Synthesis of Novel Phenanthridin-8-ol Derivatives Functionalized in the A- and C-rings by Means of a Microwave-mediated Intramolecular Diels-Alder Cycloaddition on Furan (IMDAF) Reaction

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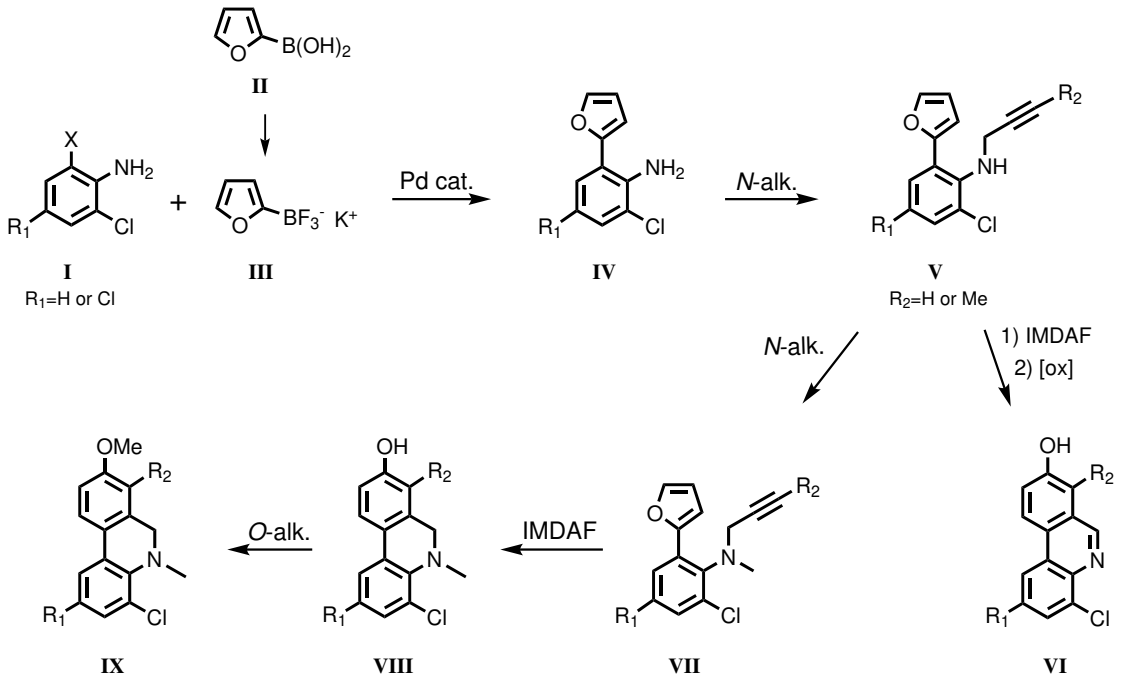
Abstract

By means of a microwave-mediated intramolecular Diels-Alder on furan (IMDAF) reaction, synthesis of ten phenanthridin-8-ol derivatives, whereof nine not previously reported in the literature, was achieved. Phenanthridin-8-ols **VI** were produced through IMDAF cyclization and UV/air oxidation of *o*-furyl-*N*-alkynylaniline substrates **V** (Scheme i), which were produced in high yields from readily available haloanilines **I** and (furan-2-yl)boronic acid **II** in three steps. Similarly, 5-methyl-5,6-dihydrophenanthridines **VIII** were produced by IMDAF cyclization of *o*-furyl-*N*-alkynyl-*N*-methylaniline substrates **VII**. An investigation into the behaviour of substrates **V** and **VII** in IMDAF reactions revealed significantly diminished reactivity upon methyl substitution at R_2. As an example of functionalization at oxygen of phenanthridin-8-ol derivatives, *O*-methylation of a selection of 5-methyl-5,6-dihydrophenanthridin-8-ols **VIII** was performed, producing corresponding 8-methoxy-5-methyl-5,6-dihydrophenanthridines **IX**. Diminished reactivity by methyl substitution at R_2 was observed in this step as well.



Scheme i: Synthesis of phenanthridin-8-ol derivatives presented in this work

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Abbreviations and symbols

μW	microwave
[ox]	oxidation
t-Bu	*tert*-butyl
Ac	acetyl
Ar	aryl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
COSY	correlation spectroscopy
DA	Diels-Alder
DCM	dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DMA	dimethylacetamide
DMF	dimethylformamide
dppp	1,3-bis(diphenylphosphino)propane
eq	equivalents
eq	molar equivalents
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
HCl	hydrochloric acid
HetAr	heteroaryl
HMBC	heteronuclear multiple-bond correlation spectroscopy
HSQC	heteronuclear single quantum coherence
IMDAF	intramolecular Diels-Alder on furan
iPr	isopropyl
Me	methyl
MeCN	acetonitrile
MnO_2	manganese dioxide
mp	melting point
MS	mass spectroscopy
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Ph	phenyl
PPA	polyphosphoric acid
PPh_3	triphenylphosphine
QBAs	quaternary benzo[c]phenanthridine alkaloids
Ra-Ni	Raney nickel
sm	starting material
TBAB	tetrabutylammonium bromide

TBAI	tetrabutylammonium iodide
Tf	triflate
Tf_2O	triflic anhydride
TFA	trifluoroacetate
TfOH	triflic acid
THF	tetrahydrofuran
UV	ultraviolet
XPhos	2-dicyclohexylphosphino-2,4,6-triisopropylbiphenyl

Contents

1 Introduction

1.1 Motivation

The urgent need for new drugs to combat so-called neglected diseases such as tuberculosis, leishmaniasis and drug-resistant bacterial infections is widely recognized.[1–6] While there has been a slight reduction in deaths since the publication of the United Nations Millennial Development Goals,[1] tuberculosis is still a major threat to global health, causing around 1.1 million deaths per year.[2] About 10 million new infections are estimated each year, of which 0.5 million are rifampicin-resistant and 3.4 percent multi drug-resistant.[4] Leishmaniasis is the second largest parasitic killer after malaria, with an estimated 600 000 to 1 million new cases annually, causing 26 000 to 65 000 deaths.[5] Due to excessive and inappropriate use of antibiotics, an epidemic of drug-resistant bacterial infections has developed over the years, leaving fear of a future scenario without any potent antimicrobial agents left.[6–8].

Because these diseases primarily affect low- and middle income countries and new drugs often are used for last-line treatment of resistant infections, investment in research and development is generally considered unprofitable by the pharmaceutical industry.[6] Fifteen out of the eighteen largest pharmaceutical companies have now abandoned the antibiotic field, manifested by a drastic reduction in the number of newly approved antibacterial drugs over the last 30 years.

Research has revealed promising antimicrobial properties of phenanthridine derivatives (Section 1.2), calling for further exploration of this class of compounds for combating neglected diseases. A method for synthesis of phenanthridine derivatives by means of a microwave-mediated intramolecular Diels-Alder on furan (IMDAF) reaction has been developed over the last ten years.[9–13]. The work presented herein concerns synthesis of novel phenanthridines using this method, with the purpose of providing new drug candidates and developing the method further.

1.2 The biological activity of phenanthridine derivatives

1.2.1 Phenanthridine

Phenanthridine **1** (Figure 1.1) is a planar[14] tricyclic heteroaromatic compound, the analog of phenanthrene containing a nitrogen heteroatom in the 5-position. Containing a 14π-electron system, it is thermodynamically stable, indicated by the fact that it is distilled at bp 349 °C without decomposition.[15] The compound is weakly basic (pK_a of 4.47[15]), slightly less so than comparable heterocycles pyridine and quinoline.[16]

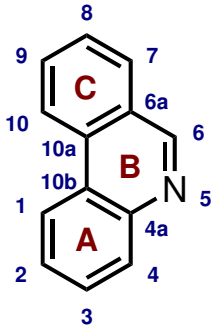

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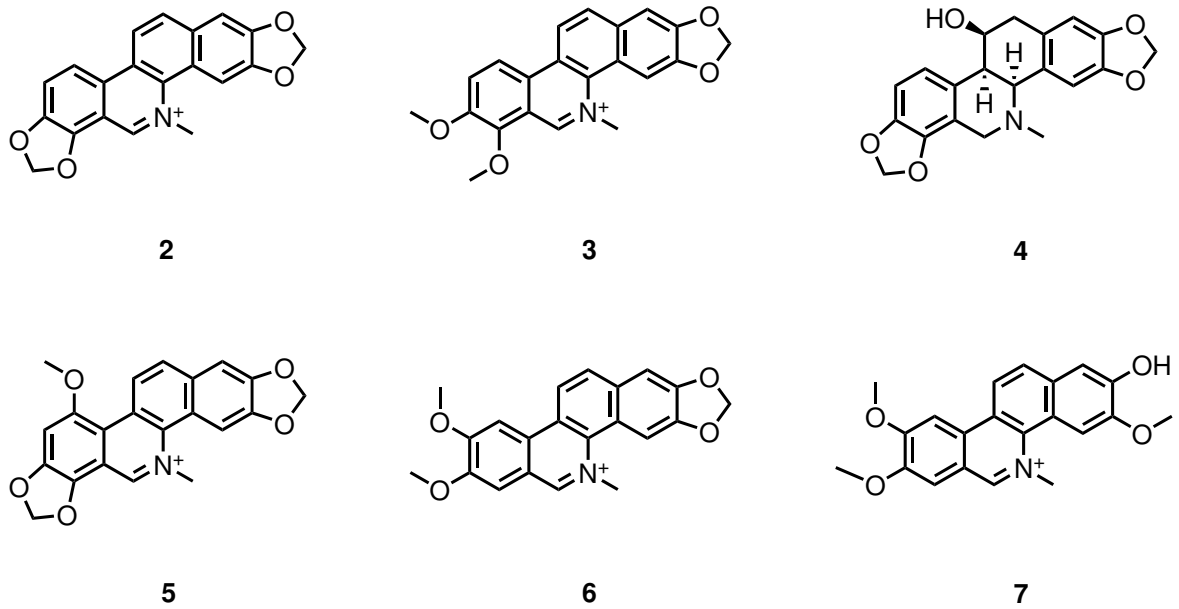
Figure 1.1: Structure and numbering of phenanthridine



2 **3** **4**

5 **6** **7**

Figure 1.2: Benzo[c]phenanthridine alkaloids

1.2.2 History of phenanthridine research

The synthesis of phenanthridine was reported as early as in 1891.[17] By that time, the presence of alkaloids sanguinarine **2**, chelerythrine **3** and chelidonine **4** (Figure 1.2) in extracts from medicinal plants of the *Papaveraceae* family was already known.[18] [19] Upon structural determination of these alkaloids in 1931, it became apparent that these alkaloids were derivatives of phenanthridine.[20] This discovery provided motivation for further exploration of the biological activity phenanthridine derivatives. Since, a multitude of new phenanthridines have been discovered in nature, and a large series of synthetic phenanthridine derivatives have been developed in the laboratory, many of which display interesting and useful biological activities.

Following the identification of phenanthridine alkaloids **2**, **3** and **4**, it was discovered in 1938 that a

number of synthetic phenanthridine derivatives were effective against *Trypanosoma congolense* and *Trypanosoma brucei* infections in cattle.[21] A later variant of these derivatives, ethidium bromide **8** (Figure 1.3), was developed in 1952 and is in use as a veterinary trypanocidal to this date.[22][23]

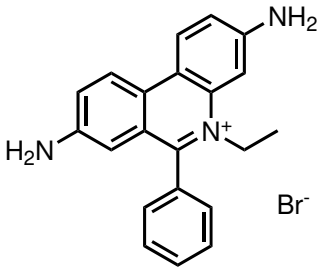


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Figure 1.3: Structure of ethidium bromide

It was discovered that these compounds were DNA intercalators with cytotoxic properties, and research into the anticancer activity of the analogous alkaloids nitidine **6** and fagaronine **7** (Figure 1.2) during the 1970s showed activity against Leukemia *in vivo*.[24][25] However, failed clinical trials in the late 1970s and fears over potential mutagenic effects of these compounds diminished interest among researchers for the next 10-20 years.[26]

This trend was reversed during the 1990s, perhaps as a result of *in vivo* experiments showing lower toxicity than feared.[27] Since, research has revealed additional antibacterial, antiviral, antitubercular and antiplasmodic properties of both synthetic and naturally occuring phenanthridine derivatives.[28][29][30][31]

1.2.3 Quaternary benzo[c]phenanthridine alkaloids

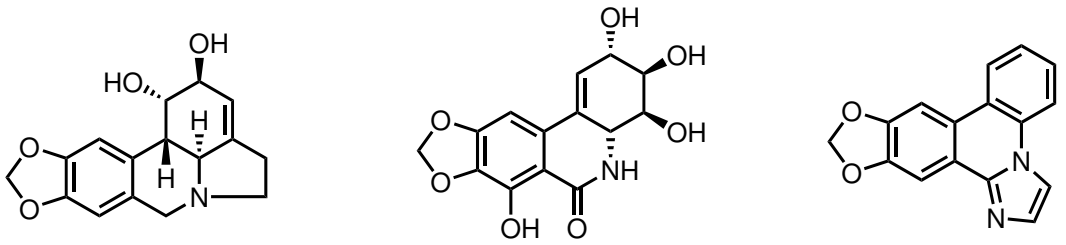
The quaternary benzo[c]phenanthridine alkaloids (QBAs) are a group of phenanthridine alkaloids characterized by a methylated quaternary iminium nitrogen in the 5-position, giving the molecules a positive charge (Figure 1.2). These alkaloids are secondary metabolites produced by plants in the *Papaveraceae* and *Rutaceae* families in response to foreign pathogens.[32] Interestingy, many of these plants have found use in traditional medicine of widely different cultures around the world independently.[33–36]

The utility of these compounds has been validated by modern medicinal research. Sanguinarine **2** and chelerythrine **3** have displayed potent antimicrobial effect, for example against methicillin-resistant *Staphylococcus aureus* (MRSA)[37] and *Mycobacterium aurum*.[30] Furthermore, related compounds nitidine **6** and fagaronine **7** have shown efficacy against leukemia[24,38] and malaria.[39–41]

1.2.4 *Amaryllidaceae* alkaloids

Another important class of phenanthridine alkaloids used in traditional medicine are the *Amaryllidaceae* alkaloids. These are characterized by reduction or functionalization of the B-ring, and differ from the QBAs by the lack of the benzo[c]-ring (Figure 1.4).

The most well-known alkaloid of this class is lycorine **9** (Figure 1.4), the major alkaloid of among others the *Amaryllis belladonna* plant, displaying anticholinesterase inhibition properties and activity against a range of tumor cell lines.[42–45] Other *Amaryllidaceae* alkaloids with similar properties include narciclasine **10** and zephycandidine A **11**.



9 **10** **11**

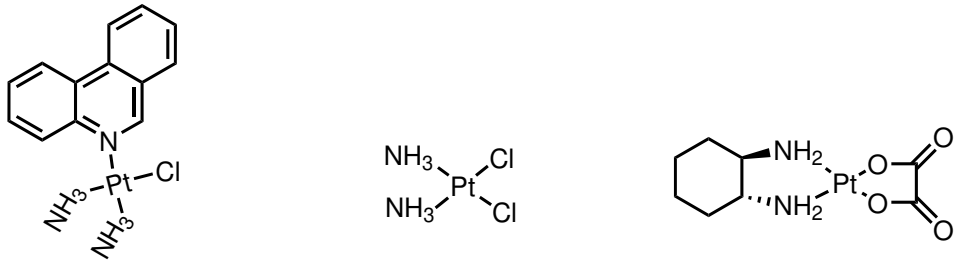
Figure 1.4: Amaryllidaceae alkaloids

1.2.5 Synthetic phenanthridine derivatives

Despite the increased interest in phenanthridines over the last twenty years, the range of biologically active synthetic phenanthridines reported in the literature is still relatively sparse. However, some notable examples are worth mentioning.

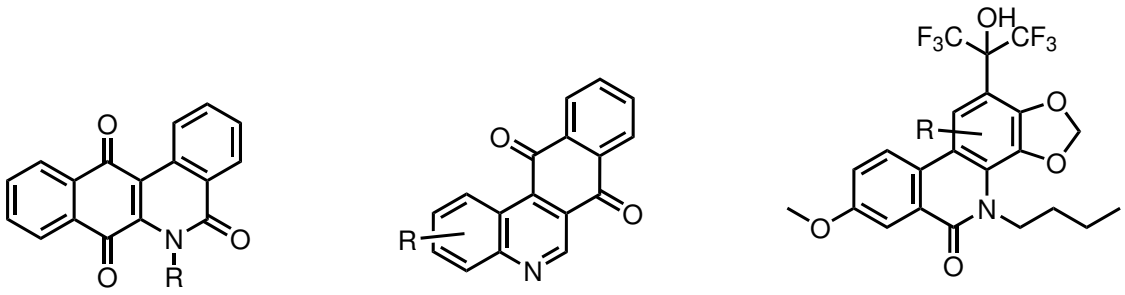
In addition to its trypanocidal activity, ethidium bromide **8** (Figure 1.3) is widely used as DNA stain in molecular biology due to its fluorescent DNA-binding properties.[26] Similarly, the related compound propidium iodide is used as a stain for evaluation of cellular DNA content.[46] Interaction with DNA is also responsible for the anti-tumor activity of phenanthriplatin **12** (Figure 1.5), displaying significantly improved potency over the FDA-approved cancer drugs cisplatin **13** and oxaliplatin **14**.[47,48]

Recently reported phenanthridine derivatives with antimicrobial properties include a series of benzo[b]phenanthridinetriones **15** (Figure 1.6), which were found to inhibit MRSA in a matter comparable or better than vancomycin.[49] The similar benzo[j]phenanthridinediones **16** showed high *in vitro* activity against *Mycobacterium tuberculosis*.[50,51] A different class of phenanthridinones **17** were found to be potent inhibitors of the hepatitis C virus.[52]



12 **13** **14**

Figure 1.5: Platin cancer drugs



15 **16** **17**

Figure 1.6: Recently reported antimicrobial synthetic phenanthridines

There is great potential for further exploration of biologically active synthetic phenanthridine derivatives. In this regard, synthesis of novel derivatives and development of methods for this purpose is of interest. The work presented herein is intended as a contribution to this cause.

1.3 Methods of phenanthridine synthesis

1.3.1 Reactivity of phenanthridine

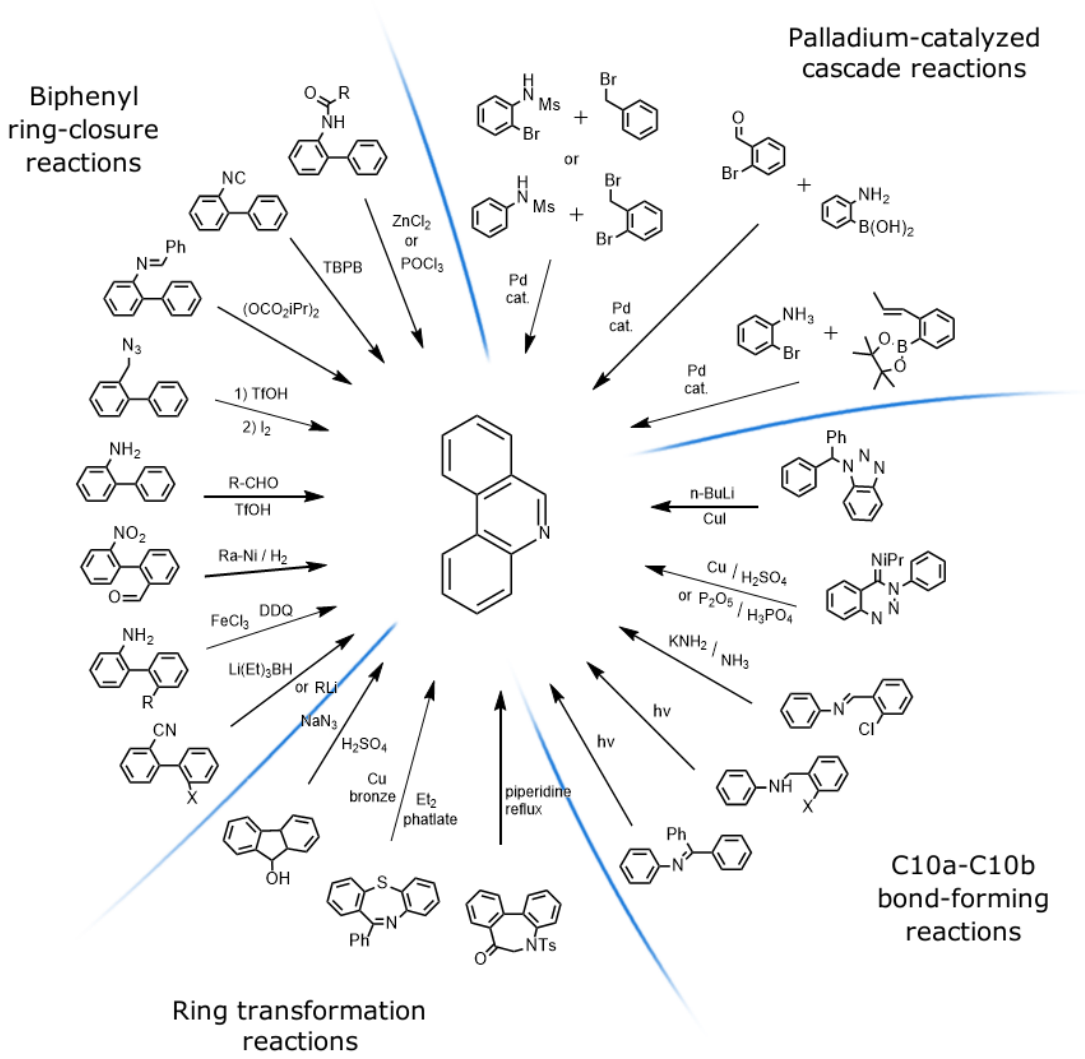
The reactivity of phenanthridine (Figure 1.1, Section 1.2) is for the most part focused around C=N bond.[53] Reaction with nucleophiles occurs at C6 and electrophiles add to N5. Oxidizing agents generally oxidize N5, while reducing agents reduce the C=N bond.

While there are examples of reactions on the A- and C-rings in the literature,[54] they are few and far between. Thus, with reactivity of phenanthridine itself being limited, functionalization is commonly achieved at the starting material rather than phenanthridine.

1.3.2 Overview of synthetic methods

While synthesis of phenanthridine itself was reported as early as 1891,[17] the diversity of methods developed throughout the 20th century was sparse. However, renewed interest in phenanthridines as pharmaceutical agents has stimulated an upsurge in reported syntheses in the literature over the last 20 years. Known reactions have been reviewed, improved and expanded, and developments in areas such as palladium-catalyzed coupling reactions and C-H activation has increased the wealth of available methods.

Literature syntheses may be divided into four major categories: Biphenyl ring-closure reactions, C10a-C10b bond-forming reactions, palladium-catalyzed cascade reactions, and ring transformation reactions (Scheme 1.1). A review of a selection of these methods follows.

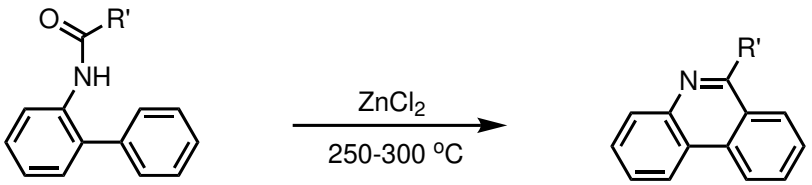


Scheme 1.1: A simplified overview of literature phenanthridine syntheses

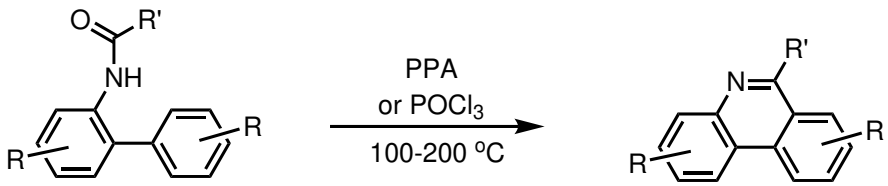
1.3.3 Biphenyl ring-closure reactions

Formation of the C6-C6a bond

Synthesis of phenanthridine was reported by Pictet and Ankersmit in 1891 (Scheme 1.2),[17] and variants of this reaction were the primary methods employed throughout the 20th century. The established variant involves dehydration of *N*-acylbiphenyl-2-amine into an activated imidoyl intermediate which cyclizes spontaneously,[55] yielding phenanthridines **19** (Scheme 1.3).[56–58]



Scheme 1.2: The Pictet-Ankersmit phenanthridine synthesis[17]



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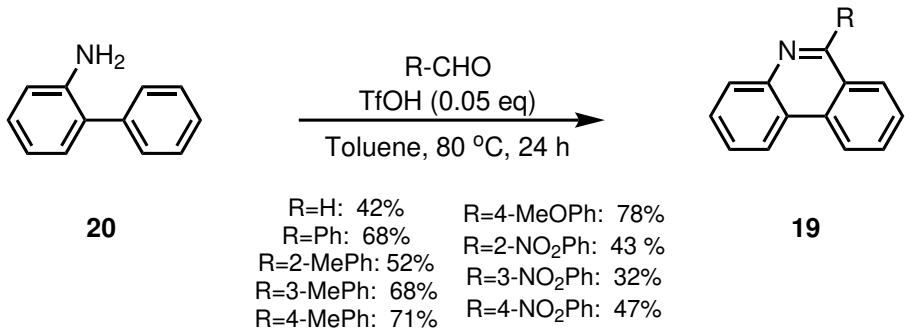
R=R'=H: 93%
R=3-Br: 85%
R=10-Br: 47%
R=H, R'=Ph: 96%
R=8-NO_2, R'=Ph: 74%
R=3-Me, R'=Ph: 80%
R=3-OH, R'=Me: 75%

19

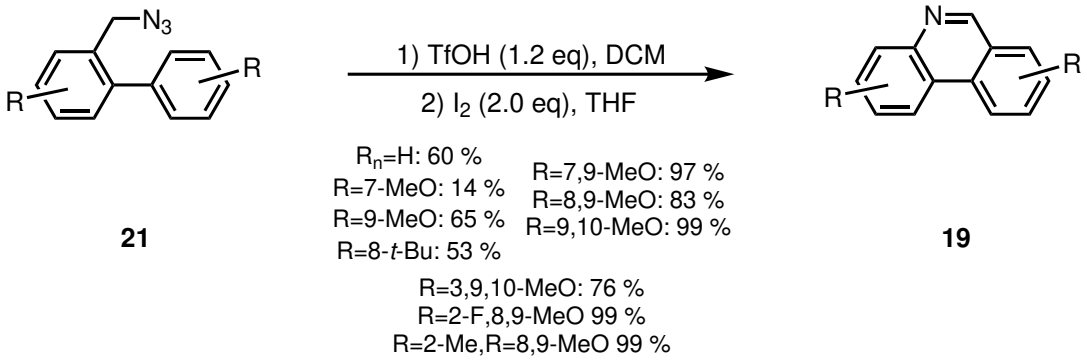
Scheme 1.3: Synthesis of phenanthridine by Bischler-Napieralsky cyclization[57–63]

In the similar Pictet-Spengler reaction, biphenyl-2-amine **20** is reacted with an aldehyde in an acid-catalyzed reaction, producing 6-substituted phenanthridines **19** (Scheme 1.4),[64] presumably via cyclization of the imide intermediate followed by oxidation of the resulting N5-C6 bond.[65]

In a more modern approach, a range of substituted phenanthridines **19** were produced from biphenyl-2-methyl azides **21**, in two steps: Treatment with triflic acid in DCM, then I_2 in THF (Scheme 1.5).[66] Formation of a C6-C6a bond might seem contradictory here, but product substitution patterns suggest a mechanism involving rearrangement of the -CH_2-N_3 side chain prior to cyclization.



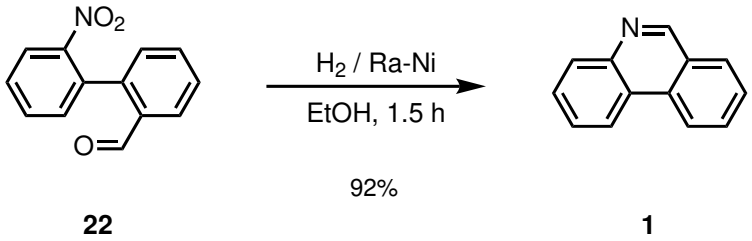
Scheme 1.4: Acid-catalyzed condensation of biphenyl-2-amine with aldehydes[64]



Scheme 1.5: Cyclization of biphenyl-2-methyl azides[66]

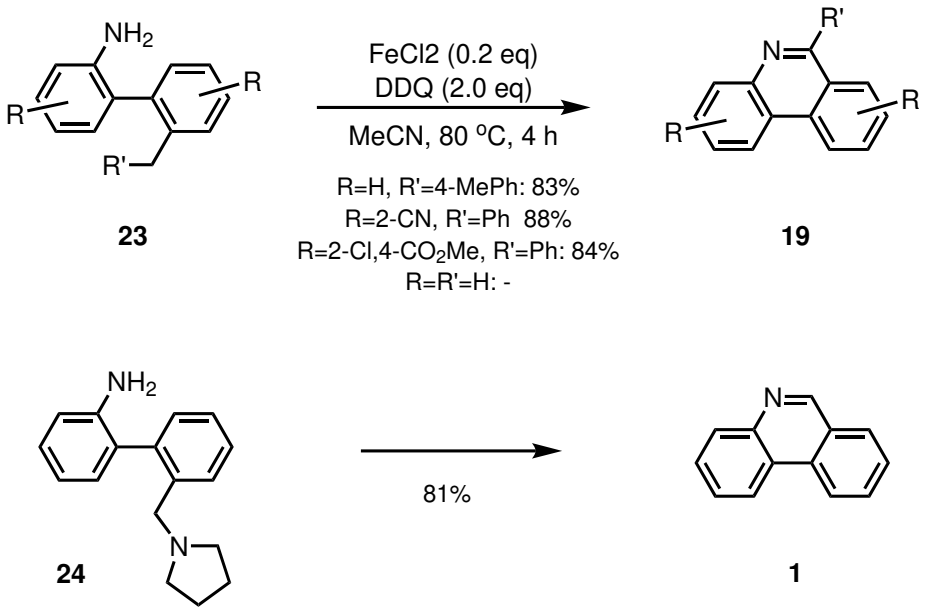
Formation of the N5-C6 bond

From a series of heterocycles synthesized by reductive cyclization of nitrobenzenes, phenanthridine **1** was made from 2-(2-nitrophenyl)benzaldehyde **22** by treatment with H_2 and Rainey nickel (Scheme 1.6).[67] Similarly, phenanthridines may also be synthesized by treating the corresponding amine with aqueous NaOH.[68]

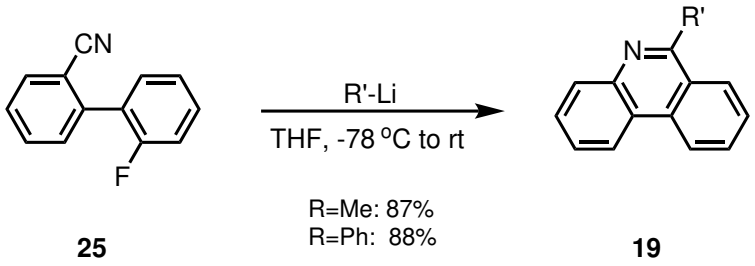


Scheme 1.6: Reductive cyclization of 2-(2-nitrophenyl)benzaldehyde[67]

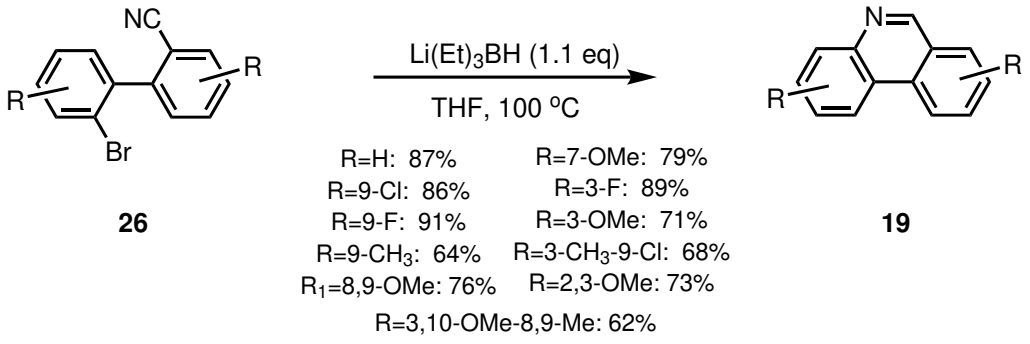
In a recent paper, synthesis of phenanthridines **19** via C-H amination of 2-(2-alkylphenyl)anilines **23** (Scheme 1.7) was reported.[69] While yields were high for a variety of substituents, R'=H or R'=Me did not produce detectable amounts of desired product. Ehen attaching a pyrrolidine-*N*-yl group to the R' position **24**, however, the group was eliminated upon cyclization, forming unsubstituted phenanthridine **1**.



Scheme 1.7: Cyclization of 2-(2-alkylphenyl)anilines via C-H amination[69]



Scheme 1.8: Anionic cyclization using organolithium reagents[70]



Scheme 1.9: Hydride-induced anionic cyclization of 2-(2-bromophenyl)benzonitriles[71]

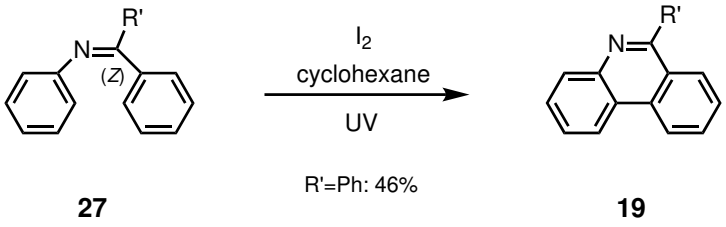
Formation of the C4a-N5 bond

The C4a-N5 bond may be formed by anionic cyclization of 2-(2-halophenyl)benzonitriles **25** and **26**. Two subtypes of this reaction are reported: Synthesis using organilithium reagents[70] (Scheme 1.8), and hydride-induced anionic cyclization using $Li(Et)_3BH$[71] (Scheme 1.9). The hydride-induced variant is notable for the number of high-yielding substitution patterns explored.

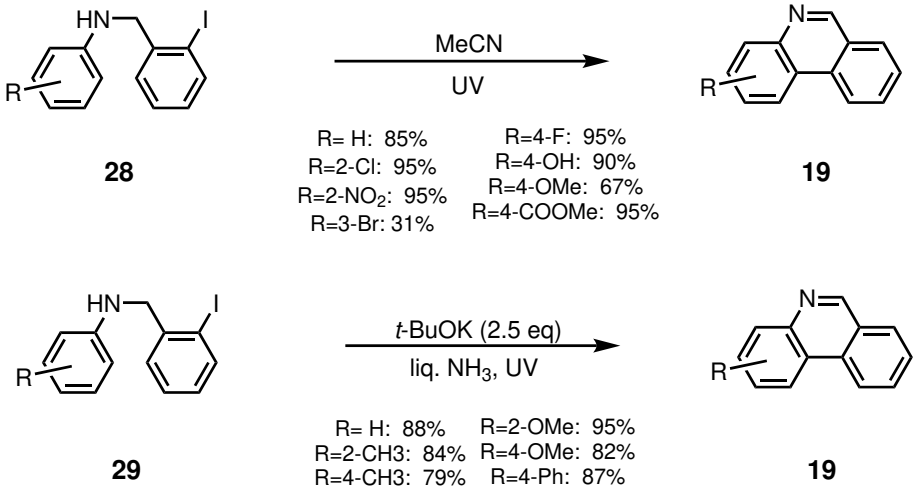
1.3.4 C10a-C10b bond-forming reactions

Photochemical cyclization

Condensation of anilines with aromatic ketones and aldehydes produce diphenylmethanimines **27**, which undergo photochemical cyclization to produce phenanthridines **19** (Scheme 1.10).[72] While this is a clean method with a potentially large scope of functionalization, reaction times are long, yields moderate and scale limited. The need for the (*Z*)-isomer also limits the utility of the condensed starting material.



Scheme 1.10: Photochemical cyclization of (Z)-diphenylmethaneimines[72]

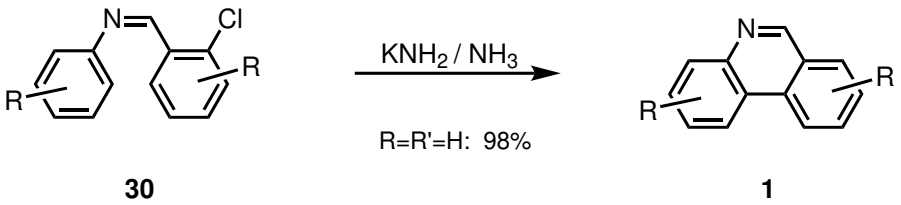


Scheme 1.11: Photochemical cyclization of N-(2-iodobenzyl)anilines in acetonitrile[73] *or t-BuOK in liquid ammonia*[74,75]

N-(2-iodobenzyl)anilines **28** and **29** undergo photochemical cyclization in acetonitrile[73] or by potassium *tert*-butoxide in liquid ammonia[74,75], producing a variety of phenanthridines **19** (Scheme 1.11). These methods have the characteristics of the preceeding one, but provide higher yields and eliminate restrictive isomeric demands on the starting material.

Cyclization through elimination-addition

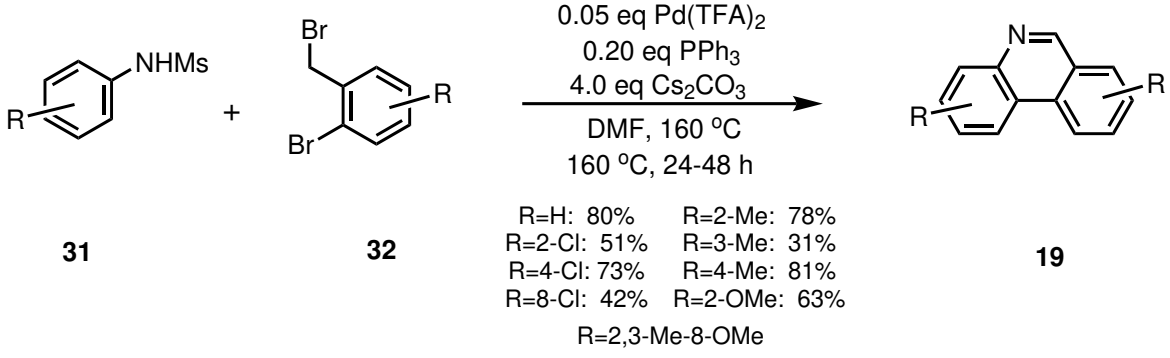
Treatment of *N*-phenyl-(2-chlorophenyl)methaneimine **30** with potassium in liquid ammonia produces phenanthridine **1** in high yield (Scheme 1.12).[76] While the analogous reaction in section 1.3.4 depend on (*Z*)-isomer starting material, this is fortunately not the case here, presumably due to attack of the imine carbon by the amide prior to cyclization.[77] High yields were obtained for a range of A- and C-ring substitutions, although substitution at C-6 was not successful.



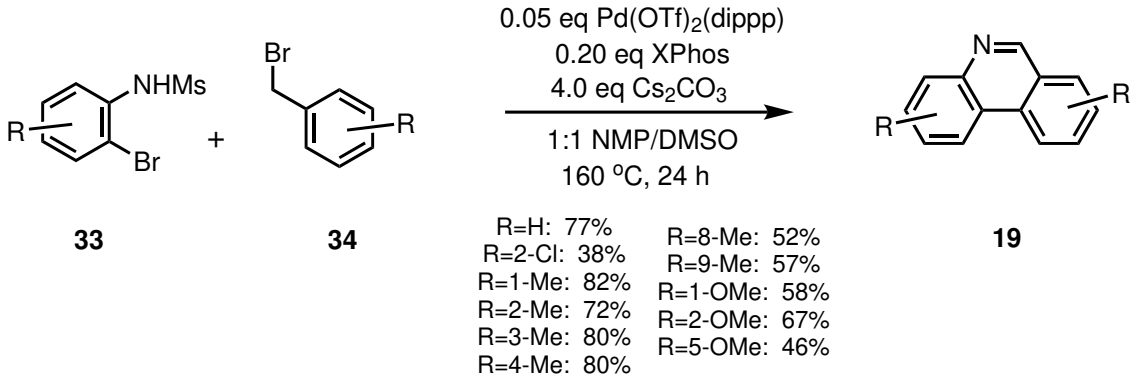
Scheme 1.12: Cyclization of N-(2-chlorobenzyl)aniline using potassium in liquid ammonia[76]

1.3.5 Palladium-catalyzed cascade reactions

Starting from *N*-mesylanilines **31** and (2-bromophenyl)bromoethanes **32**, phenanthridines **19** were produced in a palladium-catalyzed reaction (Scheme 1.13).[78] In a modified procedure, the starting material 2-bromo group was transfered to the aniline, now producing phenanthridines from *N*-mesyl-2-bromoanilines **33** and benzyl bromide **34** (Scheme 1.14).[79] Both methods provide a wide scope of functionalization in high yields, but rely on expensive catalysts and suffer from regioisomerization in some cases.

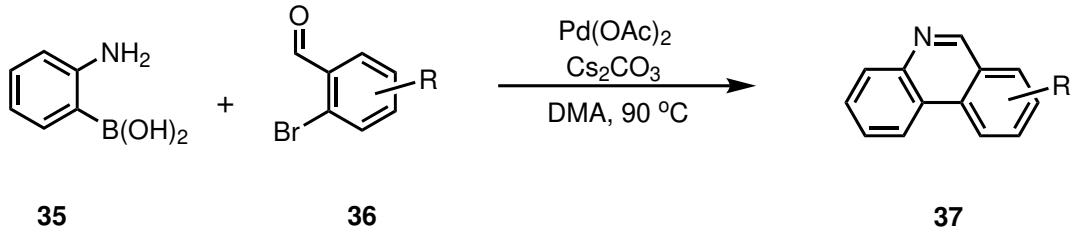


Scheme 1.13: Cascade coupling of N-mesylanilines and (2-bromophenyl)bromomethanes[78]



Scheme 1.14: Cascade coupling of N-mesyl-2-bromoanilines and benzyl bromides[79]

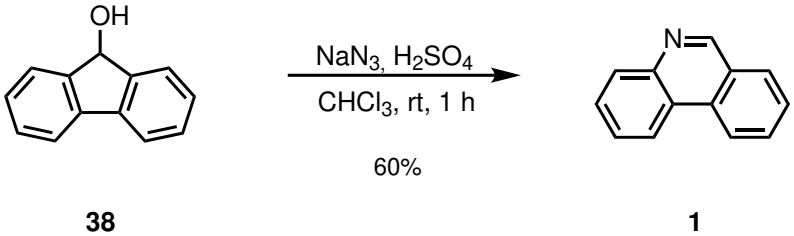
Phenanthridines may also be synthesized through cascade reactions utilizing Suzuki-Miyaura coupling. One example is the coupling of (2-aminophenyl)boronic acid **35** and 2-bromobenzaldehydes **36** to produce a variety of C-ring-substituted phenanthridines **19** in high yields (Scheme 1.15).[80]



Scheme 1.15: Suzuki-Miyaura coupling of 2-bromobenzaldehydes with (2-aminophenyl)boronic acid[80]

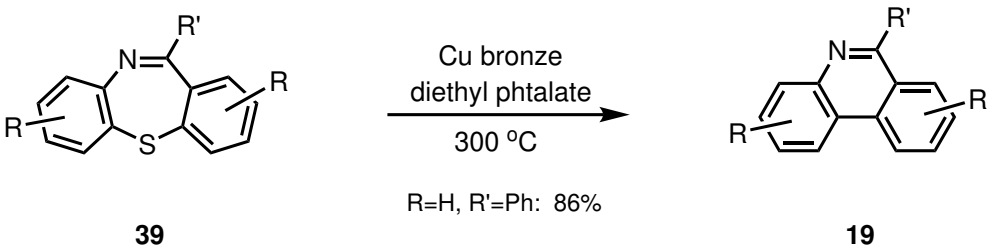
1.3.6 Ring tranformation reactions

Ring expansion of fluoren-9-ol **38** by sodium azide in concentrated sulfuric acid produces phenanthridine **1**[81] (Scheme 1.16), although yields are moderate and the reaction suffers from regioisomerization upon substution at phenyl.[82]



Scheme 1.16: Ring expansion of fluoren-9-ol[81]

11-Phenyldibenzothiazepines **39** produce 6-phenylphenanthridines **19** by pyrolytic ring contraction (Scheme 1.17), with a range of high-yielding substitutions at C-4 and C-8 explored.[83] This reaction is of particular interest due to the similarity of the starting material with the psychiatric drug quetiapine, of which synthesis is well researched.



39 **19**

Scheme 1.17: Ring contraction of 11-phenyldibenzothiazepines[83]

1.4 Development of the IMDAF reaction for synthesis of phenanthridine derivatives

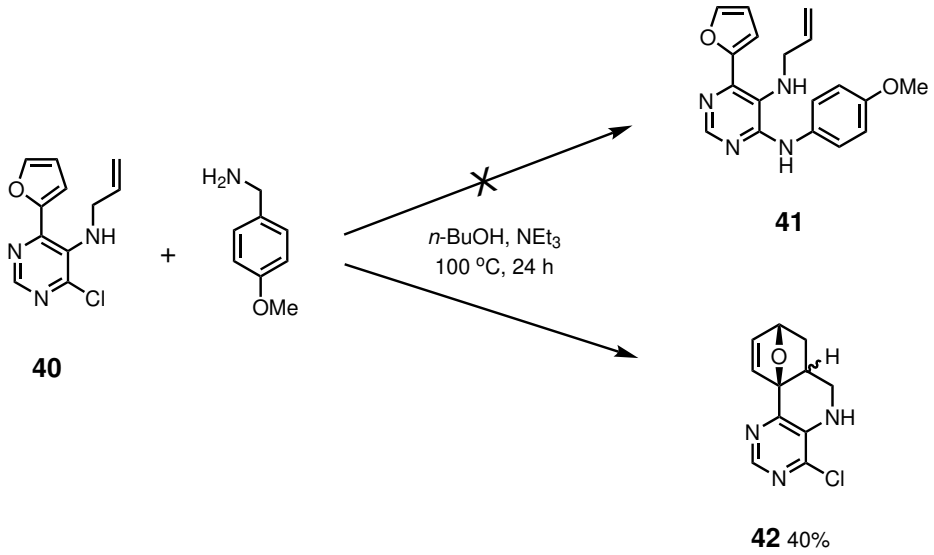
1.4.1 Background

Over the last ten years or so, our research group has investigated the use of an intramolecular Diels-Alder on furan (IMDAF) reaction for synthesis of polycyclic heterocycles, with emphasis on phenanthridines in particular.[9–13] Over the course of the research, the IMDAF reaction has proven to be a reliable method for the synthesis of a wide range of phenanthridines.

The IMDAF method offers attractive advantages over other methods of phenanthridine synthesis. Phenanthridines are synthesized from cheap and easily available starting materials in few steps. The IMDAF reaction is elegant and environmentally friendly. Furthermore, the method offers a wide scope of functionalization compared to many other methods, producing a variety of substitution patterns in both the A- and C-ring by slight modification of starting materials.

1.4.2 Discovery

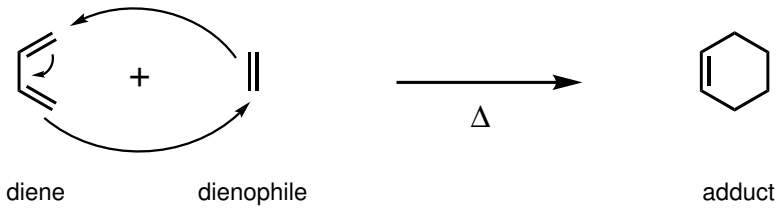
Our interest in the IMDAF reaction for this purpose was a result of a serendipitous discovery. While working on a series of antimycobacterial pyrimidines, it was discovered that rather than undergoing the expected nucleophilic aromatic substitution reaction, substrate **40** underwent an IMDAF reaction, producing the Diels-Alder adduct **42** rather than the expected product **41** (Scheme 1.18).[84] The discovery opened the door to further investigation into the reaction, improving reaction conditions and widening the substrate scope, ultimately leading to the development of the reaction for efficient phenanthridine synthesis.



Scheme 1.18: Formation of an unexpected IMDAF reaction byproduct during synthesis of antimycobacterial pyrimidines[84]

1.4.3 The Diels-Alder cycloaddition reaction

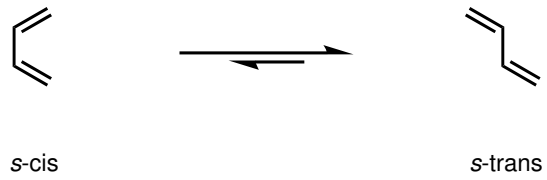
First reported by Otto Diels and Kurt Alder in 1928,[85] Diels-Alder (DA) reaction occurs between a diene and a dienophile upon heating, leading to the formation of a cyclohexene structure (Scheme 1.19).[86] As depicted, it is a concerted [4 + 2] cycloaddition reaction, rearranging four π-electrons from the diene and two π-electrons from the dienophile into two connecting single bonds and a migrated double bond.



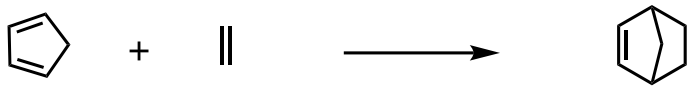
Scheme 1.19: The Diels-Alder cycloaddition reaction

To participate in the reaction, the diene must be conjugated and be able to obtain an *s*-cis conformation (Scheme 1.20).[86] Cyclic dienes permanently locked into the *s*-cis conformation, such as cyclopentadiene **43**, are favored, leading to bridged bicyclic structures, such as **44**. (Scheme 1.21). The dienophile may be an alkene or an alkyne, the latter case resulting in the formation of a cyclohexa-1,4-diene structure (Scheme 1.22).

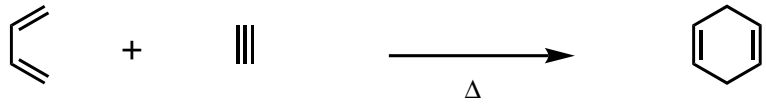
With an electron-rich diene, the attachment of an electron-withdrawing group to the dienophile results in increased reactivity as the electron density around the β-carbon is decreased, facilitating attack by the diene's π-electrons. Analogously, the reverse case of an electon-rich dienophile and electron-poor diene also favors reactivity.



Scheme 1.20: Diene conformations



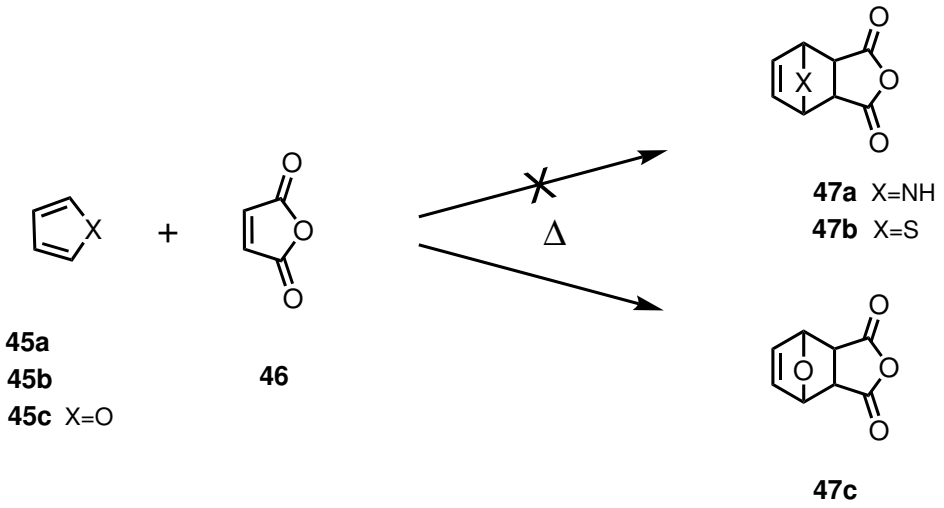
Scheme 1.21: A cyclic dienophile produces a bridged bicyclic compound



Scheme 1.22: An alkyne dienophile results in the formation of a cyclohexa-1,4-diene structure

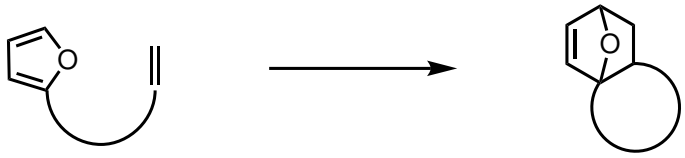
1.4.4 The IMDAF reaction

The aromatic dienes pyrrole **45a** and thiophene **45b** do not participate in ordinary DA reactions (Scheme 1.23).[87–89] This is often ascribed to the occurrence of a retro DA reaction at high temperatures, causing formed adducts to revert to the more stable aromatic starting material.[90] Furan **45c**, however, having a diminished aromatic character due to the electronegative oxygen atom, participates more readily in such reactions. This is exemplified by addition to the strong dienophile maleic anhydride **46**, which under ordinary conditions occurs with furan a dienophile, but not with pyrrole or thiophene.[87,89,91] Reaction with weaker dienophiles, however, is difficult even for furan, requiring extreme conditions to occur.[92,93]

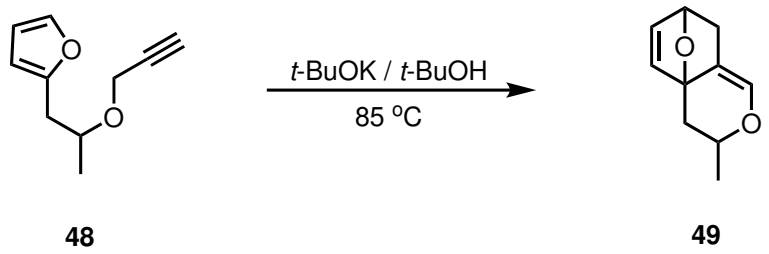


Scheme 1.23: Diels-Alder cycloaddition of heteroaromatic dienes to maleic anhydride[87,89,91]

While furan does not participate in DA cycloaddition with weaker dienophiles in bimolecular reactions under regular conditions, this is facilitated by attaching the dienophile to furan intramolecularly (Scheme 1.24).[94] For instance, cyclization of the furylalkyl propargyl ether **48** occurs when heated under basic conditions, producing the fused polycycle **49** containing the characteristic 1,4-epoxide bridge (Scheme 1.25).[94,95] As for the reactivity, it has been shown that alkyl substitution at carbon α to the furyl group increases the rate of cyclization drastically, up to 2123 times for the cyclization of **50** into **51** when R_1=R_2=Me compared to R_1=R_2=H (Scheme 1.26).[96] It is worth noting that cyclization in many cases results in a mixture of *exo* and *endo* diastereomers (Scheme 1.27), depending on the relative orientation of the epoxy bridge relative to the diastereotopic hydrogen.

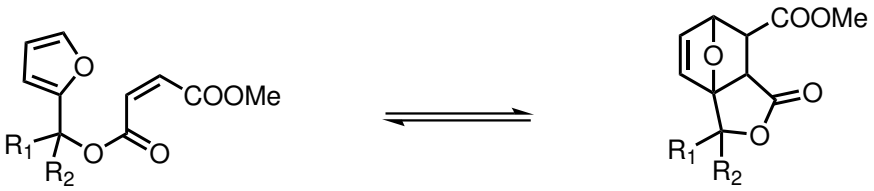


Scheme 1.24: The IMDAF reaction



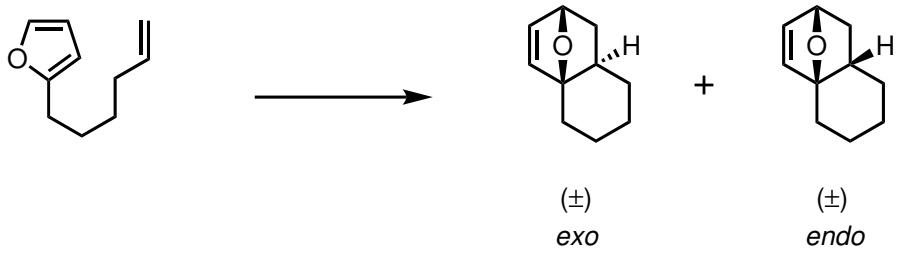
48 **49**

Scheme 1.25: IMDAF cyclization of a furylalkyl propargyl ether[94,95]



50 **51**

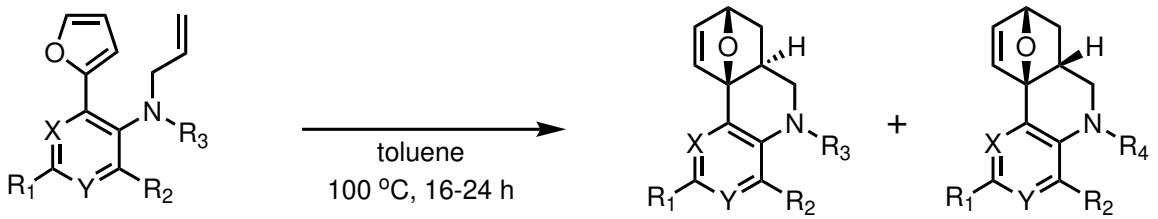
Scheme 1.26: The rate of this cyclization increases upon substitution at R_1 and R_2[96]



Scheme 1.27: Cyclization often results in exo and endo diastereomers

1.4.5 Investigation into the scope of the IMDAF reaction

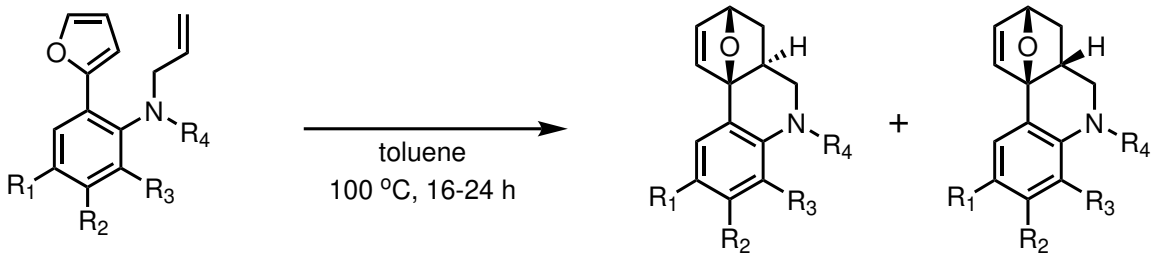
Following discovery of compound **40** undergoing IMDAF upon heating with NEt_3 in n-BuOK (Section 1.4.1, Scheme 1.18), investigation into the scope of this reaction was launched. A variety of substituted *N*-allyl-*o*-furylheteroarylamine substrates **52a–l** were synthesized and attempted cyclized into adducts **53a–l** and **54a–l** by heating in toluene (Scheme 1.28).[9] Results reveal an apparent criteria for successful cyclization: The substrate must either be substituted at R_2 or be *N*,*N*-disubstituted. Calculations support this observation by showing how the energy difference between the minimum conformation and the conformation necessary to undergo IMDAF is lowered in these cases.[9]



52a	X=N, Y=CH, R_1=R_2=R_3=H	**53a**	-	**54a** -
52b	X=N, Y=CH, R_1=R_3=H, R_2=Cl	**53b**	49% (*exo* + *endo*)	**54b**
52c	X=CH, Y=N, R_1=R_3=H, R_2=Cl	**53c**	88% (*exo* + *endo*)	**54c**
52d	X=Y=N, R_1=R_3=H, R_2=Cl	**53d**	55%	**54d** -
52e	X=Y=N, R_1=R_3=H, R_2=2-Fur	**53e**	66% (*exo* + *endo*)	**54e**
52f	X=Y=N, R_1=R_3=H, R_2=Ph	**53f**	58% (*exo* + *endo*)	**54f**
52g	X=Y=N, R_1=Cl, R_2=R_3=H	**53g**	-	**54g** -
52h	X=Y=N, R_1=2-furyl, R_2=R_3=H	**53h**	-	**54h** -
52i	X=Y=N, R_1=H, R_2=Cl, R_3=Allyl	**53i**	38%	**54i** 10%
52j	X=Y=N ,R_1=Cl ,R_2=H, R_3=Allyl	**53j**	80%	**54j** 20%
52k	X=Y=N, R_1=Cl, R_2=H, R_3=Me	**53k**	54%	**54k** 14%
52l	X=Y=N, R_1=2-Furyl, R_2=H, R_3=Allyl	**53l**	78 %	**54l** 15%

Scheme 1.28: Investigated IMDAF reactions on N-allyl-o-furylheteroarylamines[9]

The study was extended to include corresponding anilines **55a–k** (Scheme 1.29), results generally being in correspondence with earlier structure-reactivity relationship observations.[9] Overall, it was concluded that differences in number of heteroatoms in the substrate's aromatic ring had little effect on the likelihood of the IMDAF reaction occurring.



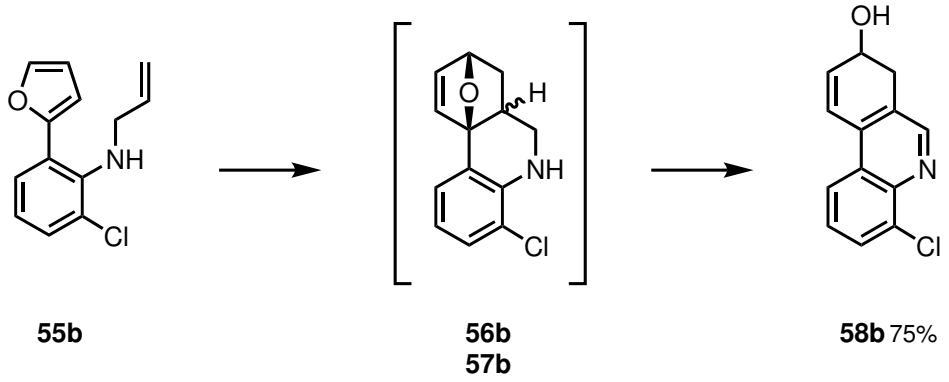
55a	R_1=R_2=R_3=H, R_4=H	**56a**	-	**57a**	-
55b	R_1=R_2, R_3=Cl, R_4=H	**56b**	33% (*exo* + *endo*)	**57b**	
55c	R_1=R_3, R_2=Cl, R_4=H	**56c**	-	**57c**	-
55d	R_1=Cl, R_3=R_2=H, R_4=H	**56d**	-	**57d**	-
55e	R_1=NO_2, R_3=R_2=H, R_4=H	**56e**	-	**57e**	-
55f	R_1=NO_2, R_2=H, R_3=Cl, R_4=H	**56f**	88 (*exo* + *endo*)	**57f**	
55g	R_1=R_2=R_3=H, R_4=Allyl	**56g**	not isolated[a]	**57g**	not isolated[a]
55h	R_1=R_2=H, R_3=Cl, R_4=Allyl	**56h**	not isolated[a]	**57h**	not isolated[a]
55i	R_1=NO_2, R_2=H, R_3=Cl, R_4=Me	**56i**	66%	**57i**	24%
55j	R_1=NO_2, R_2=H, R_3=Cl, R_4=Boc	**56j**	-	**57j**	-
55k	R_1=NO_2, R_2=H, R_3=Cl, R_4=Allyl	**56k**	76% (*exo* + *endo*)	**57k**	

Scheme 1.29: Investigated IMDAF reactions on N-allyl-o-furylanilines[9]
[a] ^{1}H-NMR of crude product shows < 1% unreacted starting material

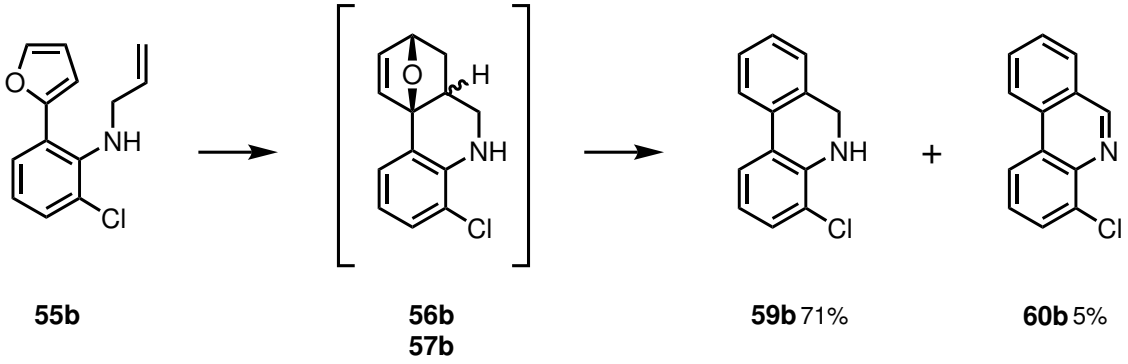
1.4.6 Ring-opening of the IMDAF adduct

On some occations, cyclization of substrate **55b** by heating in toluene produced the 7,8-dihydrophenanthridin-8-ol **58b** rather than the expected IMDAF adducts **56b** and **57b** (Scheme 1.30).[84] It was discovered that water in the toluene was catalyzing ring-opening of the adduct and subsequent oxidation of the N5-C6 bond. Furthermore, addition of 0.2 equivalents 0.5 M HCl resulted in full aromatization of the C-ring when the same compound was heated to 150 °C in acetonitrile in a microwave oven (Scheme 1.31).[10] The proposed general mechanism of this aromatization process involves opening of the 1,4-epoxy bridge to generate a cyclohex-1,3-dienol ring, followed by aromatization of the C-ring by elimination of water (Scheme 1.32).

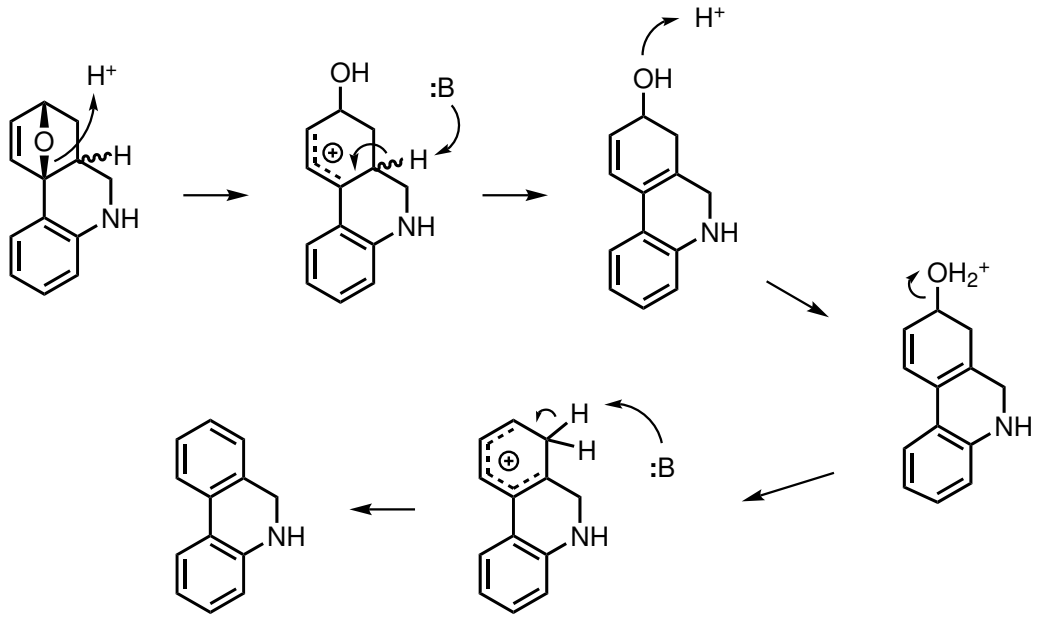
The ring-opening process provides several advantages. It opens the door to the possibility of producing interesting (aza)phenanthridines from IMDAF substrates like **52a–l** and **55a–k**. Furthermore, removal of the IMDAF adduct from solution prevents reversion back to the starting material by a retro DA reaction, increasing yields and potentially widening the substrate scope.



Scheme 1.30: Ring-opening of IMDAF adduct upon heating in wet toluene[84]



Scheme 1.31: Acid-catalyzed aromatization of the C-ring upon microwave heating in acetonitrile[10]

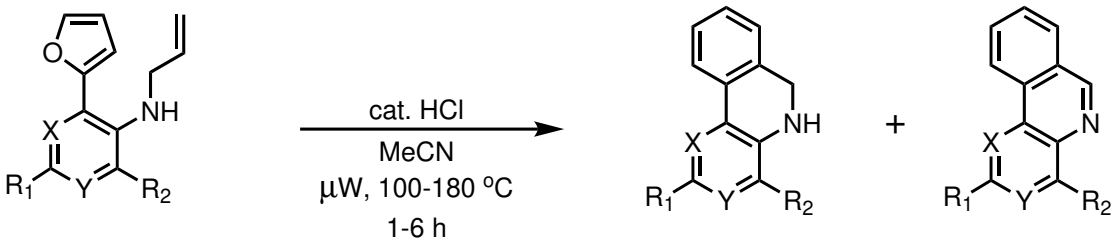


Scheme 1.32: Proposed general mechanism for acid-catalyzed aromatization of IMDAF adduct[11,84]

1.4.7 Microwave-mediated cyclization

The use of microwave irradiation is known to have a positive effect on certain intramolecular DA reactions. In some cases, substrates that are unreactive under conventional heating conditions are successfully cyclized in the microwave.[97,98] Investigation into microwave-mediated cyclization was therefore a natural continuation of our research.

Following an initial screening of solvents, degassed acetonitrile was found suitable for the purpose.[10] Upon cyclization in the presence of a catalytic amount of aqueous HCl, substrates **52a–d**,**g**,**m** and **55a–d**,**f**,**l** produced either 5,6-dihydro(aza)phenanthridines **59a–d**,**g**,**m** **61a–d**,**f**,**l** solely, or mixtures of these and corresponding (aza)phenanthridines **60a–d**,**g**,**m** **62a–d**,**f**,**l** (Scheme 1.33). Substrates **52a**,**g** and **55a**,**c**,**d**, which were unreactive by conventional heating, were now cyclized in high yields in the microwave oven. Thus, the requirement of an *ortho*-substituted or *N*,*N*-disubstituted substrate (Section 1.4.5) was no longer valid.



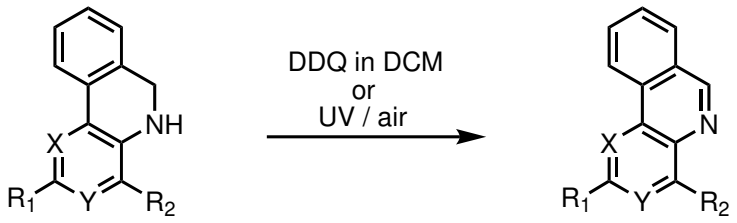
52a	X=N, Y=CH, R_1=R_2=H	**59a**	61%	**60a**	29%
52b	X=N, Y=CH, R_1=H, R_2=Cl	**59b**	86%	**60b**	9%
52c	X=CH, Y=N, R_1=H, R_2=Cl	**59c**	80%	**60c**	3%
52d	X=Y=N, R_1=H, R_2=Cl,	**59d**	86%	**60d**	-
52g	X=Y=N, R_1=Cl, R_2=H	**59g**	88%	**60g**	-
52m	X=N, Y=CCl, R_1=R_2=H	**59m**	80%	**60m**	-
55a	X=Y=CH, R_1=R_2=H	**61a**	55%	**62a**	14%
55b	X=Y=CH, R_1=H, R_2=Cl	**61b**	71%	**62b**	5%
55c	X=CH, Y=CCl, R_1=R_2=H	**61c**	63%	**62c**	20%
55d	X=Y=CH, R_1=Cl ,R_2=H	**61d**	62%	**62d**	29%
55f	X=Y=CH, R_1=NO_2, R_2=Cl	**61f**	92%	**62f**	-
55l	X=Y=CH, R_1=R_2=Cl	**61l**	95%	**62l**	-

Scheme 1.33: Microwave-mediated IMDAF reactions[10]

1.4.8 Oxidation of the N5-C6 bond

Because microwave cyclization yields 5,6-dihydro(aza)phenanthridines as the major product, development a method for the oxidation of the 5,6-dihydro(aza)phenanthridines into (aza)phenanthridines is desirable. There are numerous reports of this oxidation in the literature, for example using PCC[99] or activated MnO_2[76]. Aromatization of other partially saturated polycycles using DDQ is also known.[100,101]

While oxidation using activated MnO_2 was unsuccessful in our case,[84] DDQ in DCM was found to oxidize **59a–d**,**g**,**m** and **61a–d**,**f**,**l** to **60a–d**,**g**,**m** and **62a–d**,**f**,**l** within a few hours (Scheme 1.34).[10] Furthermore, oxidation was achieved by simply bubbling air through the microwave reaction mixture in the presence of UV-radition, although reaction times were significantly longer in some cases.[10] Both methods provided near full conversion to the (aza)phenanthridine.



59a–d,**g**,**m**
61a–d,**f**,**l**

60a–d,**g**,**m**
62a–d,**f**,**l**

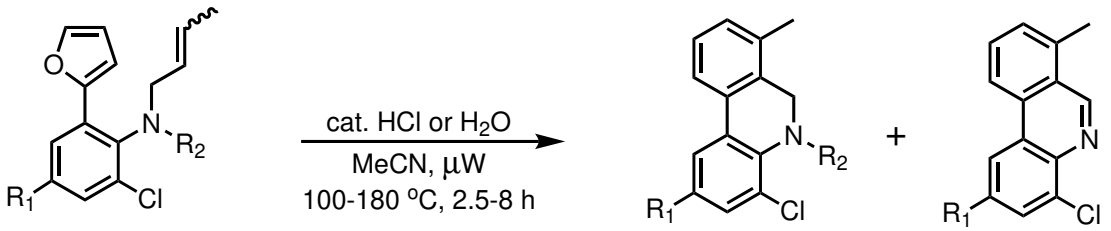
Scheme 1.34: Oxidation of the 5,6-dihydro(aza)phenanthridine N5-C6 bond

1.4.9 Synthesis of 7-methylphenanthridines

Functionalization of phenanthridines presented thus far has been limited to A-ring substitution and substitution at N5. A desire to extend the scope of functionalization sparked research into the synthesis of C-ring substituted derivatives.

By *N*-crotylation rather than *N*-allylation, substrates **63a**,**b** and **64a** were produced. When cyclized in the microwave oven, these substrates produced mixtures of 7-methyl-5,6-dihydrophenanthridines **65a**,**b** and 7-methylphenanthridines **67a**,**b** from **63a**,**b**, or the 5,7-dimethyl-5,6-dihydrophenanthridine **66a** from **64a**, in moderate to high yields (Scheme 1.35).[11] Compared to microwave-cyclization of the *N*-allyl substrates **55f**,**l**, *N*-crotyl substrates **63a**,**b** and **64a** require longer reaction times and/or higher temperatures to cyclize, indicating diminished reactivity when going from an allyl group to a crotyl group dienophile.

From the reaction mixture following cyclization, 7-methyl-5,6-dihydrophenanthridines **65a** were successfully oxidized by the UV/air method to produce 7-methylphenanthridines **67a**,**b**.[11] Resulting in a positively charged species, corresponding oxidation of the *N*-methylated counterpart **66a** is tougher and was not attempted. The use of *N*-alkylated substrates may be viewed as a method of producing stable 5,6-dihydrophenanthridines.



63a R_1=Cl, R_2=H
63b R_1=NO_2, R_2=H
64a R_1=Cl, R_2=Me

65a 77%
65b 85%
66a 66%

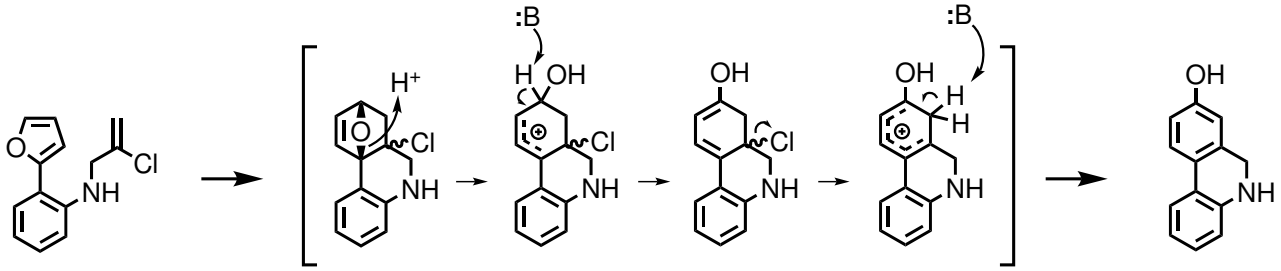
67a -[a]
67b -[a]

Scheme 1.35: 7-methylphenanthridines produced by cyclization of N-crotyl substrates[11]
[a] Observed by ^{1}H-NMR of crude product, but not isolated

1.4.10 Synthesis of phenanthridin-8-ols

Synthesis from *N*-(2-chloroallyl) substrates

Phenanthridin-8-ols may be synthesized by generating IMDAF adducts where aromatization of the C-ring occurs without elimination of water. The first strategy employed involved synthesis of *N*-(2-chloroallyl) substrates, where, upon cyclization, adducts were thought to aromatize by elimination of chloride rather than water (Scheme 1.36).[102] However, the strategy did not work as intended. Low yields of desired products were produced due to the formation of byproducts where both chloride and water was eliminated, leading to an unsubstituted C-ring. It is not clear by which mechanism such byproducts had formed.

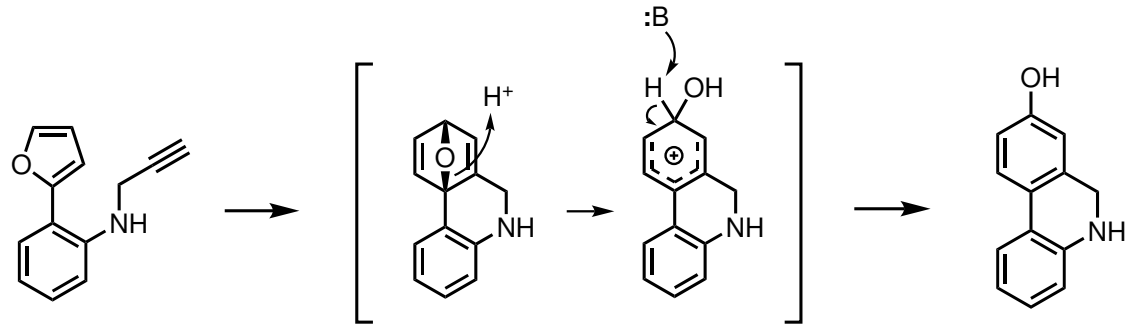


Scheme 1.36: Strategy for the synthesis of phenanthridin-8-ols from N-(2-chloroallyl) substrates

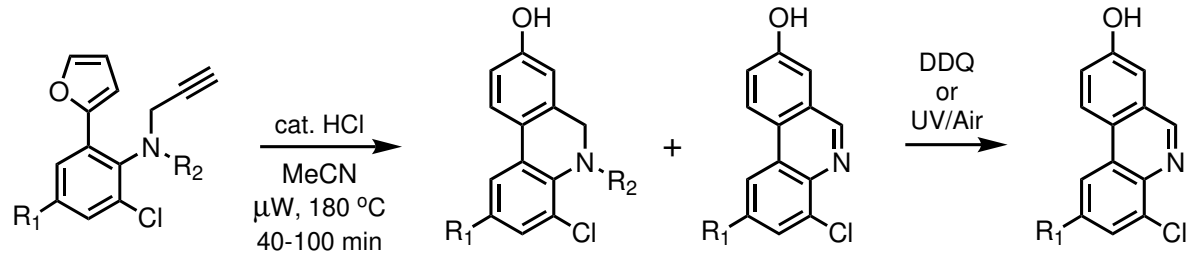
Synthesis from *N*-propargyl substrates

The next strategy deployed investigated substrates with alkyne dienophiles. Upon microwave cyclization of these, adducts with two double bonds in the C-ring are formed, enabling aromatization without elimination of water (Scheme 1.37). By *N*-propargylation, substrates **68b**,**e** and **69e** were prepared, producing upon cyclization mixtures of 5,6-dihydrophenanthridin-8-ols **70b**,**e** and phenanthridin-8-ols **72b**,**e** from **68b**,**e**, or the 5-methyl-5,6-dihydrophenanthridin-8-ol **71e** from **69**,

all in high yields (Scheme 1.38). As for the crotyl group, elevated reaction temperatures indicate diminished going from an allyl group to a propargyl group dienophile.



Scheme 1.37: Strategy for the synthesis of phenanthridin-8-ols from N-propargyl substrates



68b R_1=Cl, R_2=H
68e R_1=NO_2, R_2=H
69e R_1=NO_2, R_2=Me

70b
70e
71e 82%

72b
72e

72b 86%
72e 80%

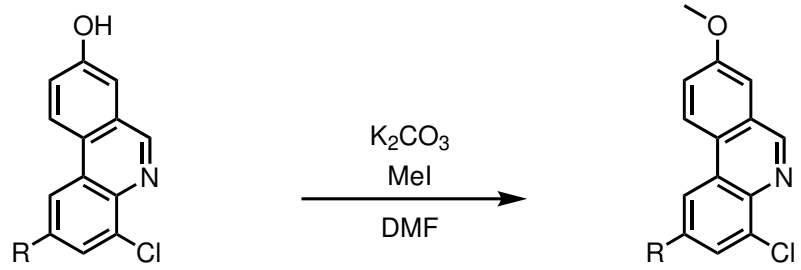
Scheme 1.38: Synthesis of phenanthridine-8-ols from N-propargyl substrates[?]

While UV/air oxidation of **70b** to **72b** occurred within a few hours, UV/air oxidation of **70e** to **72e** required 48 hours or more, leading to the preferred use of DDQ in DCM for the oxidation of the latter compound. Both oxidations afforded high yields of desired product.

1.4.11 Functionalization of phenanthridin-8-ols

Phenanthridin-8-ols are chemically analogous to phenols and undergo many of the same reactions. This opens the possibility for functionalization at oxygen. Deprotonation of the phenol under basic conditions leads to the phenolate anion, which may act as a nucleophile in various substitution reactions.

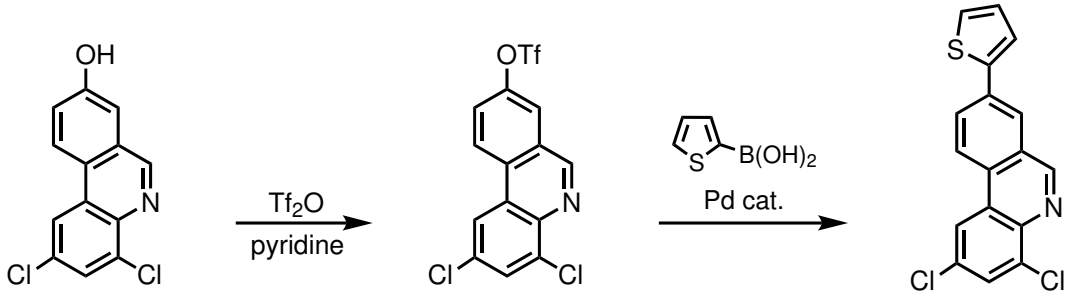
By treatment of phenanthridin-8-ols **72b**,**e** with potassium carbonate and methyl iodide in DMF, *O*-methylation was achieved, producing 8-methoxyphenanthridines **73b**,**e** (Scheme 1.39).[13] Similarly, triflation of 2,4-dichlorophenanhtridin-8-ol **72b** produced 2,4-dichlorophenanthridin-8-yl triflate **74b**, reacting with an organoboron compound in a Suzuki-Miyaura coupling reaction to produce 2,4-dichloro-8-(thiophen-2-yl)phenanthridine **75b** (Scheme 1.40).[13]



72b R=Cl
72e R=NO_2

73b 76%
73e 78%

Scheme 1.39: O-methylation of phenanthridin-8-ols[13]



72b **74b** **75b**

Scheme 1.40: Triflation followed by Suzuki-Miyaura coupling[13]

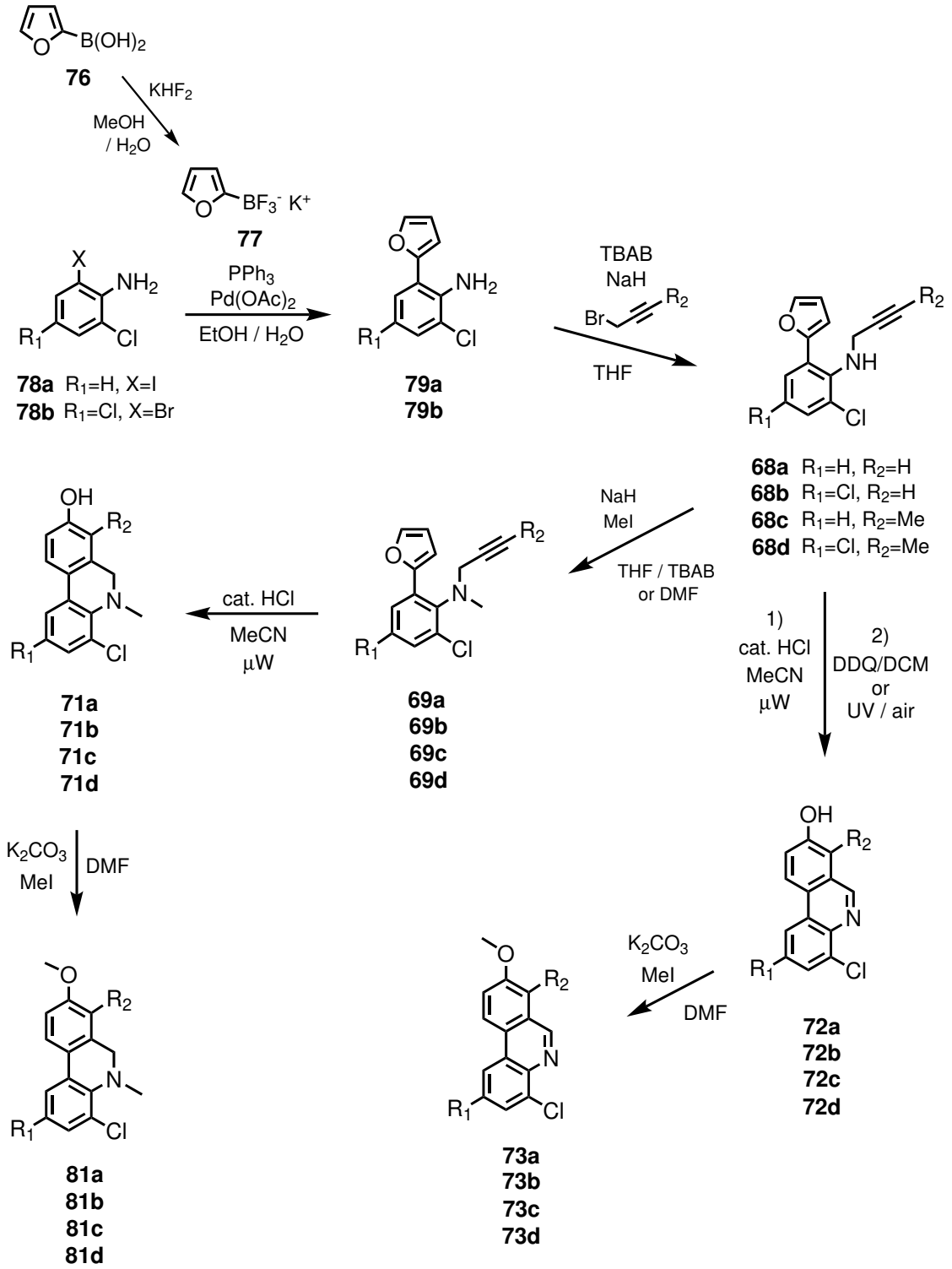
2 Results and discussion

2.1 Aim and strategy

A desire for production of novel phenanthridin-8-ol derivatives while furthering the development of the microwave-mediated intramolecular Diels-Alder on furan (IMDAF) method (Section 2.4) led to a strategy for the synthesis of phenanthridin-8-ols **72a–d**, 5,6-dihydrophenanthridin-8-ols **71a–d**, and their *O*-methylated counterparts **73a–d** and **81a–d** being devised (Scheme 2.1).

The work was aimed at supplementing previous research on three points. By utilizing 2-chloro-6-iodoaniline **78a** as starting material, the scope of the method would be expanded to include synthesis of novel 4-chlorophenanthridin-8-ols **72a**,**c**. The attachment of a but-2-ynyl rather than a propargyl group to *o*-furylanilines **79a**,**b** would produce novel phenanthridin-8-ols containing a 7-methyl group **72c**,**d**, and provide insight into the applicability of the IMDAF method to internal alkyne dienophiles. *N*-methylation of **68a–d** would lead to *o*-furyl-*N*-alkynyl-*N*-methylaniline substrates **69a–d**, which upon cyclization would provide novel 5-methyl-5,6-dihydrophenanthridin-8-ols **71a–d**.

While the original strategy included *O*-methylation of all phenanthridin-8-ol derivatives to produce novel 8-methoxyphenanthridines **73a–d** and **81a–d**, only compounds **81a**,**c** were produced due to the limited duration of the project.



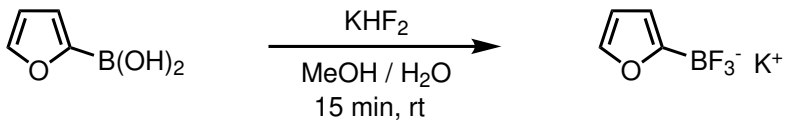
Scheme 2.1: Strategy for the synthesis of desired phenanthridin-8-ol derivatives

2.2 Synthesis of *o*-furylanilines

2.2.1 Preparation of (2-furyl)trifluoroborate

Organoboronic acids are important reagents in Suzuki-Miyaura coupling reactions.[86] Due to their Lewis acid properties, these compounds are unstable, reacting with atmospheric oxygen at room temperature.[103,104] In addition, (furan-2-yl)boronic acid **76** in particular is susceptible to protodeboronation in protic media,[105,106] limiting its use in Suzuki-Miyaura reactions carried out in ethanol. Converting the acid to a more stable salt before use is therefore desirable.

Using a literature procedure,[106] (furan-2-yl)boronic acid **76** was converted to potassium (furan-2-yl)trifluoroborate **77** in high yield by adding aqueous potassium hydrogendifluoride to the compound dissolved in methanol (Scheme 2.2).

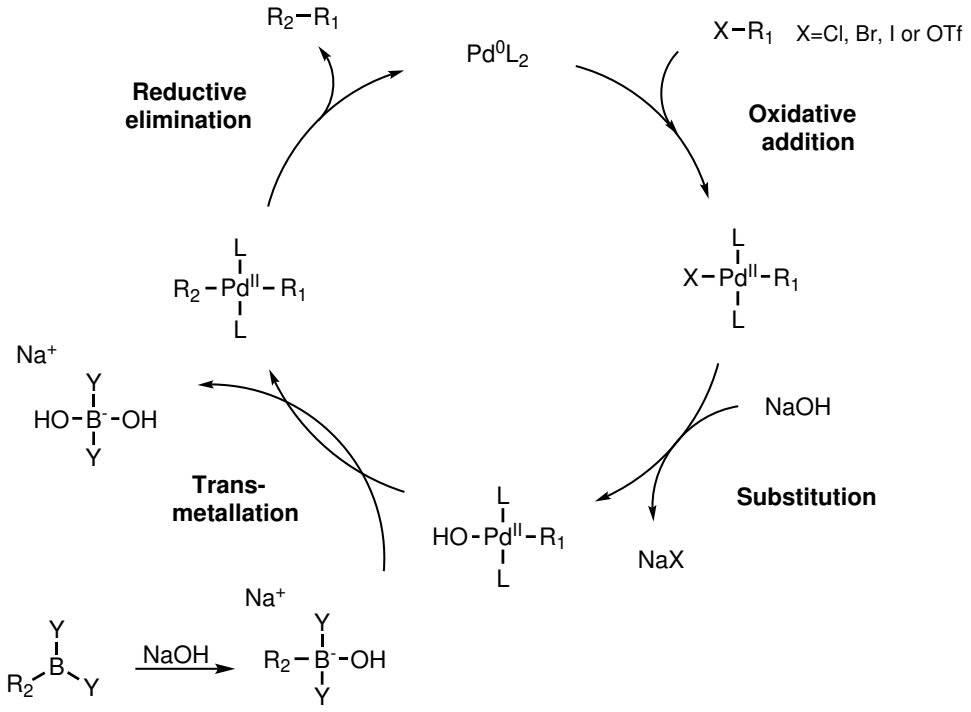


Scheme 2.2: Synthesis of potassium (furan-2-yl)trifl

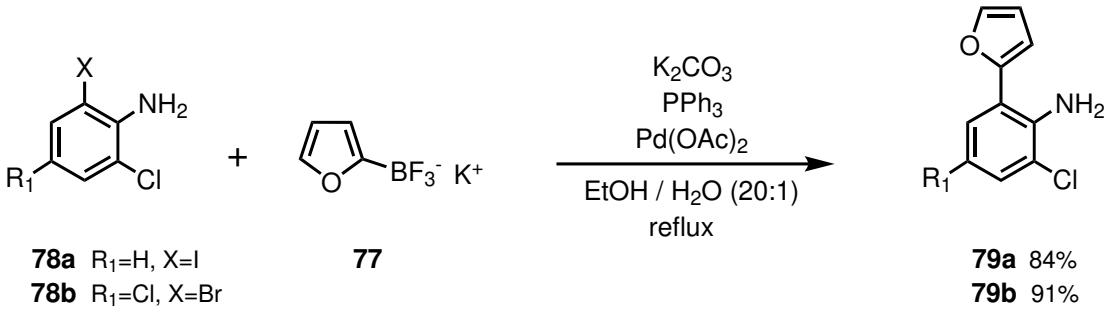
2.2.2 Suzuki-Miyaura coupling of haloanilines and (2-furyl)trifluoroborate

Reported in 1979,[107] The Suzuki-Miyaura reaction is a palladium-catalyzed coupling reaction between a vinyl or aryl halide and an oranoboron compound.[86,108,109] Offering C-C bond formation under mild conditions using easily avialable and environmentally friendly boronic acids, the reaction has achieved great popularity,[109] culminating in Akira Suzuki being awarded the Noble Prize in chemistry 2010.[110]

It is generally accepted that the reaction mechanism involves four steps (Scheme 2.3).[86,108,109] The ligand-bound palladium(0) atom undergoes oxidative addition by inserting between the R_1 group and halogen of a vinyl or aryl halide. Substitution of the halide with the more nucleophilic hydroxide enables transmetallation on the organoboron R_2 group, transferring R_2 to palladium in exchange for the hydroxide. Finally, the C-C bond is formed by reductive elimination, completing the catalytic cycle. The ligand (L) is commonly a phosphine, often triphenylphosphine, although a wide range of more complex ligands have been developed over the years.[108] While Suzuki-Miyaura reactions are commonly carried out in straight ethanol, trifluoroborate salts require the presence of water, likely due to the need for *in situ* hydrolysis prior to transmetallation.[111]



Scheme 2.3: Generally accepted mechanism of the Suzuki-Miyaura reaction[108,109]



Scheme 2.4: Suzuki-Miyaura coupling of haloanilines and potassium (furan-2-yl) trifluoroborate

Table 2.1: Reaction conditions for Suzuki-Miyaura coupling of haloanilines and potassium (furan-2-yl)trifluoroborate

entry	sm	$Pd(OAc)_2$ (eq)	PPh_3 (eq)	Reaction time (h)	Unreacted sm (%)[a]	Isolated yield **79** (%)
1	**78a**	0.05	0.25	12	15	69
2	**78a**	0.10	0.40	25	< 1	84
3	**78b**	0.05	0.25	6	< 1	91

[a] Estimated from ^{1}H-NMR spectrum of crude product

By refluxing in a weakly basic 20:1 ethanol/water mixture in the presence of palladium acetate and triphenylphosphine, haloanilines 2-chloro-6-iodoaniline **78a** and 2-bromo-4,6-dichloroaniline **78b** reacted with potassium (furan-2-yl)trifluoroborate **77** to produce corresponding *o*-furylanilines **79a** and **79b** in high yields (Scheme 2.4).

The synthesis of **79b** was performed using reaction conditions optimized in previous work (Table 2.1, entry 3).[10] Previously reported synthesis of **79a**, however, was performed using Stille coupling rather than Suzuki-Miyaura coupling.[9] When introduced to the same conditions as **78b**, conversion of **78a** to **79a** was incomplete and isolated yield moderate despite increased reaction time (entry 1). Upon doubling the amount of catalyst and leaving the reaction overnight, full conversion was achieved and satisfactory yield obtained (entry 2).

In the oxidative addition step, the nucleophilic-like attack of Pd(0) on the halide is favored by a low electron density around the halide carbon.[89]. This provides a good explanation of the higher reactivity of **78b** compared to **78a**, as the additional chloro-group of **78b** withdraws electrons from the ring.

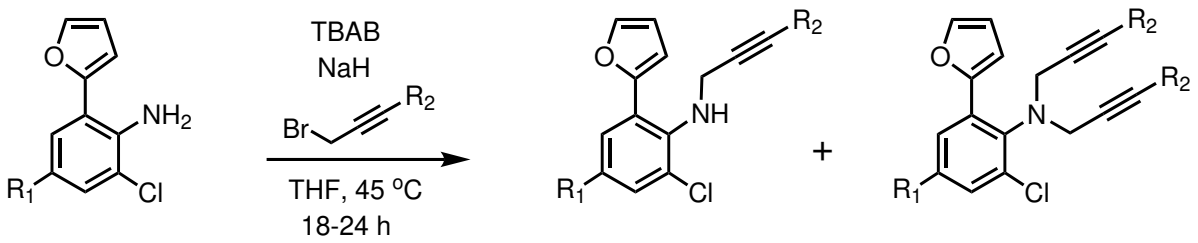
2.3 *N*-alkylation reactions

2.3.1 Synthesis of *o*-furyl-N-alkynylanilines

N-alkylation of anilines may be achieved by nucleophilic substitution where aniline acts as the nucleophile. Accordingly, *N*-alkylated *o*-furylanilines are produced by reaction of the aniline with an alkyl halide in presence of a base.

In previous work, synthesis of IMDAF substrates **55a**,**b**,**d–f**,**l** (Section 1.4.5) by *N*-allylation was attempted under various conditions in different solvents.[9,10,84] The allylations were challenging due to the ease of which *N*,*N*-diallylated byproducts formed, requiring fine tuning of reaction conditions to optimize yields of desired product. Although some success was achieved using Hünig's base with catalytic HCl or sodium/potassium hydride in toluene with 18-crown-6, the preferred method for subsequent synthesis of *N*-crotyl substrates **63a**,**b** (Section 1.4.9) and *N*-propargyl substrates **68b**,**e** (Section 1.4.10) was using tetrabutylammonium bromide (TBAB) and sodium hydride in THF.[11,13] This method was now carried over to the synthesis of *o*-furyl-*N*-alkynylanilines **68a–d** (Scheme 2.5).

Following the literature procedure for synthesis of **68b**,[13] significant amounts of unconverted starting material remained, despite allowing the reaction to run for several additional hours (Table 2.2, entry 5). An optimization study was therefore initiated, leaving the reaction overnight using varying amounts of sodium hydride and propargyl bromide to determine reaction conditions providing full conversion of starting material while minimizing the amount of *N*,*N*-dialkylated byproduct formed (entries 6 to 9). Best results were obtained using a slight excess of propargyl bromide and a larger excess of NaH (entry 8).



Scheme 2.5: N-alkynylation of o-furylanilines

Table 2.2: Optimization of N-alkynylation reaction conditions

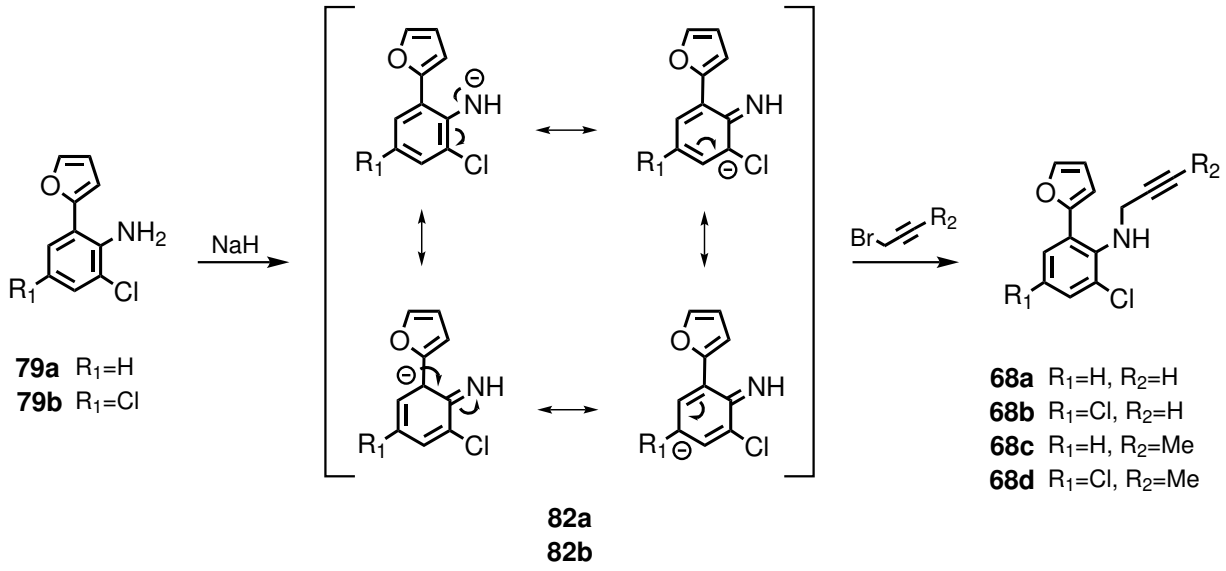
Entry	sm	NaH (eq)	Br–R2 (eq)	Unreacted sm (%)[a]	Conversion to **80** (%)[a]	Isolated yields **68** (%)	**80** (%)
1	**68a**	1.8	1.3	19	4	62	3
2	**68a**	1.8	1.8	20	4	51	3
3	**68a**	2.8	1.3	< 1	12	73	7
4	**68a**	2.8	1.3	< 1	18	57	14
5[b]	**68b**	1.8	1.6	16	4	56	3
6	**68b**	1.2	1.3	52	2	44	-
7	**68b**	1.2	1.8	29	3	52	-
8	**68b**	1.8	1.3	< 1	10	75	6
9	**68b**	1.8	1.8	< 1	14	62	8
10	**68c**	2.7	1.3	< 1	5	88	5
11	**68d**	1.8	1.3	2	8	88	4

[a] Estimated from ^{1}H-NMR spectrum of crude product

[b] Reaction time: 6 h

Extension of the optimization study to the synthesis of **68a** (Table 2.2, entries 1 to 4) revealed how the best results were achieved by simply increasing the amount of base, leaving other parameters intact (entry 3). A possible explanation of this base concentration-reactivity relationship is formation of an anilide anion intermediate as a key step in the reaction (Scheme 2.6). It is known that protonated *para*-chloroaniline (pK_a = 4.0) is a stronger acid than protonated aniline (pK_a = 4.6),[112] which may be understood by the *para*-chloro group exerting a stabilizing effect on resonance contributors of the conjugate base due to withdrawal of electrons from the ring. Accordingly, a case can be made for an even greater stabilizing effect by the *para*-chloro group on the negatively charged anilide anion **82b**, making **79b** more acidic than **79a**, thus explaining its increased reactivity per base equivalent.

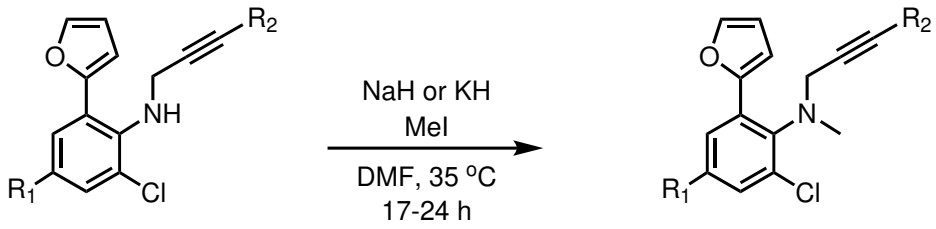
Applying the optimized procedures to the reaction on but-2-ynyl bromide produced compounds **68c** and **68d** (Table 2.2, entries 10 and 11) in high yields, proving that the change of electrophile has little effect on the outcome of the reaction. The higher yields obtained were due to slightly higher conversion to desired product and a somewhat easier purification process.



Scheme 2.6: Formation of an anilide anion intermediate

2.3.2 Synthesis of *o*-furyl-*N*-alkynyl,*N*-methylanilines

Synthesis of *o*-furyl-*N*-alkynyl-*N*-methylanilines **69a–d** was achieved by treatment of *o*-furyl-*N*-alkynylamines **68a–d** with sodium or potassium hydride and methyl iodide (Scheme 2.7). While initial trials using tetrabutylammonium iodide (TBAI) and sodium hydride in THF gave unsatisfactory conversion, switching to DMF as solvent provided much improved results. As formation of *N*,*N*-dialkylated byproducts was no longer an issue, an excess of methyl iodide could be used, and the optimization process consisted of finding the appropriate type and amount of base for the various starting materials when left to react overnight (Table 2.3).



68a R_1=H, R_2=H
68b R_1=Cl, R_2=H
68c R_1=H, R_2=Me
68d R_1=Cl, R_2=Me

69a 78%
69b 83%
69c 83%
69d 82%

Scheme 2.7: N-methylation of o-furyl-N-alkynylanilines

Table 2.3: Optimization of N-methylation reaction conditions

Entry	sm	NaH (eq)	KH (eq)	Unreacted sm (%)[a]	Isolated yield **69** (%)
1	**69a**	2.7	-	31	54
2	**69a**	4.2	-	11	58
3	**69a**	6.0	-	3	78
4	**69b**	1.8	-	2	77
5	**69b**	2.7	-	< 1	83
6	**69c**	6.0	-	31	60
7	**69c**	-	3.1	< 1	83
8	**69d**	2.7	-	< 1	82

[a] Estimated from ^{1}H-NMR spectrum of crude product

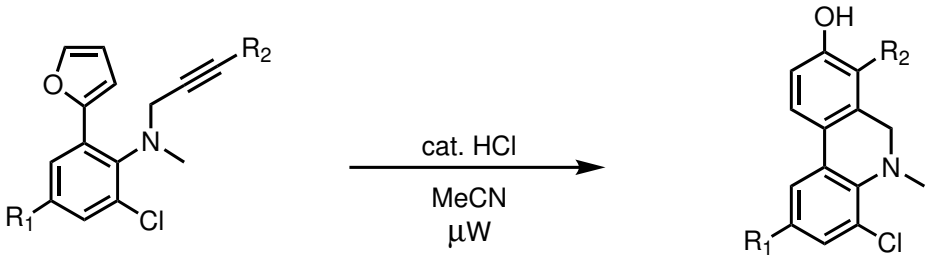
The base concentration-reactivity trend in preceeding *N*-alkynylation reactions (Section 2.3.1) persisted: Less base was needed for full conversion of starting materials containing a *para*-chloro group. Using amounts of sodium hydride comparable to the preceeding *N*-alkynylation reactions, full conversion of **68b** and **68d** was reached (Table 2.3, entries 5 and 8). Conversions of **68a** and **68c**, however, were incomplete under these conditions. Further experiments revealed that full conversion of **68a** was achievable by using a larger excess of sodium hydride (entry 3), while the stronger base potassium hydride was required for **68c** (entry 7).

Being able to use NaH for the *N*-methylation of **68a** was fortunate, as previous work on *N*-methylation of *N*-propargyl analogue **68** using potassium hydride had resulted in methylation at terminal alkyne. Containing an internal rather than terminal alkyne, *N*-methylation of **68c** does not suffer from this issue, allowing potassium hydride to be used without problems.

2.4 IMDAF reactions

2.4.1 Synthesis of 5-methyl-5,6-dihydrophenanthridin-8-ols

Following the preparation of substrates **68a–d** and **69a–d**, research was now directed towards the key step in the reaction sequence: Cyclization of these by means of a microwave-mediated intramolecular Diels-Alder on furan (IMDAF) reaction (Section 1.4). The first reactions investigated were cyclizations of *o*-furyl-*N*-alkynyl-*N*-methylanilines **69a–d**, producing 5-methyl-5,6-dihydrophenanthridin-8-ols **71a–d** in moderate to high yields (Scheme 2.8).



69a R_1=H, R_2=H
69b R_1=Cl, R_2=H
69c R_1=H, R_2=Me
69d R_1=Cl, R_2=Me

71a 89%
71b 71%
71c 70%[a]
71d 60%

Scheme 2.8: IMDAF cyclization of o-furyl-N-alkynyl-N-methylanilines
[a] Ca. 1% mol/mol trace of dichloromethane subtracted from weighed yield

The progress of these cyclizations was mapped by ^{1}H-NMR spectroscopy analysis of reaction mixture samples taken throughout the course of the reaction (Figure 2.1). At the reaction temperature of 180 °C used in earlier work,[13] cyclization of *o*-furyl-*N*-propargyl-*N*-methylaniline substrates **69a** and **69b** reached full conversion within three hours. The *N*-but-2-ynyl analog **69c**, however, proceeded notably slower, leaving twenty five percent unreacted starting material after eight hours reaction time. Clearly, substitution of a methyl group at the alkyne decreases reactivity of *N*-alkynyl-*N*-methyl substrates significantly, possibly due to the methyl group increasing the electron density of the dienophile, making reaction with the electron-rich furyl diene less favorable. By increasing the temperature to 200 °C, full conversion of **69c** and **69d** was achieved within six and seven hours respectively.

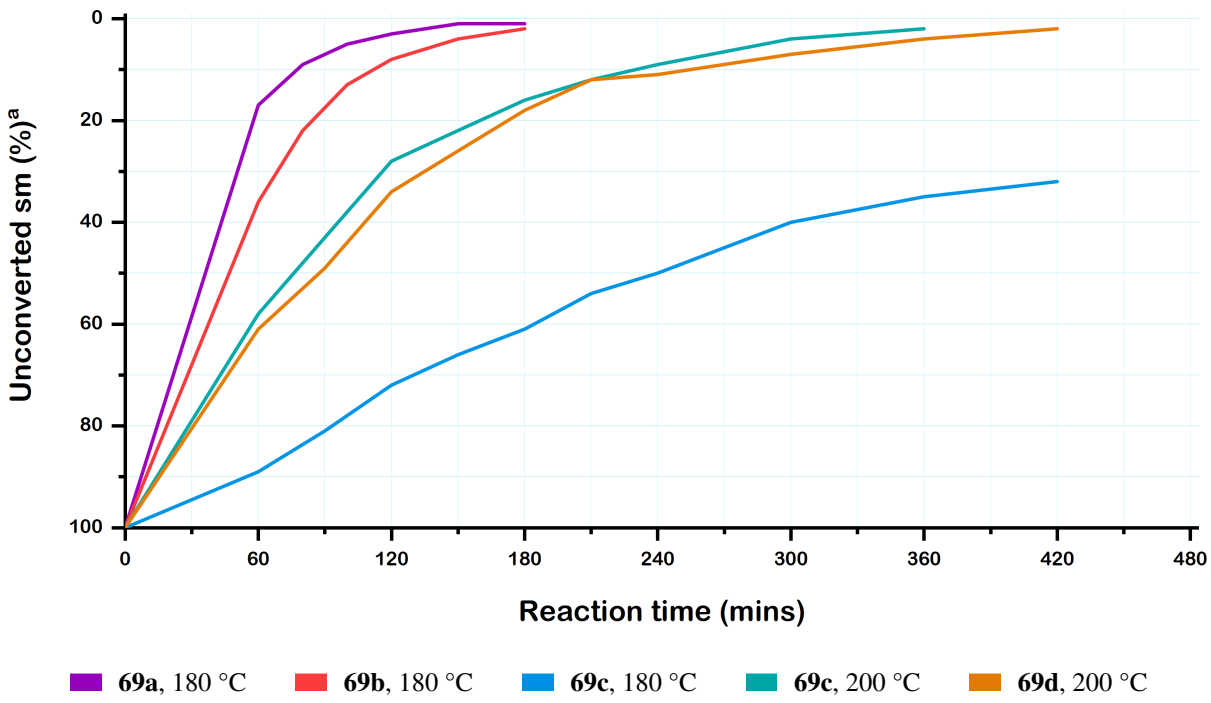


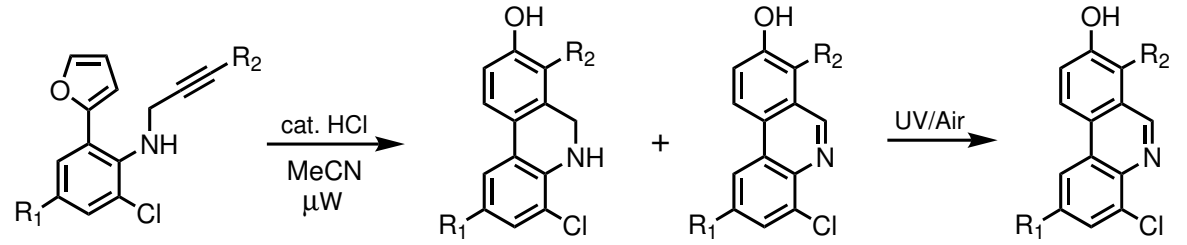
Figure 2.1: Progress of IMDAF cyclization of o-furyl-N-alkynyl-N-methylanilines at various temperatures
[a] Estimated from ^{1}H-NMR spectrum of reaction mixture

Looking at isolated yield percentages (Scheme 2.8), two apparent trends were revealed: Diminished yield by substitution of methyl at terminal alkyne and by attachment of a *para*-chloro group to the substrate. The validity of the former trend is supported by greater amounts of byproducts and decomposition observed in the crude product ^{1}H-NMR spectrum following cyclization of *N*-(but-2-ynyl)-*N*-methyl **69c**,**d** compared to *N*-propargyl-*N*-methyl **69a**,**b** substrates, also indicated by a marked darkening of the reaction mixture. In addition to lower conversion to desired product, byproducts and decomposition complicates the purification process, diminishing yields further. In this respect, results are in accordance with comparable previous research, showing how yields are diminished when going from *N*-allyl substrates **55l**,**55f** (Section 1.4.7) to corresponding *N*-crotyl substrates **63a**,**63b** (Section 1.4.9), or from *N*-propargyl subtrates **68a**,**b** to *N*-(but-2-ynyl) analogs **68c**,**d** (Section 2.4.2). A reasonable explanation for this structure-reactivity relationship is thermal decomposition caused by the harsher conditions of *N*-(but-2-ynyl)-*N*-methyl cyclizations, requiring higher temperatures and longer reaction times than cyclizations of their *N*-propargyl-*N*-methyl counterpart.

As for diminished yield by attachment of a *para*-chloro group to the substrate, this trend is of a more dubious nature. The trend is not observed for cyclization of *N*-allyl analogs **55b** and **55l** (Section 1.4.7) or *N*-alkynyl analogs **68a**,**c** and **68b**,**d** (Section 2.4.2). Furthermore, crude product ^{1}H-NMR spectra do not display significant differences in amounts of byproducts or decomposition following cyclization of corresponding substrates with **69b**,**d** or without **69a**,**c** the *para*-chloro group. The trend is therefore likely to stem from differences in the quality of purification or uncontrollable variables, and should not be considered a valid structure-reactivity relationship.

2.4.2 Synthesis of phenanthridin-8-ols

Microwave-mediated IMDAF cyclization of *o*-furyl-*N*-alkynylanilines produces mixtures of 5,6-dihydrophenanhtridin-8-ols and phenanthridine-8-ols, of which the 5,6,-dihydrophenanthridin-8-ols are further oxidized to phenanthridine-8-ols by treatment with DDQ/DCM or UV/air (Section 1.4.10).[13] Following this procedure, phenanthridine-8-ols **72a–d** were synthesized from *o*-furyl-*N*-alkynylanilines **68a–d** in variable yields (Scheme 2.9).



68a R_1=H, R_2=H	**70a**	**72a**	**72a** 72%
68b R_1=Cl, R_2=H	**70b**	**72b**	**72b** 77%[a]
68c R_1=H, R_2=Me	**70c**	**72c**	**72c** 47%[b]
68d R_1=Cl, R_2=Me	**70d**	**72d**	**72d** 42%

Scheme 2.9: IMDAF cyclization and of o-furyl-N-alkynylanilines
[a] Ca. 4% mol/mol trace of ethyl acetate subtracted from weighed yield
[b] Ca. 4% mol/mol trace of ethyl acetate subtracted from weighed yield

Mapping of the reaction progress for cyclization of *N*-alkynyl substrates **68a–d** by ^{1}H-NMR spectroscopy (Figure 2.2) revealed a structure-reactivity relationship similar to what was observed for their *N*-methylated counterparts **68a–d** (Section 2.4.1): Substitution of a methyl group at terminal alkyne decreases reactivity significantly, requiring elevated temperatures and longer reaction times for cyclization.

Comparing the reactivity of *N*-alkynyl **68a–d** (Figure 2.2) and corresponding *N*-alkynyl-*N*-methyl **69a–d** (Figure 2.1) substrates in these cyclizations show slightly diminished reactivity upon *N*-methylation. Previous research encourages this finding, reporting higher yield from cyclization of the *N*-allyl substrate **55f** compared to the corresponding *N*-allyl-*N*-methyl substrate **55i** (Section 1.4.5).[9]

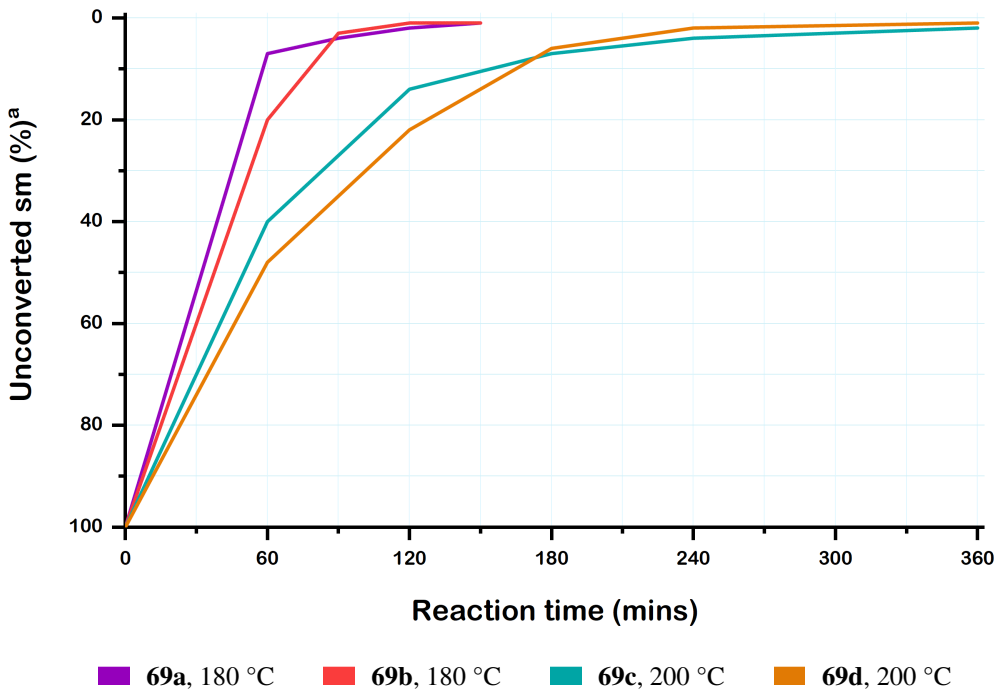


Figure 2.2: Progress of IMDAF cyclization of o-furyl-N-alkynylanilines at various temperatures
[a] Estimated from ^{1}H-NMR spectrum of reaction mixture

Following cyclization of **68a** and **68c**, two methods for oxidation of the reaction mixture were evaluated: DDQ/DCM and UV/air (Section 1.4.8). The DDQ method of oxidation has previously been successfully applied to a wide range of 5,6-dihydrophenanthridines, generally completing within a few hours.[10–13] While being a more elegant and environmentally friendly alternative, the UV/air method is not as universally applicable, requiring several days for full conversion in some cases. A desire for development of the more universal method led to DDQ being investigated first.

While previous oxidation of **70b** had provided high yields of **72b**,[13] attempts at applying this method to **70a** and **70c** were dissatisfying. The crude product was hard to dissolve, leading to heavy tailing of desired product upon purification by flash chromatography, complicating separation from residual DDQ. This provided isolated yields of merely 45 and 10 percent of **72a** and **72c** respectively. While improved purification is likely to increase yields, the method was discontinued for practical reasons.

Moving on to UV/air oxidation, thin-layer chromatography indicated full conversion of **70a** and **70** within a few hours. The resulting crude products were cleaner and easier to dissolve, simplifying the purification process. UV/air oxidation was deemed a more practical and elegant method, and thus became the method of choice for synthesis of phenanthridin-8-ols **72a–d**.

Cyclization of *N*-(but-2-ynyl) substrates **68c**,**d** provides diminished isolated yield compared to *N*-propargyl substrates **68a**,**b**, confirming the structure-reactivity relationship observed for the cyclization of corresponding *N*-alkynyl-*N*-methyl substrates (Section 2.4.1). Crude product ^{1}H-NMR spectra show increased amounts of byproducts and decomposition formed in the cyclization of *N*-(but-2-ynyl) substrates, again likely due to thermal decomposition at elevated temperatures

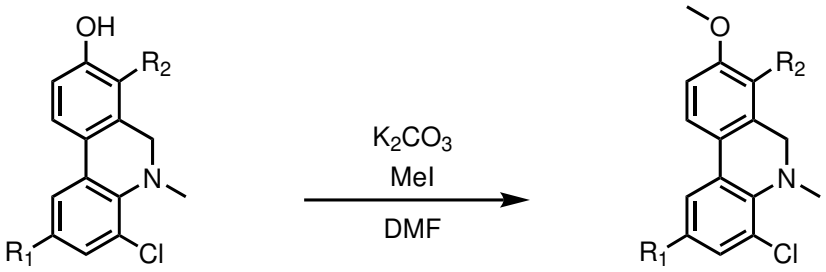
and longer reaction times. Separation of desired product from certain byproducts was difficult, diminishing yields further.

Due to common occurrence of residual grease in isolated products, phenanthridin-8-ols are routinely washed with *n*-pentane.[13] Weighing of isolated products before and after washing of compounds **72a**–**d** revealed losses of up to 15%. Higher yields may be obtained by improving the washing process or eliminating it altogether.

2.5 *O*-methylation reactions

2.5.1 Synthesis of 8-methoxy-5-methyl-5,6-dihydrophenanthridines

Comparable to phenols, phenanthridin-8-ols may be functionalized at oxygen (Section 1.4.11). Accordingly, *O*-methylation is achieved by treating the phenanthridin-8-ol with potassium carbonate and methyl iodide in DMF.[13] Using this method, 8-methoxy-5-methyl-5,6-dihydrophenanthridines **81a** and **81c** were synthesized from 5-methyl-5,6-dihydrophenanthridin-8-ols **71a** and **71c** (Scheme 2.10).



71a R_1=H, R_2=H
71c R_1=H, R_2=Me

81a 78%
81c 48%

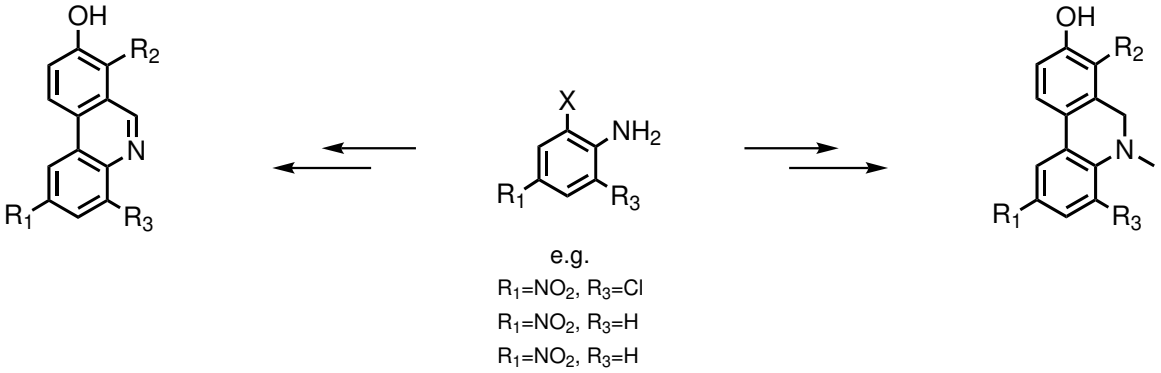
Scheme 2.10: O-methylation of 5-methyl-5,6-dihydrophenanthridin-8-ols

There were clear differences in the reactivity of **71a** and **71c** in this *O*-methylation. When allowed to react for six hours at ambient temperature, no remaining amount of **71a** was detected by ^{1}H-NMR analysis of the crude product. On the other hand, subjecting **71c** to the same reaction conditions left thiry four percent unreacted starting material. A reasonable explanation for this is the steric influence of a methyl group *ortho* to the phenol, hindering the phenolate nucleophile from approaching methyl iodide in what is likely to be a S_N2 nucleophilic substitution reaction.

Unfortunately, further optimization and extension of *O*-methylation reactions was not undertaken due to the limited duration of the project. Continuation of this work in future research is encouraged.

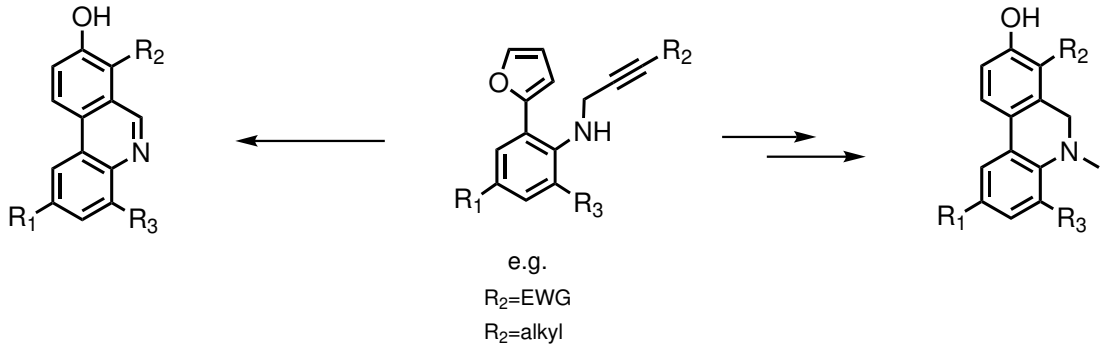
3 Future research

The A-ring substitution pattern of phenanthridin-8-ols synthesized by means of the IMDAF method stem from the aniline starting materials. By deploying different anilines, phenanthridin-8-ol analogs with a variety of substitution patterns in the A-ring may be synthesized (Scheme 3.1).

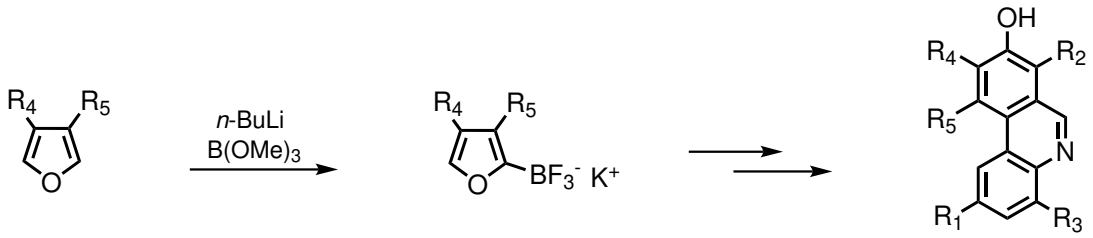


Scheme 3.1: Functionalization of the A-ring from haloaniline substitution patterns

Variations in the alkyne dienophile of *o*-furyl-*N*-alkynylaniline substrates provides phenanthridin-8-ols substituted at R_2 (Scheme 3.2). As cycloaddition of electron-poor dienophiles to electron-rich furyl dienes should increase reactivity (Section 1.4.3), attaching electron-withdrawing groups to R_2 should be feasible. Substitution of new alkyl groups at R_2 may also be explored, although it has been demonstrated in this work that substitution of methyl at this position causes diminished yields.



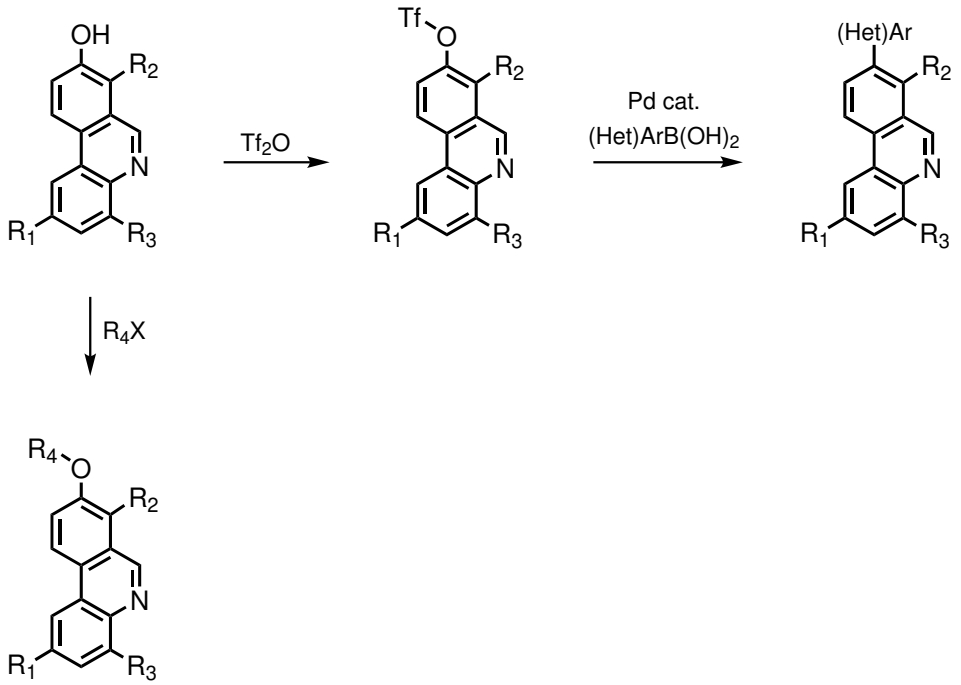
Scheme 3.2: Functionalization of the C-ring by substitution at R_2



Scheme 3.3: Use of alkylfuranes leading to novel C-ring functionalized phenanthridin-8-ols

Another pathway to enriching the scope of functionalization is preparation of substituted potassium (furan-2-yl)trifluoroborates, which following Suzuki-Miyaura coupling with haloanilines, *N*-alkynylation and IMDAF cyclization would produce phenanthridin-8-ols further substituted in the C-ring (Scheme 3.3). While this pathway has not yet been explored, implementation should be straightforward, as procedures for synthesis of potassium (furan-2-yl)trifluoroborates from commercially available alkylfuranes have been reported in recent literature.[113]

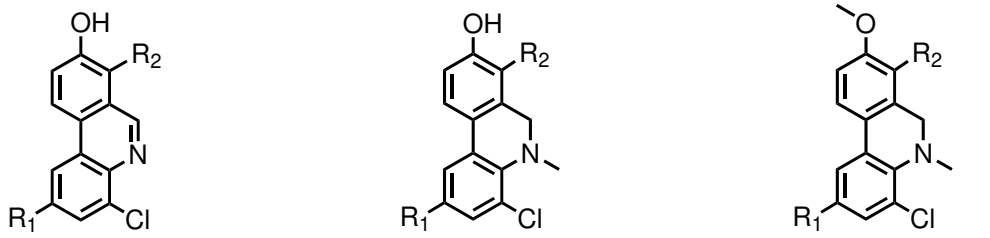
Finally, reactions at oxygen of phenanthridin-8-ols (Section 1.4.11) provide opportunities for further functionalization at C8 (Scheme 3.4). Synthesis of 8-methoxyphenanthridines described in literature[13] and herein (Section 2.5) demonstrate the potential for *O*-alkylation by treatment with an alkyl halide. Furthermore, it has been demonstrated that reaction with triflic anhydride produces (phenanthridin-8-yl)triflates undergoing Suzuki-Miyaura coupling with organoboron compounds, enabling attachment of (hetero)aryl groups at the 8-position.[13]



Scheme 3.4: Various functionalization at oxygen for future research

4 Conclusion

Deploying a microwave-mediated intramolecular Diels-Alder on furan (IMDAF) reaction as the key step, ten phenanthridin-8-ol derivatives **72a**–**d** **71a**–**d** **81a**,**c** (Scheme 4.1), whereof nine not previously reported in the literature, were successfully synthesized from readily available starting materials.



72a R_1=H, R_2=H
72b R_1=Cl, R_2=H
72c R_1=H, R_2=Me
72d R_1=Cl, R_2=Me

71a R_1=H, R_2=H
71b R_1=Cl, R_2=H
71c R_1=H, R_2=Me
71d R_1=Cl, R_2=Me

81a R_1=H, R_2=H

81e R_1=H, R_2=Me

Scheme 4.1: Phenanthridin-8-ol derivatives synthesized in this work

Following preparation of potassium (furan-2-yl)trifluoroborate **77** from (furan-2-yl)boronic acid **76**, *o*-furylanilines **79a**,**b** were made by Suzuki-Miyaura coupling of the borate to haloanilines **78a**,**b**. Reaction of these *o*-furylanilines with propargyl or (but-2-ynyl) bromide produced *o*-furyl-*N*-alkynylanilines **68a**–**d**, substrates for the IMDAF reaction. By additional *N*-methylation of **68a**–**d**, the library of IMDAF substrates was extended to include *o*-furyl-*N*-alkynyl-*N*-methylanilines **69a**–**d**. Each step in the substrate preparation parthway was optimized and high yielding.

Upon IMDAF cyclization followed by UV/air oxidation, *o*-furyl-*N*-alkynylaniline substrates **68a**–**d** produced phenanthridin-8-ols **72a**–**d**. Analogously, IMDAF cyclization of *o*-furyl-*N*-alkynyl-*N*-methylated substrates **69a**–**d** yielded 5-methyl-5,6-dihydrophenanthridin-8-ols **71a**–**d**, which were not oxidized further.

Investigation into the reactivity of the various substrates undergoing IMDAF cyclization revealed a clear structure-reactivity relationship: Reactivity was significantly diminished when going from *N*-propargyl substrates **68a**,**b** and **69a**,**b** to corresponding *N*-(but-2-ynyl) substrates **68a**,**b** and **69a**,**b**. As a consequence, cyclization of *N*-(but-2-ynyl) substrates required elevated temperatures and longer reaction times for full conversion, leading to increased amounts of byproducts and decomposition, affecting yields negatively. While cyclization of *N*-propargyl substrates into phenanthridin-8-ols **72a**,**b** and 5-methyl-5,6-dihydrophenanthridin-8-ols **71a**,**b** were generally high yielding, cyclization of corresponding *N*-(but-2-ynyl) substrates into 7-methylphenanthridin-8-ols **72c**,**d** and 5,7-dimethyl-5,6-dihydrophenanthridin-8-ols **71c**,**d** therefore provided modest yields only.

Possible explanations of this relationship include steric hindrance by the terminal methyl group and diminished reactivity of the more electron-rich *N*-(but-2-ynyl) dienophile in cycloaddition to the electron-rich furyl diene.

To conclude the research, *O*-methylation of 5-methyl-5,6-dihydrophenanthridines **71a**,**c** provided 8-hydroxy-5-methyl-5,6-dihydrophenanthridines **81a**,**c**. Under the same conditions, **71c** was significantly less reactive than **71a**, presumably due to steric hindrance by the 7-methyl group. The *O*-methylations serve as examples of functionalization at oxygen of phenanthridin-8-ol derivatives, a promising subject for future research.

5 Experimental

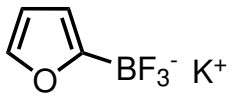
^{1}H-NMR and ^{13}C-NMR spectra were recorded using Bruker AVIII400 (400 and 100 MHz) and Bruker AVII600 (600 and 150 MHz) instruments. ^{1}H-NMR chemical shift values were calibrated relative to internal $CHCl_3$ at 7.24 ppm or DMSO-5_6 at 2.50 ppm. ^{13}C chemical shift values were calibrated relative to internal $CDCl_3$ at 77.23 ppm or DMSO-5_6 at 39.51 ppm.

Mass spectra were recorded with a Micromass Prospec Q instrument. Melting points were recorded using a Büchi Melting Point B-545 instrument. Dry THF and DMF was obtained from an MBraun MB SPS-800 solvent purification system. Microwave experiments were carried out using a sealed pressure vial in a Anton Paar GmbH Monowave 300 microwave synthesis reactor. The UV lamp used in oxidation reactions was emitting at 315–400 nm, with peaks at 352 and 368 nm.

Flash chromatography was performed on VWR 40-63 μm particle size silica gel using redistilled hexanes and DCM. The MeCN used was HPLC quality, further degassed through at least three cycles of the freeze-pump-thaw method.

(Furan-2-yl)boronic acid **76**, 2-chloro-6-iodoaniline **78a** and 2,4-dichloro-6-bromoaniline **78b** was provided by Fluorochem Ltd, Derbyshire, United Kingdom.

Synthesis of potassium (furan-2-yl)trifluoroborate (77)



77

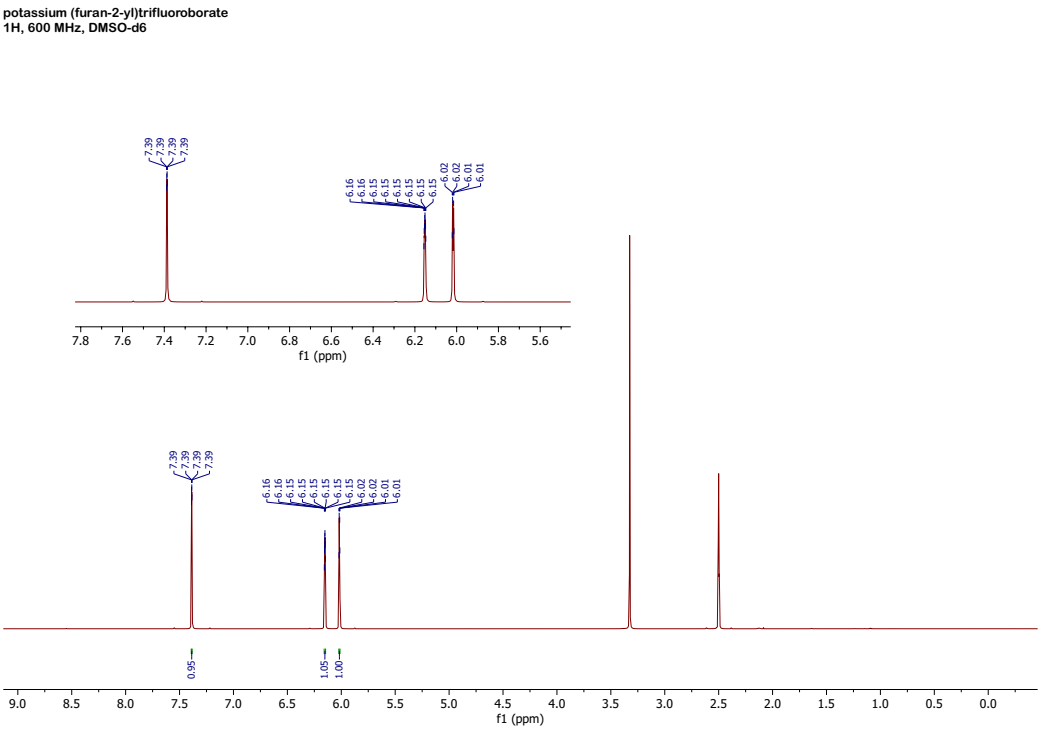
Using a literature procedure,[106] KHF_2 (52.09 g, 0.6670 mol) was added to an ice cold solution of (furan-2-yl)boronic acid (24.9 g, 0.223 mol) in methanol (60 mL). Water (150 mL) was added slowly, and the reaction was left stirring for 15 minutes at ambient temperature. The resulting foamy suspension was dried thoroughly *in vacuo* and extracted with acetone (5x100 mL). After concentrating the combined extracts, the extracted matter was redissolved in a minimum amount of acetone. Addition of diethyl ether (0.50 L) produced a fine colorless precipitate, which was filtered out and dried *in vacuo*. Yield: 30.9 g (80%), a fine grained colorless salt.

^{1}H-NMR (600 MHz, DMSO-d_6): δ 7.39 (m, 1H, H-2 or H-4), 6.15 (m, 1H, H-3), 6.02 (m, 1H, H-4 or H-2).

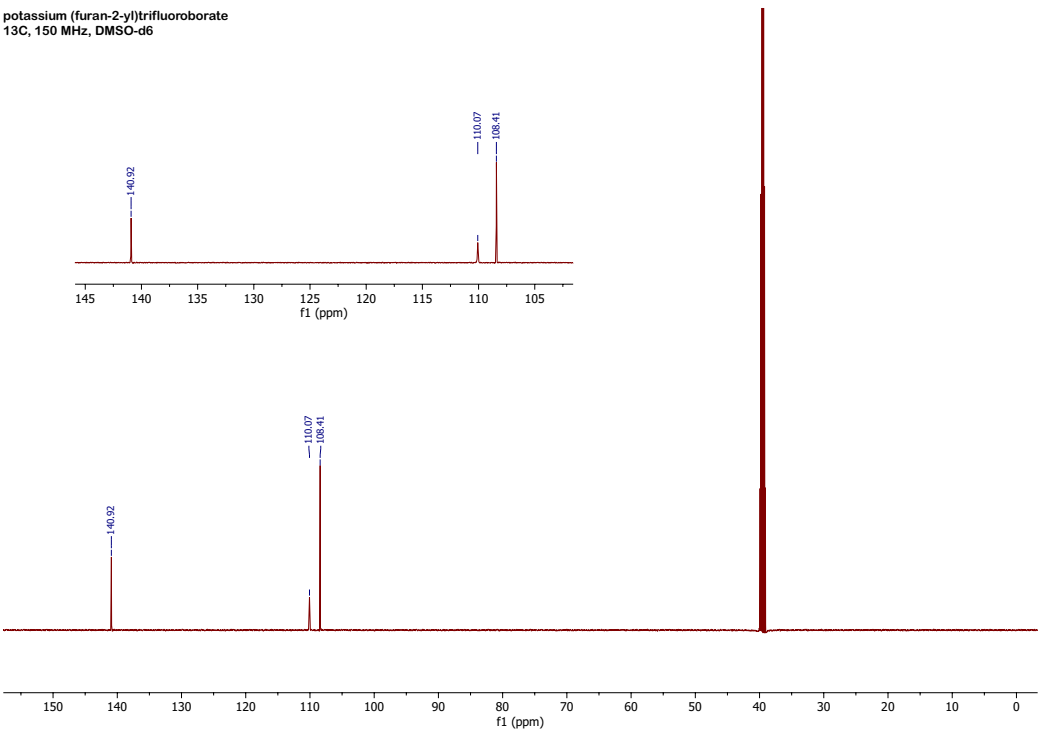
^{13}C-NMR (150 MHz, DMSO-d_6): δ 140.9 (C-2 or C-4), 110.0 (C-4 or C-2), 108.4 (C-3).

MS ESI m/z (rel %): 135/134 (100/25).

HRMS ESI: calculated for $C_4H_3BF_3O$: 135.0235, found 135.0235.

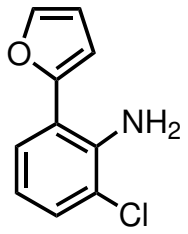


*Spectrum 1: ^{1}H-NMR spectrum of potassium (furan-2-yl)trifluoroborate (**77**)*



*Spectrum 2: ^{13}C-NMR spectrum of potassium (furan-2-yl)trifluoroborate (**77**)*

Synthesis of 2-chloro-6-(furan-2-yl)aniline (79a)



79a

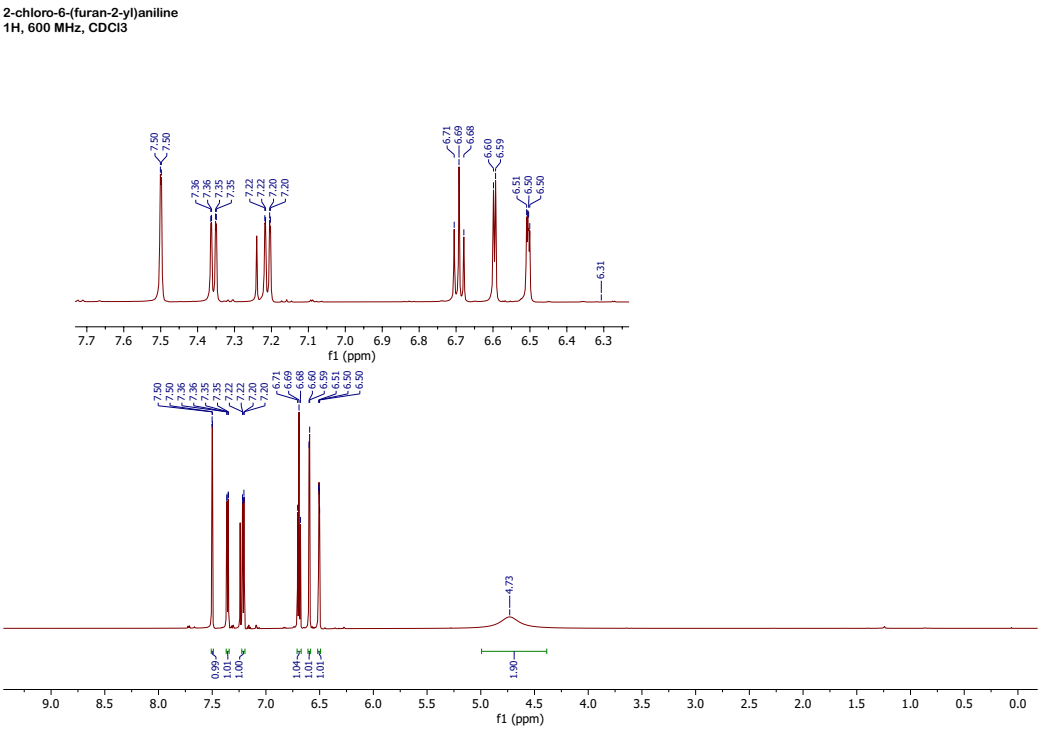
A solution of K_2CO_3 (1.81 g, 13.1 mmol), PPh_3 (921 mg, 3.51 mmol), $Pd(AcO)_2$ (199 mg, 0.885 mmol), potassium (furan-2-yl)trifluoroborate (2.27 g, 13.1 mmol) and 2-chloro-6-iodoaniline (2.21 g, 8.72 mmol) in ethanol (140 mL) and water (7 mL) was refluxed for 25 h under Ar. The mixture was filtered trough silica, solvents removed *in vacuo* and the product purified by flash chromatography (4:1 hexanes/DCM). Yield 1.42 g (84%), off-white crystals, mp 34-35 °C.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.50 (d, *J*=1.8 Hz, 1H, furyl H-5), 7.36 (dd, *J*=7.9, 1.5 Hz, 1H, H-5), 7.21 (dd, *J*=7.9, 1.5 Hz, 1H, H-3), 6.69 (t, *J*=7.9 Hz, 1H, H-4), 6.60 (d, *J*=3.4, 1H, furyl H-3), 6.50 (dd, *J*=3.4, 1.8 Hz, 1H, furyl H-4), 4.73 (s, 2H, -NH2)

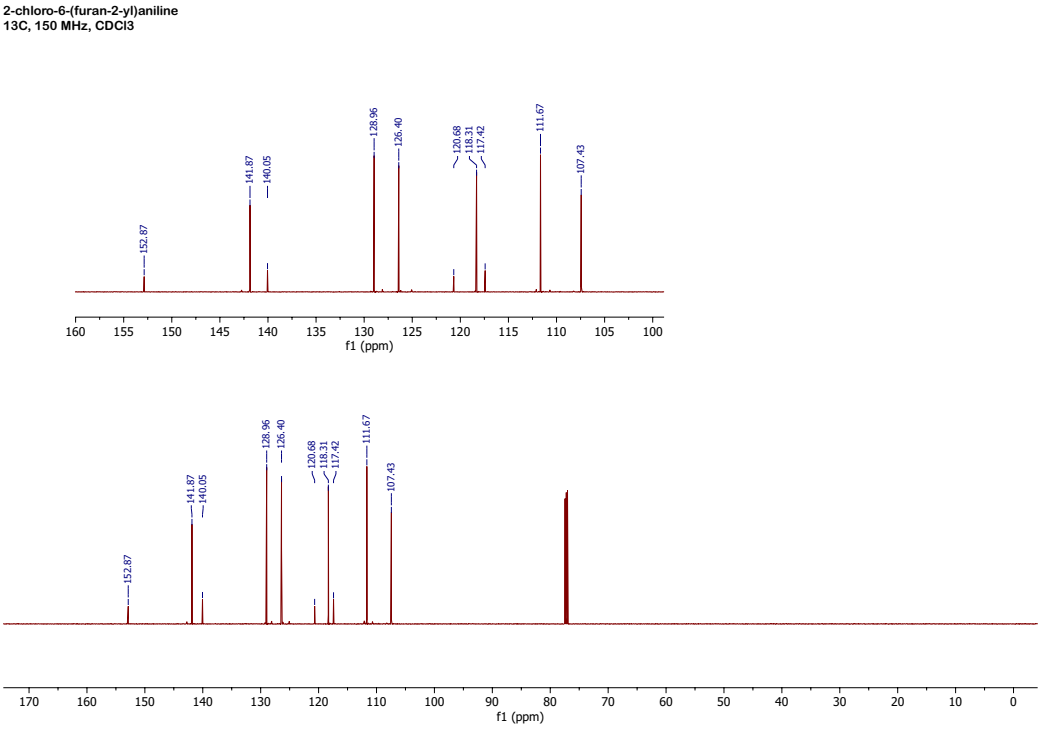
^{13}C-NMR (150 MHz, $CDCl_3$): δ 152.9 (furyl C-2), 141.9 (furyl C-5), 140.0 (C-1), 129.0 (C-3), 126.4 (C-5), 120.7 (C-2), 118.3 (C-4), 117.4 (C-6), 111.7 (furyl C-4), 107.4 (furyl C-3)

MS ESI m/z (rel %): 197/196/195/194 (4/31/11/100, MH^+), 185 (5)

HRMS ESI: calculated for $C_{10}H_9ClNO$ (MH^+): 194.0367, found 194.0367.

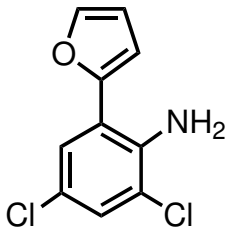


*Spectrum 3: ^{1}H-NMR spectrum of 2-chloro-6-(furan-2-yl)aniline (**79a**)*



*Spectrum 4: ^{13}C-NMR spectrum of 2-chloro-6-(furan-2-yl)aniline (**79a**)*

Synthesis of 2,4-dichloro-6-(furan-2-yl)aniline (79b)



79b

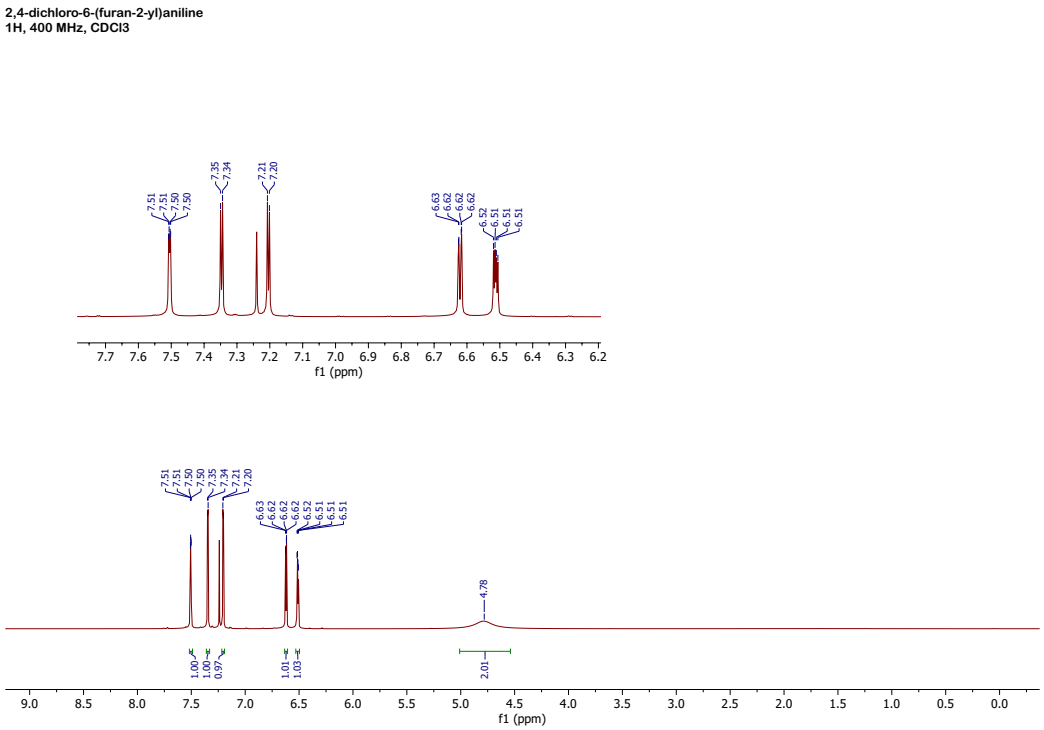
Using a literature procedure,[10] a solution of K_2CO_3 (2.61 g, 19.3 mmol), PPh_3 (822 mg, 3.14 mmol), $Pd(AcO)_2$ (142 mg, 0.634 mmol), potassium (furan-2-yl)trifluoroborate (3.25 g, 18.7 mmol) and 2-bromo-4,6-dichloroaniline (3.02 g, 12.5 mmol) in ethanol (200 mL) and water (10 mL) was refluxed for 6 h under Ar. The mixture was filtered trough silica, solvents removed *in vacuo* and the product purified by flash chromatography (45:4:1 hexanes/DCM/EtOAc). Yield 2.62 g (91%), off-white crystals, mp 66-67 °C (literature 66-68 °C[10]).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, *J*=1.8, 0.5 Hz, 1H, furyl H-5), 7.35 (d, *J*=2.4 Hz, 1H, H-5), 7.21 (d, *J*=2.4 Hz, 1H, H-3), 6.62 (dd, *J*=3.4, 0.5 Hz, 1H, furyl H-3), 6.51 (dd, *J*=3.4, 1.8 Hz, 1H, furyl H-4), 4.78 (s, 2H,-NH2).

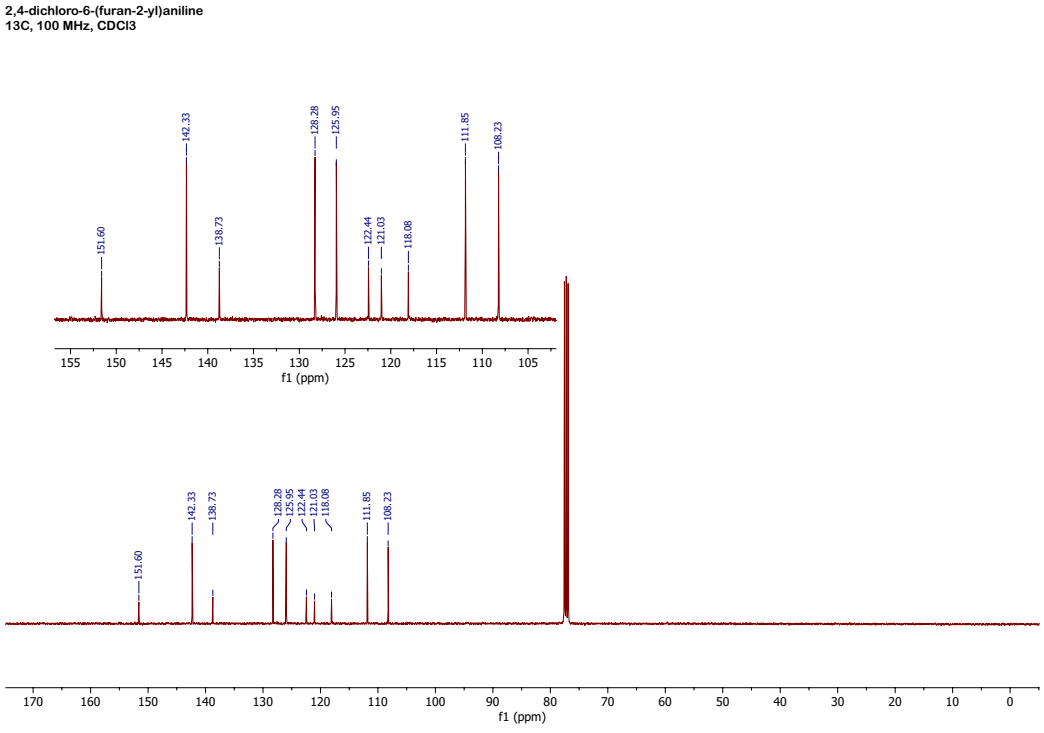
^{13}C-NMR (100 MHz, $CDCl_3$): δ 151.6 (furyl C-2), 142.3 (furyl C-5), 138.7 (C-4), 128.3 (C-3), 126.0 (C-5), 122.4 (C-6), 121.0 (C-2), 118.0 (C-1), 111.8 (furyl C-4), 108.2 (furyl C-3).

MS ESI m/z (rel %): 230/228 (65/100, MH^+).

HRMS ESI: calculated for $C_{10}H_8Cl_2NO$ (MH^+): 227.9977, found 227.9978.

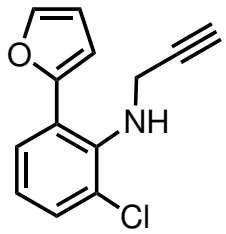


*Spectrum 5: ^{1}H-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)aniline (**79b**)*

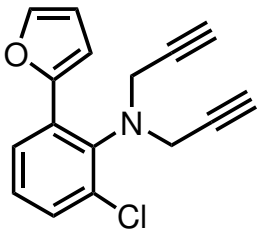


*Spectrum 6: ^{13}C-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)aniline (**79b**)*

Synthesis of
2-chloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline (68a) and
2-chloro-*N*,*N*–di(prop-2-ynyl)-6-(furan-2-yl)aniline (80a)



68a



80a

NaH (ca. 60% in mineral oil, 352 mg, 8.80 mmol) was added to a solution of TBAB (2.12 g, 6.58 mmol) and 2-chloro-6-(furan-2-yl)aniline (602 mg, 3.11 mmol) in dry THF (50 mL) under Ar. The mixture was stirred for 15 minutes at 45 °C before dropwise addition of propargyl bromide (ca. 80% in toluene, 0.38 mL, 4.0 mmol). After 22 h, the reaction was quenched with water (25 mL), extracted with DCM (5x25 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (3:1 hexanes/DCM followed by 49:1 hexanes/acetone). Yield: 528 mg (73%) of compound **68a**, clear oil, and 60 mg (7%) of compound **80a**, yellow oil.

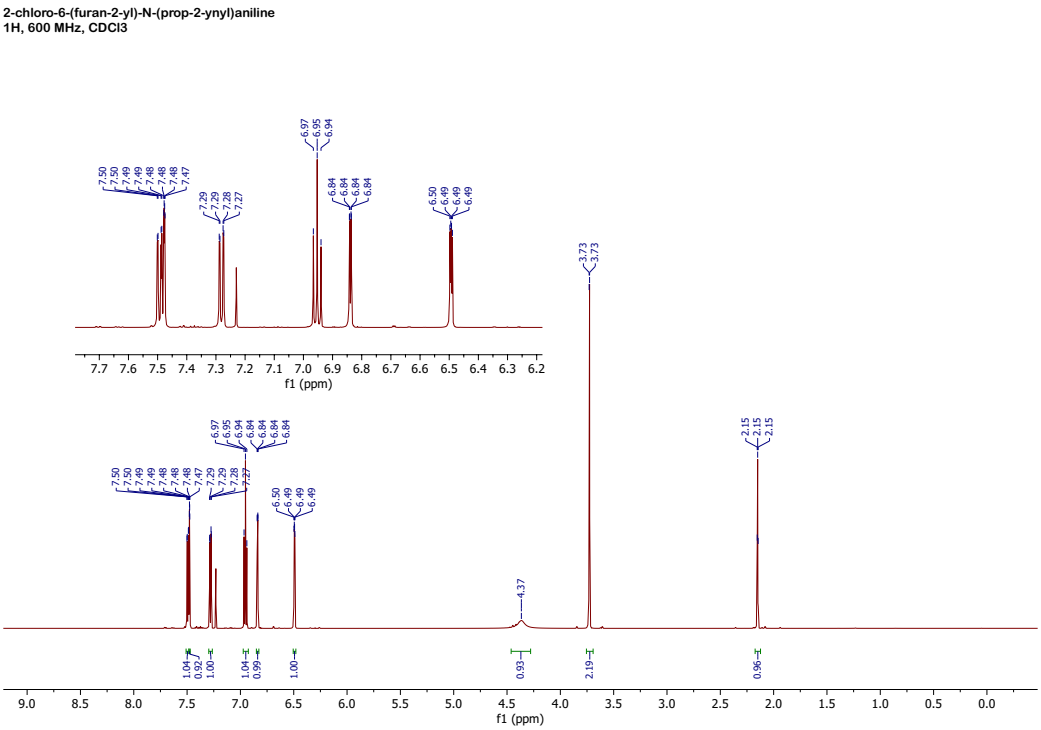
2-Chloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.49 (dd, *J*=7.8, 1.5 Hz, 1H, H-5), 7.48 (dd, *J*=1.8, 0.8 Hz, 1H, furyl H-5), 7.28 (dd, *J*=7.8, 1.5 Hz, 1H, H-3), 6.96 (t, *J*=7.8 Hz, 1H, H-4), 6.84 (dd, *J*=3.4, 0.8 Hz, 1H, furyl H-3), 6.49 (dd, *J*=3.4, 1.8 Hz, 1H, furyl H-4), 4.37 (s, 1H, NH), 3.73 (d, *J*=2.6 Hz, 2H, CH_2), 2.15 (t, *J*=2.6 Hz, 1H, C-CH).

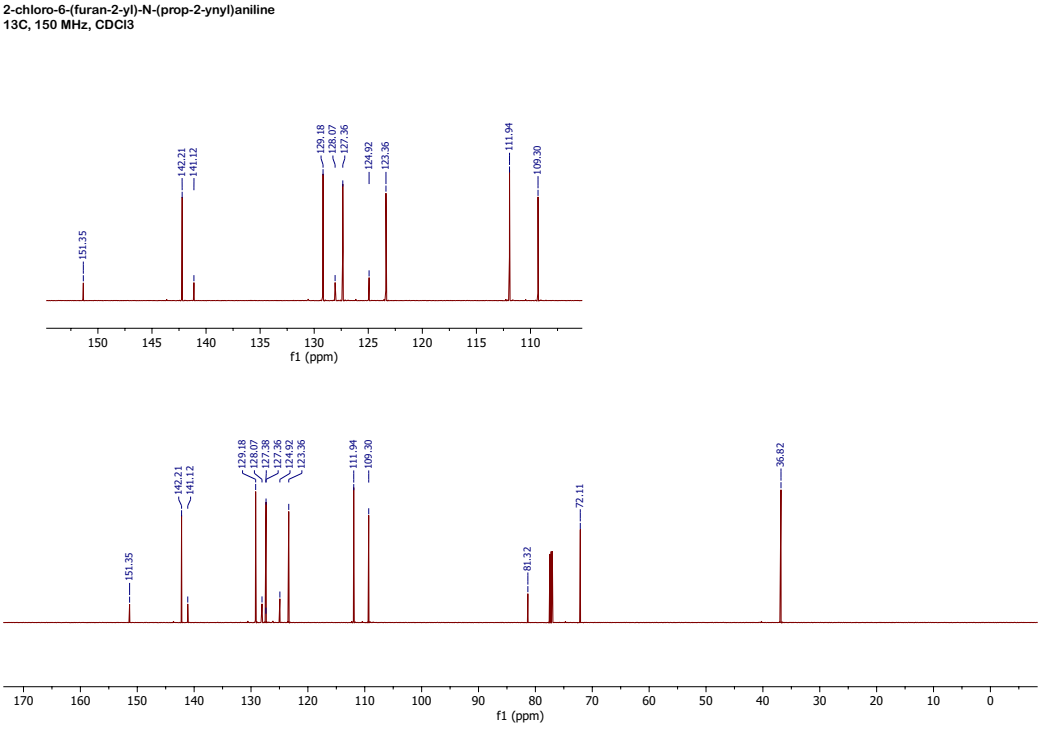
^{13}C-NMR (150 MHz, $CDCl_3$): δ 151.4 (furyl C-2), 142.2 (furyl C-3), 141.1 (C-6), 129.1 (C-3), 128.1 (C-2 or C-1), 127.4 (C-5), 124.9 (C-1 or C-2), 123.4 (C-4), 111.9 (furyl C-4), 109.3 (furyl C-5), 81.3 (**C**-CH), 72.1 (C-**C**H), 36.8 (CH_2).

MS ESI m/z (rel %): 235/234/233/232 (5/32/15/100, MH^+), 193 (15), 185 (9).

HRMS ESI: calculated for $C_{13}H_{10}ClNO$ (MH^+): 232.0524, found 232.0524.



*Spectrum 7: [1]H-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68a**)*



*Spectrum 8: [13]C-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68a**)*

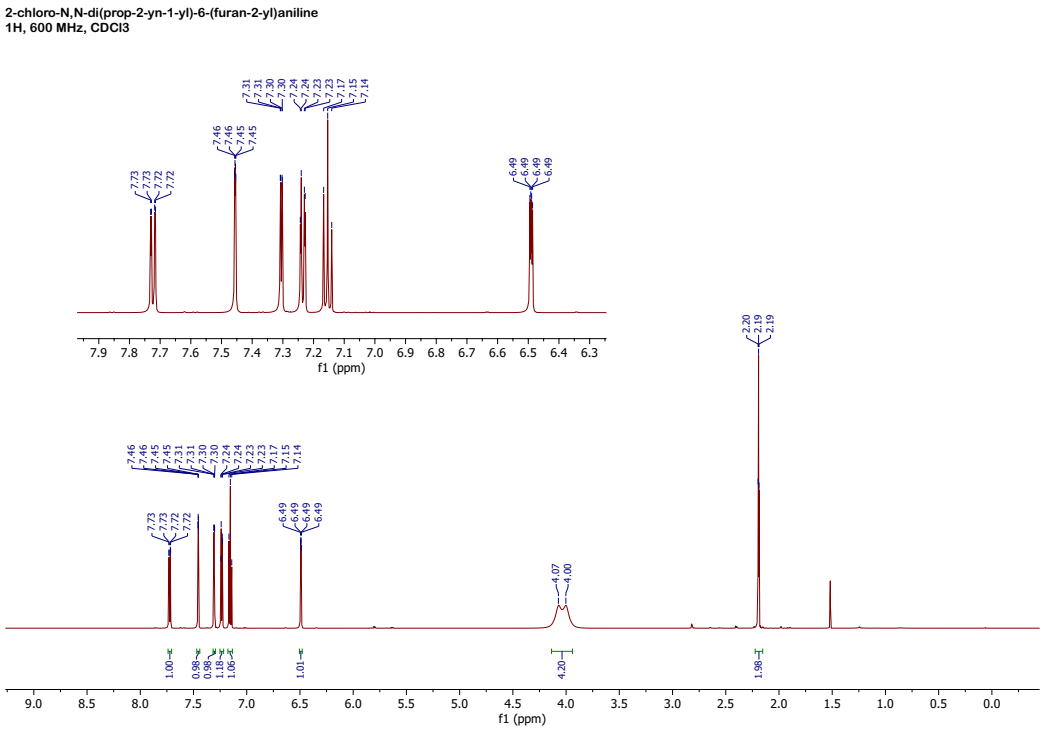
2-Chloro-*N*,*N*–di(prop-2-ynyl)-6-(furan-2-yl)aniline

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.72 (dd, *J*=7.9, 1.5 Hz, 1H, H-5), 7.46 (dd, *J*=1.6, 0.5 Hz, 1H, furyl H-5), 7.31 (dd, *J*=3.0, 0.5 Hz, 1H, furyl H-3), 7.24 (dd, *J*=7.9, 1.5 Hz, 1H, H-3), 7.15 (t, *J*=7.9 Hz, 1H, H-4), 6.49 (dd, *J*=3.0, 1.6 Hz, 1H, furyl H-4), 3.73 (d, broad, 4H, CH_2), 2.19 (t, *J*=2.6 Hz, 2H, C-CH).

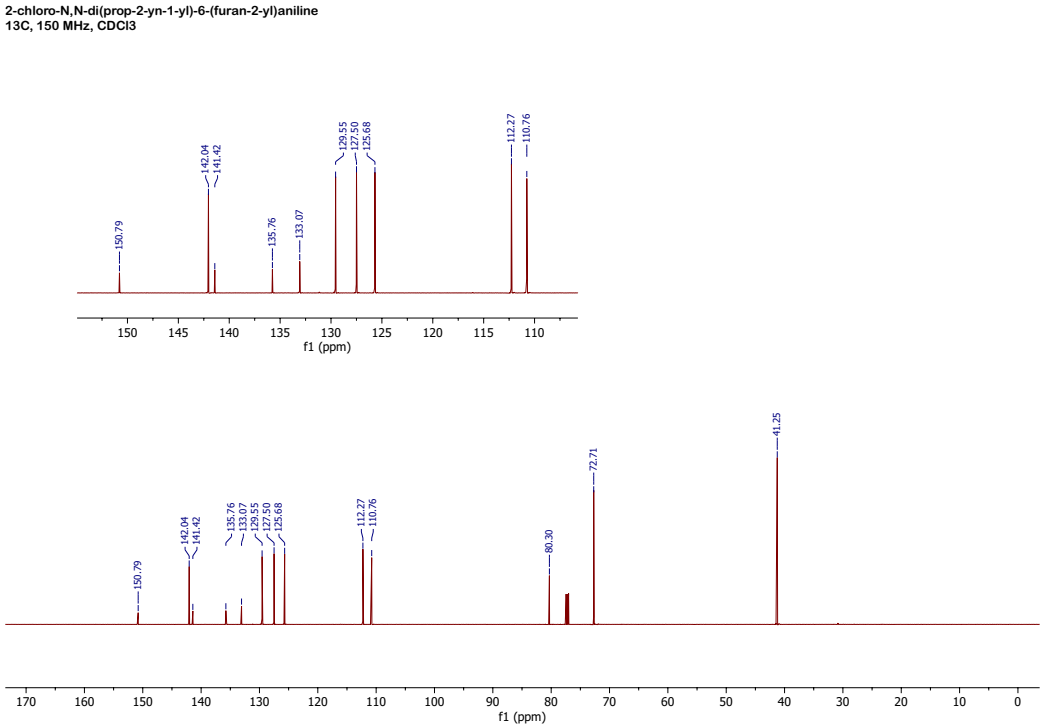
^{13}C-NMR (150 MHz, $CDCl_3$): δ 150.8 (furyl C-2), 142.0 (furyl C-5), 141.4 (C-1), 135.8 (C-2 or C-6), 133.1 (C-6 or C-2), 129.5 (C-3), 127.5 (C-4), 125.7 (C-5), 112.3 (furyl C-4), 110.8 (furyl C-3), 80.3 (**C**-CH), 72.7 (C-**C**H), 41.3 (CH_2).

MS ESI m/z (rel %): 295/294/293/292 (6/33/18/100, MNa^+), 270 (7), 185 (7).

HRMS ESI: calculated for $C_{16}H_{12}ClNNaO$ (MNa^+): 292.0500, found 292.0500.

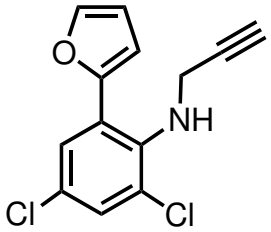


*Spectrum 9: [1]H-NMR spectrum of 2-chloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80a**)*

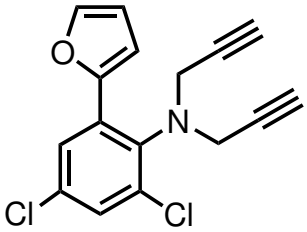


*Spectrum 10: [13]C-NMR spectrum of 2-chloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80a**)*

Synthesis of 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline (68b) and 2,4-dichloro-*N,N*–di(prop-2-ynyl)-6-(furan-2-yl)aniline (80b)



68b



80b

Using a modified literature procedure,[13] NaH (ca. 60% in mineral oil, 291 mg, 7.28 mmol) was added to a solution of TBAB (2.67 g, 8.04 mmol) and 2,4-dichloro-6-(furan-2-yl)aniline (917 mg, 4.02 mmol) in dry THF (65 mL) under Ar. The mixture was stirred for 15 minutes at 45 °C before dropwise addition of propargyl bromide (ca. 80% in toluene, 0.50 mL, 5.3 mmol). After 18 h, the reaction was quenched with water (40 mL), extracted with DCM (200+100+100 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (4:1 hexanes/DCM followed by 59:1 hexanes/acetone). Yield: 807 mg (75%) of compound **68b**, colorless crystals, mp 68-69 °C (literature 68-69 °C[13]), and 74 mg (6%) of compound **80b**, yellow oil.

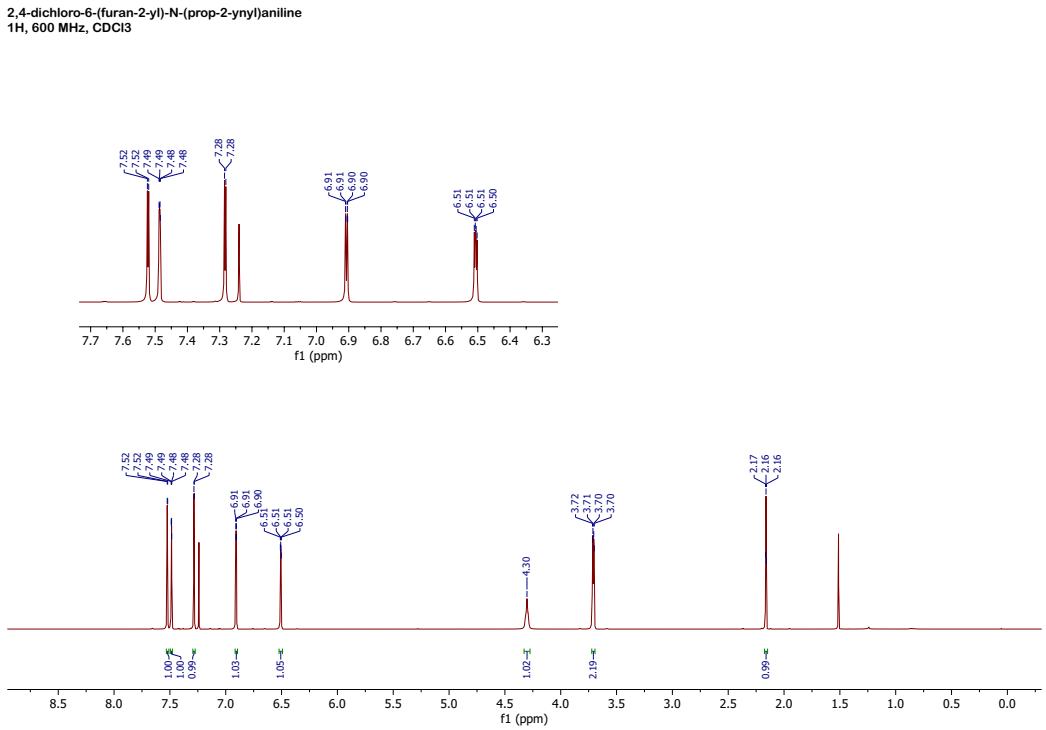
2,4-Dichloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.52 (d, *J*=2.4 Hz, 1H, H-5), 7.49 (dd, *J*=1.7, 0.7 Hz, 1H, furyl H-5), 7.28 (d, *J*=2.4 Hz, 1H, H-3), 6.91 (dd, *J*=3.3, 0.7 Hz, 1H, furyl H-3), 6.51 (dd, *J*=3.3, 1.7 Hz, 1H, furyl H-4), 4.30 (s, 1H, NH), 3.73 (d, *J*=2.6 Hz, 2H, CH_2), 2.15 (t, *J*=2.6 Hz, 1H, C-CH).

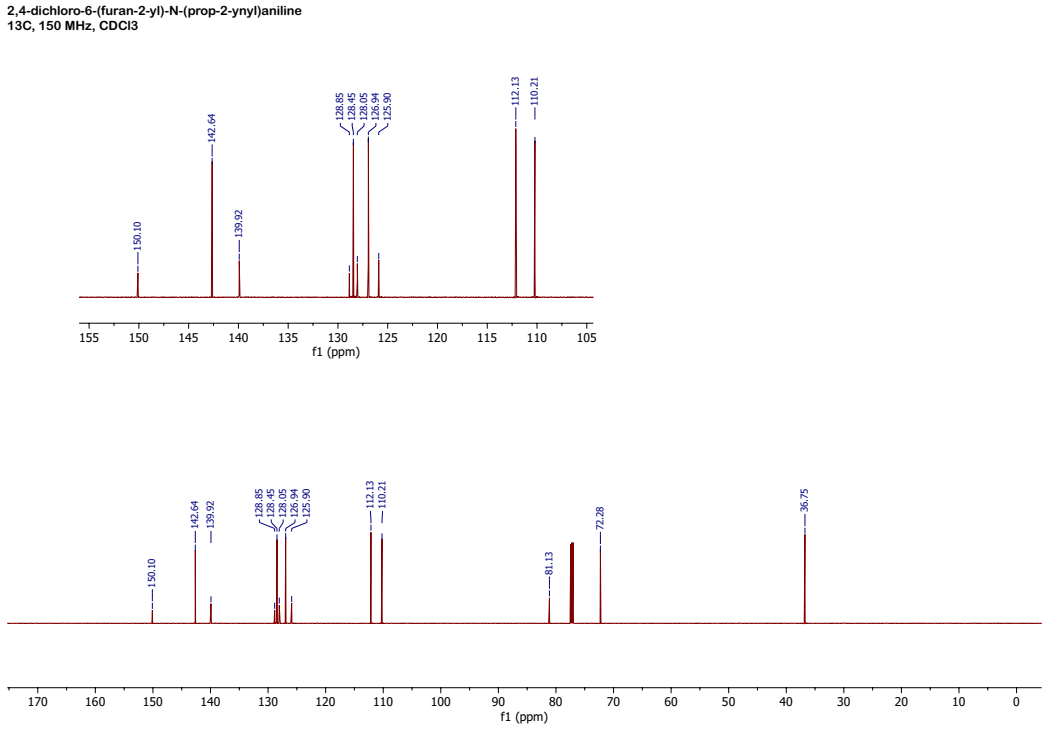
^{13}C-NMR (150 MHz, $CDCl_3$): δ 150.1 (furyl C-2), 142.6 (furyl C-5), 139.9 (C-4), 128.9 (C-1 or C-2), 128.5 (C-6), 128.1 (C-3), 126.9 (C-5), 125.9 (C-2 or C-1), 112.1 (furyl C-4), 110.2 (furyl C-3), 81.1 (**C**-CH), 72.3 (C-**C**H), 36.8 (CH_2).

MS ESI m/z (rel %): 291/290/289/288 (9/62/15/100, MNa+), 266 (4), 250 (12), 241 (8), 227 (4).

HRMS ESI: calculated for $C_{13}H_9Cl_2NNaO$ (MNa^+): 287.9953, found 287.9953.



*Spectrum 11: [1]H-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68b**)*



*Spectrum 12: [13]C-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68b**)*

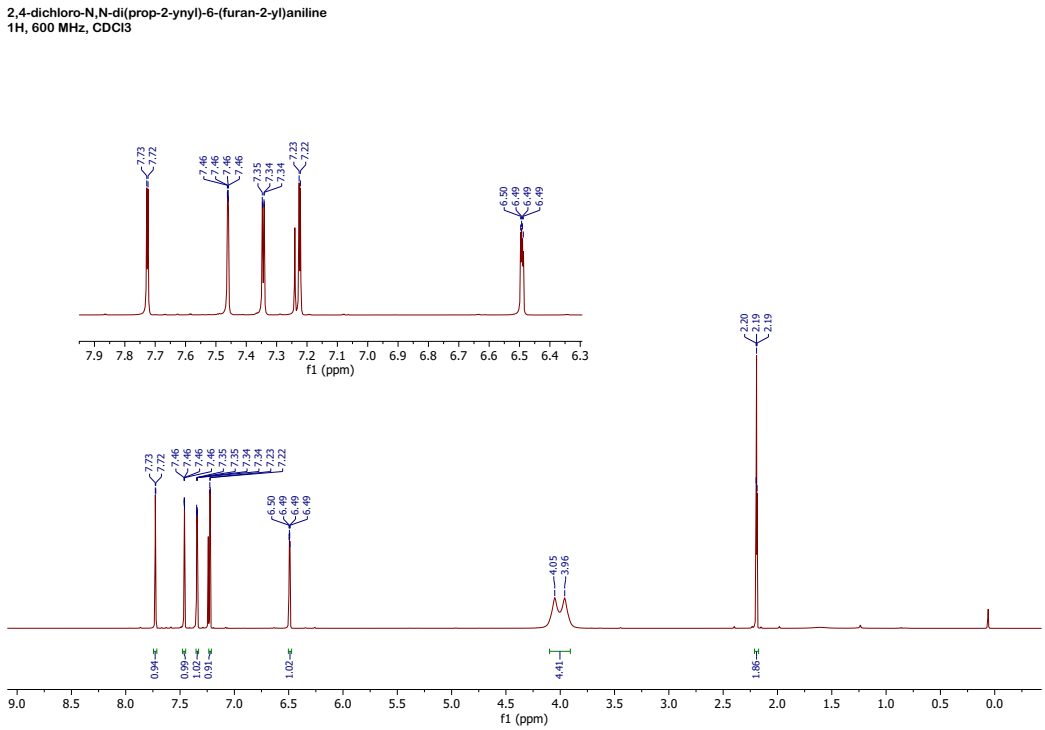
2,4-Dichloro-*N,N*–di(prop-2-ynyl)-6-(furan-2-yl)aniline

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.73 (d, *J*=2.4 Hz, 1H, H-5), 7.46 (dd, *J*=1.7, 0.5 Hz, 1H, furyl H-5), 7.34 (dd, *J*=3.5, 0.5 Hz, 1H, furyl H-3), 7.22 (d, *J*=2.4, 1H, H-3), 6.49 (dd, *J*=3.5, 1.7 Hz, 1H, furyl H-4), 4.00 (d, broad, 4H, CH_2), 2.19 (t, *J*=2.5 Hz, 2H, C-CH).

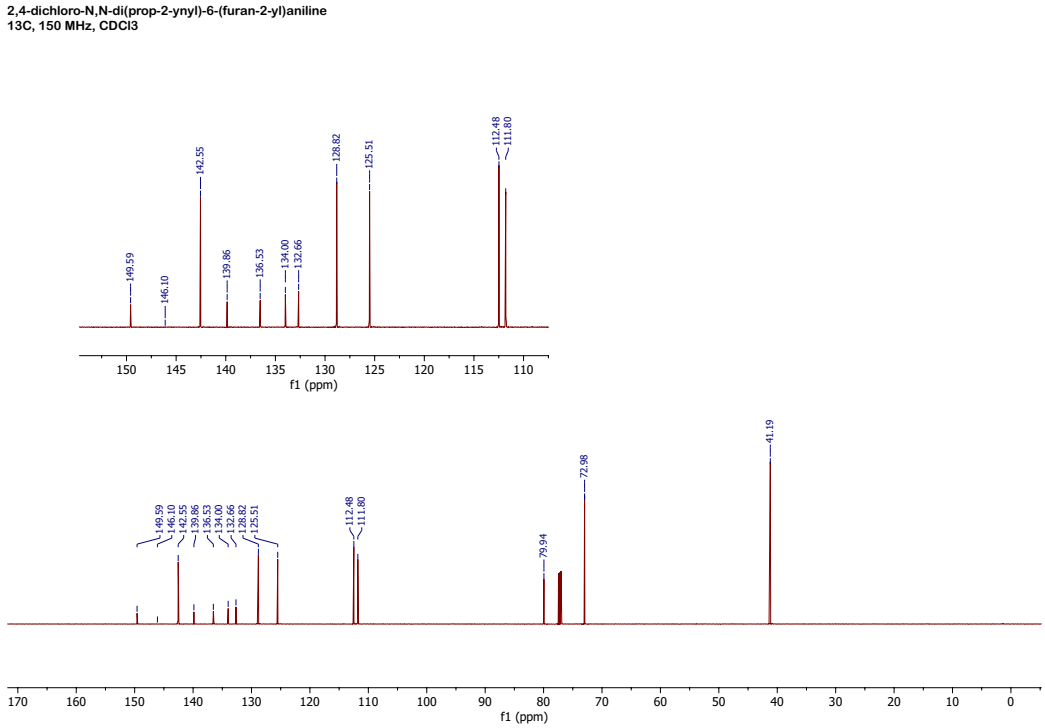
^{13}C-NMR (150 MHz, $CDCl_3$): δ 149.6 (furyl C-2), 142.5 (furyl C-5), 139.9 (C-4), 136.5 (C-2), 134.0 (C-1), 132.7 (C-6), 128.8 (C-3), 125.5 (C-5), 112.5 (furyl C-4), 111.8 (furyl C-3), 79.9 (**C**-CH), 73.0 (C-**C**H), 41.2 (CH_2).

MS ESI m/z (rel %): 329/328/327/326 (11/64/18/100, MNa^+), 306 (12), 304 (19), 185 (7).

HRMS ESI: calculated for $C_{16}H_{11}Cl_2NNaO$ (MNa^+): 326.0110, found 326.0110.

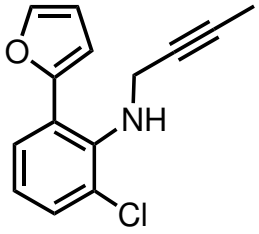


*Spectrum 13: [1]H-NMR spectrum of 2,4-dichloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80b**)*

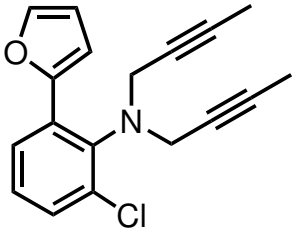


*Spectrum 14: [13]C-NMR spectrum of 2,4-dichloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80b**)*

Synthesis of
2-chloro-6-(furan-2-yl)-*N*-(but-2-ynyl)aniline (68c) and
2-chloro-*N*,*N*–di(but-2-ynyl)-6-(furan-2-yl)aniline (80c)



68c



80c

NaH (ca. 60 % in mineral oil, 221 mg, 5.54 mmol) was added to a solution of TBAB (1.39 g, 4.19 mmol) and 2-chloro-6-(furan-2-yl)aniline (397 mg, 2.05 mmol) in dry THF (35 mL) under Ar. The mixture was stirred for 15 minutes at 45 °C before dropwise addition of 1-bromo-2-butyne (0.23 mL, 2.7 mmol). After 22.5 h, the reaction was quenched with water (40 mL), extracted with DCM (3x50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (2:1 hexanes/DCM followed by 24:1 hexanes/acetone). Yield: 443 mg (88%) of compound **68c**, brown oil, and 30 mg (5%) of compound **80c**, yellow oil.

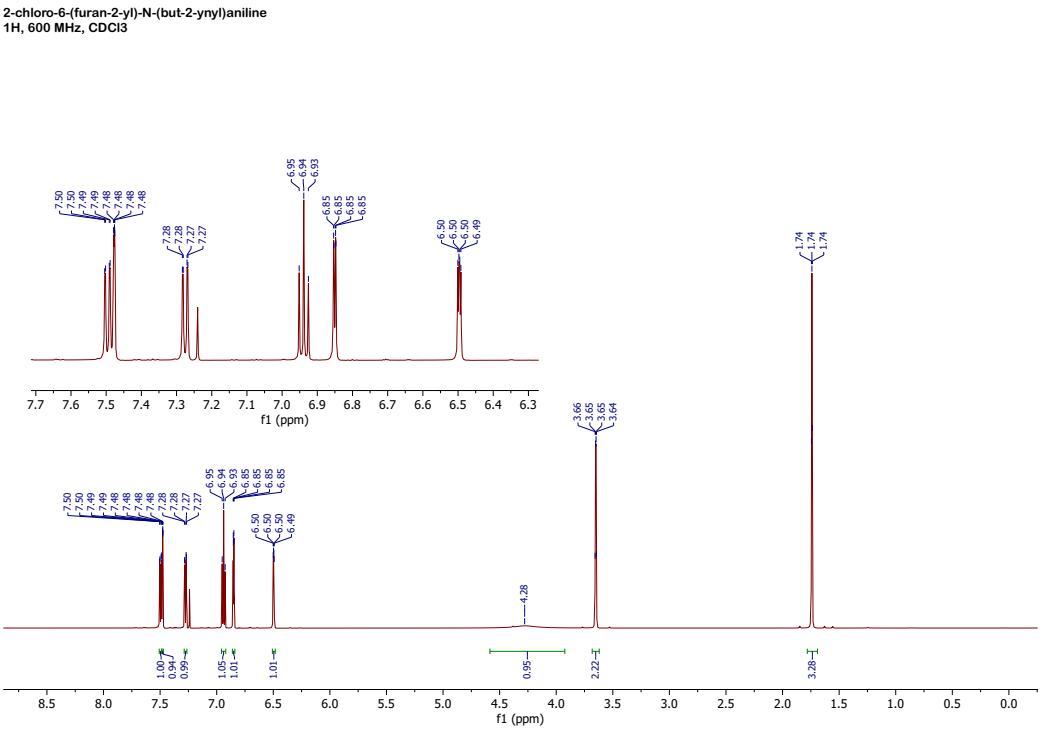
2-Chloro-6-(furan-2-yl)-*N*-(but-2-ynyl)aniline

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.50 (dd, *J*=7.8, 1.4 Hz, 1H, H-5), 7.48 (dd, *J*=1.5, 0.5 Hz, 1H, furyl H-5), 7.28 (dd, *J*=7.8, 1.4 Hz, 1H, H-3), 6.94 (t, *J*=7.8 Hz, 1H, H-4), 6.85 (dd, *J*=3.3, 0.5 Hz, 1H, furyl H-3), 6.50 (dd, *J*=3.3, 1.5 Hz, 1H, furyl H-4), 4.28 (s, 1H, NH), 3.65 (q, *J*=2.4 Hz, 2H, CH_2), 1.74 (t, *J*=2.4 Hz, 3H, C-CH^3).

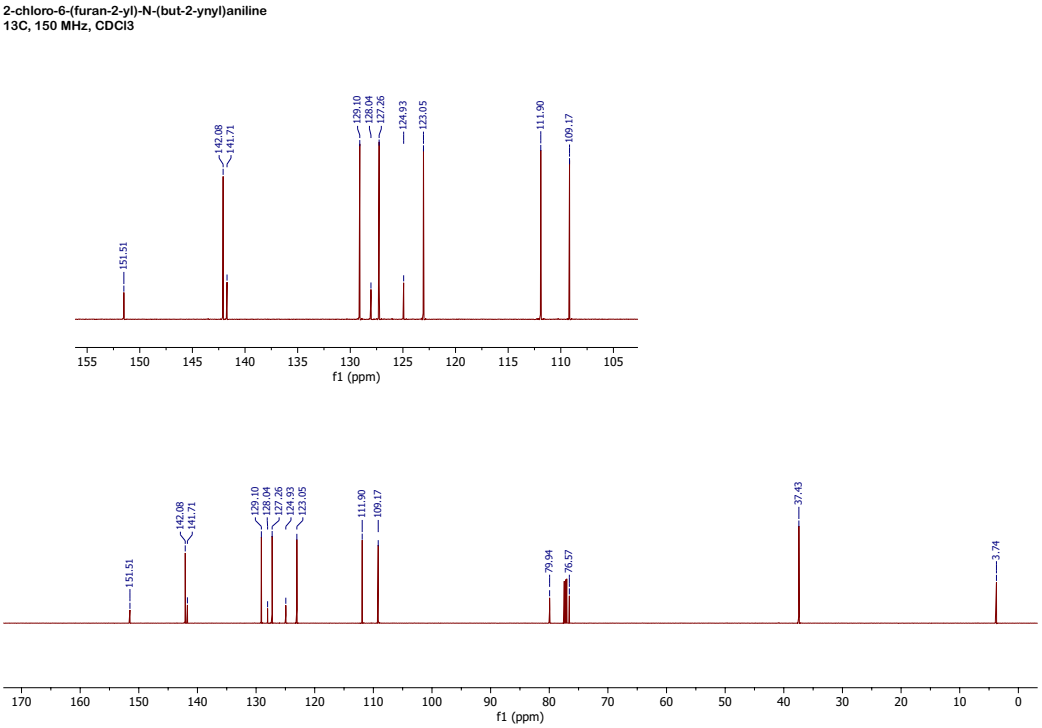
^{13}C-NMR (150 MHz, $CDCl_3$): δ 151.5 (furyl C-2), 142.1 (furyl C-5), 141.7 (C-2), 129.1 (C-3), 128.0 (C-1), 127.3 (C-5), 124.9 (C-6), 123.0 (C-4), 111.9 (furyl C-4), 109.2 (furyl C-3), 79.9 (C-**C**-CH^3), 76.6 (**C**-C-CH^3), 37.4 (CH_2), 3.7 (CH^3).

MS ESI m/z (rel %): 271/270/269/268 (5/31/15/100, MNa^+), 248 (7), 247 (3), 246 (20), 227 (3), 185 (6).

HRMS ESI: calculated for $C_{14}H_{12}ClNNaO$ (MNa^+): 268.0500, found 268.0499.



*Spectrum 15: ^{1}H-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68c**)*



*Spectrum 16: ^{13}C-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68c**)*

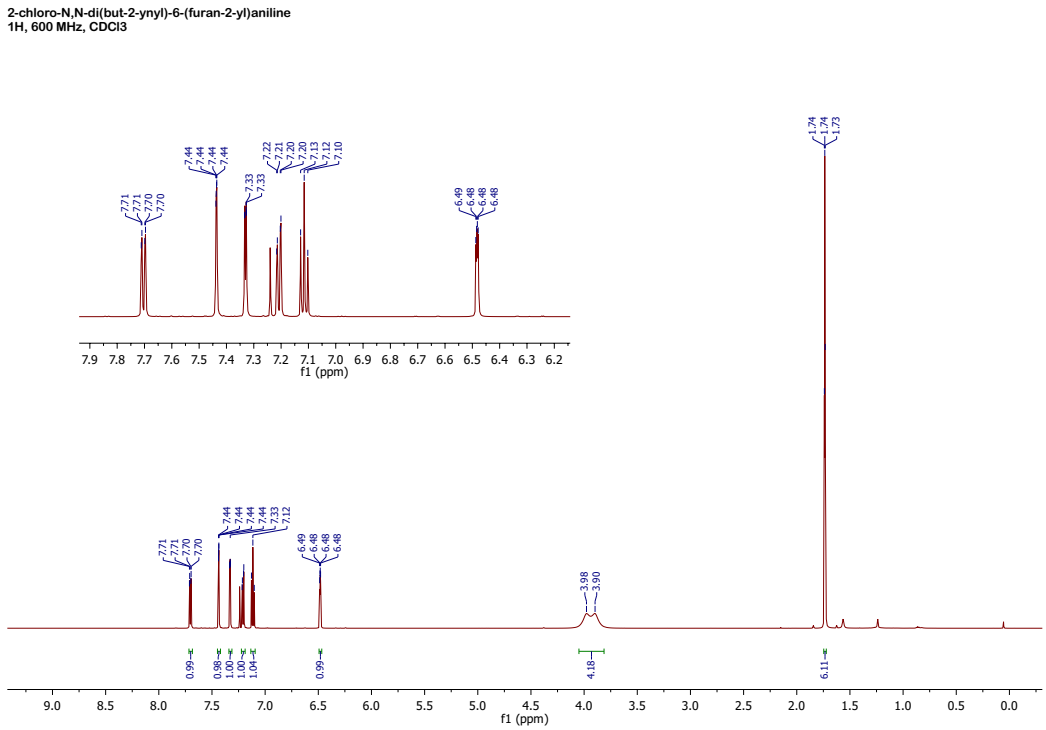
2-Chloro-*N*,*N*–di(but-2-ynyl)-6-(furan-2-yl)aniline

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.70 (dd, *J*=7.9, 1.4 Hz, 1H, H-5), 7.44 (dd, *J*=1.4, 0.6 Hz, 1H, furyl H-5), 7.33 (dd, *J*=3.4, 0.6 Hz, 1H, furyl H-3), 7.21 (dd, *J*=7.9, 1.4 Hz, 1H, H-3), 7.12 (t, *J*=7.9 Hz, 1H, H-4), 6.48 (dd, *J*=3.4, 1.4 Hz, 1H, furyl H-4), 3.94 (d, broad, 4H, CH_2), 1.74 (t, *J*=2.4 Hz, 6H, C-CH^3).

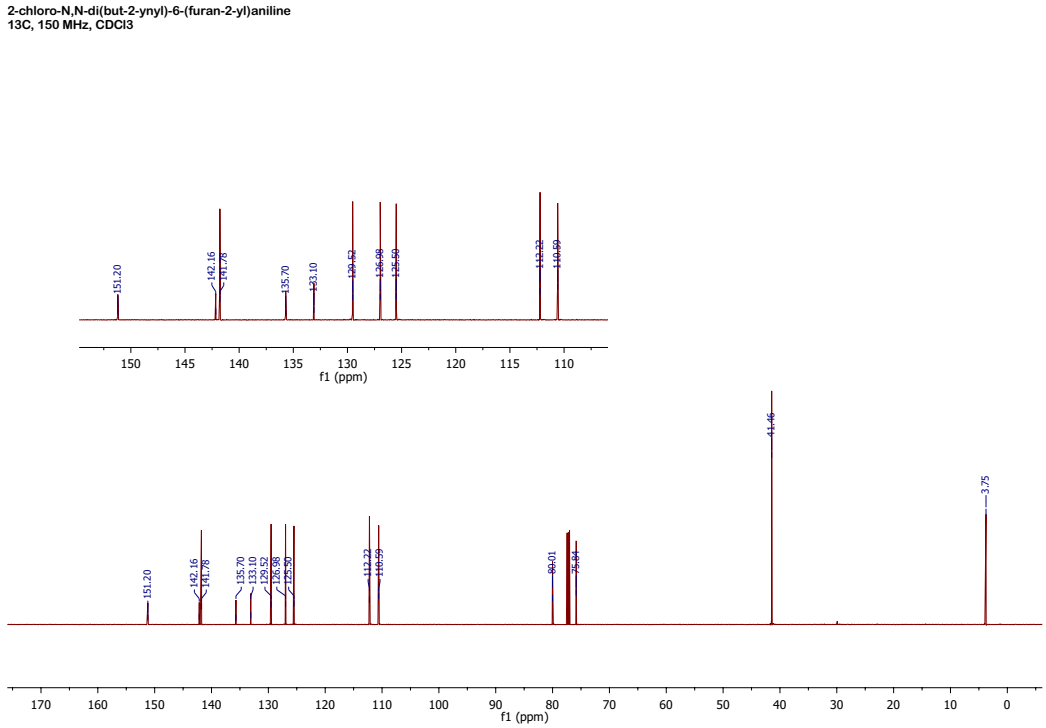
^{13}C-NMR (150 MHz, $CDCl_3$): δ 151.2 (furyl C-2), 142.2 (C-6), 141.8 (furyl C-5), 135.7 (C-2 or C-1), 133.1 (C-1 or C-2), 129.5 (C-3), 127.0 (C-4), 125.5 (C-5), 112.2 (furyl C-4), 110.6 (furyl C-3), 80.0 (C-**C**-CH^3, 75.8 (**C**-C-CH^3), 41.5 (CH_2), 3.7 (CH^3).

MS ESI m/z (rel %): 323/322/321/320 (6/32/20/100, MNa^+), 298 (27), 227 (3), 193 (2), 121 (6).

HRMS ESI: calculated for $C_{18}H_{16}ClNNaO$ (MNa^+): 320.0813, found 320.0812.

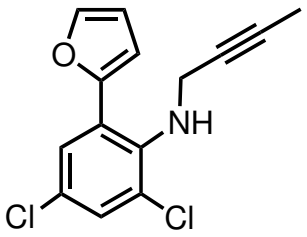


*Spectrum 17: [1]H-NMR spectrum of 2-chloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80c**)*

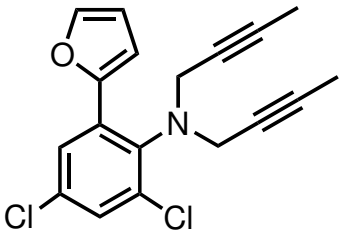


*Spectrum 18: [13]C-NMR spectrum of 2-chloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80c**)*

Synthesis of
2,4-dichloro-6-(furan-2-yl)-*N*-(but-2-ynyl)aniline (68d) and
2,4-dichloro-*N,N*–di(but-2-ynyl)-6-(furan-2-yl)aniline (80d)



68d



80d

NaH (ca. 60 % in mineral oil, 144 mg, 3.61 mmol) was added to a solution of TBAB (1.35 g, 4.07 mmol) and 2,4-dichloro-6-(furan-2-yl)aniline (453 mg, 1.99 mmol) in dry THF (35 mL) under Ar. The mixture was stirred for 15 minutes at 45 °C before dropwise addition of 1-bromo-2-butyne (0.22 mL, 2.6 mmol). After 23 h, the reaction was quenched with water (40 mL), extracted with DCM (3x50 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (3:1 hexanes/DCM followed by 29:1 hexanes/acetone). Yield: 488 mg (88%) of compound **68d**, off-white solid, mp. 65-66 °C, and 26 mg (4%) of compound **80d**, yellow oil.

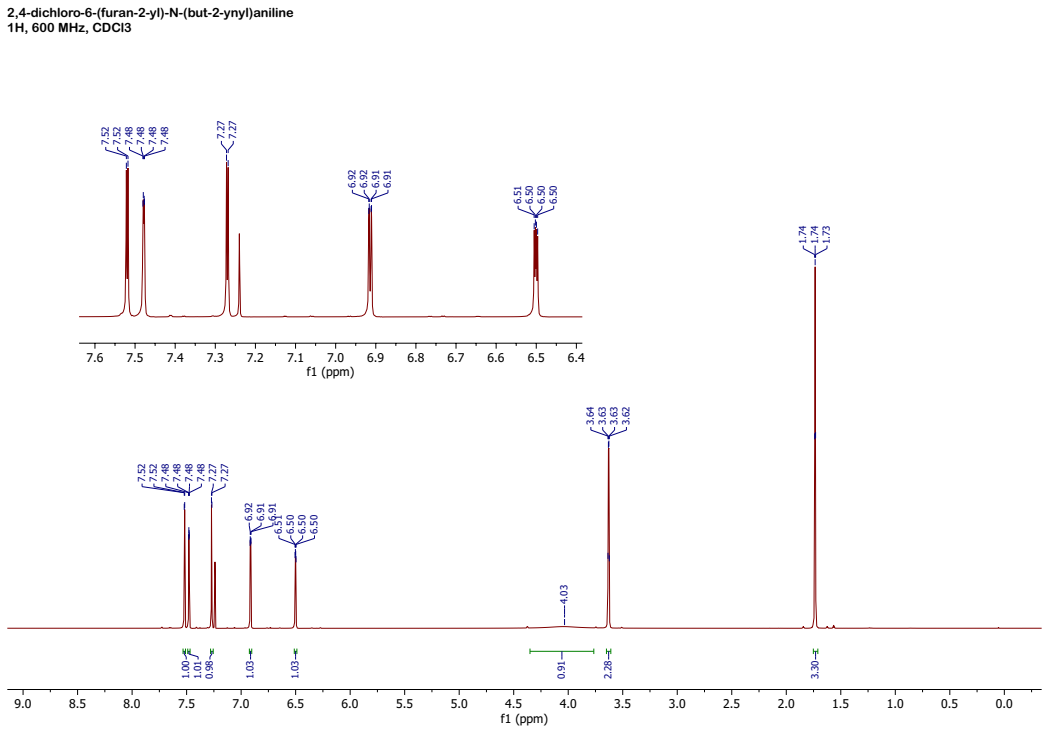
2,4-Dichloro-6-(furan-2-yl)-*N*-(but-2-ynyl)aniline

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.52 (d, *J*=2.4 Hz, 1H, H-5), 7.48 (dd, *J*=1.7, 0.5 Hz, 1H, furyl H-5), 7.27 (d, *J*=2.4 Hz, 1H, H-3), 6.91 (dd, *J*=3.4, 0.5 Hz, 1H, furyl H-3), 6.50 (dd, *J*=3.4, 1.7 Hz, 1H, furyl H-4), 4.03 (s, 1H, NH), 3.63 (q, *J*=2.4 Hz, 2H, CH_2), 1.74 (t, *J*=2.4 Hz, 3H, CH^3).

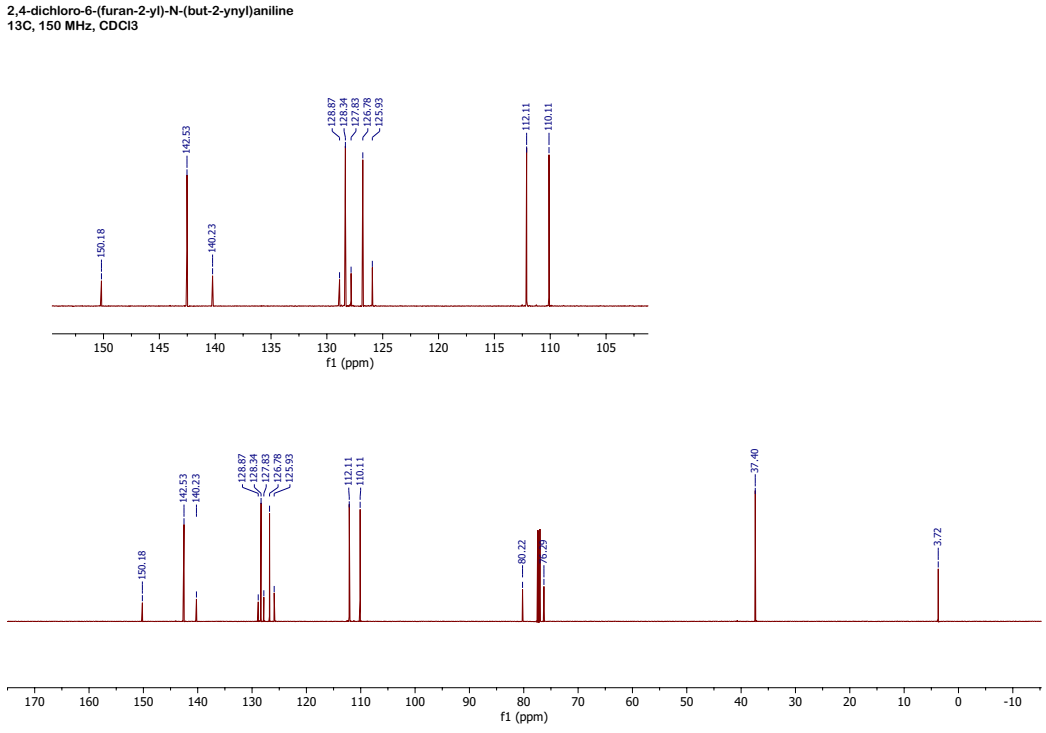
^{13}C-NMR (150 MHz, $CDCl_3$): δ 150.2 (furyl C-2), 142.5 (furyl C-5), 140.2 (C-1), 128.9 (C-4 or C-6), 128.3 (C-3), 127.8 (C-6 or C-4), 126.8 (C-2), 125.9 (C-5), 112.1 (furyl C-4), 110.1 (furyl C-3), 80.2 (C-**C**-CH^3), 76.3 (**C**-C-CH^3), 37.4 (CH_2), 3.7 (CH^3).

MS ESI m/z (rel %): 305/304/303/302 (10/64/15/100, MNa+), 280 (43), 215 (5), 185 (10).

HRMS ESI: calculated for $C_{14}H_{11}Cl_2NNaO$ (MNa^+): 302.0110, found 302.0110.



*Spectrum 19: [1]H-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68d**)*



*Spectrum 20: [13]C-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68d**)*

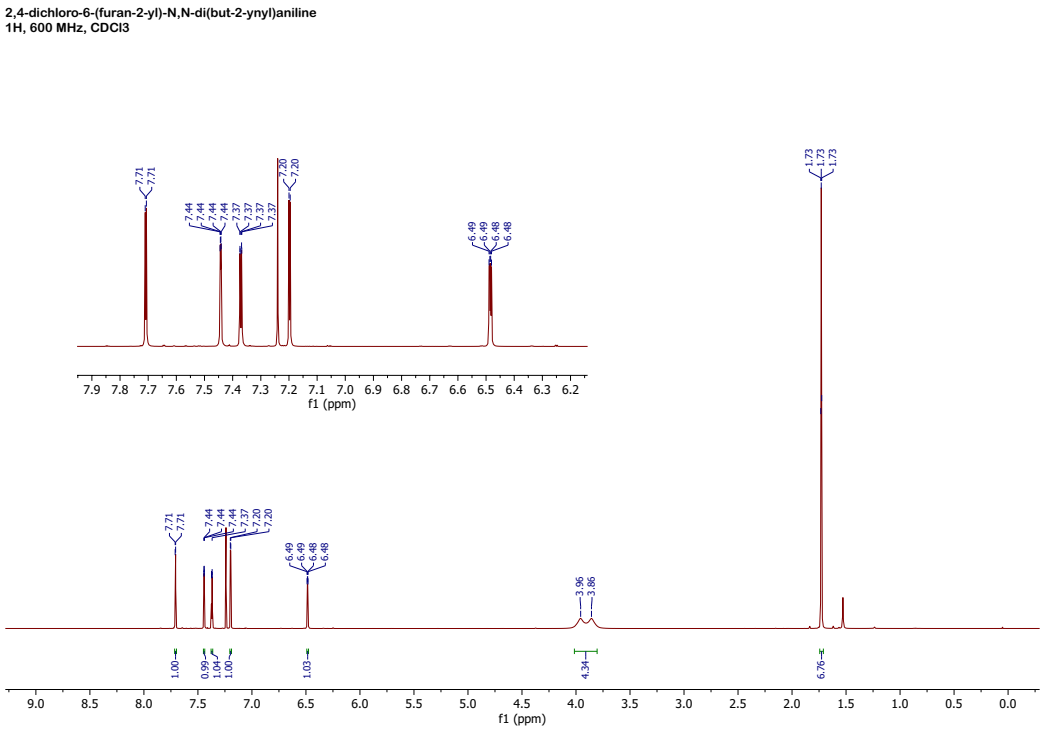
2,4-Dichloro-*N,N*–di(but-2-ynyl)-6-(furan-2-yl)aniline

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.71 (d, *J*=2.5 Hz, 1H, H-1), 7.44 (dd, *J*=1.7, 0.6 Hz, 1H, furyl H-5), 7.37 (dd, *J*=3.4, 0.6 Hz, 1H, furyl H-3), 7.20 (d, *J*=2.5, 1H, H-3), 6.48 (dd, *J*=3.4, 1.7 Hz, 1H, furyl H-4), 3.91 (d, broad, 4H, CH_2), 1.73 (t, *J*=2.5 Hz, 6H, CH^3).

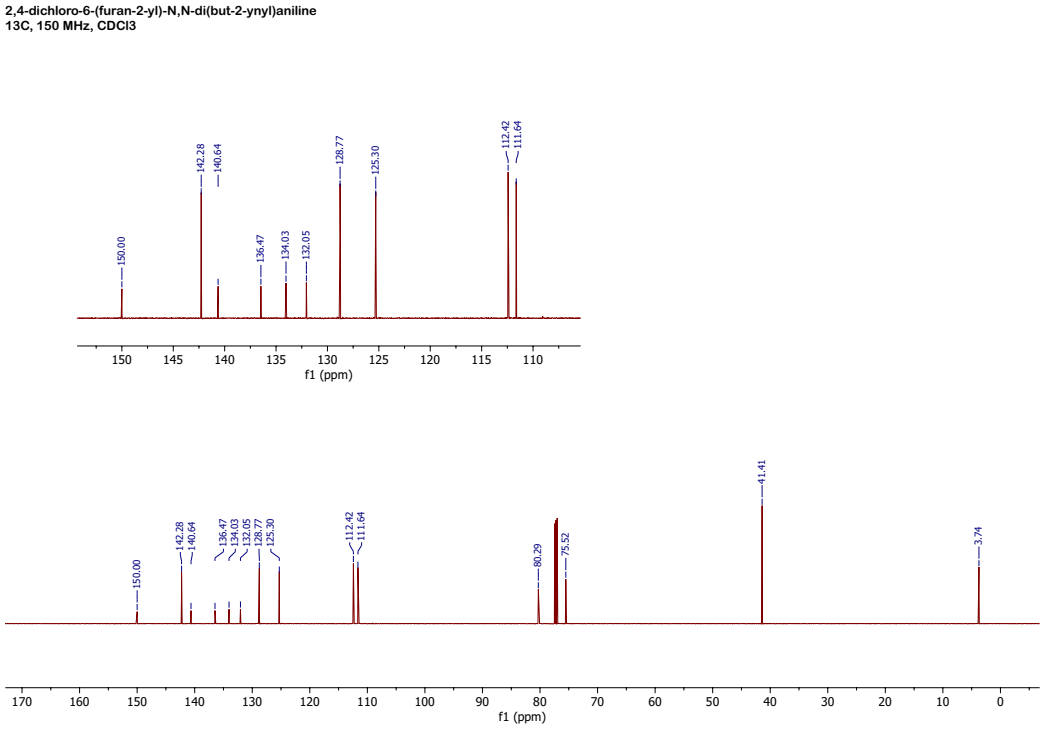
^{13}C-NMR (150 MHz, $CDCl_3$): δ 150.0 (furyl C-2), 142.3 (furyl C-5), 140.6 (C-4), 136.5 (C-2), 134.0 (C-5), 132.0 (C-6), 128.8 (C-3), 125.3 (C-1), 112.4 (furyl C-4), 111.6 (furyl C-3), 80.3 (C-**C**-CH^3), 75.5 (**C**-C-CH^3), 41.4 (CH_2), 3.7 (CH^3).

MS ESI m/z (rel %): 357/356/355/354 (4/63/19/100, MNa^+), 332 (12), 205 (7), 165 (5), 121 (12).

HRMS ESI: calculated for $C_{18}H_{15}Cl_2NNaO$ (MNa^+): 354.0423, found 354.0423.

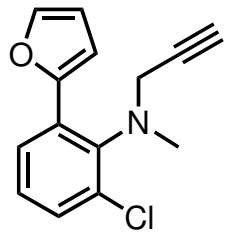


*Spectrum 21: [1]H-NMR spectrum of 2,4-dichloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80d**)*



*Spectrum 22: [13]C-NMR spectrum of 2,4-dichloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80d**)*

Synthesis of 2-chloro-6-(furan-2-yl)-*N*-methyl-*N*-(prop-2-ynyl)aniline (69a)



69a

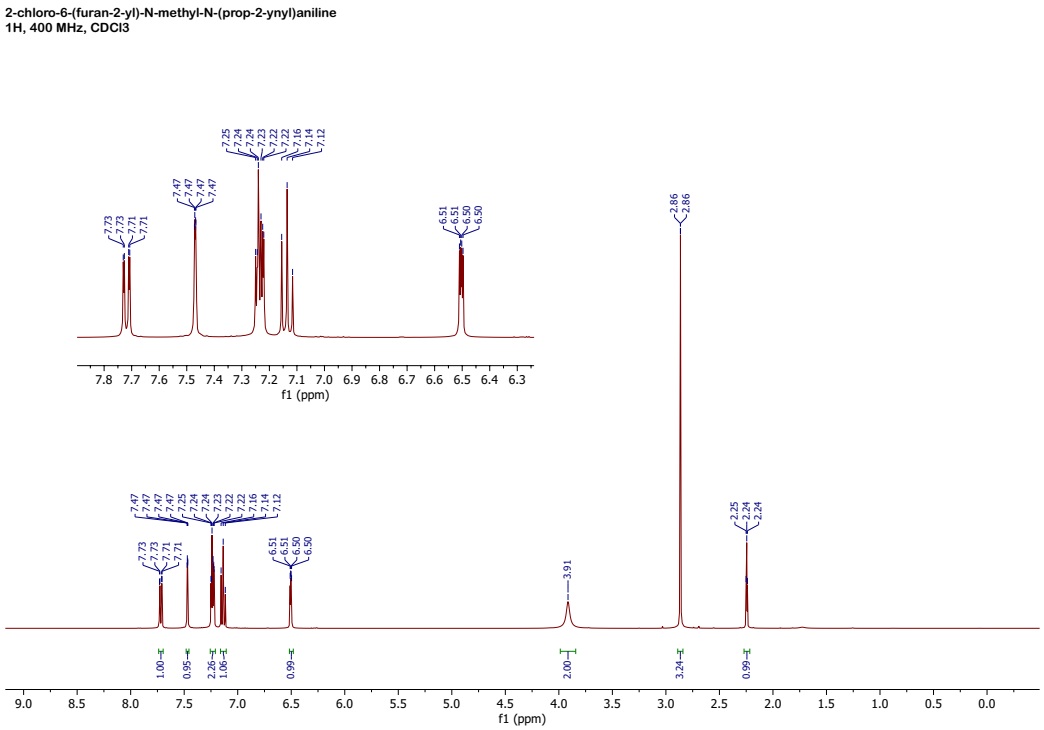
NaH (ca. 60 % in mineral oil, 332 mg, 8.31 mmol) was added to a solution of 2-chloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline (319 mg, 1.38 mmol) in dry DMF (25 mL) under Ar. The mixture was stirred for 15 minutes at 35 °C before dropwise addition of MeI (0.26 mL, 4.2 mmol). After 18 hrs, the reaction was quenched with 15 mL sat. NaCl, extracted with 3x50 mL DCM, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (9:1 hexanes/DCM). Yield: 263 mg (78%), yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.73 (dd, *J*=7.9, 1.6 Hz 1H, H-1), 7.47 (dd, *J*=1.7, 0.5 Hz, 1H, furyl H-5), 7.22 (m, 2H, H-3 and furyl H-3), 7.14 (t, *J*=7.9, H-4), 6.50 (dd, *J*=3.3, 1.7 Hz, 1H, furyl H-5), 3.91 (broad s, 2H, CH_2), 2.86 (s, 3H, N-CH^3), 2.25 (t, *J*=2.4 Hz, 1H, CH^3).

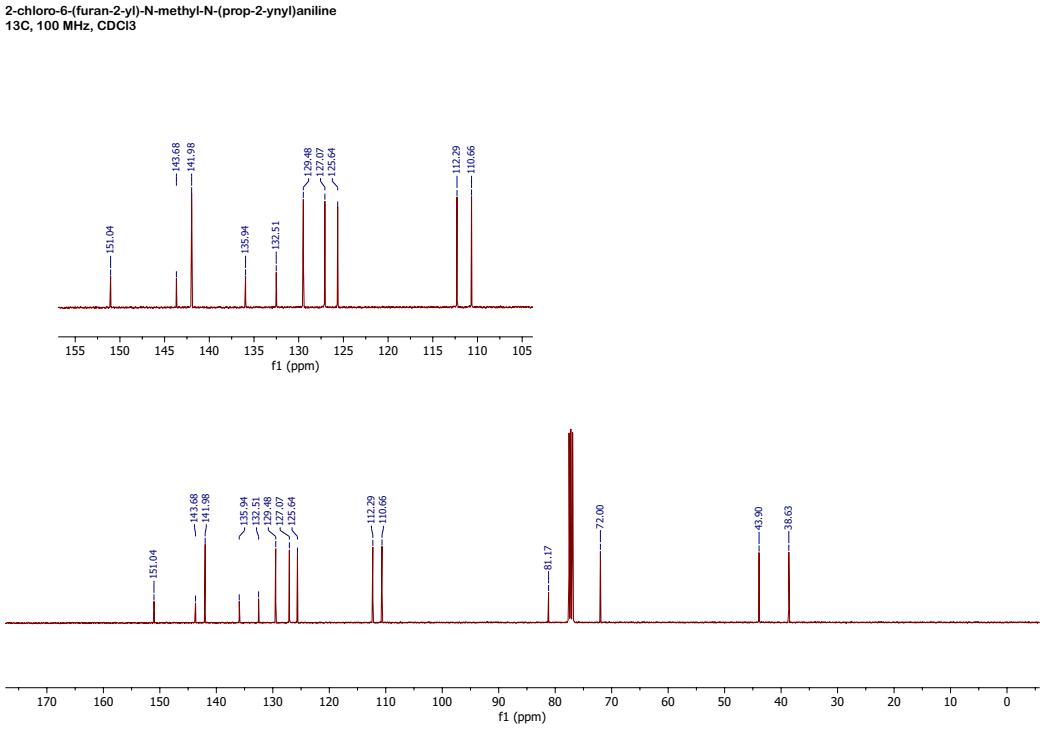
^{13}C-NMR (150 MHz, $CDCl_3$): δ 151.0 (furyl C-2), 143.7 (C-5), 142.0 (furyl C-5), 135.9 (C-2 or C-6), 132.5 (C-6 or C-2), 129.5 (C-3), 127.1 (C-4), 125.6 (C-1), 112.3 (furyl C-4), 110.7 (furyl C-3), 81.2 (**C**-CH), 72.0 (C-**C**H), 43.9 (CH_2), 38.6 (N-CH^3).

MS ESI m/z (rel %): 249/248/247/246 (5/33/15/100, MH^+), 209 (2), 207 (7), 185 (5).

HRMS ESI: calculated for $C_{14}H_{13}ClNO$ (MH^+): 246.0680, found 246.0680.

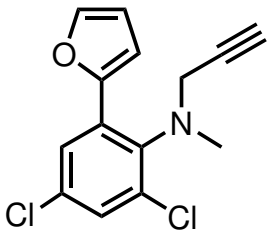


*Spectrum 23: [1]H-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69a**)*



*Spectrum 24: [13]C-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69a**)*

Synthesis of
2,4-dichloro-6-(furan-2-yl)-*N*-methyl-*N*-(prop-2-ynyl)aniline (69b)



69b

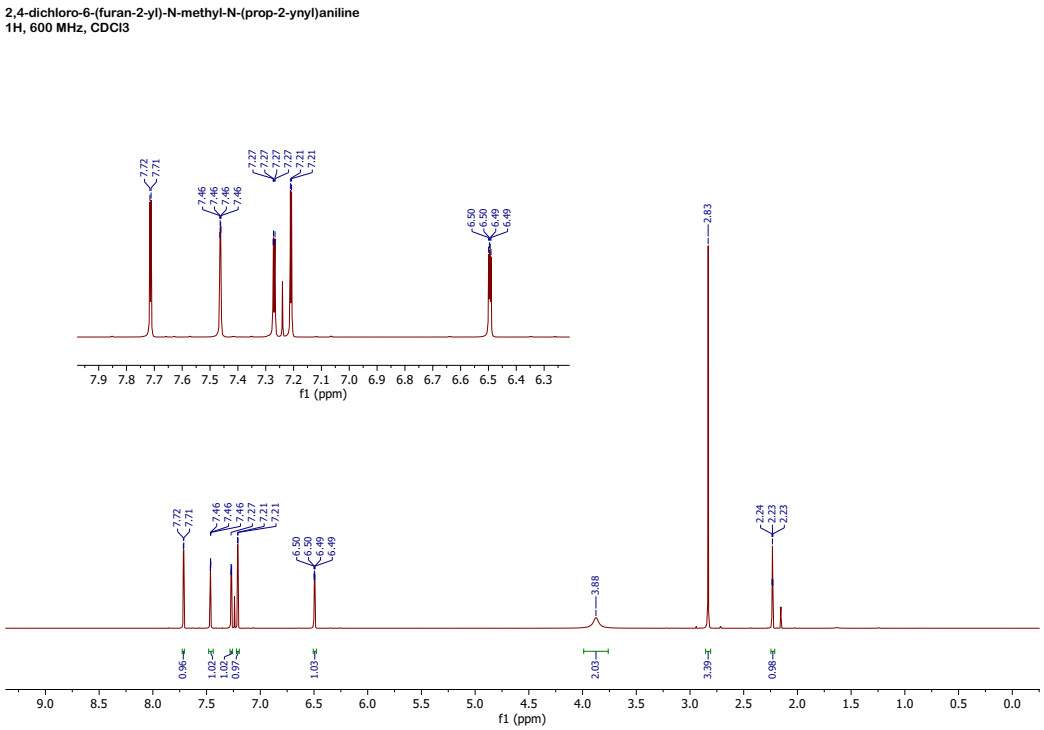
NaH (ca. 60% in mineral oil, 133 mg, 3.3 mmol) was added to a solution of compound 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline (328 mg, 1.23 mmol) in dry DMF (25 mL) under Ar. The mixture was stirred for 15 minutes at 35 °C before dropwise addition of MeI (0.25 mL, 4.0 mmol). After 17 hrs, the reaction was quenched with 15 mL sat. NaCl, extracted with 3x30 mL DCM, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (39:1 hexanes/DCM). Yield: 286 mg (83%), yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.71 (d, *J*=2.5 Hz, 1H, H-1), 7.46 (dd, *J*=1.7, 0.6 Hz, 1H, furyl H-5), 7.27 (dd, *J*=3.4, 0.6 Hz, 1H, furyl H-3), 7.21 (d, *J*=2.5 Hz, H-3), 6.49 (dd, *J*=3.4, 1.7 Hz, 1H, furyl H-4), 3.88 (broad s, 2H, CH_2), 2.83 (s, 3H, N-CH^3), 2.23 (t, *J*=2.5 Hz, 1H).

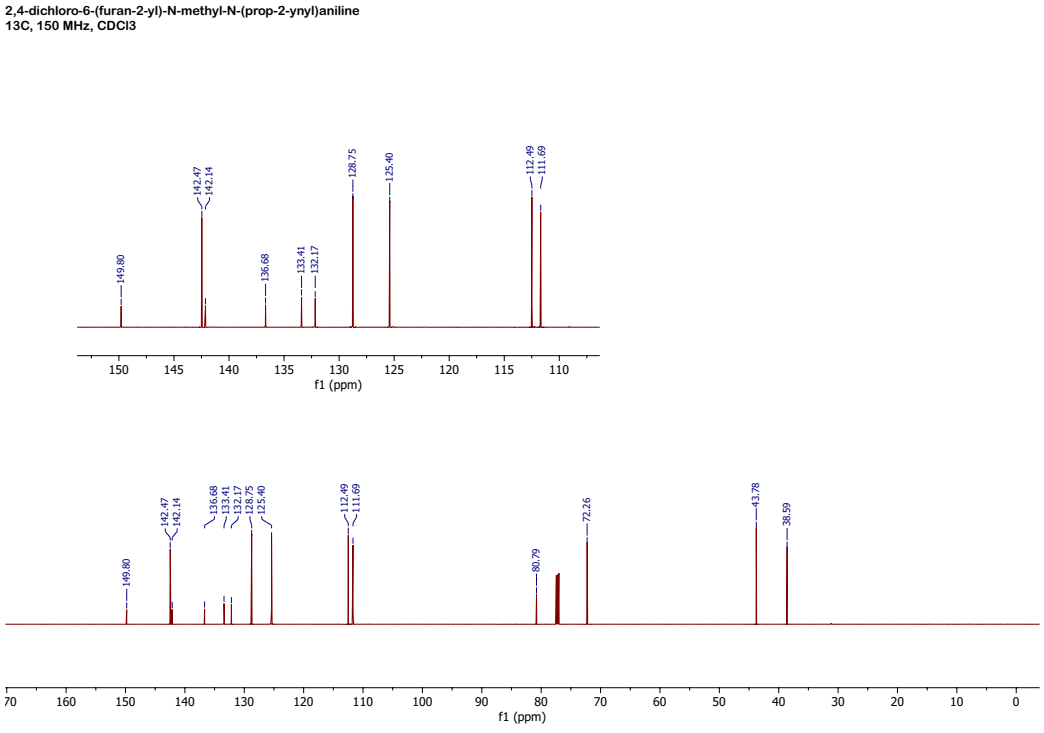
^{13}C-NMR (150 MHz, $CDCl_3$): δ 149.8 (furyl C-2), 142.5 (furyl C-5), 142.1 (C-6), 136.7 (C-2), 133.4 (C-5), 132.2 (C-4), 128.7 (C-3), 125.4 (C-1), 112.5 (furyl C-4), 111.7 (furyl C-3), 80.8 (**C**-CH), 72.3 (C-**C**H), 43.8 (CH_2), 38.6 (N-CH^3).

MS ESI m/z (rel %): 283/282/281/280 (10/63/15/100, MH^+), 227 (23), 185 (5), 165 (13), 159 (9), 135 (6).

HRMS ESI: calculated for $C_{14}H_{12}Cl_2NO$ (MH^+):280.0290, found 280.0291.

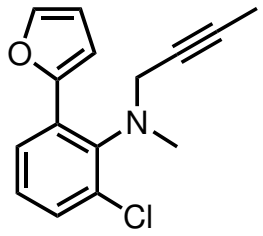


*Spectrum 25: [1]H-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69b**)*



*Spectrum 26: [13]C-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69b**)*

Synthesis of 2-chloro-6-(furan-2-yl)-*N*-methyl-*N*-(but-2-ynyl)aniline (69c)



69c

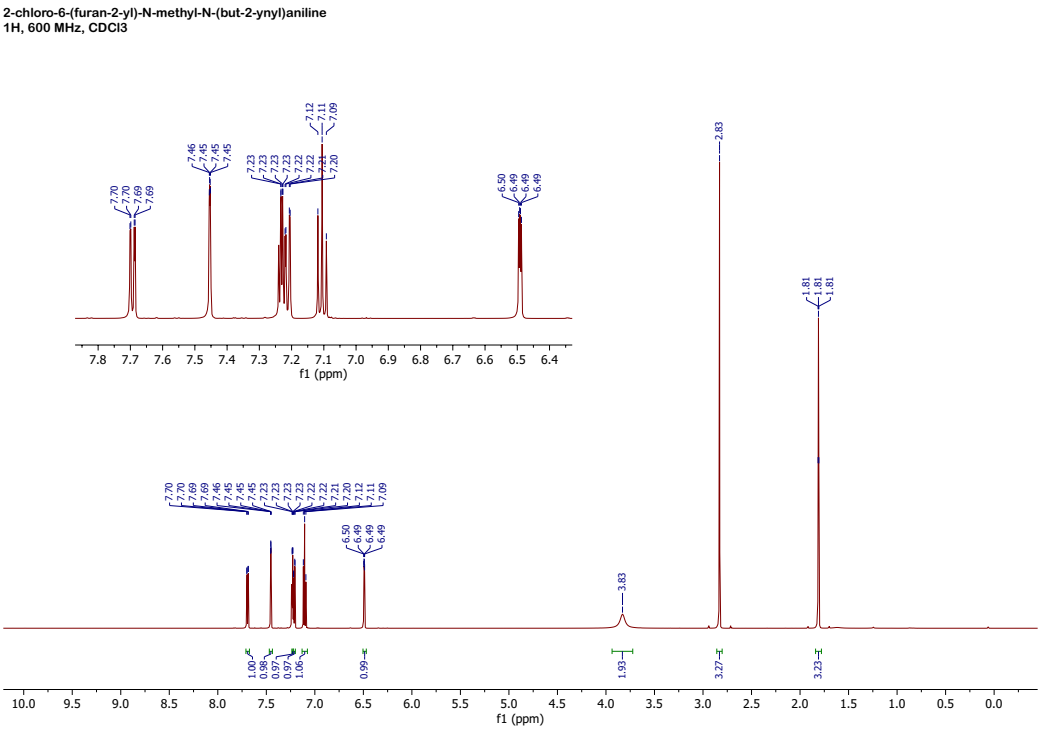
KH (ca. 35% suspension, 602 mg, 5.25 mmol) was added to an ice-cold solution of compound 2-chloro-6-(furan-2-yl)-*N*-(but-2-ynyl)aniline (414 mg, 1.68 mmol) in dry DMF (32 mL) under Ar. The mixture was stirred for 15 minutes while heating to 35 °C, and MeI (0.24 mL, 3.9 mmol) was added dropwise. After 24 h, the reaction was quenched with 20 mL sat. NaCl, extracted with 3x50 mL DCM, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (9:1 hexanes/DCM). Yield: 360 (83%), yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.69 (dd, *J*=7.9, 1.5 Hz, 1H, H-1), 7.45 (dd, *J*=1.5, 0.6 Hz, 1H, furyl H-5), 7.23 (dd, *J*=3.3, 0.6 Hz, 1H, furyl H-3), 7.21 (dd, *J*=7.9, 1.5 Hz, 1H, H-3), 7.11 (t, *J*=7.9 Hz, H-4), 6.49 (dd, *J*=3.3, 1.5 Hz, 1H, furyl H-4), 3.83 (broad s, 2H, CH^2), 2.83 (s, 3H, N-CH^3), 1.81 (t, *J*=2.4 Hz, 3H, C-CH^3).

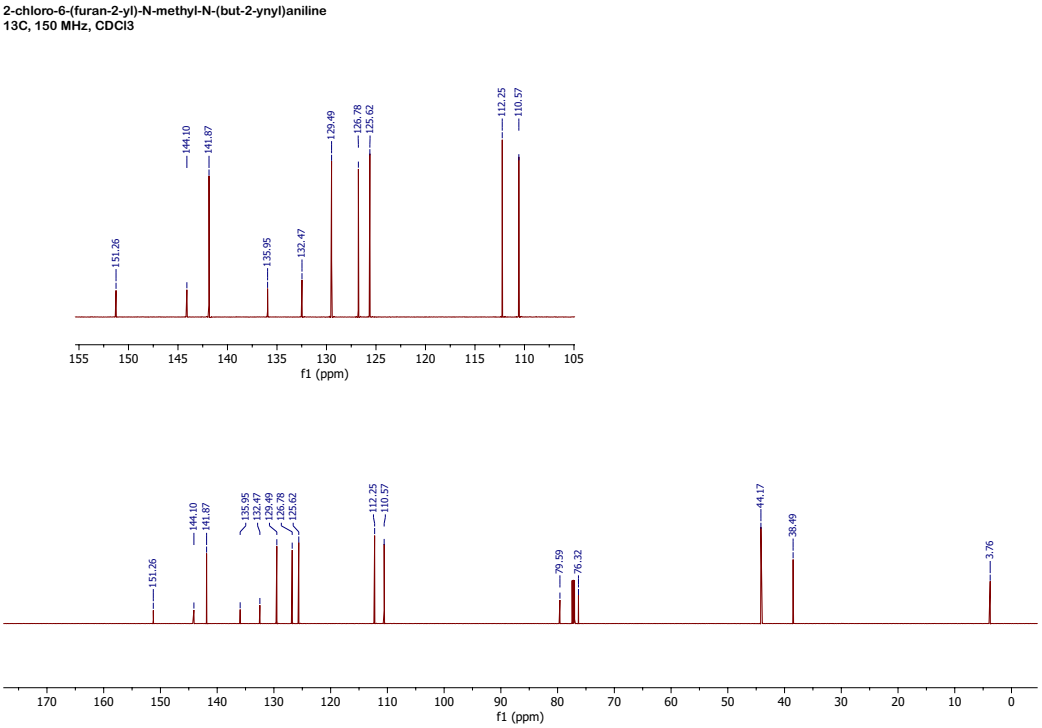
^{13}C-NMR (150 MHz, $CDCl_3$): δ 151.3 (furyl C-2), 144.1 (C-5), 141.9 (furyl C-5), 135.9 (C-6), 132.5 (C-2), 129.5 (C-3), 126.8 (C-4), 125.6 (C-1), 112.2 (furyl C-4), 110.6 (furyl C-3), 79.6 (C-**C**-CH^3), 76.3 (**C**-C-CH^3), 44.2 (CH_2), 38.5 (N-CH^3), 3.8 (C-**C**H_3).

MS ESI m/z (rel %): 263/262/261/260 (5/33/17/100, MH^+), 227 (4), 207 (6), 185 (7).

HRMS ESI: calculated for $C_{15}H_{15}ClNO$ (MH^+): 260.0837, found 260.0837.

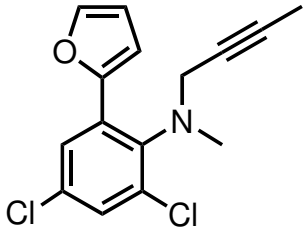


*Spectrum 27: [1]H-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69c**)*



*Spectrum 28: [13]C-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69c**)*

Synthesis of 2,4-dichloro-6-(furan-2-yl)-*N*-(but-2-ynyl)-*N*-methylaniline (69d)



69d

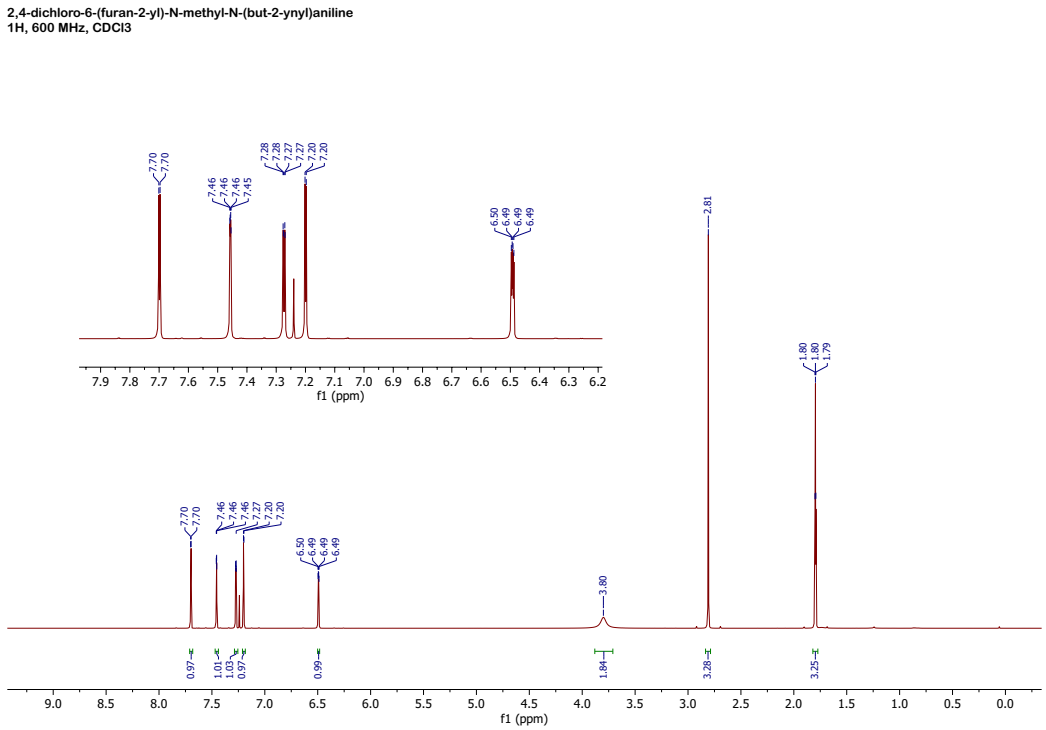
NaH (ca. 60% in mineral oil, 177 mg, 4.42 mmol) was added to a solution of 2,4-dichloro-6-(furan-2-yl)-*N*-(but-2-ynyl)aniline (454 mg, 1.62 mmol) in dry DMF (31 mL) under Ar. The mixture was stirred for 15 minutes at 35 °C, MeI (0.30 mL, 4.9 mmol) was added dropwise, and the reaction was left overnight. The reaction was quenched with 20 mL sat. NaCl, extracted with 3x50 mL DCM, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (19:1 hexanes/DCM). Yield: 390 mg (82%), yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J*=2.5 Hz, 1H, H-1), 7.46 (dd, *J*=1.8, 0.7 Hz, 1H, furyl H-5), 7.27 (dd, *J*=3.5, 0.7 Hz, 1H, furyl H-3), 7.20 (d, *J*=2.5 Hz, 1H, H-3), 6.49 (dd, *J*=3.5, 1.8 Hz, 1H, furyl H-4), 3.80 (broad s, 2H, CH_2), 2.81 (s, 3H, N-CH^3), 1.80 (t, *J*=2.5 Hz, 3H, C-CH^3).

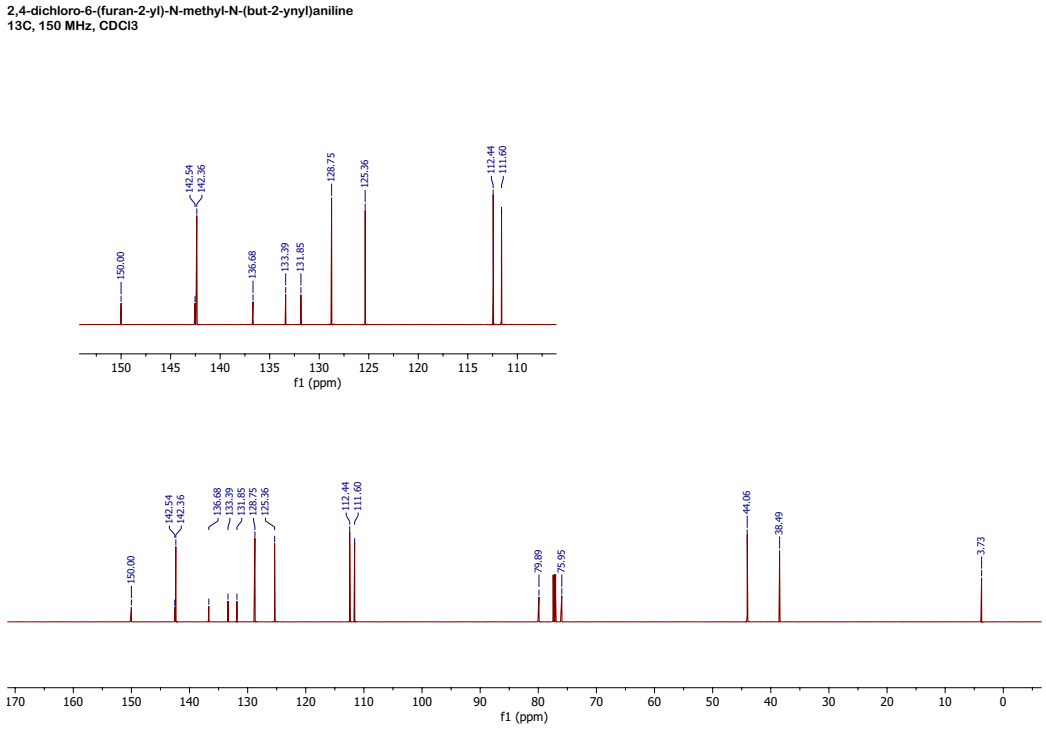
^{13}C-NMR (150 MHz, $CDCl_3$): δ 150.0 (furyl C-2), 142.5/142.4 (C-5 and furyl C-5), 136.7 (C-2 or C-6), 133.4 (C-6 or C-2), 131.8 (C-4), 128.8 (C-3), 125.4 (C-1), 112.4 (furyl C-4), 111.6 (furyl C-3), 79.9 (C-**C**-CH^3), 76.0 (**C**-C-CH^3), 44.1 (CH_2), 38.5 (N-CH^3), 3.7 (C-**C**H_3).

MS ESI m/z (rel %): 297/296/295/294 (10/64/16/100, MH^+), 241 (7), 227 (2).

HRMS ESI: calculated for $C_{15}H_{14}Cl_2NO$ (MH^+):294.0447, found 294.0447.

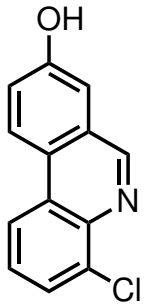


*Spectrum 29: [1]H-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69d**)*



*Spectrum 30: [13]C-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69d**)*

Synthesis of 4-chlorophenanthridin-8-ol (72a)



72a

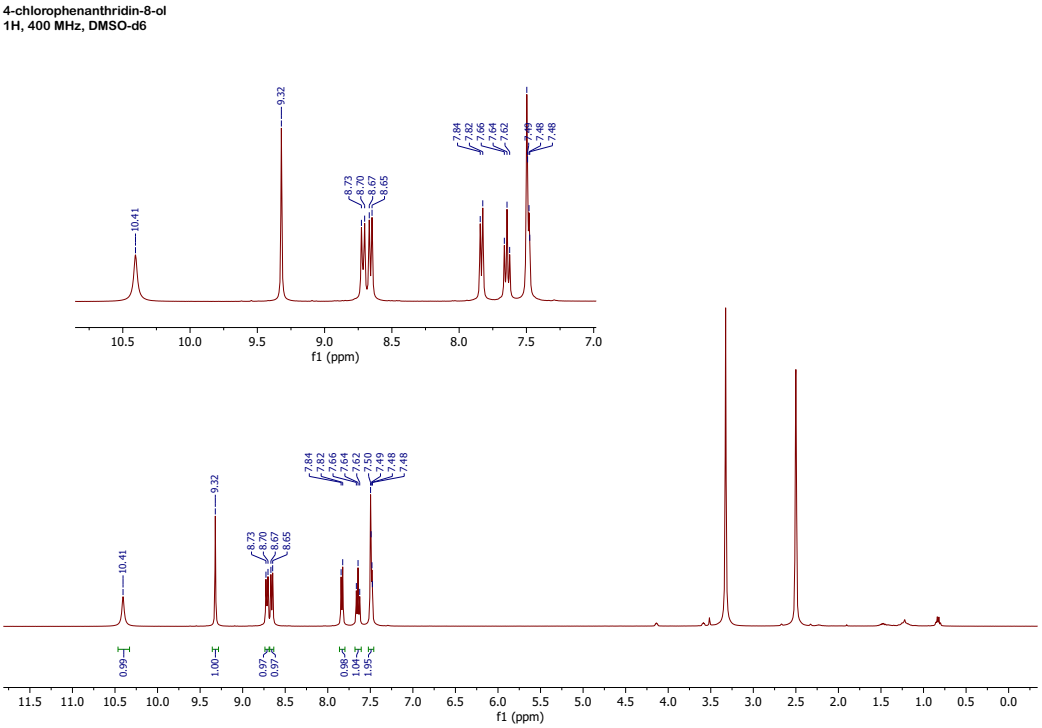
A 30 mL pressure capsule containing 2-chloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline (74 mg, 0.32 mmol) and 0.2 M HCl (2 drops) in degassed MeCN (7 mL) was heated to 180 °C for 150 min in a microwave oven. After transferring the reaction mixture to a quartz vial, air was bubbled through the solution in the presence of UV irradiation for 1 h. The product was purified by flash chromatography (3:2 hexanes/EtOAc). Yield 52 mg (72%), off-white solid, mp 219-220 °C.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.41 (s, 1H, OH), 9.32 (s, 1H, H-6), 8.71 (d, *J*=9.6 Hz, 1H, H-9), 8.65 (d, *J*=7.9 Hz, 1H, H-3), 7.83 (d, *J*=7.9 Hz, 1H, H-1), 7.64 (t, *J*=7.9 Hz, 1H, H-2), 7.49 (m, 2H, H-10 and H-7).

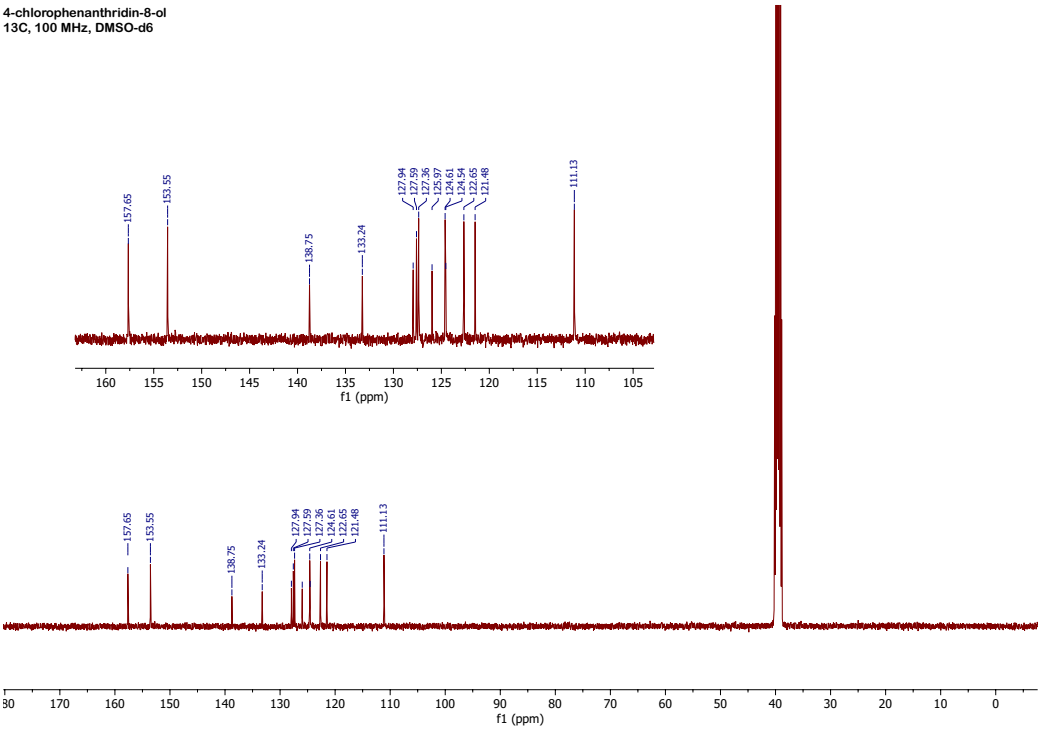
^{13}C-NMR (100 MHz, DMSO-d_6): δ 157.6 (C-10a), 153.6 (C-6), 138.8 (C-4), 133.2 (C-10b), 127.9 (C-6a), 127.6 (C-4a), 127.4 (C-1), 126.0 (C-2), 124.6 (C-8), 124.5 (C-9), 122.7 (C-7), 121.5 (C-3), 111.1 (C-10).

MS ESI m/z (rel %): 254/253/252 (32/14/100, MNa^+), 230 (93), 227 (8), 205 (8), 185 (13), 121 (8).

HRMS ESI: calculated for $C_{13}H_8ClNNaO$ (MNa^+): 252.0187, found 252.0187.

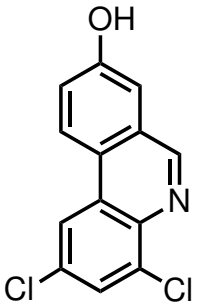


*Spectrum 31: ^{1}H-NMR spectrum of 4-chlorophenanthridin-8-ol (**72a**)*



*Spectrum 32: ^{13}C-NMR spectrum of 4-chlorophenanthridin-8-ol (**72a**)*

Synthesis of 2,4-dichlorophenanthridin-8-ol (72b)



72b

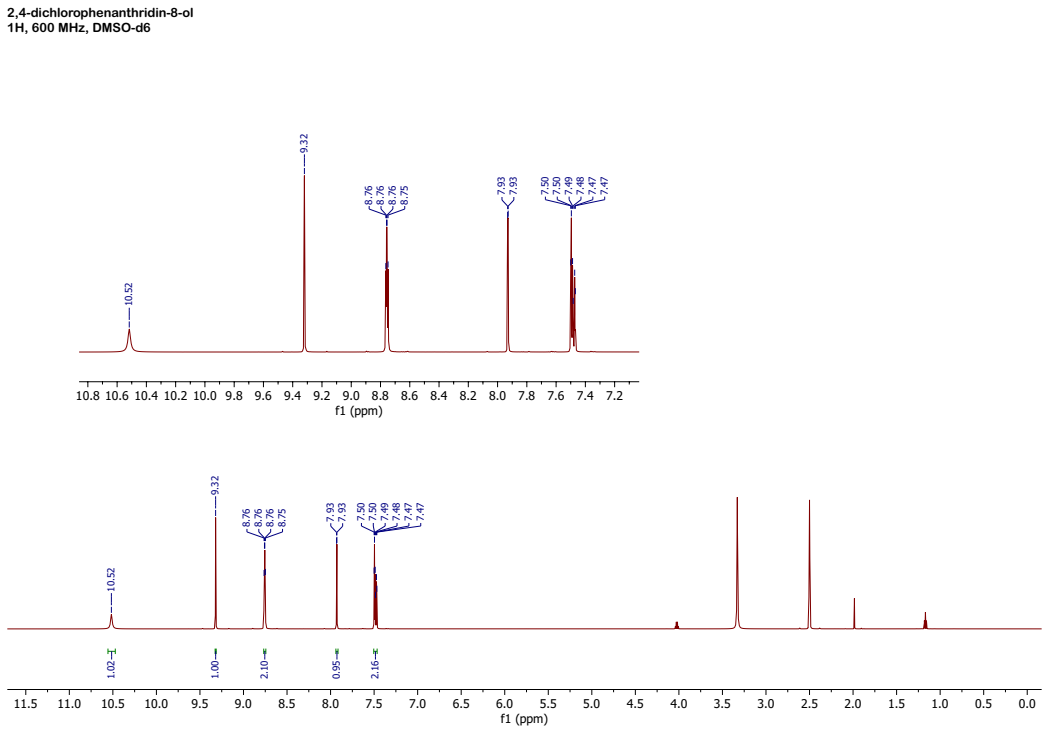
Using a literature procedure[13], a 30 mL pressure capsule containing 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline (111 mg, 0.417 mmol) and 0.2 M HCl (2 drops) in degassed MeCN (10 mL) was heated to 180 °C for 150 min in a microwave oven. After transferring the reaction mixture to a quartz vial, air was bubbled through the solution in the presence of UV irradiation for 1.5 h. The product was purified by flash chromatography (5:3 hexanes/EtOAc). Yield 85 mg (77%)[a], off-white powder, mp 294-297 °C (literature 297-298 °C[13]).

^{1}H-NMR (600 MHz, DMSO-d_6): δ 10.52 (s, 1H, OH), 9.32 (s, 1H, H-6), 8.76 (d, J=8.9 Hz, 1H, H-9), 8.76 (d, J=2.4 Hz, 1H, H-1 or H-3), 7.93 (d, J=2.4 Hz, 1H, H-3 or H-1), 7.48 (m, 2H, H-7 and H-10).

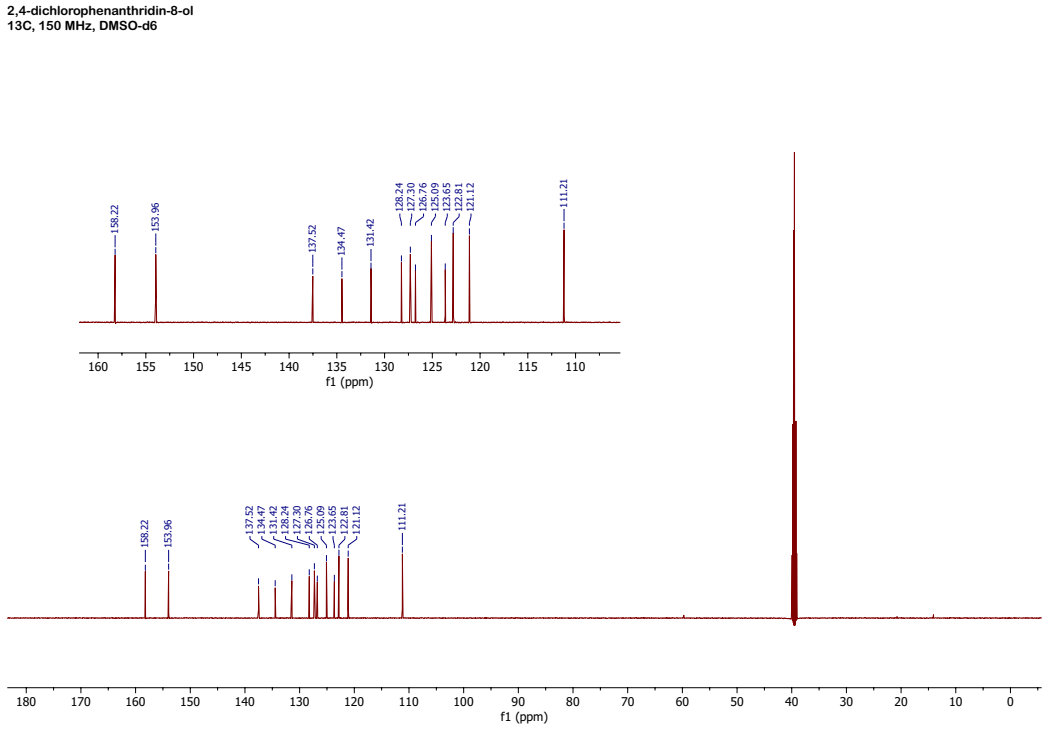
^{13}C-NMR (150 MHz, DMSO-d_6): δ 158.2 (C-10b), 154.0 (C-6), 137.5 (C10a), 134.5 (C-4), 131.4 (C-2), 128.2 (C-4a), 127.3 (C-3 or C-1), 126.8 (C-8), 125.1 (C-9), 123.6 (C-6a), 122.8 (C-7), 121.1 (C-3 or C-1), 111.2 (C-10).

MS ESI m/z (rel %): 290/289/288/287/286 (11/9/65/15/100, MNa^+), 266/265/264 (20/5/34), 121 (6).

HRMS ESI: calculated for $C_{13}H_7Cl_2NNaO$ (MNa^+): 285.9797, found 285.9796.

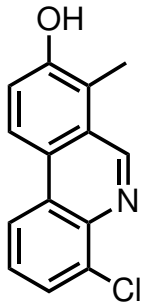


*Spectrum 33: ^{1}H-NMR spectrum of 2,4-dichlorophenanthridin-8-ol (**72b**)*



*Spectrum 34: ^{13}C-NMR spectrum of 2,4-dichlorophenanthridin-8-ol (**72b**)*

Synthesis of 4-chloro-7-methylphenanthridin-8-ol (72c)



72c

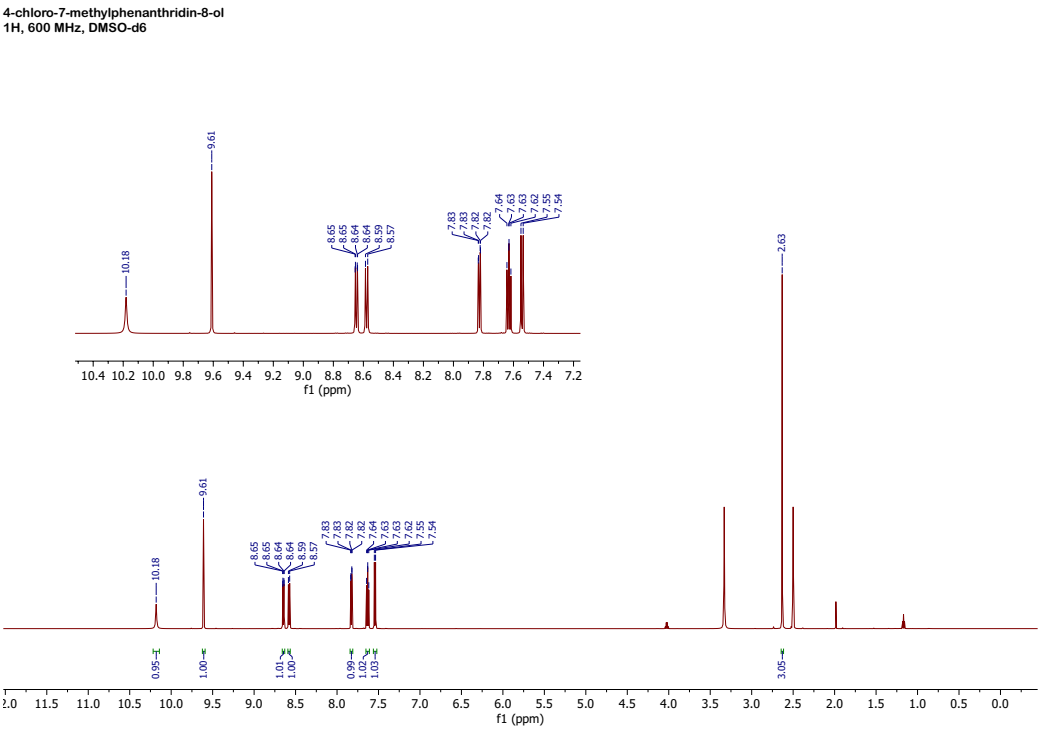
A 30 mL pressure capsule containing 2-chloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline (79 mg, 0.34 mmol) and 0.2 M HCl (2 drops) in degassed MeCN (8 mL) was heated to 200 °C for 6 h in a microwave oven. After transferring the reaction mixture to a quartz vial, air was bubbled through the solution in the presence of UV irradiation for 1.5 h. The product was purified by flash chromatography (3:1 hexanes/acetone). Yield 36 mg (47%), off-white solid, mp 264-266 °C.

^{1}H-NMR (600 MHz, DMSO-d_6): δ 10.18 (s, 1H, OH), 9.61 (s, 1H, H-6), 8.65 (dd, *J*=7.6, 1.2 Hz, 1H, H-3), 8.58 (d, *J*=8.9 Hz, 1H, H-9), 7.83 (dd, *J*=7.6, 1.2 Hz, 1H, H-1), 7.64 (t, *J*=7.6 Hz, 1H, H-2), 7.54 (d, *J*=8.9 Hz, 1H, H-10), 2.63 (s, 1H, CH^3).

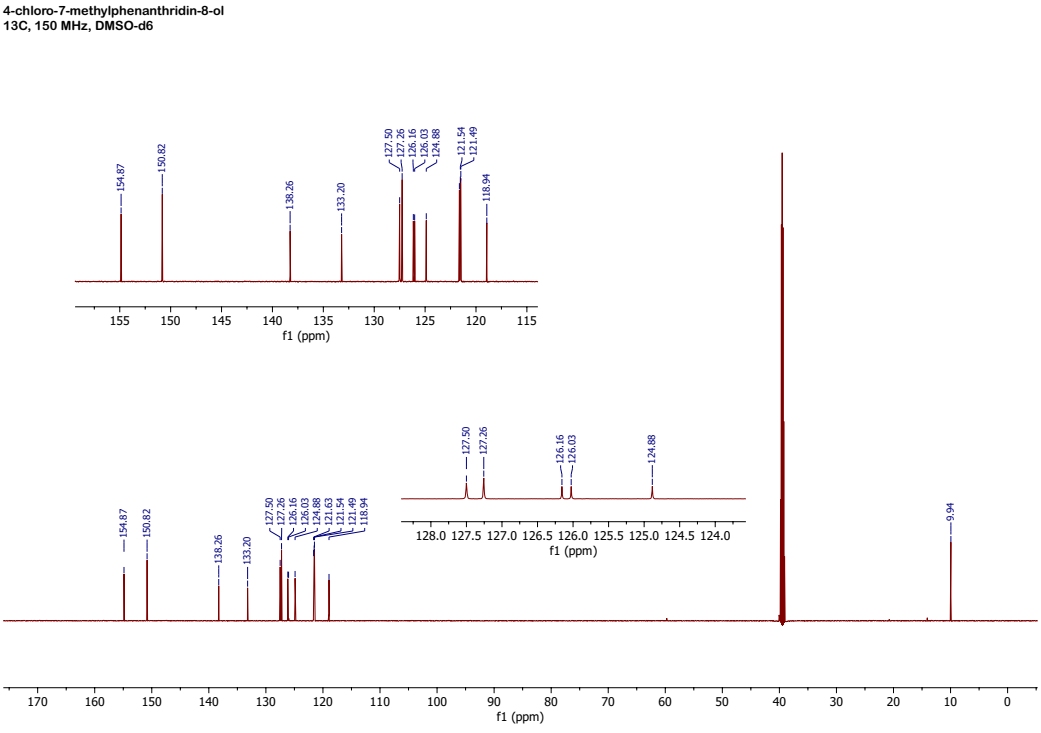
^{13}C-NMR (150 MHz, DMSO-d_6): δ 154.9 (C-10a), 150.8 (C-6), 138.3 (C-4a), 133.2 (C-4), 127.5 (C-1), 127.3 (C-2), 126.2 (C-7), 126.0 (C-8), 124.9 (C-10b), 121.6/121.5/121.5 (C-3, C-9 and C-10), 118.9 (C-6a), 9.9 (CH^3).

MS ESI m/z (rel %): 247/246/245 (33/16/100, MH^+), 227 (2), 135 (2).

HRMS ESI: calculated for $C_{14}H_{11}ClNO$ (MH^+): 244.0524, found 244.0523.

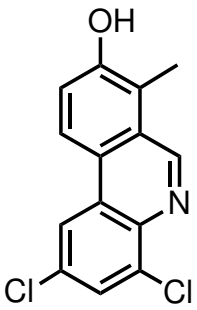


*Spectrum 35: [1]H-NMR spectrum of 4-chloro-7-methylphenanthridin-8-ol (**72c**)*



*Spectrum 36: [13]C-NMR spectrum of 4-chloro-7-methylphenanthridin-8-ol (**72c**)*

Synthesis of 2,4-dichloro-7-methylphenanthridin-8-ol (72d)



72d

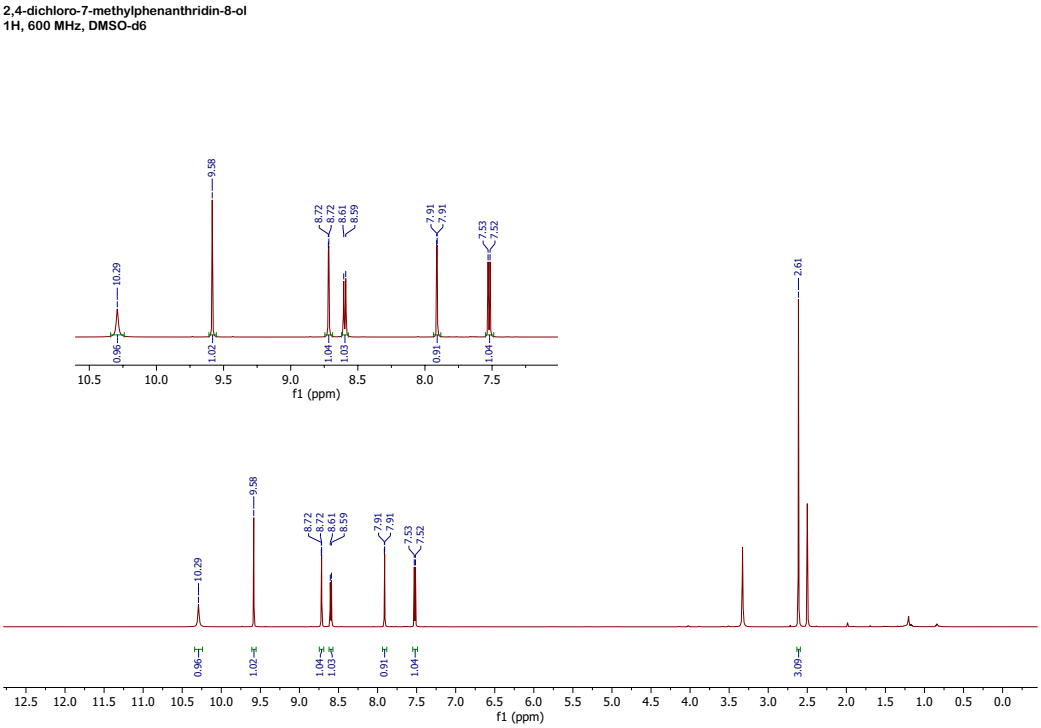
A 30 mL pressure capsule containing 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-ynyl)aniline (269 mg, 0.960 mmol) and 0.2 M HCl (5 drops) in degassed MeCN (18 mL) was heated to 200 °C for 6 h in a microwave oven. After transferring the reaction mixture to a quartz vial, air was bubbled through the solution in the presence of UV irradiation for 3 h. The product was purified by flash chromatography (4:1 hexanes/acetone). Yield 111 mg (42%), colorless flakes, mp 294-295 °C (decomposed).

^{1}H-NMR (600 MHz, DMSO-d_6): δ 10.29 (s, 1H, OH), 9.59 (s, 1H, H-6), 8.72 (d, *J*=2.1 Hz, 1H, H-1), 8.60 (d, *J*=8.9 Hz, 1H, H-9), 7.91 (d, *J*=2.1 Hz, 1H, H-3), 7.52 (d, *J*=8.9, 1H, H-10), 3.09 (s, 1H, CH_3).

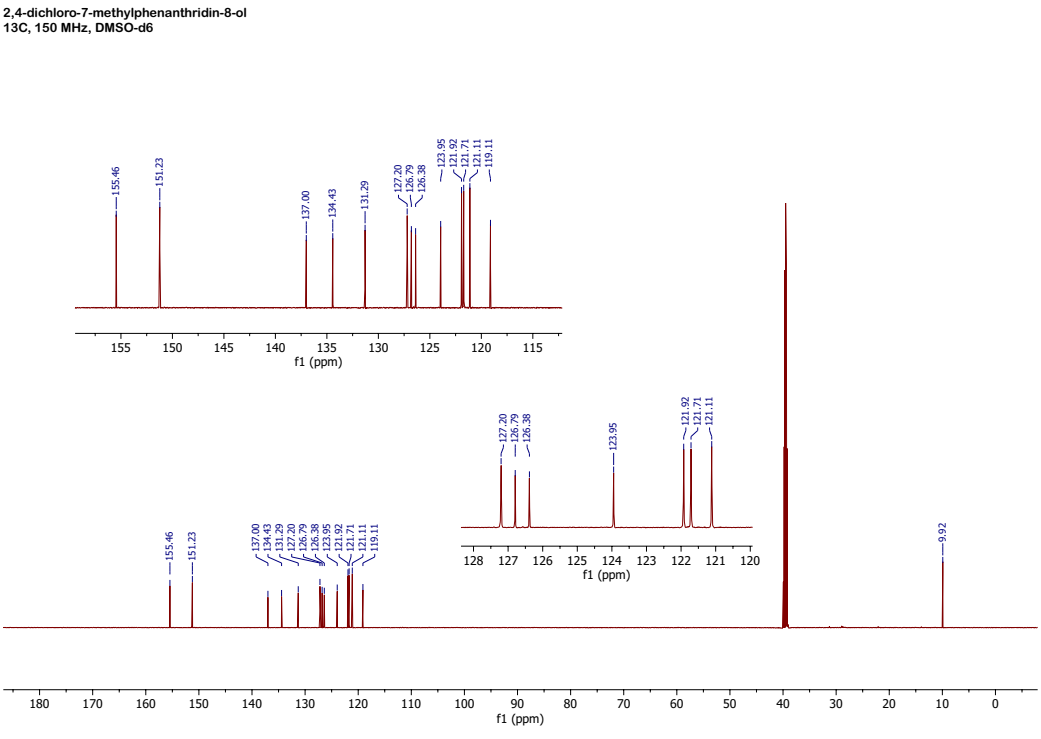
^{13}C-NMR (150 MHz, DMSO-d_6): δ 155.5 (C-10a), 151.2 (C-6), 137.0 (C-4a), 134.4 (C-2), 131.3 (C-10b), 127.2/126.8 (C-3 and C-4), 126.4 (C-7), 123.9 (C-8), 121.9/121.7 (C-10 and C-9), 121.1 (C-1), 119.1 (C-6a), 9.9 (CH^3).

MS ESI m/z (rel %): 304/303/302/301/300 (10/66/10/16/100, MNa^+), 280/278 (20/31), 121 (15).

HRMS ESI: calculated for $C_{14}H_9Cl_2NNaO$ (MNa^+): 299.9953, found 299.9953.

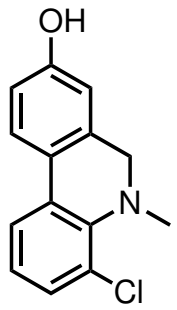


*Spectrum 37: [1]H-NMR spectrum of 2,4-dichloro-7-methylphenanthridin-8-ol (**72d**)*



*Spectrum 38: [13]C-NMR spectrum of 2,4-dichloro-7-methylphenanthridin-8-ol (**72d**)*

Synthesis of 4-chloro-5-methyl-5,6-dihydrophenanthridin-8-ol (71a)



71a

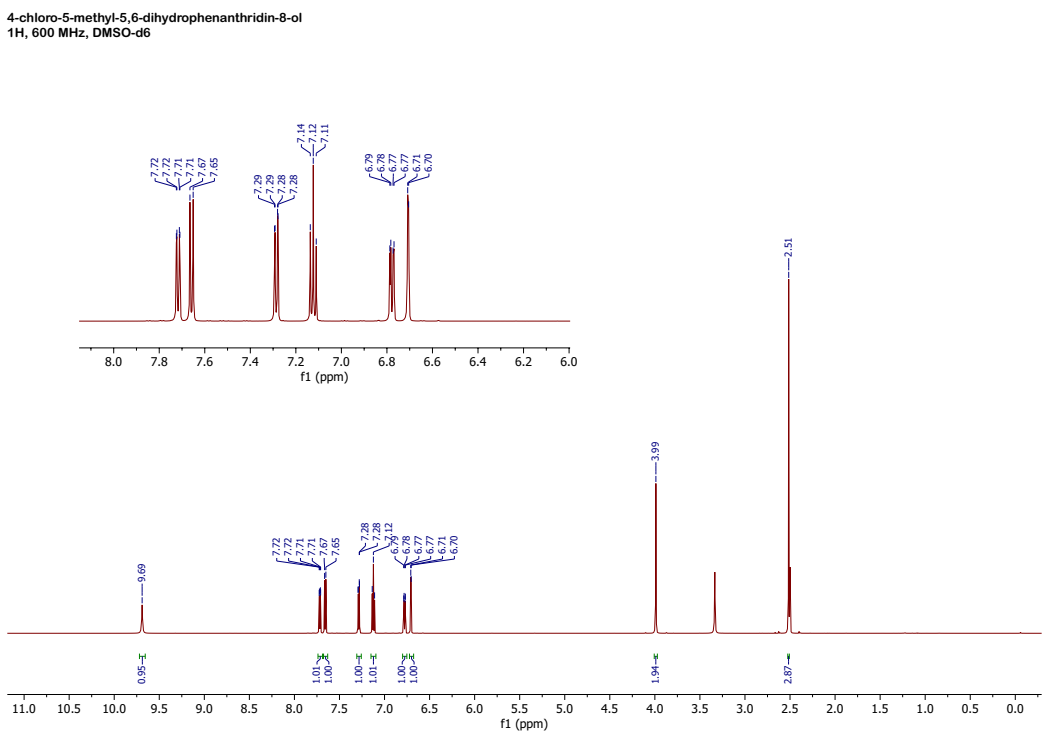
A 30 mL pressure capsule containing 2-chloro-6-(furan-2-yl)-*N*-methyl-*N*-(prop-2-ynyl)aniline (133 mg, 0.541 mmol) and 0.2 M HCl (3 drops) in degassed MeCN (10 mL) was heated to 180 °C for 150 min in a microwave oven. Solvents were removed *in vacuo*, and the product purified by flash chromatography (39:1 DCM/MeOH). Yield: 191 mg (89%), colorless crystals, mp 137-142 °C.

^{1}H-NMR (600 MHz, DMSO-d_6): δ 9.69 (s, 1H, OH), 7.73 (dd, *J*=7.8, 1.3 Hz, 1H, H-1 or H-3), 7.66 (d, *J*=8.4 Hz, 1H, H-10), 7.29 (dd, *J*=7.8, 1.3 Hz, 1H, H-3 or H-1), 7.12 (t, *J*=7.8 Hz, 1H, H-2), 6.78 (dd, *J*=8.4, 2.5 Hz, 1H, H-9), 6.71 (d, *J*=2.5, Hz, 1H, H-7), 3.99 (s, 2H, CH_2), 2.52 (s, 3H, N-CH^3).

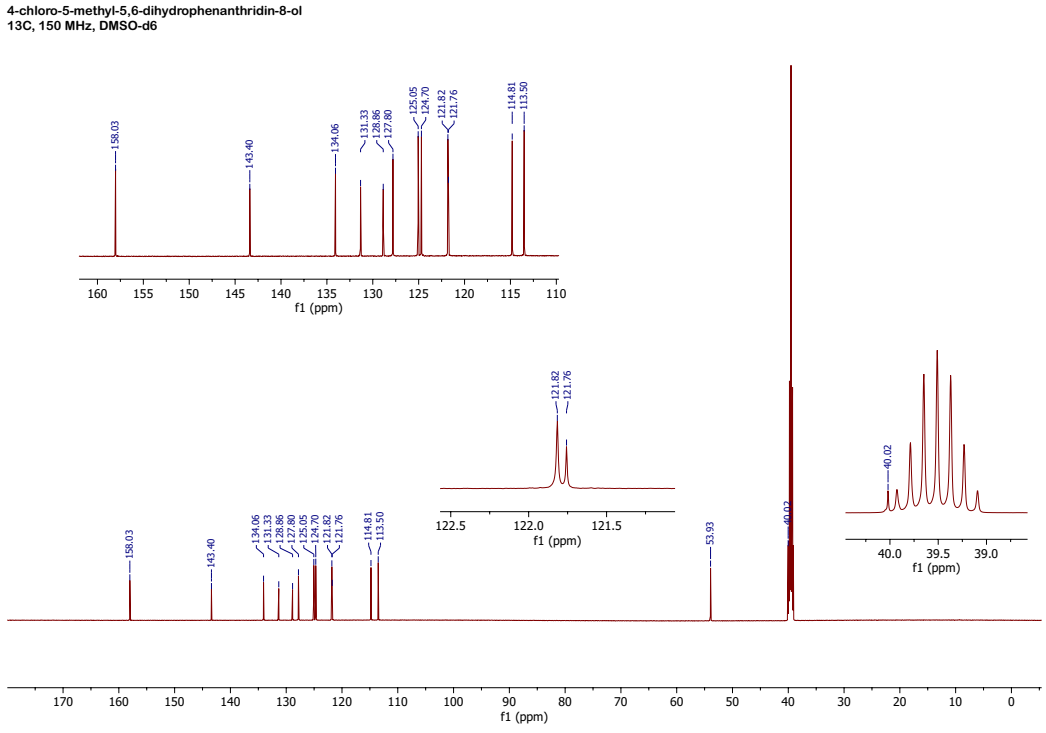
^{13}C-NMR (150 MHz, DMSO-d_6): δ 158.0 (C-8), 143.4 (C-4a), 134.1 (C-6a), 131.3 (C-10b), 128.9 (C-4), 127.8 (C-3), 125.1 (C-2), 124.7 (C-10), 121.8 (C-1), 121.8 (C-10a), 114.8 (C-9), 113.5 (C-7), 50.7 (C-6), 40.0 (N-CH^3).

MS ESI m/z (rel %): 249/248/247/246 (5/33/16/100, MH^+), 227 (3), 185 (3).

HRMS ESI: calculated for $C_{14}H_{13}ClNO$ (MH^+): 246.0680, found 246.0680.

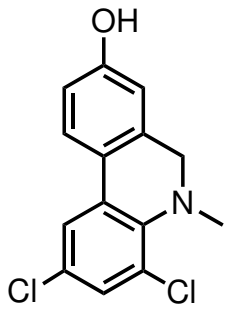


*Spectrum 39: [1]H-NMR spectrum of 4-chloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71a**)*



*Spectrum 40: [13]C-NMR spectrum of 4-chloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71a**)*

Synthesis of 2,4-dichloro-5-methyl-5,6-dihydrophenanthridin-8-ol (71b)



71b

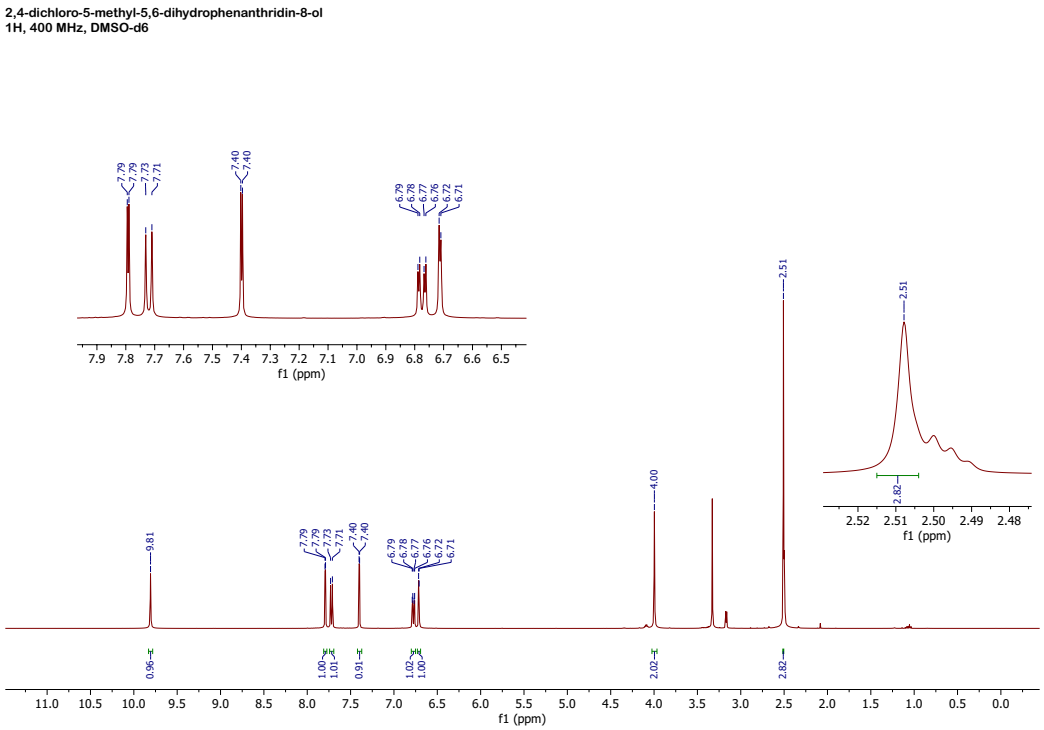
A 30 mL pressure capsule containing 2,4-dichloro-6-(furan-2-yl)-*N*-methyl-*N*-(prop-2-ynyl)aniline (237 mg, 0.846 mmol) and 0.2 M HCl (5 drops) in degassed MeCN (20 mL) was heated to 180 °C for 180 min in a microwave oven. Solvents were removed *in vacuo*, and the product purified by flash chromatography (49:1 DCM/MeOH). Yield: 169 mg (71 %), golden crystals, mp 183-187 °C.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.81 (s, 1H, OH), 7.79 (d, *J*=2.3 Hz, 1H, H-1), 7.72 (d, *J*=8.4 Hz, 1H, H-10), 7.40 (d, *J*=2.3 Hz, 1H, H-3), 6.77 (dd, *J*=8.4, 2.5 Hz, 1H, H-9), 6.71 (d, *J*=2.5 Hz, 1H, H-7), 4.00 (s, 2H, -CH_2-), 2.51 (s, 3H, N-C_3).

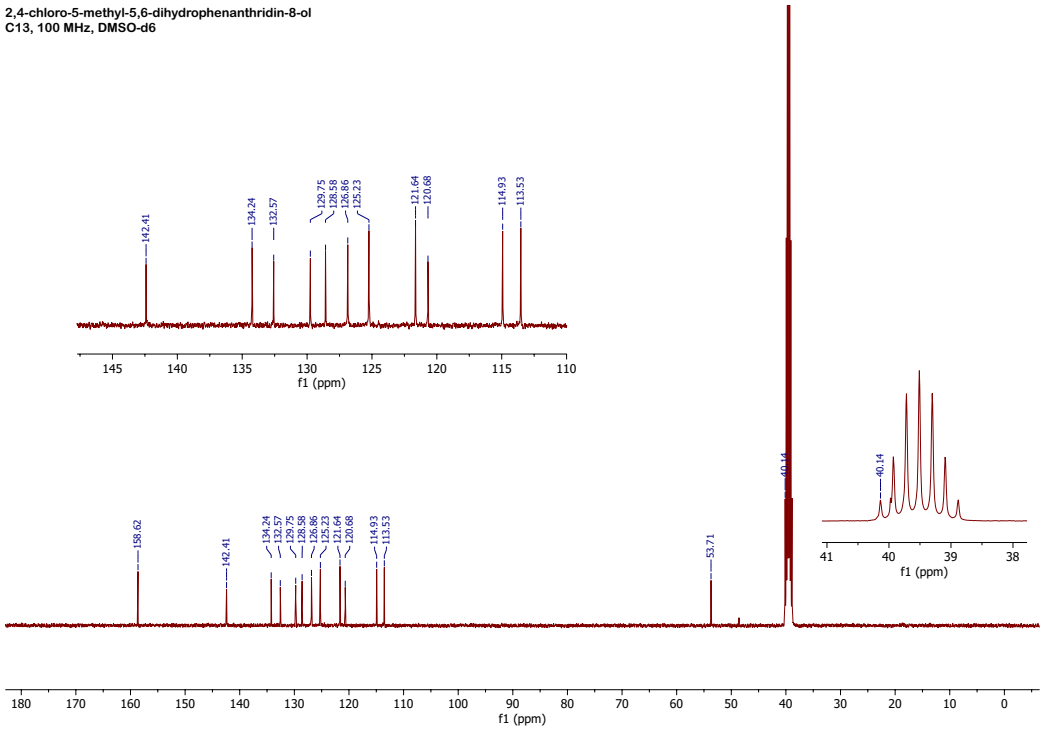
^{13}C-NMR (100 MHz, DMSO-d_6): δ 158.6 (C-8), 142.4 (C-4a), 134.2 (C-6a), 132.6 (C-10b), 129.7 (C-2), 128.6 (C-4), 126.9 (C-3), 125.2 (C-10), 121.6 (C-1), 120.7 (C-10a), 114.9 (C-9), 113.5 (C-7), 53.7 (C-6), 40.1 (N-CH^3).

MS ESI m/z (rel %): 284/283/282/281/280 (10/10/63/16/100, MH^+), 273 (8), 261 (4), 217 (3), 185 (5).

HRMS ESI: calculated for $C_{14}H_{12}Cl_2NO$ (MH^+): 280.0290, found 280.0290.

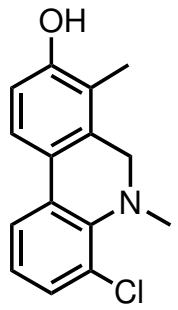


*Spectrum 41: [1]H-NMR spectrum of 2,4-dichloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71b**)*



*Spectrum 42: [13]C-NMR spectrum of 2,4-dichloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71b**)*

Synthesis of 4-chloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (71c)



71c

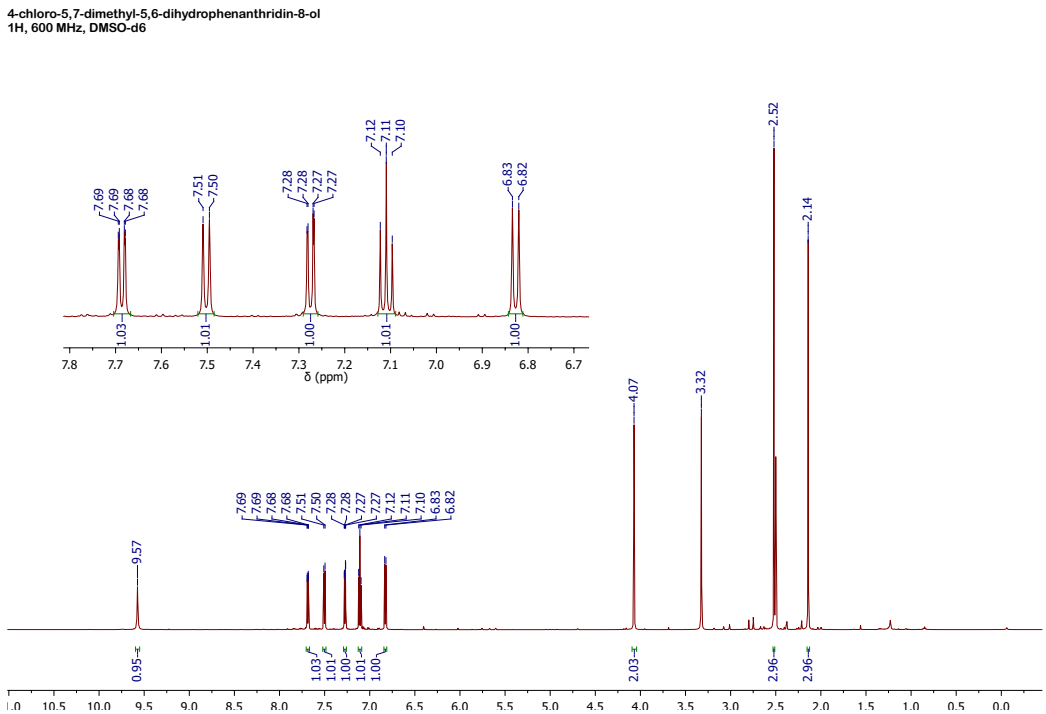
A 30 mL presure capsule containing 2-chloro-6-(furan-2-yl)-*N*-(but-2-ynyl)-*N*-methylaniline (153 mg, 0.598 mmol) and 0.2 M HCl (2 drops) in degassed MeCN (12 mL) was heated to 200 °C for 6 h in a microwave oven. Solvents were removed *in vacuo*, and the product purified by flash chromatography (149:1 DCM/MeOH). Yield: 107 mg (70%), orange crystals, mp 142-144 °C.

^{1}H-NMR (600 MHz, DMSO-d_6): δ 9.57 (s, 1H, OH), 7.68 (dd, *J*=7.9, 1.4 Hz, 1H, H-1 or H-3), 7.50 (d, *J*=8.3 Hz, 1H, H-9), 7.27 (dd, *J*=7.9, 1.4 Hz, 1H, H-3 or H-1), 7.11 (t, *J*=7.9 Hz, 1H, H-2), 6.83 (d, *J*=8.3, 1H, H-10), 4.07 (s, 2H, CH_2), 2.52 (s, 3H, N-CH^3), 2.14 (s, 3H, C-CH^3).

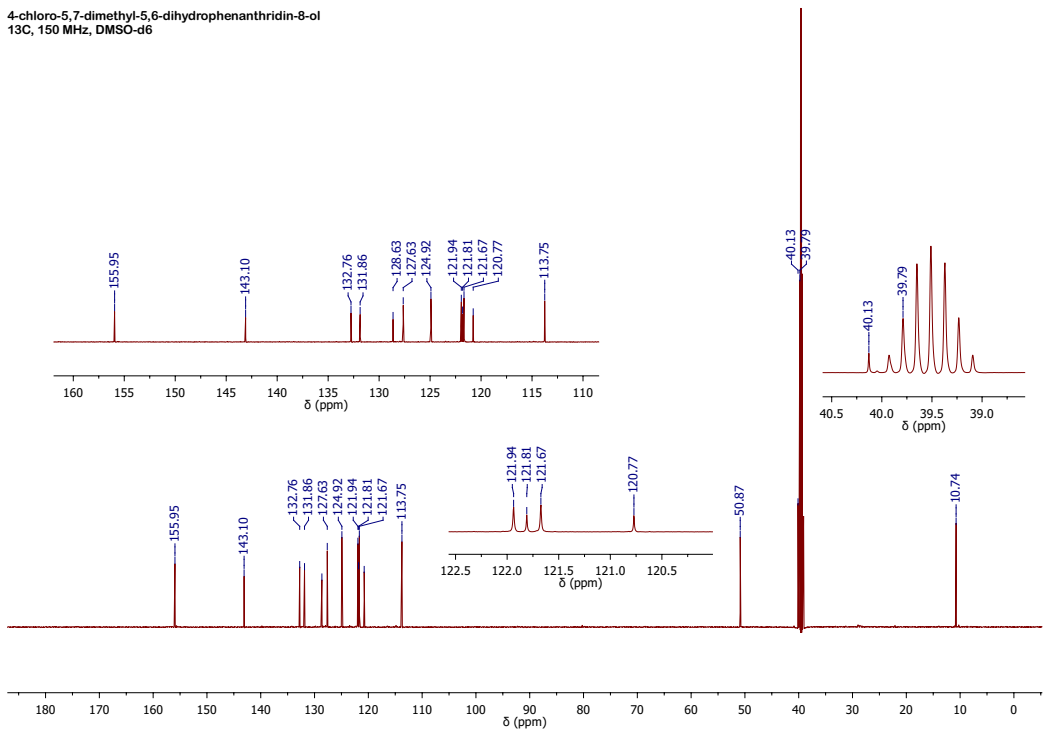
^{13}C-NMR (150 MHz, DMSO-d_6): δ 155.9 (C-8), 143.1 (C-4a), 132.8 (C-6a), 131.9 (C-10b), 128.6 (C-2 or C-4), 127.6 (C-3 or C-1), 124.9 (C-4 or C-2), 121.9/121.8/121.7 (C-1 or C-3, C-10a and C-9), 120.8 (C-7), 113.8 (C-10), 50.9 (CH_2), 40.1 (N-CH^3), 10.7 (C-CH^3).

MS ESI m/z (rel %): 263/262/261/260 (6/33/17/100, MH^+), 258 (32), 227 (3), 227 (20), 159 (7), 135 (3).

HRMS ESI: calculated for $C_{15}H_{15}ClNO$ (MH^+): 260.0837, found 260.0836.

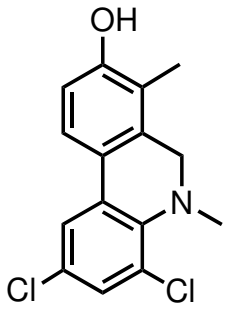


*Spectrum 43: [1]H-NMR spectrum of 4-chloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71c**)*



*Spectrum 44: [13]C-NMR spectrum of 4-chloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71c**)*

Synthesis of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (71d)



71d

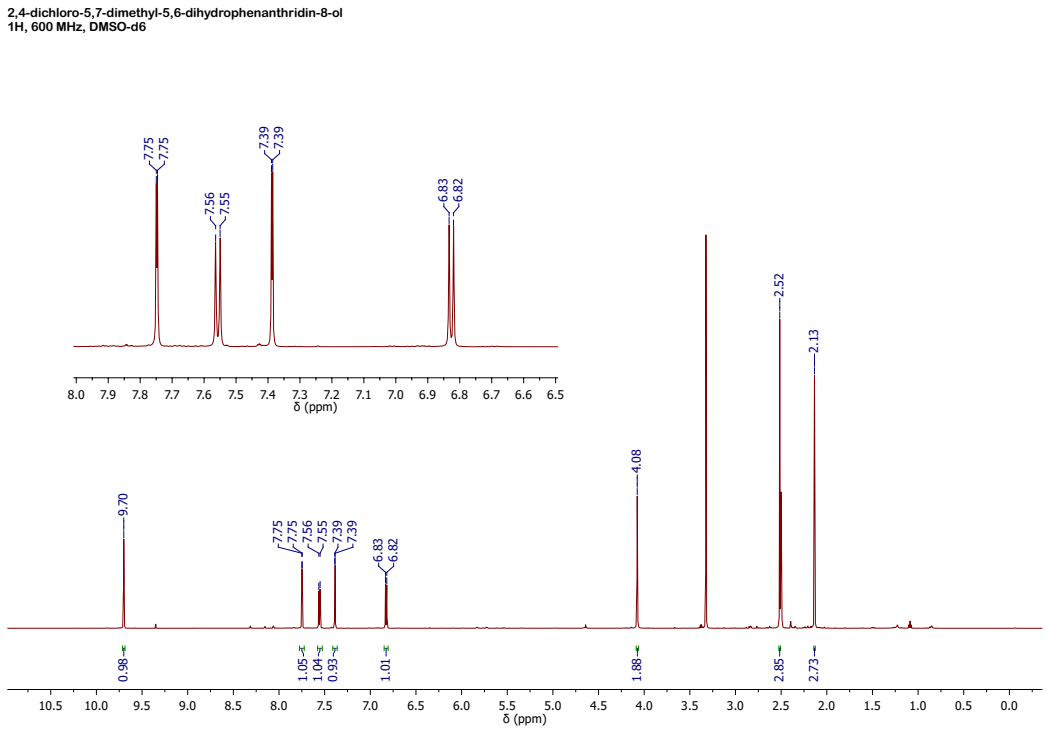
A 30 mL presure capsule containing 2,4-dichloro-6-(furan-2-yl)-*N*-(but-2-ynyl)-N-methylaniline (196 mg, 0.666 mmol) and 0.2 M HCl (2 drops) in degassed MeCN (13 mL) was heated to 200 °C for 7 h in a microwave oven. Solvents were removed *in vacuo*, and the product purified by flash chromatography (199:1 DCM/MeOH). Yield: 118 mg (60%), pink powder, mp 148-151 °C.

^{1}H-NMR (600 MHz, DMSO-d_6): δ 9.70 (s, 1H, OH), 7.75 (d, J=2.4 Hz, 1H, H-1 or H-3), 7.56 (d, J=8.4 Hz, 1H, H-9), 7.39 (d, J=2.4 Hz, 1H, H-3 or H-1), 6.83 (d, J=8.4, 1H, H-10), 4.08 (s, 2H, CH_2), 2.52 (s, 3H, N-CH^3), 2.13 (s, 3H, C-CH^3).

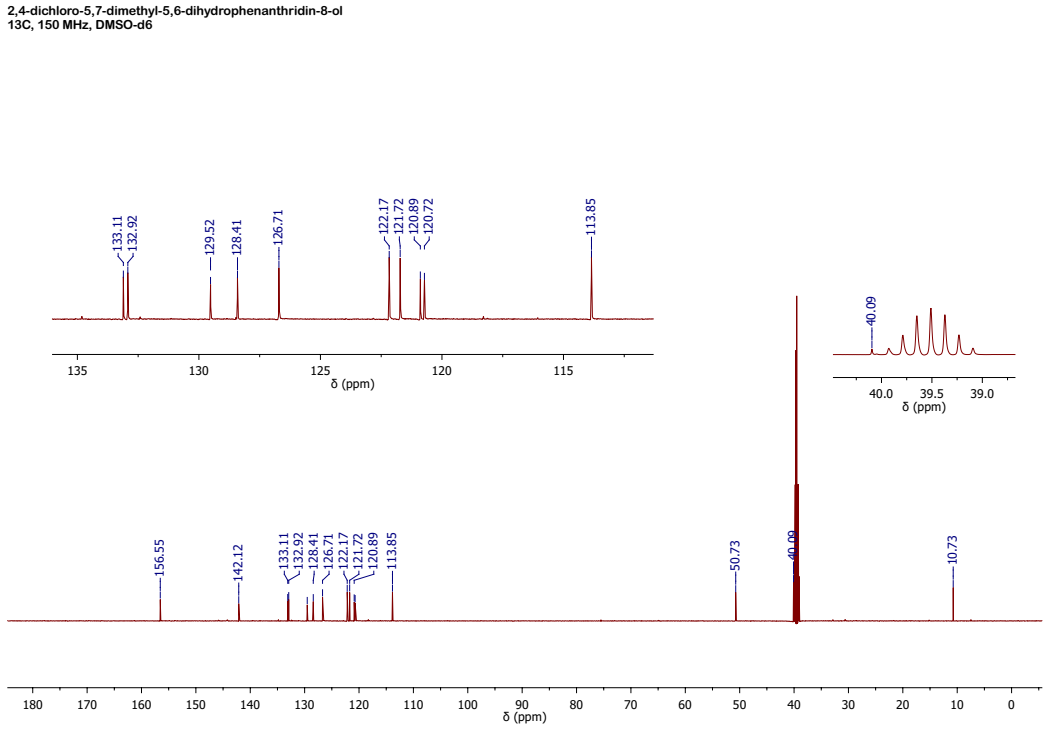
^{13}C-NMR (150 MHz, DMSO-d_6): δ 156.5 (C-8), 142.1 (C-4), 133.1/132.9 (C-6a and C-10a), 129.5 (C-4a), 128.4 (C-10b), 126.7 (C-3 or C-1), 122.2 (C-9), 121.7 (C-1 or C-3), 120.9/120.7 (C-7 and C-2), 113.8 (C-10), 50.7 (CH_2), 40.1 (N-CH^3), 10.7 (C-CH^3).

MS ESI m/z (rel %): 298/297/296/295/294 (10/11/63/17/100, MH^+), 293 (3), 292 (17), 289 (4), 227 (9), 159 (3).

HRMS ESI: calculated for $C_{15}H_{14}Cl_2NO$ (MH^+): 294.0447, found 294.0446.

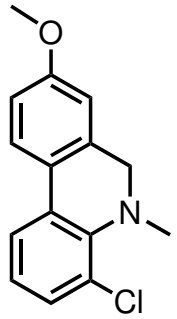


*Spectrum 45: [1]H-NMR spectrum of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71d**)*



*Spectrum 46: [13]C-NMR spectrum of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71d**)*

Synthesis of 4-chloro-8-methoxy-5-methyl-5,6-dihydrophenanthridine (81a)



81a

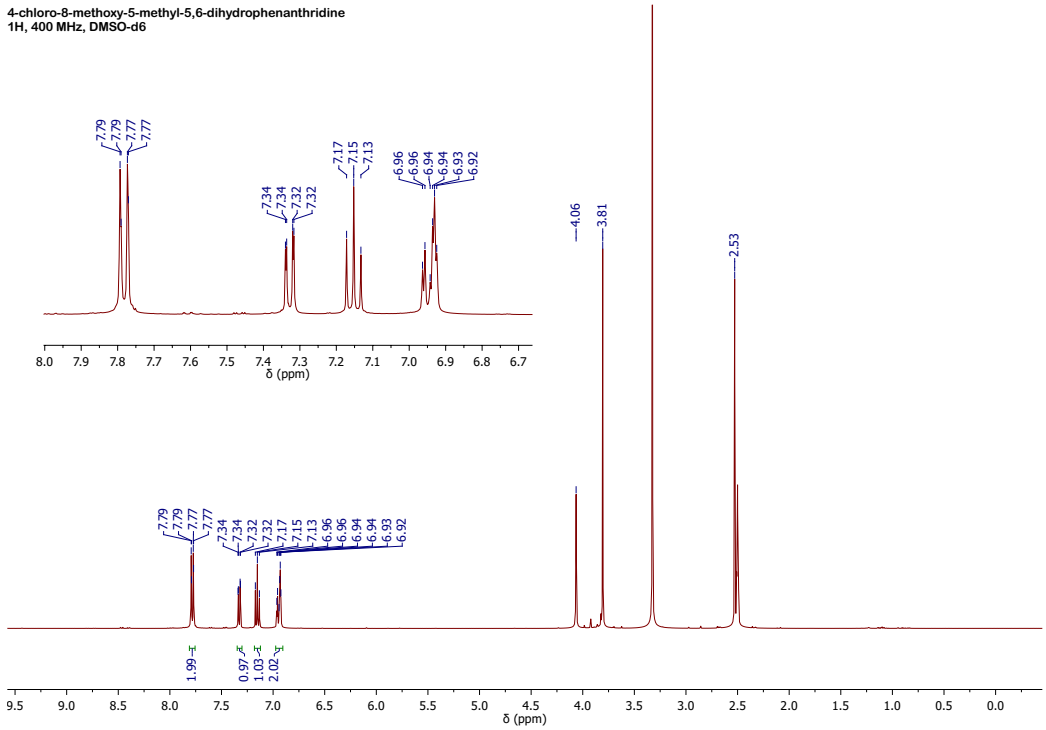
K_2CO_3 (125 mg, 0.904 mmol) was added to a solution of 4-chloro-5-methyl-5,6-dihydrophenanthridin-8-ol (111 mg, 0.452 mmol) in dry DMF (25 mL) under Ar. The mixture was stirred for 15 minutes at ambient temperature before dropwise addition of MeI (0.06 mL, 1 mmol). After 1.5 h, the reaction was quenched with 30 mL sat. NaCl, extracted with 3x30 mL EtOAc, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (DCM). Yield: 92 mg (78%), clear wax.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.78 (m, 2H, H-7 or H-9 and H-1 or H-3), 7.33 (dd, J=8.0, 1.4 Hz, 1H, H-3 or H-1), 7.15 (t, J=8.0, 1H, H-2), 6.94 (m, 2H, H-9 or H-7 and H-10), 4.05 (s, 2H, CH_2), 3.80 (s, 3H, O-CH^3), 2.52 (s, 3H, N-CH^3).

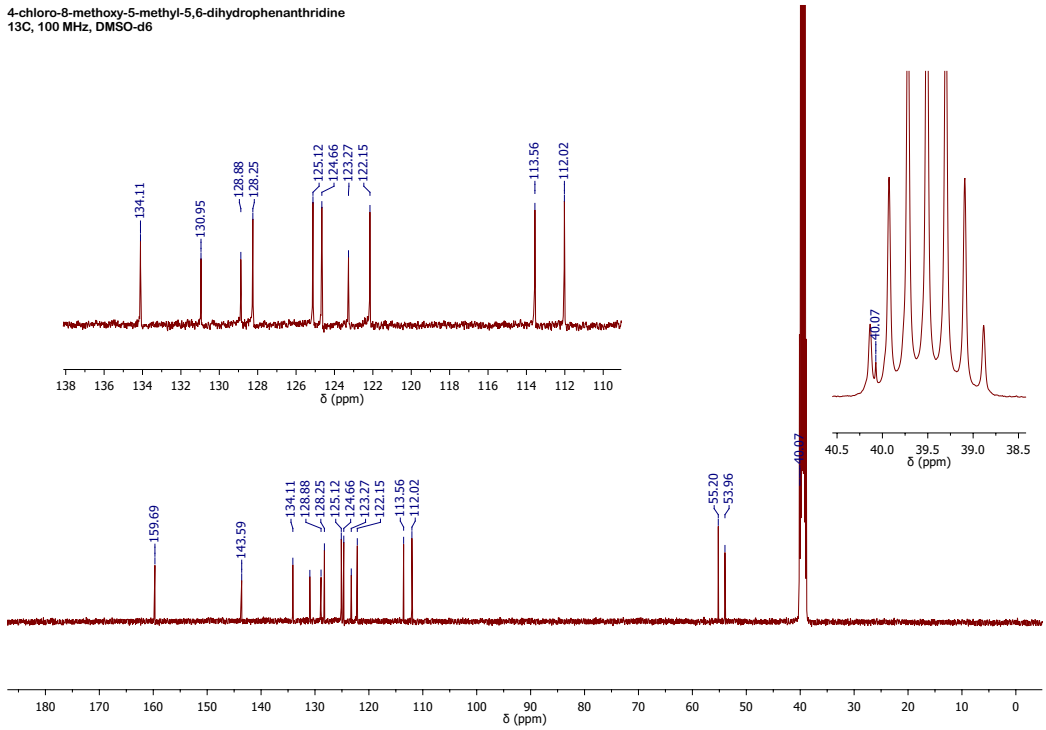
^{13}C-NMR (100 MHz, DMSO-d_6): δ 159.7 (C-8), 143.6 (C-4), 134.1 (C-4a), 131.0 (C-10a), 128.9 (C-10b), 128.3 (C-3 or C-1), 125.1 (C-2), 124.7 (C-9 or C-7), 123.3 (C-6a), 122.2 (C-1 or C-3), 113.6 (C-10), 112.0 (C-7 or C-9), 55.2 (O-CH^3), 54.0 (CH_2), 40.1 (N-CH^3).

MS ESI m/z (rel %): 262/261/260 (33/16/100, MH^+), 244 (12).

HRMS ESI: calculated for $C_{15}H_{15}ClNO$ (MH^+): 260.0837, found 260.0836.

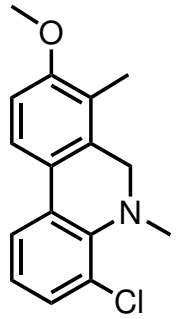


*Spectrum 47: [1]H-NMR spectrum of 4-chloro-8-methoxy-5-methyl-5,6-dihydrophenanthridine (**81a**)*



*Spectrum 48: [13]C-NMR spectrum of 4-chloro-8-methoxy-5-methyl-5,6-dihydrophenanthridine (**81a**)*

Synthesis of
4-chloro-8-methoxy-5,7-dimethyl-5,6-dihydrophenanthridine (81c)



81c

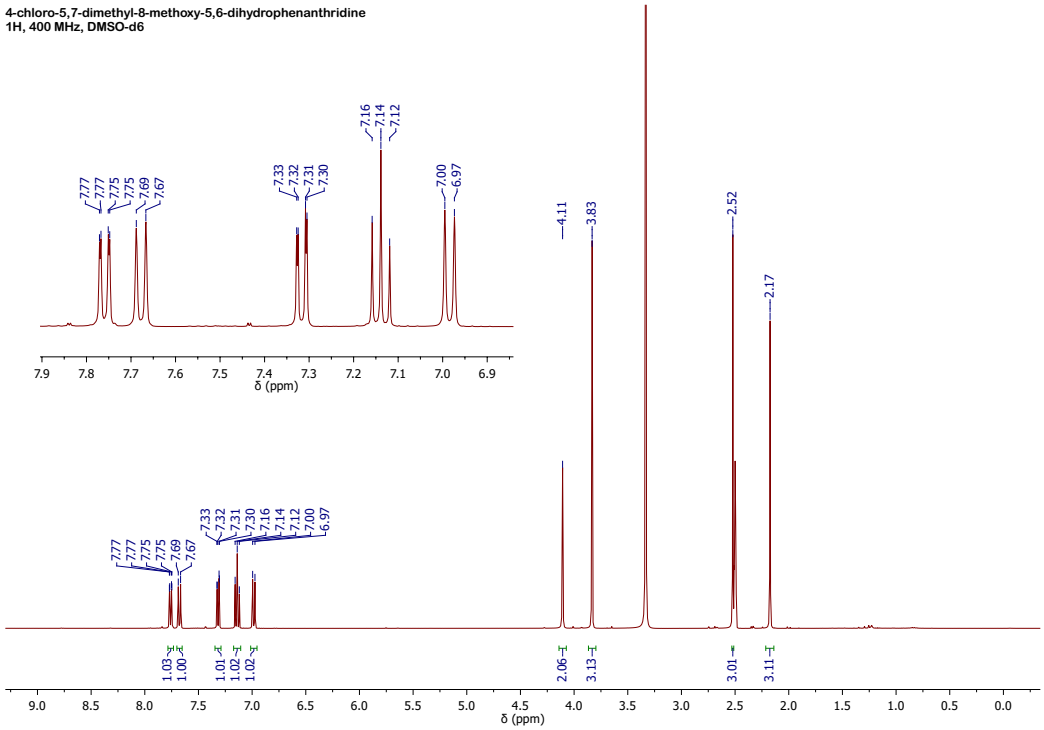
K_2CO_3 (147 mg, 1.06 mmol) was added to a solution of 4-chloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (108 mg, 0.416 mmol) in dry DMF (10 mL) under Ar. The mixture was stirred for 15 minutes at ambient temperature before dropwise addition of MeI (0.052 mL, 0.83 mmol). After 6 h, the reaction was quenched with 10 mL sat. NaCl, extracted with 3x50 mL DCM, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash chromatography (14:1 hexanes/EtOAc). Yield: 51 mg (48%), yellow wax.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.76 (dd, *J*=7.9, 1.4 Hz, 1H, H-1), 7.67 (d, *J*=9.5 Hz, 1H, H-9), 7.31 (dd, *J*=7.9, 1.4 Hz, 1H, H-3), 7.14 (t, *J*=7.9 Hz, 1H, H-2), 6.98 (d, *J*=9.5 Hz, 1H, H-10), 4.11 (s, 1H, CH_2), 3.83 (s, 1H, O-CH^3), 2.52 (s, 1H, N-CH^3), 2.17 (s, 1H, C-CH^3).

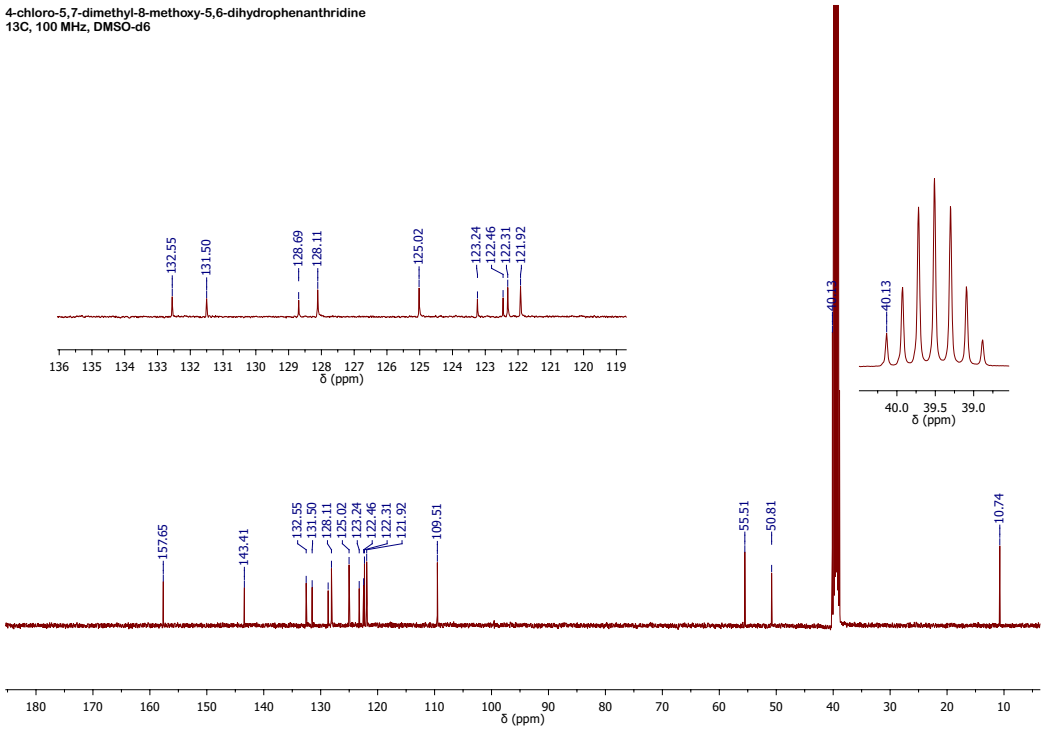
^{13}C-NMR (100 MHz, DMSO-d_6): δ 157.6 (C-8), 143.4 (C-4a), 132.6 (C-6a), 131.5 (C-10a), 128.7 (C-4), 128.1 (C-3), 125.0 (C-2), 123.2 (C-10b), 122.5/122.3 (C-7 and C-1), 121.9 (C-9), 109.5 (C-10), 55.5 (O-CH^3), 50.8 (CH_2), 40.1 (N-CH^3), 10.7 (C-CH^3).

MS ESI m/z (rel %): 276/275/274 (31/18/100, MH^+), 258 (33), 227 (10).

HRMS ESI: calculated for $C_{14}H_{15}ClNO$ (MH^+): 274.0993, found 274.0992.

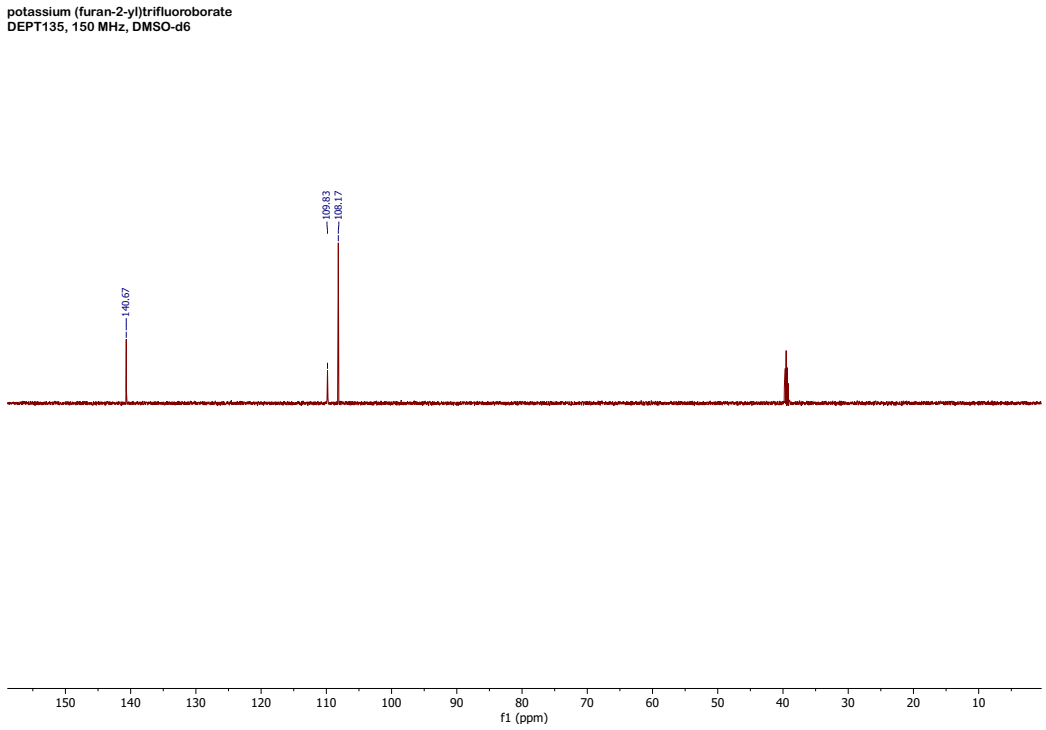


*Spectrum 49: [1]H-NMR spectrum of 4-chloro-8-methoxy-5,7-dimethyl-5,6-dihydrophenanthridine (**81c**)*

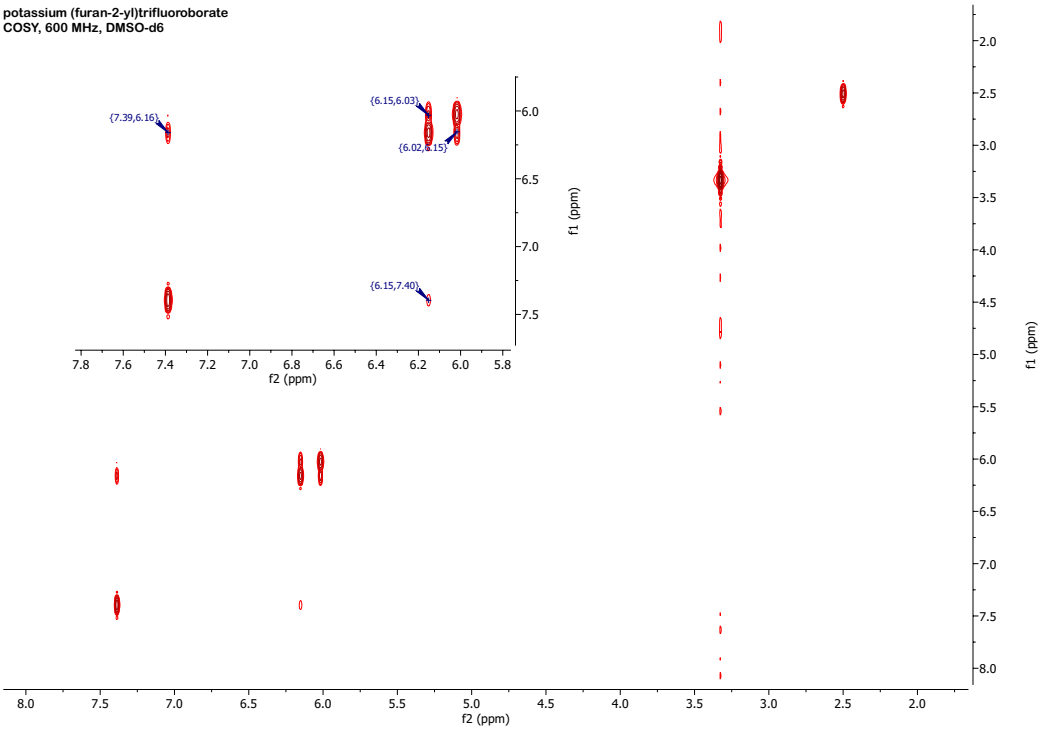


*Spectrum 50: [13]C-NMR spectrum of 4-chloro-8-methoxy-5,7-dimethyl-5,6-dihydrophenanthridine (**81c**)*

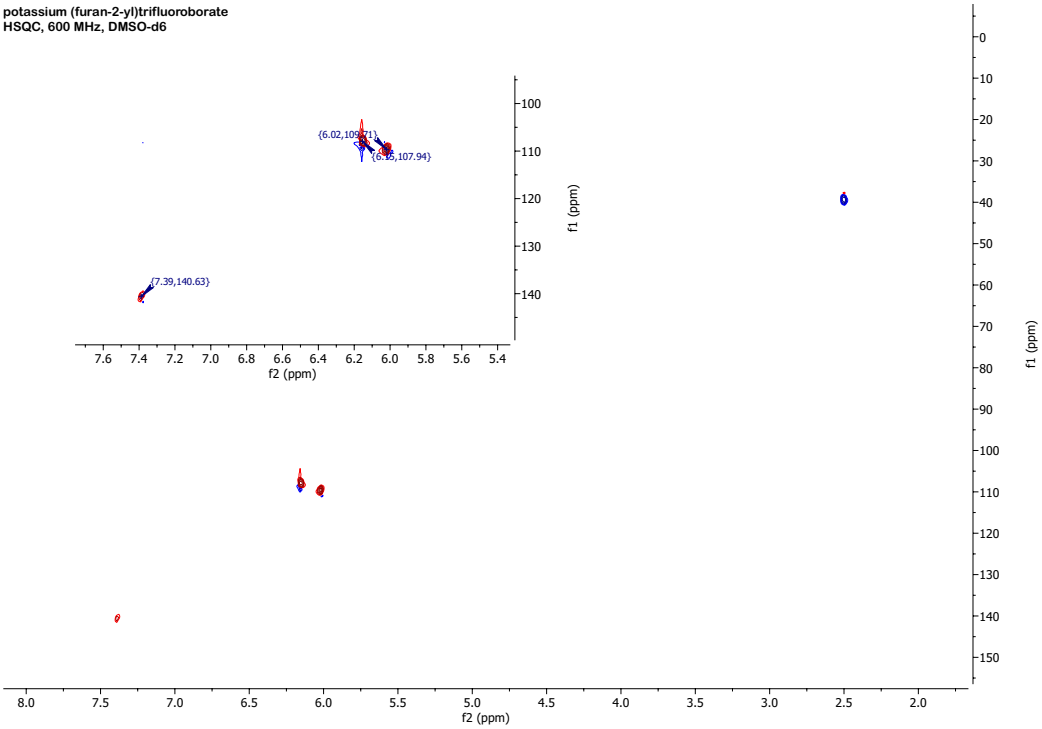
A Supplementary NMR spectra



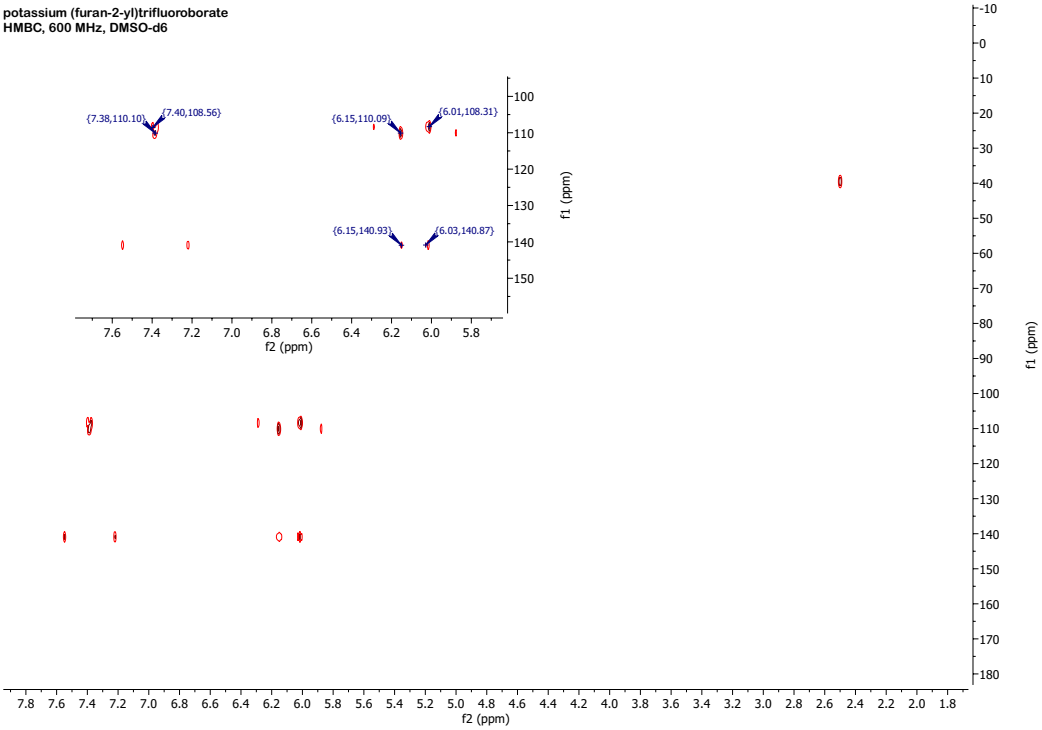
*Spectrum 51: DEPT135-NMR spectrum of potassium (furan-2-yl)trifluoroborate (**77**)*



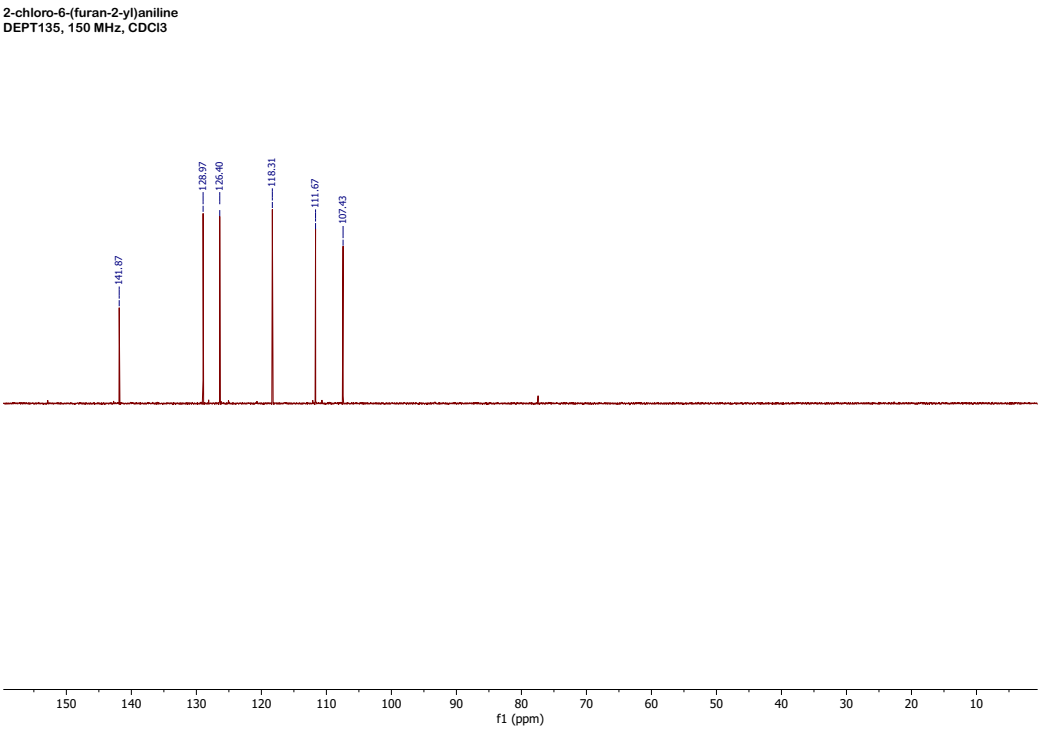
*Spectrum 52: COSY-NMR spectrum of potassium (furan-2-yl)trifluoroborate (**77**)*



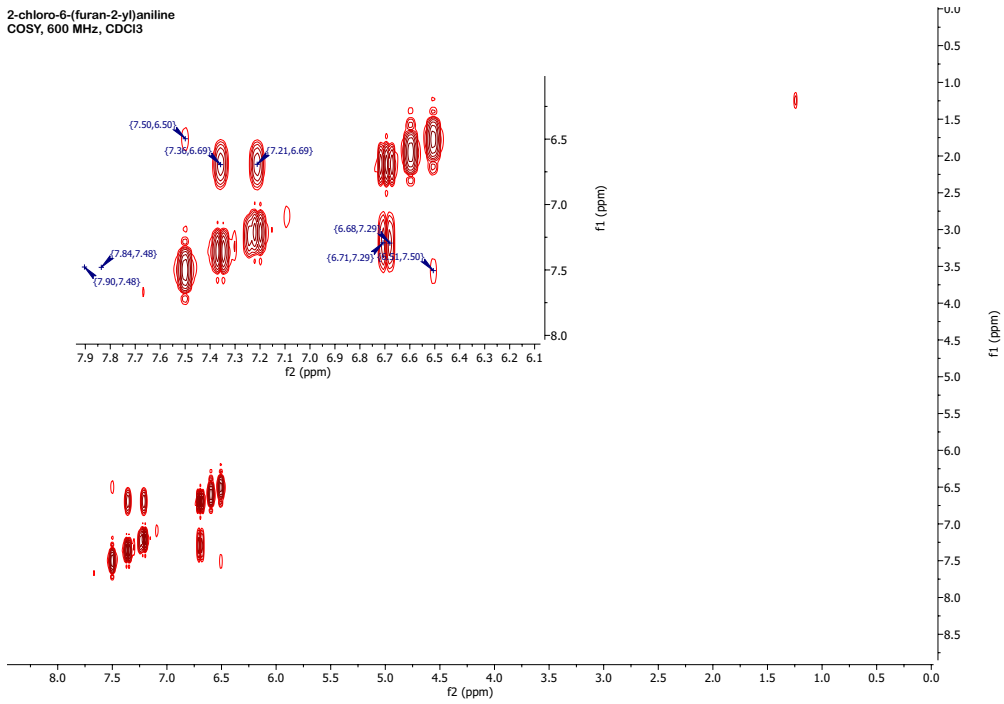
*Spectrum 53: HSQC-NMR spectrum of potassium (furan-2-yl)trifluoroborate (**77**)*



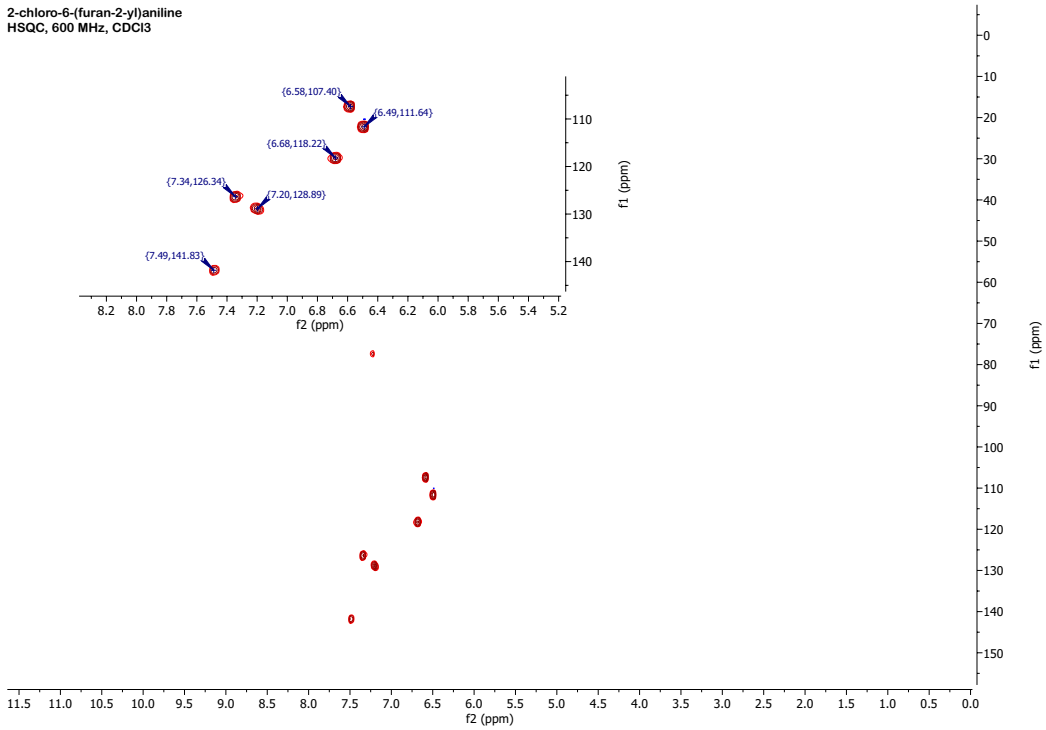
*Spectrum 54: HMBC-NMR spectrum of potassium (furan-2-yl)trifluoroborate (**77**)*



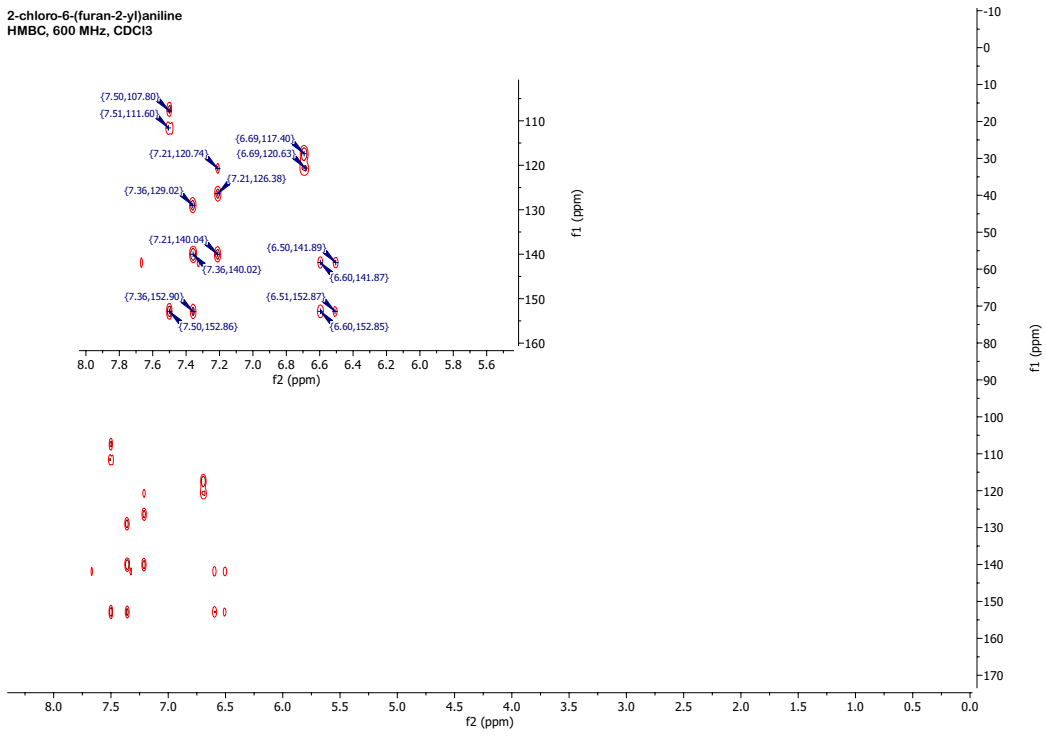
*Spectrum 55: DEPT135-NMR spectrum of 2-chloro-6-(furan-2-yl)aniline (**79a**)*



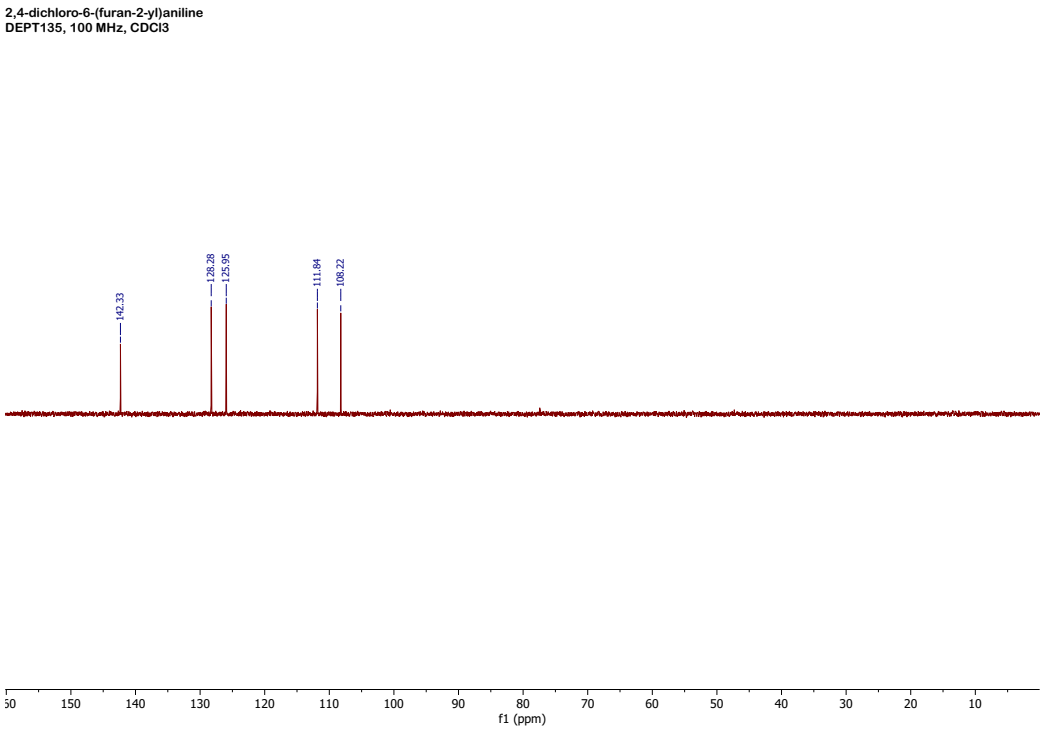
*Spectrum 56: COSY-NMR spectrum of 2-chloro-6-(furan-2-yl)aniline (**79a**)*



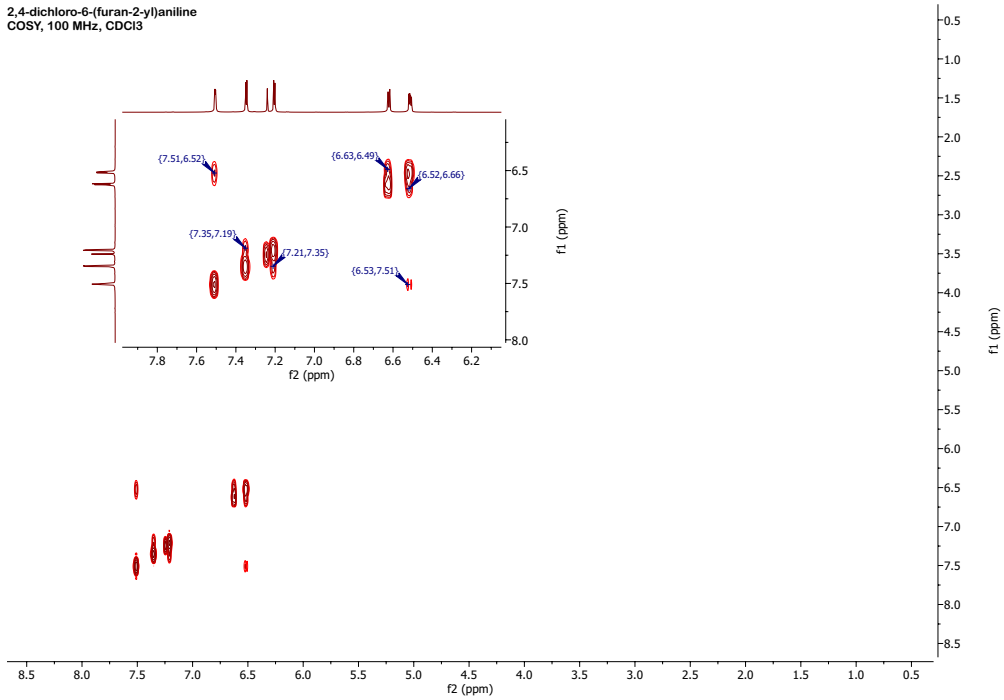
*Spectrum 57: HSQC-NMR spectrum of 2-chloro-6-(furan-2-yl)aniline (**79a**)*



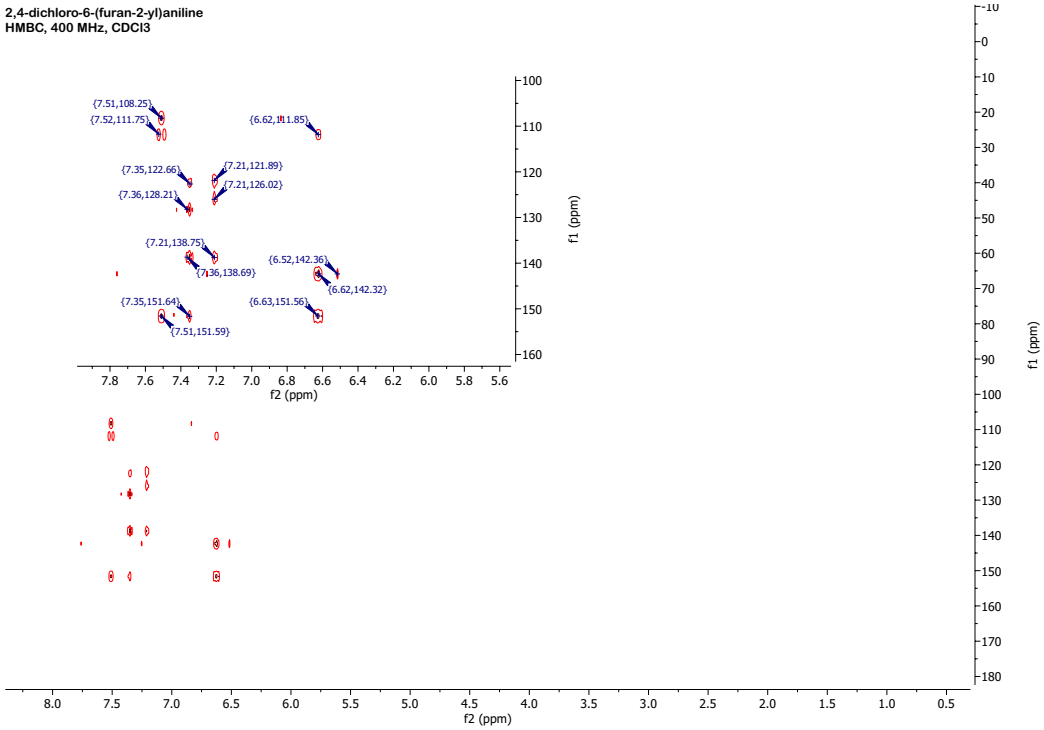
*Spectrum 58: HMBC-NMR spectrum of 2-chloro-6-(furan-2-yl)aniline (**79a**)*



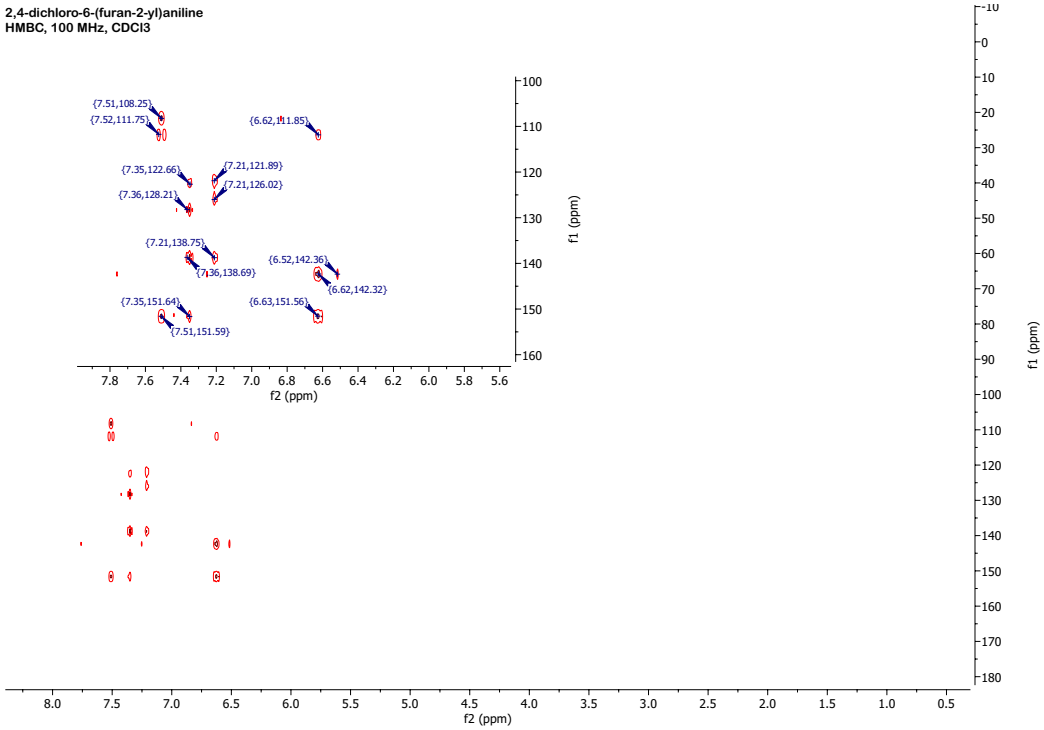
*Spectrum 59: DEPT135-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)aniline (**79b**)*



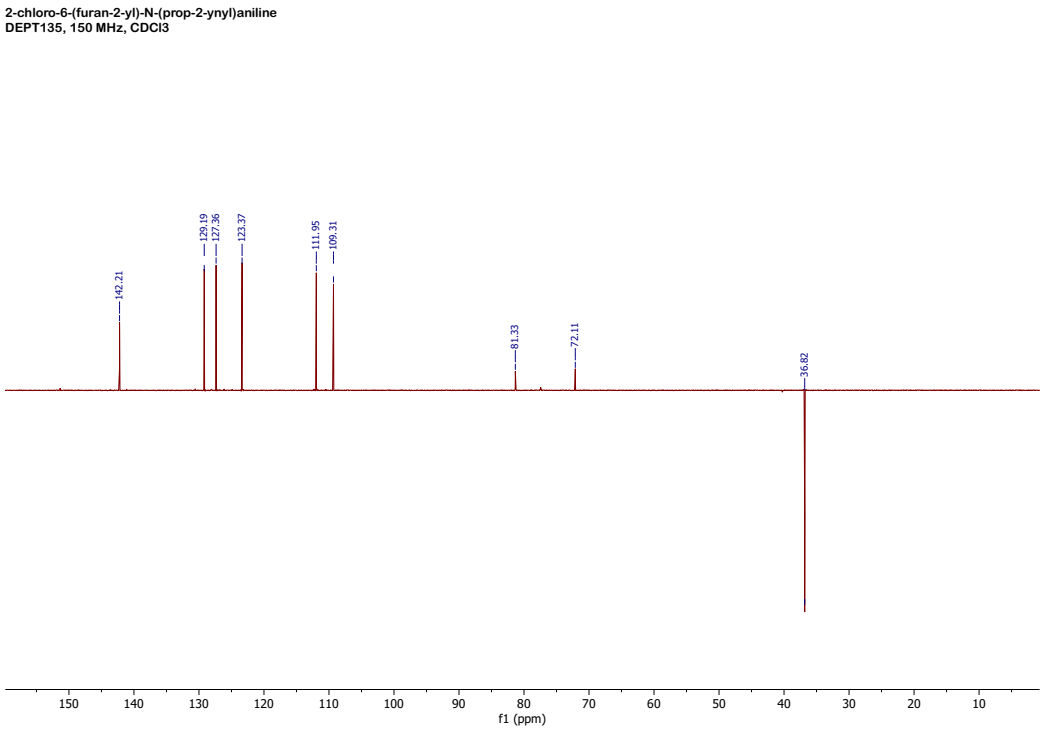
*Spectrum 60: COSY-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)aniline (**79b**)*



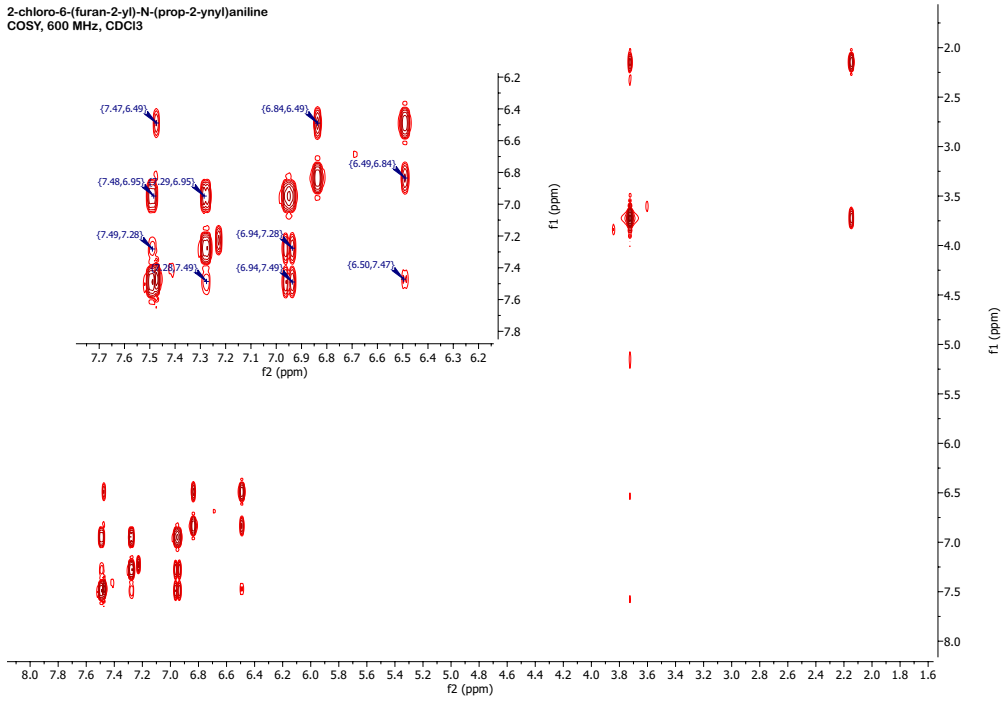
*Spectrum 61: HSQC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)aniline (**79b**)*



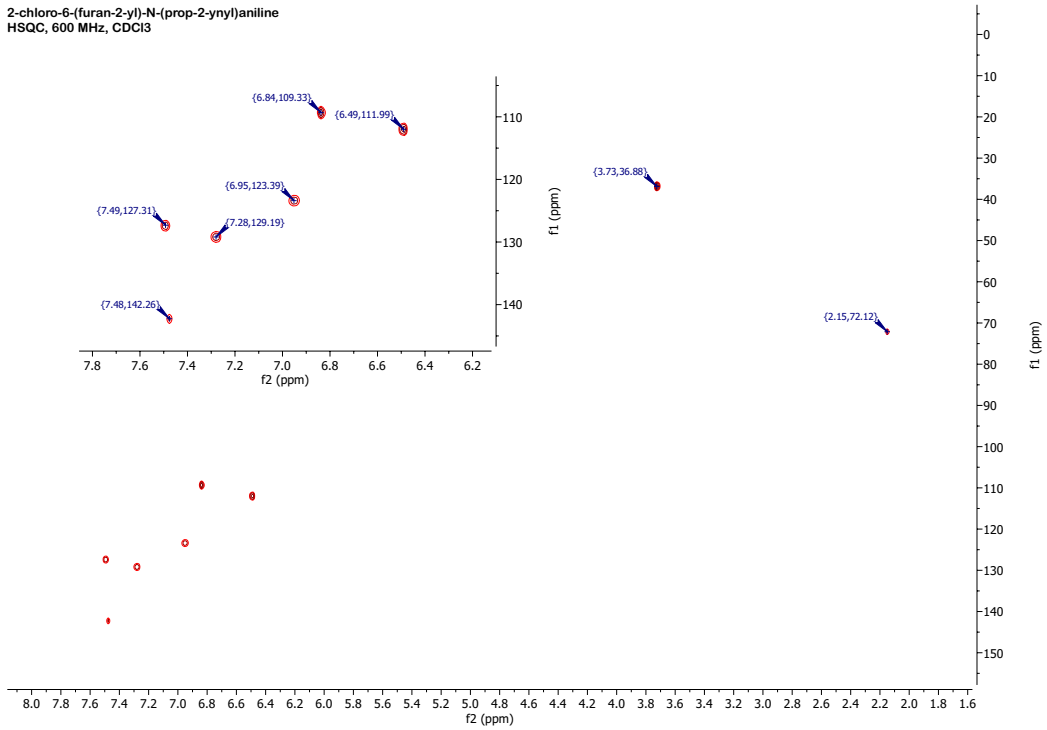
*Spectrum 62: HMBC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)aniline (**79b**)*



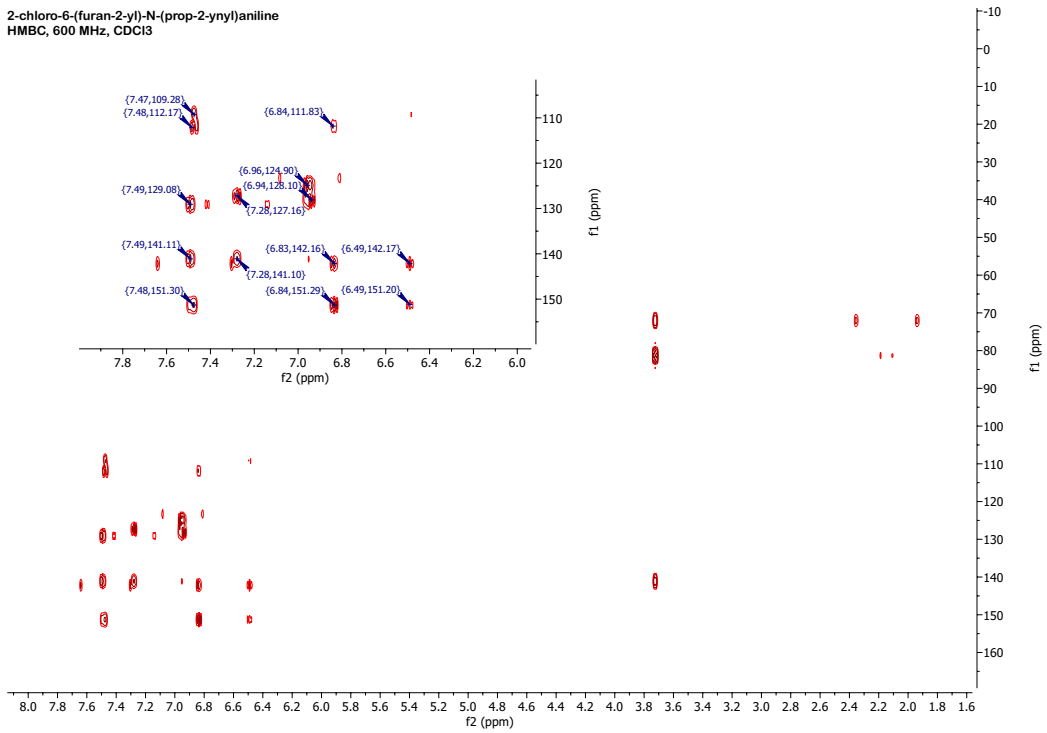
*Spectrum 63: DEPT135-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68a**)*



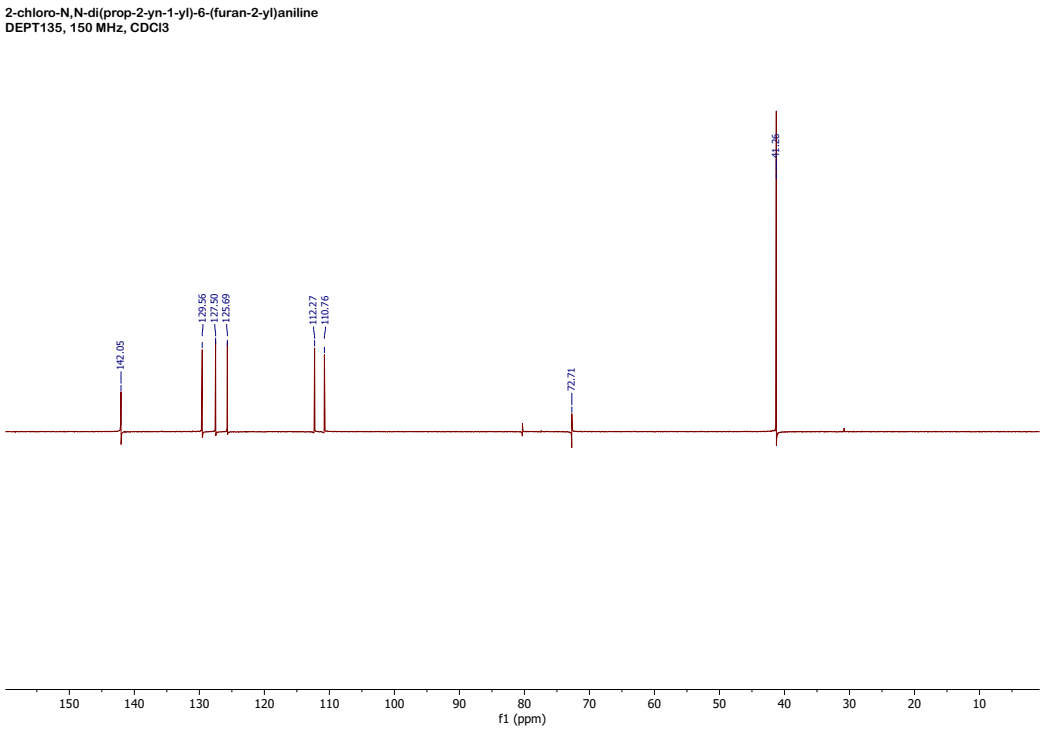
*Spectrum 64: COSY-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68a**)*



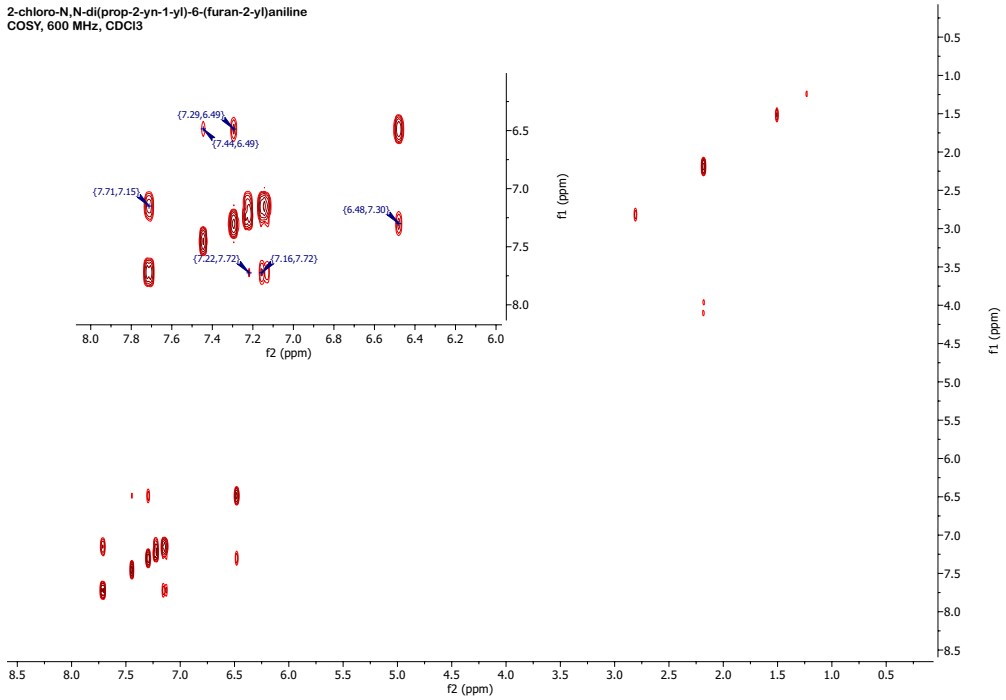
*Spectrum 65: HSQC-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68a**)*



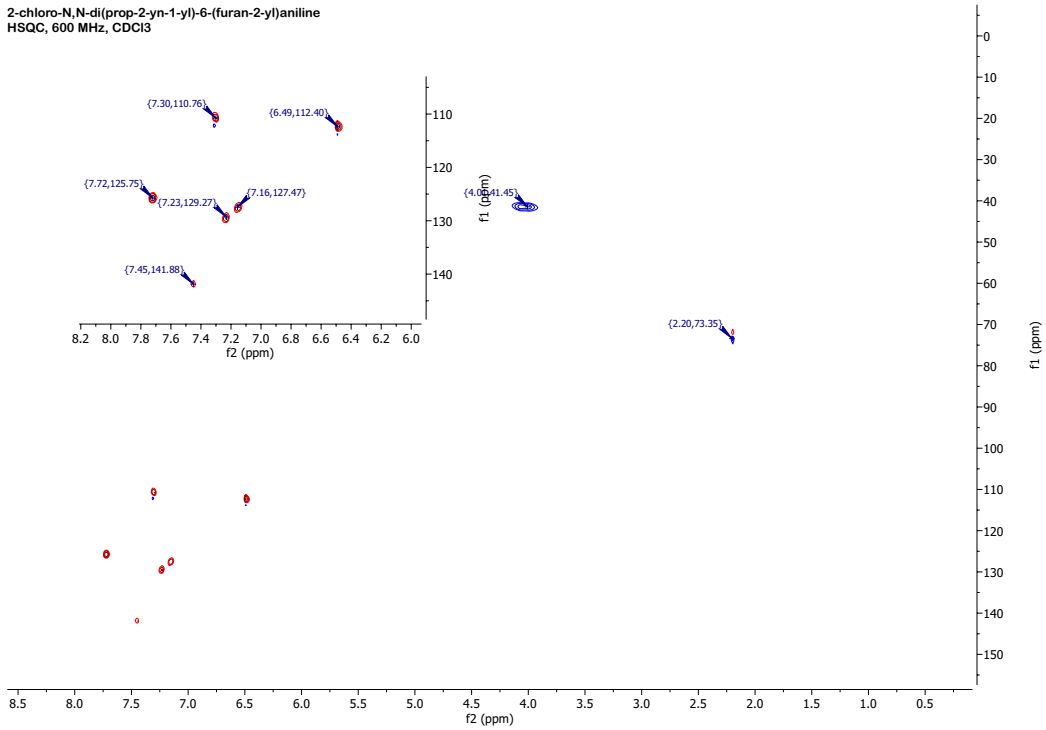
*Spectrum 66: HMBC-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68a**)*



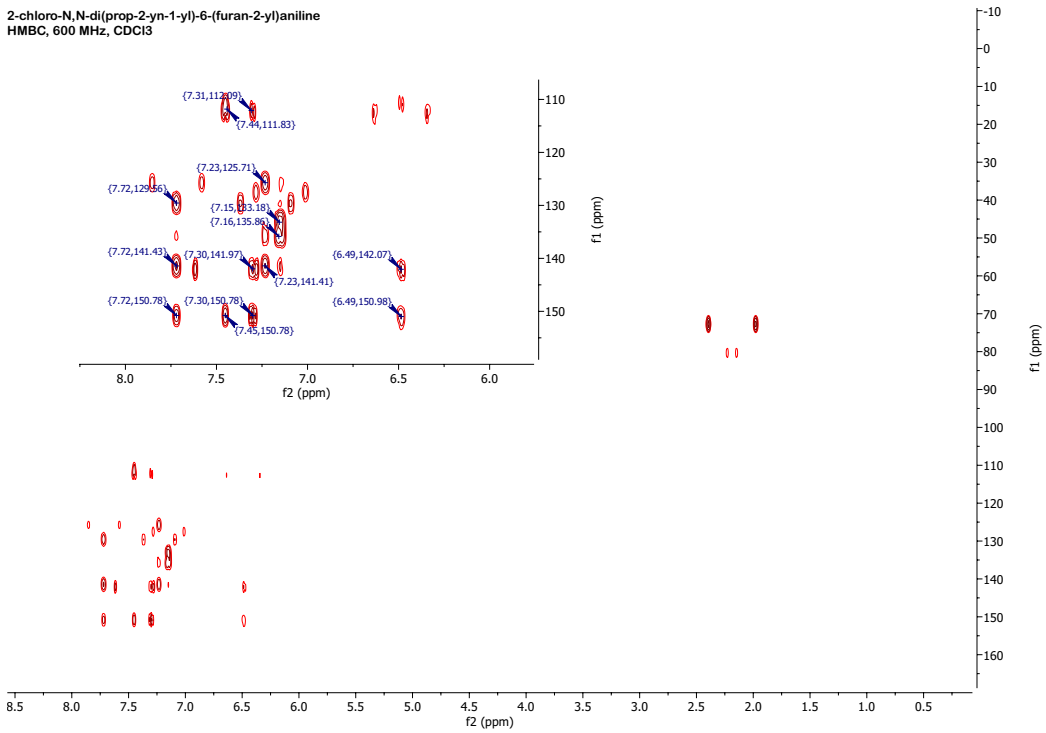
*Spectrum 67: DEPT135-NMR spectrum of 2-chloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80a**)*



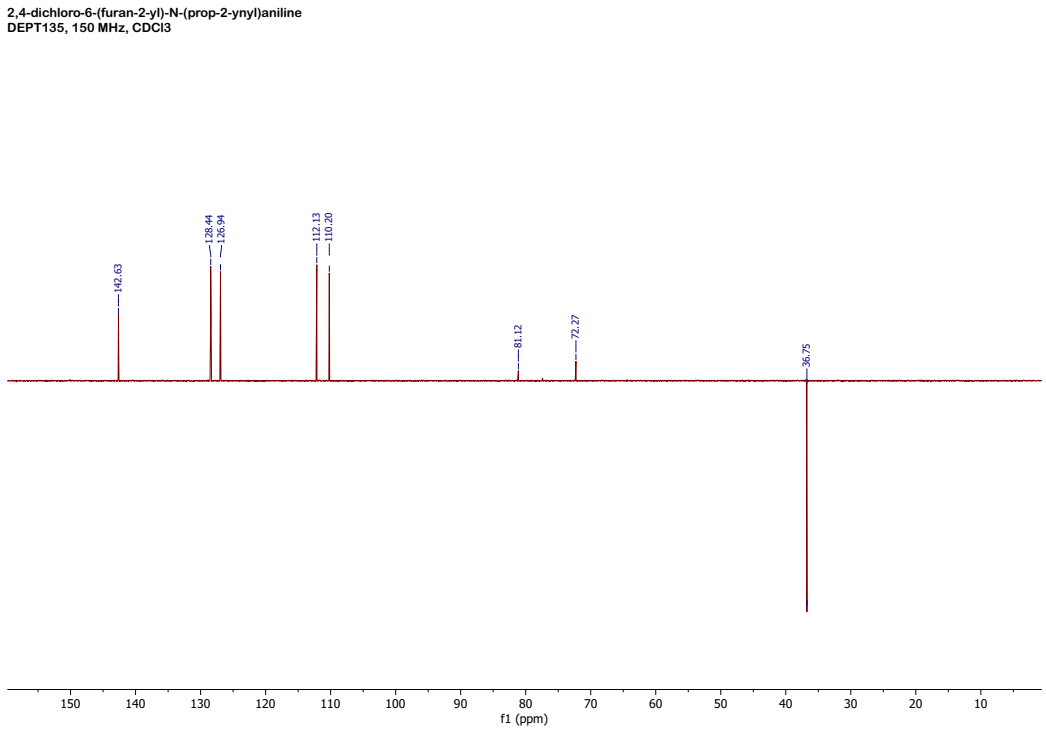
*Spectrum 68: COSY-NMR spectrum of 2-chloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80a**)*



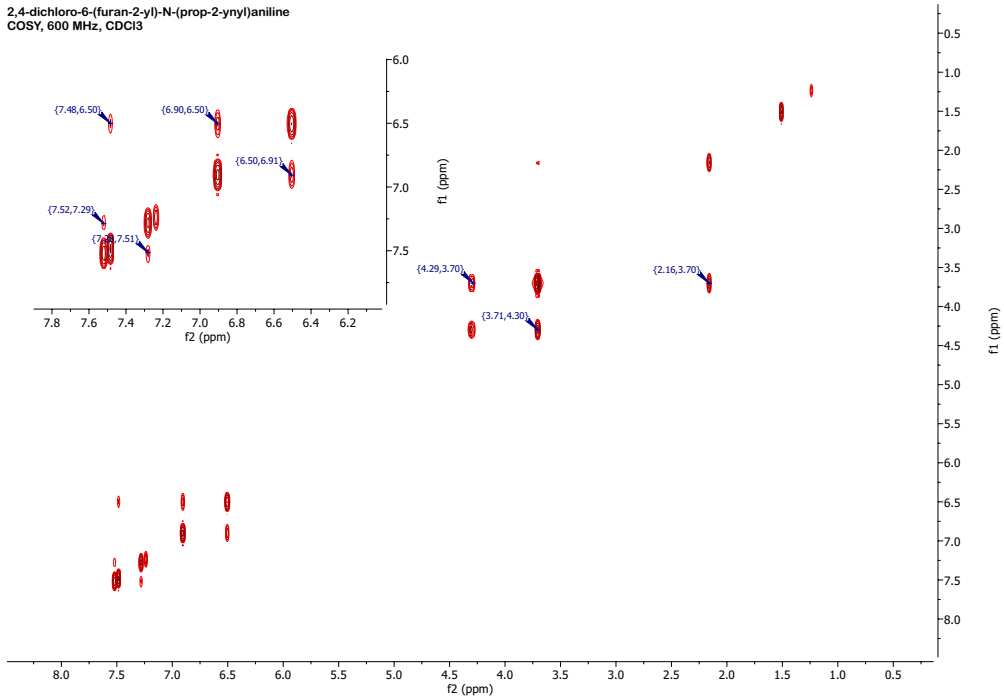
*Spectrum 69: HSQC-NMR spectrum of 2-chloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline(**80a**)*



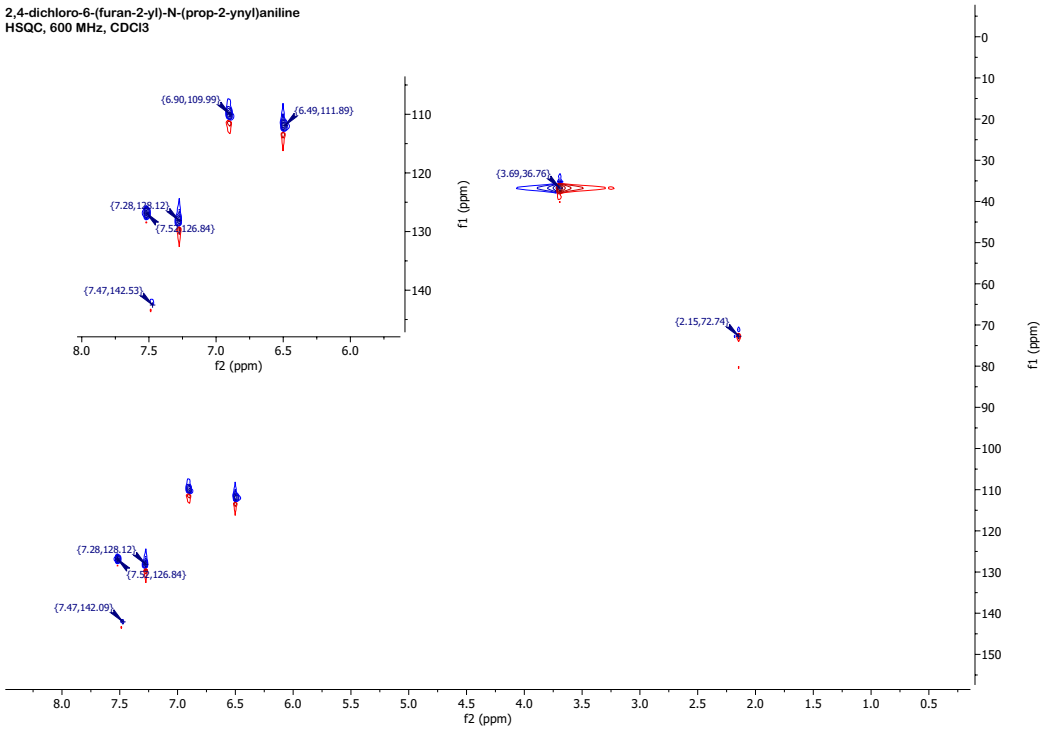
*Spectrum 70: HMBC-NMR spectrum of 2-chloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80a**)*



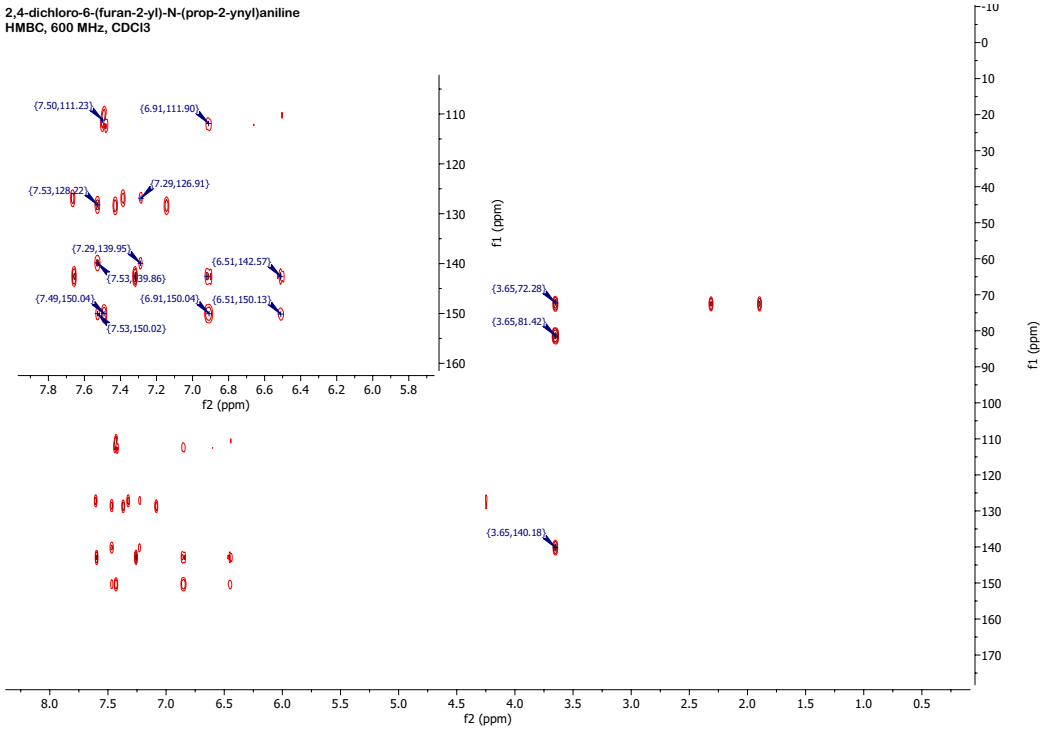
*Spectrum 71: DEPT135-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68b**)*



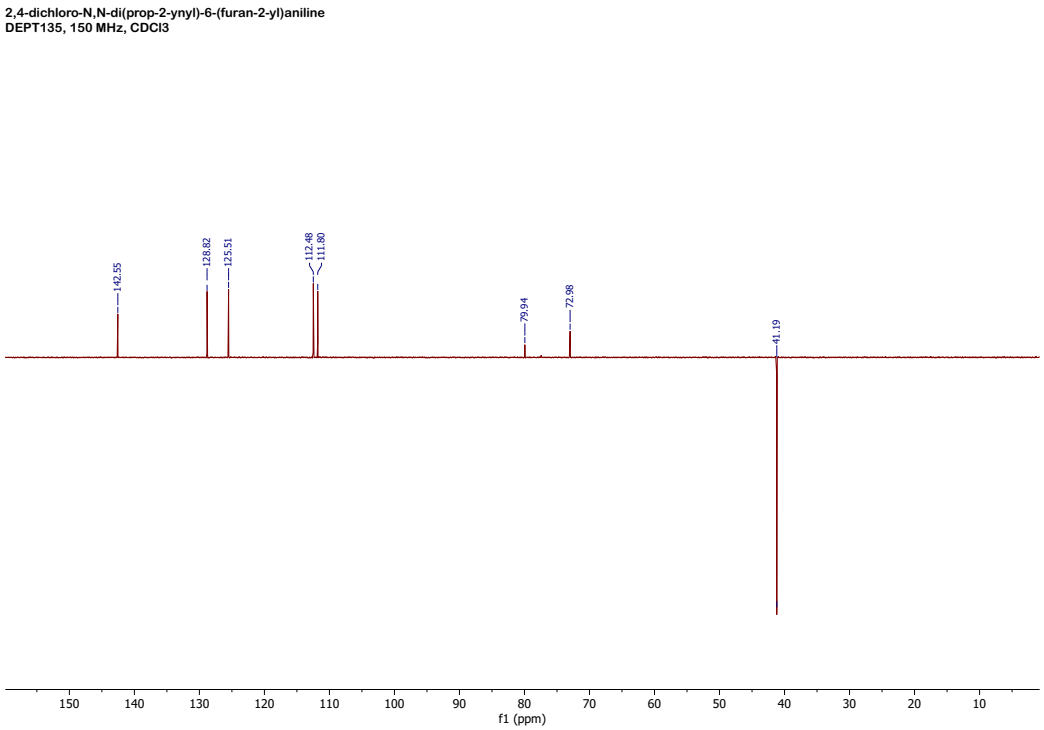
*Spectrum 72: COSY-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68b**)*



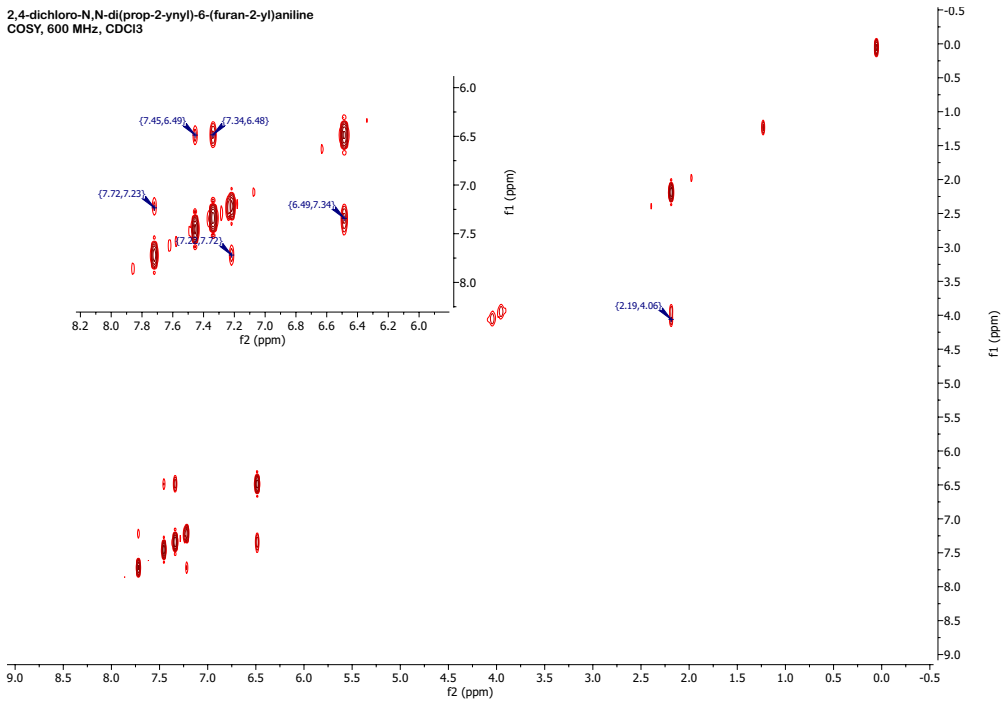
*Spectrum 73: HSQC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68b**)*



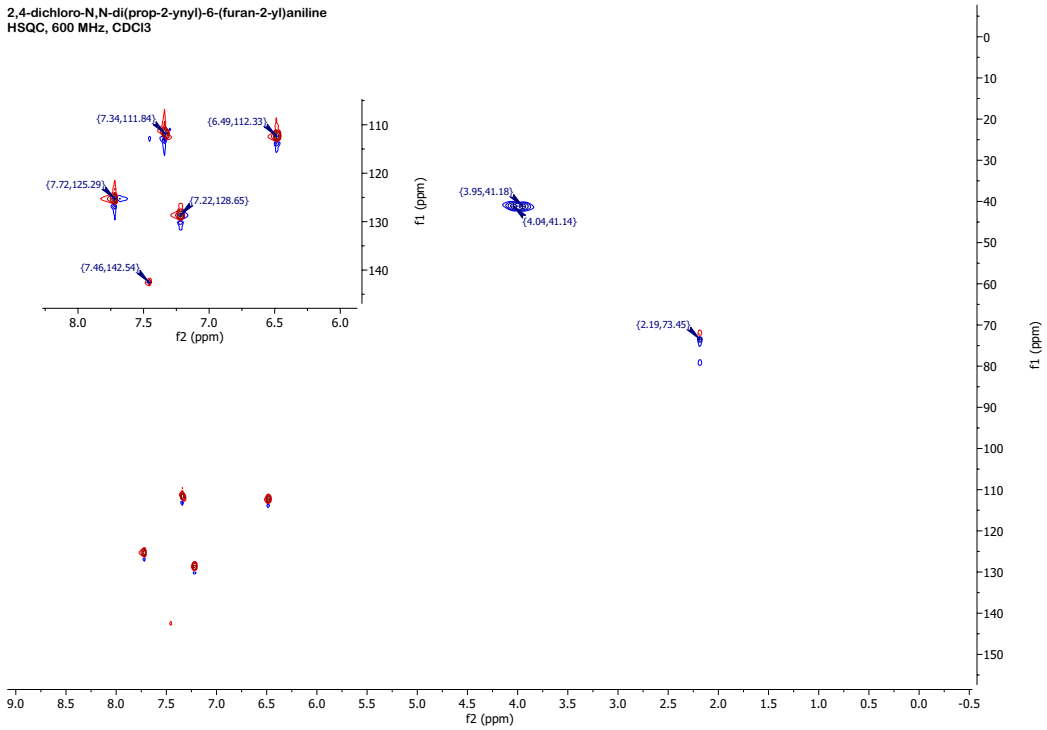
*Spectrum 74: HMBC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(prop-2-ynyl)aniline (**68b**)*



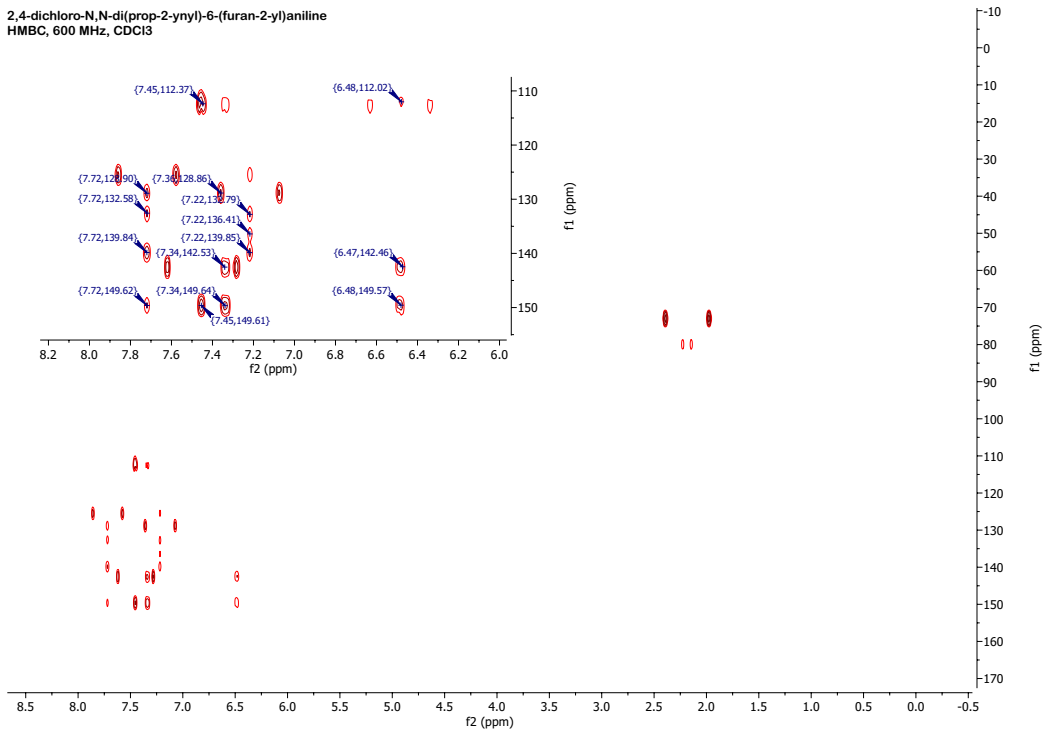
*Spectrum 75: DEPT135-NMR spectrum of 2,4-dichloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80b**)*



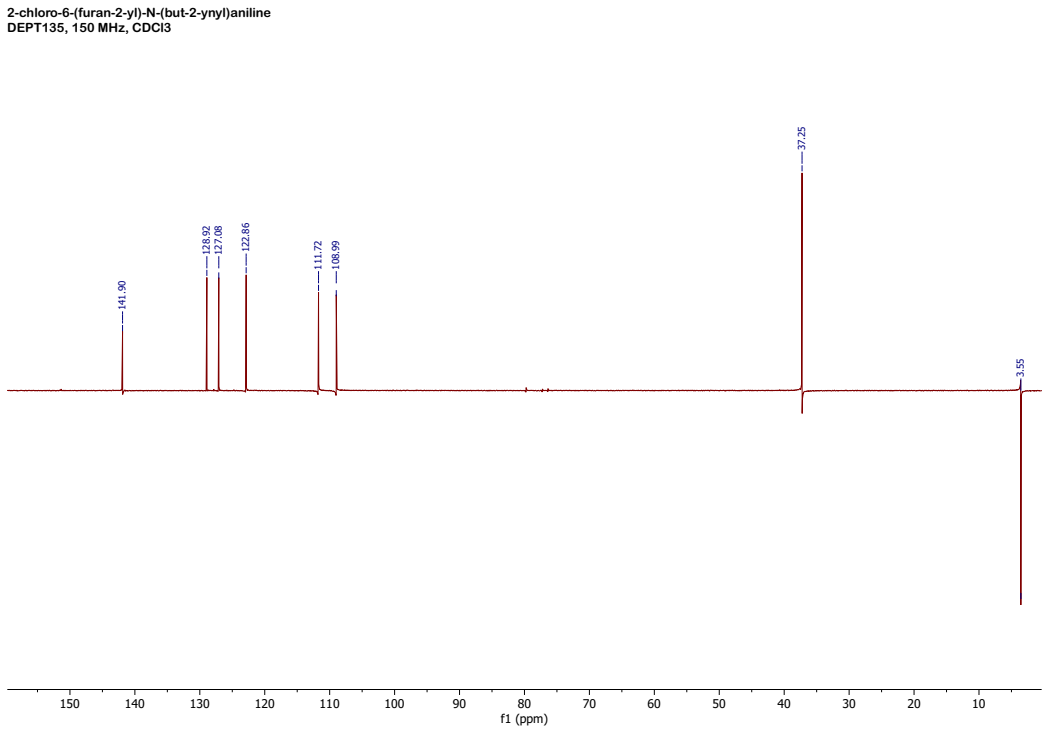
*Spectrum 76: COSY-NMR spectrum of 2,4-dichloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80b**)*



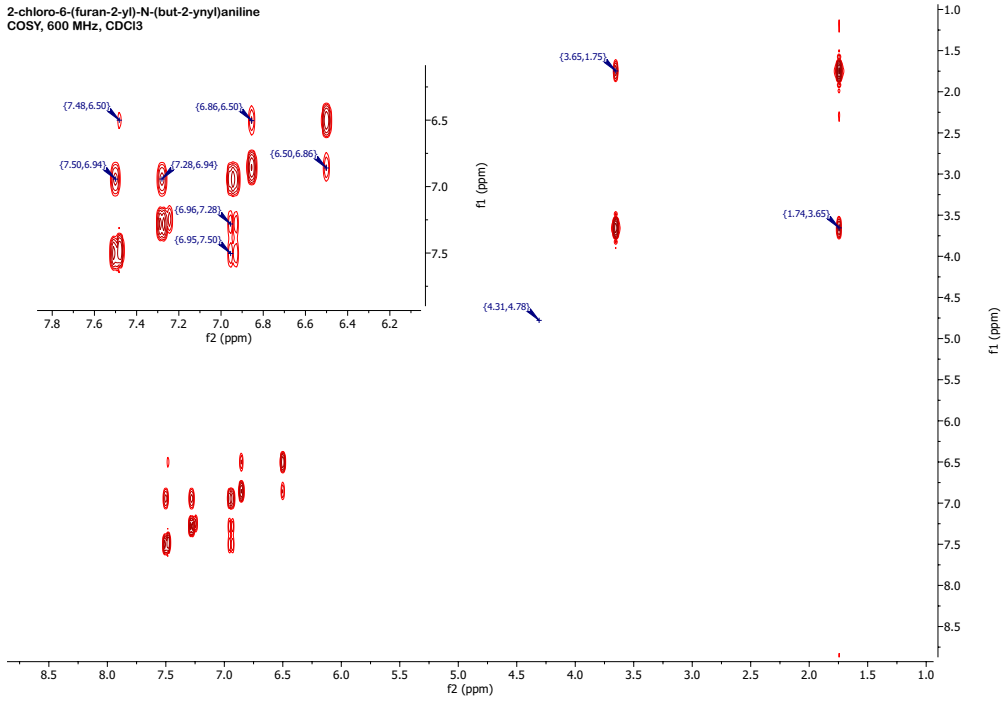
*Spectrum 77: HSQC-NMR spectrum of 2,4-dichloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline(**80b**)*



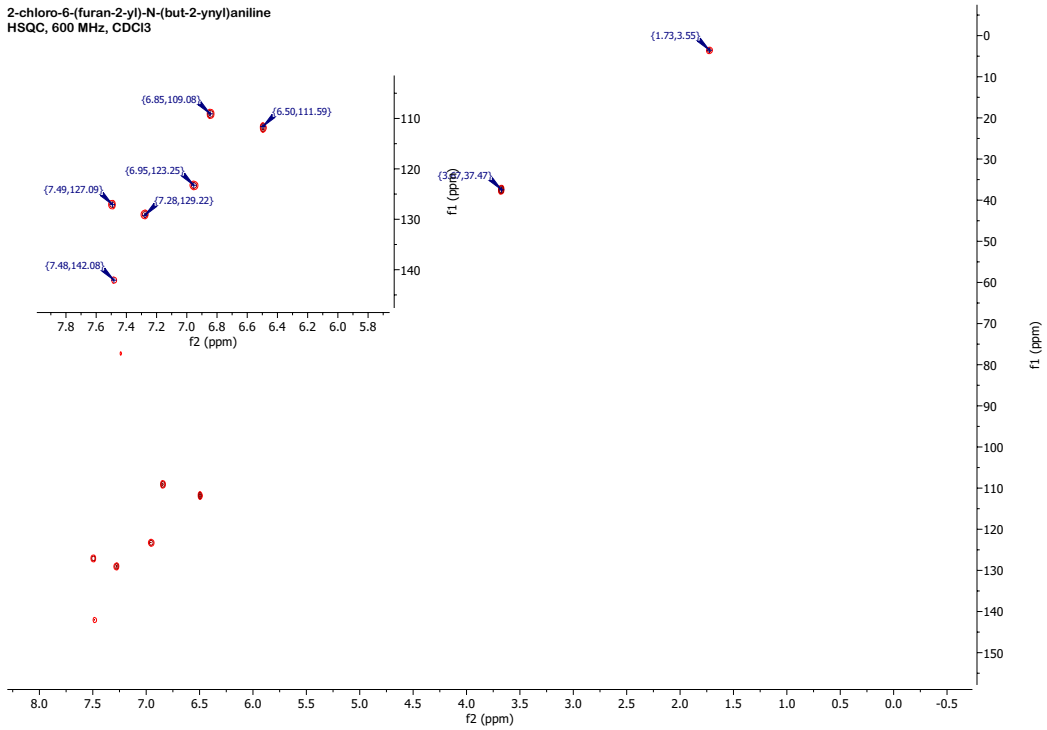
*Spectrum 78: HMBC-NMR spectrum of 2,4-dichloro-N,N–di(prop-2-ynyl)-6-(furan-2-yl)aniline (**80b**)*



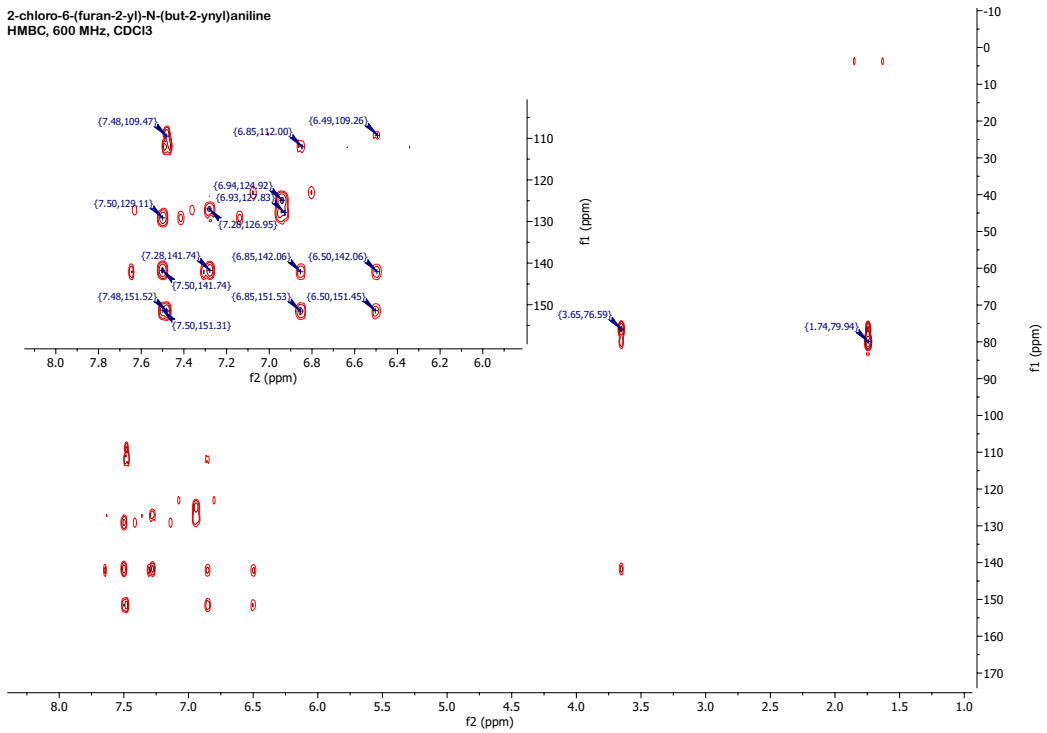
*Spectrum 79: DEPT135-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68c**)*



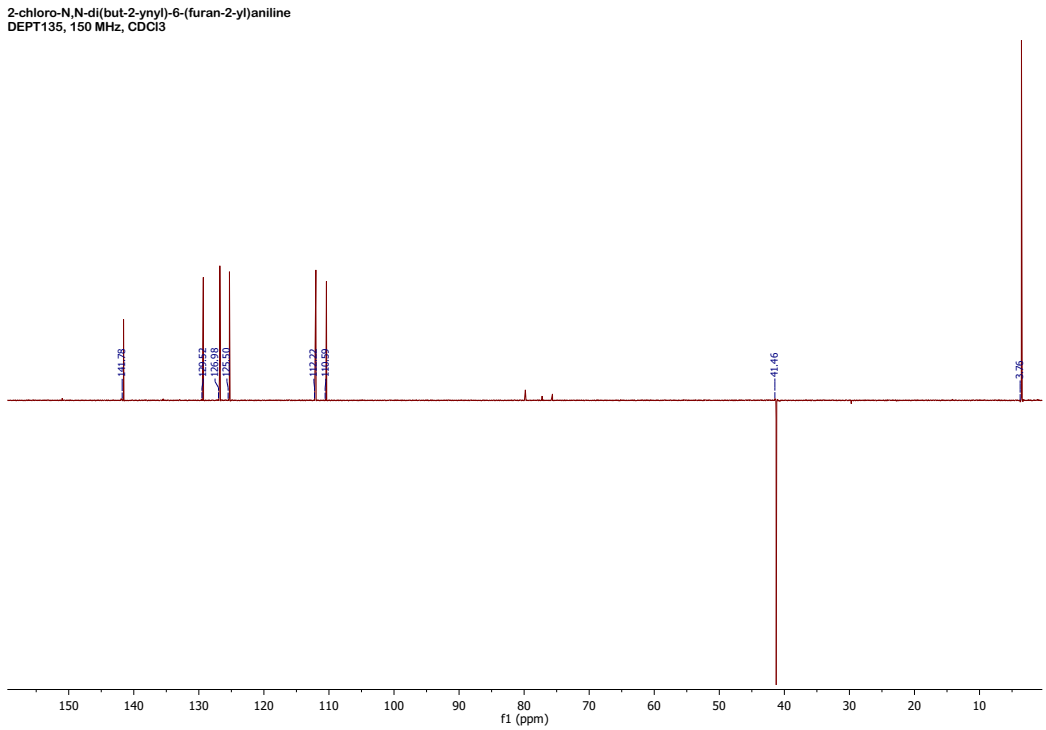
*Spectrum 80: COSY-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68c**)*



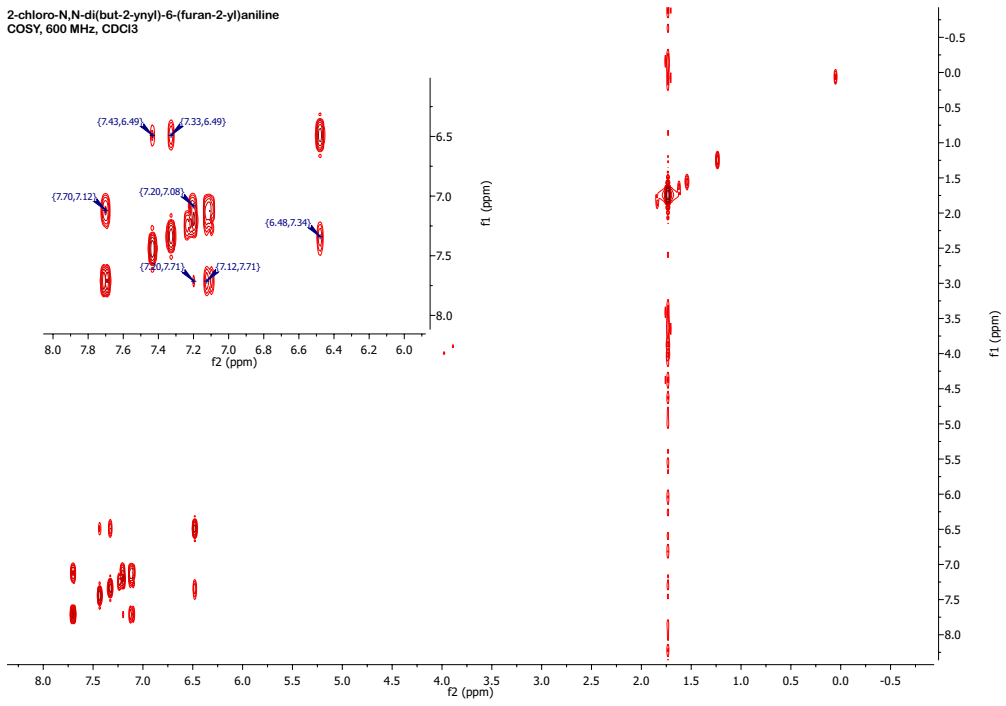
*Spectrum 81: HSQC-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68c**)*



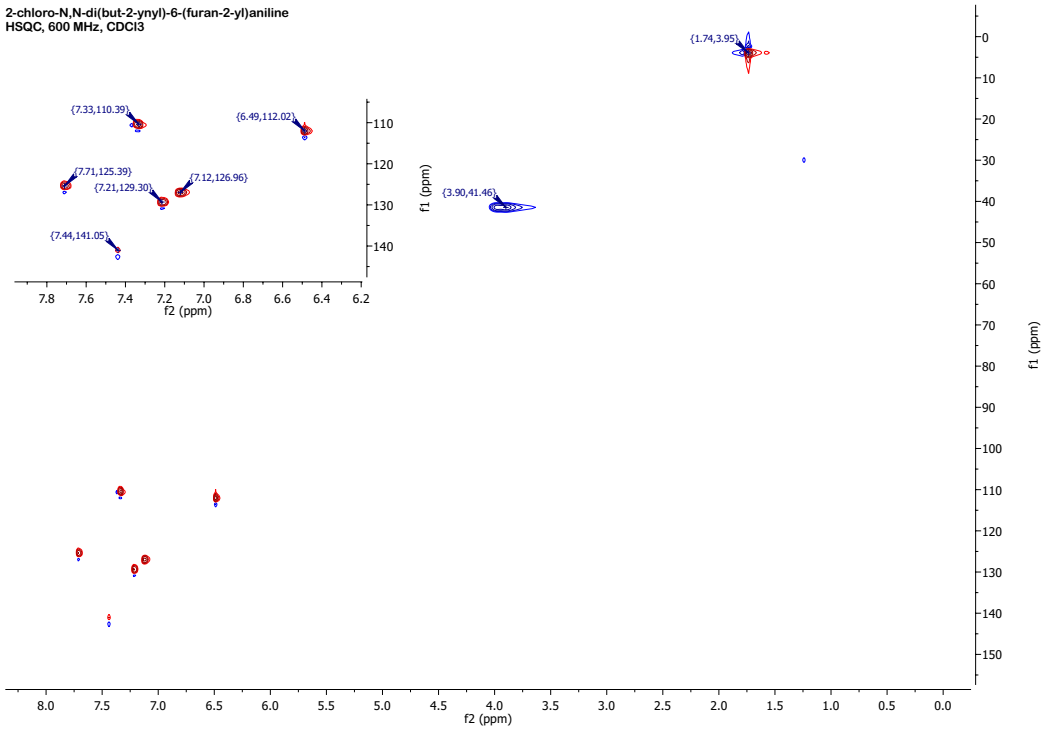
*Spectrum 82: HMBC-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68c**)*



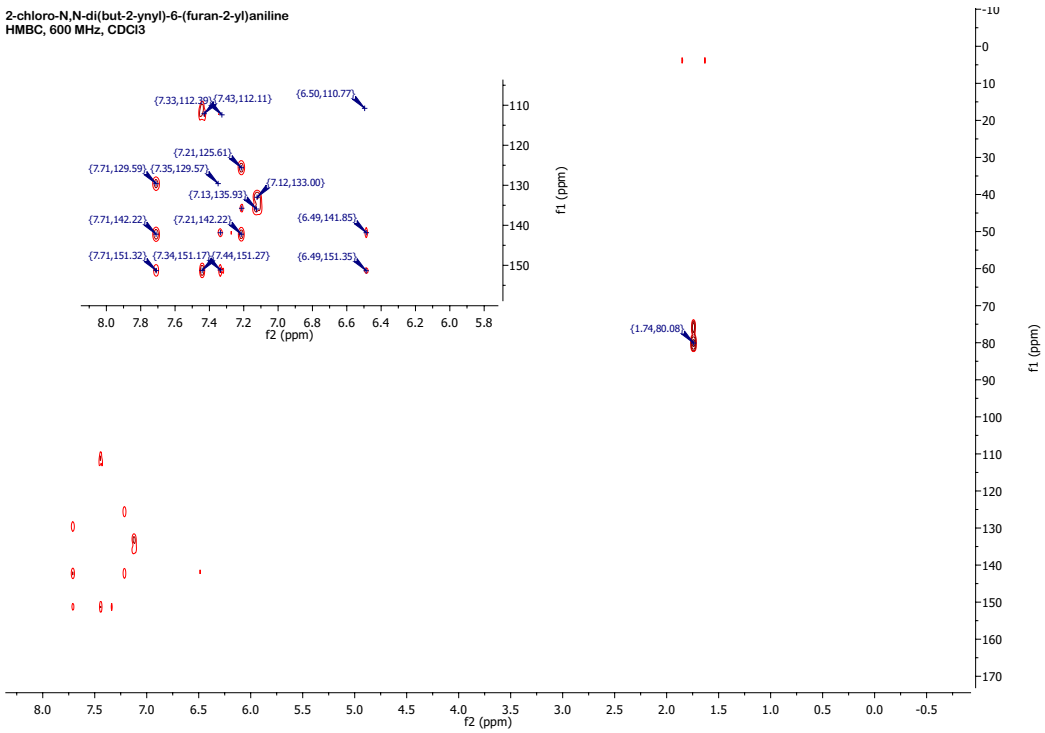
*Spectrum 83: DEPT135-NMR spectrum of 2-chloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80c**)*



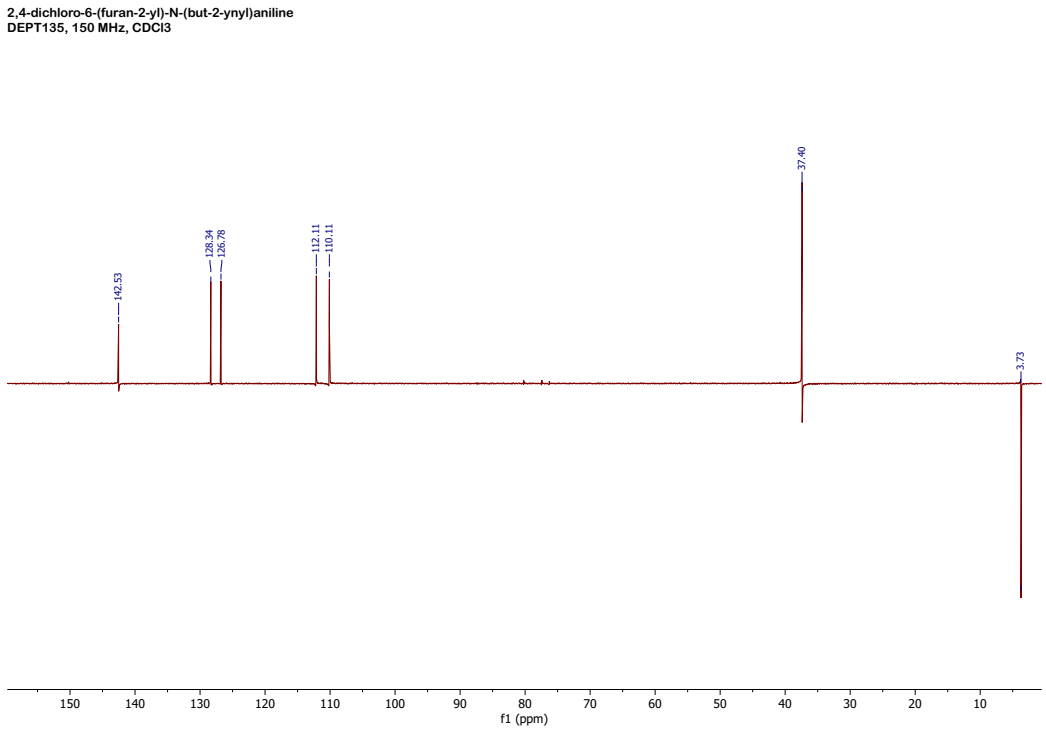
*Spectrum 84: COSY-NMR spectrum of 2-chloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80c**)*



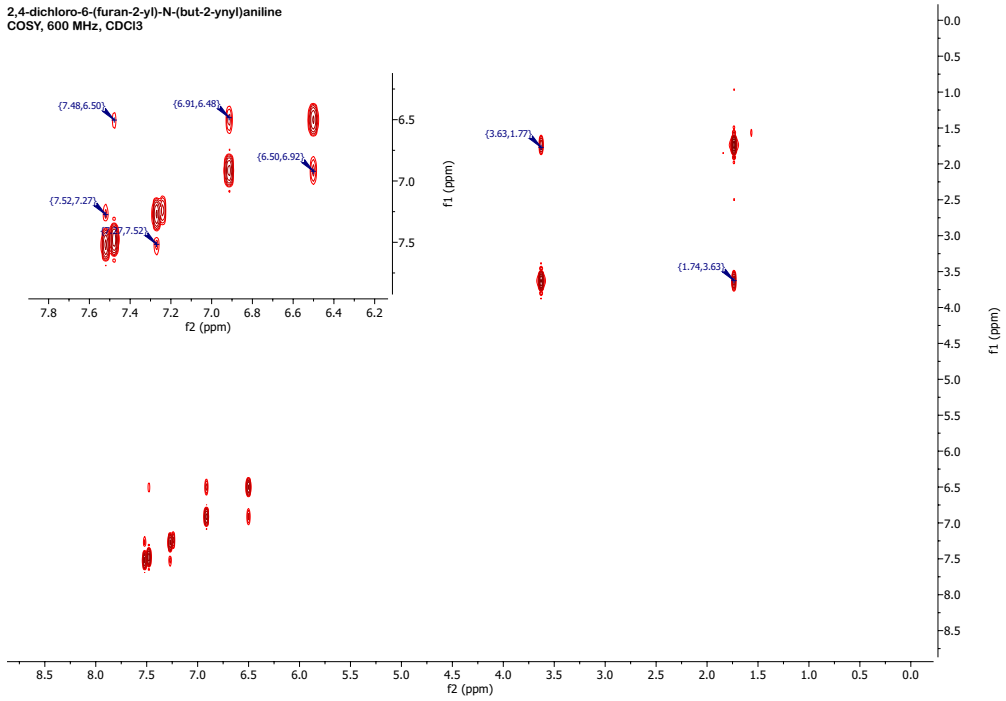
*Spectrum 85: HSQC-NMR spectrum of 2-chloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline(**80c**)*



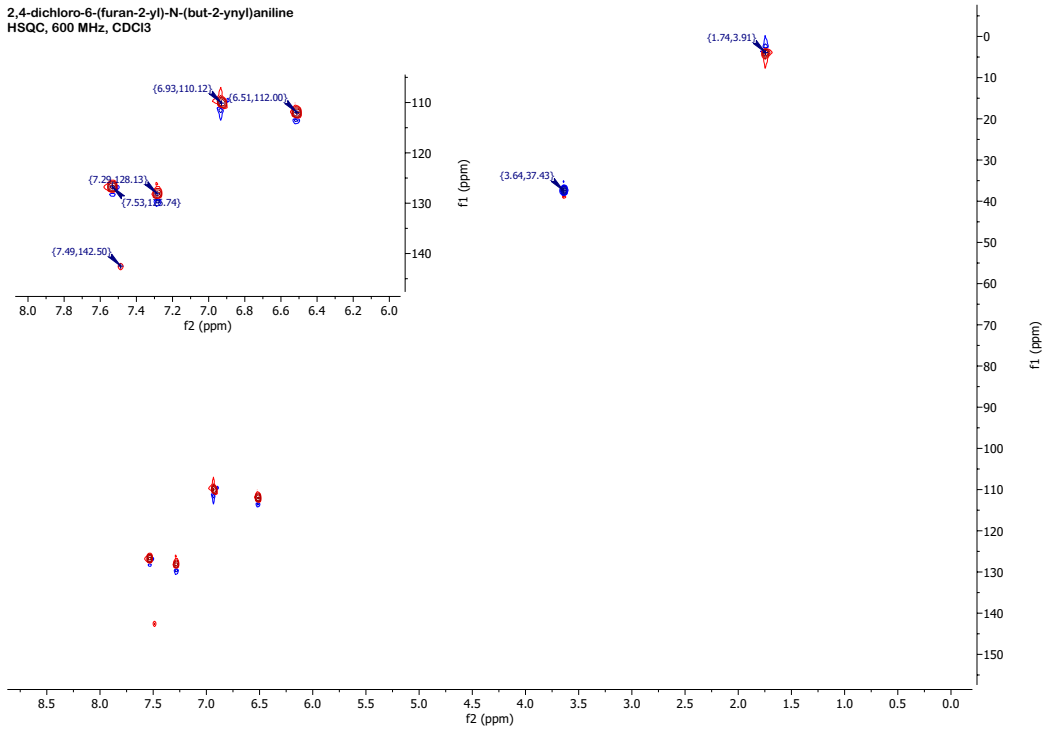
*Spectrum 86: HMBC-NMR spectrum of 2-chloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80c**)*



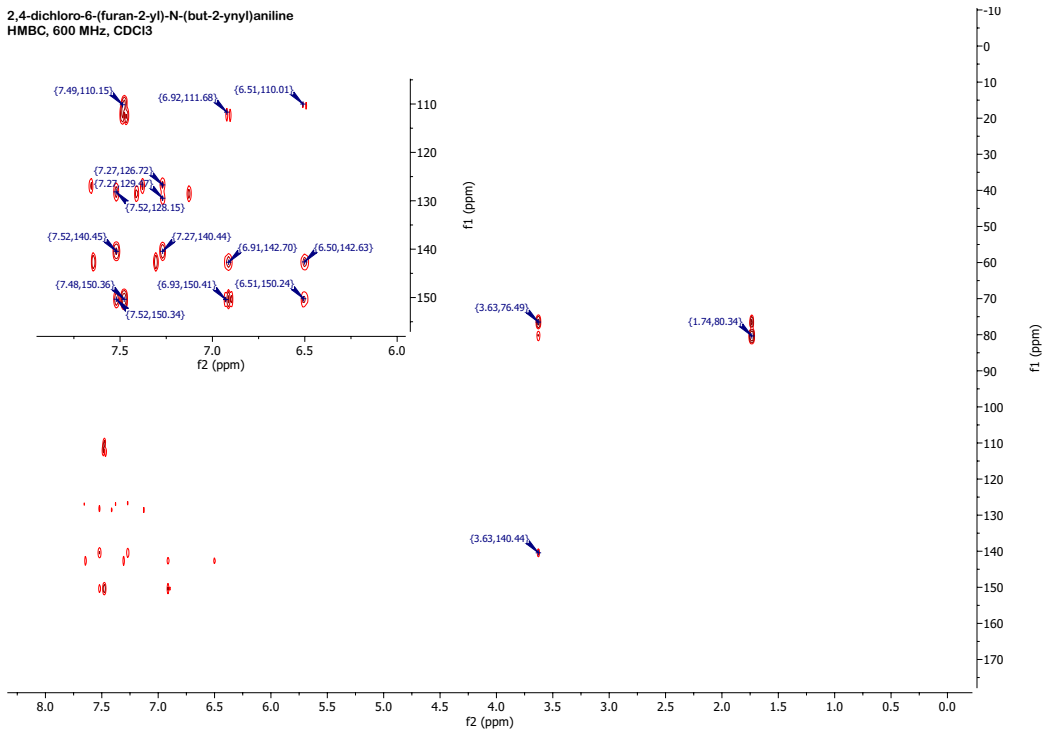
*Spectrum 87: DEPT135-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68d**)*



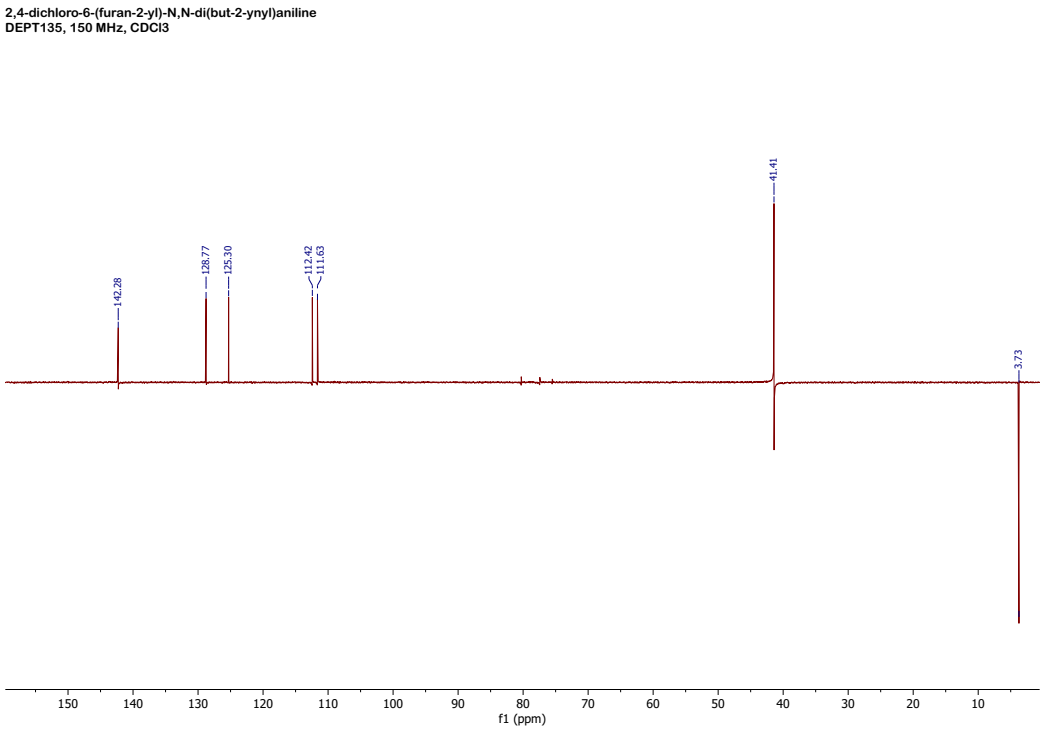
*Spectrum 88: COSY-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68d**)*



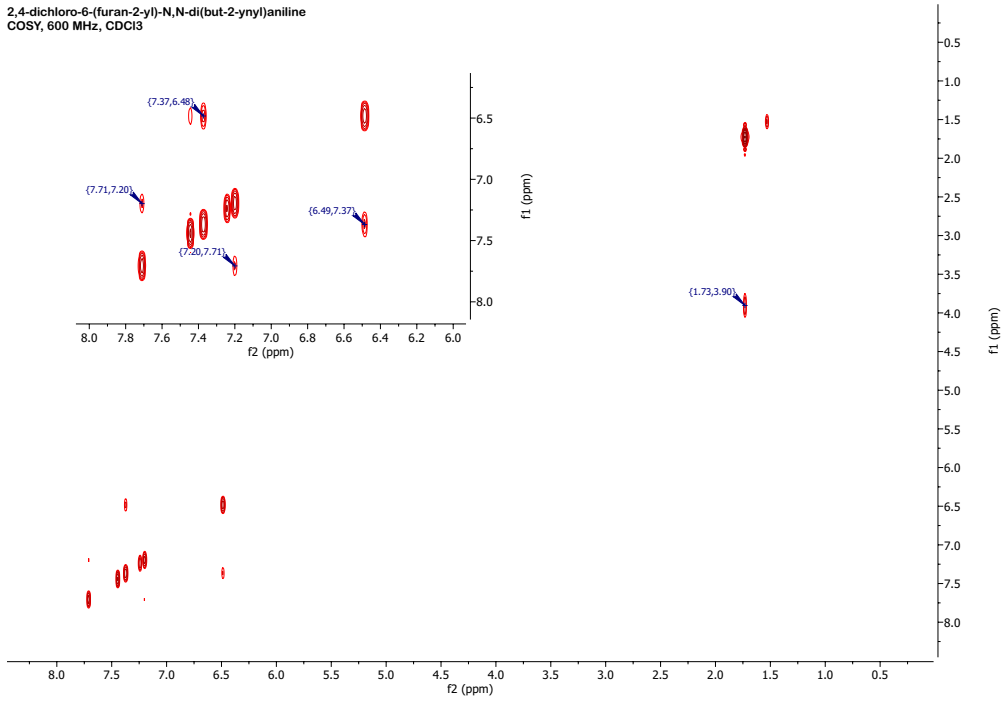
*Spectrum 89: HSQC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68d**)*



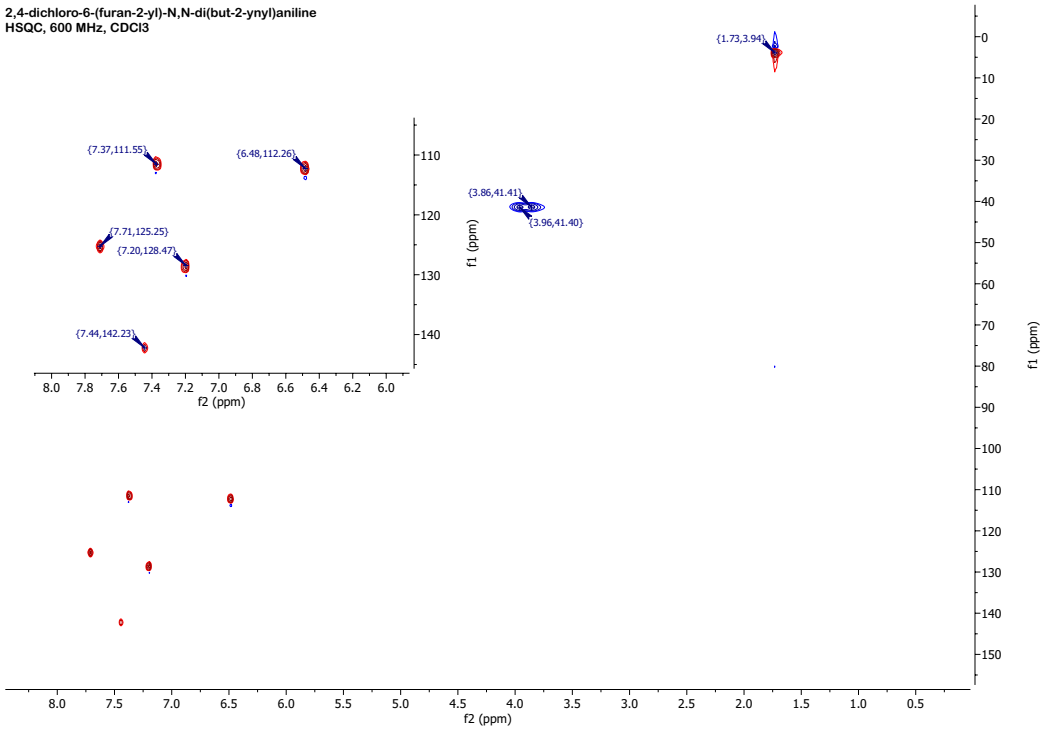
*Spectrum 90: HMBC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)aniline (**68d**)*



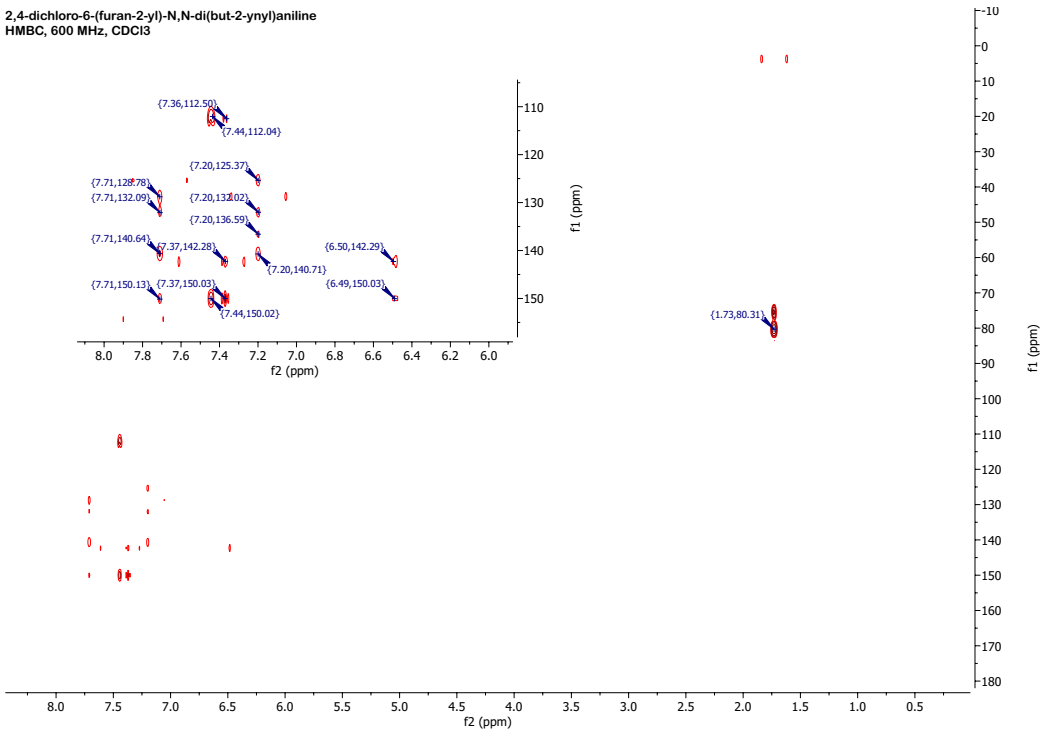
*Spectrum 91: DEPT135-NMR spectrum of 2,4-dichloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80d**)*



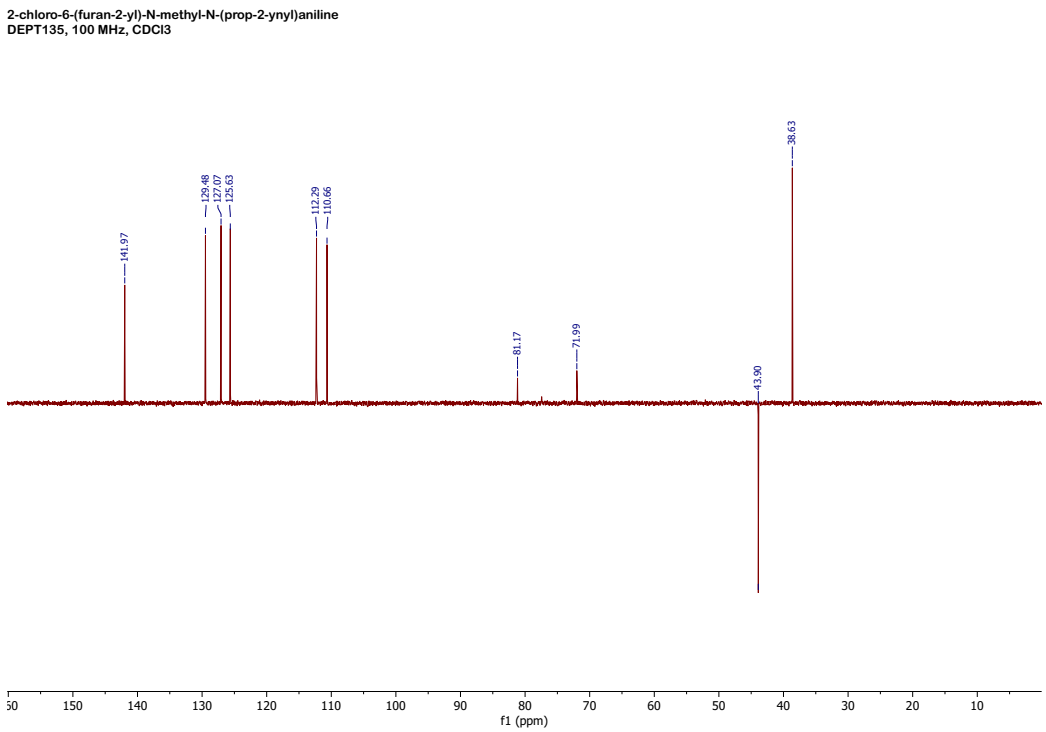
*Spectrum 92: COSY-NMR spectrum of 2,4-dichloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80d**)*



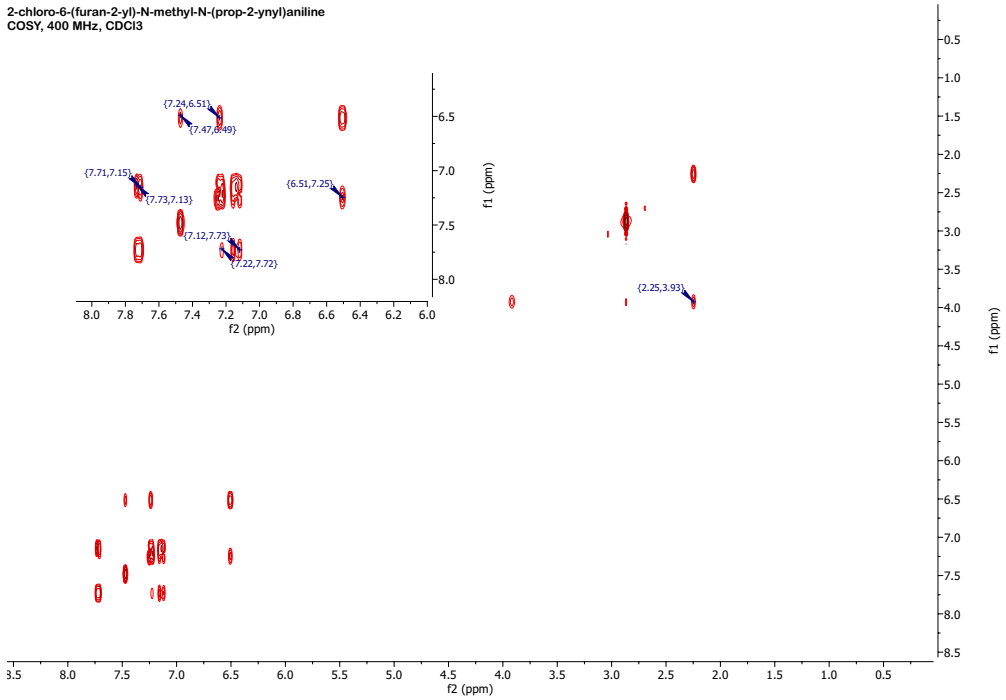
*Spectrum 93: HSQC-NMR spectrum of 2,4-dichloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline(**80d**)*



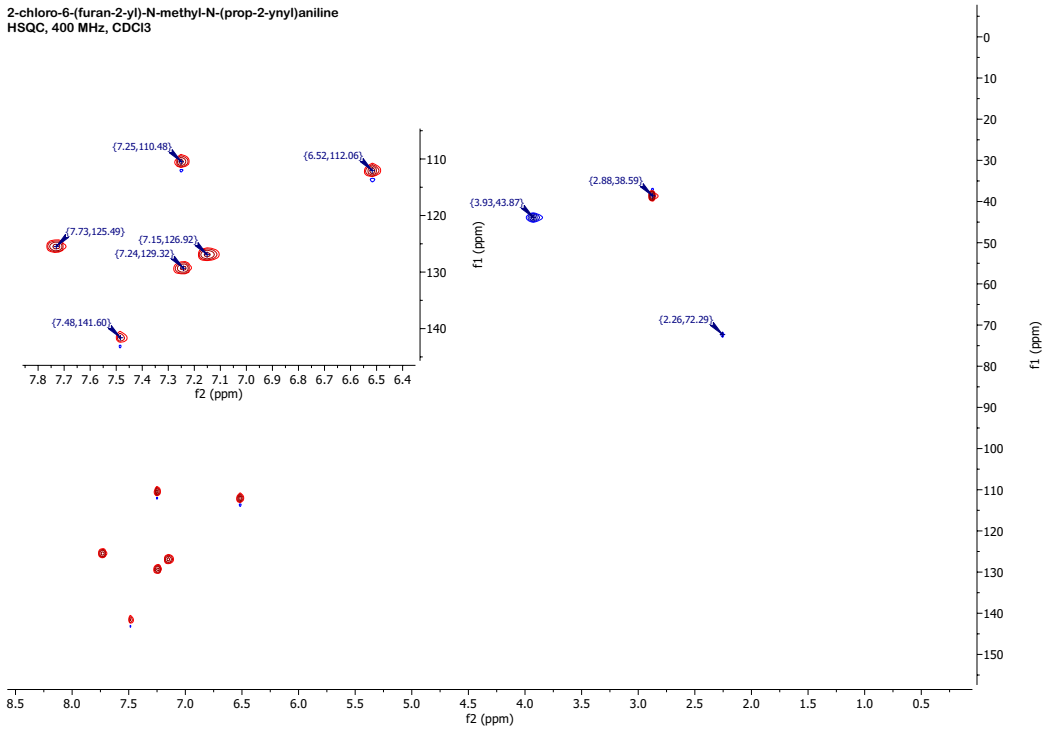
*Spectrum 94: HMBC-NMR spectrum of 2,4-dichloro-N,N–di(but-2-ynyl)-6-(furan-2-yl)aniline (**80d**)*



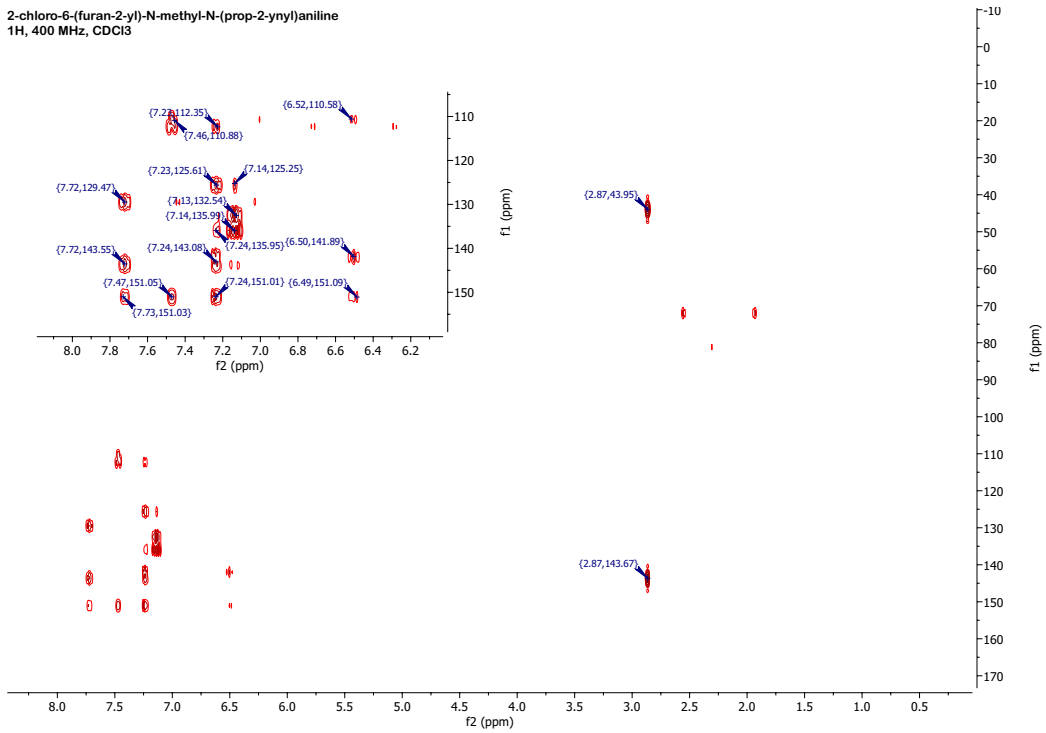
*Spectrum 95: DEPT135-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69a**)*



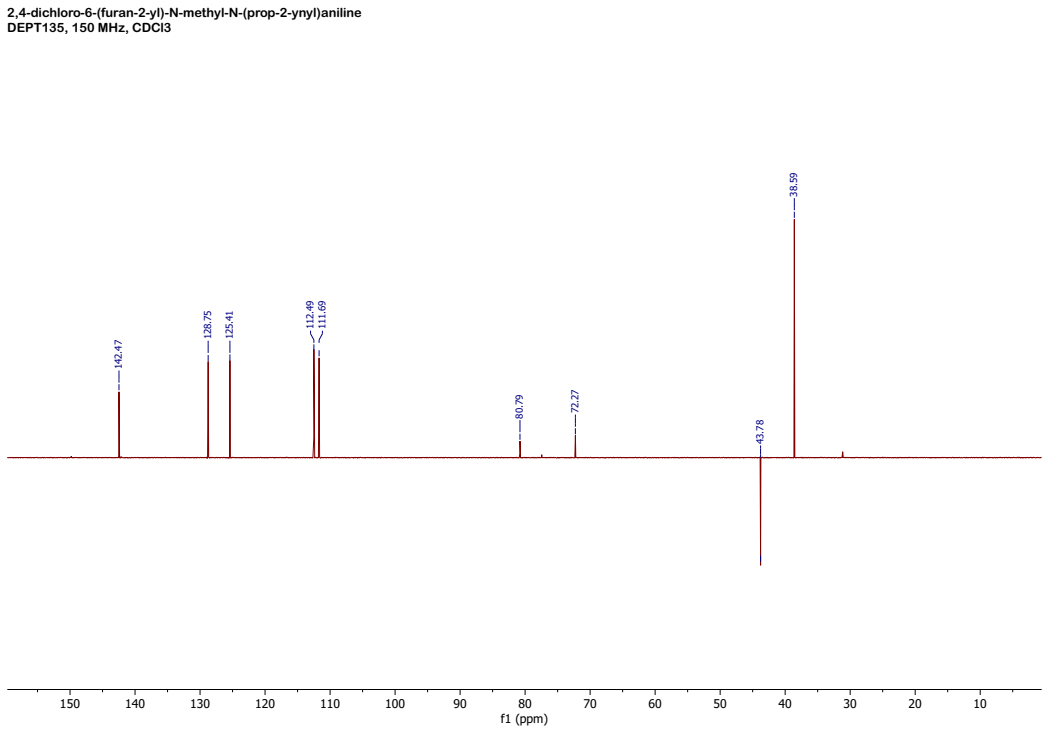
*Spectrum 96: COSY-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69a**)*



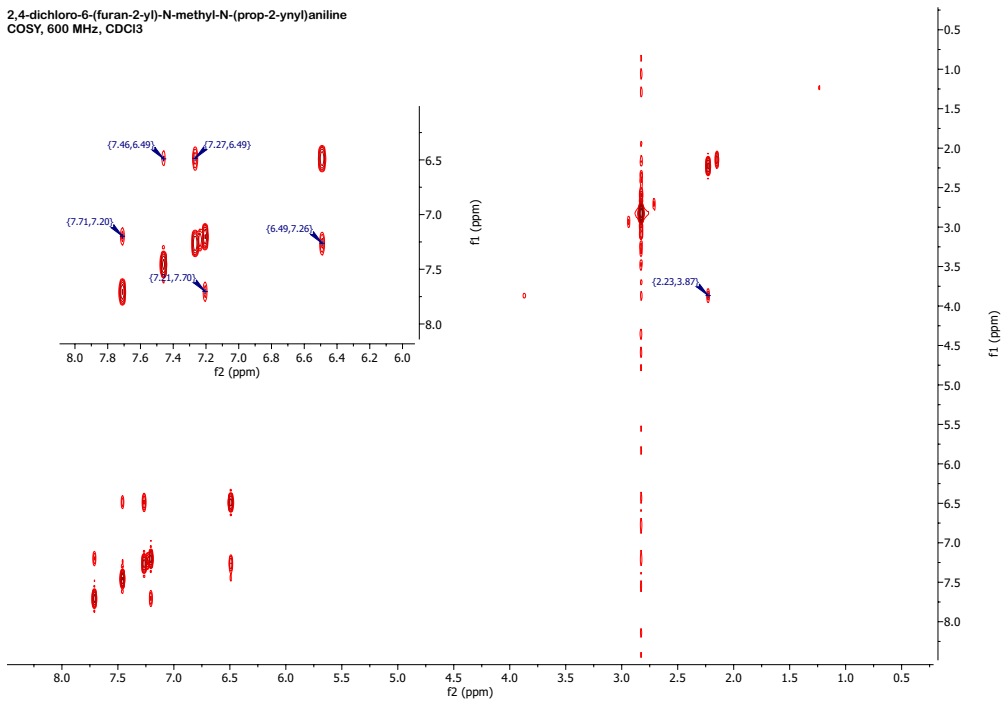
*Spectrum 97: HSQC-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69a**)*



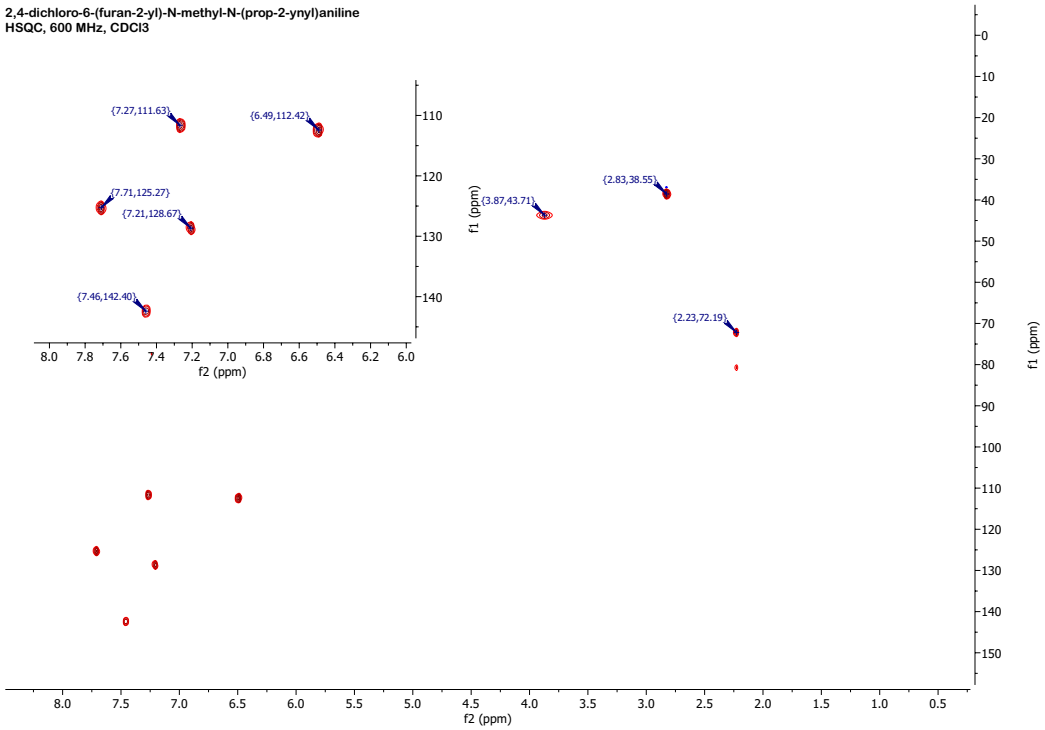
*Spectrum 98: HMBC-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69a**)*



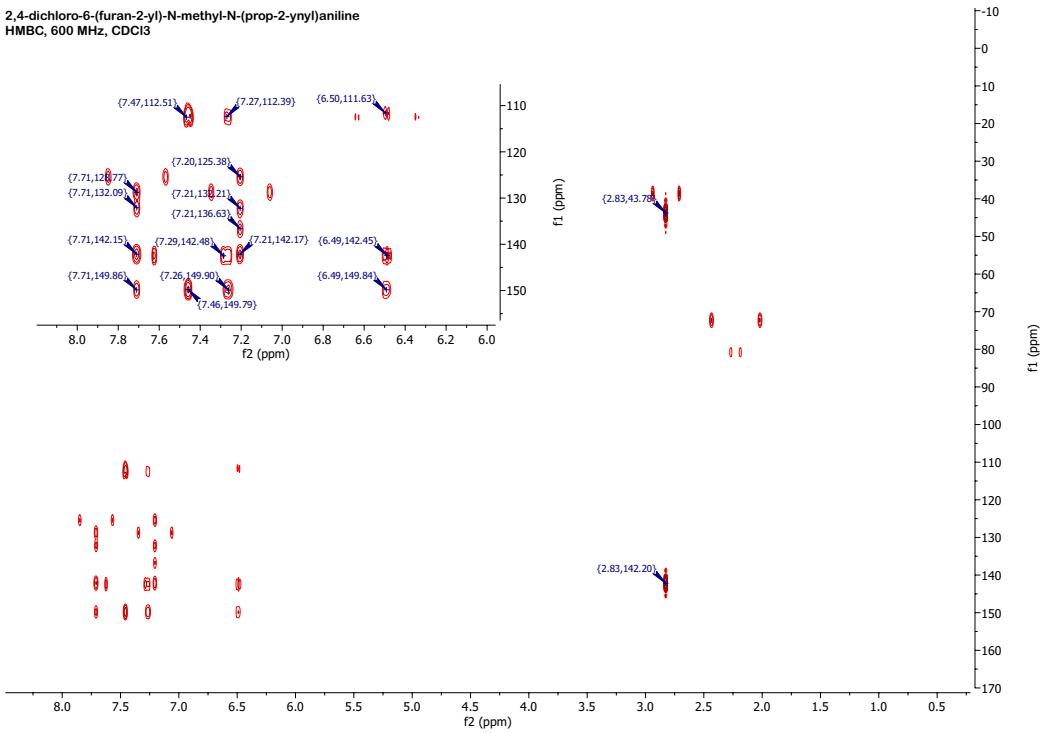
*Spectrum 99: DEPT135-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69b**)*



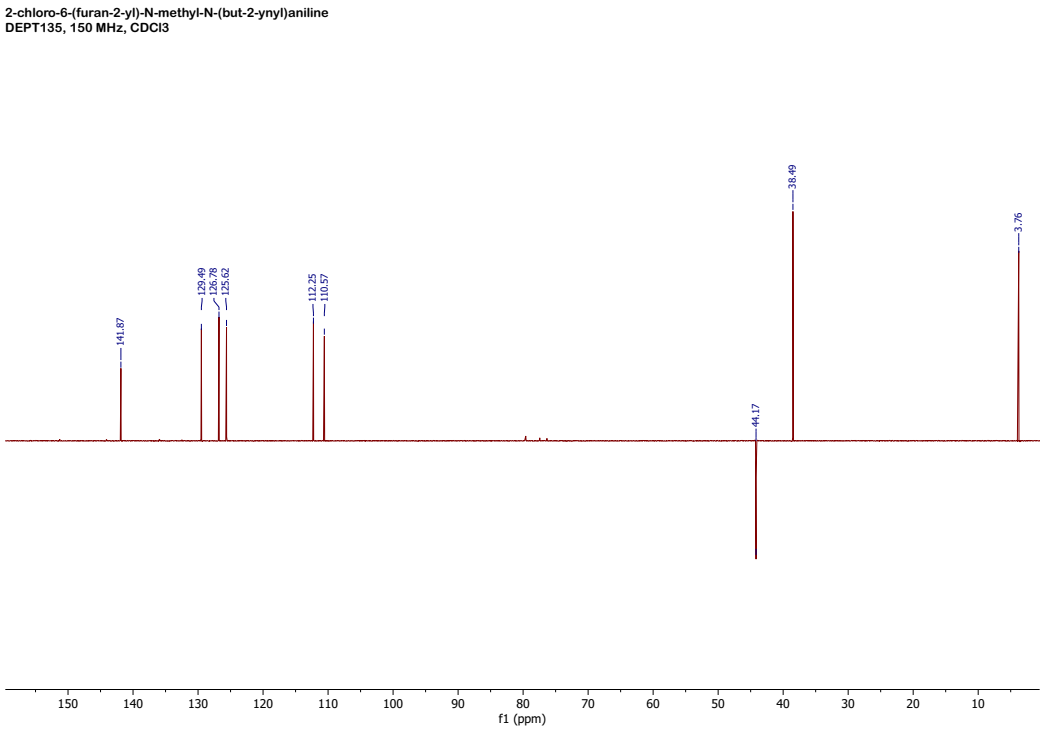
*Spectrum 100: COSY-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69b**)*



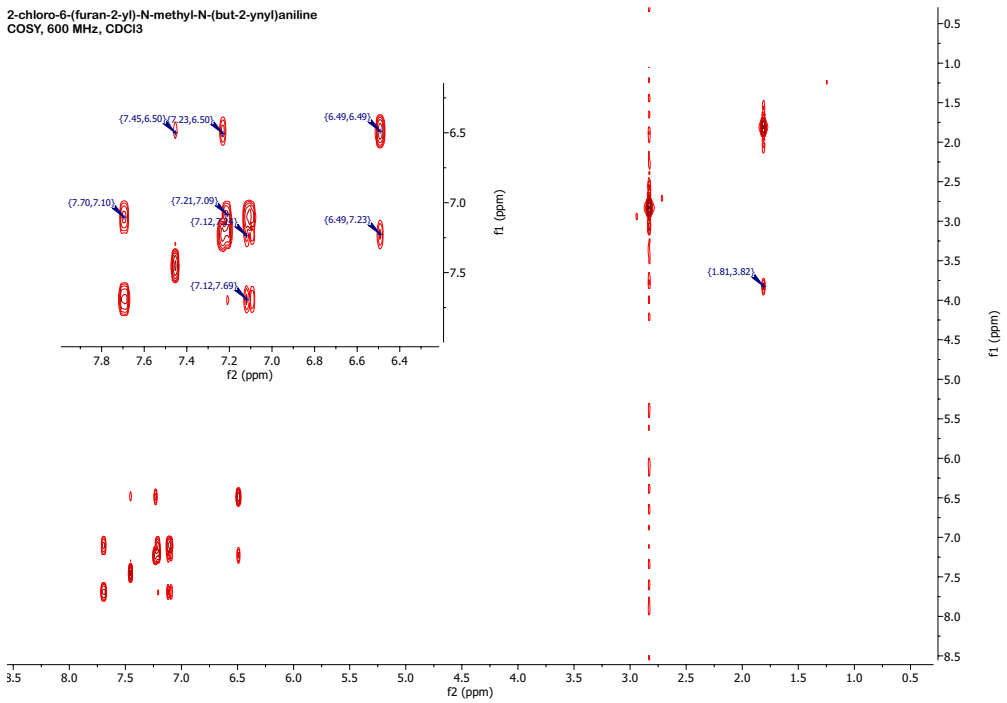
*Spectrum 101: HSQC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69b**)*



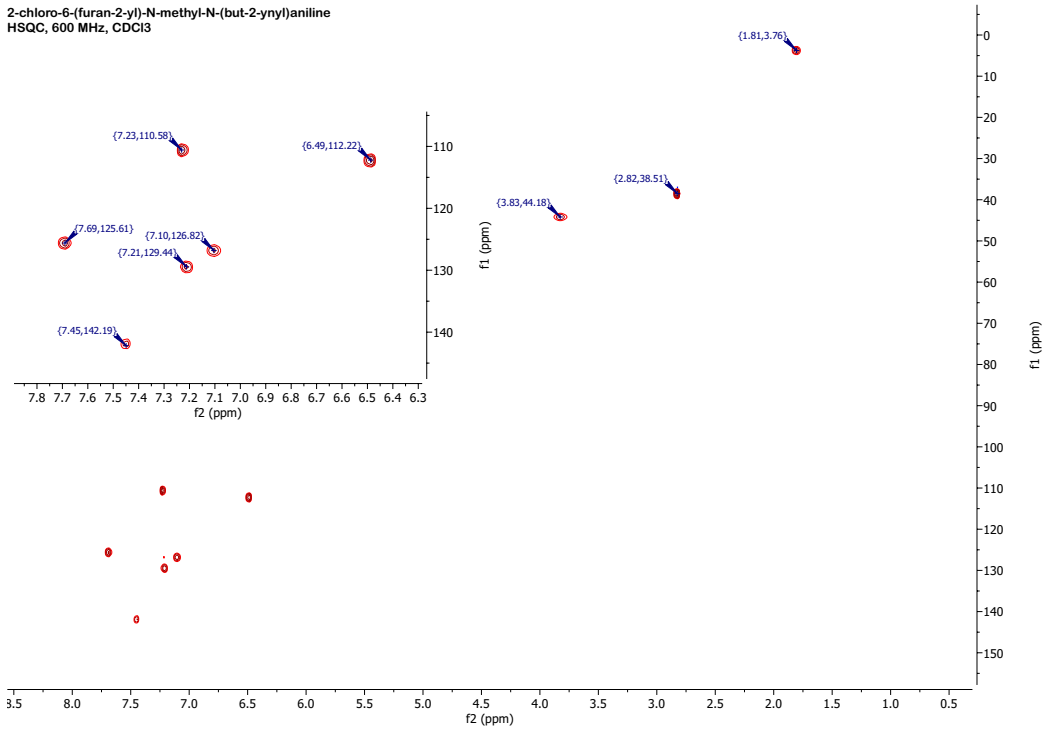
*Spectrum 102: HMBC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-methyl-N-(prop-2-ynyl)aniline (**69b**)*



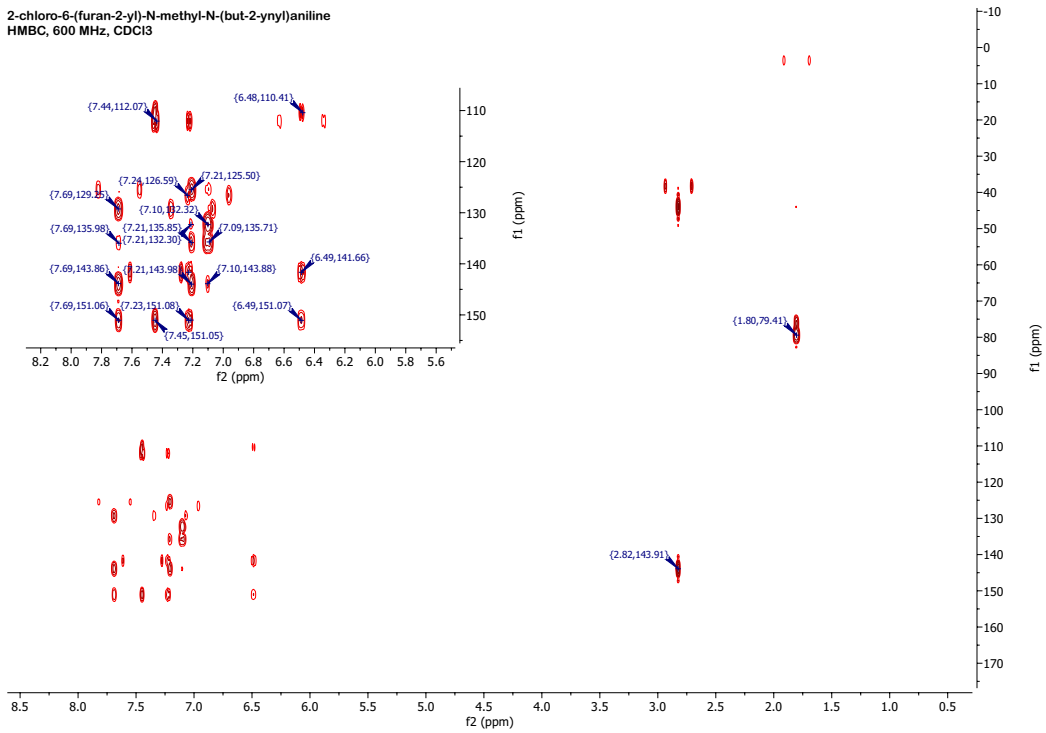
*Spectrum 103: DEPT135-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69c**)*



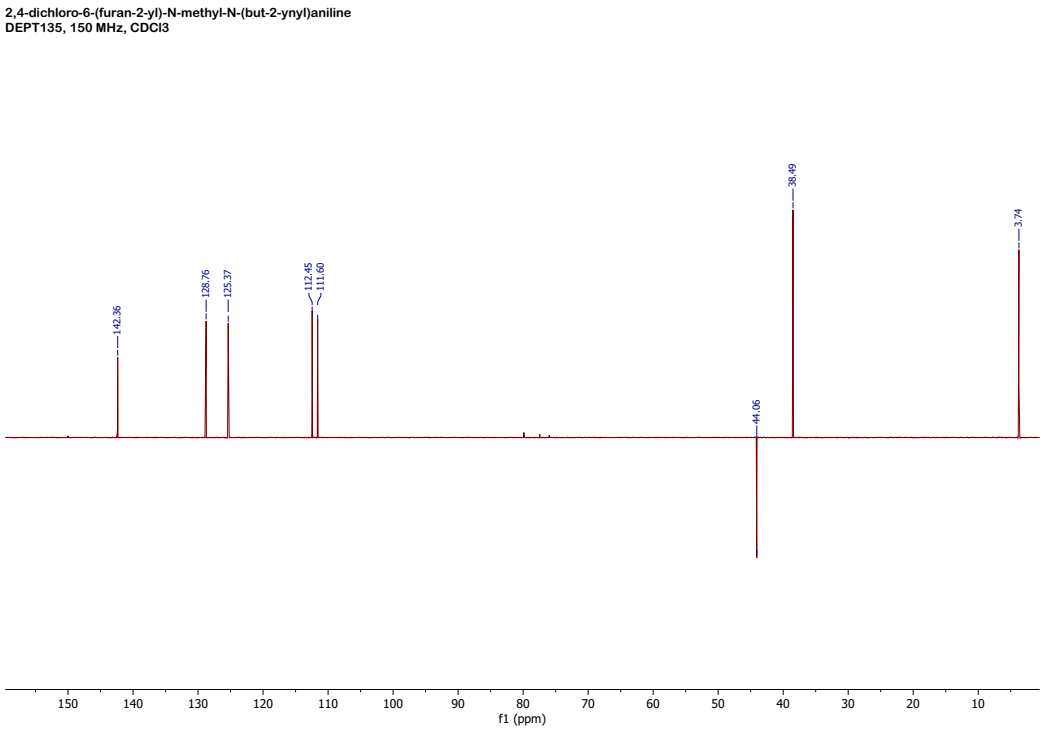
*Spectrum 104: COSY-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69c**)*



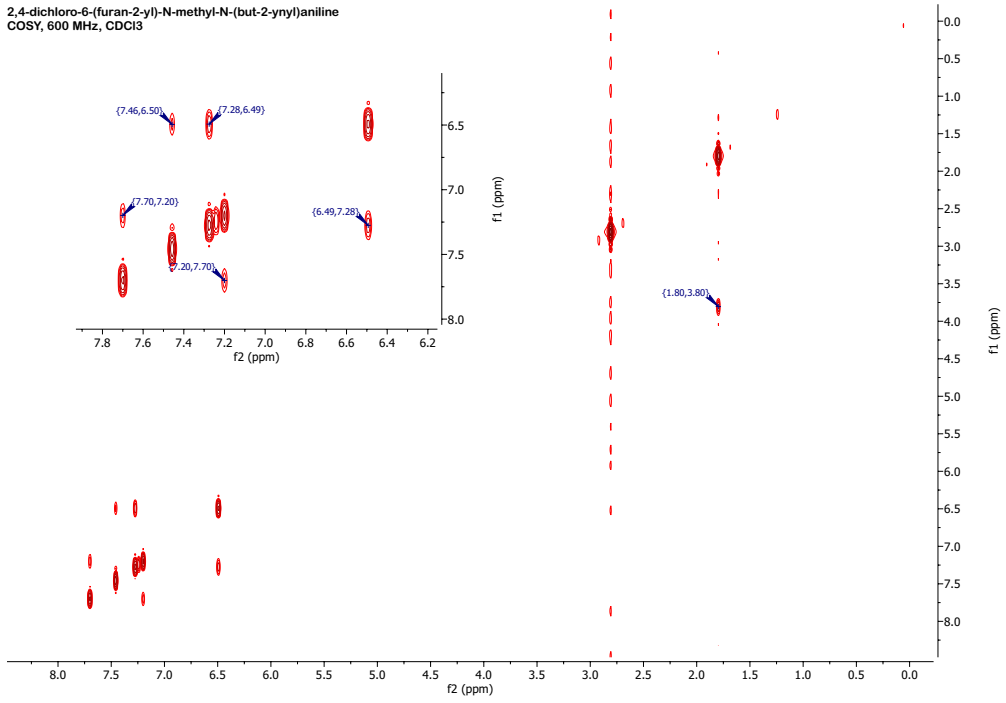
*Spectrum 105: HSQC-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69c**)*



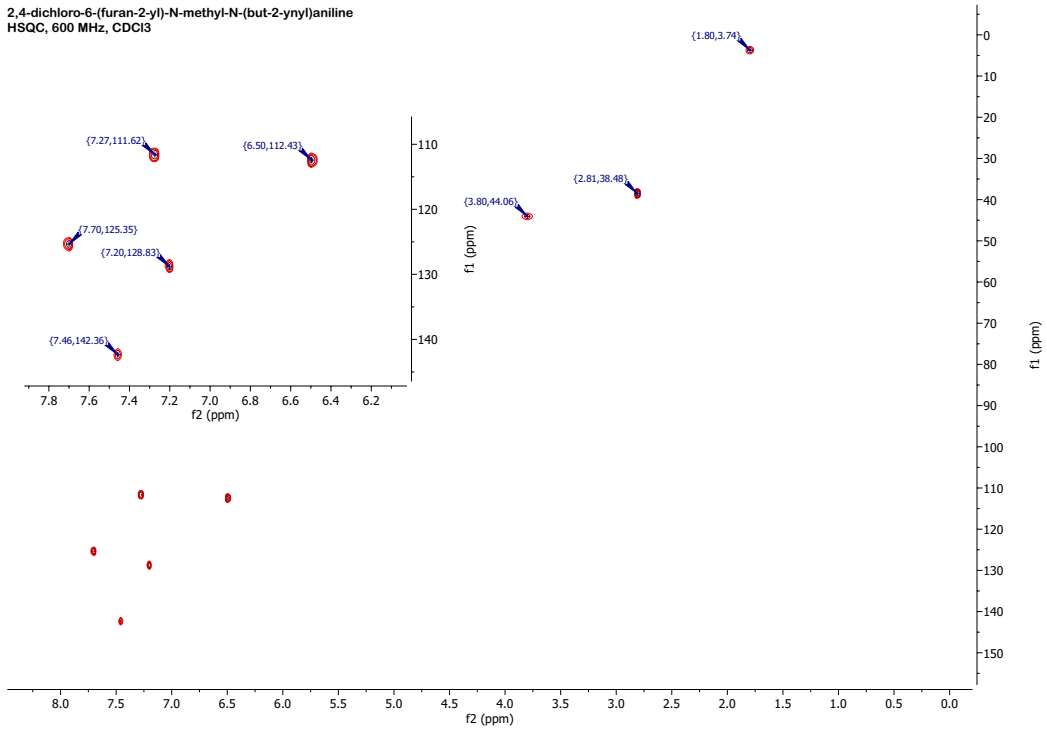
*Spectrum 106: HMBC-NMR spectrum of 2-chloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69c**)*



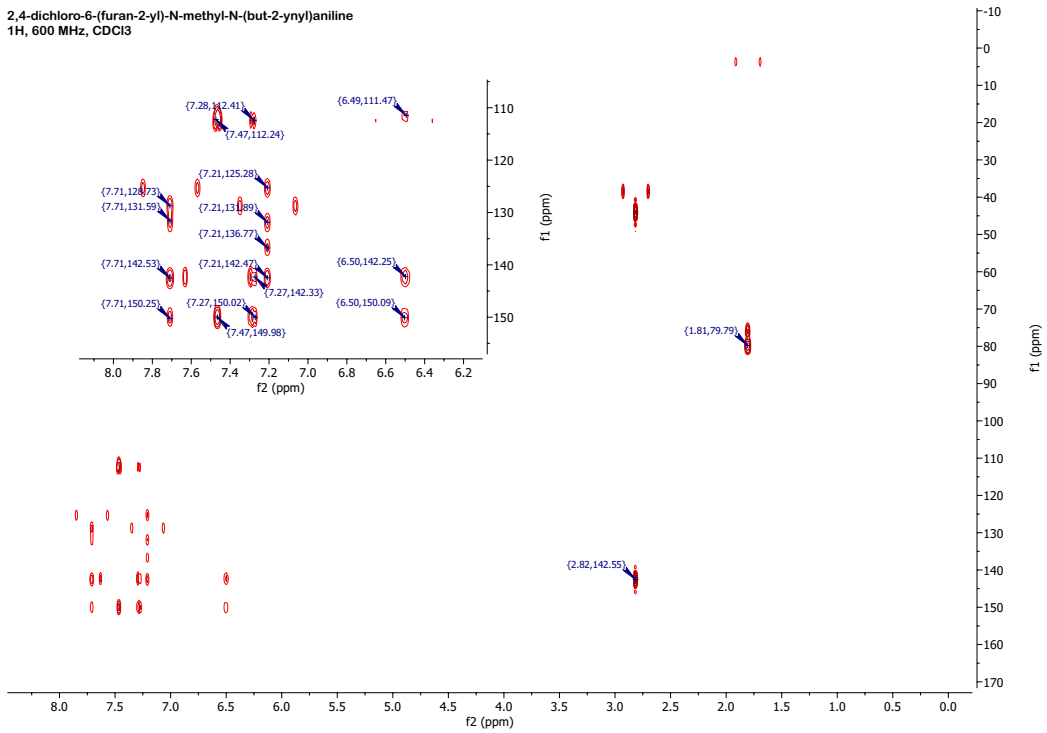
*Spectrum 107: DEPT135-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69d**)*



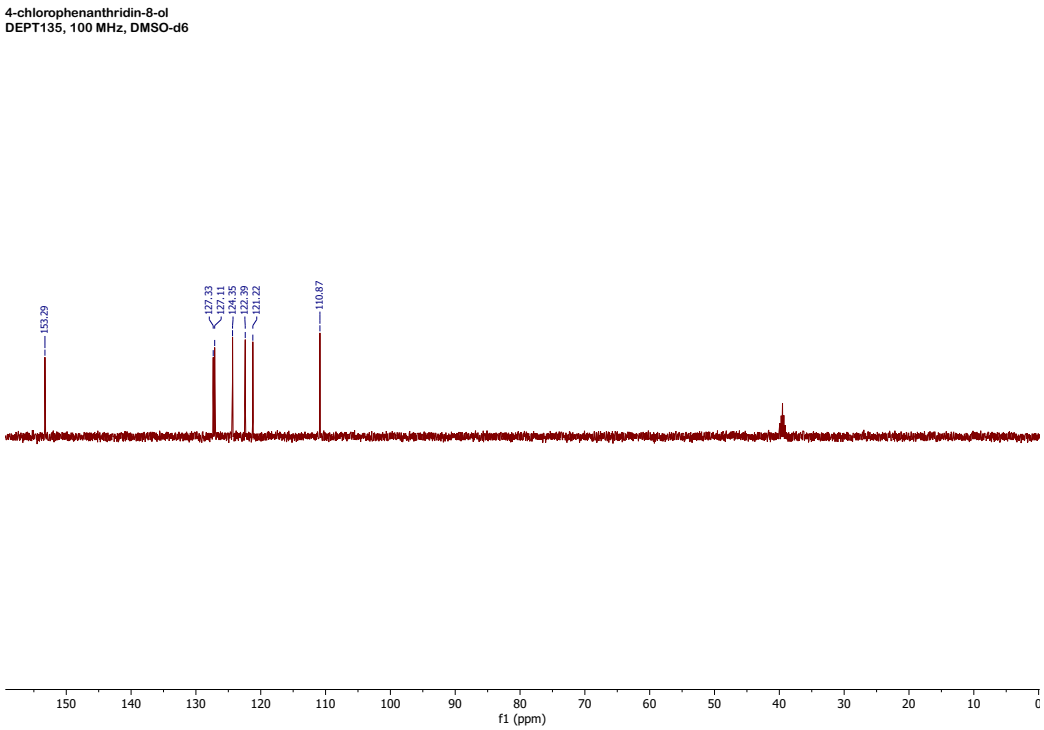
*Spectrum 108: COSY-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69d**)*



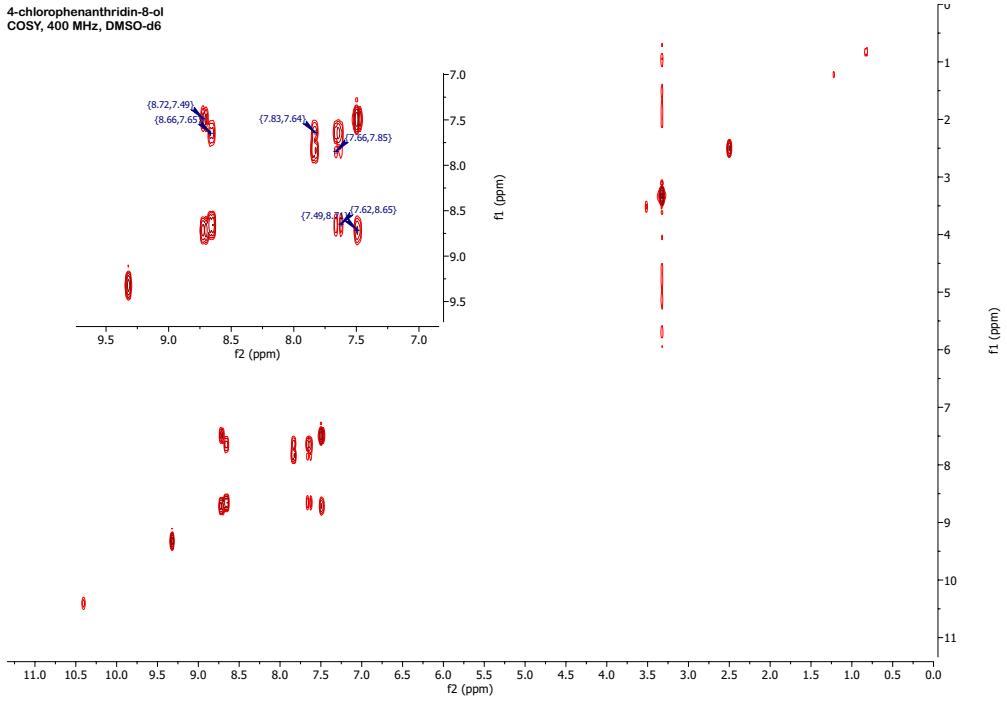
*Spectrum 109: HSQC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69d**)*



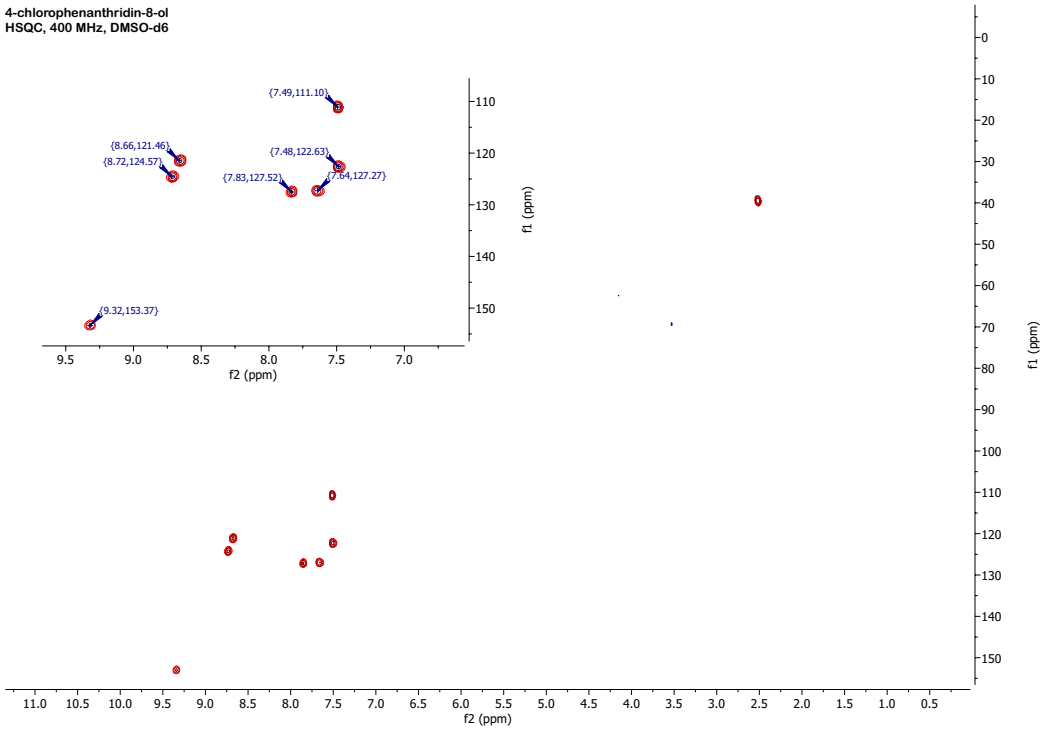
*Spectrum 110: HMBC-NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(but-2-ynyl)-N-methylaniline (**69d**)*



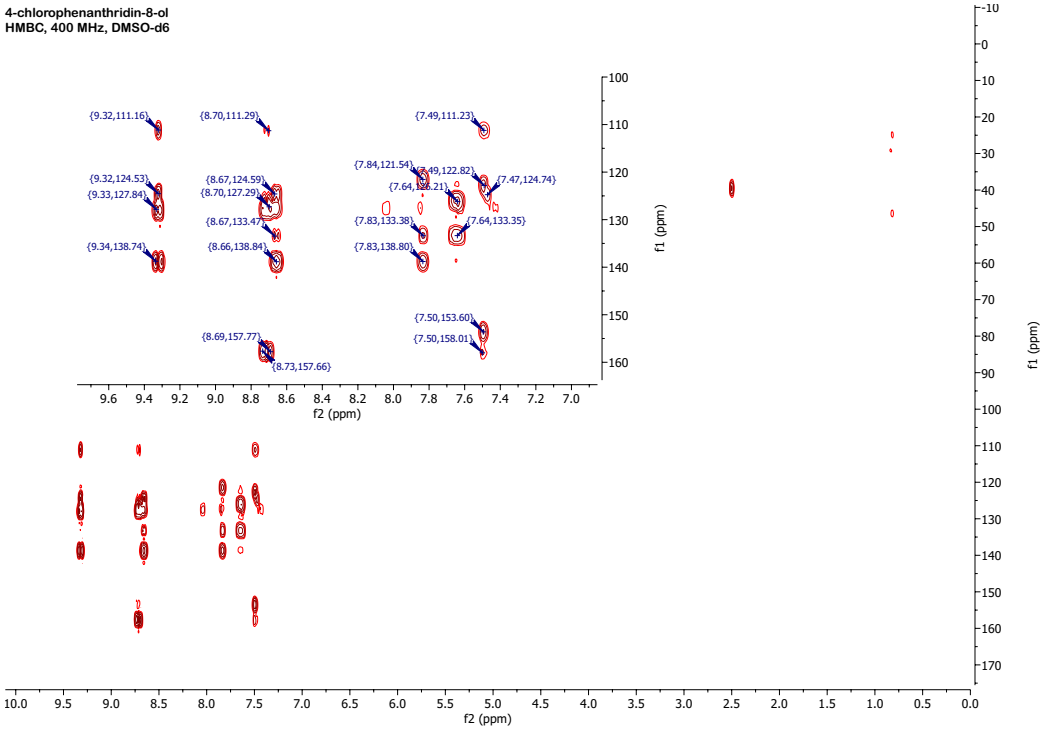
*Spectrum 111: DEPT135-NMR spectrum of 4-chlorophenanthridin-8-ol (**72a**)*



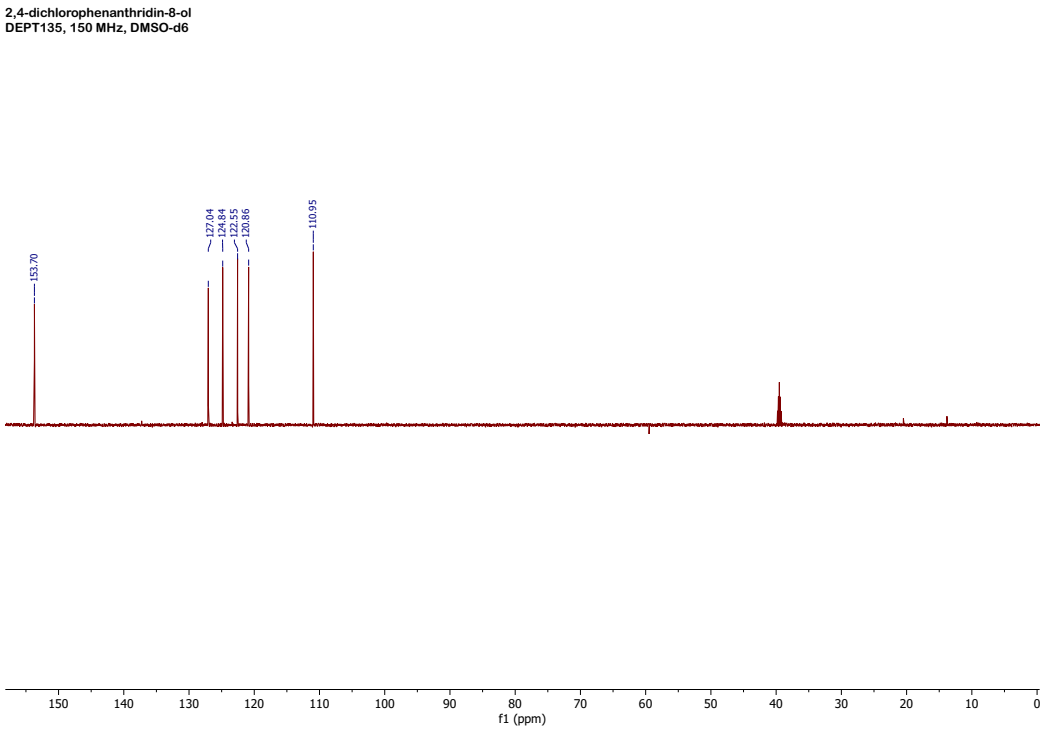
*Spectrum 112: COSY-NMR spectrum of 4-chlorophenanthridin-8-ol (**72a**)*



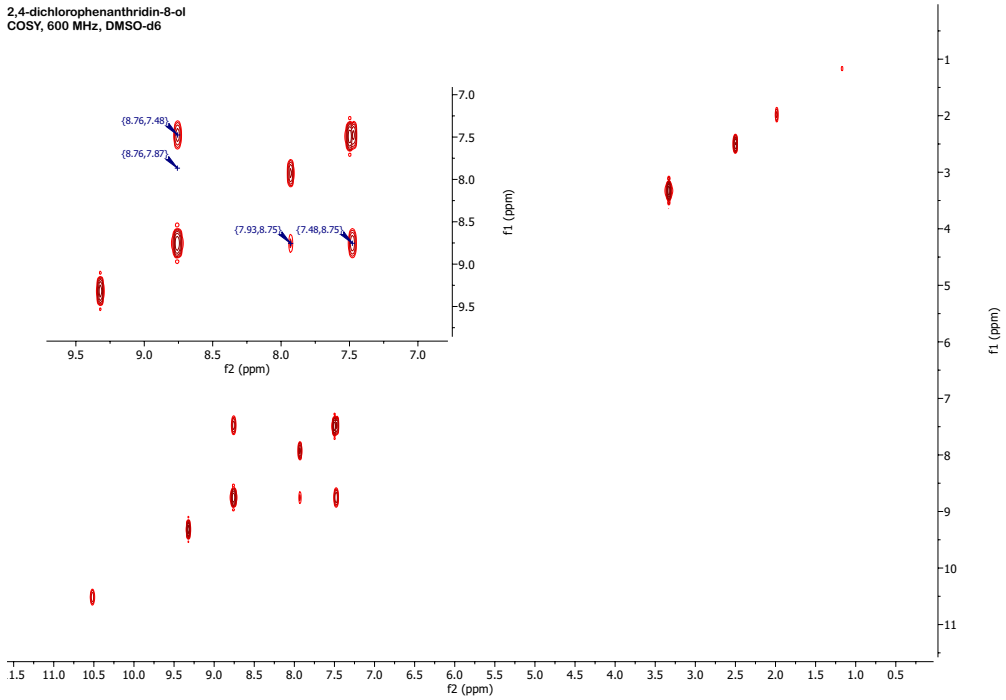
*Spectrum 113: HSQC-NMR spectrum of 4-chlorophenanthridin-8-ol (**72a**)*



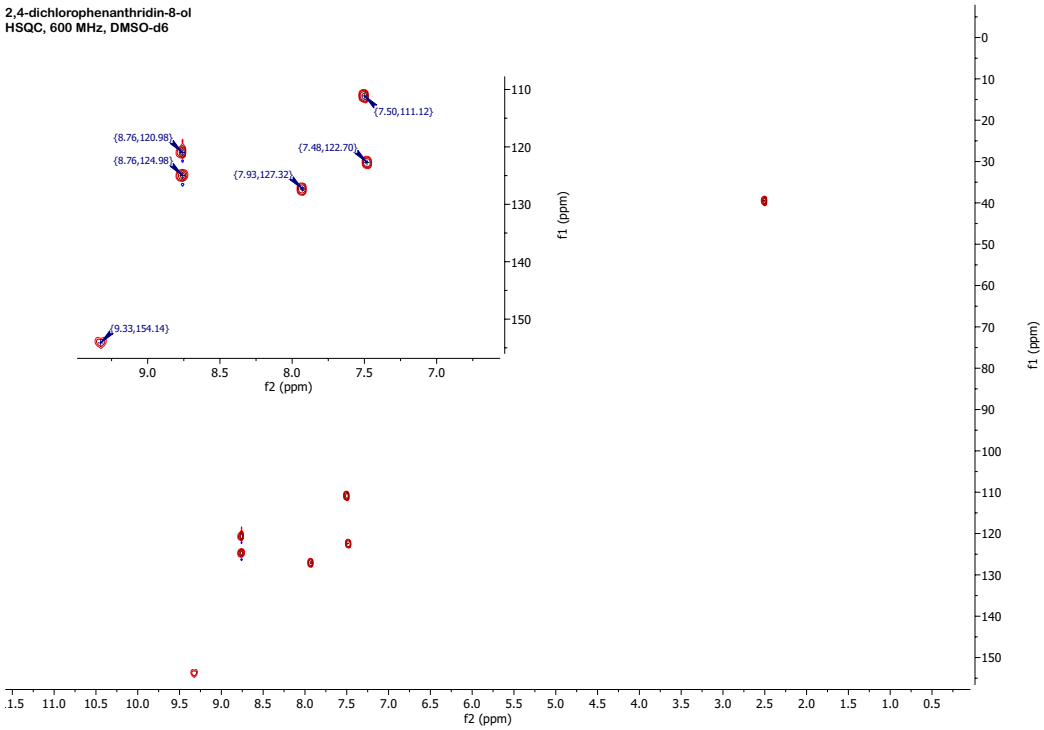
*Spectrum 114: HMBC-NMR spectrum of 4-chlorophenanthridin-8-ol (**72a**)*



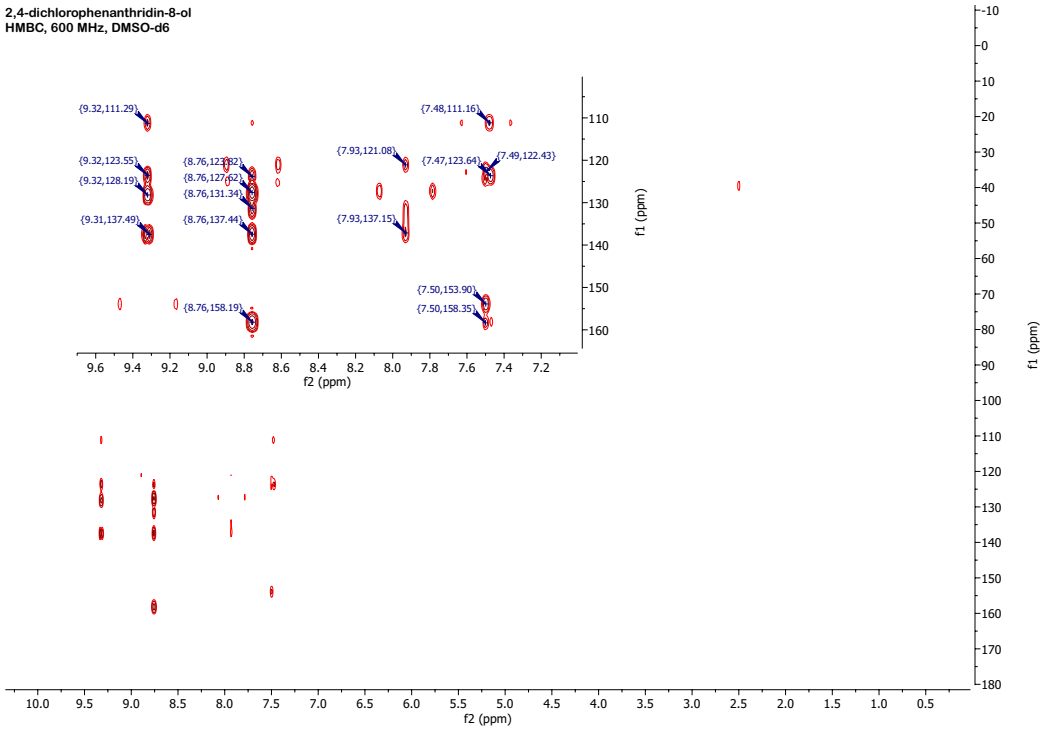
*Spectrum 115: DEPT135-NMR spectrum of 2,4-dichlorophenanthridin-8-ol (**72b**)*



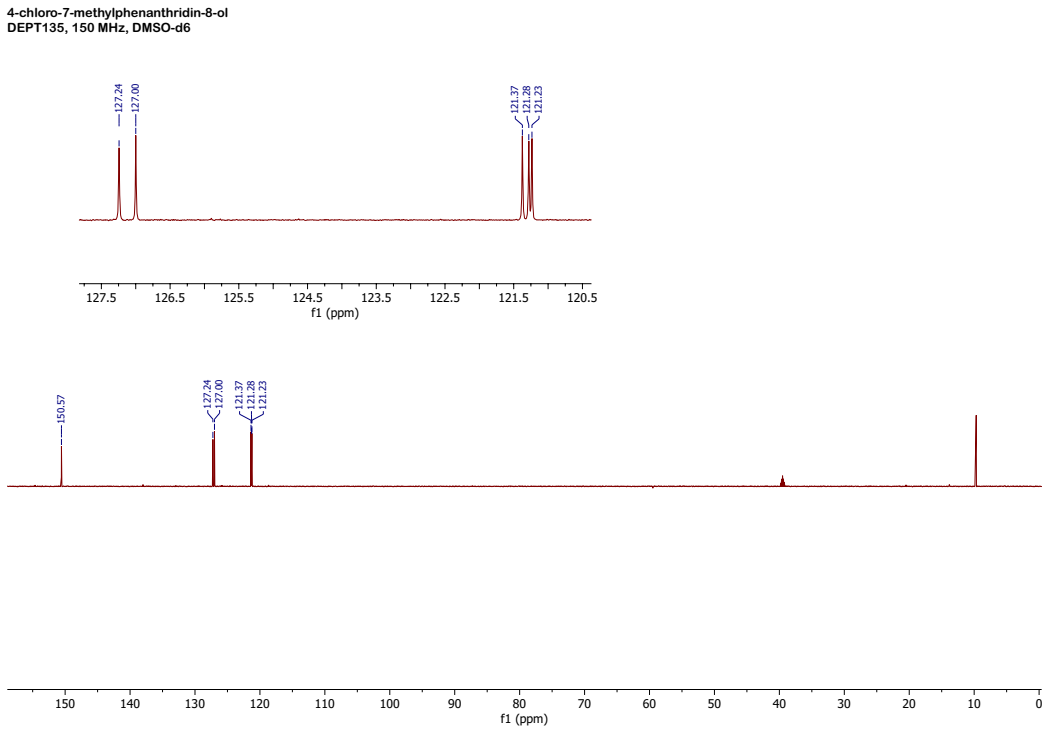
*Spectrum 116: COSY-NMR spectrum of 2,4-dichlorophenanthridin-8-ol (**72b**)*



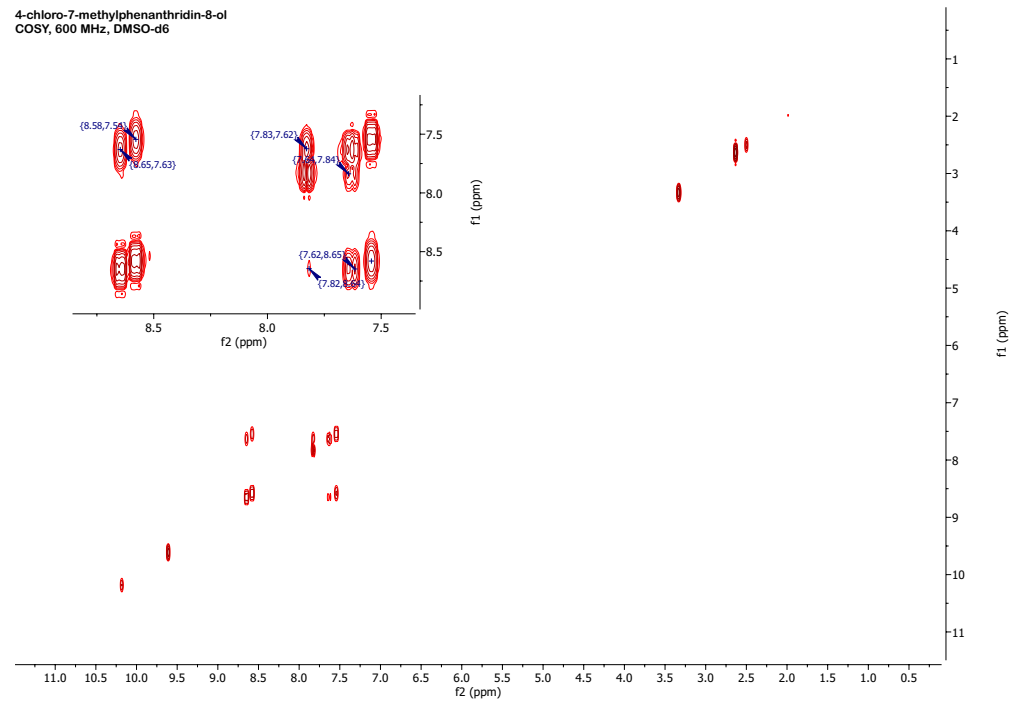
*Spectrum 117: HSQC-NMR spectrum of 2,4-dichlorophenanthridin-8-ol (**72b**)*



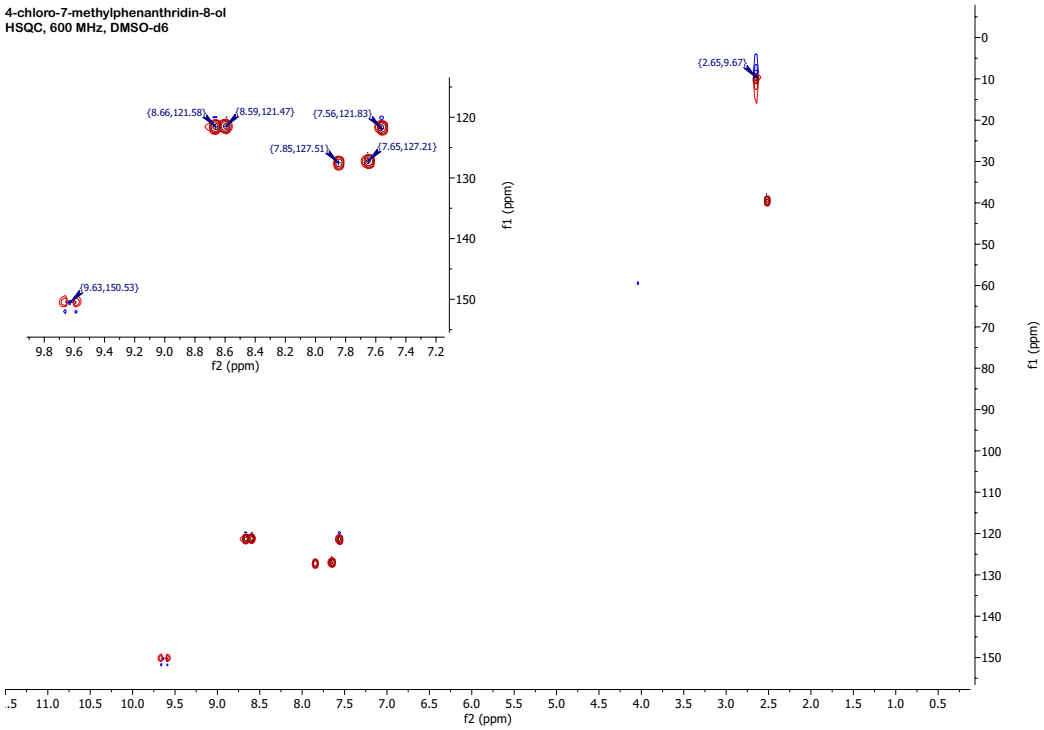
*Spectrum 118: HMBC-NMR spectrum of 2,4-dichlorophenanthridin-8-ol (**72b**)*



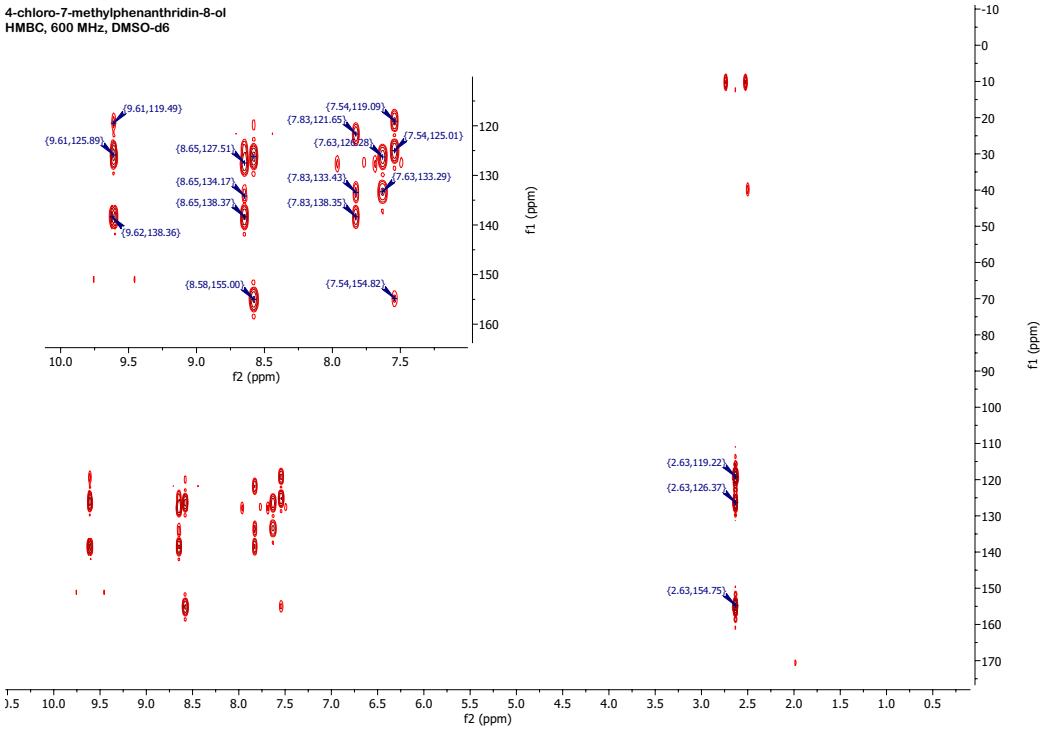
*Spectrum 119: DEPT135-NMR spectrum of 4-chloro-7-methylphenanthridin-8-ol (**72c**)*



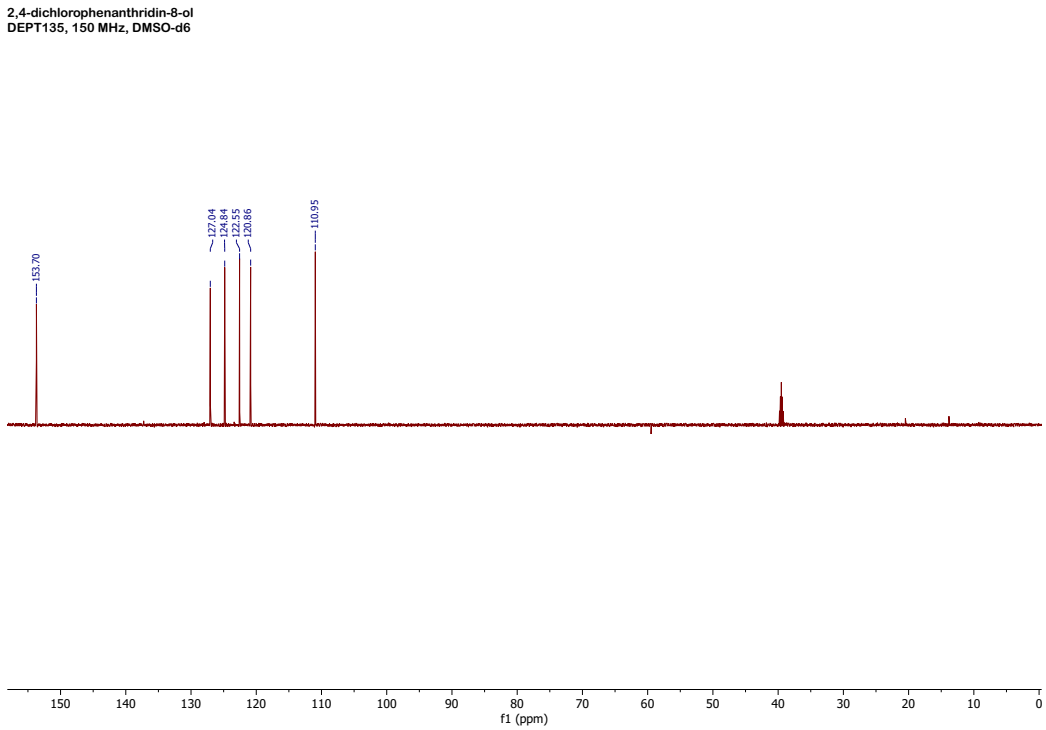
*Spectrum 120: COSY-NMR spectrum of 4-chloro-7-methylphenanthridin-8-ol (**72c**)*



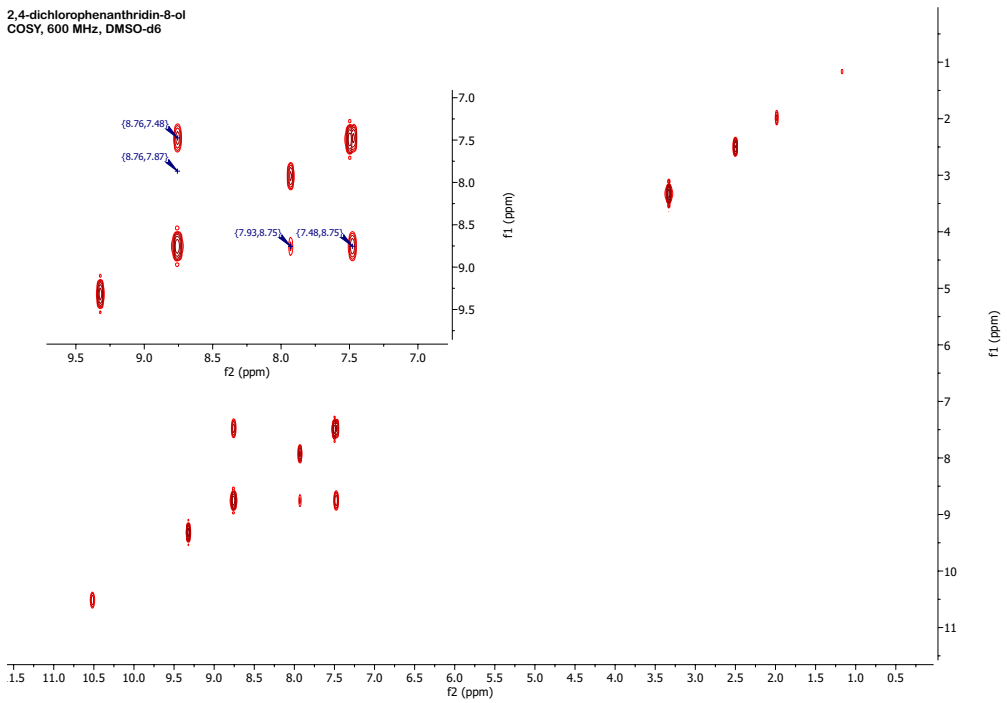
*Spectrum 121: HSQC-NMR spectrum of 4-chloro-7-methylphenanthridin-8-ol (**72c**)*



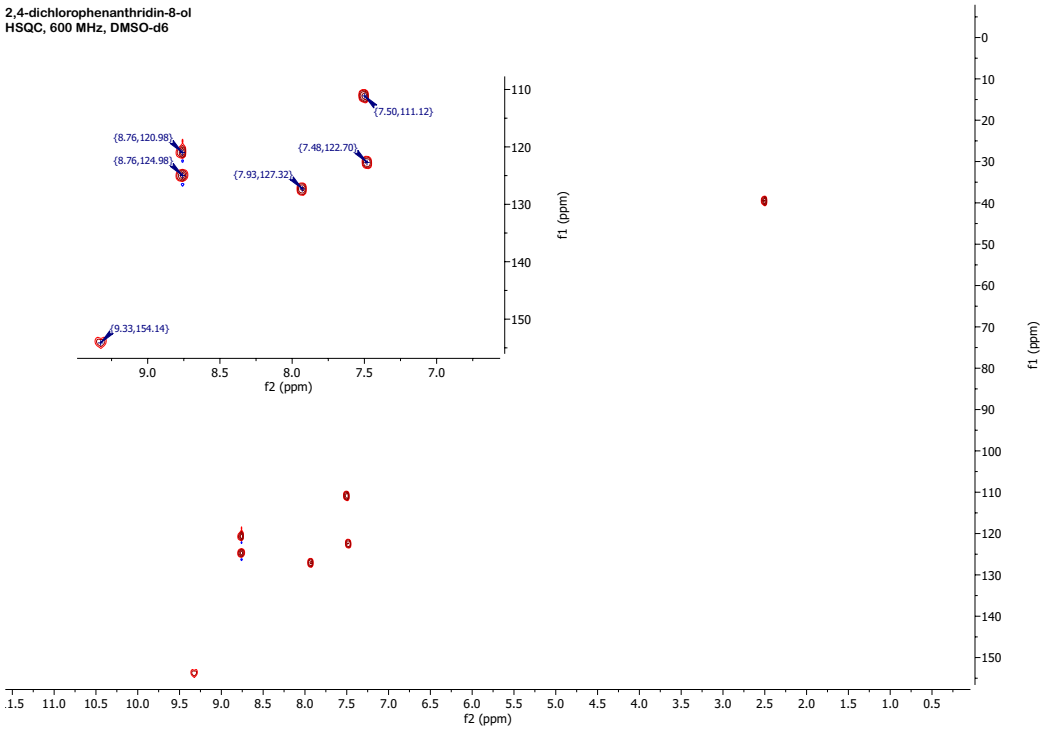
*Spectrum 122: HMBC-NMR spectrum of 4-chloro-7-methylphenanthridin-8-ol (**72c**)*



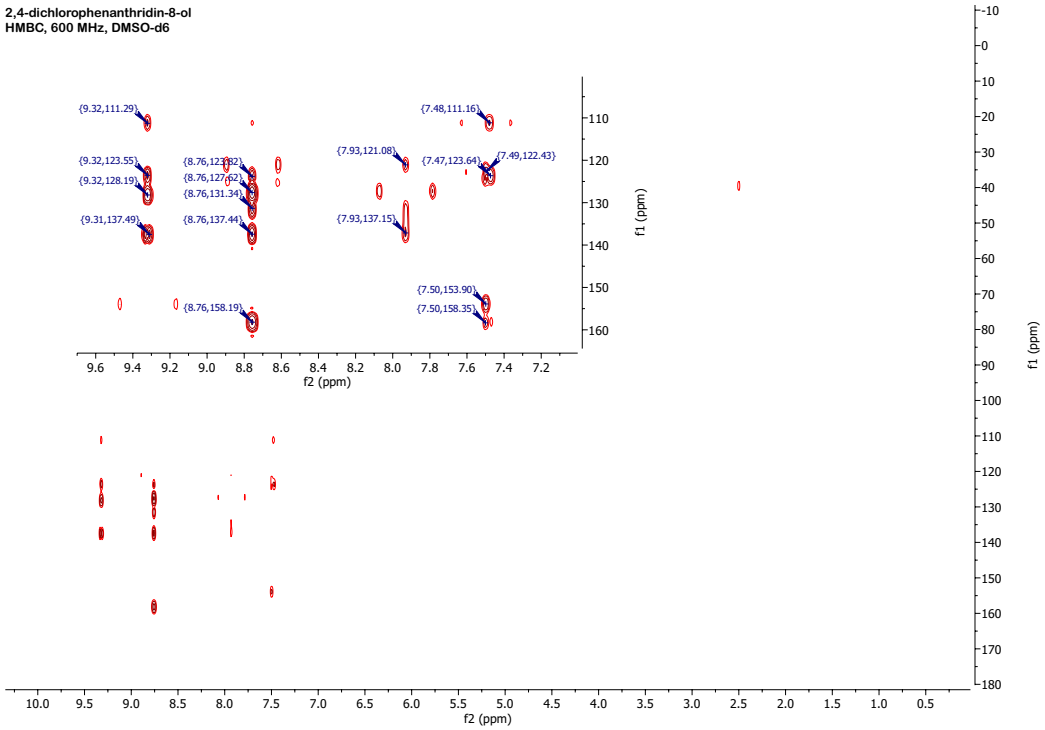
*Spectrum 123: DEPT135-NMR spectrum of 2,4-dichloro-7-methylphenanthridin-8-ol (**72d**)*



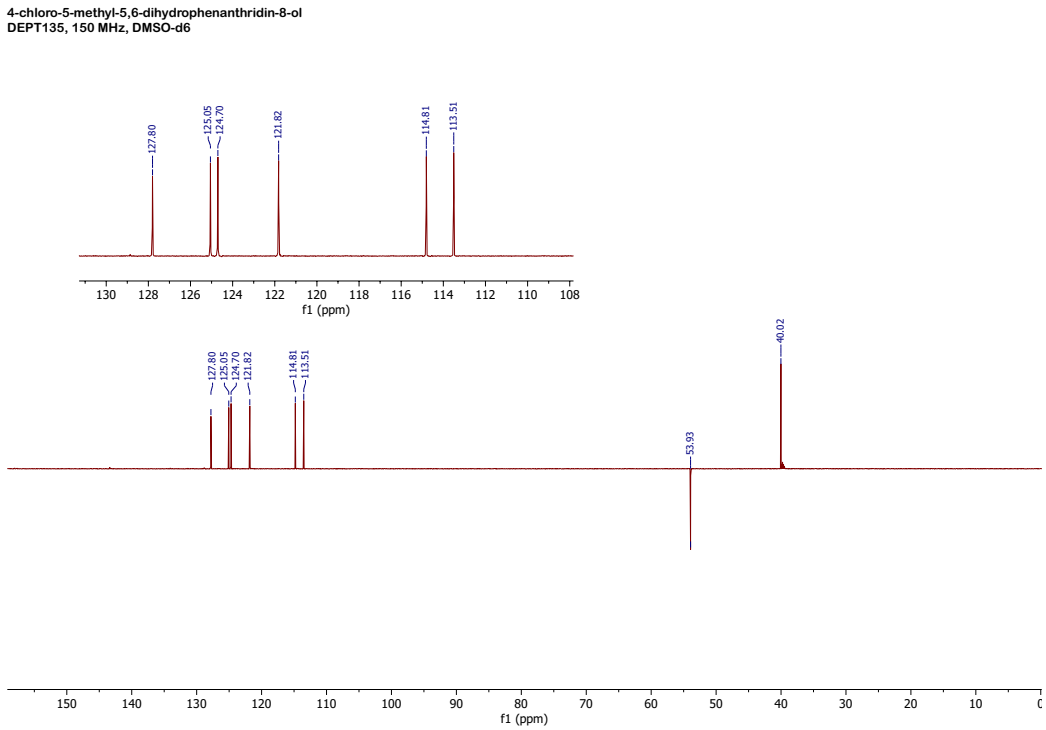
*Spectrum 124: COSY-NMR spectrum of 2,4-dichloro-7-methylphenanthridin-8-ol (**72d**)*



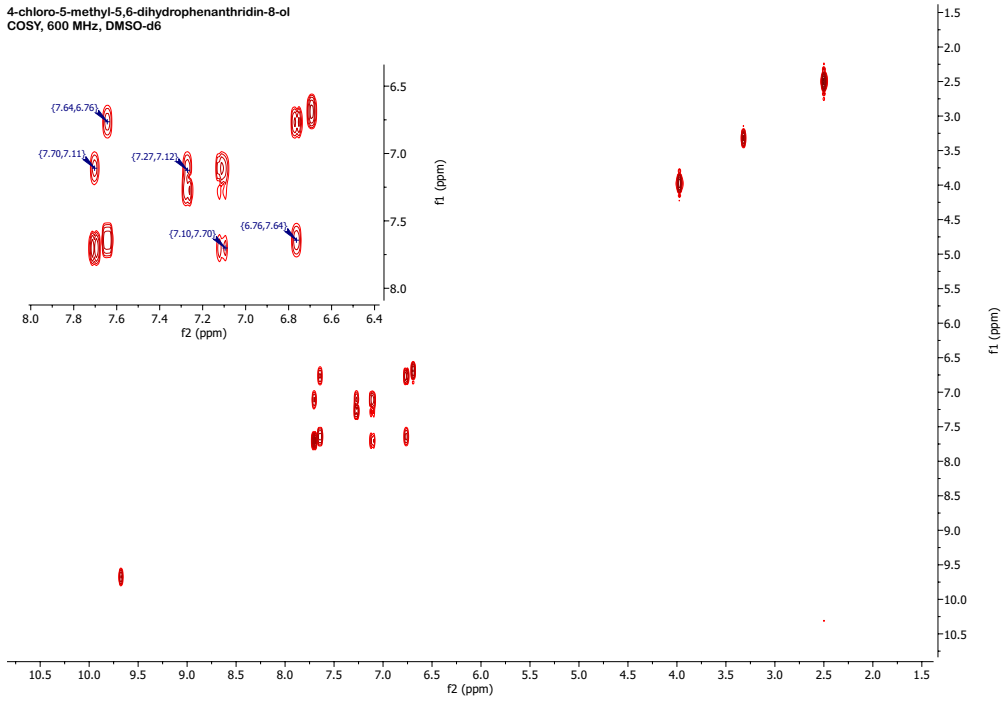
*Spectrum 125: HSQC-NMR spectrum of 2,4-dichloro-7-methylphenanthridin-8-ol (**72d**)*



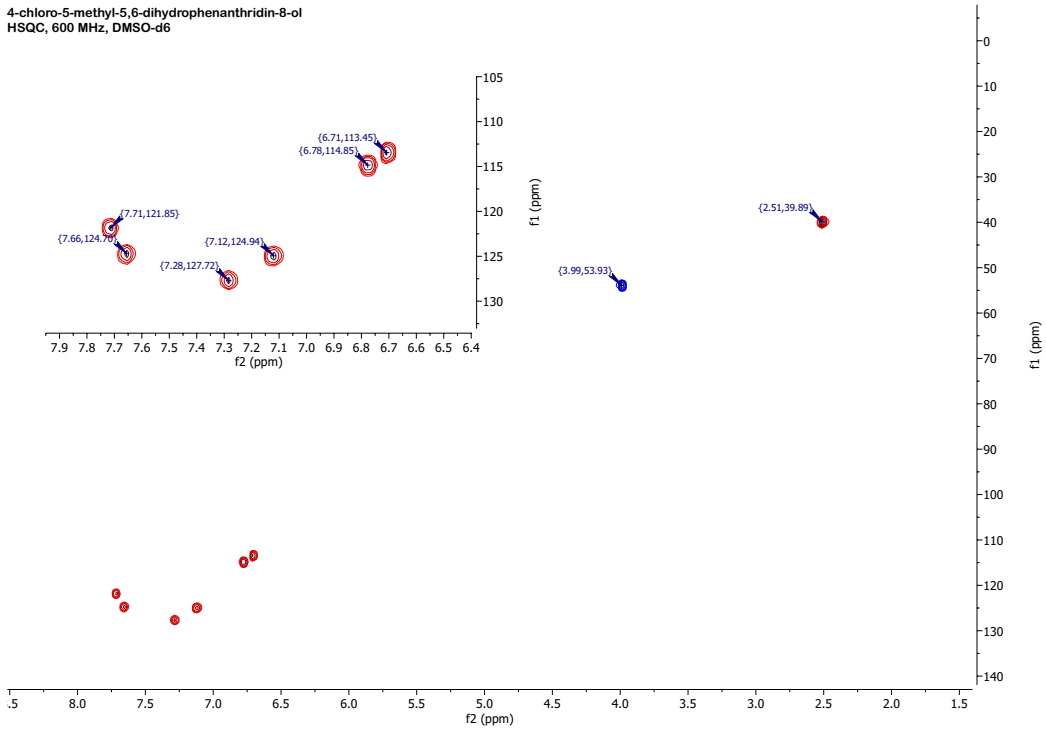
*Spectrum 126: HMBC-NMR spectrum of 2,4-dichloro-7-methylphenanthridin-8-ol (**72d**)*



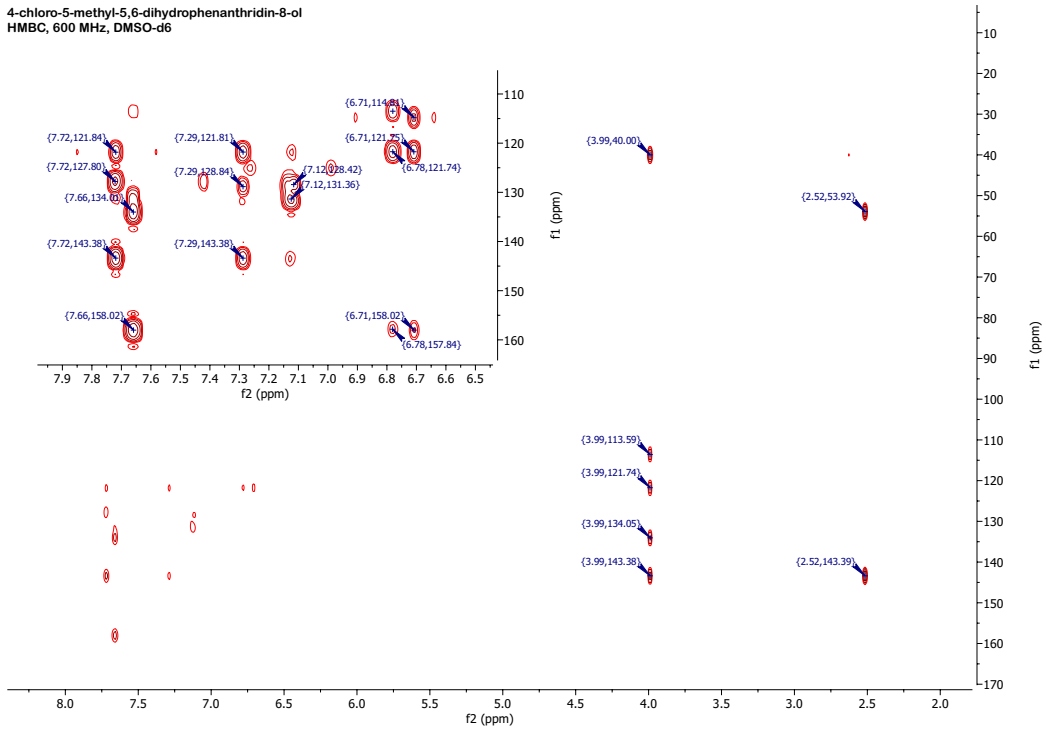
*Spectrum 127: DEPT135-NMR spectrum of 4-chloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71a**)*



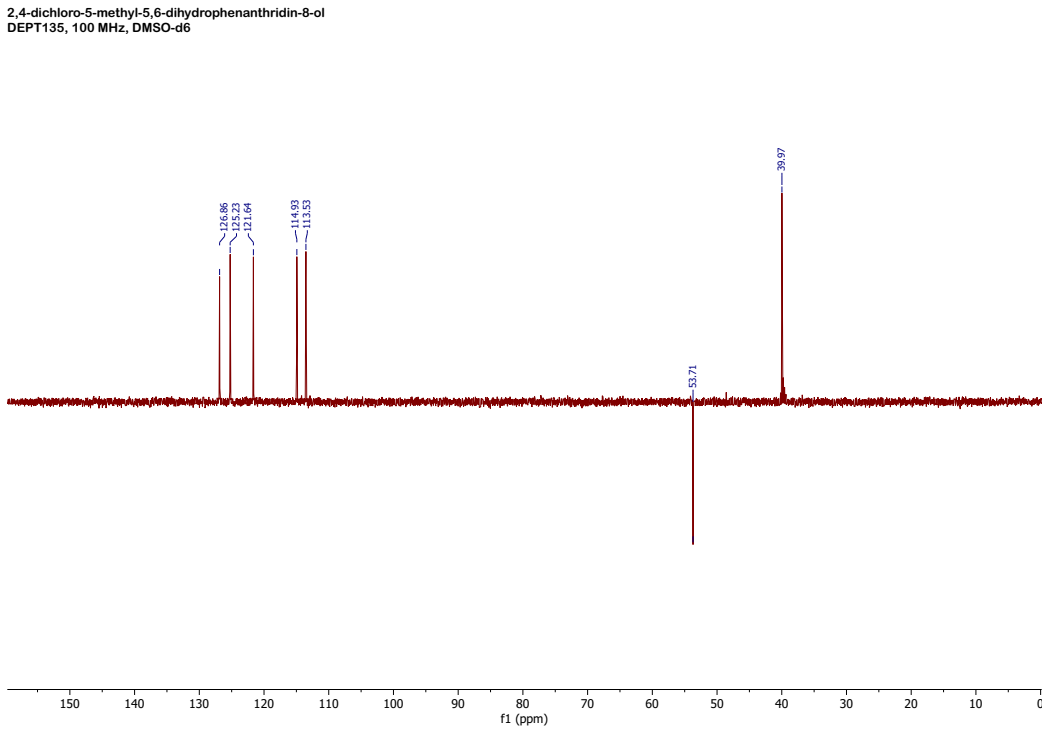
*Spectrum 128: COSY-NMR spectrum of 4-chloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71a**)*



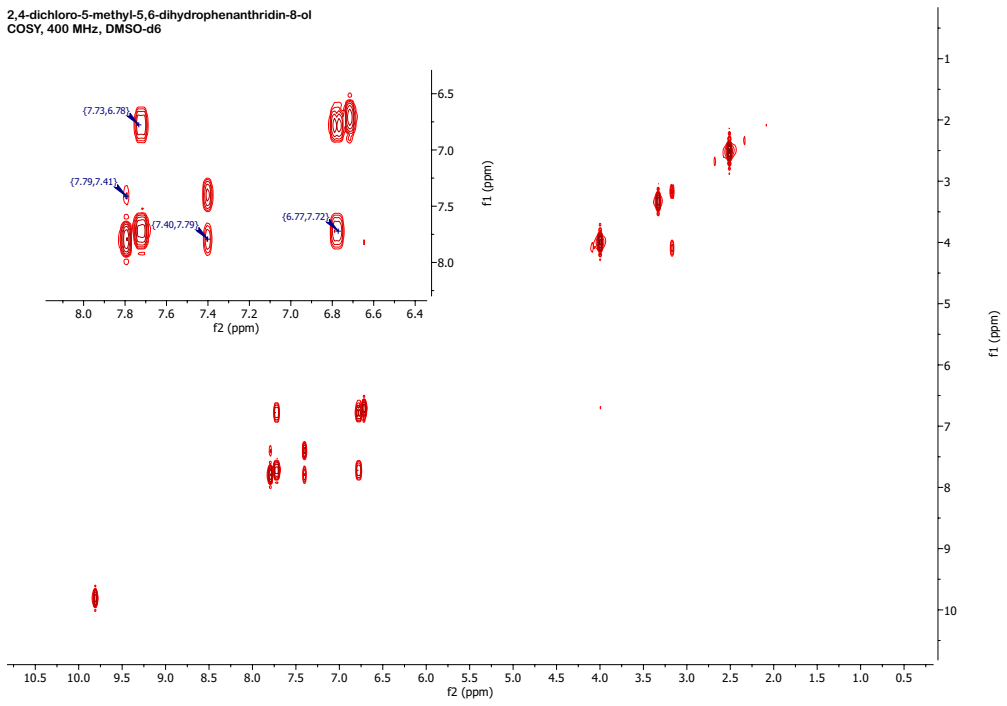
*Spectrum 129: HSQC-NMR spectrum of 4-chloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71a**)*



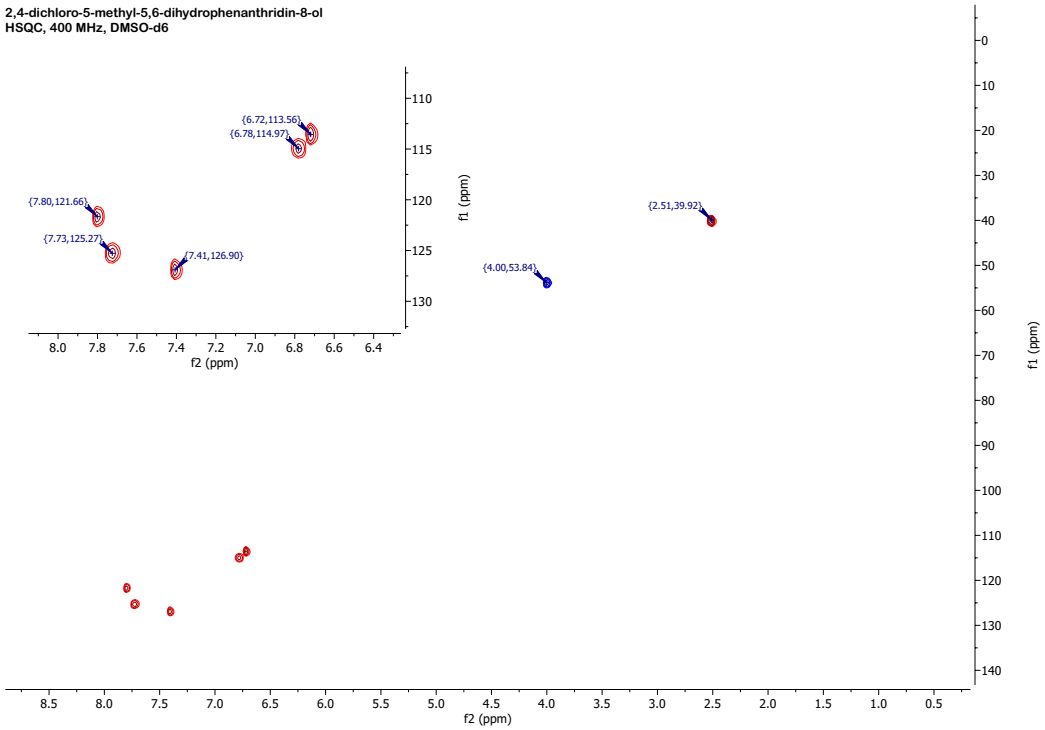
*Spectrum 130: HMBC-NMR spectrum of 4-chloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71a**)*



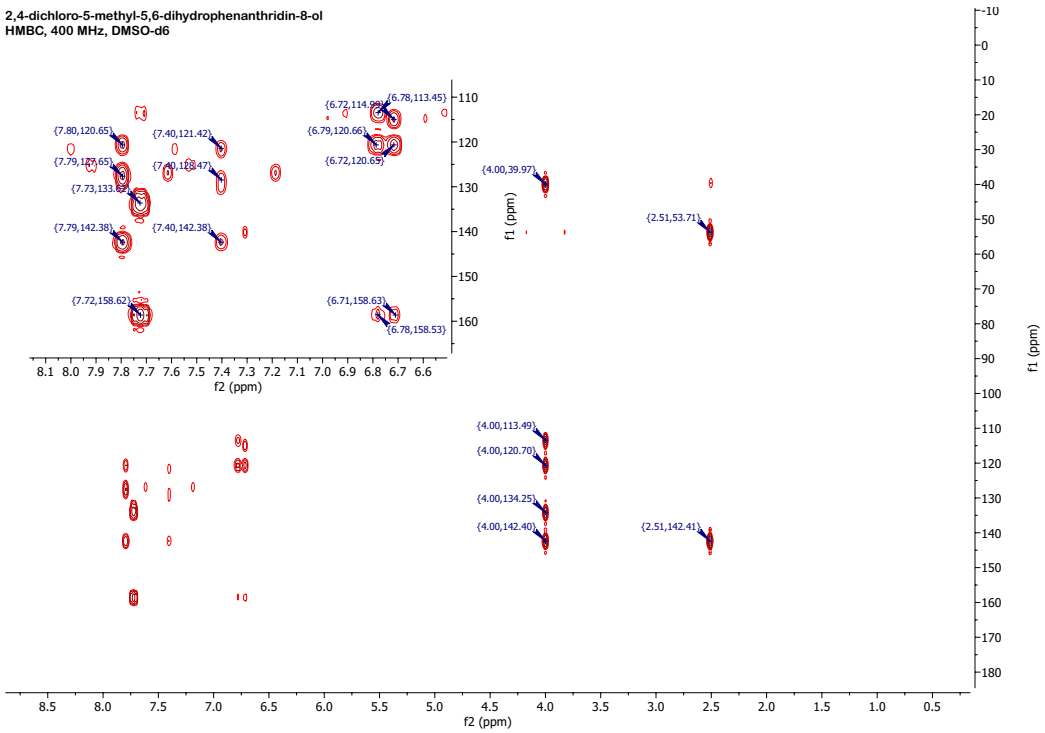
*Spectrum 131: DEPT135-NMR spectrum of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71b**)*



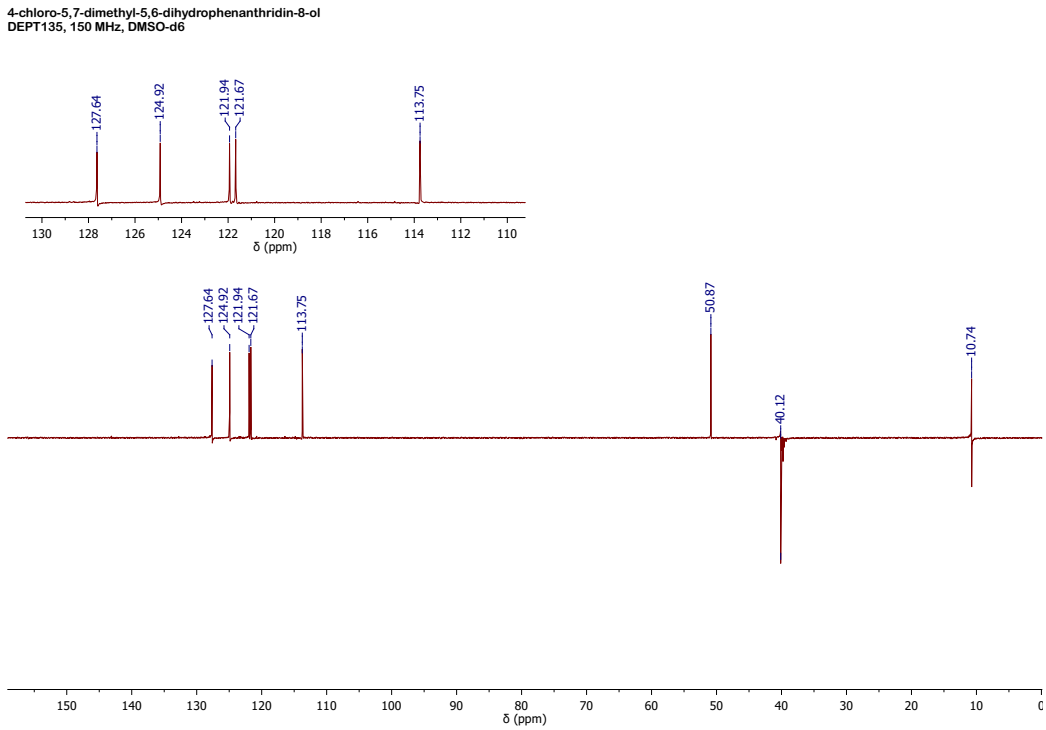
*Spectrum 132: COSY-NMR spectrum of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71b**)*



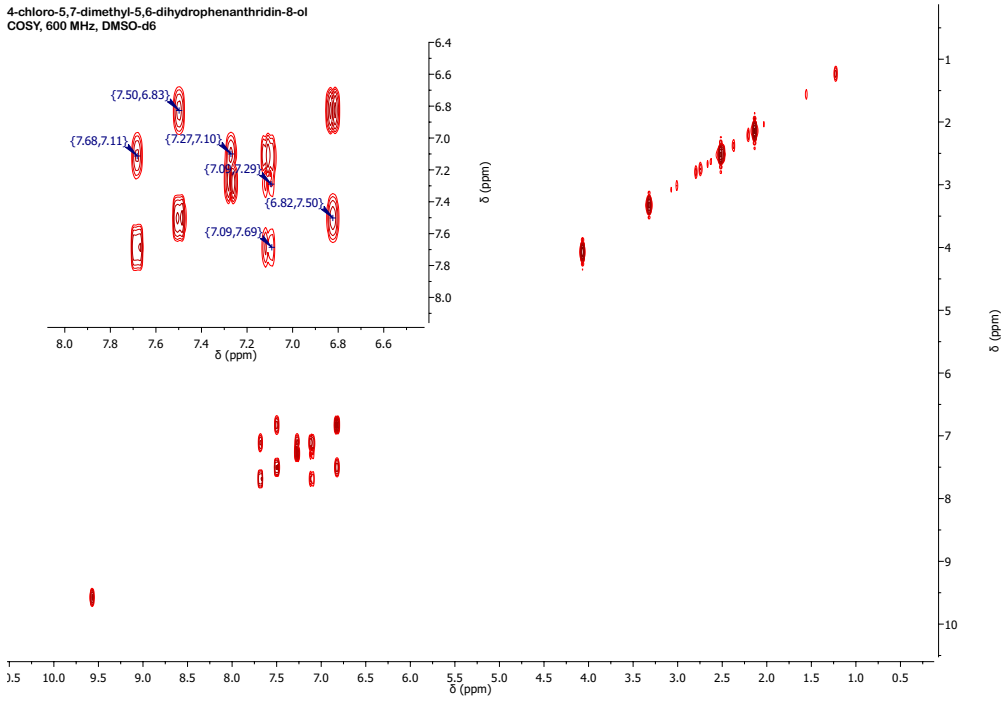
*Spectrum 133: HSQC-NMR spectrum of 2,4-dichloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71b**)*



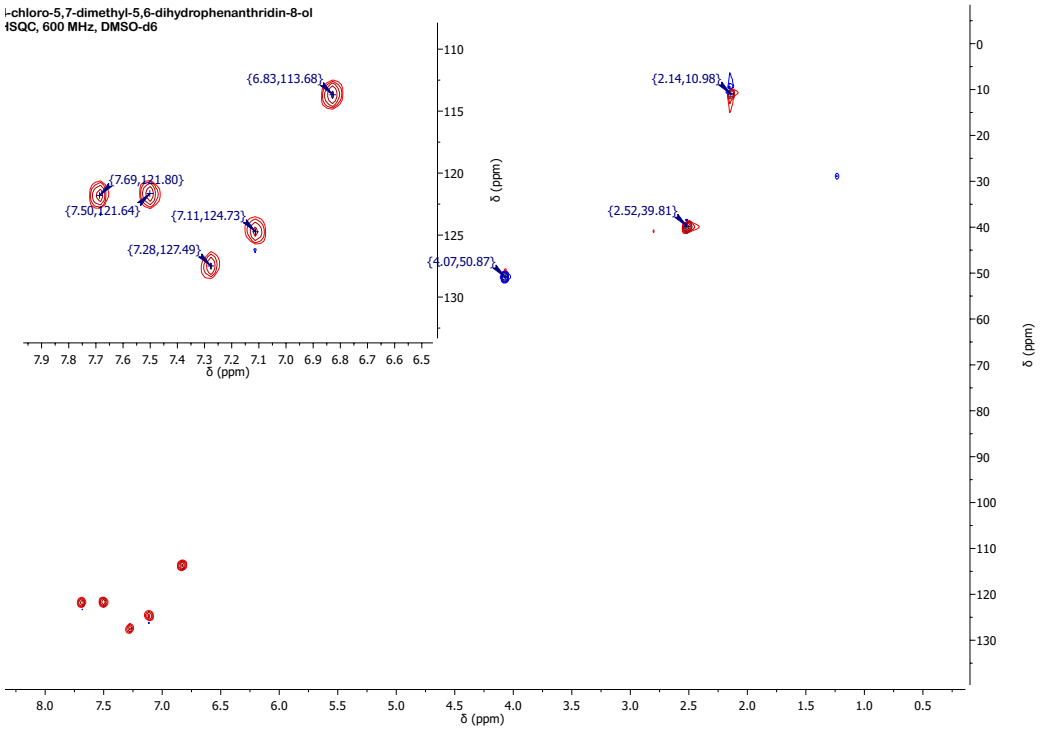
*Spectrum 134: HMBC-NMR spectrum of 2,4-dichloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**71b**)*



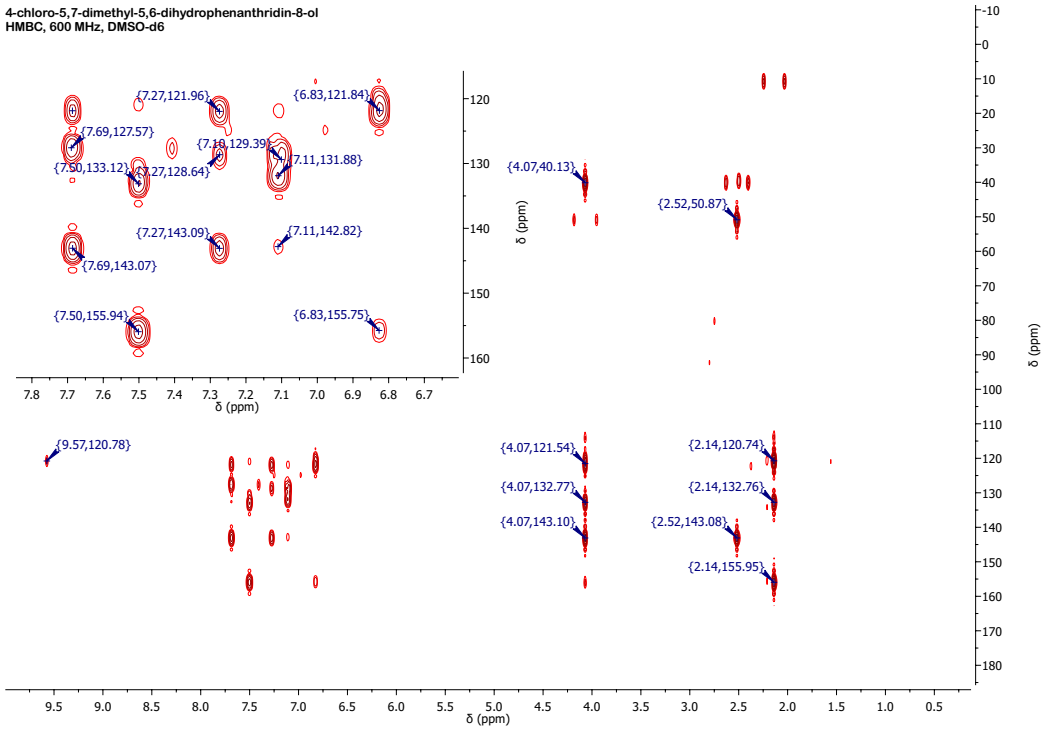
*Spectrum 135: DEPT135-NMR spectrum of 4-chloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71c**)*



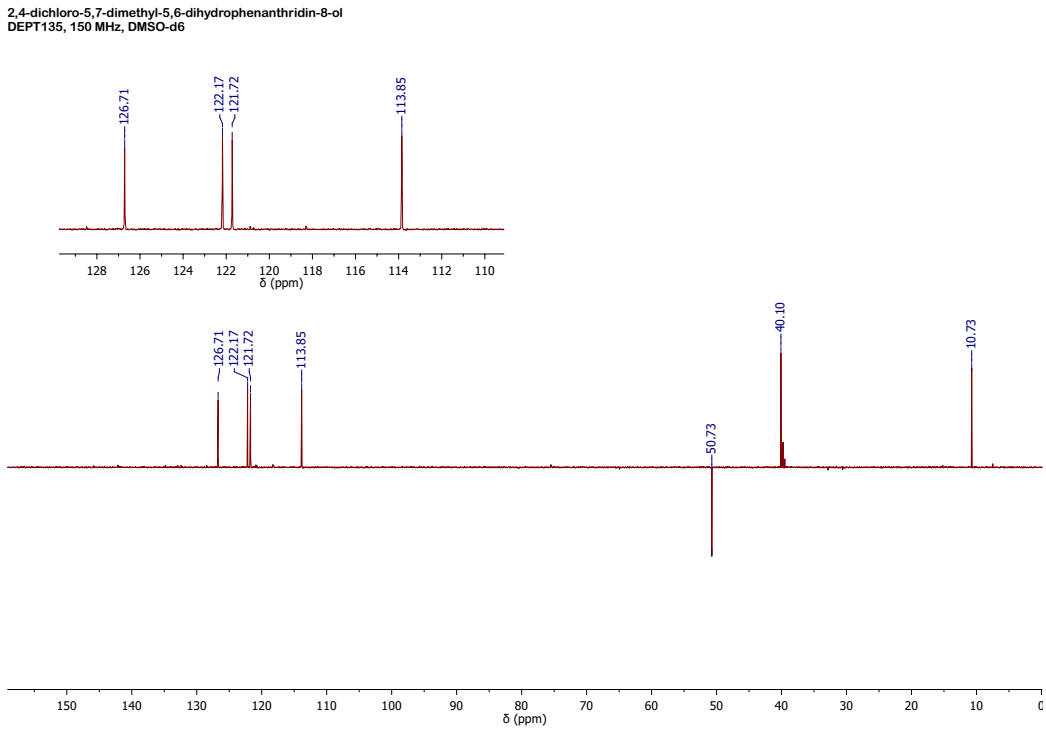
*Spectrum 136: COSY-NMR spectrum of 4-chloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71c**)*



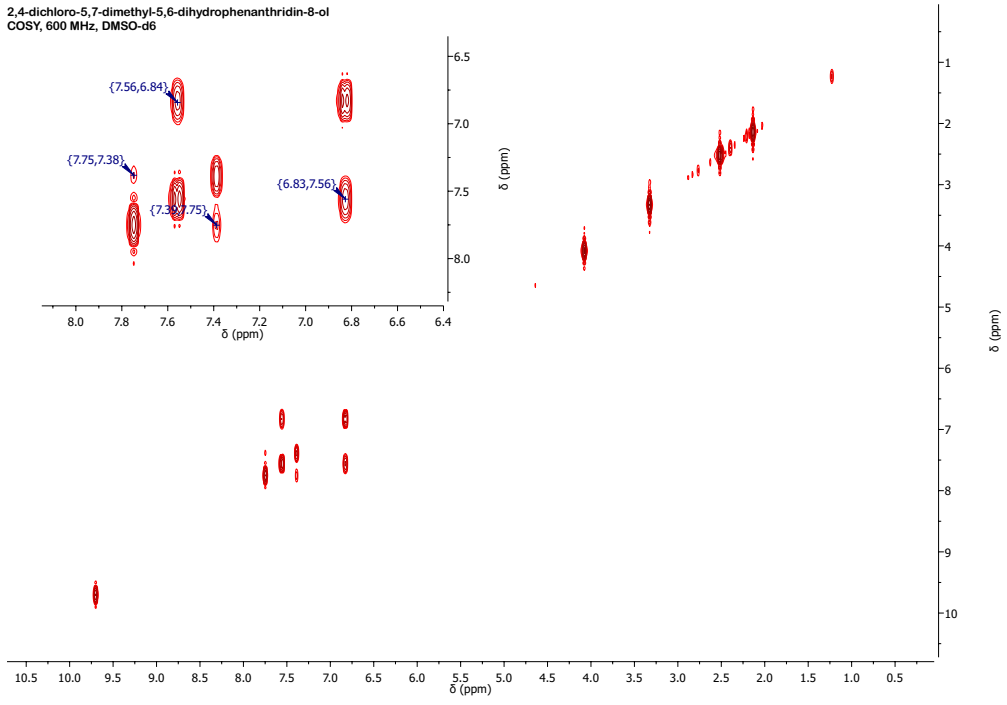
*Spectrum 137: HSQC-NMR spectrum of 4-chloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71c**)*



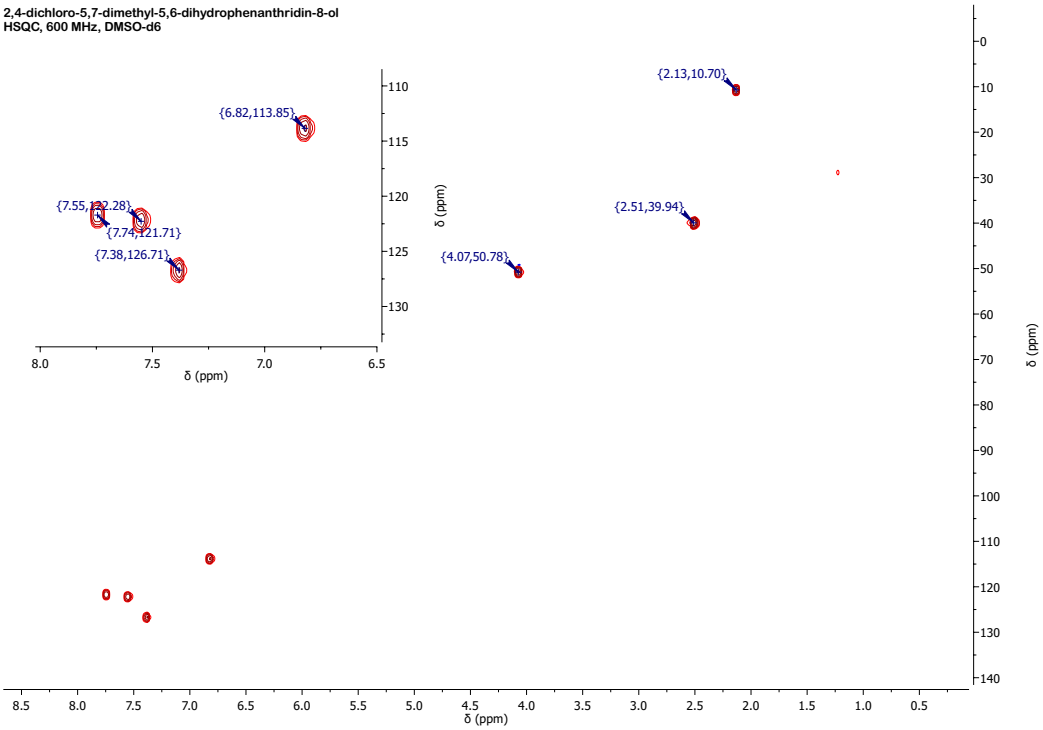
*Spectrum 138: HMBC-NMR spectrum of 4-chloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71c**)*



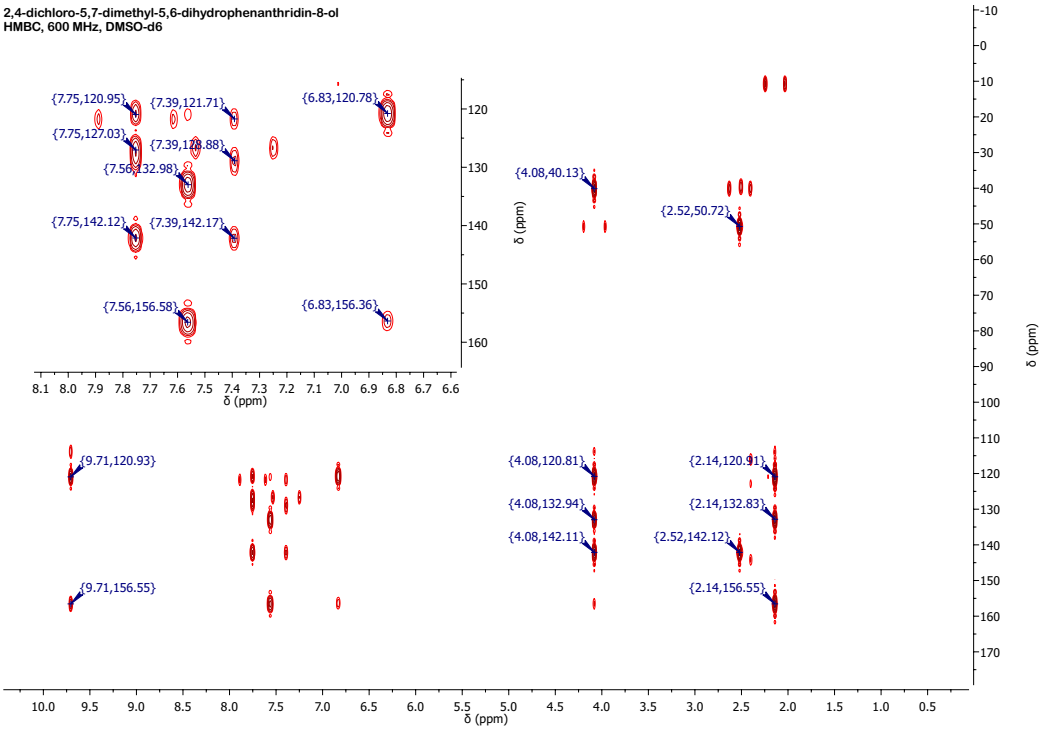
*Spectrum 139: DEPT135-NMR spectrum of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71d**)*



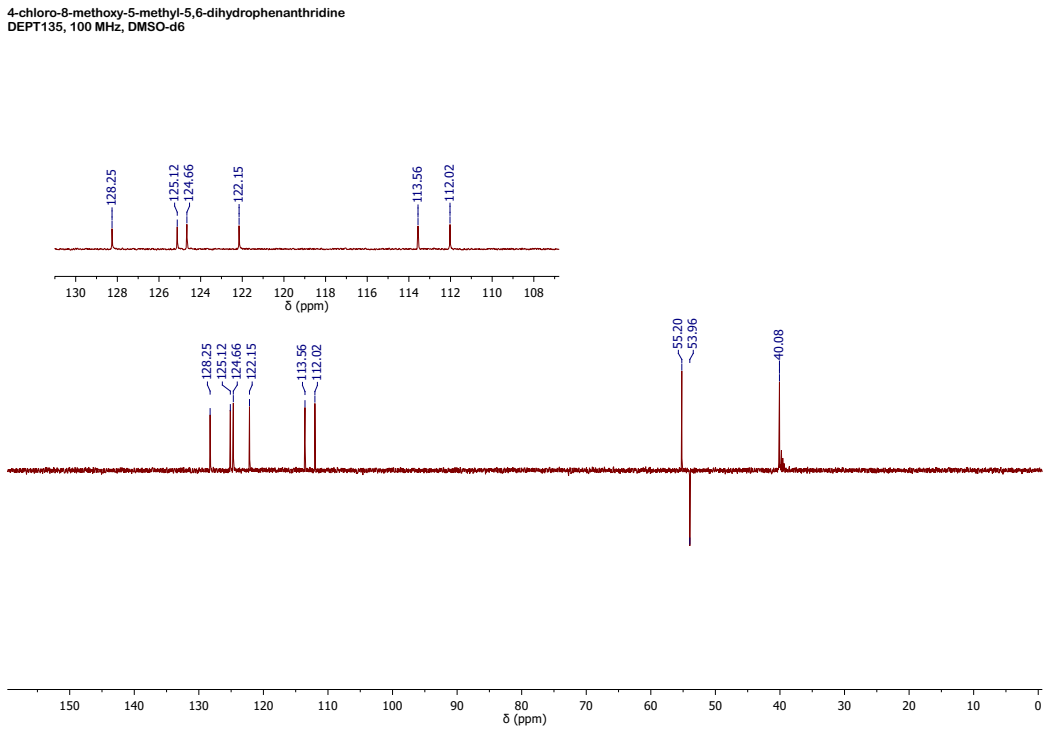
*Spectrum 140: COSY-NMR spectrum of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71d**)*



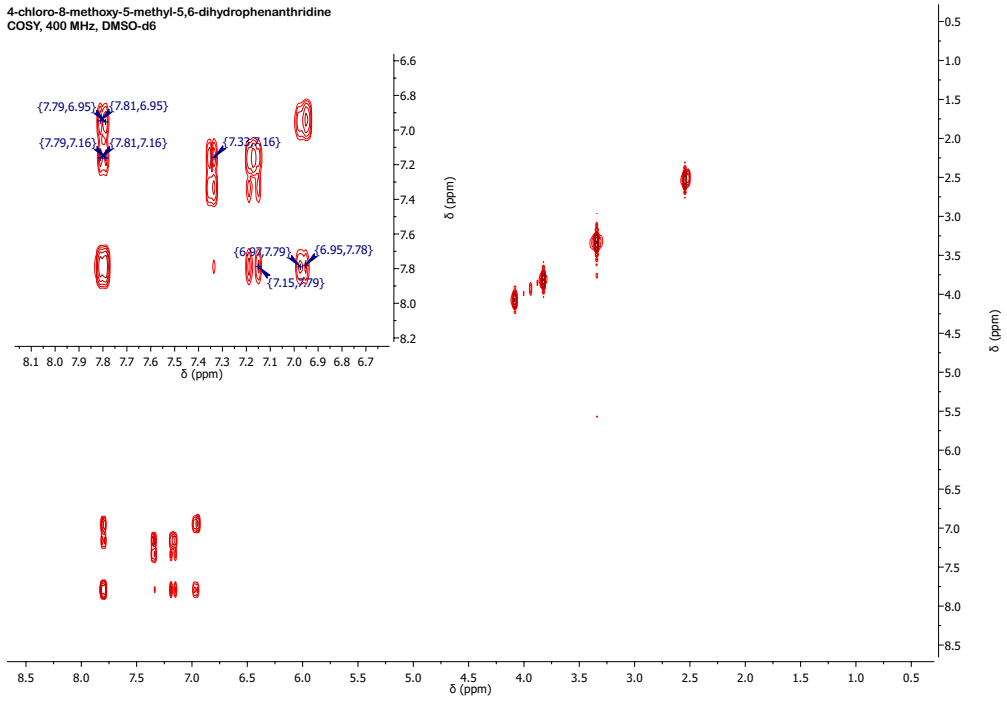
*Spectrum 141: HSQC-NMR spectrum of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71d**)*



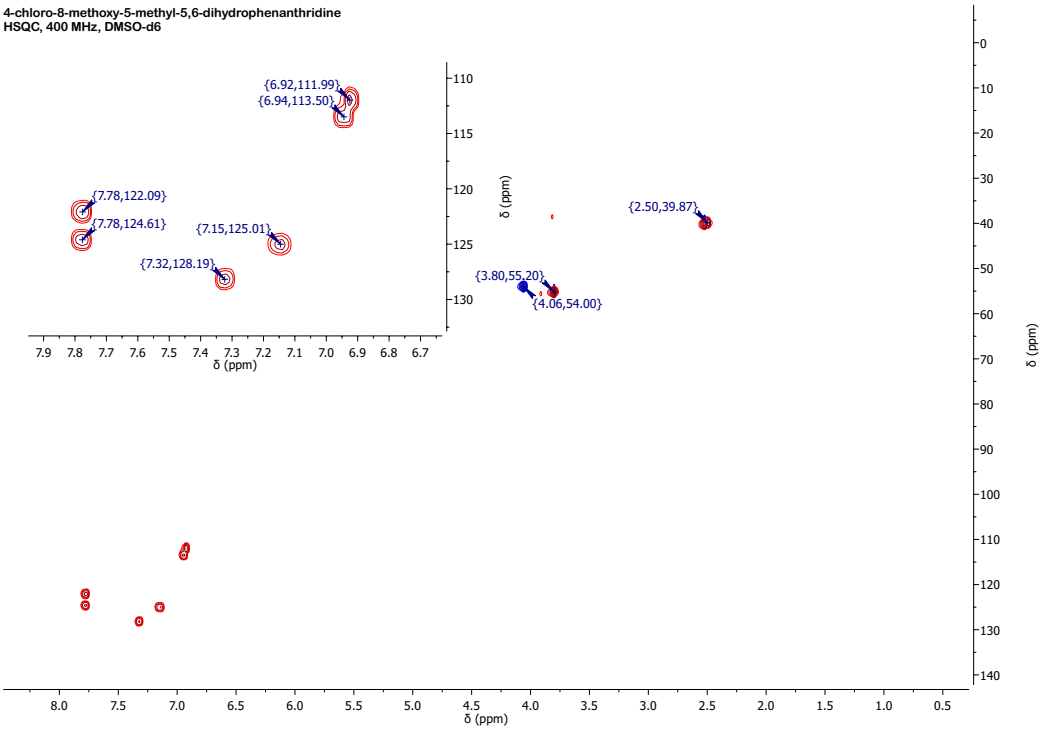
*Spectrum 142: HMBC-NMR spectrum of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridin-8-ol (**71d**)*



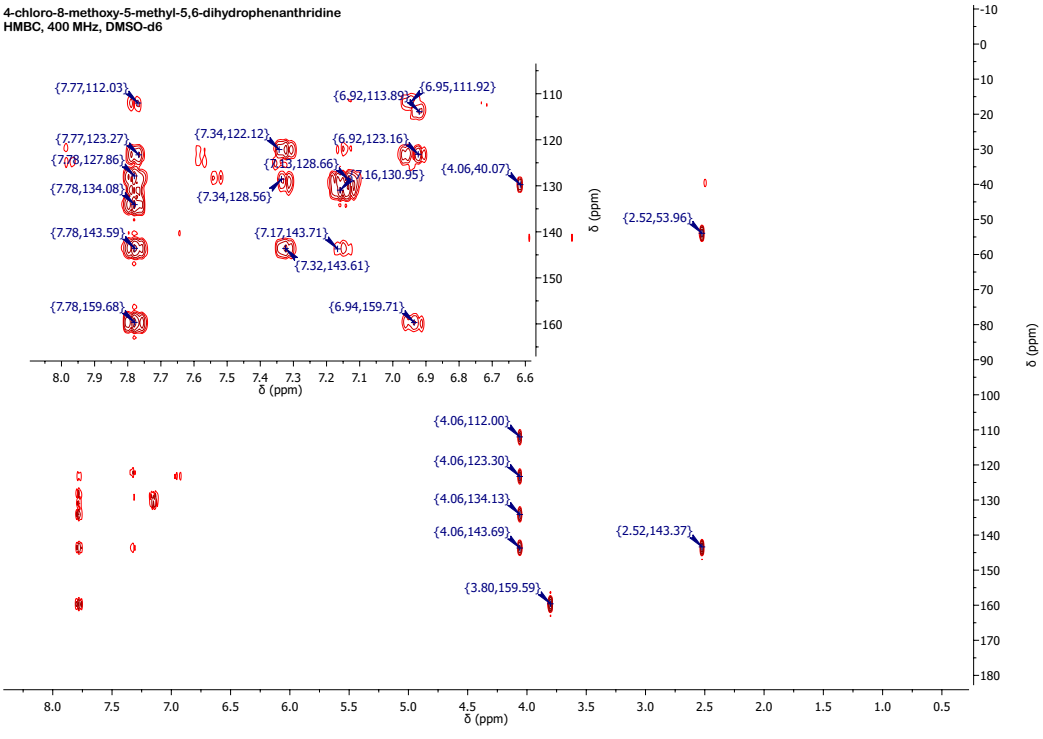
*Spectrum 143: DEPT135-NMR spectrum of 4-chloro-8-methoxy-5-methyl-5,6-dihydrophenanthridine (**81a**)*



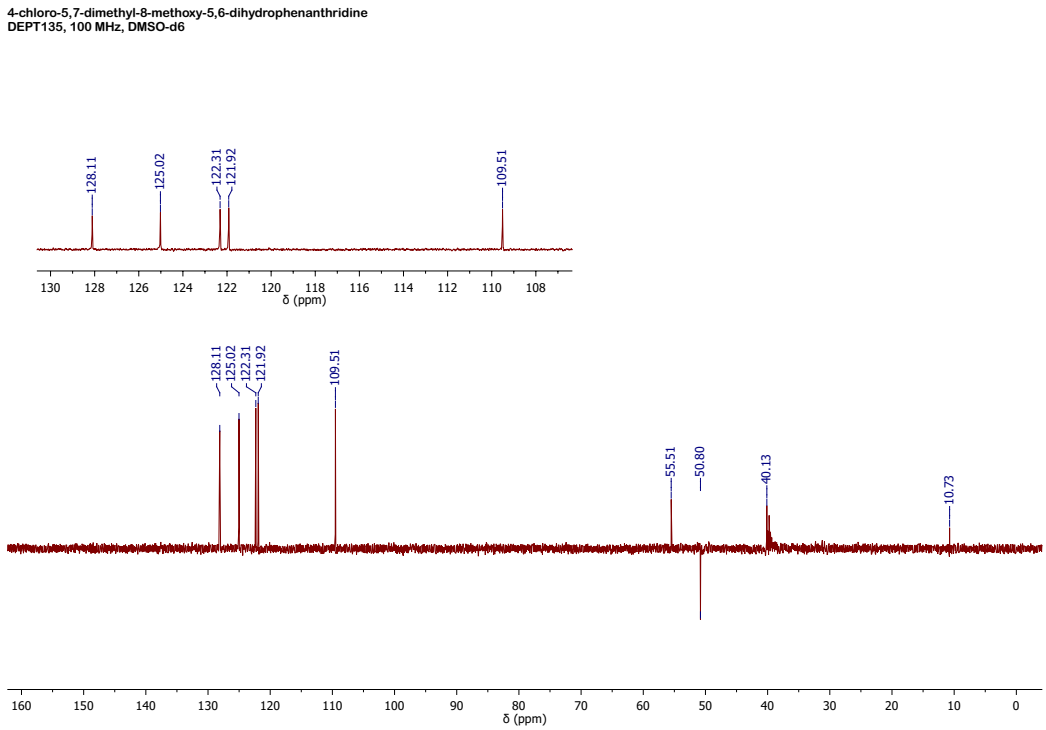
*Spectrum 144: COSY-NMR spectrum of 4-chloro-8-methoxy-5-methyl-5,6-dihydrophenanthridine (**81a**)*



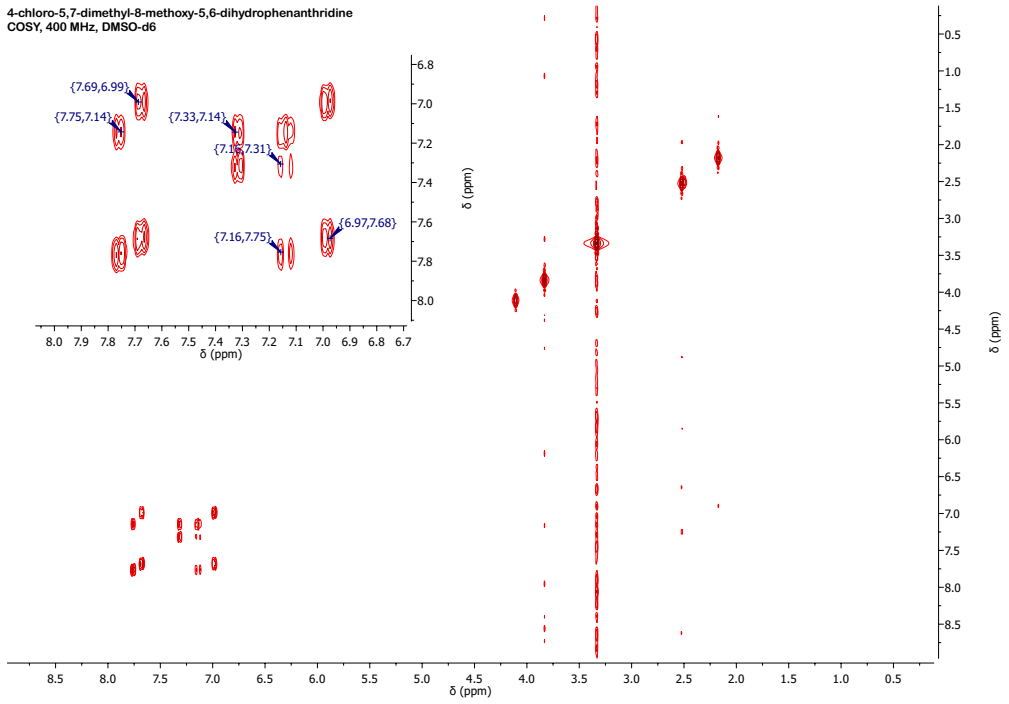
*Spectrum 145: HSQC-NMR spectrum of 4-chloro-8-methoxy-5-methyl-5,6-dihydrophenanthridine (**81a**)*



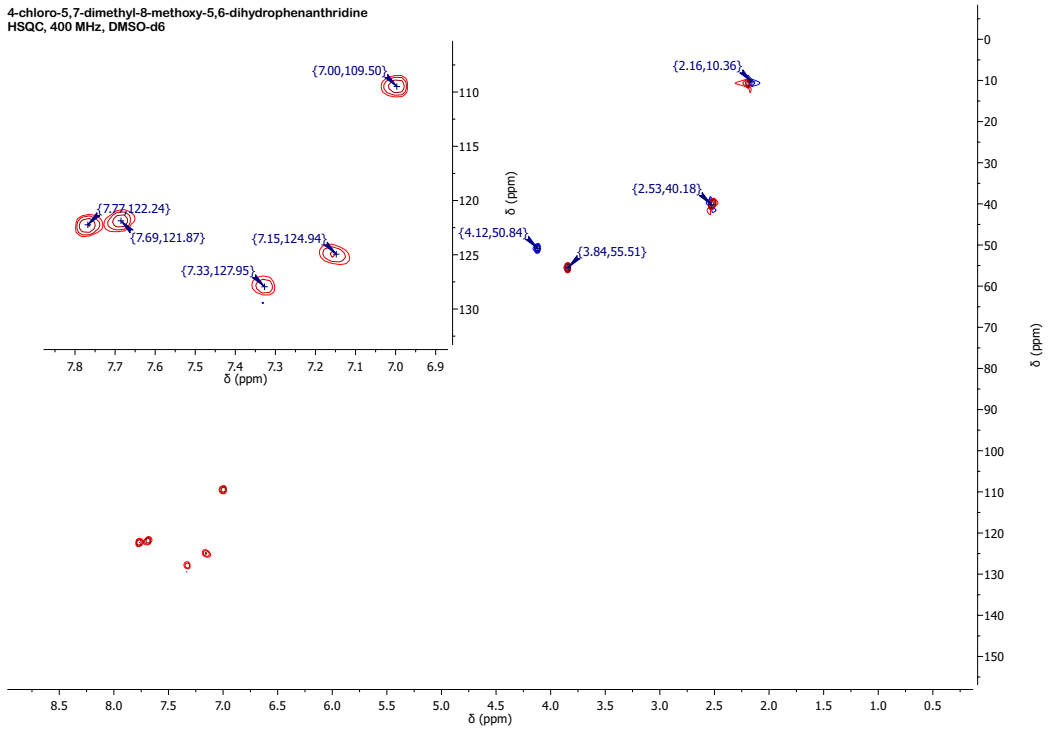
*Spectrum 146: HMBC-NMR spectrum of 4-chloro-8-methoxy-5-methyl-5,6-dihydrophenanthridine (**81a**)*



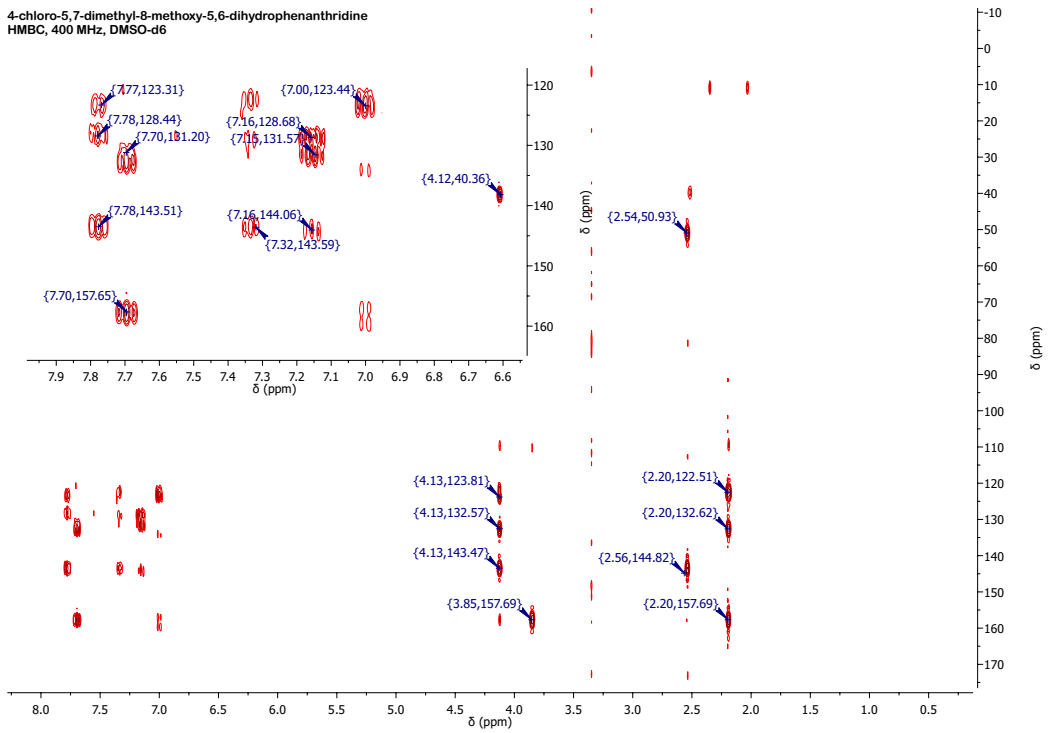
*Spectrum 147: DEPT135-NMR spectrum of 4-chloro-8-methoxy-5,7-dimethyl-5,6-dihydrophenanthridine (**81c**)*



*Spectrum 148: COSY-NMR spectrum of 4-chloro-8-methoxy-5,7-dimethyl-5,6-dihydrophenanthridine (**81c**)*



*Spectrum 149: HSQC-NMR spectrum of 4-chloro-8-methoxy-5,7-dimethyl-5,6-dihydrophenanthridine (**81c**)*



*Spectrum 150: HMBC-NMR spectrum of 4-chloro-8-methoxy-5,7-dimethyl-5,6-dihydrophenanthridine (**81c**)*

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