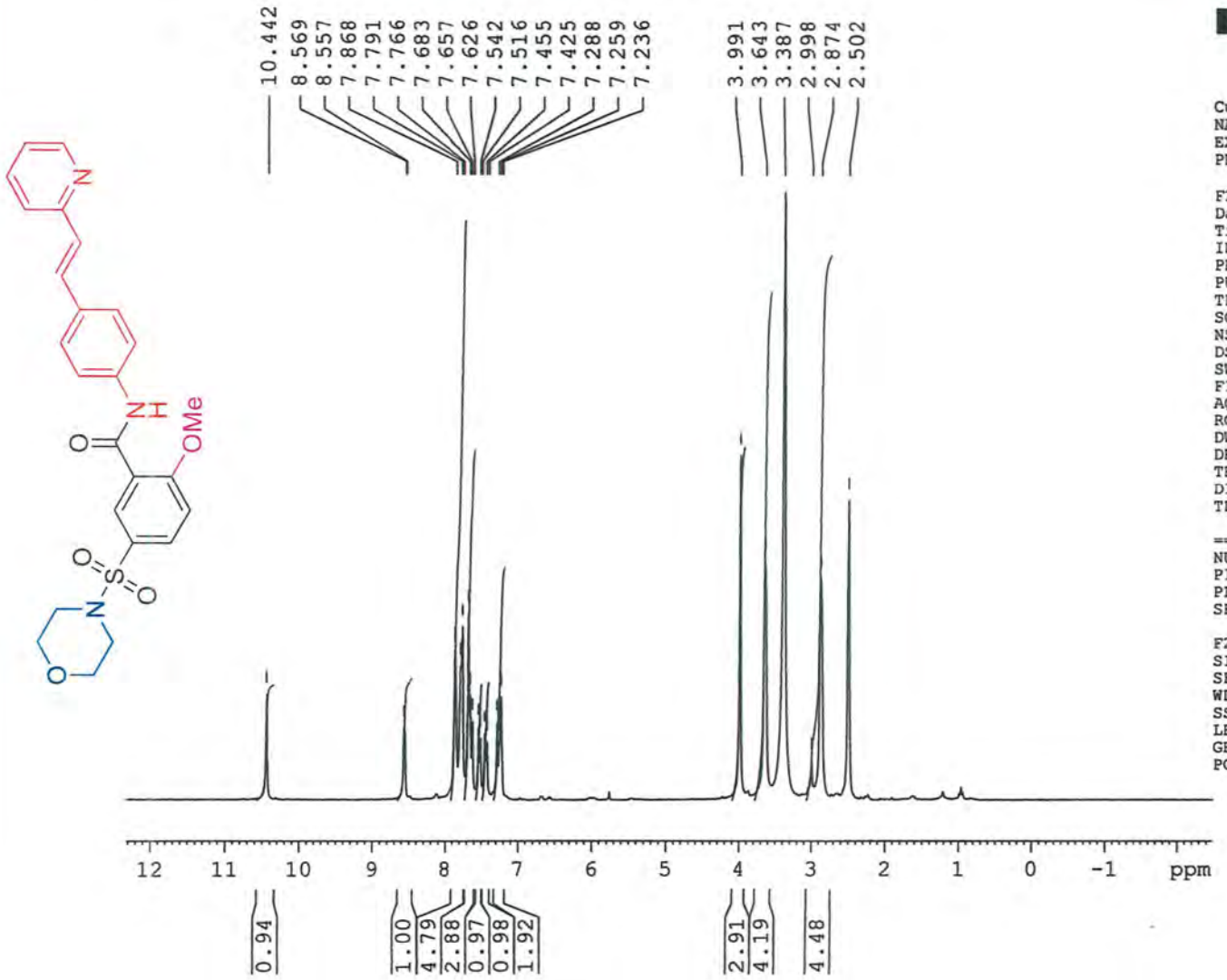
======== CHANNEL f2 ========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	2.00 dB
PL12	20.98 dB
PL13	20.00 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

SI	32768
SF	75.4677490 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

DR. ABBAS HASSAN/DANISH/DA-73_1HNMR_DMSO



BRUKER

Current Data Parameters

NAME	DA-73_1HNMR_DMSO
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20231119
Time	10.08
INSTRUM	spect
PROBHD	5 mm BBO BB-1H
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	8
DS	0
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	181
DW	81.000 usec
DE	6.00 usec
TE	291.6 K
D1	1.00000000 sec
TD0	1

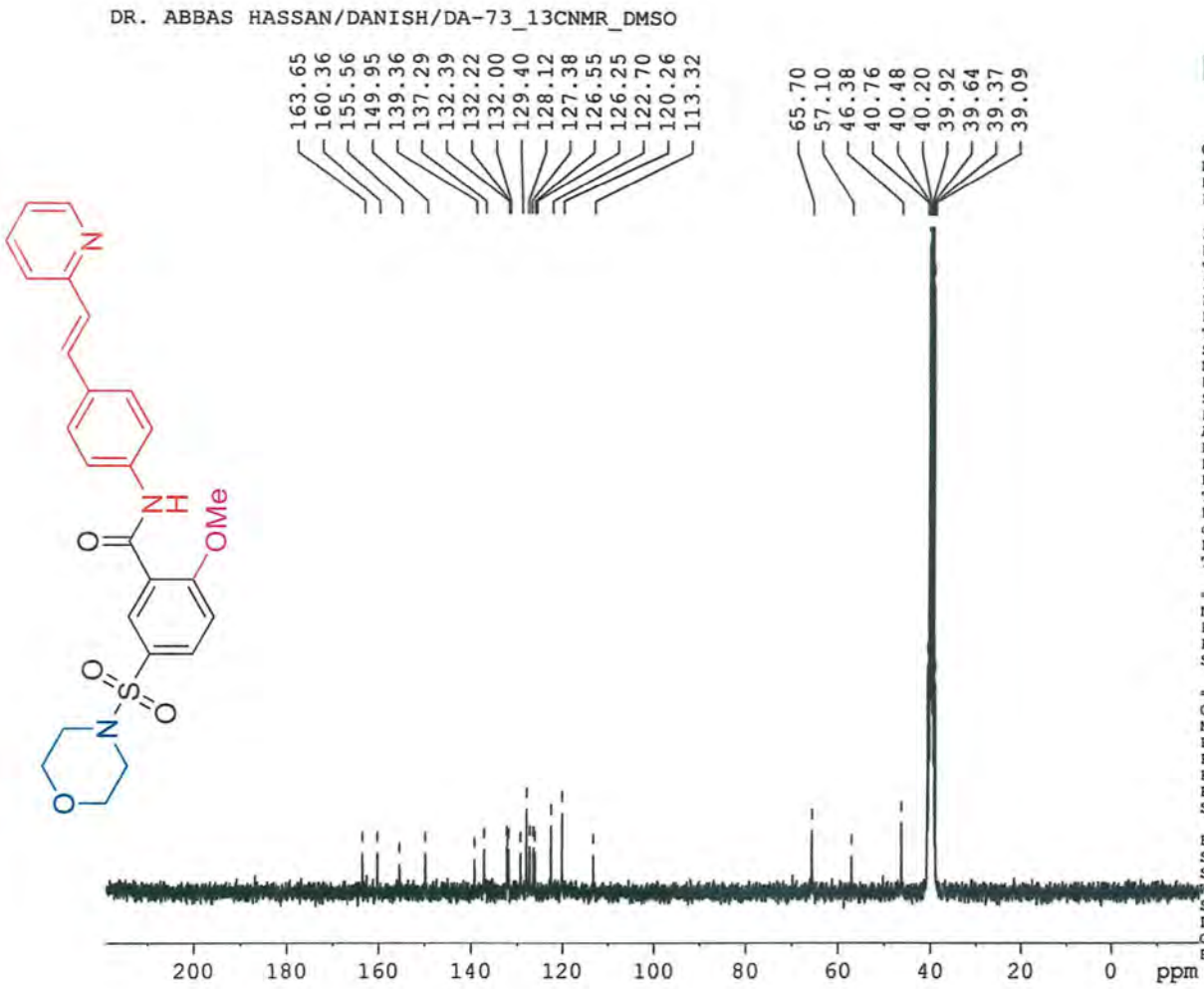
======== CHANNEL f1 ========

NUC1	1H
P1	9.00 usec
PL1	2.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

DR. ABBAS HASSAN/DANISH/DA-73_13CNMR_DMSO



BRUKER

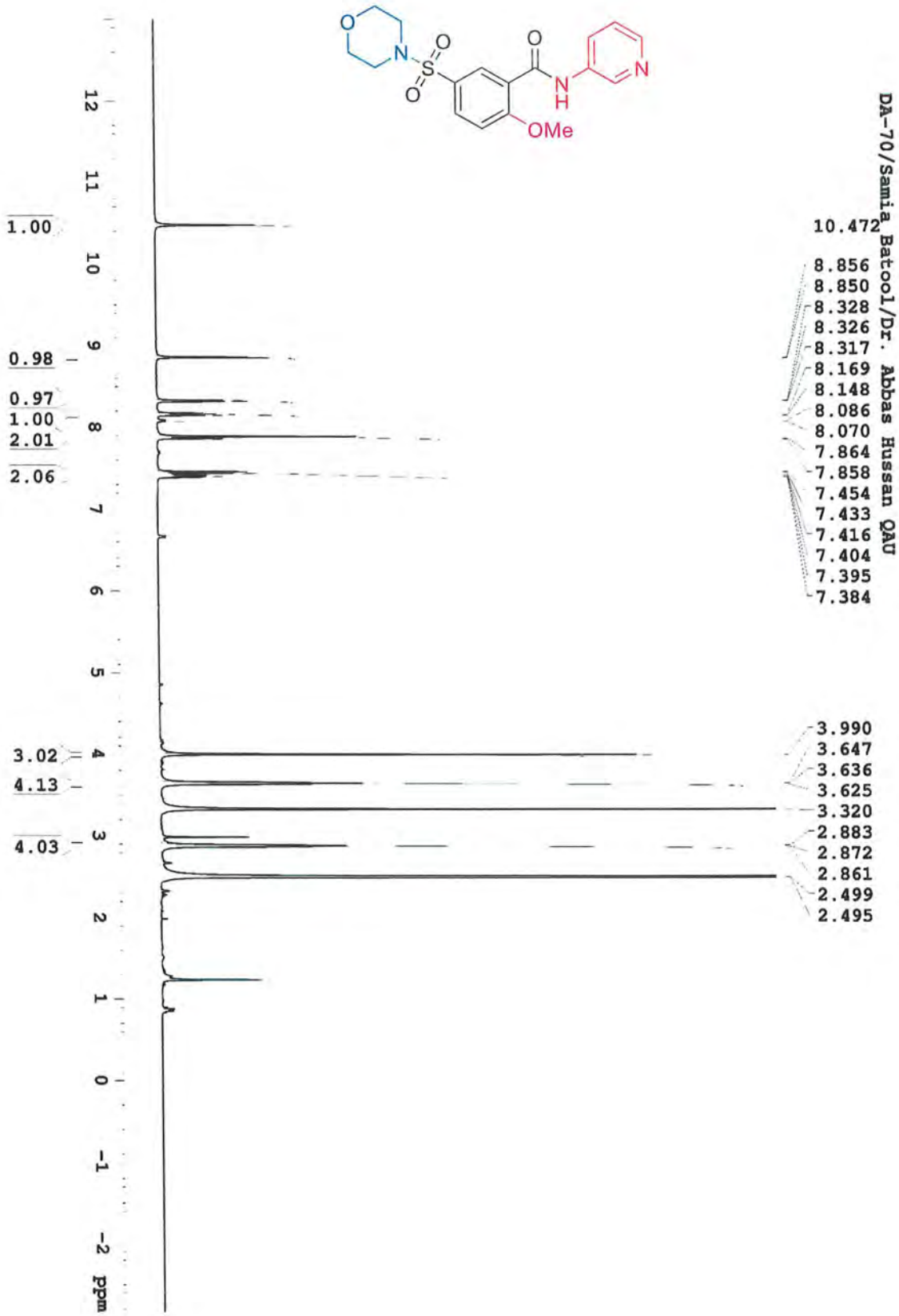
Current Data Parameters
NAME DA-73_13CNMR_DMSO
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20231119
Time 11.04
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 35968
SOLVENT DMSO
NS 1024
DS 0
SWH 17985.611 Hz
FIDRES 0.500045 Hz
AQ 0.9999604 sec
RG 8192
DW 27.800 usec
DE 6.00 usec
TE 292.8 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


DA-70/Samia Batool/Dr. Abbas Hussan QAU
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8.070
7.864
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7.433
7.416
7.404
7.395
7.384
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3.647
3.636
3.625
3.320
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1.00
0.98
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3.02
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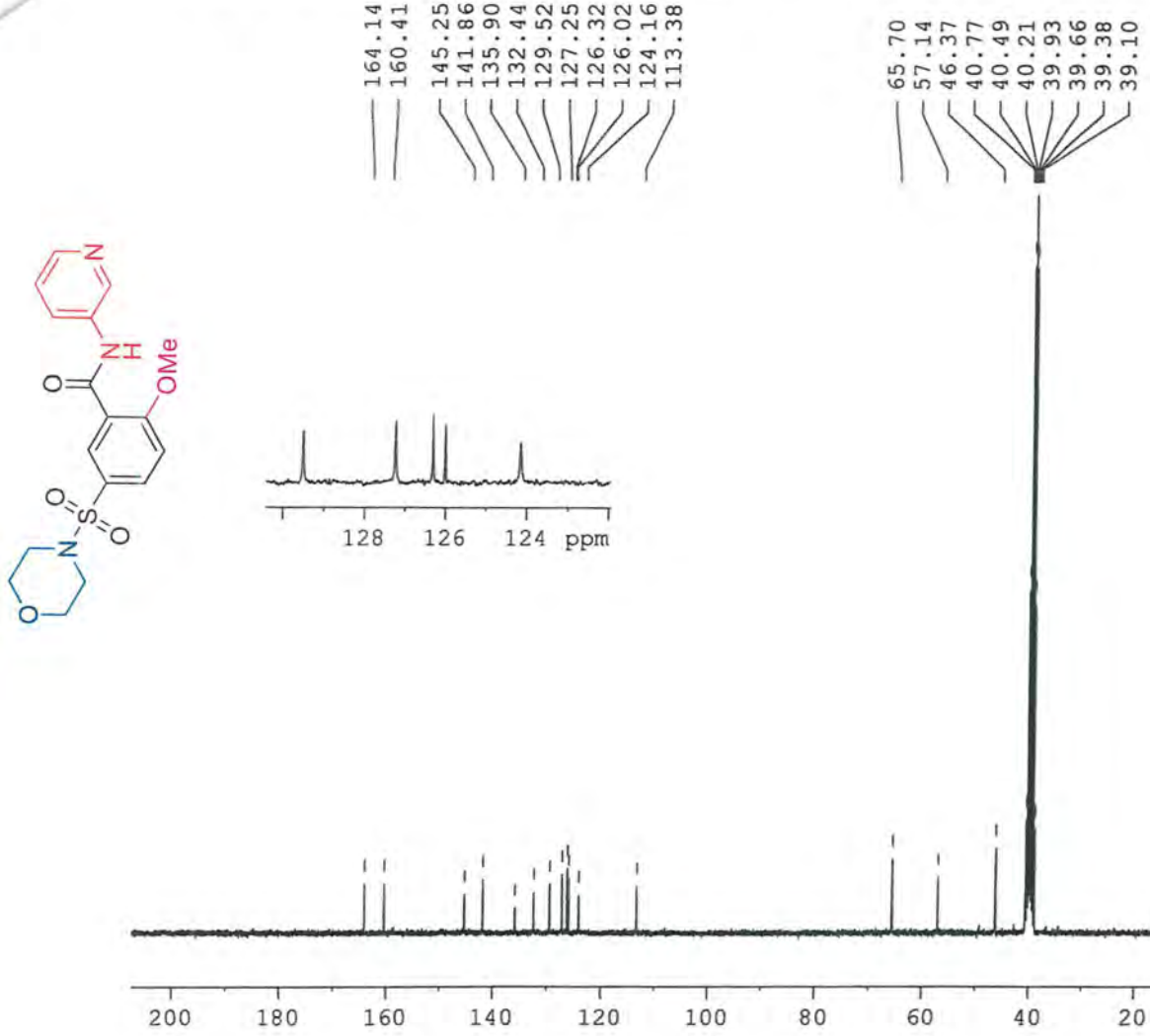
4.03
ppm

DR. ABBAS HASSAN/DANISH/DA-70_13CNMR_DMSO



BRUKER

Current Data Parameters
NAME DA-70_13CNMR_DMSO
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20231016
Time 14.37
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 35968
SOLVENT DMSO
NS 1024
DS 0
SWH 17985.611 Hz
FIDRES 0.500045 Hz
AQ 0.9999604 sec
RG 1625.5
DW 27.800 usec
DE 6.00 usec
TE 293.4 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 6.00 usec
PL1 -5.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 20.98 dB
PL13 20.00 dB
SFO2 300.1312005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

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nstrument  :    Instrument #2
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ample Name: DA-28
isc Info   : Temp 120-280c 10c/min Flow 1.5ml/min Inj 5ul
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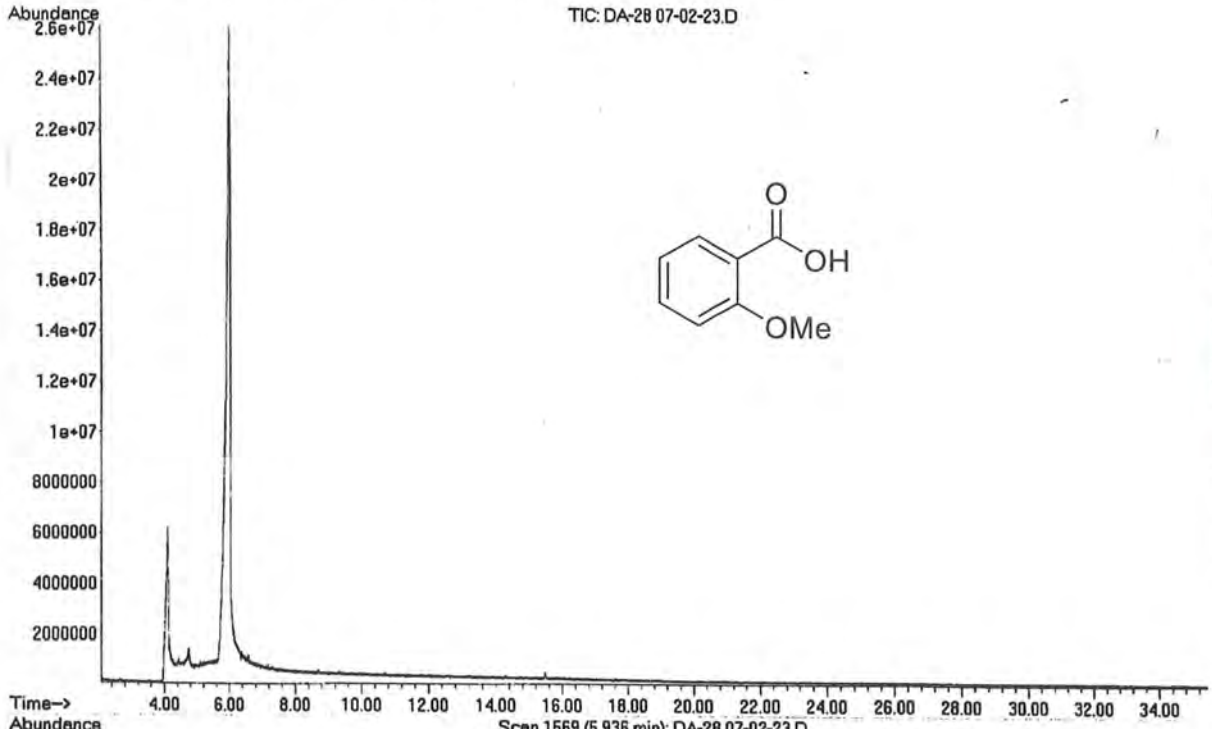

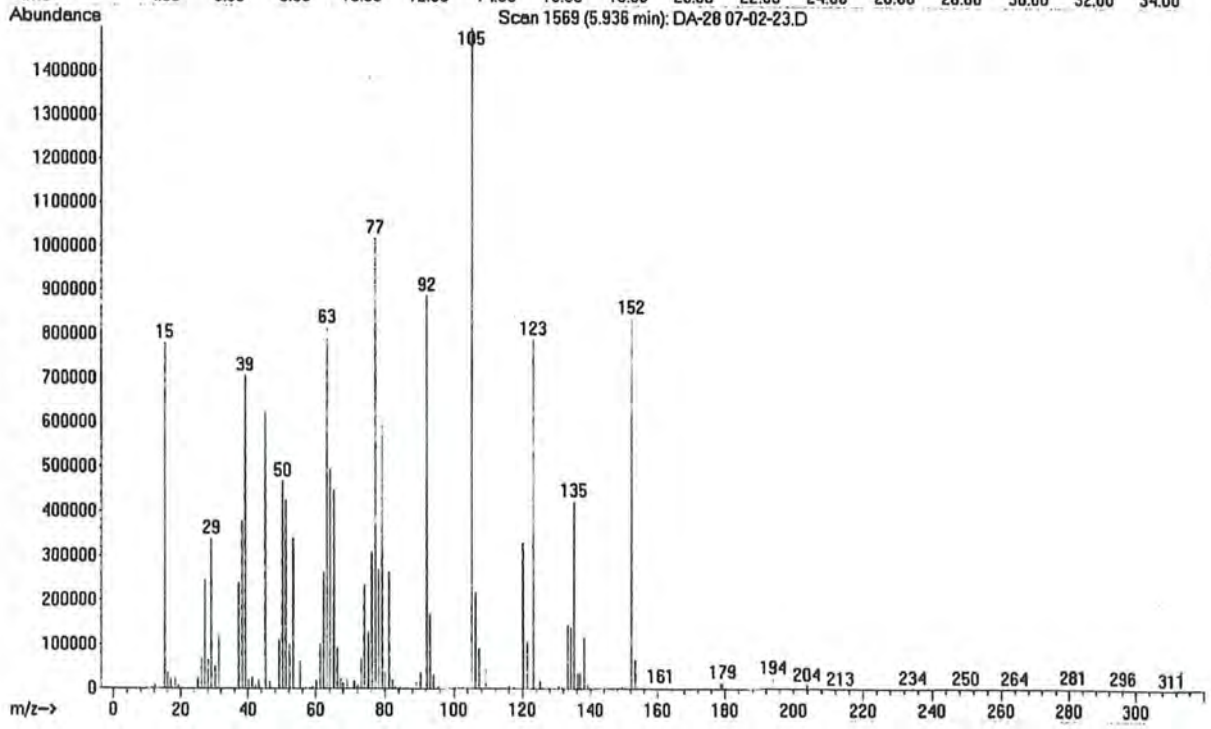

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le        :C:\MSDChem\1\DATA\2023\Dr. Abbas Hassan\Agha Danish\DA-56 21-
          07-23.D
erator    : Saqib Yasin
strument  :    Instrument #2
quired    : 21 Jul 2023  13:46      using AcqMethod LIQUID.M
mple Name: DA-56
sc Info   : Temp 120-280C 10C/min  Flow 1.5ml/min Inj 5ul
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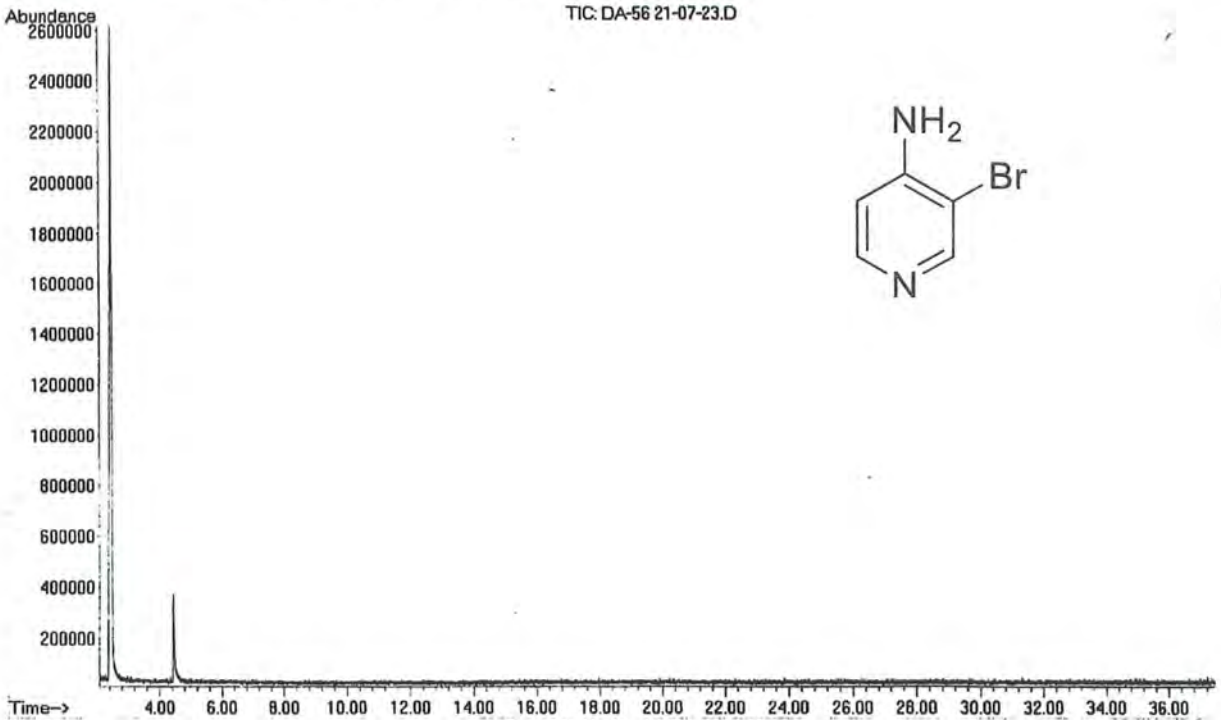
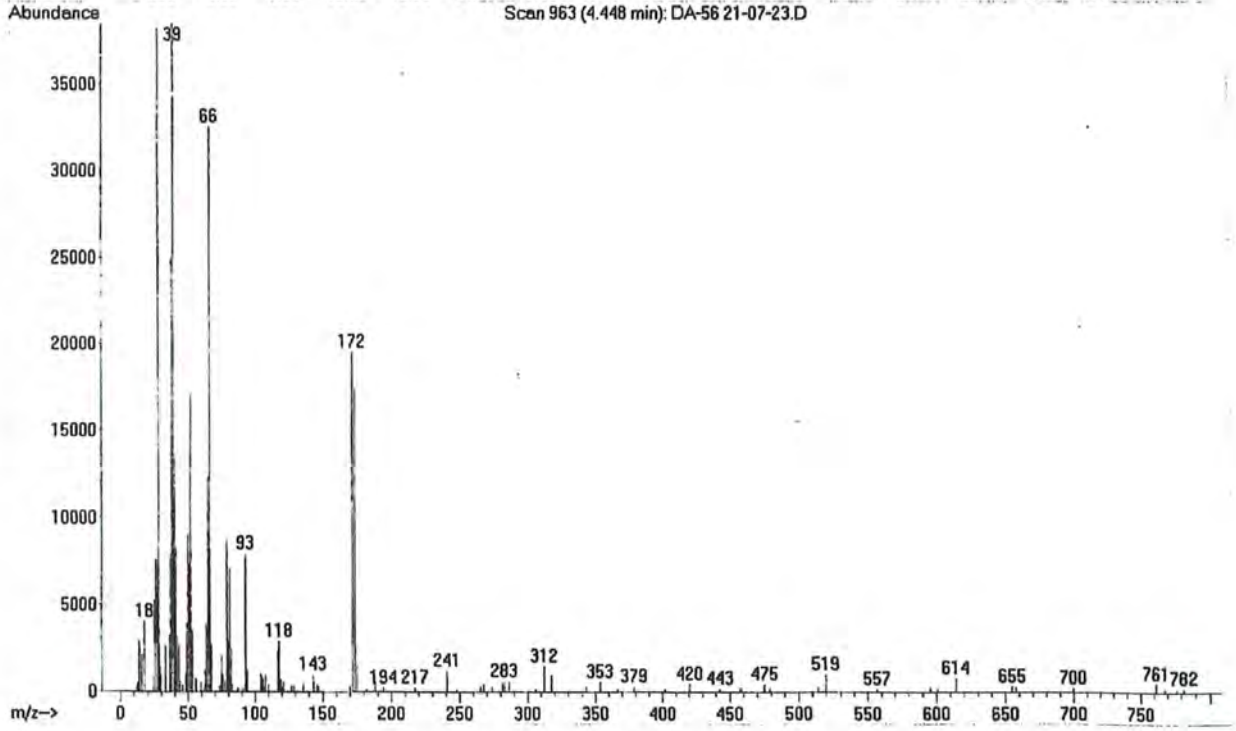
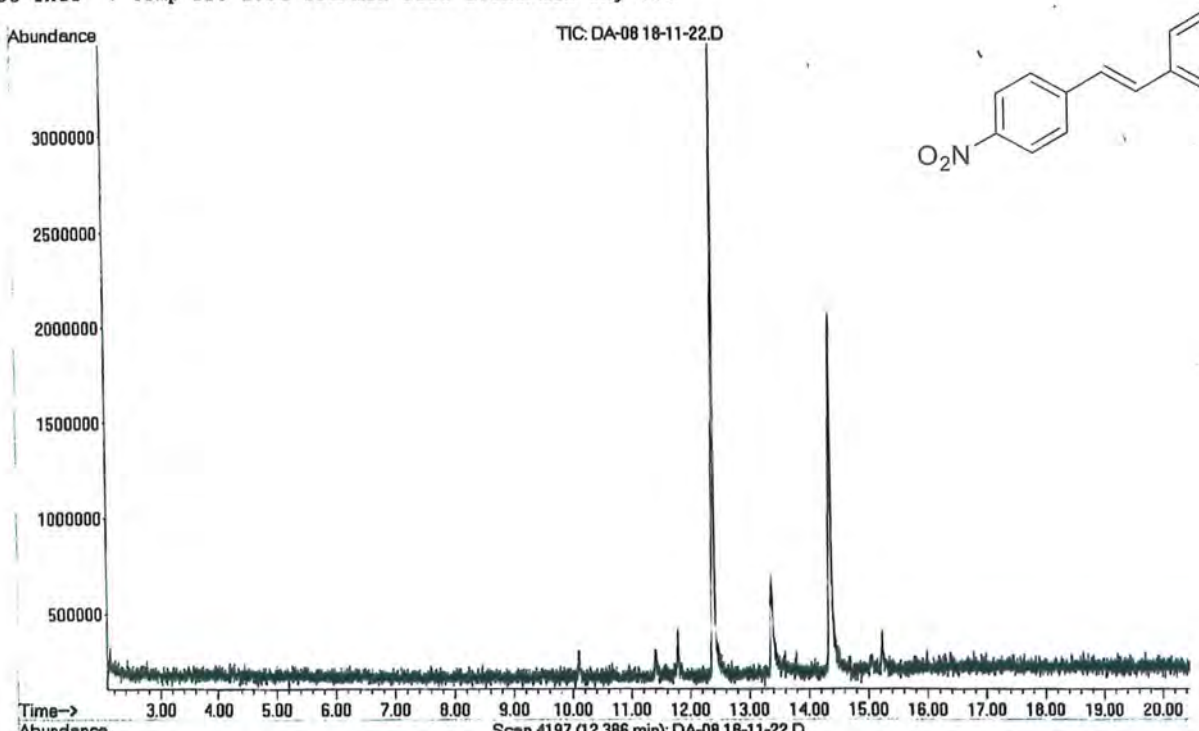
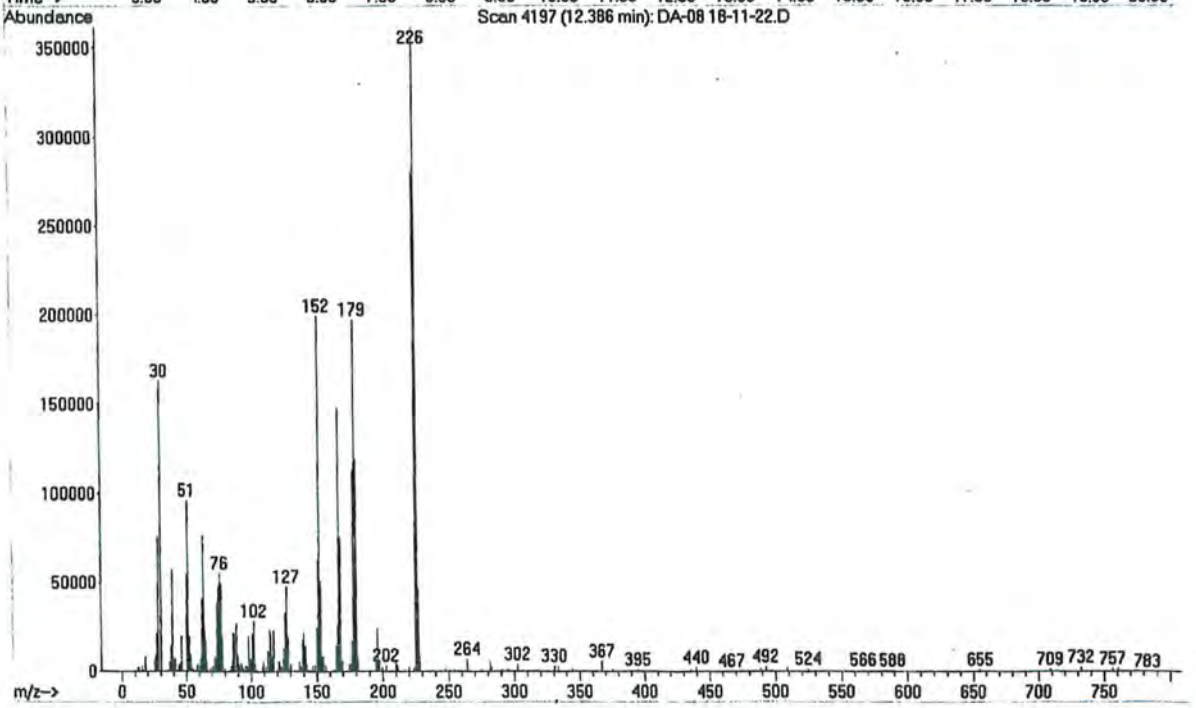


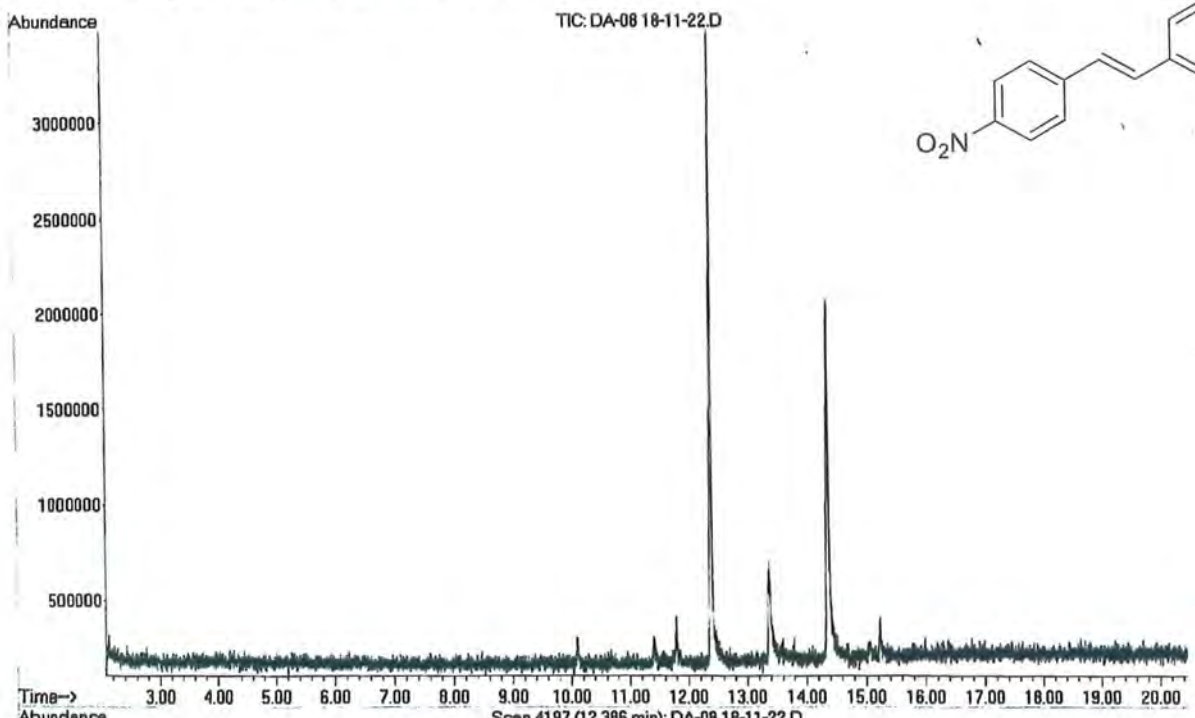


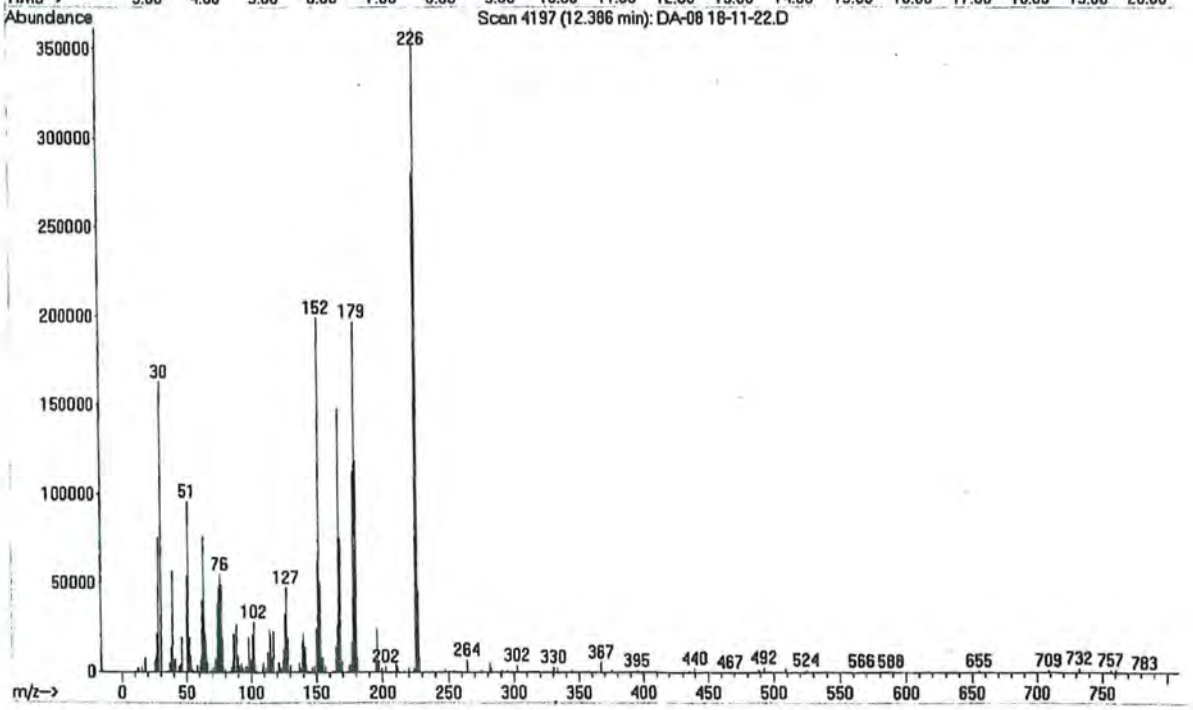
File :C:\MSDChem\1\DATA\2022\Dr.Abbas H\Agha Danish\DA-08 18-11-22.D
Operator : Saqib Yasin
Instrument : Instrument #2
Acquired : 18 Nov 2022 14:46 using AcqMethod LIQUID.M
Sample Name: DA-08
Misc Info : Temp 120-280C 10C/min Flow 1.5ml/min Inj 5ul



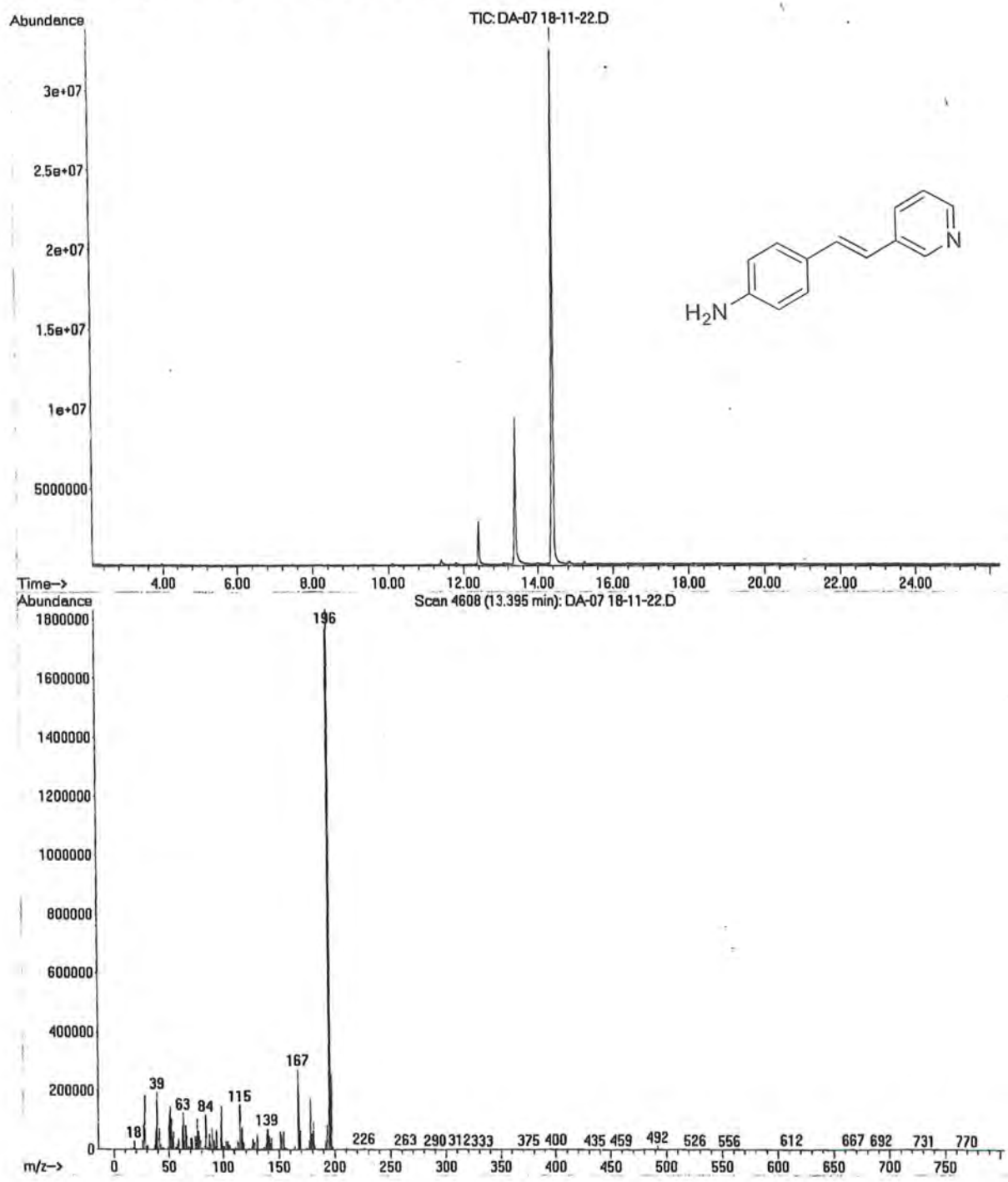


File :C:\MSDChem\1\DATA\2022\Dr.Abbas H\Agha Danish\DA-08 18-11-22.D
Operator : Saqib Yasin
Instrument : Instrument #2
Acquired : 18 Nov 2022 14:46 using AcqMethod LIQUID.M
Sample Name: DA-08
Misc Info : Temp 120-280C 10C/min Flow 1.5ml/min Inj 5ul





File :C:\MSDChem\1\DATA\2022\Dr.Abbas H\Agha Danish\DA-07 18-11-22.D
Operator : Saqib Yasin
Instrument : Instrument #2
Acquired : 18 Nov 2022 14:17 using AcqMethod LIQUID.M
Sample Name: DA-08
Misc Info : Temp 120-280C 10C/min Flow 1.5ml/min Inj 5ul



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le        : C:\MSDChem\1\DATA\2023\Dr. Abbas Hassan\Agha Danish\DA-21 01-
            02-23.D
erator    : Saqib Yasin
strument  :    Instrument #2
quired    :  1 Feb 2023   8:54      using AcqMethod LIQUID.M
mple Name : DA-21
sc Info   : Temp 120-280C 10C/min Flow 1.5ml/min Inj 5ul
```