Synthesis directed towards 8-hydroxyphenanthridines functionalized in the C-ring

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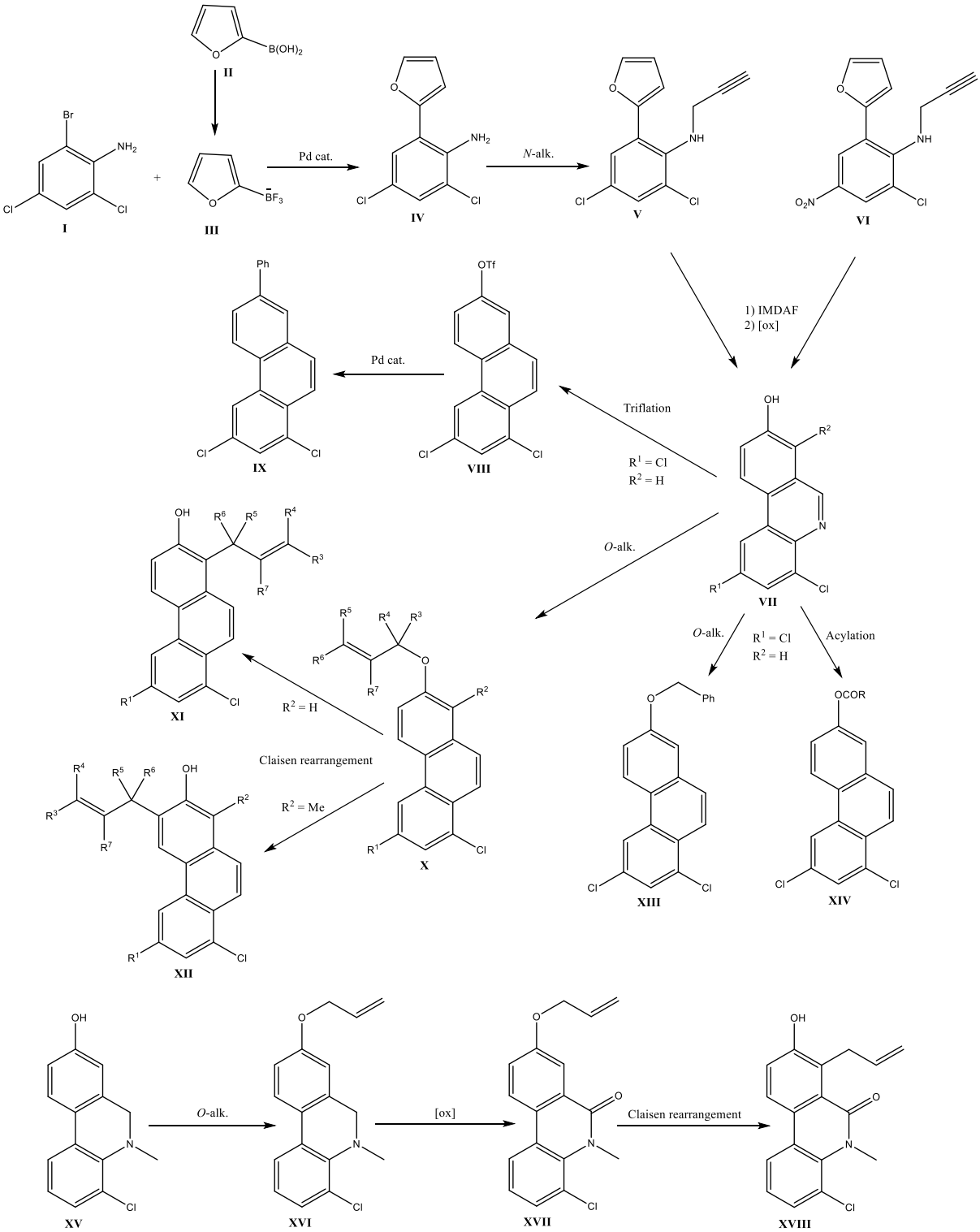
ABSTRACT

Microwave-mediated intramolecular Diels-Alder of furan (IMDAF) reactions were utilized to synthesize two 8-hydroxyphenanthridines (**VII**). Three more 8-hydroxyphenanthridines were given (**VII**, **XV**), synthesized by members of our group. All five were used for further functionalization. By *O*-alkylation, ten phenanthridines (**X**, **XIII**, **XV**) were synthesized, none previously reported in literature. Compound **XVI** oxidized when stored to compound **XVII** which were used for later synthesis. Acylation of **VII** (R^1 = Cl, R^2 = H) produced two new phenanthridinyl esters (**XIV**) while triflation of the same 8-hydroxyphenanthridine formed compound **VIII**. This compound was further used in a Suzuki coupling reaction with phenylboronic acid to produce compound **IX.** The *O*-allylated phenanthridines (**X**, **XVII**) were used in Claisen rearrangements. Five *ortho* substituted 8-hydroxyphenanthridines (**XII**) were produced and isolated, while four had complications. By analyzing the five isolated *ortho* substituted 8-hydroxyphenanthridines (**XII**), it turned out that they were selective towards *ortho* substitution in 7-position to the hydroxy group.



Scheme i: Synthesis of 8-hydroxyphenanthridine derivatives presented in this thesis.

TABLE OF CONTENT

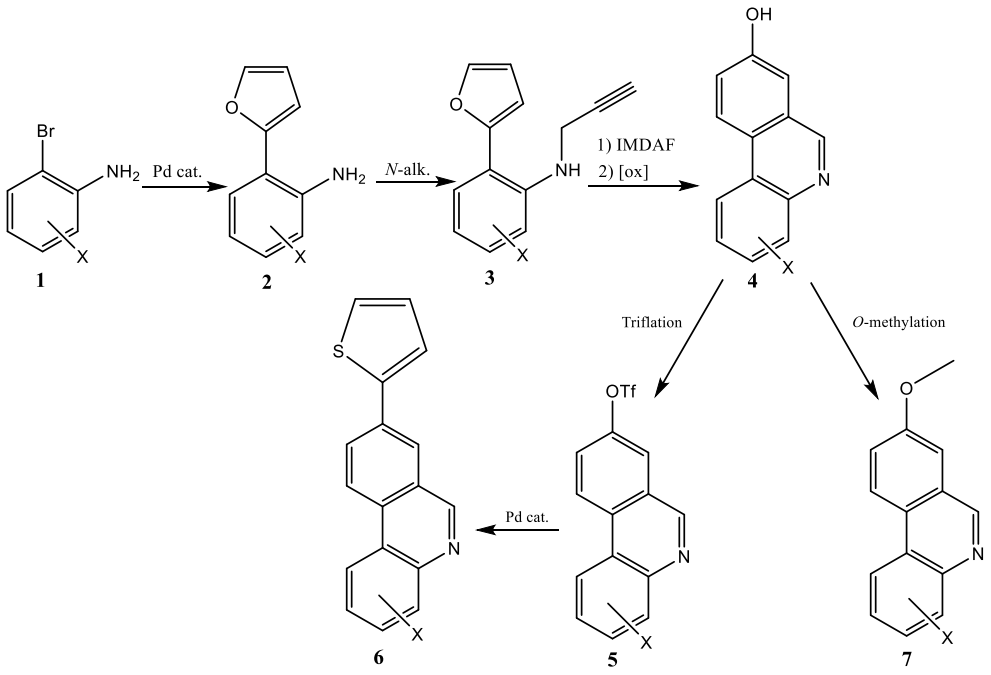
ABBREVIATIONS AND SYMBOLES

Ac	acetyl
C	carbon
^{13}C	carbon spectrum (NMR)
°C	degree Celsius
Calcd.	Calculated
COSY	correlation spectroscopy (NMR)
COVID-19	2019 novel coronavirus
d	doublet (NMR)
δ	chemical shift (NMR)
dd	doublet of doublets (NMR)
DDQ	2,4-dichloro-5,6-dicyano-1,4-bezoquinone
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ESI	electron spray ionization (MS)
Et	ethyl
et al.	et alii
GHz	gigahertz
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GNB	Gram-negative bacteria
GPB	Gram-positive bacteria h hour(s)
^{1}H	proton spectrum (NMR)
HIV	human immunodeficiency virus
HMBC	heteronuclear multiple bond correlation experiment
HRSM	high resolution mass spectra
HSQC	heteronuclear single quantum coherence spectroscopy (NMR)
hν	irradiation
Hz	hertz
IMDAF	intramolecular Diels-Alder reaction of furan

J	coupling constant (NMR)
LA	lewis acid
M	molar
m	multiplet (NMR)
Me	methyl
MHz	megahertz
MIC	minimum inhibitory concentration
Min.	Minutes
mp	melting point
MRSA	methicillin-resistant Staphylococcus aureus
MS	mass spectroscopy
MW	microwave
NMR	nuclear magnetic resonance spectroscopy
o	ortho
OTf	triflate
Ox	oxidation
p	para
QBA	quaternary benzo[c]phenanthridinium alkaloids
R	substituent
r.t.	room temperature
σ	sigma
SAR	structure activity relationship
t	triplet (NMR)
TBAB	tetrabutylammonium bromide
THF	tetrahydrofuran
UV	ultraviolet
WHO	world health organization

1. Introduction

Our group have synthesized various phenanthridines over the last ten years[1-5] with the backbone structure shown in Figure 1.1. The interest in these compounds comes from their promising antimicrobial properties. Since they have a broad spectrum of biologic activity, they have a potential to be used in medicine. 8-Hydroxiphenantridines (**4**) are available in high yields by a novel route developed in our group (Scheme 1). 8-hydroxyphenanthridines (**4**) can be utilized for further functionalization in the phenanthridine 8-position (**5**-**7**) from literature (Scheme 1).[5] This project will dive deeper into this functionalization and further use Claisen rearrangement to produce phenanthridines with *ortho* substitution to the hydroxy group.



Scheme 1.0: Novel rout**e** developed in our group.

Chapter 1 describes the motivation and the importance for synthesizing different phenanthridine derivatives, biological activities for several phenanthridine containing alkaloids and the urgent need for new antibacterial agents. This is followed by a section with earlier synthetic strategies of phenanthridines by other groups. Description of common chemistry, microwave synthesis and the discovery and development of the IMDAF-based strategy ends this chapter. Chapter 2 explains the details, discussion, observation, and results

of each compound synthesized during this project. The last chapters contain future research, a conclusion of what has been achieved, experimental details, appendix and the reference list.

1.1 Phenanthridine alkaloids in nature, their biological activities, and their importance

This section explains phenanthridine alkaloids found in nature, their biological activities and their importance in future medicine.

1.1.1 Naturally occurring phenanthridine alkaloids

Several compound classes contribute to the creation of novel drugs. One particular class is alkaloids which are nitrogen containing secondary plant metabolites often containing heterocyclic structures. Alkaloids with the backbone structure of phenanthridine (figure 1.1.), like quaternary benzo[c]phenanthridium (QBA) (figure 1.1.), have been found in plant extracts used in folk medicine and other traditional medicine.[6,7] Specific plant families that produce phenanthridine alkaloids are *Amaryllidaceae, Fumariacea, Papaveraceae* and *Rutaceae*.[8,9] The QBA has been used as an antimicrobial, antifungal and anti-flammatory agent and is therefore an important factor in phenanthridine medicine.[6,7]

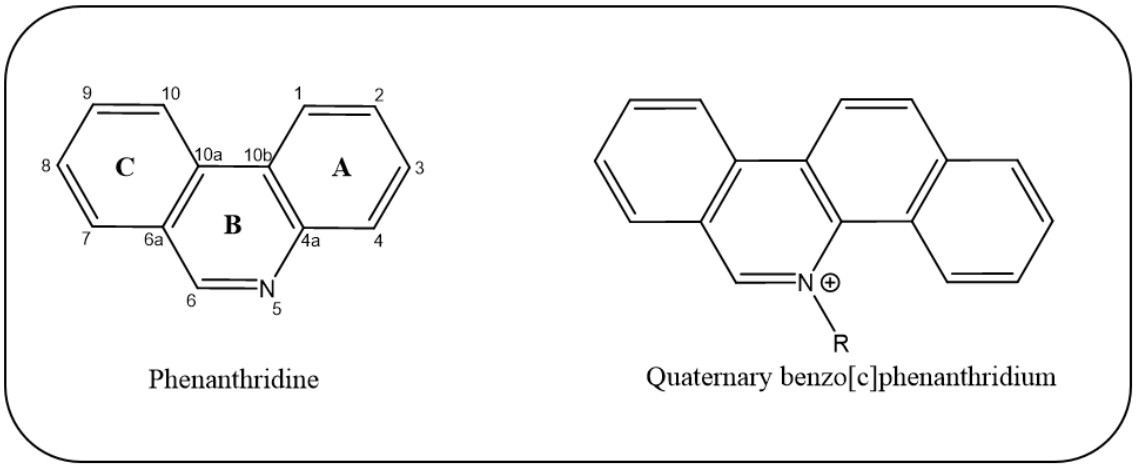


Figure 1.1. Numbering of the phenanthridine backbone ring-system and quaternary benzo[c]phenanthridium.

The biological activity of a compound is essential to determine its benefit in medicine. The phenanthridine alkaloids displayed in figure 1.2 have been studied for their biological activity towards malaria,[10] mycobacteria,[11] bacteria,[12] acetylcholinesterase inhibition,[13] an array of cancer cell lines,[14] and anti-inflammatory activity.[15]

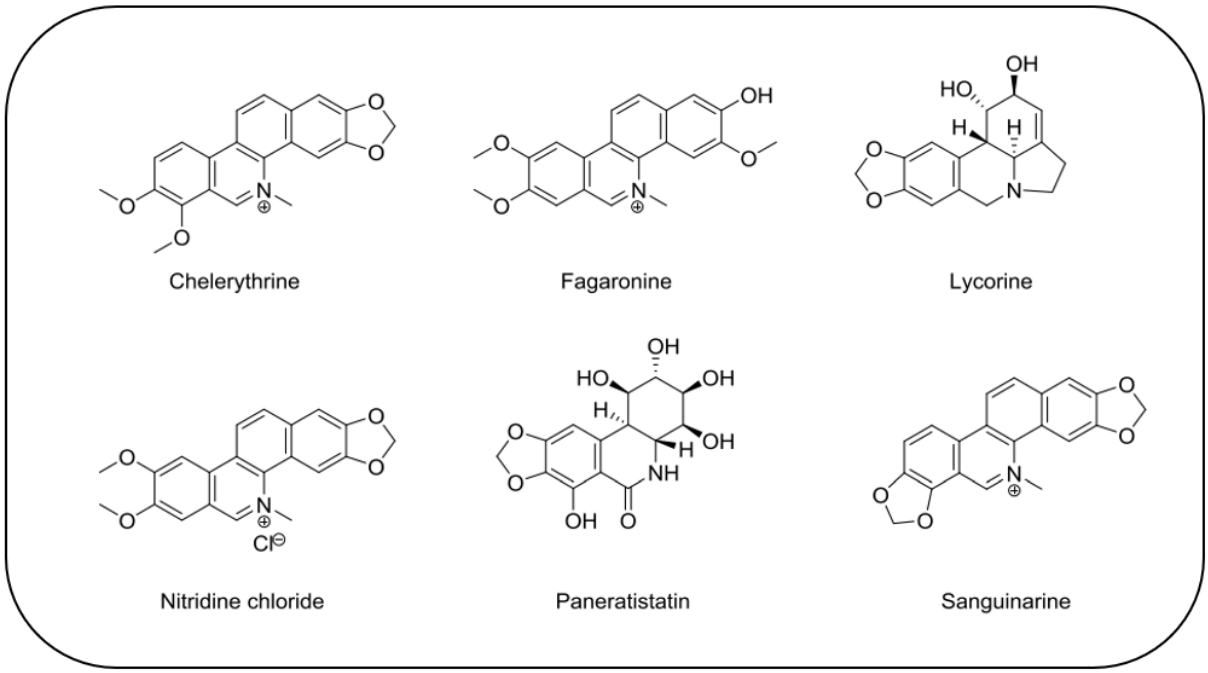


Figure 1.2: Different phenanthridine alkaloids studied for their biological activities.[10-15]

1.1.2 Phenanthridine containing compounds currently used in medicine

Phenanthridine compounds have been marketed as drugs for various diseases. Chelerythrine (CHE) and Sanguinarine (SA) are used as antimicrobial, anti-inflammatory, adrenolytic and sympatholytic and are therefore used in dentil care applications like toothpaste and mouthwash, since they exhibit ani-plaque properties.[8,16] In Africa, trypanosomiasis in livestock has been a huge challenge. The sickness is a nervous system infection, also referred to as "sleeping sickness", and will be fatal if not treated. It is transferred through the bites of tsetse flies, but the causes have decreased due to new treatment. Dimidium bromide, ethidium bromide and isometamidium chloride (figure 1.3), types of phenanthridines, have been used to assess this disease.[17,18] Besides their wide range in biological activity, another interest in the QBAs are their fluorescent properties. Ethidium bromide, propidium bromide and macarpine are utilized as DNA-binding fluorescent tags in biochemistry labs to provide information on DNA content.[6]

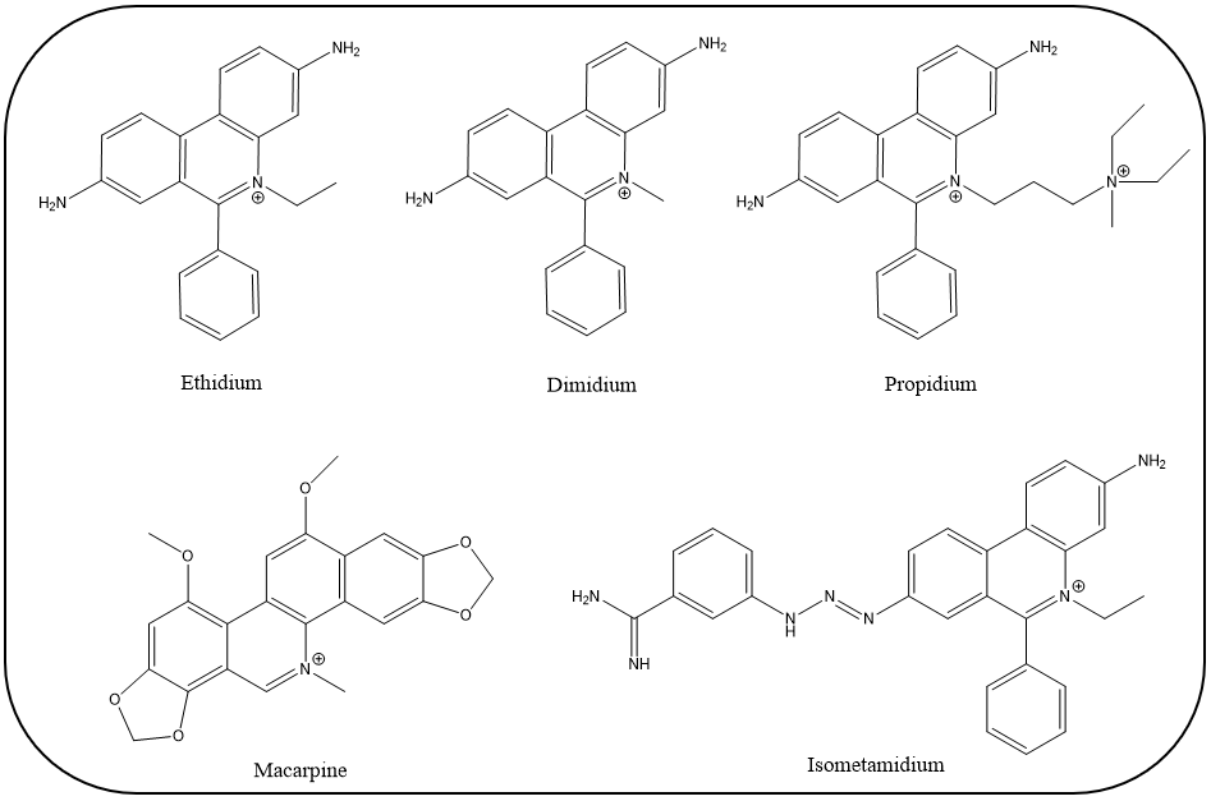


Figure 1.3: Several phenanthridine alkaloids that have been studied and employed.

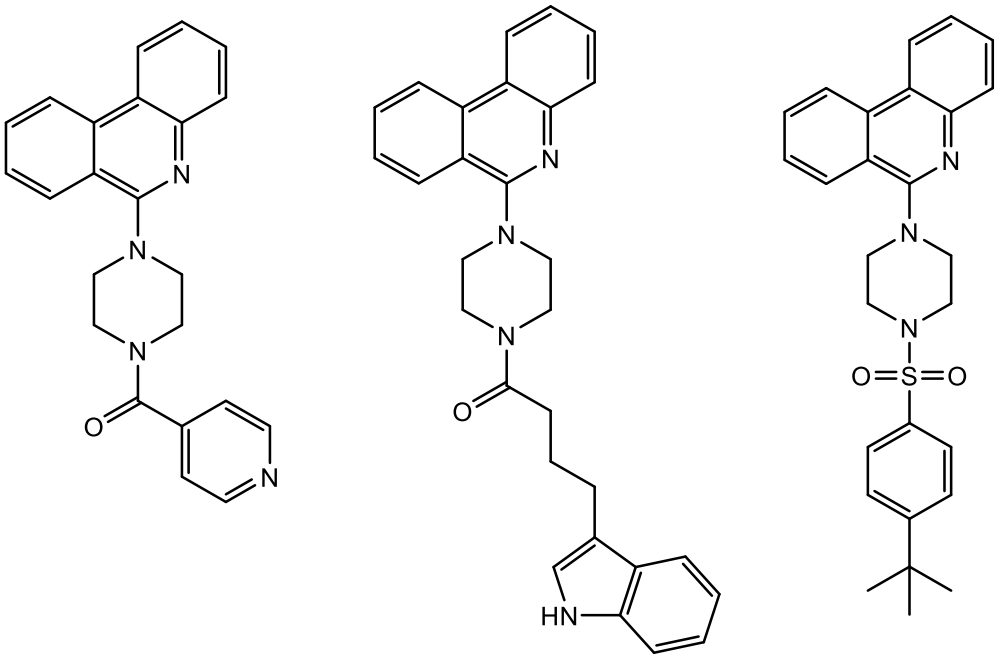
1.1.3 Problem of drug resistance and phenanthridine-based drugs in the future

In 2020, a global crisis affected the world. The COVID-19 pandemic has shown that the detection and management of new public health threats are important. Not only are new diseases a concern, but also the increase in antimicrobial resistance (AMR), which might lead toa post-antibiotic era where common illness can be mortal. The World Health Organization (WHO) launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015, to collect AMR data of selected bacterial pathogens that have the potential to infect humans. A total of 91 countries and territories have been registered throughout the previous four years, and data from over two million patients have been reported. The data collected show high rates of resistance among antimicrobials aimed to treat common bacterial infections. Bacterial infections, tuberculosis, HIV and malaria are examples of pathogens that are observed with GLASS.[19]

Bacteria can be classified in two separate categories according to their type of cell wall, Gram-positive bacteria (GPB), and Gram-negative bacteria (GNB). When treating the bacteria with iodine solution, GPB becomes purple while GNB does not. The change of color is an important tool to identify the bacteria and the treatment plan.[20] The number of both GPB and GNB that are resistant to multiple antibiotics has increased over time. The international spread of Methicillin-resistant *Staphylococcus aureus* (MRSA), a GPB, is a major concern. Researchers in the UK reduced antibiotic usage and found evidence of reduced resistance in multiple resistant GNB, but for the MRSA however, the effect was small.[21] *Escherichia coli* and *Klebsiella pneumoniae* are additionally two GNBs, whose resistance to antibiotics is currently increasing.[22,23]

The applicability of a drug is dependent on the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). MIC is the lowest concentration of an antimicrobial to inhibit the visible growth of a bacteria after overnight incubation, while MBC is the lowest concentration of antimicrobial to prevent the growth of an organism after subculture on to antibiotic-free media.[24,25] For several years, semisynthetic pencilines or vancomycin has been used for treatment. An increase has been documented in the MIC for vancomycin, and the reports suggest treatment failure and mortality by elevations in vancomycin MIC.[26] Hence, Regular surveillance of MICs of known and new antimicrobials are therefore important to find the best treatment for ill patients.

As mentioned in section 1.1.1 and 1.1.2, phenanthridines have been used as medicine for a long time. For treatment of thrombosis, chelerytrine chloride (Figure 1.2) can possibly be used,[27] and for malaria treatment, nitidine chloride (Figure 1.2) can be a lead molecule for anti-malaria drug development.[28] Different phenanthridines are synthesized around the world and screened for their biological activities. Thirty-three phenanthridines were synthesized by Naidu *et al.*[29] and screened for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* (MTB) H37Rv strain. They had MIC between 1.56 and ≥50 µg/mL, where three (**8-10**) were excellent promising candidates (Figure 1.4). At 1.56 µg/mL concentration, they inhibited 99% growth of the MTB H37Rv strain.[29]



8 **9** **10**

Figure 1.4: Phenanthridines synthesized by Naidu et al. showing antimycobacterial activity against Mycobacterium tuberculosis H37Rv strain.[29]

AMR is a major issue for today's society and the need for new drugs are rising/growing Phenanthridines have the potential to be used as new drugs, but it is still a long way to the finish line. Effectivity enhancement and properties related to absorption, distribution, metabolism, excretion and toxicity, often abbreviated "ADME-Tox", needs to be investigated further. By synthesizing phenanthridines with different functional groups, the knowledge of the structure-activity relationship (SAR) will expand, while the road to a new drug will shorten.[30]

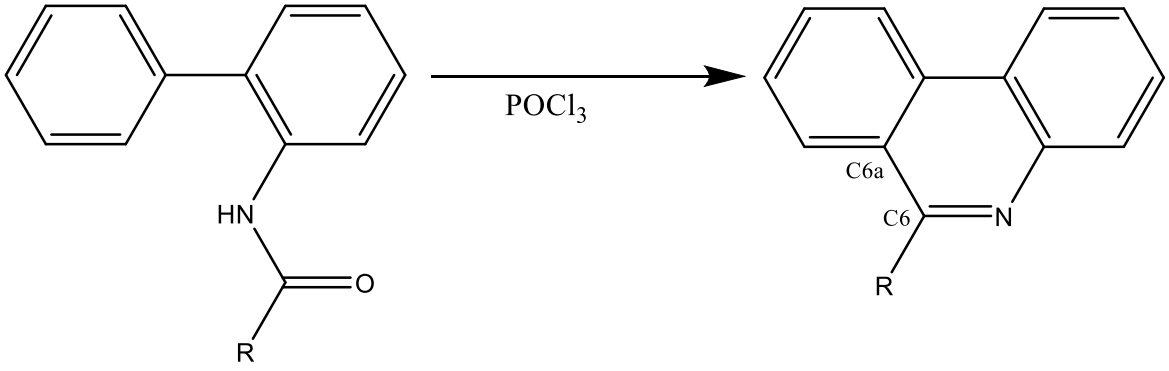
1.2 Phenanthridine synthesis in other groups

Methods of synthesizing phenanthridine have been developed throughout the 20th century and been improved and expanded. This section describes selected strategies of synthesizing phenanthridines and addresses four categories of phenanthridine synthesis. Biphenyl ring-closure reactions, C10a-C10b bond-forming reactions, palladium-catalyzed cascade reactions and ring transformation reactions.

1.2.1 Biphenyl ring-closure reactions

C6-C6a bond formation

In 1931 Morgan and Walls published a synthesis of phenanthridines.[31] It builds on the work by Pictet and Hubert where they dehydrated acetyl-*o*-xenylamines by fusion with zinc chloride.[32] This reaction had disadvantages and was improved by Morgan and Walls by changing zinc chloride with phosphorus oxychloride ($POCl_3$). C6-C6a bond forms in dehydrative ring closure of **11** to synthesize phenanthridines (**12**) (Scheme 1.1).[31]



11 **12**

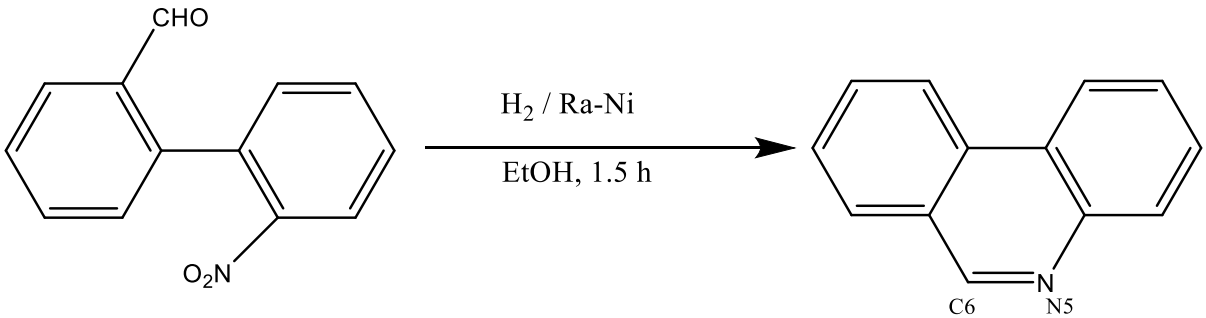
R = Et, Ph, CH_2Cl, *o*-nitrophenyl, *m*-nitrophenyl or *p*-nitrophenyl

61-80%

Scheme 1.1: Morgan-Walls reaction to yield phenanthridines (**12**).[31]

N5-C6 bond formation

Synthesis of phenanthridine (**15**) by reductive cyclization was published in 2007 by Some *et al.*[33] 2-(2-nitrophenyl)benzaldehyde (**14**) in ethanol was treated with a suspension of Ra-Ni followed by gentle bubbling through the mixture with dihydrogen to form the N5-C6 bond (Scheme 1.2). After 1.5 h and filtration, 92% phenanthridin (**15**) was isolated.[33]

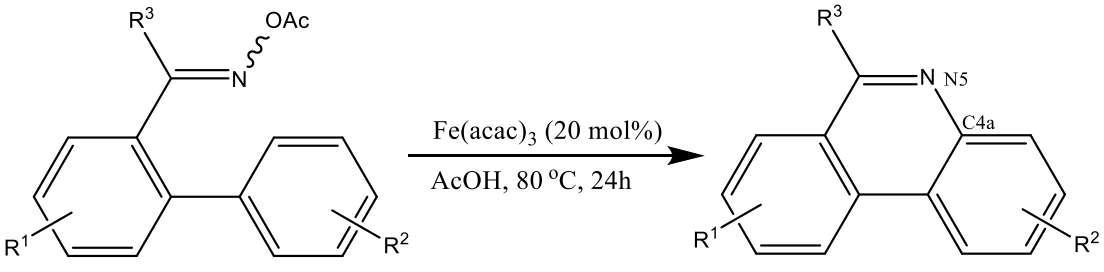


14 **15**

Scheme 1.2: Phenanthridine synthesis of reductive cyclization of 2-(2-nitrophenyl)benzaldehyde (**14**).[33]

C4a-N5 bond formation

Published in 2013 by Yoshikai and Deb,[34] phenanthridines were synthesized from *o*-acetyloximes derived from 2'-arylacetophenones, by using iron(III) acetonate in acetic acid as catalytic agent at 80 °C. *O*-Acetyloximes (**16**) underwent N-O bond cleavage and N-arylation followed by directed C-H arylation or cross-coupling (Scheme 1.3) forming a C4a-N5 bond. After 24 h it resulted in 51-93% isolated substituted phenanthridines (**17**).[34]



16 **17**

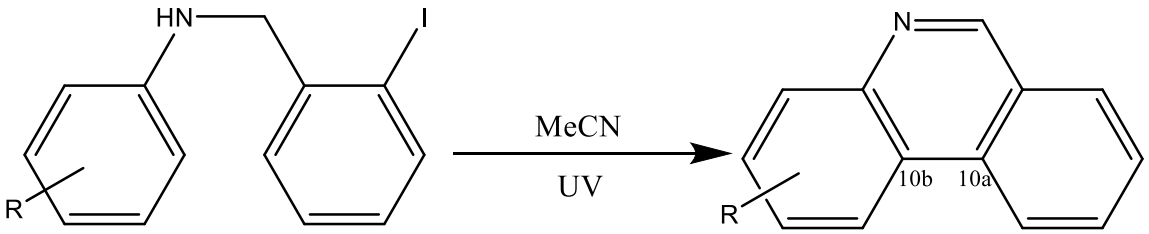
51-93%

R^1 = H, OMe or Me
R^2 = H, Cl, F, CF_3, CN, Me or OMe
R^3 = Me, Et or Ph

Scheme 1.3: Cyclization of *o*-acetyloximes (**12**) to substituted phenanthridines (**13**).[34]

1.2.2 C10a-C10b bond-forming reaction

Photochemical cyclization can be used to form the C10a-C10b bond in phenanthridines. It is a radical reaction published by Linsenmeier *et al*. in 2011.[35] Radical cleavage of the carbon-iodine bond of *N*-(2-iodobenzyl)anilines (**18**) occurs by UV-irradiation which leads to cyclization and removal of a hydrogen atom and formation of phenanthridines (**19**) (Scheme 1.4).[35]



18

R = H, Cl, NO_2, Br, F, OH, OMe or COOMe

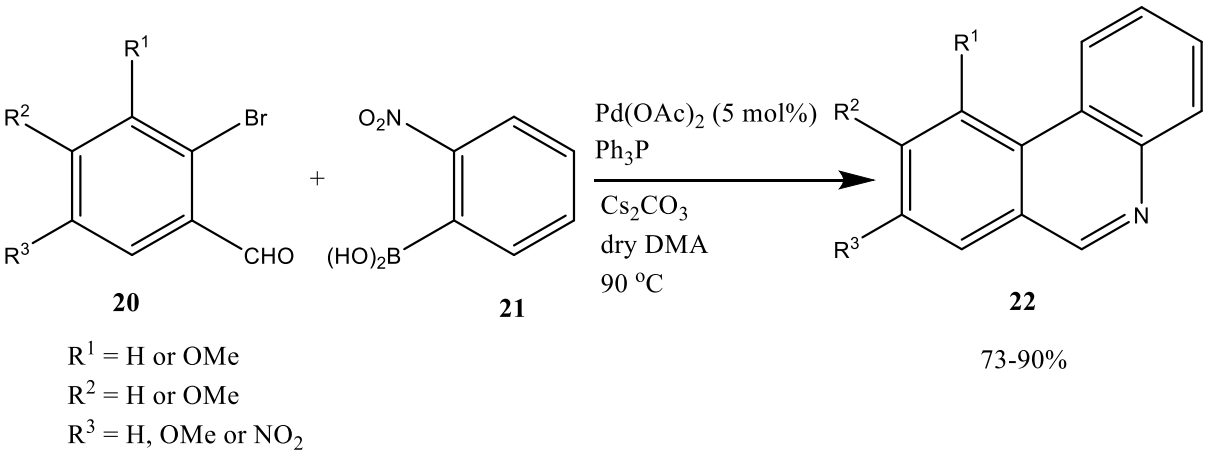
19

31-95%

Scheme 1.2: Synthesis of phenanthridines by photochemical cyclization of *N*-(2-iodobenzyl)anilines (**18**).[35]

1.2.3 Palladium-catalyzed cascade reactions

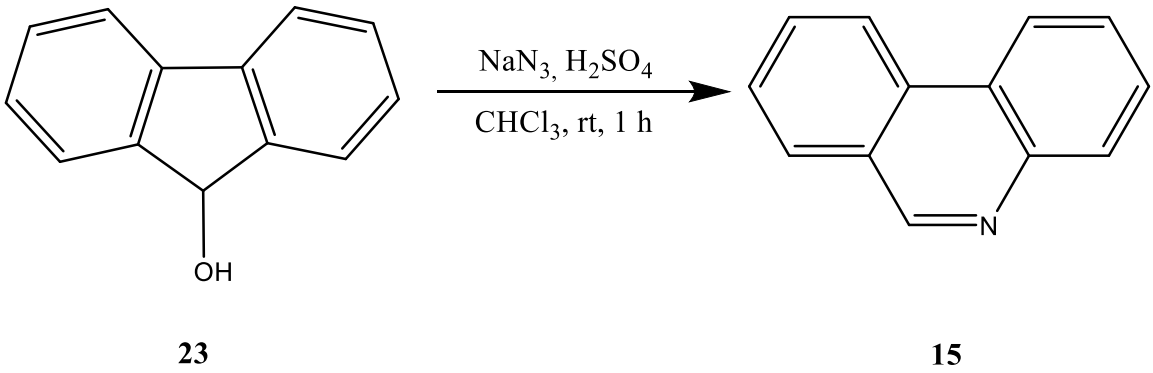
Synthesized phenanthridine by Suzuki-Miyaura coupling reaction was published in 2013 by Ray *et al.*[36] Coupling between 2-bromobenzaldehydes (**20**) and (2-aminophenyl)boronic acid (**21**) produced phenanthridines (**22**) with different functional groups on the C-ring (Scheme 1.5). Results ended with a yield between 73-90% of the substituted phenanthridines (**22**).[36]



Scheme 1.3: Palladium-catalyzed cascade reaction utilizing the Suzuki-Miyaura coupling reaction.[36]

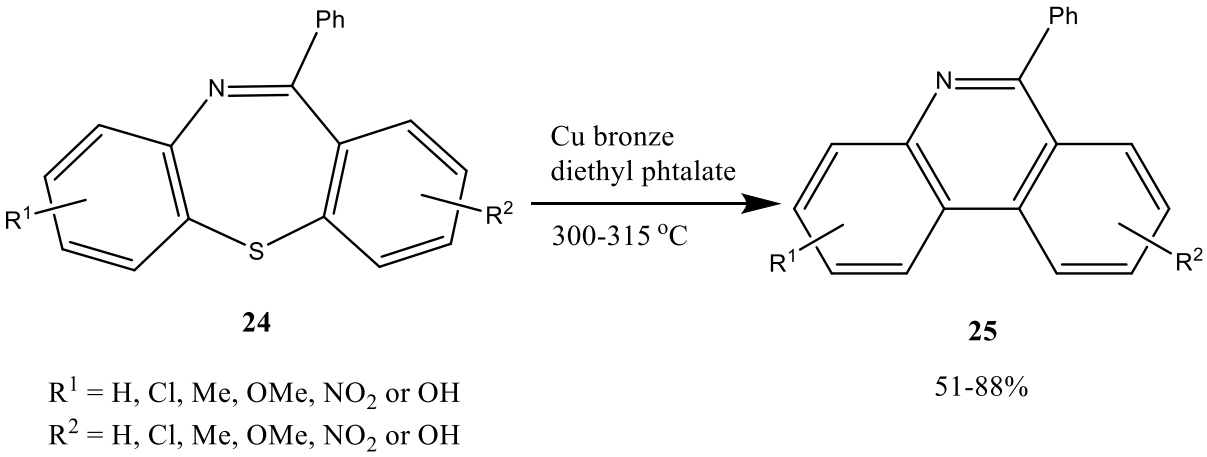
1.2.4 Ring expansion and contraction reactions

Arcus and Meslay published in 1953 a ring expansion synthesis of phenanthridine.[37] Fluoren-9-ol (**23**) was added to a solution of sodium azide, chloroform and sulphuric acid, which resulted in ring expansion to phenanthridine (**15**) (Scheme 1.6).[37]



Scheme 1.4: Synthesis of phenanthridine (**15**) by ring expansion of fluoren-9-ol (**23**).[37]

Ring contraction to form phenanthridine was published by Gault and Laudon in 1959.[38] They found out that 11-phenyldibenzothiazepines (**24**) could be converted to 6-phenylphenanthridines (**25**) in high yields. Solution of **24**, Cu bronze and diethyl phthalate in metal bath at 300-315 °C (Scheme 1.7), resulted in high yields of **25**.[38]



24

R^1 = H, Cl, Me, OMe, NO_2 or OH
R^2 = H, Cl, Me, OMe, NO_2 or OH

25

51-88%

Scheme 1.5: Synthesis of phenanthridines (**25**) by ring contraction of 11-phenyldibenzothiazepines (**24**).[38]

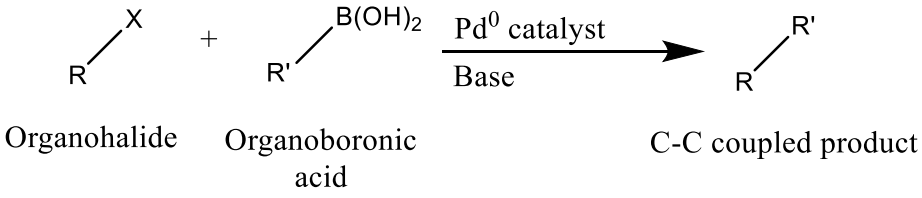
1.3 Chemistry of named reactions relevant for this work

This section deals with the chemistry named reactions used in this work to synthesize phenanthridines. A Suzuki-Miyaura coupling reaction is utilized to attach a furyl group on the aniline (Scheme 1). Intermolecular Diels-Alder reaction gave the fused phenanthridine ring system (Scheme 1). Claisen rearrangement was used to achieve ortho (*o*) substituted phenanthridines to the hydroxy group.

1.3.1 The Suzuki-Miyaura reaction

The Suzuki-Miyaura reaction, or simply Suzuki coupling reaction, was reported in 1979 by Norio Miyaura, Kinji Yamada and Akira Suzuki.[39] It is a cross-coupling reaction between aryl or vinyl boronic acids with aryl or vinyl halides, catalyzed by palladium(0) complexes. Kharash coupling, Negishi coupling and Stille coupling are some of the coupling reactions available to yield the same result, but the Suzuki coupling reaction is amongst the most efficient and applicable methods for the formation of C-C bonds (Scheme 1.8).[39,40] It needs milder reaction conditions, temperatures between 60-80 °C and results in high yields.[39] One of the disadvantages is that the reaction needs a base to fulfill the catalytic cycle, so base sensitive compounds are not suited[41] Suzuki coupling reaction has been a useful reaction for synthesizing natural product and drugs because of the variation of functional groups that can

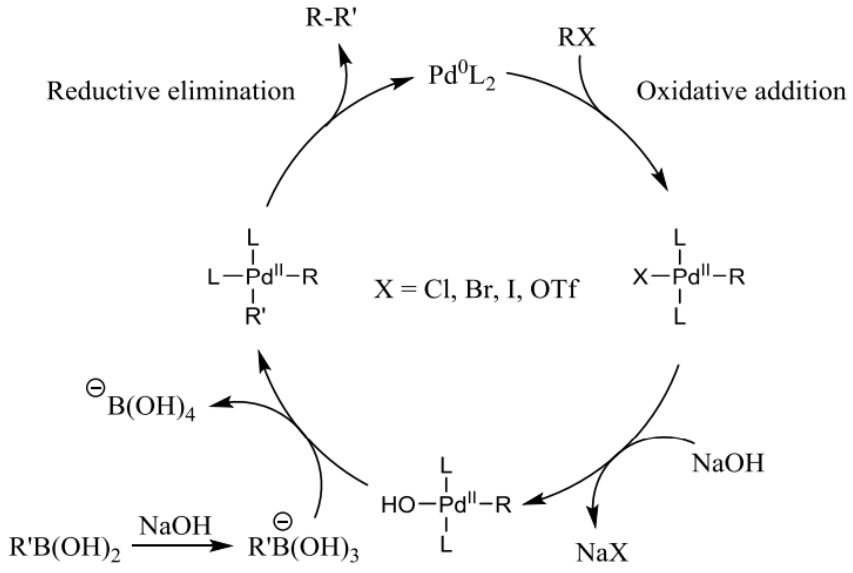
be used.[42] Divers boronic acid derivatives are obtainable, easily handled and removed from the product compared to organometallic reagents.[39] They do not pollute the environment[43] and are non-toxic.[44]



R, R' = aryl, vinyl, alkyl
X = halide, OTf

Scheme 1.8: Formation of a carbon-carbon bond between an organohalide and an organoboronic acid in a palladium (0) catalyzed Suzuki coupling reaction.

The know mechanism for the Suzuki coupling reaction is shown in scheme 1.10.[39,45] Not presented in the scheme, using $Pd(OAc)_2$, active Pd^0-complex can be achieved *in situ.*



Scheme 1.9: Accepted mechanism of the Suzuki coupling reaction.[39,45]

The basic and simple mechanism for Suzuki coupling reaction can be explained by five steps.

1. Oxidative addition of palladium (0) to the organohalide to form organopalladium species.

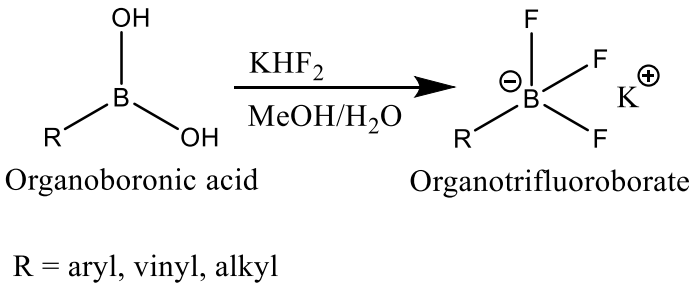
2. The formation of a hydrolyzed intermediate by addition of a base.

3. Transfer of an organic group from a boron reagent, or transmetallation, to form organopalladium trans-complex.

4. Isomerization to *cis*-complex from the trans-complex (not shown in scheme 1.10).

5. Formation of the desired product by reductive elimination and restoration of the Pd^0-complex.

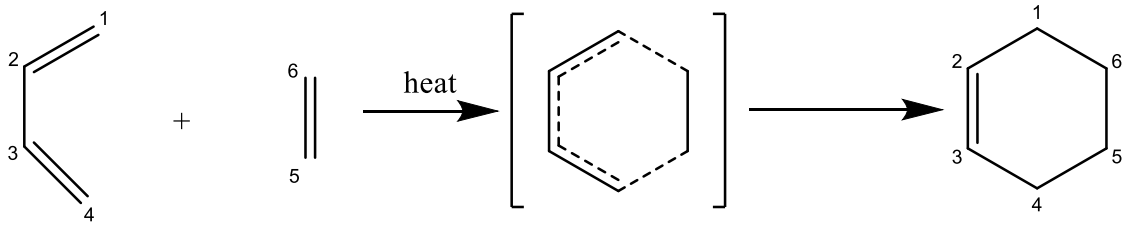
The electron density of the organohalide determines the rate of the oxidative addition. It is the rate-determining step and increases with electron poor organohalides. The halides also affect the reaction with their electron withdrawing ability. The reactivity order will then be I > OTf >Br >> Cl. For transmetallation two species must have opposite electron properties. One electron rich and one electron poor. Electron rich organoboronic reagents are favored.[46,47] Organotrifloroborate salts are also commonly used instead of boronic acids.[48] Organoboranes can react with atmospheric dioxygen and therefore degrade under atmospheric conditions. The salts are more stable and by transforming them to respective potassium trifluoroborate salts (Scheme 1.10) they will hydrolyze and form boronic acids in presence of a protic solvent and a base.[41]



Scheme 1.10: Transforming organoboronic acid to organotrifluoroborate.[49]

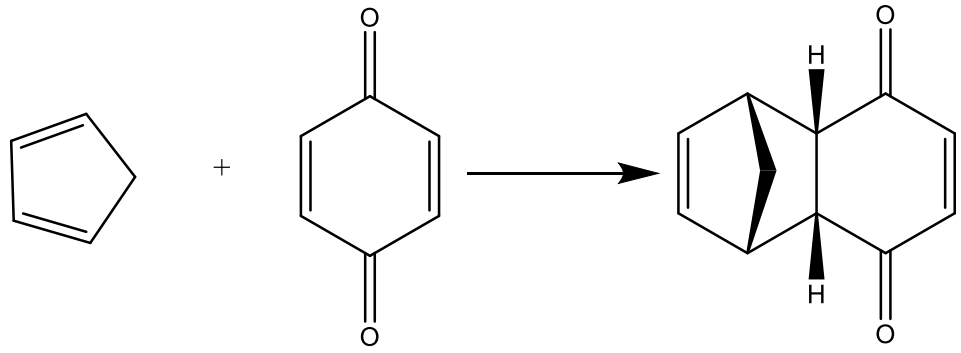
1.3.2 The Diels-Alder reaction

In 1928 published Otto Diels and Kurt Alder the Diels-Alder reaction.[50] It is a [4 + 2] cycloaddition reaction shown in Scheme 1.11.[51,52] The bonds are partially formed and broken in the transition state, indicated by the dashed lines. This means that the reaction is concerted.[52] The π-bonds, four from the diene and two from the dienophile, connect and form the cyclized product. The conjugated diene must have a *s-cis* confirmation to be able to be used in the reaction.[53]

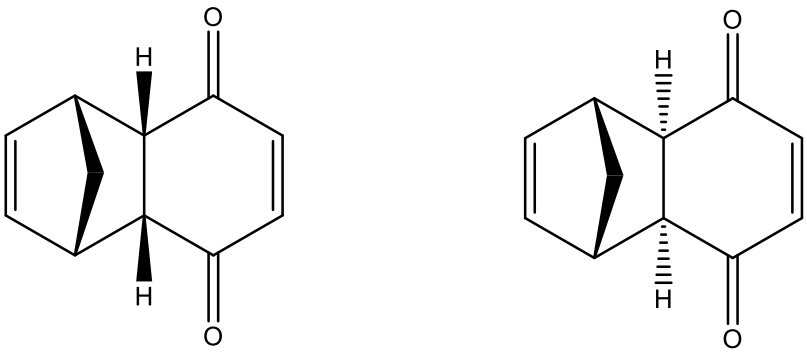


Scheme 1.11: The general Diels-Alder reaction between a diene and dienophile.[51,52]

Diels and Alder studied a reaction between cyclopentadiene as a diene and benzoquinone as a dienophile, which gives a locked diene in *cis* conformation. It leads to a bridge bicyclic structure (Scheme 1.12).[54] In Diels-Alder stereochemistry there is an *endo* effect feature. The acceptor substituent can either end up in *endo* position or *exo* position (Figure 1.5), but the most favored and observed for an intermolecular Diels-Alder is the *endo*.[55,56]



Scheme 1.12: Observed reaction by Diels and Alder.[54]

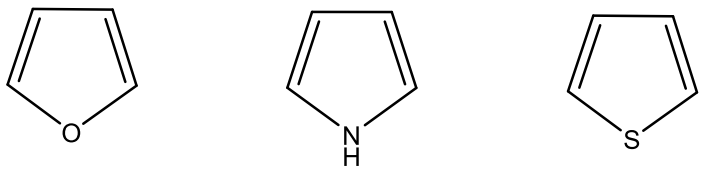


Endo product *Exo* product

Figure 1.5: *Endo* and *exo* product after an intermolecular Diels-Alder.

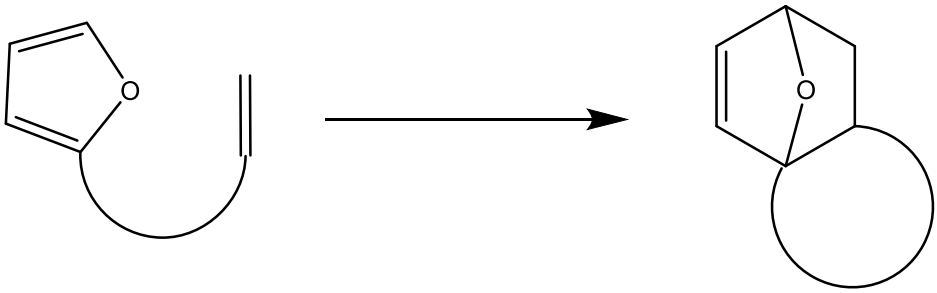
1.3.3 Intermolecular Diels-Alder reaction of furan (IMDAF)

Instead of cyclopentadiene used in Diels and Alders reaction, a furan (Figure 1.6) is used in a IMDAF reaction. Pyrrole and thiophene (Figure 1.6) have similar structure as furan, but do not participate in regular Diels-Alder reactions.[57,58] All three have a lone pair that can delocalize into the ring to give a conjugated system. The furan contains a highly electronegative oxygen that decreases its aromatic character since the delocalization is not overly effective. This makes it useful as a diene.[59] Unfortunately, Diels-Alder reactions with furan do not occur easily with weak dienophiles and requires extreme conditions.[60] By attaching the dienophile to the furan or molecule containing furan, an intermolecular Diels-Alder (IMDA) occurs and form the cyclized product (Scheme 1.13).[61]



Furan Pyrrole Thiophene

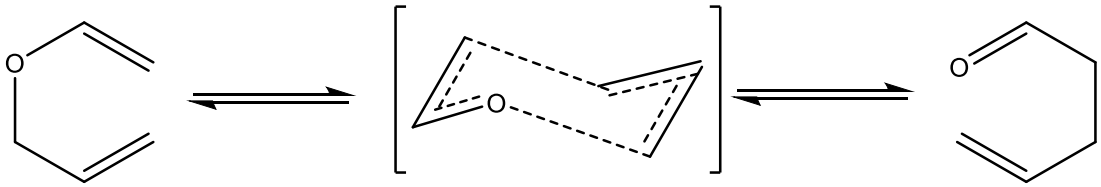
Figure 1.6: Structure of furan, pyrrole and thiophene.



Scheme 1.13: The IMDAF reaction.

1.3.4 The Claisen rearrangement reaction

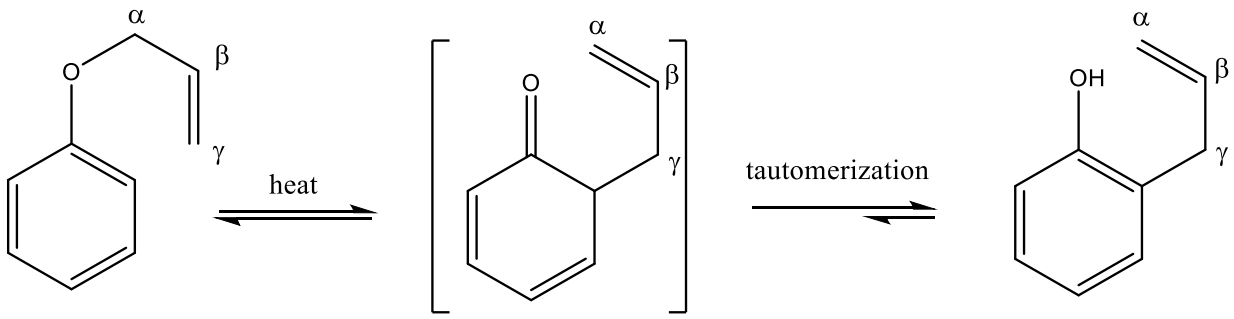
Rainer Ludwig Claisen discovered a powerful carbon-carbon bond-forming reaction in 1912, now known as the Claisen rearrangement. It is the earliest recorded example of a [3,3]-sigmatropic reaction[62,63] and is a concerted[64] pericyclic process.[62,63] Sigmatropic rearrangement is a reaction where a σ-bond migrates over one or more π systems. The numbers in the brackets define the movement of the σ-bond. In a [3,3] sigmatropic Claisen rearrangement the σ-bond is flanked when migrating by one or more π systems to a new location 3-1 and 3-1 atoms away.[56] The discovery was the transformation of allyl vinyl ether to 4-pentenal and is shown in scheme 1.14.[62] The reaction occurs with a negative activation entropy[65] and negative activation volume. It displays first-order kinetics and goes through a chair transition state of coherent p orbitals.[62]



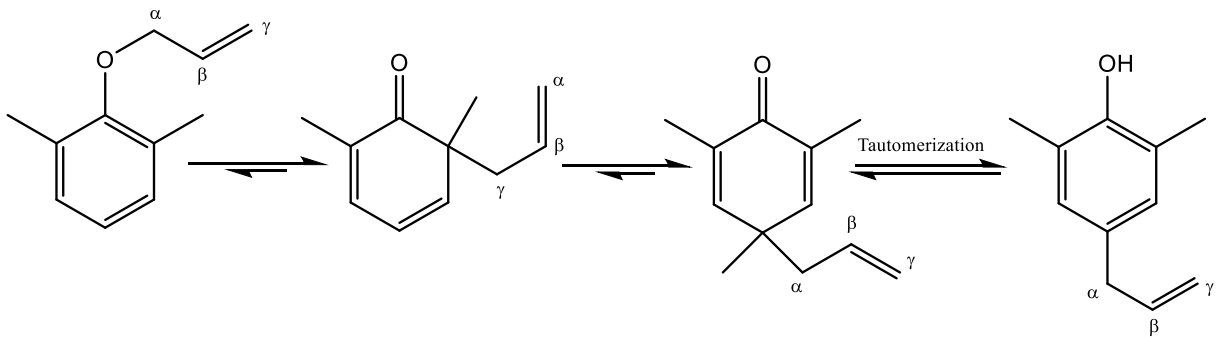
Scheme 1.14: Claisen rearrangement of allyl vinyl to 4-pentenal.[67]

Claisen rearrangement can also happen on a cyclic compound. Heating a solution of allyl phenyl ether will rearrange the allyl to the *ortho*-position (Scheme 1.15). The first step is reversible, but after the compound has tautomerized back to being aromatic, the equilibrium will be strongly shifted to the right. With presence of *meta*-substitution, the regioselectivity of

the rearrangement will be affected.[66,67] Rearrangement to the *ortho*-position is favored with electron withdrawing groups at the *meta*-position, while rearrangement to the *para*-position is favored with electron donating groups at *meta*-position. Substitution on the *ortho*-position will also lead to para substitution by two [3,3] rearrangements (Scheme 1.16).[67,68] In the first rearrangement the functional group binds to the *ortho* position breaking the aromaticity. To recover the aromatization another [3,3] rearrangement takes place before tautomerization occur, leading to a *para* substituted compound. *Ortho* or *para* substituted compounds with aldehyde or carboxylic acid will release carbon monoxide or carbon dioxide since the allyl side-chain displaces these groups.[69]



Scheme 1.15: Claisen rearrangement of allyl phenyl ether to the *o*-allyl phenol.[63]



Scheme 1.16: Two [3,3] sigmatropic rearrangements of *ortho* substituted phenyl ether to form *ortho* substituted *p*-allyl phenol.[68]

1.4 Microwave synthesis

Before use of microwave reactor in synthesis, reactions with conventional heating often took several hours or even days. With this new method, scientists could decrease reaction time and

also the solvent used by preforming reactions with small, or no amount of solvent. Today both methods are used in literature. Materials absorbing the microwaves are the most important ones. There are three different mechanisms for absorbing materials which are dipolar polarization, conduction mechanism and interfacial polarization.[70,71] Only dipolar polarization is explained in this section.

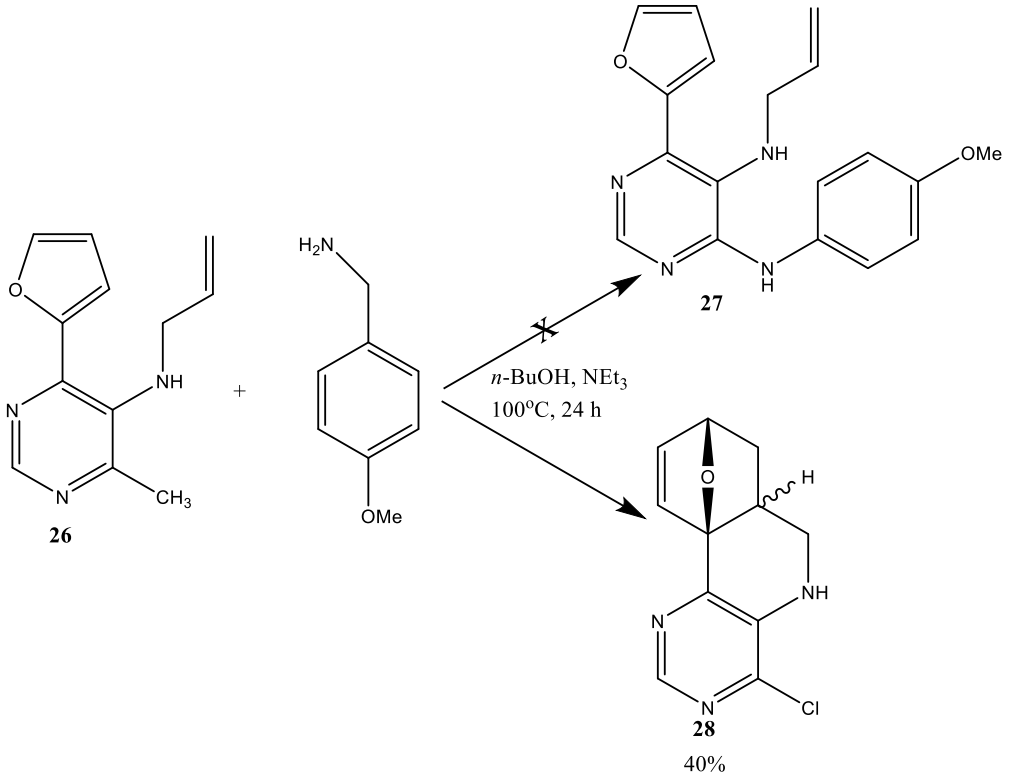
In dipolar polarization the substance must possess a dipolar-moment to generate heat. The electric field component of the microwave radiation is responsible for the heating. The dipole reorient itself to the electric field and generate heat by molecular friction. The heat generates either by interaction between polar solvent molecules or between polar solute molecules. For the heating to occur the frequency of the oscillating field has to enable sufficient inter-particle interactions. The frequency can range from 0.3-30 GHz but commonly 2.45 GHz.[70,71]

By using microwave reactors for the IMDAF reactions, yields, reaction times and stereoselectivity has been improved.[72-74] It can also be used for Claisen rearrangement reactions which needs high temperature for the reaction to happen. This can easily be done with a microwave reactor. Same as the IMDAF reaction, yields, reaction times and stereoselectivity has been improved.[75-77]

1.5 Current and previous phenanthridine synthesis strategies in our group

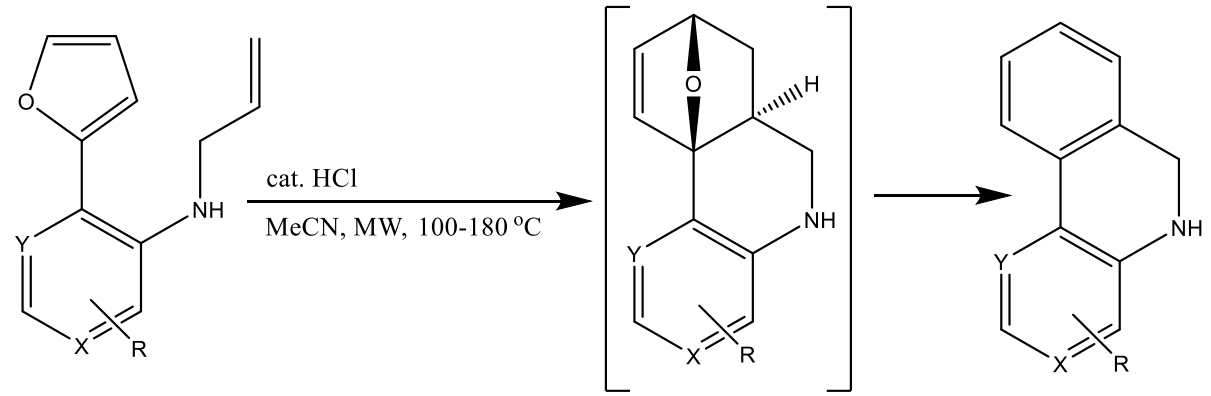
1.5.1 IMDAF-based synthesis development

The IMDAF reaction have been investigated in our group for over ten years.[1-5, 78] Read, a member of our research group, synthesized pyridines to be tested for antimycobacterial activity. When he heated compound **26** for a nucleophilic aromatic substitution reaction, a IMDAF reaction occurred where a complex ring system was formed instead (**28**) (Scheme 1.17).[79] This discovery lead to further investigation into the IMDAF reaction.

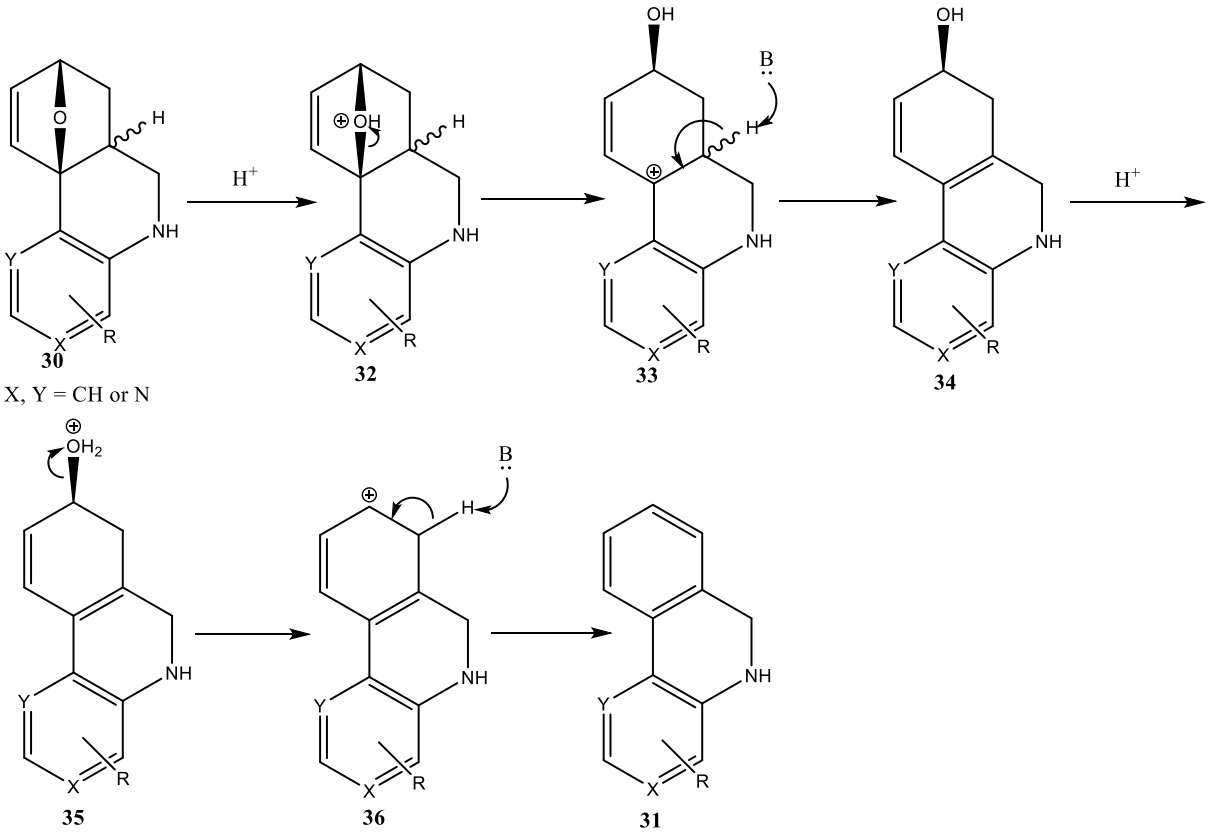


Scheme 1.17: Observed IMDAF reaction when compound **26** where heated, leading to the unexpected compound **28**.[79]

It has proven to be a reliable synthesis for producing a wide range of phenanthridines from cheap and easily obtainable starting materials with a wide scope of functionalization of the A- and C-ring. The sterically hindering substitutions in *ortho*-position to the allylamino group increased the cyclization in the IMDAF reaction.[1] A one-pot synthesis (Scheme 1.18) of dihydrophenanthridines in a microwave reactor was conducted with MeCN and 2 M HCl, where the HCl was found to ring-open and eliminate water from the IMDAF adduct (Scheme 1.19).[2,79]



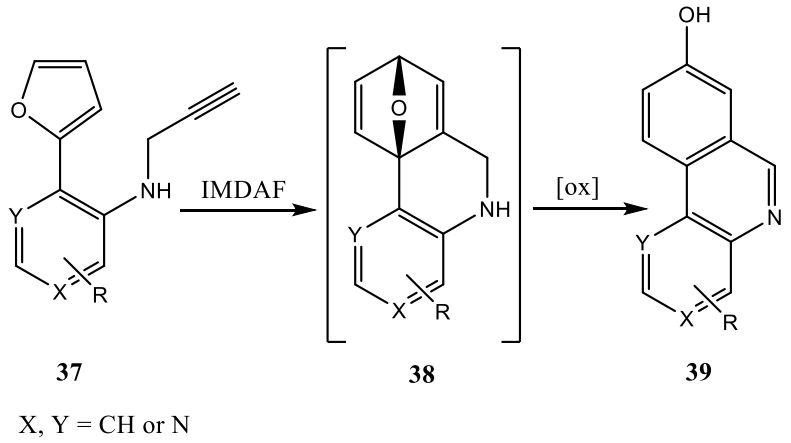
Scheme 1.18: Synthesis om IMDAF reaction in a microwave reactor.[2,79]



Scheme 1.19: Proposed mechanism for the ring opening step and water elimination of the oxynorborene ring system.[79]

The same procedure can be used for synthesis of phenanthridine-8-ols (**40**) (Scheme 1.20) by *N*-alkynylation instead of *N*-allylation of the 2-(furan-2-yl)anilines. The IMDAF reaction

provides two double bonds in the C-ring, with no elimination of water in the ring opening process. This leads to a dihydrophenanthridine with a hydroxy group in 8-position.[3,5]



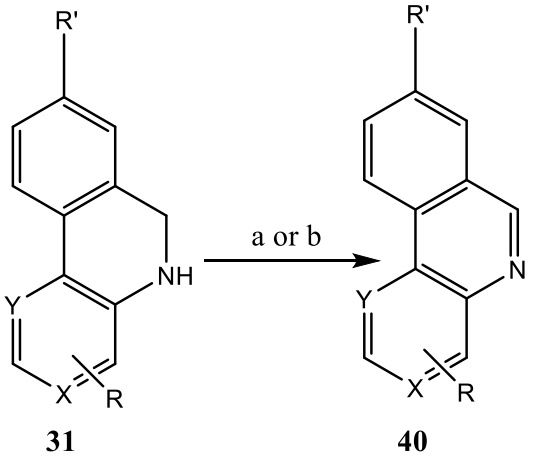
37 **38** **39**

X, Y = CH or N

Scheme 1.20: Synthesis of dihydrophenanthridine-8-ols.[3,5]

1.5.2 Dihydrophenanthridine oxidation

Oxidizing dihydrophenanthridines (**31**) is the last step to produce phenanthridines (Scheme 1.21). Two methods have been used in our group, irradiation of UV-light or in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). UV-light irradiation enabled a clean and simple two-step method to synthesize phenanthridines (**40**) with some exceptions of slow oxidation. This was overcome by oxidation in presence of DDQ.[2,79]



31 **40**

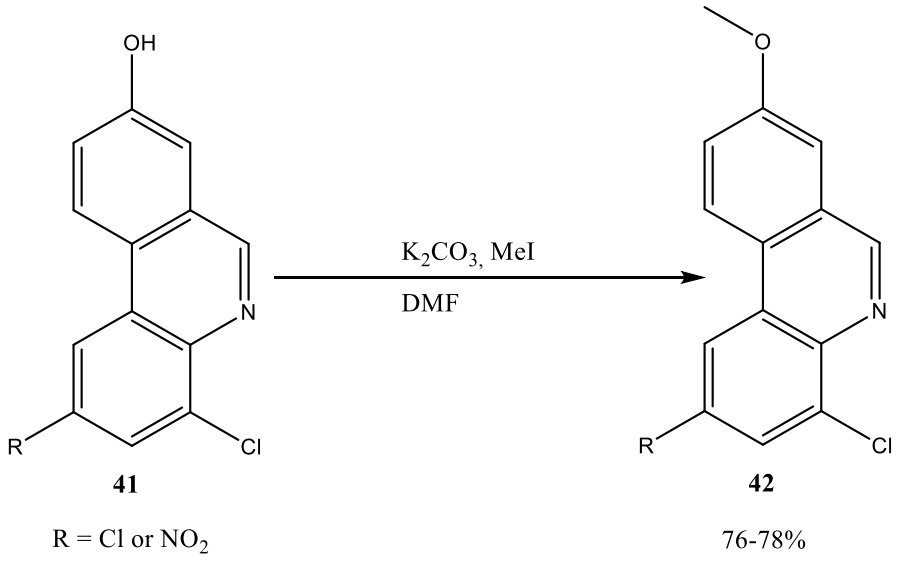
X, Y = CH or N
R' = H or OH

Scheme 1.21: Oxidation of dihydrophenanthridines. [2,76] Oxidation method: **a** – hν, air, MeCN. **b** – DDQ, CH_2Cl_2.

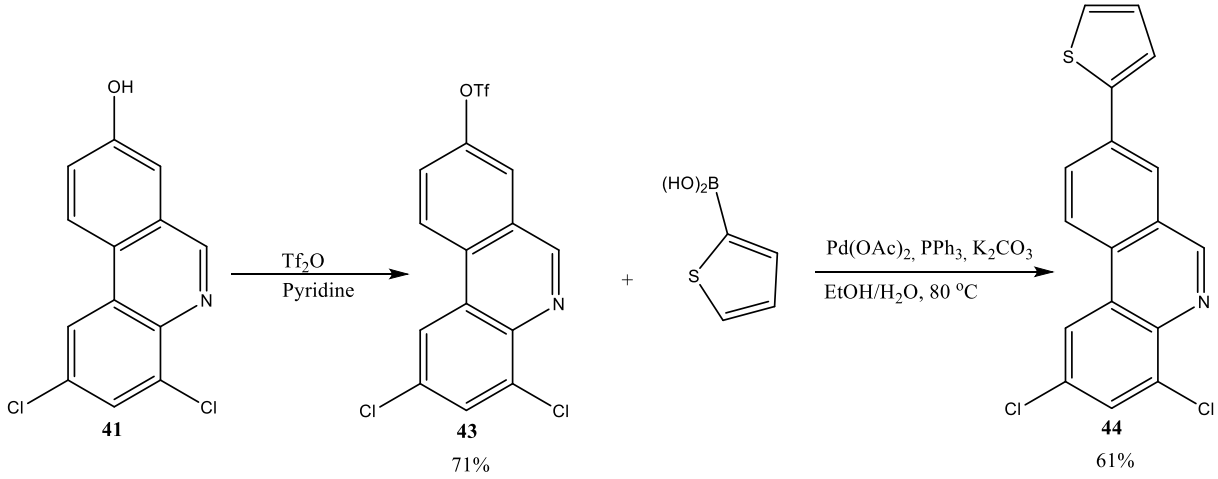
1.5.3 Phenanthridine-8-ol functionalization

Deprotonation of phenols leads to the phenolate anion, which can be used in substitution reactions as a nucleophile. Phenanthridine-8-ols can undergo many of the same reactions since they are chemically analogous to phenols.

o-Methylation of phenanthridine-8-ols (**41**) was synthesized with potassium carbonate (K_2CO_3) and methyl iodide (MeI) in DMF, producing 8-methoxyphenanthridines (**42**) (Scheme1.22).[5] 2,4-Dichloro-8-(thiophen-2-yl)phenanthridine (**44**) is achieved by triflation followed by a Suzuki-Miyaura coupling reaction with an organoboron compound (Scheme 1.23).[5]



Scheme 1.22: Synthesis of 8-methoxyphenanthridines.[5]



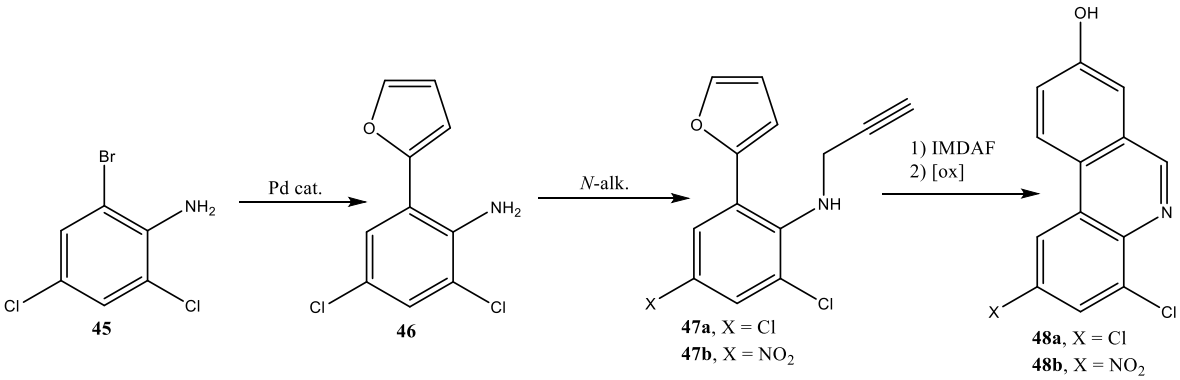
Scheme 1.23: Synthesis of 2,4-dichloro-8-(thiophen-2-yl)phenanthridine by triflation followed by Suzuki-Miyaura coupling.[5]

2. Results and discussion

This section describes the synthesis of every compound produced in this thesis.

2.1 Synthesis of 8-hydroxyphenanthridines

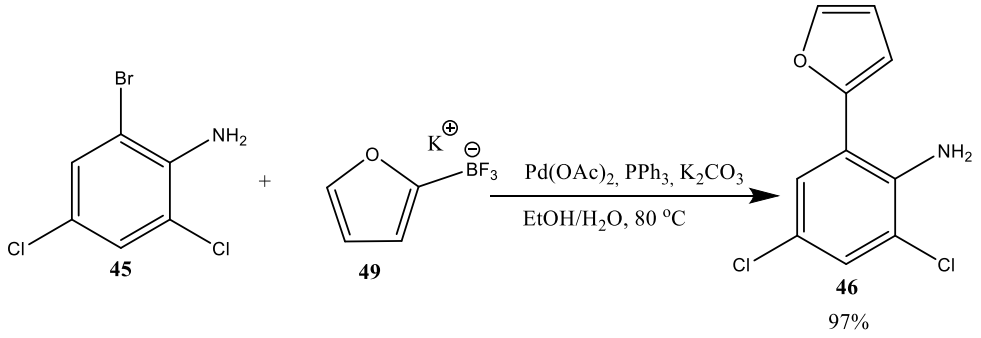
The section contains chosen starting material and their synthesis to produce 8-hydroxyphenanthridines for further functionalization in this thesis (Scheme 2.1). The synthesis strategies follow literature procedures from our group.[1,5]



Scheme 2.1: Synthesis route to produce 8-hydroxyphenanthridine.

2.1.1 Synthesis of Synthesis of 2,4-dichloro-6-(furan-2-yl)aniline (46)

8-Hydroxyphenanthridine had to be made for later experiments in this assignment. The first step was to synthesize 2,4-dichloro-6-(furan-2-yl)aniline (**46**) from 2-bromo-4,6-dichloroaniline (**45**) (Scheme 2.2) following literature procedures.[1,2] To remove inorganic salts and excess base before purifying with flash chromatography, the solvent was filtered through a silica plug before evaporating the solvent. The yield of the product was slightly higher than the reported yield.

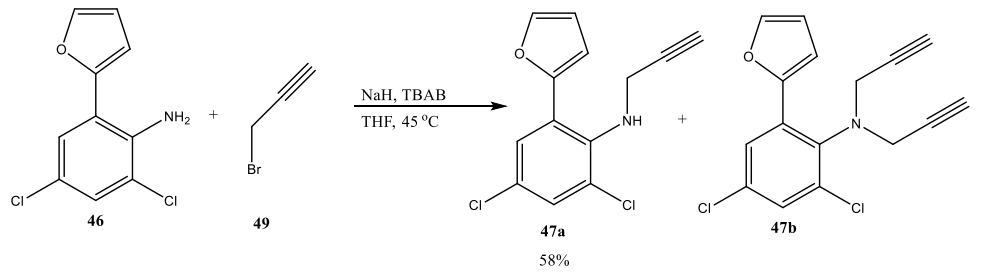


Scheme 2.2: Synthesis of 2,4-dichloro-6-(furan-2-yl)aniline (**46**) from 2-bromo-4,6-dichloroaniline (**45**).

The heteroarylboronic acids are readily degraded under the Suzuki reactions and therefore converted into a more stable salt **49** shown in Scheme 1.8. Compound **49** was already made in bulk by a previous member in our group. In the Suzuki reaction the salt is converted back into the acid.

2.1.2 Synthesis of 2,4-dichloro-6-(furan-2-yl)-N-(prop-2-yn-1-yl)aniline (46a) and 2,4-dichloro-6-(furan-2-yl)-N,N-di(prop-2-yn-1-yl)aniline (47b)

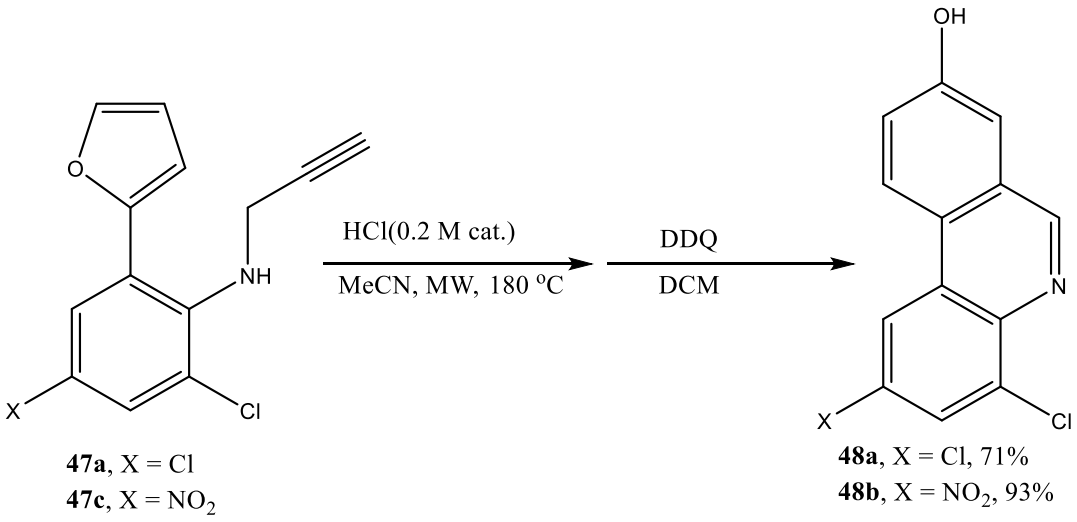
The next step was *N*-alkynylation of compound **46** with 3-bromoprop-1-yn **49** to produce **47a** following literature procedure (Scheme 2.3),[5] with **47b** as biproduct. By treating compound **46** with NaH, deprotonation of the nitrogen occurs. This makes the nitrogen an electron rich nucleophile where one of the lone pairs attacks compound **49.** A new bond is formed with **49,** while the halogen falls off. When the nitrogen is deprotonated again one more nucleophilic substitution occurs, forming compound **47b.** Minimal amounts of dialkylated biproduct were formed.



Scheme 2.3: *N*-alkynylation of 2,4-dichloro-6-(furan-2-yl)aniline (**46**) to form 2,4-dichloro-6-(furan-2-yl)-*N*-(prop-2-yn-1-yl)aniline (**47a**) and 2,4-dichloro-6-(furan-2-yl)-*N*,*N*-di(prop-2-yn-1-yl)aniline (**47b**).

2.1.3 Microwave mediated synthesis of 2,4-dichlorophenanthridin-8-ol (48a) and 4-chloro-2-nitrophenanthridin-8-ol (48b)

2-chloro-6-(furan-2-yl)-4-nitro-N-(prop-2-yn-1-yl)aniline (**46c**) was synthesized by another member of our group and used in this work.[5] By microwave irradiation a IMDAF reaction occurred to cyclize **47a** and **47c** to dihydrophenanthridine-8-ols before oxidizing with DDQ to **48a** and **48b** (Scheme 2.4). During flash chromatography for **48b**, the eluent was altered by changing it to 1:1.5:7.5 DCM:EtOAc:hexanes. The purification went slower but ended up with higher yield than reported in the literature.[5]



47a, X = Cl
47c, X = NO_2

48a, X = Cl, 71%
48b, X = NO_2, 93%

Scheme 2.4: IMDAF and oxidation of 6-(furan-2-yl)-N-(prop-2-yn-1-yl)anilines (**47**) to produce phenanthridin-8-ols **48**.

2.1.4 Other 8-hydroxyphenanthridines

Three more 8-hydroxyphenanthridines (**50**-**52**) were used for functionalization on 8-position (Figure 2.1). All three were synthesized by a member of our group.[80]

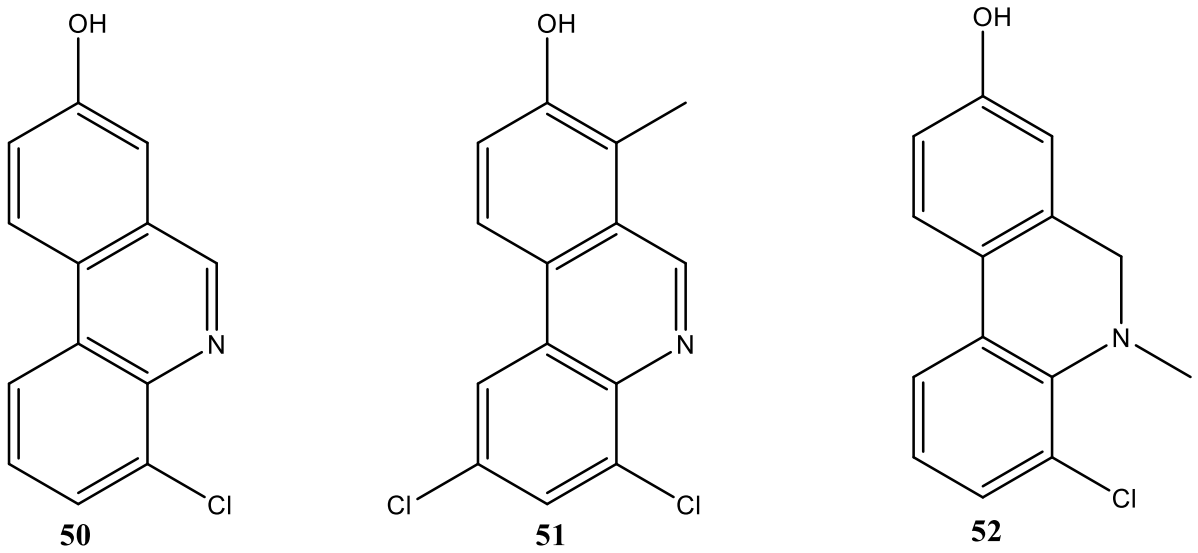


Figure 2.1: Structure of 4-chlorophenanthridine-8-ol (**50**), 2,4-dichloro-7-methylphenanthridine-8-ol (**51**) and 4-chloro-5,6-dihydrophenanthridine-8-ol (**52**).

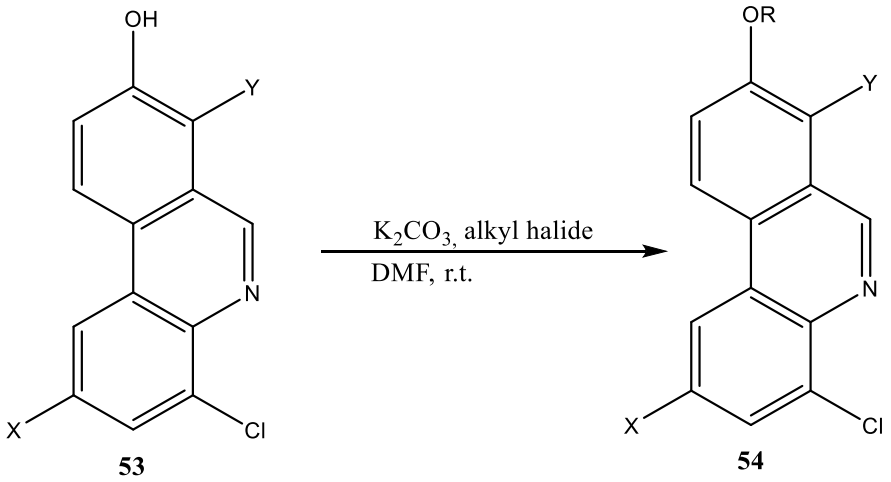
2.2 Functionalization on the 8-position of 8-hydroxyphenanthridine

2.2.1 *O*-Alkylation

This section contains *O*-alkylation reactions of 8-hydroxyphenanthridines for further testing of biological activities. The allyl ethers were synthesized mainly as starting materials for further functionalization on the C-ring by Claisen rearrangement.

2.2.1.1 O-alkylation of different 8-hydroxyphenanthridines with various reagents

8-Hydroxyphenanthridine can undergo *O*-alkylation shown in section 1.5.3 and Schemes 1.22 and 1.23. By treating 8-hydroxyphenanthridine with K_2CO_3 and an alkyl halide, *O*-alkylation occurs. Following literature procedure,[5] compounds **53-61** were synthesized shown in Scheme 2.5 and Table 2.4. Compound **57** was synthesized by treating compound **48a** with crotyl bromide mixture of *trans* and *cis*, resulting in *cis* compound **57a** and *trans* compound **57b** in a 5:1 ratio.



Scheme 2.5: *O*-alkylation of 8-hydroxyphenanthridines (**53**) by treatment of different alkyl halides.

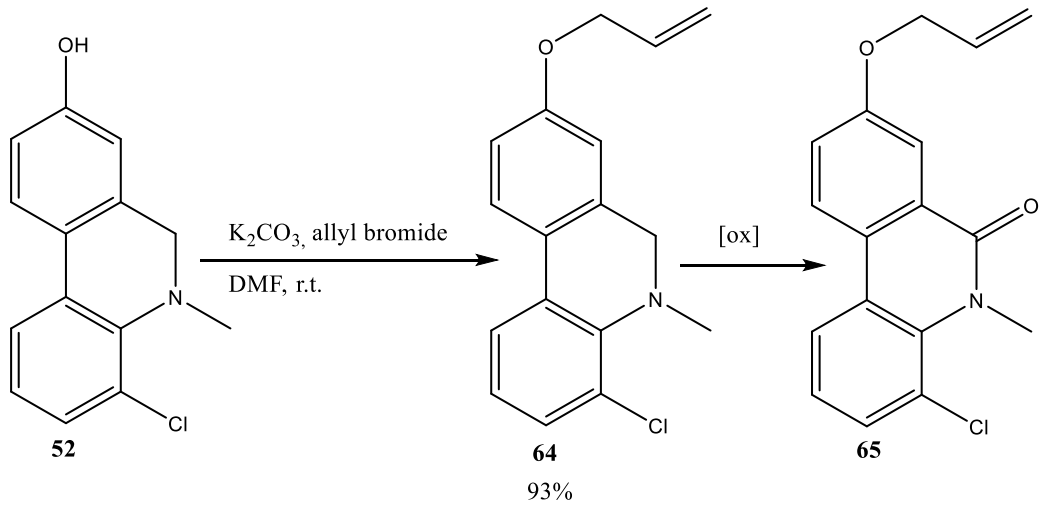
Table 2.1: Detailed description of alkyl halides and substituents for the *O*-alkylation reactions as well as isolated yield for each compound synthesized.

Entry	SM	X	Y	Alkyl halide	Product	R	Yield
1	**48a**	Cl	H	Benzyl bromide	**55**	Benzyl	93%
2	**48a**	Cl	H	Allyl bromide	**56**	Allyl	98%
3	**48a**	Cl	H	Crotyl bromide	**57a, 57b** (5:1)	But-2-en-1-yl	86%
4	**48a**	Cl	H	1-Bromo-3-methyl-2-butene	**58**	3-Methylbut-2-en-1-yl	97%
5	**48a**	Cl	H	3-Bromo-2-metylpropene	**59**	2-Methylallyl	96%
6	**48a**	Cl	H	2,3-dichloro-1-propene	**60**	2-Chloroallyl	86%
7	**48b**	NO_2	H	Allyl bromide	**61**	Allyl	78%
8	**50**	H	H	Allyl bromide	**62**	Allyl	85%
9	**51**	Cl	Me	Allyl bromide	**63**	Allyl	93%

All reactions lasted for 75 min. before the organic and water phases were separated in a separation funnel. The organic phases were purified by filtration through a silica plug and concentrated under reduced pressure. All except one reagent had boiling point under 140 ^{o}C and was evaporated under reduced pressure. Benzyl bromide on the other hand had a boiling point at 198 ^{o}C and did not evaporate *in vacuo* (ca. 50 mbar). Thus, compound **55** (Table 2.4, entry 1) was purified by flash chromatography on silica gel.

2.2.1.2 Synthesis of 8-(allyloxy)-2,4-dichloro-5-methyl-5,6-dihydrophenanthridine (64) and 8-(allyloxy)-2,4-dichloro-5-methylphenanthridin-6(5H)-one (65)

Compound **64** was synthesized from **52** the same way as the previous compound resulting in a yield of 93% as an orange oil (Scheme 2.6). It was stored in a round bottom flask in a refrigerator for three weeks, where it oxidized to a solid. The reason for long storage was the second lockdown in the COVID-19 pandemic winter 2021. The plan was to use compound **64** in a Claisen rearrangement to find out how it affected the reaction since it has a non-aromatic B-ring. The amount synthesized of compound **52** by a member of our group was all used in the *O*-alkylation reaction. To produce compound **64** the 8-hydroxyphenanthridine had to be synthesized first but there was no time.



Scheme 2.6: *O*-Alkylation of **52** to **64** followed by oxidation to **65**.

The ^{1}H NMR spectrum of compound **64** can be seen as the upper one in figure 2.2, oxidized mixture as the middle one and compound **65** as the lower one. By comparing the three spectra, small amounts of **52** are left in the oxidized mixture. Comparing the ^{1}H NMR spectra from **64** and **65**, one proton peak integrating for two protons in spectrum **64** were not visible in spectrum **65**. From the DEPT spectrum one less CH_2 carbon was also not visible. Mass spectroscopy (MS) calculated **64** to 285.0915 and **65** to 299.0708 giving a difference of 14. Since **65** oxidizes an oxygen binds itself to a carbon making a double bond and releases to protons. Adding two to 14 gives 16, Which is the same as one oxygen. The oxidized compound **65** was purified by flash chromatography.

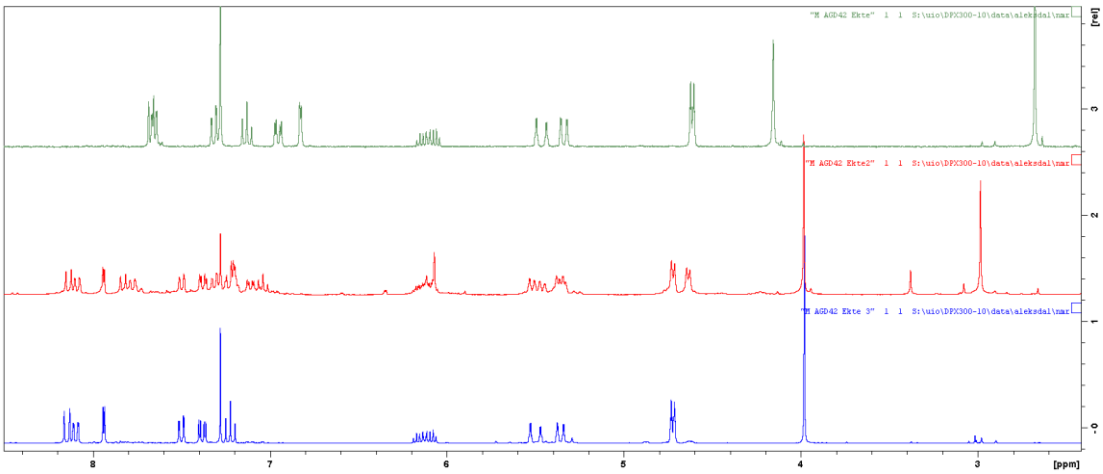
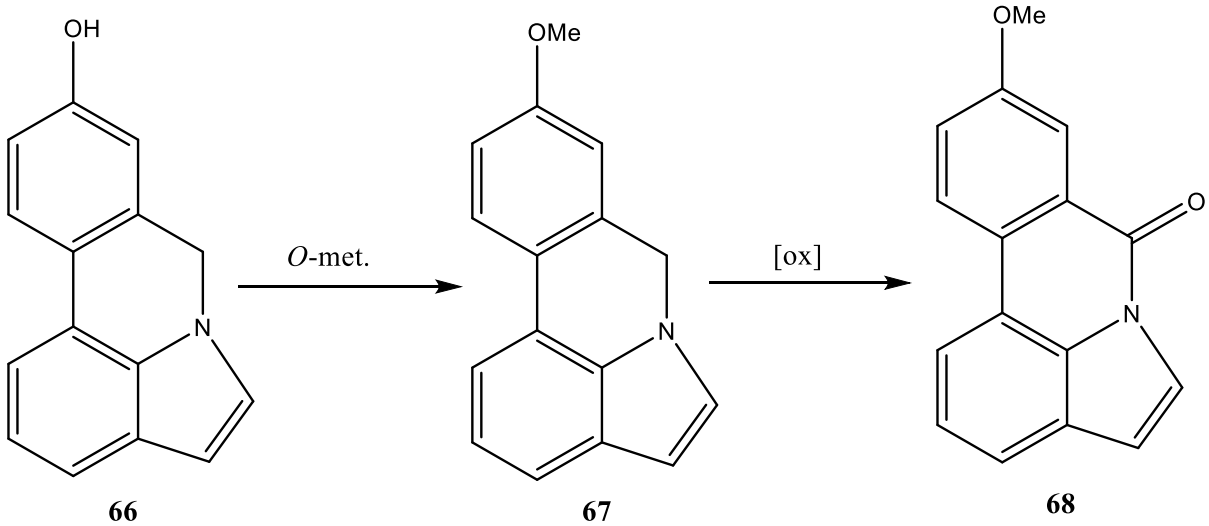


Figure 2.2: Spectra of **64** (upper), oxidized mixture (middle) and **65** (lower).

It is not the first time a phenanthridine with a non-aromatic B-ring has oxidized in our group.[5] After synthesizing 7H-pyrrolo[3,2,1-de]phenanthridin-9-ol (**66**), the phenol was *O*-methylated to produce 9-methoxy-7H-pyrrolo[3,2,1-de]phenanthridine (**67**). Compound **67** displayed limited stability, and in exposure to air it oxidized to 9-methoxy-7H-pyrrolo[3,2,1-de]phenanthridin-7-one (**68**).



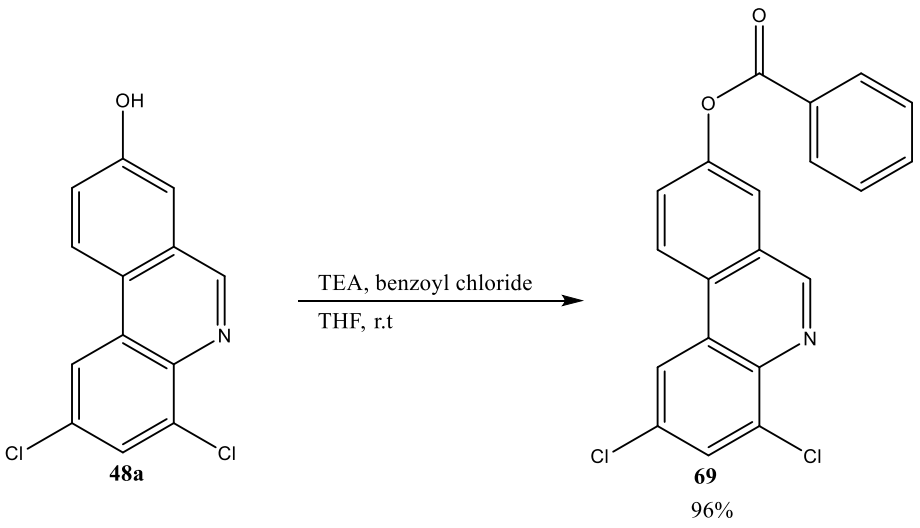
Scheme 2.7: *O*-methylation of the phenol (**66**) producing compound **67** followed by oxidation by exposure to air.

2.2.2 Synthesis of phenanthridine esters

This section contains the synthesis of phenanthridine esters.

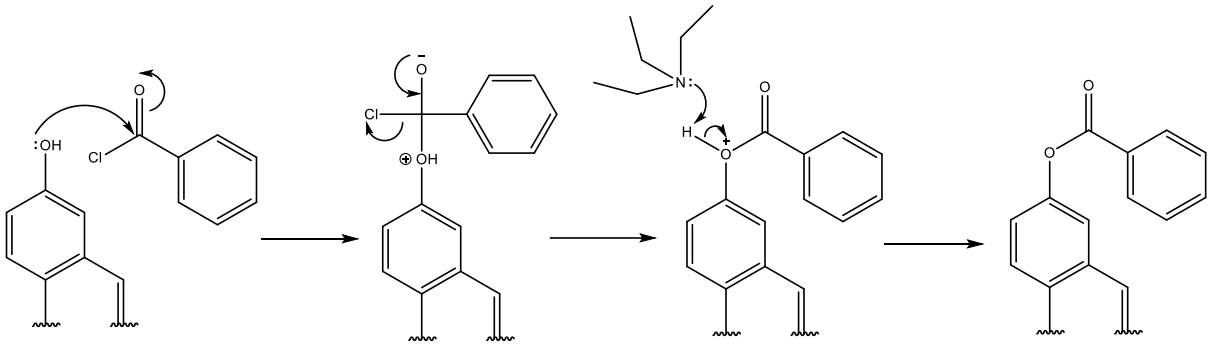
2.2.2.1 Synthesis of 2,4-dichlorophenanthridin-8-yl benzoate (69)

A reaction of an acid chloride with an alcohol is an example of an acyl transfer to produce esters.[55] Compound **69** is the product of the reaction of benzoyl chloride as the acid chloride, and 2,4-dichlorophenanthridine-8-ol (**48a**) as the alcohol following a literature procedure for the synthesis of other phenol esters (Scheme 2.8).[81] The result was a high yield of 96% of compound **69.**



Scheme 2.8: Synthesis of 2,4-dichlorophenanthridin-8-yl benzoate (**69**) from 2,3-dichlorophenanthridine-8-ol (**48a**).

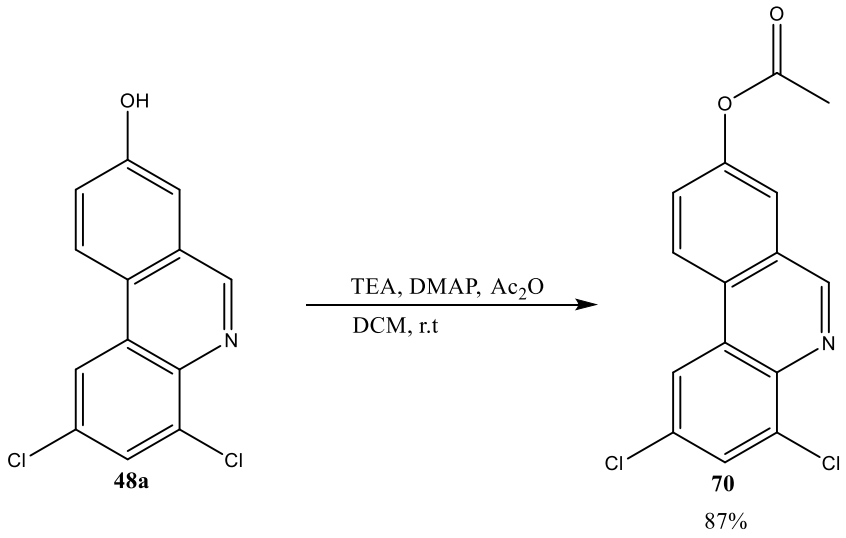
A lone pair on the oxygen of compound **48a** performs a nucleophilic attack on the electron deficient carbonyl carbon on benzoyl chloride. When the carbon-oxygen double bond reforms, a chloride ion is eliminated, and the intermediate remove a hydrogen ion by either triethylamine (TEA) or chloride ion (Scheme 2.9).



Scheme 2.9: Mechanism for the acyl transfer to form compound **69**.[55]

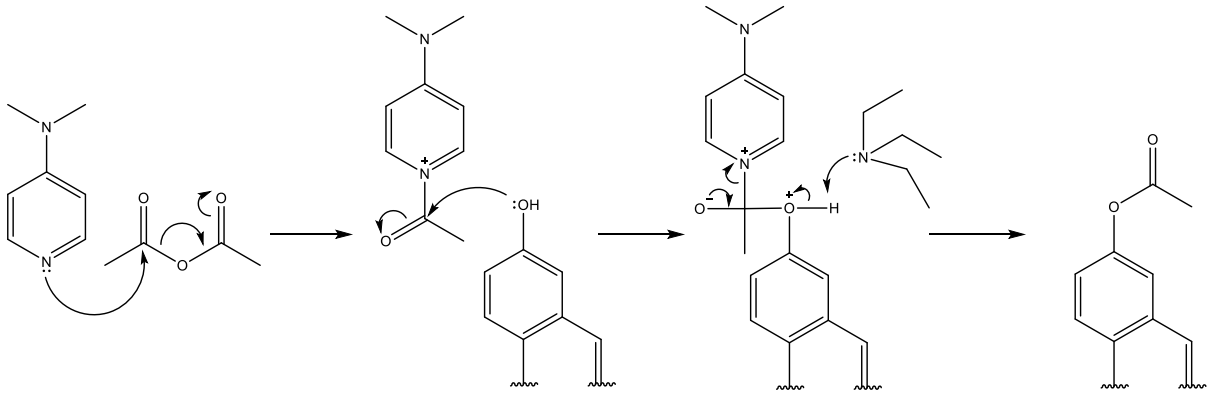
2.2.2.2 Synthesis of 2,4-dichlorophenanthridin-8-yl acetate (70)

Another way to synthesize esters are the reaction between an alcohol and an acid anhydride. Following literature,[82] compound **70** was synthesized by treating **48a** with Ac_2O and 4-dimethylaminopyridine (DMAP) in DCM (Scheme 2.10).



Scheme 2.10: Synthesis of 2,4-dichlorophenanthridin-8-yl acetate (**70**), from 2,3-dichlorophenanthridine-8-ol (**48a**).

DMAP works as a catalyst, binding with Ac_2O and forming an acylpyridinium cation (Scheme 2.11). The cation reacts with the oxygen in compound **48a** and form compound **70** and the deactivated protonated catalyst. To regenerate the catalyst, TEA deprotonates the catalyst.[83]

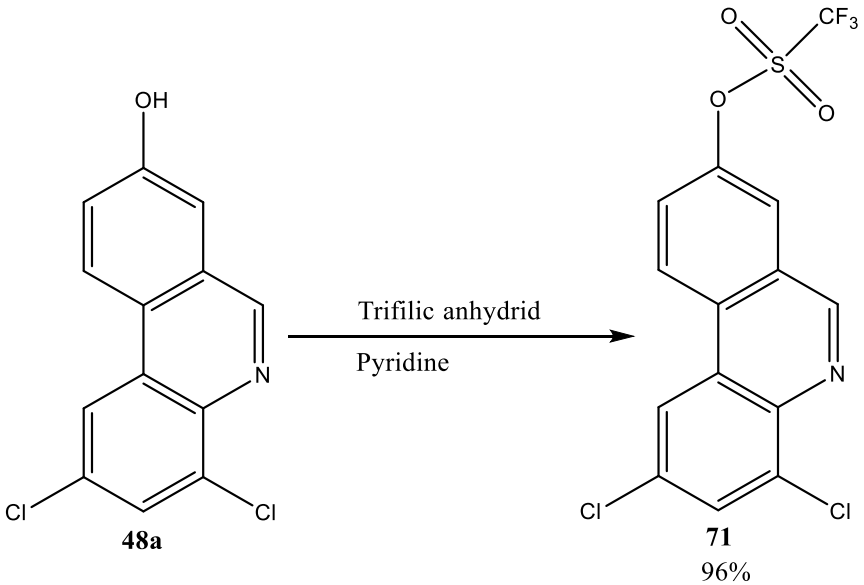


Scheme 2.11: Mechanism for acyl transfer to form compound **70** by DMAP as catalyst.[83]

2.2.3 Triflation and Suzuki coupling reaction

2.2.3.1 Synthesis of 2,4-dichlorophenanthridin-8-yl trifluoromethanesulfonate (71)

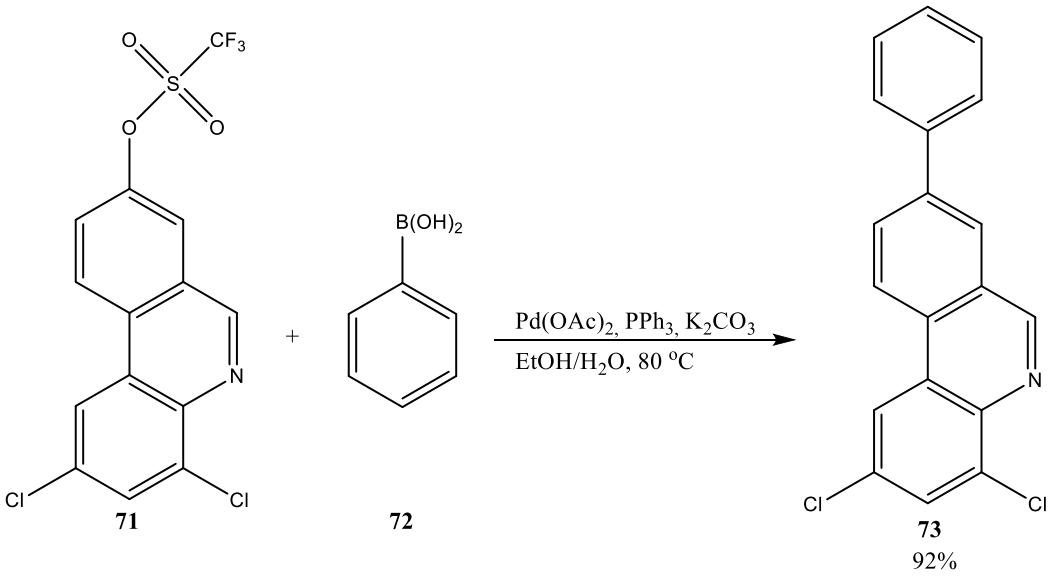
Following literature procedure[5] compound **48a** was treated with trifilic anhydride in pyridine (Scheme 2.12). The triflation produced compound **71** in a higher yield than reported.



Scheme 2.12: Triflation of compound **48a** to produce compound **71**.

2.2.3.2 Synthesis of 2,4-dichloro-8-phenylphenanthridine (73)

Compound **71** was further used in a Suzuki coupling reaction with phenylboronic acid, producing 2,4-dichloro-8-phenylphenanthridine (**73**) (Scheme 2.13). This led to a yield of 92%.



Scheme 2.13: Suzuki coupling reaction of **71** and **72**, to form **73**.

2.2.4 Conclusion

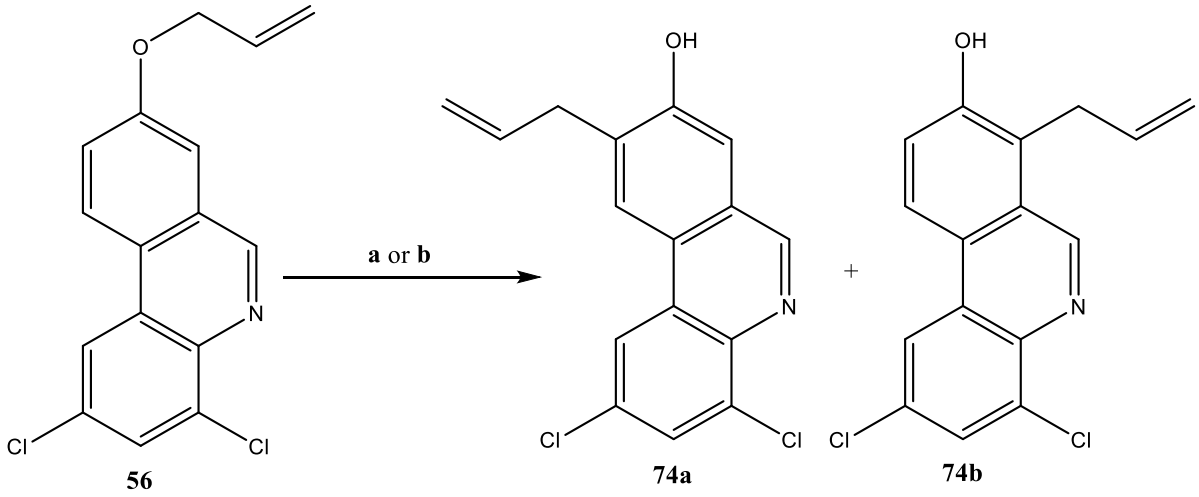
A total of 14 phenanthridines were synthesized utilizing the 8-position of the 8-hydroxyphenanthridines. Ten *O*-alkylated products (**55-64**), two phenanthridine esters (**69, 70**), 2,4-dichlorophenanthridin-8-yl trifluoromethanesulfonate (**71**) and 2,4-dichloro-8-phenylphenanthridine (**73**) were produced with yields between 78-98%. 8-(Allyloxy)-2,4-dichloro-5-methyl-5,6-dihydrophenanthridine (**64**) oxidized upon storage, leading to 8-(allyloxy)-2,4-dichloro-5-methylphenanthridin-6(5*H*)-one (**65**). For further functionalization on compound **64**, it needs to be stored in inert gas with no access to air. Because of sudden lockdown of the university due to the COVID-19 pandemic, there was no time to do it.

2.3 Claisen rearrangement

For further functionalization of 8-hydroxyphenanthridines a Claisen rearrangement was used to achieve 8-hydroxyphenanthridines with substitutes in *ortho*-position to the hydroxy group.

2.3.1 Screening of conditions for the microwave-mediated Claisen rearrangement of 8-(allyloxy)-2,4-dichlorophenanthridine (56)

Following literature procedure for Claisen rearrangement of other substrates[84] 8-(allyloxy)-2,4-dichlorophenanthridine (**56**) was dissolved in *N*,*N*-diethylaniline and irradiated with microwaves in a microwave reactor at 250 °C in one hour (Scheme 2.14). The solution was quenched with EtOAc and washed with aqueous 1 M HCl solution to remove *N*,*N*-diethylaniline. The ^{1}H NMR spectrum from the crude product showed full conversion from **56** to one of the desired products **74**. Three more reactions with *N*,*N*-diethylaniline were performed with changes of reaction time and temperature shown in Table 2.2.



Scheme 2.14: Claisen rearrangement of 8-(allyloxy)-2,4-dichlorophenanthridine (**56**) to produce compound **74**. **a** — *N*,*N*-diethylaniline, 250 °C. **b** — Toluene, 250 °C.

Even though the spectrum from the crude product for both reaction 1 and 2 showed full conversion, the yields after purification were low. By testing the acidic water phase on TLC-paper it was found that some of the product was in the aqueous solution.

Nitrogen containing aromatic rings can be protonated and form aromatic cations and salts. The lone pair of electrons, which are not part of the aromatic system, gives the basicity of these nitrogenous bases.[85,86] Since the solution is washed with 1M HCL aq., is there a possibility that the acid protonated the nitrogen of the phenanthridine forming a phenanthridine cation. The cation is attracted by the negative side of the water, and thereby dissolved in the water phase. This gives a decrease of the isolated product since some of the phenanthridine is in the water phase. The reason for washing the solution with 1 M HCL aq. Is the boiling point of *N,N*-diethylaniline. With a boiling point at 216 ^{o}C is it difficult to evaporate *in vacuo*. Toluene on the other hand has a boiling point at 111 ^{o}C and can be evaporated under reduced pressure. The solvent was thereby changed to toluene for the two next reactions. From all six reactions the best conditions were toluene as solvent, 45 min reaction time and temperature at 250 ^{o}C, resulting in a high yield.

Table 2.2: Screening of conditions for Claisen rearrangement of compound **56**.

Entry	Solvent	Reaction time	Temperature	Yield	Product distribution[a]	
					56	**74**
1	*N,N*-diethylaniline	60min	250^{o}C	45%	0	100
2	*N,N*-diethylaniline	45min	250^{o}C	47%	0	100
3	*N,N*-diethylaniline	60min	200^{o}C	18%	55	45
4	*N,N*-diethylaniline	30min	250^{o}C	40%	14	86
5	Toluene	30min	250^{o}C	70%	17	83
6	Toluene	45min	250^{o}C	95%	0	100

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

Both 7-position and 9-position of compound **56** are *ortho*-positions to the hydroxy group (Figure 2.3). From ^{1}H NMR of compounds **74** the peaks were equal to only one of the isomers **74a** and **74b**, since a mixture of both would give different peaks for position 7 and 9. By looking at the correlated spectroscopy (COSY) spectrum (Figure 2.4) two correlating peaks with *J*-coupling at 8.9 Hz were detected. For *J*-coupling that high, the protons need to be close to each other. The only protons to give a *J*-coupling at 8.9 Hz are the ones in 9- and 10-position, which means that the allyl attaches to the 7 position under the Claisen

rearrangement. If the allyl attaches to the 9-position, there would be a correlation in the HMBC spectrum between the protons in 1'-position and carbon 10. Since the only correlations for protons in 1'-position are between tertiary carbons, except the other carbons in the allyl group, will the allyl group be selective towards the 7-position, giving compound **74b**.

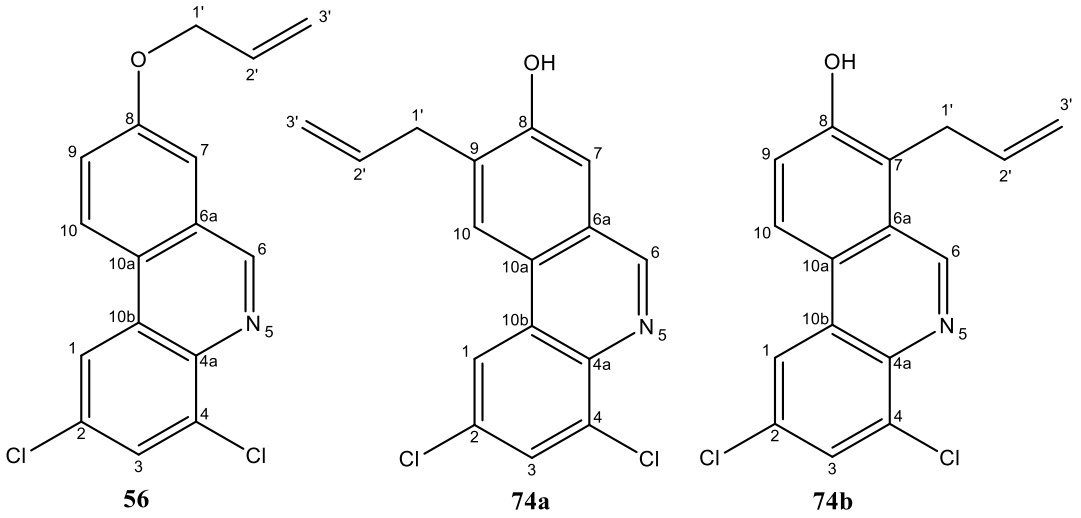


Figure 2.3: Structure and numbering of compound **56**, **74a** and **74b**.

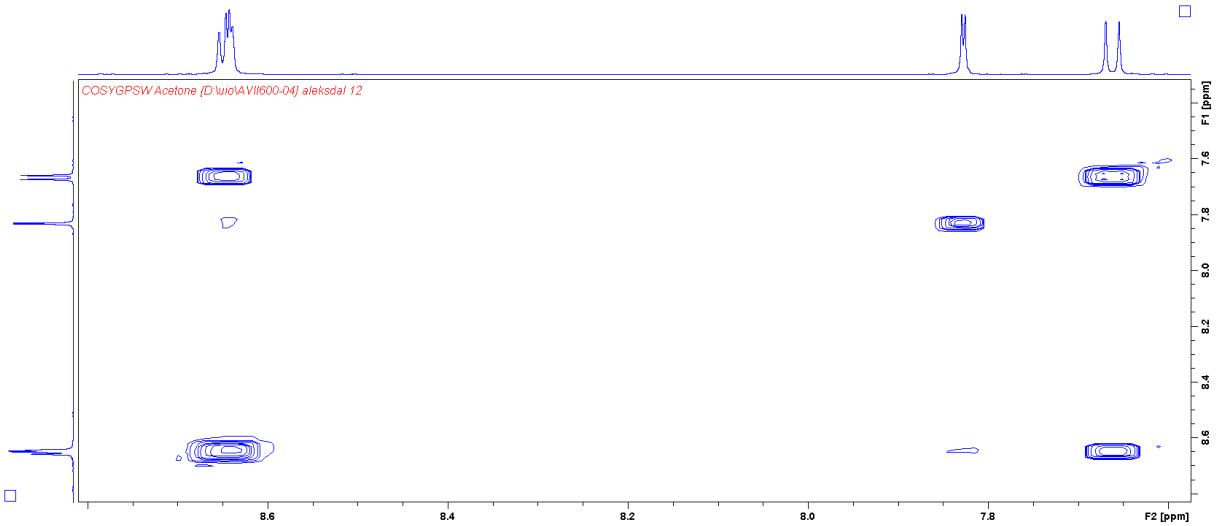
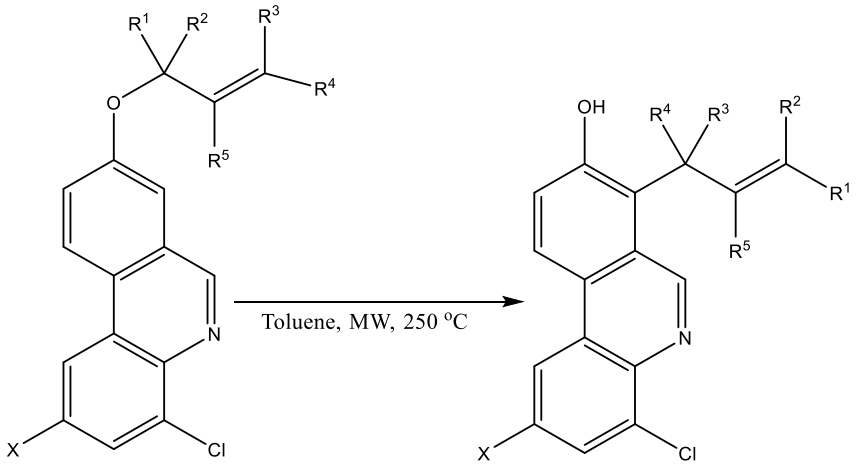


Figure 2.4: COSY spectrum of the product, zoomed in on the aromatic area.

2.3.2 Four *ortho* substituted 8-hydroxyphenanthridines synthesized by Claisen rearrangement

Compounds **75-78** were synthesized from compounds **57, 60-62** using the same conditions as entry 6 in table 2.2 (Scheme 2.15). From the ^{1}H NMR crude product spectra all four reaction had full conversion. The compounds were difficult to dissolve in DCM, EtOAc or acetone and therefore hard to transfer to the flash column. Some of the compounds were lost in both transfer and in the flash chromatography column resulting in the yields shown in table 2.3. The table also gives detail of substrate X and the R groups.



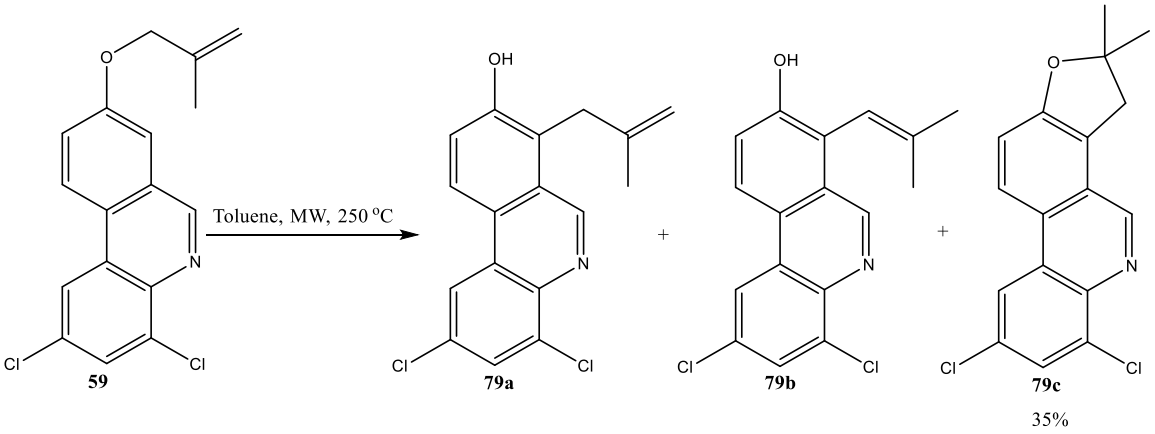
Scheme 2.15: Claisen rearrangement of **57**, **60-62** to produce **72-75**.

Table 2.2: Details for substituents and yield for each reaction.

SM	R^1	R^2	R^3	R^4	R^5	X	Product	Yield
57	H	H	H	Me	H	Cl	**75**	78%
60	H	H	H	H	Cl	Cl	**76**	83%
61	H	H	H	H	H	NO_2	**77**	63%
62	H	H	H	H	H	H	**78**	86%

2.3.3 Synthesis of 2,4-dichloro-7-(2-methylallyl)phenanthridin-8-ol (79a), 2,4-dichloro-7-(2-methylprop-1-en-1-yl)phenanthridin-8-ol (79b) and 6,8-dichloro-2,2-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridine (79c)

The same conditions as previous Claisen rearrangements were used to synthesize compound **79a** from compound **59** (Scheme 2.16). TLC of the fractions from flash chromatography indicated two compounds. The ^{1}H NMR spectrum of the least lipophilic fraction showed a mixture of two compounds in 57:43 ratio calculated by the peaks at 9.45 and 9.28 ppm (Figure 2.5). The reason for the high proton shift values are the electron withdrawing nitrogen that is bonded to the carbon the proton is attached to. This means that these two protons are bonded to carbon 6 in each molecule and can be written as H-6. Since both compounds had very similar lipophilicity, they were difficult to separate. Other purification methods, like HPLC, were not used due to lack of time.



Scheme 2.16: Claisen rearrangement of compound **59** to produce compounds **79**.

Two broad singlets at 10.36 and 10.15 ppm are hydroxy groups, one in each molecule, because of the integral values. The three peaks below 3 ppm indicates methyl groups where two peaks, at 1.47 and 2.04 ppm, integrates to around the same. These two is in the same molecule as the proton peak at 9.28 ppm. By looking at the peaks between 6.5 and 3 ppm the peak at 6.39 belongs to the proton peak at 9.28, because of the integral value. Putting all this together gives two structures where one is the desired product **79a**, while the other is the biproduct **79b**.

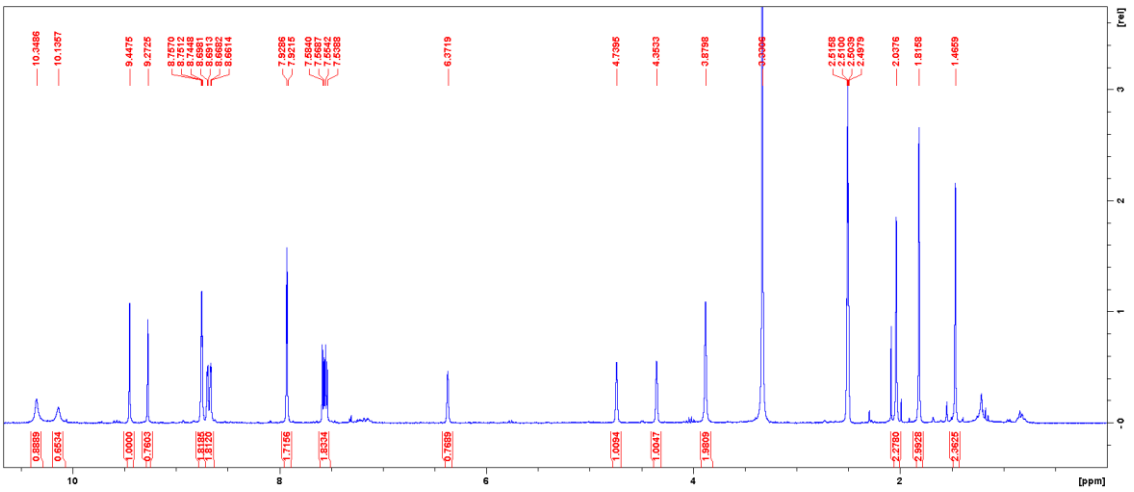


Figure 2.5: ^{1}H NMR spectrum of the mixture of compound **79a** and **79b**.

In the ^{1}H NMR spectrum (Figure 2.6) of the most lipophilic compound one proton singlet peak at 1.56 ppm integrated to 6 which means two methyl groups in the same chemical environment. A peak integrating to two can also be observed as a singlet at 3.55 ppm. This peak must be a CH_2 and belongs to the attached group. Since both the methyl peak and CH_2 peak are singlets, these carbons are bonded to tertiary carbons. A hydroxy group are not visible, which means that it is not present in the molecule, or that the oxygen is part of a ring system. In the HMBC spectrum, the protons in the CH_2 have correlations between the methyl groups and tertiary carbons. From this observation, the CH_2 is bonded to the carbon in 7-position since a bond with the carbon in 9-position results in a correlation between a CH. This resulted in the structure shown in figure 2.5. MS also gave the same amounts of atoms as the structure.

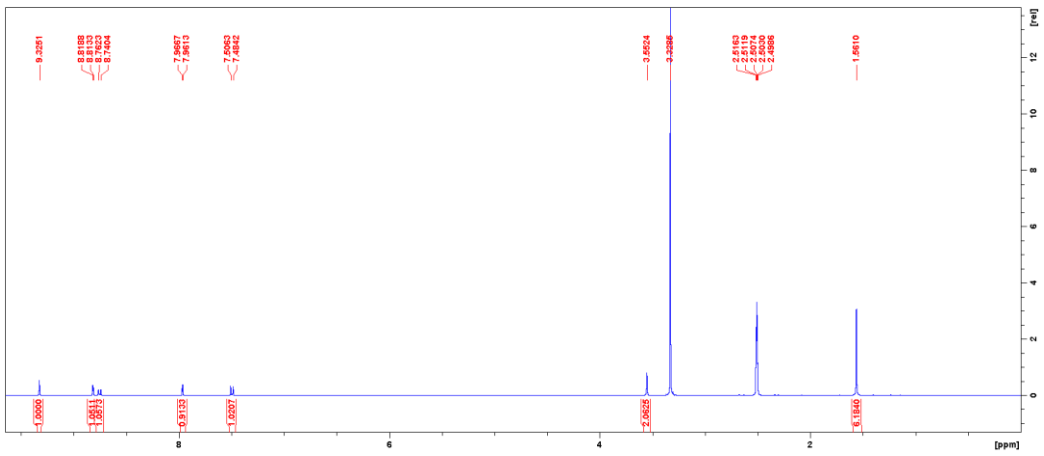
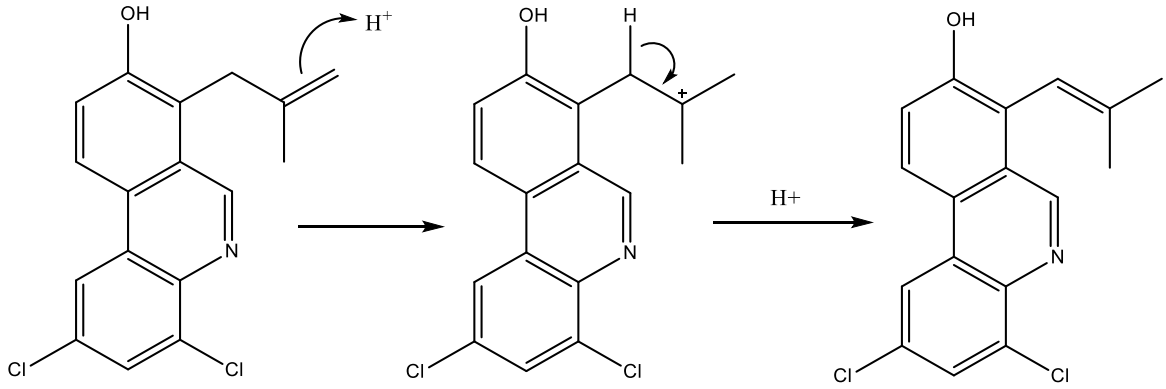
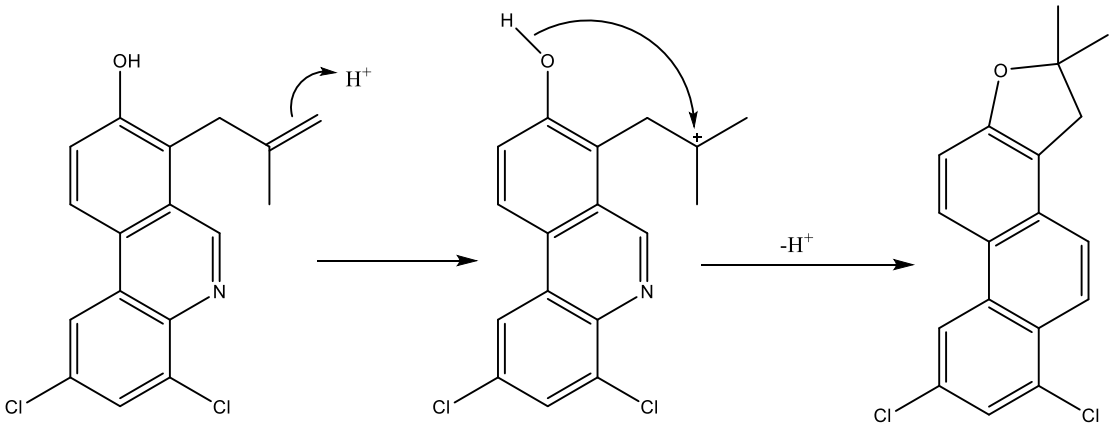


Figure 2.6: ^{1}H NMR spectrum of compound **79c**.

Both biproducts (**79b**, **79c**) can be formed after a formation of a carbocation intermediate from compound **79a**. To form the carbocation, protonation of the double bond occurs, resulting in a positive tertiary carbon. A new double bond is formed when a carbon-proton bond binds with the positive tertiary carbon, resulting in the formation of compound **79b** (Scheme 2.17). It can be assumed that 2-methylprop-1-en-1-yl is thermodynamically more stable than 2-methylallyl since the double bond is conjugated and more substituted.[87] Formation of the ring in compound **79c**, occurs when the bond between the hydrogen and oxygen in the hydroxy group attacks the positive tertiary carbon resulting in ring closer (Scheme 2.18).



Scheme 2.17: Mechanism for the migration of the double bond to form 2,4-dichloro-7-(2-methylprop-1-en-1-yl)phenanthridin-8-ol (**79b**).



Scheme 2. 18: Mechanism for the ring closing to form 6,8-dichloro-2,2-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridine (**79c**).

Compound **59** formed a carbocation which lead to two biproducts (**79b, 79c**), where the other allyloxy phenanthridines (**56**,**57**,**60**-**62**) formed the expected products. There is no use of acid in the Claisen rearrangement, so a reason could be contamination or that the amount needed for the formation to happen is so small that it is unavoidable. Metal cations can also work as a Lewis acid (LA) to form the carbocation. The stability of carbocations depends on the substitution of the carbon (Figure 2.7). Higher substitution, better stability. Tertiary carbocations are fully substituted, and therefore most stable.[51,53] The allyl groups in compounds **74, 75, 77** and **78** can only produce secondary carbocations, which are less stable. Compound **76** and **79a** have both a tertiary carbon in the allyl group. The difference is the chloride substitution in compound **76** and a methyl group in compound **79a**. Although compound **76** has a tertiary carbon in the allyl group, the carbocation is not formed. The reason could be that a tertiary carbocation with a withdrawing chloride substituent is not stable enough, and therefore not formed. Another reason could be that since they are different reaction the synthesis of compound **74** is not contaminated, and no acid or metal ion is present to form the carbocation.

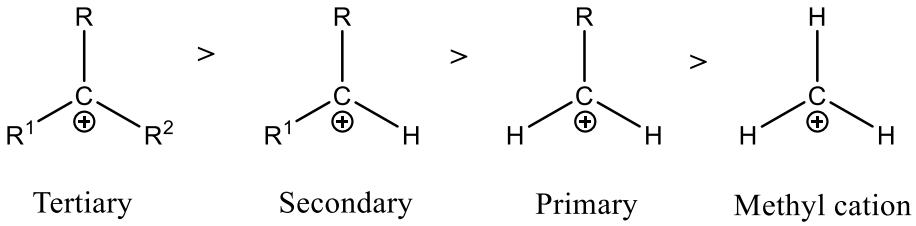
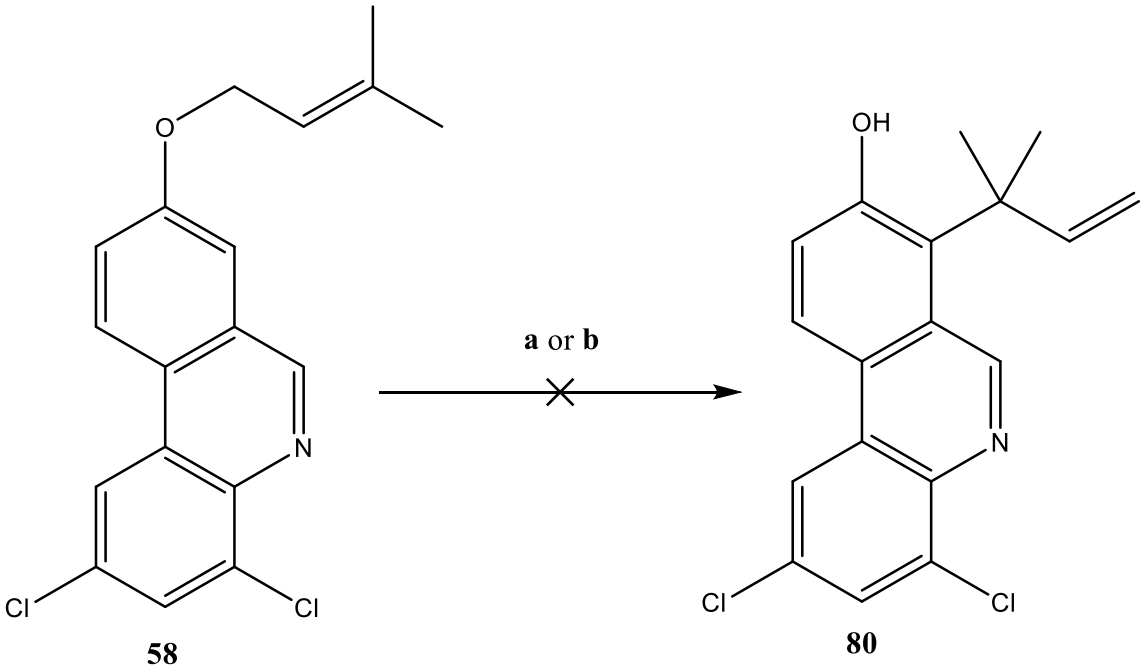


Figure 2.7: Order of stability of carbocations.[51]

2.3.4 Attempts to synthesize 2,4-dichloro-7-(2-methylbut-3-en-2-yl)phenanthridin-8-ol (80)

Claisen rearrangement of compound **58** did not occur to form compound **80** (Scheme 2.19). Instead the 2-methylbut-3-en-2-yl group was cleaved off resulting in 2,4-dichlorophenanthridine-8-ol (**48a**).



Scheme 2.19: Synthesis of **80** from **58**. **a** – Toluene, 250 ºC. **b** – *N*,*N*-diethylaniline, 250 ºC.

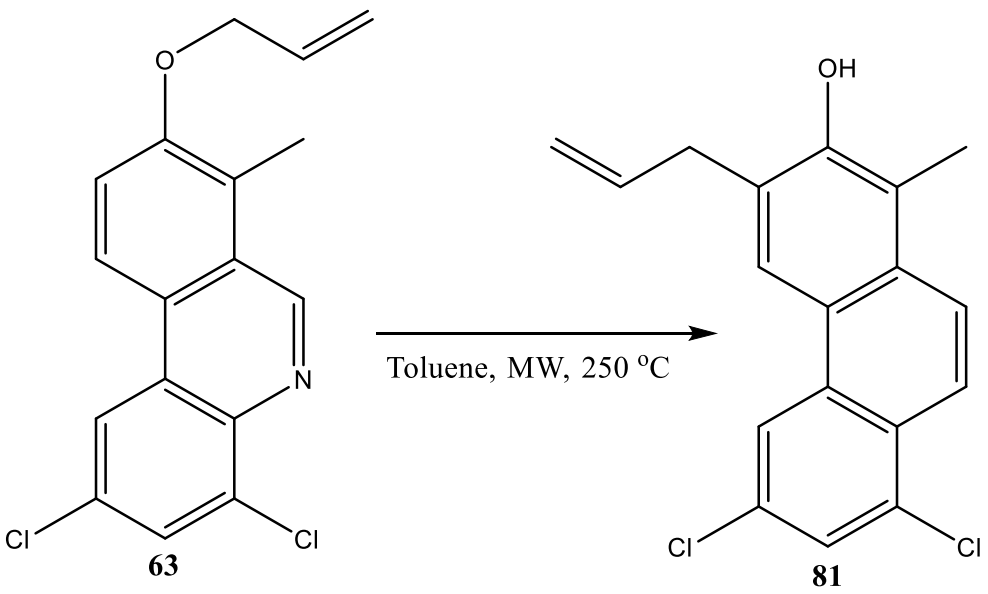
Three reactions with toluene as solvent made the septum lid crack, because of the pressure. The vapor pressure of a solvent increases quickly when it is heated above its boiling point. Since the Claisen rearrangement requires 250 ºC, the choice of solvent is important. For the reactions explained earlier is toluene a great solvent to use, since it evaporates *in vacuo*, leaving only the crude product. The lower the boiling point for a solvent is, the bigger the pressure gets with high temperature.[88-90] Toluene has a boiling point at 111 ºC which makes the pressure higher then with *N*,*N*-diethylaniline that have a boiling point at 216 ºC. Thereby one more reaction with *N*,*N*-diethylaniline were carried out for the lid to withstand the pressure. Even though the lid did not crack, it ended with the same result leading to compound **48a**. 60-85% of compound **48a** where isolated by flash chromatography (Table 2.4).

Table 2.4: Isolated 2,4-dichlorophenantridine-8-ol (**47a**) from the Claisen rearrangements of 2,4-dichloro-8-((3-methylbut-2-en-1-yl)oxy)phenanthridine (**56**).

Entry	Solvent	Compound 48a
1	Toluene	60-85%
2	*N*,*N*-Diethylaniline	73%

2.3.5 Synthesis of 9-allyl-2,4-dichloro-7-methylphenanthridin-8-ol (81)

The earlier results indicate that the 7-position is more reactive towards Claisen rearrangement then the 9-position. In compound **63** is the 7-position already occupied by a methyl group resulting in allyl rearrangement to the 9-position (Scheme 2.20). Theoretically will rearrangement for the allyl to 9-position have a longer reaction time for conversion since it is less reactive.



Scheme 2.20: Synthesis of 9-allyl-2,4-dichloro-7-methylphenanthridin-8-ol (**81**) from 8-(allyloxy)-2,4-dichloro-7-methylphenanthridine (**63**).

In the first reaction the septum lid cracked, resulting cleavage of the allyl group to give 2,4-dichloro-7-methylphenanthridine-8-ol (**51**). The second reaction stood for 3 h in the microwave reactor before the solvent was evaporated *in vacuo* and purified by flash chromatography. The TLC of the fractions showed two compounds where the most lipophilic was the unconverted allyloxy compound (**63**) with an isolated yield of 47% (9 mg). Two compounds where observed in the ^{1}H NMR spectrum of the least lipophilic compound in ratio 63:37 (Figure 2.7). By comparing ^{1}H NMR of compound **51** against the ^{1}H NMR of the mixed compound, the peaks of **51** can be observed in both (Figure 2.8). The peaks at 9.59, 8.68 and 8.54 ppm do not overlap with the spectrum peaks of **51** and belongs to the other molecule. The peak at 7.83 ppm integrates for 1.54, which means 1 proton from **51**, and one

for the other molecule. The peaks between 7 and 3 ppm is characteristic for the allyl group and belongs to the least produced compound. By looking at the proton distribution of the integrated peaks in the aromatic area, 5 protons belong to compound **51**, while 4 belong to the other compound. Looking at the *J*-couplings for each peak at the aromatic area for the unknown compound, peak 8.68 couples with 7.72. Since the coupling is small the protons are H-1 and H-3, seen in figure 2.9 and 2.10. The last peak at 8.54 is a singlet and do not couple with another proton. This must be H-10 since the allyl group is attached to 9-position. The value from the MS were also the same as the calculated mass of compound **81**. From all this information the spectrum in figure 2.7 is of **51** and **81** in ratio 63:37.

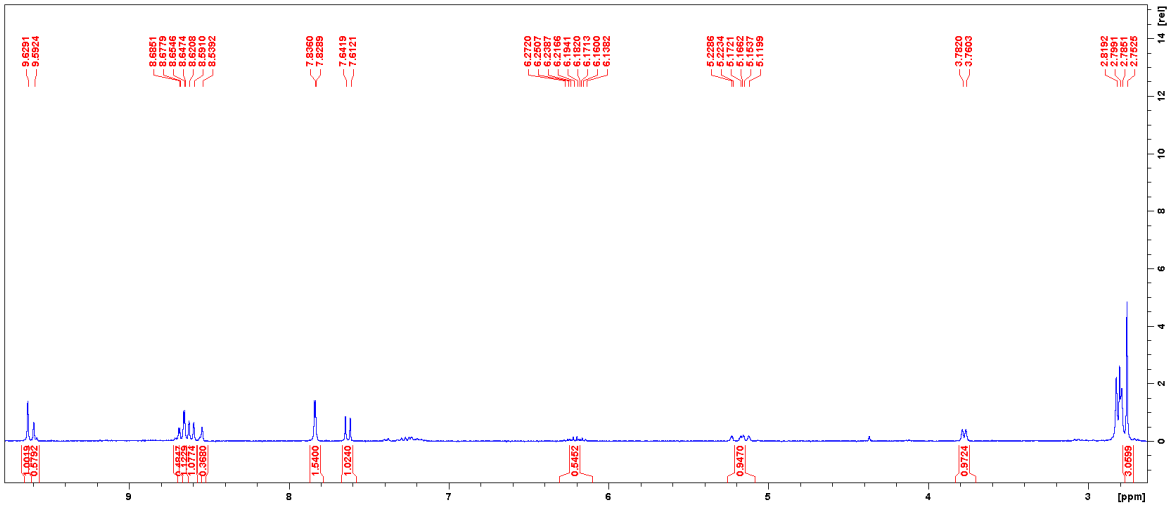


Figure 2.7: ^{1}H NMR spectrum of a mixture of compounds **81** and **51**.

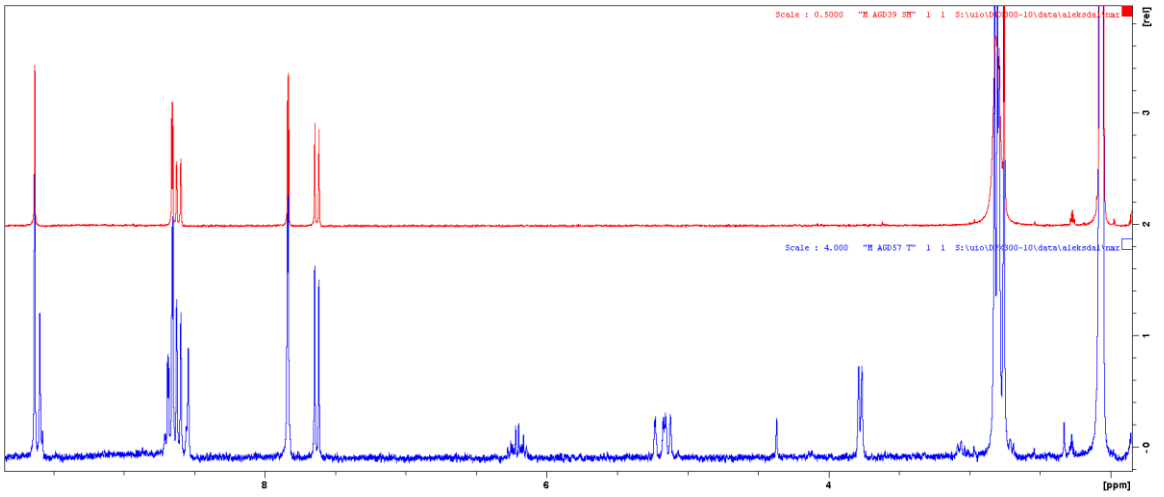


Figure 2.8: Spectra of compound **51** (upper) against the mixed compound (lower).

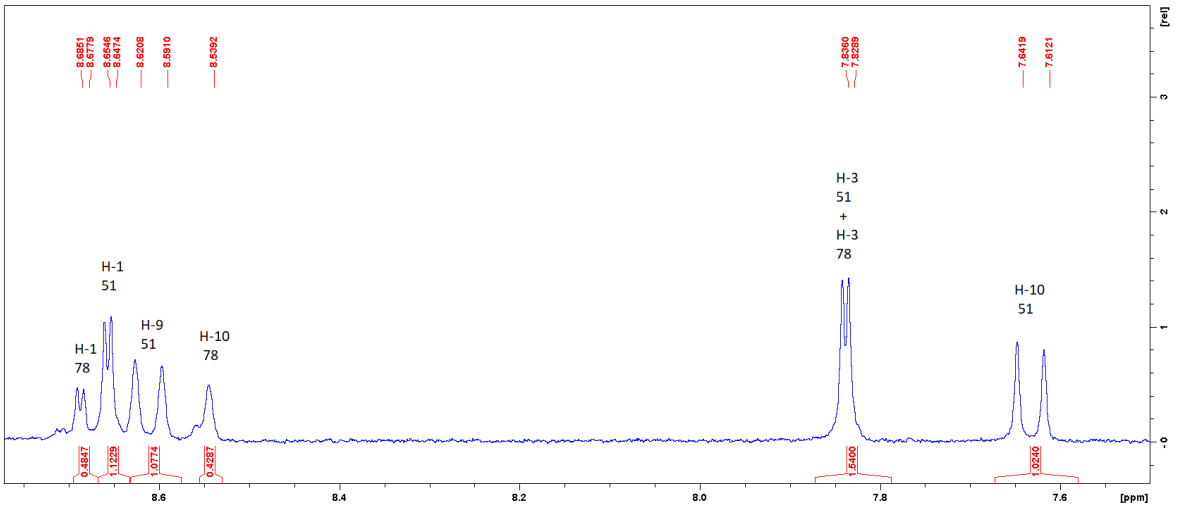


Figure 2.9: Zoomed in spectrum of the aromatic area, with numbering of compound **51** and **81**.

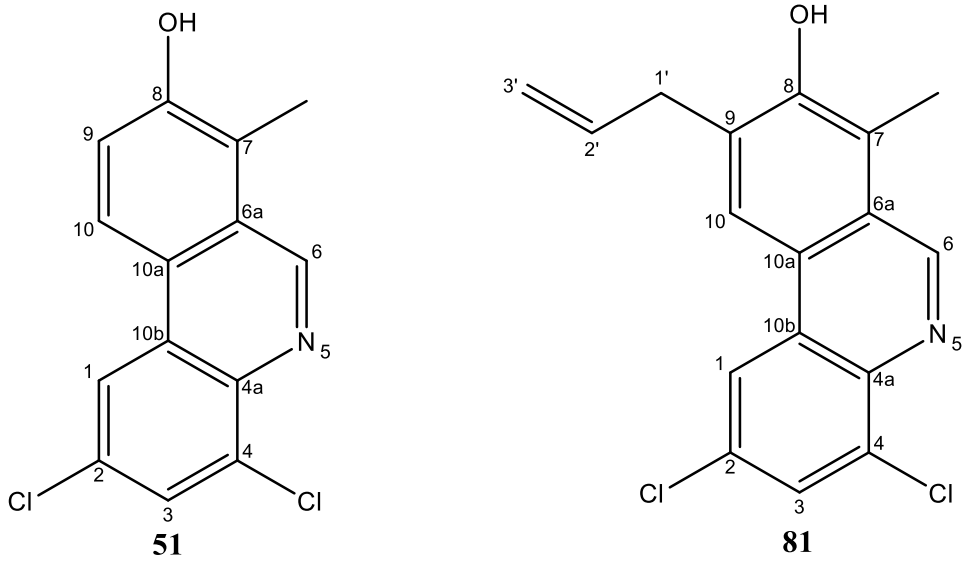
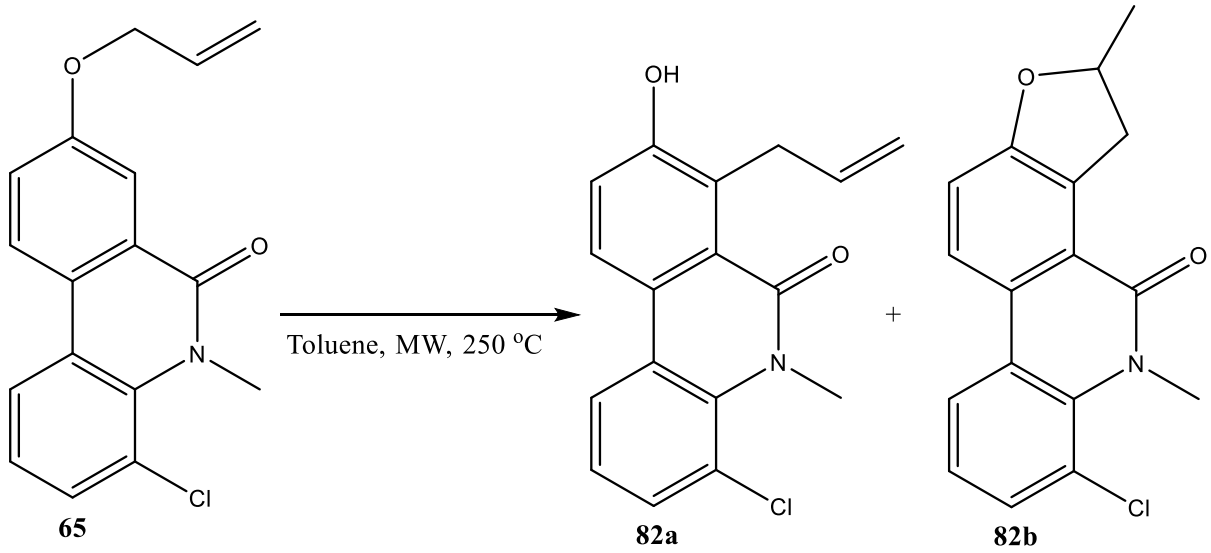


Figure 2.10: Structure with numbering of compound **51** and **81**.

The amount of the mixture was too small for further analysis. 4 mg was isolated, which gave a ^{1}H NMR, and COSY spectrum but not readable ^{13}C NMR, DEPT, HSQC and HMBC spectra. By looking at the ratio between compound **63** and **81**, and the amount of the isolated mixture, the yield for each compound was calculated to 13% of **63** and 8% of **81.** Compound **51** was synthesized by another member of our group. 53 mg of **63** was synthesized of the amount given of **51.** After two reactions with **63**, no more compound was left. With the lab time available there was no time to synthesize more of **63**.

2.4.8 Synthesis of 7-allyl-4-chloro-8-hydroxy-5-methylphenanthridin-6(5H)-one (82a) and 6-chloro-2,5-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridin-4(5H)-one (82b)

Claisen rearrangement of 8-(allyloxy)-4-chloro-5-methylphenanthridin-6(5H)-one (**65**) produced two compounds shown in Scheme 2.21.



Scheme 2.21: Synthesis of 7-allyl-4-chloro-8-hydroxy-5-methylphenanthridin-6(5H)-one (**82a**) and 6-chloro-2,5-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridin-4(5H)-one (**82b**) from 8-(allyloxy)-4-chloro-5-methylphenanthridin-6(5H)-one (**65**).

Figure 2.11 is a 1H NMR spectrum of compound **82b**. The aromatic area shows peaks integrating to a total of five. That means the allyl group has made a bond with 7-position. There is no visible hydroxy peak in the spectra, which means that it is not present in the molecule, or that the oxygen is part of a ring system. There are two methyl groups at 3.69 and 1.35 ppm. The peak at 3.69 is a singlet and is bonded with the nitrogen. The second is a dublet and is bonded with a CH. The only CH, except the ones in the aromatic area, is the multiplet at around 4.95. Since it is a multiplet and not a quaternary peak it must have a correlation to the protons at 3.83 and 3.25 ppm. These two peaks have a *J*-coupling value at 17.8, which means they are bonded to the same carbon. Calculated mass of **82b** and the value from MS was the same. From all this information Structure **82b** was outlined.

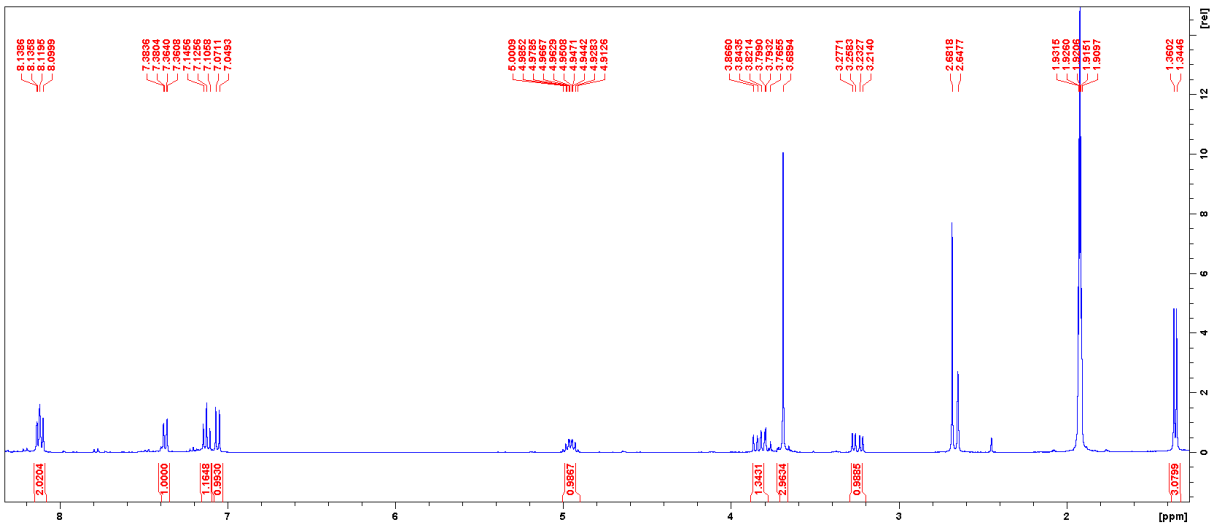
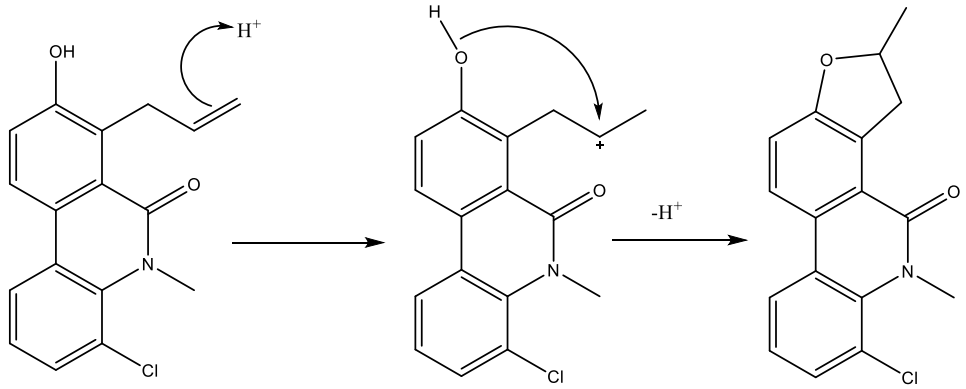


Figure 2.11: ^{1}H NMR of 6-chloro-2,5-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridin-4(5H)-one (**79b**).

Compound **82b** can be formed the same way as **79c** via a carbocation intermediate. The difference is that the carbocation produced is a secondary carbocation which are less stable then the tertiary carbocation. An acid protonates the double bond in the allyl group making a positive carbon (Scheme 2.22). The proton-oxygen bond attacks the positively carbon forming a ring leading to compound **82b.**

3 mg, of compound **82a** was isolated, 23% yield, leading to a ^{1}H NMR spectrum. ^{13}C NMR, DEPT, HSQC and HMBC spectra were too weak to use for analysis. For compound **82b** 5 mg were isolated, 38% yield, leading to a ^{1}H NMR and HSQC spectra and ^{13}C NMR and DEPT spectra without quaternary carons. COSY and HMBC spectra were to weak to use for analysis. MS value and calculated mas were the same.



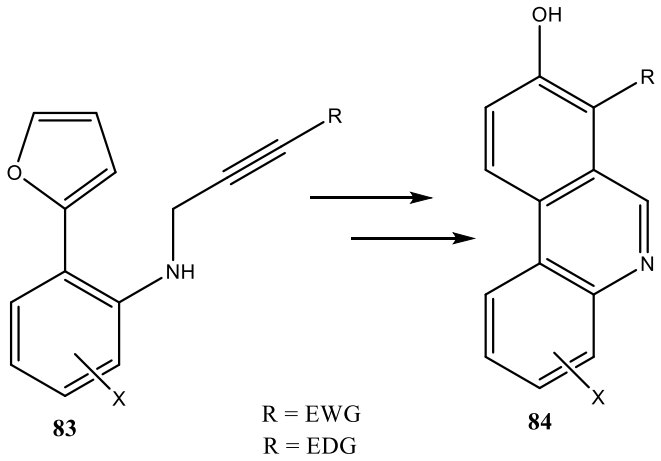
Scheme 2.22: : Mechanism for the ring closing to 6-chloro-2,5-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridin-4(5H)-one (**82b**).

2.4.9 Conclusion

From 8 Claisen rearrangements 5 were synthesized successfully with good yields. It was found that the allyl group was selective towards the 7-position for all 5 8-hydroxyphenanthridines. Claisen rearrangement of **72** gave the desired product **79a**, but some where protonated forming a tertiary carbocation which produced compounds **79b** and **79c**. When rearranging compound **58** no *ortho* substitution occurred, but instead the allyl was cleaved of, producing compound **48a**. By exploring the 9-position, compound **63** where used, which have a methyl group in 7-positon. The reaction took longer and produced compound **51** and small amounts of the desired compound **81**. To see have a non-aromatic B-ring effected the reaction, compound **64** was produced. Because of the second lockdown in the pandemic, compound **64** oxidized to compound **65**. This was used in the Claisen rearrangement and produced the desired compound **82a**. From **82a** a secondary carbocation was formed forming a ring with the oxygen producing compound **82b**.

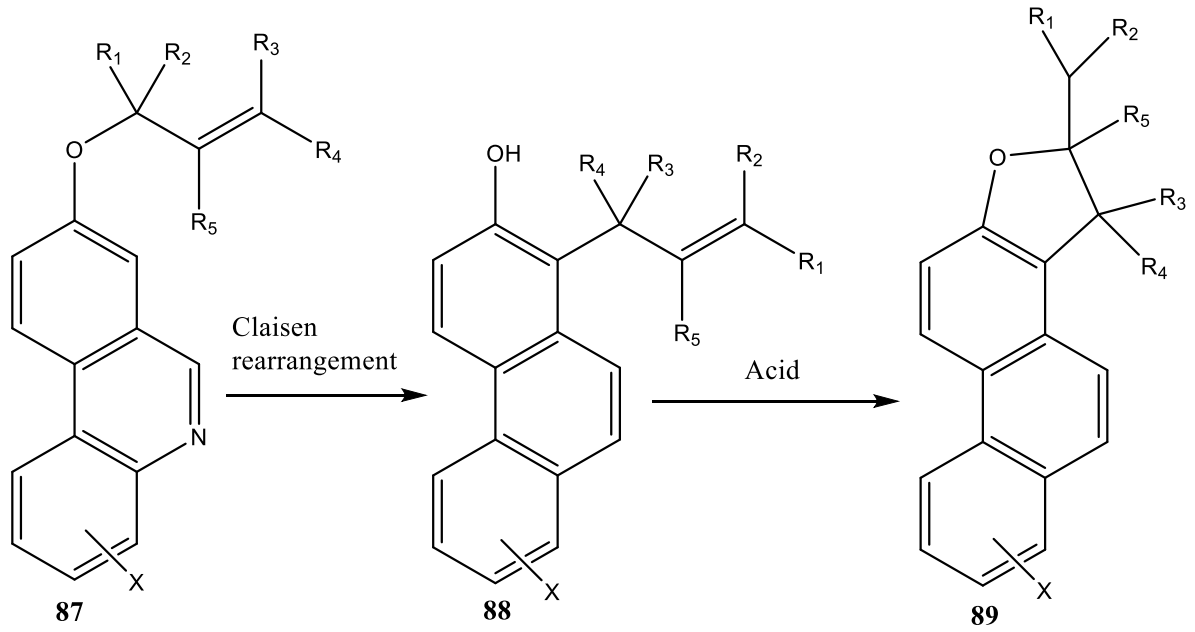
3. Future research

Allyloxyphenanthridins provide opportunities for further functionalization by undergoing a Claisen rearrangement to produce phenanthridine-8-ols with *ortho* allylated to the hydroxy group. Based on the reactions performed in this project is 7-position in phenanthridines more favored in Claisen rearrangement then 9-position. By substitution on the C-ring, it can affect the reaction and may lead to substitution on 9-positon. Since the reaction with 8-(allyloxy)-2,4-dichloro-7-methylphenanthridine (**63**) went poorly, an electron withdrawing group in 7-position may lead to the desired product. A variation in the alkyne dienophile of *o*-furyl-*N*-alkynylaniline substrates produces 8-hydroxyphenanthridines with substitution at R (Scheme 3.1).



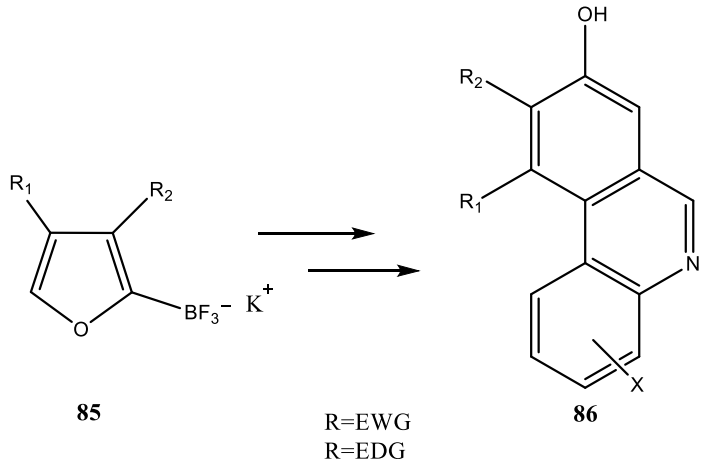
Scheme 3.1: Functionalization of the C-ring at 7-position.

Claisen rearrangement of 2,4-dichloro-8-((2-methylallyl)oxy)phenanthridine (**59**) led to two biproducts were one of them formed a ring with the oxygen. An Acid protonated the double bond leading to a tertiary carbocation which reacted further with the oxygen. By treating compound **88** with acid, full conversion to compound **89** may occur. This reaction can be further investigated by Claisen rearrangement with different substituted allyl groups.



Scheme 3. 2: Claisen rearrangement followed by protonation of the doble bond leading to a cyclic ring.

Another way to functionalize the C-ring is to use substituted potassium (furan-2-yl)trifluoroborates to form 8-hydroxyphenanthridines with C-ring substitution. A substitution at R_1 in scheme 3.2 can lead to a better reactivity towards 9-positon.



Scheme 3. 3: 8-hydroxyphenanthridines with a functionalized C-ring by use of alkylfuranes.

4. Conclusion

During the work of this thesis nineteen phenanthridines where successfully synthesized whereof eighteen not previously reported in the literature.

O-alkylation of 8-hydroxyphenanthridines were successfully synthesized producing compounds **55**-**64, 66**-**68** with high yields. Compound **68**s 8-position where further functionalized by Suzuki coupling, attaching a phenyl forming compound **70**. Since compound **64** oxidized upon storage to **65**, the desired reaction did not occur. **65** were functionalized further with Claisen rearrangement resulting in small amounts of desired product (**79a**) and cyclized biproduct (**79b**).

By microwave-mediated Claisen rearrangement 5 *ortho* substituted 8-hydroxyphenanthridines were synthesized in good yields with selectivity towards the 7-position. Compound **71b** were synthesized from **56** six times with change of reaction time, temperature, and solvent. From these six reactions, the conditions for best yield was 45 min, 250 ^{o}C and toluene as solvent.

Compound **69** gave the desired compound **76a**, but also two biproducts (**76b, 76c**). These were made when **76a** were protonated which produced a tertiary carbocation. The carbocation reacted further, producing compound **76b** and **76c**.

Claisen rearrangement of **58** gave no *ortho* substituted compound **75**, but instead the allyl was cleaved of, producing **48a**.

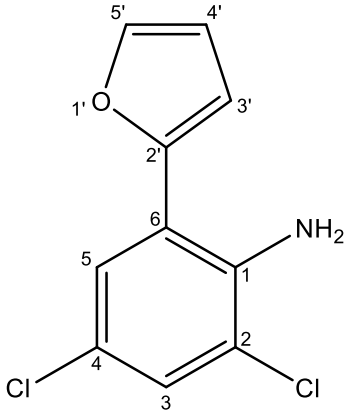
For the 7-position substituted **63**, was the reaction time longer since the attachment of an allyl group in 9-position is not favored. This led to production of compound **51** with small amounts of the desired compound **78**.

Compound **64** has a non-aromatic B-ring to observe what affect it gives the reaction. Claisen rearrangement of compound **64** was not done since it oxidized to **65** while stored under the second lockdown in the COVID-19 pandemic. **65** was further used in the Claisen rearrangement producing compound **79a**. A compound with a ring with the oxygen was also produced since **79a** were protonated and produced a carbocation. The oxygen-hydrogen bond attacked the positively carbon, resulting in a ring structure and compound **79b.**

5. Experimental

Bruker AVII600 instrument, Bruker AVIII400 instrument and Bruker DPX300 were used to record ^{1}H NMR spectra at 600 MHz, 400 MHz and 300 MHz. Bruker AVII600 instrument and Bruker AVIII400 instrument were also used to record decoupled ^{13}C NMR at 150 MHz and 100 MHz. The *J* values are reported in Hertz. To record mass spectra under electron spray, a Micromass Prospec Q instrument was used. For purification of products silica gel (Merck no. 09385) was used in flash chromatography. The dry solvents (DCM, DMF and THF) were collected from a solvent purification system (MB SPS-800 MBraun, Garching, Germany). Pyridine, *N*,*N*-diethylaniline and toluene were distilled before use. Both hexanes and EtOAc were redistilled for use in flash chromatography. For MeCN to be used in cyclisation experiment, it had to be degassed. The freeze-pump-thaw method was used, by crystallizing MeCN with N_2(l) and melting it under high vacuum. This was repeated until bubbles did not appear under the melting part. For microwave experiments a sealed pressure vial was used in a microwave synthesis reactor Monowave 300. By using a Büchi Melting Point B-545 instrument, melting points could be determined. 2-Chloro-6-(furan-2-yl)-4-nitro-N-(prop-2-yn-1-yl)aniline (**47b**),[5] potassium(furan-2-yl)trifluoroborate (**49**),[80] 4-chlorophenanthridin-8-ol (**50**),[80] 2,4-dichloro-7-methylphenanthridin-8-ol (**51**)[80] and 4-chloro-5-methyl-5,6-dihydrophenanthridin-8-ol (**53**)[80] were synthesized according to literature procedures by other members of our group. The rest of the reagents were commercially available and used as received.

Synthesis of 2,4-dichloro-6-(furan-2-yl)aniline (46)



46

2-Bromo-4,6-dichloroaniline (**45**) (3.00 g, 12.5 mmol), potassium-2-furyltrifluoroborate (**49**) (3.30 g, 19.0 mmol), K_2CO_3 (2.50 g, 18.1 mmol), PPh^3 (0.819 g, 3.12 mmol) and $Pd(OAc)_2$ (0.144 g, 0.641 mmol) were added to a round bottom flask with EtOH (200 mL) and water (10 mL). A condenser with a septum was connected to the flask and the flask was placed in an oil bath at 80 °C. The solution stirred for 5 h before it was concentrated under reduced pressure and isolated by flash chromatography on silica gel eluted with 1:4:45 EtOAc:DCM:hexanes.

Yield: 2.75 g (97%) as a pale pink solid.

Data from literature.[1]

^{1}H NMR (400 MHz, CDCl3) δ 7.52 (dd, *J* = 1.8 and 0.8 Hz, 1H, H-5'), 7.36 (d, *J* = 2.4, 1H, H-5), 7.22 (d, *J* = 2.4, 1H, H-3), 6.63 (dd, *J* = 3.4, 0.8, 1H, H-3'), 6.53 (dd, *J* = 3.4, 1.8, 1H, H-4'), 4.65 (s, 2H, NH2).

HRMS ESI calcd. for $C_{10}H_7Cl_2NO$ 226.9905, found 226.9903

M.p. 66-68 °C.

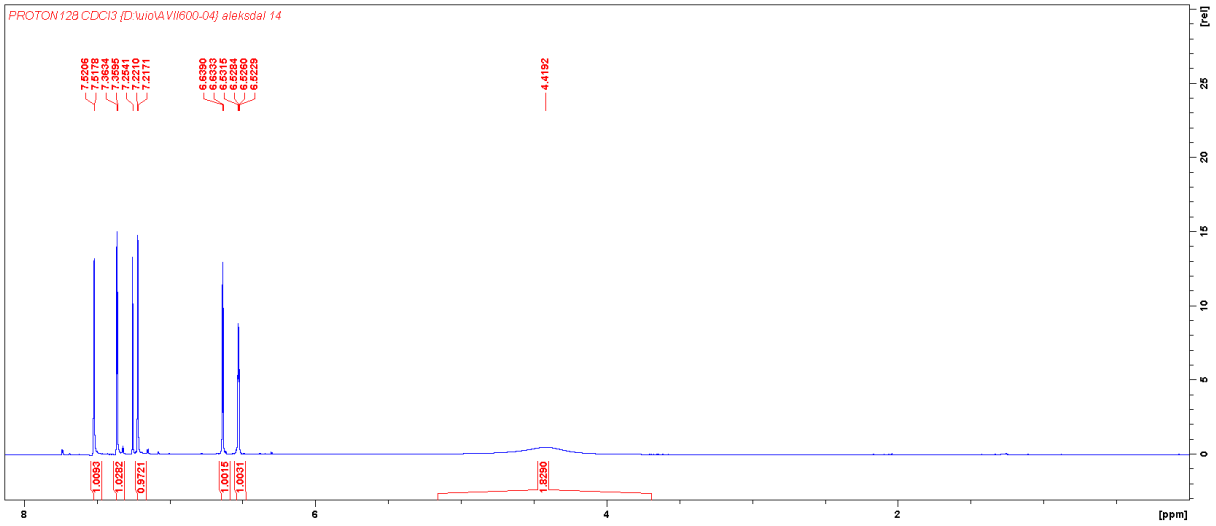
Data from experiment.

^{1}H NMR (400 MHz, CDCl3) δ 7.52 (d, *J* = 1.8, 1H, H-5'), 7.36 (d, *J* = 2.3, 1H, H-5), 7.22 (d, *J* = 2.3, 1H, H-3), 6.64 (d, *J* = 3.4, 1H, H-3'), 6.53 (dd, *J* = 3.4 and 1.8 Hz, 1H, H-4'), 4.42 (s, 2H, NH2).

HRMS ESI calcd. for $C_{10}H_7Cl_2NO$ 226.9905, found 226.9903

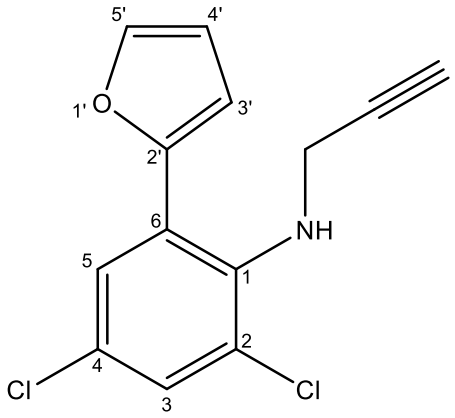
M.p. 67-68 °C.

^{1}H NMR, HRMS ESI and m.p coincides with the literature and no further analysis was performed.[1]



Spectrum 1: 600 MHz, CDCl^3, ^{1}H NMR spectrum of 2,4-dichloro-6(furan-2-yl)aniline (**46**).

Synthesis of 2,4-dichloro-6-(furan-2-yl)-N-(prop-2-yn-1-yl)aniline (47a)



47a

Compound **46** (0.527 mg, 2.31 mmol) and TBAB (1.50 g, 4.62 mmol) were added to a stirring solution of THF (50 mL) in a round bottom flask under argon. An ice bath was used to lower the temperature to around 0 ^{o}C, before NaH (0.111 g, 4.62 mmol, 60% in mineral oil) was added and after 10 min propargyl bromide (0.260 mL, 3.47 mmol) was added with a syringe. The flask was placed in an oil bath at 45 ^{o}C and stirred for 18 h before the solution was transferred to a separation funnel with water (40 mL) and EtOAc (60 mL). The water phase was extracted with EtOAc (60 mL, 50 mL and 45 mL) and the combined organic phases were dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The crude product was isolated by flash chromatography on silica gel eluted with 4:1 hexanes:DCM.

Yield: 0.354g (58%) as a pale pink solid.

Data from literature.[5]

^{1}H NMR (600 MHz, CDCl3): δ = 7.55 (d, *J* = 2.5 Hz, 1 H, 5-H), 7.51 (d, *J* = 1.8 Hz, 1 H, 5'-H), 7.30 (d, *J* = 2.5 Hz, 1 H, 3-H), 6.94 (d, *J* = 3.4 Hz, 1 H, 3'-H), 6.53 (dd, *J* = 3.4, 1.8 Hz, 1 H, 4'-H), 4.33 (br s, 1 H, NH), 3.72 (d, *J* = 2.3 Hz, 2 H, NCH2), 2.18 (t, *J* = 2.3 Hz, 1 H, ≡CH).

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

M.p. 68-69 ^{o}C.

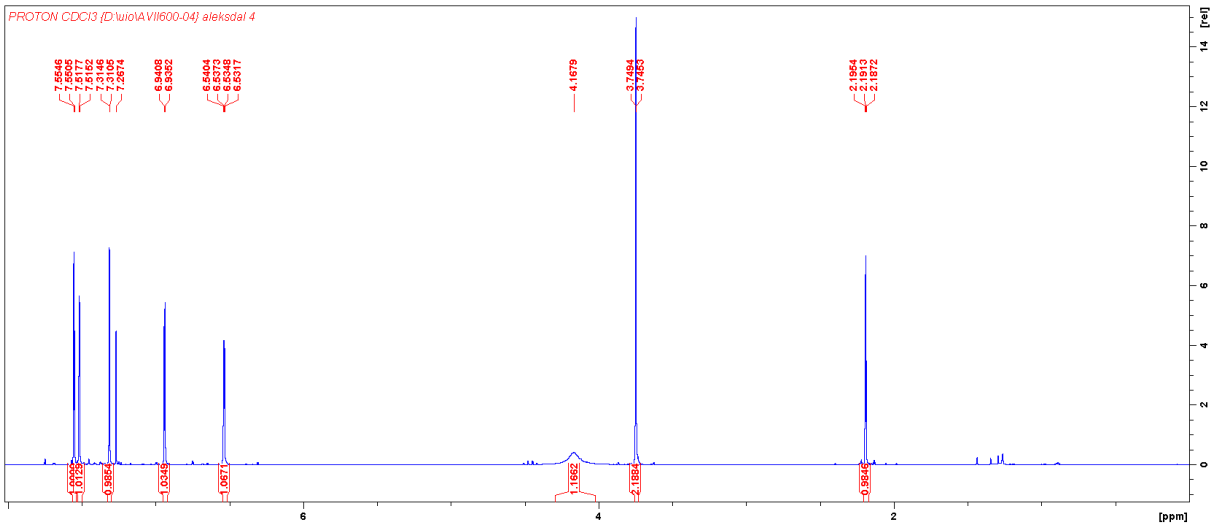
Data from experiment.

^{1}H NMR (600 MHz, CDCl3): δ = 7.55 (d, *J* = 2.5 Hz, 1 H, 5-H), 7.51 (d, *J* = 1.8 Hz, 1 H, 5'-H), 7.31 (d, *J* = 2.5 Hz, 1 H, 3-H), 6.94 (d, *J* = 3.4 Hz, 1 H, 3'-H), 6.54 (dd, *J* = 3.4, 1.8 Hz, 1 H, 4'-H), 4.17 (br s, 1 H, NH), 3.75 (d, *J* = 2.3 Hz, 2 H, NCH2), 2.19 (t, *J* = 2.3 Hz, 1 H, ≡CH).

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

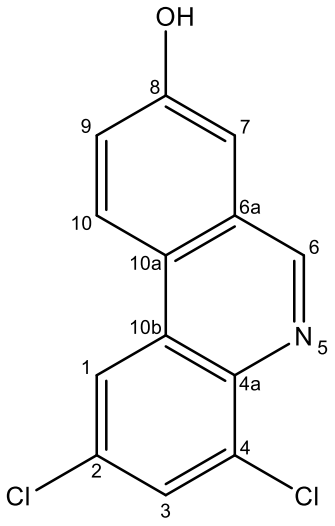
M.p. 68-69 ºC.

^{1}H NMR, HRMS ESI and m.p coincides with the literature and no further analysis was performed.[5]



Spectrum 2: 600 MHz, CDCl3, ^{1}H NMR spectrum of 2,4-dichloro-6-(furan-2-yl)-N-(prop-2-yn-1-yl)aniline (**47a**).

Synthesis of 2,4-dichlorophenanthridin-8-ol (48a)



48a

Compound **47a** (0.867 g, 3.83 mmol) was dissolved in degassed acetonitrile (20 mL) and transferred to a pressure vial. The vial was filled with argon and 2 drops of HCl (0.2 M) was added to the solution. The solution stirred for 2.5 h at 180 ^{o}C in a microwave reactor before it was cooled down to 55 ^{o}C and transferred to a round bottom flask. The crude product was dissolved in dry DCM (30 mL) in a round bottom flask with a septum and DDQ (0.909 g, 4.00 mmol) was added to the solution. After 1.5 h of stirring at r.t, the solution was concentrated under reduced pressure before it was isolated by flash chromatography on silica gel eluted with 5:3:2 hexanes:EtOAc:DCM.

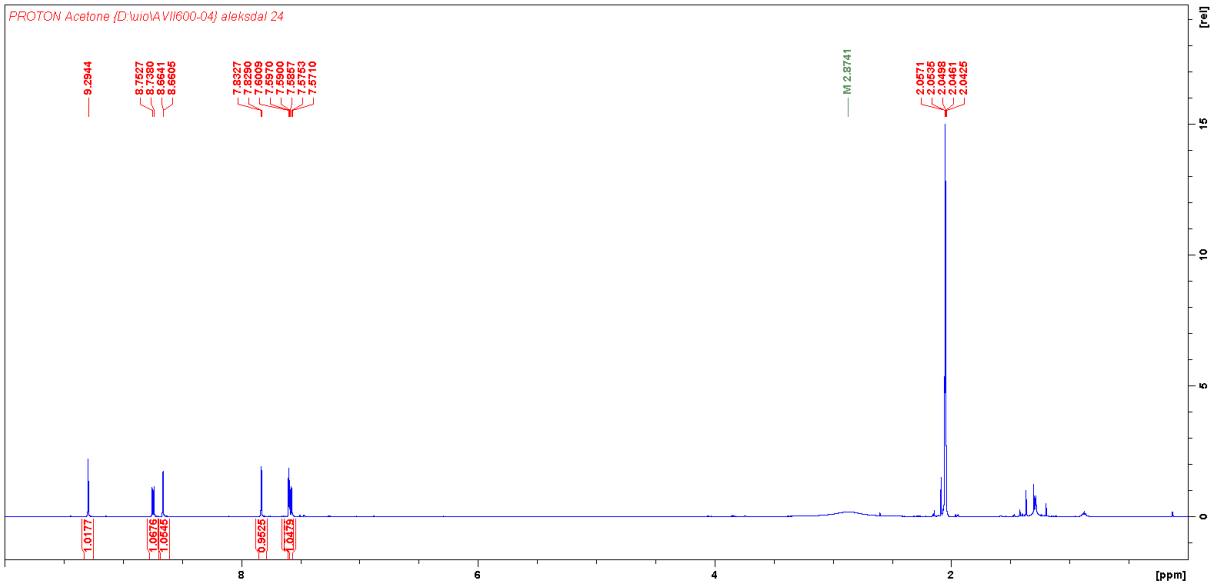
Yield: 0.612 g (71%) as a colorless solid.

^{1}H NMR (600 MHz, Acetone-D_6) δ 9.29 (s, 1H, H-6), 8.75 (d, *J* = 8.8 Hz, 1H, H-10), 8.66 (d, *J* = 2.2 Hz, 1H, H-1), 7.83 (d, *J* = 2.2 Hz, 1H, H-3), 7.80 (d, *J* = 2.4 Hz, 1H, H-7), 7.58 (dd, *J* = 2.5 Hz and 8.8 Hz, 1H, H-9).

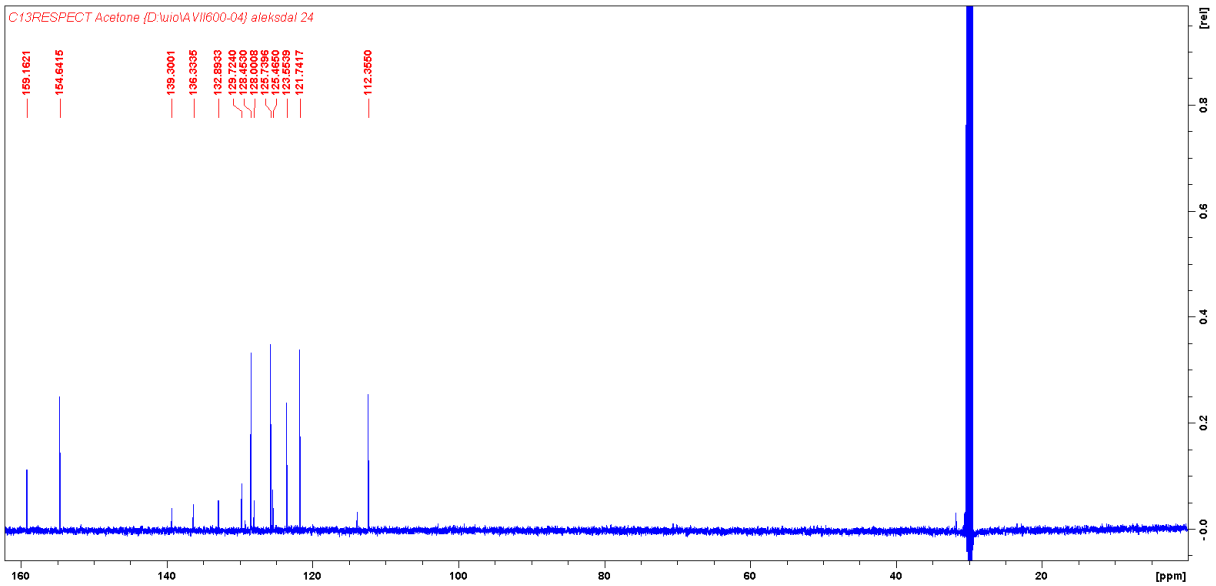
^{13}C NMR (150 MHz, Acetone-D_6) δ 159.16 (C-8), 154.64 (CH-6), 139.30 (C-4a), 136.33 (C-4), 132.89 (C-2), 129.72 (C-6a), 128.45 (CH-3), 128.00 (C-10b), 125.74 (CH-10), 125.47 (C-10a), 123.55 (CH-9), 121.74 (CH-1), 112.36 (CH-7).

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

M.p. 296-297 ^{o}C.

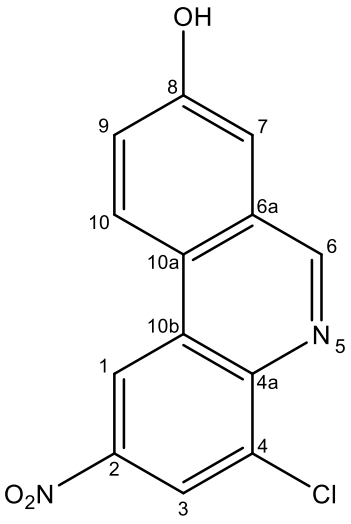


Spectrum 3: 600 MHz, Acetone-D_6, ^{1}H NMR spectrum of 2,4-dichlorophenanthridine-8-ol (**48a**).



Spectrum 4: 150 MHz, Acetone-D_6, ^{13}C NMR spectrum of 2,4-dichlorophenanthridine-8-ol (**48a**).

Synthesis of 4-chloro-2-nitrophenanthridin-8-ol (48b)



48b

Compund **47b** (170 mg, 0.620 mmol) was dissolved in degassed acetonitrile (10 mL) and transferred to a pressure vial filled with argon. 2 drops of HCl (0.2 M) was added before the solution stirred for 40 min at 180 °C in a microwave reactor. The solution was cooled down to 55 °C and transferred to a round bottom flask and concentrated under reduced pressure. The crude product was dissolved in dry DCM (20 mL) under argon and DDQ (182 mg, 0.800 mmol) was added. After 2.5 h of stirring in r.t, the solution was concentrated under reduced pressure before it was purified by flash chromatography on silica gel eluted with 1:1.5:7.5 DCM:EtOAc:hexanes.

Yield: 156 mg (93%) as a yellow solid.

Data from literatur.[5]

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.67 (s, 1 H, OH), 9.51 (br s, 1 H, 6-H), 9.45 (d, J = 2.3 Hz, 1 H, 1-H), 8.92– 8.89 (m, 1 H, 10-H), 8.53 (d, J = 2.3 Hz, 1 H, 3-H), 7.58–7.55 (m, 2 H, 7-H and 9-H).

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

M.p. 317–318 °C.

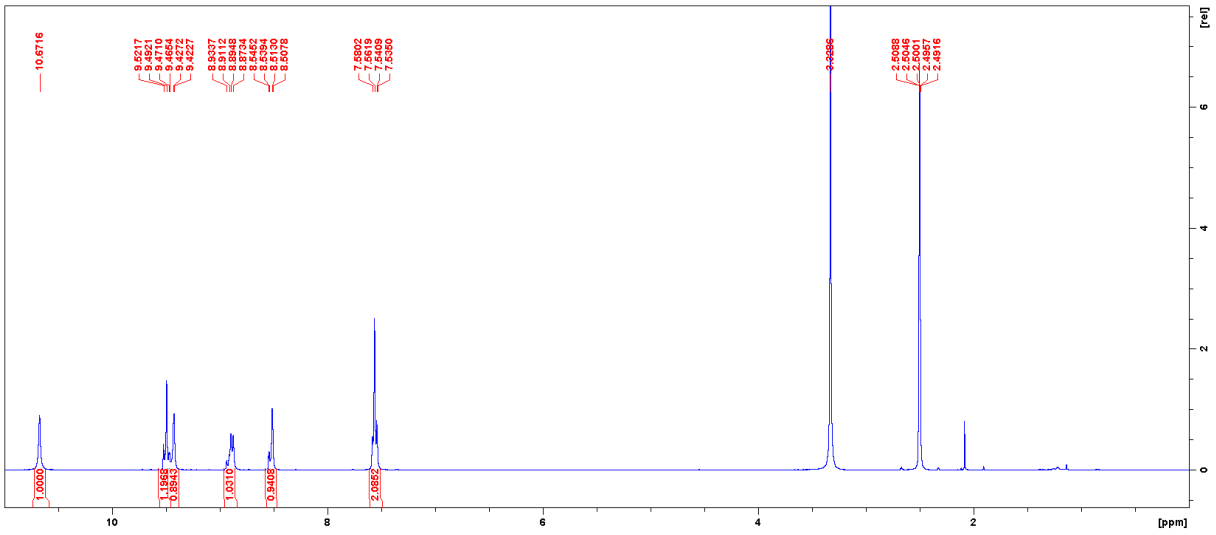
Data from experiment.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.67 (s, 1 H, OH), 9.49 (br s, 1 H, 6-H), 9.43 (s, 1 H, 1-H), 8.93– 8.87 (m, 1 H, 10-H), 8.55-8,51 (m, 1 H, 3-H), 7.58–7.54 (m, 2 H, 7-H and 9-H).

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

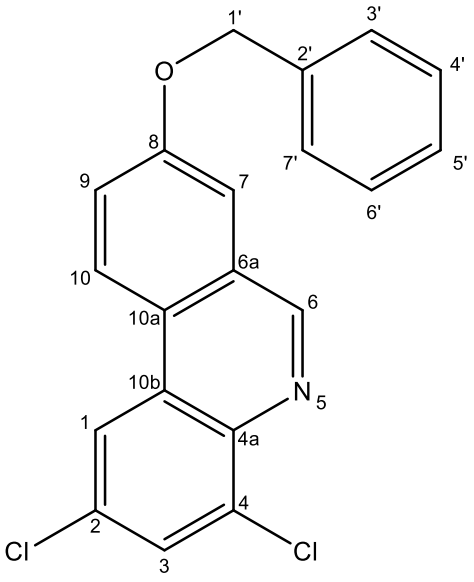
M.p. 316-317 °C.

^{1}H NMR, HRMS ESI and m.p coincides with the literature and no further analysis was performed.[5]



Spectrum 5: 400 MHz, DMSO-d_6, ^{1}H NMR spectrum of 4-chloro-2-nitrophenanthridin-8-ol (**48b**).

Synthesis of 8-(benzyloxy)-2,4-dichlorophenanthridine (55)



55

Compound **47a** (40.0 mg, 0.150 mmol) and K_2CO_3 (42.0 mg, 0.300 mmol) was added to a stirring degassed flask containing dry DMF (10 mL). After 15 min of stirring, benzyl bromide (38.0 µL, 0.320 mmol) was added with a syringe. The mixture was quenched with water (25 mL) after 75 min of stirring, and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered through a plug of silica gel, eluted with hexanes (200 mL) and then EtOAc (250 mL) and concentrated under reduced pressure. The compound was then isolated by flash chromatography on silica gel eluted with 2:3:5 DCM:EtOAc:hexanes.

Yield 50.0 mg (93%) as colorless crystals.

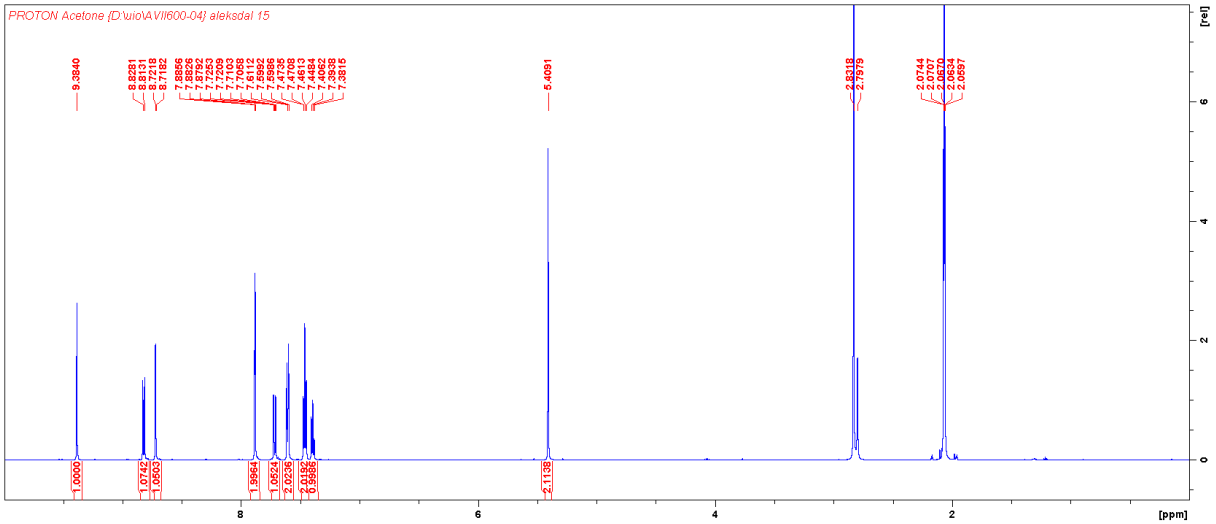
^{1}H NMR (600 MHz, Acetone-D_6) δ 9.38 (s, 1H, H-6), 8.82 (d, *J* = 9.0 Hz, 1H, H-10), 8.72 (d, *J* = 2.2 Hz, 1H, H-1), 7.89-7.88 (m, 2H, H-3 and H-7), 7.72 (dd, *J* = 2.7 Hz and 9.0 Hz, 1H, H-9), 7.61-7.60 (m, 2H, H-3’ and H-7’), 7.47-7.45 (m, 2H, H-4’ and H-6’), 7.41-7.38 (m, 1H, H-5’), 5.41 (s, 2H, H-1’).

^{13}C NMR (150 MHz, Acetone-D_6) δ 159.34 (C-8), 153.72 (CH-6), 138.61 (C-4a), 136.77 (C-2’), 135.38 (C-4), 132.03 (C-2), 128.54 (CH-4’ and CH-6’), 128.50 (C-6a), 128.07 (CH-5’),

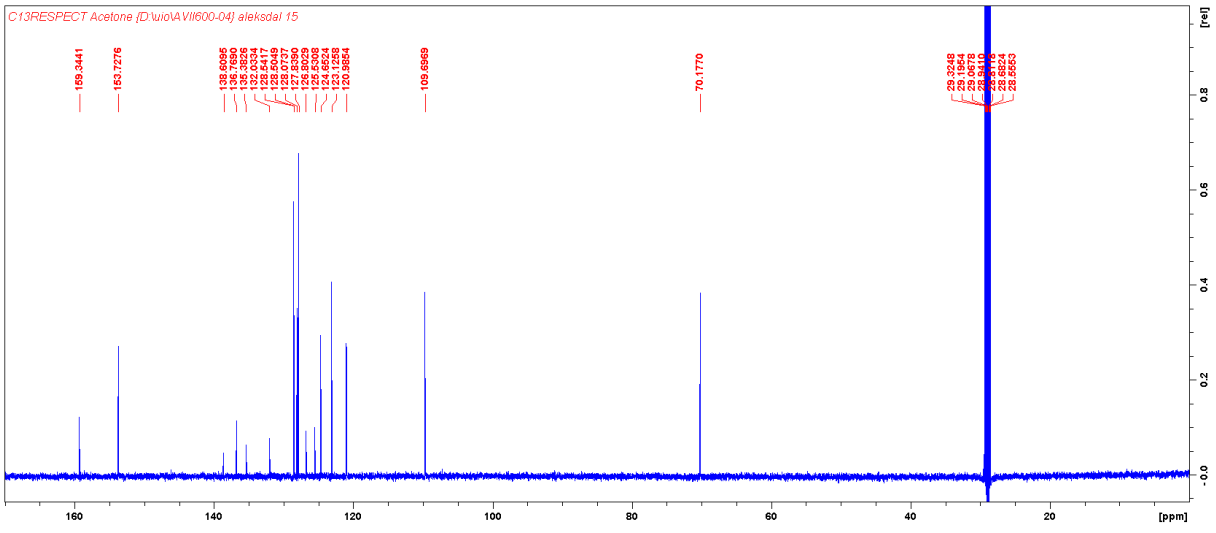
127.84 (CH-3, CH-3’ and CH-7’), 126.80 (C-10b), 125.53 (C-10a), 124.65 (CH-10), 123.13 (CH-9), 120.99 (CH-1), 109.70 (CH-7), 70.18 (CH_2-1’).

HRMS ESI calcd. for $C_{20}H_{13}Cl_2NO$ 353.0374, found 353.0368.

M.p. 178-179ºC.

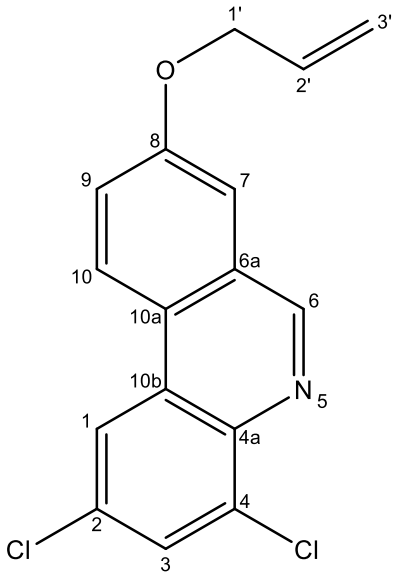


Spectrum 6: 600 MHz, Acetone-D_6, ^{1}H NMR spectrum of 8-(benzyloxy)-2,4-dichlorophenanthridine (**55**).



Spectrum 7: 150 MHz, Acetone-D_6, ^{13}C NMR spectrum of 8-(benzyloxy)-2,4-dichlorophenanthridine (**55**).

Synthesis of 8-(allyloxy)-2,4-dichlorophenanthridine (56)



56

Compound **47a** (300 mg, 1.14 mmol) and K_2CO_3 (315 mg, 2.28 mmol) were added to a stirring solution of dry DMF (20 mL) under argon. After 15 min of stirring, allyl bromide (0.200 mL, 2.28 mmol) was added and the solution continued stirring at r.t for 75 min. The solution was then transferred to a separation funnel with water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered through a plug of silica gel, eluted with hexanes (200 mL) and then EtOAc (250 mL) and concentrated under reduced pressure.

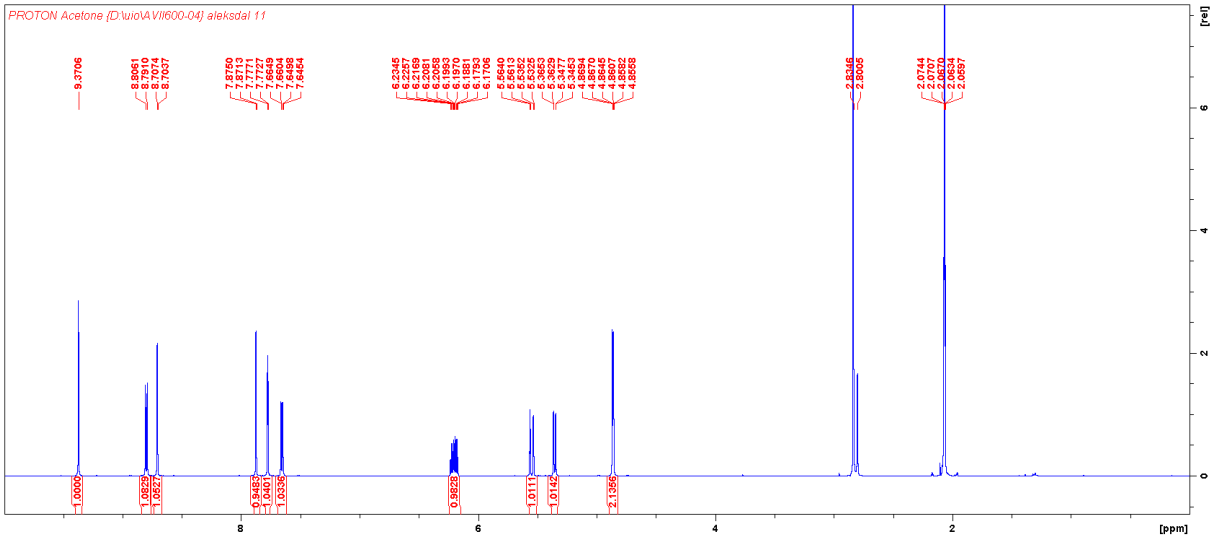
Yield: 340 mg (98%) as a colorless solid.

^{1}H NMR (600 MHz, Acetone-D_6) δ 9.37 (s, 1H, H-6), 8.80 (d, *J* = 9.0 Hz, 1H, H-10), 8.71 (d, *J* = 2.2 Hz, 1H, H-1), 7.88 (d, *J* = 2.2 Hz, 1H, H-3), 7.77 (d, *J* = 2.6 Hz, 1H, H-7), 7.66 (dd, *J* = 2.7 Hz and 8.7 Hz, 1H, H-9), 6.23-6.17 (m, 1H, H-2'), 5.56-5.53 (m, 1H, H-3'), 5.37-5.35 (m, 1H, H-3'), 4.86-4.87 (m, 2H, H-1').

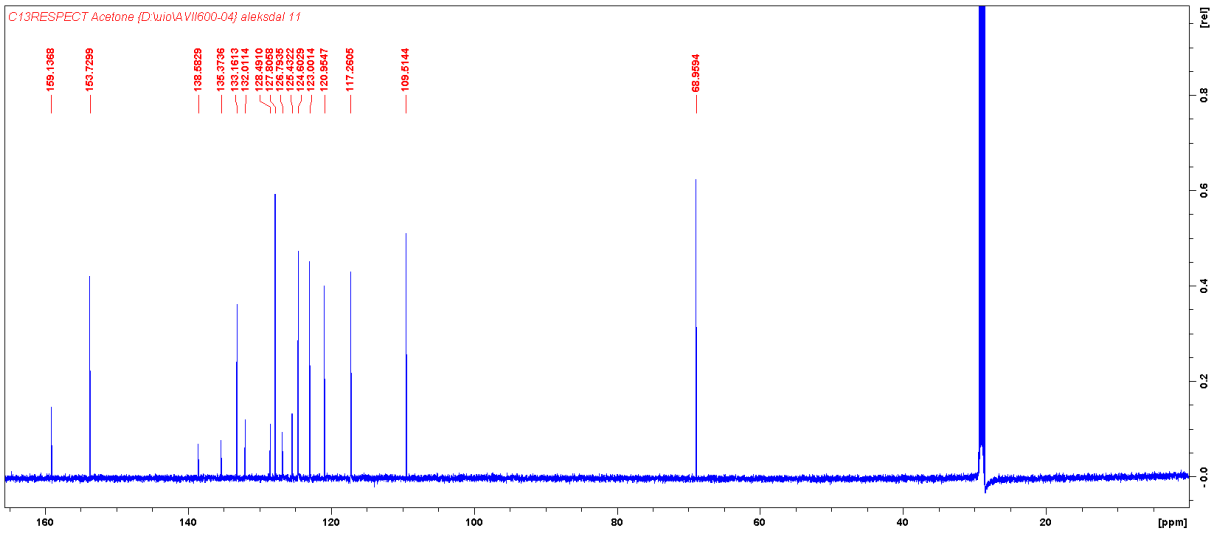
^{13}C NMR (150 MHz, Acetone-D_6) δ 159.14 (C-8), 153.73 (CH-6), 138.58 (C-4a), 135.37 (C-4), 133.16 (CH-2'), 132.01 (C-2), 128.49 (C-6a), 127.81 (CH-3), 126.79 (C-10b), 125.43 (C-10a), 124.60 (CH-10), 123.00 (CH-9), 120.95 (CH-1), 117.26 (CH_2-3'), 109.51 (CH-7), 68.96 (CH_2-1').

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

M.p. 152-153°C.

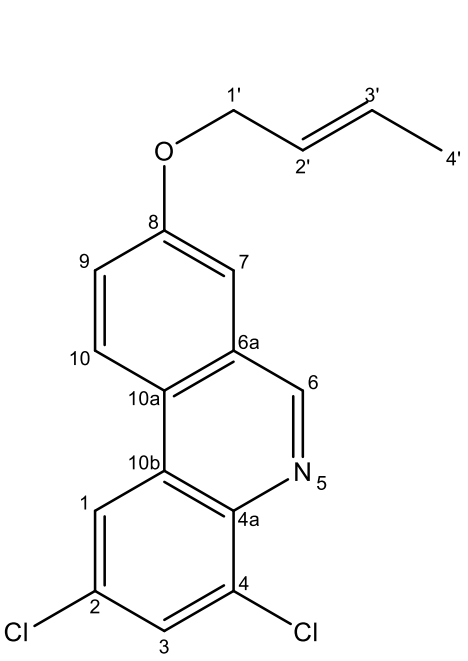


Spectrum 8: 600 MHz, Acetone-D_6, ^{1}H NMR 8-(allyloxy)-2,4-dichlorophenanthridine (**56**).

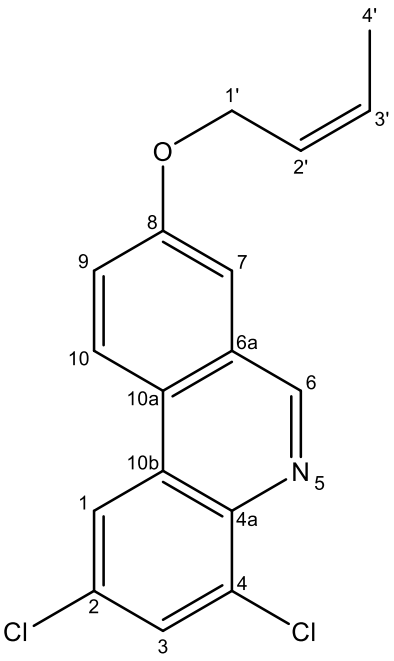


Spectrum 9: 150 MHz, Acetone-D_6, ^{13}C NMR 8-(allyloxy)-2,4-dichlorophenanthridine (**56**).

Synthesis of (*E*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (57a) and (*Z*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (57b)



57a



57b

Compound **47a** (50.4 mg, 0.190 mmol) and K_2CO_3 (52.5 mg, 0.380 mmol) was added to a stirring solution of dry DMF (10 mL) at r.t under argon. After 15 min crotyl bromide (40.0 µL, 0.380 mmol) was added and the solution stirred for 75 min. The solution was transferred to a separation funnel containing water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered through a plug of silica gel, eluted with hexanes (200 mL) and then EtOAc (250 mL) and concentrated under reduced pressure.

Yield: 52.0 mg (86%) 5:1 *E/Z* as a colorless solid.

NMR data are reported for the major isomer.

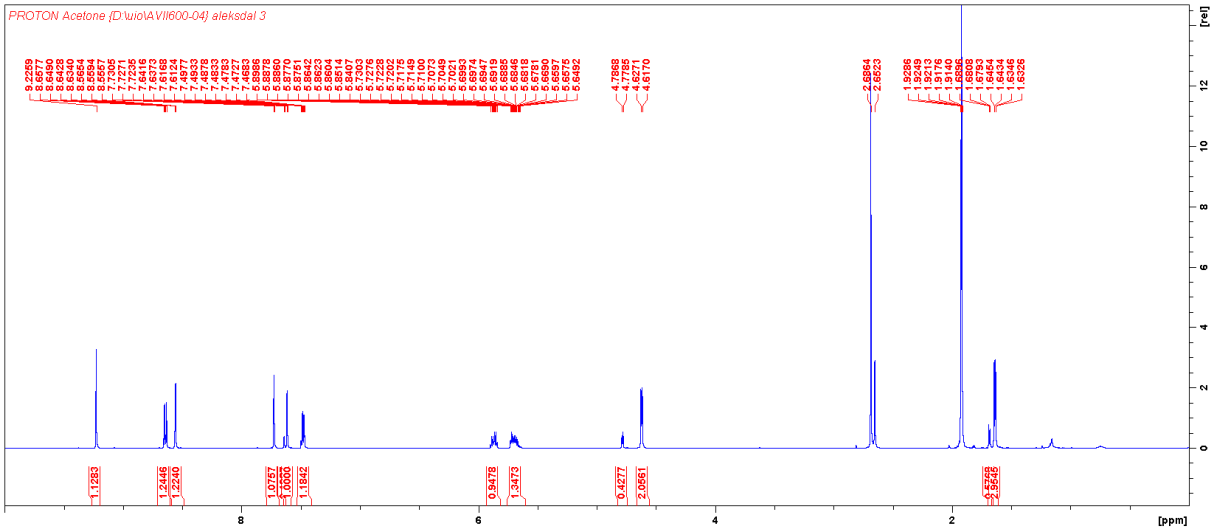
^{1}H NMR (600 MHz, Acetone-D_6) δ 9.35 (s, 1H, H-6), 8.77 (d, *J* = 9.0 Hz, 1H, H-10), 8.69 (d, *J* = 2.2 Hz, 1H, H-1), 7.85 (d, *J* = 2.2 Hz, 1H, H-3), 7.74 (d, *J* = 2.7 Hz, 1H, H-7), 7.61 (dd, *J* = 2.7 Hz and 9.0Hz, 1H, H-9), 6.03-5.97 (m, 1H, H-2'), 5.86-5.79 (m, 1H, H-3'), 4.75 (d, *J* = 6.1 Hz, 2H, H-1'), 1.77 (dd, *J* = 1.2 Hz and 6.5 Hz, 3H, H-4').

^{13}C NMR (150 MHz, Acetone-D_6) δ 160.29 (C-8), 154.74 (CH-6), 139.54 (C-4a), 136.35 (C-4), 132.97 (C-2), 131.39 (CH-2'), 129.51 (C-6a), 128.73 (CH-3), 127.81 (C-10b), 126.85

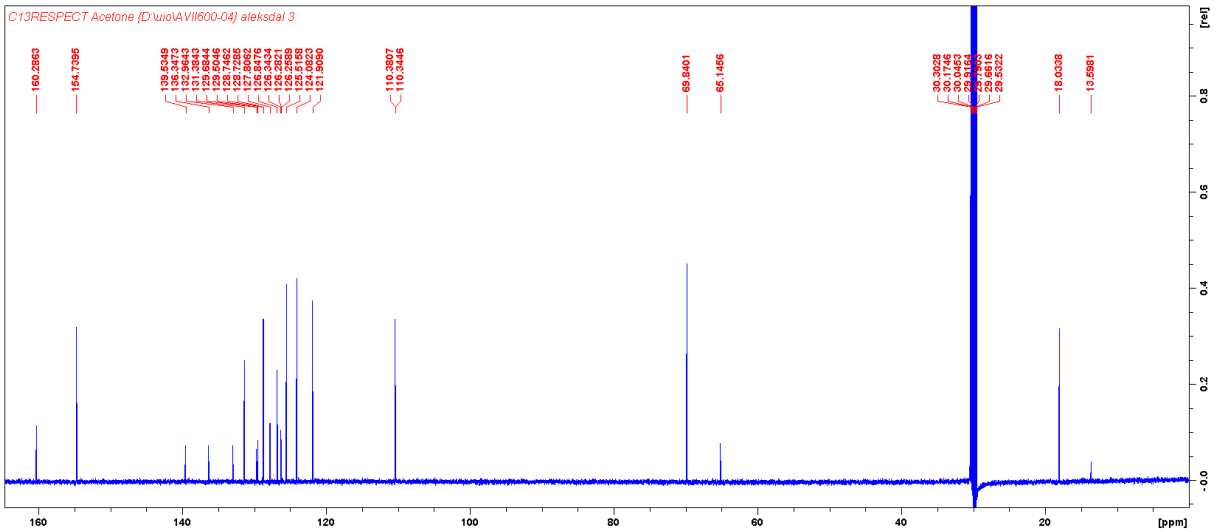
(CH-3'), 126.28 (C-10a), 125.52 (CH-10), 124.08 (CH-9), 121.91 (CH-1), 110.38 (CH-7), 69.84 (CH_2-1'), 18.03 (CH_3-4').

HRMS ESI calcd. for $C_{17}H_{13}Cl_2NO$ 317.0374, found 317.0364.

M.p. 140-141°C.

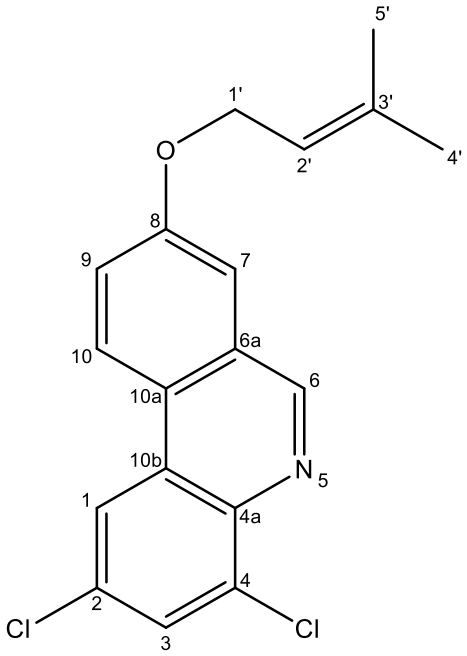


Spectrum 10: 600 MHz, Acetone-D_6, ^{1}H NMR spectrum of (E)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57a**) and (Z)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57b**).



Spectrum 11: 150 MHz, Acetone-D_6, ^{13}C NMR spectrum of (E)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57a**) and (Z)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57b**).

Synthesis of 2,4-dichloro-8-((3-methylbut-2-en-1-yl)oxy)phenanthridine (58)



58

To a stirring solution of dry DMF (10 mL) at r.t under argon, compound **47a** (50.5 mg, 0.190 mmol) and K_2CO_3 (52.5 mg, 0.380 mmol) were added. After 15 min 1-bromo-3-methyl-2-butene (56.6 mg, 0.380 mmol) was added and after 75 min of stirring the solution was transferred to a separation funnel with water (25 mL). The water phase was extracted with EtOAc (3 x 25 mL) and the combined organic phases were dried ($MgSO_4$). The solution was filtered through a plug of silica gel, eluted with hexanes (200 mL) and then EtOAc (250 mL) and concentrated under reduced pressure.

Yield: 61.0 mg (97%) as a colorless solid.

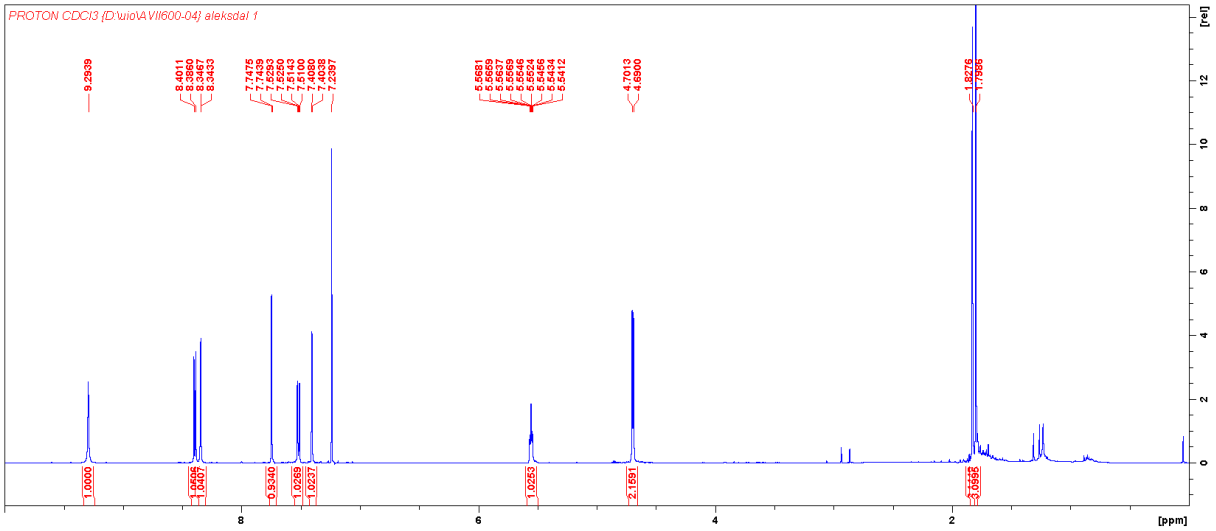
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.29 (s, 1H, H-6), 8.39 (d, *J* = 9.0 Hz, 1H, H-10), 8.35 (d, *J* = 2.1 Hz, 1H, H-1), 7.75 (d, *J* = 2.1 Hz, 1H, H-3), 7.52 (dd, *J* = 2.5 Hz and 9.0 Hz, 1H, H-9), 7.41 (d, *J* = 2.5 Hz, 1H, H-7), 5.57-5.54 (m, 1H, H-2'), 4.70 (d, *J* = 6.8 Hz, 2H, H-1'), 1.83 (s, 3H, H-4'), 1.80 (s, 3H, H-5').

^{13}C NMR (150 MHz, $CDCl_3$) δ 159.44 (C-8), 153.56 (CH-6), 139.60 (C-3'), 138.28 (C-4a), 135.20 (C-4), 132.88 (C-2), 128.55 (CH-3), 128.26 (C-6a), 126.89 (C-10b), 125.91 (C-10a),

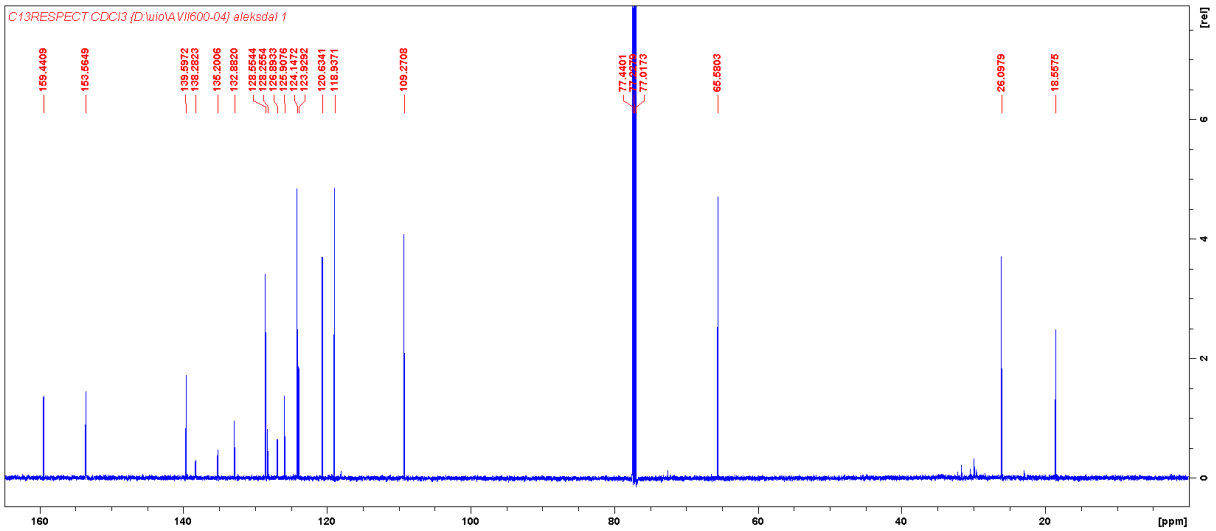
124.15 (CH-10), 123.93 (CH-9), 120.63 (CH-1), 118.94 (CH-2'), 109.27 (CH-7), 65.58 (CH_2-1'), 26.10 (CH_3-4'), 18.56 (CH_3-5').

HRMS ESI calcd. for $C_{18}H_{15}Cl_2NO$ 331.0531, found 331.0524.

M.p. 165-166 °C.

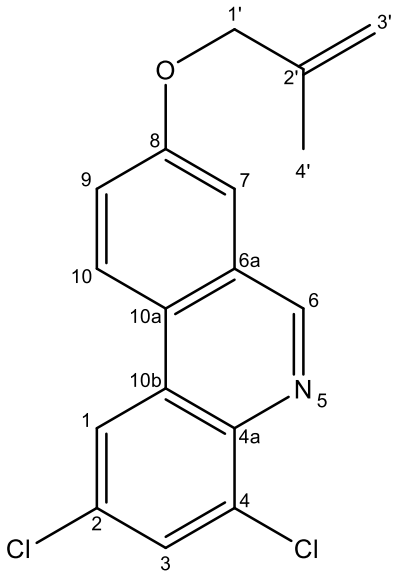


Spectrum 12: 600 MHz, $CDCl_3$, ^1H NMR spectrum of 2,4-dichloro-8-((3-methylbut-2-en-1-yl)oxy)phenanthridine (**58**).



Spectrum 13: 150 MHz, $CDCl_3$, ^{13}C NMR spectrum of 2,4-dichloro-8-((3-methylbut-2-en-1-yl)oxy)phenanthridine (**58**).

Synthesis of 2,4-dichloro-8-((2-methylallyl)oxy)phenanthridine (59)



59

Compound **47a** (50,0 mg, 0.19 mmol) and K_2CO_3 (52.5 mg, 0.380 mmol) was added to a stirring solution of dry DMF (10 mL) at r.t under argon. After 15 min 3-bromo-2-methylpropene (40.0 µL, 0.38 mmol) was added and the solution stirred for 75 min. The solution was transferred to a separation funnel containing water (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered through a plug of silica gel, eluted with hexanes (200 mL) and then EtOAc (250 mL) and concentrated under reduced pressure.

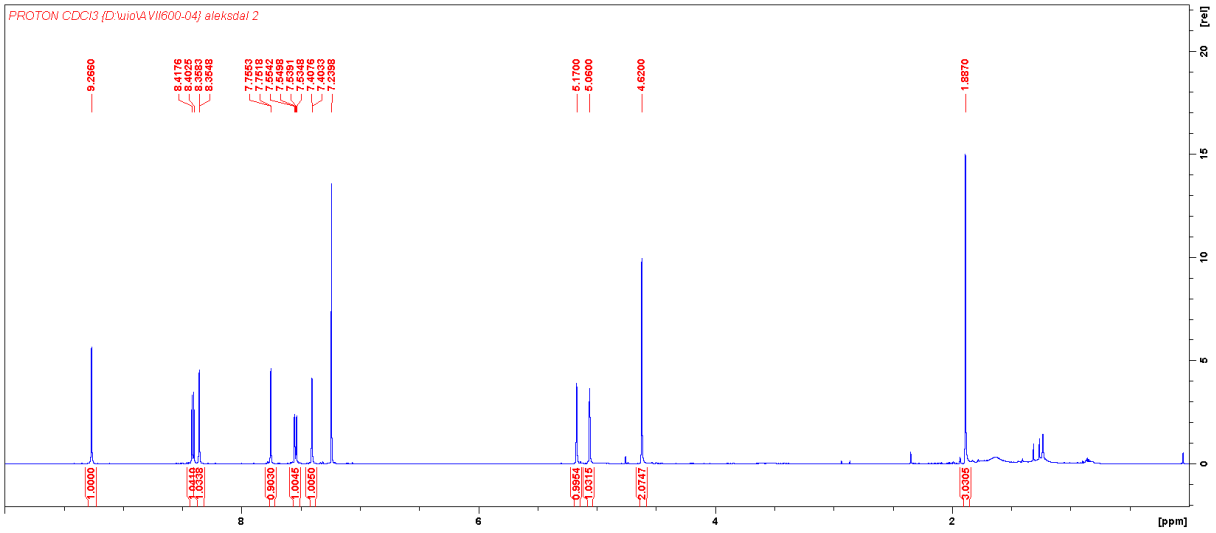
Yield: 58.0 mg (96%) as a colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.27 (s, 1H, H-6), 8.41 (d, *J* = 9.1 Hz, 1H, H-10), 8.36 (d, *J* = 2.1 Hz, 1H, H-1), 7.75 (d, *J* = 2.1 Hz, 1H, H-3), 7.54 (dd, *J* = 2.6 Hz and 9.1 Hz, 1H, H-9), 7.41 (d, *J* = 2.6 Hz, 1H, H-7), 5.17 (s, 1H, H-3'), 5.06 (s, 1H, H-3'), 4.62 (s, 2H, CH_2-1'), 1.89 (s, 3H, CH_3-4').

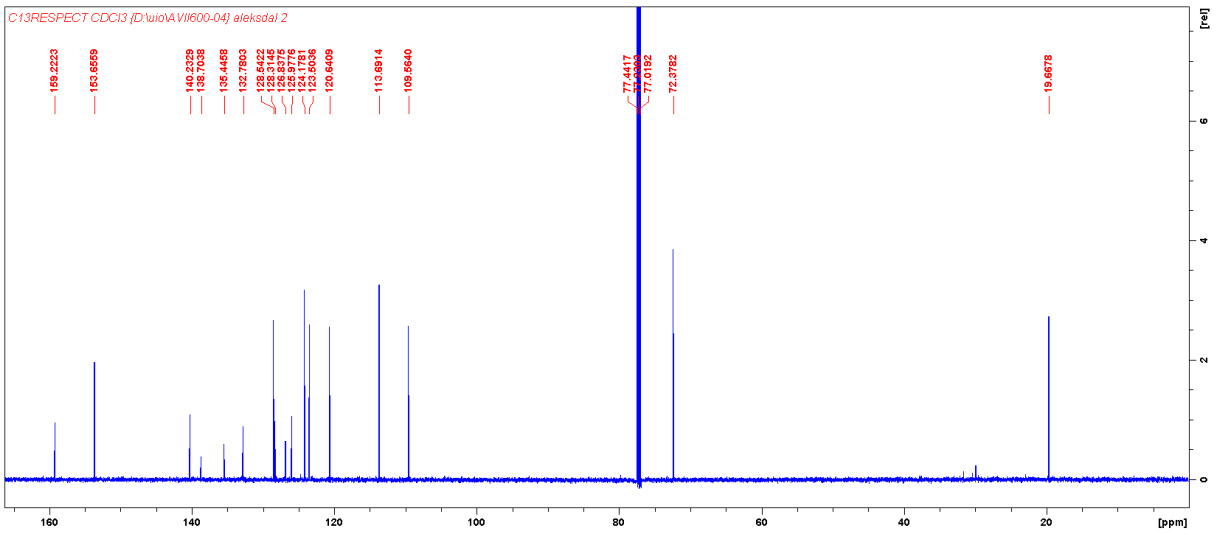
^{13}C NMR (150 MHz, $CDCl_3$) δ 159.22 (C-8), 153.66 (CH-6), 140.23 (C-2'), 138.70 (C-4a), 135.46 (C-4), 132.78 (C-2), 128.54 (CH-3), 128.31 (C-6a), 126.84 (C-10b), 125.98 (C-10a), 124.18 (CH-10), 123.50 (CH-9), 120.64 (CH-1), 113.69 (CH_2-3'), 109.56 (CH-7), 72.38 (CH_2-1'), 19.67 (CH_3-4').

HRMS ESI calcd. for $C_{17}H_{13}Cl_2NO$ 317.0374, found 317.0368.

M.p. 154-155°C.

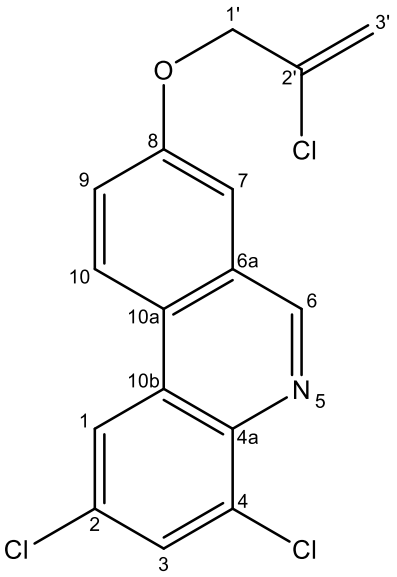


Spectrum 14: 600 MHz, $CDCl_3$, ^1H NMR spectrum of 2,4-dichloro-8-((2-methylallyl)oxy)phenanthridine (**59**).



Spectrum 15: 150 MHz, $CDCl_3$, ^{13}C NMR spectrum of 2,4-dichloro-8-((2-methylallyl)oxy)phenanthridine (**59**).

Synthesis of 2,4-dichloro-8-((2-chloroallyl)oxy)phenanthridine (60)



60

To a stirring solution of dry DMF (10 mL) at r.t under argon, compound **47a** (50.1 mg, 0.190 mmol) and K_2CO_3 (52.5 mg, 0.380 mmol) were added. After 15 min 2,3-dichloropropene (42.2 mg, 0.380 mmol) was added and after 75 min of stirring the solution was transferred to a separation funnel with water (25 mL). The water phase was extracted with EtOAc (3 x 25 mL) and the combined organic phases were dried ($MgSO_4$). The solution was filtered through a plug of silica gel, eluted with hexanes (200 mL) and then EtOAc (250 mL) and concentrated under reduced pressure.

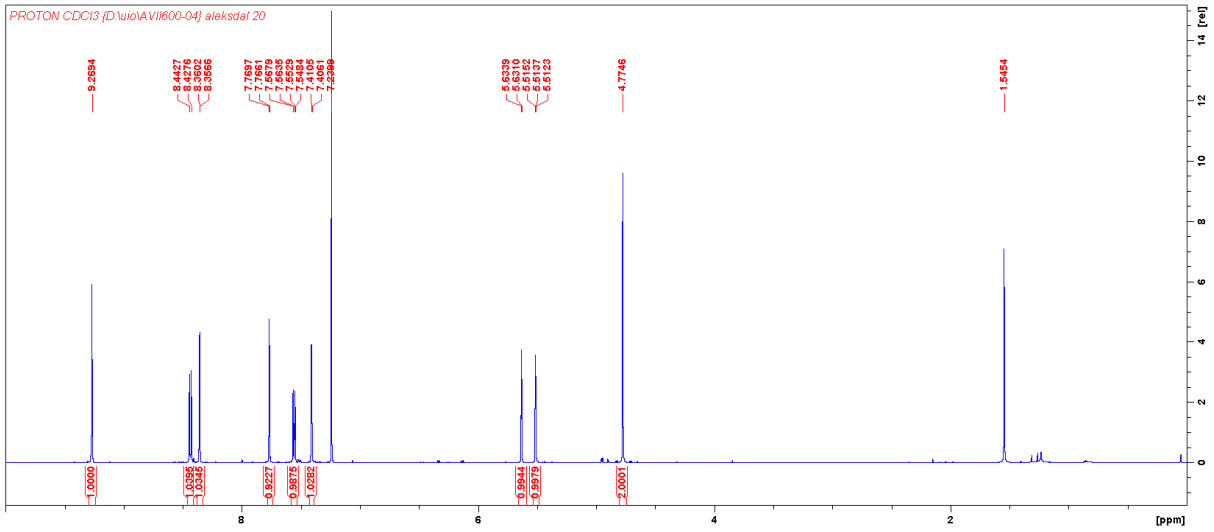
Yield: 55.0 mg (86%) as a colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.27 (s, 1H, H-6), 8.44 (d, *J* = 9.1 Hz, 1H, H-10), 8.36 (d, *J* = 2.2 Hz, 1H, H-1), 7.77 (d, *J* = 2.2 Hz, 1H, H-3), 7.56 (dd, *J* = 2.6 Hz and 9.1 Hz, 1H, H-9), 7.41 (d, *J* = 2.6 Hz, 1H, H-7), 5.63 (d, *J* = 1.7 Hz, 1H, H-3'), 5.51 (d, *J* = 1.7 Hz, 1H, H-3'), 4.77 (s, 2H, H-1').

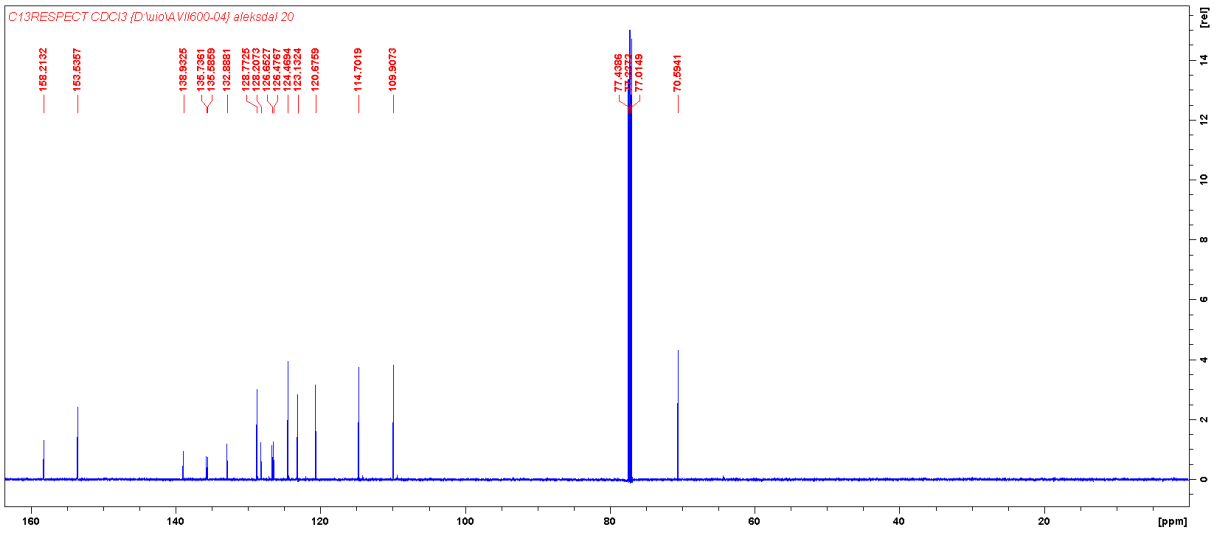
^{13}C NMR (150 MHz, $CDCl_3$) δ 158.21 (C-8), 153.53 (CH-6), 138.93 (C-4a), 135.73 (C-4), 135.58 (C-2'), 132.89 (C-2), 128.77 (CH-3), 128.21 (C-6a), 126.65 (C-10b), 126.48 (C-10a), 124.47 (CH-10), 123.13 (CH-9), 120.67 (CH-1), 114.70 (CH_2-3'), 109.91 (CH-7), 70.59 (CH_2-1').

HRMS ESI calcd. for $C_{16}H_{10}Cl_3NO$ 336.9828, found 336.9822.

M.p. 169-170 °C.

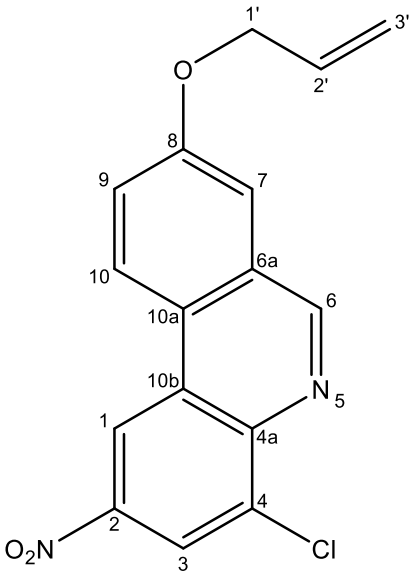


Spectrum 16: 600 MHz, $CDCl_3$, ^1H NMR spectrum of 2,4-dichloro-8-((2-chloroallyl)oxy)phenanthridine (**60**).



Spectrum 17: 150 MHz, $CDCl_3$, ^{13}C NMR spectrum of 2,4-dichloro-8-((2-chloroallyl)oxy)phenanthridine (**60**).

Synthesis of 8-(allyloxy)-4-chloro-2-nitrophenanthridine (61)



61

Compound **48b** (100 mg, 0.370 mmol) and K_2CO_3 (101 mg, 0.740 mmol) was dissolved in dry DMF (10 mL) under argon. After 15 min of stirring, allyl bromide (60.0 µL, 0.740 mmol) was added with a syringe, and the solution stirred for 75 min at r.t. The solution was transferred to a separation funnel with water (25 mL), and the aqueous phase was extracted with EtOAc (3 x 25 mL). The organic phase was dried ($MgSO_4$), filtered through a plug of silica eluted with hexanes (200 mL) followed by EtOAc (250 mL) and concentrated under reduced pressure.

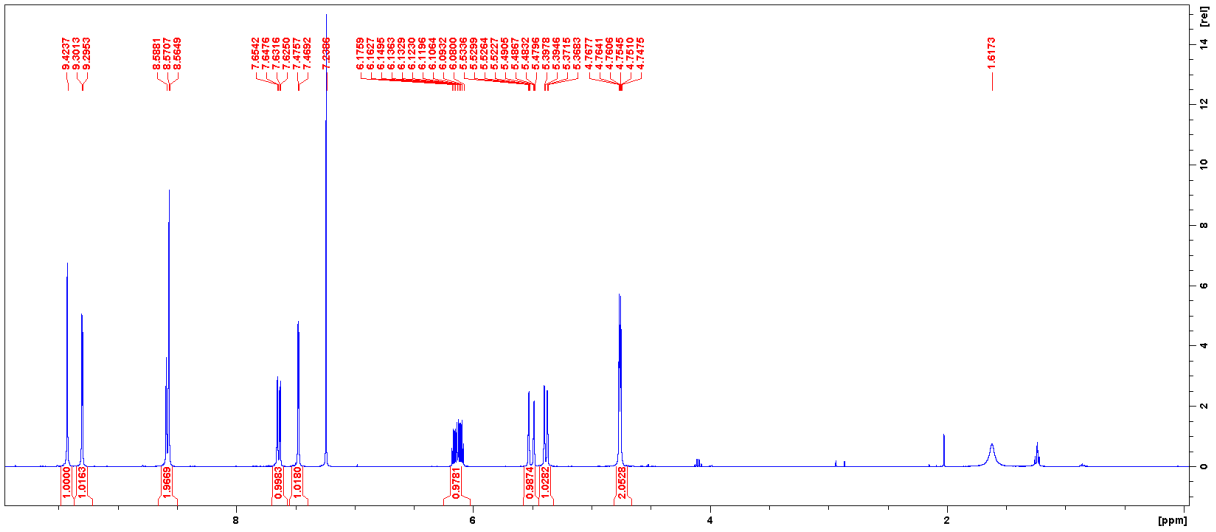
Yield: 91.0 mg (78%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H, H-6), 9.30 (d, *J* = 2.4 Hz, 1H, H-1), 8.58 (d, *J* = 9.3 Hz, 1H, H-10), 8.57 (d, *J* = 2.4 Hz, 1H, H-3), 7.64 (dd, *J* = 2.6 Hz and 9.0 Hz, 1H, H-9), 7.47 (d, *J* = 2.6 Hz, 1H, H-7), 6.18-6.08 (m, 1H, H-2'), 5.53-5.48 (m, 1H, H-3'), 5.40-5.37 (m, 1H, H-3'), 4.77-4.75 (m, 2H, H-1').

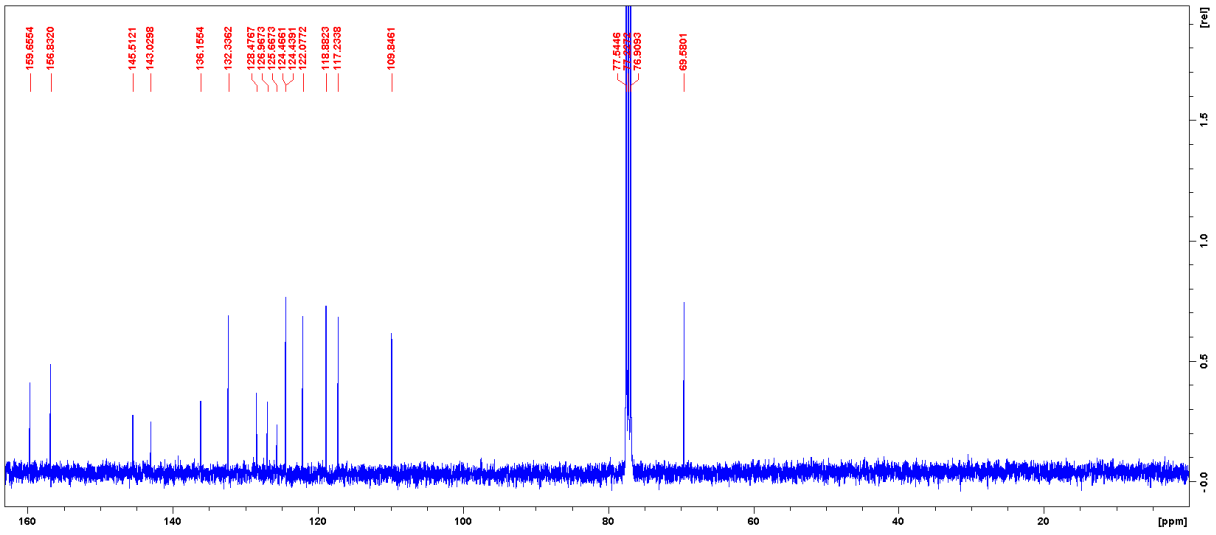
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.66 (C-8), 156.83 (CH-6), 145.51 (C-2), 143.03 (C-4a), 136.16 (C-4), 132.34 (CH-2'), 128.48 (C-6a), 126.97 (C-10a), 125.67 (C-10b), 124.47 (CH-9 or CH-10), 124.44 (CH-9 or CH-10), 122.08 (CH-3), 118.88 (CH_2-3'), 117.23 (CH-1), 109.85 (CH-7), 69.58 (CH_2-1').

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

M.p. 180-181 ^{o}C.

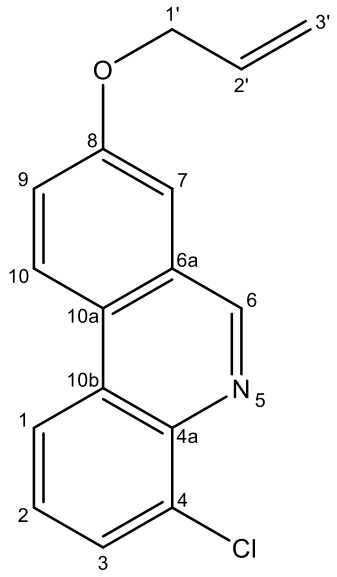


Spectrum 18: 400 MHz, $CDCl_3$, ^{1}H NMR spectrum of 8-(allyloxy)-4-chloro-2-nitrophenanthridine (**61**).



Spectrum 19: 100 MHz, $CDCl_3$, ^{13}C NMR spectrum of 8-(allyloxy)-4-chloro-2-nitrophenanthridine (**61**).

Synthesis of 8-(allyloxy)-4-chlorophenanthridine (62)



62

A round bottom flask with dry DMF (10 mL), compound **50** (60.6 mg, 0.260 mmol) and K_2CO_3 (72.4 mg, 0.520 mmol) stirred under argon for 15 min before allyl bromide (45.0 µL, 0.520 mmol) was added. The solution was transferred to a separation funnel with water (25 mL) after 75 min, and extracted with EtOAc (3 x 25 mL). The organic phase was dried ($MgSO_4$), filtered through a plug of silica eluted with hexanes (200 mL) followed by EtOAc (250 mL) and concentrated under reduced pressure.

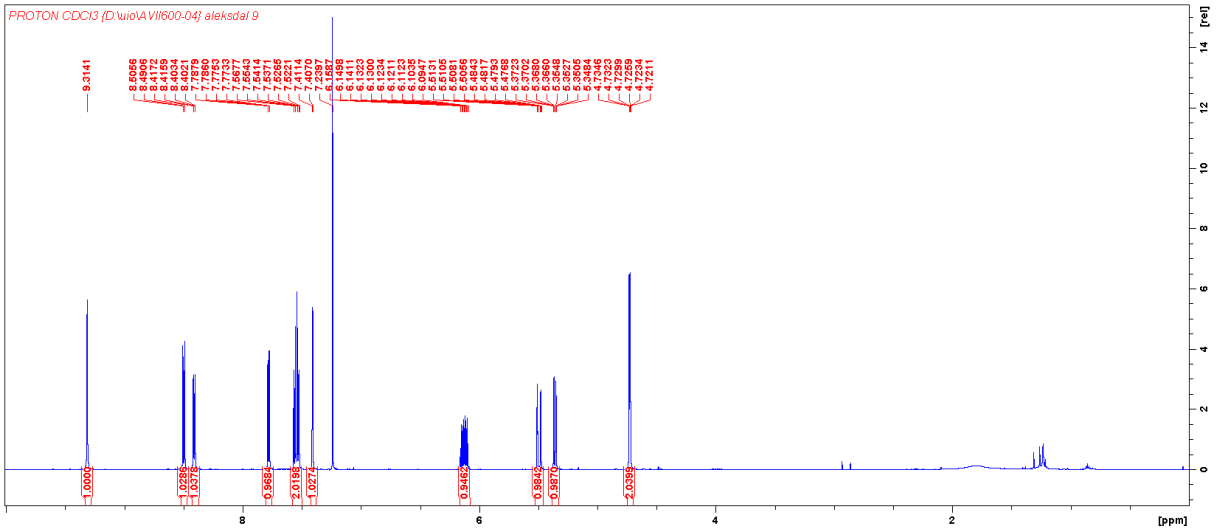
Yield: 63.0 mg (85%) as a colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.31 (s, 1H, H-6), 8.50 (d, *J* = 9.0 Hz, 1H, H-10), 8.41 (dd, *J* = 0.8 Hz and 8.3 Hz, 1H, H-1), 7.78 (dd, *J* = 1.2 Hz and 7.6 Hz, 1H, H-3), 7.55 (t, *J* = 8.0 Hz, 1H, H-2), 7.53 (dd, *J* = 2.6 Hz and 9.0 Hz, 1H, H-9), 7.41 (d, *J* = 2.6 Hz, 1H, H-7), 6.16-6.09 (m, 1H, H-2'), 5.51-5.48 (m, 1H, H-3'), 5.37-5.35 (m, 1H, H-3'), 4.73-4.72 (m, 2H, H-1').

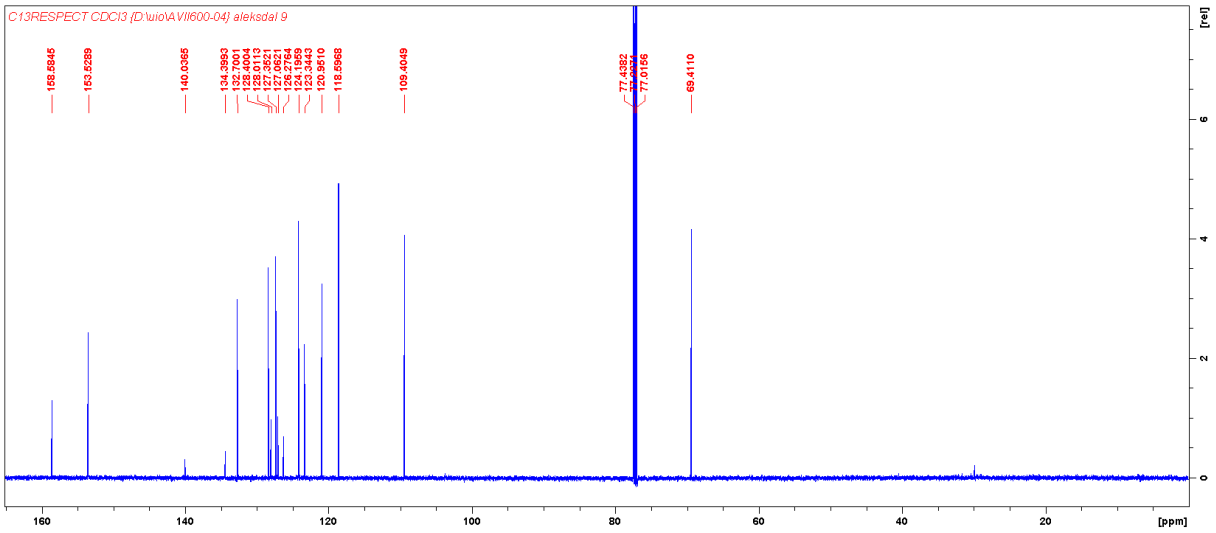
^{13}C NMR (150 MHz, $CDCl_3$) δ 158.58 (C-8), 153.53 (CH-6), 140.04 (C-4a), 134.40 (C-4), 132.70 (CH-2'), 128.40 (CH-3), 128.01 (C-10a), 127.35 (CH-2), 127.06 (C-6a), 126.28 (C-10b), 124.19 (CH-10), 123.34 (CH-9), 120.95 (CH-1), 118.60 (CH_2-3'), 109.40 (CH-7), 69.41 (CH_2-1').

HRMS ESI calcd. for $C_{16}H_{12}ClNO$ 269.0607, found 269.0602.

M.p. 99-100 °C.

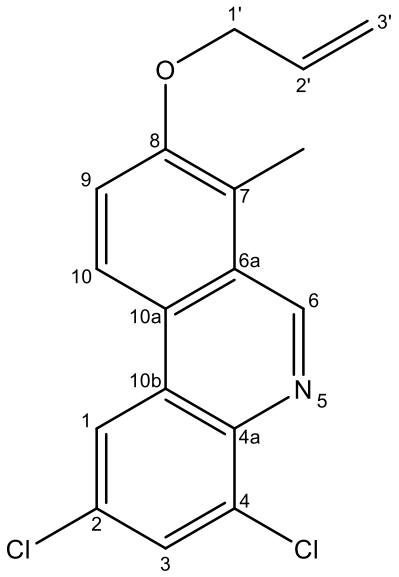


Spectrum 20: 600 MHz, $CDCl_3$, ^1H NMR spectrum of 8-(allyloxy)-4-chlorophenanthridine (**62**).



Spectrum 21: 150 MHz, $CDCl_3$, ^{13}C NMR spectrum of 8-(allyloxy)-4-chlorophenanthridine (**62**).

Synthesis of 8-(allyloxy)-2,4-dichloro-7-methylphenanthridine (63)



63

Compound **51** (50.1 mg, 0.180 mmol) and K_2CO_3 (38.7 mg, 0.360 mmol) was added to a stirring round bottom flask with dry DMF (10 mL) under argon. The solution stirred in r.t. for 15 min before allyl bromide (24.0 µL, 0.360 mmol) was added. After 75 min the solution was transferred to a separation funnel with water (25 mL) and was extracted with EtOAc (3 x 25 mL). The organic phase was dried ($MgSO_4$), filtered through a plug of silica eluted with hexanes (200 mL) then EtOAc (250 mL) and concentrated under reduced pressure.

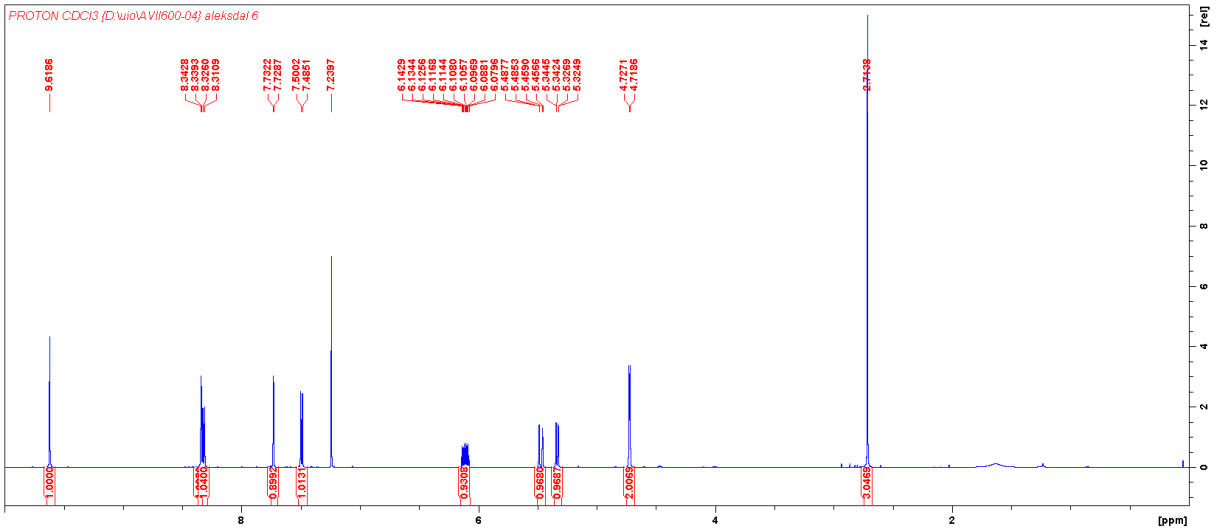
Yield: 53.0 mg (93%) as a colorless solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.62 (s, 1H, H-6), 8.34 (d, *J* = 2.1 Hz, 1H, H-1), 8.32 (d, *J* = 9.1 Hz, 1H, H-10), 7.73 (d, *J* = 2.1 Hz, 1H, H-3), 7.49 (d, *J* = 9.1 Hz, 1H, H-9), 6.14-6.08 (m, 1H, H-2'), 5.49-5.46 (m, 1H, H-3'), 5.34-5.33 (m, 1H, H-3'), 4.73-4.72 (m, 2H, H-1'), 2.71 (s, 3H, CH_3 on C-7).

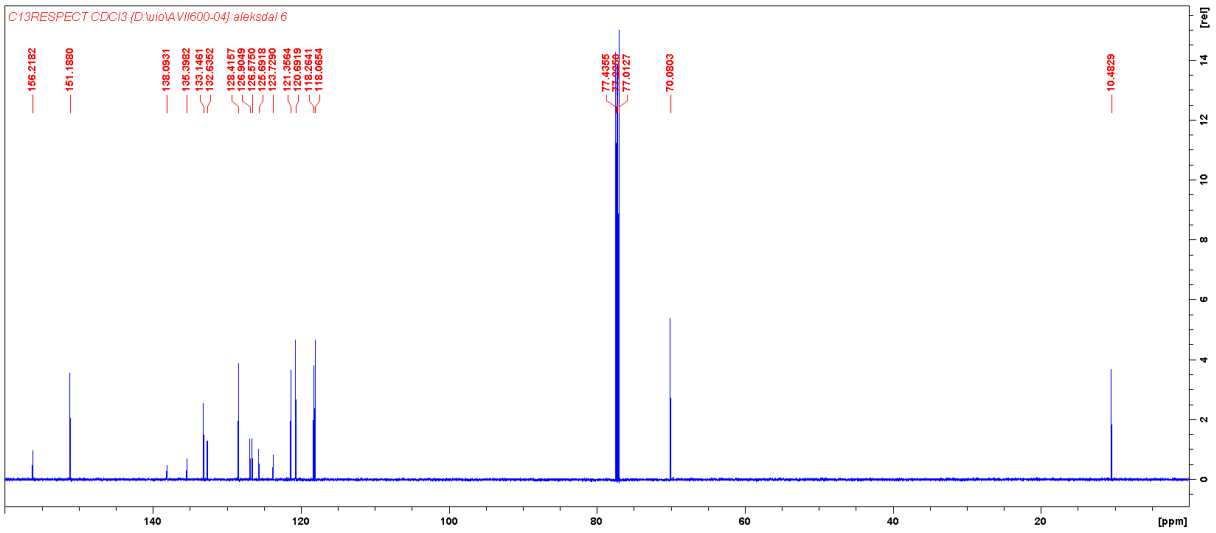
^{13}C NMR (150 MHz, $CDCl_3$) δ 156.22 (C-8), 151.19 (CH-6), 138.09 (C-4a), 135.40 (C-4), 133.14 (CH-2'), 132.63 (C-2), 128.41 (CH-3), 126.90 (C-6a), 126.57 (C-10b), 125.69 (C-10a), 123.73 (C-7), 121.35 (CH-10), 120.69 (CH-1), 118.26 (CH-9), 118.06 (CH_2-3'), 70.08 (CH_2-1'), 10.48 (CH_3 on C-7).

HRMS ESI calcd. for $C_{17}H_{13}Cl_2NO$ 317.0374, found 317.0368.

M.p. 167-168 °C.

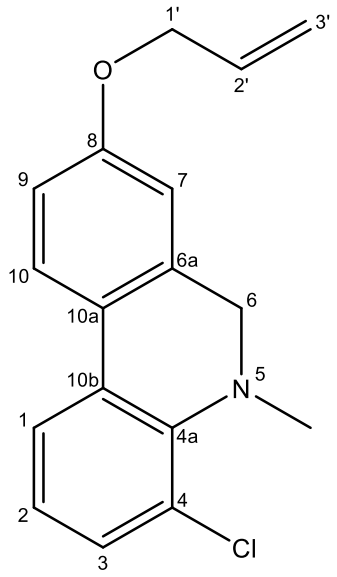


Spectrum 22: 600 MHz, $CDCl_3$, ^{1}H NMR spectrum of 8-(allyloxy)-2,4-dichloro-7-methylphenanthridine (**63**).



Spectrum 23: 150 MHz, $CDCl_3$, ^{13}C NMR spectrum of 8-(allyloxy)-2,4-dichloro-7-methylphenanthridine (**63**).

Synthesis of 8-(allyloxy)-4-chloro-5-methyl-5,6-dihydrophenanthridine (64)



64

A solution of compound **52** (48.0 mg, 0.200 mmol), K_2CO_3 (55.3 mg, 0.400 mmol) and dry DMF (10 mL) stirred at r.t under argon for 15 min before adding allyl bromide (35.0 µL, 0.400 mmol) with a syringe. The solution was transferred to a separation funnel after 75 min, containing water (25 mL). The aqueous phase was extracted with EtOAc (3 x 25 mL), and the combined organic phase was dried ($MgSO_4$). The solution was filtered through a plug of silica eluted with hexanes (200 mL) followed by EtOAc (250 mL) and concentrated under reduced pressure.

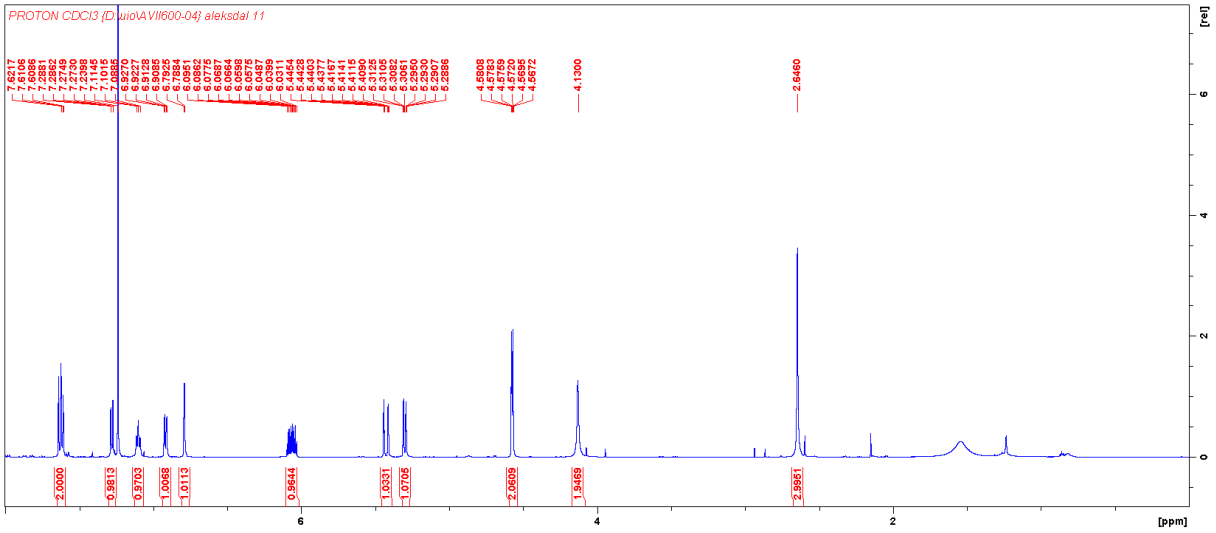
Yield: 52.0 mg (93%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.6 Hz, 1H, H-10), 7.62 (dd, *J* = 1.2 Hz and 7.9 Hz, 1H, H-1), 7.28 (dd, *J* = 1.2 Hz and 7.9 Hz, 1H, H-3), 7.10 (app t, *J* = 7.9 Hz, 1H, H-2), 6.92 (dd, *J* = 2.5 Hz and 8.5 Hz, 1H, H-9), 6.79 (d, *J* = 2.5 Hz, 1H, H-7), 6.10-6.03 (m, 1H, H-2'), 5.45-5.41 (m, 1H, H-3'), 5.31-5.29 (m, 1H, H-3'), 4.58-4.57 (m, 2H, H-1'), 4.13 (bs, 2H, H-6), 2.65 (s, 3H, CH_3- on C-5).

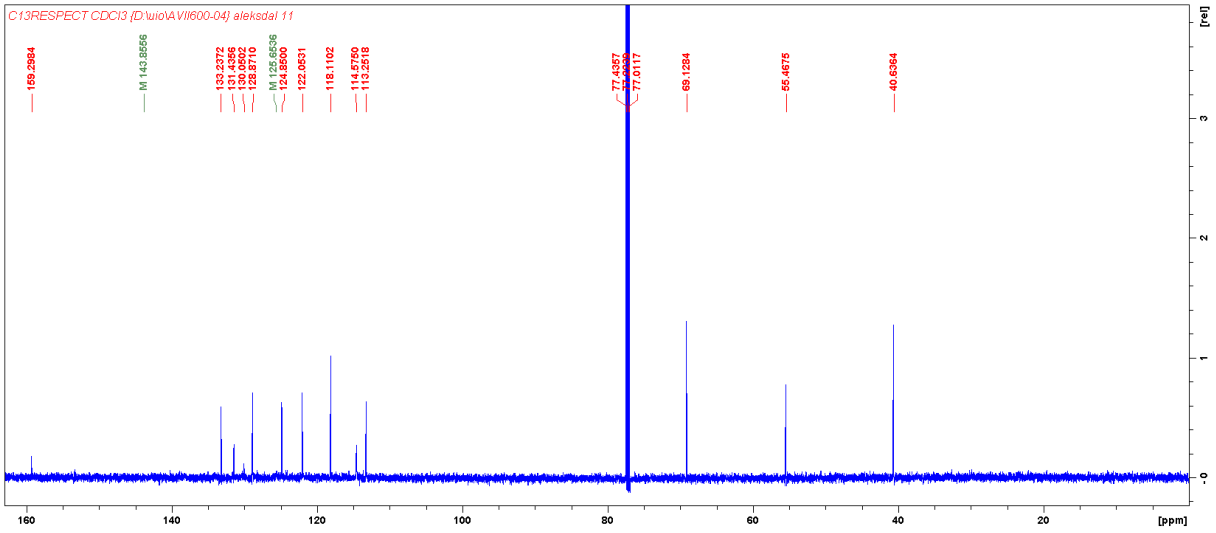
^{13}C NMR (150 MHz, $CDCl_3$) δ 159 (C-8), 143.86 (C-4)*, 133.24 (CH-2'), 131.44 (C-6a), 130.05 (C-10b), 128.87 (CH-3), 125.65 (CH-2)*, 124.85 (CH-10), 122.05 (CH-1), 118.11 (CH_2-3'), 114.58 (CH-9), 113.25 (CH-7), 69.13 (CH_2-1'), 55.47 (CH_2-6), 40.64 (CH_3- on C-5).

*found from HSQC and HMBC.

HRMS ESI calcd. for $C_{17}H_{16}ClNO$ 285.0920, found 285.0855.

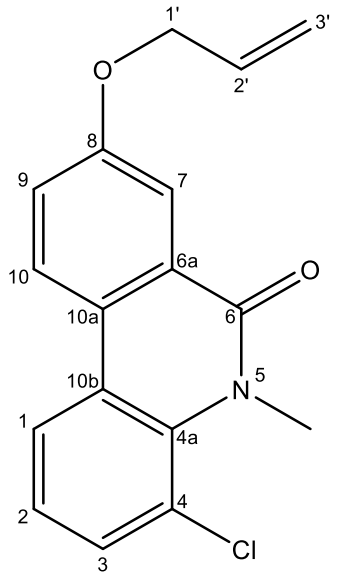


Spectrum 24: 600 MHz, $CDCl_3$, ^1H NMR spectrum of 8-(allyloxy)-4-chloro-5-methyl-5,6-dihydrophenanthridine (**64**).



Spectrum 25: 150 MHz, $CDCl_3$, ^{13}C NMR spectrum of 8-(allyloxy)-4-chloro-5-methyl-5,6-dihydrophenanthridine (**64**).

Synthesis of 4-chloro-5-methyl-8-propoxyphenanthridin-6(5H)-one (65)



65

8-(Allyloxy)-4-chloro-5-methyl-5,6-dihydrophenanthridine (**64**) oxidized to a solid while being stored. A small amount of **64** were left. It stood in the refrigerator for three weeks because of the second lockdown in the COVID-19 pandemic winter 2021. The mixture was purified by flash chromatography on silica gel eluted with 0.25:0.75:9 DCM:EtOAc:hexanes.

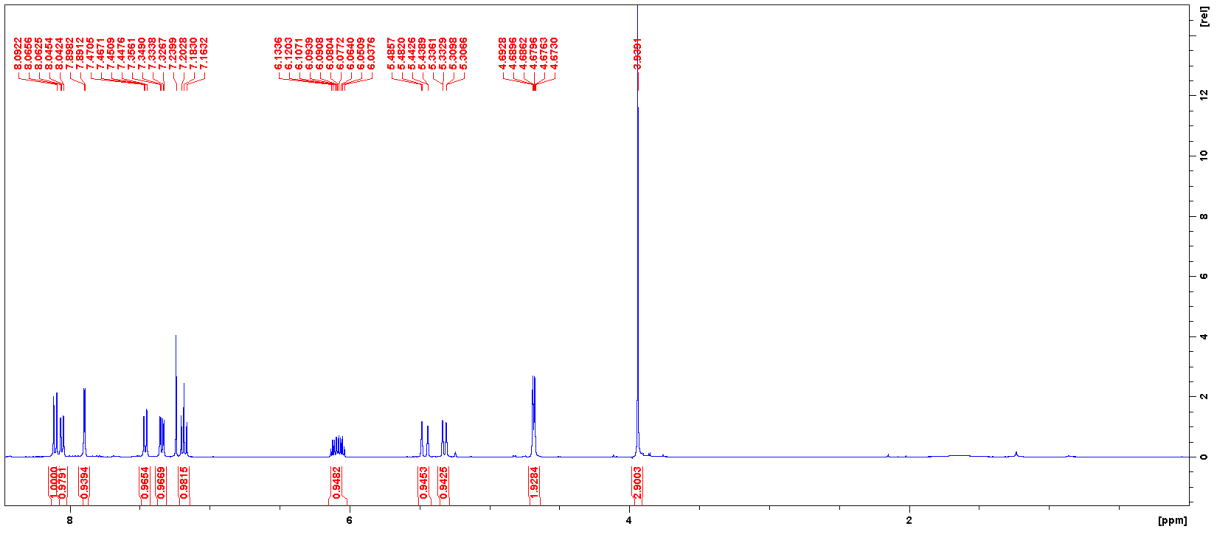
22 mg of compound **65** were isolated as a yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.9 Hz, 1H, H-10), 8.05 (dd, *J* = 1.2 Hz and 7.9 Hz, 1H, H-1), 7.89 (d, *J* = 2.8 Hz, 1H, H-7), 7.46 (dd, *J* = 1.2 Hz and 7.9 Hz, 1H, H-3), 7.34 (dd, *J* = 2.8 Hz and 8.9 Hz, 1H, H-9), 7.18 (app t, *J* = 7.9 Hz, 1H, H-2), 6.13-6.04 (m, 1H, H-2'), 5.49-5.44 (m, 1H, H-3'), 5.34-5.31 (m, 1H, H-3'), 4.69-4.67 (m, 2H, H-1'), 3.94 (s, 3H, CH_3- on C-5).

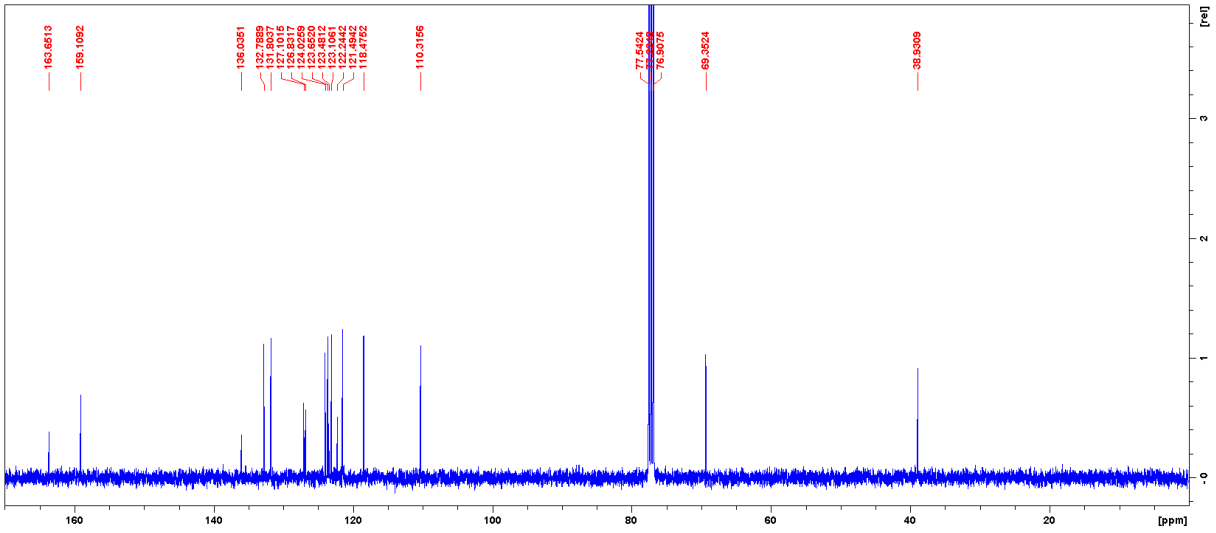
^{13}C NMR (150 MHz, $CDCl_3$) δ 163.65 (C-6), 159.11 (C-8), 136.04 (C-4a), 132.79 (CH-2'), 131.80 (CH-3), 127.10 (C-10b), 126.83 (C-10a), 124.03 (CH-10), 123.65 (CH-2), 123.48 (C-6a), 123.11 (CH-9), 122.24 (C-4), 121.49 (CH-1), 118.48 (CH_2-3'), 110.32 (CH-7), 69.35 (CH_2-2'), 38.93 (CH_3- on C-5).

HRMS ESI calcd. for $C_{17}H_{14}ClNO_2$ 299.0713, found 299.0703.

M.p. 100-101 °C.

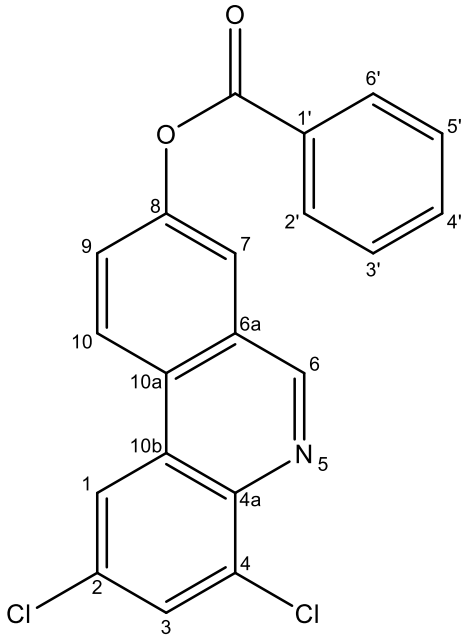


Spectrum 26: 400 MHz, $CDCl_3$, ^1H NMR spectrum of 4-chloro-5-methyl-8-propoxyphenanthridin-6(5H)-one (**65**).



Spectrum 27*:* 100 MHz, $CDCl_3$, ^{13}C NMR spectrum of 4-chloro-5-methyl-8-propoxyphenanthridin-6(5H)-one (**65**).

Synthesis of 2,4-dichlorophenanthridin-8-yl benzoate (69)



69

Compound **47a** (52.8 mg, 0.200 mmol) was dissolved in THF (2 mL) an put in an ice bath to lower the temperature. When it was around 0 ^{o}C, TEA (55.0 µL, 0.400 mmol) was added. After 5 min of stirring Benzoyl bromide (46.0 µL, 0.400 mmol) was added dropwise over 10 min. When the solution had stirred for 1 h in an ice bath, it was transferred to a separation funnel with brine (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure.

Yield: 71.0 mg (96%) as a colorless solid.

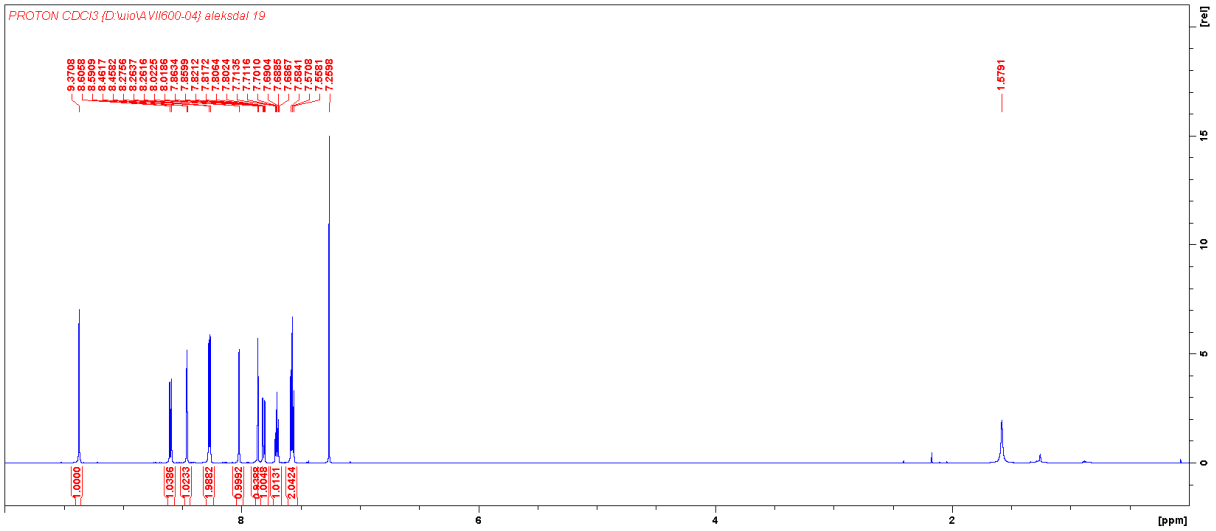
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.37 (s, 1H, H-6), 8.60 (d, *J* = 8.9 Hz, 1H, H-10), 8.46 (d, *J* = 2.1 Hz, 1H, H-1), 8.28-8.26 (m, 2H, H-3' and H-7'), 8.02 (d, *J* = 2.4 Hz, 1H, H-7), 7.86 (d, *J* = 2.1 Hz, 1H, H-3), 7.81 (dd, *J* = 2.4 Hz and 8.9 Hz, 1H, H-9), 7.69-7.71 (m, 1H, H-5'), 7.56-7.58 (m, 2H, H-4' and H-6').

^{13}C NMR (150 MHz, $CDCl_3$) δ 164.94 (C-1'), 153.52 (CH-6), 150.93 (C-8), 139.31 (C-4a), 135.58 (C-4), 134.14 (CH-5'), 132.95 (C-2), 130.34 (CH-3' and CH-7'), 129.44 (CH-3),

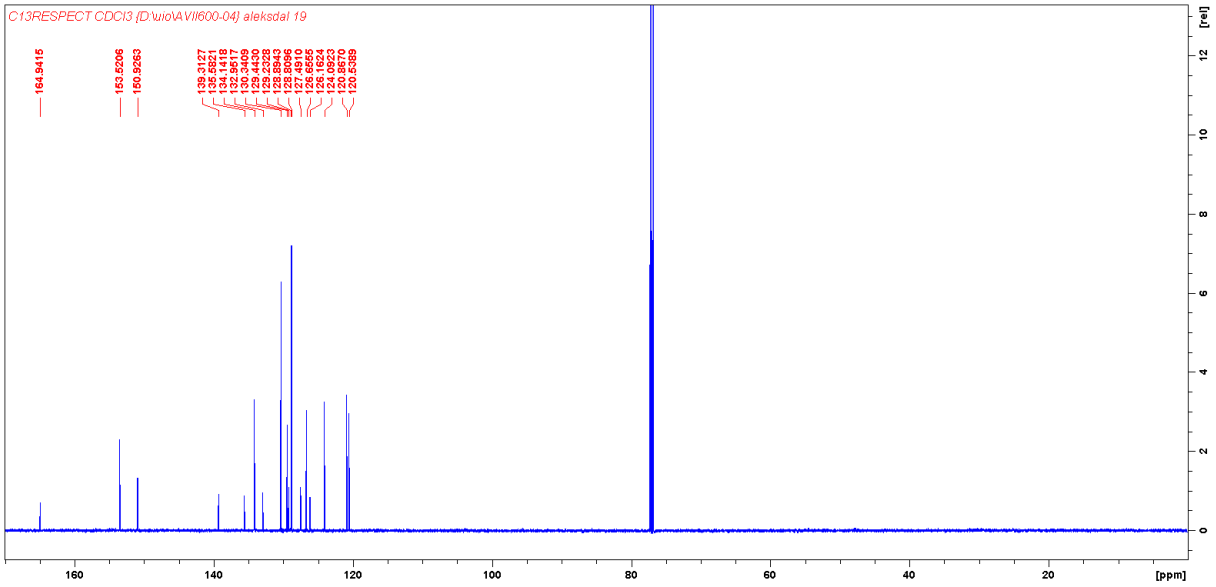
129.23 (C-2'), 128.89 (C-6a), 128.81 (CH-4' and CH-6'), 127.49 (C-10a), 126.65 (CH-9), 126.16 (C-10b), 124.09 (CH-10), 120.87 (CH-1), 120.54 (CH-7).

HRMS ESI calcd. for $C_{20}H_{11}Cl_2NO_2$ 367.0167, found 367.0161.

M.p. 221-222°C.

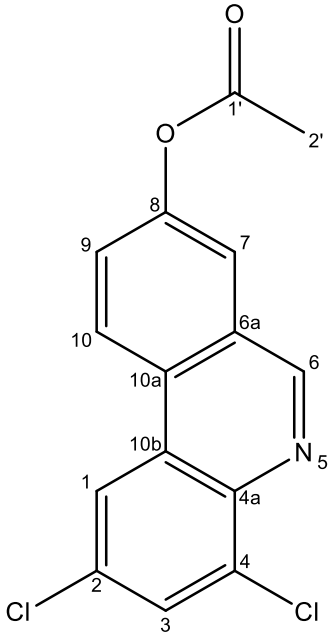


Spectrum 28: 600 MHz, $CDCl_3$, ^1H NMR spectrum of 2,4-dichlorophenanthridin-8-yl benzoate (**69**).



Spectrum 29: 150 MHz, $CDCl_3$, ^{13}C NMR spectrum of 2,4-dichlorophenanthridin-8-yl benzoate (**69**).

Synthesis of 2,4-dichlorophenanthridin-8-yl acetate (70)



70

TEA (52.0 µL, 0.380 mmol) and DMAP (0.650 mg, 5.32 x 10^{-3} mmol) was added to a stirring solution of compound **48a** (50.0 mg, 0.190 mmol) in DCM (3 mL). The solution was put in an ice bath and when the temperature was around 0 ºC, Ac_2O (36.0 µL, 0.380 mmol) was added dropwise, and the ice batch was removed. After 20 min of stirring at r.t., the solution was transferred to a separation funnel with DCM (25 mL). The organic phase was washed with water (25 mL) followed by brine (2 x 25 mL), dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The solution was isolated by flash chromatography eluted with 2:3:5 DCM:EtOAc:hexanes.

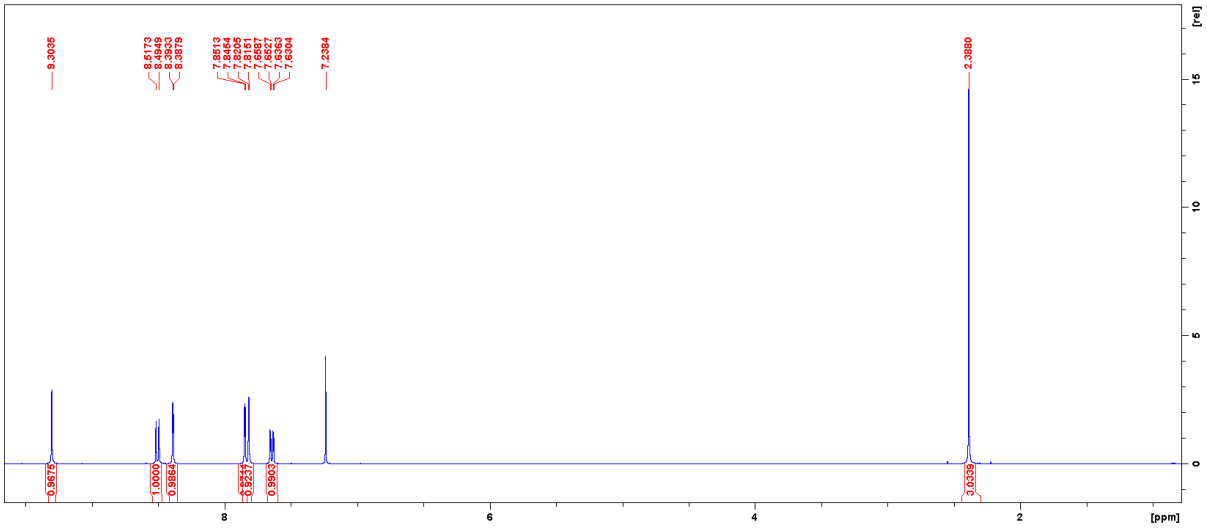
Yield: 50.0 mg (87%) as a colorless solid.

^{1}H NMR (600 MHz, Acetone-D_6) δ 9.30 (s, 1H, H-6), 8.51 (d, *J* = 9.0 Hz, 1H, H-10), 8.39 (d, *J* = 2.2 Hz, 1H, H-1), 7.85 (d, *J* = 2.4 Hz, 1H, H-7), 7.82 (d, *J* = 2.2 Hz, 1H, H-3), 7.64 (dd, *J* = 2.4 Hz and 9.0 Hz, 1H, H-9), 2.39 (s, 1H, H-2').

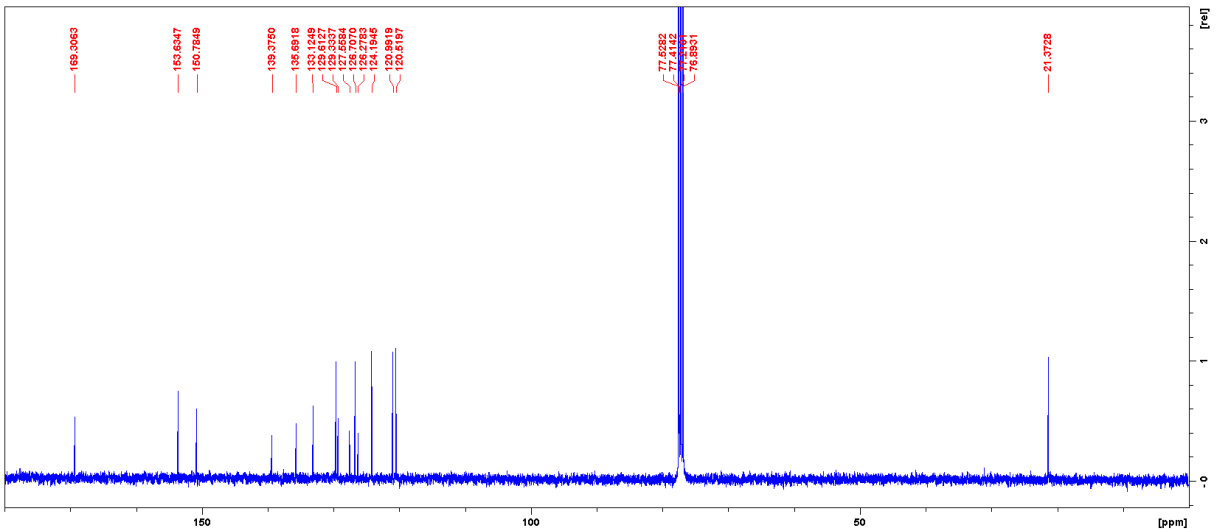
^{13}C NMR (150 MHz, Acetone-D_6) δ 169.32 (C-1'), 153.65 (CH-6), 150.86 (C-8), 139.39 (C-4a), 135.71 (C-4), 133.14 (C-2), 129.63 (CH-3), 129.35 (C-10a), 127.58 (C-6a), 127.72 (CH-9), 126.30 (C-10b), 124.21 (CH-10), 121.01 (CH-1), 120.54 (CH-7), 21.39 (CH_3-2').

HRMS ESI calcd. for $C_{15}H_9Cl_2NO_2$ 305.0010, found 305.0004.

M.p. 209-210 °C.

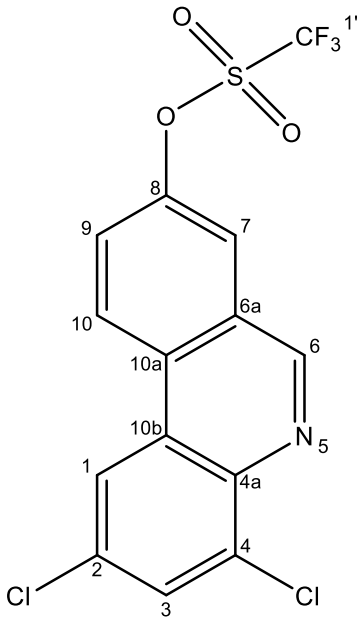


Spectrum 30: 400 MHz, $CDCl_3$, ^{1}H NMR spectrum of 2,4-dichlorophenanthridin-8-yl acetate (**70**).



Spectrum 31: 100 MHz, $CDCl_3$, ^{13}C NMR spectrum of 2,4-dichlorophenanthridin-8-yl acetate (**70**).

Synthesis of 2,4-dichlorophenanthridin-8-yl trifluoromethanesulfonate (71)



71

Argon was used to degas a flask with a stirring solution of compound **48a** (150 mg, 0.570 mmol) in pyridine (3 mL). The flask was put in an ice bath and when the temperature was around 0 ^oC, Trifilic anhydride (0.210 mL, 1.26 mmol) was added dropwise. The solution stirred at 0 ^oC for 10 min before the ice bath was removed. After 48 hours of stirring at r.t., the solution was transferred to a separation funnel with EtOAc (25 mL). The organic phase

was washed with 1M aq. $CuSO_4$ (3 x 25 mL), dried ($MgSO_4$), filtrated through a silica plug, eluted with DCM, and concentrated under reduced pressure.

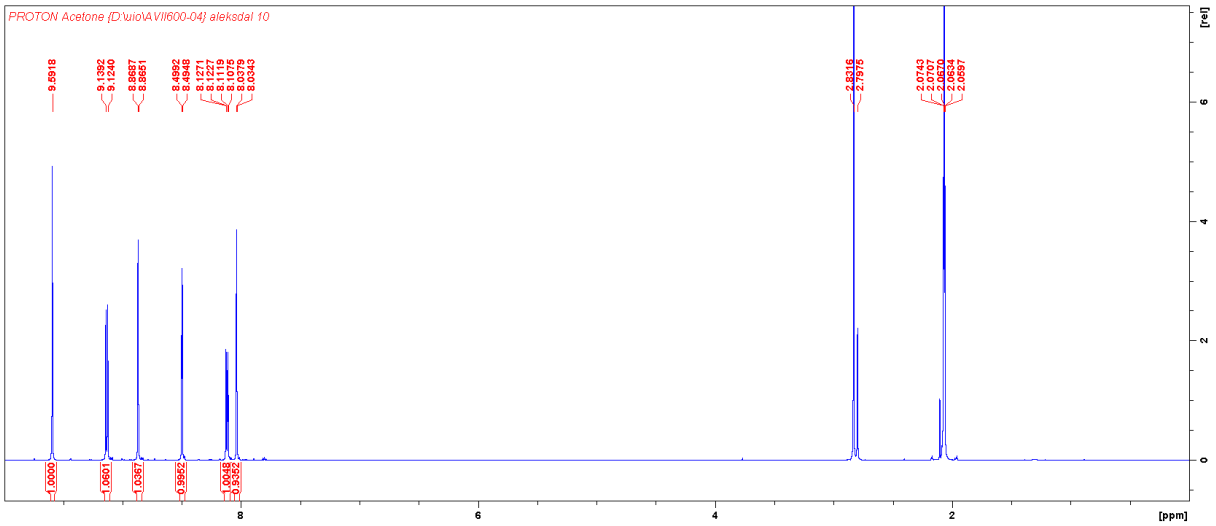
Yield: 217 mg (96%) as a colorless powder.

^{1}H NMR (600 MHz, Acetone-D_6) δ 9.59 (s, 1H, H-6), 9.13 (d, *J* = 9.1 Hz, 1H, H-10), 8.87 (d, *J* = 2.2 Hz, 1H, H-1), 8.50 (d, *J* = 2.6 Hz, 1H, H-7), 8.12 (dd, *J* = 2.6 Hz and 9.1 Hz, 1H, H-9), 8.04 (d, *J* = 2.2 Hz, 1H, H-3).

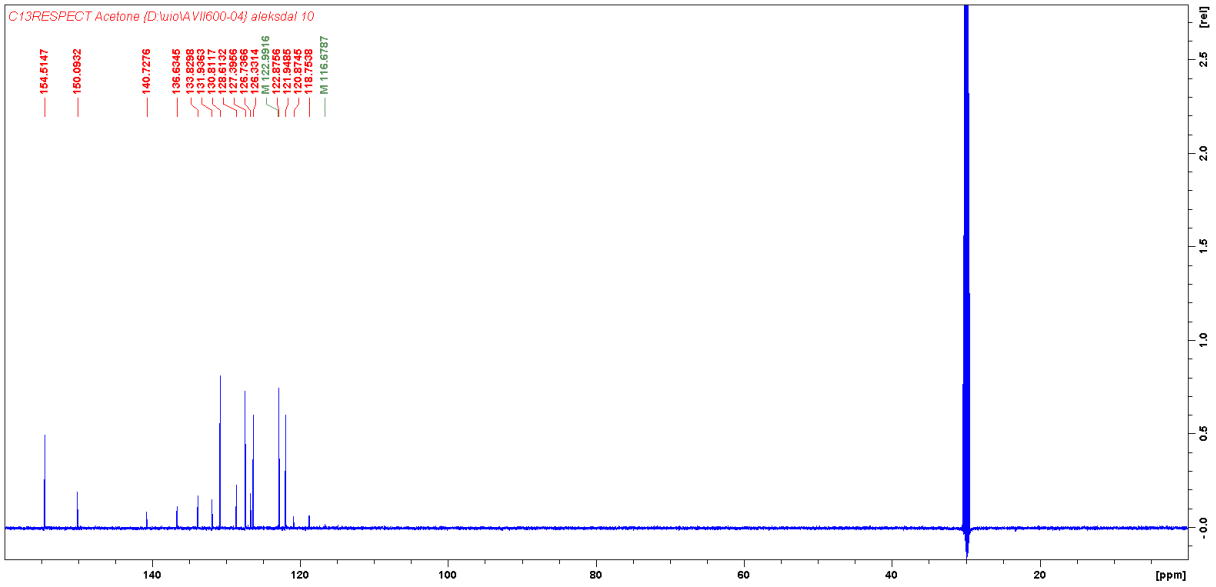
^{13}C NMR (150 MHz, Acetone-D_6) δ 154.51 (CH-6), 150.09 (C-8), 140.73 (C-4a), 136.63 (C-4), 133.83 (C-2), 131.94 (C-10a), 130.81 (CH-3), 128.61 (C-6a), 127.40 (CH-10), 126.74 (C-10b), 126.33 (CH-9), 122.88 (CH-1), 121.95 (CH-7), 119.81 (q, *J* = 320 Hz, C-1').

HRMS ESI calcd. for $C_{14}H_6Cl_2F_3NO_3S$ 394.9398, found 394.9392.

M.p. 148-149 °C.

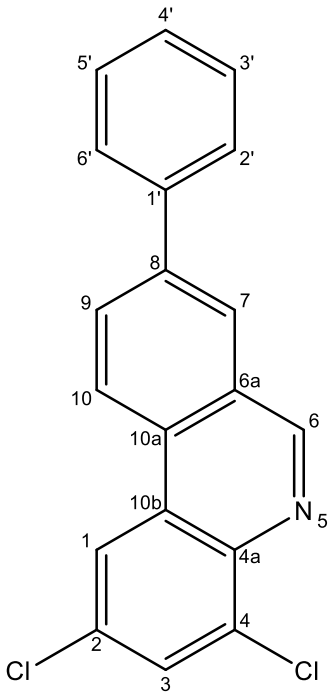


Spectrum 32: 600 MHz, Acetone-D_6, ^{1}H NMR spectrum of 2,4-dichlorophenanthridin-8-yl trifluoromethanesulfonate (**71**).



Spectrum 33: 150 MHz, Acetone-D_6, ^{13}C NMR spectrum of 2,4-dichlorophenanthridin-8-yl trifluoromethanesulfonate (**71**).

Synthesis of 2,4-dichloro-8-phenylphenanthridine (73)



73

K_2CO_3 (35.0 mg, 0.250 mmol), PPh_3 (18.0 mg, 0.060 mmol), $Pd(OAc)_2$ (16.0 mg, 0.070 mmol) and $PhB(OH)_2$ (31.0 mg, 0.250 mmol) were added to a stirring solution of compound **71** (75.0 mg, 0.190 mmol), EtOH (9.5 mL) and water (0.5 mL) under argon. An oil bath was used to raise the temperature of the solution to 80 ^oC, and after 24 h of stirring, the solution was filtrated through a plug of silica, eluted with DCM. The filtrate was dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The solution was isolated by flash chromatography eluted with 0.5:1:8.5 DCM:EtOAc:hexanes.

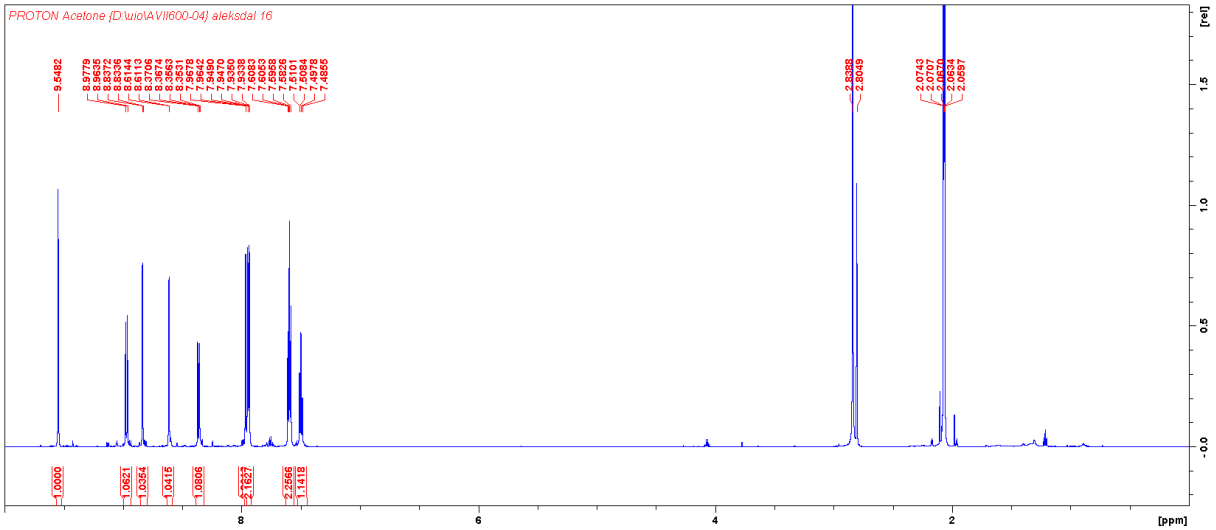
Yield: 85.0 mg (92%) as a colorless powder.

^{1}H NMR (600 MHz, Acetone-D_6) δ 9.55 (s, 1H, H-6), 8.97 (d, *J* = 8.6 Hz, 1H, H-10), 8.84 (d, *J* = 2.2 Hz, 1H, H-1), 8.61 (d, *J* = 1.9 Hz, 1H, H-7), 8.36 (dd, *J* = 1.9 Hz and 8.6 Hz, 1H, H-9), 7.97 (d, *J* = 2.2 Hz, 1H, H-3), 7.95-7.93 (m, 2H, H-2' and H-6'), 7.61-7.58 (m, 2H, H-3' and H-5'), 7.51-7.49 (m, 1H, H-4').

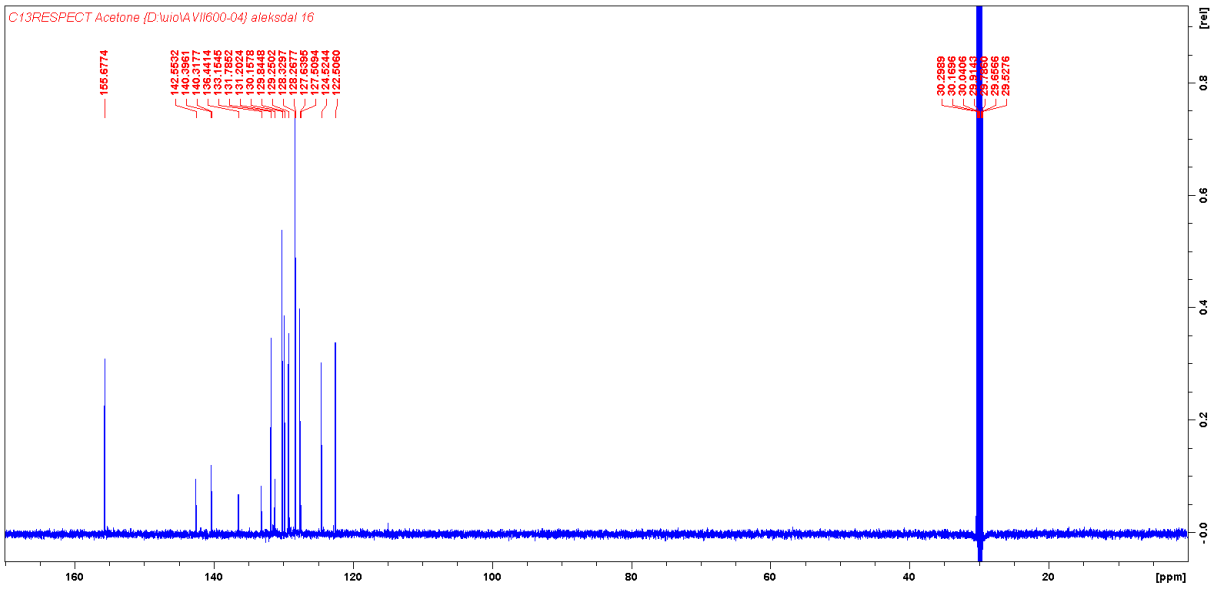
^{13}C NMR (150 MHz, Acetone-D_6) δ 155.68 (CH-6), 142.55 (C-8), 140.40 (C-1' or C-4a), 140.32 (C-1' or C-4a), 136.44 (C-4), 133.15 (C-2), 131.79 (CH-9), 131.20 (C-10a), 130.16 (CH-3' and CH-5'), 129.84 (CH-3), 129.25 (CH-4'), 128.33 (C-6a), 128.27 (CH-2' and CH-6'), 127.64 (CH-7), 127.51 (C-10b), 124.52 (CH-10), 122.51 (CH-1).

HRMS ESI calcd. for $C_{19}H_{11}Cl_2N$ 323.0269, found 323.0263.

M.p. 182-183 ^oC.

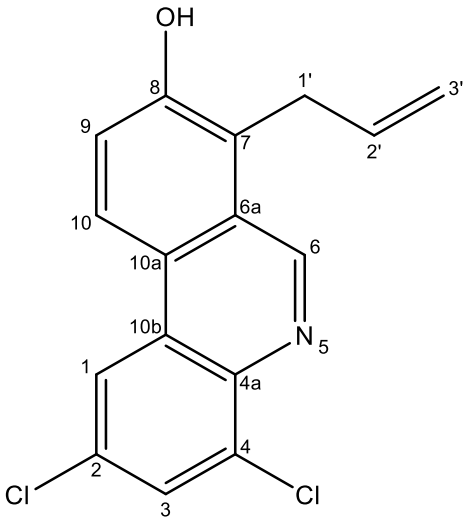


Spectrum 34: 600 MHz, Acetone-D_6, ^{1}H NMR spectrum of 2,4-dichloro-8-phenylphenanthridine (**73**).



Spectrum 35: 150 MHz, Acetone-D_6, ^{13}C NMR spectrum of 2,4-dichloro-8-phenylphenanthridine (**73**).

Synthesis of 7-allyl-2,4-dichlorophenanthridin-8-ol (71b)



71b

Compound **55** (40.0 mg, 0.130 mmol) was added to a pressure vial with toluene (4 mL) and a magnetic stirrer under argon. The vial with the solution stirred at 250 ^{o}C for 45 min in a microwave reactor and cooled down to 55 ^{o}C before it was removed. The solution was transferred to a round bottom flask and concentrated under reduced pressure to remove the solvent. The crude product was then isolated by flash chromatography eluted with 0.25:0.75:9 DCM:EtOAc:hexanes.

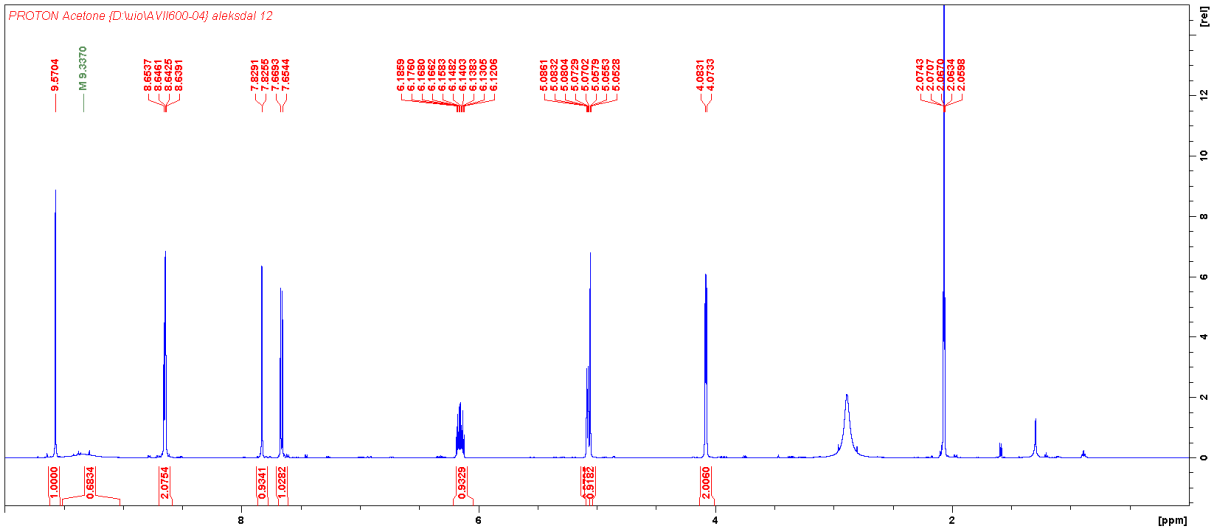
Yield: 38.0 mg (95%) as a colorless solid.

^{1}H NMR (600 MHz, Acetone-D_6) δ 9.57 (s, 1H, H-6), 9.34 (bd, 1H, -OH), 8.65 (d, *J* = 8.8 Hz, 1H, H-10), 8.64 (d, *J* = 2.2 Hz, 1H, H-1), 7.83 (d, *J* = 2.2 Hz, 1H, H-3), 7.66 (d, *J* = 8.9 Hz, 1H, H-9), 6.19-6.12 (m, 1H, H-2'), 5.09-5.07 (m, 1H, H-3'), 5.06-5.05 (m, 1H, H-3'), 4.08 (d, *J* = 5.9 Hz, 2H, H-1').

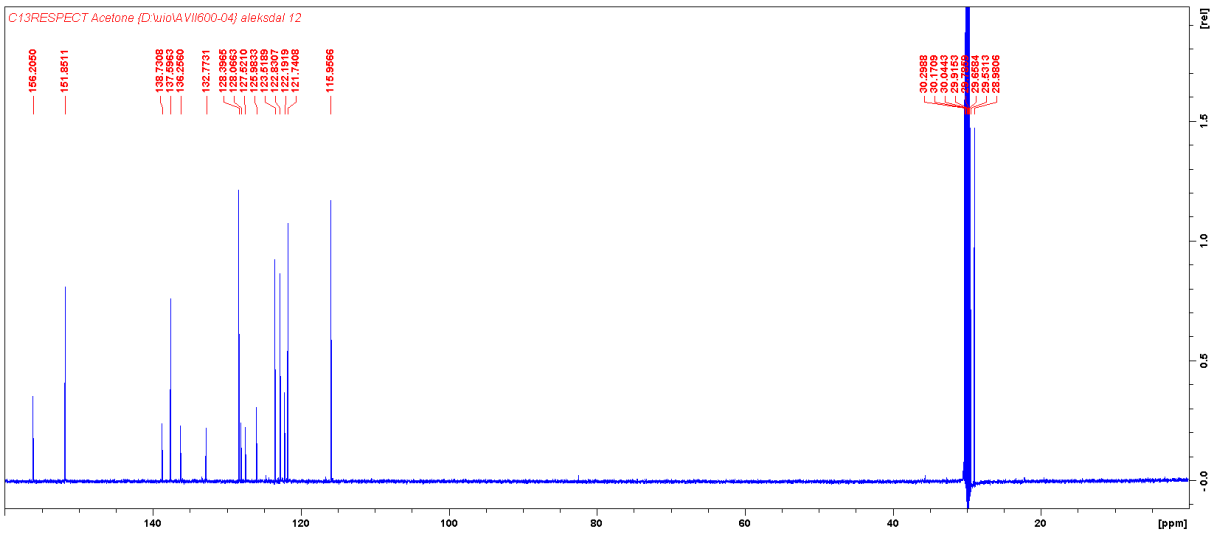
^{13}C NMR (150 MHz, Acetone-D_6) δ 156.21 (C-8), 151.85 (CH-6), 138.73 (C-4a), 137.60 (CH-2'), 136.26 (C-4), 132.77 (C-2), 128.40 (CH-3), 128.07 (C-6a or C-10b), 127.52 (C-6a or C-10b), 125.98 (C-10a), 123.52 (CH-10), 122.83 (CH-9), 122.19 (C-7), 121.74 (CH-1), 115.96 (CH_2-3'), 28.98 (CH_2-1').

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

M.p. 250-251^{o}C.

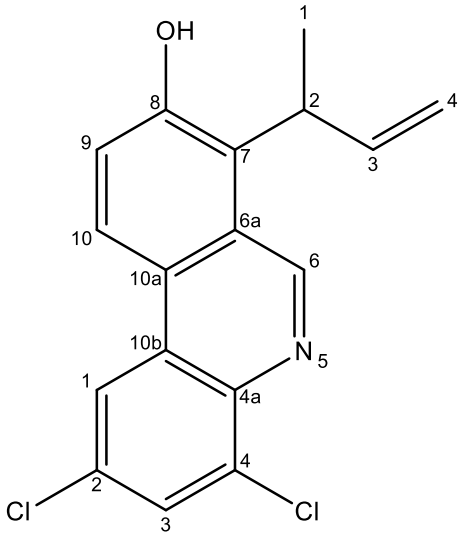


Spectrum 36: 600 MHz, Acetone-D_6, ^{1}H NMR spectrum of 7-allyl-2,4-dichlorophenanthridin-8-ol (**74b**).



Spectrum 37: 150 MHz, Acetone-D_6, ^{13}C NMR spectrum of 7-allyl-2,4-dichlorophenanthridin-8-ol (**74b**).

Synthesis of 7-(but-3-en-2-yl)-2,4-dichlorophenanthridin-8-ol (75)



75

Compound **57** (30.0 mg, 0.090 mmol) was dissolved in toluene (4 mL) and transferred to a pressure vial with a magnetic stirrer under argon. The solution stirred for 45 min at 250 ^{o}C in a microwave instrument, transferred to a round bottom flask and concentrated under reduced pressure. The crude product was purified by flash chromatography eluted with 0.25:0.75:9 DCM:EtOAc:hexanes.

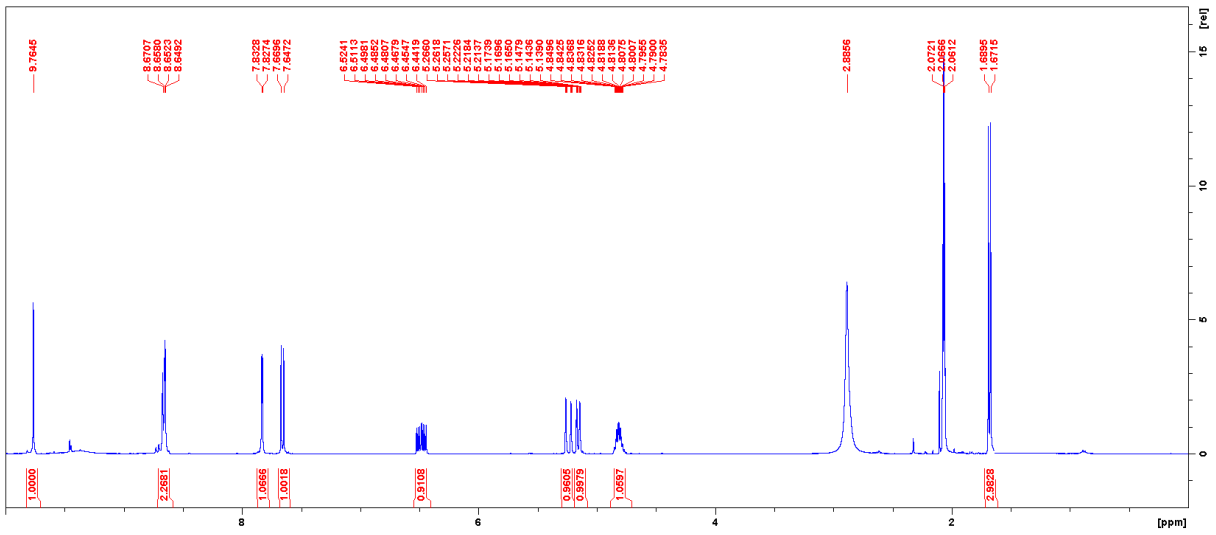
Yield: 23.0 mg (78%) as a colorless solid.

^{1}H NMR (400 MHz, Acetone-D_6) δ 9.76 (s, 1H, H-6), 8.67-8.65 (m, 2H, H-1 and H-10) 7.83 (d, *J* = 2.1 Hz, 1H, H-3), 7.66 (d, *J* = 9.0 Hz, 1H, H-9), 6.52-6.44 (m, 1H, H-2'), 5.27-5.21 (m, 1H, H-3'), 5.17-5.14 (m, 1H, H-3'), 4.85-4-78 (m, 1H, H-1'), 1.68 (d, *J* = 7.2 Hz, 3H, CH_3- on C-1').

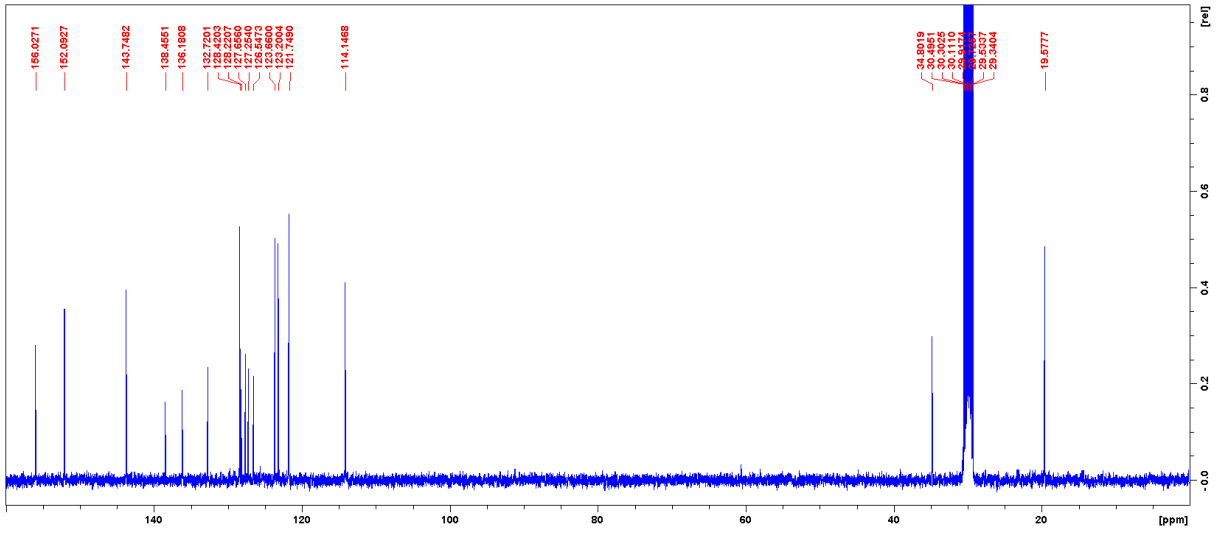
^{13}C NMR (100 MHz, Acetone-D_6) δ 156.03 (C-8), 152.09 (CH-6), 143.75 (CH-2'), 138.45 (C-4a), 136.18 (C-4), 132.72 (C-2), 128.42 (CH-3), 128.22 (C-10a), 127.66 (C-6a), 127.25 (C-7), 126.55 (C-10b), 123.66 (CH-10), 123.20 (CH-9), 121.75 (CH-1), 114.15 (CH_2-3'), 34.80 (CH-1'), 19.58 (CH_3 on C-1').

HRMS ESI calcd. for $C_{17}H_{13}Cl_2NO$ 317.0374, found 317.0369.

M.p. 240-241^{o}C.

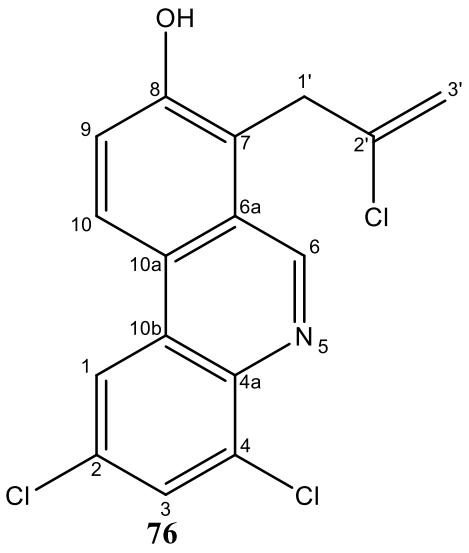


Spectrum 38: 400 MHz, Acetone-D_6, ^{1}H NMR spectrum of 7-(but-3-en-2-yl)-2,4-dichlorophenanthridin-8-ol (**75**).



Spectrum 39: 100 MHz, Acetone-D_6, ^{13}C NMR spectrum of 7-(but-3-en-2-yl)-2,4-dichlorophenanthridin-8-ol (**75**).

Synthesis of 2,4-dichloro-7-(2-chloroallyl)phenanthridin-8-ol (76)



76

A pressure vial with compound **60** (35.0 mg, 0.104 mmol) and toluene (4 mL) under argon, stirred for 45 min at 250 ºC in a microwave instrument before it was transferred to a round bottom flask and concentrated under reduced pressure. The crude product was purified by flash chromatography eluted with 0.25:0.75:9 DCM:EtOAc:hexanes.

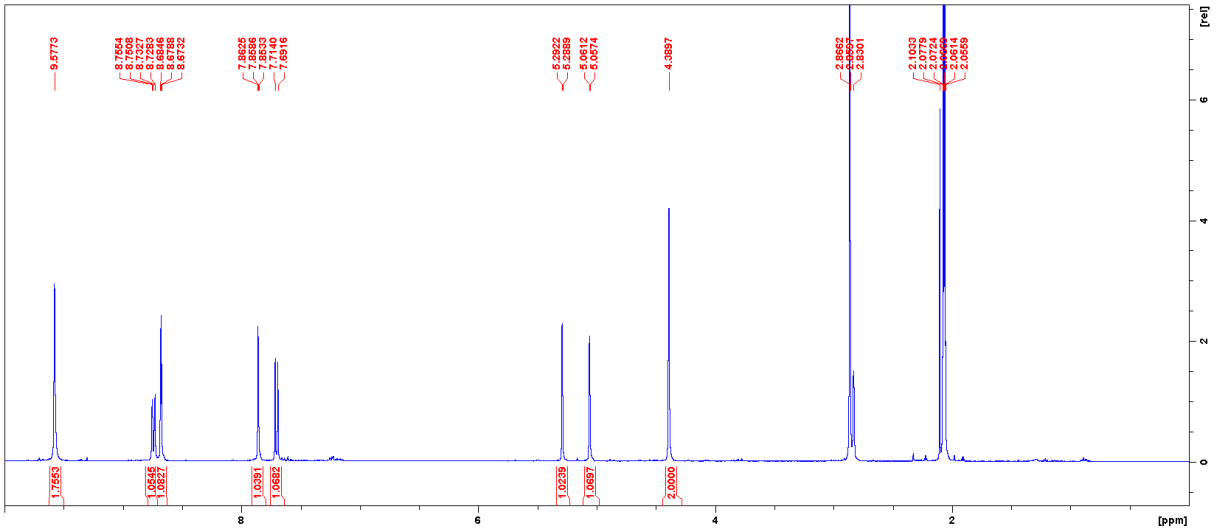
Yield: 29.2 mg (83%) as a colorless solid.

^{1}H NMR (400 MHz, Acetone-D_6) δ 9.57 (s, 2H, H-6 and -OH), 8.74 (d, *J* = 8.9 Hz, 1H, H-10), 8.68 (d, *J* = 2.2 Hz, 1H, H-1), 7.85 (d, *J* = 2.2 Hz, 1H, H-3), 7.69 (d, *J* = 8.9 Hz, 1H, H-9), 5.28-5.27 (m, 1H, H-3'), 5.05-5.04 (m, 1H, H3'), 4.38 (s, 2H, H-1').

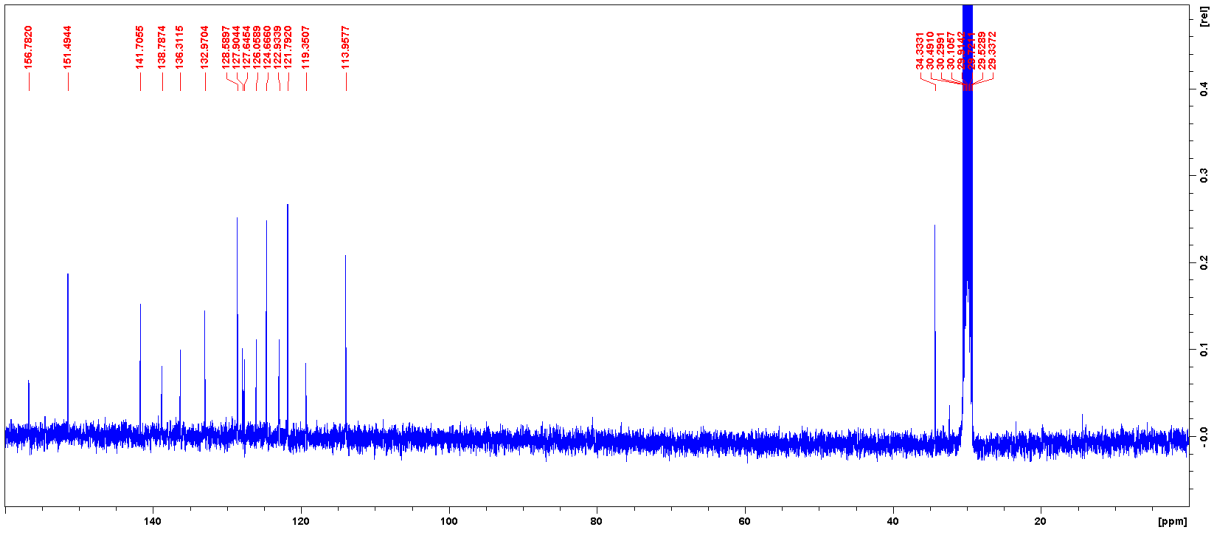
^{13}C NMR (100 MHz, Acetone-D_6) δ 156.78 (C-8), 151.49 (CH-6), 141.71 (C-2'), 138.79 (C-4a), 136.31 (C-4), 132.97 (C-2), 128.59 (CH-3), 127.90 (C-6a), 127.65 (C-10b), 126.06 (C-10a), 124.67 (CH-10), 122.93 (CH-9), 121.79 (CH-1), 119.35 (C-7), 113.96 (CH_2-3'), 34.33 (CH_2-1').

HRMS ESI calcd. for $C_{16}H_{10}Cl_3NO$ 336.9828, found 336.9822.

M.p. 264-265 ºC.

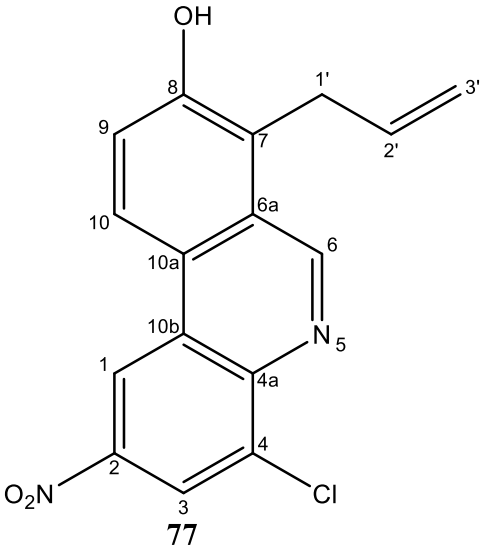


Spectrum 40: 400 MHz, Acetone-D_6, ^{1}H NMR spectrum of 2,4-dichloro-7-(2-chloroallyl)phenanthridin-8-ol (**76**).



Spectrum 41: 100 MHz, Acetone-D_6, ^{13}C NMR spectrum of 2,4-dichloro-7-(2-chloroallyl)phenanthridin-8-ol (**76**).

Synthesis of 7-allyl-4-chloro-2-nitrophenanthridin-8-ol (77)



77

A solution of compound **61** (35.0 mg, 0.110 mmol) dissolved in toluene (4 mL) was transferred to a pressure vial. The vial was filled with argon before stirring in a microwave reactor at 250 ºC. After 45 min the solution was transferred to a round bottom flask and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, eluted with 0.25:0.75:9 DCM:EtOAc:hexanes.

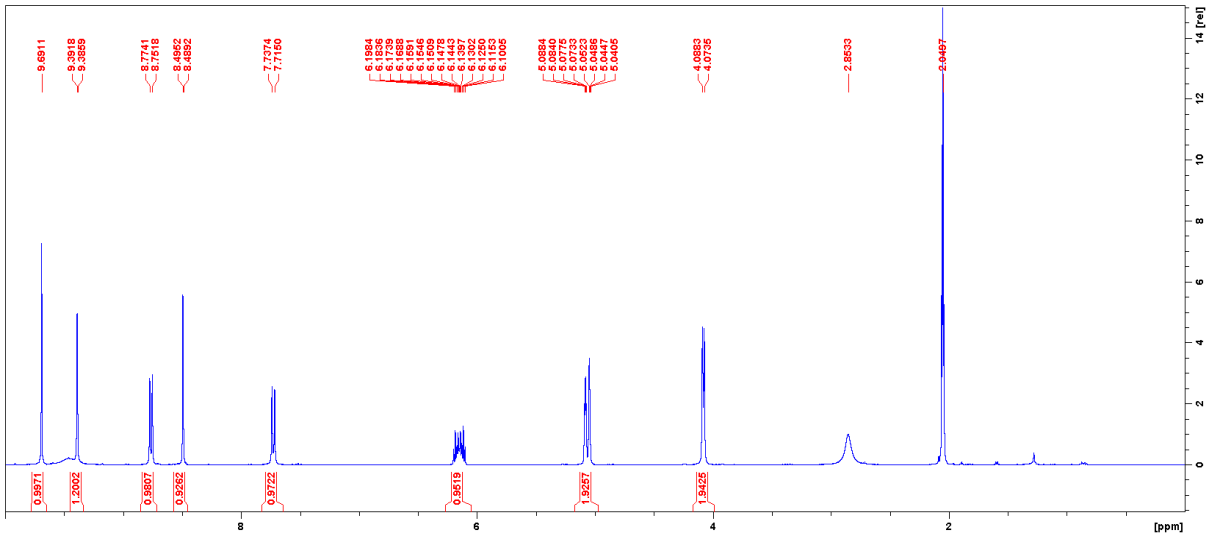
Yield: 22.0 mg (63%) as a yellow solid.

^{1}H NMR (400 MHz, acetone-D_6) δ 9.69 (s, 1H, H-6), 9.39 (d, *J* = 2.4 Hz, 1H, H-1), 8.76 (d, *J* = 8.9 Hz, 1H, H-10), 8.49 (d, *J* = 2.4 Hz, 1H, H-3), 7.73 (d, *J* = 8.9 Hz, 1H, H-9), 6.20-6.10 (m, 1H, H-2'), 5.09-5.07 (m, 1H, H-3'), 5.05-5.04 (m, 1H, H-3'), 4.09-4.07 (m, 2H, H-1').

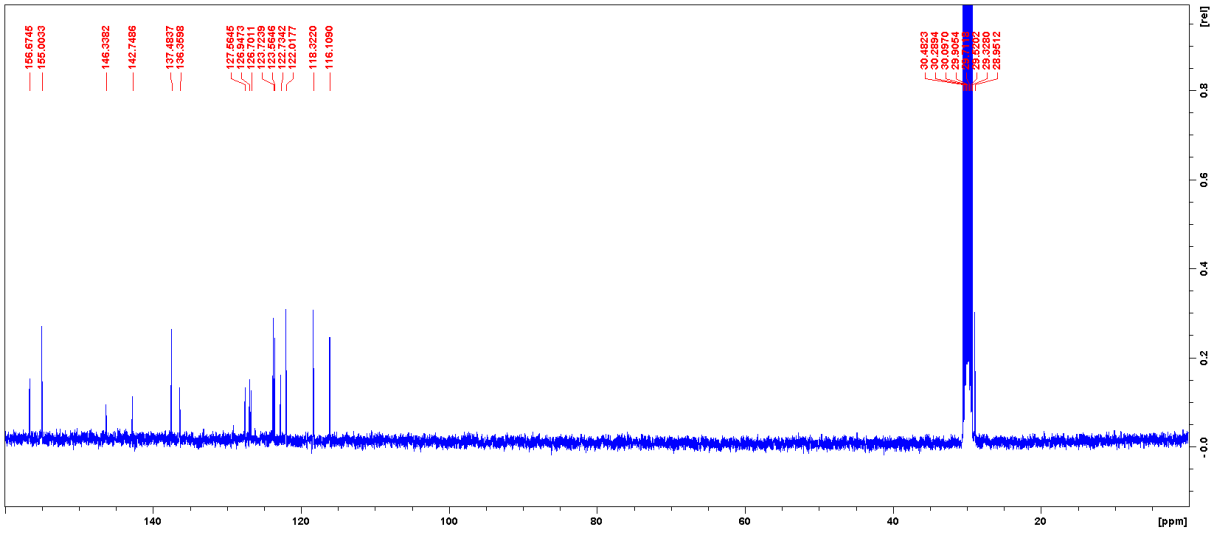
^{13}C NMR (100 MHz, acetone-D_6) δ 156.67 (C-8), 155.00 (CH-6), 146.33 (C-2), 142.74 (C-4a), 137.48 (CH-2'), 136.35 (C-4), 127.56 (C-6a), 126.94 (C-10a), 126.69 (C-10b), 123.72 (CH-10), 123.56 (CH-9), 122.73 (C-7), 122.01 (CH-3), 118.32 (CH-1), 116.10 (CH_2-3'), 28.94 (CH_2-1').

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

M.p. 249-250 ºC.

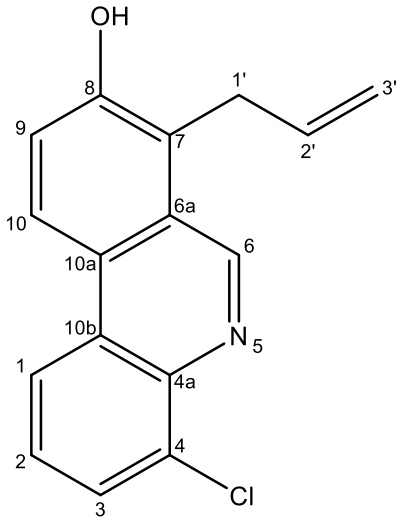


Spectrum 42: 400 MHz, Acetone-D_6, ^{1}H NMR spectrum of 7-allyl-4-chloro-2-nitrophenanthridin-8-ol (**77**).



Spectrum 43: 100 MHz, Acetone-D_6, ^{13}C NMR spectrum of 7-allyl-4-chloro-2-nitrophenanthridin-8-ol (**77**).

Synthesis of 7-allyl-4-chlorophenanthridin-8-ol (78)



78

Compound **62** (35.0 mg, 0.130 mmol) and toluene (4 mL) was added to a pressure vial under argon. The solution stirred for 45 min at 250 ºC in a microwave instrument before it was transferred to a round bottom flask and concentrated under reduced pressure. The crude product was purified by flash chromatography eluted with 0.25:0.75:9 DCM:EtOAc:hexanes.

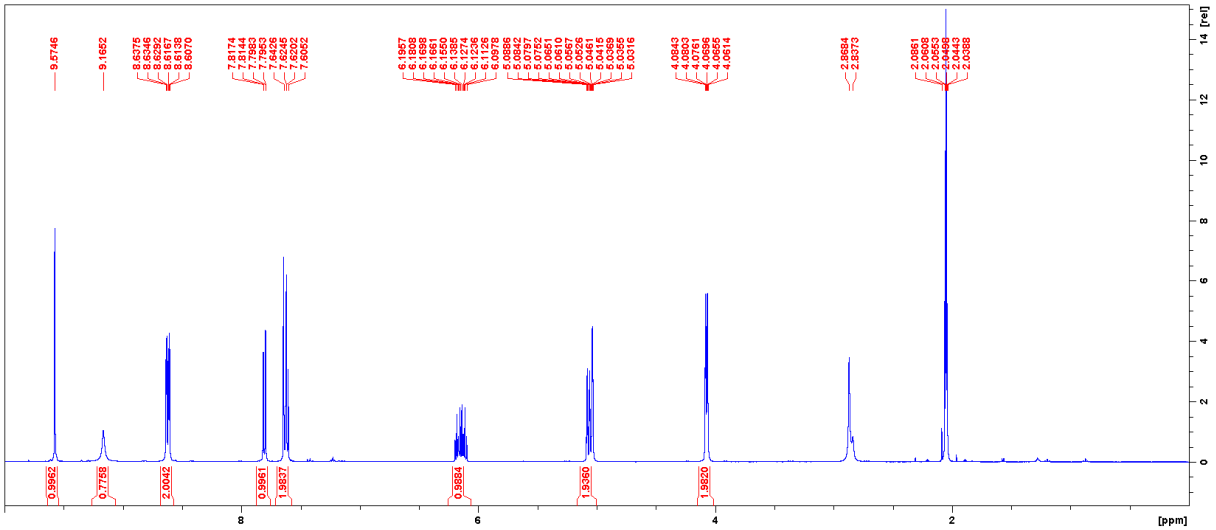
Yield: 30. mg (86%) as a colorless solid

^{1}H NMR (400 MHz, Acetone-D_6) δ 9.57 (s, 1H, H-6), 9.17 (bs, 1H, -OH), 8.63 (dd, *J* = 1.2 Hz, 1H, H-1), 8.62 (d, *J* = 8.9 Hz, 1H, H-10), 7.81 (dd, *J* = 1.2 Hz, 1H, H-3), 7.62 (app t, 1H, H-2), 7.63 (d, *J* = 8.9 Hz, 1H, H-9), 6.20-6.10 (m, 1H, H-2'), 5.09-5.05 (m, 1H, H-3'), 5.05-5.03 (m, 1H, H-3'), 4.08-4.06 (m, 2H, H-1').

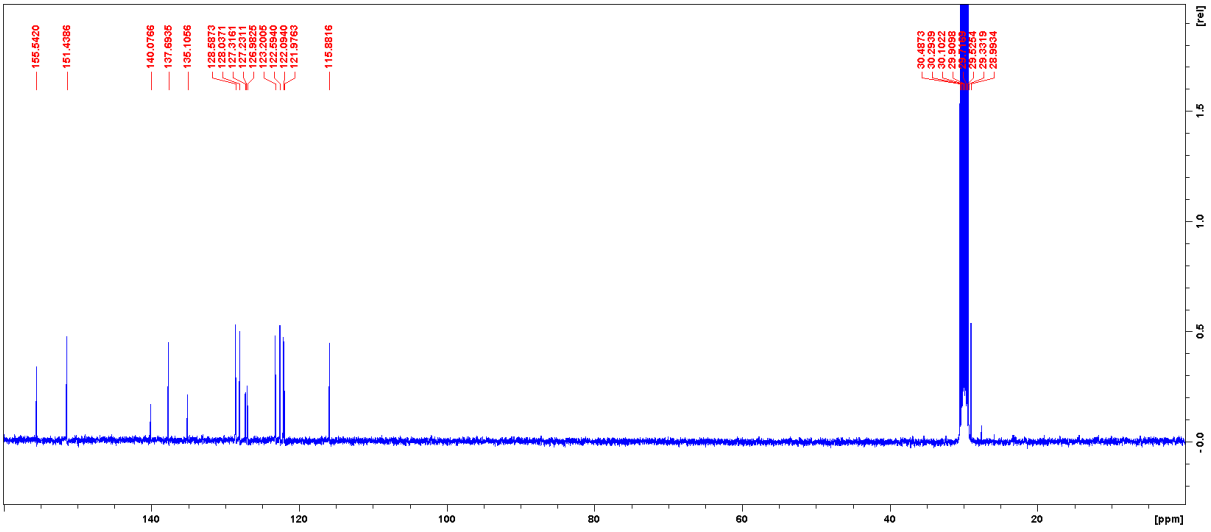
^{13}C NMR (100 MHz, Acetone-D_6) δ 155.54 (C-8), 151.44 (CH-6), 140.08 (C-4a), 137.70 (CH-2'), 135.11 (C-4), 128.59 (CH-3), 128.04 (CH-2), 127.32 (C-10a), 127.23 (C-10b), 126.99 (C-6a), 123.20 (CH-10), 122.60 (CH-9), 122.10 (CH-1), 121.98 (C-7), 115.88 (CH_2-3'), 29.00 (CH_2-1').

HRMS ESI calcd. for $C_{16}H_{12}ClNO$ 269.0607, found 269.0602.

M.p. 245-246 ºC.

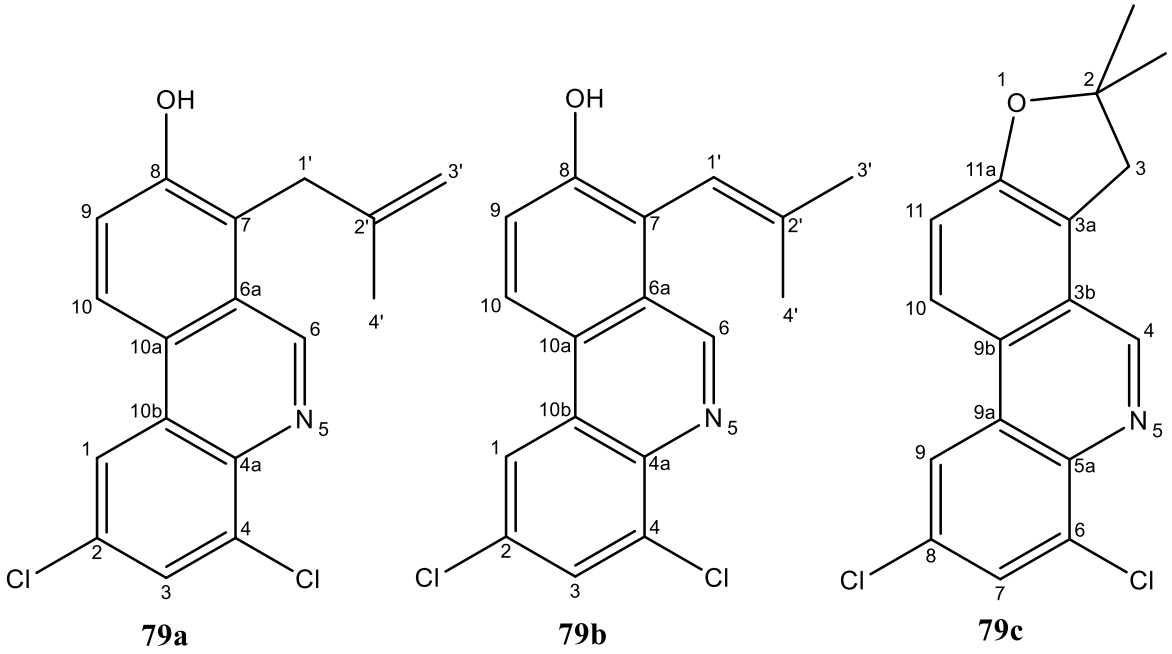


Spectrum 44: 400 MHz, Acetone-D_6, ^{1}H NMR spectrum of 7-allyl-4-chlorophenanthridin-8-ol (**78**).



Spectrum 45: 100 MHz, Acetone-D_6, ^{13}C NMR spectrum of 7-allyl-4-chlorophenanthridin-8-ol (**78**).

Synthesis of 2,4-dichloro-7-(2-methylallyl)phenanthridin-8-ol (79a), 2,4-dichloro-7-(2-methylprop-1-en-1-yl)phenanthridin-8-ol (79b) and 6,8-dichloro-2,2-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridine (79c)



Compound **59** (35.0 mg, 0.110 mmol) was dissolved in toluene (4 mL) and added to a pressure vial under argon. The solution stirred for 45 min at 250 ^{o}C in a microwave reactor, before it was transferred to a round bottom flask and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluted with 0.25:0.75:9 DCM:EtOAc:hexanes.

Yield* (**79a**): 9.63 mg (28%) as a colorless solid.

Yield* (**79b**): 7.27 mg (21%) as a colorless solid.

Yield (**79c**): 12.2 mg (35%) as a colorless solid.

*calculated from the isolated mixture and ratio of **79a** and **79b**.

^{1}H NMR of 79a (400 MHz, DMSO-d_6) δ 10.36 (s, 1H, -OH), 9.45 (s, 1H, H-6), 877-8.75 (m, 1H, H-1), 8.70-8.67 (m, 1H, H-10), 7.94-7.93 (m, 1H, H-3), 7.57 (d, *J* = 8.9 Hz, 1H, H-9), 4.74 (s, 1H, H-3'), 4.35 (s, 1H, H-3'), 3.88 (s, H2, H-1'), 1.82 (s, 3H, H-4').

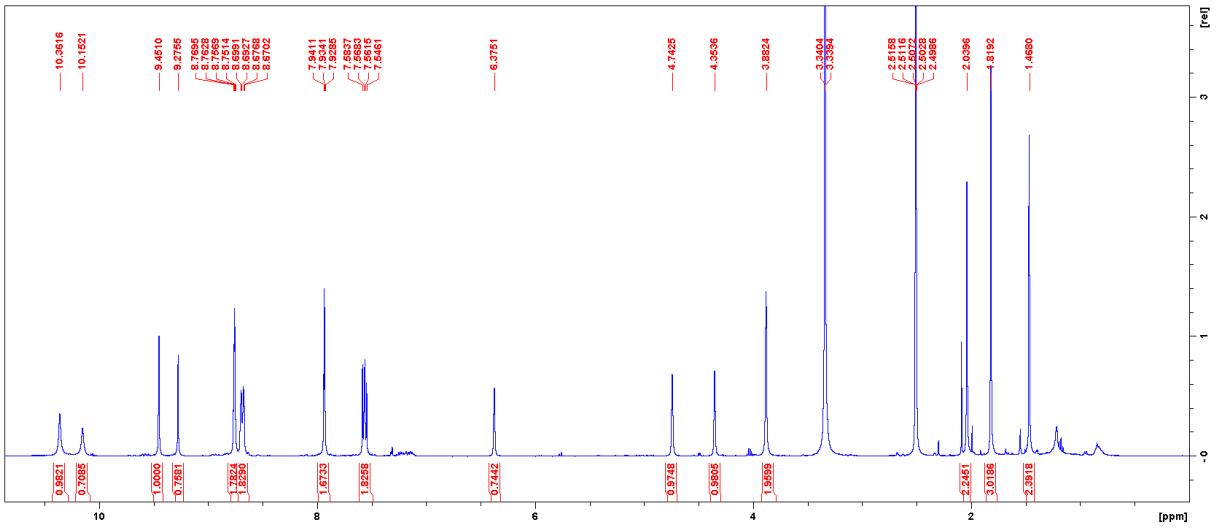
^{1}H NMR of 79b (400 MHz, DMSO-d_6) δ 10.15 (s, 1H, -OH), 9.28 (s, 1H, H-6), 8.77-8.75 (m, 1H, H-1), 8.70-8.67 (m, 1H, H-10), 7.94-7.93 (m, 1H, H-3), 7.56 (d, *J* = 8.9 Hz, 1H, H-9), 6.38 (s, 1H, H-1'), 2.04 (s, 3H, H-3'), 1.47 (s, 3H, H-4').

^{1}H NMR of 79c (400 MHz, DMSO-d_6) δ 9.31 (s, 1H, H-4), 8.79 (d, *J* = 2.1 Hz, 1H, H-9), 8.73 (d, *J* = 8.8 Hz, 1H, H-11), 7.95 (d, *J* = 2.1 Hz, 1H, H-7), 7.49 (d, *J* = 8.8 Hz, 1H, H-7), 3.54 (s, 1H, H-3), 1.56 (s, 6H, methyl on 2).

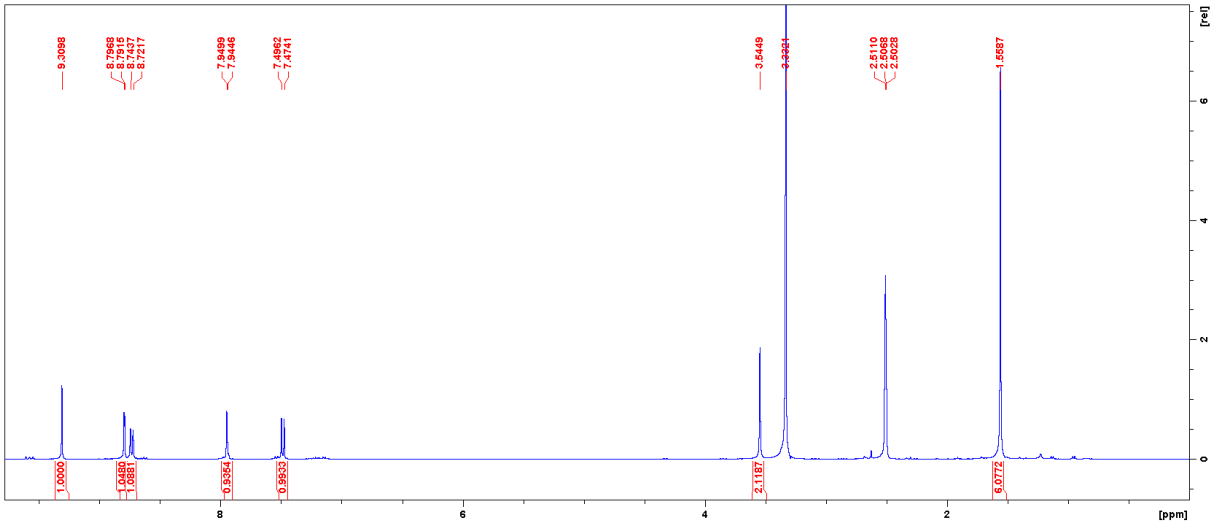
^{13}C NMR of 79c (100 MHz, DMSO-d_6) δ 159.41 (C-11a), 151.77 (CH-4), 137.80 (C-5a), 135.13 (C-6), 132.13 (C-8), 127.85 (CH-7), 127.55 (C-9b), 124.92 (C-3a or C-9a), 124.69 (CH-11), 124.31 (C-3a or C-9a), 123.27 (C-3b), 121.79 (CH-9), 116.50 (CH-10), 89.77 (C-2), 28.61 (CH_3-on 2).

M.p for 79c: 204-205 ^{o}C.

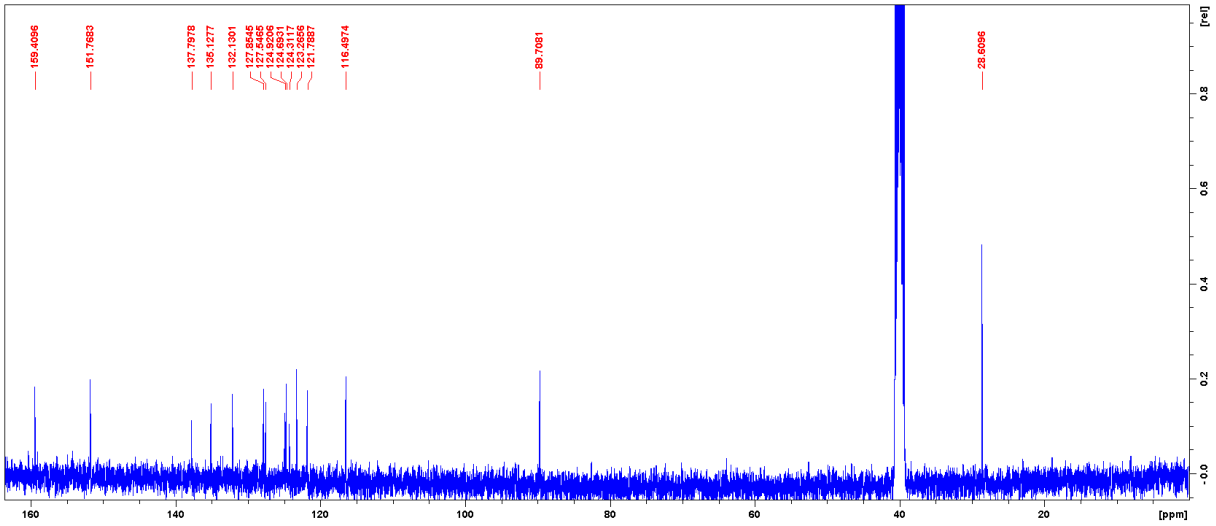
HRMS ESI for all three compounds, calcd. for $C_{17}H_{13}Cl_2NO$ 317.0374, found 317.0368.



Spectrum 46: 400 MHz, Acetone-D_6, ^{1}H NMR spectrum of 2,4-dichloro-7-(2-methylallyl)phenanthridin-8-ol (**79a**), 2,4-dichloro-7-(2-methylprop-1-en-1-yl)phenanthridin-8-ol (**79b**)

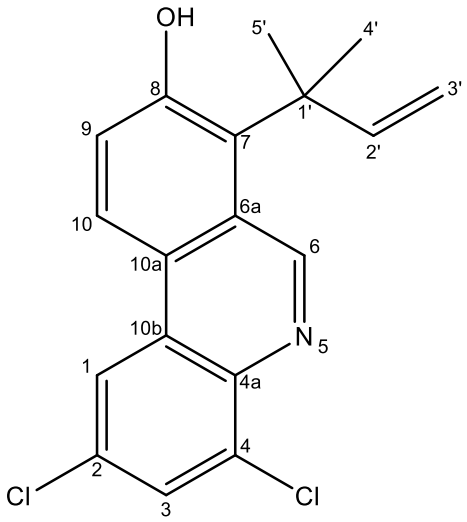


Spectrum 47: 400 MHz, Acetone-D_6, ^{1}H NMR spectrum of 6,8-dichloro-2,2-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridine (**79c**).



Spectrum 48: 400 MHz, Acetone-D_6, ^{13}C NMR spectrum of 6,8-dichloro-2,2-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridine (**79c**).

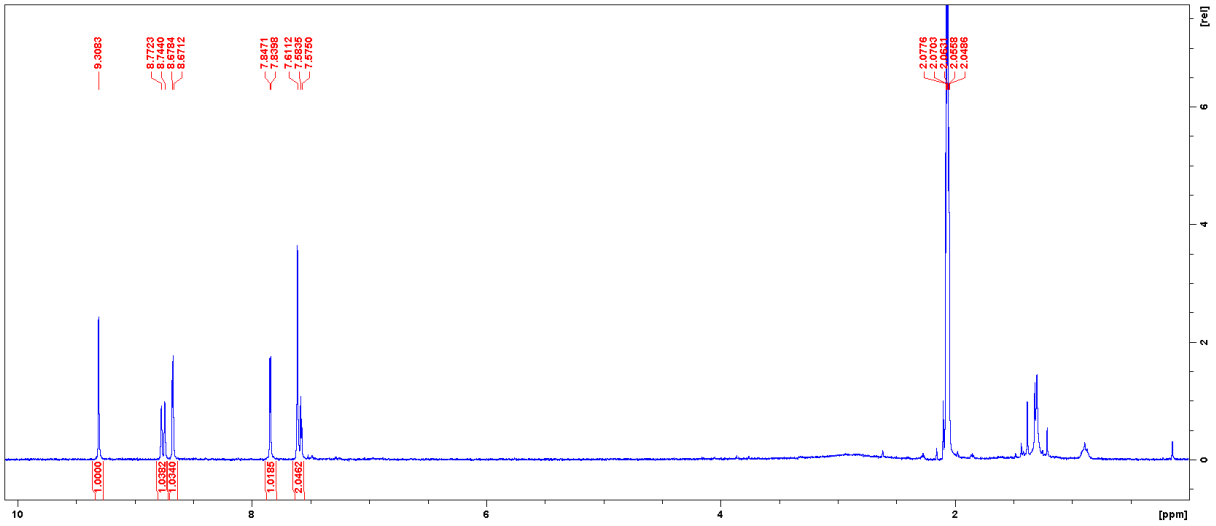
Synthesis of 2,4-dichloro-7-(2-methylbut-3-en-2-yl)phenanthridin-8-ol (80)



80

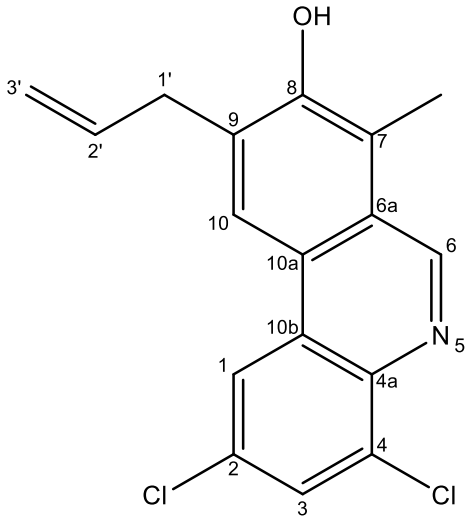
Compound **58** (50.3 mg, 0.150 mmol) and toluene (4 mL) were added to a pressure vial under argon. The solution stirred for 45 min at 250 ^{o}C in a microwave reactor, before it was transferred to a round bottom flask and concentrated under reduced pressure. By looking at the ^{1}H NMR of the crude product, the allyl group could not be seen. The allyl had been cleaved of resulting in production of compound **48a**. The crude product was purified by flash chromatography on silica gel eluted with 0.25:0.75:9 DCM:EtOAc:hexanes.

Isolated yield of compound **48a**: 33.4 mg (85%) as a colorless solid.



Spectrum 49: ^{1}H NMR spectrum of compound **48a**.

Synthesis of 9-allyl-2,4-dichloro-7-methylphenanthridin-8-ol (81)

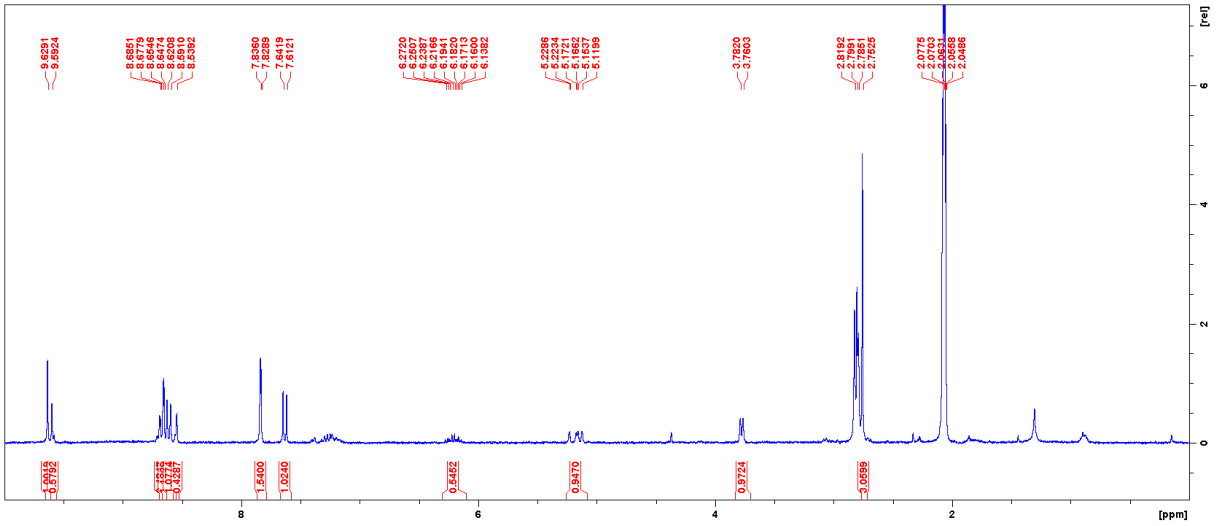


81

Compound **63** (19 mg, 0.060 mmol) was added to a pressure vial with toluene (4 mL) under argon. The solution stirred in the microwave instrument for 45 min at 250 ^{o}C before it was transferred to a round bottom flask and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluted with 0.25:0.75:9 DCM:EtOAc:hexanes. The isolated compound contained both **81** and **51** in a 37:63 ratio,

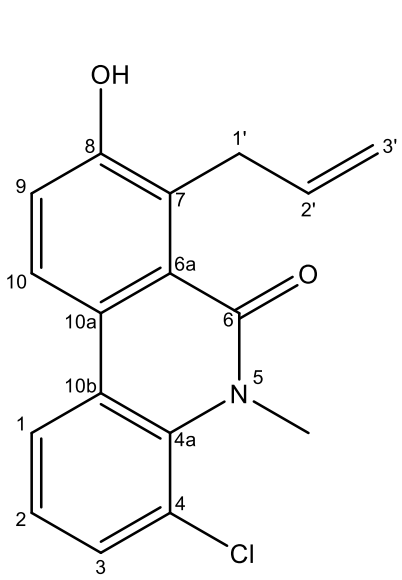
^{1}H NMR (300 MHz, acetone-D_6) δ 9.59 (s, 1H, H-6), 8.68 (d, *J* = 2.1 Hz, 1H, H-1), 8.54 (s, 1H, H-10), 7.83 (d, *J* = 2.1 Hz, 1H, H-3), 6.27-6.14 (m, 1H, H-2'), 5.23-5.12 (m, 2H, H-3'), 3.78-3.76 (m, 2H, H-1').

HRMS ESI calcd. for $C_{17}H_{13}Cl_2NO$ 317.0374, found 317.0368.

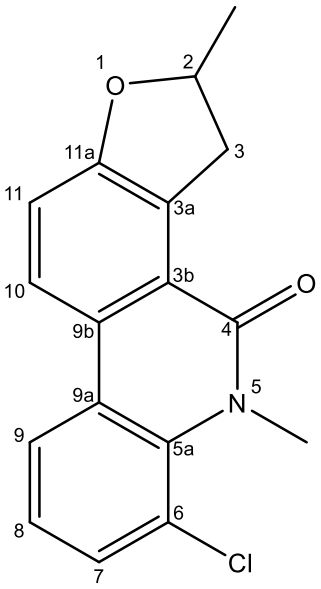


Spectrum 50: 400 MHz, Acetone-D_6, ^1H NMR spectrum of compound **81** and **85.**

Synthesis of 7-allyl-4-chloro-8-hydroxy-5-methylphenanthridin-6(5H)-one (82a) and 6-chloro-2,5-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridin-4(5H)-one (82b)



82a



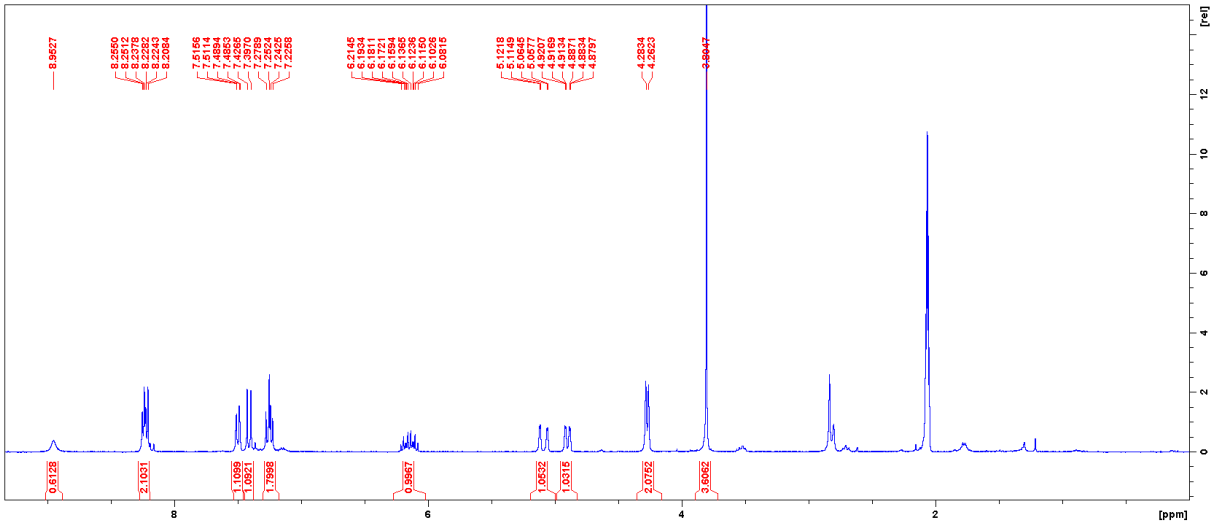
82b

Compound **65** (13.0 mg, 0.043 mmol) was dissolved in toluene (4 mL) and transferred to a pressure vial under argon. The solution stirred in the microwave reactor for 45 min at 250 ^{o}C, before it was transferred to a round bottom flask and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluted with 0.25:0.75:9 DCM:EtOAc:hexanes.

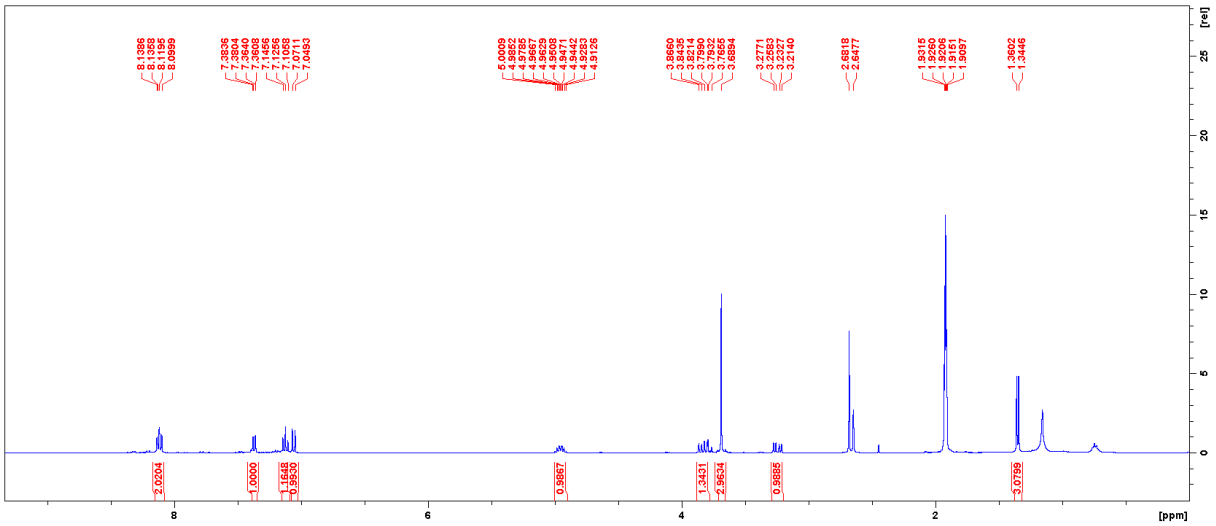
^{1}H NMR of 82a (300 MHz, acetone-D_6) δ 8.95 (s, 1H, -OH), 8.24 (dd, *J* = 1.2 and 8.0 Hz, 1H, H-1), 8.22 (d, *J* = 8.8 Hz, 1H, H-10), 7.50 (dd, *J* = 1.2 and 7.8 Hz, 1H, H-3), 7.41 (d, *J* = 8.8 Hz, 1H, H-9), 7.28-7.23 (m, 1H, H-2), 6.21-6.08 (m, 1H, H-2'), 5.12-5.06 (m, 1H, H-3'), 4.92-4.88 (m, 1H, H-3'), 4.28-4.26 (m, 2H, H-1'), 3.80 (s, 3H, NCH_3).

^{1}H NMR of 82b (400 MHz, Acetone-D_6) δ 8.14-8.10 (m, 2H, H-9 and H-10), 7.37 (dd, 1H, H-7), 7.13 (app t, 1H, H-8), 7.06 (d, 1H, H-11), 5.00-4.91 (m, 1H, H-2), 3.83 (dd, 1H, H-3), 3.69 (s, 3H, NCH_3), 3.26 (dd, 1H, H-3), 1.35 (s, 3H, CH_3 on 2).

HRMS ESI calcd. for both $C_{17}H_{14}ClNO_2$ 299.0713, found 299.0707.

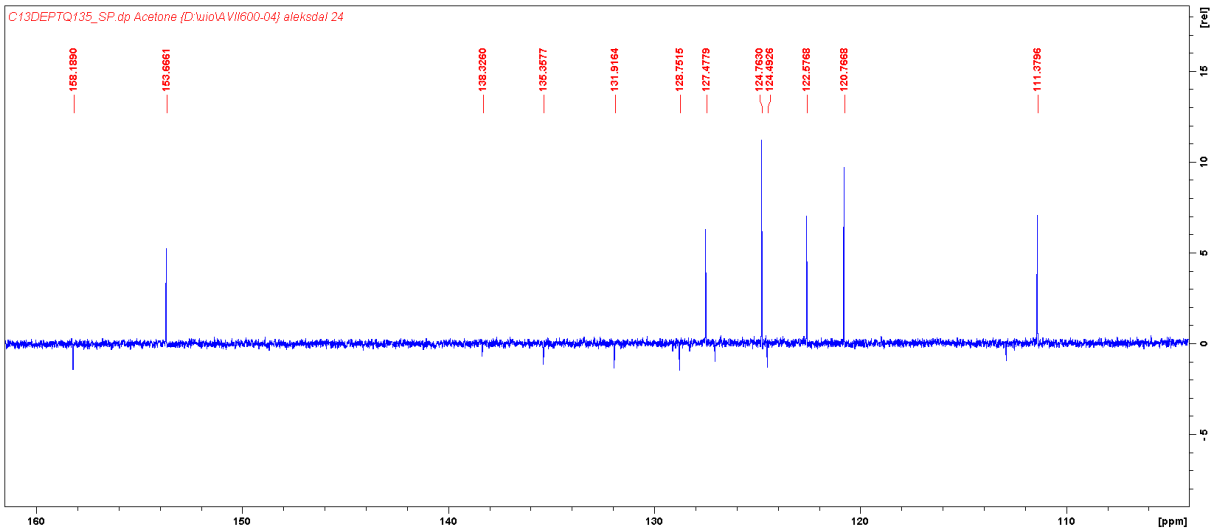


Spectrum 51: 300 MHz, Acetone-D_6, ^1H NMR spectrum of 7-allyl-4-chloro-8-hydroxy-5-methylphenanthridin-6(5H)-one (**82a**).

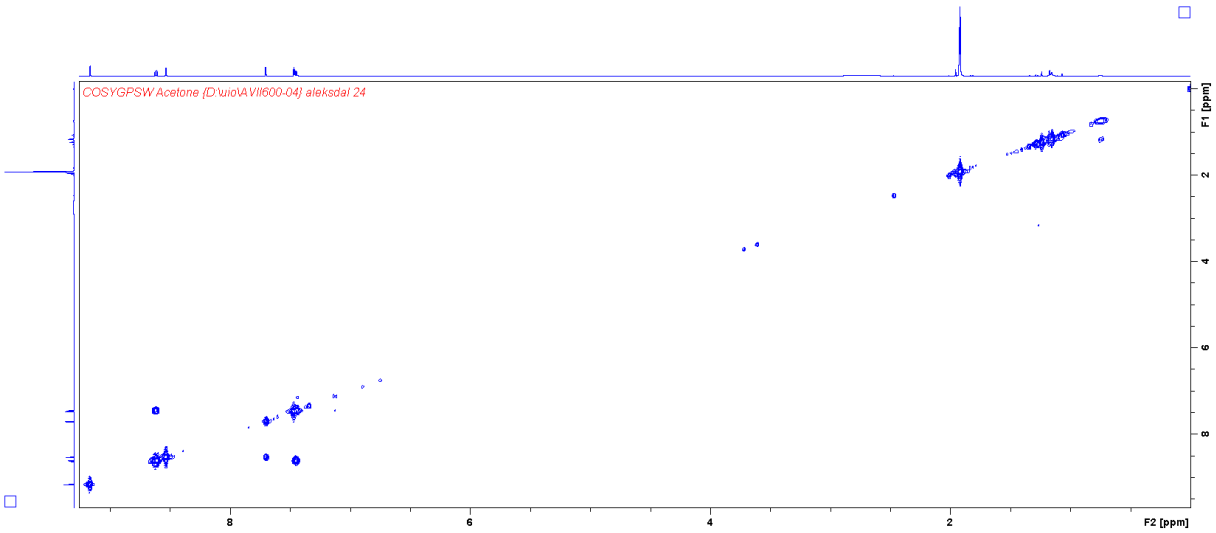


Spectrum 52: 400 MHz, Acetone-D_6, ^1H NMR spectrum of 6-chloro-2,5-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridin-4(5H)-one (**82b**).

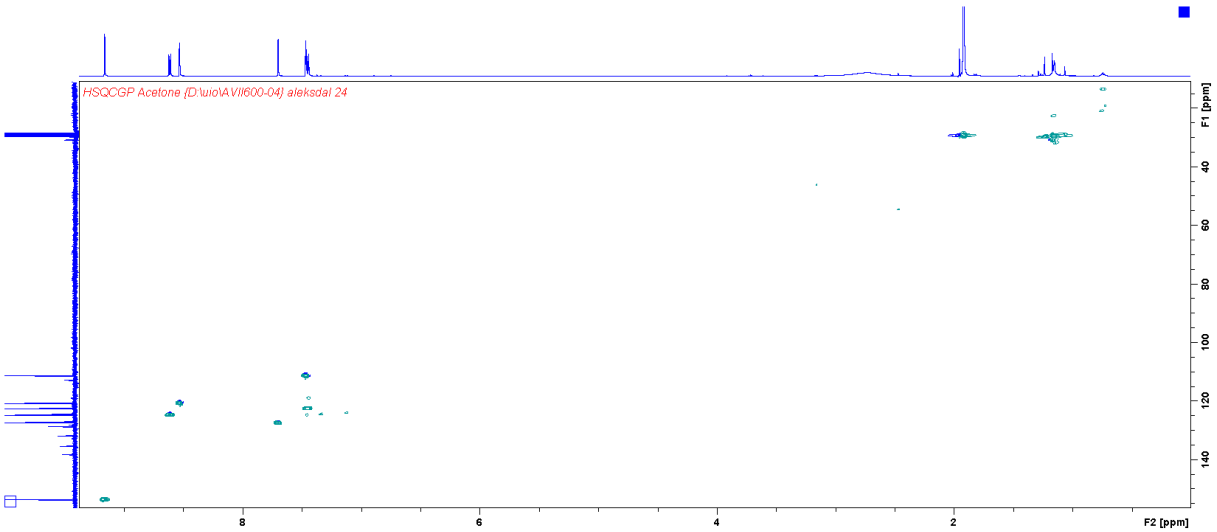
6. Appendix



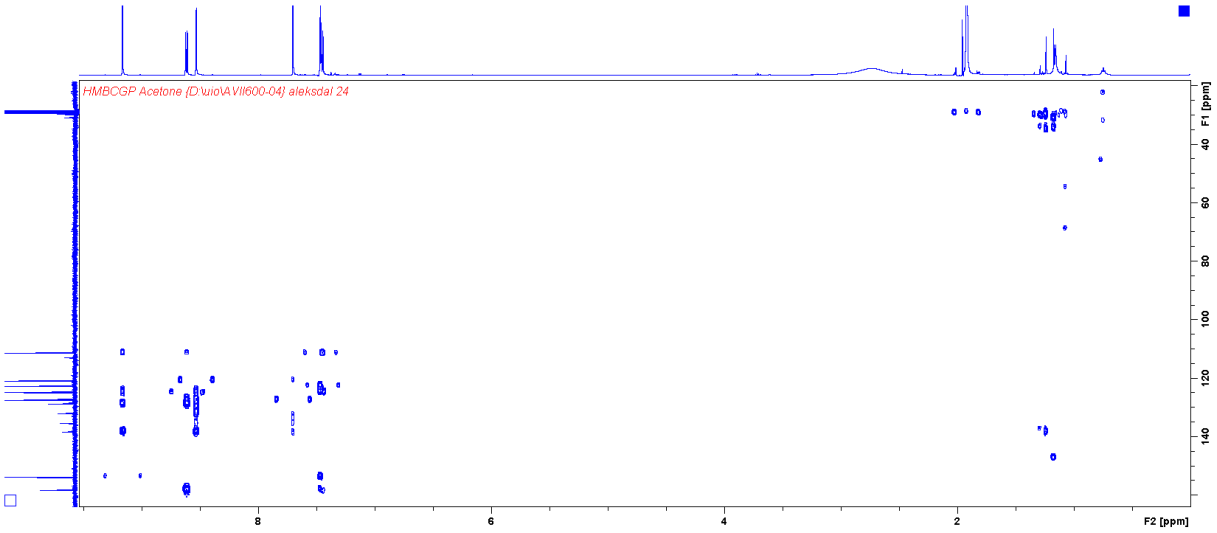
Spectrum 53: 600 MHz, Acetone-D_6, DEPTQ of 2,4-dichlorophenanthridin-8-ol (**48a**).



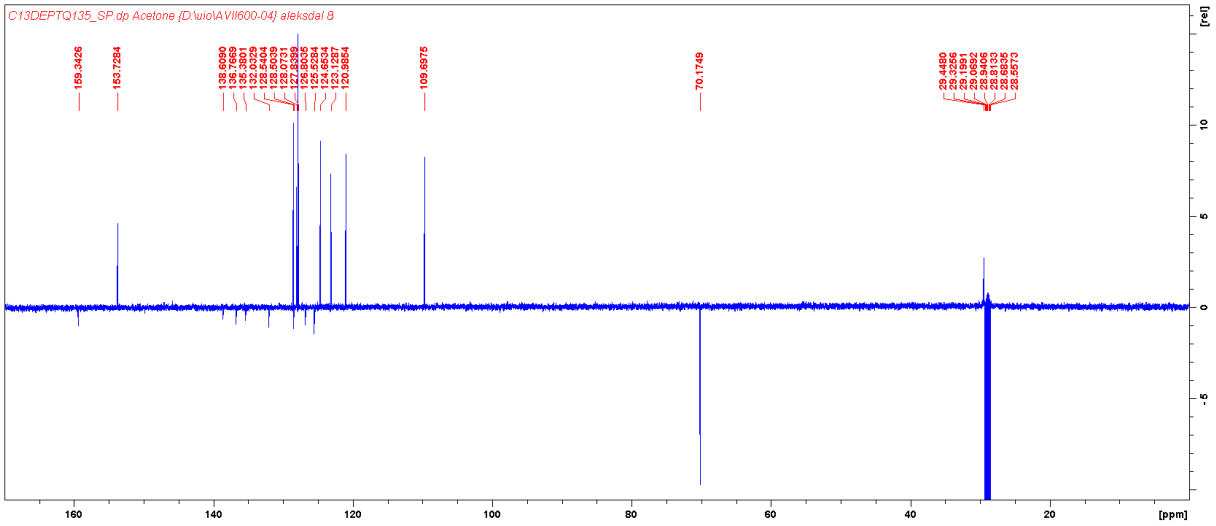
Spectrum 54: 600 MHz, Acetone-D_6, COSY of 2,4-dichlorophenanthridin-8-ol (**48a**).



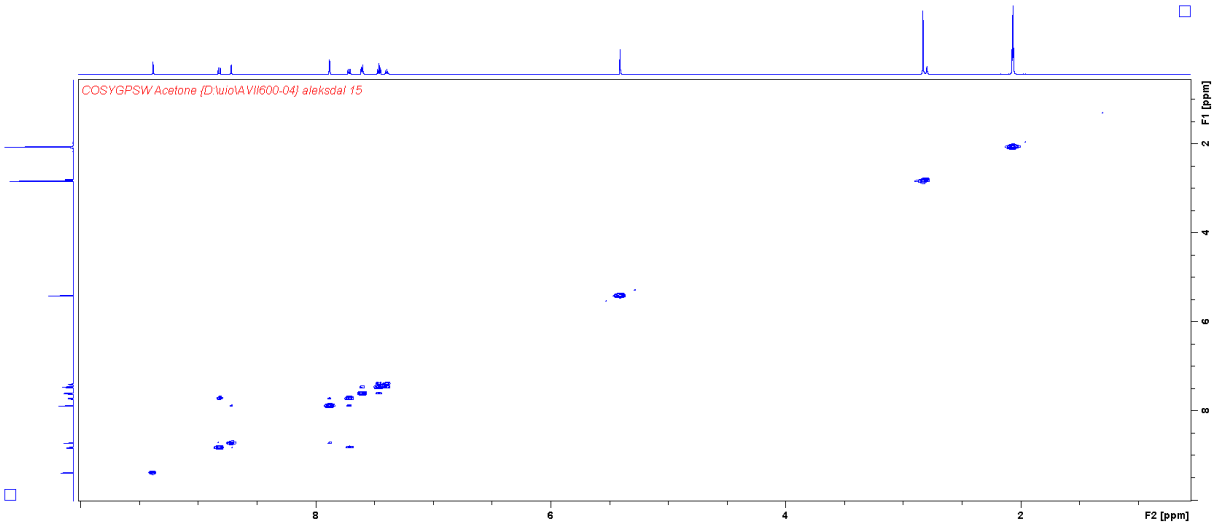
Spectrum 55: 600 MHz, Acetone-D_6, HSQC of 2,4-dichlorophenanthridin-8-ol (**48a**).



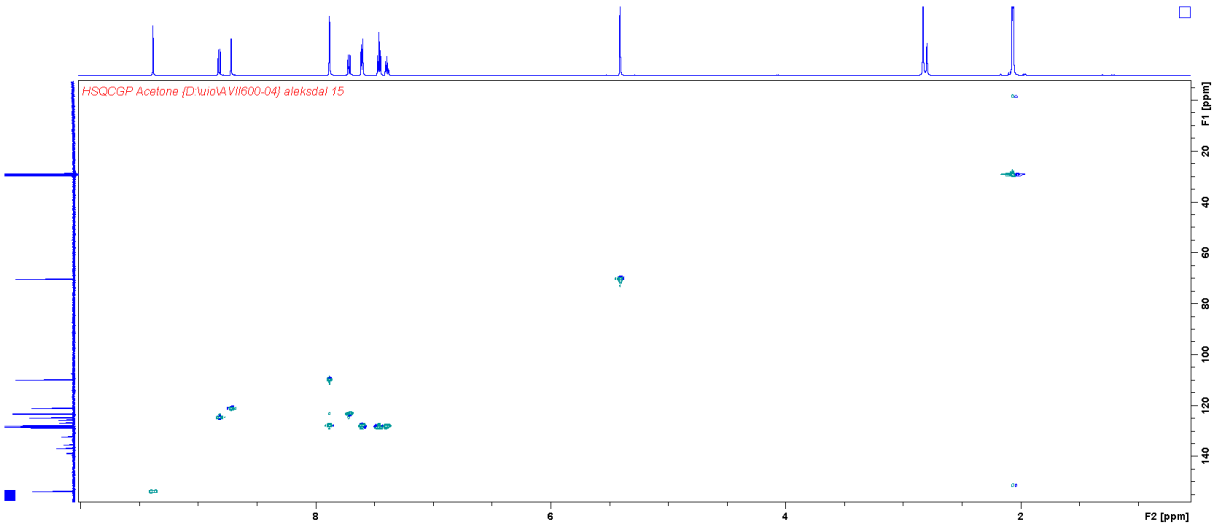
Spectrum 56*:* 600 MHz, Acetone-D_6, HMBC of 2,4-dichlorophenanthridin-8-ol (**48a**)



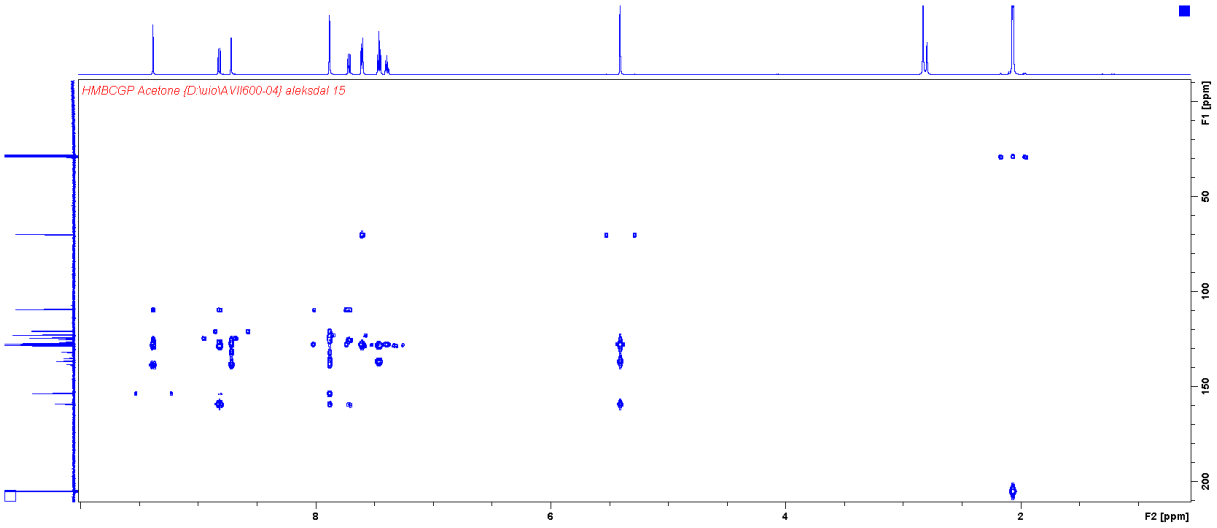
Spectrum 57: 600 MHz, Acetone-D_6, DEPTQ of 8-(benzyloxy)-2,4-dichlorophenanthridine (**55**).



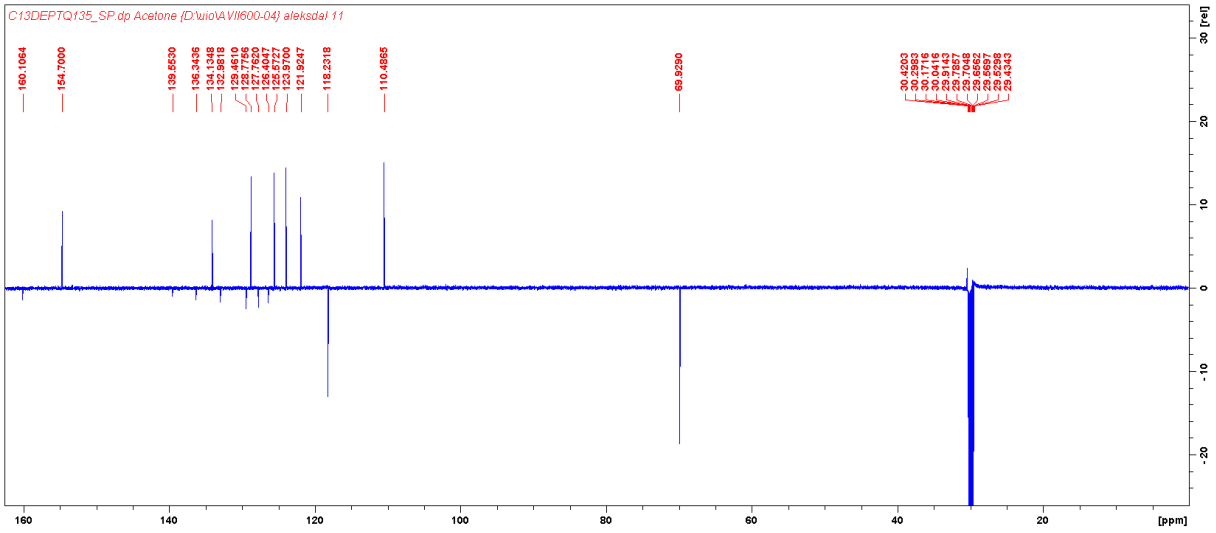
Spectrum 58: 600 MHz, Acetone-D_6, COSY of 8-(benzyloxy)-2,4-dichlorophenanthridine (**55**).



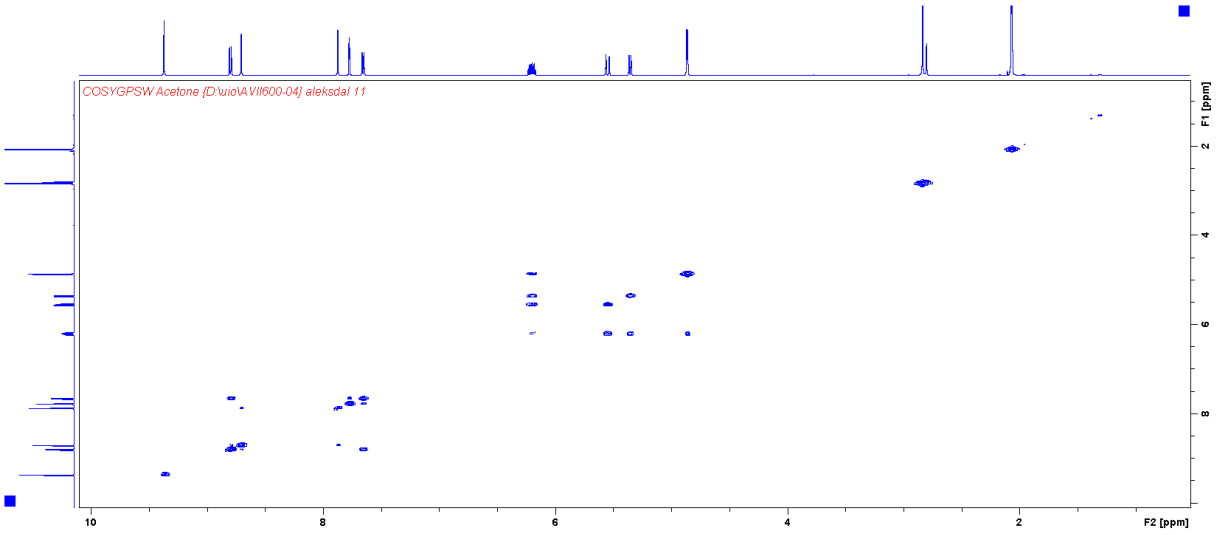
Spectrum 59: 600 MHz, Acetone-D_6, HSQC of 8-(benzyloxy)-2,4-dichlorophenanthridine (**55**).



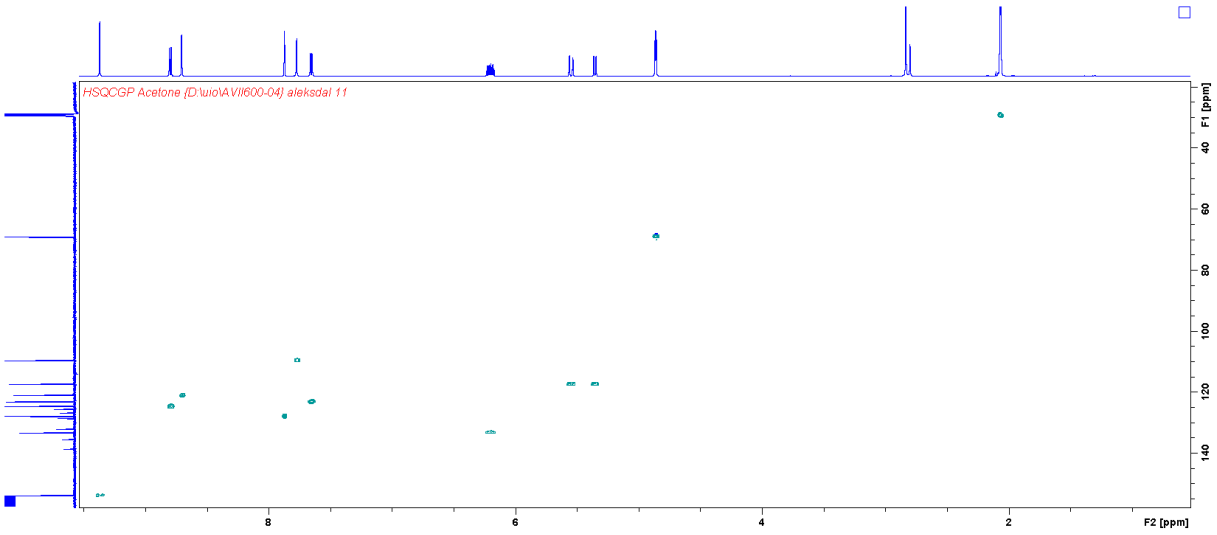
Spectrum 60: 600 MHz, Acetone-D_6, HMBC of 8-(benzyloxy)-2,4-dichlorophenanthridine (**55**).



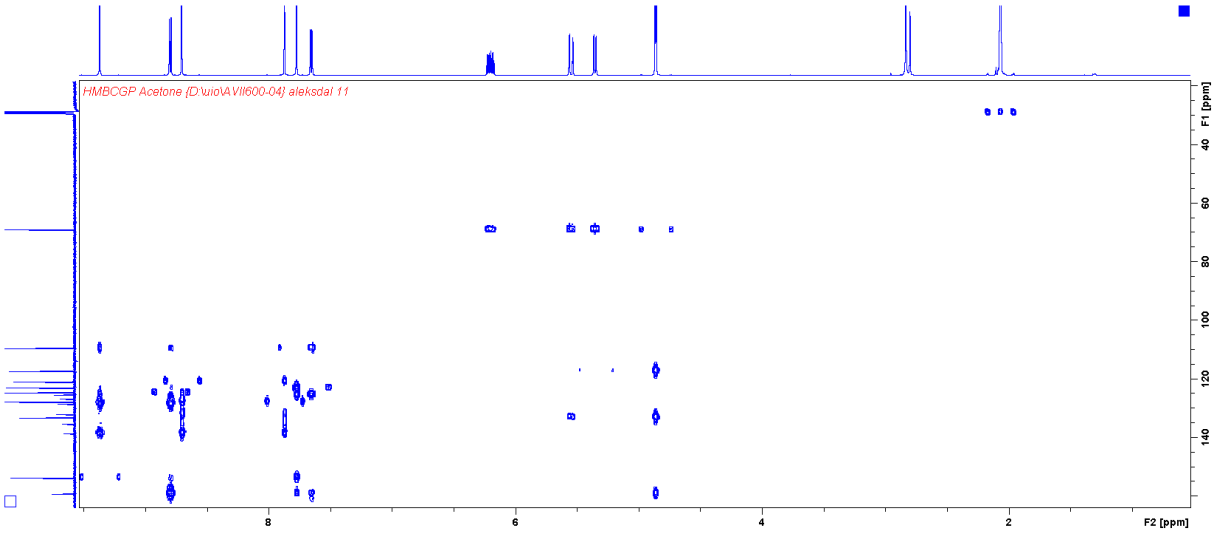
Spectrum 61: 600 MHz, Acetone-D_6, DEPTQ of 8-(allyloxy)-2,4-dichlorophenanthridine (**56**).



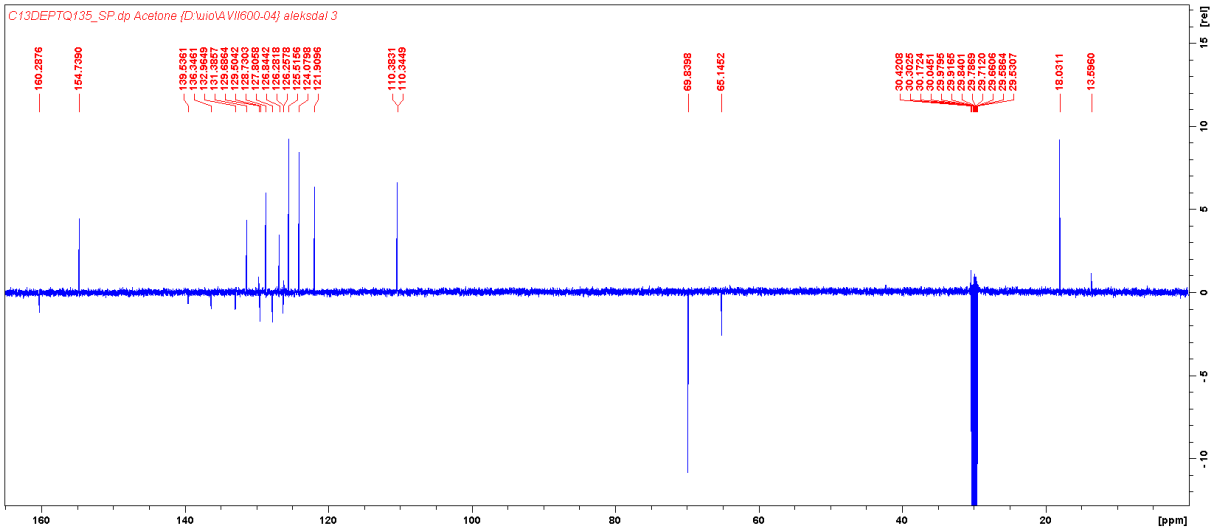
Spectrum 62: 600 MHz, Acetone-D_6, COSY of 8-(allyloxy)-2,4-dichlorophenanthridine (**56**).



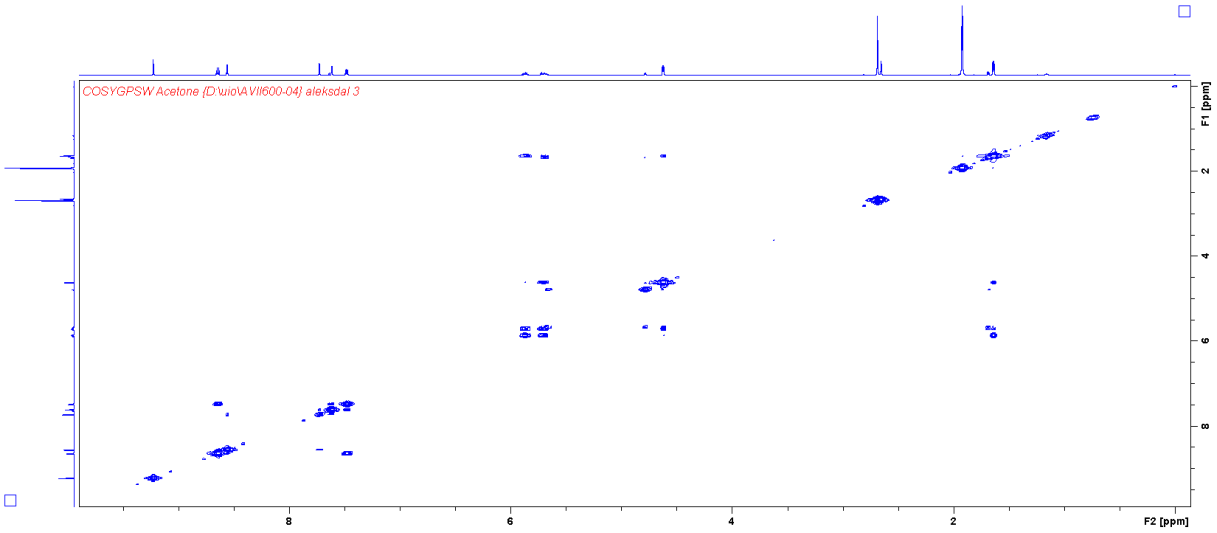
Spectrum 63: 600 MHz, Acetone-D_6, HSQC of 8-(allyloxy)-2,4-dichlorophenanthridine (**56**).



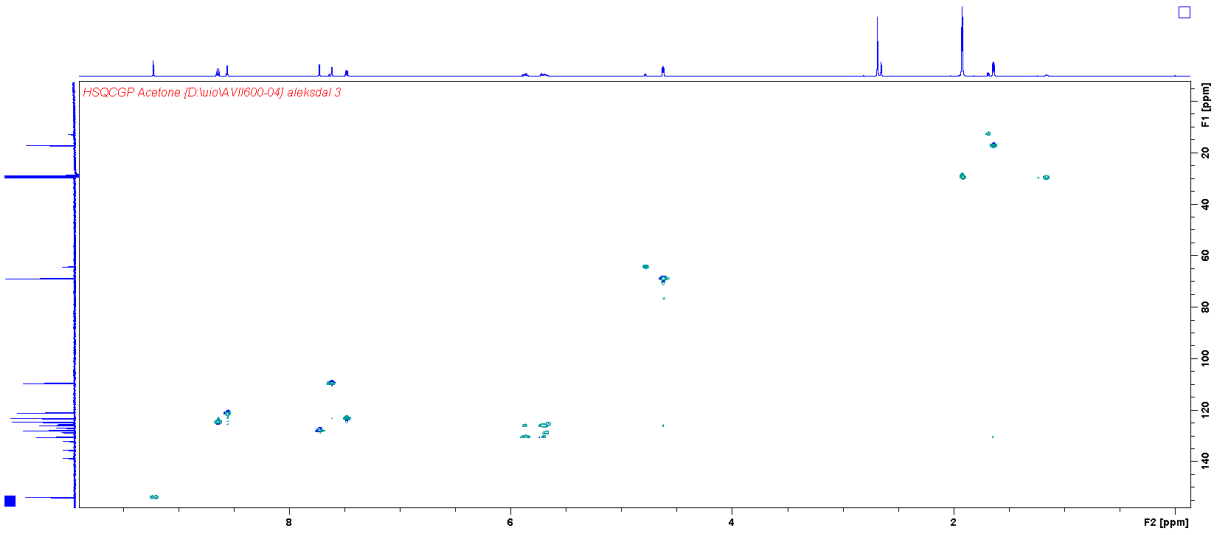
Spectrum 64: 600 MHz, Acetone-D_6, HMBC of 8-(allyloxy)-2,4-dichlorophenanthridine (**56**).



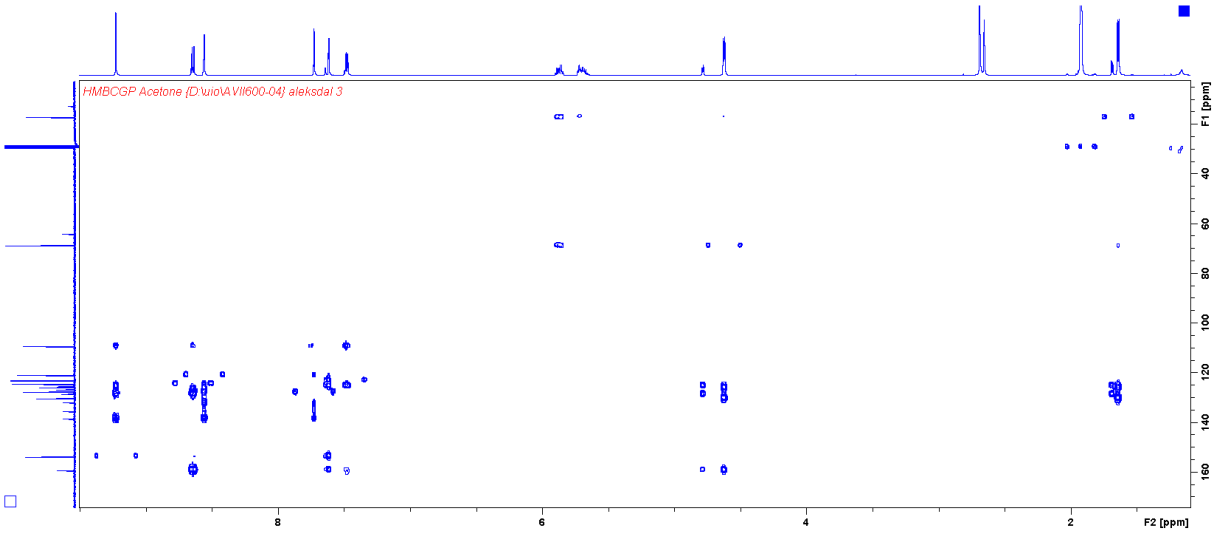
Spectrum 65: 600 MHz, Acetone-D_6, DEPTQ of (*E*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57a**) and (*Z*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57b**).



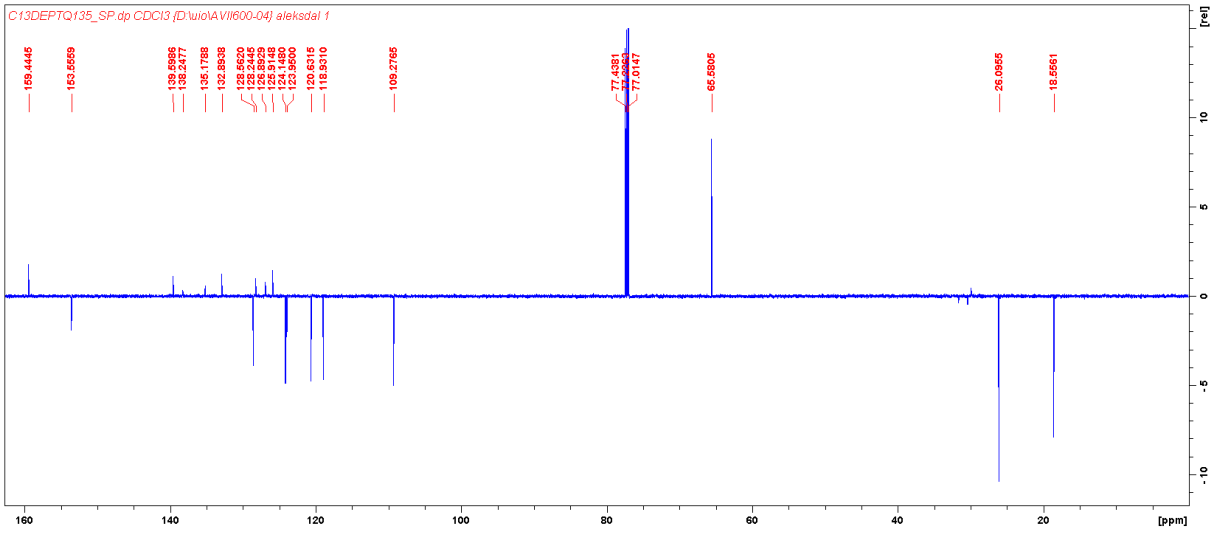
Spectrum 66: 600 MHz, Acetone-D_6, COSY of (*E*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57a**) and (*Z*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57b**)



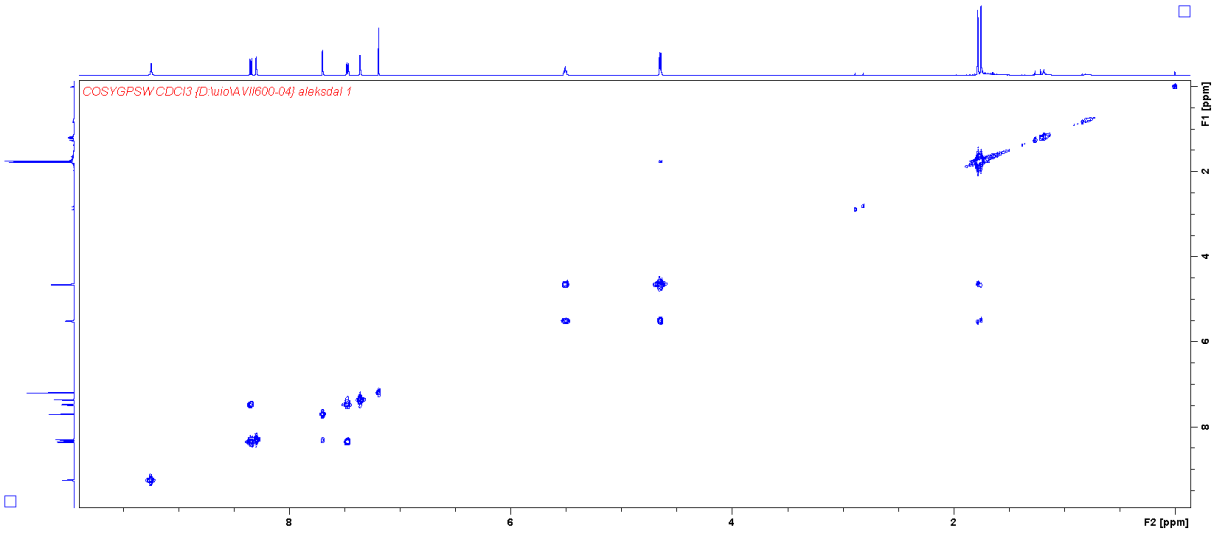
Spectrum 67: 600 MHz, Acetone-D_6, HSQC of (*E*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57a**) and (*Z*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57b**).



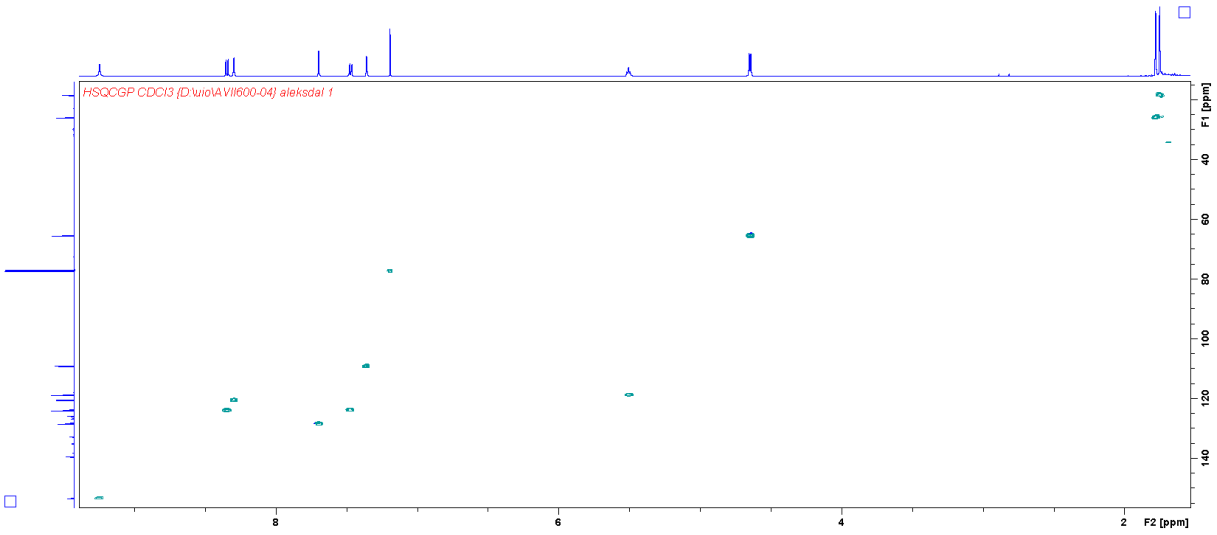
Spectrum 68: 600 MHz, Acetone-D_6, HMBC of (*E*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57a**) and (*Z*)-8-(but-2-en-1-yloxy)-2,4-dichlorophenanthridine (**57b**).



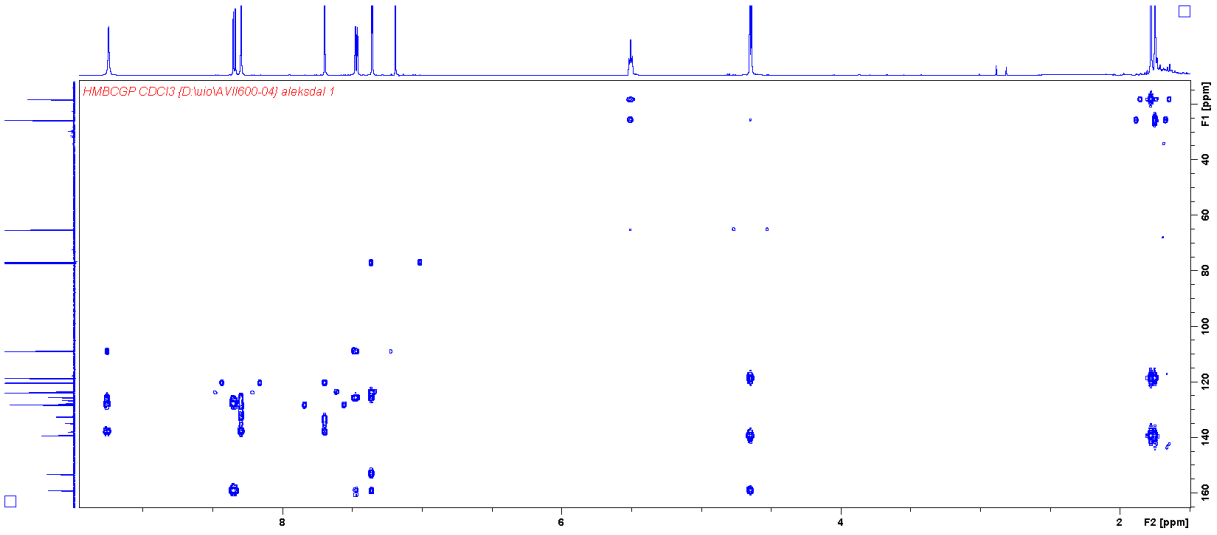
Spectrum 69: 600 MHz, $CDCl_3$, DEPTQ of 2,4-dichloro-8-((3-methylbut-2-en-1-yl)oxy)phenanthridine (**58**).



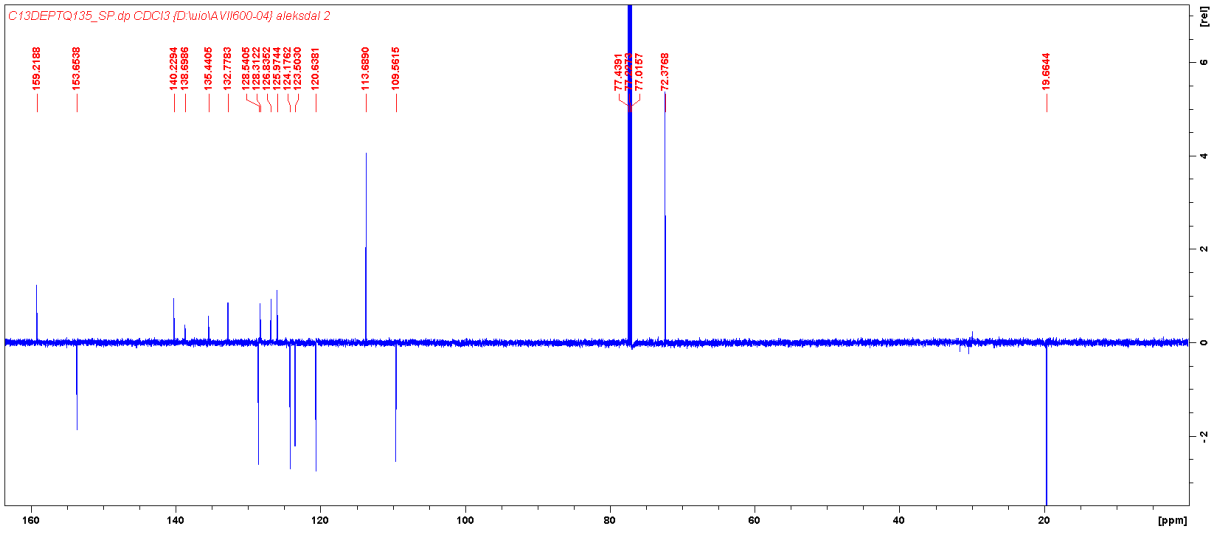
Spectrum 70: 600 MHz, $CDCl_3$, COSY of 2,4-dichloro-8-((3-methylbut-2-en-1-yl)oxy)phenanthridine (**58**).



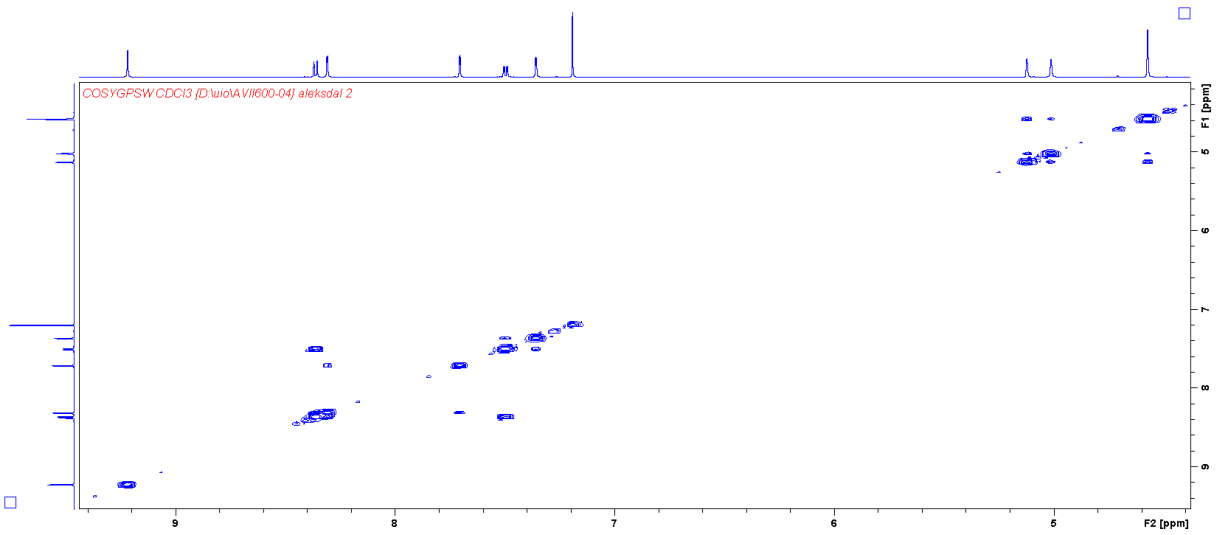
Spectrum 71: 600 MHz, $CDCl_3$, HSQC of 2,4-dichloro-8-((3-methylbut-2-en-1-yl)oxy)phenanthridine (**58**).



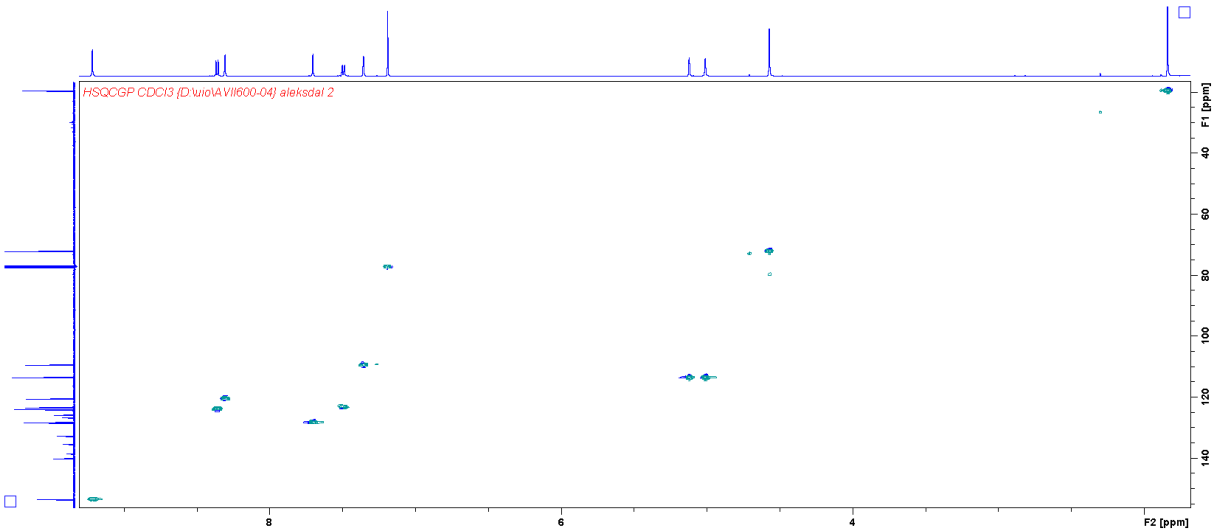
Spectrum 72: 600 MHz, $CDCl_3$, HMBC of 2,4-dichloro-8-((3-methylbut-2-en-1-yl)oxy)phenanthridine (**58**).



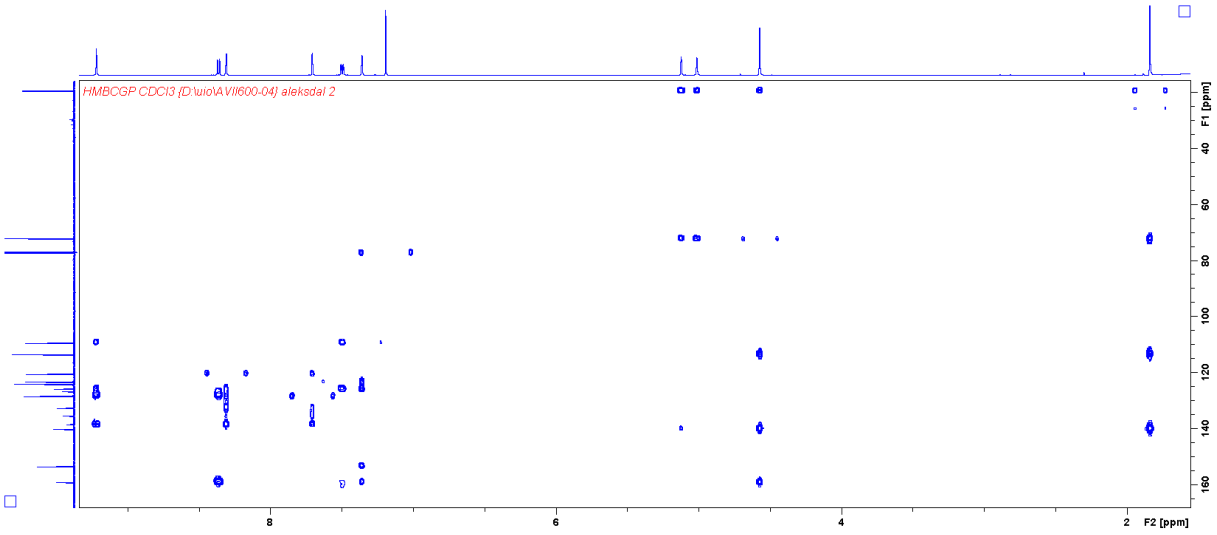
Spectrum 73: 600 MHz, $CDCl_3$, DEPTQ of 2,4-dichloro-8-((2-methylallyl)oxy)phenanthridine (**59**).



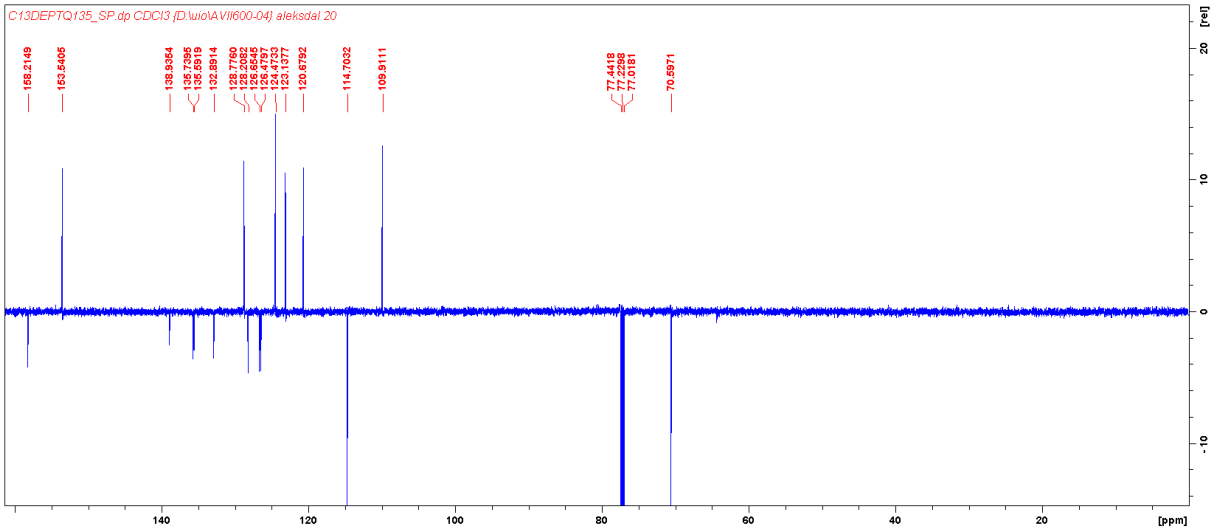
Spectrum 74: 600 MHz, $CDCl_3$, COSY of 2,4-dichloro-8-((2-methylallyl)oxy)phenanthridine (**59**).



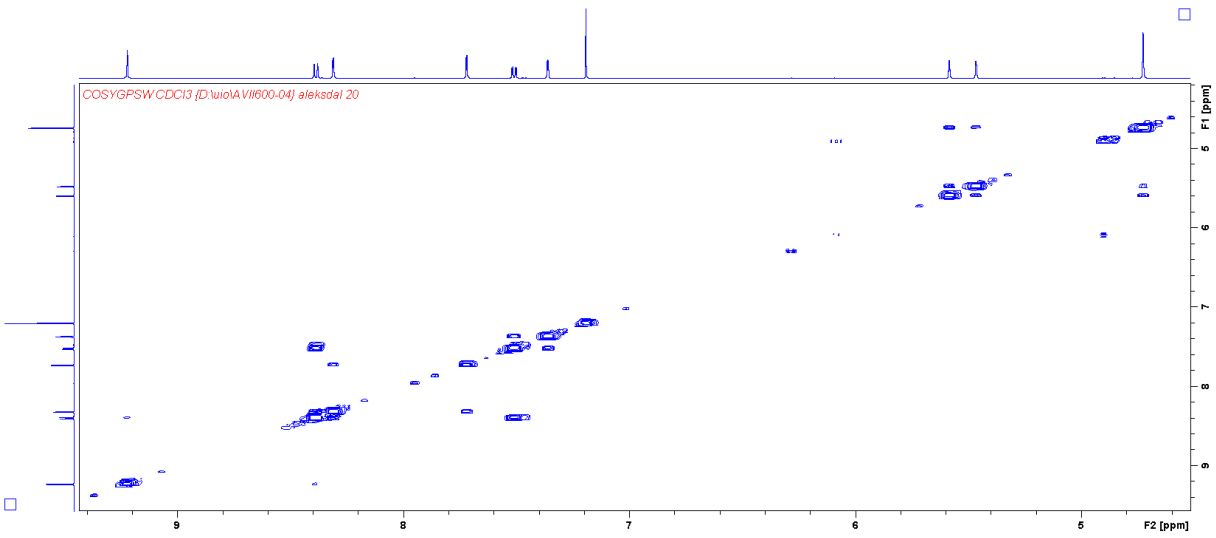
Spectrum 75: 600 MHz, $CDCl_3$, HSQC of 2,4-dichloro-8-((2-methylallyl)oxy)phenanthridine (**59**).



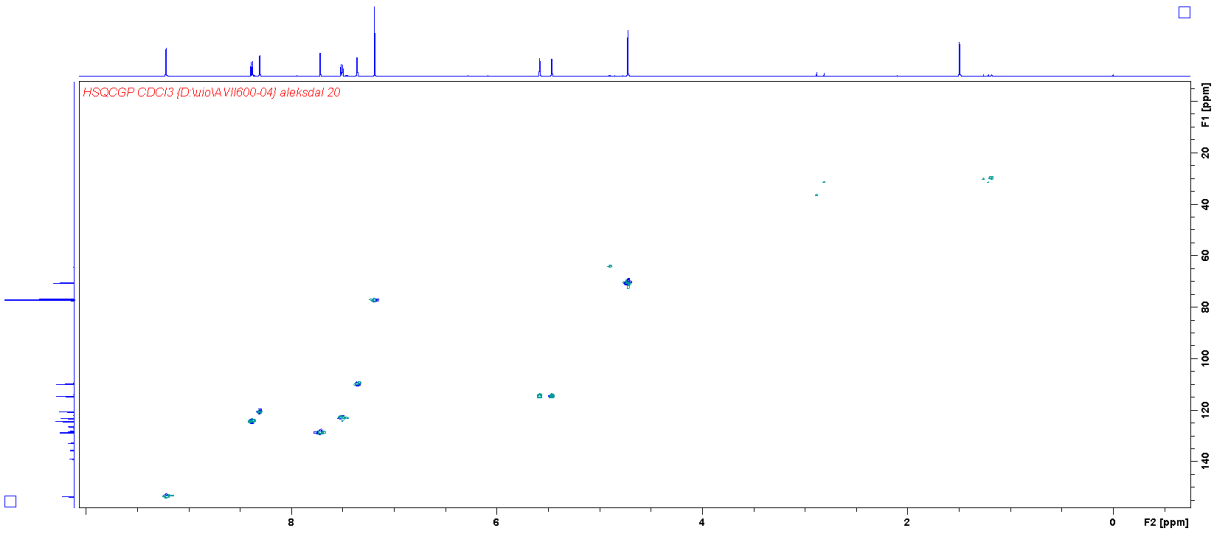
Spectrum 76: 600 MHz, $CDCl_3$, HMBC of 2,4-dichloro-8-((2-methylallyl)oxy)phenanthridine (**59**).



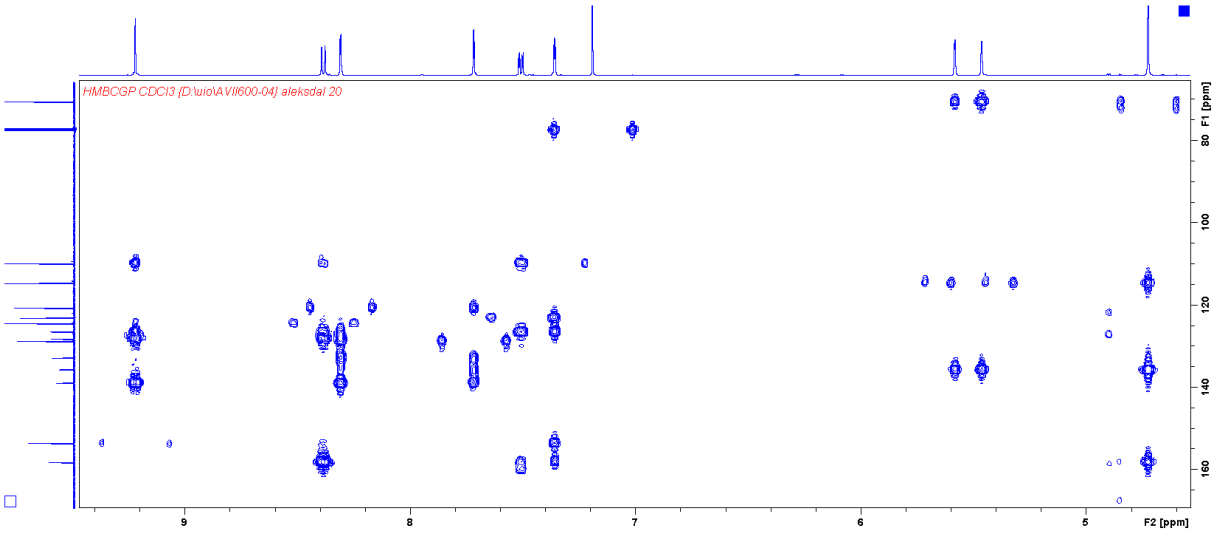
Spectrum 77: 600 MHz, $CDCl_3$, DEPTQ of 2,4-dichloro-8-((2-chloroallyl)oxy)phenanthridine (**60**).



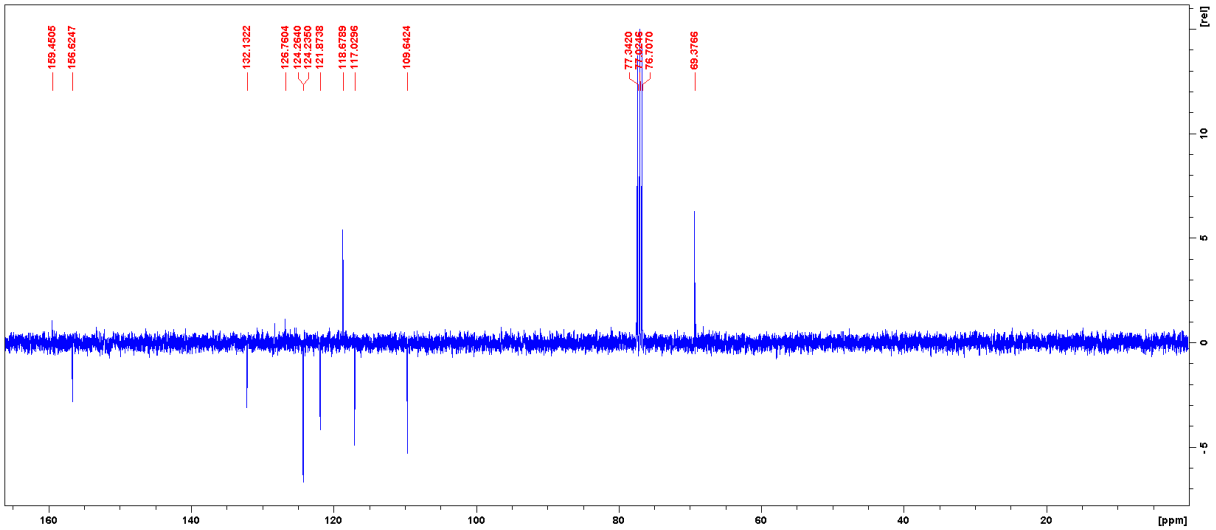
Spectrum 78: 600 MHz, $CDCl_3$, COSY of 2,4-dichloro-8-((2-chloroallyl)oxy)phenanthridine (**60**).



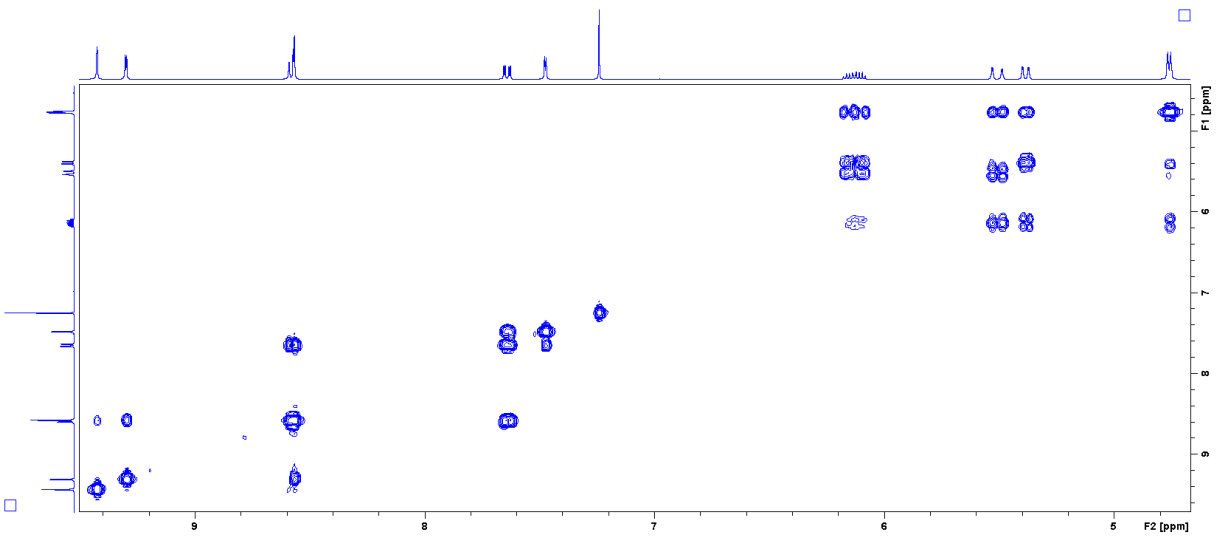
Spectrum 79: 600 MHz, $CDCl_3$, HSQC of 2,4-dichloro-8-((2-chloroallyl)oxy)phenanthridine (**60**).



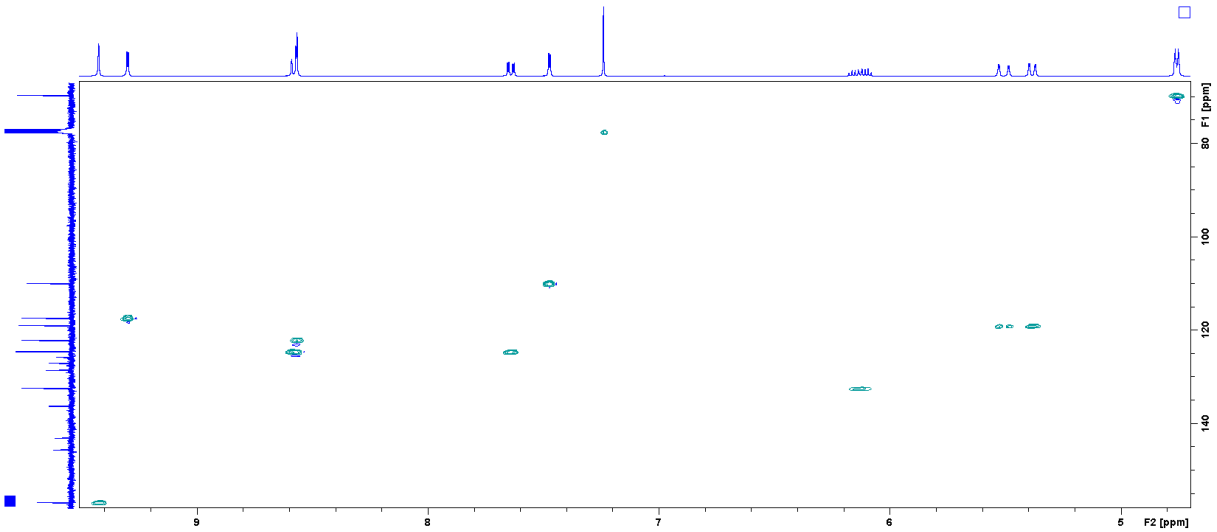
Spectrum 80: 600 MHz, $CDCl_3$, HMBC of 2,4-dichloro-8-((2-chloroallyl)oxy)phenanthridine (**60**).



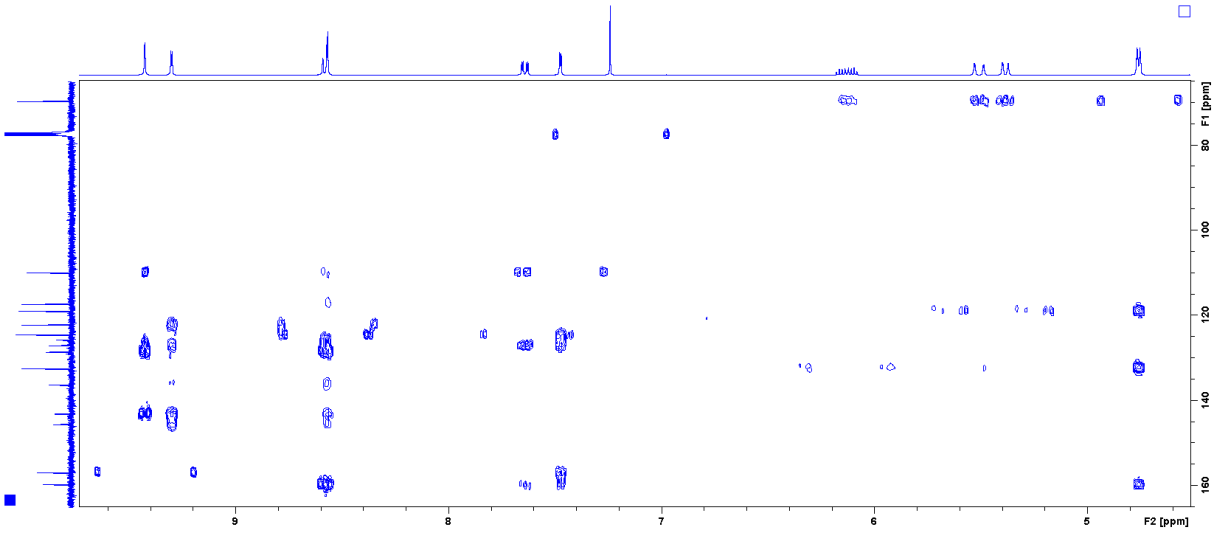
Spectrum 81: 400 MHz, $CDCl_3$, DEPTQ of 8-(allyloxy)-4-chloro-2-nitrophenanthridine (**61**).



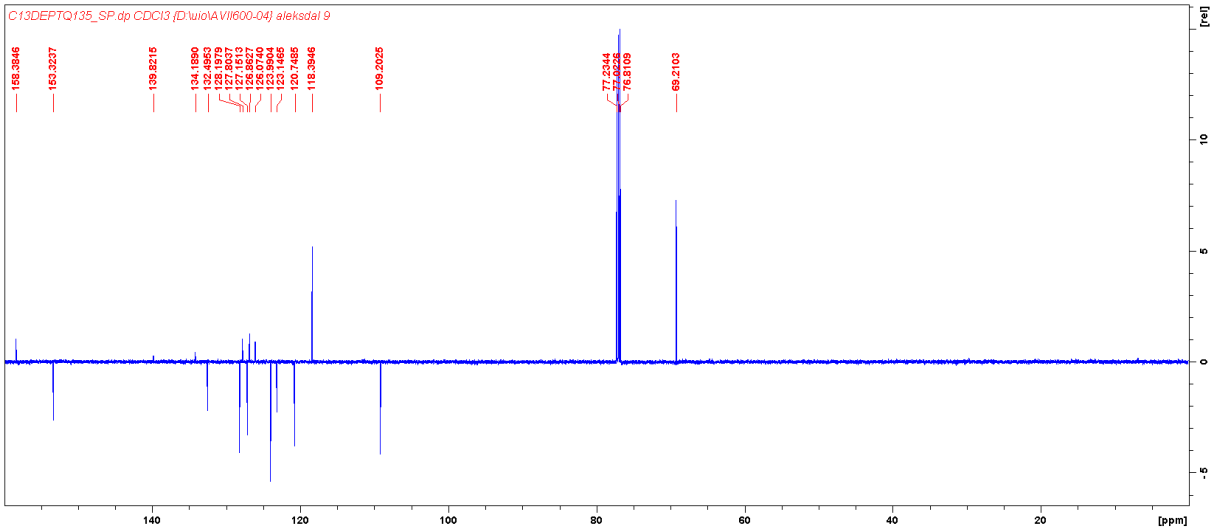
Spectrum 82: 400 MHz, $CDCl_3$, COSY of 8-(allyloxy)-4-chloro-2-nitrophenanthridine (**61**).



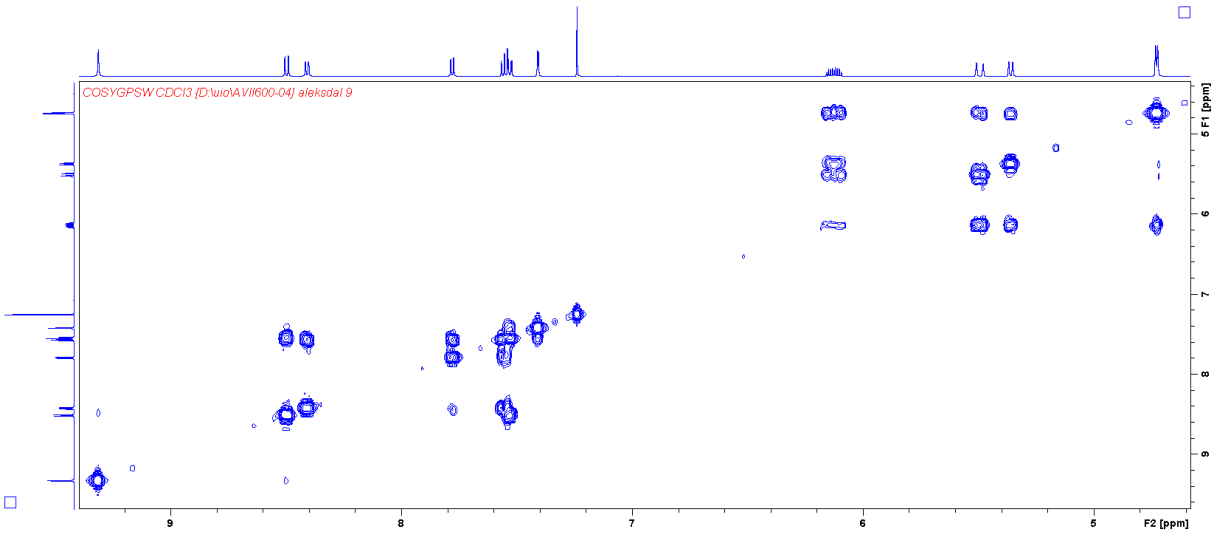
Spectrum 83: 400 MHz, $CDCl_3$, HSQC of 8-(allyloxy)-4-chloro-2-nitrophenanthridine (**61**).



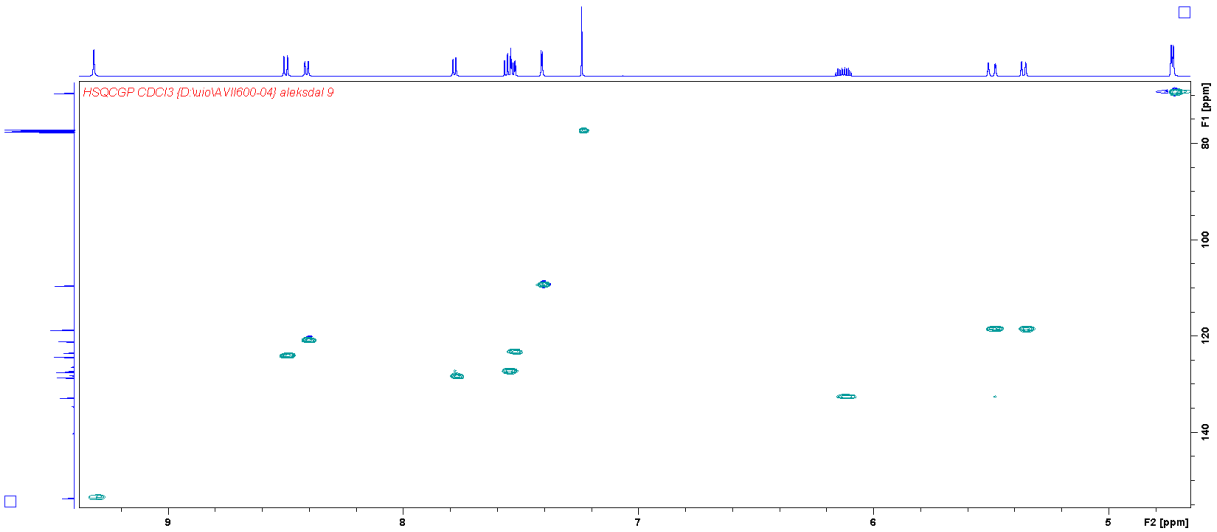
Spectrum 84: 400 MHz, $CDCl_3$, HMBC of 8-(allyloxy)-4-chloro-2-nitrophenanthridine (**61**).



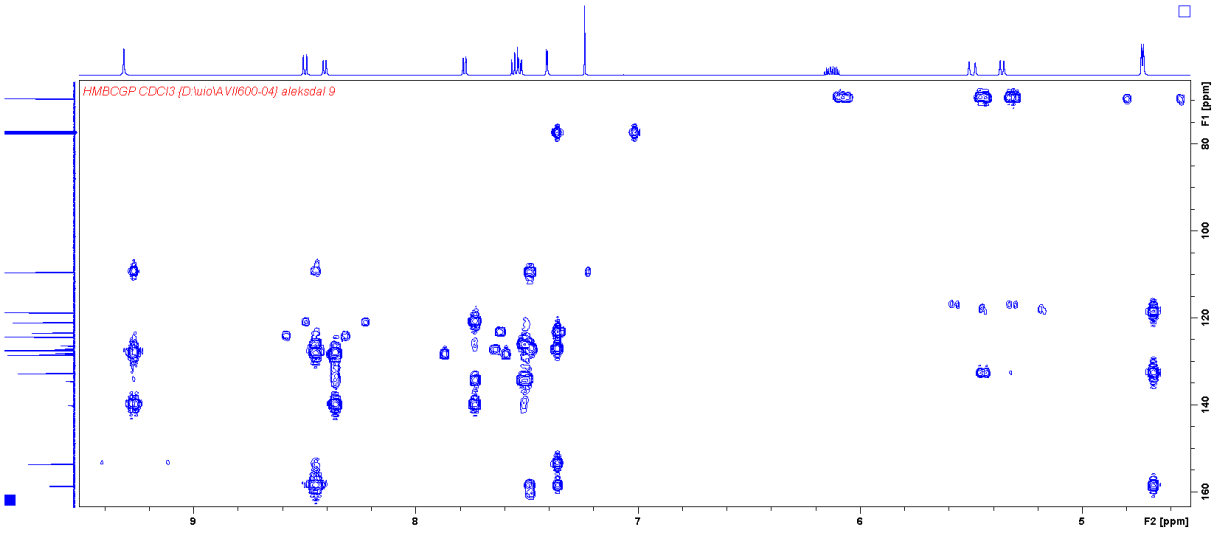
Spectrum 85: 600 MHz, $CDCl_3$, DEPTQ of 8-(allyloxy)-4-chlorophenanthridine (**62**).



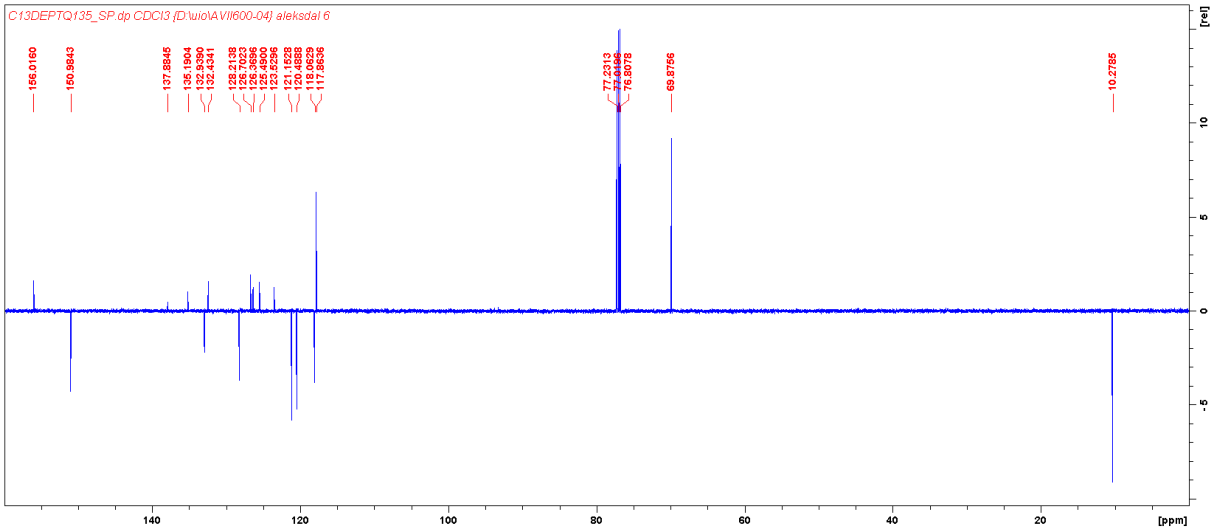
Spectrum 86: 600 MHz, $CDCl_3$, COSY of 8-(allyloxy)-4-chlorophenanthridine (**62**).



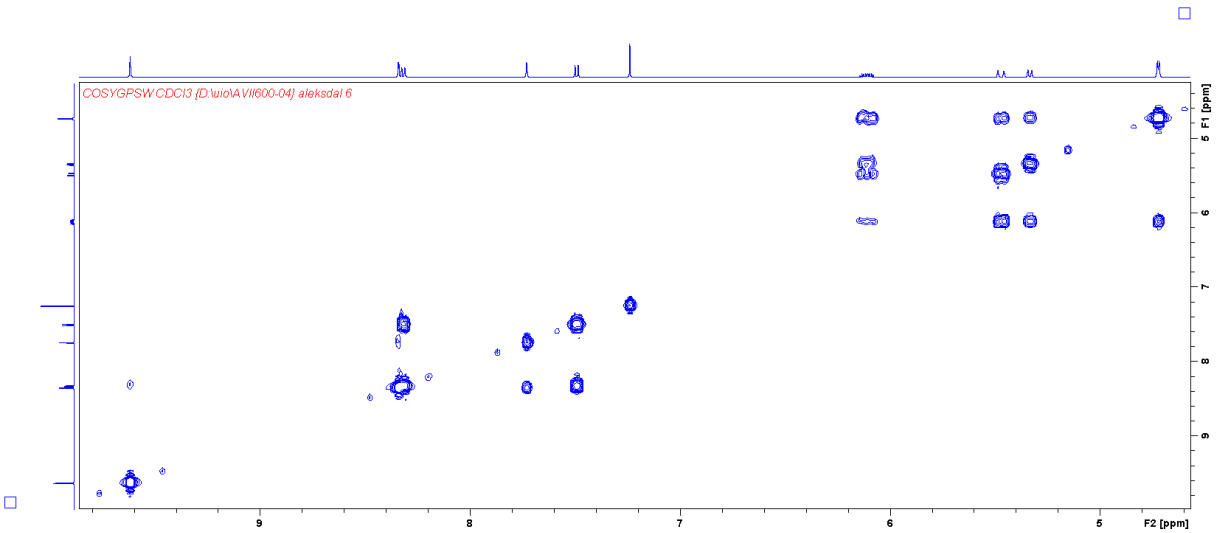
Spectrum 87: 600 MHz, $CDCl_3$, HSQC of 8-(allyloxy)-4-chlorophenanthridine (**62**).



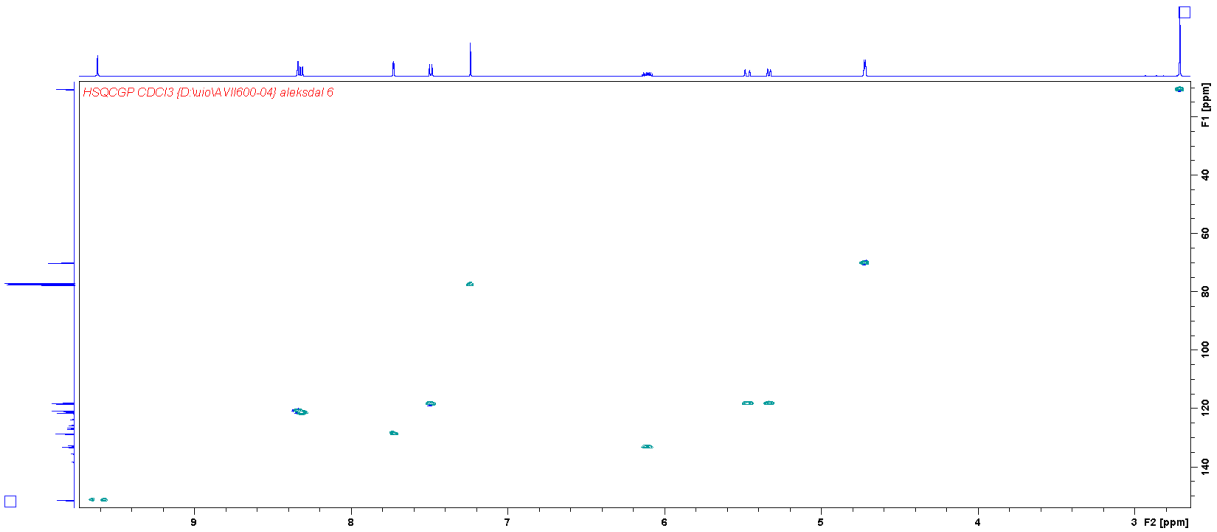
Spectrum 88: 600 MHz, $CDCl_3$, HMBC of 8-(allyloxy)-4-chlorophenanthridine (**62**).



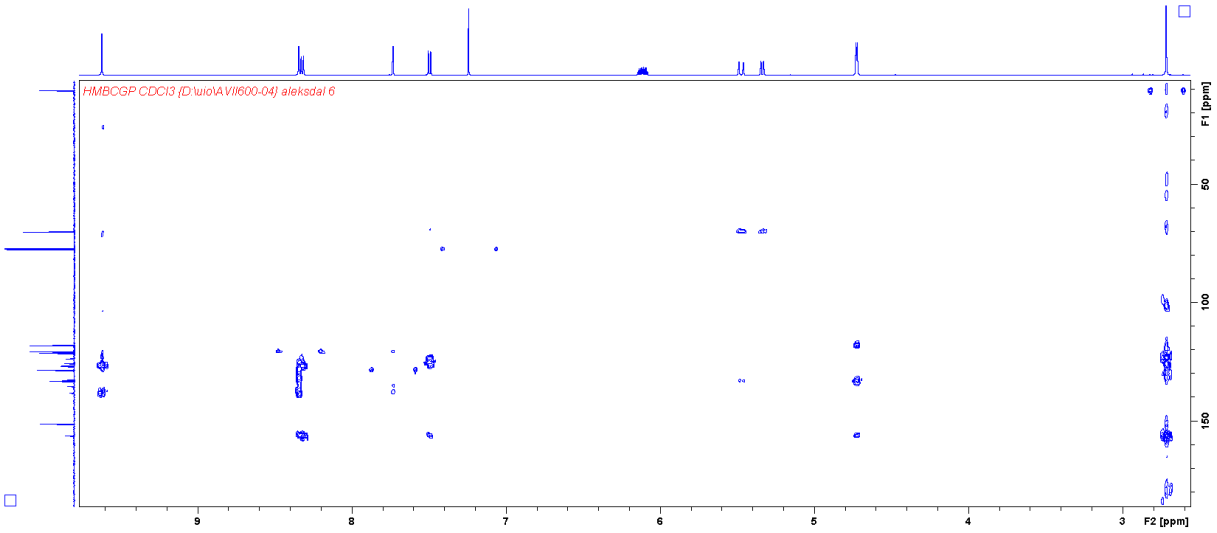
Spectrum 89: 600 MHz, $CDCl_3$, DEPTQ of 8-(allyloxy)-2,4-dichloro-7-methylphenanthridine (**63**).



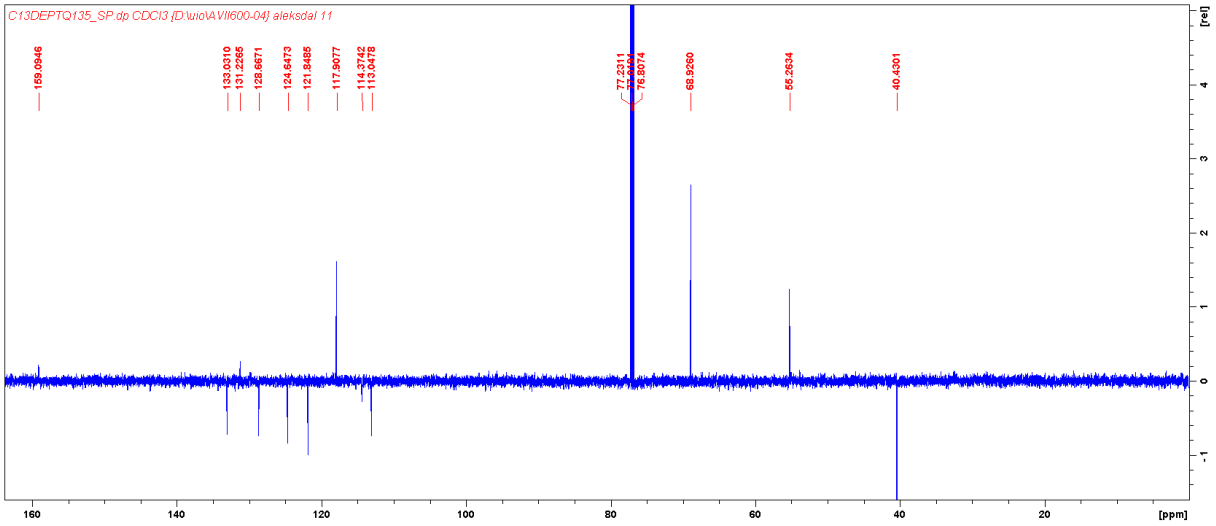
Spectrum 90: 600 MHz, $CDCl_3$, COSY of 8-(allyloxy)-2,4-dichloro-7-methylphenanthridine (**63**).



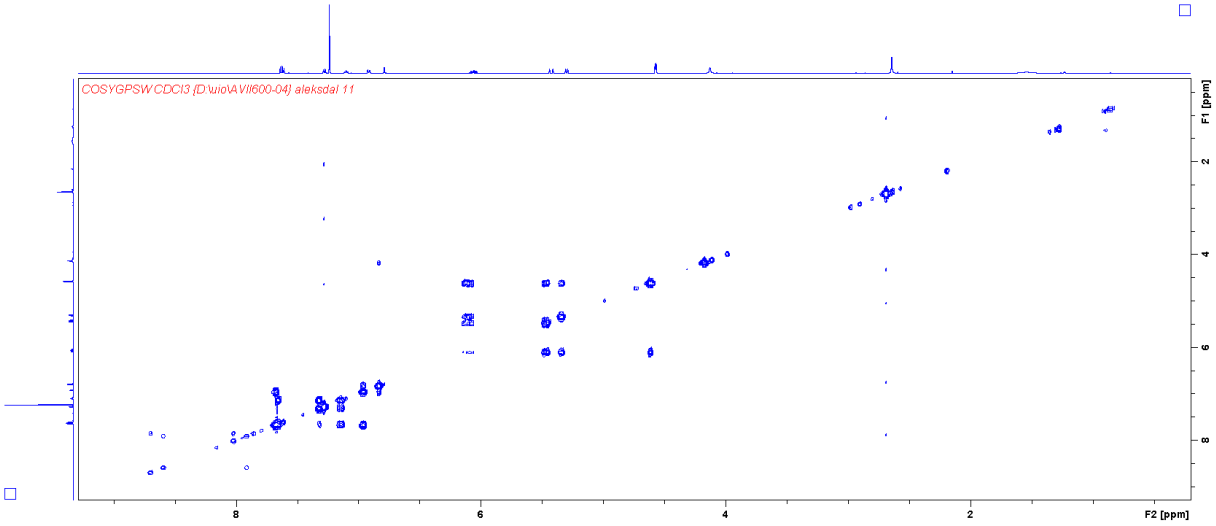
Spectrum 91: 600 MHz, $CDCl_3$, HSQC of 8-(allyloxy)-2,4-dichloro-7-methylphenanthridine (**63**).



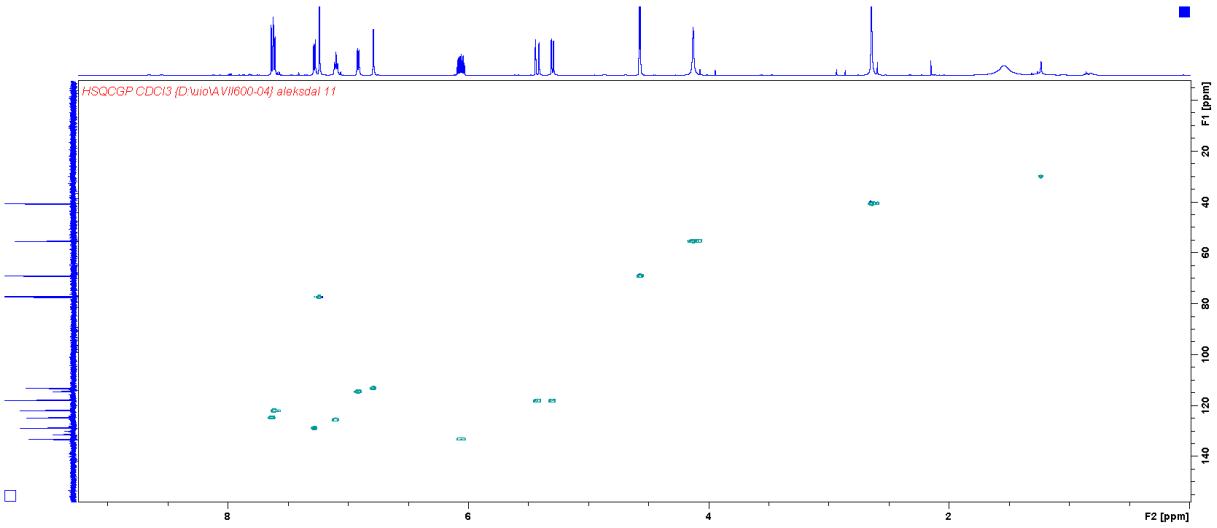
Spectrum 92: 600 MHz, $CDCl_3$, HMBC of 8-(allyloxy)-2,4-dichloro-7-methylphenanthridine (**63**).



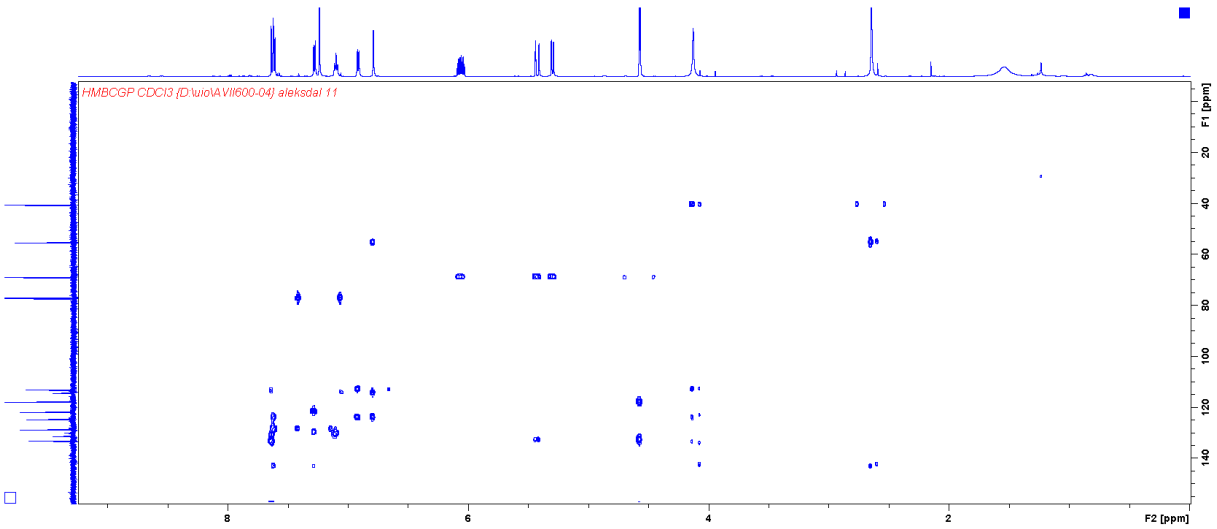
Spectrum 93: 600 MHz, $CDCl_3$, DEPT of 8-(allyloxy)-4-chloro-5-methyl-5,6-dihydrophenanthridine (**64**).



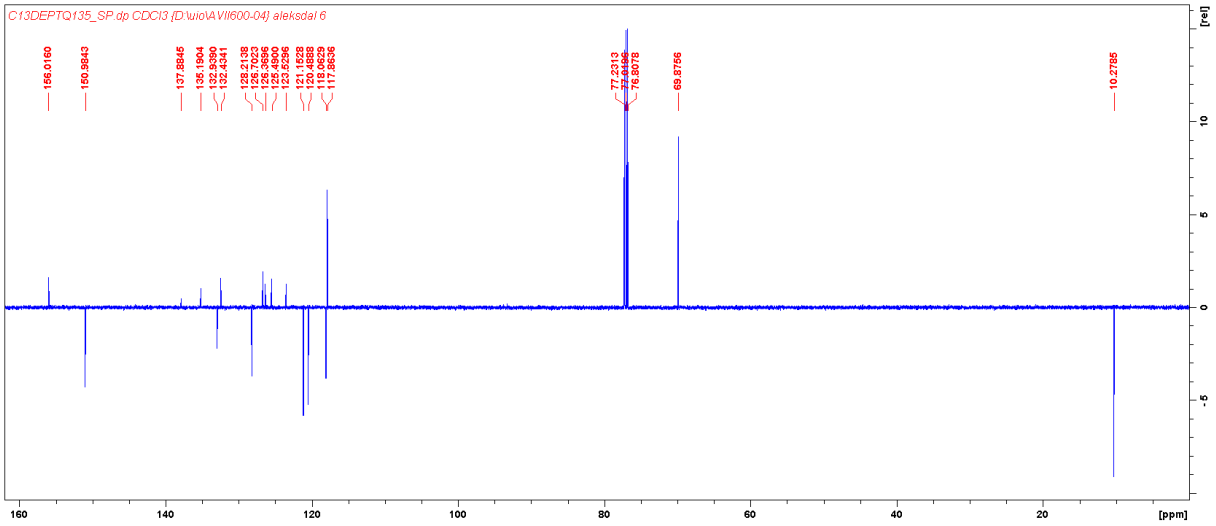
Spectrum 94: 600 MHz, $CDCl_3$, COSY of 8-(allyloxy)-4-chloro-5-methyl-5,6-dihydrophenanthridine (**64**).



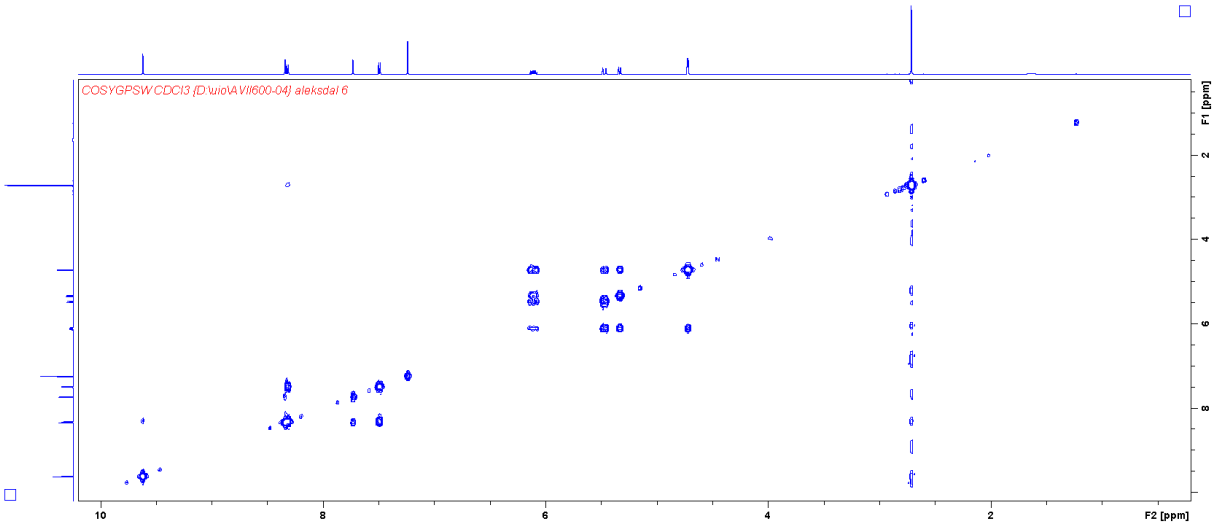
Spectrum 95: 600 MHz, $CDCl_3$, HSQC of 8-(allyloxy)-4-chloro-5-methyl-5,6-dihydrophenanthridine (**64**).



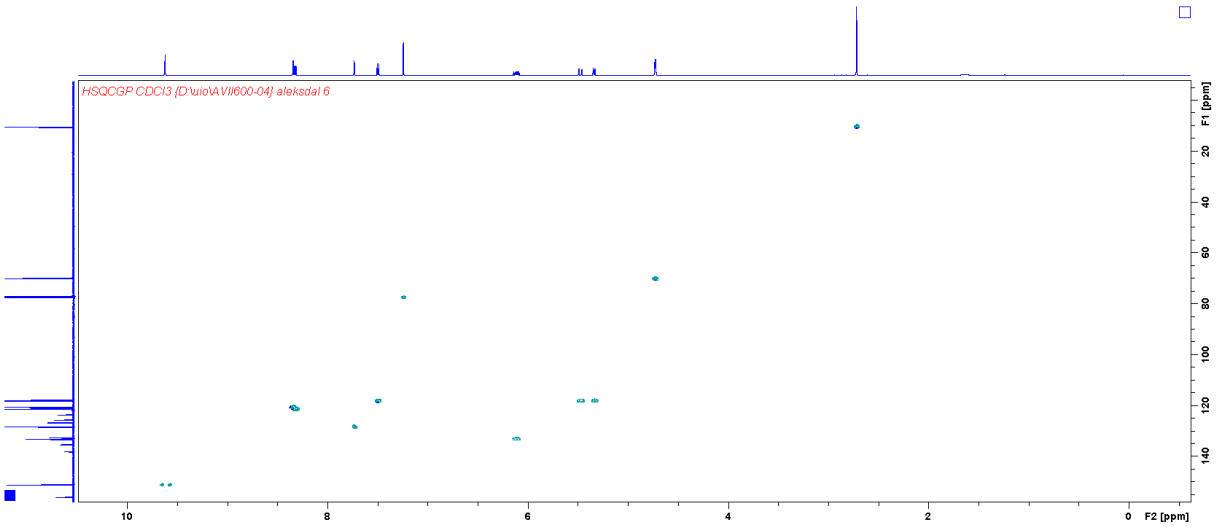
Spectrum 96: 600 MHz, $CDCl_3$, HMBC of 8-(allyloxy)-4-chloro-5-methyl-5,6-dihydrophenanthridine (**64**).



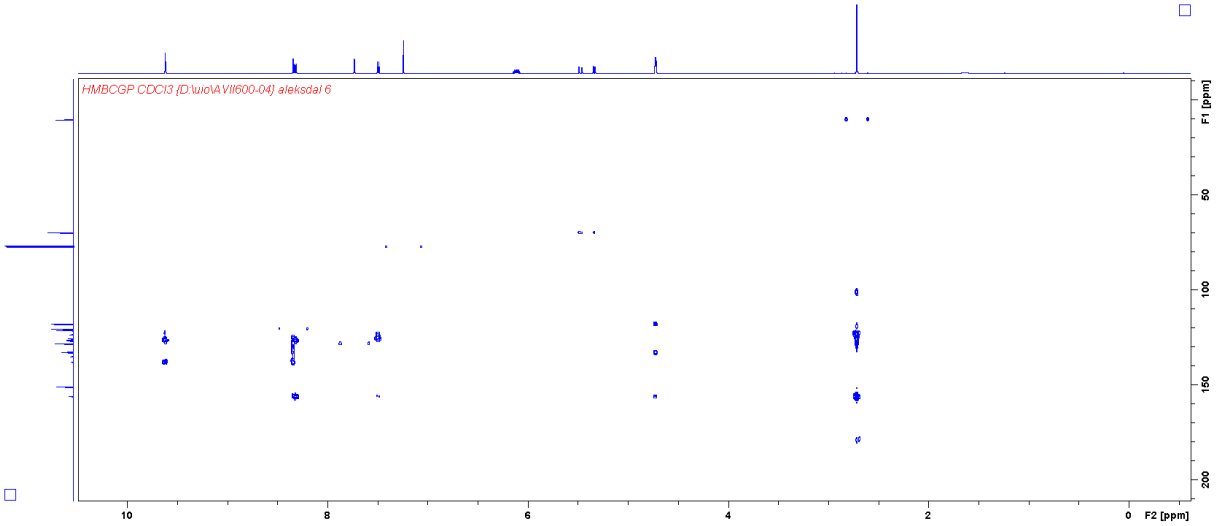
Spectrum 97: 600 MHz, $CDCl_3$, DEPT of 4-chloro-5-methyl-8-propoxyphenanthridin-6(5H)-one (**65**).



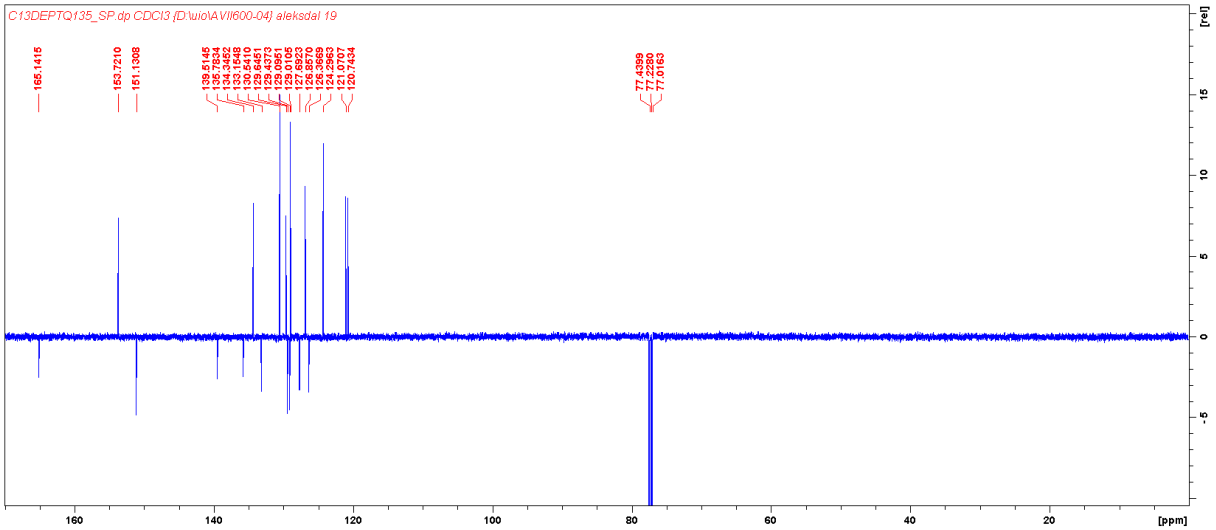
Spectrum 98: 600 MHz, $CDCl_3$, COSY of 4-chloro-5-methyl-8-propoxyphenanthridin-6(5H)-one (**65**).



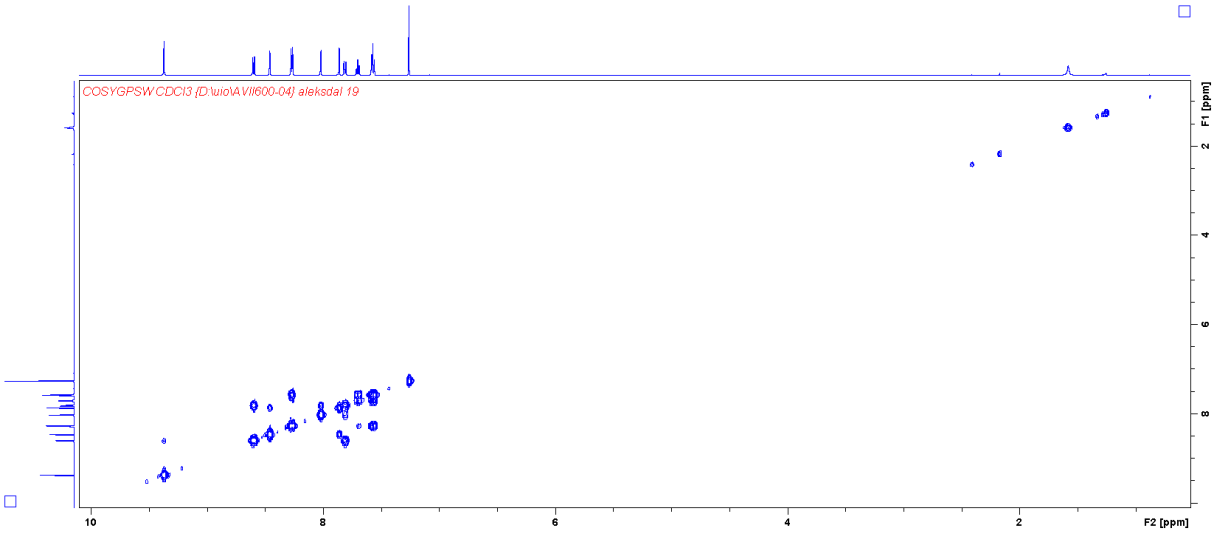
Spectrum 99: 600 MHz, $CDCl_3$, HSQC of 4-chloro-5-methyl-8-propoxyphenanthridin-6(5H)-one (**65**).



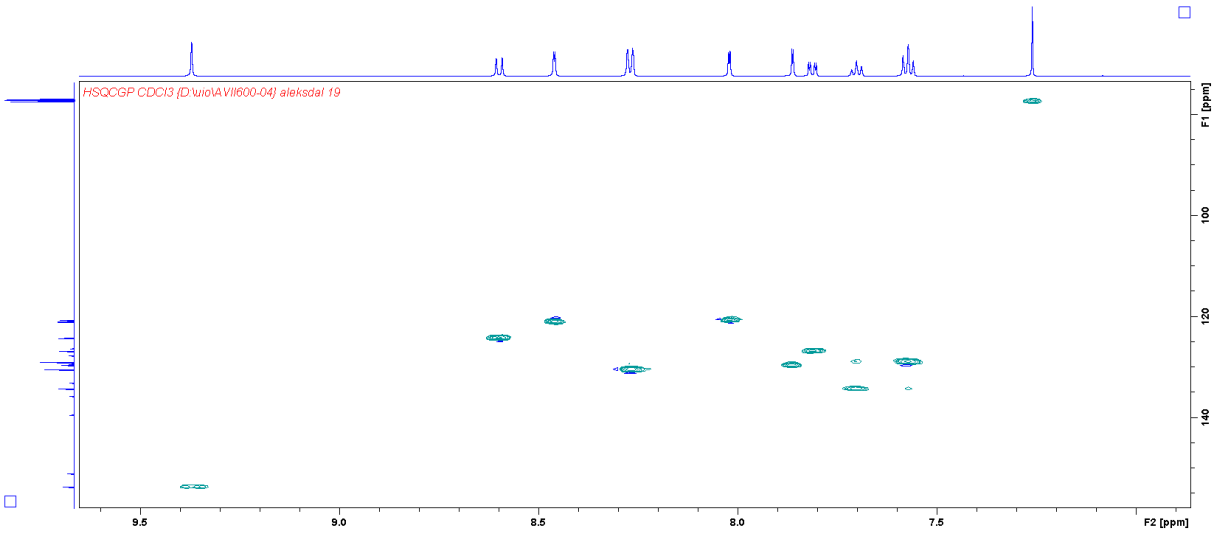
Spectrum 100: 600 MHz, $CDCl_3$, HMBC of 4-chloro-5-methyl-8-propoxyphenanthridin-6(5H)-one (**65**).



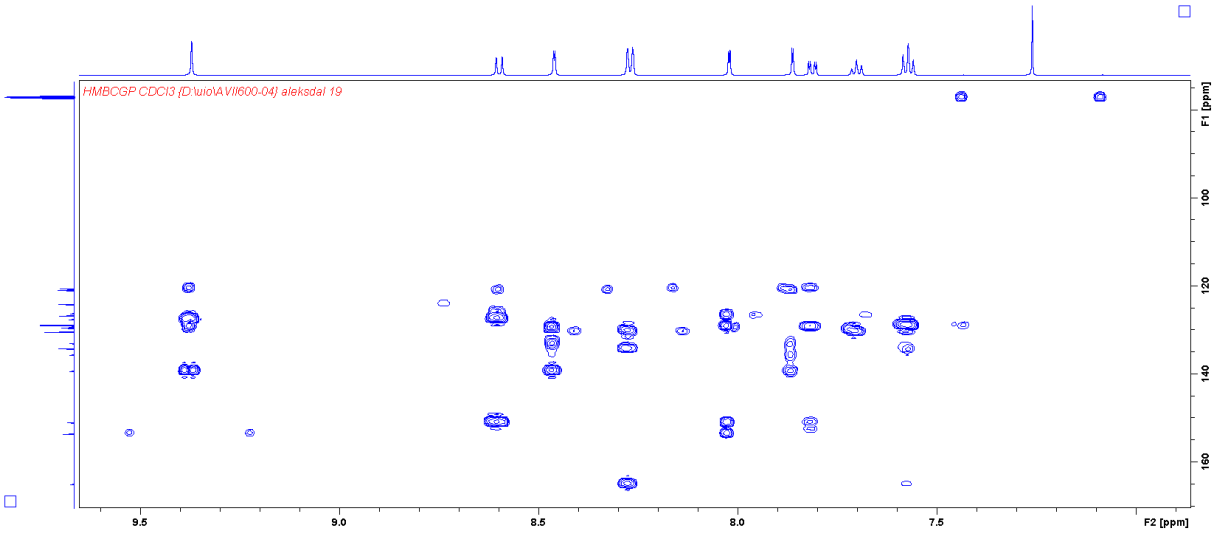
Spectrum 101: 600 MHz, $CDCl_3$, DEPTQ of 2,4-dichlorophenanthridin-8-yl benzoate (**69**).



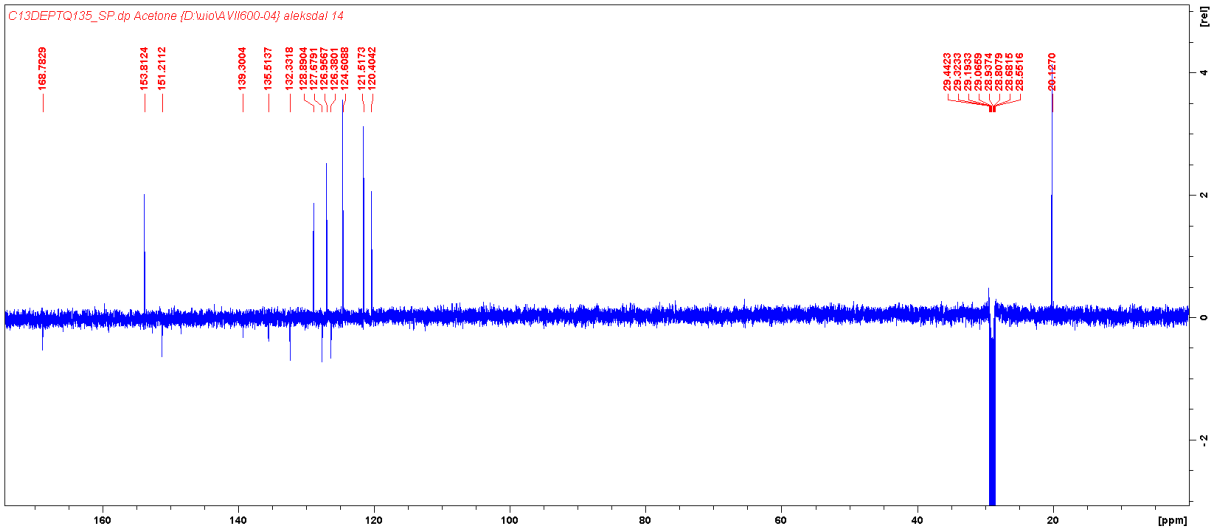
Spectrum 102: 600 MHz, $CDCl_3$, COSY of 2,4-dichlorophenanthridin-8-yl benzoate (**69**).



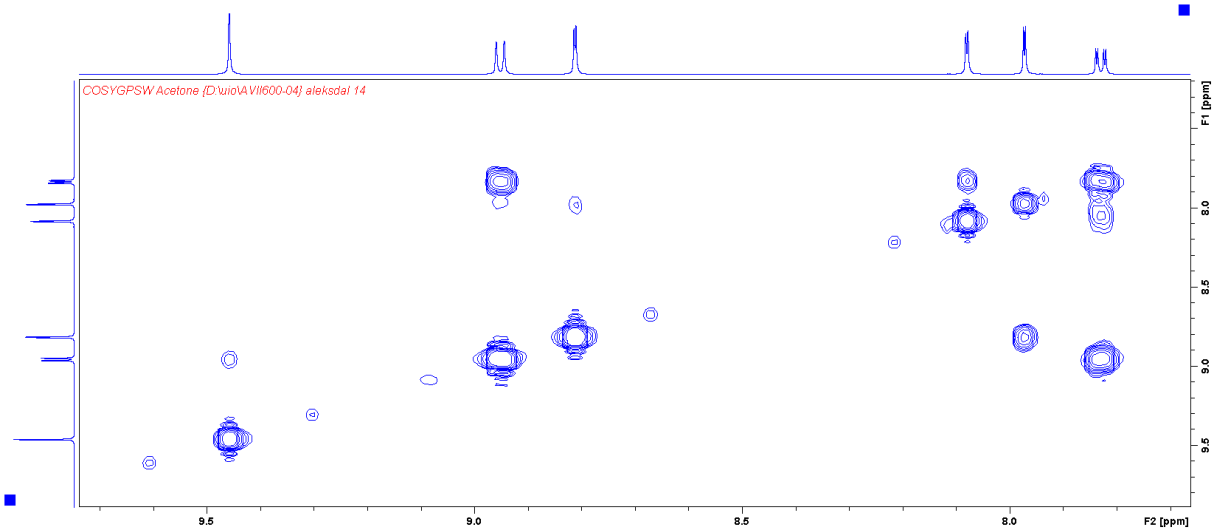
Spectrum 103: 600 MHz, $CDCl_3$, HSQC of 2,4-dichlorophenanthridin-8-yl benzoate (**69**).



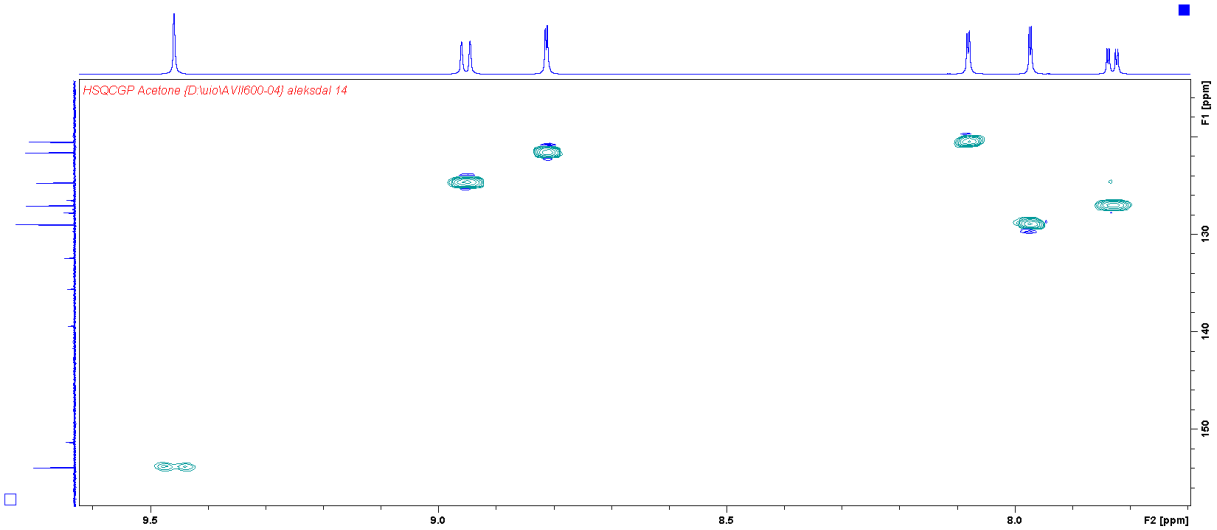
Spectrum 104: 600 MHz, $CDCl_3$, HMBC of 2,4-dichlorophenanthridin-8-yl benzoate (**69**).



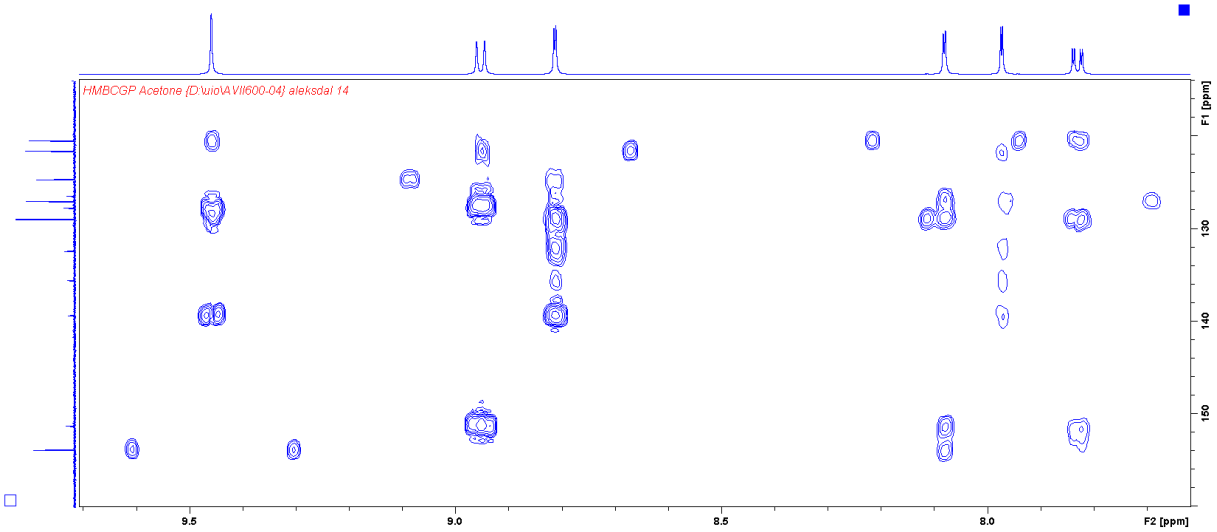
Spectrum 105: 600 MHz, Acetone-D_6, DEPTQ of 2,4-dichlorophenanthridin-8-yl acetate (**70**).



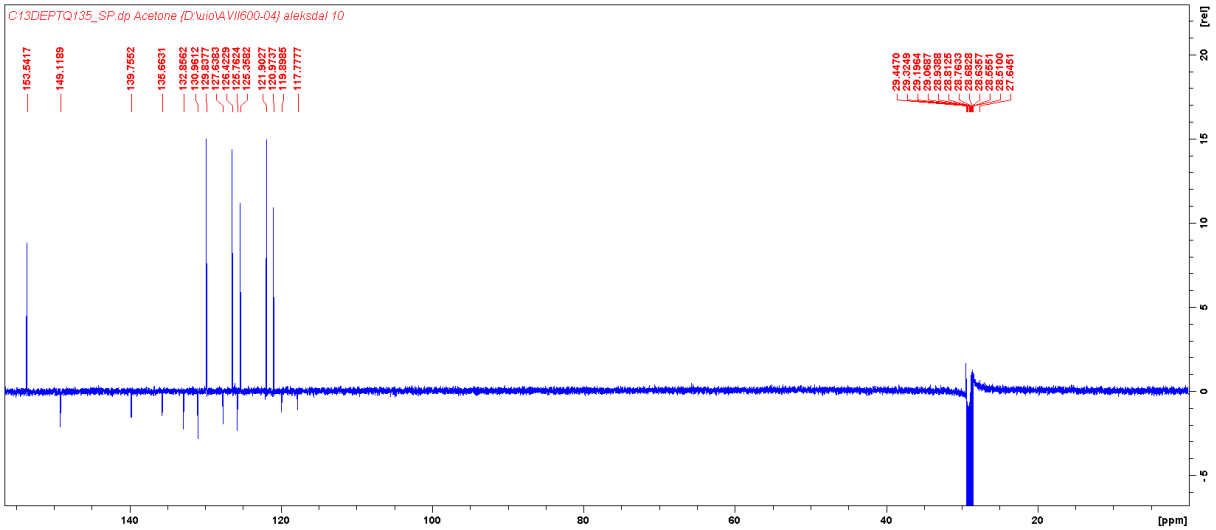
Spectrum 106: 600 MHz, Acetone-D_6, COSY of 2,4-dichlorophenanthridin-8-yl acetate (**70**).



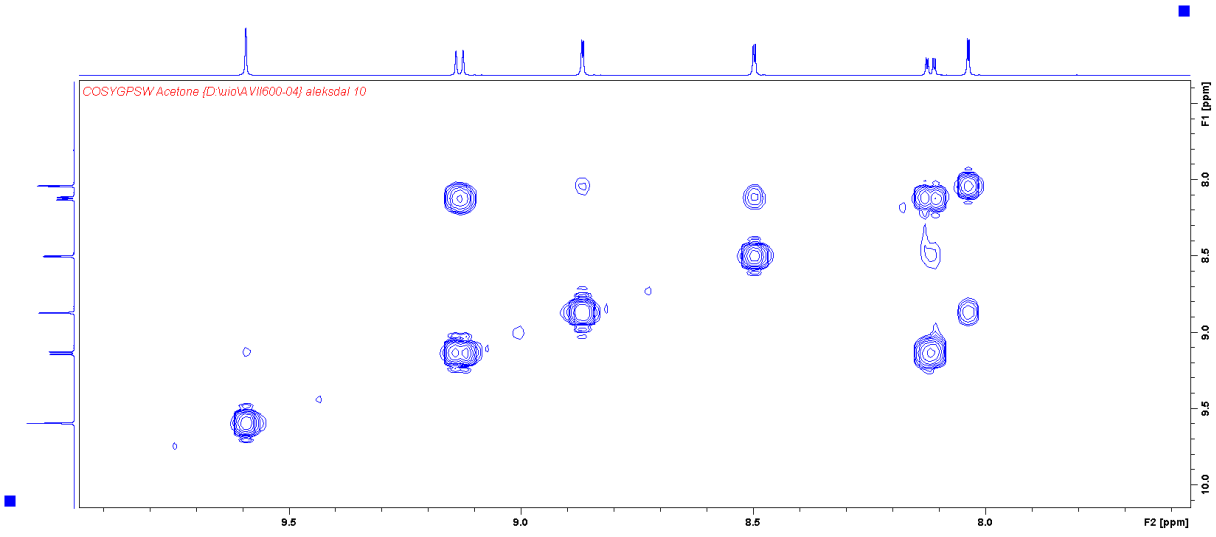
Spectrum 107: 600 MHz, Acetone-D_6, HSQC of 2,4-dichlorophenanthridin-8-yl acetate (**70**).



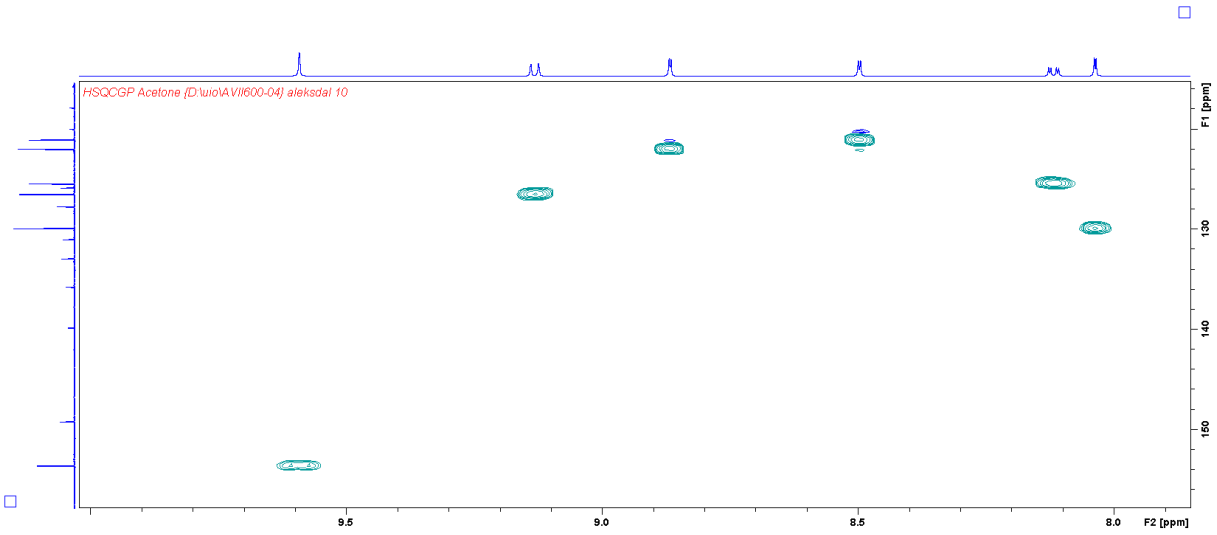
Spectrum 108: 600 MHz, Acetone-D_6, HMBC of 2,4-dichlorophenanthridin-8-yl acetate (**70**).



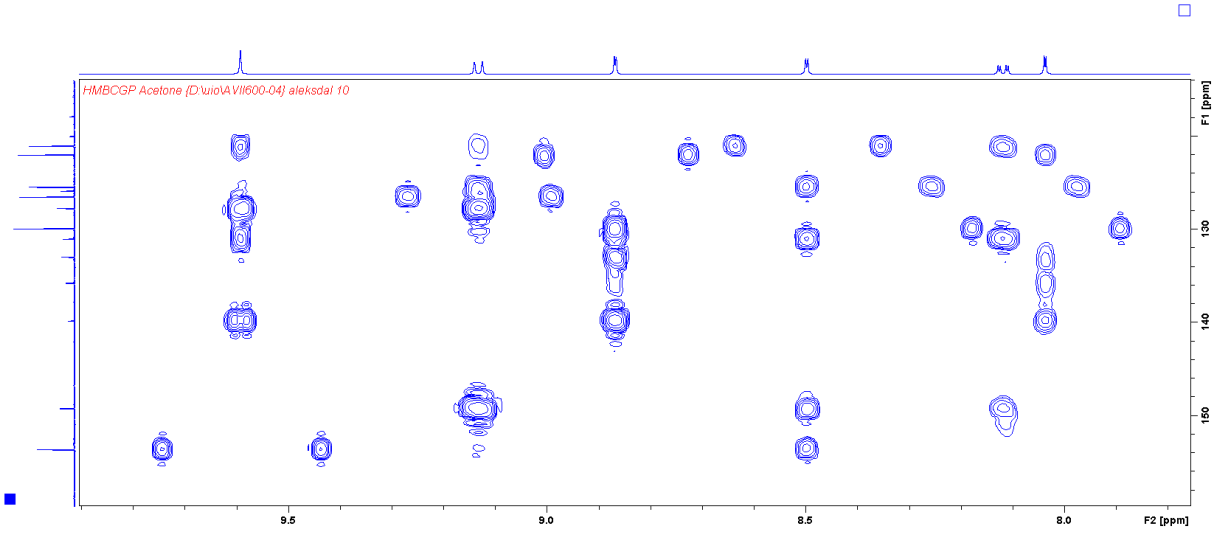
Spectrum 109: 600 MHz, Acetone-D_6, DEPTQ of 2,4-dichlorophenanthridin-8-yl trifluoromethanesulfonate (**71**).



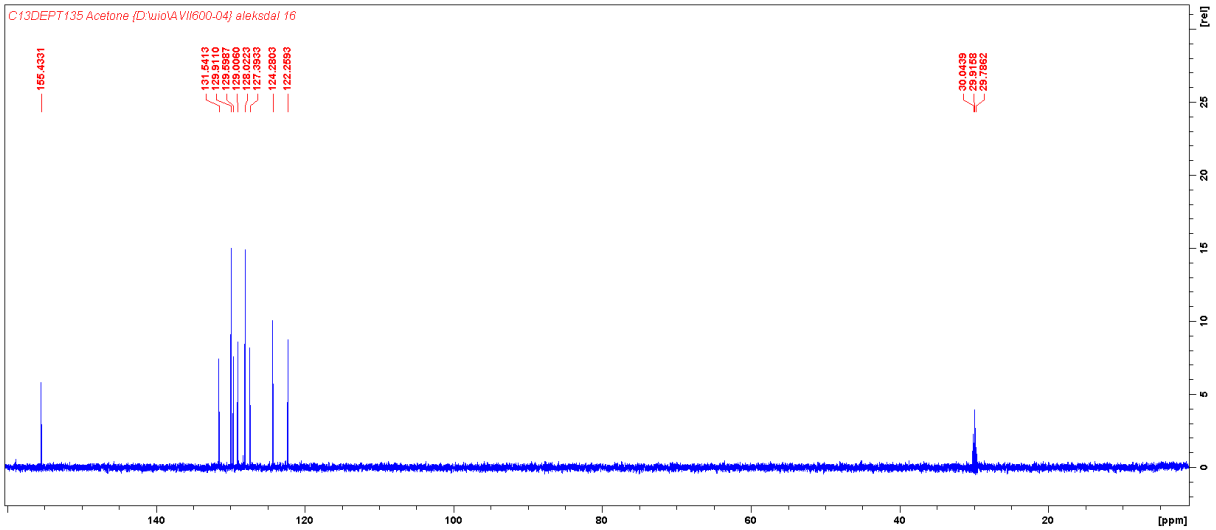
Spectrum 110: 600 MHz, Acetone-D_6, COSY of 2,4-dichlorophenanthridin-8-yl trifluoromethanesulfonate (**71**).



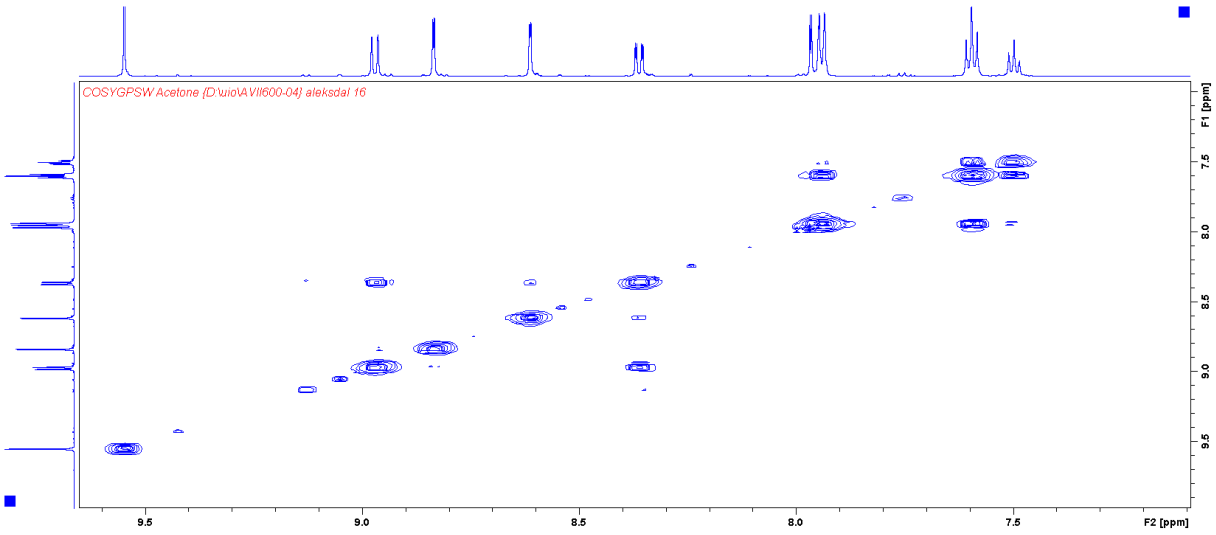
Spectrum 111: 600 MHz, Acetone-D_6, HSQC of 2,4-dichlorophenanthridin-8-yl trifluoromethanesulfonate (**71**).



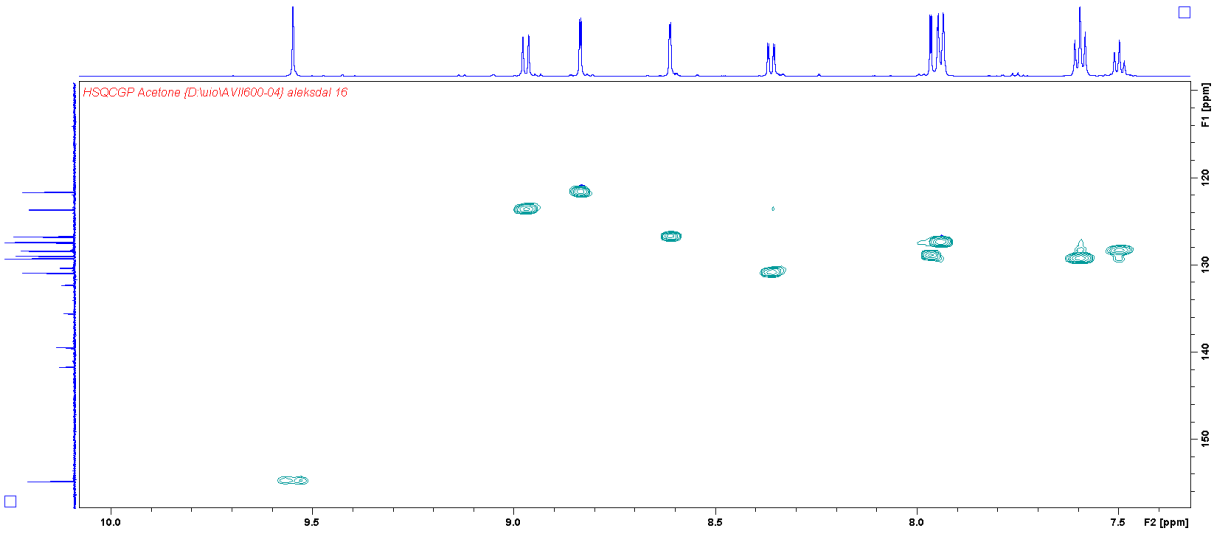
Spectrum 112: 600 MHz, Acetone-D_6, HMBC of 2,4-dichlorophenanthridin-8-yl trifluoromethanesulfonate (**71**).



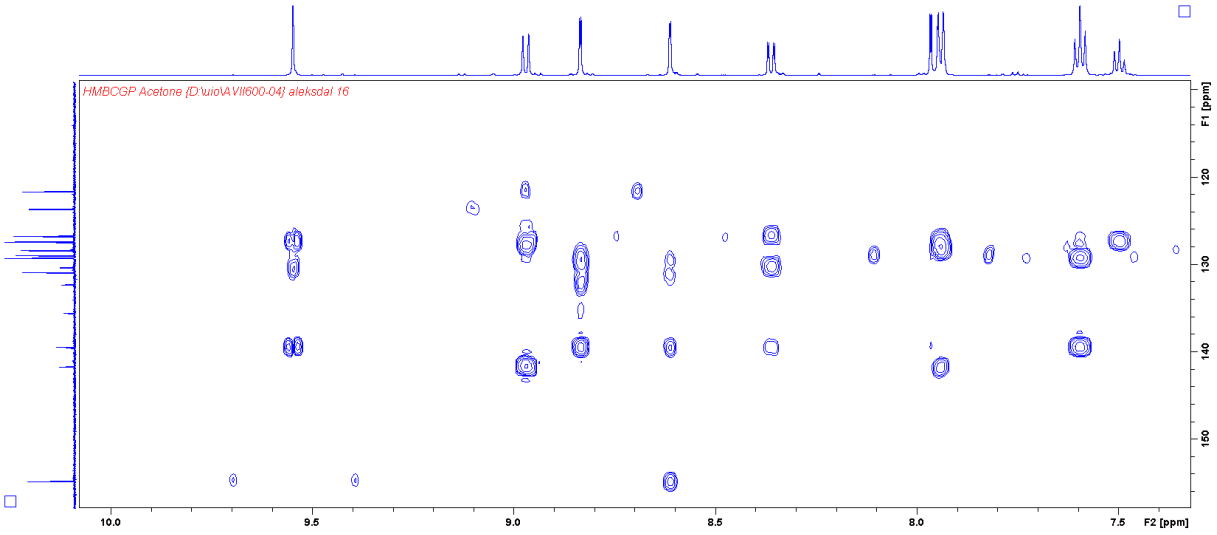
Spectrum 113: 600 MHz, Acetone-D_6, DEPTQ of 2,4-dichloro-8-phenylphenanthridine (**73**).



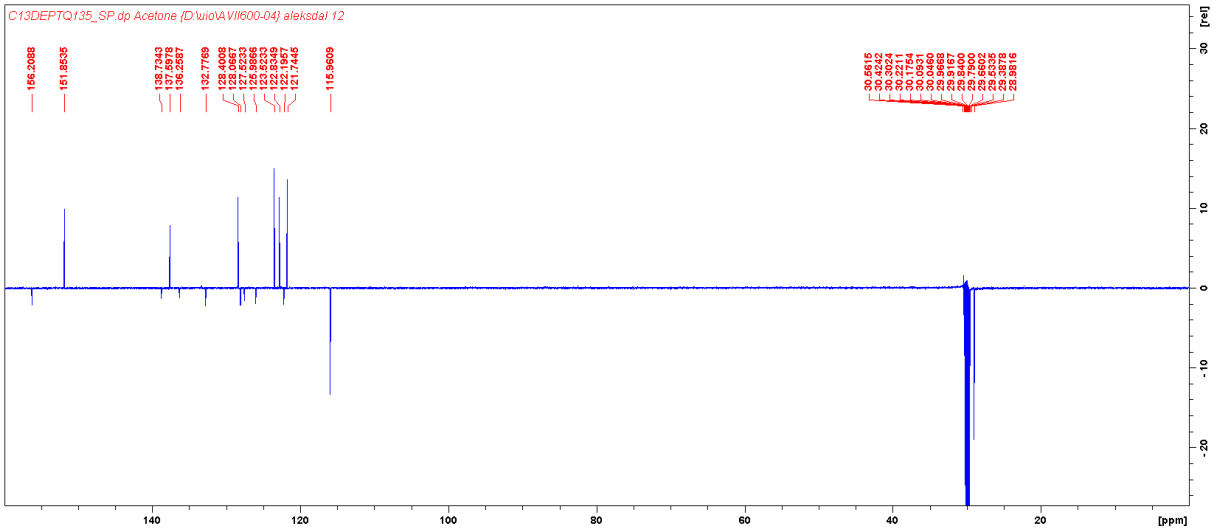
Spectrum 114: 600 MHz, Acetone-D_6, COSY of 2,4-dichloro-8-phenylphenanthridine (**73**).



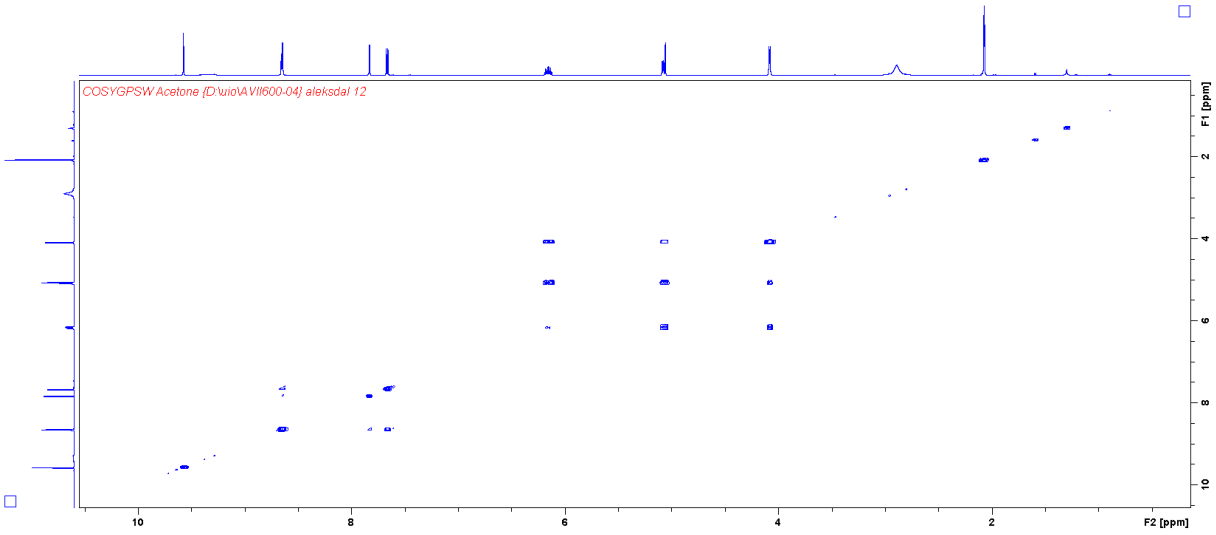
Spectrum 115: 600 MHz, Acetone-D_6, HSQC of 2,4-dichloro-8-phenylphenanthridine (**73**).



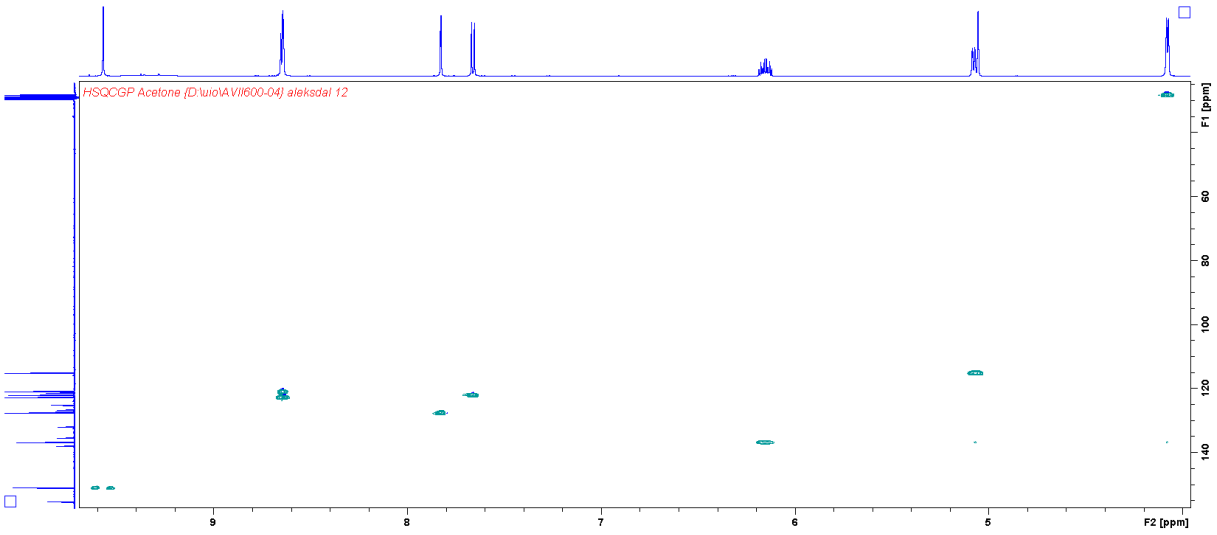
Spectrum 116: 600 MHz, Acetone-D_6, HMBC of 2,4-dichloro-8-phenylphenanthridine (**73**).



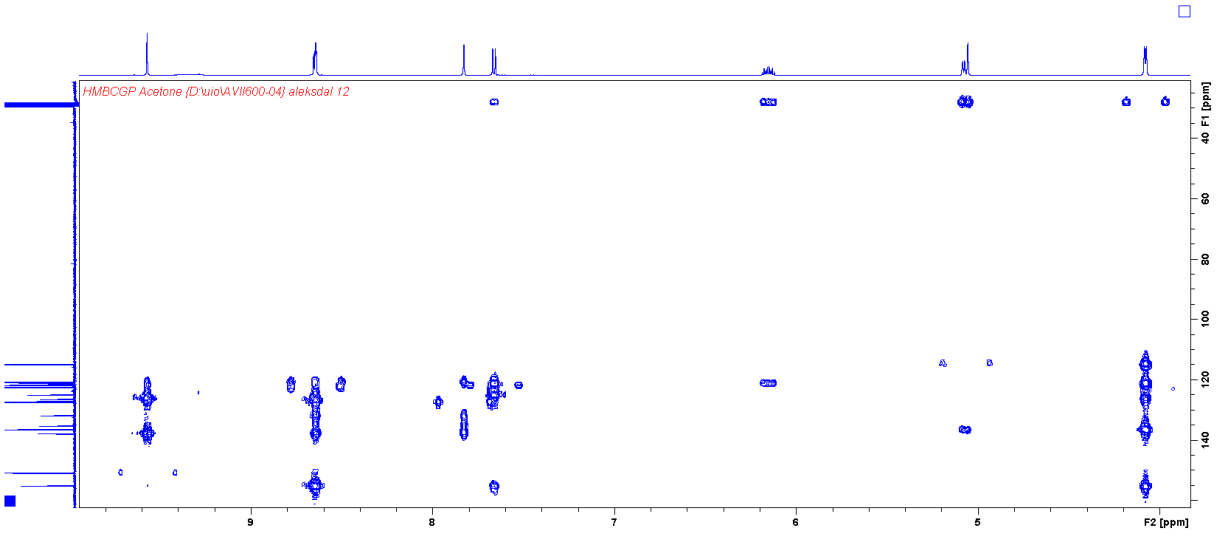
Spectrum 117: 600 MHz, Acetone-D_6, DEPTQ of 7-allyl-2,4-dichlorophenanthridin-8-ol (**74b**).



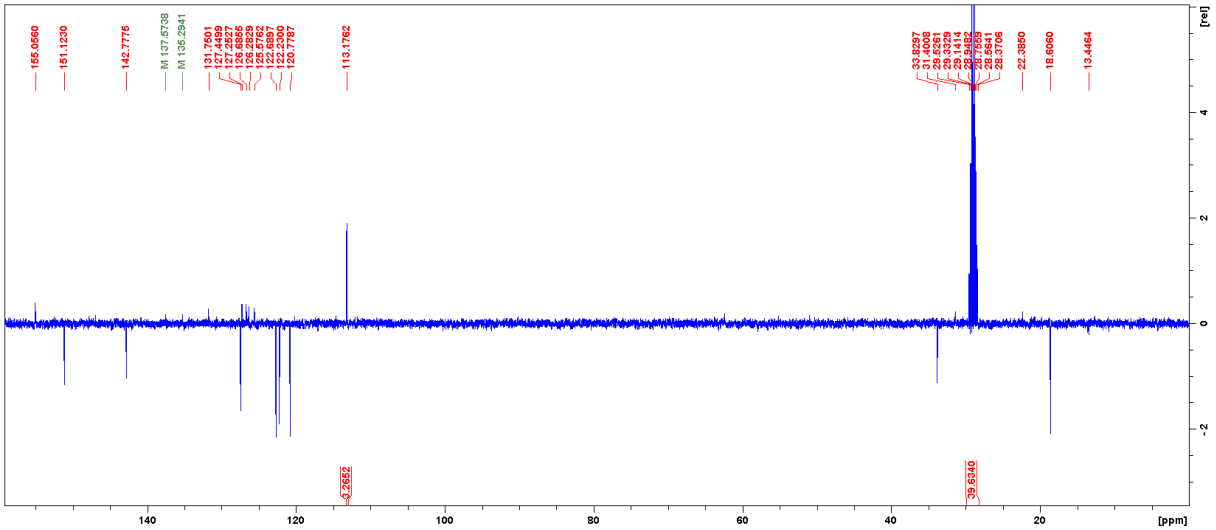
Spectrum 118: 600 MHz, Acetone-D_6, COSY of 7-allyl-2,4-dichlorophenanthridin-8-ol (**74b**).



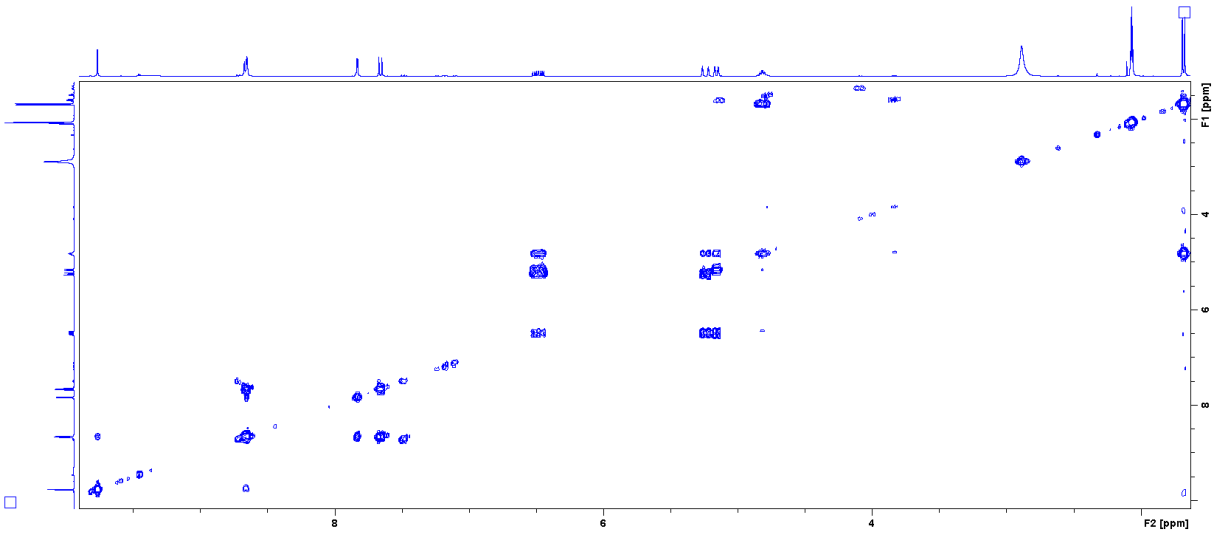
Spectrum 119: 600 MHz, Acetone-D_6, HSQC of 7-allyl-2,4-dichlorophenanthridin-8-ol (**74b**).



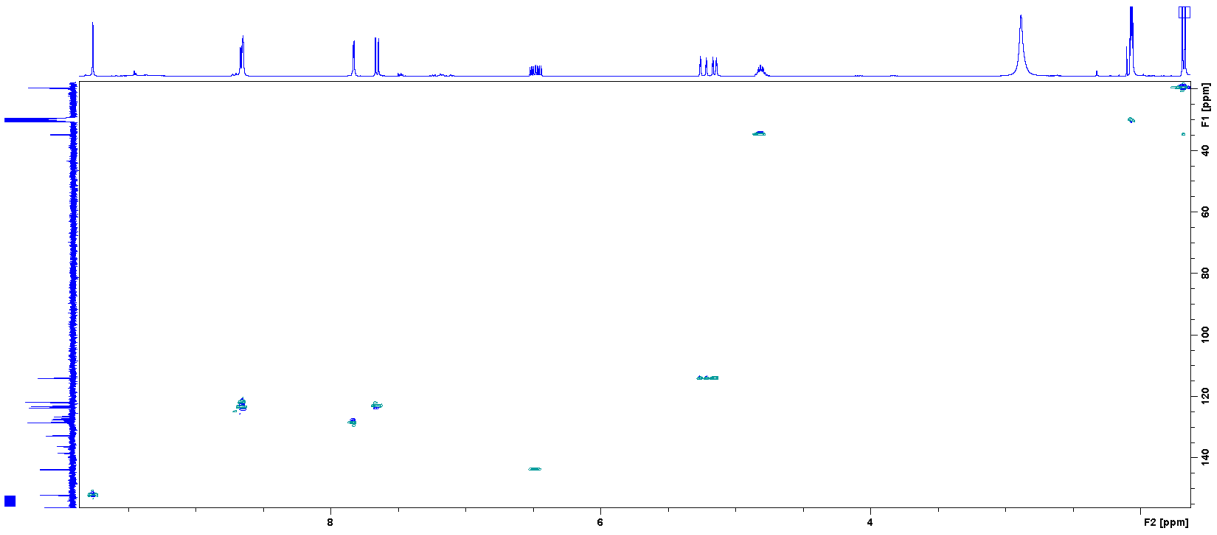
Spectrum 120: 600 MHz, Acetone-D_6, HMBC of 7-allyl-2,4-dichlorophenanthridin-8-ol (**74b**).



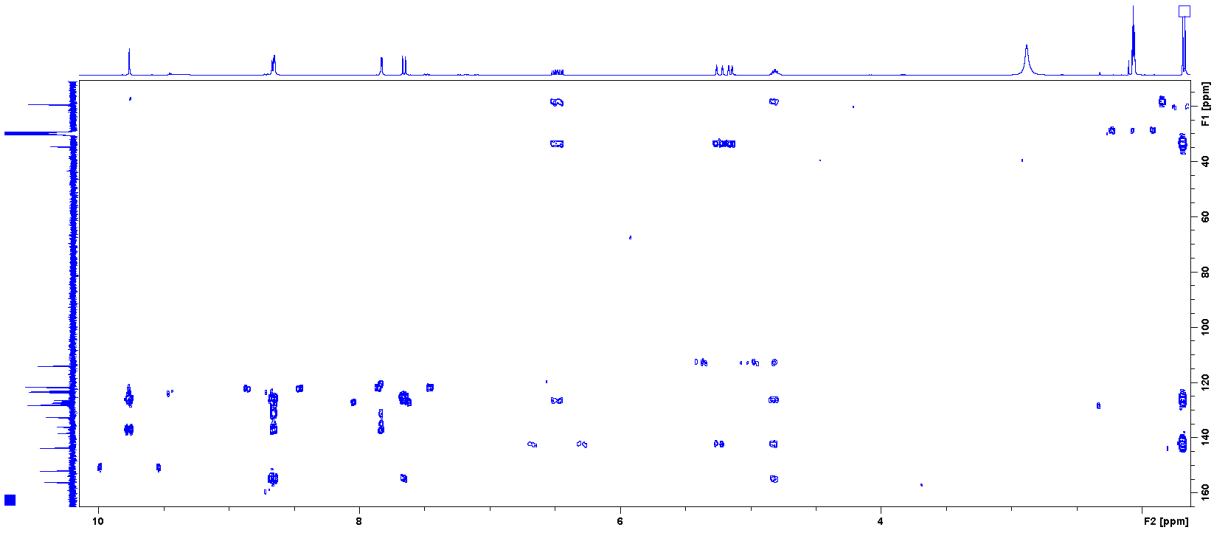
Spectrum 121: 400 MHz, Acetone-D_6, DEPTQ of 7-(but-3-en-2-yl)-2,4-dichlorophenanthridin-8-ol (**75**).



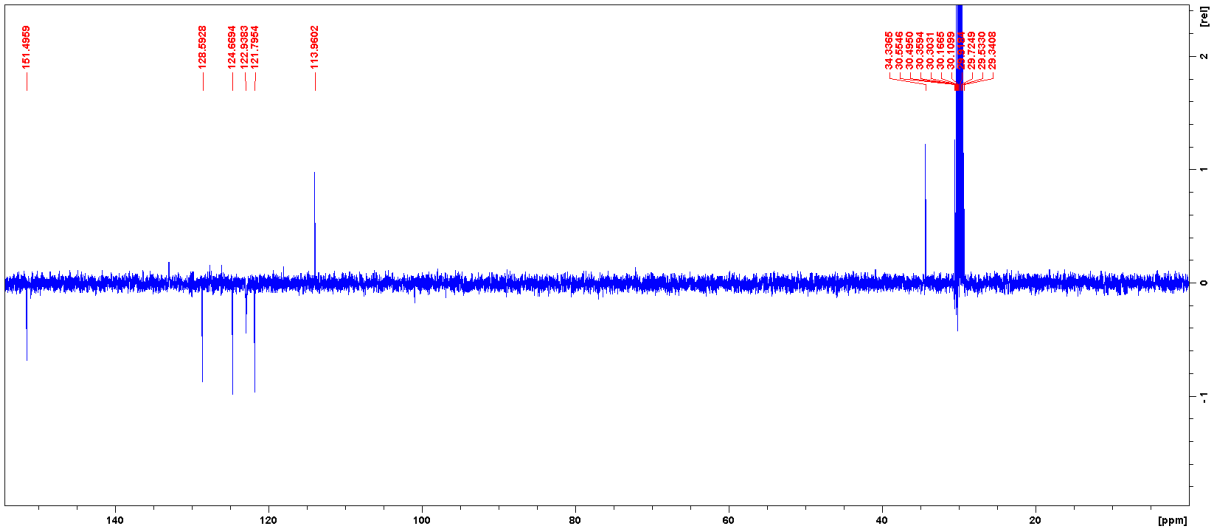
Spectrum 122: 400 MHz, Acetone-D_6, COSY of 7-(but-3-en-2-yl)-2,4-dichlorophenanthridin-8-ol (**75**).



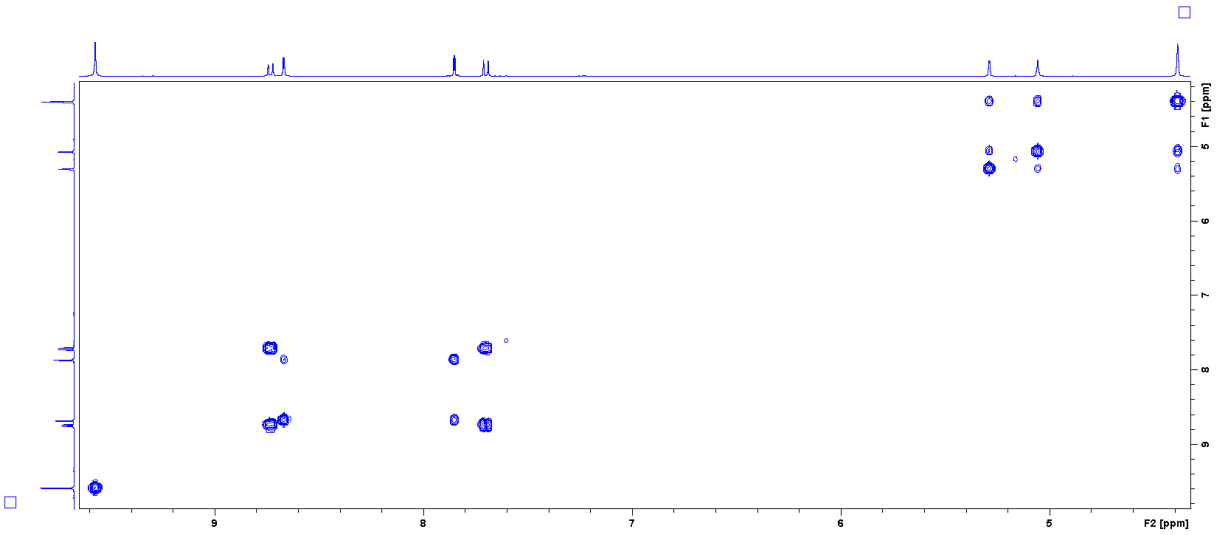
Spectrum 123: 400 MHz, Acetone-D_6, HSQC of 7-(but-3-en-2-yl)-2,4-dichlorophenanthridin-8-ol (**75**).



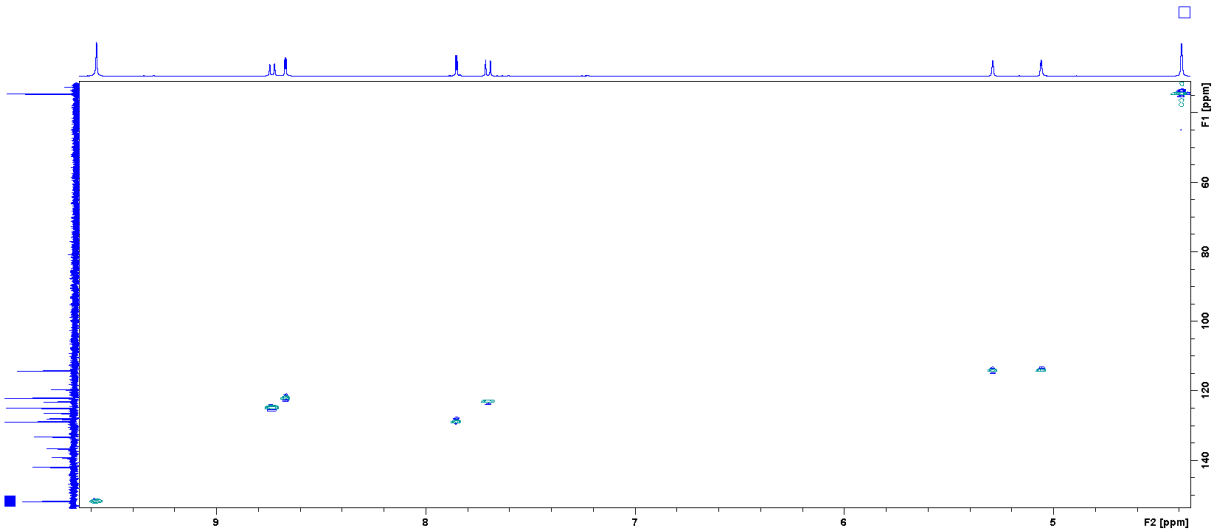
Spectrum 124: 400 MHz, Acetone-D_6, HMBC of 7-(but-3-en-2-yl)-2,4-dichlorophenanthridin-8-ol (**75**).



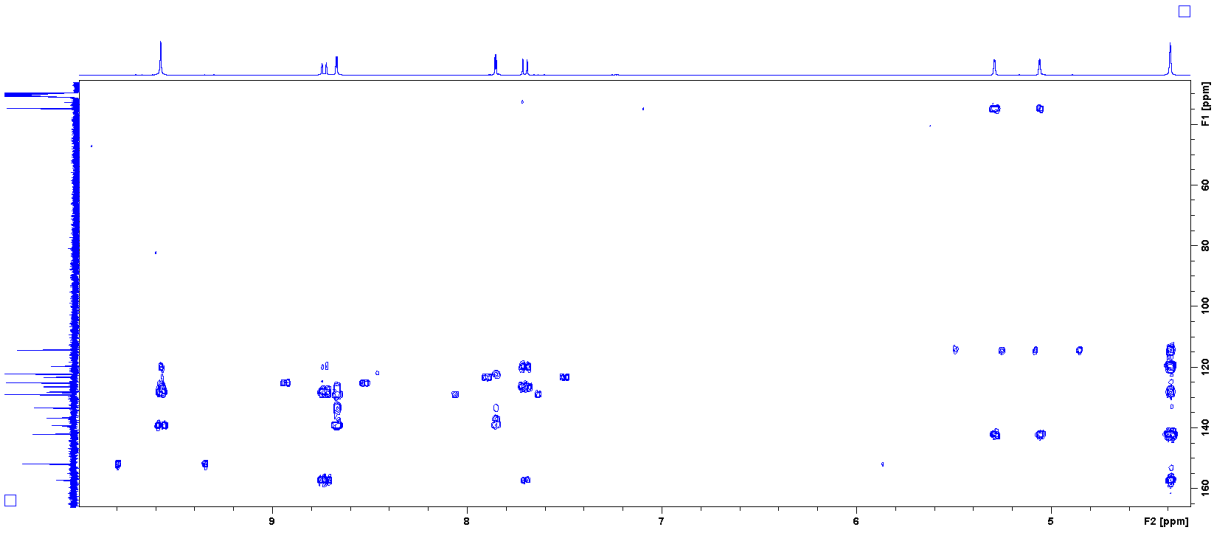
Spectrum 125: 400 MHz, Acetone-D_6, DEPTQ of 2,4-dichloro-7-(2-chloroallyl)phenanthridin-8-ol (**76**).



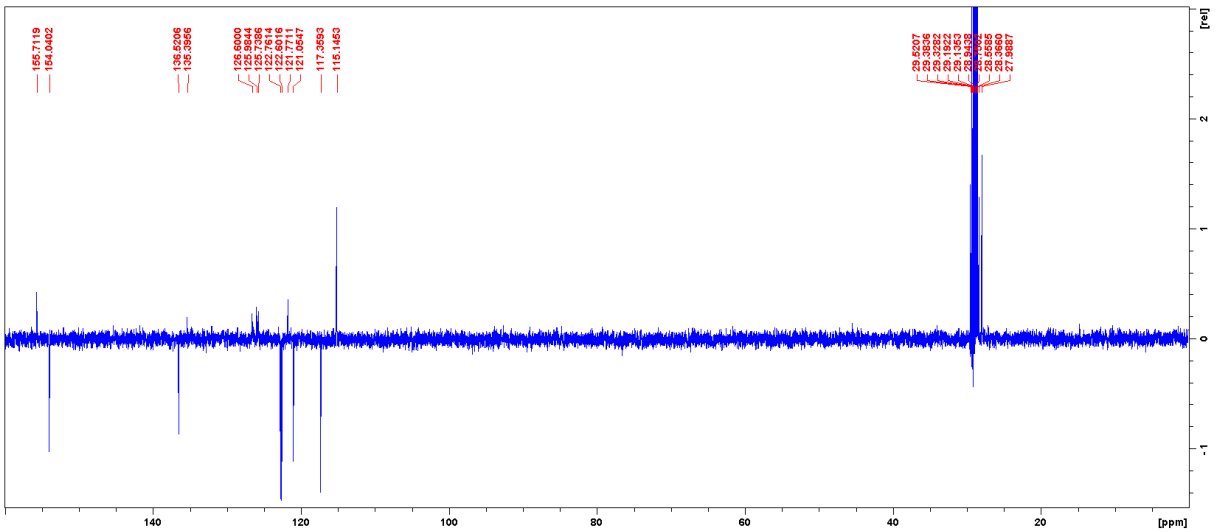
Spectrum 126: 400 MHz, Acetone-D_6, COSY of 2,4-dichloro-7-(2-chloroallyl)phenanthridin-8-ol (**76**).



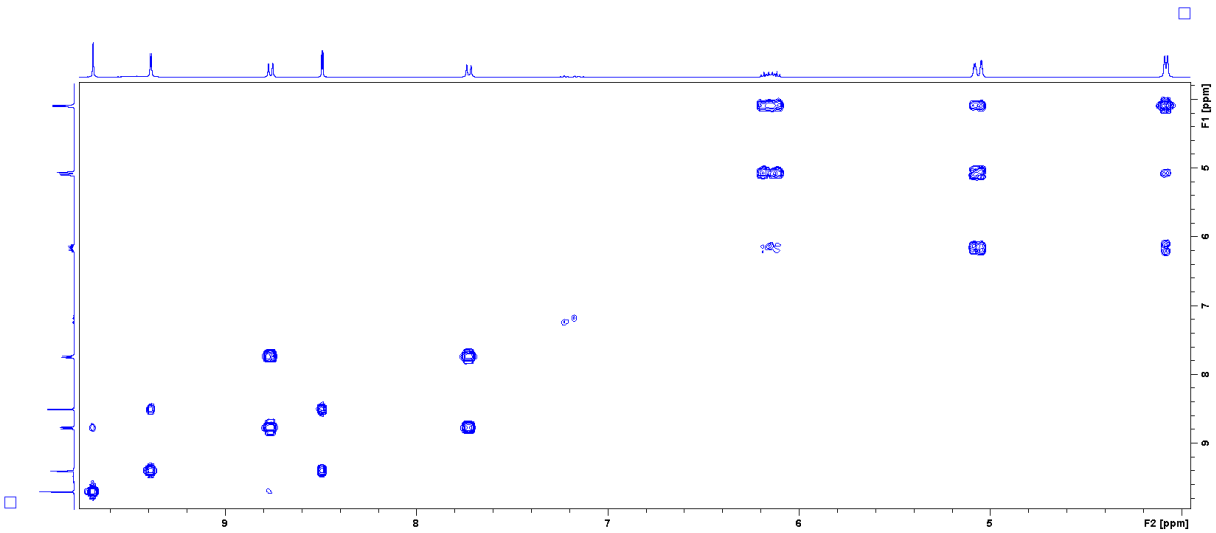
Spectrum 127: 400 MHz, Acetone-D_6, HSQC of 2,4-dichloro-7-(2-chloroallyl)phenanthridin-8-ol (**76**).



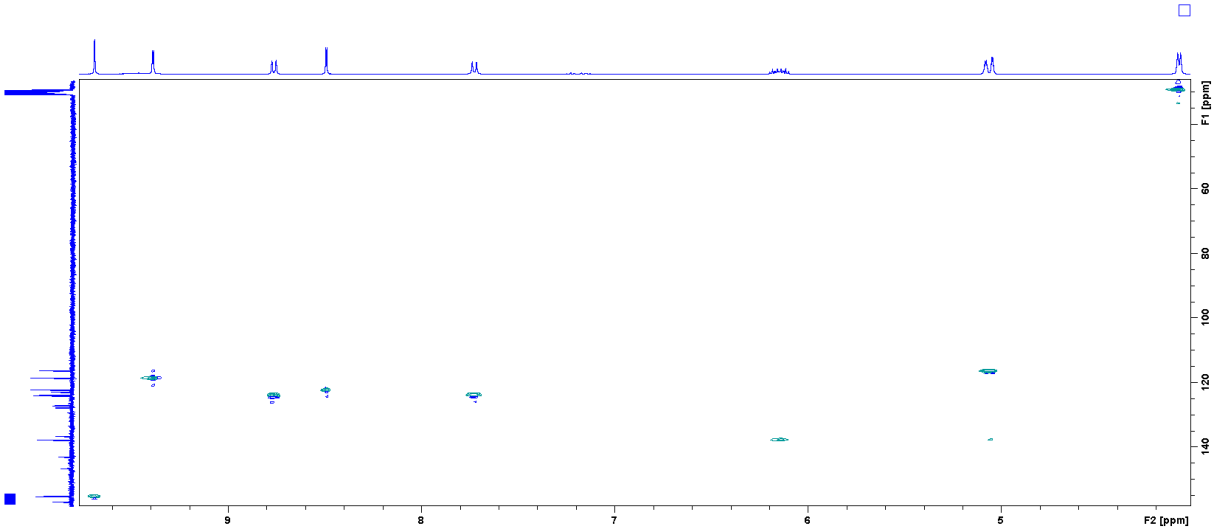
Spectrum 128: 400 MHz, Acetone-D_6, HMBC of 2,4-dichloro-7-(2-chloroallyl)phenanthridin-8-ol (**76**).



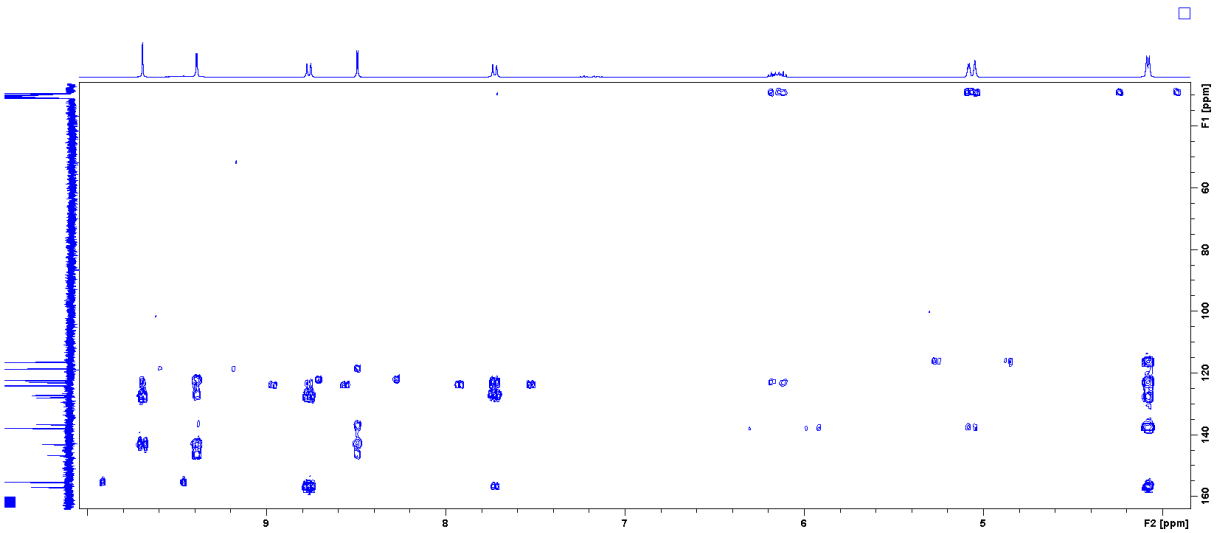
Spectrum 129: 400 MHz, Acetone-D_6, DEPTQ of 7-allyl-4-chloro-2-nitrophenanthridin-8-ol (**77**).



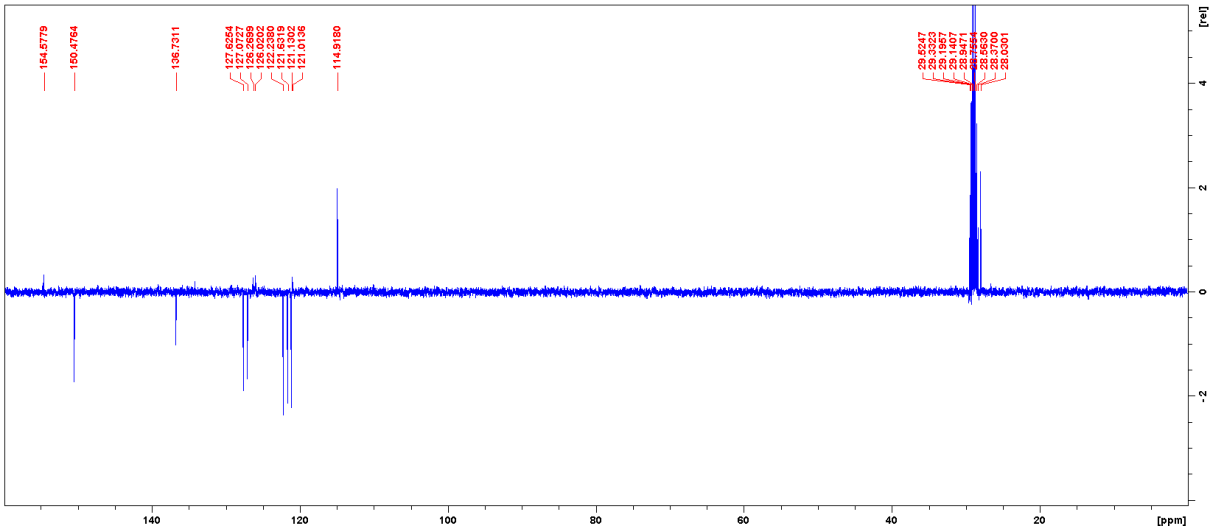
Spectrum 130: 400 MHz, Acetone-D_6, COSY of 7-allyl-4-chloro-2-nitrophenanthridin-8-ol (**77**).



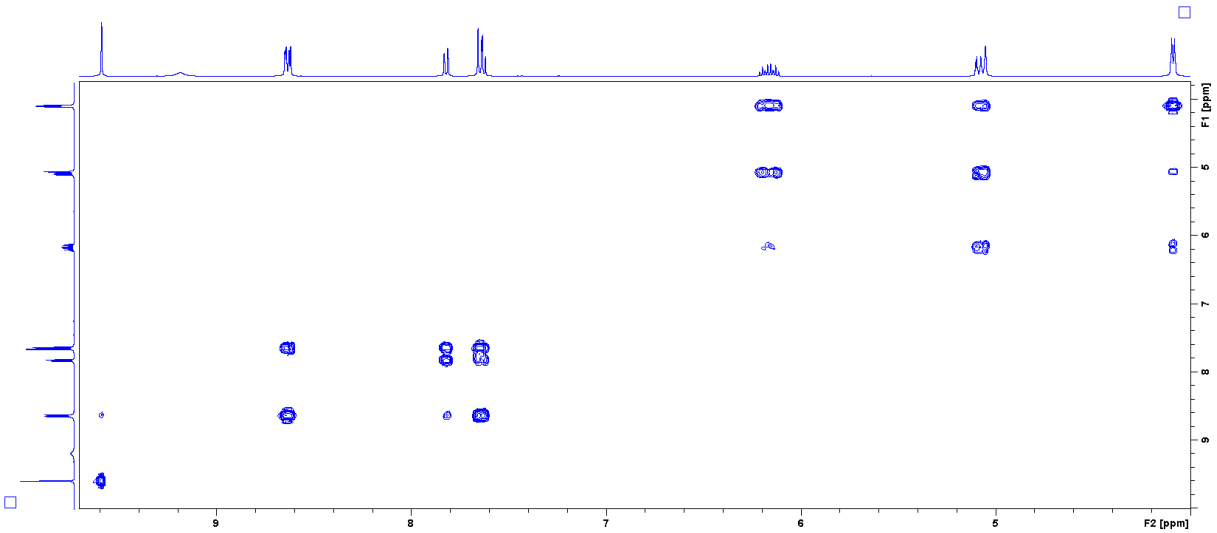
Spectrum 131: 400 MHz, Acetone-D_6, HSQC of 7-allyl-4-chloro-2-nitrophenanthridin-8-ol (**77**).



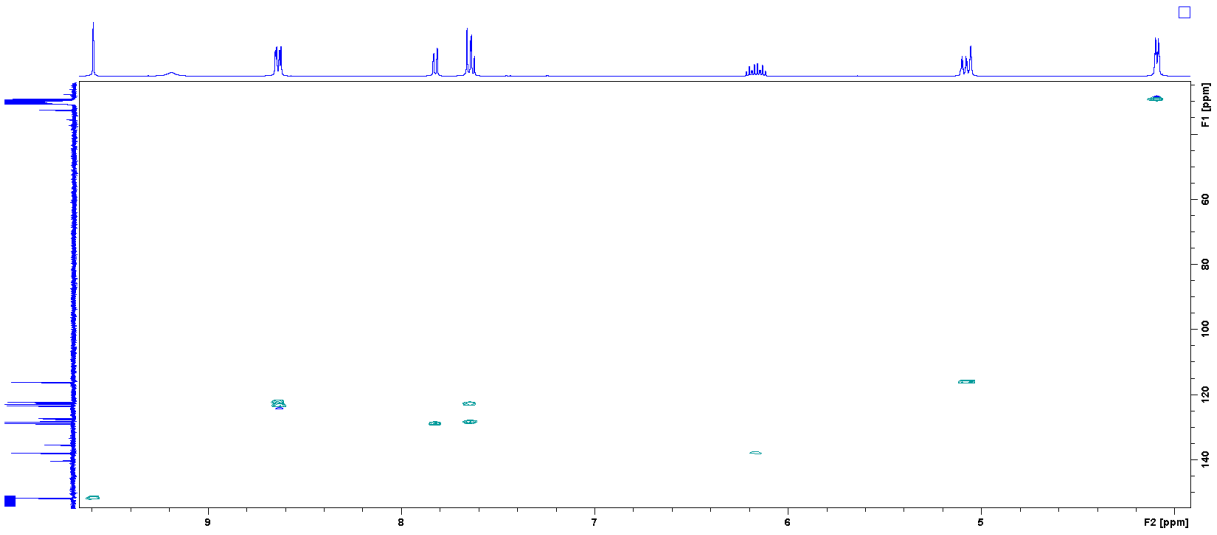
Spectrum 132: 400 MHz, Acetone-D_6, HMBC of 7-allyl-4-chloro-2-nitrophenanthridin-8-ol (**77**)



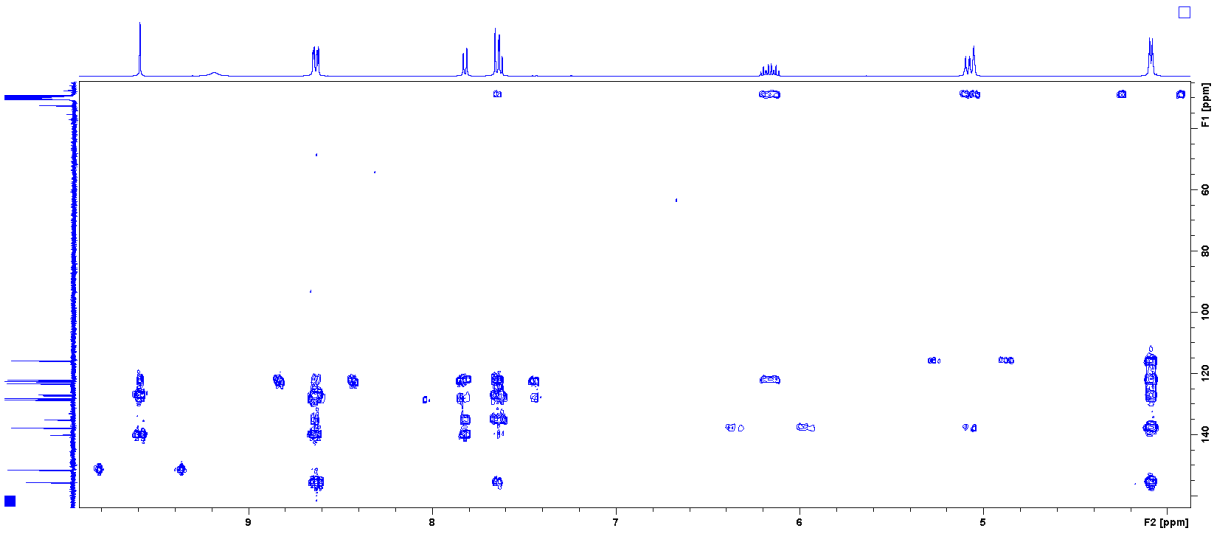
Spectrum 133: 400 MHz, Acetone-D_6, DEPTQ of 7-allyl-4-chlorophenanthridin-8-ol (**78**).



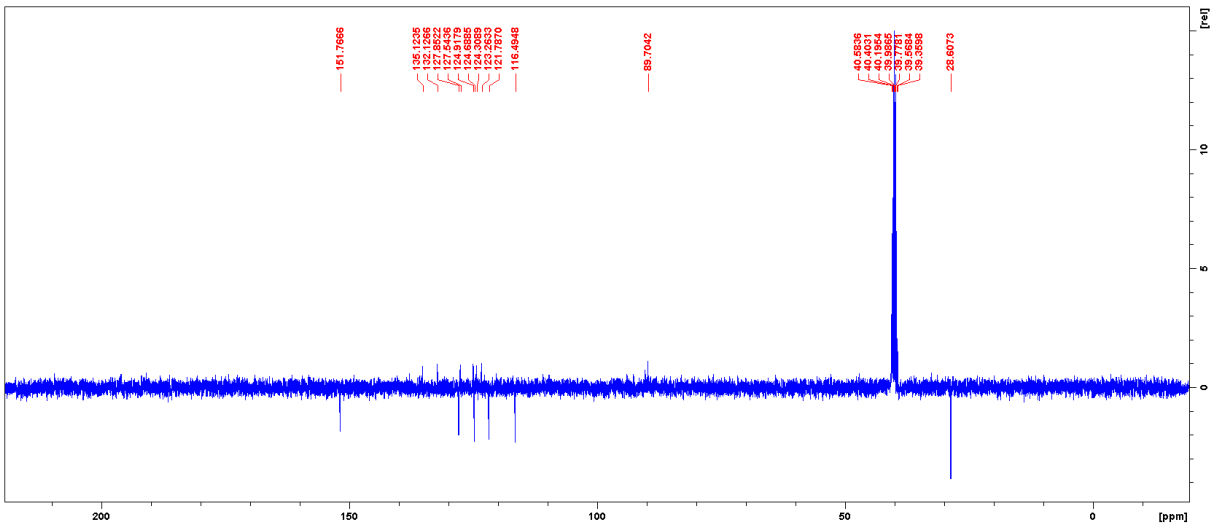
Spectrum 134: 400 MHz, Acetone-D_6, COSY of 7-allyl-4-chlorophenanthridin-8-ol (**78**).



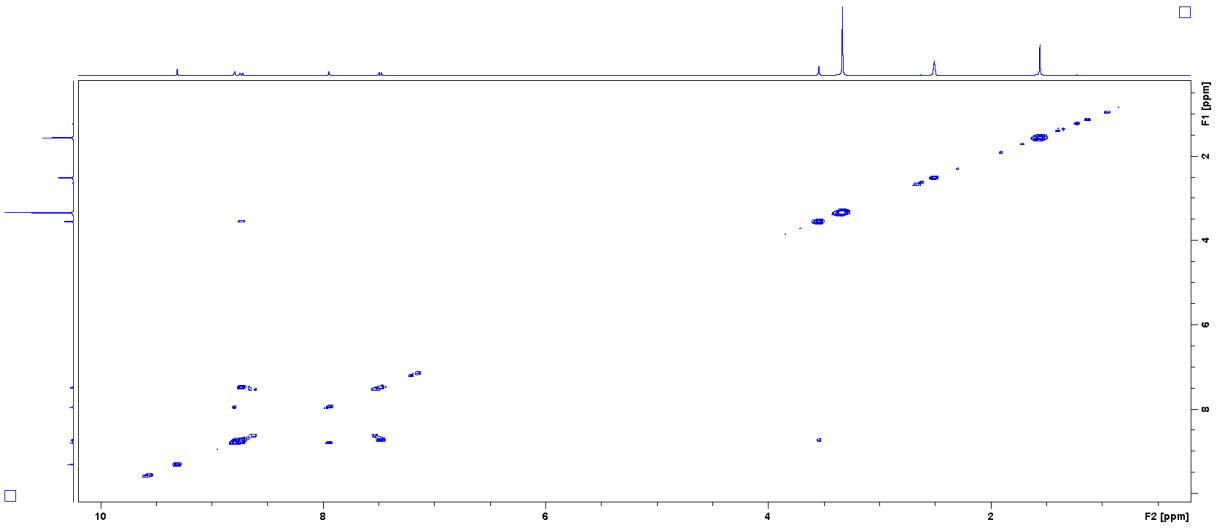
Spectrum 135: 400 MHz, Acetone-D_6, HSQC of 7-allyl-4-chlorophenanthridin-8-ol (**78**).



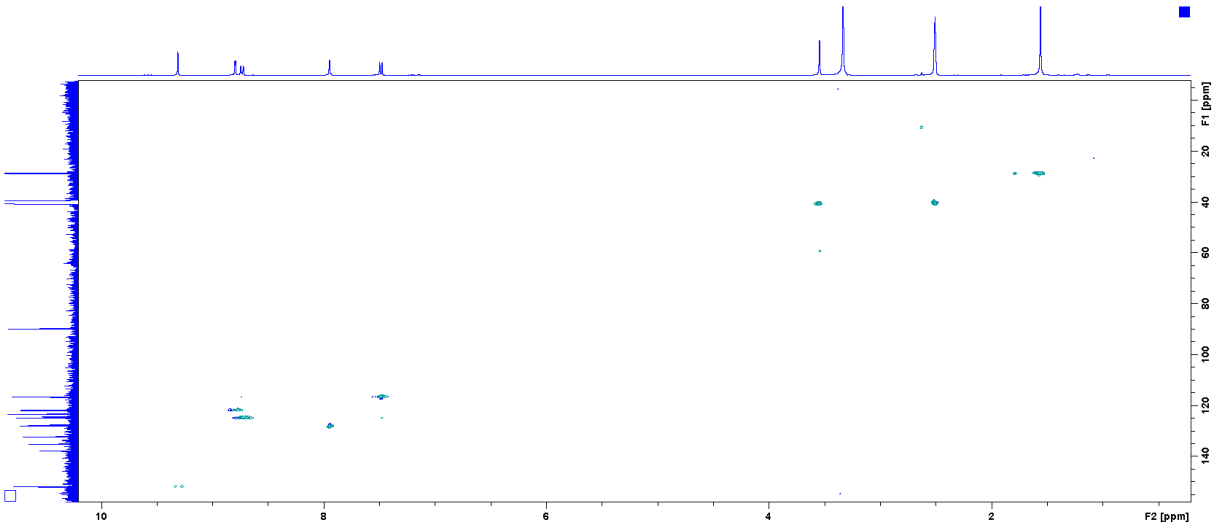
Spectrum 136: 400 MHz, Acetone-D_6, HMBC of 7-allyl-4-chlorophenanthridin-8-ol (**78**).



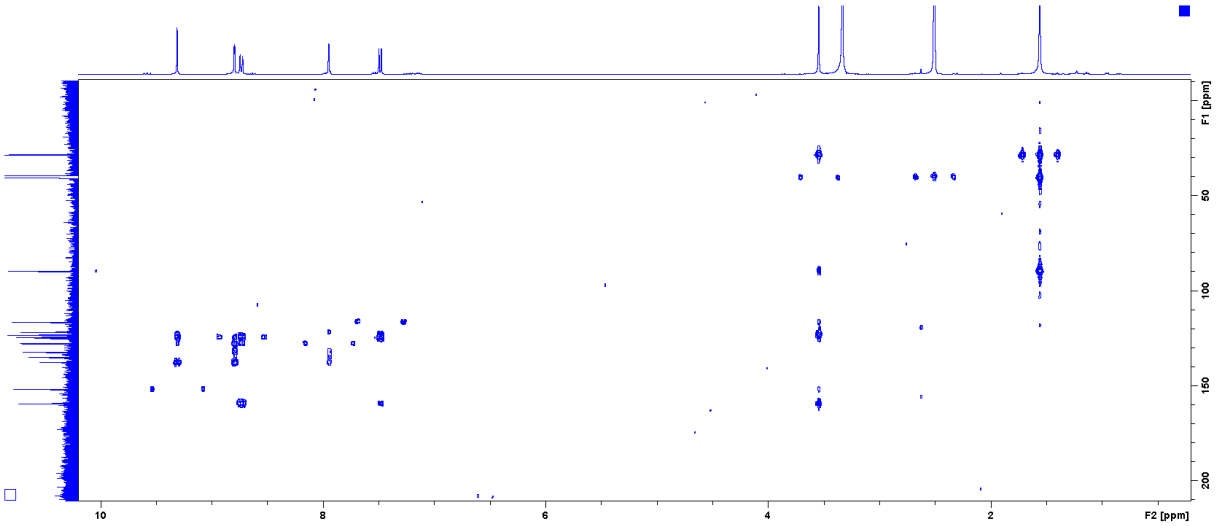
Spectrum 137: 400 MHz, Acetone-D_6, DEPT spectrum of 6,8-dichloro-2,2-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridine (**79c**).



Spectrum 138: 400 MHz, Acetone-D_6, COSY spectrum of 6,8-dichloro-2,2-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridine (**79c**).



Spectrum 139: 400 MHz, Acetone-D_6, HSQC spectrum of 6,8-dichloro-2,2-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridine (**79c**).



Spectrum 140: 400 MHz, Acetone-D_6, ^{1}H NMR spectrum of 6,8-dichloro-2,2-dimethyl-2,3-dihydrofuro[3,2-i]phenanthridine (**79c**).

7. References

[1] Read, M. L.; Krapp, A.; Miranda, P. O.; Gundersen, L.-L. *Tetrahedron*, 2012, *68(7)*, 1869-1885.

[2] Read, M. L.; Gundersen, L.-L. *Journal of Organic Chemistry*, 2013, *78(3)*, 1311-1316.

[3] Gulbrandsen, H. S.; Hennum, M.; Osheka, M.; Read, M. L.; Gundersen, L.-L. *European Journal of Organic Chemistry*, 2014, *2014(36)*, 8182-8190.

[4] Gulbrandsen, H.; S.; Alfaro, J. L. D.; Read, M. L.; Gundersen, L.-L. *European Journal of Organic Chemistry*, 2017, *2017(16)*, 2305-2311.

[5] Gulbrandsen, H. S.; Serigstad, H.; Read, M. L.; Joos, I.; Gundersen, L.-L. *European Journal of Organic Chemistry*, 2019, *2019(35)*, 6044-6052.

[6] Slaninová, I.; Slanina, J.; Táborská, E. *Cytometry Part A*, 2007, *71A*, 700-708.

[7] Niu, X.-F.; Zhou, P.; Li, W.-F.; Xu, H.-B. *Fitoterapia*, 2011, *82*, 620-625.

[8] Zdařilová, A.; Vrzal, R.; Rypka, M.; Ulrichová, J.; Dvořák, Z. *Food and Chemical Toxicology*, 2006, *44(2)*, 242-249.

[9] Jin, Zhong. Amaryllidaceae and Sceletium alkaloids. *Natural Product Reports*, 2013, *3(6)*, 849-868.

[10] Gakunju, D.; Mberu, E.; Dossaji, S.; Gray, A.; Waigh, R.; Waterman, P.; Watkins, W. Antimicrob. *Agents Chemother*, 1995, *39(12)*, 2606-2609.

[11] Newton, S. M.; Lau, C.; Gurcha, S. S.; Besra, G. S.; Wright, C. W. J. *Ethnopharmacol*, 2002, *79*, 57-67.

[12] Miao, F.; Yang, X.-J.; Zhou, L.; Hu, H.-J.; Zheng, F.; Ding, X.-D.; Sun, D.-M.; Zhou, C.-D.; Sun, W. *Natural Product research*, 2011, *25(9)*, 863-875.

[13] Nair, J.; van Staden, J. *Food and chemical toxicology*, 2013, *62*, 262–275.

[14] Lamoral-Theys, D.; Andolfi, A.; Van Goietsenoven, G.; Cimmino, A.; Le Calvé, B .; Wauthoz, N.; Mégalizzi, V.; Gras, T.; Bruyère, C.; Dubois, J.; Mathieu, V.; Kornienko, A.; Kiss, R.; Evidente, A. *Journal of Medicinal Chemistry*. 2009, *52*, 6244-6256.

[15] Lenfeld, J.; Kroutil, M.; Marsalek, E.; Slavik, J.; Preininger, V.; Simanek, V. *Planta Medica* 1981, *43*, 161-165.

[16] Dvorak, Z.; Kuban, V.; Klejdus, B.; Hlavac, J.; Vicar, J.; Ulrichova, J.; Simanek, V., *Heterocycles*, 2006, *68*, 2403-2422.

[17] Stevenson, P.; Sones, K. R.; Gicheru, M. M.; Mwangi, E. K., *Acta Tropica*, 1995, *59(2)*, 77-84.

[18] Bentivoglio, M. *Journal of the Neurological Sciences*, 2015, *357*, E465-E466.

[19] (WHO) Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2020; World Health Organization (WHO): 2020.

[20] Budin, G.; Chung, H. J.; Lee, H.; Weissleder, R. *Angewandte Chemie (International Ed.)*, 1012, *51*(31), 7752-7755.

[21] Cornaglia, G. *Clinical Microbiology and Infection*, 2009, 15(3), 209-211.

[22] Wolfensberger, A.; Kuster, S. P.; Marchesi, M.; Zbinden, R.; Hombach, M. *Antimicrobial Resistance & Infection Control*, 2019, 8(1), 193.

[23] (WHO) Antimicrobial resistance: global report on surveillance 2014; World Health Organization (WHO): 2014.

[24] Andrews, J. M. *Journal of Antimicrobial Chemotherapy*, 2001, *48*, 5-16.

[25] Lambert, R.J.W.; Pearson, J. *Journal of Applied Microbiology*, 2000, 88(5), 784-790.

[26] Kalil, A. C.; Van Schooneveld, T. C.; Fey, P. D.; Rupp, M. E. *The Journal of the American Medical Association*, 2014, 312(15), 1552-1564.

[27] Ko, F. N.; Chen, I. S.; Wu, S. J.; Lee, L. G.; Haung, T. F.; Teng, C. M.; Ko, F. N. *Biochimica et Biophysica Acta*, 1990, *1052*, 360-365.

[28] Bouquet, J.; Rivaud, M.; Chevalley, S.; Deharo, E.; Jullian, V.; Valentin, A. *Malaria Journal*, 2012, *11*, 67.

[29] Naidu, K. M.; Nagesh, H. N.; Singh, M.; Sriram, D.; Yogeeswari, P.; Sekhar, G. C.; Venkata, K. *European Journal of Medicinal Chemistry*, 2015, *92*, 415-426.

[30] Lemke, T. L.; Williams, D. A.; Roche, V. F.; Zito, S. W. Foye's Principles of Medicinal Chemistry; 6th ed.; Lippincott Williams & Wilkins, 2012.

[31] Morgan, G. T.; Walls, L. P. (1931). *Journal of the Chemical Society*, 1931, 2447-2456.

[32] Pictet, A.; Hubert, A. *Berichte der deutschen chemischen Gesellschaft.* 1896, *29*, 1182-1189.

[33] Some, S.; Ray, J. K.; Banwell, M. G.; Jones, M.; *Tetrahedron*, 2007, *48*, 3609-3612.

[34] Deb, I.; Yoshikai, N. *Organic Letters*, 2013, 15(16), 4254-4257.

[35] Linsenmeier, A. M.; Williams, C. M.; Bräse, S. *Journal of Organic Chemistry*, 2011, 76(21), 9127-9132.

[36] Dhara, S.; Ghosh, M.; Ray, J. K. *Synlett*, 2013, *24(17)*, 2263-2265.

[37] Arcus, C.; Mesley, R. *Journal of the Chemical Society*, 1953, 178-181.

[38] Galt, R. H. B.; Loudon, J. D. (1959). *Journal of the Chemical Society*, 1959, 885-889.

[39] Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Letters*, 1979, *20*, 3437.

[40] Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron*, 2002, *58*, 9633-9695.

[41] Molander, G. A.; Canturk, B. *Angewandte Chemie (International Edition)*, 2009, *48*, 9240-9261.

[42] Astruc, D. *Analytical and Bioanalytical Chemistry*, 2011, *399*, 1811-1814.

[43] Benderdour, M.; Bui-Van, T.; Dicko, A.; Belleville, F. *Journal of Trace Elements in Medicine and Biology*, 1998, *12*, 2-7.

[44] Weir, R.; Fisher, R. *Toxicology and Applied Pharmacology*, 1972, *23*, 351-364.

[45] Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *Journal of the American Chemical Society*, 1985, *107*, 972-980.

[46] Miyaura, N.; Suzuki, A. *Chemical Reviews*, 1995, *95*, 2457-2483.

[47] Hartwig, F. J. *Organotransition Metal Chemistry: From Bonding to Catalysis; 1st ed.; University Science Books*, Mill Valley, California, 2010.

[48] Gurjral, S. S.; Khatri, S.; Riyal, P.; Gahlot, V. *Indo Global Journal of Pharmaceutical Sciences*, 2012, *2(4)*, 351-367.

[49] Molander, G. A.; Biolatto, B. *The Journal of Organic Chemistry*, 2003, *68*, 4302-4314.

[50] Diels, O; Alder, K. *Liebigs Annalen der Chemie,*1928, *460*, 98-122.

[51] Duret, G.; Le Fouler, V.; Bisseret, P.; Bizet, V.; Blanchard, N. *European Journal of Organic Chemistry,* 2017, *46*, 6816-6830.

[52] Fox, M. A.; Whiteseell, J. K. *Organic Chemistry,* Jones and Bartlett, 1994.

[53] Bruice, P. Y. *Organic Chemistry,* Pearson, 7th edition, 2014.

[54] Nawrat, C. C.; Moody, C. J. *Angewandte Chemie (International Ed.),* 2014, *53(8)*, 2056-2077.

[55] Anslyn E. V.; Dougherty D. A. *Modern Physical Organic Chemistry*, University Science Books, 2006.

[56] Dolata, D. P.; Harwood, L. M. *Journal of the American Chemical Society*, 1992, *114*, 10738-10746.

[57] Joule, J.; Mills, K. *Heterocyclic Chemistry*, Blackwell, 5th edition, 2010.

[58] Reinhoudt, D. N.; Trompenaars, W. P.; Geevers, J. *Tetrahedron Letters,* 1976, *17(51),* 4777-4780.

[59] Loudon, M. *Organic Chemistry*, Borgasorus Books, 2009.

[60] Dauben, W. G.; Krabbenhoft, H. O. *Journal of the American Chemical Society*, 1976, *98(7),* 1992-1993.

[61] Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron,* 1997, *53(42),* 14179-14233.

[62] Ganem, B. *Angewandte Chemie (International Ed.),* 1996, *35(9)*, 936-945.

[63] Berski, S.; Durlak, P. *New Journal of Chemistry,* 2016, *4(1)*, 8717-8726.

[64] Braun, M.; Meletis, P.; Schrader, W. *European Journal of Organic Chemistry, 2010(28),* 5369-5372.

[65] Hansen, H. -J.; Scmid, H. *Tetrahedron 1974, 30*, 1959-1969.

[66] White, W. N.; Slater, C. D. *Journal of Organic Chemistry,* 1961, *26(10)*, 3631-3638.

[67] Gozzo, F. C.; Fernandes, S. A.; Rodrigues, D. C.; Eberlin, M. N.; Marsaioli, A. J. *Journal of Organic Chemistry,* 2003, *68(14),* 5493-5499.

[68] Conroy, H.; Firestone, R. A. *Journal of the American Chemical Society*, 1953, *75(10)*, 2530-2531.

[69] Claisen, L.; Eisleb, O. *Justus Liebig's Annalen Der Chemie*, 1913, 401(1), 21-119.

[70] Grewal, A. S.; Kumar, K.; Redhu, S.; Bhardwaj, S. *International Research Journal of Pharmaceutical and Applied Sciences*, 2013, *3(5)*, 278-285.

[71] Perreux, L.; Loupy, A. *Tetrahedron*, 2001, *57*, 9199-9223.

[72] Jha, M.; Guy, S.; Chou, T.-Y. *Tetrahedron Letters*, 2011, *52*, 4337-4341.

[73] Mihovilovic, M. D.; Leisch, H. G.; Mereiter, K. *Tetrahedron Letters*, 2004, *45*, 7087-7090.

[74] Kiyoi, T.; Reid, M.; Francis, S.; Davies, K.; Laats, S.; McArthur, D.; Easson, A.-M.; Kiyoi, Y.; Tarver, G.; Caulfield, W.; Gibson, K.; Wishart, G.; Morrison, A. J.; Adam, J. M.; Ray, P. *Tetrahedron Letters*, 2011, *52*, 3413-3416.

[75] Koyama, E.; Ito, N.; Sugiyama, J.; Barham, J. P.; Norikane, Y.; Azumi, R.; Ohneda, N; Ohno, Y.; Yoshimura, T; Odajima, H.; Okamoto, T. *Journal of Flow Chemistry*, 2018, *8(3)*, 147-156.

[76] Mehl, F.; Bombarda, I.; Franklin, C.; Gaydou, E. M. *Synthetic Communications*, 2010, *40(3)*, 462-468.

[77] Horikoshi, S.; Watanabe, T.; Kamata, M.; Suzuki, Y.; Serpone, N. *RSC Advances*, 2015, *5(110)*, 90272-90280.

[78] Read, M.; Brændvang, M.; Miranda, P.; Gundersen, L.-L. *Bioorganic & Medicinal Chemistry*, 2010, 18, 3885-3897.

[79] Read, M. L., Ph.D. thesis. University of Oslo, 2013.

[80] Bjerkmann, M. S. Ms. thesis. University of Oslo, 2019.

[81] Levinn, C. M.; Steiger, A. K.; Pluth, M. D. *ACS Chemical Biology*, 2019, *14(2)*, 170-175.

[82] Boschi, D.; Tron, G. C.; Lazzarato, L.; Chegaev, K.; Cena, C.; Di Stilo, A.; Giorgis, M.; Bertinaria, M.; Fruttero, R.; Gasco, A. Journal of medicinal chemistry. 2006, 49(10), 2886–2897.

[83] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry (5th edition),* Kluwer Academic/Plenum Publisher, 2001.

[84] Schmidt, B.; Riemer, M.; and Schilde, U. *European Journal of Organic Chemistry* 2015, 34, 7602-611.

[85] Clayden, J.;Greeves, N; Warren, S; Wothers, P. *Organic Chemistry,* Oxford University Press, 2001.

[86] Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications (2nd edition)*, Wiley-VCH, 2003.

[87] Whangbo, M. H.; Stewart, K. R. *Journal of Organic Chemistry,* 1982, *47(4),* 736-38.

[88] Leadbeater, N.E. *Microwave Chemistry as a Tool of Sustainable Chemistry*. CRC Press, 2010.

[89] Kappe, C.O.; Stadler, A.; Dallinger, D. *Microwaves in Organic and Medicinal Chemistry*. WileyVCH-Verlag, 2012.

[90] Bacher, A. *Microwave Chemistry in Organic Synthesis.* UCLA, 2016.