University of Sussex

Expanding the Scope of the Bohlmann-Rahtz Reaction: New Routes to 3-Nitropyridines, δ-Carbolines, and β-Carbolines

By

Tyler Woodrow Nichols

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School of Life Sciences

University of Sussex

DECLARATION

I hereby declare that this thesis has not been and will not be, submitted in whole or in part to another University for the award of any other degree.

Signed ………………………………………

(*Tyler W. Nichols*)

Date: 6th September, 2022

ABSTRACT

Chapter One opens with an overview of the role of pyridines in the pharmaceutical industry. This is followed by an in-depth survey of literature methods that have been reported for pyridine synthesis, including the Bohlmann-Rahtz reaction. The chapter concludes with the aims of this project.

Chapter Two delineates the development and optimization of a new $ZnBr_2$-catalyzed method for the synthesis of 2,3,6-trisubstituted and 2,3,4,6-tetrasubstituted 3-nitropyridines using the Bohlmann-Rahtz reaction. This culminates in the synthesis and characterization of two libraries of 3-nitropyridines. The scope of this new Bohlmann-Rahtz reaction is then expanded to facilitate the synthesis of 2,3-disubstituted and 2,3,4-trisubstituted 3-nitropyridines.

Chapter Three describes a DPPE-mediated reaction for the cyclization of 3-nitropyridines into substituted δ-carbolines. The rest of the chapter then describes the development of a PPh_3-mediated method for the cyclization of 3-nitropyridines into substituted β-carbolines. It concludes with the synthesis of the β-carboline natural product harmine.

ABBREVIATIONS

°C	Degrees Celsius
AcOH	Acetic acid
aq.	Aqueous
AβC	Aromatized β-carboline
BNR	Bischler-Napieralski reaction
BR	Bohlmann-Rahtz
cBBR	Consecutive three- and four-component Bagley-Bohlmann-Rahtz
CHN	Elemental analysis
conc.	Concentrated
DCM	Dichloromethane
DHP	Dihydropyridine
DHβC	Dihydro-β-carboline
DMAc	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DPPE	1,2-bis(diphenylphosphino)ethane
EAS	Electrophilic aromatic substitution
EI	Electron impact
equiv.	Equivalent
ESI	Electrospray ionization
EtOH	Ethanol
h	Hour(s)
HCl	Hydrochloric acid
HIV	Human immuno-deficiency virus
HNO$_3$	Nitric acid
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
IBX	2-iodoxybenzoic acid
IR	Infrared

J	Coupling constant
$KMnO_4$	Potassium permanganate
LC-MS	Liquid chromatography-mass spectroscopy
M	Molar
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MeOH	Methanol
MICROCOS	Microwave-assisted Combinatorial Synthesis
min	Minute(s)
$Mo(CO)_6$	Molybdenum hexacarbonyl
mol%	Molar percentage
MS	Mass spectrometry
n-BuLi	n-Butyllithium
n.d.	Not determined
n.r.	No reaction
N_2O_5	Nitrogen pentoxide
NaN_3	Sodium azide
$NaNO_2$	Sodium nitrite
NaOH	Sodium hydroxide
NBS	*N*-bromosuccinimide
NEt_3	Triethylamine
NH_4Cl	Ammonium chloride
NH_4OAc	Ammonium acetate
NMR	Nuclear magnetic resonance
NSAID	Non-steroidal anti-inflammatory drug
Pd/C	Palladium on carbon
PhMe	Toluene
pK_a	Acid dissociation constant
PPh_3	Triphenylphosphine
PPI	Proton-pump inhibitor
ppm	Parts per million
PSR	Pictet-Spengler reaction
rt	Room temperature

SO$_2$	Sulfur dioxide
*t*BuOK	Potassium *tert*-butoxide
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TH*β*C	Tetrahydro-*β*-carboline
TLC	Thin-layer chromatography
TsOH	*p*-Toluenesulfonic acid
VNS	Vicarious nucleophilic substitution
W	Watts
ZnBr$_2$	Zinc(II) bromide
ZnCl$_2$	Zinc(II) chloride
δ	Chemical shift
μg	Microgram(s)
μM	Micromolar

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CHAPTER ONE: Introduction

Properties and applications of pyridines

The pyridine ring (**1**) is a frequently encountered structure (**Figure 1**) in natural products chemistry, drug design, agrochemicals, and other areas of industry.[1] The name '*pyridine*' is derived from the Greek word '*pyr*', which means fire, and a general suffix for aromatic bases, '*idine*'. This is a reference to the way pyridine bases were first isolated through the pyrolysis of bones. During destructive distillation, the glycerol and nitrogenous compounds in bone oil are known to break down into simple aldehydes, ketones, and ammonia, which then condense into pyridines. Thomas Anderson isolated the first purified pyridine base (picoline) from coal tar (produced from bones) in 1846. It was not until the end of the century that synthetic methods for pyridine compounds began to appear in the literature, and it took until the 1930s before this class of compounds was recognized as having valuable medicinal and industrial applications.

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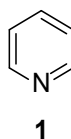
Figure 1: The heterocycle pyridine (**1**).

Human physiology depends upon key pyridine-containing compounds to function properly.[2,3] The pyridine-based vitamins (**Figure 2**) nicotinic acid (**2**), nicotinamide (**3**) (together known as 'niacin' or vitamin B_3), and pyridoxine (vitamin B_6, **3**) are all essential for healthy metabolism. The niacin-derived dinucleotides NAD^+ and $NADP^+$ are found in all living cells, where they act as electron carriers during redox reactions and are converted into NADH and NADPH, respectively.[3] Without the ubiquitous electron transport system that is based around this redox reaction, life on any level would be impossible.
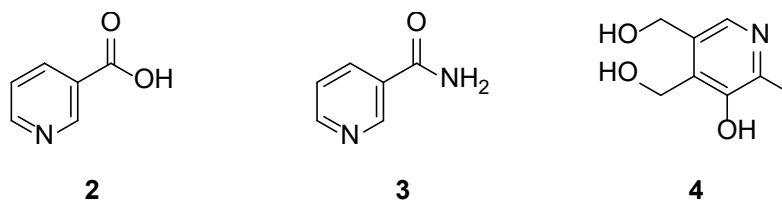
Figure 2: Structures of nicotinic acid (**2**), nicotinamide (**3**), and pyridoxine (**4**).

Pharmaceutical applications

Human metabolism sometimes converts simple pyridines into pyridinium ions through oxidation and methylation pathways.[2] Although the kidneys often eliminate these toxic metabolites before they can accumulate in the body, this has led to a tendency in modern drug design to substitute pyridine moieties with metabolically stable bioisosteres. Nevertheless, the pyridine ring remains an attractive heterocyclic moiety in rational drug design because it confers potentially favourable physical properties like increased hydrophilicity, enhanced stability, weak basicity, and its tendency to participate in hydrogen bonding.[4] As such, there are dozens of examples of pharmaceuticals that contain a pyridine moiety, several of which are so-called 'blockbuster drugs'.[2,5] One example of how pyridines have been used in rational drug design (**Scheme 1**) is the antifungal agent isavuconazole (**8**), a treatment for infections such as mucormycosis and aspergillosis.[6] While a highly active compound in its own right, the clinical utility of isavuconazole (**8**) is severely limited by its poor water solubility, which necessitated the development of a prodrug.[7] In 2015, the FDA approved isavuconazonium sulfate (**7**), a prodrug with favorable water solubility (>100 mg/mL) which is efficiently metabolized by esterases into the active drug, isavuconazole.[4,6,7] This enhanced water solubility profile was largely due to the added pyridine moiety; when a benzene ring was used instead, the analogous prodrug was about ten-times less soluble than **7** was.
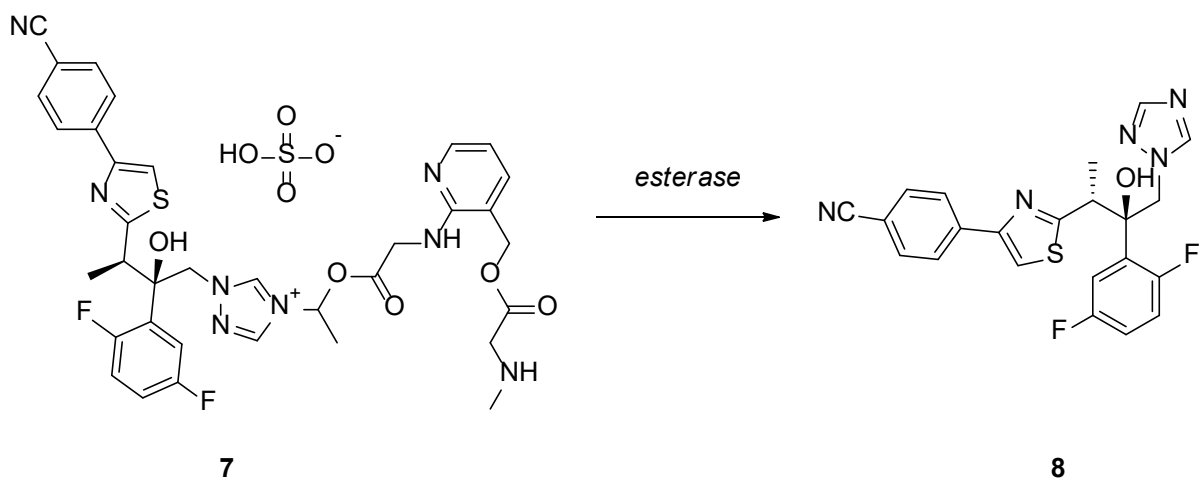
Scheme 1: Isavuconazonium sulfate (**7**) is a pro-drug for the antifungal isavuconazole (**8**).

Pyridines are valued as bioisosteres for other nitrogenous heterocycles, amines, and amides.[2] They can replace these features due to their similar physiochemical properties. This is done with the aim of improving drug efficacy, oral bioavailability, membrane permeability, *in vivo* stability, or pharmacokinetics. Pyridine moieties were used as bioisosteres for imidazole during the development of first-generation antihistamines (**Figure 3**).[4] Histamine (**9**) is a neurotransmitter that is comprised of two functional groups: an imidazole ring and a primary amine. The antihistamines chlorpheniramine (**10**) and mepyramine (**11**) mimic the structure of histamine, with a pyridine ring in place of an imidazole.[8] This explains their high affinities for the H_1 histamine receptor, and their antagonism at this site is responsible for their desired effects of allergy relief and sedation.
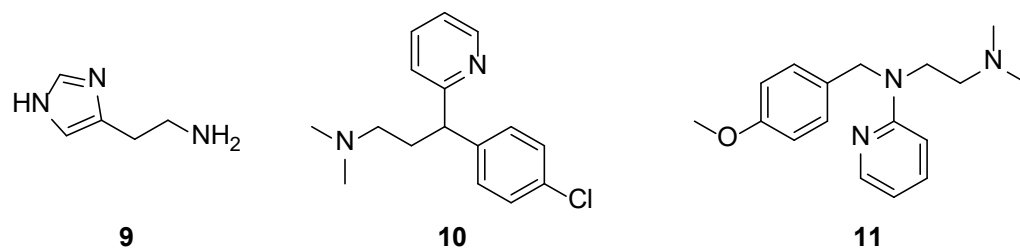
Figure 3: Structures of chlorpheniramine (**10**) and mepyramine (**11**) mimic histamine.

The replacement of a benzene ring with a pyridine ring can have a dramatic impact on pharmacology. For example, mirtazapine (*Remeron*) (**12**) is a commonly prescribed tetracyclic antidepressant with potent antihistamine and sedative properties, which features a pyridine moiety fused to an azepane core (**Figure 4**).[9] **12** differs from its predecessor mianserin (**13**), an antidepressant with a similar yet distinct pharmacological profile, only by the replacement of a benzene moiety with the pyridine ring. While **13** has high affinity for the norepinephrine transporter (NET), and acts as a norepinephrine reuptake inhibitor (NRI), **12** does not.[10]
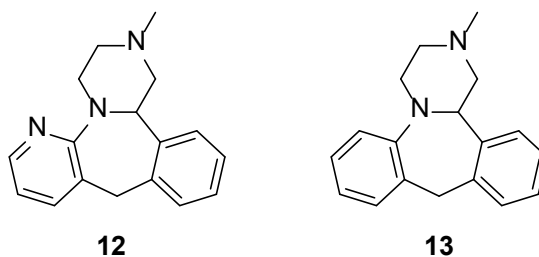
Figure 4: Structures of mirtazapine (**12**) and mianserin (**13**).

Methods for *de novo* synthesis of pyridines

From a synthetic standpoint, pyridine-containing drugs can be divided into two general categories: compounds in which the pyridine ring is derived from common, commercially

available precurors; or compounds where *de novo* synthetic methods are used to access

unique, substituted pyridines that are otherwise unavailable.[2] This section will discuss

general synthetic methods for *de novo* pyridine ring annulation. The different methods will

be categorized according to how many synthetic fragments (synthons) are brought together

to form the pyridine ring.[1]

Pyridines: Synthesis by [5+1] Disconnection
This class of methods uses only a 5-carbon synthon and a suitable nitrogen source (**Scheme
2**).[1] The 5-carbon fragment is generally a 1,5-dicarbonyl compound **14**, which can be reacted

with ammonia to give a dihydropyridine (DHP) **15.** The DHP intermediate is easily

aromatized into the final pyridine **16** with an oxidant, usually nitric acid. Alternatively, an

unsaturated 1,5-dicarbonyl compound **17** can be treated with ammonia to access the pyridine

in a single step. This route is facile but limited by commercial and synthetic access to the 1,5

dicarbonyl precursors.
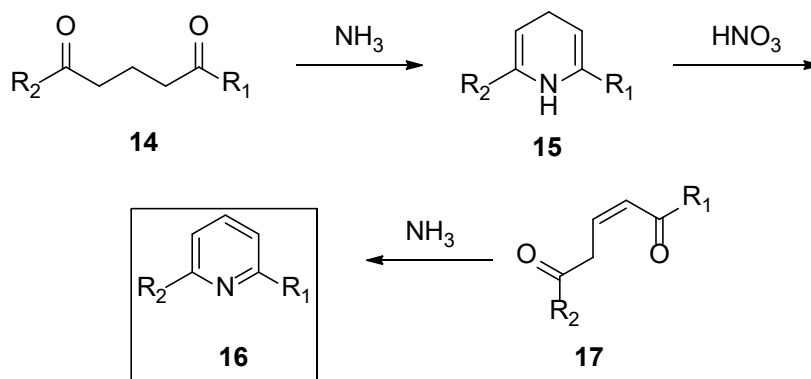
Scheme 2: Pyridine ring annulation by [5+1] disconnection.

Pyridines: synthesis by [4+2] disconnection
This type of disconnection can occur in two different patterns on the pyridine ring, but both

examples proceed *via* a Diels-Alder reaction (**Scheme 3**).[1] In the first example, a 1,3-diene

and a nitrile were heated to 400 °C, which furnished pyridine **18** in 99% yield.[11] The second

example was an intramolecular Diels-Alder reaction with a series of 1,3-diynyl bis-α,β-

unsaturated hydrazones, which were prepared beforehand *via* Glaser-Eglinton coupling.[12]

This system produced a library of 2,2'-bipyridine compounds **19** in up to 87% yield.
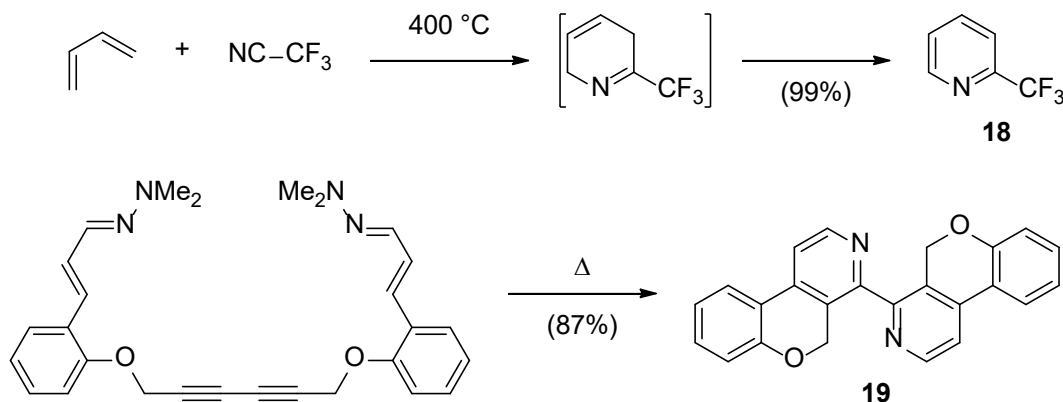
Scheme 3: Pyridines **18** and **19** were synthesized by [4+2] disconnection.

Pyridines: synthesis by [2+2+2] disconnection
This type of disconnection pattern was used in Ramsay's original 1876 synthesis of pyridine

from acetylene and hydrogen cyanide gas.[1] Today, a cobalt(I)-catalyzed variation of this

reaction (**Scheme 4**) is used for the commercial production of alkylpyridines. Chelucci (1990)

used this reaction to produce a series of optically active 2-pyrrolidinyl-pyridines **20** from

acetylene and an L-proline derivative in over 90% yield.
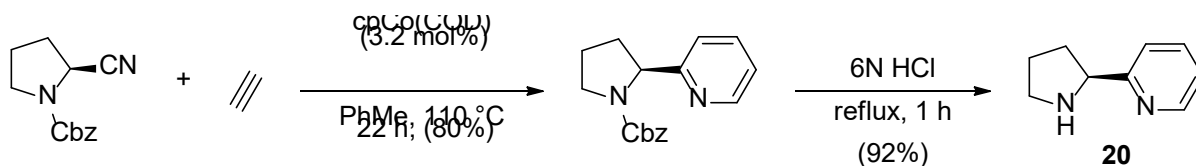
Scheme 4: Synthesis of pyridine **20** by [2+2+2] disconnection.

Pyridines: synthesis by [2+2+1+1] disconnection

The [2+2+1+1] methods for pyridine synthesis are 3- or 4-component reactions and comprise some of the most well-known routes to pyridine scaffolds. The two main archetypes to address are the Hantzsch-type reactions and the Chichibabin reaction.

Hantzsch pyridine synthesis

One of the most well-known methods for pyridine formation is the two-step Hantzsch pyridine synthesis (**Scheme 5**).[13] First reported in 1881 by Arthur Rudolf Hantzsch, the classical 4-component Hantzsch DHP synthesis condensed two equivalents of a 1,3-dicarbonyl compound **21**, with one equivalent of an aldehyde **22** and an ammonium source, forming a symmetrical 1,4-DHP **23** (also known as a 'Hantzsch ester').[1,14,15] An additional oxidation step is usually required to isolate the aromatized pyridine **24**. Part of what lends the Hantzsch-type reactions such enduring appeal are their relatively mild conditions. They are often carried out in ethanol and the ability to use many kinds of aromatic aldehydes enhances their versatility.[16] The basicity of the ammonium species alone is also usually strong enough to eschew the addition of another alkaline reagent into the reaction. The purification process that follows a Hantzsch-type reaction is simple, with recrystallization

often being sufficient. Hantzsch-type reactions are also useful because they enable substitution at every position of the pyridine ring.
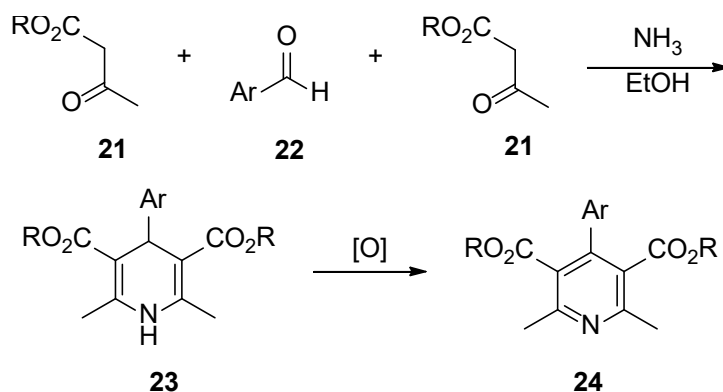
Scheme 5: General outline of a Hantzsch-type pyridine synthesis.

While most Hantzsch-type methods use 1,3-dicarbonyl compounds, other species with electron-withdrawing groups have also been employed, such as nitriles.[13] However, the 3- or 4-component reaction can be limited to the production of symmetrical DHPs. Fortunately, through a combination of careful planning and ingenuity, it is feasible to circumvent many of these limitations. For example, the β-blocker felodipine (**25**) is an unsymmetrical DHP widely prescribed as an anti-hypertensive drug. When the classical Hantzsch-type reaction was modified into a 3-component system, incorporating separate enone formation *via* Knoevenagel condensation (**Scheme 6**) and cyclocondensation with an enamine, the unsymmetrical DHP felodipine (**25**) was successfully synthesized (yield not stated).[16,17]
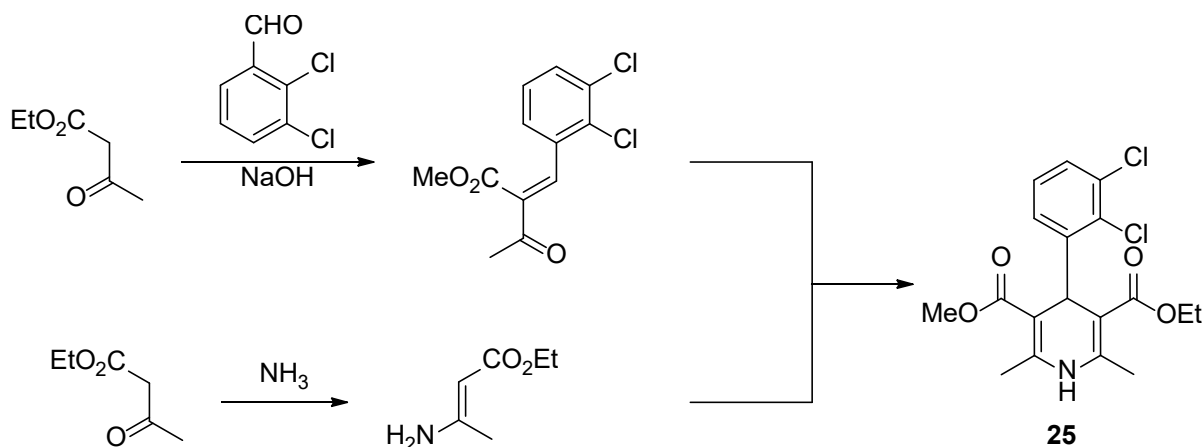
Scheme 6: Hantzsch-type synthesis of the DHP anti-hypertensive drug felodipine (**25**).

In recent years, microwave-assisted Hantzsch-type methods have been developed that reduce reaction times and solvent use, without compromising yields. For example, the Cotterill group (1998) reported a microwave-assisted Hantzsch-type method (**Scheme 7**) that provided access to aromatized pyridines in a single step.[13,18] In this solvent-free system with bentonite, ammonium nitrate generated nitric acid *in situ*, which spontaneously oxidized the DHPs. Because of the non-selective nature of the reaction, by using two 1,3-dicarbonyls in the same flask, the group could generate a mixture of symmetrical and unsymmetrical pyridines. This allowed the group to develop a Microwave-assisted Combinatorial Synthesis (MICROCOS) method with easy purification and short reaction time resulting in a quickly-generated, structurally diverse library of pyridines.
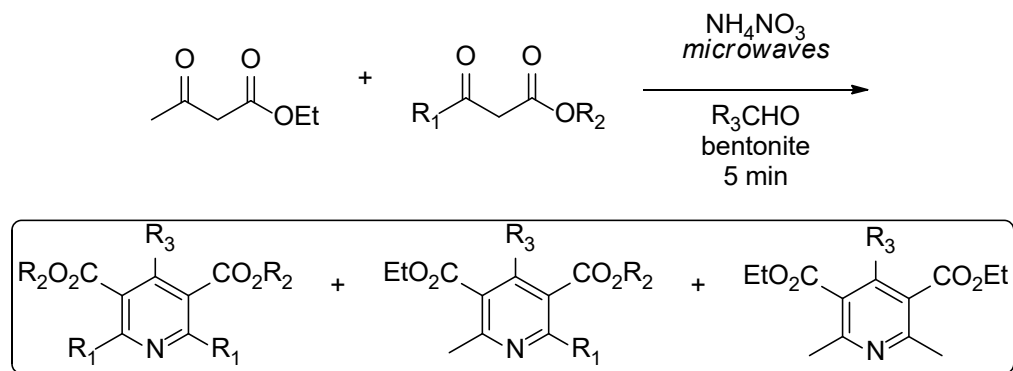
Scheme 7: Hantzsch-type Microwave-assisted Combinatorial Synthesis (MICROCOS).

Chichibabin reaction

Chichibabin first reported a pseudo-four-component cylocondensation route to pyridines in 1906, the mechanism of which is shown in **Scheme 8**.[13,19] Their original conditions condensed three equivalents of an enolizable aldehyde with one equivalent of ammonia under high pressure, which formed a pyridine along with minor side products. These conditions have since been revised to reduce side product formation by instead using an aldehyde, one equivalent of ammonium acetate, and either *a)* two equivalents of enolizable ketone or *b)* one equivalent enolizable ketone and one equivalent of a 1,3-dicarbonyl compound.[13] Acetophenone derivatives are the most frequently encountered substrates, but the Chichibabin reaction is tolerant of a variety of other substrates, namely cyclic ketones, 1,3-inanedione, malononitrile, and β-carbonylnitriles.
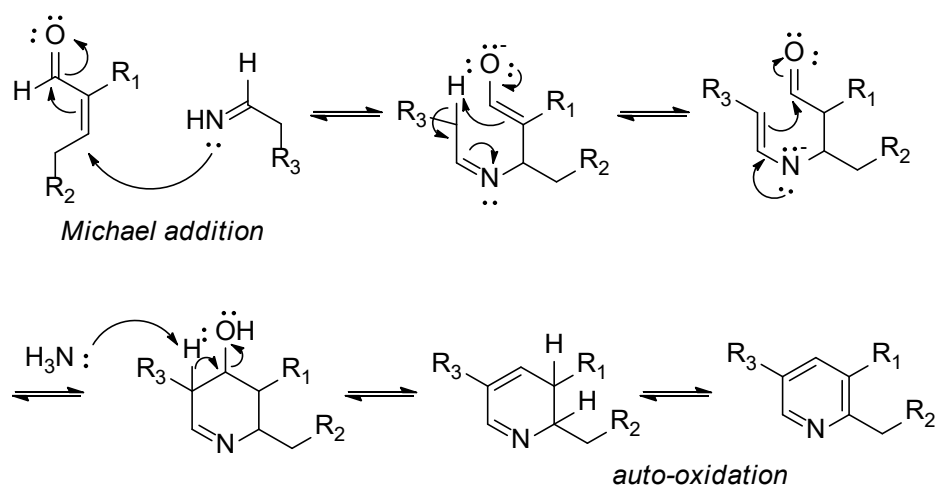
Scheme 8: Suggested mechanism for the Chichibabin reaction.

The most common types of Chichibabin reactions facilitate the synthesis of 2,4,6-triarylpyridines ('Kröhnke pyridines') from aromatic aldehydes and acetophenones.[13] For example, the Tu group (2005) have reported a microwave-assisted Chichibabin-type reaction (**Scheme 9**) for the synthesis of 2,4,6-triarylpyridines and 4'-aryl-2,2':6',2"-terpyridines.[20] When 1-(pyridin-2-yl)ethanone was heated with 4-chlorobenzaldehyde and ammonium acetate in glycol, terpyridine **26** was isolated in 91% yield.
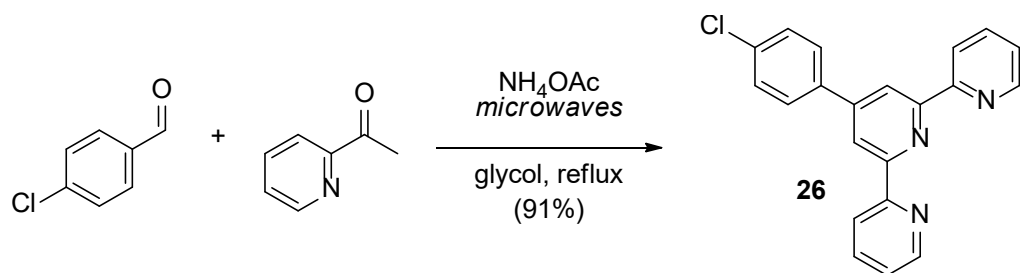
Scheme 9: Microwave-assisted Chichibabin-type synthesis of terpyridine **26**.

Pyridines: synthesis by [3+3] disconnection

Bohlmann-Rahtz pyridine synthesis

The Bohlmann-Rahtz (BR) pyridine synthesis was first described in 1957.[13,21,22] The original conditions involved two steps, leading to the synthesis of trisubstituted pyridines. First, there was Michael addition of an ethylnyl ketone to an enamine, which furnished an aminodiene intermediate in high yield. The aminodiene needed to be isolated and subjected to high temperatures (120-170 °C) to induce C=C E/Z isomerization. This encouraged spontaneous cyclodehyration, resulting in a 2,3,6-trisubstituted pyridine in up to 85% yield. **Scheme 10** depicts the suggested 2-step mechanism for the Bohlmann-Rahtz reaction.

Michael addition   *cyclodehydration*
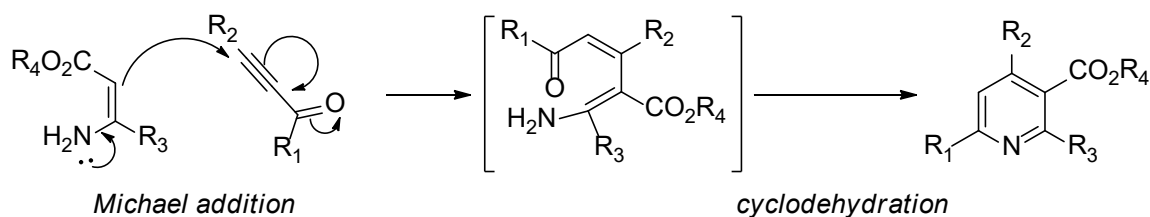
Scheme 10: Suggested mechanism for the Bohlmann-Rahtz reaction: Michael addition followed by E/Z-isomerization and cyclodehydration.

The BR reaction displays similarities with the Hantzsch-type reactions, except it uses two 3-carbon donors instead of a [2+2+1+1] pseudo-four-component system.[1,22] However, the BR has a major advantage over the Hantzsch-type systems by not requiring a separate oxidation step, thus providing direct, regioselective access to 2,3,6-trisubstituted and 2,3,4,6-tetrasubstituted pyridines. This system is versatile enough to allow for diverse libraries to be generated, with high atom economy. Yet one important drawback of the original BR reaction was that it required isolation of the aminodiene intermediate, and then harsh conditions to

induce isomerization and aromatization, which was cumbersome and needed improvement. This was likely a contributing factor to why the BR reaction was seldom used between 1957 and 1998, when the Moody group "rediscovered" this method (**Scheme 11**) and used it in the total synthesis of the antibiotic promothiocin A (**27**).[22,23] The 2,3,6-trisubstituted pyridine (**28**) was synthesized using the BR reaction. This intermediate was incorporated into promothiocin A (**27**) after 11 additional steps.
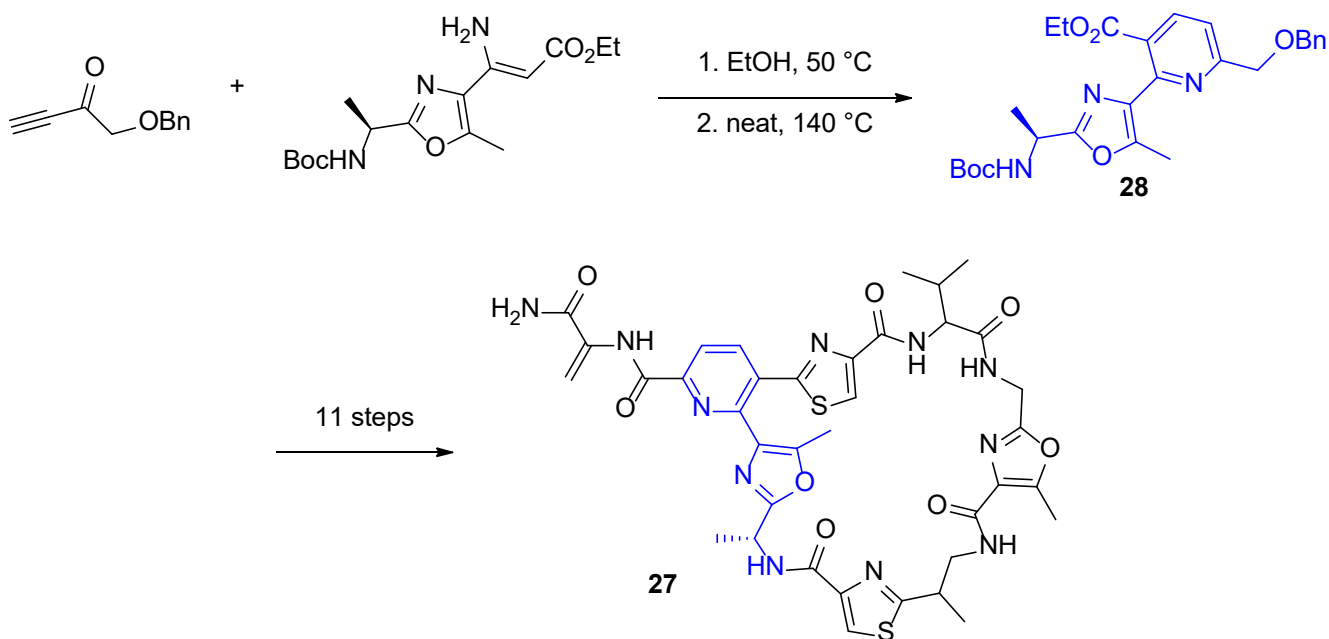
Scheme 11: BR reaction used to synthesize pyridine **28**, core of promothiocin A (**27**).

In 2001, the Bagley group demonstrated that when the aminodiene intermediate was isolated and heated to 50 °C in a 5:1 mixture of toluene and acetic acid, the expected pyridine was obtained in quantitative yield.[24] Since they had discovered a way to induce C=C *E/Z-*isomerization under these milder conditions, the group then developed a single-step BR reaction for the synthesis of polysubstituted pyridines (**Scheme 12**). The acid-catalyzed BR

reaction between enamine **29** and alkynone **30** furnished 2,3,4,6-tetrasubstituted pyridine **31** in 95% yield.
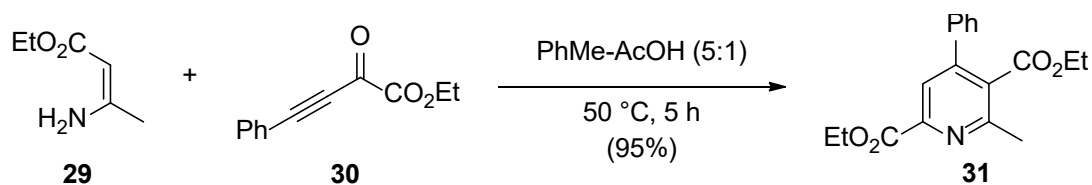
Scheme 12: Acid-catalyzed BR reaction used to synthesize pyridine **31**.

In 2002, the Bagley group reported a three-component, single-step variation of the BR reaction whereby a β-ketoester was treated with an ammonia source (ammonium acetate) to form an enaminoester *in situ* (**Scheme 13**).[25] For example, when β-ketoester **32** was reacted with alkynone **33** and ammonium acetate in the presence of zinc(II) bromide in toluene at reflux, pyridine **34** was isolated in 96% yield. Again, no additional oxidation step was required because the starting materials were in an oxidation state appropriate for transformation to the desired product.
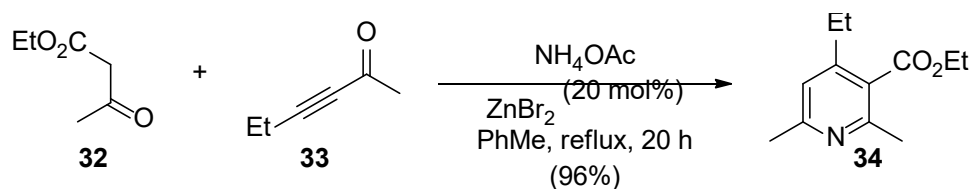
Scheme 13: Three-component BR reaction used to synthesize pyridine **34**.

A mild acid-free alternative has also been developed (**Scheme 14**) whereby an acid-sensitive β-ketoester or acetoacetamide **35** was stirred in ethanol at reflux with an alkynone and excess ammonium acetate.[26] The Bagley group used this variant to synthesize dimethyl sulfomycinamate, the oxazole-thiazole-pyridine core of the thiopeptide antibiotics

sulfomycin I-III.[27] The BR reaction furnished the pyridine intermediate **36** in 81% yield. An

additional 6 steps were required to access the final product, dimethyl sulfomycinamate.
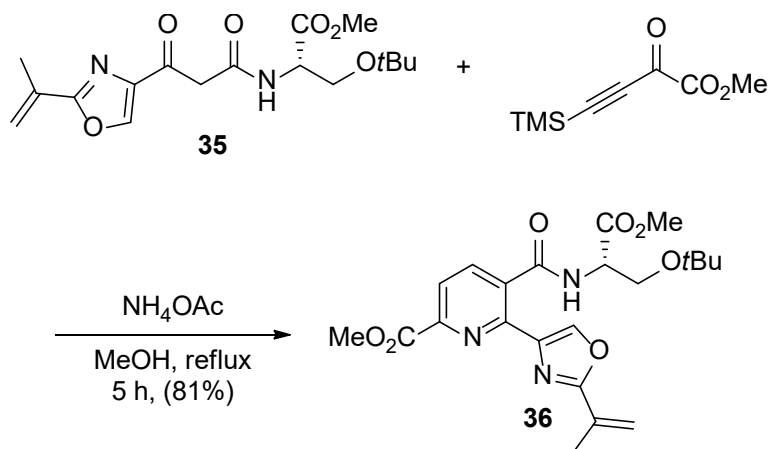
Scheme 14: Acid-free BR reaction used to synthesize pyridine **36**.

One feature that narrows the range of applications for the BR reaction is the limited

commercial availability of alkynones. In many cases, the alkynones must be synthesized in-

house beforehand. To address this concern, the Bagley group (2003) developed a one-pot BR

reaction (**Scheme 15**) which instead used propargylic alcohols (reacted with benzamidine, an

enamine, or a β-ketoester) to generate polysubstituted pyrimidines and pyridines.[28] For the

synthesis of pyridines from enamines, the optimal solvent system was a 5:1 mixture of

DMSO and acetic acid; from β-ketoesters, a 5:1 mixture of toluene and acetic acid was used.

A suitable oxidant (IBX for enamines, manganese dioxide for β-ketoesters) was added to the

reaction mixture to generate the alkynone *in situ* from the propargylic alcohol. When enamine

37 was stirred with 1-phenylprop-2-yn-1-ol and IBX in DMSO-AcOH at 65 °C overnight,

pyridine **38** was isolated in 70% yield.
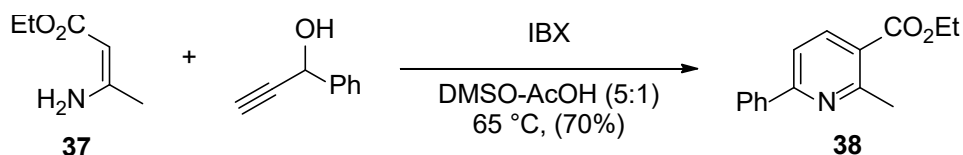
Scheme 15: Tandem oxidation-heteroannulation of a propargylic alcohol.

Aulakh and Ciufolini (2009) have developed a new route to the pyridine core of thiopeptide antibiotics using a variant of the BR reaction, which was informed by the Bagley group's work.[29] First, selenium dioxide was used to oxidize a 2-methylthiazole into its corresponding thiazolyl ynone. The ynone was then heated with a highly functionalized aromatic ketone (**Scheme 16**) and an excess of ammonium acetate in acetic acid at reflux for 8 hours. After purification, pyridine **39** was isolated in 63% yield.
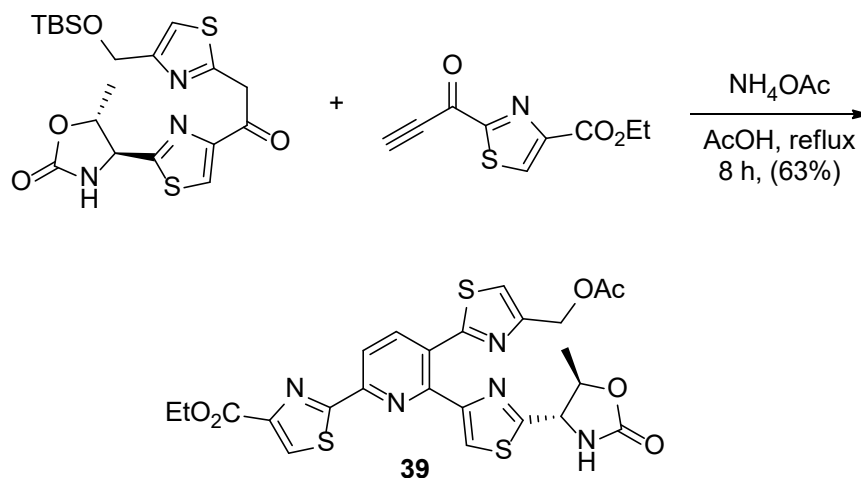
Scheme 16: BR reaction used to synthesize thiopeptide core pyridine **39**.

Dohe and Müller (2016) have recently described an ingenious one-pot, consecutive three- and four-component Bagley-Bohlmann-Rahtz (cBBR) reaction (**Scheme 17**) that generated substituted alkynones *in situ* using Sonogashira coupling.[30] Once the alkynone had been generated in the first step, acetic acid and enamine **29** were injected into the reaction vessel

and the mixture was stirred at 100 °C for 24 hours. When 4-fluorobenzoyl chloride and acetylene were used as the starting materials, pyridine **40** was isolated in 55% yield.
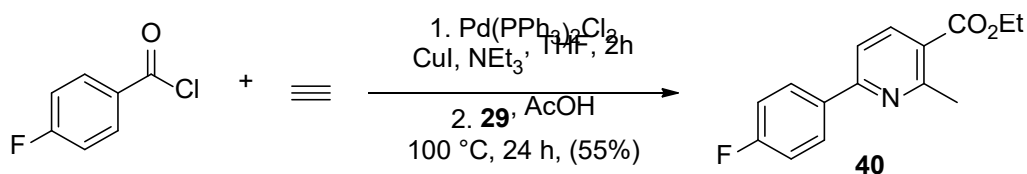
Scheme 17: One-pot cBBR reaction with *in situ* alkynone formation.

In 2016, the Bagley group reported a new microwave-assisted BR reaction for rapid, regioselective access to 2-aminonicotinates (**Scheme 18**).[31] Ethyl 2-amidinoacetate (**41**) was condensed with various ethynyl ketones in ethanol using microwave irradiation at 150 °C for 90 minutes. The reaction was carried out with either the hydrochloride salt of **41** under acidic conditions (5:1 EtOH-AcOH), or under basic conditions using the free-base form of **41**; the basic conditions were usually higher yielding. The crude reaction mixture was rapidly purified by immobilization on a Biotage Isolute® SCX-2 (sulfonic acid resin) column, followed by elution with ethanolic ammonia (2 M). When alkynone **42** was used as the substrate, 2-aminonicotinate **43** was isolated in 92% yield.
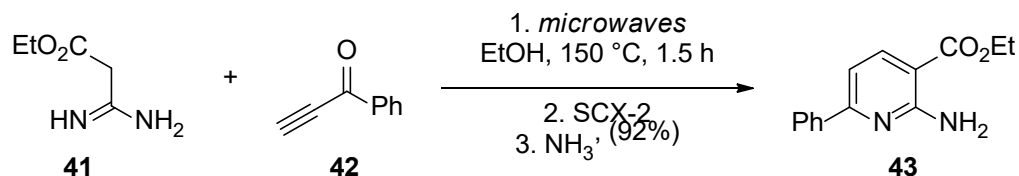
Scheme 18: Microwave-assisted synthesis of 2-aminonicotinate **43**.

3-Nitropyridines: known methods for their synthesis

The first synthesis of 3-nitropyridine (**44**) was reported in 1912.[32] Since then, many new methods have appeared in the literature. The addition of a nitro group as a *β*-substituent

(**Figure 5**) enhances the π-orbital deficiency of the pyridine ring, which has several potentially useful implications for its subsequent reactivity.[33] Namely, it renders the pyridine more vulnerable to nucleophilic attack, opening the door for nucleophilic substitutions and ring-opening reactions that would otherwise be unfavorable. Additionally, the β-nitro group also increases the relative C-H acidity of any aliphatic side chains located at the α- or γ-positions, rendering them more vulnerable to electrophilic attack.
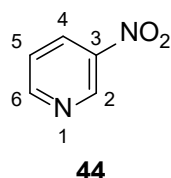
Figure 5: Structure of 3-nitropyridine (**44**).

There are three main categories of synthetic methods that have been devised to access 3-nitropyridine-containing scaffolds: pyridine nitration, transformation of non-pyridine heterocyclic compounds, and cyclization reactions between two or more acyclic precursors.[33] Most 3-nitropyridines are produced *via* the nitration of substrates that have been activated for EAS.[34] Since pyridines only undergo electrophilic aromatic substitution (EAS) when subjected to unusually harsh reaction conditions, attempts to access 3-nitropyridine (**44**) *via* direct nitration of pyridine (**1**) with HNO_3/H_2SO_4 (**Scheme 20**) will generally give unsatisfactory yields (variously reported between 6% and 12%).[35] Pyridine (**1**) undergoes direct nitration at a rate 10^{22} times slower than benzene does.
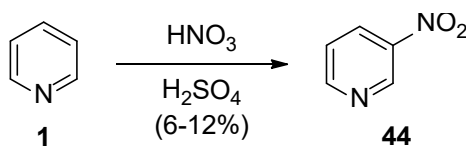
Scheme 19: Nitration of pyridine (**1**) with HNO_3/H_2SO_4.

The low reactivity of pyridine in EAS is due in part to the protonation of pyridine in these highly acidic conditions. This is best illustrated (**Scheme 20**) by the case of 2,6-dichloropyridine (**45**), where the two electron-withdrawing chlorine atoms flanking the pyridinyl nitrogen allow the pyridine to remain in free-base form under acidic conditions. Therefore, pyridine **45** will undergo direct nitration more readily than an unsubstituted, protonated pyridine.[36,37]
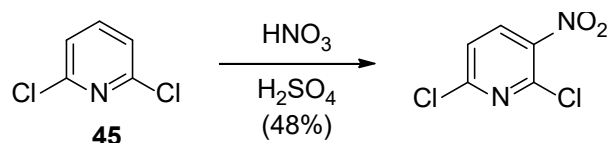
Scheme 20: Nitration of 2,6-dichloropyridine (**45**).

The poor reactivity of the pyridine ring is further exemplified by the findings of the Olah group (1965), who observed that nitronium tetrafluoroborate, a potent nitration reagent, does not nitrate any pyridinyl carbon atoms (**Scheme 21**).[38] Instead, there was total selectivity for nitration of the pyridinyl nitrogen atom. After only 15 minutes of treatment with nitronium tetrafluoroborate, the *N*-nitropyridinium tetrafluoroborate salt **46** was isolated in near-quantitative yield.
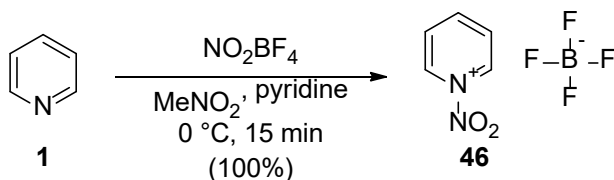
Scheme 21: Nitration of **1** with NO$_2$BF$_4$.

The Bakke group (2005) have developed several improved methods for the nitration of pyridines, which gave substantially higher yields.[34] Their first reported method (**Scheme 22**) used liquid SO$_2$ as solvent with N$_2$O$_5$ as the nitrating reagent at -11 °C. Since using this

method to nitrate 4-phenylpyridine (**47**) only produced 3-nitro-4-phenylpyridine (**48**), whereas the HNO_3/H_2SO_4 method preferentially nitrates the phenyl ring, the Bakke group deduced that this nitration does not proceed by an EAS mechanism.

Ph
N_2O_5
SO_2, -11 °C
(13%)
Ph
NO_2

47   **48**
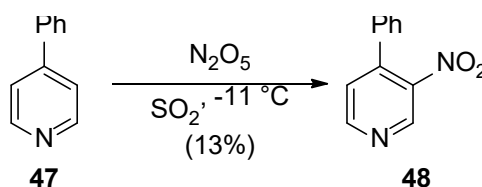
Scheme 22: Nitration of **47** using liquid SO_2.

The Bakke group expanded upon these findings with a simplified method (**Scheme 23**) that obviated the need for liquid SO_2.[34] Instead, the pyridine **47** was treated with N_2O_5 in nitromethane. Next, the reaction mixture was poured into saturated aqueous SO_2. This generally worked better than their original method, with **48** isolated in 68% yield.

Ph
1. N_2O_5, $MeNO_2$
2. SO_2 (aq.)
(68%)
Ph
NO_2

47   **48**
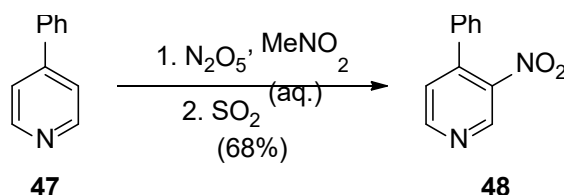
Scheme 23: Nitration of **47** using aqueous SO_2.

Using NMR spectroscopy (**Scheme 24**), the group determined that an *N*-nitropyridinium nitrate **49** intermediate was formed during the reaction with N_2O_5.[34] Then, in the aqueous SO_2 phase, a dihydropyridine sulfonic acid **50** was formed when the hydrogen sulfite ion attacked at position C-2 of the *N*-nitropyridinium ion. The actual formation of the 3-nitropyridine (**44**) itself proceeded from an intramolecular mechanism, where the nitro group migrated from the pyridinyl nitrogen to position C-3. The molecule then reacted with another

hydrogen sulfite ion, forming tetrahydropyridine intermediate **51**. Finally, re-aromatization expelled the remaining sulfonic acid group and formed 3-nitropyridine (**44**).
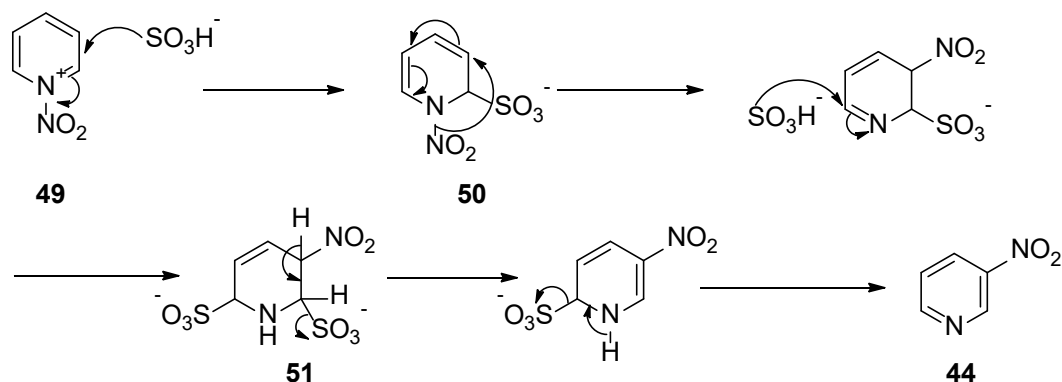
Scheme 24: Suggested mechanism for N_2O_5/SO_2-mediated nitration of pyridines.

This reaction was subsequently adapted by Suzuki and colleagues (1997) as a variation of their previously reported '*kyodai* nitration' (**Scheme 25**).[35] *N*-Nitropyridinium nitrate was first generated by treating **1** with nitrogen dioxide and ozone gas. When the resulting crude mixture was poured into saturated aqueous SO_2, 3-nitropyridine (**44**) was isolated in 62% yield. This reaction probably proceeded *via* a similar mechanism to the Bakke method.
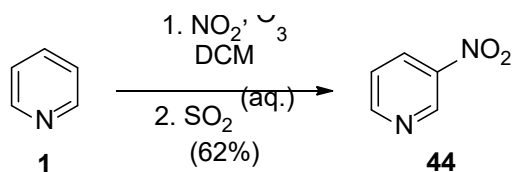
Scheme 25: *Kyodai* nitration of **1**.

The Katritzky group (2005) generated N_2O_5 *in situ* to directly nitrate pyridine (**1**) using only nitric acid and trifluoroacetic anhydride (**Scheme 26**).[37] After stirring for 10 hours, the reaction mixture was slowly added to a chilled solution of sodium metabisulfite; following work-up and purification, 3-nitropyridine (**44**) was isolated in 83% yield. In addition to the fact that these reagents were much easier to obtain than dinitrogen pentoxide, there was

generally an improvement in yields compared to the original Bakke method, even when applied to substituted pyridines and isoquinolines.
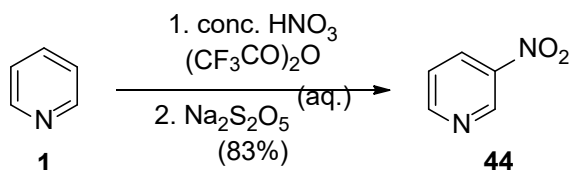
Scheme 26: Nitration of **1** using $Na_2S_2O_5$.

3-Nitropyridines: ring annulation from acyclic precursors

There are many known methods to access 3-nitropyridines from acyclic precursors. According to Yurovskaya and Afanasev (1991), the key distinguishing feature that allows for the categorization of these methods is which carbon-carbon bond is formed during the reaction (**Figure 6**).[33]
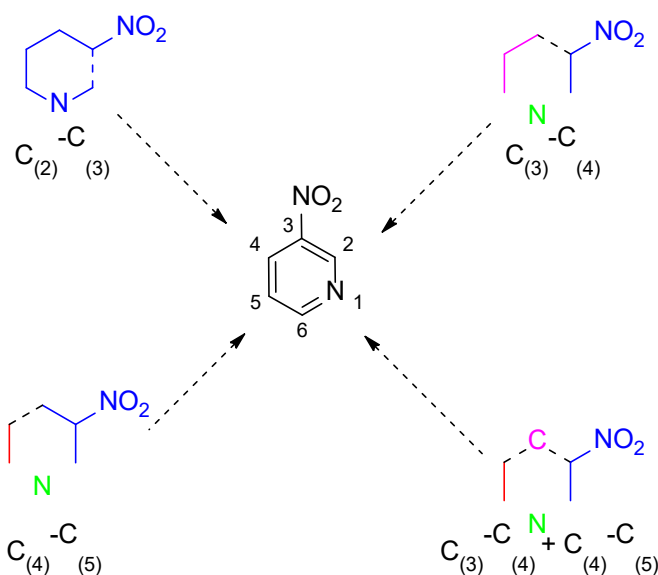
Figure 6: Different categories of 3-nitropyridine ring annulation from acyclic precursors.

The most common methods for 3-nitropyridine ring annulation from acyclic precursors depend upon the formation of a C_3-C_4 bond (**Figure 7**).[33] In this case, a 2-carbon donor is the nitro-bearing component; this can consist of a nitroacetate, an α-nitrocarbonyl compound, or a *vic*-amino nitroalkane. The corresponding 3-carbon donor can be either an α,β-unsaturated carbonyl compound or a β-dicarbonyl compound.
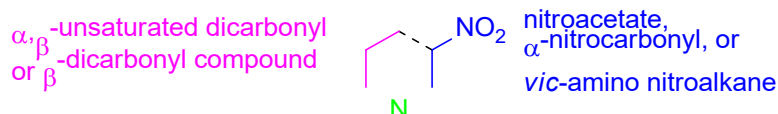
Figure 7: Formation of the $C_{(3)}$-$C_{(4)}$ bond.

For example, Troschütz and Lückel (1992) synthesized a 2,3,4,6-tetrasubstituted nitropyridine **54** under Hantzsch-type conditions (**Scheme 27**).[39] (*E*)-4-Phenylbut-3-en-2-one was condensed with 2-nitroethene-1,1-diamine (**52**) in ethanol and acetic acid for 8 hours under reflux, which gave the unsymmetrical 1,4-dihydropyridine intermediate **53** in 52% yield. The final 3-nitropyridine **54** was isolated in 26% yield after oxidation and recrystallization.
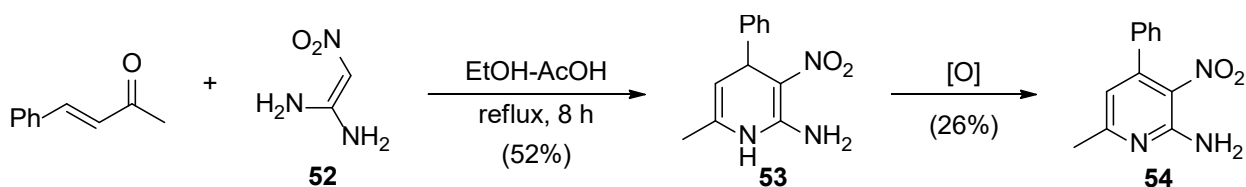
Scheme 27: Hantzsch-type synthesis of 2,3,4,6-tetrasubstituted nitropyridine **54**.

Another class of methods facilitate the formation of a C_2-C_3 bond (**Figure 8**), which is relatively uncommon in the literature.[33] These methods have mostly been used to synthesize heteroannulated polycyclic compounds, rather than free 3-nitropyridines.
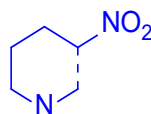
Figure 8: Formation of the C(2)-C(3) bond.

In one example, Molina (1989) used a tandem aza-Wittig/electrocyclization strategy (**Scheme 28**) for pyridine ring annulation during α-carboline synthesis.[40] When iminophosphorane **55** was stirred with an isocyanate in toluene at reflux for 12 hours, α-carboline **56** was isolated in 97% yield after recrystallization.
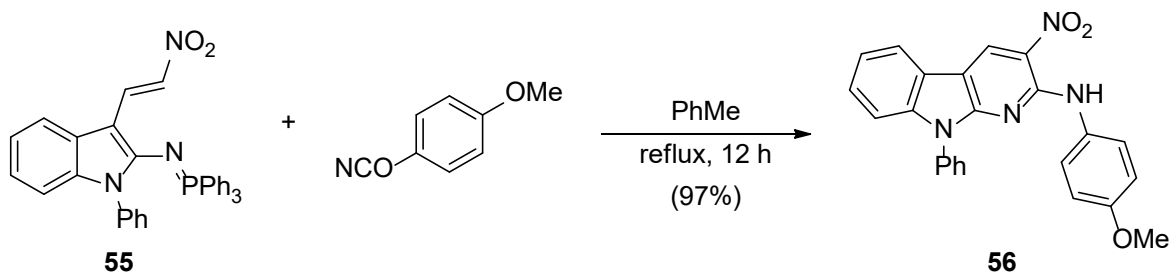
Scheme 28: Synthesis of α-carboline **56** from iminophosphorane **55**.

Nitropyridine synthesis from other heterocycles

The most well-documented routes to access 3-nitropyridines through the transformation of other heterocycles use 5-nitropyrimidines as substrates, which was first reported in 1982.[41,42] Because the 5-nitropyrimidine ring is deficient in π-electrons, it is easily opened by many nucleophiles.[33] The versatility of these methods allows for great structural diversity, and it is possible to access many 3-nitropyridine derivatives. For example (**Scheme 29**), heating 2-methyl-5-nitropyrimidine (**57**) in aqueous NaOH generated 2-amino-5-nitropyridine (**58**) albeit in 8% isolated yield.
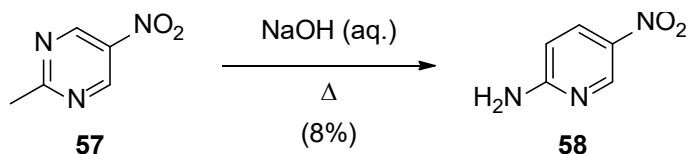
Scheme 29: Synthesis of 3-nitropyridine **58**.

In this case, the hydroxide nucleophile was believed to have attacked at the electron-deficient 4-position of 5-nitropyrimidine **57**, which opened the ring (**Scheme 30**).[41,42] This was followed by an intramolecular rearrangement, culminating with cyclodehydration into the new pyridine ring system of **58**. This is a variant of what is known as an 'Addition of the Nucleophile, Ring Opening, and Ring Closing' (ANRORC) mechanism.
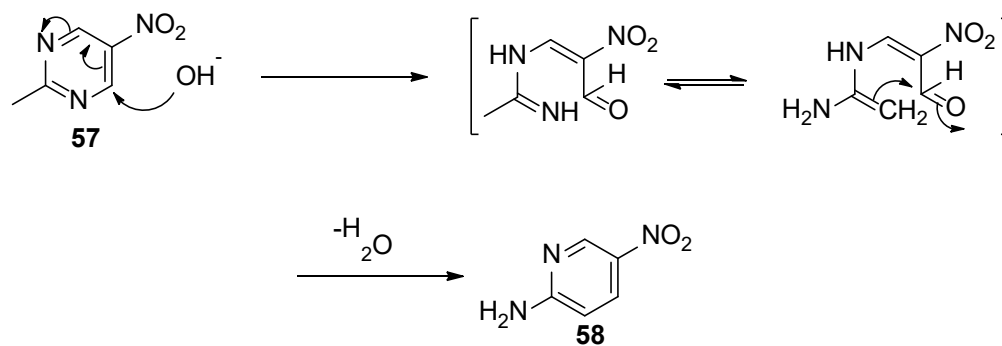
Scheme 30: *Suggested ANRORC mechanism for transformation of 5-nitropyrimidine 57.*

Other heterocycles that have been successfully transformed into 3-nitropyridines include 1-methyl-3,5-dinitro-2-pyridone, chromenes, nitromethyl γ-pyrones, triphenyloxazinium salts, and isatin.[33] Asahara and colleagues (2017) have developed a novel ring transformation method (**Scheme 31**) for the synthesis of 3-nitropyridines from dinitropyridones.[43–45] When an aromatic ketone was reacted with dinitropyridone **59**, the 6-arylated 3-nitropyridine **60** was isolated in 90% yield. Alternatively, treatment of the substrate with an aldehyde afforded 5-substituted 3-nitropyridines in 29-85% yield.
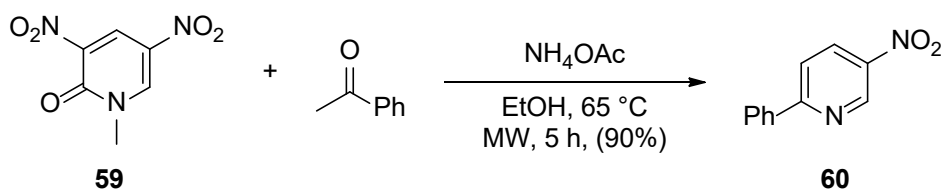
Scheme 31: *Transformation of dinitropyridone **59**.*

δ-carboline natural products and their biological properties

δ-Carboline natural products have been the subject of fewer publications than *β*-carbolines have, likely because they occur much less frequently in nature than their *β*-carboline counterparts.[46] The most important examples of *δ*-carboline natural products are the isoquinoline alkaloids (**Figure 9**) cryptolepine (**61**) and quindoline (**62**), two closely related benzo-*δ*-carbolines which were isolated from the West African plant *Cryptolepis sanguinolenta* (Apocynaceae). While cryptolepine (**61**) has been shown to possess anti-trypanosomal, anti-plasmodial, and cytotoxic properties *in vitro*, quindoline (**62**) appears to lack these qualities.[46,47] Owing to these potentially medicinal properties, cryptolepine (**61**) and its analogues have been investigated as possible treatments for malaria and other diseases, but at present it does not appear that there are any *δ*-carbolines that have entered into clinical use.[46,48]
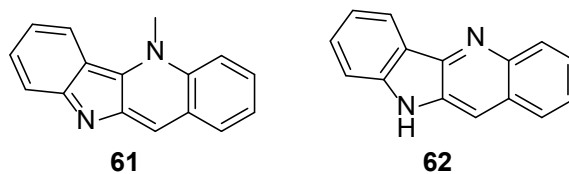
Figure 9: Structures of cryptolepine (**61**) and quindoline (**62**).

Synthetic δ-Carbolines and their biological properties

Arzel and colleagues (2001) have assayed a series of synthetic cryptolepine analogues for their anti-plasmodial, anti-trypanosomal, and cytotoxic properties.[46] δ-Carbolines which possessed a methyl substituent at position N-5 displayed greater activity against *Plasmodium falciparum* and *Trypanosoma cruzi*, along with increased cytotoxicity against mammalian cells (L6 cell line), than their non-methylated counterparts did. This is in accordance with previous findings that have shown cryptolepine (**61**) to be more biologically active than its non-methylated analogue quindoline (**62**). Cytotoxicity of the cryptolepine analogues was further increased when position C-11 was alkylated (**Figure 10**), with 11-methyl-cryptolepinium chloride (**63**) being especially toxic ($IC_{50} = 1.4$ μM). 1-methyl-δ-carbolinium chloride (**64**) was shown to have low cytotoxicity ($IC_{50} > 230$ μM) with strong anti-plasmodial activity ($IC_{50} = 1.6$ μM). Intracellular localization studies suggested that these properties were mediated by interactions with the DNA of the parasite.
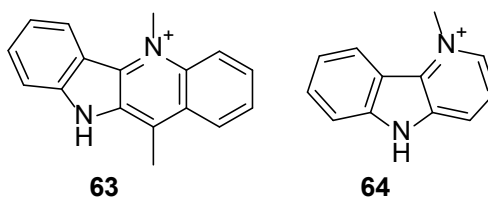
Figure 10: Structures of δ-carbolines **63** and **64**.

The Ablordeppey group (2011) synthesized a series of cryptolepine-derived δ-carbolines and their ring-opened analogues for evaluation as anti-fungal, anti-bacterial, and cytotoxic agents.[47] Cytotoxicity against mammalian kidney fibroblasts (Verbo) was first decreased by removal of the benzene functionality of the benzo-δ-carboline scaffold and the addition of a ω-cyclohexylpentyl moiety to the indole nitrogen (**Figure 11**). The resulting library of compounds such as **65** were then screened against selected fungi (*Candida albicans*,

Cryptococcus neoformans, and *Aspergillus fumigatus*) and bacteria (*Staphylococcus aureus,* MRSA*, Escherichia coli*, and *Mycobacterium intracellulare*). All of the screened δ-carbolinium compounds were more active anti-bacterial agents than cryptolepine (**61**) was. δ-Carbolinium iodide **65** was a particularly interesting example, with high potency against MRSA (IC_{50} = 1.62 µg/mL; MIC = 2.5 µg/mL; MBC = 2.5 µg/mL) and *M. intracellulare* (IC_{50} = 0.7 µg/mL; MIC = 1.3 µg/mL; MBC = 5.0 µg/mL). Opening the δ-carboline ring appeared to have little effect on these activities.
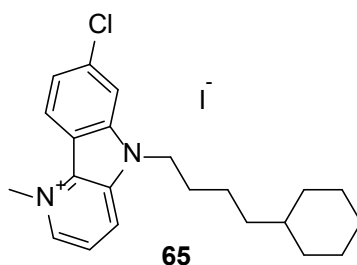
Figure 11: Synthetic δ-carbolinium iodide **65** was a potent antibacterial agent.

Methods for δ-Carboline synthesis

Cadogan Reaction

Use of the Cadogan reaction is another approach that has found application in the synthesis of δ-carbolines by deoxygenation of a corresponding *C*-nitroso precursor. Sir John Ivan George Cadogan published the first description of a triethyl phosphite- or triphenylphosphine-mediated deoxygenation of aromatic *C*-nitroso compounds in 1963.[49] This was used to induce ring-closure of 2-nitrosobiphenyl compounds into carbazoles. In 1965, Cadogan expanded upon these findings (**Scheme 32**) by reducing 2-nitrobiphenyl (**66**) into carbazole (**67**) through treatment with boiling triethylphosphite.[50]
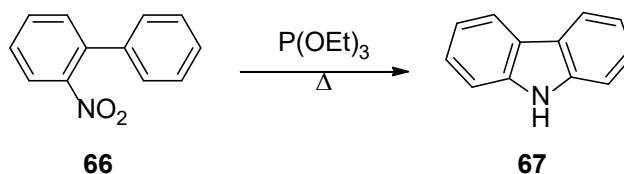
Scheme 32: The Cadogan reaction was used to synthesize carbazole (**67**) from **66**.

Although there are now other alternative reagents to access the carbazole scaffold (such as those offered by palladium catalysis), variants of the Cadogan reaction still offer some of the best routes to substituted carbazoles.[51] The suggested mechanism for the Cadogan reaction is shown in **Scheme 33**, with 2-nitrobiphenyl (**66**) being subjected to intramolecular cyclization into carbazole (**67**).
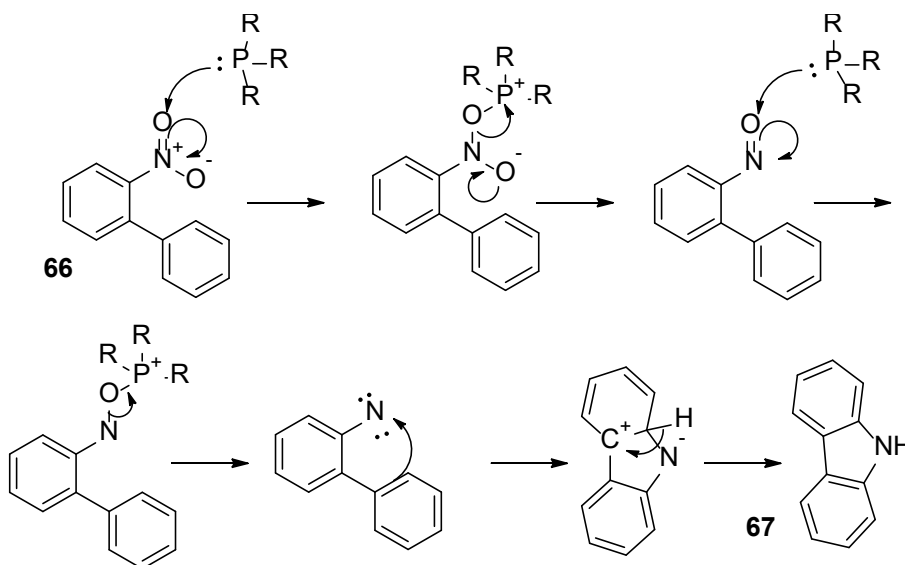
Scheme 33: Suggested mechanism for the Cadogan reaction, yielding carbazole (**67**).

In over 50 years since these original conditions were described, many improvements and variations of the Cadogan reaction have appeared in the literature. As with many of the other named reactions that have been discussed so far, some of the most important advances have occurred in microwave-assisted synthesis. Of relevance to this thesis is the reaction described

by Freeman and colleagues (**Scheme 34**), whereby nitrobiphenyl compounds were heated with triphenylphosphine in *o*-dichlorobenzene under microwave irradiation.[52] The highest-yielding example was the reaction with nitrobiphenyl **68** which furnished carbazole **69** in 99% yield.
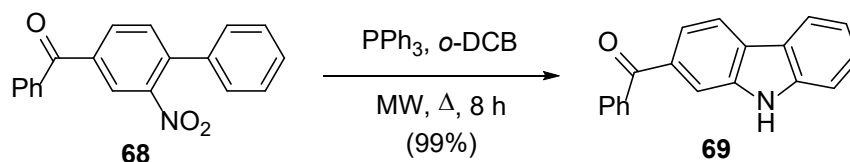
Scheme 34: Microwave-assisted synthesis of carbazole **69**.

Aside from carbazoles, Cadogan-type reactions have also been used to access many other fused heterocyclic scaffolds such as indoles, indazoles, phenothiazines, benzimidazoles, quinolines, and benzoxazoles.[51] It is also possible to use variants of the Cadogan reaction to access the four carboline isomers.[53] In fact, in the original 1963 paper, Cadogan treated 3-*o*-nitrosophenylpyridine (**70**) with triethyl phosphite in cold benzene (**Scheme 35**), which gave a 4:1 mixture of *α*-carboline (**71**) and *γ*-carboline (**72**).[49]
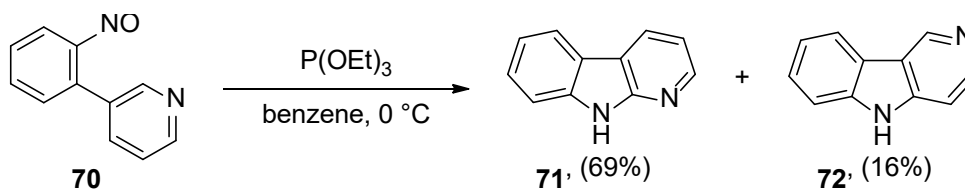
Scheme 35: *Synthesis of α-carboline (71) and γ-carboline (72).*

However, when the same conditions were applied to 2-*o*-nitrosophenylpyridine (**73**), none of the expected *δ*-carboline (**75**) was isolated (**Scheme 36**). In this case, there was a quantitative conversion of nitroso compound **73** into pyrido[1,2-*b*]indazole (**74**).[49]
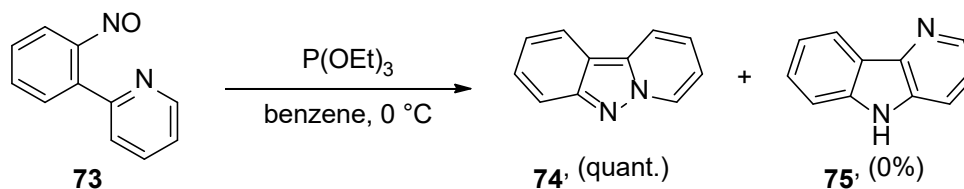
Scheme 36: Cadogan-type synthesis of pyrido[1,2-b]indazole (74).

Recently (2018), the Detert group have reported a new microwave-assisted Cadogan method (**Scheme 37**) which they used to access 9 δ-carbolines and 2 benzo-β-carbolines, in modest to excellent yields, starting from 2-aryl-3-nitropyridines.[53,54] The 3-nitropyridines were suspended in neat triethylphosphite and the mixture was subjected to microwave irradiation at 200 °C for 15 minutes. This reaction furnished δ-carbolines in 33-83% yield and benzo-β-carbolines in 51-75% yield. The Detert group tried to extend this methodology to the synthesis of α-carbolines also, but attempts to use 3-nitro-4-arylpyridine precursors as substrates were less successful (0-8% yield).
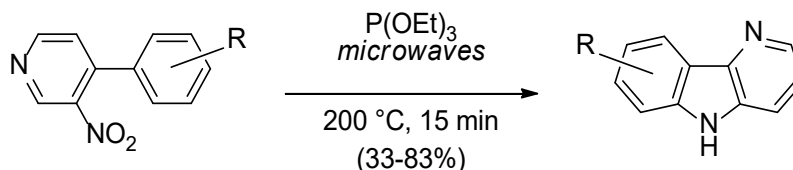
Scheme 37: Microwave-assisted synthesis of δ-carbolines.

The Sagitullina group (2019) have employed a molybdenum-catalyzed variant of the Cadogan reaction to reductively cyclize 2-aryl-3-nitropyridines into δ-carbolines (**Scheme 38**), including the tetracyclic natural product quindoline (**62**).[55] This triphenylphosphine-based reaction was used to cyclize 3-nitropyridine **76** into δ-carboline **77**. The cyclohexyl moiety of **77** was oxidized with Pd/C, forming quindoline (**62**).
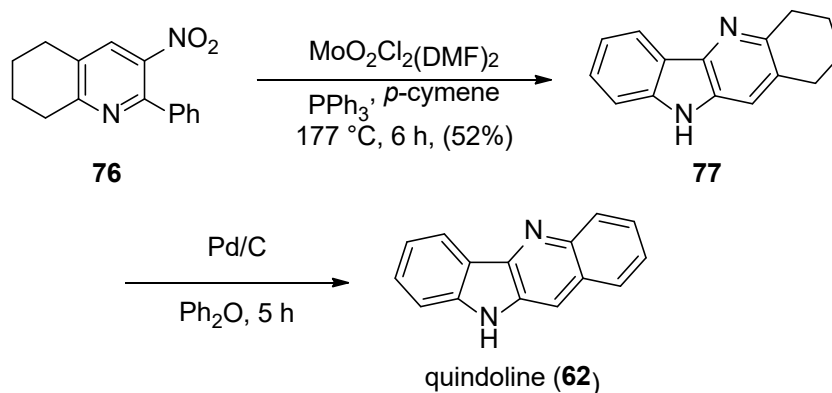
Scheme 38: *Synthesis of quindoline (62) starting from 3-nitropyridine 76.*

Introduction to *β*-carbolines

9*H*-Pyrido[3,4-*b*]indole (**78**) is a hetero-tricyclic organic compound which serves as the parent molecule for a large class of alkaloids known as the *β*-carbolines (**Figure 12**).[56] A frequently encountered motif in nature, *β*-carbolines have been isolated from disparate species of plants, fungi, microbes, marine invertebrates, insects, and mammals. *β*-Carbolines have also been detected in foodstuffs, tobacco smoke, alcoholic drinks, and even as endogenous alkaloids in the human body. The ubiquity of these compounds in nature and their potential impact on public health has attracted considerable attention in recent years. *β*-Carbolines sometimes possess interesting pharmacological properties, and several have been investigated as potential treatments for a broad spectrum of conditions including cancer, HIV, malaria, Alzheimer's disease, erectile dysfunction, anxiety, and depression, with nearly a dozen in clinical use.
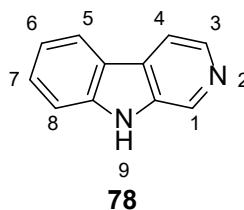
Figure 12: 9*H*-Pyrido[3,4-b]indole (**78**), also called *β*-carboline.

Natural products incorporating a *β*-carboline scaffold

β-Carboline natural products can firstly be classified by the degree of saturation on their pyridine ring (**Figure 13**).[57] The three main subtypes consist of aromatized *β*-carbolines (*β*Cs), 3,4-dihydro-*β*-carbolines (DH*β*Cs), and 1,2,3,4-tetrahydro-*β*-carbolines (TH*β*Cs). This brief review will focus primarily on *β*Cs. It is also not unusual for *β*-carboline alkaloids to occur as 2-methyl quaternary ammonium salts in nature. So, in addition to their free-base forms, *β*-carboline natural products have been isolated as cations, anions, or zwitterions, depending on pH and the choice of extraction solvent. *β*-Carboline natural products are often heavily substituted, and the additional functional groups on both the pyridine and indole ring systems can profoundly influence the basicity of these alkaloids. It is worth noting that the pyridinic nitrogen is more alkaline than the pyrrolic nitrogen.[58]
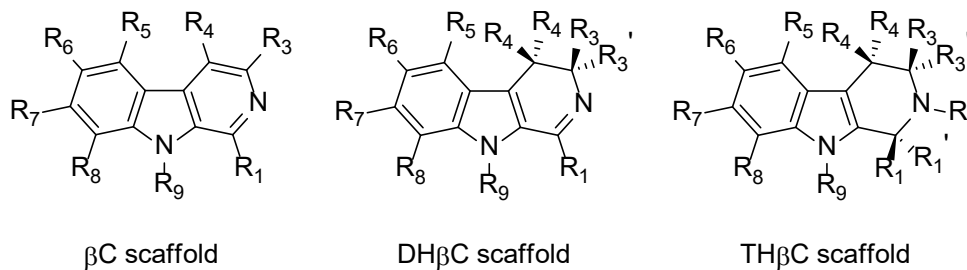
Figure 13: *β*-Carboline scaffolds classified by pyridine saturation.

In 1841, Goebel extracted the DH*β*C harmaline (**79**) from the seeds of *Peganum harmala* (**Figure 14**).[59] This was the earliest *β*-carboline to be isolated, followed by similar natural

products like the *β*C analogue called harmine (**80**) and the TH*β*C analogue called tetrahydroharmine (**81**), which were also isolated from extracts of *P. harmala*. Another frequently encountered harmala alkaloid, harmalol (**82**), differs from harmaline (**79**) by the lack of an *O*-methyl group.

79   **80**   **81**   **82**
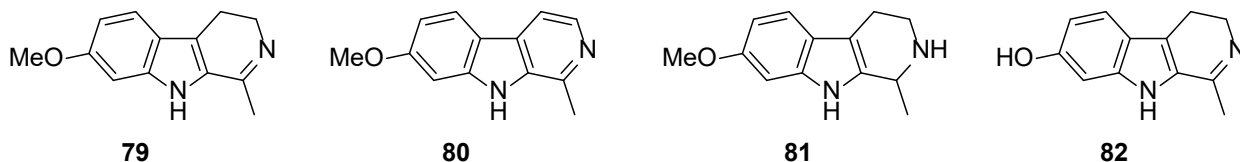
Figure 14: The structures of four harmala alkaloids.

As a potent monoamine oxidase inhibitor (MAOI), the effects of harmine (**80**) on the CNS have attracted considerable attention, with antidepressant properties occasionally being reported.[60] Isolated *β*-carbolines have displayed *in vitro* and *in vivo* activities suggestive of antidepressant potential.[60] The *in vitro* studies have generally shown *β*-carbolines to act as selective inhibitors of MAO-A, which is the MAO subtype most associated with the metabolism of the neurotransmitters serotonin and noradrenaline, both of which are involved in the aetiology of clinical depression.

Endogenous *β*-carboline alkaloids

Harman (**83**) is an endogenous *β*-carboline alkaloid that has been detected in human brain, liver, and heart tissue samples, as well as in blood and urine (**Figure 15**).[60] However, it is not clear what physiological roles **83** plays in the body, if any. Harman (**83**) is also commonly encountered in coffee, wine, and tobacco smoke. When administered to laboratory animals, **83** is notable for its steeply dose-dependent nature, shifting from an anticonvulsant at low

doses to a pro-convulsant at high doses. Like harmine (**80**), harman (**83**) has been observed to possess some antidepressant activity, possibly stemming from a combination of inverse agonism at benzodiazepine receptors, effects on serotonergic/noradrenergic neurotransmission (from MAO-A inhibition), and the induction of a neuroendocrine response. Harmine (**80**) has also been detected as an endogenous *β*-carboline alkaloid in the human body, but again without any obvious physiological role.

83
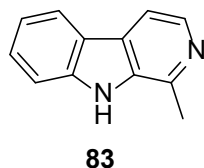
Figure 15: Structure of harman (**83**).

Other β-carboline natural products

Aside from the harmala alkaloids, other classes of *β*-carbolines include eudistoma alkaloids, eudistomidins, eudistalbins, manzamines, and canthines (**Figure 16**). The marine alkaloid eudistomin A (**84**), was isolated from the tunicate *Eudistoma olivaceum*.[57] Eudistomidin A (**85**) was isolated from the Okinawan tunicate *Eudistoma glaucus*, and eudistalbin A (**86**) was isolated from *Eudistoma album*. Manzamine A (**87**) was discovered in an Okinawan sponge of the genus *Haliclona*.[61] Canthin-6-one (**88**) was extracted from the plant *Pentaceras australis*.[62] In addition to these classes of monomeric *β*-carboline alkaloids, several dimeric *β*-carbolines have been documented in nature. For instance, the amine-linked bivalent *β*-carboline plakortamine C (**89**) was isolated from the sponge *Plakortis nigra*.[63]

84

85

86

87

88

89
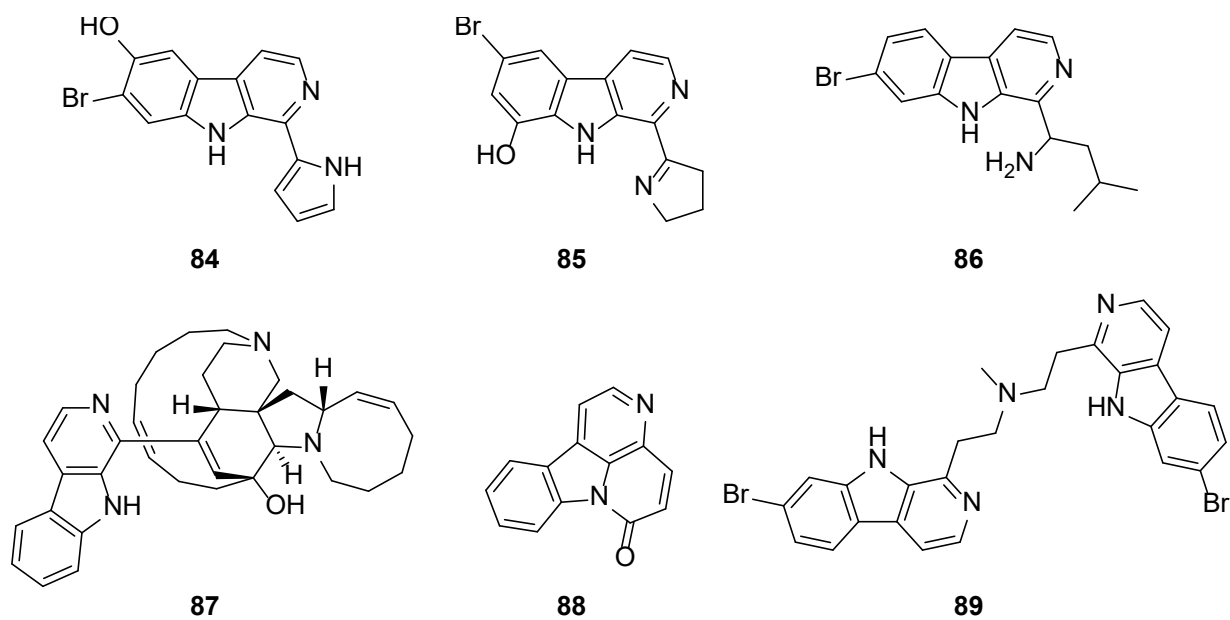
Figure 16: Other examples of β-carboline natural products.

β-carbolines as anti-cancer agents

β-Carboline alkaloids have been used in some systems of traditional medicine for the treatment of malignancies and have also been shown to possess antiproliferative properties *in vitro*.[64] In recent years, many examples of synthetic *β*-carbolines have appeared in the literature with promising anticancer activities. The antitumor activities of *β*-carbolines have been attributed to several mechanisms including DNA intercalation and the inhibition of key enzymes (monoamine oxidase (MAO), cyclin-dependent kinases (CDKs), Polo-like kinases (PLKs), and topoisomerases I/II).[65]

For example. Cao and colleagues (2015), have described a series of bivalent *β*-carboline hybrids (**Figure 17**) with antitumor properties, such as hybrid **90**.[66] The *β*-carboline natural product flazin (**91**), isolated from the fungus *Suillus granulatus*, was found to possess weak

activity against HIV-1, which inspired the Zheng group (2007) to develop (**Scheme 39**) the semi-synthetic analogue flazinamide (**92**).[67]

90
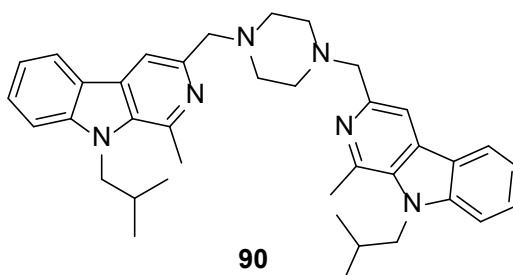
Figure 17: Bivalent *β*-carboline hybrid **90** exerted antiangiogenic effects.

91   **92**
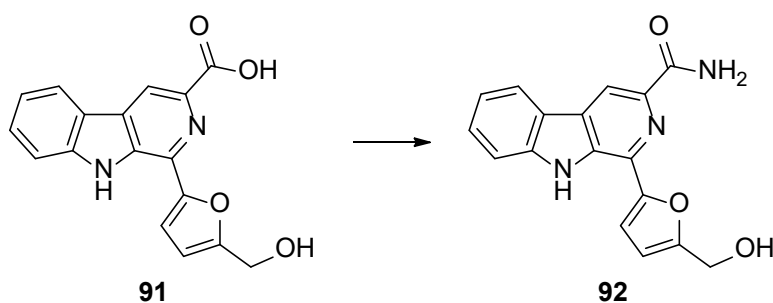
Scheme 39: Flazin (**91**) and flazinamide (**92**).

β-carbolines as GABAergic drugs

Abecarnil (**93**) is an anxiolytic *β*-carboline (**Figure 18**) with similar effects on the GABAergic neurotransmission as the classical benzodiazepines.[68,69] The drug made it all the way to clinical trials, but due to its essentially identical side effect profile compared to the benzodiazepines it was hoped to compete with, and its negligible improvements in efficacy, development of **93** was ultimately abandoned.
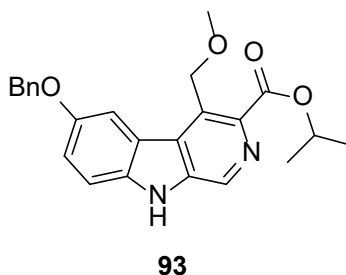
Figure 18: Abecarnil (**93**) has anxiolytic properties.

Methods for *β*-carboline synthesis

Pictet-Spengler reaction

The Pictet-Spengler Reaction (PSR) was discovered in 1911 by Amè Pictet and Theodor Spengler at the University of Geneva.[70,71] Their original conditions involved heating *β*-phenylethylamine with dimethoxymethane and hydrochloric acid, which triggered a cycloaddition that furnished the alkaloid tetrahydroisoquinoline (THIQ). The first recorded use of the PSR to synthesize a TH*β*C occurred in 1928 (**Scheme 40**), when G.J. Tatsui formed tetrahydroharman (**94**) by heating tryptamine with acetaldehyde and sulfuric acid.[70,72] The PSR has since been used to synthesize many other heterocyclic compounds, mainly indoles such as TH*β*Cs and isoquinolines.
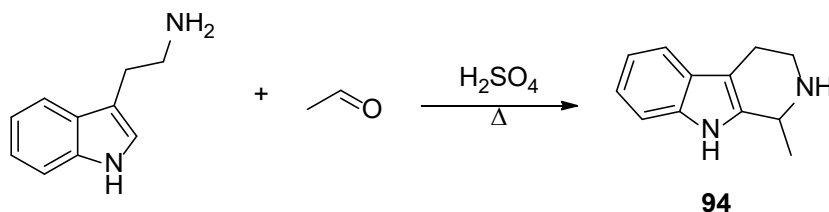
Scheme 40: The PSR was used to synthesize tetrahydroharman (**94**).

An additional dehydrogenation step is usually required to access *B*Cs using the PSR.[73] This can be achieved using common reagents such as elemental sulfur, silver, platinum, Pd/C, or

2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). While the aromatization of THβCs is often facile and high yielding, in some cases it has proven to be a significant challenge. Selenium dioxide or the chromium-based 'Jones reagent' have occasionally found niche applications where the standard reagents were unsuccessful.[74–76] For example (**Scheme 41**), THβC **95** could not be aromatized using sulfur or Pd/C, but selenium dioxide fully oxidized it to the βC **96** in 77% yield.[75]
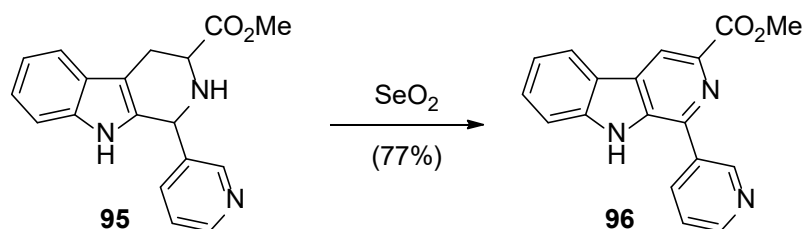
Scheme 41: Selenium-mediated oxidation of THβC **95**.

Bischler-Napieralski reaction

The classical Bischler-Napieralski reaction (BNR) was first reported in 1893.[77] Like the PSR, the BNR starts with a tryptophan or tryptamine derivative, except in this case it must be acylated prior to use (**Scheme 42**).[73] The acylated substrate **97** is treated with a reagent such as phosphorous pentoxide or phosphoryl chloride to initiate cyclodehydration into the corresponding DHβC **98**. Again, dehydrogenation is needed to access the βC **99**. While the BNR generally requires harsher reaction conditions than the PSR uses, the DHβC intermediates it produces are easier to oxidize into BCs than the THβCs formed by PSR were. This explains why the BNR has found many applications in β-carboline synthesis.
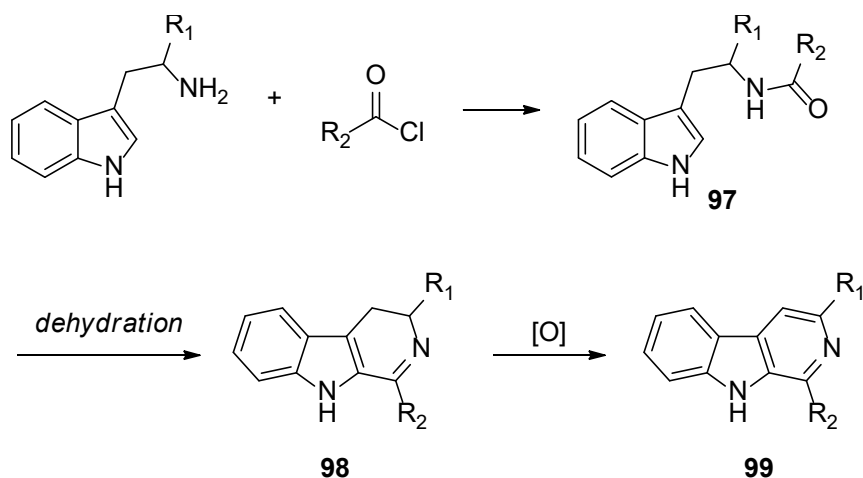
Scheme 42: BNR-type synthesis and oxidation forming compound **99**.

Hino (1989) used the BNR (**Scheme 43**) to synthesize eudistomins H (**103**) and I (**102**).[73,78] Tryptamine was first acylated with Boc-L-proline, and then intermediate **100** was treated with the desiccant polyphosphoric ester (PPE). The DHβC **101** was isolated in 74% yield, and then dehydrogenation by DDQ furnished eudistomin I (**102**) in 90% yield. After bromination of **102** by NBS, eudistomin H (**103**) was isolated in 80% yield.
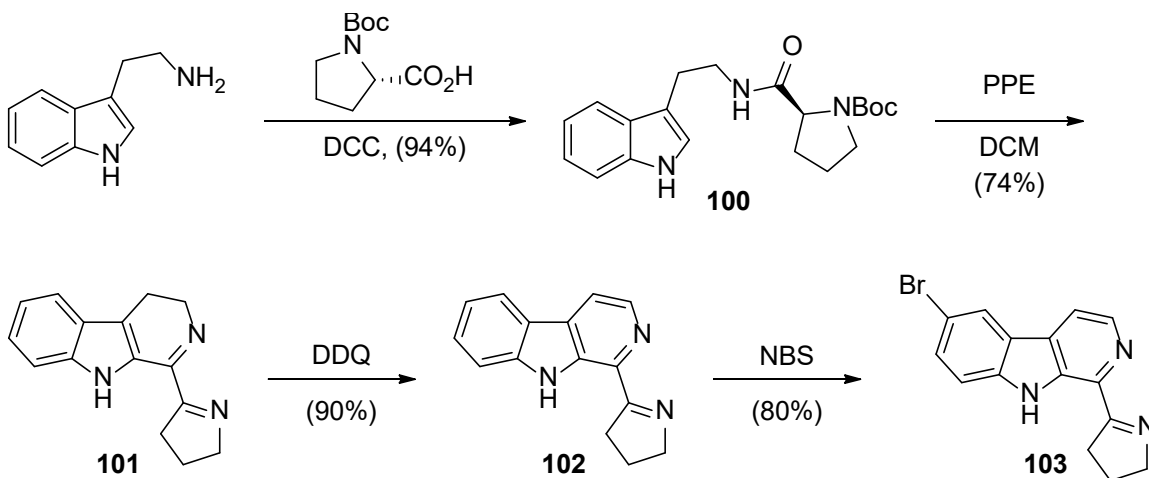
Scheme 43: BNR-type reaction used to synthesize eudistomins H (**103**) and I (**102**).

Cadogan reaction

In 1968, the Kametani group reported the reaction between 4-(2-nitrophenyl)nicotinates and triethyl phosphite.[79] The pyridines were obtained from a Hantzsch-type reaction, and then boiled in excess triethyl phosphite (**Scheme 44**). This produced a mixture of βCs and benzo[c-2,7]naphthyridines. For instance, when nicotinate **104** was used as the substrate, βC **105** was isolated in 20% yield. Despite the poor yields, this provided evidence that the Cadogan reaction could provide access to the βC scaffold.
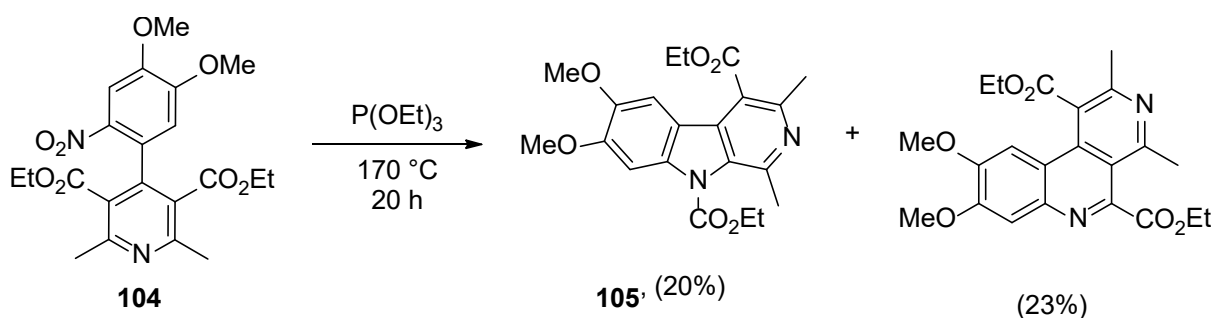
Scheme 44: Treatment of nicotinate **104** with P(OEt)$_3$ furnished βC **105**.

Organic synthesis using sealed-tube reactors

In 2016, Kappe and colleagues documented the development of a new type of sealed-tube reactor that mimics the performance of microwave reactors by using only conductive heating.[80] This small reactor, the Monowave 50 by Anton Paar GmbH, is safe enough for bench-top use without the need for a fume cupboard and reactions reach a maximum temperature of 250 °C (at 20 bar). Like a microwave, this reactor rapidly heats the reaction mixture to the selected temperature, and then the reaction mixture is stirred with super-heating above solvent boiling point for up to 4 hours. When the reaction is complete, the *vial* is rapidly cooled and is safe to handle within minutes. For comparison with microwave

heating, in the synthesis of 2-methyl-1*H*-benzo[*d*]imidazole from the reaction (**Scheme 45**) between 1,2-diaminobenzene and acetic acid at 200 °C for 5 minutes, the two heating methods gave virtually identical yields.[80]
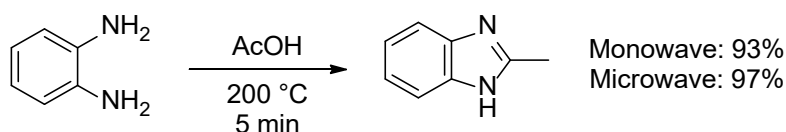
Scheme 45: Monowave 50 heating provided similar yields to microwave irradiation.

Project Goals

It is evident from the available literature that pyridines are of particular interest to modern drug design and manufacturing. It is therefore not surprising that many synthetic pathways to this vital heterocyclic scaffold have been developed. One such method is the Bohlmann-Rahtz (BR) reaction, which is noteworthy due to its predictable regioselectivity, its well-understood conditions, and its often-high efficiency. Although the BR reaction has been applied to the synthesis of a wide array of substituted pyridines, it has never been applied to the synthesis of 3-nitropyridines. 3-Nitropyridines in turn provide important synthetic intermediates that can be employed in the synthesis of carbolines, which possess interesting and diverse biological properties. This thesis aims to bring all these areas together and realize not only a new route to 3-nitropyridines with the potential to introduce diversity at multiple positions and considerable structural complexity, but also to apply these intermediates in the synthesis of carboline scaffolds.

To that end, the proposed goals of this project are as follows:

1. Expand the scope of the Bohlmann-Rahtz reaction to facilitate the synthesis of novel, structurally diverse 3-nitropyridines, with favorable yields (**Scheme 46**).

Scheme 46: Proposed Bohlmann-Rahtz reaction for access to 3-nitropyridines.

2. Modify a diverse assortment of 3-nitropyridines into other heterocyclic scaffolds, namely δ-carbolines and β-carbolines (**Scheme 47**).

Scheme 47: 3-Nitropyridines will provide access to δ-carbolines and β-carbolines.
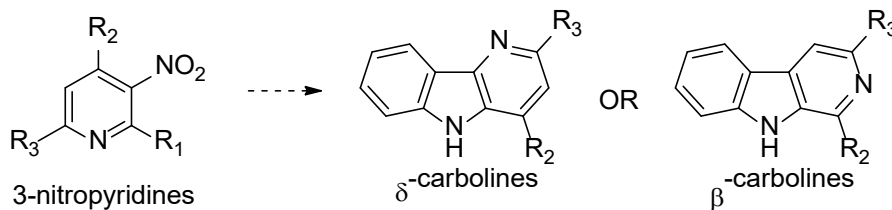
This research will generate the first reported route to 3-nitropyridines through the Bohlmann-Rahtz reaction and will subsequently provide new pathways to highly functionalized heterocyclic scaffolds, possibly of interest to future drug discovery efforts.

CHAPTER TWO:

A Bohlmann-Rahtz reaction for the synthesis of 3-nitropyridines.

Results and Discussion

Bohlmann-Rahtz reaction for 3-nitropyridine synthesis

While there has never been a reported Bohlmann-Rahtz (BR) reaction for the synthesis of 3-nitropyridines, previous work with aminocrotonates published by the Bagley group has demonstrated that the BR reaction gave satisfactory results when using an enamine with an electron-withdrawing group at the β-position (**Scheme 48**).[22] For example, when aminocrotonate **96** was condensed with 3-butyn-2-one (**105**), the ethyl nicotinate **106** was isolated in 77% yield. This led to the hypothesis that a β-nitroenamine could function analogously to **37** in reaction with a suitable Michael acceptor such as **105**.
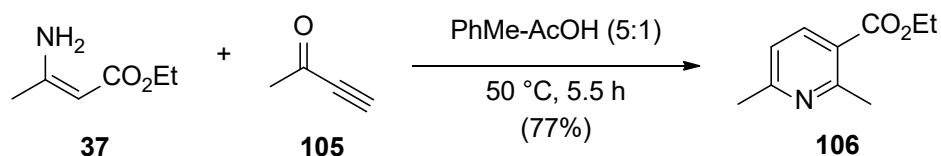
Scheme 48: The BR reaction was used to access ethyl nicotinate **106**.

As illustrated in **Scheme 49**, a pathway from β-nitroenamines to δ-carbolines and β-carbolines was envisaged, where the BR reaction would be used to generate aryl-3-nitropyridine precursors. 3-Nitropyridines with aryl substituents at position C-2 would be suitable for cyclization into δ-carbolines, while 3-nitropyridines with aryl substituents at position C-4 would be suitable for cyclization into β-carbolines.
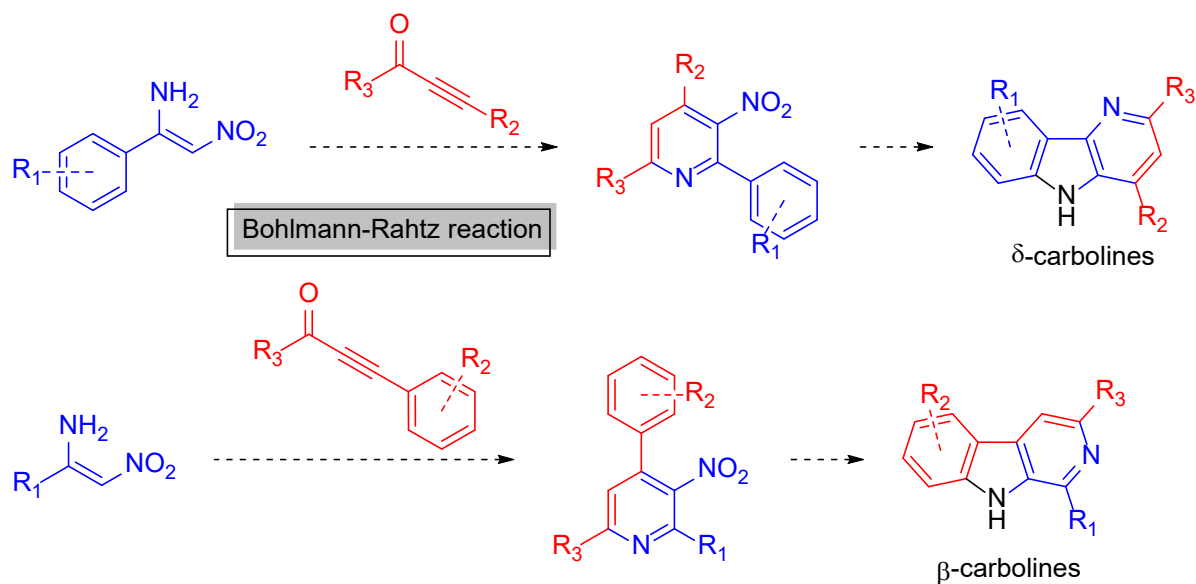
Scheme 49: Proposed pathways to *δ*-carbolines and *β*-carbolines from a 3-nitroenamine precursor, by way of a BR reaction optimized for 3-nitropyridine synthesis.

Synthesis of nitroolefins

In 1998, Seko and Komoto reported the first direct amination of *β*-nitroolefins with methoxylamine, an example of vicarious nucleophilic substitution (VNS).[81] This metal-free method was used to synthesize 11 *β*-nitroenamines in 30-94% yield (**Scheme 50**), with no requirement for a leaving group at the *β*-position. In their procedure, a *β*-nitroolefin was stirred at room temperature in DMF with methoxylamine (1.25 equiv.), then potassium *tert*-butoxide (3 equiv.) was added dropwise to the reaction mixture over 5 minutes. After stirring for an additional 0.1 to 3 hours, the reaction was quenched with saturated ammonium chloride. Subsequent removal of solvent and purification with column chromatography led to the desired *β*-nitroenamine.
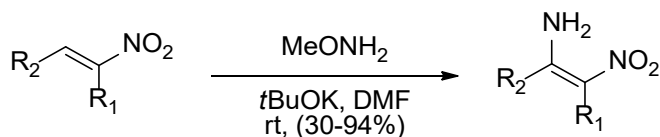
Scheme 50: Direct methoxylamine-mediated amination of β-nitroolefins.

Since methoxylamine is only commercially available as the hydrochloride salt, this original procedure has been expanded upon by other groups to facilitate the use of methoxylamine hydrochloride.[82] β-Nitroolefin **107** and methoxylamine hydrochloride were stirred in cold DMF (**Scheme 51**), with dropwise addition of triethylamine. The precipitated triethylammonium chloride was removed by filtration, and then the reaction proceeded as originally described by Seko and Komoto.[81] These modified amination conditions were used to synthesize β-nitroenamine **108** in 69% isolated yield (after trituration with ether).
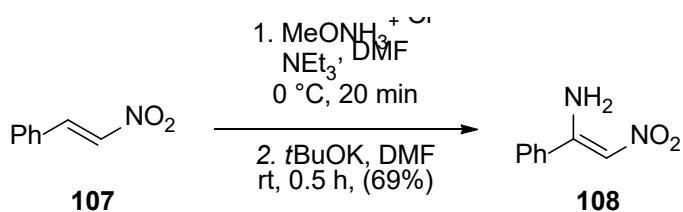
Scheme 51: Direct amination of β-nitroolefin **107**.

Using ^{1}H NMR spectroscopy (**Figure 19**), with DMSO-d_6 as the solvent, the spectrum for β-nitroenamine **108** showed two characteristic broad singlets at $\delta = 8.94$ and 9.42 ppm. These corresponded to the two hydrogens of the amino group, with distinct chemical shifts due to one N-H participating in an intramolecular hydrogen bond with an oxygen on the β-nitro group.
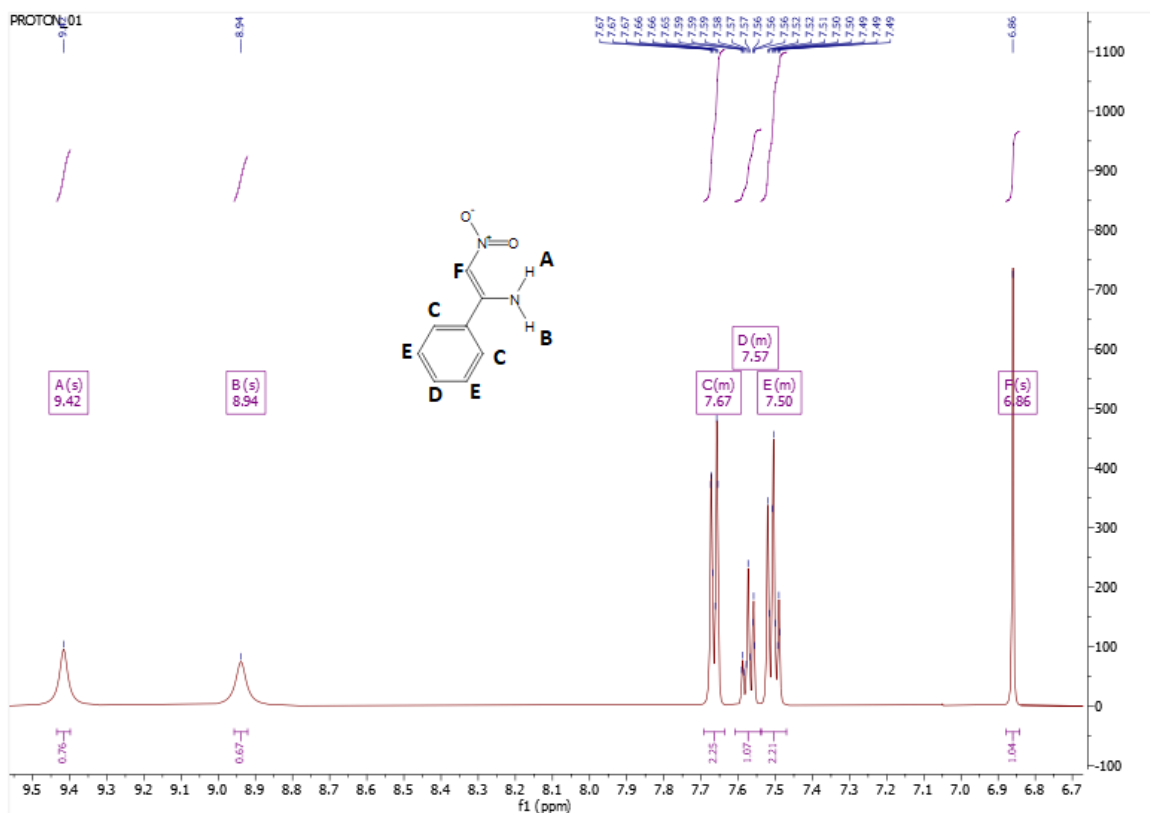
Figure 19: ^{1}H NMR spectrum of β-nitroenamine **108**.

This reaction is believed to have proceeded *via* the mechanism proposed by Seko and Komoto (**Scheme 52**).[81] Methoxylamine attacked at the α-position of β-nitroolefin **107**, followed by deprotonation at the β-position by *tert*-butoxide. A second equivalent of *tert*-butoxide then deprotonated the α-position, leading to elimination of the *N*-methoxyl group, which formed the imine intermediate **109**. Finally, mildly acidic work-up with saturated NH$_4$Cl solution completed the reaction and furnished the product, β-nitroenamine **108**.
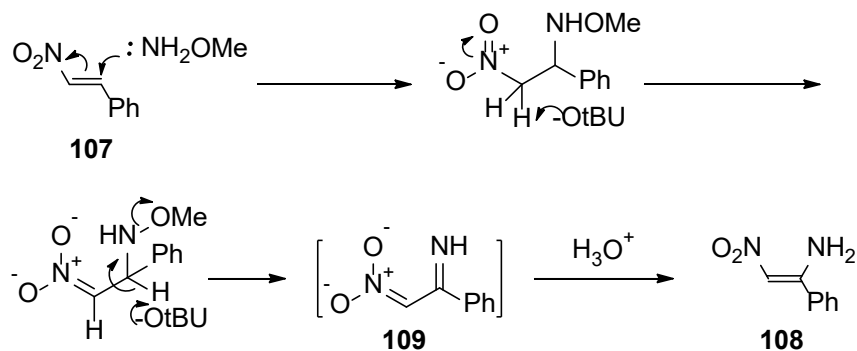
Scheme 52: Suggested mechanism for amination of **107**.

X-ray crystallography was used (**Figure 20**) to confirm the stereochemistry and constitution of β-nitroenamine **108.** The resolved crystal structure showed that this enamine was present in the *Z*-configuration, which was in accordance with the proposed mechanism. Both intramolecular and intermolecular hydrogen bonding interactions were also shown, which agreed with the observations from ¹H NMR spectral data.
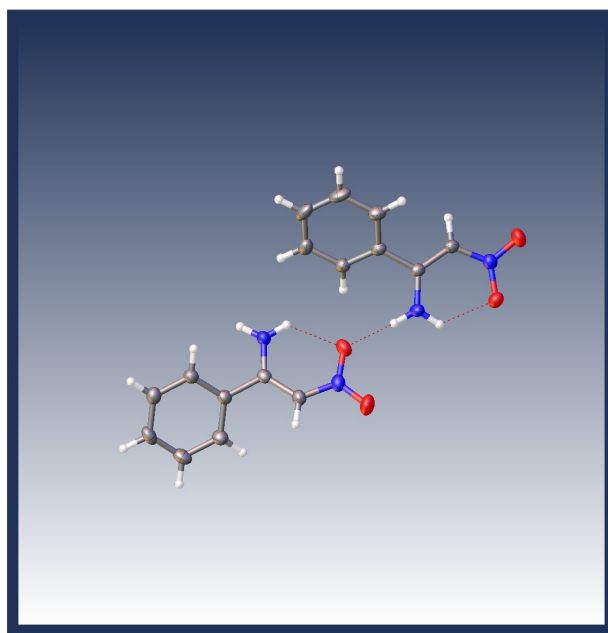
Figure 20*: Crystal structure of enamine **108**.

First library of aromatic β-nitroenamines

The methoxylamine-mediated amination procedure described in the previous section was used to prepare a series of 8 aromatic *β*-nitroenamines from commercially available *β*-nitroolefins, in up to 80% yield (**Table 2.1**).

Scheme showing conversion of R_1–CH=CH–NO_2 to product:

1. MeONH$_3^+$ Cl$^-$, NEt$_3$, DMF, 0 °C, 20 min
2. *t*BuOK, DMF, rt, 0.5 h

giving R_1–C(NH$_2$)=CH–NO_2
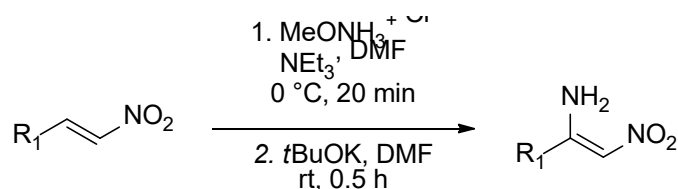
Table 2.1: Synthesis of aromatic *β*-nitroenamines *via* direct amination of *β*-nitroolefins.

Entry	R₁	Product	Yield (%)[a]
1	phenyl	**108**	69
2	(4-isopropyl)phenyl	**110**	80
3	(4-benzyloxy)phenyl	**111**	56
4	2-furanyl	**112**	55
5	(4-fluoro)phenyl	**113**	58
6	(4-bromo)phenyl	**114**	58
7	(3-chloro)phenyl	**115**	55

[a] Isolated yield after purification by trituration with cold diethyl ether.

A solution of nitroolefin (1 equiv.) and methoxylamine hydrochloride (1.25 equiv.) in DMF was cooled to °C, and then triethylamine (1.25 equiv.) was added and the reaction was stirred for 15 min. Precipitate was removed by filtration, and the filtrate was added dropwise to a flask containing potassium *tert*-butoxide (3 equiv.) in DMF in ice bath. After addition of filtrate, the reaction mixture was left to stir for 0.5 h and then quenched with sat. aqueous NH₄Cl. The solvent was removed *in vacuo* and the crude solid was partitioned between EtOAc and water. The organic extract was washed with brine (x2), dried over Na₂SO₄ and solvent removed *in vacuo*. Trituration with cold diethyl ether furnished the pure *β*-nitroenamine.

Due to the lack of commercially available (*E*)-1-nitroprop-1-ene, an alternative pathway to aliphatic *β*-nitroenamines was required. A known two-step procedure (**Scheme 53**) starting from commercially available *N,N*-dimethylacetamide dimethyl acetal (**117**) was used to

synthesize the intermediate **118**, followed by the aliphatic β-nitroenamine **119**, which was isolated in 72% yield.[83,84]
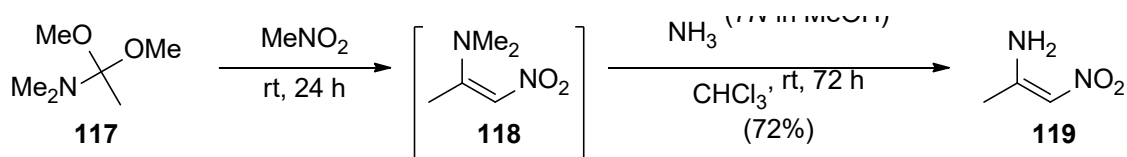
Scheme 53: Synthesis of aliphatic β-nitroenamine **119**.

Initial proof of concept

To test the *via*bility of the proposed BR reaction for 3-nitropyridine synthesis, the reactivity of β-nitroenamine **108** with 3-butyn-2-one (**105**) was probed under a series of catalyst-free conditions (**Table 2.2**). The first reaction (**entry 1**) used the classical BR reaction conditions, with the reaction carried out in ethanol at 50 °C. While there was evidence of the reaction progressing based upon TLC analysis after 5 hours, it was decided to leave the reaction mixture stirring for 24 hours. Additional TLC analysis still revealed a mixture of product and starting material **108**, with no side products observed. After workup and column chromatography, a 3% yield of the 3-nitropyridine **120** was isolated. When the temperature was increased to reflux and the reaction mixture was stirred for 24 hours (**entry 2**), a 66% yield of the product **120** was isolated after purification. When 4-(trimethylsilyl)-3-butyn-2-one (**121**) was used as the substrate (**entry 3**) instead of 3-butyn-2-one (**105**) under these conditions, 3-nitropyridine **120** was isolated in 46% yield. This result suggested that a terminal substituent at position C-4 of the 3-butyn-2-one (**105**) scaffold decreased its reactivity, which has previously been observed by the Bagley group.[22] It was concluded that the BR reaction could be used to access 3-nitropyridines *via* the reaction between a β-nitroenamine and an alkynone when heated in ethanol at reflux for 24 hours.
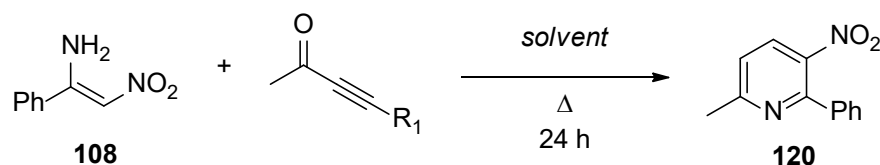
Table 2.2: Catalyst-free BR reaction of β-nitroenamine **108** and alkynone **105** or **121**.

| Entry	Alkynone	R_1	Solvent	Conditions	Product	Yield (%)[a]
1	**105**	H	EtOH	50 °C, 24 h	**120**	3
2	**105**	H	EtOH	Reflux, 24 h	**120**	66
3	**121**	SiMe$_3$	EtOH	Reflux, 24 h	**120**	46

[a] Isolated yield after column chromatography.

A solution of the β-nitroenamine (1.0 mmol) and alkynone (1.5 mmol) in ethanol was stirred under varying temperatures for 24 h. The ethanol was removed *in vacuo*, and the crude material was dissolved in EtOAc. The resulting slurry was filtered through silica, and the filtrate was washed sequentially with water, sat. aqueous NaHCO$_3$ solution (x2) and brine (x2), dried over Na$_2$SO$_4$, and evaporated *in vacuo*. Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*), gave the pure 3-nitropyridine.

The identity of the isolated 3-nitropyridine product **120** was confirmed using spectral data from ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, and infrared (IR) spectroscopy. Because our in-house mass spectrometer was unable to ionize this series of pyridines, additional confirmation was instead provided by elemental (CHN) analysis. ^{1}H NMR spectroscopy in CDCl$_3$ (**Figure 21**) revealed the presence of two doublets (J = 8.3 Hz) that resonated at δ = 7.27 ppm and 8.07 ppm, corresponding to H-5 and H-4 of the pyridine ring, respectively. The three hydrogens of the 6-methyl group were visible as a singlet at δ = 2.71 ppm. This methyl group was also observed using ^{13}C NMR spectroscopy, where it appeared as the only singlet in the aliphatic region (δ = 24.76 ppm). IR spectral data showed a strong absorption band at ν 1514 cm^{-1}, which was an N-O stretch indicative of the β-nitro group. Elemental analysis of this 3-nitropyridine was expected to show 67.28% carbon, 4.71% hydrogen and 13.08% nitrogen. Elemental analysis revealed an observed composition of 67.17% carbon, 4.78% hydrogen, and 12.98% nitrogen, which were all within 0.1% of the expected values.
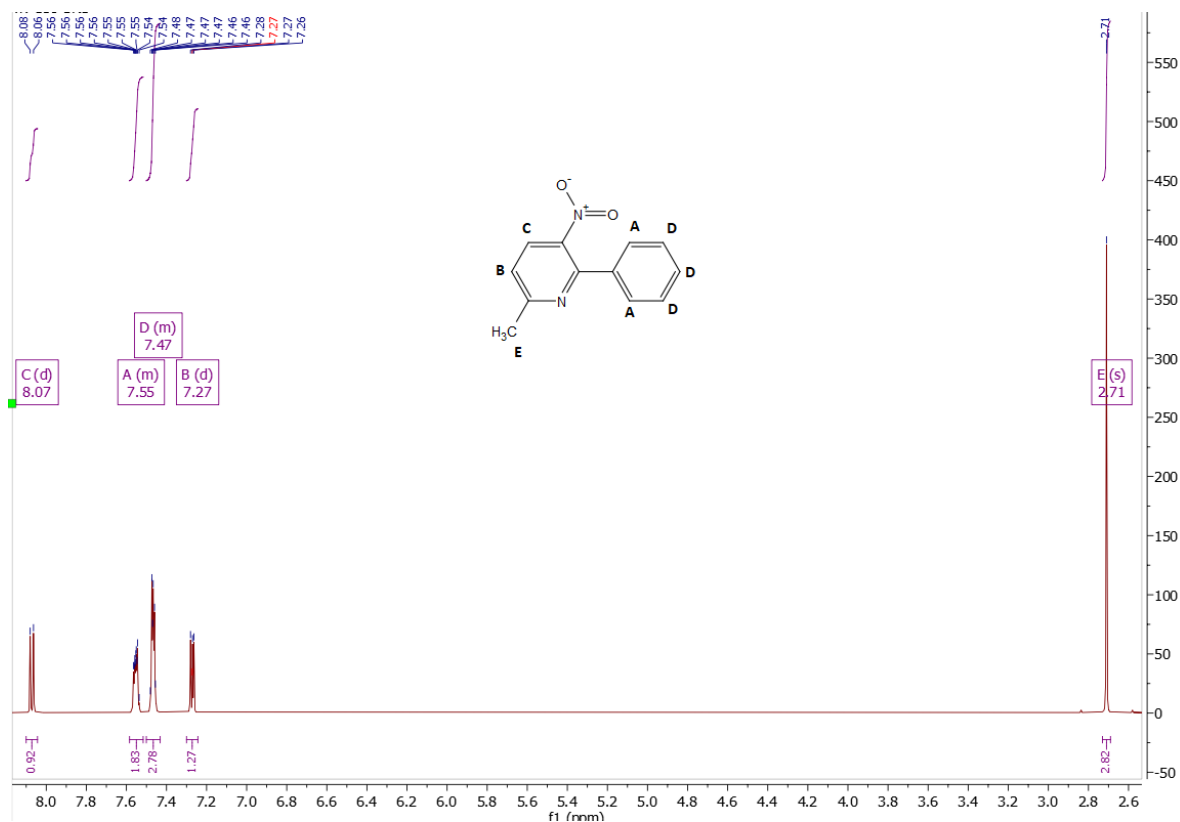
Figure 21: ^{1}H NMR spectrum for nitropyridine **120**.

Lewis acids and Brønsted acids as catalysts

Lewis acids are often employed to catalyze organic reactions and Lewis acid catalysis is one of the fastest-growing fields of study in organic synthesis.[85] The first step of the Bohlmann-Rahtz (BR) reaction (**Scheme 54**) consists of a Michael addition between the Michael acceptor (alkynone **105**) and the Michael donor (β-nitroenamine **105**). Previous research by the Bagley group has demonstrated that both Brønsted acids and Lewis acids catalyze the Michael addition step, as well as the C=C bond E/Z-isomerization required for the final cyclodehydration step.[22] In the past, this has eliminated the requirement to isolate and heat the aminodiene intermediate **122**, which was necessary under the original BR reaction conditions. Indeed, the catalyst-free BR reaction which was used to synthesize 3-

nitropyridine **120** was not complicated by the presence of an aminodiene intermediate **122**. Lewis acid catalysis facilitates the BR reaction to proceed at lower reaction temperatures and to furnish higher yields than it does under catalyst-free conditions. Therefore, it was assumed that the addition of a Lewis acid catalyst to the BR reaction between a *β*-nitroenamine and an alkynone would increase the isolated yield of the 3-nitropyridine product.
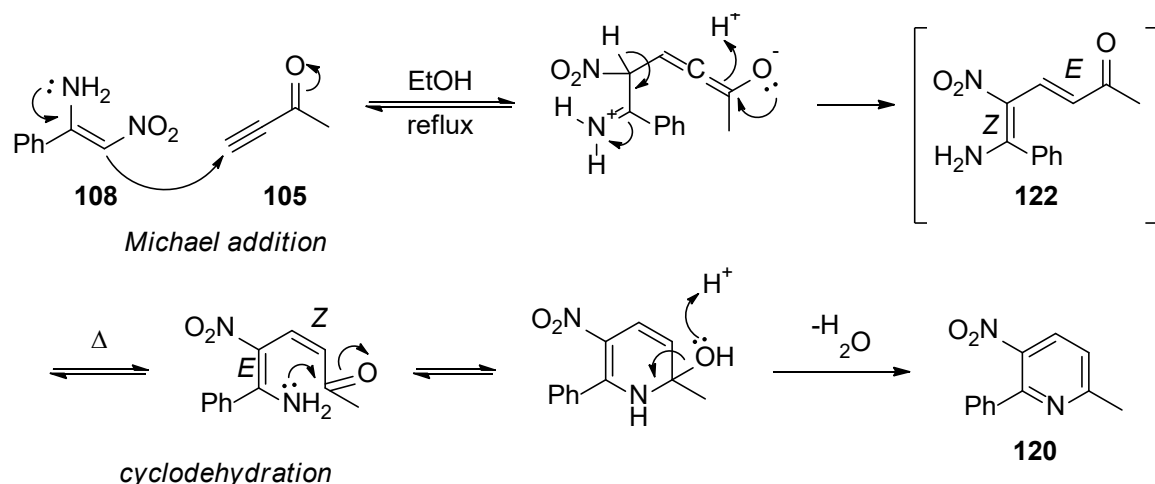
**Scheme 54:** Suggested mechanism for BR reaction between *β*-nitroenamine **108** and **105**.

4-Phenyl-3-butyn-2-one (**123**) was chosen as the alkynone substrate to use for optimization studies (**Table 2.3**) due to the lower reactivity of 3-butyn-2-one derivatives with substituents at position C-4. When alkynone **123** (1.5 equiv.) and *β*-nitroenamine **108** (1 equiv.) were stirred in ethanol at reflux for 24 hours (**entry 1**), only trace amounts of 3-nitropyridine **124** were isolated after purification. When the same reaction was carried out in a 5:1 mixture of ethanol-acetic acid (**entry 2**), 3-nitropyridine **124** was isolated in 6% yield. A few Lewis acids that had previously shown success in related Bohlmann-Rahtz procedures were then investigated. Use of the Lewis acid iron(III) chloride (**entry 3**) increased the isolated yield of 3-nitropyridine **124** to 11%, but this was still poorly efficient. The most encouraging

catalyst was the Lewis acid zinc(II) bromide (**entry 4**), which furnished 3-nitropyridine **124** in 37% isolated yield. Out of the catalysts tested, it was concluded that zinc(II) bromide could be the catalyst of choice for improving the yield of the BR reaction for the synthesis of 3-nitropyridines. However, as this yield was still quite low, it was hoped that increasing the reaction temperature would facilitate the formation of 3-nitropyridine product **124** in higher yield.
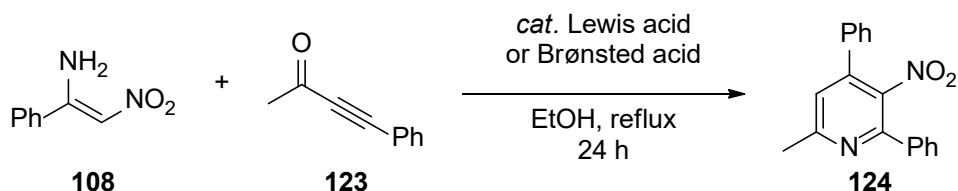
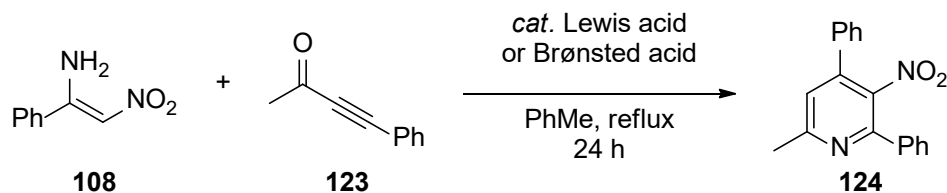**Table 2.3:** Effects of acid catalysis on the BR reaction between **108** and alkynone **123**.

Entry	Catalyst	Catalyst Loading	Product	Yield (%)[a]
1	None	N/A	**124**	*trace*
2	AcOH	1:5 *v/v*	**124**	6
3	FeCl$_3$	15 mol%	**124**	11
4	ZnBr$_2$	15 mol%	**124**	37

[a] Isolated yield after column chromatography.

A solution of the β-nitroenamine (1.0 mmol) and alkynone (1.5 mmol) in ethanol was stirred at reflux in the presence of a catalyst for 24 h. The ethanol was removed *in vacuo*, and the crude material was dissolved in EtOAc. The resulting slurry was filtered through silica, and the filtrate was washed sequentially with water, sat. aqueous NaHCO$_3$ solution (x2) and brine (x2), dried over Na$_2$SO$_4$, and evaporated in vacuo. Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*), gave the pure 3-nitropyridine.

Toluene (PhMe), which had previously been shown to be a suitable solvent for the BR reaction, was chosen as the solvent for further optimization studies (**Table 2.4**) due to its higher boiling point compared to ethanol.[22] When the β-nitroenamine **108** (1 equiv.) and alkynone **123** (1.5 equiv.) were stirred in toluene at reflux for 24 hours without catalyst (**entry 1**), only a trace amount of 3-nitropyridine **124** was isolated. The addition of a Brønsted acid (AcOH-PhMe 1:5) furnished an isolated yield of 8% (**entry 2**). The same Lewis acids were

investigated that had previously been found to be successful in the Bohlmann-Rahtz pyridine synthesis.[22] Use of 15 mol% iron(III) chloride (**entry 3**) furnished the product **124** in 54% isolated yield whereas 15 mol% zinc(II) bromide (**entry 6**) again performed better, with 67% isolated yield of 3-nitropyridine **124**. Since both Lewis acid catalysts performed dramatically better in toluene than they did in ethanol, it was decided to study the effect of varying Lewis acid concentrations on isolated yields. In the case of iron(III) chloride, increasing the concentration to 30 mol% (**entry 4**) had little effect on the isolated yield (52%). However, increasing the quantity of iron(III) chloride to 50 mol% (**entry 5**) decreased the isolated yield to 38%. Conversely, with zinc(II) bromide there was virtually no change in yield as the stoichiometry increased, with 30 mol% (**entry 7**) and 50 mol% (**entry 8**) furnishing 68% and 71% isolated yields of 3-nitropyridine **124**, respectively. Therefore, it was concluded that 15 mol% was the ideal zinc(II) bromide stoichiometry for this reaction.

Table 2.4: Effects of acid catalysis on the BR reaction between **108** and alkynone **123**.

| Entry	Catalyst	Catalyst Loading	Product	Yield (%)[a]
1	None	N/A	**124**	trace
2	AcOH	1:5 *v/v*	**124**	8
3	FeCl₃	15 mol%	**124**	54
4	FeCl₃	30 mol%	**124**	52
5	FeCl₃	50 mol%	**124**	38
6	ZnBr₂	15 mol%	**124**	72
7	ZnBr₂	30 mol%	**124**	68
8	ZnBr₂	50 mol%	**124**	71

[a] Isolated yield after column chromatography.

A solution of the β-nitroenamine (1.0 mmol) and alkynone (1.5 mmol) in toluene was stirred at reflux in the presence of a catalyst for 24 h. The toluene was removed *in vacuo*, and the crude material was dissolved in EtOAc. The resulting slurry was filtered through silica, and the filtrate was washed sequentially with water, sat. aqueous $NaHCO_3$ solution (x2) and brine (x2), dried over Na_2SO_4, and evaporated in vacuo. Purification by flash column chromatography on silica, eluting with pentane-Et₂O (3:1 *v/v*), gave the pure 3-nitropyridine.

Synthesis of the first library of substituted 3-nitropyridines

A series of 21 substituted 3-nitropyridines were synthesized using the system of 15 mol% zinc(II) bromide in toluene at reflux for 24 hours (**Table 2.5**). β-Nitroenamines (1 equiv.) were reacted with one of 3 commercially available alkynones (1.5 equiv.): 3-butyn-2-one (**105**), 4-phenyl-3-butyn-2-one (**123**), or 3-hexyn-2-one (**125**). For the 3-nitropyridines synthesized from β-nitroenamine **108**, the products of the reactions with alkynones **105** (**entry 1**) or **123** (**entry 2**) were isolated in virtually identical yields (71% and 72%, respectively). However, when the 4-substituted alkynone **125** was used instead (**entry 3**) the isolated yield fell to 11%. This pattern was also seen with the 3-chlorinated analogues (**entry**

4-6) derived from *β*-nitroenamine **115**. The 4-fluorinated (**entry 7-8**) and 4-brominated (**entry 10-11**) analogues (derived from *β*-nitroenamines **113** and **114**, respectively) had larger differences between isolated yields of the 4-H and 4-phenyl compounds. The 7% isolated yield of the 4-fluorinated compound (**entry 9**) derived from alkynone **125** was in accordance with the low yields observed for the other substrates in their reactions with the unreactive hexynone **125**. The highest isolated yield (74%) was observed from the reaction between *β*-nitroenamine **114** and alkynone **105** where R_2 = H (**entry 10**). The 2-furanyl (**entry 15-16**) and *N*-morpholinyl (**entry 17-18**) derivatives were generally isolated in lower yields than their phenyl counterparts. The two examples where the aliphatic *β*-nitroenamine **119** was used (**entry 19-20**) furnished 3-nitropyridines in modest (28-44%) yields compared to their aromatic analogues. It was concluded that the BR reaction was tolerant of a wide variety of substrates, allowing access to substituted 3-nitropyridines in generally modest to high yields, with some exceptions.
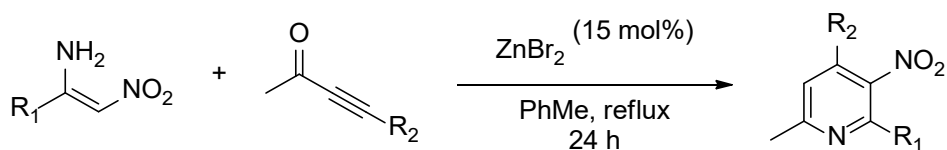
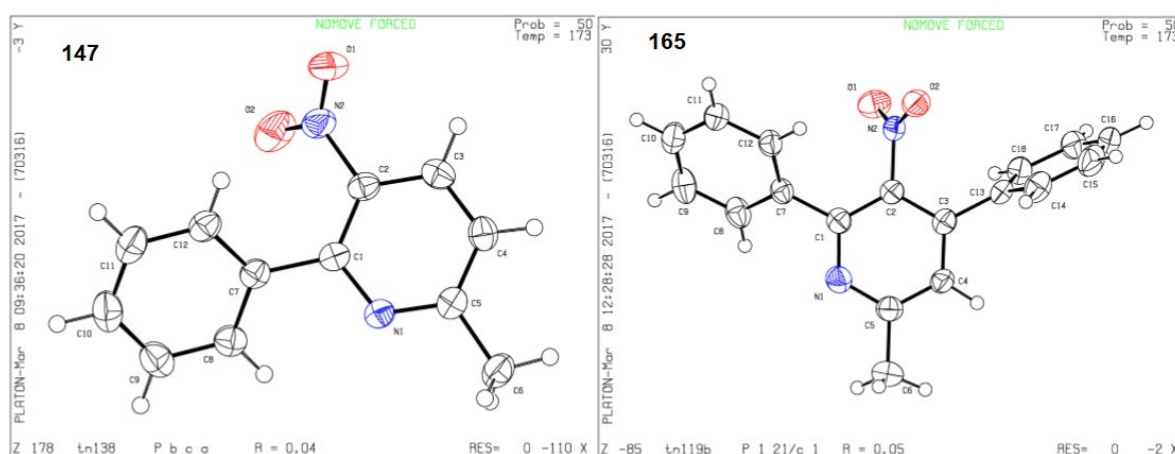**Table 2.5:** Synthesis of a library of 3-nitropyridines using the BR reaction.

Entry	Enamine	Alkynone	R_1	R_2	Product	Yield (%)[a]
1	**108**	**105**	C_6H_5	H	**120**	71
2	**108**	**123**	C_6H_5	C_6H_5	**124**	72
3	**108**	**125**	C_6H_5	C_2H_5	**126**	11
4	**115**	**105**	3-ClC$_6$H$_4$	H	**127**	72
5	**115**	**123**	3-ClC$_6$H$_4$	C_6H_5	**128**	70
6	**115**	**125**	3-ClC$_6$H$_4$	C_2H_5	**129**	11
7	**113**	**105**	4-FC$_6$H$_4$	H	**130**	63
8142	**113**	**123**	4-FC$_6$H$_4$	C_6H_5	**131**	32
9	**113**	**125**	4-FC$_6$H$_4$	C_2H_5	**132**	7
10	**114**	**105**	4-BrC$_6$H$_4$	H	**133**	74
11	**114**	**123**	4-BrC$_6$H$_4$	C_6H_5	**134**	20
12	**110**	**105**	4-iPrC$_6$H$_4$	H	**135**	71
13	**111**	**105**	4-BnOC$_6$H$_4$	H	**136**	61
14	**111**	**123**	4-BnOC$_6$H$_4$	C_6H_5	**137**	62
15	**112**	**105**	2-furanyl	H	**138**	50
16	**112**	**123**	2-furanyl	C_6H_5	**139**	27
17	**116**[b]	**105**	N-morpholinyl	H	**140**	39
18	**116**[b]	**123**	N-morpholinyl	C_6H_5	**141**	32
19	**119**	**105**	CH$_3$	H	**142**	44
20	**119**	**123**	CH$_3$	C_6H_5	**143**	28

[a] Isolated yield after column chromatography.

[b] (*E*)-1-morpholino-2-nitroethenamine (**167**), purchased and used as received from Enamine Ltd.

A solution of a *β*-nitroenamine (1.0 mmol), alkynone (1.5 mmol), and zinc(II) bromide (15 mol%) in toluene was stirred at reflux for 24 h. The toluene was removed *in vacuo*, and the crude material was dissolved in EtOAc. The resulting slurry was filtered through silica, and the filtrate was washed sequentially with water, sat. aqueous NaHCO$_3$ solution (x2) and brine (x2), dried over Na$_2$SO$_4$, and evaporated in vacuo. Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*), gave the pure 3-nitropyridine.
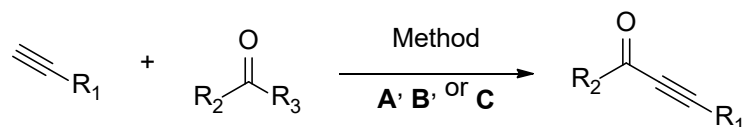
X-Ray crystallographic studies were used to confirm the substitution pattern of the 2,3,6-trisubstituted 3-nitropyridine **120** and the 2,3,4,6-tetrasubstituted 3-nitropyridine **124**. The resolved crystal structures (**Figure 22**) indicated that this method offered total regiocontrol, which is typical of the BR reaction.[22] Therefore, this route to 3-nitropyridines was expected to proceed *via* the same 2-step mechanism that has been previously proposed in this chapter for the BR reaction: a Michael addition of the *β*-nitroenamine to the alkynone, followed by *E/Z*-isomerization and cyclodehydration into the 3-nitropyridine product.

Figure 22: Crystal structures of 3-nitropyridines **120** (left) and **124** (right).

Synthesis of substituted alkynones

The first library of substituted 3-nitropyridines had demonstrated that the BR reaction was compatible with a wide variety of *β*-nitroenamines. However, the limited commercial availability of alkynones was a major restriction that prevented the introduction of any substituent at position C-6 other than a methyl group. This limitation also barred the incorporation of any aromatic groups other than a phenyl moiety into position C-4. To address these issues, a series of substituted alkynones were prepared in-house according to literature procedures (**Table 2.6**), in isolated yields ranging from 41-81% (**entry 1-7**).

$$\text{alkyne} + R_2\overset{O}{\underset{R_3}{\parallel}} \xrightarrow[\text{A, B, or C}]{\text{Method}} R_2\overset{O}{\parallel}\!\!-\!\!\equiv\!\!-R_1$$

Table 2.6: Synthesis of alkynones from alkynes and: (**A**) *N*-methoxy-*N*-methylacetamide; (**B**) ethyl trifluoroacetate; or (**C**) ethyl 2-(methoxy(methyl)amino)-2-oxoacetate.

Entry	Reagent	R_1	R_2	Product	Yield (%)[a]
1	**A**	4-MeOC$_6$H$_4$	CH$_3$	**144**	73
2	**A**	4-FC$_6$H$_4$	CH$_3$	**145**	59
3	**B**	C$_6$H$_5$	CF$_3$	**146**	74
4	**B**	4-MeOC$_6$H$_4$	CF$_3$	**147**	41
5	**C**	C$_6$H$_5$	CO$_2$Et	**148**	45
6	**C**	4-MeOC$_6$H$_4$	CO$_2$Et	**149**	41
7	**D**[b]	H	C$_6$H$_5$	**150**	81

[a] Isolated yield after column chromatography.

[b] Single-step oxidation of 1-phenyl-2-propyn-1-ol with Dess-Martin periodinane in DCM.

Synthesis of the second library of substituted 3-nitropyridines

The alkynones that were synthesized in the previous section were reacted with either β-nitroenamine **108** or **119**, which generated a second library of 3-nitropyridines (**Table 2.7**). In general, yields for this series of 3-nitropyridines were substantially lower than those of the first library. The two examples with a methyl substituent at position C-6 (**entry 1-2**) were isolated in some of the highest yields (28% and 24%, respectively) of this series. The product of the reaction between β-nitroenamine **119** and alkynone **190** (**entry 3**) was also isolated in relatively high yield (33%). Its (4-methoxy)phenyl analogue (**entry 4**) was isolated in significantly lower yield (14%), which could be due to the reduced reactivity of the Michael acceptor. Both ethyl esters (**entry 5-6**) were isolated in similarly poor yields (15% and 21%, respectively). Finally, the only example of a 3-nitropyridine with an aromatic substituent at position C-6 (**entry 7**) was isolated in modest yield (27%).
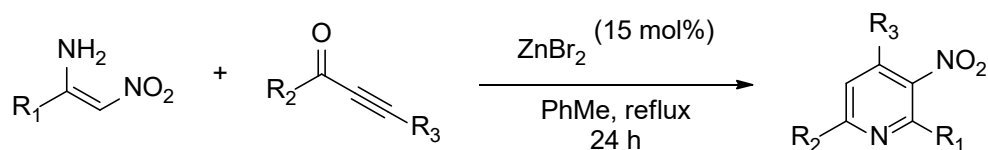
Table 2.7: Synthesis of the second library of 3-nitropyridines using the BR reaction.

| Entry	Enamine	Alkynone	R_1	R_2	R_3	Product	Yield (%)[a]
1	**119**	**144**	CH_3	CH_3	4-MeOC$_6$H$_4$	**151**	28
2	**119**	**145**	CH_3	CH_3	4-FC$_6$H$_4$	**152**	24
3	**119**	**146**	CH_3	CF_3	C_6H_5	**153**	33
4	**119**	**147**	CH_3	CF_3	4-MeOC$_6$H$_4$	**154**	14
5	**119**	**148**	CH_3	CO_2Et	C_6H_5	**155**	15
6	**119**	**149**	CH_3	CO_2Et	4-MeOC$_6$H$_4$	**156**	21
7	**108**	**150**	C_6H_5	C_6H_5	H	**157**	27

[a] Isolated yield after column chromatography.

A solution of a β-nitroenamine (1.0 mmol), alkynone (1.5 mmol), and zinc(II) bromide (15 mol%) in toluene was stirred at reflux for 24 h. The toluene was removed *in vacuo*, and the crude material was dissolved in EtOAc. The resulting slurry was filtered through silica, and the filtrate was washed sequentially with water, sat. aqueous NaHCO$_3$ solution (x2) and brine (x2), dried over Na$_2$SO$_4$, and evaporated in vacuo. Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*), gave the pure 3-nitropyridine.

Synthesis of 3-nitro-2-aminopyridines

Although it had been clearly demonstrated that the BR reaction was tolerant of a myriad of aliphatic and aromatic substituents for the synthesis of 3-nitropyridines, it was not known whether these conditions were amenable to the introduction of an amino group into position C-2. 2-Nitroethene-1,1-diamine (**159**) was synthesized (**Scheme 55**) through treatment of (2-nitroethene-1,1-diyl)bis(methylsulfane) (**158**) with 7N methanolic ammonia.[86] Enamine **159** was then reacted with alkynone **105,** and 6-methyl-3-nitropyridin-2-amine (**160**) was isolated in 21% yield. The identity of 3-nitro-2-amino pyridine **160** was inferred using ^{1}H NMR spectroscopy. Although in this case the amino group was not discerned in CDCl$_3$, the two doublets ($J = 8.5$ Hz) at $\delta = 6.59$ and 8.30 ppm were diagnostic of a pyridine ring, with these

peaks correlating to C-5 and C-4, respectively. IR spectroscopy established the presence of a primary amine functional group with an N-H stretch at ν 3318.
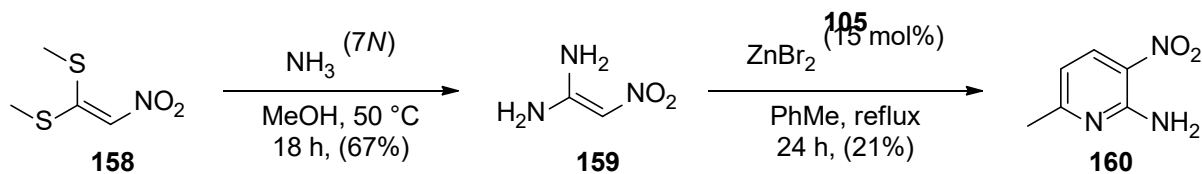
Scheme 55: Synthesis of 3-nitropyridin-2-amine **160**.

Bohlmann-Rahtz reaction using prop-2-ynals

While the Bohlmann-Rahtz (BR) reaction between β-nitroenamines and alkynones had provided rapid access to structurally diverse 3-nitropyridines in generally favourable yields, there were limitations as to the types of β-carbolines that could hypothetically be derived from these precursors. For instance, since every 3-nitropyridine synthesized using this method was endowed with a substituent at the C-6 position, this meant that any β-carbolines derived from those 3-nitropyridines would always be functionalized at position C-3. This made the development of an alternative method for the synthesis of 2,3-disubstituted and 2,3,4-trisubstituted 3-nitropyridines an attractive endeavour. Therefore, a new Bohlmann-Rahtz method was envisaged which utilized prop-2-ynal derivatives instead of alkynones (**Scheme 56**). This new pathway would hopefully provide synthetic access to analogues of certain β-carboline natural products, such as harmine (**80**).
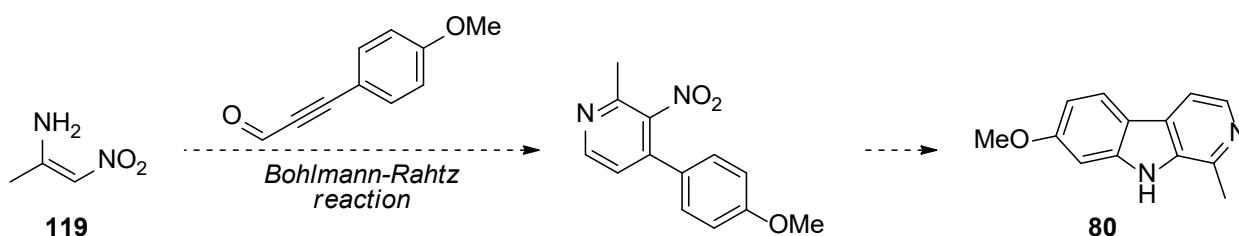
Scheme 56: Feasible pathway to the *β*-carboline natural product harmine (**80**), by way of a BR reaction between *β*-nitroenamine **119** and a prop-2-ynal derivative.

Synthesis of prop-2-ynals

A series of prop-2-ynal derivatives were synthesized starting from terminal alkynes, according to a literature procedure (**Table 2.8**).[87] After purification using column chromatography, the target prop-2-ynals were furnished in 15-68% yield (**entry 1-7**).
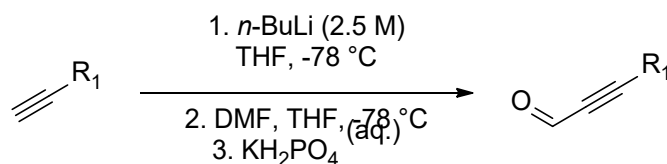
**Table 2.8:** Synthesis of substituted prop-2-ynals from terminal alkynes.

Entry	R$_1$	Product	Yield (%)[a]
1	phenyl	**161**	52
2	(4-methoxy)phenyl	**162**	47
3	(3,5-dimethoxy)phenyl	**163**	57
4	(4-*tert*-butyl)phenyl	**164**	68
5	(4-bromo)phenyl	**165**	15
6	cyclopropyl	**166**	26

[a] Isolated yield after column chromatography.

An alkyne (1 equiv.) reacted with *n*-BuLi (1.1 equiv) in THF under argon. After 15 min, dry DMF (2 equiv.) was added and the mixture was left to stir for 1 h. The mixture was poured into sat. KH$_2$PO$_4$ solution, and then partitioned between EtOAc and water, washed with brine (x2), and dried over Na$_2$SO$_4$. Solvent was removed *in vacuo* and then the crude material was purified using flash colum chromatography eluting with hexane-EtOAc (19:1 *v/v*), which furnished the pure prop-2-ynal.

BR reaction: using prop-2-ynals for 3-nitropyridine synthesis

The substituted prop-2-ynals (1.5 mmol) were condensed with β-nitroenamine **119** (1 mmol) using the established Bohlmann-Rahtz (BR) conditions of zinc(II) bromide (15 mol%) in toluene (6 mL) at reflux for 24 hours (**Table 2.9**). The 4-cyclopropyl analogue **172** (**entry 6**) was isolated in the highest yield (15%). The phenyl (**167**) and 4-(methoxy)phenyl (**168**) analogues (**entry 1-2**) were isolated in similar yields (13% and 12%, respectively). The lowest-yielding 3-nitropyridine of the series was the 3,5-(dimethoxy)phenyl analogue **169** (**entry 3**) which was isolated in 1% yield. The other two aromatic 3-nitropyridines (**entry 4-5**) were isolated in 5 to 8% yield. All isolated yields for this series of 3-nitropyridines were below 20%, suggesting that prop-2-ynals were either intrinsically less reactive than the 3-butyn-2-ones were, or that the target 3-nitropyridines were not the favoured products.
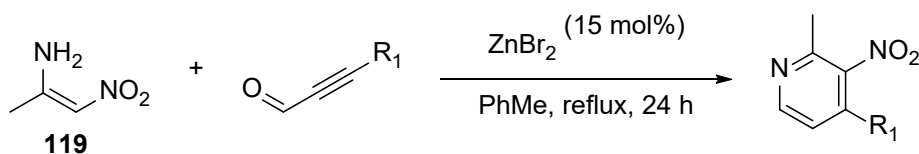
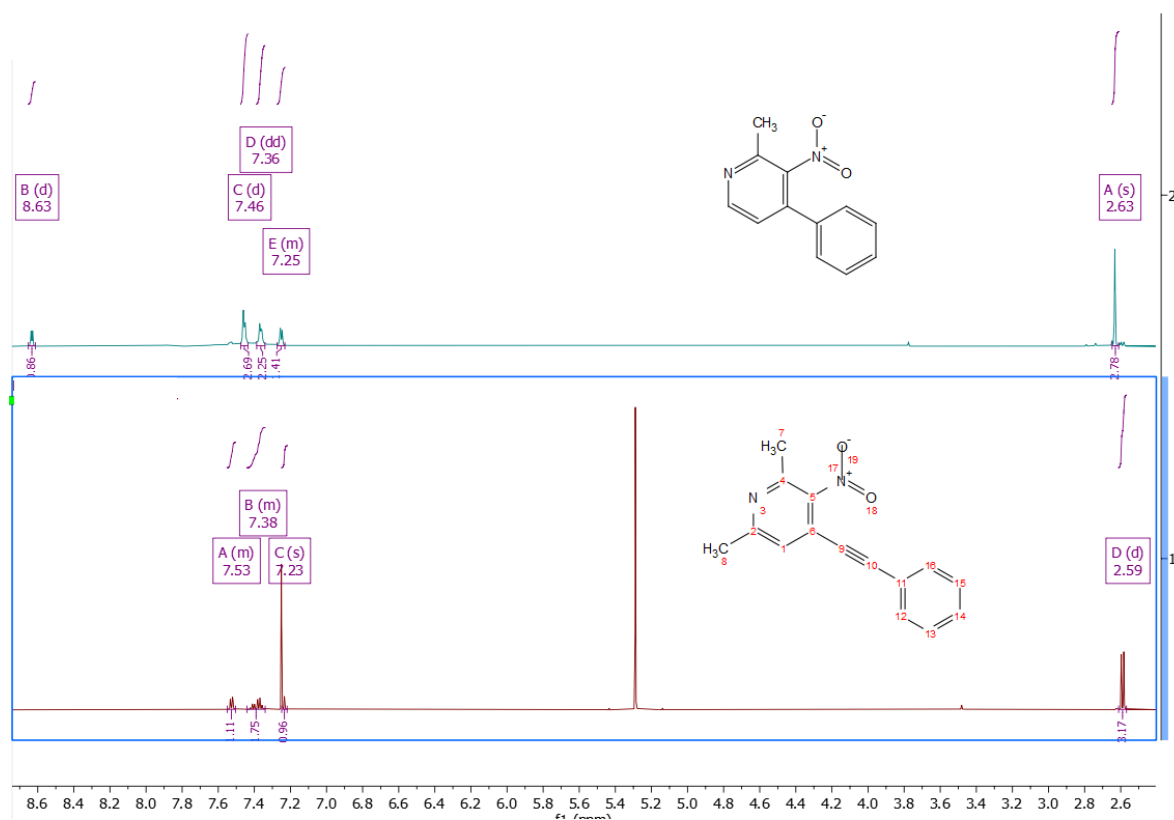**Table 2.9:** Synthesis of 3-nitropyridines from β-nitroenamine **119** and prop-2-ynals.

Entry	Enamine	Prop-2-ynal	R_1	Product	Yield (%)[a]
1	**119**	**161**	C_6H_5	**167**	13
2	**119**	**162**	4-MeOC_6H_5	**168**	12
3	**119**	**163**	$3,5\text{-(MeO)}_2C_6H_5$	**169**	1
4	**119**	**164**	$4\text{-}t\text{BuC}_6H_5$	**170**	8
5	**119**	**165**	4-BrC_6H_5	**171**	5
6	**119**	**166**	cyclopropyl	**172**	15

[a] Isolated yield after column chromatography.

A solution of the β-nitroenamine (1.0 mmol), prop-2-ynal (1.5 mmol), and $ZnBr_2$ (34 mg, 0.15 mmol) in toluene (6 mL) was stirred at reflux for 24 hours. The toluene was removed in vacuo, and the crude material was dissolved in EtOAc. The resulting slurry was filtered through silica, and the filtrate was washed sequentially with water, sat. aqueous $NaHCO_3$ solution (x2) and brine (x2), dried over Na_2SO_4, and evaporated *in vacuo*. Purification by flash column chromatography on silica, gave the pure β-nitropyridine.

Detection of an unwanted side-product

Further investigation by LC-MS analysis revealed the presence of a major impurity in the crude reaction mixture of **167**. Subsequent analysis using ^{1}H NMR spectroscopy suggested the identity of the impurity may have been generated by a competing Hantzsch-type reaction. Based on this data alone (**Figure 23**), it was not possible to conclude with certainty what the identity of this unwanted side product was, but this compound was easily differentiated from the Bohlmann-Rahtz product **167** by the presence of two 3-hydrogen singlets ($\delta = 2.59$ ppm) arising from the two methyl groups on the pyridine ring of this compound. Conversely, the Bohlmann-Rahtz product showed a 3-hydrogen singlet ($\delta = 2.63$ ppm), arising from the sole methyl group at position C-2 of the pyridine ring. Furthermore, the side product had only one singlet in the aromatic region ($\delta = 7.23$ ppm), presumably arising from the sole pyridinyl hydrogen at position C-5 of that compound. The Bohlmann-Rahtz product **167** showed a pair of doublets ($J = 5.0$ Hz*)* in the aromatic region resonating at $\delta = 8.63$ and 7.46 ppm, which were indicative of the two neighbouring hydrogens on the pyridine ring at positions C-5 and C-6.

Figure 23: ^{1}H NMR spectra for pyridine **167** (above) and possible side product (below).

Conclusions

In summary, the Bohlmann-Rahtz reaction has been modified to facilitate the synthesis of 3-nitropyridines in one step, starting from substituted alkynones and either aromatic or aliphatic β-nitroenamines. This process has been optimized to furnish 2,3,6-trisubstituted and 2,3,4,6-tetrasubstituted 3-nitropyridines in up to 74% yield using Lewis acid catalysis. For this system, the catalytic activity of zinc(II) bromide was demonstrated to be superior to that of iron(III) chloride or toluene-acetic acid (5:1 v/v). In general, yields were higher with aromatic substituents at positions C-2 and C-4, while aliphatic substituents at C-4 gave especially poor

yields. This reaction was also shown to tolerate the introduction of an amino group into position C-2, which provided access to substituted 3-nitro-2-aminopyridines.

Additionally, the scope of this new BR reaction was expanded to facilitate the synthesis of 2,3-disubstituted and 2,3,4-trisubstituted 3-nitropyridines, albeit in low isolated yields. A small library of 3-nitropyridines was synthesized and characterized. It was subsequently demonstrated that when a *β*-nitroenamine and a prop-2-ynal derivative were reacted under the established zinc(II) bromide-catalyzed conditions, a Hantzsch-type reaction could have operated in parallel with the Bohlmann-Rahtz reaction and be responsible for the low yields. Given the very low yields obtained in the synthesis of these alpha-unsubstituted pyridines, this approach was not investigated further in favour of other studies.

CHAPTER THREE

Synthesis of δ-carbolines and β-carbolines from 3-nitropyridines

Results and Discussion

One of the stated goals of this project was to develop a method for the synthesis of novel β-carbolines and δ-carbolines from 3-nitropyridines. Since 3-nitropyridines with an aromatic functionality at position C-2 (**Scheme 57**) were furnished in higher yields and from more readily available starting materials, δ-carbolines were prioritized as the first synthetic targets. It was hoped that once the ideal system for the cyclization of 3-nitropyridines into δ-carbolines had been discovered, that methodology could then be extrapolated to the synthesis of β-carbolines. Based on the available literature related to the Cadogan reaction and its previously described applications, it was hypothesized that some variant of that reaction would provide access to δ-carbolines in acceptable yields.
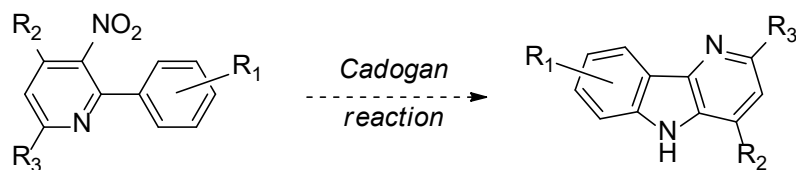
Scheme 57: Possible route to δ-carbolines from 3-nitropyridines.

Since the classical iteration of the Cadogan reaction employed boiling triethylphosphite as the reducing agent, this was chosen as the first reagent to assess for its ability to induce cyclization in 3-nitropyridines. When 3-nitropyridine **120** was stirred in triethylphosphite at reflux for 24 hours (**Scheme 58**), TLC analysis indicated the presence of several side products, which frustrated purification efforts and encouraged the pursuit of reagents that would offer more facile and cost-effective purification procedures. A yield was not determined in this case as other methods in the literature gave better results before this reaction mixture could be purified. It was concluded that another reducing agent needed to be used for the Cadogan-type cyclization of 3-nitropyridines.
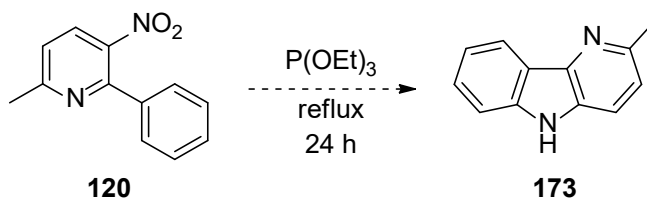
**Scheme 58:** P(OEt)$_3$-mediated cyclization of **120**.

Triphenylphosphine is another reagent that has frequently been employed as a reducing agent for Cadogan-type cyclizations. When 3-nitropyridine **120** was stirred with triphenylphosphine (4 equiv.) in DMF at reflux for 24 hours (**Scheme 59**), the target δ-carboline **173** was isolated in 39% yield. Based on LC-MS and proton NMR spectroscopic analysis, it was evident that triphenylphosphine was effective for inducing the reductive cyclization of 3-nitropyridine **120** into δ-carboline **173**; however, the triphenylphosphine oxide generated by the reaction proved to be a major challenge to remove during purification. Given that the removal of triphenylphosphine oxide was problematic, efforts to find an alternative reagent and easier purification procedure were carried out
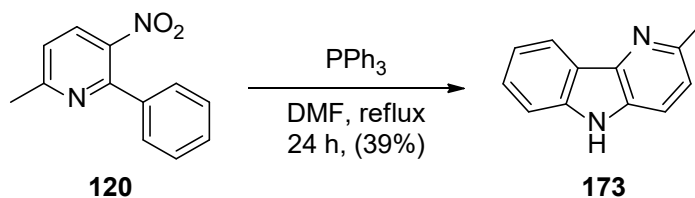
Scheme 59: PPh$_3$-mediated cyclization of **120**.

The identity of δ-carboline **173** was confirmed using ^{1}H NMR spectroscopy and high-resolution mass spectroscopy (HRMS). With DMSO-d$_6$ as the solvent, the ^{1}H NMR spectrum of **173** (**Figure 21**) showed a singlet at δ = 11.26 ppm corresponding to the secondary amine moiety of the indole core. An additional singlet at δ = 2.61 ppm was correlated with the

methyl substituent of the pyridinyl moiety. The aromatic region was comprised of 6 peaks which correlated with the 6 methine hydrogens of the carbocyclic and pyridinyl functionality. HRMS (POS ESI) analysis showed a pseudo-molecular ion ([M+H]$^+$) peak with a mass of 183.0917, which established the molecular formula of δ-carboline **173** as $C_{12}H_{10}N_2$.
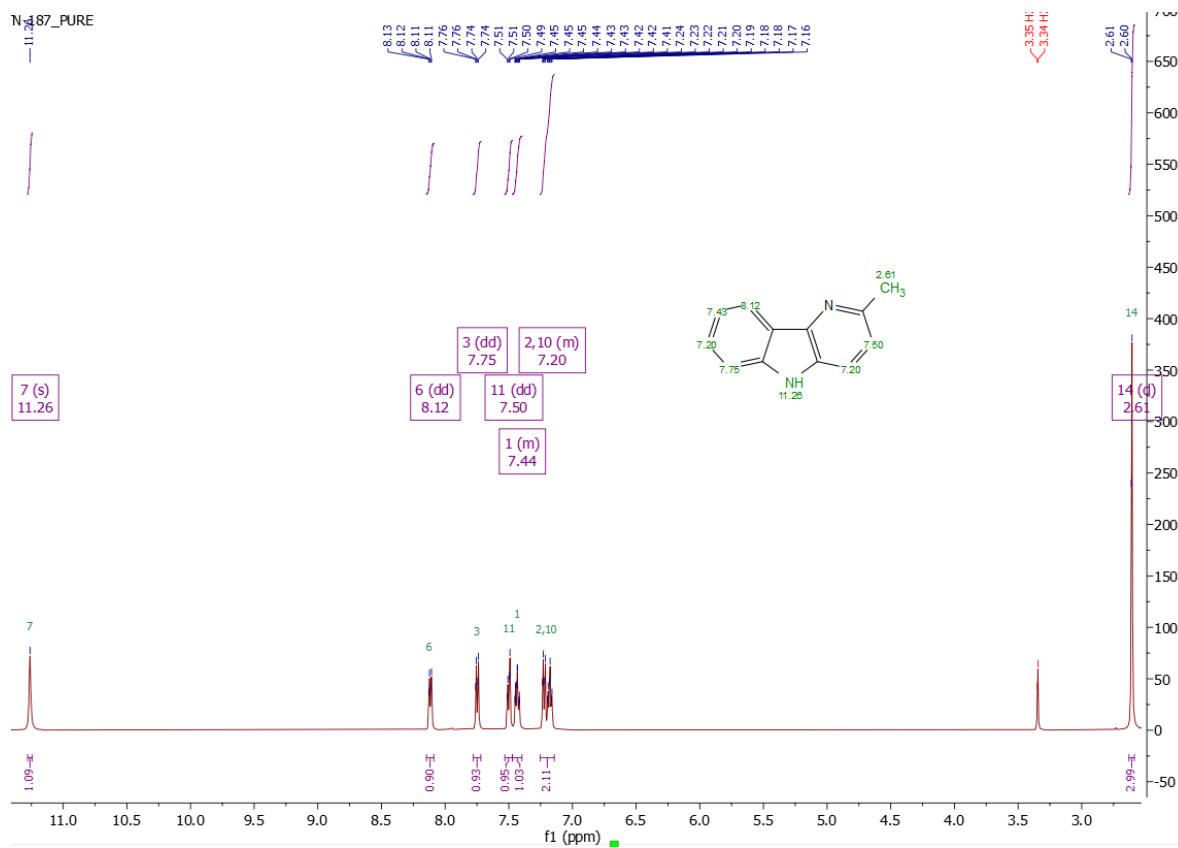
**Figure 24:** ^{1}H NMR spectrum for δ-carboline **173** in DMSO-d$_6$.

The Yang group (2011) have developed a solvent-free variant of the Cadogan reaction which used 1,2-bis(dipenylphosphino)ethane (DPPE) to synthesize a series of δ-carbolines (**Scheme 60**) and carbazoles.[88] In their work, 3-nitro-2-phenylpyridines or 2-nitrobiphenyl compounds were heated at 150 °C for 5 hours in neat DPPE. This furnished a library of 17 δ-carbolines (50-90% yield) and 5 carbazoles (33-98% yield), including intermediates for the syntheses of the drug carvedilol and the natural product glycozolicine. This DPPE-

mediated Cadogan reaction appeared to offer a more environmentally friendly alternative to triethylphosphite, and this reaction was shown to be more tolerant of strongly polar functional groups than the triphenylphosphine-mediated reaction was.
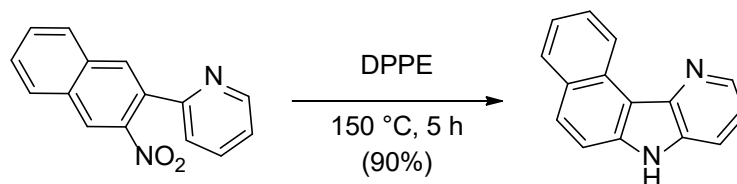
Scheme 60: DPPE-mediated Cadogan reaction.

Pyridine **120** was stirred with DPPE (1.1 equiv.) at 150 °C for 5 hours (**Scheme 61**), without solvent. Although both DPPE oxide and DPPE dioxide were detected by LC-MS analysis, purification by column chromatography was noticeably more facile than it had been when triphenylphosphine was used. After purification, δ-carboline **173** was isolated in 55% yield. This result established DPPE as the reagent of choice for δ-carboline synthesis.
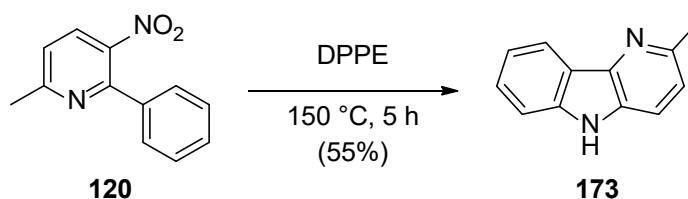
Scheme 61: DPPE-mediated cyclization of **120**.

Synthesis of a δ-carboline library

The established DPPE-mediated Cadogan reaction was used to prepare a 6-membered library of δ-carbolines, with substituents at positions C-3 and C-7 (**Table 3.1**). δ-Carboline **173** (**entry 1**), which was the least substituted example, was isolated in the highest yield (55%). The 7-halogenated δ-carbolines **174** and **175** (**entry 2-3**) were isolated in virtually identical yields to one another (46% and 48%, respectively). The 7-alkylated δ-carboline **176** (**entry**

4) was furnished in slightly lower yield than the halogenated compounds (42%). δ-Carboline **177** featured the introduction of a bulky benzyloxy substituent (**entry 5**) to position C-7, which decreased the isolated yield to 37%. δ-Carboline **178** was the only example to feature a phenyl substituent at position C-2 (**entry 6**), which had a detrimental effect on the isolated yield (26%). It was concluded that the DPPE-mediated Cadogan reaction was tolerant of a structurally diverse array of 3-nitropyridine substrates, which generally provided synthetic access to δ-carbolines in modest isolated yields.
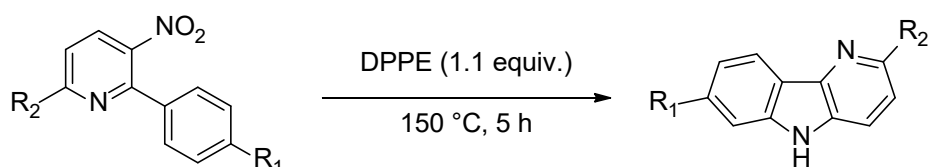
Table 3.1: DPPE-mediated synthesis of δ-carbolines from 3-nitropyridines.

Entry	Precursor	R_1	R_2	Product	Yield (%)^a
1	**120**	H	CH_3	**173**	55
2	**130**	F	CH_3	**174**	46
3	**133**	Br	CH_3	**175**	48
4	**135**	iPr	CH_3	**176**	42
5	**136**	OBn	CH_3	**177**	37
6	**157**	H	C_6H_5	**178**	26

^{a} Isolated yield after column chromatography.

3-nitropyridine (1.0 equiv.) was stirred with DPPE (1.1 equiv.) at 150 °C for 5 h. After cooling, the reaction mixture was then partitioned between water and EtOAc. The organic phase was washed sequentially with water (2x30 mL) and brine (2x30 mL), dried over Na_2SO_4, and evaporated *in vacuo*. Purification by flash column chromatography on silica gave the pure δ-carboline.

It is proposed that this reaction proceeded *via* a similar mechanism to the Cadogan reaction (**Scheme 62**). In the case of 3-nitropyridine **120**, first DPPE attacked one of the oxygens of the nitro group, leading to deoxygenation and the formation of the 3-nitrosopyridine intermediate **179**. DPPE then deoxygenated the nitroso group of **179**, which formed the

nitrene intermediate **180**. Spontaneous intramolecular cyclization of nitrene **180** and subsequent re-aromatization furnished δ-carboline **173**.
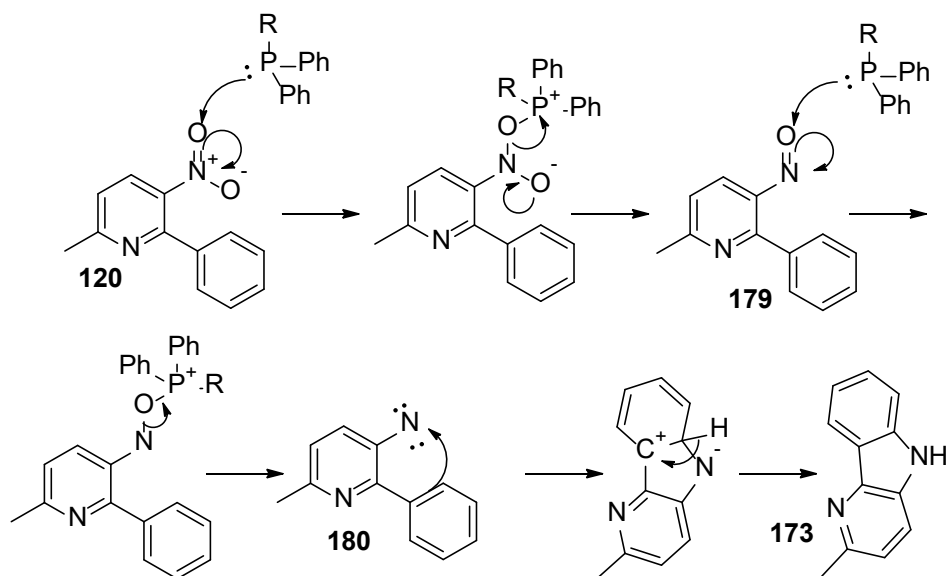
Scheme 62: Suggested mechanism for the DPPE-mediated Cadogan reaction of **120**.

X-ray crystallography was used to confirm the constitution of the 7-brominated δ-carboline **175** and the 7-isopropyl δ-carboline **176**. The resolved crystal structures (**Figure 22**) of **175** and **176** demonstrated the regioselectivity of the DPPE-mediated Cadogan reaction, which supported the mechanism proposed in **Scheme 62**.
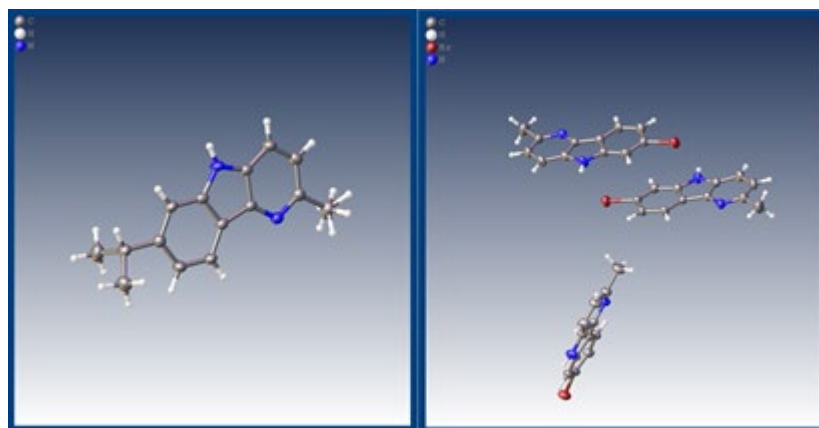
Figure 25: Crystal structures of carbolines **175** (*right*) and **176** (*left*).

Synthesis of β-carbolines

It had now been established that the majority of 3-nitropyridines from Chapter Two were amenable to the synthesis of δ-carbolines using DPPE. These 3-nitropyridine precursors each had aryl substituents at position C-2, which participated in the Cadogan reaction. However, there were several members of the 3-nitropyridine library that were endowed with aryl substituents at position C-4 instead. This substitution pattern was hoped to lead (**Scheme 63**) to the formation of β-carbolines instead of δ-carbolines when subjected to similar conditions as the previous series.
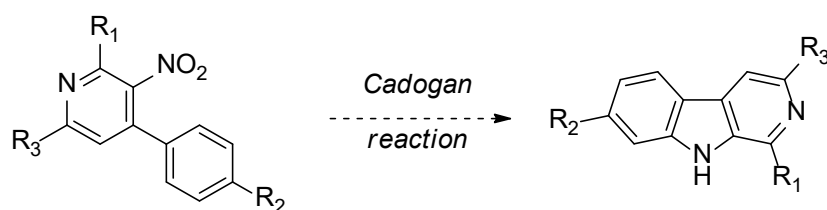
Scheme 63: Proposed route to β-carbolines from 3-nitropyridines.

DPPE-mediated synthesis of β-carbolines from 3-nitropyridines

Since the DPPE-mediated cyclization of 2-aryl-3-nitropyridines into δ-carbolines had given satisfactory results, it was expected that treatment of 4-aryl-3-nitropyridines with DPPE would be a suitable reaction for β-carboline synthesis. To test the *via*bility of this reaction, 3 of the 4-aryl-3-nitropyridines were stirred with DPPE (1.1 equiv.) at 150 °C for 5 hours (**Table 3.2**). It was evident that the DPPE-mediated Cadogan reaction was less effective for the synthesis of β-carbolines from 4-aryl-3-nitropyridines than it had been for the synthesis of δ-carbolines from 2-aryl-3-nitropyridines.
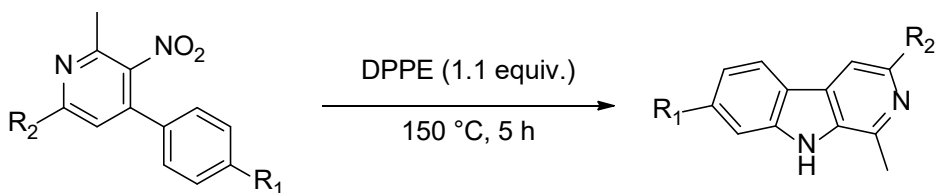
Table 3.2: DPPE-mediated synthesis of β-carbolines from 3-nitropyridines.

Entry	Nitropyridine	R_1	R_2	Product	Yield (%)[a]
1	**143**	H	Me	**181**	9
2	**151**	MeO	Me	**182**	2
3	**153**	H	CF$_3$	**183**	5

[a] Isolated yield after column chromatography.

3-nitropyridine (1.0 equiv.) was stirred with DPPE (1.1 equiv.) at 150 °C for 5 h. After cooling, the reaction mixture was then partitioned between water and EtOAc. The organic phase was washed sequentially with water (2x30 mL) and brine (2x30 mL), dried over Na$_2$SO$_4$, and evaporated *in vacuo*. Purification by flash column chromatography on silica gave the pure β-carboline.

However, it was apparent from both TLC analysis and LC-MS analysis that there was a major impurity present in each of the DPPE-mediated reactions. After separation of the side product using column chromatography, ^{1}H NMR spectroscopy was used to elucidate the identity of the impurity formed during the synthesis of β-carboline **182**, which was inferred to be the 3-aminopyridine **184**. In CD$_3$OD, the ^{1}H NMR spectrum (**Figure 26**) of β-carboline **182** had an aromatic region that resonated as 2 singlets at $\delta = 7.96$ and 7.06 ppm (c-4 and C-8) and 2 doublets at $\delta = 8.08$ and 6.95 ppm (C-5 and C-6); the aliphatic region included 3 singlets at $\delta = 3.94$, 2.90, and 2.73 ppm, arising from the *O*-methyl group (C-7) and the 2 methyl groups (C-1 and C-3). Conversely, the ^{1}H NMR spectrum (CD$_3$OD) for 3-aminopyridine **184**, contained a singlet at $\delta = 7.25$ ppm (arising from the proton at C-5) and 2 doublets at $\delta = 7.31$ and 7.00 ppm (arising from 2 protons at C-2′ /C-6′ and 2 protons at C-3′ /C-5′ , respectively) in the aromatic region; the aliphatic region showed 3 singlets at $\delta = 3.83$, 2.58, and 2.50 ppm, from *O*-methyl group (C-4′) and methyl groups (C-1 and C-6).
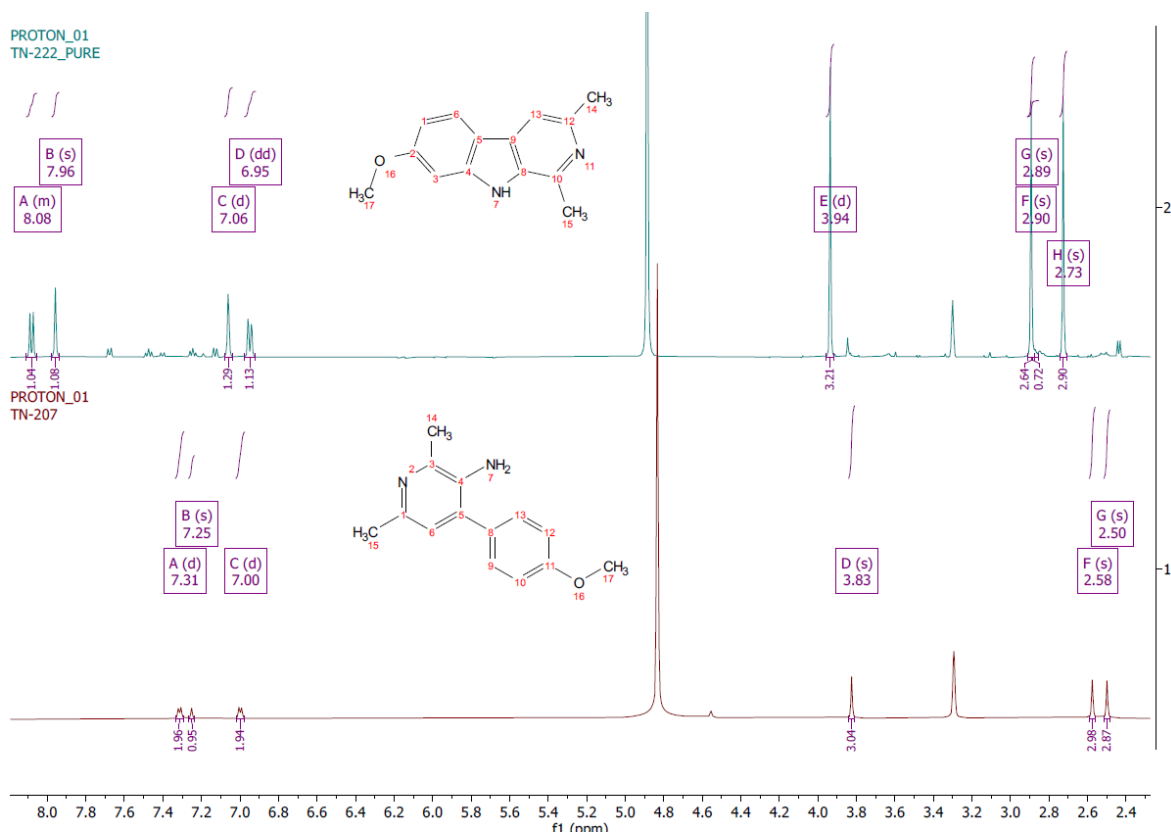
Figure 26: ^{1}H NMR spectra of β-carboline **182** (top) and 3-aminopyridine **184** (bottom).

After the DPPE-mediated Cadogan reaction of 3-nitropyridine **151** (**Scheme 64**), the side product inferred to be 3-amino-pyridine **184** was obtained in 53% yield. When compared to the very low 2% isolated yield of β-carboline **182**, this reaction was clearly not feasible for the purposes of this project. It was apparent that another reaction was needed to circumvent the formation of unwanted side products.
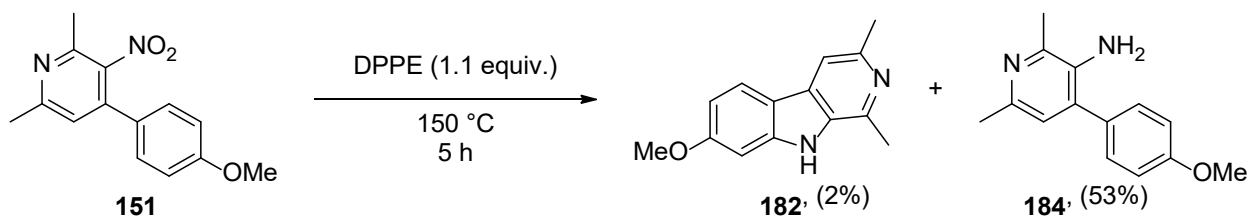
Scheme 64: The reaction of **151** with DPPE mostly formed an unwanted side product.

Synthesis of *β*-carbolines from 3-nitropyridines

The Radosevich group (2017) have reported a Cadogan-type reaction (**Scheme 65**) which used a novel phosphetane (**185**) as a catalyst to promote the formation of heterocyclic scaffolds from aromatic nitro-compounds. Of note, 2-phenylpyridine **186** had been used to synthesize pyrido[1,2-*b*]indazole (**187**) in 99% isolated yield. It was hypothesized that this reaction could be modified to enable the synthesis of *β*-carbolines.
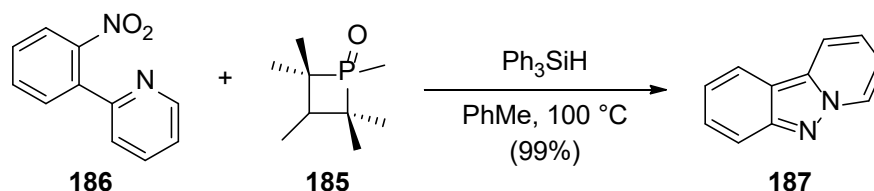
Scheme 65: Phosphetane **185** was used to promote the synthesis of **187**.

Phosphetane **185** is not commercially available, so it was prepared in-house (**Scheme 66**) according to the Radosevich's procedure (they reported a 43% yield).[89] First, alkene **188** was reacted with phosphorus trichloride and aluminium trichloride in DCM, which furnished intermediate **189** in 69% yield. Intermediate **189** was then treated with methylmagnesium bromide, left to stir at 35 °C for 4 hours, and then quenched with saturated ammonium chloride solution. Crude phosphetane **185** precipitated from the reaction mixture and was washed with DCM and filtered. The resulting organic phase was washed with water, dried, and then the solvent was removed with rotary evaporation. The combined solids were triturated with diethyl ether and 185 was isolated as a colourless solid in 25% yield.
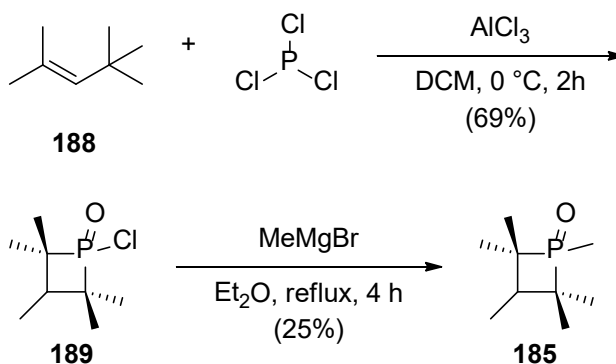
Scheme 66: Procedure used for the synthesis of phosphetane **185**.

3-Nitropyridine **151** was then reacted (**Scheme 67**) with triphenylsilane and phosphetane **185** in toluene at 100 °C. Initially, it was decided to use the same loading of **185** (15 mol%) as the Radosevich group had used. However, even after 48 hours under these conditions, only a trace amount of the desired β-carboline **182** was detected by TLC analysis and LC-MS. It was decided to increase the stoichiometry of **185** to 1.0 equivalents, with the reaction continuing to be monitored by LC-MS analysis. A rapid increase in the concentration of product **182** was observed, and after 4 hours the reaction was stopped. Following work-up and column chromatography, β-carboline **182** was isolated in 17% yield.
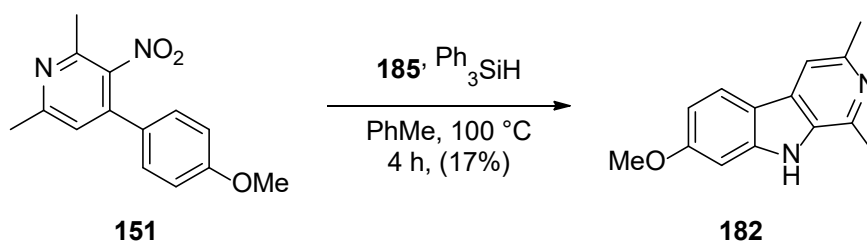
Scheme 67: Synthesis of **182**, promoted by phosphetane **185**.

When 3-nitropyridine **143** was subjected to the same conditions (**Scheme 68**), β-carboline **181** was isolated in 7% yield. The **185**-mediated reaction did not appear to offer much improvement in terms of yield compared to the use of DPPE. It was concluded that another

pathway to β-carbolines was needed, preferably using entirely commercially available reagents.
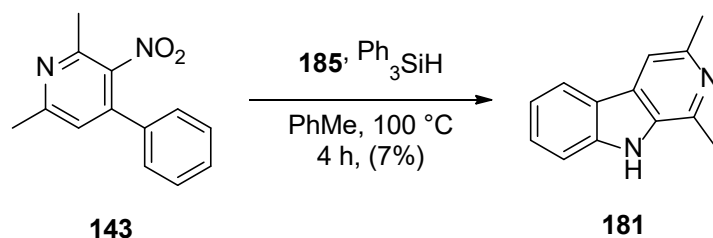
Scheme 68: Synthesis of **181**, as catalyzed by **185**.

**Carbon monoxide-mediated synthesis of β-carbolines from 3-nitropyridines**
The Driver group (2015) have reported a Pd(II)-catalyzed reaction for the synthesis of *N*-heteroarenes from nitroarenes using carbon monoxide (CO) as the reducing agent.[90,91] Molybdenum hexacarbonyl was used to generate CO *in situ* using a two-chambered reactor, eschewing the need to handle and store hazardous cannisters of CO gas. One of the reactions that the Driver group reported (**Scheme 69**) was the synthesis of carbazole (**191**) in 40% yield from 2-nitrobiphenyl (**190**). It was hypothesized that this reaction could be applied to the synthesis of β-carbolines from 3-nitropyridines.
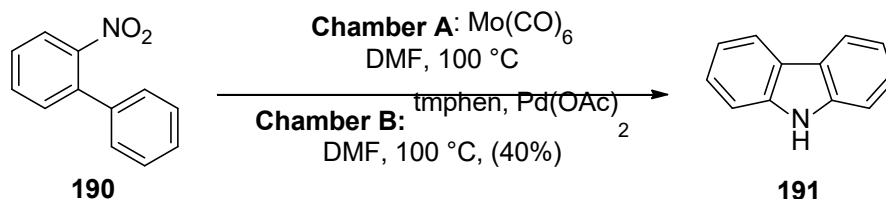
Scheme 69: CO-mediated synthesis of carbazole (**191**) from **190**.

To test the *via*bility of this reaction (**Scheme 70**), 3-nitropyridine **143** was reacted (**A**) with CO in the presence of catalytic Pd(OAc)$_2$ (5 mol%) and the ligand tmphen (10 mol%). After 24 hours, none of the desired β-carboline **181** was detected by LC-MS analysis. Increasing the loading of Pd catalyst to 10 mol%, using a different ligand (phen), and increasing

temperature to 120 °C (**B**) did not form any trace of **181**. It was concluded that this CO-mediated reaction was not suitable for β-carboline synthesis.
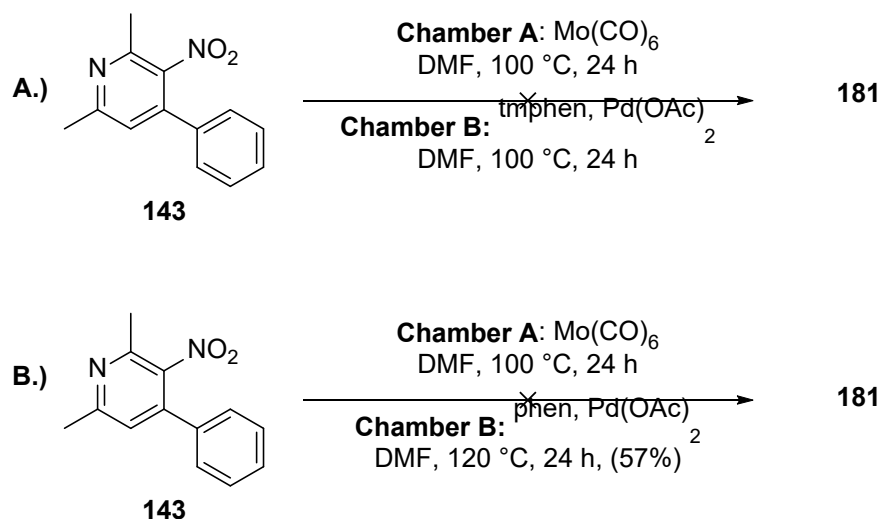
**Scheme 70:** Both attempts to use Mo(CO)$_6$ and Pd(OAc)$_2$ as reagents to form β-carboline **181** from 3-nitropyridine **143** were unsuccessful.

PPh$_3$-mediated synthesis of β-carbolines from 3-nitropyridines

The Spencer group (2017) have reported the microwave-assisted synthesis of substituted carbazoles from 2-nitrobiphenyls (**Scheme 71**).[92] This reaction was carried out under harsh conditions, at 200 °C with dimethylacetamide (DMAc) as the solvent. For instance, when 2-nitrobiphenyl **192** was reacted with PPh$_3$ under microwave irradiation for 2 hours, substituted carbazole **193** was isolated in 34% yield. It was hypothesized that reacting 3-nitropyridines with PPh$_3$ at high temperature would facilitate β-carboline synthesis.
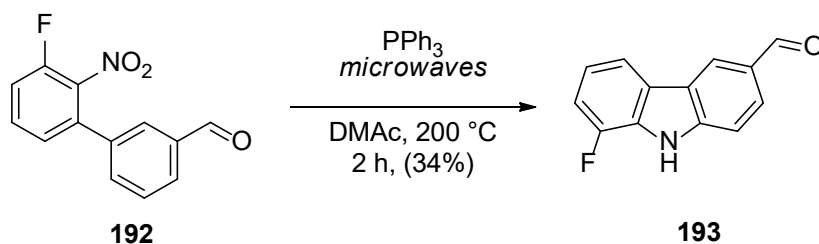
Scheme 71: Microwave-assisted synthesis of carbazole **193**.

3-Nitropyridine **143** was reacted with PPh$_3$ (2.5 equiv.) in DMAc at 200 °C for 2 hours under microwave irradiation (300 W initial power) (**Scheme 72**). After work-up and column chromatography, *β*-carboline **181** was isolated in 13% yield. While this was a low yield, it demonstrated that the PPh$_3$-mediated Cadogan reaction was a *via*ble route to *β*-carbolines.
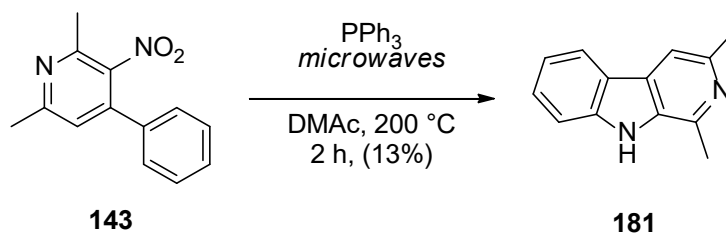

Scheme 72: Microwave-assisted synthesis of **181**.

It had previously been determined by the Freeman group (2005) that yields from the Cadogan reaction were more dependent upon temperature than solvent polarity.[52] In general, increasing reaction temperature should increase yields. With the microwave-assisted reaction already operating at 200 °C, it was not practical to attempt to increase the temperature further using that heating method. However, convective heating using the Monowave® 50 sealed tube reactor has several advantages over microwave heating that made it an attractive alternative. First, the sealed tube reactor was small enough to be operated on the bench as opposed to a dedicated fume cupboard, as was the case for microwaves. Second, and most importantly, it would enable the Cadogan reaction in DMAc to be heated to 250 °C with the reactor pressurized to 20 bar. To test these conditions, 3-nitropyridine **143** was reacted with PPh$_3$ (2.5 equiv.) in DMAc at 250 °C (20 bar) for 4 hours (**Scheme 73**). After work-up and column chromatography, *β*-carboline **181** was isolated in 22% yield. There did not appear to be any 3-aminopyridine **184** formed during this procedure.
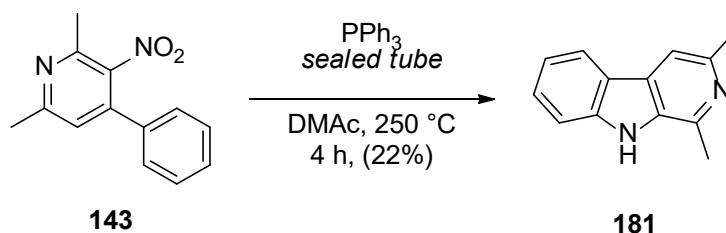
Scheme 73: Synthesis of **181** using a sealed tube reactor.

Encouraged by this result, a small library of β-carbolines were prepared using the sealed tube reaction between 3-nitropyridines and PPh₃ in DMAc (**Table 3.3**). Product **181** (**entry 1**) was isolated in significantly higher yield (22%) than the DPPE- or phosphetane **185**-mediated reactions (9% and 7%, respectively). Product **182** (**entry 2**) was isolated in higher yield (11%) than it had been following the DPPE-mediated reaction (2%) but slightly lower yield than had been obtained using phosphetane **185** (17%). Products **183** and **193** (**entry 3** and **4**) were isolated in the highest yields of the series (62% and 27%, respectively). It appears that the strongly electron-withdrawing trifluoromethyl functionality at position C-6 of the 3-nitropyridine scaffold has a profound influence on the reactivity of these compounds during the Cadogan reaction. However, it is not clear what accounts for the large disparity between the yields of structurally similar β-carbolines **183** and **193**.
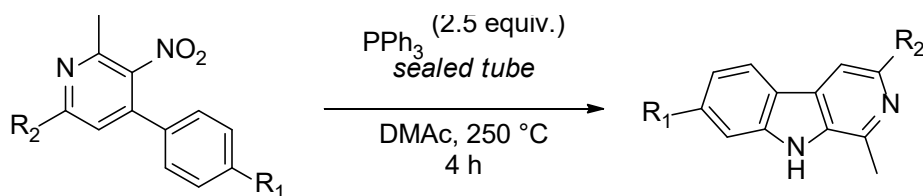
Table 8: PPh₃-mediated synthesis of *β*-carbolines using a sealed tube reactor.

Entry	SM	R₁	R₂	Product	Yield (%)ᵃ
1	**143**	H	Me	**181**	22
2	**151**	MeO	Me	**182**	11
3	**153**	H	CF₃	**183**	62
4	**154**	MeO	CF₃	**193**	30

ᵃ Isolated yield after column chromatography.

The reaction vessel was charged with a 3-nitropyridine (1 equiv.), PPh₃ (2.5 equiv.), a stirrer bar, and dimethylacetamide. The tube was inserted into the high temperature reactor and left to stir at 250 °C for 4 hours. The reaction mixture was filtered through silica and was concentrated *in vacuo*. The mixture was then taken up in ethyl acetate and transferred to a separating funnel. The organic layer was washed sequentially with water (x2) and brine (2x) and dried over Na₂SO₄. The solvent was removed *in vacuo* and then the crude solid was purified using column chromatography.

The regioselectivity of this reaction was confirmed by the crystallographic data and ¹H NMR spectroscopy. The substitution pattern of the *β*-carboline **183** was resolved and the crystal structure is shown in **Figure 49.** Based on this information, it is proposed that the PPh₃-mediated Cadogan reaction for the synthesis of *β*-carboline proceeds through a similar mechanism to the one described at the beginning of this chapter.
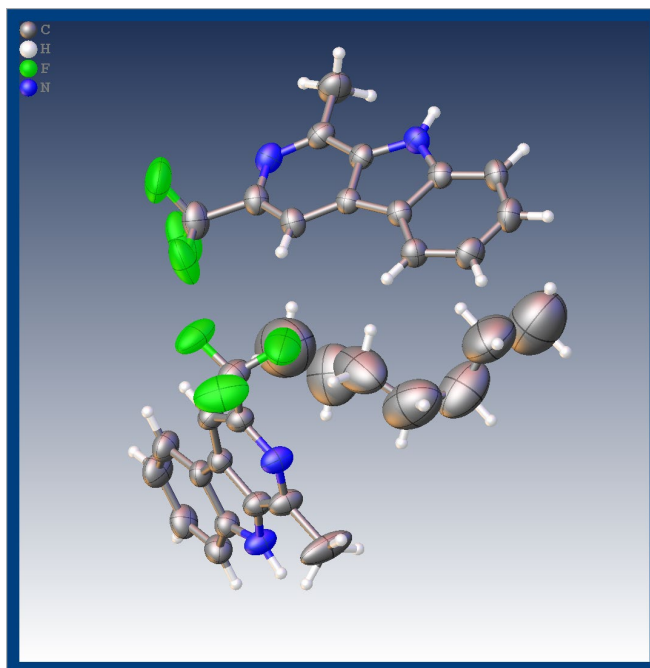
Figure 27: Resolved crystal structure of **183**.

Two-step synthesis of the natural product harmine

Previously, only trisubstituted 4-aryl-3-nitropyridines (from Chapter Two) had been used to synthesize 3-methyl-*β*-carbolines, but it was desirable to develop a novel route towards the synthesis of the natural product harmine (**80**). This would require the cyclization of disubstituted 4-aryl-3-nitropyridine **168** (from Chapter Three). In this case, microwave heating was used (the Monowave 50 reactor was no longer available for use), with **168** and PPh$_3$ allowed to react at 200 °C under microwave irradiation for 4 hours (**Scheme 74**). After work-up and column chromatography, harmine (**80**) was isolated in 18% yield.
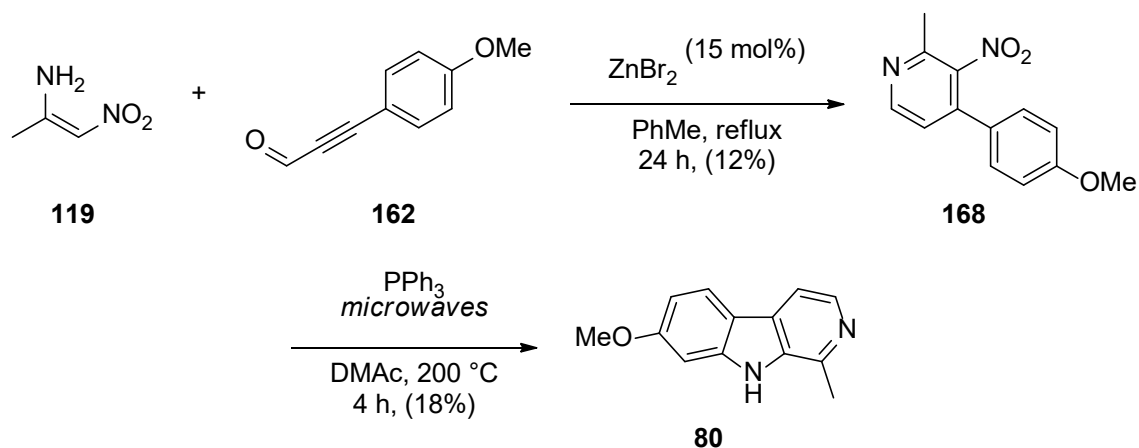
Scheme 74: Two-step synthesis of harmine (**80**) from enamine **119** and ynal **162**.

Conclusions

In summary, it has been shown that both triphenylphosphine and DPPE were suitable reagents for the Cadogan-type cyclization of 3-nitropyridines into δ-carbolines, with DPPE being the preferred reagent. The DPPE-mediated Cadogan reaction was used to synthesize a library of 6 δ-carbolines, generally in modest isolated yields (26-55%). This reaction was shown to be tolerant of several different functional groups including alkyl groups, halogens, and aromatic moieties. Based on the data generated from ^{1}H NMR spectroscopy and x-ray crystallography, it was proposed that the DPPE-mediated Cadogan reaction proceeded *via* a mechanism analogous to that of the triphenylphosphine-mediated Cadogan reaction, which has previously been described in the literature. It is evident that the DPPE-mediated Cadogan reaction has several advantages over the earlier methods which employed triethylphosphite or triphenylphosphine, namely the solvent-free conditions and relatively facile purification requirements.

Attempts to apply the same DPPE-mediated reaction that was ideal for the synthesis of δ-carbolines toward the synthesis of β-carbolines were unsatisfactory. Most of the isolated yields were below 10%. The reaction was further confounded by the presence of an undesired 3-aminopyridine impurity, which was determined to be the major product

A novel phosphetane catalyst **185** was synthesized and applied for the first time to the synthesis of β-carbolines. While there was higher selectivity for β-carbolines, the isolated yields were only marginally better than were those observed with DPPE. It was decided that the small increase in yield did not justify the continued use of a reagent that was not commercially available.

Attempts to induce cyclization of 3-nitropyridines using a CO-mediated reaction were completely unsuccessful. In both examples, there was total selectivity for production of the undesired 3-aminopyridine side product.

When a microwave-assisted, PPh$_3$-mediated Cadogan reaction was used, the β-carboline **181** was produced, but in only 13% yield. When the reaction temperature was increased from 200 °C to 250 °C by switching from microwave heating to conventional sealed-tube reactor (Monowave 50) heating, the isolated yield of **181** increased to 22%. This reaction was used to synthesize a small 5-membered library, with yields ranging from 8% to 62%. Finally, the microwave-assisted, PPh$_3$-mediated Cadogan reaction was used synthesize the natural product harmine (**204**), in 18% isolated yield.

CHAPTER FOUR:

Conclusions and future work.

Conclusions:

In Chapter Two, a new Bohlmann-Rahtz (BR) reaction (**Scheme 81**) for the synthesis of 3-nitropyridines in one step starting from *β*-nitroenamines and substituted alkynones was described. This reaction was tolerant of both aromatic and aliphatic *β*-nitroenamines. This reaction optimized using Lewis acid catalysis, with zinc(II) bromide being the most effective catalyst. The BR reaction was used to synthesize a large library of 2,3,6-trisubstituted and 2,3,4,6-tetrasubstituted 3-nitropyridines in up to 74% yield. It was also possible to access 3-nitro-2-aminopyridines. It was concluded that this BR reaction provided a quick, one-step route to heavily substituted 3-nitropyridines in modest to excellent yields. This is especially promising because some of the 3-nitropyridines that can be synthesized using this method may serve as precursors towards to synthesis of biologically active natural products of pharmaceutical interest.

Next, it was decided to extend the scope of this new BR reaction to allow for the use of prop-2-ynals in place of alkynones (**Figure 82)**. This would provide access to 3-nitropyridines without substituents at position C-6. The same zinc(II) bromide-catalyzed conditions from the earlier series were used to synthesize a small library of 2,3-disubstituted and 2,3,4-trisubstituted 3-nitropyridines, albeit generally in poor yields. It was concluded that further optimization was needed in order to improve conversion to the 3-nitropyridine product and circumvent the formation of unwanted side product(s). However, one of the 3-nitropyridines generated by this reaction was used as a precursor for the natural product harmine (**80**).

In Chapter Three, DPPE was used to synthesize a series of δ-carbolines in up to 55% yield using a Cadogan-type reaction (**Figure 83**). This reaction was tolerant of a wide variety of functional groups, which may be a useful feature when using the δ-carboline scaffold to build more complex molecules. It was concluded that the solvent-free conditions, commercial availability, and simple purification make DPPE an especially attractive reagent for Cadogan reactions.

Unfortunately, the DPPE-mediated Cadogan reaction was not suitable for the synthesis of β-carbolines. Several reagents and reaction conditions were assessed, but some only produced unwanted 3-aminopyridines. Finally, a PPh_3-mediated Cadogan under very forcing conditions in either a sealed tube reactor or under microwave irradiation (200-250 °C) increased yields, although they were inconsistent (ranging from 8-62 %). Finally, the microwave assisted Cadogan reaction was used to synthesize the natural product harmine (**204**) in 18% yield.

Future Work:

While the work in Chapter Two outlined a new BR reaction for 3-nitropyridine synthesis and applied that reaction to a wide variety of substrates, its success was limited to reactions that used alkynones and not prop-2-ynals. More time needs to be dedicated to the optimization of the BR with prop-2-ynals because the 3-nitropyridines generated by this reaction are of great use towards the synthesis of β-carboline natural products and their analogues, some of which may have medicinal value in the future.

The work in Chapter Three laid the foundation for a new synthetic pathway that the BR reaction can feed into: carboline synthesis. Currently, another member of the Bagley group is working towards the synthesis of 3-azidopyridines from 3-aminopyridines (which in turn were reduced from 3-nitropyridines), opening the door for a library of carbolines synthesized through visible-light mediated reactions under mild conditions. It is hoped that the yields will surpass those seen with the Cadogan reaction and its variations.

CHAPTER FIVE:

Experimental

General Materials and Methods

All reactions were performed in a fume hood under air unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian 500 MHz spectrometer; chemical shifts are reported in ppm, with TMS as an internal standard; multiplicities are described using standard conventions (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, td = triplet of doublets, m = multiplet); coupling constants are recorded in Hz. LCMS analyses were performed on a 5 μm C18 110 Å column and compound purity was determined using a 30-minute gradient elution using water-acetonitrile with 0.1% formic acid (5 min at 5%, 5%-95% over 20 min, 5 min at 95%) with the UV detector at λ 254 nm. High resolution mass spectrometry (HRMS) by electrospray ionization (ESI) was performed by Dr Alaa Abdul-Sada (University of Sussex). HRMS by electron impact (EI) was performed by James Tweedy (University of Glasgow). Elemental analyses were carried out by Stephen Boyer (London Metropolitan University). TLC visualization was accomplished under UV light and with the aid of an aqueous potassium permanganate stain. Yields refer to isolated yields after purification by flash column chromatography or trituration; where noted, some products underwent additional recrystallization to remove trace impurities.

Experimental details for Chapter 2

General procedure 2.1 for the synthesis of β-nitroenamines

β-Nitroenamines were synthesized according to a modified procedure from Seko and Komoto.[81] The nitroolefin (1 equiv.) and methoxylamine hydrochloride (1.25 equiv.) were dissolved in DMF (2 mL) and the solution was cooled to 0 °C. Triethylamine (1.25 equiv.) was added to the flask, and the reaction mixture was stirred for 15 minutes. The flask was left to stand at room temperature for 5 minutes, and the precipitated triethylammonium chloride was removed by filtration. The filtrate was added dropwise over 30 minutes to a stirred solution of potassium *tert*-butoxide (3 equiv.) in DMF (8 mL). After the addition was complete, the reaction vessel was removed from the ice bath and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was quenched with sat. aqueous NH_4Cl solution (25 mL) and the DMF was removed *in vacuo*, as an azeotrope with heptane. The crude solid was partitioned between EtOAc and water and the organic extract was washed with brine (x2), dried over Na_2SO_4, and evaporated *in vacuo*. Trituration with cold diethyl ether gave the pure *β*-nitroenamine.
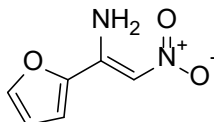
Synthesis of (*Z*)-2-nitro-1-phenylethenamine (**108**).
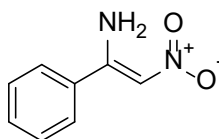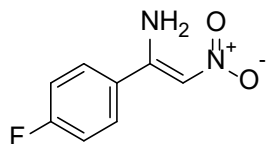

The title compound was synthesized according to general procedure 2.1, using a solution of (*E*)-(2-nitrovinyl)benzene (**143**) (4.48 g, 30.0 mmol) and methoxylamine HCl (3.13 g, 37.5

mmol) in DMF (50 mL) in a 100 mL round-bottom flask, triethylamine (3.80 g, 37.5 mmol), and a solution of potassium *tert*-butoxide (10.1 g, 90.0 mmol) in DMF (80 mL) to give the *title compound* (3.4 g, 68%) as bright yellow crystals, mp 102–103 °C (Et$_2$O) (lit. mp 105-106 °C).[55] δ_H (500 MHz, DMSO-d_6)/ppm 9.42 (br. s, 1H, NH), 8.94 (br. s, 1H, NH), 7.67 (d, J = 7.5 Hz, 2H, H-2′/H-6′), 7.57 (t, J = 7.5 Hz, 1H, H-4′), 7.50 (t, J = 7.5 Hz, 2H, H-3′/H-5′), 6.86 (s, 1H, H-2); δ_C (126 MHz, DMSO-d_6)/ppm 158.6 (C), 133.6 (C), 132.0 (CH), 129.3 (CH), 127.7 (CH), 109.6 (CH); anal. calcd. for C$_8$H$_8$N$_2$O$_2$: C, 58.53; H, 4.91; N, 17.06; Found: C, 58.47; H, 5.04; N, 16.97; LCMS purity (UV) = 97%, tR: 10.0 min. LCMS purity (positive ion, TIC) = 97%, tR:10.0 min. IR (cm^{-1}) 3392, 3363, 3273, 3186, 3133, 3062, 1626, 1583, 1538, 1462, 1444, 1415, 1261, 1179, 1155, 1110, 1079, 1003, 986, 919, 846, 828, 769, 730, 700, 670. Spectral data were in agreement with literature values.[93]
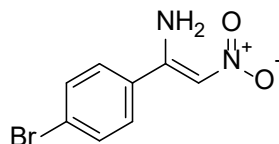
Synthesis of (*Z*)-2-nitro-1-[4-(propan-2-yl)phenyl]ethen-1-amine (**110**).
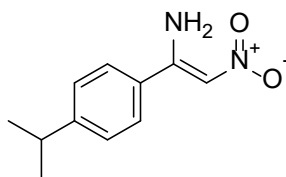
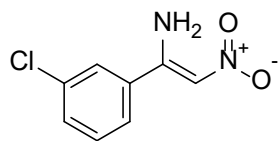

The title compound was synthesized according to general procedure 2.1, using a solution of 1-[(*E*)-2-nitroethenyl]-4-(propan-2-yl)benzene (5.55 g, 29.0 mmol) and methoxylamine HCl (3.03 g, 36.3 mmol) in DMF (50 mL) in a 100 mL round-bottom flask, triethylamine (3.67 g, 36.3 mmol), and a solution of potassium *tert*-butoxide (9.77 g, 87.0 mmol) in DMF (80 mL to give *title compound* (4.8 g, 80%) as pale yellow crystals, mp 139-140 °C (Et$_2$O). δ_H (500 MHz, DMSO-d$_6$)/ppm δ 9.40 (br. s, 1H, NH), 8.88 (br. s, 1H, NH), 7.59 (d, J = 8.4 Hz, 2H, H-2′/H-6′), 7.37 (d, J = 8.3 Hz, 2H, H-3′/H-5′), 6.86 (s, 1H, H-2), 2.94 (hept, J = 6.9 Hz, 1H, 4′-C*H*(CH$_3$)$_2$), 1.21 (d, J = 6.9 Hz, 6H, 4′-CH(C*H$_3$*)$_2$); δ_C (126 MHz, DMSO-d$_6$)/ppm 158.6

(C), 152.9 (C), 131.0 (C), 127.8 (CH), 127.3 (CH), 109.4 (CH), 33.8 (CH), 24.0 (CH$_3$); anal.

calcd. for C$_{11}$H$_{14}$N$_2$O$_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.97; H, 6.96; N, 13.59;

LCMS purity (UV) = 99%, tR: 15.46 min. LCMS purity (positive ion, TIC) = 99.2%, tR:

15.46 min. IR (cm^{-1}) 3381, 3281, 3222, 3180, 3153, 2962, 2926, 1611, 1577, 1538, 1455,

1421, 1395, 1364, 1279, 1245, 1153, 1113, 1051, 999, 958, 926, 950, 830, 778, 754, 725,

696, 974.

Synthesis of (*Z*)-1-[4-(benzyloxy)phenyl]-2-nitroethen-1-amine (**111**).
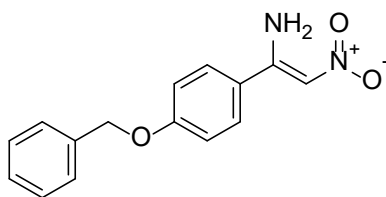
The title compound was synthesized according to general procedure 2.1, using a solution of

1-(benzyloxy)-4-[(*E*)-2-nitroethenyl]benzene (1.05 g, 4.11 mmol) and methoxylamine HCl

(429 mg, 5.14 mmol) in DMF (7 mL) in a 50 mL round-bottom flask, triethylamine (520 mg,

5.14 mmol), and a solution of potassium *tert*-butoxide (1.38 g, 12.33 mmol) in DMF (11 mL)

to give the *title compound* (619 mg, 56%) as beige crystals, mp 171-172 °C (Et$_2$O). δ_H (500

MHz, DMSO-d$_6$)/ppm 9.41 (br. s, 1H, NH), 8.86 (br. s, 1H, NH), 7.65 (d, *J* = 8.9 Hz, 2H, H-

2′/H-6′), 7.45 (d, *J* = 7.2 Hz, 2H, H-2″/H-6″), 7.40 (t, *J* = 7.2 Hz, 2H, H-3″/H-5″), 7.33 (t,

1H, *J* = 7.1 Hz, 1H, H-4″), 7.13 (d, *J* = 8.8 Hz, 2H, H-3′/H-5′), 6.88 (s, 1H, H-2), 5.19 (s, 2H,

4′-OCH$_2$); δ_C (126 MHz, DMSO-d$_6$)/ppm 161.6 (C), 158.2 (C), 137.1 (C), 129.5 (CH), 128.9

(CH), 128.4 (CH), 128.1 (CH), 125.5 (C), 115.6 (CH), 109.0 (CH), 69.9 (CH$_2$); anal. calcd.

for C$_{15}$H$_{14}$N$_2$O$_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.49; H, 5.28; N, 10.25; LCMS

purity (UV) = 93%, tR: 16.32 min. LCMS purity (positive ion, TIC) = 93.0%, tR 16.31 min.

IR (cm^{-1}) 3353, 3258, 3178, 3146, 3035, 2230, 1899, 1606, 1542, 1499, 1461, 1453, 1391, 1303, 1250, 1235, 1186, 1111, 1097, 1032, 1017, 1001, 989, 958, 904, 863, 832, 798, 763, 739, 687.

Synthesis of (*Z*)-1-(furan-2-yl)-2-nitroethenamine (**112**).

The title compound was synthesized according to general procedure 2.1, using a solution of 2-[(*E*)-2-nitroethenyl]furan (1.0 g, 7.20 mmol) and methoxylamine HCl (752 mg, 9.0 mmol) in DMF (18 mL) in a 100 mL round-bottom flask, triethylamine (911 mg, 9.0 mmol), and a solution of potassium *tert*-butoxide (2.42 g, 21.6 mmol) in DMF (23 mL) to give *the title compound* (610 mg, 55%) as a golden-brown solid, mp 133-134 °C (lit. mp 133-134 °C).[93] δ_H (500 MHz, DMSO-d$_6$)/ppm 9.16 (br. s, 1H, NH), 8.80 (br. s, 1H, NH), 7.98 (d, *J* = 1.7 Hz, 1H, H-5′), 7.52 (d, *J* = 3.7 Hz, 1H, 3′-H), 7.10 (s, 1H, H-2), 6.74 (dd, *J* = 3.6, 1.7 Hz, 1H, H-4′); δ_C (126 MHz, DMSO-d$_6$)/ppm 147.4 (CH), 146.7 (C), 145.9 (C), 115.4 (CH), 113.4 (CH), 107.0 (CH); anal. calcd. for C$_6$H$_6$N$_2$O$_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.59; H, 3.91; N, 17.79. LCMS purity (UV) = 97%, tR 7.5 min. LCMS purity (positive ion, TIC) = 97%, tR: 7.6 min. IR (cm^{-1}) 3366, 3265, 3217, 3135, 3119, 2261, 1683, 1619, 1581, 1543, 1492, 1455, 1404, 1379, 1278, 1232, 1121, 1097, 1077, 931, 886, 841, 738, 696. Spectral data were agreement with literature values.[93]

Synthesis of (*Z*)-1-(4-fluorophenyl)-2-nitroethen-1-amine (**113**).

The title compound was synthesized according to general procedure 2.1, using a solution of

(*E*)-1-fluoro-4-(2-nitrovinyl)benzene (5.13 g, 30.68 mmol) and methoxylamine HCl (3.20 g,

38.35 mmol) in DMF (50 mL) in a 250 mL round-bottom flask, triethylamine (3.88 g, 38.35

mmol), and a solution of potassium *tert*-butoxide (10.33 g, 92.0 mmol) in DMF (70 mL) to

give *the title compound* (3.2 g, 58%) as bright yellow crystals, mp 144-146 °C (ether) (lit.

mp 129-131 °C).[94] δ_H (500 MHz, DMSO-d_6)/ppm 9.38 (br. s, 1H, NH), 8.92 (br. s, 1H, NH),

7.73 (dq, J = 8.8, 3.5 Hz, 2H, H-2′/H-6′), 7.35 (t, J = 8.8 Hz, 2H, H-3′/H-5′), 6.84 (s, 1H, H-

2).; δ_C (126 MHz, DMSO-d_6)/ppm 164.6 (d, J = 249.5 Hz, C), 157.5 (C), 130.4 (d, J = 9.0

Hz, CH), 130.0 (d, J = 3.2 Hz, C), 116.4 (d, J = 21.9 Hz, CH), 110.0 (CH); anal. calcd. for

$C_8H_7FN_2O_2$: C, 52.75; H, 3.87; N, 15.38. Found: C, 52.66; H, 3.76; N, 15.24; LCMS purity

(UV) = 95%, tR: 10.75 min. LCMS purity (positive ion, TIC) = 94.7%, tR: 10.78 min. IR

(cm^{-1}) 3353, 3262, 3152, 3064, 2719, 2215, 1916, 1626, 1603, 1554, 1519, 1465, 1419, 1300,

1275, 1241 1223 1099, 1017, 986, 965, 951, 845, 794, 765, 733, 719, 701, 665. Spectral data

were in agreement with literature values.[94]

Synthesis of (*Z*)-1-(4-bromophenyl)-2-nitroethen-1-amine (**114**).

The title compound was synthesized according to general procedure 2.1, using a solution of (*E*)-1-bromo-4-(2-nitrovinyl)benzene (1.18 g, 5.16 mmol) and methoxylamine HCl (538 mg, 6.44 mmol) in DMF (8 mL) in a 50 mL round-bottom flask, triethylamine (652 mg, 6.44 mmol), and a solution of potassium *tert*-butoxide (1.74 g, 15.47 mmol) in DMF (11 mL) to give *the title compound* (726 mg, 58%) as yellow crystals, mp 180-182 °C (ether); δ_H (500 MHz, DMSO-d$_6$)/ppm 9.36 (s, 1H, NH), 8.92 (s, 1H, NH), 7.69 (d, *J* = 8.6 Hz, 2H, H-2'/H-6'), 7.60 (d, *J* = 8.6 Hz, 2H, H-3'/H-5'), 6.84 (s, 1H); δ_C (126 MHz, DMSO-d$_6$)/ppm 157.4 (C), 132.8 (C), 132.3 (CH), 129.9 (CH), 125.6 (C), 109.7 (CH); anal. calcd. for $C_8H_7BrN_2O_2$: C, 39.53; H, 2.90; N, 11.53. Found: C, 39.42; H, 2.82; N, 11.49; LCMS purity (UV) = 97%, tR: 13.24 min. LCMS purity (positive ion, TIC) = 97.1%, tR 13.24 min. IR (cm^{-1}) 3356, 3258, 3212, 3179, 3150, 2233, 1615, 1589, 1537, 1461, 1403, 1247, 1122, 1069, 1011, 994, 947, 829, 769, 740, 730, 692, 656.

Synthesis of (*Z*)-1-(3-chlorophenyl)-2-nitroethen-1-amine (**115**).

The title compound was synthesized according to general procedure 2.1, using a solution of (*E*)-1-chloro-3-(2-nitrovinyl)benzene (1.31 g, 7.15 mmol) and methoxylamine HCl (747 mg, 8.94 mmol) in DMF (12 mL) in a 100 mL round-bottom flask, triethylamine (905 mg, 8.94 mmol), and a solution of potassium *tert*-butoxide (2.41 g, 21.45 mmol) in DMF (19 mL) to

give *the title compound* (782 mg, 55%) as a beige solid, mp 134-136 °C (ether); δ_H (500 MHz,

DMSO-d_6)/ppm 9.33 (br. s, 1H, NH), 8.94 (br. s, 1H, NH), 7.73 (t, J = 1.9 Hz, 1H, phenyl),

7.62 (ddt, J = 10.0, 7.9, 1.2 Hz, 2H, phenyl), 7.53 (t, J = 7.9 Hz, 1H, phenyl), 6.86 (s, 1H, H-

2); δ_C (126 MHz, DMSO-d_6)/ppm 157.0 (C), 135.6 (C), 134.0 (C), 131.7 (CH), 131.2 (CH),

127.7 (CH), 126.6 (CH), 109.9 (CH); Analysis calcd. for $C_8H_7ClN_2O_2$: C, 48.38; H, 3.55; N,

14.11. Found: C, 48.39; H, 3.40; N, 13.96; LCMS purity (UV) = 96%, tR: 13.05 min. LCMS

purity (positive ion, TIC) = 96.5%, tR: 13.05 min. IR (cm^{-1}) 3371, 3268, 3211, 3127, 3064,

2242, 1619, 1577, 1554, 1538, 1497, 1460, 1428, 1403, 1292, 1271, 1252, 1176, 1123, 1083,

985, 897, 868, 801, 785, 755, 708, 684, 655.

Synthesis of (*Z*)-1-nitroprop-1-en-2-amine (**119**).
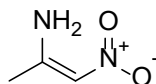
Enamine **119** was synthesized according to the procedure from Babievskii *et al* (1970).[83]

Nitromethane (22.83 g, 374.0 mmol) was added dropwise into 100 mL round-bottom flask

containing 1,1-dimethoxy-*N*,*N*-dimethylethan-1-amine (**117**) (24.93 g, 187.0 mmol) at room

temperature, and the reaction mixture was stirred for 24 hours. Residual nitromethane was

removed *in vacuo*. Without additional purification, the intermediate (*Z*)-*N*,*N*-dimethyl-1-

nitroprop-1-en-2-amine (**118**) was stirred at room temperature in a mixture of chloroform

(400 mL) and 7*N* methanolic ammonia (375 mL) for 72 hours. The crude material was

partitioned between EtOAc and water, then washed with brine (x2). The organic fraction was

dried over Na_2SO_4, and then the solvent was removed *in vacuo*. Trituration with cold diethyl

ether gave *the title compound* (13.82 g, 72%) as a red-orange wax, mp 96-97 °C (hexane) (lit.

mp 97-98 °C).[95] δ_H (500 MHz, Chloroform-*d*)/ppm 9.10 (br. s, 1H, NH), 6.50 (s, 1H, H-2),

6.12 (br. s, 1H, NH), 2.02 (s, 3H, CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 156.8 (C), 110.9 (CH), 20.1 (CH$_3$); anal. Calcd. for C$_3$H$_6$N$_2$O$_2$: C, 35.29; H, 5.92; N, 27.44. Found: C, 35.35; H, 5.90; N, 27.29; LCMS purity (UV) = 93%, tR: 4.72 min. LCMS purity (positive ion, TIC) = 92.9%, tR: 4.72 min. Spectral data were agreement with literature values.[95]

Synthesis of 2-nitroethene-1,1-diamine (**159**).
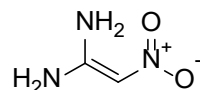
Enamine **159** was prepared according to a modified procedure from Stucky *et al* (1997).[86] In a 250 mL round-bottom flask, 1,1-bis(methylsulfanyl)-2-nitroethene (**158**) (5.8 g, 35.3 mmol) was dissolved in 7N methanolic ammonia (60 mL) at 50 °C, and the reaction mixture was stirred for 18 hours. The solvent was removed *in vacuo*. Trituration with cold methylene chloride gave *the title compound* (2.46 g, 67%) as yellow crystals, mp 198-201 °C (lit. mp 203-205 °C).[96] δ_H (600 MHz, DMSO-*d$_6$*)/ppm 7.11 (br. s, 4H, NH$_2$, with D$_2$O exchange), 6.29 (s, 1H, H-2); δ_C (151 MHz, DMSO-d6)/ppm 159.17, 99.03. Spectral data were in agreement with literature values.[96]

**General procedure 2.2A for the synthesis of substituted alkynones**

These butyn-2-one derivatives were prepared according to the procedure from Schmidt *et* al (2015).[97] *n*-BuLi (2.5M, 1.05 equiv.) was injected slowly through a septum into a round-bottom flask containing a stirred solution of substituted ethynylbenzene (1 equiv.) in THF at -78 °C, under argon. The reaction mixture was stirred at -78 °C for 15 minutes, at which point *N*-methoxy-*N*-methylacetamide (1.17 equiv.) was injected through the septum into the reaction vessel. The reaction mixture was stirred at -78 °C for 2.5 hours. The reaction was

quenched by the addition of 2.0 M HCl (2.5 mL). The reaction mixture was then partitioned

between water and diethyl ether and washed sequentially with sat. aqueous $NaHCO_3$ solution

(x2) and brine (x2). The organic fraction was dried over Na_2SO_4, and the solvent was

removed *in vacuo*. Purification by flash column chromatography on silica, eluting with

hexane-EtOAc (19:1 *v/v*) furnished the pure alkynone.

Synthesis of 4-(4-methoxyphenyl)but-3-yn-2-one (**144**).
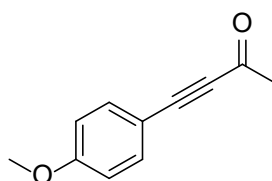
The title compound was synthesized according to general procedure 2.2A, using *n*-BuLi (3.7

mL, 2.5M), a solution of 1-ethynyl-4-methoxybenzene (1.19 g, 9.00 mmol) in THF (140 mL)

in a 250 mL round-bottom flask, and *N*-methoxy-*N*-methylacetamide (1.09 g, 10.50 mmol)

to give the *title compound* (1.15 g, 73%) as a golden wax, mp 24-26 °C (lit. mp 25-28 °C).[97]

δ_H (500 MHz, Chloroform-*d*)/ppm 7.49 (d, *J* = 8.4 Hz, 2H, H-2′/H-6′), 6.87 (d, *J* = 8.3 Hz,

2H, H-3′/H-5′), 3.81 (s, 3H, 4′-OCH$_3$), 2.41 (s, 3H, 1-CH$_3$); δ_C (126 MHz, Chloroform-

d)/ppm 184.60 (C), 161.65 (C), 135.09 (CH), 114.35 (CH), 111.61 (C), 91.47 (C), 88.22 (C),

55.38 (CH$_3$), 32.60 (CH$_3$); HRMS (POS ESI) anal. calcd. for $C_{11}H_{10}NaO_2$ [M+Na]$^+$: 197.06;

found 197.0573. IR (cm^{-1}) 3320, 2964, 2934, 2841, 2554, 2195, 2163, 2142, 1963, 1719,

1602 , 1569, 1508, 1460, 1442, 1357, 1279, 1250, 1150, 1109, 975, 832, 806, 697, 633, 579.

Spectral data were in agreement with literature values.[97,98]

Synthesis of 4-(4-fluorophenyl)but-3-yn-2-one (**145**).
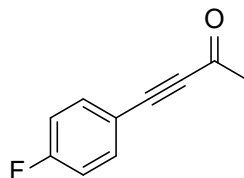
The title compound was synthesized according to general procedure 2.2A, using *n*-BuLi (3.2 mL, 2.5M), a solution of 1-ethynyl-4-fluorobenzene (913 mg, 7.60 mmol) in THF (120 mL) in a 250 mL round-bottom flask, and *N*-methoxy-*N*-methylacetamide (917 mg, 8.90 mmol) to give the *title compound* (726 mg, 59%) as a yellow oil. δ_H (500 MHz, Chloroform-*d*)/ppm 7.56 (d, 2H, H-2′/H-6′), 7.07 (d, 2H, H-3′/H-5′), 2.43 (s, 1H, CH). HRMS (POS ESI) anal. calcd. for $C_{10}H_7FNaO$ $[M+Na]^+$: 185.04; found 185.0373. Spectral data were in agreement with literature values.[99]

General procedure 2.2B for the synthesis of substituted alkynones

These alkynones were prepared according to a modified procedure from Hsieh and colleagues.[100] *n*-BuLi (2.5 M, 1.1 equiv.) was injected slowly through a septum into a round-bottom flask containing a stirred solution of ethynylbenzene (1 equiv.) in THF at -78 °C, under argon. The reaction mixture was stirred at -78 °C for 1 hour, at which point ethyl trifluoroacetate (1.5 equiv.) was injected through the septum into the reaction vessel. The reaction mixture was stirred at -78 °C for 2.5 hours. The reaction mixture was then partitioned between water and diethyl ether and washed sequentially with sat. aqueous NH_4Cl solution (30 mL x 2) and brine (30 mL x 2). The organic fraction was dried over $MgSO_4$, and the solvent was removed *in vacuo*. Purification by flash column chromatography on silica, eluting with hexane-EtOAc (9:1 *v/v*) furnished the pure alkynone.

Synthesis of 1,1,1-trifluoro-4-phenylbut-3-yn-2-one (**146**).
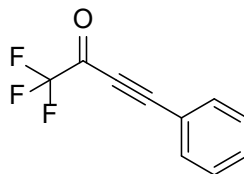
The title compound was synthesized according to general procedure 2.2B, using *n*-BuLi (1.3

mL, 3.30 mmol), a solution of ethynylbenzene (306 mg, 3.00 mmol) in THF (6 mL) in a 50

mL round-bottom flask, and ethyl trifluoroacetate (640 mg, 4.50 mmol) to give the *title*

compound (437 mg, 74%) as a golden oil; δ_H (500 MHz, Chloroform-*d*)/ppm (d, J = 7.8 Hz,

2H, H-2′/H-6′), 7.61 – 7.54 (m, 1H, H-4′), 7.45 (t, J = 7.8 Hz, 2H, H-3′/H-5′). IR (cm^{-1}) 3676,

3398, 3063, 2935, 2365, 2199, 2164, 1999, 1702, 1598, 1541, 1491, 1447, 1358, 1263, 1249,

1155, 1123, 1095, 1071, 1048, 998, 896, 823, 758, 686, 641. Spectral data were in agreement

with literature values.[100]

Synthesis of 1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-one (**147**).
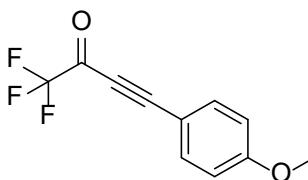
The title compound was synthesized according to general procedure 2.2B, using *n*-BuLi (4.1

mL, 10.25 mmol), a solution of 1-ethynyl-4-methoxybenzene (1.04 g, 7.86 mmol) in THF

(12 mL) in a 100 mL round-bottom flask, and ethyl trifluoroacetate (1.12 g, 7.86 mmol) to

give the *title compound*

(737 mg, 41%) as a golden oil; δ_H (500 MHz, Chloroform-*d*)/ppm 7.63 (d, J = 9.0 Hz, 2H, H-2′/H-6′), 6.94 (d, J = 8.9 Hz, 2H, H-3′/H-5′), 3.87 (s, 3H, 4′-CH₃). Spectral data were in agreement with literature values.[101]

General procedure 2.2C for the synthesis of substituted alkynones

These alkynones were synthesized according to a procedure from the Bagley group.[102] *n*-BuLi (2.5M, 1.05 equiv.) was injected slowly through a septum into a round-bottom flask containing a stirred solution of ethynylbenzene (1.05 equiv.) in THF at -78 °C, under argon. The reaction mixture was stirred at -78 °C for 30 minutes and was then added dropwise into a solution containing ethyl 2-(methoxy(methyl)amino)-2-oxoacetate (1 equiv.) in THF. The reaction mixture was stirred at -78 °C for 2.5 hours. The reaction mixture was poured over ice (20 g) and partitioned between 20% H_3PO_4 solution (60 mL) and diethyl ether (60 mL) and washed sequentially with 10% H_3PO_4 solution (x2) and brine (x2). The organic fraction was dried over $MgSO_4$, and the solvent was removed *in vacuo*. Purification by flash column chromatography on silica, eluting with hexane-EtOAc (6:1 *v/v*) furnished the pure alkynone.

Synthesis of ethyl 2-oxo-4-phenylbut-3-ynoate (**148**).
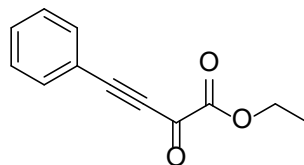
This compound was synthesized according to General Procedure 2.2C, using *n*-BuLi (5 mL, 2.5M), a solution of ethynylbenzene (1.27 g, 12.40 mmol) in THF (30 mL) in a 250-mL round-bottom flask, and a solution containing ethyl 2-(methoxy(methyl)amino)-2-oxoacetate (1.91 g, 11.85 mmol) in THF (120 mL). Purification by flash column chromatography on

silica, eluting with hexane-EtOAc (6:1 *v/v*) gave the *title compound* (1.07 g, 45%) as a viscous yellow oil. HRMS (POS ESI) anal. calcd. for $C_{12}H_{10}NaO_3$ [M+Na]$^+$: 225.05; found 225.0522. IR (cm^{-1}) 3334, 2981, 2237, 1742, 1592, 1537, 1444, 1371, 1337, 1297, 1261, 1217, 1095, 1052, 867, 833, 759, 691. Spectral data were in agreement with literature values.[102]

Synthesis of ethyl 4-(4-methoxyphenyl)-2-oxobut-3-ynoate (**149**).
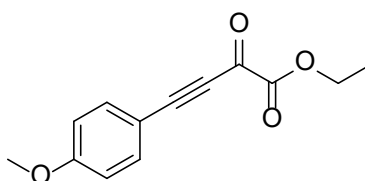
The title compound was synthesized according to general procedure 2.2C, using *n*-BuLi (2.5 mL, 2.5M), a solution of 1-ethynyl-4-methoxybenzene (820 mg, 6.20 mmol) in THF (15 mL) in a 100 mL round-bottom flask, and a solution of ethyl 2-(methoxy(methyl)amino)-2-oxoacetate (1.00 g, 6.20 mmol) in THF (60 mL) giving the *title compound* (591 mg, 41%) as a viscous, orange oil; δ_H (600 MHz, Chloroform-*d*)/ppm 7.63 (d, *J* = 8.8 Hz, 2H, H-2′/H-6′), 6.92 (d, *J* = 8.8 Hz, 2H, H-3′/H-5′), 4.40 (q, *J* = 7.1 Hz, 2H, 1-CO$_2$*CH$_2$*CH$_3$), 3.86 (s, 3H, 4′-OCH$_3$), 1.42 (t, *J* = 7.2 Hz, 3H, 1-CO$_2$CH$_2$*CH$_3$*); δ_C (151 MHz, Chloroform-d)/ppm 164.10, 132.40, 130.41, 114.43, 113.77, 55.66, 55.50; HRMS (POS ESI) anal. calcd. for $C_{13}H_{12}NaO_4$ [M+Na]$^+$: 255.06; found 255.0628. Spectral data were in agreement with literature values.[103]

Procedure 2.2D for the synthesis of substituted alkynones

Synthesis of 1-phenylprop-2-yn-1-one (**150**).
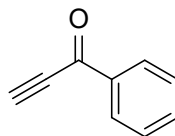
The title compound was synthesized according to the procedure developed by Ge and colleagues (2012).[104] Dess-Martin periodinane (14.12 g, 33.3 mmol) was added to a stirred solution of 1-phenyl-2-propyn-1-ol (4.00 g, 30.3 mmol) in methylene chloride (50 mL) at 0 °C. The solution was stirred for 18 hours, gradually warming to room temperature. The reaction mixture was filtered through a silica pad, the pad was washed gently with methylene chloride, and the pooled organic filtrate was washed sequentially with sat. $NaHCO_3$ solution (x2) and brine (x2), then dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude solid was purified by flash column chromatography on silica, eluting with hexane-EtOAc (20:1 *v/v*), which gave the *title compound* (3.18 g, 81%) as off-white plates, mp 48-50 °C (lit. mp 49-50 °C)[102]; δ_H (500 MHz, Chloroform-*d*)/ppm 8.16 (d, $J = 8.0$ Hz, 2H, H-2′/H-6′), 7.67 – 7.59 (m, 1H, H-4′), 7.49 (t, $J = 8.0$ Hz, 2H, H-3′/H-5′), 3.45 (s, 1H, H-3); δ_C (151 MHz, Chloroform-d)/ppm 177.43 (C=O), 136.10 (C), 134.56 (CH), 129.71 (CH), 128.69 (CH), 80.84 (CH), 80.24 (C); HRMS (POS ESI) anal. calcd. for C_9H_7O [M+H]$^+$: 131.05; found 131.0505. Spectral data were in agreement with literature values.[102]

General procedure 2.3 for the synthesis of β-nitropyridines

In a 25-mL round-bottom flask, a solution of the *β*-nitroenamine (1.0 mmol), ethynylketone (1.5 mmol), and ZnBr$_2$ (34 mg, 0.15 mmol) in toluene (6 mL) was stirred at reflux for 24 hours. The toluene was removed *in vacuo*, and the crude material was dissolved in EtOAc. The resulting slurry was filtered through silica, and the filtrate was washed sequentially with water, sat. aqueous NaHCO$_3$ solution (x2) and brine (x2), dried over Na$_2$SO$_4$, and evaporated *in vacuo*. Purification by flash column chromatography on silica, gave the pure *β*-nitropyridine.

Synthesis of 6-methyl-3-nitro-2-phenylpyridine (**120**).
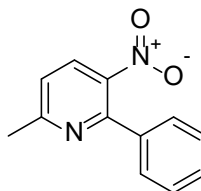
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **108** (164 mg, 1.0 mmol) and 3-butyn-2-one **105** (102 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*), gave the *title compound* (152 mg, 71%) as pale yellow crystals, mp 66-67 °C (hexane); δ_H (500 MHz, Chloroform-*d*)/ppm 8.07 (d, *J* = 8.3 Hz, 1H, H-4), 7.58 – 7.52 (m, 2H, H-2′/H-6′), 7.50 – 7.43 (m, 3H, H-3′/H-4′/H-5′), 7.27 (d, *J* = 8.3 Hz, 1H, H-5), 2.71 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 162.3 (C), 152.5 (C), 144.2 (C), 136.8 (C), 132.5 (CH), 129.5 (CH), 128.6 (CH), 128.1 (CH), 121.9 (CH), 24.8 (CH$_3$); anal. calcd. for C$_{12}$H$_{10}$N$_2$O$_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.17; H, 4.78; N, 12.98.; LCMS purity (UV) = 95%, tR: 16.63 min. LCMS purity (positive ion, TIC) = 95.0%, tR: 16.63 min. IR (cm^{-1}) 3076,

3061, 2988, 2864, 2163, 1980, 1936, 1684, 1584, 1569, 1514, 1435, 1370, 1354, 1321, 1242, 1217, 1154, 1110, 1081, 1027, 1003, 986, 930, 889, 841, 827, 785, 749, 731, 698.

Synthesis of 6-methyl-3-nitro-2,4-diphenylpyridine (**124**).
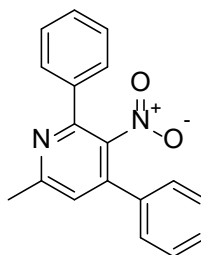
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **108** (164 mg, 1.0 mmol) and 4-phenyl-3-butyn-2-one (**123**) (216 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (208 mg, 72%) as pale yellow crystals, mp 125−127 °C (MeOH); δ_H (500 MHz, Chloroform-*d*)/ppm 7.65 – 7.58 (m, 2H, H-2′/H-6′), 7.46 (q, *J* = 3.1 Hz, 6H, phenyl), 7.43 – 7.36 (m, 2H, H-2″/H-6″), 7.22 (s, 1H, H-5), 2.71 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 160.0 (C), 150.6 (C), 144.5 (C), 143.0 (C), 136.1 (C), 134.4 (C), 129.7 (CH), 129.6 (CH), 129.0 (CH), 128.8 (CH), 128.0 (CH), 127.6 (CH), 123.4 (CH), 24.6 (CH$_3$); anal. calcd. for C$_{18}$H$_{14}$N$_2$O$_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.36; H, 4.53; N, 9.55.; LCMS purity (UV) = 94%, t$_R$ 21.55 min. LCMS purity (positive ion, TIC) = 93.8%, t$_R$ 21.54 min. IR (cm^{-1}) 3063, 2924, 2202, 1963, 1669, 1607, 1590, 1579, 1551, 1493, 1445, 1403, 1380, 1365, 1317, 1261, 1212, 1181, 1158, 1078, 1053, 1029, 999, 927, 911, 889, 879, 868, 837, 800, 762, 731, 696, 653.

Synthesis of 4-ethyl-6-methyl-3-nitro-2-phenylpyridine (**126**).
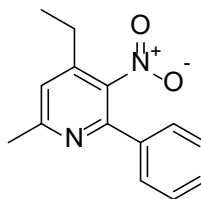
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine 108(164 mg, 1.0 mmol) and 3-hexyn-2-one (**125**) (144 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et2O (3:1 *v/v*) gave the *title compound* (27 mg, 11%) as yellow solid; δ_H (500 MHz, Chloroform-*d*)/ppm 7.60 – 7.57 (m, 2H, H-2'/H-6'), 7.46 – 7.42 (m, 3H, H-3'/H-4'/H-5'), 7.13 (s, 1H, H-5), 2.68 (q, *J* = 7.5 Hz, 2H, 4-*CH₂*CH₃), 2.65 (s, 3H, 6-CH₃), 1.31 (t, *J* = 7.6 Hz, 3H, 4-CH₂*CH₃*); δ_C (126 MHz, Chloroform-*d*)/ppm 159.9 (C), 150.3 (C), 145.7 (C), 145.3 (C), 136.3 (C), 129.5 (CH), 128.7 (CH), 127.9 (CH), 122.3 (CH), 24.5 (CH), 24.1 (CH₃), 13.9 (CH₃); anal. calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. HRMS (POS EI) analysis calcd. for $C_{14}H_{14}N_2O_2$ (m/z): 242.11; found 242.1055. LCMS purity (UV) = 93%, tR: 19.93 min. LCMS purity (positive ion, TIC) = 93.3%, tR: 19.93 min. IR (cm⁻¹) 2976, 2928, 1739, 1595, 1580, 1558, 1526, 1498, 1451, 1414, 1365, 1341, 1260, 1198, 1157, 1077, 1031, 918, 872, 835, 799, 761, 732

Synthesis of 2-(3-chlorophenyl)-6-methyl-3-nitropyridine (**127**).
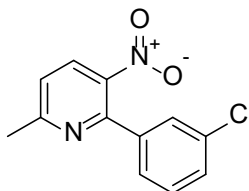
The title compound was synthesized according to general procedure 2.3, using β-nitroenamine **115** (199 mg, 1.0 mmol) and 3-butyn-2-one (**105**) (102 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 v/v) gave the *title compound* (178 mg, 72%) as yellow crystals, mp 109-110 °C (MeOH); δ_H (500 MHz, Chloroform-*d*)/ppm 8.11 (d, J = 8.3 Hz, 1H, H-4), 7.57 (s, 1H, H-2′), 7.43 (dt, J = 7.3, 2.0 Hz, 1H, H-6′), 7.39 – 7.33 (m, 2H, H-4′/H-5′), 7.30 (d, J = 8.3 Hz, 1H, H-5), 2.70 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 162.6 (C), 151.2 (C), 144.0 (C), 138.6 (C), 134.6 (C), 132.7 (CH), 129.8 (CH), 129.6 (CH), 128.4 (CH), 126.2 (CH), 122.5 (CH), 24.7 (CH$_3$); anal. calcd. for C$_{12}$H$_9$ClN$_2$O$_2$: C, 57.96; H, 3.65; N, 11.27. Found: C, 57.87; H, 3.75; N, 11.08; LCMS purity (UV) = 94%, tR: 19.02 min. LCMS purity (positive ion, TIC) = 94.5%, tR: 19.01 min. IR (cm^{-1}) 3081, 2923, 2859, 2161, 1967, 1936, 1760, 1709, 1588, 1577, 1564, 1523, 1508, 1480, 1454, 1412, 1375, 1353, 1289, 1266, 1244, 1220, 1159, 1123, 1079, 1055, 1038, 1000, 988, 970, 904, 881, 834, 794, 770, 754, 729, 690.

Synthesis of 2-(3-chlorophenyl)-6-methyl-3-nitro-4-phenylpyridine (**128**).
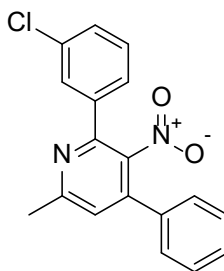
The title compound was synthesized according to general procedure 2.3, using β-nitroenamine **115** (199 mg, 1.0 mmol) and 4-phenyl-3-butyn-2-one (**123**) (216 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 v/v) gave the *title compound* (227 mg, 70%) as orange crystals, mp 112-114 °C (MeOH); δ_H (500

MHz, Chloroform-*d*)/ppm 7.67 (s, 1H, H-2′), 7.48 – 7.41 (m, 5H, phenyl), 7.41 – 7.33 (m, 3H, phenyl), 7.25 (s, 1H, H-5), 2.71 (s, 3H, 6-CH$_3$).; δ_C (126 MHz, Chloroform-*d*)/ppm 160.26 (C), 149.06 (C), 144.48 (C), 143.18 (C), 137.75 (C), 134.85 (C), 134.13 (C), 130.02 (CH), 129.85 (CH), 129.70 (CH), 129.09 (CH), 128.59 (d, J = 3.3 Hz, CH), 127.59 (CH), 125.89 (CH), 123.98 (d, J = 3.4 Hz, CH), 24.60 (CH$_3$); anal. calcd. for C$_{18}$H$_{13}$ClN$_2$O$_2$: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.45; H, 4.04; N, 8.82; LCMS purity (UV) = 97%, tR: 23.89 min. LCMS purity (positive ion, TIC) = 97.1%, tR: 23.88 min. IR (cm^{-1}) 3071, 2963, 2885, 2201, 1963, 1894, 1767, 1589, 1566, 1543, 1526, 1496, 1478, 1449, 1428, 1399, 1379, 1318, 1260, 1213, 1187, 1167, 1094, 1079, 1057, 1025, 921, 884, 879, 855, 835, 803, 803, 787, 763, 739, 722.

Synthesis of 2-(3-chlorophenyl)-4-ethyl-6-methyl-3-nitropyridine (**129**).
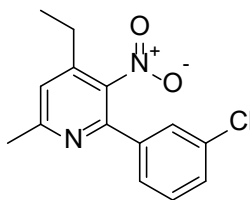
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **1115** (199 mg, 1.0 mmol) and 3-hexyn-2-one (**125**) (144 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (59 mg, 11%) as a yellow solid; δ_H (500 MHz, Chloroform-*d*)/ppm 7.60 (s, 1H, H-2′), 7.44 – 7.38 (m, 2H, phenyl), 7.38 – 7.32 (m, 1H, phenyl), 7.15 (s, 1H, H-5), 2.67 (q, J = 7.5 Hz, 2H, 4-*CH$_2$*CH$_3$), 2.64 (s, 3H, 6-CH$_3$), 1.30 (t, J = 7.6 Hz, 3H, 4-CH$_2$*CH$_3$*); δ_C (126 MHz, Chloroform-*d*)/ppm 160.2 (C), 148.8 (C), 145.5 (C), 137.9 (C), 134.8 (C), 130.0 (C), 129.7 (CH), 128.4 (CH), 128.4 (CH), 125.8 (CH), 122.9 (CH), 122.8

(CH), 88.3 (CH), 24.6 (CH), 24.5 (CH), 24.1 (CH$_3$), 14.0 (CH$_2$), 13.9 (CH$_3$); anal. calcd. for

C$_{14}$H$_{13}$ClN$_2$O$_2$: C, 60.77; H, 4.74; N, 10.12. LCMS purity (UV) = 87%, tR: 22.68 min. LCMS

purity (positive ion, TIC) = 86.8%, tR: 22.66 min. IR (cm^{-1}) 2928, 1741, 1593, 1569, 1557,

1526, 1480, 1434, 1412, 1363, 1260, 1198, 1159, 1082, 1035, 999, 932, 878, 837, 802, 784,

724

<div align="center">Synthesis of 2-(4-fluorophenyl)-6-methyl-3-nitropyridine (130).</div>
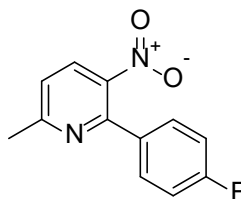
The title compound was synthesized according to general procedure 2.3, using β-

nitroenamine **113** (182 mg, 1.0 mmol) and 3-butyn-2-one (**105**) (102 mg, 1.5 mmol).

Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*)

gave the *title compound* (146 mg, 63%) as pale yellow crystals, mp 128-129 °C (hexane); δ_H

(500 MHz, Chloroform-*d*)/ppm 8.07 (d, *J* = 8.3 Hz, 1H, H-4), 7.59 – 7.51 (m, 2H, H-2′/H-

6′), 7.27 (d, *J* = 8.3 Hz, 1H, H-5), 7.20 – 7.11 (m, 2H, H-3′/H-5′), 2.70 (s, 3H, 6-CH$_3$); δ_C

(126 MHz, Chloroform-*d*)/ppm 163.60 (d, *J* = 249.6 Hz, C), 162.39 (C), 151.41 (C), 144.06

(C), 132.84 (d, *J* = 3.6 Hz, C), 132.61 (CH), 130.19 (d, *J* = 8.6 Hz, CH), 122.02 (CH), 115.74

(d, *J* = 21.9 Hz, CH), 24.73 (CH$_3$); anal. calcd. for C$_{12}$H$_9$FN$_2$O$_2$: C, 62.07; H, 3.91; N, 12.06.

Found: C, 62.05; H, 4.00; N, 11.99; LCMS purity (UV) = 98%, tR: 17.20 min. LCMS purity

(positive ion, TIC) = 97.6%, tR: 17.19 min. IR (cm^{-1}) 3079, 3061, 2925, 2852, 1954, 1898,

1693, 1606, 1589, 1571, 1505, 1440, 1412, 1370, 1348, 1303, 1287, 1220, 1165, 1155, 1104,

1045, 1016, 962, 890, 839, 806, 773, 733, 712, 702, 683.

Synthesis of 2-(4-fluorophenyl)-6-methyl-3-nitro-4-phenylpyridine (**131**).
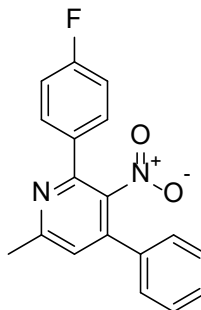
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **113** (182 mg, 1.0 mmol) and 4-phenyl-3-butyn-2-one (**123**) (216 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (88 mg, 29%) as an orange solid; δ_H (500 MHz, Chloroform-*d*)/ppm 7.66 – 7.58 (m, 2H, H-2′/H-6′), 7.48 – 7.43 (m, 3H, H-3″/H-4″/H-5″), 7.41 – 7.36 (m, 2H, H-2″/H-6″), 7.22 (s, 1H, H-5), 7.14 (t, J = 8.7 Hz, 2H, H-3′/H-5′), 2.70 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 163.66 (d, *J* = 249.9 Hz, C), 160.06 (C), 149.42 (C), 144.47 (C), 143.08 (C), 134.23 (C), 132.17 (d, *J* = 3.4 Hz, C), 130.10 (d, *J* = 8.6 Hz, CH), 129.62 (CH), 129.04 (CH), 127.58 (CH), 123.53 (CH), 115.91 (d, *J* = 21.9 Hz, CH), 24.58 (CH$_3$); anal. calcd. for C$_{18}$H$_{13}$FN$_2$O$_2$: C, 70.12; H, 4.25; N, 9.09. Found: C, 70.20; H, 4.35; N, 8.88; LCMS purity (UV) = 90%, tR: 21.90 min. LCMS purity (positive ion, TIC) = 89.8%, tR: 21.89 min. IR (cm^{-1}) 3062, 2926, 2204, 1671, 1607, 1599, 1589, 1528, 1512, 1495, 1447, 1424, 1381, 1363, 1301, 1226, 1160, 1099, 1078, 1053, 1015, 1001, 910, 879, 844, 833, 795, 762, 731.

Synthesis of 2-(4-fluorophenyl)-4-ethyl-6-methyl-3-nitropyridine (**132**).
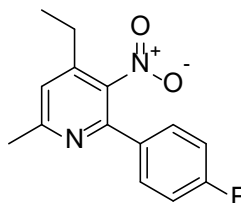
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **113** (182 mg, 1.0 mmol) and 3-hexyn-2-one (**125**) (144 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (19 mg, 7%) as a yellow gum; δ_H (500 MHz, Chloroform-*d*)/ppm 7.58 – 7.54 (m, 2H, H-2′/H-6′), 7.15 – 7.11 (m, 2H, H-3′/H-5′), 7.10 (s, 1H, H-5), 2.66 (q, *J* = 7.6 Hz, 2H, 4-*CH$_2$*CH$_3$), 2.63 (s, 3H, 6-CH$_3$), 1.29 (t, *J* = 7.6 Hz, 3H, 4-CH$_2$*CH$_3$*); δ_C (126 MHz, Chloroform-*d*)/ppm 163.58 (d, *J* = 249.8 Hz, C), 160.00 (C), 149.11 (C), 145.56 (C), 145.40 (C), 132.32 (d, *J* = 3.4 Hz, C), 129.95 (d, *J* = 8.7 Hz, CH), 122.42 (CH), 115.87 (d, *J* = 21.7 Hz, CH), 24.56 (CH$_2$), 24.07 (CH$_3$), 13.96 (CH$_3$); anal. calcd. for C$_{14}$H$_{13}$FN$_2$O$_2$: C, 64.61; H, 5.03; N, 10.76. LCMS purity (UV) = 93%, tR: 20.52 min. LCMS purity (positive ion, TIC) = 92.9%, tR: 20.53 min. HRMS (POS EI) analysis calcd. for C$_{12}$H$_9$FN$_2$O$_2$ (m/z): 260.10; found 260.0961. IR (cm^{-1}) 2927, 1907, 1740, 1601, 1557, 1524, 1513, 1465, 1430, 1404, 1368, 1304, 1261, 1223, 1203, 1163, 1099, 1070, 1035, 1018, 947, 927, 881, 868, 847, 837, 791, 741, 718.

Synthesis of 2-(4-bromophenyl)-6-methyl-3-nitropyridine (**133**).
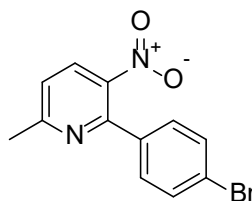
The title compound was synthesized according to general procedure 2.3, using β-nitroenamine **114** (243 mg, 1.0 mmol) and 3-butyn-2-one (**105**) (102 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 v/v) gave the *title compound* (216 mg, 74%) as orange crystals, mp 106-108 °C (hexane); δ_H (500 MHz, Chloroform-d)/ppm 8.09 (d, $J = 8.3$ Hz, 1H, H-4), 7.60 (d, $J = 8.7$ Hz, 2H, H-2′/H-6′), 7.43 (d, $J = 8.6$ Hz, 2H, H-3′/H-5′), 7.29 (d, $J = 8.3$ Hz, 1H, H-5), 2.70 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-d)/ppm 162.6 (C), 151.4 (C), 144.0 (C), 135.8 (C), 132.7 (CH), 131.8 (CH), 129.8 (CH), 124.1 (C), 122.3 (CH), 24.7 (CH$_3$); anal. calcd. for C$_{12}$H$_9$BrN$_2$O$_2$: C, 49.17; H, 3.09; N, 9.56. Found: C, 49.12; H, 3.05; N, 9.43; LCMS purity (UV) = 95%, tR: 19.54 min. LCMS purity (positive ion, TIC) = 94.7%, tR: 19.55 min. IR (cm^{-1}) 3089, 2924, 2864, 2163, 1941, 1909, 1673, 1595, 1577, 1564, 1542, 1513, 1490, 1443, 1400, 1352, 1306, 1292, 1276, 1238, 1219, 1186, 1157, 1107, 1070, 1047, 1010, 971, 890, 836, 823, 772, 736, 719, 708.

Synthesis of 2-(4-Bromophenyl)-6-Methyl-3-Nitro-4-Phenylpyridine (**134**).
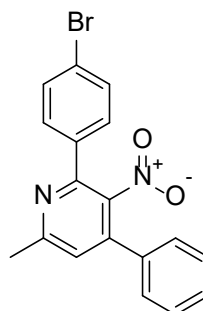
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **114** (243 mg, 1.0 mmol) and 4-phenyl-3-butyn-2-one (**123**) (216 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (216 mg, 74%) as an orange solid; δ_H (500 MHz, Chloroform-*d*)/ppm 7.59 (d, *J* = 8.5 Hz, 2H, H-2′/H-6′), 7.49 (d, *J* = 8.3 Hz, 2H, H-3′/H-5′), 7.49 – 7.42 (m, 3H, H-3″/H-4″/H-5″), 7.42 – 7.35 (m, 2H, H-2″/H-6″), 7.24 (s, 1H, H-5), 2.70 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 160.2 (C), 149.4 (C), 144.4 (C), 143.2 (C), 135.0 (C), 134.2 (C), 132.0 (CH), 129.7 (CH), 129.6 (CH), 129.1 (CH), 127.6 (CH), 124.4 (C), 123.7 (CH), 24.6 (CH$_3$); anal. calcd. for C$_{18}$H$_{13}$BrN$_2$O$_2$: C, 58.56; H, 3.55; N, 7.59. Found: C, 58.39; H, 3.68; N, 7.47; LCMS purity (UV) = 95%, tR: 24.27 min. LCMS purity (positive ion, TIC) = 94.6%, tR: 24.26 min.

Synthesis of 6-methyl-3-nitro-2-[4-(propan-2-yl)phenyl]pyridine (**135**).
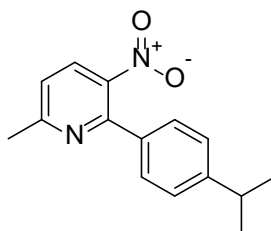
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **110** (206 mg, 1.0 mmol) and 3-butyn-2-one (**105**) (102 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (182 mg, 71%) as an orange solid, mp 46-51 °C (MeOH); δ_H (500 MHz, Chloroform-*d*)/ppm 8.03 (d, *J* = 8.3 Hz, 1H, H-4), 7.48 (d, *J* = 8.2 Hz, 2H, H-2′/H-6′), 7.31 (d, *J* = 8.1 Hz, 2H, H-3′/H-5′), 7.22 (d, *J* = 8.2 Hz, 1H, H-5), 2.95 (hept, *J* = 6.9 Hz, 1H, 4′-*CH*(CH$_3$)$_2$), 2.68 (s, 3H, 6-CH$_3$), 1.27 (d, J = 7.0 Hz, 6H, 4′-CH*(CH$_3$)$_2$*); δ_C (126 MHz,

Chloroform-*d*)/ppm 162.22 (C), 152.52 (C), 150.48 (C), 144.08 (C), 134.13 (CH), 132.49 (d, *J* = 3.3 Hz, CH), 128.06 (CH), 126.87 (CH), 121.60 (d, *J* = 2.5 Hz, CH), 34.01 (CH$_2$), 24.80 (d, *J* = 2.9 Hz, CH$_3$), 23.84 (CH$_3$); anal. calcd. for C$_{15}$H$_{16}$N$_2$O$_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.28; H, 6.43; N, 10.85. LCMS purity (UV) = 98%, tR: 21.53 min. LCMS purity (positive ion, TIC) = 98.3%, tR: 21.53 min. IR (cm^{-1}) 3072, 2964, 2929, 2869, 2902, 1921, 1689, 1612, 1579, 1567, 1516, 1467, 1445, 1417, 1376, 1354, 1301, 1292, 1279, 1238, 1219, 1188, 1156, 1117, 1107, 1058, 991, 972, 956, 921, 889, 844, 832, 775, 762, 745

Synthesis of 2-[4-(benzyloxy)phenyl]-6-methyl-3-nitropyridine (**136**).
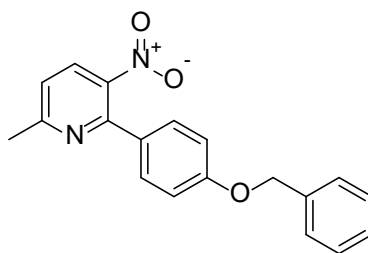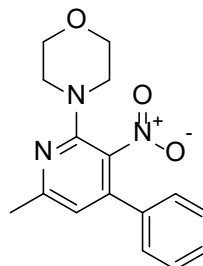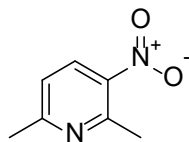

The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **111** (270 mg, 1.0 mmol) and 3-butyn-2-one (**105**) (102 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v*/*v*) gave the *title compound* (195 mg, 61%) as a bright yellow crystals, mp 110−111 °C (MeOH); δ$_H$ (500 MHz, Chloroform-*d*)/ppm 8.01 (d, *J* = 8.2 Hz, 1H, H-4), 7.52 (d, *J* = 8.6 Hz, 2H, H-2′/H-6′), 7.44 (d, *J* = 7.1 Hz, 2H, H-2″/H-6″), 7.40 (t, *J* = 7.4 Hz, 2H, H-3″/H-5″), 7.37 − 7.30 (m, 1H, H-4″), 7.20 (d, *J* = 8.3 Hz, 1H, H-5), 7.05 (d, *J* = 8.6 Hz, 2H, H-3′/H-5′), 5.12 (s, 2H, 4′-OCH$_2$), 2.68 (s, 3H, 6-CH$_3$); δ$_C$ (126 MHz, Chloroform-*d*)/ppm 162.12 (C), 160.01 (C), 151.88 (C), 143.93 (C), 136.61 (C), 132.56 (CH), 129.69 (CH), 129.16 (C), 128.62 (CH), 128.06 (CH), 127.47 (CH), 121.35 (CH), 115.09 (CH), 70.04 (CH$_2$), 24.80 (CH$_3$); anal. calcd. for C$_{19}$H$_{16}$N$_2$O$_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.05; H, 5.13; N, 8.72; LCMS purity

(UV) = 94%, tR: 21.56 min. LCMS purity (positive ion, TIC) = 94.4%, tR: 21.55 min. IR

(cm^{-1}) 3076, 2952, 1989, 1916, 1693, 1609, 1587, 1568, 1514, 1468, 1457, 1442, 1418, 1393,

1373, 1346, 1316, 1288, 1236, 1186, 1119, 1108, 1082, 1047, 1008, 1001, 919, 890, 863, 837,

816, 776, 752, 699.

Synthesis of 2-[4-(benzyloxy)phenyl]-6-methyl-3-nitro-4-phenylpyridine (**137**).
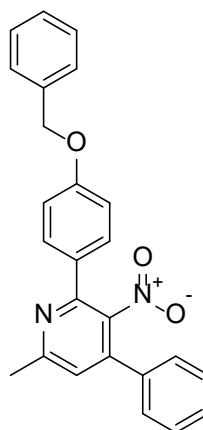
The title compound was synthesized according to general procedure 2.3, using *β*-

nitroenamine **111** (270 mg, 1.0 mmol) and 4-phenyl-3-butyn-2-one (**123**)   (216 mg, 1.5

mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O

(3:1 *v/v*) gave the *title compound* (247 mg, 62%) as pale yellow crystals, mp 125−126 °C

(MeOH); δ_H (500 MHz, Chloroform-*d*)/ppm 7.57 (d, *J* = 8.9 Hz, 2H, H-2′/H-6′), 7.48 – 7.42

(m, 5H, phenyl), 7.41 – 7.36 (m, 4H, phenyl), 7.36 – 7.31 (m, 1H, H-4″), 7.17 (s, 1H, H-5),

7.04 (d, *J* = 8.8 Hz, 2H, H-3′/H-5′), 5.11 (s, 2H, 4′-OCH$_2$), 2.69 (s, 3H, 6-CH$_3$); δ_C (126 MHz,

Chloroform-*d*)/ppm 160.0 (C), 159.8 (C), 150.0 (C), 144.3 (C), 143.0 (C), 136.6 (C), 134.5

(C), 129.5 (CH), 129.5 (CH), 129.0 (CH), 128.7 (CH), 128.6 (C), 128.1 (CH), 127.6 (CH),

127.5 (CH), 122.9 (CH), 115.2 (CH), 70.0 (CH$_2$), 24.6 (CH$_3$); HRMS (POS ESI) calcd. for

C$_{25}$H$_{21}$N$_2$O$_3^+$ (M+H): 397.1547, found 397.1547; anal. calcd. for C$_{25}$H$_{20}$N$_2$O$_3$: C, 75.74; H,

5.09; N, 7.07. Found: C, 75.61; H, 5.04; N, 7.02; LCMS purity (UV) = 91%, tR: 25.39 min.

LCMS purity (positive ion, TIC) = 90.8%, tR: 25.39 min. IR (cm^{-1}) 3076, 1609, 1589, 1568,

1514, 1470, 1442, 1418, 1393, 1368, 1347, 1316, 1289, 1236, 1186, 1119, 1081, 1048, 1006,

947, 920, 882, 864, 838, 816, 798, 776, 763, 750, 699.

Synthesis of 2-(furan-2-yl)-6-methyl-3-nitropyridine (**138**).
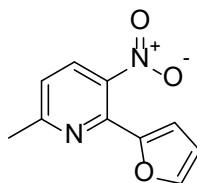
The title compound was synthesized according to general procedure 2.3, using *β*-

nitroenamine **112** (154 mg, 1.0 mmol), 3-butyn-2-one (**105**) (102 mg, 1.5 mmol). Purification

by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title*

compound (103 mg, 50%) as pale yellow crystals, mp 83-87°C (hexane); δ_H (500 MHz,

Chloroform-*d*)/ppm 7.85 (d, *J* = 8.3 Hz, 1H, H-4), 7.55 (dd, *J* = 1.8, 0.8 Hz, 1H, H-4′), 7.17

– 7.12 (m, 2H, H-5/H-4′), 6.55 (dd, *J* = 3.5, 1.8 Hz, 1H, H-5′), 2.65 (s, 3H, 6-CH$_3$); δ_C (126

MHz, Chloroform-*d*)/ppm 161.71 (C), 149.49 (C), 144.91 (C), 140.62 (C), 131.92 (CH),

121.55 (CH), 113.15 (CH), 112.01 (CH), 109.99 (CH), 24.62 (CH$_3$); anal. calcd. for

C$_{10}$H$_8$N$_2$O$_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.71; H, 4.04; N, 13.65.; LCMS purity

(UV) = 98%, tR: 15.47 min. LCMS purity (positive ion, TIC) = 98.2%, tR: 15.47 min. IR

(cm^{-1}) 3145, 3080, 2926, 2855, 1947, 1607, 1565, 1517, 1488, 1432, 1378, 1346, 1289, 1252,

1236, 1219, 1166, 1117, 1081, 1054, 1035, 1012, 997, 973, 932, 887, 864, 835, 825, 766,

743, 728, 665.

Synthesis of 2-(furan-2-yl)-6-methyl-3-nitro-4-phenylpyridine (**139**).
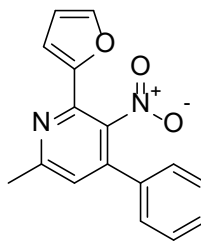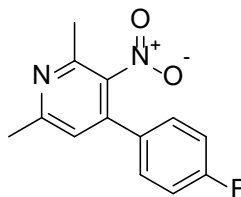

The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **112** (154 mg, 1.0 mmol) and 4-phenyl-3-butyn-2-one (**123**) (216 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (75 mg, 27%) as dark amber crystals. δ_H (500 MHz, Chloroform-*d*)/ppm 7.57 – 7.53 (m, 1H, H-5′), 7.47 – 7.41 (m, 3H, H-3″/H-4″/H-5″), 7.40 – 7.35 (m, 2H, H-2″/H-6″), 7.15 (d, *J* = 3.5 Hz, 1H, H-3′), 7.08 (s, 1H, H-5), 6.53 (dd, *J* = 3.6, 1.8 Hz, 1H, H-4′), 2.66 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 159.86 (C), 149.14 (C), 144.99 (C), 143.04 (C), 141.04 (C), 139.34 (C), 134.09 (C), 129.58 (CH), 128.94 (CH), 127.71 (CH), 123.02 (CH), 113.02 (CH), 112.09 (CH), 24.54 (CH$_3$); anal. calcd. for C$_{16}$H$_{12}$N$_2$O$_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.47; H, 4.22; N, 9.87. LCMS purity (UV) = 92%, tR: 20.70 min. LCMS purity (positive ion, TIC) = 91.7%, tR: 20.71 min. IR (cm^{-1}) 3141, 3115, 2925, 1967, 1746, 1599, 1569, 1549, 1528, 1497, 1489, 1448, 1363, 1231, 1215, 1190, 1148, 1130, 1079, 1056, 1032, 1016, 945, 926, 886, 877, 863, 835, 798, 784, 755, 737, 702,

Synthesis of 4-(6-methyl-3-nitropyridin-2-yl)morpholine (**140**).
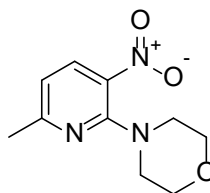
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **116** (173 mg, 1.0 mmol) and 3-butyn-2-one (**105**) (102 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (88 mg, 39%) as bright yellow crystals, mp 80-81 °C (hexane); δ_H (500 MHz, Chloroform-*d*)/ppm 8.08 (d, J = 8.2 Hz, 1H, H-4), 6.62 (d, J = 8.2 Hz, 1H, H-5), 3.81 (t, J = 4.7 Hz, 4H, H-3′/H-5′), 3.47 (t, J = 4.8 Hz, 4H, H-2′/H-6′), 2.47 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 162.2 (C), 152.3 (C), 136.0 (CH), 130.8 (C), 113.6 (CH), 66.6 (CH$_2$), 48.5 (CH$_2$), 24.1 (CH$_3$); anal. calcd. for C$_{10}$H$_{13}$N$_3$O$_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.73; H, 5.72; N, 18.71; LCMS purity (UV) = 97%, tR: 15.14 min. LCMS purity (positive ion, TIC) = 97.2%, tR: 15.14 min. IR (cm^{-1}) 3362, 3256, 3095, 2982, 2910, 2851, 1666, 1590, 1570, 1483, 1455, 1439, 1429, 1389, 1367, 1320, 1303, 1266, 1248, 1217, 1192, 1150, 1113, 1084, 1065, 1045, 1020, 967, 958, 928, 882, 843, 816, 754, 731, 691, 664.

Synthesis of 4-(6-methyl-3-nitro-4-phenylpyridin-2-yl)morpholine (**141**).

The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **116** (173 mg, 1.0 mmol) and 4-phenyl-3-butyn-2-one (**123**) (216 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (97 mg, 32%) as bright yellow crystals, mp 116−118 °C (MeOH); δ_H (500 MHz, Chloroform-*d*)/ppm 7.44 – 7.38 (m, 3H, H-2″/H-4″/H-6″), 7.32 – 7.26 (m, 2H, H-3″/H-5″), 6.66 (s, 1H, H-5), 3.78 (t, *J* = 4.6 Hz, 4H, H-3′/H-5′), 3.36 (t, *J* = 4.7 Hz, 4H, H-2′/H-6′), 2.48 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 158.61 (C), 151.60 (C), 145.08 (C), 135.37 (C), 135.11 (C), 129.02 (CH), 128.71 (CH), 127.35 (CH), 117.02 (CH), 66.75 (CH$_2$), 48.77 (CH$_2$), 24.39 (CH$_3$); ν_{max} (neat)/cm^{-1} 3061, 2973, 2853, 2837, 2207, 1768, 1545, 1519, 1370, 1111; HRMS (POS ESI) calcd. for C$_{16}$H$_{18}$N$_3$O$_3^+$ [M+H]: 300.1343, found 300.1331; anal. calcd. for C$_{16}$H$_{17}$N$_3$O$_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.11; H, 5.57; N, 14.15; LCMS purity (UV) = 95%, tR: 20.45 min. LCMS purity (positive ion, TIC) = 94.9%, tR: 20.44 min. IR (cm^{-1}) 3061, 2973, 2919, 2893, 2853, 2837, 2208, 1980, 1768, 1697, 1665, 1606, 187, 1545,1519, 1498, 1447, 1422, 1381, 1370, 1361, 1353, 1307, 1277, 1265, 1240, 1211, 1180, 1161, 1147, 1111, 1079, 1069, 1056, 1027, 1009, 989, 930, 895, 855, 835, 808, 789, 766, 731, 704, 670.

Synthesis of 2,6-dimethyl-3-nitropyridine (**142**).

The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **119** (102 mg, 1.0 mmol) and 3-butyn-2-one (**105**) (102 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (57 mg, 44%) as a yellow solid, mp 34-37 °C (ether) (lit.[6] mp 37 °C); δ_H (500 MHz, Chloroform-*d*)/ppm 8.16 (d, *J* = 8.4 Hz, 1H, H-4), 7.15 (d, *J* = 8.4 Hz, 1H, H-5), 2.80 (s, 3H, 2-CH$_3$), 2.59 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*) 163.0 (C), 153.3 (C), 143.6 (C), 132.8 (CH), 121.4 (CH), 24.7 (CH$_3$), 24.1 (CH$_3$); anal. calcd. for C$_7$H$_8$N$_2$O$_2$: C, 55.26; H, 5.30; N, 18.41. LCMS purity (UV) = 89%, tR: 11.15 min. LCMS purity (positive ion, TIC) = 88.8%, tR: 11.16 min. IR (cm^{-1}) 3062, 2999, 2935, 2856, 2437, 2178, 1971, 1687, 1594, 1578, 1515, 1460, 1449, 1392, 1376, 1366, 1354, 1271, 1249, 1212, 1157, 1089, 1036, 1026, 986, 935, 842, 834, 750, 723, 710.

Synthesis of 2,6-dimethyl-3-nitro-4-phenylpyridine (**143**).
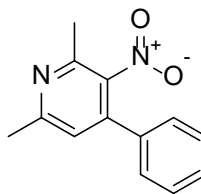
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **119** (102 mg, 1.0 mmol) and 4-phenyl-3-butyn-2-one (**123**) (216 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (63 mg, 28%) as yellow crystals, mp 66-67 °C (2-propanol)

(lit. mp 68-70 °C)[105]; δ_H (500 MHz, Chloroform-*d*)/ppm 7.46 – 7.42 (m, 3H, H-2′/H-4′/H-6′), 7.36 – 7.33 (m, 2H, H-3′/H-5′), 7.08 (s, 1H, H-5), 2.62 (s, 3H, 2-CH$_3$), 2.59 (s, 3H, 6-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 159.8 (C), 149.7 (C), 145.1 (C), 142.4 (C), 134.5 (C), 129.5 (CH), 129.0 (CH), 127.5 (CH), 122.3 (CH), 24.4 (CH$_3$), 20.7 (CH$_3$); anal. calcd. for C$_{13}$H$_{12}$N$_2$O$_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.28; H, 5.36; N, 12.15; LCMS purity (UV) = 92%, t_R: 17.71 min. LCMS purity (positive ion, TIC) = 91.8%, t_R: 17.72 min. Spectral data were in agreement with literature values.[106]

Synthesis of 4-(4-methoxyphenyl)-2,6-dimethyl-3-nitropyridine (**151**).
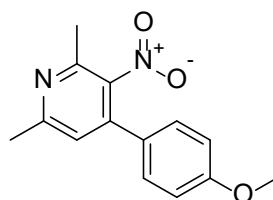
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **119** (276 mg, 2.67 mmol) and alkynone **144** (700 mg, 4.0 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (193 mg, 28%) as a yellow solid. mp 75-77 °C. δ_H (600 MHz, Chloroform-*d*)/ppm 7.30 (d, *J* = 8.5 Hz, 2H, H-2′/H-6′), 7.06 (s, 1H, H-5), 6.96 (d, *J* = 8.4 Hz, 2H, H-3′/H-5′), 3.84 (s, 3H, 4′-OCH$_3$), 2.60 (s, 3H, 2-CH$_3$), 2.57 (s, 3H, 6-CH$_3$); δ_C (151 MHz, Chloroform-*d*)/ppm 160.66 (C), 159.57 (C), 149.59 (C), 145.15 (C), 141.98 (C), 128.87 (CH), 126.60 (C), 122.17 (CH), 114.58 (CH), 55.34 (CH$_3$), 24.41 (CH$_3$), 20.59 (CH$_3$); HRMS (POS EI) analysis calcd. for C$_{14}$H$_{14}$N$_2$O$_3$ (m/z): 258.10; found 258.1004. IR (cm^{-1}) 2981, 2920, 2856, 1718, 1596, 1446, 1368, 1283, 1253, 1231, 1104, 1043, 1027, 1002, 839, 770, 696. Spectral data were in agreement with literature values.[106]

Synthesis of 4-(4-fluorophenyl)-2,6-dimethyl-3-nitropyridine (**152**).

The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **119** (204 mg, 2.0 mmol) and alkynone **145** (487 mg, 3 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (116 mg, 24%) as an orange gum; δ_H (600 MHz, Chloroform-*d*)/ppm 7.33 (dd, *J* = 8.4, 5.2 Hz, 2H, 4-phenyl), 7.26 (s, 1H, 4-phenyl), 7.13 (t, *J* = 8.5 Hz, 2H, 4-phenyl), 7.05 (s, 1H, H-5), 2.62 (s, 3H, 2-CH$_3$), 2.59 (s, 3H, 6-CH$_3$); δ_C (151 MHz, Chloroform-*d*)/ppm 163.46 (d, *J* = 250.2 Hz, C), 159.87 (C), 149.81 (C), 145.06 (C), 141.37 (C), 130.48 (d, *J* = 3.5 Hz, C), 129.50 (d, *J* = 8.3 Hz, CH), 122.19 (CH), 116.23 (d, *J* = 22.0 Hz, CH), 24.43 (CH$_3$), 20.64 (CH$_3$); δ_F (376 MHz, Chloroform-*d*)/ppm -111.23 (tt, *J* = 8.7, 5.3 Hz); HRMS (POS EI) analysis calcd. for C$_{13}$H$_{11}$FN$_2$O$_2$ (m/z): 246.08, found 246.0805.

Synthesis of 2-methyl-3-nitro-4-phenyl-6-(trifluoromethyl)pyridine (**153**).
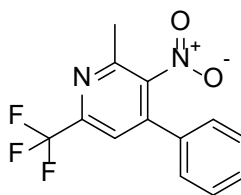
The title compound was synthesized according to general procedure 2.3, using **119** (210 mg, 2.05 mmol) and alkynone **146** (610 mg, 3.08 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (189 mg, 33%) as a yellow solid. δ_H (500 MHz, Chloroform-*d*)/ppm 7.65 (s, 1H, H-5), 7.49 (q, J = 7.3 Hz, 3H, H-2′/H-4′/H-6′), 7.39 (d, J = 7.1 Hz, 2H, H-3′/H-5′), 2.68 (s, 3H, 2-CH$_3$).

Synthesis of 4-(4-methoxyphenyl)-2-methyl-3-nitro-6-(trifluoromethyl)pyridine (**154**).
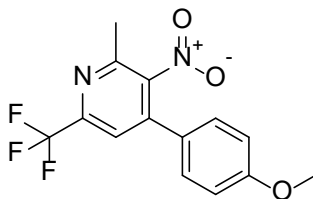
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **119** (91 mg, 0.89 mmol) and alkynone **147** (307 mg, 1.34 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (40 mg, 14%) as a pale orange wax. δ_H (600 MHz, Chloroform-*d*)/ppm 7.61 (s, 1H, H-5), 7.33 (d, *J* = 8.7 Hz, 2H, H-3′/H-5′), 6.99 (d, *J* = 8.9 Hz, 2H, H-2′/H-6′), 3.85 (s, 3H, 4′-OCH$_3$), 2.66 (s, 3H, 2-CH$_3$); δ_C (151 MHz, Chloroform-*d*)/ppm 161.37, 151.60, 148.15 – 147.73 (m), 143.26, 129.06, 125.00, 120.01 (q, *J* = 2.8 Hz), 114.95, 55.41, 20.44.

Synthesis of ethyl 6-methyl-5-nitro-4-phenylpicolinate (**155**).
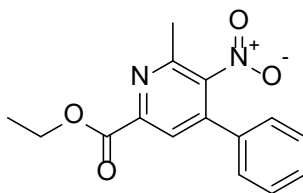
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **119** (340 mg, 3.33 mmol) and alkynone **148** (1.00 g, 5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (147 mg, 15%) as an orange gum. δ_H (600 MHz, Chloroform-*d*)/ppm 8.06 (s, 1H, H-5), 7.52 – 7.44 (m, 3H, H-2′/H-4′/H-6′), 7.42 – 7.37 (m, 2H, H-3′/H-5′), 4.50 (q, *J* = 7.2 Hz, 2H, 6-CO$_2$CH$_2$CH$_3$), 2.70 (s, 3H, 2-CH$_3$), 1.44 (t, *J* = 7.2 Hz, 3H, 6-CO$_2$CH$_2$CH$_3$); δ_C (151 MHz, Chloroform-*d*)/ppm 163.72 (C), 150.94 (C), 148.33 (C), 143.03 (C), 133.37 (C),

130.11 (CH), 129.25 (CH), 127.60 (CH), 124.67 (CH), 62.58 (CH$_2$), 20.66 (CH$_3$), 14.25 (CH$_3$).

Synthesis of ethyl 4-(4-methoxyphenyl)-6-methyl-5-nitropicolinate (**156**).
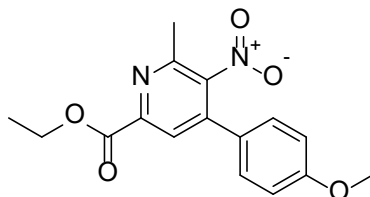
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine 119 (66 mg, 0.65 mmol) and alkynone **149** (224 mg, 0.97 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (44 mg, 21%) as an orange gum. δ_H (500 MHz, Chloroform-*d*)/ppm 8.04 (s, 1H, H-5), 7.33 (d, *J* = 8.7 Hz, 2H, H-3′/H-5′), 6.96 (d, *J* = 8.6 Hz, 2H, H-2′/H-6′), 4.49 (q, *J* = 7.2 Hz, 2H, 6-CO$_2$*CH$_2$*CH$_3$), 3.82 (s, 3H, 4′-OCH$_3$), 2.66 (s, 3H, 2-CH$_3$), 1.42 (t, *J* = 7.2 Hz, 3H, 6-CO$_2$CH$_2$*CH$_3$*); δ_C (126 MHz, Chloroform-*d*)/ppm 163.81 (C), 161.13 (C), 150.83 (C), 148.17 (C), 148.09 (C), 142.56 (C), 129.06 (C), 125.40 (CH), 124.57 (CH), 114.80 (CH), 62.51 (CH$_2$), 55.37 (CH$_3$), 20.60 (CH$_3$), 14.24 (CH$_3$); HRMS (POS ESI) analysis calcd. for C$_{16}$H$_{16}$N$_2$NaO$_5$ [M+Na]$^+$: 339.10; found 339.0951. IR (cm^{-1}) 2993, 2944, 1742, 1675, 1600, 1513, 1444, 1249, 1174, 1090, 1014, 990, 843, 762, 657.

Synthesis of 3-nitro-2,6-diphenylpyridine (**157**).
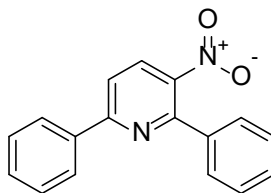
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine 108 (136 mg, 0.83 mmol) and alkynone **150** (162 mg, 1.24 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (63 mg, 27%) as a yellow solid, mp 100-102 °C (ether); $δ_H$ (500 MHz, Chloroform-*d*)/ppm 8.13 (d, *J* = 8.6 Hz, 1H, H-4), 8.07 – 8.01 (m, 2H, phenyl), 7.74 (d, *J* = 8.5 Hz, 1H, H-5), 7.61 – 7.54 (m, 2H, phenyl), 7.48 – 7.38 (m, 7H, phenyl); $δ_C$ (126 MHz, Chloroform-*d*)/ppm 159.5 (C), 152.7 (C), 144.6 (C), 137.1 (C), 136.8 (C), 133.4 (CH), 130.6 (CH), 129.7 (CH), 129.0 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 118.4 (CH); anal. calcd. for C$_{17}$H$_{12}$N$_2$O$_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.75; H, 4.47; N, 9.97; LCMS purity (UV) = 94.8%, tR: 22.30 min. LCMS purity (positive ion, TIC) = 95%, tR: 20.31 min. IR (cm^{-1}) 2962, 1568, 1512, 1452, 1431, 1348, 1261, 1017, 867, 848, 805, 770, 754, 689.

Synthesis of 6-methyl-3-nitropyridin-2-amine (**160**).
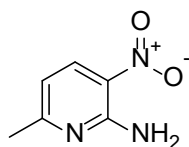
The title compound was synthesized according to general procedure 2.3, using *β*-nitroenamine **159** (103 mg, 1.0 mmol) and 3-butyn-2-one (**105**) (136 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 *v/v*) gave the *title compound* (33 mg, 21%) as bright yellow crystals, mp 150-152 °C (ether) (lit mp 156-158 °C).[107] $δ_H$ (600 MHz, Chloroform-*d*)/ppm 8.30 (d, *J* = 8.5 Hz, 1H, H-4), 6.59 (d,

J = 8.5 Hz, 1H, H-5), 2.46 (s, 3H, 6-CH$_3$). δ_C (151 MHz, Chloroform-*d*)/ppm 166.33 (C), 152.97 (C), 135.20 (CH), 113.72 (CH), 24.82 (CH$_3$). IR (cm^{-1}) 3471, 3318 (NH), 3185, 3053, 1638 (C=C), 1584, 1465, 1435, 1312, 1256, 1216, 1135, 1060, 1016, 789, 773, 735, 708. Spectral data were in agreement with literature values.[108]

General procedure 2.4 for the synthesis of substituted prop-2-ynals.

The prop-2-ynals were synthesized according to a modified method from Journet *et al* (1998).[109] Under inert atmosphere, the alkyne (1 equiv) was dissolved in anhydrous THF at -78 °C. *n*-BuLi (1.1 equiv) was slowly injected into the reaction vessel. After addition was complete, the reaction mixture was stirred for 15 min. Anhydrous DMF (2 equiv) was injected into the reaction vessel. The reaction mixture was stirred for 1 hour, after which the contents of the reaction vessel were poured into a vigorously stirring solution of saturated KH$_2$PO$_4$. The mixture was the partitioned between aqueous phase and ethyl acetate. The crude solid was partitioned between EtOAc and water, then washed with brine (x2). The organic fraction was dried over Na$_2$SO$_4$, and the solvent was removed *in vacuo.* Purification by flash column chromatography on silica, eluting with hexane-EtOAc (19:1 *v/v*) furnished the pure prop-2-ynal.

Synthesis of 3-(4-methoxyphenyl)prop-2-ynal (**162**)
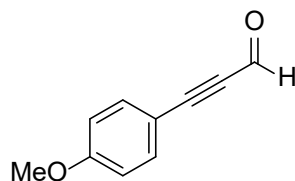
The title compound was synthesized according to General Procedure 2.4, using a solution of 1-ethynyl-4-methoxybenzene (660 mg, 5 mmol) in THF (12.5 mL), *n*-BuLi (2.2 mL, 5.5

mmol), and DMF (0.77 mL, 10 mmol), 2 equiv Purification by flash column chromatography on silica, eluting with hexane-EtOAc (19:1 *v/v*) gave the *title compound* (377 mg, 47%) as an orange wax. mp 46-48 °C (lit. mp 46-48 °C).[110] δ_H (500 MHz, Chloroform-*d*)/ppm 9.39 (s, 1H, H-1), 7.56 (d, *J* = 8.7 Hz, 2H, H-2′/H-6′), 6.91 (d, *J* = 8.9 Hz, 2H, H-3′/H-5′), 3.85 (s, 3H, 4′-OCH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 176.80 (C), 162.13 (C), 135.47 (CH), 114.49 (CH), 111.13 (C), 96.62 (C), 88.75 (C), 55.48 (CH$_3$); HRMS (POS ESI) analysis calculated for $C_{10}H_9O_2$ [M+H]$^+$: 161.06; found 161.0597. Spectral data were in agreement with literature values.[110]

Synthesis of 3-(3,5-dimethoxyphenyl)prop-2-ynal (**163**).
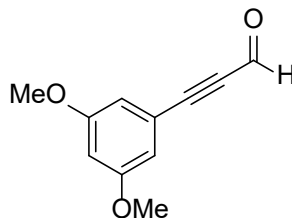
The title compound was synthesized according to general procedure 2.4, using 1-ethynyl-3,5-dimethoxybenzene (1.48 g, 9.1 mmol), anhydrous THF (20.5 mL), *n*-BuLi (4 mL, 10.0 mmol), and DMF (1.4 mL, 18.2 mmol). Purification by flash column chromatography on silica, eluting with hexane-EtOAc (19:1 *v/v*) gave the *title compound* (990 mg, 57%) as yellow crystals. mp 92-95 °C (lit. mp 94.6-95.2 °C).[111] δ_H (600 MHz, Chloroform-*d*)/ppm 9.35 (s, 1H, H-1), 6.68 (s, 2H, H-2′/H-6′), 6.53 (s, 1H, H-4′), 3.74 (s, 6H, 3′-OCH$_3$/5′-OCH$_3$); δ_C (151 MHz, Chloroform-*d*)/ppm 176.66 (C), 160.65 (C), 120.50 (C), 110.78 (CH), 104.56 (CH), 94.90 (C), 87.65 (C), 55.44 (CH$_3$). IR (cm^{-1}) 2964, 2876, 2185, 1646, 1590, 1424, 1356, 1200, 1180, 1160, 1062, 1024, 861, 834, 825, 676, 660. Spectral data were in agreement with literature values.[111]

Synthesis of 3-(4-tert-butylphenyl)prop-2-ynal (**164**).
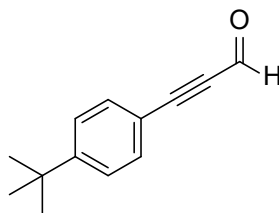
The title compound was synthesized according to general procedure 2.4, using 1-(*tert*-butyl)-4-ethynylbenzene (1.11 g, 7.0 mmol), THF (15.8 mL), *n*-BuLi (3.1 mL, 7.7 mmol), and DMF (1.1 mL, 14 mmol). Purification by flash column chromatography on silica, eluting with hexane-EtOAc (19:1 *v/v*) gave the *title compound* (886 mg, 88%) as a yellow wax. mp 39-41 °C (lit. mp 41-43 °C).[110] δ_H (600 MHz, Chloroform-d)/ppm 9.40 (s, 1H), 7.56 – 7.52 (m, 2H), 7.44 – 7.39 (m, 3H), 1.32 (s, 12H); δ_C NMR (151 MHz, Chloroform-d)/ppm 176.99, 155.21, 133.26, 125.84, 116.27, 96.04, 88.41, 35.15, 31.00; HRMS (POS ESI) analysis calculated for $C_{13}H_{15}O$ [M+H]$^+$: 187.11; found 187.1117. IR (cm^{-1}) 2963, 2868, 2191, 1685, 1661, 1604, 1364, 1267, 1186, 1107, 1017, 982, 835, 564, 547, 527. Spectral data were in agreement with literature values.[110]

Synthesis of 3-(4-bromophenyl)prop-2-ynal (**165**).
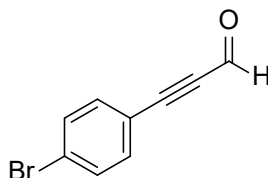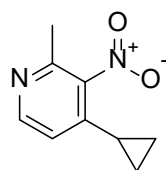

The title compound was synthesized according to general procedure 2.4, using alkyne (815 mg, 4.5 mmol), THF (10.2 mL), *n*-BuLi (2 mL, 5.0 mmol), and DMF (0.7 mL, 9.0 mmol). Purification by flash column chromatography on silica, eluting with hexane-EtOAc (19:1 *v/v*)

gave the *title compound* (145 mg, 57%) as an orange wax. mp 90-93 °C (lit. mp 96-98 °C).[110]

δ_H (500 MHz, Chloroform-d)/ppm 9.39 (s, 1H), 7.56 – 7.50 (m, 2H), 7.46 – 7.41 (m, 2H). IR

(cm^{-1}) 2922, 2852, 2190, 1652, 1583, 1486, 1394, 1263, 1176, 1069, 1010, 981, 821, 758.

Spectral data were in agreement with literature values.[110]

Synthesis of 3-cyclopropylprop-2-ynal (**166**).
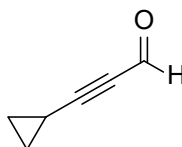
The title compound was synthesized according to general procedure 2.4, using

ethynylcyclopropane (1.26 g, 19.0 mmol), THF (48.0 mL), *n*-BuLi (8.4 mL, 21.0 mmol), and

DMF (2.9 mL, 38.0 mmol). Purification by flash column chromatography on silica, eluting

with hexane-EtOAc (19:1 *v/v*) gave the *title compound* (476mg, 26%) as an orange oil. (lit.

bp 155 °C).[112] δ_H (600 MHz, Chloroform-d)/ppm 5.17 (d, J = 1.2 Hz, 1H), 3.92 (qd, J = 7.1,

1.5 Hz, 1H), 1.84 (d, J = 1.7 Hz, 2H), 1.06 (td, J = 7.1, 1.5 Hz, 2H); δ_C (151 MHz,

Chloroform-d)/ppm 170.84 (C=O), 60.07 (CH$_2$), 60.06 (CH$_2$), 53.34 (C), 20.52 (C), 13.77

(CH).

General Procedure 2.5 for the synthesis of 3-nitropyridines using prop-2-ynals

In a 25-mL round-bottom flask, a solution of the β-nitroenamine (1.0 mmol), prop-2-ynal

(1.5 mmol), and ZnBr$_2$ (34 mg, 0.15 mmol) in toluene (6 mL) was stirred at reflux for 24

hours. The toluene was removed *in vacuo*, and the crude material was dissolved in EtOAc.

The resulting slurry was filtered through silica, and the filtrate was washed sequentially with

water, sat. aqueous NaHCO$_3$ solution (x2) and brine (x2), dried over Na$_2$SO$_4$, and evaporated

in vacuo. Purification by flash column chromatography on silica, gave the pure β-nitropyridine.

Synthesis of 2-methyl-3-nitro-4-phenylpyridine (**167**).
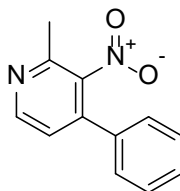
The title compound was synthesized according to general procedure 2.5, using β-nitroenamine **119** (102 mg, 1.0 mmol) and 3-phenylpropiolaldehyde (195 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 v/v) gave the *title compound* (23 mg, 13%) as a brown gum. δ_H (600 MHz, Chloroform-*d*)/ppm 8.63 (d, *J* = 5.0 Hz, 1H, H-6), 7.46 (m, 3H, H-2′/H-4′/H-6′), 7.36 (dd, *J* = 6.8, 2.2 Hz, 2H, H-3′/H-5′), 7.25 (d, *J* = 5.1 Hz, 1H, H-5), 2.63 (s, 3H, 2-CH$_3$); δ_C (151 MHz, Chloroform-*d*)/ppm 150.34 (CH), 150.17 (C), 142.05 (C), 134.09 (C), 132.24 (C), 129.69 (CH), 129.11 (CH), 127.55 (CH), 122.87 (CH), 20.60 (CH$_3$); HRMS (POS EI) analysis calculated for C$_{12}$H$_{10}$N$_2$O$_2$ (m/z): 214.07; found 214.0742.

Synthesis of 4-(4-methoxyphenyl)-2-methyl-3-nitropyridine (**168**).
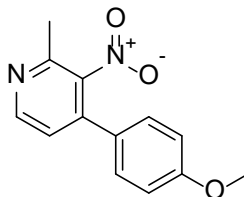
The title compound was synthesized according to general procedure 2.5, using β-nitroenamine **119** (102 mg, 1.0 mmol) and prop-2-ynal **162** (240 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 v/v) gave the *title*

compound (29 mg, 12%) as an orange gum. δ_H (600 MHz, Chloroform-*d*)/ppm 8.63 – 8.56 (m, 1H, H-6), 7.31 (d, *J* = 6.5 Hz, 2H, H-2′/H-6′), 7.27 – 7.22 (m, 1H, H-5), 6.97 (d, *J* = 6.4 Hz, 2H, H-3′/H-5′), 3.84 (s, 3H, 4′-OCH$_3$), 2.61 (s, 3H, 2-CH$_3$); δ_C (151 MHz, Chloroform-*d*)/ppm 160.79 (C), 150.24 (C), 150.07 (CH), 141.62 (C), 128.95 (CH), 126.16 (C), 122.79 (CH), 114.67 (CH), 55.37 (CH$_3$), 20.58 (CH$_3$). IR (cm^{-1}) 3077, 2924, 2209, 2161, 2150, 2059, 2011, 1729, 1598, 1531, 1515, 1464, 1412, 1363, 1293, 1252, 1179, 1102, 1082, 1033, 853, 830, 764, 745, 717, 614, 593, 554. Spectral data were in agreement with literature values.[113]

Synthesis of 4-(3,5-dimethoxyphenyl)-2-methyl-3-nitropyridine (**169**).
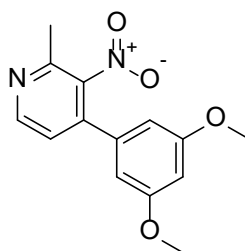
The title compound was synthesized according to general procedure 2.5, using *β*-nitroenamine **119** (428 mg, 4.2 mmol) and prop-2-ynal **163** (285 mg, 1.5 equiv.). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 v/v) gave the *title compound* (11 mg, 1%) as a golden gum. δ_H (500 MHz, Chloroform-*d*)/ppm 8.66 – 8.59 (m, 1H, H-6), 7.26 (d, J = 4.3 Hz, 2H, H-2′/H-6′), 6.52 (d, J = 5.3 Hz, 1H, H-5), 6.50 – 6.46 (m, 1H, H-4′), 3.80 (s, 6H, 3′-OCH$_3$/H-5′-OCH$_3$), 2.63 (s, 3H, 2-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 161.10 (C), 150.18 (CH), 141.98 (C), 122.66 (CH), 109.99 (C), 105.74 (CH), 101.50 (CH), 55.47 (CH$_3$), 20.59 (CH$_3$); HRMS (POS EI) analysis calculated for C$_{14}$H$_{14}$N$_2$O$_4$ (m/z): 274.10; found 274.0954. IR (cm^{-1}) 3054, 1710, 1542, 1479, 1437, 1318, 1258, 1206, 1143, 1113.

Synthesis of 4-(4-tert-butylphenyl)-2-methyl-3-nitropyridine (**170**).
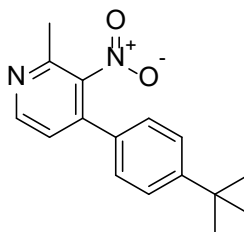
The title compound was synthesized according to general procedure 2.5, using *β*-nitroenamine 119 (102 mg, 1.0 mmol) and prop-2-ynal **164** (279 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 v/v) gave the *title compound* (22 mg, 8%) as a golden gum. δ_H (600 MHz, Chloroform-*d*)/ppm 8.61 (d, *J* = 5.0 Hz, 1H, H-6), 7.46 (d, *J* = 8.1 Hz, 2H, H-2′/H-6′), 7.31 (d, *J* = 8.1 Hz, 2H, H-3′/H-5′), 7.24 (d, *J* = 5.0 Hz, 1H, H-5), 2.62 (s, 3H, 2-CH$_3$), 1.32 (s, 9H, 4′-(CH$_3$)$_3$); δ_C (151 MHz, Chloroform-*d*)/ppm 152.99 (C), 150.22 (C), 150.08 (CH), 146.92 (C), 141.96 (C), 131.06 (C), 127.27 (CH), 126.13 (CH), 122.89 (CH), 31.17 (CH$_3$), 20.56 (CH$_3$); HRMS (POS EI) analysis calculated for C$_{16}$H$_{18}$N$_2$O$_2$ (m/z): 270.14; found 270.1368. IR (cm^{-1}) 2963, 1595, 1532, 1463, 1362, 1267, 1095, 1019, 853, 828, 760, 737, 694, 580, 559.

Synthesis of 4-(4-bromophenyl)-2-methyl-3-nitropyridine (**171**).
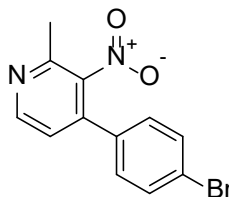
The title compound was synthesized according to general procedure 2.5, using *β*-nitroenamine **119** (51 mg, 0.5 mmol) and prop-2-ynal **165** (157 mg, 0.75 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 v/v) gave the *title*

compound (8 mg, 5%) as an orange gum. δ_H (600 MHz, Chloroform-*d*)/ppm 8.64 (d, *J* = 5.1 Hz, 1H, H-6), 7.59 (d, *J* = 8.2 Hz, 2H, H-2′/H-6′), 7.26 – 7.20 (m, 3H, H-5/H-3′/H-5′), 2.62 (s, 3H, 2-CH$_3$); δ_C (151 MHz, Chloroform-d)/ppm 150.60 (C), 150.38 (CH), 148.02 (CH), 140.93 (C), 132.93 (C), 132.43 (CH), 129.14 (CH), 124.43 (CH), 122.57 (CH), 20.64 (CH$_3$); HRMS (POS EI) analysis calculated for C$_{12}$H$_9$BrN$_2$O$_2$ (m/z): 291.98; found 291.9847. IR (cm^{-1}) 2924, 2853, 1699, 1599, 1558, 1531, 1488, 1463, 1361, 1323, 1259, 1175, 1070, 1035, 1011, 888, 851, 821, 803, 757, 729, 675, 627, 604, 568.

Synthesis of 4-cyclopropyl-2-methyl-3-nitropyridine (**172**).

The title compound was synthesized according to general procedure 2.5, using *β*-nitroenamine **119** (102 mg, 1.0 mmol) and prop-2-ynal **166** (141 mg, 1.5 mmol). Purification by flash column chromatography on silica, eluting with pentane-Et$_2$O (3:1 v/v) gave the *title compound* (26 mg, 15%) as a golden gum. δ_H (600 MHz, Chloroform-*d*)/ppm 8.40 (d, *J* = 5.3 Hz, 1H, H-6), 6.71 (d, *J* = 5.3 Hz, 1H, H-5), 2.52 (s, 3H, 2-CH$_3$), 1.84 (tt, *J* = 8.5, 5.0 Hz, 1H, H-1′), 1.16 – 1.07 (m, 2H, H-2′/H-3′), 0.84 – 0.78 (m, 2H, H-2′/H-3′); δ_C (151 MHz, Chloroform-*d*)/ppm 150.01 (C), 149.43 (CH), 149.16 (C), 145.13 (C), 117.44 (C), 29.66 (CH), 20.35 (CH), 10.50 (CH$_2$), 9.76 (CH$_3$); HRMS (POS EI) analysis calculated for C$_9$H$_{10}$N$_2$O$_2$ (m/z): 178.19. IR (cm^{-1}) 3054, 1526, 1444, 1434, 1350, 1220, 1172, 1121, 1091, 787, 762, 740.

Experimental Details for Chapter 3.

General procedure 3.1 for DPPE-mediated synthesis of δ-carbolines

δ-Carbolines were synthesized according to a modified procedure from Peng *et al.*[88] A glass reaction vial was charged with the corresponding nitropyridine (1.0 equiv.), DPPE (1.1 equiv.) and a stirrer bar. The mixture was stirred under conventional heating at 150 °C for 5 hours, allowed to cool and then partitioned between water and EtOAc. The organic phase was washed sequentially with water (2x30 mL) and brine (2x30 mL), dried over Na_2SO_4, and evaporated *in vacuo*. Purification by flash column chromatography on silica gave the pure δ-carboline.

Synthesis of 2-methyl-5*H*-pyrido[3,2-*b*]indole (**173**).
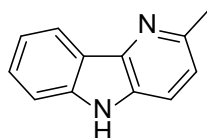
The title compound was prepared according to general procedure **3.1**, using 3-nitropyridine **120** (214 mg, 1.0 mmol) and DPPE (438 mg, 1.1 mmol). Purification by flash column chromatography on silica, eluting with EtOAc-light petroleum (1:1 *v/v*), gave the *title compound* (100 mg, 55%) as a pale-orange solid, mp 269-272 °C (MeOH) (lit. mp 275 °C)[114]; δ_H (500 MHz, DMSO-d_6)/ppm 11.26 (s, 1H, NH), 8.12 (d, J = 8 Hz, 1H, 9-H), 7.75 (d, J = 8 Hz, 1H, 4-H), 7.50 (d, J = 8 Hz, 1H, 6-H), 7.43 (t, J = 8 Hz, 1H, 7-H), 7.22 (d, J = 8 Hz, 1H, 3-H), 7.18 (t, J = 8 Hz, 1H, 8-H), 2.61 (s, 3H, 2-CH_3); δ_C (126 MHz, DMSO-d_6)/ppm 149.6 (C), 141.0 (C), 140.9 (C), 131.5 (C), 127.4 (CH), 121.9 (C), 120.4 (CH), 120.4 (CH), 119.5 (CH), 118.8 (CH), 112.1 (CH), 24.4 (CH_3); HRMS (POS ESI) analysis calculated for

$C_{12}H_{11}N_2$ $[M+H]^+$: 183.0917; found 183.0917. IR (cm^{-1}) 3137, 3010, 2941, 2863, 2798, 2733, 1631, 1476, 1442, 1344, 1269, 1224, 1145, 830, 817, 774, 617. Spectral data were in agreement with literature values.[114]

Synthesis of 2-methyl-7-(propan-2-yl)-5*H*-pyrido[3,2-*b*]indole (**174**).
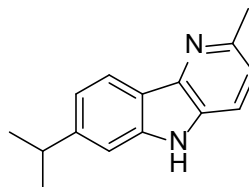
The title compound was prepared according to general procedure 3.1, using 3-nitropyridine **135** (51 mg, 0.2 mmol) and DPPE (88 mg, 0.22 mmol). Purification by flash column chromatography on reverse phase silica, eluting with 1% formic acid in MeCN-water, gave the *title compound* (19 mg, 42%) as a pale-yellow solid, mp 214-216 °C (MeOH); δ_H (600 MHz, Methanol-d_4)/ppm 8.19 (d, $J = 8$ Hz, 1H, 9-H), 7.73 (d, $J = 8$ Hz, 1H, 4-H), 7.33 (s, 1H, 6-H), 7.22 (d, $J = 8$ Hz, 1H, 3-H), 7.13 (dd, $J = 8$, 1.5 Hz, 1H, 8-H), 3.06 (sept, $J = 7$ Hz, 1H, 7-*CH*(CH$_3$)$_2$), 2.67 (s, 3H, 2-CH$_3$), 1.33 (d, $J = 7$ Hz, 6H, CH*(CH$_3$)$_2$*); δ_C (151 MHz, Methanol-d_4)/ppm 149.1 (C), 148.8 (C), 141.6 (C), 140.5 (C), 131.9 (C), 120.0 (C), 119.4 (CH), 119.0 (CH), 118.7 (CH), 118.5 (CH), 108.2 (CH), 108.2 (CH), 23.3 (CH$_3$), 22.1 (CH$_3$); HRMS (POS ESI) analysis calculated for $C_{15}H_{17}N_2$ $[M+H]^+$: 225.1386; found 225.1386.

Synthesis of 7-(benzyloxy)-2-methyl-5*H*-pyrido[3,2-*b*]indole (**177**).
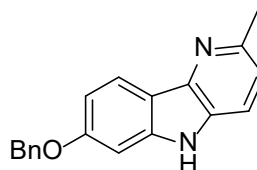
The title compound was prepared according to general procedure 3.1, using 3-nitropyridine **136** (64 mg, 0.2 mmol) and DPPE (88 mg, 0.22 mmol). Purification by flash column chromatography on silica, eluting with EtOAc-light petroleum (1:1 *v/v*), gave the *title compound* (22 mg, 37%) as a pale-yellow solid, mp 207-209 °C (MeOH); δ_H (600 MHz, Methanol-d_4)/ppm 8.16 (d, J = 8.7 Hz, 1H, 9-H), 7.67 (d, J = 8.2 Hz, 1H, 4-H), 7.47 (d, J = 7.5 Hz, 2H, H-2'/H-6'), 7.37 (t, J = 7.5 Hz, 2H, H-3'/H-5'), 7.30 (t, J = 7.5 Hz, 1H, H-4'), 7.17 (d, J = 8.2 Hz, 1H, 3-H), 7.03 (d, J = 2.2 Hz, 1H, 6-H), 6.92 (dd, J = 8.7, 2.2 Hz, 1H, 8-H), 5.17 (s, 2H, 7-OCH$_2$), 2.65 (s, 3H, 2-CH$_3$); δ_C (151 MHz, Methanol-d_4)/ppm 159.6 (C), 148.7 (C), 142.6 (C), 140.7 (C), 137.3 (C), 131.8 (C), 128.1 (CH), 127.5 (CH), 127.1 (CH), 121.1 (CH), 118.5 (CH), 118.3 (CH), 114.9 (C), 109.6 (CH), 95.4 (CH), 69.9 (CH$_2$), 22.1 (CH$_3$); HRMS (POS ESI) analysis calculated for C$_{19}$H$_{17}$N$_2$O [M+H]$^+$: 289.1335; found 289.1335; HRMS (POS EI) analysis calculated for C$_{19}$H$_{16}$N$_2$O (*m/z*): 288.1263; found 288.1263.
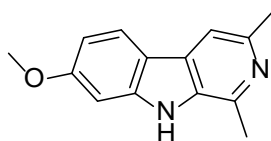
Synthesis of 7-fluoro-2-methyl-5*H*-pyrido[3,2-*b*]indole (**174**).
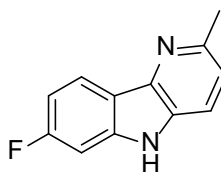
The title compound was synthesized according to the general procedure, using 3-nitropyridine **130** (58 mg, 0.25 mmol) and DPPE (112 mg, 0.28 mmol). The crude solid was purified using column chromatography on silica gel (50% EtOAc in light petroleum). The title compound was isolated as a pale-orange solid, 46% yield (23 mg, 0.12 mmol). (MeOH); δ_H (600 MHz, Methanol-d_4)/ppm 8.27 (dd, J = 8.7, 5.5 Hz, 1H, 9-H), 7.76 (d, J = 8.3 Hz, 1H,

4-H), 7.27 (d, J = 8.3 Hz, 1H, 3-H), 7.17 (dd, J = 9.7, 2.3 Hz, 1H, 6-H), 6.99 (td, J = 9.1, 2.2 Hz, 1H, 8-H), 2.68 (s, 3H, 2-CH$_3$); δ_C (151 MHz, Methanol-d_4)/ppm 163.03 (d, J = 242.3 Hz), 149.58, 121.56 (d, J = 10.5 Hz), 119.66, 118.93, 107.60, 107.44, 97.27 (d, J = 26.6 Hz), 22.11; HRMS (POS ESI) analysis calculated for $C_{12}H_{10}FN_2$ [M+H]$^+$: 201.08; found 201.0823. IR (cm^{-1}) 3137, 3010, 2941, 2863, 2799, 2733, 1631, 1476, 1442, 1385, 1344, 1442, 1269, 1224, 1145, 1106, 830, 817, 774, 617.

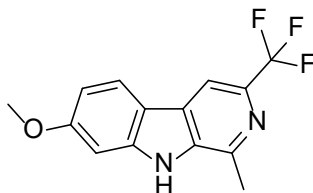Synthesis of 7-bromo-2-methyl-5H-pyrido[3,2-b]indole (**175**).
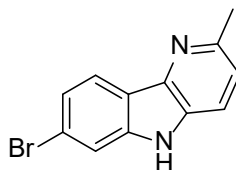
The title compound was synthesized according to the general procedure, using 3-nitropyridine **133** (953 mg, 3.25 mmol) and DPPE (1.43 g, 3.6 mmol). The crude solid was purified using column chromatography on silica gel (50% EtOAc in light petroleum). The title compound was isolated as orange crystals, 4% yield (37 mg, 0.13 mmol). δ_H (600 MHz, DMSO-d_6)/ppm 11.42 (s, 1H, 5-NH), 8.06 (d, J = 8.3 Hz, 1H, 9-H), 7.80 (d, J = 8.3 Hz, 1H, 4-H), 7.71 (d, J = 1.7 Hz, 6-H), 7.31 (dd, J = 8.3, 1.7 Hz, 1H, 8-H), 7.27 (d, J = 8.3 Hz, 1H, 3-H), 2.60 (s, 3H, 2-CH$_3$); δ_C (151 MHz, DMSO-d_6)/ppm 150.35 (C), 141.67 (C), 140.04 (C), 131.85 (C), 122.51 (CH), 122.10 (CH), 121.07 (CH), 120.82 (C), 120.21 (C), 119.56 (CH), 114.74 (CH), 24.30 (CH$_3$); HRMS (POS EI) analysis calculated for $C_{12}H_9BrN_2$ (m/z): 259.99; found 259.9949. IR (cm^{-1}) 3112, 3014, 2920, 2847, 2782, 2720, 1619, 1437, 1333, 1267, 1229, 1048, 904, 815, 772, 641, 612.

Synthesis of 2-phenyl-5*H*-pyrido[3,2-*b*]indole (**178**).
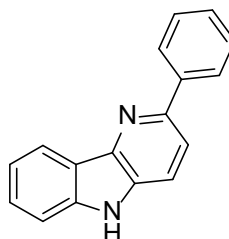
The title compound was synthesized according to the general procedure, using 3-nitropyridine **150** (47 mg, 0.17 mmol) and DPPE (171 g, 0.43 mmol). The crude solid was purified using column chromatography on silica gel (5% MeOH in methylene chloride). The title compound was isolated as a pale-orange solid, 55% yield (23 mg, 0.09 mmol). δ_H (600 MHz, Methanol-d_4)/ppm 8.40 (d, J = 7.9 Hz, 1H, 9-H), 8.00 (d, J = 8.1 Hz, 2H, 2′-H/6′-H), 7.93 (d, J = 8.4 Hz, 1H, 4-H), 7.82 (d, J = 8.5 Hz, 1H, 3-H), 7.55 – 7.47 (m, 3H, 6-H/7-H/4′-H), 7.44 – 7.36 (m, 2H, 3′-H/5′-H), 7.26 (tt, J = 6.6, 1.9 Hz, 1H, 8-H); HRMS (POS ESI) analysis calculated for $C_{17}H_{13}N_2$ [M+H]$^+$: 245.11; found 245.1073; HRMS (POS EI) analysis calculated for $C_{17}H_{12}N_2$ (m/z): 244.10; found 244.1000. IR (cm^{-1}) 3330, 3162, 1624, 1597, 1493, 1472, 1429, 1389, 1320, 1298, 1229, 918, 828, 816, 790, 765, 733, 691.

4-(4-methoxyphenyl)-2,6-dimethylpyridin-3-amine (**184**).
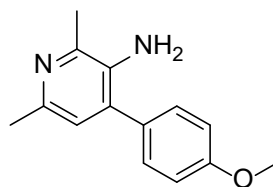
The title compound was encountered as an unwanted side product during the reaction between 3-nitropyridine **151** (163 mg, 0.63 mmol) and DPPE (274 mg, 0.69 mmol). The crude solid was purified using column chromatography on silica gel (5% MeOH in methylene chloride). The title compound was isolated as a bright yellow solid (76 mg, 53%). δ_H (600

MHz, Chloroform-*d*)/ppm 7.35 (d, *J* = 8.3 Hz, 2H, H-2′/H-6′), 6.99 (d, *J* = 8.3 Hz, 2H, H-3′/H-5′), 6.80 (s, 1H, 5-H), 3.84 (s, 3H, 4′-OCH$_3$), 3.66 (br. s, 2H, 3-NH$_2$), 2.48 (s, 3H, 2-CH$_3$), 2.47 (s, 3H, 6-CH$_3$); δ_C (151 MHz, Chloroform-*d*)/ppm 159.57 (C), 146.07 (C), 142.52 (C), 135.67 (C), 135.09 (C), 129.69 (CH), 129.30 (CH), 122.50 (CH), 114.49 (C), 55.34 (CH$_3$), 22.65 (CH$_3$), 20.07 (CH$_3$).

General procedure 3.2 for the synthesis of β-carbolines

The 3-nitropyridine (1.0 equiv.), triphenylphosphine (2.5 equiv.) and DMAc (2 mL) were added to an Anton Paar G10 reaction vial (10 mL) and the vial was sealed with a silicone cap. The resulting solution was stirred under conventional heating in an Anton Paar Monowave 50 reactor at 250 °C for 4 h. The solution was cooled, diluted with EtOAc (50 mL) and H$_2$O (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over anhydrous MgSO$_4$ and evaporated *in vacuo*. Purification by flash column chromatography on silica, eluting with 5% MeOH in methylene chloride, gave the *β*-carboline.

Synthesis of 1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole (**181**).
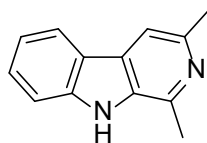
The title compound was synthesized according to the general procedure, using 3-nitropyridine **143** (57 mg, 0.25 mmol) and triphenylphosphine[30] (165 mg, 0.63 mmol), gave the *title compound* (11 mg, 22%) as a brown solid, mp 182-185 °C (MeOH) (lit. mp 186-

187 °C)[115]; δ_H (500 MHz, Methanol-d_4)/ppm 8.08 (d, J = 8 Hz, 1H), 7.74 (s, 1H), 7.56 – 7.47 (2H), 7.20 (ddd, J = 8, 6, 2 Hz, 1H), 2.76 (s, 3H, 1-CH$_3$), 2.63 (s, 3H, 3-CH$_3$); δ_C (126 MHz, Methanol-d_4)/ppm 144.7 (C), 140.3 (C), 133.1 (C), 129.8 (C), 128.1 (C), 121.3 (C), 121.0 (CH), 119.2 (CH), 111.6 (CH), 111.4 (CH), 88.3 (CH), 21.6 (CH$_3$), 17.7 (CH$_3$). IR (cm^{-1}) 2851, 1968, 1845, 1625, 1456, 1336, 1250, 749, 646. Spectral data were in agreement with literature values.[115]

Synthesis of 7-methoxy-1,3-dimethyl-9H-pyrido[3,4-b]indole (**182**).

The title compound was synthesized according to the general procedure, using 3-nitropyridine **151** (124 mg, 0.48 mmol), triphenylphosphine (315 mg, 1.2 mmol), and DMAc (1 mL), gave the *title compound* (12 mg, 11%) as a pale-yellow solid, mp 203-204 °C (MeOH) (lit. mp 207-208 °C)[115]; δ_H (500 MHz, Methanol-d_4)/ppm 8.08 (d, J = 9 Hz, 1H, 5-H), 7.96 (s, 1H, 4-H), 7.06 (d, J = 2 Hz, 1H, 8-H), 6.95 (dd, J = 9, 2 Hz, 1H, 6-H), 3.94 (s, 3H, 7-OCH$_3$), 2.89 (s, 3H, 1-CH$_3$), 2.73 (s, 3H, 3-CH$_3$); δ_C (151 MHz, Methanol-d_4)/ppm 161.0, 159.7, 148.9, 142.4, 128.7, 126.3, 122.4, 114.1, 54.4, 22.5, 18.7; HRMS (POS ESI) anal. calcd. for C$_{14}$H$_{15}$N$_2$O [M+H]$^+$: 227.12; found 227.1179. Spectral data were in agreement with literature values.[115]

Synthesis of 1-methyl-3-(trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole (**183**).
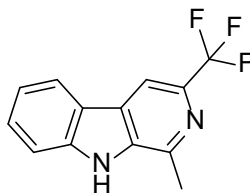
The title compound was synthesized according to the general procedure, using 3-nitropyridine **153** (189 mg, 0.67 mmol), triphenylphosphine (446 mg, 1.7 mmol), and DMAc (1 mL), gave the *title compound* (104 mg, 62%) as a pale amber solid, mp 154-156 °C (MeOH); δ_H (600 MHz, Methanol-d_4)/ppm 8.34 (s, 1H, 4-H), 8.21 (dt, J = 8, 1 Hz, 1H, 5-H), 7.62 (dt, J = 8, 1 Hz, 1H, 8-H), 7.58 (ddd, J = 8, 7, 1 Hz, 1H, 6-H), 7.30 (ddd, J = 8, 7, 1 Hz, 1H, 7-H), 2.85 (s, 3H, 1-CH$_3$); δ_C (151 MHz, Methanol-d_4)/ppm 164.17 (C), 143.05 (C), 141.45 (d, J = 13.0 Hz, C), 135.82 (d, J = 8.0 Hz, CH), 128.04 (d, J = 145.0 Hz, CH), 125.28 – 118.67 (m, CH), 111.83 (CH), 110.32 (q, J = 3.3 Hz, CH), 18.3 (CH$_3$); δ_F (376 MHz, Methanol-d_4)/ppm -66.72; HRMS (POS ESI) anal. calcd. for C$_{13}$H$_{10}$F$_3$N$_2$ [M+H]$^+$: 251.0791; found 251.0791. IR (cm^{-1}) 3157, 1635, 1578, 1512, 1459, 1362, 1272, 1169, 1116, 1094, 937, 893, 779, 743, 713, 649.

Synthesis of 7-methoxy-1-methyl-3-(trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole (**193**).

The title compound was synthesized according to the general procedure, using 3-nitropyridine **154** (134 mg, 0.43 mmol), triphenylphosphine (289 mg, 1.7 mmol), and DMAc (1 mL). The title compound was isolated as a golden solid, yield 30% (32 mg). δ_H (600 MHz,

Methanol-d_4)/ppm 8.20 (s, 1H, 4-H), 8.04 (d, J = 8.7 Hz, 1H, 5-H), 7.06 (d, J = 2.2 Hz, 1H, 8-H), 6.90 (dd, J = 8.7, 2.2 Hz, 1H, 6-H), 3.90 (s, 3H, 7-OCH₃), 2.80 (s, 3H, 1-CH₃); δ_C (151 MHz, Methanol-d_4)/ppm 161.52 (C), 143.16 (C), 142.04 (C), 135.81 (d, J = 9.7 Hz, C), 128.00 (C), 122.27 (C), 114.97 (CH), 110.45 (CH), 109.45 (q, $_3J_{CF}$ = 3.2 Hz, CH), 94.14 (CH), 54.59 (CH₃), 18.19 (CH₃); δ_F (376 MHz, Methanol-d_4)/ppm -66.77; HRMS (POS ESI) anal. calcd. for $C_{14}H_{12}F_3N_2O$ [M+H]⁺: 281.09; found 281.0896; HRMS (POS EI) anal. calcd. for $C_{14}H_{11}F_3N_2O$ (m/z): 280.08; found 280.0823. IR (cm⁻¹) 3161, 3112, 1630, 1360, 1273, 1201, 1163, 1121, 1093, 1026, 930, 825, 811.

Synthesis of 7-methoxy-1-methyl-9H-pyrido[3,4-b]indole (**80**).
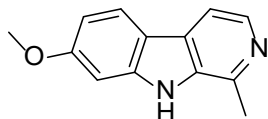
To a 10 mL reaction vial was added 3-nitropyridine **168** (57 mg, 0.25 mmol), triphenylphosphine (165 mg, 0.63 mmol) and DMA (2 mL). The vial was sealed with a silicone cap. The resulting solution was stirred under microwave irradiation at 200 °C for 4 h. The solution was cooled and diluted with EtOAc (50 mL) and H2O (50 mL). Crude product was extracted with EtOAc (3 X 30 mL). The organic extracts were washed with brine (3 X 50 mL) and dried over anhydrous MgSO₄. The suspension was filtered, and the filtrate was concentrated under a reduced pressure to yield crude product that was purified by column chromatography on silica gel (5% MeOH in methylene chloride). The title compound was synthesized according to the general procedure, using 4-(4-methoxyphenyl)-2-methyl-3-nitropyridine (77 mg, 0.32 mmol), triphenylphosphine (210 mg mg, 0.8 mmol), and DMAc

(1 mL). The title compound was isolated as a beige solid, yield 18% (12 mg). Beige solid, mp 261-264 °C (MeOH) (lit. mp 262-264 °C [116]); δ_H (600 MHz, Methanol-d_4)/ppm 8.08 (d, $J = 5.5$ Hz, 1H), 7.96 (d, $J = 8.7$ Hz, 1H), 7.77 (d, $J = 5.5$ Hz, 1H), 7.02 (d, $J = 2.2$ Hz, 1H), 6.85 (dd, $J = 8.7, 2.2$ Hz, 1H), 3.89 (s, 3H), 2.75 (s, 3H); δ_C (151 MHz, Methanol-d_4)/ppm 161.20, 142.82, 140.57, 136.40, 134.83, 131.61, 129.32, 128.81, 128.49, 122.09, 115.48, 114.94, 111.90, 109.54, 93.98, 54.53, 18.00. Spectral data were in agreement with literature values.[116]

<center>Synthesis of 1,2,2,3,4,4-hexamethylphosphetane-1-oxide (185).</center>
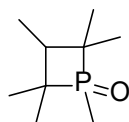
First, a round-bottom flask was charged with 6.7 g (50 mmol) of aluminum trichloride and a stir bar, then sealed with a septum and the flask evacuated with argon. Then methylene chloride (30 mL) was injected into the flask and the mixture was cooled to 0 °C using and ice bath. At this point, phosphorus trichloride (4.4 mL, 50 mmol) was injected into the flask and stirred for 10 minutes. 2,4,4-trimethyl-2-pentene (188) (7.8 mL, 50 mmol) was injected into the flask gradually over 10 min. After addition was complete, the flask was left to stir at 0 °C for 2 hours. The reaction was then slowly quenched with the addition of DI water (30 mL) over 30 min. In a separatory funnel, methylene chloride (2x50 mL) was used to extract the organic layer. After washing the organic phase with water once more (30 mL), the combined aqueous phases were washed with methylene chloride (50 mL) and the combined organic phases were dried over Na_2SO_4. After filtration, the organic phase was concentrated over rotary evaporation, yielding a vibrant white solid (6.72 g, 34.5 mmol).

This solid (**189**) was added into a two-neck flask, and one neck was fitted with a septum while the other was fitted with a condenser topped with a septum. The flask was purged and filled with argon, and then dry diethyl ether (32 mL) was injected into the flask. The reaction mixture was cooled to 0 °C using an ice bath, while stirring. A commercial solution of MeMgBr (3M in Et$_2$O, 16 mL, 48 mmol, 1.1 equiv.) was slowly injected over 10 min. The reaction mixture was then heated to 35 °C and stirred for 4 h, followed by cooling to 0 °C using ice bath. The reaction was quenched using sat. aqueous ammonium chloride (8 mL), which caused a white solid to precipitate. The reaction mixture was decanted into a separatory funnel, and DI water was added (25 mL). Methylene chloride (2x20 mL) was then used to extract the aqueous layer. The solid precipitate was then triturated with methylene chloride (2x100 mL) and filtered under vacuum. The combined methylene chloride phases were washed with DI water (2x30 mL), and then dried over Na$_2$SO$_4$, filtered, and dried under rotary evaporation. The resulting off-white solid was triturated with cold diethyl ether (2x50 mL) under vacuum filtration, which gave the *title compound* (1.51 g, 17%) as a pearl-white solid. δ_H (500 MHz, Chloroform-*d*)/ppm 1.51 – 1.44 (m, 4H, \1-CH$_3$/3-H), 1.21 (d, *J* = 16.1 Hz, 6H, 2-H/4-H), 1.10 (d, *J* = 18.4 Hz, 6H, 2′-H/4′-H), 0.84 (d, *J* = 7.1 Hz, 3H, 3-CH$_3$); δ_C (126 MHz, Chloroform-*d*)/ppm 45.45 (d, J_{PC} = 59.4 Hz, C), 42.62 (d, J_{PC} = 6.1 Hz, CH), 24.69 (d, J_{PC} = 3.6 Hz, CH$_3$), 17.42 (d, J_{PC} = 4.4 Hz, CH$_3$), 9.84 (d, J_{PC} = 41.3 Hz, CH$_3$), 6.95 (d, J_{PC} = 23.3 Hz, CH$_3$); HRMS (POS ESI) anal. calcd. for C$_9$H$_{19}$NaOP [M+Na]$^+$: 197.11; found 197.1066. Spectral data were in agreement with literature values.[89]

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Supporting Information

Chapter Two.

(*Z*)-nitro-1-[4-(propan-2-yl)phenyl]ethen-1-amine (108)

δH (500 MHz, DMSO-d6)

PROTON_01

A (s)
9.42

1" (s)
8.94

D (t)
7.57

C (d)
7.67

E (t)
7.50

F (s)
6.86

3.40 H2O

2.50 dmso
2.50 dmso
2.49 dmso
2.49 dmso

Peaks (ppm): 9.42, 8.94, 7.67, 7.67, 7.66, 7.65, 7.59, 7.59, 7.58, 7.57, 7.57, 7.56, 7.56, 7.52, 7.52, 7.51, 7.50, 7.50, 7.49, 7.49, 6.86

Integrations: 0.77, 0.68, 2.23, 1.08, 2.21, 1.03

f1 (ppm)

δ_C (126 MHz, DMSO-d_6)

HSQC

gHSQCAD_01

{2.49,40.31}dmso

{6.86,109.85}

{7.67,125.79}
{7.79,129.39}
{7.66,127.81}
{7.52,131.55}
{7.22,129.34}
{7.57,131.97}

f1 (ppm)

f2 (ppm)

HMBC

gHMBCAD_01

124

Analyst
Date

Administrator
20 January 2017 14:02

%T

1717.21cm-1

1974.14cm-1

2222.01cm-1

2711.79cm-1

3391.49cm-1

3062.33cm-1

1583.18cm-1

845.86cm-1

3362.55cm-1

3272.82cm-1

1462.47cm-1

919.16cm-1

3133.15cm-1

1002.81cm-1

1444.20cm-1

729.60cm-1

3185.53cm-1

1179.24cm-1 787.55cm-1
1079.28cm-1
1154.59cm-1 828.45cm-1
744.44cm-1
670.00cm-1

1625.80cm-1

1537.98cm-1

985.55cm-1
1109.67cm-1

1261.20cm-1

768.58cm-1

1415.33cm-1

699.74cm-1

cm-1

124   20 January 2017

Page 1

Synthesis of (*Z*)-2-nitro-1-[4-(propan-2-yl)phenyl]ethen-1-amine (**110**).

δ_H (500 MHz, DMSO-d$_6$)

δ_C (126 MHz, DMSO-d$_6$)

HMBC

120

63

Analyst
Date

Administrator
20 January 2017 13:57

%T

3380.83cm-1 3221.98cm-1
3179.82cm-1
3153.43cm-1
3281.03cm-1
2962.16cm-1
2926.09cm-1
1577.36cm-1
1152.71cm-1
1364.05cm-1
926.35cm-1
998.94cm-1
957.90cm-1
1420.69cm-1
754.45cm-1
1092.63cm-1
1538.38cm-1
1395.24cm-1
695.78cm-1
849.96cm-1
1610.88cm1454.94cm-1
829.49cm-1
673.60cm-1
1051.25cm-1
1279.17cm-1 1112.75cm-1
1244.70cm-1
724.98cm-1
778.39cm-1

cm-1

120   20 January 2017

Synthesis of (*Z*)-1-[4-(benzyloxy)phenyl]-2-nitroethen-1-amine (**111**).

<u>δ_H(500 MHz, DMSO-d$_6$</u>

PROTON_01

9.41
8.86
7.67 7.66 7.66 7.65 7.64 7.64 7.46 7.46 7.45 7.44 7.41 7.41 7.40 7.39 7.38 7.38 7.35 7.35 7.34 7.33 7.33 7.32 7.32 7.14 7.13 7.12 7.11
6.88
5.19
3.30 H2O
2.50 dmso 2.50 dmso 2.49 dmso 2.49 dmso 2.49 dmso

G (s)
9.41

D (s)
8.86

A (d)
7.65

B (t)
7.40

C (d)
7.13

H (s)
6.88

E (d)
7.45

I (t)
7.33

F (s)
5.19

1.01
1.01
2.09 2.00 2.03 0.96 2.02 0.94
1.93

f1 (ppm)
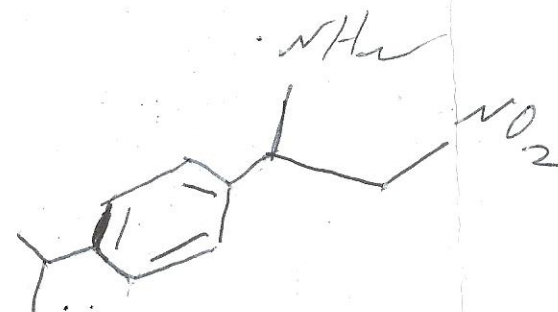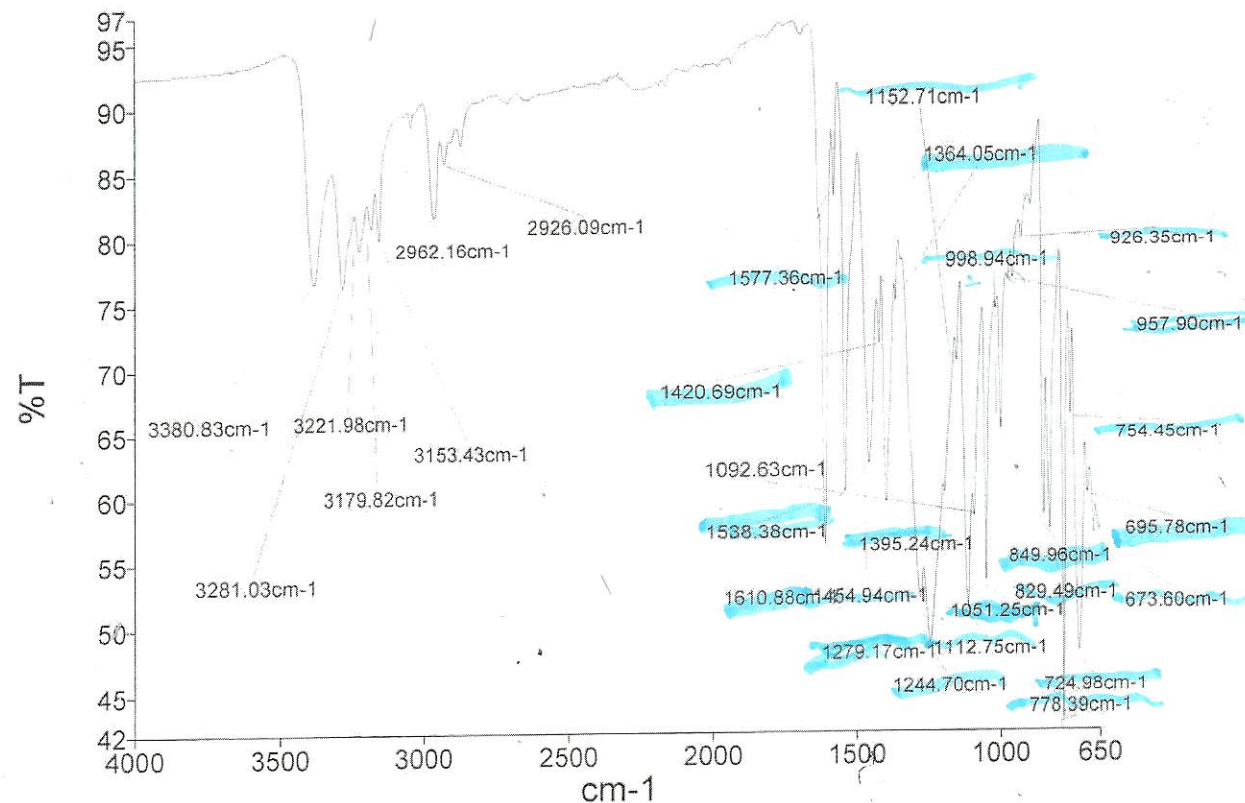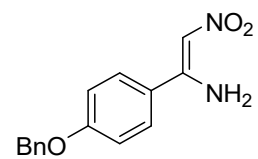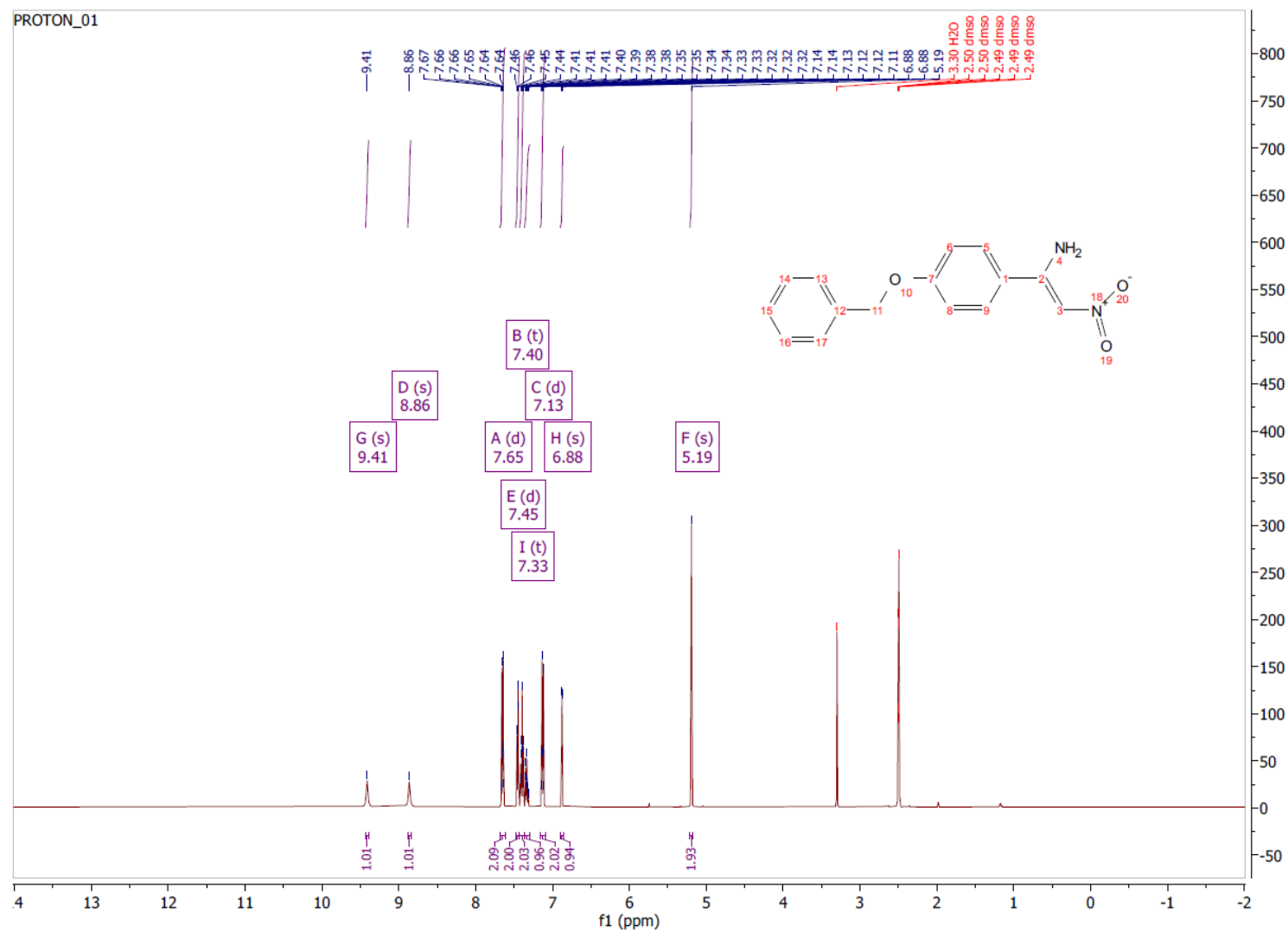
δ_C(126 MHz, DMSO-d$_6$)

HSQC

HMBC

135

Analyst
Date

Administrator
20 January 2017 14:22

IR spectrum, %T vs cm-1

Peaks labeled on spectrum:
3352.63cm-1
3258.07cm-1
3178.37cm-1
3146.31cm-1
3034.88cm-1
2230.30cm-1
1899.32cm-1
1605.97cm-1
1541.99cm-1
1499.31cm-1
1460.87cm-1
1452.76cm-1
1391.20cm-1
1320.86cm-1
1302.64cm-1
1250.20cm-1
1234.81cm-1
1185.52cm-1
1110.94cm-1
1097.19cm-1
1031.66cm-1
1017.27cm-1
1000.91cm-1
988.81cm-1
957.54cm-1
903.91cm-1
862.93cm-1
797.74cm-1
762.79cm-1
738.79cm-1
721.61cm-1
687.13cm-1
882.42cm-1

—————— 131   20 January 2017

Handwritten structure: BnO—C6H4—C(NH2)=CH—NO2 (NH2, NO2 labeled)

Handwritten peak list:
1606
1542
1499
1461
1453
1391
1303
1250
1235
1186
1111

1097
1032
1017
1001
989
958
904
863
832
798
763
739
687

Synthesis of (*Z*)-1-(furan-2-yl)-2-nitroethenamine (**112**).

PROTON_01

B (s)
8.80

C (s)
9.17

E (d)
7.52

A (d)
7.98

D (s)
7.10

F (dd)
6.74

(126 MHz, DMSO-d$_6$)

HSQC

gHSQCAD_01

{7.52,115.52}
A
7.52,115.52

HMBC

gHMBCAD_01

112

G2

Analyst
Date

Administrator
20 January 2017 13:51

PerkinElmer Spectrum Versi
20 January 20

%T

96
95
90
85
80
75
70
65
60
55
50
45
44

4000   3500   3000   2500   2000   1500   1000   650

cm-1

3366.24cm-1
3265.23cm-1
3216.84cm-1
3135.17cm-1
3118.79cm-1
2260.85cm-1
1682.89cm-1
1580.85cm-1
1542.87cm-1
1618.58cm-1
1492.47cm-1
1379.01cm-1
1455.33cm-1
841.29cm-1
1077.45cm-1
886.05cm-1
1232.26cm-1
985.85cm-1
931.37cm-1
1403.68cm-1
737.99cm-1
695.99cm-1
1023.65cm-1
1278.40cm-1
1120.79cm-1
1096.67cm-1
764.18cm-1

112   18 January 2017

H2N   NO2

1619   1077
1581   931
1543   886
1492   841
1455   738
1404   698
1379
1278
1232
1121
1097

Page 1

Synthesis of (*Z*)-1-(4-fluorophenyl)-2-nitroethen-1-amine (**113**).

(500 MHz, DMSO-d$_6$)

(126 MHz, DMSO-d$_6$)

CARBON_01

Peak labels (ppm): 165.43, 163.45, 157.51, 130.47, 130.40, 129.97, 129.95, 116.43, 116.26, 109.60

DMSO solvent peaks (ppm): 40.65, 40.55, 40.48, 40.39, 40.31, 40.22, 40.05, 39.89, 39.72, 39.55

Assignments:
- B (d) 164.62
- C (s) 157.51
- E (d) 129.96
- F (d) 130.44
- A (d) 116.35
- D (s) 109.60

Integrations: 0.46, 0.57, 2.55, 0.52, 2.51, 1.39

HSQC

HMBC

gHMBCAD_01

127

Analyst   Administrator
Date   20 January 2017 14:12

3353.32cm-1
3262.14cm-1
3151.56cm-1
3063.96cm-1
2719.12cm-1
2215.16cm-1
1915.79cm-1
1625.88cm-1
1603.14cm-1
1554.22cm-1
1465.45cm-1
1518.90cm-1
1300.06cm-1
1418.90cm-1
1168.79cm-1
1275.37cm-1
1223.29cm-1
1241.26cm-1
1098.53cm-1
1016.61cm-1
951.32cm-1
965.02cm-1
986.32cm-1
844.65cm-1
719.17cm-1
665.34cm-1
793.73cm-1
701.32cm-1
733.07cm-1
764.75cm-1

%T

cm-1

127   20 January 2017

H_2N

NO_2

1626   1017
1603   986
1554   965
1518   951
1465   845 ← 794
1419   765
1300   733
1275   719
1241   701
1223   665   Page 1
1099

(*Z*)-1-(4-bromophenyl)-2-nitroethen-1-amine (**114**).

(500 MHz, DMSO-d$_6$)

(126 MHz, DMSO-d$_6$)

HMBC

HSQC

gHSQCAD_01

129

Analyst
Date

Administrator
20 January 2017 14:17

%T

93
90
85
80
75
70
65
60
55
51

4000 3500 3000 2500 2000 1500 1000 650

cm-1

3356.47cm-1
3257.64cm-1
3211.70cm-1
3149.80cm-1
3178.82cm-1
2233.34cm-1
1615.05cm-1
1589.22cm-1
1536.95cm-1
1460.89cm-1
1403.44cm-1
1390.57cm-1
1247.19cm-1
1122.40cm-1
1069.03cm-1
1011.00cm-1
993.97cm-1
947.12cm-1
829.29cm-1
768.53cm-1
740.35cm-1
729.66cm-1
691.67cm-1
655.70cm-1

129   20 January 2017

1615   829
1589   762
1537   740
1461   730
1403   692
1247   656
1122
1069
1011
994
947

Synthesis of (*Z*)-1-(3-chlorophenyl)-2-nitroethen-1-amine (**115**).

(500 MHz, DMSO-d_6)

PROTON_01

F (s) 9.33
B (s) 8.94
D (ddt) 7.62
C (t) 7.73
A (t) 7.53
E (s) 6.86

(126 MHz, DMSO-d_6)

HSQC

gHSQCAD_01

{6.86,110.29}

{7.61,126.62}
{7.73,127.89}   {7.62,126.62}
{7.52,131.14}

{2.49,40.40} dmso

f1 (ppm)

f2 (ppm)

HMBC

gHMBCAD_01

Analyst
Date

Administrator
20 January 2017 14:07

IR Spectrum (%T vs cm-1), labeled peaks:

- 3370.75cm-1
- 3267.76cm-1
- 3210.95cm-1
- 3127.10cm-1
- 3064.12cm-1
- 2242.09cm-1
- 1619.17cm-1
- 1576.65cm-1
- 1553.74cm-1
- 1538.48cm-1
- 1497.33cm-1
- 1459.56cm-1
- 1427.68cm-1
- 1402.64cm-1
- 1292.20cm-1
- 1270.70cm-1
- 1252.09cm-1
- 1176.24cm-1
- 1083.24cm-1
- 985.47cm-1
- 897.36cm-1
- 867.66cm-1
- 800.60cm-1
- 784.94cm-1
- 769.19cm-1
- 755.16cm-1
- 707.65cm-1
- 683.89cm-1
- 654.75cm-1

X-axis: cm-1 (4000, 3500, 3000, 2500, 2000, 1500, 1000, 650)
Y-axis: %T (99, 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 47)

125   20 January 2017

Handwritten structure: benzene ring with Cl substituent, connected to a carbon bearing NH2 and =CH-NO2

Handwritten list (left column):
Cl
1619
1577
1554
1530
1497
1460
1428
1403
1292
1271
1252

Handwritten list (right column):
1176
1123
1083
985
897
868
801
785
755
708

Synthesis of (*Z*)-1-nitroprop-1-en-2-amine (**119**)

$$\text{CH}_3-\underset{\underset{}{\overset{\displaystyle NH_2}{|}}}{C}=CH-NO_2$$

PROTON_01
TN-163_recryst

9.10

7.26 cdcl3

6.50

6.12

2.02

D (s)
9.10

A (s)
6.50

B (s)
6.12

C (s)
2.02

1.30

0.78

1.31

2.62

f1 (ppm)

HSQC

gHSQCAD_01
TN-163_recryst

HMBC

2-nitroethene-1,1-diamine (**159**).

$$\text{structure of 2-nitroethene-1,1-diamine}$$

(600 MHz, DMSO-*d*₆)

CARBON_01

B (s)
159.17

A (s)
99.03

159.17

99.03

40.29 dmso
40.18 dmso
40.16 dmso
40.04 dmso
40.02 dmso
39.90 dmso
39.76 dmso
39.62 dmso
39.48 dmso
39.34 dmso

0.58

1.00

f1 (ppm)

4-(4-methoxyphenyl)but-3-yn-2-one (**144**).

(500 MHz, Chloroform-*d*)

PROTON_02
TN-190_carbon

7.50
7.50
7.49
7.49
7.48
—7.26 cdcl3
6.87
6.87
6.86
6.86
4.10
4.08
3.81
3.81
2.41
2.40
—2.01 H2O

A (d)	B (d)	C (s)	D (s)
7.49	6.87	3.81	2.41

2.04
2.08
3.03
2.85

f1 (ppm)

CARBON_01
TN-190_carbon

184.60

161.65

135.09

114.35
111.61

91.47
88.22

77.33 cdd3
77.07 cdd3
76.82 cdd3

55.38

32.60

5
O
2
3
CH3
1
4
11
6
10
7
9
8
H3C
13
O
12

F (s)
184.60

I (s)
161.65

B (s)
135.09

C (s)
111.61

G (s)
114.35

D (s)
88.22

H (s)
91.47

A (s)
55.38

E (s)
32.60

0.40

0.49

2.82

3.59
0.28

0.48
0.45

1.50

0.99

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

HSQC

gHSQCAD_01
TN-190_carbon

(126 MHz, Chloroform-*d*)

(188)

Acquisition Date   29/05/2018 15:43:37

...a\Alinanopos\TYLER_9844_000001.d
...20090608esi
OT ESI   TN-421

Operator   Administrator
Instrument   apex-III
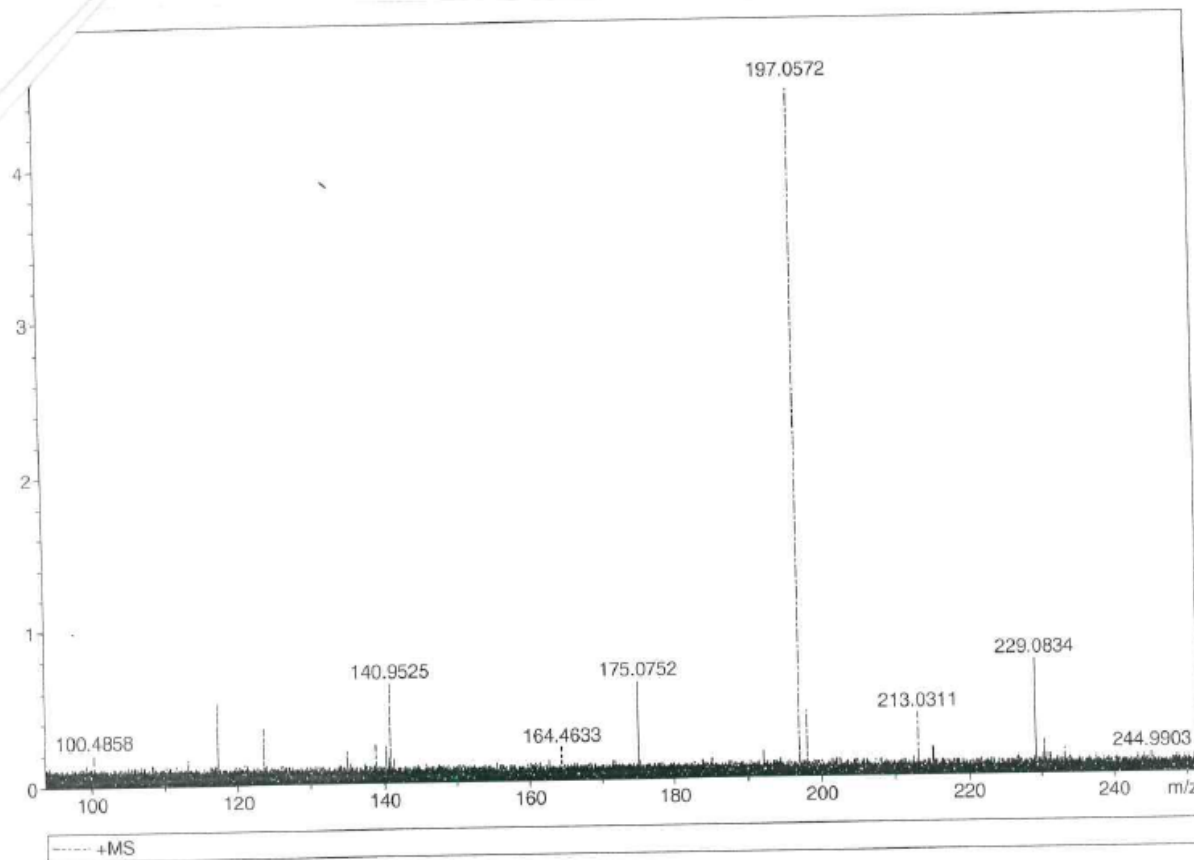
Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 11 H 10 Na 1 O 2	0.019	197.0573	0.64	10.44	2.06	6.50	ok	even

Analyst

Date

PEService

29 March 2019 17:10

Ketone

IR Spectrum, %T vs cm-1

Peaks labelled:
- 2847.8
- 2937.90cm-1
- 1735.41cm-1
- 1510.87cm-1
- 1598.64cm-1
- 1092.51cm-1
- 1023.95cm-1
- 835.65cm-1
- 1254.33cm-1
- 1171.46cm-1
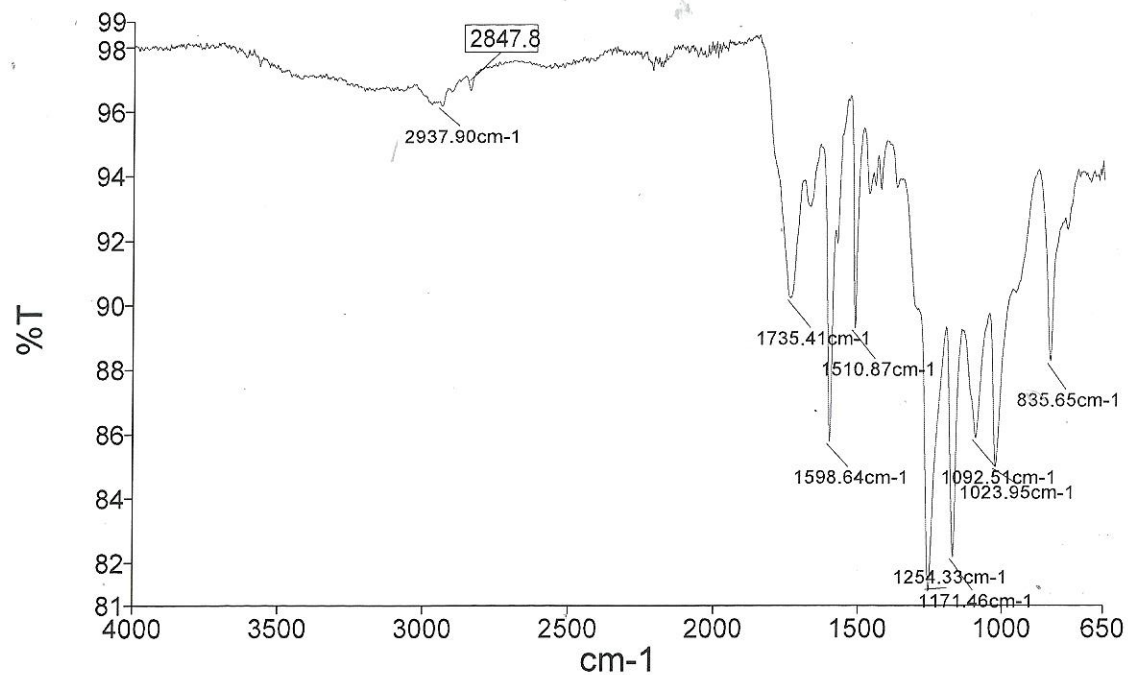
Sample Name	Description	Quality Checks
258	Sample 004 By PEService Date Friday, March 29 2019	The Quality Checks give rise to a Weak Bands warning for the sample.
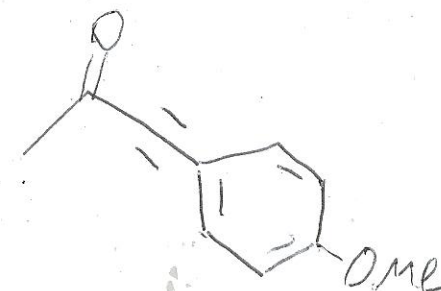
Synthesis of 1,1,1-trifluoro-4-phenylbut-3-yn-2-one (**146**).

(500 MHz, Chloroform-*d*)

PROTON_01
TN-178

7.69, 7.69, 7.69, 7.68, 7.67, 7.67, 7.59, 7.59, 7.59, 7.57, 7.57, 7.56, 7.56, 7.47, 7.47, 7.45, 7.44, 7.44, 7.26 cdd 3

A (m)
7.57

B (d)
7.68

C (t)
7.45

2.03 1.00 1.97

f1 (ppm)

Analyst

Date

Administrator

29 March 2019 18:34

Alkynone

IR Spectrum peak labels:

- 3676.23cm-1, 98.85%T
- 3397.80cm-1, 97.75%T
- 3063.25cm-1, 97.25%T
- 2937.75cm-1, 96.97%T
- 2365.16cm-1, 98.65%T
- 1998.55cm-1, 98.43%T
- 2163.81cm-1, 92.80%T
- 1540.92cm-1, 87.83%T
- 1446.89cm-1, 85.59%T
- 1597.67cm-1, 85.98%T
- 858.19cm-1, 83.83%T
- 1491.15cm-1, 87.92%T
- 784.32cm-1, 81.68%T
- 1357.95cm-1, 89.07%T
- 762.21cm-1, 85.08%T, 79.67%T
- 822.68cm-1, 80.41%T
- 1263.10cm-1, 74.75%T
- 1249.18cm-1, 69.73%T
- 1095.19cm-1, 65.11%T
- 1071.21cm-1, 66.20%T
- 997.64cm-1, 61.31%T
- 1702.17cm-1, 60.67%T
- 640.83cm-1, 59.57%T
- 2199.01cm-1, 57.20%T
- 1122.54cm-1, 59.92%T
- 719.15cm-1
- 757.57cm-1, 47.62%T
- 686.16cm-1, 46.62%T
- 1154.96cm-1, 38.47%T
- 1047.91cm-1, 36.15%T

Axis: %T vs cm-1 (4000 – 550)

Sample Name	Description	Quality Checks	Pathlength (mm)
297	Sample 092 By Administrator Date Friday, March 29 2019	The Quality Checks do not report any warnings for the sample.	54

Handwritten list:

1598
1541
1491
1447
1358
1263
1249
1155
1123
1095
1071
1040

998
3960
823
758
686
641

1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-yn-2-one (**147**).
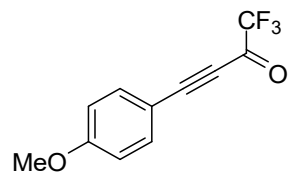
(500 MHz, Chloroform-*d*)
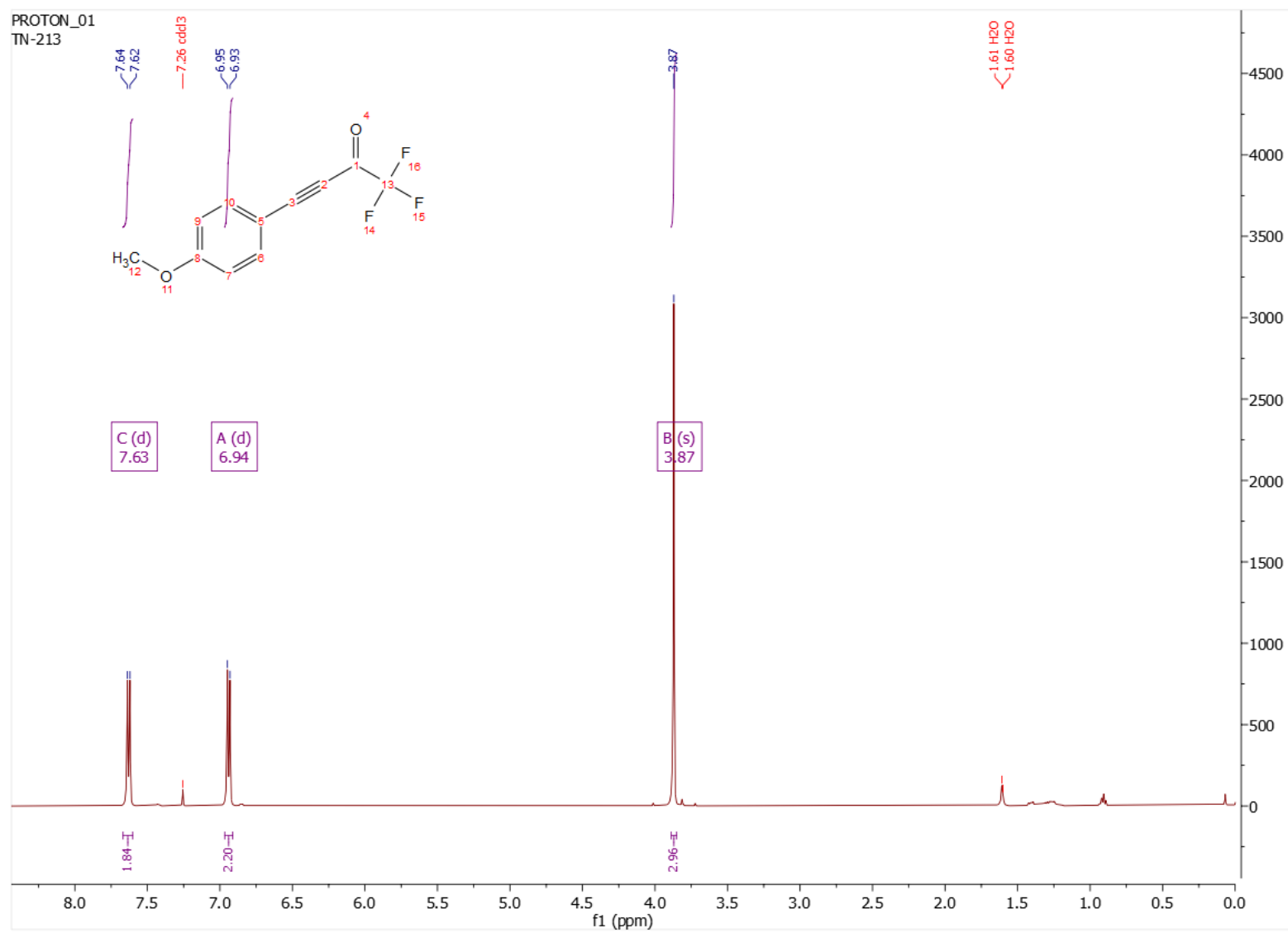
Analyst   Administrator

Date   29 March 2019 18:34

582.58cm-1, 99.46%T

1980.53cm-1, 99.35%T

2039.04cm-1, 98.81%T

1301.01cm-1, 98.16%T
643.58cm-1, 97.95%T
626.59cm-1, 97.72%T
743.85cm-1, 98.03%T

1510.84cm-1, 97.39%T
1251.27cm-1, 97.71%T   712.10cm-1, 97.29%T
1210.88cm-1, 97.01%T

1694.92cm-1, 96.17%T 691.54cm-1 832.98.73%T 96.76%T

1598.70cm-1, 96.30%T

2171.96cm-1, 96.12%T   1045.98cm-1, 95.56%T   567.89cm-1, 96.13%T

%T — cm-1 axis: 4000 3500 3000 2500 2000 1500 1000 550
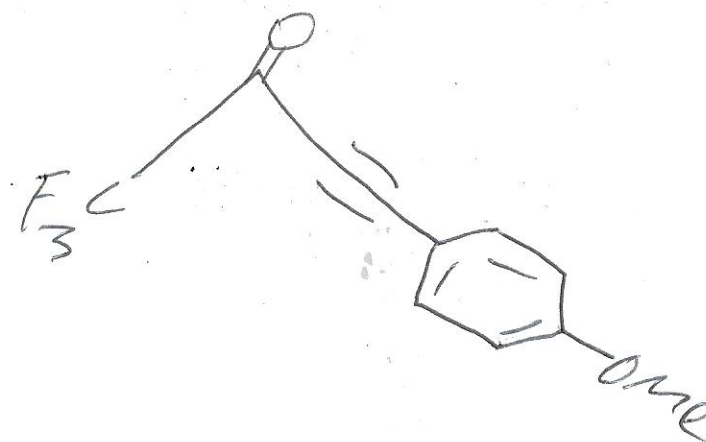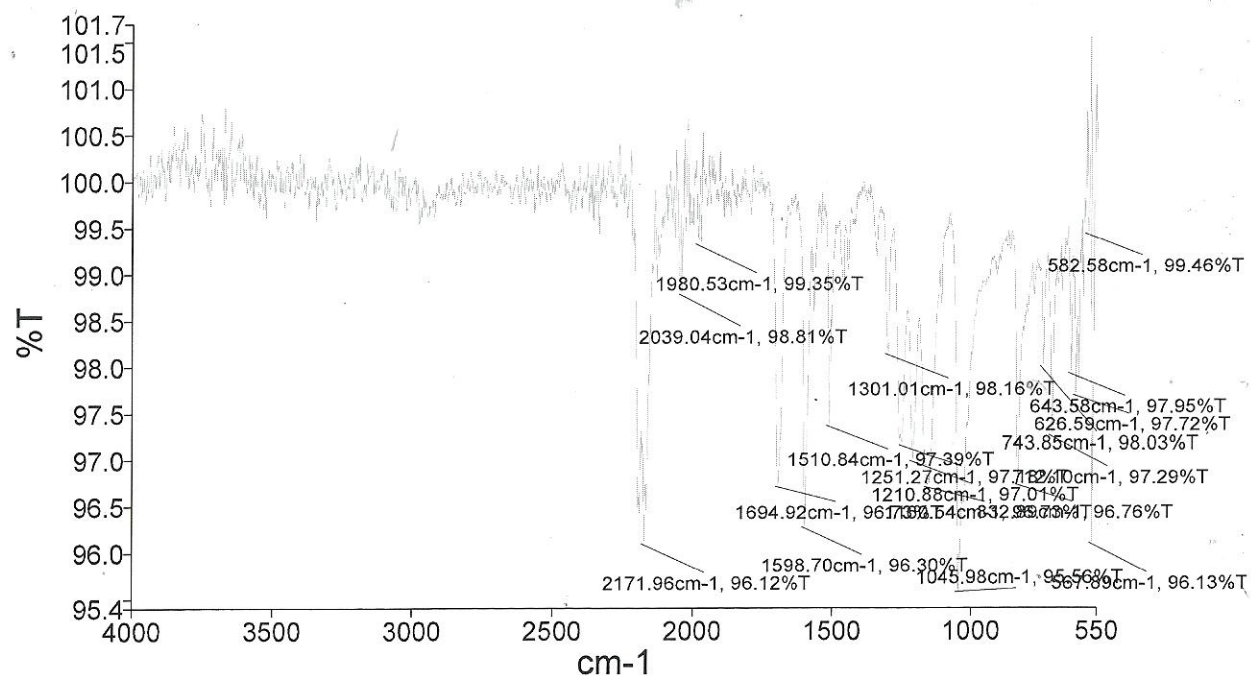
Sample Name	Description	Quality Checks	Pathlength (mm)
213	Sample 094 By Administrator Date Friday, March 29 2019	The Quality Checks give rise to multiple warnings for the sample.	54

ethyl 2-oxo-4-phenylbut-3-ynoate (**148**).

Analyst

Date

PEService
29 March 2019 17:05

%T

99
98
96
94
92
90
88
86
84
82

3334.4
2980.5
2236.5
1443.85cm-1
866.66cm-1
1296.59cm-1
1370.81cm-1
1261.00cm-1
1051.88cm-1
833.16cm-1
691.41cm-1
1536.75cm-1
758.76cm-1
1591.74cm-1
1094.97cm-1
1339.41cm-1
1741.79cm-1
1216.49cm-1

4000   3500   3000   2500   2000   1500   1000   650

cm-1
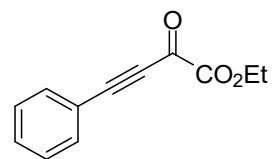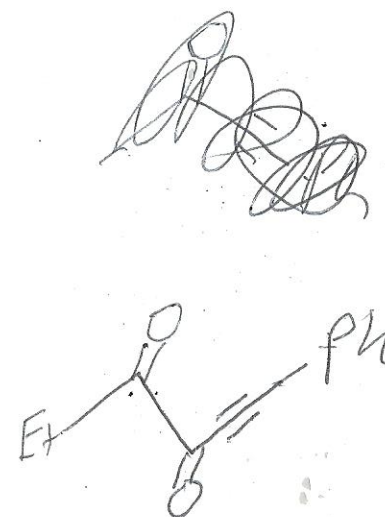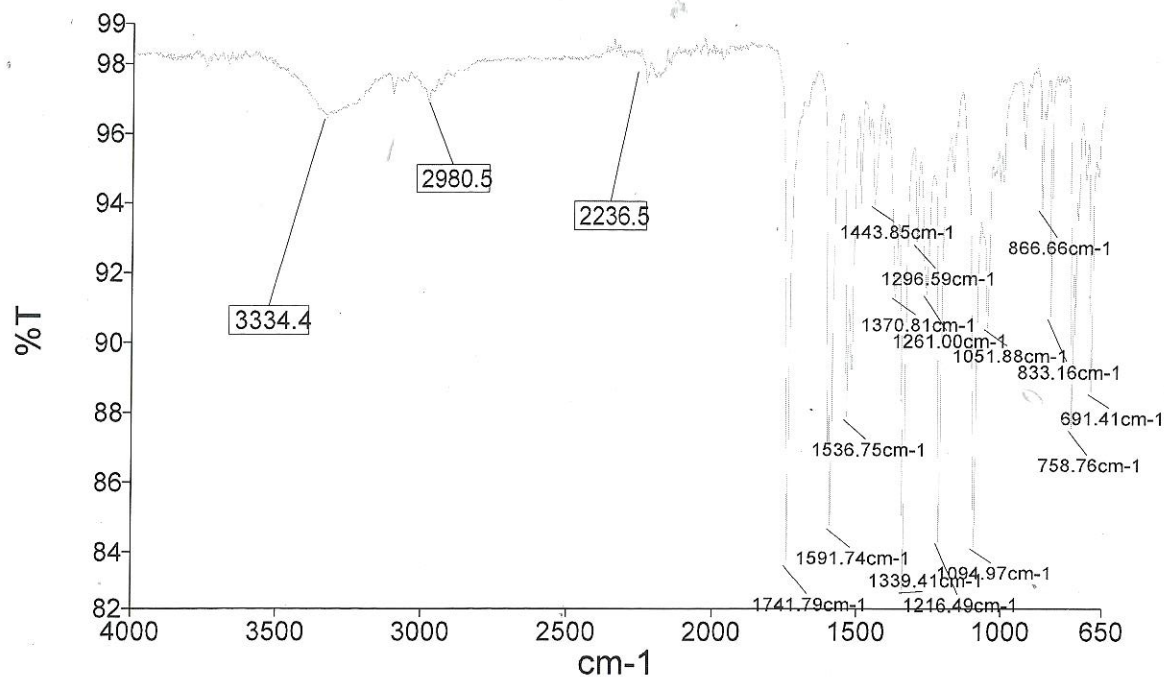
Sample Name	Description	Quality Checks
246	Sample 003 By PEService Date Friday, March 29 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

ethyl 4-(4-methoxyphenyl)-2-oxobut-3-ynoate (**149**).
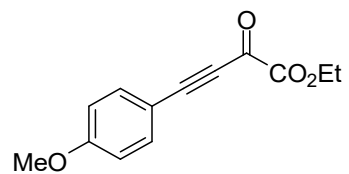
(600 MHz, Chloroform-*d*)
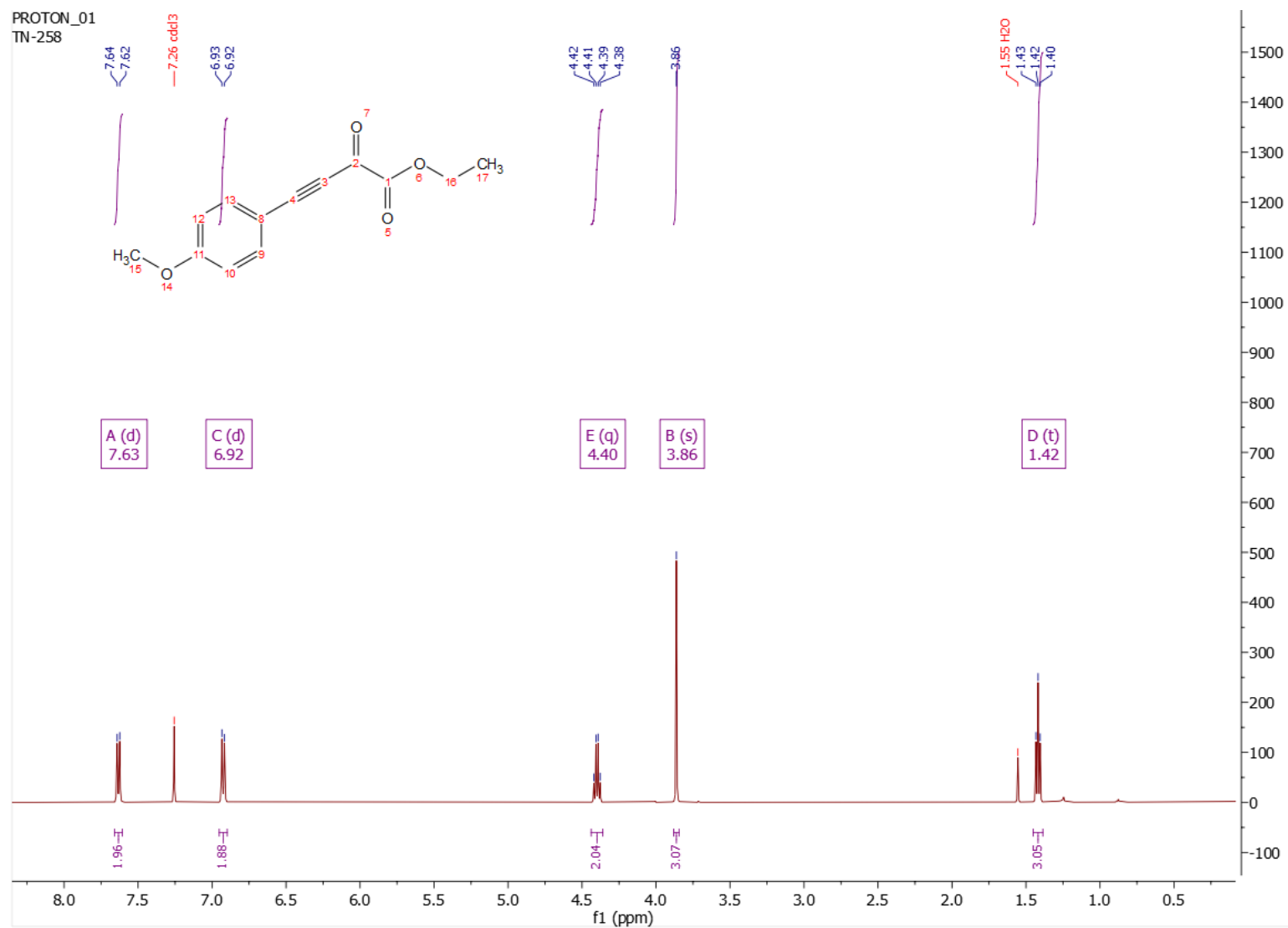
PROTON_01
TN-258

A (d)
7.63

C (d)
6.92

E (q)
4.40

B (s)
3.86

D (t)
1.42

7.64
7.62

7.26 cdd3

6.93
6.92

4.42
4.41
4.39
4.38

3.86

1.55 H2O

1.43
1.42
1.40

1.96

1.88

2.04

3.07

3.05

f1 (ppm)

Generic Display Report
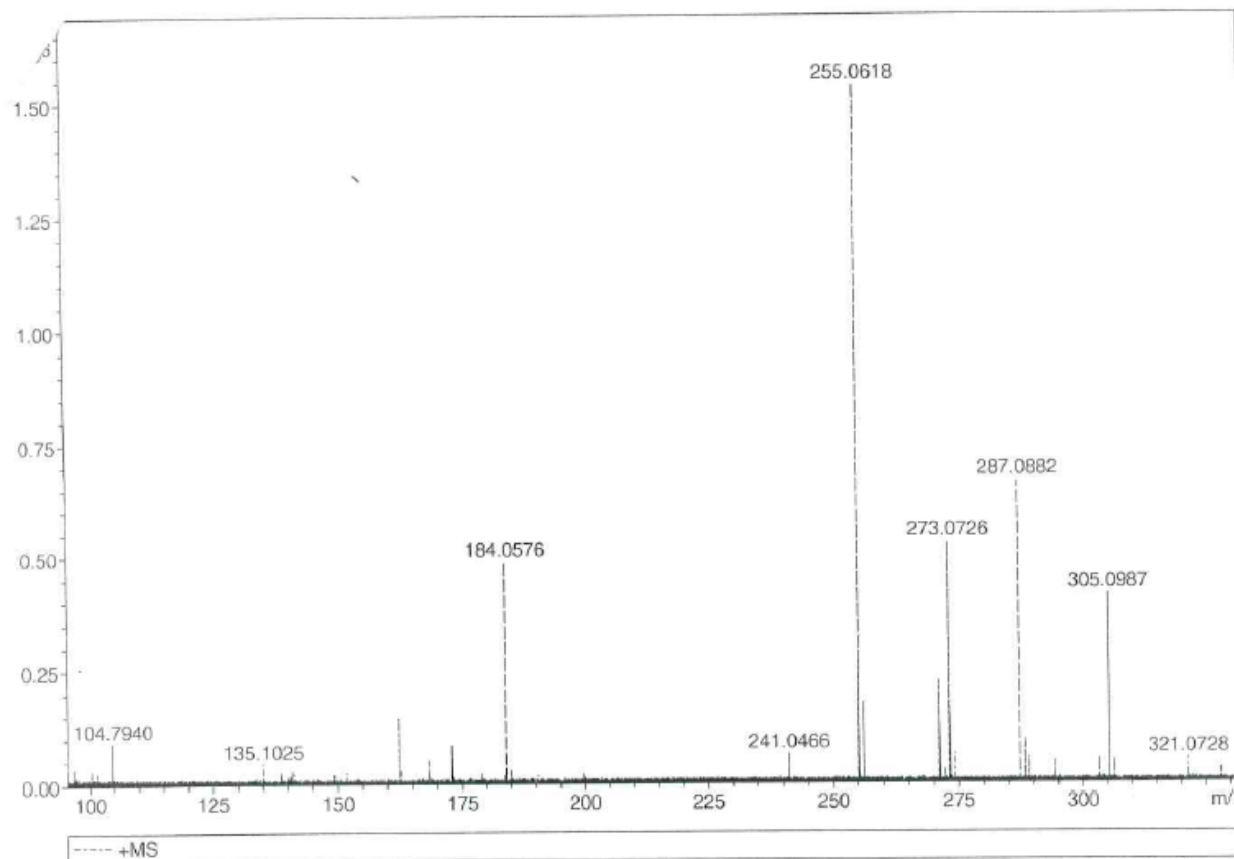
Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 13 H 12 Na 1 O 4	0.027	255.0628	3.90	3.11	0.79	7.50	ok	even

4-(4-fluorophenyl)but-3-yn-2-one (145).

7.59 7.58 7.56 7.55 7.55 7.54

7.08 7.07 7.05

2.44 2.43

A (m)
7.56

B (m)
7.07

C (s)
2.43

0.77

1.15

1.08
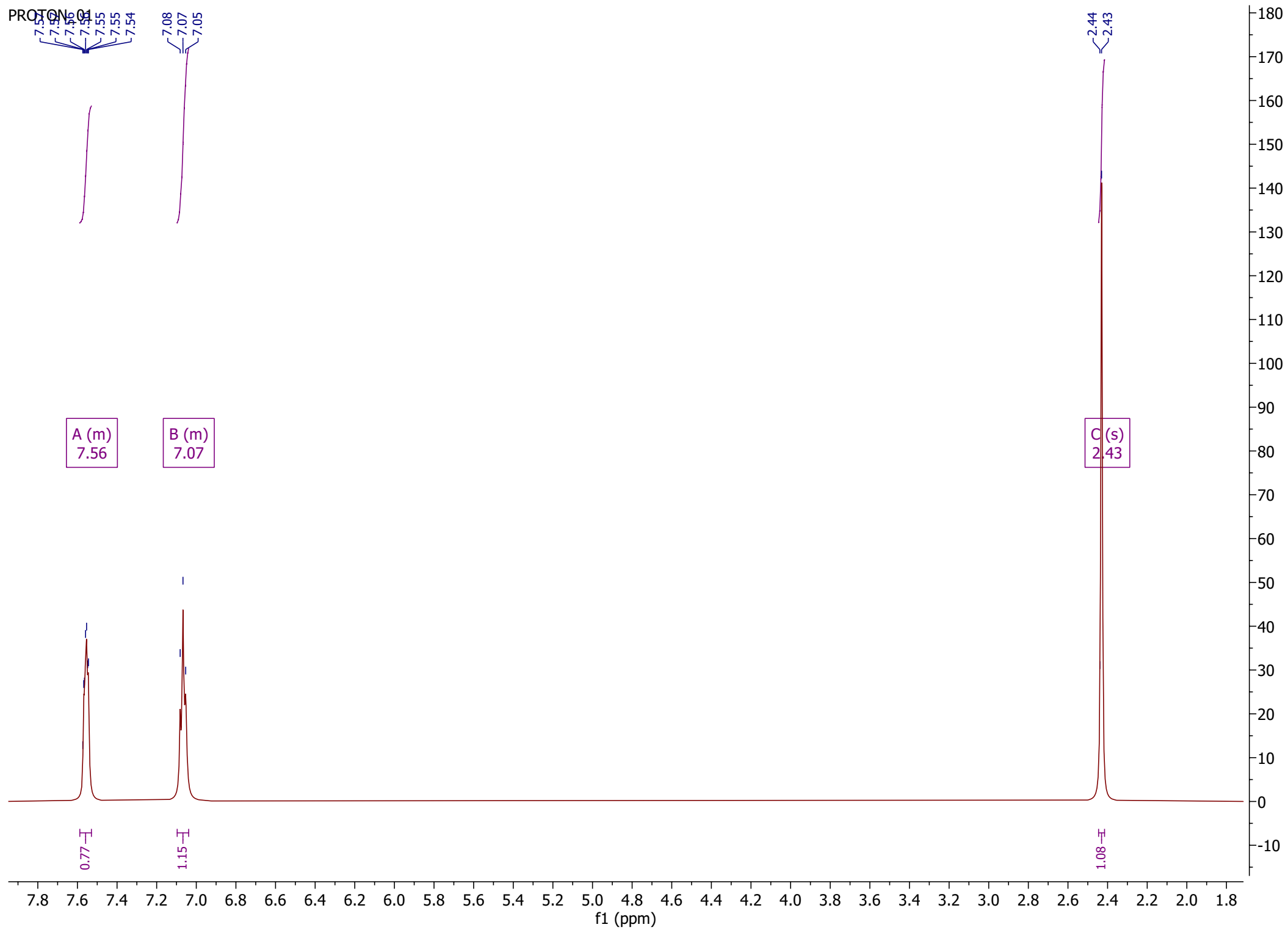
1-phenylprop-2-yn-1-one (**150**).

(500 MHz, Chloroform-*d*)

PROTON_01
TN-181

8.17
8.16
8.16
8.16
8.15
8.15
8.15
7.64
7.63
7.63
7.61
7.61
7.51
7.51
7.50
7.49
7.48
7.48
7.26 cdcl3
3.45
1.67 H2O

A (d)
8.16

C (t)
7.49

D (m)
7.63

B (s)
3.45

CH

2.02
0.69
2.05
0.90

f1 (ppm)

TN-181
TYLERr116208 325 (6.322)

1: TOF MS ES+
1.16e4

Mass spectrum with peaks labeled: 100.9911, 115.0546, 117.0718, 131.0178, 131.0505, 131.0833, 141.0000, 145.0631, 146.9972, 147.0790, 160.0250, 163.0752, 167.1068, 168.1124, 177.0078, 185.0577, 190.0434, 206.1135, 214.0894, 217.0788, 219.0983, 221.1151, 228.1584, 238.1459, 245.0980, 249.1146, 253.1476

Elemental Composition Report

Single Mass Analysis
Tolerance = 200.0 PPM   /   DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Even Electron Ions
2 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 7-10   H: 0-100   O: 1-1
TN-181
TYLERr116208 325 (6.322)

1: TOF MS ES+
1.16e+004

```
100    100.9911           131.0505     146.9972        167.1068      177.0078  190.0434 214.0894 219.0983    238.1459  245.0980  251.1287 263.1115
 %
  0
      100    110    120    130    140    150    160    170    180    190    200    210    220    230    240    250    260      m/z
```
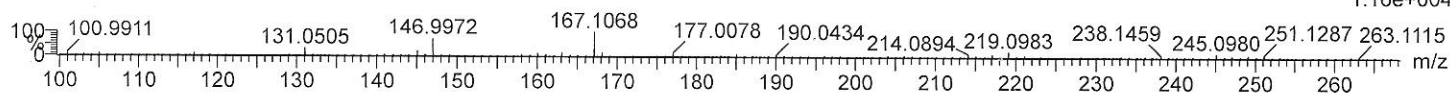
Minimum:				-1.5	
Maximum:		5.0	200.0	50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Formula
131.0505	131.0497	0.8	6.1	6.5	C9 H7 O

6-methyl-3-nitro-2-phenylpyridine (**120**).

(500 MHz, Chloroform-*d*)

PROTON_01
TN-138 BR1

8.08
8.06
7.56
7.56
7.56
7.55
7.55
7.55
7.54
7.54
7.48
7.47
7.47
7.47
7.46
7.46
7.28
7.27 cdcl3
7.27
7.26
1.55 H2O
2.71

C (d)
8.07

A (m)
7.56

D (m)
7.47

B (d)
7.27

E (s)
2.71

0.96
2.02
2.99
1.29
2.74

f1 (ppm)

(126 MHz, Chloroform-*d*)

CARBON_01
TN-138

162.31
152.50
144.21
136.81
132.50
129.49
128.63
128.10
121.92
77.32 cdcl3
77.07 cdcl3
76.81 cdcl3
24.76

A (s)
128.63

G (s)
144.21

I (s)
132.50

C (s)
121.92

D (s)
162.31

F (s)
152.50

H (s)
136.81

B (s)
128.10

J (s)
24.76

E (s)
129.49

0.37
0.33
0.30
0.39
1.56
1.24
2.93
2.43
1.63
0.82

f1 (ppm)

HSQC

gHSQCAD_01
TN-138

{2.70,24.76}
A
2.70,24.76

D
{7.25,122.02} 122.02
{7.56,128.27}
B
7.47,128.86
{7.47,128.86}
{8.05,132.57}

f1 (ppm)

f2 (ppm)

HMBC

gHMBCAD_01
TN-138

{7.26,24.75}
{2.55,24.75}
{2.81,24.75}
{2.55,38.00}
{2.81,38.00}
{2.68,121.94}
{7.43,127.92}
{7.45,128.62}
{7.61,129.09}
{7.55,127.92}
{8.03,144.10}
{7.45,136.71}
{8.05,144.10}
{7.24,144.10}
{7.54,152.54}
{2.68,162.39}
2.68,162.39

f1 (ppm)

f2 (ppm)

138

Analyst   Administrator
Date   18 January 2017 12:04

%T vs cm-1 spectrum with labeled peaks:

3075.90cm-1
3060.57cm-1
2987.97cm-1
2864.27cm-1
2162.60cm-1
1979.74cm-1
1936.47cm-1
1683.64cm-1   1184.54cm-1   1110.47cm-1
1047.61cm-1   1002.86cm-1
986.28cm-1
930.29cm-1
1216.71cm-1
1242.33cm-1
888.93cm-1
1026.95cm-1
841.44cm-1
1583.93cm-1
1080.95cm-1
1153.89cm-1
1290.44cm-1   785.17cm-1
1321.28cm-1
1568.76cm-1   1369.78cm-1   730.99cm-1
1434.90cm-1
1513.58cm-1   826.81cm-1
1353.67cm-1
697.94cm-1   748.87cm-1

138   18 January 2017

Handwritten structure and list:

NO2
Ph

1684   1081
1594   1027 1003
1568   930   986
1514   889
1435?
1370 1354   841
1242 1321   827
1217   785 749
1154   731
1110   698   Page 1

Synthesis of 6-methyl-3-nitro-2,4-diphenylpyridine (**124**).

(500 MHz, Chloroform-*d*)

PROTON_01
TN-119_recryst

7.63, 7.62, 7.62, 7.61, 7.60, 7.48, 7.47, 7.46, 7.45, 7.41, 7.40, 7.40, 7.39, 7.39, 7.28, 7.26 cdcl3, 7.22

2.71

1.60 H2O
1.60 H2O

0.09, 0.08, 0.00

E (q)
7.46

D (m)
7.61

C (s)
7.22

B (m)
7.40

A (s)
2.71

1.99, 6.10, 1.93, 0.89

3.08

f1 (ppm)

(126 MHz, Chloroform-*d*)

HSQC

gHSQCAD_01
TN-119_recryst

A
2.70,24.41 {2.70,24.41}

D
{7.21,127.?} 123.34
{7.46,129.20}
B
{7.?9,127.64}

HMBC

gHMBCAD_01
TN-119_recryst

{2.57,24.52}
{2.83,24.52}

{2.70,123.35}

{7.47,127.68}
{7.23,127.80}
{7.22,134.37}
{7.22,144.45}
{7.37,142.93}
{7.60,150.55}
{2.70,160.04}
A
2.70,160.04
{7.22,160.04}

Analyst   Administrator
Date   18 January 2017 11:56

96
95

1053.36cm-1 731.26cm-1 1403.03cm-1 926.63cm-1
1578.78cm-1

90

1261.01cm-1

85

80

911.43cm-1

878.61cm-1

75   3063.04cm-1   1212.18cm-1   1158.28cm-1

1029.16cm-1

70

%T   2924.07cm-1

65   1963.31cm-1   888.80cm-1

1181.00cm-1

60   2201.99cm-1   998.73cm-1
                                                        1493.41cm-1 652.67cm-1
55   836.59cm-1

1606.53cm-1
50   1445.41cm-1   800.45cm-1
        1669.31cm-1   867.97cm-1
45   1316.93cm-1   1364.55cm-1 1550.67cm-1

40   1379.92cm-1   1590.45cm-1   761.89cm-1
              1077.66cm-1   1523.95cm-1   696.04cm-1
36
  4000   3500   3000   2500   2000   1500   1000   650
                        cm-1

—————— TN-118   16 January 2017

4-ethyl-6-methyl-3-nitro-2-phenylpyridine (**126**).

(500 MHz, Chloroform-*d*)

PROTON_01
TN-155 yellow wax post-column

Peak labels (left cluster): 7.59, 7.59, 7.59, 7.58, 7.58, 7.57, 7.57, 7.45, 7.45, 7.44, 7.44, 7.44, 7.43, 7.43, 7.43, 7.27 cdcl3, 7.13

Peak labels (middle cluster): 2.70, 2.68, 2.67, 2.65

Peak label: 1.61 H2O

Peak labels (right cluster): 1.33, 1.31, 1.30

D (m)
7.44

E (ddd)
7.58

F (s)
7.13

C (q)
2.68

B (s)
2.65

A (t)
1.31

Integrals: 1.90, 3.02, 0.99, 1.71, 3.29, 3.10

f1 (ppm)

(126 MHz, Chloroform-*d*)

CARBON_01
TN-155 yellow wax post-column

Peaks labeled: 159.93, 150.29, 145.69, 145.27, 136.30, 129.52, 128.73, 127.93, 122.26, 77.26 cdcl3, 77.01 cdcl3, 76.75 cdcl3, 24.53, 24.07, 13.93

Assignments:
- G (s) 159.93
- E (s) 150.29
- C (s) 145.27
- A (s) 145.69
- F (s) 136.30
- D (s) 129.52
- B (s) 127.93
- L (s) 128.73
- H (s) 122.26
- J (s) 24.07
- I (s) 24.53
- K (s) 13.93

HSQC

gHSQCAD_01
TN-155 yellow wax post-column

HMBC

gHMBCAD_01
TN-155 yellow wax post-column

[Mass Spectrum]
Data : 240919 - Tyler Nichols - TN.155 - 001   Date : 24-Sep-2019 09:45
Instrument : JEOL MStation JMS-700(2)
Sample :
Note :
Inlet : Direct   Ion Mode : EI+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.32 min   Scan# : (3,7)   Temp : 3276.7 deg.C
BP : m/z 242.1789   Int. : 461.55 (4839700)
Output m/z range : 50 to 353   Cut Level : 0.00 %
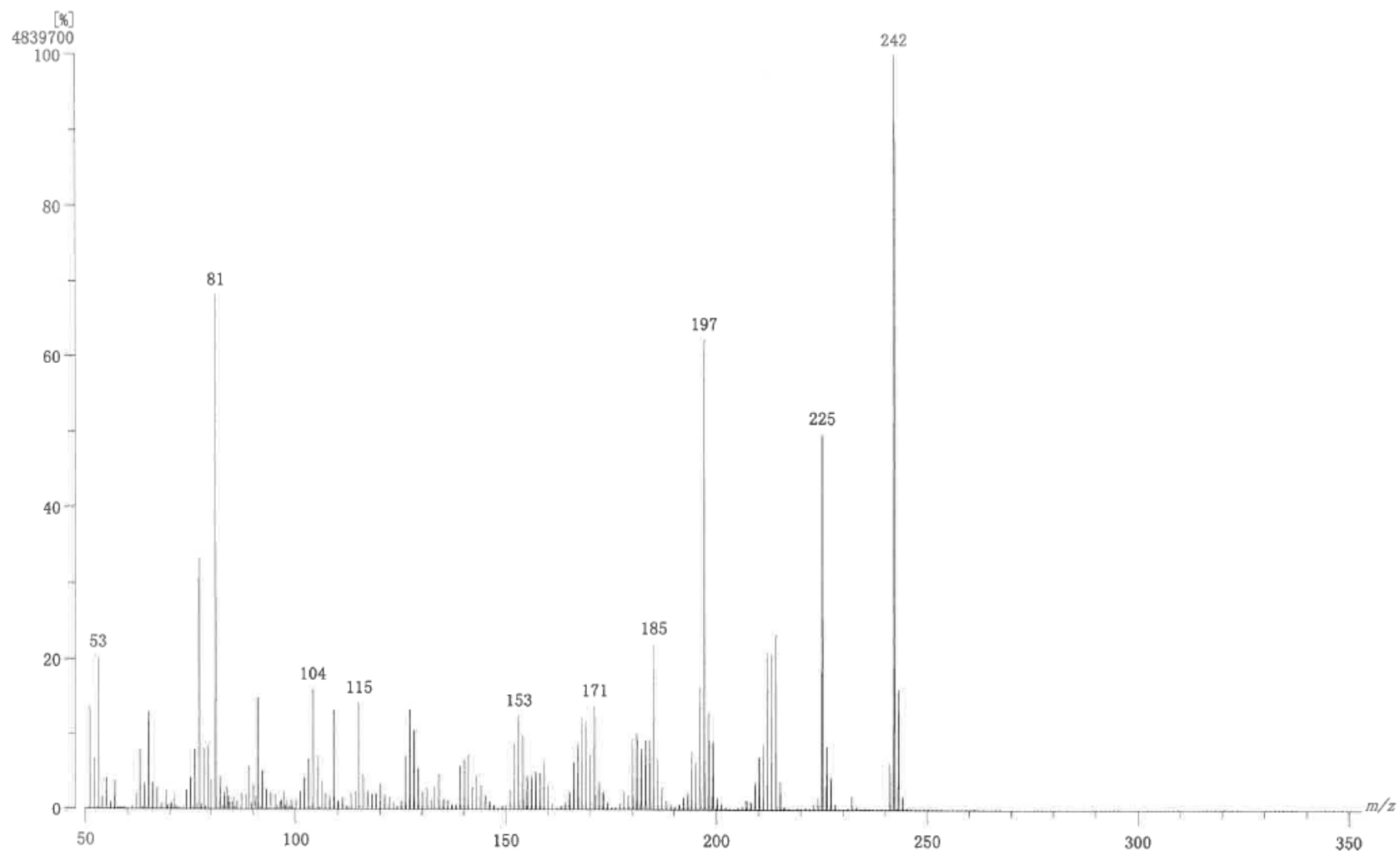
Data : 240919 - Tyler Nichols - TN.155 - 002   Date : 24-Sep-2019 09:49
Instrument : Station
Sample :
Note : Positive Ion EI
Inlet : Direct   Ion Mode : EI+
RT : 0.50 min   Scan# : (4,6)
Elements : C 14/0, H 14/0, N 2/0, O 2/0
Mass Tolerance   : 1000ppm, 5mmu if m/z < 5, 50mmu if m/z > 50
Unsaturation (U.S.) : -0.5 - 50.0

	Observed m/z	Int%	Err[ppm / mmu]	U.S.	Composition
1	242.1046	100.00	-3.8 / -0.9	9.0	C14 H14 N2 O2
	243.1070	17.60			

155

Analyst　　　　　　　　Administrator
Date　　　　　　　　　23 January 2017 16:54
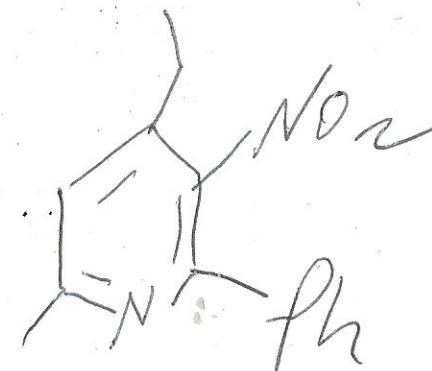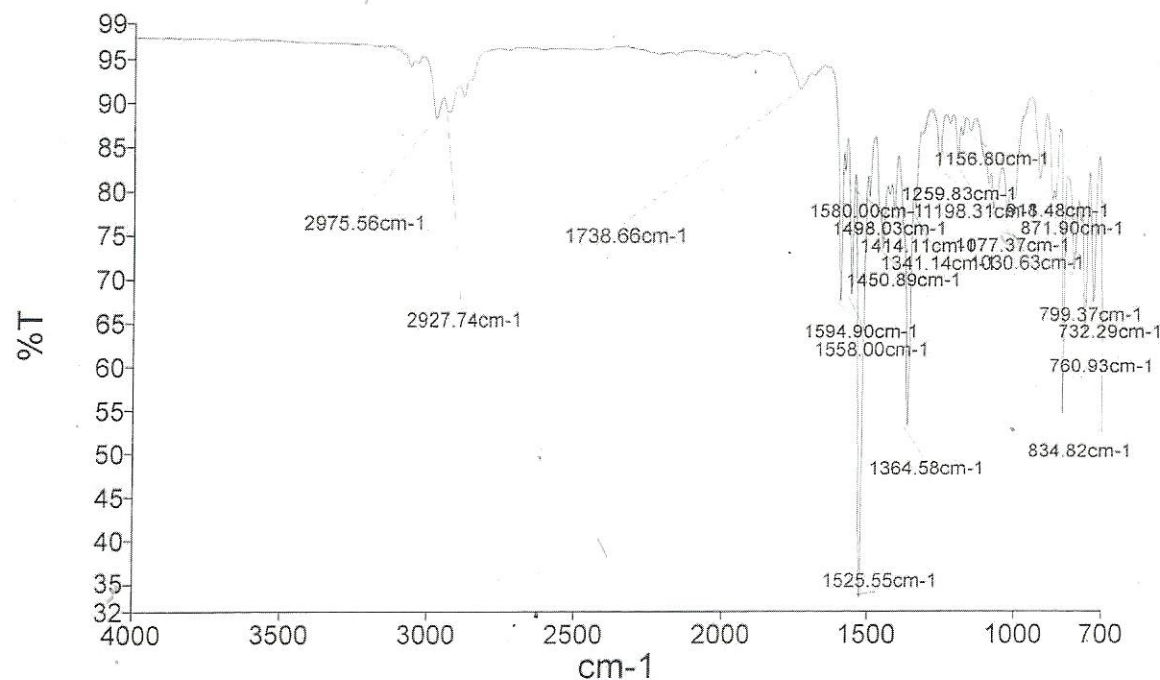
Sample Name	Description	Quality Checks
155	23 January 2017	The Quality Checks do not report any warnings for the sample.

Peak labels on spectrum:
2975.56cm-1
2927.74cm-1
1738.66cm-1
1156.80cm-1
1259.83cm-1
1580.00cm-11198.31cm-11013.48cm-1
1498.03cm-1　　　871.90cm-1
1414.11cm1077.37cm-1
1341.14cm1030.63cm-1
1450.89cm-1
1594.90cm-1
1558.00cm-1
799.37cm-1
732.29cm-1
760.93cm-1
834.82cm-1
1364.58cm-1
1525.55cm-1

%T (y-axis)
cm-1 (x-axis)

2-(3-chlorophenyl)-6-methyl-3-nitropyridine (**129**).

(500 MHz, Chloroform-*d*)

PROTON_01
TN-140_recryst

8.11
8.10
7.58
7.57
7.57
7.44
7.44
7.43
7.43
7.42
7.42
7.40
7.39
7.37
7.36
7.36
7.36
7.35
7.34
7.34
7.34
7.31
7.30
7.26 cdcl3
3.48
3.47
2.70
1.58 H2O
0.07
-0.01

C (d)
7.30

B (dt)
7.43

E (d)
8.11

A (s)
7.57

D (m)
7.36

F (s)
2.70

0.98
0.90
1.02
2.09
1.05
2.96

f1 (ppm)

CARBON_01
TN-140_recryst

162.67
151.21
143.97
138.54
134.67
132.75
129.80
129.59
128.37
126.19
122.54
88.27
77.27 cdcl3
77.01 cdcl3
76.76 cdcl3
24.78

D (s)
129.59

I (s)
143.97

F (s)
134.67

A (s)
126.19

E (s)
162.67

B (s)
151.21

H (s)
138.54

G (s)
129.80

L (s)
24.78

K (s)
132.75

J (s)
122.54

C (s)
128.37

0.47
0.36
0.35
0.40
0.51
1.39
1.31
1.43
1.25
1.78
1.77
0.98

f1 (ppm)

gHMBCAD_01
TN-140_recryst

{-0.00,0.01}

{7.31,24.85}   {2.57,24.85}
               {2.82,24.85}

{7.43,126.20}   {7.34,128.30}
{7.57,126.20}   {7.35,134.63}
{7.31,132.76}   {7.41,128.42}
               {7.57,134.75}
{8.11,151.27}
{8.10,144.00}   {7.30,144.00}
{7.57,151.27}   {7.34,151.27}
{7.31,162.63}   {7.29,162.63}

{2.70,122.56}

{2.70,162.63}
A
2.70,162.63

153

Analyst
Date

Administrator
23 January 2017 16:44

IR spectrum. %T vs cm-1. Labelled peaks:

- 2976.29
- 2927.59cm-1
- 1740.73cm-1
- 1593.40cm-1
- 1568.92cm-1
- 1556.95cm-1
- 1525.81cm-1
- 1479.77cm-1
- 1434.43cm-1
- 1412.00cm-1
- 1363.07cm-1
- 1260.07cm-1
- 1198.28cm-1
- 1158.57cm-1
- 1082.03cm-1
- 1035.18cm-1
- 999.26cm-1
- 932.06cm-1
- 877.76cm-1
- 836.94cm-1
- 801.55cm-1
- 784.05cm-1
- 723.55cm-1

Sample Name	Description	Quality Checks
153	23 January 2017	The Quality Checks do not report any warnings for the sample.

2-(3-chlorophenyl)-6-methyl-3-nitro-4-phenylpyridine (**128**).
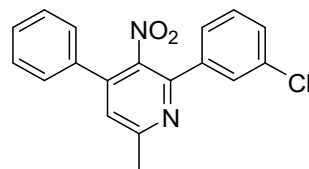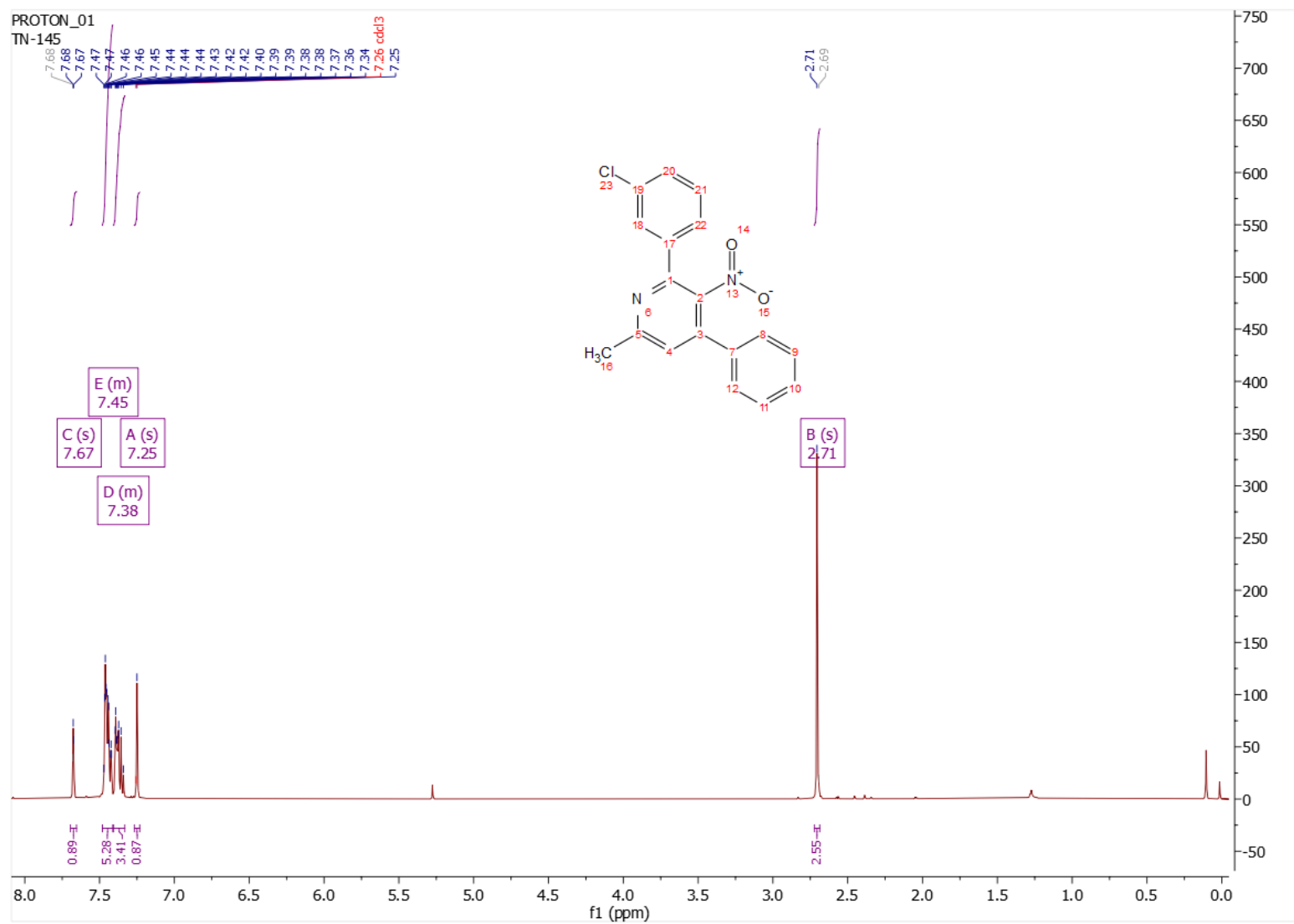
PROTON_01
TN-145

E (m)
7.45

C (s)
7.67

A (s)
7.25

D (m)
7.38

B (s)
2.71

(126 MHz, Chloroform-*d*)

HMBC

145

53

Analyst
Date

Administrator
23 January 2017 16:28

1767.19cm-1

3071.03cm-1

2884.57cm-1

1186.84cm-961.57cm-1

1398.54cm-1
1318.10cm-1   855.14cm-1
1167.01cm-1

2962.83cm-1

2201.44cm-1

1894.16cm-1

1963.39cm-1

1566.43cm-1   921.28cm-1
1477.81cm-12.79cm-1
1260.27cm-001.32cm-1
1427.58cm-1
1449.16cm-11056.80cm-1
1379.26cm-1025.02cm-1   879.07cm-1
1495.89cm-11094.36cm-1
1588.73cm-1   1079.02cm-739.10cm-1
884.05cm-1

1542.64cm-1

835.37cm-1
721.82cm-1
1362.62cm-1   802.76cm-1

1525.94cm-1   786.69cm-1
763.04cm-1

%T

4000   3500   3000   2500   2000   1500   1000   700
cm-1
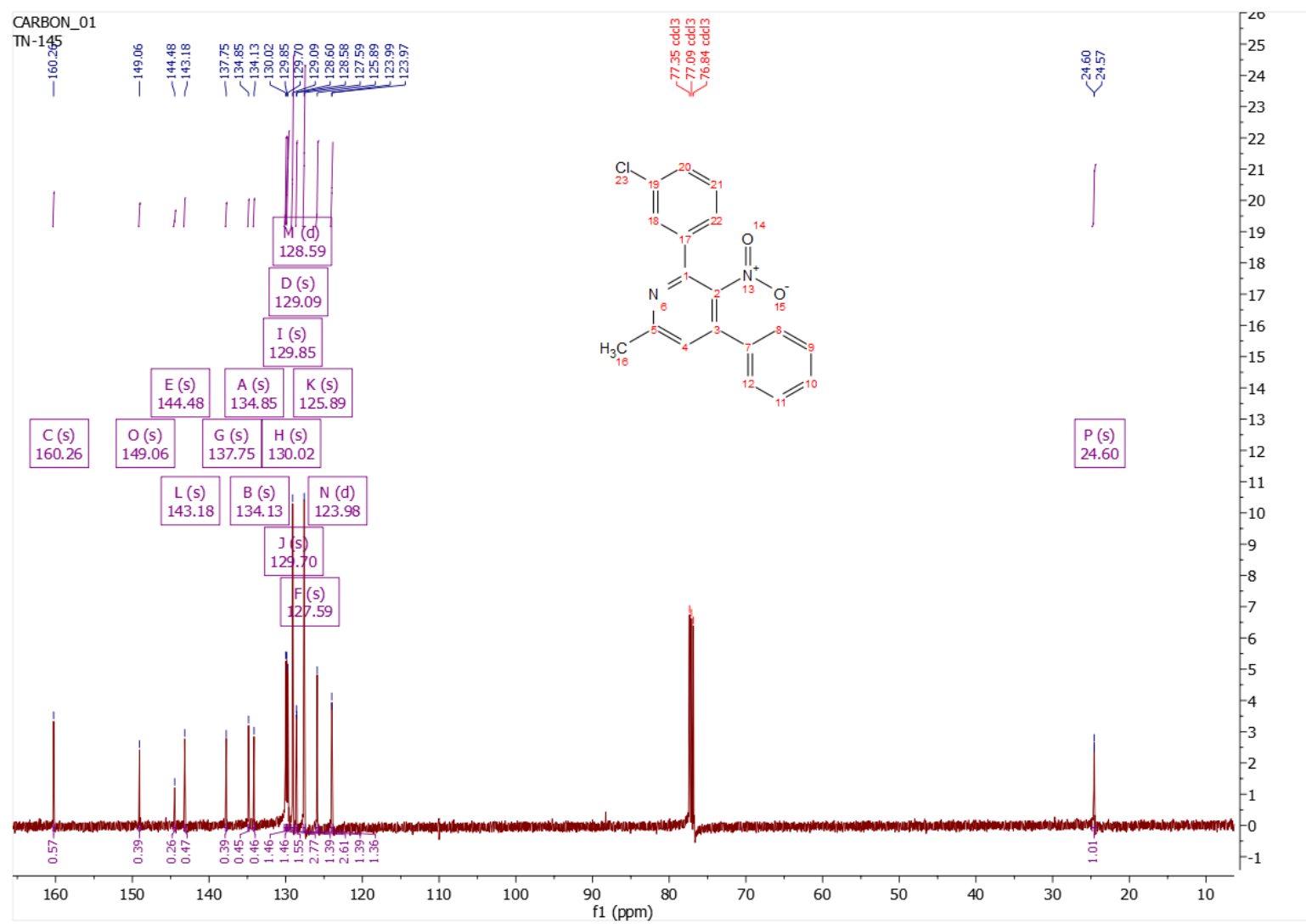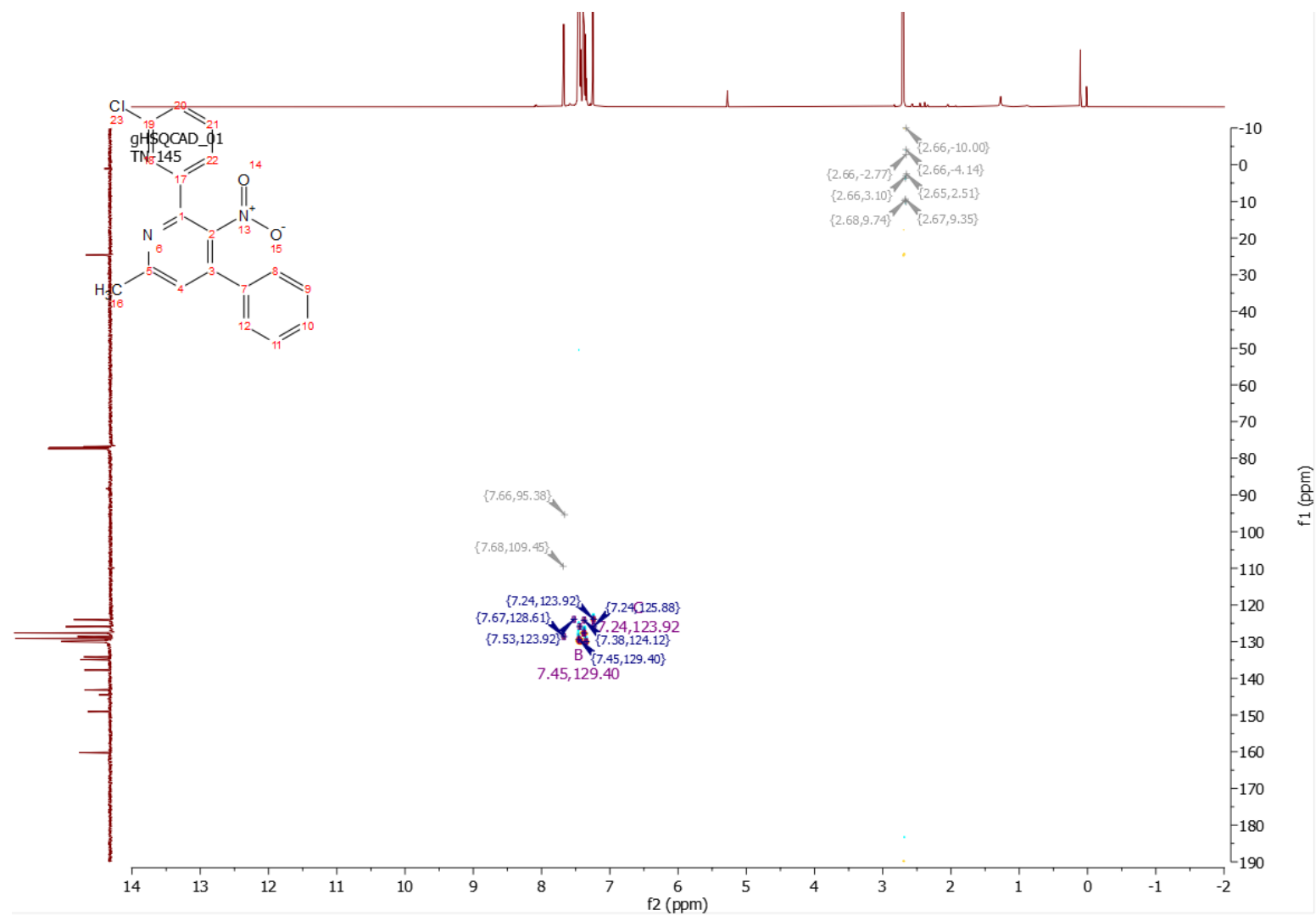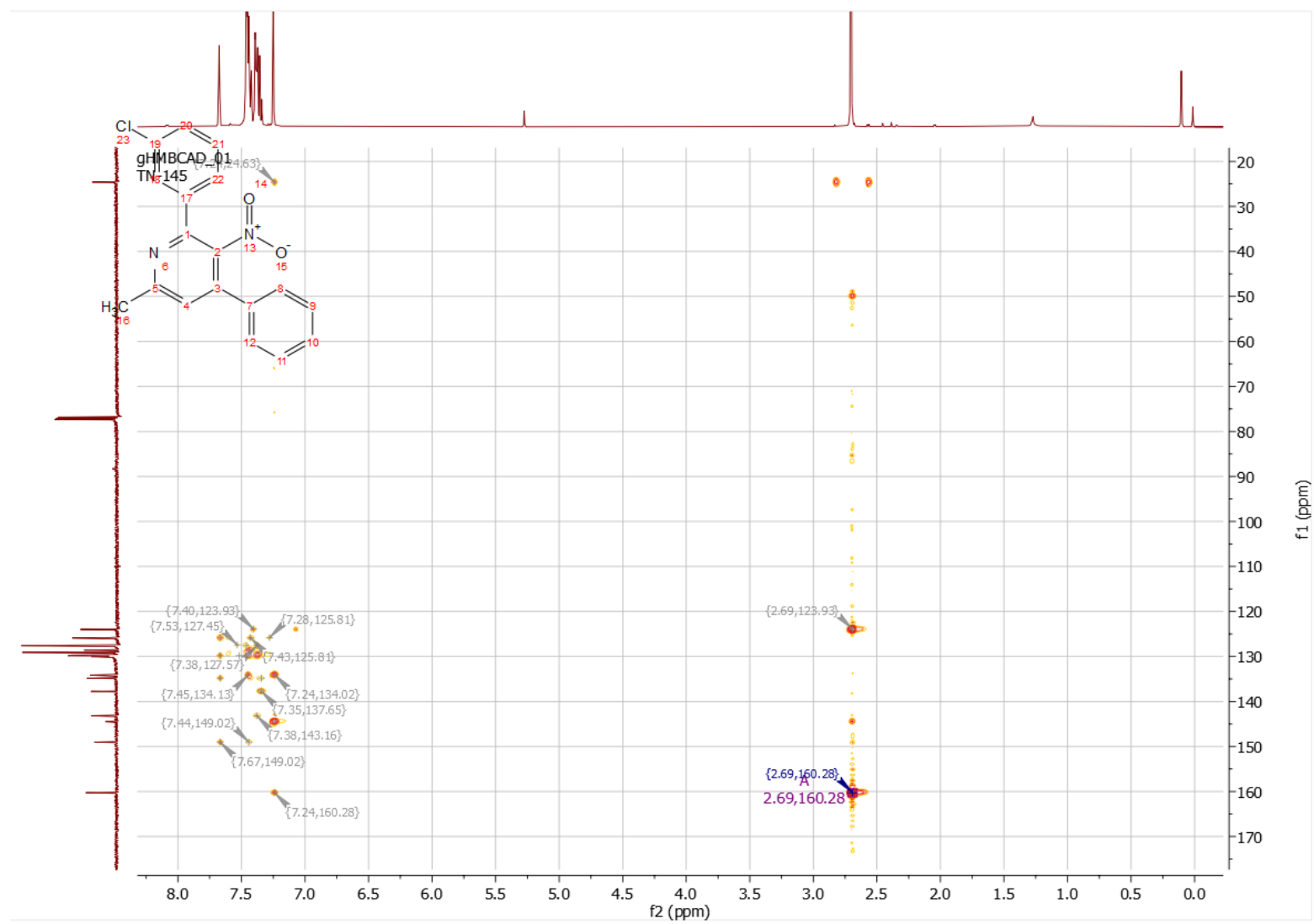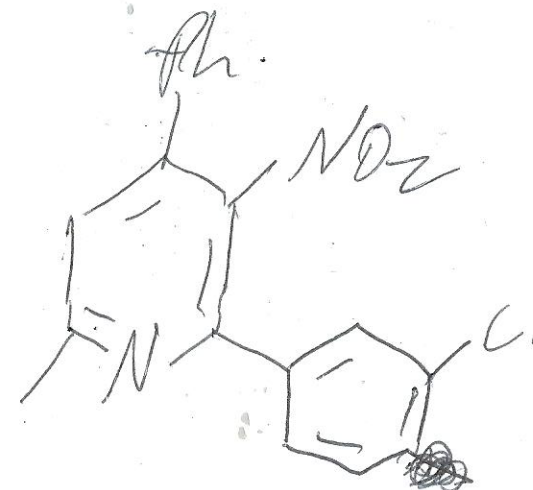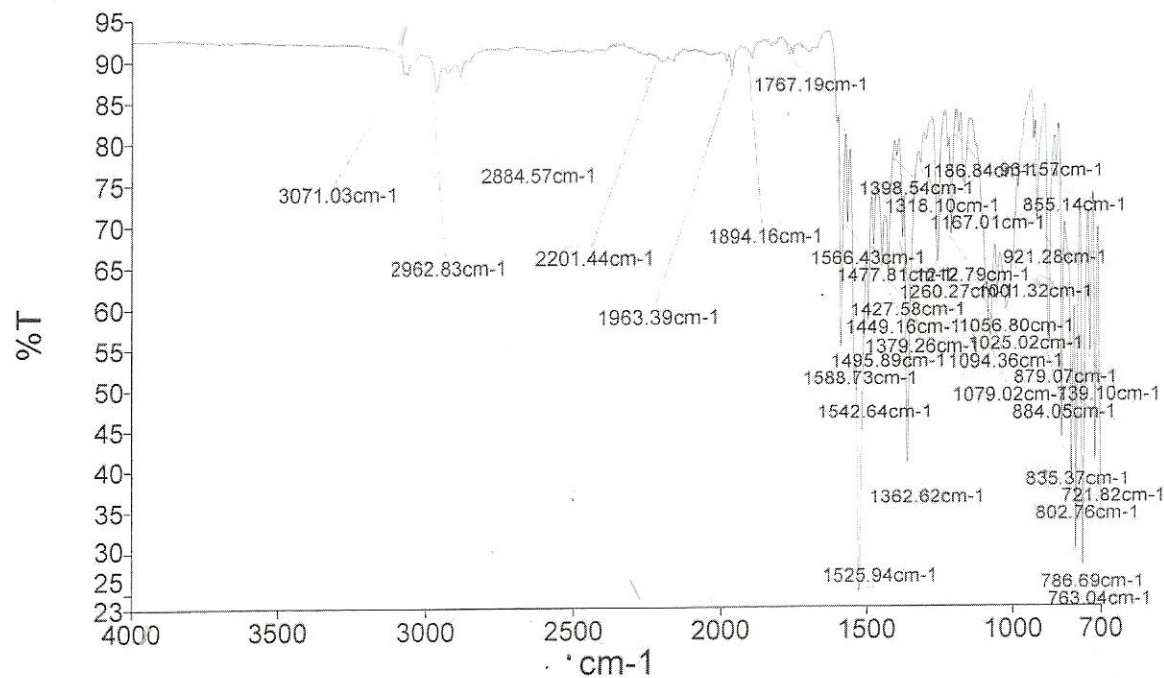
Sample Name	Description	Quality Checks
145	23 January 2017	The Quality Checks give rise to a Negative Bands warning for the sample.

2-(3-chlorophenyl)-4-ethyl-6-methyl-3-nitropyridine (**125**).

PROTON_01

7.61
7.60
7.60
7.42
7.42
7.41
7.40
7.40
7.39
7.36
7.34
7.33
7.26 cdcl3
7.15

2.68
2.67
2.65
2.64

—1.61 H2O

1.31
1.30
1.28

F (m)
7.41

B (s)
7.60

A (s)
7.15

G (m)
7.34

E (q)
2.67

D (s)
2.64

C (t)
1.30

0.97
2.05
1.07
0.94

1.77
3.17

3.03

f1 (ppm)

CARBON_01

gHSQCAD_01

gHMBCAD_01

{-0.01,0.01} {-0.05,1.06}
{0.19,1.06}
{2.51,11.26} {1.16,13.95}
{7.15,24.26} {2.67,13.95} {2.77,11.37} {1.42,13.95}
{2.54,24.14} {1.30,24.14} {1.29,23.21}
{1.22,29.42}
{1.22,34.57}
{2.77,37.85}

{6.98,122.91} {2.64,122.91}
{7.41,128.42}
{7.60,125.73} {7.31,122.91} {1.43,135.69}
{7.41,129.71}
{7.60,134.75} {2.67,145.53} {2.38,145.88} {1.21,145.29}
{7.35,137.91} {1.30,145.53}
{7.15,145.53}
{7.40,148.81}
{2.64,160.17}
A
2.64,160.17
{7.15,160.17}

{-0.05,217.47}

2-(4-fluorophenyl)-6-methyl-3-nitropyridine (**130**).

(500 MHz, Chloroform-*d*)

PROTON_01
TN-141

A (d)
8.07

C (m)
7.55

B (m)
7.16

E (d)
7.27

D (s)
2.70

gHSQCAD_01
TN-141

{7.15,115.77}
C
7.15,115.77

{7.26,122.02}
A
7.26,122.02

{7.55,130.22}
D
7.55,130.22

{8.06,132.76}

f1 (ppm)

f2 (ppm)

gHMBCAD_01
TN-141

{2.81,24.75}   {2.55,24.75}
{2.81,37.88}   {2.55,38.00}

{7.30,115.61}   {7.14,115.73}

{2.68,122.06}

{7.53,130.15}

{7.14,132.73}

{8.05,143.86}

{8.05,151.37}   {7.27,143.98}

{7.52,151.37}

{7.12,164.50}

{8.07,162.39}   {7.25,162.39}

{2.68,162.39}
2.68,162.39

141

44

Anályst   Administrator
Date   20 January 2017 14:37

%T

3079.06cm-1
3061.33cm-1
2924.59cm-1
2852.01cm-1
1954.39cm-1
1897.99cm-1
1692.95cm-1
1605.92cm-1
1589.02cm-1
1571.18cm-1
1505.04cm-1
1440.49cm-1
1411.76cm-1
1370.19cm-1
1348.08cm-1
1302.82cm-1
1286.66cm-1
1219.54cm-1
1164.62cm-1
1155.04cm-1
1104.25cm-1
1044.93cm-1
1016.43cm-1
962.13cm-1
889.82cm-1
839.48cm-1
805.91cm-1
773.21cm-1
733.17cm-1
711.70cm-1
701.62cm-1
682.52cm-1

cm-1

141   20 January 2017

2-(4-fluorophenyl)-6-methyl-3-nitro-4-phenylpyridine (**131**).
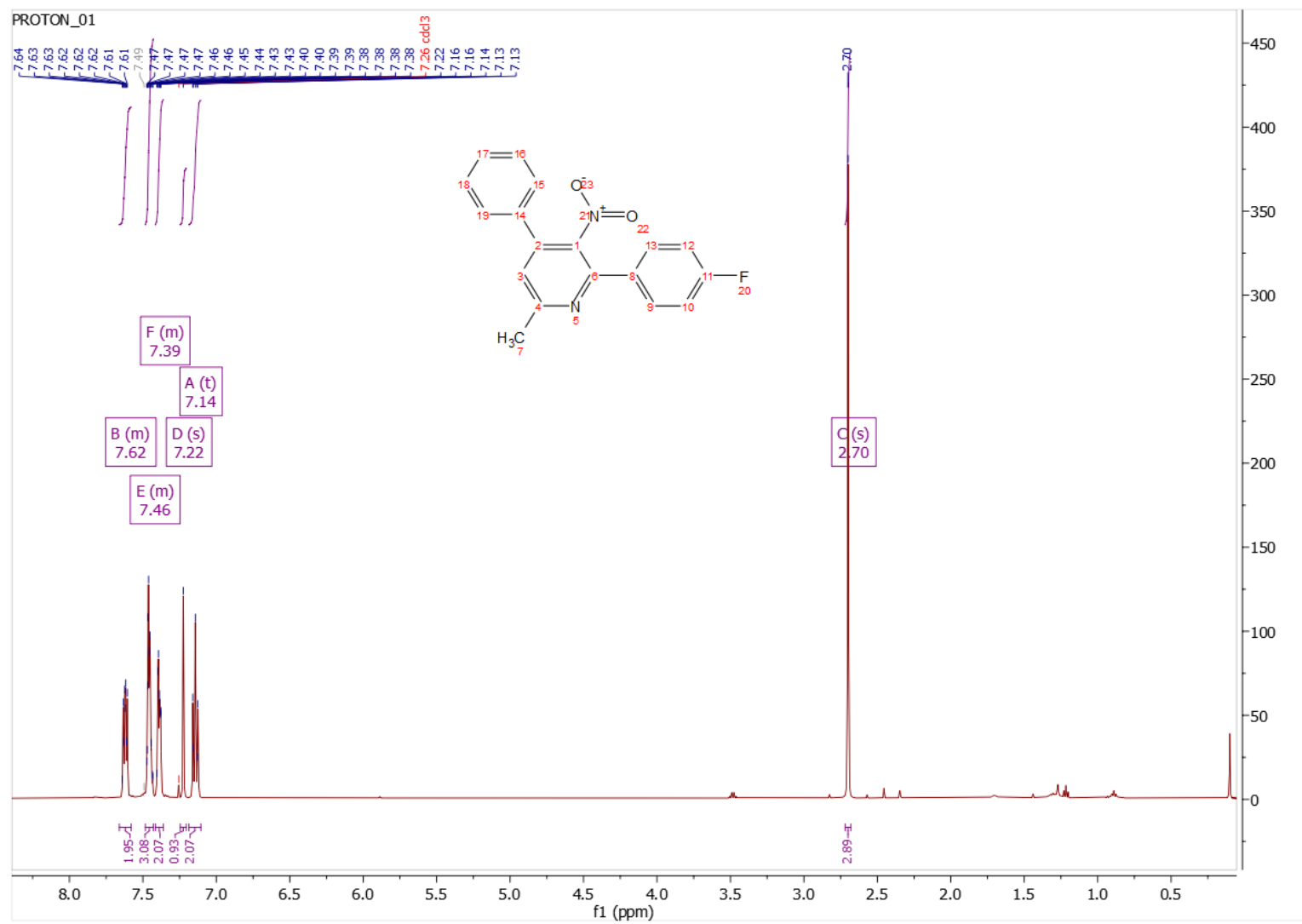
PROTON_01

F (m)
7.39

A (t)
7.14

B (m)
7.62

D (s)
7.22

E (m)
7.46

C (s)
2.70

(126 MHz, Chloroform-*d*)

HMBC

gHMBCAD_01

{7.22,24.61} {2.57,24.61}
{2.82,24.61}

{7.14,116.00} {2.70,123.62}
{7.47,127.48} {7.40,127.60}
{7.22,134.16}
{7.44,127.60} {7.39,129.59}
{7.46,134.16}
{7.22,142.95}
{7.63,149.39} {7.61,149.39} {2.70,160.06} {2.35,161.11}
2.70,160.06
{7.14,162.63} {7.22,160.06}

146

Analyst   Administrator
Date   23 January 2017 16:33

Sample Name	Description	Quality Checks
146	23 January 2017	The Quality Checks do not report any warnings for the sample.

2-(4-fluorophenyl)-4-ethyl-6-methyl-3-nitropyridine (**132**).
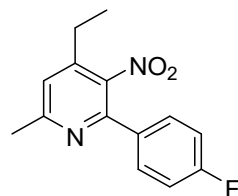
Chemical Formula: C$_{14}$H$_{13}$FN$_2$O$_2$

Molecular Formula: 260.26 g/mol

(500 MHz, Chloroform-*d*)
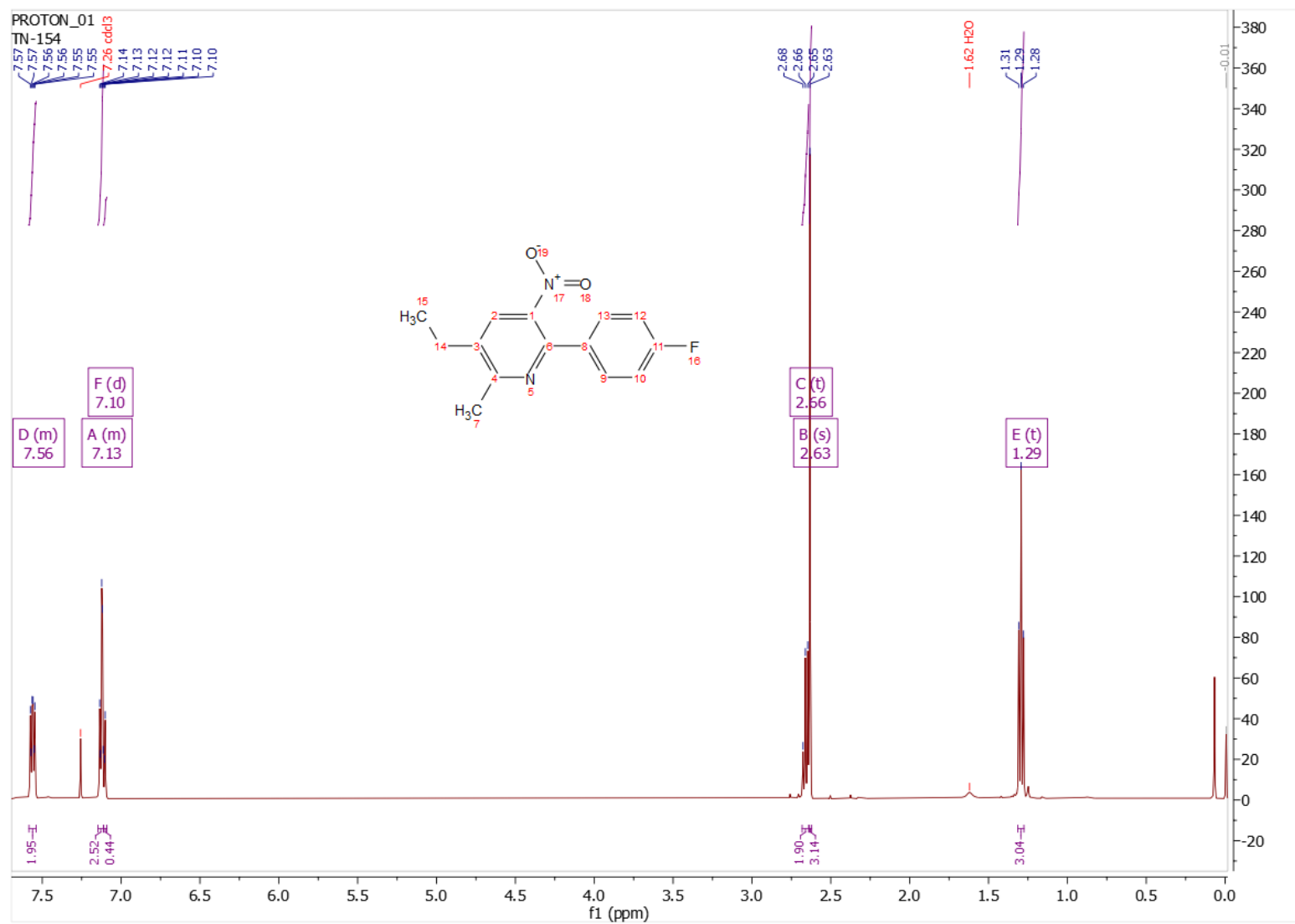
(126 MHz, Chloroform-*d*)
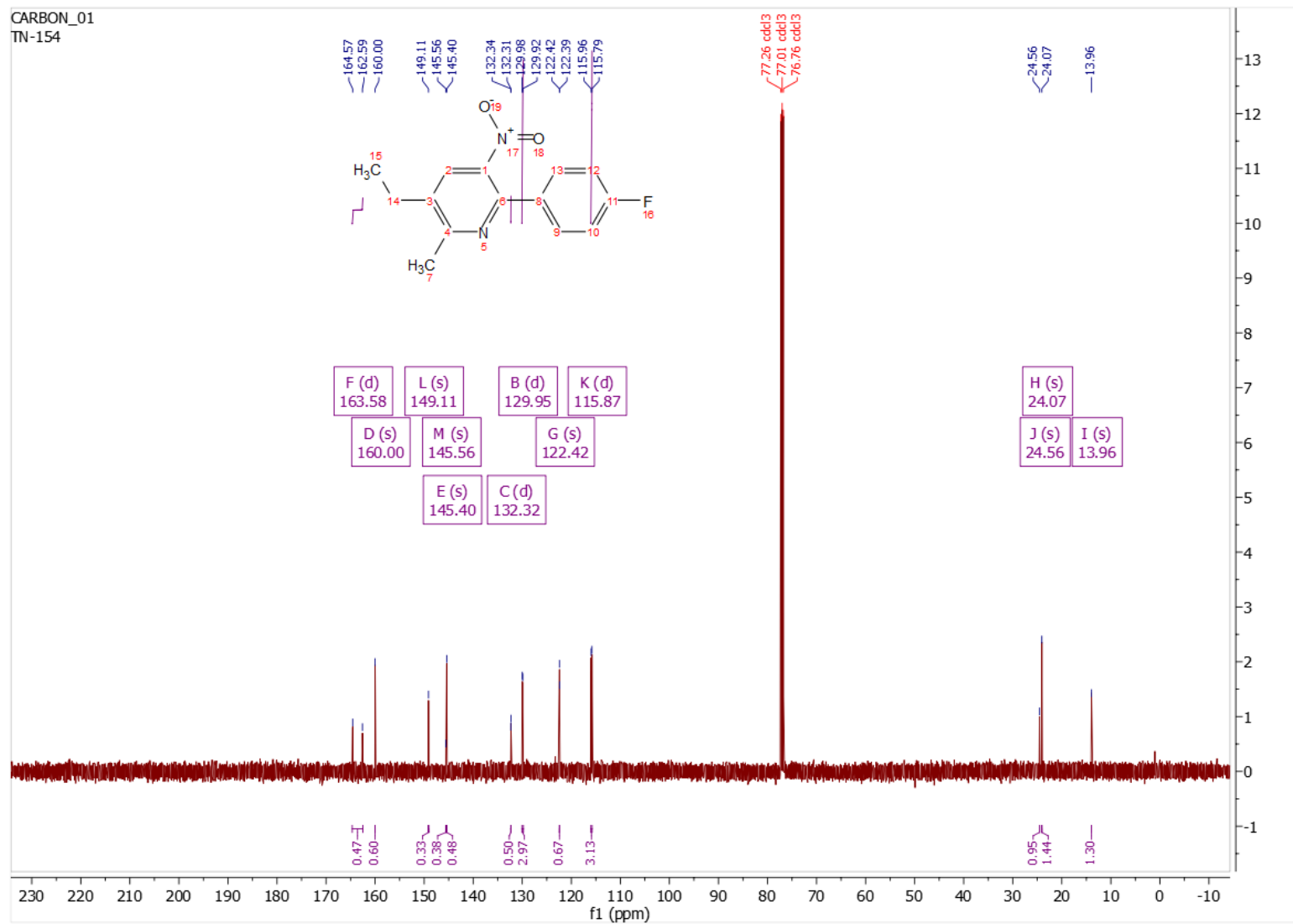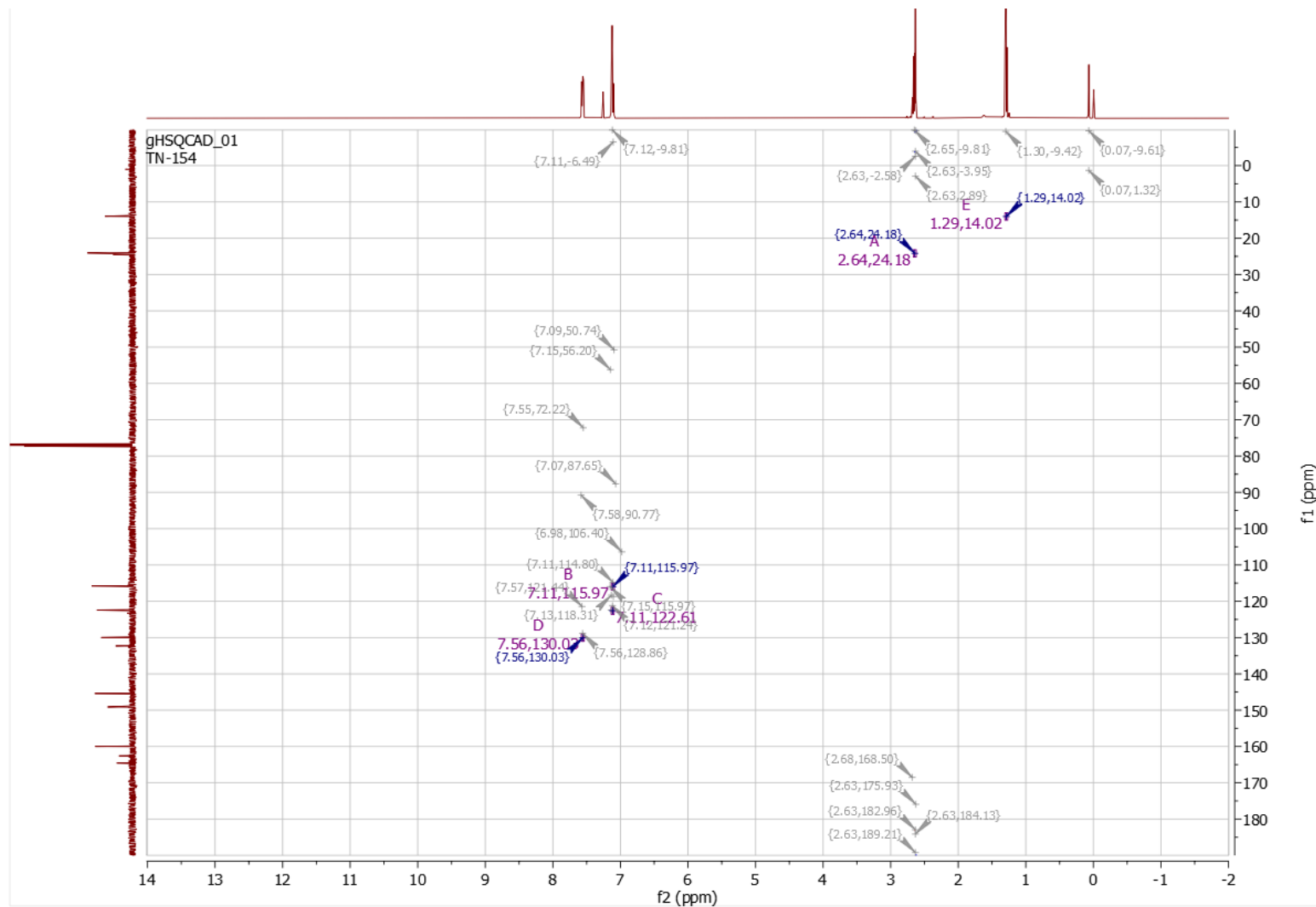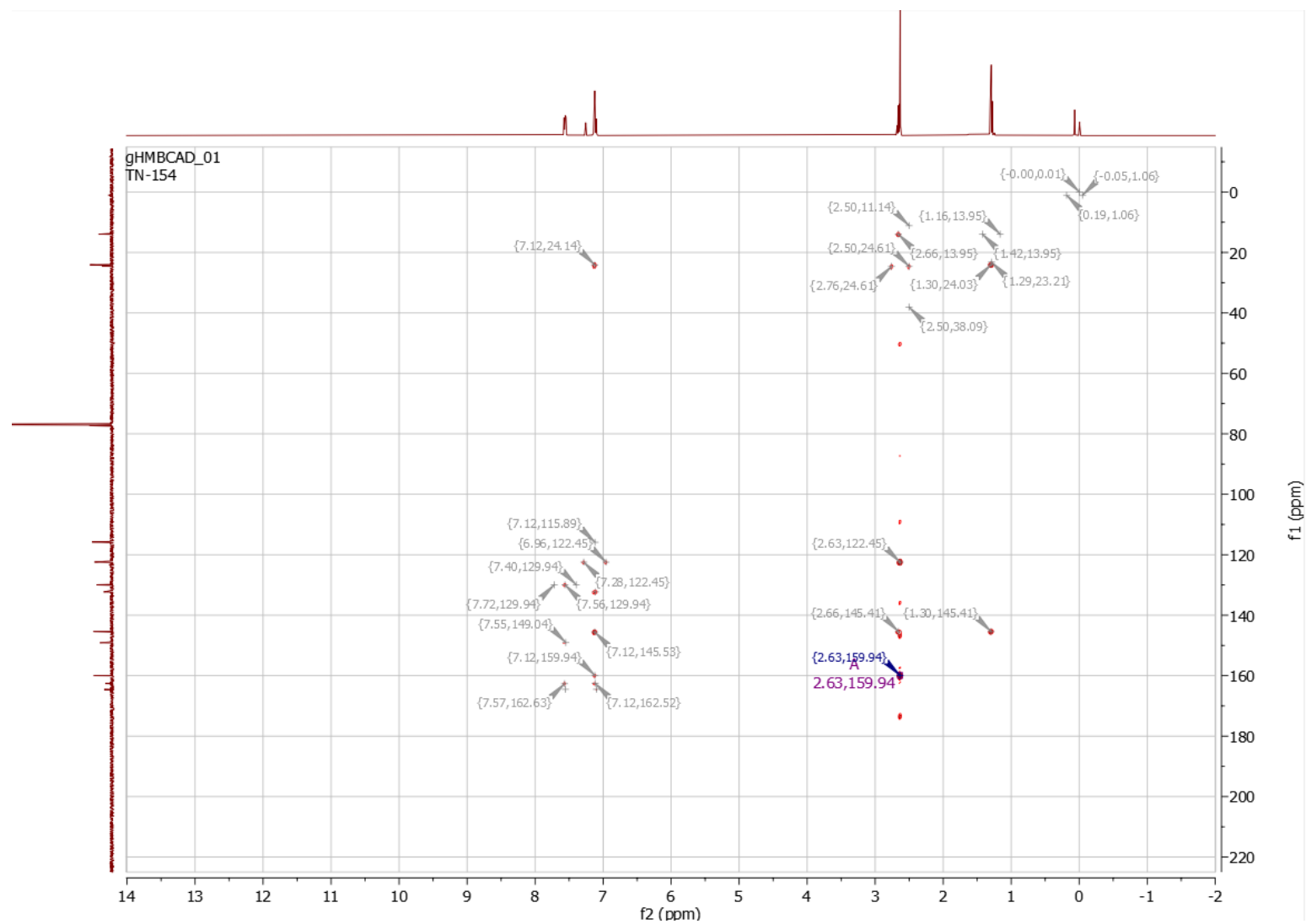
CARBON_01
TN-154
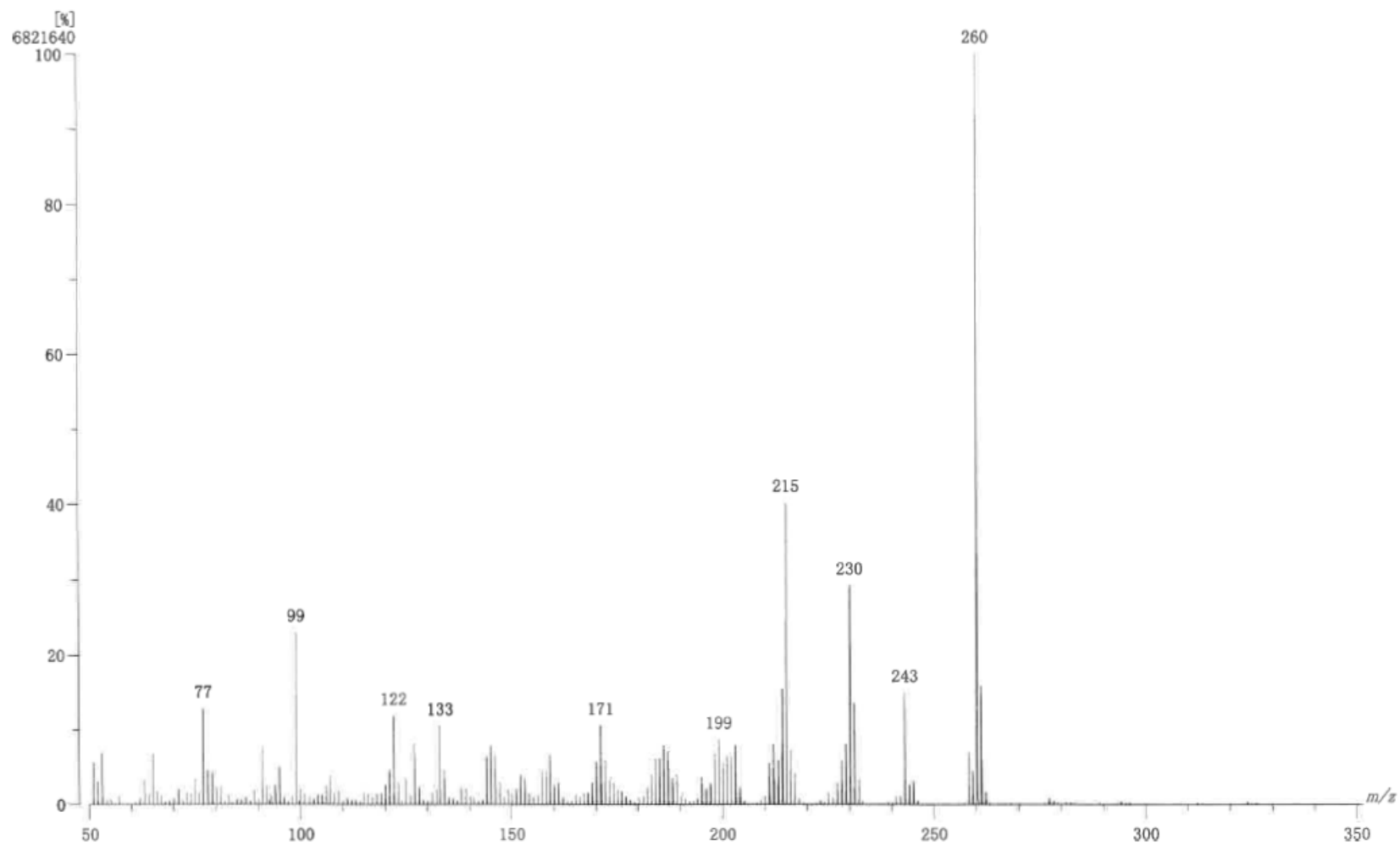
```
[ Theoretical Ion Distribution ]
Molecular Formula : C14 H13 F N2 O2
                         (m/z   260.0961, MW   260.2678, U.S.  9.0)
Base Peak :   260.0961, Averaged MW :   260.2667(a),   260.2674(w)


    m/z       INT.
  260.0961 100.0000*******************************************************************
  261.0992  16.3822**********
  262.1018   1.6549*
  263.1043   0.1250
  264.1068   0.0074
  265.1094   0.0003
```

154

Analyst   Administrator

Date   23 January 2017 16:49

104
100

90   946.61cm-1
            1260.74cm-927.29cm-1
80   1304.35cm-1   740.83cm-1
1907.04cm-1   1034.78cm-1
            1017.97cm-718.16cm-1
            1099.19cm-1
2927.07cm-1   1740.11cm-1   880.54cm-1
70   1403.50cm-1
            1430.30cm-1070.17cm-1
%T   1464.93cm-1   868.44cm-1
            1203.19cm-1820.58cm-1
60   1557.32cm-1

1601.11cm-1 1163.39cm-1
50   791.02cm-1
                           836.91cm-1
40   1368.04cm-1
            1223.02cm-1
                           847.43cm-1
30   1523.77cm-1
26   1513.00cm-1

4000 3500 3000 2500 2000 1500 1000 700

cm-1
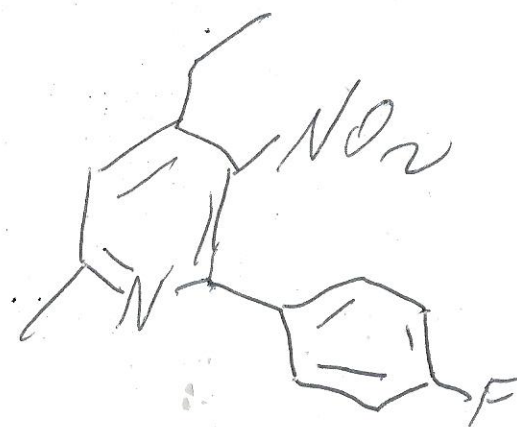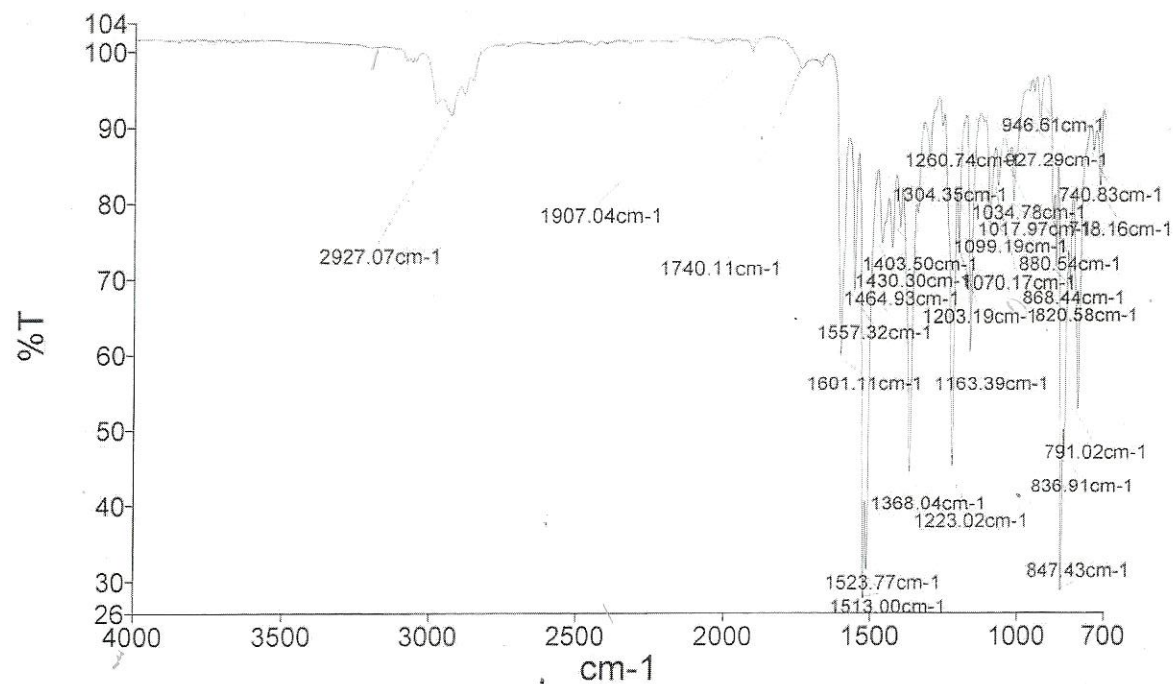
Sample Name	Description	Quality Checks
154	23 January 2017	The Quality Checks do not report any warnings for the sample.

2-(4-bromophenyl)-6-methyl-3-nitropyridine (**133**).

500 CDCl3

PROTON_01
TN-143 BR6

8.10
8.08
7.62
7.61
7.60
7.59
7.44
7.43
7.42
7.41
7.30
7.28
7.27 cdcl3
2.70

D (d)
8.09

B (d)
7.60

E (d)
7.43

A (d)
7.29

C (s)
2.70

0.9
2.00
2.04
1.10
2.85

f1 (ppm)

126 CDCl3

gHSQCAD_01
TN-143

B {2.68,24.80}
2.68,24.80

{7.57,83.65}

{8.09,118.84}
{8.07,123.16}
D
7.27,122.36
{7.27,122.36}
A
{7.29,124.31}
7.41,129.79
{7.60,129.59}
{7.41,129.79}
{7.59,131.94}
F {7.41,133.11}
7.41,133.11

gHMBCAD_01
TN-143

{2.55,11.50}
{2.81,11.50}
{2.81,24.75}
{2.55,24.75}
{2.81,37.88}
{2.55,38.00}
{-0.01,-0.10}
{0.18,1.07}

{7.41,124.17} {7.59,123.93}
{7.41,131.79}
{7.26,129.68}
{2.68,122.29}
{7.40,130.03}
{7.41,132.73}
{7.41,135.42}
{8.07,143.75} {7.28,143.86}
{8.09,151.37} {7.40,151.48}
{2.68,162.62}
A
2.68,162.62
{7.29,162.62} {7.27,162.62}

143

Analyst

Date

Administrator
20 January 2017 14:47

94
90
85
80
75
70
65
60
55
50
45
40
35
30
28

%T

4000   3500   3000   2500   2000   1500   1000   650

cm-1

3089.39cm-1
2923.54cm-1
2863.54cm-1
2163.40cm-1
1941.01cm-1
1908.90cm-1
1672.86cm-1
1542.44cm-1
1595.39cm-1
1489.59cm-1
1577.45cm-1
1442.66cm-1
1564.31cm-1
1237.61cm-1
889.55cm-1
708.30cm-1
1400.29cm-1
1306.24cm-1
1219.36cm-1
1275.81cm-1
1292.08cm-1
1047.47cm-1
1185.57cm-1
1261.57cm-1
970.68cm-1
1106.74cm-1
1156.96cm-1
735.72cm-1
1069.98cm-1
1010.23cm-1
718.84cm-1
823.15cm-1
1352.13cm-1
1513.49cm-1
771.88cm-1
836.30cm-1

143   20 January 2017

2-(4-Bromophenyl)-6-Methyl-3-Nitro-4-Phenylpyridine (**134**).

500 cdcl3

PROTON_01
TN-176

7.60
7.59
7.58
7.50
7.48
7.47
7.46
7.46
7.45
7.44
7.44
7.40
7.39
7.39
7.38
7.37
7.37
7.26 cdcl3
7.24

2.70

1.64 H2O

D (m)
7.38

E (d)
7.49

A (d)
7.59

F (s)
7.24

C (dd)
7.46

B (s)
2.70

2.13
1.97
3.06
2.06
0.93

2.85

f1 (ppm)
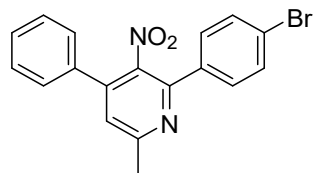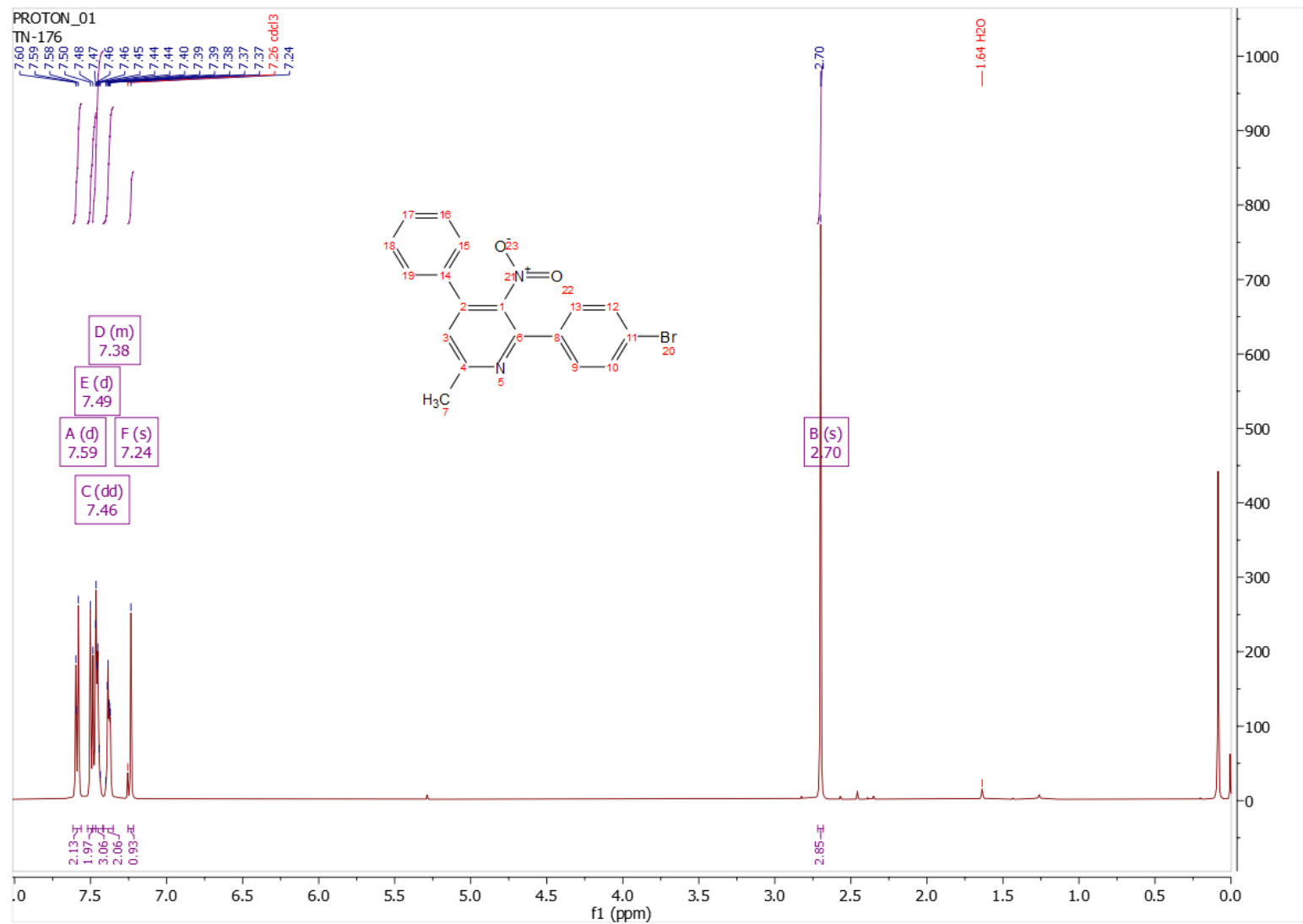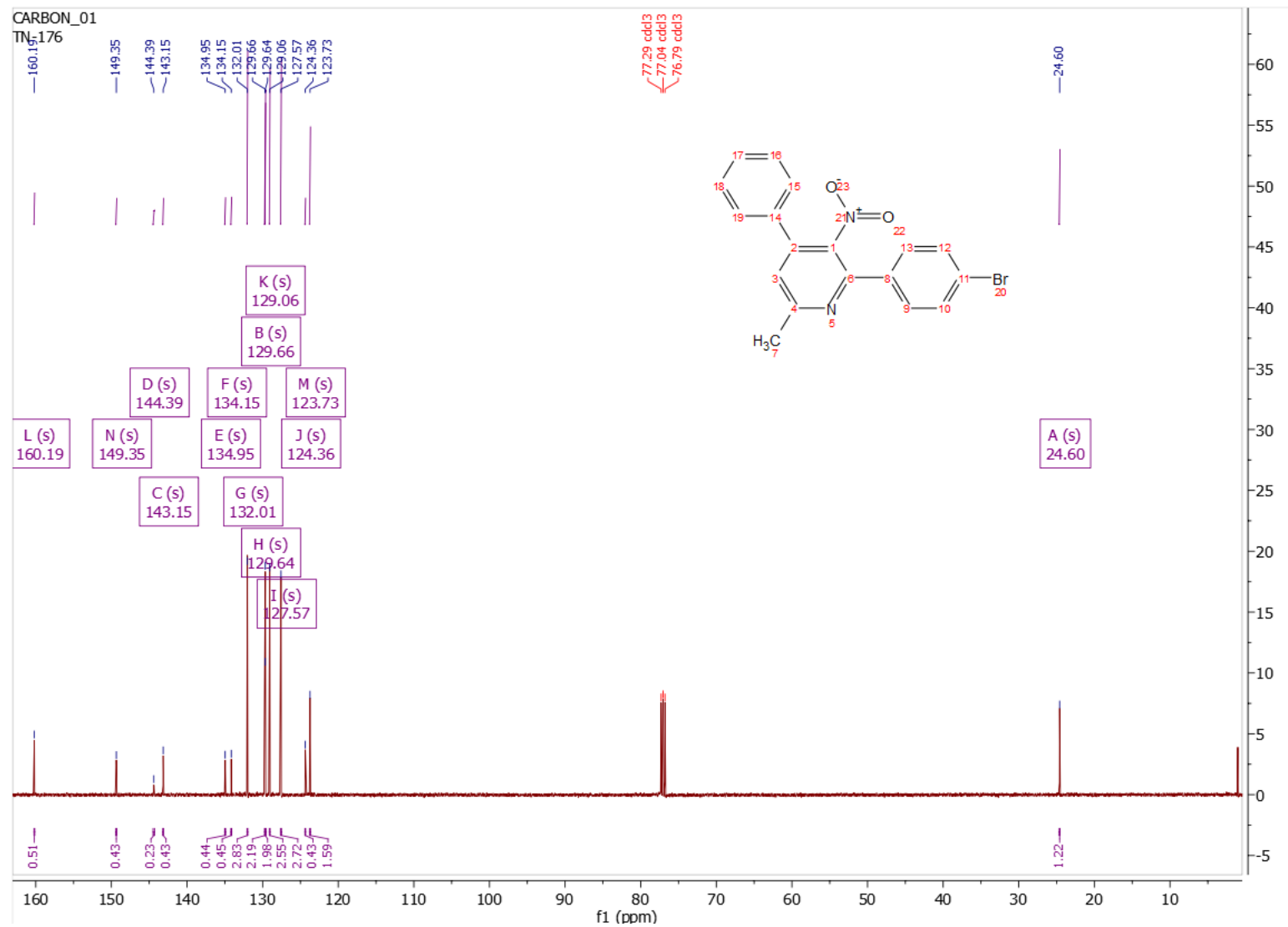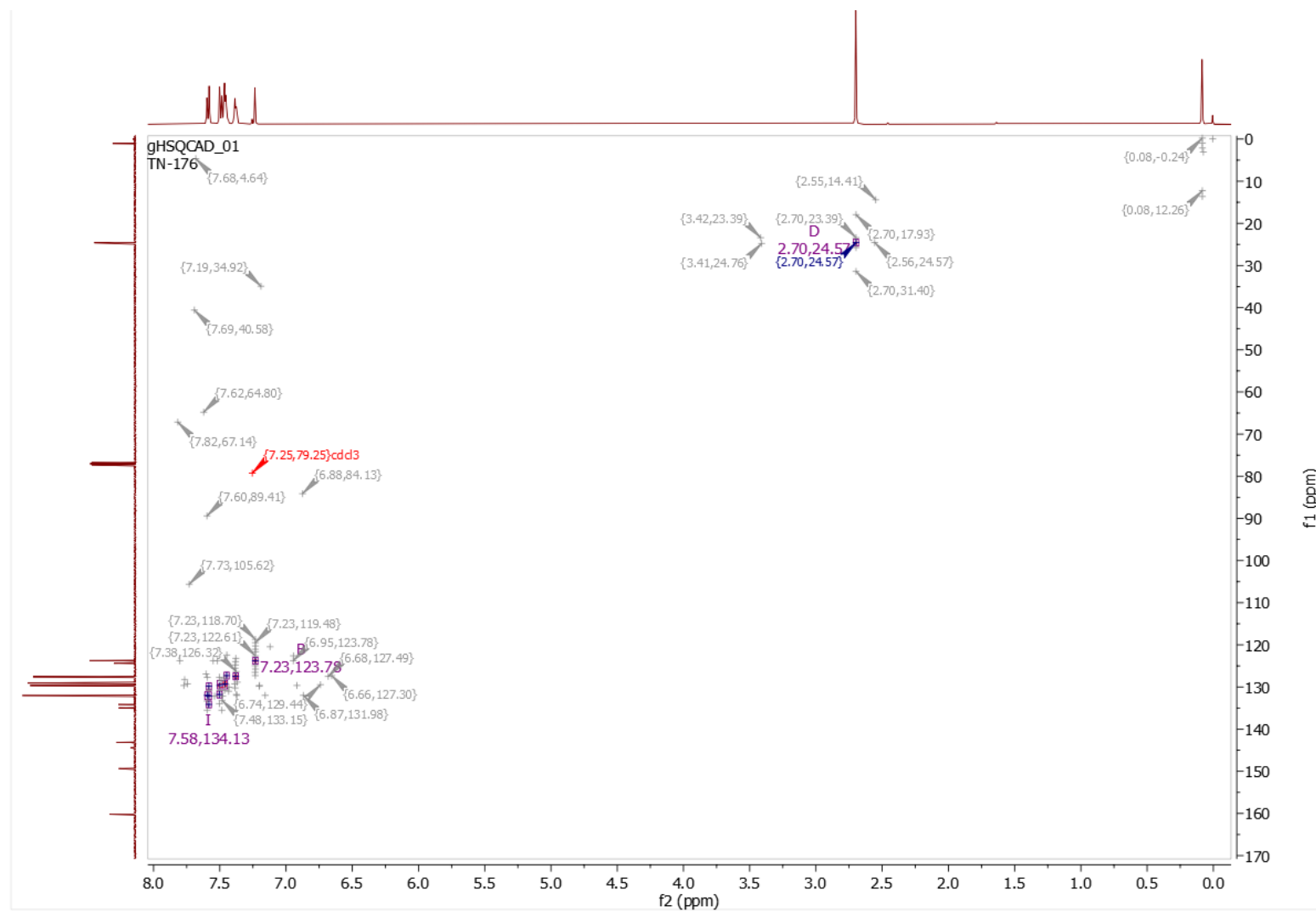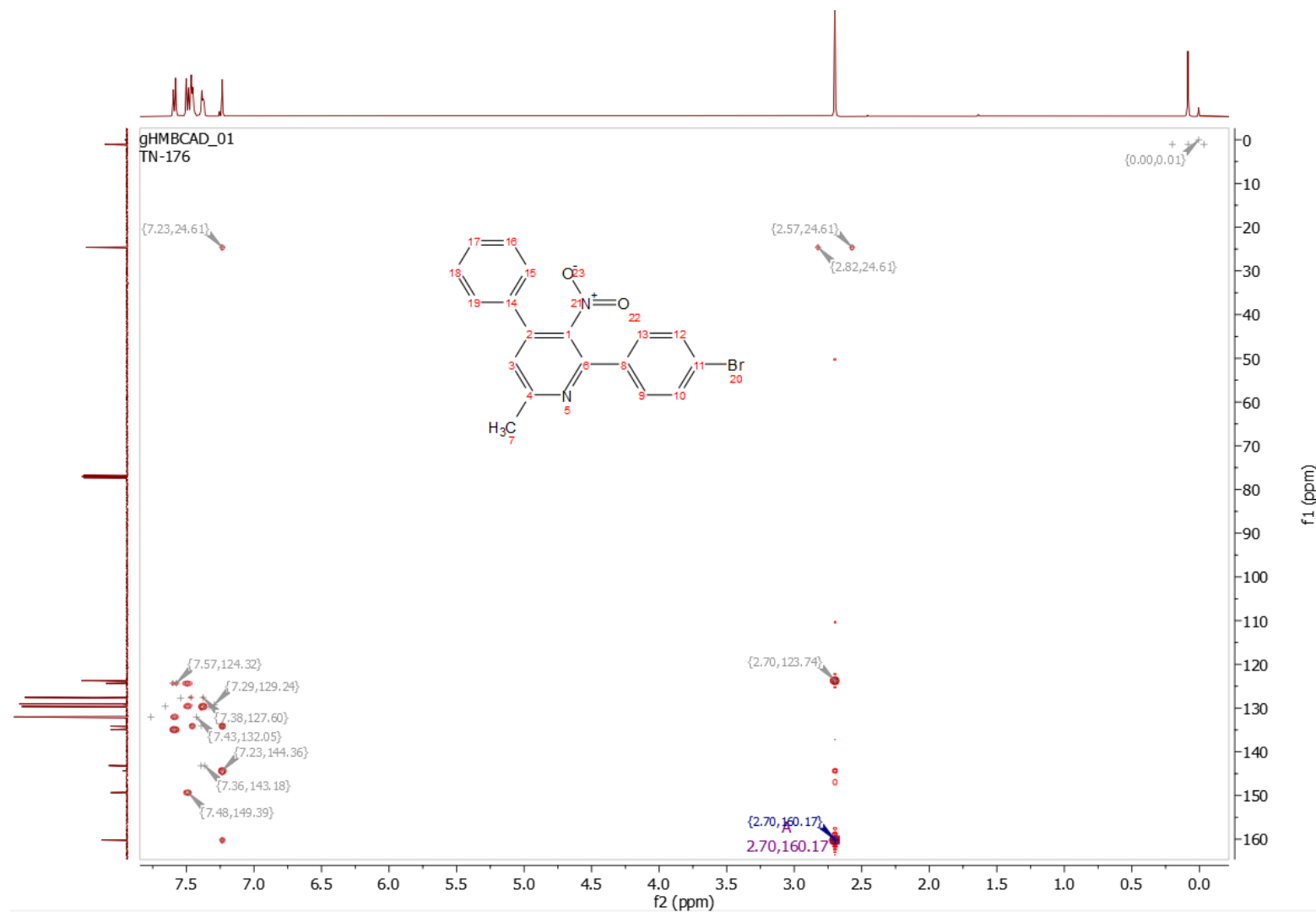
126 cdcl3

HSQC

6-methyl-3-nitro-2-[4-(propan-2-yl)phenyl]pyridine (**135**).

500 cdcl3

PROTON_01
TN-144 after further drying yellow wax

8.04
8.02
7.48
7.48
7.47
7.47
7.32
7.31
7.30
7.26 cdcl3
7.23
7.22

2.98
2.97
2.95
2.94
2.93
2.68

1.64 H2O

1.28
1.26

E (d)
8.03

A (d)
7.31

D (d)
7.48

C (d)
7.22

G (s)
2.68

F (hept)
2.95

B (d)
1.27

0.92
1.81
1.84
0.94
1.01
2.70
5.56

f1 (ppm)

126 cdcl3

CARBON_01
TN-144 after further drying yellow wax

Label	Peak
A (s)	162.22
B (s)	152.52
C (s)	150.48
D (s)	144.08
E (s)	134.13
F (d)	132.49
G (d)	121.60
H (s)	128.06
I (s)	126.87
J (d)	24.80
L (s)	34.01
O (s)	23.84

gHSQCAD_01
TN-144 after further drying yellow wax

gHMBCAD_01
TN-144 after further drying yellow wax

144

56

Analyst   Administrator
Date   23 January 2017 17:34

99

90

80   3072.40cm-1   1921.24cm-1688.81cm-1   921.16cm-1
                                                                             991.44cm-1
                                                                             955.68cm-1
                                                                              889.12cm-1
                                                                             972.03cm-1
                                                             1279.44cm-1
70   1612.20cm-1   1188.44cm-1
                                                     1466.89cm-1116.90cm-1
                                                     1291.65cm-119.62cm-1
                            2902.41cm-1   1376.29cm-1041.76cm-1
60   1106.97cm-1
                                                     1218.90cm-1
                                                     1301.11cm-1   744.59cm-1
      2964.43cm-1   1417.13cm-1
%T   1058.38cm-761.97cm-1
50   2868.63cm-1   1155.74cm-1
                                                     1566.91cm-237.64cm-1
                                                     1578.67cm-1
                                                     1444.86cm-1
40   2929.48cm-1
                                                                          774.88cm-1
                                                                          832.01cm-1
30   1354.27cm-1   844.39cm-1
                                                     1516.47cm-1

20
  4000   3500   3000   2500   2000   1500   1000   700
                              cm-1

Sample Name	Description	Quality Checks
144	23 January 2017	The Quality Checks do not report any warnings for the sample.

Page 1

2-[4-(benzyloxy)phenyl]-6-methyl-3-nitropyridine (**136**).

500 cdcl3

PROTON_01
TN-151_recryst

H (t)
7.40

D (d)
7.20

A (d)
8.01

B (d)
7.52

E (d)
7.05

F₁ (s)
5.12

G (s)
2.68

C (d)
7.44

I (m)
7.34

f1 (ppm)

126 cdcl3

gHMBCAD_01
TN-151_recryst

Analyst   Administrator
Date   20 January 2017 14:27

3075.81cm-1
2951.96cm-1
1989.03cm-1   1693.37cm-1
1915.73cm-1
1467.63cm-11081.69cm-1
1373.12cm-1047.15cm-1
889.68cm-1
1456.97cm-1   919.14cm-1
1417.50cm-1   862.92cm-1
1119.28cm-1
1288.01cm-1
1392.69cm-107.89cm-1
1315.99cm-1
1609.04cm-1
816.02cm-1
1586.73cm-1
1441.70cm-1   775.81cm-1
1568.33cm-1
1007.72cm-1
1001.06cm-1
1186.28cm-1
1346.10cm-1   836.55cm-1
699.22cm-1
1514.13cm-1   752.33cm-1
1235.96cm-1

%T

4000   3500   3000   2500   2000   1500   1000   650
cm-1

151   20 January 2017

2-[4-(benzyloxy)phenyl]-6-methyl-3-nitro-4-phenylpyridine (**137**).

500 cdcl3

PROTON_01

E (m)
7.45

G (m)   B (d)
7.39   7.04

F (d)   A (s)
7.57   7.17

C (m)
7.34

D (s)
5.11

H (s)
2.69

126 cdcl3

HSQC

gHSQCAD_01
TN-151_recryst

E {2.68,24.41}
2.68,24.41

{5.10,69.96}
5.10,69.96

{7.03,115.12}
7.03,115.12

{7.16,122.94}
7.16,122.94

{7.56,129.40}

{7.43,127.44}

f1 (ppm)

f2 (ppm)

HMBC

152

Analyst   Administrator
Date   20 January 2017 14:32

152   20 January 2017

Spectrum peak labels:

- 3075.76cm-1
- 1315.73cm-1
- 947.02cm-1
- 1417.56cm-1
- 1081.28cm-1
- 1047.67cm-1
- 1469.51cm-1
- 864.32cm-1
- 1118.69cm-798.00cm-1
- 1392.50cm-1
- 1289.18cm- 919.83cm-1
- 1367.78cm-1
- 816.27cm-1
- 762.99cm-1
- 776.30cm-1
- 1588.49cm-1
- 1608.71cm-1
- 881.56cm-1
- 1442.13cm-1
- 1568.42cm+1
- 1185.63cm-1
- 1347.29cm-1
- 838.17cm-1
- 1006.02cm-1
- 1514.23cm-1
- 749.94cm-1
- 699.17cm-1
- 1236.38cm-1

Peak list (handwritten):

1609	1236	
1589	1186	798
1568	1119	776
1514	1081	763
1470	1048	750
1442	1006	699
1418	947	
1393	920	
1368	882	
1347	864	
1316	838	
1289	816	

Structure labels: Ph, NO₂, OBn

Page 1

2-(furan-2-yl)-6-methyl-3-nitropyridine (**138**).

500 cdcl3

PROTON_01
TN-139

7.86
7.84
7.56
7.55
7.55
7.27
7.27 cdcl3
7.15
7.14
7.14
7.13
6.55
6.55
6.55
6.54

2.65

A (dd)
7.55

C (d)
7.85

E (m)
7.14

D (dd)
6.55

B (s)
2.65

0.98
1.02
2.03
1.00

2.97

f1 (ppm)

126 cdcl3

CARBON_01
TN-139

161.71

149.49
144.91
140.62

131.92

121.55

113.15
112.01
109.99

77.27 cdcl3
77.01 cdcl3
76.76 cdcl3

24.62

1.00

D (s)
161.71

B (s)
144.91

E (s)
149.49

G (s)
140.62

C (s)
131.92

J (s)
121.55

H (s)
112.01

F (s)
113.15

I (s)
109.99

A (s)
24.62

0.44
0.43
1.11
0.38
1.53
2.09
1.35
1.54
0.04
1.08

f1 (ppm)

HSQC

gHSQCAD_01
TN-139

{2.51,24.57}
E
2.65,24.57
{2.79,24.57}   {2.65,24.57}

O 15
N+
13   14
O

2
1
3
8
O
12
11
6
9
10
4
N
5
H3C
7

{6.43,58.35}

{7.25,110.89}
C
7.14,113.23
{6.55,110.11}
{7.14,113.23}
{5.84,107.96}
{5.8 112.06}
D
{5.55,112.06}
{6.55,112.06}
{5.84,112.06}

{7.14,121.63}
A
7.14,121.63
{7.15,121.63}

{7.84,131.79}
F
7.85,131.88
{7.85,131.98}

{7.55,145.07}
B
7.55,145.07

HMBC

139

Analyst   Administrator
Date   18 January 2017 12:13

96
90
85
80
75
70
65
60
55
50
45
40
35
29

%T

4000   3500   3000   2500   2000   1500   1000   650
cm-1

1165.92cm-1
1081.32cm-1
973.04cm-1
996.85cm-1
1236.32cm-1
3145.44cm-1
2854.69cm-1   1947.25cm-1
886.85cm-1
1378.04cm-1
2926.23cm-1   1053.72cm-1
1251.92cm-1
3080.22cm-1   1432.16cm-1   1034.96cm-1
1606.71cm-1   1117.37cm-1
931.88cm-1   864.08cm-1
1012.34cm-1
1487.95cm-1   834.82cm-1   665.30cm-1
1565.07cm-1   728.20cm-1
1219.36cm-1
824.97cm-1
1517.42cm-1   1289.43cm-1   766.13cm-1
742.72cm-1
1345.75cm-1

———   139   18 January 2017

NO2

1607   1166   766
1565   1117   743
1517   1081   728
1480   1054   665
1432   1035
1378   1012
1346   997 < 973
1284   932
1236 1252   827
          864
1219   835
          825

Page 1

2-(furan-2-yl)-6-methyl-3-nitro-4-phenylpyridine (**139**).

500 cdcl3

PROTON_01
TN-147

E (d)
7.15

C (m)
7.44

A (m)
7.55

B (s)
7.08

F (dd)
6.53

D (m)
7.37

G (s)
2.66

f1 (ppm)

126 cdcl3

HSQC

gHSQCAD_01
TN-147

HMBC

gHMBCAD_01
TN-147

147

Analyst

Date

Administrator
23 January 2017 16:20

IR spectrum with labeled peaks:
2924.67cm-1
3141.31cm-1
3114.95cm-1
1967.29cm-1
1746.08cm-1
1569.42cm-1
1548.66cm-1
1599.44cm-1
1447.73cm-1
1497.17cm-1
1363.14cm-1
1488.55cm-1
1528.07cm-1
1130.01cm-1
1189.63cm-1   925.76cm-1
1078.81cm-1
1215.30cm-1   784.07cm-1
1001.87cm-1
1055.80cm-1
1148.31cm-1   1100cm-1
1231.16cm-   876.51cm-1
944.89cm-1
1015.73cm-1
863.07cm-1
1032.09cm-1   -62cm-1
835.42cm-1
737.27cm-1
754.51cm-1
702.29cm-1

%T axis: 95, 90, 85, 80, 75, 70, 65, 60, 55, 50, 45, 42
x-axis: 4000, 3500, 3000, 2500, 2000, 1500, 1000, 700
cm-1

Sample Name	Description	Quality Checks
147-	23 January 2017	The Quality Checks do not report any warnings for the sample.

Ph NO2

1599   1079   740
1569   1056   784
1549   1032   755
1528   1016   737
1497   945   702
1489   926
1448   886
1363   877
1231?1215   863
1190
1148
1130

4-(6-methyl-3-nitropyridin-2-yl)morpholine (**140**).

500 cdcl3

PROTON_01
TN-142 BR5

A (d)
8.08

D (d)
6.62

C (t)
3.81

E (t)
3.47

B (s)
2.47

126 cdcl3

HSQC

gHSQCAD_01
TN-142

{3.47,1.92} {2.42,-9.61} {2.43,-10.00} {0.05,0.94}
{3.75,8.37} {2.43,-2.77}

{4.05,60.97}
B {3.47,66.44}
{3.7 3.47,66.44
{3.44,89.51}

{8.20,104.18} {6.61,103.98}

{6.60,113.76}
A
6.60,113.76

HMBC

142

Analyst   Administrator
Date   20 January 2017 14:42

142   20 January 2017

Spectrum peak labels:
3362.12cm-1 3095.00cm-1 2981.74cm-1
3255.91cm-1
2909.54cm-1 2850.90cm-1
1665.90cm-1 1388.85cm-1
1366.65cm-1 664.16cm-1 691.08cm-1
1149.56cm-1
1455.46cm-1 927.58cm-1
1266.43cm-1
1045.26cm-1
1065.11cm-1 731.49cm-1
1083.79cm-1
1191.96cm-1
1020.31cm-1
1303.06cm-1 843.34cm-1
1429.00cm-1 958.30cm-1
1438.76cm-1 967.18cm-1
1247.63cm-1 881.64cm-1
1217.26cm-1
1590.05cm-1
1569.90cm-1 1113.23cm-1 816.22cm-1
1482.94cm-1 754.32cm-1
1320.43cm-1

Handwritten lists:

1590	1217	816
1570	1192	754
1483	1150	731
1455	1113	
1439	1084	691
1429	1065	664
1309	1045	
1367	1020	
1320	967	
1303	950	
1266	926	
1248	882	
	843	

NO2

Page 1

4-(6-methyl-3-nitro-4-phenylpyridin-2-yl)morpholine (**141**).

500 cdcl3

PROTON_01
TN-156 yellow needles after MeOH recryst

A (m)
7.29

B (m)
7.41

C (s)
6.66

E (t)
3.78

F (t)
3.36

D (d)
2.48

f1 (ppm)

126 cdcl3

CARBON_01
TN-156_yellow needles after MeOH recryst.

A (s) 135.11
I (s) 151.60
K (s) 129.02
E (s) 158.61
D (s) 145.08
F (s) 135.37
C (s) 127.35
B (s) 117.02
G (s) 66.75
J (s) 48.77
H (s) 24.39
L (s) 128.71

HSQC

gHSQCAD_01
TN-156 yellow needles after MeOH recryst

{-0.00,-0.04}
{0.07,0.93}

{2.48,16.95}   {2.48,17.93}
{2.48,23.20}   {2.48,24.37}
B
2.48,24.37
{2.48,25.54}
{2.48,31.79}

{3.36,44.29}   {3.36,46.05}
{3.36,48.78}
E
3.36,48.78
{3.36,47.61}
{3.36,49.96}

A   H
3.78,66.75 3.49,66.75
{3.78,60.89}
{3.77,65.58}
{3.77,68.70}
{3.78,70.85}
{3.78,72.61}

F
6.66,117.14
{6.66,115.77}
{6.66,117.14}
{6.66,118.31}

C   D
7.41,128.86 7.29,127.30
{7.28,125.34}
{7.41,125.69}
{7.29,126.12}
{7.41,130.23}
{7.41,130.81}

HMBC

gHMBCAD_01
TN-156 yellow needles after MeOH recryst

156

Analyst
Date

Administrator
20 January 2017 14:55

%T

3061.45cm-1

1664.83cm-1

2207.69cm-1

1979.67cm-1 1697.43cm-1

1605.94cm-1

788.60cm-1

2972.68cm-1

2837.03cm-1

1161.24cm-1
1380.58cm-1   807.83cm-1
1078.69cm-1
2853.19cm-1 1767.62cm-1   1306.87cm-1 929.64cm-1
1055.87cm-1
1147.39cm-1 735.81cm-1
2919.17cm-1   1239.79cm-1 008.72cm-1
1370.45cm-1 026.97cm-1
2893.05cm-1   1068.73cm-1
1211.14cm-1
1277.17cm-1 938.92cm-1
1179.72cm-1 895.11cm-1   669.56cm-1
1446.70cm-1
1545.43cm-1 054.69cm-1 855.00cm-1
1421.55cm-1
1587.19cm-1
1352.63cm-1
1360.88cm-1
1497.86cm-1   834.78cm-1
1519.04cm-1   1111.24cm-1 704.25cm-1
766.43cm-1

4000   3500   3000   2500   2000   1500   1000   650
cm-1

156   20 January 2017

1587	1277	1009
1545	1265	989
1519	1240	930
1498	1211	895
1447	1180	855
1422	1161	835
1361	1147	808
1370	1111	789
1361	1079	766
1353	1069	736
1307	1056	704
	1027	670
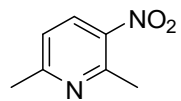
Ph
NO2

Page 1

2,6-dimethyl-3-nitropyridine (**142**).

500 cdcl3
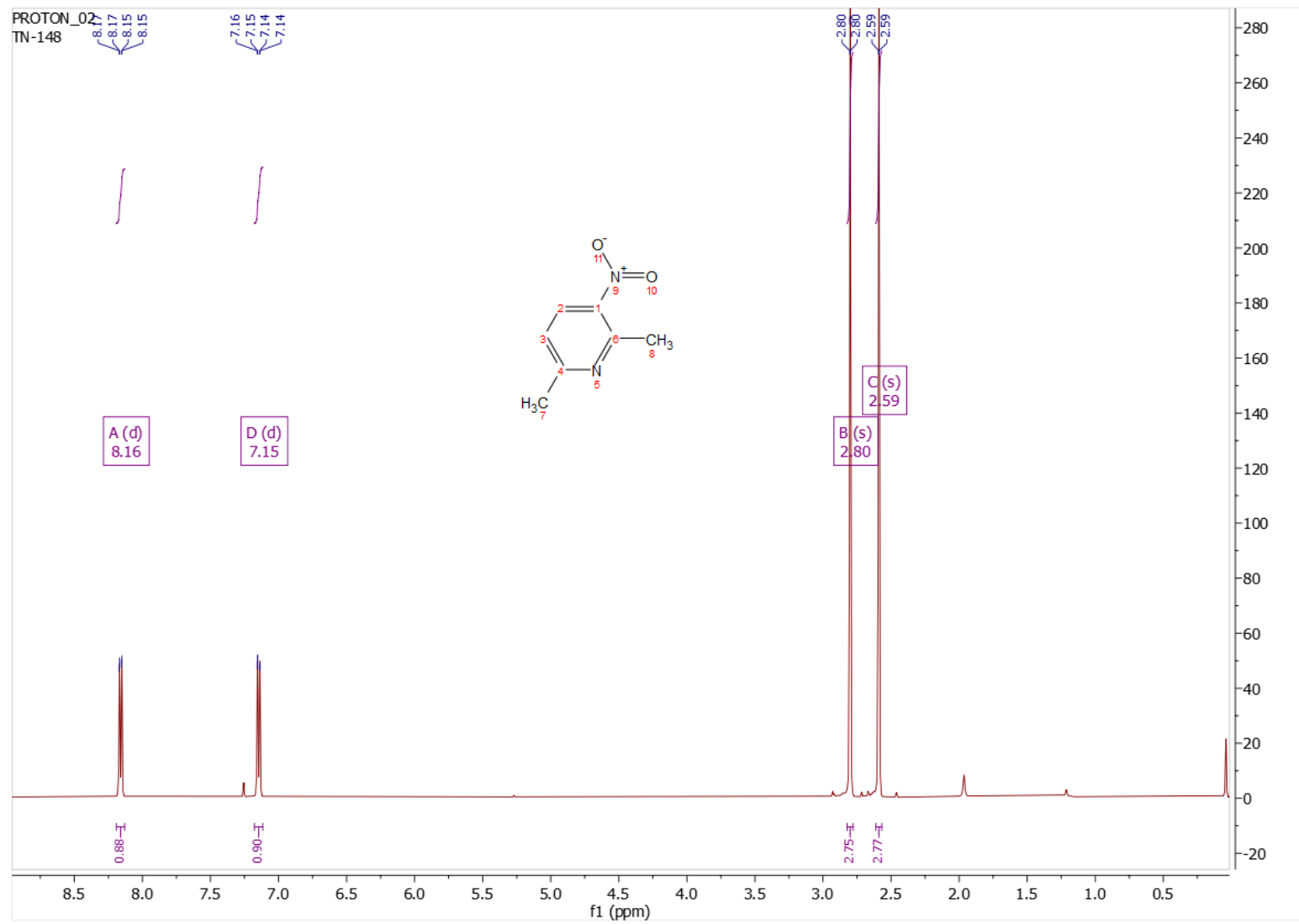
126 cdcl3
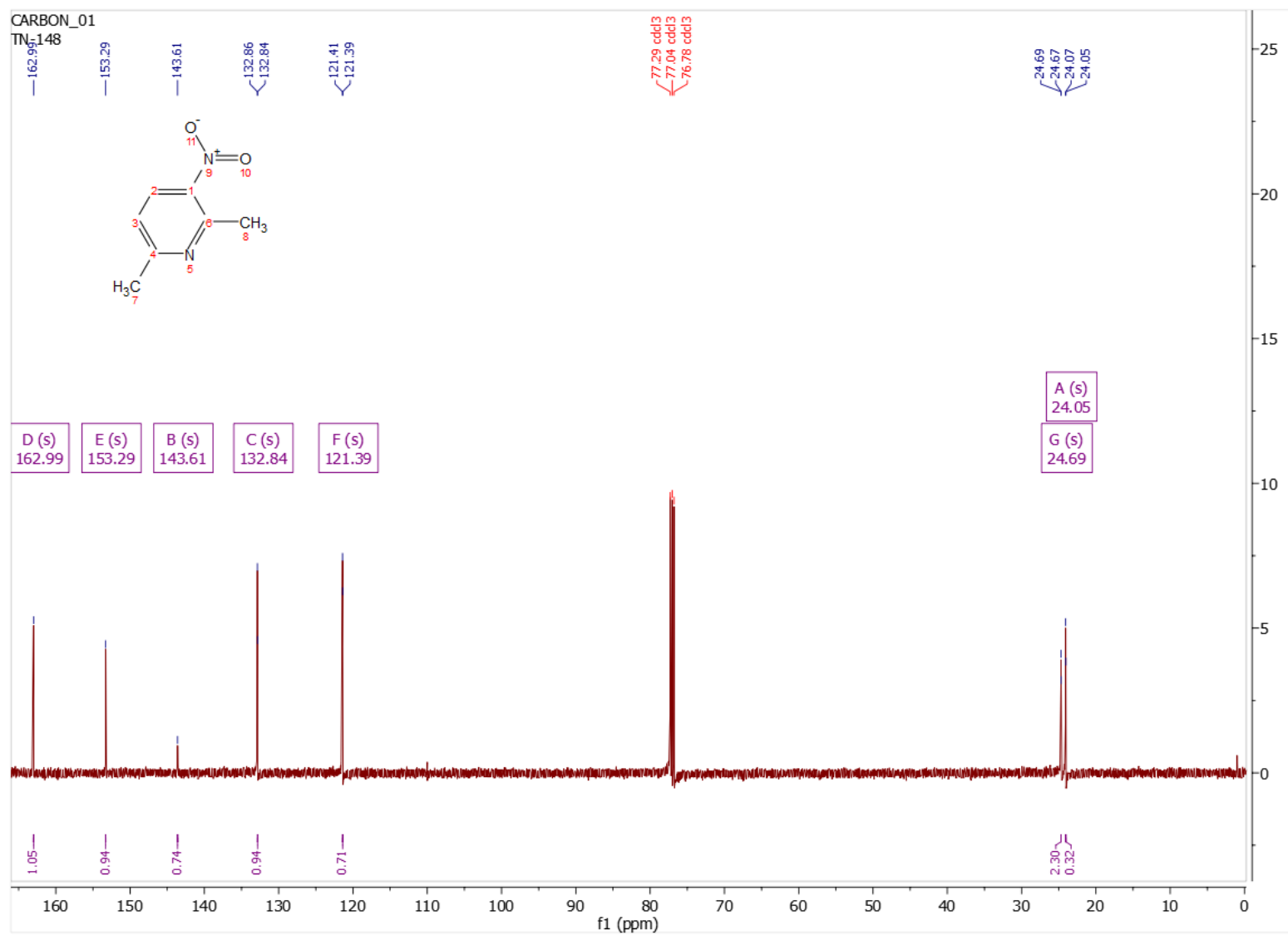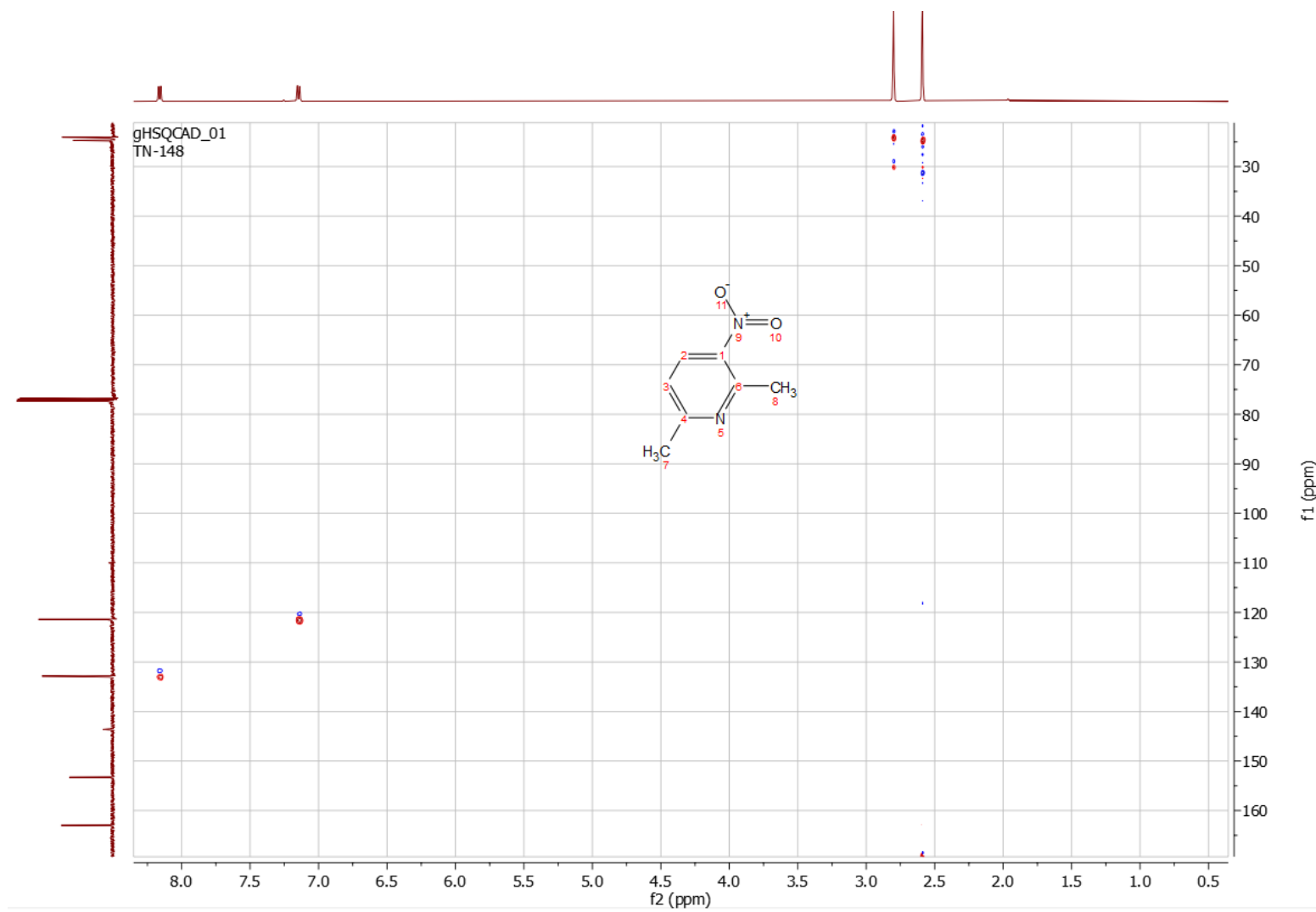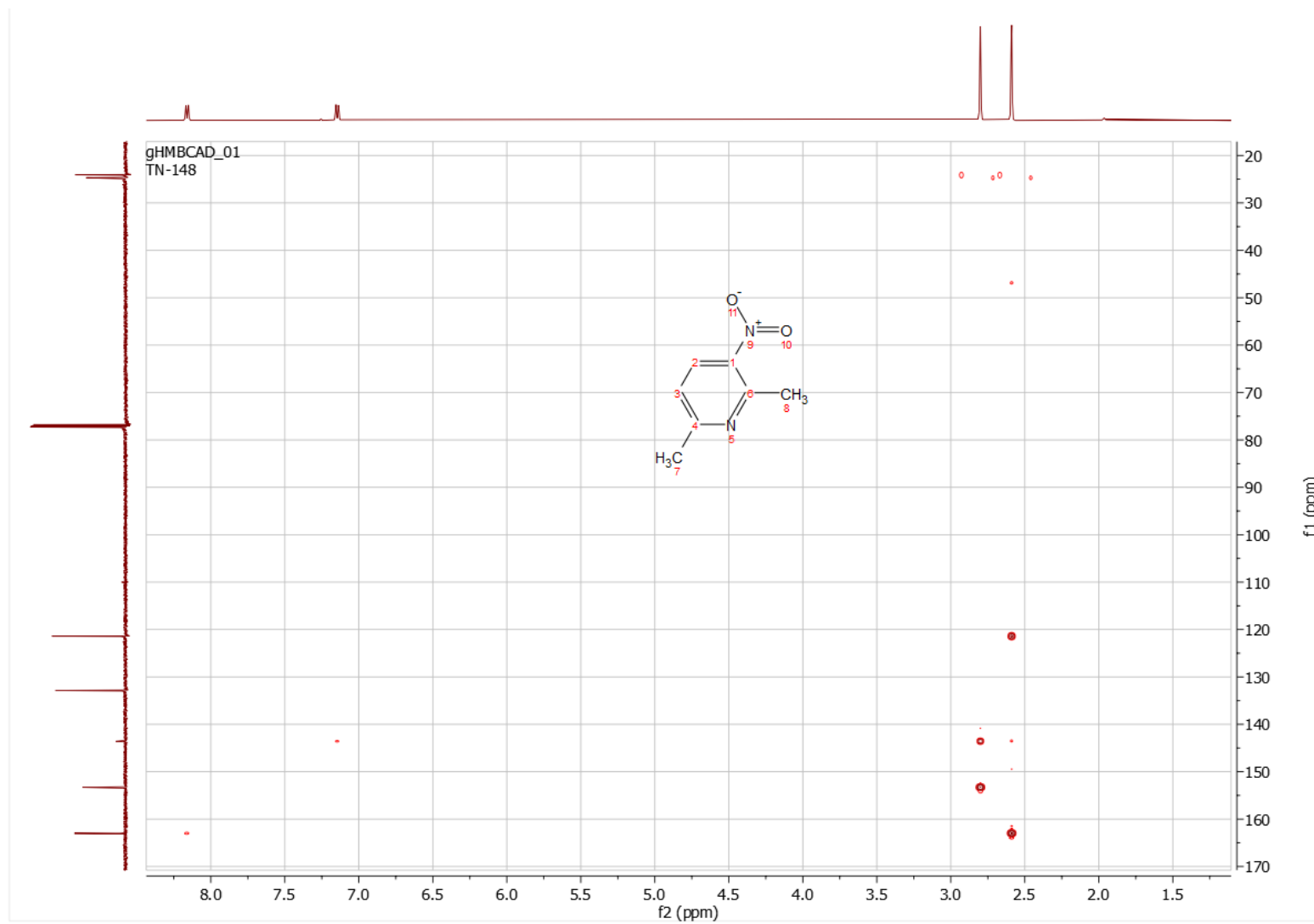
HSQC

gHSQCAD_01
TN-148

HMBC

gHMBCAD_01
TN-148

Analyst   Administrator
Date   23 January 2017 16:38
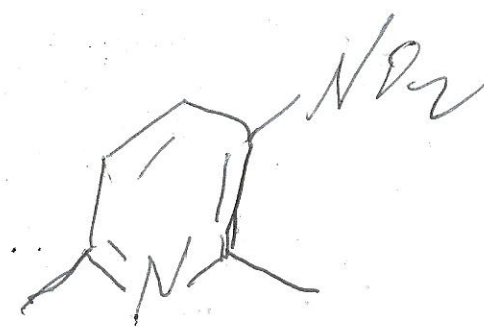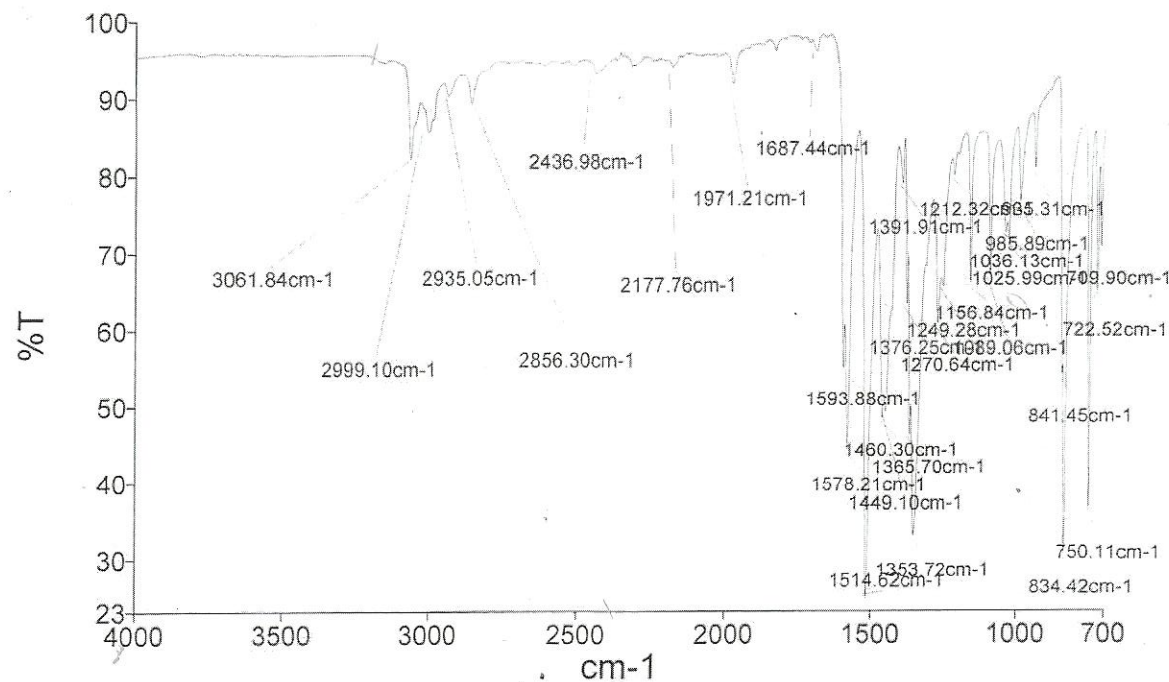
Sample Name	Description	Quality Checks
148	23 January 2017	The Quality Checks do not report any warnings for the sample.

2,6-dimethyl-3-nitro-4-phenylpyridine (**143**).

500 cdcl3

PROTON_01
TN-164
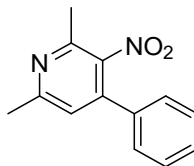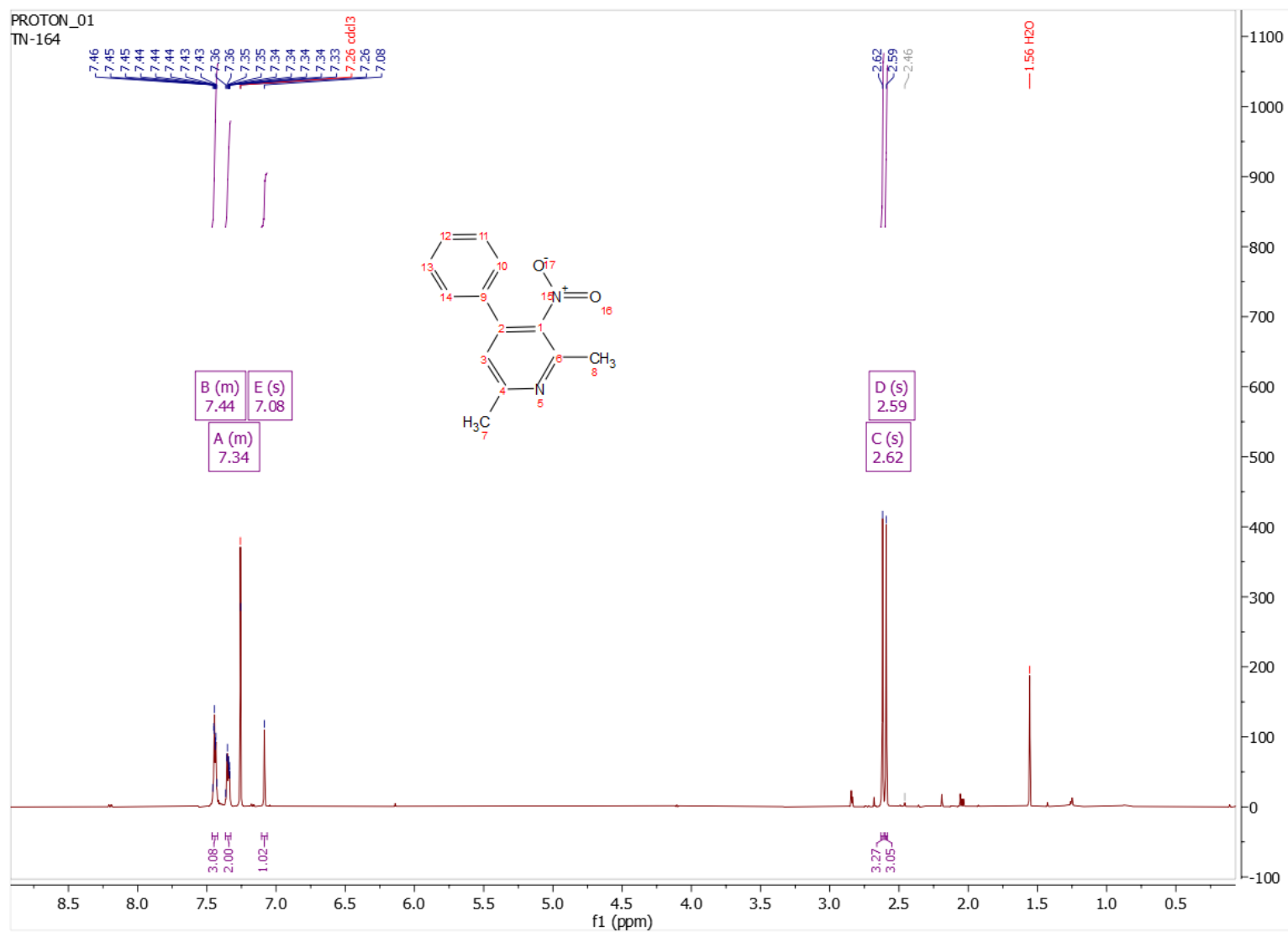
4-(4-methoxyphenyl)-2,6-dimethyl-3-nitropyridine (**151**)

600, cdcl3

151 cdcl3

CARBON_01
TN-208

160.66, 159.5, 149.59, 145.15, 141.98, 128.87, 126.60, 122.17, 114.58, 77.20 cdcl3, 76.99 cdcl3, 76.78 cdcl3, 55.34, 29.68, 24.41, 20.59, 1.00

J (s)
60.66

A (s)
149.59

G (s)
145.15

L (s)
141.98

I (s)
126.60

F (s)
128.87

K (s)
122.17

E (s)
114.58

B (s)
55.34

D (s)
24.41

H (s)
20.59

0.48, 0.64, 0.36, 0.26, 0.51, 2.79, 0.57, 1.47, 3.04, 1.32, 0.80, 1.22

HSQC

HMBC

gHMBCAD_01
TN-208

{-0.00,-0.09}
{0.07,0.85}
{7.06,24.29}
{6.95,114.55}
{2.60,122.17}
{6.95,126.51}
{7.29,128.85}
{7.06,126.51}
{7.28,141.98}
{7.06,145.15}
{2.57,145.15}
{2.57,149.60}
{7.06,159.57}
{6.95,160.62}
{3.83,160.62}
{2.60,159.57}
A
2.60,159.57
{7.29,160.62}

f1 (ppm)

f2 (ppm)

[Mass Spectrum]
Data : 270919 - Tyler Nichols - TN248 - 001   Date : 27-Sep-2019 08:07
Instrument : JEOL MStation JMS-700(2)
Sample :
Note :
Inlet : Direct   Ion Mode : EI+
Spectrum Type : Normal Ion [MF-Linear]
RT : 0.25 min   Scan# : (3,7)   Temp : 3276.7 deg.C
BP : m/z 258.1926   Int. : 339.74 (3562468)
Output m/z range : 50 to 352   Cut Level : 0.00 %
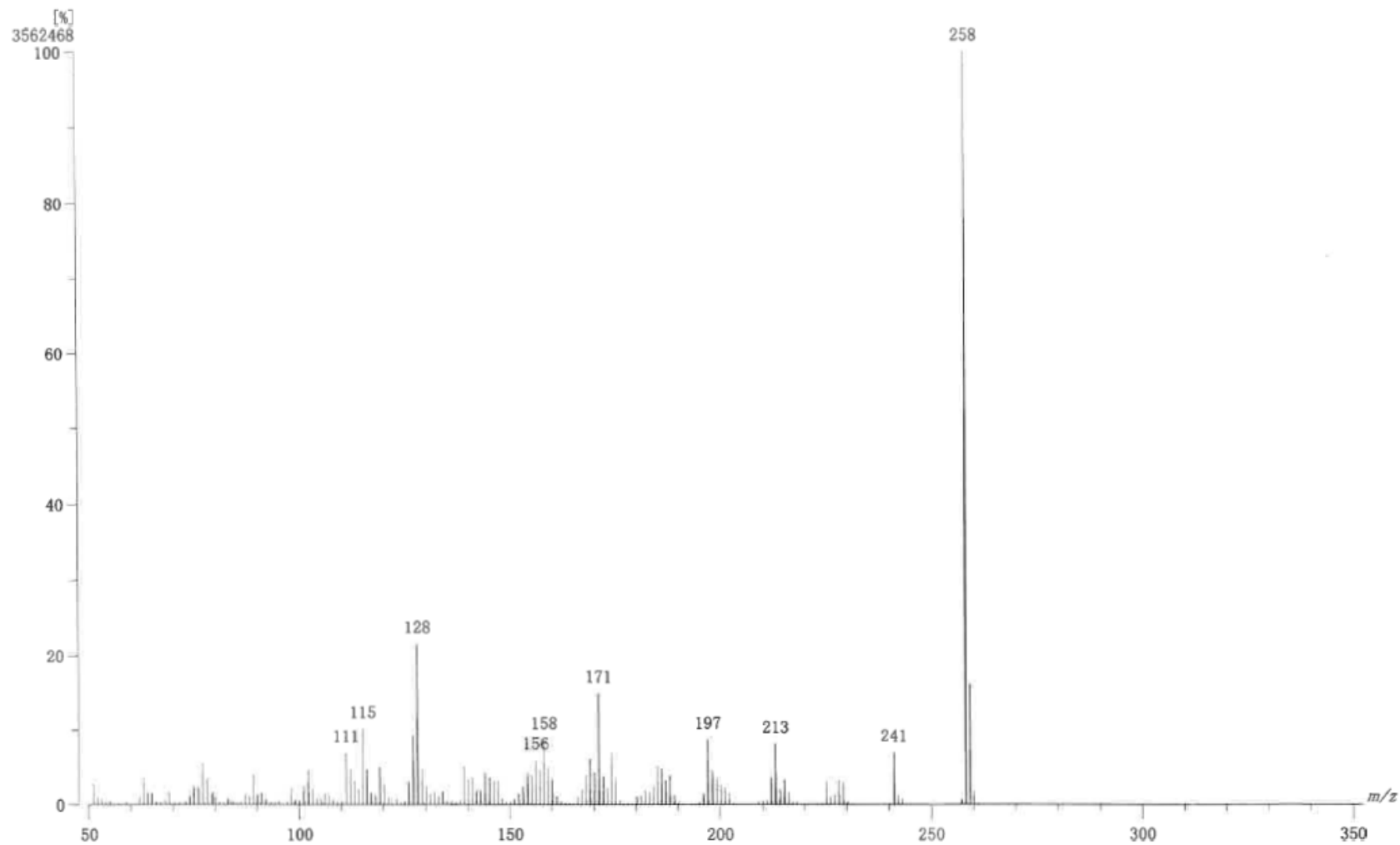
```
[ Theoretical Ion Distribution ]
Molecular Formula : C14 H14 N2 O3
                        (m/z    258.1004, MW    258.2768, U.S.   9.0)
Base Peak :    258.1004, Averaged MW :    258.2754(a),    258.2761(w)


    m/z       INT.
  258.1004 100.0000*********************************************************************
  259.1035  16.4202**********
  260.1060   1.8616*
  261.1085   0.1585
  262.1109   0.0107
  263.1134   0.0006
```

Analyst

Date

PEService

29 March 2019 18:09

Pyridine one

NO_2

%T

2980.5

2855.9

2920.2

1595.60cm-1

1368.36cm-1

839.19cm-1

1001.54cm-1

1446.34cm-1 74.83cm-1

1042.65cm-1

1026.90cm-1

770.03cm-1

1717.80cm-1

1282.62cm-1

1252.59cm-1

1103.66cm-1

1231.20cm-1

695.68cm-1

cm-1

4000 3500 3000 2500 2000 1500 1000 650
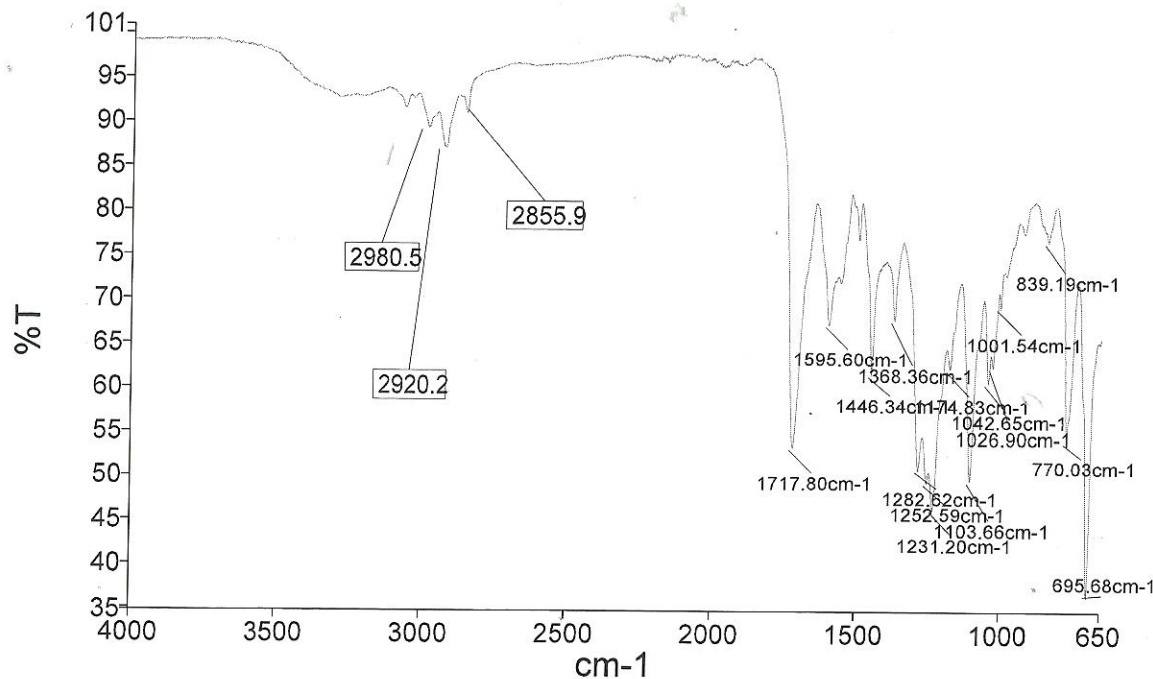
Sample Name	Description	Quality Checks
201	Sample 009 By PEService Date Friday, March 29 2019	The Quality Checks do not report any warnings for the sample.
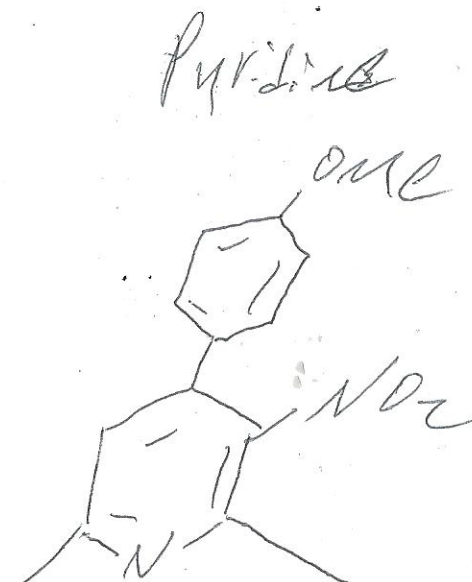
4-(4-fluorophenyl)-2,6-dimethyl-3-nitropyridine (**152**).

600 cdcl3

7.34
7.34
7.33
7.32
7.26
7.15
7.14 cdcl3
7.13
7.12
7.05

2.62
2.59

1.58 H2O

F (s)
7.05

E (dd)
7.33

B (t)
7.13

C (s)
7.26

D (s)
2.59

A (s)
2.62

1.90
0.61
1.84
0.88

2.96
2.80

f1 (ppm)

151 cdcl3

376 cdcl3

A (tt)
-111.23

HSQC

gHSQCAD_01
TN-219

{0.05,-0.80} {0.07,0.76}
{2.54,-4.12}

{2.57,20.51}
A
2.59,20.51   E
{2.59,24.42}
{2.60,24.22}

{7.31,67.42}

{7.10,114.53} {7.13,116.29}
B
{7.13,116.29} {7.05,122.16}
7.13,116.29   7.05,122.16
{7.34,129.39}
D
7.34,129.39

f1 (ppm)

f2 (ppm)

HMBC
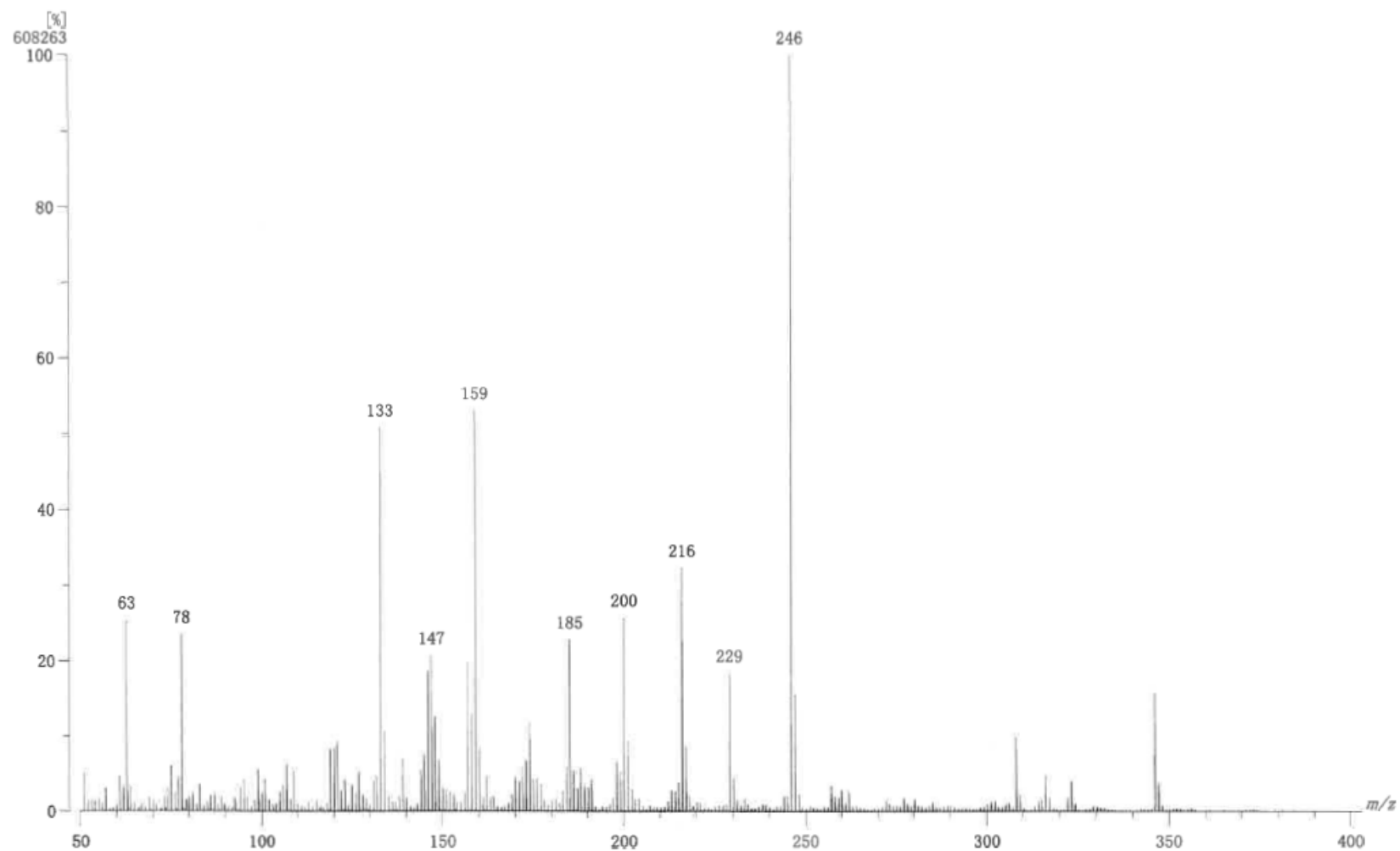
```
[ Theoretical Ion Distribution ]
Molecular Formula : C13 H11 F N2 O2
                        (m/z   246.0805, MW   246.2409, U.S.   9.0)
Base Peak :   246.0805, Averaged MW :   246.2400(a),   246.2407(w)

   m/z      INT.
 246.0805 100.0000*********************************************************
 247.0835  15.2699*********
 248.0860   1.4850*
 249.0885   0.1085
 250.0911   0.0062
 251.0936   0.0003
```

2-methyl-3-nitro-4-phenyl-6-(trifluoromethyl)pyridine (**153**).

500 cdcl3

PROTON_01
TN-202 after column (Frac 1. + Frac 2.)

Peaks: 7.65, 7.52, 7.51, 7.49, 7.48, 7.46, 7.39, 7.38, 7.25, 2.68, 1.67 H2O

D (q) 7.49
C (s) 7.65
B (d) 7.39
A (s) 2.68

Integrations: 0.94, 3.15, 1.99, 2.93

4-(4-methoxyphenyl)-2-methyl-3-nitro-6-(trifluoromethyl)pyridine (**154**).

600 cdcl3

PROTON_01
TN-217

7.61, 7.34, 7.34, 7.33, 7.33, 7.32, 7.32, 7.25 cdcl3, 6.99, 6.99, 6.98, 6.98, 6.97

3.85, 3.85

2.66

1.63 H2O

A (s) 7.61
B (d) 7.33
C (d) 6.99
D (s) 3.85
E (s) 2.66

0.92, 1.93, 2.01, 3.16, 2.99

f1 (ppm)

151 cdcl3

CARBON_01
TN-217

161.37, 151.60, 148.50, 148.26, 148.03, 147.86, 147.80, 143.26, 129.06, 125.00, 123.39, 121.57, 120.04, 120.02, 120.00, 119.98, 119.75, 114.95, 77.20 cdcl3, 76.99 cdcl3, 76.78 cdcl3, 55.41, 30.17, 29.67, 20.44

K (m)
148.38

F (s)
125.00

E (s)
114.95

G (s)
151.60

H (s)
129.06

B (q)
120.01

D (s)
55.41

C (s)
20.44

HSQC

gHSQCAD_01
TN-217

HMBC

gHMBCAD_01
TN-217

ethyl 6-methyl-5-nitro-4-phenylpicolinate (**155**).

600 cdcl3

PROTON_01
TN-252

B (s)
8.06

C (m)
7.39

D (m)
7.48

A (q)
4.50

F (s)
2.70

E (t)
1.44

f1 (ppm)

151 cdcl3

CARBON_01
TN-252

HSQC

HMBC

gHMBCAD_01
TN-252

{2.80,20.54} {2.58,20.66}

{1.43,62.51}

{8.06,148.08} {2.69,148.08} {2.69,150.89}

A
2.69,150.89

f1 (ppm)

f2 (ppm)
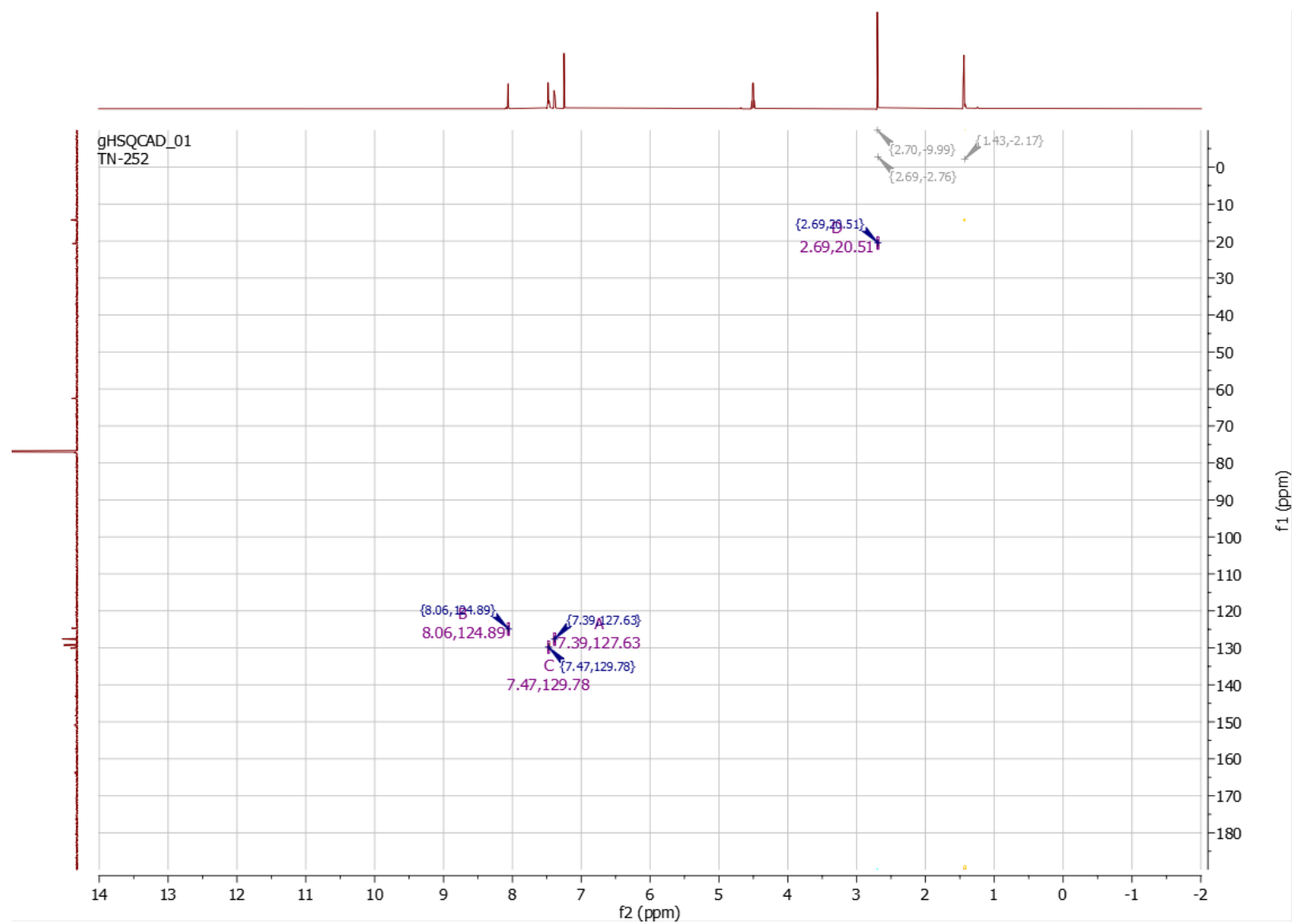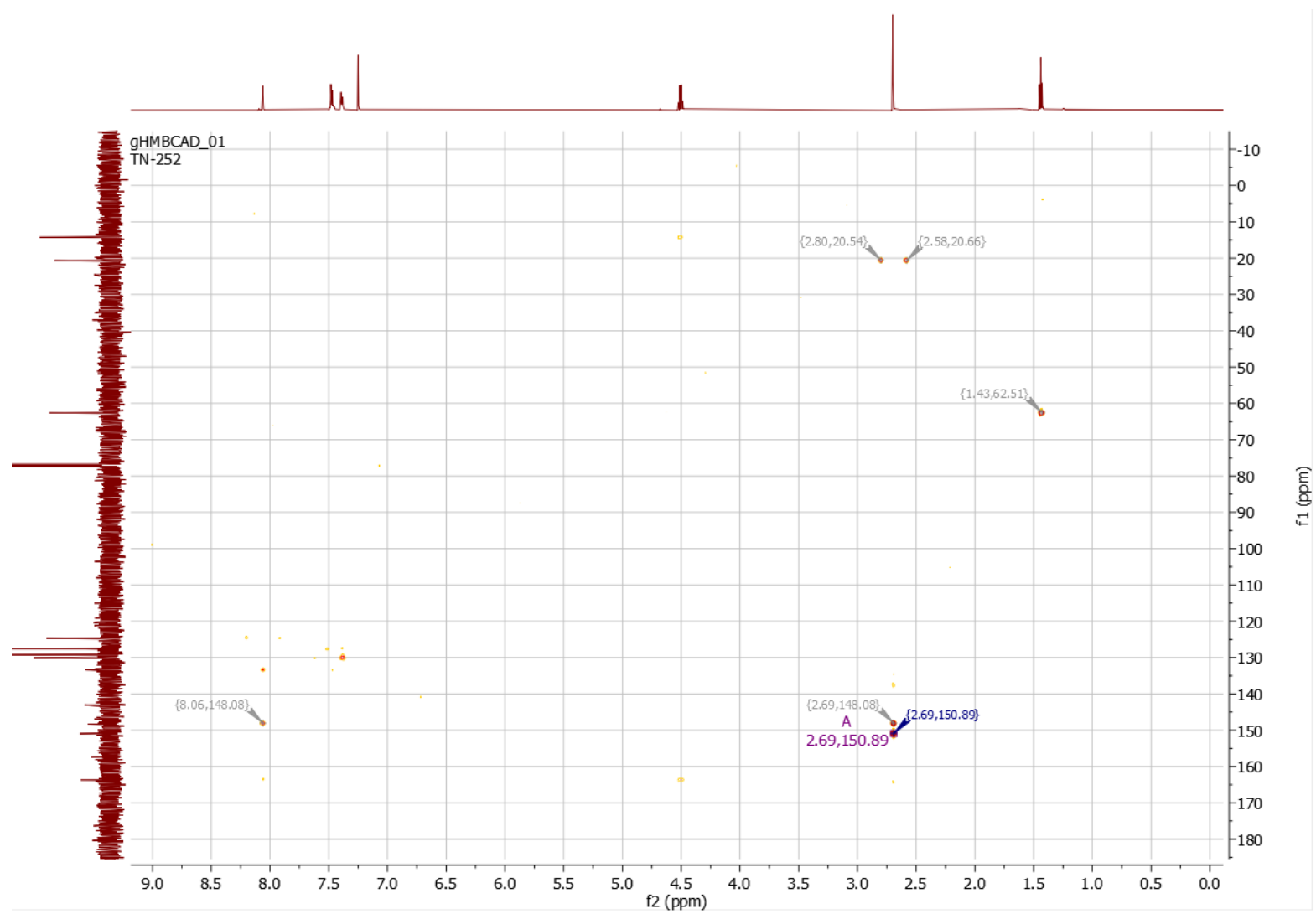
ethyl 4-(4-methoxyphenyl)-6-methyl-5-nitropicolinate (**156**).

500 cdcl3
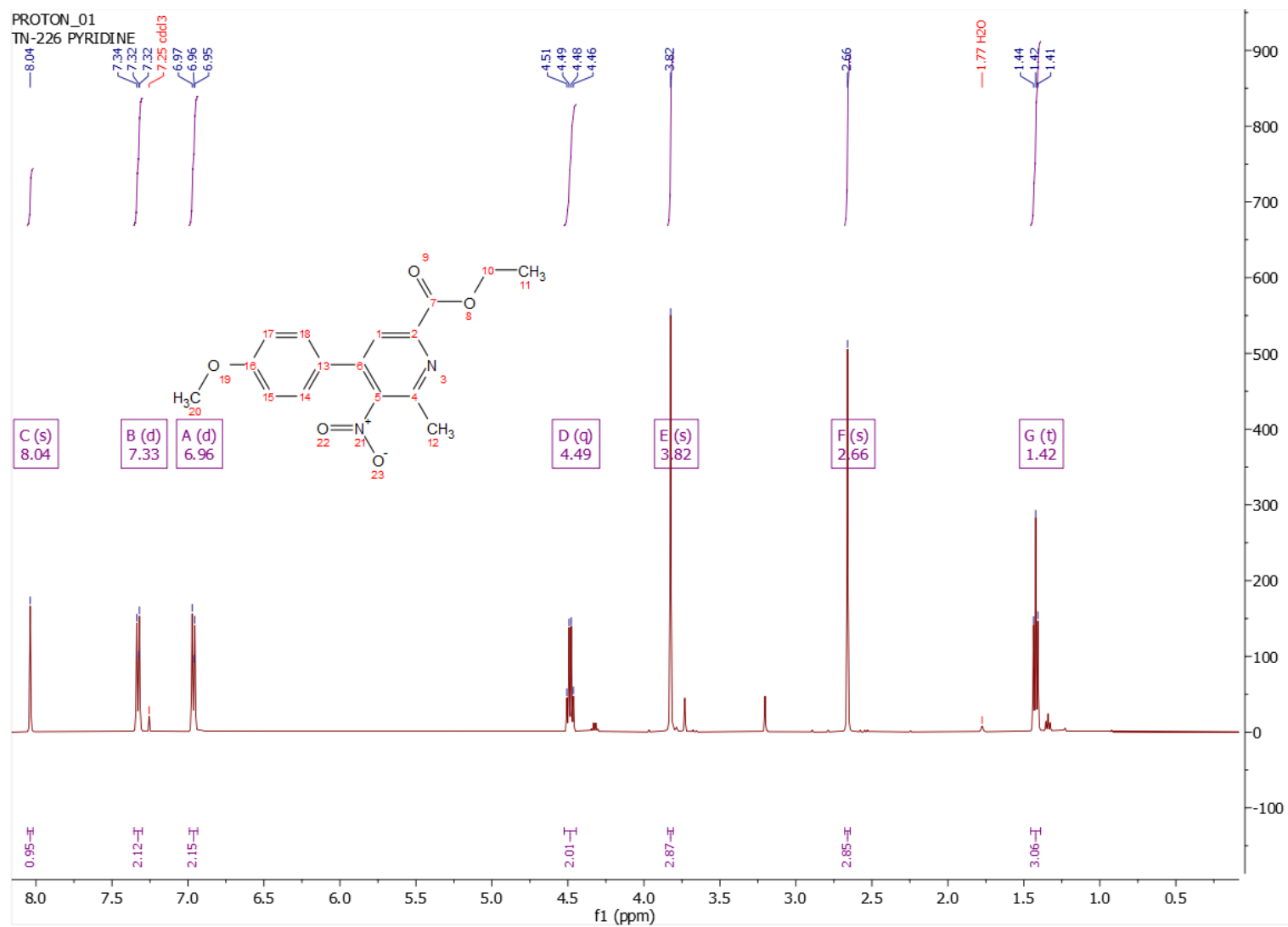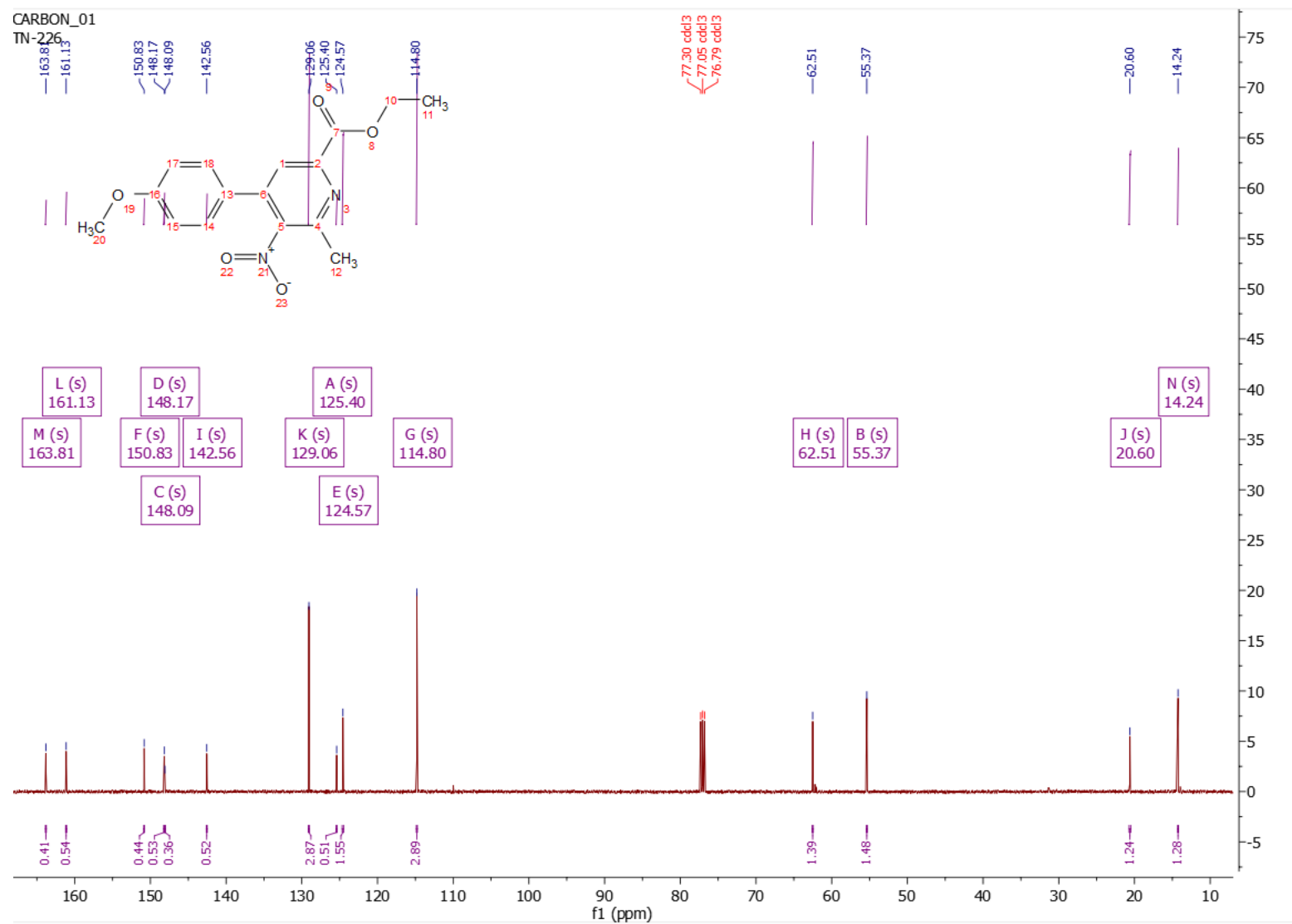
PROTON_01
TN-226 PYRIDINE

C (s) 8.04
B (d) 7.33
A (d) 6.96
D (q) 4.49
E (s) 3.82
F (s) 2.66
G (t) 1.42

126 CDCL3

CARBON_01
TN-226

Peak assignments:

Label	Shift (ppm)
L (s)	161.13
M (s)	163.81
D (s)	148.17
F (s)	150.83
C (s)	148.09
I (s)	142.56
A (s)	125.40
K (s)	129.06
E (s)	124.57
G (s)	114.80
H (s)	62.51
B (s)	55.37
N (s)	14.24
J (s)	20.60

Generic Display Report

Intens.
$\times 10^5$

339.0952

2.0

1.5

1.0

140.7520

0.5

317.1133

115.4560   169.5553   197.0837   226.1028   259.1427   277.7098   366.6349

150   200   250   300   350   m/z

········ +MS

Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 16 H 16 N 2 Na 1 O 5	0.017	339.0951	-0.23	11.06	3.75	9.50	ok	even

Analyst   PEService

Date   29 March 2019 18:17

Peaks: 2992.6, 2944.3, 1742.37cm-1, 1675.26cm-1, 1599.68cm-1, 1513.17cm-1, 1443.77cm-1, 1285.58cm-1, 1248.82cm-1, 1173.99cm-1, 1114.62cm-1, 1089.84cm-1, 1014.40cm-1, 990.28cm-1, 843.46cm-1, 761.87cm-1, 656.85cm-1

pyridine

EtO
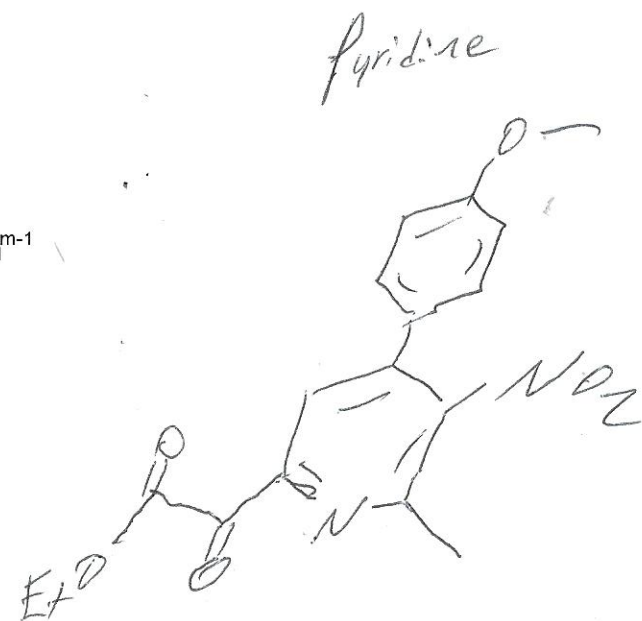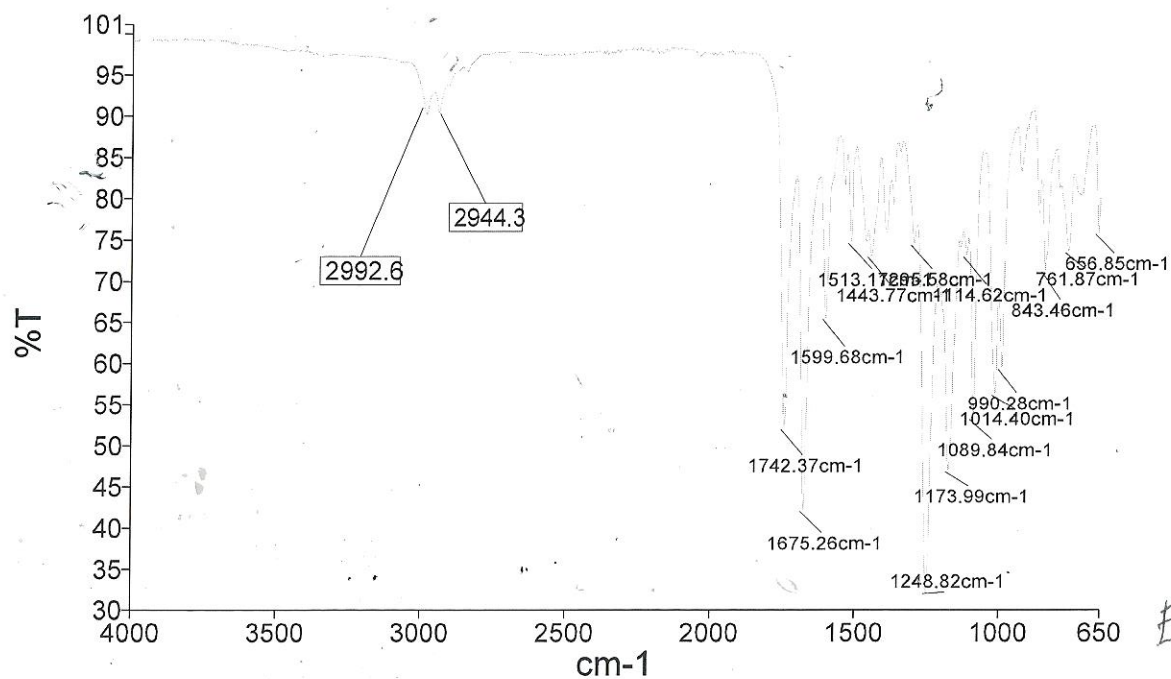
Sample Name	Description	Quality Checks
260	Sample 010 By PEService Date Friday, March 29 2019	The Quality Checks do not report any warnings for the sample.

3-nitro-2,6-diphenylpyridine (**157**).
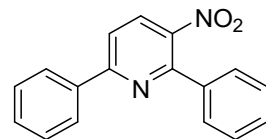
500 CDl3
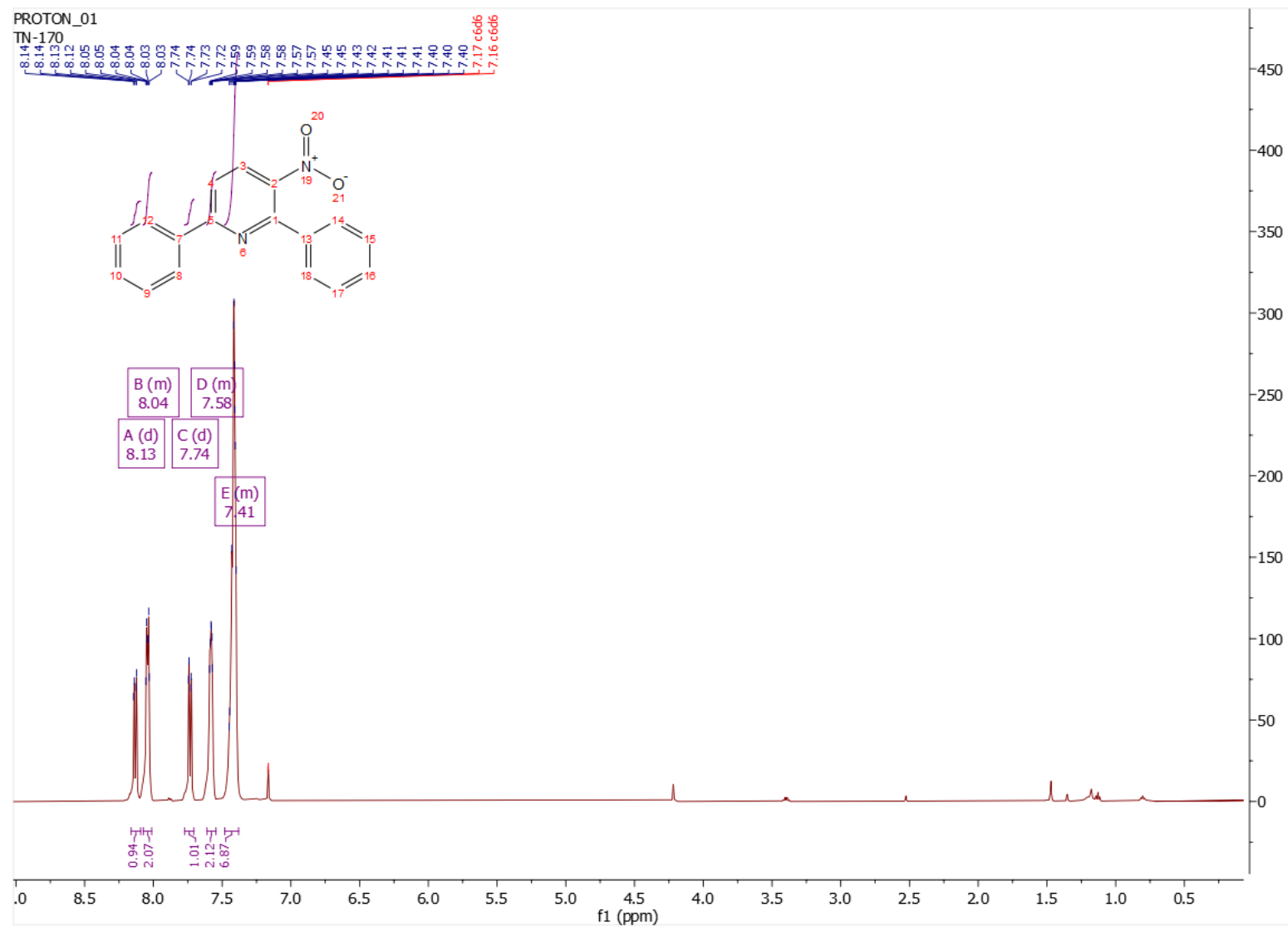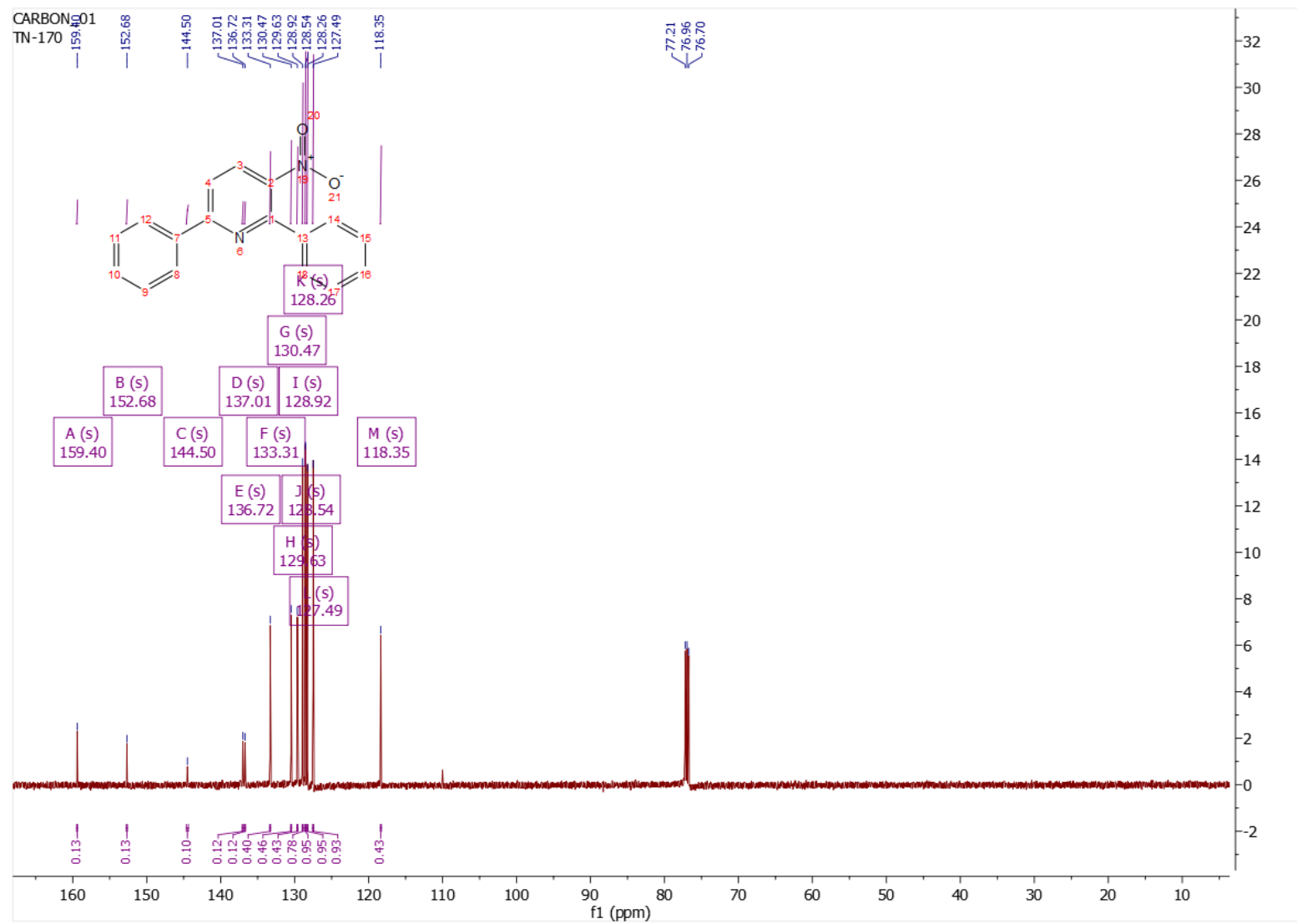
PROTON_01
TN-170

B (m) 8.04
D (m) 7.58
A (d) 8.13
C (d) 7.74
E (m) 7.41

126 CDCl3

HSQC

gHSQCAD_01
TN-170

HMBC

gHMBCAD_01
TN-170

Analyst

Date

PEService

29 March 2019 18:27

%T

2961.87cm-1

1452.09cm-1

1260.90cm-1

847.73cm-1

1017.17cm-1

1431.18cm-1

770.25cm-1

867.29cm-1

804.93cm-1

1511.96cm-1

1567.68cm-1

1348.24cm-1

753.82cm-1

688.83cm-1

cm-1

4000 3500 3000 2500 2000 1500 1000 650
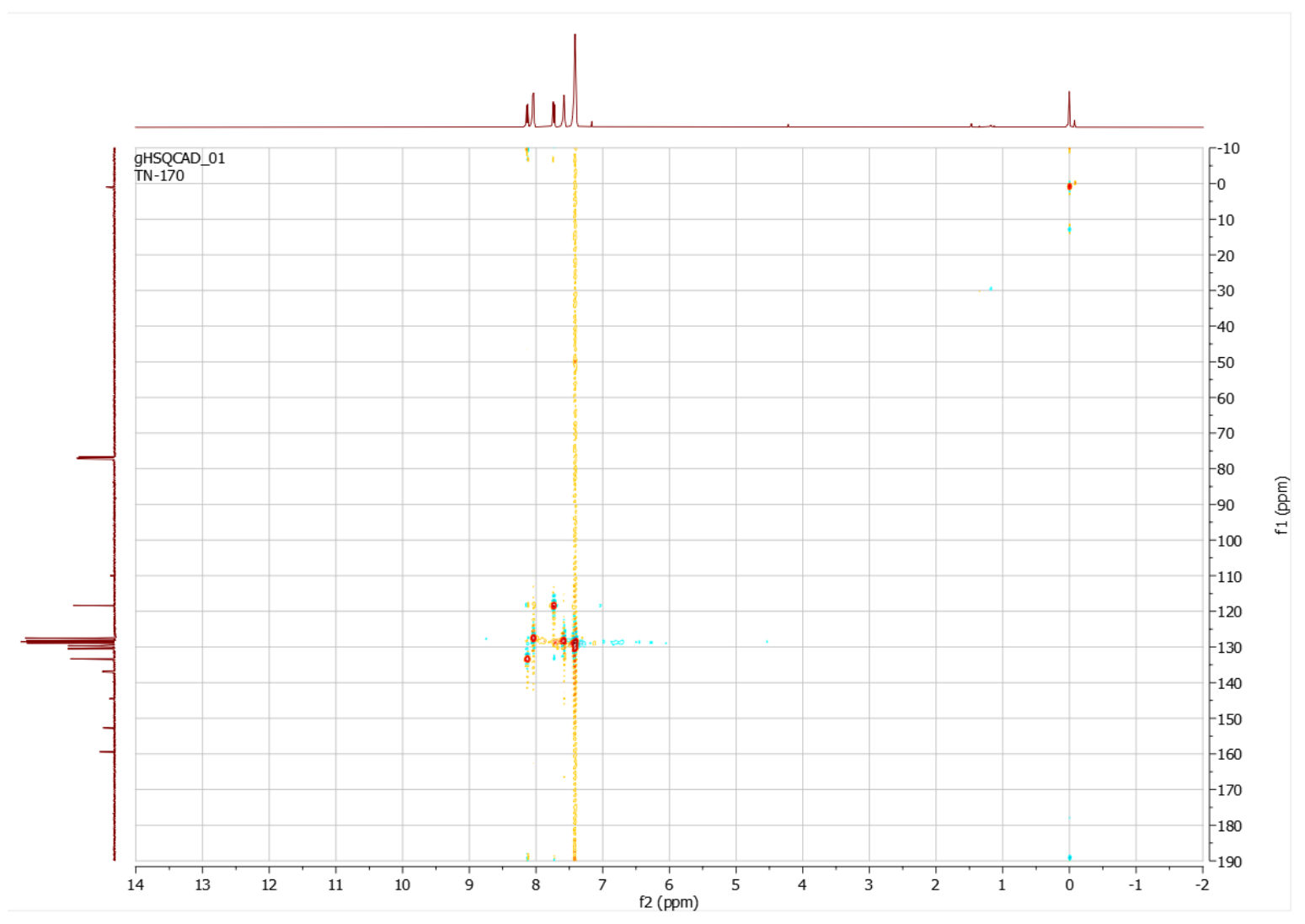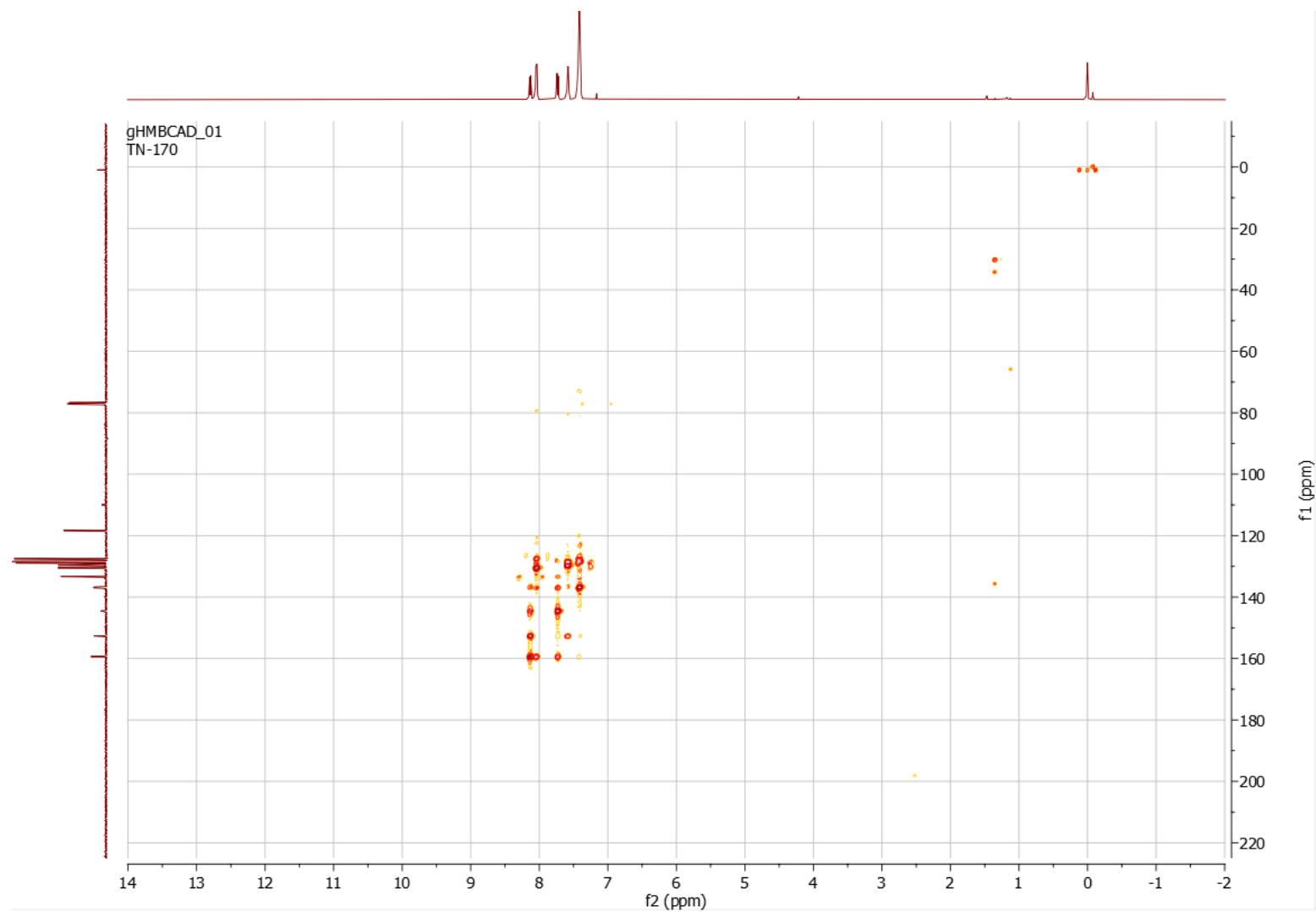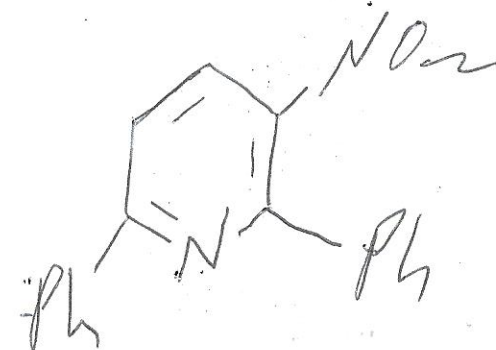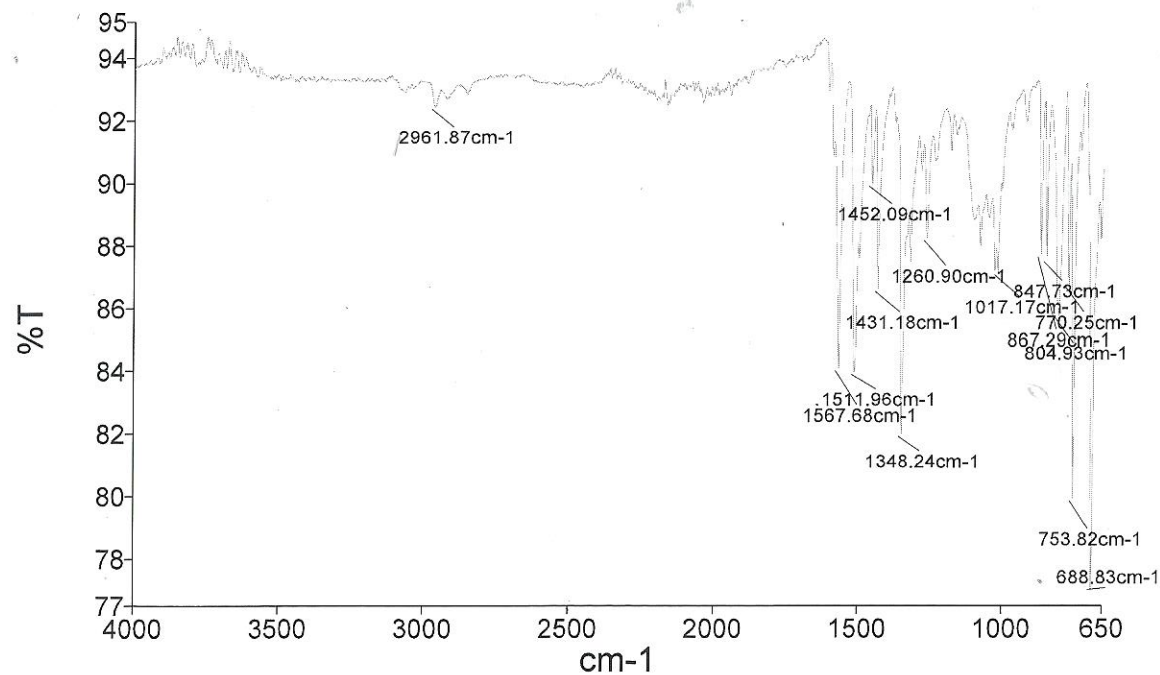
Sample Name	Description	Quality Checks
170	Sample 012 By PEService Date Friday, March 29 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

Synthesis of 6-methyl-3-nitropyridin-2-amine (**160**).
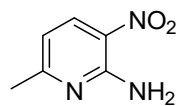
600 cdcl3
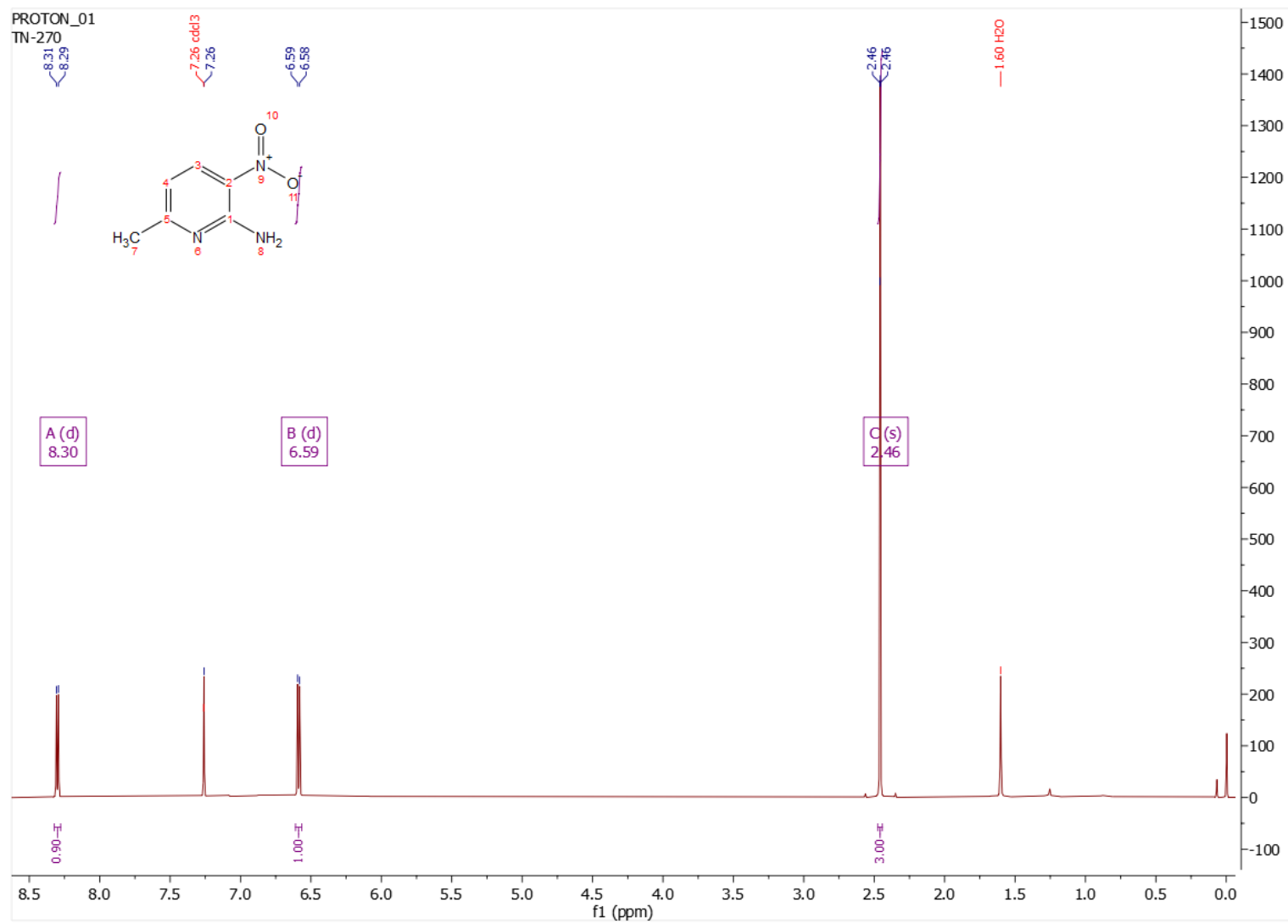
PROTON_01
TN-270

A (d)
8.30

B (d)
6.59

C (s)
2.46

151 cdcl3

CARBON_01
TN-270

166.33
152.97
135.20
113.72
77.21 cdcl3
76.78 cdcl3
24.82

D (s)
166.33

E (s)
152.97

C (s)
135.20

A (s)
113.72

B (s)
24.82

0.72
0.53
1.82
1.67
1.01

f1 (ppm)

HSQC

gHSQCAD_01
TN-270

Analyst

Date

PEService

29 March 2019 18:21

Peaks labeled on spectrum: 3471.2, 3318.3, 3184.56cm-1, 3053, 1637.67cm-1, 1583.55cm-1, 1465.21cm-1, 1435.25cm-1, 1256.04cm-1, 1312.19cm-1, 1216.04cm-1, 1184.81cm-1, 1060.42cm-1, 915.76cm-1, 773.45cm-1, 788.89cm-1, 707.52cm-1, 735.29cm-1
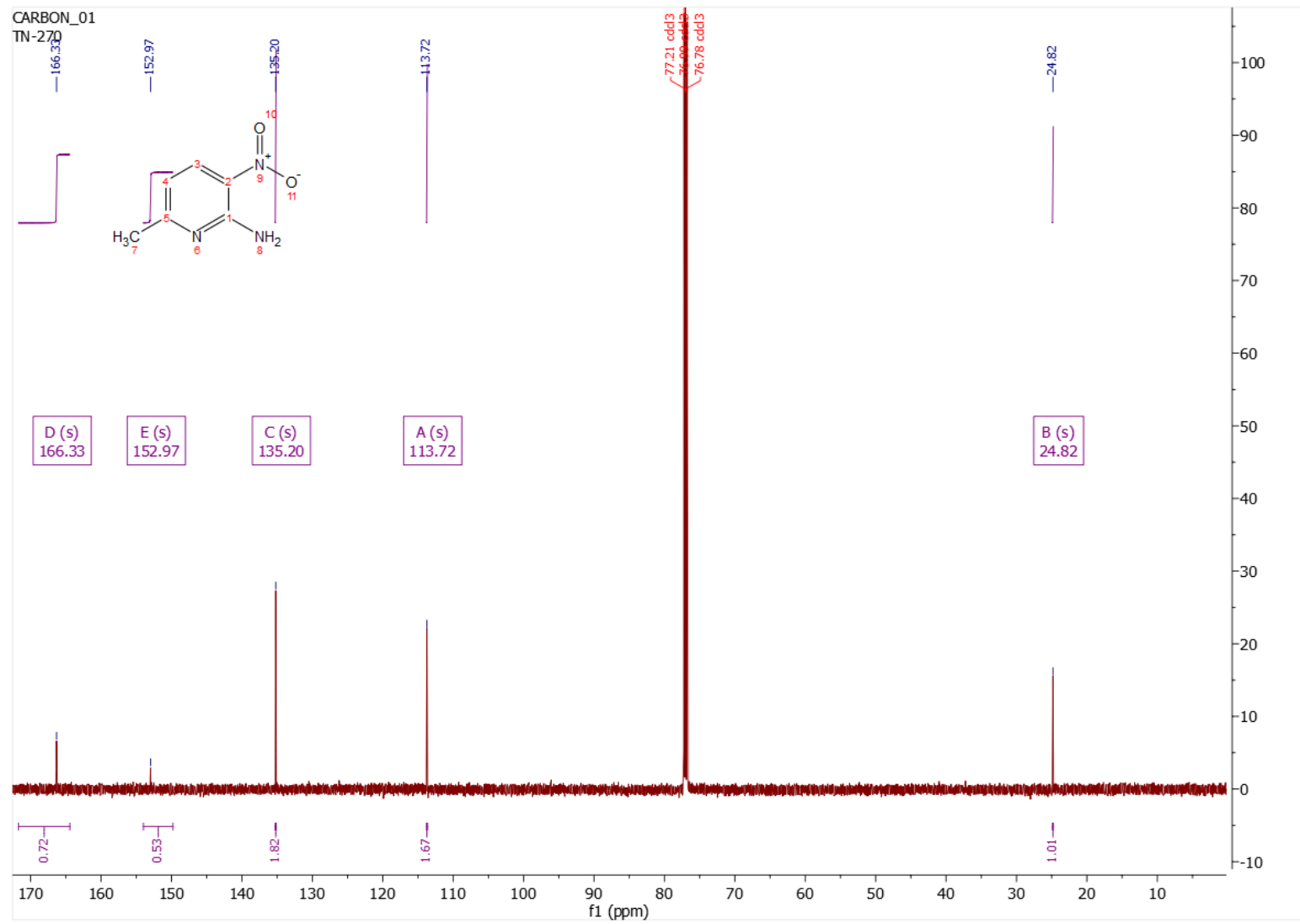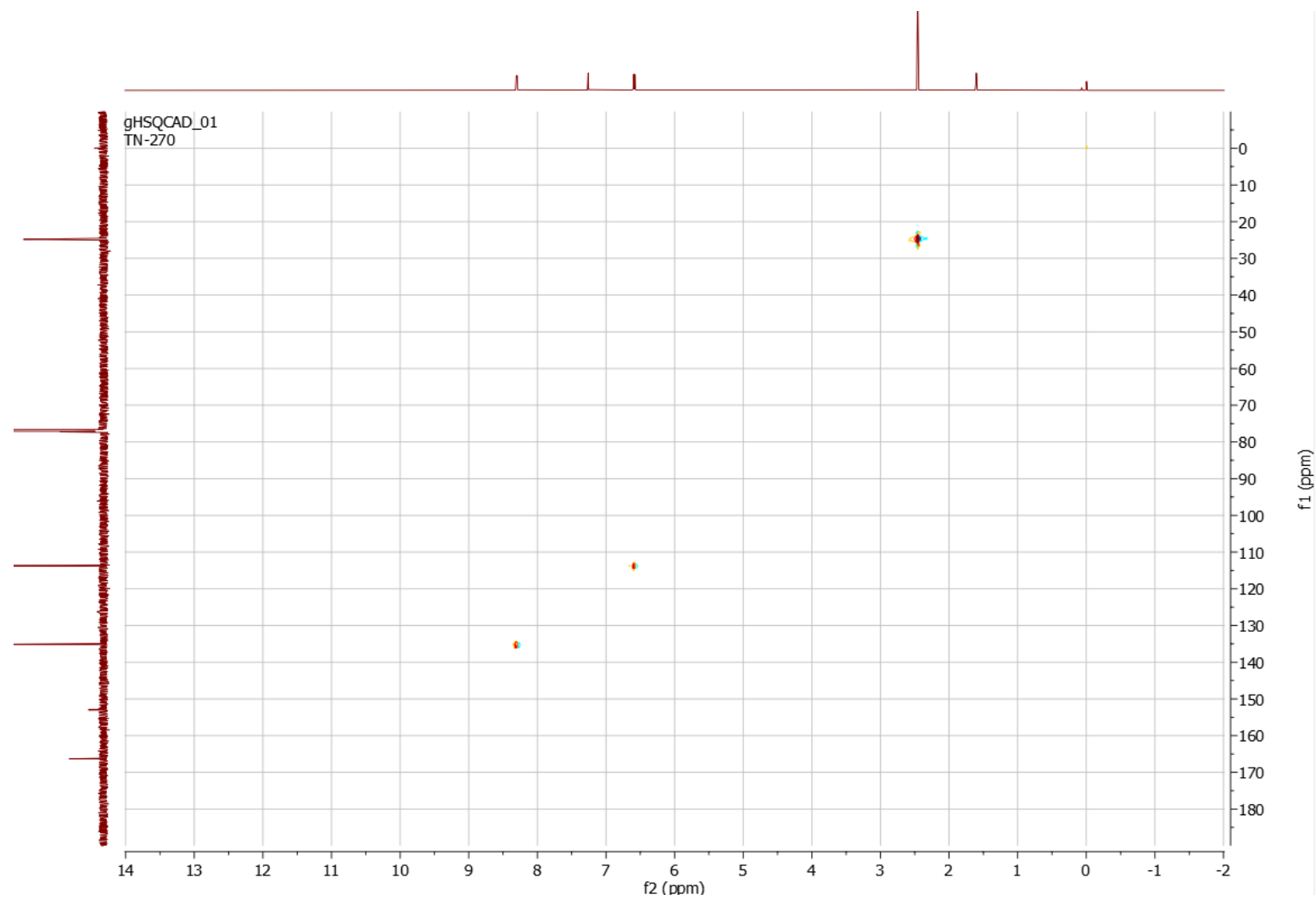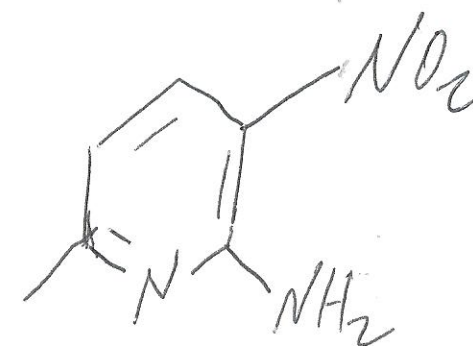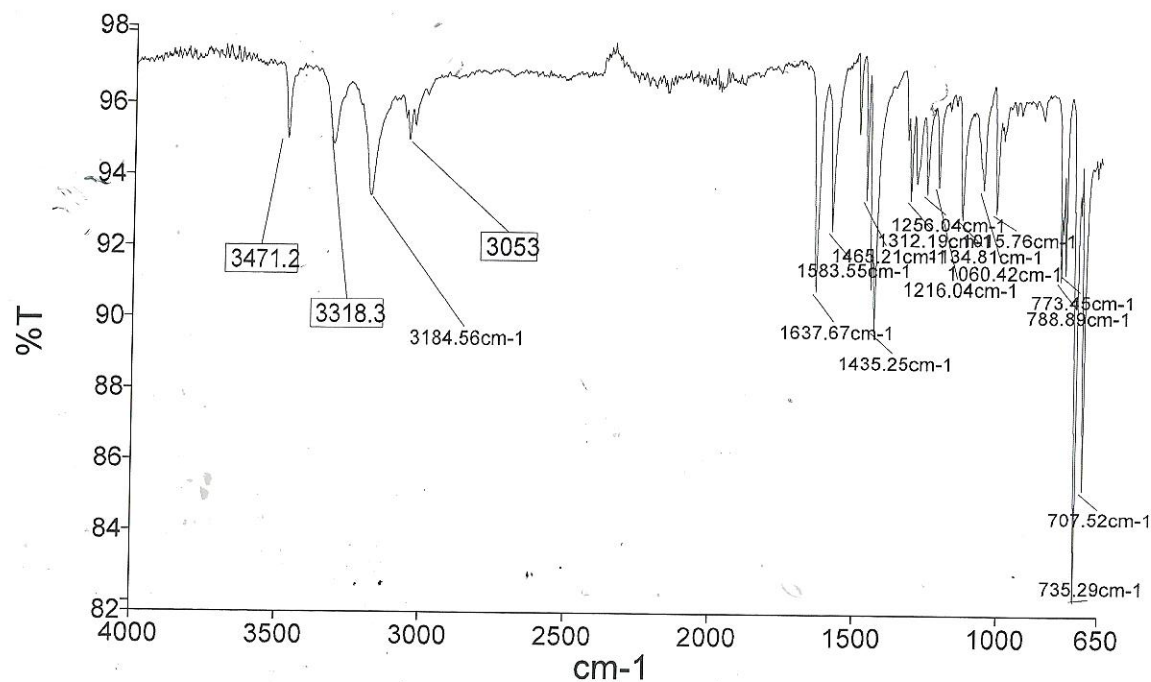
Sample Name	Description	Quality Checks
270	Sample 011 By PEService Date Friday, March 29 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

CHAPTER 3

3-(4-methoxyphenyl)prop-2-ynal (**162**).
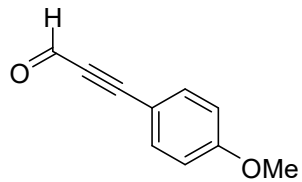
500 CDCl3
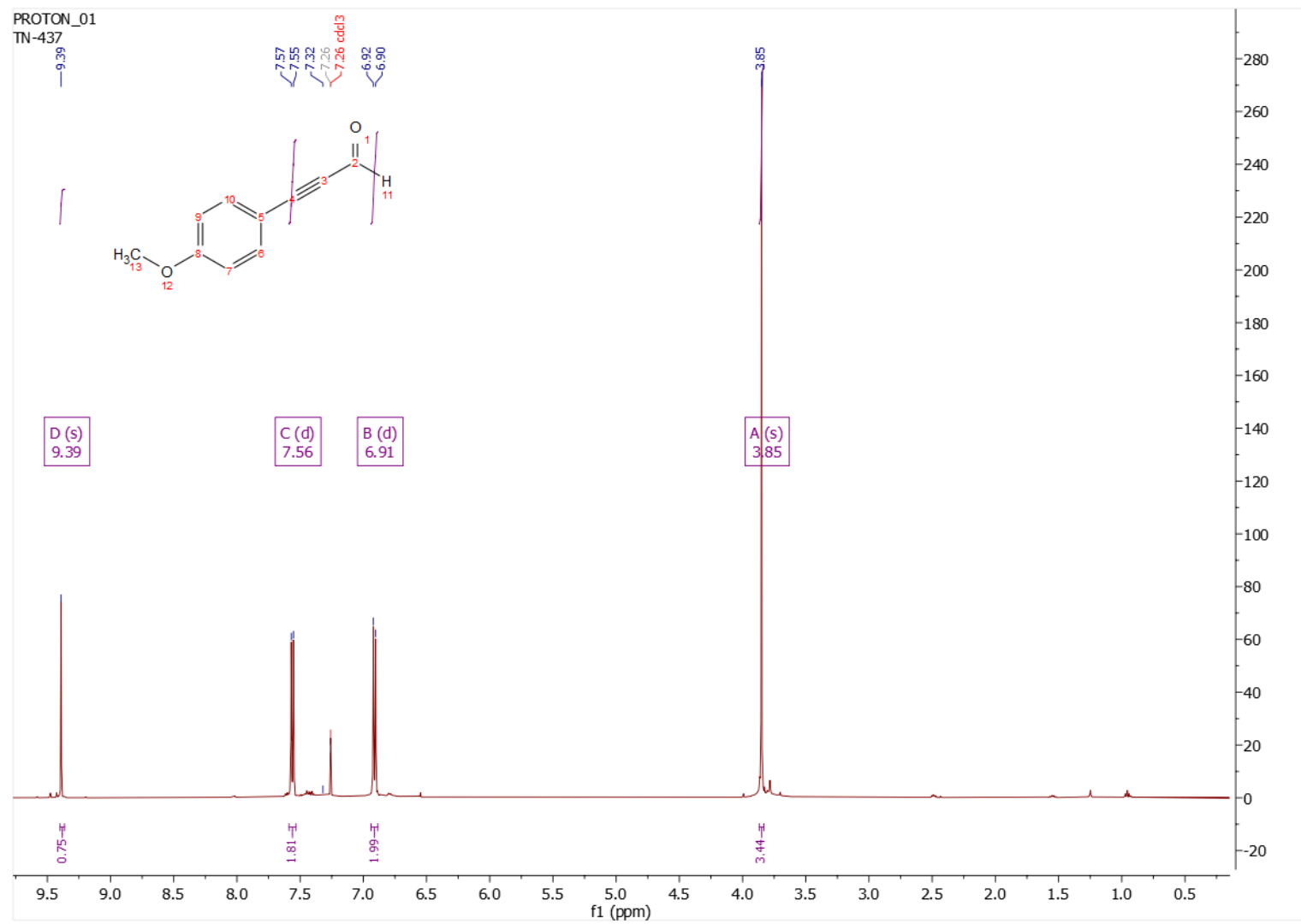
126 cdcl3
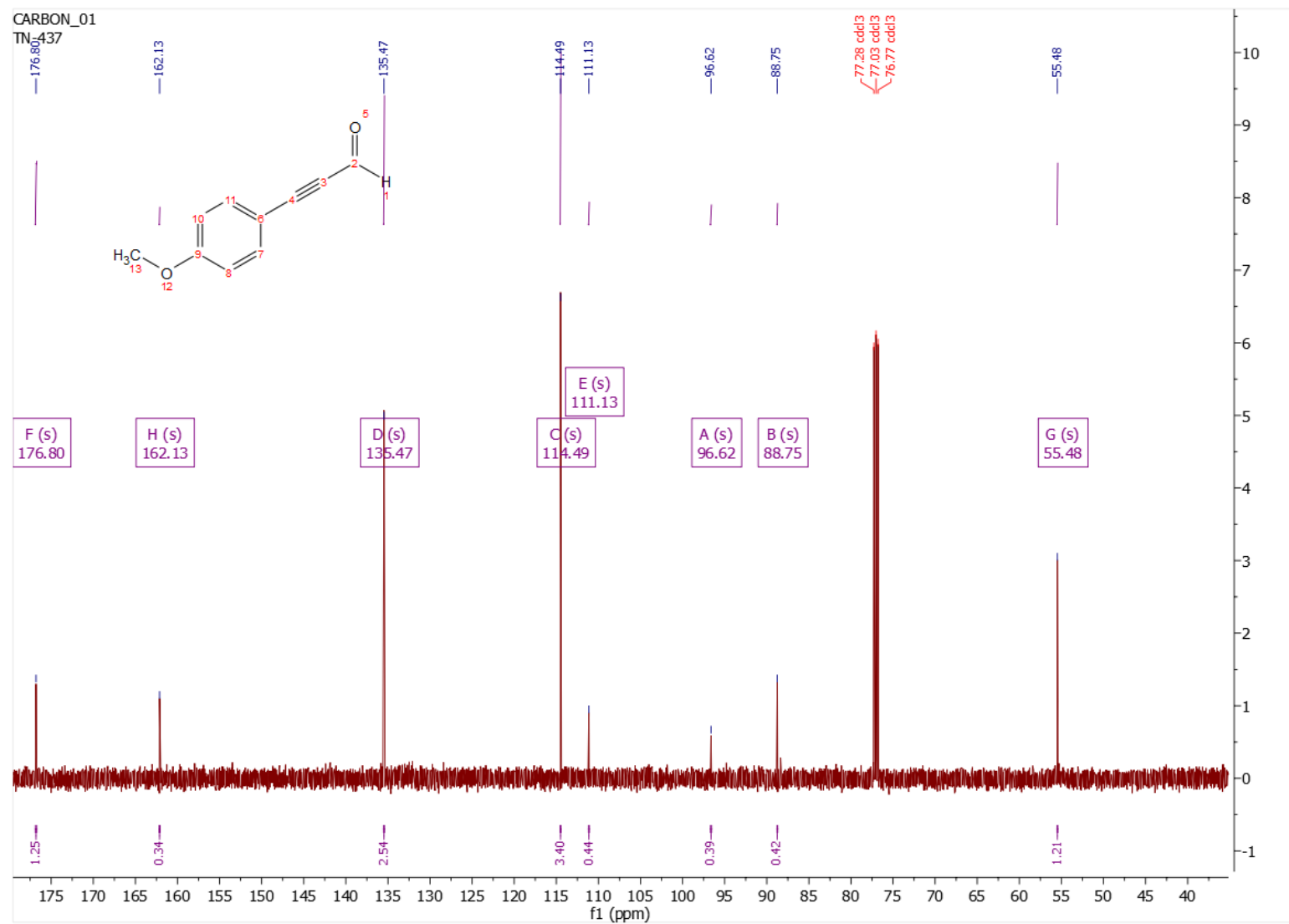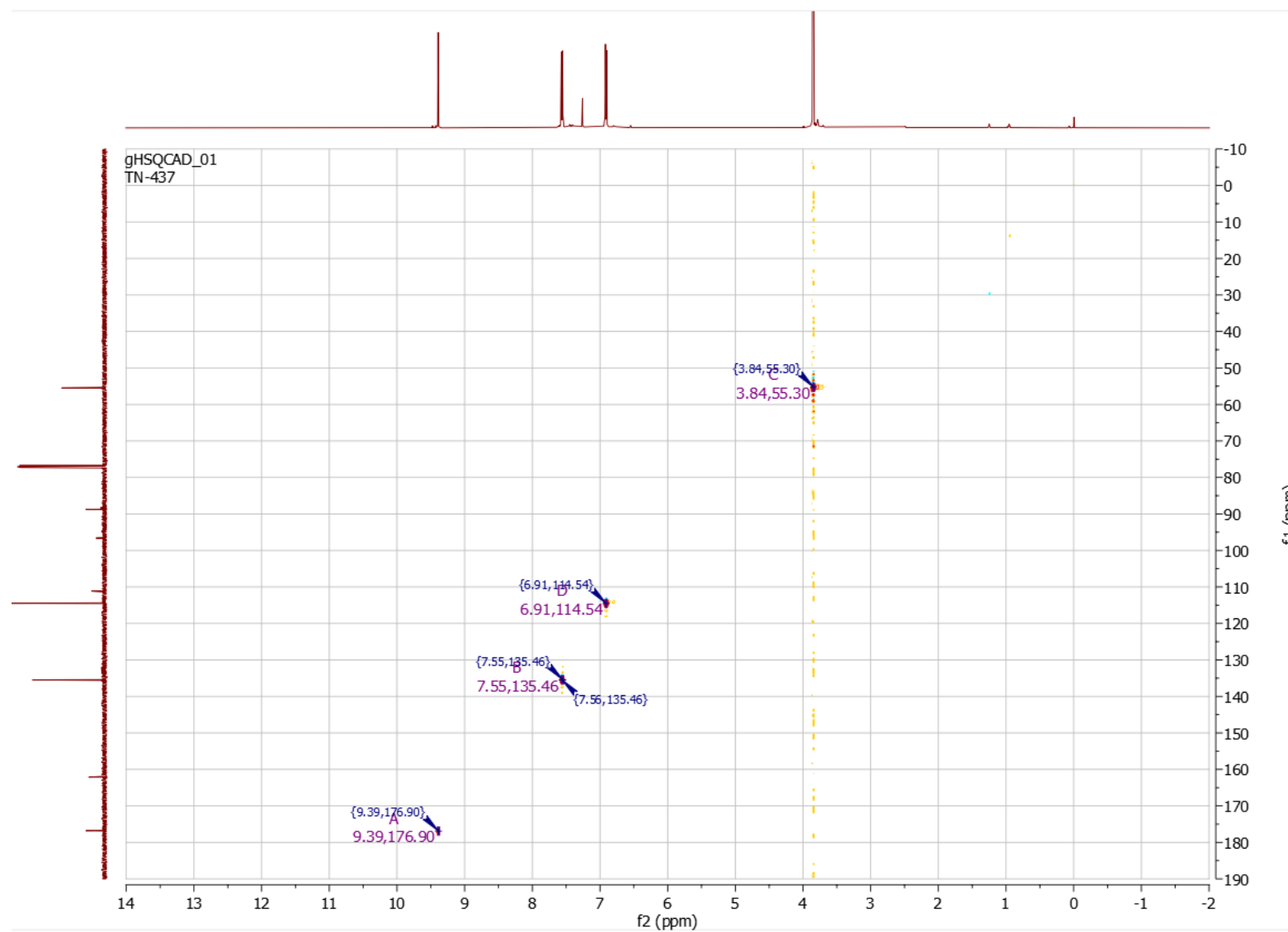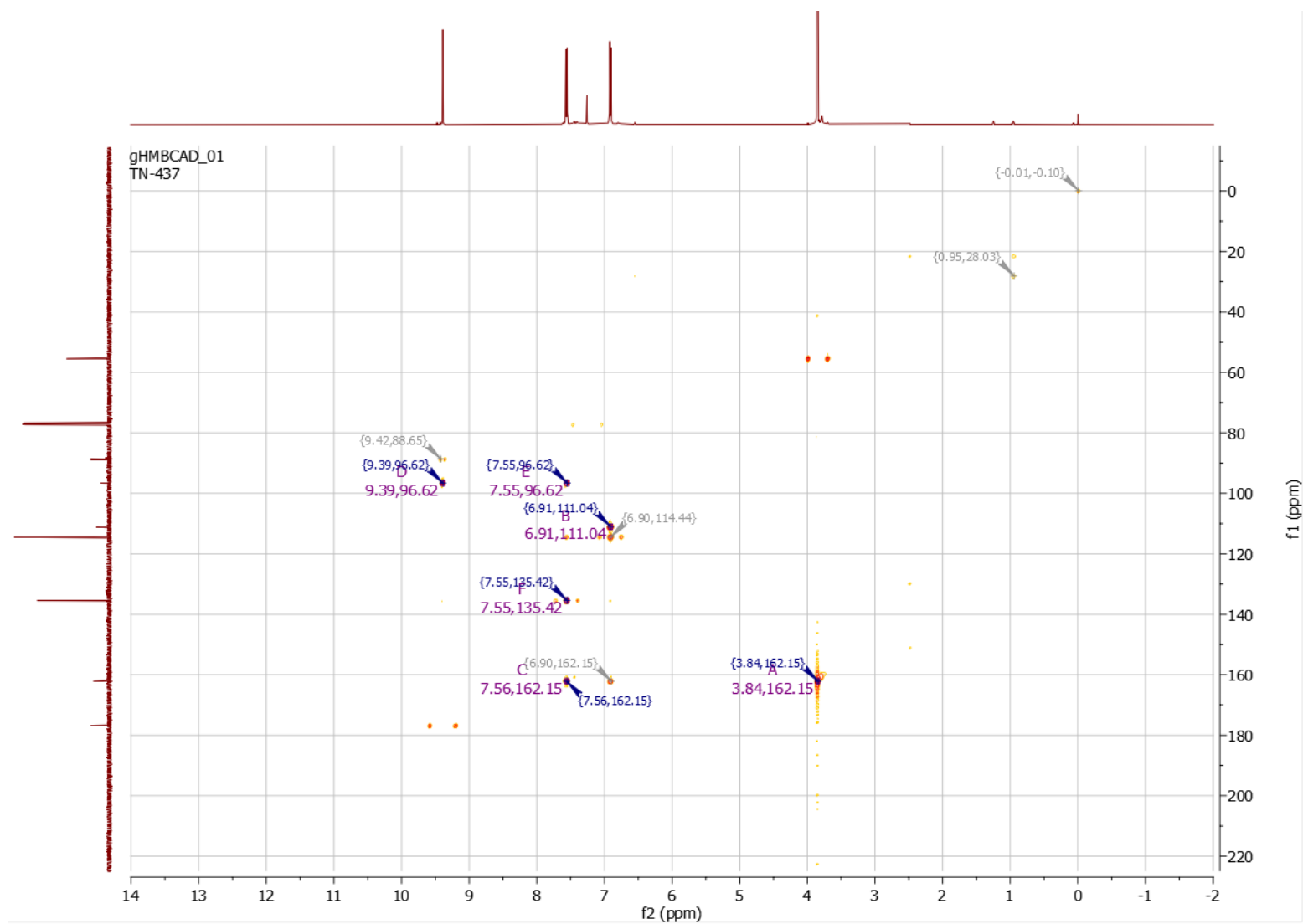
CARBON_01
TN_437

176.80

162.13

135.47

114.49
111.13

96.62

88.75

77.28 cdcl3
77.03 cdcl3
76.77 cdcl3

55.48

F (s)
176.80

H (s)
162.13

D (s)
135.47

E (s)
111.13

C (s)
114.49

A (s)
96.62

B (s)
88.75

G (s)
55.48

1.25

0.34

2.54

3.40

0.44

0.39

0.42

1.21

175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40
f1 (ppm)

HSQC

HMBC

Intens.
x10^5

1.2 —   161.0595

1.0 —

0.8 —

0.6 —
                                                                215.0675

0.4 —   140.9525

      106.3656   175.0751

0.2 —
                                                    204.0346   229.1222

        100   120   140   160   180   200   220   m/z

——— +MS
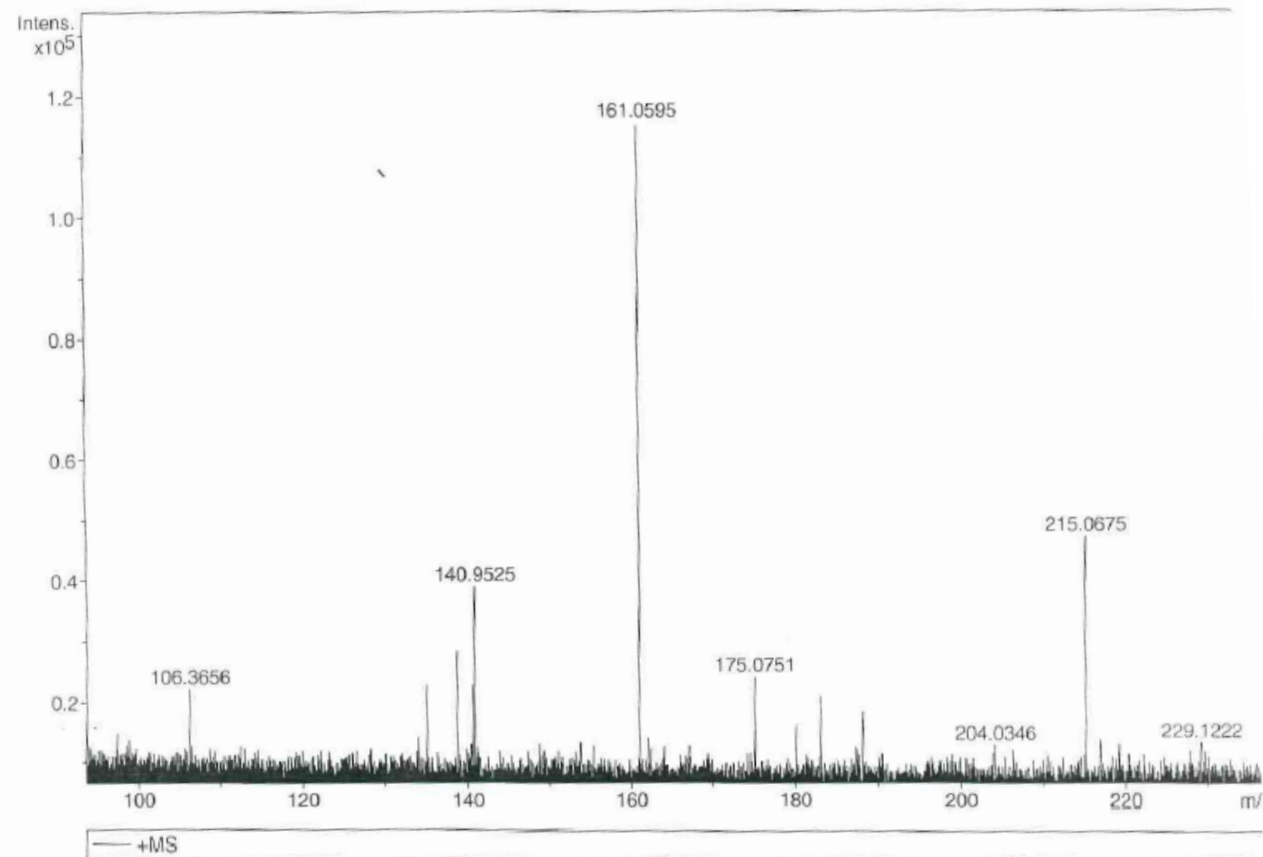
Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 10 H 9 O 2	0.045	161.0597	1.43	-0.27	-0.04	6.50	ok	even

Analyst   PEService

Date   29 March 2019 16:56

Peak labels on spectrum:
- 2939.4
- 2847.4
- 2177.64cm-1
- 1649.93cm-1
- 1597.48cm-1
- 1508.02cm-1
- 1249.29cm-1
- 1170.92cm-1
- 1023.15cm-1
- 976.89cm-1
- 829.28cm-1
- 803.78cm-1
- 709.29cm-1
- 582.47cm-1
- 529.97cm-1
- 520.18cm-1
- 537.81cm-1

X-axis: cm-1 (4000, 3500, 3000, 2500, 2000, 1500, 1000, 515)
Y-axis: %T (98, 90, 80, 70, 60, 50, 40, 30, 20, 15)
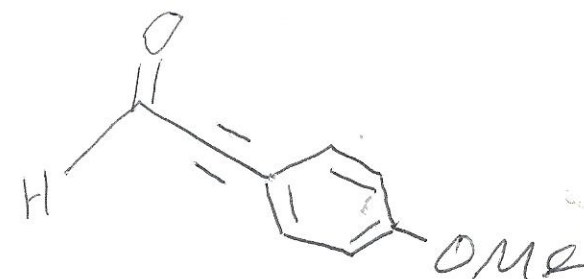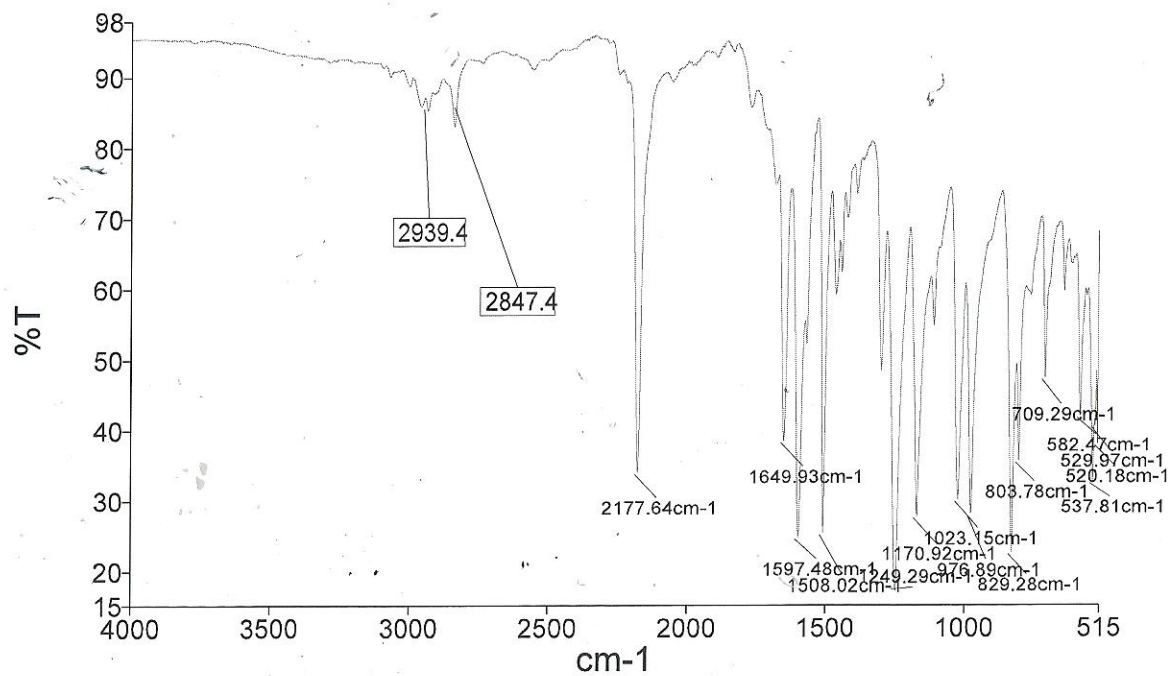
Sample Name	Description	Quality Checks
437	Sample 002 By PEService Date Friday, March 29 2019	The Quality Checks give rise to a Negative Bands warning for the sample.

3-(3,5-dimethoxyphenyl)prop-2-ynal (**163**).

600 CDCl3

PROTON_01
TN-447

D (s) 9.35

A (s) 6.53

B (s) 6.68

C (s) 3.74

6.68
6.53

3.74
3.61

1.30

0.97
0.68

7.05

f1 (ppm)
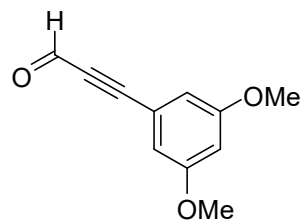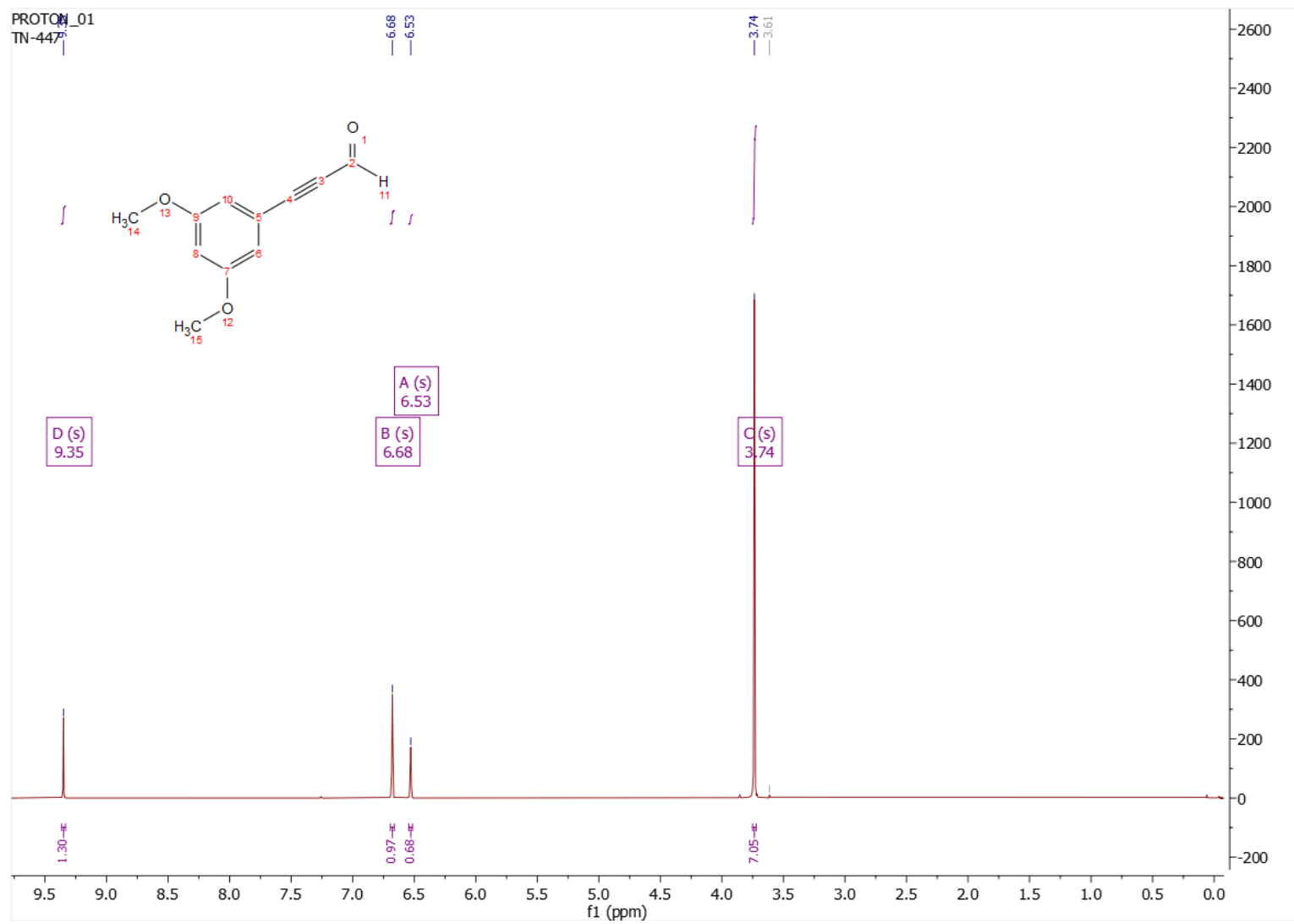
151 CDCl3
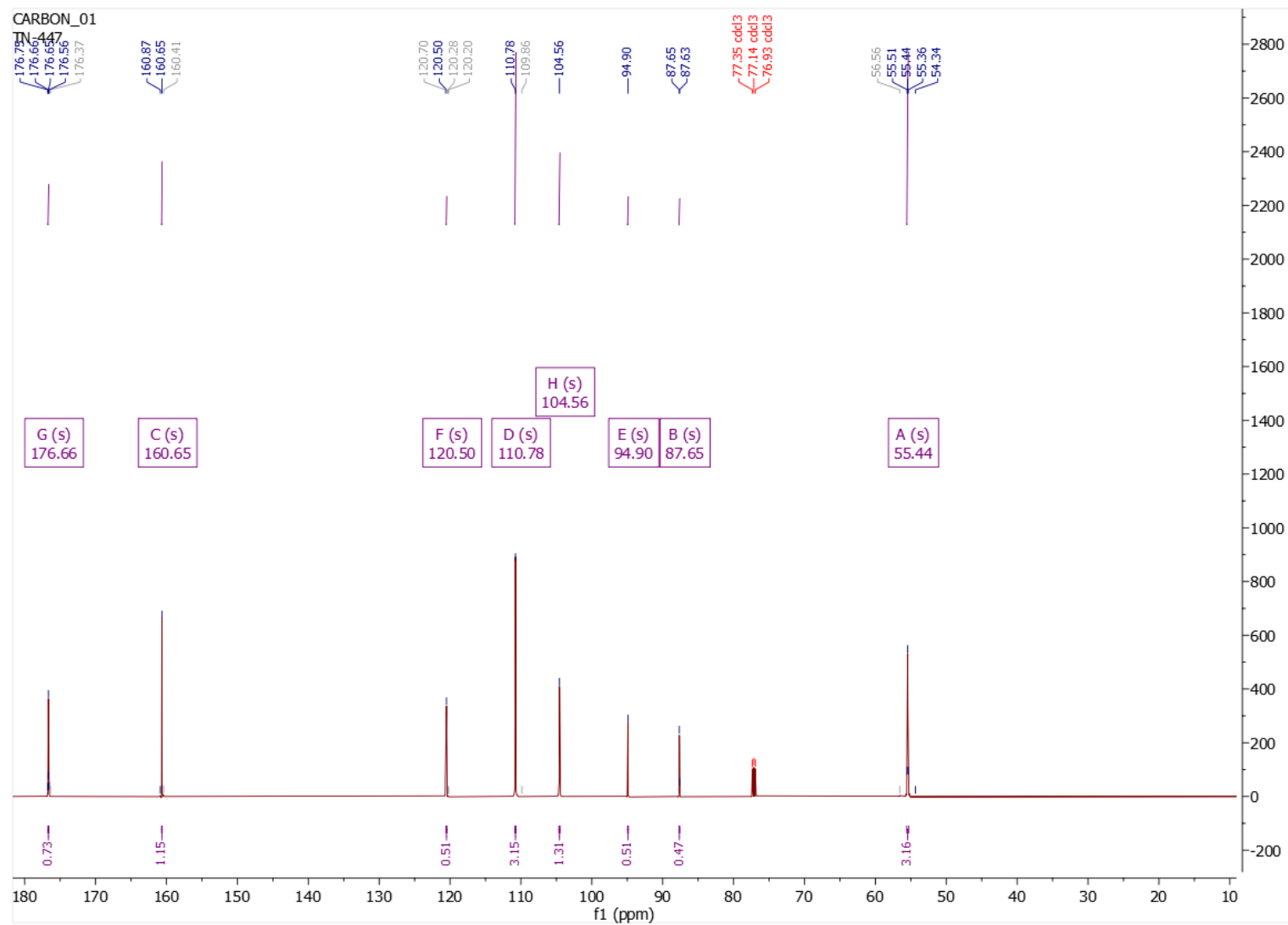
HSQC

HMBC

3-(4-tert-butylphenyl)prop-2-ynal (**164**).

PROTON_01

A (s) 9.40
B (m) 7.54
C (m) 7.42
D (s) 1.32

9.40
7.55 7.55 7.54 7.54 7.53 7.53 7.43 7.42 7.42 7.41 7.41 7.41
7.25 cdcl3
5.29
1.41 H2O
1.32

0.94
2.41 2.59
12.06

f1 (ppm)

Analyst
Date

PEService
29 March 2019 16:29

%T

98
95
90
85
80
75
70
65
60
55
50
47

4000   3500   3000   2500   2000   1500   1000   515

cm-1

2868.3

2190.6

2962.73cm-1

1685.35cm-1
1603.89cm-1
1660.56cm-1

1363.93cm-1
1186.43cm-1
981.65cm-1
1016.67cm-1

1266.75cm-1
1107.13cm-1

835.09cm-1
563.87cm-1

527.00cm-1
547.00cm-1
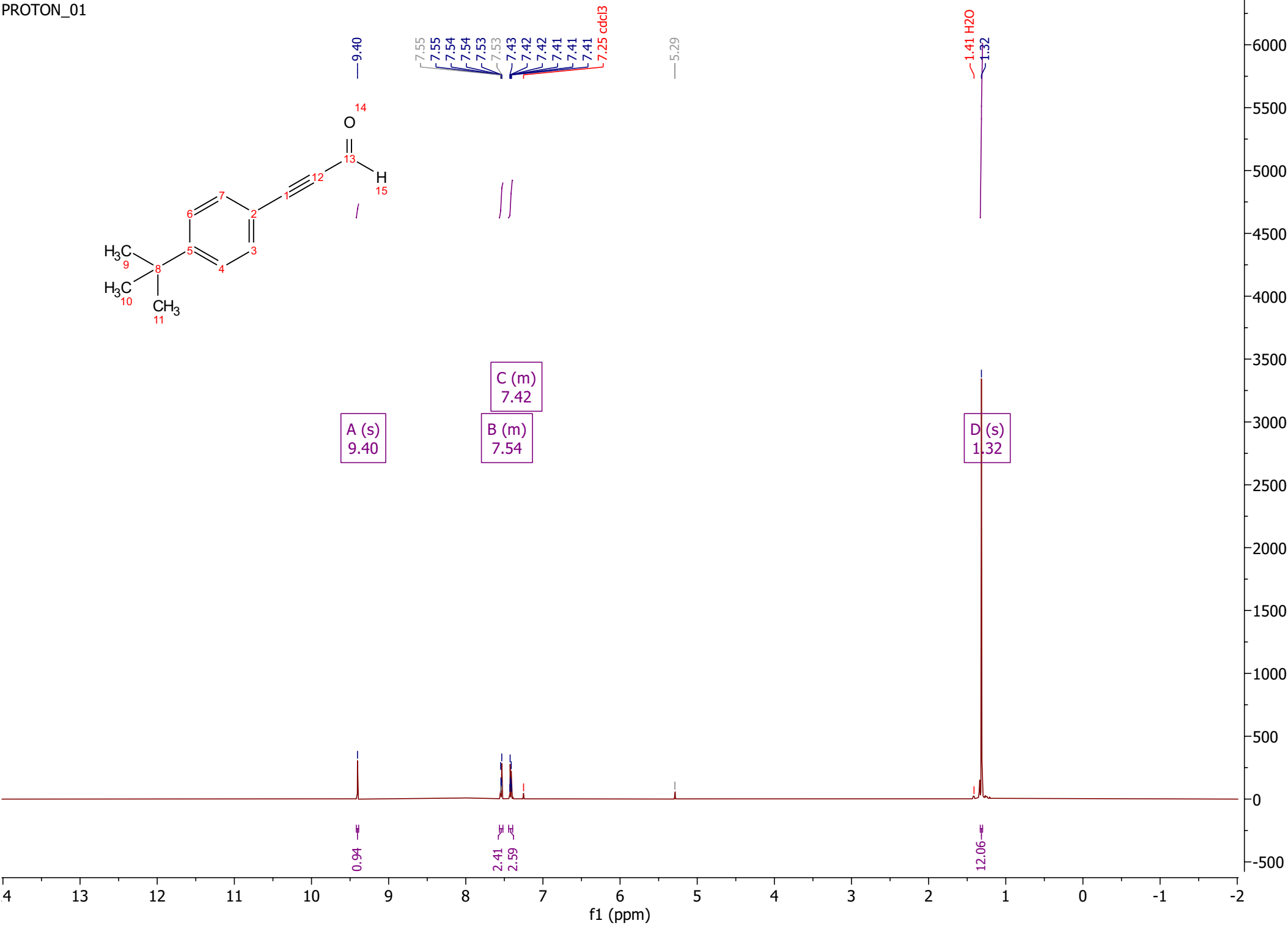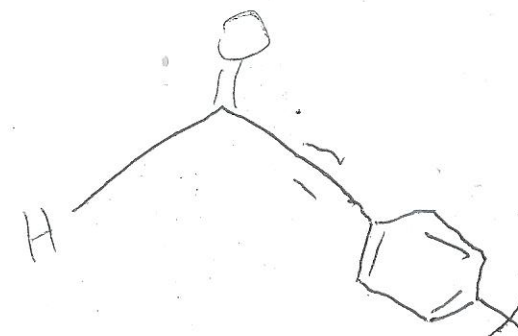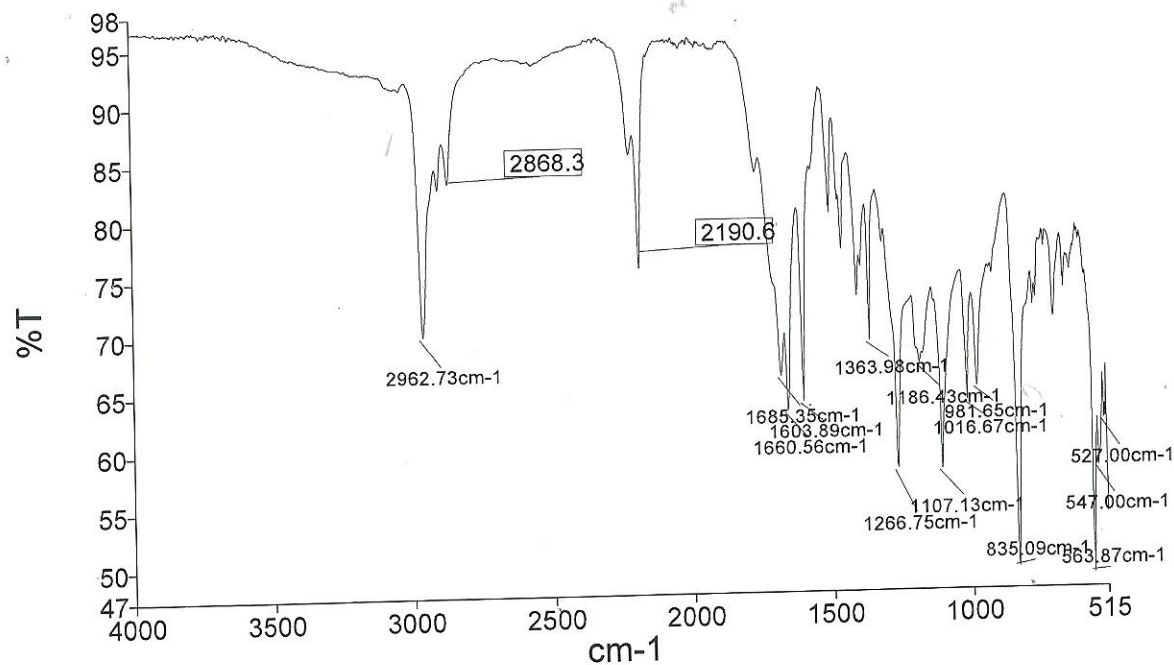
Sample Name	Description	Quality Checks
443	Sample 130 By PEService Date Friday, March 29 2019	The Quality Checks do not report any warnings for the sample.

CARBON_01
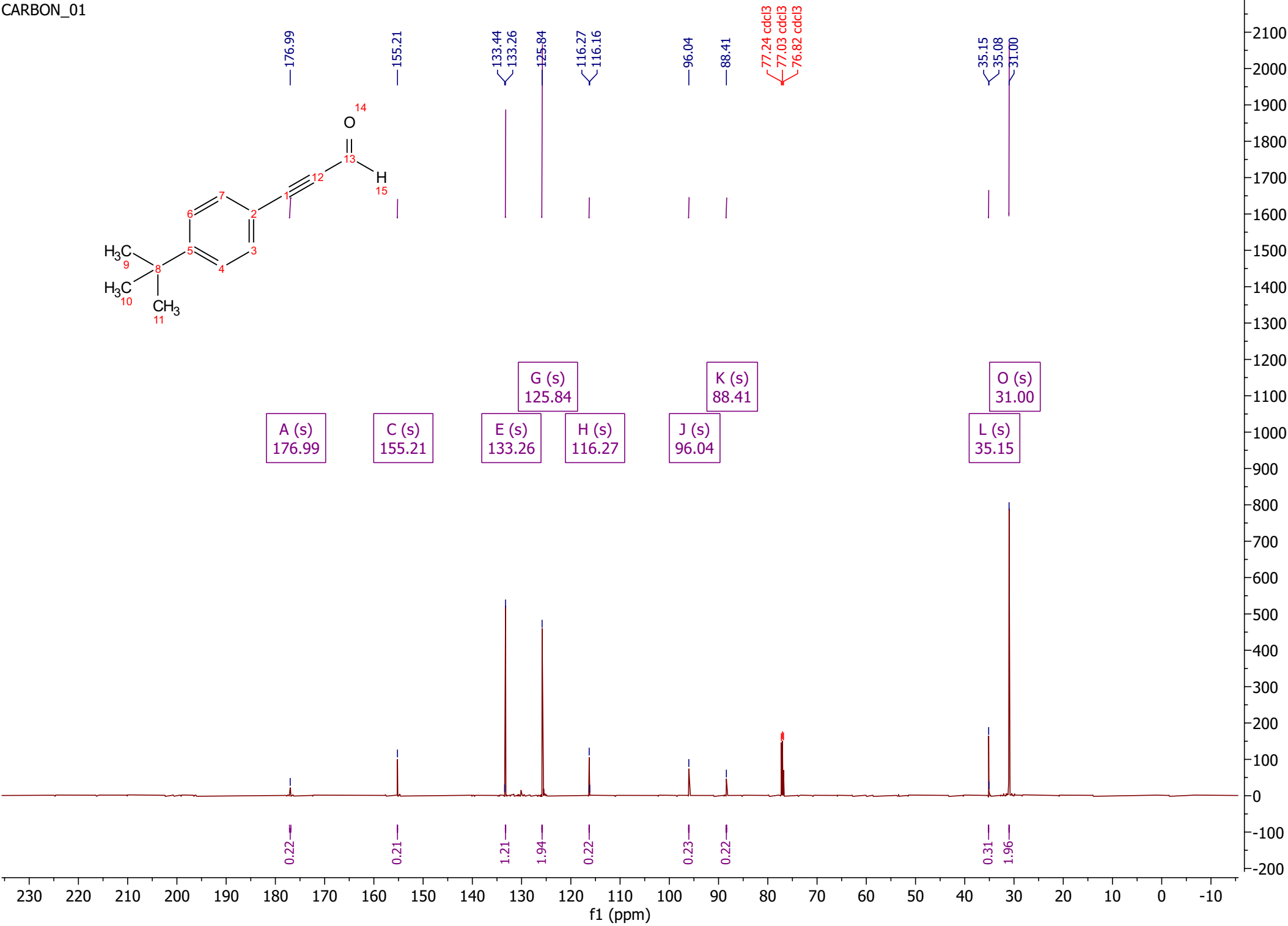
3-(4-bromophenyl)prop-2-ynal (165).

PROTON_01
TN-454

A (s)
9.39

B (m)
7.53

C (m)
7.43

f1 (ppm)

Analyst

Date

PEService
29 March 2019 17:24

%T vs cm-1

- 2852.13cm-1
- 2922.11cm-1
- 2190.21cm-1
- 1651.74cm-1
- 1583.44cm-1
- 1485.74cm-1
- 1393.62cm-1
- 1376134cm-1
- 1263.40cm-1
- 1069.15cm-1
- 1009.83cm-1
- 980.53cm-1
- 821.09cm-1
- 758.09cm-1
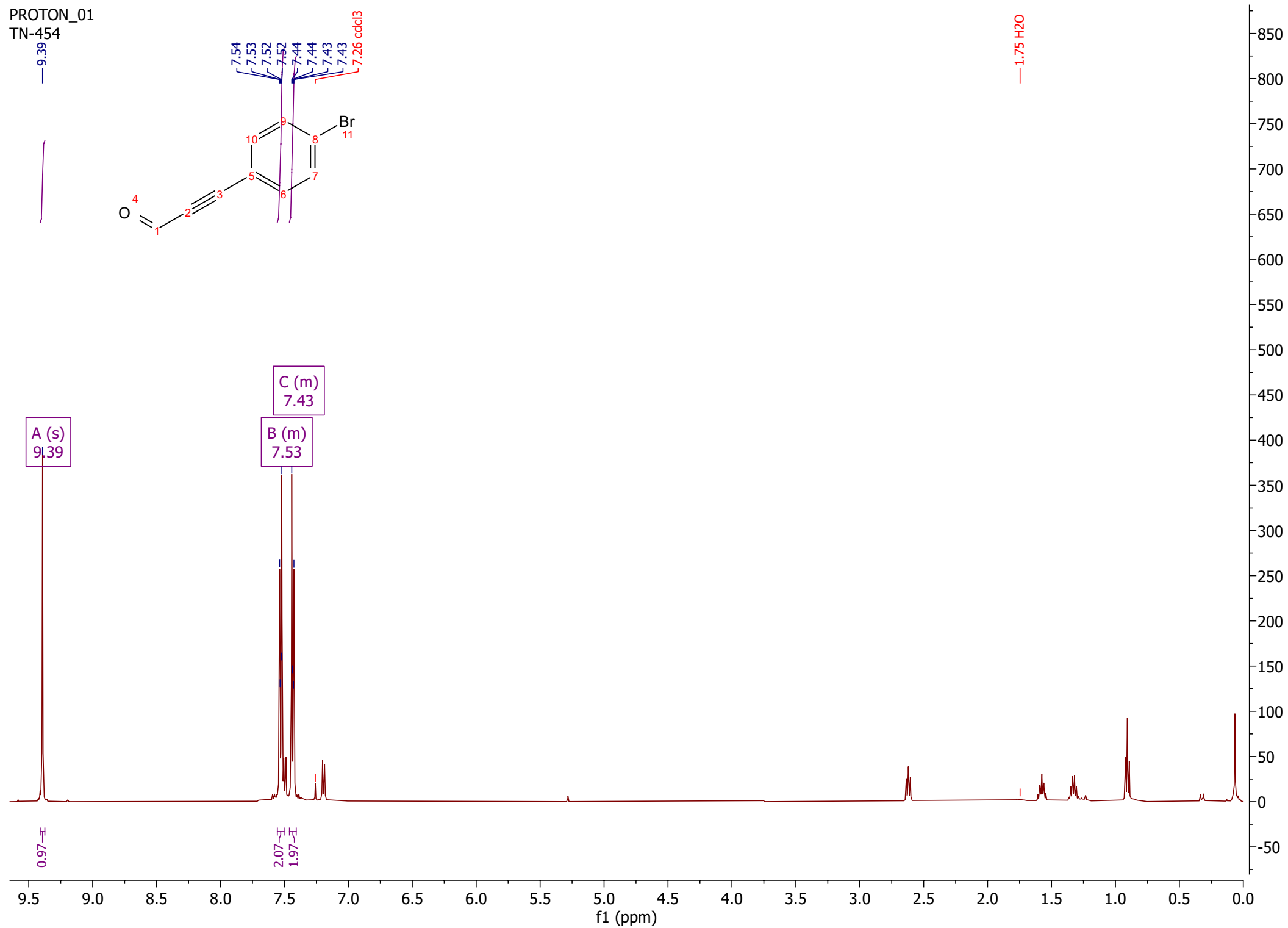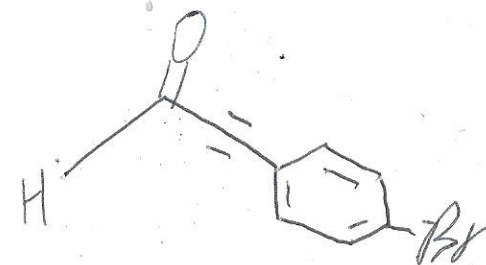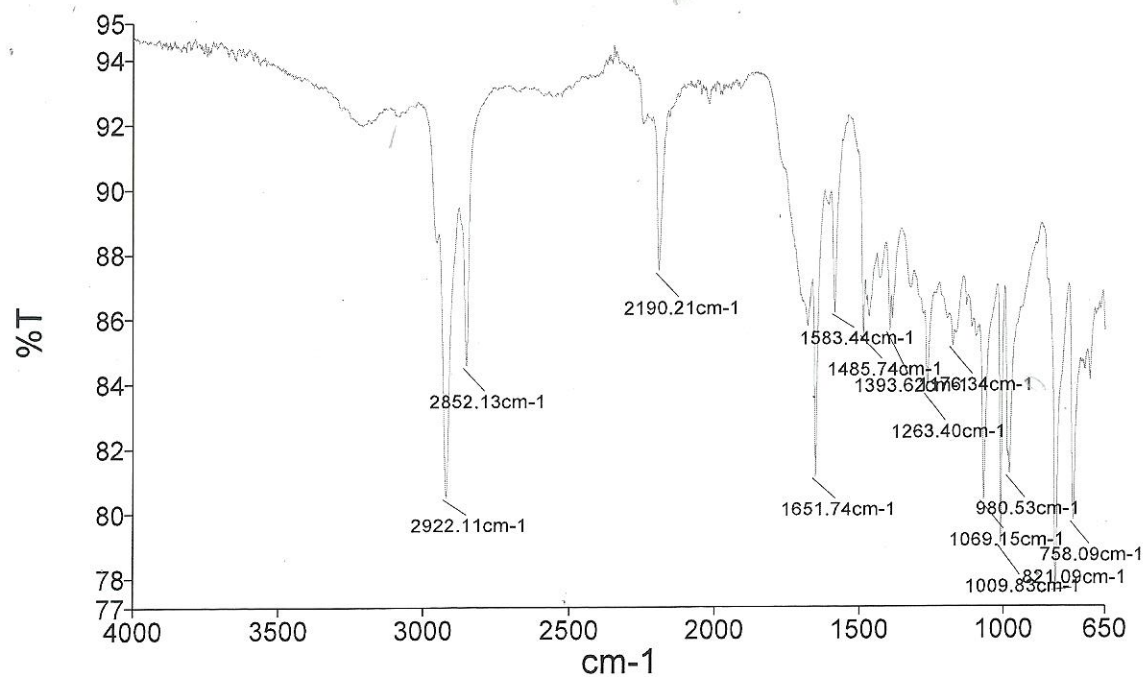
Sample Name	Description	Quality Checks
454	Sample 006 By PEService Date Friday, March 29 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

3-cyclopropylprop-2-ynal (166).
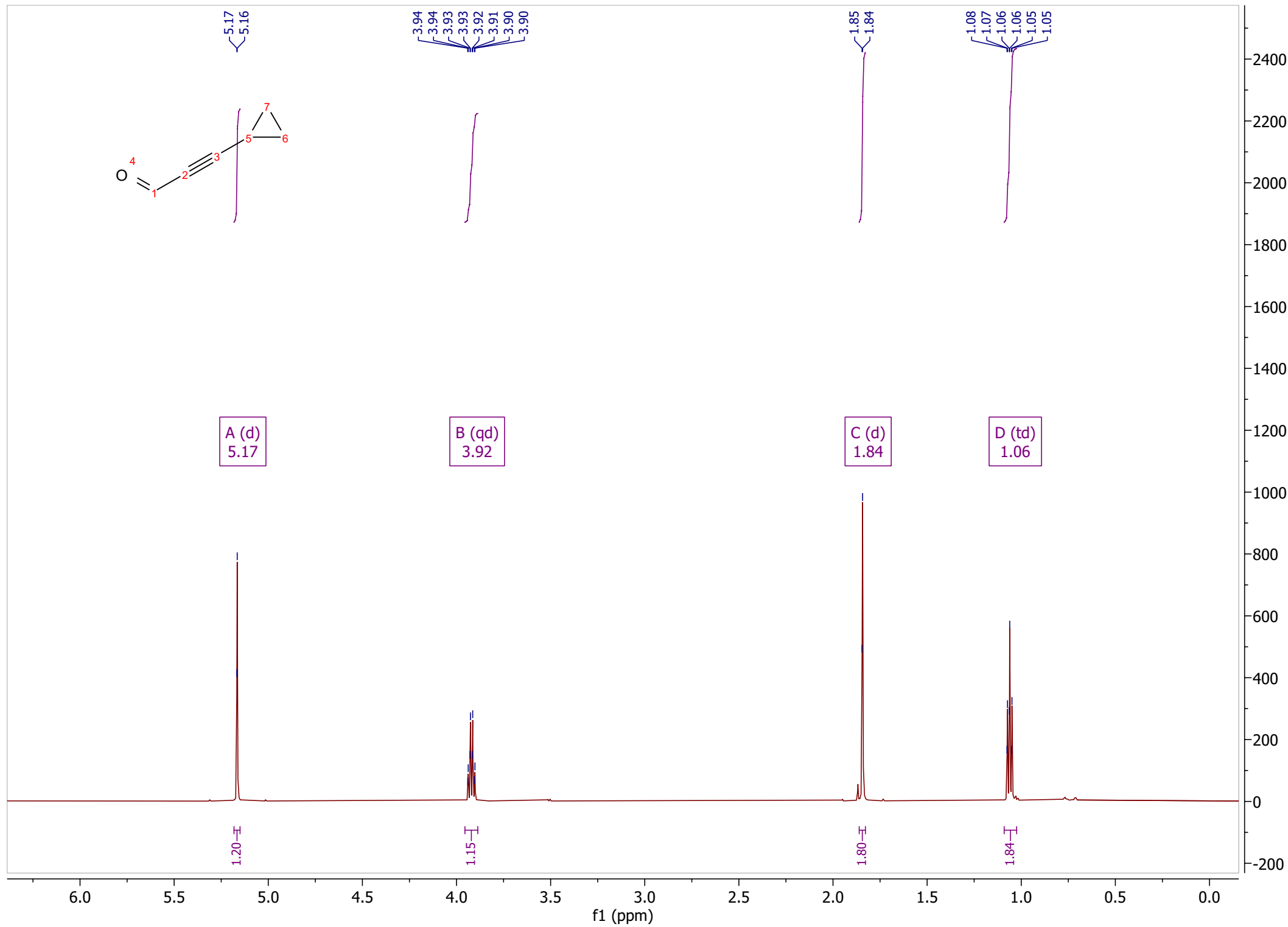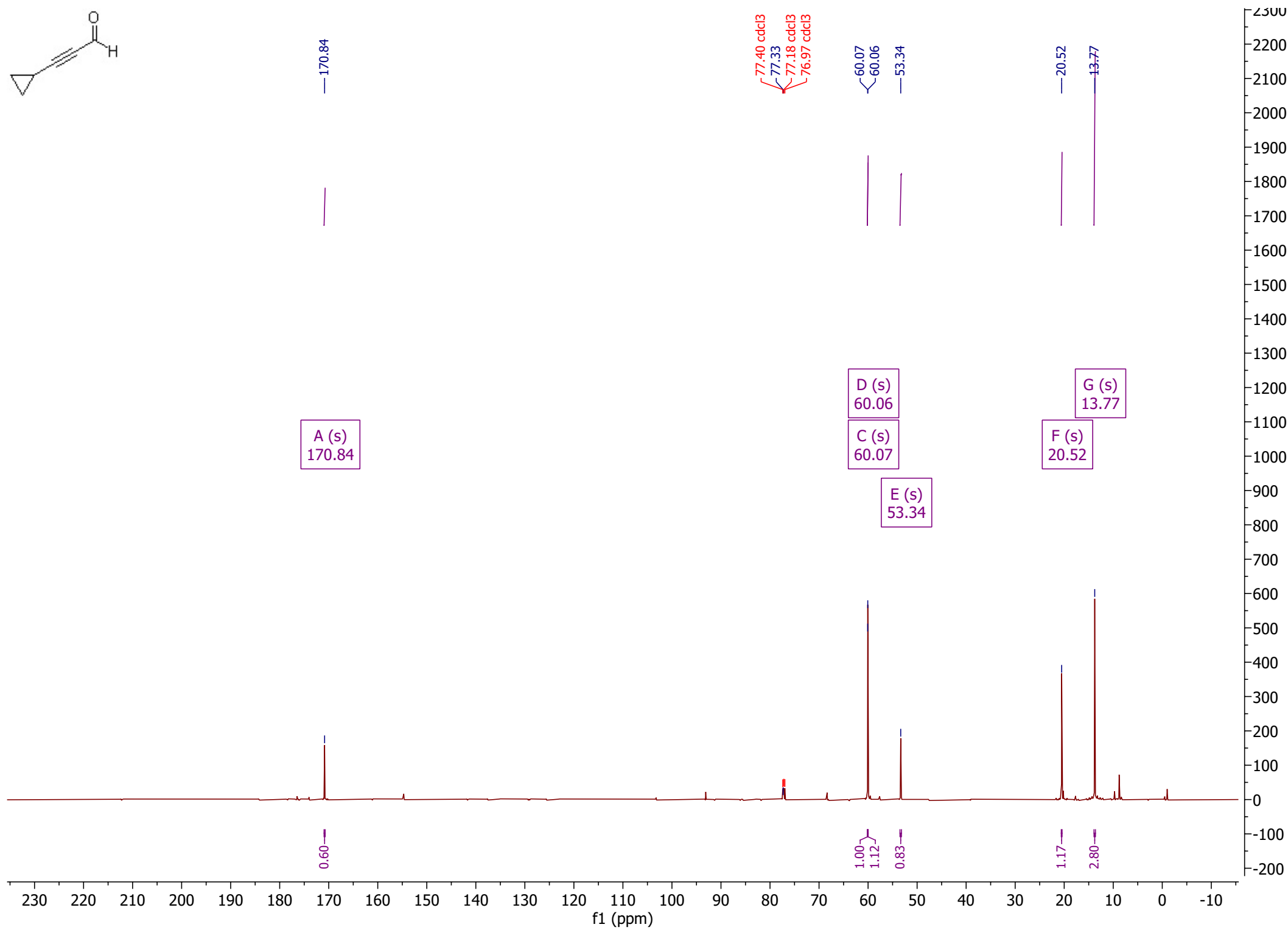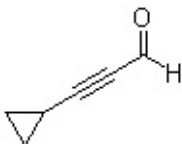
4-(4-methoxyphenyl)-2-methyl-3-nitropyridine (**168**).

600 CDCl3

PROTON_01
TN-440

A (m)
8.60

E (m)
7.24

F (d)
7.31

B (d)
6.97

D (s)
3.84

C (s)
2.61

151 CDCl3

CARBON_01
TN-440

160.79 150.24 150.07 141.62 128.95 126.16 122.79 114.67 77.27 cdcl3 77.02 cdcl3 76.76 cdcl3 55.37 20.58

0.77 0.56 2.32 0.79 4.09 0.85 2.23 3.92 18.23 14.87 11.93 1.92 1.09

f1 (ppm)

HSQC

gHSQCAD_01
TN-440
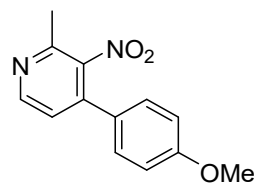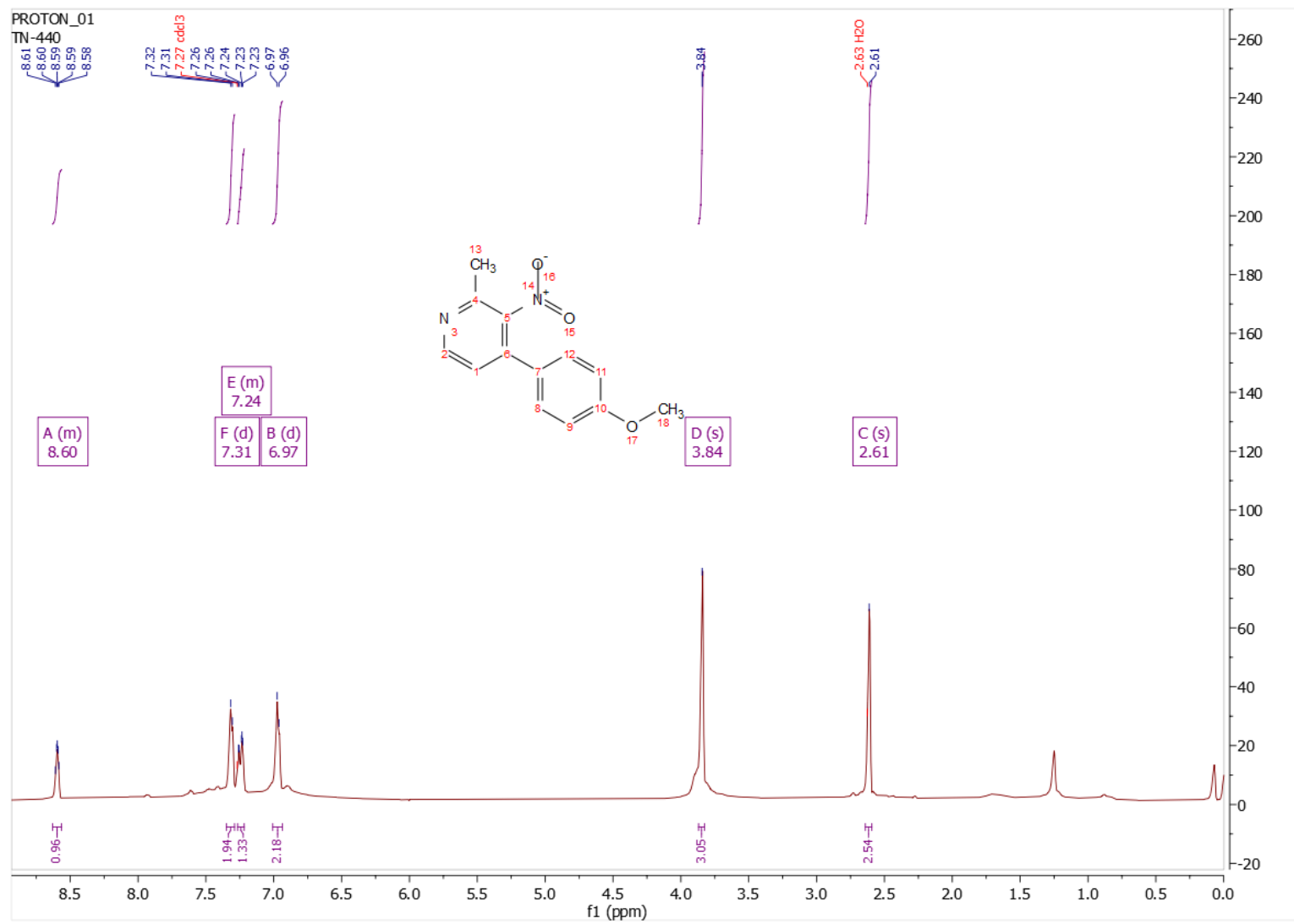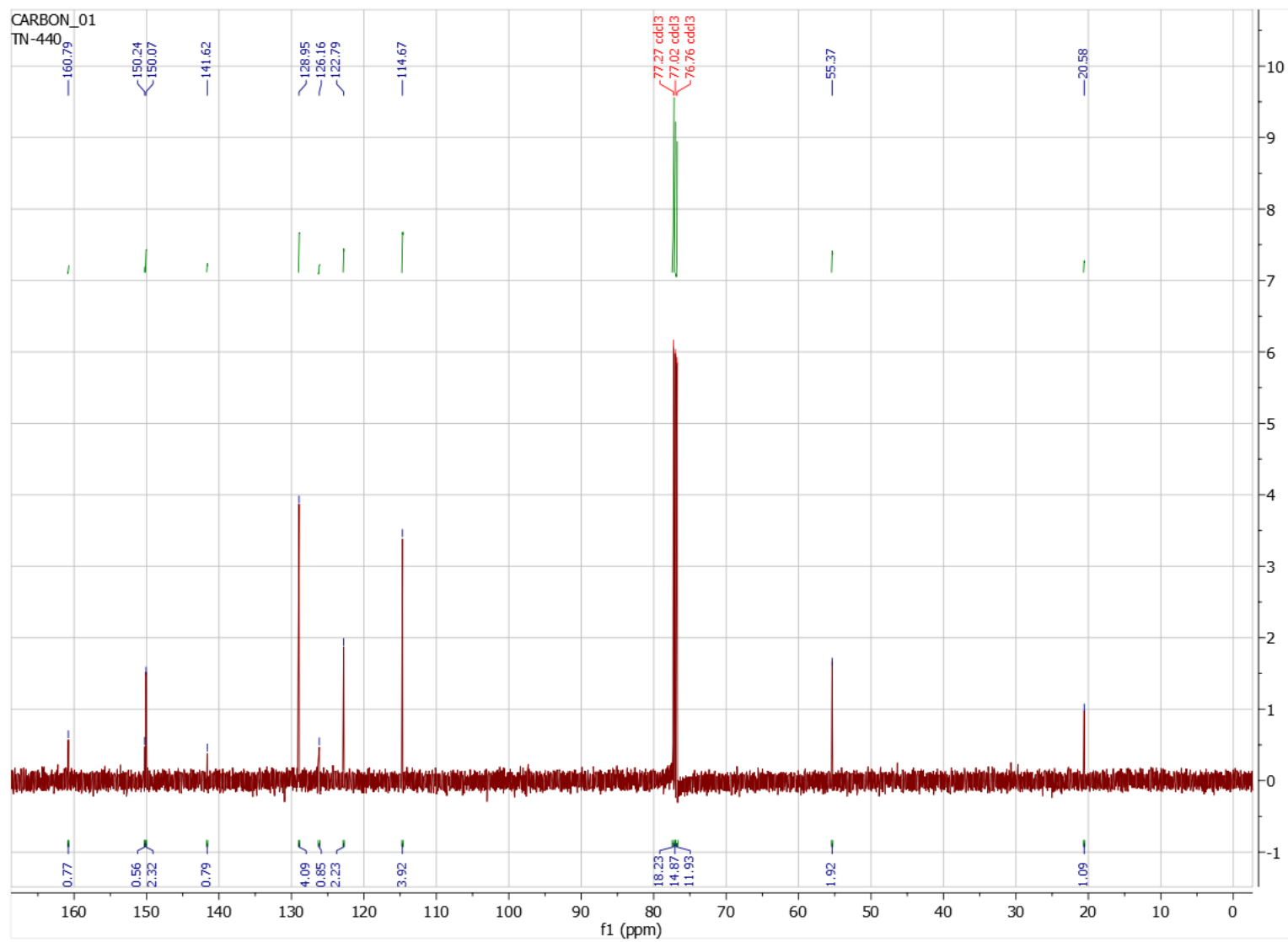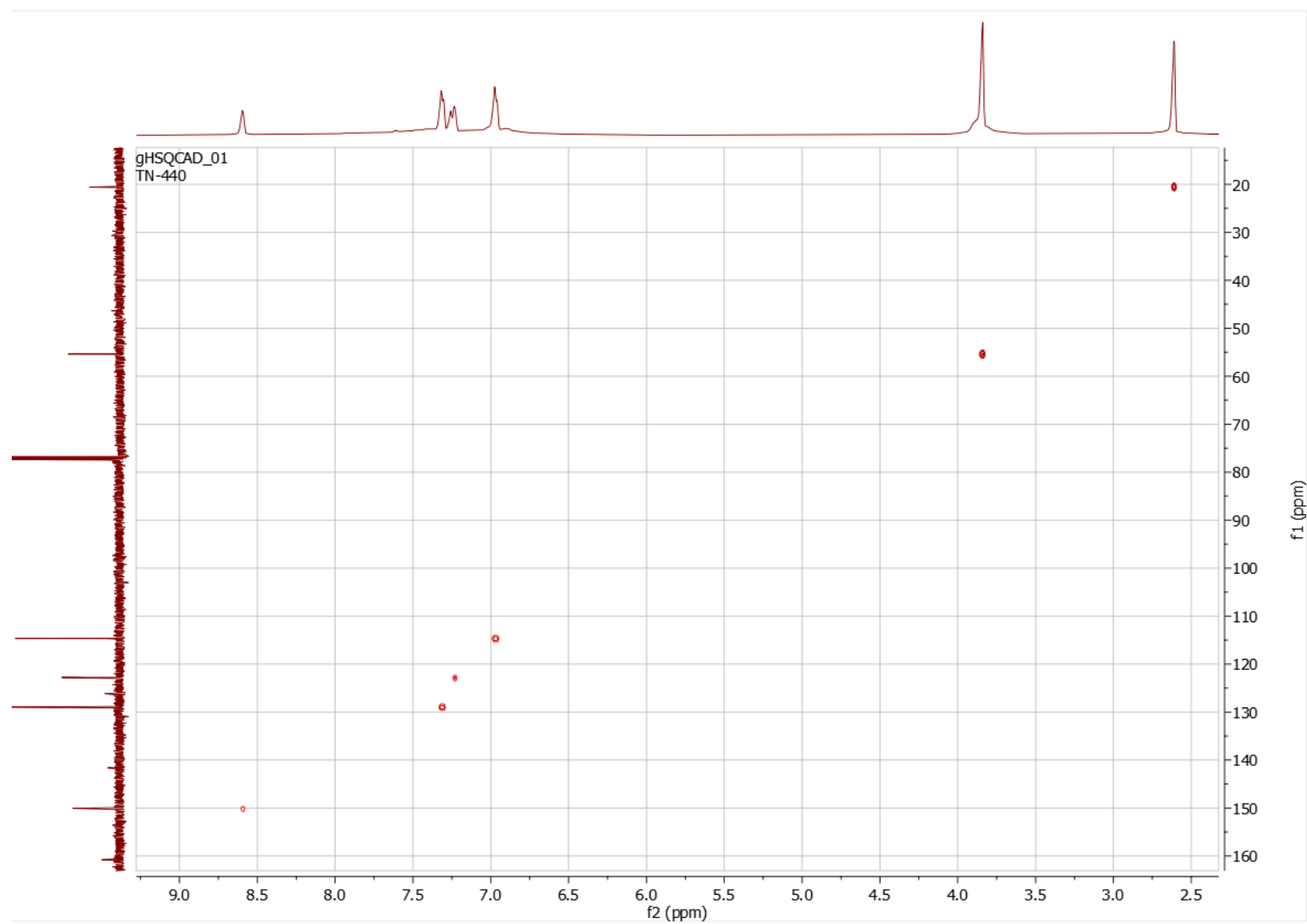
HMBC

Analyst
Date

Administrator
29 March 2019 15:39

1293.29cm-1, 96.59%T
1411.55cm-1, 97.44%T
1082.18cm-1, 96.02%T
1463.84cm-1, 96.50%T
1102.32cm-1, 94.77%T
1514.86cm-1, 93.77%T
717.14cm-1, 98.09
1362.58cm-1, 96.68%T
1178.76cm-1, 96.23%T
3077.22cm-1, 99.56%T
2058.83cm-1, 99.66%T
745.11cm-1, 99.95%T
2010.82cm-1, 99.27%T
2149.79cm-1, 99.69%T
2923.81cm-1, 97.43%T
2209.46cm-1, 99.72%T
613.66cm-1, 97.36%T
2160.93cm-1, 99.76%T
593.41cm-1, 97.08%T
554.41cm-1, 96.63%T
852.65cm-1, 96.01%T
1728.5
763.73cm-1, 97.45%
829.71cm-1, 94.70%T
1597.94cm-1, 95.41%T
1033.10cm-1, 94.43%T
1530.99cm-1, 93.82%T
1252.37cm-1, 92.28%T

%T
cm-1

Sample Name	Description	Quality Checks	Pathlength (mm)
440	Sample 000 By Administrator Date Friday, March 29 2019	The Quality Checks give rise to multiple warnings for the sample.	54

Analyst

Date

%T

98
96
94
92
90
88
86
84
82
80
79

2964.4

2876

2184.97cm-1

1355.52cm-1

1180.00cm-1

1424.04cm-1

1024.37cm-1

1645.86cm-1

675.55cm-1

1590.21cm-1 1199.60cm-1 825.11cm-1
861.45cm-1
834.04cm-1
1061.55cm-1
1160.25cm-1 660.00cm-1

4000   3500   3000   2500   2000   1500   1000   650

cm-1
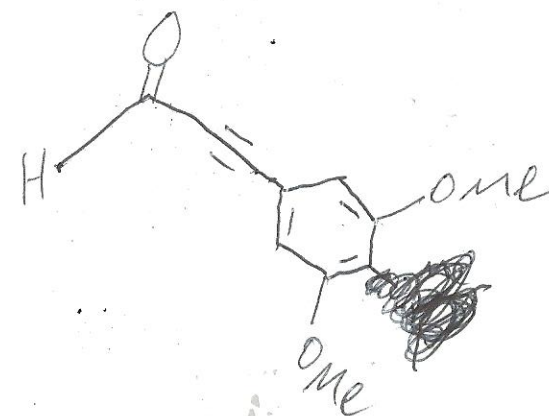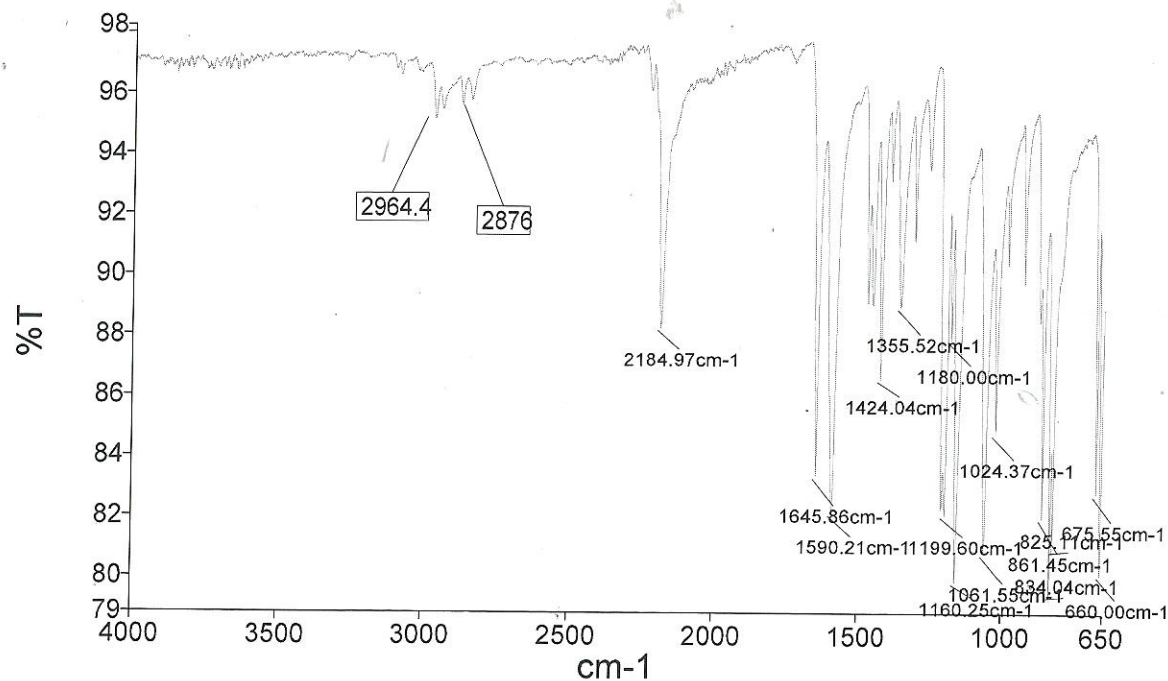
Sample Name	Description	Quality Checks
447	Sample 005 By PEService Date Friday, March 29 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

2-methyl-3-nitro-4-phenylpyridine (**167**).
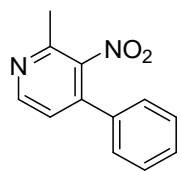
600 CDCl3
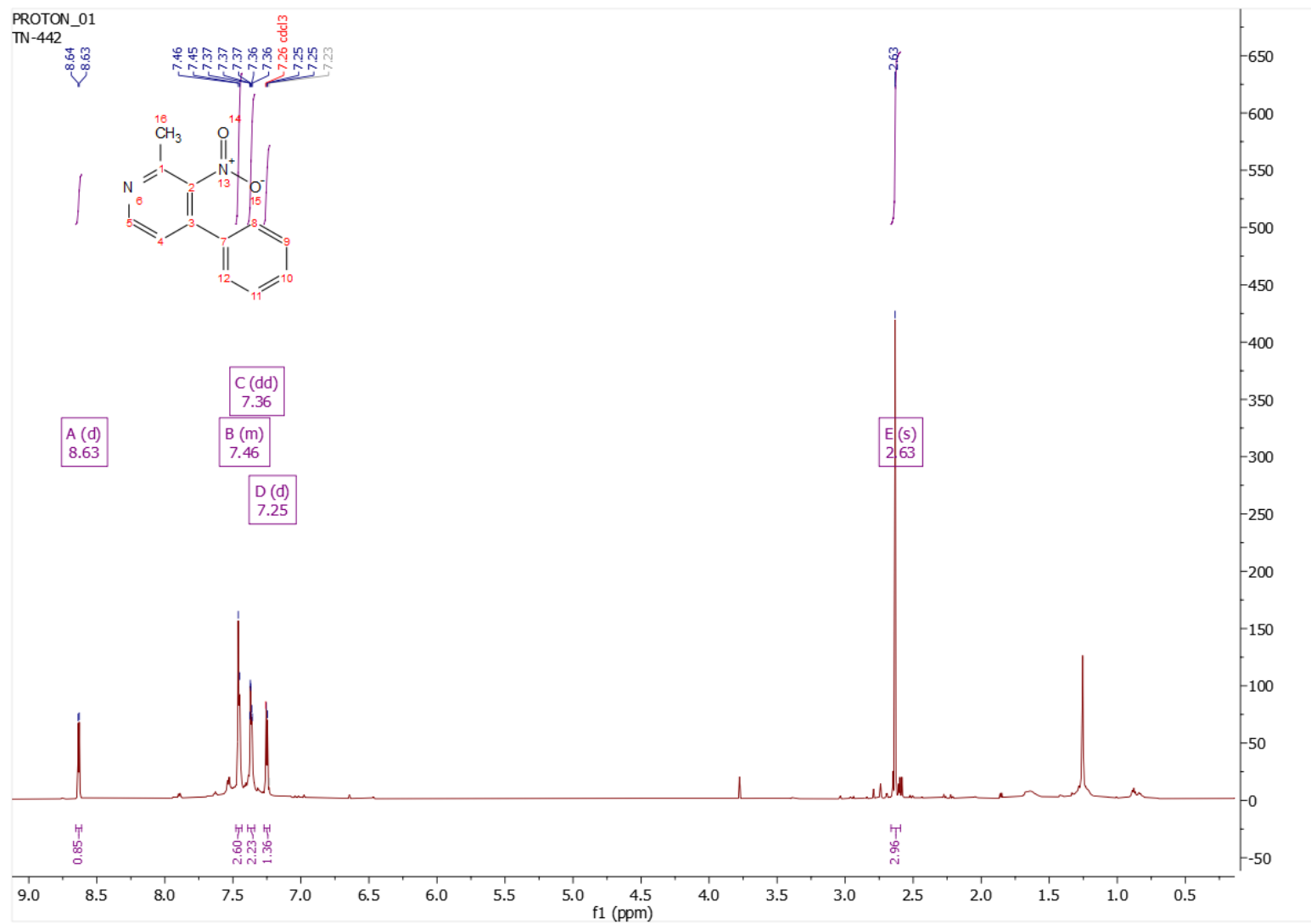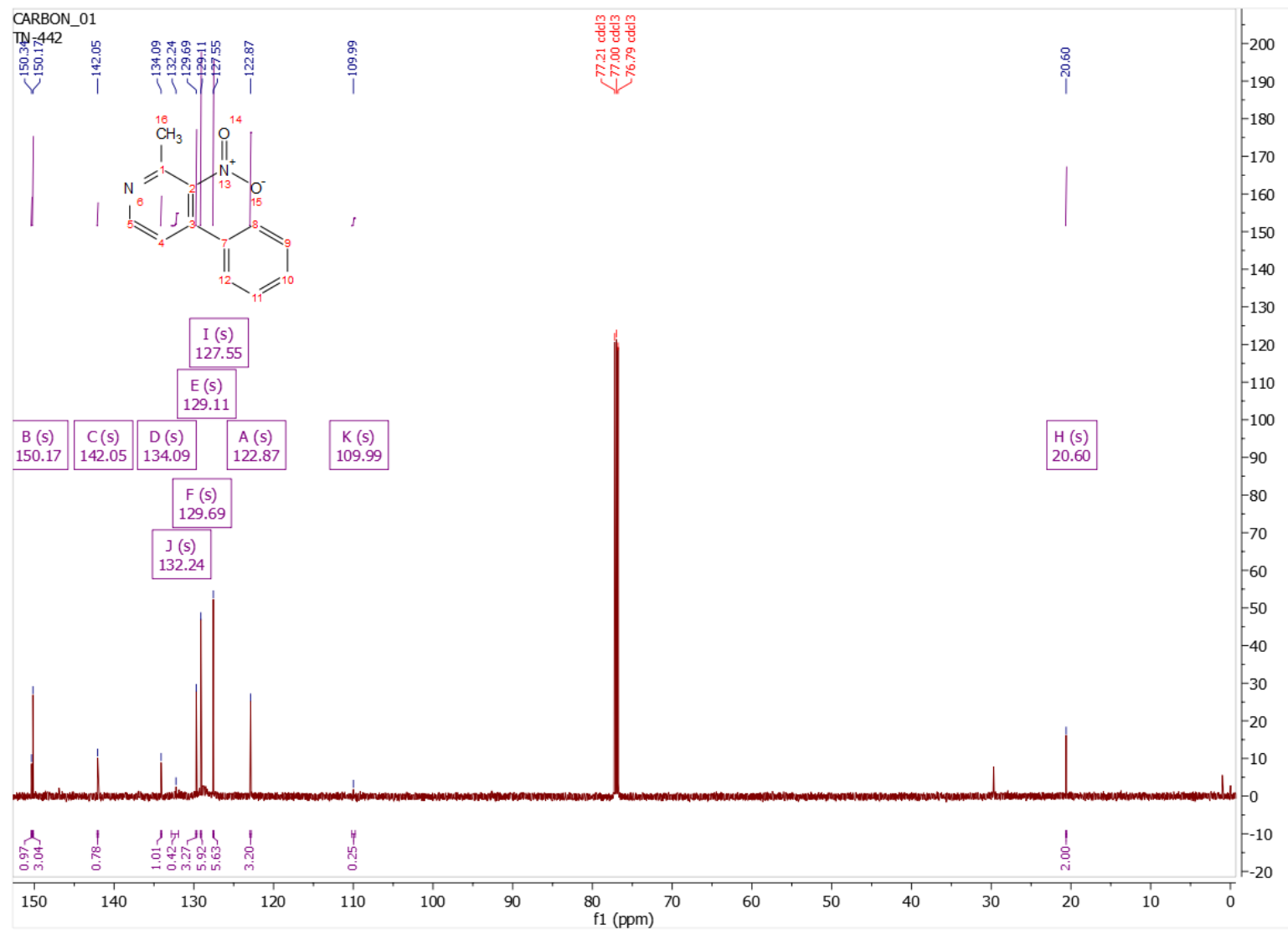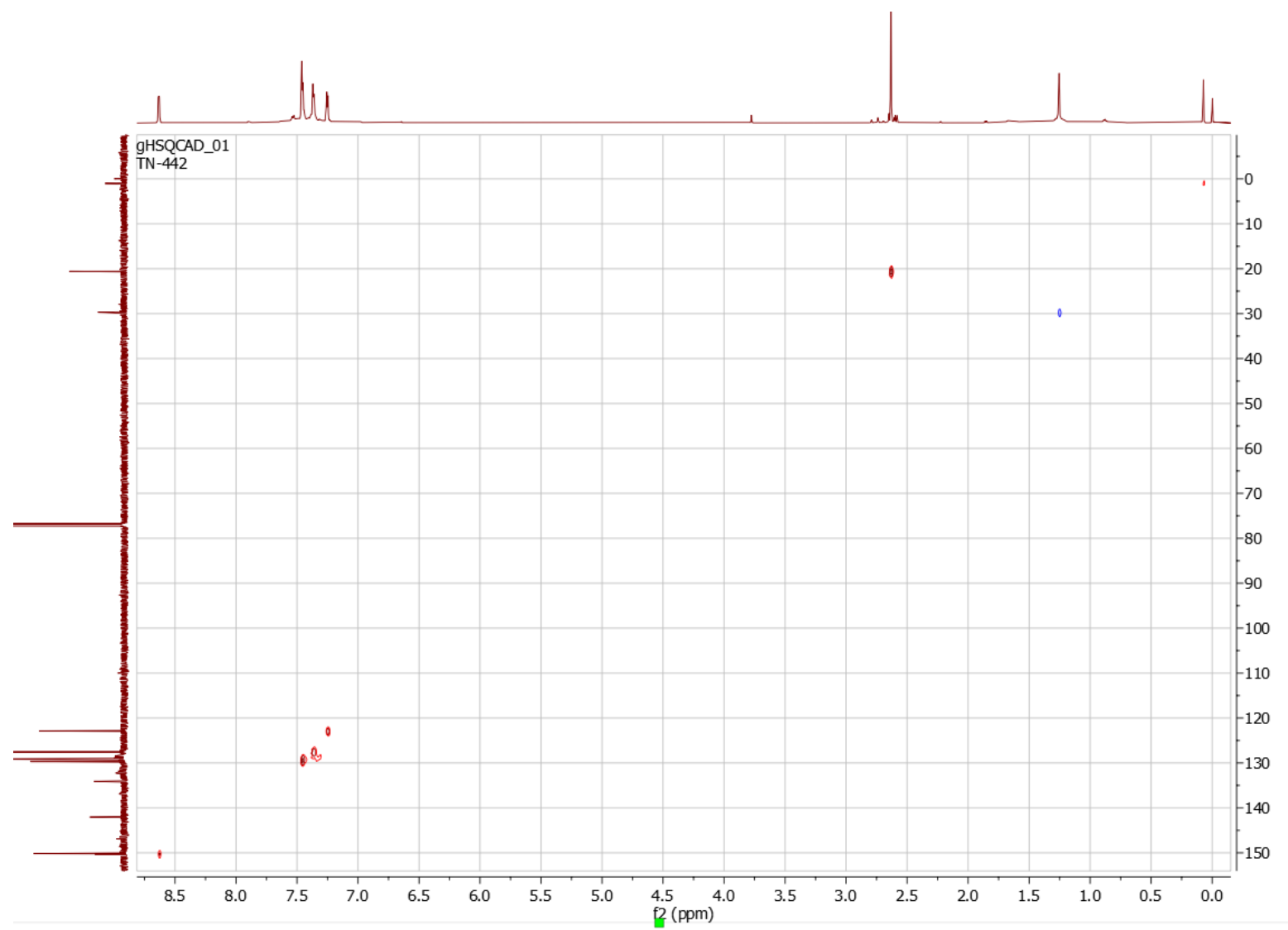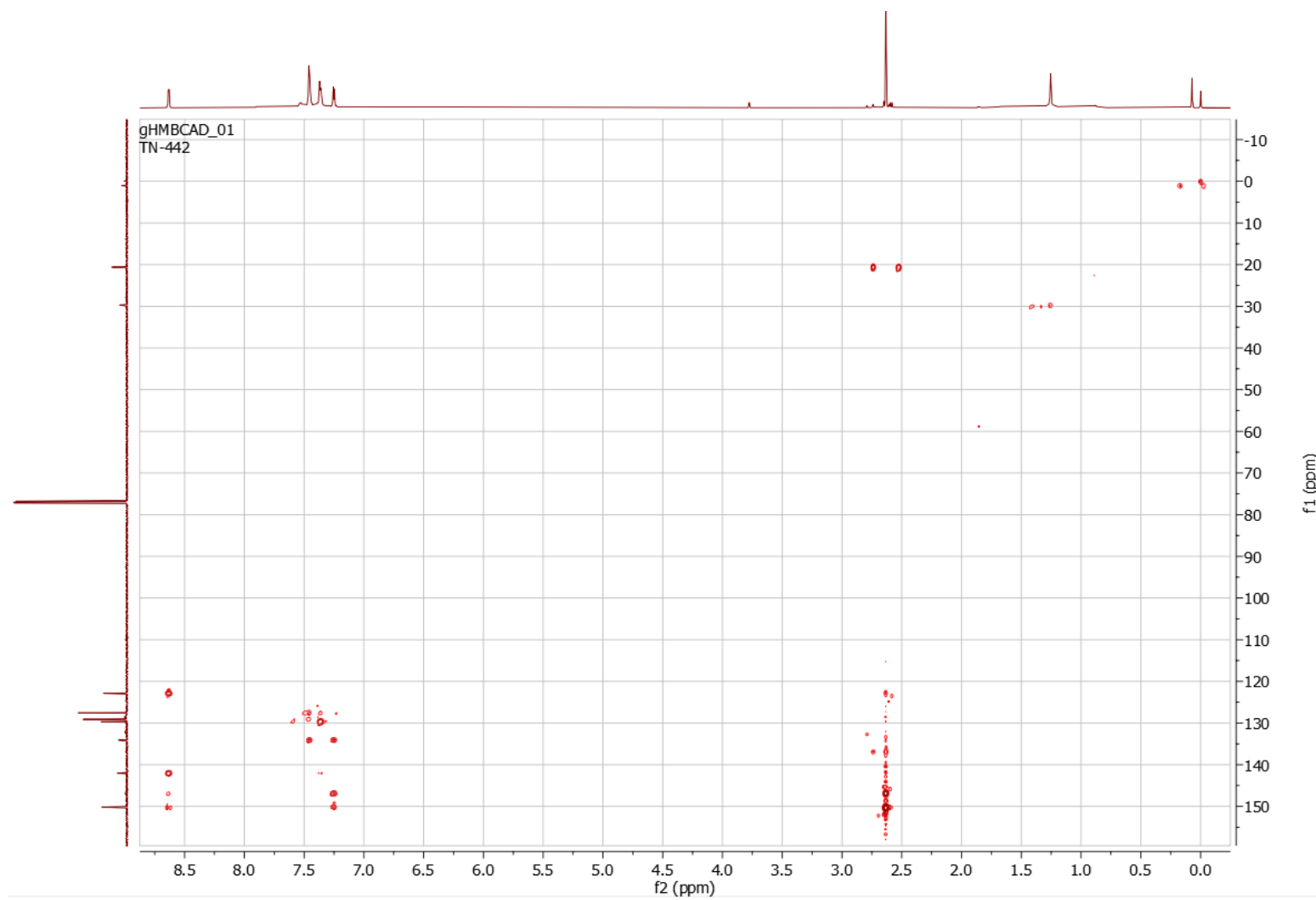
PROTON_01
TN-442

A (d)
8.63

B (m)
7.46

C (dd)
7.36

D (d)
7.25

E (s)
2.63

151 CDCl3

HSQC

gHSQCAD_01
TN-442

HMBC

gHMBCAD_01
TN-442
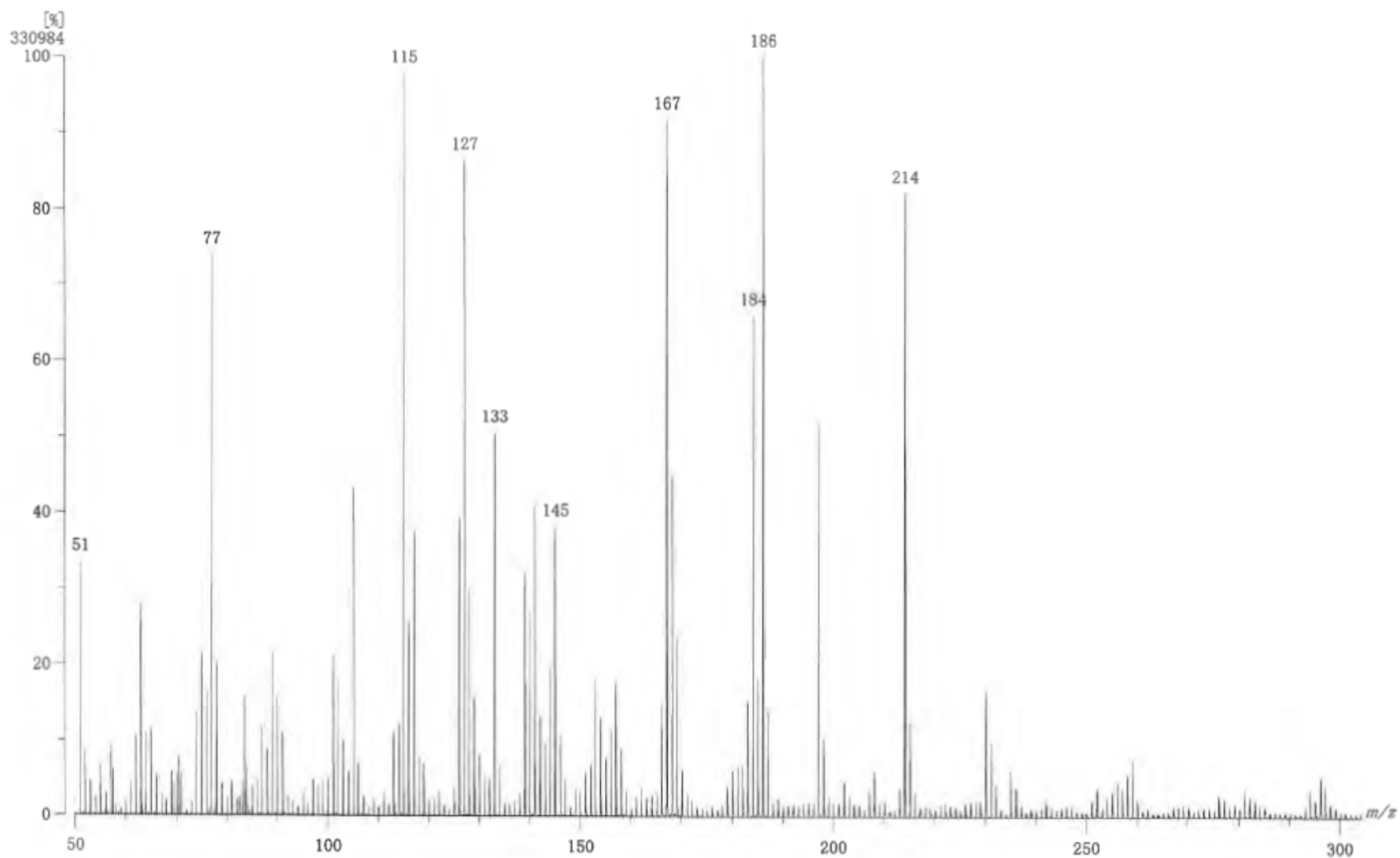
```
[ Theoretical Ion Distribution ]
Molecular Formula : C12 H10 N2 O2
                        (m/z   214.0742, MW   214.2236, U.S.  9.0)
Base Peak :   214.0742, Averaged MW :   214.2227(a),   214.2235(w)

    m/z       INT.
 214.0742 100.0000*****************************************************************
 215.0773  14.1577********
 216.0797   1.3276*
 217.0822   0.0938
 218.0847   0.0051
 219.0872   0.0002
```

4-(3,5-dimethoxyphenyl)-2-methyl-3-nitropyridine (**169**).
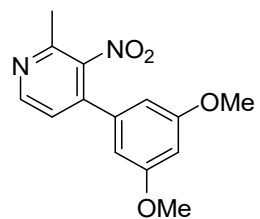
500 CDCl3
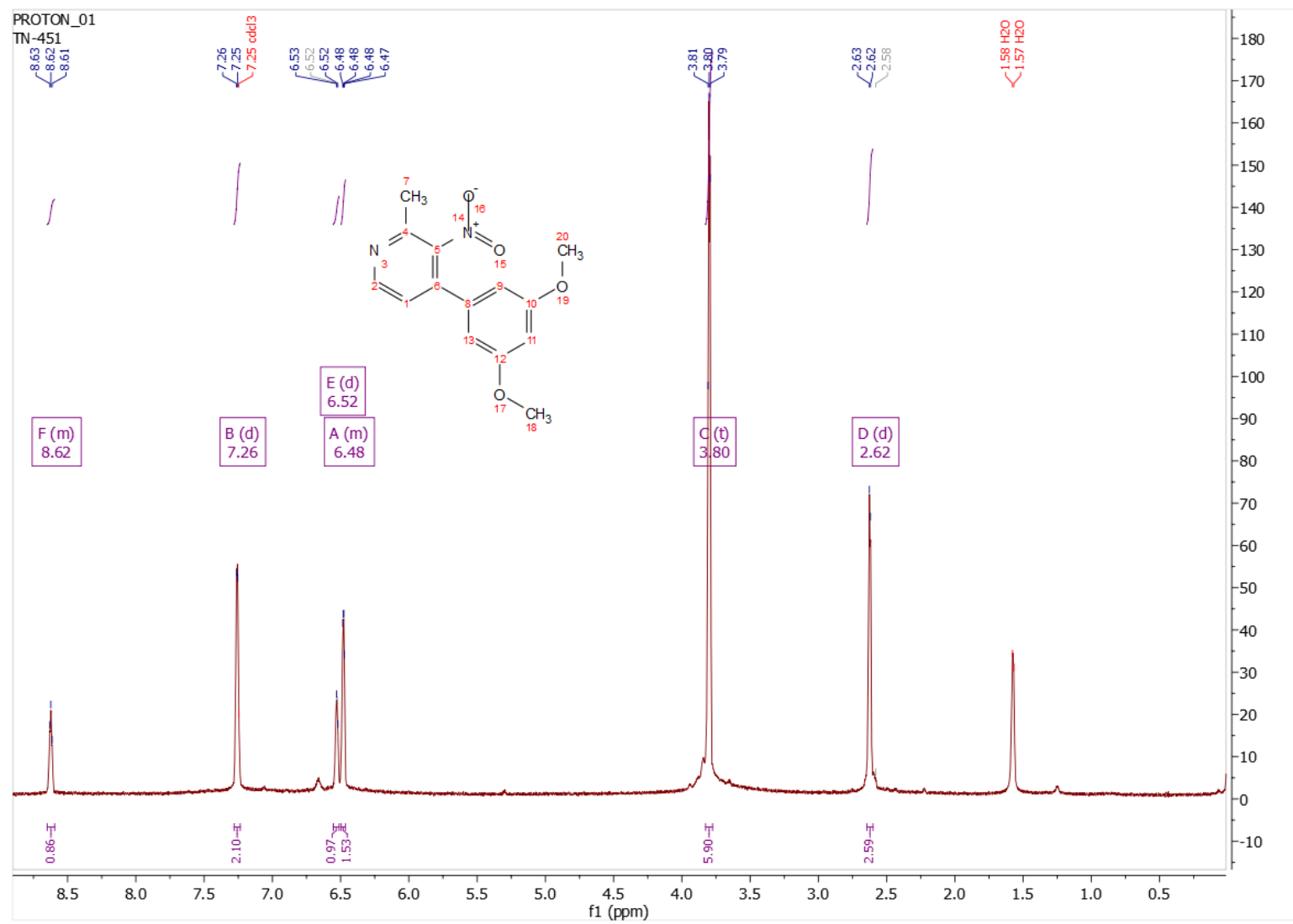
126 CDCl3
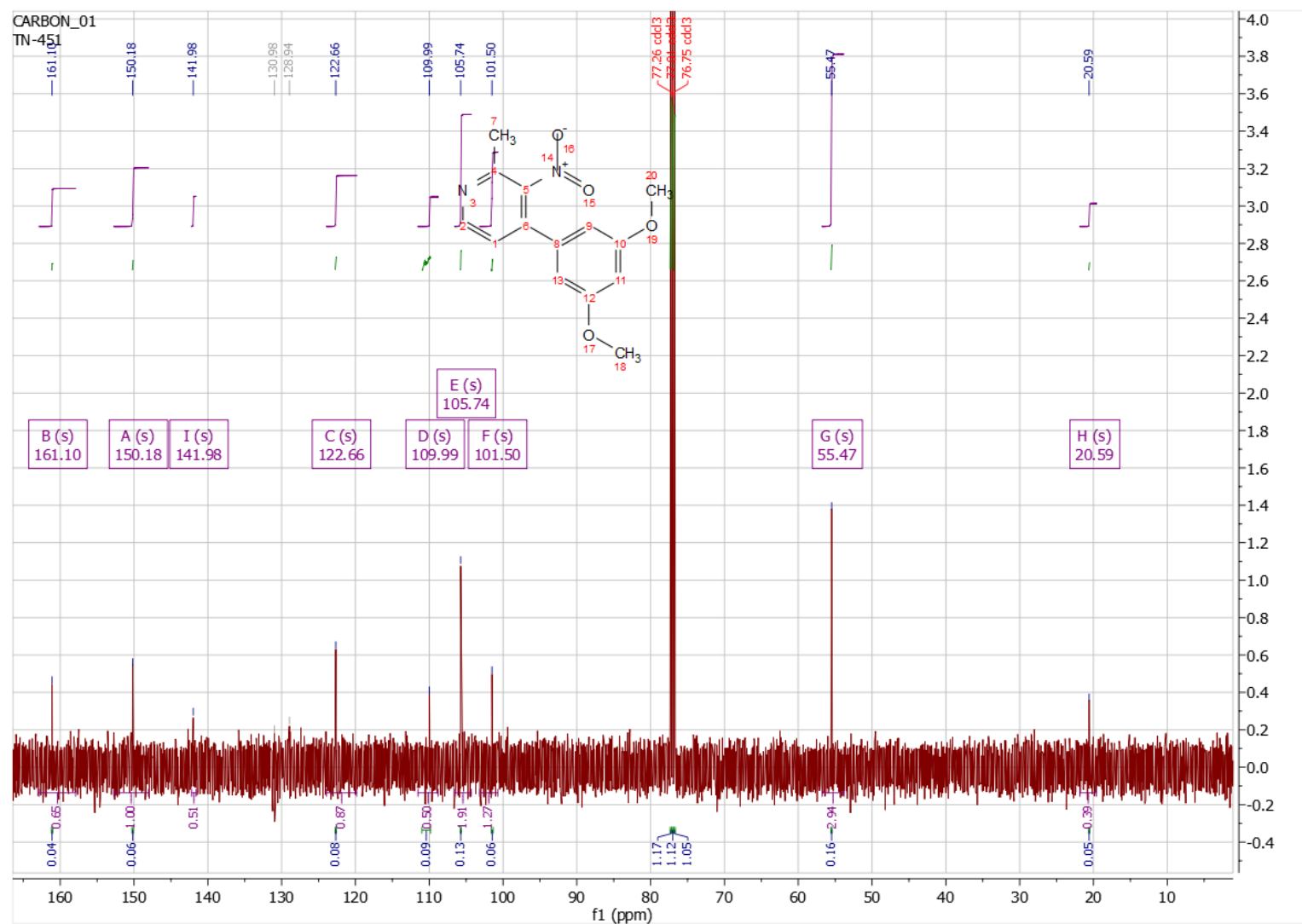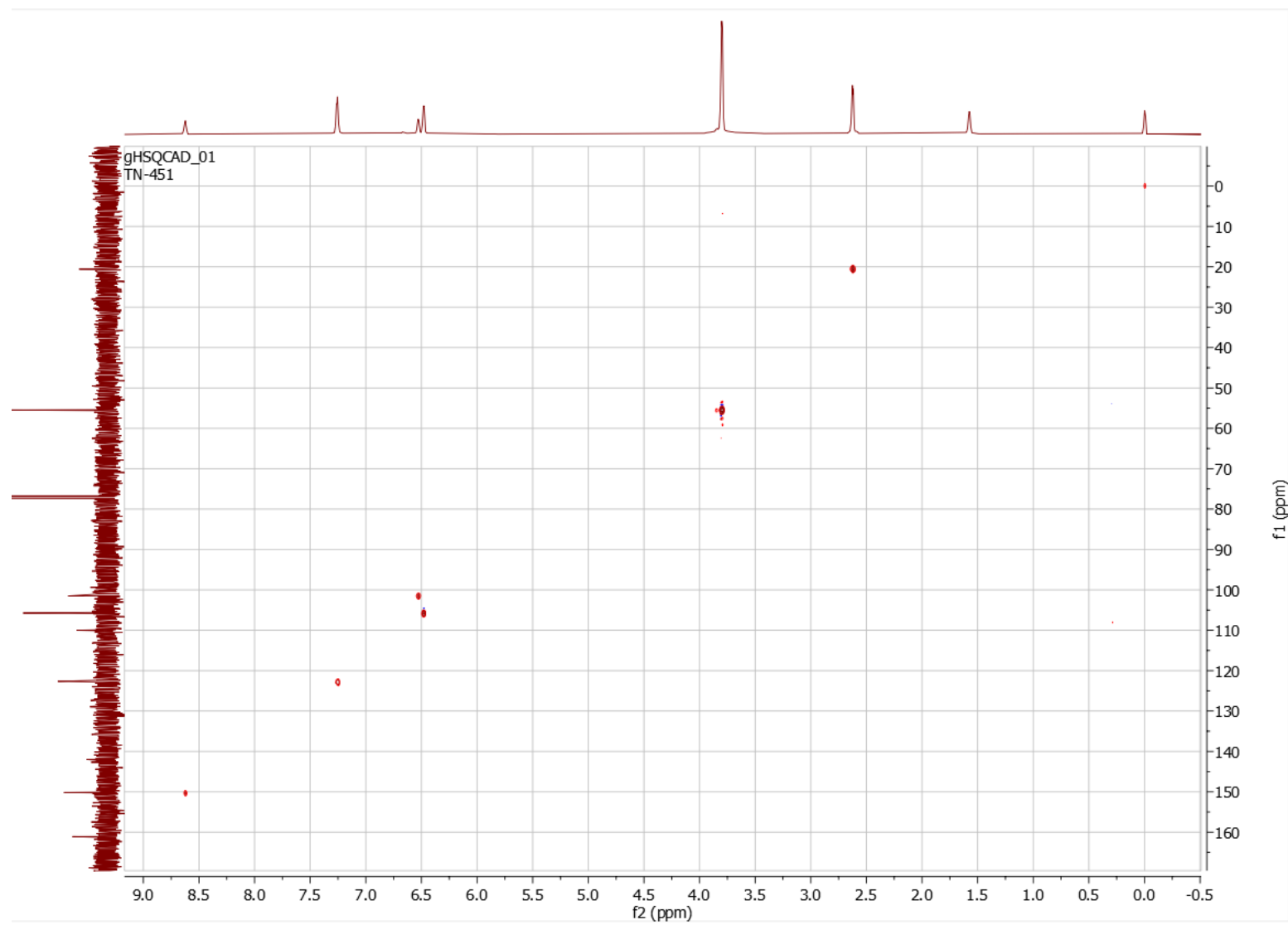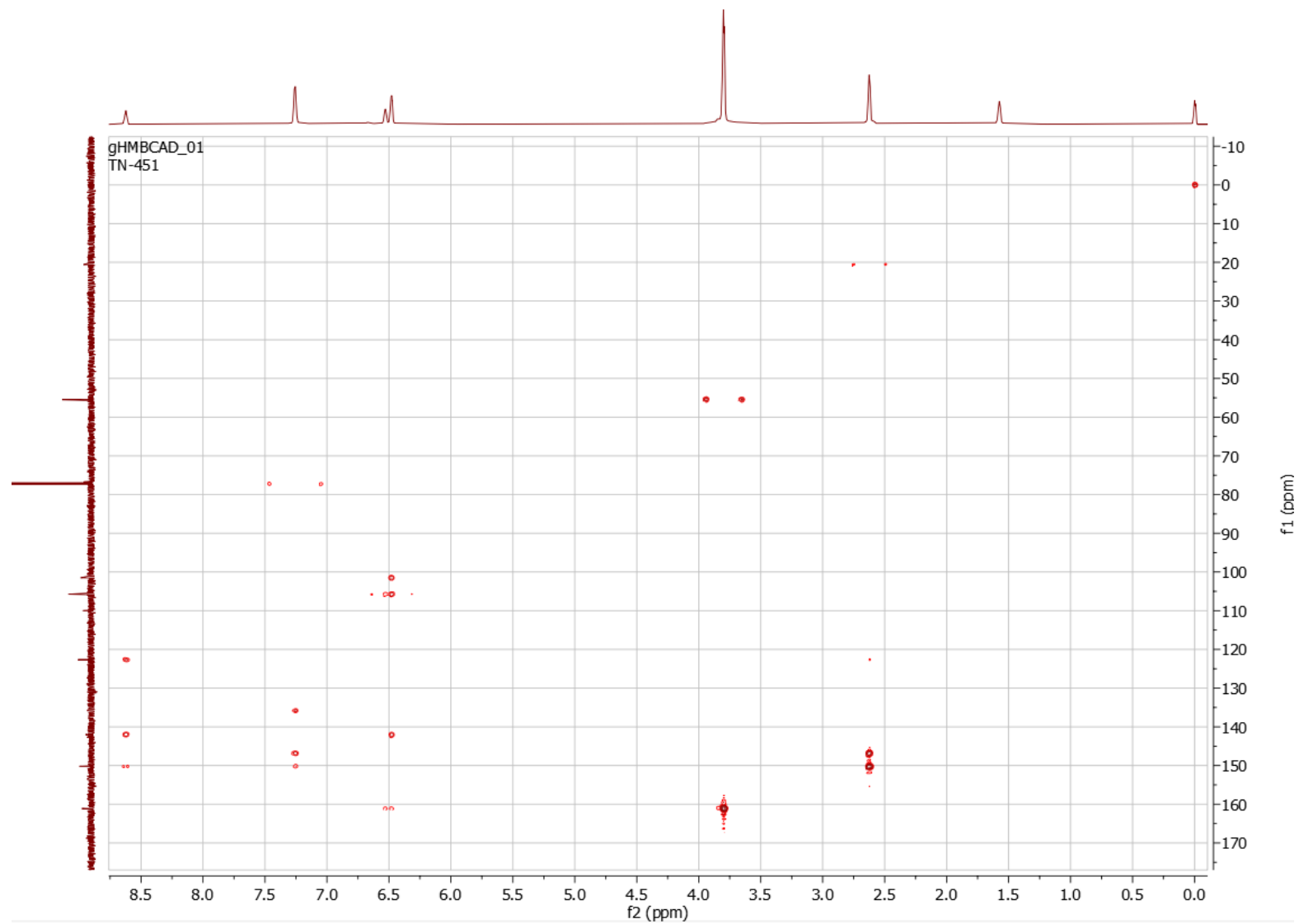
HSQC

gHSQCAD_01
TN-451

HMBC

gHMBCAD_01
TN-451
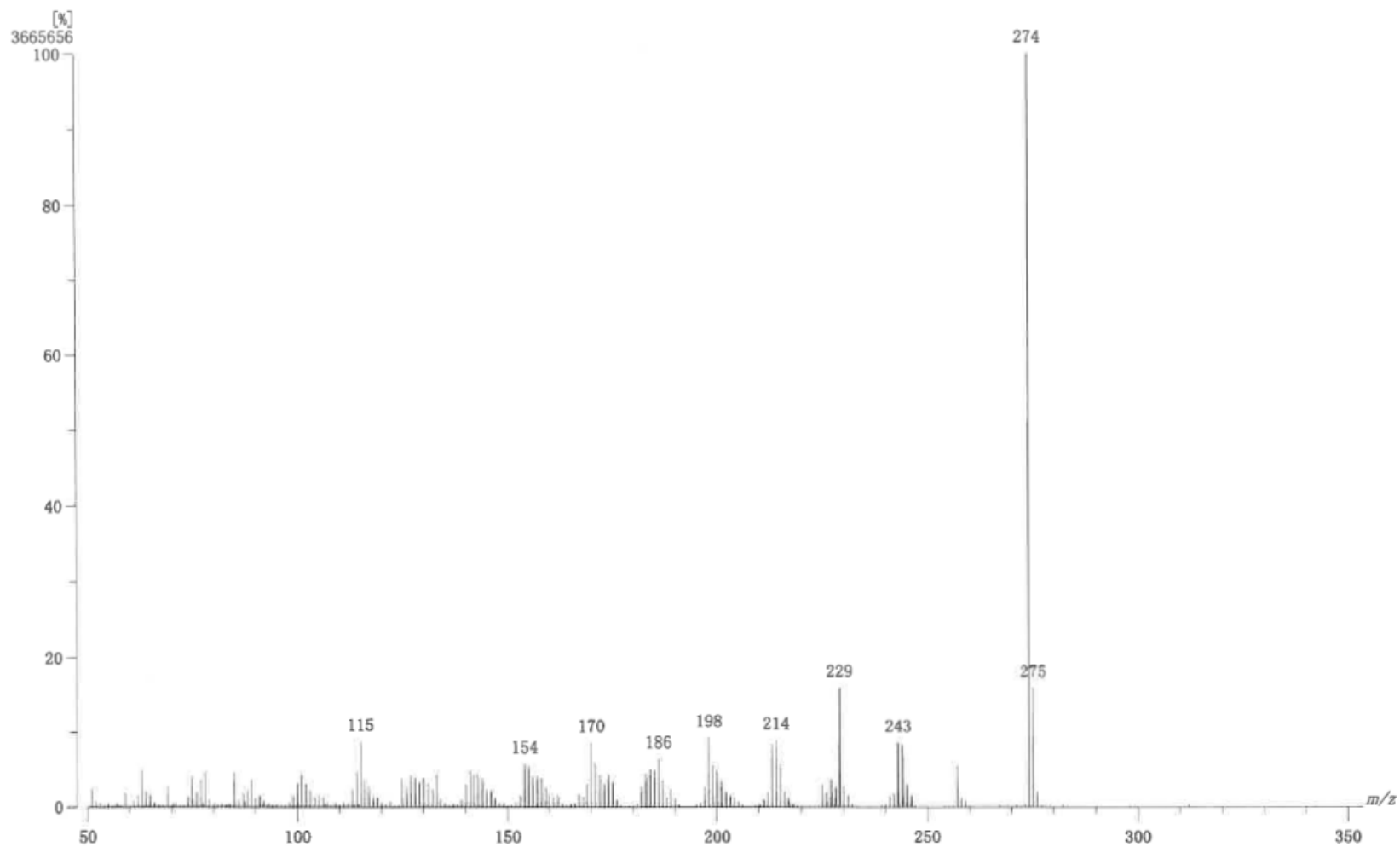
```
[ Theoretical Ion Distribution ]
Molecular Formula : C14 H14 N2 O4
                        (m/z   274.0954, MW   274.2762, U.S.  9.0)
Base Peak :   274.0954, Averaged MW :   274.2747(a),   274.2754(w)


   m/z       INT.
 274.0954 100.0000*********************************************************************
 275.0984  16.4583**********
 276.1008   2.0683*
 277.1033   0.1921
 278.1057   0.0145
 279.1081   0.0009
```

Analyst   PEService
Date   20 March 2019 16:43

1038.83cm-1 763.43cm-1
864.48cm-1
943.55cm-1

3054.4

1317.5

1709.57cm-1

1257.9

1143.06cm-1

1542.1

1113.08cm-1

1206.11cm-1

1436.8

1479

A

cm-1

4000   3500   3000   2500   2000   1500   1000   600

MeO

OMe

NO$_2$

N
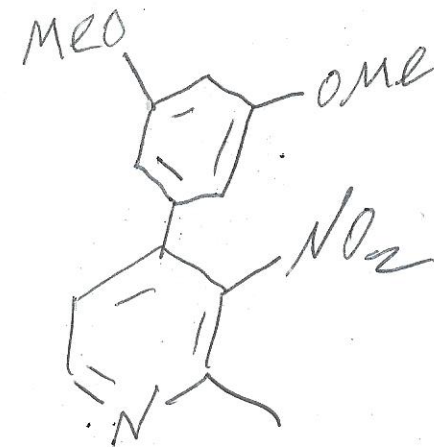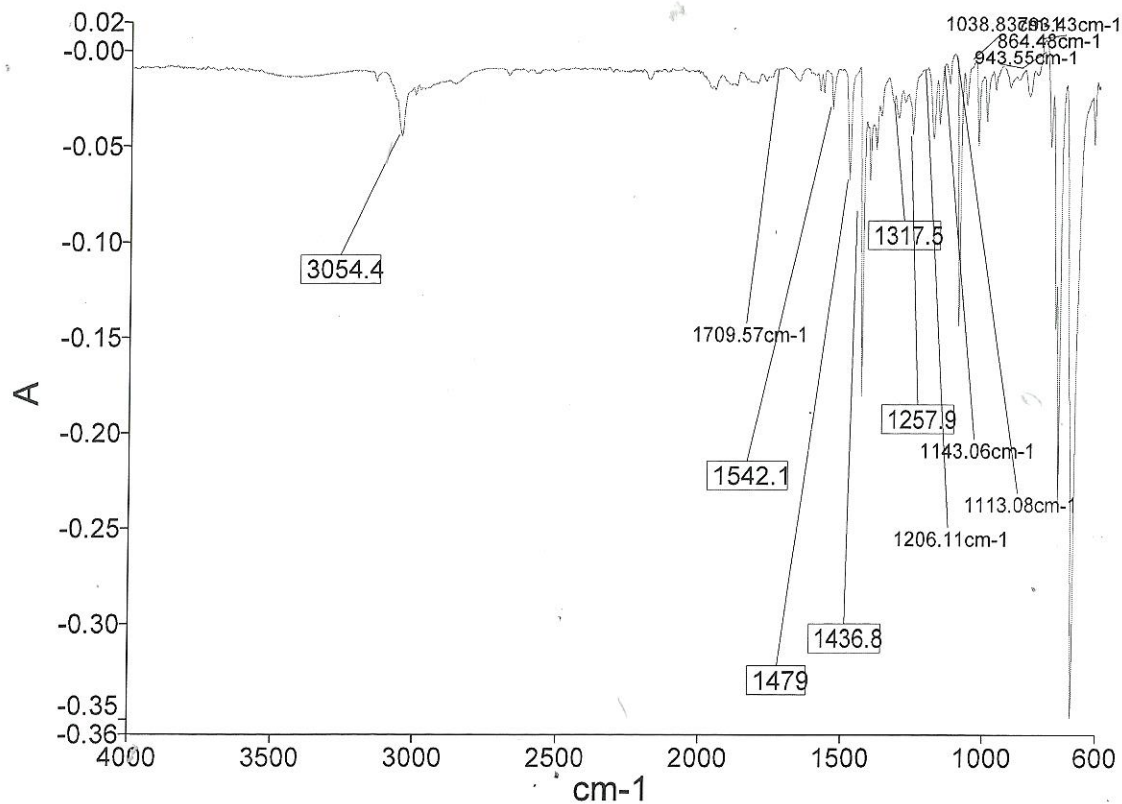
PEService 95   Sample 095 By
                 PEService Date
                 Wednesday, March
                 20 2019

TN-451

Page 1

4-(4-tert-butylphenyl)-2-methyl-3-nitropyridine (**170**).
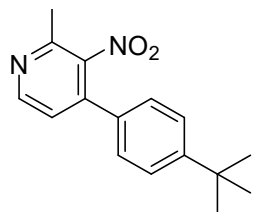
600 CDCl3
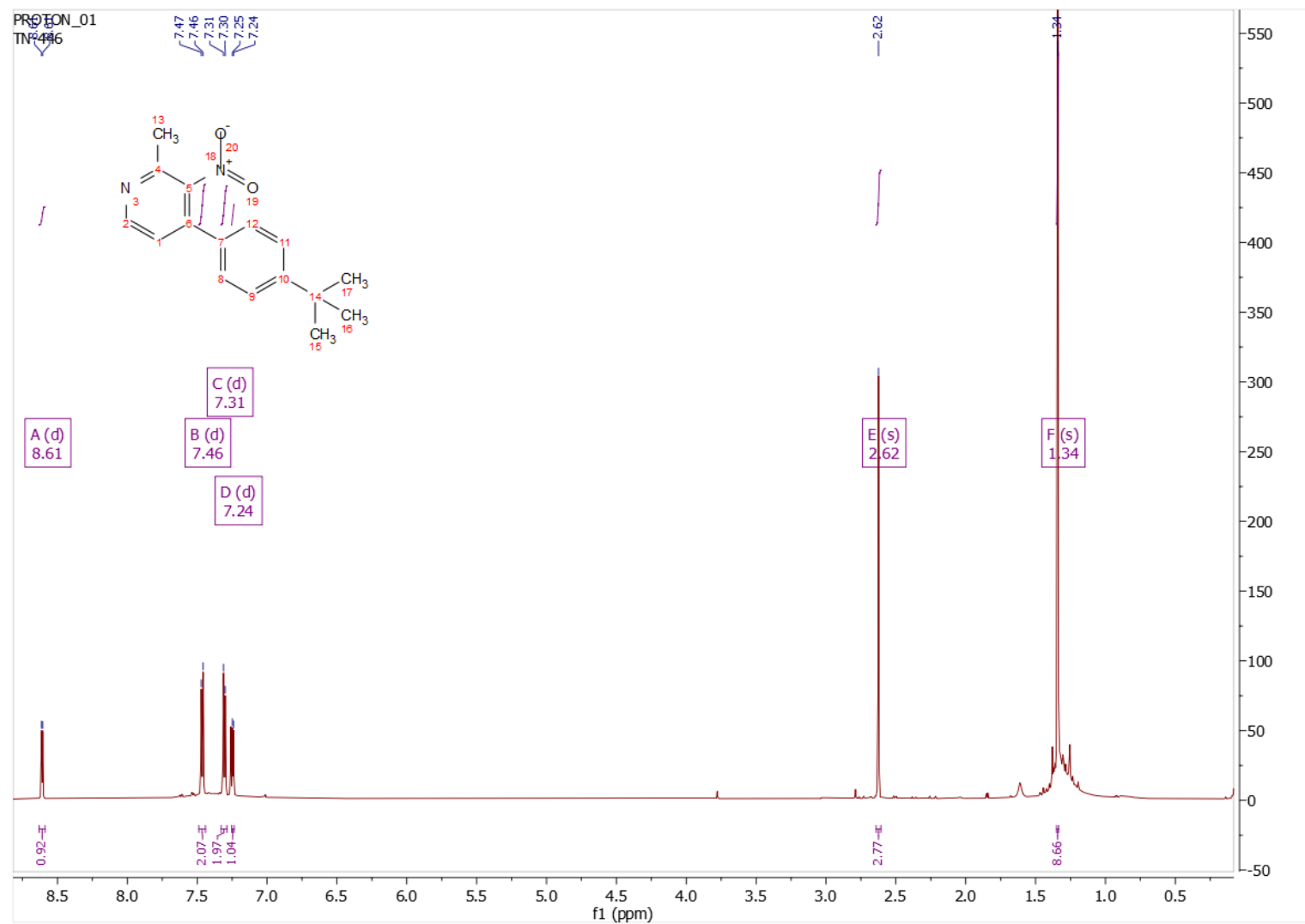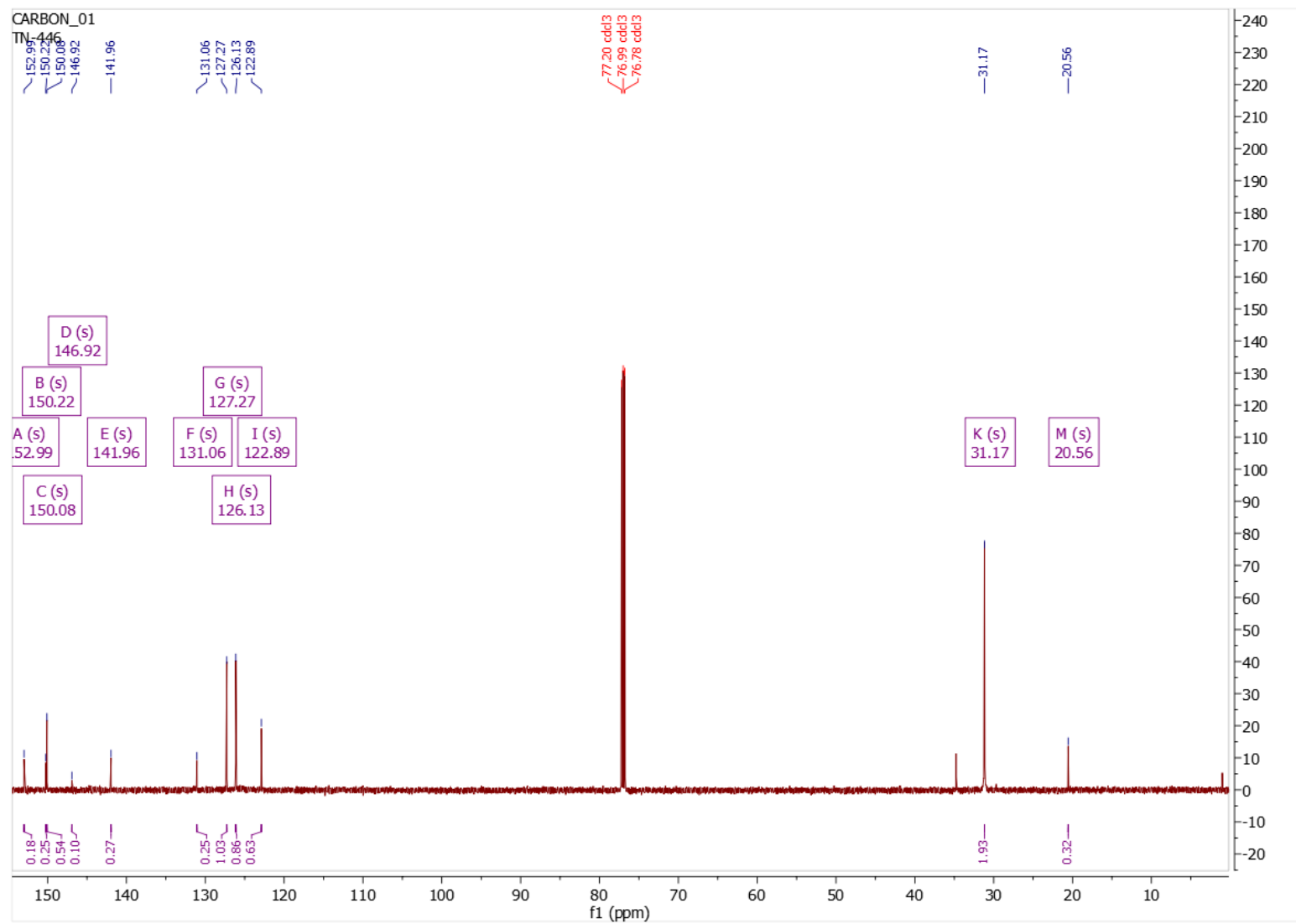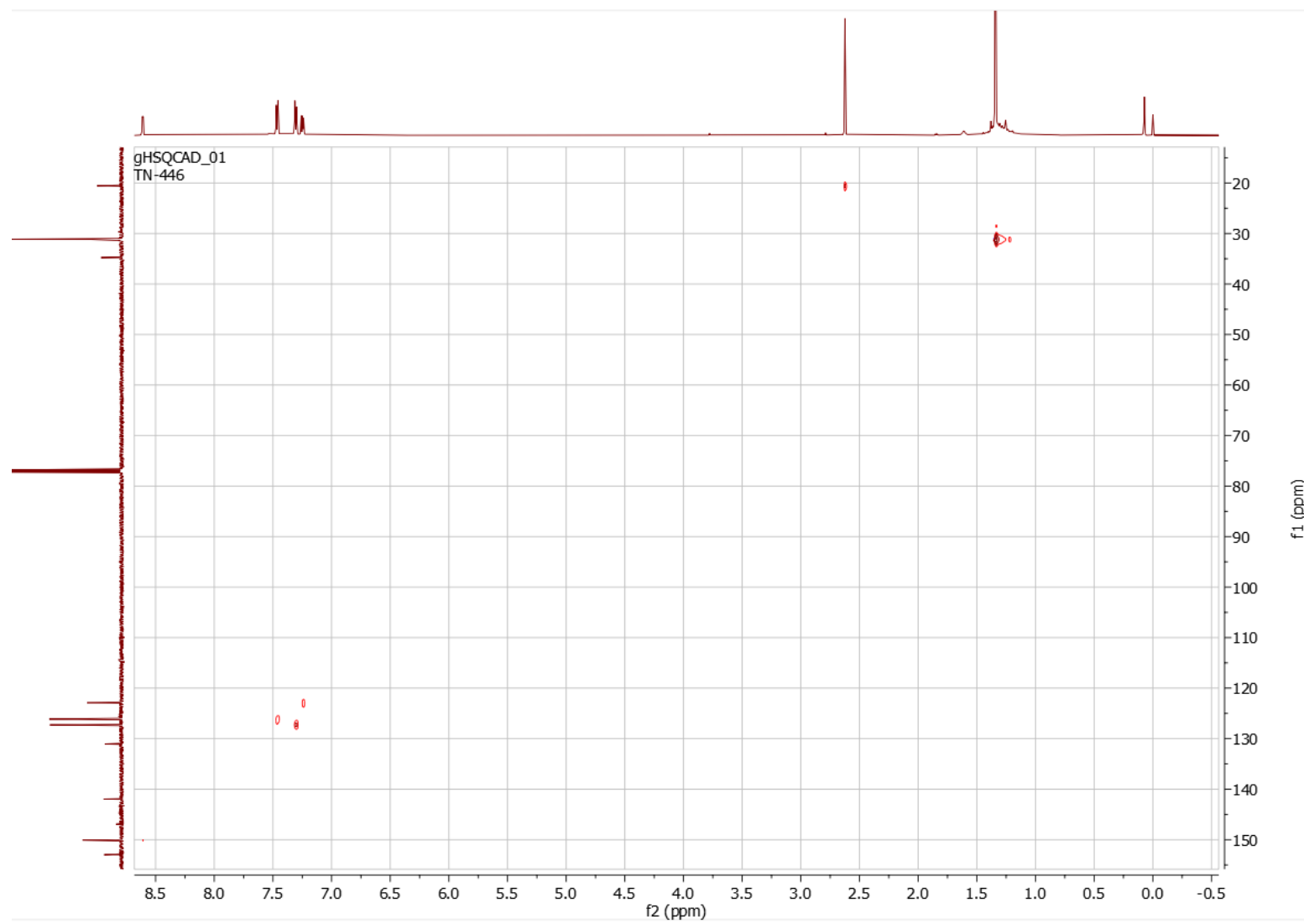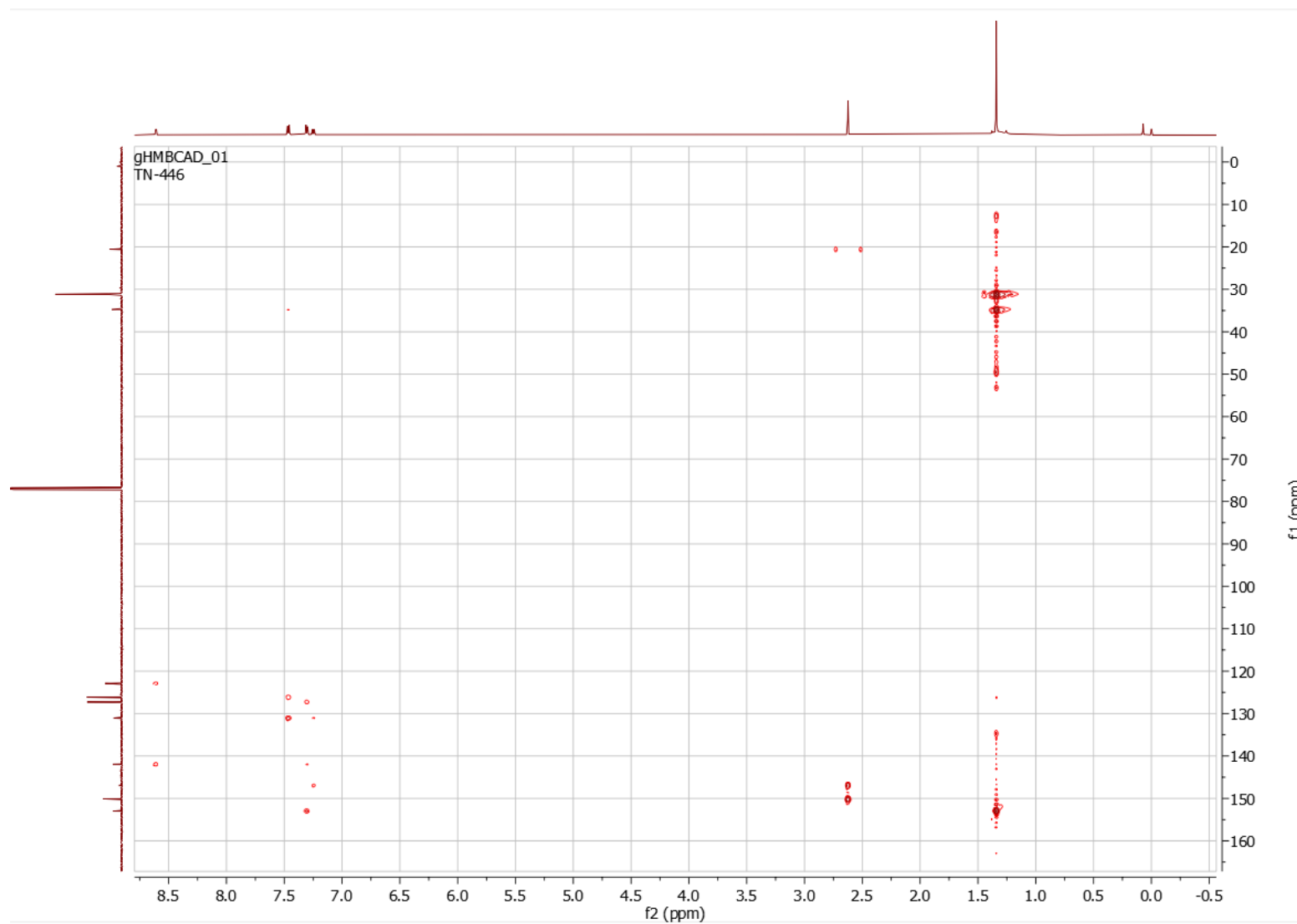
A (d)
8.61

B (d)
7.46

C (d)
7.31

D (d)
7.24

E (s)
2.62

F (s)
1.34

151 CDCl3

HSQC

gHSQCAD_01
TN-446

HMBC

gHMBCAD_01
TN-446
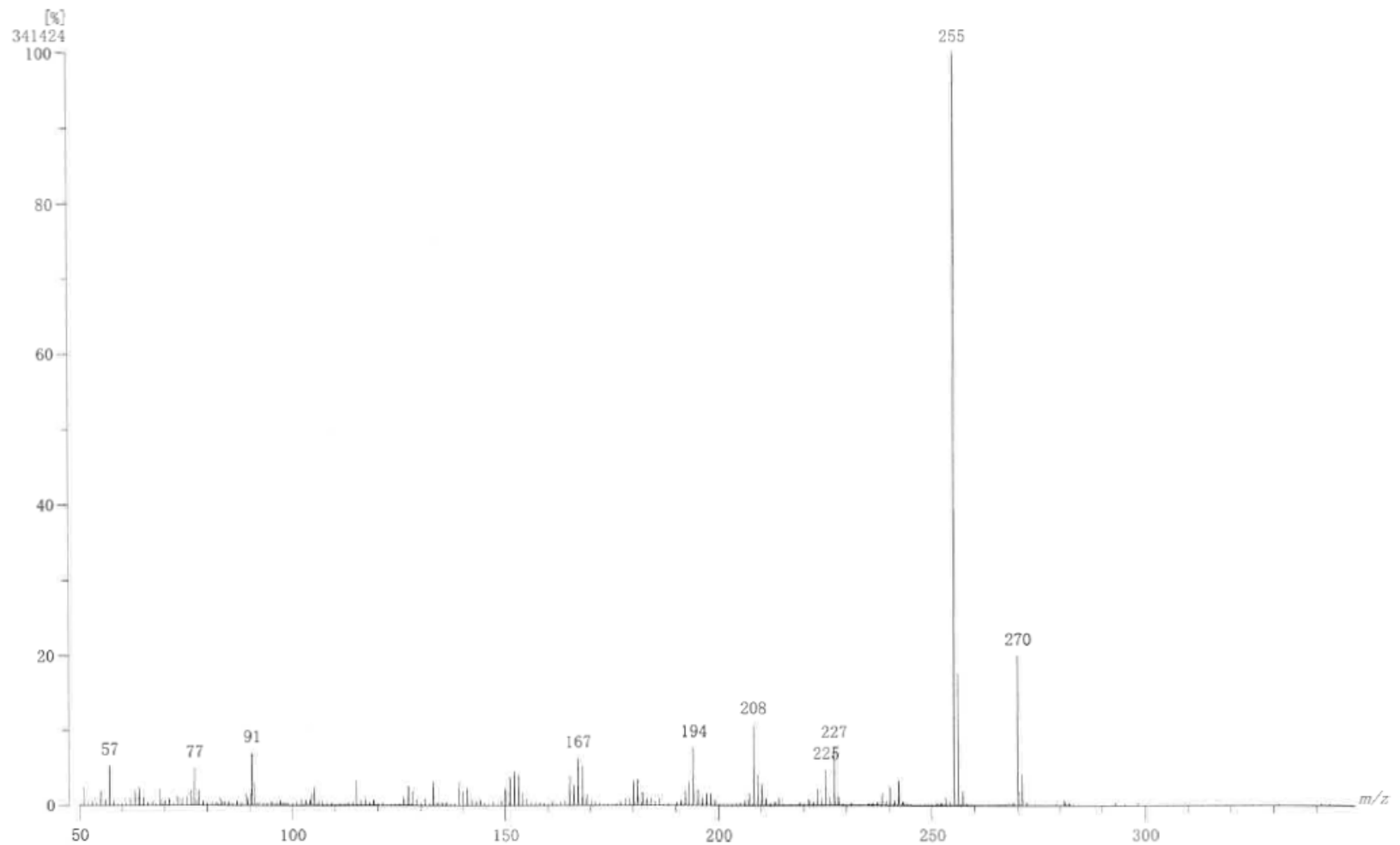
[Theoretical Ion Distribution]
Molecular Formula : C16 H18 N2 O2
                        (m/z   270.1368, MW   270.3311, U.S.   9.0)
Base Peak :   270.1368, Averaged MW :   270.3295(a),   270.3302(w)

    m/z   INT.
  270.1368 100.0000**
  271.1399 18.6066**********
  272.1426   2.0317*
  273.1452   0.1639
  274.1478   0.0104
  275.1504   0.0005

Analyst

Date

PEService

29 March 2019 15:02

2963.17cm-1

1462.90cm-1

1018.54cm-1 769.38cm-1

1095.43cm-1   580.27cm-1

1595.23cm-1 1266.56cm-1   693.98cm-1

559.31cm-1

852.89cm-1

736.86cm-1

1362.25cm-1

828.03cm-1

1531.66cm-1

%T

4000   3500   3000   2500   2000   1500   1000   550

cm-1
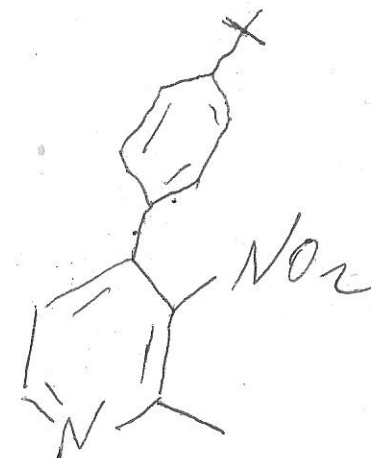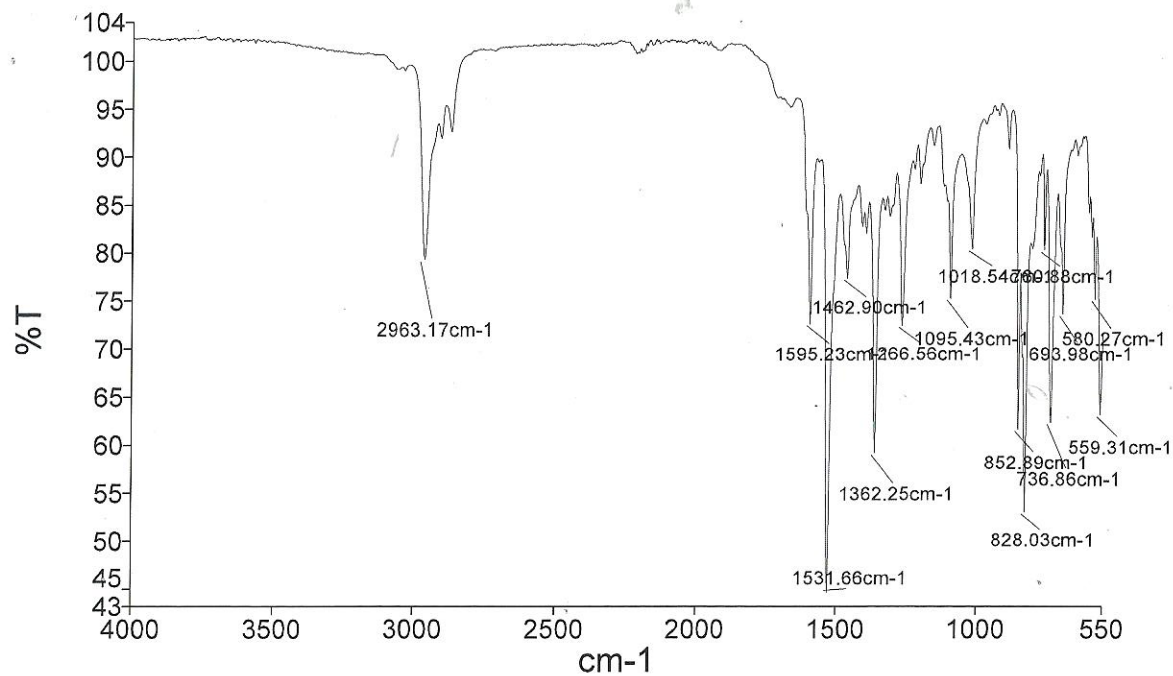
Sample Name	Description	Quality Checks
446	Sample 143 By PEService Date Friday, March 29 2019	The Quality Checks do not report any warnings for the sample.

NO₂

4-(4-bromophenyl)-2-methyl-3-nitropyridine (**171**).

600 CDCl3
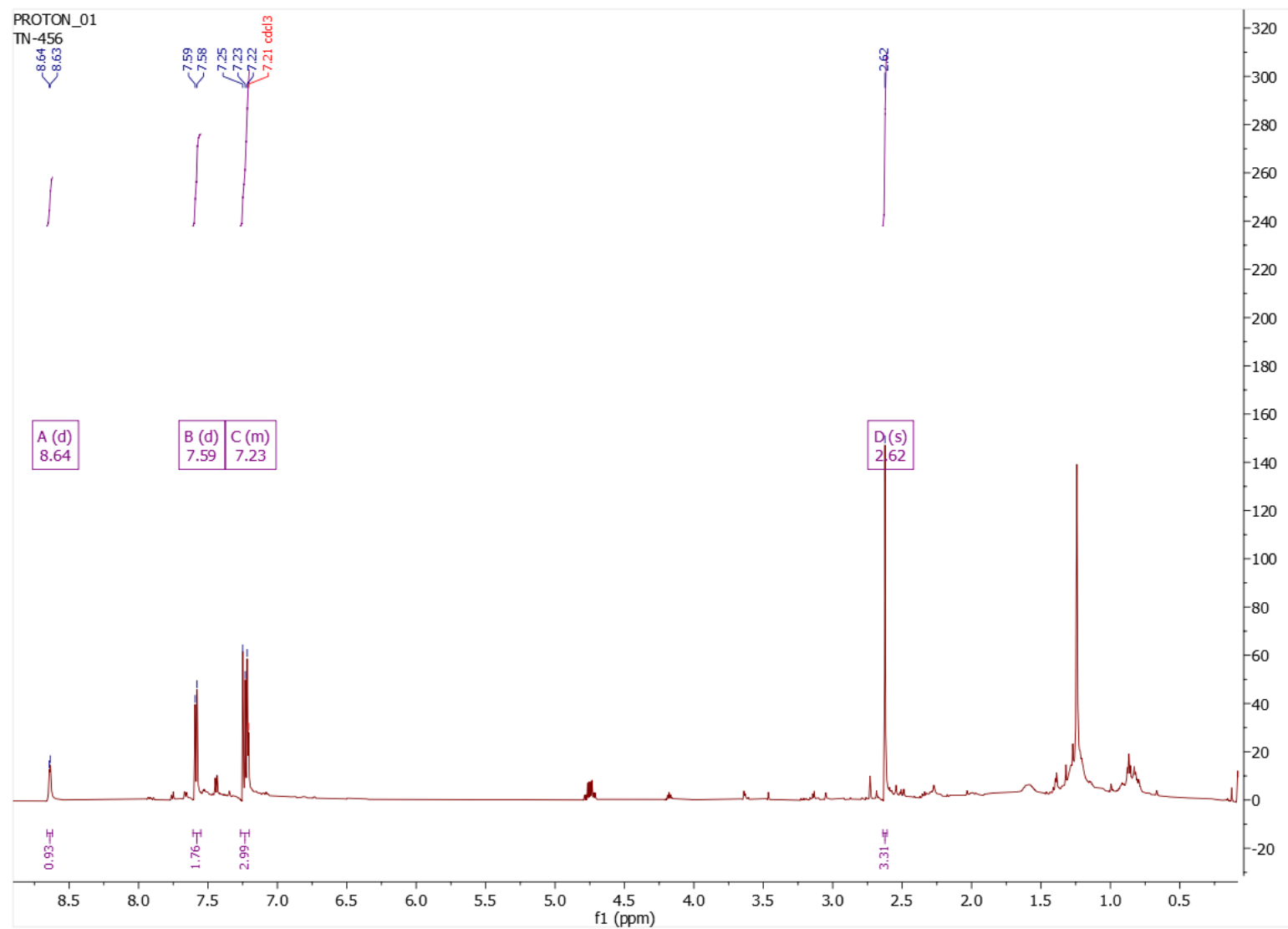
PROTON_01
TN-456

8.64
8.63
7.59
7.58
7.25
7.23
7.22
7.21 cdcl3
2.62

A (d)
8.64

B (d)
7.59

C (m)
7.23

D (s)
2.62

0.93
1.76
2.99
3.31

f1 (ppm)
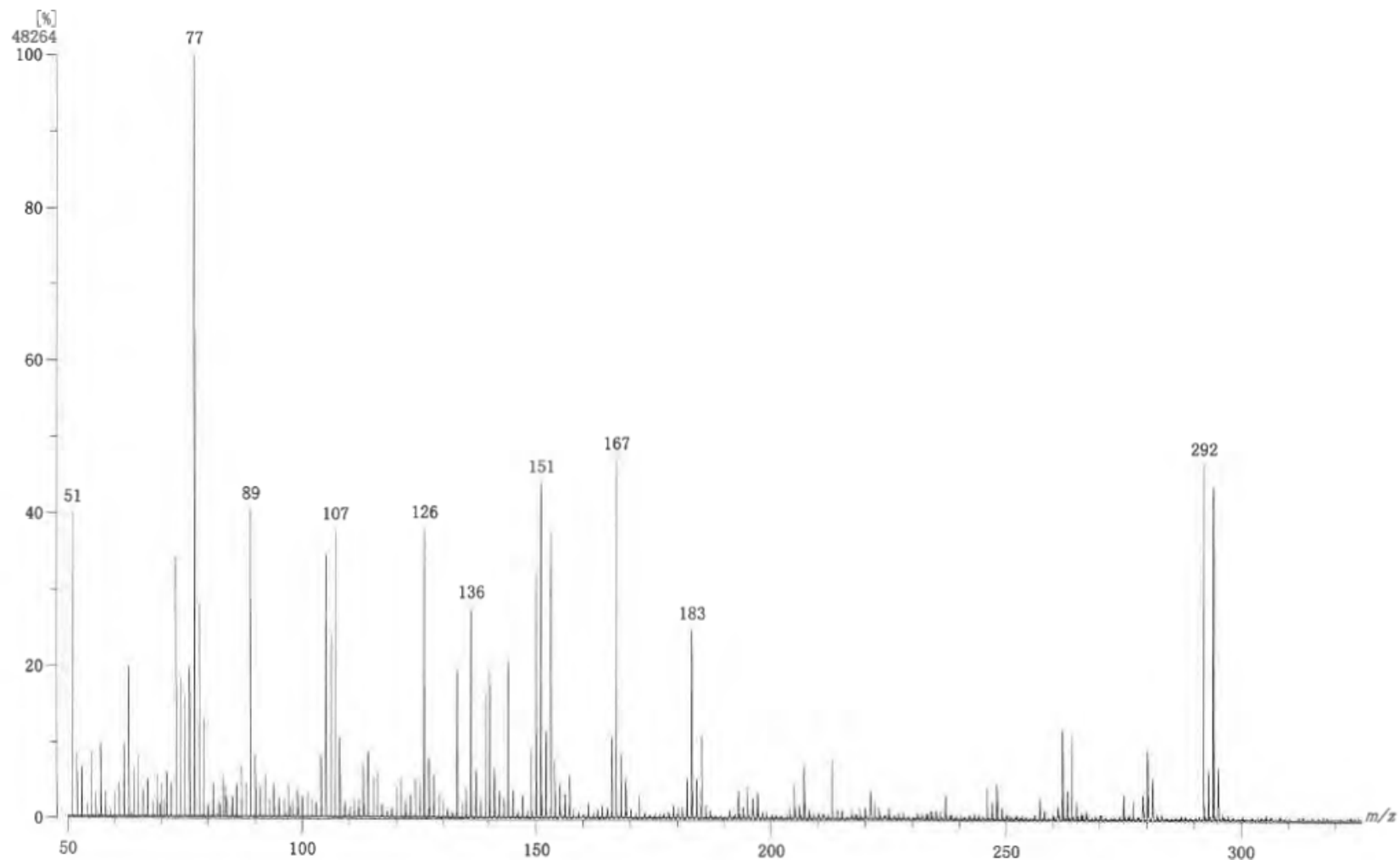
```
[ Theoretical Ion Distribution ]
Molecular Formula : C12 H9 Br N2 O2
                         (m/z    291.9847, MW   293.1197, U.S.   9.0)
Base Peak :    291.9847, Averaged MW :    293.1185(a),    293.1224(w)

    m/z        INT.
  291.9847 100.0000*************************************************************
  292.9878  14.1577********
  293.9828  98.6051************************************************************
  294.9858  13.8660********
  295.9882   1.2965*
  296.9907   0.0914
  297.9932   0.0050
  298.9956   0.0002
```

Analyst   Administrator
Date   29 March 2019 15:58

1699.26cm-1, 86.74%T
1463.48cm-1, 77.26%T
603.61cm-1, 86.30%T
2221.07cm-1, 96.92%T
2148.08cm-1, 97.27%T
1973.99cm-1, 97.36%T
2018.47cm-1, 97.45%T
1986.40cm-1, 97.49%T
1323.48cm-1, 79.77%T
2852.71cm-1, 87.52%T
1034.98cm-1, 75.31%T
674.48cm-1, 85.28%T
567.51cm-1, 85.39%T
728.94cm-1, 82.50%T
2923.77cm-1, 81.68%T
1175.14cm-1, 80.23cm-1, 86.54%T
888.21cm-1, 82.98%T
1557.84cm-1, 76.13%T
756.82cm-1, 74.42%T
1487.54cm-1, 75.33%T
1259.46cm-1, 73.25%T
802.50cm-1, 71.13%T
1360.77cm-1, 69.00%T
850.95cm-1, 67.89%T
1070.34cm-1, 66.46%T
1599.15cm-1, 76.16%T
1010.59cm-1, 58.60%T
821.13cm-1, 58.09%T
1530.81cm-1, 59.83%T

%T vs cm-1

Sample Name	Description	Quality Checks	Pathlength (mm)
456	Sample 091 By Administrator Date Friday, March 29 2019	The Quality Checks do not report any warnings for the sample.	54

4-cyclopropyl-2-methyl-3-nitropyridine (**172**).
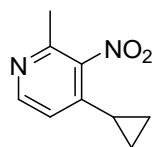
CDCl3 600

PROTON_01
TN-466

8.41
8.40

7.25 cdcl3
7.25

6.71
6.70

2.52
1.86
1.85
1.84
1.84
1.83
1.83
1.82
1.81
1.13
1.13
1.13
1.12
1.12
1.12
1.11
1.11
1.11
1.11
1.10
1.10
0.82
0.81
0.81
0.81
0.80
0.80
0.79

A (d)
8.40

B (d)
6.71

C (s)
2.52

D (tt)
1.84

E (m)
1.12

F (m)
0.81

0.91

0.95

2.91

0.93

2.19

2.10

f1 (ppm)

151 CDCl3

Analyst   PEService

Date   20 March 2019 16:59

Peaks labeled on spectrum: 3053.9, 1525.57cm-1, 1444.04cm-1, 1433.5, 1349.94cm-1, 1090.6, 1171.67cm-1, 739.6, 1220.12cm-1, 1120.55cm-1, 762.42cm-1, 787.13cm-1

X-axis: cm-1 (4138 4000, 3500, 3000, 2500, 2000, 1500, 1000, 738)

Y-axis: %T (163, 160, 155, 150, 145, 140, 135, 130, 125, 120, 115, 110, 105, 100)

Sample Name	Description	Quality Checks
PEService 94 TN-466	Sample 094 By PEService Date Wednesday, March 20 2019	The Quality Checks give rise to multiple warnings for the sample.

2,6-dimethyl-3-nitro-4-(phenylethynyl)pyridine (**167 side product**).

600 CDCl3

PROTON_01
TN-478 MAJOR IMPURITY

E (m)
7.41

A (m)   D (s)
7.53   7.23

F (m)
7.37

C (s)
2.58

B (s)
2.60

f1 (ppm)
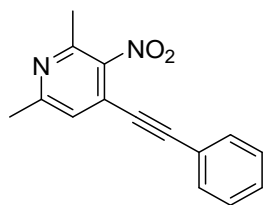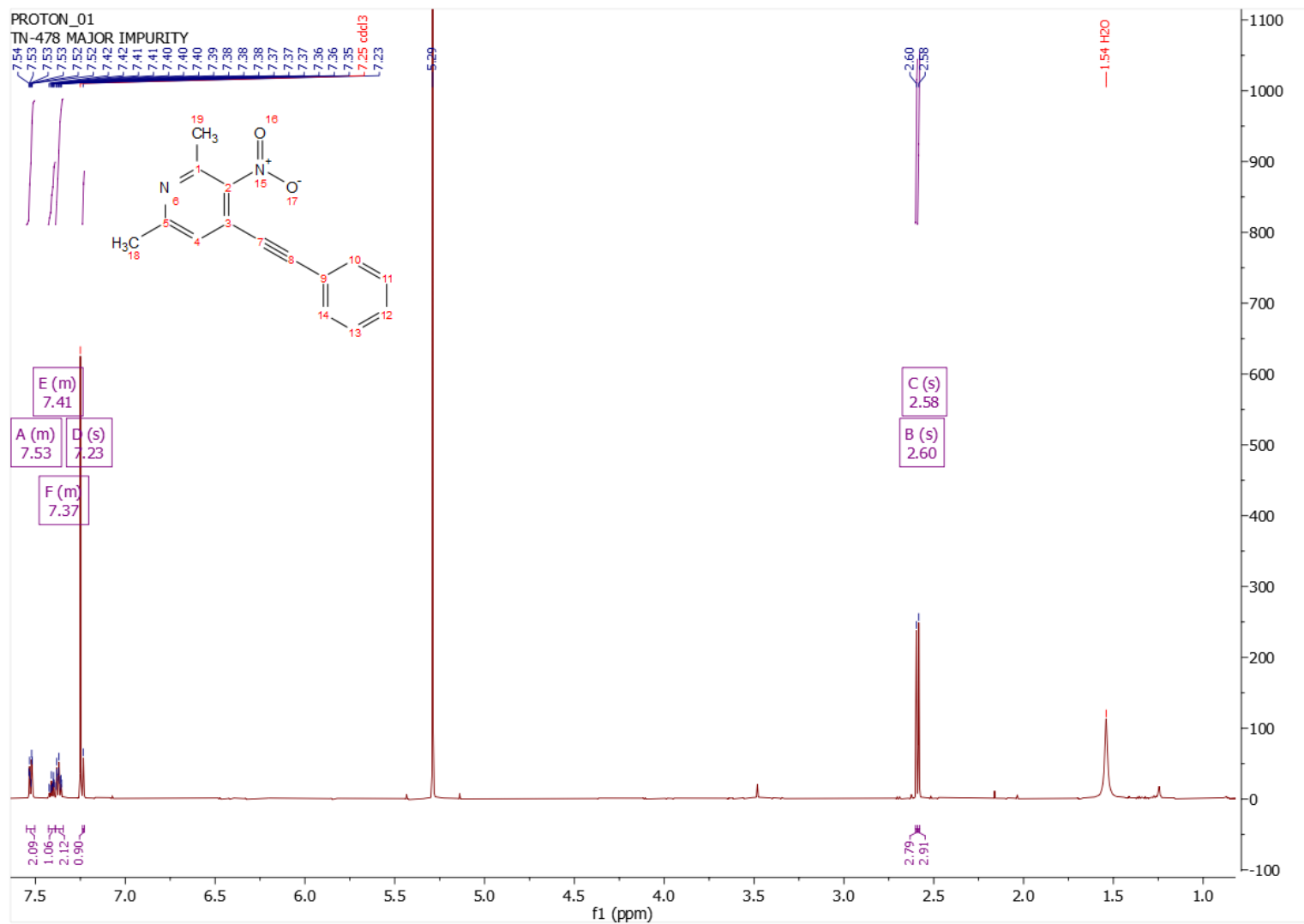
CHAPTER THREE

Synthesis of 2-methyl-5*H*-pyrido[3,2-*b*]indole (**173**).

500 DMSO
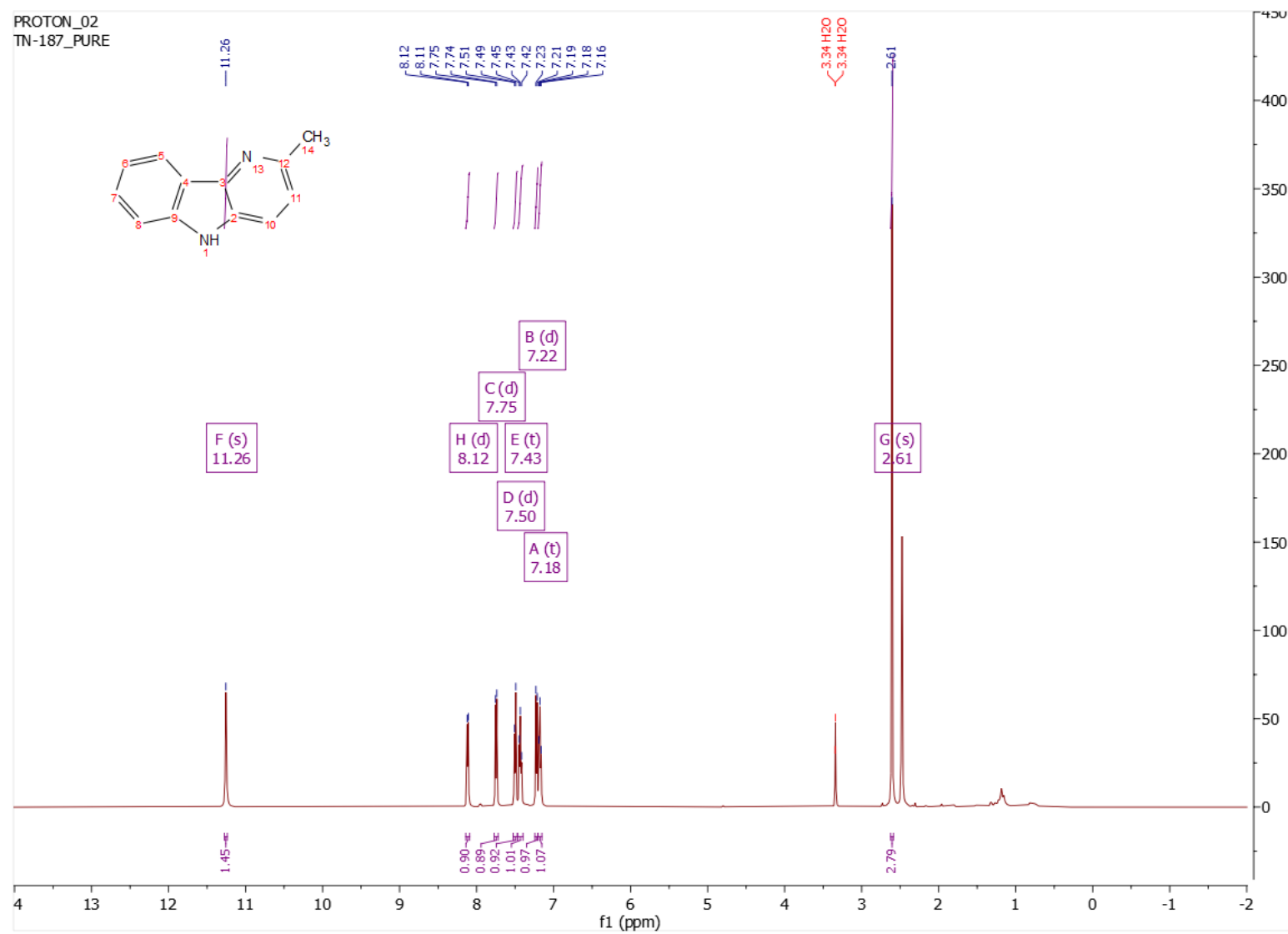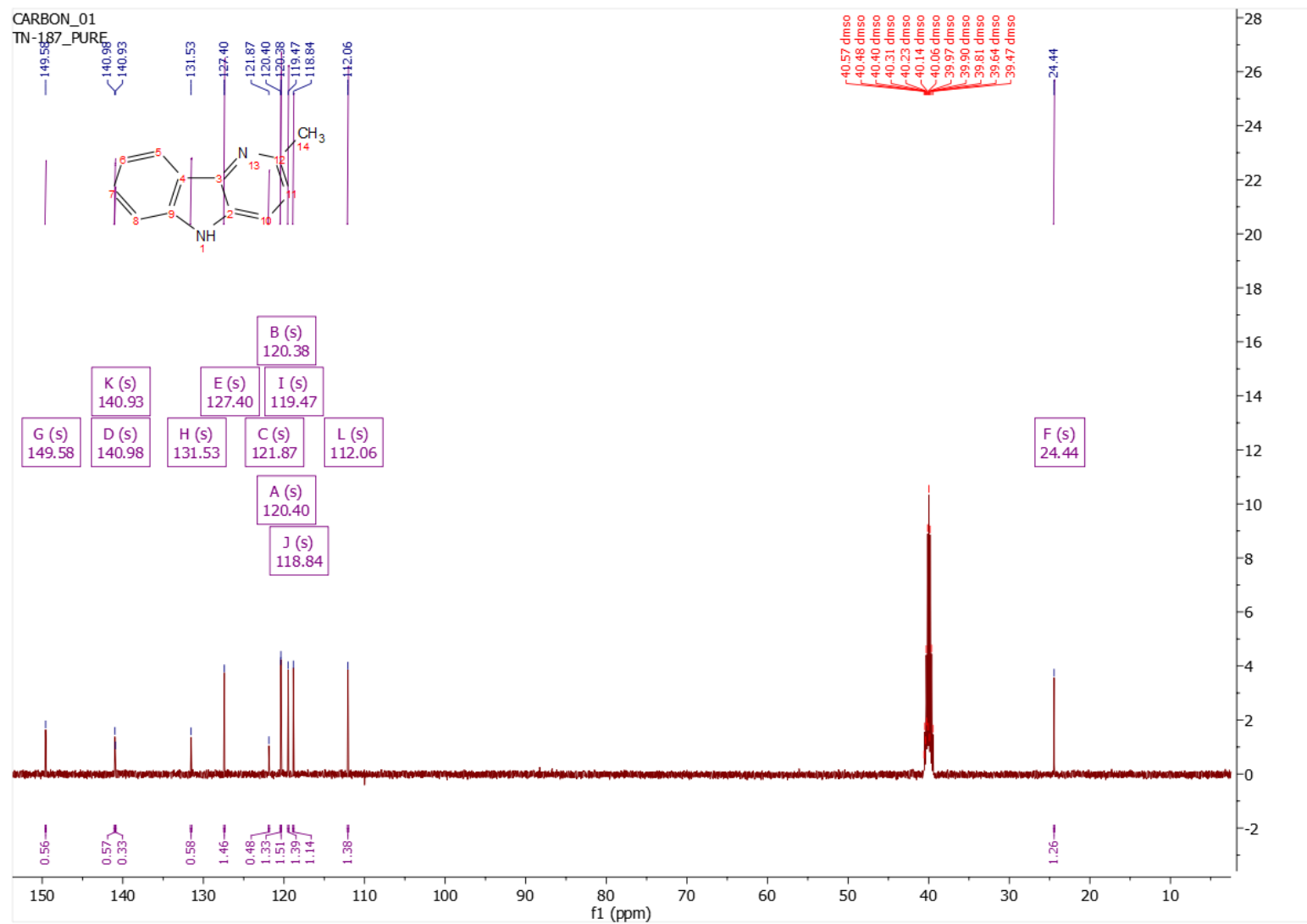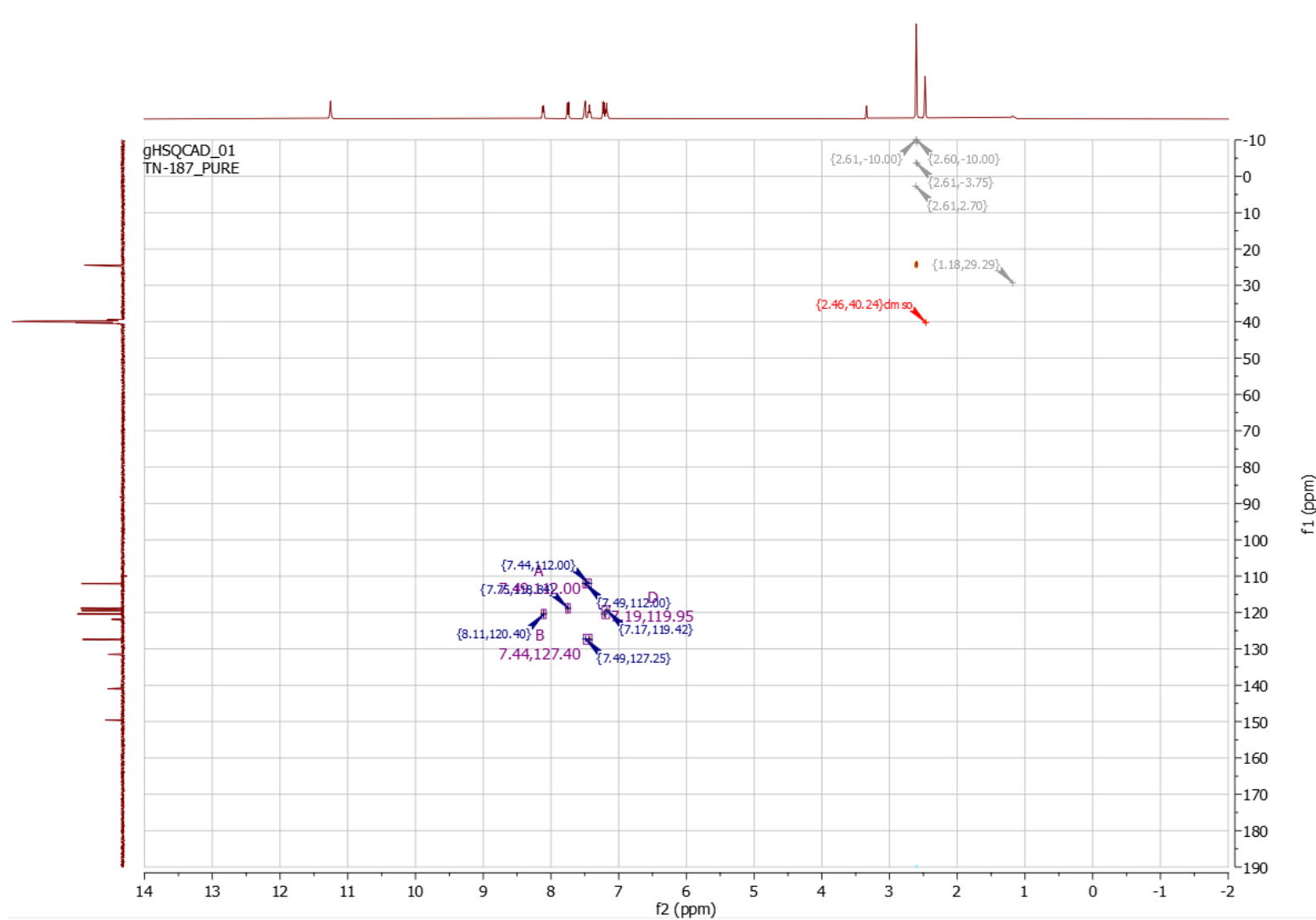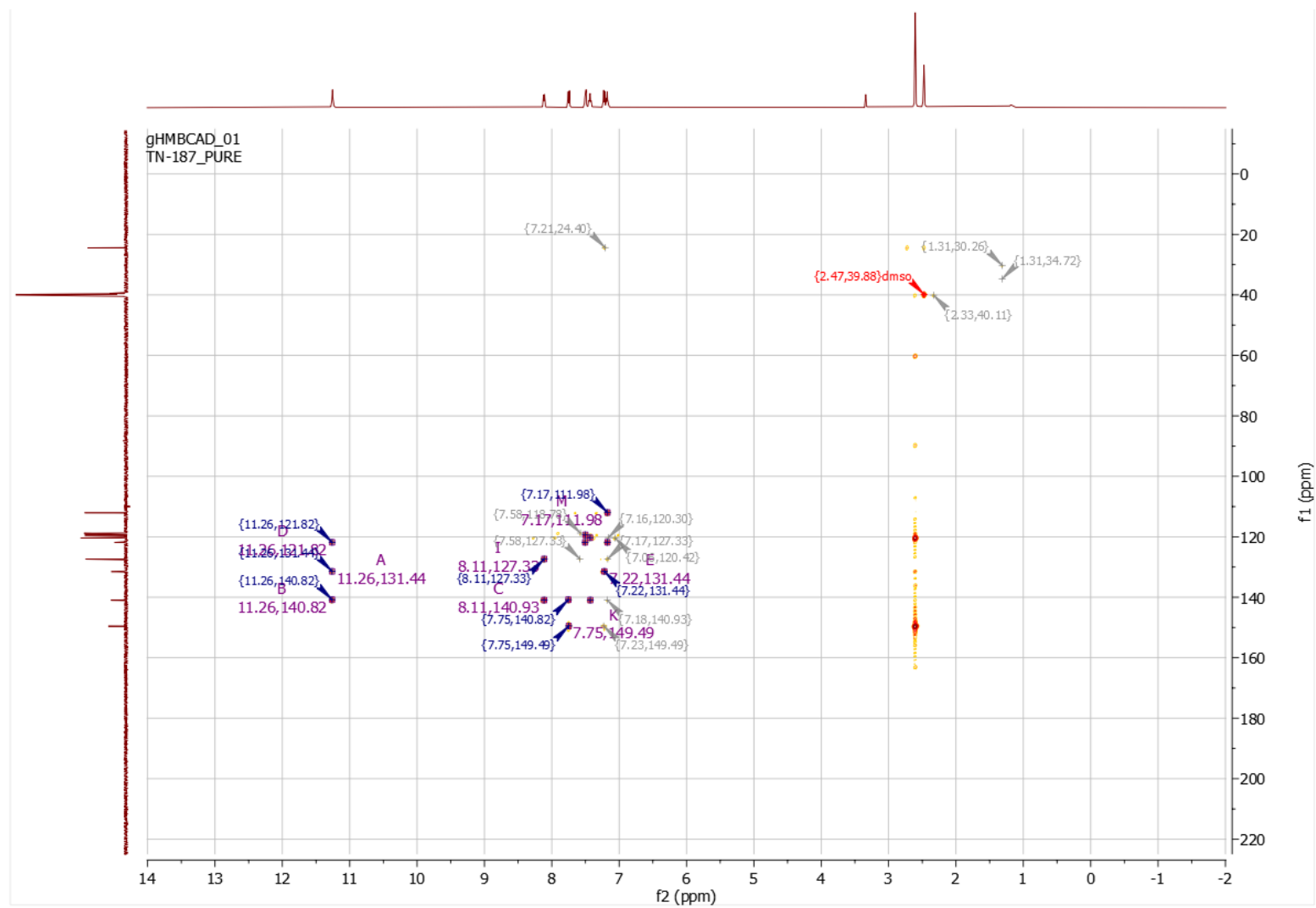
PROTON_02
TN-187_PURE

F (s)
11.26

C (d)
7.75

B (d)
7.22

H (d)
8.12

E (t)
7.43

D (d)
7.50

A (t)
7.18

G (s)
2.61

126 DMSO

CARBON_01
TN-187_PURE

G (s) 149.58
K (s) 140.93
D (s) 140.98
H (s) 131.53
E (s) 127.40
B (s) 120.38
I (s) 119.47
C (s) 121.87
A (s) 120.40
J (s) 118.84
L (s) 112.06
F (s) 24.44

HSQC

HMBC
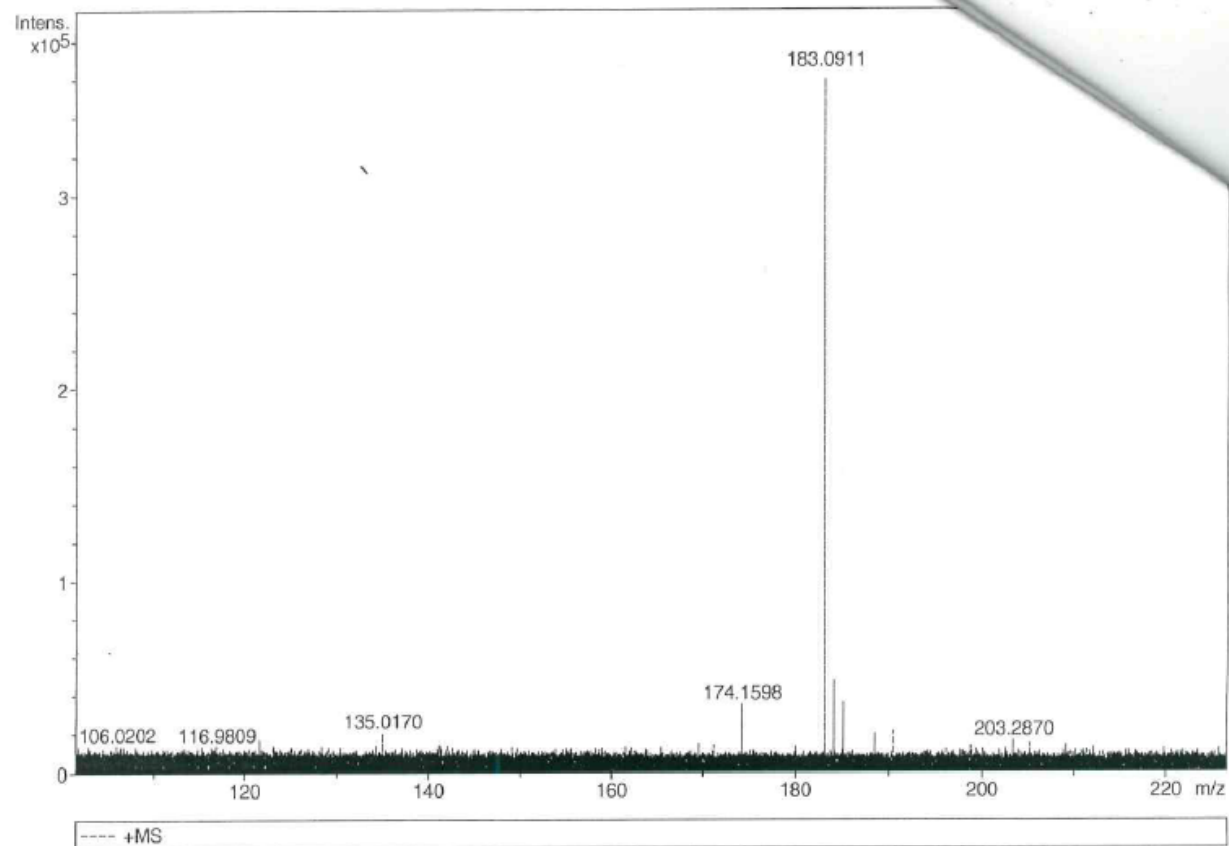
Generic Disp...

Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 12 H 11 N 2	0.052	183.0917	2.93	0.22	0.04	8.50	ok	even

7-fluoro-2-methyl-5*H*-pyrido[3,2-*b*]indole (**174**).

600 methanol

PROTON_01
TN-199

A (dd)
8.27

B (d)
7.76

C (d)
7.27

D (dd)
7.17

E (td)
6.99

F (s)
2.68

8.28
8.27
8.27
8.26

7.77
7.76

7.27
7.26
7.19
7.18
7.17
7.17

7.00
7.00
6.99
6.98
6.97
6.97

3.30 cd3od
3.30 cd3od
3.29 cd3od
3.29 cd3od
3.29 cd3od

2.68

0.92
0.92
1.05
0.94
1.06
3.11

f1 (ppm)
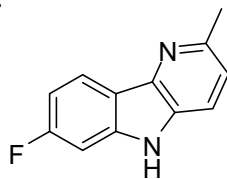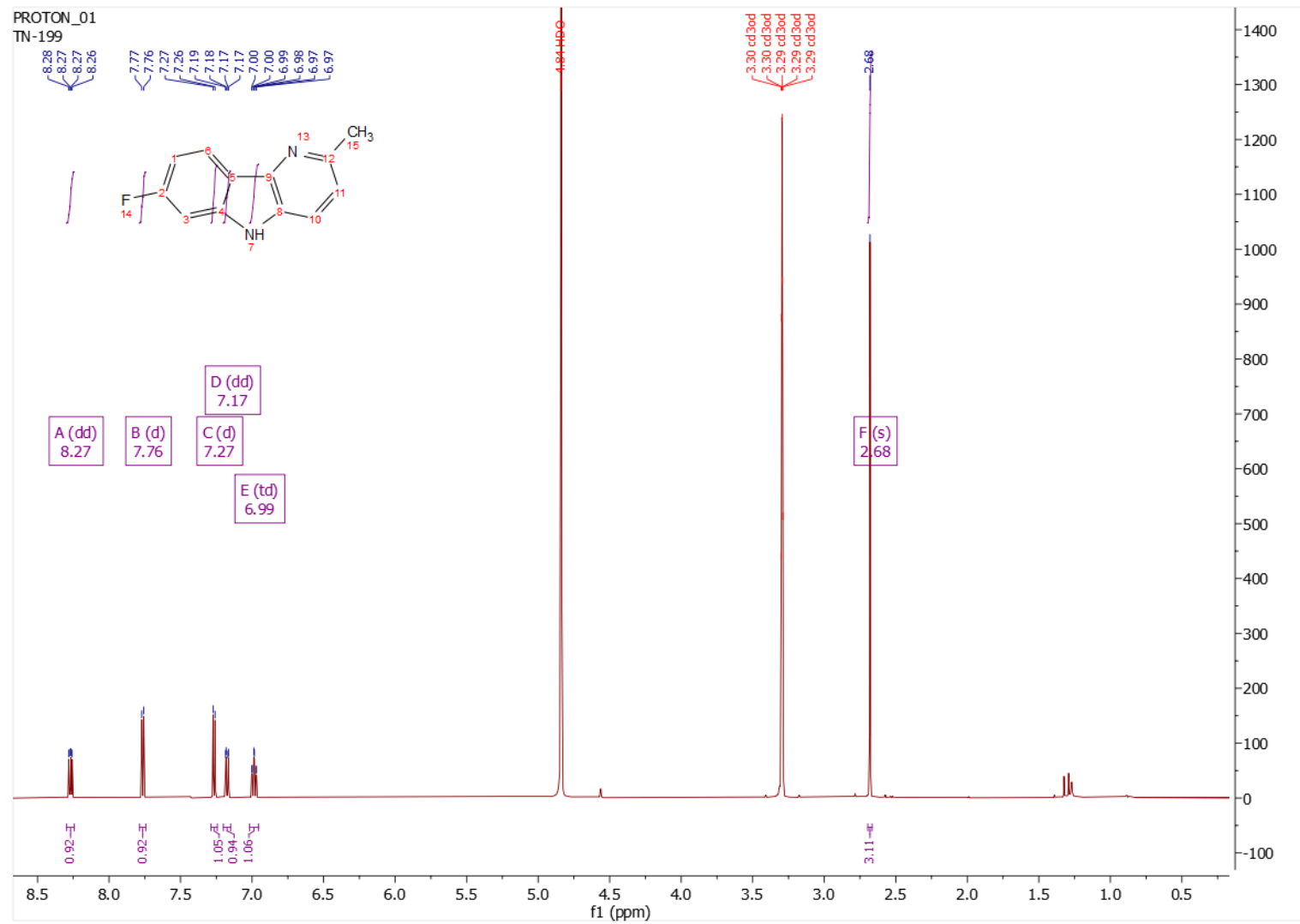
151 methanol

Generic Display Report

(256)
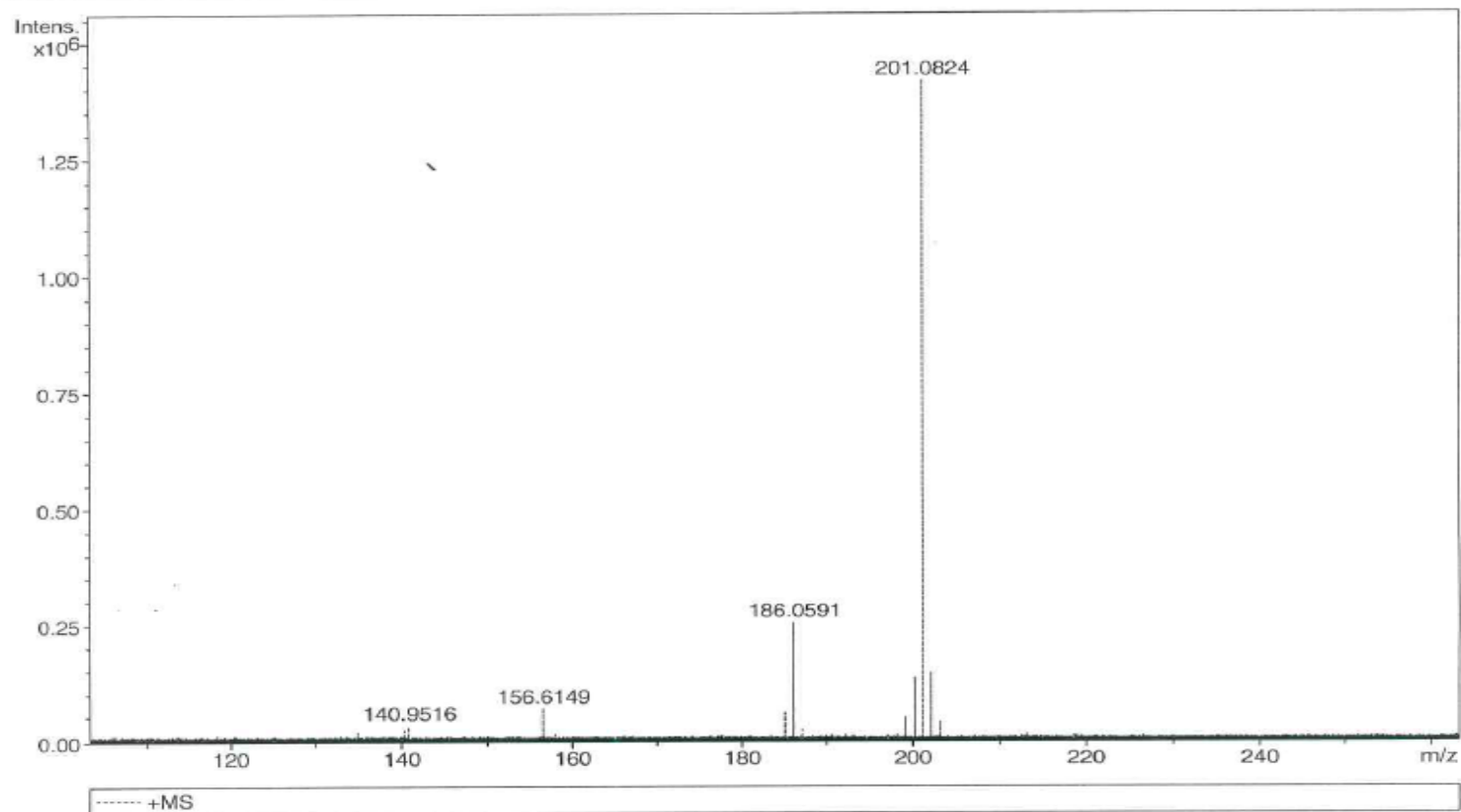
Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 12 H 10 F 1 N 2	0.029	201.0823	-0.68	-2.13	-0.43	8.50	ok	even

Analyst

Date

PEService
20 March 2019 17:55

%T

cm-1

- 3136.7
- 3010.2
- 2940.8
- 2863.3
- 2798
- 2732.7
- 1475.5
- 1630.6
- 1442.24cm-1
- 1384.68cm-1
- 1343.85cm-1
- 1269.29cm-1
- 1224.40cm-1
- 1145.27cm-1
- 1106.23cm-1
- 817.31cm-1
- 830.08cm-1
- 773.77cm-1
- 616.83cm-1
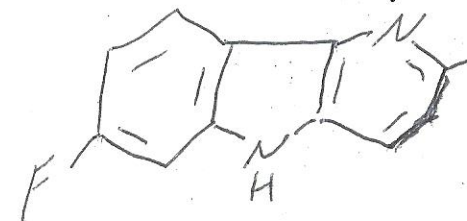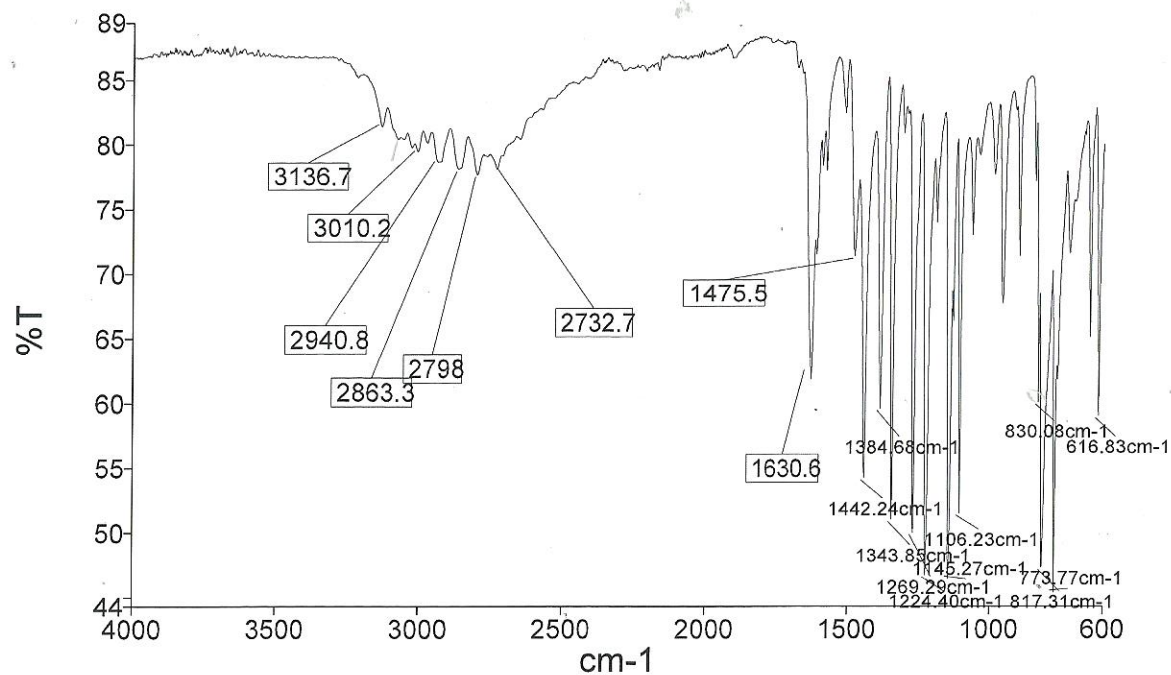
Sample Name	Description	Quality Checks
PEService 103

TN-199 | Sample 103 By PEService Date Wednesday, March 20 2019 | The Quality Checks do not report any warnings for the sample. |

7-bromo-2-methyl-5*H*-pyrido[3,2-*b*]indole (**175**).
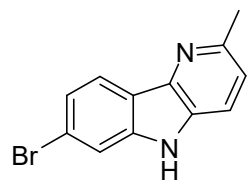
600 DMSO
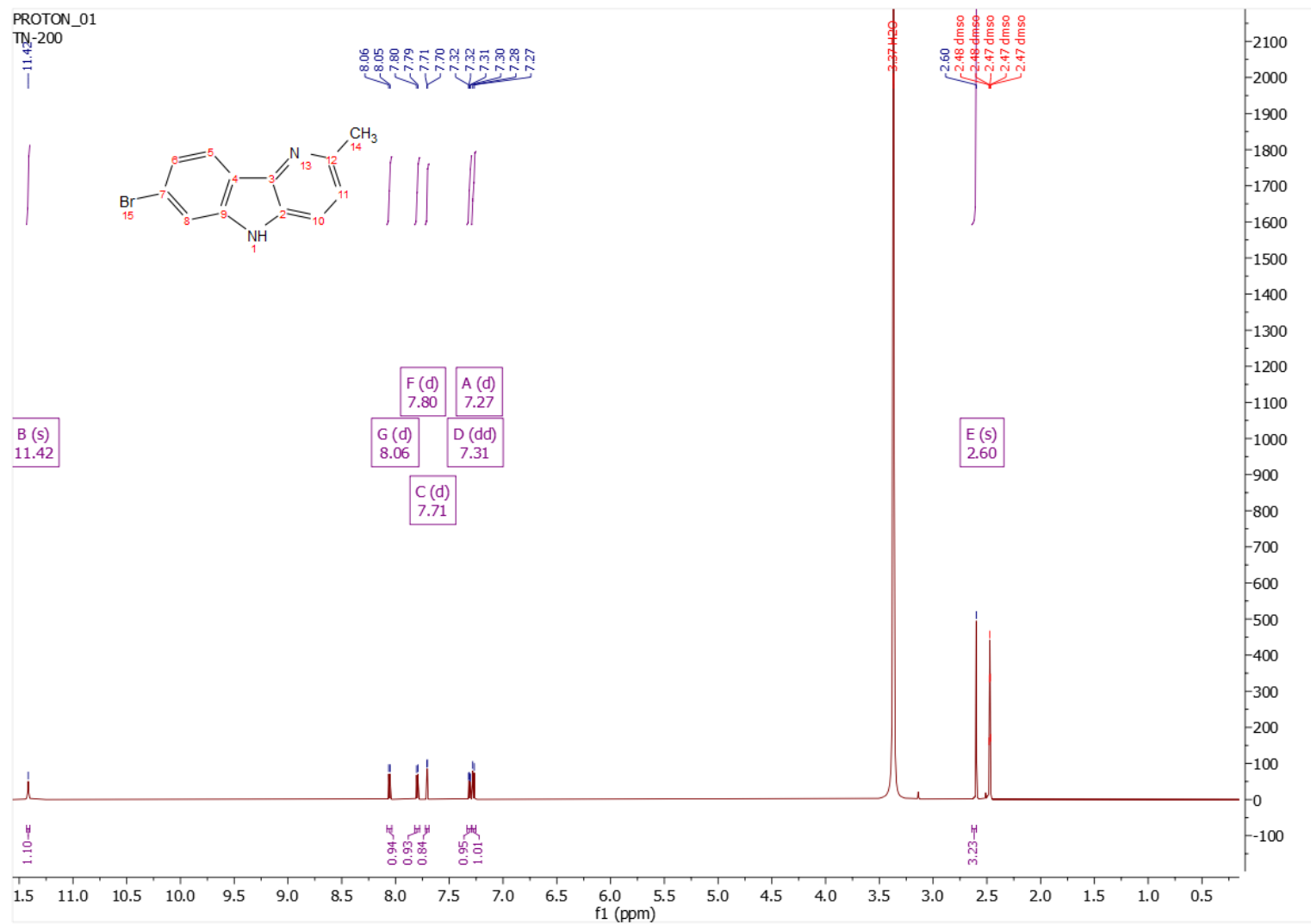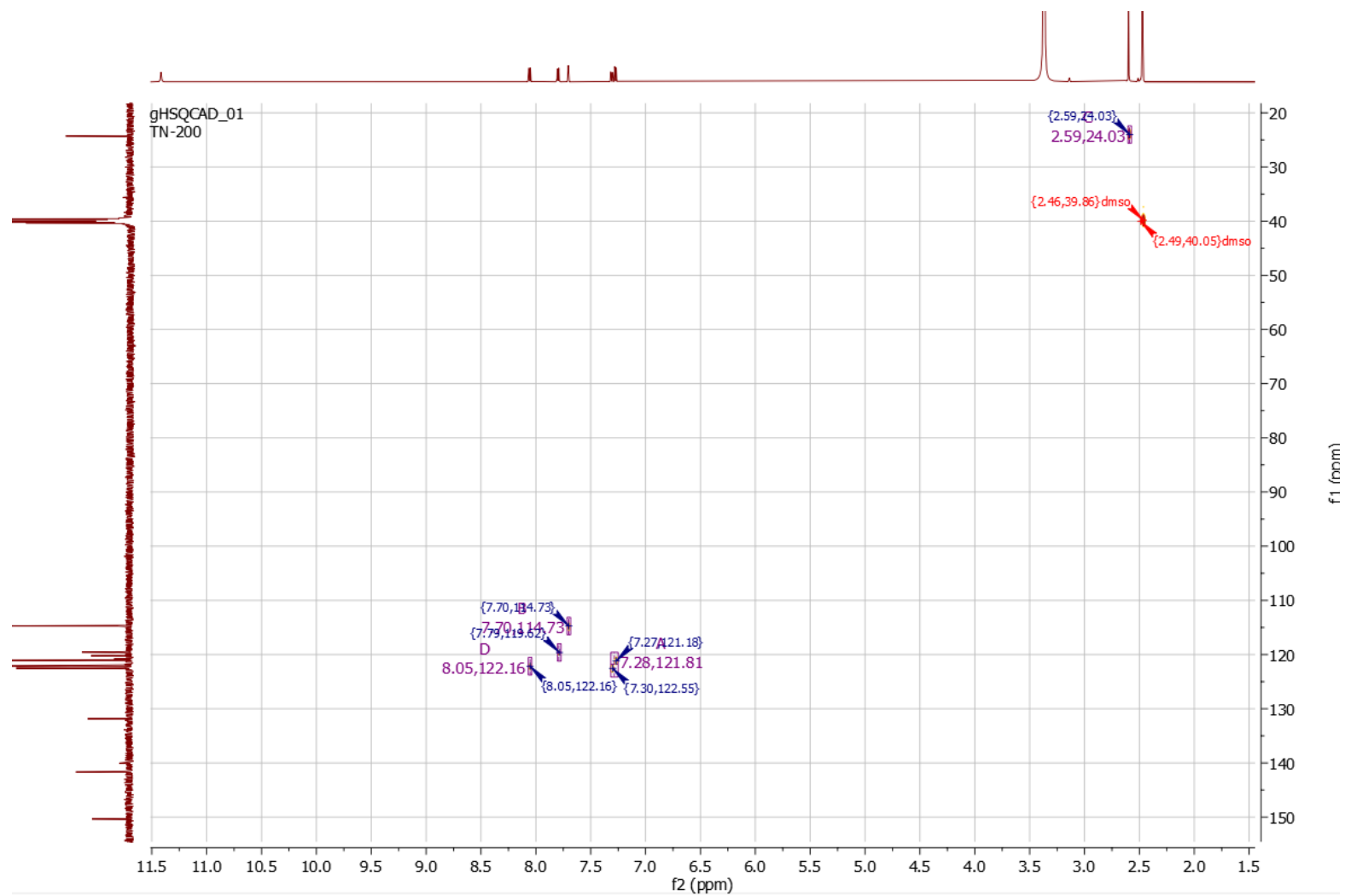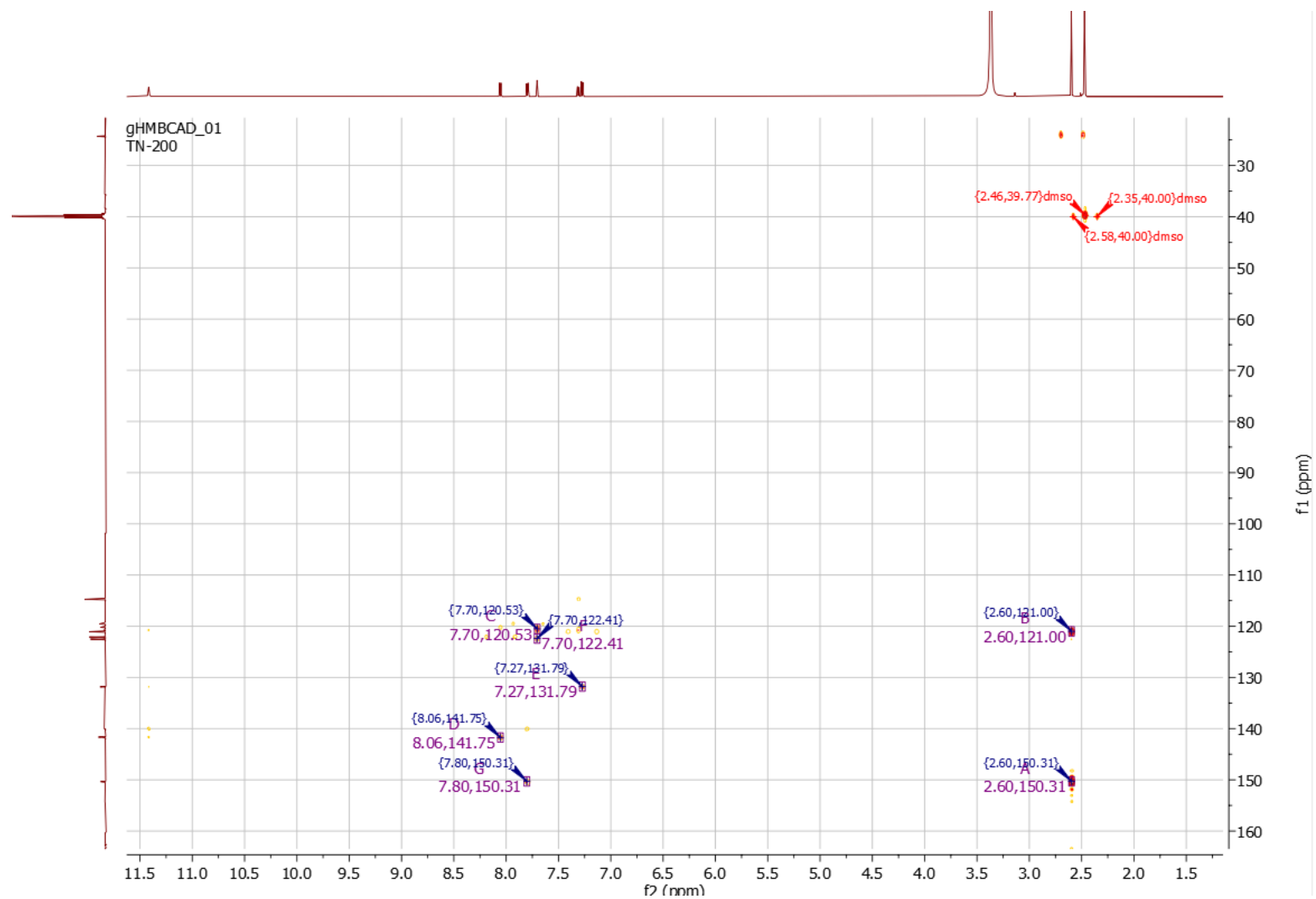
PROTON_01
TN-200

11.42

8.06
8.05
7.80
7.79
7.71
7.70
7.32
7.31
7.30
7.28
7.27

3.37 H2O

2.60
2.48 dmso
2.48 dmso
2.47 dmso
2.47 dmso

B (s)
11.42

F (d)
7.80

A (d)
7.27

G (d)
8.06

D (dd)
7.31

C (d)
7.71

E (s)
2.60

1.10

0.94
0.93
0.84

0.95
1.01

3.23

f1 (ppm)

151 DMSO

HSQC

gHSQCAD_01
TN-200

{2.59,24.03}
2.59,24.03

{2.46,39.86}dmso
{2.49,40.05}dmso

{7.70,114.73}
{7.70,114.73}
{7.79,119.62}
{7.27,121.18}
D
{7.28,121.81}
8.05,122.16
{8.05,122.16} {7.30,122.55}

HMBC

gHMBCAD_01
TN-200

{2.46,39.77}dmso   {2.35,40.00}dmso
{2.58,40.00}dmso

{7.70,120.53}   {7.70,122.41}   {2.60,121.00}
7.70,120.53 7.70,122.41   2.60,121.00

{7.27,131.79}
7.27,131.79

{8.06,141.75}
8.06,141.75

{7.80,150.31}   {2.60,150.31}
7.80,150.31   2.60,150.31

f1 (ppm)
f2 (ppm)
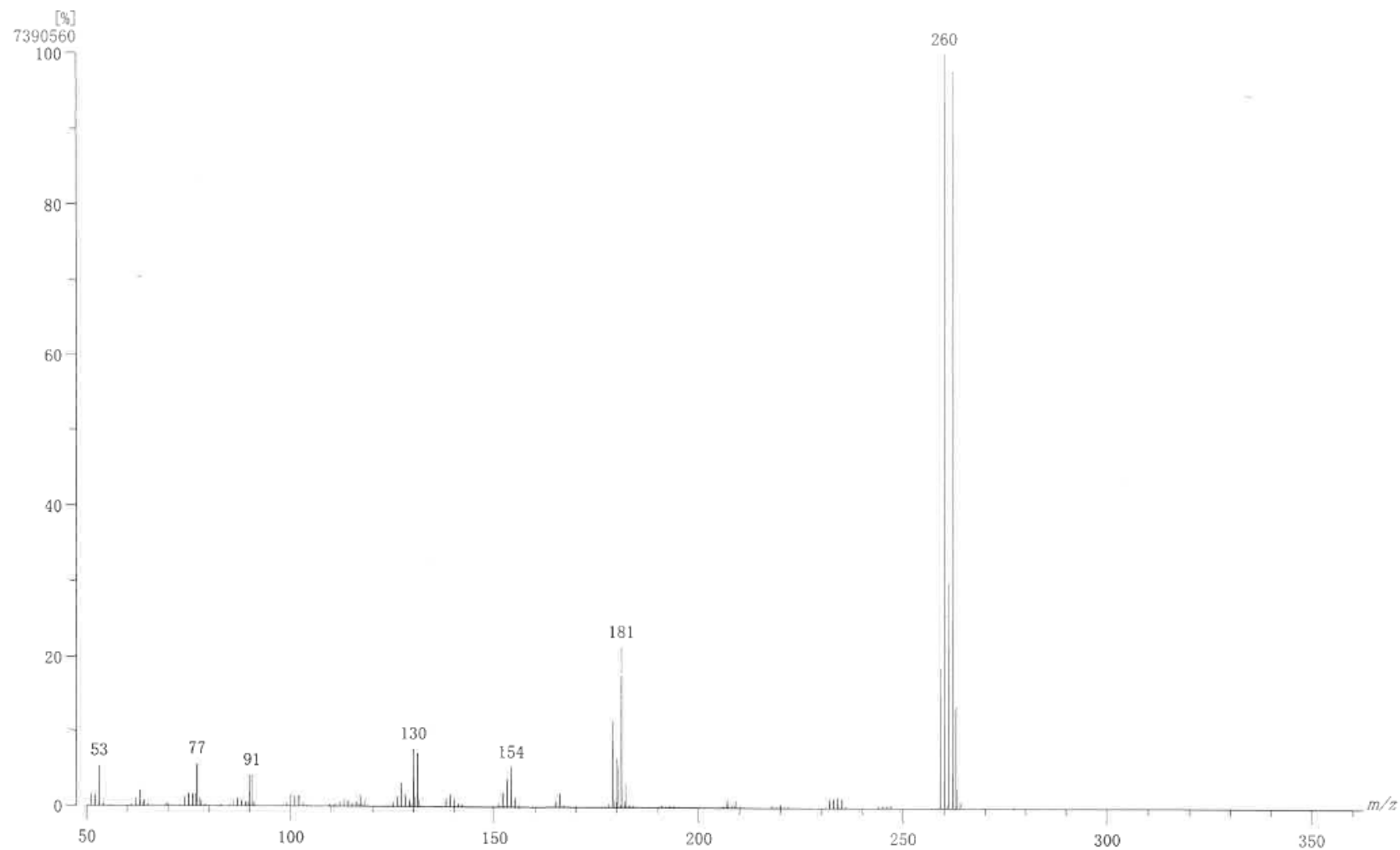
```
[ Theoretical Ion Distribution ]
Molecular Formula : C12 H9 Br N2
                       (m/z   259.9949, MW   261.1209, U.S.  9.0)
Base Peak :   259.9949, Averaged MW :   261.1198(a),   261.1242(w)

   m/z      INT.
 259.9949 100.0000*************************************************************
 260.9979  14.0815********
 261.9929  98.1934************************************************************
 262.9959  13.7346********
 263.9989   0.8919*
 265.0018   0.0355
 266.0047   0.0010
```

Analyst

Date

PEService
20 March 2019 17:50

%T

96

94

92

90

88 3112.2

86 3014.3 2720.4

84 2920.4

2781.6

82 2847

80

79

4000   3500   3000   2500   2000   1500   1000   600

cm-1

1619.22cm-1   1047.76cm-1   612.24cm-1

1332.57cm-1   641.43cm-1

1437.04cm-1   904.00cm-1

1229.37cm-1

1267.29cm-1

771.70cm-1
815.09cm-1
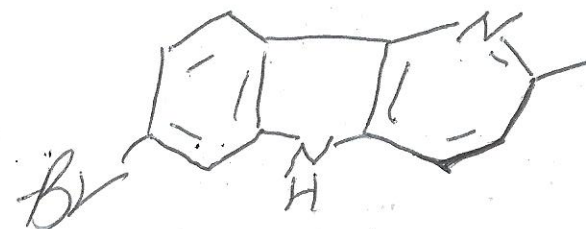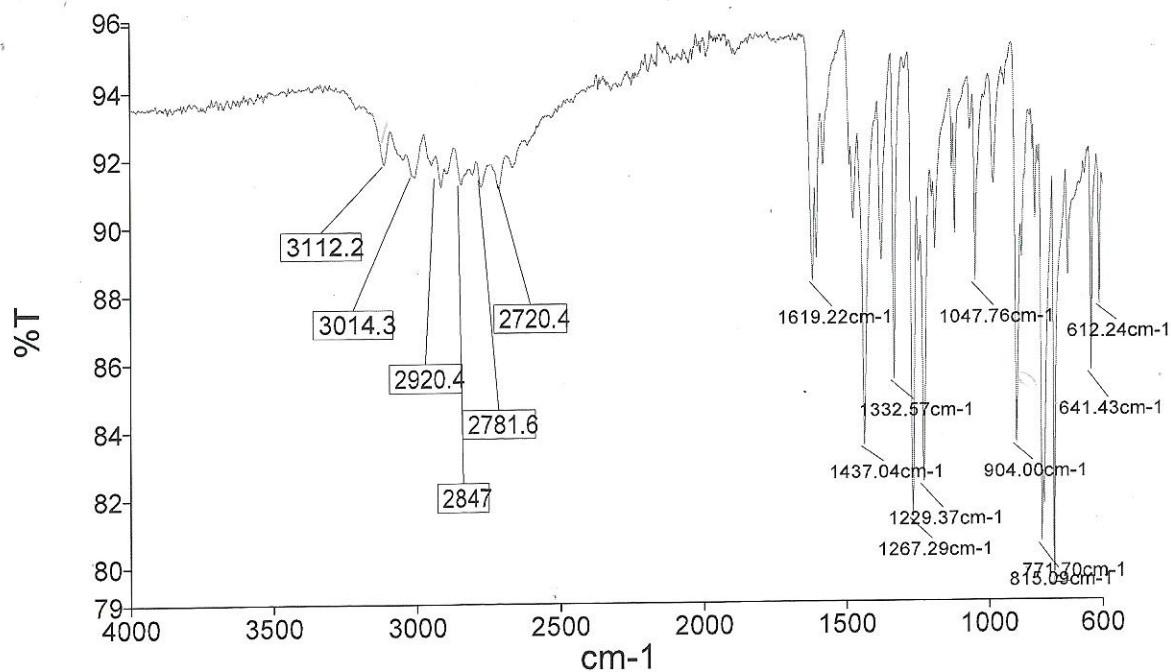
Sample Name	Description	Quality Checks
PEService 102 (TN-193)	Sample 102 By PEService Date Wednesday, March 20 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

2-methyl-7-(propan-2-yl)-5*H*-pyrido[3,2-*b*]indole (**176**).
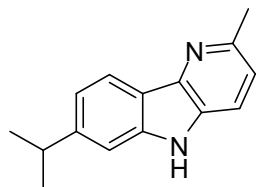
600 methanol
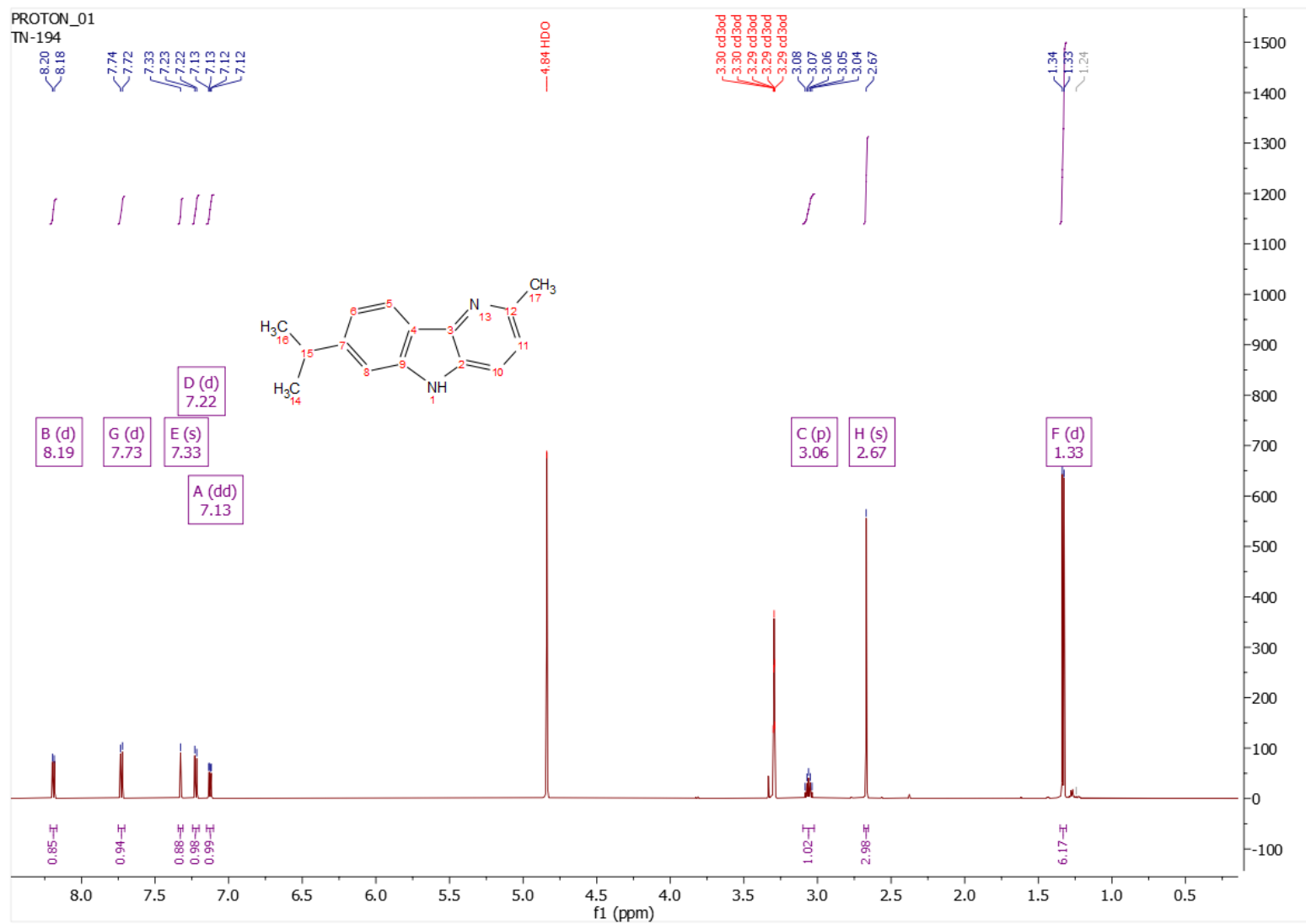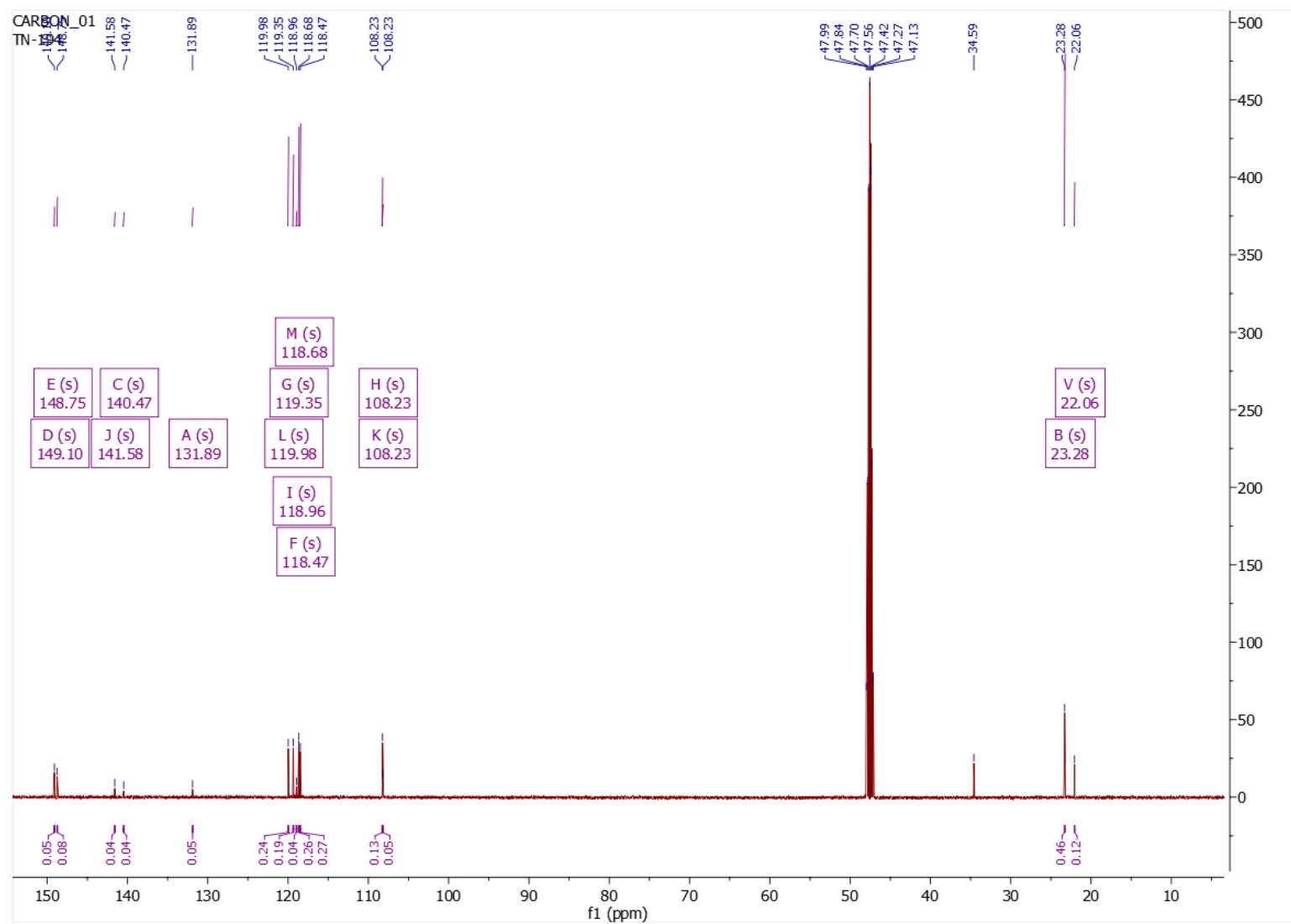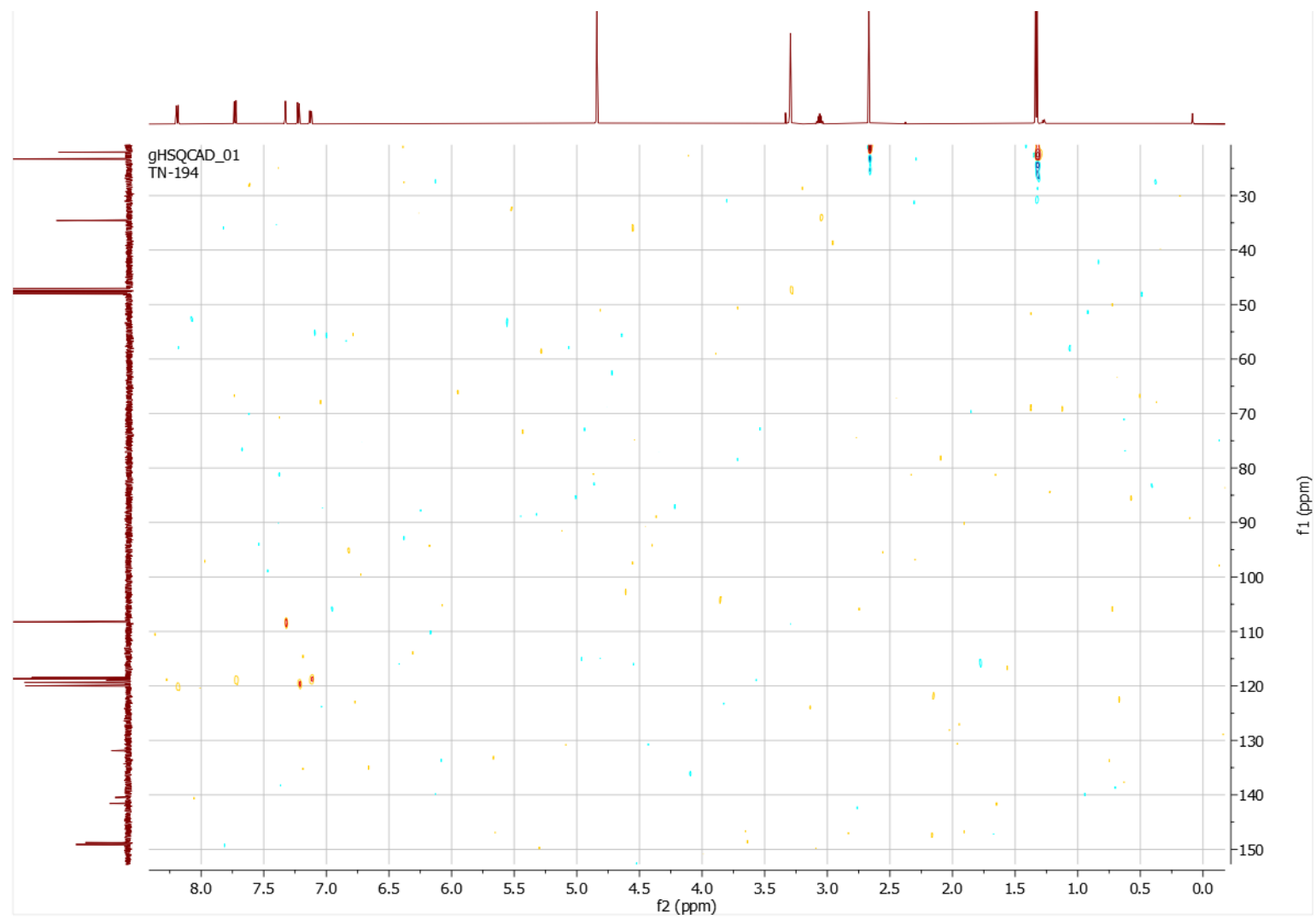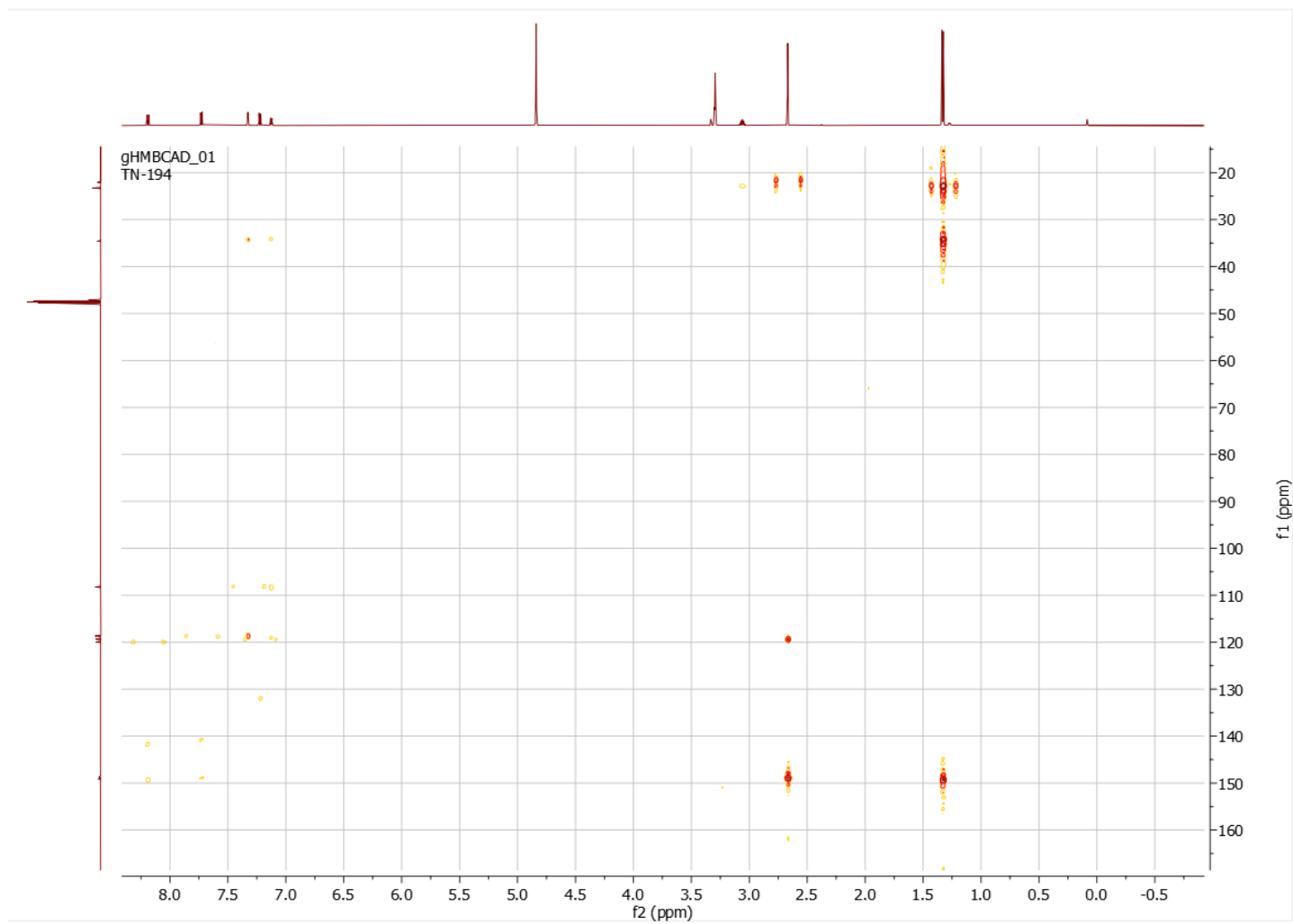
PROTON_01
TN-194

8.20
8.18

7.74
7.72
7.33
7.23
7.22
7.13
7.12
7.12

4.84 HDO

3.30 cd3od
3.30 cd3od
3.29 cd3od
3.29 cd3od
3.29 cd3od
3.08
3.07
3.06
3.05
3.04
2.67

1.34
1.33
1.24

B (d)
8.19

G (d)
7.73

E (s)
7.33

D (d)
7.22

A (dd)
7.13

C (p)
3.06

H (s)
2.67

F (d)
1.33

0.85

0.94

0.88
0.98
0.99

1.02

2.98

6.17

f1 (ppm)

151 methanol

HSQC

gHSQCAD_01
TN-194

HMBC

gHMBCAD_01
TN-194

Generic Display Report
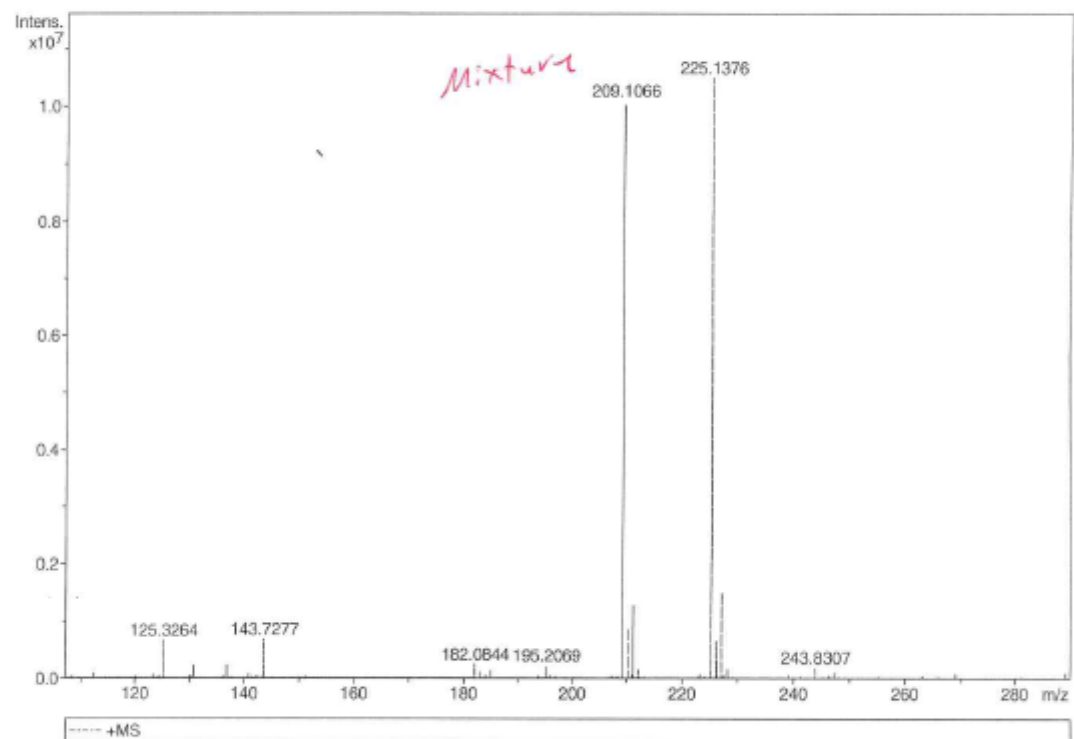
Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 15 H 17 N 2	0.084	225.1386	4.65	2.03	0.46	8.50	ok	even

7-(benzyloxy)-2-methyl-5*H*-pyrido[3,2-*b*]indole (**177**).
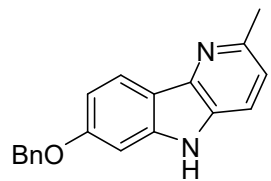
600 methanol
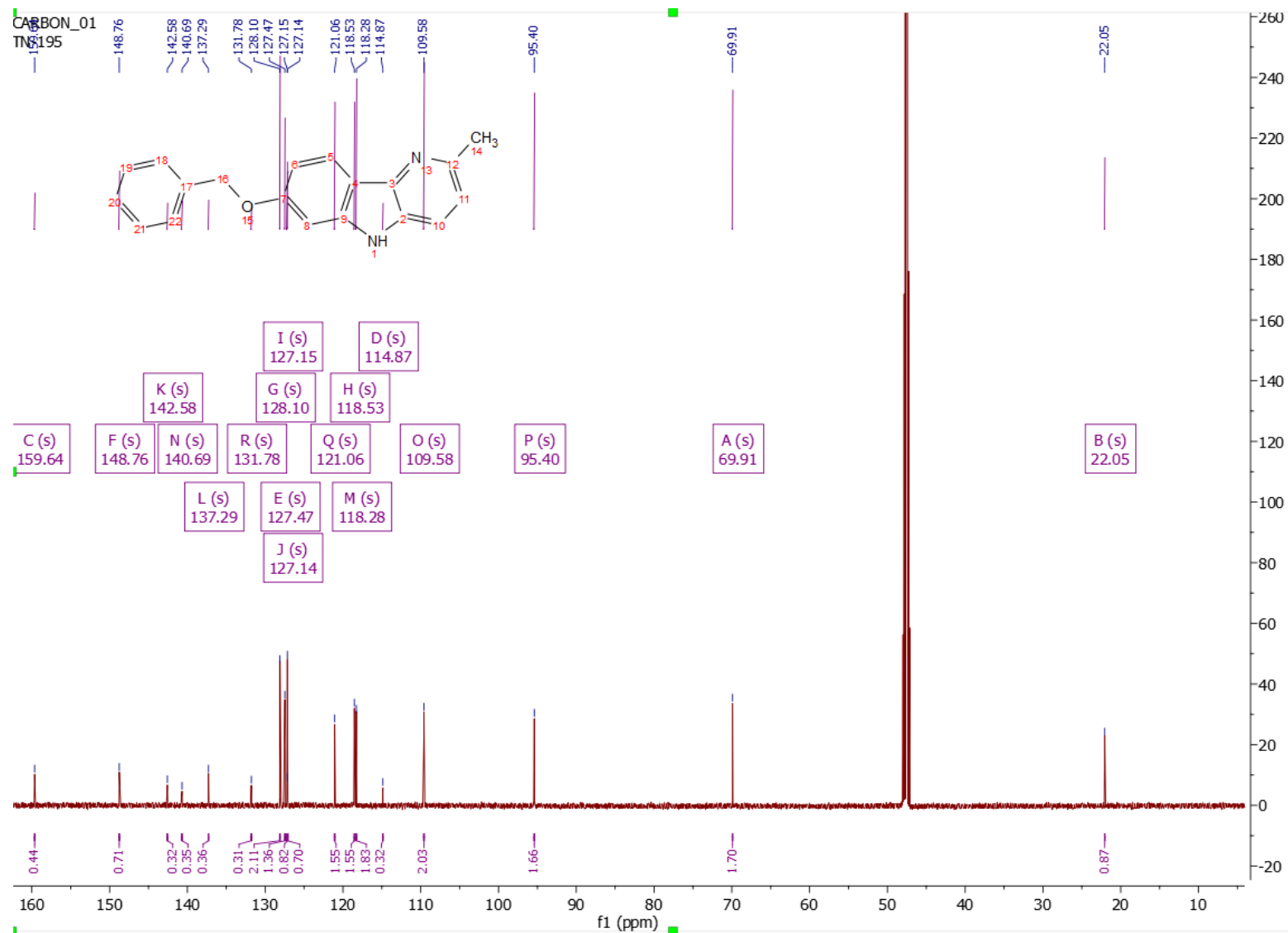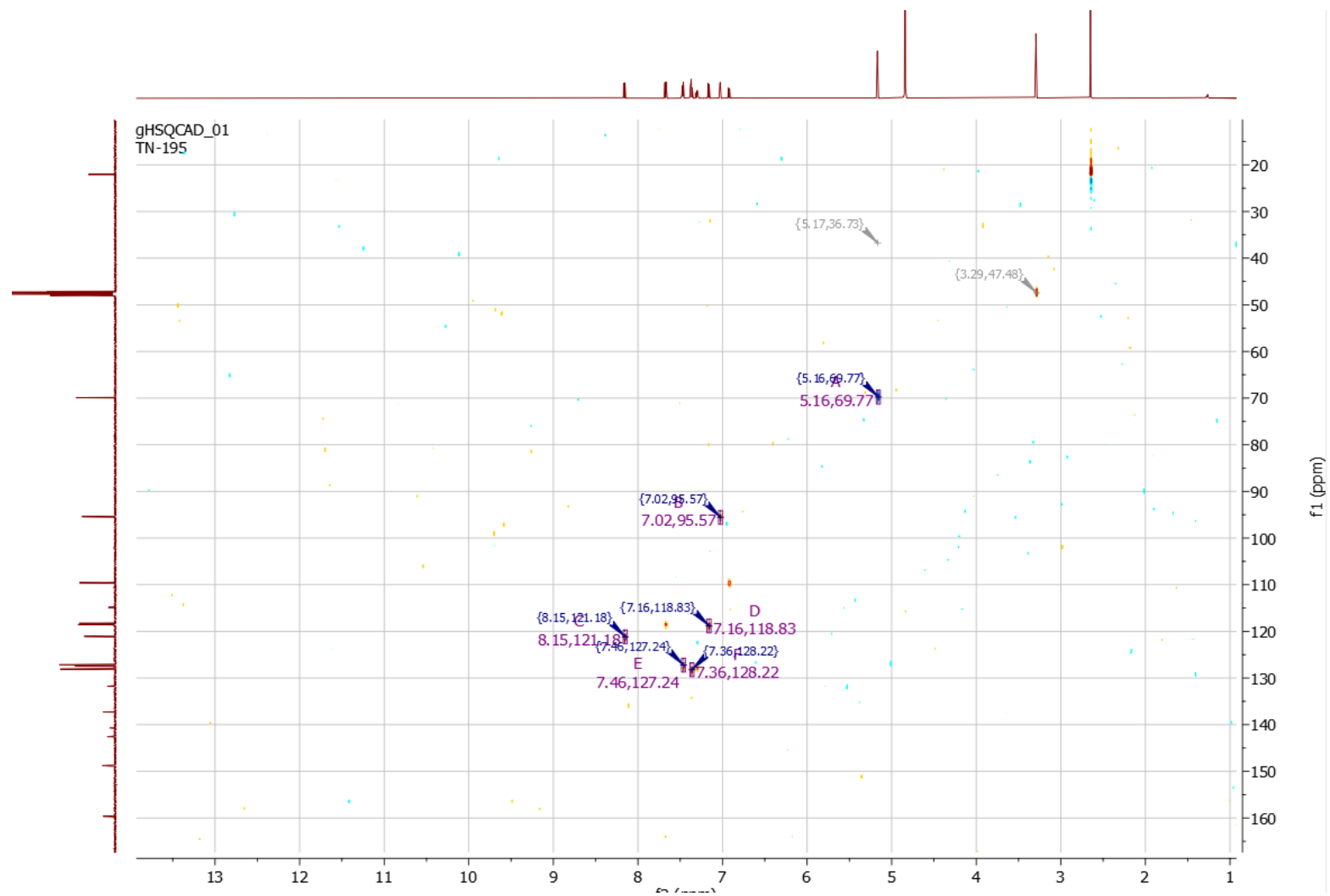
PROTON_01
TN-195

151 methanol

HSQC

HMBC
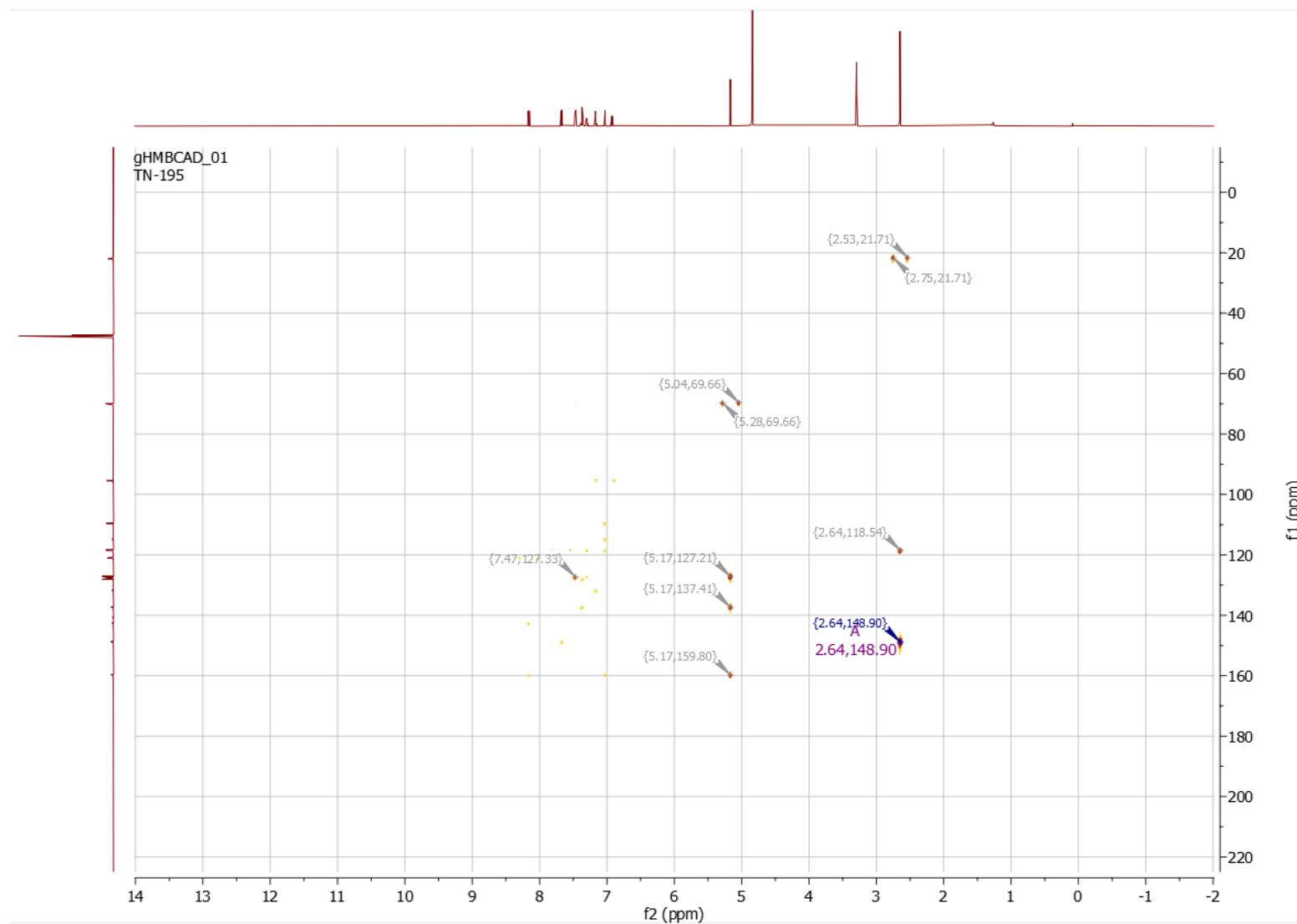
(259)
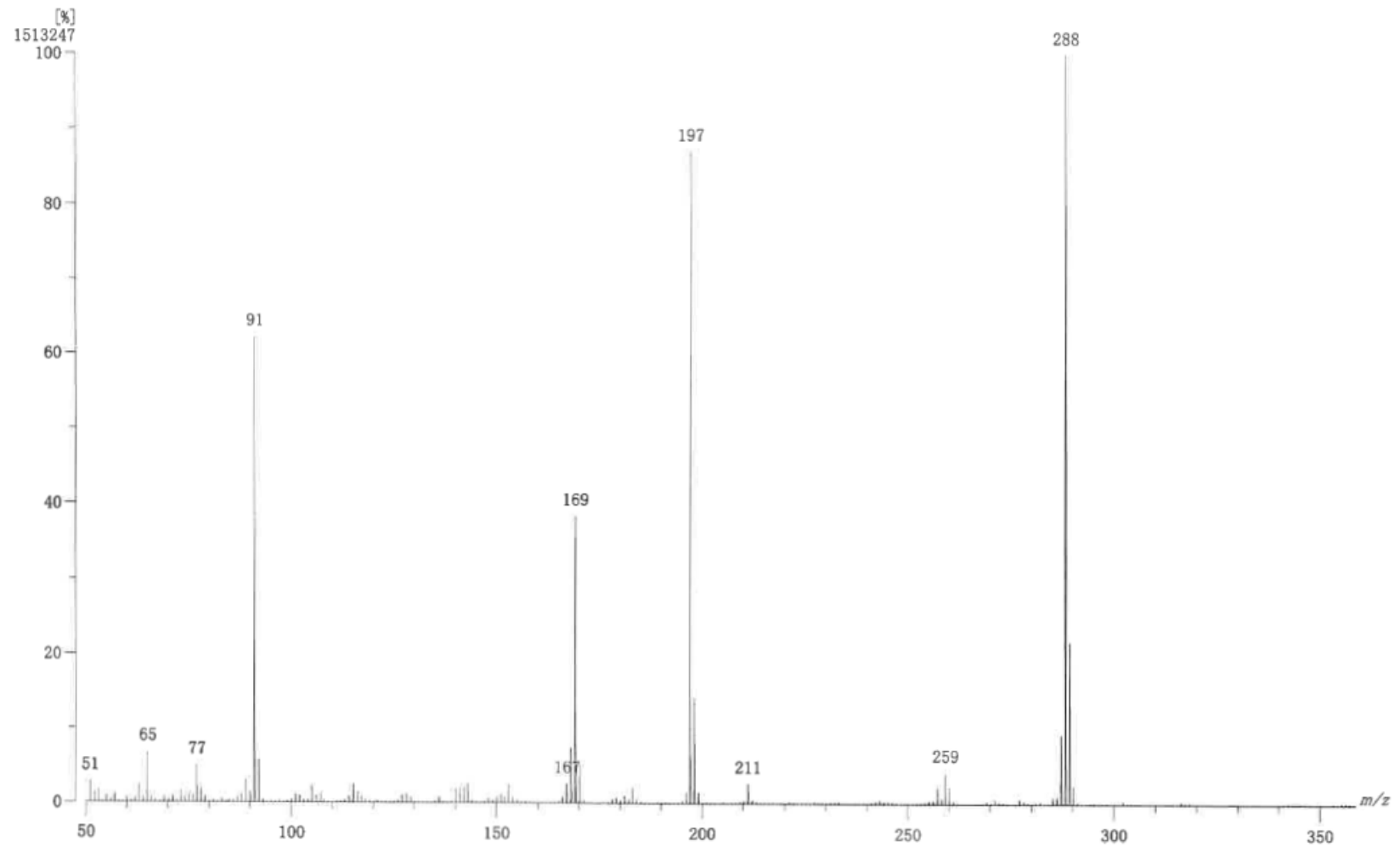
```
[ Theoretical Ion Distribution ]
Molecular Formula : C19 H16 N2 O
                        (m/z   288.1263, MW   288.3488, U.S. 13.0)
Base Peak :   288.1263, Averaged MW :   288.3477(a),   288.3484(w)

   m/z      INT.
 288.1263 100.0000*************************************************************
 289.1294  21.9052*************
 290.1324   2.4808*
 291.1352   0.1939
 292.1380   0.0116
 293.1408   0.0005
```

sis Info

ysis Name   D:\Data\Alinanopos\TYLER_10938_000001.d
thod   pos20090608esi
ample Name   POS ESI   TN-195
Comment

Acquisition Date   24/09/2019 15:13:25

Operator   Administrator
Instrument   apex-III

(259)

----- +MS
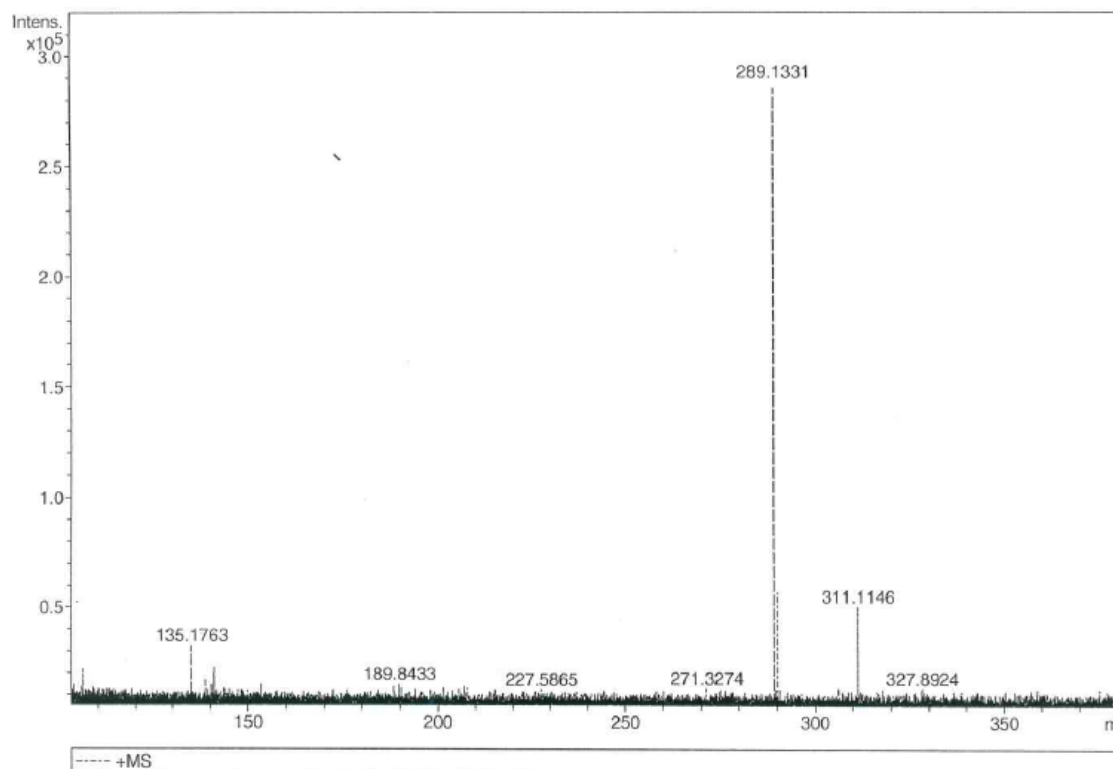
Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 19 H 17 N 2 O 1	0.017	289.1335	1.65	1.56	0.45	12.50	ok	even

2-phenyl-5*H*-pyrido[3,2-*b*]indole (**178**).

600 methanol

A (d)
8.40

B (d)
8.00

C (d)
7.93

D (d)
7.82

E (m)
7.40

F (tt)
7.26

G (m)
7.50

	Observed m/z	Int%	Err[ppm / mmu]	U.S.	Composition
1	244.1001	92.56	+0.2 / +0.1	13.0	C17 H12 N2
	245.1073	21.24			

Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 17 H 13 N 2	0.021	245.1073	1.51	4.48	1.10	12.50	ok	even

Analyst

Date

PEService

29 March 2019 17:49

%T

3330.4

3161.5

1493.39cm-1

1597

1623.98cm-1

1429.22cm-1

1471.82cm-1

1389.14cm-1

1297.92cm-1

1229.28cm-1

1320.15cm-1

917.76cm-1
790.33cm-1
815.53cm-1
827.66cm-1

764.81cm-1

690.95cm-1

733.33cm-1

cm-1

4000 3500 3000 2500 2000 1500 1000 650
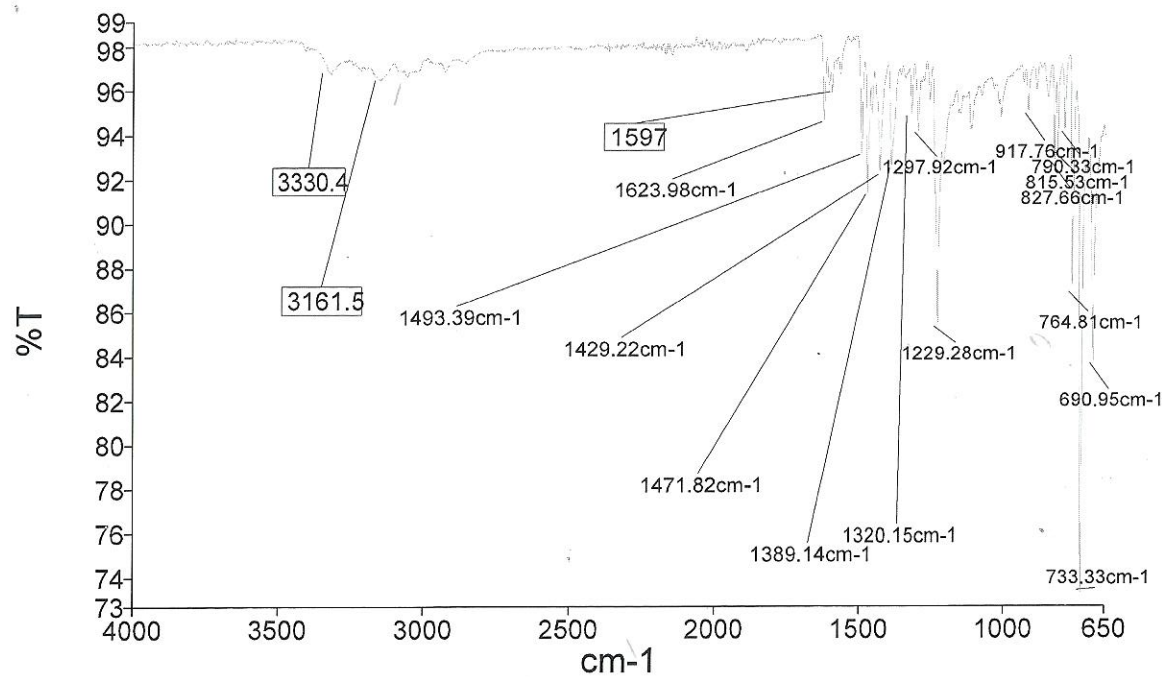
Sample Name	Description	Quality Checks
211	Sample 008 By PEService Date Friday, March 29 2019	The Quality Checks give rise to a Weak Bands warning for the sample.
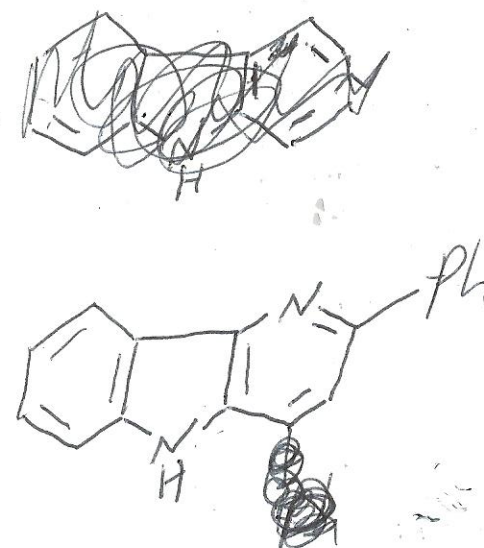
4-(4-methoxyphenyl)-2,6-dimethylpyridin-3-amine (**184**).

600 cdcl3

PROTON_01
TN-410

G (d) 7.35
F (d) 6.99
C (s) 6.80
E (s) 3.66
D (s) 3.84
B (s) 2.47
A (s) 2.48

151 cdcl3

CARBON_01
TN-410

I (s) 159.57
H (s) 146.07
A (s) 142.52
F (s) 135.67
E (s) 135.09
G (s) 129.30
D (s) 129.69
J (s) 122.50
K (s) 114.49
L (s) 55.34
B (s) 20.07
C (s) 22.65

HSQC

gHSQCAD_01
TN-410

{2.46,-9.99}
{2.46,3.50}
{2.47,19.92}
{2.46,22.27}
2.47,19.92
2.46,22.27
{3.83,55.11}
3.83,55.11
{6.80,122.55}
D
{7.35,129.58}
6.80,122.55
A
{6.85,122.74}
7.35,129.58

f1 (ppm)
f2 (ppm)

HMBC

gHMBCAD_01
TN-410
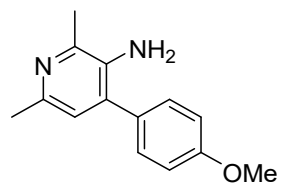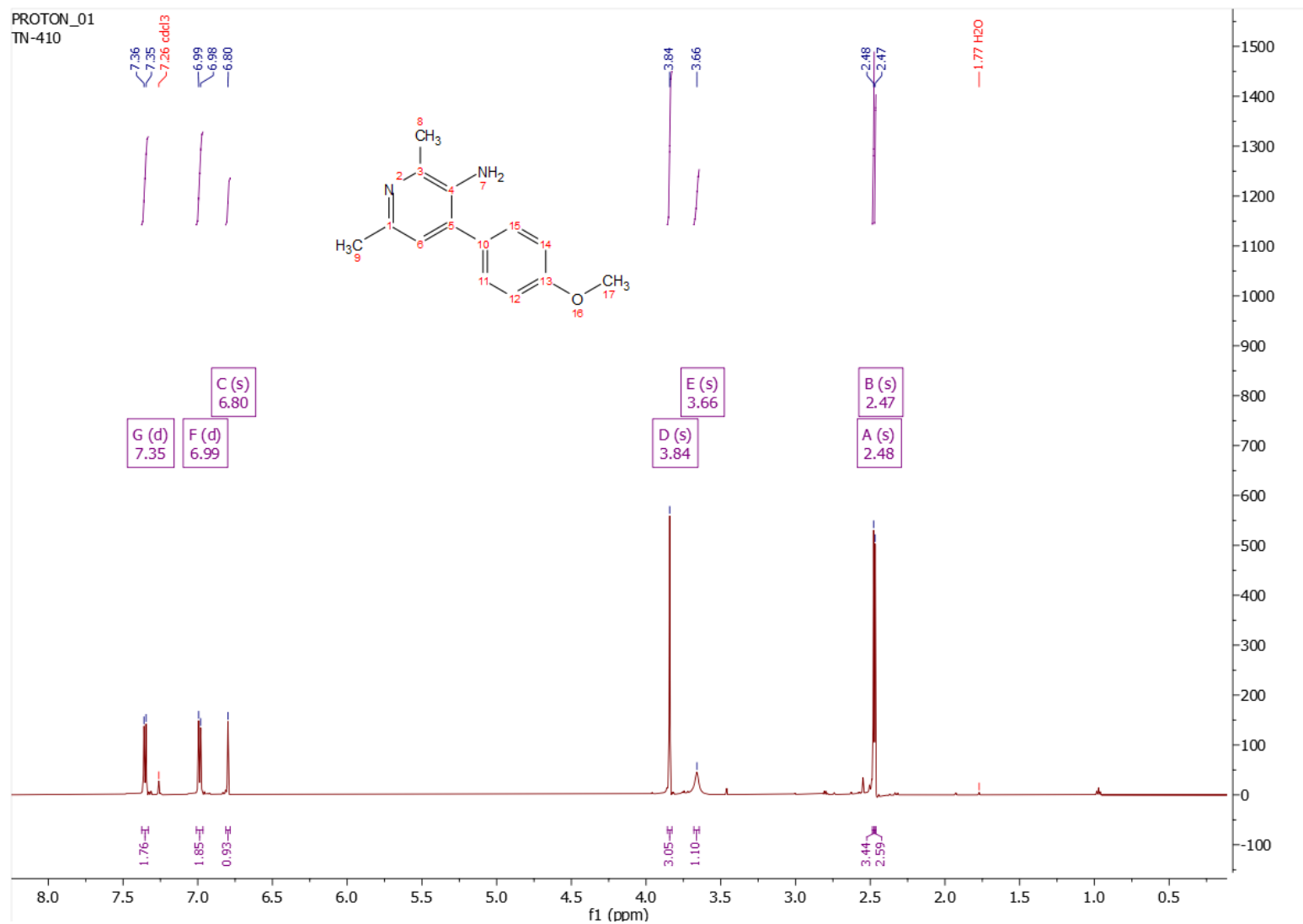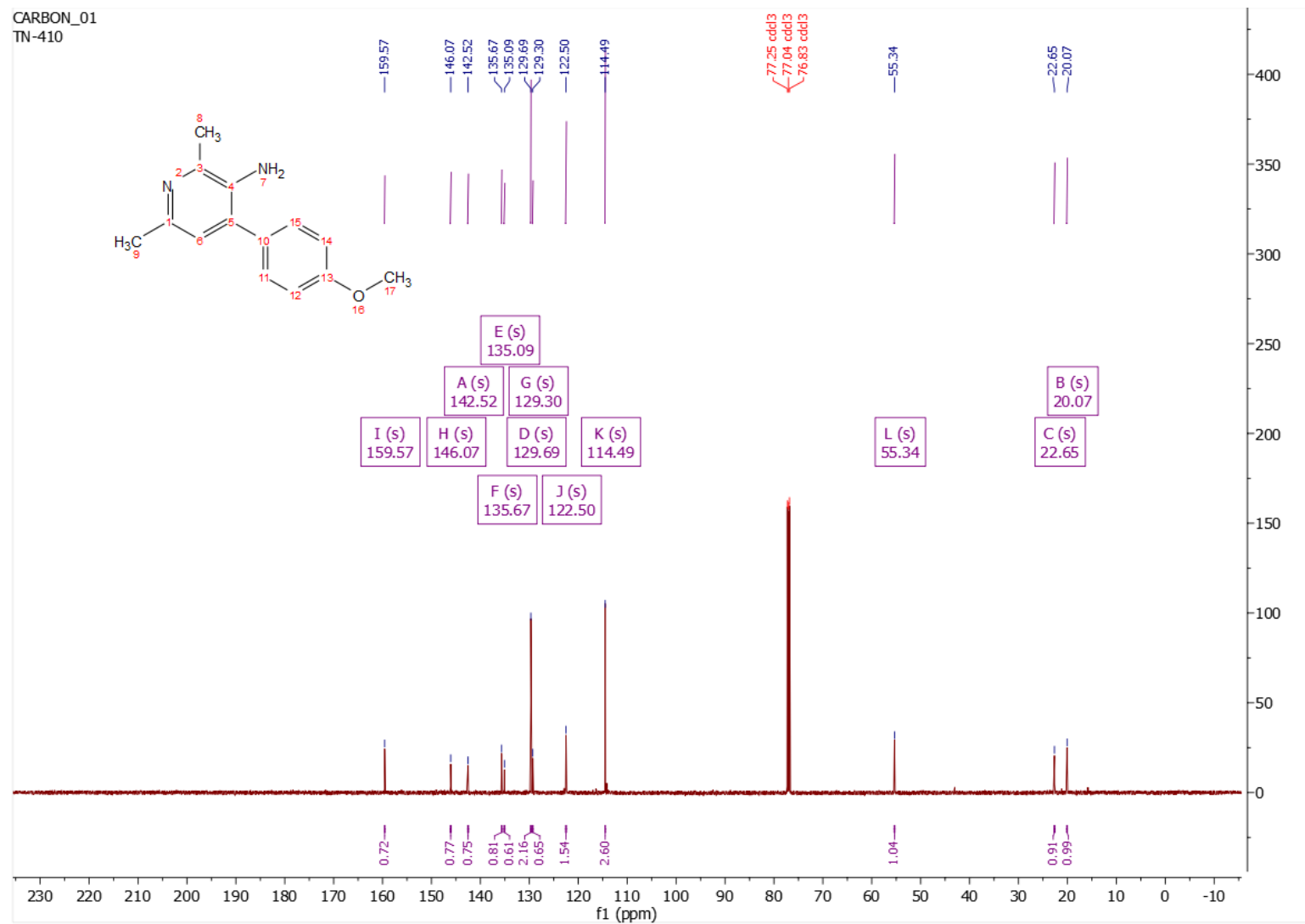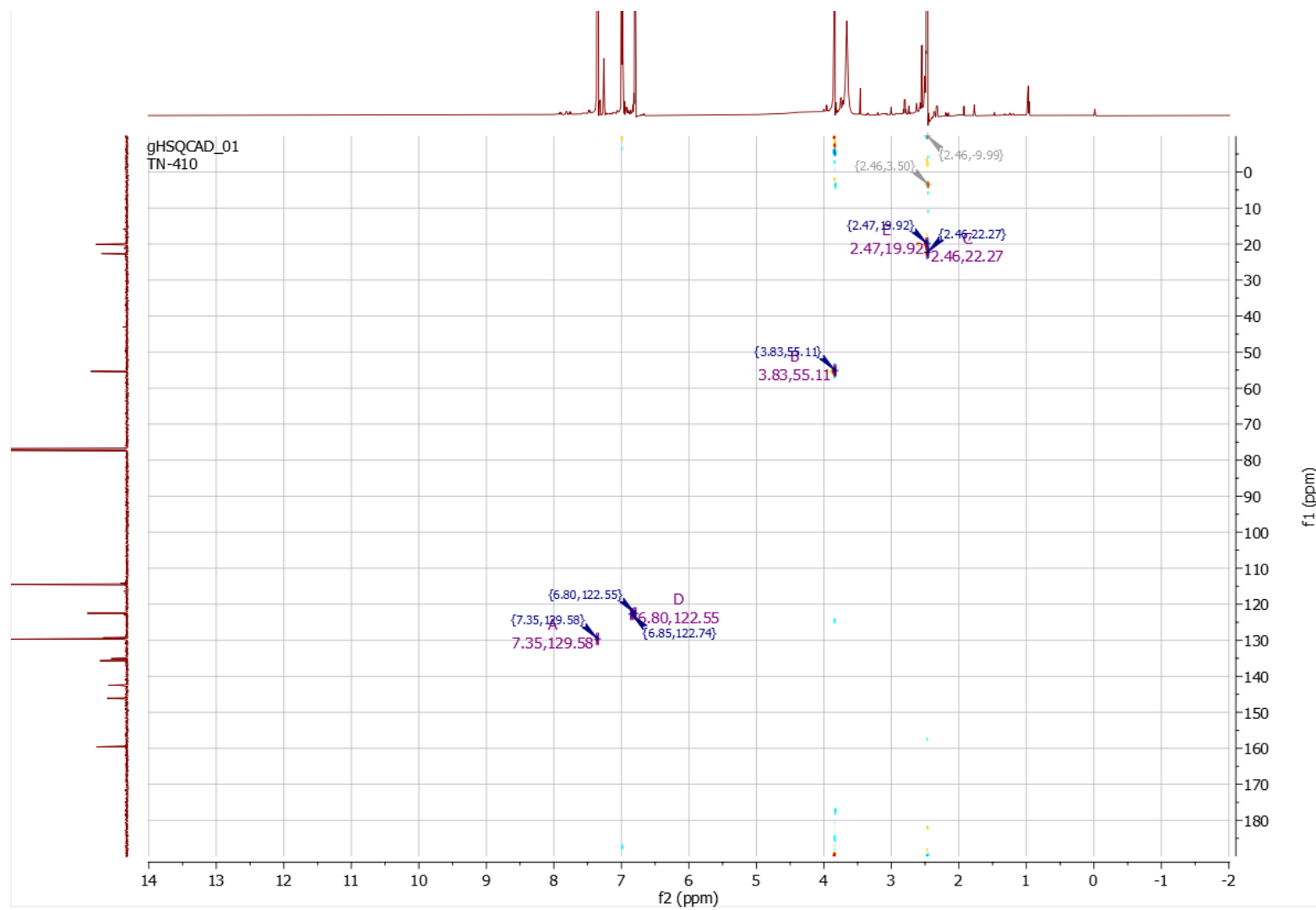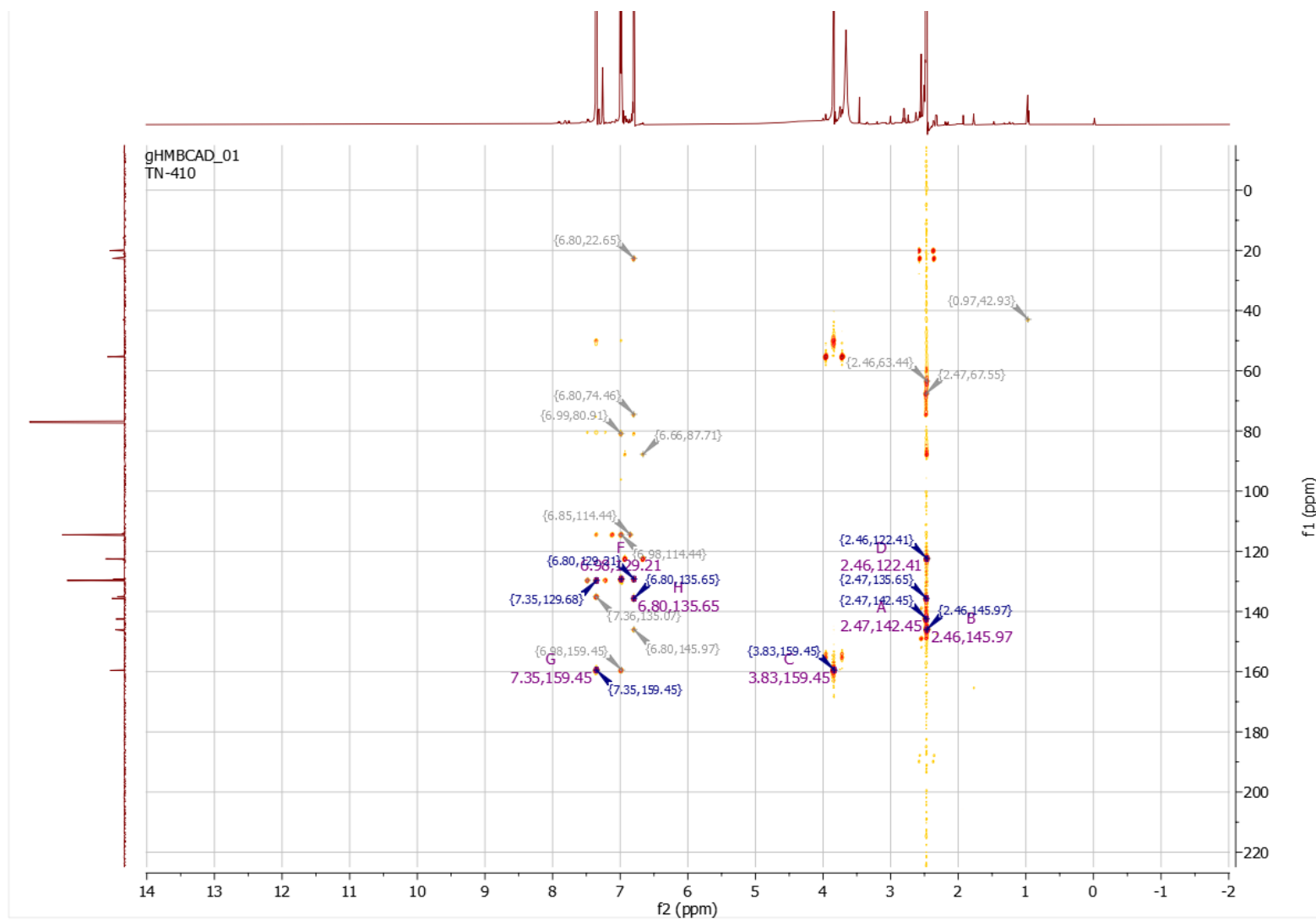
1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole (**181**).
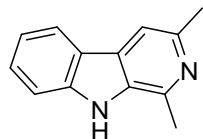
Chemical Formula: C$_{13}$H$_{12}$N$_2$

Molecular Weight: 196.25 g/mol

500 methanol
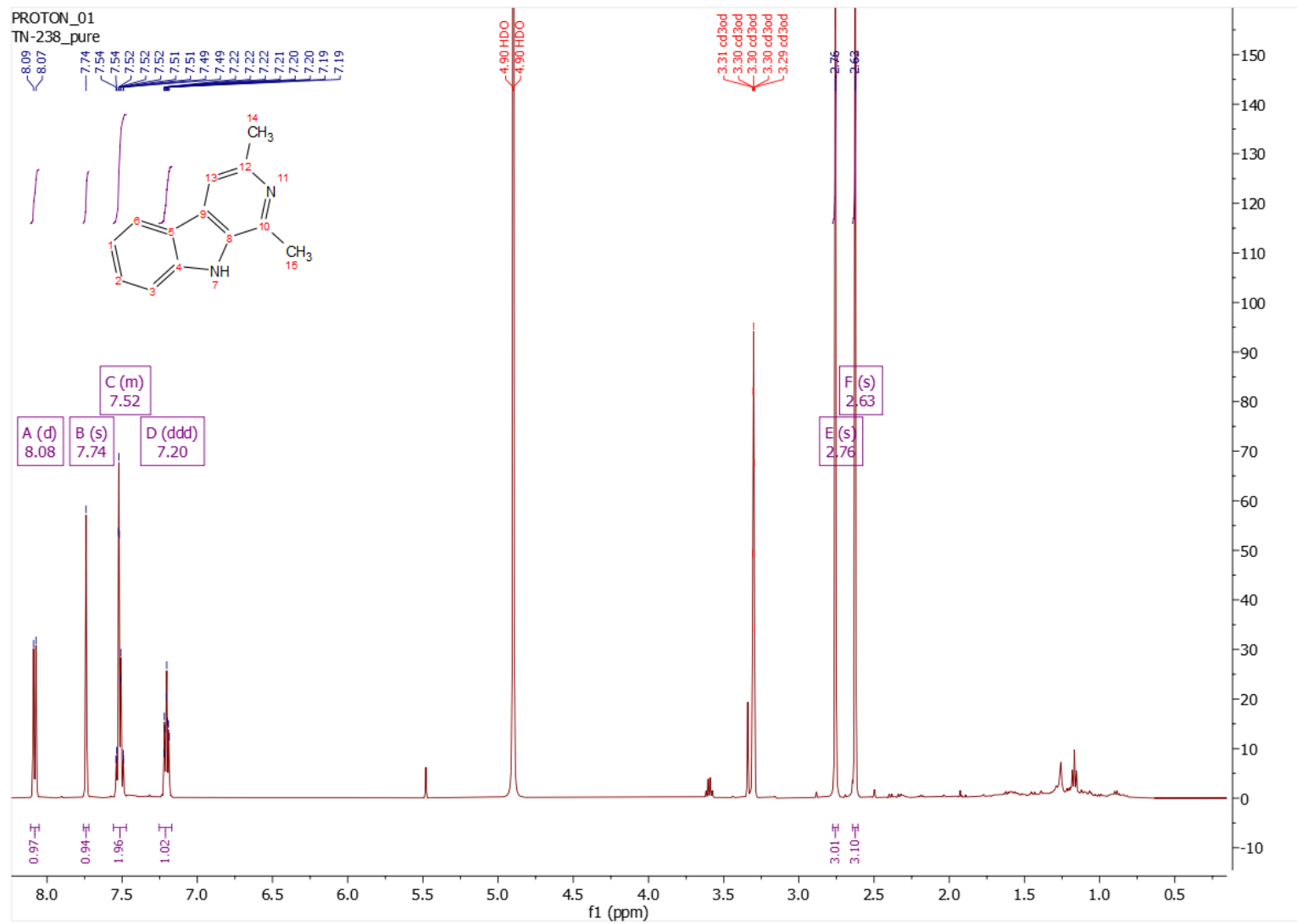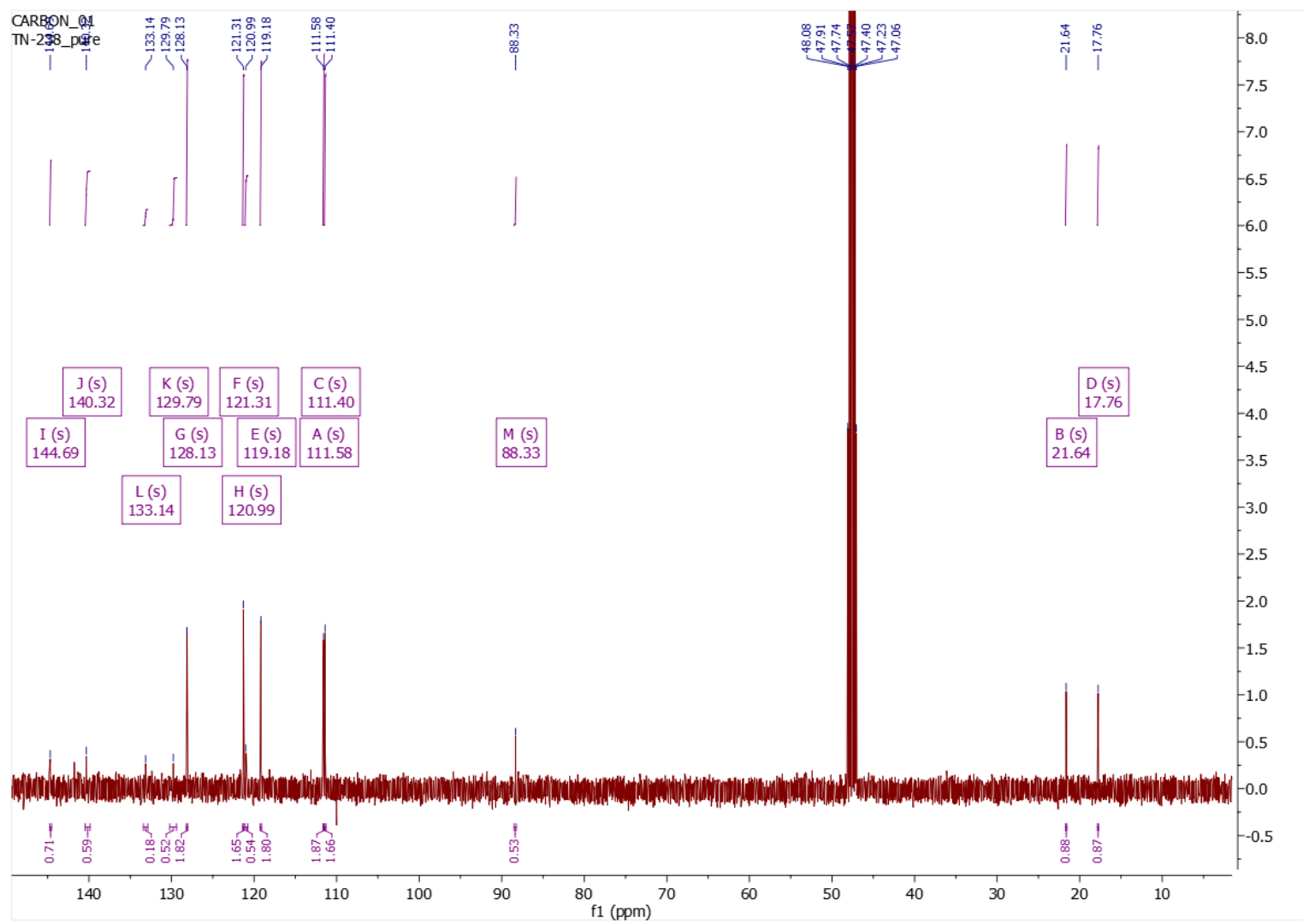
PROTON_01
TN-238_pure

A (d) 8.08
B (s) 7.74
C (m) 7.52
D (ddd) 7.20
E (s) 2.76
F (s) 2.63

126 methanol

Analyst

Date

PEService
20 March 2019 17:45

%T

2851

1968.17cm-1 1625.17cm-1

1845.37cm-1 1456.22cm-1

1335.86cm-1

646.47cm-1

1249.95cm-1

748.79cm-1

cm-1
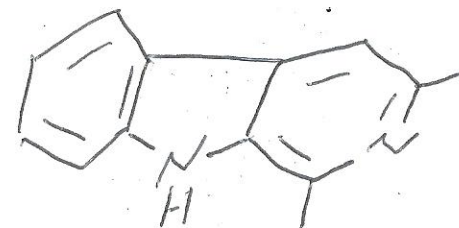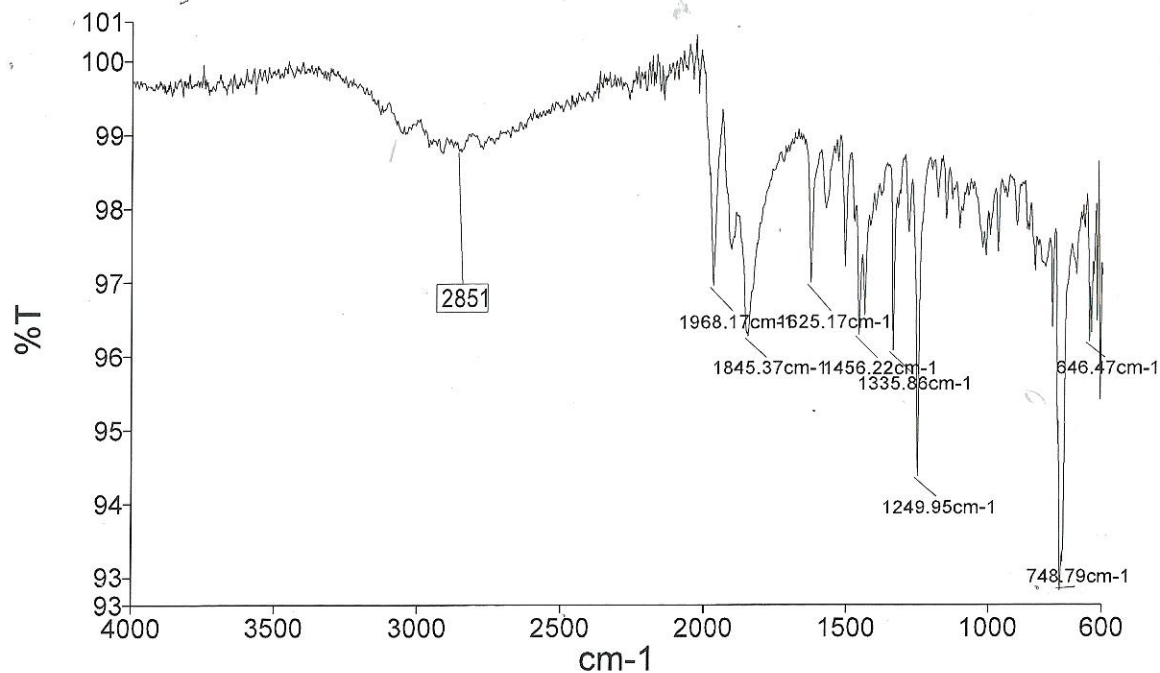
Sample Name	Description	Quality Checks
PEService_101 TN-238	Sample 101 By PEService Date Wednesday, March 20 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

7-methoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indole (**182**).
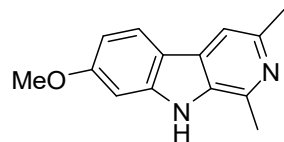
Chemical Formula: $C_{14}H_{14}N_2O$

Molecular Weight: 226.28 g/mol

500 methanol

PROTON_01
TN-222_PURE

Generic Display Report

(397)

Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 14 H 15 N 2 O 1	0.071	227.1179	0.58	-7.19	-1.64	8.50	ok	even

1-methyl-3-(trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole (**183**).
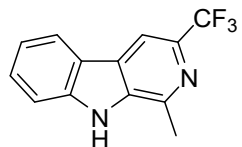
Chemical Formula: $C_{13}H_9F_3N_2$

Molecular Weight: 250.22 g/mol

600 methanol

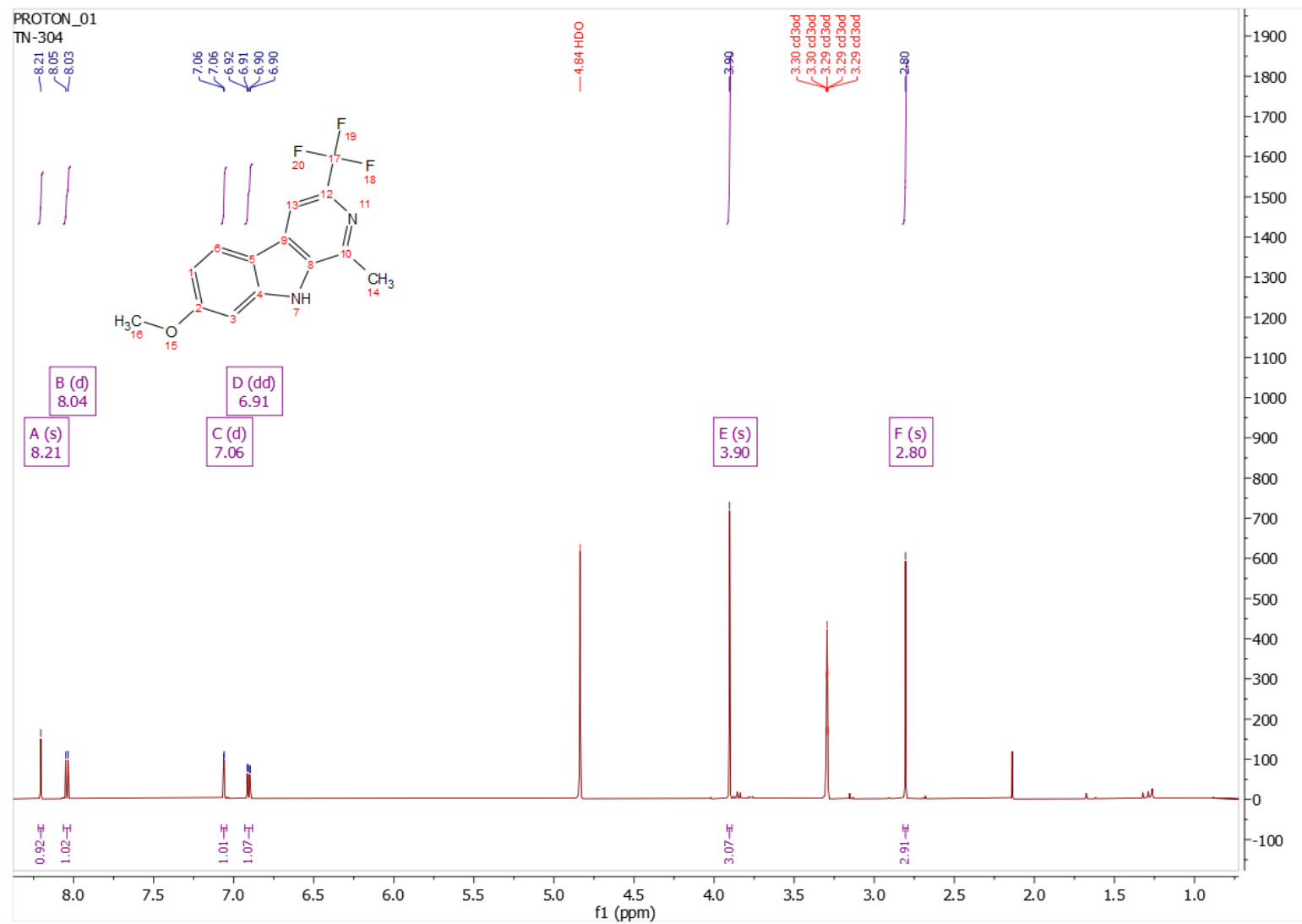PROTON_01
TN-299

8.34
8.21
8.21
8.20
8.20
8.20
7.63
7.63
7.62
7.62
7.61
7.59
7.59
7.58
7.58
7.57
7.57
7.31
7.31
7.30
7.30
7.29
7.28

4.84 HDO

3.32 cd3od
3.30 cd3od
3.30 cd3od
3.29 cd3od
3.29 cd3od
3.29 cd3od

2.85

B (dt)
8.21

E (ddd)
7.58

F (s)
8.34

D (dt)
7.62

A (s)
2.85

C (ddd)
7.30

0.92
1.00

0.94
1.07

1.07

3.01

f1 (ppm)

151 methanol

HSQC

gHSQCAD_01
TN-299

{2.85,18.15}
2.85,18.15

{3.29,47.67}

{8.35,110.43}
8.35,110.43

{7.62,111.80}
7.62,111.80

{8.21,121.38}
8.21,121.38

{7.30,120.21}
7.30,120.21

{7.59,128.61}
7.59,128.61

f1 (ppm)

f2 (ppm)

HMBC

gHMBCAD_01
TN-299

{7.31,111.86}

{8.35,121.24}
{7.31,121.24}

{8.22,128.51}
{7.64,121.24}

{8.35,135.77}
{2.85,135.77}

{7.59,141.40}
{2.85,143.04}

{8.22,141.40}
2.85,143.04

f1 (ppm)

f2 (ppm)

Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 13 H 10 F 3 N 2	0.086	251.0791	3.28	3.28	0.82	8.50	ok	even

Analyst

Date

PEService

20 March 2019 18:01

%T

3157.1

1634.7

1459.2

1512.2

1577.6

779.38cm-1

937.02cm-1

648.65cm-1

893.31cm-1

1169.10cm-1

712.78cm-1

1361.58cm-1

1094.00cm-1

1271.55cm-1

1116.14cm-1

742.80cm-1

cm-1
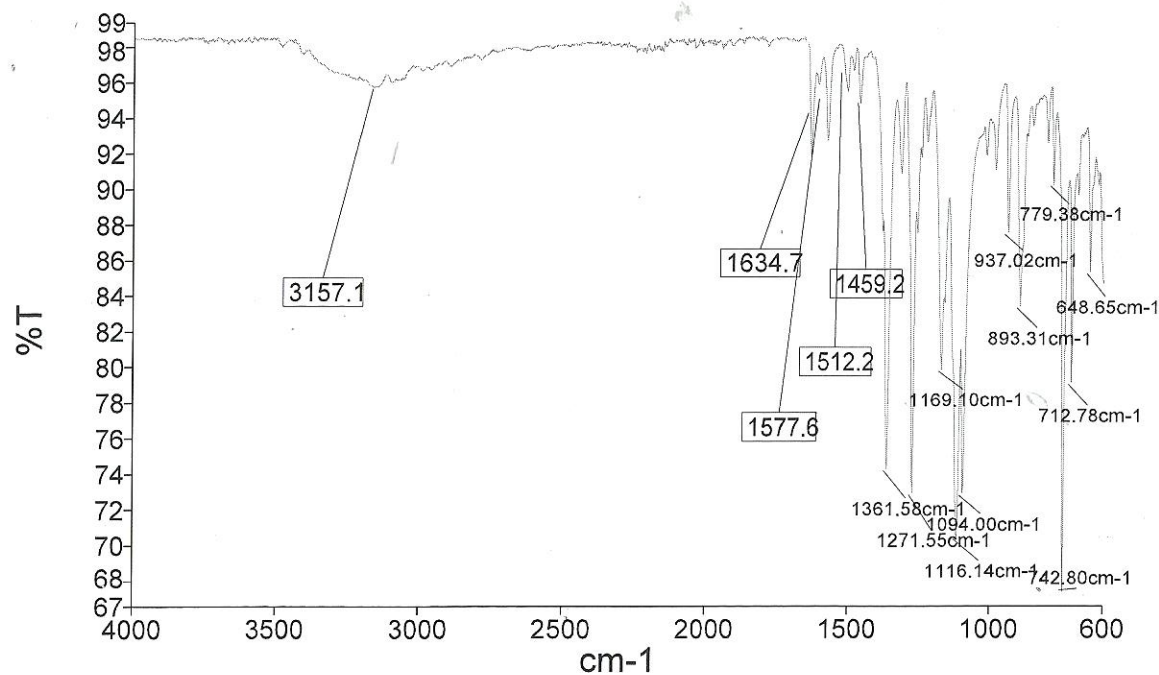
Sample Name	Description	Quality Checks
PEService 104 TN-299	Sample 104 By PEService Date Wednesday, March 20 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

7-methoxy-1-methyl-3-(trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole (**193**).
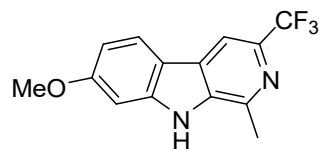
Chemical Formula: $C_{14}H_{11}F_3N_2O$

Molecular Weight: 280.25 g/mol

600 methanol

PROTON_01
TN-304

A (s) 8.21
B (d) 8.04
C (d) 7.06
D (dd) 6.91
E (s) 3.90
F (s) 2.80

151 methanol

HSQC

gHSQCAD_01
TN-304

HMBC

gHMBCAD_01
TN-304
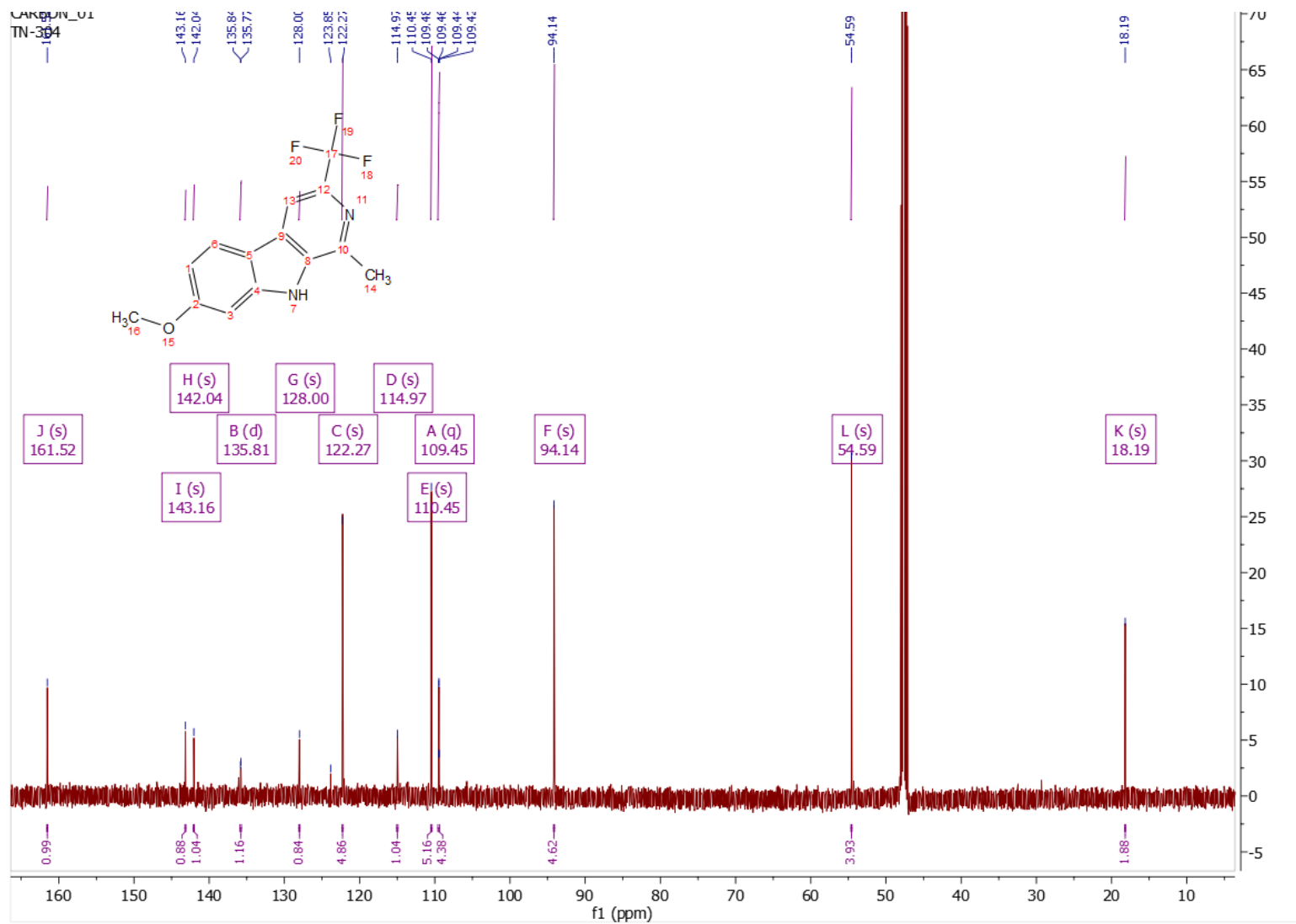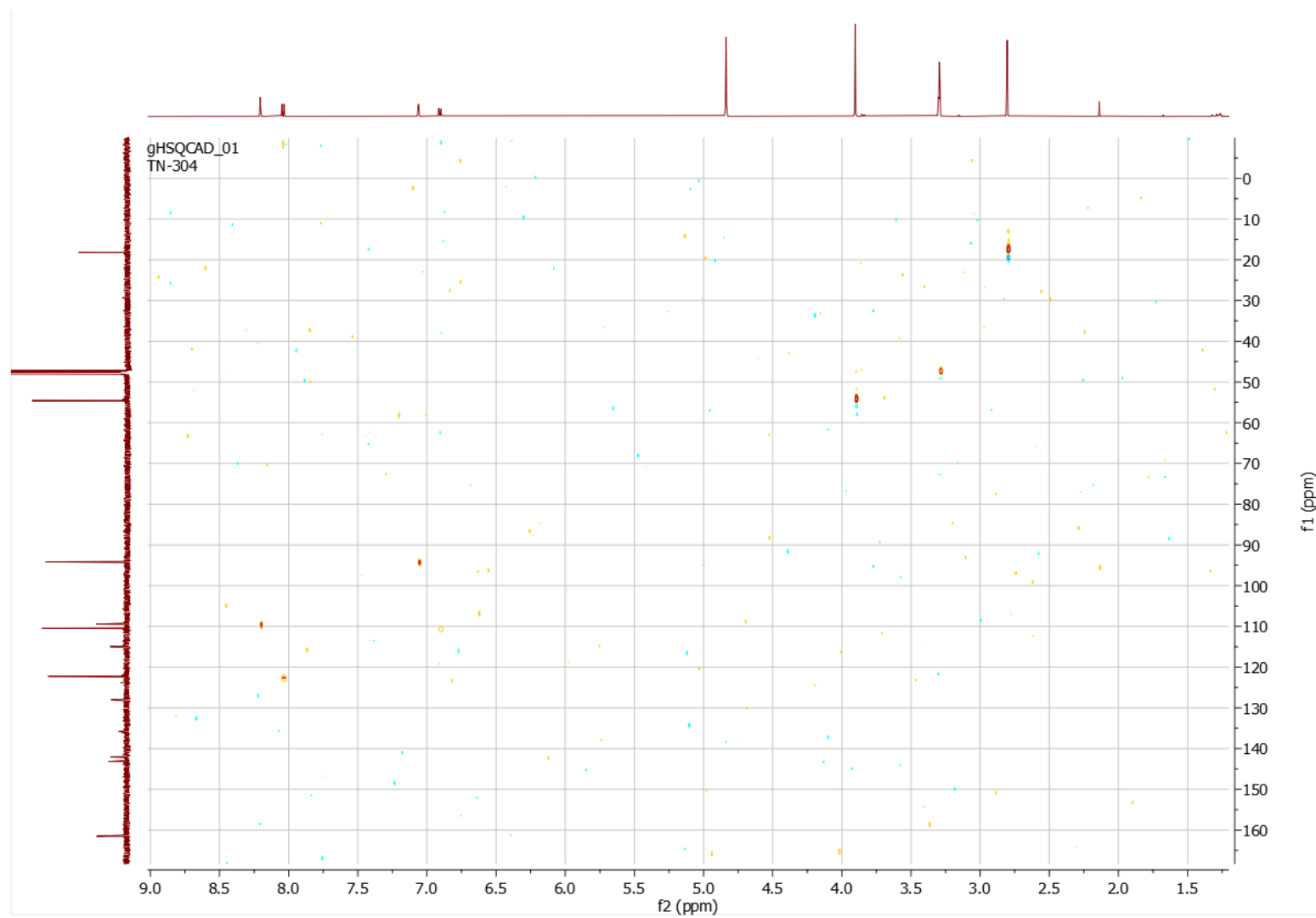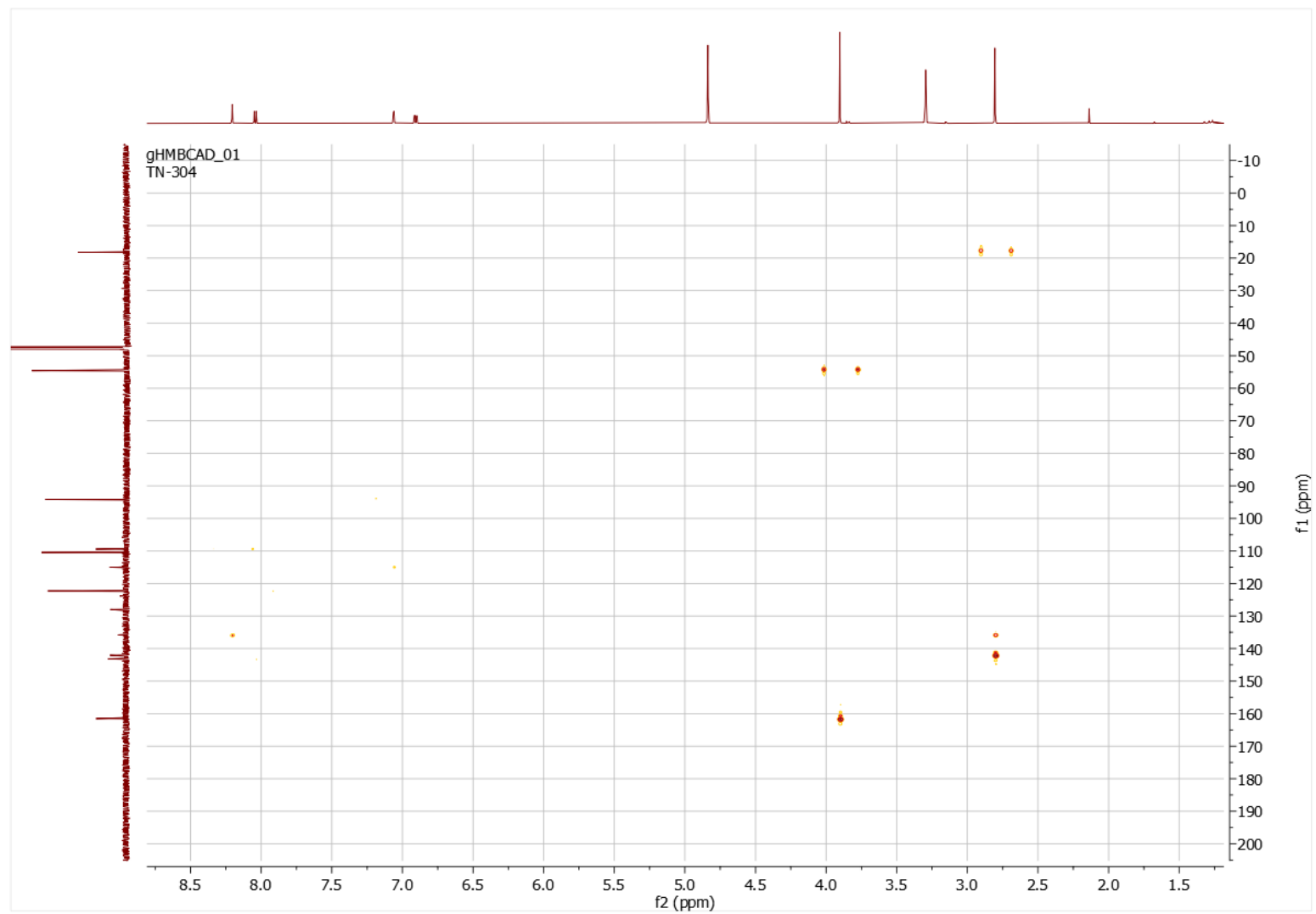
Analysis Info

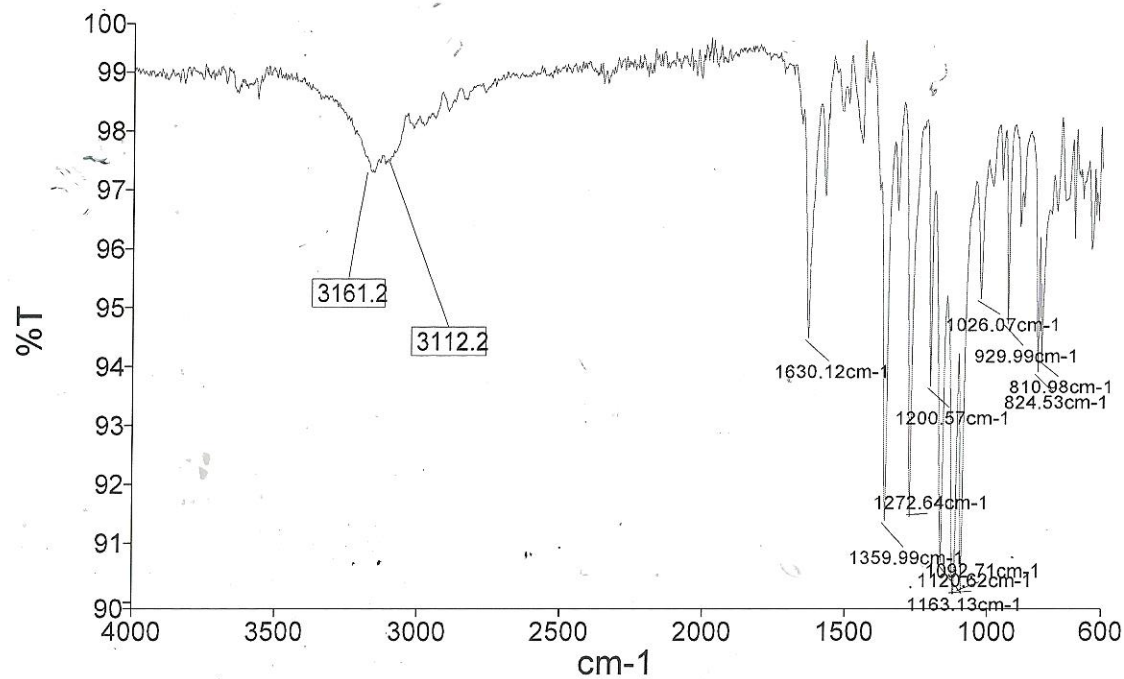|	
Analysis Name	D:\Data\Alinanopos\TYLER_10930_000001.d
Method	pos20090608esi
Sample Name	POS ESI TN-304
Comment	

Acquisition Date   24/09/2019 15:10:07

Operator	Administrator
Instrument	apex-III

------ +MS
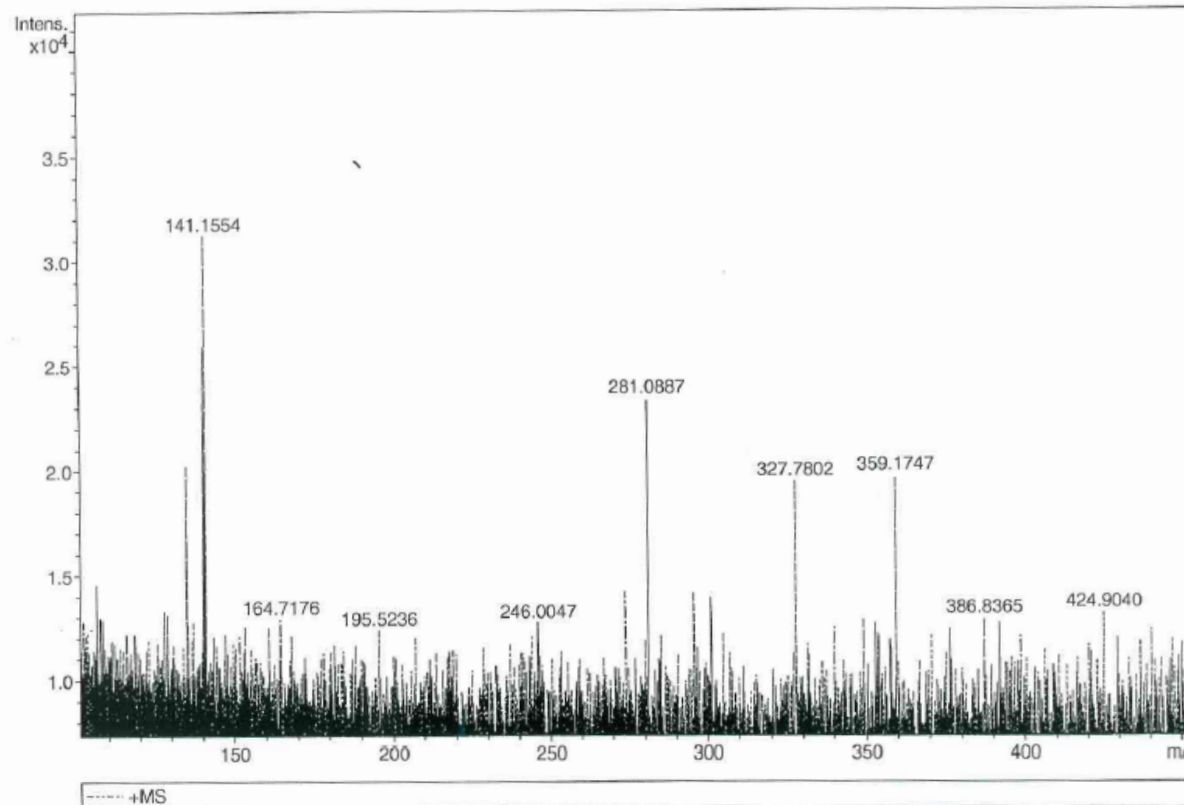
Sum Formula	Sigma	m/z	Err [ppm]	Mean Err [ppm]	Err [mDa]	rdb	N Rule	e⁻
C 14 H 12 F 3 N 2 O 1	0.266	281.0896	3.44	-188.25	-53.04	8.50	ok	even

Analyst   PEService
Date   20 March 2019 17:29
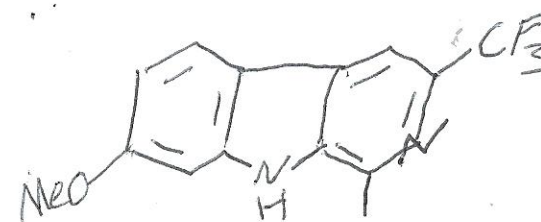
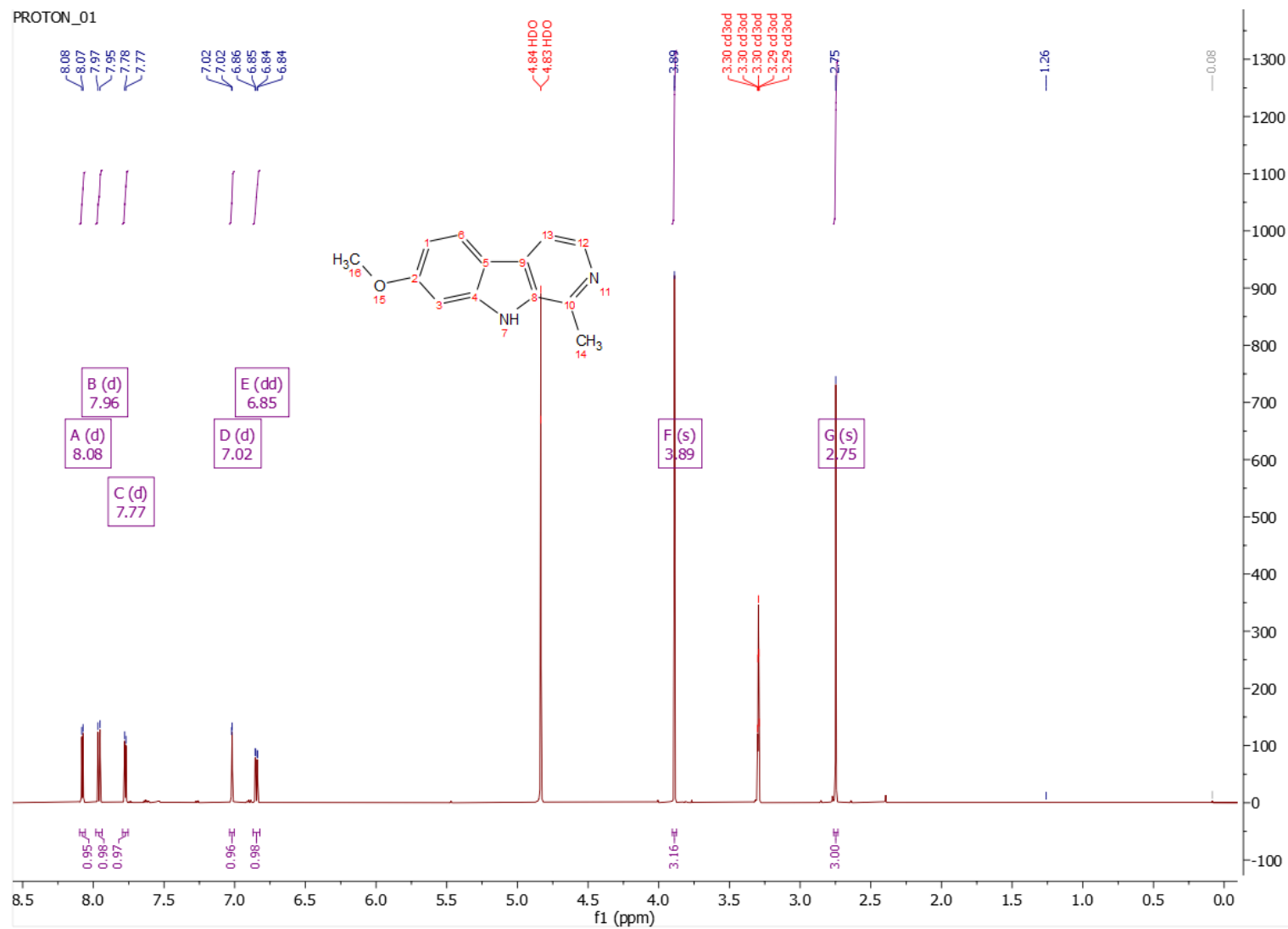| Sample Name	Description	Quality Checks
PEService 98 TN-304	Sample 098 By PEService Date Wednesday, March 20 2019	The Quality Checks give rise to a Weak Bands warning for the sample.

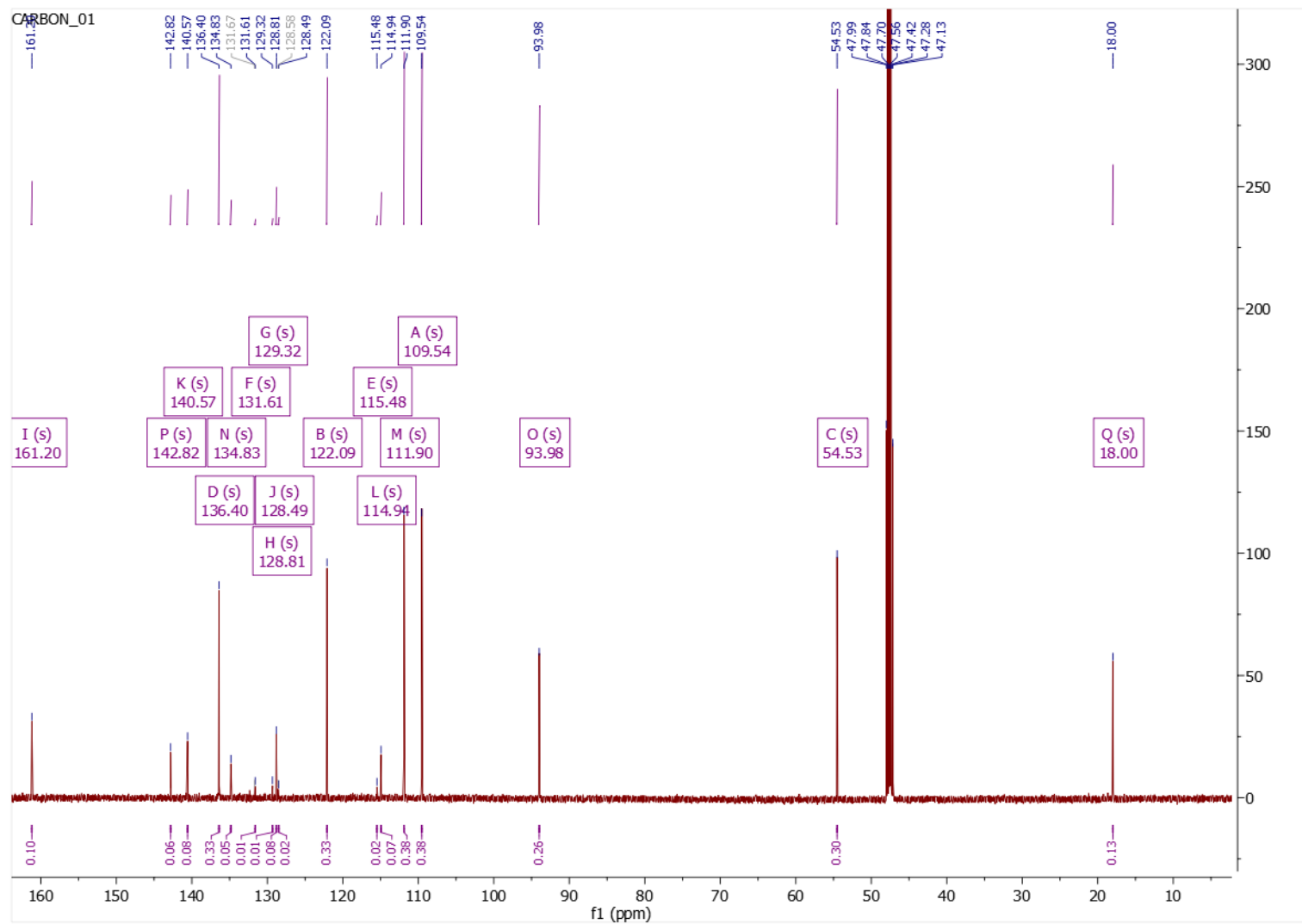7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole (**80**).
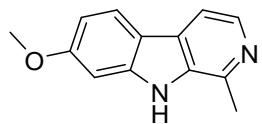
Chemical Formula: $C_{13}H_{12}N_2O$
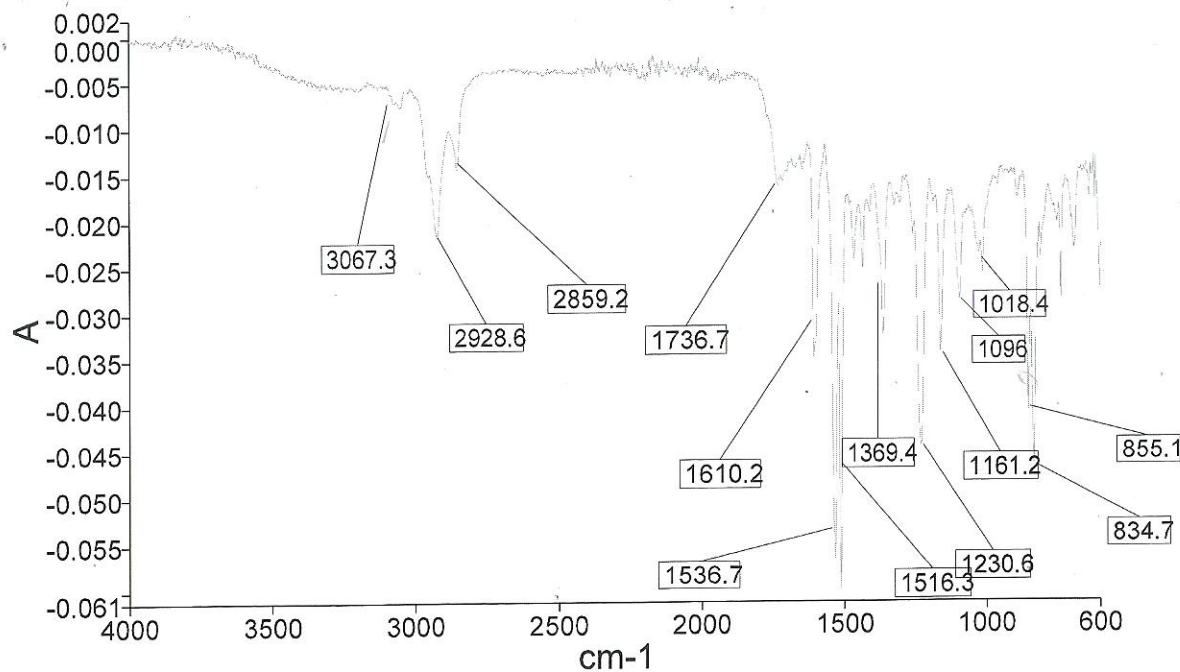
Molecular Weight: 212.25 g/mol

600 methanol

PROTON_01

151 methanol

Analyst

Date

PEService
20 March 2019 17:15

Harmine (circled)

3067.3

2859.2

2928.6

1736.7

1018.4

1096

1610.2

1369.4

1161.2

855.1

1536.7

1516.3

1230.6

834.7

cm-1

Sample Name	Description	Quality Checks
PEService 97 (TN-488)	Sample 097 By PEService Date Wednesday, March 20 2019	The Quality Checks give rise to multiple warnings for the sample.

142
394
382
410
396
397
408
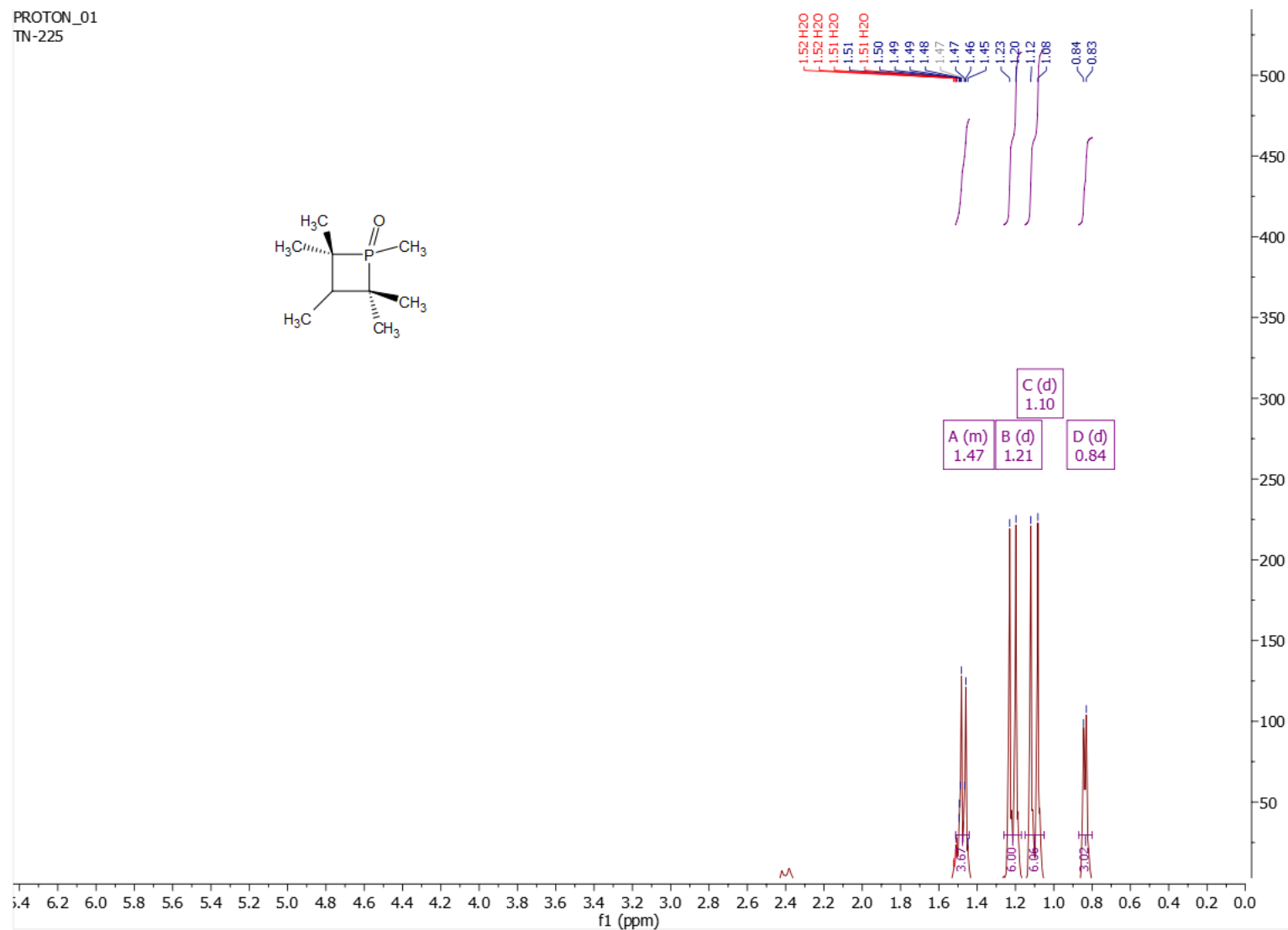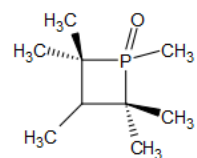
1,2,2,3,4,4-hexamethylphosphetane-1-oxide (**185**).
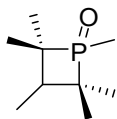
Chemical Formula: $C_9H_{19}OP$

Molecular Weight: 174.22 g/mol

500 cdcl3

PROTON_01
TN-225

A (m) 1.47
B (d) 1.21
C (d) 1.10
D (d) 0.84

f1 (ppm)

126 cdcl3

CARBON_01
TN-225

B (d)
45.45

D (d)
42.62

A (d)
24.69

F (d)
17.42

E (d)
6.95

C (d)
9.84