NTNU – Trondheim
Norwegian University of
Science and Technology

Regioselective Preparation of 1,2,3-Triazoles for Bioactive Studies Based on Marine Bioprospecting

Ole Kudsk Hansen

Chemical Engineering and Biotechnology
Submission date: June 2015
Supervisor: Odd Reidar Gautun, IKJ
Co-supervisor: Thomas Aleksander Bakka, IKJ

Norwegian University of Science and Technology
Department of Chemistry

Honour Pledge

I hereby declare that the work presented in this thesis has been conducted independently and in full accordance with the rules and regulations for the integrated Mas- ter's degree in Chemical Engineering and Biotechnology at the Norwegian University of Science and Technology.

Ole Kudsk Hansen

Preface

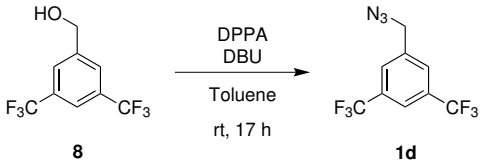
This Master's Thesis, titled "Regioselective Preparation of 1,2,3-Triazoles for Bioactive Studies Based on Marine Bioprospecting" is carried out in cooperation with my supervisor, Associate Professor Odd Reidar Gautun and co-supervisor, PhD Candidate Thomas Alexander Bakka, as the final part of the study program Chemical Engineering and Biotechnology at NTNU. The project is continuation and development of a project I carried out in the fall semester in 2014, also for Associate Professor Odd Reidar Gautun. It is a part of an overall project titled "Biology-Driven Synthesis – from Marine Natural Products to Commercial Leads" which is a collaborative effort from the Norwegian universities in Tromsø, Bergen, Stavanger and Trondheim, together the biodiscovery center MabCent.

I would like to thank my supervisor for support and guidance during the project and also PhD Candidate Thomas Bakka for focusing my project and providing tips and tricks and great tunes in the lab. I would also like to thank Susana Villa Gonzalez for providing MS analyses. Finally I have to thank family and friends for support and back-up during my years at NTNU and also a special thanks to LA1K and JBS for providing me with social input between long sessions in the lab.

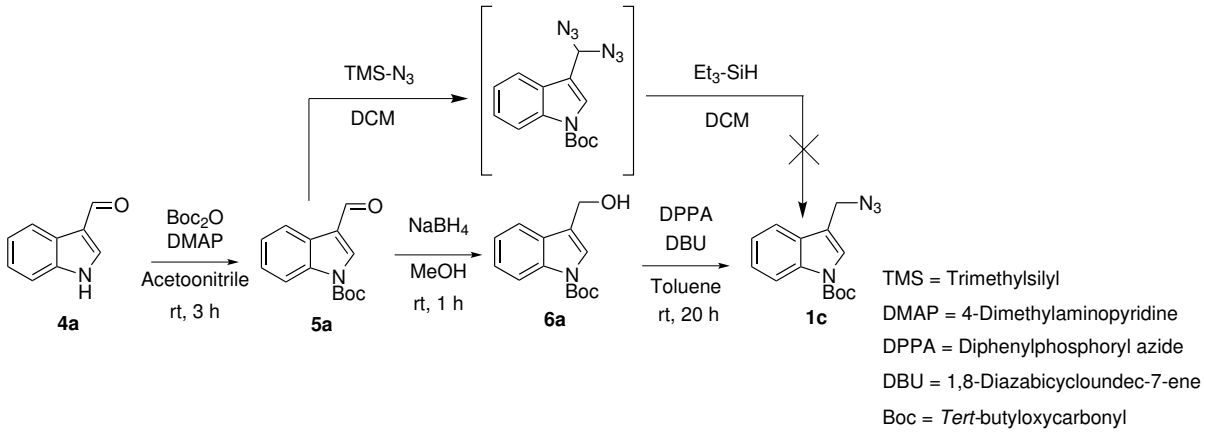
Ole Kudsk Hansen

1 Sammendrag

Azidene **1d** og **1c** ble fremstilt ved å følge litteraturprosedyrer. Azidene blir brukt som startmaterialer i kobber- og ruthenium-katalyserte 1,3-dipolare sykloaddisjoner med de N-beskyttede alkynene **2a** og **2b** for å lage henholdsvis 1,4-disubstituerte *1H*-1,2,3-triazoler og 1,5-disubstituerte *1H*-1,2,3-triazoler. En nylig publisert fremgangsmåte for å fremstille **1c** i ett steg fra aldehydet **5a** ble testet, men reaksjonen ga ikke noe azidprodukt. Azidet **1c** ble syntetisert i en mer tradisjonell fremgangsgmåte, via alkoholet **6a** (Scheme **??**)

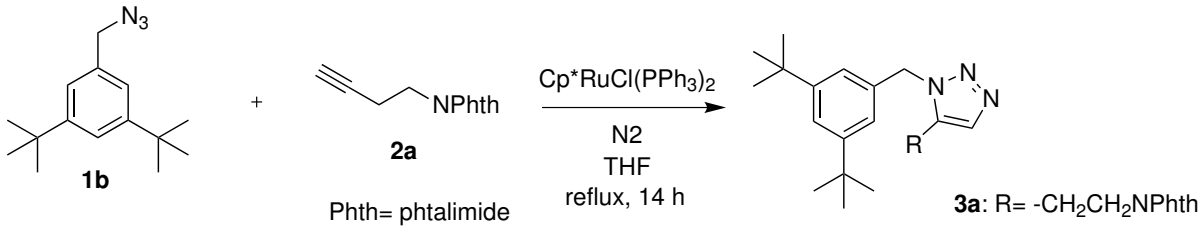


Scheme 1.1: Syntese of azid **1d**

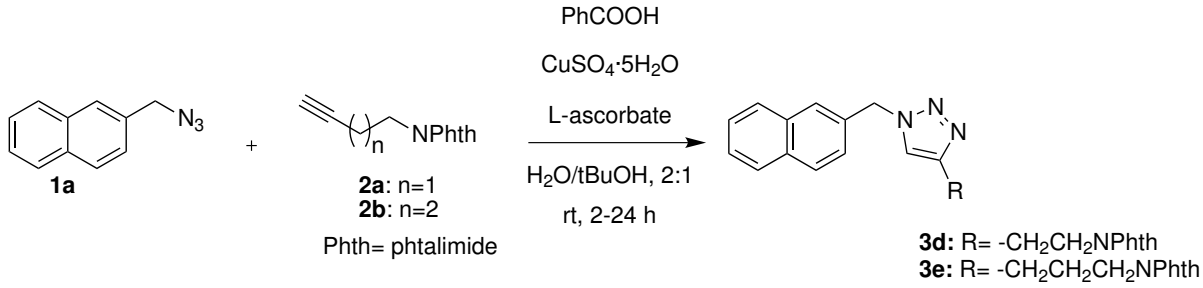


Scheme 1.2: Synteseveier for fremstilling av azid **1c**. Den øverste fremgangsmåten ga ikke ønsket produkt.

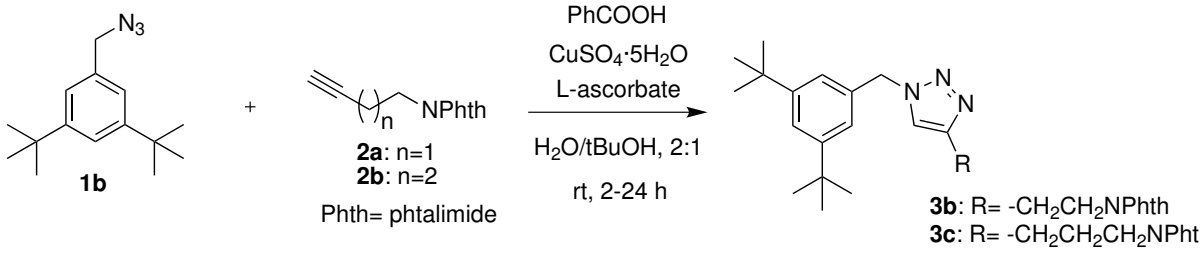
Den nye 1,5-disubstituerte *1H*-1,2,3-triazolen **3a** ble syntetisert fra azidet **1b** og N-beskyttet alkyn (**2a**) i en ruthenium-katalysert 1,3-dipolar sykloaddisjon basert på en litteraturprosedyre. Etter kromatografisk opprensning **3a** ble **3a** oppnådd i et ytbytte på 47%.



Scheme 1.3: Ruthenium-katalysert syntese av den 1,5-disubstituerte *1H*-1,2,3-triazolen **3a**



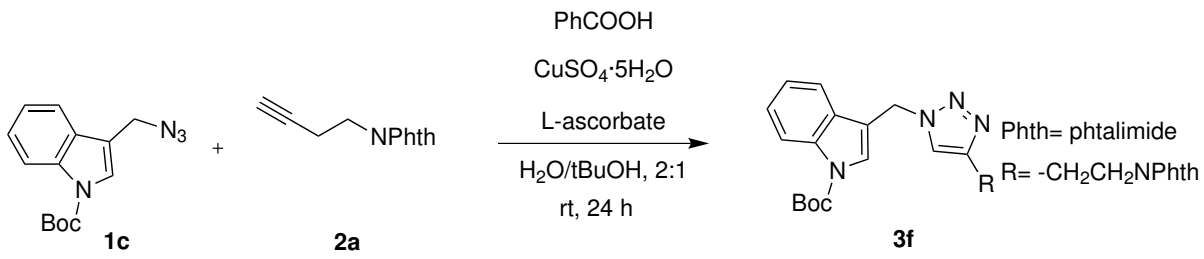
Scheme 1.4: Kobber-katalysert syntese av de 1,4-disubstituerte *1H*-1,2,3-triazolene **3d** og **3e**



Scheme 1.5: Kobber-katalysert syntese av de 1,4-disubstituerte *1H*-1,2,3-triazolene **3b** og **3c**

De nye 1,4-disubstituerte *1H*-1,2,3-triazolene **3b**–**f** ble fremstilt i kobber-katalyserte 1,3-dipolare sykloaddisjoner mellom azidene **1a**, **1b**, **1c** og de N-beskyttede alkynene **2a** og **2b**.

Produkt **3b** ble fremstilt med et utbytte på 52% ulike opprensningsmetoder (kromatografisk opprensning og utfelling av produkt). Produkt **3c** ble fremstilt med et råutbytte på 75%. Produkt **3d** ble fremstilt med et råutbytte på 75%. Produkt **3e** ble fremstilt med et råutbytte på 75%. Produkt **3f** ble fremstilt med et råutbytte på 75%.

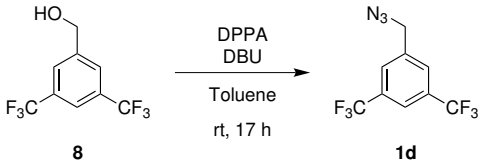


Scheme 1.6: Kobber-katalysert syntese av den 1,4-disubstituerte *1H*-1,2,3-triazolen **3f**

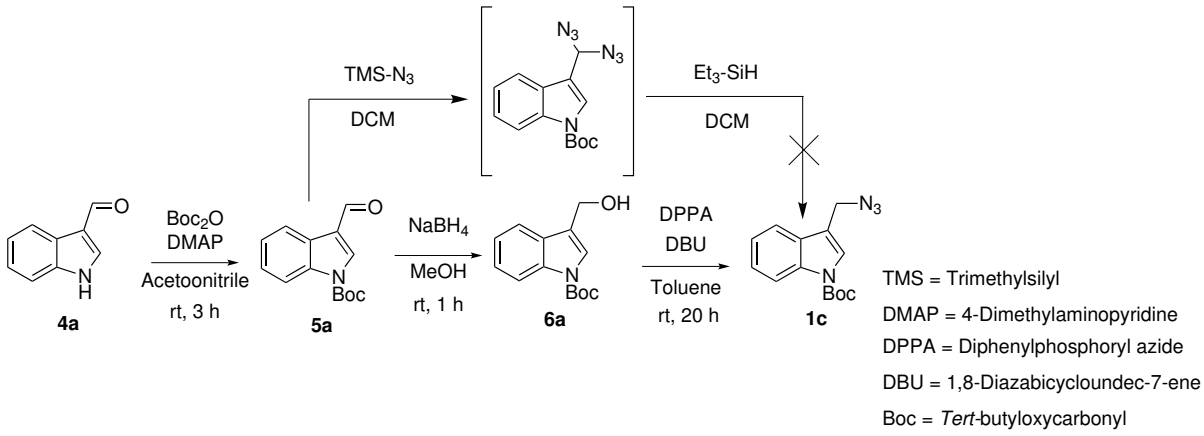
Den N-beskyttede triazolen **3b** ble avbeskyttet til det respektive aminet **7b** ved hydrazinolyse. Opparbeidelsen var utfordrende og førte til betydelige tap av produkt.

2 Abstract

The azides **1d** and **1c** were prepared using literature procedures. The azides serve as starting materials in copper- and ruthenium-catalyzed 1,3-dipolar dipolar cycloadditions to N-protected alkynes **2a** and **2b**, to afford 1,4-disubstituted *1H*-1,2,3-triazoles and 1,5-disubstituted *1H*-1,2,3-triazoles, respectively. A recently published procedure for preparing **1c** in one step from the aldehyde **5a** was tested, but no product was obtained. The azide was synthesized by a more traditional approach, via the alchohol **6a** (Scheme 2.2).

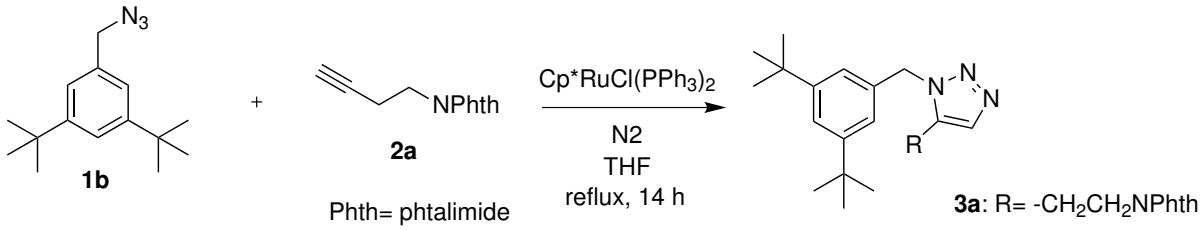


Scheme 2.1: Synthesis of azide **1d**

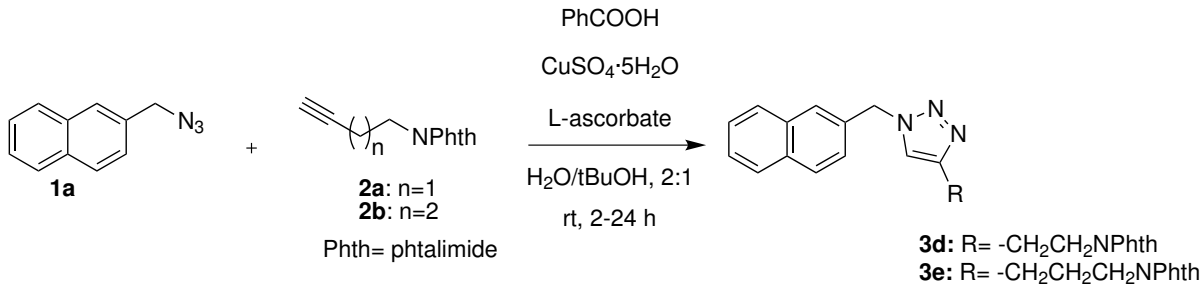


Scheme 2.2: Pathways for preparation of azide **1c**. The upper, one-pot procedure did not produce the desired product.

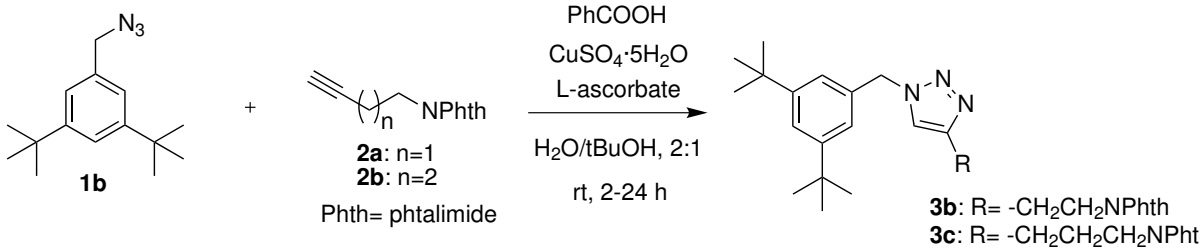
The novel 1,5-disubstituted *1H*-1,2,3-triazole **3a** was synthesized from azide **1b** and N-protected alkyne **2a** in a ruthenium-catalyzed 1,3-dipolar cycloaddition based on a literature procedure. **3a** was obtained in a yield of 47%, after chromatographic purification.



Scheme 2.3: Ruthenium-catalysed synthesis of the 1,5-disubstituted *1H*-1,2,3-triazole **3a**



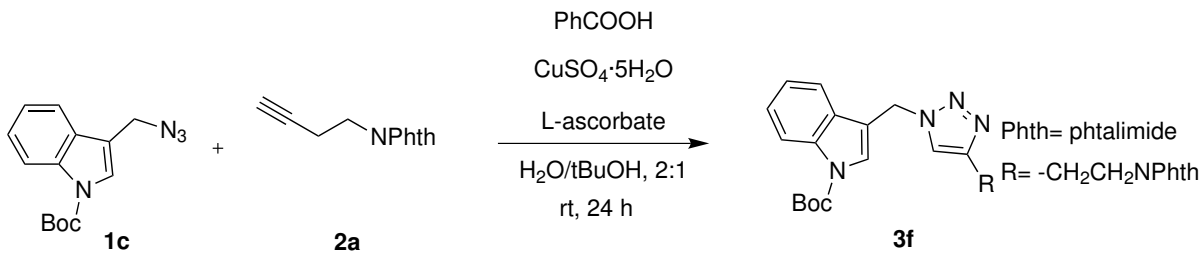
Scheme 2.4: Copper-catalysed synthesis of 1,4-disubstituted *1H*-1,2,3-triazoles **3d** and **3e**



Scheme 2.5: Copper-catalysed synthesis of 1,4-disubstituted *1H*-1,2,3-triazoles **3b** and **3c**

The novel 1,4-disubstituted *1H*-1,2,3-triazoles **3b**–**f** were prepared in copper-catalyzed 1,3-dipolar cycloaddtions between azides **1a**, **1b**, **1c** and the N-protected alkynes **2a** and **2b**.

Product **3b** was obtained in a yield of 52% after trying different purification methods (chromatographic purification and precipitation of product). Product **3c** was obtained in a crude yield of 75%. Product **3d** was obtained in a crude yield of 88%. Product **3e** was obtained in a crude yield of 49%. Product **3f** was obtained in a crude yield of 71%.



Scheme 2.6: Copper-catalysed synthesis of the 1,4-disubstituted *1H*-1,2,3-triazoles **3f**

The N-protected triazole **3b** was deprotected to the corresponding amine **7b** by hydrazinolysis. The product was **7b** was identified using 1D and 2D ^{1}H NMR and ^{13}C NMR experiments. Work-up without significant loss of product proved challenging due to the 2,3-dihydrophthalazine-1,4-dione byproduct.

Contents

3 List of acronyms and abbreviations

AIDS	Acquired Immune Deficiency Syndrome
Ar	Aryl
br.	Broad
COSY	Correlation Spestroscopy
Cp*	Pentamethylcyclopentadienyl
Cq	Quarternary carbon
d	Doublet
DBU	1,8-Diazobicycloundec-7ene
dd	Doublet of doublets
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
DPPA	Diphenyl phosphoryl azide
Eq.	Equivalents
h	Hours
HMBC	Heteronuclar Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Coherence
J	Coupling constant in NMR
Litt.	Litterature
MS	Mass Spectroscopy
M	Multiplisity

NMR	Nuclear Magnetic Resonnans
Phth	Phtalimide
ppm	Parts per million
quint	Quintet
RF	Retention Factor in chromatography
rt	Room temperature
s	Singlet
Substr.	Substrate
t	Triplet
td	Triplet of doublets
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
red.	Reducing

Part I

Introduction

Pathogenic resistance to conventional antibiotics is a growing concern worldwide.[1][2] It affects a broad range of human infection diseases including tuberculosis, cholera, malaria and AIDS. A number of human pathogens are developing multidrug resistance to conventional antibiotics, including common strains of Gram-negative bacteria such as *Escherichia coli*. Introduction of new derivatives of conventional antibiotics is only a temporary solution, as resistance mechanisms quickly develop resistance towards the new derivatives. To combat this threat, new antimicrobial strategies are needed. Examples of novel antimicrobial strategies, are the inhibiton of enzymes responsible for decomposition of antibiotics in antibiotic resistant bacteria, inhibition of biofilm formation.[3]

4 Project scope

4.1 Overall project scope

The project is a part of a project at NTNU, which is part of an overall project aiming to develop novel antimicrobial agents based on marine bioactive compounds.[2] The overall project is titled *Biology-Driven Synthesis – from Marine Natural Products to Commercial Leads* and is a multi-diciplinary collaboration of scientists from the Norwegian universities in Tromsø, Bergen, Stavanger and Trondheim (UoT, UoB, UoS and NTNU) together with the biodiscovery centre at UoT (MabCent[4]) - a Centre of Research Based Innovation (SF) on "Marine Bioactives and Drug Discovery" and the associated industrial partners. **The main objective of the overall project is to develop bioactive natural compounds, isolated and charaterized by MabCent, into synthetic lead compounds attractive for the pharmaceutical and biotechnological industry.**

The project at NTNU is led by Associate Professor Odd Reidar Gautun and PhD Canditate Thomas Alexander Bakka. **The main focus of the project at NTNU is develop synthetic pathways for new antimicrobial agents based to meet a growing demand for such compounds.**[2]

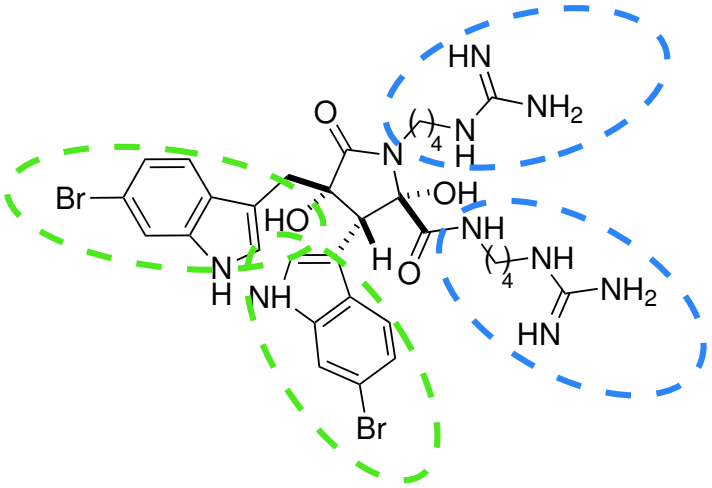


Figure 1: Eusynstelamides. Indole ligands are circled in green and alkylguanidine ligands are circled in blue.

MabCent has isolated a number of novel natural bioactive compounds. Out of these structures, the eusynstelamides (Figure 1) have been chosen as a main focus of the project group at NTNU. Due to the complex stereochemistry of the eusynstelamides, it has been concluded that the project should be based on a simpler scaffold.[2] 1,2,3-Triazoles have been found to be an attractive candidate for such a scaffold, due to their wide use in medicinal chemistry[5] and the efficient and selective "click" syntheses available for of 1,5-disubstituted- and 1,4-disubstituted *1H*-1,2,3-triazoles[6].[7] Essential ligands in eusynstelamides appear to be an indole and an alkylguanidine group (cf. Figure 1) which fulfill a pharmacophore model which can be described as a short cationic ligand (alkylguanidine) attached to a bulky group (indole).[8] **In the project at NTNU, a library of triazoles with bulky ligands like indole and charged ligands like alkylguanidine will be prepared.**

4.2 Subproject scope

In an earlier project, the aryl methyl azides **1a** and **1b** (Figure 3) were prepared.

The aim of this subproject is to prepare the aryl methyl azides 1c–e and use azides 1a–e in copper-catalyzed 1,3-dipolar cycloaddition with alkynes, to afford N-protected 1,4-disubstituted *1H*-1,2,3-triazoles and ruthenium-catalyzed 1,3-dipolar cycloaddition with alkynes, to afford N-protected 1,5-

disubstituted *1H*-1,2,3-triazoles, shown in Schemes 4.1, 4.2 and 4.4. The 1,5-disubstituted *1H*-1,2,3-triazole **3g** (Figure 4.1 was synthesized in an earlier project using a ruthenium catalyst.

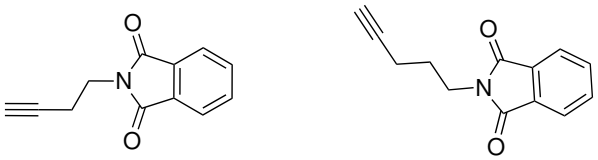


Figure 2: Alkynes.

Starting materials for the azides **1d**, **1c** and **1e** are the corresponding aryl methyl alcohol and aldehydes, respectively. The N-protected alkynes **2a** and **2b** (Figure 2) have been prepared by PhD Candidate Thomas Alexander Bakka. Reliable syntheses of the azides are to be established, based on literature procedures. A library of the triazoles **3a**–**q**, most of which are novel, are to be synthesized based on "click" chemistry procedures by Sharpless et al.[9,10],[6] Tornøe et al.[11] and Rogers and Melander.[7]

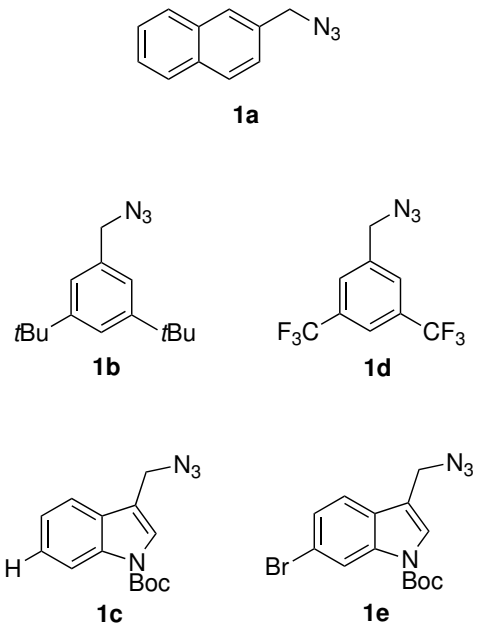
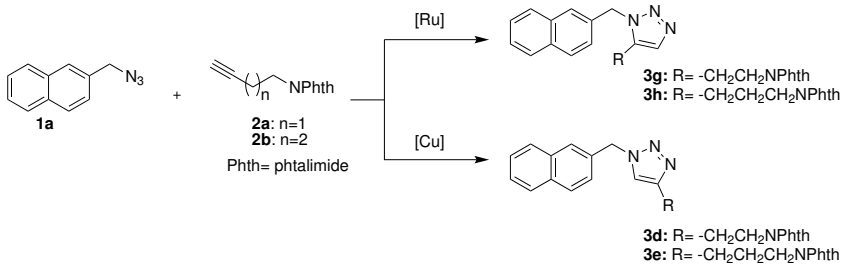
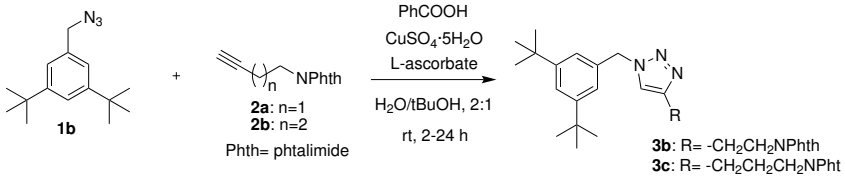


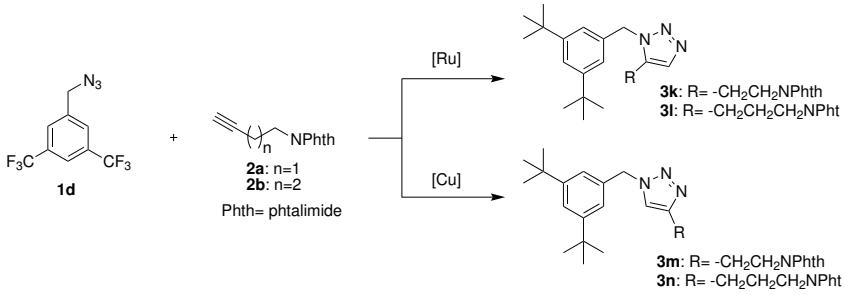
Figure 3: Azides.



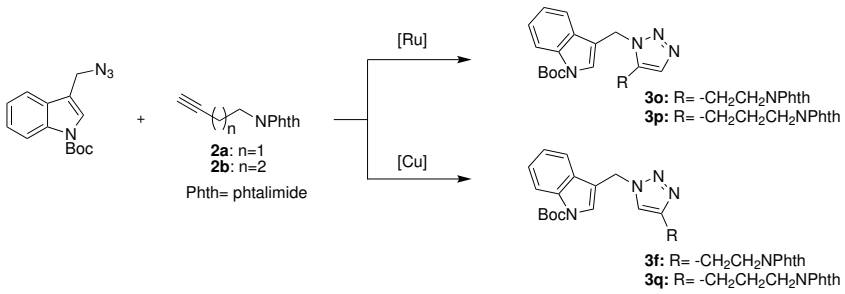
Scheme 4.1



Scheme 4.2



Scheme 4.3



Scheme 4.4

Part II

Theory

5 Traditional antibiotics

Antimicrobial agents are compounds which either kill or inhibit growth of bacteria,[12] respectively bactericidal and bacteristatic agents. Two main groups of antimicrobial agents are used to treat infectious bacterial disease: antibiotics and chemotherapeutic agents. Antibiotics are natural bactericidal or bacteristatic compounds produced by certain microorganisms while chemotherapeutic agents are synthetically made. The most important microbes producing antibiotics are the molds *Penicillium* and *Cephalosporium*, which produce β-lactam antibiotics; Actinomycetes, a group of spore-forming bacteria producing a range of non-β-lactam antibiotics; and certain *Bacillus* species, such as *B. polymyxa* and *B. subtilis* (producing polypeptide antibiotics) and *B. cereus* (producing zwittermicin). The main methods of action of common antibiotics are inhibition of bacterial cell wall synthesis, inhibition of translation, inhibition of nucleic acid synthesis and disruption of cell membrane structure. In addition, some compounds work in conjunction with other antibiotics by inhibiting enzymes which break down the main antibiotic. An example of this is clavulanic acid, which inhibits β-lactamase, an enzyme responsible for breakdown of β-lactam.[13]

6 Antibiotic resistance

With the ever growing use of antibiotics globally has followed a growing misuse in antibiotic treatment of both humans and animals, causing selection and spread of resistance in bacteria against important antibiotic compounds.[1] As a consequence, antibacterial agents are becoming less effective. Common bacterial infections, which have been readily treatable since the discovery of Penicillin, are becoming increasingly difficult to treat as a result of resistance towards important antibiotic classes. Throughout the 20th century, new classes of antibacterial drugs were rapidly discovered in a race against resistant

bacteria. New classes of antibacterial drugs could be used to treat bacteria which were resistant to older classes of antibacterials. However, the last completely new classes of antibacterials were discovered in the 1980s and since then, emergence of multiple drug resistant microorganisms has been a growing concern. To avoid a "post-antibiotic age" it is essential to develop new antibacterial drugs with novel antimicrobial strategies. Such strategies can be developed from a target based approach, with modern biochemical techniques enabling very precise targeting at a molecular level. Examples of such novel targets for inhibition of bacterial metabolism include cell division, fatty acid biosynthesis, biosynthesis of aminoacyl-tRNAs, quorum sensing, bacterial two-component signal transduction, and proton motive force.[14] Alternatively, a reversed-genomics approach can be utilized, in which a promising active antimicrobial compound is developed into a lead structure.[15]

7 Eusynstelamide

The approach in this project is a reversed-genomics one, in the sense that the lead compounds are triazoles designed to mimic the eusynstelamides, which are marine natural compounds known to possess bioactivity.[16] The pharmacophore model of eusynstelamides consists of two cationic amino acid residues and two bulky residues.[8] Hansen et al.[17] have synthesized small cationic peptidomimetics which are highly potent against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), and *Staphylococcus aureus*, confirming the pharmacophore model. As mentioned in section 4.1, the essential ligands in the eusynstelamides are indole and alkylguanidine, where indole provides the bulky, lipophilic characteristic and alkylguanidine provides the charged end of the compound.

8 Triazoles

The triazole ring is an important organic heterocycle, consisting of a five-membered diunsaturated ring structure of three nitrogen atoms and two carbon atoms. The heterocycle occurs in a 1,2,3-isomer and a 1,2,4-isomer, with respect to the location of nitrogen in

the ring.[5] The two isomers of triazole are shown in Scheme 4.

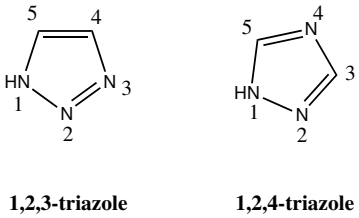


Figure 4: Triazole isomers

As aromatic, electron rich systems, triazole derivatives are able to bind to various enzymes and receptors in biological systems via weak interactions such as hydrogen bonds, coordination bonds, ion-dipole, cation-π, π-π stacking, hydrophobic effect or van der Waals forces, consequently displaying a broad spectrum of biological activities.[18] The triazole ring can also be employed as a linker of other bioactive pharmacophore fragments to produce new drug molecules. These advantages have established triazoles as important pharmacological scaffolds for development of drugs with a broad range of biological activity, many of which are already on the market. Pharmacological activities include antimicrobial, antiviral, anticancer, antifungal, anti-inflammatory, antidepressant, antitubercular, antioxidant, local anaesthetic, antiobesity, antidiabetic, anti-Parkinson's, analgesic, antimalarial, antianxiety, antihistaminic, antiepileptic, antineoplastic, antihypertensive.[5] Examples of commercial triazole drugs are the antifungals fluconazole, voriconazole and itraconazole (Figure 5).

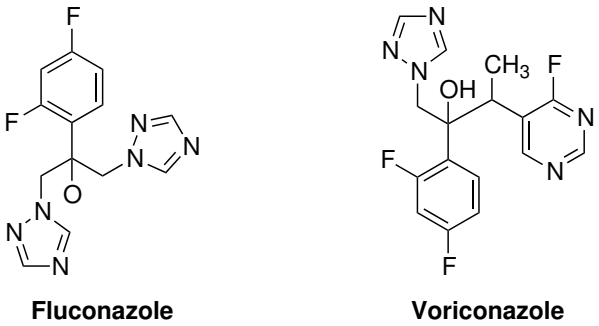
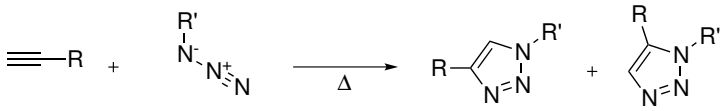


Figure 5: Commercial triazole-based antifungals

Chemically, the triazoles are well suited for medicinal applications because they are stable to acid and base hydrolysis, reductive and oxidative conditions. The structure is also relatively resistant to metabolic degradation.[19]

9 Huisgen cycloaddition

1,3-Dipolar cycloadditions between azides and alkynes or alkenes, to yield disubstituted triazoles, are known as Huisgen dipolar cycloadditons, after the work of Huisgen in the 1960's.[20] These uncatalyzed reactions require substantial heating and long reaction times and give a mixture of 1,4-disubstituted and 1,5-disubstituted triazole products.[10] An example of a Huisgen 1,3-dipolar cycloadditon is shown in Scheme 9.1.



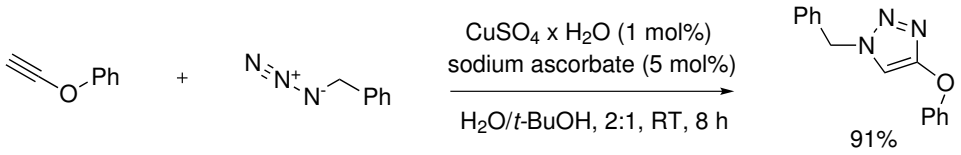
Scheme 9.1: An example of a Huisgen 1,3-dipolar [3+2] cycloadditon.

10 "Click" chemistry

Sharpless et al. published an article on Huisgen cycloadditions and similar reactions in 2001,[9] describing these reactions as "spring loaded". The reactions follow examples in nature, where modular units are joined quickly. The term "click chemistry" was coined[9] because the modules seem to "click" together. A set of criteria for click reactions was written: "The reaction must be modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantio-selective). The required process characteristics include simple reaction conditions (ideally, the process should be insensitive to oxygen and water), readily available starting materials and reagents, the use of no solvent or a solvent that is benign (such as water) or easily removed, and simple product isolation.".[9] The groups of Sharpless et al.[10] and Tornøe et al.[11] reported independently that Huisgen 1,3-dipolar cycloadditions between alkynes and azides could be improved by using Cu(I) salts as catalysts (Scheme 10.1).

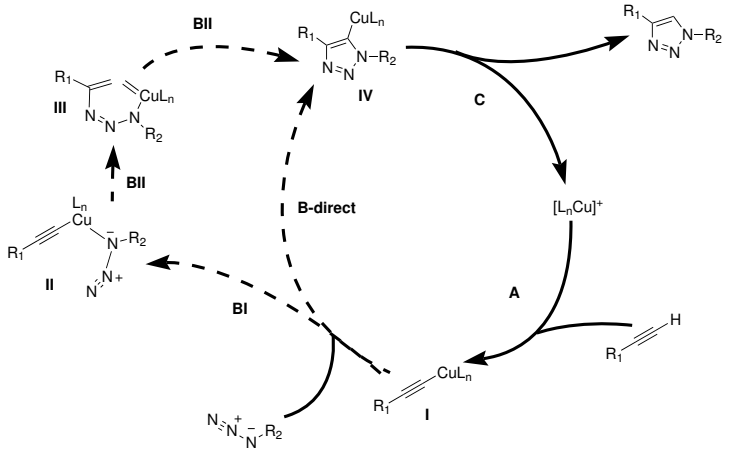
The copper-catalyzed reactions gave regiospecific 1,4-disubstituted 1,2,3-triazoles at much shorter reaction times and at ambient temperatures. Cu(I) salts could be used directly, with acetonitrile as a co-solvent and a nitrogen source, to afford 1,4-disubstituted 1,2,3-triazoles, but these reactions gave undesired byproducts. It was found that a better alternative was the *in situ* generation of Cu(I) from Cu(II) salts and a weak reducing

agent. This reaction was very robust, working with different solvents such at *tert*butyl alcohol, ethanol or water with no effort to exclude oxygen. High yields and purity were reported. Thus, the Cu(I)-catalyzed cycloaddition fulfils the criteria for click chemistry.



Scheme 10.1: Cu(I)-catalysed 1,3 dipolar cycloadditon of a benzyl azide and an alkyne, yielding the 1,4-disubstituted 1,2,3 triazole in good yields. The Cu(I) salt is generated *in situ* from Cu(II).[10]

The catalytic cycle for cupper-catalyzed cycloadditions is proposed to proceed through a stepwise annealing sequence shown in Scheme 10.2 (BI-BII-BII) rather than the concerted cycloaddition (B-direct).

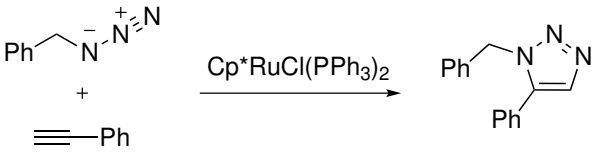


Scheme 10.2: The proposed catalytic cycle for cupper-catayzed cycloadditions. The pathway BI-BII-BIII is thermodynamically favored over the concerted cycloaddtion in pathway B-direct.[10]

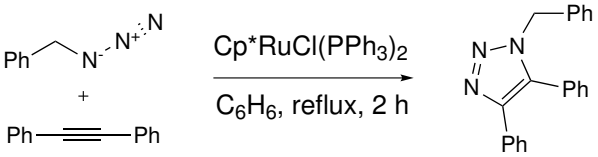
The regioselective formation of 1,5-disubstituted 1,2,3-triazoles from alkynes and azides was accomplished in 2005 using a ruthenium-based catalyst.[6] [Cp*RuCl]-catalysts, such as Cp*RuCl$(PPh_3)_2$, Cp*RuCl(NBD) and Cp*RuCl(COD) were found to be the most effective.

These catalysts gave complete conversion and only the 1,5-regioisomer. Test reactions with benzyl azide and a range of different alkynes revealed that alkyne type did not influence the reaction much, while choice of azides proved more important. Primary aliphatic

azides gave excellent yields, tertiery azides gave low yields and required higher catalyst loading and extended reaction time. Reactions with aryl azides gave poor conversion and unwanted byproducts. Reactions were performed under nitrogen atmosphere in refluxing solvents, typically benzene, toluene or THF. Ru-catalyzed reactions can also form triazoles from internal alkynes. Schemes 10.3 and 10.4 show Ru-catalyzed 1,3-dipolar cycloadditons.

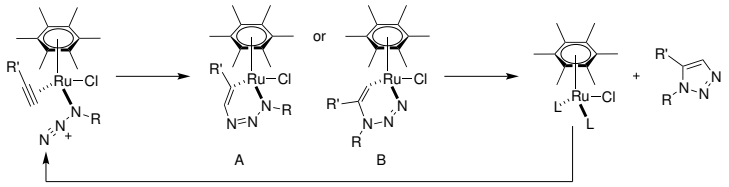


Scheme 10.3: Ru(II)-catalysed 1,3 dipolar cycloadditon of benzyl azide and phenylacetylene yielding the 1,5-disubstituted 1,2,3 triazole[6]



Scheme 10.4: Ru(II)-catalysed 1,3 dipolar cycloadditon of benzyl azide and an internal alkyne yielding the 1,4,5-trisubstituted 1,2,3 triazole[6]

The catalytic cycle for ruthenium-catalyzed cycloadditions is proposed to go through a six-membered ruthenacycle (Scheme 10.5), by oxidative coupling of alkyne and azide on the ruthenium catalyst.[6]



Scheme 10.5: The proposed catalytic cycle for ruthenium-catayzed cycloadditions. Sharpless et al. find the A more likely than the B. The catalyst used here is a [Cp*RuCl]-catalyst.[6]

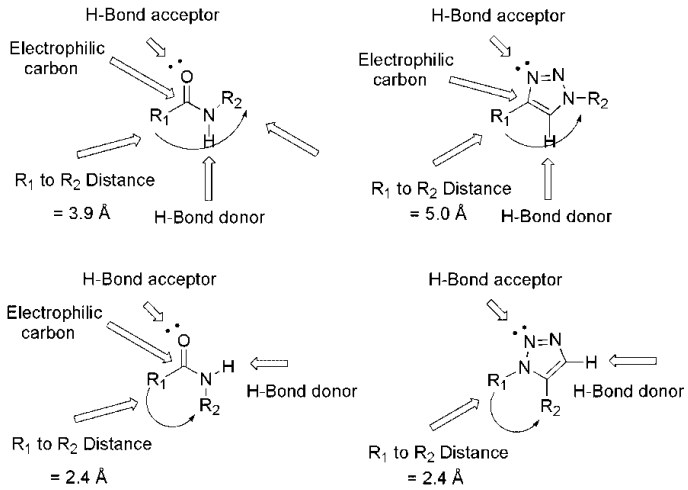
During drug discovery, the goal is often to synthesize a library of similar compounds, typically a common scaffold, with a range of different substituents, in order to identify lead compounds with desired biological function. In this application, click chemistry is

an excellent tool, as it enables the researcher to develop many compounds quickly and efficiently, with high yields, few steps and minimal purification.The discoveries of Cu- and Ru-catalyzed regioselective formation of 1,2,3-triazole have made the triazole moiety an attractive scaffold within medicinal chemistry, as triazoles can be prepared with a great variation of substituents, and the substituent attachment to the ring can be directed with the use of catalysts.

11 Bioisosteres

Bioisosteres are structurally distinct compounds which are recognized as similar structures by biological systems.[21] Bioisosteres offer flexibility when working towards a target compound intended to be bioactive. If the target compound relies on a labile structural element, a bioisostere of the labile element can be found and used to mimic the labile element in the final compound. Classical bioisosteres are structurally simple groups which mimic each other, such as -NH and -OH, D and H, RSH and ROH. Non-classical bioisosteres are structurally distinct. They can have different number of atoms and exhibit different steric and electronic properties to the moiety they mimic.

Triazole containing compounds have shown a wide range of biological activity.[19] As a bioisostere, triazole has been proposed to mimic an amide bond, as presented in Figure 11.1. The 1,4-disubstituted triazole would mimic a *Z*-amide bond, where the lone pair on N(3) acts as the lone pair on carbonyl in the amide, the C(5)H in triazole can act as an H-bond donor like the NH in amide, and the electrophilic C(4) resembles the carbonyl C in amide. Equivalently, the 1,5-disubstituted triazole would mimic an *E*-amide bond.

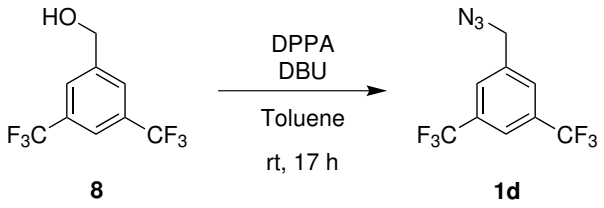


Scheme 11.1: How 1,4- and 1,5-disubstituted triazoles theoretically act as bioisosteres of amides. Figure from Tron *et al.*[19]

Part III

Results and discussion

12 Azidation of 3,5-bis(trifluoromethyl)benzyl alcohol

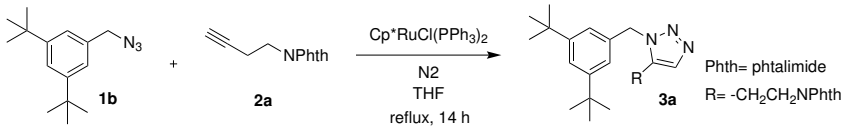


Scheme 12.1

1-(Azidomethyl)-3,5-bis(trifluoromethyl)benzene **(1d)** was obtained from the alcohol **8**, using DPPA for *in situ* generation of azide and DBU as a base, according to procedures by Melander and Rogers,[7] for converting aryl methyl alcohols to aryl methyl azides. The procedure was first described by Thompson et al.[22] The crude yield was 79% but the yield of the pure product **1d** after column purification was very low (6%). Melander and Rogers[7] report yields of 95% after purification, while Thompson et al. report 94% yield.[22] TLC analysis (15% EtOAc in Pentane) of the crude product revealed two spots, one with a low RF (0.6), believed to be unreacted alcohol and one with a higher RF (0.8), believed to be the azide product. In an optimal reaction, the only byproduct formed is the DBU salt of diphenyl phosphate, which is water soluble.[22] The acid wash should remove any excess DBU and leave only the azide product, excess DPPA and unreacted alcohol. The two major components in the crude product are thought to be azide product **1d** and unreacted alcohol. During purification the two components identified by TLC were separated. Due to the large difference in yield between the crude product and the purified azide product, it could be suspected that conversion was low in the reaction and a large amount of unreacted alcohol was present in the crude product. However, the combined fractions of byproducts from the column yielded the same low amount as the main product **1d**. This indicates that a large amount of substance was lost on the

column. An optimization of eluent could improve yields.

13 2-(2-(1-(3,5-Di-tert-butylbenzyl)-1H-1,2,3-triazol-5-yl)ethyl)isoindoline-1,3-dione (3a)

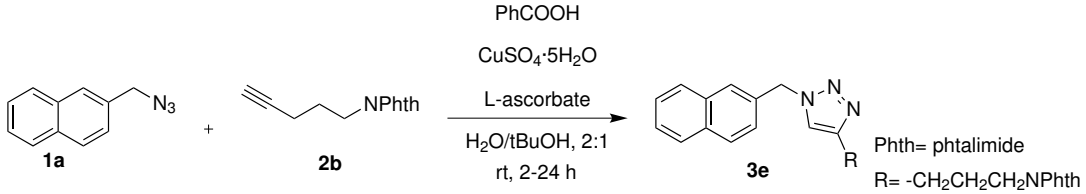


Scheme 13.1

1,5-1*H*-1,2,3-triazoles have been prepared by the author in an earlier project, based on procedures by Sharpess et al.[6] and Farooq.[23] The 1,3-dipolar cycloaddition between **1b** and **2a** gave 0.114g of 1,5-1*H*-1,2,3-triazole **3a** after chromatographic purification, which is a yield of 49%. The product **3a** was identified by 1D ^{1}H NMR and ^{13}C NMR, 2D NMR (COSY, HMBC, HSQC) and MS (Appendix A). The assigned shifts can be found in Table 1.

The yield is lower than expected from a click reaction, which is characterized by high yields. The product **3a** eluted out in the last fractions from the column and thus, it is possible that the product did not elute completely. A gradient elution might have improved yields.

14 2-(3-(1-(Naphthalen-2-ylmethyl)-1H-1,2,3-triazol-4-yl)propyl)isoindoline-1,3-dione (3e)

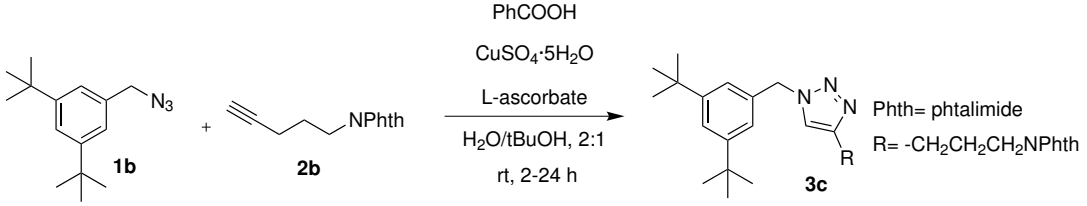


Scheme 14.1

a) The cupper-catalyzed 1,3-dipolar cycloaddition of **1a** and **2b** resulted in 0.376 g of 1,4-disubstituted 1*H*-1,2,3-triazole **3e**, which is a yield of 49%. The low yield is mostly caused by loss of product when the reaction vessel tipped over during stirring overnight. The triazol **3e** was identified by comparing the ^{1}H NMR spectrum to previously recorded spectra of similar triazols in the project group. Based on the ^{1}H NMR spectrum (Appendix **??**), the product was deemed sufficiently pure without further purification. An important distinction between the cupper-catalyzed 1,4-disubstituted 1*H*-1,2,3-triazole reaction and the ruthenium-catalyzed 1,5-disubstituted 1*H*-1,2,3-triazole reaction is that the cupper-catalyzed products often can be used without further purification than simple aqueous work-up, while for the ruthenium-catalyzed reactions, the ruthenium catalyst must be removed by chromatographic purification.

b) The reaction was repeated to afford 0.317 g of **3e**, in an excellent yield of 95%. The reaction mixture was diluted to a concentration of 0.18 M of aryl methyl azide, compared to the first (a) parallel, which had a concentration of 0.78 M of aryl methyl azide. In the first parallel, it was observed that a semi-solid precipitate formed after stirring overnight, while in the more dilute parallel b, this precipitate remained suspended. Suspension of solids via dilution and vigorous stirring is believed to be important to drive the reaction to completion. The high yield (95%) of **3e** supports this thesis.

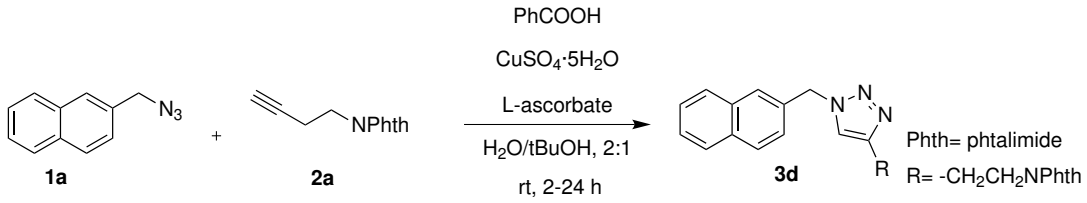
15 2-(3-(1-(3,5-Di-tert-butylbenzyl) -1H-1,2,3-triazol-4-yl)propyl)isoindoline-1,3-dione (3c)



Scheme 15.1

1,3-Cycloaddition of **1b** to **2b** afforded 0.552 g of 1,4-1*H*-1,2,3-triazole **3c** in a yield of 75%. A small volume of the solvent was used, giving a concentration of 0.7 M of **1b** in the reaction mixture. Dilution of the reaction mixture might have resulted in a higher yield. The product was obtained as a thick oil and did not solidify even after evaporating on high vacuum overnight. Residual solvents are probably responsible for the product not solidifying, considering the other similar triazoles prepared were solid at room temperature.

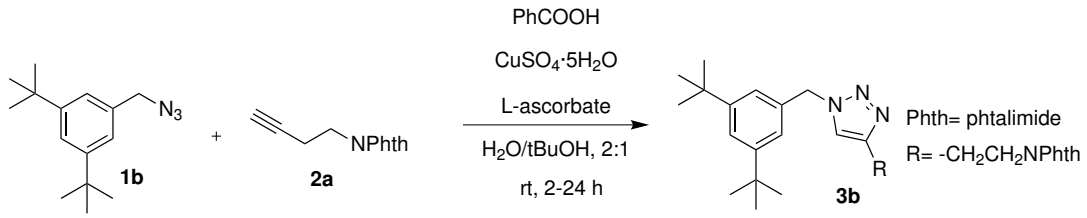
16 2-(2-(1-(Naphthalen-2-ylmethyl) -1H-1,2,3-triazol-4-yl)ethyl)isoindoline-1,3-dione (3d)



Scheme 16.1

The 1,4-1*H*-1,2,3-triazole **3d** was obtained in a good yield of 88%.

17 2-(2-(1-(3,5-Di-tert-butylbenzyl) -1H-1,2,3-triazol-4-yl)ethyl)isoindoline-1,3-dione (3b)

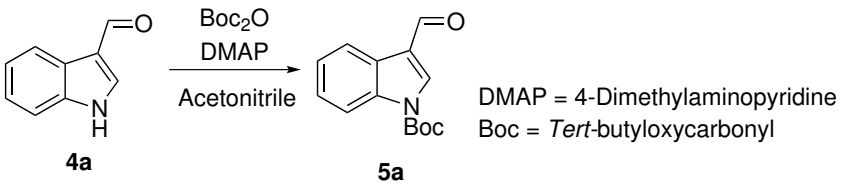


Scheme 17.1

The 1,4-1*H*-1,2,3-triazole **3b** was prepared in a yield of 52%, after purification. The crude product was attempted purified first by dissolving in DCM and then adding pentane, to

induce precipitation of **3b**, according to a genera method developed by PhD Candidate Thomas Alexander Bakka. A white precipitate was formed and filtered off on filter paper. ^{1}H NMR of the solid show that the precipitate did consist of pure **3b**, as expected, but due to the precipitate being very fine, a substantial amount of **3b** passed through the paper filter. A new attempt of filtering was attempted, using celite as a filter. This yielded some product, also pure **3f**, but some **3b** still passed through the celite. Lastly, a silica column was used to separate the remaining **3b** from the contaminants. A considerable amount of **3b** was obtained from the column. The precipitation and filtering purification method was tested in an attempt to simplify purification and avoid the loss in yield often associated with column chromatography. The method proved viable for obtaining a pure product, but the loss of product in the filtrate was large. Other methods of filtering, such as using Dowex as a filter medium, might improve yields.

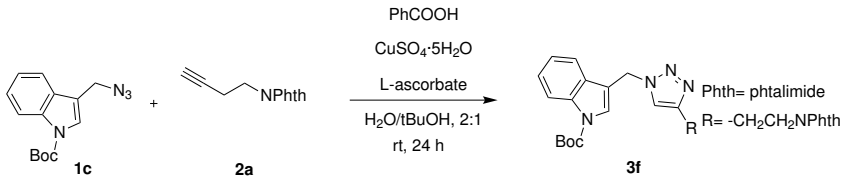
18 Tert-butyl 3-formyl-1H-indole-1-carboxylate (5a)



Scheme 18.1

Indole carboxaldehyde **(4a)** was N-protected with boc anhydride to form **5a**. The procedure for Boc-protection is well described in literature and a procedure for protection of **4a** has been published by Giraud et al.,[24] amongst others. Excellent yields of 95% and 89% were obtained and, based on TLC and ^{1}H NMR spectra, the products were deemed sufficiently clean without further purification.

19 Tert-butyl 3-((4-(3-(1,3-dioxoisoindolin-2-yl)propyl) -1H-1,2,3-triazol-1-yl)methyl)-1H-indole-1-carboxylate (3f)



Scheme 19.1

A crude product of the 1,4-1*H*-1,2,3-triazole **3f** was obtained in a yield of 71%. The ^{1}H NMR and ^{13}C NMRspectra of the product revealed that the reaction had not gone to completion and a substantial amount of starting material (alkyne **2a** and azide **1c**) was present in the crude product. Due to time concerns, the product could not be purified before characterization. Based on other triazoles prepared, purification by column chromatography, using a mixture of EtOAc and DCM as the eluent, could be a suitable purification method. Nevertheless, **3f** was identified in the spectra (see Section 31 for a discussion on the NMR spectra). The triazole **3f** was also detected in the HRMS analysis of the crude product.

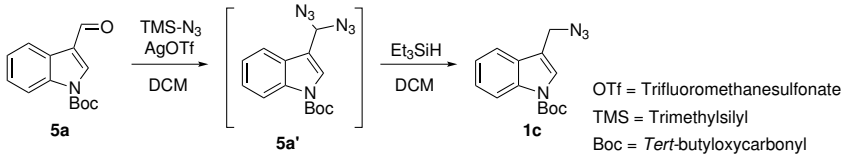
20 Attempted deprotection of N-protected 3a to amine 7a

The N-protected **3a** was attempted deprotected using hydrazinolysis. The residue obtained after 5 h revealed that the residue contained only the protected **3a** and no amine, showing that no reaction had occurred. The procedure developed by PhD Candidate Thomas Bakka called for heating the reaction mixture to reflux, a step which was overlooked due to a misunderstanding. The lack of heating is believed to be the reason no deprotection was observed. A brief discussion of the ^{1}H NMR spectrum of the residue is given in Section **??**.

21 Preparation of 2-(1-(3,5-di-tert-butylbenzyl) -1H-1,2,3-triazol- 4-yl)ethanamine 7b

The N-protected **3b** was deprotected by hydrazinolysis, using the correct procedure with reflux. A fluffy solid was obtained upon evaporation of the solvent. This crude product consists of the unprotected amine **7b** mixed with the main byproduct 2,3-dihydrophthalazine-1,4-dione[25] from the freed phthalimide moiety. This byproduct forms an insoluble slurry in organic solvents of low polarity, such as DCM. Trying to extract the amine from the slurry by filtering causes loss of product. Attempts to purify the crude products on a silica column, using a strong eluent mixture resulted in very low or no yields, as the amine remained in the stationary phase. An alternative method of converting phthalimides to primary amines is the mild procedure developed by Osby et al., using $NaBH_4$/2-propanol followed by treatment with acetic acid.[26] This method yields the lactone phthalide as the byproduct, which should be easily removed by a simple aqueous work-up.

22 Attempted one-pot azidation of Boc-protected indole carboxaldehyde to afford 1c



Scheme 22.1

A procedure by Pramanik and Ghorai[27] was followed in an attempt to prepare the azide **1c** from the corresponding aldehyde **5a**. Two attempts were made without locating the expected product in the obtained residues. In both attempts, only the unreacted aldehyde **5a** was present in the crude product. The diazide intermediate (**5a'** cf. Scheme 22.1) was not found in the spectra, showing that the first azidation step of the reaction did not proceed. The reaction was followed on TLC in the first step to determine when all of the

aldehyde **5a** was consumed to diazide **5a'**, but without a diazide standard this proved difficult. A ^{1}H NMR sample of the reaction mixture at this stage could have helped in determining if diazide **5a'** was present. It is possible that a larger excess of TMS$-N_3$ and a longer reaction time for the first step would generate the desired diazde **5a'**.

23 Tert-butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate (6a)

The procedure for Boc-protection of the amine on **4a** to **5a**, and the subsequent reduction of the aldehyde to the corresponding alcohol **6a**, are well documented procedures and proceeded in excellent yields with no need for further purification before the azidation step. (It can be noted that the author has in an earlier project had several failed attempts to reduce the indole carboboxaldehyde to alcohol due to an unreactive batch of $NaBH_4$, so good reagents are needed.)

24 Tert-butyl 3-(azidomethyl)-1H-indole-1-carboxylate (1c)

The one-pot procedure to afford the azide **1c** was abandoned for a more traditional approach of first reducing the aldehyde **5a** to the corresponding alcohol **6a** before converting the alcohol **6a** to the azide **1c**, using DPPA and DBU. The reaction is well documented in literature and a procedure by Suzuki et al. was followed.[28] Triazol **1c** was obtained in a yield of 53% after purification. The yield is low, but acceptable. Further optimization of the purification step could improve yields.

Part IV

Spectroscopy

Proton and carbon shifts were assigned using 1D ^{1}H NMR and ^{13}C NMRand 2D NMR techniques (COSY, HSQC, HMBC). Some ^{1}H NMR spectra contain solvent peaks from ethyl acetate at $\delta = 1.26$ ppm and 2.05 (in $CDCl_3$), water at $\delta = 1.56$ ppm (in $CDCl_3$), DCM at 5.30 ppm (in $CDCl_3$), chloroform at $\delta = 7.26$ ppm (in $CDCl_3$) and *tert*-butanol at 1.28 ppm (in $CDCl_3$). Shifts of common solvents can be found in an article by Gottlieb et al.[29]

25 Starting materials

The N-protected alkyne **2a** has the following shifts: ^{1}H NMR $\delta = 2.00$ (1H, t, J = 2.7 Hz, CH), 2.62 (2H, td, J = 7.1, 2.7 Hz, 2H), 3.9 (2H, t, J = 7.1 Hz, CH2), 7.68-7.80 (2H, m, CH), 7.80-7.91 (2H, m, CH) ppm ^{13}C NMRδ = 18.2, 36.5, 70.2, 80.2, 123.3 (2C), 131.9 (2C), 133.9 (2C), 167.9 (2C) ppm[30]

The N-protected alkyne **2b** has the following shifts: ^{1}H NMR $\delta = 1.78$ (2H, quint, J = 7.1 Hz, CH2), 1.82 (1H, d, J = 2.6 Hz, CH), 2.12 (2H, td, J = 7.1, 2.6 Hz, CH2), 3.65 (2H, t, J = 7.1 Hz), 7.55-7.60 (2H, m, CH), 7.65-7.70 (2H, m, CH) ppm. ^{13}C NMRδ = 16.2, 27.2, 37.0, 69.0, 83.2, 123.1 (2C), 132.0 (2C), 133.8 (2C), 168.2 (2C) ppm.[30]

26 2-(2-(1-(3,5-Di-tert-butylbenzyl)-1H-1,2,3-triazol-5-yl)ethyl)isoindoline-1,3-dione (3a)

Table 1 shows assigned ^{13}C NMRand ^{1}H NMR shifts of the product **3a**, with splitting patterns and coupling constants, in correspondence to the numbering in Figure 6.

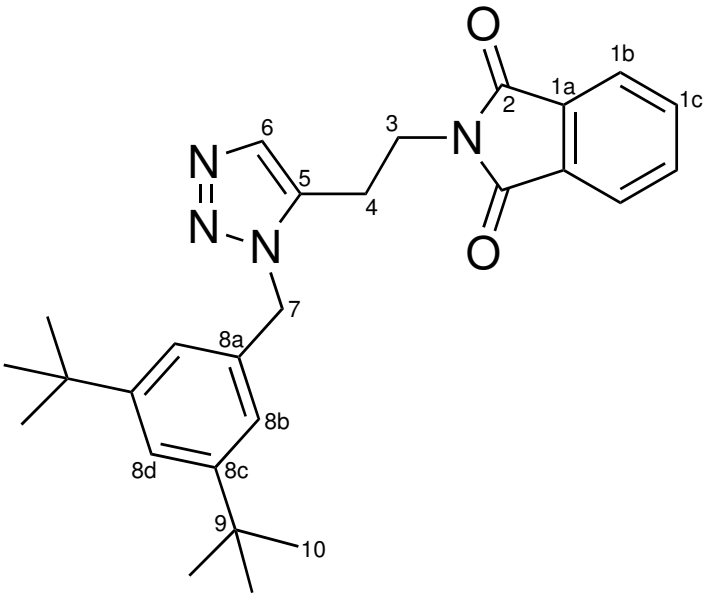


Figure 6

Table 1: Assigned shifts for **3a**

Carbon no.	δ **H [ppm]**	**M**	**J [Hz]**	δ **C [ppm]**
1a	Cq	-	-	131.8
1b	7.83	dd	3.1, 5.3	123.4
1c	7.73	dd	3.1, 5.6	134.2
2	Cq	-	-	167.8
3	3.84	t	7.5	35.9
4	2.96	t	7.5	22.4
5	Cq	-	-	131.1
6	7.56	s	-	52.6
7	5.59	s	-	52.6
8a	Cq	-	-	133.9
8b	7.05	s	-	121.7
8c	Cq	-	-	151.7
8d	7.35	t	1.7	122.3
9	Cq	-	-	34.9
10	1.26	s	-	31.4

The 2H singlet at 5.59 ppm is characteristic of the triazole **3a**, with the corresponding

protons having a lower shift of 4.30 ppm in the azide. In the triazole product, the elecron density is drawn more to the triazole ring, thus deshielding the protons on carbon 7. The emergence of a 1H singlet at 7.56 ppm is a clear indication of triazole product, as this shift can is not found in the alkyne nor the azide. The value and multiplisity of the 7.56 ppm shift is in agreement with expectations for the single proton in the triazole ring. The spectra for **3a** are shown in Appendix A.

27 2-(3-(1-(Naphthalen-2-ylmethyl) -1H-1,2,3-triazol-4-yl) propyl)isoindoline-1,3-dione (3e)

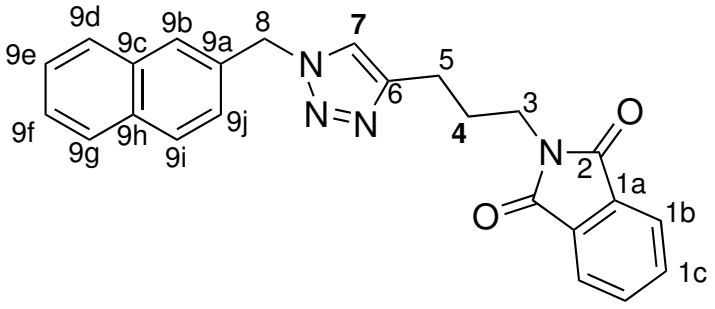


Figure 7

The product **3e** was not purified and the spectra contain contaminants, prominently residual azide **1a**. Certain shift are characteristic of triazole, suggesting that **3e** is present in the product. In the ^{1}H NMR spectrum, the singlet peak at 5.63 (2H) ppm is from the protons on carbon 8 in the triazole **3e**. The shift of the corresponding protons in the azide is 4.50 ppm. The broad singlet at 7.36 ppm is believed to be the proton at carbon 7 in the triazole ring, as this shift is not present in the spectrum of the azide **1a**. The two doublet of doublets at 7.70 and 7.68 ppm are from the protons in the phthalimide group.

In the ^{13}C NMRspectrum an important peak is 23.0 ppm from carbon 5. This is significantly higher than the corresponding shift in the alkyne **2b** of 16.2 ppm,[30] indicating that the triazole **3e** is present in the product. The shifts for carbon 6 could not be

assigned. It is expected to be around 130 ppm, but due to the unpure sample there are several peaks in this region. The non-quarternary naphthalene carbons have very similar shifts in the region 122-128 and the individual shifts were not assigned. Table 2 presents the shifts which were assigned for **3e**.

Table 2: Assigned shifts for **3e**

Carbon no.	δ **H [ppm]**	**M**	**J [Hz]**	δ **C [ppm]**
1a	Cq	-	-	133.8
1b	7.70-7.68	m	-	123.2
1c	7.70-7.68	m	-	133.8
2	Cq	-	-	168.3
3	3.73	t	6.7	37.2
4	2.06	quint	7.8	28.1
5	2.76	t	7.4	23.0
7	7.37-7.32	m	-	121.1
8	5.65	s	-	54.1
9a	Cq	-	-	132.2
9c	Cq	-	-	130.0
9h	Cq	-	-	132.2

The spectra for **3e** are shown in Appendix **??**.

28 2-(2-(1-(3,5-Di-tert-butylbenzyl) -1H-1,2,3-triazol-4-yl)ethyl)isoindoline-1,3-dione (3b)

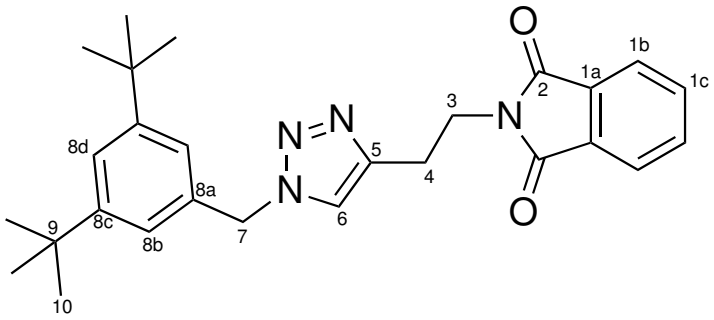


Figure 8

Table 3 shows assigned ^{13}C NMRand ^{1}H NMR shifts of the product **3b**, with splitting patterns and coupling constants, in correspondence to the numbering in Figure 8.

One carbon peak could not be found in the ^{13}C NMRspectrum, while other carbon peaks were very small, due to a dilute sample. Carbon 1a and carbon 5 have very similar shifts, around 130 ppm. In product **3a**, carbon 1a was assigned a shift of 131.8 ppm, while carbon 5 was assigned a shift of 131.1 ppm. By comparing spectra from **3b** with spectra from **3a** it is likely that the 132.1 ppm carbon shift in **3b** belongs to carbon 1a, while carbon 5 is expected to have a shift slightly lower, around 131 ppm. Given that all other shifts are in agreement with expected values and shifts in previously prepared, similar compounds, it is believed that **3b** is identified, but the carbon 5 peak is too weak to see in the spectrum. The HRMS analysis supports this conclusion.

The 2H singlet at 5.46 ppm is characteristic of the protons binding to carbon 7 in the triazole **3b**, significantly higher than the corresponding protons of 4.30 in the azide, as was the case for **3a**. The alkyne has a proton shift at the terminal carbon on the chain of 1.96 ppm. This shift is not present in the ^{1}H NMR spectrum of **3b**, indicating that the alkyne has been completely converted to triazole. The ^{1}H NMR shift at 3.12 ppm in the **3b** spectrum belongs to the carbon 4 protons. The corresponding protons in the alkyne have significantly lower a shift of 2.62 ppm, again indicating that the alkyne has

been converted triazole.

Table 3: Assigned shifts for **3b**

Carbon no.	δ **H [ppm]**	**M**	**J [Hz]**	δ **C [ppm]**
1a	Cq	-	-	132.1
1b	7.81	dd	3.0, 5.5	123.3
1c	7.69	dd	3.0, 5.5	133.8
2	Cq	-	-	167.9
3	3.99	t	7.6	37.5
4	3.12	t	7.3	24.9
5	Cq	-	-	*
6	7.33	s	-	121.1
7	5.46	s	-	54.7
8a	Cq	-	-	133.9
8b	7.09	d	2.0	122.4
8c	Cq	-	-	151.8
8d	7.41	t	2.0	122.7
9	Cq	-	-	34.9
10	1.29	s	-	31.4

*Peak missing. See section 28 for discussion.

The spectra for **3b** are shown in Appendix **??**.

29 2-(3-(1-(3,5-Di-tert-butylbenzyl) -1H-1,2,3-triazol-4-yl)propyl) isoindoline-1,3-dione 3c

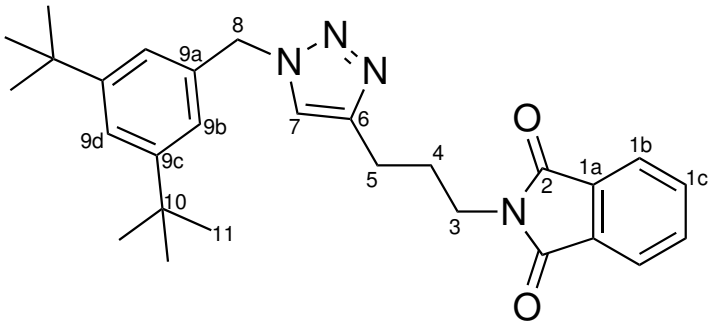


Figure 9

Table 4 shows assigned shifts of **3c**.

The ^{1}H NMR and ^{13}C NMRspectra of **3c** are very similar to the spectra of **3b**, with the difference being that **3c** has an extra carbon peak and a quintet from the protons on carbon 4. The ^{1}H NMR singlet at 5.46 ppm is from the protons on carbon 8 and shows that the triazole **3c** was formed. Another sign of triazole formation is the ^{13}C NMRshift at 23.1 ppm from carbon 5 which is significantly higher than the corresponding shift of 16.2 ppm in the alkyne **2b**.[30] The 121.1 ppm shift of carbon 7 could not be seen in the 1D ^{13}C NMRspectrum but was visible in the 2D HSQC spectrum, coupled to the singlet proton with a shift of 7.36 ppm. The peak of carbon 6 could not be found in any of the spectra, as was the case with **3b**.

Table 4: Assigned shifts for **3c**

Carbon no.	δ **H [ppm]**	**M**	**J [Hz]**	δ **C [ppm]**
1a	Cq	-	-	132.1
1b	7.83	dd	3.0, 5.4	123.2
1c	7.71	dd	3.1, 5.5	133.9
2	Cq	-	-	168.4
3	3.74	t	7.1	37.3
4	2.06	quint	7.3	28.2
5	2.75	t	J = 7.7	23.1
6	Cq	-	-	*
7	7.39	t	1.7	121.1
8	5.46	s	-	54.7
9a	Cq	-	-	134.0
9b	7.09	d	1.9	122.3
9c	Cq	-	-	151.7
9d	7.39	t	1.7	122.7
10	Cq	-	-	34.9
11	1.29	s	-	31.4

*Peak missing. See section 29 for discussion.

The spectra for **3c** are shown in Appendix C.

30 2-(2-(1-(Naphthalen-2-ylmethyl) -1H-1,2,3-triazol-4-yl)ethyl) isoindoline-1,3-dione (3d)

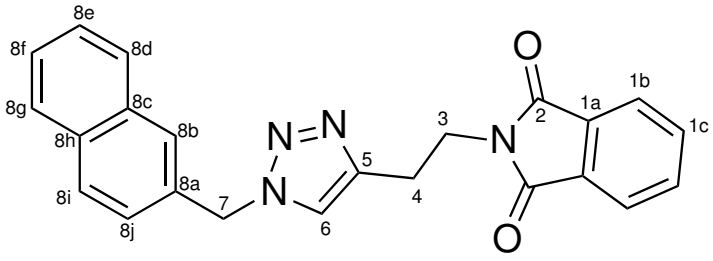


Figure 10

Table 5 shows assigned shifts for **3d**. The shifts for carbons 8c–i could not be assigned because the shifts are so similar. Like with the other triazoles prepared, the ^{1}H NMR shift at 5.64 ppm, belonging to the protons on carbon 7, is a sign of the trizole **3d**. The ^{13}C NMRshift at 24.9 ppm, belonging to carbon 4 is also a sign of **3d**. Unreacted alkyne **2a** can be seen in the ^{1}H NMR spectrum by the peaks 3.89 and 2.62 ppm.

Table 5: Assigned shifts for **3d**

Carbon no.	δ **H [ppm]**	**M**	**J [Hz]**	δ **C [ppm]**
1b	7.74	dd	3.0, 5.5	123.2
1c	7.65	dd	3.0, 5.3	133.9
2	Cq	-	-	168.1
3	3.98	t	7.1	37.4
4	3.13	t	7.5	24.9
6	7.34	br. s	-	121.2
7	5.64	dd	3.3, 6.3	54.2
8a	Cq	-	-	132.2
8b	7.68	br. s	-	127.1
8j	7.30	dd	1.6, 8.3	125.9

The spectra for **3d** are shown in Appendix D.

31 Tert-butyl 3-((4-(3-(1,3-dioxoisoindolin-2-yl)propyl) -1H-1,2,3-triazol-1-yl)methyl)-1H-indole-1-carboxylate 3f

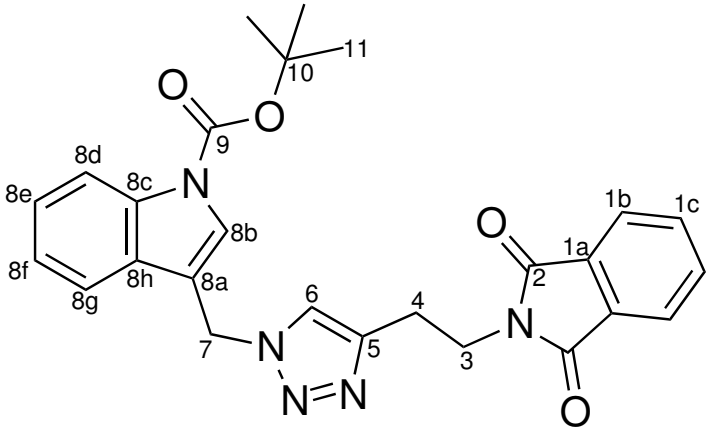


Figure 11

The crude product of the triazole **3f** was not purified. Consequently, the NMR spectra of the product contain a significant amount of contaminants, mainly from unreacted starting material. However, certain peaks in the spectra are characteristic of triazole, indicating that some **3f** product was formed, even though the reaction did not go to completion. Table 6 shows the values of ^{13}C NMRand ^{1}H NMR shifts which could be identified from the spectra, in correspondence with the numbering in Figure 11.

The singlet at 5.67 ppm in the ^{1}H NMR spectrum is a clear sign of triazole formation, the peak belonging to the two protons on carbon number 7 in the triazole **3f**. The corresponding protons in the azide **1c** have a shift of 4.47 ppm. This observation is consistent with the other triazoles prepared. The alkyne **2a** has shifts 2.62 (td, J = 2.7, 7.2 Hz) and 3.89 (t) ppm in the non-aromatic region. These shifts can be found in the ^{1}H NMR spectrum of the crude product of **3f**, revealing that unreacted alkyne is present. In the same region of the ^{1}H NMR spectrum of **3f** are a triplet peak at 3.16 and a triplet peak at 3.98 ppm. These are believed to be from protons on carbon 4 and 3, respectively. These shifts are in agreement with corresponding shifts on the other triazoles prepared. In the aromatic region it is more challenging to distinguish which peaks are from unreacted

starting material and which are from the triazole **3f**. Because the aromatic protons on the indole moiety and the phthalimide moiety are several bonds away from the triazole ring, the proton shifts are not expected to be significantly different from those in the starting materials. A broad singlet at 7.62 ppm is believed to be from the single proton at carbon 6 in the triazole ring.

The ^{13}C NMRspectrum of the crude sample of **3f** contains shifts from both starting materials and the triazole. The peaks at 70.3 is a clear alkyne shift from **2a**, belonging to the terminal carbon at the alkyne end. The peak at 46.2 ppm is from the azide **1c**. A small peak at 24.8 ppm is believed to be from carbon 4 in the triazole, which is in agreement with the shift observed at corresponding carbons in the other triazoles prepared.

Table 6: Assigned shifts for **3f**

Carbon no.	δ **H [ppm]**	**M**	**J [Hz]**	δ **C [ppm]**
2	Cq	-	-	168.0
3	39.8	t	6.8	37.4
4	3.16	t	6.9	24.8
8b	8.15	br. s	-	115.4
8c	Cq	-	-	135.7
8d	7.60	d	8.0	119.1
8e	7.36	td	6.2, 8.3	124.9
8f	7.28	td	0.9, 7.6	123.0
8g	7.62	s	-	124.9
8h	Cq	-	-	129.1
9	Cq	-	-	149.5
11	1.68	s	-	28.2

The spectra for **3f** are shown in Appendix F.

32 Attempted one-pot azidation of Boc-protected indole carboxaldehyde (1c)

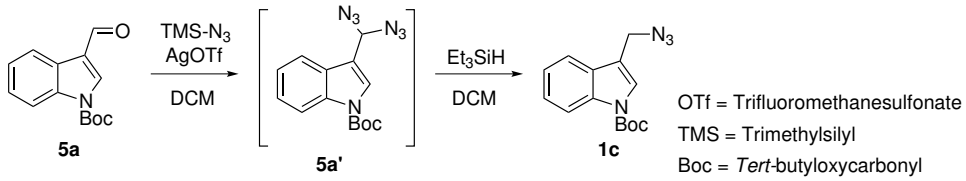


Figure 12

The one-pot azidation of **5a** to the azide **1c** was attempted twice using a procedure by Pramanik and Ghorai.[27] In the ^{1}H NMR spectra both products of the two attempts all peaks coincide with those of the aldehyde **5a**. A 2H singlet peak at 4.47 ppm was expected from the azide **1c**,[31] but no peaks were found in the interval 7.25–1.70 ppm. The reaction proceeds through a diazide intermediate **5a'**. Various diazides prepared by Pramanik and Ghorai are reported to have a singlet peak in the interval 5.70–5.83 ppm, but no peaks were found near this interval. The spectra show that neither the diazide **5a'** nor the target azide **1c** were formed. The spectra for the residue are shown in Appendix **??**.

33 Attempted preparation 2-(1-(3,5-di-tert-butylbenzyl) -1H-1,2,3-triazol- 5-yl)ethanamine (7a)

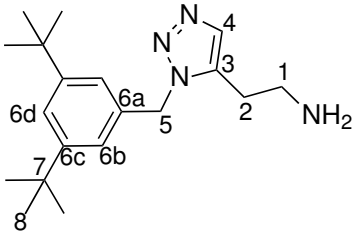


Figure 13

The ^{1}H NMR spectrum of the crude product from the attempted deprotection of **3a** to **7a** contained only peaks belonging to the protected **3a**. The important peaks are 3.85 (2H,

t, J = 7.5 hz) and 2.96 (2H, t, J = 7.5 Hz) which are identical to the peaks corresponding to carbon 3 and 4 in the protected **3a**, showing that **3a** was not deprotected. In the deprotected amine **7a**, these peaks are expected to be significantly lower. The spectra for **7a** are shown in Appendix J.

34 Preparation of 2-(1-(3,5-di-tert-butylbenzyl) -1H-1,2,3-triazol- 4-yl)ethanamine (7b)

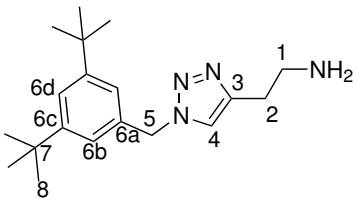


Figure 14

34.1 First parallel

In the ^{1}H NMR spectrum of amine **7b** the aromatic peak at 7.41 ppm (1H, deformed triplet) belongs to the proton on carbon 5d. The doublet at 7.09 (2H) ppm belongs to the protons on carbons 3b. The proton on carbon 3 was expected to have a shift close to the shift of the corresponding proton in the protected **3b** (7.33 ppm), but this shift was not found. The protons on carbon 2 have a shift of 2.86 ppm in a triplet and the protons on carbon 1 have a shift of 3.05 in a broad singlet. These shifts are significantly lower than in the protected **3b**, an indication that the phthalimide functionality has been removed.

34.2 Second parallel

As mentioned in the previous section, the proton on carbon 3 in **7b** was expected to have a shift of ∼7.33 ppm, equal to the corresponding proton in the protected **3b**. This peak was very weak in the spectrum. A multiplet is present at 7.31–7.27 ppm which integrates to 0.8H. It is possible that this is the missing proton from carbon 3 and that the weak triplet at 7.33 ppm is the corresponding proton in a residue of protected **3b**.

Two aromatic peaks detected are 7.40 (1H, t) and 7.09 (2H, d, J = 1.7 Hz) belonging to the protons on carbon 5d and 5b, respectively.

Important peaks in the ^{13}C NMRspectrum of **7b** are carbon 1 at 41.2 ppm and carbon 2 at 28.8 ppm. These peaks are higher than their corresponding peaks of 37.5 and 24.9 ppm in the protected **3b**, suggesting that the phthalimide protection has been removed.

The spectra for **3b** are shown in Appendix K.

35 Conclusion

Syntheses for preparation of azide **1c** were studied. The recently published procedure for one-pot azidation of the aldehyde **5a** to azide **1c** did not prove successful. No reaction was observed using the reported conditions. The azide **1c** was obtained through an older literature procedure, via the alcohol **6a**. Azide **1c** was used in a subsequent copper-catalyzed 1,3-dipolar cycloaddition to afford the novel 1,4-disubstituted *1h*-1,2,3-triazole **3f**. The procedure was based on literature procedures for regioselective 1,3-dipolar cycloaddition.

The 1,5-disubstituted *1h*-1,2,3-triazole **3a** was synthesized using a ruthenium-catalyzed 1,3-dipolar cycloaddition.

The triazoles **3b, 3c, 3d** and **3e** were prepared using copper-catalysed 1,3-dipolar cycloadditions. Most were obtained in acceptable yields, but material was lost in purification steps. Further work is needed to improve purification procedures. Nevertheless, the procedure has proved viable for the regioselective preparation of a range of triazoles, fulfilling an important step of the project scope.

The N-protected triazole **3b** was deprotected by hydrozinolysis to afford the corresponding amine **7a**. The obtained yields and purity were low, due to difficult work-up. Other methods of deprotection should be tested, such as $NaBH_4$/2-propanol followed by acetic acid.

The project set out to prepare a large library of triazoles, but it was not within the time frame to test them all. Further studies in the project group will be to prepare the remaining target triazoles **3g–q** and their derivatization via amines to the alkylguanidine ligands to fulfill the pharmacophore model of the eusynstelamides.

Part V

Experimental

36 General methods

36.1 Chemicals and solvents

Chemicals and solvents were supplied by Sigma-Aldrich, Fluka Chemica, Riedel de Haën, VWR and Fischer Scientific.

2-(But-3-yn-1-yl)isoindoline-1,3-dione **(2a)**[32] and 2-(pent-4-yn-1-yl)isoindoline-1,3-dione **(2b)**[33] were prepared by PhD Candidate Thomas Alexander Bakka.

3,5-Bis(trifluoromethyl)benzyl azide **(1b)** and 2-(Azidomethyl)-naphtalene **(1a)** were prepared by the author in an earlier project, based on procedures derived by Suzuki et al.,[28] Gallina et al.[34] and Gassensmith et al.[35]

Dry THF was optained from a Braun MB SPS-800 Purification System.

36.2 Spectroscopy

NMR spectra were recorded using Bruker Advance DPX400 or 600 MHz Bruker Advance III instruments. Samples were dissolved in $CDCl_3$ using TMS as internal standard. Spectroscopic data were analyzed using Bruker Topspin 3.1. Shifts are reported in ppm and were assigned using 1D ^{1}H NMR , 1D ^{13}C NMRand 2D HSQC, COSY, HMBC experiments. ChemBioDraw Ultra 12 was also used as an aid in assigning shifts.

IR spectra were recorded on a Thermo Nicolet Nexus FT-IR instrument.

High resolution mass spectra: Accurate mass determination in positive and negative mode was performed on a "Synapt G2-S" Q-TOF instrument from Waters^{TM}. Samples were ionized by the use of ASAP probe (APCI). Calculated exact mass and spectra processing was done by Waters^{TM} Software (Masslynxs V4.1 SCN871).

36.3 Chromatography

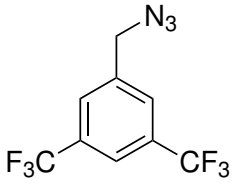
Column chromatography was performed using silica gel from Fluka Chemica (40-63 μm). TLC analyses were performed on silica gel 60 F_{254} from Merck. UV (312 nm) or 5% phosphomolybdic acid in EtOH were used for detection.

36.4 Other equipment

Melting points were measured on a Gallenkamp melting point apparatus.

37 Azidation of 3,5-bis(trifluoromethyl)benzyl alcohol

The procedure is based on the procedures reported by Thompson et al.[22] and Melander and Rogers.[7]

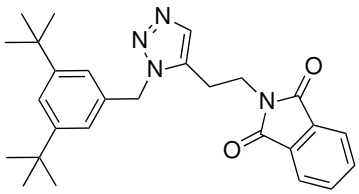


1d

3,5-Bis(trifluoromethyl)benzyl alcohol (0.431, 1.76 mmol)) was dissolved in toluene (10 mL) and diphenylphosphoryl azide (439 μL, 2.04 mmol) was added at rt. The solution was cooled to 0 ℃ before 1,8-diazobicycloundec-7-ene (336 μL, 2.25 mmol) was added dropwise over 35 minutes. The solution was allowed to slowly reach rt and was stirred for 17 hours. The solution was washed with water (3 x 5 mL) and HCl (1 M, 7 mL), dried over $MgSO_4$, filtered and evaporated under vacuum. After evaporation, a clear oil of low viscosity (0.308 g) was obtained. The crude product was purified on a silica column, using 15% by volume EtOAc in pentane as eluent. Product **1d** was obtained as a clear oil (0.027 g, 6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (1H, s), 7.79 (2H, s), 4.55 (2H, s). The ^{1}H NMR spectrum (Appendix M) is consistent with data reported in litterature.[36]

38 2-(2-(1-(3,5-Di-tert-butylbenzyl)-1H-1,2,3-triazol-5-yl)ethyl)isoindoline-1,3-dione (3a)

The procedure is based on procedures reported by Sharpless et al.[6] and Farooq.[23]



3a

Cp*RuCl(PPh_3)$_2$ (0.007 g, 0.01 mmol) was added to a round bottom flask under inert, dry conditions. 2-(But-3-yn-1-yl)isoindoline-1,3-dione **(2a)** (0.109 g, 0.55 mmol) was added to a separate flask, flushed dry with nitrogen and dissolved in dry THF (2.5 mL). The alkyne solution **(2a)** was added to the reaction flask containing the ruthenium catalyst in one portion. 3,5-Bis(trifluoromethyl)benzyl azide **(1b)** (0.141 g, 0.57 mmol) was added to a separate flask, flushed dry with nitrogen and dissolved in dry THF (2.5 mL). The azide solution **(1b)** was added to the reaction flask containing the ruthenium catalyst and alkyne in one portion. A total of 5 mL of solvent was used.

The resulting mixture was stirred at reflux for 13.5 hours. The solvent was evaporated under vacuum. A red-brown solid (0.217 g) was obtained. The crude product was purified on a silica column, using 1:3 EtOAc:DCM as eluent. Product **3a** was obtained as a yellow, hard wax (0.114 g, 47%) Melting point: 118.1-119.0 ℃.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (2H, dd, J = 3.1, 5.3 Hz), 7.73 (2H, dd, J = 3.1, 5.6 Hz), 7.56 (1H, s), 7.35 (1H, t), 7.05 (2H, d), 5.59 (2H, s), 3.84 (2H, t, J = 7.5 Hz), 2.96 (2H, t, J = 7.5 Hz), 1.26 (18H, s).

^{13}C NMR(400 MHz, $CDCl_3$) δ = 22.4, 31.4, 34.4, 35.9, 52.6, 121.7, 123.4, 131.8, 133.1, 133.2, 133.9, 134.2, 151.7, 167.8.

IR: 2961 (w), 1772 (w), 1720 (s), 1600 (w), 1460 (w), 1444 (w), 1425 (w), 1399 (m), 1369 (m), 1335 (w), 1246 (w), 1228 (w), 1188 (w), 1127 (w), 1087 (w), 990 (w), 981 (w), 891 (w), 880 (w), 842 (w), 792 (w), 752 (w), 715 (s), 621 (w), 607 (w).

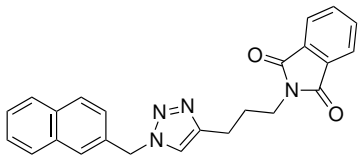
MS: calculated mass for [M]*-ion: 444.2525, found: 444.2520 The NMR, IR and MS spectra for **3a** are shown in Appendix A.

39 1,4-disubstituted 1*H*-1,2,3-triazoles

General procedure for preparation of 1,4-disubstituted 1*H*-1,2,3-triazoles The procedure is based on the procedure published by Melander and Rogers.[7]

The terminal alkyne (1 eq) was dissolved in a 1:2 mixture of tert-butanol and water. Benzoic acid (0.1 eq) was added, before addition of cupper sulfate pentahydrate (0.01 eq) and L-ascorbate (0.02 eq) as aqueous solutions (1 M). Lastly, the azide (1.05 eq) was added in one portion. The resulting mixture was stirred vigorously while monitored via TLC analysis (eluent: 1:3, EtOAc:DCM), reactions were generally stirred until completion (2-24 h). The reaction mixture was extracted with dichloromethane and the extract washed with water and in some reactions with brine. The organic extract was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Some products were purified by chromatography.

39.1 2-(3-(1-(Naphthalen-2-ylmethyl) -1H-1,2,3-triazol-4-yl)propyl)isoindoline-1,3-dione (3e)



3e

a) 2-(Azidomethyl)-naphtalene **(1a)** (0.355 g, 1.94 mmol, 1.01 eq), 2-(pent-4-yn-1-yl)isoindoline-1,3-dione **(2b)** (0.410 g, 1.92 mmol, 1.00 eq), benzoic acid (0.024 g, 0.20 mmol, 0.10 eq), cupper sulfate pentahydrate (0.02 mmol, 0.01 eq), L-ascorbate (0.04 mmol, 0.02 eq). Solvent, water:tert-butanol, 2:1 (2.5 mL); reaction time, 23 h; brine wash; yield 0.376 g (49%), yellow-grey solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85-7.79 (5H, m), 7.73 (1H, s), 7.70-7.68 (2H, m), 7.52-7.49 (2H, m), 7.37-7.32 (2H, m), 5.65 (2H, s), 3.73 (2H, t, J= 6.7 Hz), 2.76 (2H, t, J = 7.4 Hz), 2.06 (2H, quint, J = 7.2 Hz). The ^{1}H NMR spectrum is shown in Appendix E.

b) 2-(Azidomethyl)-naphtalene **(1a)** (0.164 g, 0.89 mmol, 1.06 eq), 2-(pent-4-yn-1-yl)isoindoline-1,3-dione **(2b)** (0.1784 g, 0.84mmol, 1.00 eq), benzoic acid (0.014 g, 0.12 mmol, 0.14 eq), cupper sulfate pentahydrate (0.01 mmol, 0.01 eq), L-ascorbate (0.02 mmol, 0.02 eq). Solvent, water:tert-butanol, 2:1 (5 mL); reaction time, 22 h; brine wash; yield 0.317 g (95%), off-white solid. Melting point: 69.0-71.1 ℃.

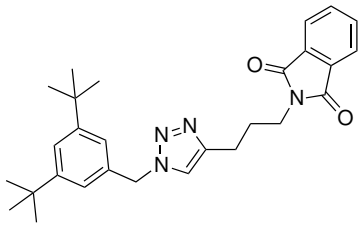
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 (4H, m), 7.73 (1H, s), 7.69 (2H, m), 7.50 (2H, m), 7.36 (1H, s), 5.65 (2H, s), 3.73 (2H, t, J= 6.7 Hz), 2.76 (2H, t, J = 7.4 Hz), 2.06 (2H, quint, J = 7.8, 14.9 Hz) ppm.

^{13}C NMR(400 MHz, $CDCl_3$) δ = 168.3, 133.8, 133.2, 130.0, 123.2, 121.1, 54.1, 37.2, 28.1, 23.0 ppm.

IR: 3267 (w), 2937 (w), 2360 (w), 2097 (w), 1772 (w), 1700 (s), 1602 (w), 1509 (w), 1466 (w), 1439 (w), 1396 (m), 1363 (m), 1324 (w), 1270 (w),1117 (w), 1088 (w), 1018 (m), 884 (m), 818 (m), 788 (m), 761 (m), 717 (s), 688 (m).

MS: calculated mass for [M]*-ion: 396.1586, found: 396.1579. The NMR, IR and MS spectra for **3e** are shown in Appendix E.

39.2 2-(3-(1-(3,5-Di-tert-butylbenzyl) -1H-1,2,3-triazol-4-yl)propyl)isoindoline-1,3-dione (3c)



3c

1-(Azidomethyl)-3,5-di-tert-butylbenzene **(1b)** (0.413 g, 1.68 mmol, 1.05 eq), 2-(pent-4-yn-1-yl)isoindoline-1,3-dione **(2b)** (0.341 g, 1.60 mmol, 1.00 eq), benzoic acid (0.022 g, 0.18 mmol, 0.11 eq), cupper sulfate pentahydrate (0.02 mmol, 0.01 eq), L-ascorbate (0.03 mmol, 0.02 eq). Solvent, water:tert-butanol, 2:1 (2.5 mL); reaction time, 24 h; brine wash; yield 0.552 g (75%), viscous green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (2H, dd, J = 3.1, 5.4 Hz), 7.71 (2H, dd, J = 3.1, 5.5 Hz), 7.39 (1H, t, J = 1.7), 7.34 (1H, br.

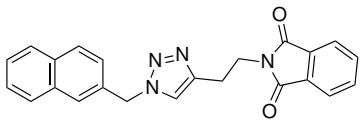
s), 7.09 (2H, d, J = 1.9 Hz), 5.46 (2H, s), 3.74 (2H, t, J = 7.1 Hz), 2.75 (2H, t, J = 7.7 Hz), 2.06 (2H, quint, J = 7.3 Hz), 1.29 (18 H, s) ppm.

^{13}C NMR(400 MHz, $CDCl_3$) δ = 168.4, 151.7, 134.0 133.9, 132.1, 123.2, 122.7, 122.3, 121.1, 54.7, 37.3, 34.9, 31.4, 28.2, 23.1 ppm.

IR: 2954 (w), 2866 (w), 2092 (w), 1770 (w), 1707 (s), 1601 (w), 1466 (w), 1436 (w), 1394 (m), 1362 (m), 1248 (w), 1201 (w), 1171 (w), 1107 (w), 1048 (w), 1024 (w), 883 (w), 789 (w), 718 (s), 653 (w), 621 (w).

MS: calculated mass for [M]*-ion: 458.2682, found: 458.2677. The NMR, IR and MS spectra for **3c** are shown in Appendix C.

39.3 2-(2-(1-(Naphthalen-2-ylmethyl) -1H-1,2,3-triazol-4-yl)ethyl)isoindoline-1,3-dione (3d)



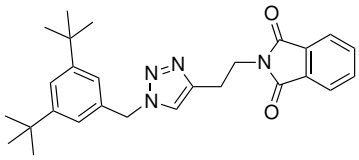
3d

2-(Azidomethyl)-naphtalene **(1a)** (0.532 g, 2.90 mmol, 1.06 eq), 2-(but-3-yn-1-yl)isoindoline-1,3-dione **(2a)** (0.549 g, 2.75 mmol, 1.00 eq), benzoic acid (0.038 g, 0.31 mmol, 0.11 eq), cupper sulfate pentahydrate (0.03 mmol, 0.01 eq), L-ascorbate (0.06 mmol, 0.02 eq). Solvent, water:tert-butanol, 2:1 (5 mL); reaction time, 8 h; yield 0.929 g (88%), off-white, fluffy solid. Melting point: 167.3-168.0 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87-7.80 (4H, m), 7.74 (2H, dd, J = 3.0, 5.5 Hz), 7.68 (1H, br. s), 7.65 (2H, dd, J = 3.0, 5.3 Hz), 7.52 (2H, dd, J = 3.3, 6.3 Hz), 7.34 (1H, br. s), 7.30 (1H, dd, J = 1.6, 8.3 Hz), 5.64 (2H, s), 3.98 (2H, t, J = 7.1 Hz), 3.13 (2H, t, J = 7.5 Hz).

^{13}C NMR(400 MHz, $CDCl_3$) δ = 168.1, 134.1, 133.9, 133.3, 133.1, 132.2, 132.0, 129.1, 128.0, 127.8, 127.1, 126.7, 126.6, 126.4, 125.2, 123.4, 123.2, 54.2, 37.5, 24.9. IR: 1770 (w), 1716 (m), 1463 (w), 1439 (w), 1397 (w), 1370 (m), 1334 (w), 1239 (w), 1119 (w), 1004 (w), 992 (w), 868 (w), 818 (m), 739 (m), 717 (s).

HRMS (ASAP+): m/z calculated for $C_{23}H_{18}N_4O_2$ [M]*: 382.1430, found: 382.1426. The ^{1}H NMR , ^{13}C NMR, IR and MS spectra for **3d** are shown in Appendix D.

39.4 2-(2-(1-(3,5-Di-tert-butylbenzyl) -1H-1,2,3-triazol-4-yl)ethyl)isoindoline-1,3-dione (3b)



3b

a) 1-(Azidomethyl)-3,5-di-tert-butylbenzene **(1b)** (0.637 g, 2.60 mmol, 1.05 eq), 2-(but-3-yn-1-yl)isoindoline-1,3-dione **(2a)** (0.491 g, 2.47 mmol, 1.00 eq), benzoic acid (0.034 g, 0.28 mmol, 0.11 eq), cupper sulfate pentahydrate (0.03 mmol, 0.01 eq), L-ascorbate (0.06 mmol, 0.02 eq). Solvent, water:tert-butanol, 2:1 (6 mL); reaction time, 24 h; crude yield 1.647 g. The crude product was attempted purified first by dissolving the product in DCM (3 mL) and then diluting with pentane (30 mL), yielding a white suspension. The suspension was filtered through four layers of filter paper, yielding a white, crystalline solid (0.262 g). The paper filtrate was filtered through celite and the celite was subsequently extracted with DCM (4x40 mL). The extract was evaporated under reduced pressure, yielding a white crystalline product (0.1527 g). The celite filtrate was purified on a silica column, using a 1:3 mixture of ethyl acetate and DCM. The column purification yielded a white, crystalline solid (0.165 g). The ^{1}H NMR spectra of the three purified products (filter paper residue, celite residue and column product) were identical. Combined, the three purified products yielded 0.579 g (52%) of **3b**. Melting point: 141.0-141.6 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (2H, dd, J = 3.0, 5.5 Hz), 7.69 (2H, dd, J = 3.0, 5.5 Hz), 7.41 (1H, t, J = 2.0 Hz), 7.33 (1H, s), 7.09 (2H, d, J = 2.0 Hz), 5.46 (2H, s), 3.99 (2H, t, J = 7.6 Hz), 3.12 (2H, t, J = 7.3 Hz), 1.29 (18 H, s).

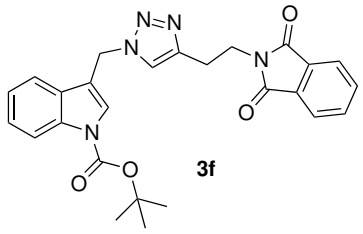
^{13}C NMR(400 MHz, $CDCl_3$): 24.9, 31.4, 34.9, 37.5, 54.7, 121.1, 122.4, 122.7, 123.3, 132.1, 133.8, 133.9, 151.8, 167.9.

IR: 2952 (w), 1775 (w). 1707 (m), 1434 (w), 1405 (w), 1248 (w), 1100 (w), 1055 (w), 992 (w), 869 (w), 713 (s).

HRMS (ASAP+): m/z calculated for $C_{27}H_{32}N_4O_2$ [M]*: 444.2525, found: 444.2526. The ^{1}H NMR , ^{13}C NMR, IR and MS spectra for **3b** are shown in Appendix B.

The experiment was repeated in a larger scale: b) 1-(Azidomethyl)-3,5-di-tert-butylbenzene **(1b)** (1.793 g, 7.31 mmol, 0.95 eq), 2-(but-3-yn-1-yl)isoindoline-1,3-dione **(2a)** (1.519 g, 7.62 mmol, 1.00 eq), benzoic acid (0.102 g, 0.84 mmol, 0.11 eq), cupper sulfate pentahydrate (0.08 mmol, 0.01 eq), L-ascorbate (0.02 mmol, 0.02 eq). Solvent, water:tert-butanol, 2:1 (20 mL); reaction time, 24 h; crude yield 3.280 g (101 %), yellowish-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (2H, dd, J = 3.1, 5.5 Hz), 7.69 (2H, dd, J = 3.1, 5.5 Hz), 7.41 (1H, t, J = 2.0 Hz), 7.33 (1H, s), 7.09 (2H, d, J = 2.0 Hz), 5.46 (2H, s), 3.99 (2H, t, J = 7.6 Hz), 3.12 (2H, t, J = 7.3 Hz), 1.29 (18 H, s). The ^{1}H NMR spectrum is shown in Appendix B.

39.5 Tert-butyl 3-((4-(3-(1,3-dioxoisoindolin-2-yl)propyl) -1H-1,2,3-triazol-1-yl)methyl)-1H-indole-1-carboxylate (3f)



3f

Tert-butyl 3-(azidomethyl)-1H-indole-1-carboxylate **(1c)** (0.190 g, 0.68 mmol, 1.05 eq), 2-(but-3-yn-1-yl)isoindoline-1,3-dione **(2a)** (0.129 g, 0.65 mmol, 1.00 eq), benzoic acid (0.001 g, 0.08 mmol, 0.12 eq), cupper sulfate pentahydrate (0.007 mmol, 0.01 eq), L-ascorbate (0.007 mmol, 0.02 eq). Solvent, water:tert-butanol, 2:1 (2 mL); reaction time, 24 h; crude yield 0.223 g (71 %), dark yellow solid. Melting point: 90.5-91.0 ℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.15 (1H, br s), 8.10 (0.4H, dd, J = 1.4, 3.2 Hz), 7.87-7.85 (2H, m), 7.76-7.71 (3H, m), 7.68-7.66 (6.7H, m), 7.62 (1H, s), 7.60 (1.7H, d, J = 8.0 Hz), 7.36 (2H, td, J = 6.2, 8.3 Hz), 7.28 (1.4H, td, J = 0.9, 7.6 Hz), 7.20 (0.4H, t, J = 7.5 Hz), 5.67 (0.6H, s), 4.47 (2.8 H, s), 3.98 (0.7H, t, 6.8 Hz), 3.89 (2H, t, J = 7.2 Hz), 3.16 (0.7H, t, J = 6.9 Hz), 2.62 (2H, td, J = 2.7, 7.2 Hz), 1.96 (1H, t, J = 2.8 Hz), 1.69 (3H, s), 1.68 (12.6 H, s) ppm.

^{13}C NMR(600 MHz, $CDCl_3$) δ = 168.1, 149.5, 135.7, 129.1, 124.9, 123.0, 115.4, 119.1, 37.4, 28.2 ppm.

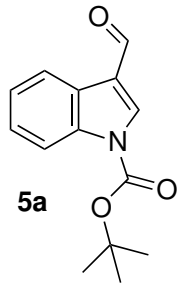
IR: 3252 (w), 2358 (w), 2093 (w), 1766 (w), 1703 (s), 1450 (m), 1468 (w), 1429 (m), 1386 (m), 1369 (m), 1336 (m), 1307 (m), 1257 (m), 1153 (s), 1115 (w), 1087 (m), 1018 (w), 995 (w), 850 (w), 783 (m), 767 (s), 746 (s), 722 (s), 713 (s), 681 (w), 624 (w).

HRMS (ASAP+): m/z calculated for $C_{26}H_{25}N_5O_4$ [M+H]*: 472.1985, found 472.1985.

The ^{1}H NMR , ^{13}C NMR, IR and MS spectra for **3f** are shown in Appendix F.

40 Tert-butyl 3-formyl-1H-indole-1-carboxylate (5a)

The procedure is based on the procedure published by Giraud et al.[24]



To a solution of indole carboxaldehyde **(4a)** (0.247 g, 1.7 mmol, 1 eq.) in acetonitrile (6 ml) was added di-tert-butyl bicarbonate (0.491 g, 2.25 mmol, 1.3 eq) before addition of 4-dimethylaminopyridine (0.043 g, 0.35 mmol, 0.2 eq). The mixture was stirred for 3 h. Water (20 mL) was added and the reaction mixture was extracted with DCM (3x15 mL). The extract was dried over $MgSO_4$ and the solvent was removed under reduced pressure, yielding a crude product of **5a** as a white solid (0.399 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.11 (1H, s), 8.29 (1H, d, J = 7.8 Hz), 8.24 (1H, s), 8.15 (1H, d, J = 8.3), 7.42 (1H, td, J = 1.3, 7.4 Hz), 7.37 (1H, td, J = 1.3, 7.4 Hz), 3.00 (1H, s), 1.70 (9H, s). The ^{1}H NMR shifts were consistent with literature.[24] The ^{1}H NMR spectrum is shown in Appendix H.

The experiment was repeated yielding 3.524 g (89%) of **5a**.

41 Attempted deprotection of phthalimides to respective amines

The procedure for hydrazinolysis of phthalimide protected species is based on the Ing-Manske procedure[37] and procedures developed by PhD Candidate Thomas Alexander Bakka.

41.1 Attempted preparation of 2-(1-(3,5-di-tert-butylbenzyl)-1H-1,2,3-triazol-5-yl)ethanamine (7a)

2-(2-(1-(3,5-Di-tert-butylbenzyl)-1H-1,2,3-triazol-5-yl)ethyl)isoindoline-1,3-dione **(3a)** (0.074 g, 0.17 mmol, 1 eq) was dissolved in EtOH (96%, 8 mL). Hydrazine hydrate (50-60%, 0.87 mmol, 5 eq) was added in two portions over 1 h. The mixture was stirred for 5 h and evaporated. A white solid was obtained (0.044 g). No amine product could be detected in the ^{1}H NMR spectrum of the white solid (Appendix J). An IR spectrum of the solid is shown in Appendix J.

41.2 Preparation of 2-(1-(3,5-di-tert-butylbenzyl) -1H-1,2,3-triazol-4-yl)ethanamine (7b)

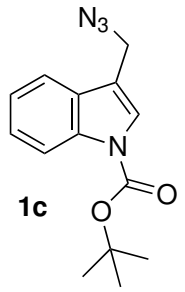
a) 2-(2-(1-(3,5-Di-tert-butylbenzyl)-1H-1,2,3-triazol-4-yl)ethyl)isoindoline-1,3-dione **(3b)** (0.235 g, 0.53 mmol, 1 eq) was dissolved in EtOH (absolute, 25 mL). Hydrazine hydrate (64-65%, 1.27 mmol, 2.4 eq) was added in one portion and the mixture was heated at reflux for 4 h. The solvent was removed under reduced pressure, yielding a white solid (0.266 g). A portion of the crude product (0.130 g) was attempted purified on a silica column, using a 70:30:3 mixture of chloroform, MeOH and NH_3 (aq) (25%) as eluent. An off-white solid containing product **7b** (0.043 g) was obtained from the column. The ^{1}H NMR spectrum of the solid is shown in Appendix K.

b) The experiment was repeated in a larger scale:

2-(2-(1-(3,5-Di-tert-butylbenzyl)-1H-1,2,3-triazol-4-yl)ethyl)isoindoline-1,3-dione **(3b)** (0.954 g, 2.15 mmol, 1 eq) was dissolved in EtOH (absolute, 80 mL). Hydrazine hydrate (50-60%, 17.7 mmol, 8 eq) was added in one portion and the mixture was heated at reflux for 3 h. The solvent was removed under reduced pressure, yielding a fluffy, white solid (0.986 g). A portion of the crude product (0.112 g) was attempted purified on a silica column, using a 70:30:3 mixture of chloroform, MeOH and NH_3(aq, 25%) as eluent. No material was obtained from the column. A portion of the crude product (0.604 g) was suspended in DCM (30 mL) and filtered through a celite plug. The filtrate was evaporated under reduced pressure, yielding **7b** as a yellow oil (0.261 g). ^{1}H NMR , ^{13}C NMR and IR spectra of the product are shown in Appendix K.

42 Attempted one-pot azidation of Boc-protected indole carboxaldehyde

Conversion of Boc-protected indole carboxaldehyde **(5a)** to azide **(1c)** was attempted using a procedure by Pramanik and Ghorai.[27]



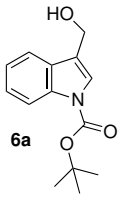
a) Tert-butyl 3-formyl-1*H*-indole-1-carboxylate **(5a)** (1.018 g, 4.15 mmol, 1 eq) was dissolved in DCM (12 mL) and the solution was cooled to 0 ℃. Azidotrimethylsilane (1.5 mL, 11.6 mmol, 2.8 eq) was added to the stirred solution, followed by addition of silver triflate (0.110 g, 0.43 mmol, 0.1 eq). The mixture was stirred at 0 ℃ for 1 h. Triethylsilane (1.3 mL, 8.3 mmol, 2.0 eq) was added dropwise over 45 min at 0 ℃. The solution was allowed to reach ambient temperature and was stirred for 12 h. The reaction mixture

was extracted with DCM, washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, yielding an off-white solid (0.998 g). No azide product were detected in the ^{1}H NMR spectrum of the solid (Appendix **??**).

b) Tert-butyl 3-formyl-1H-indole-1-carboxylate **(5a)** (0.218 g, 0.89 mmol, 1 eq) was dissolved in DCM (2.5 mL) and the solution was cooled to 0 ℃. Azidotrimethylsilane (0.35 mL, 2.51 mmol, 2.8 eq) was added to the stirred solution, followed by addition of silver triflate (0.028 g, 0.11 mmol, 0.1 eq). The mixture was stirred at 0 ℃ for 3 h. Triethylsilane (0.28 mL, 1.75 mmol, 2.0 eq) was added dropwise over 30 min at 0 ℃. The solution was allowed to reach ambient temperature and was stirred for 13 h. The reaction mixture was extracted with DCM, washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, yielding an off-white solid (0.2219 g). No azide product were detected in the ^{1}H NMR spectrum of the solid (Appendix L).

43 Tert-butyl 3-(hydroxymethyl) -1H-indole-1-carboxylate (6a)

Tert-butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate **(6a)** was prepared based on a procedure by Silverstein et al.[38]



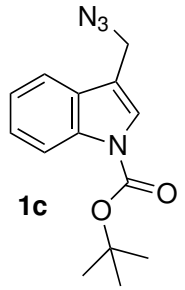
Tert-butyl 3-formyl-1H-indole-1-carboxylate **(5a)** (0.124 g, 0.50 mmol, 1 eq) was suspended in MeOH (5 mL). Sodium borohydride (0.072 g, 1.90 mmol, 3.8 eq) was added in one portion. The resulting mixture was stirred for 1 h. Water (10 mL) was added an the aqueous phase was adjusted to pH 12 by addition of a saturated solution of K_2CO_3. The aqueous phase was extracted with Et_2O (4x15 mL) and dried over $MgSO_4$. The extract was concentrated under reduced pressure, yielding **6a** as a white solid (0.107 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.14 (1H, d, J = 8.0 Hz), 7.66 (1H, d, J = 7.8 Hz),

7.60 (1H, s), 7.34 (1H, td, J = 1.4, 7.8 Hz), 7.28-7.24 (1H, m), 4.85 (2H, s), 1.66 (9H, s). The ^{1}H NMR spectrum (Appendix I) is consistent with data reported in litterature.[39]

The experiment was repeated in a 12.8 scale, yielding **6a** yellowish white solid (1.345 g, 85%).

44 Tert-butyl 3-(azidomethyl) -1H-indole-1-carboxylate (1c)

Tert-butyl 3-(azidomethyl)-1H-indole-1-carboxylate **(1c)** was prepared based on a procedure by Suzuki et al.[28]



a) Tert-butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate **(6a)** (0.320 g, 1.29 mmol, 1.00 eq) was dissolved in toluene (15 mL). Diphenylphosphoryl azide (0.300 mL, 1.40 mmol, 1.09 eq) was added in one portion at rt. The resulting mixture was cooled to 0 ℃and 1,8-dizobicycloundec-7-ene (0.210 mL, 1.40 mmol, 1.09 eq) was added dropwise over 35 minutes. The mixture was allowed to temper to rt and was stirred for 20 h. The reaction mixture was extracted with Et_2O (4x5 mL) and washed with water (15 mL) and brine (15 mL). The extract was dried over $MgSO_4$ and the solvent was removed under reduced pressure, yielding a waxy yellow solid (0.3473 g). The crude product was purified on a silica column, using a 1:3 mixture of pentane and ethyl acetate as eluent. Product **1c** was obtained from the column as a white solid (0.185 g, 53%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.16 (1H, br), 7.62 (1H, br), 7.60 (1H, d, J = 7.9 Hz), 7.36 (1H, td, J = 1.1, 8.1 Hz), 7.28 (1H, td, J = 1.0, 7.3 Hz), 4.47 (2H, s), 1.68 (9H, s). The ^{1}H NMR spectrum (Appendix M) is consistent with data reported in litterature.[31]

The experiment was repeated in a 3.2 scale, yielding a crude product of **1c** as a waxy yellow solid (1.102 g, 89%).

References

[1] World Health Organization and others, Antimicrobial resistance: global report on surveillance. 2014.

[2] Gautun, O. R. Synthesis of Novel Antibiotics Inspired by Marine Natural Products. 2013.

[3] Geske, G. D.; Wezeman, R. J.; Siegel, A. P.; Blackwell, H. E. *J. Am. Chem. Soc.* **2005**, *127*, 12762–12763.

[4] www.mabcent.no.

[5] Kharb, R.; Sharma, P. C.; Yar, M. S. *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 1–21.

[6] Zhang, L.; Chen, X.; Xue, P.; Sun, H. H.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.*. **2005**, *127*, 15998–15999.

[7] Rogers, S. A.; Melander, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 5229–5231.

[8] Strøm, M. B.; Haug, B. E.; Skar, M. L.; Stensen, W.; Stiberg, T.; Svendsen, J. S. *J. Med. Chem.* **2003**, *46*, 1567–1570.

[9] Kolb, H. C.; Finn, M.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.

[10] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem.* **2002**, *114*, 2708–2711.

[11] Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.

[12] Todar, K. Todar's Online Textbook of Bacteriology. 2008-2012; http://textbookofbacteriology.net/antimicrobial.html.

[13] Townsend, C. A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 583–589.

[14] Aminov, R. I. *Front. Microbiol.* **2010**, *1*.

[15] von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Häbich, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5072–5129.

[16] Rocha-Santos, T.; Duarte, A. C. *Analysis of Marine Samples in Search of Bioactive Compounds*; Elsevier, 2014; Vol. 65; pp 5–12.

[17] Hansen, T.; Ausbacher, D.; Flaten, G. E.; Havelkova, M.; Strøm, M. B. *J. Med. Chem.* **2011**, *54*, 858–868.

[18] H Zhou, C.; Wang, Y. *Curr. Med. Chem.* **2012**, *19*, 239–280.

[19] Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278–308.

[20] Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 633–645.

[21] Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529–2591.

[22] Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. *J. Org. Chem.* **1993**, *58*, 5886–5888.

[23] Farooq, T. Synthesis of some nitrogen heterocycles of medicinal relevance. PhD thesis, UiB, 2012.

[24] Giraud, F.; Akué-Gédu, R.; Nauton, L.; Candelon, N.; Debiton, E.; Théry, V.; Anizon, F.; Moreau, P. *Eur. J. Med. Chem.* **2012**, *56*, 225–236.

[25] Khan, M. N. *J. Org. Chem.* **1996**, *61*, 8063–8068.

[26] Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093–2096.

[27] Pramanik, S.; Ghorai, P. *Org. Lett.* **2014**, *16*, 2104–2107.

[28] Suzuki, T.; Ota, Y.; Kasuya, Y.; Mutsuga, M.; Kawamura, Y.; Tsumoto, H.; Nakagawa, H.; Finn, M.; Miyata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 6817–6820.

[29] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.

[30] Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C.; Terlizzi, R. *Eur. J. Org. Chem* **2004**, *2004*, 3447–3458.

[31] Fuwa, H.; Sasaki, M. *Organic & Biomolecular Chemistry* **2007**, *5*, 2214–2218.

[32] Wu, Y.; Raveendranath, P. Processes for the preparation of N-substituted phthalimides. 2007; US Patent 7,253,291.

[33] Li, Y.; Marks, T. J. *J. Org. Chem.* **1996**, *118*, 9295–9306.

[34] Gallina, M. E.; Baytekin, B.; Schalley, C.; Ceroni, P. *Chem. Euro. J.* **2012**, *18*, 1528–1535.

[35] Gassensmith, J. J.; Barr, L.; Baumes, J. M.; Paek, A.; Nguyen, A.; Smith, B. D. *Org. Lett.* **2008**, *10*, 3343–3346.

[36] Pardin, C.; Keillor, J. W.; Lubell, W. D. Cinnamoyl inhibitors of transglutaminase. 2013; US Patent App. 14/015,047.

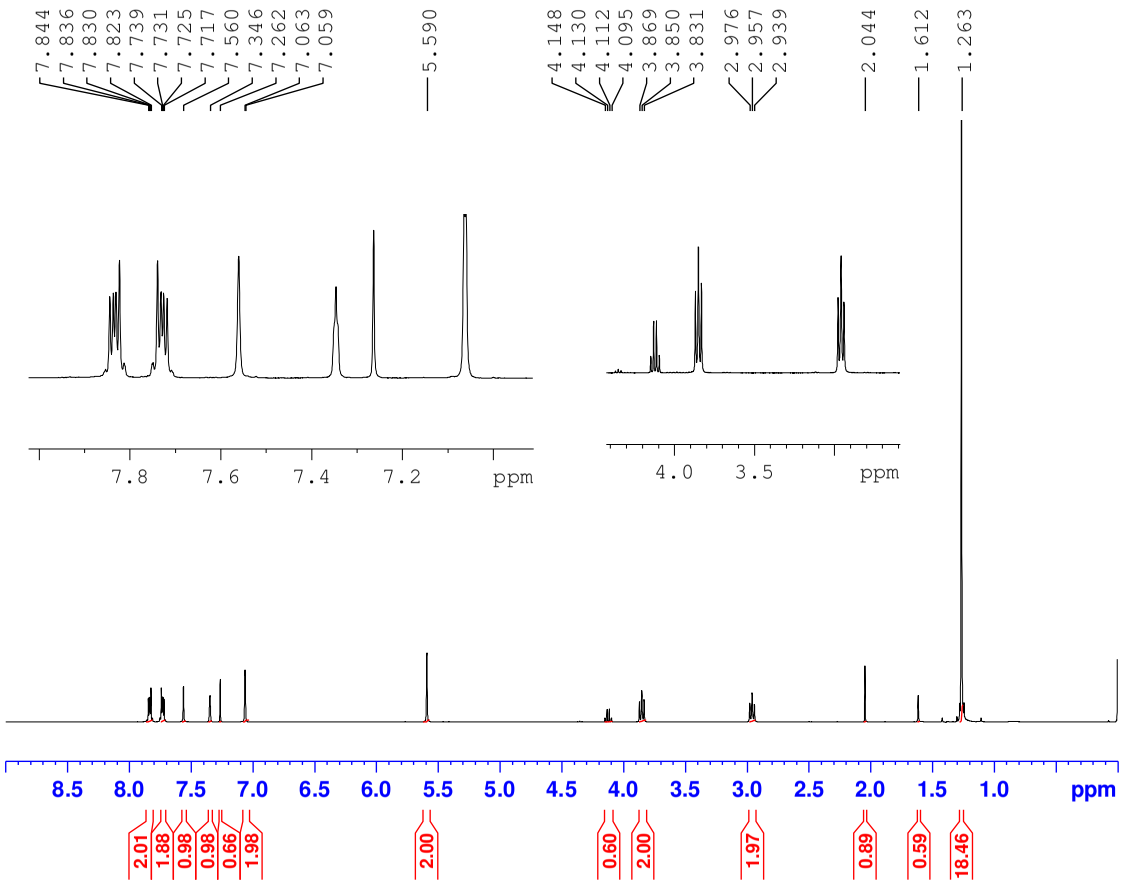
[37] Ing, H. R.; Manske, R. H. F. *J. Am. Chem. Soc. (Resumed)* **1926**, *129*, 2348–2351.

[38] Silverstein, R. M.; Ryskiewicz, E. E.; Chaikin, S. W. *J. Am. Chem. Soc.* **1954**, *76*, 4485–4486.

[39] Kobayashi, S.; Miyamura, H.; Akiyama, R.; Ishida, T. *J. Am. Chem. Soc.* **2005**, *127*, 9251–9254.

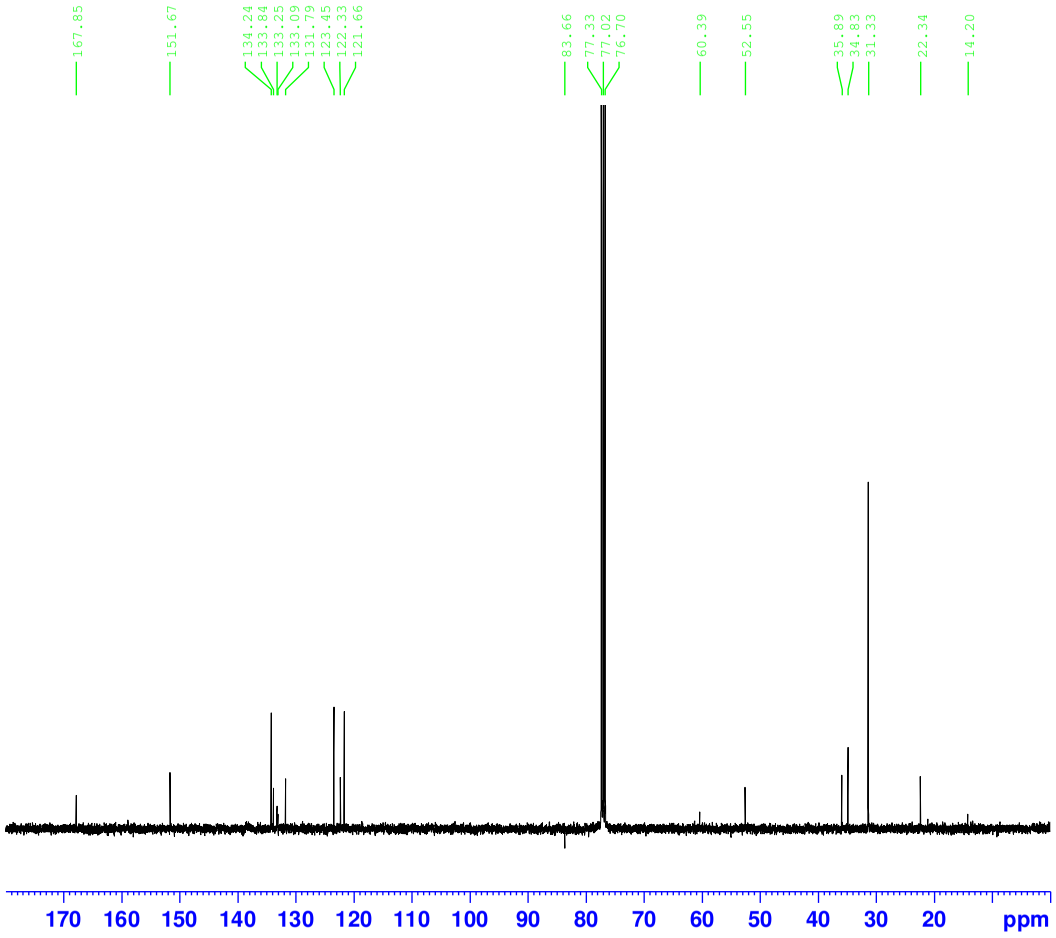
A Spectra of 3a

A.1 ^{1}H NMR spectrum of 3a



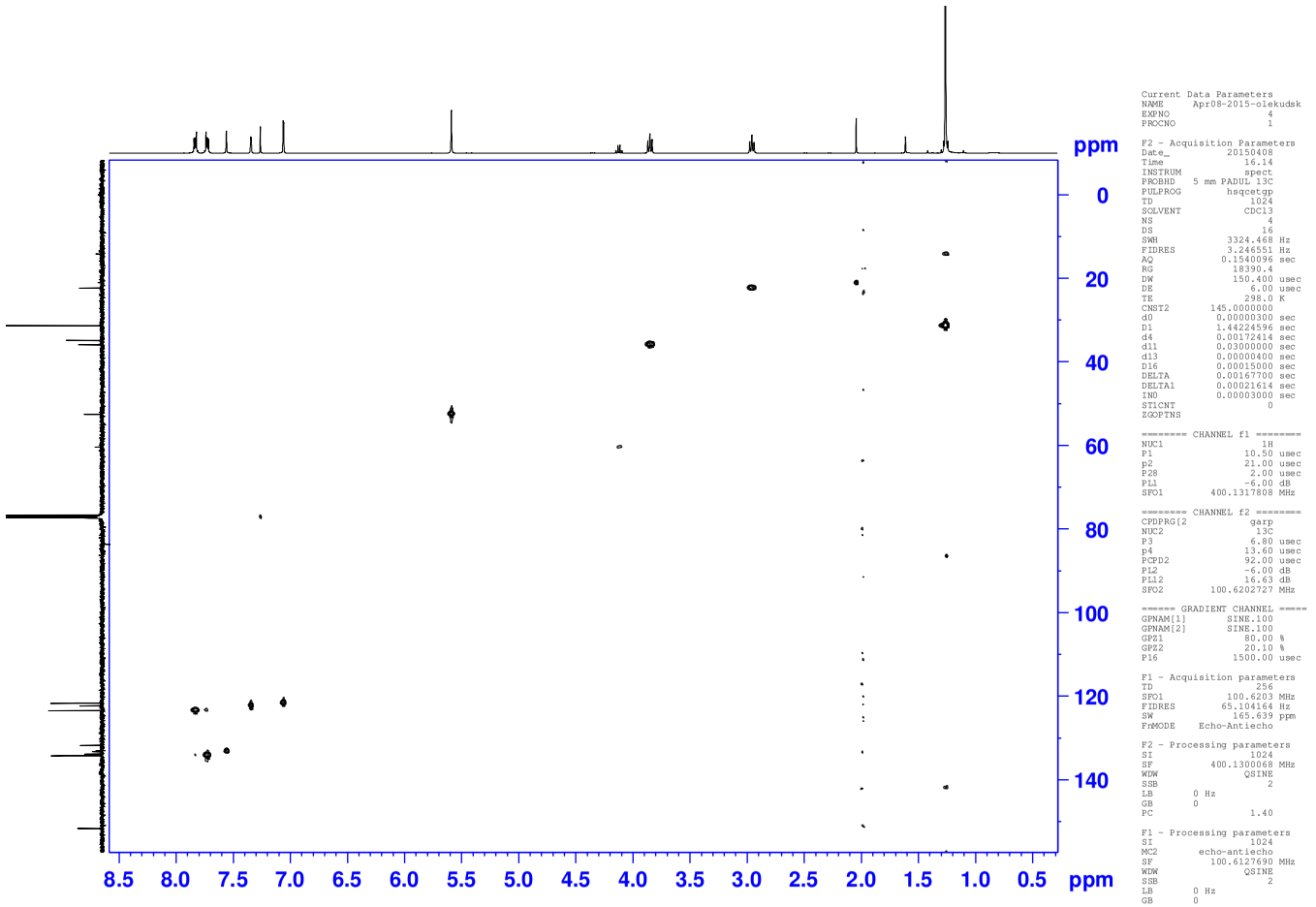

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20150408
Time                 13.04
INSTRUM              spect
PROBHD    5 mm PADUL 13C
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH                8278.146 Hz
FIDRES             0.126314 Hz
AQ                 3.9583745 sec
RG                     406.4
DW                  60.400 usec
DE                   6.00 usec
TE                   298.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                   10.50 usec
PL1                  -6.00 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                    32768
SF            400.1300068 MHz
WDW                     EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.00
```

A.2 ^{13}C NMRspectrum of 3a



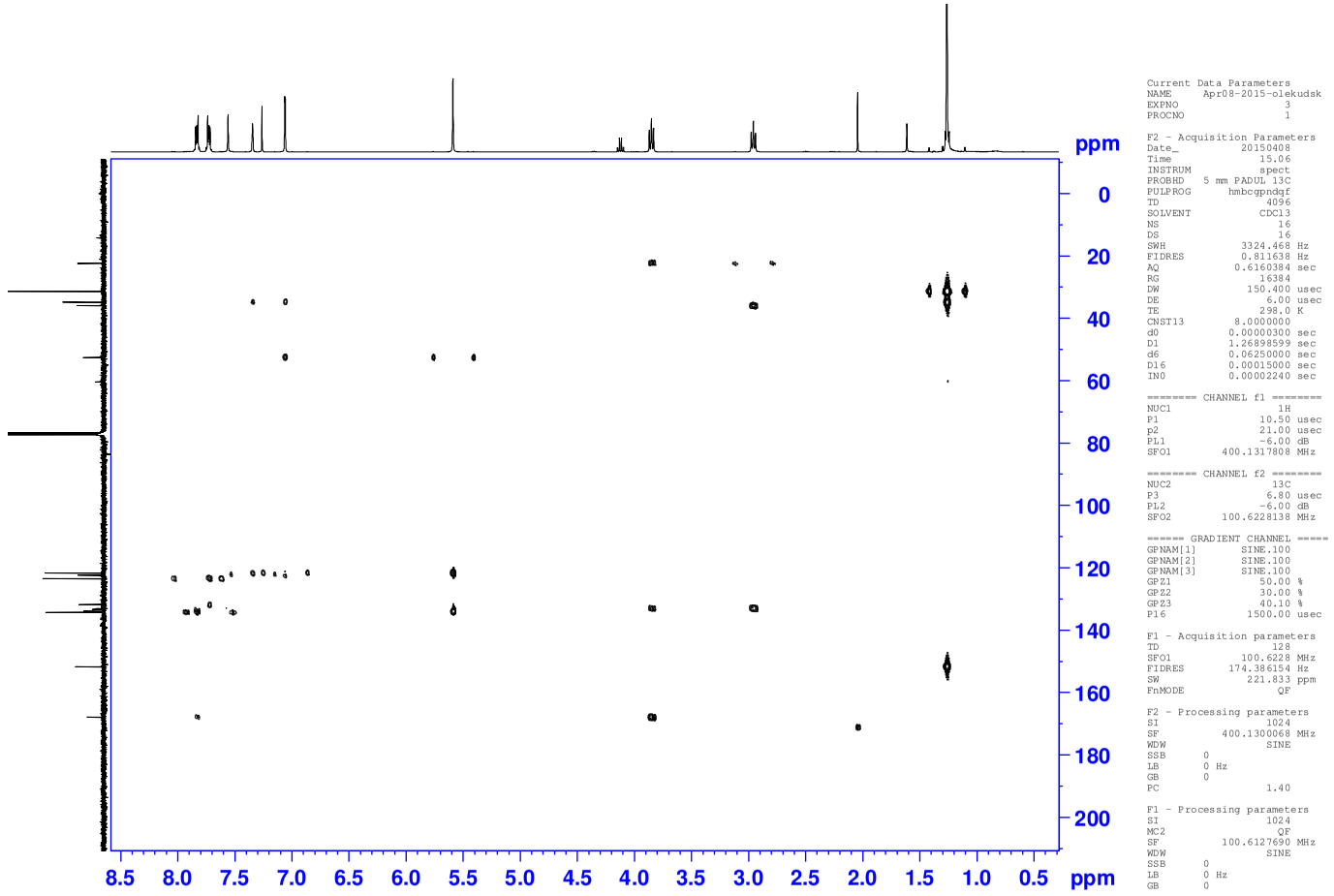

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_           20150408
Time              13.26
INSTRUM           spect
PROBHD   5 mm PADUL 13C
PULPROG           zgpg30
TD                65536
SOLVENT           CDCl3
NS                  457
DS                    4
SWH           23980.814 Hz
FIDRES         0.365918 Hz
AQ            1.3664256 sec
RG                  128
DW               20.850 usec
DE                6.00 usec
TE                298.0 K
D1           2.00000000 sec
d11          0.03000000 sec
DELTA        1.89999998 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 6.50 usec
PL1                -6.00 dB
SFO1        100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG[2         waltz16
NUC2                1H
PCPD2              95.00 usec
PL2                -6.00 dB
PL12               13.13 dB
PL13               18.50 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF          100.6127690 MHz
WDW                 EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

A.3 HSQC spectrum of 3a



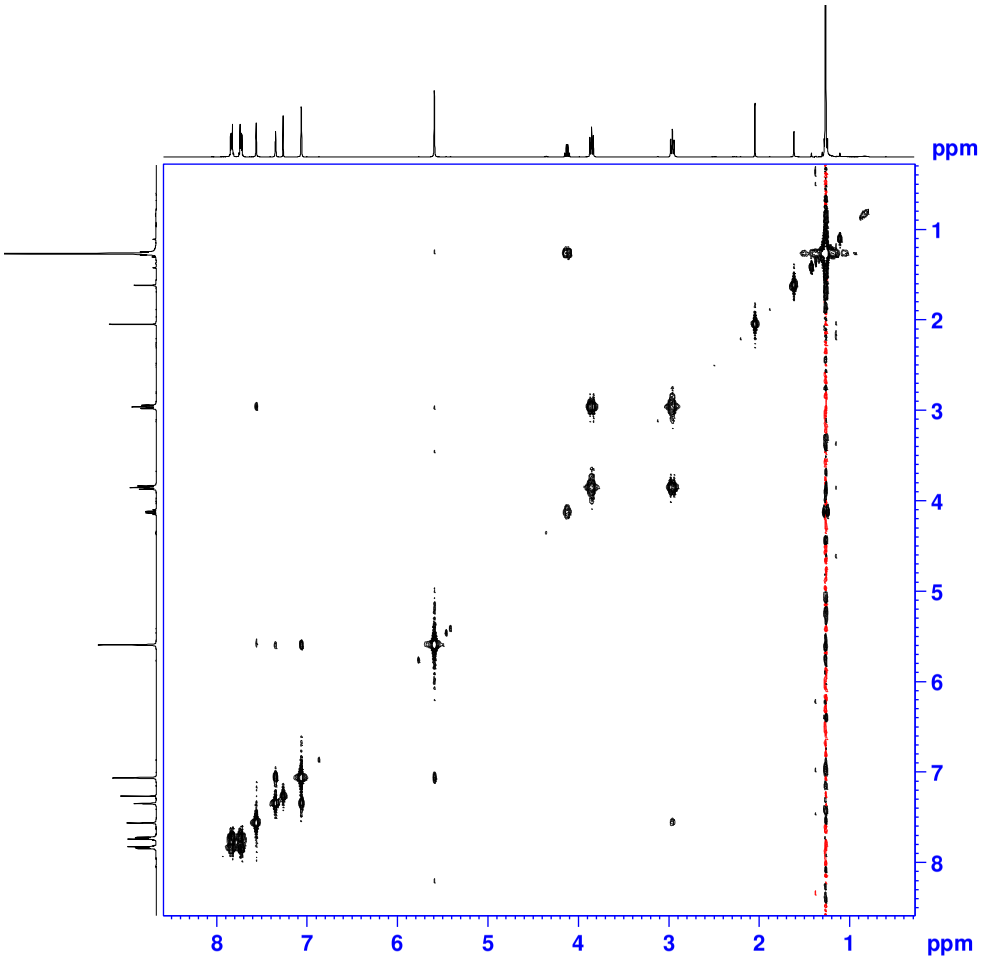

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                       4
PROCNO                      1

F2 - Acquisition Parameters
Date_              20150408
Time                 16.14
INSTRUM              spect
PROBHD   5 mm PADUL 13C
PULPROG            hsqcetgp
TD                    1024
SOLVENT              CDCl3
NS                       4
DS                      16
SWH                3324.468 Hz
FIDRES             3.246551 Hz
AQ                 0.1540096 sec
RG                   18390.4
DW                   150.400 usec
DE                     6.00 usec
TE                   298.0 K
CNST2             145.0000000
d0                 0.00000300 sec
D1                 1.44224596 sec
d4                 0.00172414 sec
d11                0.03000000 sec
d13                0.00000400 sec
D16                0.00015000 sec
DELTA              0.00167700 sec
DELTA1             0.00021614 sec
IN0                0.00003000 sec
ST1CNT                      0
ZGOPTNS

======== CHANNEL f1 ========
NUC1                       1H
P1                      10.50 usec
p2                      21.00 usec
P28                      2.00 usec
PL1                     -6.00 dB
SFO1             400.1317808 MHz

======== CHANNEL f2 ========
CPDPRG[2                 garp
NUC2                      13C
P3                       6.80 usec
p4                      13.60 usec
PCPD2                   92.00 usec
PL2                     -6.00 dB
PL12                    16.63 dB
SFO2             100.6202727 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]             SINE.100
GPNAM[2]             SINE.100
GPZ1                    80.00 %
GPZ2                    20.10 %
P16                   1500.00 usec

F1 - Acquisition parameters
TD                         256
SFO1             100.6203 MHz
FIDRES            65.104164 Hz
SW                  165.639 ppm
FnMODE       Echo-Antiecho

F2 - Processing parameters
SI                        1024
SF               400.1300068 MHz
WDW                      QSINE
SSB                         2
LB          0 Hz
GB          0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2             echo-antiecho
SF               100.6127690 MHz
WDW                      QSINE
SSB                         2
LB          0 Hz
GB          0
```

A.4 HMBC spectrum of 3a



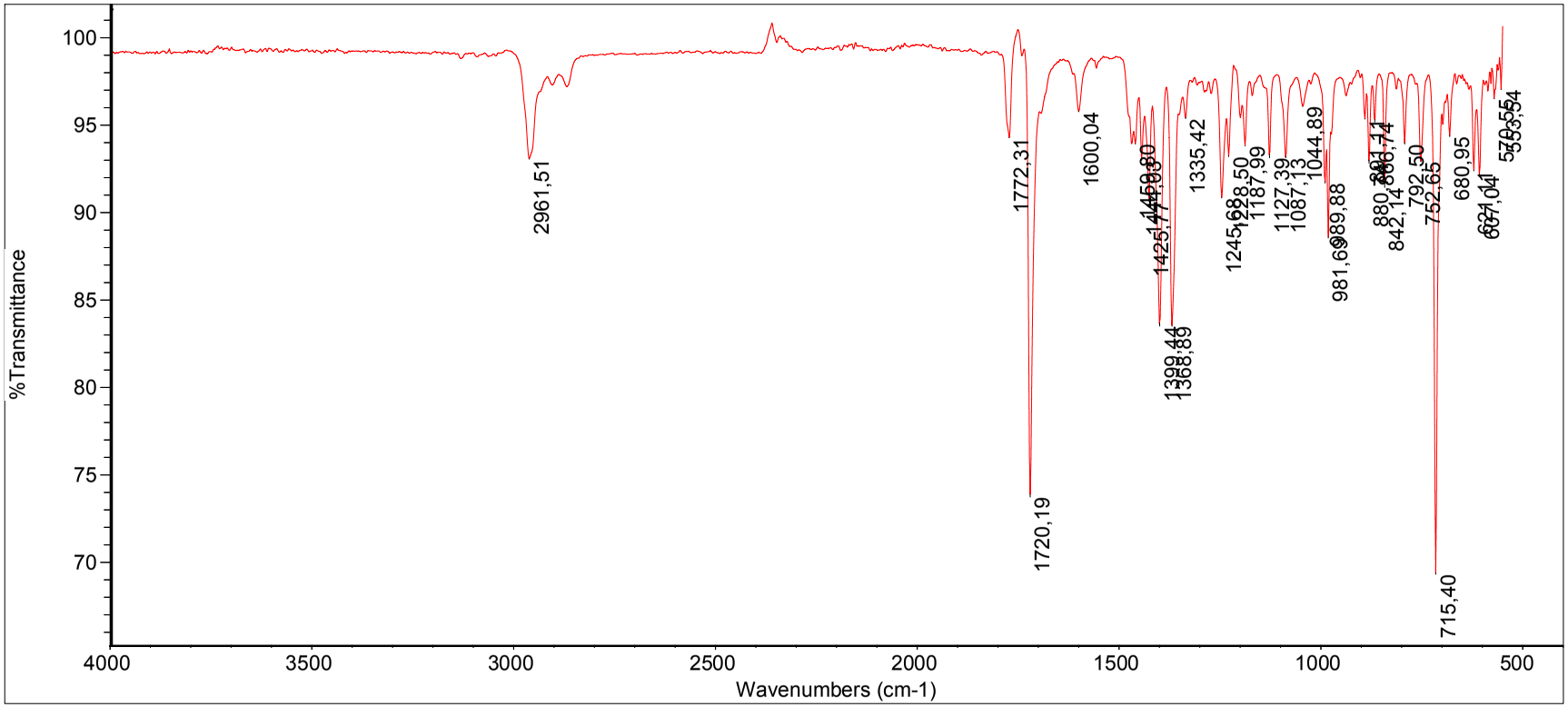

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                       3
PROCNO                      1

F2 - Acquisition Parameters
Date_           20150408
Time              15.06
INSTRUM           spect
PROBHD   5 mm PADUL 13C
PULPROG       hmbcgpndqf
TD                4096
SOLVENT           CDCl3
NS                  16
DS                  16
SWH            3324.468 Hz
FIDRES         0.811638 Hz
AQ             0.6160384 sec
RG                16384
DW              150.400 usec
DE                6.00 usec
TE                298.0 K
CNST13         8.0000000
d0             0.00000300 sec
D1             1.26898599 sec
d6             0.06250000 sec
D16            0.00015000 sec
IN0            0.00002240 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.50 usec
p2                21.00 usec
PL1               -6.00 dB
SFO1         400.1317808 MHz

======== CHANNEL f2 ========
NUC2                13C
P3                 6.80 usec
PL2               -6.00 dB
SFO2         100.6228138 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPNAM[3]         SINE.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
P16              1500.00 usec

F1 - Acquisition parameters
TD                  128
SFO1           100.6228 MHz
FIDRES        174.386154 Hz
SW              221.833 ppm
FnMODE              QF

F2 - Processing parameters
SI                 1024
SF           400.1300068 MHz
WDW                SINE
SSB       0
LB        0 Hz
GB        0
PC                 1.40

F1 - Processing parameters
SI                 1024
MC2                 QF
SF           100.6127690 MHz
WDW                SINE
SSB       0
LB        0 Hz
GB        0
```

A.5 COSY spectrum of 3a




```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                       5
PROCNO                      1

F2 - Acquisition Parameters
Date_              20150408
Time                  16.44
INSTRUM               spect
PROBHD    5 mm PADUL 13C
PULPROG           cosygpqf
TD                     2048
SOLVENT               CDCl3
NS                        2
DS                        8
SWH                3324.468 Hz
FIDRES             1.623275 Hz
AQ                 0.3080192 sec
RG                     161.3
DW                   150.400 usec
DE                     6.00 usec
TE                    298.0 K
d0                 0.00000300 sec
D1                 1.37138498 sec
d13                0.00000400 sec
D16                0.00015000 sec
IN0                0.00030080 sec

======== CHANNEL f1 ========
NUC1                      1H
P0                     10.50 usec
P1                     10.50 usec
PL1                    -6.00 dB
SFO1           400.1317808 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]           SINE.100
GPZ1                  10.00 %
P16                 1500.00 usec

F1 - Acquisition parameters
TD                       128
SFO1               400.1318 MHz
FIDRES            25.972406 Hz
SW                     8.308 ppm
FnMODE                    QF

F2 - Processing parameters
SI                       1024
SF              400.1300068 MHz
WDW                      SINE
SSB           0
LB            0 Hz
GB            0
PC                     1.40

F1 - Processing parameters
SI                       1024
MC2                       QF
SF              400.1300068 MHz
WDW                      SINE
SSB           0
LB            0 Hz
GB            0
```

A.6 IR spectrum of 3a



A.7 MS spectrum of 3a

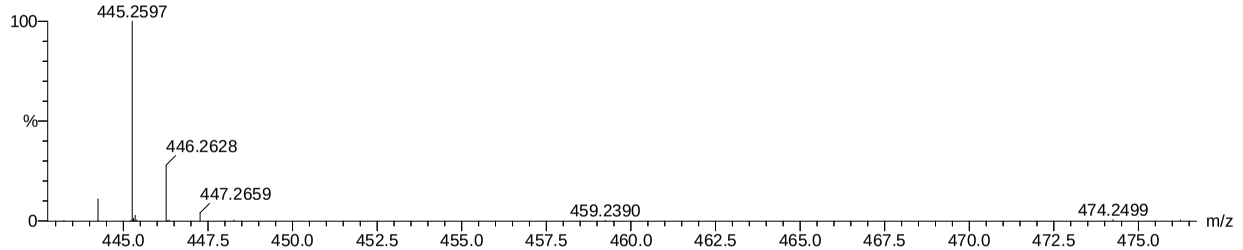
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
1581 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 N: 0-50 O: 0-100

NT-MSLAB-Operator-SVG
2015-201 192 (3.738) AM2 (Ar,35000.0,0.00,0.00); Cm (181:192)

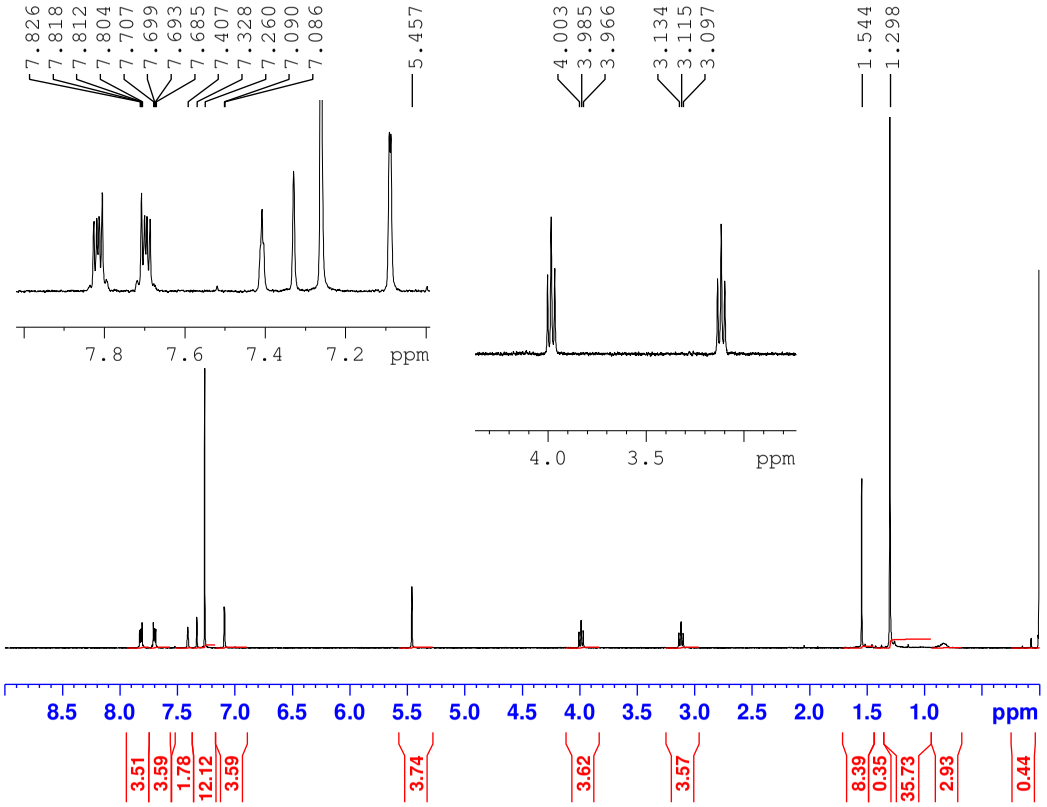
1: TOF MS ASAP+
3.45e+007



Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
444.2520	444.2525	-0.5	-1.1	14.0	225.3	0.733	48.03	C27 H32 N4 O2
	444.2512	0.8	1.8	9.0	225.7	1.061	34.61	C26 H36 O6
	444.2530	-1.0	-2.3	7.0	227.0	2.427	8.83	C12 H28 N16 O3
	444.2517	0.3	0.7	2.0	227.1	2.461	8.53	C11 H32 N12 O7

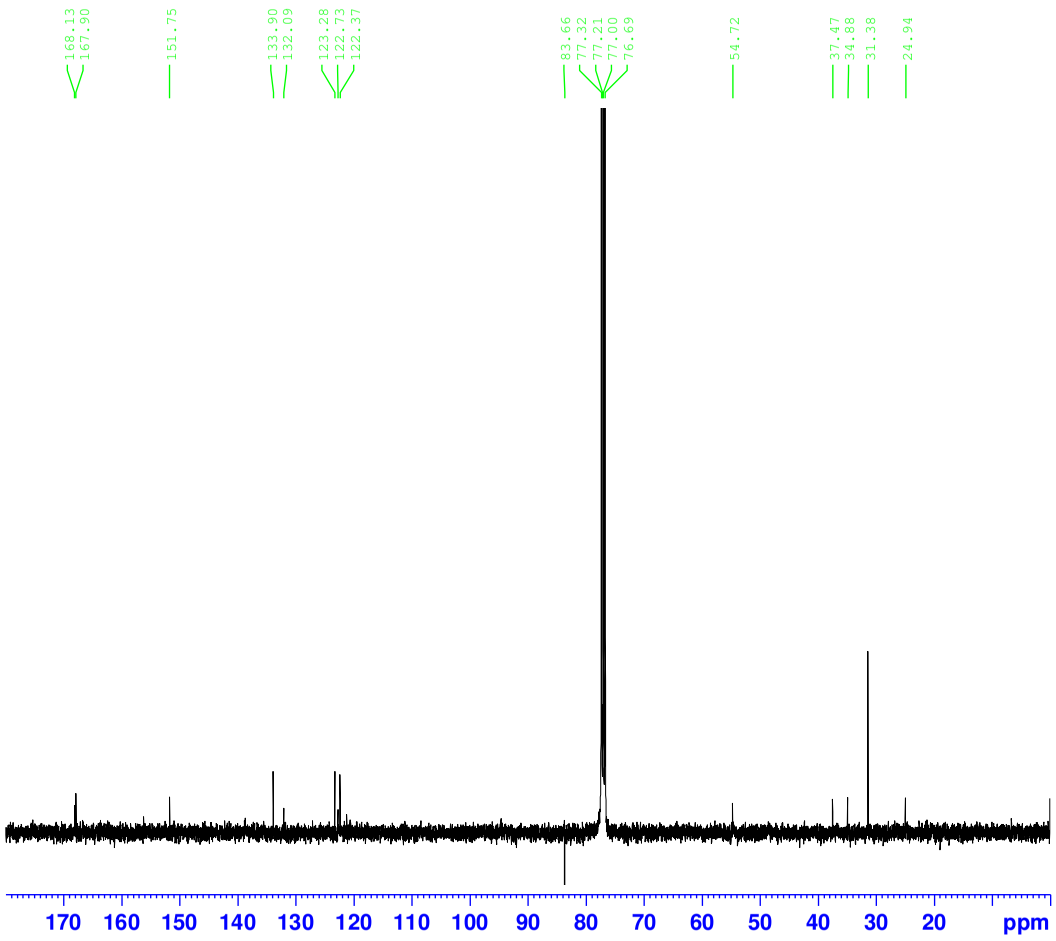
B Spectra of 3b

B.1 ^{1}H NMR spectrum of 3b



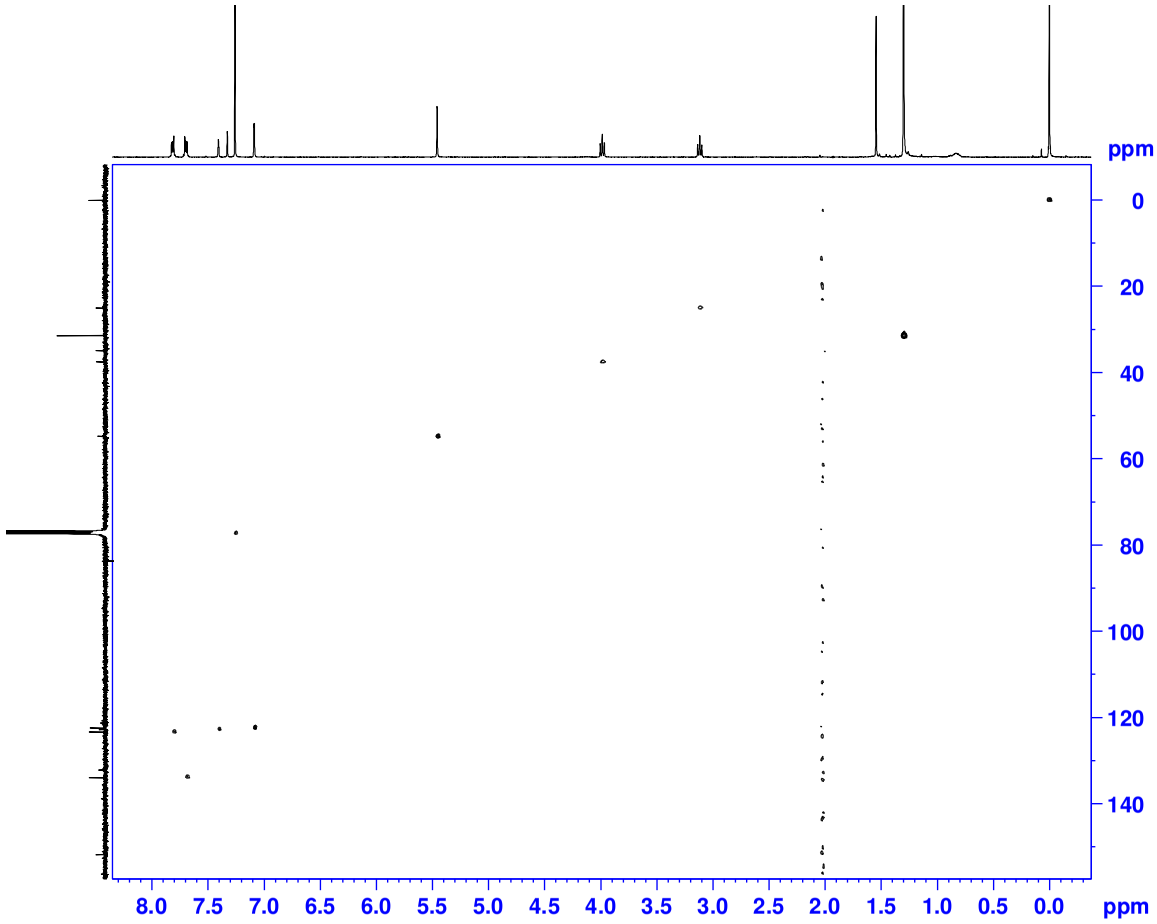

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                       6
PROCNO                      1

F2 - Acquisition Parameters
Date_              20150408
Time                  13.38
INSTRUM               spect
PROBHD   5 mm PADUL 13C
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9583745 sec
RG                    912.3
DW                 60.400 usec
DE                  6.00 usec
TE                  298.0 K
D1              1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                  10.50 usec
PL1                 -6.00 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                   32768
SF            400.1300079 MHz
WDW                     EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

B.2 ^{13}C NMRspectrum of 3b



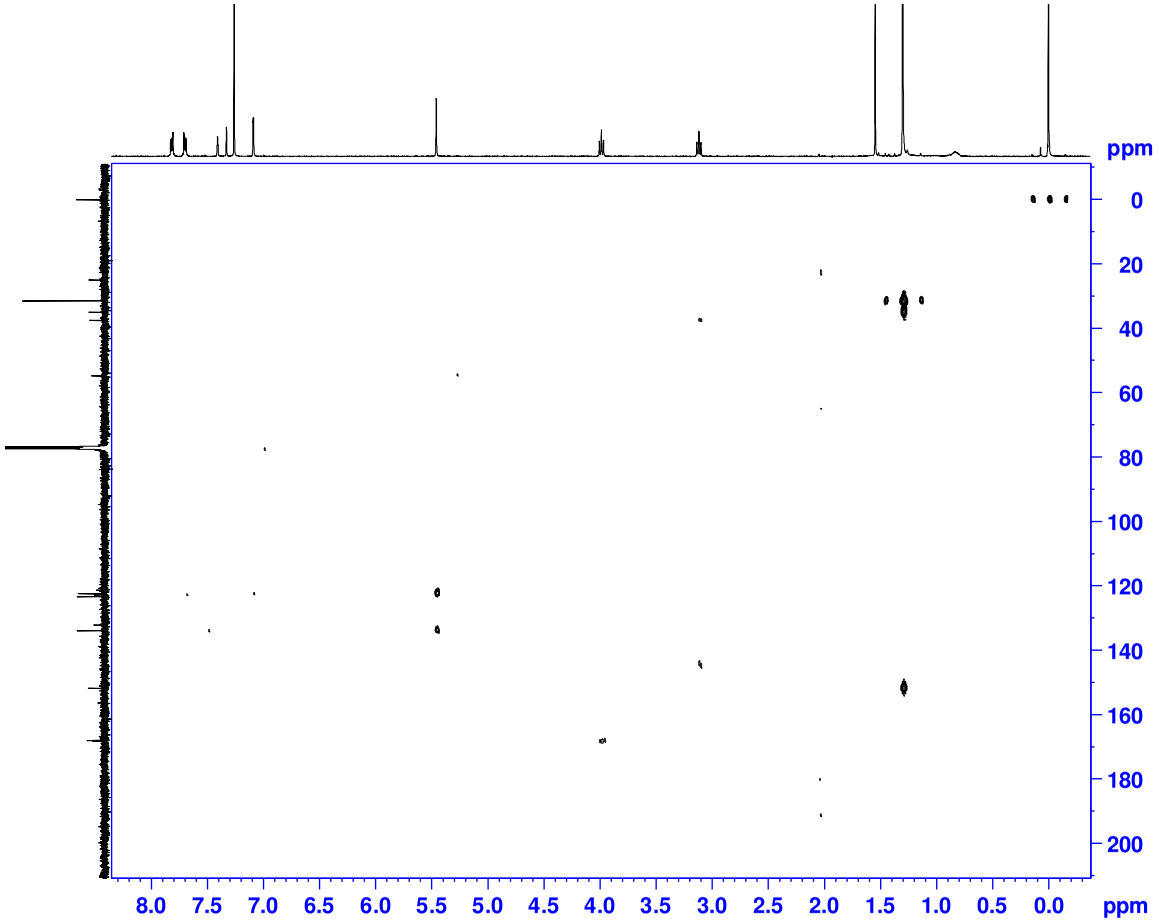

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                       7
PROCNO                      1

F2 - Acquisition Parameters
Date_            20150408
Time                18.52
INSTRUM             spect
PROBHD   5 mm PADUL 13C
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                   2048
DS                      4
SWH             23980.814 Hz
FIDRES          0.365918 Hz
AQ              1.3664256 sec
RG                   90.5
DW                20.850 usec
DE                 6.00 usec
TE                 298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   13C
P1                    6.50 usec
PL1                  -6.00 dB
SFO1         100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG[2           waltz16
NUC2                   1H
PCPD2                95.00 usec
PL2                  -6.00 dB
PL12                 13.13 dB
PL13                 18.50 dB
SFO2         400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF           100.6127690 MHz
WDW                      EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```

B.3 HSQC spectrum of 3b



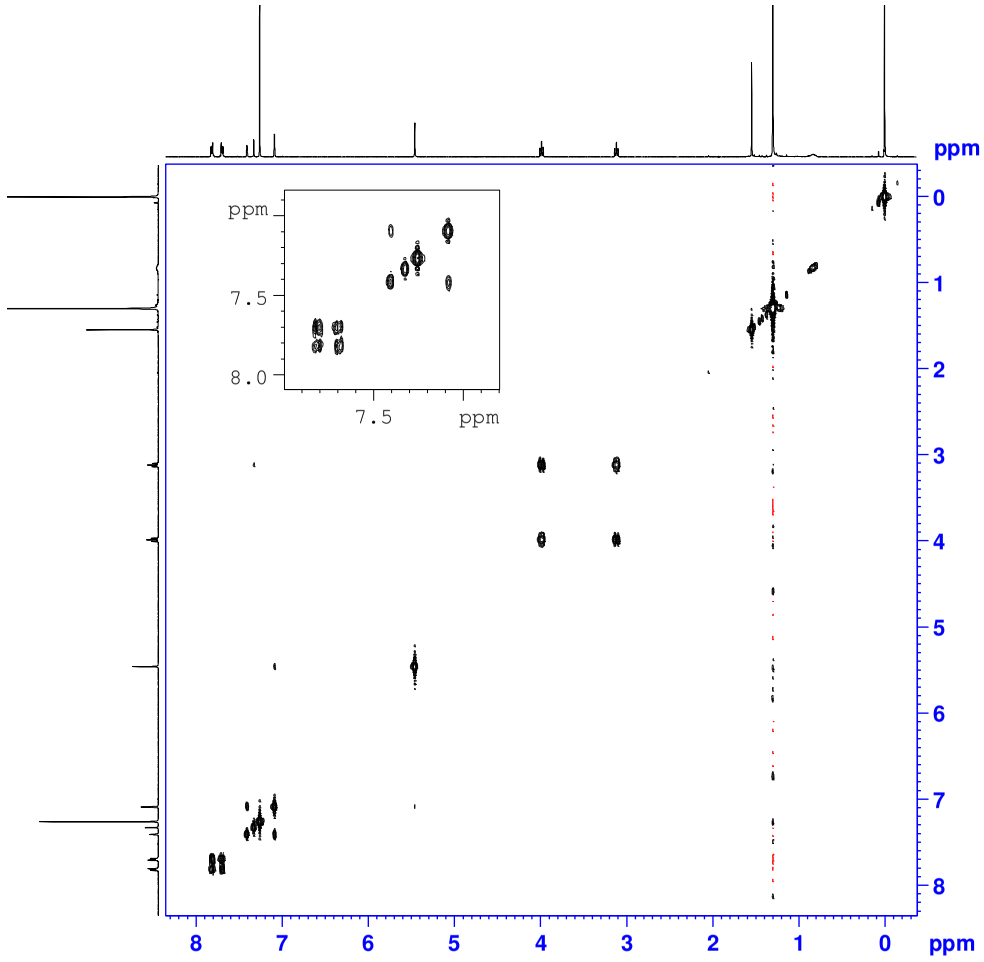

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                       9
PROCNO                      1

F2 - Acquisition Parameters
Date_              20150408
Time                 20.03
INSTRUM                spect
PROBHD    5 mm PADUL 13C
PULPROG          hsqcetgp
TD                   1024
SOLVENT               CDCl3
NS                       4
DS                      16
SWH               3491.620 Hz
FIDRES               3.409785 Hz
AQ                0.1466368 sec
RG                   18390.4
DW                  143.200 usec
DE                    6.00 usec
TE                  298.0 K
CNST2           145.0000000
d0               0.00000300 sec
D1               1.44941401 sec
d4               0.00172414 sec
d11              0.03000000 sec
d13              0.00000400 sec
D16              0.00015000 sec
DELTA            0.00167700 sec
DELTA1           0.00021614 sec
IN0              0.00003000 sec
STICNT                      0
ZGOPTNS

======== CHANNEL f1 ========
NUC1                      1H
P1                     10.50 usec
p2                     21.00 usec
P28                     2.00 usec
PL1                    -6.00 dB
SFO1           400.1316044 MHz

======== CHANNEL f2 ========
CPDPRG[2                garp
NUC2                      13C
P3                      6.80 usec
p4                     13.60 usec
PCPD2                  92.00 usec
PL2                    -6.00 dB
PL12                   16.63 dB
SFO2           100.6202727 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]          SINE.100
GPNAM[2]          SINE.100
GPZ1                  80.00 %
GPZ2                  20.10 %
P16                 1500.00 usec

F1 - Acquisition parameters
TD                       256
SFO1               100.6203 MHz
FIDRES            65.104164 Hz
SW                  165.639 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                      1024
SF              400.1300079 MHz
WDW                     QSINE
SSB                         2
LB          0 Hz
GB          0
PC                      1.40

F1 - Processing parameters
SI                      1024
MC2          echo-antiecho
SF               100.6127690 MHz
WDW                     QSINE
SSB                         2
LB          0 Hz
GB          0
```

B.4 HMBC spectrum of 3b



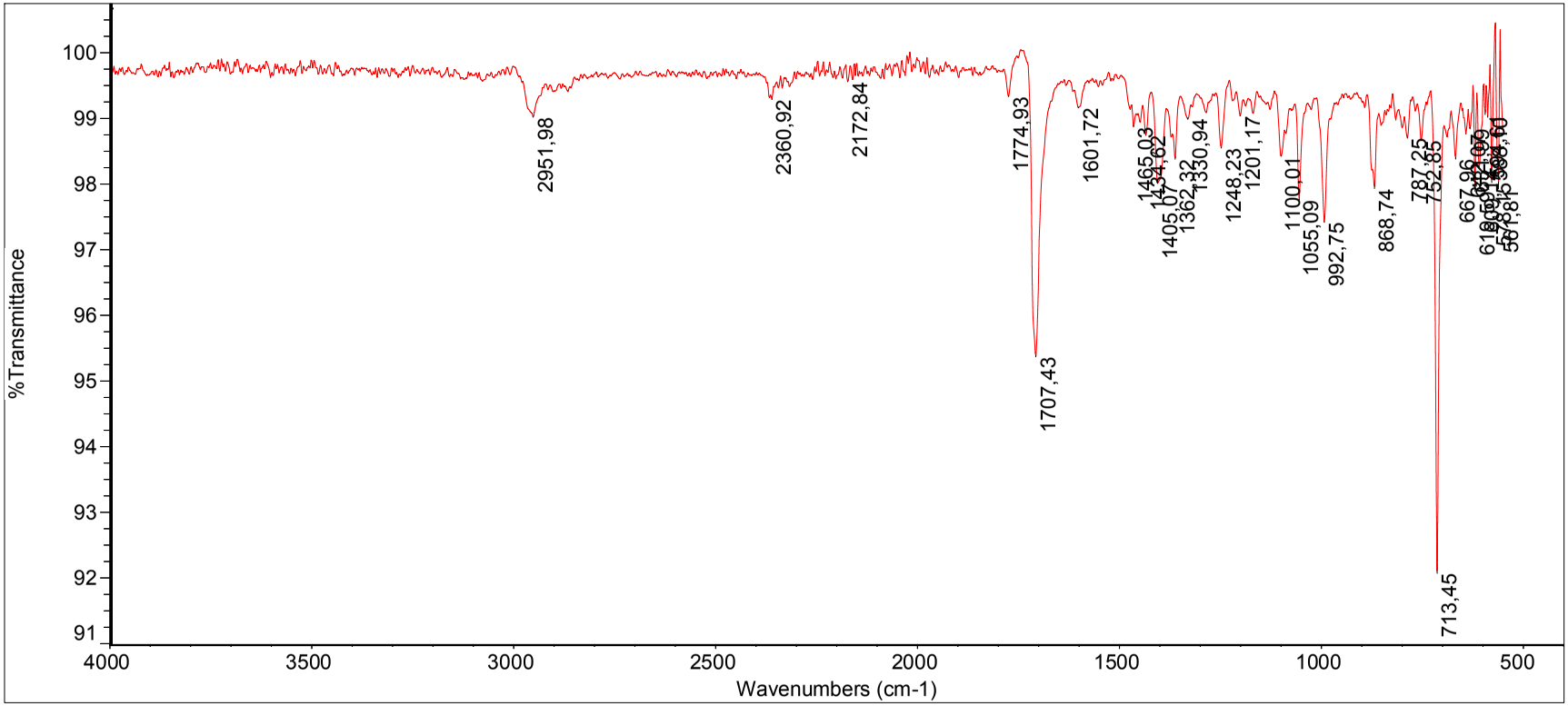

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                       8
PROCNO                      1

F2 - Acquisition Parameters
Date_           20150408
Time              18.55
INSTRUM           spect
PROBHD    5 mm PADUL 13C
PULPROG       hmbcgpndqf
TD                4096
SOLVENT           CDCl3
NS                  16
DS                  16
SWH            3491.620 Hz
FIDRES            0.852446 Hz
AQ             0.5865472 sec
RG                16384
DW              143.200 usec
DE                6.00 usec
TE              298.0 K
CNST13         8.0000000
d0             0.00000300 sec
D1             1.29765701 sec
d6             0.06250000 sec
D16            0.00015000 sec
IN0            0.00002240 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.50 usec
p2                 21.00 usec
PL1                -6.00 dB
SFO1         400.1316044 MHz

======== CHANNEL f2 ========
NUC2                 13C
P3                  6.80 usec
PL2                -6.00 dB
SFO2         100.6228138 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPNAM[3]         SINE.100
GPZ1                50.00 %
GPZ2                30.00 %
GPZ3                40.10 %
P16               1500.00 usec

F1 - Acquisition parameters
TD                   128
SFO1           100.6228 MHz
FIDRES         174.386154 Hz
SW               221.833 ppm
FnMODE                QF

F2 - Processing parameters
SI                  1024
SF           400.1300079 MHz
WDW                 SINE
SSB       0
LB        0 Hz
GB        0
PC                  1.40

F1 - Processing parameters
SI                  1024
MC2                   QF
SF           100.6127690 MHz
WDW                 SINE
SSB       0
LB        0 Hz
GB        0
```

B.5 COSY spectrum of 3b




```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      10
PROCNO                      1

F2 - Acquisition Parameters
Date_              20150408
Time                 20.32
INSTRUM              spect
PROBHD    5 mm PADUL 13C
PULPROG          cosygpqf
TD                   2048
SOLVENT              CDCl3
NS                       2
DS                       8
SWH               3491.620 Hz
FIDRES            1.704893 Hz
AQ                0.2932736 sec
RG                     512
DW                 143.200 usec
DE                   6.00 usec
TE                 298.0 K
d0              0.00000300 sec
D1              1.38572097 sec
d13             0.00004000 sec
D16             0.00015000 sec
IN0             0.00028640 sec

======== CHANNEL f1 ========
NUC1                   1H
P0                  10.50 usec
P1                  10.50 usec
PL1                 -6.00 dB
SFO1          400.1316044 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPZ1                10.00 %
P16               1500.00 usec

F1 - Acquisition parameters
TD                     128
SFO1              400.1316 MHz
FIDRES           27.278282 Hz
SW                   8.726 ppm
FnMODE                  QF

F2 - Processing parameters
SI                     1024
SF            400.1300079 MHz
WDW                    SINE
SSB         0
LB          0 Hz
GB          0
PC                     1.40

F1 - Processing parameters
SI                     1024
MC2                     QF
SF            400.1300079 MHz
WDW                    SINE
SSB         0
LB          0 Hz
GB          0
```

B.6 IR spectrum of 3b



B.7 MS spectrum of 3b

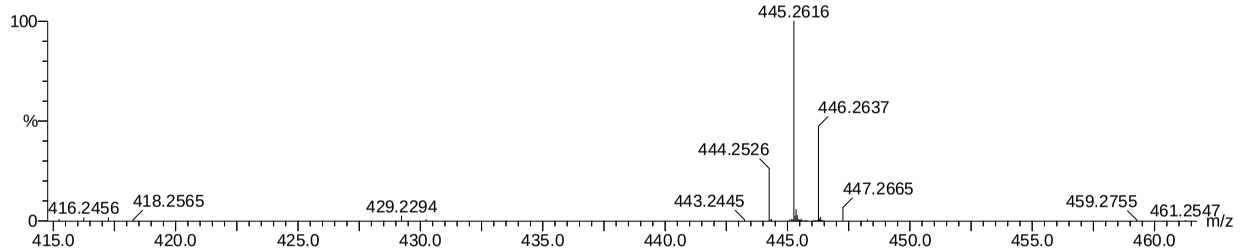
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
1581 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 N: 0-50 O: 0-100

NT-MSLAB-Operator-SVG
2015-202 275 (5.358) AM2 (Ar,35000.0,0.00,0.00); Cm (270:278)

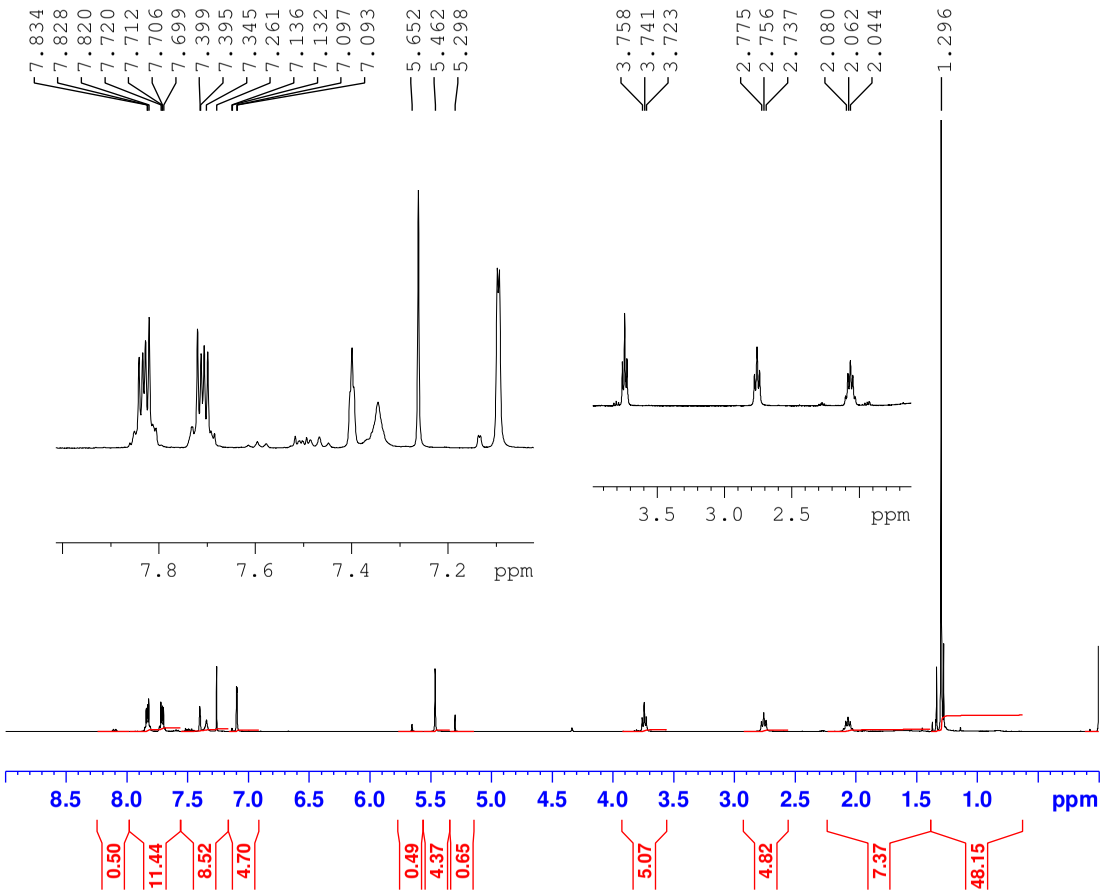
1: TOF MS ASAP+
1.18e+008



Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
444.2526	444.2525	0.1	0.2	14.0	675.1	0.374	68.80	C27 H32 N4 O2
	444.2530	-0.4	-0.9	7.0	676.5	1.816	16.26	C12 H28 N16 O3
	444.2517	0.9	2.0	2.0	676.6	1.901	14.94	C11 H32 N12 O7

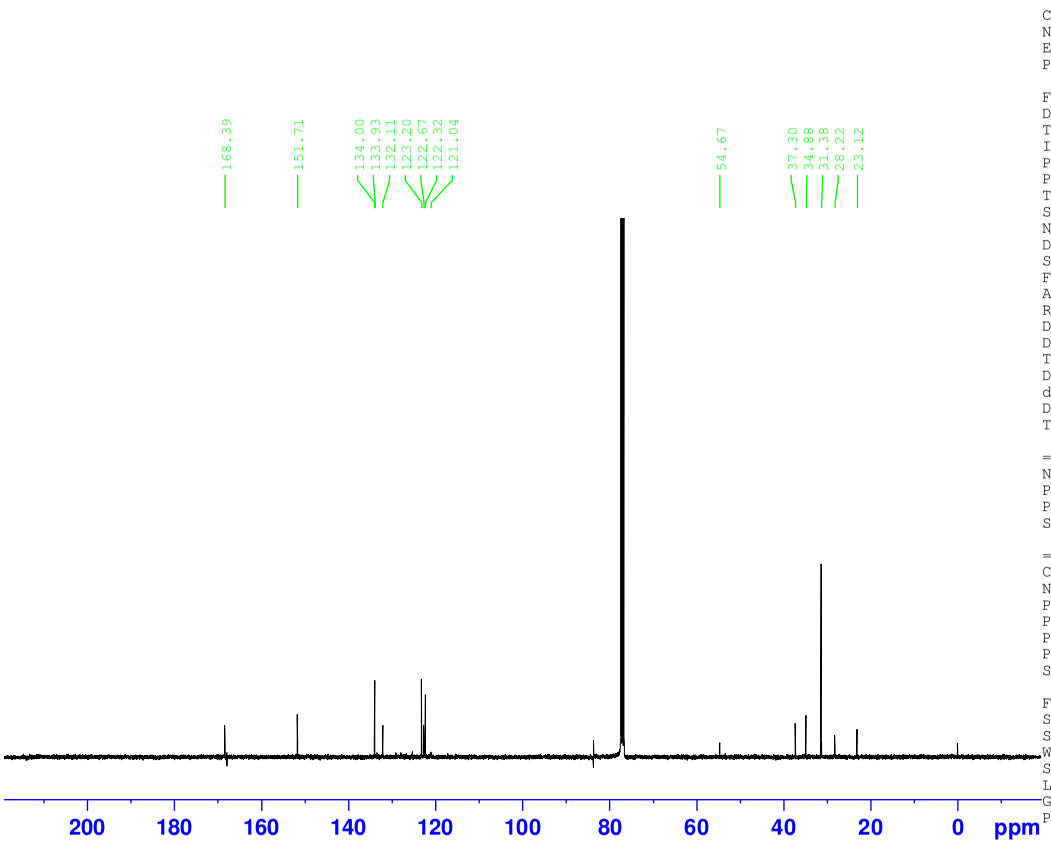
C Spectra of 3c

C.1 ^{1}H NMR spectrum of 3c



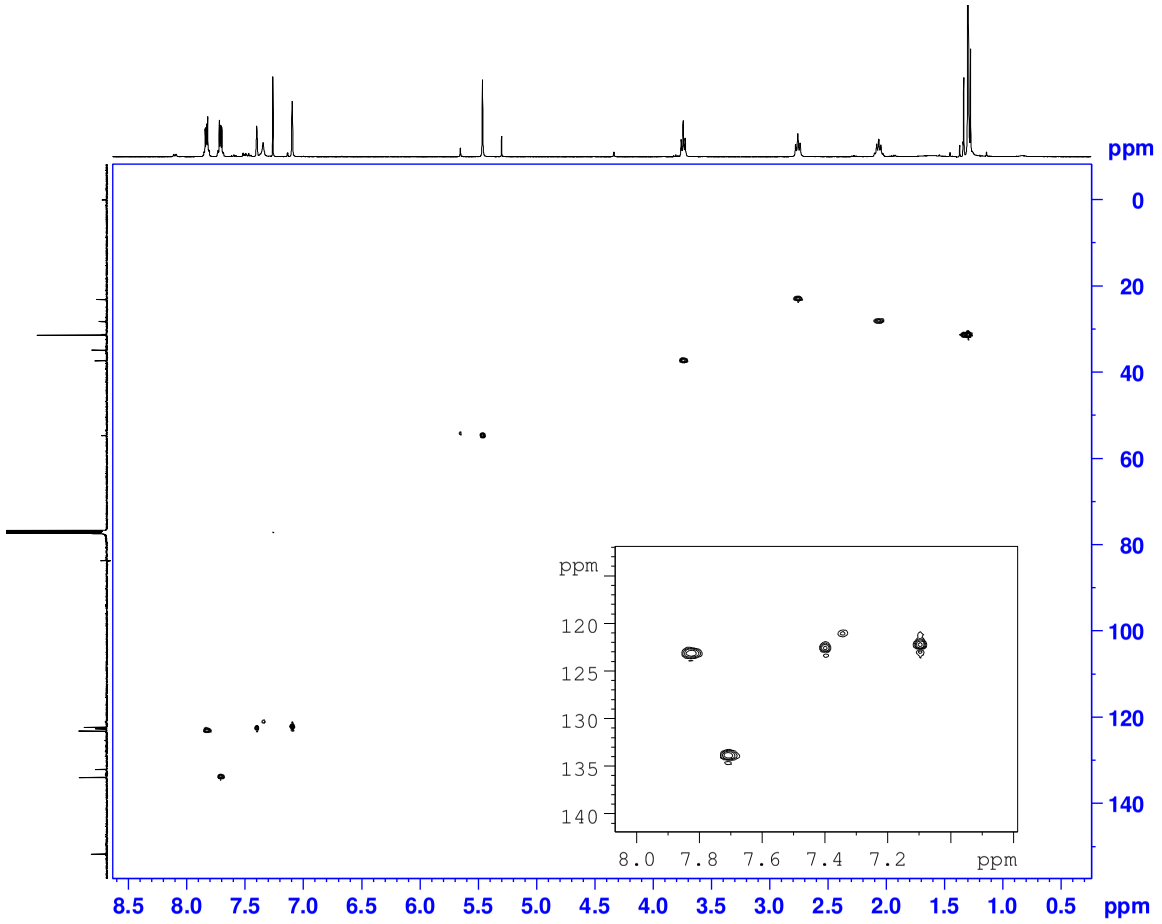

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      21
PROCNO                      1

F2 - Acquisition Parameters
Date_                20150409
Time                     0.57
INSTRUM                spect
PROBHD    5 mm PADUL 13C
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                 8278.146 Hz
FIDRES              0.126314 Hz
AQ                3.9583745 sec
RG                      456.1
DW                   60.400 usec
DE                    6.00 usec
TE                    298.0 K
D1               1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                    10.50 usec
PL1                   -6.00 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                     32768
SF             400.1300074 MHz
WDW                       EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

C.2 ^{13}C NMRspectrum of 3c



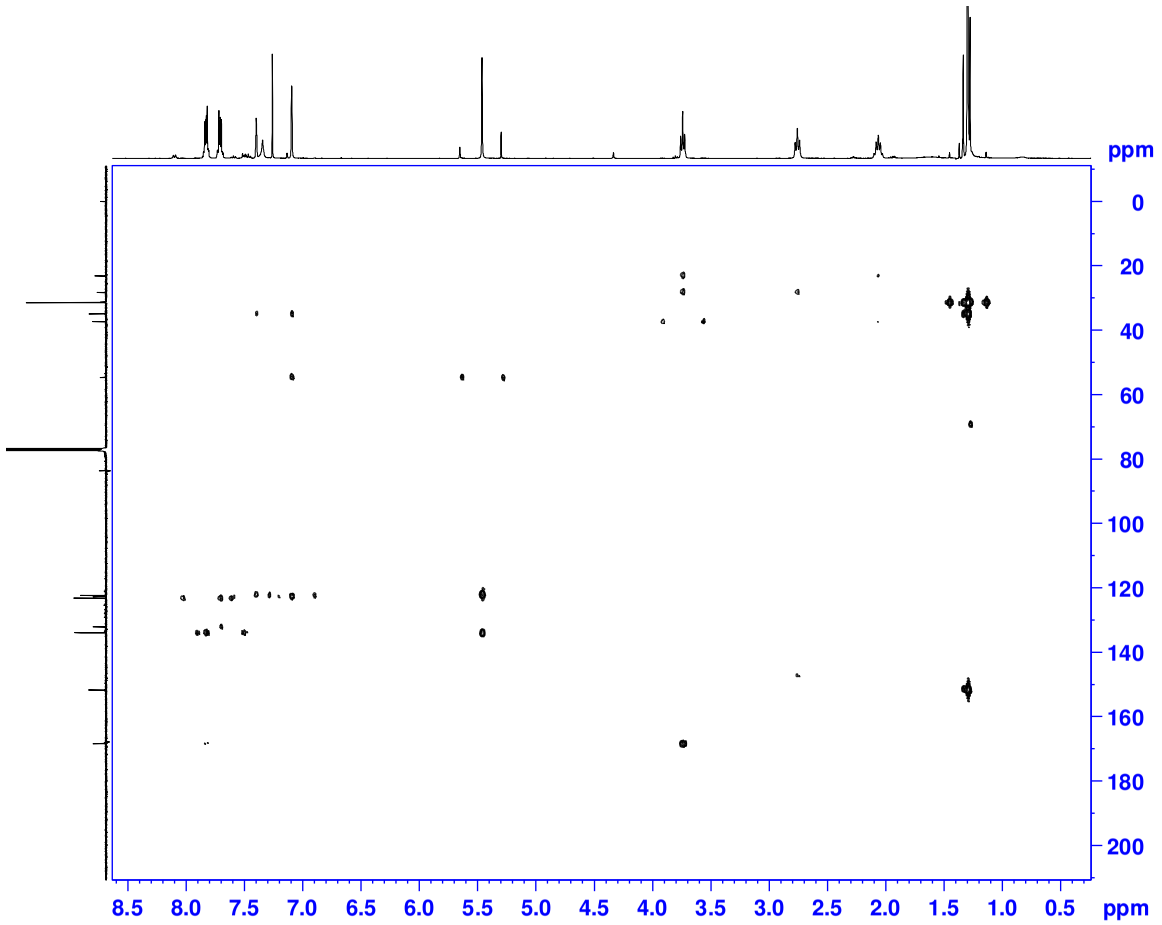

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      22
PROCNO                      1

F2 - Acquisition Parameters
Date_              20150409
Time                   2.57
INSTRUM               spect
PROBHD   5 mm PADUL 13C
PULPROG             zgpg30
TD                   65536
SOLVENT              CDC13
NS                    2048
DS                       4
SWH             23980.814 Hz
FIDRES           0.365918 Hz
AQ               1.3664256 sec
RG                     181
DW                20.850 usec
DE                 6.00 usec
TE                 298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
DELTA         1.89999998 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                   6.50 usec
PL1                 -6.00 dB
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG[2           waltz16
NUC2                  1H
PCPD2                95.00 usec
PL2                  -6.00 dB
PL12                 13.13 dB
PL13                 18.50 dB
SFO2          400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF            100.6127690 MHz
WDW                     EM
SSB       0
LB                    1.00 Hz
GB        0
PC                    1.40
```

C.3 HSQC spectrum of 3c



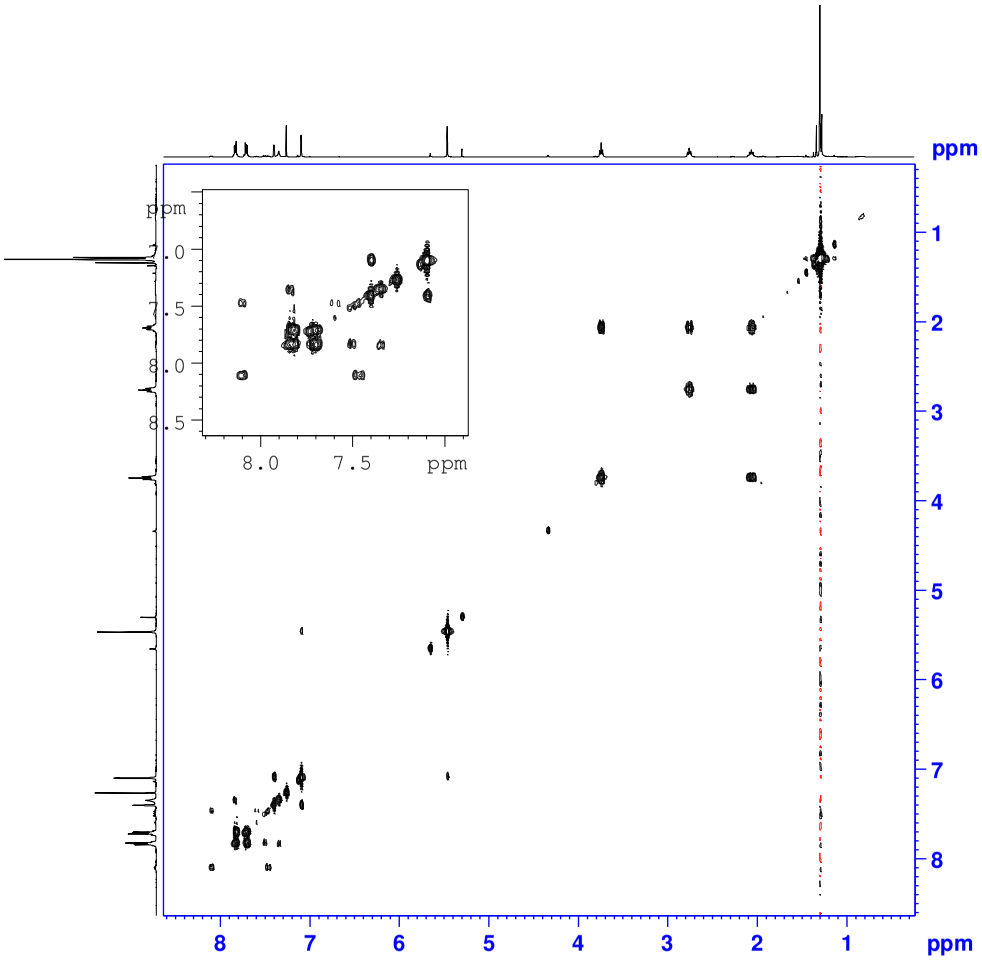

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      24
PROCNO                      1

F2 - Acquisition Parameters
Date_            20150409
Time                4.08
INSTRUM             spect
PROBHD   5 mm PADUL 13C
PULPROG          hsqcetgp
TD                  1024
SOLVENT              CDCl3
NS                      4
DS                     16
SWH              3360.215 Hz
FIDRES           3.281460 Hz
AQ              0.1523712 sec
RG                 18390.4
DW                148.800 usec
DE                  6.00 usec
TE                298.0 K
CNST2         145.0000000
d0             0.00000300 sec
D1             1.44326997 sec
d4             0.00172414 sec
d11            0.03000000 sec
d13            0.00000400 sec
D16            0.00015000 sec
DELTA          0.00167700 sec
DELTA1         0.00021614 sec
IN0            0.00003000 sec
STSCNT                  0
ZGOPTNS

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.50 usec
p2                  21.00 usec
P28                  2.00 usec
PL1                 -6.00 dB
SFO1         400.1317829 MHz

======== CHANNEL f2 ========
CPDPRG[2               garp
NUC2                    13C
P3                   6.80 usec
p4                  13.60 usec
PCPD2               92.00 usec
PL2                 -6.00 dB
PL12                16.63 dB
SFO2         100.6202727 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPZ1                80.00 %
GPZ2                20.10 %
P16               1500.00 usec

F1 - Acquisition parameters
TD                     256
SFO1          100.6203 MHz
FIDRES        65.104164 Hz
SW              165.639 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                    1024
SF           400.1300074 MHz
WDW                  QSINE
SSB                      2
LB         0 Hz
GB         0
PC                    1.40

F1 - Processing parameters
SI                    1024
MC2        echo-antiecho
SF            100.6127690 MHz
WDW                  QSINE
SSB                      2
LB         0 Hz
GB         0
```

C.4 HMBC spectrum of 3c



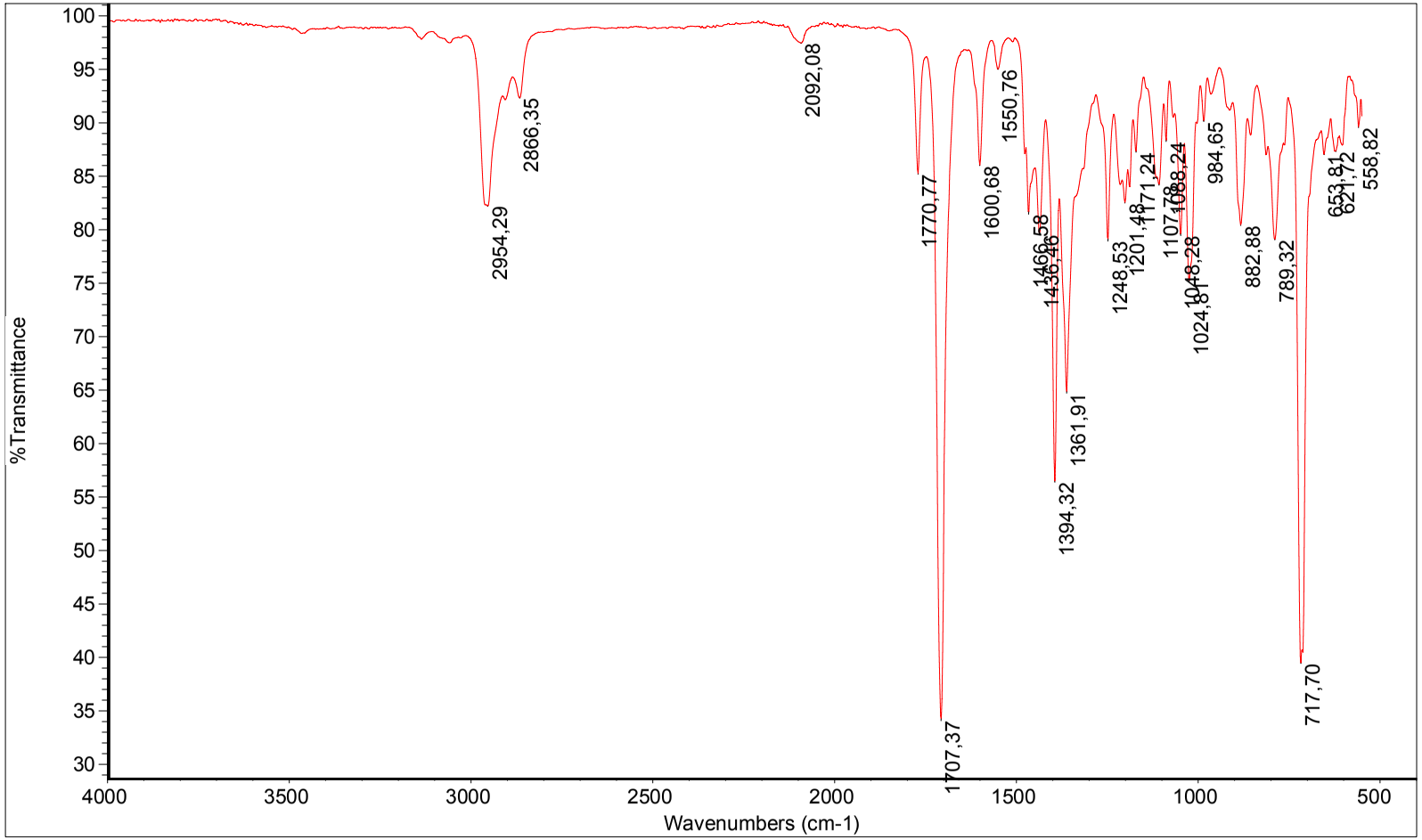

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      23
PROCNO                      1

F2 - Acquisition Parameters
Date_                20150409
Time                     3.00
INSTRUM                 spect
PROBHD    5 mm PADUL 13C
PULPROG       hmbcgpndqf
TD                       4096
SOLVENT               CDC13
NS                         16
DS                         16
SWH                3360.215 Hz
FIDRES            0.820365 Hz
AQ                0.6094848 sec
RG                   23170.5
DW                   148.800 usec
DE                      6.00 usec
TE                     298.0 K
CNST13            8.0000000
d0                0.00000300 sec
D1                1.27308202 sec
d6                0.06250000 sec
D16               0.00015000 sec
IN0               0.00002240 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      10.50 usec
p2                      21.00 usec
PL1                     -6.00 dB
SFO1           400.1317829 MHz

======== CHANNEL f2 ========
NUC2                      13C
P3                       6.80 usec
PL2                     -6.00 dB
SFO2           100.6228138 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]          SINE.100
GPNAM[2]          SINE.100
GPNAM[3]          SINE.100
GPZ1                 50.00 %
GPZ2                 30.00 %
GPZ3                 40.10 %
P16                1500.00 usec

F1 - Acquisition parameters
TD                       128
SFO1              100.6228 MHz
FIDRES           174.386154 Hz
SW                   221.833 ppm
FnMODE                    QF

F2 - Processing parameters
SI                       1024
SF             400.1300074 MHz
WDW                      SINE
SSB          0
LB           0 Hz
GB           0
PC                       1.40

F1 - Processing parameters
SI                       1024
MC2                       QF
SF             100.6127690 MHz
WDW                      SINE
SSB          0
LB           0 Hz
GB           0
```

C.5 COSY spectrum of 3c




```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      25
PROCNO                      1

F2 - Acquisition Parameters
Date_              20150409
Time                   4.37
INSTRUM               spect
PROBHD   5 mm PADUL 13C
PULPROG           cosygpqf
TD                    2048
SOLVENT               CDC13
NS                        2
DS                        8
SWH               3360.215 Hz
FIDRES            1.640730 Hz
AQ                0.3047424 sec
RG                    203.2
DW                  148.800 usec
DE                    6.00 usec
TE                  298.0 K
d0                0.00000300 sec
D1                1.37343299 sec
d13               0.00000400 sec
D16               0.00015000 sec
IN0               0.00029760 sec

======== CHANNEL f1 ========
NUC1                      1H
P0                    10.50 usec
P1                    10.50 usec
PL1                   -6.00 dB
SFO1          400.1317829 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]          SINE.100
GPZ1                 10.00 %
P16                1500.00 usec

F1 - Acquisition parameters
TD                      128
SFO1              400.1318 MHz
FIDRES           26.251680 Hz
SW                    8.398 ppm
FnMODE                   QF

F2 - Processing parameters
SI                      1024
SF              400.1300074 MHz
WDW                     SINE
SSB       0
LB        0 Hz
GB        0
PC                      1.40

F1 - Processing parameters
SI                      1024
MC2                      QF
SF              400.1300074 MHz
WDW                     SINE
SSB       0
LB        0 Hz
GB        0
```

C.6 IR spectrum of 3c



C.7 MS spectrum of 3c

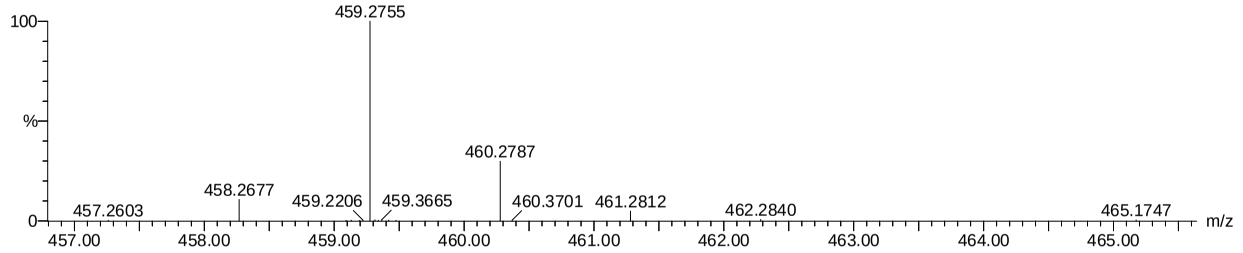
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
1713 formula(e) evaluated with 4 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 N: 0-50 O: 0-100

NT-MSLAB-Operator-SVG
2015-203 120 (2.342) AM2 (Ar,35000.0,0.00,0.00); Cm (115:161)

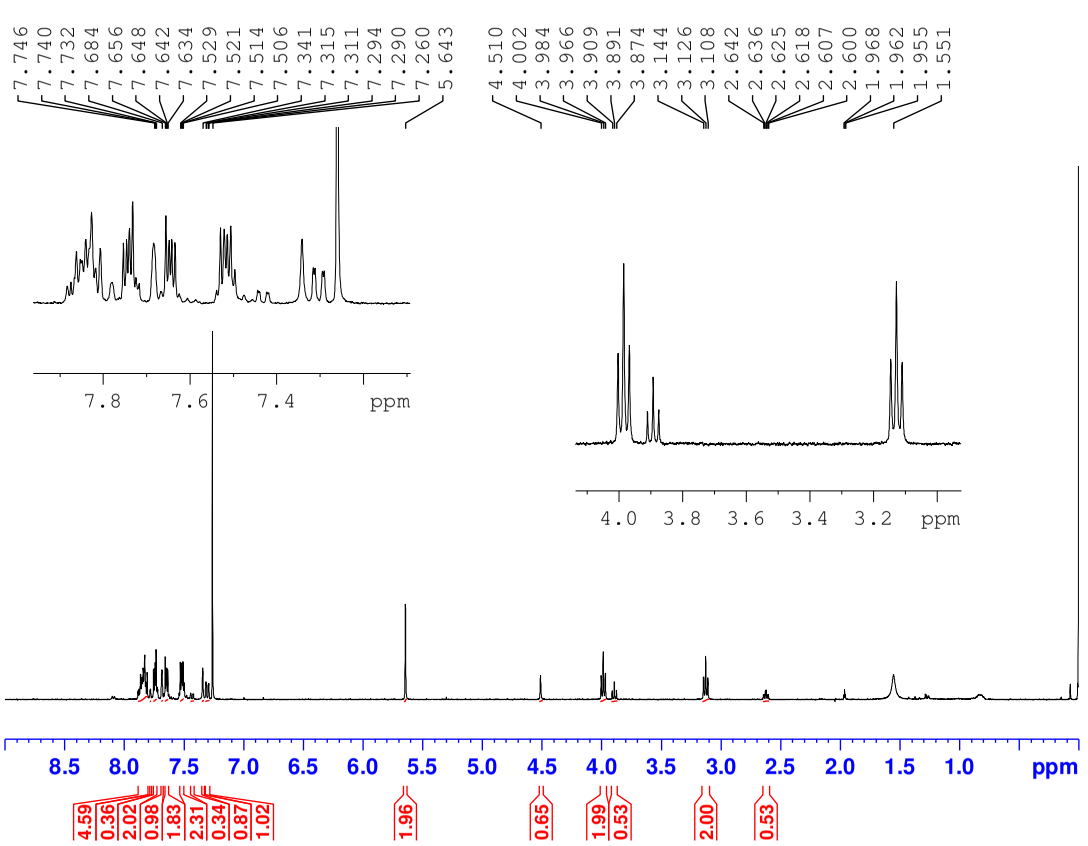
1: TOF MS ASAP+
1.57e+006



Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
458.2677	458.2682	-0.5	-1.1	14.0	216.8	0.753	47.11	C28 H34 N4 O2
	458.2668	0.9	2.0	9.0	217.1	1.074	34.18	C27 H38 O6
	458.2687	-1.0	-2.2	7.0	218.4	2.335	9.68	C13 H30 N16 O3
	458.2673	0.4	0.9	2.0	218.5	2.404	9.04	C12 H34 N12 O7

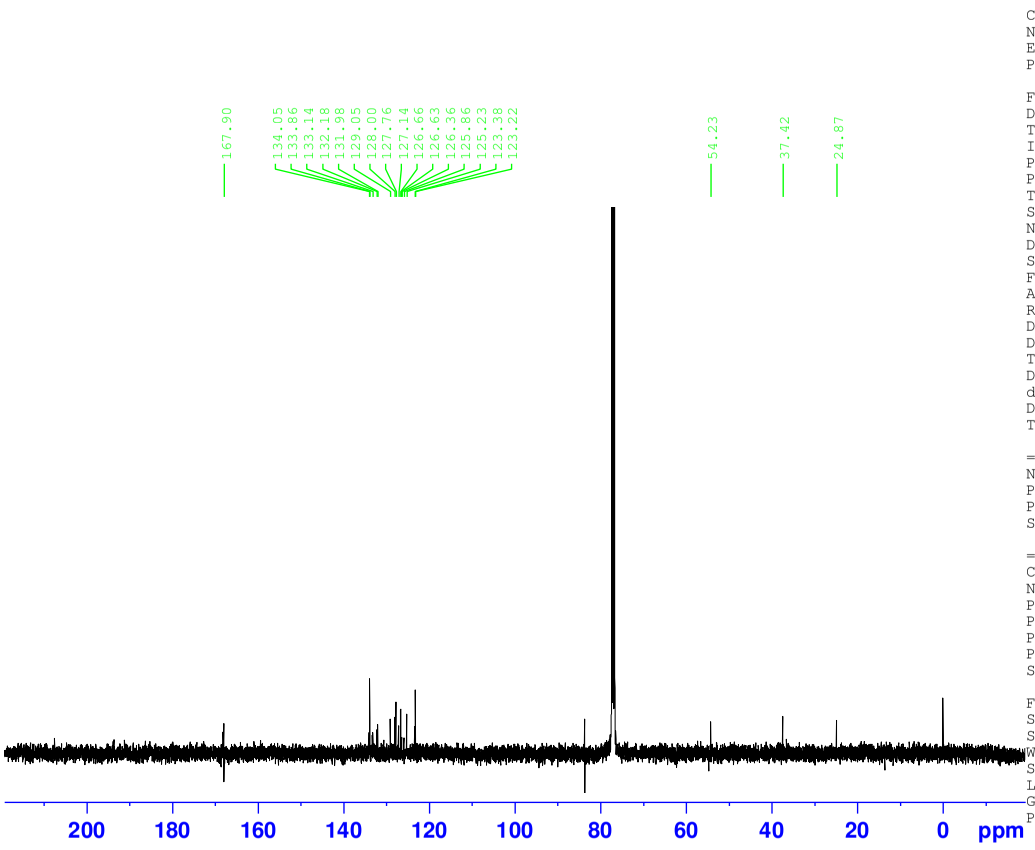
D Spectra of 3d

D.1 ^{1}H NMR spectrum of 3d



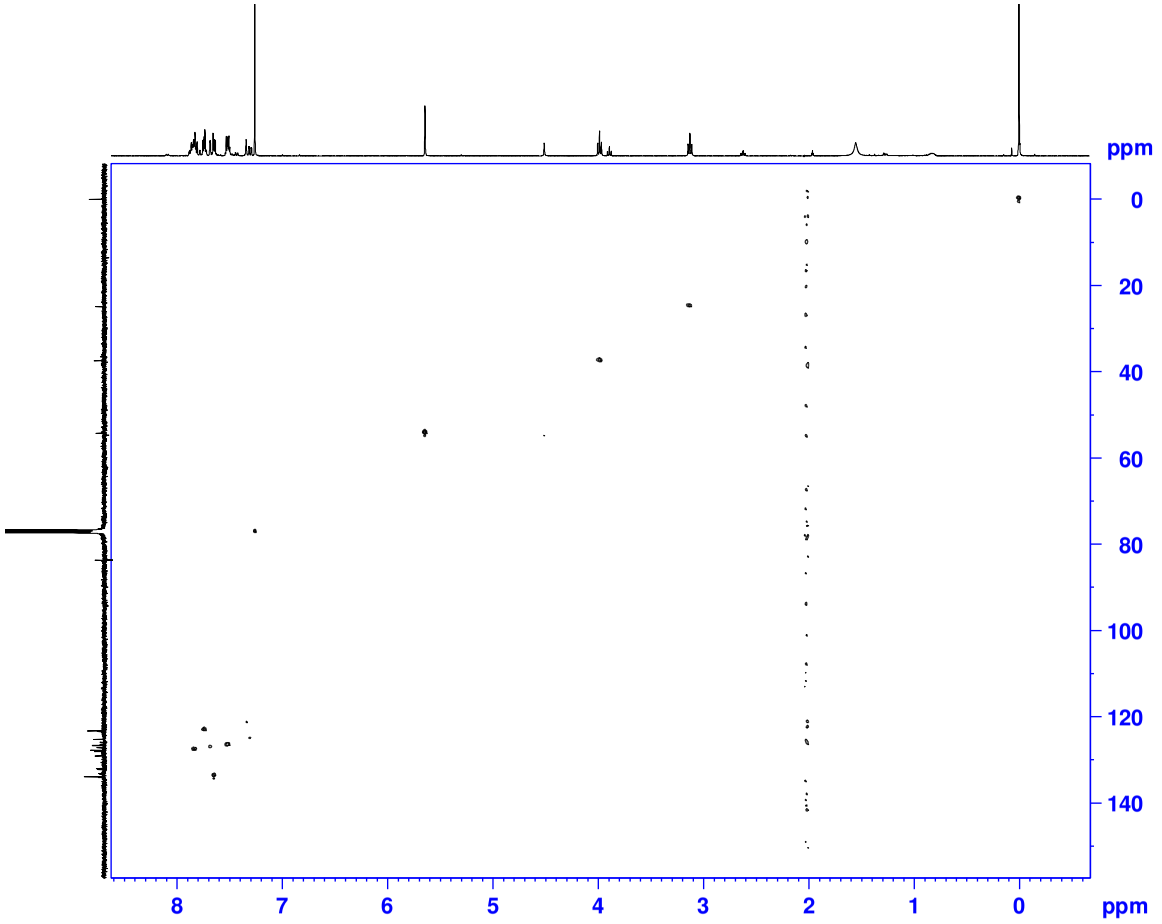

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                  16
PROCNO                  1

F2 - Acquisition Parameters
Date_           20150408
Time               21.05
INSTRUM            spect
PROBHD    5 mm PADUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9583745 sec
RG                 912.3
DW                60.400 usec
DE                 6.00 usec
TE                298.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                   1H
P1                 10.50 usec
PL1                -6.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300080 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

D.2 ^{13}C NMRspectrum of 3d



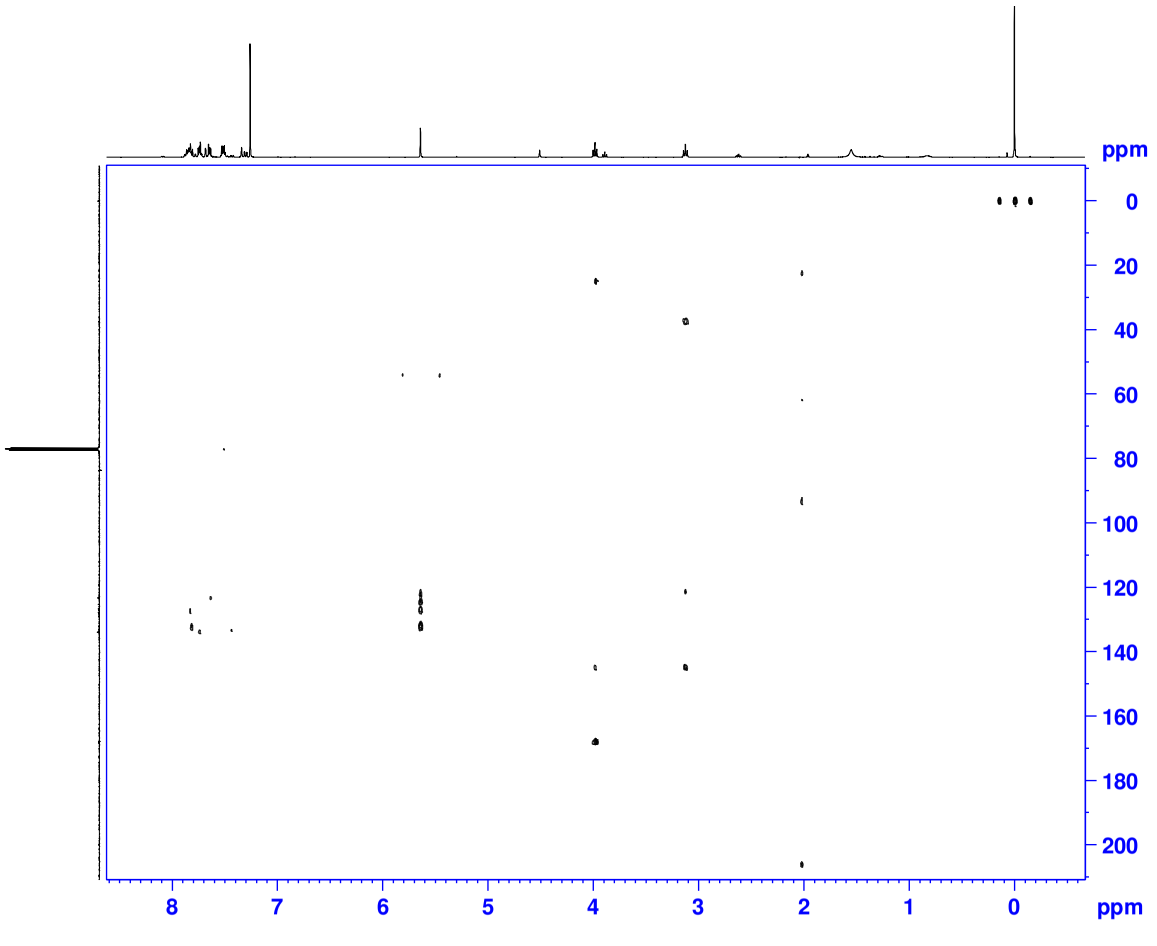

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      17
PROCNO                      1

F2 - Acquisition Parameters
Date_              20150408
Time                  23.04
INSTRUM               spect
PROBHD   5 mm PADUL 13C
PULPROG             zgpg30
TD                   65536
SOLVENT              CDC13
NS                    2048
DS                       4
SWH              23980.814 Hz
FIDRES            0.365918 Hz
AQ                1.3664256 sec
RG                    101.6
DW                   20.850 usec
DE                    6.00 usec
TE                   298.0 K
D1               2.00000000 sec
d11              0.03000000 sec
DELTA            1.89999998 sec
TD0                         1

======== CHANNEL f1 ========
NUC1                    13C
P1                     6.50 usec
PL1                   -6.00 dB
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG[2             waltz16
NUC2                    1H
PCPD2                 95.00 usec
PL2                   -6.00 dB
PL12                  13.13 dB
PL13                  18.50 dB
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                     32768
SF             100.6127690 MHz
WDW                       EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

D.3 HSQC spectrum of 3d



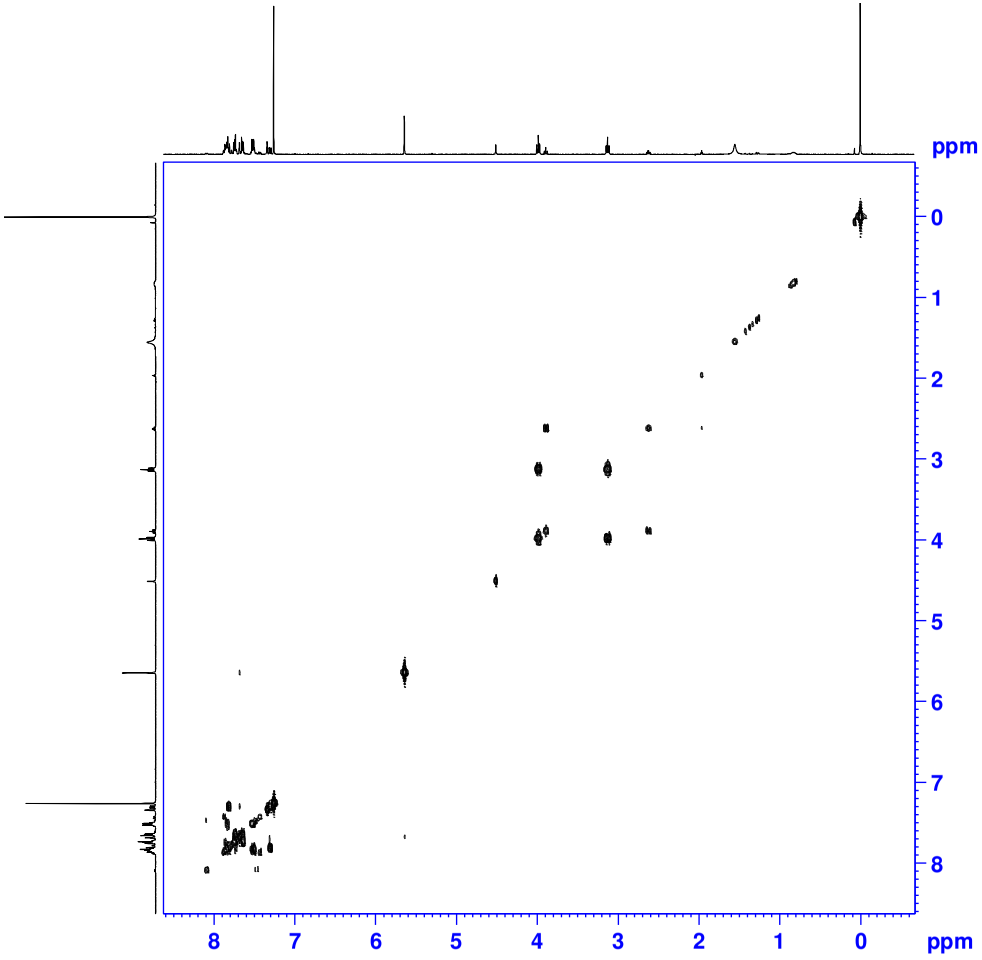

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      19
PROCNO                      1

F2 - Acquisition Parameters
Date_               20150409
Time                    0.16
INSTRUM                spect
PROBHD   5 mm PADUL 13C
PULPROG             hsqcetgp
TD                      1024
SOLVENT                CDCl3
NS                         4
DS                        16
SWH                3720.238 Hz
FIDRES             3.633045 Hz
AQ                0.1376256 sec
RG                   18390.4
DW                  134.400 usec
DE                    6.00 usec
TE                    298.0 K
CNST2             145.0000000
d0                 0.00000300 sec
D1                 1.45862997 sec
d4                 0.00172414 sec
d11                0.03000000 sec
d13                0.00000400 sec
D16                0.00015000 sec
DELTA              0.00167700 sec
DELTA1             0.00021614 sec
IN0                0.00003000 sec
STSCNT                     0
ZGOPTNS

======== CHANNEL f1 ========
NUC1                       1H
P1                      10.50 usec
p2                      21.00 usec
P28                      2.00 usec
PL1                     -6.00 dB
SFO1             400.1315994 MHz

======== CHANNEL f2 ========
CPDPRG[2                 garp
NUC2                      13C
P3                       6.80 usec
p4                      13.60 usec
PCPD2                   92.00 usec
PL2                     -6.00 dB
PL12                    16.63 dB
SFO2             100.6202727 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]             SINE.100
GPNAM[2]             SINE.100
GPZ1                    80.00 %
GPZ2                    20.10 %
P16                   1500.00 usec

F1 - Acquisition parameters
TD                         256
SFO1             100.6203 MHz
FIDRES            65.104164 Hz
SW                   165.639 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                        1024
SF               400.1300080 MHz
WDW                      QSINE
SSB                          2
LB          0 Hz
GB          0
PC                       1.40

F1 - Processing parameters
SI                        1024
MC2          echo-antiecho
SF               100.6127690 MHz
WDW                      QSINE
SSB                          2
LB          0 Hz
GB          0
```

D.4 HMBC spectrum of 3d



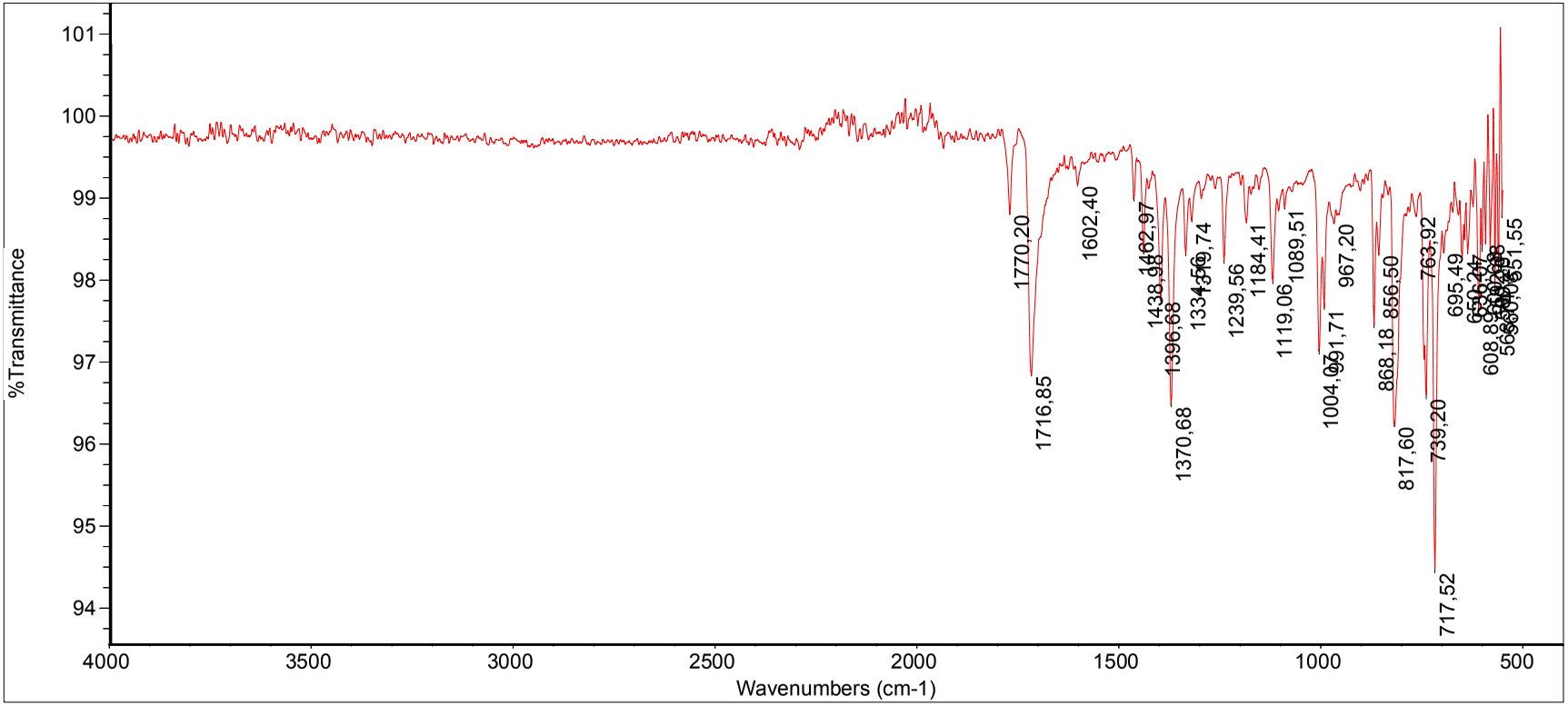

```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      18
PROCNO                      1

F2 - Acquisition Parameters
Date_            20150408
Time                23.07
INSTRUM             spect
PROBHD    5 mm PADUL 13C
PULPROG       hmbcgpndqf
TD                  4096
SOLVENT             CDCl3
NS                    16
DS                    16
SWH              3720.238 Hz
FIDRES           0.908261 Hz
AQ               0.5505024 sec
RG                   26008
DW                134.400 usec
DE                  6.00 usec
TE                 298.0 K
CNST13          8.0000000
d0              0.00000300 sec
D1              1.33452201 sec
d6              0.06250000 sec
D16             0.00015000 sec
IN0             0.00002240 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.50 usec
p2                  21.00 usec
PL1                 -6.00 dB
SFO1          400.1315994 MHz

======== CHANNEL f2 ========
NUC2                  13C
P3                   6.80 usec
PL2                 -6.00 dB
SFO2          100.6228138 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPNAM[3]         SINE.100
GPZ1                50.00 %
GPZ2                30.00 %
GPZ3                40.10 %
P16               1500.00 usec

F1 - Acquisition parameters
TD                   128
SFO1            100.6228 MHz
FIDRES         174.386154 Hz
SW                221.833 ppm
FnMODE                QF

F2 - Processing parameters
SI                   1024
SF            400.1300080 MHz
WDW                  SINE
SSB       0
LB        0 Hz
GB        0
PC                   1.40

F1 - Processing parameters
SI                   1024
MC2                    QF
SF            100.6127690 MHz
WDW                  SINE
SSB       0
LB        0 Hz
GB        0
```

D.5 COSY spectrum of 3d




```
Current Data Parameters
NAME      Apr08-2015-olekudsk
EXPNO                      20
PROCNO                      1

F2 - Acquisition Parameters
Date_               20150409
Time                    0.45
INSTRUM                spect
PROBHD    5 mm PADUL 13C
PULPROG             cosygpqf
TD                      2048
SOLVENT                CDCl3
NS                         2
DS                         8
SWH                 3720.238 Hz
FIDRES              1.816522 Hz
AQ                  0.2752512 sec
RG                      574.7
DW                    134.400 usec
DE                      6.00 usec
TE                    298.0 K
d0                  0.00000300 sec
D1                  1.40415299 sec
d13                 0.00000400 sec
D16                 0.00015000 sec
IN0                 0.00026880 sec

======== CHANNEL f1 ========
NUC1                       1H
P0                      10.50 usec
P1                      10.50 usec
PL1                     -6.00 dB
SFO1               400.1315994 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]             SINE.100
GPZ1                    10.00 %
P16                   1500.00 usec

F1 - Acquisition parameters
TD                         128
SFO1                400.1316 MHz
FIDRES             29.064360 Hz
SW                      9.298 ppm
FnMODE                     QF

F2 - Processing parameters
SI                        1024
SF                  400.1300080 MHz
WDW                       SINE
SSB       0
LB        0 Hz
GB        0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2                        QF
SF                  400.1300080 MHz
WDW                       SINE
SSB       0
LB        0 Hz
GB        0
```

D.6 IR spectrum of 3d



D.7 MS spectrum of 3d

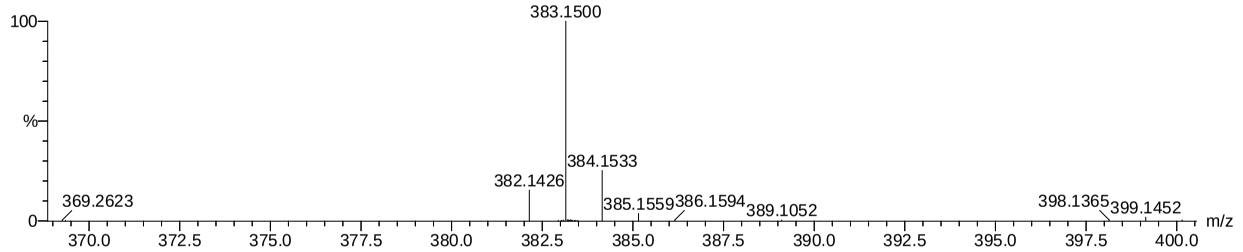
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
1062 formula(e) evaluated with 5 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 N: 0-50 O: 0-100

NT-MSLAB-Operator-SVG
2015-204 166 (3.239) AM2 (Ar,35000.0,0.00,0.00); Cm (163:171)

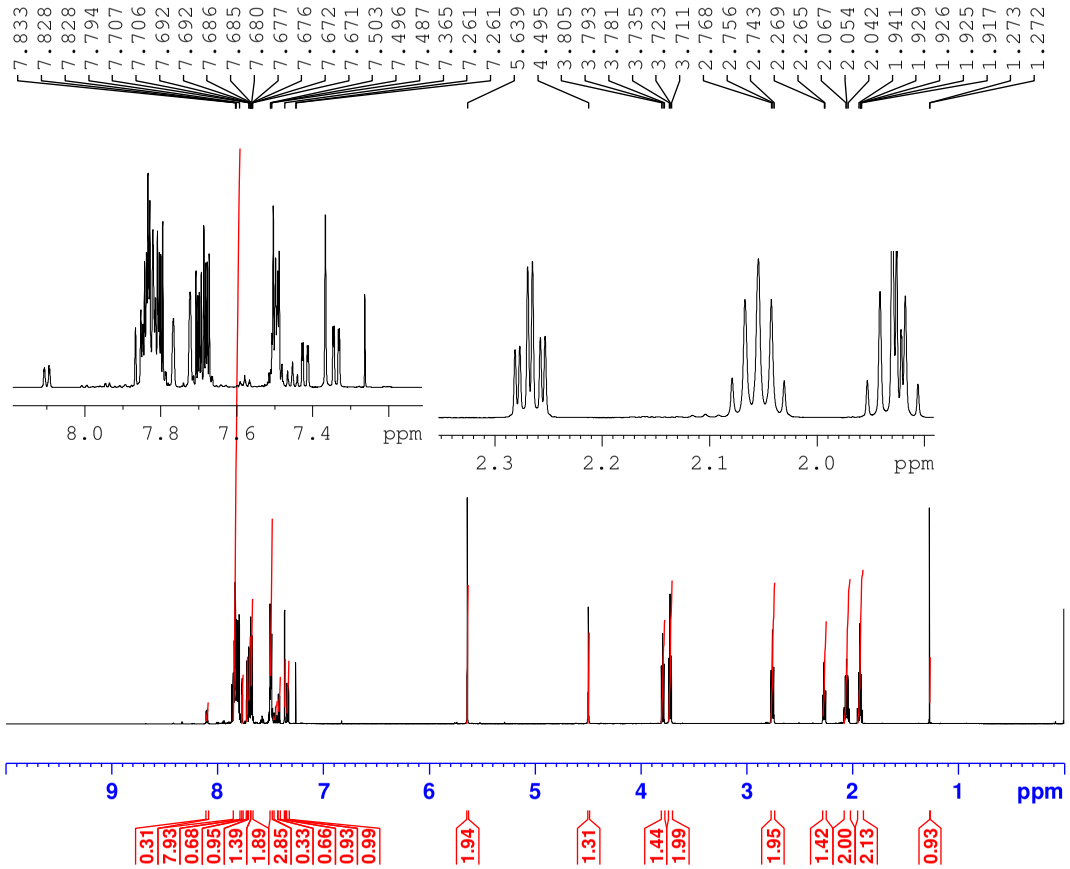
1: TOF MS ASAP+
2.44e+005



Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
382.1426	382.1430	-0.4	-1.0	17.0	213.6	0.915	40.07	C23 H18 N4 O2
	382.1421	0.5	1.3	5.0	215.5	2.880	5.61	C7 H18 N12 O7
	382.1435	-0.9	-2.4	10.0	215.6	2.938	5.30	C8 H14 N16 O3
	382.1435	-0.9	-2.4	-1.0	214.2	1.576	20.68	C10 H26 N2 O13
	382.1416	1.0	2.6	12.0	213.9	1.261	28.34	C22 H22 O6

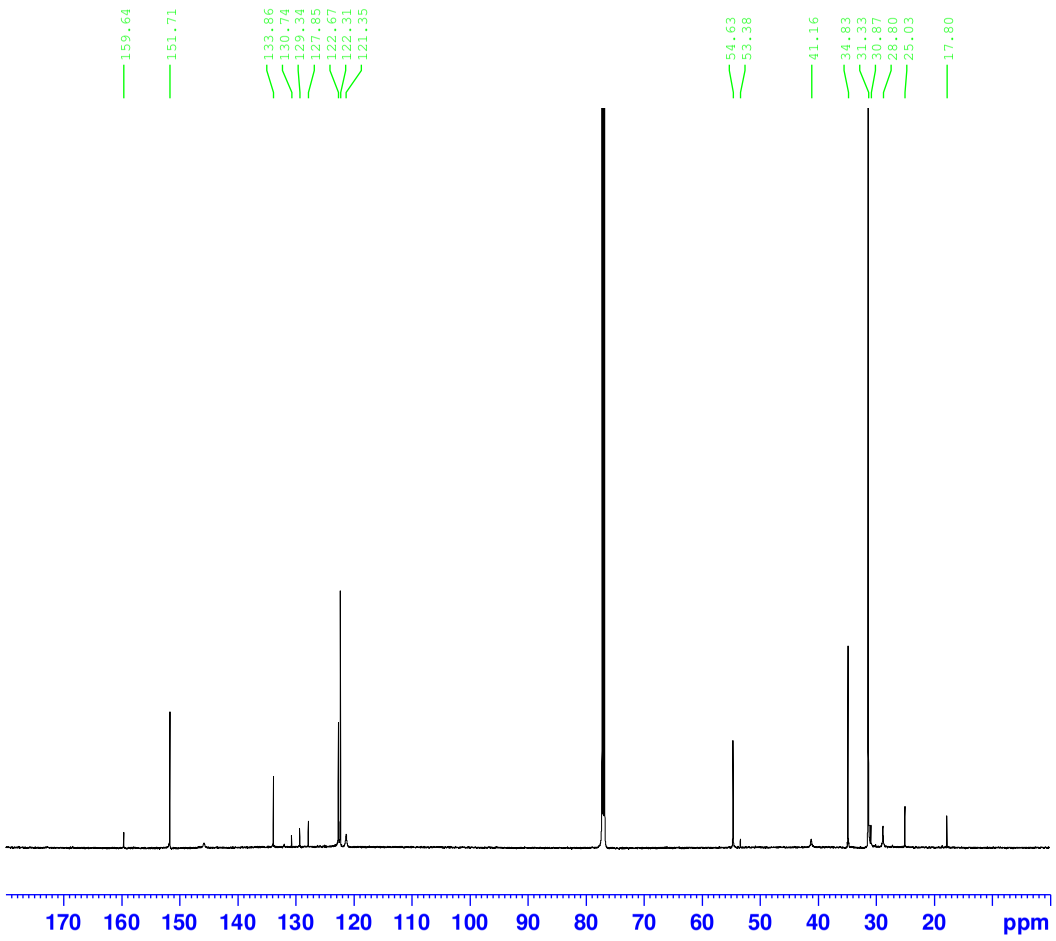
E Spectra of 3e

E.1 ^{1}H NMR spectrum of 3e



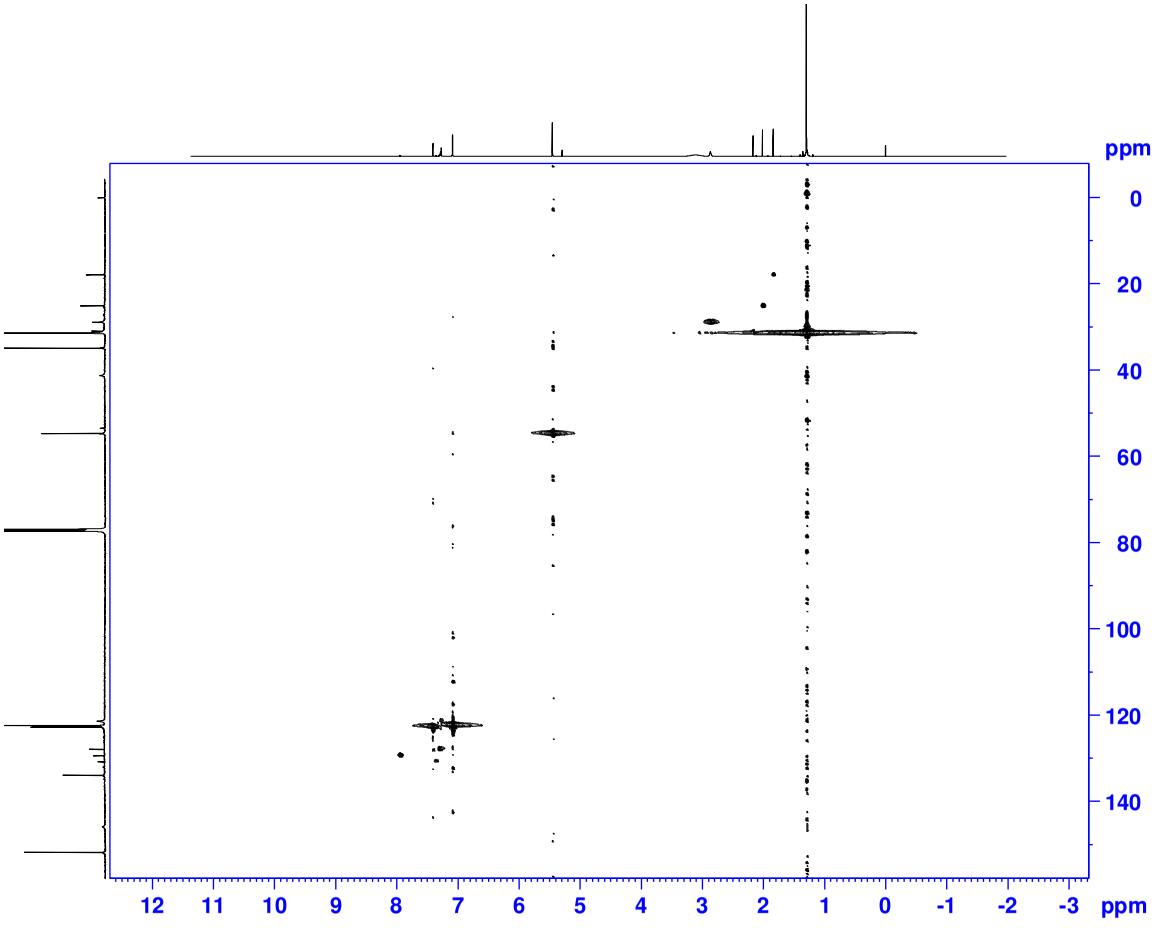

```
Current Data Parameters
NAME           OKH0906-4
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150616
Time               16.32
INSTRUM            spect
PROBHD   5 mm CPQCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     0
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                  45.2
DW                62.400 usec
DE                48.96 usec
TE                300.0 K
D1             2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.2328255 MHz
NUC1                   1H
P1                 10.48 usec
PLW1          5.01189995 W

F2 - Processing parameters
SI                131072
SF            600.2300138 MHz
WDW                   EM
SSB       0
LB        0 Hz
GB        0
PC                  0.80
```

E.2 ^{13}C NMRspectrum of 3e



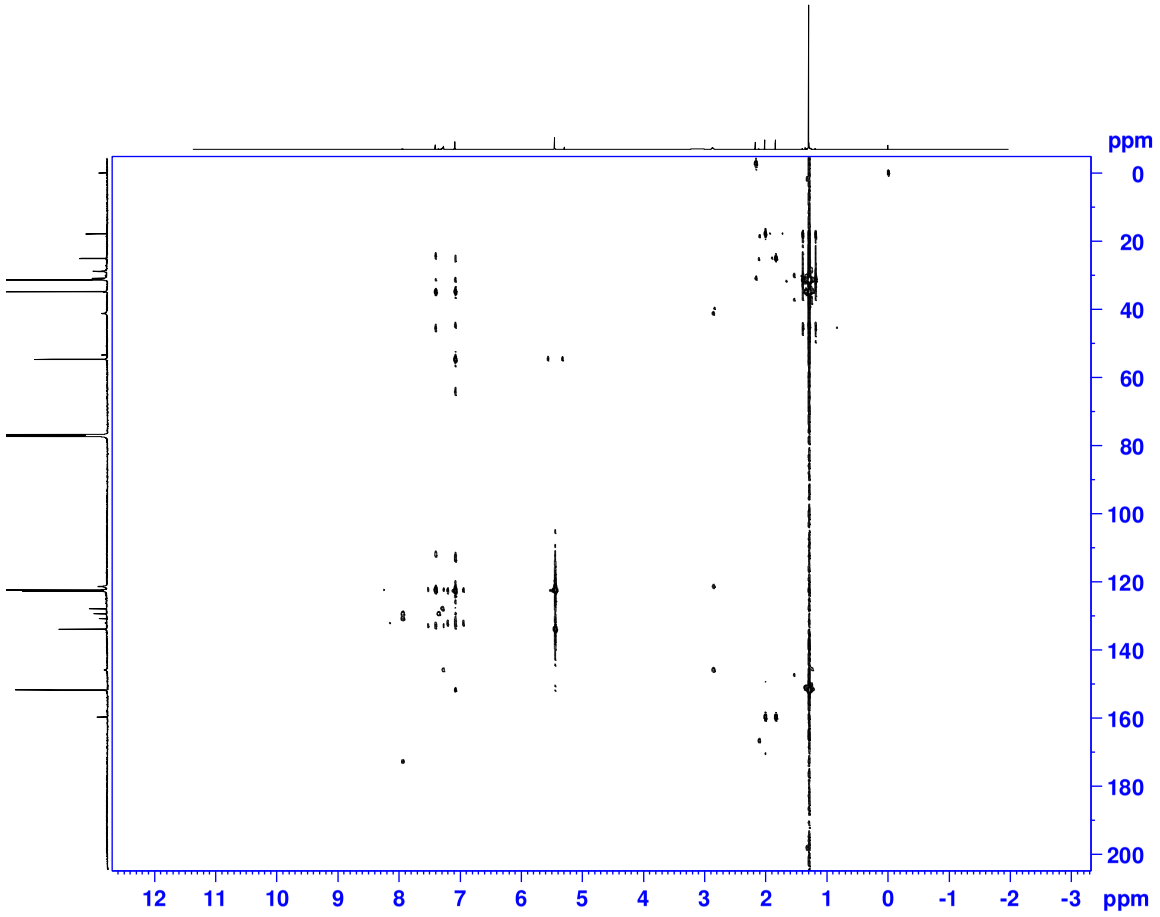

```
Current Data Parameters
NAME                 okh0906-1
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20150616
Time                     20.30
INSTRUM                  spect
PROBHD     5 mm CPQCI 1H-
PULPROG                 zgpg30
TD                      131072
SOLVENT                   CDCl3
NS                          512
DS                            2
SWH                  31512.605 Hz
FIDRES                0.240422 Hz
AQ                    2.0796757 sec
RG                          203
DW                       15.867 usec
DE                       76.64 usec
TE                       300.0 K
D1                  1.50000000 sec
D11                 0.03000000 sec
TD0                           1

======== CHANNEL f1 ========
SFO1                150.9430468 MHz
NUC1                        13C
P1                       11.80 usec
PLW1                93.32499695 W

======== CHANNEL f2 ========
SFO2                600.2324009 MHz
NUC2                        1H
CPDPRG[2                waltz65
PCPD2                    70.00 usec
PLW2                 5.01189995 W
PLW12                0.06222900 W
PLW13                0.03049200 W

F2 - Processing parameters
SI                          65536
SF                  150.9279615 MHz
WDW                            EM
SSB              0
LB                        3.00 Hz
GB               0
PC                        1.40
```

E.3 HSQC spectrum of 3e



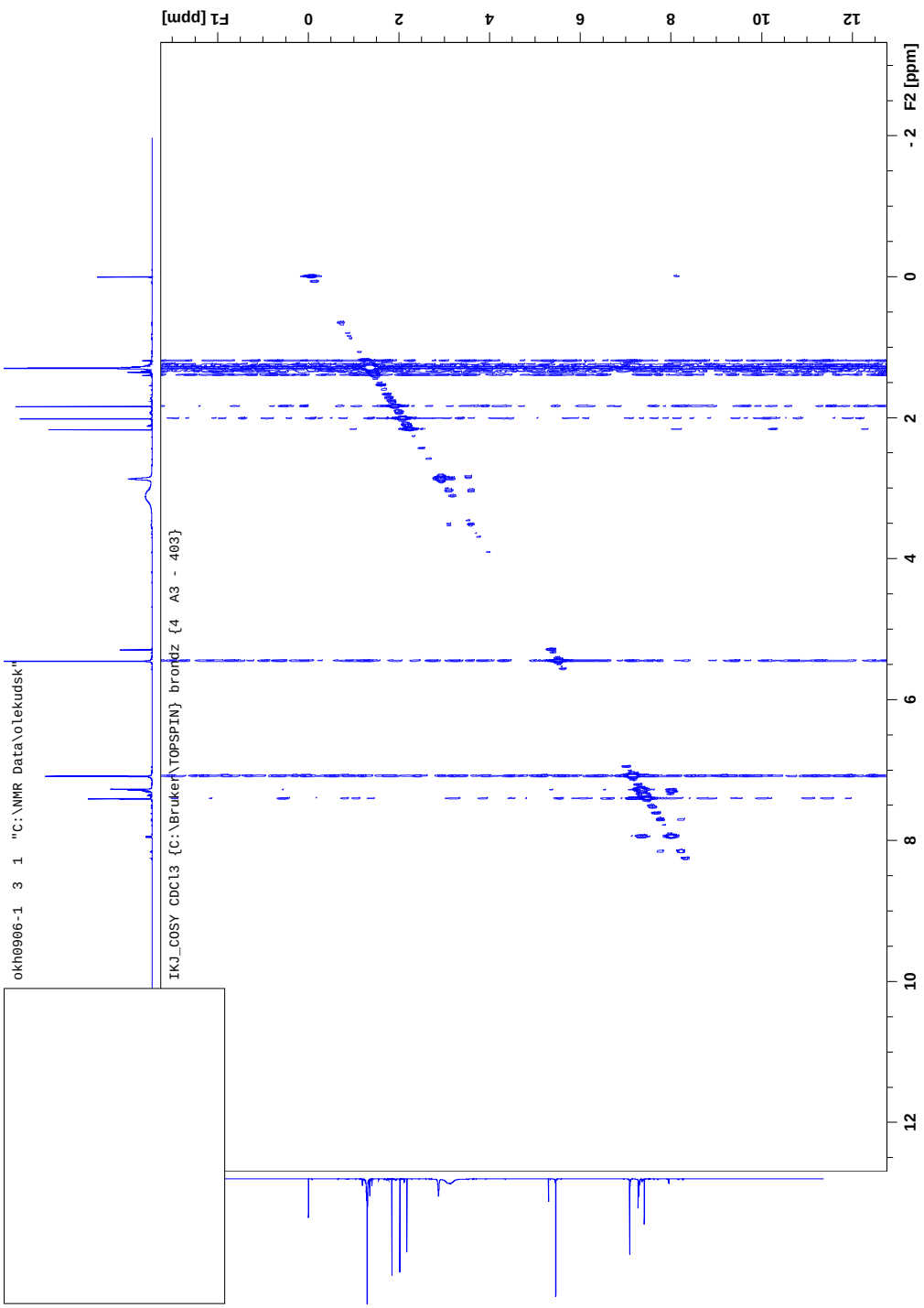

```
Current Data Parameters
NAME                  okh0906-1
EXPNO                         4
PROCNO                        1

F2 - Acquisition Parameters
Date_               20150616
Time                      20.35
INSTRUM                   spect
PROBHD    5 mm CPQCI 1H-
PULPROG   hsqcedetgpsisp.2
TD                        2048
SOLVENT                   CDCl3
NS                           4
DS                          16
SWH                  9615.385 Hz
FIDRES               4.695012 Hz
AQ                   0.1064960 sec
RG                         203
DW                      52.000 usec
DE                      40.00 usec
TE                      300.0 K
CNST2                145.0000000
CNST17               -0.5000000
D0                   0.00000300 sec
D1                   1.00000000 sec
D4                   0.00172414 sec
D11                  0.03000000 sec
D16                  0.00020000 sec
D21                  0.00344828 sec
D24                  0.00086207 sec
IN0                  0.00002000 sec

======== CHANNEL f1 ========
SFO1                600.2328255 MHz
NUC1                        1H
P1                        9.83 usec
P2                       19.66 usec
P28          0 usec
PLW1               5.01189995 W

======= CHANNEL f2 =======
SFO2                150.9392694 MHz
NUC2                        13C
CPDPRG[2                 garp4
P3                       11.80 usec
P14                     500.00 usec
P24                    2000.00 usec
PCPD2                    60.00 usec
PLW0          0 W
PLW2               93.32499695 W
PLW12               3.60960007 W
SPNAM[3] Crp60,0.5,20.1
SPOAL3                    0.500
SPOFFS3   0 Hz
SPW3               19.85400009 W
SPNAM[7]     Crp60comp.4
SPOAL7                    0.500
SPOFFS7   0 Hz
SPW7               19.85400009 W

===== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[2]       SMSQ10.100
GPZ1                    80.00 %
GPZ2                    20.10 %
P16                   1000.00 usec

F1 - Acquisition parameters
TD                          64
SFO1                150.9393 MHz
FIDRES              390.625000 Hz
SW                  165.630 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                        2048
SF                600.2300129 MHz
WDW                       QSINE
SSB                           2
LB           0 Hz
GB           0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2          echo-antiecho
SF                150.9279540 MHz
WDW                       QSINE
SSB                           2
LB           0 Hz
GB           0
```

E.4 HMBC spectrum of 3e

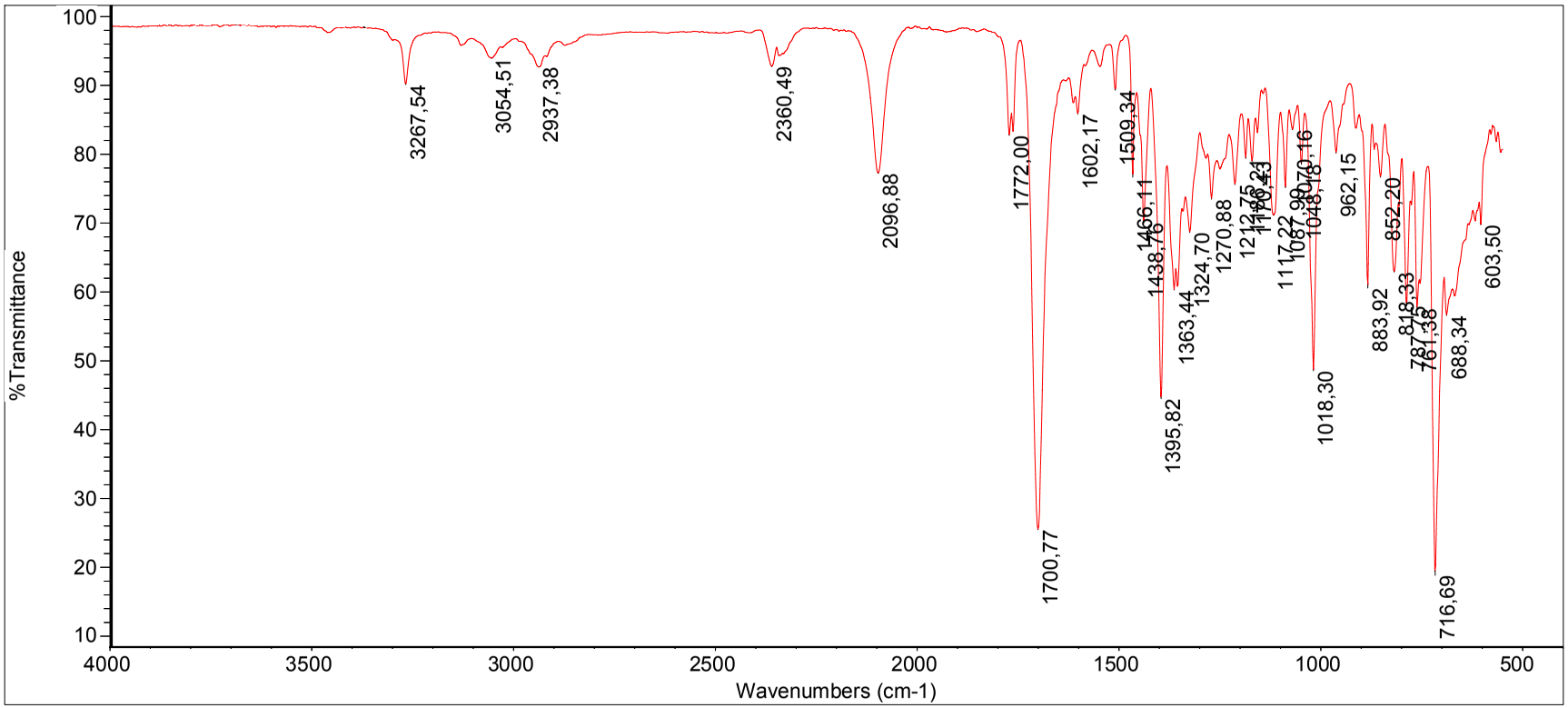



```
Current Data Parameters
NAME                  okh0906-1
EXPNO                         5
PROCNO                        1

F2 - Acquisition Parameters
Date_               20150616
Time                    20.42
INSTRUM                 spect
PROBHD     5 mm CPQCI 1H-
PULPROG    hmbcetgpl3ndpr
TD                      4096
SOLVENT                 CDCl3
NS                         8
DS                        16
SWH                  9615.385 Hz
FIDRES               2.347506 Hz
AQ                   0.2129920 sec
RG                       203
DW                    52.000 usec
DE                    40.00 usec
TE                    300.0 K
CNST6               125.0000000
CNST7               155.0000000
CNST13                7.0000000
CNST30                0.5981153
D0                    0.00000300 sec
D1                    1.00000000 sec
D6                    0.07142857 sec
D11                   0.03000000 sec
D12                   0.00002000 sec
D16                   0.00020000 sec
IN0                   0.00001580 sec

======== CHANNEL f1 ========
SFO1                600.2328255 MHz
NUC1                        1H
P1                        9.83 usec
P2                       19.66 usec
PLW1                 5.01189995 W
PLW9                 0.00001937 W

======== CHANNEL f2 ========
SFO2                150.9430468 MHz
NUC2                       13C
P3                       11.80 usec
P24                    2000.00 usec
PLW2                93.32499695 W
SPNAM[7]            Crp60comp.4
SPOAL7                   0.500
SPOFFS7   0 Hz
SPW7                19.85400009 W

====== GRADIENT CHANNEL =====
GPNAM[1]            SMSQ10.100
GPNAM[3]            SMSQ10.100
GPNAM[4]            SMSQ10.100
GPNAM[5]            SMSQ10.100
GPNAM[6]            SMSQ10.100
GPZ1                      80.00 %
GPZ3                      14.00 %
GPZ4                      -8.00 %
GPZ5                      -4.00 %
GPZ6                      -2.00 %
P16                    1000.00 usec

F1 - Acquisition parameters
TD                          256
SFO1                150.943 MHz
FIDRES              123.615509 Hz
SW                  209.652 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                         2048
SF                  600.2300129 MHz
WDW                        QSINE
SSB       0
LB        0 Hz
GB        0
PC                         1.40

F1 - Processing parameters
SI                         1024
MC2           echo-antiecho
SF                  150.9279540 MHz
WDW                        QSINE
SSB                           2
LB        0 Hz
GB        0
```

E.5 COSY spectrum of 3e



E.6 IR spectrum of 3e



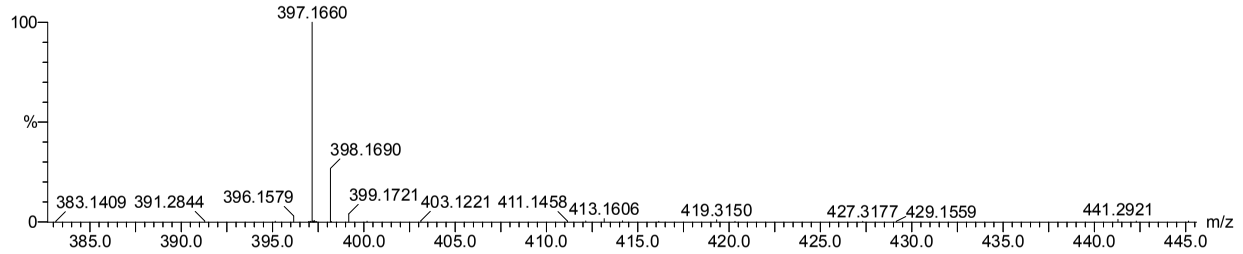
E.7 MS spectrum of 3e

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Odd Electron Ions
1169 formula(e) evaluated with 3 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 N: 0-50 O: 0-100
NT-MSLAB-Operator-SVG
2015-205 198 (3.859) AM2 (Ar,35000.0,0.00,0.00); Cm (189:200)

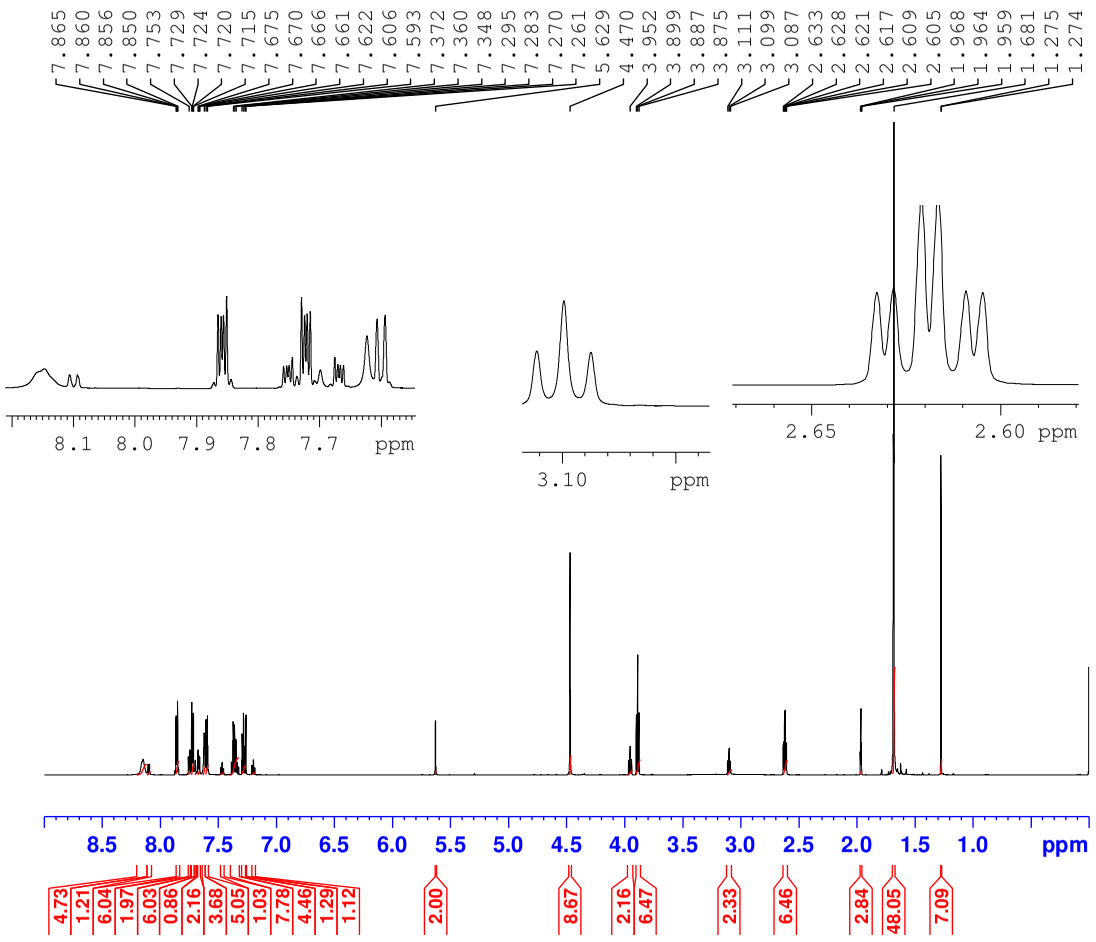
1: TOF MS ASAP+
7.37e+005



Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
396.1579	396.1586	-0.7	-1.8	17.0	243.0	0.666	51.39	C24 H20 N4 O2
	396.1573	0.6	1.5	12.0	243.3	0.936	39.23	C23 H24 O6
	396.1578	0.1	0.3	5.0	244.7	2.368	9.37	C8 H20 N12 O7

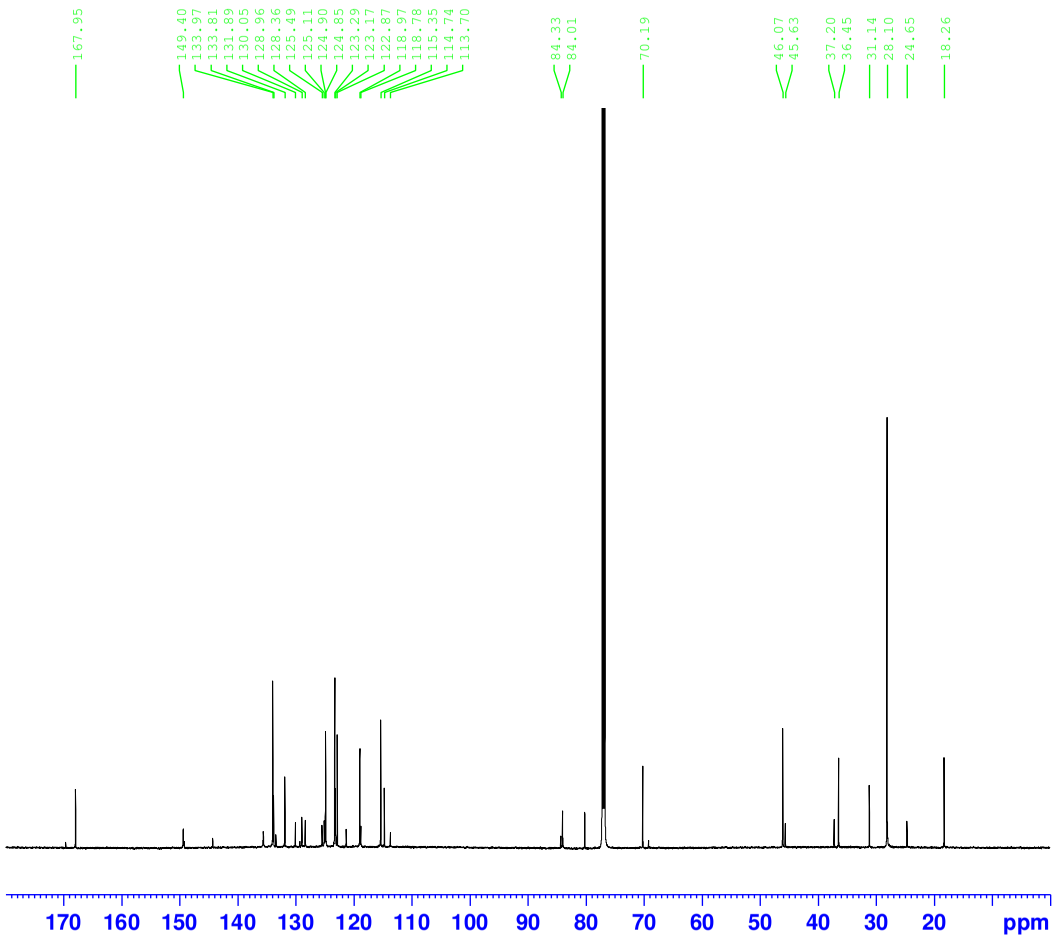
F Spectra of 3f

F.1 ^{1}H NMR spectrum of 3f



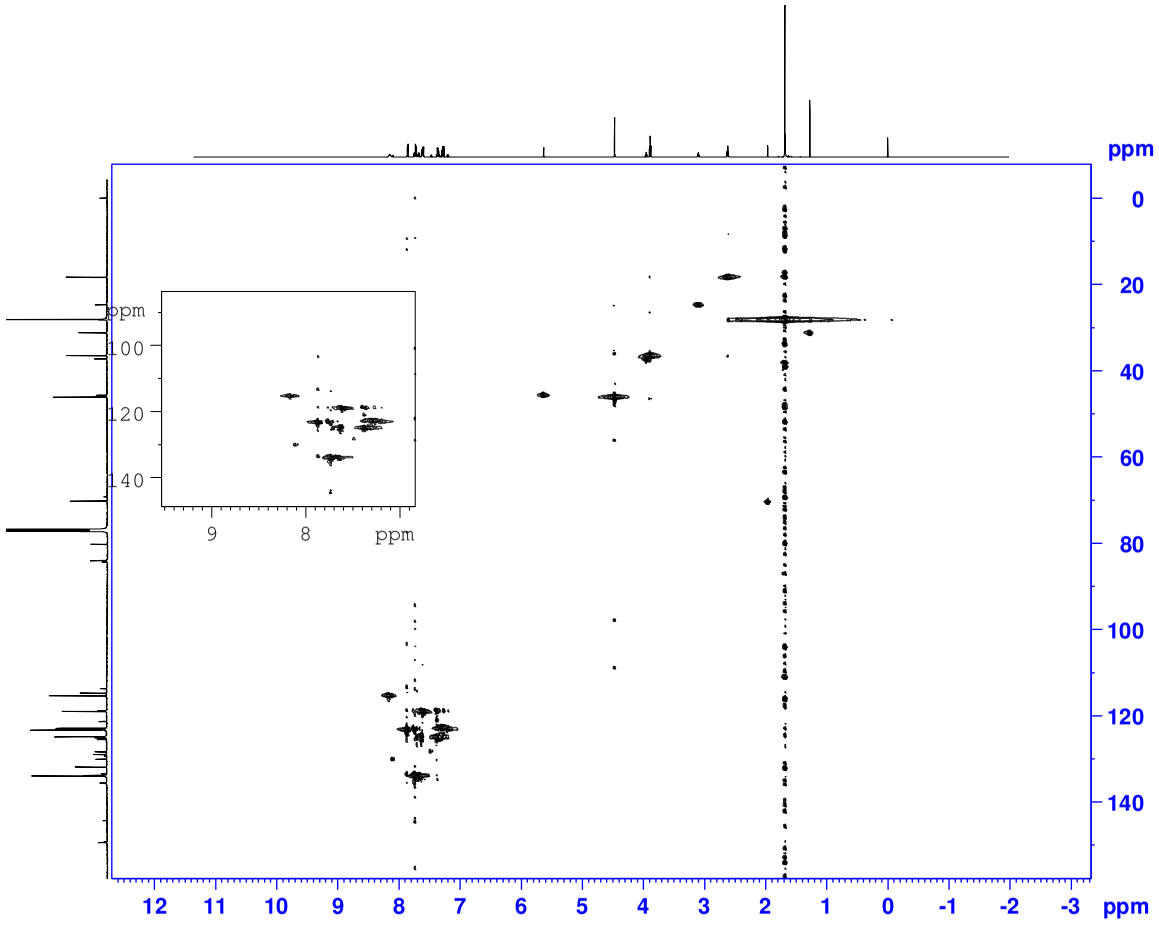

```
Current Data Parameters
NAME            OKH0906-3
EXPNO                  15
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150617
Time                4.04
INSTRUM            spect
PROBHD    5 mm CPQCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     0
SWH             8012.820 Hz
FIDRES             0.122266 Hz
AQ              4.0894465 sec
RG                    64
DW                 62.400 usec
DE                 49.11 usec
TE                 300.0 K
D1              2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          600.2328255 MHz
NUC1                  1H
P1                 9.80 usec
PLW1           5.01189995 W

F2 - Processing parameters
SI                131072
SF            600.2300137 MHz
WDW                   EM
SSB       0
LB        0 Hz
GB        0
PC                  0.80
```

F.2 ^{13}C NMRspectrum of 3f



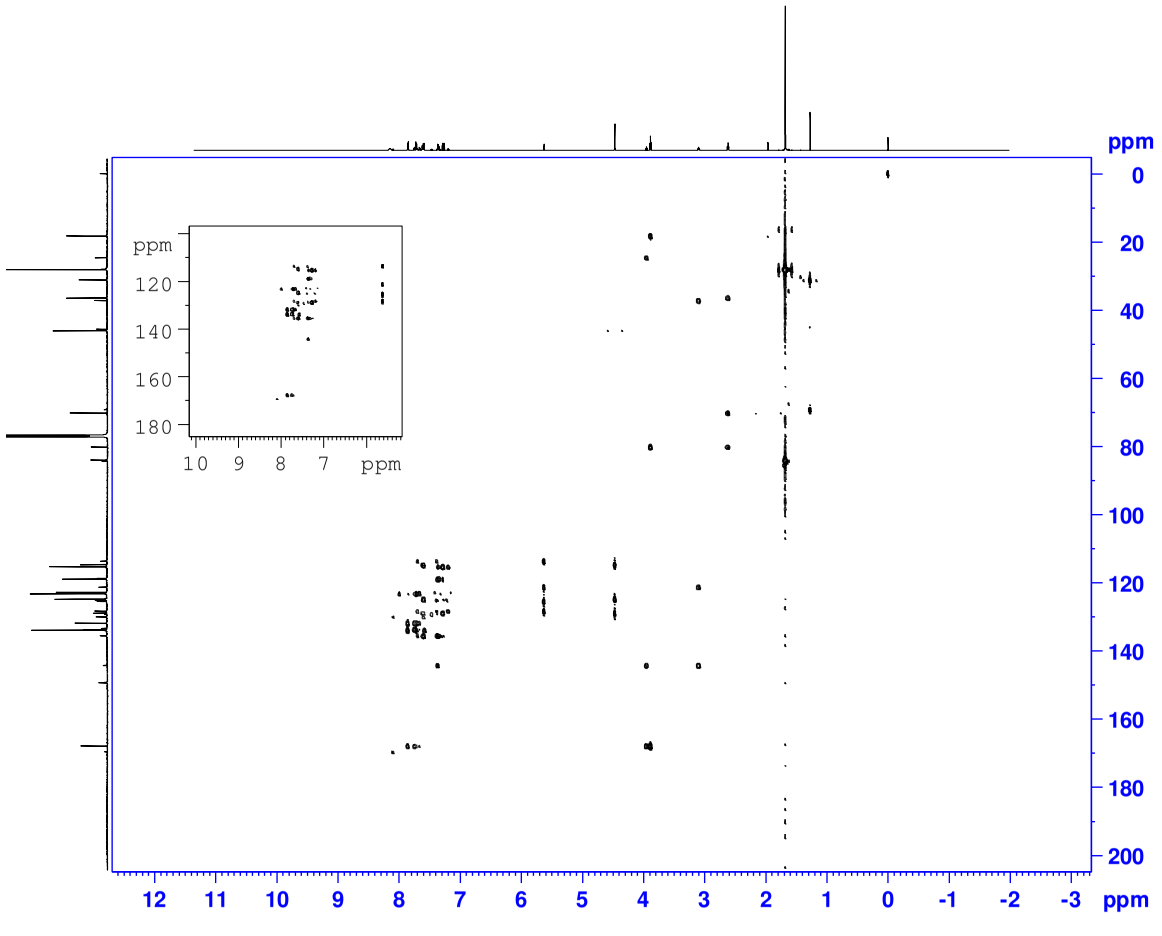

```
Current Data Parameters
NAME            OKH0906-3
EXPNO                  16
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150617
Time                4.37
INSTRUM             spect
PROBHD   5 mm CPQCI 1H-
PULPROG            zgpg30
TD                 131072
SOLVENT              CDCl3
NS                     512
DS                       2
SWH            31512.605 Hz
FIDRES          0.240422 Hz
AQ             2.0796757 sec
RG                     203
DW                15.867 usec
DE                 76.64 usec
TE                 300.0 K
D1            1.50000000 sec
D11           0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          150.9430468 MHz
NUC1                  13C
P1                 11.80 usec
PLW1          93.32499695 W

======== CHANNEL f2 ========
SFO2          600.2324009 MHz
NUC2                  1H
CPDPRG[2           waltz65
PCPD2              70.00 usec
PLW2           5.01189995 W
PLW12          0.06222900 W
PLW13          0.03049200 W

F2 - Processing parameters
SI                  65536
SF            150.9279677 MHz
WDW                    EM
SSB       0
LB                  3.00 Hz
GB        0
PC                  1.40
```

F.3 HSQC spectrum of 3f



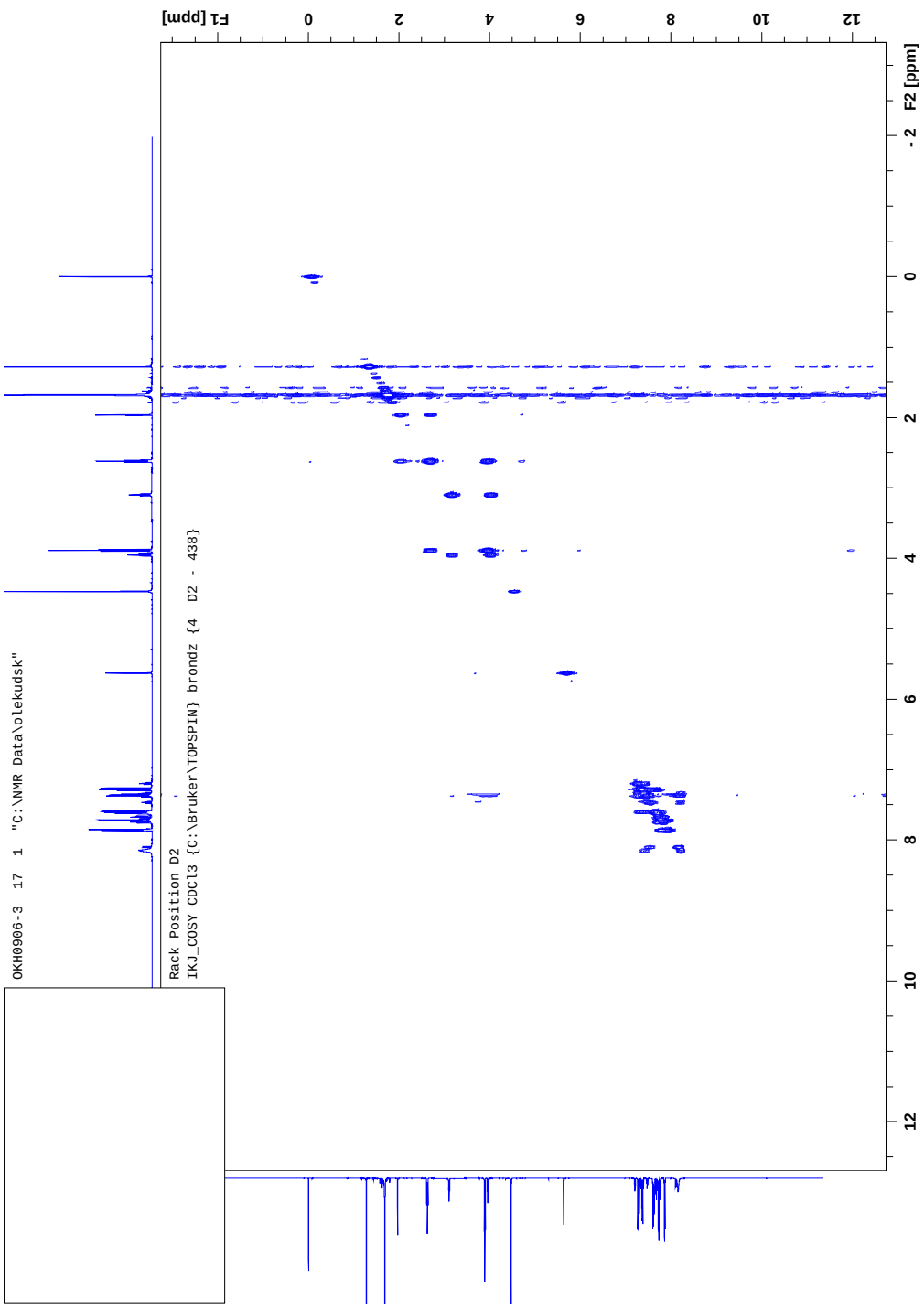

```
Current Data Parameters
NAME                 OKH0906-3
EXPNO                       18
PROCNO                       1

F2 - Acquisition Parameters
Date_               20150617
Time                    4.42
INSTRUM                 spect
PROBHD    5 mm CPQCI 1H-
PULPROG   hsqcedetgpsisp.2
TD                      2048
SOLVENT                 CDCl3
NS                         4
DS                        16
SWH                 9615.385 Hz
FIDRES              4.695012 Hz
AQ                  0.1064960 sec
RG                        203
DW                     52.000 usec
DE                     40.00 usec
TE                     300.0 K
CNST2               145.0000000
CNST17               -0.5000000
D0                   0.00000300 sec
D1                   1.00000000 sec
D4                   0.00172414 sec
D11                  0.03000000 sec
D16                  0.00020000 sec
D21                  0.00344828 sec
D24                  0.00086207 sec
IN0                  0.00002000 sec

======== CHANNEL f1 ========
SFO1                600.2328255 MHz
NUC1                        1H
P1                       9.80 usec
P2                      19.60 usec
P28          0 usec
PLW1                 5.01189995 W

======== CHANNEL f2 ========
SFO2                150.9392694 MHz
NUC2                        13C
CPDPRG[2                 garp4
P3                      11.80 usec
P14                    500.00 usec
P24                   2000.00 usec
PCPD2                   60.00 usec
PLW0         0 W
PLW2                93.32499695 W
PLW12                3.60960007 W
SPNAM[3] Crp60,0.5,20.1
SPOAL3                   0.500
SPOFFS3   0 Hz
SPW3                19.85400009 W
SPNAM[7]    Crp60comp.4
SPOAL7                   0.500
SPOFFS7   0 Hz
SPW7                19.85400009 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[2]       SMSQ10.100
GPZ1                    80.00 %
GPZ2                    20.10 %
P16                   1000.00 usec

F1 - Acquisition parameters
TD                         64
SFO1                150.9393 MHz
FIDRES              390.625000 Hz
SW                  165.630 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                      2048
SF                600.2300129 MHz
WDW                     QSINE
SSB                         2
LB           0 Hz
GB           0
PC                      1.40

F1 - Processing parameters
SI                      1024
MC2          echo-antiecho
SF                150.9279540 MHz
WDW                     QSINE
SSB                         2
LB           0 Hz
GB           0
```

F.4 HMBC spectrum of 3f

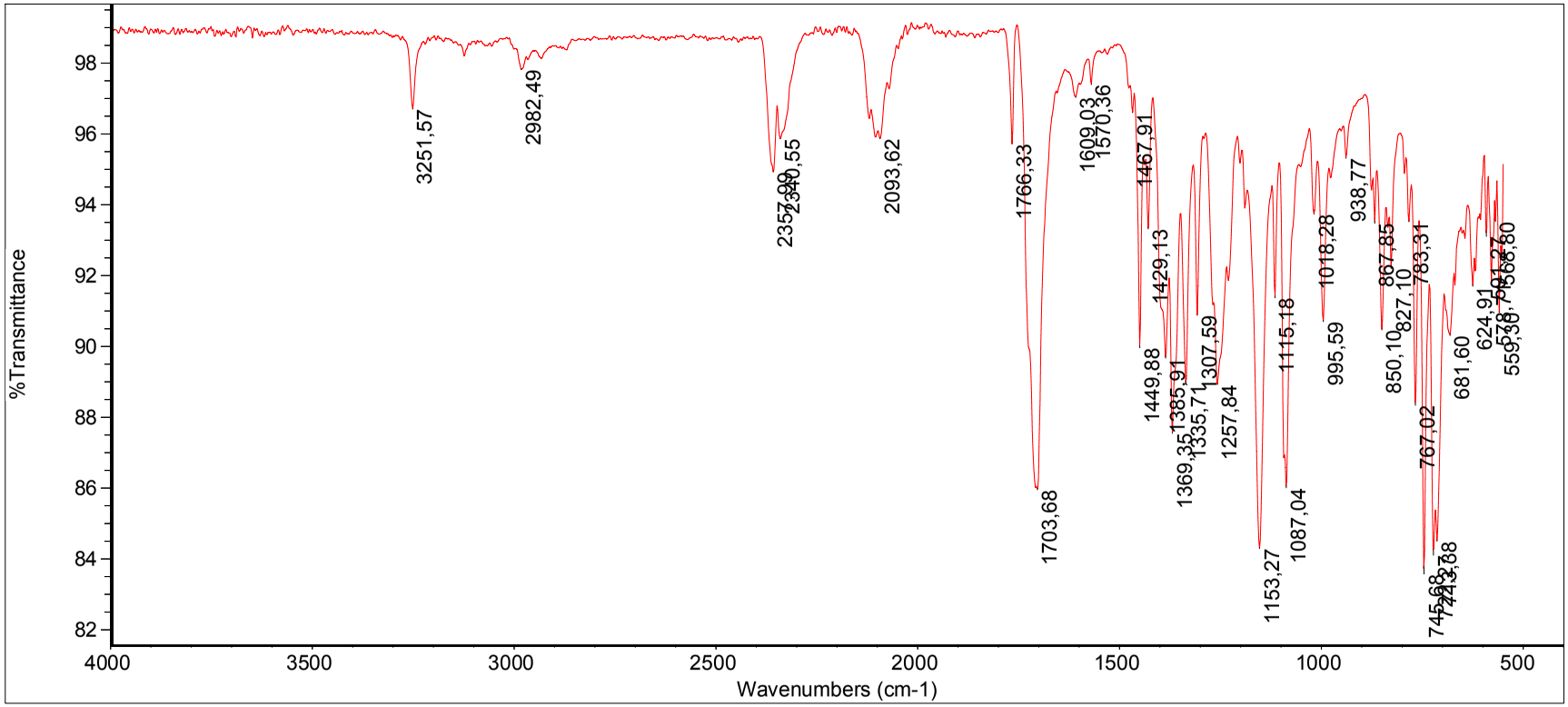



```
Current Data Parameters
NAME            OKH0906-3
EXPNO                  19
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150617
Time                4.49
INSTRUM             spect
PROBHD   5 mm CPQCI 1H-
PULPROG   hmbcetgpl3ndpr
TD                  4096
SOLVENT             CDCl3
NS                     8
DS                    16
SWH              9615.385 Hz
FIDRES           2.347506 Hz
AQ               0.2129920 sec
RG                   203
DW                52.000 usec
DE                40.00 usec
TE                300.0 K
CNST6          125.0000000
CNST7          155.0000000
CNST13           7.0000000
CNST30           0.5981153
D0               0.00000300 sec
D1               1.00000000 sec
D6               0.07142857 sec
D11              0.03000000 sec
D12              0.00002000 sec
D16              0.00020000 sec
IN0              0.00001580 sec

======== CHANNEL f1 ========
SFO1          600.2328255 MHz
NUC1                     1H
P1                    9.80 usec
P2                   19.60 usec
PLW1             5.01189995 W
PLW9             0.00001927 W

======== CHANNEL f2 ========
SFO2          150.9430468 MHz
NUC2                     13C
P3                   11.80 usec
P24                2000.00 usec
PLW2            93.32499695 W
SPNAM[7]     Crp60comp.4
SFOAL7                 0.500
SPOFFS7    0 Hz
SPW7            19.85400009 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[3]       SMSQ10.100
GPNAM[4]       SMSQ10.100
GPNAM[5]       SMSQ10.100
GPNAM[6]       SMSQ10.100
GPZ1                80.00 %
GPZ3                14.00 %
GPZ4                -8.00 %
GPZ5                -4.00 %
GPZ6                -2.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                    256
SFO1           150.943 MHz
FIDRES         123.615509 Hz
SW             209.652 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                   2048
SF            600.2300129 MHz
WDW                  QSINE
SSB       0
LB        0 Hz
GB        0
PC                   1.40

F1 - Processing parameters
SI                   1024
MC2        echo-antiecho
SF            150.9279540 MHz
WDW                  QSINE
SSB                     2
LB        0 Hz
GB        0
```

F.5 COSY spectrum of 3f



F.6 IR spectrum of 3f



F.7 MS spectrum of 3f

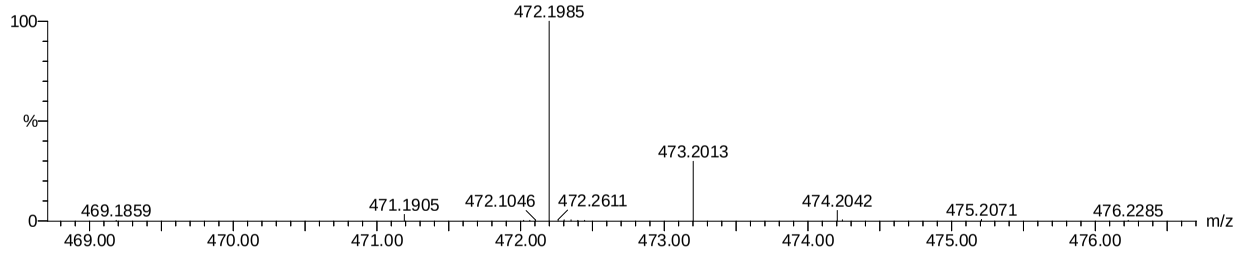
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 3.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
1861 formula(e) evaluated with 6 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 1-500 H: 0-1000 N: 0-50 O: 0-100

NT-MSLAB-Operator-SVG
2015-206 271 (5.271) AM2 (Ar,35000.0,0.00,0.00); Cm (229:271)

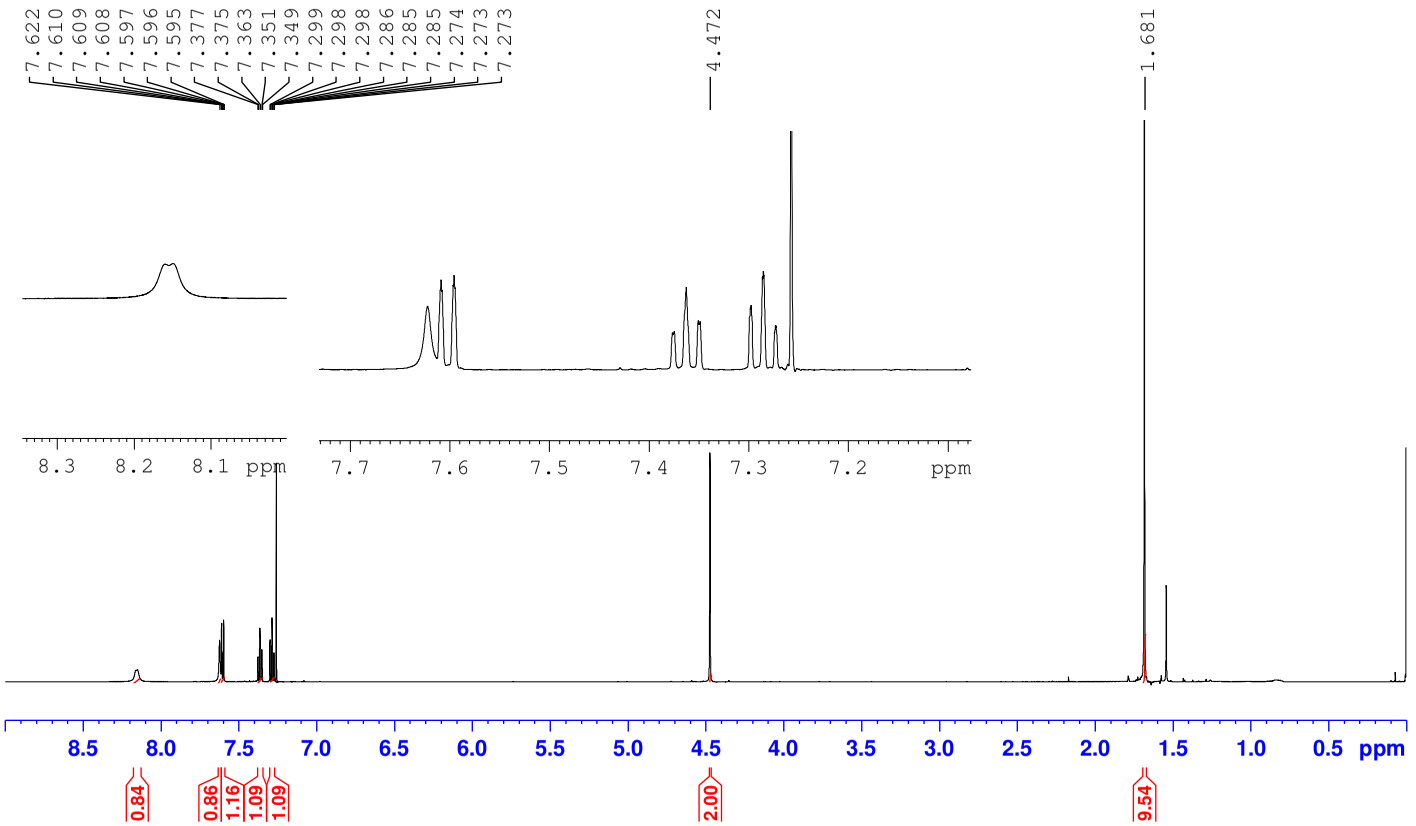
1: TOF MS ASAP+
1.13e+006



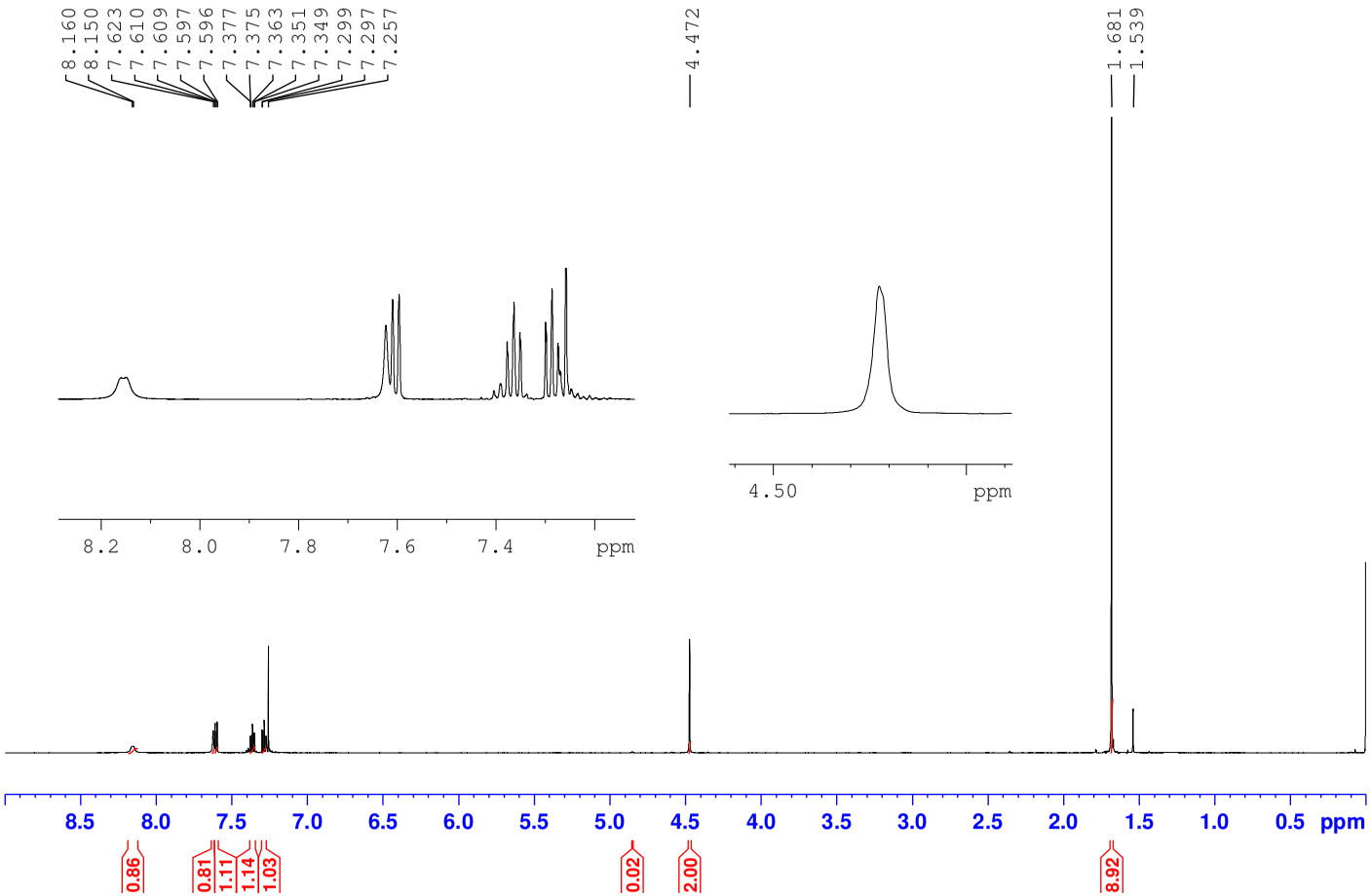
Minimum:				-1.5				
Maximum:		5.0	3.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
472.1985	472.1985	0.0	0.0	16.5	117.7	0.001	99.92	C26 H26 N5 O4
	472.1990	-0.5	-1.1	9.5	135.7	17.938	0.00	C11 H22 N17 O5
	472.1990	-0.5	-1.1	-1.5	133.1	15.429	0.00	C13 H34 N3 O15
	472.1976	0.9	1.9	4.5	136.4	18.670	0.00	C10 H26 N13 O9
	472.1998	-1.3	-2.8	21.5	126.6	8.919	0.01	C27 H22 N9
	472.1971	1.4	3.0	11.5	125.1	7.363	0.06	C25 H30 N O8

G Spectra of 1c

G.1 ^{1}H NMR spectrum of 1c, first parallel

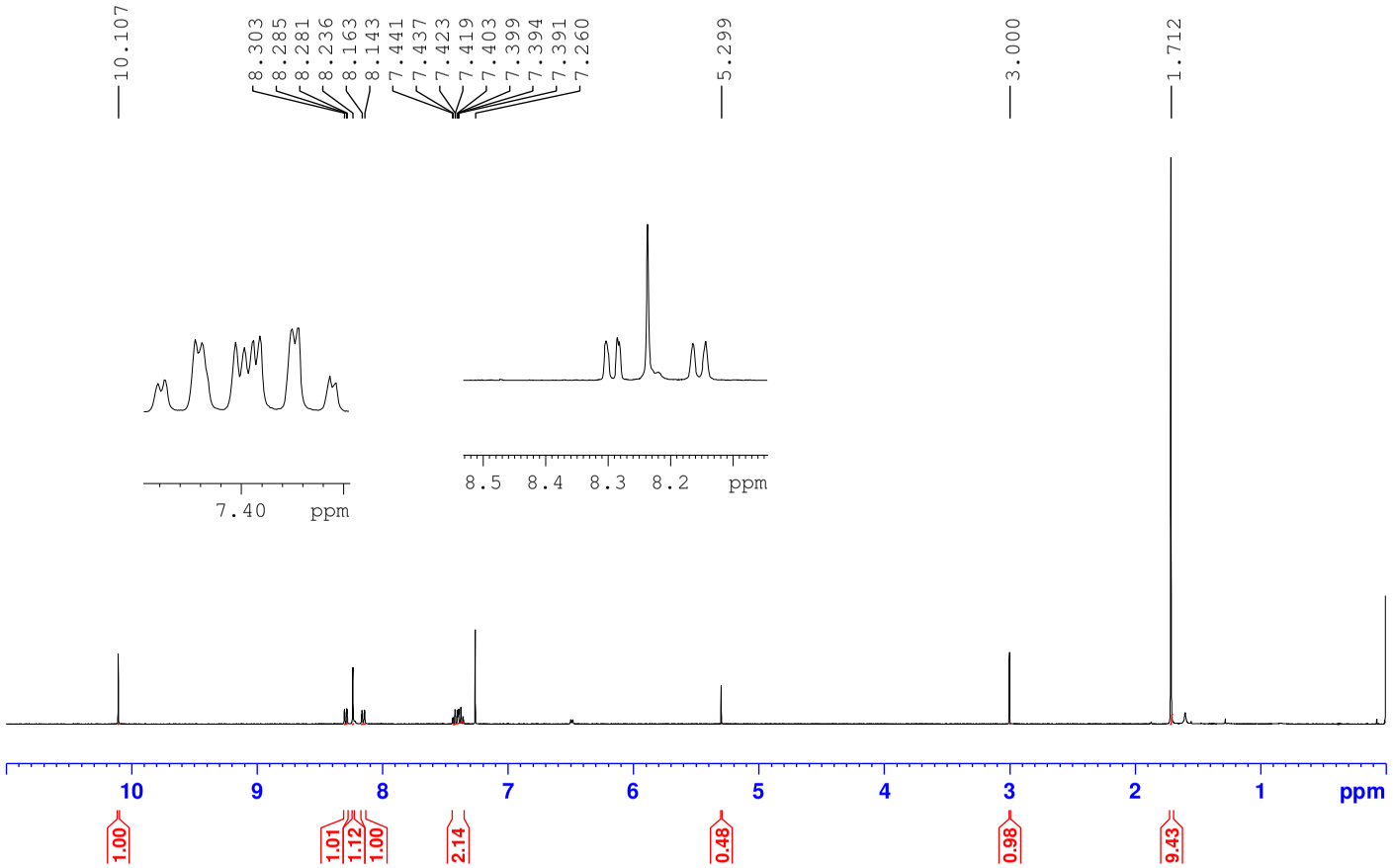


G.2 ^{1}H NMR spectrum of 1c, second parallel

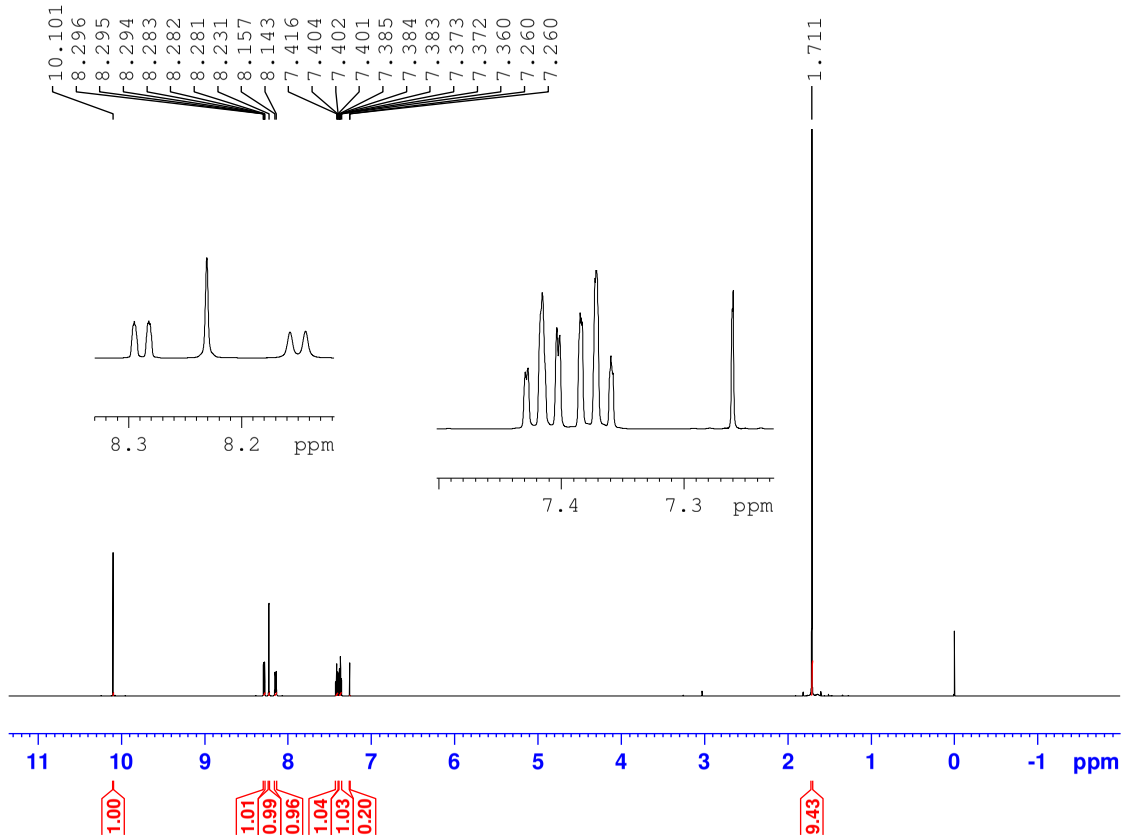


H Spectra of 5a

H.1 ^{1}H NMR spectrum of 5a, first parallel



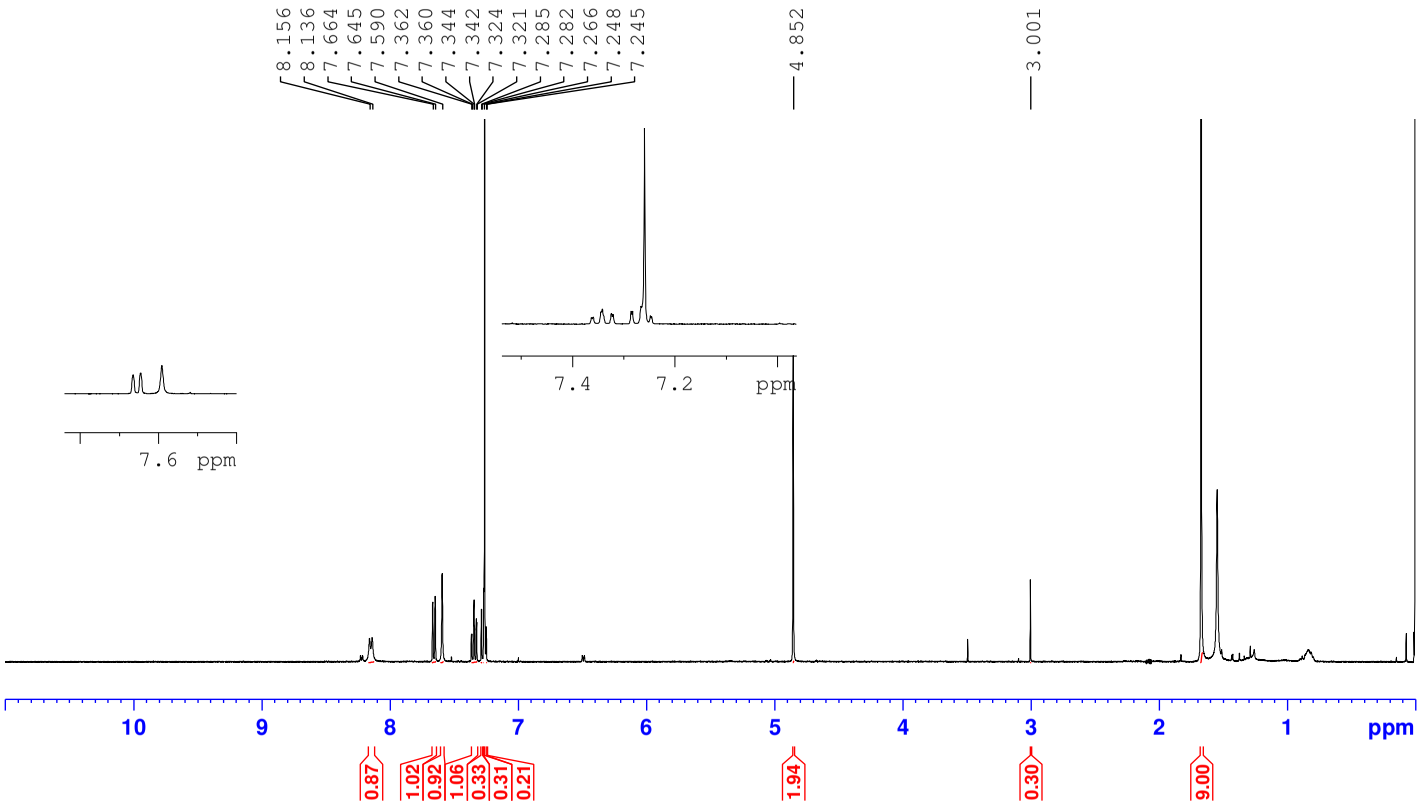
H.2 ^{1}H NMR spectrum of 5a, second parallel



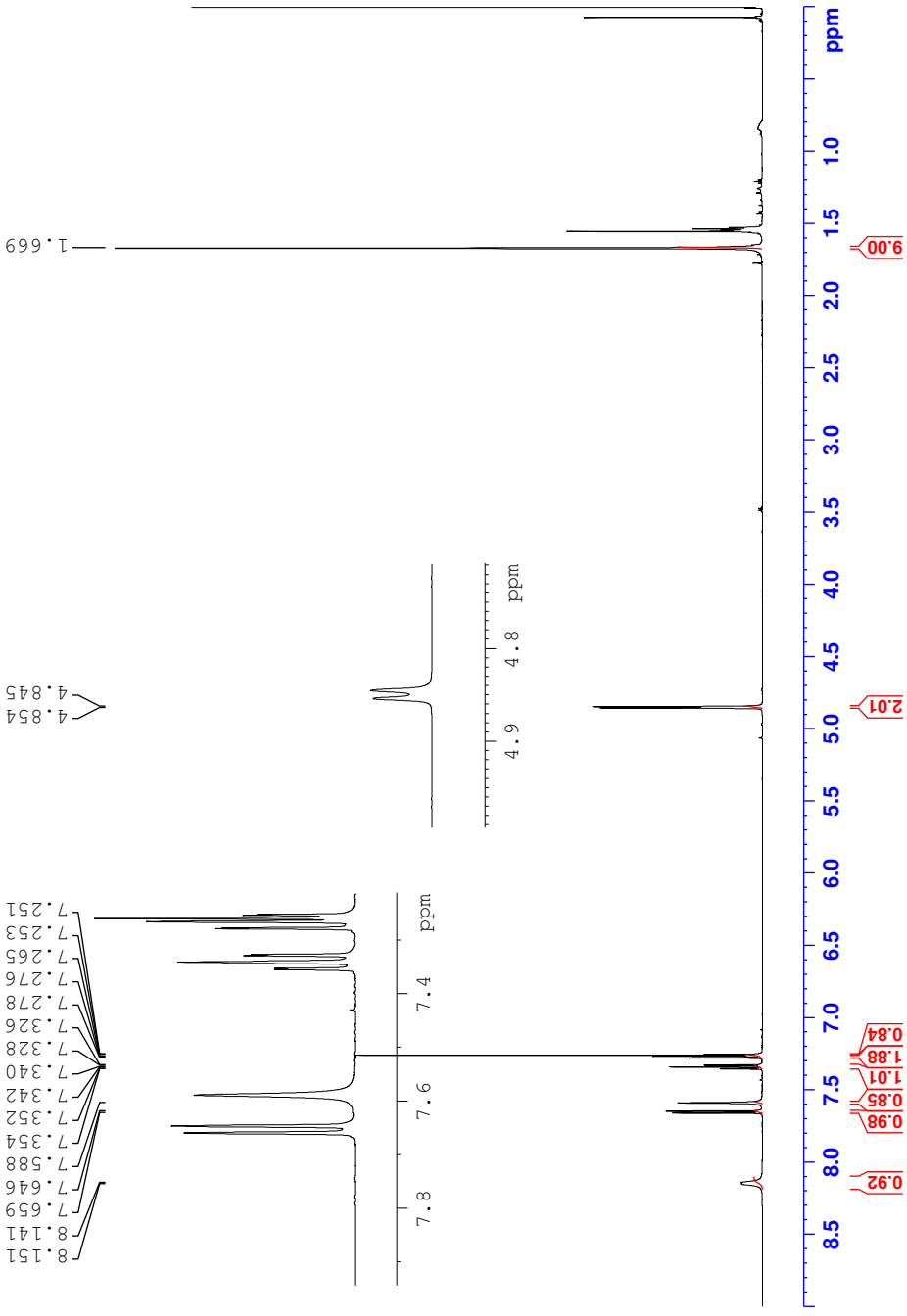

```
Current Data Parameters
NAME                  OKH0906-5
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20150616
Time                      21.39
INSTRUM                   spect
PROBHD    5 mm CPQCI 1H-
PULPROG                   zg30
TD                       65536
SOLVENT                  CDCl3
NS                           8
DS                           0
SWH                   8012.820 Hz
FIDRES                0.122266 Hz
AQ                    4.0894465 sec
RG                         80.6
DW                       62.400 usec
DE                       49.10 usec
TE                       300.0 K
D1                    2.00000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1                600.2328255 MHz
NUC1                        1H
P1                        9.83 usec
PLW1                5.01189995 W

F2 - Processing parameters
SI                       131072
SF                  600.2300150 MHz
WDW                         EM
SSB          0
LB           0 Hz
GB           0
PC                        0.80
```

I Spectra of 6a

I.1 ^{1}H NMR spectrum of 6a, first parallel

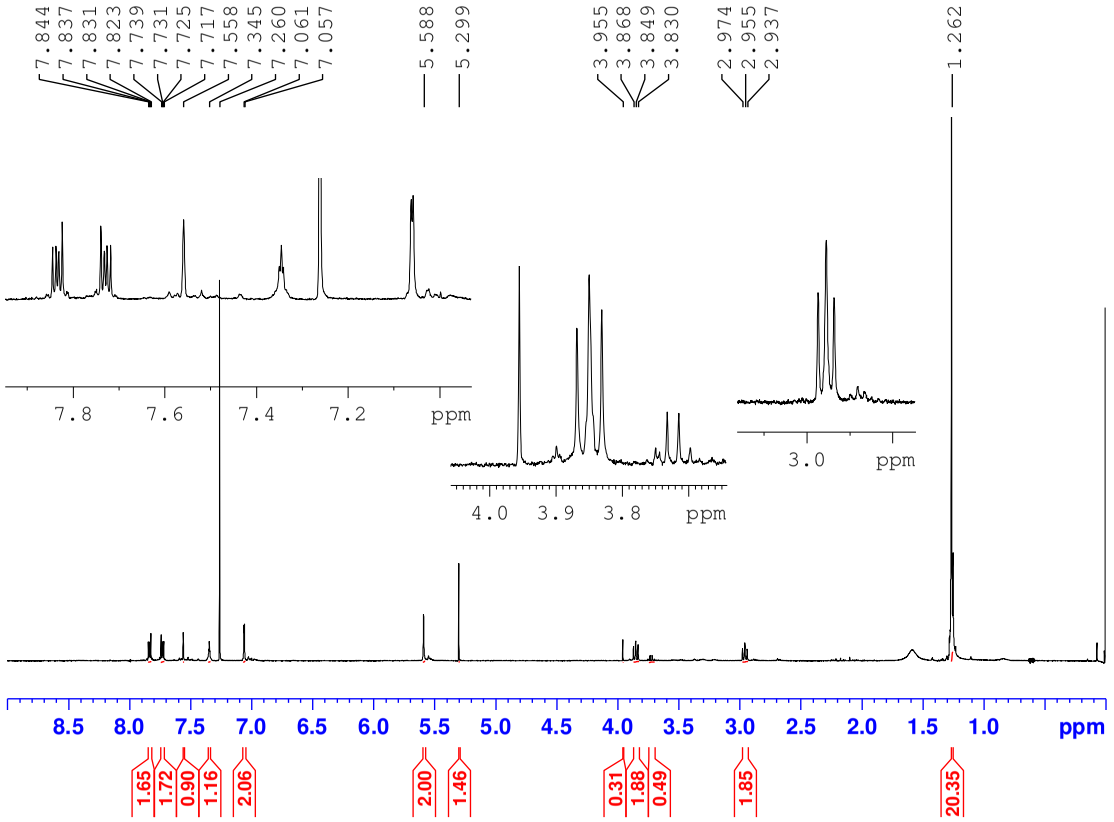


I.2 ^{1}H NMR spectrum of 6a, second parallel



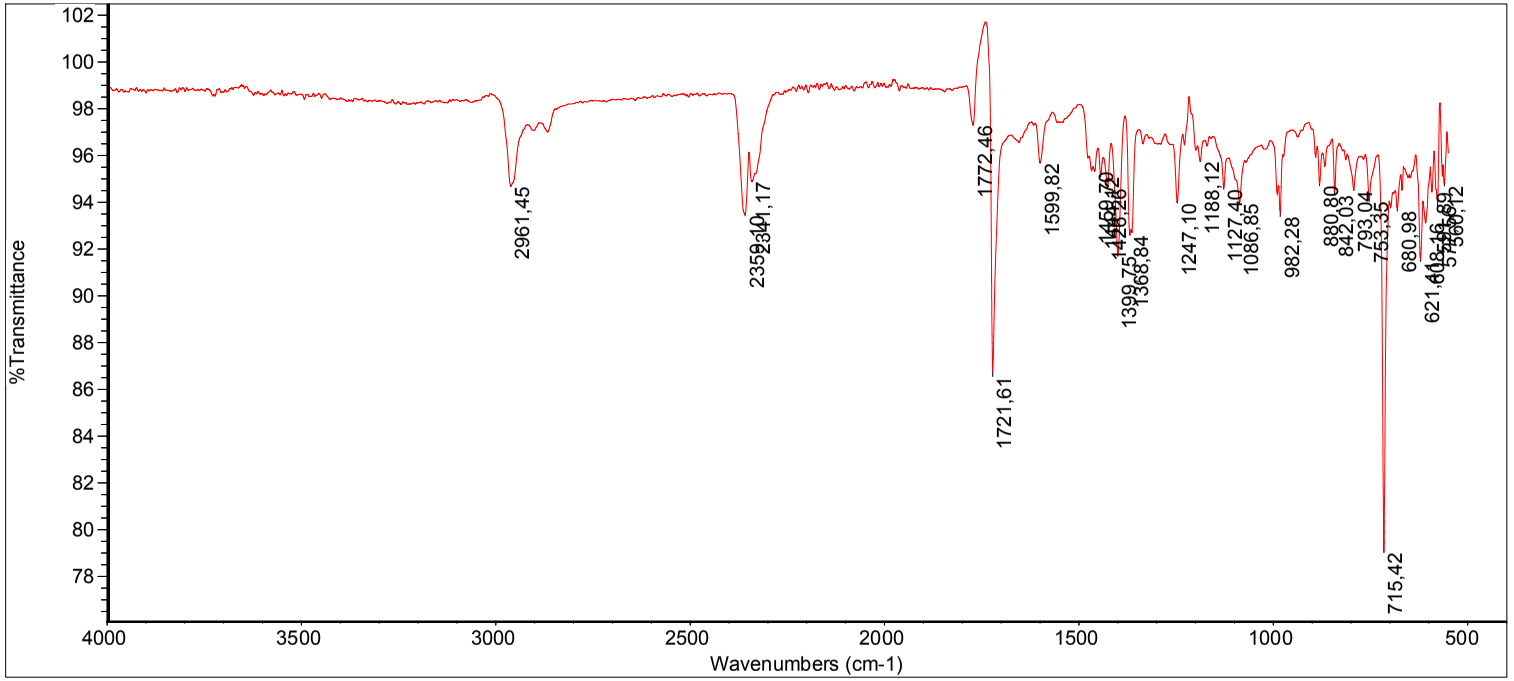
J Spectra of the residue obtained in an attempt to prepare 7a

J.1 ^{1}H NMR spectrum of the residue obtained in an attempt to prepare 7a



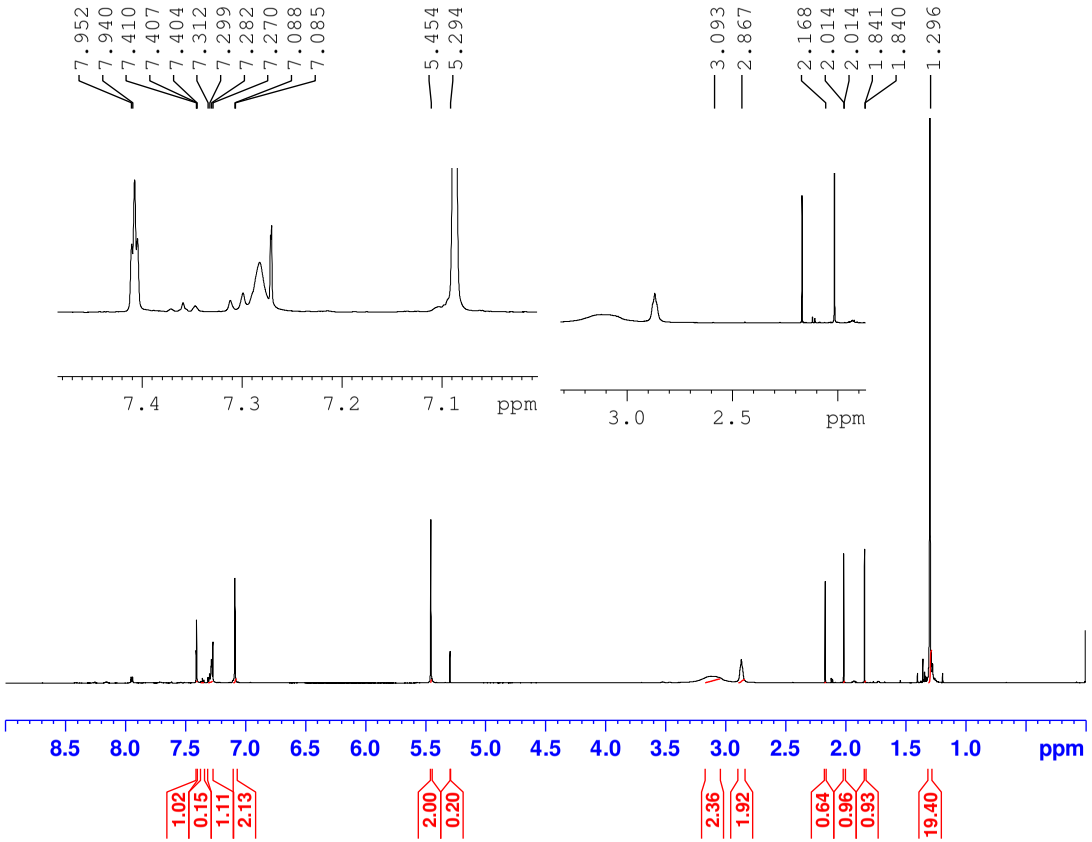

```
Current Data Parameters
NAME      Feb19-2015-olekudsk
EXPNO                       2
PROCNO                      1

F2 - Acquisition Parameters
Date_            20150220
Time                6.59
INSTRUM            spect
PROBHD   5 mm PADUL 13C
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                   128
DS                     0
SWH             8278.146 Hz
FIDRES             0.126314 Hz
AQ              3.9583745 sec
RG                  1024
DW                60.400 usec
DE                 6.00 usec
TE                298.0 K
D1           2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                   1H
P1                 10.50 usec
PL1                -6.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 32768
SF           400.1300079 MHz
WDW                   no
SSB       0
LB        0 Hz
GB        0
PC                  1.00
```

J.2 IR spectrum the residue obtained in an attempt to prepare 7a



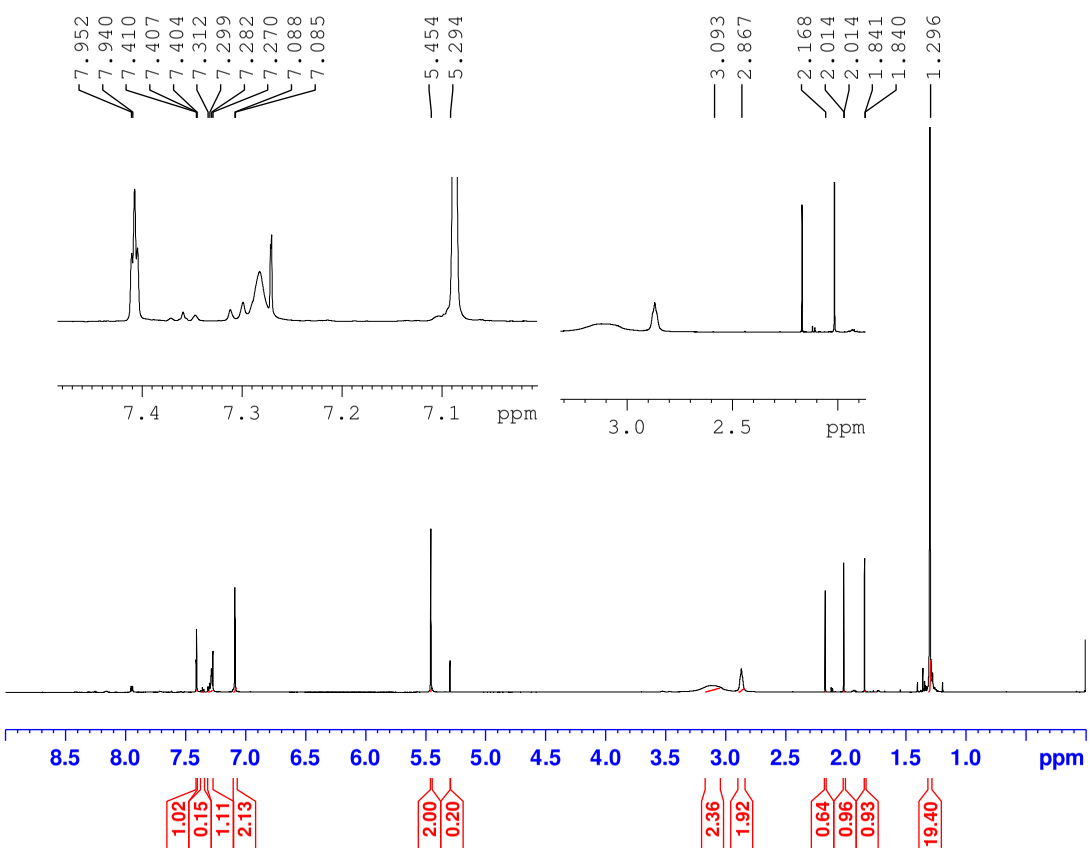
K Spectra of 7b

K.1 ^{1}H NMR spectrum of 7b purified on a silica column



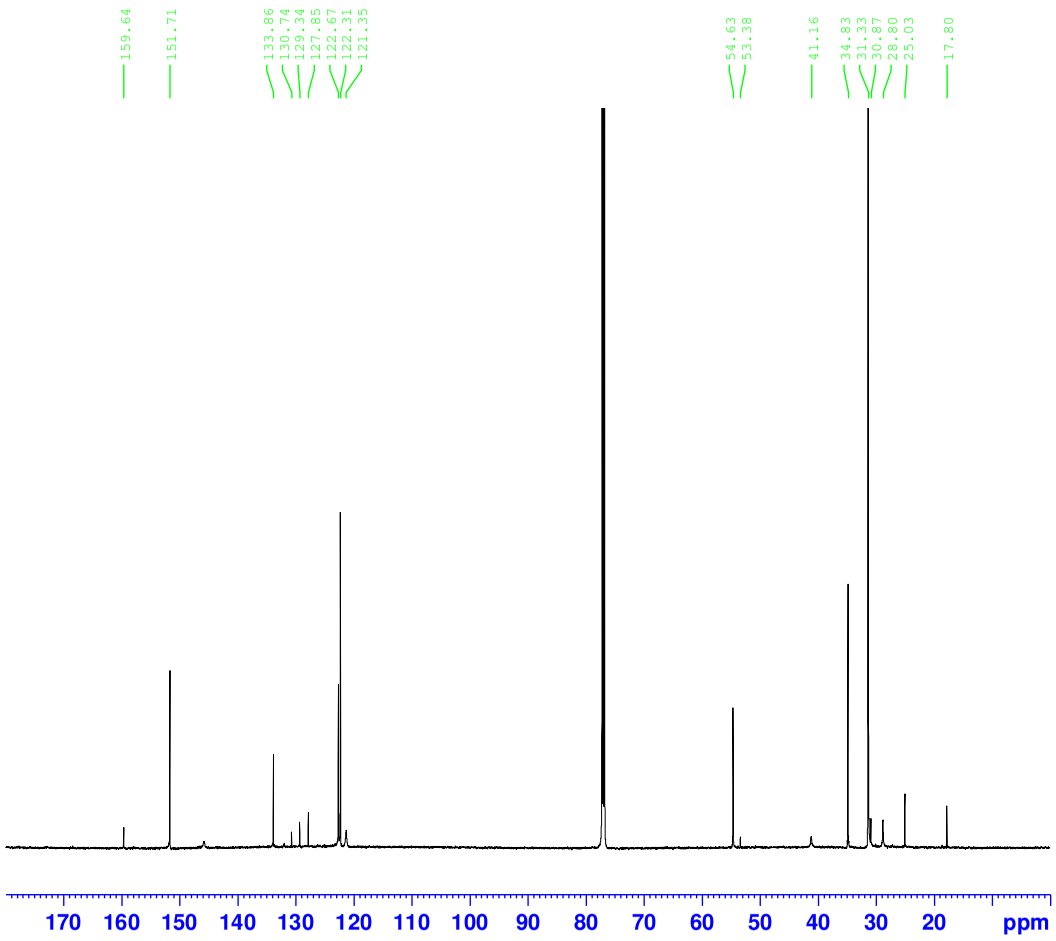

```
Current Data Parameters
NAME           okh0906-1
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150616
Time               19.57
INSTRUM            spect
PROBHD   5 mm CPQCI 1H-
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     0
SWH             8012.820 Hz
FIDRES          0.122266 Hz
AQ              4.0894465 sec
RG                  40.3
DW                62.400 usec
DE                49.10 usec
TE                300.0 K
D1           2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         600.2328255 MHz
NUC1                1H
P1                9.83 usec
PLW1         5.01189995 W

F2 - Processing parameters
SI                131072
SF           600.2300075 MHz
WDW                  EM
SSB       0
LB        0 Hz
GB        0
PC                 0.80
```

K.2 ^{1}H NMR spectrum of 7b filtered through celite



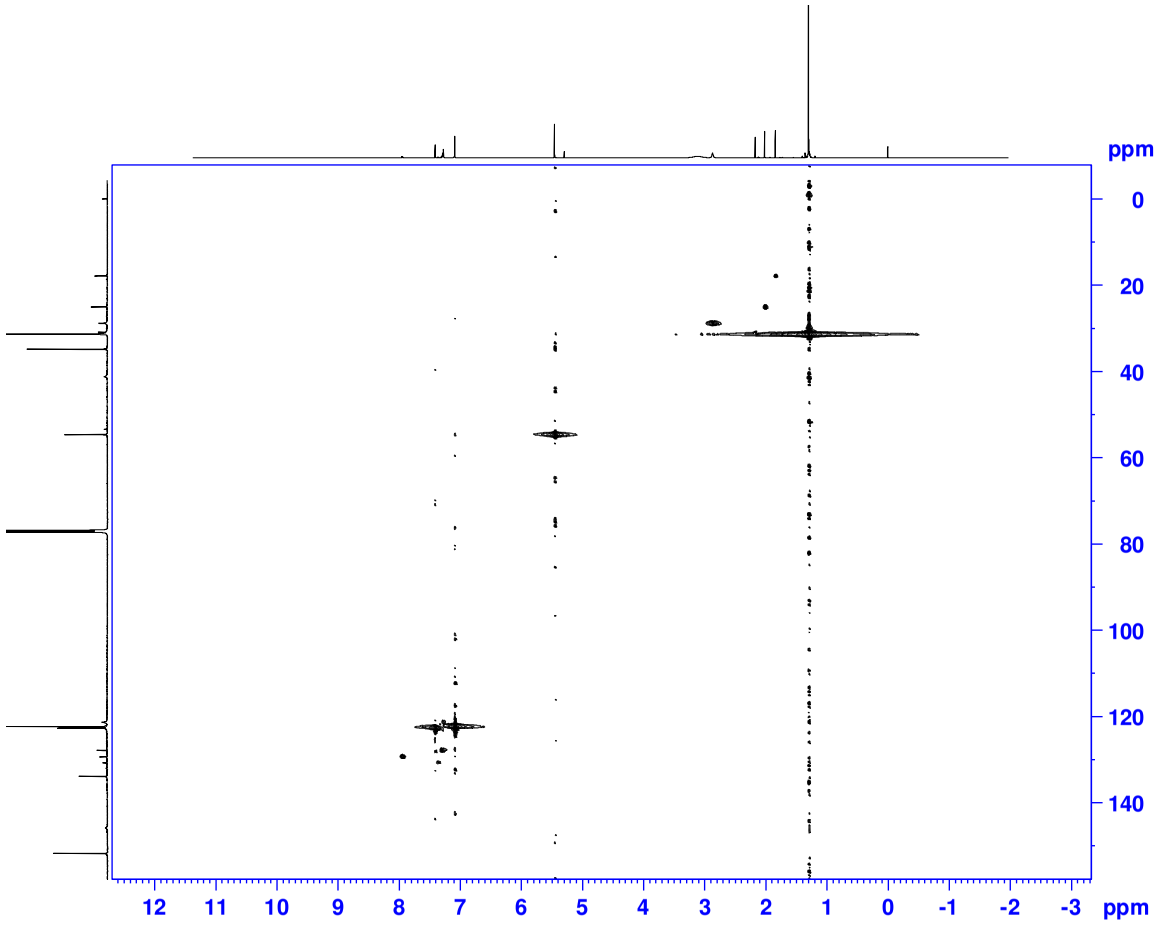

```
Current Data Parameters
NAME            okh0906-1
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150616
Time                19.57
INSTRUM             spect
PROBHD    5 mm CPQCI 1H-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                      8
DS                      0
SWH              8012.820 Hz
FIDRES           0.122266 Hz
AQ               4.0894465 sec
RG                   40.3
DW                 62.400 usec
DE                 49.10 usec
TE                 300.0 K
D1            2.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          600.2328255 MHz
NUC1                   1H
P1                   9.83 usec
PLW1          5.01189995 W

F2 - Processing parameters
SI                 131072
SF            600.2300075 MHz
WDW                    EM
SSB       0
LB        0 Hz
GB        0
PC                   0.80
```

K.3 ^{13}C NMRspectrum of 7b



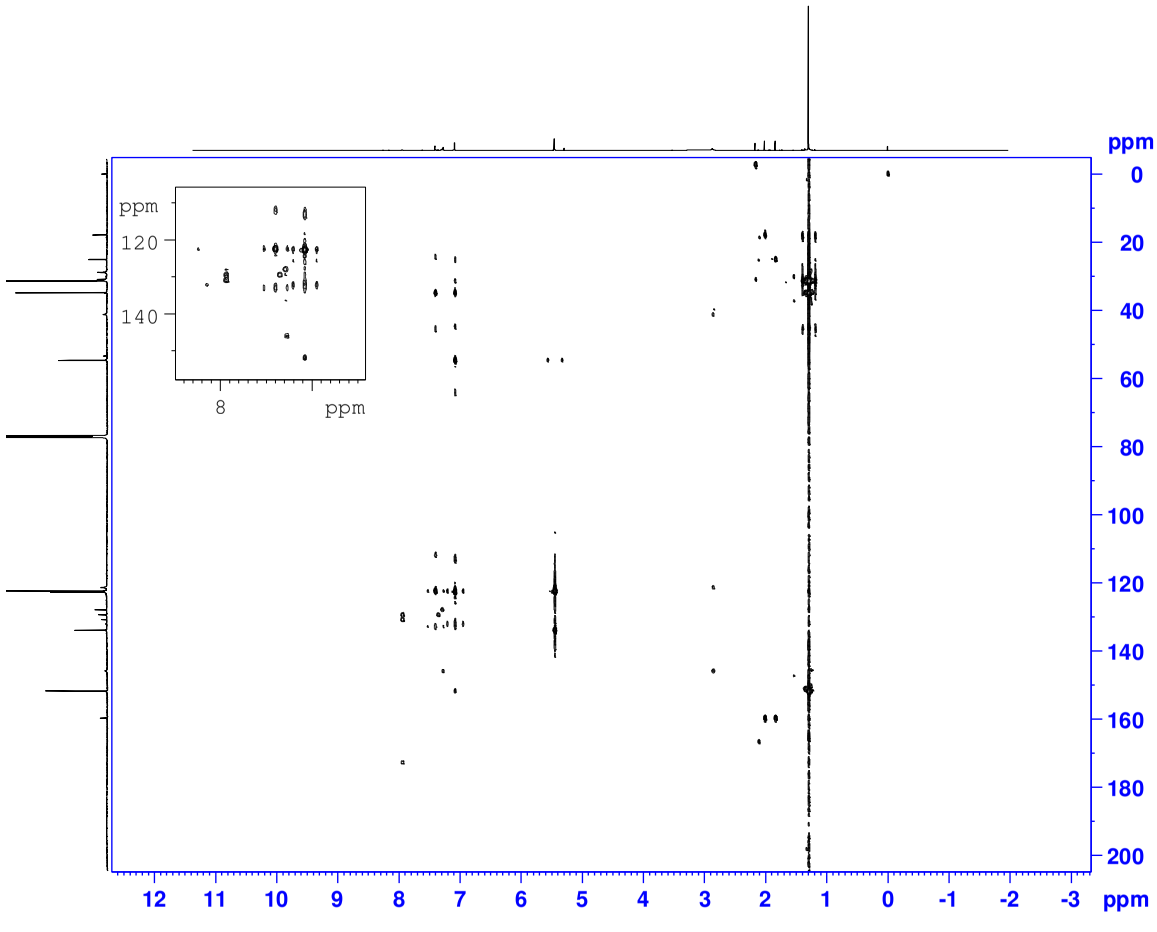

```
Current Data Parameters
NAME          okh0906-1
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20150616
Time              20.30
INSTRUM           spect
PROBHD   5 mm CPQCI 1H-
PULPROG          zgpg30
TD               131072
SOLVENT            CDCl3
NS                   512
DS                     2
SWH           31512.605 Hz
FIDRES         0.240422 Hz
AQ            2.0796757 sec
RG                   203
DW               15.867 usec
DE                76.64 usec
TE                300.0 K
D1           1.50000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1        150.9430468 MHz
NUC1                13C
P1                11.80 usec
PLW1        93.32499695 W

======== CHANNEL f2 ========
SFO2        600.2324009 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 usec
PLW2          5.01189995 W
PLW12         0.06222900 W
PLW13         0.03049200 W

F2 - Processing parameters
SI                 65536
SF          150.9279615 MHz
WDW                   EM
SSB       0
LB                 3.00 Hz
GB        0
PC                 1.40
```

K.4 HSQC spectrum of 7b



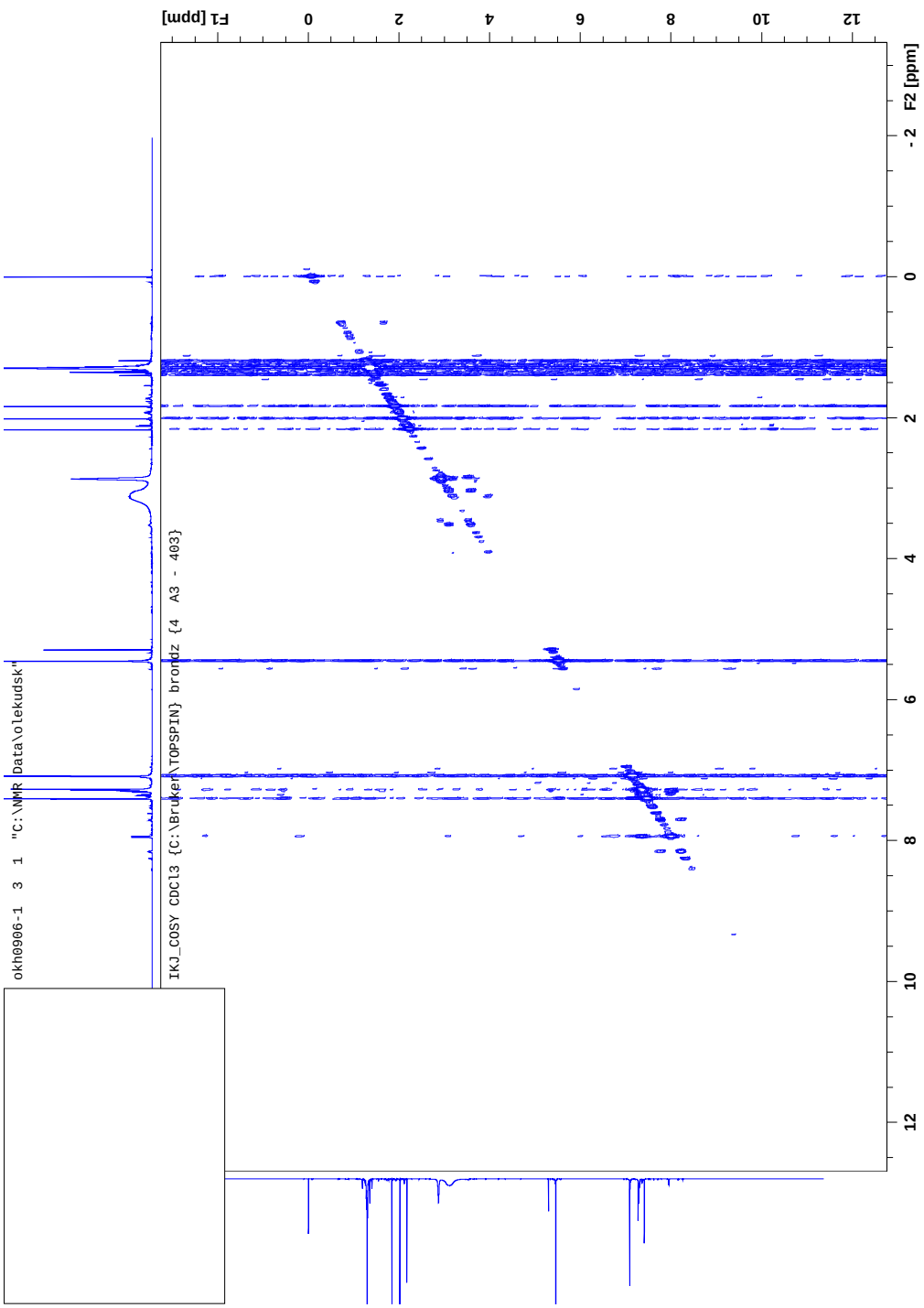

```
Current Data Parameters
NAME            okh0906-1
EXPNO                   4
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150616
Time                20.35
INSTRUM             spect
PROBHD   5 mm CPQCI 1H-
PULPROG  hsqcedetgpsisp.2
TD                  2048
SOLVENT             CDCl3
NS                     4
DS                    16
SWH              9615.385 Hz
FIDRES           4.695012 Hz
AQ               0.106496 sec
RG                    203
DW                 52.000 usec
DE                 40.00 usec
TE                 300.0 K
CNST2          145.0000000
CNST17          -0.5000000
D0              0.00000300 sec
D1              1.00000000 sec
D4              0.00172414 sec
D11             0.03000000 sec
D16             0.00020000 sec
D21             0.00344828 sec
D24             0.00086207 sec
IN0             0.00002000 sec

======== CHANNEL f1 ========
SFO1            600.2328255 MHz
NUC1                    1H
P1                   9.83 usec
P2                  19.66 usec
P28          0 usec
PLW1            5.01189995 W

======== CHANNEL f2 ========
SFO2            150.9392694 MHz
NUC2                    13C
CPDPRG[2                garp4
P3                  11.80 usec
P14                500.00 usec
P24               2000.00 usec
PCPD2               60.00 usec
PLW0         0 W
PLW2           93.32499695 W
PLW12           3.60960007 W
SPNAM[3] Crp60,0.5,20.1
SPOAL3                0.500
SPOFFS3   0 Hz
SPW3            19.85400009 W
SPNAM[7]     Crp60comp.4
SPOAL7                0.500
SPOFFS7   0 Hz
SPW7            19.85400009 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
GPZ2               20.10 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                    64
SFO1            150.9393 MHz
FIDRES        390.625000 Hz
SW                165.630 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                  2048
SF            600.2300129 MHz
WDW                 QSINE
SSB                     2
LB           0 Hz
GB           0
PC                   1.40

F1 - Processing parameters
SI                  1024
MC2          echo-antiecho
SF            150.9279540 MHz
WDW                 QSINE
SSB                     2
LB           0 Hz
GB           0
```

K.5 HMBC spectrum of 7b

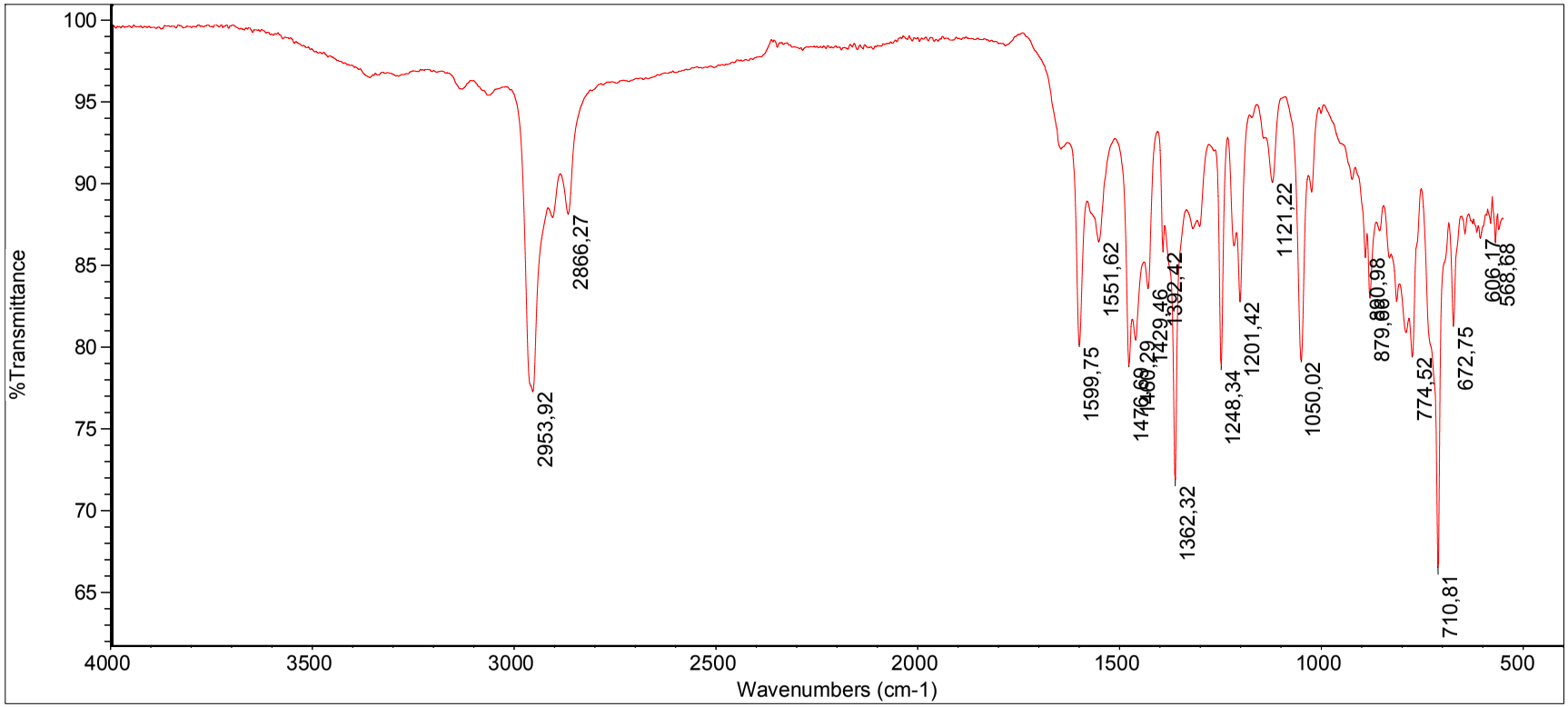



```
Current Data Parameters
NAME                 okh0906-1
EXPNO                        5
PROCNO                       1

F2 - Acquisition Parameters
Date_               20150616
Time                    20.42
INSTRUM                  spect
PROBHD     5 mm CPQCI 1H-
PULPROG    hmbcetgpl3ndpr
TD                       4096
SOLVENT                  CDCl3
NS                          8
DS                         16
SWH                  9615.385 Hz
FIDRES               2.347506 Hz
AQ                   0.2129920 sec
RG                         203
DW                      52.000 usec
DE                      40.00 usec
TE                      300.0 K
CNST6               125.0000000
CNST7               155.0000000
CNST13                7.0000000
CNST30                0.5981153
D0                    0.00003300 sec
D1                    1.00000000 sec
D6                    0.07142857 sec
D11                   0.03000000 sec
D12                   0.00002000 sec
D16                   0.00020000 sec
IN0                   0.00001580 sec

======== CHANNEL f1 ========
SFO1                600.2328255 MHz
NUC1                        1H
P1                        9.83 usec
P2                       19.66 usec
PLW1                 5.01189995 W
PLW9                 0.00001937 W

======== CHANNEL f2 ========
SFO2                150.9430468 MHz
NUC2                        13C
P3                       11.80 usec
P24                    2000.00 usec
PLW2                93.32499695 W
SPNAM[7]            Crp60comp.4
SPOAL7                    0.500
SPOFFS7  0 Hz
SPW7                19.85400009 W

====== GRADIENT CHANNEL ====
GPNAM[1]            SMSQ10.100
GPNAM[3]            SMSQ10.100
GPNAM[4]            SMSQ10.100
GPNAM[5]            SMSQ10.100
GPNAM[6]            SMSQ10.100
GPZ1                     80.00 %
GPZ3                     14.00 %
GPZ4                     -8.00 %
GPZ5                     -4.00 %
GPZ6                     -2.00 %
P16                   1000.00 usec

F1 - Acquisition parameters
TD                         256
SFO1                150.943 MHz
FIDRES              123.615509 Hz
SW                  209.652 ppm
FnMODE     Echo-Antiecho

F2 - Processing parameters
SI                        2048
SF                600.2300129 MHz
WDW                       QSINE
SSB          0
LB           0 Hz
GB           0
PC                        1.40

F1 - Processing parameters
SI                        1024
MC2            echo-antiecho
SF                150.9279540 MHz
WDW                       QSINE
SSB                          2
LB           0 Hz
GB           0
```

K.6 COSY spectrum of 7b

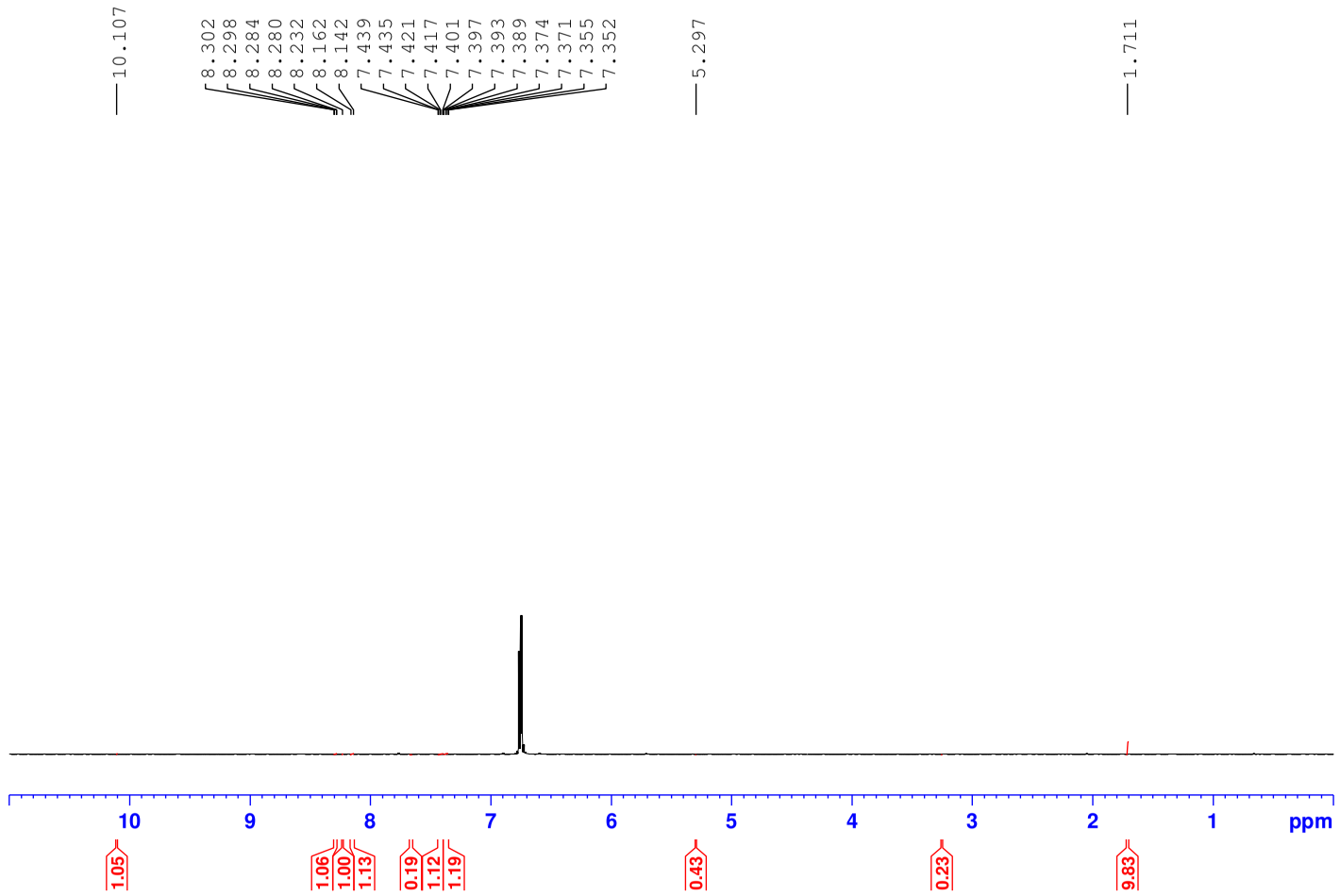


K.7 IR spectrum of 7b

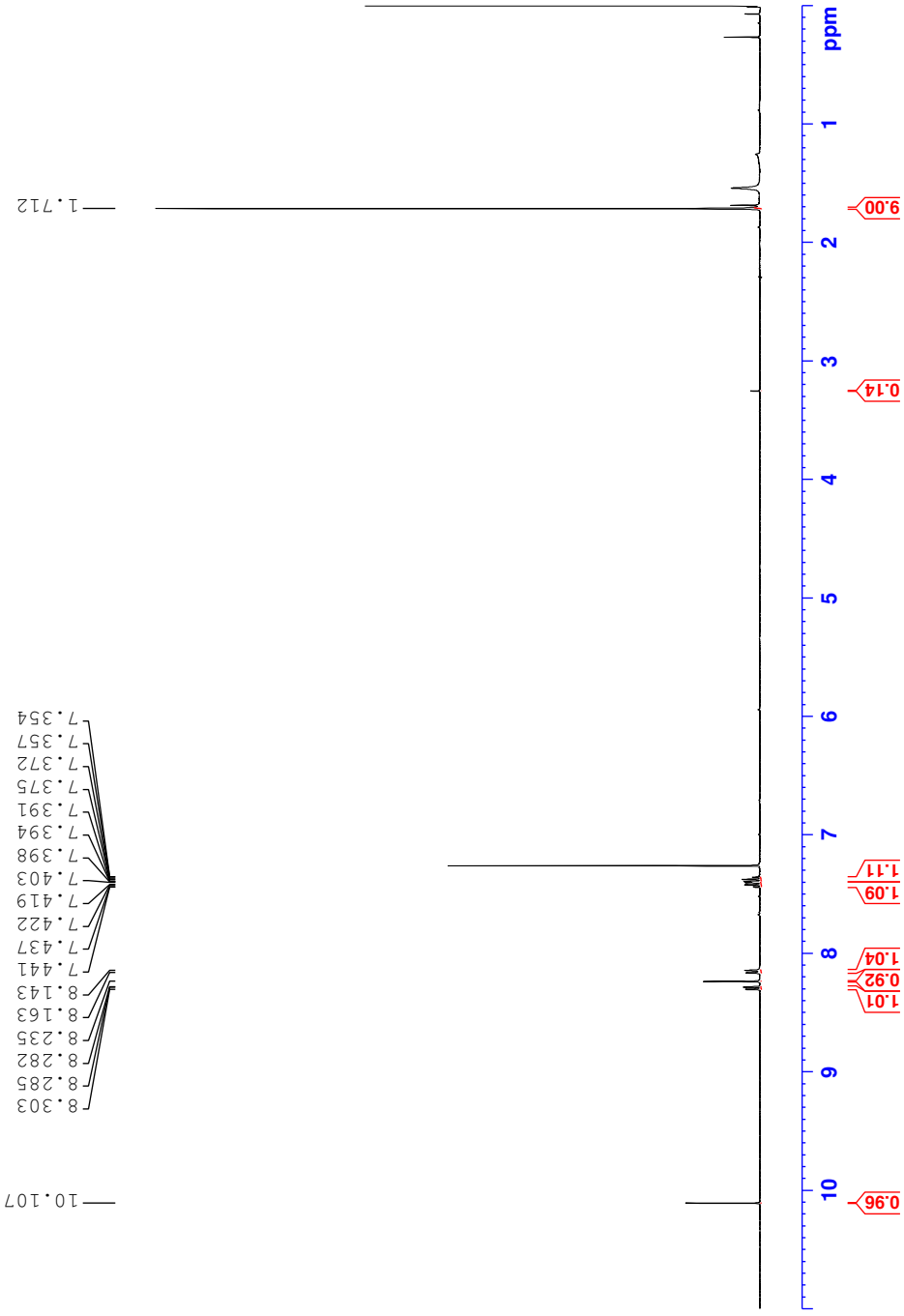


L ^{1}H NMR Spectra of the residues obtained in the attempted one-pot synthesis of 1c from 5a

L.1 ^{1}H NMR spectrum of residue, first parallel

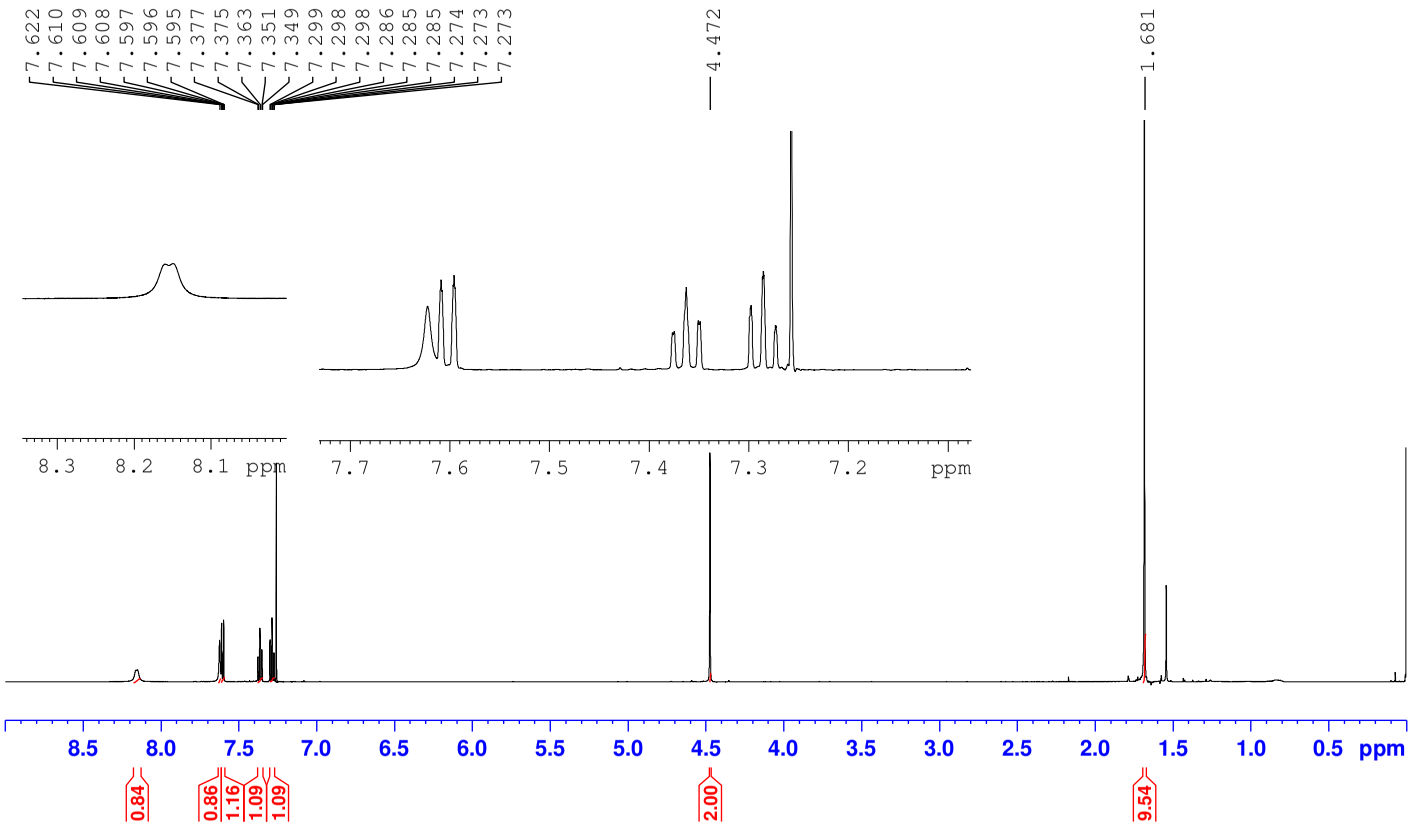


L.2 ^{1}H NMR spectrum residue, second parallel



M Spectra of 1c

M.1 ^{1}H NMR spectrum of 1c, first parallel



M.2 ^{1}H NMR spectrum of 1c, second parallel