Synthesis of 8-hydroxyphenanthridines employing Intramolecular Diels-Alder of Furan as the key step

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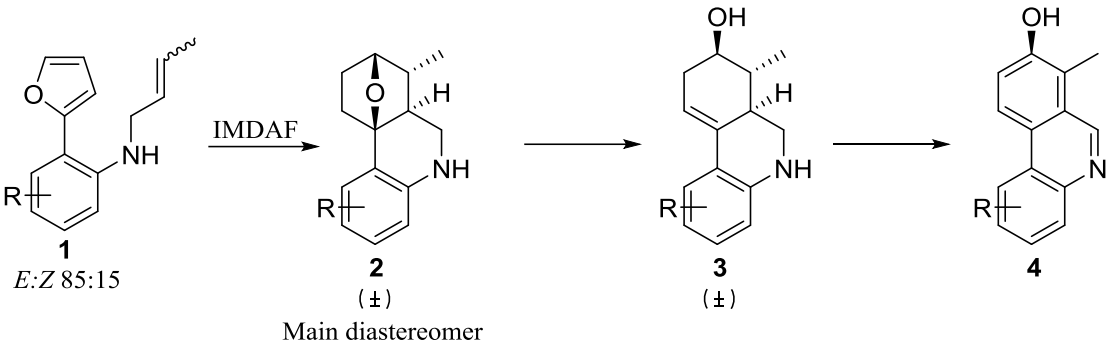
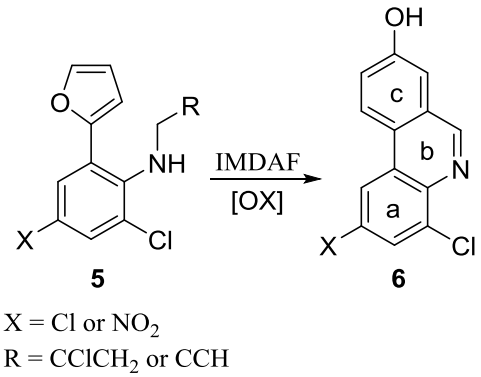
Abstract

A synthetic strategy towards 8-hydroxyphenanthridines (**6**) was previously developed in our group, where intramolecular Diels-Alder of furan (IMDAF) was the key step (Scheme 1).[1] This was a continuation of a previous work as well.



Scheme 1. Previous strategy towards 8-hydroxyphenanthridine.

This strategy turned out to be not very efficient and a new and more robust strategy was planned out. The new strategy doesn't involve diastereomers and is focused on obtaining 8-hydroxyphenanthridines in high yields, which later on can be explored for a fully functionalized ring c.



Scheme 2. The new strategy towards high yielding 8-hydroxyphenanthridine IMDAF.

(Note: Numbering of compounds used in this abstract is not the same as the numbering in the report.)

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Abbreviations and symbols

Ac	acetyl
C	carbon
^{13}C	carbon spectrum (NMR)
°C	degree Celsius
Calcd.	Calculated
COSY	correlation spectroscopy (NMR)
d	doublet (NMR)
δ	chemical shift (NMR)
dd	doublet of doublets (NMR)
DDQ	2,4-dichloro-5,6-dicyano-1,4-bezoquinone
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ESI	electron spray ionization (MS)
eq.	equivalent(s)
Et	ethyl
et al.	*et alii*
EtOAc	ethyl acetate
EtOH	ethanol
FtsZ	filamenting temperature-sensitive mutant Z
GNB	Gram-negative bacteria
GPB	Gram-positive bacteria
h	hour(s)
^{1}H	proton spectrum (NMR)
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation experiment
HRSM	high resolution mass spectra
HSQC	heteronuclear single quantum coherence spectroscopy (NMR)
hν	irradiation
Hz	hertz
IMDAF	intramolecular Diels-Alder reaction of furan
J	coupling constant (NMR)

L	ligand
LA	lewis acid
M	molar
m	multiplet (NMR)
Me	methyl
MeCN	acetonitrile
MeI	iodomethane
MHz	megahertz
MIC	minimum inhibitory concentration
Min	Minutes
mp	melting point
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	mass spectroscopy
MW	microwave
n.a.	not available
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear overhauser effect spectroscopy (NMR)
o	ortho
OAc	acetate
OTf	triflate
Ox	oxidation
p	para
R	substituent
r.t.	room temperature
σ	sigma
SAR	structure activity relationship
t	triplet (NMR)
TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
THF	tetrahydrofuran
UV	ultraviolet
WHO	world health organization

1. Introduction

Previously our group has synthesized different phenanthridines employing intramolecular Diels-Alder reaction of furans (IMDAF)[1-3] This project intended to explore the synthesis of 8-hydroxyphenanthridines which was only synthesized in low yields previously. The phenanthridine compound class is an interesting one due to a broad spectrum of biological activity. Which makes some of the compounds excellent for a potential use in medicine and drugs. Synthesis and chemistry of 8-hydroxyphenanthridines and their intermediates will be discussed herein.

The first sections describes the motivation for synthesis of different phenanthridine derivatives, with a general description of the known biological activities for several phenanthridine containing alkaloids. The section also describes an urgent need for novel antibacterial agents and is followed by a section describing some strategies employed towards synthesizing phenanthridine derivatives. A section describing common chemistry, including Suzuki-Miyaura, intermolecular Diels-Alder and IMDAF, and is followed by a description of microwave synthesis and the strategy employed towards synthesis in our group. Chapter 2 contains in-depth details regarding synthesis of individual compounds, discussion, observations and results encountered during this project. A prospect of the future with possible new synthesis opportunities based on the work of this project and a conclusion of what has been achieved follows. The report is finished of by experimental details, appendix and the reference list.

1.1. Motivation for the synthesis of phenanthridine derivatives

This section describes the naturally occurring phenanthridine alkaloids, their known biological activity and their current and potential use in medicine.

1.1.1. Naturally occurring phenanthridines

Phenanthridines have a backbone structure as shown in Figure . The naturally occurring ones are classified as alkaloids. Alkaloids are nitrogen containing secondary plant metabolites, commonly containing heterocyclic structures. Naturally occurring phenanthridines are well known, extracts from quaternary benzo[C]phenanthridine alkaloid (QBA) containing plants have previously been used in folk medicine.[4] QBAs have been extensively studied and are of great medicinal interest.[4-5]

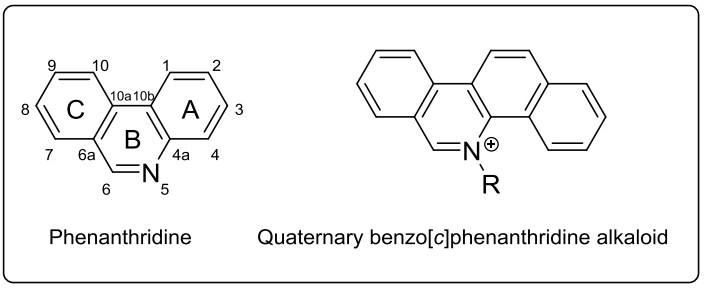


Figure 1.1. The phenanthridine backbone with numbering of the ring-system and a general QBA compound.

Amongst several of the plant families known to produce phenanthridine alkaloids, are the Amaryllidaceae, Caprifoliaceae, Fumariacea, Papaveraceae and Rutaceae families.[6-7]

1.1.2. Biological activity and current use in medicine

Certain phenanthridine alkaloids displays interesting biological activities, several of these compounds are displayed in Figure 1.2. Different compounds in Figure 1.2 exhibit activity towards bacteria,[8] cancer cell lines,[9-10] malaria,[11] mycobacteria,[12] as well as anti-inflammatory activity[13] and acetylcholinesterase inhibition.[14]

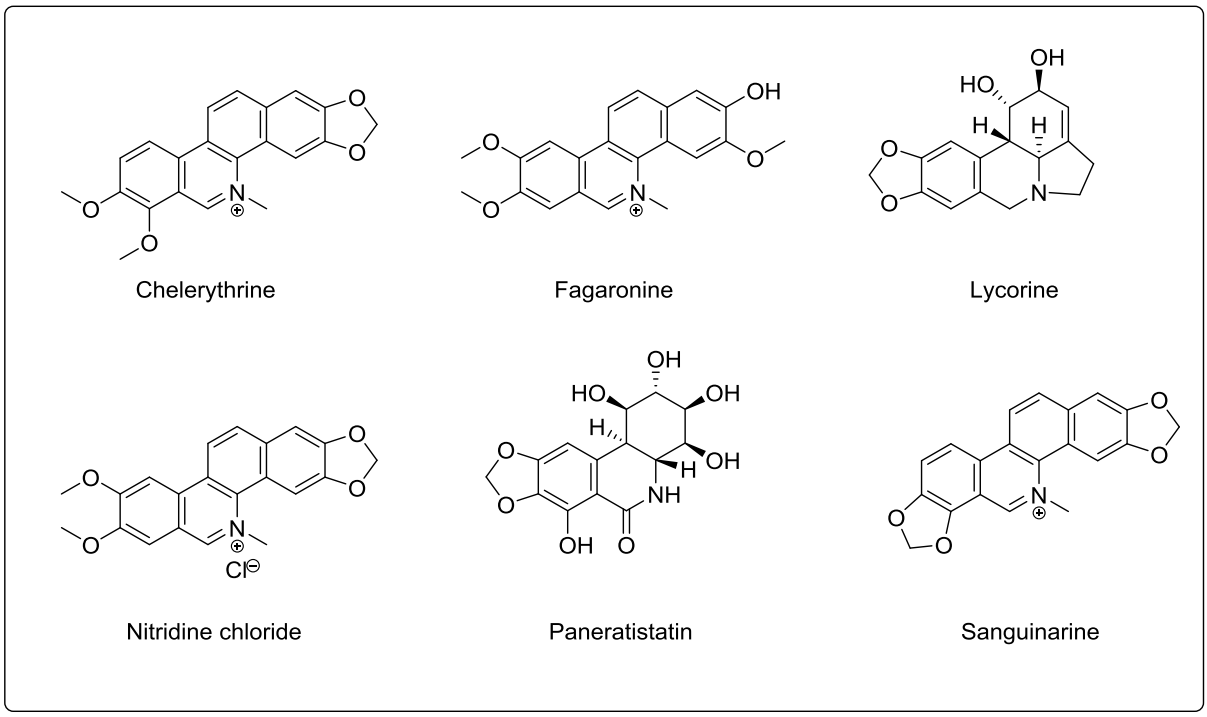


Figure 1.2. Named phenanthridine alkaloids, which have been studied for their biological activity.[8-15]

Disregarding traditional medicine, several naturally occurring and synthetic phenanthridine containing compounds have been, or is currently marketed as drugs. Compounds displayed in Figure 1.3 are employed for various reasons. Ethidium bromide, propidium iodide and marcarpine, are employed as DNA-binding fluorescent tags in biochemistry labs, and is a significant part of multiparameter flow cytometry diagnostic methods.[4] Dimidium bromide, ethium bromide and isometamidium chloride have been employed as trypanocides for cattle, especially in Kenya.[16] Chelerythrine and sanguinarine exhibit anti-plaque properties, and are therefore employed in dental care applications.[17] In Russia, a mixture of these two QBAs is marketed as an anti-fungal and anti-inflammatory drug.[18-19]

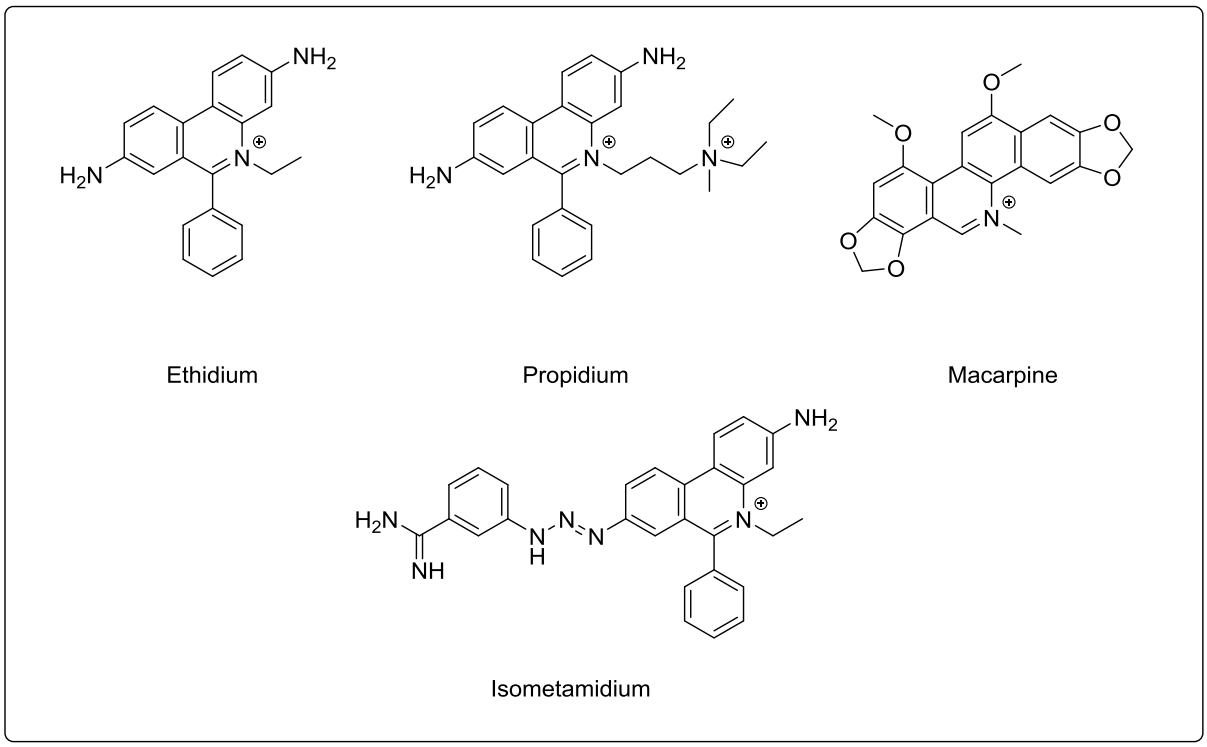


Figure 1.3. Several phenanthridine containing compounds employed for their biological activity in medicine and laboratories.

1.1.3. Future prospects for phenanthridine containing drugs, countering drug resistance

In 2014 the World Health Organization (WHO) published a report on the growing public health threat, stemming from antimicrobial resistance, describing a post-antibiotic era, in which common infections can lead to death. The report is extensive and covers data from 114 countries and includes observations on bacterial infections, tuberculosis, HIV and malaria.[20] Methicillin-resistant Staphylococcus aureus (MRSA) is becoming a very serious threat, and mortality rates various places in the world rises. Vancomycin (Figure 1.4) is one of the current employed drugs against MRSA infections. There are however serious side effects, reports of treatment failures, and an emergence of vancomycin-resistant MRSA. This leads to an urgent requirement for alternative anti-MRSA therapies.[21]

As with the anit-MRSA therapies, there is a scientific consensus that new and effective antibacterial agents are gravely needed.[21-22] Between 1940 and 1970, most of the antibacterial agents currently on the market were discovered, through extensive screening of natural

products. Drug resistance has been observed for all of the classes discovered during that time period.[23]

The drug resistance problem has mostly been restricted to Gram-poitive bacteria (GPB), but drug resistant Gram-negative bacteria (GNB) are emerging. MRSA and enterococci are two examples of drug resistant GPB. Escherichia coli (E-coli) and Klebsiella pneumoniae are two examples of emerging drug resistant GNB.[22]

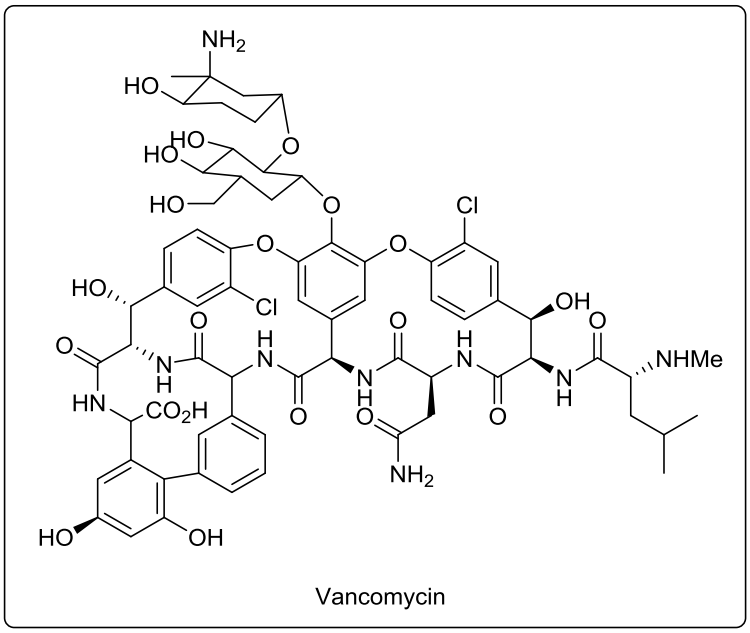


Figure 1.4. Structure of Vancomycin, a drug used more and more frequently against MRSA infections.[21]

The measurement for antibacterial activity of a compound is through its minimum inhibitory concentration (MIC). It is defined as the lowest concentration of an antimicrobial that inhibits the visible growth of a microorganism after overnight incubation. Minimum bactericidal concentration (MBC) is defined as the lowest concentration of antimicrobial that will prevent the growth of an organism, after subculture to antibiotic-free media. MICs are used by laboratories as a diagnostic tool to confirm resistance, but also as a research tool to determine the in vitro activity of new antimicrobials.[24]

MIC values have been measured for several naphtyridines, compounds **14-17** in Figure 1.5. These were synthesized by Chrzastek et al., and their respective MIC values was measured to between 0.1-1.2 µg/mL for Staphylococcus aureus, similar measurements were observed against other GPB. Measurements against GNB were also conducted, and their values ranged

between 0.2-12 µg/mL.[25] The MIC values are comparable to those of vancomycin already mentioned.[26]

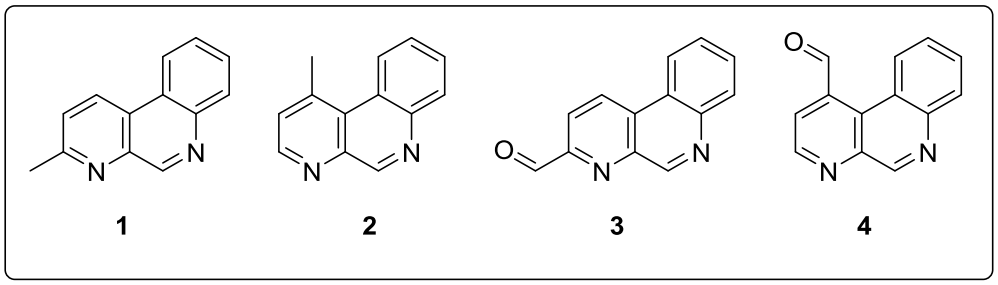


Figure 1.5. Naphtyridines showing significant antibacterial activity. Synthesized by Chrzastek *et al.*

QBAs with single digit µg/mL MIC values towards GPBs that are drug-sensitive and drug-resistant were synthesized by Parhi *et al*. in 2012. The observed activity concludes that the synthesized QBAs were generally more potent than currently available antibiotics, especially towards the drug-resistant bacteria, but less towards drug-sensitive bacteria.[27]

The already mentioned sanguinarine has been found to utilize a different mechanism of action than available antibacterial agents. This mechanism works by inhibiting a protein named FtsZ, which is a key protein involved in prokaryotic cell division. The inhibition of cytokinesis was observed for both GPB and GNB. It is theorized that developing resistance to FtsZ targeting drugs is improbable, if not impossible, by altering the FtsZ itself. This is because the FtsZ is an essential protein in almost all prokaryotes, along with the observation that FtsZ is conserved during treatment. The MIC value (25 µg/mL) is not comparable to antibacterial agents on the market and sanguinarine is suspected to have harmful adverse effects in mammals.[8, 28]

As mentioned in Section 1.1.2, phenanthridine alkaloids displays a range of biological activities, and not only antibacterial. A traditional malaria treatment employs nitidine chloride (Figure 1.2), this alkaloid is considered a lead molecule in the anti-malaria drug development.[29] Chelerythrine chloride (Figure 1.2) has a possible use in the treatment of thrombosis, as it exhibits antiplatelet properties.[30]

Certain phenanthridines are exhibiting anti-tumor activity and non-toxicity towards mammalian cells.[9, 31-32] Another type of phenanthridine called “phenanthriplatin”, which is a platinum-bound phenanthridine displayed in Figure 1.6.

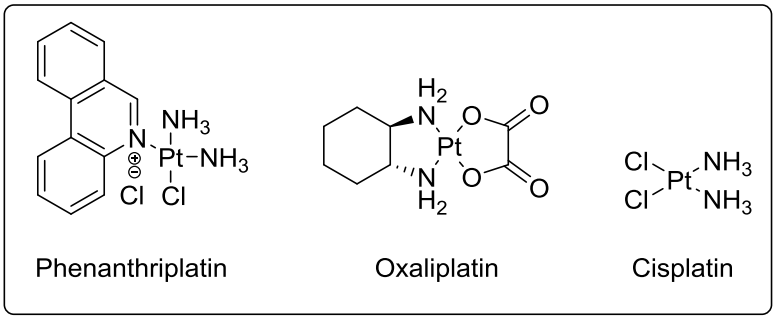


Figure 1.6. Platinum-based anti-tumor drugs currently in use, whereas compound 17 is a phenanthridine.

Phenanthriplatin has been screened for its anti-tumor activity, and it is reported to exhibit significantly higher activity than cisplatin and oxaliplatin, which are two drugs approved by the Food and drug Administraion.[33] A very potent compound against mycobacteria is displayed in Figure 1.7, this class of compounds (benzo[*j*]phenanthridines) were synthesized by De Kimpe et al. These compounds are not yet suited for medical use, as a high toxicity and unacceptable selectivity renders them dangerous to use, therefore synthesis of different derivatives and similar compounds has been encouraged by the author.[34]

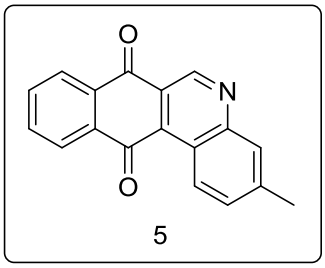


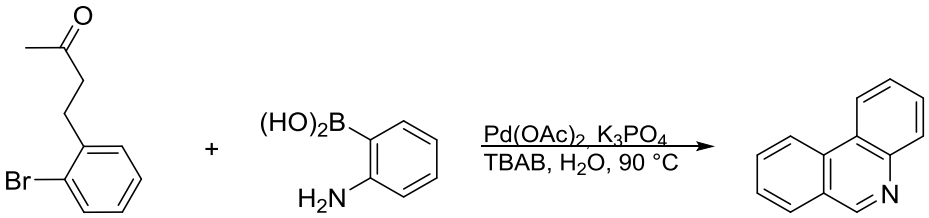
Figure 1.7. 3-methylbenzo[j]phenanthridine-7,12-dione, a phenanthridine exhibiting very potent anti-mycobacteria activity.[34]

When presented with the reports given above, it is evident that some phenanthridine containing compounds have a huge potential in drug based medical treatment. The finish line is not here yet, and a tremendous amount of work is required to enhance the effectivity and properties of these compounds. Properties that needs enhancement is related to absorption, distribution, metabolism, excretion and toxicity. When all of these properties are enhanced in a compound, it will be suitable as a drug. One way to alter the phenanthridines properties is introducing different functional groups, this is done by screening many derivatives, and will lead to understanding the structure-activity-relationship (SAR).[35] As the knowledge about the SAR grows, it will be easier to determine what effect different functional groups in different positions will have, and the search will become narrower. When starting a screening like this, a flexible and relatively simple synthesis route to phenanthridines is desired.

1.2. Current and previous strategies for synthesis of phenanthridines in other groups

This section describes published strategies employed by other research groups towards the synthesis of phenanthridines.

Synthesis of phenanthridine, as published by Gosh et al. at the department of chemistry at the Indian Institute of Technology in 2013.[36] It is a palladium-catalyzed reaction, which was achieved by treating 2-aminophenylboronic acid with a β-(2-bromoaryl)-α,β-unsaturated carbonyl compound in the presence of $Pd(OAc)_2$ catalyst, K_3PO_4 base, and TBAB (tetrabutylammonium bromide) in water at 90°C and atmospheric pressure(Scheme 1.1).

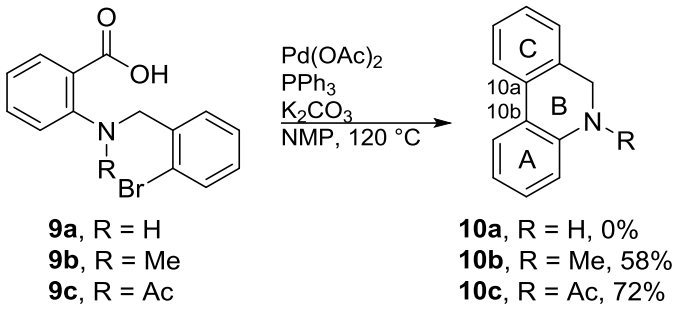


6 **7** **8**

Scheme 1.1. Palladium-catalyzed synthesis of phenanthridine.

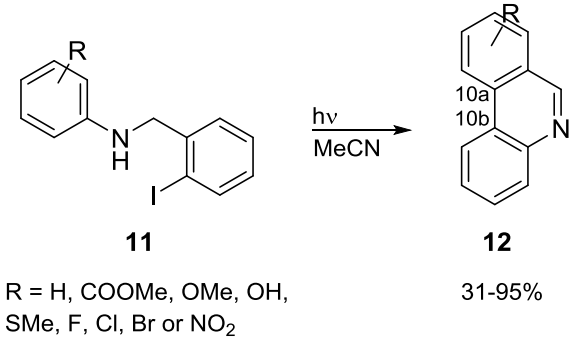
The method was discovered by screening through various catalysts, bases and two times with PPh_3 as a ligand. These reaction conditions are considered mild and reagents are readily available.

Bond formation between C10a-C10b as the key step is considered the most common synthesis strategy of phenanthridines in the literature. [1, 34, 37] This is often achieved through palladium-catalyzed carbon-carbon bond formation. Shen et al. employed this strategy to synthesize *N*-substituted phenanthridines from substituted *N*-(o-bromobenzyl)anilines (Scheme 1.2).[37]



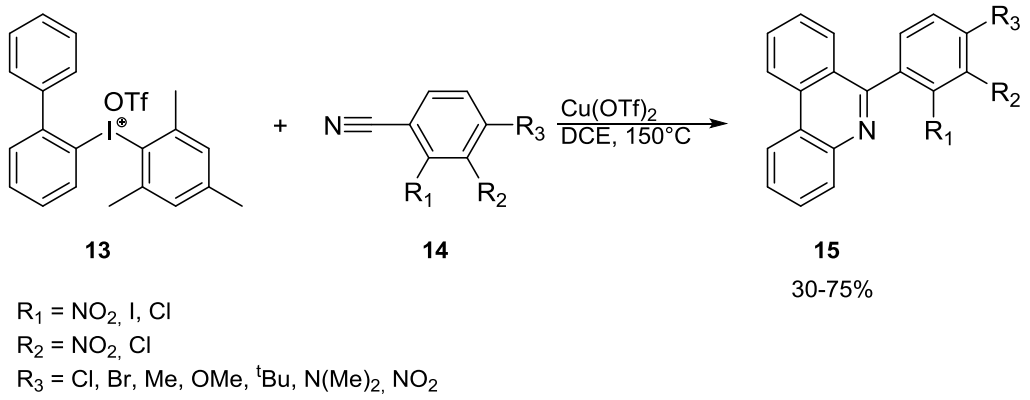
Scheme 1.2. Palladium-catalyzed synthesis of phenanthridines by formation of the C10a-C10b bond.[37]

Published by Linsenmeier et al., bond formation between C10a-C10b is achievable through radical reactions by UV-irradiation(Scheme 1.3).[38]



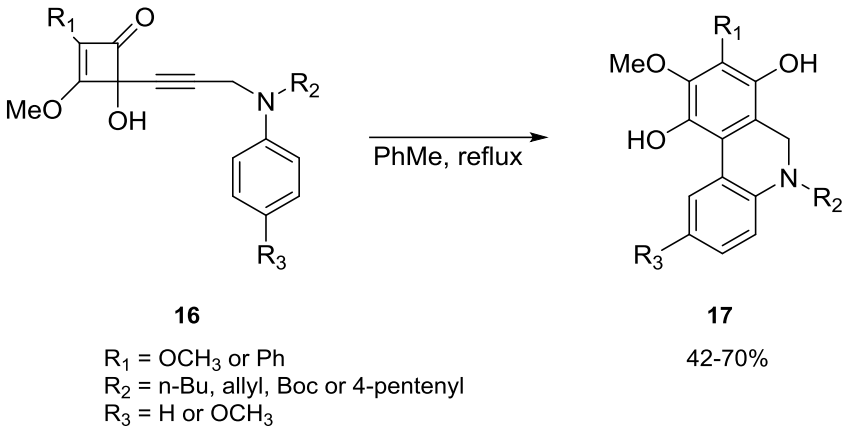
Scheme 1.3. Photochemically initiated radical reaction towards bond formation between C10a-C10b.[38]

Li et al. synthesized phenanthridine derivatives via cascade annulation of diaryliodonium salts and nitriles with varying results (Scheme 1.4).[39]



Scheme 1.4. Synthesis of phenanthridines via cascade annulation of nitriles, 15 derivatives in total.

Finally, Moore *et al*. synthesized phenanthridines through the means of ring expansion reactions, reportedly through radical or transition-metal catalyzed mechanism(Scheme 1.5).[40-41]



16

R_1 = OCH_3 or Ph
R_2 = n-Bu, allyl, Boc or 4-pentenyl
R_3 = H or OCH_3

17

42-70%

Scheme 1.5. Synthesis of phenanthridine derivatives by means of ring expansion.[41]

This strategy is not well explored, while it produces highly substituted phenanthridine derivatives, it often employs complex starting materials.

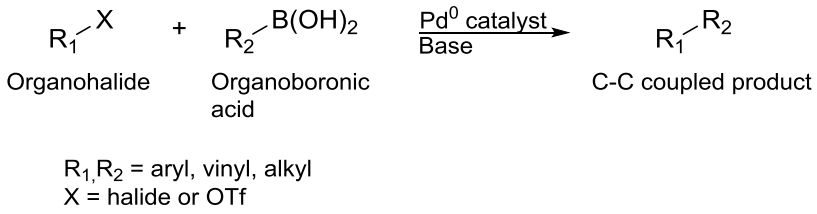
1.3. Chemistry of named reactions

This section describes the common chemistry named reactions employed during the synthesis of phenanthridines in our group. To introduce a furyl group, a Suzuki-Miyuara coupling reaction was employed as described in Section 1.3.1. Common chemistry of the intermolecular Diels-Alder reaction is described in Section 1.3.2. The fusing of the phenanthridine ring system was achieved by employing an intramolecular Diels-Alder of furan (IMDAF) reaction as described in Section 1.3.3.

1.3.1. The Suzuki-Miyaura reaction

First reported in 1979, this reaction between organoboranes and organohalides, employing palladium as a catalyst, gave new ways to form carbon carbon-bonds(Scheme 1.6).[42] It is commonly referred to as the Suzuki coupling reaction. The discovery and expansion of this synthetic method lead to Akira Suzuki receiving the Nobel Prize in chemistry in 2010. With its high flexibility, the Suzuki-Miyaura reaction is now one of the most important cross-coupling reactions for carbon-carbon bond formation.[43] The scope of the reaction is far-reaching,[44] employs mild reaction conditions, and exhibits tolerance towards most functional

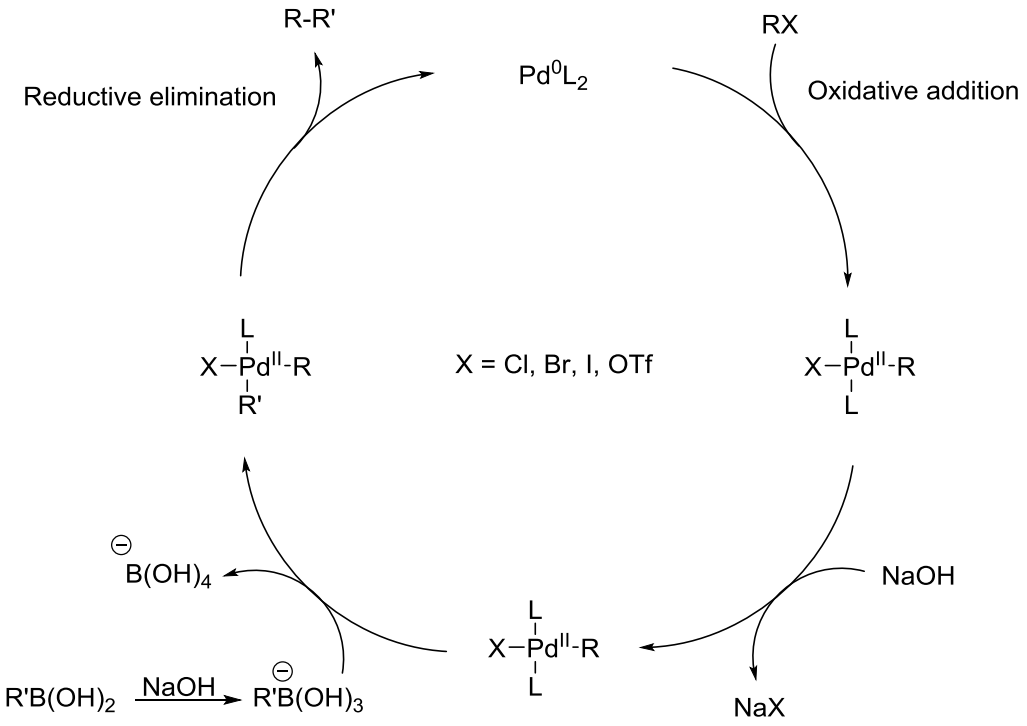
groups, which has made the Suzuki coupling a very common choice when synthesizing drugs and natural products.[45]



Scheme 1.6. A general example of carbon-carbon bond formation through a Suzuki-Miyaura reaction between an organohalide and an organoboronic acid.

A large amount of organoboronic acids are commercially available. Organoboranes have been shown to be non-toxic,[46] easily removed from reaction products, and environmentally friendly.[47] With a catalyst loading observed as low as 0.001 mol%,[48] the reaction is attractive towards industrial synthesis.[49]

The generally accepted mechanism of reaction for which the Suzuki-Miyaura coupling reaction follows, is displayed in Scheme 1.7.[44, 50] Activation of the catalyst is not displayed in the scheme, but this is commonly achieved by *in situ* generation of the active Pd^0-complex from a less unstable source such as $Pd(OAc)_2$.



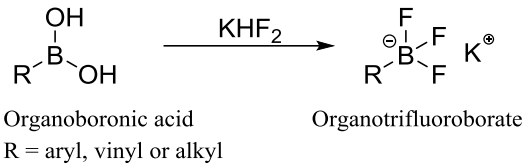
Scheme 1.7. The generally accepted mechanism of the Suzuki-Miyaura reaction.[50-51]

The displayed mechanism (Scheme 1.7) above is divided into four individual steps, these four and an additional step not shown is listed below.

1. Oxidative addition of the organohalide to a low-coordinate Pd^0 complex, yielding a Pd^{II}-complex.
2. Unique for the Suzuki-Miyaura reaction, hydrolysis of the Pd^{II}-complex in the presence of a base, forming the respective halide salt.
3. Transfer of an organic group from a boron reagent to the Pd^{II}-complex, i.e. transmetallation.
4. Isomerization from a trans-complex to a cis-complex, this step is not shown in Scheme 1.7.
5. Reductive elimination recovers the initial Pd^0-complex and forms a carbon-carbon bond between two organic molecules.

The rate-determining step for catalytic cycles, including the one displayed in Scheme 1.7, is the first step, oxidative addition.[44, 51] Electron poor organohalides are optimal for the Suzuki reaction, as the rate of oxidative addition increases with decreasing electron density of the organohalide.[51] The rate of reaction is affected by the halide employed, with the reactivity order being I > Br, OTf >> Cl. Transmetallation is favored by the organoboronic reagents being electron rich,[51] which is contrary to the oxidative addition. Reductive elimination is favored by the two organic moieties having opposite electronic properties, i.e. one moiety is electron rich and one is electron poor. σ-Donating ligands bound to the palladium-complex facilitate oxidative addition, while steric ligands facilitate reductive elimination.

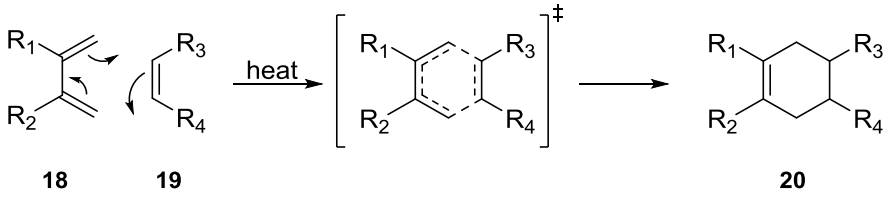
Finally, the Suzuki-Miyaura coupling reaction has at least two disadvantages compared to other palladium-catalyzed reactions. Compounds sensitive to bases are not suited for this coupling reaction, due to the necessity of a base to fulfill the catalytic cycle. Organoboranes used in the coupling reaction are generally not stable under atmospheric conditions, reacting with atmospheric dioxygen results in decomposition of the reagent.[52] To increase the shelf life of the organoboran reagents, they are converted into their respective potassium trifluoroborate salts, as displayed in Scheme 1.8.[53]



Scheme 1.8. Literature procedure for the conversion of an organoboronic acid to its respective potassium organotrifluoroborate.

1.3.2. The intermolecular Diels-Alder reaction

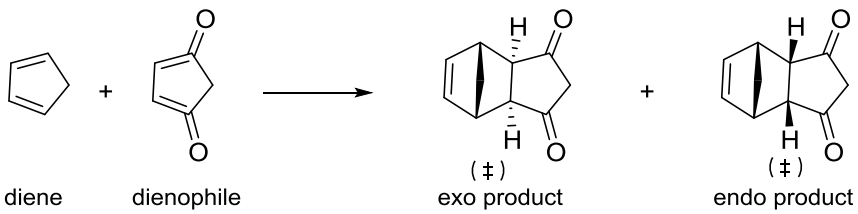
First reported in 1928 by Diels and Alder, it is a [4 + 2] cycloaddition reaction. The mechanism of reaction is displayed in Scheme 1.9.[54] As depicted in Scheme 1.9, the mechanism is concerted,[55] all bonds are formed and broken in a single step. The reaction is proceeded by heating the mixture, but Lewis acids and organic catalysts have been found to increase the rate of reaction, as well as the stereoselectivity.[55-56]



Scheme 1.9. The general Diels-Alder cycloaddition reaction between a diene and dienophile.

A year after the first discovery was reported, Diels-Alder reactions involving furans as a diene was reported,[57] despite furans being an aromatic system.[58] Furans are commonly employed in synthesis of natural products and the use has been extensively explored.[59]

As displayed in Scheme 1.10 Diels-Alder reaction can occur with either endo or exo stereochemistry. The stereochemistry depends on the orientation of the substrates during the reaction. Most often, endo stereochemistry is observed because of overlap between non-bonding orbitals in the two substrates ().[60]



Scheme 1.10. Formation of exo and edndo products after an intermolecular Diels-Alder reaction.

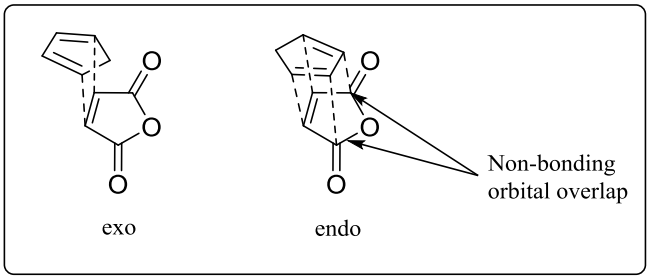
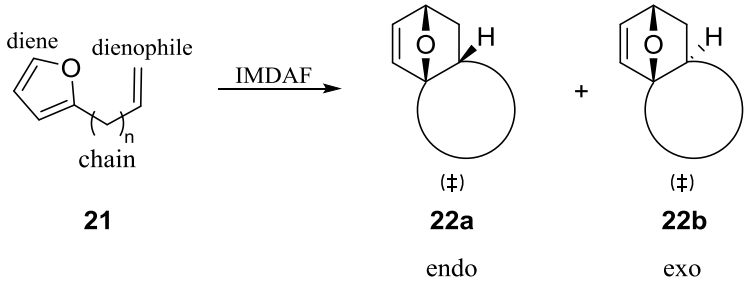


Figure 1.8. Illustrating the orbital overlap during formation of the exo and endo products displayed in Scheme 1.10.

1.3.3. The intramolecular Diels-Alder reaction of furan (IMDAF)

The IMDAF reaction can lead to complex fused ring systems, one example is displayed in Scheme 1.11. Compound **21** is commonly divided into three part; the diene, the dienophile and the chain connecting the two.



21 **22a** **22b**

endo exo

Scheme 1.11. Example of an IMDAF reaction where the substrate is quite simple.

IMDAF cyclization products of 2-furanyl substrates commonly adapt the exo stereoselectivity.[3, 61-62]

1.4. Current and previous strategies for synthesis of phenanthridines in our group

This section describes the use of microwave irradiation as the heating source for IMDAF reactions, the development of IMDAF-based synthesis of phenanthridines in our group and lastly oxidation of dihydrophenanthridine compounds.

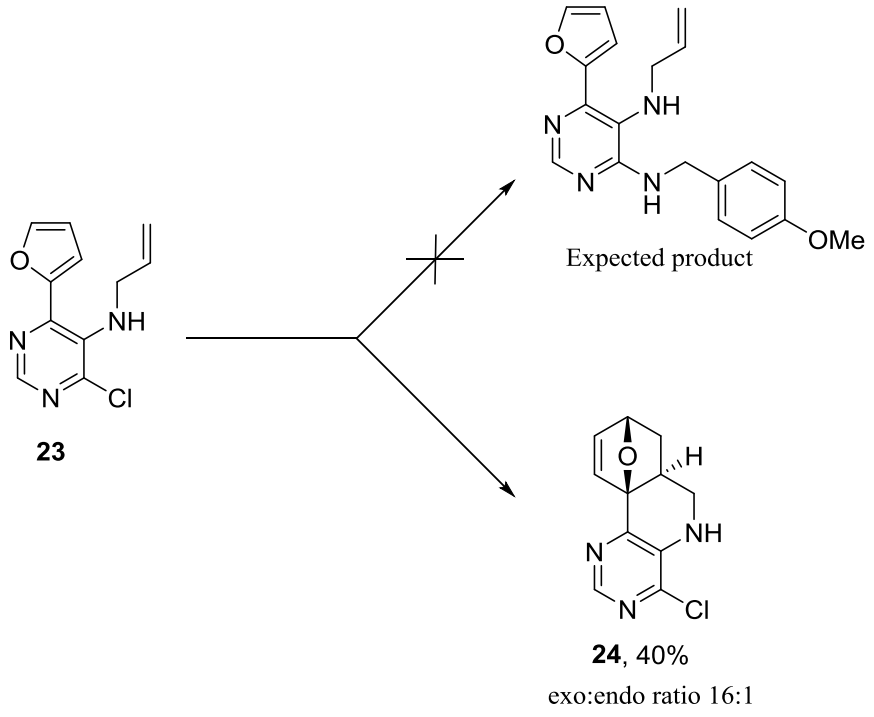
1.4.1. Microwave synthesis

Microwave reactors employ microwave irradiation as the heating source to heat reaction mixtures. Conventional heating sources is commonly oil baths or heating mantles. Dielectric heating occurs when polar molecules are polarized, this is a consequence of dipole-dipol interactions with the electromagnetic field.[63] Energy absorbed dissipates as heat due to intermolecular friction from being in an agitated state, this happens at a high frequency, commonly 2,45 GHz. As non polar solvents do not absorb microwave radiation, only polar solvents are suitable for microwave-mediated synthesis.

IMDAF reactions have been shown to be improved by employing microwave reactors in our group.[1-2] The improvement applies to yields, reaction times and stereoselectivity. The advantage of employing microwave reactors versus conventional heating appears to be rapid heating and even heat distribution.[64]

1.4.2. Development of IMDAF-based synthesis of phenanthridines

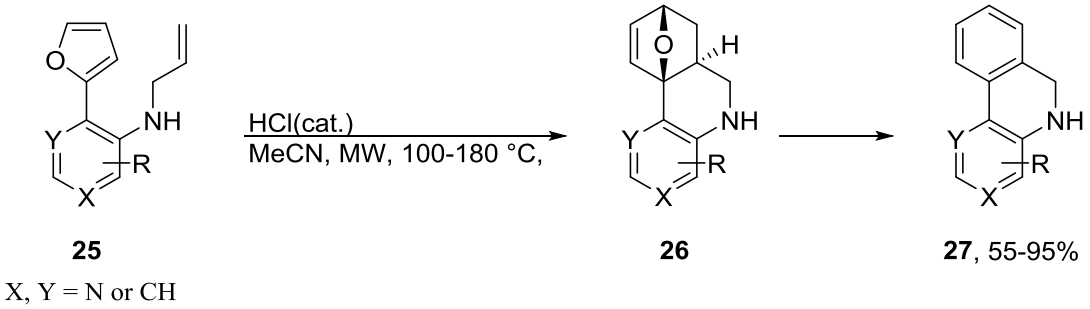
Our group was previously synthesizing pyridines to be tested for antimycobacterial activity.[2, 65] While heating one of the synthetic intermediates (Compound **23**, Scheme 1.12), the compound underwent an IMDAF to form a complex ring system.



Scheme 1.12. Initial discovery of IMDAF reactions towards phenanthridines in our group.

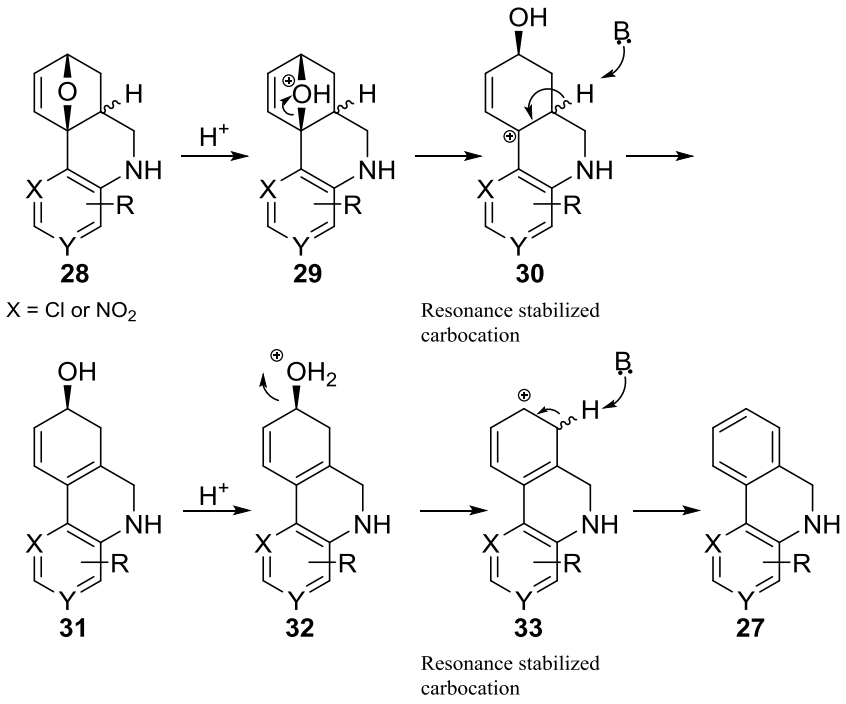
This discovery lead to exploration of IMDAF employing (hetero)arenes with allylamino or allyloxy substituents.[3] It was revealed that substrates with sterically hindering substituents in ortho-position to the allylamino group underwent IMDAF more readily, which was supported by computational studies. Exo stereoselectivity was observed for all substrates that cyclized to give similar ring-systems as that of compound **24**.

The studies conducted after initial discovery lead to a microwave-mediated one-pot synthesis of dihydrophenanthridines (Compound **27**, Scheme 1.13)



Scheme 1.13. Microwave-mediated one-pot synthesis of dihydrophenanthridines from compound 25.

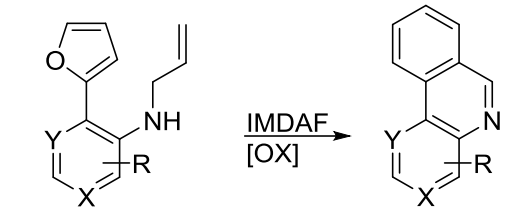
The ring-opening step and water elimination from the IMDAF adduct are displayed in Scheme 1.14.[3]



Scheme 1.14. Proposed mechanism for the ring opening step and water elimination of the oxynorborene ring system.[3]

1.4.3. Oxidation of dihydrophenanthridines

It was found that most dihydrophenanthridines synthesized by IMDAF readily underwent oxidation to phenanthridines by irradiation of UV-light.[3] This allowed for a clean and simple two step synthesis of fully aromatic phenanthridines as displayed in .



25
X, Y = N or CH

34, 69-92%

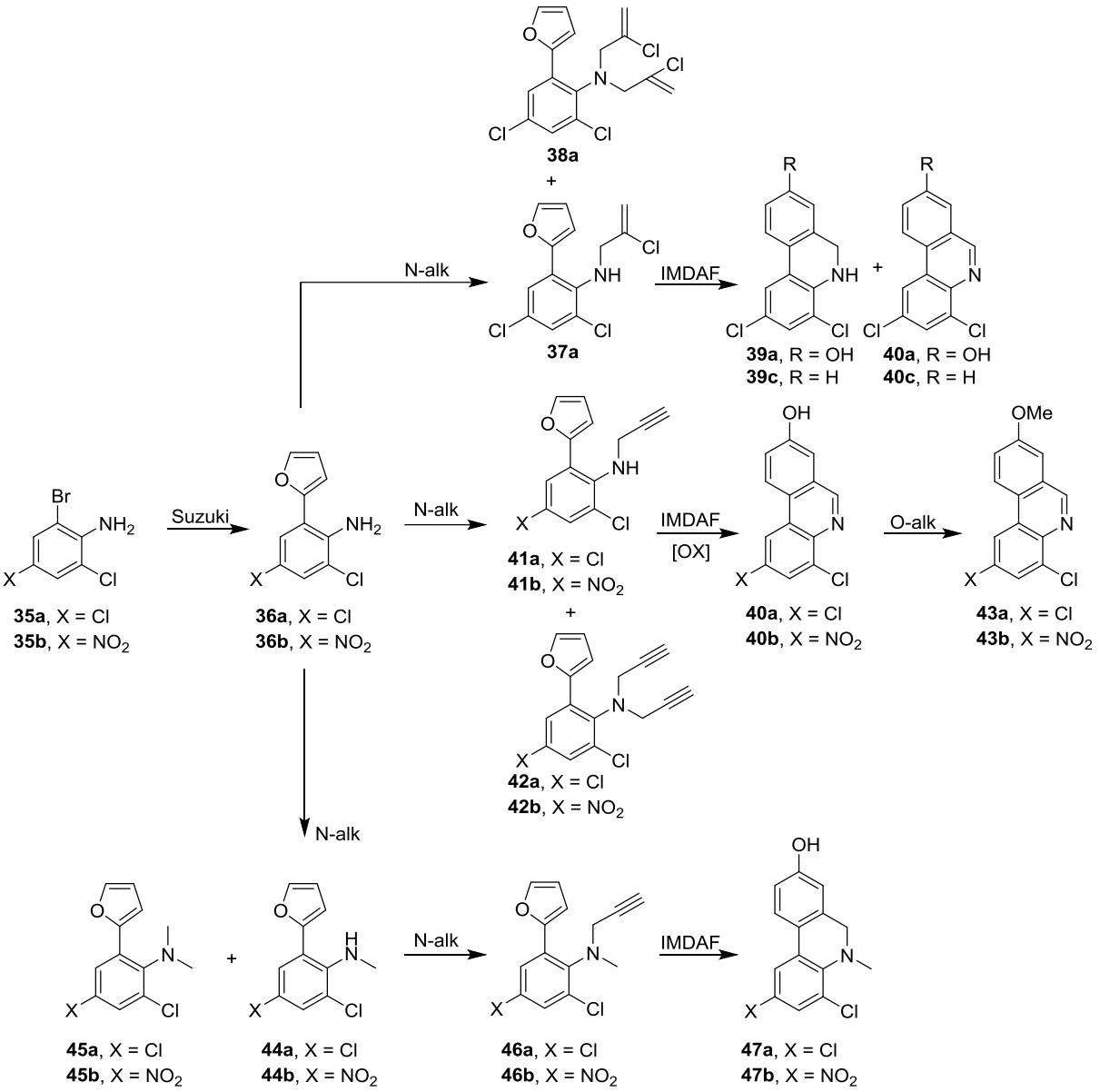
Scheme 1.15. Microwave mediated one-pot synthesis of fully aromatic phenanthridines from compound 25.

The mechanism of the oxidation with UV-irradiation and air is currently not known.

2,3-Dichloro-5,6-dicyano- 1,4-benzoquinone (DDQ) was employed if oxidation by UV/Air did not proceed to completion or the oxidation was too slow.

2. Synthesis and discussion

This section describes the synthesis of every compound made during the work of this thesis, as shown below in Scheme 2.1.



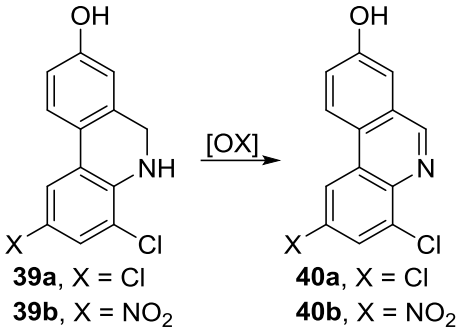
Scheme 2.1. Commercially available compounds **74** as the starting material for every compound synthesized during this thesis.

2.1. Starting materials: Choice and synthesis

This section describes the choice of starting materials, their synthesis and problems encountered during synthesis. Choice of starting material for the 8-hydroxophenanthridine compounds is built on previous success in our group, explained in Section 2.1.1.

2.1.1. Previously employed strategies

As explained in Section 1.4 it was found that a sterically hindering group in the ortho position to the alkylamino group exerts a positive effect during the IMDAF reactions.[3] It was previously observed that an electronegative group in the para position also affects the reactivity, though it is only assumed that it is the electronegativity of the group that is the contributor.[1, 3] The observation of a chloride group in the ortho position, and a chloride or nitro group at the para position is concluded that it was sufficiently effective.[1, 3] The effect of the electronegative group at the para position also affects the rate of oxidation, from 5,6-dihydrophenanthridine to phenanthridine shown in Scheme 2.2.



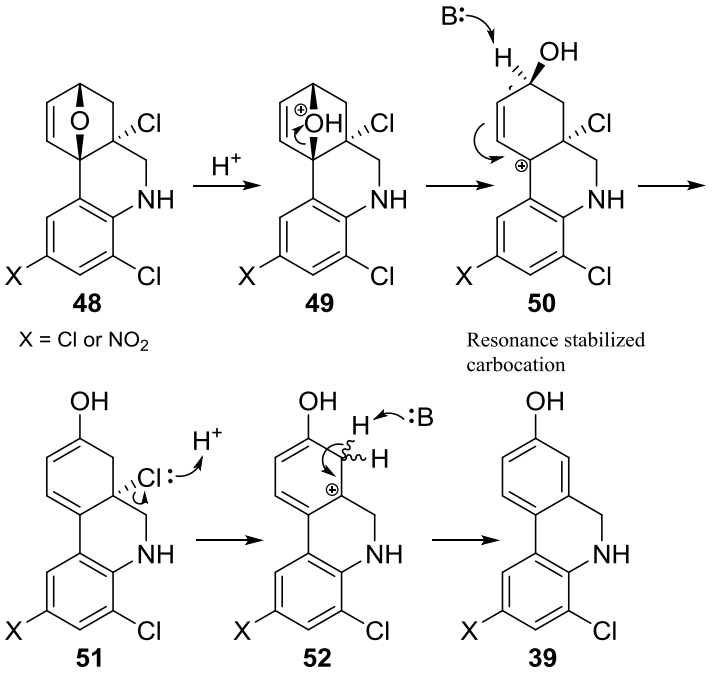
Scheme 2.2. Oxidation of 5,6-dihydrophenanthridines to their fully aromatic substrate

While the effect of the sterically hindering chloride in the ortho position has been calculated and observed previously, there has not been conducted any work to explore this further during this thesis. The effect of the electronegative group in the para position is both observed previously and during the work of this thesis.[1, 3]

2.1.2. Strategies towards phenanthridin-8-ol derivatives

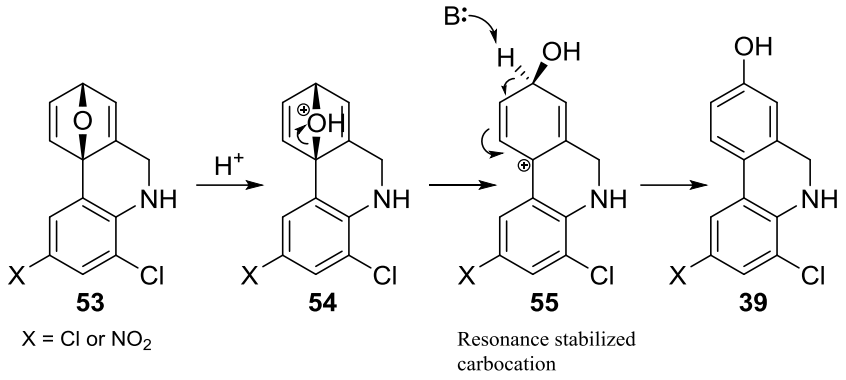
Efficient ways to synthesize different phenanthridines within our group has been found, amongst these phenanthridines previously synthesized, there is only one example of 8-hydroxyphenanthridine.[1] Taking the presumed ring opening mechanism into account shown in Scheme 1.14, which eliminates the desired hydroxyl-group as water, certain alkyl side chains should be able to prevent this, and give the desired result.[2-3] The result is however not great,

and a more detailed discussion about this is given in Section 2.2.1. In Scheme 2.3 shown below, a mechanism presumed to give the desired result was the first thought out strategy of this thesis towards 8-hydroxyphenanthridine. Here, a better leaving group is introduced, which reduces the chance for water elimination.



Scheme 2.3. The assumed mechanism for the IMDAF reaction ring opening step with the *N*-chloroallyl substituted aniline. It is presumed that the mechanism to remove the chloride is an E1 type, as the chloride and proton are not situated 180 °C apart. It is not known which of the two protons eliminates.[66]

Due to unsatisfactory selectivity in the ring opening step, with the method shown in Scheme 2.3 which is described in detail in Section 2.2.1, another strategy had to be employed. Work on indoles were being done in our group at the time, which had good success in retaining the hydroxy-group. In this work propargyl-*N*-substituted indoles were used and the presumed ring opening mechanism for the propargyl-*N*-substituted aniline in an IMDAF reaction is shown in Scheme 2.4.



Scheme 2.4. Shows the presumed mechanism for the IMDAF reaction ring opening step with the N-propargyl substituted aniline.

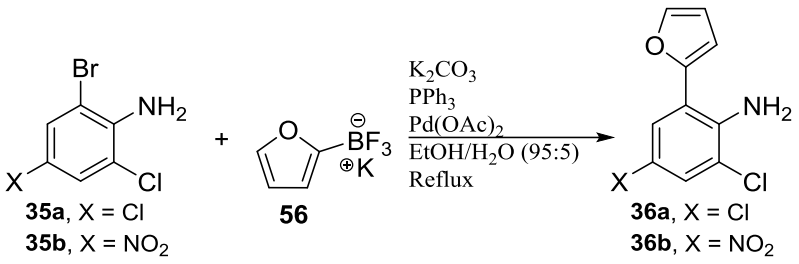
This strategy worked as intended, compounds **53** reacted selectively to compounds **39**, and is described in detail in Section 2.2.2.

2.1.3. Synthesis of 2,4-dichloro-6-(furan-2-yl)aniline and 2-chloro-6-(furan-2-yl)-4-nitroaniline

The first step in the synthesis process of 8-hydroxyphenanthridines is synthesizing the *o*-(furyl)-anilines. These were synthesized from 2-bromo-4,6-dichloroaniline and 2-bromo-chloro-4-nitroanaline, using a literature procedure previously employed in our group.[1, 3] The procedure was altered slightly, during the flash chromatography, a gradient was applied to the eluent system as total separation was difficult when unconverted start material was present. This alteration also decreased the amount of tailing during the flash chromatography. Another difference only pertaining to the synthesis of compound **36b**, it stirred for 16 hours longer than the literature procedure, to be sure there were not any uncoverted starting material left.[1]

Yields for the Suzuki-Miyaura cross-coupling reactions was lower than for the literature procedure, at 85 % for compound **36a** and 52 % for compound **36b**.[1] The suspected reasons for this, is different for the two reactions. For compound **36a**, a not insignificant amount of unconverted start material was present, making the flash chromatography difficult, while also reducing the total amount of product. This problem did not occur for compound **36b**, as the reaction underwent full conversion, but the compound tailed a significant amount on the during flash columnography, to the point that triphenylphosphine oxide and other unknown impurities co-eluted, reducing the amount of fractions that could be used in later steps.

Compounds **36a** and **36b** were synthesized with the conditions and reagents displayed in Scheme 2.5.

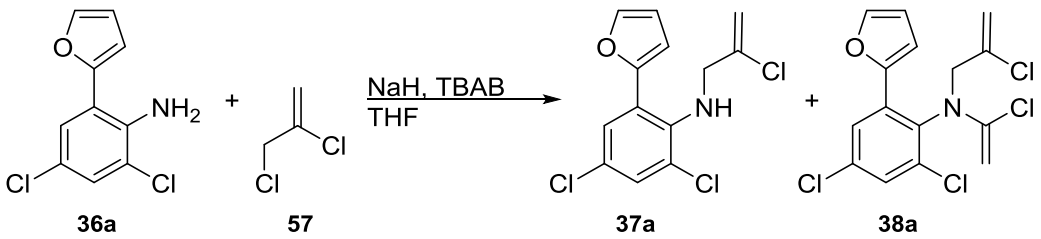


Scheme 2.5. The reaction conditions and reagents for the Suzuki coupling reaction.

Compound **56** was made in bulk from a literature procedure by another person in our group.[67] The commercially available 2-furanylboronic acid, which is the starting material for compound **56**, would also result in compounds **36**, if employed directly during a Suzuki-coupling reaction. As described in Section 1.3.1, heteroarylboronic acids have a short shelf life, which is less of a problem after converting them to the more stable salt, potassium trifluoroborate. The salt is converted back to the acid during the reaction, and it is the acid that is the active reagent.[53]

2.1.4. Synthesis of 2,4-dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline

Our group has previously studied allylation of a broad array of anilines with different reaction conditions.[3] To deprotonate the aniline nitrogen, NaH and crown ethers were employed, which had great success. Crown ethers were used to stabilize the alkali metal ions in Na and K in organic solvents.[68] Unsatisfactory results with the use of crown ethers in another study, turned to employment of tetrabutylammoniumbromide(TBAB) instead, which proved to give satisfactory results.[1] Therefore the *N*-alkylation were performed with NaH in the presence of TBAB as displayed in Scheme 2.6.



Scheme 2.6. Reagents for the N-chloroallylation, which was only done for the dichloro substrate, as the IMDAF reaction displayed unsatisfactory selectivity towards the 8-hydroxyphenanthridine.

For the reasons stated above, and because the substrates previously readily produced *N*,*N*-allylated products, a screening was conducted to find reaction conditions that gave satisfactory results, which is summarized in Table 2.1 below.[1, 3]

With the best reaction conditions a satisfactory enough isolated yield was achieved, and compound **37a** could readily be made from compound **36a**.

Table 2.1. Screening conditions for the N-chloroallylation displayed in Scheme 2.6 – Base: NaH

Entry	Eq. 2,3 dichloroprop-1-en	Eq. Base	Solvent	Temp(°C)	Time(h)	Eq. TBAB	Ratio of SM/N-Alk/N,N-Alk[a]			Yield[b,f] (%)
							SM	N-Alk	N,N-Alk	
1	1.4	1.0	THF	r.t.	2.5	1.0	65	35	0	n.a.[c]
2	1.4	1.0	THF	45 °C	4.5	1.0	61	39	0	18
3	2.1	1.7	THF	45 °C	60	1.0	51	45	4	n.a.[d]
4	4.2	3.0	THF	45 °C	20	1.0	18	79	3	65
5	4.2	3.0	THF	66 °C[e]	42	3.0	39	61	0	n.a.[d]
6	4.2	3.0	THF	45 °C	20	3.0	6	87	7	57

[a]by ^{1}H NMR of the crude product.

[b]of isolated products.

[c]not isolated.

[d]conversion unsatisfactory, no flash chromatography performed.

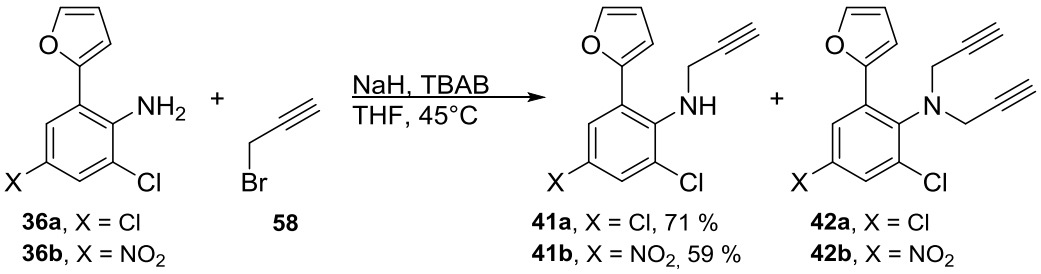
[e]Reflux.

[f]N,N-chloroallyl was never completely isolated, and no yields can be given.

2.1.5. Synthesis of 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-yn-1-yl)aniline and 2-chloro-6-(furan-2-yl)-4-nitro-*N*-(prop-2-yn-1-yl)aniline

The unsatisfactory selectivity under the ring opening step in the IMDAF reaction with compound **76a**, caused the need for a new strategy. As explained in section 2.1.2, the substrate that was chosen as the next candidate for success, was an *N*-propargylated aniline.

Results from the *N*-chloroallylation was satisfactory enough to try the same procedure, when changing from 2,3-dichloroprop-1-ene to 3-bromoprop-1-yn. An overview of the reactions with reagents are shown in Scheme 2.7.



36a, X = Cl
36b, X = NO_2

58

41a, X = Cl, 71 %
41b, X = NO_2, 59 %

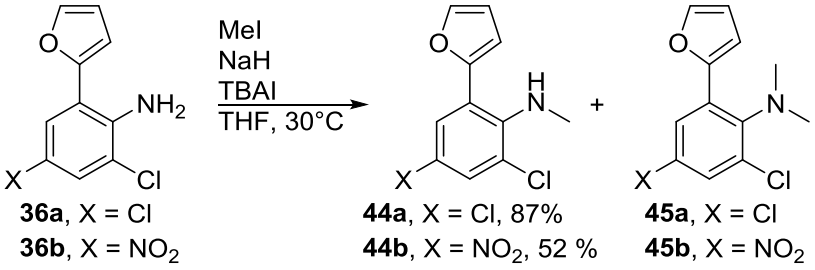
42a, X = Cl
42b, X = NO_2

Scheme 2.7. Reagents and products for the propargylation.

At over 50 % isolated yield, further optimization was not attempted and compound **41** could readily be made from compound **36**.

2.1.6. Synthesis of 2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline and 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline

As explained in section 2.1.7, an attempt to methylate compound **78a** was conducted as displayed in Scheme 2.9, which did not produce isolated compound **81a**. The next strategy was then to reverse the *N*-alkylation order and *N*-methylate first, following similar procedures previously employed in our group.[1, 3] The reaction was done as displayed in Scheme 2.8.

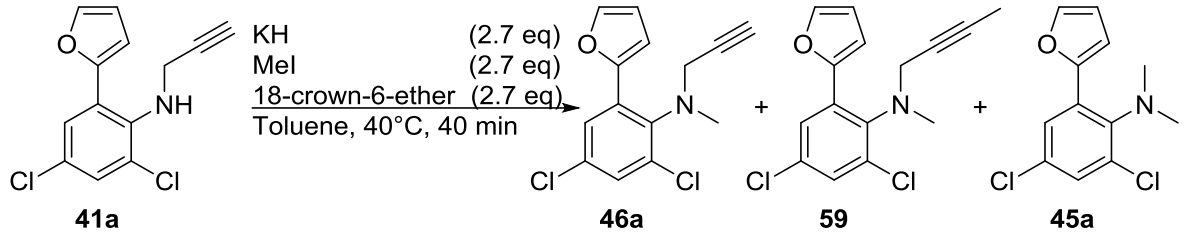


Scheme 2.8. Reagents, reaction conditions and products for N-methylation of compound 36.

The reaction turned out to be slower than expected. It was expected that this reaction went faster than both the *N*-chloroallylation and *N*-propargylation. This was expected as MeI is a less sterically hindered electrofile and I^- is a more stabilized anion than Br^- and Cl^-.[66] While the reactions were slower, compound **44a** was a lot more selectively made, which can indicate that the σ-donation from the alkylchain affects the *N*,*N*-dialkylation more than expected.

2.1.7. Synthesis of 2,4-dichloro-6-(furan-2-yl)-*N*-methyl-*N*-(prop-2-yn-1-yl)aniline and 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitro-*N*-(prop-2-yn-1-yl)aniline

To understand more about the effect of removing the last *N*-hydrogen, a methyl group is the least property-altering group as its replacement. An *N*-methylation of compound **41a** was attempted with a procedure used previously in our group, with other alkyliodide reagents.[1, 3] Reagents, conditions and products are displayed in Scheme 2.9 below.



Scheme 2.9. Reagents, reaction conditions and products for the *N*-methylation of compound 41a.

As can be seen in Scheme 2.9, more products than what at first was expected, formed. In hindsight, terminal alkyn hydrogens are weakly acidic with a pK_a value around 25. Strong bases such as alkaline hydrides can, as observed during the reaction displayed in Scheme 2.*9*, deprotonate the the terminal alkyn hydrogen in compound # and thereby be substituted with an electrofile present, such as MeI in this case. *p*-Chloro and *p*-nitroaniline has a pK_a of 3.98 and 1.00 respectively, which indicates that the remaining N-hydrogen in compound **41a** is substituted first and then the terminal alkyn hydrogen. This also coincides with the lack of the product only substituted on the terminal alkyn.

Amongst the products formed, compound **45a** was one of them, the propargyl group was substituted with a methyl group, though only in 9 %, data is from ^{1}H NMR of the crude product. The product ratio is displayed in Table 2.2.

Table 2.2. The product formation ratio of the reaction displayed in Scheme 2.9.

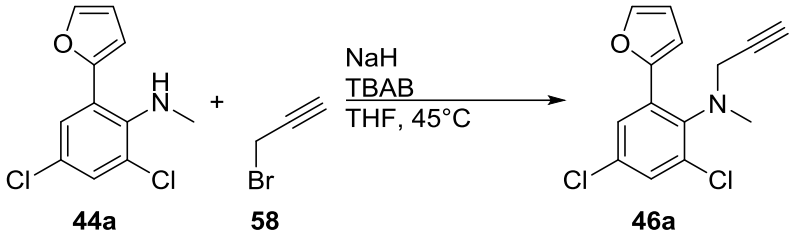
Substrate	**46a**	**59**	**45a**
Ratio[a] (%)	70	21	9

[a]from ^{1}H NMR of the crude product

The ratio of formation aslo indicates that the substitution on of the terminal alkyn hydrogen is second to the *N*-hydrogen substitution, while the substitution of the propargyl group is even less.

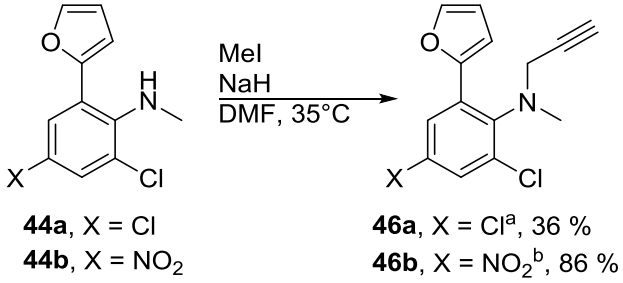
Instead of trying to optimize the reaction conditions, a change of strategy was employed. Doing the *N*-methylation before the *N*-propargylation should produce the wanted product with fewer complications. Since an *N*-methyl group has no acidic hydrogen and the propargylbromide is a less reactive electrofile, unwanted substitution should not happen.

Propargylation of the *N*-methyl was first attempted with conditions similar to those compound **41a** was synthesized with, as displayed in Scheme 2.*10*.



Scheme 2.10. Reagents, reaction conditions and products after N-propargylation of compound 44.

After 48 hours only 17 % of compound **46a** formed, from ^{1}H NMR of the crude product. The reaction was worked up and isolation was attempted. Though compound **46a** was isolated from the start material, it was not clean. Since the reaction was as slow as it was, and the compound was not pure, a new reaction was conducted with reaction conditions similar to those previously used in our group.[1, 3] Reactants and products are displayed in Scheme 2.11.



Scheme 2.11. Reagents, reaction conditions and products for compound 44 to 46.
[a]Reaction mixture stirred for 24 hours, then an additional 2.0 eq NaH and MeI was added and stirred for another 48 hours.
[b]Reaction mixture stirred for 2 hours**.**

Observation of the results from reactions displayed in Scheme 2.11 confirms the effects of the electronegative group in para position of the aniline. It seems that the methyl group reduces the acidity of the *N*-hydrogen, this is also observed in the methylation of **44a**. The stability is countered by the higher electronegativity of the nitro group, which can explain the difference in reactivity between compound **44a** and **44b** towards *N*-propargylation.

No further attempts at optimizing the reaction conditions was conducted as enough isolated compound for the IMDAF was acquired.

Another student in our group did an *N*-methylation of compound **41a**, with NaH and TBAI in THF.[1] This reaction did not lead to compound **59**, which indicates that NaH is not strong enough of a base coupled with TBAI to deprotonate the terminal alkyl in compound **41a**, in a significant enough manner to produce a noticeable amount of compound **59**. This reaction was done after compound **46** was produced as described above.

2.1.8. *N*-(but-2-yn-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline and *N*-(but-2-yn-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline

To study the biological activity of different groups on the 8-hydroxyphenanthridines, another substrate was to be synthesized, target compounds are shown in Figure 2.1.

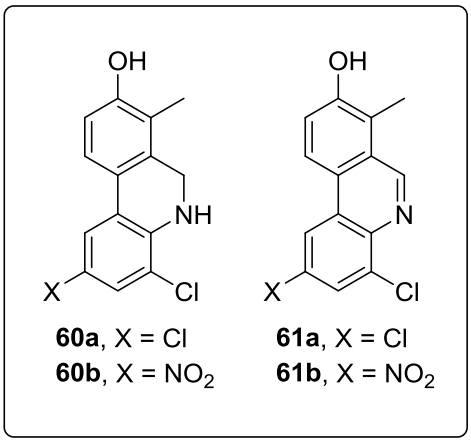
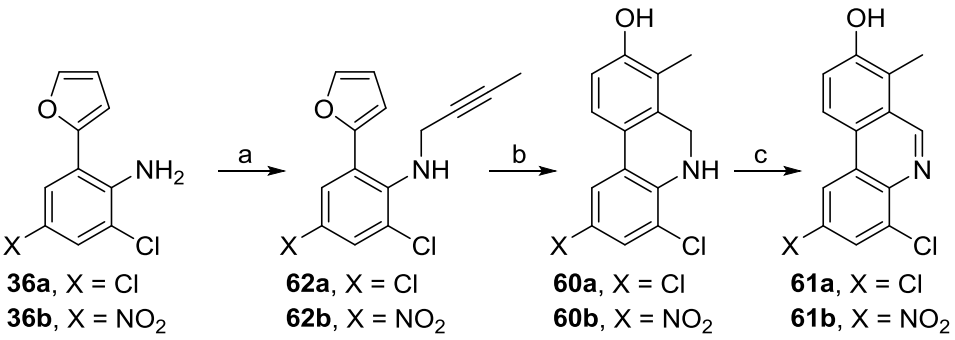


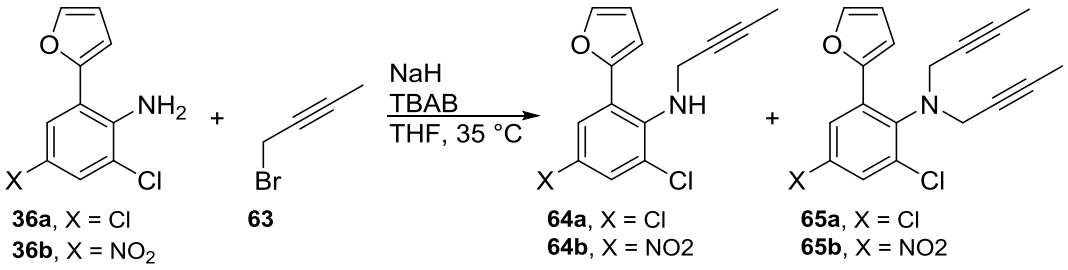
Figure 2.1. Target compounds to be tested for biological activity.

The strategy to synthesize compound **61** is displayed in Scheme 2.12.



Scheme 2.12. a - NaH, TBAB, 1-bromobut-2-yne, THF. b - HCl (cat.), MeCN, Microwave. c - UV/Air, MeCN or DDQ, DCM.

As the electrofile during step a in Scheme 2.12 is very similar to compound **58** in Scheme 2.*7*, similar reaction conditions were employed, as displayed in Table 2.*3*. Reagents and products are displayed in Scheme 2.13.



Scheme 2.13. Reagents and products by N-substitution of compound 36 with compound 63.

Table 2.3. Reaction conditions and product ratios.

Entry	Substrate	Eq. 107	Eq. NaH	Eq. TBAB	Time (h)	Ratio of compounds[a] (%)		
						SM	N-Alk	N,N-Alk
1	Cl	2.0	2.0	2.0	19	0	54	46
2	Cl	2.0	2.0	2.0	1	12	83	5
3	NO_2	1.2	1.5	1.1	1.25	16	76	8

During the first attempt at synthesizing compound **64a**, TLC analysis was performed after one, and three hours of stirring. The spot that were showing on the TLC plate were mistaken for the start material, from experience of the previous *N*-alkylations, TLC's always displayed start material, and always slightly apart from the mono-N-alkylated product. During the second attempt, a TLC analysis were performed after 30 minutes and the start material was displayed clearly. The reaction was stopped when the start material could no longer be observed by TLC analysis, which was after an hour, though it was not observed by TLC analysis, an ^{1}H NMR of the crude product displayed that 12 % of compound **36a** was unconverted. This did not seem like a problem at the time, as the TLC analysis indicated a reasonable difference in retention times. The separation would however prove to be difficult, two attempts at flash chromatography were performed, where compound **36a** co-eluted precisely with compound **64a**.

A more careful approach towards synthesizing compound **64b** was employed, but the same problem as for compound **64a** was encountered during the flash chromatography of compound **64b**.

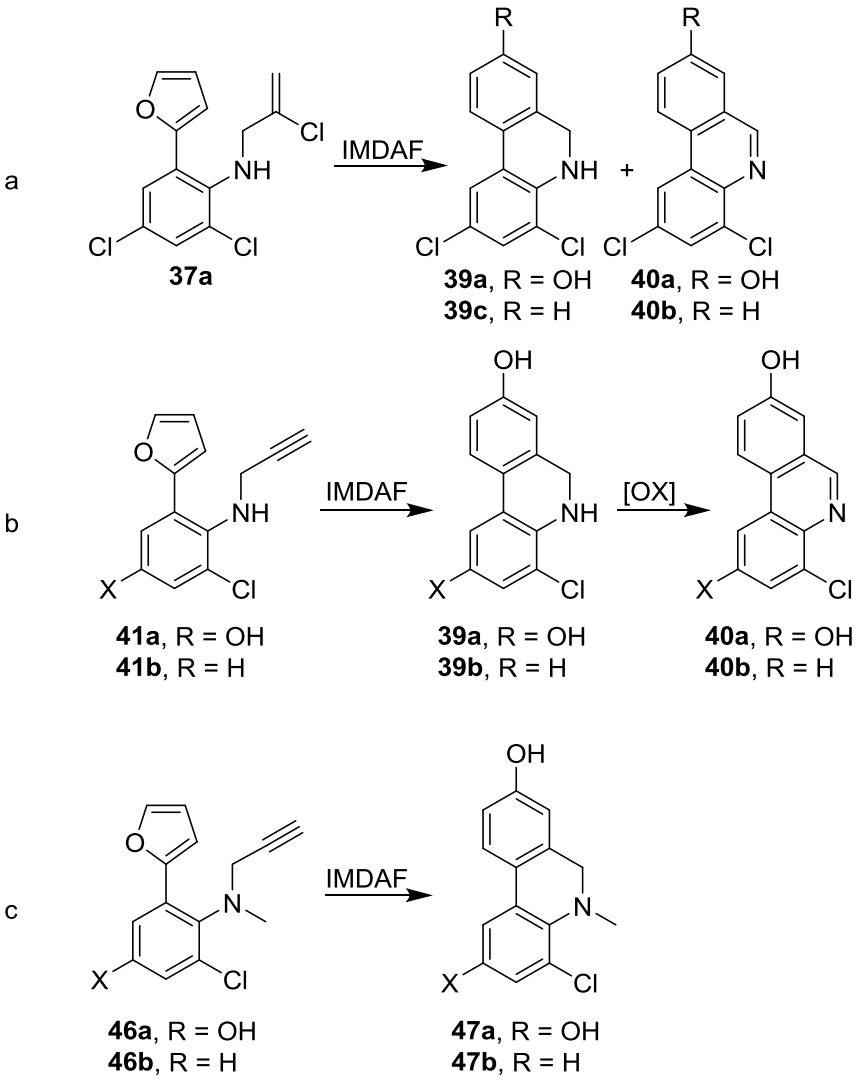
Further optimization of the reaction conditions for compound **64** needs to be conducted.

2.1.9. Problems encountered during isolation and purification

To isolate *N*-alkylated anilines, flash chromatography were performed on all substrates. During the flash chromatography, compounds that exhibits very different R_f values from a TLC analysis, co-elutes if one of the compounds is in a very different scale than the other. The highest similarity in scale that co-eluted was a ratio of 16:84. This problem turned isolation of products into a problem when the TLC analysis did not display the smaller scale compound.

2.2. Employing a microwave mediated IMDAF reaction towards phenanthridin-8-ol derivatives

This section describes the synthesis of 8-hydroxyphenanthridines, mediated by microwave irradiation, with an IMDAF type reaction. Scheme 2.14 displays an overview of the microwave mediated IMDAF reactions which will be described.



Scheme 2.14. An overview of the microvave mediated IMDAF reactions conducted during the work of this thesis.

2.2.1. Using chloroallyl substituted aniline as starting material

This section describes the first strategy towards synthesizing 8-hydroxyphenanthridines, and is as displayed in Scheme 2.14, reaction a.

2.2.1.1. Screening conditions for 2,4-phenanthridin-8-ol

A screening of the reaction conditions was conducted as displayed in

Table 2.4.

Table 2.4. Screened conditions for reaction a in Scheme 2.14 along with product ratio - Addidative - H_2O (cat.)

Entry	Temp (°C)	Time (h)	Ratio of compounds[a] (%)					Ratio	
			40a	**39a**	**40c**	**39c**	**37a**	R = OH	R = H
1	150	1.0	37	13	23	27	0	50	50
2	150	3.0	48	6	31	16	0	54	46
3	120	1.0	29	7	13	17	34	55	45
4	180	0.5	42	7	32	20	0	48	52

[a]from ^{1}H NMR of the crude product.

What can be observed from the result of the screening process, is only a miniscule change in the ratio of R = OH and R = H amongst the products, respectively 50/50 ± 5. We know from what is described in Section 1.4.2 and 2.2.1.2, that loss of the hydroxy group happens after the ring closing step. From Scheme 2.3 we know that loss of the hydroxy group, aswell as the ring opening step is acid catalyzed, and in eliminating the chloride group hydrogen chloride is formed. Thereby creating a more acidic environment, further enhancing the reactivity. A probable reaction mechanism where both the hydroxy- and chloride group is eliminated has not yet been found.

While the selectivity was not great, an attempt to isolate the different compounds were conducted in each case. While compound **39a** was only observed in the crude product,

compounds **40a**, **40c** and **39c** were all observed after flash chromatography. Though **40a** and **40c** was isolated, they were not pure, a significant amount of "grease" like hydrocarbons were observed on ^{1}H NMR. Another setback is the fact that compound #a seemed to oxidize into compound #a on the silica gel during flash chromatography. Figure 2.*2* displays an example of how the TLC plate of the different fractions after flash chromatography would look.

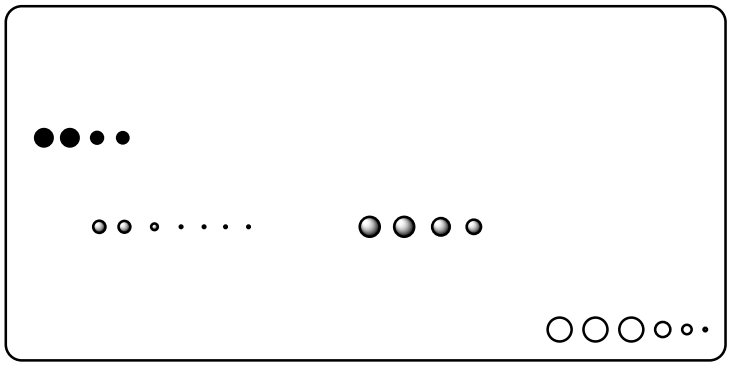
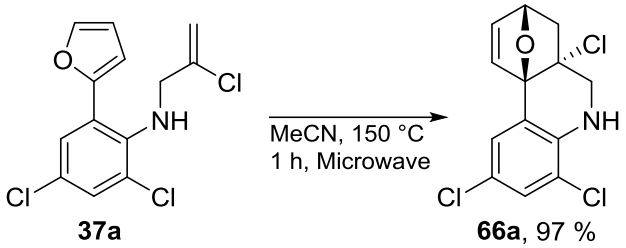


Figure 2.2. An example of how a TLC plate would look after a flash chromatography of reactions displayed in Table 2.4. Solid black = 39c - Grey = 40c - Black circles = 40a

The situation displayed in Figure 2.2 can stem from one of three cases. First, compound **39c** oxidizes into compound **39c** on the silica gel as mentioned. Second, some of compound **40c** co-eluted with compound **40c**. Third, some of compound **39**c oxidized and then co-eluted with the remaining compound **39c**. The second case is improbable, as there are not a scarcity of compound **40a**. If there were a scarcity of compound **40a**, it could potentially co-elute with compound **40a**, because their similar polarity and structure would cause them to attract each other. This was reproducible, and in each attempt at isolating the different products, it resulted in a similar separation pattern as that which is displayed in Figure 2.2.

2.2.1.2. Microwave mediated synthesis of (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine

As a proof of the fact that the hydroxy group is eliminated during the ring opening step, an attempt to synthesize the IMDAF adduct of **37a**, was conducted as displayed in Scheme 2.15.



Scheme 2.15. Reactants, reaction conditions and product for the IMDAF reaction of compound **37a** where acid is excluded.

Compound **37a** reacted selectively into compound **66a**. The sole product of the reaction was the exo-adduct, as strongly indicated by 1D - selective-noesy NMR. A quick structure optimization with certain bond lengths are shown in Figure 2.3, Figure 2.4 and Figure 2.5.

The bond lenghts are subject to inaccuracies as the structure was optimized with ChemDraws 3D program.

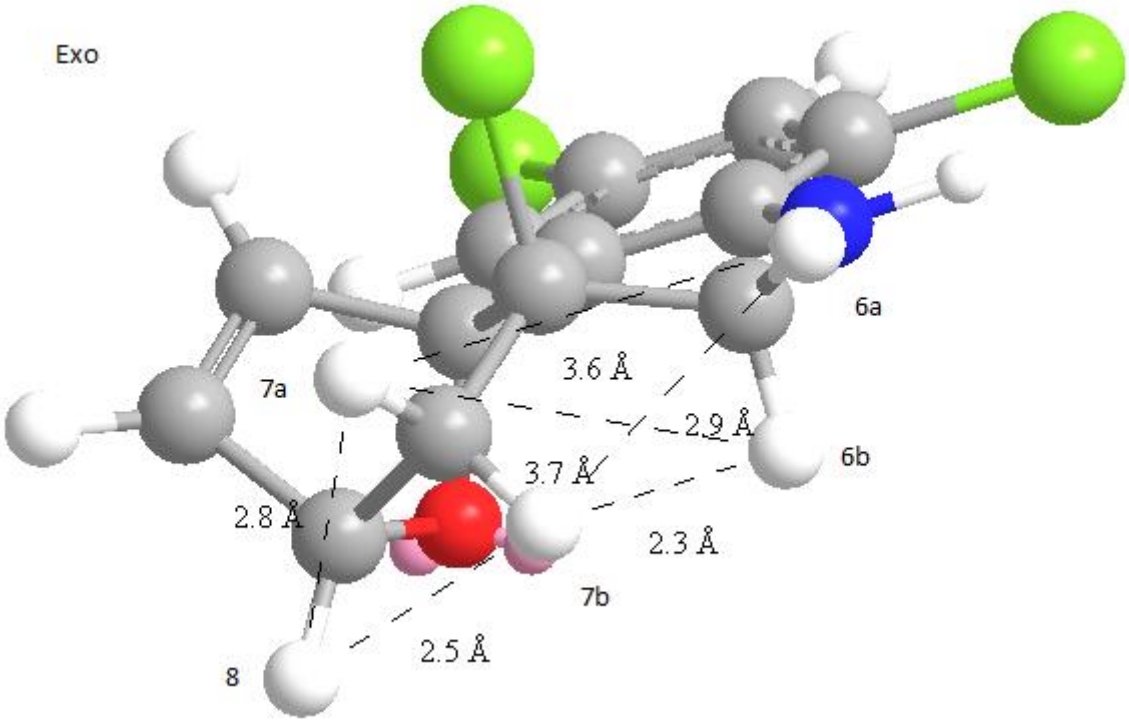


Figure 2.3. Displays the distance between certain hydrogens in the exo-adduct of compound **66a.**

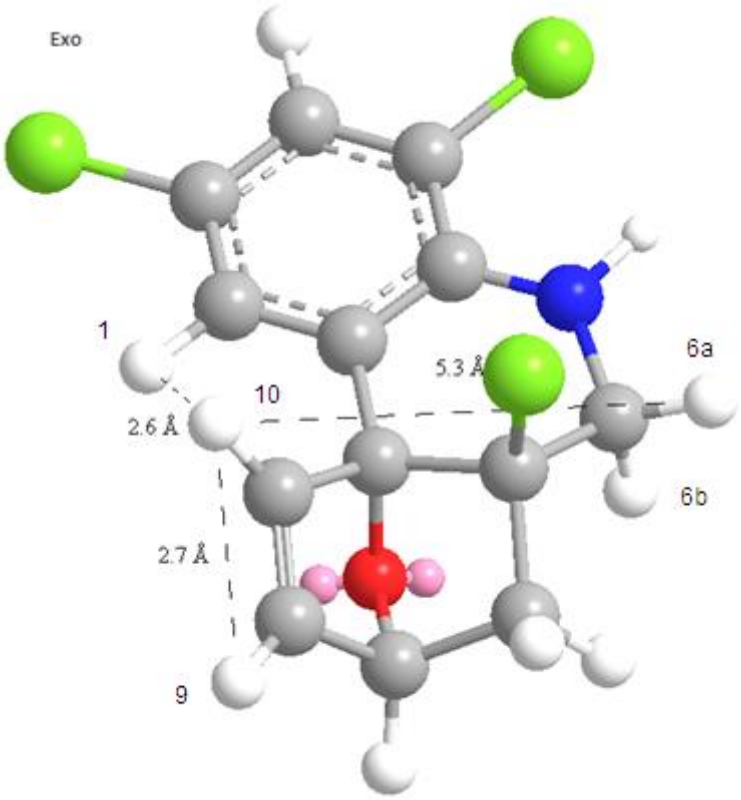


Figure 2.4. Displays the distance between certain hydrogens in the exo-adduct of compound **66a.**

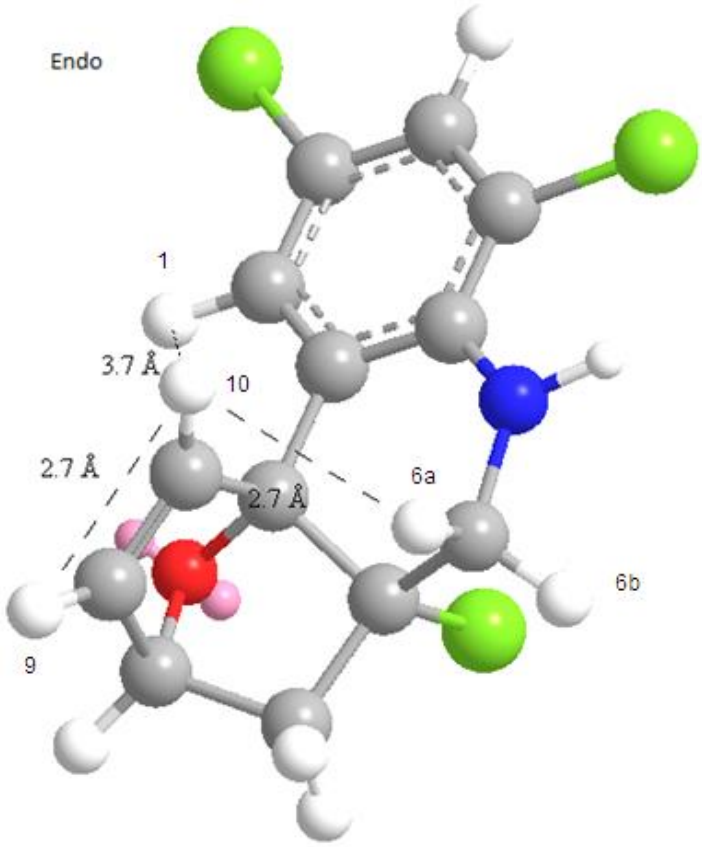
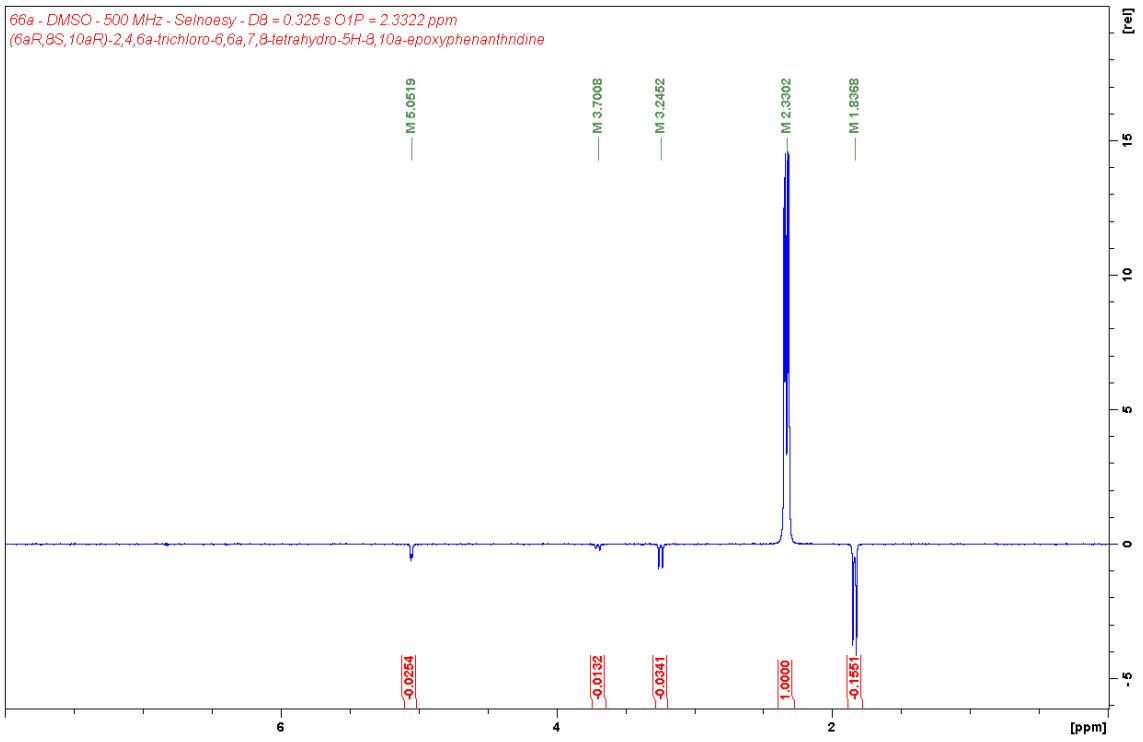
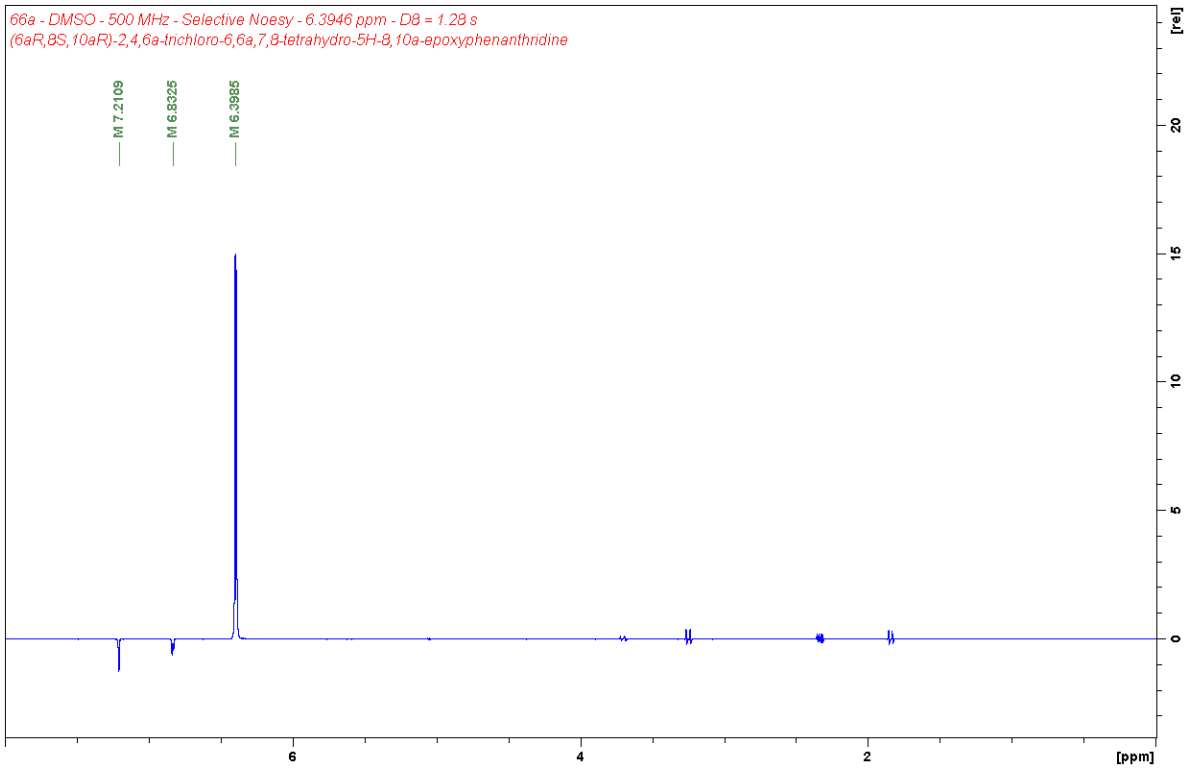


Figure 2.5. Displays the distance between certain hydrogens in the endo-adduct of compound **66a.**

What will determine if it is endo or exo is the existence of a NOESY signal between H-1 and H-10 as well as a signal between 7b and 8 (distance not included for endo in the figure).



Spectrum 1. 500 MHz, DMSO, Selective NOESY for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine, focused on H-7b.



Spectrum 2. 500 MHz, DMSO, Selective NOESY for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine, focused on H-10.

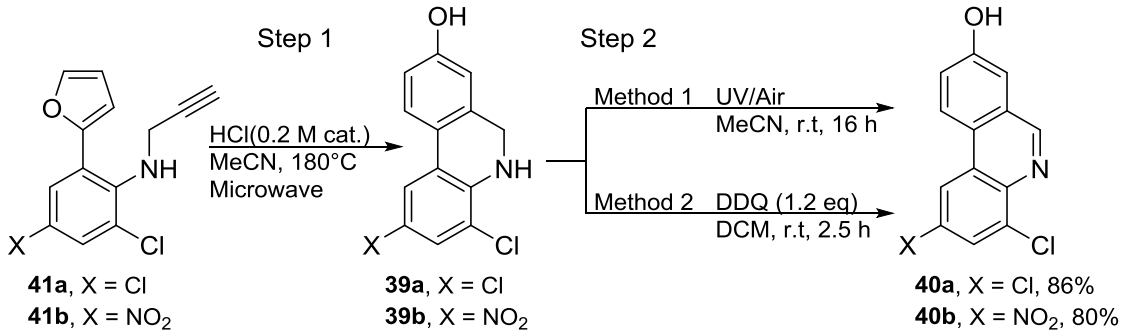
From Spectrum 1 and Spectrum 2, both predicted signals for the exo adduct are observed, and the signal between H-10 and H-6a predicted for the endo adduct is not.

2.2.2. Using propargyl substituted aniline as starting material

This section will describe the synthesis of 8-hydroxyphenanthridines employing compounds **41** and **46** as starting material, displayed as b and c in Scheme 2.14.

2.2.2.1. Microwave mediated two step synthesis of 2,4-dichlorophenanthridin-8-ol and 4-chloro-2-nitrophenanthridin-8-ol

While the IMDAF reaction of compound **37a** displayed a ~50/50 selectivity towards compound **40a**, compound **41** reacted selectively to compound **40** in a two-step reaction, as displayed in Scheme 2.16 below.



Scheme 2.16. Step 1: X = Cl: 100 min, X = NO_2: 40 min - Step 2, method 1: Only 40a was successfully oxidized with this method - Step 2, method 2: Both substrates were successfully oxidized with this method.

As observed in Scheme 2.16, compound **40** can readily be synthesized from compound **41**. A small screening for reaction conditions was conducted first, as displayed in Table 2.5.

Table 2.5. Screening for reaction conditions, step 1 in Scheme 16 - Temp: 180°C - Solvent: MeCN - Additive: HCl (0.2 M)

Entry	Substrate	Time	Unconverted SM
1	Cl	90	~1
2	NO_2	30	~1

As a precaution, an extra 10 minutes was added during the microwave step to ensure that there was no residual starting material remaining.

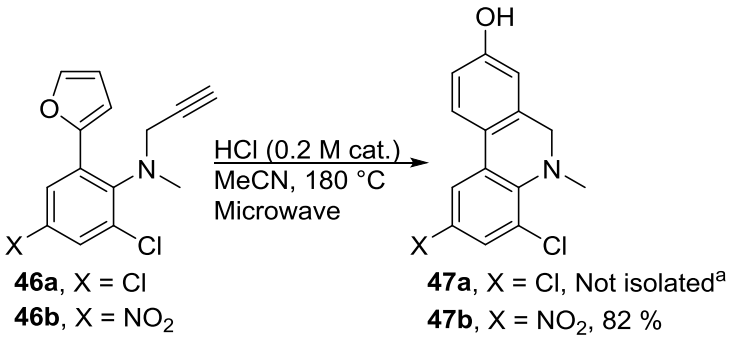
While compound **39a** readily oxidized with method 1 over 16 hours, compound **39b** only oxidized fully when the concentration was low, 1 mg/ml, and over 48 hours. When the oxidation was attempted at a higher concentration, the ratio of compounds ended at 77:23 for compound **39b** and **40b** respectively, after 48 hours. Compound **39** oxidized fully with method 2 over 2.5 hours. Though method 2 was faster and oxidized both substrates completely, the flash chromatography was more difficult. Compound **40** trail a lot during flash chromatography and ends up co-eluting with the reduced DDQ.

It was expected that compound **39b** would be more difficult to oxidize, as this has been the general case with a very electronegative group at position 2, in this and previous cases that group is a nitro group.[1, 3] In this case there is also another possible explanation, compound **40b** precipitates during the oxidation, which can block UV-radiation from the remaining start material. This was not the case when the concentration was low, unfortunately the quartz-glass beaker required for UV-oxidation could not contain more than ~15 mL solvent.

After isolation by flash chromatography, the products had to be washed with pentane to remove residual aliphatic hydrocarbons, which successfully purified the products.

2.2.2.2. Microwave mediated synthesis of 2,4-dichloro-5-methyl-5,6-dihydrophenanthridin-8-ol and 4-chloro-5-methyl-2-nitro-5,6-dihydrophenanthridin-8-ol

As already mentioned, obtaining the 5,6-dihydro substrate is beneficial in the study of how the phenanthridines biological activity is altered when it is not fully aromatized. Since compound **39** was unobtainable through flash chromatography after the IMDAF reaction of compound **41**, substituting the remaining N-hydrogen with a methyl group would serve the same purpose, and change its chemical properties the least. Compound **46** was synthesized as displayed in Scheme 2.17.



Scheme 2.17. Reactants and conditions for the IMDAF reaction of compound 46 - Reaction times; X = Cl: 110 min, X = NO_2: 60 min
[a]Due to co-elution with other unknown compounds.

The reaction towards compound **47b** was selective and only one product formed. It was found that the reaction towards **47a** was selective, but the crude product was stored over a weekend before the flash chromatography could be performed. This was found to have a severe detrimental effect on the compound. Small amounts of compound **40a** formed, along with other unknown compounds. Compound **40a** was separable from compound **47a**, but not from three other compounds (indicated by a TLC analysis). There was no time left to repeat the experiment, as all of compound **46a** was used in the first reaction. As with compound **40b**, compound **47b** had to be washed with pentane, which successfully purified it.

2.2.3. Conclusion

Selective reaction conditions towards 8-hydroxyphenanthridine was not found for compound **37a**, and no reaction mechanism where both the hydroxy- and chloride group is eliminated has been found.

The second strategy towards 8-hydroxyphenanthridine was successful, compounds **41** selectively produced compound **40** in a two step reaction. Though only compound **40a** was successfully oxidized in a larger scale with method a (Scheme 2.16), both compound **40a** and **40b** was oxidized with method b (Scheme 2.16). The two step reaction produced satisfactory yields after washing with pentane.

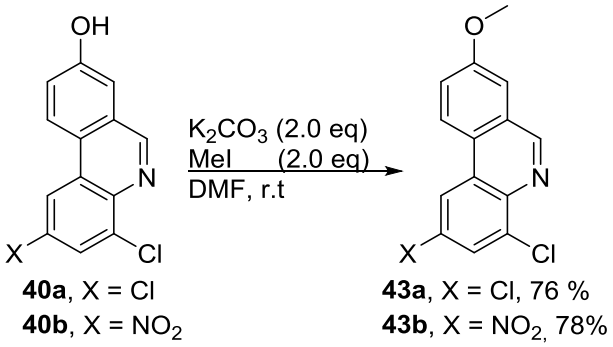
Compound **46b** reacted selectively towards compound **47b** with the IMDAF reaction and produced satisfactory yields after washing with pentane.

2.3. Methylation of phenanthridin-8-ol derivatives

This section describes the O-methylation of compounds **40** to further study biological activity of phenanthridines.

2.3.1. Synthesis of 2,4-dichloro-8-methoxyphenanthridine and 4-chloro-8-methoxy-2-nitrophenanthridine

8-Methoxyphenanthridine was synthesized as displayed in Scheme 2.*18*.



Scheme 2.18. Reactants and reaction conditions for O-mehtylation of compound 40 - Reaction times: X = Cl, 75 min - X = NO_2, 40 min.

Compound **40** reacted selectively towards compounds **43**. As with previous phenanthridines in this thesis, the compounds had to be washed with pentane, which successfully purified them.

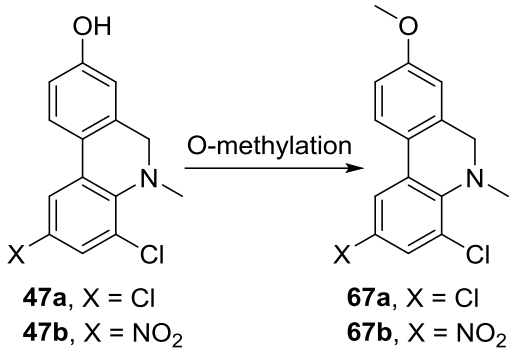
2.3.2. Conclusion

Compound **43** was successfully synthesized from compound **40**, isolated by flash chromatography and purified by washing with pentane.

3. Future research

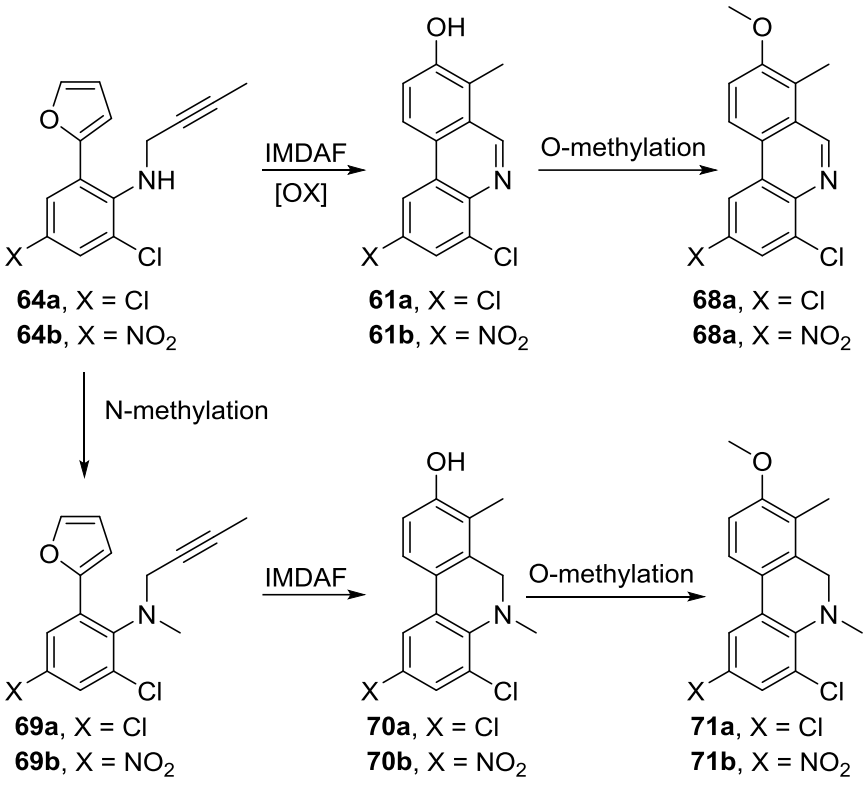
During the work of this thesis three 8-hydroxy- and two 8-methoxyphenanthridines has successfully been synthesized. There are more substrates which would yield interesting information related to the SAR.

Methylation of compound **47** as was done for compounds **40**, will provide two more substrates to be tested for biological activity, as displayed in Scheme 3.1.



Scheme 3.1. Opportunity for further synthesis on compound 47.

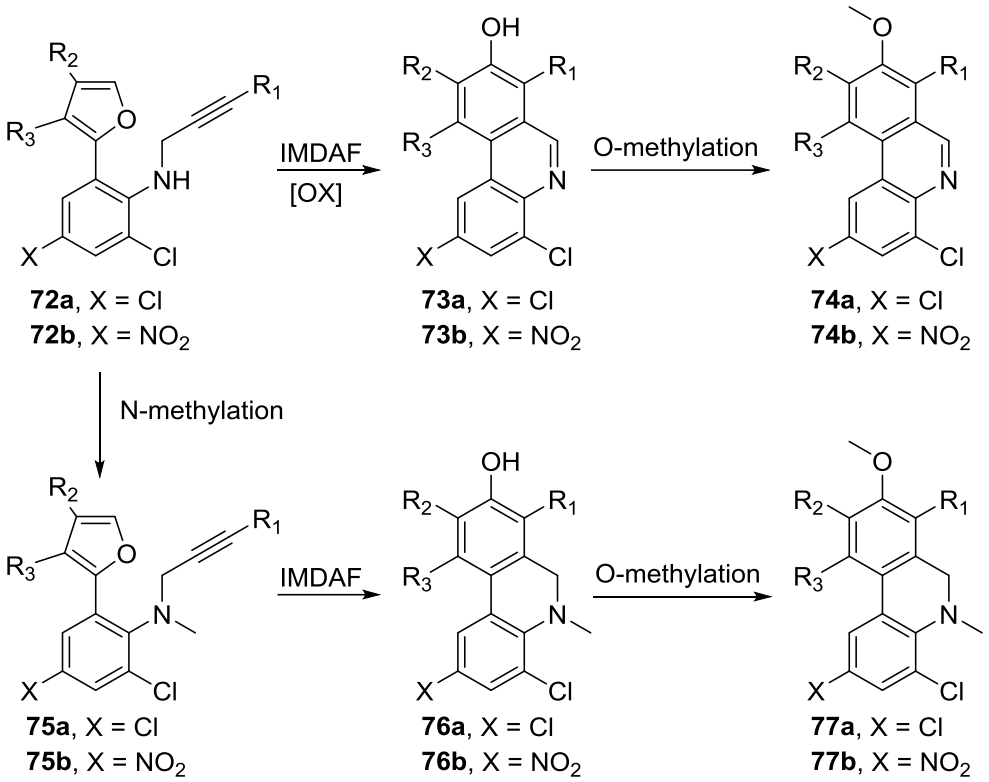
More work towards different 8-hydroxy- and 8-methoxyphenanthridine substrates can be conducted. Completing the screening for optimal reaction conditions towards compounds **64**, will provide the possible means to produce 7-methylated 8-hydroxyphenanthridines. This can in turn produce four more 8-hydroxyphenanthridines and four 8-methoxyphenanthridines, in the same manner as those synthesized during the work of this thesis, which will be tested for their biological activity. These substrates are displayed in Scheme 3.2.



Scheme 3.2. Opportunity for further synthesis of 7-methyl 8-hydroxyphenanthridine substrates.

If the synthesis of compound **64** and **69** is successful, new means of synthesizing 7-substituted 8-hydroxyphenanthridines has been found (Scheme 3.3).

Finally, by employing substituted 2-furanyl moieties, a fully substituted ring C can be obtained, as displayed in Scheme 3.3.[1]



Scheme 3.3. Possible opportunities for a fully substituted C-ring.

4. Conclusion

During the work of this thesis, several 8-hydroxy- and 8-methoxyphenanthridines has been synthesized by microwave-mediated IMDAF reactions. Despite the difficulty when isolating the *N*-alkylated anilines required, when small amounts of starting material was present after the alkylation.

The first strategy employed towards synthesizing 8-hydroxyphenanthridines, using compound **37a** as the starting material was only semi successful, a ~50/50 selectivity of compounds **40a** and **40c** was found. No probable reaction mechanism as to why the selectivity is low, has yet been found. The IMDAF adduct of compound **37a** (Compound **66a**) is not stabile, and shows a ~50/50 selectivity even at 3-4 °C, under which it was stored.

Our second strategy turned out to be successful, the IMDAF reaction when employing compounds **41** and **46** as the starting materials, were selective. 8-Hydroxyphenanthridines can readily be synthesized, as well as the 5,6-dihydro substrates.

Isolation of the starting materials for the IMDAF reactions (compounds **37a**, **41a** and **64**), were at times difficult. When only small amounts of compound **36a** were still present after *N*-alkylation, it co-eluted with the *N*-alkylated product, even if the two compounds seemingly have different R_f values when isolated, or by TLC analysis.

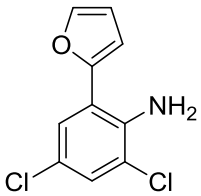
Though isolation of the dichloro substrates were difficult, the nitro substrates had to be N-alkylated with care, as they were more prone to N,N-alkylation. The isolation was on the other hand easier, as the same co-elution did not occur (except for compound **64b**).

Finally, an optimization of the reaction conditions for compounds **64** were started, but the co-elution problem also occurred with this substrate. Letting the reactions stir for 15-30 minutes longer, should N-alkylate the last of the starting material, which would solve this issue.

5. Experimental

The ^{1}H-NMR spectra were recorded at 800 MHz, 600 MHz, 500 MHz or 300 MHz using Bruker AVIIIHD800, AVII600, DRX500 or DPX300 instruments respectively. The decoupled ^{13}C-NMR spectra were recorded at 200 MHz, 150 MHz, 125 MHz or 75 MHz with the aforementioned instruments. All *J* values are reported in Hertz. Mass spectra under electron spray conditions were recorded with a Micromass Prospec Q instrument. Flash chromatography was performed on silica gel (Merck no. 09385). The UV lamp used in oxidation reactions was emitting at 315–400 nm with peaks at 352 and 368 nm. TBAB and compound **36** were dried under high vacuum over night before the experiments. Dry DCM, DMF and THF was obtained from a solvent purification system (MB SPS-800 MBraun, Garching, Germany). Hexanes used in flash chromatography was redistilled from technical grade hexanes. MeCN (HPLC quality) was degassed using the freeze-pump-thaw method with $N_2(l)$. The freeze-pump-thaw method consisted of crystallizing MeCN with liquid nitrogen, smelting the MeCN under high vacuum, which was repeated three times. Microwave experiments were carried out in a sealed pressure vessel in a microwave synthesis reactor Monowave 300. Potassium(furan-2-yl)trifluoroborate was synthesized in bulk by another member of our group. All other reagents were commercially available and used as received.

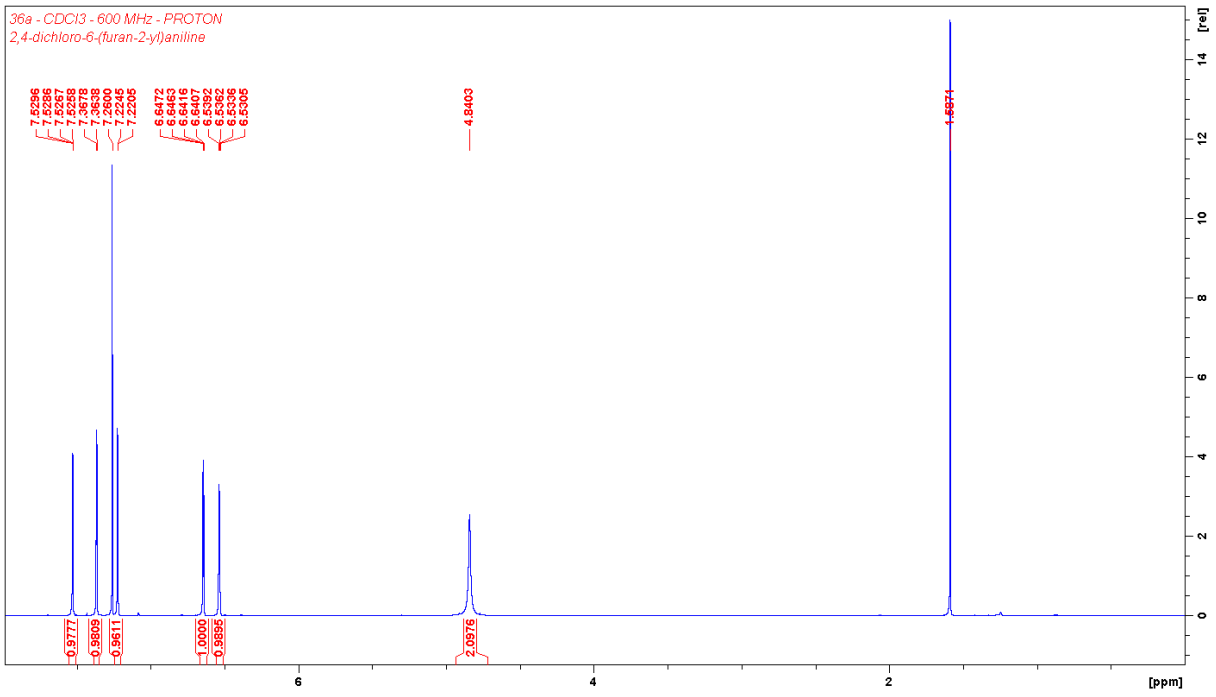
Synthesis of 2,4-dichloro-6-(furan-2-yl)aniline (36a)[1]



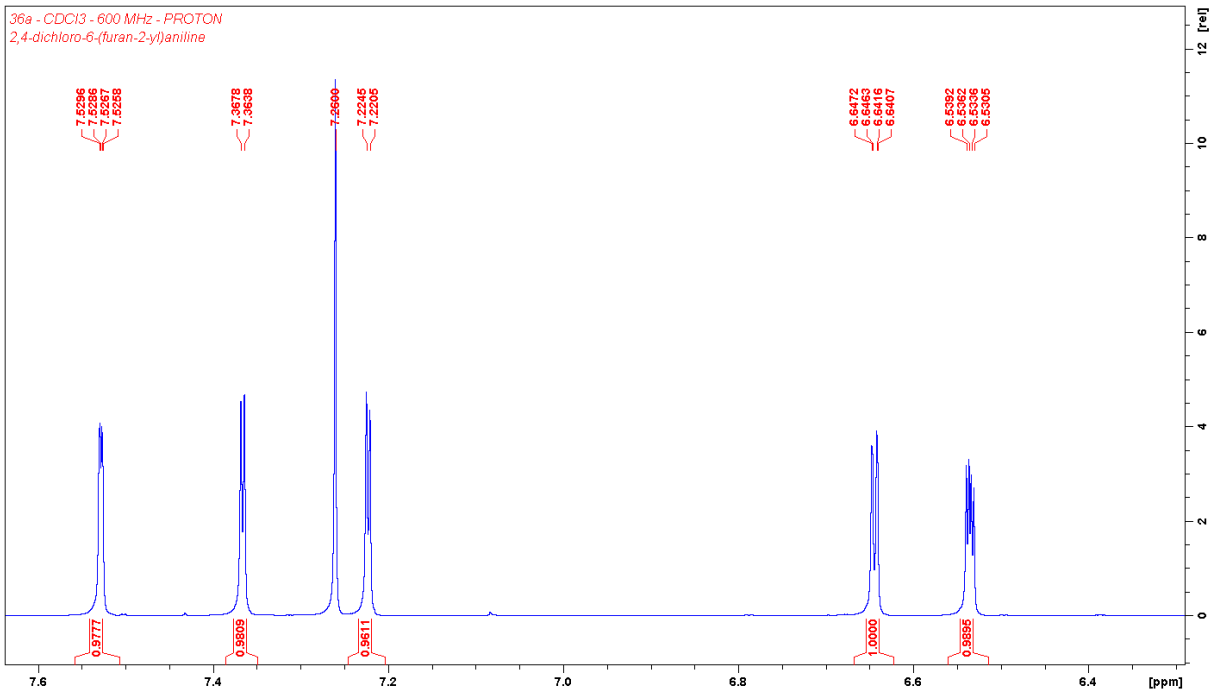
36a

Potassium carbonate (2.50 g, 18.1 mmol), potassium (furan-2-yl)trifluoroborate (3.29 g, 18.9 mmol), triphenylphosphine (803 mg, 3.06 mmol) and palladium acetate (131 mg, 0.585 mmol) were subsequently added to a stirring solution of 2-bromo-4,6-dichloroaniline (**35a**) (3.32 g, 13.8 mmol) in EtOH/H2O 95:5 (v/v) (160 mL). The resulting mixture was degassed with Ar and refluxed for 5 h. The reaction mixture was filtered through silica gel eluting with CH2Cl2 (150 mL), and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel using EtOAc/DCM/hexanes (1:4:45) with a gradient. Yield 2.42 g (85%) as a pale pink solid.

^{1}H NMR coincides with the literature and no further analysis was performed.[1]

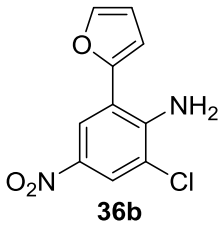


Spectrum 3. 600 MHz, $CDCl_3$, ^{1}H NMR spectrum of 2,4-dichloro-6(furan-2-yl)aniline **(36a).**



Spectrum 4. 600 MHz, $CDCl_3$, ^1H NMR spectrum of 2,4-dichloro-6(furan-2-yl)aniline **(36a)** expanded**.**

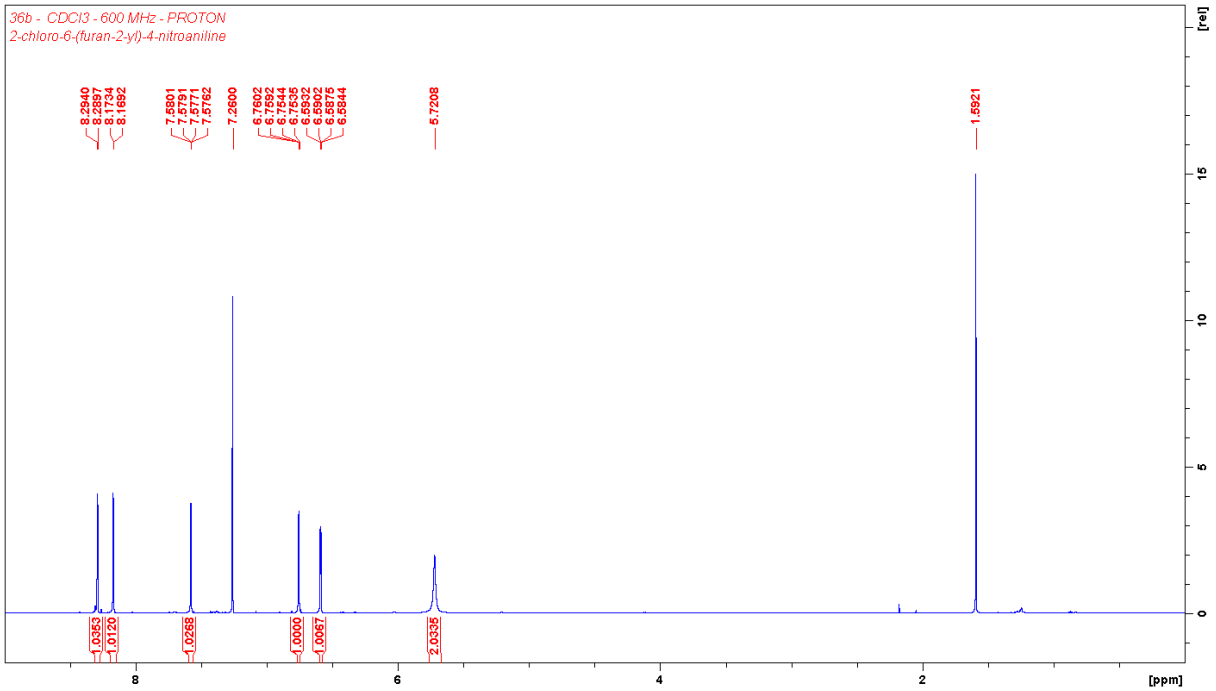
Synthesis of 2-chloro-6-(furan-2-yl)-4-nitroaniline (36b)[1]



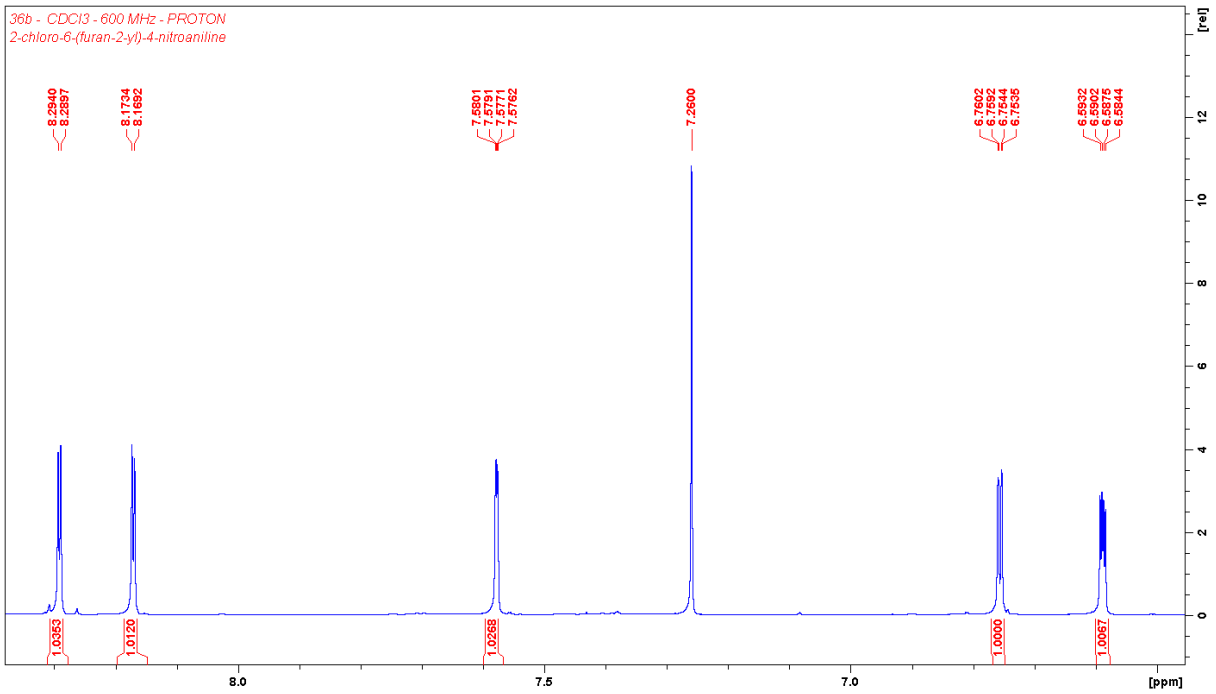
36b

Potassium carbonate (2.76 g, 20.0 mmol), potassium (furan-2-yl)trifluoroborate (2.61 g, 15.0 mmol), triphenylphosphine (692 mg, 2.64 mmol) and palladium acetate (171 mg, 0.763 mmol) were subsequently added to a stirring solution of 2-chloro -6-(furan-2-yl)-4-nitro aniline (**35b**) (2.53 g, 10.1 mmol) in EtOH/H2O 95:5 (v/v) (200 mL). The resulting mixture was degassed with Ar and refluxed for 21 h. The reaction mixture was filtered through silica gel eluting with DCM (200 mL), and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel eluting with EtOAc/DCM/hexanes (1:4:45) with a gradient. Yield 1.29 g (55%) as a yellow solid.

^{1}H NMR coincides with the literature and no further analysis was performed.[1]

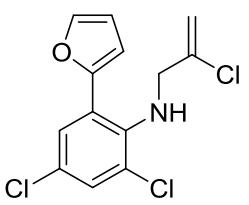


Spectrum 5. 600 MHz, $CDCl_3$, ^{1}H NMR spectrum of 2-chloro-6-(furan-2-yl)-4-nitroaniline **(36b).**

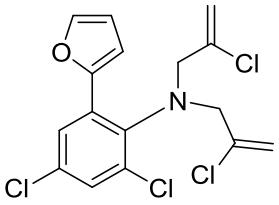


Spectrum 6. 600 MHz, $CDCl_3$, ^1H NMR spectrum of 2-chloro-6-(furan-2-yl)-4-nitroaniline **(36b)** expanded**.**

Synthesis of 2,4-Dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline (37a) and 2,4-dichloro-*N*.*N*-bis(2-chloroallyl)-6-(furan-2-yl)aniline (38a)



37a



38a

60% NaH in mineral oil (105.2 mg) was extracted with pentane (3 x 15 mL). The residual pentane was removed under reduced pressure. Pure NaH (75.4 mg, 3.14 mmole) remained, the flask was degassed with Ar (g) and THF (25 mL) was added to the flask using a needle. 2,4-Dichloro-6-(furan-2-yl)aniline (**36a**) (199.5 mg, 0.87 mmole) and TBAB (293.0 mg, 0.9 mmole) was subsequently added to the flask. The flask was degassed with Ar (g) for 10 minutes, then 2,3-dichloroprop-1-ene (407.7 mg, 3.67 mmole) was added to the mixture through the septum and the mixture stirred for 20 hours at 45 °C. The reaction was quenched with 25 mL water. The aqueous phase was extracted with 3x75 mL DCM, the combined extracts were dried with $MgSO_4$, filtered, concentrated under reduced pressure and separated by flash chromatography on silica gel. Eluted with 2.5 column volumes of DCM/Hexanes 1:99 and 3 column volumes of DCM/Hexanes 7:93. Yield 172 mg (65 %) of compound **37a** as a pale yellow oil and 14.8 mg (5 %) of compound **38a** as a yellow oil.

2,4-Dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline **(37a)**

^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.51 (dd, *J* = 1.8, 0.6 Hz, 1H, H-5 in furyl), 7.46 (d, *J* = 2.45 Hz, 1H, H-5), 7.29 (d, *J* = 2.5 Hz, 1H, H-3), 6.79 (dd, *J* = 3.4, 0.6 Hz, 1H, H-3 in furyl), 6.52 (dd, *J* = 3.4, 1.8 Hz, 1H, H-4 in furyl), 5.22 (m, 2H, $NHCH_2C(Cl)C\underline{H_2}$), 4.62 (br s, 1H, NH), 3.68 (s, 2H, $NHC\underline{H_2}C(Cl)CH_2$).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 150.35 (C-2 in furyl), 142.51 (C-5 in furyl), 139.87 (C-1), 139.75 ($NHCH_2\underline{C}(Cl)CH_2$), 128.63 (C-3), 127.60 (C-2), 127.41 (C-5), 126.86 (C-4), 124.70 (C-6), 114.04 ($NHCH_2C(Cl)\underline{C}H_2$), 111.96 (C-4 in furyl), 109.81 (C-3 in furyl), 53.12 ($NH\underline{C}H_2C(Cl)CH_2$).

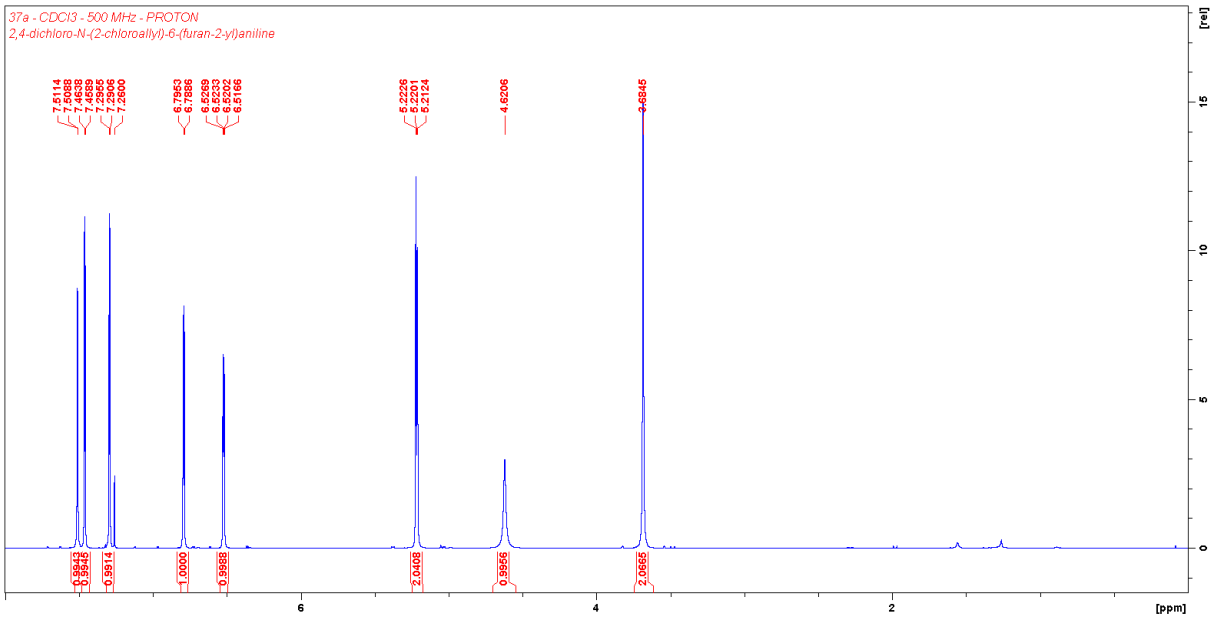
HRMS ESI calcd for $C_{13}H_{10}Cl_3NO$ 300.9828, found 300.9823.

2,4-dichloro-*N*.*N*-bis(2-chloroallyl)-6-(furan-2-yl)aniline (**38a**)

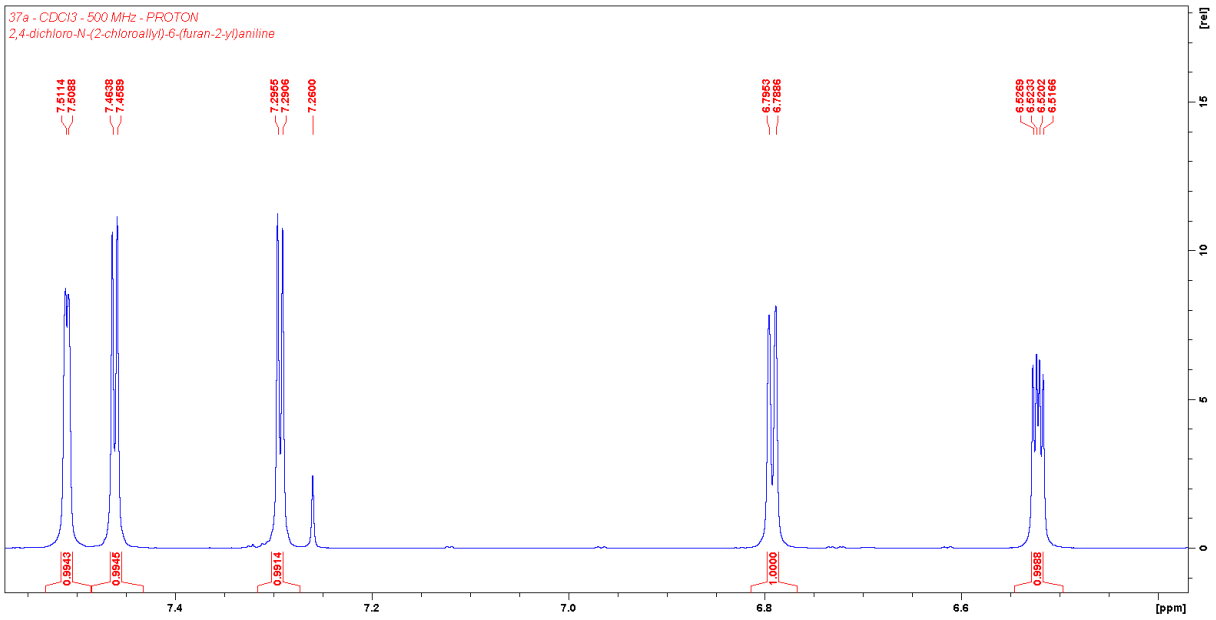
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 1.8 Hz, 1H, H-4 in furyl), 7.50 (d, *J* = 2.5 Hz, 1H, H-5), 7.34 (d, *J* = 2.5 Hz, 1H, H-3), 6.86 (d, *J* = 3.4 Hz, 1H, H-3 in furyl), 6.52 (dd, *J* = 3.4, 1.8 Hz, 1H, H-4 in furyl), 5.37 (s, 2H, $N(CH_2C(Cl)C\underline{H_2})_2$), 5.30 (s, 2H, $N(CH_2C(Cl)C\underline{H_2})_2$), 3.85 (s, 4H, $N(C\underline{H_2}C(Cl)CH_2)_2$).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 150.35 (C-2 in furyl), 142.94 (C-5 in furyl), 141.45 (C-1), 138.81 ($N(CH_2\underline{C}(Cl)CH_2)_2$), 135.67 (C-2), 132.14 (C-6), 130.92 (C-4), 128.05 (C-5), 115.78 ($N(CH_2C(Cl)\underline{C}H_2)_2$), 112.14 (C-4 in furyl), 110.84 (C-3 in furyl), 58.74 ($N(\underline{C}H_2C(Cl)CH_2)_2$).

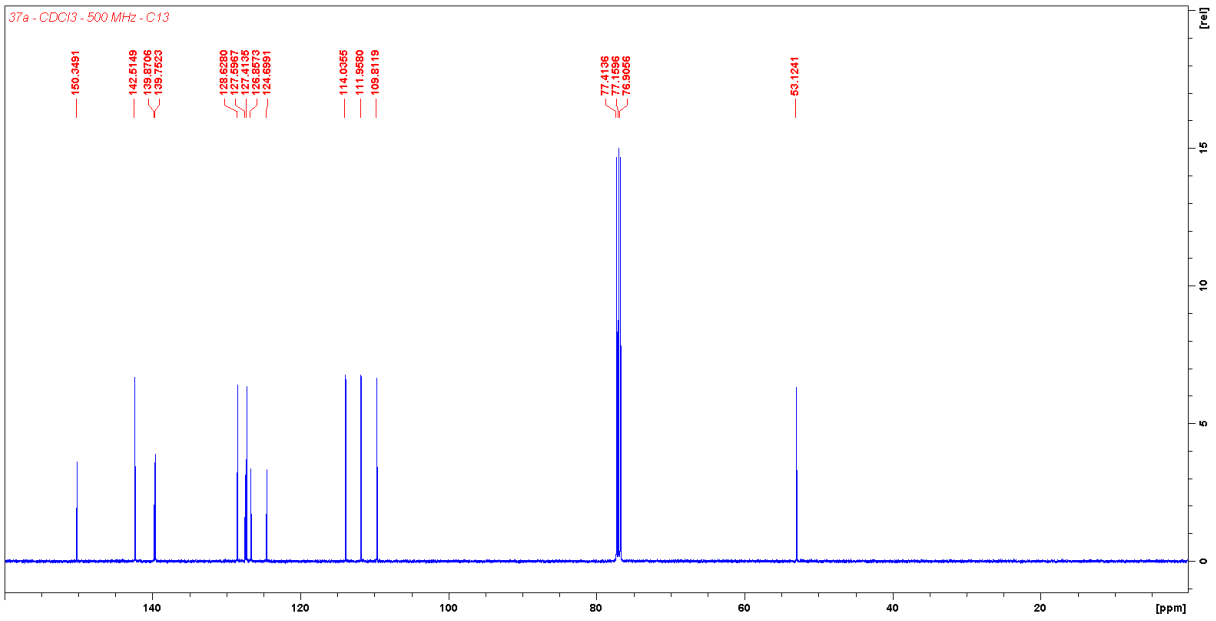
HRMS ESI calcd for $C_{16}H_{13}Cl_4NO$ 374.9751, found 374.9746.



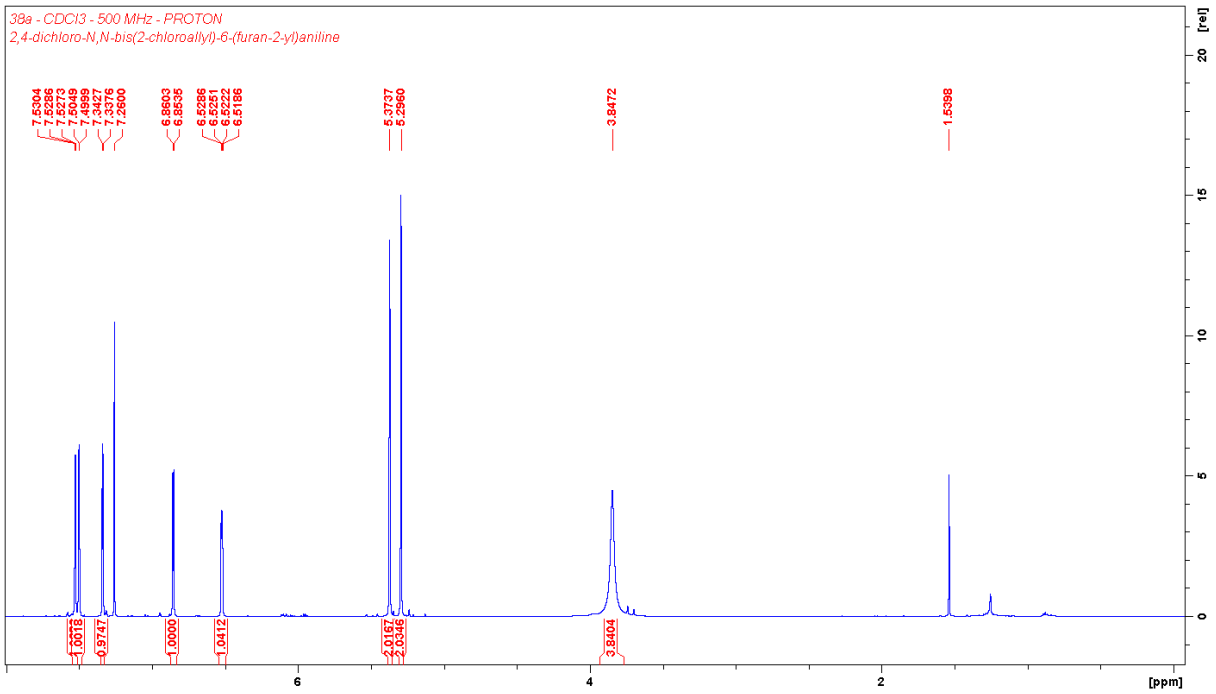
Spectrum 7. 500 MHz, $CDCl_3$, ^{1}H NMR spectrum of 2,4-Dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline **(37a).**



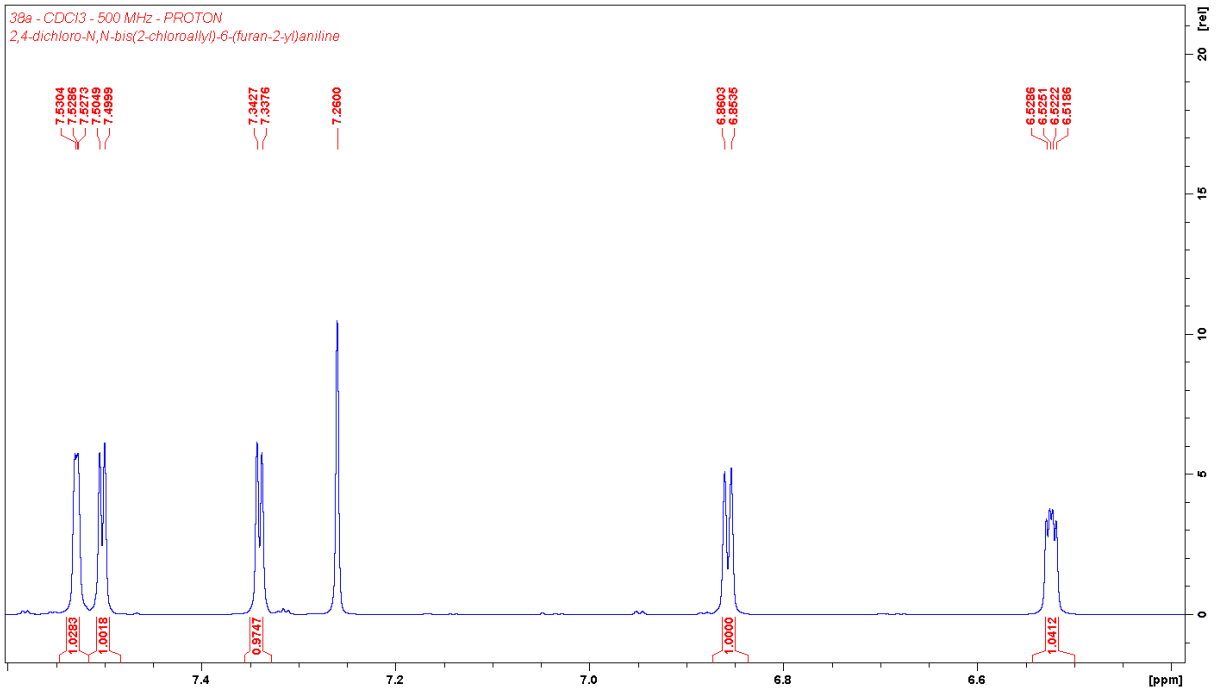
Spectrum 8. 500 MHz, $CDCl_3$, ^{1}H NMR spectrum of 2,4-Dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline **(37a)** expanded**.**



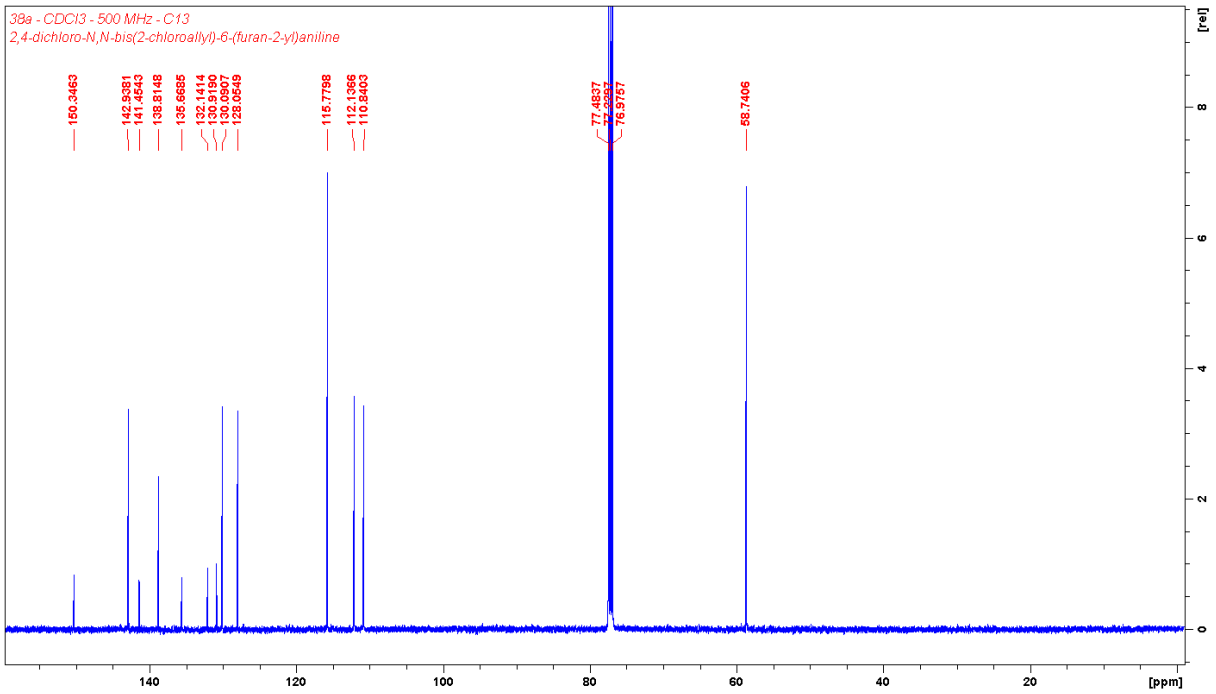
Spectrum 9. 125 MHz, $CDCl_3$, ^{13}C NMR spectrum of 2,4-Dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline **(37a).**



Spectrum 10. 500 MHz, $CDCl_3$, ^1H NMR spectrum of 2,4-Dichloro-*N.N*-bis(2-chloroallyl)-6-(furan-2-yl)aniline **(38a).**

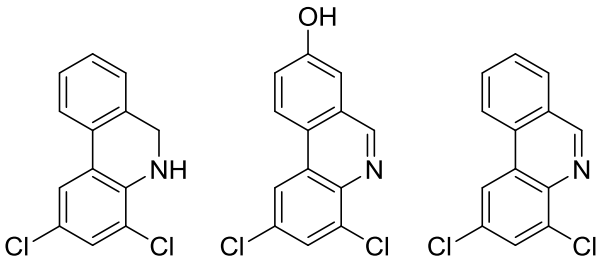


Spectrum 11. 500 MHz, $CDCl_3$, ^1H NMR spectrum of 2,4-Dichloro-*N.N*-bis(2-chloroallyl)-6-(furan-2-yl)aniline **(38a)** expanded.



Spectrum 12. 125 MHz, $CDCl_3$, ^{13}C NMR spectrum of 2,4-Dichloro-*N*.*N*-bis(2-chloroallyl)-6-(furan-2-yl)aniline **(38a).**

Synthesis of 2,4-dichloro-5,6-dihydrophenanthridine (39c), 2,4-dichlorophenanthridin-8-ol (40a) and 2,4-dichlorophenanthridine (40c)



39c **40a** **40c**

Procedure for compound **39a**, **40a** and **40c** employing compound **37a**. Compound **37a** (220.0 mg, 0.7 mmole) was weighed in a pressure vial, degassed MeCN (15 mL) was added to the vial and the vial was degassed with Ar (10 min). The lid was taken off under a stream of Ar and two drops of water was added. The lid was put back on and the capsule was degassed for another 5 minutes. The mixture stirred at 150 °C for three hours in a microwave reactor. The capsule was cooled down to 60 °C and was taken out of the microwave oven. The mixture was transferred to a round bottomed flask and concentrated under reduced pressure. The mixture was dry loaded onto a 4 cm column and compounds were attempted isolated with flash chromatography, eluted with 15:85 DCM/Hexanes and swapped to 60:40 EtOAc/Hexanes after compound **39c** and **40c** eluted from the column. No isolated yields can be reported when employing compound **37a**.

2,4-Dichloro-5,6-dihydrophenanthridine (**39c**).

^{1}H-NMR (800 MHz, DMSO): δ 7.80 (d, *J* = 7.1 Hz, 1H), 7.73 (d, *J* =2.2 Hz, 1H), 7.30 (m, 3H), 7.22 (d, *J* = 7.1 Hz, 1H), 6.03 (s, 1 H, N-H), 4.39 (s, 2 H, H-6).

^{13}C-NMR (200 MHz, DMSO): δ 141.31, 132.26, 129.74, 128.36, 127.68, 127.64, 126.19, 123.17, 122.85, 121.89, 120.55, 118.37, 44.78.

HRMS ESI calcd for $C_{13}H_9Cl_2N$ 249.0112, found 249.105.

2,4-Dichlorophenanthridin-8-ol (**40a**).

^{1}H-NMR (600 MHz, DMSO) δ 10.52 (s, 1H, OH), 9.33 (s, 1H, H-6), 8.78-8.76 (m, 2H, H-3 and H-9), 7.95 (d, *J* = 2.1 Hz, 1H, H-3), 7.51-7.47 (m, 2H, H-7 and H-10).

^{13}C-NMR (150 MHz, DMSO) δ 158.23 (C-8), 153.98 (C-6), 137.53 (C-4a), 134.47 (C-4), 131.43 (C-2), 128.25 (C-6a or 10b), 127.32 (C-3), 126.78 (C-6a or 10b), 125.11 (C-9), 123.67 (C-10a), 122.83 (C-10), 121.14 (C-1), 111.21 (C-7).

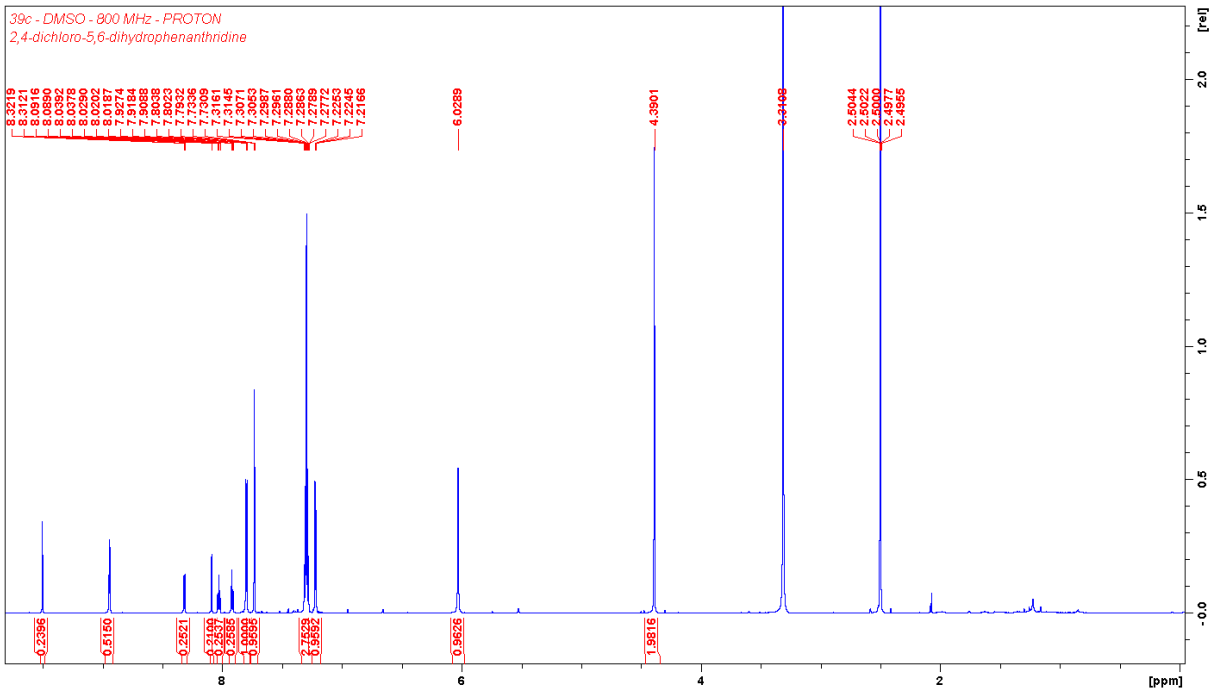
HRMS ESI calcd for $C_{13}H_7Cl_2NO$ 262.9905, found 262.9900.

2,4-Dichlorophenanthridine (**40c**).

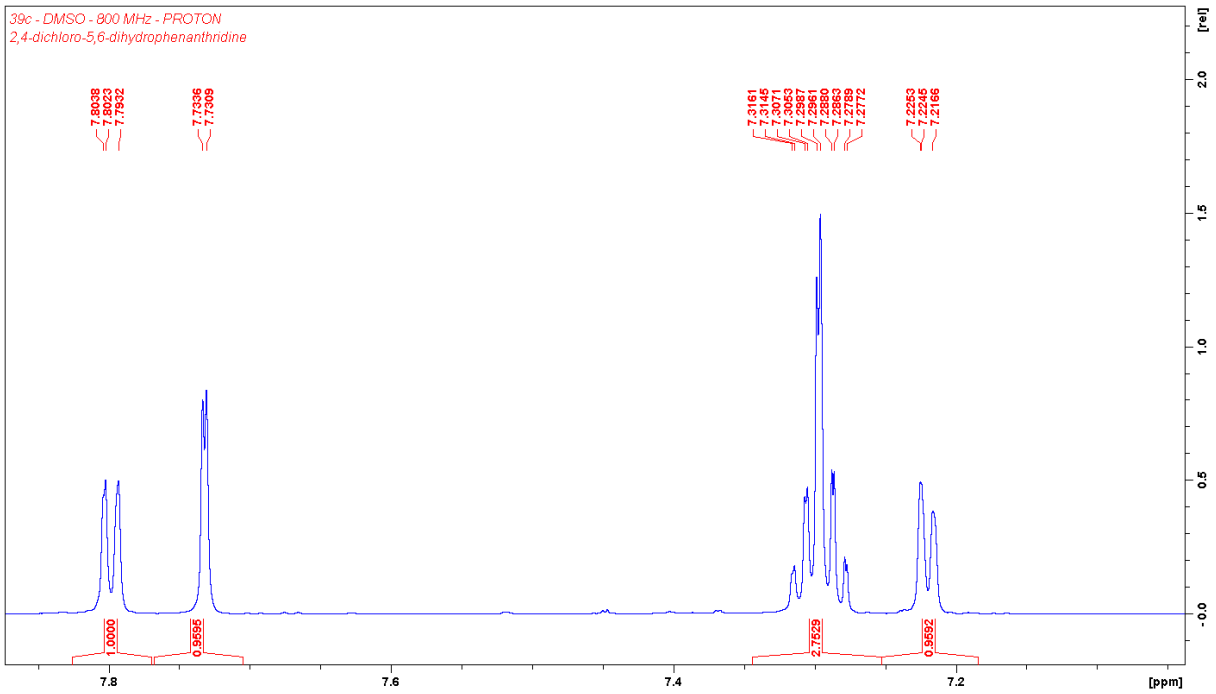
^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.52 (d, 1H, *J* = 8.0 Hz, 1 H), 8.45 (d, *J* = 2.2 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.94-7.90 (m, Hz, 1 H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.81-7.78 (m, 1H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 154.41, 139.58, 135.57, 132.73, 132.02, 131.56, 129.29, 129.04, 126.77, 126.77, 126.65, 122.40, 121.12.

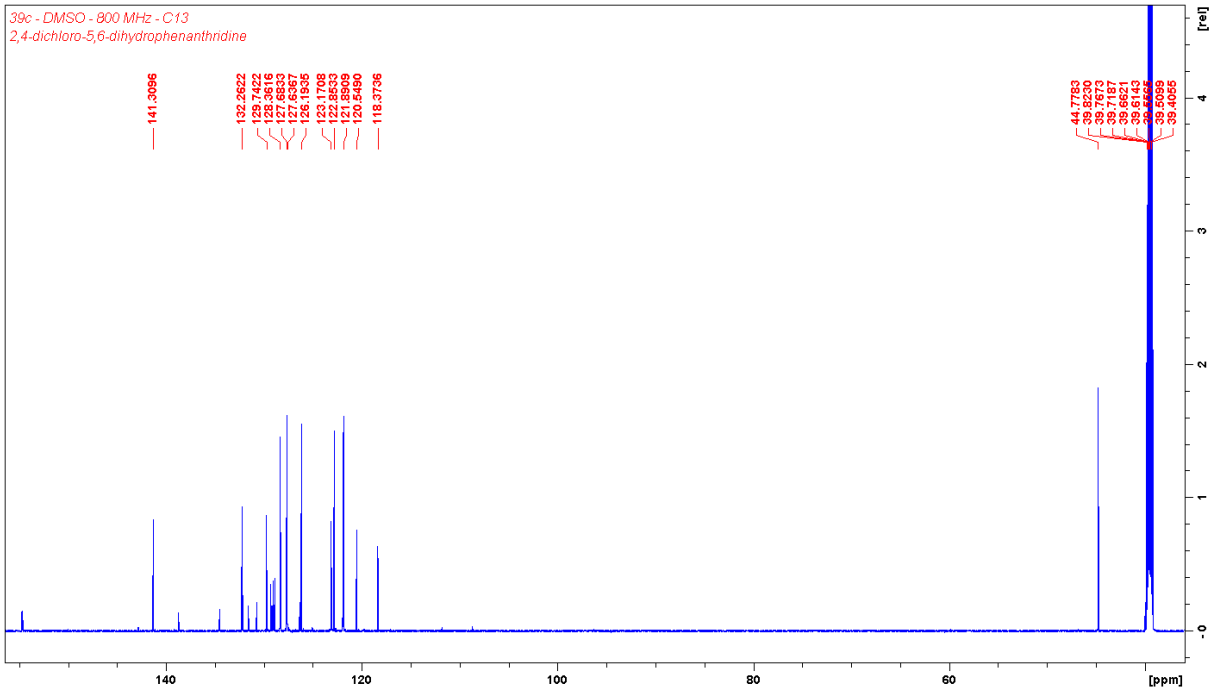
HRMS ESI calcd m/z for $C_{13}H_7Cl_2N$ 262.9905, found 246.9950.



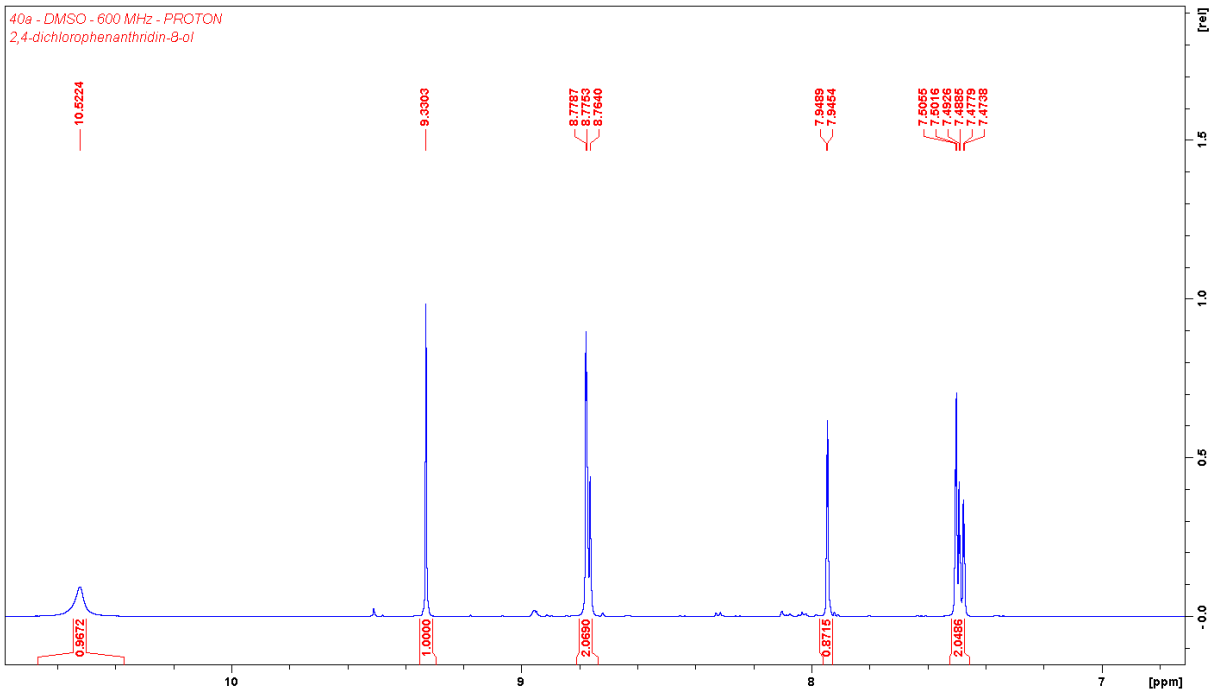
Spectrum 13. 800 MHz, DMSO, ^{1}H NMR of 2,4-dichloro-5,6-dihydrophenanthridine (**39c**), with compound 40c present.



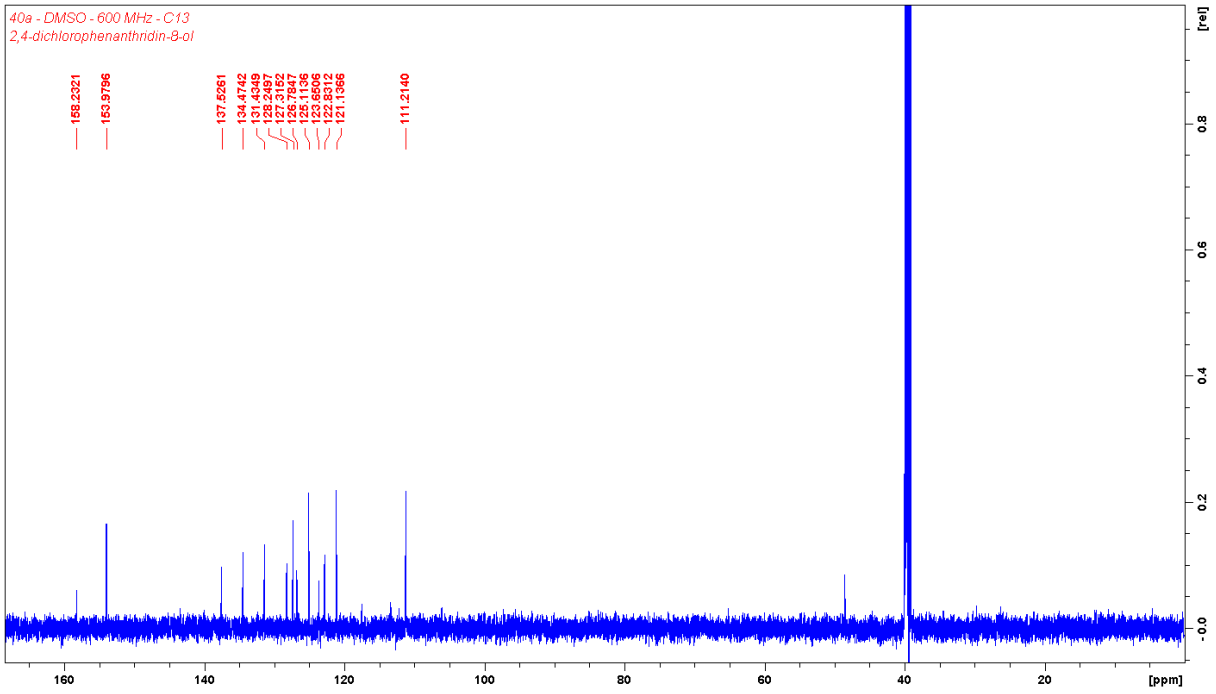
Spectrum 14. 800 MHz, DMSO, ^{1}H NMR of 2,4-dichloro-5,6-dihydrophenanthridine (**39c**), expanded**.**



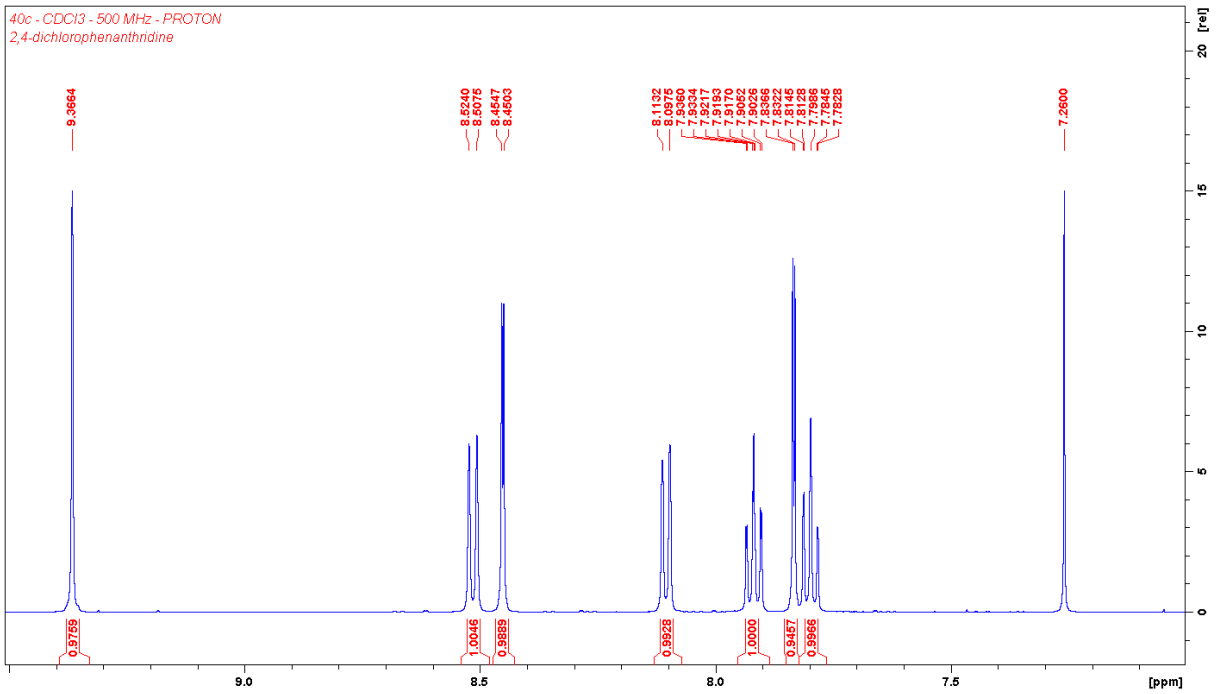
Spectrum 15. 200 MHz, DMSO, ^{13}C NMR of 2,4-dichloro-5,6-dihydrophenanthridine (**39c**), peaks from compound **40c** is not marked.



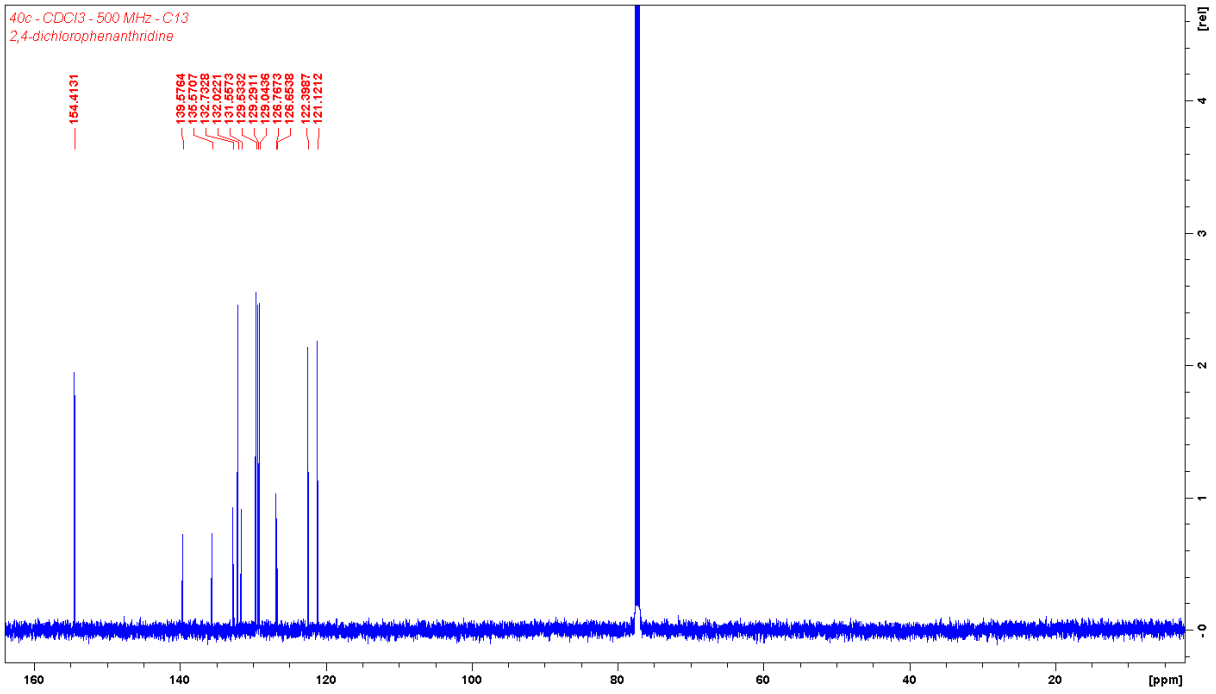
Spectrum 16. 600 MHz, DMSO, ^{1}H NMR of 2,4-dichlorophenanthridin-8-ol (**40a**).



Spectrum 17. 150 MHz, DMSO, ^{13}C NMR of 2,4-dichlorophenanthridin-8-ol (**40a**).

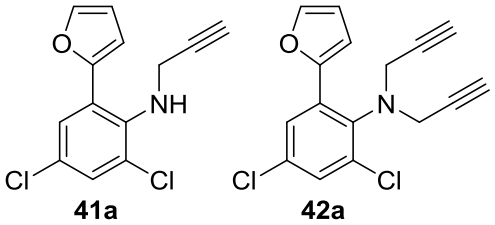


Spectrum 18. 500 MHz, $CDCl_3$, ^{1}H NMR of 2,4-dichlorophenanthridine (**40c**).



Spectrum 19. 150 MHz, $CDCl_3$, ^{13}C NMR of 2,4-dichlorophenanthridine (**40c**).

Synthesis of 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-yn-1-yl)aniline (41a) and 2,4-dichloro-6-(furan-2-yl)-*N*,*N*-di(prop-2-yn-1-yl)aniline (42a)



2,4-Dichloro-6-(furan-2-yl)aniline (**36a**)(410 mg, 1.80 mmol) and TBAB (1.08 g, 3.7 mmol) were subsequently added to stirring THF (30 mL, dry). The flask was degassed with Ar (5 min) before NaH (ca 60% in mineral oil)(135 mg, 3.36 mmol) was added. The resulting mixture stirred for 15 minutes before propargylbromide (**58**)(0.29 mL, 2.6 mmol) was added. The mixture stirred at 45 °C for 1.5 h and was quenched with water (25 mL). The aqueous phase was extracted with DCM (3 x 15 mL), the combined extracts were dried and filtered, and concentrated under reduced pressure. The compounds were isolated with flash chromatography on silica gel, eluted with acetone/hexanes 1:49. Yield 341 mg (71 %) of compound **41a** as a pale pink solid and 70 mg (13 %) of **42a** as a yellow oil.

2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-yn-1-yl)aniline (**41a**)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.5 Hz, 1H, H-5), 7.51 (d, *J* = 1.8 Hz, 1H, H-5 in furyl), 7.30 (d, *J* = 2.5 Hz, 1H, H-3), 6.94 (d, *J* = 3.4 Hz, 1H, H-3 in furyl), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1H, H-4 in furyl), 4.33 (br s, 1H, NH), 3.72 (d, *J* = 2.3 Hz, 2H, $NHC\underline{H}_2CCH$), 2.18 (t, *J* = 2.3 Hz, 1H, $NHCH_2CC\underline{H}$).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 149.94 (C-2 in furyl), 142.61 (C-5 in furyl), 139.70 (C-1), 128.88 (C-2 or C-4), 128.33 (C-3), 128.05 (C-2 or C-4), 126.80 (C-5), 125.84 (C-6), 112.16 (C-4 in furyl), 110.19 (C-3 in furyl), 81.10 ($NHCH_2\underline{C}CH$), 72.26 ($NHCH_2C\underline{C}H$), 36.64 ($NH\underline{C}H_2CCH$).

HRMS ESI calcd for $C_{13}H_9Cl_2NO$ 265.0061, found 265.0056.

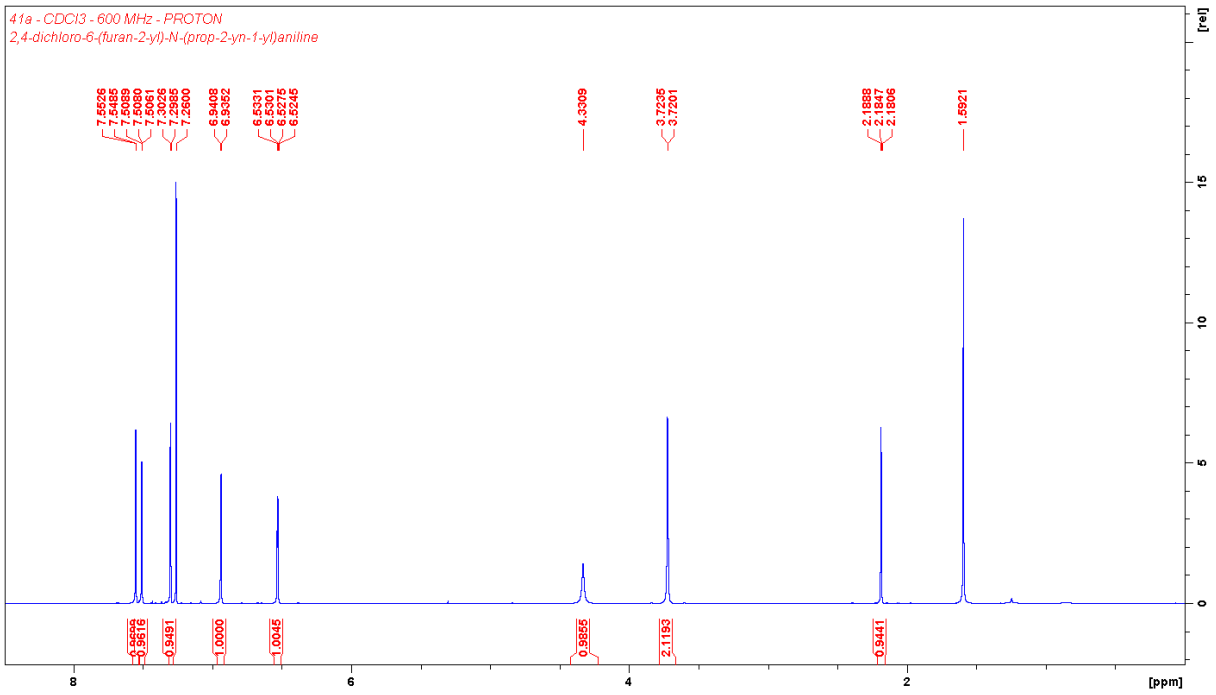
Melting point 68-69 °C.

2,4-dichloro-6-(furan-2-yl)-*N*,*N*-di(prop-2-yn-1-yl)aniline (**42a**)

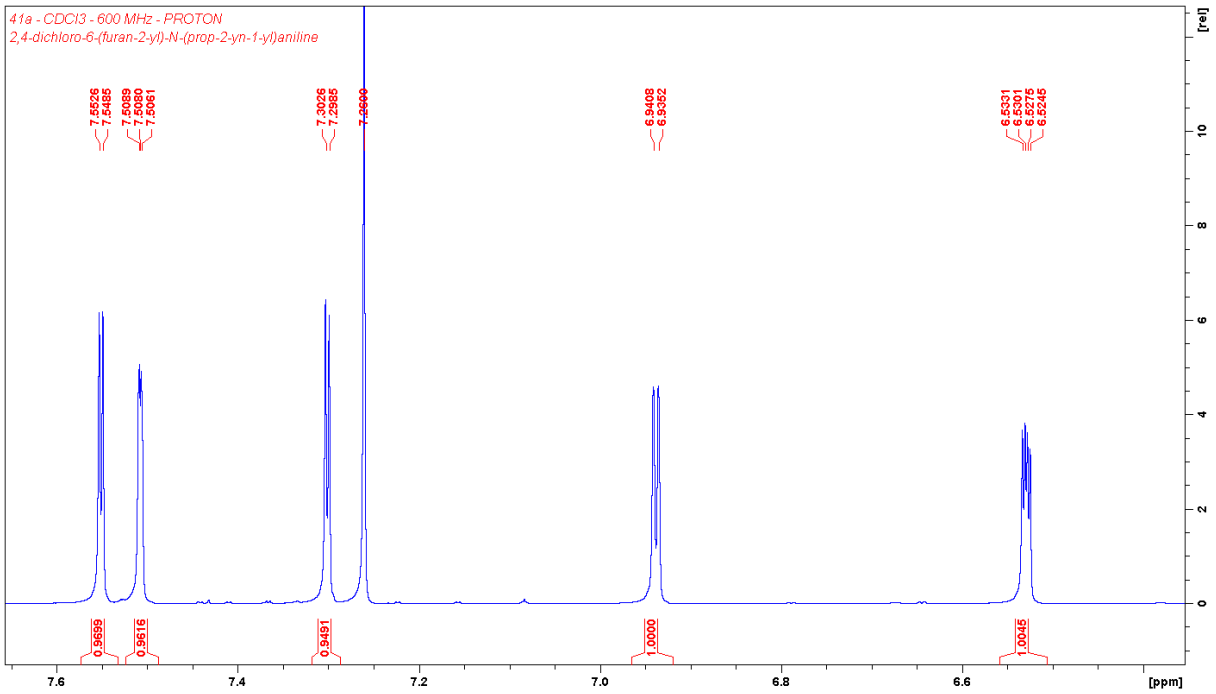
^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 2.5 Hz, 1H, H-5), 7.48 (d, *J* = 1.7 Hz, 1H, H-5 in furyl), 7.37 (d, *J* = 3.4 Hz, 1H, H-3 in furyl), 7.24 (d *J* = 2.5 Hz, 1H, H-3), 6.51 (dd, *J* = 3.4, 1.7 Hz, 1H, H-4 in furyl), 4.09 (d, *J* = 16.3 Hz, 2H, $N(C\underline{H_2}CCH_3)_2$), 3.95 (d, *J* = 16.3 Hz, 2H, $N(C\underline{H_2}CCH_3)_2$), 2.22 (t, *J* = 2.5 Hz, 2H, $N(CH_2CC\underline{H_3})_2$).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 149.48 (C-2 in furyl), 142.52 (C-5 in furyl), 139.73 (C-1), 136.42 (C-2), 133.85 (C-6), 132.60 (C-4), 128.77 (C-3), 125.39 (C-5), 112.50 (C-4 in furyl), 111.78 (C-3 in furyl), 79.91 ($N(CH_2\underline{C}CH_3)_2$), 72.98 ($N(CH_2C\underline{C}H_3)_2$), 41.10 ($N(\underline{C}H_2CCH_3)_2$).

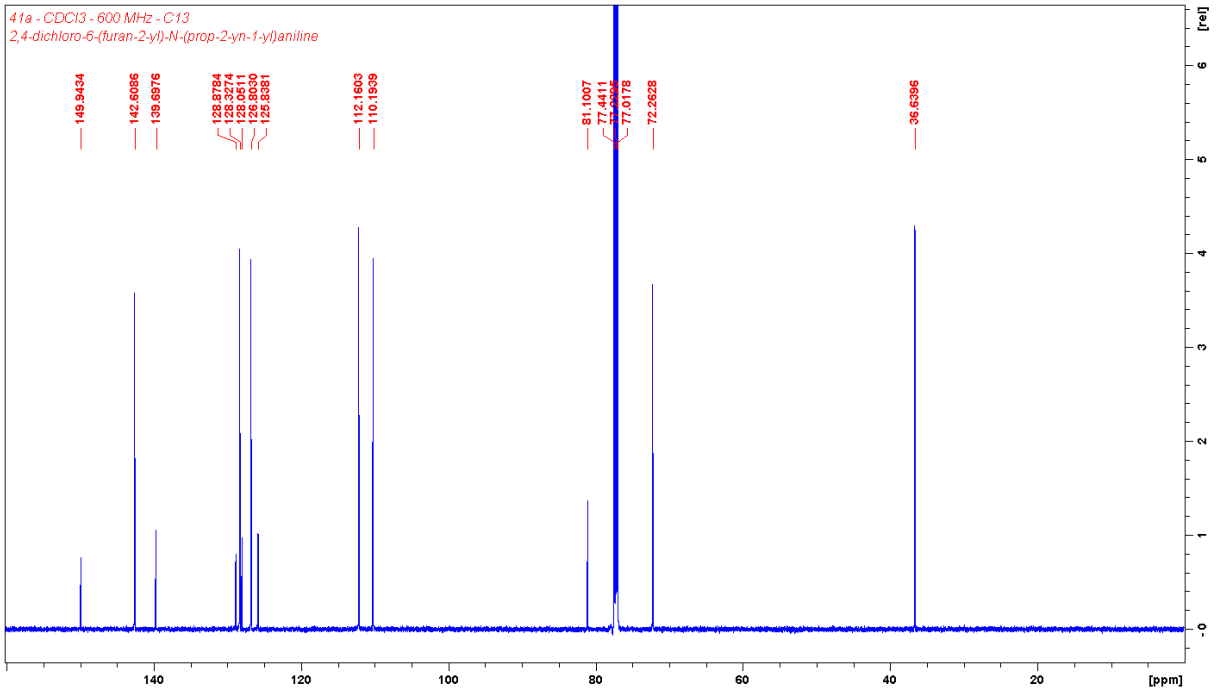
HRMS ESI calcd for $C_{16}H_{11}Cl_2NO$ 303.0218, found 303.0212.



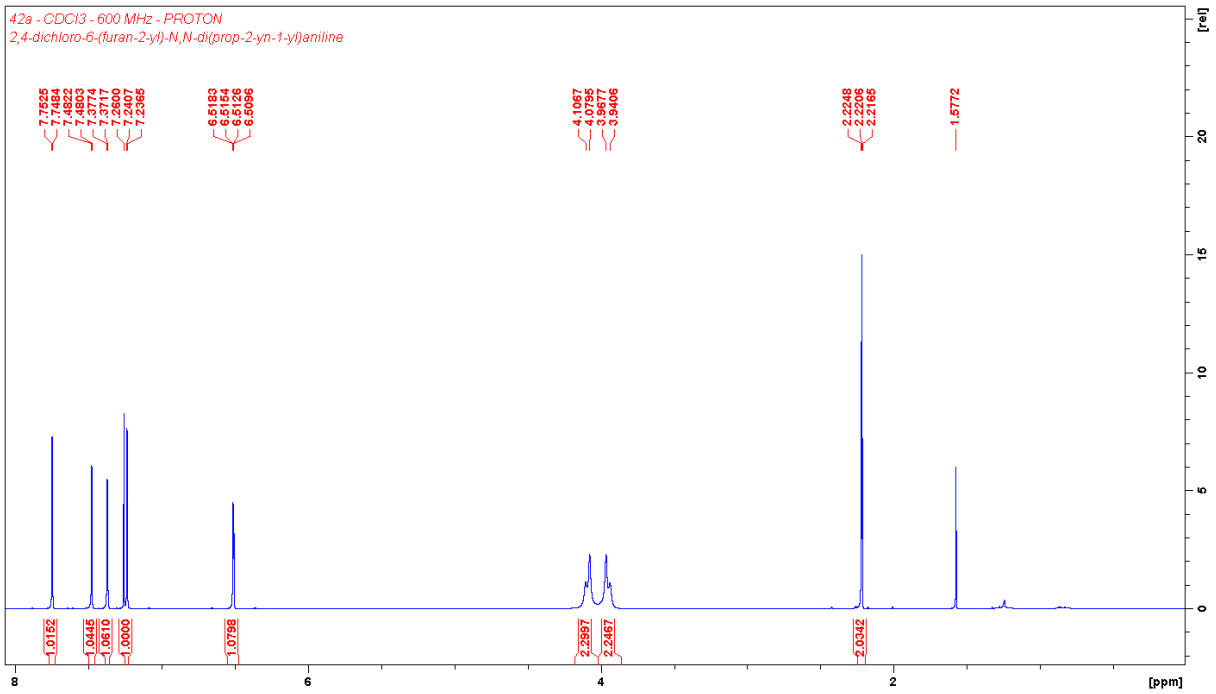
Spectrum 20. 600 MHz, $CDCl_3$ ^{1}H NMR for 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-yn-1-yl)aniline (**41a**).



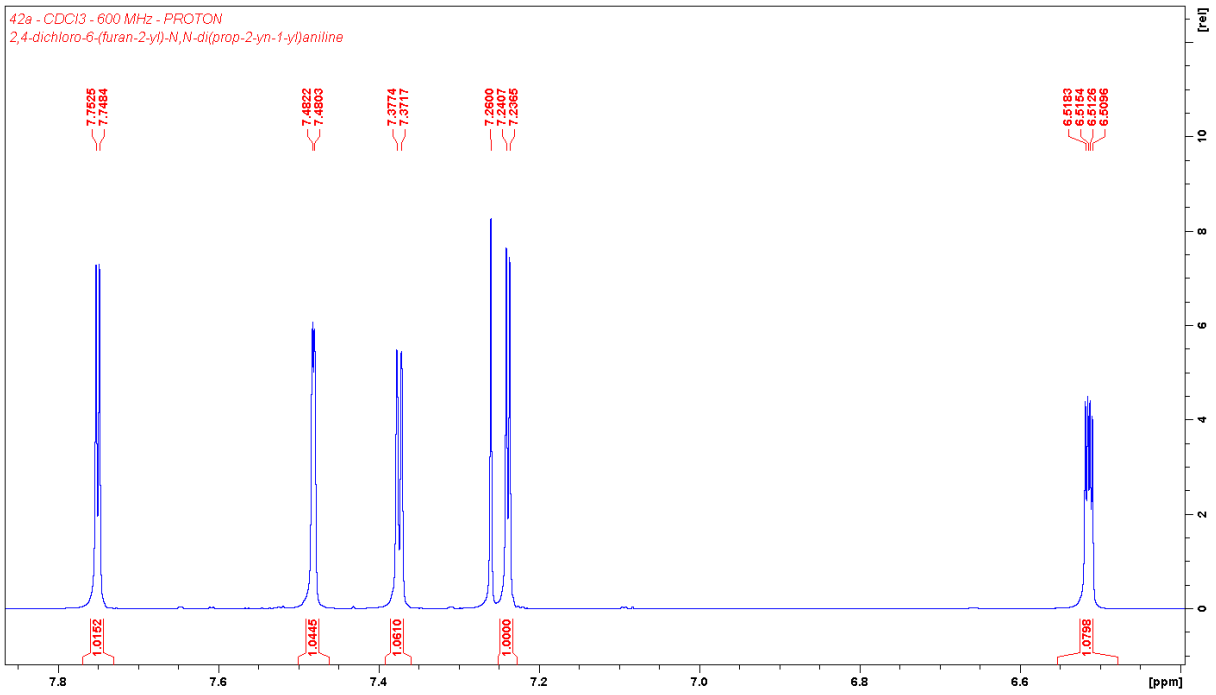
Spectrum 21. 600 MHz, $CDCl_3$ ^{1}H NMR for 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-yn-1-yl)aniline (**41a**) expanded.



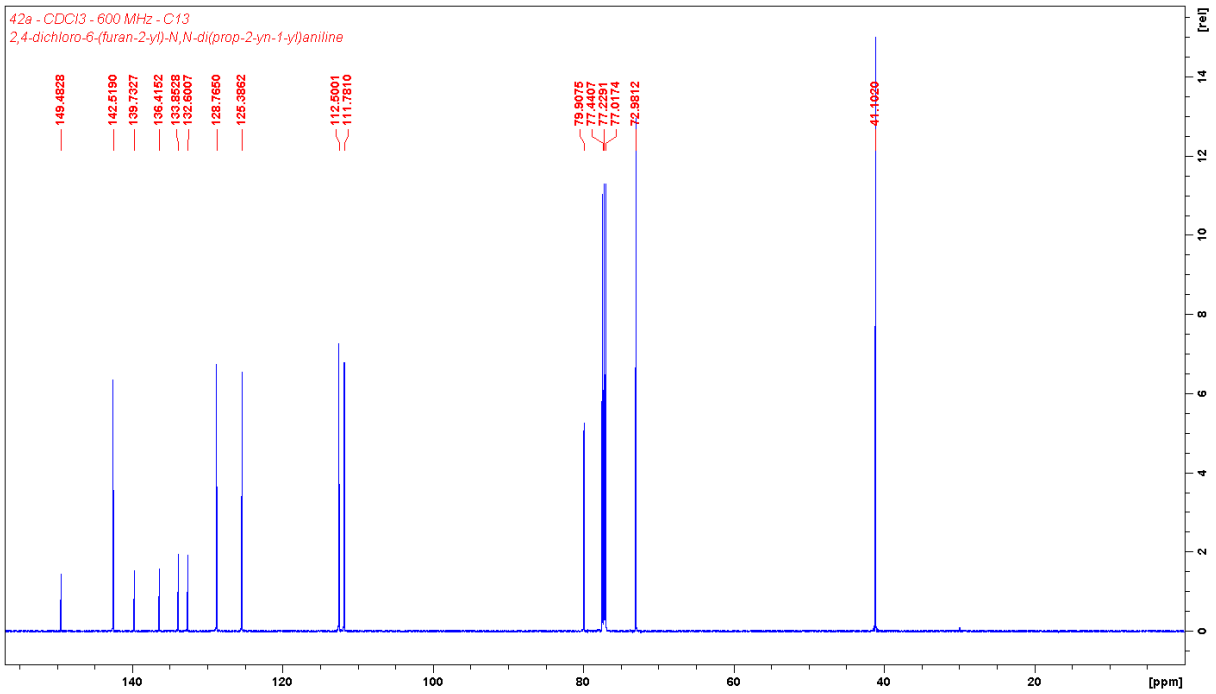
Spectrum 22. 150 MHz, $CDCl_3$ ^{13}C NMR for 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-yn-1-yl)aniline (**41a**).



Spectrum 23. 600 MHz, $CDCl_3$ ^1H NMR for 2,4-dichloro-6-(furan-2-yl)-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42a**).

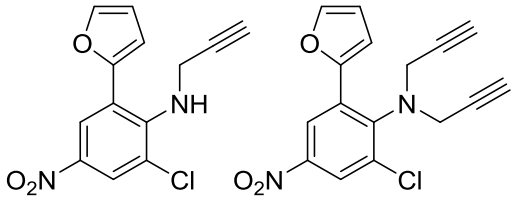


Spectrum 24. 600 MHz, $CDCl_3$ ^1H NMR for 2,4-dichloro-6-(furan-2-yl)-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42a**) expanded.



Spectrum 25. 150 MHz, $CDCl_3$ ^{13}C NMR for 2,4-dichloro-6-(furan-2-yl)-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42a**).

Synthesis of 2-chloro-6-(furan-2-yl)-4-nitro-*N*-(prop-2-yn-1-yl)aniline (41b) and 2-chloro-6-(furan-2-yl)-4-nitro-*N*,*N*-di(prop-2-yn-1-yl)aniline (42b)



2-Chloro-6-(furan-2-yl)-4-nitroaniline (**36b**)(371 mg, 1.55 mmol) and TBAB (913 mg, 2.83 mmol) were subsequently added to stirring THF (40 mL, dry). The flask was degassed with Ar (5 min) before NaH (ca 60% in mineral oil)(114 mg, 2.84 mmol) was added. The resulting mixture stirred for 15 minutes before propargylbromide (**58**)(0.36 mL, 3.2 mmol) was added. The mixture stirred at 45 °C for 5 h and was quenched with water (25 mL). The aqueous phase was extracted with DCM (3 x 15 mL), the combined extracts were dried and filtered, and concentrated under reduced pressure. The compounds were isolated with flash chromatography on silica gel, eluted with acetone/hexanes 2:48. Yield 255 mg (59 %) of compound **41b** as a yellow solid and 98 mg (20 %) of **42b** as a yellow solid.

2-Chloro-6-(furan-2-yl)-4-nitro-*N*-(prop-2-yn-1-yl)aniline (**41b**)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.4 Hz, H1, H-5), 8.22 (d *J* = 2.6 Hz, 1H, H-3), 7.56 (dd, *J* = 1.8, 0.6 Hz, 1H, H-5 in furyl), 6.76 (dd, *J* = 3.3, 0.6 Hz, 1H, H-3 in furyl), 6.57 (dd, *J* = 3.3, 1.8 Hz, 1H, H-4 in furyl), 5.11 (t, *J* = 6.4 Hz, 1H, NH), 3.81 (dd, *J* = 6.4, 2.5 Hz, 2H, $NHC\underline{H_2}CCH_3$), 2.24 (t, *J* = 2.5 Hz, 1H, $NHCH_2CC\underline{H_3}$).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 149.46 (C-2 in furyl), 147.12 (C-1), 143.11 (C-5 in furyl), 140.52 (C-4), 124.78 (C-2), 124.74 (C-3), 124.67 (C-5), 120.92 (C-6), 112.20 (C-4 in furyl), 110.65 (C-3 in furyl), 80.02 ($NHCH_2\underline{C}CH_3$), 73.00 ($NHCH_2C\underline{C}H_3$), 35.83 ($NH\underline{C}H_2CCH_3$).

HRMS ESI calcd for $C_{13}H_9ClN_2O_3$ 276.0302, found 276.0296.

Melting point 86-87 °C.

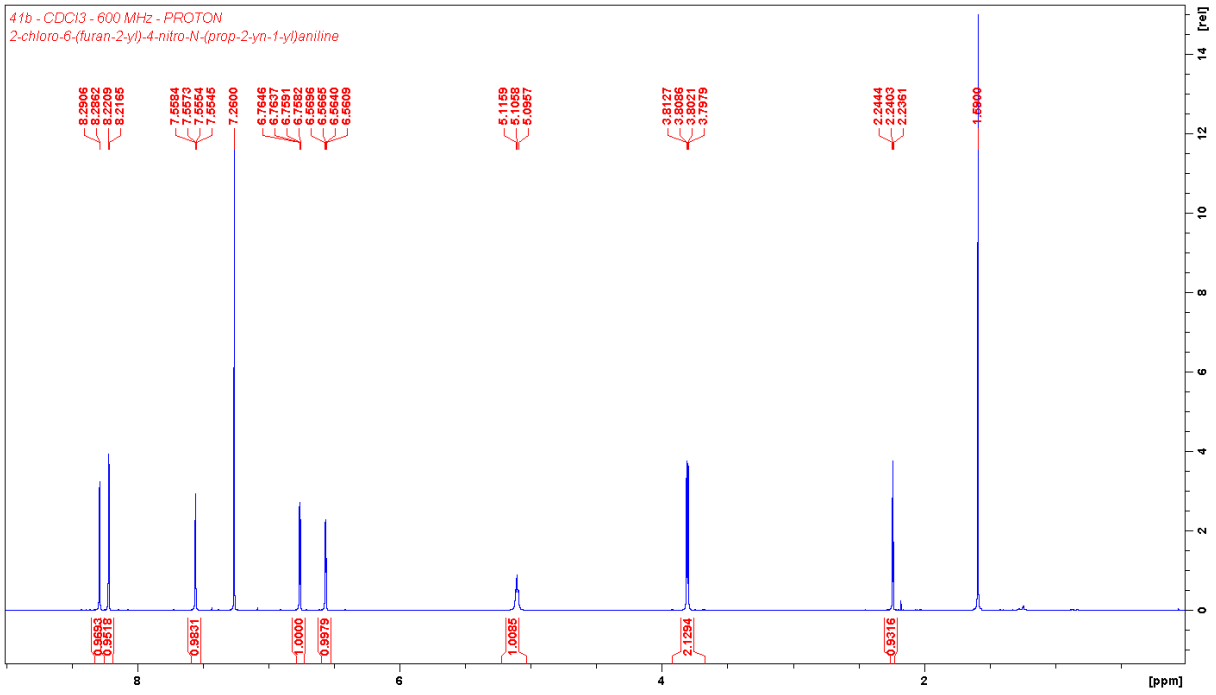
2-Chloro-6-(furan-2-yl)- 4-nitro-*N*,*N*-di(prop-2-yn-1-yl)aniline (**42b**)

^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.8 Hz, 1H, H-5), 8.12 (d, *J* = 2.8 Hz, 1H, H-3), 7.55 (d, *J* = 1.7 Hz, 1H, H-5 in furyl), 7.33 (d, *J* = 3.4, 1H, H-3 in furyl), 6.55(dd, *J* = 3.4, 1.7 Hz, 1H, H-4 in furyl), 4.07 (s, 4H, $N(C\underline{H_2}CCH)_2$), 2.27 (t, *J* = 2.4 Hz, 2H, $N(CH_2CC\underline{H})_2$).

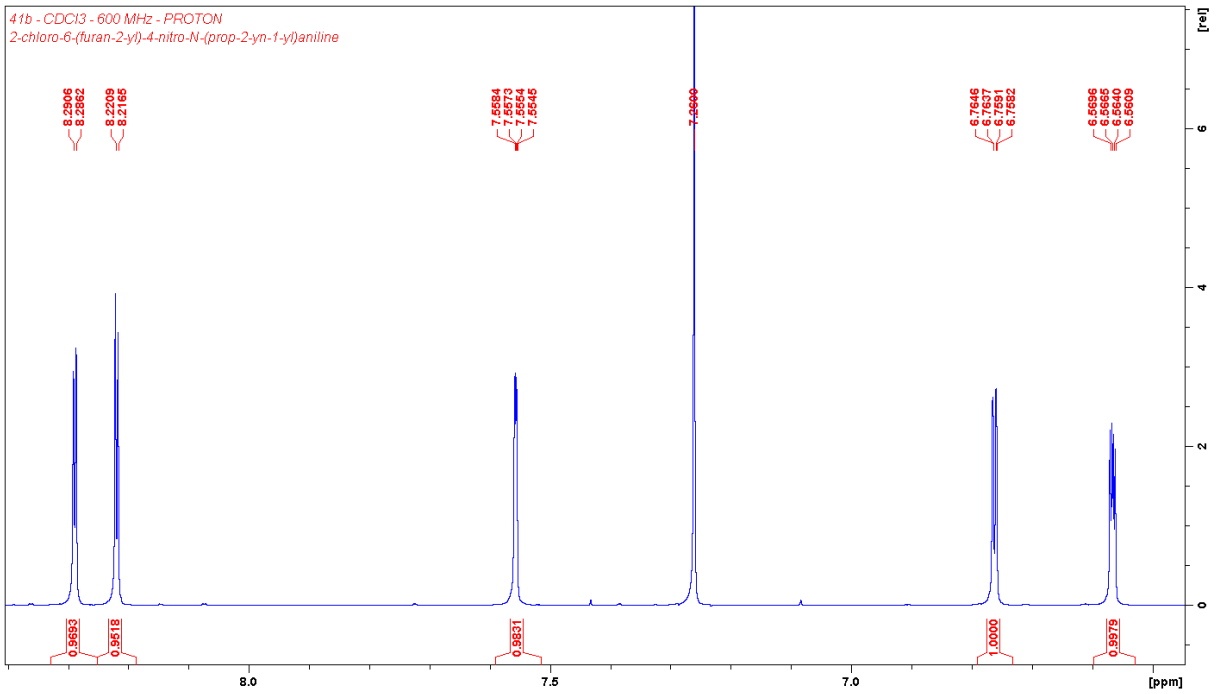
^{13}C-NMR (150 MHz, $CDCl_3$) δ 148.79 (C-2 in furyl), 146.87 (C-1), 145.49 (C-4), 143.32 (C-5 in furyl), 135.89 (C-2), 132.84 (C-6), 124.12 (C-3), 121.00 (C-5), 112.67 (C-4 in furyl), 112.04 (C-3 in furyl), 79.23 ($N(CH_2\underline{C}CH)_2$), 73.50 ($N(CH_2C\underline{C}H)_2$), 41.11 ($N(\underline{C}H_2CCH)_2$).

HRMS ESI calcd for $C_{16}H_{11}ClN_2O_3$ 314.0458, found 314.0452.

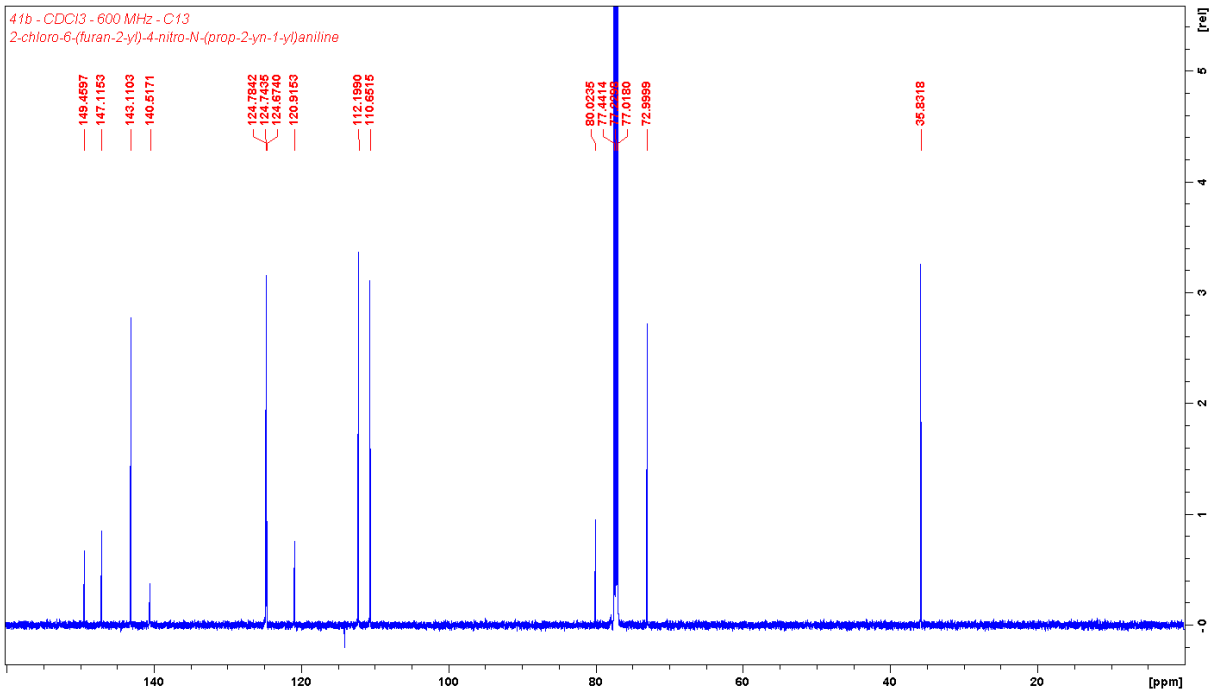
Meling point 76-78 °C.



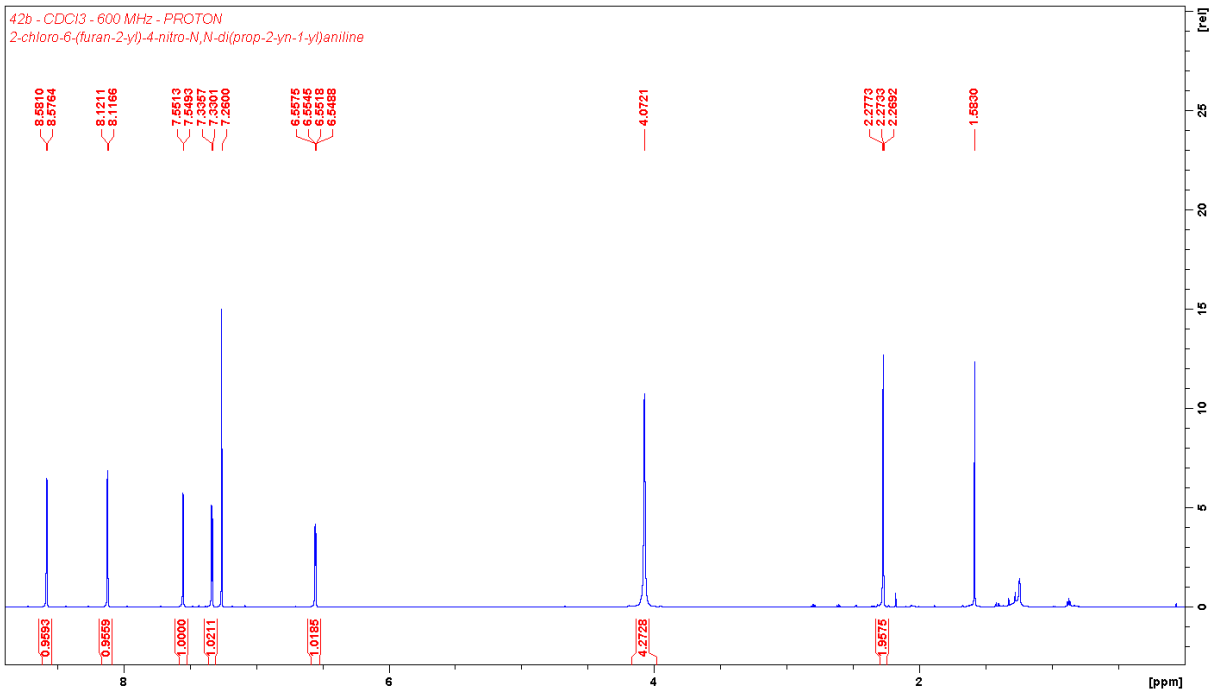
Spectrum 26. 600 MHz, $CDCl_3$ ^{1}H NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*-(prop-2-yn-1-yl)aniline (**41b**).



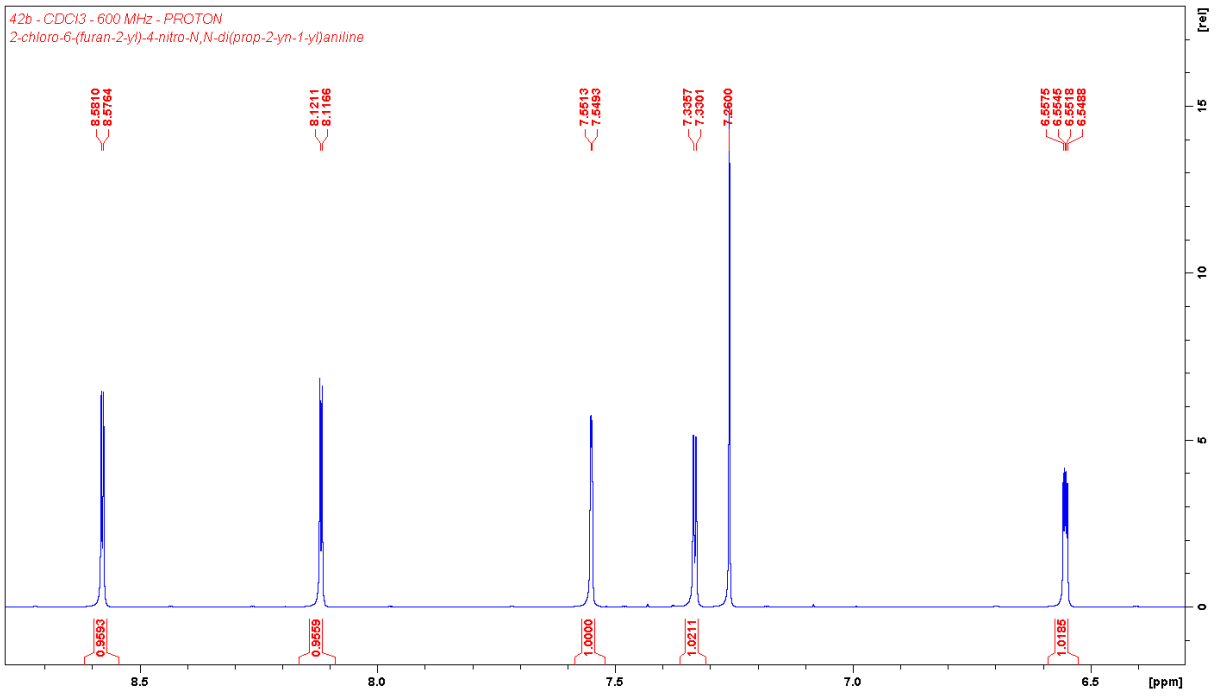
Spectrum 27. 600 MHz, $CDCl_3$ ^{1}H NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*-(prop-2-yn-1-yl)aniline (**41b**) expanded.



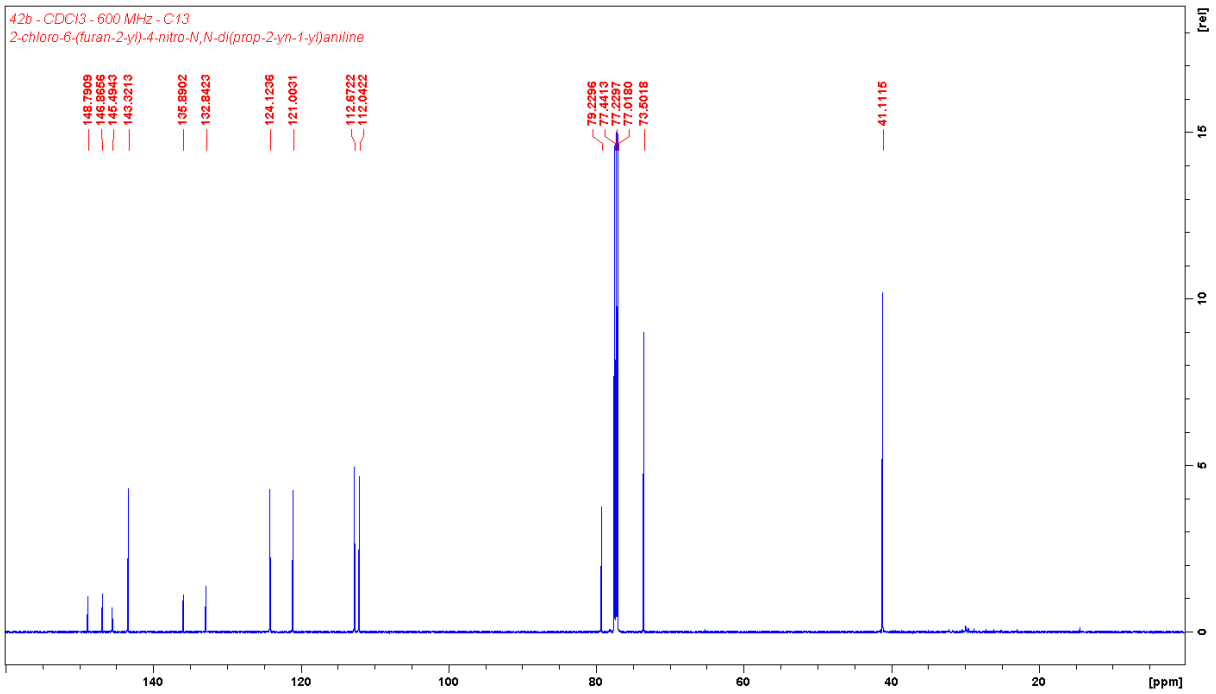
Spectrum 28. 150 MHz, $CDCl_3$ ^{13}C NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*-(prop-2-yn-1-yl)aniline (**41b**).



Spectrum 29. 600 MHz, $CDCl_3$ ^1H NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42b**).

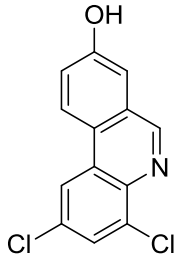


Spectrum 30. 600 MHz, $CDCl_3$ ^1H NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42b**).



Spectrum 31. 150 MHz, $CDCl_3$ ^{13}C NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42b).**

Synthesis of 2,4-dichlorophenanthridin-8-ol (40a)



40a

Compound **41a** (For method A and B respectively: 106 mg, 0.40 mmol, 98 mg, 0.37 mmol) was weighed in a pressure vial, degassed MeCN (15 mL) was added and the flask was degassed with Ar (10 min). Two drops HCl (0.2 M) was added to the flask under an Ar stream. The mixture stirred in the microwave reactor at 180 °C for 100 min and it was cooled to 60 °C before taken out.

Method A, the mixture was transferred to a quartz vial and a needle pumping air was put into the solution. The mixture stirred with air bubbling through under UV light for 16 hours before being concentrated under reduced pressure and isolated with flash chromatography on silica gel. It was eluted with EtOAc/hexanes 2:3, concentrated under reduced pressure and washed with pentane (3 x 10 mL) before being concentrated under reduced pressure again. Yield 91 mg (86 %) as a white solid.

Method B, the mixture was concentrated under reduced pressure and transferred to a dry flask. DCM (20 mL, dry), was added and the flask was degassed with Ar. DDQ (102 mg, 0.45 mmol) was added and the mixture stirred at room temperature for 2.5 h before being concentrated under reduced pressure and isolated with flash chromatography. It was eluted with DCM/EtOAc/hexanes 2:3:5, concentrated under reduced pressure and washed with pentane (3 x 10 mL) before being concentrated under reduced pressure again. Yield 78 mg (80 %) as a white solid.

^{1}H-NMR (600 MHz, DMSO) δ 10.52 (s, 1H, OH), 9.33 (s, 1H, H-6), 8.78-8.76 (m, 2H, H-3 and H-9), 7.95 (d, *J* = 2.1 Hz, 1H, H-3), 7.51-7.47 (m, 2H, H-7 and H-10).

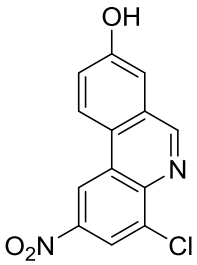
^{13}C-NMR (150 MHz, DMSO) δ 158.23 (C-8), 153.98 (C-6), 137.53 (C-4a), 134.47 (C-4), 131.43 (C-2), 128.25 (C-6a or 10b), 127.32 (C-3), 126.78 (C-6a or 10b), 125.11 (C-9), 123.67 (C-10a), 122.83 (C-10), 121.14 (C-1), 111.21 (C-7).

HRMS ESI calcd for $C_{13}H_7Cl_2NO$ 262.9905, found 262.9900.

Melting point 297-298 °C.

See Spectrum 16 and Spectrum 17.

Synthesis of 4-chloro-2-nitro-phenanthridin-8-ol (40b)



40b

Compound **41b** (102 mg, 0.37 mmol) was weighed in a pressure vial, degassed MeCN (15 mL) was added and the flask was degassed with Ar (10 min). Two drops HCl (0.2 M) was added to the flask under an Ar stream. The mixture stirred in the microwave reactor at 180 °C for 40 min and was cooled down to 60 °C before taken out. The mixture was concentrated under reduced pressure and transferred to a dry flask. DCM (20 mL, dry), was added and the flask was degassed with Ar. DDQ (101 mg, 0.44 mmol) was added and the mixture stirred at room temperature for 2.5 h before being concentrated under reduced pressure and isolated with flash chromatography. It was eluted with DCM/EtOAc/hexanes 1:2:2, concentrated under reduced pressure and washed with pentane (3 x 10 mL) before being concentrated under reduced pressure again. Yield 81 mg (80 %) as a yellow solid.

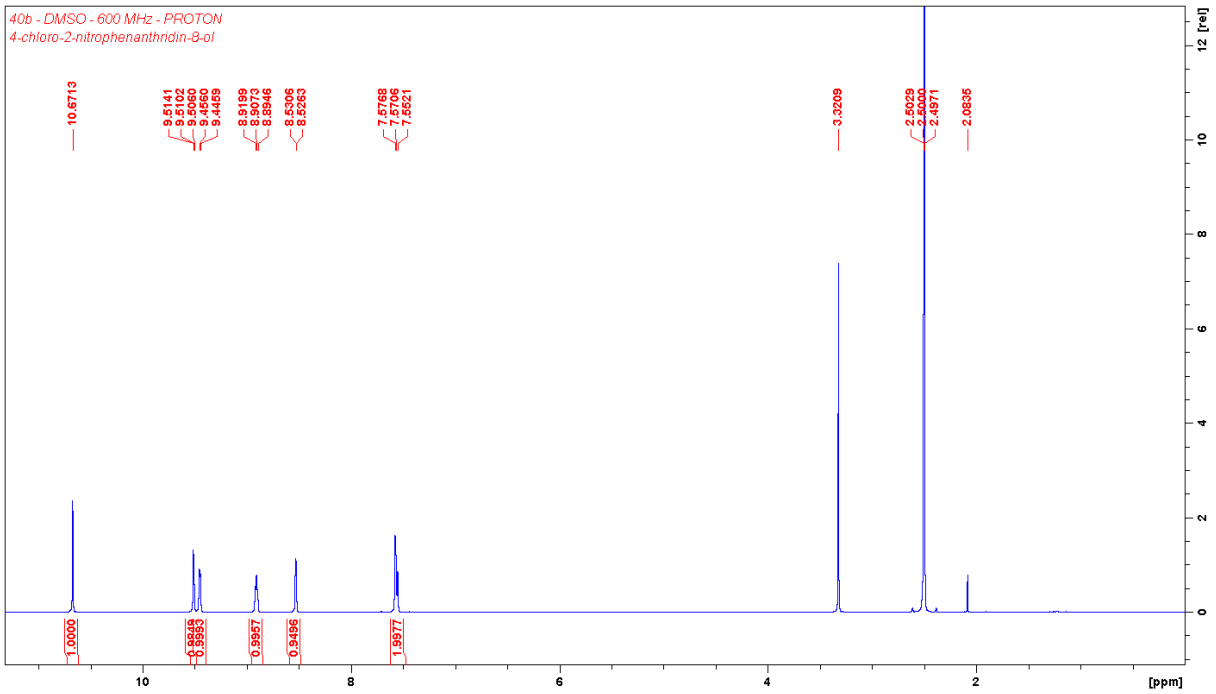
^{1}H-NMR (600 MHz, DMSO) δ 10.67 (s, 1H, OH), 9.51 (m, 1H, H-6), 9.45 (m, 1H, H-1), 8.91 (m, 1H, H-10), 8.53 (m, 1H, H-3), 7.57 (m, 2H, H-7 and H-9).

^{13}C-NMR (150 MHz, DMSO) δ 158.69 (C-8), 157.18 (C-6), 145.10 (C-2), 141.62 (C-4a), 134.52 (C-4), 128.33 (C-6a or 10b), 125.42 (C-6a or 10b), 125.34 (C-10), 124.57 (C-10a), 123.60 (C-9), 121.04 (C-3), 117.71 (C-1), 111.64 (C-7).

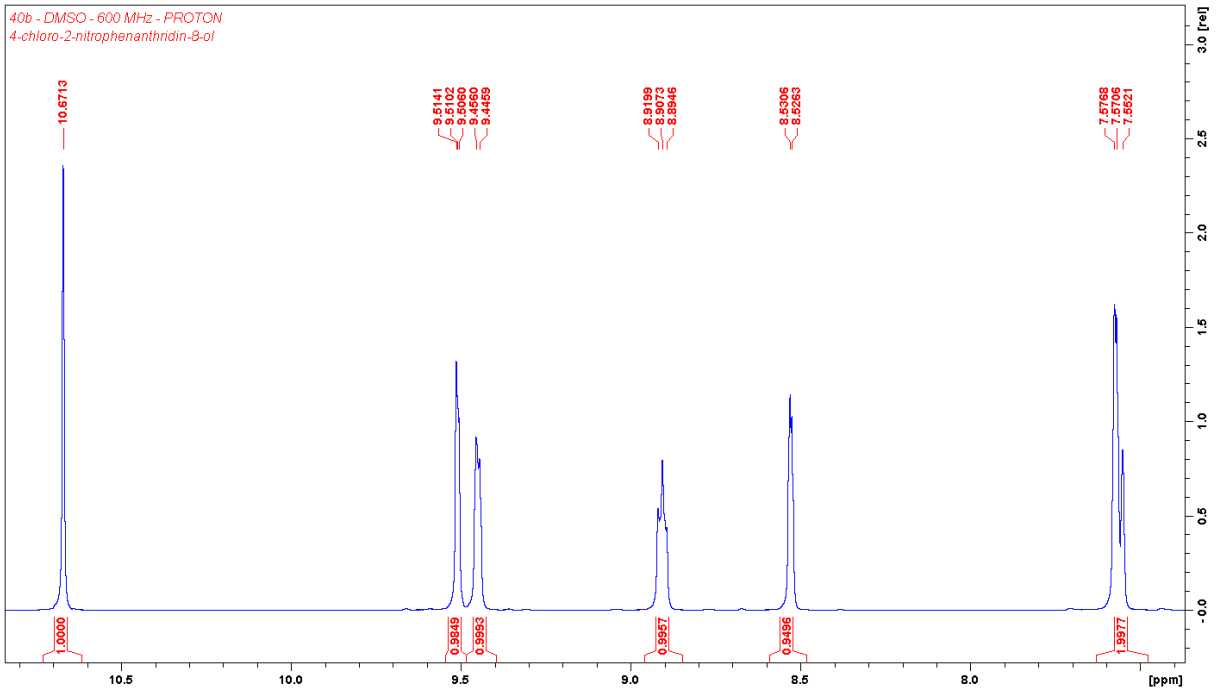
HRMS ESI calcd for $C_{13}H_7ClN_2O_3$ 274.0145, found 274.0139.

Melting point 317-318 °C.

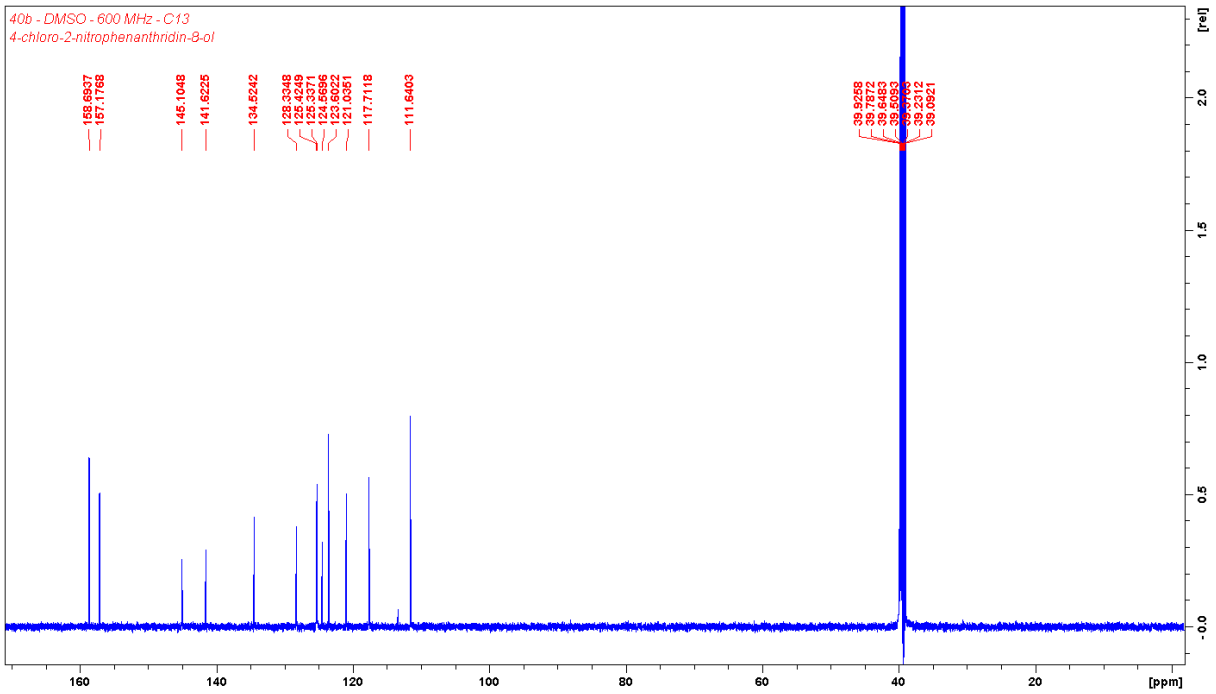
HRMS ESI for compound (**39b**) calcd for $C_{13}H_9ClN_2O_3$ 276.0302, found 274.0296, taken from the intermediate.



Spectrum 32. 600 MHz, DMSO, ^{1}H NMR of 4-chloro-2-nitrophenanthridin-8-o (**40b**).

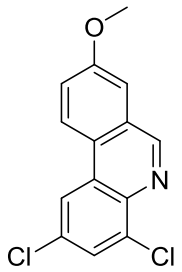


Spectrum 33. 600 MHz, DMSO, ^{1}H NMR of 4-chloro-2-nitrophenanthridin-8-ol (**40b**) expanded.



Spectrum 34. 150 MHz, DMSO, ^{13}C NMR of 4-chloro-2-nitrophenanthridin-8-ol (**40b**).

Synthesis of 2,4-dichloro-8-methoxyphenanthridine (43a)



43a

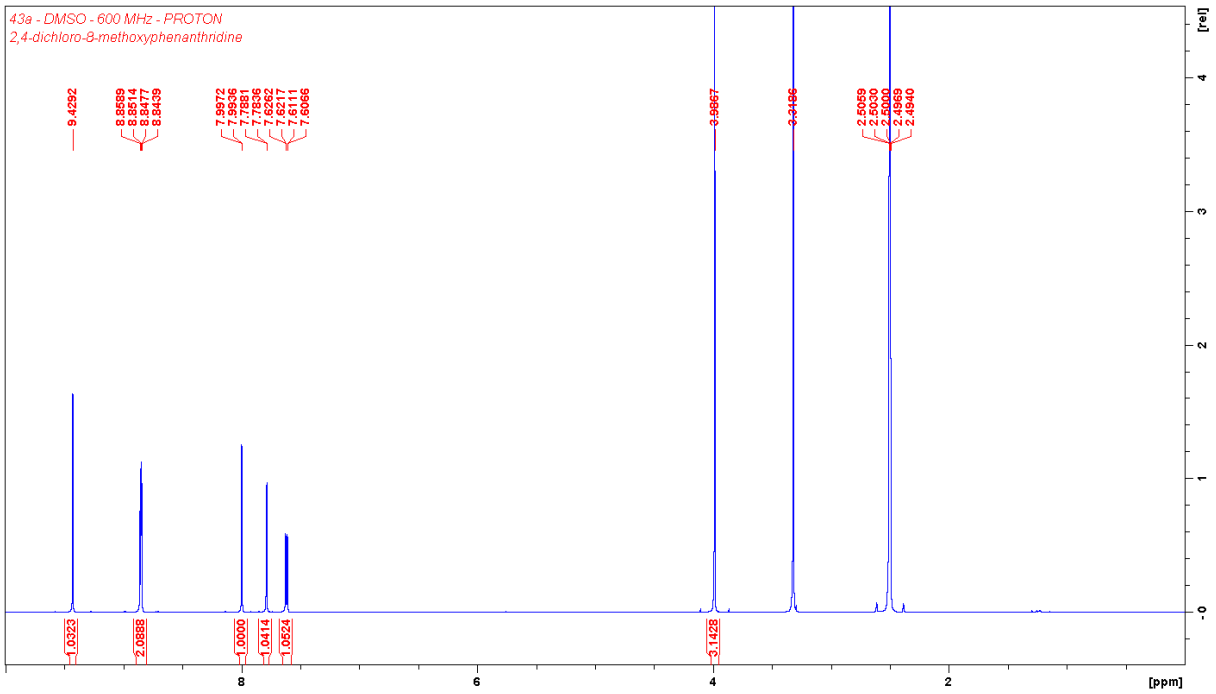
Compound **40a** (39 mg, 0.15 mmol) and K_2CO_3 (42 mg, 0.31 mmol) was subsequently added to a degassed flask containing DMF (10 mL, dry). The mixture stirred for 15 min before MeI (20 µL, 0.32 mmol) was added. The mixture stirred for 75 min before it was quenched with water (25 mL). The aqueous phase was extracted with EtOAc (3 x 25 mL), the combined organic phases were dried and filtered. The filtrate was then filtrated through silica gel, eluted with hexanes (200 mL) and then EtOAc (250 mL) before being washed with pentane (3 x 10mL). Yield 31 mg (76 %) as a white solid.

^{1}H-NMR (600 MHz, DMSO) δ 9.43 (s, 1H, H-6), 8.85 (d, *J* = 9.0 Hz, 1H, H-10), 8.85 (d, *J* = 2.2 Hz, 1H, H-1), 8.00 (d, *J* = 2.2 Hz, 1H, H-3), 7.79 (d, *J* = 2.7, 1H, H-7), 7.62 (dd, *J* = 9.0, 2.7, 1H, H-9), 3.99 (s, 3H, OMe).

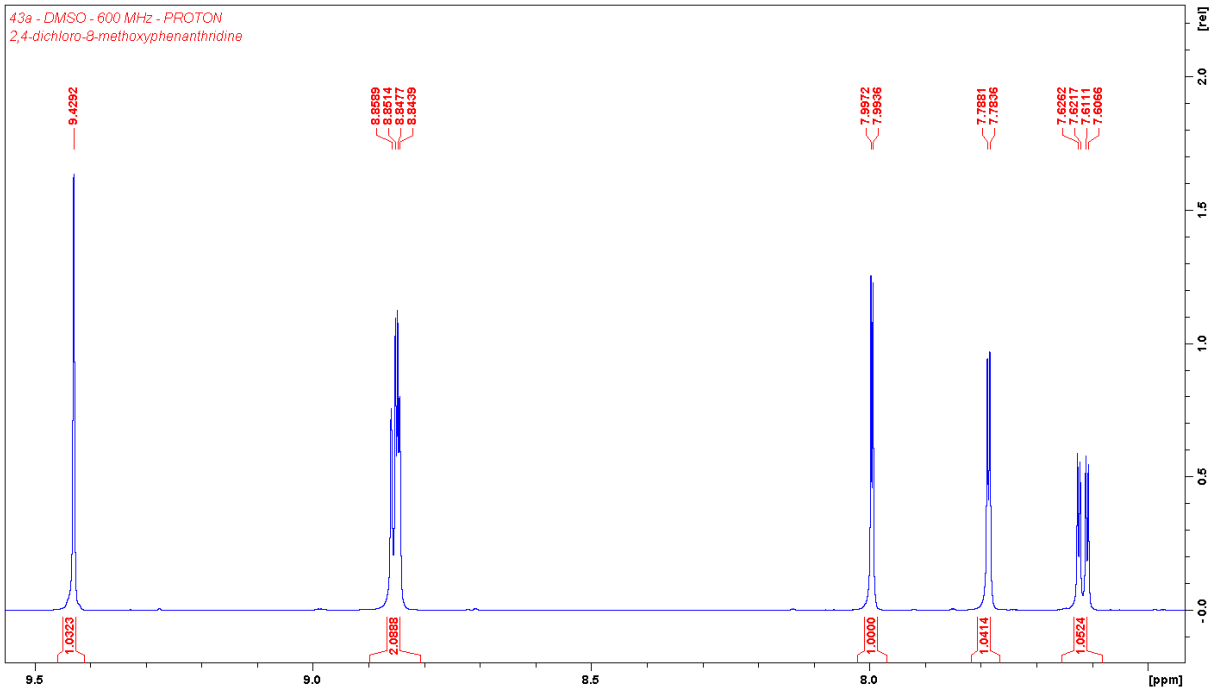
^{13}C-NMR (150 MHz, DMSO) δ 159.66 (C-8), 154.01 (C-6), 137.87 (C-4a), 134.50 (C-4), 131.60 (C-2), 128.03 (C-10b), 127.78 (C-3), 126.53 (C-6a or 10a), 125.03 (C-10), 124.98 (C-6a or 10a), 122.75 (C-9), 121.44 (C-1), 108.71 (C-7), 55.74 (OMe).

HRMS ESI calcd for $C_{14}H_9Cl_2NO$ 277.0061, found 277.0055.

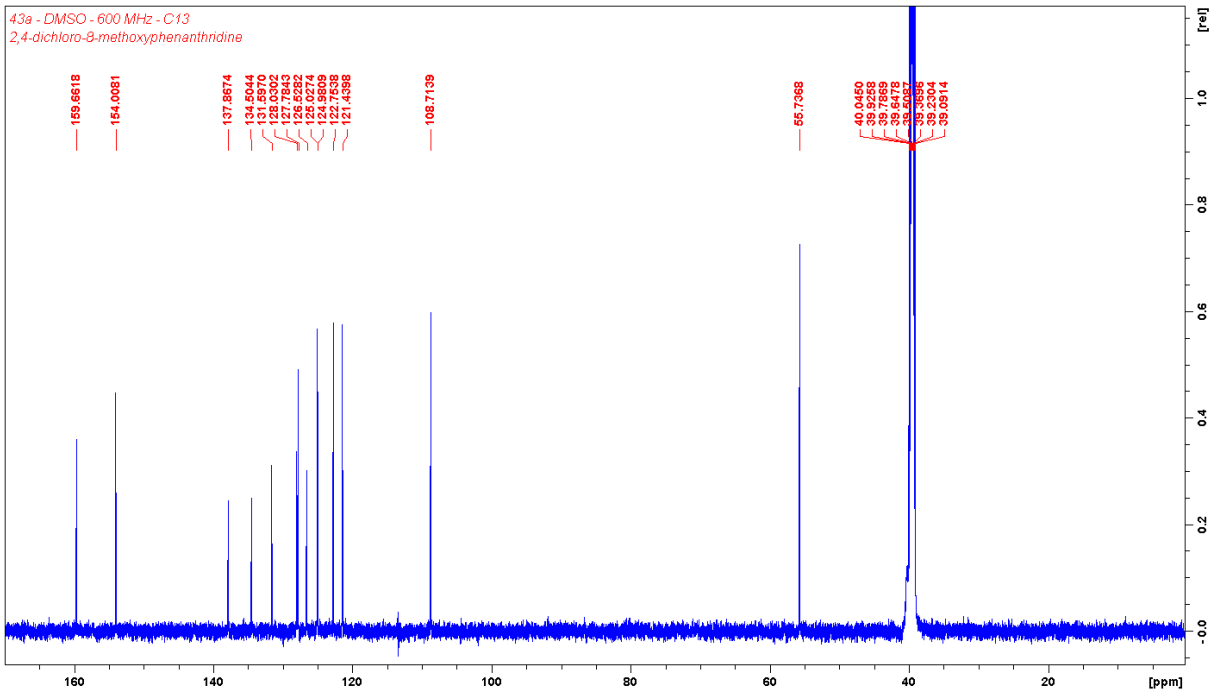
Melting point 192-193 °C.



Spectrum 35. 600 MHz, DMSO, ^{1}H NMR of 2,4-dichloro-8-methoxyphenanthridine (**43a**).

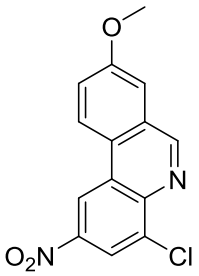


Spectrum 36. 600 MHz, DMSO, ^{1}H NMR of 2,4-dichloro-8-methoxyphenanthridine (**43a**) expanded.



Spectrum 37. 150 MHz, DMSO, ^{13}C NMR of 2,4-dichloro-8-methoxyphenanthridine (**43a**).

Synthesis of 4-chloro-8-methoxy-2-nitrophenanthridine (43b)



43b

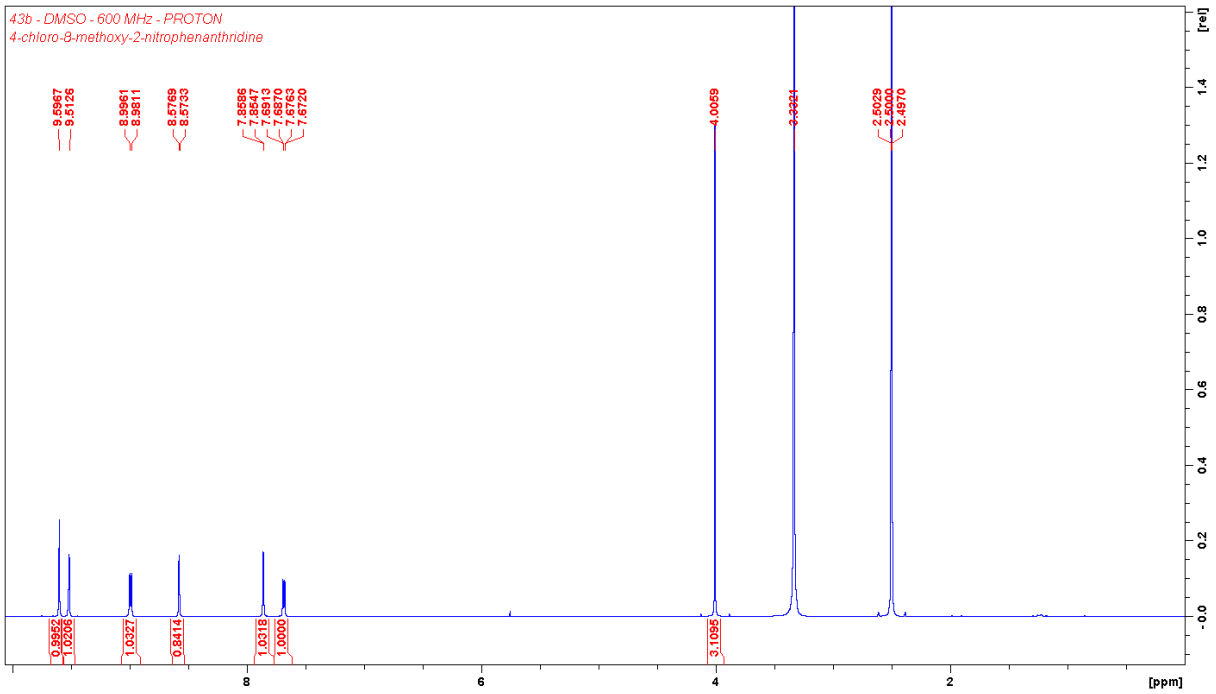
Compound **40b** (40 mg, 0.15 mmol) and K_2CO_3 (71 mg, 0.51 mmol) were subsequently added to a degassed flask containing DMF (10 mL, dry). The mixture stirred for 15 min before MeI (18 µL, 0.29 mmol) was added. The mixture stirred for 75 min before it was quenched with water (25 mL). The aqueous phase was extracted with EtOAc (4 x 25 mL), the combined organic phases were dried and filtered. It was concentrated under reduced pressure and isolated by flash chromatograpy, eluted with DCM/hexanes 3:7 (280 mL) then EtOAc/hexanes 1:1. The product was washed with pentane (3 x 10mL). Yield 33 mg (78 %) as a yellow solid.

^{1}H-NMR (600 MHz, DMSO) δ 9.60 (s, 1H, H-6), 9.51 (d, *J* = 1.7 Hz, 1H, H-1), 8.99 (d, *J* = 9.0 Hz, 1H, H-10), 8.58 (d, *J* = 1.7 Hz, 1H, H-3), 7.86 (d, *J* = 2.5 Hz, 1H, H-7), 7.68 (dd, *J* = 9.0, 2.5 Hz, 1H, H-9), 4.01 (s, 3H, OMe).

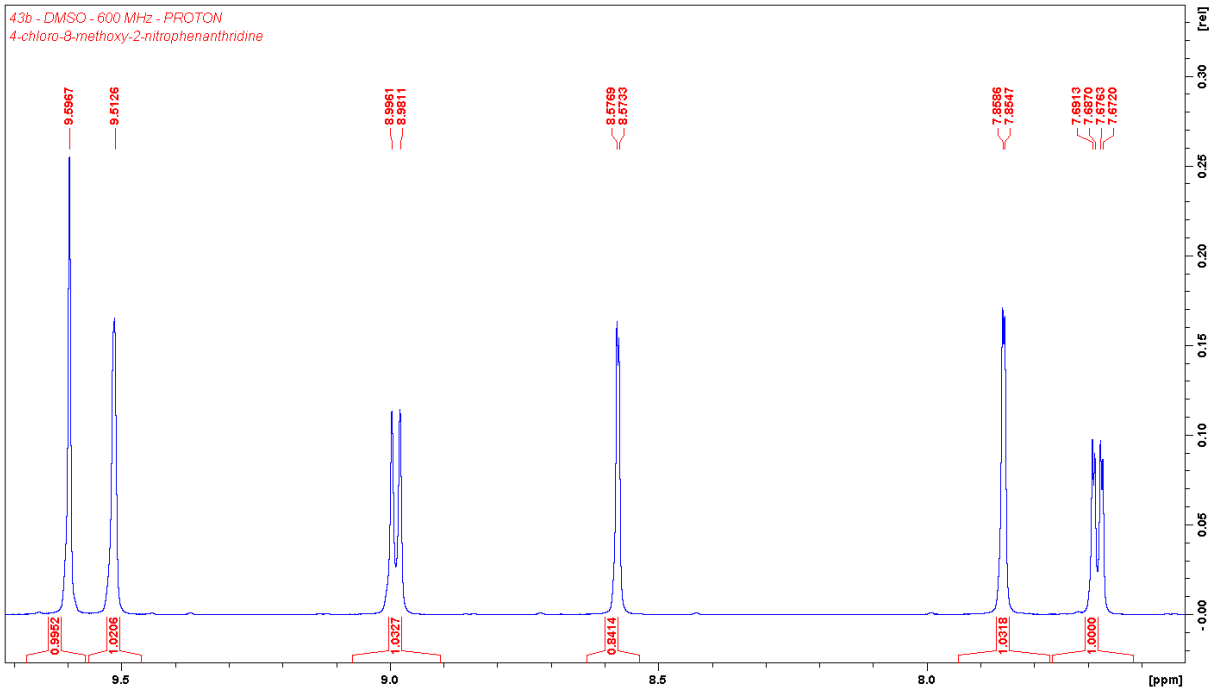
^{13}C-NMR (150 MHz, DMSO) δ 160.07 (C-8), 157.20 (C-6), 145.24 (C-2), 141.96 (C-4a), 134.60 (C-4), 128.17 (C-6a), 125.98 (C-10a), 125.29 (C-10), 125.23 (C-10b), 123.56 (C-9), 121.52 (C-3), 118.10 (C-1), 109.17 (C-7), 55.87 (OMe).

HRMS ESI calcd for $C_{14}H_9ClN_2O_3$ 288.0302, found 288.0295.

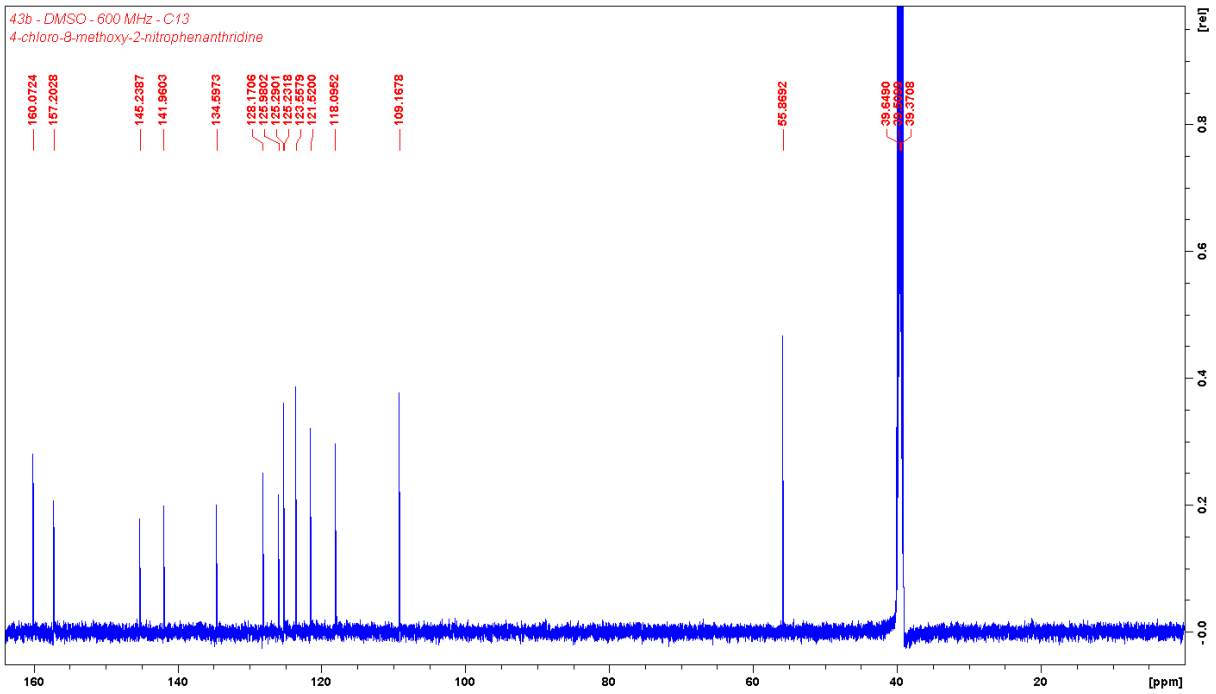
Melting point 254-255 °C.



Spectrum 38. 600 MHz, DMSO, ^{1}H NMR of 4-chloro-8-methoxy-2-nitrophenanthridine (**43b**).

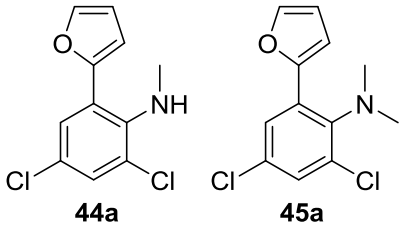


Spectrum 39. 600 MHz, DMSO, ^{1}H NMR of 4-chloro-8-methoxy-2-nitrophenanthridine expanded (**43b**).



Spectrum 40 150 MHz, DMSO, ^{1}H NMR of 4-chloro-8-methoxy-2-nitrophenanthridine (**43b**).

Synthesis of 2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (44a) and 2,4-dichloro-6-(furan-2-yl)-*N.N*-dimethylaniline



44a **45a**

A stirring mixture of compound **36a** (202 mg, 0.88 mmol) and TBAI (402 mg, 1.10 mmol) in THF (20 mL, dry) was degassed with Ar (5 min) before NaH (ca 60 %)(90 mg, 2.25 mmol) was added. The mixture stirred for 15 min and MeI (136 µL, 2.18 mmol) was added, the resulting mixture stirred for 19 hours in a sealed flask at 30 °C. The reaction was quenched with water (25 mL) and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic phase was dried, filtered and concentrated under reduced pressure. The compounds were isolated by flash chromatography, eluted with acetone/hexanes 1:49. Yield 184 mg (87 %) as a yellow oil for compound **44a** and 9 mg (4 %) as yellow oil for compound **45a**.

2,4-Dichloro-6-(furan-2-yl)-*N*-methylaniline **(44a)**

^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 1.7, 0.7 Hz, 1H, H-5 in furyl), 7.46 (d, *J* = 2.4 Hz, 1H, H-5), 7.27 (d, *J* = 2.4 Hz, 1H, H-3), 6.78 (dd, *J* = 3.3, 0.7 Hz, 1H, H-3 in furyl), 6.51 (dd, *J* = 3.3, 1.7 Hz, 1H, H-4 in furyl), 4.09 (br s, 1H, NH), 2.66 (s, 3H, NHMe).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 150.58 (C-2 in furyl), 142.99 (C-1), 142.24 (C-5 in furyl), 128.46 (C-3), 127.55 (C-1), 126.86 (C-2), 125.84 (C-4), 124.01 (C-6), 111.93 (C-4 in furyl), 109.90 (C-3 in furyl). 34.46 (NHMe).

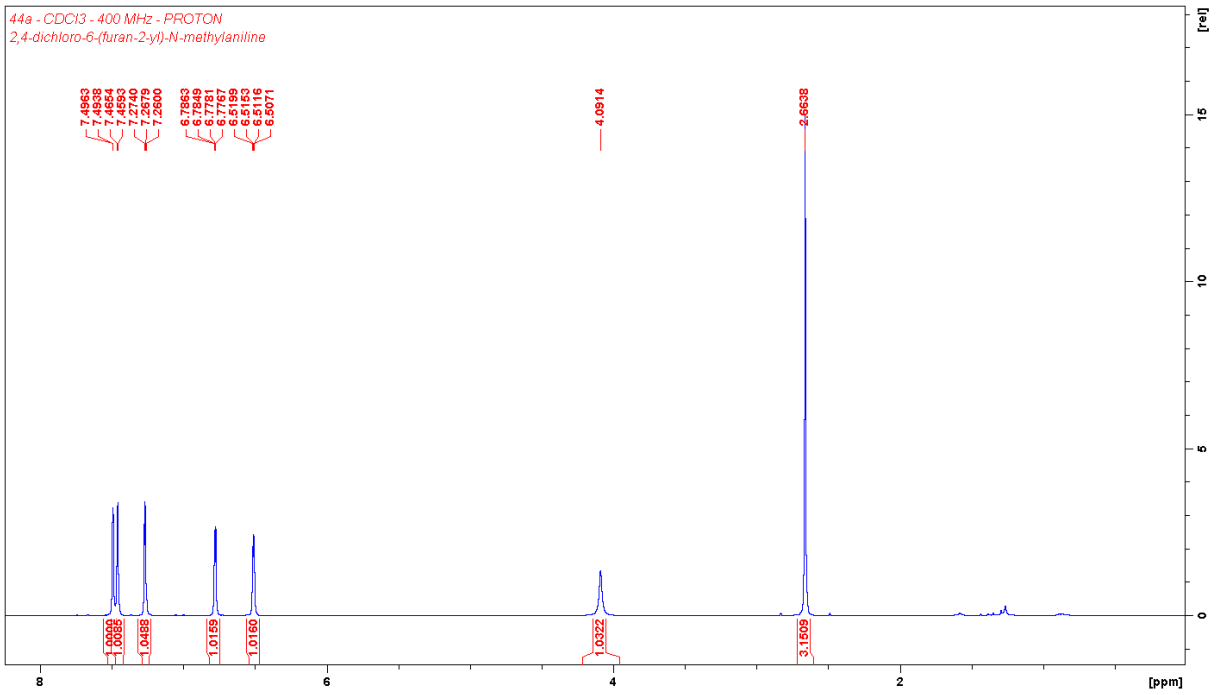
HRMS ESI calcd for $C_{11}H_9Cl_2NO$ 241.0061, found 241.0055.

2,4-Dichloro-6-(furan-2-yl)-*N.N*-dimethylaniline **(45a)**

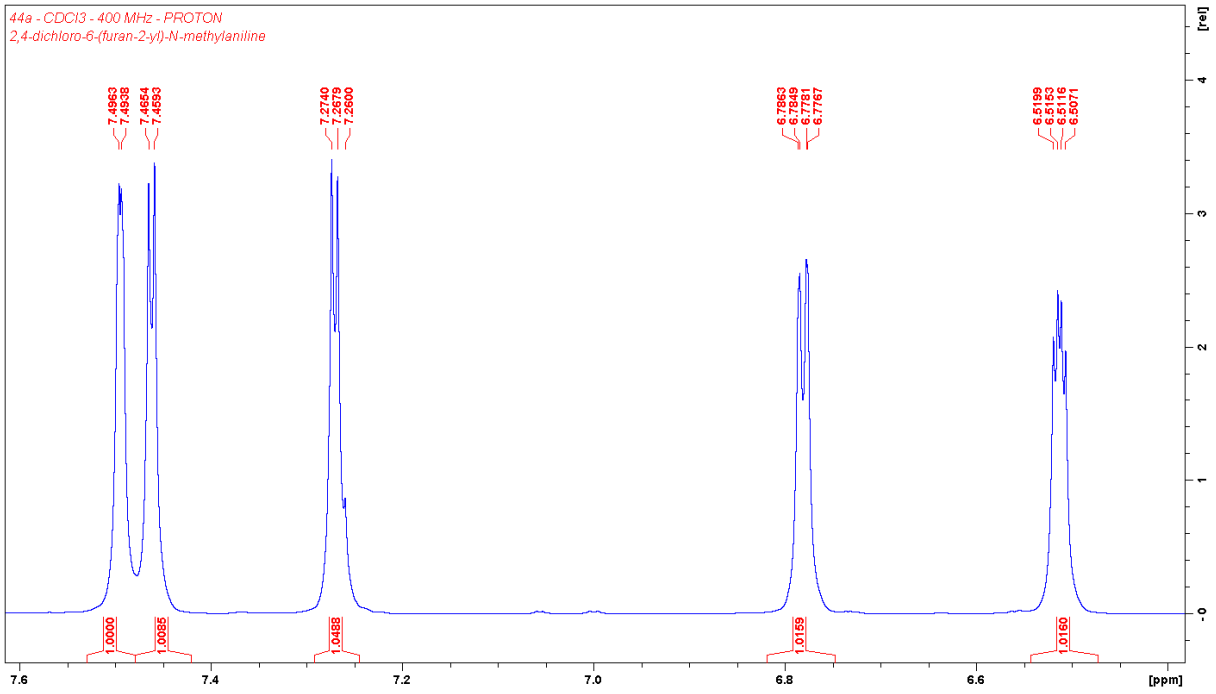
^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.5 Hz, 1H, H-5), 7.48 (dd, *J* = 1.8, 0.6 Hz, 1H, H-5 in furyl), 7.23 (d, *J* = 2.5 Hz, 1H, H-3), 6.98 (dd, *J* = 3.4, 0.6 Hz, 1H, H-3 in furyl), 6.50 (dd, *J* = 3.4, 1.8 Hz, 1H, H-4 in furyl), 2.78 (s, 6H, $N(Me)_2$).

^{13}C-NMR (150 MHz, $CDCl_3$) δ 150.27 (C-2 in furyl), 144.00 (C-1), 142.32 (C-5 in furyl), 136.62 (C-2), 132.73 (C-6), 131.13 (C-4), 128.88 (C-3), 125.46 (C-5), 112.33 (C-4 in furyl), 110.93 (C-3 in furyl), 41.61 ($N(Me)_2$).

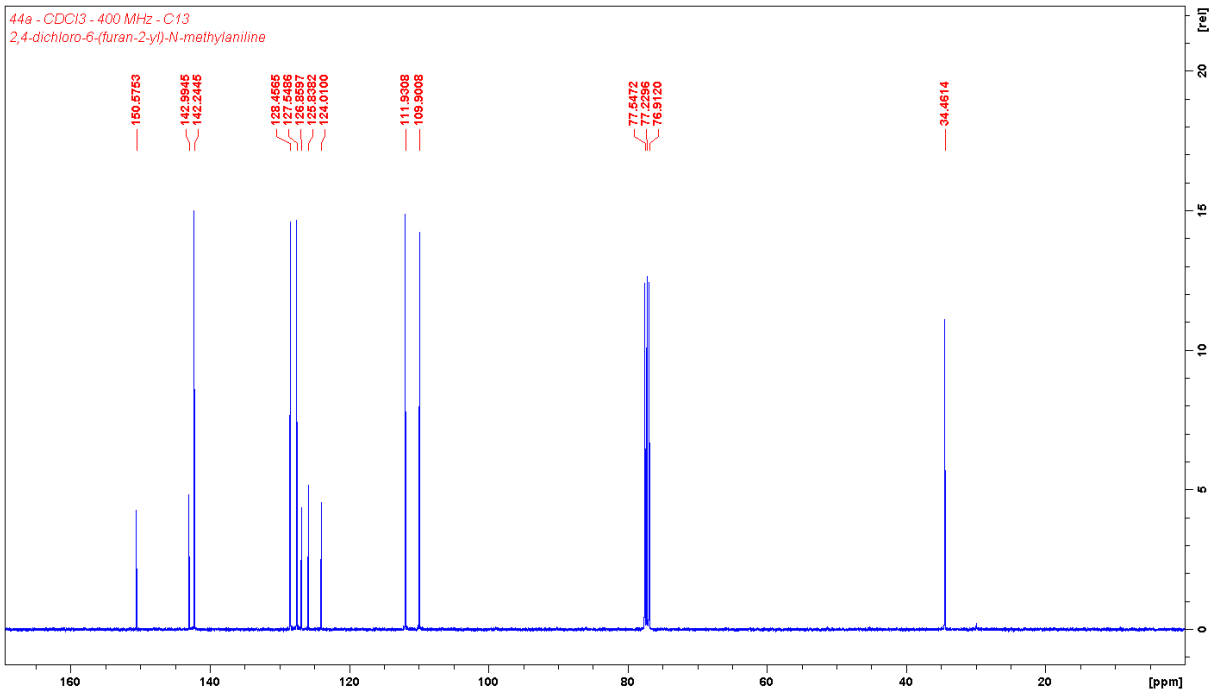
HRMS ESI calcd for $C_{12}H_{11}Cl_2NO$ 255.0218, found 255.9825.



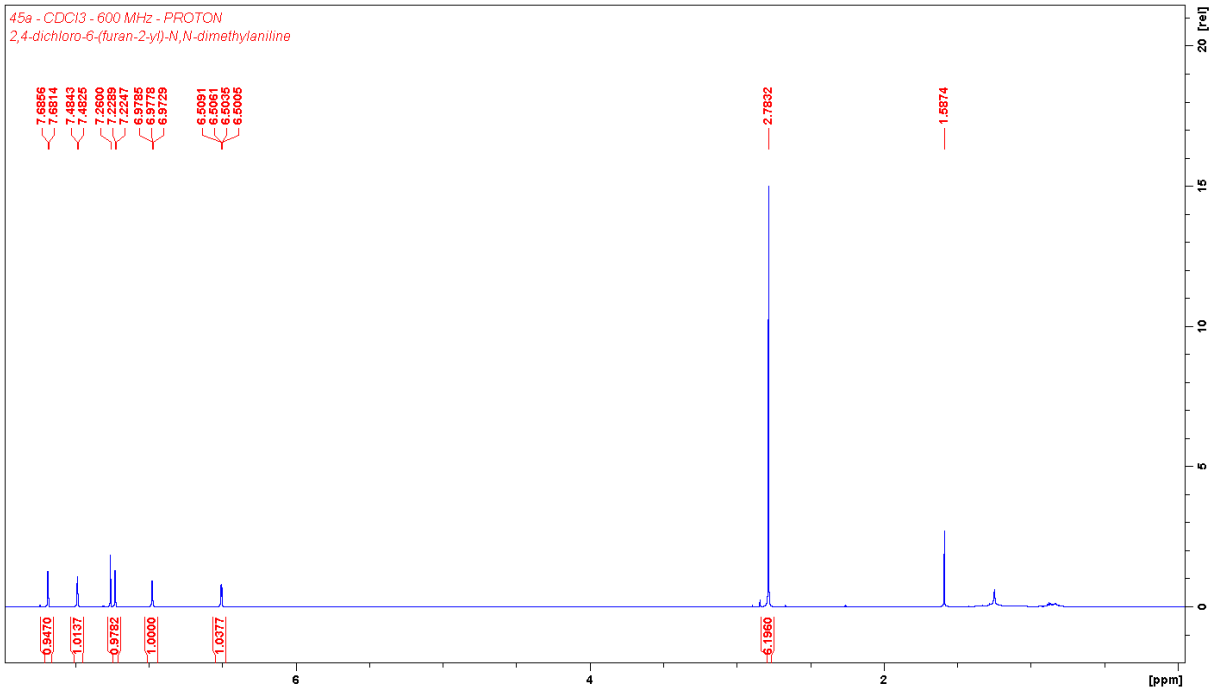
Spectrum 41. 400 MHz, $CDCl_3$, ^1H NMR of 2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**44a**).



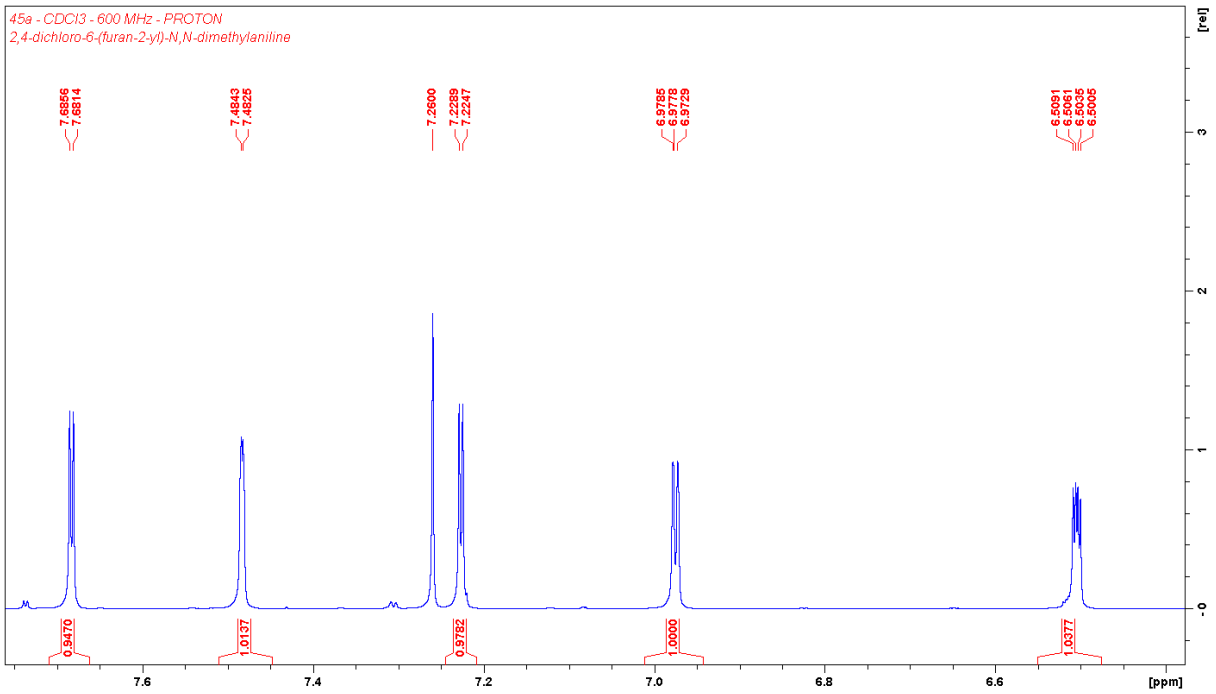
Spectrum 42. 400 MHz, $CDCl_3$, ^1H NMR of 2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**44a**) expanded.



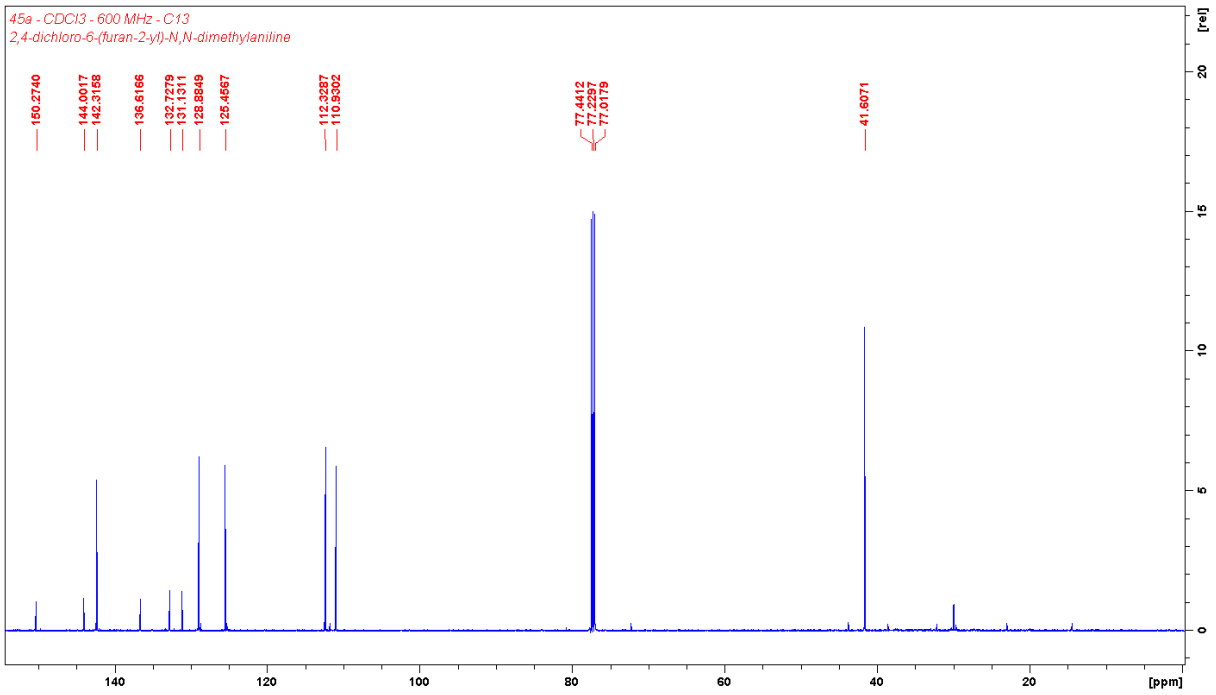
Spectrum 43. 100 MHz, $CDCl_3$, ^{13}C NMR of 2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**44a**).



Spectrum 44. 600 MHz, $CDCl_3$, ^{1}H NMR of 2,4-dichloro-6-(furan-2-yl)-*N.N*-dimethylaniline (**45a**).

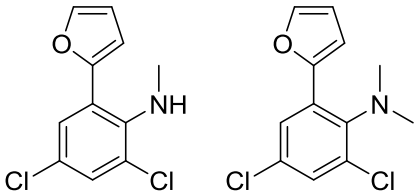


Spectrum 45. 600 MHz, $CDCl_3$, ^1H NMR of 2,4-dichloro-6-(furan-2-yl)-*N.N*-dimethylaniline (**45a**) expanded.



Spectrum 46. 150 MHz, $CDCl_3$, ^{13}C NMR of 2,4-dichloro-6-(furan-2-yl)-*N.N*-dimethylaniline (**45a**).

Synthesis of 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline (44b) and 2-chloro-6-(furan-2-yl)-*N.N*-dimethyl-4-nitroaniline (45b)



44b **45b**

A stirring mixture of compound **36b** (200 mg, 0.84 mmol) and TBAI (374 mg, 1.01 mmol) in THF (20 mL, dry) was degassed with Ar (5 min) before NaH (ca 60 %)(66 mg, 1.7 mmol) was added. The mixture stirred for 15 min and MeI (63 µL, 1.01 mmol) was added, the resulting mixture stirred for 24 hours in a sealed flask at 30 °C. The reaction was quenched with water (25 mL) and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic phase was dried, filtered and concentrated under reduced pressure. The compounds were isolated by flash chromatography, eluted with acetone/hexanes 2:48. Yield 110 mg (52 %) as a yellow solid for compound **44b** and 39 mg (17 %) as yellow solid for compound **45b**. Unconverted compound **36b** accounts for 20 %.

2-Chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline **(44b)**

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 2.7 Hz, 1H, H-5), 8.14 (d, *J* = 2.7 Hz, 1H, H-3), 7.52 (dd, *J* = 1.6, 0.9 Hz, 1H, H-5 in furyl), 6.54-6.52 (m, 2H, H-3 and H-4 in furyl), 5.21 (br s, 1H, NH), 2.73 (s, 3H, NHMe).

^{13}C-NMR (125 MHz, $CDCl_3$) δ 150.29 (C-2 in furyl), 149.50 (C-1), 142.51 (C-5 in furyl), 137.79 (C-4), 127.09 (C-3), 125.44 (C-5), 121.35 (C-2), 116.81 (C-6), 111.90 (C-3 in furyl), 110.46 (C-4 in furyl), 32.87 (NHMe).

HRMS ESI calcd for $C_{11}H_9ClN_2O_3$ 252.0302, found 252.0296.

Melting point 79-81 °C

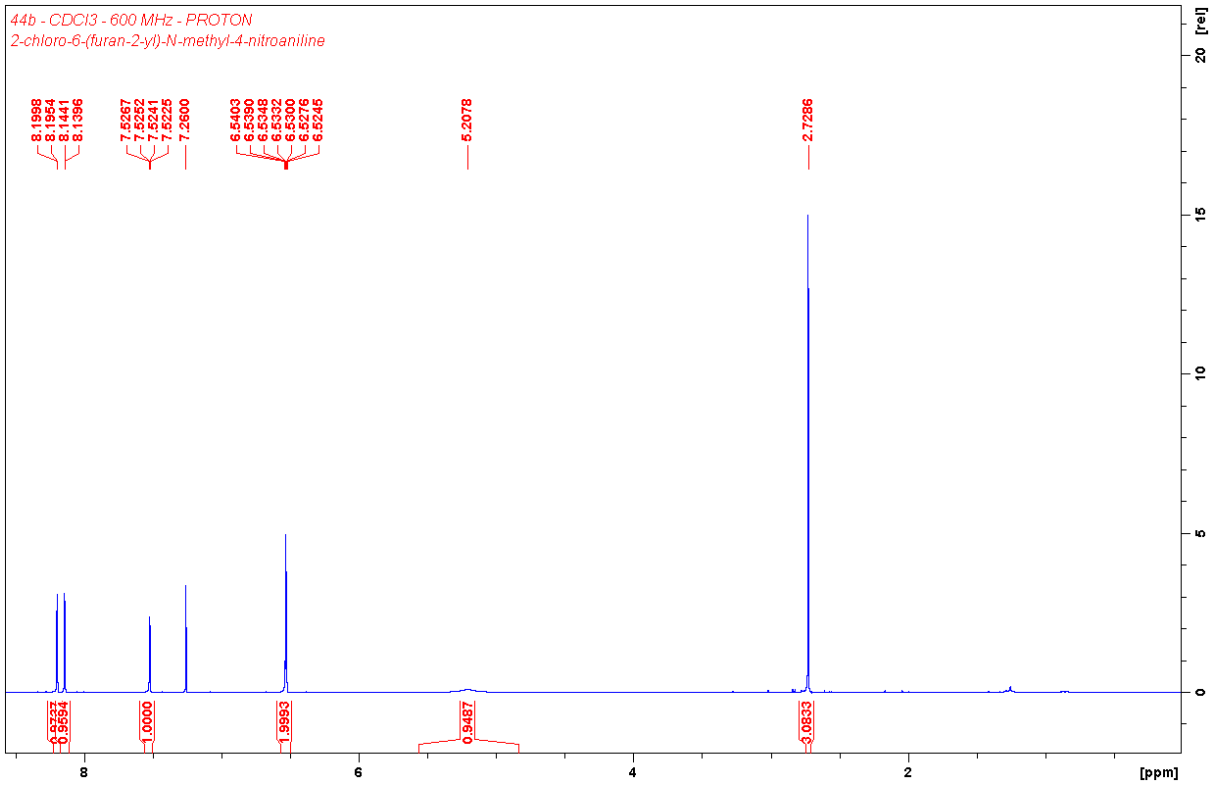
2-Chloro-6-(furan-2-yl)-*N.N*-dimethyl-4-nitroaniline **(45b)**

^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.8 Hz, 1H, H-5), 8.13 (d, *J* = 2.8 Hz, 1H, H-3), 7.55 (dd, *J* = 1.8, 0.7 Hz, 1H, H-5 in furyl), 6.80 (dd, *J* = 3.4, 0.7 Hz, 1H, H-3 in furyl), 6.54 (dd, *J* = 3.4, 1.8 Hz, 1H, H-4 in furyl), 2.84 ($N(Me)_2$).

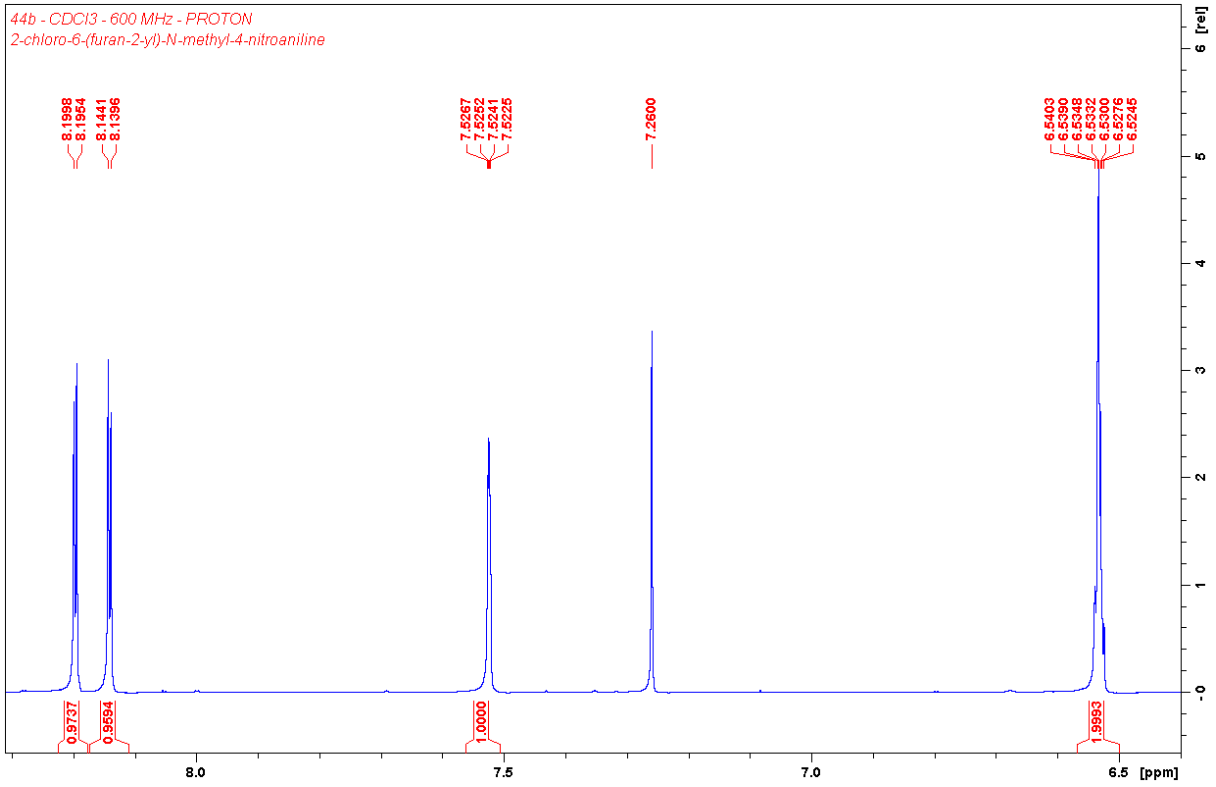
^{13}C-NMR (150 MHz, $CDCl_3$) δ 151.85 (C-1), 150.12 (C-2 in furyl), 143.67 (C-4), 143.02 (C-5 in furyl), 134.46 (C-2), 130.48 (C-6), 124.86 (C-3), 122.62 (C-5), 112.36 (C-4 in furyl), 110.71 (C-3 in furyl), 42.12 ($N(Me)_2$).

HRMS ESI calcd for $C_{12}H_{11}ClN_2O_3$ 266.0458, found 266.0452.

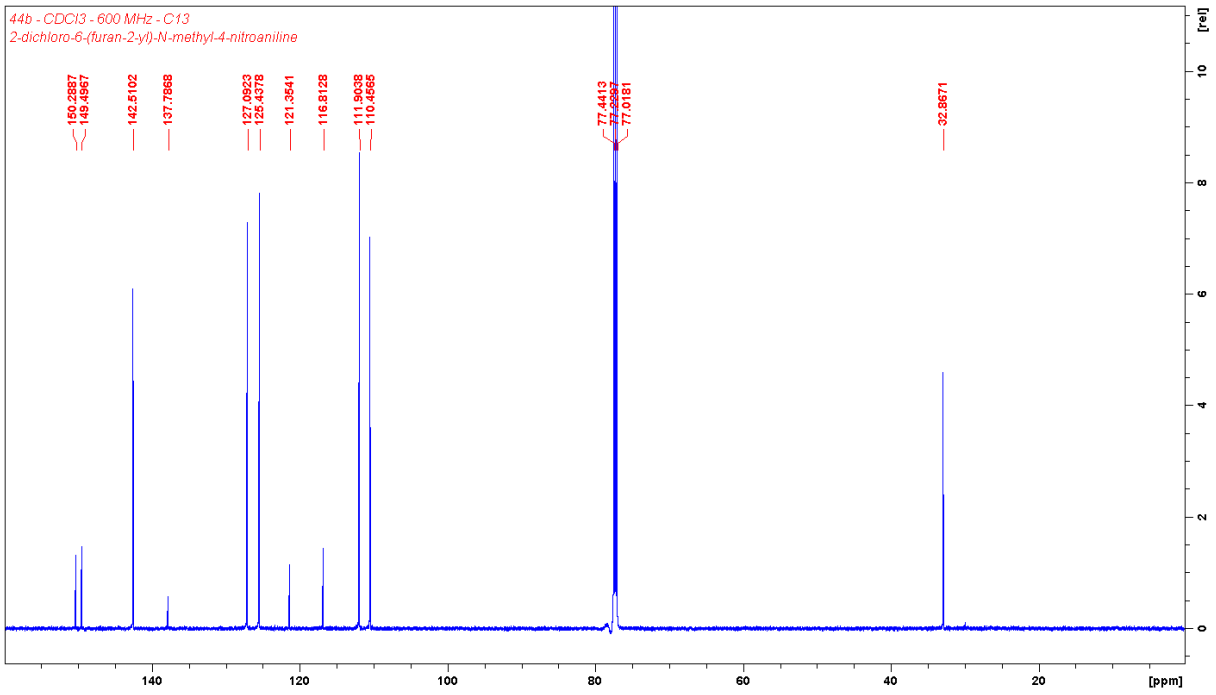
Melting point 62-64 °C



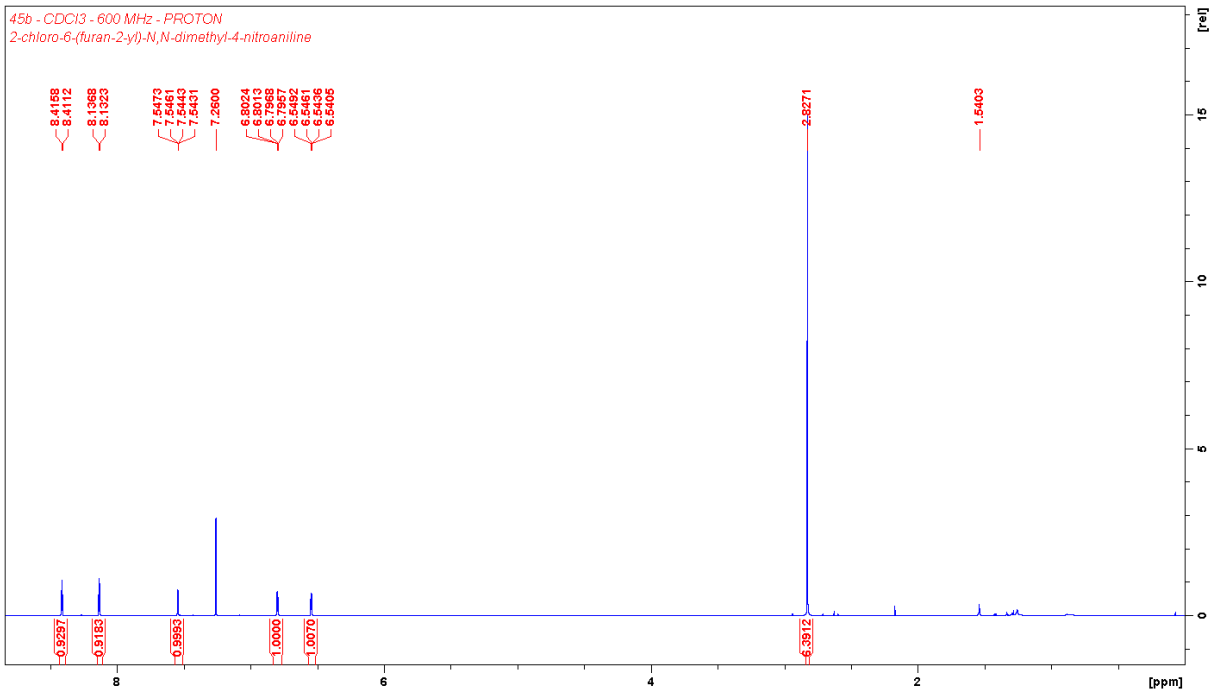
Spectrum 47. 600 MHz, $CDCl_3$ ^{1}H NMR for 2-Chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline (**44b**).



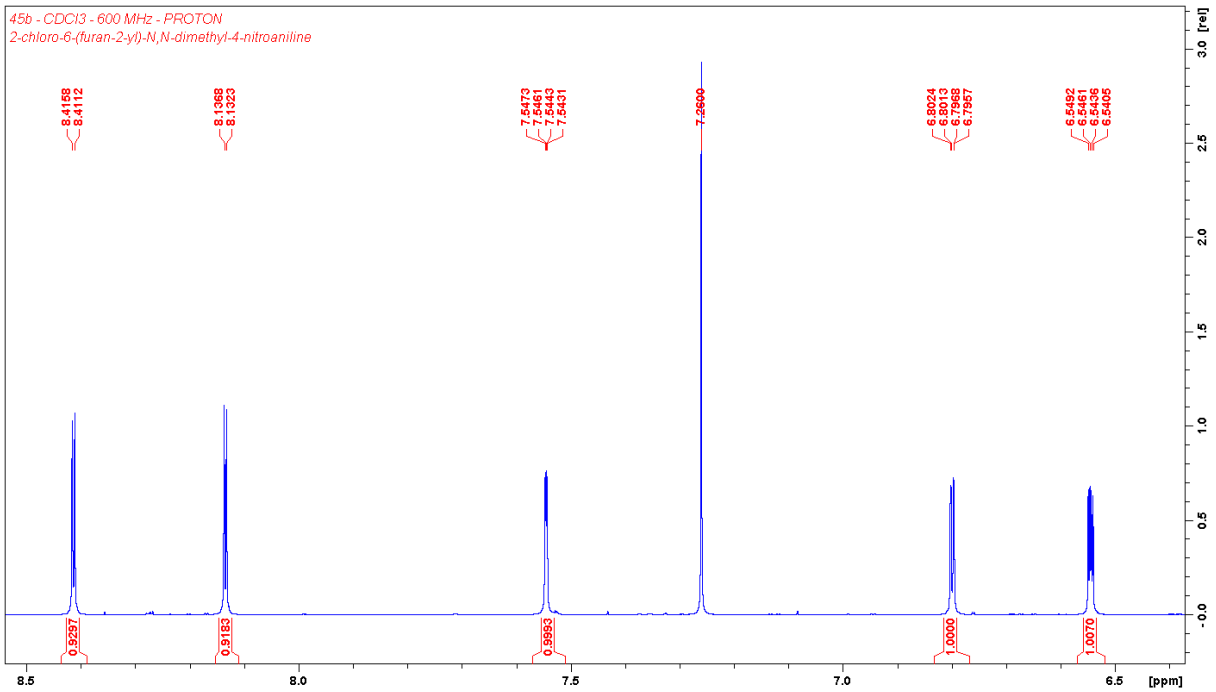
Spectrum 48 600 MHz, $CDCl_3$ ^{1}H NMR for 2-Chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline (**44b**) expanded.



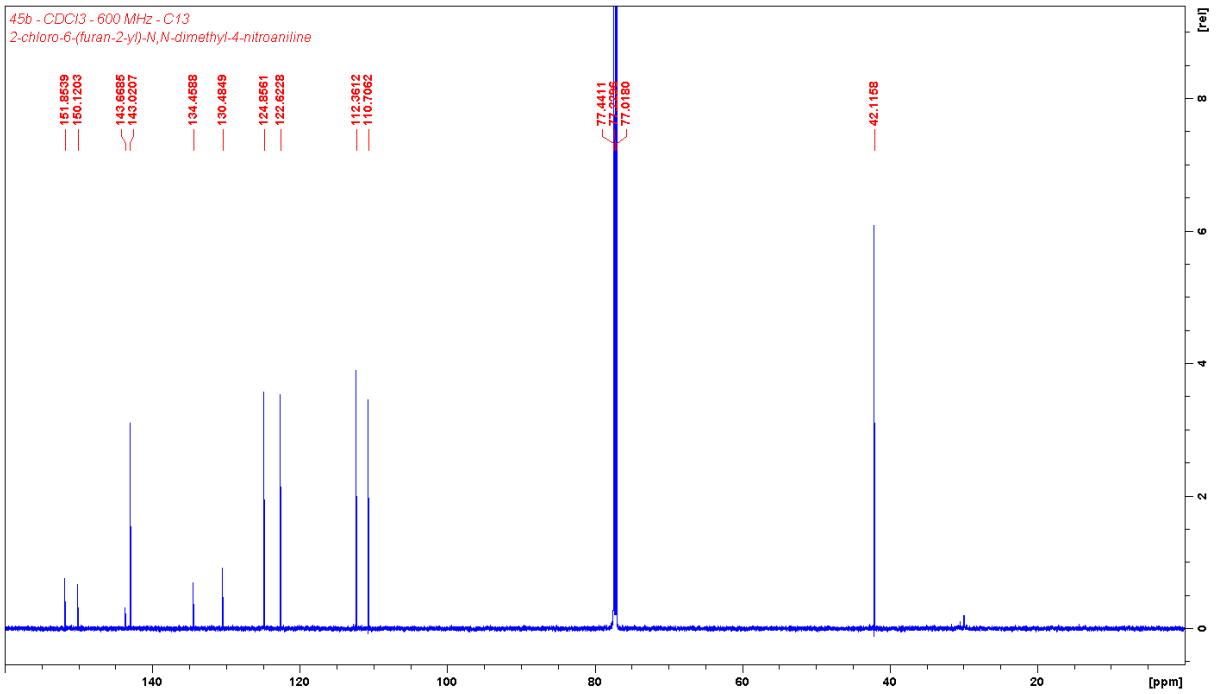
Spectrum 49. 150 MHz, $CDCl_3$ ^{13}C NMR for 2-Chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline (**44b**).



Spectrum 50. 600 MHz, $CDCl_3$ ^1H NMR for 2-Chloro-6-(furan-2-yl)-*N.N*-dimethyl-4-nitroaniline (**45b**).

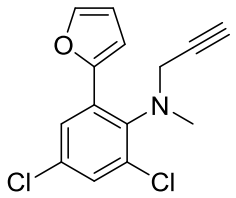


Spectrum 51. 600 MHz, $CDCl_3$ ^1H NMR for 2-Chloro-6-(furan-2-yl)-*N.N*-dimethyl-4-nitroaniline (**45b**) expanded.



Spectrum 52. 150 MHz, $CDCl_3$ ^{13}C NMR for 2-Chloro-6-(furan-2-yl)-*N.N*-dimethyl-4-nitroaniline (**45b**).

Synthesis of 2,4-dichloro-6-(furan-2-yl)-*N*-methyl-*N*-(prop-2-yn-1-yl)aniline (46a)

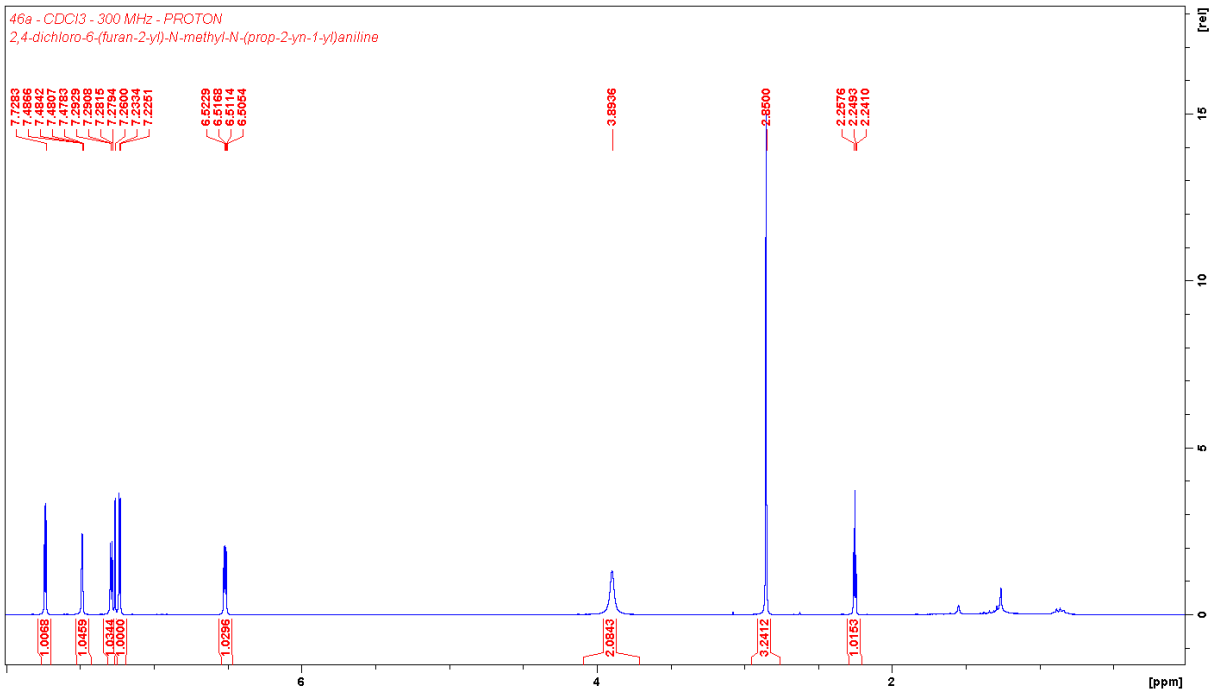


46a

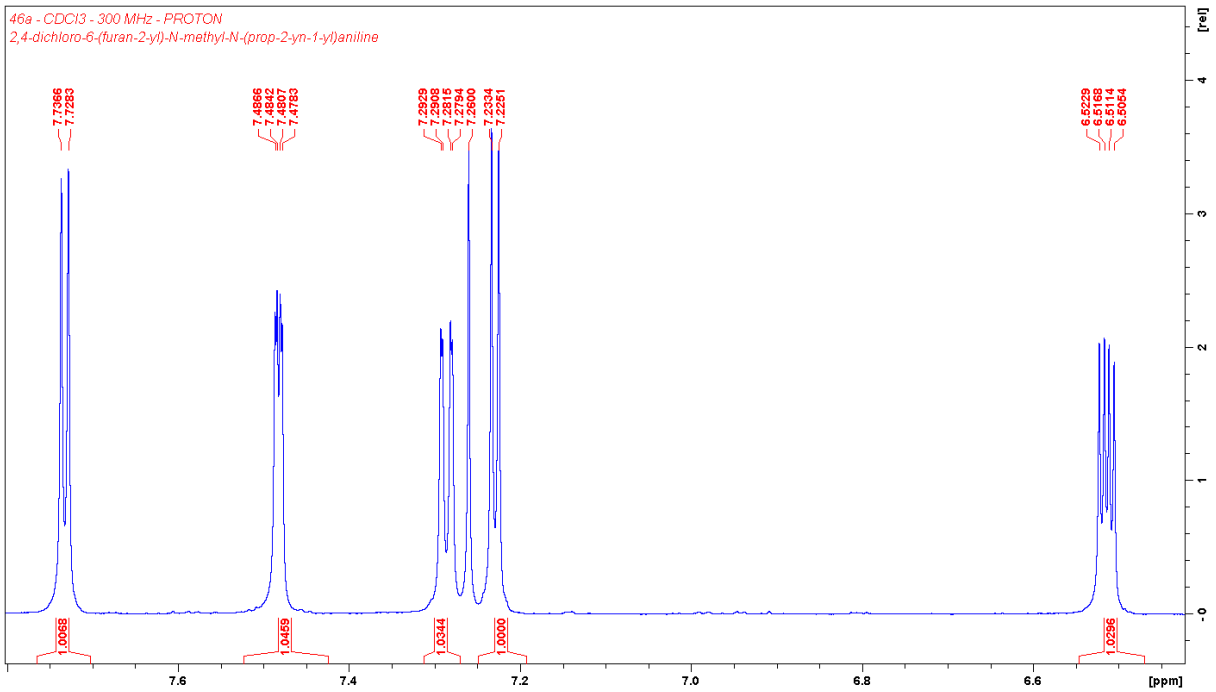
NaH (ca 60% in mineral oil)(50 mg, 1.2 mmole) were added to a degassed solution of compound **44a** (150 mg, 0.62 mmol) in DMF (10 mL, dry). The resulting mixture stirred for 15 min before propargylbromide (**58**)(138 µL, 1.2 mmol) was added. The mixture stirred at 35 °C for 24 hours in a sealed flask before NaH (ca 60% in mineral oil)(71 mg, 1.8 mmol) and propargylbromide (**58**)(138 µL, 1.2 mmol) were subsequently added. The mixture stirred for another 48 hours at 35 °C in a sealed flask before being quenched with 25 mL water. The aqueous phase was extracted with DCM (3 x 15 mL), dried, filtered and concentrated under reduced pressure. The compound was isolated by flash chromatography, eluted with hexanes. Yield 63 mg (36 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.5 Hz, 1H, H-3 or H-5), 7.48 (dd, *J* = 1.8, 0.6 Hz, 1H, H-5 in furyl), 7.29 (dd, *J* = 3.4, 0.6 Hz, 1H, H-3 in furyl), 7.23 (d, *J* = 2.5 Hz, 1H, H-3 or H-5), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1H, H-4 in furyl), 3.89 (s, 2H, NMeC$\underline{H_2}$CCH), 2.85 (s, 3H, N$\underline{Me}$$CH_2$CCH), 2.25 (t, *J* = 2.5 Hz, 1H, NMeCH_2C$\underline{C}$H).

HRMS ESI calcd for $C_{14}H_{11}Cl_2NO$ 279.0218, found 279.0212.

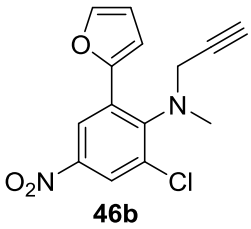


Spectrum 53. 300 MHz, $CDCl_3$, ^1H NMR of 2,4-dichloro-6-(furan-2-yl)-*N*-methyl-*N*-(prop-2-yn-1-yl)aniline (**46a**).



Spectrum 54. 300 MHz, $CDCl_3$, ^1H NMR of 2,4-dichloro-6-(furan-2-yl)-*N*-methyl-*N*-(prop-2-yn-1-yl)aniline (**46a**) expanded.

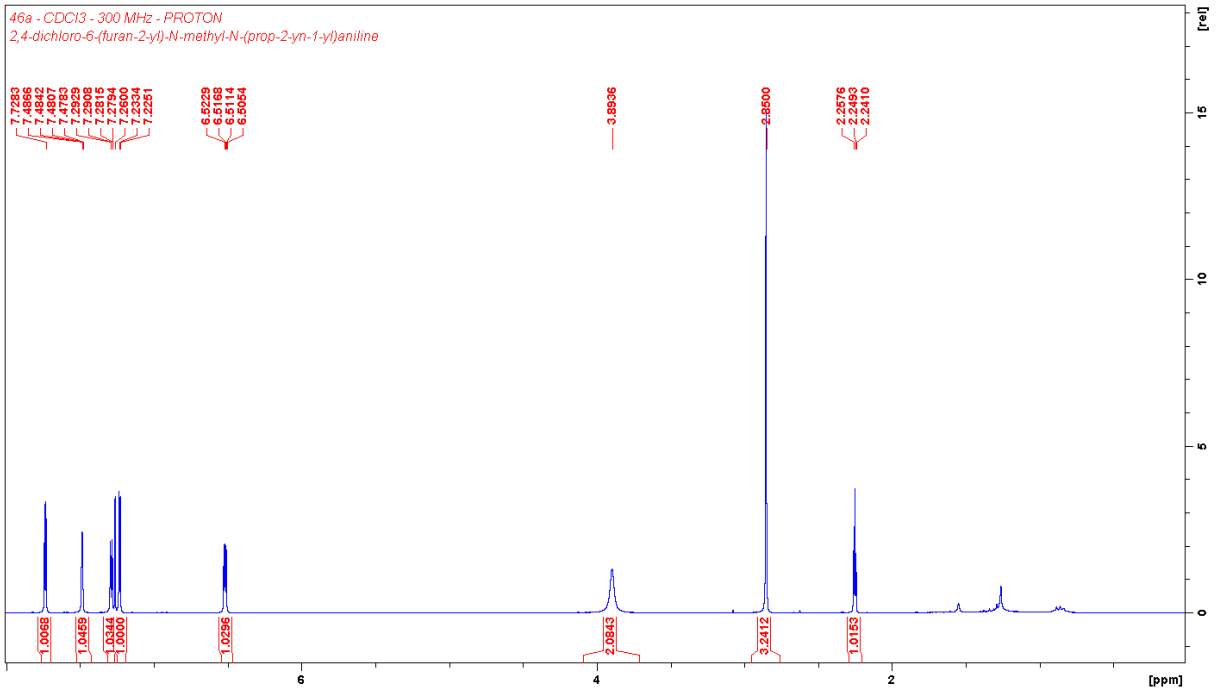
Synthesis of 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitro-*N*-(prop-2-yn-1-yl)aniline (46b)



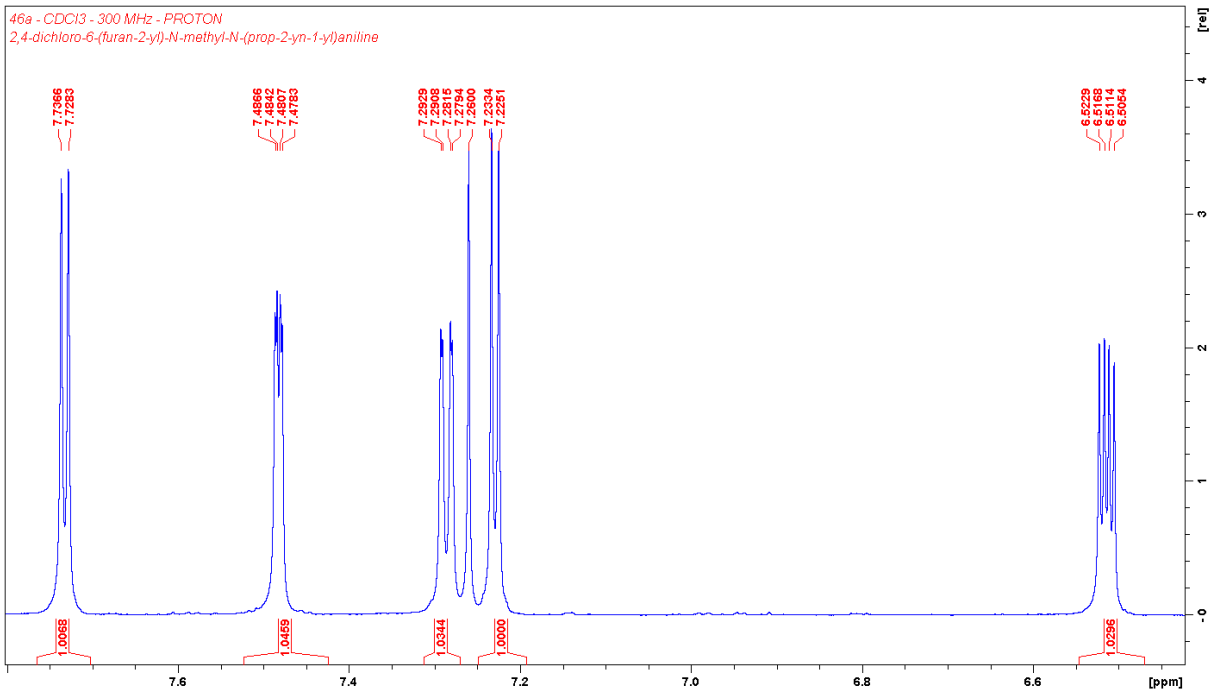
46b

NaH (ca 60% in mineral oil)(38 mg, 0.95 mmole) were added to a degassed solution of compound **44b** (120 mg, 0.48 mmol) in DMF (10 mL, dry). The resulting mixture stirred for 15 min before propargylbromide (**58**)(106 µL, 1.07 mmol) was added. The mixture stirred at 35 °C for 2 hours in a sealed flask before being quenched with 25 mL water. The aqueous phase was extracted with DCM (3 x 15 mL), dried, filtered and concentrated under reduced pressure. The compound was isolated by flash chromatography, eluted with DCM/hexanes 1:9. Yield 119 mg (86 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.7 Hz, 1H, H-3 or H-5), 8.11 (d, *J* = 2.7 Hz, 1H, H-3 or H-5), 7.55 (dd, *J* = 1.8, 0.6 Hz, 1H, H-5 in furyl), 7.17 (dd, *J* = 3.4, 0.6 Hz, 1H, H-3 in furyl), 6.55 (dd, *J* = 3.4, 1.8 Hz, 1H, H-4 in furyl), 3.92 (d, *J* = 2.5 Hz, 2H, NMeC$\underline{H_2}$CCH), (s, 3H, N$\underline{Me}$$CH_2$CCH), (t, *J* = 2.5 Hz, 1H, NMeCH_2C$\underline{C}$$\underline{H}$).

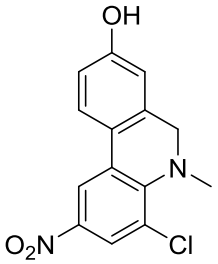


Spectrum 55. 300 MHz, $CDCl_3$, ^{1}H NMR of 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitro-*N*-(prop-2-yn-1-yl)aniline (**46b**).



Spectrum 56. 300 MHz, $CDCl_3$, ^1H NMR of 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitro-*N*-(prop-2-yn-1-yl)aniline (**46b**) expanded.

Synthesis of 4-chloro-5-methyl-2-nitro-5,6-dihydrophenanthridin-8-ol (47b)



47b

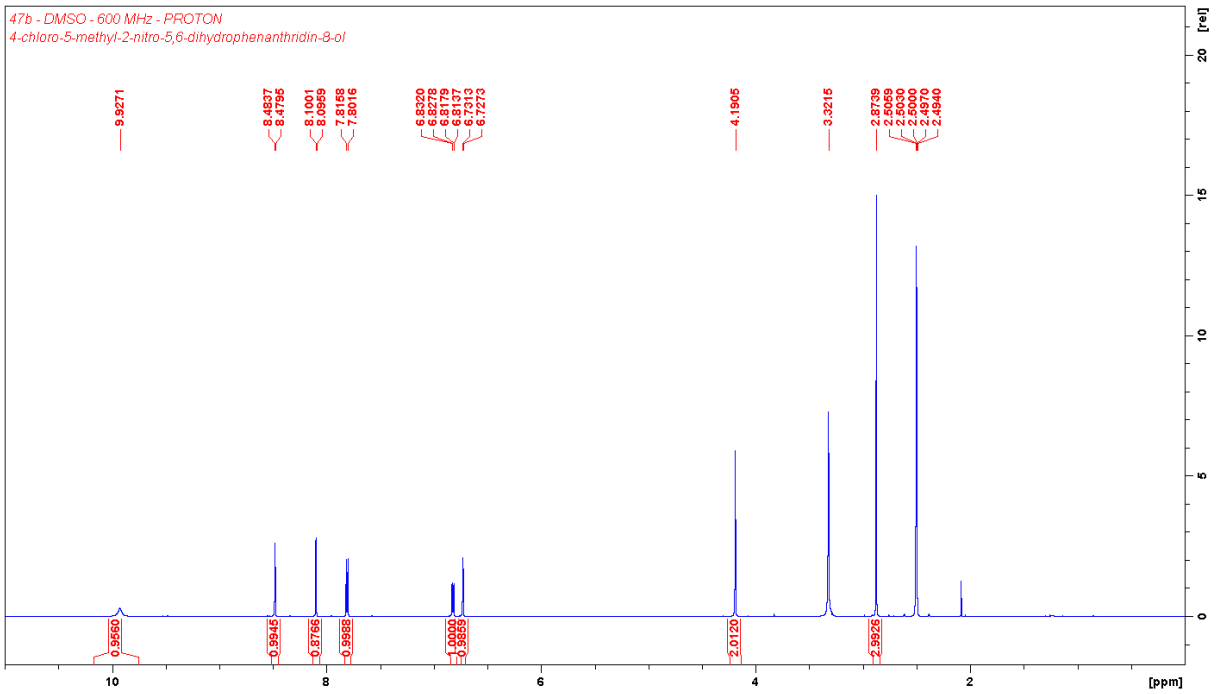
Compound **46b** (89 mg, 0.31 mmol) was weighed in a pressure vial, degassed MeCN (15 mL) was added and the flask was degassed with Ar (10 min). Two drops HCl (0.2 M) was added to the flask under an Ar stream. The mixture stirred in the microwave reactor at 180 °C for 40 min and was cooled down to 60 °C before taken out and concentrated under reduced pressure. The compound was isolated by flash chromatography, eluted by EtOAc/hexanes 3:7, and washed with pentane (3 x 10 mL). Yield 73 mg (82 %) as a red solid.

^{1}H-NMR (600 MHz, DMSO) δ 9.93 (br s, 1H, OH), 8.48 (d, *J* = 2.5 Hz, 1H, H-1), 8.10 (d, *J* = 2.5 Hz, 1H, H-3), 7.81 (d, *J* = 8.5 Hz, 1H, H-10), 6.82 (dd, *J* = 8.5, 2.5 Hz, 1H, H-9), 6.73 (d, *J* = 2.5 Hz, 1H, H-7), 4.19 (br s, 2H, H-6), 2.87 (br s, 3H, NMe).

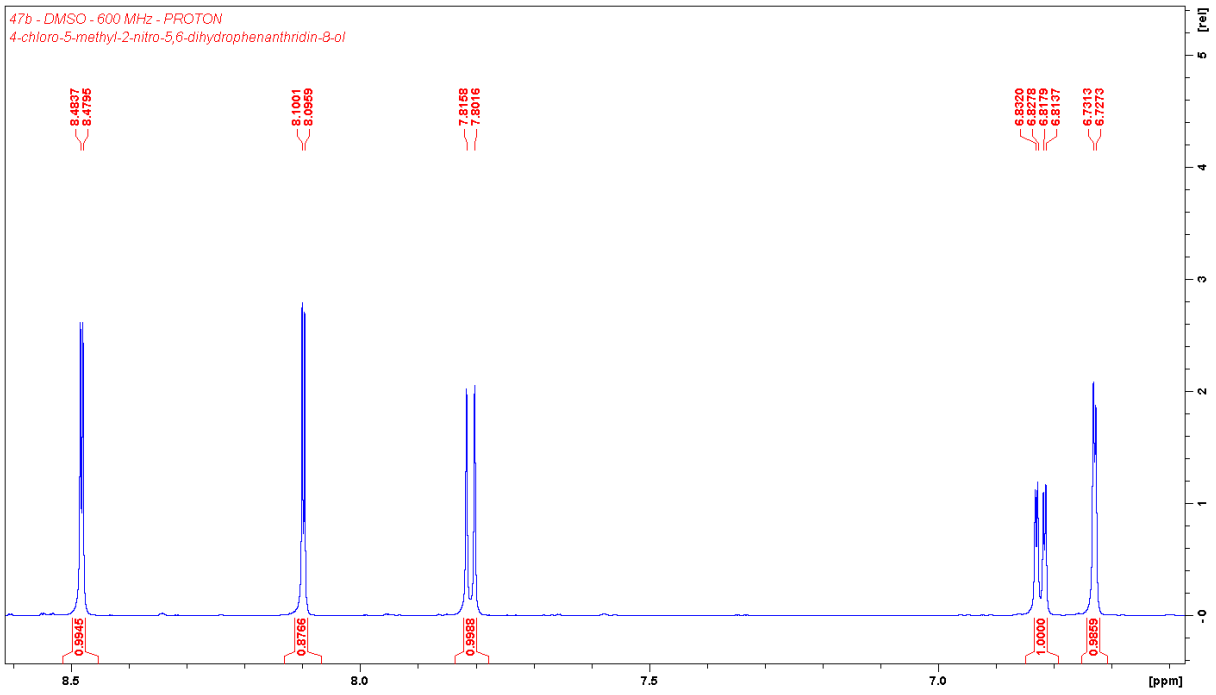
^{13}C-NMR (150 MHz, DMSO) δ 158.91 (C-8), 149.08 (C-4a), 142.16 (C-2), 134.21 (C-2), 130.36 (C-10b), 126.70 (C-4), 125.38 (C-10), 123.25 (C-3), 120.27 (C-10a), 116.58 (C-1), 115.31 (C-9), 112.99 (C-7), 53.50 (C-6), 41.19 (NMe).

HRMS ESI calcd for $C_{14}H_{11}ClN_2O_3$ 290.0458, found 290.0452.

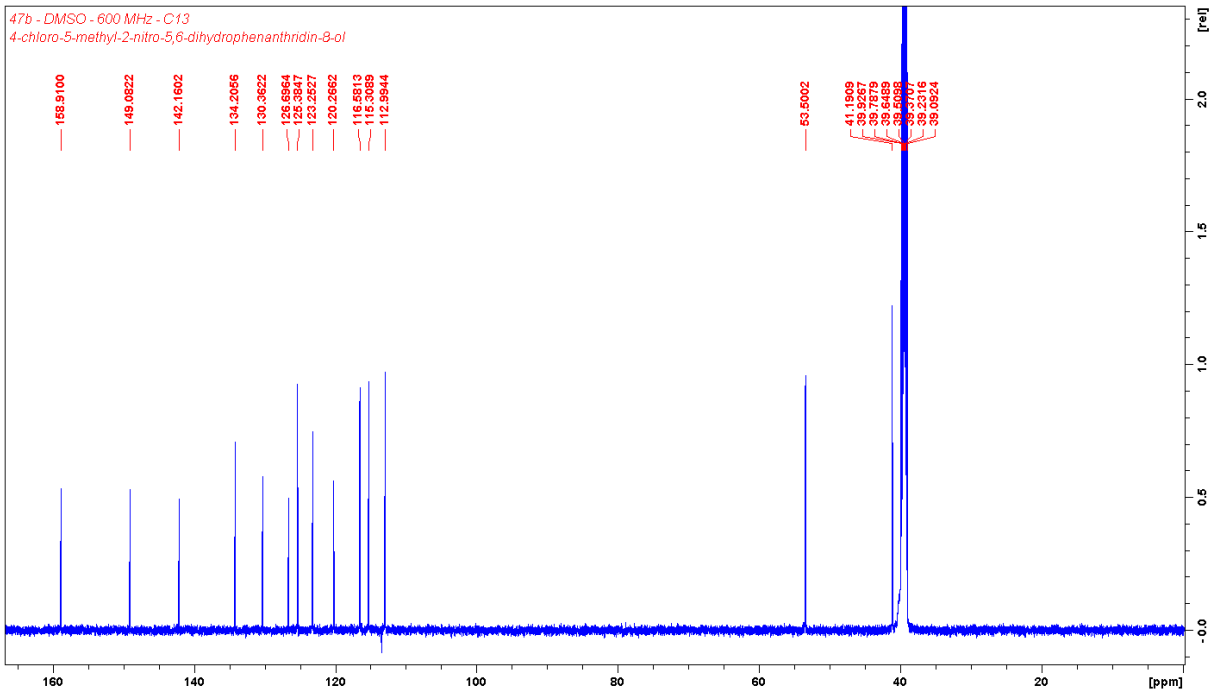
Melting point 173-175 °C.



Spectrum 57. 600 MHz, DMSO, ^{1}H NMR of 4-chloro-5-methyl-2-nitro-5,6-dihydrophenanthridin-8-ol (**47b**).

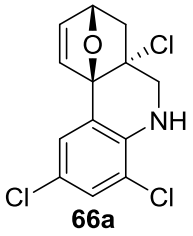


Spectrum 58. 600 MHz, DMSO, ^{1}H NMR of 4-chloro-5-methyl-2-nitro-5,6-dihydrophenanthridin-8-ol (**47b**) expanded.



Spectrum 59. 150 MHz, DMSO, ^{13}C NMR of 4-chloro-5-methyl-2-nitro-5,6-dihydrophenanthridin-8-ol (**47b**).

Synthesis of (6aS,8S,10aS)-2,4-dichloro-6a-methyl-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (66a)



66a

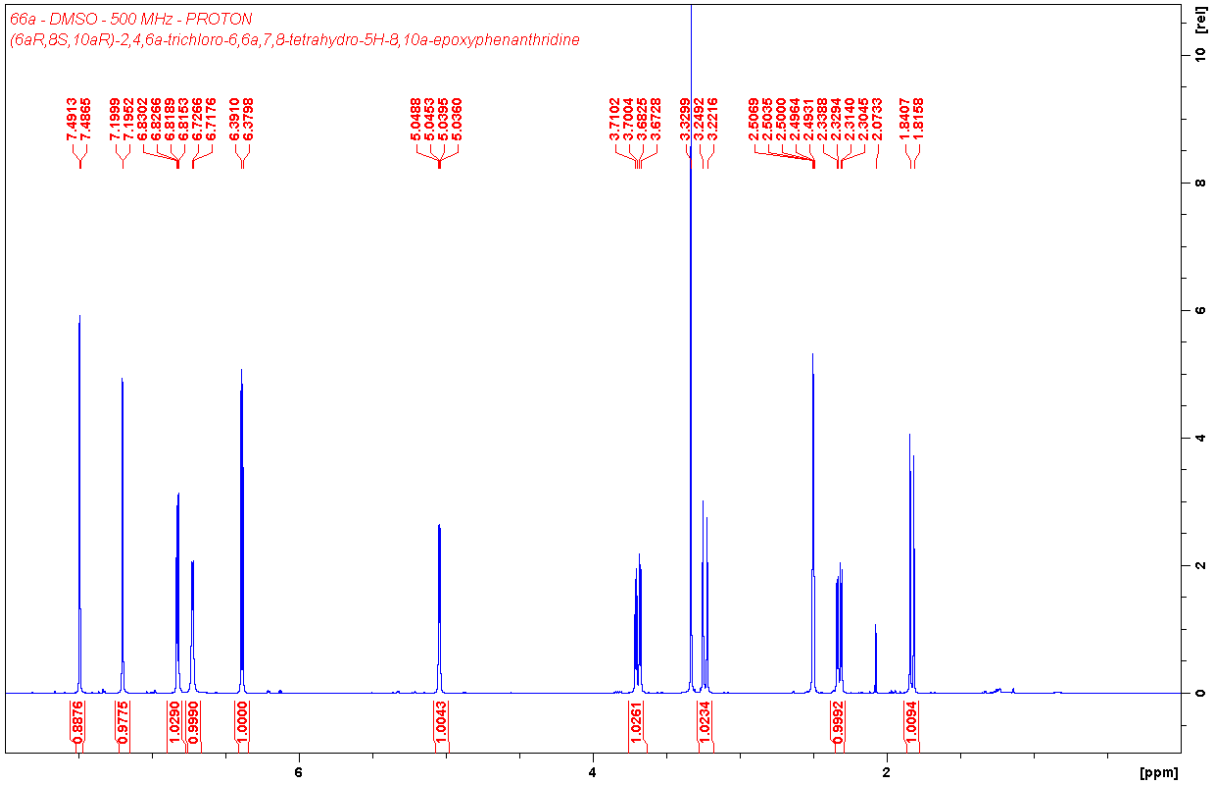
Compound **37a** (168.0 mg, 0,5 mmole) was added to a pressure vial. Degassed MeCN (15 mL) was added to the pressure vial and it was degassed with Ar (10 min). The vial was put in a microwave reactor where it stirred at 150 °C for 1 hour. The compound was concentrated under reduced pressure. Yield compound **66a** (0.163 g, 97 %) as a pale yellow solid.

^{1}H NMR (500 MHz, DMSO) δ = 7.49 (d, *J* = 2.4 Hz, 1 H, H-3), 7.20 (d, *J* = 2.3 Hz, 1 H, H-1), 6.82 (dd, *J* = 1.8, 5.6 Hz, 1 H, H-9), 6.72 (d, *J* = 4.6 Hz, 1 H, H-5), 6.39 (d, *J* = 5.5 Hz, 1 H, H-10), 5.04 (dd, *J* = 1.9, 4.7 Hz, 1 H, H-8), 3.69 (dd, *J* = 4.9, 13.83 Hz, 1 H, H-6a), 3.24 (d, *J* = 13.7 Hz, 1 H, H-6b), 2.32 (dd, *J* = 4.8, 12.4 Hz, 1 H, H-7b), 1.84 (d, *J* = 12.4 Hz, 1 H, H-7a).

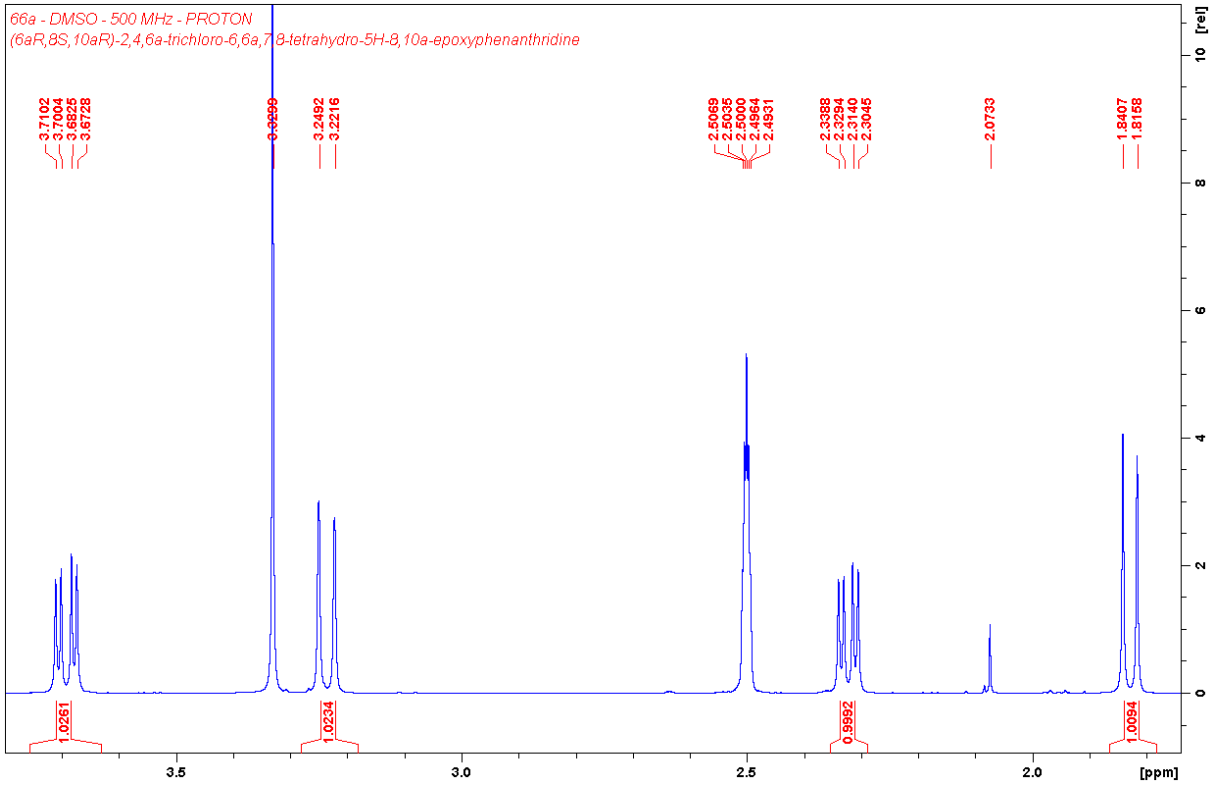
^{13}C NMR (125 MHz, DMSO) 140.46, 139.52, 135.10, 129.63, 129.25, 118.85, 118.27, 117.42, 86.16, 78.06, 62.66, 51.58, 42.08.

Configurations was confirmed by several 1D selective NOESY experiments.

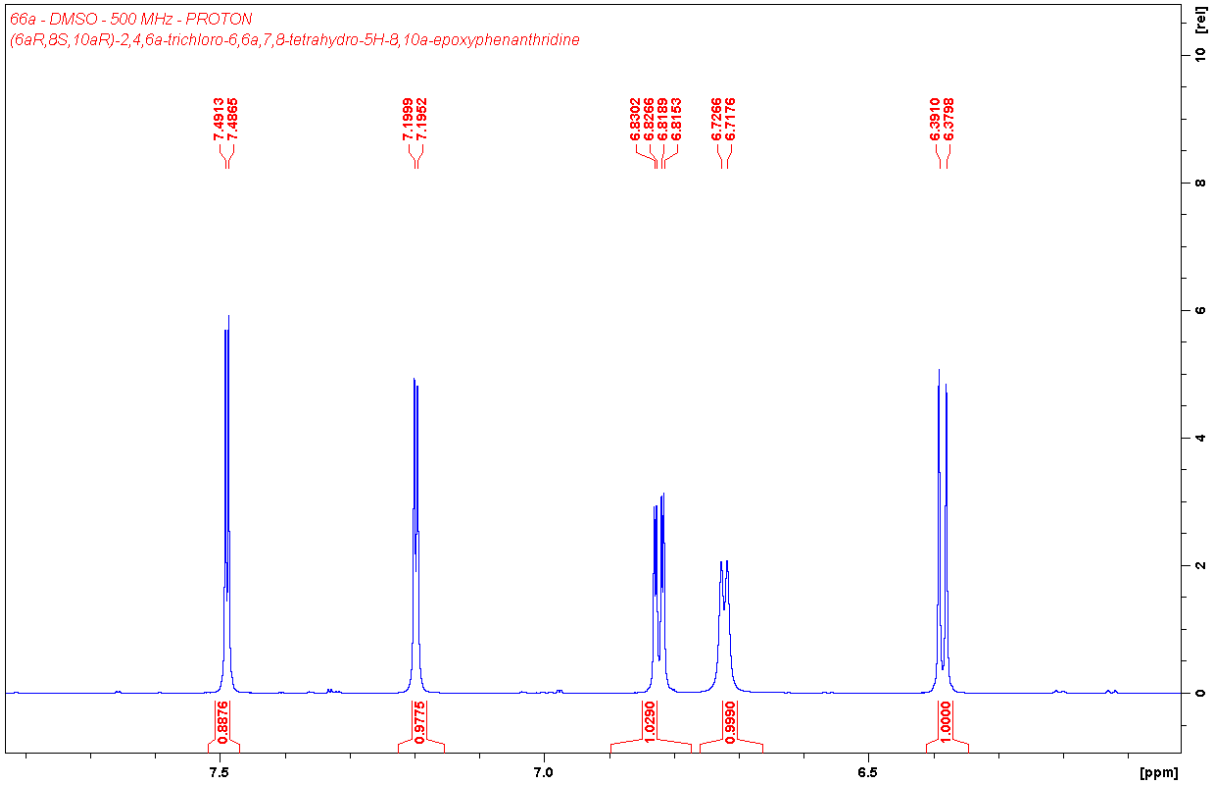
HRMS ESI calcd for $C_{13}H_{10}Cl_3NO$ 300.9828, found 300.9822.



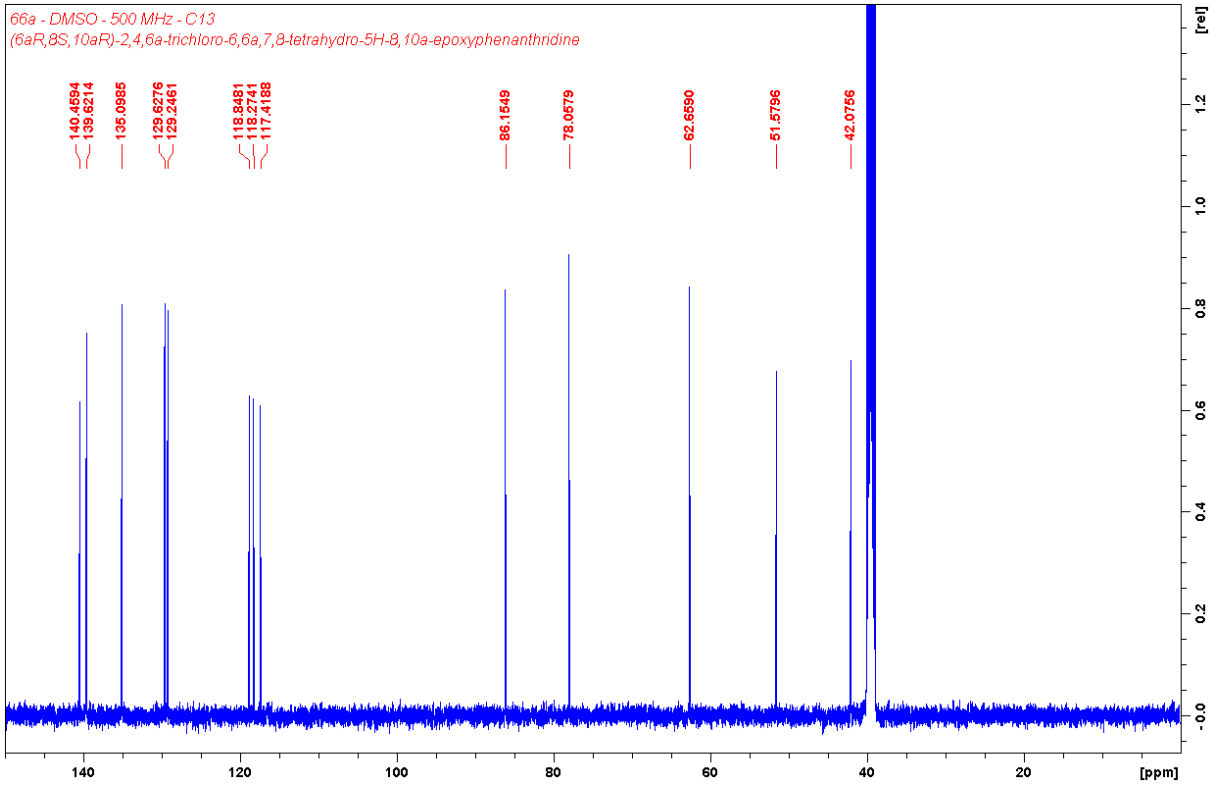
Spectrum 60. 500 MHz, DMSO, ^{1}H NMR for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (**66a**).



Spectrum 61. 500 MHz, DMSO, ^{1}H NMR for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (**66a**) expanded-1.

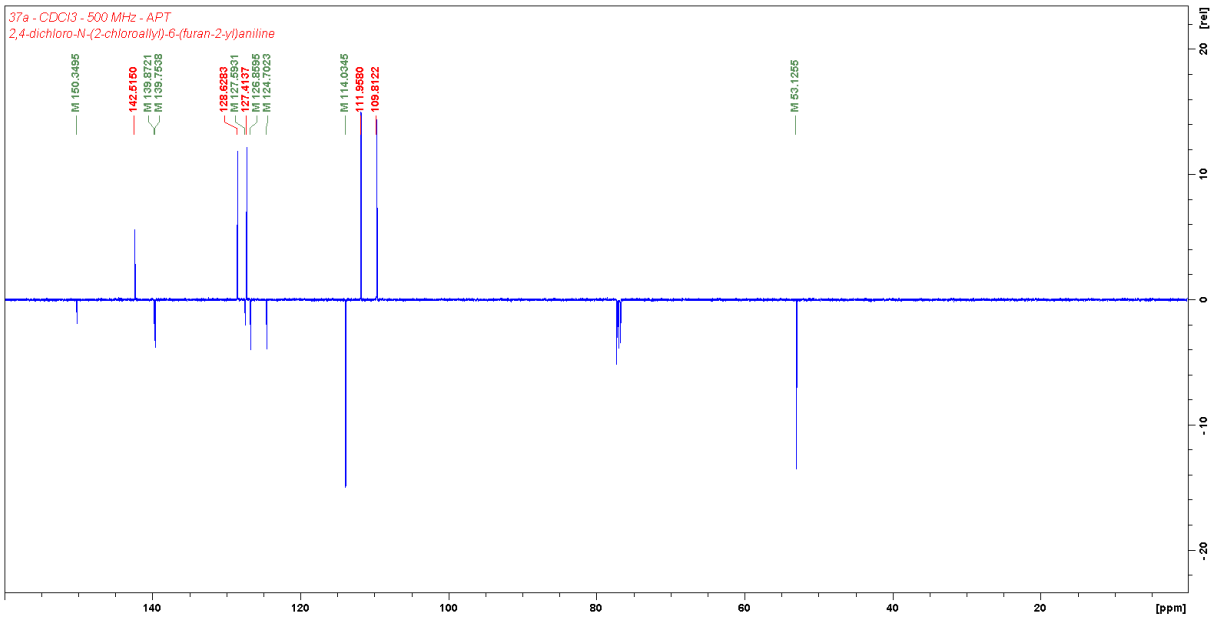


Spectrum 62. 500 MHz, DMSO, ^{1}H NMR for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (**66a**) expanded-2.

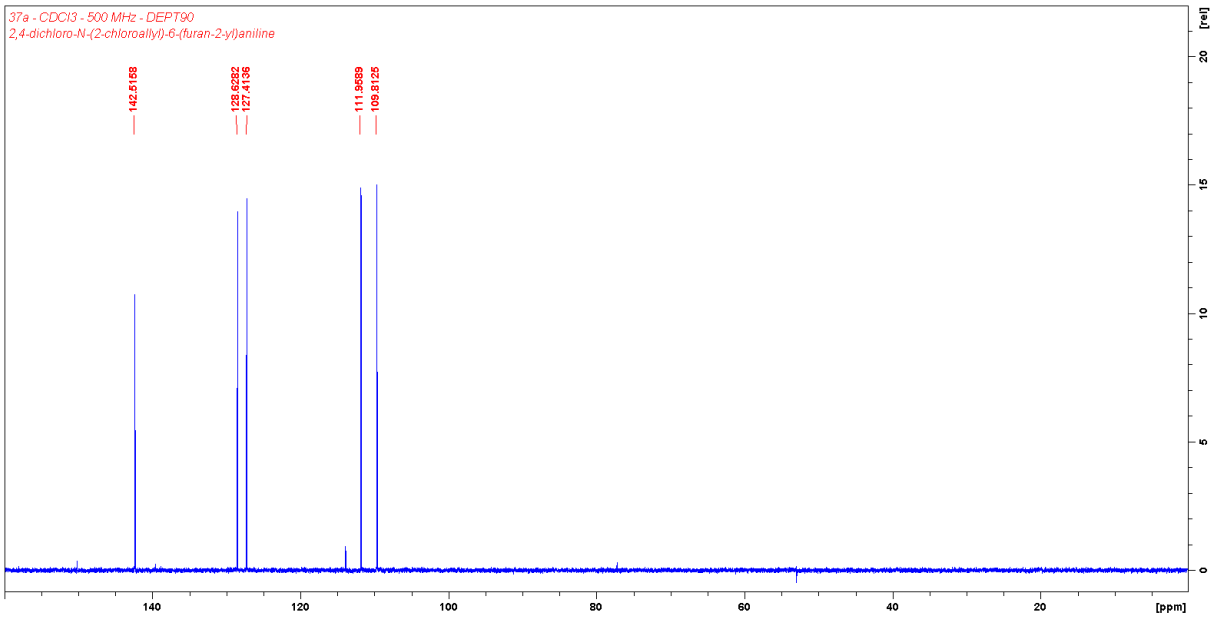


Spectrum 63. 125 MHz, DMSO, ^{13}C NMR for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (**66a**).

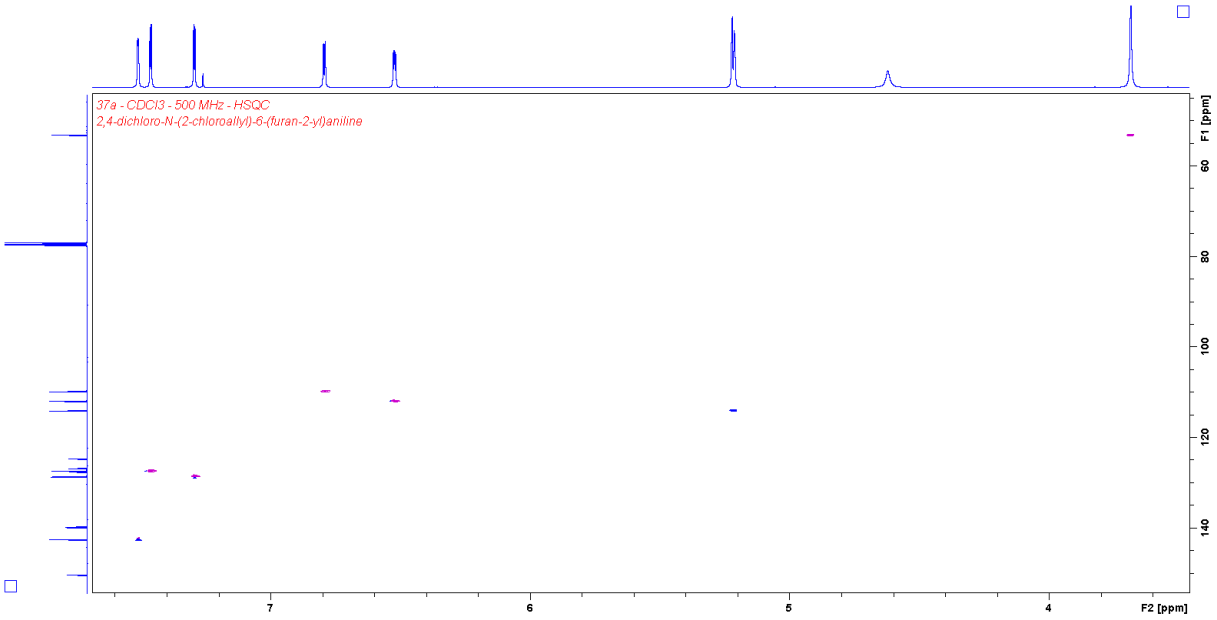
6. Appendix



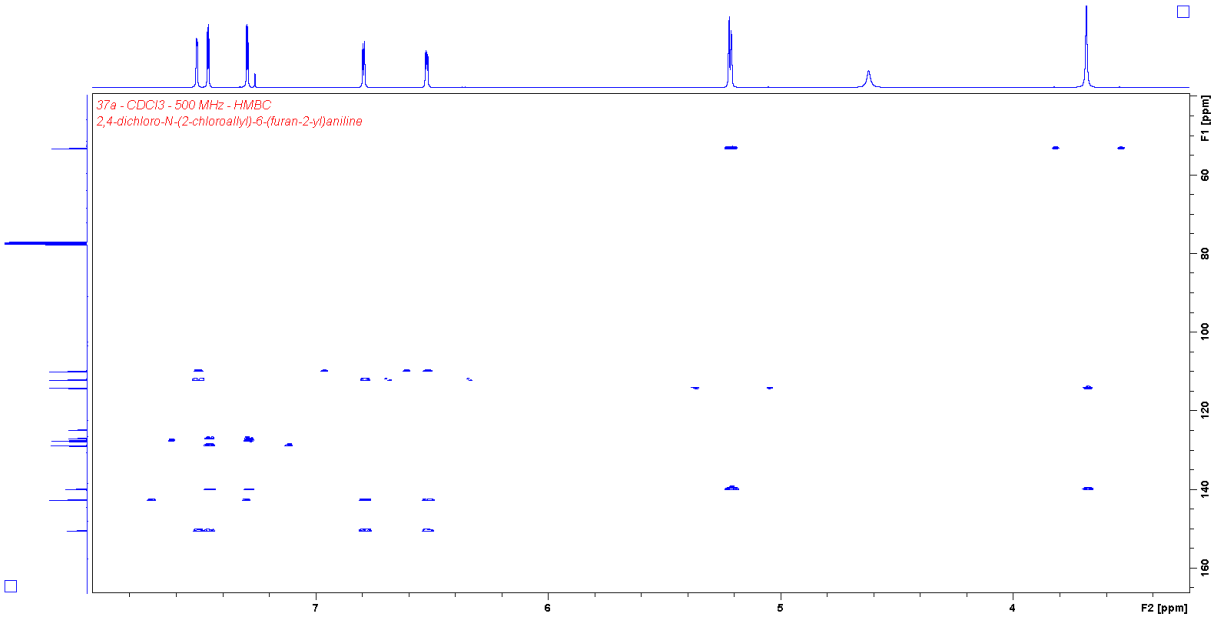
Spectrum 64. 125 MHz, APT NMR for 2,4-dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline (**37a**).



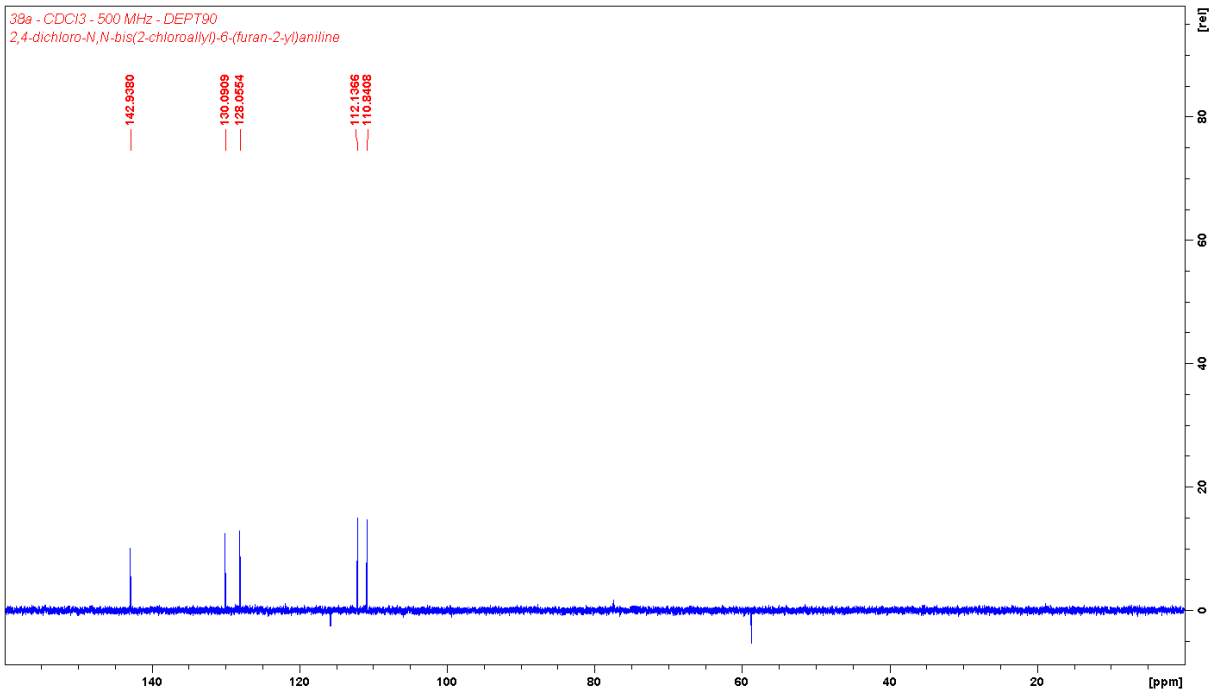
Spectrum 65. 125 MHz, DEPT90 NMR for 2,4-dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline (**37a**).



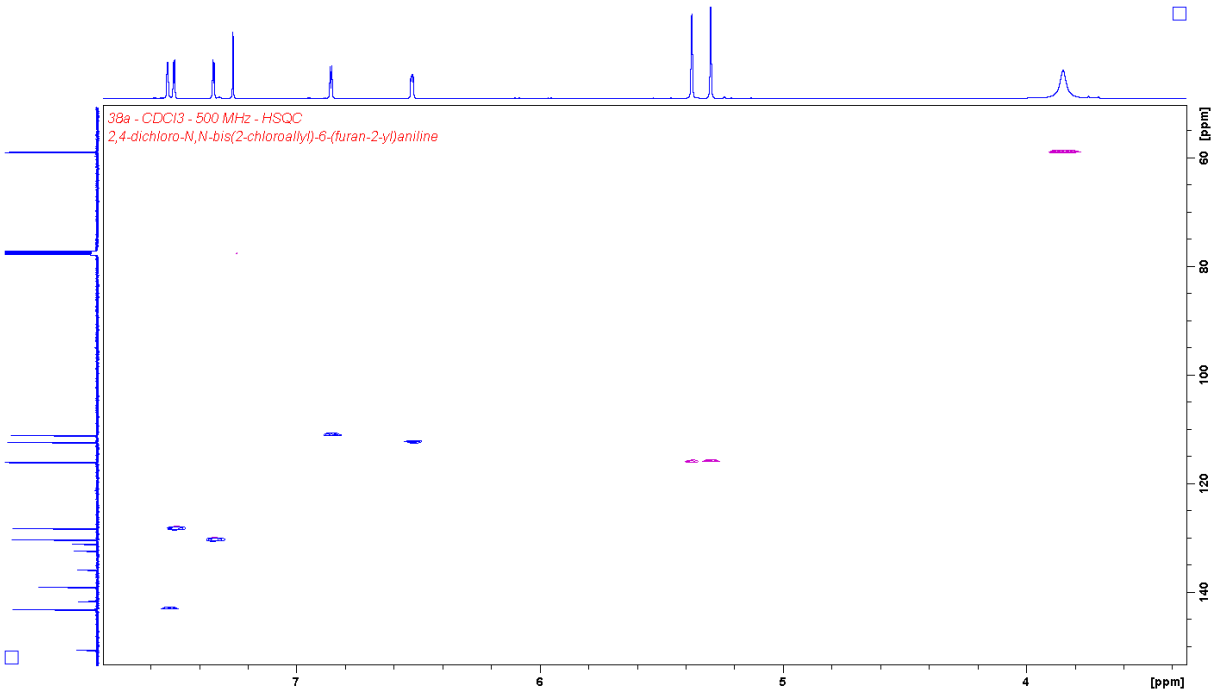
Spectrum 66. 125 MHz, HSQC NMR for 2,4-dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline (**37a**).



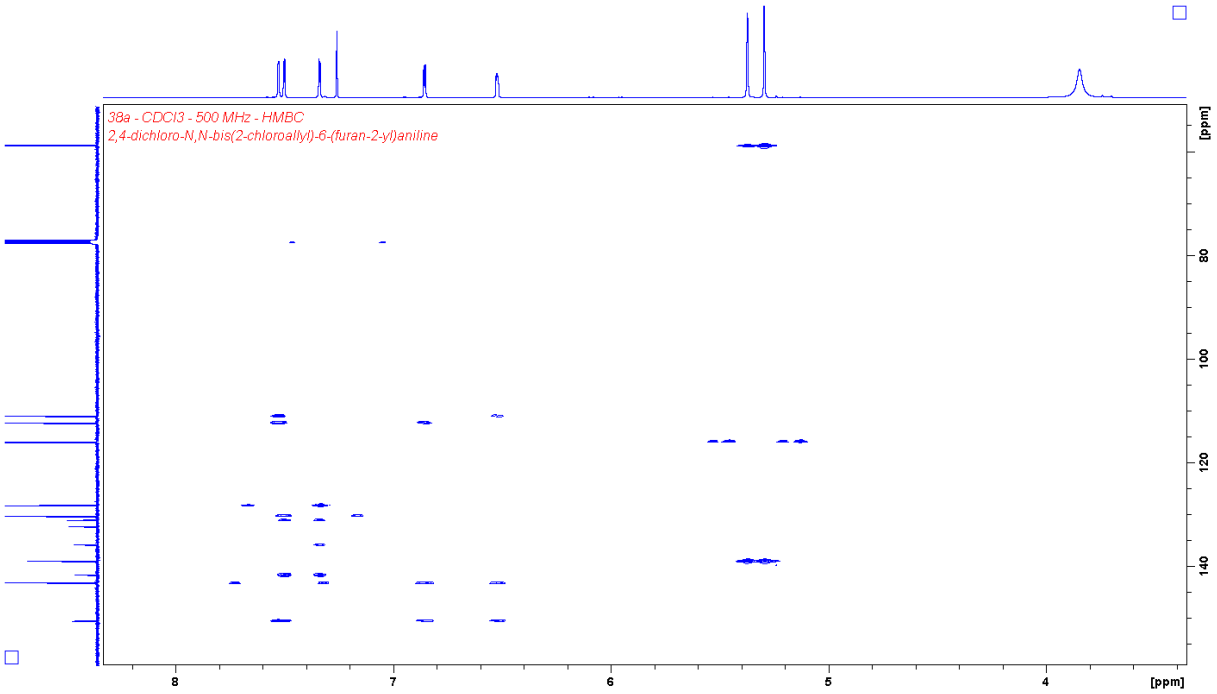
Spectrum 67. 125 MHz, HMBC NMR for 2,4-dichloro-*N*-(2-chloroallyl)-6-(furan-2-yl)aniline (**37a**).



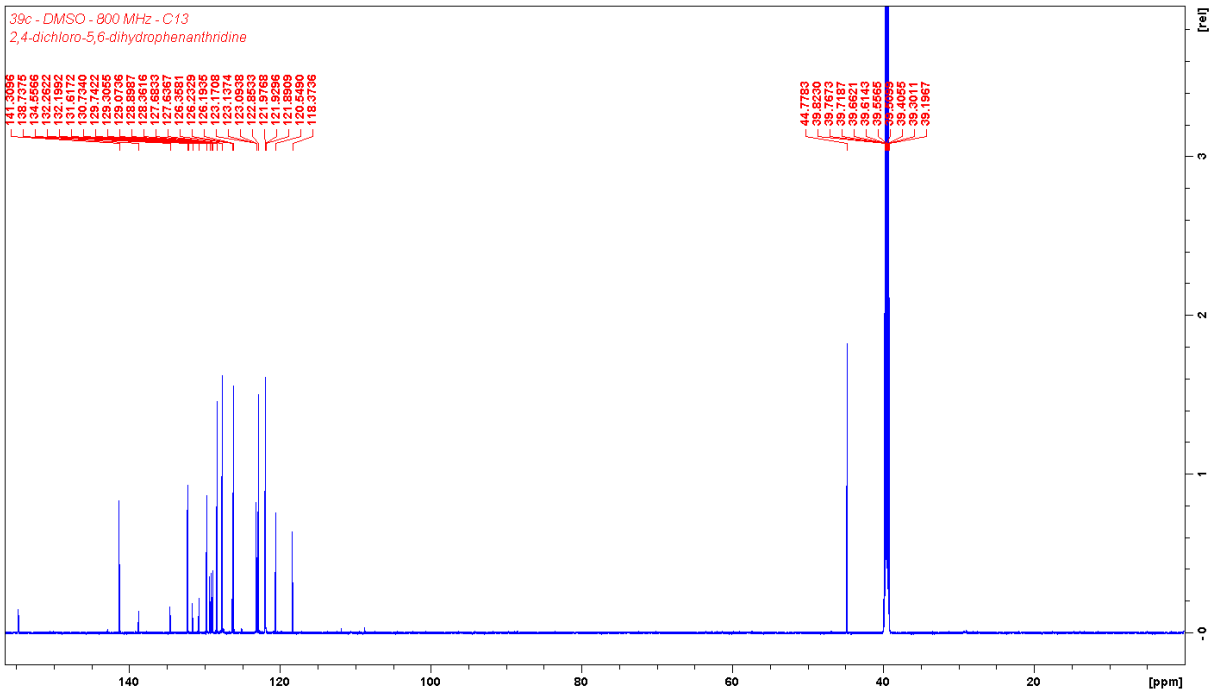
Spectrum 68. 125 MHz, DEPT90 NMR for 2,4-dichloro-*N*-*N*-bis(2-chloroallyl)-6-(furan-2-yl)aniline (**38a**).



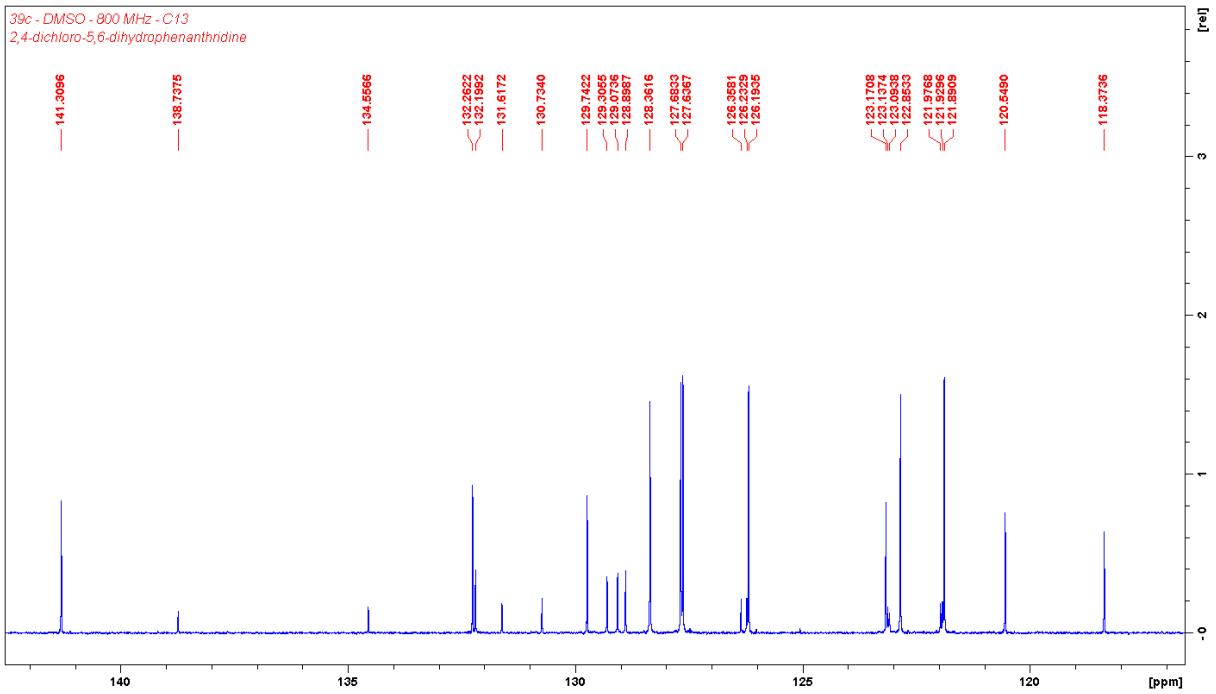
Spectrum 69. 125 MHz, HSQC NMR for 2,4-dichloro-*N*-*N*-bis(2-chloroallyl)-6-(furan-2-yl)aniline (**38a**).



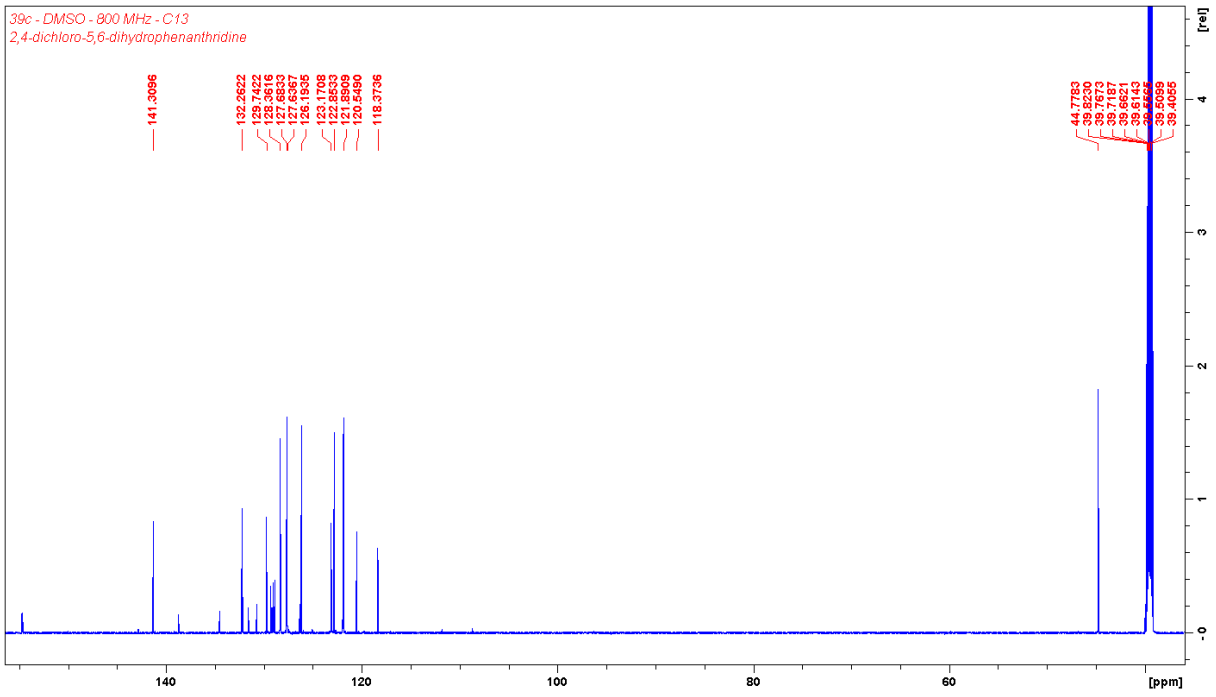
Spectrum 70. 125 MHz, HMBC NMR for 2,4-dichloro-*N*-*N*-bis(2-chloroallyl)-6-(furan-2-yl)aniline (**38a**).



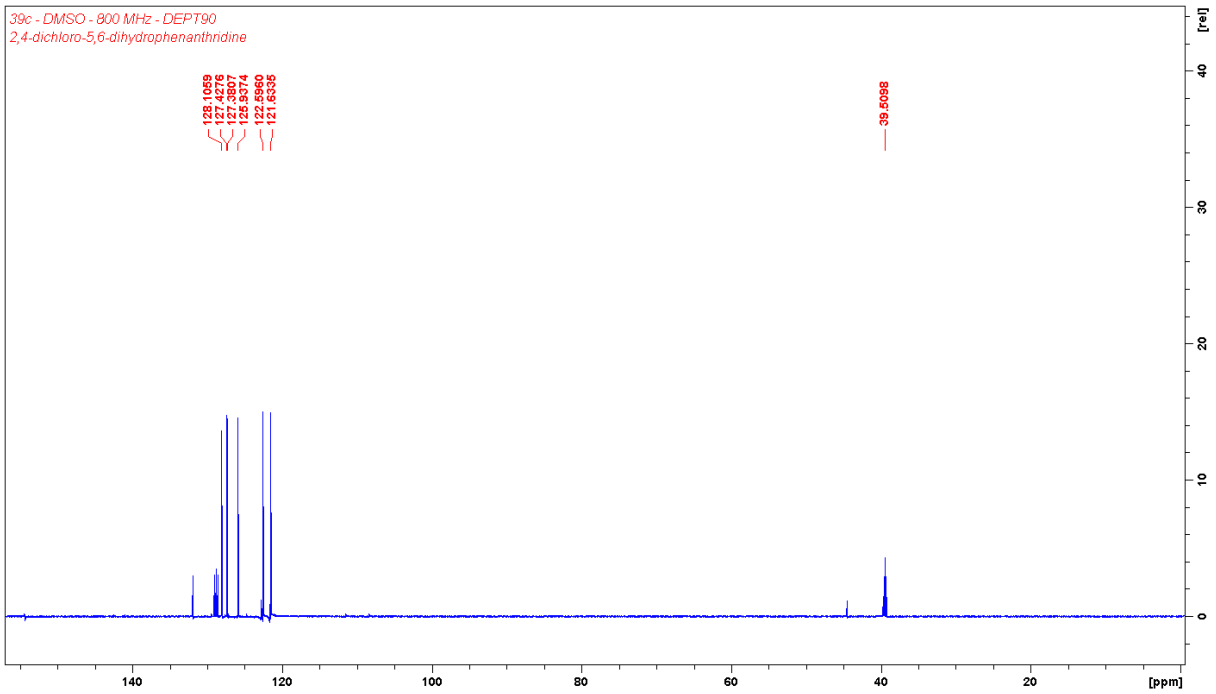
Spectrum 71. 200 MHz, ^{13}C NMR for 2,4-dichloro-5,6-dihydrophenanthridine (**39c**).



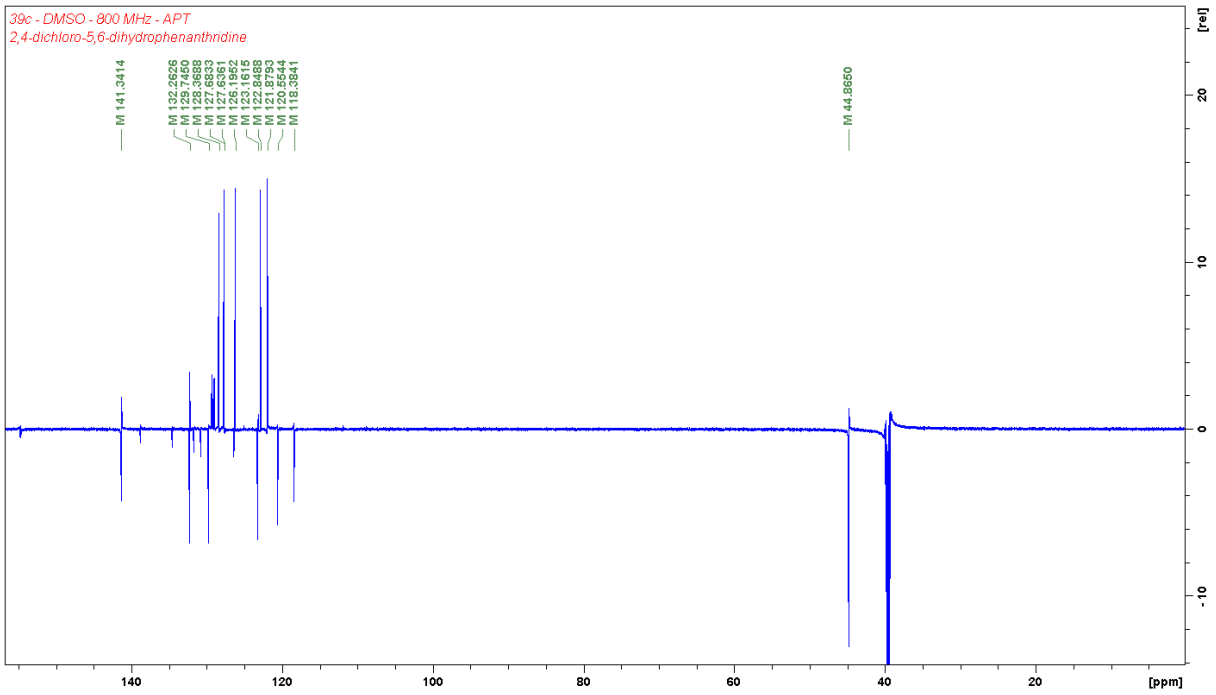
Spectrum 72. 200 MHz, ^{13}C NMR for 2,4-dichloro-5,6-dihydrophenanthridine (**39c**).



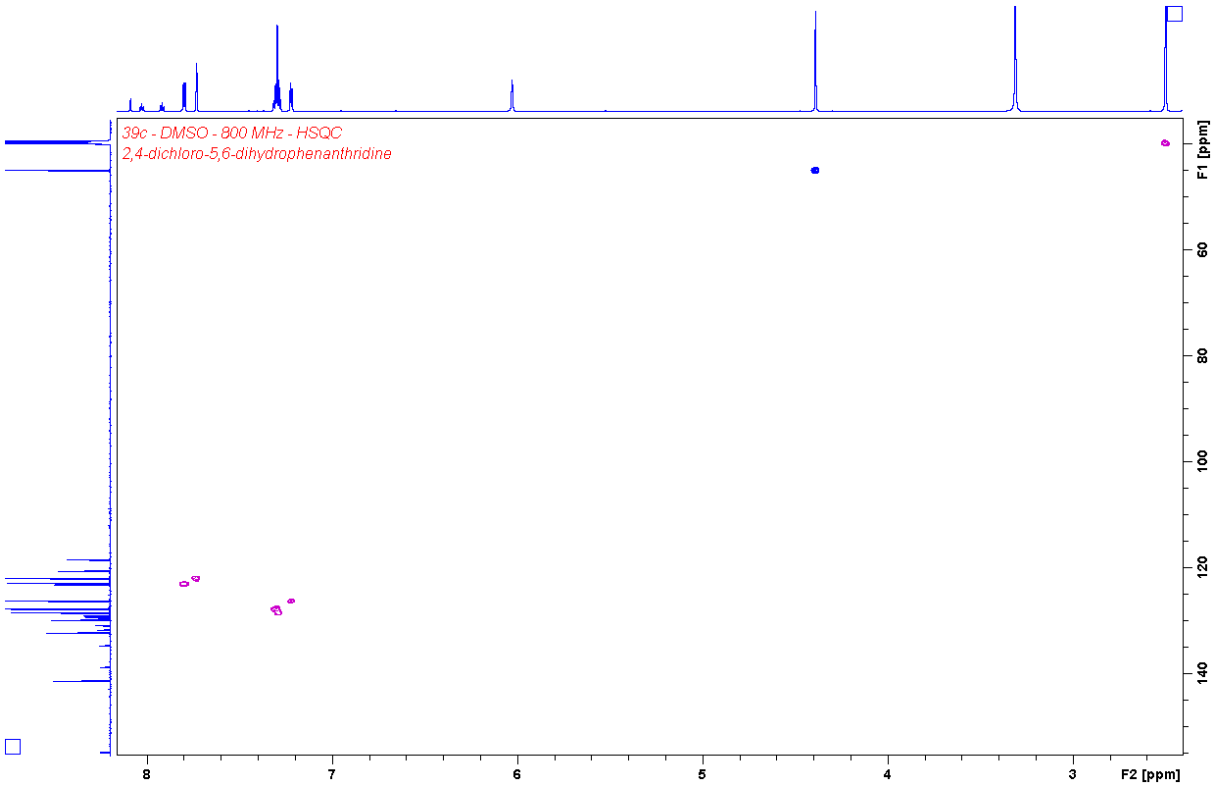
Spectrum 73. 200 MHz, ^{13}C NMR for 2,4-dichloro-5,6-dihydrophenanthridine (**39c**), only compound **39c** marked.



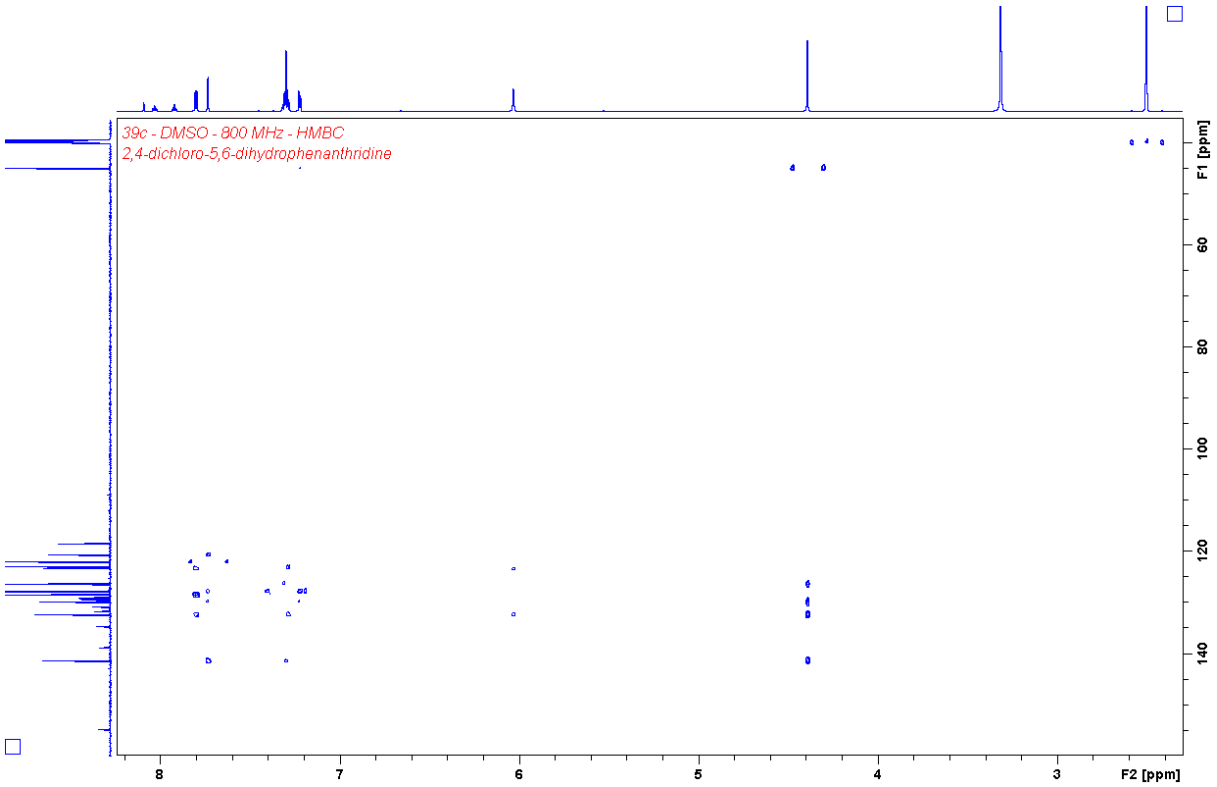
Spectrum 74. 200 MHz, DEPT90 NMR for 2,4-dichloro-5,6-dihydrophenanthridine (**39c**).



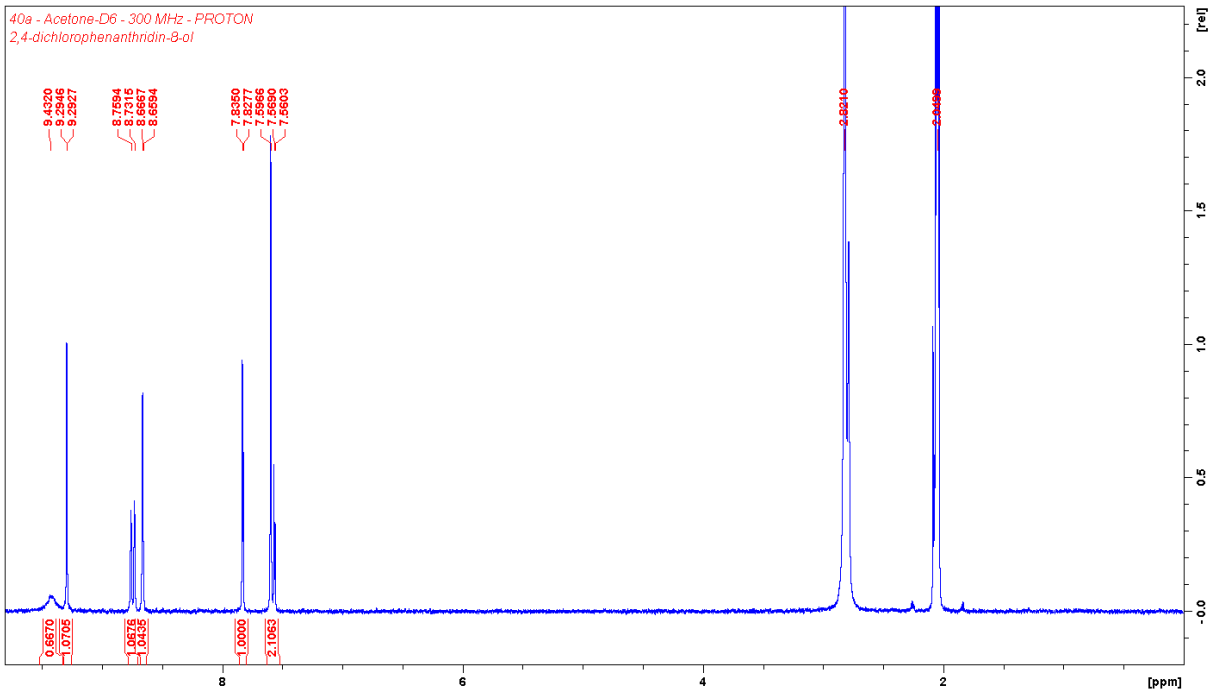
Spectrum 75. 200 MHz, APT NMR for 2,4-dichloro-5,6-dihydrophenanthridine (**39c**).



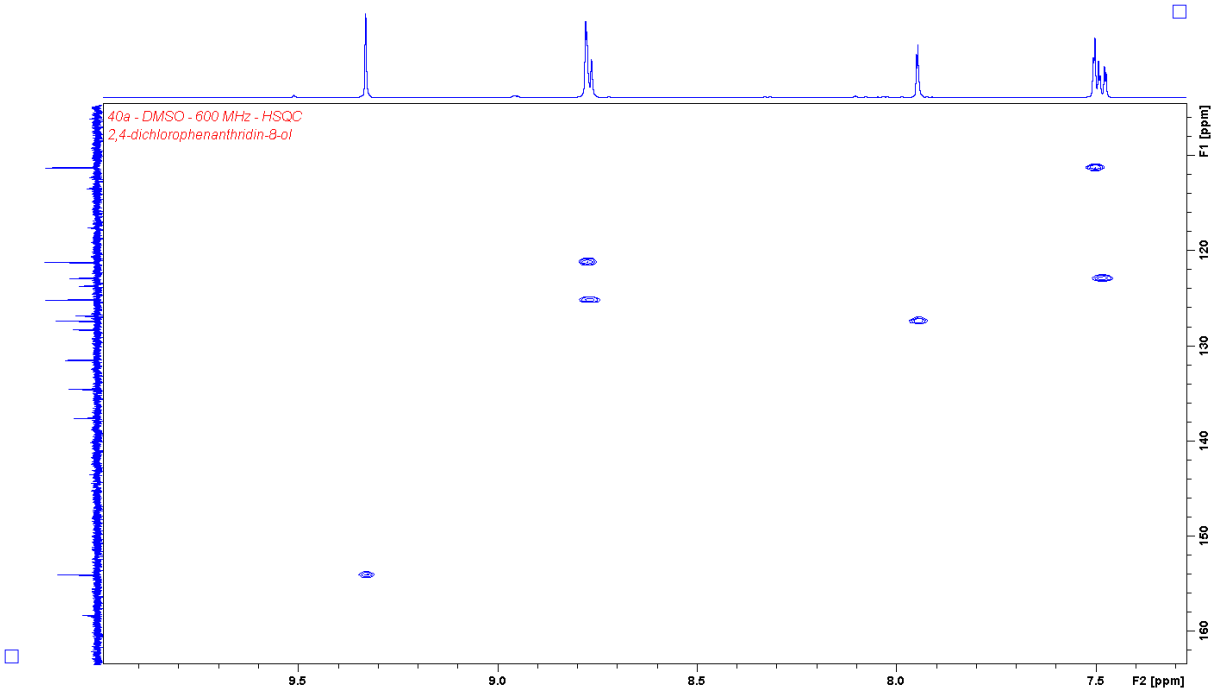
Spectrum 76. 200 MHz, HSQC NMR for 2,4-dichloro-5,6-dihydrophenanthridine (**39c**).



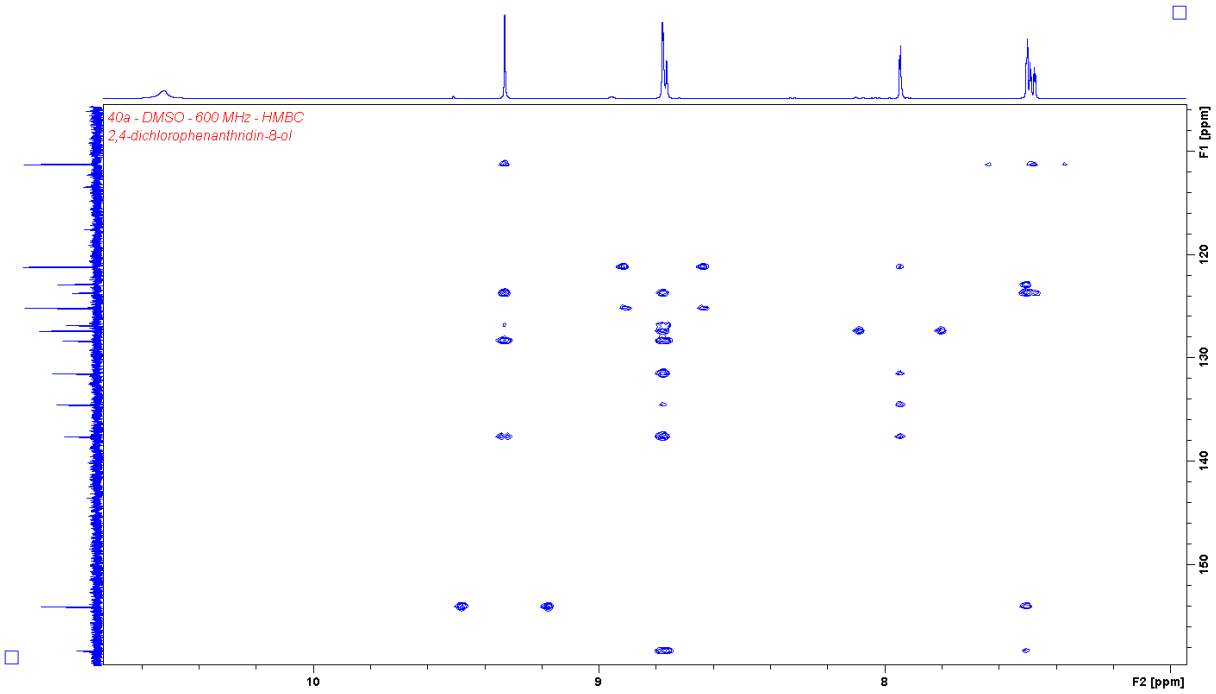
Spectrum 77. 200 MHz, HMBC NMR for 2,4-dichloro-5,6-dihydrophenanthridine (**39c**).



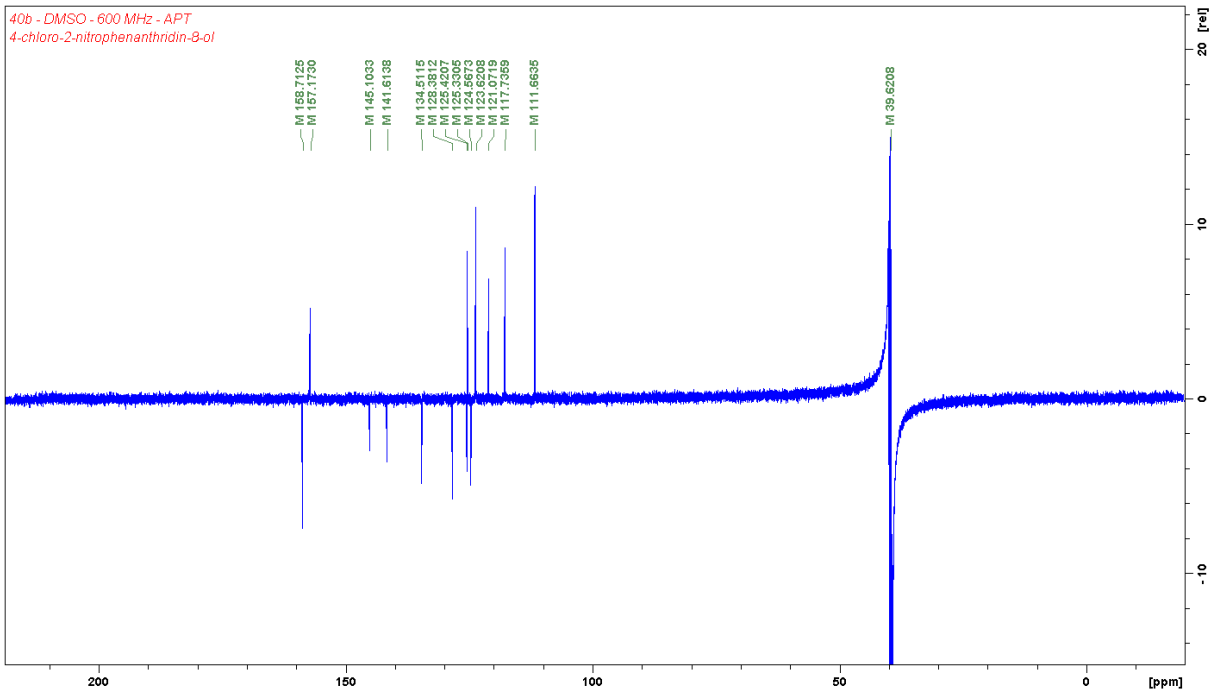
Spectrum 78. 300 MHz, Acetone-D6, ^{1}H NMR for 2,4-dichlorophenanthridin-8-ol (**40a**) pure compound.



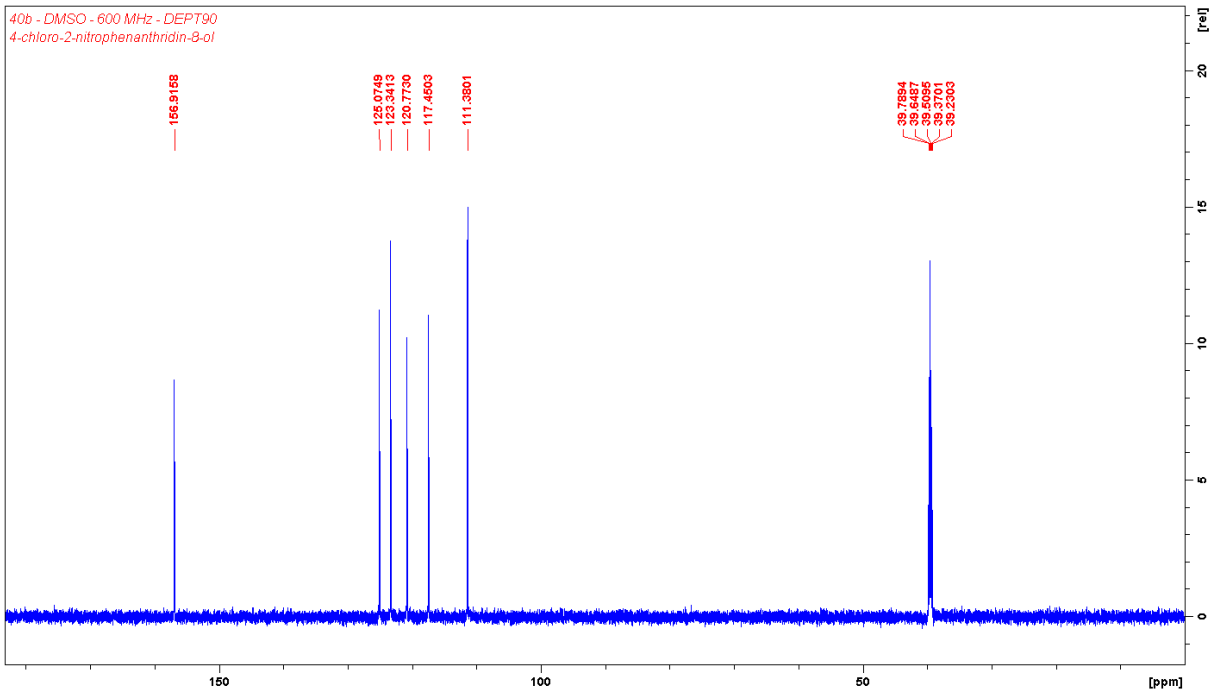
Spectrum 79. 150 MHz, DMSO, HSQC NMR for 2,4-dichlorophenanthridin-8-ol (**40a**).



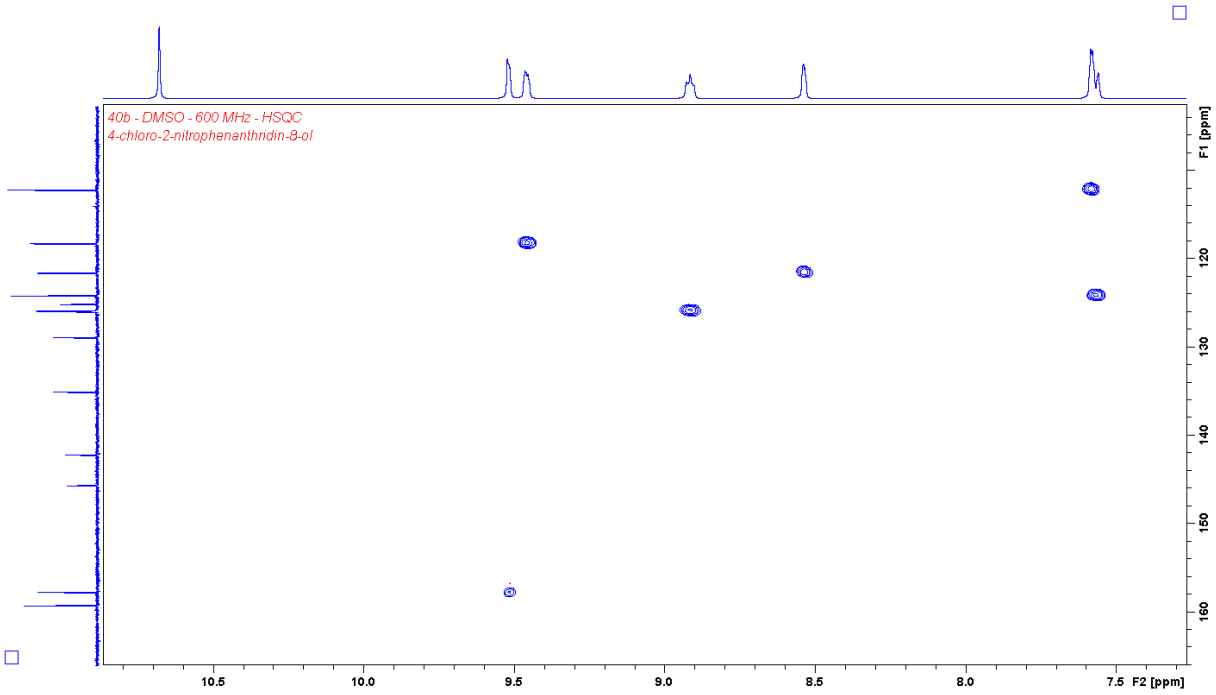
Spectrum 80. 150 MHz, DMSO, HSQC NMR for 2,4-dichlorophenanthridin-8-ol (**40a**).



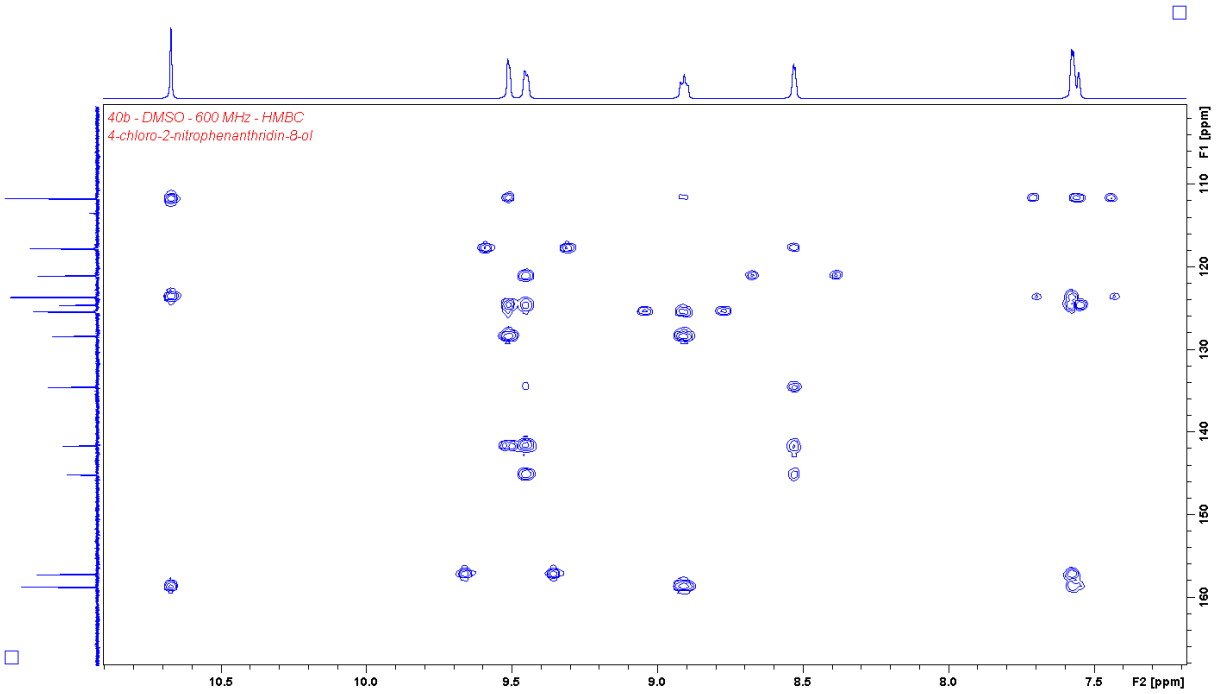
Spectrum 81. 150 MHz, DMSO, APT NMR for 4-chloro-2-nitrophenanthridin-8-ol (**40b**).



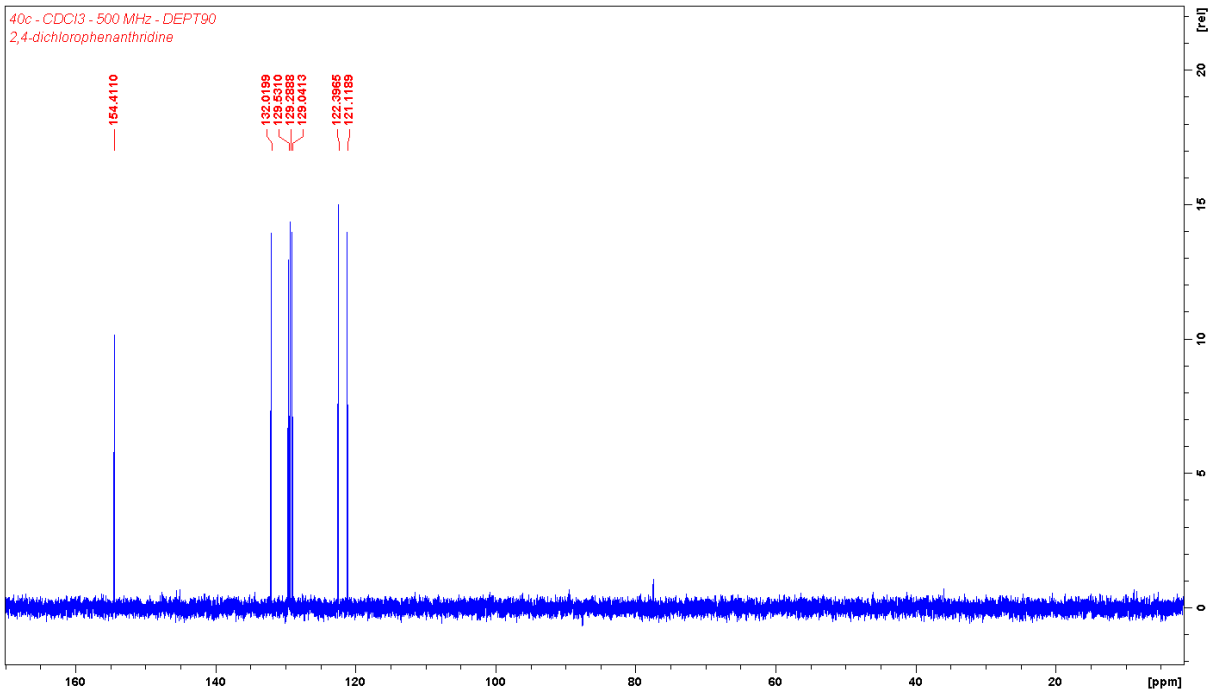
Spectrum 82. 150 MHz, DMSO, DEPT90 NMR for 4-chloro-2-nitrophenanthridin-8-ol (**40b**).



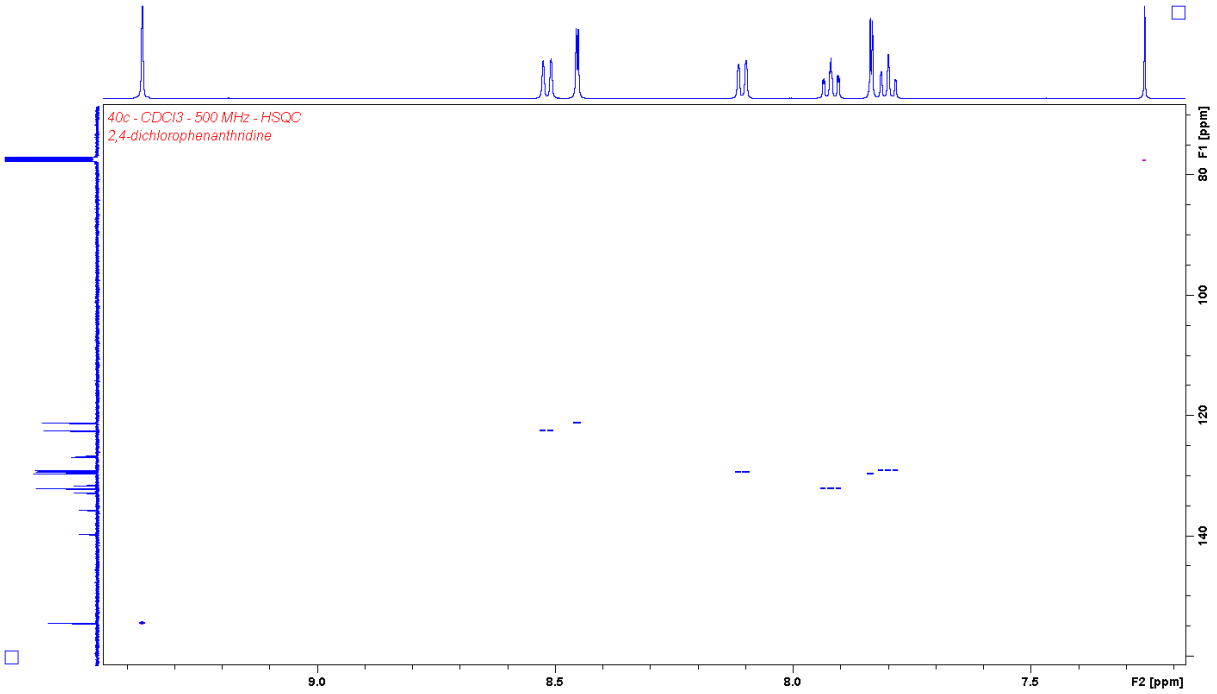
Spectrum 83. 150 MHz, DMSO, HSQC NMR for 4-chloro-2-nitrophenanthridin-8-ol (**40b**).



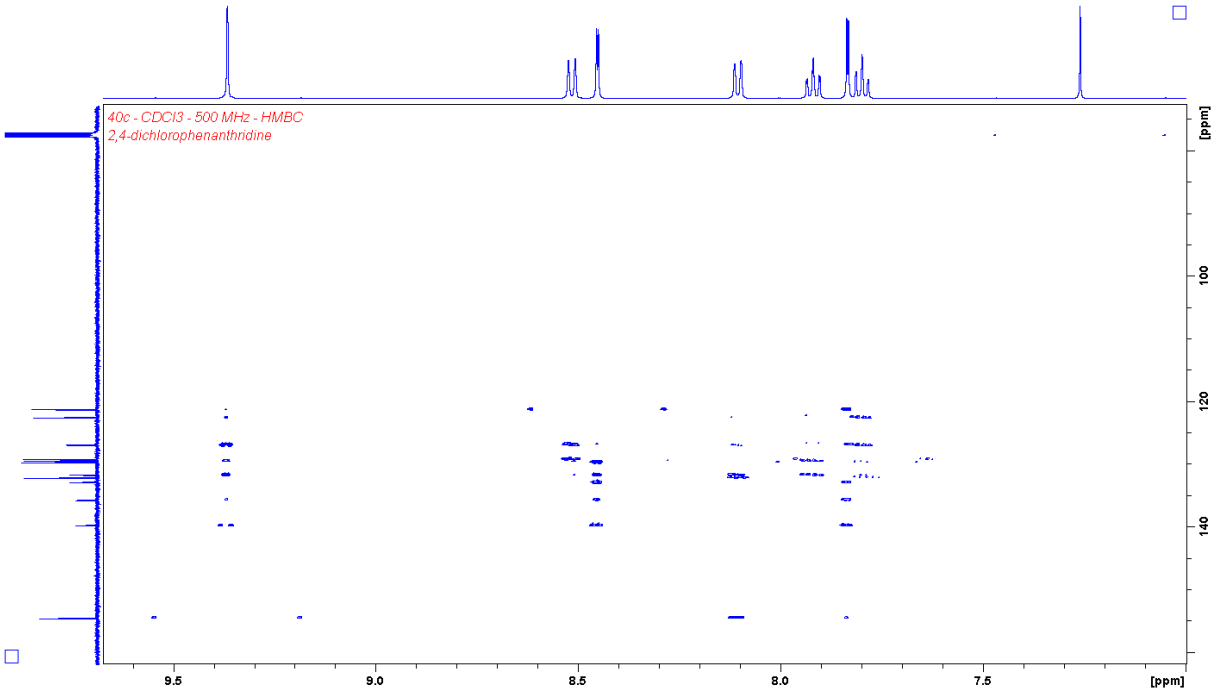
Spectrum 84. 150 MHz, DMSO, HMBC NMR for 4-chloro-2-nitrophenanthridin-8-ol (**40b**).



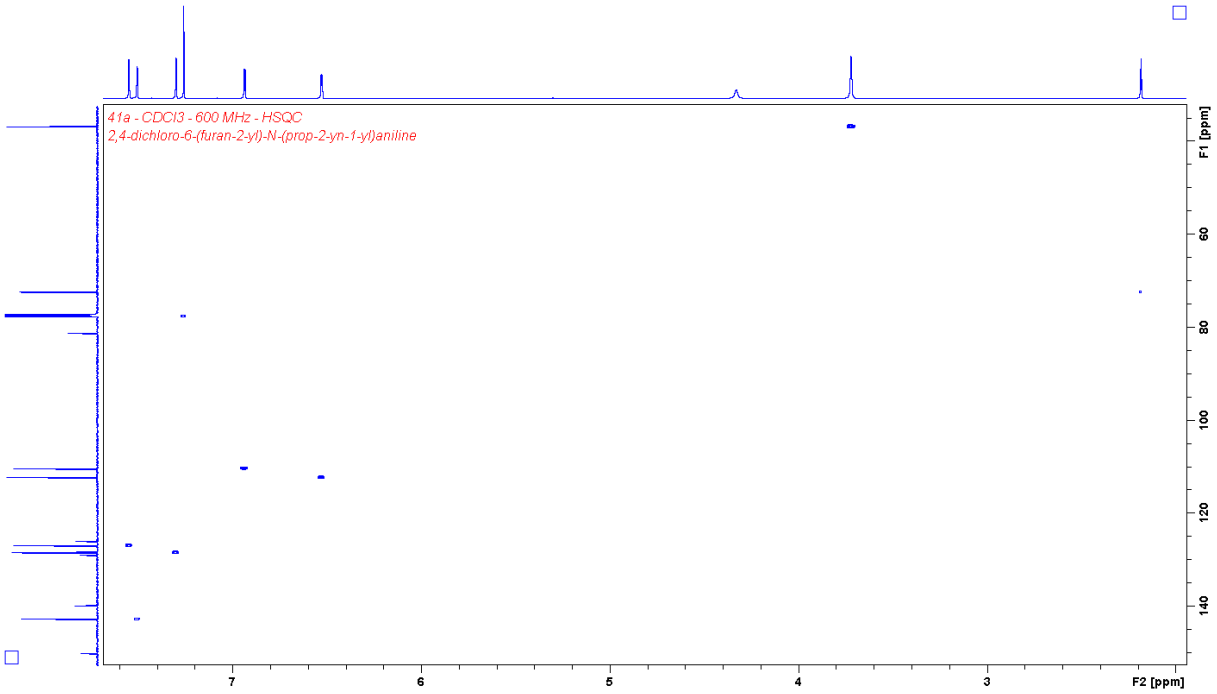
Spectrum 85. 125 MHz, DMSO, DEPT90 NMR for 2,4-dichlorophenanthridine (**40c**).



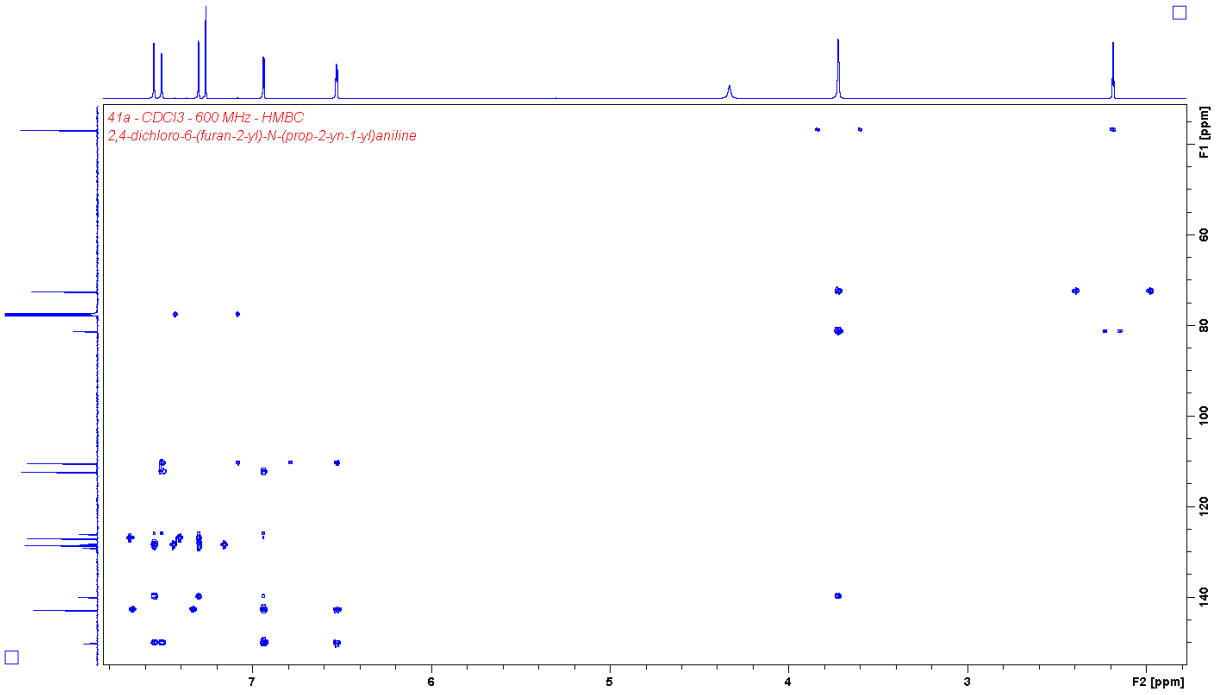
Spectrum 86. 125 MHz, DMSO, HSQC NMR for 2,4-dichlorophenanthridine (**40c**).



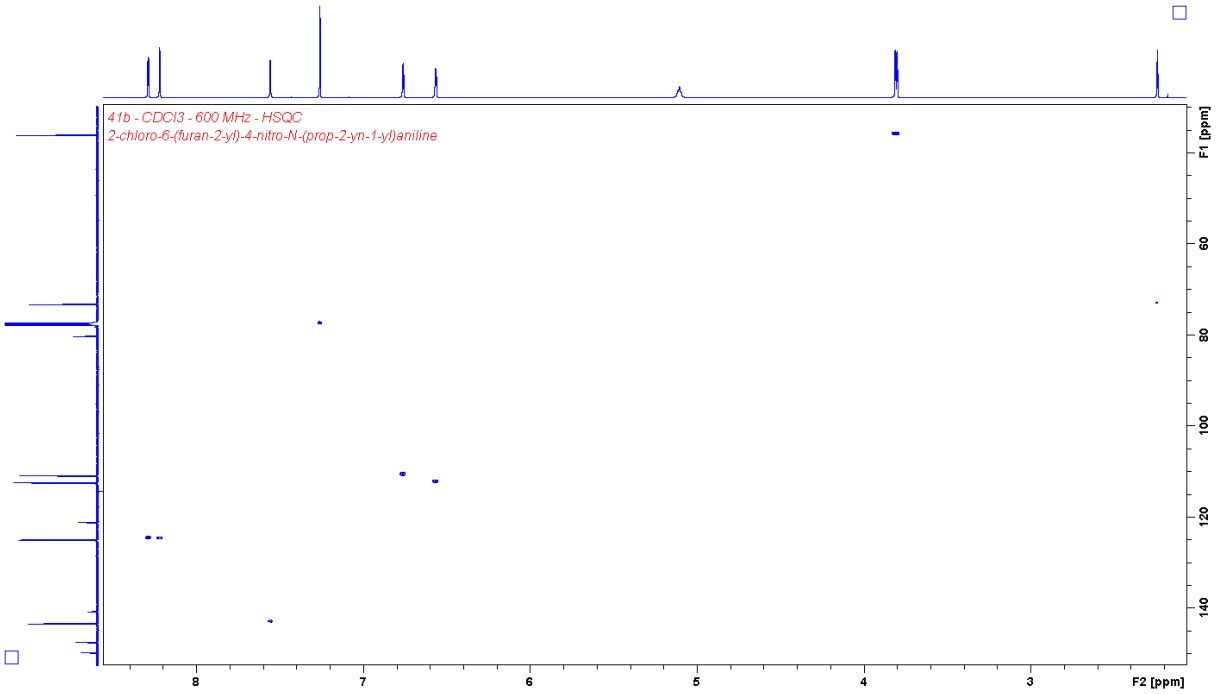
Spectrum 87. 125 MHz, DMSO, HMBC NMR for 2,4-dichlorophenanthridine (**40c**).



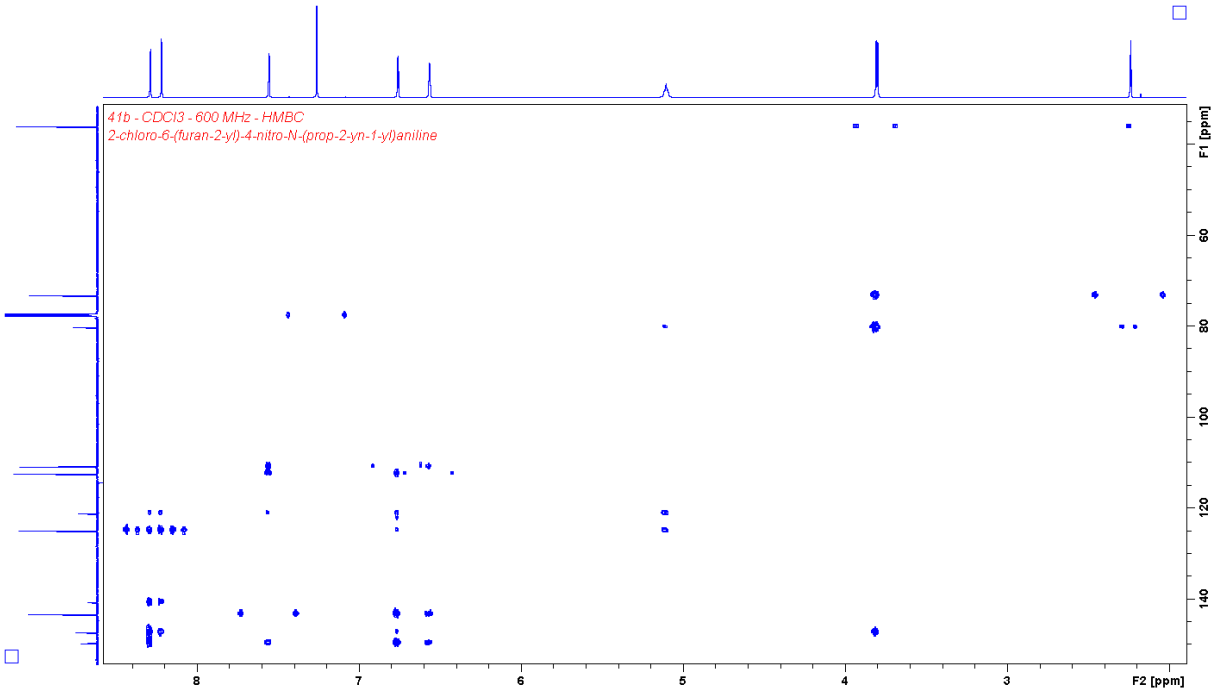
Spectrum 88. 150 MHz, $CDCl_3$, HSQC NMR for 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-yn-1-yl)aniline (**41a**).



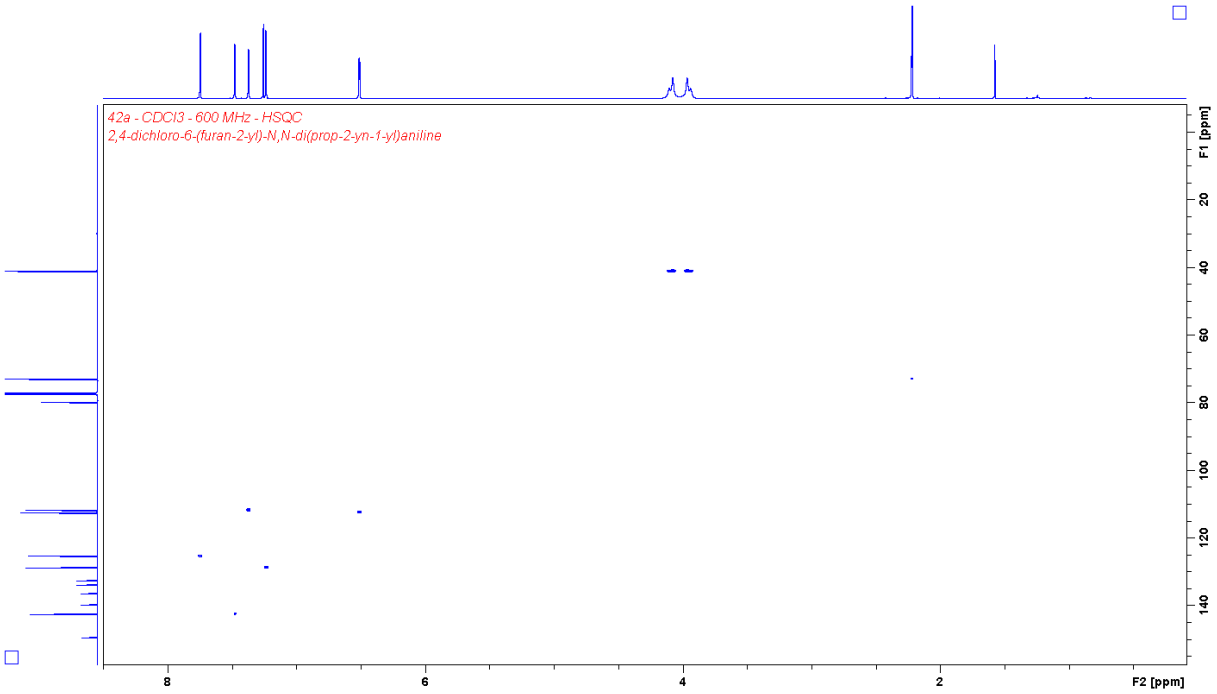
Spectrum 89. 150 MHz, $CDCl_3$, HMBC NMR for 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-yn-1-yl)aniline (**41a**).



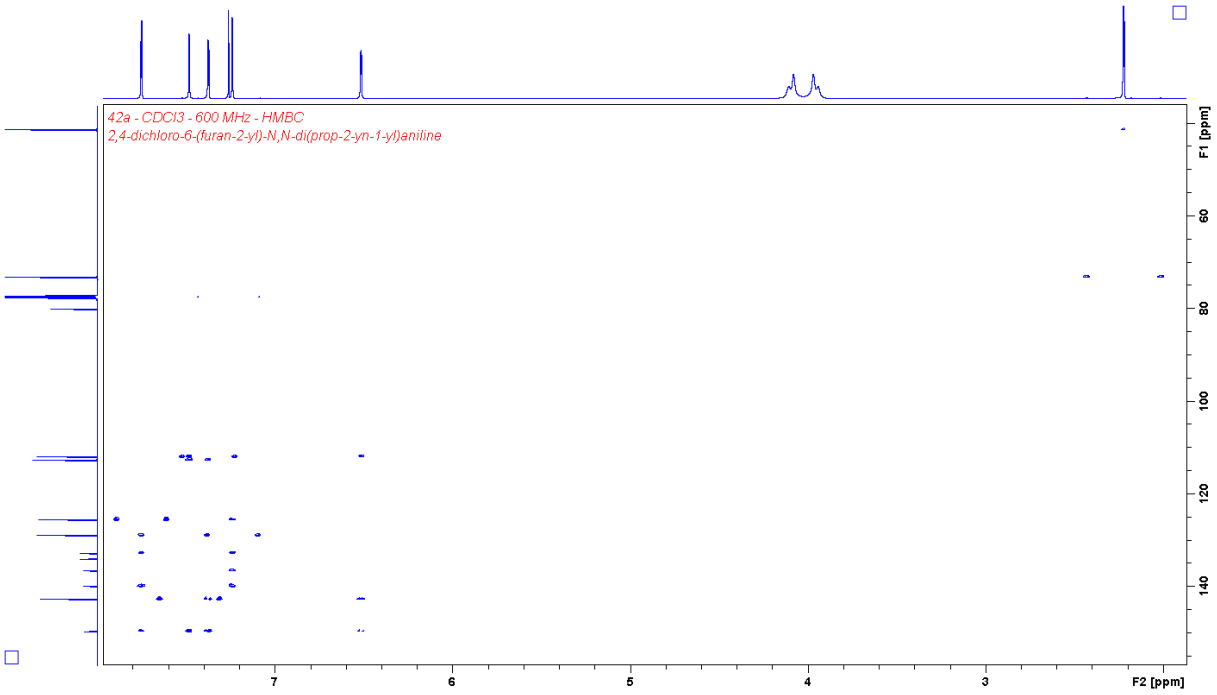
Spectrum 90. 150 MHz, $CDCl_3$, HSQC NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*-(prop-2-yn-1-yl)aniline (**41b**).



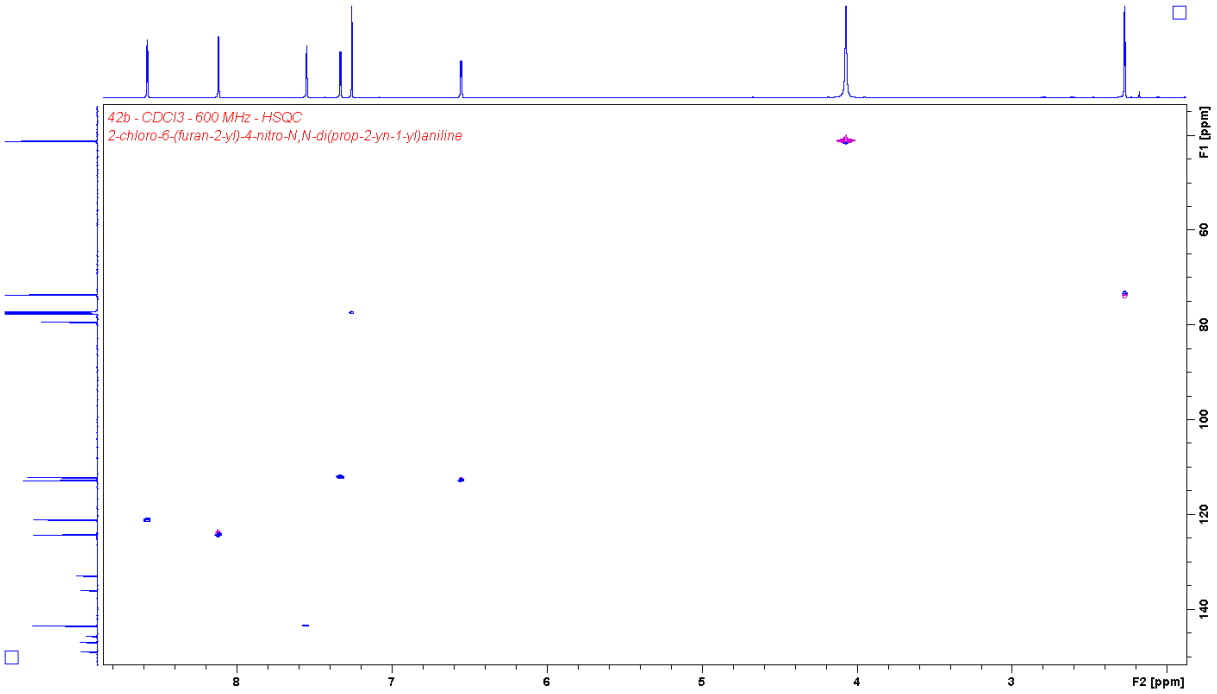
Spectrum 91. 150 MHz, $CDCl_3$, HMBC NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*-(prop-2-yn-1-yl)aniline (**41b**).



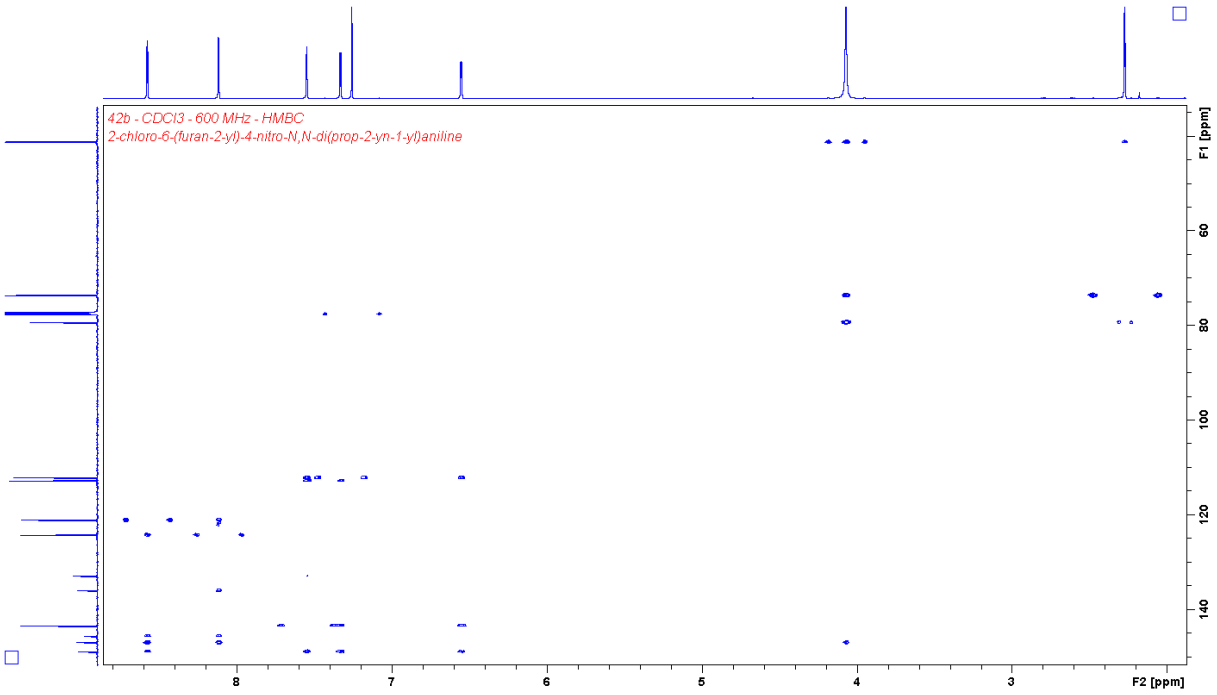
Spectrum 92. 150 MHz, $CDCl_3$, HSQC NMR for 2,4-dichloro-6-(furan-2-yl)-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42a**).



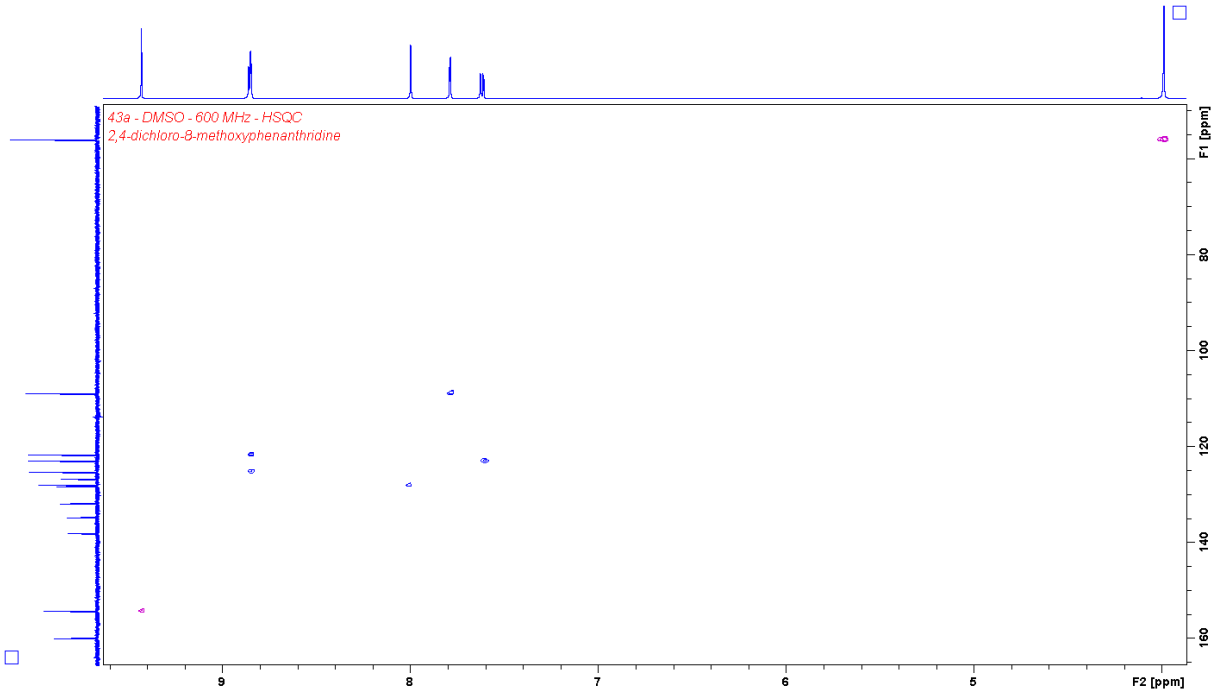
Spectrum 93. 150 MHz, $CDCl_3$, HMBC NMR for 2,4-dichloro-6-(furan-2-yl)-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42a**).



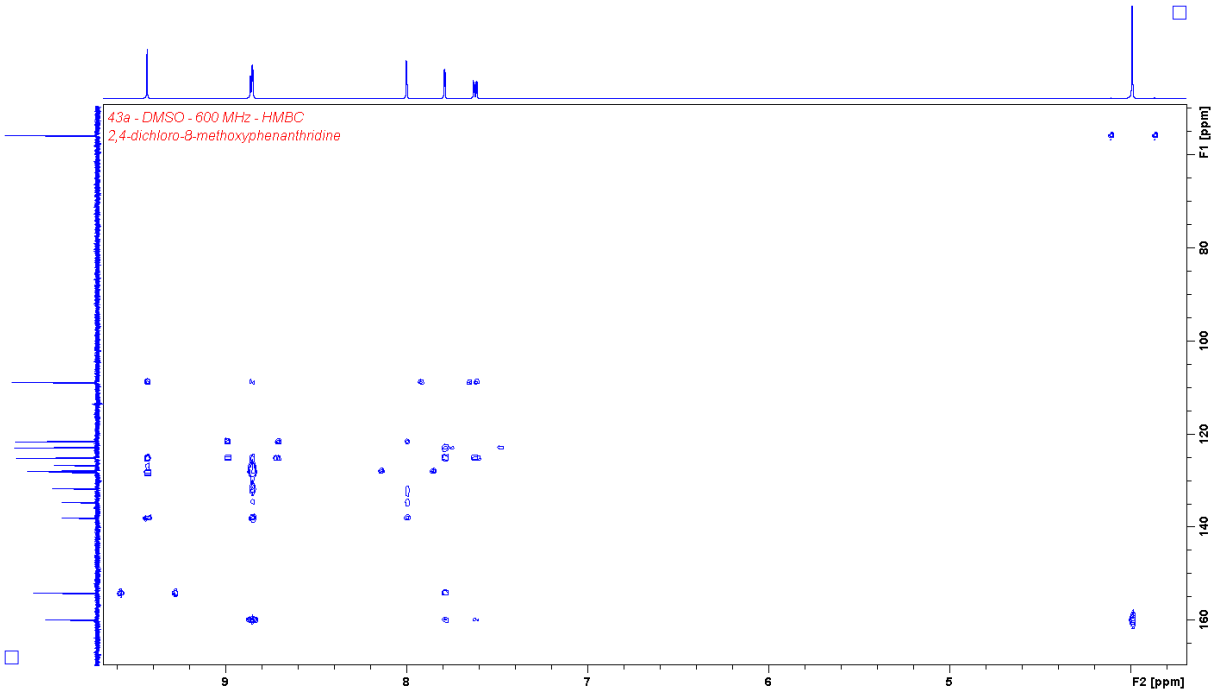
Spectrum 94. 150 MHz, $CDCl_3$, HSQC NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42b**).



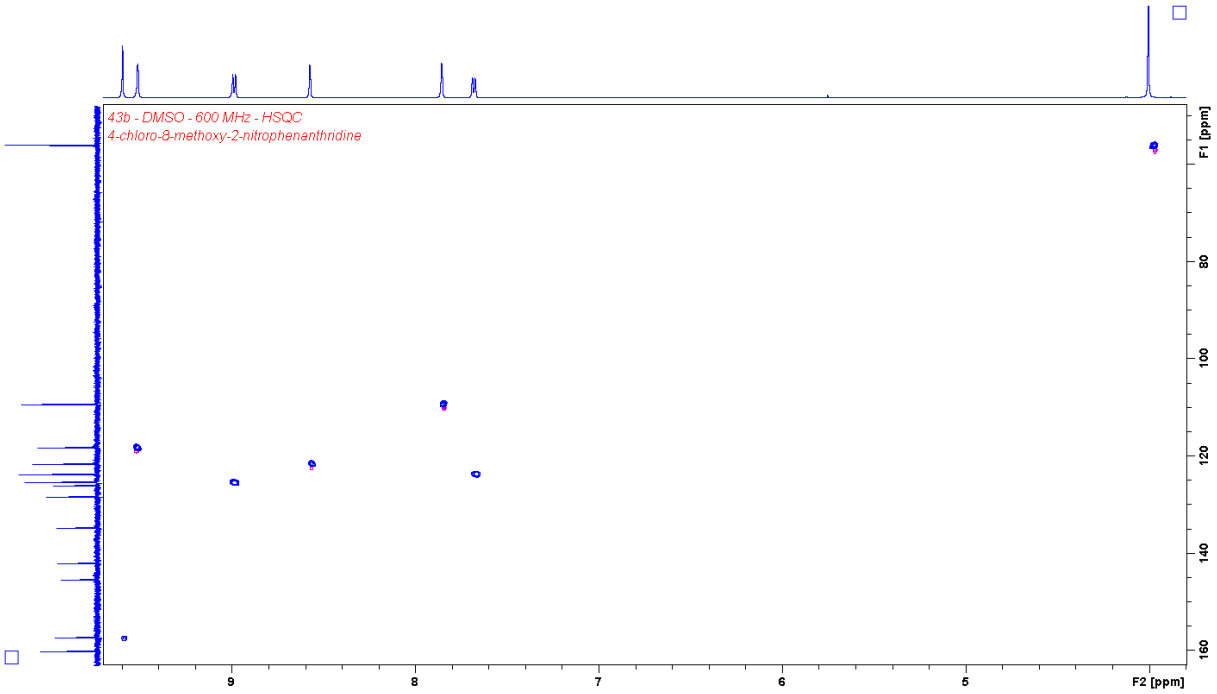
Spectrum 95. 150 MHz, $CDCl_3$, HMBC NMR for 2-chloro-6-(furan-2-yl)-4-nitro-*N*.*N*-di(prop-2-yn-1-yl)aniline (**42b**).



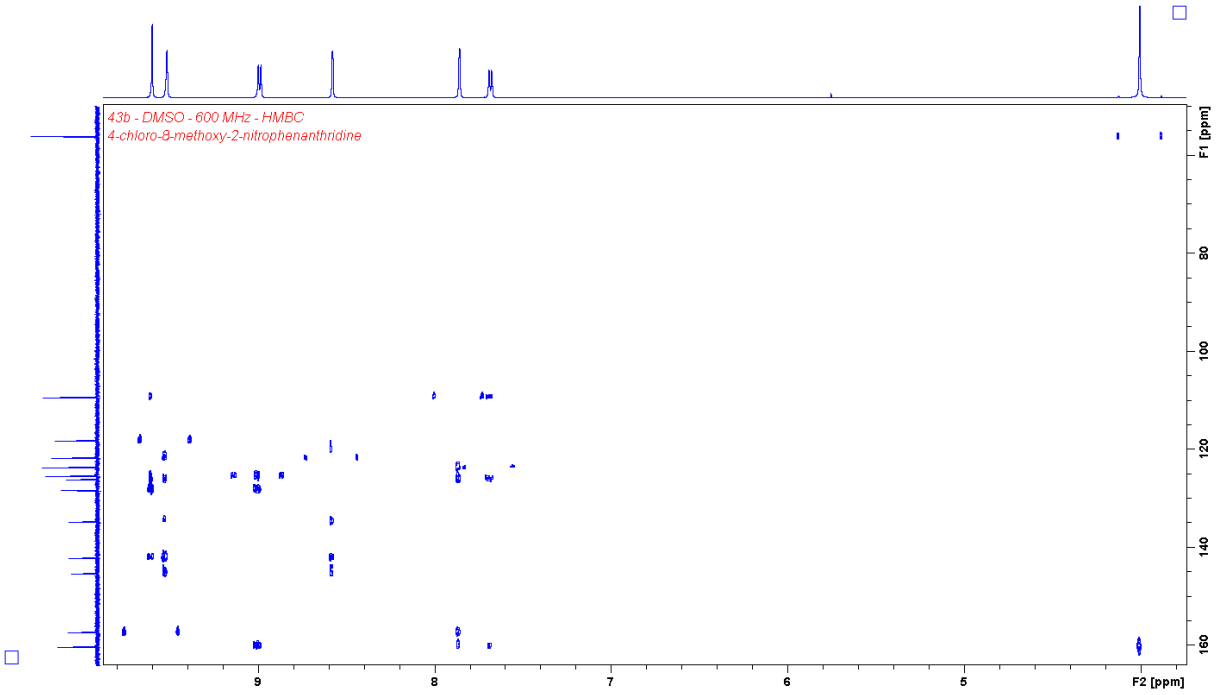
Spectrum 96. 150 MHz, DMSO, HSQC NMR for 2,4-dichloro-8-methoxyphenanthridine (**43a**).



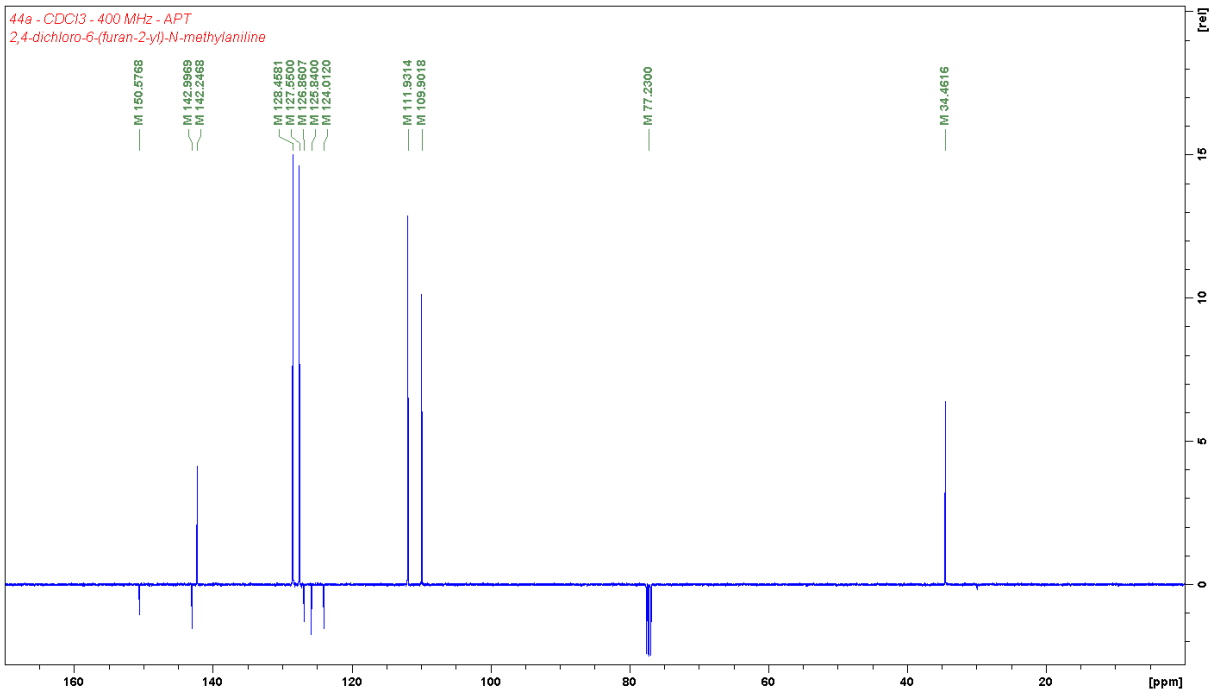
Spectrum 97. 150 MHz, DMSO, HMBC NMR for 2,4-dichloro-8-methoxyphenanthridine (**43a**).



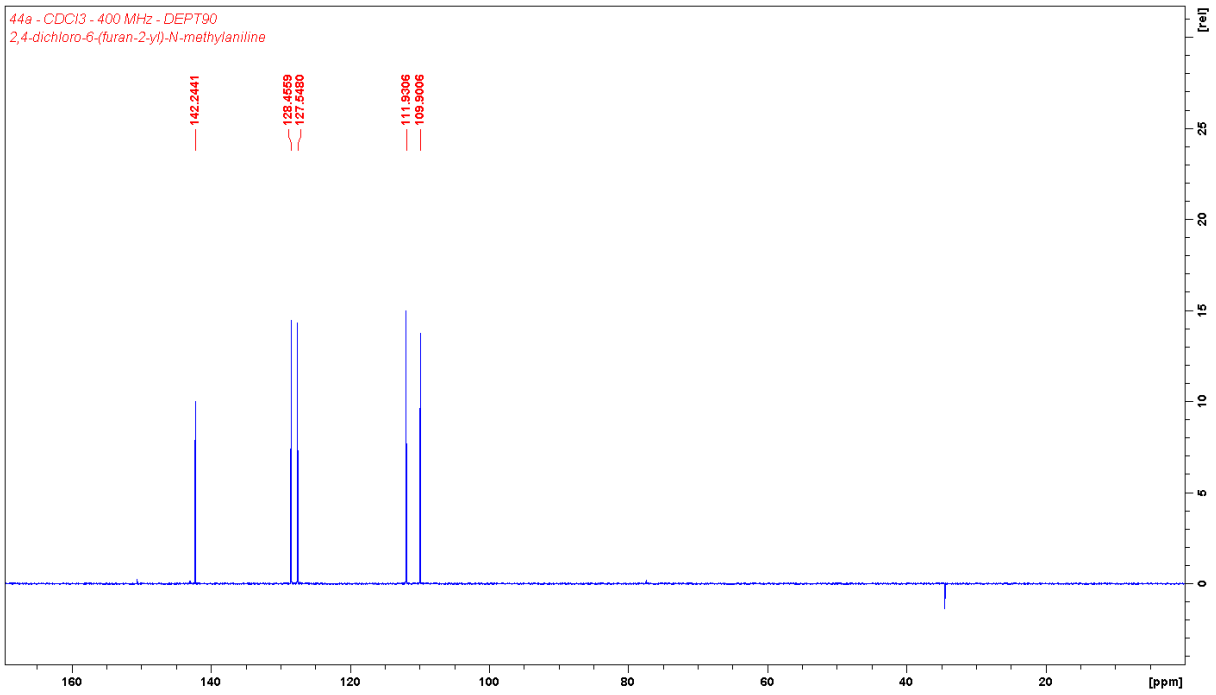
Spectrum 98. 150 MHz, DMSO, HSQC NMR for 4-chloro-8-methoxy-4-nitrophenanthridine (**43b**).



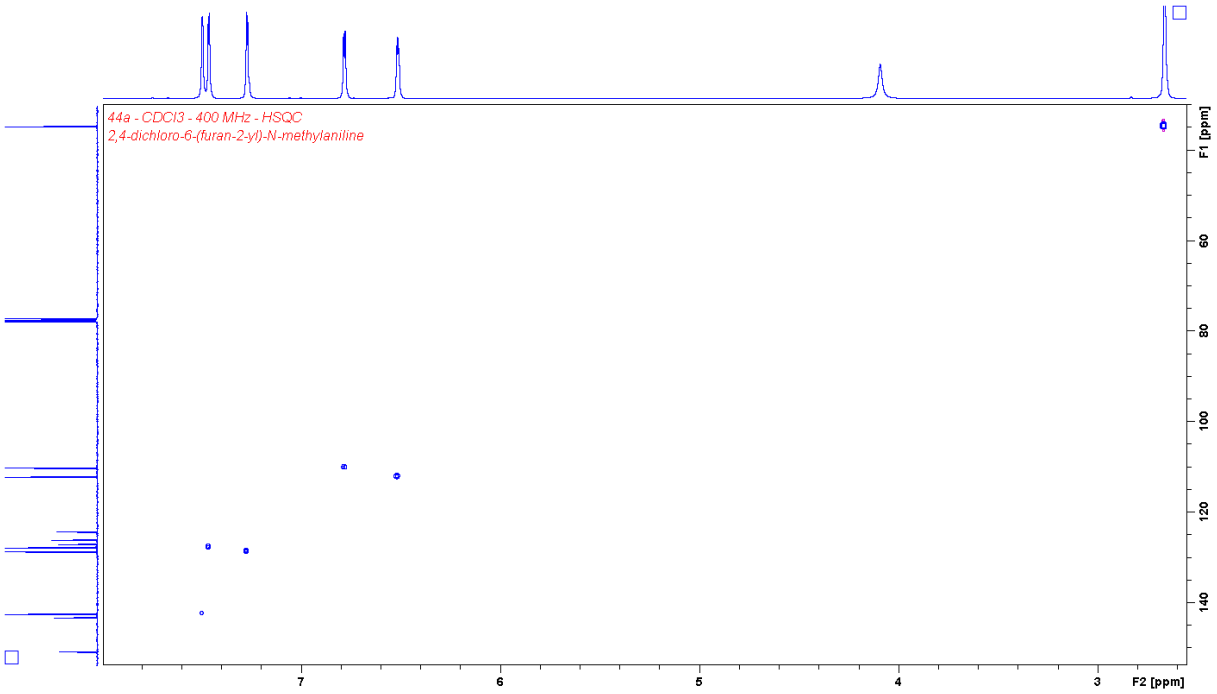
Spectrum 99. 150 MHz, DMSO, HMBC NMR for 4-chloro-8-methoxy-4-nitrophenanthridine (**43b**).



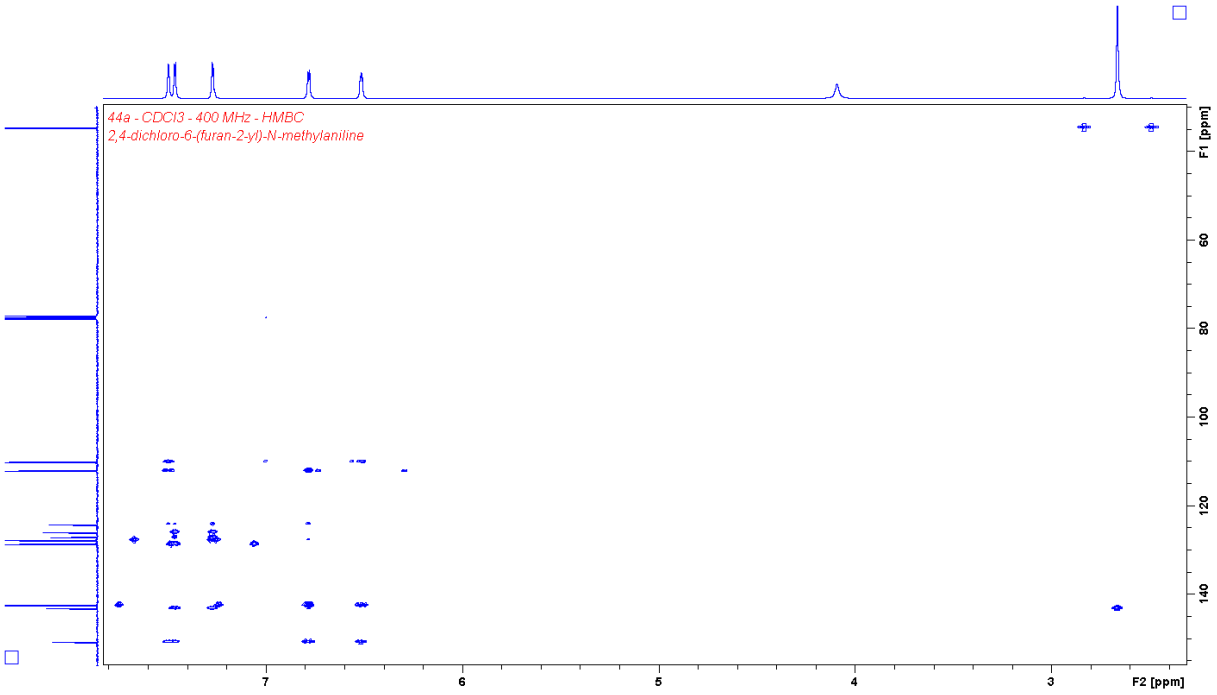
Spectrum 100. 100 MHz, APT NMR for 2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**44a**).



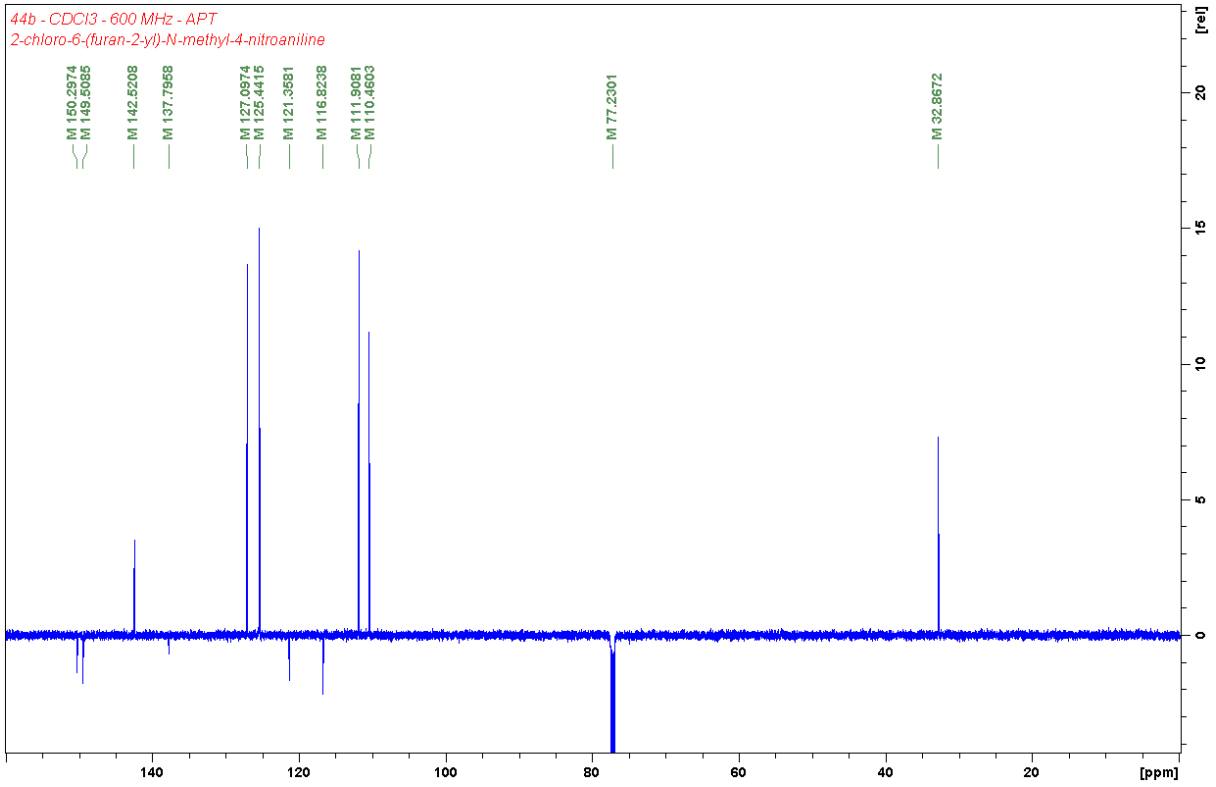
Spectrum 101. 100 MHz, DEPT NMR for 2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**44a**).



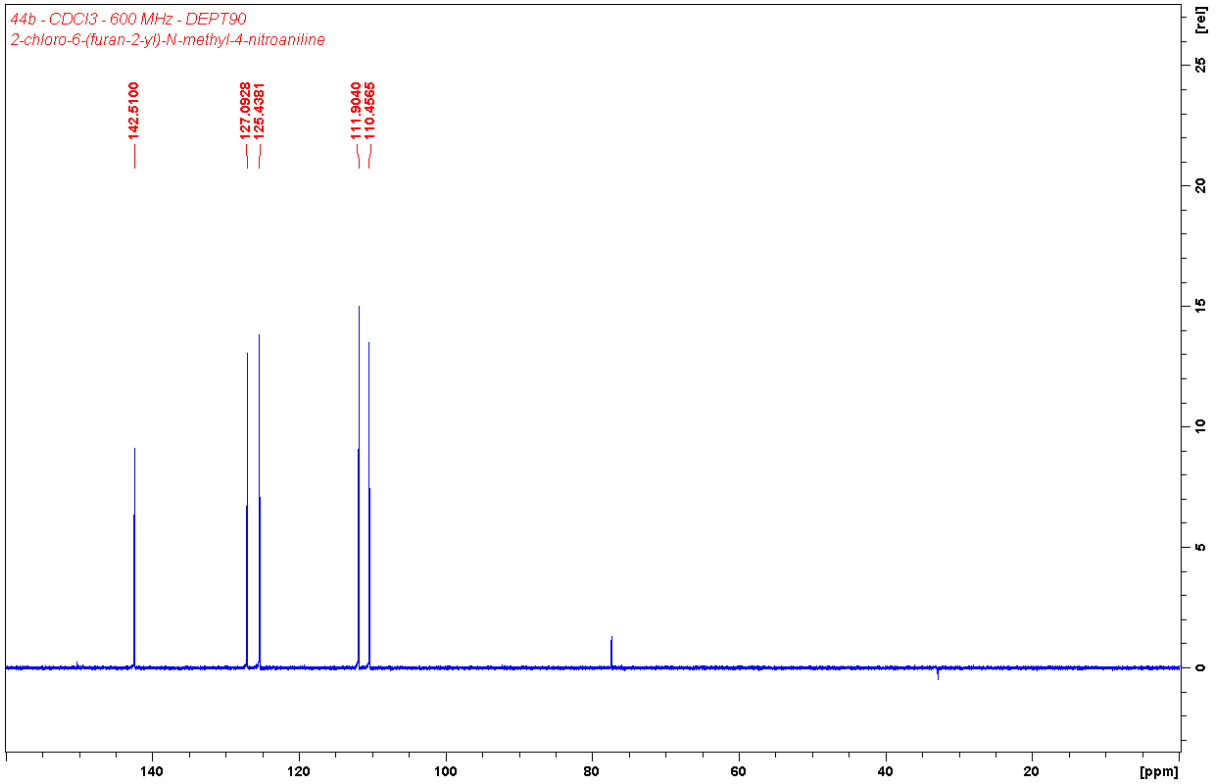
Spectrum 102. 100 MHz, HSQC NMR for 2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**44a**).



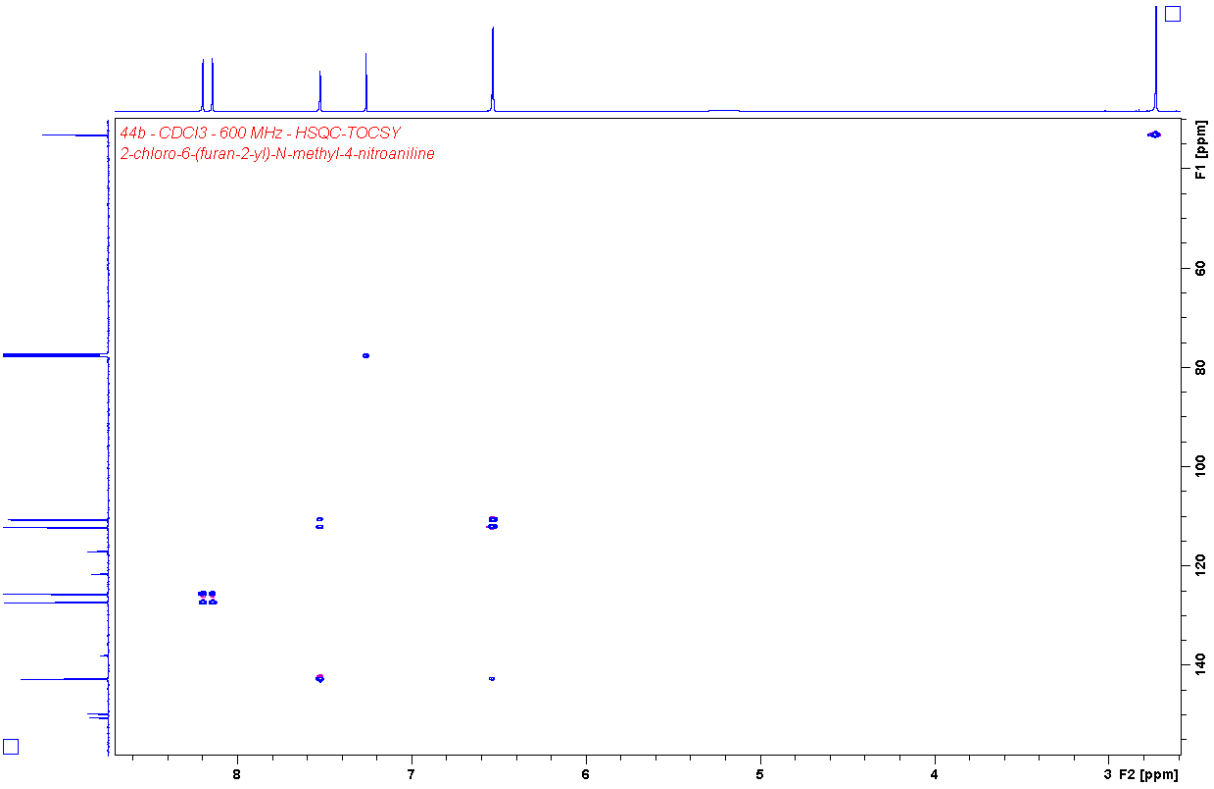
Spectrum 103. 100 MHz, HMBC NMR for 2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**44a**).



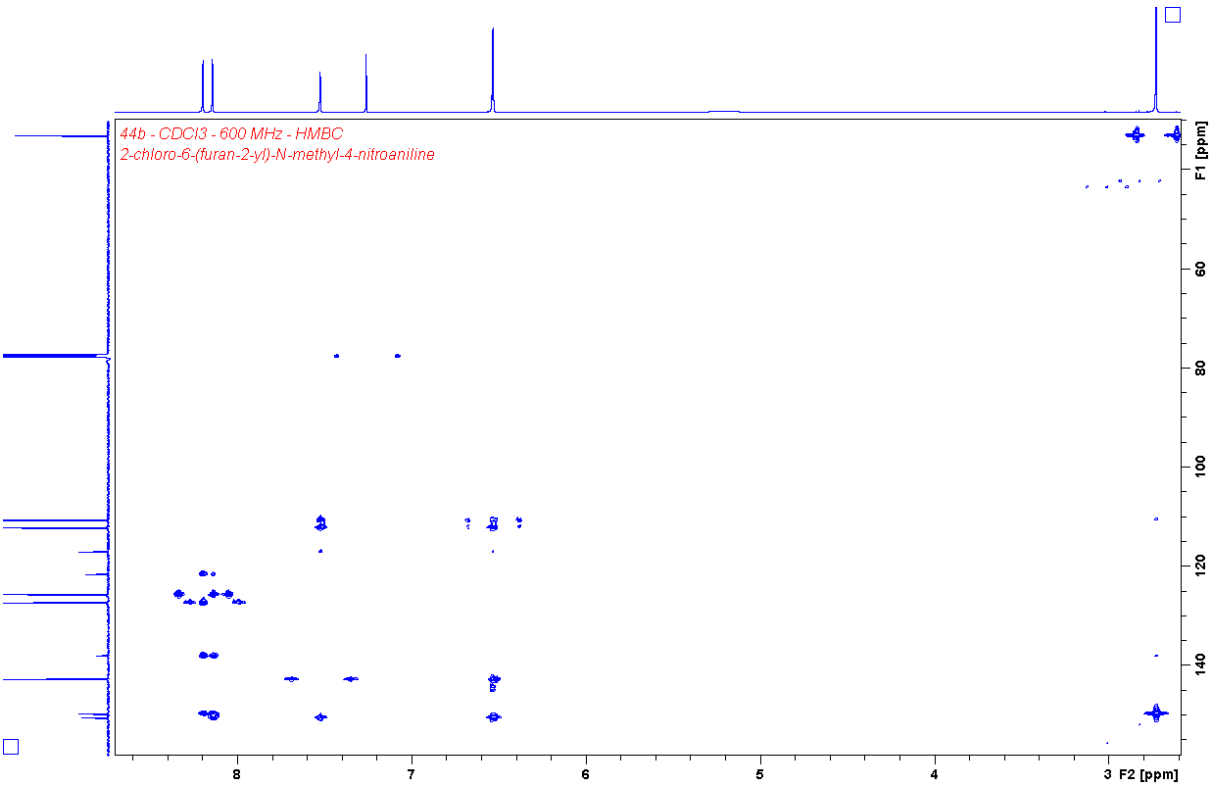
Spectrum 104. 150 MHz, APT NMR for 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline (**44b**).



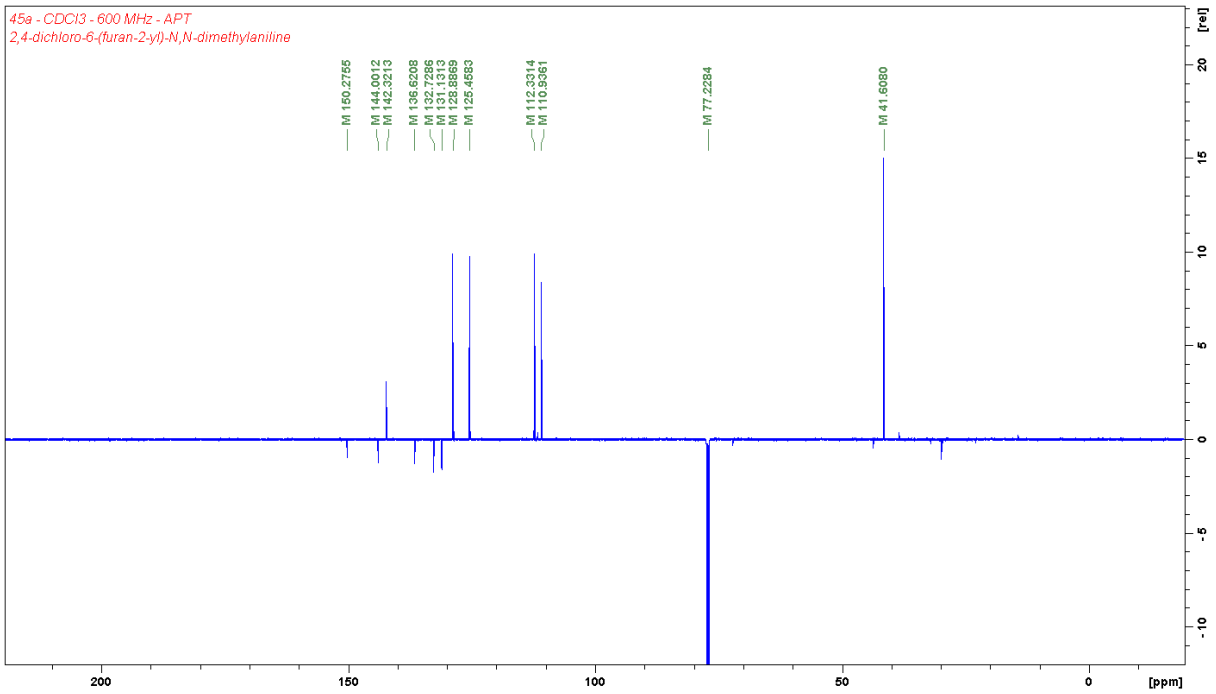
Spectrum 105. 150 MHz, DEPT90 NMR for 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline (**44b**).



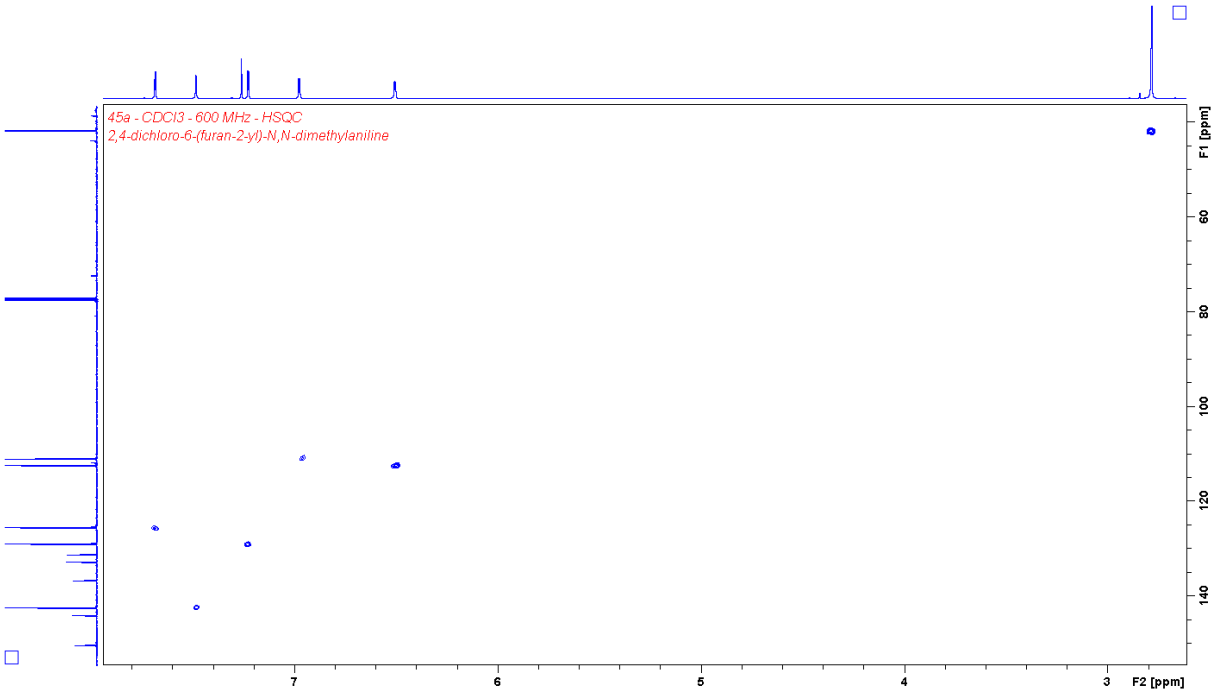
Spectrum 106. 150 MHz, HSQC-TOCSY NMR for 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline (**44b**).



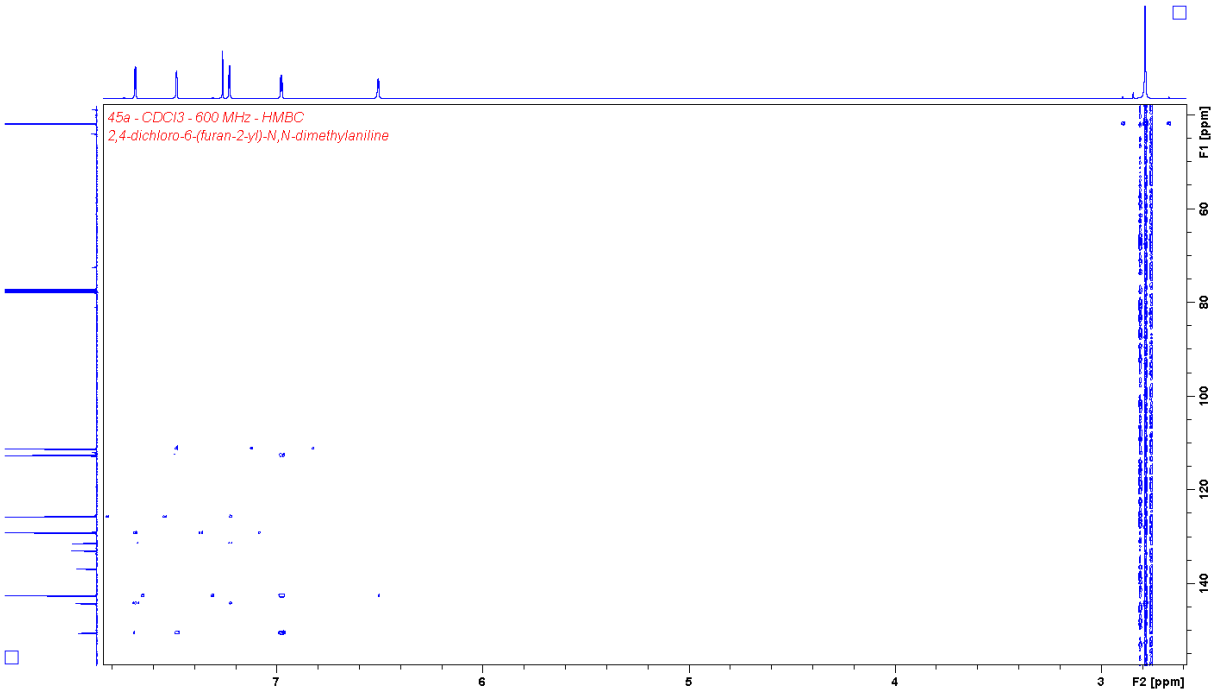
Spectrum 107. 150 MHz, HMBC NMR for 2-chloro-6-(furan-2-yl)-*N*-methyl-4-nitroaniline (**44b**).



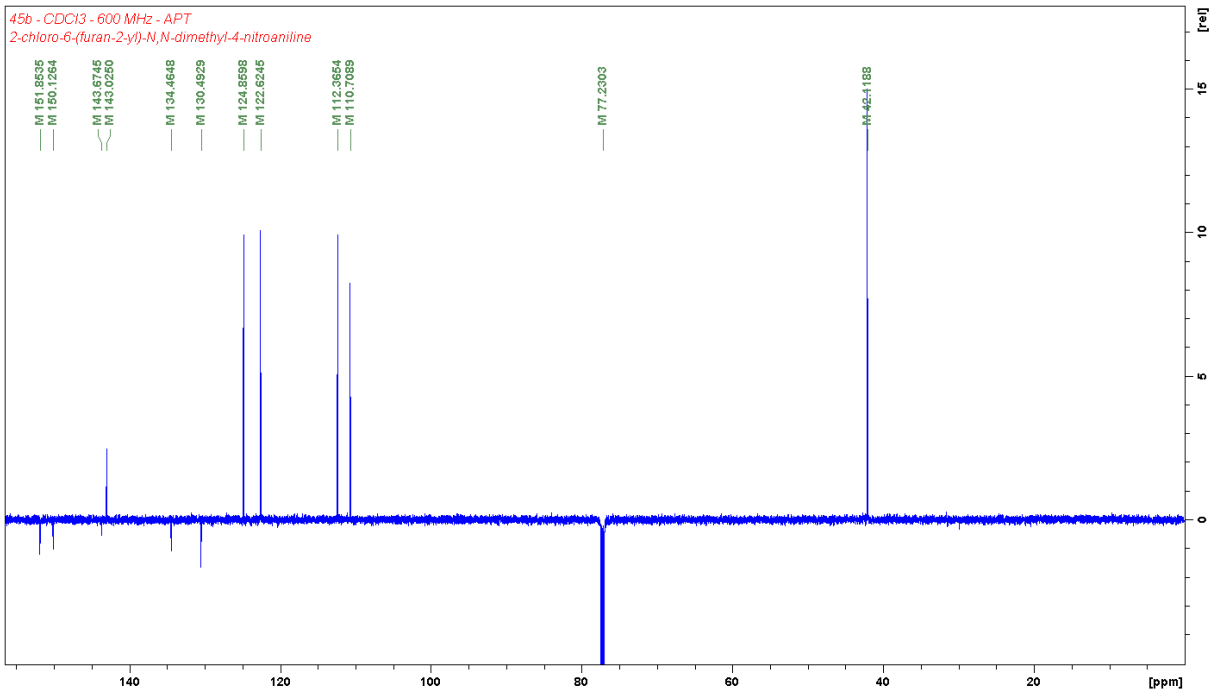
Spectrum 108. 150 MHz, APT NMR for 2,4-dichloro-6-(furan-2-yl)-*N.N*-dimethylaniline (**45a**).



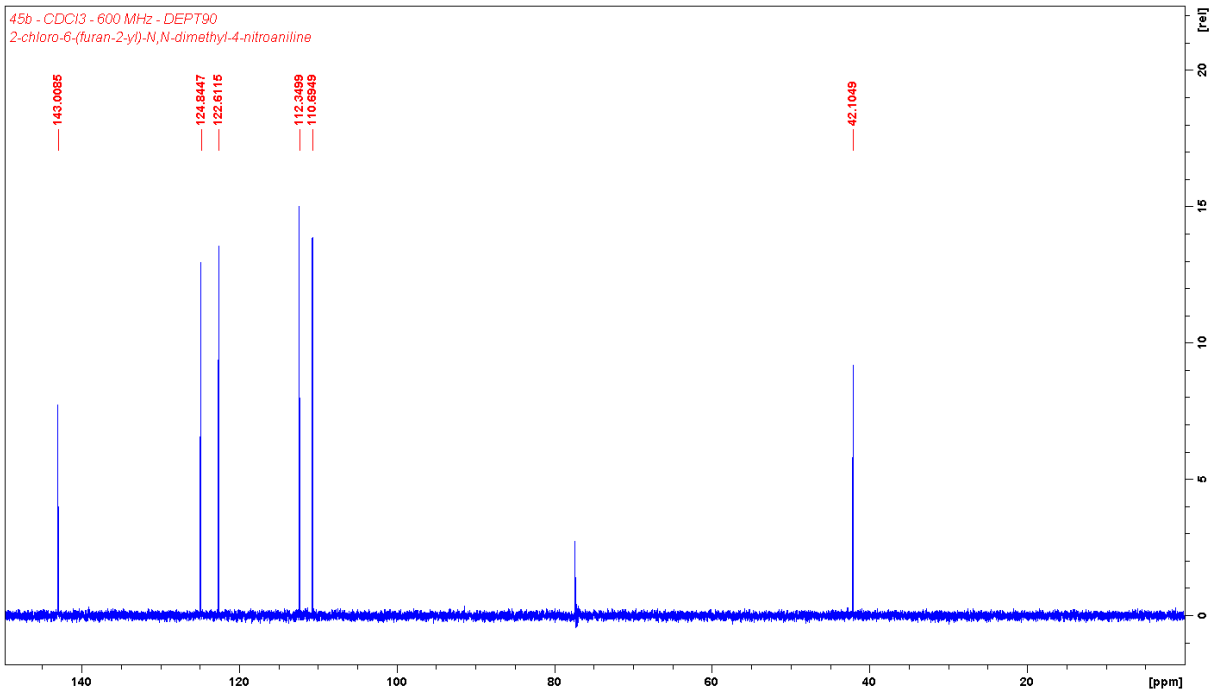
Spectrum 109. 150 MHz, HSQC NMR for 2,4-dichloro-6-(furan-2-yl)-*N.N*-dimethylaniline (**45a**).



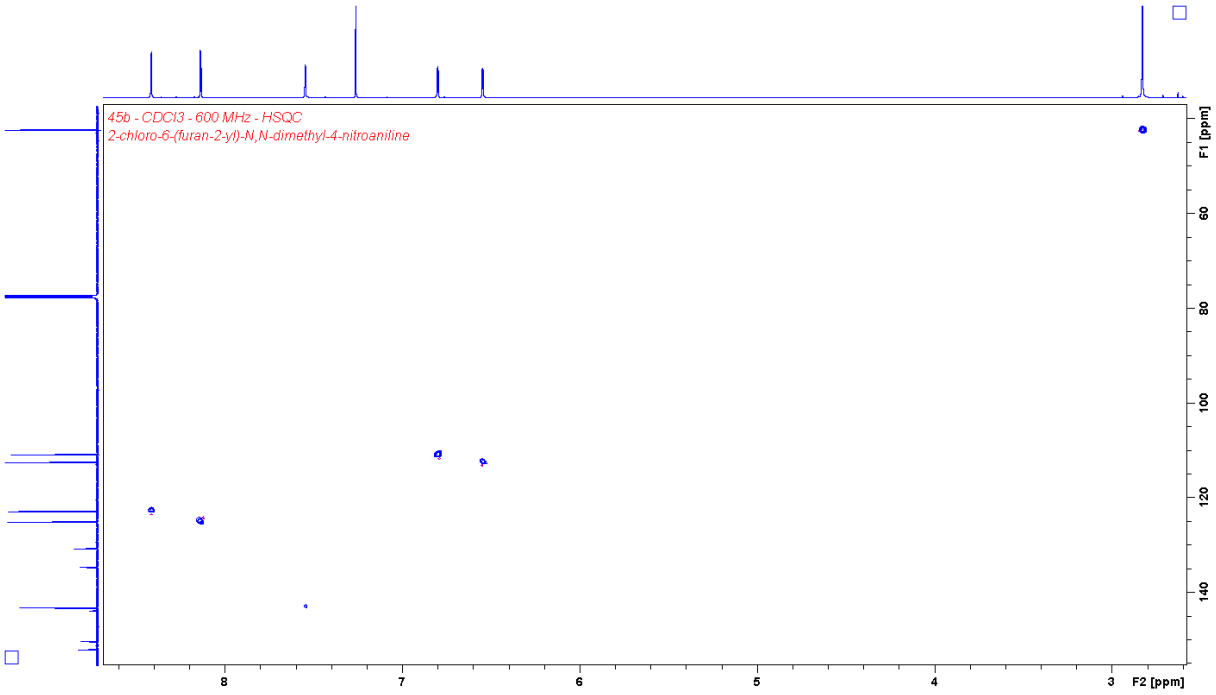
Spectrum 110. 150 MHz, HMBC NMR for 2,4-dichloro-6-(furan-2-yl)-*N.N*-dimethylaniline (**45a**).



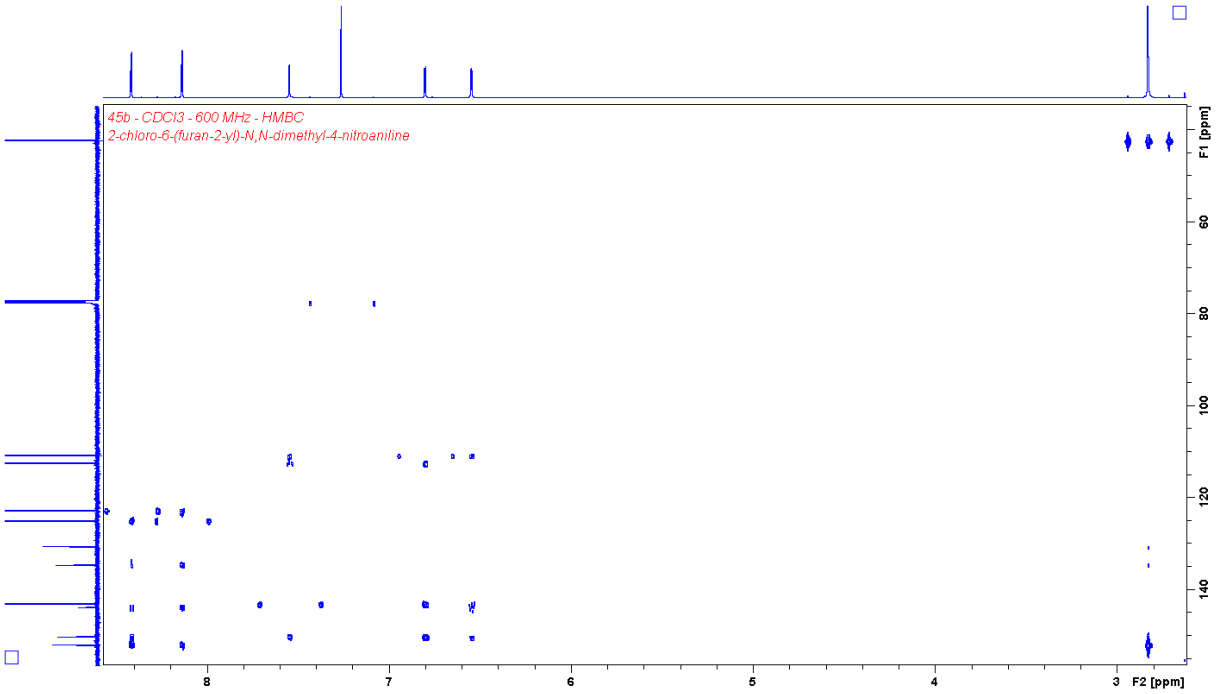
Spectrum 111. 150 MHz, APT NMR for 2-chloro-6-(furan-2-yl)-*N.N*-dimethyl-4-nitroaniline (**45b**).



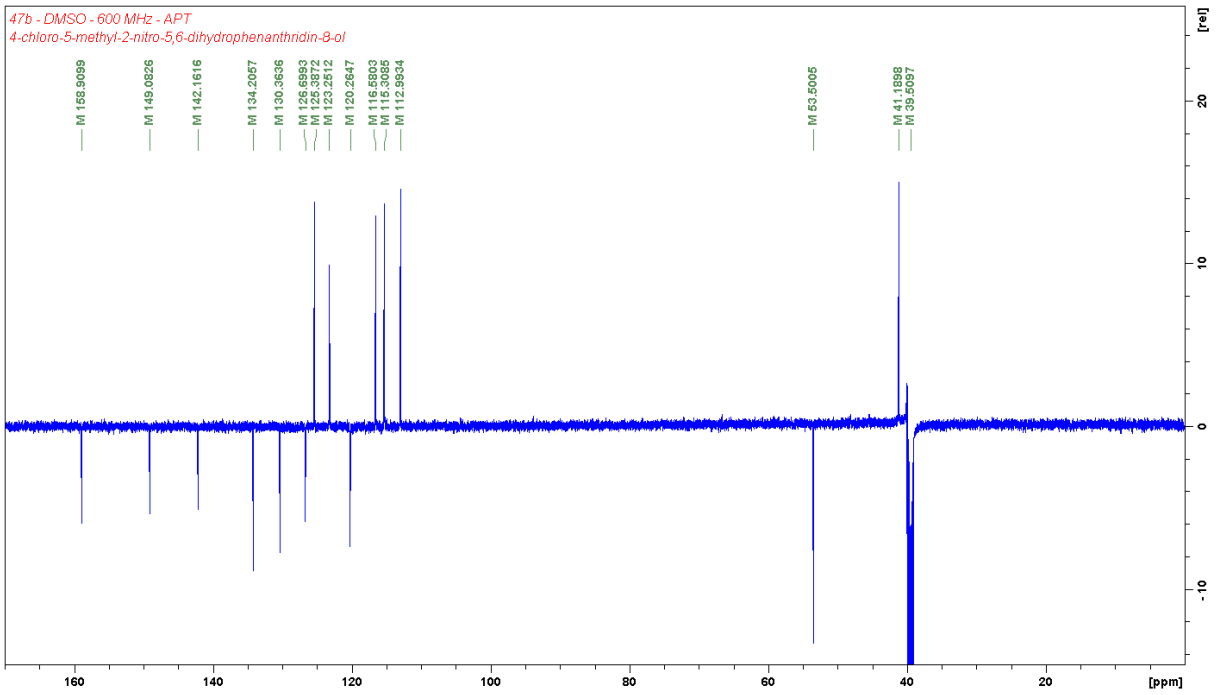
Spectrum 112. 150 MHz, DEPT90 NMR for 2-chloro-6-(furan-2-yl)-*N*.*N*-dimethyl-4-nitroaniline (**45b**).



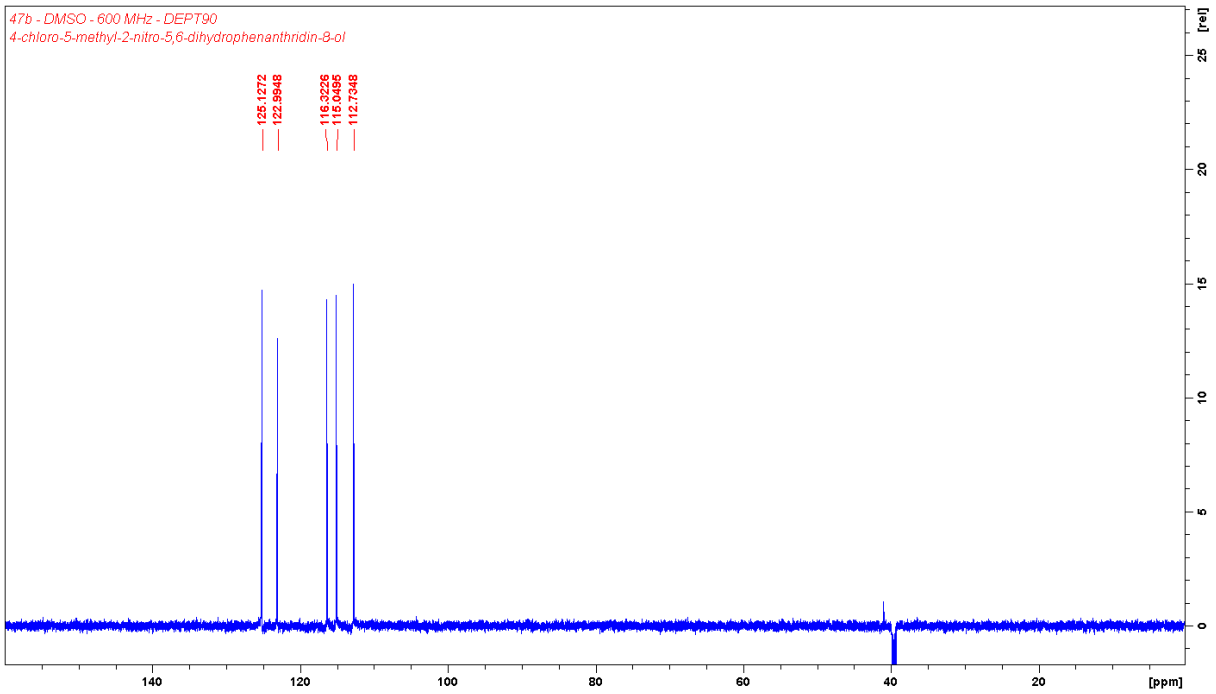
Spectrum 113. 150 MHz, HSQC NMR for 2-chloro-6-(furan-2-yl)-*N*.*N*-dimethyl-4-nitroaniline (**45b**).



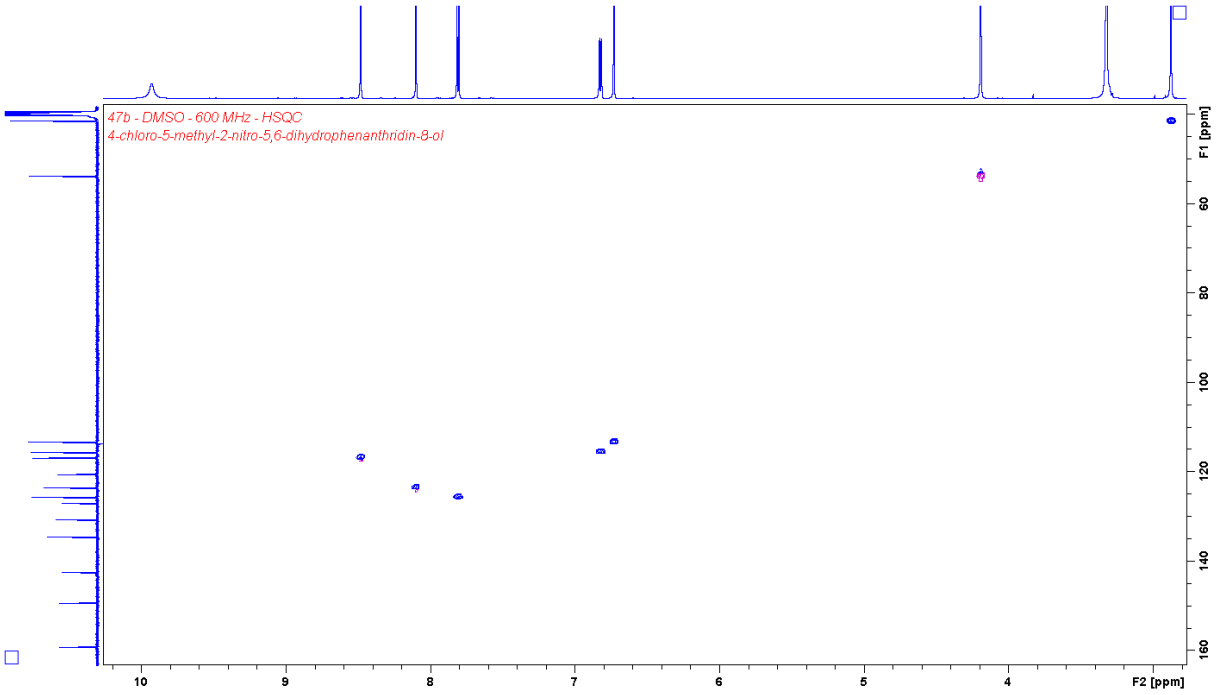
Spectrum 114. 150 MHz, HMBC NMR for 2-chloro-6-(furan-2-yl)-*N.N*-dimethyl-4-nitroaniline (**45b**).



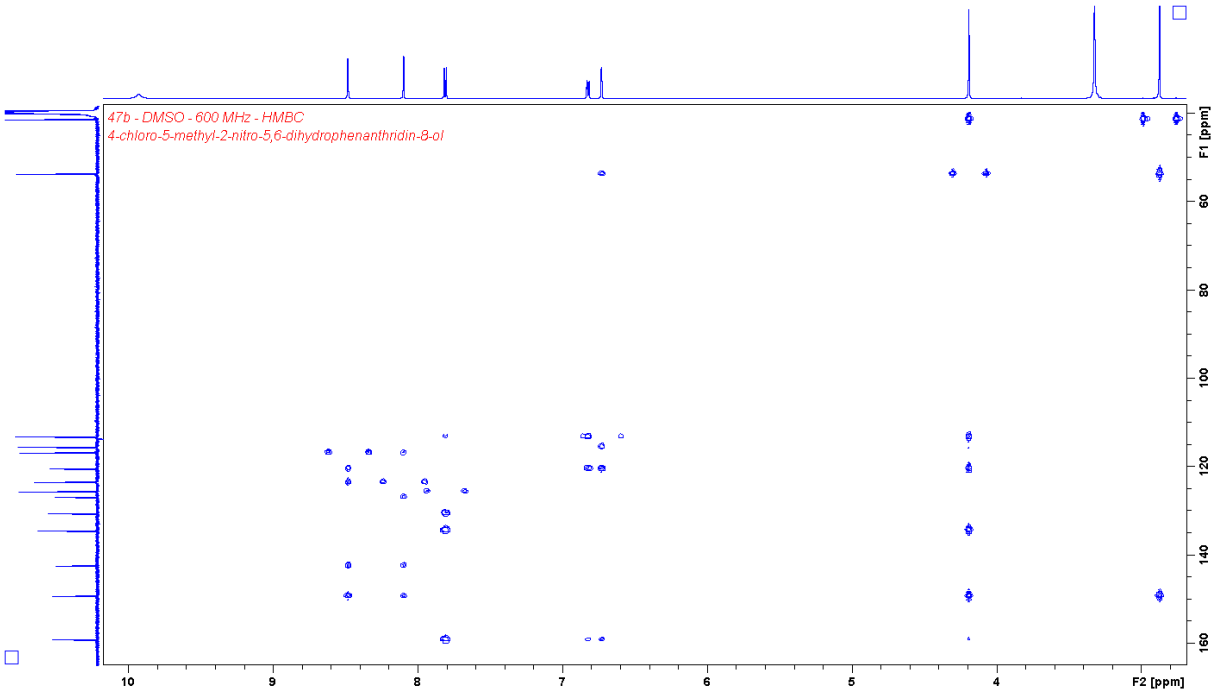
Spectrum 115. 150 MHz, APT NMR for 4-chloro-5-methyl-2-nitro-5,6-dihydrophenanthridin-8-ol (**47b**).



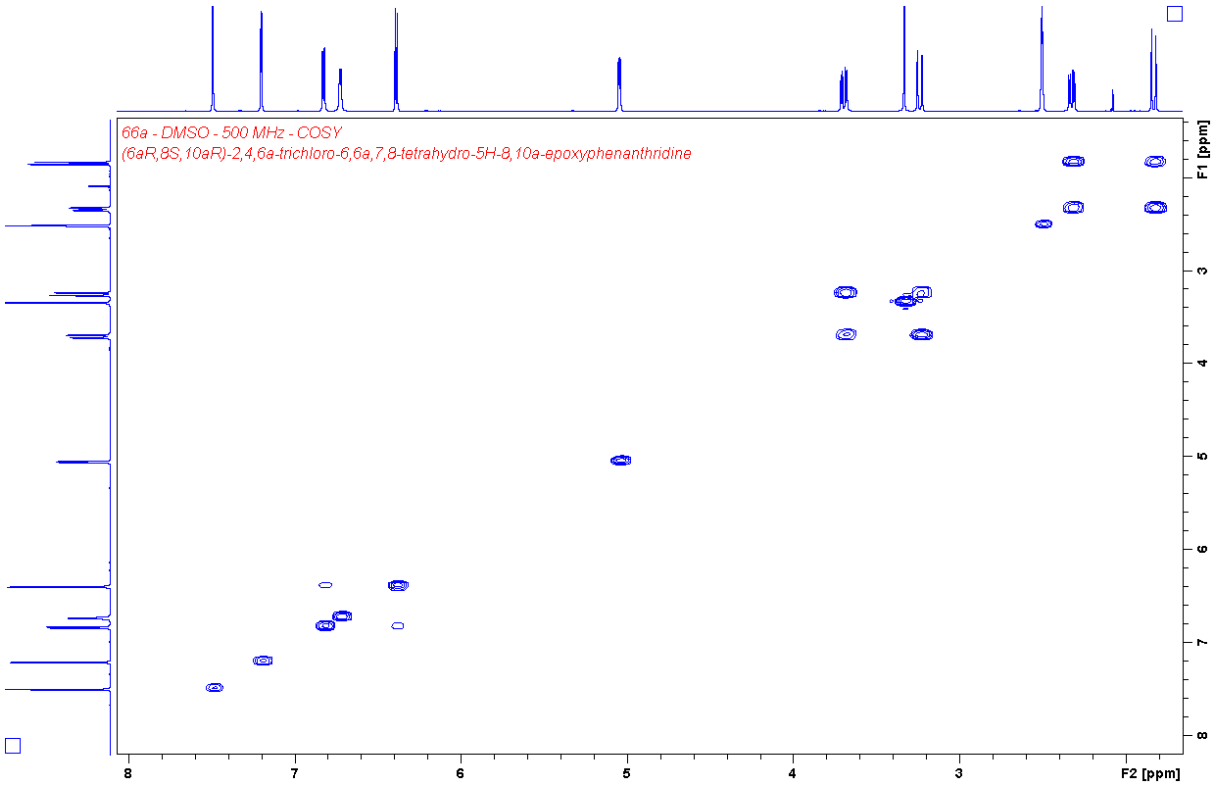
Spectrum 116. 150 MHz, DEPT90 NMR for 4-chloro-5-methyl-2-nitro-5,6-dihydrophenanthridin-8-ol (**47b**).



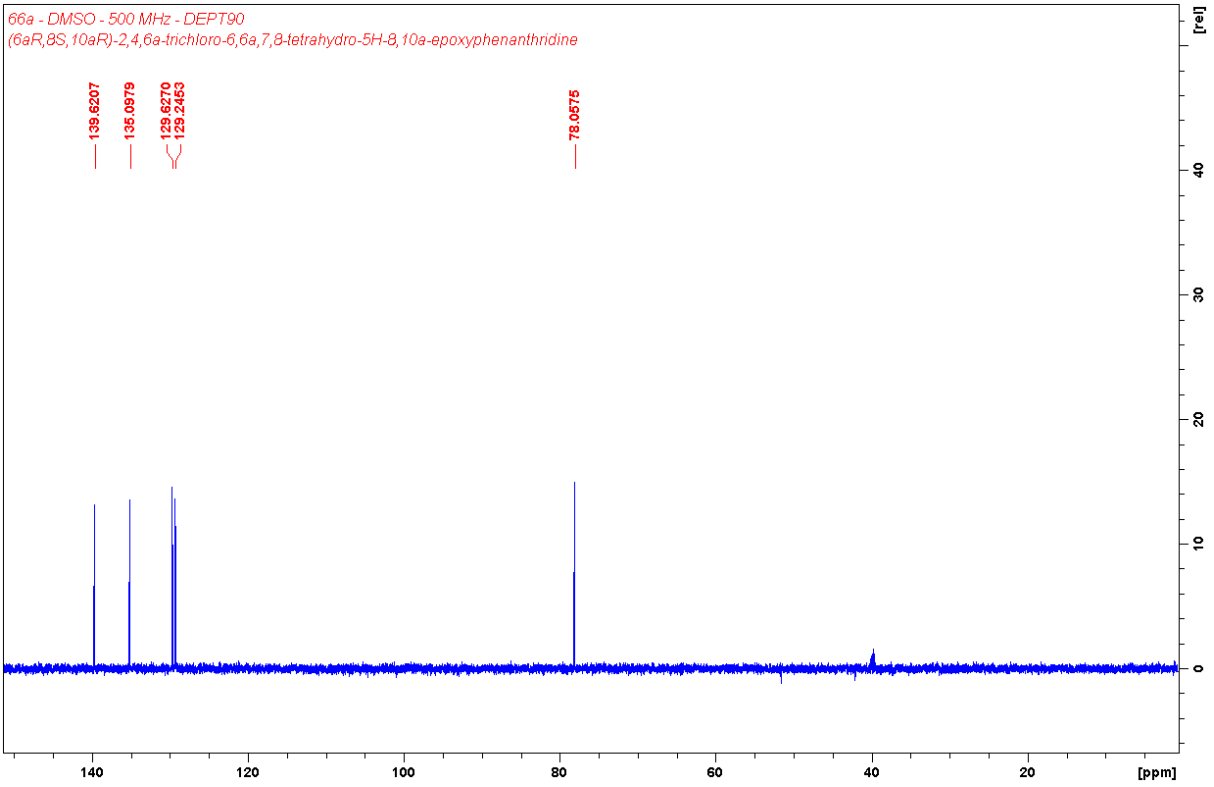
Spectrum 117. 150 MHz, HSQC NMR for 4-chloro-5-methyl-2-nitro-5,6-dihydrophenanthridin-8-ol (**47b**).



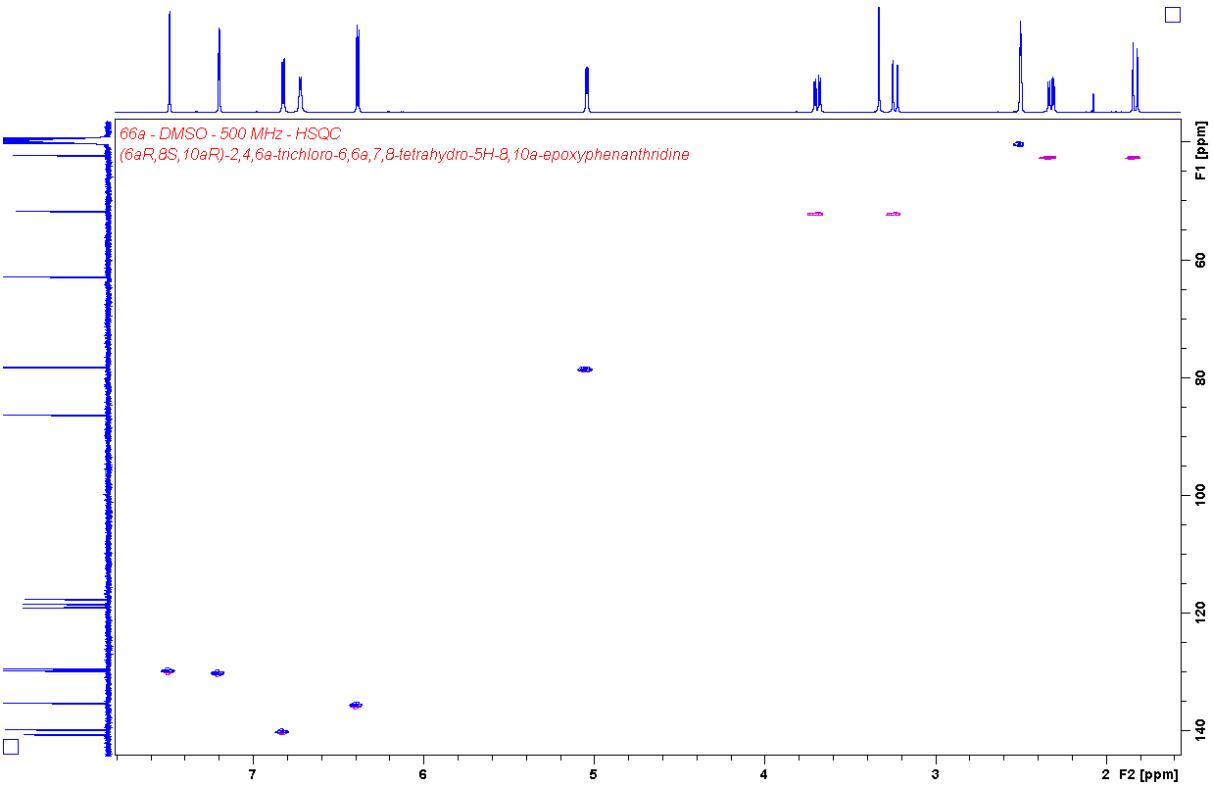
Spectrum 118. 150 MHz, HMBC NMR for 4-chloro-5-methyl-2-nitro-5,6-dihydrophenanthridin-8-ol (**47b**).



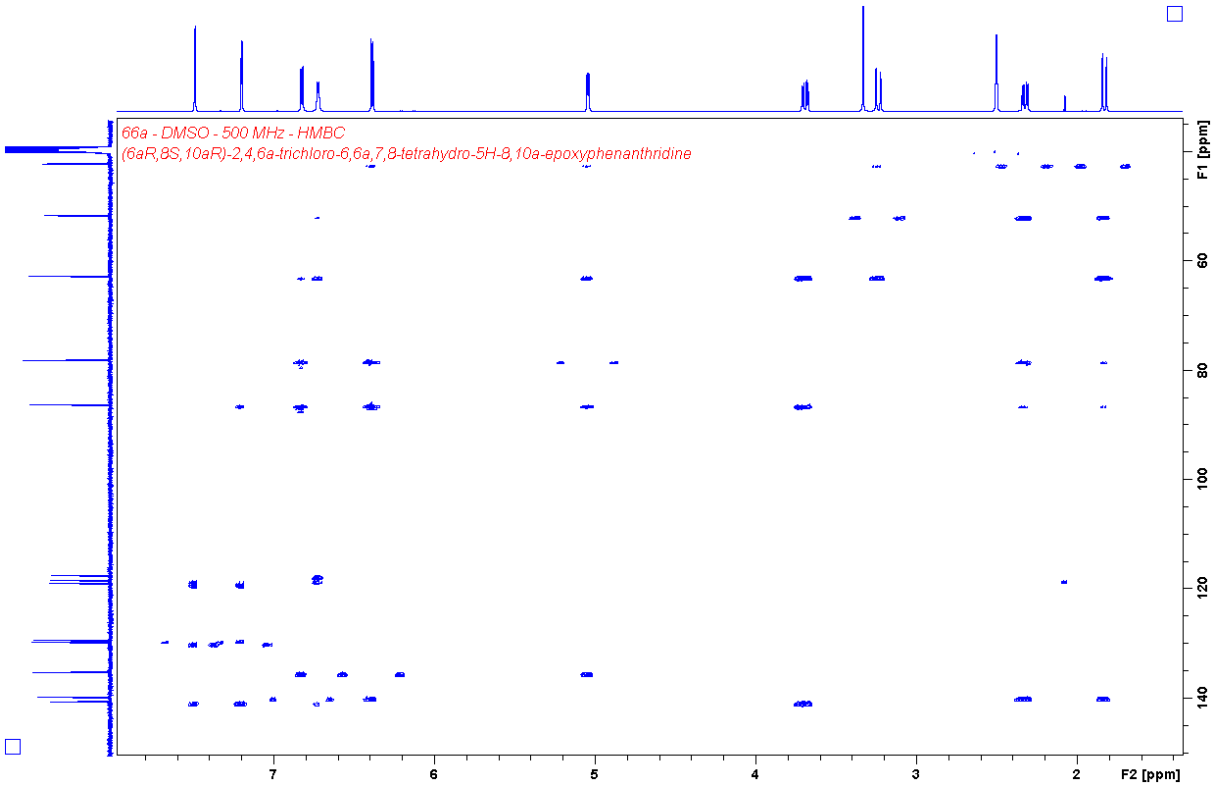
Spectrum 119. 500 MHz, DMSO, COSY NMR for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (**66a**).



Spectrum 120. 125 MHz, DMSO, DEPT90 NMR for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (**66a**).



Spectrum 121. 125 MHz, DMSO, HSQC NMR for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (**66a**).



Spectrum 122. 125 MHz, DMSO, DEPT90 NMR for (6aR,8S,10aR)-2,4,6a-trichloro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (**66a**).

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