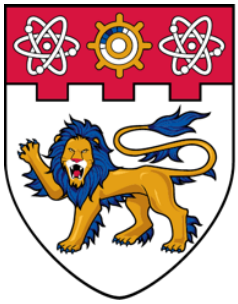

NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

SYNTHESIS OF DENSELY FUNCTIONALIZED PYRROLES FROM UNPROTECTED CARBOHYDRATES

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School of Chemistry, Chemical Engineering and Biotechnology

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Synthesis of Densely Functionalize Pyrroles from Unprotected Carbohydrates

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A thesis submitted to Nanyang Technological University in partial fulfillment of the requirement for the degree of Doctor of Philosophy

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research, is free of plagiarised materials, and has not been submitted for a higher degree to any other University or Institution.

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Authorship Attribution Statement

This thesis contains material from 1 paper published in the following peer reviewed journals in which I am listed as an author.

Chapter 2 is published as Xia, Mengxin, Mallikharjuna Rao Lambu, Madhu Babu Tatina, and Zaher MA Judeh. "A Practical Synthesis of Densely Functionalized Pyrroles via a Three-Component Cascade Reaction between Carbohydrates, Oxoacetonitriles, and Ammonium Acetate." *The Journal of Organic Chemistry* 86(1), 2020, 837-849. DOI: 10.1021/acs.joc.0c02381.

The contributions of the co-authors are as follows:

- Assoc. Prof. Zaher MA Judeh, Dr. Mallikharjuna Rao Lambu, and I developed the pyrrole synthesis methodology.
- I synthesized derived the pyrroles.
- Dr. Madhu Babu Tatina and Dr. Mallikharjuna Rao Lambu provided technical support in NMR spectroscopy.
- I performed the NMR spectroscopy, FT-IR, LC-MS, and data analysis.
- I wrote the manuscript with the help of Assoc. Prof. Zaher MA Judeh. Assoc. Prof. Zaher MA Judeh provided the initial project direction and edited the manuscript drafts.

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Abstract

Carbohydrates are important feedstock owing to their huge natural abundance, cheap price, and interesting properties. Compared with traditional fossil fuels, carbohydrates are suitable for synthesizing heterocycles because they are rich in functional groups such as hydroxyl, aldehyde, ketone, amino, and carboxylic acid moieties. Carbohydrates are considered as sustainable materials, and therefore, their direct conversion to various intermediates is of industrial relevance.

Pyrroles are a class of nitrogen heterocycles with diverse bioactivities including anti-inflammatory, anti-bacterial, anti-cancer, and anti-oxidative properties. The activity of pyrrole-based drugs is tuned with the type of substituents on the pyrrole core and on the substitution pattern on the core pyrrole ring. Therefore, huge attention has been paid to synthesizing suitably functionalized pyrroles. Although several syntheses have been successfully developed for pyrroles, green, cheap, and sustainable pyrrole synthesis methods are highly desired. In this work, green and practical methods using carbohydrates as the starting material for pyrrole synthesis will be explored and developed.

In Chapter One, an overview of carbohydrates and their usage as feedstocks was provided. A description of pyrroles and their use as drug compounds was included. Additionally, several pyrrole syntheses were introduced along with comments on their advantages and disadvantages.

In Chapter Two, unactivated carbohydrates, oxoacetonitriles, and ammonium acetate were combined in one-pot reaction to produce densely functionalized pyrroles in yields ranging from 75-96%. Novel pyrrolo-glycosides were produced *via* disaccharides. This Et_3N-catalyzed three-component reaction proceeded with exclusive chemo-, regio- and stereo-selectivities. It showed a wide substrate scope with high atom-economy and worked well at a 2-gram scale, indicating the possibility of large-scale synthesis. The functional groups on the pyrrole ring allows for the creation of more complicated compounds. The reaction proceeded through cascade mechanism comprising a few intermediates elucidated from mass spectrometry analysis. This work represents a significant step forward in the sustainable synthesis of densely functionalized pyrroles from inexpensive and easily accessible carbohydrates.

In Chapter Three, a one-pot, three-component reaction between unprotected sugars, primary amines, and 3-oxoacetonitriles gave *N*-substituted 2,3,5-functionalized pyrroles or *N*-substituted 2,3,4-functionalized pyrroles in excellent yields. The selectivity of the reaction is easily controlled by altering the order in which substrates are added. Different kinds of sugars, primary amines, and oxoacetonitriles all reacted easily demonstrating a wide substrate scope. The research provides a straightforward procedure for incorporating nitrogen into sugars to create important *N*-heterocyclic molecules that can be further modified to make natural products and drug intermediates.

In Chapter Four, *N*-substituted 2-amino-3-cyanopyrrole key framework was synthesized by combining unprotected carbohydrates, malononitrile, and primary amines in one-pot in up to 86% yield. This AcOH-catalyzed multicomponent reaction occurred under mild conditions in EtOH at 60 ^{o}C within 2 hours. It tolerated a broad substrate scope and worked smoothly on large scale (4 g). The usefulness of the synthesized pyrroles was demonstrated by converting their functional groups into other

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In Chapter Five, the reaction between α-hydroxyketones, oxoacetonitriles, and primary amines selectively gave *N*-substituted 2,3,5-functionalized 3-cyanopyrroles in up to 90% isolated yields. Here again, the reaction demonstrated broad substrate scope, proceeded under mild conditions (AcOH as a catalyst, EtOH, 70 ^{o}C, 3 h) and worked also on a large gram scale. Single-crystal X-ray diffraction and NMR experiments confirmed the structures of the 3-cyanopyrroles. The reaction can proceed through three pathways demonstrating the reactivity of the starting materials.

Overall, the dissertation focuses on developing novel one-step multicomponent selective synthesis of suitably substituted pyrrole from cheap carbohydrates. The protocols developed in this thesis provide various choices for synthesizing pyrroles with different substituents and different substitution pattern from both aldoses and ketoses. Large-scale reactions and excellent yields show the potential for these reactions to be practical at the industrial scale. The usefulness of the synthesized pyrroles was demonstrated for the synthesis of robust intermediates that can be used for the synthesis of drug candidates. The possible reaction pathways to obtain the pyrroles have been studied deeply using NMR and LC-MC to provide evidence for the mechanistic speculations presented in the literature. It is our hope that this can be realized one day to contribute to saving our planet.

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List of Abbreviations

Ac_2O – Acetic anhydride

ACN – Acetonitrile

AcOH – Acetic acid

$AgCO_3$ – Silver carbonate

CD_3OD – Methanol-d4 (deuterated methanol)

$CeCl_3$ – Cerium(III) chloride

$CHCl_3$ – Chloroform

CSA – Camphorsulfonic acid

$Cu(OTf)_2$ – Copper(II) trifluoromethanesulfonate

DABCO – 1,4-Diazabicyclo[2.2.2]octane

DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM/CH_2Cl_2 – Dichloromethane

DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DES – Deep eutectic solvent

DMAP – 4-Dimethylaminopyridine

DMF - Dimethylformamide

DMSO – Dimethyl sulfoxide

DNA – Deoxyribonucleic acid

Et_3N - Triethylamine

EtOAc – Ethyl acetate

EtOH - Ethanol

$FeCl_2$ – Ion(II) chloride

GHG – Greenhouse gases

H_2O - Water

HCOOH – Formic acid

HIV – Human immunodeficiency virus

HMF – Hydroxymethylfurfural

HRMS – High resolution mass spectrometry

$In(OTf)_3$ – Indium(III) trifluoromethanesulfonate

$InBr_3$ – Indium(III) bromide

$InCl_3$ – Indium(III) chloride

K_2CO_3 – Potassium carbonate

LC-MS – Liquid chromatography-mass spectrometry

MCR – Multi-component reaction

MeOH/CH3OH - Methanol

$Mn(OAc)_3$ – Manganese(II) acetate

NaH – Sodium hydride

NaOAc – Sodium acetate

NaOMe – Sodium methoxide

n-BuLi – *n*-Butyllithium

NH_4OAc – Ammonium acetate

NMP – N-Methyl-2-pyrrolidone

NMR – Nuclear magnetic resonance

NSAID – Nonsteroidal anti-inflammatory drug

PTSA – *p*-Toluenesulfonic acid

RNA – Ribonucleic acid

$Sc(OTf)_3$ – Scandium(III) trifluoromethanesulfonate

TBAB – Tetrabutylammonium bromide

TBAF – Tetrabutylammonium fluoride

TBAHS – Tetrabutylammonium hydrogen sylfate/bisulfate

t-BuOK – Potassium *t*-butoxide

TFA – Trifluoroacetic acid

THF – Tetrahydrofuran

TLC – Thin-layer chromatography

TosMIC – Toluenesulfonylmethyl isocyanide

XRD – X-ray crystallography

$Yb(OTf)_3$ – Ytterbium(III) trifluoromethanesulfonate

$Zn(OTf)_2$ – Zinc(II) trifluoromethanesulfonate

$ZnCl_2$ – Zinc(II) chloride

Chapter 1. Introduction and Scope of Thesis

1.1 Carbohydrates

Carbohydrates are important compounds that exist abundantly in nature, they play a critical role by providing physical, chemical, and biological properties to both natural and industrial molecules.[1] Also, carbohydrates act as one of the major energy supplying compounds.[2, 3] Additionally, carbohydrates may be converted to coal and petroleum through millions of years of chemical and physical processes.[1]

In biological systems, carbohydrates are involved in numerous biological activities such as cell-cell recognition, cellular transport, and cell adhesion. Likewise, carbohydrates are responsible for multiple functions, including control of growth and differentiation in almost every living organism, due to their presence in cells or on cell membranes as glycopeptides, glycoproteins, glycolipids, and nucleic acids.[4-7]

Plenty of carbohydrate derivatives have critical bioactivities, including some well-known carbohydrate-related compounds.[1, 8, 9] Every nucleotide, for example, contains a ribose or deoxyribose, and nucleotides are the most important essential genetic building blocks of DNA and RNA (Figure 1-1). Puromycin, a common amino-nucleoside antibiotic, has been used to select genetically modified cells (Figure 1). Paromomycin, an amino sugar, has been found and clinically applied to treat acute and chronic intestinal amebiasis (Figure 1-1). Muramic acid, itself and its derivatives are backbone components of many bacterial cell walls (Figure 1-1). Furthermore, the mannose-derived *N*-linked mannoside $(Man)_9(GlcNAc)_2$ is a component in the design of a carbohydrate-based vaccine against HIV (Figure 1-1).[9, 10] Additionally, more research is being conducted to develop anti-inflammatory drugs from mannose.[11]

In organic chemistry, carbohydrates and their derivatives serve as ‘chiral pool’ compounds,[1] because of their contributions to the enantioselective synthesis of bioactive molecules, such as the nucleotides and mannose derivatives mentioned above.[8, 9, 11, 12] In industry,

carbohydrates produce edible sugars and food,[13] lumber, papers, pulps, and diverse types of fibers,[14] and they are used as drug ingredients as well (i.e. starch as a drug carrier [15]).

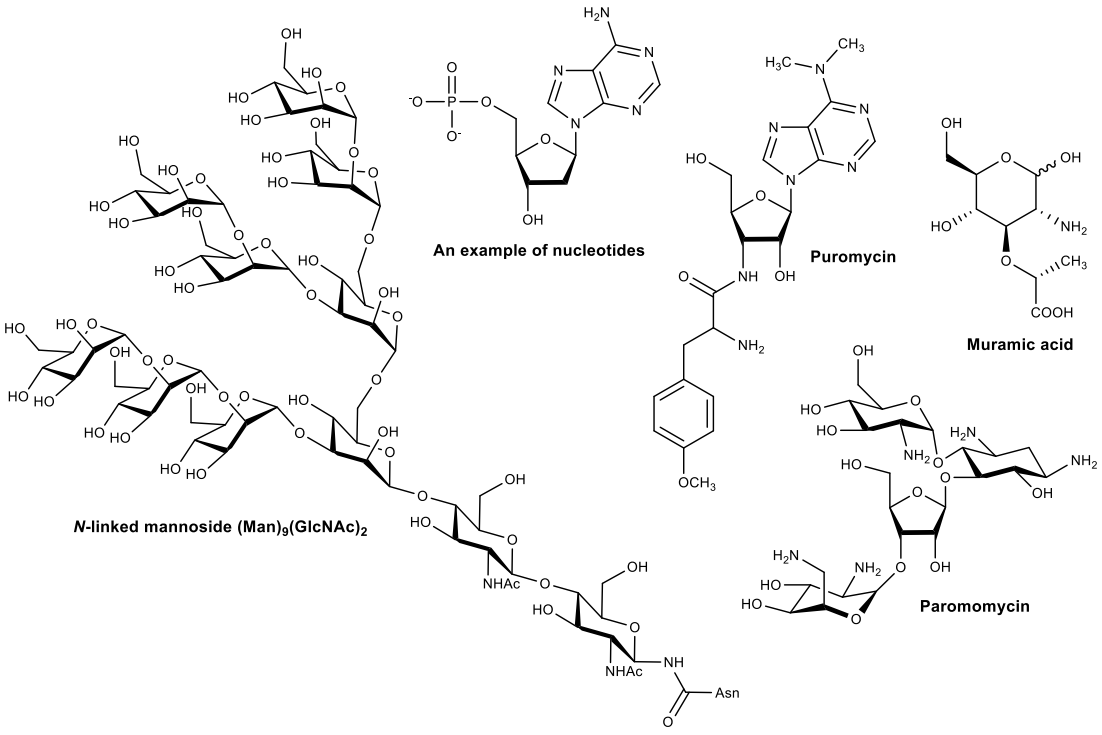


Figure 1-1. Examples of useful bioactive carbohydrates and their derivatives.

Carbohydrates have attracted huge interest from researchers and chemists because of their wide participation in different fields, but problems still exist in the extraction, structure/configuration identification, synthesis, and modification of these carbohydrates. Carbohydrates are excellent tools to help humans understand organisms, develop cutting-edge medical treatments, and overcome the upcoming feedstock shortage.

1.1.1 Classification of carbohydrates

According to the chemical structures, carbohydrates are classified and divided into two groups: sugars and non-sugars. Carbohydrates that contain one to ten monosaccharide units are named ‘sugar’ while those that comprise more than ten monosaccharide units and do not have a sweet taste are termed ‘non-sugar’. Additionally, carbohydrates that contain three to ten monosaccharide units are called oligosaccharides (Figure 1-2).[16]

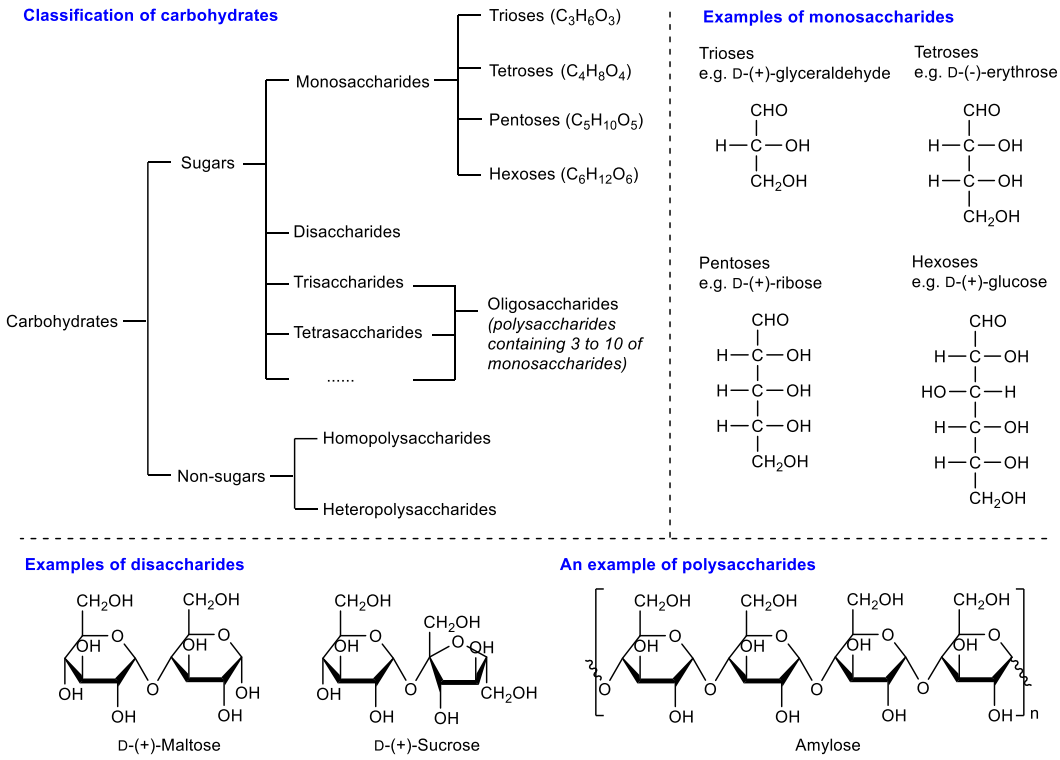


Figure 1-2. Classification of carbohydrates.

Monosaccharides are represented by the formula $C_nH_{2n}O_n$. They are optically active and soluble in water and organic solvents with high polarity. Monosaccharides can be sub-categorized into aldoses and ketoses. An aldose is a saccharide with a carbon backbone chain with an aldehyde group on the end carbon and hydroxy groups connected to all the other carbons. Ketoses can be differentiated from aldoses because their terminal side is a hydroxymethyl linked with a ketone (Figure 1-3, a).[12, 17]

The sugar 'D' and 'L' configurations are identified by the OH group of the bottom asymmetric carbon when the CHO group is at the top of the formula in the Fischer projection. If it is located on the right, it is designated with a 'D', and vice versa (Figure 1-3, b). Actually, all naturally occurring monosaccharides are D- sugars. The symbol (+) or (-) indicates the direction of optical rotation resulting from the polarimeter; the (+) mains dextro-rotatory (clockwise direction), whereas the (-) mains laevorotatory (anti-clockwise direction). All naturally occurring monosaccharides are dextro-rotatory, except fructose and erythrose.[12, 17]

Furthermore, there is substantial evidence that monosaccharides exist in a cyclic molecular form; thus, monosaccharide structures can be divided into - and -based on their stereochemistry. For instance, two ring forms of D-glucose are known to exist in nature: α-D-glucose and β-D-glucose. In the chain formulae, the α- structure is the name given to the configuration of a cyclic sugar where the oxygen on the anomeric carbon is on the opposite facets of the ring, contrasting with β- which is where the two substituents are on the same facet of the ring (Figure 1-3, c).[12, 17]

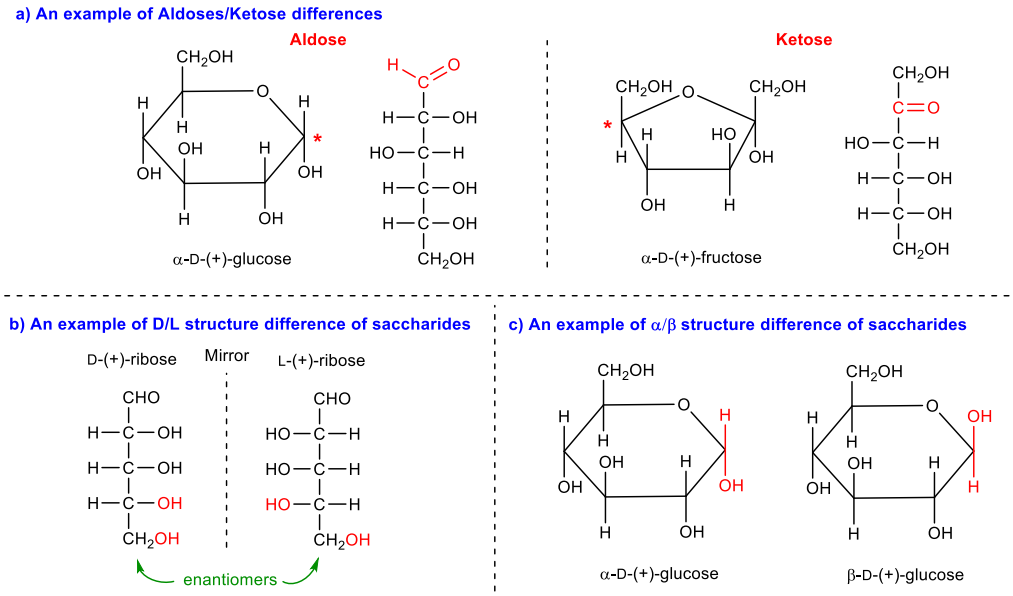


Figure 1-3. Structures of aldoses/ketoses, D/L configurations and α/β structures.

1.1.2 Carbohydrates as sustainable materials for synthesis of feedstocks

The fast growth in population and economies worldwide has led to a sharp increase in global energy consumption. Petrol resources are being over-consumed as global demand rises; their depletion has caused the rapid growth of their price. At the same time, burning fossil fuels causes environmental pollution and releases greenhouse gases (GHG). Based on these situations, people are starting to find alternatives to fossil fuels and petrochemicals to solve environmental

pollution, among renewable resources, carbohydrates are an attractive candidate because they are cheap, available in abundance, and sustainable.

The productivity and prices (in Euro) in bulky quantities of the eight cheapest carbohydrates and acid/alcohol derivatives are listed in Table 1-1, with comparison to those fundamental chemicals from petrol fuel sources that are all below € 10/kg.[18, 19]

Table 1-1. Annual production volume and prices of simple sugars, sugar-derived alcohols and acids as compared to petrochemically derived basic chemicals and solvents.[18, 19]

		World production	Price
Sugars	Sucrose	130 000 000	0.20
	D-Glucose	30 000 000	0.30
	Lactose	295 000	0.60
	D-Fructose	60 000	1.00
	Isomaltose	70 000	2.00
	Maltose	3000	3.00
	D-Xylose	25 000	4.50
	L-Sorbose	60 000	7.50
Sugar alcohols	D-Sorbitol	650 000	1.80
	Erythritol	30 000	2.25
	Xylitol	30 000	5.00
	D-Mannitol	30 000	8.00
Sugar-derived acids	Citric acid	1 500 000	1.00
	D-Gluconic acid	60 000	1.40
	L-Lactic acid	150 000	1.75
	L-Tartaric acid	35 000	6.00
	L-Ascorbic acid	80 000	8.00
	L-Glutamic acid	1 5000 000	1.20
	L-Lysine	740 000	2.00
Petrochemicals	Ethylene	90 000 000	0.40
	Propylene	45 000 000	0.35
	Benzene	23 000 000	0.40
	Terephthalic acid	12 000 000	0.70
	Aniline	1 300 000	0.95
	Acetaldehyde	900 000	1.10
	Adipic acid	1 500 000	1.70

Solvents	Methanol	25 000 000	0.15
	Toluene	6 500 000	0.25
	Acetone	3 200 000	0.55

The comparison result is surprising and appealing since cheap saccharides and their derivatives, such as acids and alcohols, are also within the comparable price range as basic petrochemicals and solvents like ethylene, acetaldehyde, or methanol. In fact, the utilization of carbohydrates would be much greener than fossil-based feedstocks. Most of the fossil-based resources are hydrocarbons, they lack functional groups and oxygen or nitrogen atoms. Substitutions such as hydroxyl, carbonyl, acid, ester, and amino groups need to be introduced to them to obtain the industrially important intermediates. On the other hand, sugars are fully functionalized with hydroxyl, aldehyde, or ketone groups, and thus are highly hydrophilic (Figure 1-4).[18] Based on the differences in their structures and element composition, modifying those fossil resources is likely to be a complex and wasteful process, with significant carbon dioxide emissions; while converting carbohydrates to viable chemicals only requires a reduction in oxygen content and the introduction of several unsaturated bonds, resulting in less carbon dioxide emissions.[18-20]

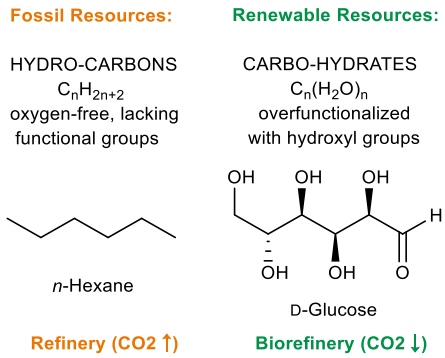


Figure 1-4. Hydrocarbons vs carbohydrates as industrial raw materials.[18]

Carbohydrates are appealing materials, but challenges are present when utilizing them. For example, the cost of consumption to produce fuel ethanol from saccharide-based feedstocks is 60-70%, which is too high to afford.[21] Most carbohydrates that occur in nature are complex

polysaccharides such as chitin, lignocellulose, and hemicellulose, which are difficult to apply unless they are converted into smaller units.[1] Meanwhile, these small units and derived chemicals must maintain their chirality, carbon backbones, reactivity, and important functional groups to keep them as useful biomass resources.

In organic synthesis, carbohydrates and their derivatives contain plenty of functional groups, but problems also exist when using carbohydrates in synthesis. First, sugars are poly-functionalized compounds, the selectivity and stereo-control are problematic due to the chirality and multiple groups. To ensure high regio- and stereoselectivity, classic organic synthesis relies on protection/deprotection strategies.[22, 23] Such approaches often result in complicated synthetic procedures that are tedious and time-consuming.

Moreover, most of the carbohydrates are only soluble in water or aqueous solutions, while numerous reactions in organic chemistry are conducted in non-aqueous systems. This incompatibility has posed huge problems for reactions between carbohydrates and some organic compounds.

1.1.3. Present industrial chemicals derived from carbohydrates

Existing carbohydrate conversion methods are microbial-based fermentation,[24] thermocatalytic or pyrolytic processes, and chemical-catalytic methods. Among these methods, the least commercialized strategies are the chemical-catalytic methods.

Nevertheless, chemical-catalytic carbohydrate handling processes have high potential to become the future's leading technology, because they are timesaving, versatile, cheap, and have less carbon dioxide emissions. At present, plenty of important chemicals have been obtained from cellulose and hemicellulose using chemical, enzymatic, or chemo-enzymatic processes (Figure 1-5).[20] Furthermore, among all the carbohydrate-derived industrial intermediates shown

in Figure 1-5, the most valuable and useful chemicals are 2-furaldehyde (furfural) and hydroxymethylfurfural (HMF).[19, 25]

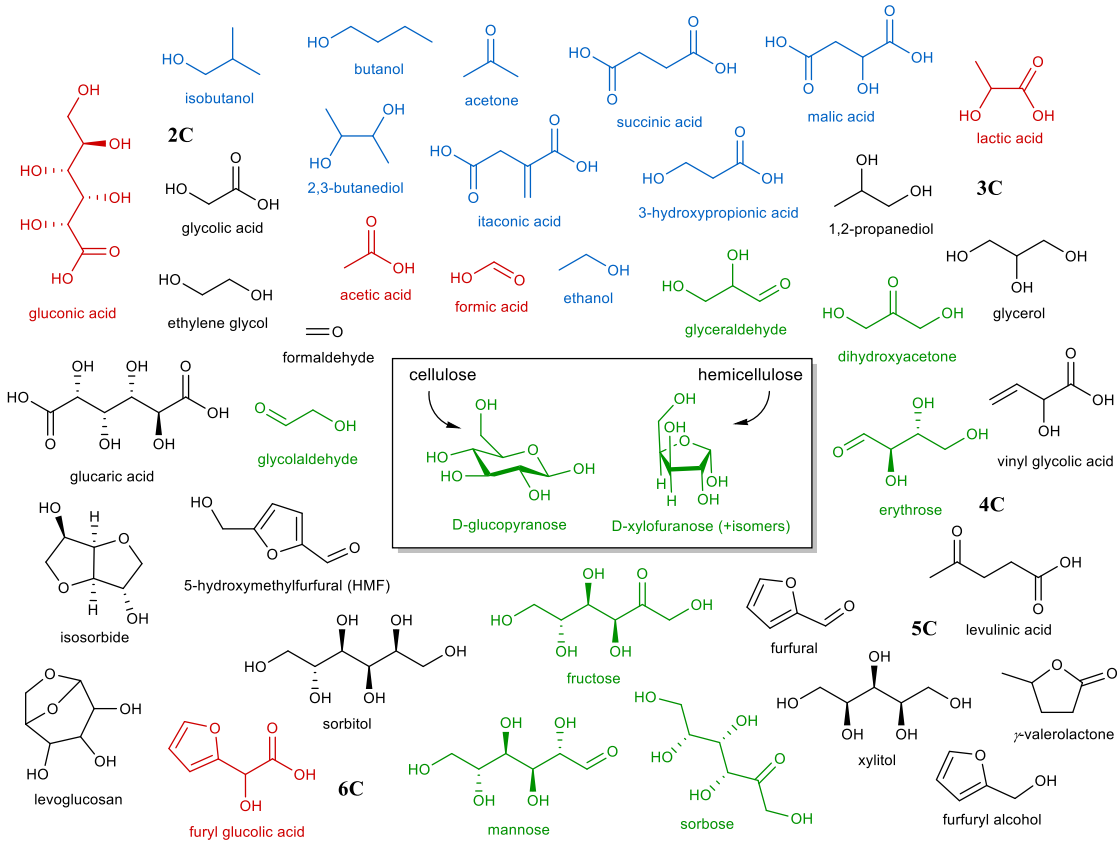


Figure 1-5. Prominent conversion products of carbohydrates. Green: sugars. Black: via chemical catalysis. Blue: via bio-catalysis. Red: via bio-and/or chemical catalysis.[20]

1.1.3.1 2-Furaldehyde

Furfural (2-furaldehyde) is the only unsaturated organic chemical that is produced in large quantities (over 200,000 tons per year). Transformation of carbohydrates to furfural involves adding aqueous acid to agricultural or forestry wastes that contain pentosans under high temperatures. In this process, the pentosans will be hydrolysed to pentoses (mostly D-xylose), and then undergo dehydration and cyclization to give furfural.[26-28]

The chemistry of furfural is well-established, providing a host of versatile industrial intermediates in the short procedures (Figure 1-6). Furfural is the key substrate in

commercialized manufacture of furan because furan can be obtained by furfural through simple catalytic decarbonization. Because of the high modification potential of furfural, it provides a biomass-based alternative to its petrochemical production via the dehydration of 1,4-butanediol. The further prominence of these furanic chemicals is that their rings can be adjusted to produce various other established chemicals. For instance, decyclization of furfural or furfuryl alcohol can provide levulinic acid, and maleic anhydride is also producible from furfural or furan.[19]

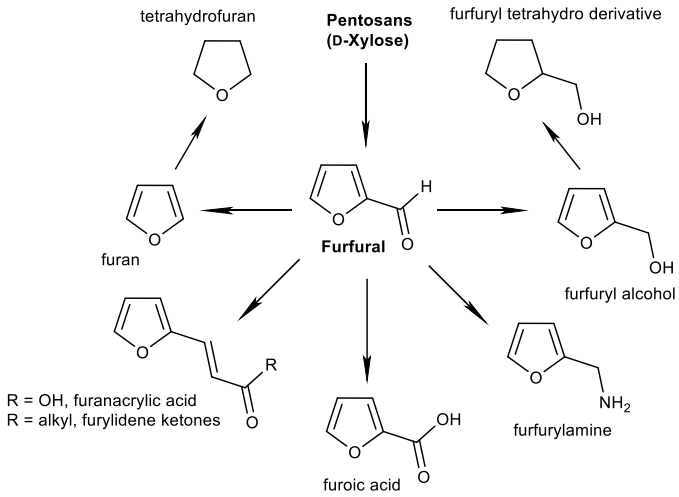


Figure 1-6. Furanic commodity chemicals derived from pentosans in agricultural wastes.[19]

1.1.3.2 Hydroxymethylfurfural

Like furfural, hydroxymethylfurfural (HMF) is a simple heterocycle with high industrial value. The production of HMF is viable by the acid dehydration of D-glucose, D-fructose, and inulin, and these processes have already been commercialized.[19, 25, 29] Among these starting materials, D-fructose undergoes a faster reaction than D-glucose because of its less stability.[30] Also, HMF can also be obtained from furfural through a simple process.[31] HMF is a flexible precursor in the library of other high industrial potential intermediates such as 2,5-diformylfuran, 2,5-furandicarboxylic acid, and 5,5'-(oxybis(methylene)) bis(furan-2-carbaldehyde) (Figure 1-7). The protocols to produce these intermediates are mature and are being adapted on a large scale.[32]

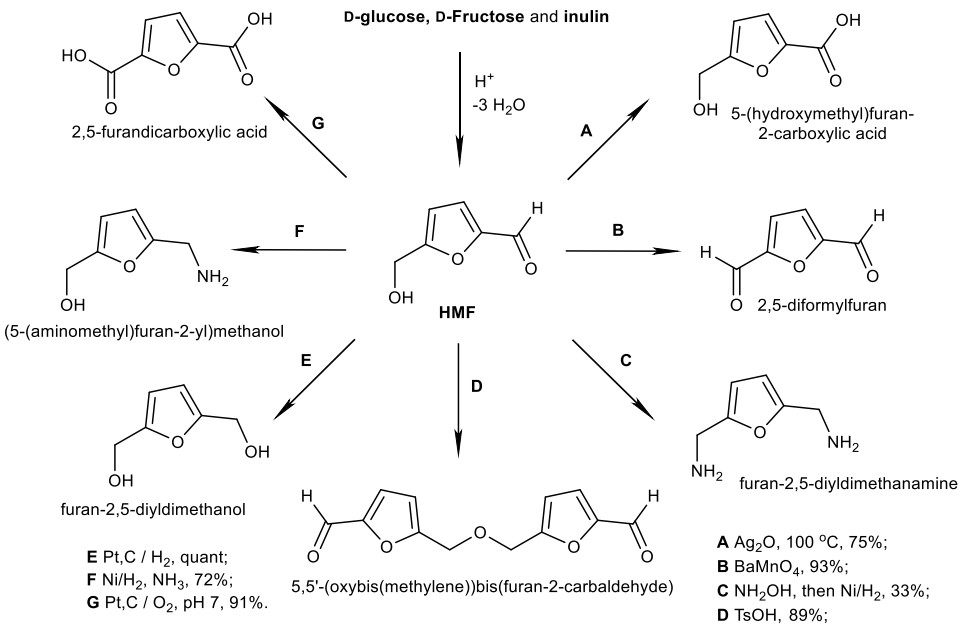


Figure 1-7. Versatile intermediates derived from hydroxymethylfurfural (HMF).[19]

1.1.4 Conversion of carbohydrates to furans and early work from our lab

The Knoevenagel condensation of carbohydrates and 1,3-dicarbonyl compounds in acidic conditions was first published by Garcia Gónzalez in the 1950s. He developed a $ZnCl_2$-catalyzed reaction between D-glucose and 1,3-dicarbonyl compounds to give polyhydroxyalkyl 2,3,5-functionalized furans (Figure 1-8).[33]

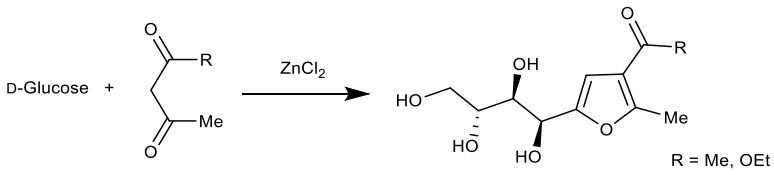


Figure 1-8. $ZnCl_2$-catalyzed synthesis of polyhydroxyalkyl furans from D-glucose and 1,3-dicarbonyl compounds.

The Garcia Gónzalez 's $ZnCl_2$-catalyzed Knoevenagel reaction provided an important entry to synthesize intermediates of bioactive molecules. It has become the first step of the synthesis of selective inhibitors of α-L-fucosidases,[34] D- and L-serine [35] and furanosyl α-C-glycosides [36]. (Figure 1-9)

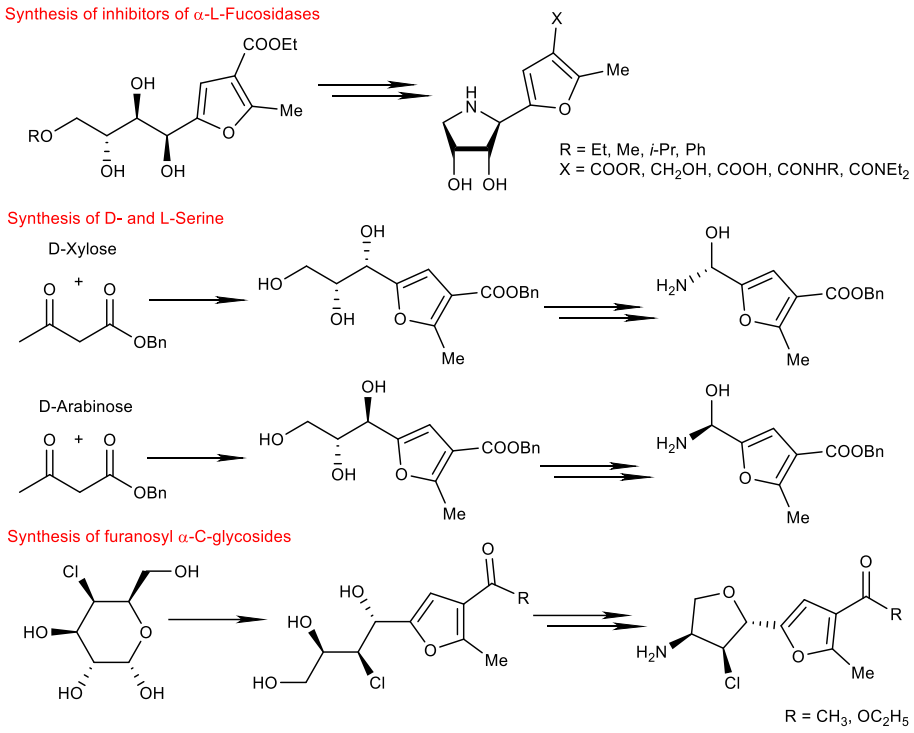


Figure 1-9. Synthesis of bioactive molecules with Garcia Gónzalez as the first step.

Misra and Agnihotri discovered the Knoevenagel condensation of different aldoses with 2,4-pentandione or ethyl acetoacetate using $CeCl_3 \cdot 7H_2O$ in aqueous condition, this reaction obtained higher yields than the previous reaction (Figure 1-10).[37] Under this reaction condition, pentoses produced furans with polyhydroxyalkyl side chains, whereas the polyhydroxyl chains of hexoses and disaccharides got cyclized and yield β-linked hydroxylated tetrahydrofuranylfuran derivatives.

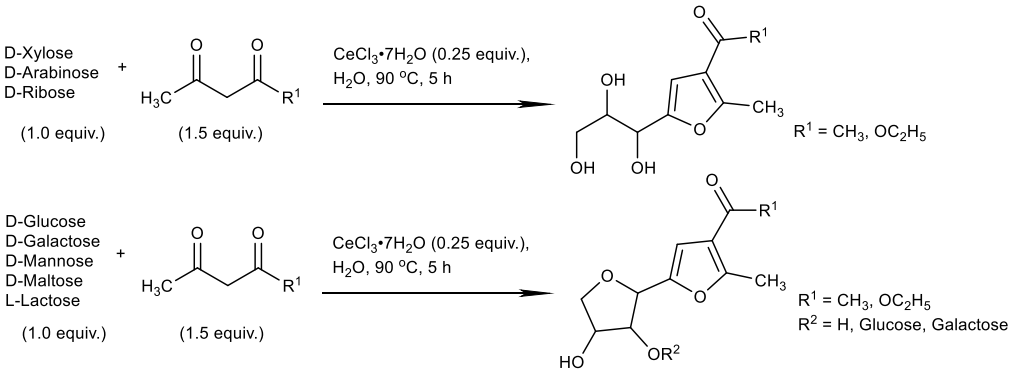


Figure 1-10. Synthesis of multi-substituted furans from aldose and 1,3-dicarbonyl compounds with $CeCl_3$ by Misra and Agnihotri.

Later, Yadav *et al.* reported similar reaction catalyzed by $InCl_3$ which gave similar products and yields.[38] Two other substrates, cyclohexane-1,3-dione and 5,5-dimethylcyclohexane-1,3-dione, were tested with D-glucose in this study, and β-linked tetrahydrobenzofuranyl glycosides were obtained (Figure 1-11).

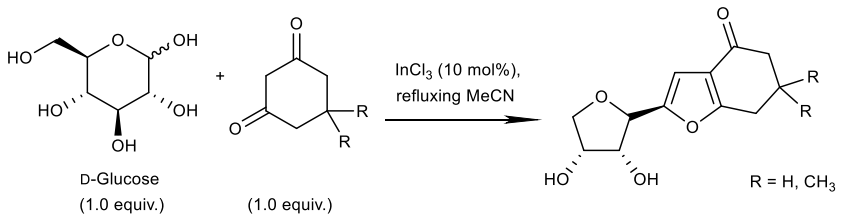


Figure 1-11. $InCl_3$-catalized synthesis of multi-substituted furans from aldose and 5,5-dimethylcyclohexane-1,3-dione.

Sato *et al.* reported the $Sc(OTf)_3$-catalized reaction between D-ribose and cyclohexane-1,3-dione to give 6,6-dimethyl-6,7-dihydrobenzofuran-4(5*H*)-one, promoted by. But interestingly, when catalysing this reaction by scandium cation-exchanged montmorillonite (Sc^{3+}-mont.), the 3,3,6,6-tetramethyl-9-tetrahydroxybutyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2*H*)-dione was formed instead (Figure 1-12).[39]

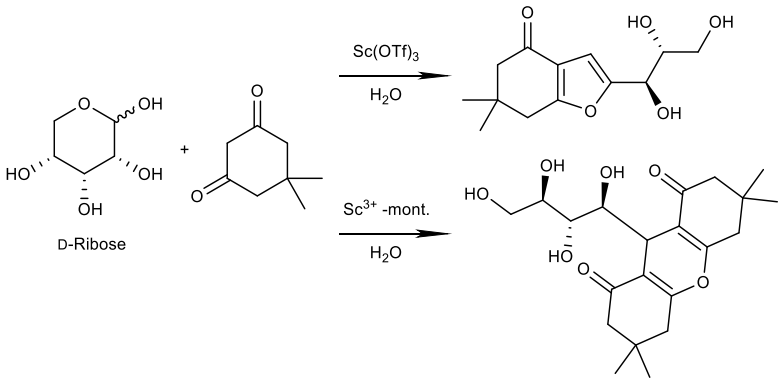


Figure 1-12. Synthesis of multi-substituted furans from ribose and 5,5-dimethylcyclohexane-1,3-dione with $Sc(OTf)_3$ and Sc^{3+}-month.

Yet, problems exist in these acid-catalyzed furan synthesis methods. First, when using pentoses, the products usually contain an un-annulated polyhydroxyalkyl chain; however, the polyhydroxyalkyl chain on products from hexoses and disaccharides is annulated. The annulated

furan products largely limited the following modifications of the furan products, and the reactions might provide enantiomorphs at the same time, which raised purification problems. Besides, only 1,3-dicarbonyl compounds were investigated in these protocols, thus restricting the variety of the furans. Because of these disadvantages, multi-step modifications are required to get the intended furans from the products.

After so many studies on furan synthesis under acidic conditions, some researchers tended to explore it in basic conditions. However, when barbituric acids were applied to replace the general 1,3-dicarbonyl compounds, the reaction with D-glucosamine only generated C-glycosyl barbiturates instead of furans (Figure 1-13, i).[40, 41] When the same reaction was conducted with Meldrum's acid in in DMF, 3,6-anhydro-1,4-lactones were obtained as major products (Figure 1-13, ii).[42-44]

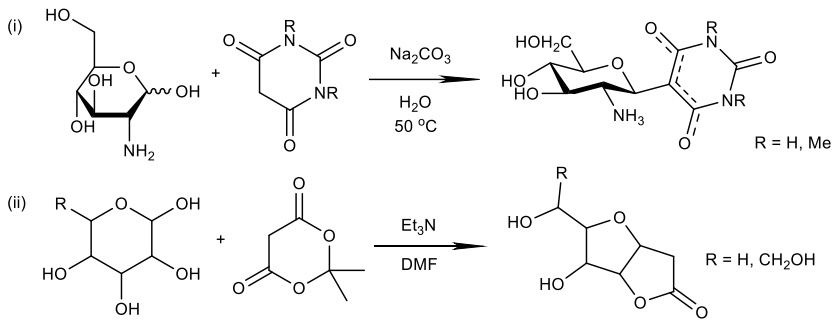


Figure 1-13. Reaction of carbohydrates with barbituric acids, and reaction of aldose and Meldrum's acid with Et_3N in DMF.

Although it appears that all attempts to synthesize furan from carbohydrates under basic conditions failed, our group reported the Et_3N-catalyzed reaction between unprotected carbohydrates and active nitriles successfully. This is a one-pot, selective reaction that gives multi-functionalized furans in aqueous basic conditions. In this reaction, a total of ten different carbohydrates were used, covering hexoses, pentoses, and disaccharides. (Figure 1-14).[45] This reaction achieved almost quantitative yield and with excellent atom economy, and successfully

provided furans with an un-annulated polyhydroxyalkyl chain from both hexoses and disaccharides.

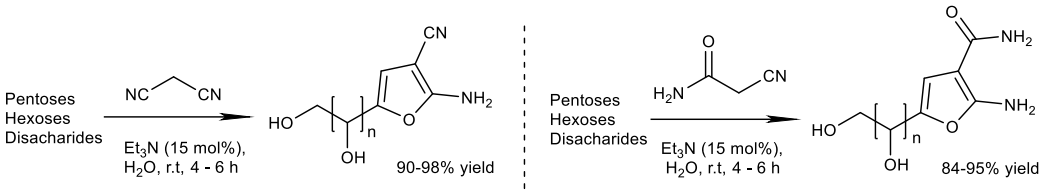


Figure 1-14. Synthesis of multi-functionalized furans from carbohydrates reported.

1.1.5 Conversion of carbohydrates to *N*-heterocycles

Many bioactive *N*-heterocycles are derived from carbohydrates in nature. For instance, the nucleoside analogues are formed by an *N*-heterocycle plus a sugar moiety. The nucleosides uridine **1** contains uracil heterocycle, deoxythymidine **2** contains thymine heterocycle, and cytidine **3** contains cytosine heterocycle coupled to the sugar moiety, they are essential building blocks for the synthesis of DNA and RNA (Figure 1-15). Likewise, carbohydrate-derived *N*-heterocycles are also abundant in plants. Vicine **4** and Convicine **5** are β-glucopyranoside pyrimidine derivatives found in fava beans and cause the human disease *favism*. Another example of pyrimidine nucleoside is the arabinoside charine **6**, a constituent of Momordica charantina (Figure 1-15).

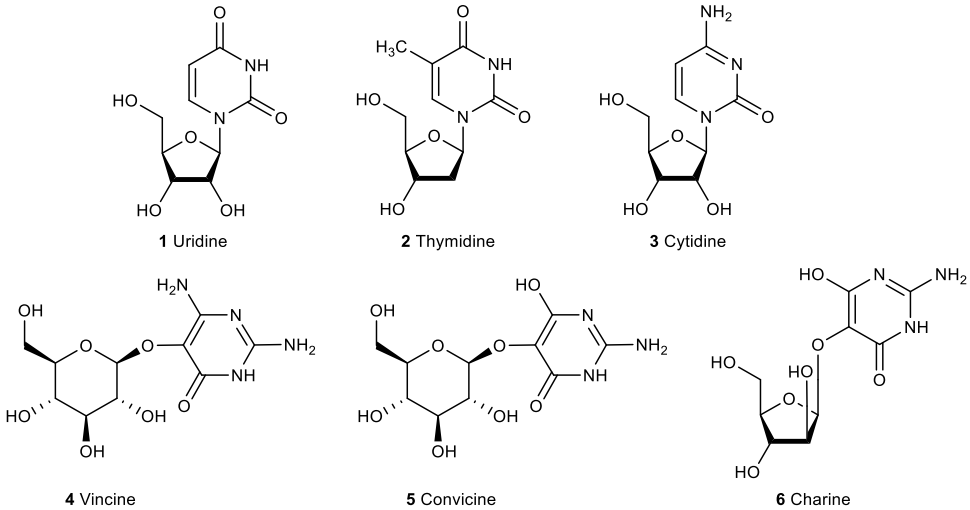


Figure 1-15. Sugar linked *N*-heterocycles nucleoside analogues and natural products.

Carbohydrates have been extensively used to introduce chirality in synthetic processes due to their highly functionalized structures, and the presence of plenty of chiral centers.[46, 47] Based on these advantageous properties, many important compounds have been generated from carbohydrates, such as natural occurring polyhydroxypyrrolidine **7**-**9**, therapeutic molecules **10**-**15**, and *N*-heterocyclic acyclonucleosides **16**-**18**.[48] (Figure 1-16)

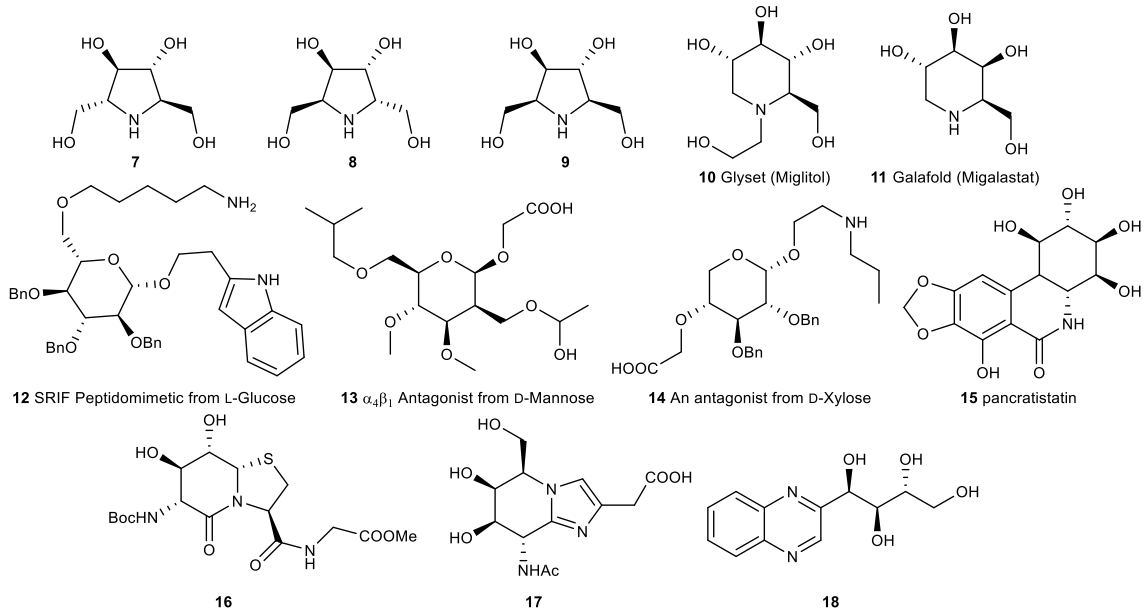


Figure 1-16. Important molecules generated from carbohydrates.

The improvement of present methodologies and the development of new synthesis routes have led to the accessibility of more *N*-heterocycle molecules from carbohydrates, such as pyrroles, pyridines, pyrazines, imidazoles, and pyrazoles.

Through the reaction between galactaric acid and ammonia, the pyrrole ring can be obtained from D-galactose.[49] The tetrahydroxylalkyl pyrroles **19** and **20** are attainable by reacting D-glucosamine with 1,3-dicarbonyl compounds under mild basic condition, while product **20** is also viable from a three-component reaction between D-fructose, acetylacetone, and ammonium carbonate.[50] Moreover, the polyhydroxyl chain can be adjusted in multiple ways: oxidation can

shorten the chain and provide pyrrole acid **21**, and heating will cyclize the hydroxy groups to form the pyrrole C-glycoside **22**. (Figure 1-17)

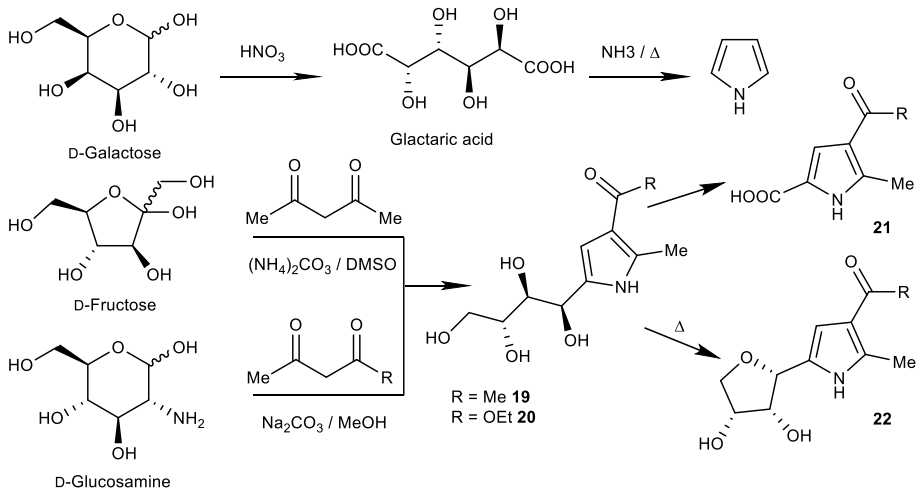


Figure 1-17. Synthesis of pyrrole derivatives from carbohydrates and modifications of polyhydroxyalkyl chain.

Avalos *et al.* reported the reaction of L-arabinose derivative **23** with different glyoxals to give the imidazole sugar derivative **24**. Imidazolo-pyridine **25** was resulted by mesylation of **24** followed by intramolecular nucleophilic substitution and catalytic debenzylation.[51] (Figure 1-18)

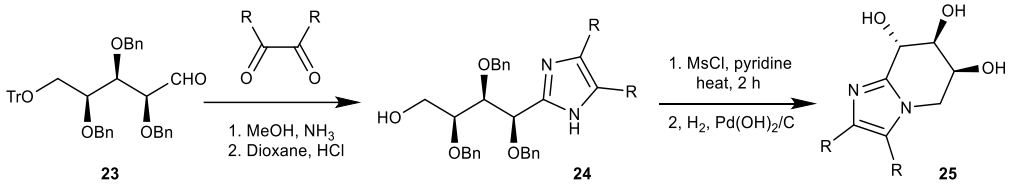


Figure 1-18. Imidazole and imidazolo-pyridine derivatives synthesized from L-arabinose derivative.

Andreas Brust *et al.* reported a simple and green synthesis method from carbohydrates and formamidine acetate catalyzed by ammonium carbonate to obtain polyhydroxyalkyl imidazoles **26**. This reaction is applicable to a library of reducing mono- and di-saccharides, as well as substituted formamidine acetate.[52] (Figure 1-19)

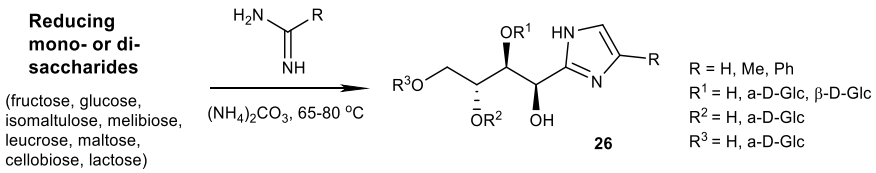


Figure 1-19. Imidazole synthesis from reducing mono- and di- saccharides.

Later, the same group described a procedure to synthesize polycyclic *N*-heterocycles quinoxalines, 1,2,4-triazines and pyrazoloquinoxalines.[53] This reaction began with the formation of intermediate **27** from reducing mono- and di-saccharides and phenylhydrazine, and it was from **27** that the most important 1,2-dicarbonyl sugar intermediates, **28** and **29**, were obtained. The quinoxalines **31**, 1,2,4-triazines **32** and pyrazoloquinoxalines **33** were made by cyclizing 1,2-dicarbonyl sugar intermediates **28** and **29** with 2,3-diaminomaleonitrile, hydrazine carboximidamide or 3,4-dihalogen substituted-o-phenylenediamine accordingly. (Figure 1-20, example using palatinose as the starting material)

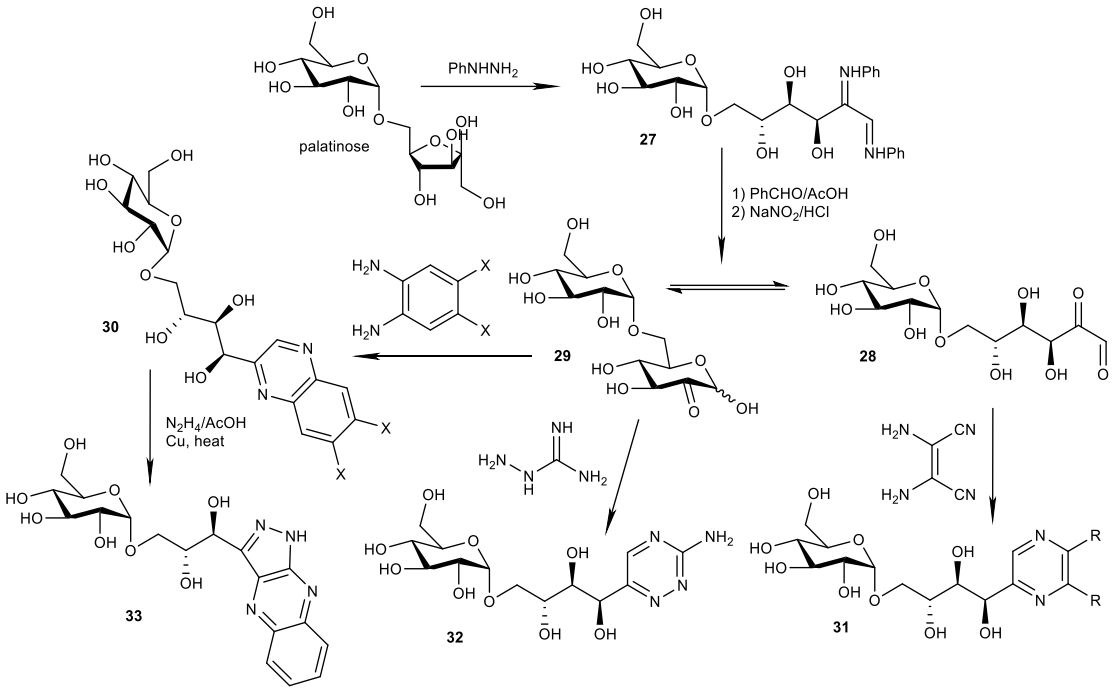


Figure 1-20. Synthesis of polycyclic *N*-heterocycles quinoxalines, 1,2,4-triazines and pyrazoloquinoxalines from reducing sugars (example using palatinose as starting material).

The selective synthesis of key intermediates from carbohydrates is also challenging. To avoid the problems caused by similar reactivity of carbohydrates' multiple functional groups, 2-C-formyl glycal **35** has emerged as a versatile intermediate because of the presence of an α,β-unsaturated carbonyl moiety.[54] The 2-C-formyl glycal **35** was synthesized through the Vilsmeier

Haack reaction,[55] and allowed the straightforward formation of a series of bioactive *N*-heterocycles **36**-**40**. Additionally, 2-C-Formyl glycal **35** is an ideal building block for chemo-, regio- and stereo-selective glycosidation, nucleophilic addition/substitution, and cycloaddition reactions (Figure 1-21).

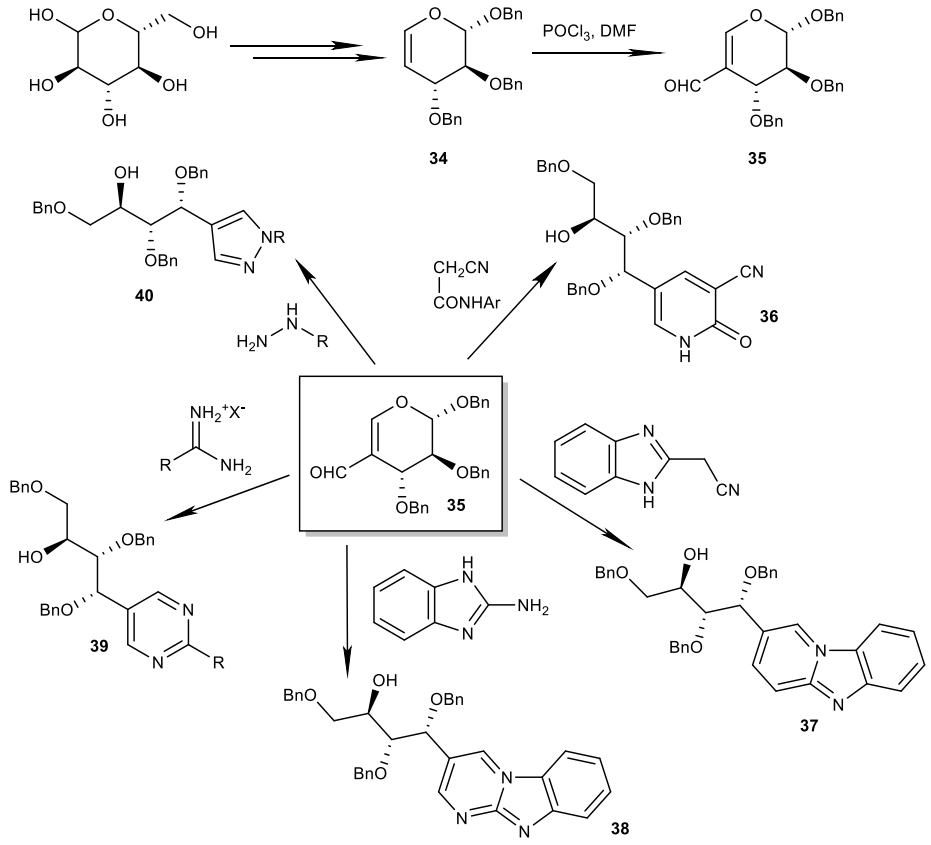


Figure 1-21. Synthesis of *N*-heterocycles from 2-formyl glycals.

1.2 Pyrroles

Pyrrole is a five-membered *N*-heterocyclic compound with the formula C_4H_4N. They act as key constituents in biological systems to form hydrogen bonds, coordinate metals, and offer stacking interactions.[56-58] Pyrroles are an important scaffold in many celebrated natural compounds such as heme and related porphinoid co-factors, vitamin B12, chlorophyll a, pyoluteorin and L-tryptophan (Figure 1-22).[58]

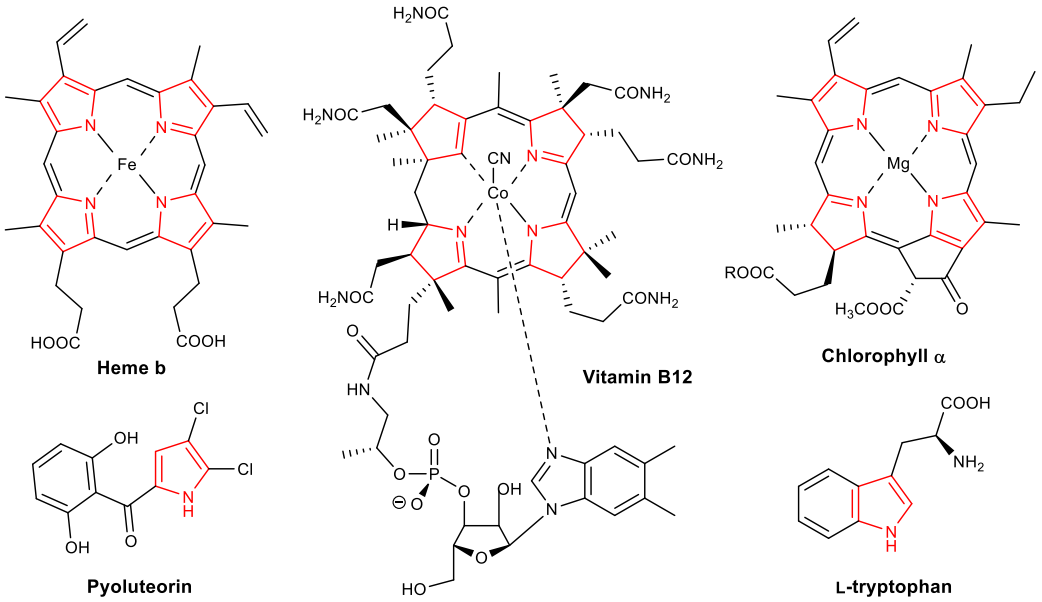


Figure 1-22. Examples of celebrated natural pyrroles.

Pyrroles are of growing applicability in many fields, such as material science, nonlinear optics, medical science, and supramolecular chemistry.[59-62] They exhibit remarkable chemical, biological and pharmacological properties such as anti-inflammatory,[63, 64] anti-bacterial/fungal and anti-viral,[65, 66] anti-tumor and anti-cancer [67] and anti-oxidative [68] properties. Examples of bioactive pyrroles and pyrrole drugs are shown in Figure 1-23.

The wide range of biological properties displayed by pyrroles has stimulated significant interest in the pharmaceutical industry, and numerous pyrrole drugs have already been commercialized based on their properties. The following sections will introduce the effects and bioactivities of several famous medicinal pyrroles: Atorvastatin, Sunitinib, BM212 and its derivatives, and pyrrole-based NSAIDs (nonsteroidal anti-inflammatory drugs).

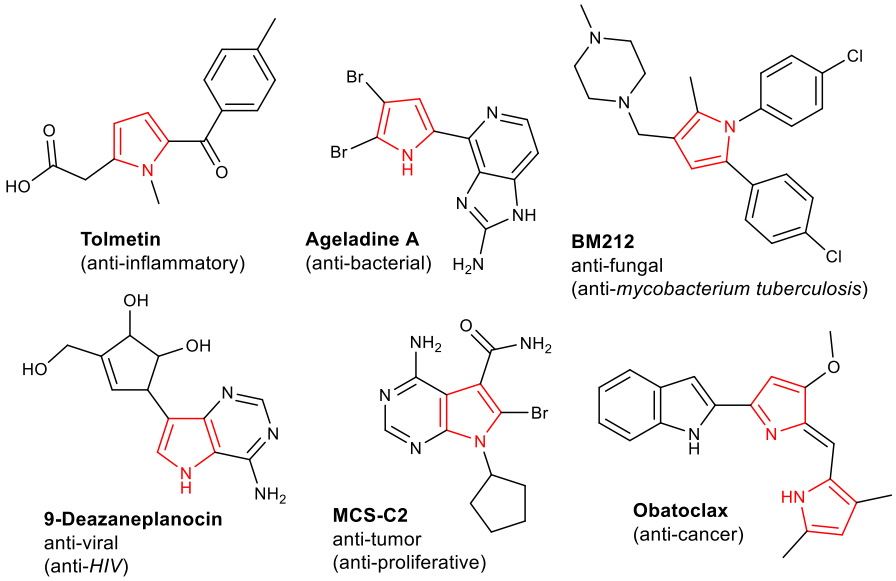
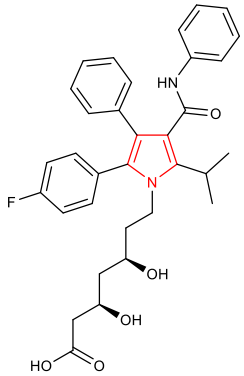


Figure 1-23. Examples of pyrrole derivatives with important properties.

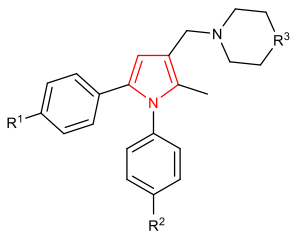
1.2.1 Pyrroles as bioactive molecules

1.2.1.1 Atorvastatin



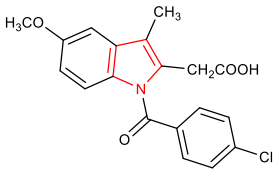
Atorvastatin, marketed by Pfizer as 'Lipitor®', is used to prevent cardiovascular disease (i.e., heart attack and stroke), treat abnormal lipid levels (dyslipidemia) and kidney disease. Atherosclerosis is the main cause of cardiovascular disease, while hypercholesterolaemia is the major factor in the development of atherosclerosis. Atorvastatin was designed as the inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, and thus lowers cholesterol to restrain the development of atherosclerosis.[69] Besides, Atorvastatin is a commonly used medicine because it can treat the complications of plenty of diseases that trigger cardiovascular problems.[70, 71]

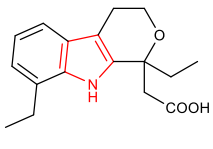
1.2.1.2 BM212 and its derivatives

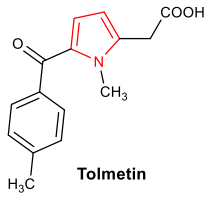


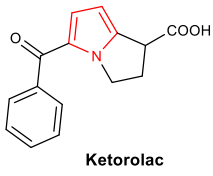
Tuberculosis is a harmful disease that is initiated by *Mycobacterium tuberculosis*, and it causes many deaths every year. To treat *tuberculosis*, the pyrrole derivative BM212 (1,5-diaryl-2-methyl-3-(4-methylpiperazin-1-yl)methyl-pyrrole) was developed.[72] BM212 is a potent mycobacterial membrane protein Large 3 (MmpL3) inhibitor, with both anti-fungal and anti-mycobacterial properties. Besides the effect against *Mycobacterium tuberculosis*, BM212 also possesses a strong and efficient inhibitory effect against non-tuberculosis mycobacteria and intracellular mycobacteria and has shown strong activity towards other drug-resistant mycobacteria.[73]

1.2.1.3 Pyrrole-based NSAIDs (nonsteroidal anti-inflammatory drugs)









The nonsteroidal anti-inflammatory drugs (NSAIDs) are an important class of drugs, they have been the most frequently prescribed medications worldwide for decades.[74] The nonsteroidal anti-inflammatory drugs have a broad range of therapeutic usage because of their antipyretic, analgesic and anti-inflammatory properties, and researchers have started to explore their cancer-preventing effects recently.[75] Pyrrole rings are essential cores for these drugs. For instance, the nonsteroidal anti-inflammatory drugs indomethacin (Indacin®) and etodolac (Etodine®) are indole derivatives, and tolmetin (Rumatol®) and ketorolac (Ketolac®) are pyrrole derivatives.[61, 64, 76]

1.2.2 Early pyrroles synthesis methods

, Substituted pyrroles were synthesized in 1884 by cyclo-condensation of α-aminoketones with β-diketones or β-ketoesters by L. Knorr (Figure 1-24).[77, 78] The Knorr synthesis is one of the most employed reactions in pyrrole synthesis. However, the application of this method is restricted because α-aminoketones can easily self-condense to form a pyrazine, which always happens when the β-diketones or β-ketoesters are not reactive enough.

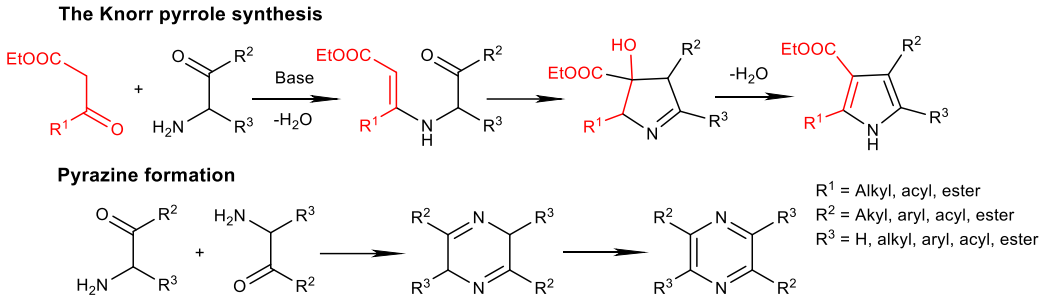


Figure 1-24. The Knorr pyrrole synthesis and the pyrazine formation (α-amino ketones self-condensation).

In the same year, another pyrrole synthesis method was developed by Paal, and was named "Paal–Knorr synthesis". This is a reaction between 1,4-dicarbonyl compounds and ammonia or primary amines, operated in neutral or weak acidic condition.[79] From the same reaction, furans and thiophenes can be selectively obtained by condensing ,4-dicarbonyl compounds with different compounds. (Figure 1-25)

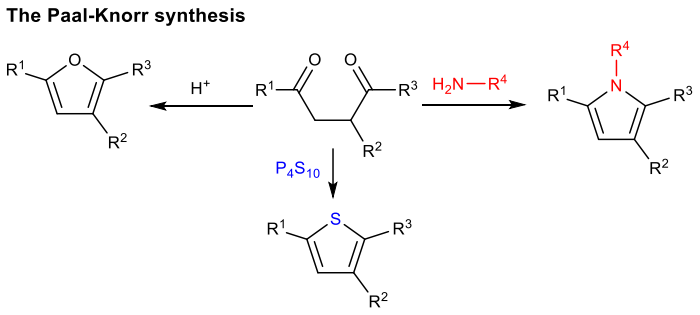


Figure 1-25. The Paal–Knorr synthesis.

Later, in 1890, Hantzsch reported a three-component reaction to synthesize pyrroles. This reaction involved refluxing an equimolar mixture of α-chloroacetone and acetoacetic ester in

aqueous ammonia media. The reaction was initiated by a stable enamine intermediate (ethyl β-aminocrotonate) (Figure 1-26).[80, 81]

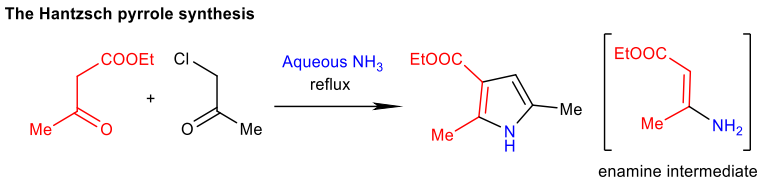


Figure 1-26. The Hantzsch pyrrole synthesis.

1.2.3 General pyrrole synthesis methods

Active methylene compounds are one of the key compounds in pyrrole synthesis. Active methylene compounds are those in which a methylene group (-CH_2-) is sandwiched between two strong electron-withdrawing groups, usually carbonyl groups, cyano groups, etc. Active methylenes can be roughly classified as α-activated nitriles, 2-(2-oxo-2-phenylethyl)malononitrile, α-activated isonitriles, α-azidoesters, ethyl 2-aminoacetate hydrochloride, carbethoxyacetamidine, alkyl 2-nitroacetate and β-dicarbonyls.[82] Although substituted pyrroles can be transferred from naked pyrrole rings, pyrrole synthesis from active methylenes is more attractive and convenient because active methylenes offer a wide range of libraries of functional groups and are able to provide bioactive pyrroles in fewer procedures. (Figure 1-27)

The active methylene compounds α-activated nitriles, α-activated isonitriles, and β-dicarbonyls are the most frequently utilized starting materials in abundant pyrrole synthesis protocols. The pyrrole synthesis methods from α-activated nitriles, α-activated isonitriles, and β-dicarbonyls will be selectively introduced in the following sections.

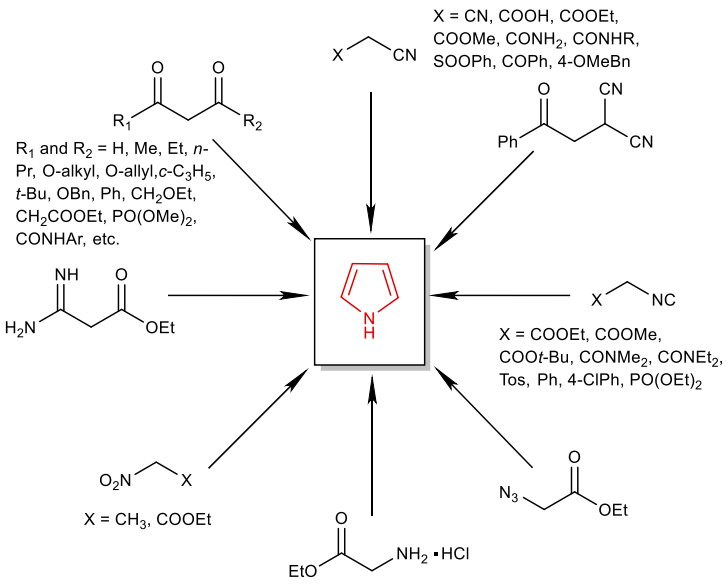


Figure 1-27. Synthesis of pyrroles from active methylenes.

1.2.3.1 Pyrrole synthesis from α-activated nitriles

One of the most effective α-activated nitriles is malononitrile. In 1961, K. Gewald published a base-catalyzed reaction between an α-aminoketone (3-aminobutan-2-one) and malononitrile to form a 2-amino-3-cyano pyrrole (Figure 1-28).[83]

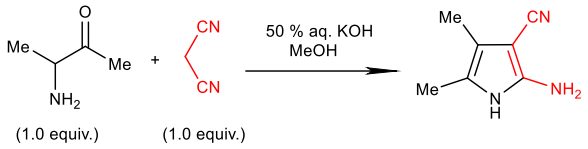


Figure 1-28. Pyrrole synthesis from α-aminoketone and malononitrile.

Later in 1975, H. J. Roth described a pyrrole synthesis approach by reacting α-hydroxyketones, primary amines and malononitrile in refluxing toluene. The reaction proceeded through α-aminoketone intermediate to give substituted 2-amino-3-cyano-4,5-substituted pyrroles (Figure 1-29).[84] This method expanded the substrates of 2-amino-1-substituted-pyrrole-3-carbonitrile products by applying different α-hydroxyketones and primary amines.

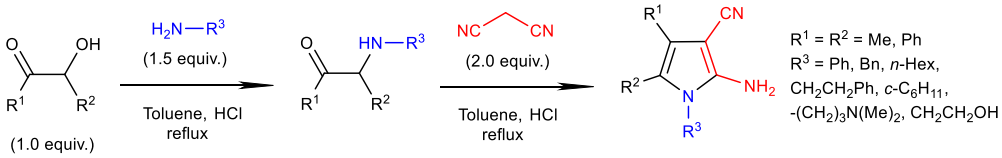


Figure 1-29. Pyrrole synthesis from α-hydroxyketone, primary amines and malononitrile.

In 2006 and 2008, Magda M. F. Ismail et al.[85] and Dalal A. Abou El Ella et al.[86] reported two similar pyrrole synthesis methods by reacting malononitrile, sodium ethoxide and 4-((2-oxo-2-phenylethyl)amino)benzensulfonamide in refluxing ethanol. The 4-((2-oxo-2-phenylethyl)amino)benzensulfonamide was synthesized from phenacyl bromide and 4-aminobenzenesulfonamide in an extra step. Later, the same group (Mostafa M. Ghorab et al.)[87] expanded the substrates from 4-aminobenzenesulfonamide to sulfathiazole or sulfapyridine, and thus made corresponding α-(arylphenylamino)-acetophenones for the following reaction with malononitrile. (Figure 1-30)

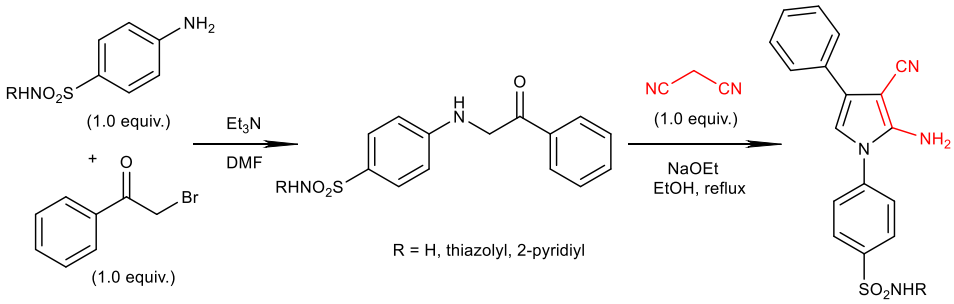


Figure 1-30. Pyrrole synthesis from α-(arylphenylamino)-acetophenone and malononitrile.

Anastasiya V. Agafonova *et al.* reported a 2-amino-3-cyano pyrrole synthesis method from isoxazole and malononitrile.[88] This reaction is catalyzed by $FeCl_2 \cdot 4H_2O$ with the addition of Et_3N in dioxane under 80 °C (Figure 1-31). This reaction is versatile because it expanded the substitutions on 4- and 5- position of pyrrole products, but most isoxazoles require an extra step to prepare.

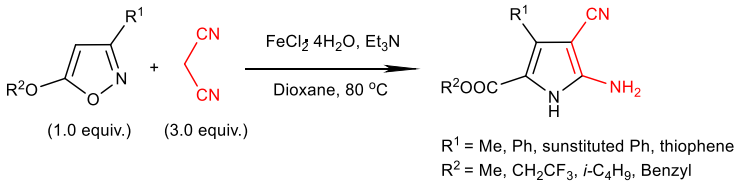


Figure 1-31. Pyrrole synthesis from isoxazole and malononitrile.

Kan Wang and Alexander Domling published a Et_3N-catalyzed reaction from substituted aldehydes, *N*-protected α-amino acetophenones and α-activated nitriles, conducted in

trifluoroethanol under 70 °C (Figure 1-32).[89] This reaction when applied to a library of aldehydes and α-activated nitriles, enabled the synthesis of diverse 2-amino pyrrole derivatives.

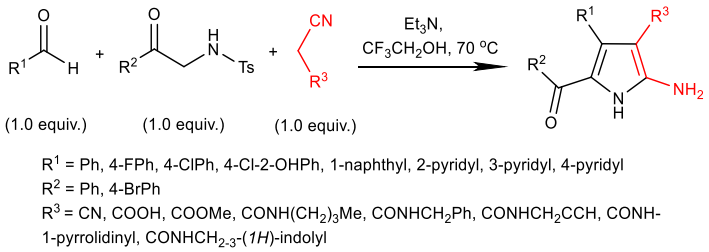


Figure 1-32. Pyrrole synthesis from substituted aldehydes, α-amino acetophenones and α-activated nitriles.

Comparing with previous procedures, Y. Yu and co-workers described a novel and much greener way to obtain multi-functionalized 2-amino-1*H*-pyrroles. This method is catalyst-free and proceed only by stirring vinyl azides and α-cyano derivatives in aqua/EtOH under 80 °C for 2-8 h (Figure 1-33).[90] This synthesis route also achieved good yields.

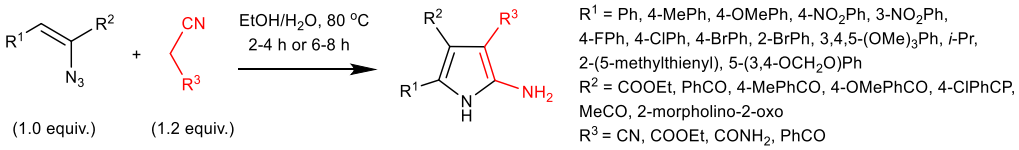


Figure 1-33. Pyrrole synthesis from vinyl azides and α-activated nitriles.

All reactions mentioned above gave 2-amino-3-cyano pyrrole derivatives. The 2-amino-3-cyano pyrrole derivatives are important precursor for preparing medicinally vital pyrrole derivatives such as pyrrolo[2,3-d]pyrimidine derivatives,[87] pyrrolo[1,2-a]-pyrimidines derivatives,[91] and 2,3,4,5-tetrahydropyrrolo[1,2-a][1,3]-diazepine.[92] (Figure 1-34)

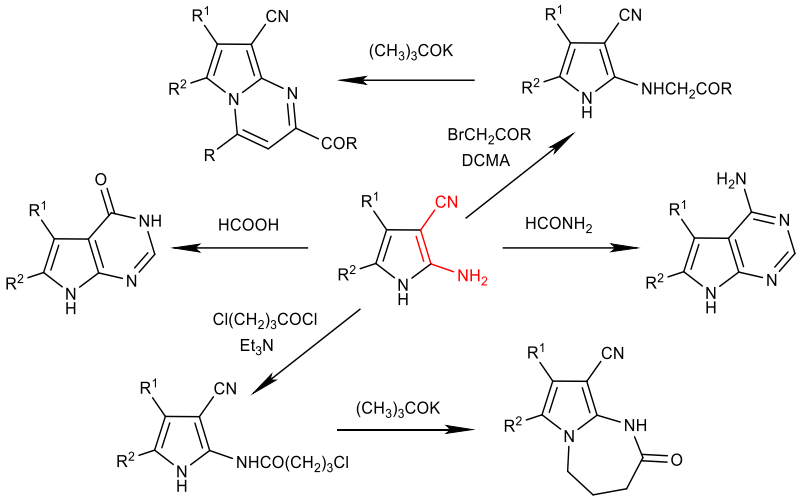


Figure 1-34. Modification of 2-amino-3-cyano pyrroles to medicinally vital pyrrole derivatives.

1.2.3.2 Pyrrole synthesis from α-activated isonitriles

One of the signature pyrrole synthesis reactions from α-activated isonitriles is the 'The Barton–Zard reaction'.[93] This base-catalyzed reaction started with Michael addition of an α-isocyanoacetate to a nitroalkene, followed by cyclization and nitrous acid elimination to obtain the N-unsubstituted pyrrole products. Both guanidine and DBU can promote this reaction, while DBU requires longer reaction time. (Figure 1-35)

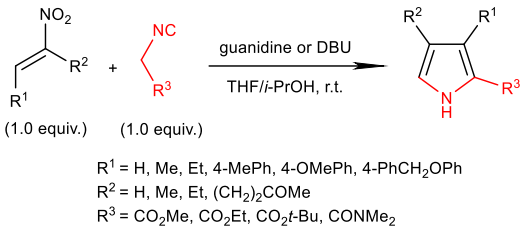


Figure 1-35. Pyrrole synthesis from nitroalkenes and α-activated isonitriles.

Methyl isocyanoacetate and ethyl isocyanoacetate are frequently used α-activated isonitriles in pyrrole synthesis reactions. The substrates of the Barton–Zard reaction was extended by Ono and Maruyama. They used nitroalkenes with long alkyl chains to prepare the intermediates for synthesizing lipophilic polypyrroles and porphyrins. This reaction was

proceeded by stirring nitroalkenes ,ethyl isocyanoacetate and the catalyst DBU in THF at room temperature.[94] In this reaction, the nitroalkenes with longer alkyl chains were made from aldehydes and nitroalkanes through the nitroalcohols. (Figure 1-36)

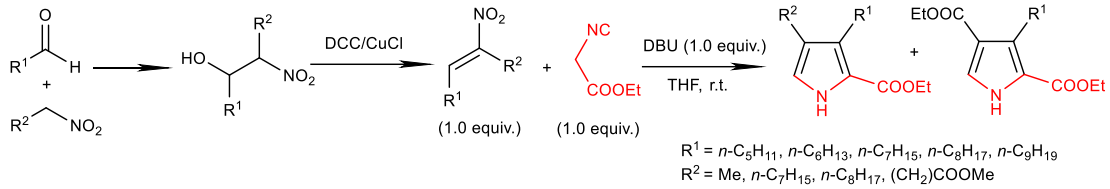


Figure 1-36. Pyrrole synthesis from nitroalkenes and ethyl isocyanoacetate.

James L. Bullington *et al.* discovered a reaction between α,β-unsaturated nitriles and methyl isocyanoacetate at 0 °C under nitrogen protection, boosted by *t*-BuOK.[95] (Figure 1-37) In this work, the process to convert the natural product Ningalin B from the product methyl 4-(3,4-dimethoxyphenyl)-3-(2,4,5-trimethoxyphenyl)-1*H*-pyrrole-2-carboxylate in two steps was also reported. (Figure 1-38)

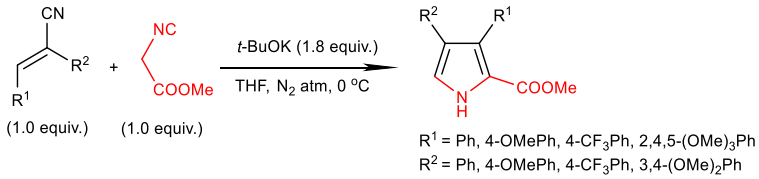


Figure 1-37. Pyrrole synthesis from α,β-unsaturated nitriles and methyl isocyanoacetate.

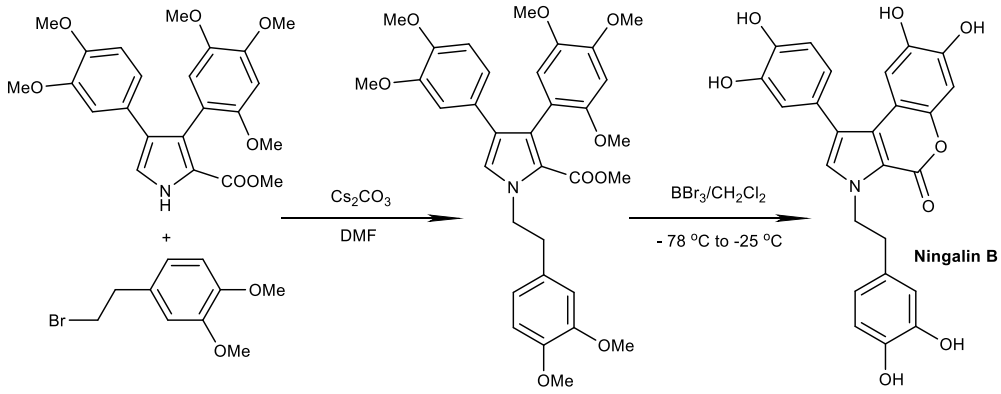


Figure 1-38. Synthesis of pyrrole natural product Ningalin B.

Except methyl isocyanoacetate and ethyl isocyanoacetate, tosylmethyl isocyanide (TosMIC) is also a commonly used α-activated isonitrile. Wenteng Chen *et al.* reported a NaH-

catalyzed pyrrole formation reaction between vinyl azides and tosylmethyl isocyanide.[96] In this work, a three-component reaction was also used. Knoevenagel condensation between 3-nitrobenzaldehyde and ethyl 2-azidoacetate in the presence of NaH for 2 h at -15 °C gave vinyl azide, and then addition of TosMIC gave the final product. This one-pot reaction provide convenience for the uncommercialized vinyl azides, and thus widened the substrate scope. (Figure 1-39)

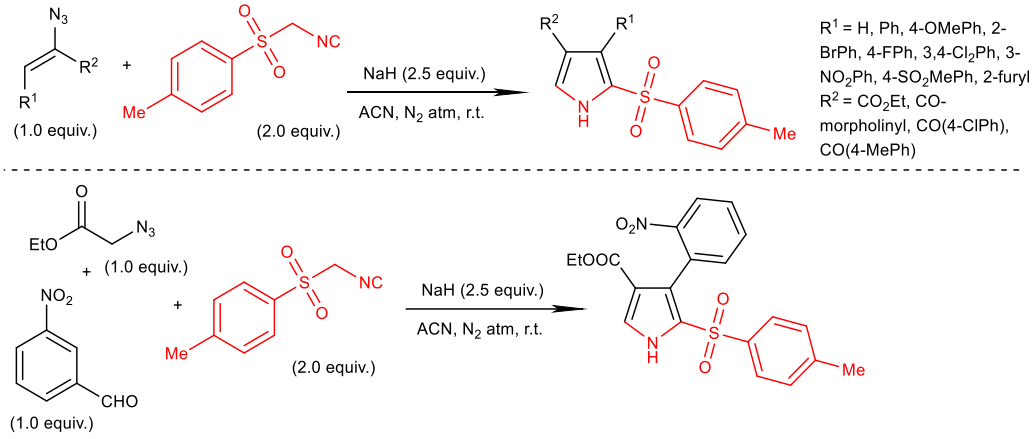


Figure 1-39. Pyrrole synthesis from vinyl azides and tosylmethyl isocyanide.

Palakodety Radha Krishna *et al.* disclosed a pyrrole 2-deoxy-C-ribosides synthesis strategy from α,β-unsaturated ester or aryl sulfonyl ester and tosylmethyl isocyanide.[97] This method started with synthesis esters from (*R*) and (*S*)-2,3-*O*-isopropylidene glyceraldehydes, followed by *n*-BuLi-promoted reaction between the esters and tosylmethyl isocyanide.(Figure 1-40) Pyrrole 2-deoxy-C-ribosides can be obtained by removing the protecting groups. This strategy enabled the formation of pyrrole with a chiral sugar moiety, which are important building blocks of bioactive pyrroles.

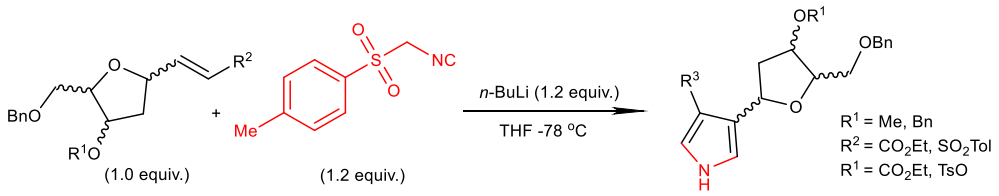


Figure 1-40. Pyrrole synthesis from α,β-unsaturated ester/aryl sulfonyl ester and tosylmethyl isocyanide.

In 2013, Meng Gao *et al.* published a $AgCO_3$-catalyzed cycloaddition click reaction between terminal alkynes and α-activated isonitriles in NMP at 80 °C.[98] This reaction was viable for a broad scope of alkynes and α-activated isonitriles, and has achieved high yields. (Figure 1-41)

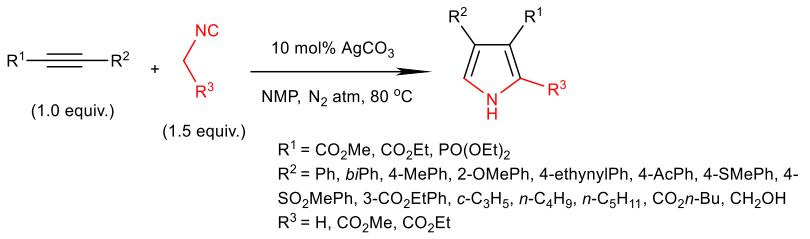


Figure 1-41. Pyrrole synthesis from terminal alkynes and α-activated isonitriles.

1.2.3.3 Pyrrole synthesis from β-dicarbonyls

In 2012, Manojit Pal *et al.* published a three-component reaction to generate 1,2,3,4-substituted pyrroles. The products were obtained regio-selectively from acetylacetone, primary amines and phenacyl bromide in the presence of 10 mol% $Yb(OTf)_3$ in one-pot at 80 °C to 85 °C (Figure 1-42, **I**).[99] In the same year, H. M. Meshram *et al.* described a 1,2,3,5-functionalized pyrrole synthesis procedure from similar substrates acetylacetone, primary amines and phenacyl bromide. This reaction was catalyzed by 10 mol% DABCO in water under 60 °C (Figure 1-42, **II**).[100] Both these two reactions are applicable for various kinds of primary amines substituted with alkyl, alkylaryl and aryl moieties, and their different regio-selectivities allow to synthesize tetra-substituted pyrrole derivatives accordingly.

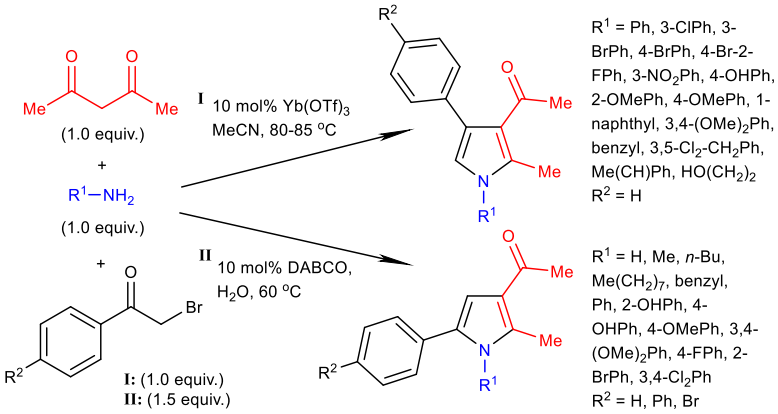


Figure 1-42. Pyrrole synthesis from primary amines, phenacyl bromide and acetylacetone.

In 2008, Shunsuke Chiba *et al.* described two poly-substituted NH pyrrole synthesis protocols. The 2,3,4,5-tetrasubstituted pyrrole formation from vinyl azides and 1,3-dicarbonyl compounds were processed by (i) a thermal-catalyzed reaction in toluene (Figure 1-43, **I**), or (ii) a 5 mol% $Cu(OTf)_2$ catalyzed 1,4-addition in ACN with the presence of water (Figure 1-43, **II**). These two methods enable to synthesize regioisomeric pyrroles from same vinyl azides. For example, when process (i) lead to α-phenyl β-ethoxycarbonyl pyrroles, process (ii) gave α-ethoxycarbonyl β-phenyl pyrroles. Later, the same group published another $Mn(OAc)_3$ boosted reaction between same substrates. This reaction provides 2,3,5-substituted pyrroles (Figure 1-43, **III**).

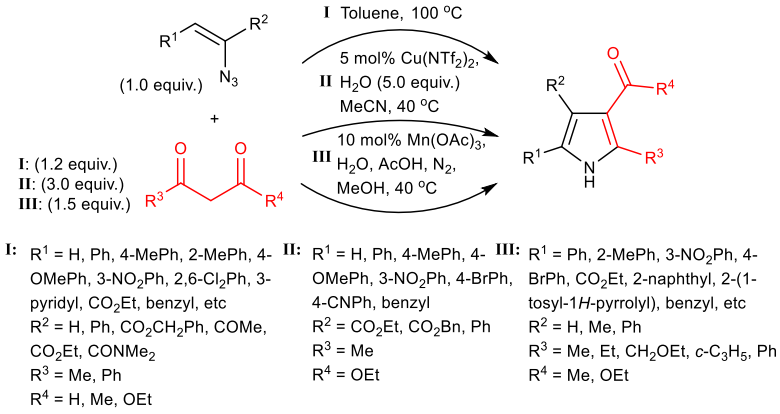


Figure 1-43. Pyrrole synthesis from vinyl azides and 1,3-dicarbonyl compounds.

Fatemeh Tamaddon *et al.* reported three protocol for generating 2,3,4,5-functionalized pyrroles from α-hydroxyketones and 1,3-dicarbonyl compounds: (i) a solvent-free reaction

promoted by 5 mol% molybdate sulfuric acid (Figure 1-44, **I**);[101] (ii) a solvent-free reaction catalyzed by 5 mol% silica sulfuric acid (Figure 1-44, **II**);[102] and (iii) a catalyst-free reaction in refluxing EtOH/H_2O system (Figure 1-44, **III**).[103] Later, Darshak R. Trivedi *et al.* reported a neat reaction under 90 °C to make the NH tetra-substituted pyrroles.[104] All these reactions are simple and have accomplished high yields.

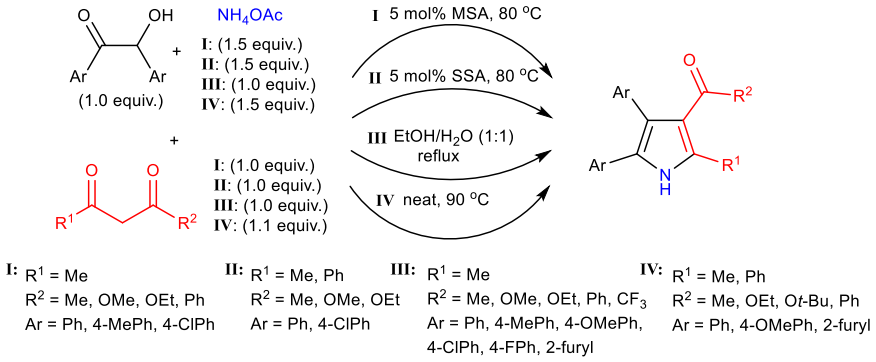


Figure 1-44. Pyrrole synthesis from α-hydroxyketones and 1,3-dicarbonyl compounds.

Victorio Cadierno *et al.* reported a Ru-complex catalyzed three-component reaction to give the pentasubstituted pyrroles. This reaction was between secondary propargylic alcohols, β-dicarbonyls and primary amines, promoted by the 16-electron allylruthenium(II) complex [Ru(η_3-2-C_3H_4Me)(CO)(1,10-bis(diphenylphosphino)ferrocene)][SbF_5] and TFA (Figure 1-45, **I**).[105] Later in 2010, the same group described a NH pyrrole synthesis method using the same Ru-complex jjby using the *tert*-butyl carbamate (Figure 1-45, **II**).[106] These two methods together made a versatile poly-substituted pyrrole synthesis strategy.

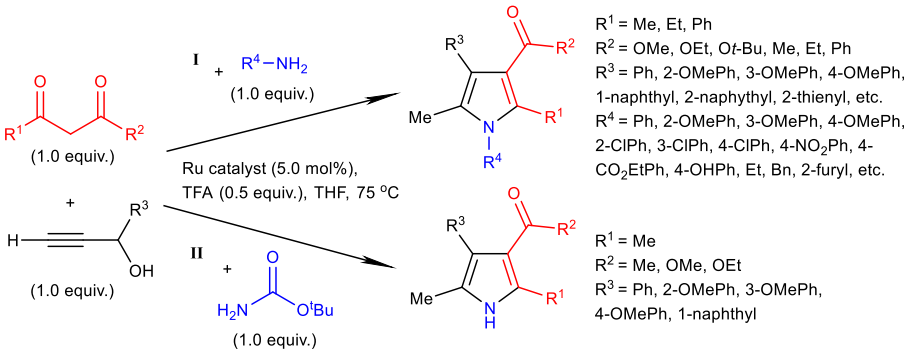


Figure 1-45. Pyrrole synthesis from secondary propargylic alcohols, primary amines and β-dicarbonyls.

1.2.4 Pyrrole synthesis from carbohydrates

1.2.4.1 Pyrrole synthesis from amino sugars

Since some of these methods use starting materials with aldehyde, ketone or acid groups, researchers began to manipulate carbohydrates as one of the starting materials for pyrrole synthesis. Carbohydrates provide cheaper and greener starting materials, poly functional groups, chiral centers, hydrophilicity, and also provide "handles" for future transformations to pharmaceutical intermediates.

The early pyrrole synthesis was accomplished by Garcia Gónzalez *et al.* in 1965. The pyrrole derivative were afforded by condensation of D-glucosamine with 2,4-pentandione in aqueous acetone in the presence of sodium carbonate, the yield is around 85% (Figure 1-46).[50]

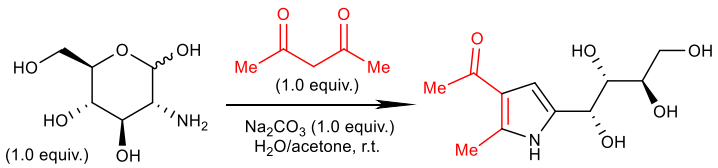


Figure 1-46. The Garcia Gónzalez pyrrole synthesis reaction from D-glucosamine and 1,3-dicarbonyl compounds.

Later in 1980, Garcia Gónzalez *et al.* again reported a similar pyrrole synthesis approach utilizing 2-amino-2-deoxy heptoses and cyclic 1,3-dicarbonyl compounds under basic aqueous acetone condition.[107] However, the yield of this reaction is only around 20%. (Figure 1-47)

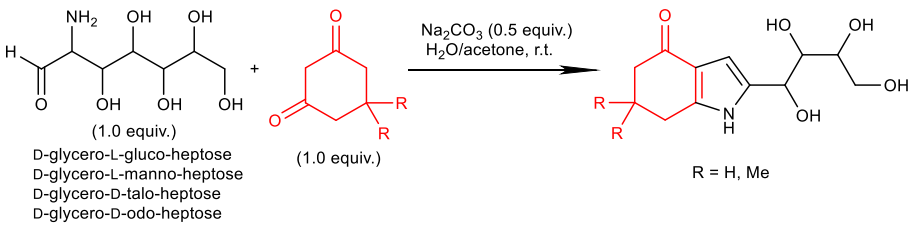


Figure 1-47. 5-Polyhydroxyalkyl pyrrole synthesis from 2-amino-2-deoxy heptoses and cyclic 1,3-dicarbonyl compounds.

Inspired by the Garcia Gónzalez reaction, several pyrrole synthesis reactions were reported with amino sugars as starting materials. In 1984, Juan A. Galbis Perez *et al.* reported a pyrrole synthesis route from 2-deoxy-2-substituted amino sugars. This $NaHCO_3$-catalyzed reaction was carried out in $EtOH/H_2O$ at 50 °C with 2-deoxy-2-(ethylamino)-L-glucose or 2-deoxy-2-(ethylamino)-D-glycero-L-gluco-heptopyranose, and 2,4-pentanedione or ethyl 3-oxobutanoate, to obtain the 2-methyl-5-(L-arabino-tetritol-1-yl)pyrrole or 2-methyl-5-(D-galacto-pentitol-2-yl)pyrrole accordingly.[108] Acetylated 2-deoxy-2-substituted amino sugars were also demonstrated to work smoothly in this reaction. (Figure 1-48)

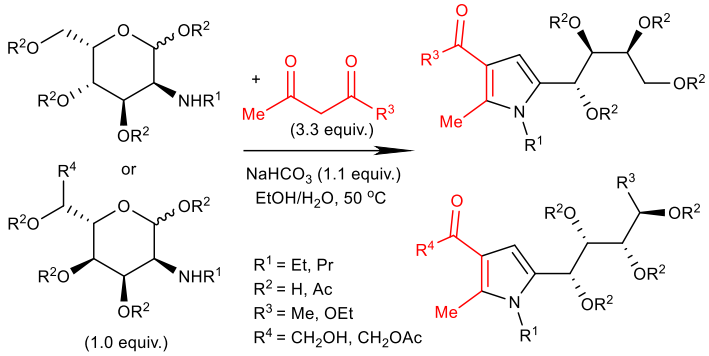


Figure 1-48. 5-Polyhydroxyalkyl pyrrole synthesis from 2-deoxy-2-substituted amino sugars and 1,3-dicarbonyl compounds.

In 1989, A. Gomez Sanchez *et al.* described another reaction using D-glucosamine. They replaced 1,3-dicarbonyl compounds with nitroacetone, reacting with D-glucosamine in refluxed MeOH, and resulted the 2-methyl-3-nitro-5-polyhydroxyalkyl pyrrole.[109] (Figure 1-49)

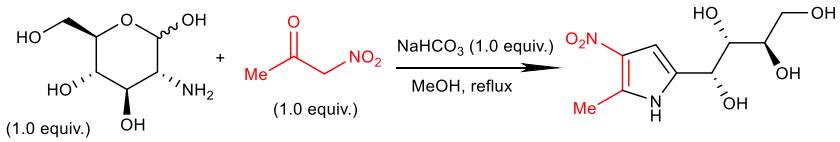


Figure 1-49. 5-Polyhydroxyalkyl pyrrole synthesis from D-glucosamine and nitroacetone.

1.2.4.2 Pyrrole synthesis from modified carbohydrates

Although the concept of applying carbohydrates as starting materials is environmentally friendly, the disadvantages of early pyrrole synthesis from carbohydrates are obvious: the low yields, insufficient substrate scope, and expensive amino sugars largely reduced the practicality of these reactions. To avoid using amino sugars, which are highly priced and have limited natural species, researchers turn to using normal carbohydrates. However, difficulties occurred when restricting the reaction positions of carbohydrates, many researchers decided to modify carbohydrates by adding protecting groups and adjusting functional groups.

A 4-polyacetoxyalkyl pyrrole synthesis procedure was discovered by A. Gomez Sanchez *et al.* The 4-polyacetoxyalkyl pyrroles were obtained by refluxing the open-chain sugar nitro-olefins and 3-aminocrotonic esters in EtOH. The open-chain sugar nitro-olefins used are D-gluco- and D-galacto-3,4,5,6,7-penta-acetoxy-l-nitrohept-1-ene.[110] (Figure 1-50)

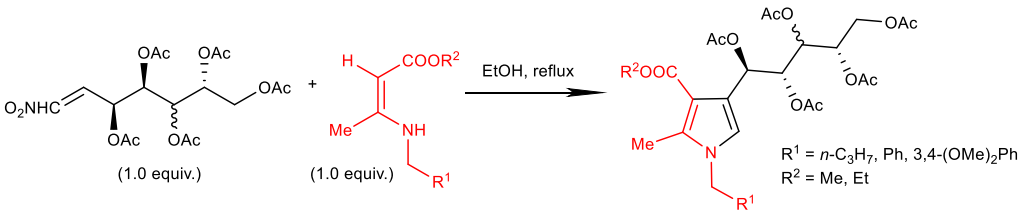


Figure 1-50. 4-Polyhydroxyalkyl pyrrole synthesis from open-chain sugar nitro-olefins and 3-aminocrotonic esters.

Tanmaya Pathak *et al.* published a poly-functionalized pyrrole synthesis procedure from vinyl sulfone-modified carbohydrates and ethyl isocyanoacetate. All vinyl sulfone-modified carbohydrates **1-12** were generated through complex protecting and functionalizing steps and then reacted with the ethyl isocyanoacetate under *t*-BuOK catalysis (Figure 1-51).[111] This method is capable of getting the densely functionalized cyclic pyrroles with the sugar moiety, but the tedious process of obtaining the vinyl sulfone-modified carbohydrates, and the huge amount of ethyl isocyanoacetate required make this reaction inefficient.

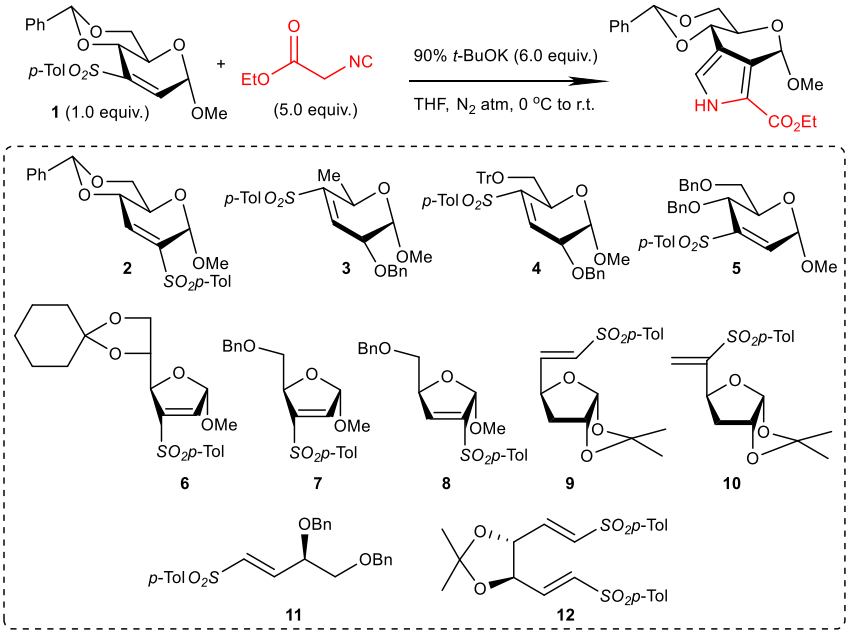


Figure 1-51. Pyrrole synthesis from vinyl sulfone-modified carbohydrates and ethyl isocyanoacetate.

Ao Zhang *et al.* first reported a 2-polyhydroxyalkyl pyrrole synthesis protocol by stirring glucose-derived 4-(benzyloxy)-3-((benzyloxy)methyl)-2-oxabicyclo[4.1.0]heptan-5-one and primary amines in DCM at 40 °C, catalyzed by 10 mol% $InBr_3$ (Figure 1-52).[112] Several other carbohydrate-derived 1,2-cyclopropa-3-pyranones react smoothly with benzylamine.

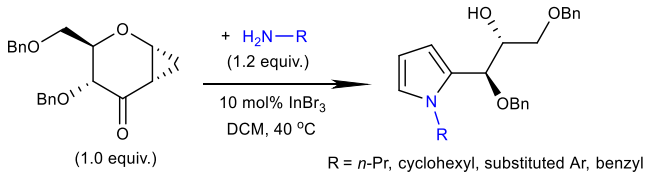


Figure 1-52. 2-Polyhydroxyalkyl pyrrole synthesis from sugar 1,2-cyclopropa-3-pyranones and primary amines.

The reaction proceeded through the ketone **I** which combines with the amine to form imine intermediate **II** in the present of $InBr_3$. Ring expansion and intramolecular nucleophilic attack give intermediate **IV**. After ring cleavage and dehydration, the final pyrrole product **VI** was generated. (Figure 1-53)

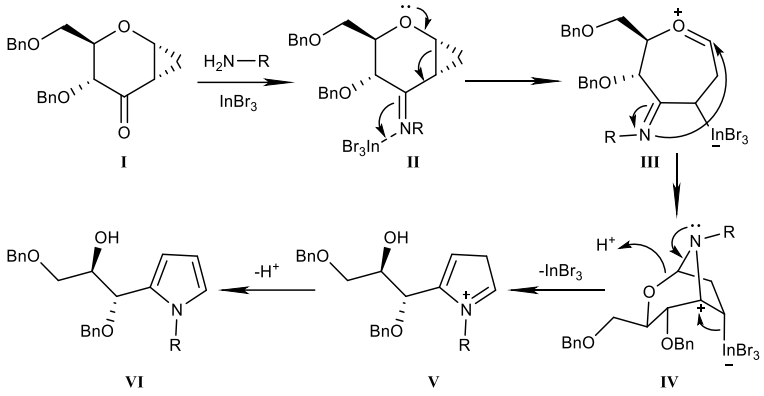


Figure 1-53. Mechanism of Ao Zhang *et al.* reported pyrrole synthesis reaction.

Soon after, Huawu Shao *et al.* published a 3-polyhydroxyalkyl pyrrole route from 1,2-cyclopropanated sugars and primary amines. This reaction was promoted by 5 mol% $Zn(OTf)_2$ in DCM at 40 °C (Figure 1-54).[113] The 1,2-cyclopropanated sugars were made from the allylic C-galactoside or coordinating pentose in several steps.[112, 114]

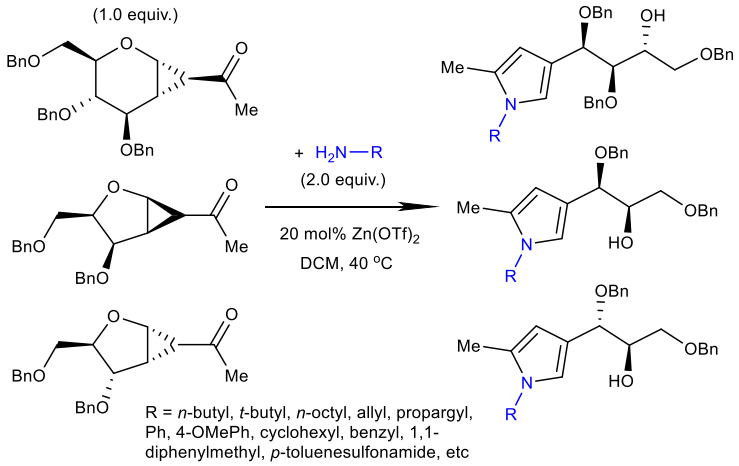


Figure 1-54. 3-Polyhydroxyalkyl pyrrole synthesis from 1,2-cyclopropanated sugars and primary amines.

The reaction was begun by coordinating $Zn(OTf)_2$ to 1,2-cyclopropanated sugar to activate the carbonyl group from the sugar and open the ring to provide the zwitterionic intermediate **II**. It was assumed that the amine would attack both the α- and β-face of the anomeric carbon and thus resulting in intermediates **III** and **V**. After the nitrogen atom attack the carbonyl group to generate six-five fused ring intermediate **VII**, followed by anomerization and elimination of $Zn(OTf)_2$, product **XI** was formed. (Figure 1-55)

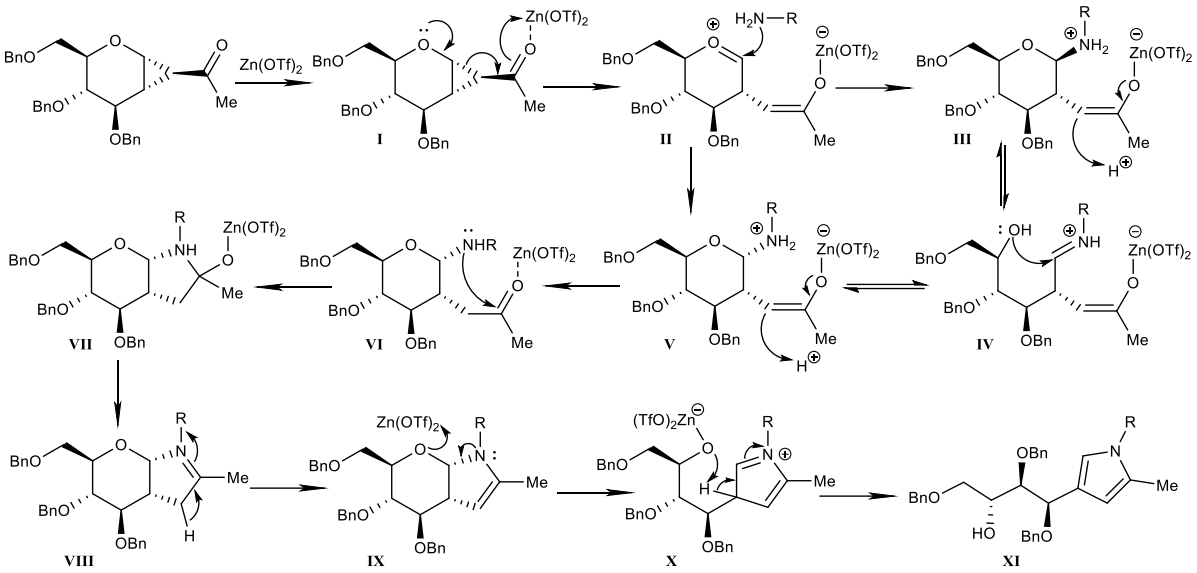


Figure 1-55. Mechanism of Huawu Shao *et al.* reported pyrrole synthesis reaction.

B.V. Subba Reddy *et al.* described a reaction to generate 3-polyhydroxylalkyl pyrroles. This was a catalyst-free reaction between 2-C-formyl glycals and α-amino acids that proceeded in xylene under 120 °C.[115] Both cyclic and non-cyclic α-amino acids work smoothly through this reaction (Figure 1-56). However, the synthesis of 2-C-formyl glycals from general sugars involves a number of protection/deprotection steps, which are time-consuming.[55]

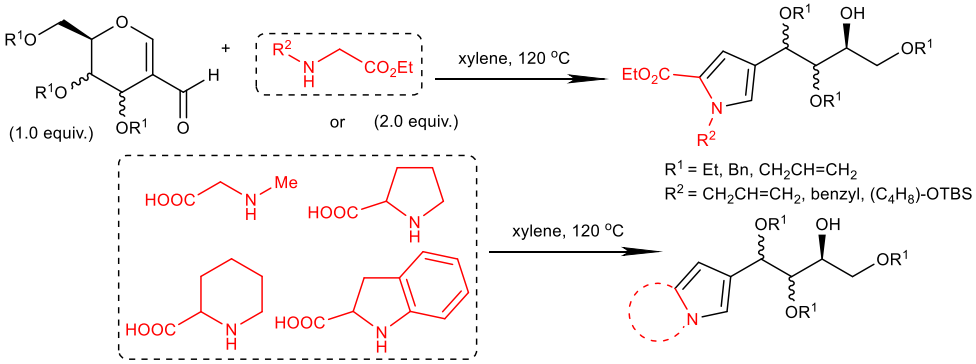


Figure 1-56. 3-Polyhydroxyalkyl pyrrole synthesis from 2-C-formyl glycals and α-amino acids.

The reaction started by the reaction of 2-C-formyl glycals **I** with α-amino acids to form the aminol intermediate **II**. Intermediate **II** converts to intermediate **III**. The azomethine ylide intermediate **V** was obtained via the dehydration of intermediate **VI**, which was a tautomer of

III. By intramolecular cyclization and ring open processes, 3-polyhydroxyalkyl pyrrole product **VII** was provided. (Figure 1-57)

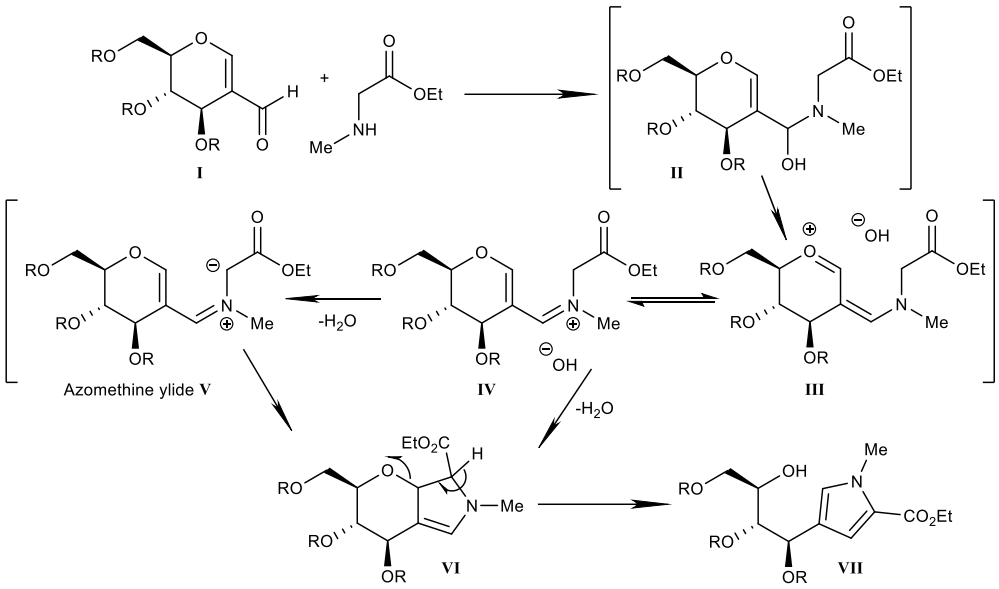


Figure 1-57. Mechanism of Subba Reddy *et al.* reported pyrrole synthesis reaction.

These pyrrole synthesis protocols from modified carbohydrates enabled the preservation of the polyhydroxyalkyl chain, increased product yields, and heavily expanded the substrate scope of both carbohydrates and amines. Nonetheless, the carbohydrates they use necessitate a number of time- and chemical-intensive steps to functionalize. Simple and one-step pyrrole synthesis methods from unprotected cheap carbohydrates are of greater interest.

1.2.4.3 Pyrrole synthesis from unprotected carbohydrates

Sangho Koo *et al.* reported a straightforward method of synthesizing 2-formyl pyrroles from naked sugars. This oxalic acid-promoted reaction between sugars and amines, in DMSO at 90 ^{o}C gave good yields.[116] The important industrial intermediates 5-hydroxymethyl-2-formyl pyrroles were successfully obtained.(Figure 1-58) Also, when employing amino esters and amino acids, pyrrole alkaloid natural products such as pyrrolo[1,4]oxazin-3-ones (Figure 1-58, i), Lobechine (Figure 1-58, ii), and (-)-Hanishin (Figure 1-58, iii) can be made in short

procedures. This is a practical method of utilizing unmodified sugars to provide important pyrrole intermediates and natural products.

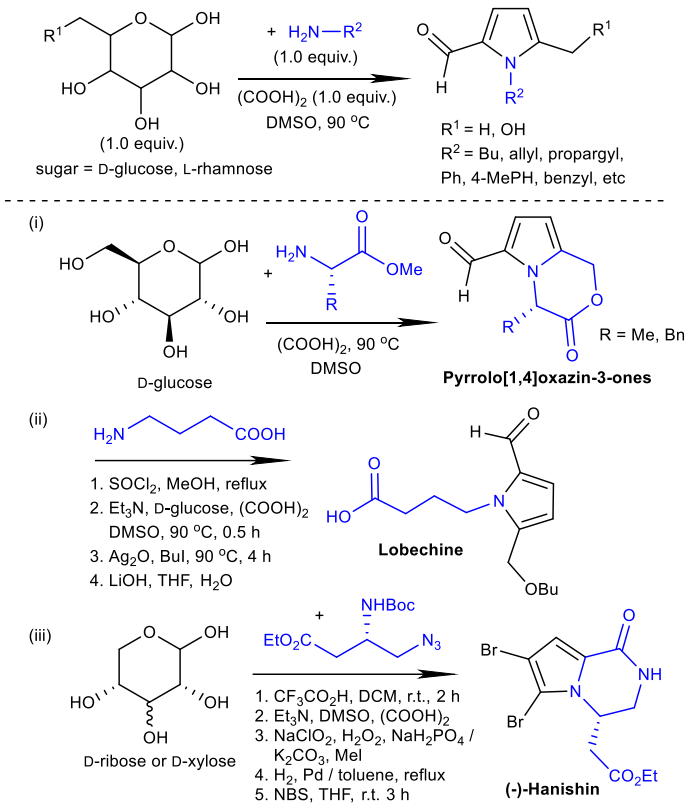


Figure 1-58. Synthesis of 2-formyl and pyrrole natural products from sugar and amines.

The tentative reaction mechanism was raised, beginning by D-glucose transfer into the 3-deoxyglucosone intermediate **IV** through the ring opening of glucosamine **I** and the Maillard reaction. The enamine intermediate **V** was generated by the addition of amine to the intermediate **IV**, along with dehydration. After intramolecular cyclization and subsequent dehydration of **V**, followed by amine removal, the 5-hydroxymethyl-2-formyl pyrrole product **VIII** was attained. (Figure 1-59)

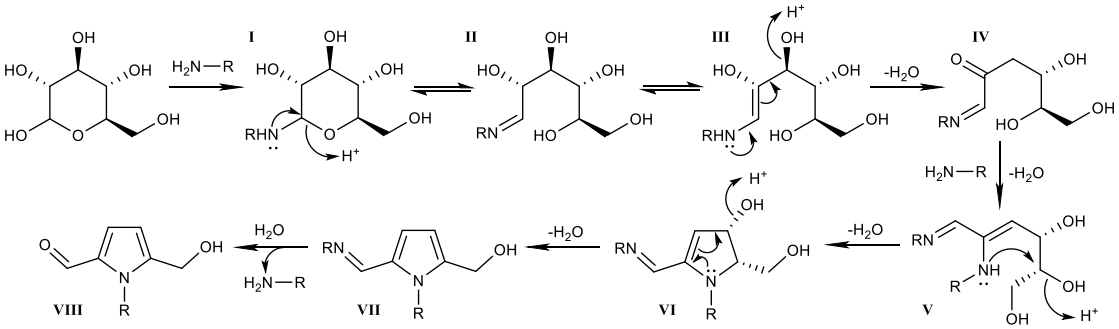


Figure 1-59. Mechanism of Sangho Koo *et al.* reported pyrrole synthesis reaction.

Yadav *et al.* reported a $InCl_3$-catalyzed protocol that results in annulated pyrroles. In this reaction, sugars undergo a smooth combination with amines and 1,3-diketones at 80 °C, conducted in water (Figure 1-60).[38] For simpler purification, the $InCl_3$-catalyzed reaction was followed by one-pot acetylation with Ac_2O and DMAP. This reaction works well on both pentose and hexoses, and both aldoses and ketoses.

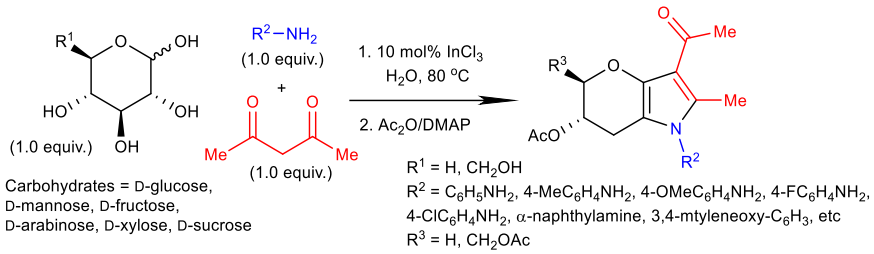


Figure 1-60. Annulated pyrrole synthesis from unprotected sugar, 1,3-diketones and primary amines promoted by $InCl_3$.

The reaction first went through the formation of enaminoketone **I** from amine and 1,3-diketone, followed by the cyclization of **I** and sugar to provide the tautomer intermediates **II** and **III**. After intramolecular cyclization, aromatization, and dehydration, annulated pyrrole product **VII** was obtained. (Figure 1-61)

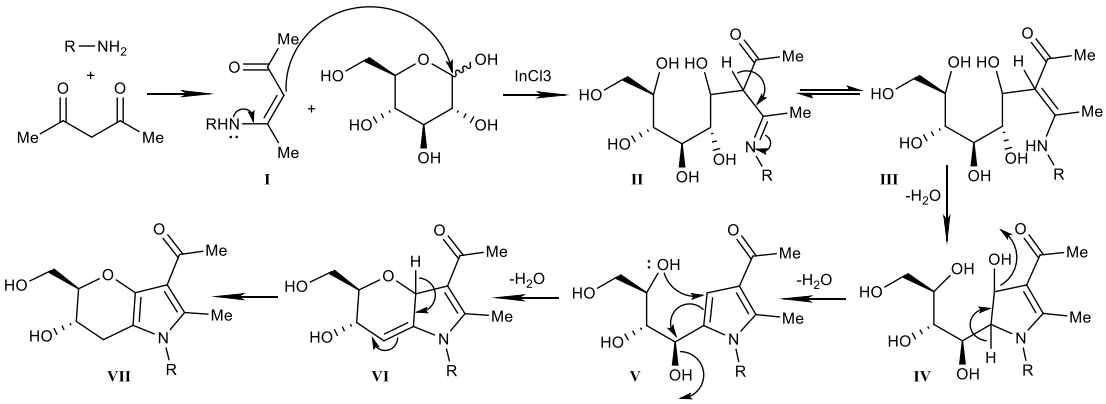


Figure 1-61. Mechanism of Yadav *et al.* reported pyrrole synthesis reaction.

Lingaiah Nagarapu *et al.* discovered a solvent-free method to synthesis annulated pyrroles. This reaction proceeds through in-situ generating enamine intermediates from primary

amines and 1,3-dicarbonyl compounds, followed by condensation of the intermediates with aldoses (xylose and mannose), catalyzed by 10 mol % of TBAB at 80 °C. Acetylation was done in one-pot for easier purification (Figure 1-62).[117] This method presents obvious advantages, such as the simple experimental procedure, high yields, and industrial viability. Also, it uses a catalytic amount of simple Lewis acid TBAB to boost the reaction, which is more environmentally friendly than using metallic catalysts.

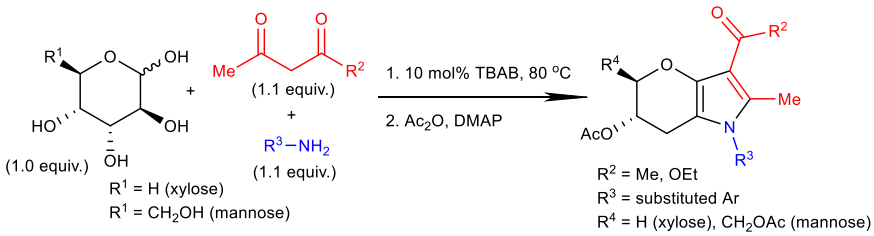


Figure 1-62. Annulated pyrrole synthesis from unprotected sugar, 1,3-dicarbonyl compounds and primary amines catalyzed by TBAB.

Sunil M. Rokade *et al.* reported a catalyst-free reaction between carbohydrates, primary amines, and 1,3-dicarbonyl compounds in a deep eutectic solvent (DES) system under 80 °C and obtained the annulated pyrrole products in high yields (Figure 1-63).[118] This protocol provides additional benefits, such as straightforward experimental execution and broad applicability for obtaining bioactive pyrrole derivatives.

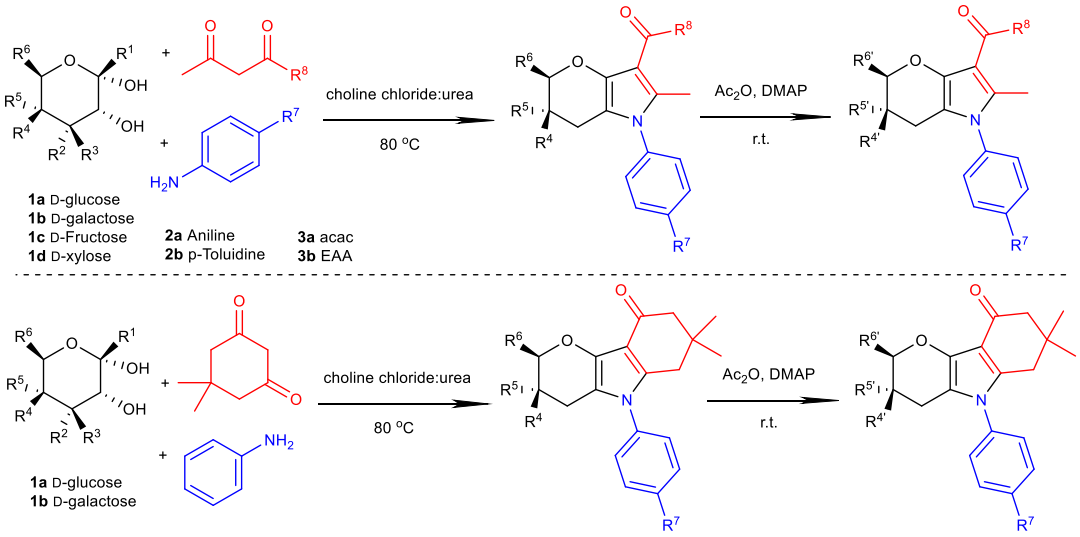


Figure 1-63. Annulated pyrrole synthesis from carbohydrates, 1,3-dicarbonyl compounds and primary amines in a deep eutectic solvent (DES) system.

Compared with the protocols mentioned in sections *1.2.4.1* and *1.2.4.2*, the advantages of these pyrrole synthesis reactions from unprotected sugars above are apparent: they achieved lower costs, higher yields, simpler procedures, and expanded the substrate scope. However, in these reactions, disaccharides were not studied, insufficient active methylene compounds were investigated except for the 1,3-dicarbonyl compounds, only annulated products were obtained, and no proof of the reaction mechanisms was provided.

Pyrrole synthesis using active methylenes as one of the major starting materials is extremely useful since it enables the formation of a library of multi-functionalized pyrrole derivatives. The three-component reactions between carbohydrates, active methylenes, and amines are of great potential because they are atom-efficient, cheap, green, and offer polyhydroxy groups and chiral centers for further modification.

Multicomponent reactions (MCRs) are reactions between at least three starting materials, reactants will combine in a domino process to give a final product that maintains major atom sections of all the substrates.[119-122] Multicomponent reactions have several features: reactions through simple one-pot operations, have high atom economy, and allow high product diversity and complexity.[123] The MCRs are commendable because they avoid some of the need for reaction intermediate separation and purification, and thus greatly diminish chemicals or solvent waste from these operations. Therefore, the development of new MCR methodologies is regarded as an important aspect of green chemistry. Moreover, the flexible substrates of multicomponent reactions make them very powerful for the synthesis of diverse bioactive molecules and drug candidates.[124, 125] Based on these advantages, the expansion and improvement of multicomponent reactions are becoming one of the leading edges in organic synthesis. In recent years, increasing studies have been done on MCRs that directly lead to

heterocycles, especially for pyrroles.[126, 127] In the previous *1.2.4* section, several multi-component reactions of pyrrole synthesis were mentioned.

1.3 Research gap and rational of this dissertation

In the last few decades, significant efforts have been made towards utilization of carbohydrates as industrial feedstocks and organic raw materials for obvious reasons. Carbohydrates are important cheap sustainable materials with great promise as feedstocks. However, because of the complex chirality and multiple functional groups, precise synthesis of target compounds from carbohydrates is challenging. Previously, pyrrole synthesis procedures from amino sugars were reported, yet the practicality of these methods were limited by the high price and limited variety of amino sugars. Plenty of studies also tried to use common sugars such as D-glucose, but tedious protection/deprotection steps were required to obtain the target products. Later, reactions that successfully applied naked sugars to give poly-functionalized pyrroles in one-pot were published, but only products with annulated sugar side chain were obtained, and these restricted modifications of these intermediates to target products. Further development of simple, cheap, stereo-selective, and green synthetic methods from unprotected sugars are of great interests. In this dissertation, efforts were focussed on the direct synthesis of poly-functionalized pyrroles from unactivated and unprotected carbohydrates. Our investigations focused on synthesis of *N*-unsubstituted and *N*-substituted densely functionalized pyrroles with an open sugar chain. Our investigations aimed at making the developed routes practical, sustainable, efficient, and avoided the use of metal catalysis or expensive catalysts. Since the most employed active methylenes in the earlier studies were the 1,3-dicarbonyl compounds, we used oxoacetonitriles and malononitrile which offer nitrogen moieties for further transformations and homologations.

1.4 Objectives

The objectives of this dissertation are:

1. To synthesize densely functionalized *N*-unsubstituted and *N*-substituted pyrroles from unactivated and unprotected carbohydrates using multicomponent reaction approaches.
2. Ensure the reactions are efficient, practical, and scalable by conducting the reactions at gram scale.
3. To demonstrate the utility of the synthesized pyrroles and convert them into important building blocks.
4. To provide evidence for the reaction mechanism.

Chapter 2. A Practical Synthesis of Densely Functionalized Pyrroles v*ia* A Three-Component Cascade Reactions Between Carbohydrates, Oxoacetonitriles and Ammonium Acetate

2.1 Introduction

The direct conversion of unprotected and unactivated carbohydrates to useful scaffolds and fine chemicals is of great interest for environmental and sustainable considerations.[47, 52, 128] Therefore, significant efforts have been invested in this endeavor.[129-131] Specifically, the conversion of carbohydrates to oxygen and nitrogen heterocycles is highly desirable due to their importance in the pharmaceutical, cosmetic, food, and material science industries.[47, 52, 128] The conversion of carbohydrates to oxygen heterocycles has seen greater success in comparison to their nitrogen counterparts.[18, 19] One such well-investigated conversion is the García González reaction between carbohydrates and 1,3-dicarbonyls to produce substituted furans.[33, 50, 132] We previously extended the scope of this reaction and prepared furans decorated with amine, amide, aldehyde and hydroxymethyl functionalities under environmentally benign conditions.[45]

However, the equivalent synthesis of pyrrole heterocycles (unsubstituted at NH) from carbohydrates is problematic and not practical. This synthesis was demonstrated in the years 1950s-1970s by mainly reacting natural amino sugars with 1,3-dicarbonyls, and also by reacting a mixture of sugars, 1,3-dicarbonyls and ammonia source.[33, 50, 132-140] Unfortunately, the reaction using natural amino sugars is limited due to the high cost of these amino sugars and their limited commercial availabilities in comparison to sugars. Moreover, the reaction gave mixtures of products.[33, 50, 132-137] On the other hand, the reaction between sugars, 1,3-dicarbonyls and ammonia source gave insignificant pyrrole yields since a complex mixture of nonselective products was formed or was limited in scope. Additionally, the synthesized pyrroles from these two routes are always substituted with a carbonyl moiety and lack functional group variations necessary for further transformations.[33, 50, 132-137] On the other hand, synthesis of *N*-substituted

pyrroles by reacting α-hydroxy-carbonyl compounds, cyanoacetate, and primary amines was described by Sowell et. al (Figure 2-1).[20] Therefore, it is highly advantageous to develop a practical synthesis of densely functionalized pyrroles directly from cheap and widely available sustainable materials such as sugars (Figure 2-1).

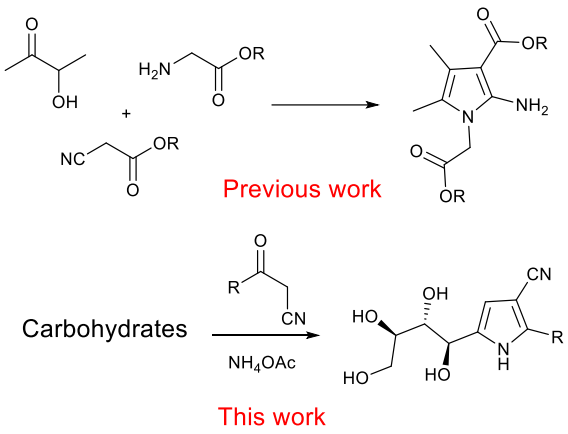
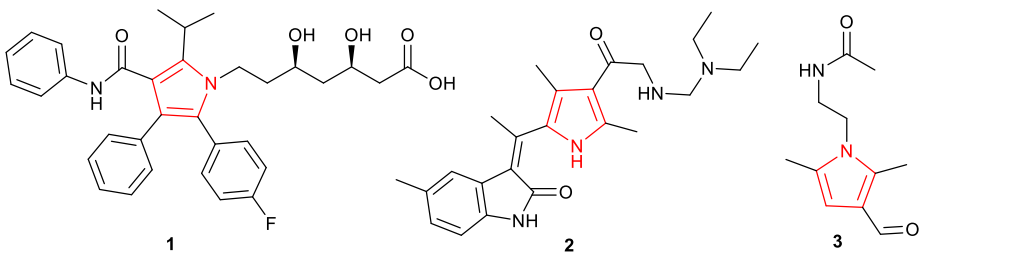


Figure 2-1. Three-component synthesis of pyrroles.

Pyrroles[56, 61, 141-144] are nitrogen heterocyclic compounds embedded in many plant and marine natural products such as chlorophylls,[145] porphyrins,[146, 147] prodigiosin[148] and prodoginine.[148] They possess wide bioactivities such as antitumor,[149-154] antimycobacterial,[73, 155-157] anti-inflammatory,[63, 158-160] and antiviral activities.[161, 162] Several pyrrole-based drugs are commercially available including the blockbuster atorvastatin **1**,[70] sunitinib **2**,[163] and aloracetam **3** (Figure 2-2).[164] Therefore, the development of practical and sustainable methods for the synthesis of densely functionalized pyrroles that are amenable to easy transformations to useful intermediates or final products is of great interest.



1 Atorvastatin (Lipitor) controls production of cholesterol

2 Sunitinib treats renal cancer

3 Aloracetam treats Alzheimer's disease

Figure 2-2. Structures of pyrrole-based commercial drugs.

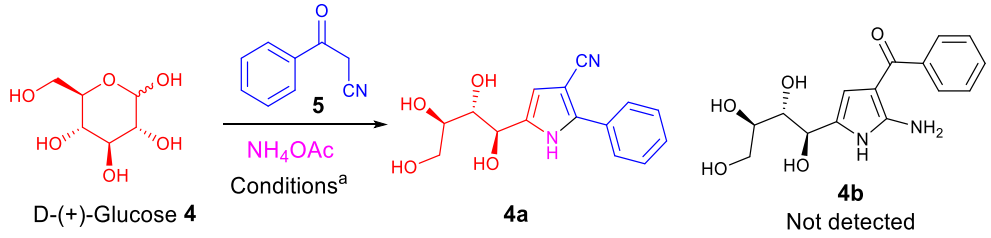
Herein, we disclose an efficient, one-step synthesis of densely functionalized pyrroles *via* a three-component cascade reaction between unprotected sugars, oxoacetonitriles and ammonium acetate in excellent yields. We also demonstrate the practicality of this reaction at a 2-gram scale and show the usefulness of the synthesized pyrroles for the preparation of important heterocycles. Furthermore, mass spectrometry of the reaction intermediates supported the proposed mechanism.

2.2 Results and discussion

Initial experiments started by heating a mixture of D-(+)-glucose **4**, benzoylacetonitrile **5** and NH_4OAc in the presence of Et_3N in H_2O. Previously, these reaction conditions were optimum for the synthesis of densely substituted furans and therefore, were tested initially.[45] The three-component reaction successfully gave the densely functionalized polyhydroxyalkyl 2-phenyl pyrrole-3-carbonitrile **4a** in 45% yield (Table 2-1, entry 1). The other possible pyrrole **4b** was not observed (see mechanism later). Attempts to increase the yield of pyrrole **4a** by adding sodium lauryl sulphate surfactant to the reaction mixture to enhance the solubility of benzoylacetonitrile **5** in H_2O were not fruitful. However, the reaction in CH_3OH, CH_3OH/H_2O mixture and DMF solvents gave better yields of pyrrole **4a** while DMSO gave the lowest yield of 36% (Table 2-1, entries 2-5). DMF emerged as the best solvent giving pyrrole **4a** in 92% yield due to its better solubilizing power of the reaction components (Table 2-1, entry 4). Upon replacing Et_3N with AcOH, the reaction also proceeded to give pyrrole **4a** 88% yield (Table 2-1, entry 6). However, in the absence of Et_3N or AcOH, the reaction did not proceed (Table 2-1, entry 7). Attempts to make the reaction catalytic by reducing Et_3N or AcOH gave lower yields (results not shown). The optimum reaction temperature was

found to be 80 °C since higher temperatures led to decomposition indicated by turning of the reaction mixtures from yellow to black while lower temperature gave trace amount of pyrrole **4a** despite increasing the reaction time (Table 2-1, entry 8-9).

Table 2-1: Optimization of the reaction conditions for the synthesis of polyhydroxyalkyl 2-phenyl pyrrole-3-carbonitrile 4a.[a]



Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield
1	Et_3N (0.5)	H_2O	80 °C	4	45
2	Et_3N (0.5)	CH_3OH	80 °C	4	60
3	Et_3N (0.5)	CH_3OH+H_2O (1:1)	80 °C	4	68
4	Et_3N (0.5)	DMF	80 °C	4	92
5	Et_3N (0.5)	DMSO	80 °C	4	36
6	AcOH (0.5)	DMF	80 °C	4	88
7	No Et_3N or AcOH	DMF	80 °C	4	ND[c]
8	Et_3N (0.5)	DMF	100 °C	4	82
9	Et_3N or AcOH (0.5)	DMF	r.t.	24	Trace

[a]Reaction conditions: A mixture of D-(+)-glucose **4** (1.0 mmol), benzoylacetonitrile **5** (1.0 mmol), NH_4OAc (1.0 mmol) and the catalyst was stirred in the solvent (3 mL) at 80 °C for 4 h. [b] Isolated yields. [c] ND: not detected.

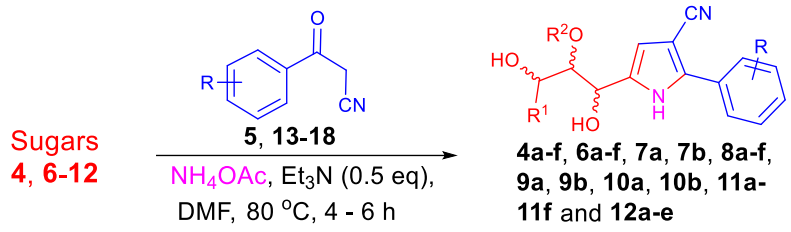
2.3 Scope of the reaction

Under the optimized reaction condition (Table 2-1, entry 4), we then explored the scope of the three-component cascade reaction by reacting different sugars including

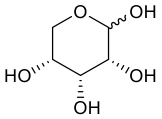
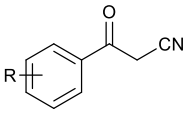
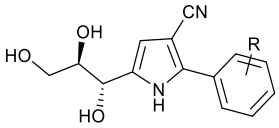
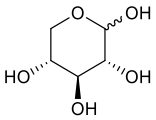
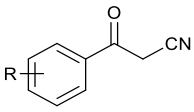
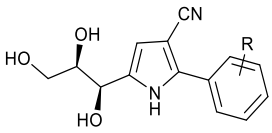
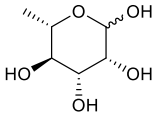
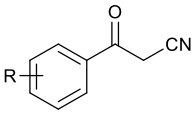
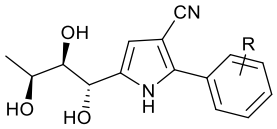
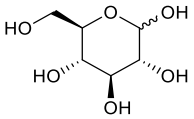
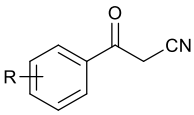
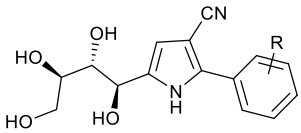
pentoses **6-8**, hexoses **4** and **9** and disaccharides **10-12** with several (substituted) benzoylacetonitriles **5** and **13-18** (Table 2-2). All of the sugars **4** and **6-12** reacted smoothly to give the densely functionalized pyrroles **4a-f**, **6a-f**, **7a**, **7b**, **8a-f**, **9a**, **9b**, **10a**, **10b**, **11a-11f** and **12a-e** in excellent 80-96% isolated yields. The type of sugar or its stereochemistry as well as the type of the substituents on the benzoylacetonitriles **5** and **13-17** has little effect on the yield of the products (Table 2-2). However, disaccharides **10-12** required a longer reaction time to give the products due to lower reactivities.

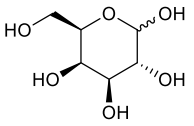
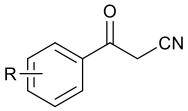
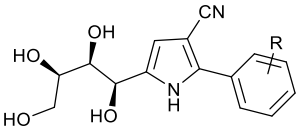
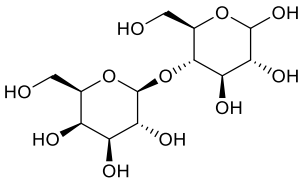
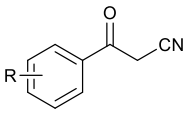
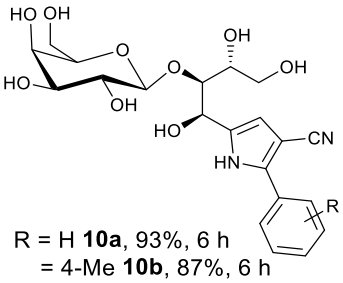
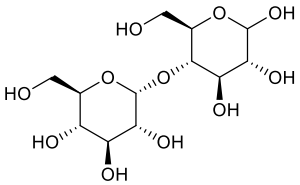
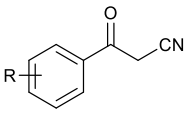
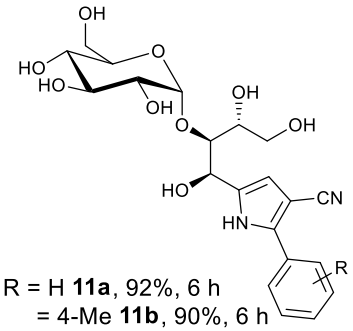
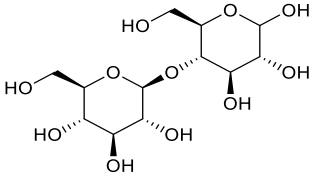
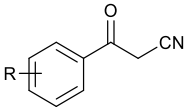
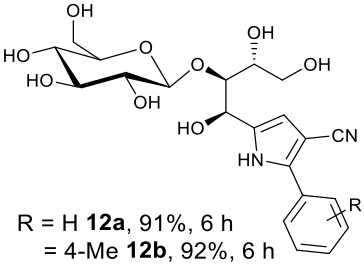
Polyhydroxyalkyl 2-phenyl pyrrole-3-carbonitriles **4a-f**, **6a-f**, **7a**, **7b**, **8a-f**, **9a**, **9b**, **10a**, **10b**, **11a-11f** and **12a-e** show high water solubility due to the extensive hydrogen bonding provided by the NH and OH groups. Consequently, these pyrroles are insoluble in $CHCl_3$, CH_2Cl_2 or EtOAc but soluble in MeOH. The crude pyrroles were obtained as gums by evaporating the reaction mixtures under reduced pressure. However, Et_3N could not be removed completely (^{1}H NMR) under reduced pressure nor by triturating the gums with organic solvents such as EtOAc or CH_2Cl_2 due to strong hydrogen bonding. Therefore, the pyrroles **4a-f**, **6a-f**, **7a**, **7b**, **8a-f**, **9a**, **9b**, **10a**, **10b**, **11a-11f** and **12a-e** were purified by flushing the residual gums through silica gel column chromatography using CH_2Cl_2/MeOH as eluent (95:5 for **6a-f**, **7a**, **7b**, **8a-f**; 90:10 for **4a-f**, **9a**, **9b**; and 80:20 for **10a**, **10b**, **11a-11f**, **12a-e**) to give pure off-white-yellow solids. The slight differences in yields could be attributed to losses during chromatographic separation.

Table 2-2: Scope of the Et_3N-catalyzed three-component cascade reaction between sugars 4 and 6-12, benzoylacetonitriles 5 and 13-17 and NH_4OAc for the synthesis of densely functionalized polyhydroxyalkyl 2-phenyl pyrrole-3-carbonitrile 4a-f, 6a-f, 7a, 7b, 8a-f, 9a, 9b, 10a, 10b, 11a-f and 12a-e.



R = H, 4-Me, 4-OMe, 4-F, 4-Br, 4-Cl, 2-Cl
R^1 = H, Me, CH_2OH
R^2 = H, glucose, galactose

Entry	Sugars **4** and **6-12**	Benzoylacetonitriles **5** and **13-17**	Pyrroles yield (%),[a] reaction time
1	 D-(+)-Ribose **6**	 R = H **5** = 4-Me **13** = 4-OMe **14** = 4-F **15** = 4-Br **16** = 4-Cl **17**	 R = H **6a**, 96%, 4 h = 4-Me **6b**, 95%, 4 h = 4-OMe **6c**, 86%, 4 h = 4-F **6d**, 88%, 4 h = 4-Br **6e**, 84%, 4 h = 4-Cl **6f**, 85%, 4 h
2	 D-(+)- Xylose **7**	 R = H **5** = 4-Me **13**	 R = H **7a**, 96%, 4 h = 4-Me **7b**, 94%, 4 h
3	 L-(+)- Rhamnose **8**	 R = H **5** = 4-Me **13** = 4-OMe **14** = 4-F **15** = 4-Br **16** = 2-Cl **18**	 R = H **8a**, 96%, 4 h = 4-Me **8b**, 89%, 4 h = 4-OMe **8c**, 85%, 4 h = 4-F **8d**, 83%, 4 h = 4-Br **8e**, 80%, 4 h = 2-Cl **8f**, 82%, 4 h
4	 D-(+)-Glucose **4**	 R = H **5** = 4-Me **13** = 4-OMe **14** = 4-F **15** = 4-Br **16** = 2-Cl **18**	 R = H **4a**, 92%, 4 h = 4-Me **4b**, 90%, 4 h = 4-OMe **4c**, 88%, 4 h = 4-F **4d**, 87%, 5 h = 4-Br **4e**, 81%, 5 h = 2-Cl **4f**, 80%, 5 h

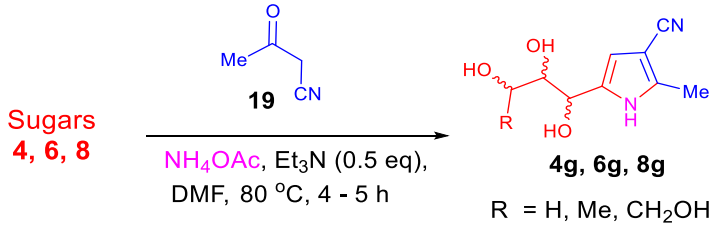
5	 D-(+)-Galactose **9**	 R = H **5** = 4-Me **6**	 R = H **9a**, 90%, 4 h = 4-Me **9b**, 86%, 4 h
6	 L-(+)-Lactose **10**	 R = H **5** = 4-Me **6**	 R = H **10a**, 93%, 6 h = 4-Me **10b**, 87%, 6 h
7	 D-(+)-Maltose **11**	 R = H **5** = 4-Me **13** = 4-OMe **14** = 4-F **15** = 4-Br **16** = 2-Cl **18**	 R = H **11a**, 92%, 6 h = 4-Me **11b**, 90%, 6 h = 4-OMe **11c**, 87%, 6 h = 4-F **11d**, 86%, 6 h = 4-Br **11e**, 89%, 6 h = 2-Cl **11f**, 82%, 6 h
8	 D-(+)- Cellobiose **12**	 R = H **5** = 4-Me **13** = 4-OMe **14** = 4-F **15** = 4-Br **16**	 R = H **12a**, 91%, 6 h = 4-Me **12b**, 92%, 6 h = 4-OMe **12c**, 84%, 6 h = 4-F **12d**, 84%, 6 h = 4-Br **12e**, 87%, 6 h

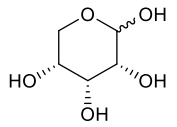
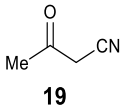
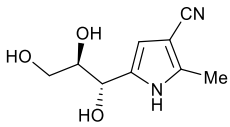
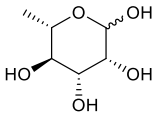
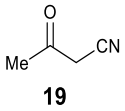
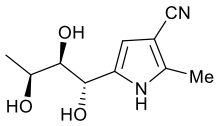
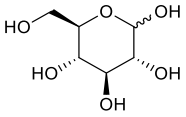
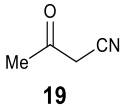
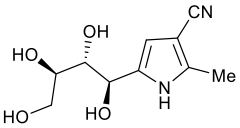
Reaction conditions: A mixture of the sugar **4**, **6-12** (1.0 mmol), substituted benzoylacetonitrile **5**, **13-18** (1.0 mmol), NH_4OAc (1.0 mmol) and Et_3N (0.5 mmol) was stirred in DMF (3 mL) at 80 ^oC for 4-6 h. [a] Isolated yields.

Further, the reaction also proceeded smoothly with 3-oxobutanenitrile **19** (Table 2-3). For example, the reaction using representative sugars **4**, **6** and **8** gave the densely functionalized

polyhydroxyalkyl 2-methyl pyrrole-3-carbonitrile **4g**, **6g** and **8g** in 75-80% yield within 5 hours. Similarly, these products were highly polar due to an extensive hydrogen bonding network.

Table 2-3: Scope of the Et_3N-catalyzed three-component cascade reaction between sugars 4, 6 and 8, 3-oxobutanenitrile 19 and NH_4OAc for the synthesis of densely functionalized polyhydroxyalkyl 2-methyl pyrrole-3-carbonitrile 4g, 6g and 8g.

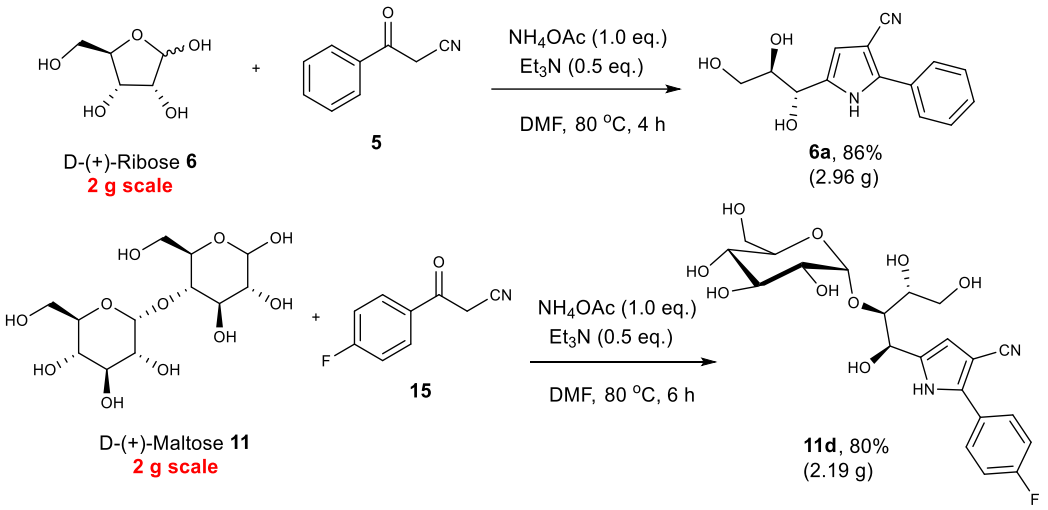


Entry	Sugars **4, 6** and **8**	3-Oxobutanenitrile **19**	Pyrroles yield (%),[a] reaction time
1	 D-(+)-Ribose **6**	 **19**	 **6g**, 80%, 4 h
2	 L-(+)- Rhamnose **8**	 **19**	 **8g**, 76%, 4 h
3	 D-(+)-Glucose **4**	 **19**	 **4g**, 75%, 5 h

Reaction conditions: A mixture of the sugar **4**, **6** and **8**(1.0 mmol), 3-oxoacetonitrile **19** (1.0 mmol), NH_4OAc (1.0 mmol) and Et_3N (0.5 mmol) was stirred in DMF (3 mL) at 80 °C for 4-5 h. [a] Isolated yields.

2.4 Large scale reactions

The practicality and amenability of this reaction to large scale is demonstrated by reacting 2 g of D-(+)-ribose **6** with benzoylacetonitrile **5** to give pyrrole **6a** in 86% yield. Also, the reaction between 2 g of D-(+)-maltose **11** with 4-fluorobenzoylacetonitrile **15** gave pyrrole **11d** in 80% yield (Scheme 2-1).

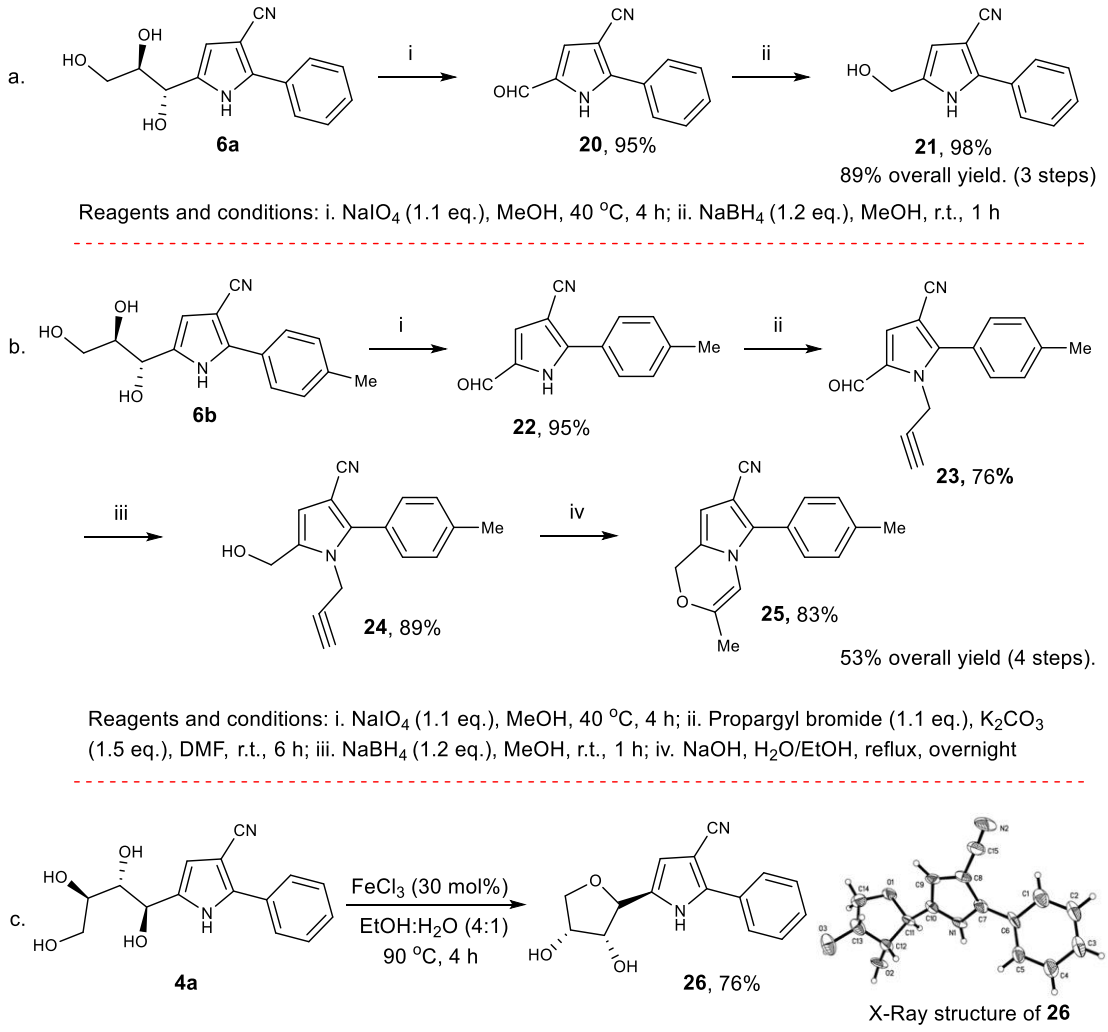


Scheme 2-1. 2-Gram scale synthesis of densely functionalized pyrroles 6a and 11d from D-(+)-ribose 6 and D-(+)-maltose 11.

2.5 Application of the synthesized pyrroles

The densely functionalized pyrroles **4a-g**, **6a-g**, **7a**, **7b**, **8a-g**, **9a**, **9b**, **10a**, **10b**, **11a-11f** and **12a-e** contain important functional groups (CN, NH, OH as well as aromatic ring) that can either be left without modifications or transformed to other relevant functional groups (e.g. COOH, CHO, CH_2OH etc) to be used as handles to synthesize building blocks for fine chemicals, natural products and pharmaceuticals.[117] As a demonstration, and since formyl pyrroles and hydroxymethyl pyrroles are important building blocks for many natural products,[163] pyrrole **6a** was converted to 5-formyl pyrrole **20** in 95% yield which in turn was converted to 5-hydroxymethyl pyrrole **21** in almost quantitative yield (Scheme 2-2a).[165] Further, we demonstrated efficient synthesis of pyrroloozazine **25** in 53% overall yield from pyrrole **6b** through a series of reactions as shown in Scheme 2-2b.[166, 167] There are very limited routes to

synthesize pyrroloozazine despite their many reported bioactivities.[168, 169] Our approach represents a sustainable synthesis with high substitution at the pyrrole ring and gives excellent overall yield. Additionally, *C*-glycoside **26** was synthesized smoothly in 76% yield by simple treatment of pyrrole **4a** with $FeCl_3$ (Scheme 2-2c).[117] The stereochemistry of *C*-glycoside **26** was unambiguously confirmed by single-crystal X-ray analysis as shown in Scheme 2c.[170] The X-ray structure of *C*-glycoside **26** indirectly also confirms the structure of **4a**. *C*-Glycosides are important compounds with many biological activities and are used as therapeutic drugs.[171-173] Pyrrole *C*-glycosides are important building block of porphyrin glycoconjugates.[171-173] These reaction demonstrate the wide use of the pyrrole substrates synthesized in this work.



Scheme 2-2. Transformation of pyrroles 6a, 6b and 4a into useful building blocks.

2.6 Proposed reaction mechanism

The proposed mechanism of this three-component cascade reaction is shown in Figure 2-3. Knoevenagel condensation between benzoylacetonitrile **5** and D-(+)-glucose **4** gives intermediate **I**. Dehydration of **I** gives **II** which undergoes oxa-Micheal addition to give III. Ring opening of III gives dienol **IV** which undergoes ketolization to give dienone **V**. Finally, Paal-Knorr reaction between intermediate **V** and NH_4OAc gives intermediate **VI** which dehydrates to give the pyrrole **4a**.[77, 79]

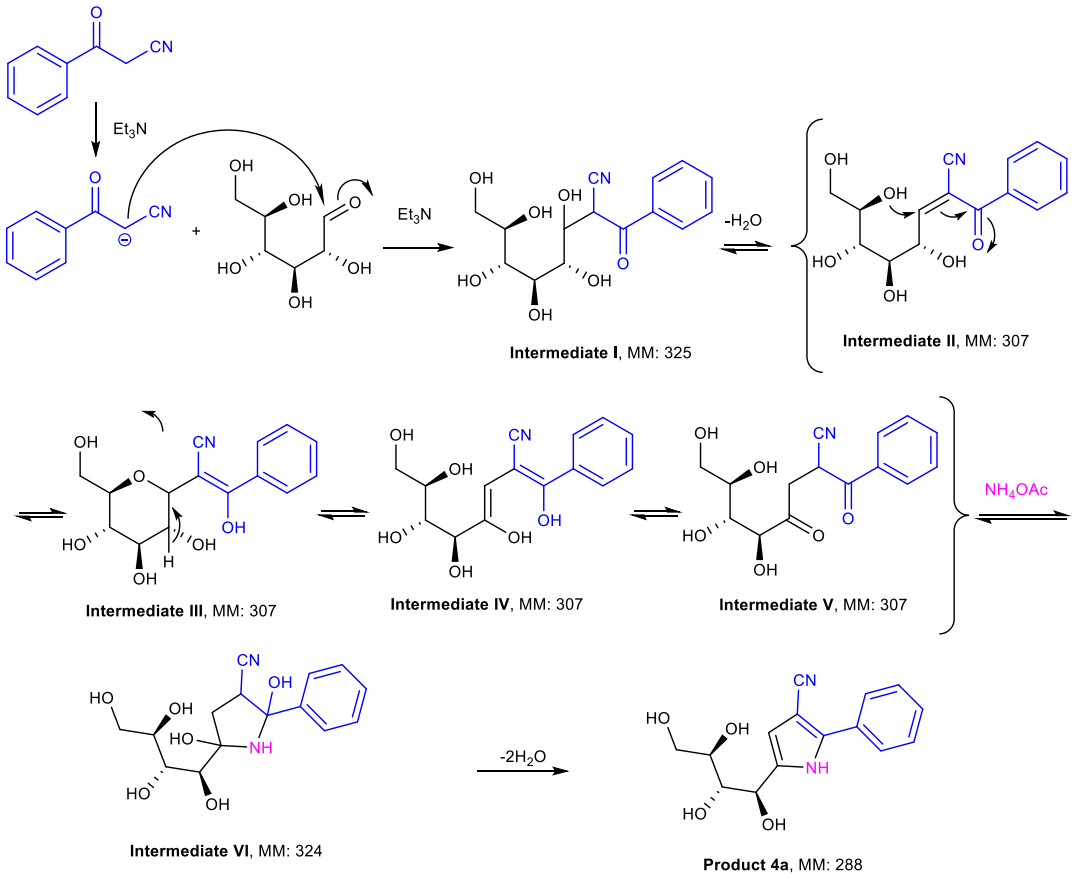


Figure 2-3. Plausible reaction mechanism showing the intermediates with their molecular mass (MM).

Attempts to provide evidence for the above proposed mechanism using ^{1}H NMR spectroscopy to detect the intermediates were not successful due to the formation of several products thus making the spectra difficult to interpret. However, when the reaction progress was followed using mass spectrometry over 4 hours, the proposed intermediates

I-VI could be accounted for from the mass spectral peaks in Figure 2-4 and Table 2-4. At the start of the reaction, and judging from the abundance of the peaks, the intermediates **I-VI** were predominant. As the reaction progressed, they disappeared and converted to the product **4a** at the end of 3.5 hours.

Table 2-4: Assignment of the peaks from mass spectra in Figure 3 to intermediates I-V and product 4a.

Reaction intermediate/product	Molecular mass (MM)	Peaks
I	325	325 $[M]^+$, 326 $[M+1]^+$
II, **III**, **IV** and **V**	307	307 (not observed), 308 $[M+1]^+$, 309 $[M+2]^+$
VI	324	324 (not observed), 325 $[M+1]^+$, 326 $[M+2]^+$
product **4a**	288	271 [M-17 (-OH)]$^+$, 289 $[M+1]^+$, 290 $[M+2]^+$

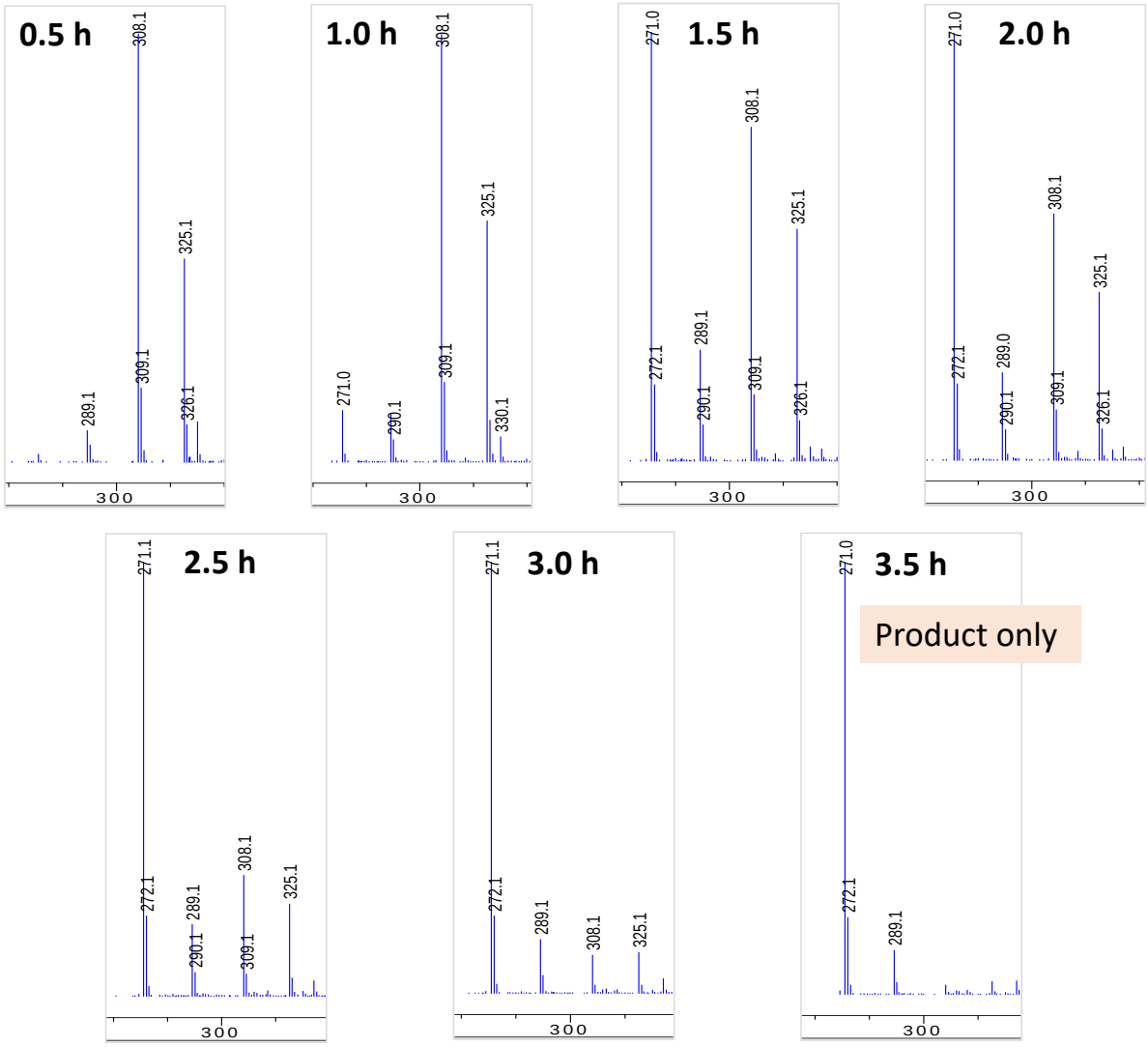


Figure 2-4. Part of the LC-MS spectra of the reaction fractions showing the intermediates at different time intervals.

2.7 Conclusions

Unprotected and unactivated sugars were converted to densely functionalized pyrroles. A practical three-component cascade reaction between sugars **4** and **6-12**, oxoacetonitriles **5** and **13-19**, and ammonium acetate afford the pyrroles in excellent yields. This metal-free and environmentally benign reaction use inexpensive sugars, Et_3N catalyst and proceed with high atom economy. The pyrroles were designed to have functional group handles to build more complex structures or be transformed to other functional group handles for further modifications

as demonstrate with several examples. This method has high potential for large-scale production of building blocks with important properties. Application of this method for the synthesis of pharmacologically relevant compounds and chain lengthening using -CN, -NH_2 and -CHO substituents is currently being explored.

2.8 Experimental Section

2.8.1 Materials and methods

All chemicals were purchased from Sigma-Aldrich or Alfa Aesar and were used as received without further purification. Commercial AR grade solvents were used as received from Merck without further distillation. IR were recorded by Bruker MPA FT-IR**.** ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance DPX 300. ^{13}C NMR spectra were recorded at 75.47 MHz on a Bruker Avance DPX 300. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. HRMS were measured using a hybrid quadrupole time-of-flight (Q-TOF) detector on Qstar XL MS/MS system. LC-MS spectra were recorded on Agilent 6530 LC-MS. Analytical TLC was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness) and the plates were visualized using UV radiation (254 nm) and stained in ceric ammonium sulfate solution with heating. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh).

2.8.2 General Procedure: Synthesis of the polyhydroxyalkyl 2-phenyl pyrrole-3-carbonitrile 4a-g, 6a-g, 7a, 7b, 8a-g, 9a, 9b, 10a, 10b, 11a-f and 12a-e.

To a stirred solution of the sugar (1.0 equiv.), oxoacetonitriles (1.0 equiv.) and NH_4OAc (1.0 equiv.) in DMF (3 ml) was added Et_3N (0.5 equiv.) at room temperature. The resulting mixture was stirred at 80 ^{o}C (oil bath) until complete consumption of starting materials as indicated by TLC (4-6 h). The reaction mixture was evaporated to dryness under vacuum to give the crude product as off-white foam. The foam was eluted through silica gel column chromatography using

$MeOH/CH_2Cl_2$ (5:95 for pentoses; 10:90 for hexoses; and 20:80 for disaccharides) and the pure products were collected. All reactions were conducted using 1.0 mmol of the sugars.

All NMR spectra and other data are listed in Appendix.

Chapter 3. Selective One-pot Cascade Synthesis of *N*-substituted Highly Functionalized Pyrroles from Unprotected Sugars, Primary Amines, and Oxoacetonitriles

3.1 Introduction

Sustainable conversion of carbohydrates to value-added chemicals is highly desirable.[24, 174] Specifically, conversion of carbohydrates to nitrogen heterocycles is important since they find many applications in the pharmaceutical, food, cosmetic, nutraceutical and material science industries.[20, 175-178]

In the 1950s, Gónzalez and co-workers obtained *N*-substituted keto-functionalized pyrrole heterocycles by condensing *N*-substituted amino sugars with 1,3-dicarbonyls (Figure 3-1, a).[33,50] However, this reaction was restricted in scope since the starting *N*-substituted amino sugars itself required multi-step synthesis involving inefficient and time-consuming protection/deprotection methodologies that lack atom economy. Besides, the reaction usually gave low ~30% yields and uses expensive amino sugars (in comparison to sugars).[33,50] Moreover, only keto-functionalized pyrroles were demonstrated since the scope of 1,3-dicarbonyl equivalents such as 1,3-dinitriles and 3-oxonitriles were not reported. Recently, the Gónzalez reaction was successfully attempted between sugars, 1,3-dicarbonyls and anilines as an external source of nitrogen *albeit* annulated keto-pyrroles were obtained (Figure 3-1, b).[118, 179, 180] Though this is a welcome improvement, however, the scope of the reaction remained limited to only 1,3-dicarbonyls and anilines. Reactions with alkyl-, benzyl-, allyl-amines, etc. were not reported.[118, 179, 180] Besides, although annulated pyrroles are important structures, annulation limits further manipulations to other desired pyrroles.[118, 179, 180]

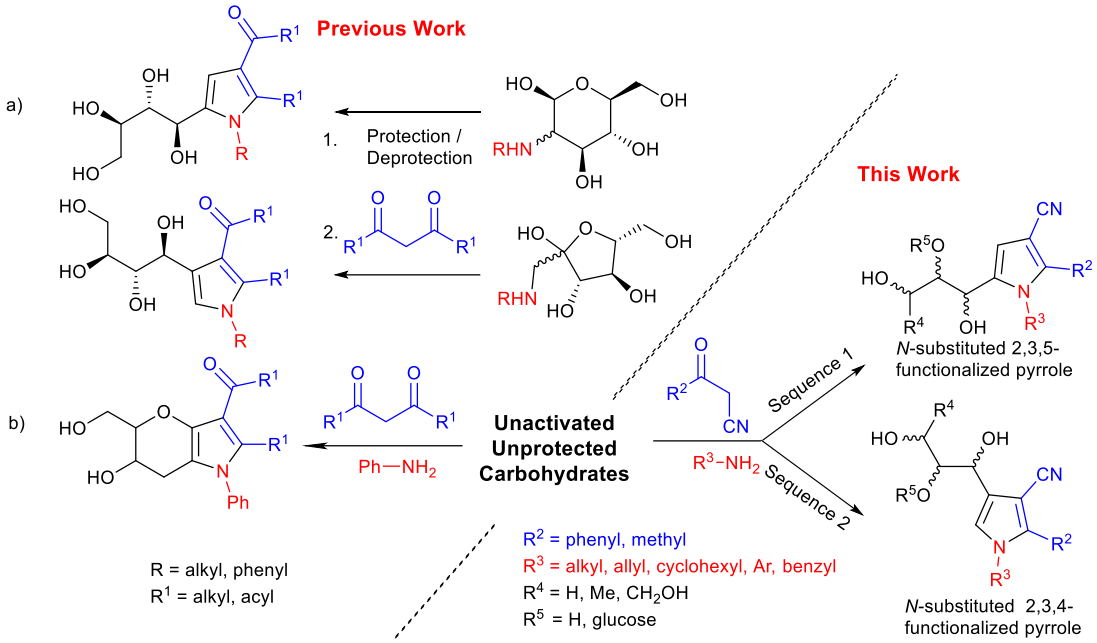


Figure 3-1. Pyrrole synthesis methods in the previous and present work.

Majority of the pyrroles found in nature and those used as intermediates in the pharmaceutical industry are *N*-substituted pyrroles. Previously, we developed a convenient synthesis of *N*-unsubstituted 2,3,5-functionalized pyrroles using NH_4OAc as the source of nitrogen.[181] However, to convert these *N*-unsubstituted pyrroles to *N*-substituted pyrroles, several extra impractical steps including protection/deprotection steps are needed. Therefore, a direct versatile synthesis of *N*-substituted highly functionalized pyrroles that are amenable for easy manipulations is highly desirable. This synthesis becomes even more attractive industrially when multicomponent cascade reactions employing common and cheap starting materials and reagents are employed.

Pyrroles are important heterocyclic compounds owing to their exciting chemical and biological properties.[56, 61, 182] They show anti-bacterial,[65] anti-fungal,[66] anti-inflammatory,[63] anti-oxidative,[68] anti-tumor and ionotropic[183] properties. Several commercial drugs including atorvastatin[70] sunitinib[184] and aloracetam[56] contain pyrrole rings as integral part of their framework. Hence, direct and cheap sustainable synthesis of pyrroles from carbohydrates will be valuable.

Herein, we report a versatile one-pot selective synthesis of *N*-substituted 2,3,5-functionalized pyrroles and *N*-substituted 2,3,4-functionalized pyrroles in excellent yields using cheap unprotected sugars. We demonstrate the wide-scope of this three-component and metal-free reaction and provide evidence for its mechanism.

3.2 Results and Discussion

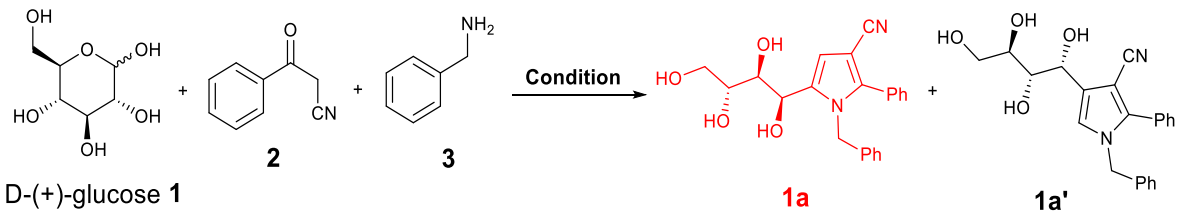
The investigation started by mixing D-(+)-glucose **1** (1 mmol), benzoylacetonitrile **2** (1.0 equiv.) and benzylamine **3** (1.0 equiv.) together in the presence of AcOH (1.0 equiv.) as a catalyst in DMF at 80 ^{o}C (Table 1). DMF was selected to ensure complete dissolution and mixing of the reactants since initial reactions in water were ineffective due to the poor solubility and mixing of benzoylacetonitrile **2** and benzylamine **3**.[45] This three-component reaction gave two different products (TLC) which were identified spectroscopically as 1-benzyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile **1a** and 1-benzyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile **1a′** with a total isolated yield of 52% in 72:28 ratio (Table 1, entry 1). The optimization of the synthesis of pyrroles **1a** and **1a′** is discussed separately below.

3.2.1 Reaction optimization for the three-component cascade synthesis of 1-benzyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile 1a: a *N*-benzyl 2,3,5-substituted pyrrole

After screening several catalysts (Table 3-1, entries 2-8) including triethylamine (Et_3N), tetrabutylammonium bromide (TBAB), tetrabutylammonium fluoride (TBAF), sodium acetate (NaOAc), *p*-toluenesulfonic acid (PTSA), camphorsulfonic acid (CSA) and tetrabutyammonium bisulfate (TBAHS), TBAHS emerged as very promising giving complete selectivity of pyrrole **1a** *albeit* in low yield of 20% (Table 3-1, entry 8). The lower yield was attributed to

decomposition products (TLC) and difficulties while purifying the highly polar pyrrole **1a**. Indeed, a decrease in the reaction temperature to 60 °C increased the yield of pyrrole **1a** to 51% but decreased the selectivity since a mixture of **1a** and **1a′** was obtained in 88:12 (Table 3-1, entry 9). However, replacing DMF with EtOH gave pyrrole **1a** in 47% yield with complete selectivity (Table 3-1, entry 10). Switching to EtOH allowed for easier purification by simple evaporation of the reaction mixture followed by chromatography. Since this transformation could be initiated by the reaction of benzylamine **3** with either D-(+)-glucose **1** (masked aldehyde) or with benzoylacetonitrile **2** (see mechanism later), the sequence of substrate addition was also examined rather than adding all substrates "together" at the same time (Table 3-1, entries 11-13). Sequence 1 where benzoylacetonitrile **2** (1.0 equiv.), benzylamine **3** (1.0 equiv.) and TBAHS (1.0 equiv.) were stirred in EtOH at 60 °C for 3 h before addition of D-(+)-glucose **1** (1.0 mmol) and continuing stirring for another 5 h gave the highest 60% yield of pyrrole **1a** with complete selectivity (Table 3-1, entry 11 *vs* entry 12). In sequence 2, addition of benzoylacetonitrile **2** and D-(+)-glucose **1** were reversed and a mixture of the pyrroles **1a** and **1a′** in 74:26 ratio in lower 45% yield was obtained. Hence, sequence 1 was made catalytic and 0.5 equiv. TBAHS gave the best results where pyrrole **1a** was obtained in 58 % yield with complete selectivity (Table 3-1, entry 13).

Table 3-1: Optimization of the reaction conditions for the three-component synthesis of 1-benzyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile 1a.



Entry	Catalyst (equiv.)	Sequence of additions	Solvent	Temp. (°C)	Time (h)	Yield (%) [a]	**1a:1a′** ratio (%) [b]

1	AcOH (1.0)	Together [c]	DMF	80 °C	8	52	72:28
2	Et_3N (1.0)	Together	DMF	80 °C	8	38	ND[f]:100
3	TBAB (1.0)	Together	DMF	80 °C	8	24	ND:100
4	TBAF (1.0)	Together	DMF	80 °C	8	16	ND:100
5	NaOAc (1.0)	Together	DMF	80 °C	8	32	ND:100
6	PTSA (1.0)	Together	DMF	80 °C	8	21	77:23
7	CSA (1.0)	Together	DMF	80 °C	8	14	60:40
8	TBAHS (1.0)	Together	DMF	80 °C	8	20	100:ND
9	TBAHS (1.0)	Together	DMF	60 °C	8	51	88:12
10	TBAHS (1.0)	Together	EtOH	60 °C	8	47	100:ND
11	TBAHS (1.0)	Sequence 1 [d]	EtOH	60 °C	8	60	100:ND
12	TBAHS (1.0)	Sequence 2 [e]	EtOH	60 °C	8	45	74:26
13	TBAHS (0.5)	Sequence 1	EtOH	60 °C	8	58	100:ND

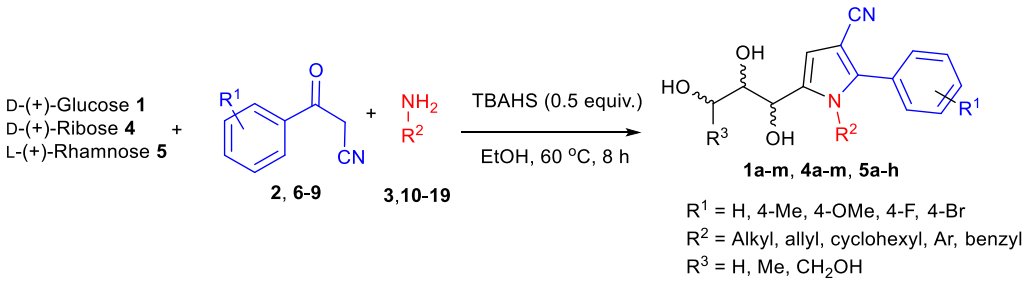
[a] Isolated yields. [b] Ratios measured using NMR. [c] Together: add D-(+)-glucose **1** (1.0 mmol), benzoylacetonitrile **2** (1.0 mmol), benzylamine **3** (1.0 mmol) and the catalyst (1.0 mmol) consecutively in 3 mL solvent and stir the mixture for 8 h at the given temperature. [d] Sequence 1: first stir benzoylacetonitrile **2** (1.0 mmol), benzylamine **3** (1.0 mmol) and TBAHS in 3 mL EtOH at 60 °C for 2 h. Next, add D-(+)-glucose **1** (1.0 mmol) to the mixture and continue the reaction for another 6 h. [e] Sequence 2: first stir D-(+)-glucose **1** (1.0 mmol), benzylamine **3** (1.0 mmol) and TBAHS in 3 mL EtOH at 60 °C for 2 h. Next, add benzoylacetonitrile **2** (1.0 mmol) to the mixture and continue the reaction for another 6 h. [f] ND: not detected.

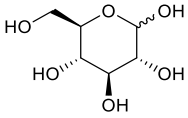
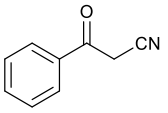
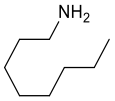
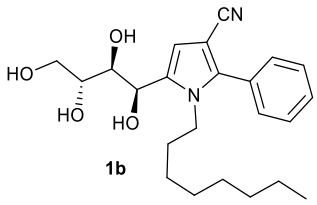
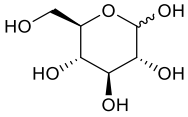
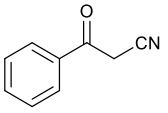
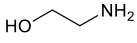
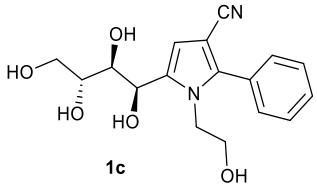
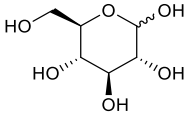
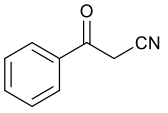
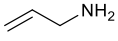
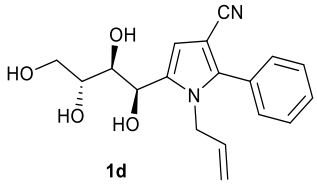
3.2.2 Substrate Scope for the there-component cascade synthesis of *N*-substituted 2,3,5-functionalized pyrrole

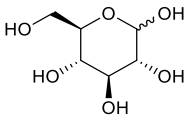
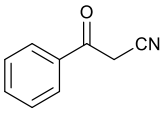
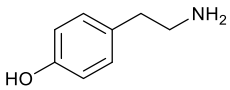
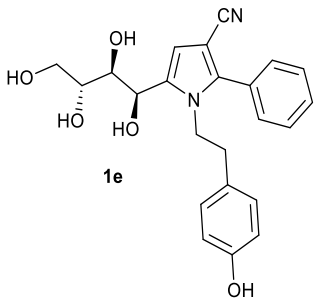
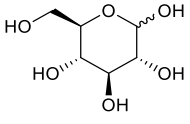
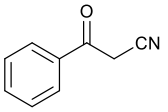
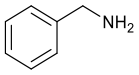
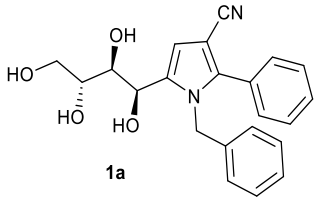
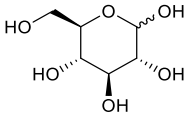
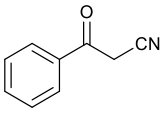
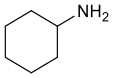
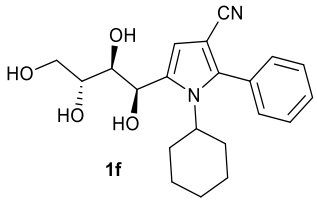
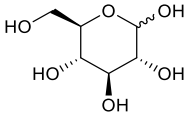
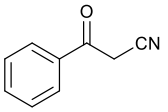
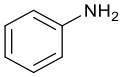
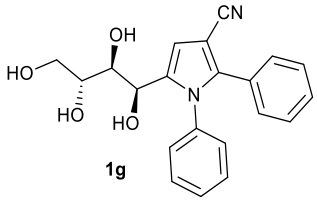
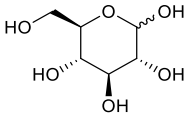
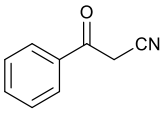
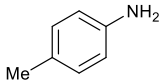
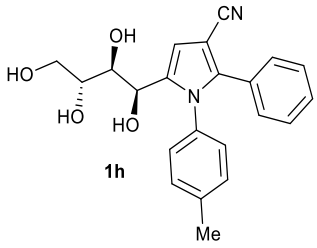
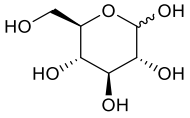
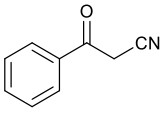
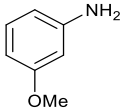
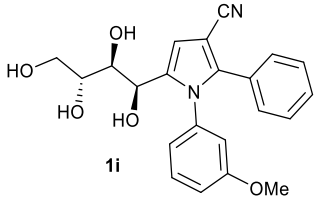
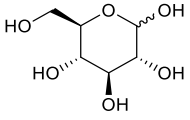
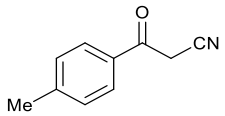
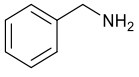
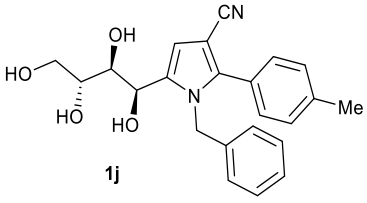
The scope of the reaction was investigated by reacting different sugars including D-(+)-glucose 1, D-(+)-ribose 4, and L-(+)-rhamnose 5 with several benzoylacetonitriles 2, 6-9 and primary amines 3, 10-19 (Table 3-2) under the optimized sequence 1 conditions (Table 3-1, entry 13). All the sugars 1, 4 and 5 reacted smoothly to give the *N*-substituted 2,3,5-functionalized pyrroles 1a-m, 4a-m and 5a-h in 50-73% isolated yields with complete selectivity. The type of the sugar and the type of the substituents on the benzoylacetonitriles 2, 6-9 have no major influence on the yield of the products. However, the products yield decreased as the nucleophilicity of the amines decreased in the order aliphatic amines > benzylamines > anilines (Table 3-2). The pure pyrroles 1a-m, 4a-m and 5a-h were simply obtained by evaporation of the

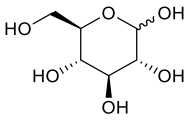
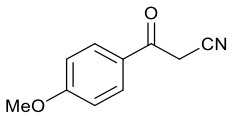
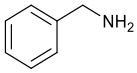
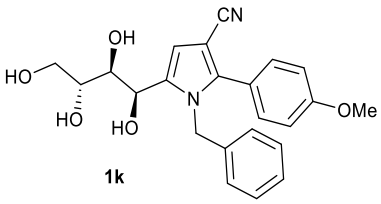
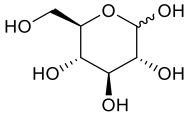
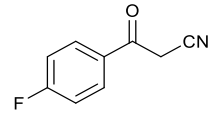
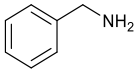
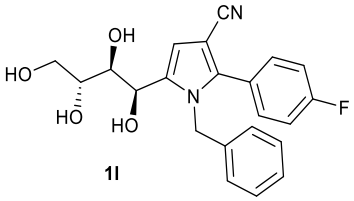
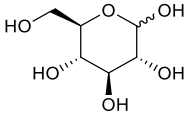
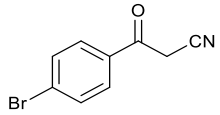
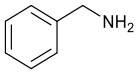
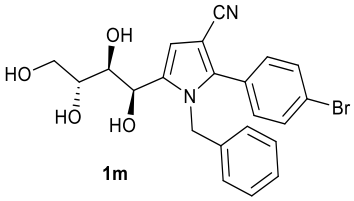
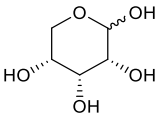
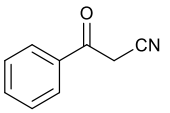
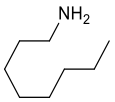
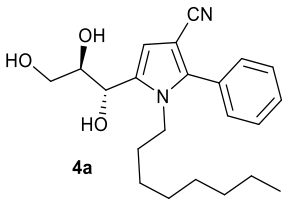
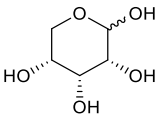
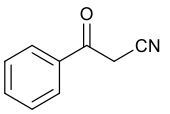
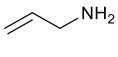
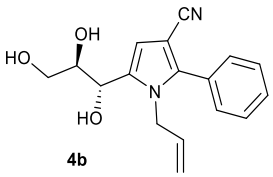
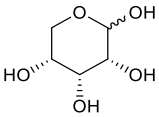
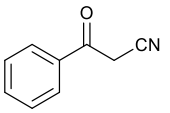
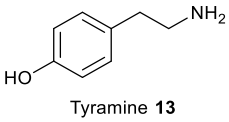
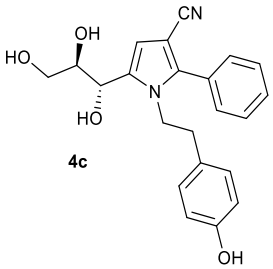
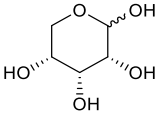
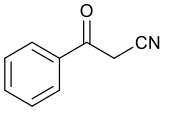
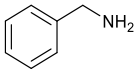
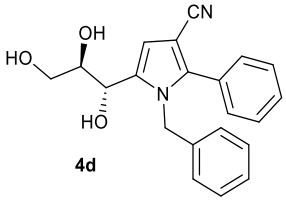
reaction mixtures followed by silica gel column chromatography purification using a mixture of MeOH and CH_2Cl_2. These products were highly polar due to the extensive hydrogen bonding network.

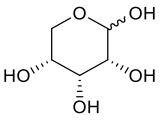
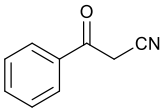
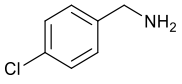
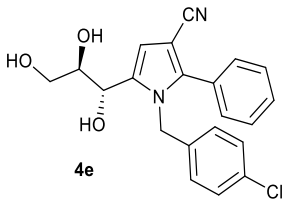
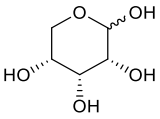
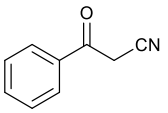
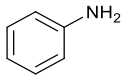
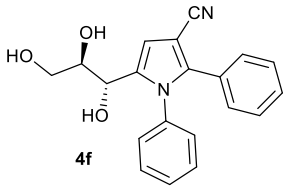
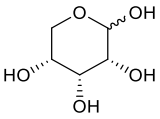
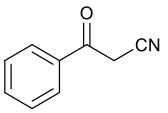
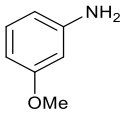
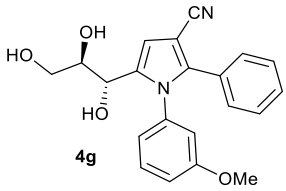
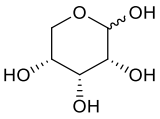
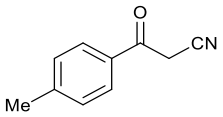
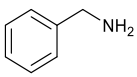
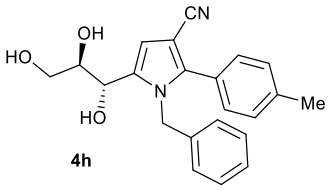
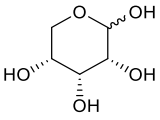
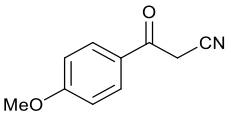
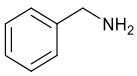
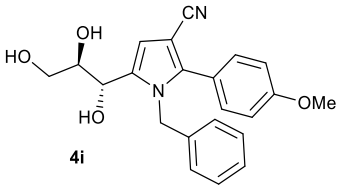
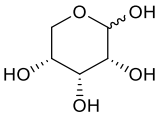
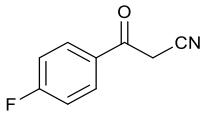
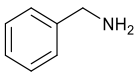
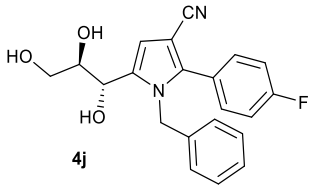
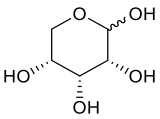
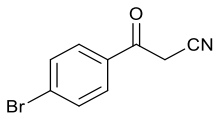
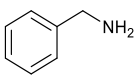
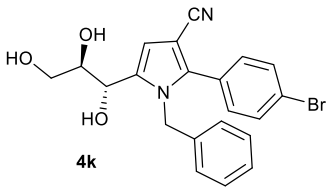
Table 3-2: Substrate scope of the TBAHS-catalyzed three-component cascade reaction between sugars 1, 4 and 5, benzoylacetonitriles 2 and 6-9, and primary amines 3 and 10-19 for the synthesis of densely functionalized pyrroles 1a-l, 4a-m and 5a-h. [a]

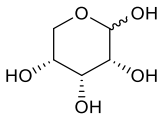
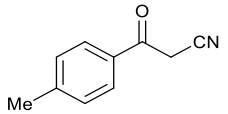
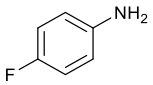
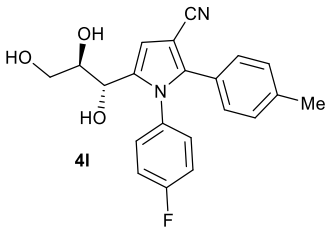
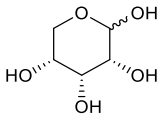
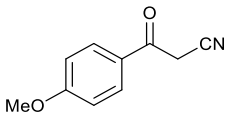
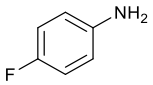
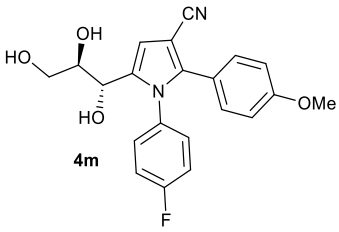
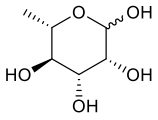
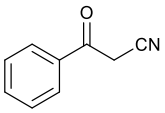
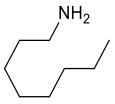
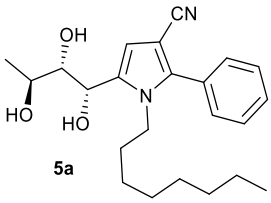
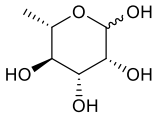
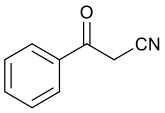
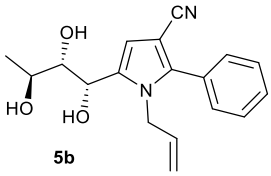
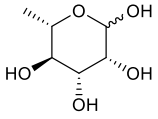
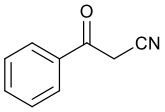
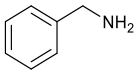
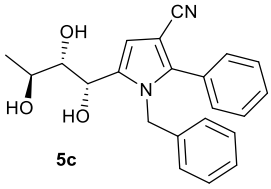
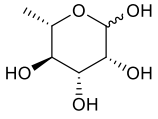
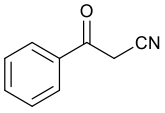
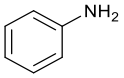
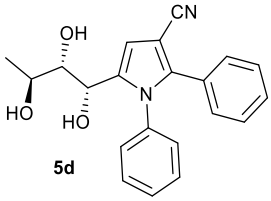
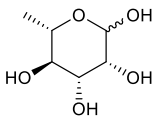
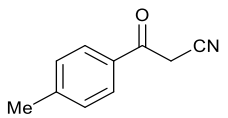
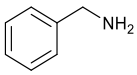
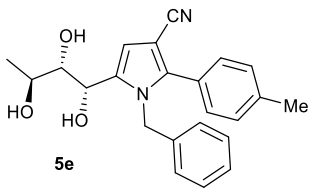


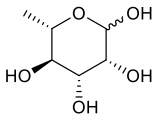
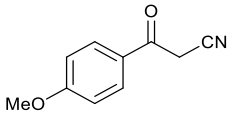
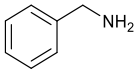
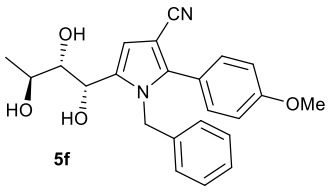
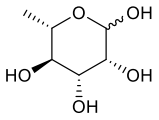
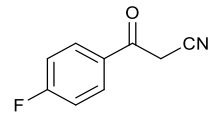
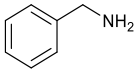
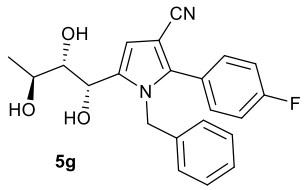
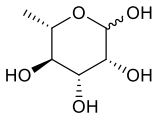
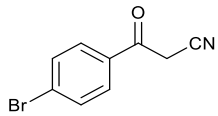
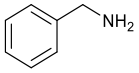
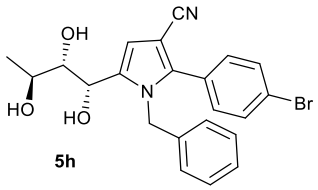
Entry	Sugar	Benzoylacetonitriles	Primary amines	Product	Yield (%)[b]
1	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Octylamine **10**	 **1b**	65
2	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Ethanolamine **11**	 **1c**	68
3	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Allylamine **12**	 **1d**	68

4	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Tyramine **13**	 **1e**	65
5	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Benzylamine **3**	 **1a**	58
6	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Cyclohexylamine **14**	 **1f**	61
7	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Aniline **15**	 **1g**	52
8	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 p-Toluidine **16**	 **1h**	52
9	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 m-Anisidine **17**	 **1i**	50
10	 D-(+)-Glucose **1**	 4-Methyl benzoylacetonitrile **6**	 Benzylamine **3**	 **1j**	60

11	 D-(+)-Glucose **1**	 4-Methoxy benzoylacetonitrile **7**	 Benzylamine **3**	 **1k**	62
12	 D-(+)-Glucose **1**	 4-Fluoro benzoylacetonitrile **8**	 Benzylamine **3**	 **1l**	57
13	 D-(+)-Glucose **1**	 4-Bromo benzoylacetonitrile **9**	 Benzylamine **3**	 **1m**	53
14	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Octylamine **10**	 **4a**	72
15	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Allylamine **12**	 **4b**	71
16	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Tyramine **13**	 **4c**	70
17	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Benzylamine **3**	 **4d**	70

18	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 4-Chloro benzylamine **18**	 **4e**	61
19	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Aniline **15**	 **4f**	63
20	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 m-Anisidine **17**	 **4g**	62
21	 D-(+)-Ribose **4**	 4-Methyl benzoylacetonitrile **6**	 Benzylamine **3**	 **4h**	67
22	 D-(+)-Ribose **4**	 4-Methoxy benzoylacetonitrile **7**	 Benzylamine **3**	 **4i**	73
23	 D-(+)-Ribose **4**	 4-Fluoro benzoylacetonitrile **8**	 Benzylamine **3**	 **4j**	66
24	 D-(+)-Ribose **4**	 4-Bromo benzoylacetonitrile **9**	 Benzylamine **3**	 **4k**	62

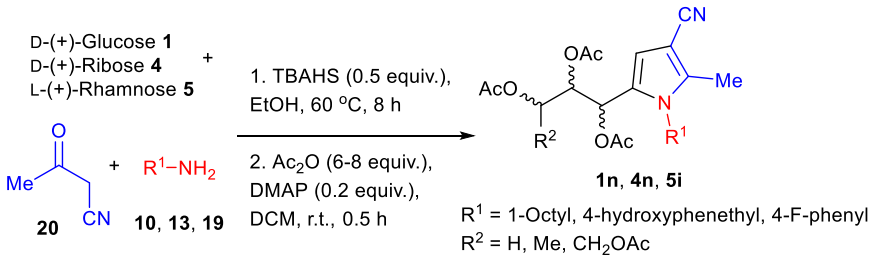
25	 D-(+)-Ribose **4**	 4-Methyl benzoylacetonitrile **5**	 4-Fluoro Aniline **19**	 **4l**	58
26	 D-(+)-Ribose **4**	 4-Methoxy benzoylacetonitrile **6**	 4-Fluoro Aniline **19**	 **4m**	62
27	 L-(+)-Rhamnose **5**	 Benzoylacetonitrile **2**	 Octylamine **10**	 **5a**	70
28	 L-(+)-Rhamnose **5**	 Benzoylacetonitrile **2**	 Allylamine **12**	 **5b**	70
29	 L-(+)-Rhamnose **5**	 Benzoylacetonitrile **2**	 Benzylamine **3**	 **5c**	67
30	 L-(+)-Rhamnose **5**	 Benzoylacetonitrile **2**	 Aniline **14**	 **5d**	60
31	 L-(+)-Rhamnose **5**	 4-Methyl benzoylacetonitrile **6**	 Benzylamine **3**	 **5e**	63

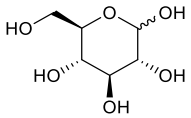
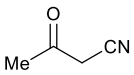
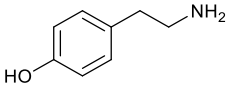
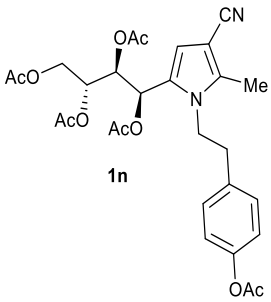
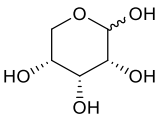
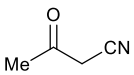
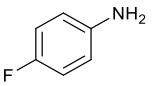
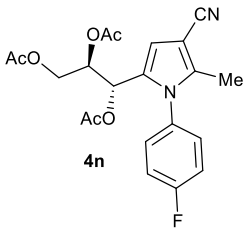
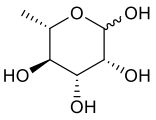
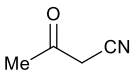
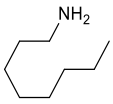
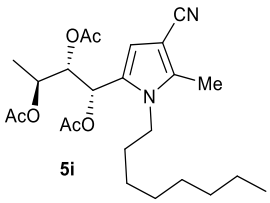
32	 L-(+)-Rhamnose **5**	 4-Methoxy benzoylacetonitrile **7**	 Benzylamine **3**	 **5f**	64
33	 L-(+)-Rhamnose **5**	 4-Fluoro benzoylacetonitrile **8**	 Benzylamine **3**	 **5g**	61
34	 L-(+)-Rhamnose **5**	 4-Bromo benzoylacetonitrile **9**	 Benzylamine **3**	 **5h**	59

[a] A mixture of sugar **1**, **4** or **5** (1.0 mmol), benzoylacetonitrile **2** or **6**-**9** (1.0 mmol), primary amine **3** or **10**-**19** (1.0 mmol) and TBAHS (0.5 mmol) was stirred in EtOH (3 mL) at 60 ºC for 8 h following sequence 1. [b] Isolated yields.

Further, the scope of the reaction was extended to 3-oxobutanenitrile **20** using representative sugars and primary amines and found to proceed smoothly (Table 3-3). For example, the reaction between 3-oxobutanenitrile **20**, sugars **1**, **4** and **5**, and primary amines **10**, **13** and **17** selectivity gave the pyrroles **1n**, **4n** and **5i** in 56-60% overall yield after acylation. The un-acetylated pyrroles were even more polar than pyrroles **1a**-**l**, **4a**-**m** and **5a**-**h** due to the extensive hydrogen bonding network and the lower polarity of the methy1 substituent in comparison to the phenyl counterpart. Therefore, they were best purified and characterized after acetylation using acetic anhydride. The framework of pyrrole **4n** resembles the COX-2 selective NSAID,[63, 185] which demonstrates the power of this three-component cascade reaction for the synthesis of pyrrole-based natural products or pharmacophores in a much shorter route.

Table 3-3: Substrate scope of the TBAHS-catalyzed three-component cascade reaction between sugars 1, 4 and 5, 3-oxobutaneacetonitrile 20, and primary amines 10, 13 and 19 for the synthesis of pyrroles 1n, 4n and 5i. [a]



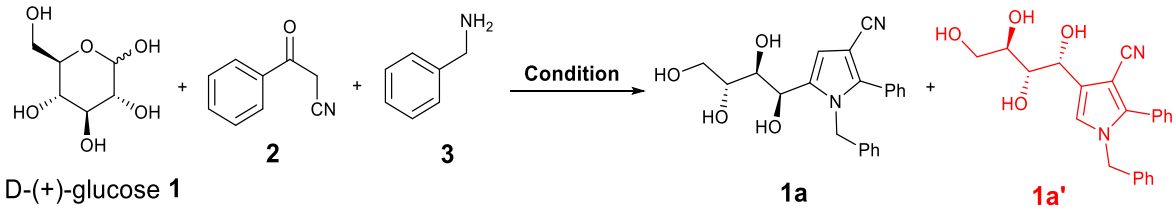
Entry	Sugare	Oxoacetonitrile	Primary Amines	Product	Yield (%)[b]
1	 D-(+)-Glucose **1**	 3-Oxobutanenitrile **20**	 Tyramine **13**	 **1n**	56
2	 D-(+)-Ribose **4**	 3-Oxobutanenitrile **20**	 4-Fluoro Aniline **19**	 **4n**	58
3	 L-(+)-Rhamnose **5**	 3-Oxobutanenitrile **20**	 Octylamine **10**	 **5i**	60

[a] A mixture of sugars **1** or **4** or **5** (1.0 mmol), 3-oxobutanenitrile **20** (1.0 mmol), primary amine **10** or **13** or **19** (1.0 mmol) and TBAHS (0.5 mmol) was stirred in EtOH (3 mL) at 60 °C for 8 h following sequence 1. [b] Isolated yield.

3.2.3 Reaction optimization for the three-component cascade synthesis of 1-benzyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile 1a′: a N-benzyl 2,3,4-substituted pyrrole

Based on the optimization results in Table 1, pyrrole **1a′** is preferentially formed under sequence 2 conditions. Therefore, following sequence 2, a mixture of D-(+)-glucose **1**, benzylamine **3** and Et_3N (1.0 mmol) as a catalyst was heated at 60 °C in EtOH or DMF for 2 h followed by addition of benzoylacetonitrile **2** and further stirring the mixture for 4 h (Table 3-4, entries 1 and 2). However, the reaction gave pyrrole **1a′** with complete selectivity *albeit* in a maximum of 20% yield. Therefore, we screened other catalysts including 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), K_2CO_3, NaOAc, TBAB, and AcOH (Table 3-4, entry 3-7). AcOH gave the best yield of 57% and best selectivity with pyrroles **1a**:**1a′** ratio as 6:94 (Table 3-4, entry 7). The results under sequence 1 or "together" conditions were not better (Table 3-1, entry 7 *vs* 8 *vs* 9). Finally, the reaction was made catalytic by using 0.5 equiv. AcOH under sequence 1 conditions where it gave pyrrole **1a′** in 59% yield and 94% selectivity (Table 3-4, entry 10).

Table 3-4: Optimization of the reaction conditions for the there-component synthesis of 1-benzyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile 1a′.



Entry	Catalyst (equiv.)	Sequence of addition	Solvent	Temp. (°C)	Time (h)	Yield (%) [a]	**1a:1a′** ratio (%) [b]
1	Et_3N (1.0)	Sequence 2 [c]	EtOH	60 °C	6	Trace	-
2	Et_3N (1.0)	Sequence 2	DMF	60 °C	6	20	ND[f]:100
3	DBU (1.0)	Sequence 2	EtOH	60 °C	6	23	65:35

4	K_2CO_3 (1.0)	Sequence 2	EtOH	60 °C	6	Trace	-
5	NaOAc (1.0)	Sequence 2	EtOH	60 °C	6	52	50:50
6	TBAB (1.0)	Sequence 2	EtOH	60 °C	6	Trace	-
7	AcOH (1.0)	Sequence 2	EtOH	60 °C	6	57	6:94
8	AcOH (1.0)	Together [d]	EtOH	60 °C	6	47	58:42
9	AcOH (1.0)	Sequence 1 [e]	EtOH	60 °C	6	52	72:28
10	AcOH (0.5)	Sequence 2	EtOH	60 °C [g]	6	59	4:96

[a] Isolated yields. [b] Measured using NMR. [c] Sequence 2: first stir D-(+)-glucose **1** (1.0 mmol), benzylamine **3** (1.0 mmol) and the catalyst in 3 mL solvent at 60 °C for 2 h. Next, add benzoylacetonitrile **2** (1.0 mmol) to the mixture and continue the reaction for another 4 h. [d] Together: add D-(+)-glucose **1** (1.0 mmol), benzoylacetonitrile **2** (1.0 mmol), benzylamine **3** (1.0 mmol) and AcOH (1.0 mmol) consecutively in 3 mL EtOH and stir the mixture for 6 h at 60 °C. [e] Sequence 1: first stir benzoylacetonitrile **2** (1.0 mmol), benzylamine **3** (1.0 mmol) and AcOH in 3 mL EtOH at 60 °C for 2 h. Next, add D-(+)-glucose **1** (1.0 mmol) to the mixture and continue the reaction for another 4 h. [f] ND: not detected.

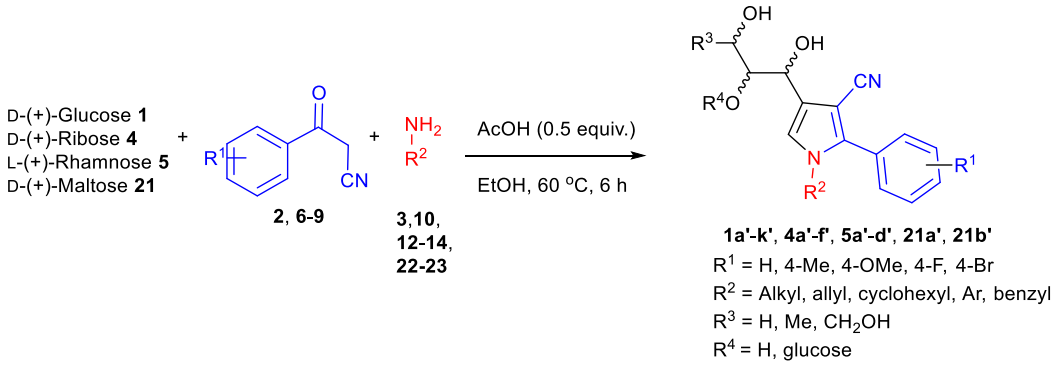
3.2.4 Substrate Scope for the three-component cascade synthesis of *N*-substituted 2,3,4-functionalized pyrroles

With the optimized conditions in hand according to sequence 1 (Table 3-4, entry 10), we next investigated the substrate scope by reacting several sugars including D-(+)-glucose **1**, D-(+)-ribose **4**, L-(+)-rhamnose **5** and D-(+)-maltose **21**, benzoylacetonitriles **2** and **6**-**9**, and primary amines **3**, **10**, **12**-**14** and **22**-**23** (Table 3-5). All the reactions proceeded smoothly to give the desired *N*-substituted 2,3,4-functionalized pyrroles **1a′**-**k′**, **4a′**-**f′**, **5a′**-**d′** and **21a′** and **21b′** in 45-88% isolated yields and excellent selectivities (Table 3-5). Disaccharide D-(+)-maltose **21** gave the lowest yields where pyrrole **21a′** was obtained in 53% and pyrrole **21b′** was obtained in 45% (Table 3-5 entries 1-21 vs 22 and 23). In agreement with the results obtained during the synthesis of *N*-substituted 2,3,5-functionalized pyrroles (Table 3-2), sugars **1**, **4** and **5**, and benzoylacetonitriles **2** and **6**-**9** have no major influence on the yield of the pyrroles **1a′**-**k′**, **4a′**-**f′** and **5a′**-**d′**, and the yields using aliphatic amines are higher than benzylamines (Table 3-5). However, in contrast, anilines which gave low yield of *N*-substituted 2,3,5-functionalized

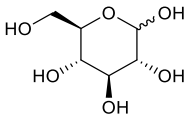
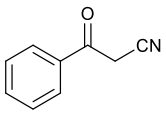
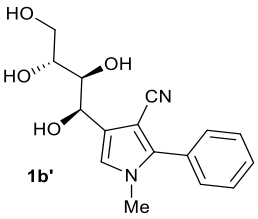
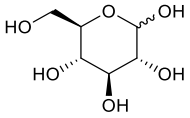
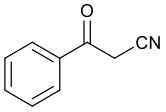
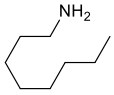
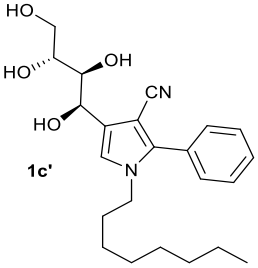
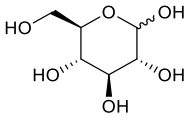
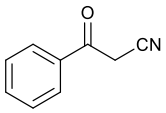
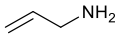
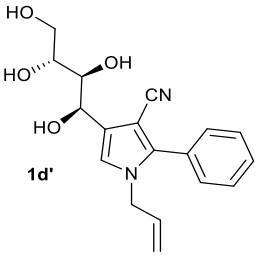
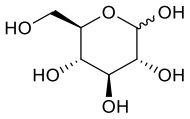
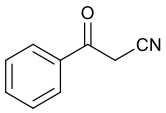
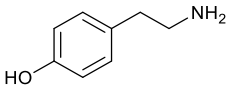
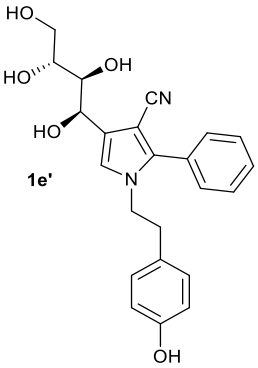
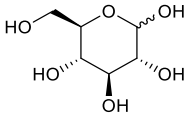
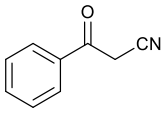
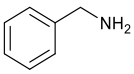
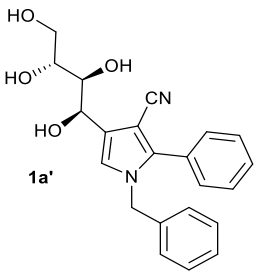
pyrroles did not react under sequence 1 conditions. The lack of reactivity is attributed to aniline lower nucleophilicity in comparison to aliphatic and benzylamines. Additionally, disaccharide **21** gave lower yields in comparison to monosaccharides (Table 3-5 entries 23 and 23 vs 2, 7, 13, 17, 18 and 21).

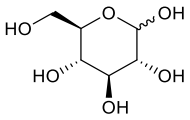
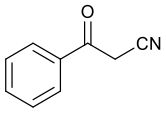
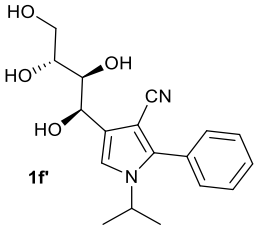
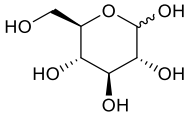
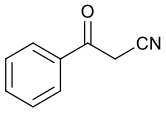
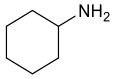
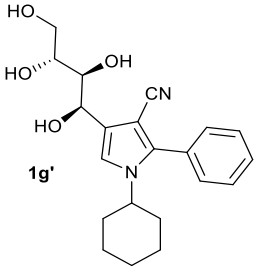
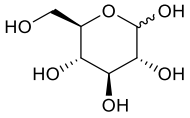
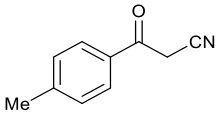
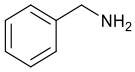
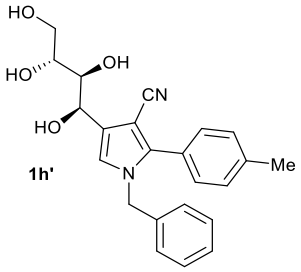
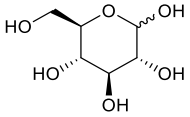
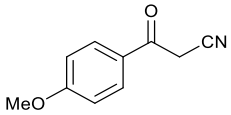
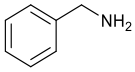
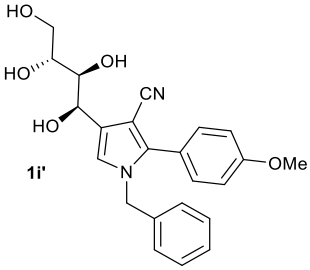
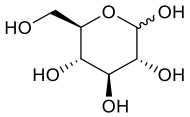
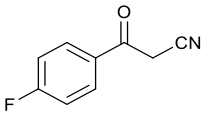
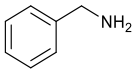
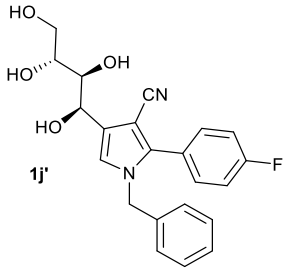
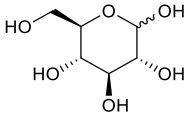
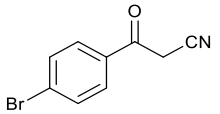
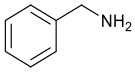
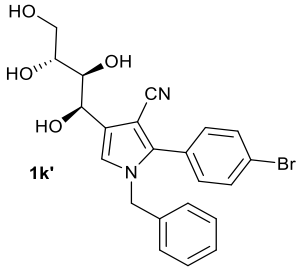
Excellent product selectivities ranging from 89-100% were obtained in all cases. The selectivity did not depend on the type of sugar, its stereochemistry, benzoylacetonitriles or the amine. The products were purified similarly using silica gel column chromatography using MeOH/CH_2Cl_2 eluent: 8:92 for D-(+)-glucose **1** products; 5:95 for D-(+)-ribose **4** and L-(+)-rhamnose **5** products; 20:80 for D-(+)-maltose **21** products.

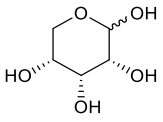
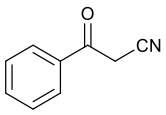
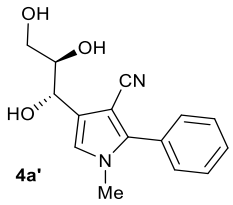
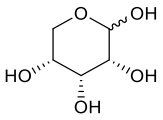
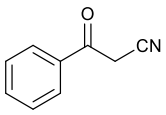
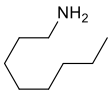
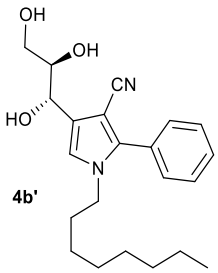
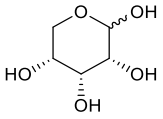
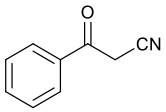
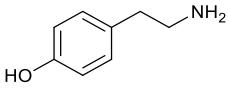
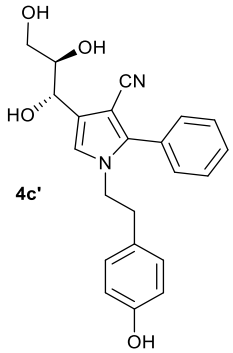
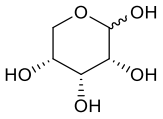
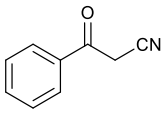
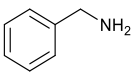
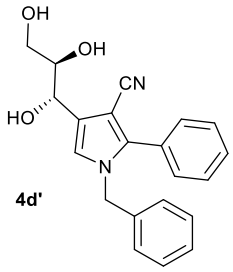
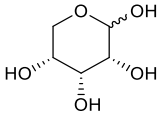
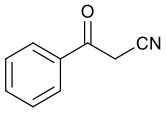
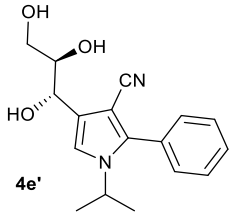
Table 3-5: Substrate scope of the AcOH-catalyzed three-component cascade reaction between sugars 1, 4, 5 and 21, benzoylacetonitriles 2 and 6-9, and primary amines 3, 10, 12-14 and 22-23 for the synthesis of N-substituted 2,3,4-functionalized pyrroles 1a′-k′, 4a′-f′, 5a′-d′, 21a′ and 21b′. [a]

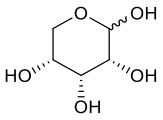
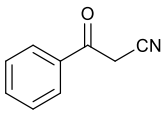
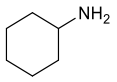
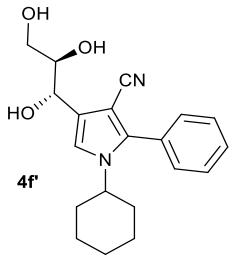
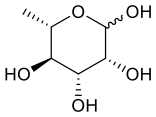
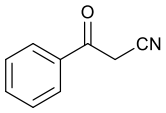
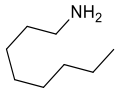
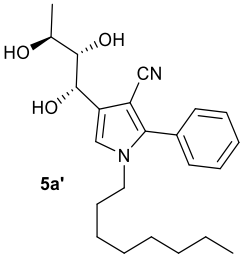
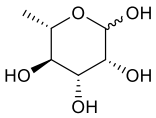
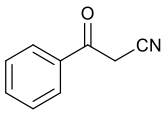
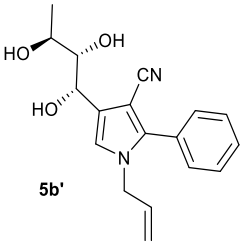
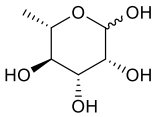
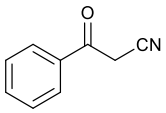
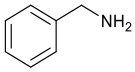
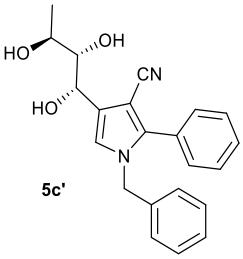
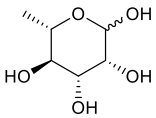
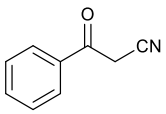
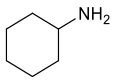
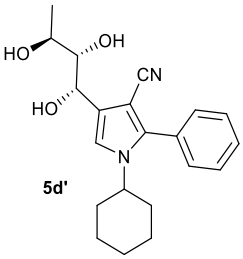


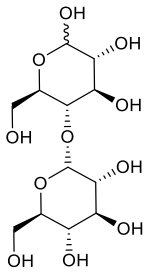
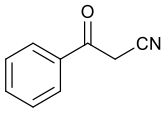
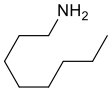
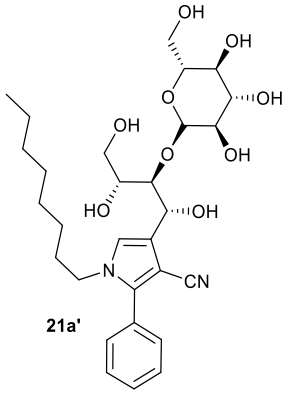
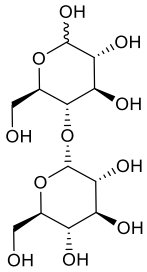
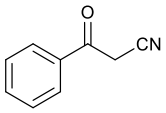
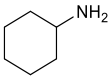
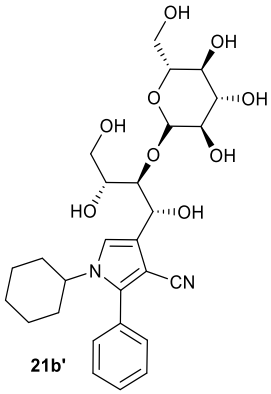
Entry[a]	Sugar	Benzoyl-acetonitriles	Primary Amines	Product	Yield (%)[b] (selectivity) (%)[c]

1	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Methylamine **22**	 **1b'**	66 (100)
2	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Octylamine **10**	 **1c'**	66 (96)
3	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Allylamine **12**	 **1d'**	64 (93)
4	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Tyramine **13**	 **1e'**	69 (92)
5	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Benzylamine **3**	 **1a'**	59 (96)

6	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Isopropylamine **23**	 **1f'**	82 (97)
7	 D-(+)-Glucose **1**	 Benzoylacetonitrile **2**	 Cyclohexylamine **14**	 **1g'**	59 (92)
8	 D-(+)-Glucose **1**	 4-Methyl benzoylacetonitrile **6**	 Benzylamine **3**	 **1h'**	57 (93)
9	 D-(+)-Glucose **1**	 4-Methoxy benzoylacetonitrile **7**	 Benzylamine **3**	 **1i'**	56 (97)
10	 D-(+)-Glucose **1**	 4-Fluoro benzoylacetonitrile **8**	 Benzylamine **3**	 **1j'**	54 (95)
11	 D-(+)-Glucose **1**	 4-Bromo benzoylacetonitrile **9**	 Benzylamine **3**	 **1k'**	60 (89)

12	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Methylamine **22**	 **4a'**	68 (100)
13	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Octylamine **10**	 **4b'**	78 (95)
14	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Tyramine **13**	 **4c'**	73 (95)
15	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Benzylamine **3**	 **4d'**	67 (96)
16	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Isopropylamine **23**	 **4e'**	88 (95)

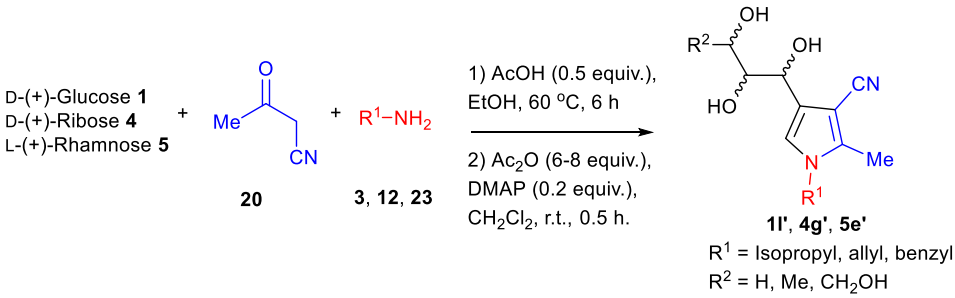
17	 D-(+)-Ribose **4**	 Benzoylacetonitrile **2**	 Cyclohexylamine **14**	 **4f'**	78 (98)
18	 L-(+)-Rhamnose **5**	 Benzoylacetonitrile **2**	 Octylamine **10**	 **5a'**	70 (94)
19	 L-(+)-Rhamnose **5**	 Benzoylacetonitrile **2**	 Allylamine **12**	 **5b'**	72 (95)
20	 L-(+)-Rhamnose **5**	 Benzoylacetonitrile **2**	 Benzylamine **3**	 **5c'**	65 (92)
21	 L-(+)-Rhamnose **5**	 Benzoylacetonitrile **2**	 Cyclohexylamine **14**	 **5d'**	72 (100)

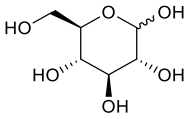
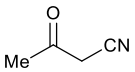
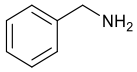
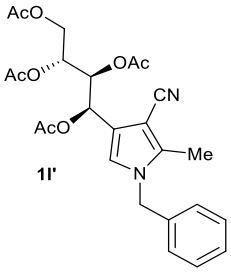
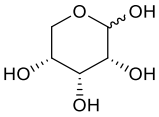
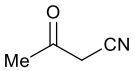
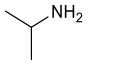
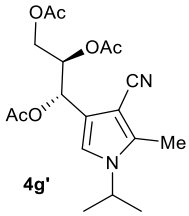
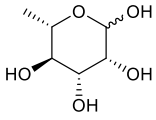
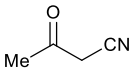
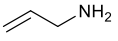
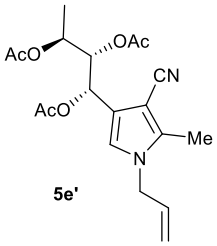
22	 D-(+)-Maltose **21**	 Benzoylacetonitrile **2**	 Octylamine **10**	 **21a'**	53 (100)
23	 D-(+)-Maltose **21**	 Benzoylacetonitrile **2**	 Cyclohexylamine **14**	 **21b'**	45 (100)

[a] The reactions were conducted following sequence 1 using sugars **1**, **4**, **5** and **21** (1.0 mmol), benzoylacetonitrile **2** and **6-9** (1.0 mmol), primary amine **3**, **10**, **12-14** and **22-23** (1.0 mmol) and AcOH (0.5 mmol) in EtOH (3 mL). In case of D-(+)-ribose **4**, the reactions were conducted at 50 ^{o}C. [b] Yield of isolated product. [c] The ratio calculated using NMR.

Additionally, the reaction also proceeded well using 3-oxobutanenitrile **20** (Table 3-6). To exemplify this, the reaction between sugars **1**, **4** and **5**, 3-oxobutanenitrile **20**, and primary amines **3**, **12** and **23** gave the desired *N*-substituted 2,3,4-functionalized pyrroles **1l′**, **4g′** and **5e′** in 42-72% overall yield after acetylation in excellent >92% selectivities. Again here, the un-acetylated pyrroles were more polar than pyrroles **1l′**, **4g′** and **5e′** and were best purified using chromatography after acetylation using acetic anhydride.

Table 3-6: Substrate scope of the AcOH-catalyzed three-component cascade reaction between sugars 1, 4 and 5, 3-oxobutaneacetonitrile 20, and primary amines 3, 12 and 23 for the synthesis of *N*-substituted 2,3,4-functionalized pyrroles 1l′, 4g′ and 5e′. [a]



Entry	Sugar	3-oxobutaneacetonitrile	Primary Amines	Product	Yield (%)[b] (Selectivity) (%)[c]
1	 D-(+)-Glucose **1**	 3-Oxobutanenitrile **20**	 Benzylamine **3**	 **1l'**	42 (100)
2	 D-(+)-Ribose **4**	 3-Oxobutanenitrile **20**	 Isopropylamine **23**	 **4g'**	72 (100)
3	 L-(+)-Rhamnose **5**	 3-Oxobutanenitrile **20**	 Allylamine **12**	 **5e'**	57 (92)

[a] The reactions were conducted following sequence 1 using sugars **1**, **4** and **5** (1.0 mmol), 3-oxobutanenitrile **20** (1.0 mmol), primary amines **3**, **11** and **21** (1.0 mmol) and AcOH (0.5 mmol) in EtOH (3 mL) at 60 °C for 6 h. [b] Yield of isolated product. [c] The ratio calculated using NMR.

3.3 Single-crystal X-ray crystallographic analysis

Compounds **4j** and **1i′** as representatives of *N*-substituted 2,3,5-functionalized pyrroles and *N*-substituted 2,3,4-functionalized pyrroles, respectively, were crystallized from MeOH/Hexane. Their single-crystal X-ray crystallographic analysis confirmed the assigned structures from 2D NMR as shown in Figure 3-3.

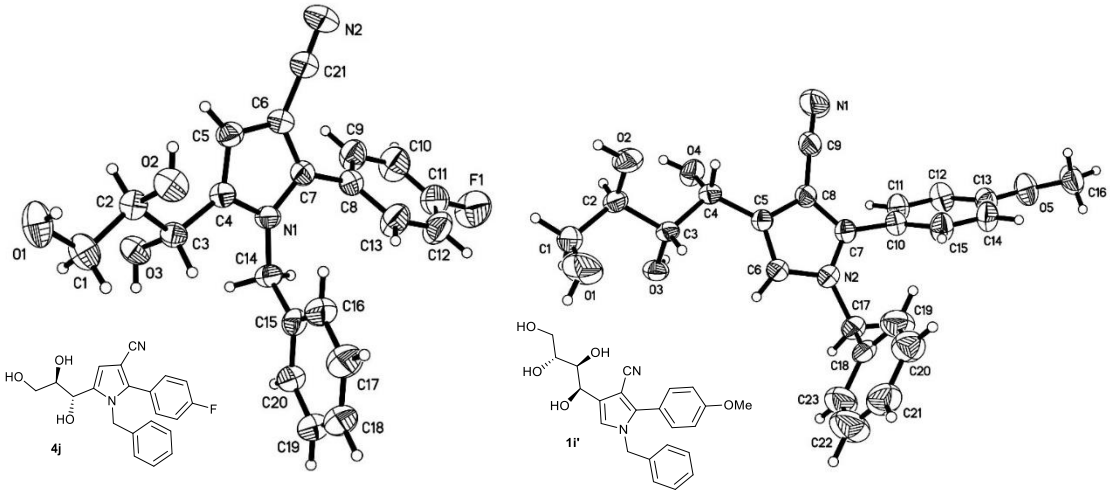


Figure 3-3. Structures of pyrrole 4j (CCDC 2053919) and pyrrole 1i′ (CCDC 2053920) as determined by single-crystal X-ray diffractions.

3.4 Mechanistic considerations

Since the three-component reaction between D-(+)-glucose 1, benzoylacetonitrile 2, and benzylamine 3 produced two different products (Table 3-1), this suggested two different reaction pathways. It is hypothesized that benzylamine 3 could have reacted with the two carbonyl compounds, D-(+)-glucose 1 (masked aldehyde open structure) and benzoylacetonitrile 2, to produce intermediates which reacted differently to give pyrroles 1a and 1a′.

The proposed formation of *N*-benzyl 2,3,5-functionalized pyrrole 1a is outlined in Figure 4. Reaction between benzoylacetonitrile 2 and benzylamine 3 following sequence 1 gives imine **I** which tautomerizes to enamine **II**. Both **I** and **II** were observed in the mass spectra (Both have

same molecular weight of 234; observed: $[M+H]^+$ = 235 and $[M+2H]^+$ = 236) upon analysis of the crude reaction mixture. Knoevenagel condensation between enamine **II** and D-(+)-glucose 1 gives intermediate **III** which upon deprotonation gives intermediate **IV**. Dehydration of **IV** gives **V** which undergoes ketolization to ketone **VI**. Finally, cyclization of **VI** gives **VII** which upon aromatization through dehydration give pyrrole **1a**. (Figure 3-4)

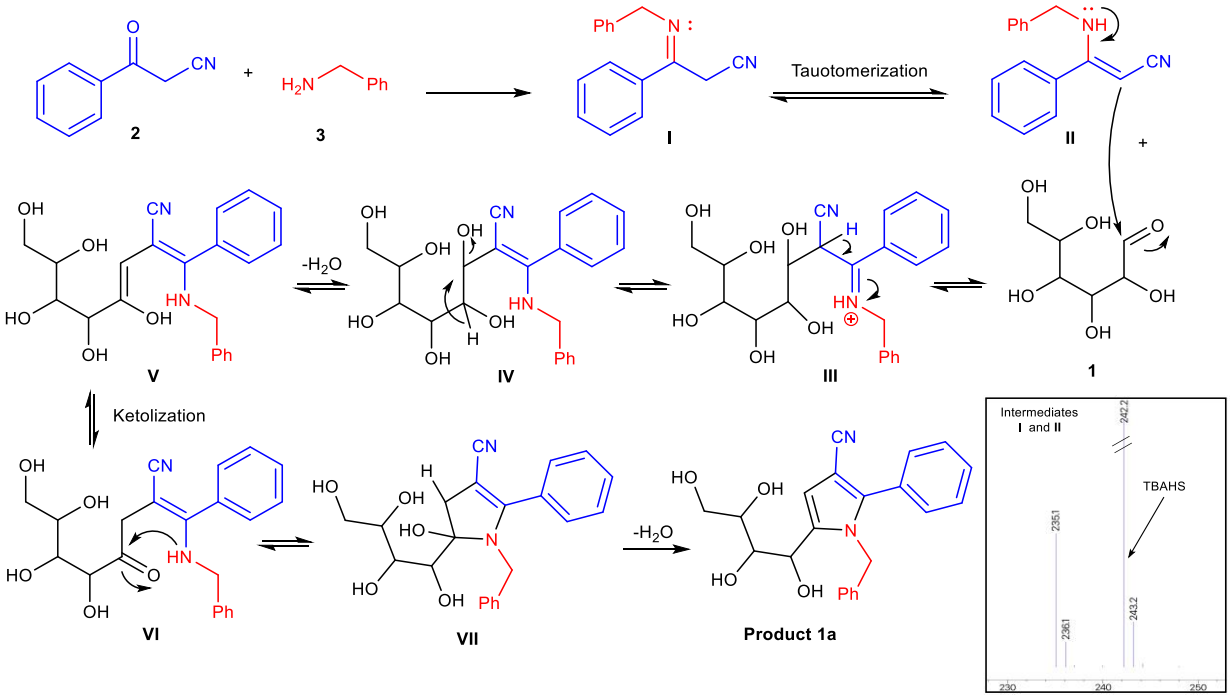


Figure 3-4. Proposed mechanism for the formation of *N*-substituted 2,3,5-functionalized pyrroles.

In the case of *N*-substituted 2,3,4-benzyl pyrrole **1a′**, reaction between D-(+)-glucose **1** and benzylamine **3** according to sequence 2 gives the Schiff base **I** (Figure 3-5). Acid-catalyzed Amadori rearrangement of **I** gives keto amine **II**. Consequently, reaction of **II** with benzoylacetonitrile **3** gives intermediate **III** which upon dehydration gives intermediate **V**. Intramolecular cyclization of **V** followed by deprotonation and dehydration affords product **1a′**.

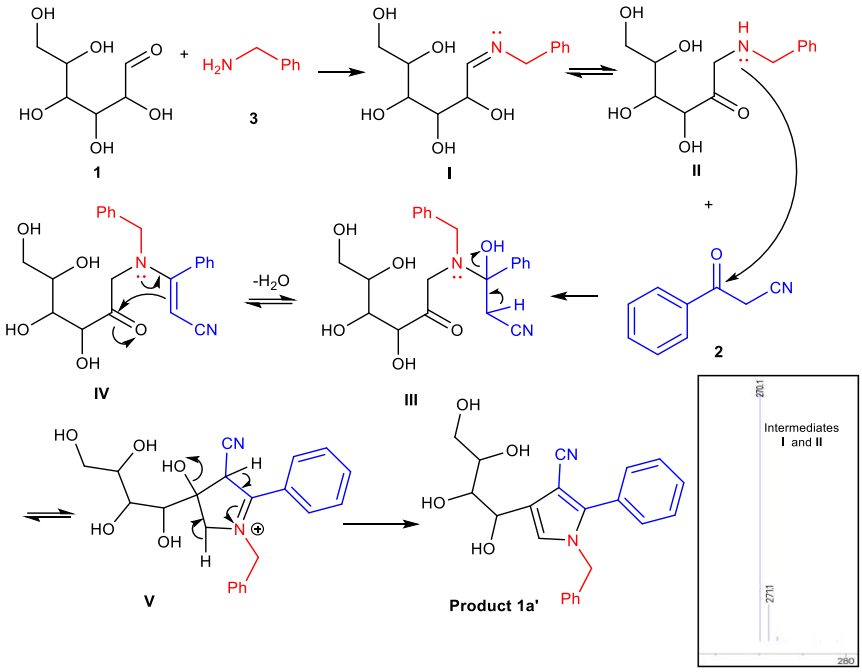


Figure 3-5. Proposed mechanism for the formation of *N*-substituted 2,3,4-functionalized pyrroles.

3.5 Conclusion

A three-component cascade reaction was developed to synthesize *N*-substituted 2,3,-functionalized pyrroles and *N*-substituted 2,3,5-functionalized pyrroles from simple unactivated sugars. The reaction showed a wide scope and generality for sugars, oxoacetonitriles and primary amines giving up to 88% yield. This one-step reaction add value to sugars through formation of densely functionalized pyrroles as attractive intermediated for further manipulation to natural products and pharmaceutical intermediates. We are currently applying the synthesis of preparation of pyrrole natural products.

3.6 Experimental Section

3.6.1 Materials and methods

All chemicals and AR grade solvents were obtained from Sigma-Aldrich, Merck or Alfa Aesar and were used as received without further purification. IR spectra were recorded using Bruker MPA FT-IR machine. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance DPX 300. ^{13}C NMR spectra were recorded at 75.47 MHz using the same machine. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. HRMS were measured using a hybrid Quadrupole Time-of-Flight (Q-TOF) on Qstar XL MS/MS system. LC-MS spectra were recorded using Agilent 6530 LC-MS. Analytical TLC was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness). The plates were visualized using UV radiation (254 nm) or stained in ceric ammonium sulfate solution with heating to detect the reaction spots. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh).

3.6.2 General Procedure 1: *N*-substituted 2,3,5-functionalized pyrroles 1a-m, 4a-m, 5a-h, 1n, 4n and 5i

To a stirred solution of benzoylacetonitrile (1.0 equiv.) and primary amine (1.0 equiv.) in EtOH (3 ml) at room temperature was added TBAHS (0.5 equiv.). The resulting mixture was heated at 60 ^{o}C for 3 h. The sugar (1.0 equiv.) was to the mixture and the reaction further stirred at the same temperature until complete consumption of starting materials as indicated by TLC (6 h). The reaction mixture was then evaporated to dryness under vacuum to give the crude product as a foam. The foam was purified using silica gel column chromatography using $MeOH/CH_2Cl_2$ as eluant (3:97 for pentoses; 5:95 for hexoses; and 20:80 for disaccharides) to give the pure products. All reactions were conducted using 1.0 mmol of the sugars. This general procedure was used to prepare *N*-substituted 2,3,5-functionalized pyrroles **1a**-**m**, **4a**-**m**, **5a**-**h**, **1n**, **4n** and **5i**.

3.6.3 General Procedure 2: Synthesis of *N*-benzyl 2,3,4-substituted pyrroles 1a′-k′, 4a′-f′, 5a′-d′, 21a′, 21b′, 1l′, 4g′ and 5e′

AcOH (0.5 equiv.) was added to a stirred solution of the benzoylacetonitrile (1.0 equiv.) and primary amine (1.0 equiv.) in EtOH (3 mL) at room temperature. The resulting mixture was stirred at 60 ^{o}C for 2 h. The sugar (1.0 equiv.) was then added to the stirred mixture until complete consumption of the starting materials as indicated by TLC (4 h for pentose and hexose; 6 h for disaccharide). The reaction mixture was then evaporated to dryness under vacuum to give the crude product as a foam. The foam was purified using silica gel column chromatography using MeOH/CH_2Cl_2 as eluant (3:97 for pentoses and 5:95 for hexoses; 20:80 for disaccharides) to give the pure products. All reactions were conducted using 1.0 mmol of the sugars. This general procedure was used to prepare *N*-substituted 2,3,4-functionalized pyrroles **1a′-k′**, **4a′-f′**, **5a′-d′** and **21a′**, **21b′**, **1f′**, **4g′** and **5e′**.

All NMR spectra and other data are listed in Appendix.

Chapter 4. Acetic acid-catalyzed Selective Synthesis of *N*-substituted 2-Amino-3-cyanopyrroles *via* a Three-component Reaction Between Carbohydrates, Primary amines and Malononitrile

4.1 Introduction

Direct conversion of carbohydrates to useful chemicals is highly desirable.[18, 186-188] Several platforms have already been successfully established at the industrial scale.[189, 190] Efficient utilization of carbohydrates to generate nitrogen heterocycles having multiple functional groups is challenging and also highly attractive considering their use as intermediates in the food, cosmetic, drug and material science industries.[191]

Pyrroles are important nitrogen heterocycles with widespread applications in material science, molecular recognition and coordination, and as intermediates for conversion into complex heterocycles.[56, 61, 192, 193] They also possess several bioactivities including anti-inflammatory (e.g. pyrrolopyridine derivatives), anti-bacterial, anti-fungal, and anti-cancer (e.g. Ribociclib for treatment of breast cancer) and anti-myelosuppression activities (e.g. Trilaciclib for treatment of myelosuppression) (Figure 4-1).[61, 67, 194-197] In particular, pyrroles decorated with functional groups are important intermediates since such groups act as handles for further conversion into more useful functional compounds. Specifically, 2-amino-3-cyanopyrroles are key structures that can be converted easily using their amino and cyano functional groups into various drugs and bioactive compounds such as aminopyrazoles, 6-oxopyrrolo[2,3-b]pyridines, benzylidenimino-pyrroles and 4,6-diamino-pyrrolo[2,3-b]pyridines in just one or two steps.[87, 196, 198, 199] The vicinal arrangement of the amino and cyano groups is critical to facilitating the construction of various heterocyclic structures (Figure 4-1). Additional functional groups on pyrrole core are also advantageous, especially in place of R^1 (Figure 4-1). Therefore, it is highly desirable to synthesize pyrroles decorated with multiple functional groups.

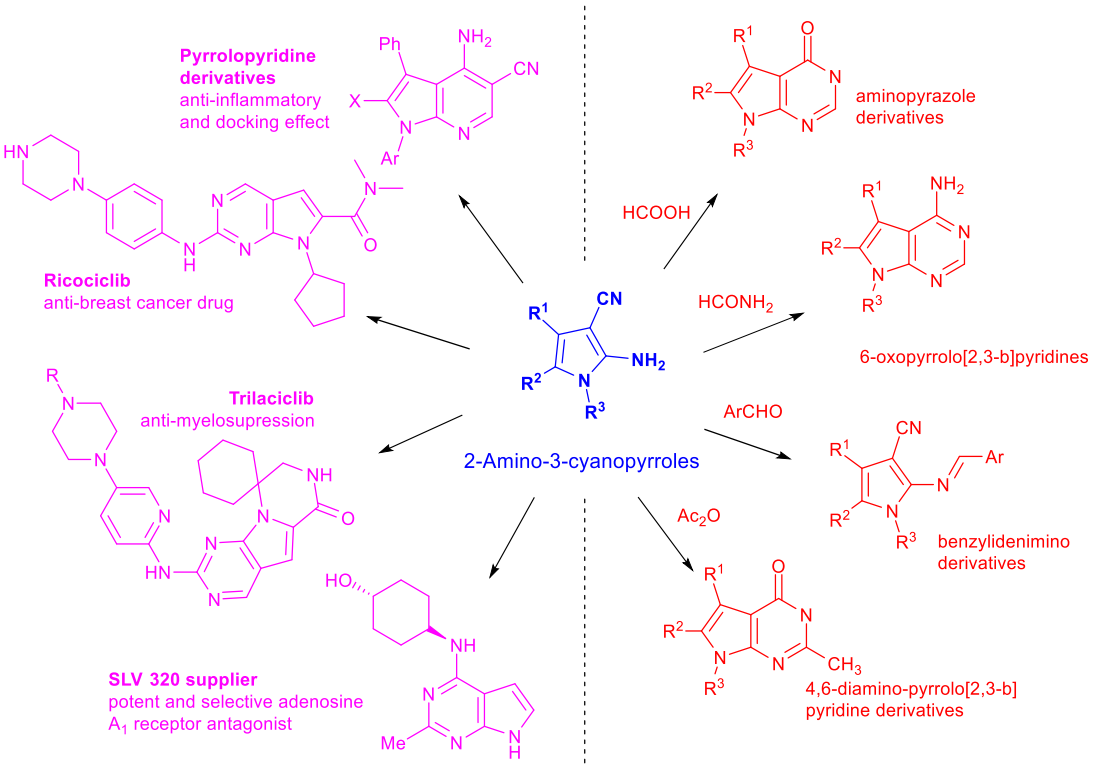


Figure 4-1. Use of 2-amino-3-cyanopyrroles as a key structure to obtain important heterocycles.

The synthesis of 2-amino-3-cyanopyrroles (Figure 4-2) has been reported earlier. Recent examples include the condensation between acrylmalononitriles and primary amines (Figure 4-2 (i)),[200] the cyclization between arylidenemalononitriles and ethyl glycinate hydrochloride using I_2 (Figure 4-2 (ii)),[201] and the reaction between isoxazoles and malononitrile in the presence of $FeCl_2$ (Figure 4-2 (iii)).[88] However, these reactions suffer from three main disadvantages: (i) they require starting materials that themselves require preparation (i.e. multistep process), (ii) none of the starting materials are considered sustainable, (iii) they employ high boiling point solvents such as DMF/toluene/dioxane and some require metal catalysts.

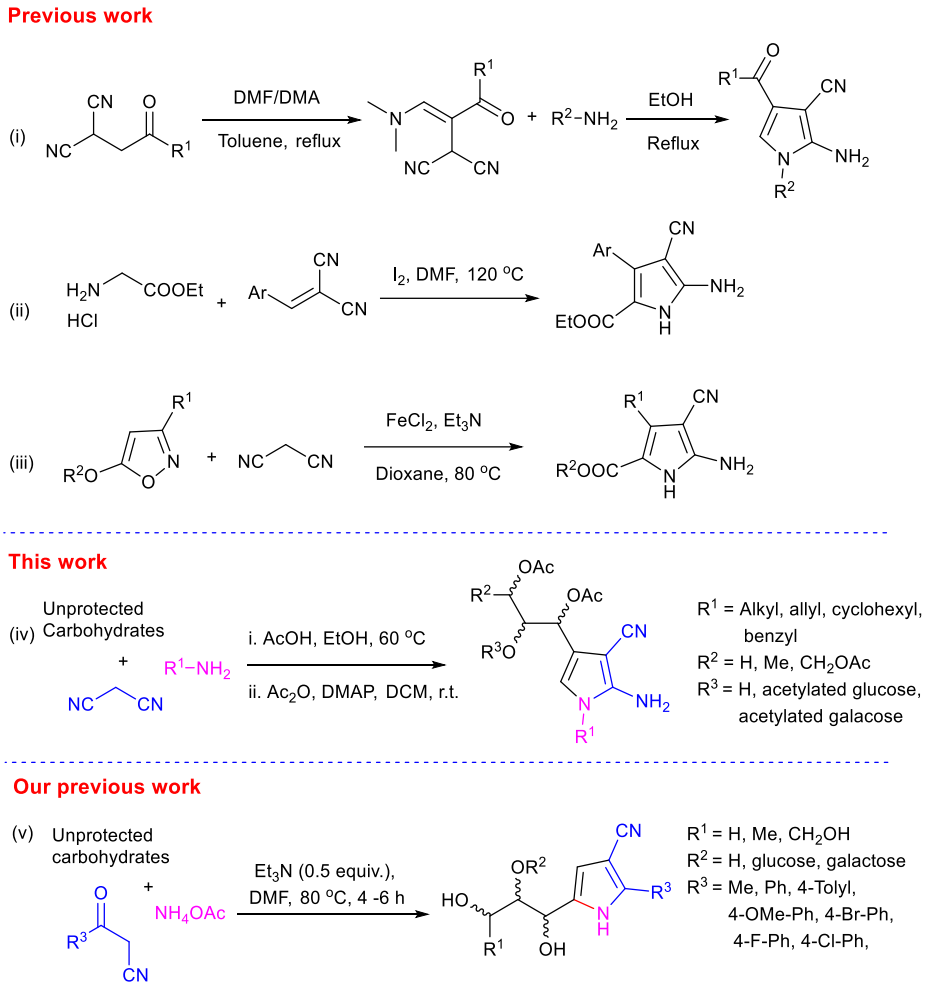


Figure 4-2. Previous and proposed syntheses of 2-amino-3-cyanopyrroles.

Direct and practical synthesis of the key 2-amino-3-cyanopyrrole framework from sustainable materials is therefore highly desired. Previously, we reported a three-component reaction between unactivated carbohydrates, oxoacetonitriles, and ammonium acetate which gave *N*-unsubstituted pyrrole-3-carbonitriles (Figure 4-2, (v)).[181] Hence, it was logical to develop the synthesis of the key 2-amino-3-cyanopyrrole framework (Figure 4-2, (iv)). Since, the majority of the pyrroles are substituted at the nitrogen (Figure 4-1), it is advantageous to develop a direct synthesis that gives *N*-substituted 2-amino-3-cyanopyrroles to eliminate the need for further derivatization of the NH. The substituent at the nitrogen (e.g. alkene substituents) can also act as a handle for further reactions.

In this work, we report a practical, three-component synthesis of *N*-substituted 2-amino-3-cyanopyrroles *via* the reaction between unfunctionalized carbohydrates, primary amines, and

malononitrile. We also demonstrate the scope of this one-pot reaction using monosaccharides and disaccharides and demonstrate its practicality on large scale. LC-MS and NMR spectroscopy provided evidence for the plausible reaction mechanism while X-ray crystallography confirmed the structure.

4.2 Results and Discussion

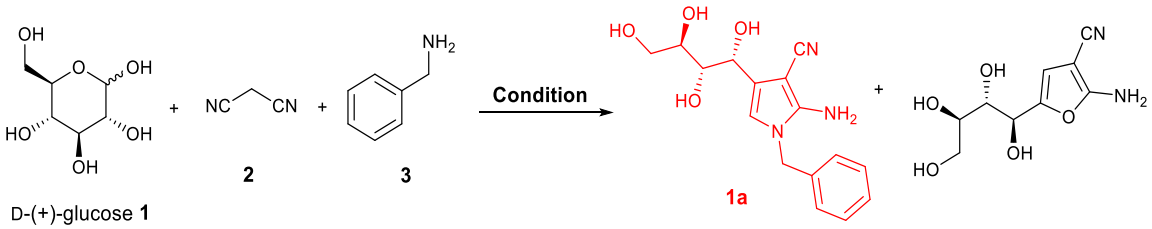
4.2.1 Reaction optimization

The investigation started by mixing "together" D-(+)-glucose **1** (1 mmol, 1.0 equiv.), malononitrile 2 (1.1 equiv.), and benzylamine **3** (1.0 equiv.) in one-pot in the presence of AcOH (1.0 equiv.) as the catalyst in EtOH at 60 ^{o}C (Table 4-1, entry 1). The reaction gave furan **1a′** as the sole product (Table 4-1, entry 1) in 86% yield.[45] This indicated the exclusion of benzylamine **3** from this three-component reaction. Therefore, the reaction was attempted in sequence to force benzylamine **3** to react. Hence, in sequence 1, a mixture of D-(+)-glucose **1** (1 mmol, 1.0 equiv.), benzylamine **3** (1.0 equiv.) and AcOH (1.0 equiv.) was stirred in EtOH at 60 ^{o}C for 2 h (Table 4-1, entry 2). Malononitrile **2** (1.1 equiv.) was then added to the mixture and the reaction was stirred for another hour. In sequence 2, the reaction was attempted in the same fashion but the sequence of addition of D-(+)-glucose **1** and malononitrile **2** was reversed (Table 4-1, entry 3). Sequence 1 exclusively gave the desired 2-amino-1-benzyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile **1a** in 68% yield while sequence 2 exclusively gave furan **1a′** in 66% yield (Table 4-1 entry 2 vs entry 3).

Using sequence 1, we then screened several catalysts including triethylamine (Et_3N), potassium carbonate (K_2CO_3), zinc chloride ($ZnCl_2$), *p*-toluenesulfonic acid (PTSA), camphorsulfonic acid (CSA) and formic acid (HCOOH) (Table 4-1, entries 4-9). The reaction using AcOH, $ZnCl_2$ and PTSA provided pyrrole **1a** exclusively (Table 4-1, entries 2, 4, and 5). Interestingly, HCOOH gave an almost equal mixture of pyrroles **1a** and **1a′** while CSA was

inactive perhaps due to its weak acidity (Table 4-1, entries 6 and 7 respectively). However, bases such as Et_3N and K_2CO_3 gave furan **1a′** exclusively in higher yields (Table 4-1, entries 8 and 9). The formation of furan **1a′** is not surprising and is reasoned to have occurred according to our previously published mechanism.[11] Although the yield of pyrrole **1a** from PTSA is slightly higher than AcOH (75% vs 70%), we chose AcOH as the preferred catalyst due to ease of purification and faster reaction time (Table 4-1, entry 5 vs 10). It is noted that the reaction using water gave the starting materials unchanged where both malononitrile **2** and benzylamine **3** are insoluble (Table 4-1, entry 11).

Table 4-1: Optimization of the reaction conditions for the three-component synthesis of 2-amino-1-benzyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile 1a. [a]



Entry	Catalyst (equiv.)	Sequence of adding reagents	Solvent	Time (h)	Yield (%)[b]	**1a**:**1a′** ratio[c]
1	AcOH (1.0)	Together[d]	EtOH	3	86	0:100
2	AcOH (1.0)	Sequence 1[e]	EtOH	2+1	68	100:0
3	AcOH (1.0)	Sequence 2[f]	EtOH	2+1	66	0:100
4	$ZnCl_2$ (1.0)	Sequence 1	EtOH	2+1	53	100:0
5	PTSA (1.0)	Sequence 1	EtOH	2+1	75	100:0
6	HCOOH (1.0)	Sequence 1	EtOH	2+1	82	48:52
7	CSA (1.0)	Sequence 1	EtOH	2+1	ND[g]	ND
8	Et_3N (1.0)	Sequence 1	EtOH	2+1	92	0:100
9	K_2CO_3 (1.0)	Sequence 1	EtOH	2+1	80	0:100
10	**AcOH (1.0)**	**Sequence 1**	**EtOH**	**1+1**	**70**	**100:0**
11	AcOH (1.0)	Sequence 1	H_2O	2+1	ND	ND
12	AcOH (0.5)	Sequence 1	EtOH	2+1	72	89:11

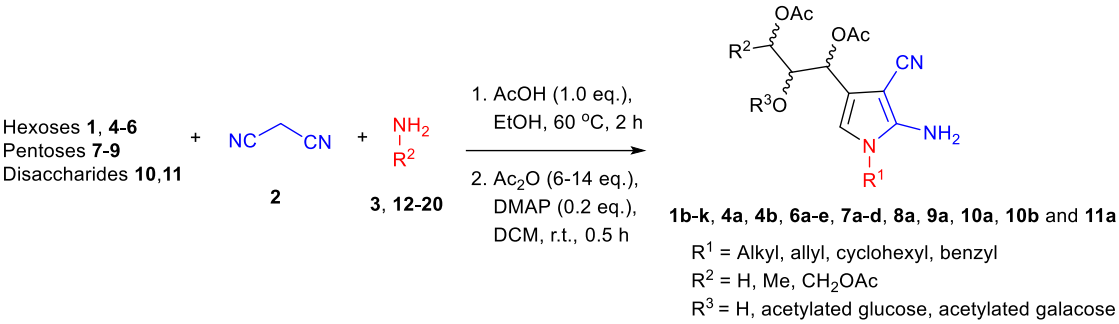
[a] All reaction were conducted under 60 °C. [b] Isolated yields. [c] Ratios measured using NMR. [d] "Together": add D-(+)-glucose **1** (1.0 mmol), malononitrile **2** (1.1 mmol), benzylamine **3** (1.0 mmol) and AcOH (1.0 mmol) consecutively in EtOH (3 mL) and stir the mixture for 3 h at 60 °C. [e] Sequence 1: first stir D-(+)-glucose **1** (1.0 mmol), benzylamine **3** (1.0 mmol) and the

catalyst in EtOH (3 mL) at 60 ^{o}C for 2 h. Next, add malononitrile **2** (1.1 mmol) to the mixture and continue the reaction for another 1 h. [f] Sequence 2: first stir malononitrile **2** (1.1 mmol), benzylamine **3** (1.0 mmol) and the catalyst in EtOH (3 mL) at 60 ^{o}C for 2 h. Next, add D-(+)-glucose **1** (1.0 mmol) to the mixture and continue the reaction for another 1 h. [g] ND: not detected.

4.2.2 Substrate Scope

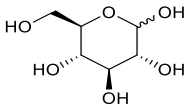
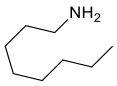
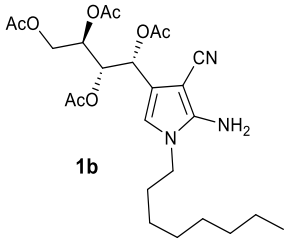
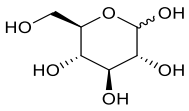
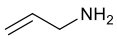
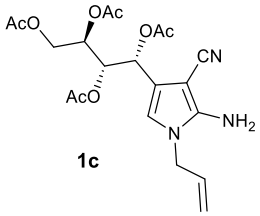
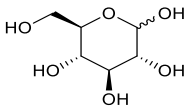
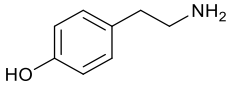
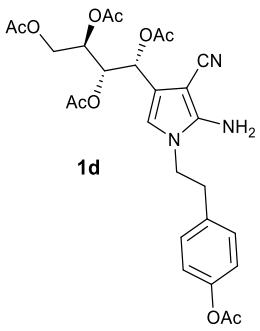
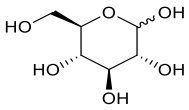
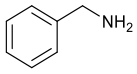
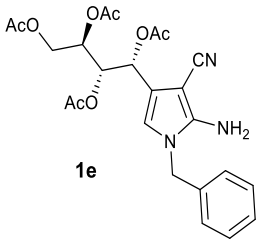
The scope of the reaction was investigated by reacting different sugars including D-(+)-glucose **1**, D-(+)-galactose **4**, D-(+)-mannose **5**, L-(+)-rhamnose **6**, D-(+)-ribose **7**, D-(+)-xylose **8**, D-(+)-arabinose **9**, L-(+)-lactose **10** and D-(+)-cellobiose **11** with malononitrile **2** and a variety of primary amines **12-20** (Table 4-2) under the optimized sequence 1 conditions (Table 4-1, entry 10). All of the sugars **1** and **4-11** reacted smoothly to give the acetylated *N*-substituted 2,3,4-functionalized pyrroles **1b-k**, **4a**, **4b**, **6a-e**, **7a-d**, **8a**, **9a**, **10a**, **10b** and **11a** in 58-86% isolated yields with complete selectivity after *in-situ* acetylation. The yield of the products was not affected by the type of the primary amine, the type, and chirality of the hexoses and pentoses but generally was lower with disaccharides (Table 4-2, entries 1-24 *vs* 25-27). The pure pyrroles **1b-k**, **4a**, **4b**, **6a-e**, **7a-d**, **8a**, **9a**, **10a**, **10b,** and **11a** were simply obtained by evaporation of the reaction mixtures followed by silica gel column chromatography purification using a mixture of EtOAc/hexane. The *in-situ* acetylation was performed to allow for easy characterization and simplify the chromatography purification process due to the high polarity of the unacetylated compounds due to many hydroxyl groups. COSY, HSQC, and HMBC NMR experiments on compounds **1j** and **6d** (Supporting Information, p74-77) and single-crystal x-ray crystallography on **21** (See Scheme 4-2) confirmed the structure and of the products.

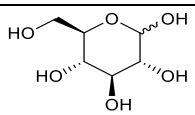
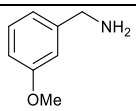
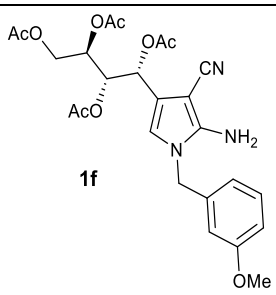
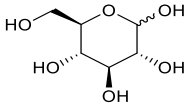
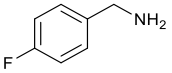
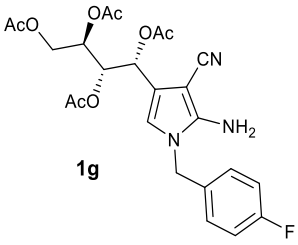
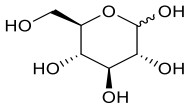
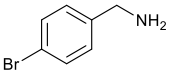
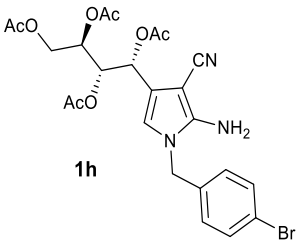
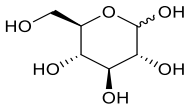
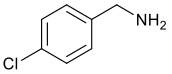
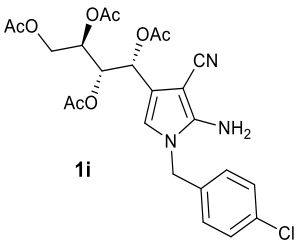
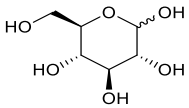
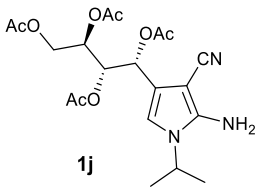
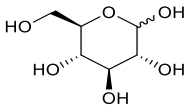
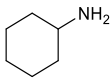
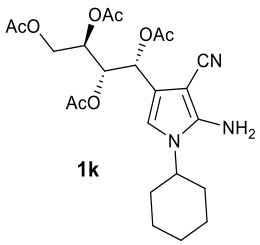
Table 4-2: Substrate scope of the AcOH-catalyzed three-component cascade reaction between sugars 1, and 4-11, malononitrile 2, and primary amines 3 and 12-20 for the synthesis of pyrroles 1b-k, 4a, 4b, 6a-e, 7a-d, 8a, 9a, 10a, 10b, and 11a. [a]

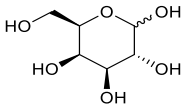
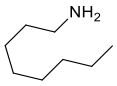
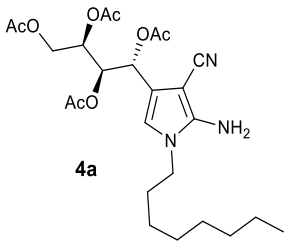
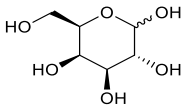
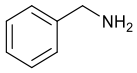
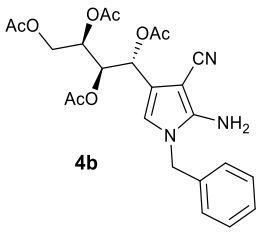
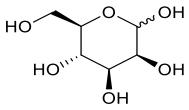
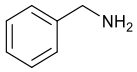
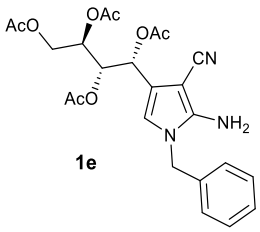
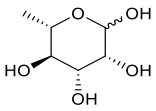
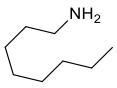
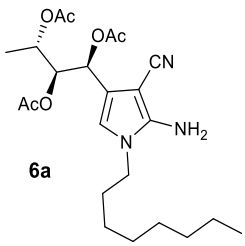
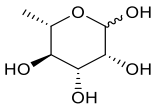
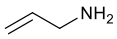
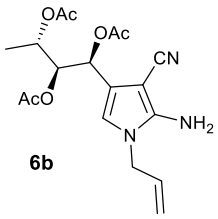
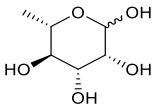
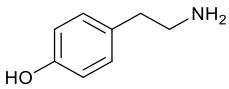
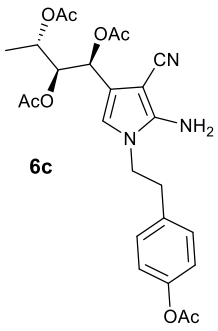


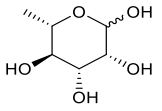
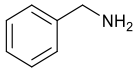
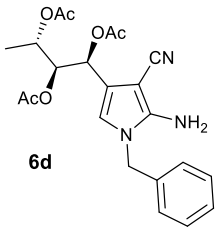
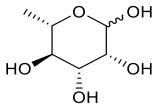
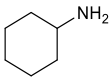
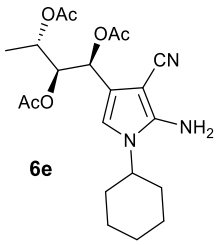
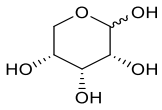
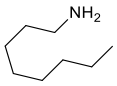
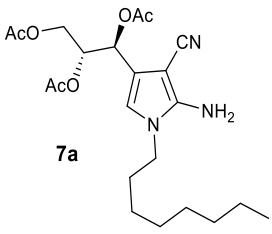
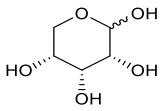
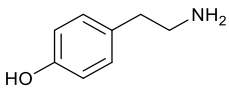
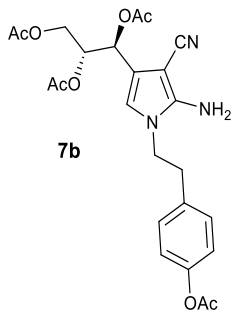
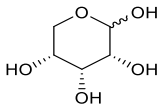
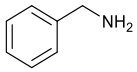
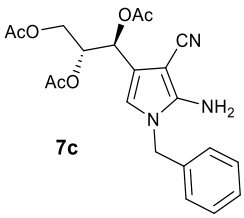
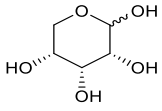
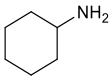
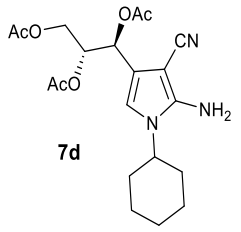
1b-k, **4a**, **4b**, **6a-e**, **7a-d**, **8a**, **9a**, **10a**, **10b** and **11a**

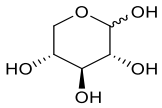
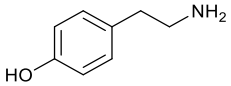
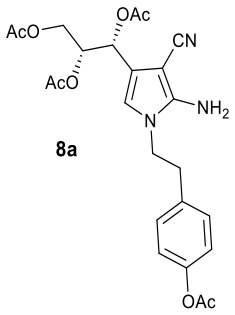
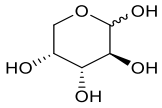
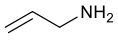
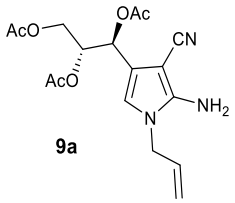
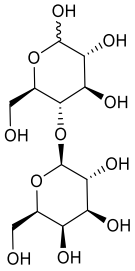
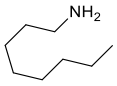
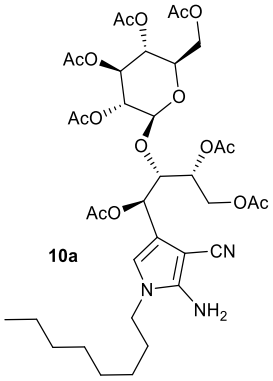
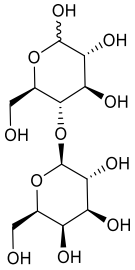
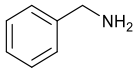
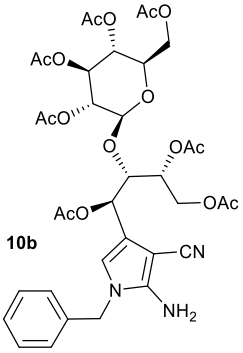
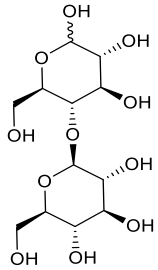
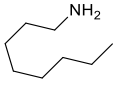
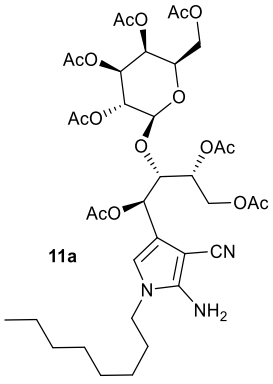
R^1 = Alkyl, allyl, cyclohexyl, benzyl
R^2 = H, Me, CH_2OAc
R^3 = H, acetylated glucose, acetylated galacose

Entry	Carbohydrate	Primary Amines	Product	Yield[b]
1	 D-(+)-Glucose **1**	 Octylamine **12**	 **1b**	78%
2	 D-(+)-Glucose **1**	 Allylamine **13**	 **1c**	71%
3	 D-(+)-Glucose **1**	 Tyramine **14**	 **1d**	72%
4	 D-(+)-Glucose **1**	 Benzylamine **3**	 **1e**	70%

5	 D-(+)-Glucose **1**	 3-Methoxy Benzylamine **15**	 **1f**	75%
6	 D-(+)-Glucose **1**	 4-Fluoro Benzylamine **16**	 **1g**	70%
7	 D-(+)-Glucose **1**	 4-Bromo Benzylamine **17**	 **1h**	68%
8	 D-(+)-Glucose **1**	 4-Chloro Benzylamine **18**	 **1i**	68%
9	 D-(+)-Glucose **1**	 Isopropylamine **19**	 **1j**	80%
10	 D-(+)-Glucose **1**	 Cyclohexylamine **20**	 **1k**	74%

11	 D-(+)-Galactose **4**	 Octylamine **12**	 **4a**	80%
12	 D-(+)-Galactose **4**	 Benzylamine **3**	 **4b**	72%
13	 D-(+)-Mannose **5**	 Benzylamine **3**	 **1e**	70%
14	 L-(+)-Rhamnose **6**	 Octylamine **12**	 **6a**	86%
15	 L-(+)-Rhamnose **6**	 Allylamine **13**	 **6b**	78%
16	 L-(+)-Rhamnose **6**	 Tyramine **14**	 **6c**	79%

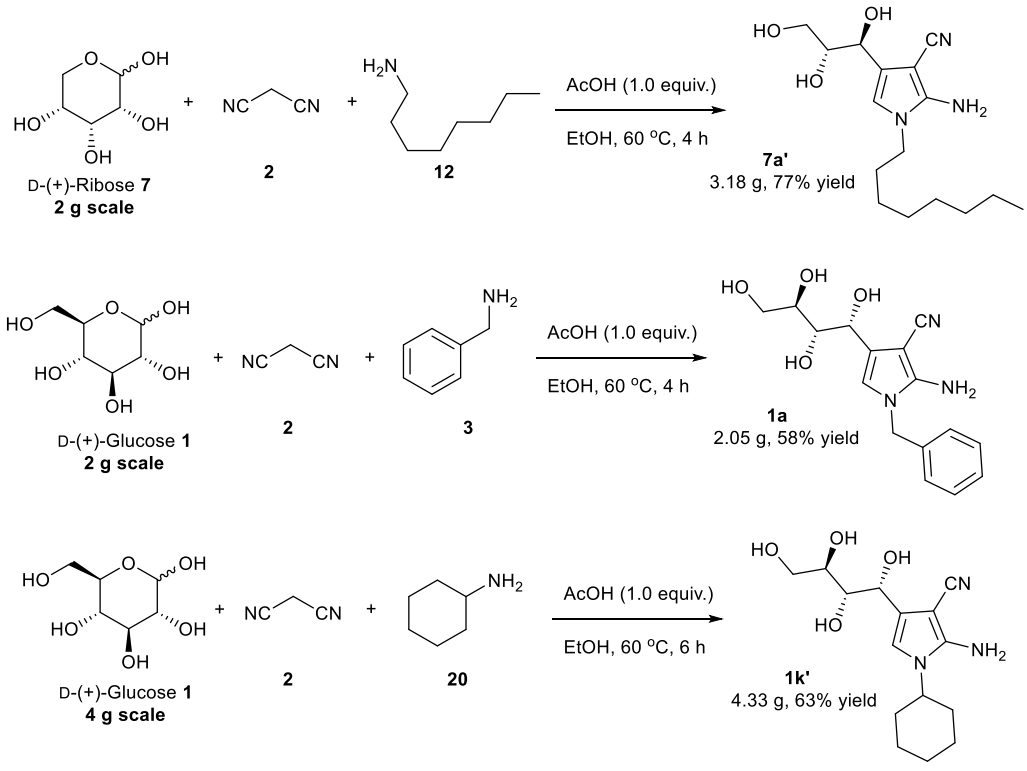
17	 L-(+)-Rhamnose **6**	 Benzylamine **3**	 **6d**	76%
18	 L-(+)-Rhamnose **6**	 Cyclohexylamine **20**	 **6e**	83%
19	 D-(+)-Ribose **7**	 Octylamine **12**	 **7a**	84%
20	 D-(+)-Ribose **7**	 Tyramine **14**	 **7b**	78%
21	 D-(+)-Ribose **7**	 Benzylamine **3**	 **7c**	74%
22	 D-(+)-Ribose **7**	 Cyclohexylamine **20**	 **7d**	84%

23	 D-(+)-Xylose **8**	 Tyramine **14**	 **8a**	76%
24	 D-(+)-Arabinose **9**	 Allylamine **13**	 **9a**	70%
25	 D-(+)-Lactose **10**	 Octylamine **12**	 **10a**	68%
26	 D-(+)-Lactose **10**	 Benzylamine **3**	 **10b**	58%
27	 D-(+)-Cellobiose **11**	 Octylamine **12**	 **11a**	66%

[a] Following sequence 1, a mixture of the sugars **1**, **4-11** (1.0 mmol), malononitrile **2** (1.1 mmol), primary amines **3**, **12-20** (1.0 mmol) and AcOH (1.0 mmol) was stirred in EtOH (3 mL) at 60 ^{o}C for 2 h. In case of pentoses **7-9**, the reactions were conducted at 50 ^{o}C. In case of disaccharides **10** or **11**, the reactions were conducted using DMF (3 mL). In-situ acylation using Ac_2O (6-14 equ.) was conducted by evaporating EtOH or DMF first, suspending the residue in DCM (5 mL), addition of DMAP (0.2 equ.), and stirring the reaction mixture at room temperature for 0.5 h. [b] Isolated yields.

4.3 Lage scale reaction

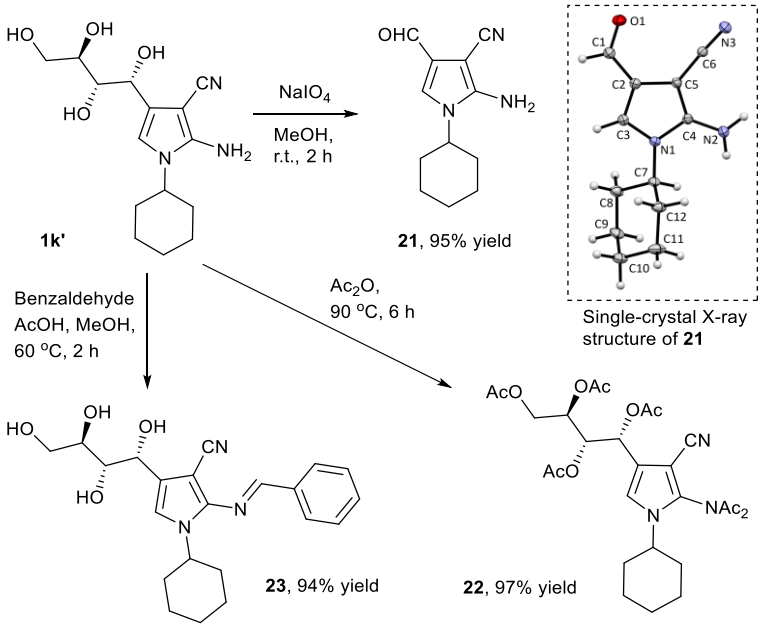
The reaction was attempted at a 2-4 grams scale to demonstrate its practicality. The reaction between D-(+)-ribose **7** (2 g), malononitrile **2,** and octylamine **12** provides pyrrole product **7a'** in 77% isolated yield (Scheme 4-1). The reaction between D-(+)-glucose **1** (2 g), malononitrile **2,** and benzylamine **3** gave pyrrole **1a** in a 58% isolated yield. Further, the reaction between D-(+)-glucose **1** (4 g), malononitrile **2,** and cyclohexylamine **20** gave pyrrole **1k'** in 63% isolated yield (Scheme 4-1). This demonstrates the ease of scalability of the reaction.



Scheme 4-1. Gram scale reactions of D-(+)-ribose 7 and D-(+)-glucose 1.

4.4 Manipulation of the functional groups of *N*-substituted 2-amino-3-cyanopyrroles

The *N*-substituted 2-amino-3-cyanopyrroles contain -OH, -CN, -NH_2 functional groups that can be utilized or modified to obtain useful intermediates.[87, 199, 202] To demonstrate this, the polyhydroxyalkyl 2-amino-3-cyanopyrrole **1k'** was converted to 2-amino-3-cyano-4-formylpyrrole **21** in 95% yield (Scheme 4-2).[203] The formyl group is a versatile group that can also be converted to or used to obtain other functionalities. The structure of pyrrole **21** was unambiguously confirmed by single-crystal X-ray diffraction (CCDC 2154828), which indirectly confirm the structures of pyrroles **1b-k**, **4a**, **4b**, **6a-e**, **7a-d**, **8a**, **9a**, **10a**, **10b** and **11a**. The hydroxy and amine groups of polyhydroxyalkyl 2-amino-3-cyanopyrrole **1k'** can be fully acetylated using acetic anhydride to provide pyrrole **22** in 97 % yield where the cyano group can then be modified independently for further selective manipulation. Additionally, the amine group of polyhydroxyalkyl 2-amino-3-cyanopyrrole **1k'** was selectively reacted with benzaldehyde to provide pyrrole **23** in 94 % yield (Scheme 4-2). Many bioactive pyrroles contain imine functionality.[87, 199, 204]



Scheme 4-2. Manipulation of the functional groups of *N*-substituted 2-amino-3-cyanopyrrole

4.5 Mechanistic considerations

A plausible reaction mechanism for the formation of pyrrole **1b'** according to sequence 1 is shown in Figure 3. Condensation between D-(+)-glucose **1** and octylamine **12** gives the Schiff base **I**. Acid-catalyzed Amadori rearrangement of **I** via eneaminol **II** gives the open-chain Amadori product **III**. Consequently, the Knoevenagel reaction of **III** with malononitrile **2** gives intermediate **IV** which upon intramolecular cyclization gives intermediate **V**. Subsequently, intermediate **V** undergoes aromatization to provide pyrrole **1b'** (Figure 4-3).

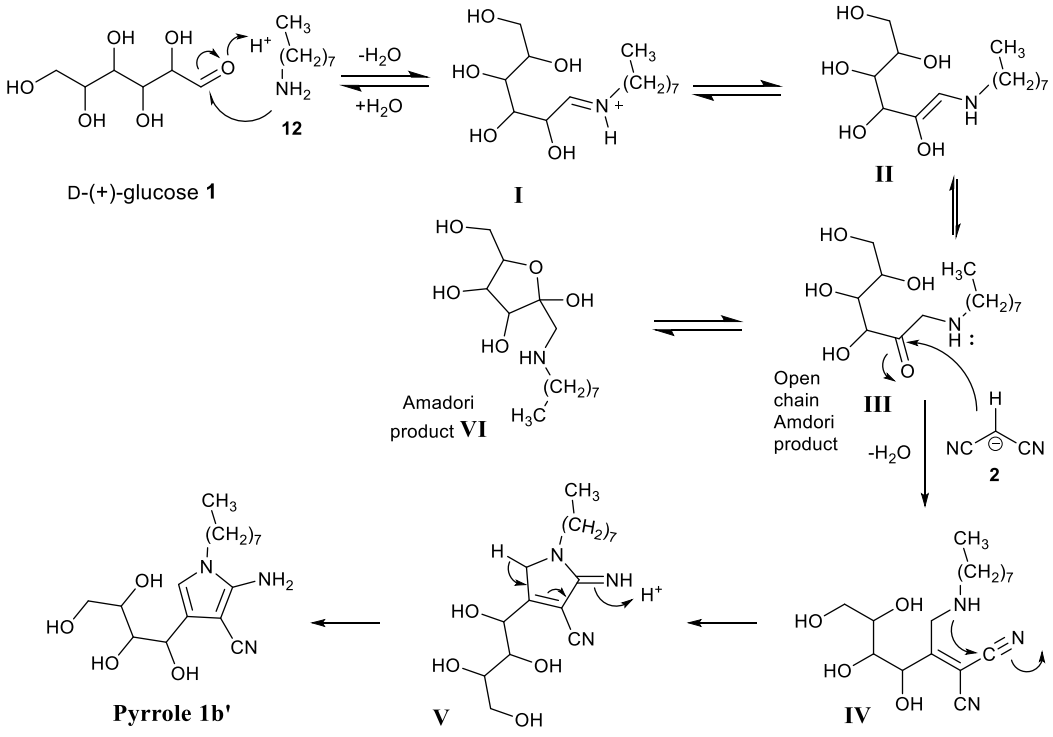


Figure 4-3. Proposed mechanism for the formation of pyrrole 1b'.

Evidence for the above-proposed mechanism is supported by ^{1}H NMR and LC-MS experiments (Figures 4-4 and 4-5). In these experiments, the reaction between D-(+)-glucose **1**, malononitrile **2**, and octylamine **12** was performed in CD_3OD according to sequence 1, and

reaction samples were taken at several time intervals (0 min to 2 hours) to follow its progress and examine for intermediates.

In the ^{1}H NMR experiment, the reaction between the α- and β- epimers of D-(+)-glucose **1** with octylamine **12** was clearly observed by the gradual and complete disappearance of α-H1 at δ 5.18/5.19 ppm and β-H1 at δ 4.57/4.55 ppm over 1 hour (Figure 4-4). There are also changes in the chemical shifts and multiplicities of the rest of the D-(+)-glucose **1** peaks as the reaction progresses. As expected, there were no significant chemical shift changes in the octyl protons. Upon addition of malononitrile **2**, and after 70 min., new characteristics peaks for H2 at δ 6.27 ppm and for H3 at δ 4.81/4.80 ppm of pyrrole **1b'** appeared and their intensity increased as the reaction progressed till 2 h. In a separate experiment, attempts to isolate Schiff base **I** or the Amadori open-chain product **III** were unsuccessful. Instead, purification of the crude product using column chromatography gave Amadori product **VI** whose identity was confirmed by NMR analysis and comparison to the literature data (Figure 4-4).[205] It should be noted that under acidic conditions, Amadori product **VI** is in equilibrium with the Amadori open-chain product **III** which is believed to serve as the intermediate that reacts with malononitrile **2** to give pyrrole **1b'**.

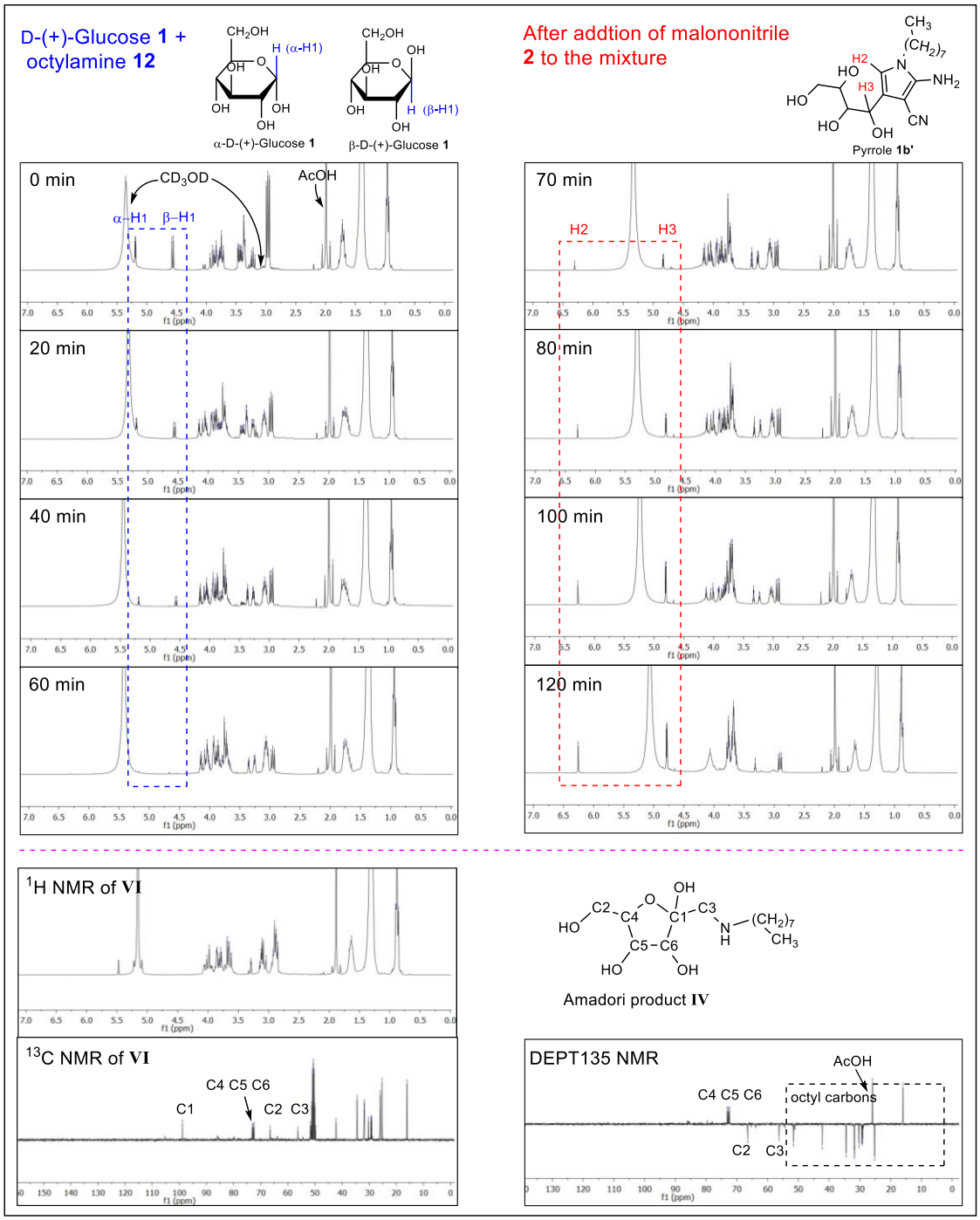


Figure 4-4. (a) NMR spectra of the reaction of D-(+)-glucose 1, malononitrile 2 and octylamine 12 leading to the formation of pyrrole 1b' taken at different times intervals. (b) NMR spectra of Amadori product VI.

In the LC-MS experiment, spectral analysis of the reaction samples revealed peaks for **I**, **II**, **III**, **IV**, and pyrrole **1b'** (Figure 4-5). The structures of **I**, **II**, **III**, and **IV** are isomeric with a molecular

mass of 291. They showed the same mass spectral peaks at 292 $[M+1]^+$ and 293 $[M+2]^+$. Pyrrole **1b'** with molecular mass of 339 showed spectral peaks at the expected values of 322 [M-17 (-OH)]$^+$, 340 $[M+1]^+$, and 341 $[M+2]^+$.

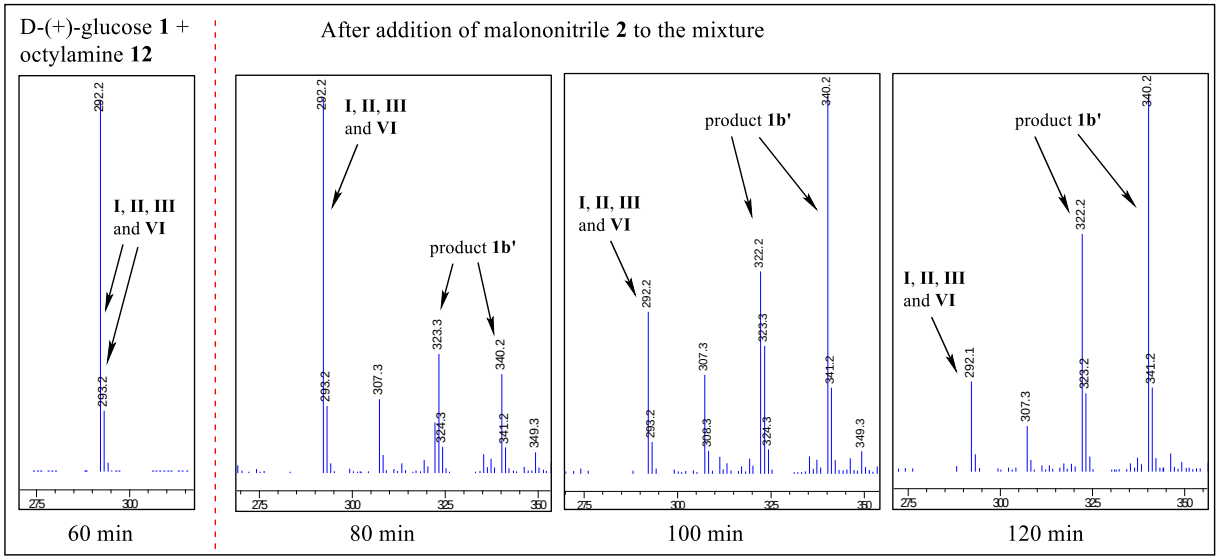


Figure 4-5. Sections of the LC-MS spectra of the reaction of D-(+)-glucose 1, malononitrile 2, and octylamine 12 leading to the formation of pyrrole 1b' were taken at different time intervals.

The above ^{1}H NMR and LC-MS experiments provide reasonable evidence for the proposed mechanism. Specifically, isolation and characterization of the Amadori product **IV** provide credibility for this mechanism.

4.6 Conclusion

In summary, we have developed a three-component reaction between unprotected sugars, malononitrile, and primary amines to synthesize *N*-substituted 2-amino-3-cyano-4-functionalized pyrroles. The reaction was simply catalyzed using AcOH, proceeded under mild reaction conditions (EtOH, 60 ^{o}C, 2 hours), tolerated wide substrate scope, and worked at a scale up to 4-gram. Mechanistically, and as supported by NMR and LC-MS experiments, the reaction proceeded through a cascade process involving Schiff base formation, Amadori rearrangement,

Knoevenagel reaction, and aromatization. This approach offers a green pathway for the synthesis of *N*-substituted 2-amino-3-cyano-4-functionalized pyrrole key framework by utilizing sustainable carbohydrates to replace the more complex traditional starting materials. Further research on the utility of this approach for the synthesis of commercial pyrrole-based drugs and application using other carbohydrates is underway.

4.7 Experimental Section

4.7.1 Materials and methods

All chemicals and AR grade solvents were obtained from Sigma-Aldrich, Merck or Alfa Aesar and were used as received without further purification. IR spectra were recorded using a Bruker MPA FT-IR machine. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance DPX 300. ^{13}C NMR spectra were recorded at 75.47 MHz using the same machine. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. HRMS were measured using a hybrid Quadrupole Time-of-Flight (Q-TOF) on Qstar XL MS/MS system. LC-MS spectra were recorded using Agilent 6530 LC-MS. Analytical TLC was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness). The plates were visualized using UV radiation (254 nm) or stained in ceric ammonium sulfate solution with heating to detect the reaction spots. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh).

4.7.2 General Procedure (Sequence 1): Synthesis of *N*-substituted 2-amino-3-cyano-4-functionalized pyrroles 1b-k, 4a, 4b, 6a-e, 7a-d, 8a, 9a, 10a, 10b and 11a

The sugar (1 mmol, 1.0 equiv.), primary amine (1.0 equiv.) and AcOH (1.0 equiv.) were mixed in EtOH (3 ml) at room temperature and the reaction was stirred at 60 ^{o}C for 1 h. Malononitrile (1.1 equiv.) was then added to the mixture and the reaction was continued for another 1 h whereby complete consumption of the starting materials was observed as indicated by TLC. The reaction mixture was then evaporated to dryness under vacuum to give the crude product as a foam.

i) Acetylation of the foam: Ac_2O (6–14 equiv., 2.0 equiv. for each hydroxyl group), and DMAP (0.2 equiv.) were added to a stirred suspension of the foam in DCM (5 mL) and the reaction was further stirred for 0.5 h. The reaction mixture was then evaporated to dryness and the crude product was purified using silica gel column chromatography using Hexane/EtOAc as eluant (60:40 for pentoses; 55:45 for hexoses; and 50:50 for disaccharides) to give the pure acetylated products.

ii) The foam could also be purified directly using silica gel column chromatography using MeOH/CH_2Cl_2 as eluant (5:95 for pentoses; 10:9 for hexoses; and 20:80 for disaccharides) to give the pure products.

All reactions were conducted using 1.0 mmol of the sugars. This general procedure was used to prepare *N*-substituted 2-amino-3-cyano-4-functionalized pyrroles **1b**-**k**, **4a**, **4b**, **6a**-**e**, **7a**-**d**, **8a**, **9a**, **10a**, **10b** and **11a**.

All NMR spectra and other data are listed in Appendix.

Chapter 5. Selective one-step synthesis of *N*-substituted densely functionalized 3-cyanopyrroles *via* AcOH-catalyzed reaction of α-hydroxyketones, oxoacetonitriles, and primary amines

5.1 Introduction

Pyrroles are a class of nitrogen heterocycles with important applications in the pharmaceutical and material science industries.[61, 141, 206] Owing to their diverse bioactivities such as anti-inflammatory,[63] anti-bacterial,[72] anti-tumor,[67] and anti-oxidative bioactivities,[207] several pyrrole-based drugs have been successfully marketed to treat various conditions (Figure 5-1). Additionally, many pyrrole-based drug candidates have shown great promise to treat various conditions (Figure 5-1). Therefore, continuous efforts have been invested in designing simple, efficient, and sustainable routes to synthesize suitably substituted pyrroles with specific handles for easy modifications to the final dugs. In this regard, special attention is given to synthesizing 3-cyanopyrroles since the cyano handle can easily be converted to -CXN functionality (where X = H, H_2, O, or simply nothing). This -CXN functionality appears in many drugs and drug candidates (Figure 5-1).[71, 72, 74, 184, 208, 209]

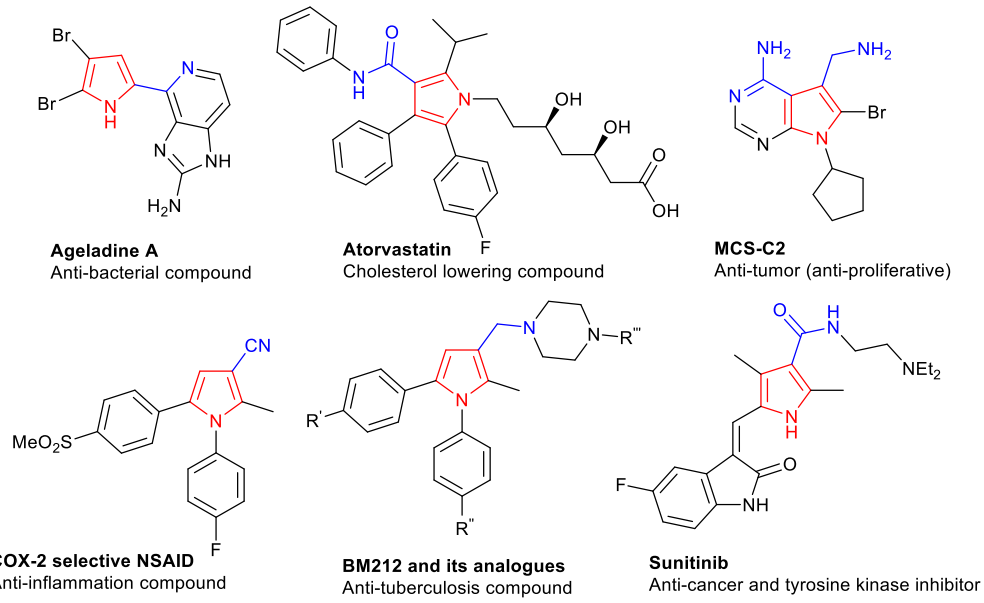


Figure 5-1. Examples of bioactive pyrrole-based compounds having a -CXN moiety (in blue).

Previous efforts to synthesize 3-cyanopyrroles include (i) the nickel(II) bis(acetylacetonate)-catalyzed reaction between azirines and active methylene compounds reported in 1977 (Figure 5-2, i);[210] (ii) the reaction between 1-nitro-1-cyclopropyl ketones and primary amines followed by oxidizing the formed dihydropyrroles using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the desired pyrroles (Figure 5-2, ii);[211] and (iii) the reaction between α-hydroxyketones, malononitrile and primary amines (Figure 5-2, iii).[212] However, the first two reactions require extra steps to prepare the complex starting materials, use metals to catalyze the reactions, and are multistep syntheses. The last reaction works when the substituents at the α-hydroxyketones are similar (R^1 and R^1 both either methyl or phenyl, Figure 5-1, iii) and the starting material itself is not considered sustainable. In this reaction, when the substituents are different several products are formed which reduces the yields and complicate separation. Moreover, these reactions are conducted at high temperatures > 90 ^{o}C in toluene. Additionally, other inefficient multistep reactions introduced the cyano handle on a preformed pyrrole and usually use heavy metals or toxic reagents.[213] These disadvantages, encourages the search for a more robust, practical, and sustainable methodology.

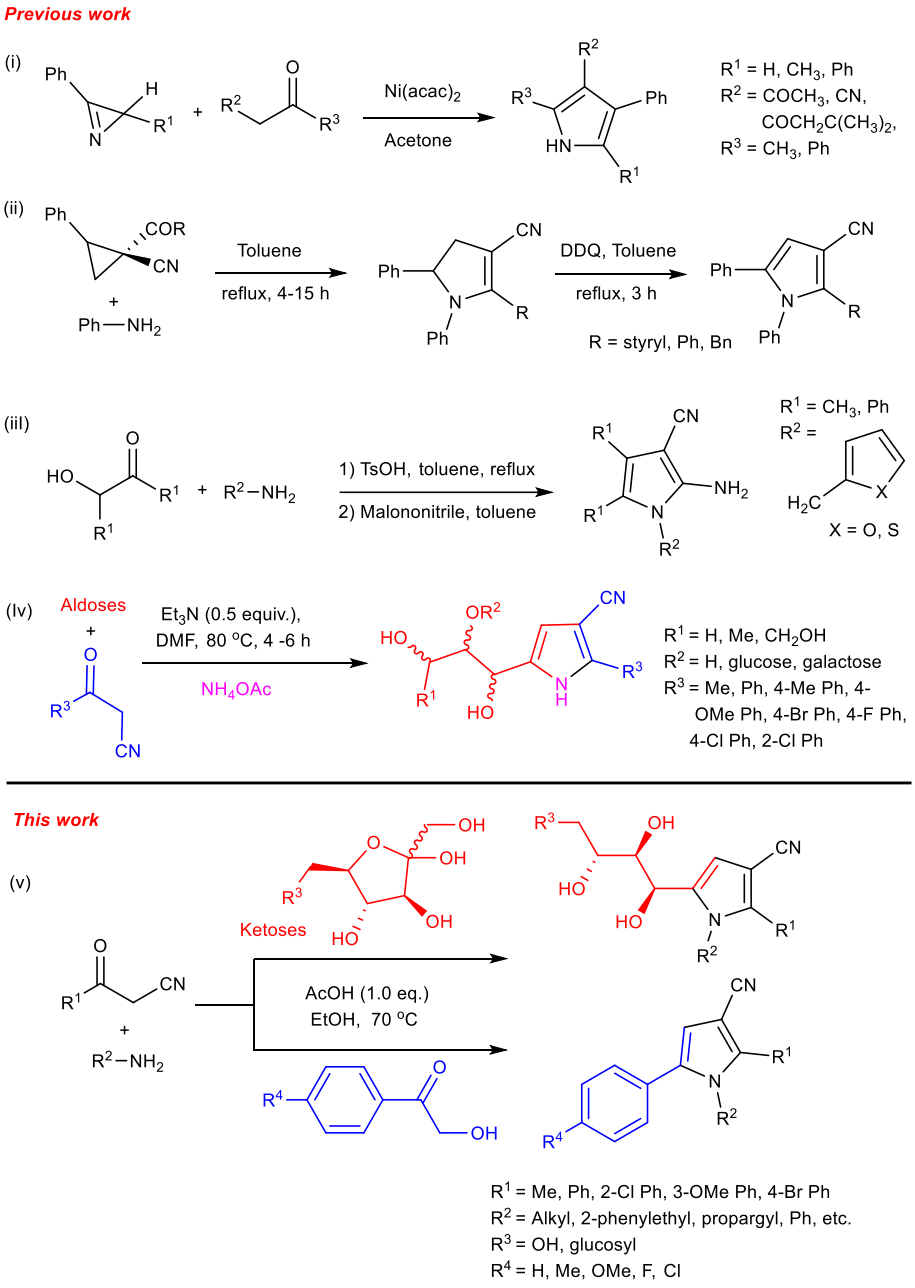


Figure 5-2. Previous and proposed work for the synthesis of 3-cyanopyrroles.

Earlier, we developed a cascade reaction between aldoses, oxoacetonitriles, and NH_4OAc to synthesize *N*-unsubstituted 3-cyanopyrroles (Figure 5-2, (iv)).[214] Based on the previous work, we envisioned that ketoses, which are effectively α-hydroxyketones, can be ideal substrates for the synthesis of functionalized pyrroles having the desired 3-cyano moiety (Figure 5-1, (iii)). When they react with primary amines, they should give *N*-substituted 3-cyanopyrroles. Ketoses are cheap, sustainable materials, and can introduce chirality in the pyrrole framework. Moreover,

the polyhydroxyalkyl chain can easily be converted into several functional groups. It is also beneficial to establish general reaction conditions that work for other α-hydroxyketones such as phenacyl alcohols to add diversity to the substituents on the core 3-cyanopyrrole structure (Figure 5-1, (v)). Another important objective in this work is to achieve complete selectivity while using differently substituted α-hydroxyketones ($R^1 \neq R^1$, Figure 5-1, iii) which has proven to be challenging in previous reports.

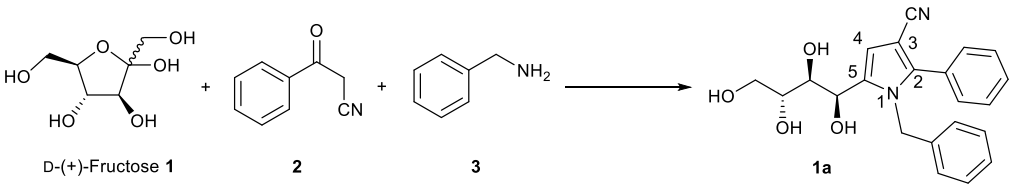
Herein, we report a selective three-component reaction between α-hydroxyketones (ketoses and phenacyl alcohols), oxoacetonitriles, and primary amines to synthesize densely functionalized 3-cyanopyrroles. This AcOH-catalyzed reaction gave the desired 3-cyanopyrroles in 53-90% yields and worked successfully on a gram scale. The structures of the 3-cyanopyrroles were confirmed using single-crystal X-ray analysis and a plausible reaction mechanism was also provided.

5.2 Reaction optimization

We started the investigation by stirring D-(+)-fructose **1** (1 mmol, 1.0 eq.), benzoylacetonitrile **2** (1.0 eq.), and benzylamine **3** (1.1 eq.) in one-pot in the presence of AcOH (1.0 eq.) in EtOH (3 mL) at 70 ^{o}C for 3 h (Table 5-1, entry 1). The reaction gave 1-benzyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile **1a** (*N*-substituted 2,3,5-functionalized 3-cyanopyrrole) in 77% yield (Table 5-1, entry 1). Under these conditions, complete selectivity was obtained and *N*-substituted 2,3,5-functionalized 3-cyanopyrrole **1a** was the only product recovered. Attempts to increase the yield of **1a** by increasing the temperature or reaction time were unsuccessful and lead to more decomposition products indicated by a darkening of the reaction mixture. Next, several acidic and basic catalysts were examined. Except for $ZnCl_2$, which gave **1a** in 46% yield, other acids including *p*-toluenesulfonic acid (PTSA) and camphor sulfonic acid (CSA), and bases including triethylamine (Et_3N), sodium

hydroxide (NaOH), potassium carbonate (K_2CO_3) and sodium methoxide (NaOMe) did not give the desired product and the starting materials were recovered back (Table 5-1, entry 2-8). Changing EtOH solvent to acetonitrile (ACN) or dimethylformamide (DMF) did not improve the yield of **1a** (Table 5-1, entry 1 *vs* 9 *vs* 10). Further, attempts to reduce the equivalents of AcOH from 1 to 0.5 reduced the yield of **1a** dramatically (Table 5-1, entry 1 *vs* 11). Therefore, we concluded the optimum conditions to be 1 equivalent of AcOH in EtOH at 70 ^oC for 3 h (Table 5-1, entry 1).

Table 5-1: Optimization of the reaction conditions for the three-component synthesis of 3-cyanopyrrole 1a.



Entry	Catalyst (eq.)	Solvent	Yield (%)[a]
1	**AcOH (1.0)**	**EtOH**	**77**
2	$ZnCl_2$ (1.0)	EtOH	46
3	PTSA (1.0)	EtOH	ND[b]
4	CSA (1.0)	EtOH	ND
5	Et_3N (1.0)	EtOH	Trace
6	NaOH (1.0)	EtOH	ND
7	K_2CO_3 (1.0)	EtOH	ND
8	NaOMe (1.0)	EtOH	ND
9	AcOH (1.0)	ACN	69
10	AcOH (1.0)	DMF	76
11	AcOH (0.5)	EtOH	58

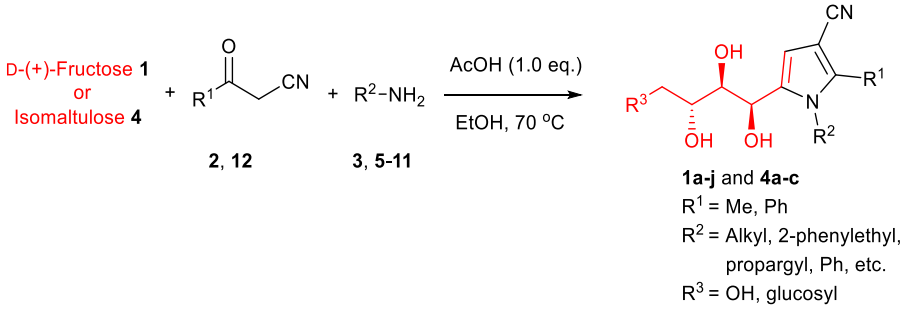
[a]Isolated yields. All reactions were conducted at 70 ^oC for 3 h using 3 mL of the solvent. [b]ND: Not detected.

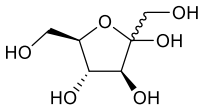
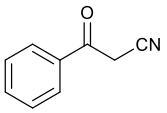
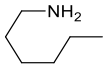
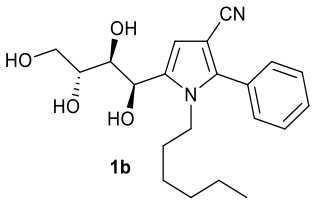
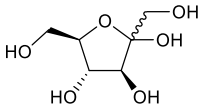
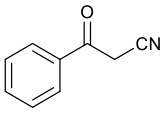
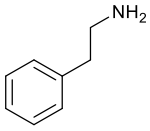
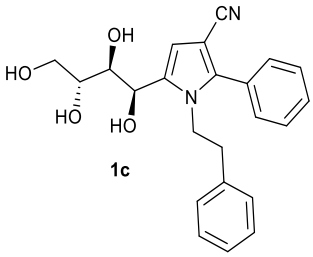
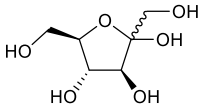
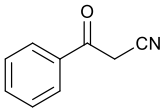
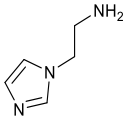
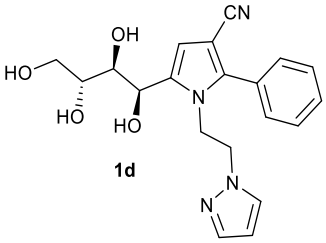
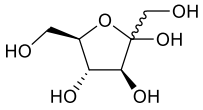
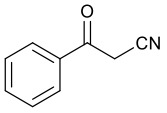
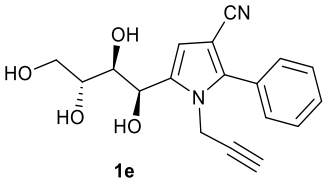
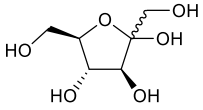
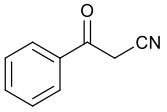
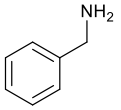
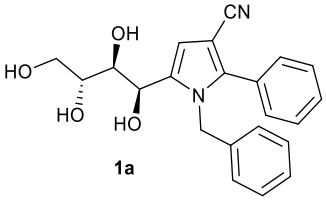
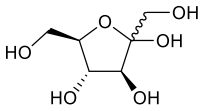
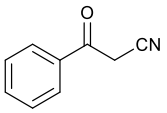
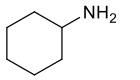
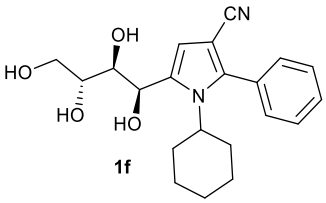
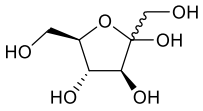
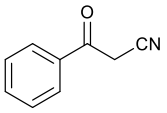
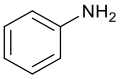
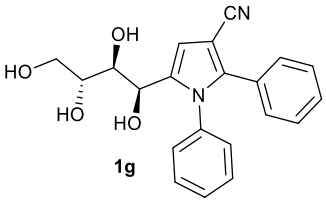
5.3 Substrate Scope

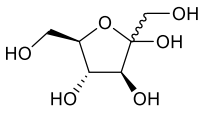
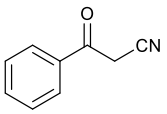
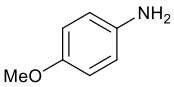
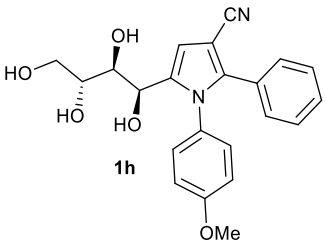
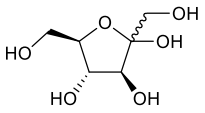
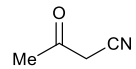
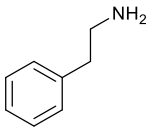
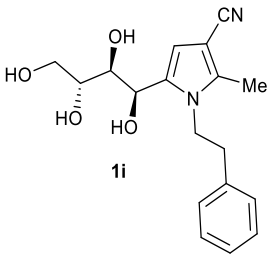
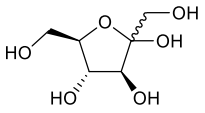
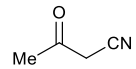
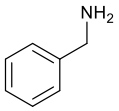
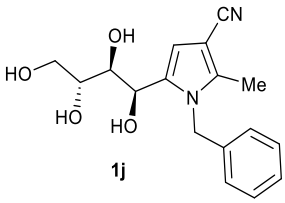
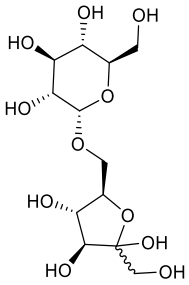
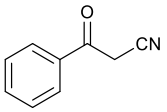
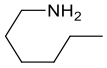
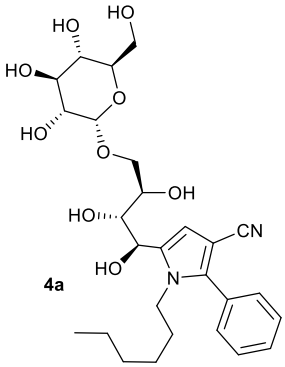
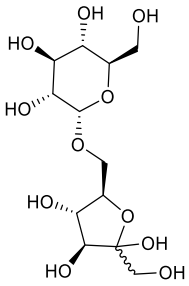
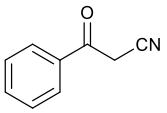
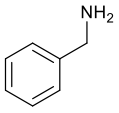
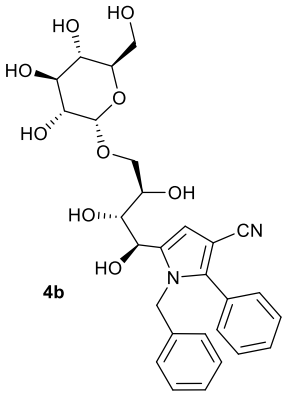
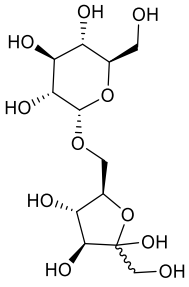
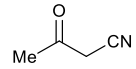
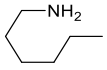
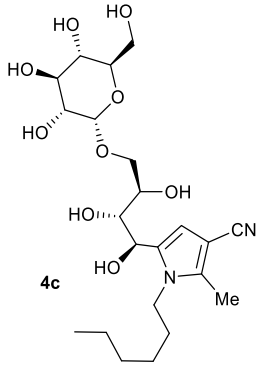
Initially, the scope of the reaction was investigated by reacting different ketoses including D-(+)-fructose **1** and isomaltulose (also known as palatinose) **4** with primary

amines **3** and **5-11** and oxoacetonitriles **2** and **12**, (Table 2) under the optimized condition (Table 5-1, entry 1). The selected ketoses were representative of mono- and disaccharides, the amines were representative of primary, secondary, unsaturated, aliphatic, aromatic, and heterocyclic amines while the oxoacetonitriles were representative of aliphatic and aromatic nitriles. Ketoses **1** and **4** reacted selectively to give the *N*-substituted 2,3,5-functionalized 3-cyanopyrroles **1a-j** and **4a-c** in 55-86% isolated yields. In particular, 3-cyanopyrroles **4a-c** are interesting structures since they combine both a pyrrole moiety and a sugar moiety and are water-soluble.[215] The yield of the 3-cyanopyrroles **1a-j** and **4a-c** was affected by the type of sugar and the type of the primary amine. Hence, D-(+)-fructose/amines provide higher yields than isomaltulose/amines (Table 5-2, entries 1-6 vs 11-13) and aliphatic amines provided higher yields than aromatic amines due to their higher nucleophilicity (Table 5-2, entries 1-6 vs 7-8). All the 3-cyanopyrroles **1a-j** and **4a-c** were purified by column chromatography using a mixture of MeOH/DCM (5-10% MeOH/DCM for **1a-j** and 15-20% MeOH/DCM for **4a-c**). The high polarity of the 3-cyanopyrroles is attributed to extensive hydrogen bonding in the polyhydroxyalkyl chains.

Table 5-2: Substrate scope of the AcOH-catalyzed three-component reaction between ketoses 1, and 4, primary amines 3 and 5-11, and oxoacetonitriles 2 and 12 for the selective synthesis of 3-cyanopyrroles 1a-j and 4a-c.[a]



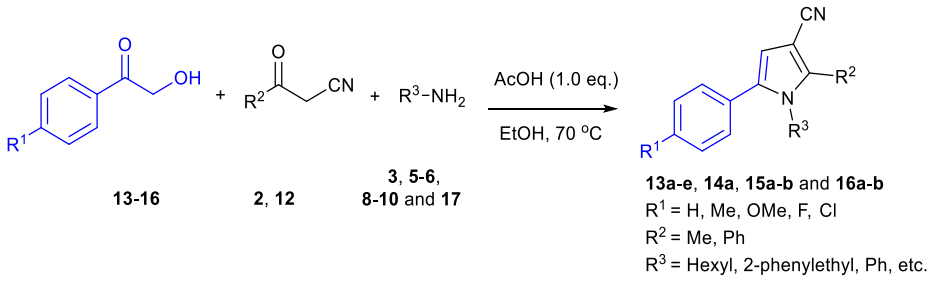
No.	Ketose	Oxoacetonitrile	Amine	3-Cyanopyrrole	Yield[b]
1	 D-(+)-Fructose **1**	 Benzoylacetonitrile **2**	 Hexylamine **5**	 **1b**	86
2	 D-(+)-Fructose **1**	 Benzoylacetonitrile **2**	 2-Phenylethylamine **6**	 **1c**	84
3	 D-(+)-Fructose **1**	 Benzoylacetonitrile **2**	 2-(1*H*-imidazol-1-yl)ethanamine **7**	 **1d**	73
4	 D-(+)-Fructose **1**	 Benzoylacetonitrile **2**	 Propargylamine **8**	 **1e**	75
5	 D-(+)-Fructose **1**	 Benzoylacetonitrile **2**	 Benzylamine **3**	 **1a**	77
6	 D-(+)-Fructose **1**	 Benzoylacetonitrile **2**	 Cyclohexylamine **9**	 **1f**	72
7	 D-(+)-Fructose **1**	 Benzoylacetonitrile **2**	 Aniline **10**	 **1g**	61

8	 D-(+)-Fructose **1**	 Benzoylacetonitrile **2**	 *p*-Anisidine **11**	 **1h**	60
9	 D-(+)-Fructose **1**	 3-oxobutanenitrile **12**	 2-Phenylethylamine **6**	 **1i**	71
10	 D-(+)-Fructose **1**	 3-oxobutanenitrile **12**	 Benzylamine **3**	 **1j**	67
11	 Isomaltulose **4**	 Benzylacetonitrile **2**	 Hexylamine **5**	 **4a**	68
12	 Isomaltulose **4**	 Benzylacetonitrile **2**	 Benzylamine **3**	 **4b**	55
13	 Isomaltulose **4**	 3-oxobutanenitrile **12**	 Hexylamine **5**	 **4c**	57

[a] A mixture of ketoses **1** or **4** (1.0 mmol), oxoacetonitriles **2** or **12** (1.0 mmol), primary amines **3** or **5-11** (1.1 mmol) and AcOH (1.0 mmol) were stirred in EtOH (3 mL) at 70 °C for 3 h. [b] Isolated yields.

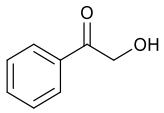
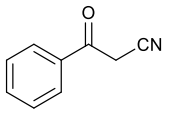
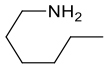
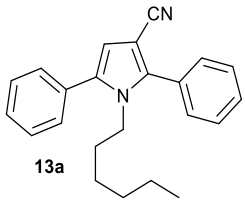
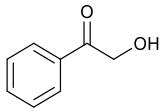
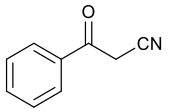
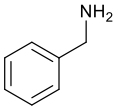
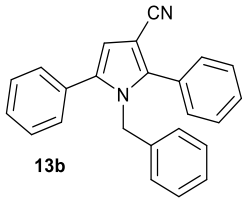
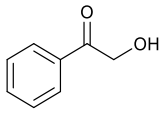
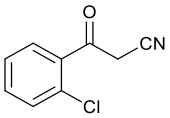
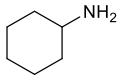
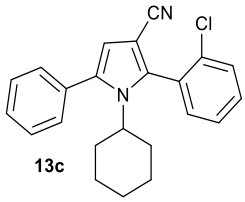
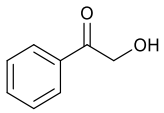
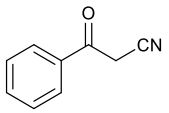
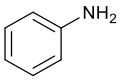
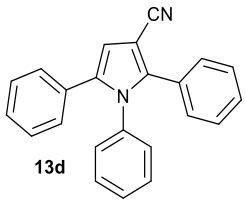
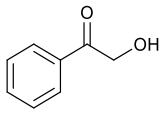
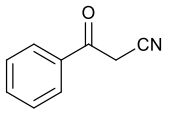
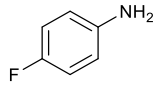
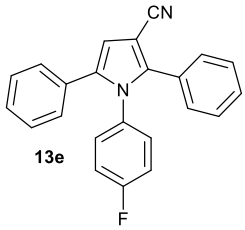
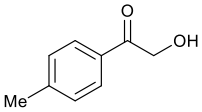
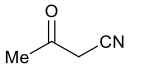
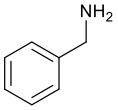
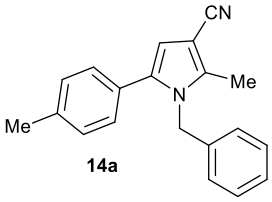
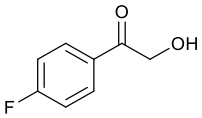
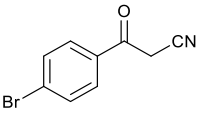
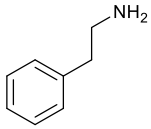
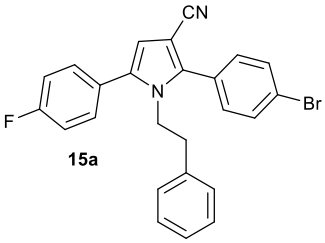
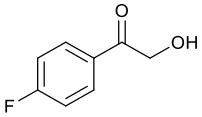
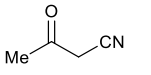
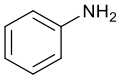
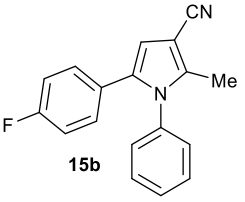
Next, the reactivity of phenacyl alcohols **13-16** as the α-hydroxyketone was tested under the optimum conditions (Table 5-1, entry 1) to further extend the scope of this reaction and examine the selectivity. Additionally, phenacyl alcohols would also give diversity to the substituents on the 3-cyanopyrrole core. The reaction between phenacyl alcohols **13-16**,[216] oxoacetonitriles **2** and **12**, and primary amines **3**, **5**, **6**, **8-10** and **17** selectively gave the desired *N*-substituted 2,3,5-functionalized 3-cyanopyrroles **13a-e, 14a**, **15a-b**, and **16a-b** in excellent 70-90% isolated yields. Again, aromatic amines generally gave lower yields than aliphatic amines due to their lower nucleophilicity. 3-Cyanopyrroles **13a-e, 14a**, **15a-b**, and **16a-b** were purified using silica gel column chromatography using a mixture of 5-35% EtOAc/Hexane. These 3-cyanopyrroles showed lower polarity compared to 3-cyanopyrroles **1a-j** and **4a-c** due to lower hydrogen bonding.

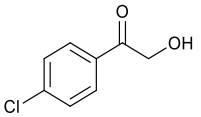
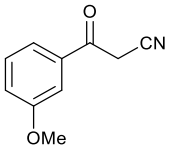
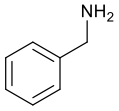
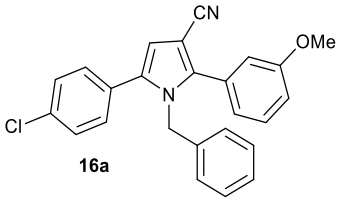
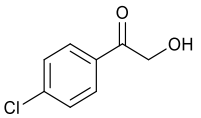
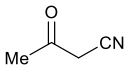
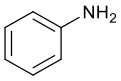
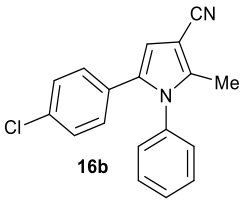
Table 5-3: Substrate scope of the AcOH-catalyzed three-component reaction between phenacyl alcohols 13-16, oxoacetonitriles 2, 12, and primary amines 3, 5, 6, 8-10, and 17 for the selective synthesis of 3-cyanopyrroles 13a-e, 14a, 15a-b, and 16a-b.[a]



13-16 | **2**, **12** | **3**, **5-6**, **8-10** and **17**

13a-e, **14a**, **15a-b** and **16a-b**
R^1 = H, Me, OMe, F, Cl
R^2 = Me, Ph
R^3 = Hexyl, 2-phenylethyl, Ph, etc.

No.	α-Hydroxyketone	Oxoacetonitrile	Amine	3-Cyanopyrrole	Yield[b]
1	 Phhenacyl alcohol **13**	 Benzoylacetonitrile **2**	 Hexylamine **5**	 **13a**	90
2	 Phhenacyl alcohol **13**	 Benzoylacetonitrile **2**	 Benzylamine **3**	 **13b**	88
3	 Phhenacyl alcohol **13**	 2-Chloro benzoylacetonitrile **19**	 Cyclohexylamine **9**	 **13c**	86
4	 Phhenacyl alcohol **13**	 Benzoylacetonitrile **2**	 Aniline **10**	 **13d**	80
5	 Phhenacyl alcohol **13**	 Benzoylacetonitrile **2**	 4-Fluoro aniline **17**	 **13e**	77
6	 2-Hydroxy-1-(*p*-tolyl)ethan-1-one **14**	 3-oxobutanenitrile **11**	 Benzylamine **3**	 **14a**	74
7	 1-(4-Fluorophenyl)-2-hydroxyethan-1-one **15**	 4-Bromo benzoylacetonitrile **20**	 2-Phenylethylamine **6**	 **15a**	82
8	 1-(4-Fluorophenyl)-2-hydroxyethan-1-one **15**	 3-oxobutanenitrile **12**	 Aniline **10**	 **15b**	70

9	 1-(4-Chlorophenyl)-2-hydroxyethan-1-one **16**	 3-Methoxy benzoylacetonitrile **21**	 Benzylamine **3**	 **16a**	84
10	 1-(4-Chlorophenyl)-2-hydroxyethan-1-one **16**	 3-oxobutanenitrile **12**	 Aniline **10**	 **16b**	70

[a] A mixture of phenacyl alcohols **13-16** (1.0 mmol), oxoacetonitriles **2** or **12** (1.0 mmol), and primary amines **3**, **5**, **6**, **8-10** and **17** (1.1 mmol) were stirred in EtOH (3 mL) at 70 ^{o}C for 3 h. [b] Isolated yields.

The structures of 3-cyanopyrroles **1c** and **13c** and the substitution pattern on the pyrrole ring were unambiguously confirmed by single-crystal X-ray diffraction analysis. The crystal structures of 3-cyanopyrroles **1c** (CCDC 2154839) and **13c** (CCDC 2154829) (Figure 5-3) combined with the NMR data (see supporting information) also confirmed the structures of pyrroles **13a-e, 14a**, **15a-b**, and **16a-b**.

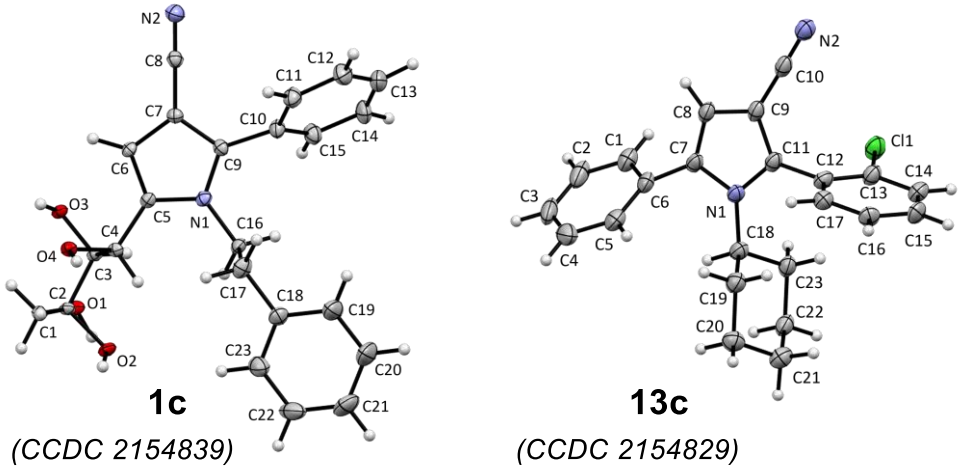
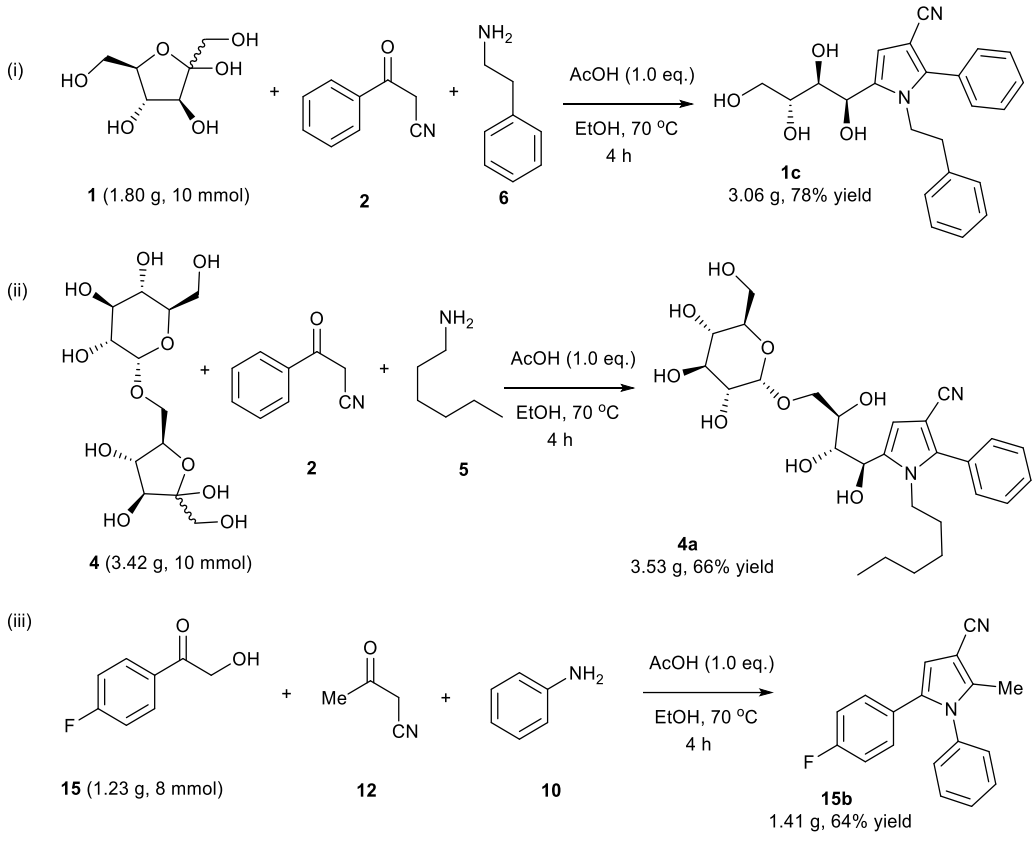


Figure 5-3. Single-crystal XRD of 3-cyanopyrroles 1c and 13c (displacement ellipsoids are drawn at the 50% probability level).

5.4 Large-scale reactions

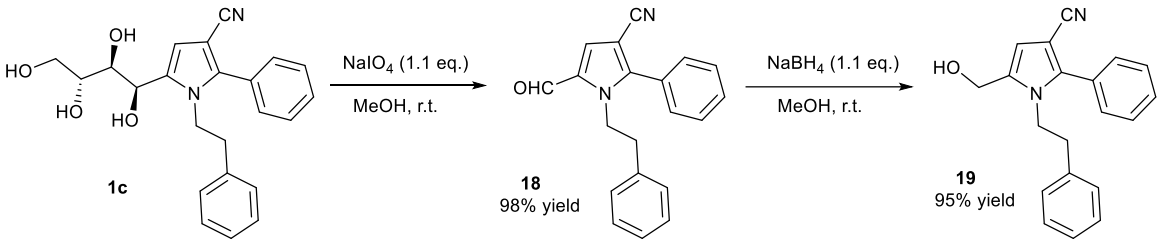
To examine the practicality of this one-step synthesis, the reactions were conducted using 8-10 mmol of the α-hydroxyketones. D-(+)-Fructose **1** (1.80 g, 10 mmol), benzoylacetonitrile **2,** and benzylamine **3** reacted to give 3-cyanopyrrole **1c** in 78% isolated yield (Scheme 5-1, (i)). Similarly, isomaltulose **4** (3.42 g, 10 mmol), benzoylacetonitrile **2,** and hexylamine **5** reacted to give 3-cyanopyrrole **4a** in 66% isolated yield (Scheme 5-1, (ii)). Additionally, 1-(4-fluorophenyl)-2-hydroxyethan-1-one **15** (1.23 g, 8 mmol), 3-oxobutanenitrile **12** and aniline **10** reacted to give 3-cyanopyrrole **15b** in 64% isolated yield (Scheme 5-1, iii). All large-scale reactions worked smoothly and selectively to give the desired 3-cyanopyrroles which demonstrated the potential of this route even on a larger scale.



Scheme 5-1. Large-scale reactions for the synthesis of 3-cyanopyrroles 1c, 4a, and 15b.

5.5 Structural modification of the synthesized pyrroles

The polyhydroxyalkyl chains of 3-cyanopyrroles **1a-j** are useful handles for easy modifications into other functional groups. For example, the polyhydroxyalkyl chain of pyrrole **1c** was oxidized effectively using sodium periodate to an aldehyde moiety thus generating 5-formyl 3-cyanopyrroles **18** in 98% yield (Scheme 5-2).[203, 217] Further, reduction of the formyl group of **23** using sodium borohydride gave 5-hydroxymethyl 3-cyanopyrroles **19** in 95% yield (Scheme 5-2).[218] Both the aldehyde and hydroxyl groups can be used for homologation reactions or transformations to other functional groups. The 5-formyl and 5-hydroxymethyl groups are important functional substitutions that enable further modifications of 3-cyanopyrroles to become bioactive molecules or natural products.[32, 202]



Scheme 5-2. Modification of the polyhydroxyalkyl chain of 3-cyanopyrroles 1c to give 3-cyanopyrroles 18 and 19.

5.6 Mechanistic considerations

Plausible reaction pathways are shown in Figure 4. In path A, the AcOH-catalyzed reaction between the α-hydroxyketones and amines gives the imine intermediate **I** which tautomerizes to intermediate **II**. The reaction of **II** with oxoacetonitriles gives enaminone intermediate **III** which upon cyclization, and dehydration gives intermediate **IV**. Finally, the aromatization of **IV** gives the product (Figure 5-4, path A).[212] In path B, oxoacetonitriles react first with primary amines to give the enamine intermediate **V** which condenses with the α-hydroxyketones to give **VI**. Intermediate **VI** tautomerizes to **VII** which upon intermolecular cyclization and loss of water gives **VIII**. Aromatization of **VIII** then gives the product (Figure 5-4, path B). In path C, the condensation between oxoacetonitriles and α-hydroxyketones gives

intermediate **IX** which upon condensation with the primary amines gives intermediate **X** which isomerizes to intermediate **XI**. The product was formed from intermediate **XI** after intramolecular cyclization, dehydration, and aromatization (Figure 5-4, path C).

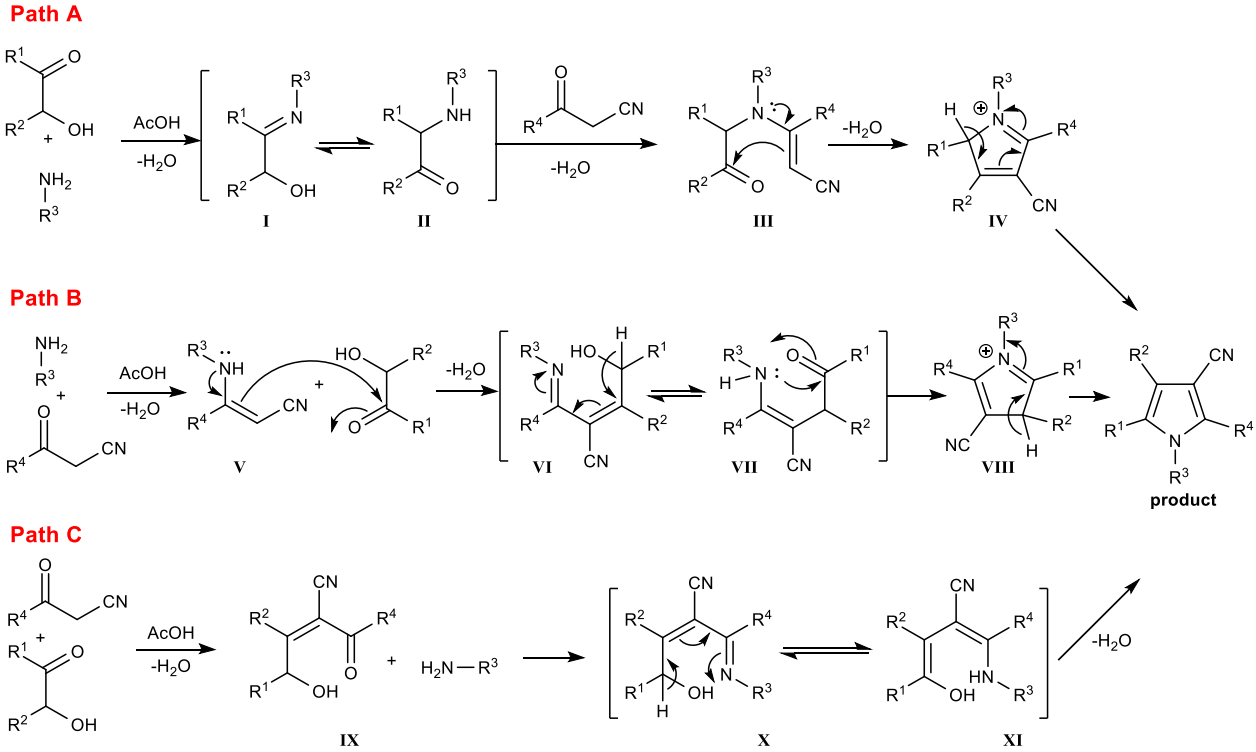


Figure 5-4. Proposed mechanism for the formation of functionalized 3-cyanopyrroles.

In all three pathways, the reaction proceeded with very high atom efficiency. Water was the only molecule lost during this three-component reaction.

5.7 Conclusion

In summary, we established an efficient and simple three-component reaction between α-hydroxyketones, oxoacetonitriles, and primary amines to selectively give densely functionalized 3-cyanopyrroles in 55-90% isolated yields. The structure and the substitution pattern of the products were unambiguously confirmed by single-crystal X-ray analysis. The practicality of this method was demonstrated on large-scale syntheses of several pyrroles. Currently, we are expanding the scope of this reaction and using the process to synthesize

different pyrrole-based drug candidates and intermediates such as the anti-tuberculosis drugs BM212, BM521, and BM533.

5.8 Experimental Section

5.8.1 Materials and methods

All chemicals and AR grade solvents were obtained from Sigma-Aldrich, Merck or Alfa Aesar and were used as received without further purification. IR spectra were recorded using Bruker MPA FT-IR machine. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance DPX 300 or recorded at 400 MHz Bruker Avance III 400 (BBFO 400). ^{13}C NMR spectra were recorded at 75.47 MHz on a Bruker Avance DPX 300 or recorded at 101 MHz Bruker Avance III 400 (BBFO 400). Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. HRMS were measured using a hybrid Quadrupole Time-of-Flight (Q-TOF) on Qstar XL MS/MS system. LC-MS spectra were recorded using Agilent 6530 LC-MS. Single-crystal X-ray crystallographic analysis was done using Bruker D8 Quest. Analytical TLC was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness). The plates were visualized using UV radiation (254 nm) or stained in ceric ammonium sulfate solution with heating to detect the reaction spots. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). All NMR spectra and other data are listed in Appendix.

Chapter 6. Conclusion and Future Prospects

6.1 Research outcome and conclusions

This thesis developed direct, practical, and efficient routes for converting carbohydrates into nitrogen heterocycles in one-pot three-component fashion under mild conditions with high selectivity and atom economy.

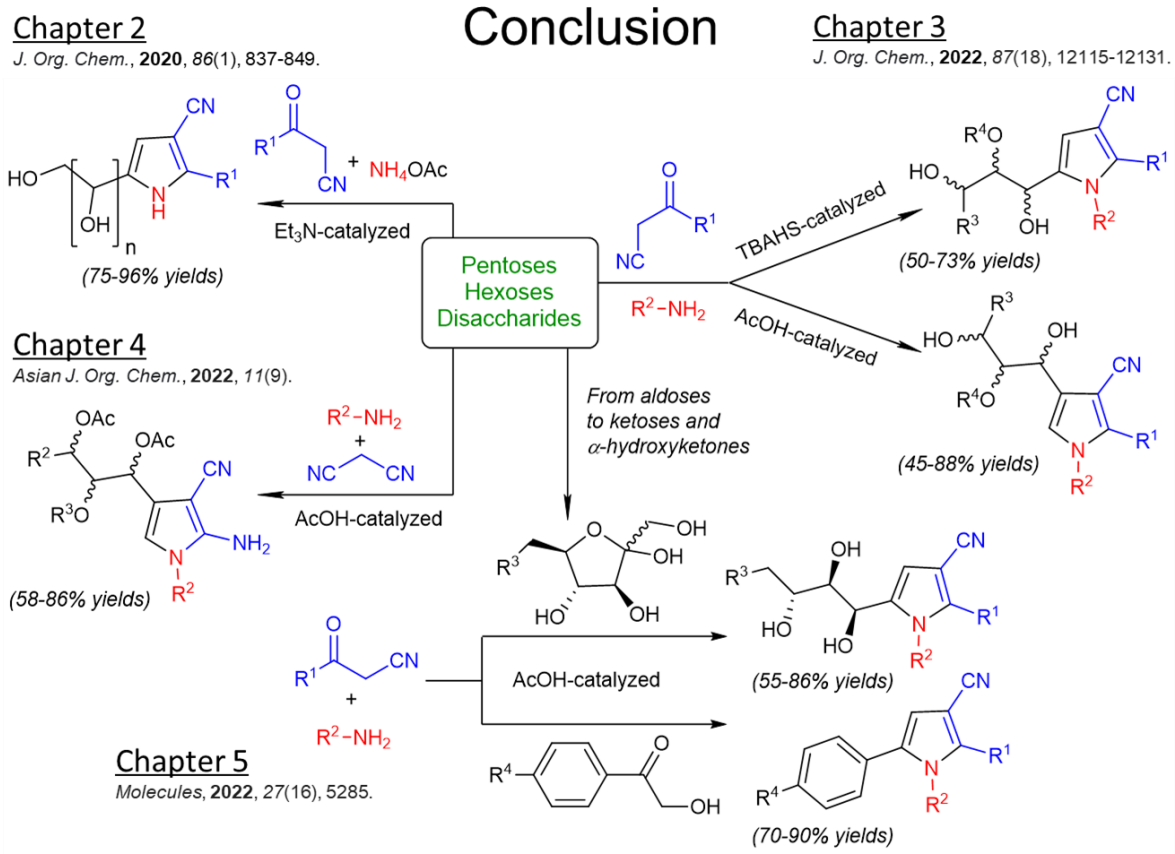


Figure 6-1. Summary of Chapter 2-5.

In the first work (chapter 2), a three-component reaction that synthesized 2,3,5-poly-substituted *N*-unsubstituted pyrroles from common carbohydrates, oxoacetonitriles, and ammonium acetate was reported. This is a metal-free reaction with great regio- and stereo-selectivities and high yields (75-95%), catalyzed by simple Et_3N. This reaction proceeded smoothly with a variety of substrates, including various mono- and di-saccharides, as well as oxoacetonitriles. To exhibit the industrial potential of this method, two-gram scale reactions were done on D-ribose and D-maltose, and no obvious decrease was shown in the yields. All products

were demonstrated with an open sugar chain at the 5- position, which enabled further oxidation, reduction, addition, and cyclization to give vital pyrrole intermediates such as 5-formyl pyrrole, 5-hydroxymethyl pyrrole, 5-*C*-glycoside pyrrole, and bicyclic pyrrole. A plausible mechanism was proposed and evidenced by LC-MS. This approach provides a simple and efficient way of pyrrole synthesis from cheap carbohydrates.

In the second work (chapter 3), two three-component cascade *N*-substituted pyrrole synthesis protocols from unactive carbohydrates, oxoacetonitriles, and primary amines were described. The two protocols could lead to 2,3,5- or 2,3,4- substituted pyrrole products, respectively, by simply changing the adding sequence of the starting materials and catalysts. Adequate substrates were tested through the reactions, including several aldoses, and alkyl, allyl, cyclohexyl, benzyl, and aromatic amines. Single-crystal X-ray analysis demonstrated the absolute configuration of both groups of products, and reasonable mechanisms were presented.

The third work (chapter 4) discussed an AcOH-catalyzed one-pot 2-amino-3-cyano-4-poolyhydoxylalkyl pyrrole synthesis procedure from sugars, malononitrile, and primary amines. This method overcomes the problem that sugars react extremely fast with malononitrile to obtain furans and thus causes the difficulty of inserting amines by first forming a sugar-amine intermediate, followed by adding malononitrile. Because of the high polarity of products, the acetylation process was done in the same pot after the reaction for easier purification. This reaction produced high yields of 58-86% from eleven mono- and di-saccharides and demonstrated excellent yield on a four-gram scale. The reaction mechanism was proven by both LC-MS and NMR spectroscopy, and modifications of the 2-amino-3-cyano products were done to demonstrate their potential for developing medical molecules.

The fourth work (chapter 5) established an efficient and simple three-component reaction between α-hydroxyketones, oxoacetonitriles, and primary amines to selectively give densely functionalized 3-cyanopyrroles in 55-90% isolated yields. The structure and the substitution

pattern of the products were unambiguously confirmed by single-crystal X-ray analysis. The practicality of this method was demonstrated on large-scale syntheses of several pyrroles. Currently, we are expanding the scope of this reaction and using the process to synthesize different pyrrole-based drug candidates and intermediates such as the anti-tuberculosis drugs BM212, BM521, and BM533.

The routes we have developed has the following advantages (i) efficient one-pot reactions, simple procedures, high yields, and exclusive regio- and stereo selectivities were obtained; (ii) the use of expensive amino sugars and metal catalysts was avoided; (iii) broad substrate scope; (iv) pyrrole derivatives with an open sugar chain were obtained, and useful modifications were demonstrated; (v) plausible mechanisms were proposed and evidence provided by NMR and LC-MS

6.2 Future prospects

We have made an important step for the synthesis of nitrogen heterocycles from carbohydrates. To make further impact, and based on the studies and observation from our work, we propose the following future work:

1. When using aniline as the reactive amine, not all methods worked smoothly, and new type of compounds were observed. Aniline and its derivatives are an important group of amines which brings aromatic rings. Previously, we attempted to use strong Lewis acid such as $In(OTf)_3$ to promote the reaction between D-glucose, oxoacetonitriles, and aniline. However, the tricyclic product, (2*R*,3*S*)-2-(hydroxymethyl)-10-phenyl-3,4,5,10-tetrahydro-2*H*-pyrano[2,3-b]quinoxalin-3-ol or (2*R*,3*S*)-2-(hydroxymethyl)-5-phenyl-3,4-dihydro-2*H*,5*H*-10λ_2-pyrano[2,3-b]quinoxalin-3-ol was obtained unexpectedly. The structure was proposed using 1D and 2D NMR spectroscopy. In future work, the structure

should be confirmed, and the scope of the reaction should be explored. These scaffolds are new, and they could have interesting bioactivity.

2. Expansion of the reaction to form indoles such as 4,5,6,7-tetrahydro-1*H*-indole. This will potentially give rise to new methods and short protocols to indole synthesis. In our previous work, various α-hydroxyketones were successfully applied as starting materials in the pyrrole synthesis, and drug candidates were obtained in simple procedures. By switching common α-hydroxyketones to hydroxycyclohexanone dimer, substituted 4,5,6,7-tetrahydro-1*H*-indole can be provided in single step.
3. Application of the methodologies developed in this thesis to synthesize drug molecules and drug candidates such as COX-2 selective NSAID compounds and antituberculosis compounds BM212, BM521, and BM533.

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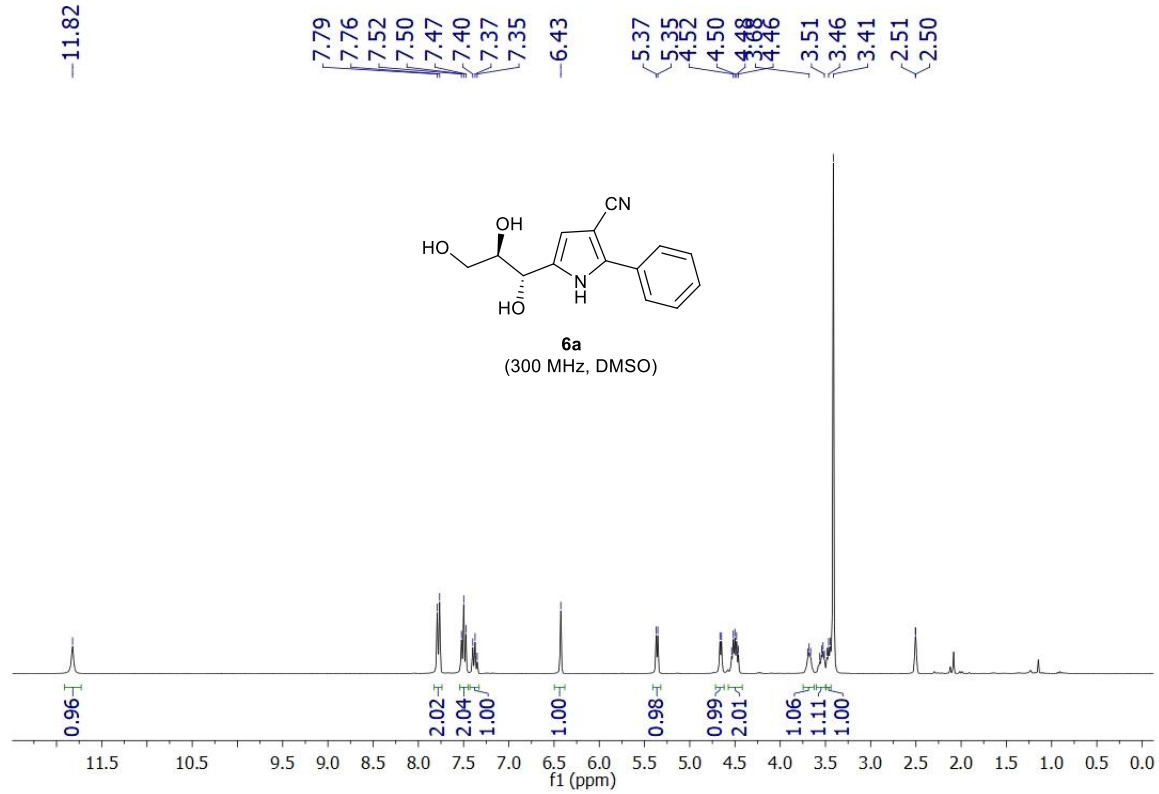
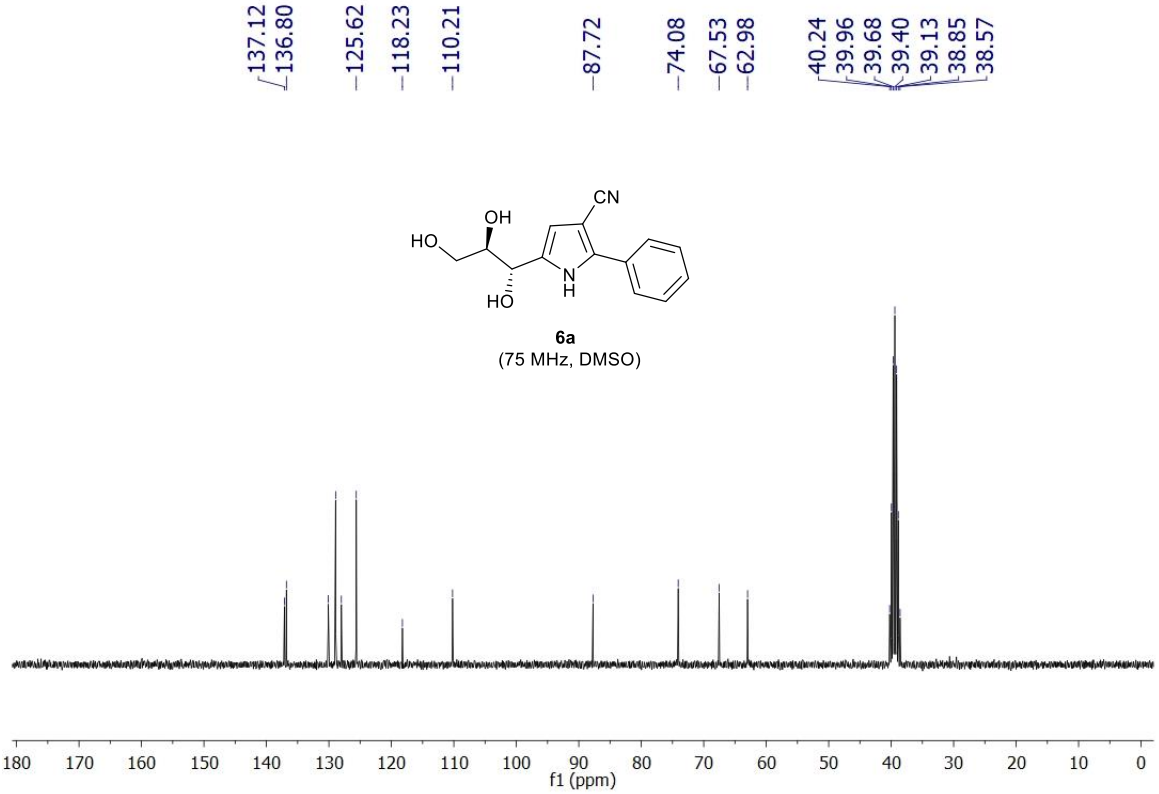
1. Supporting Information for Chapter 2

1.1 ^{1}H and ^{13}C NMR spectra

^{1}H and ^{13}C NMR spectra of **6a**

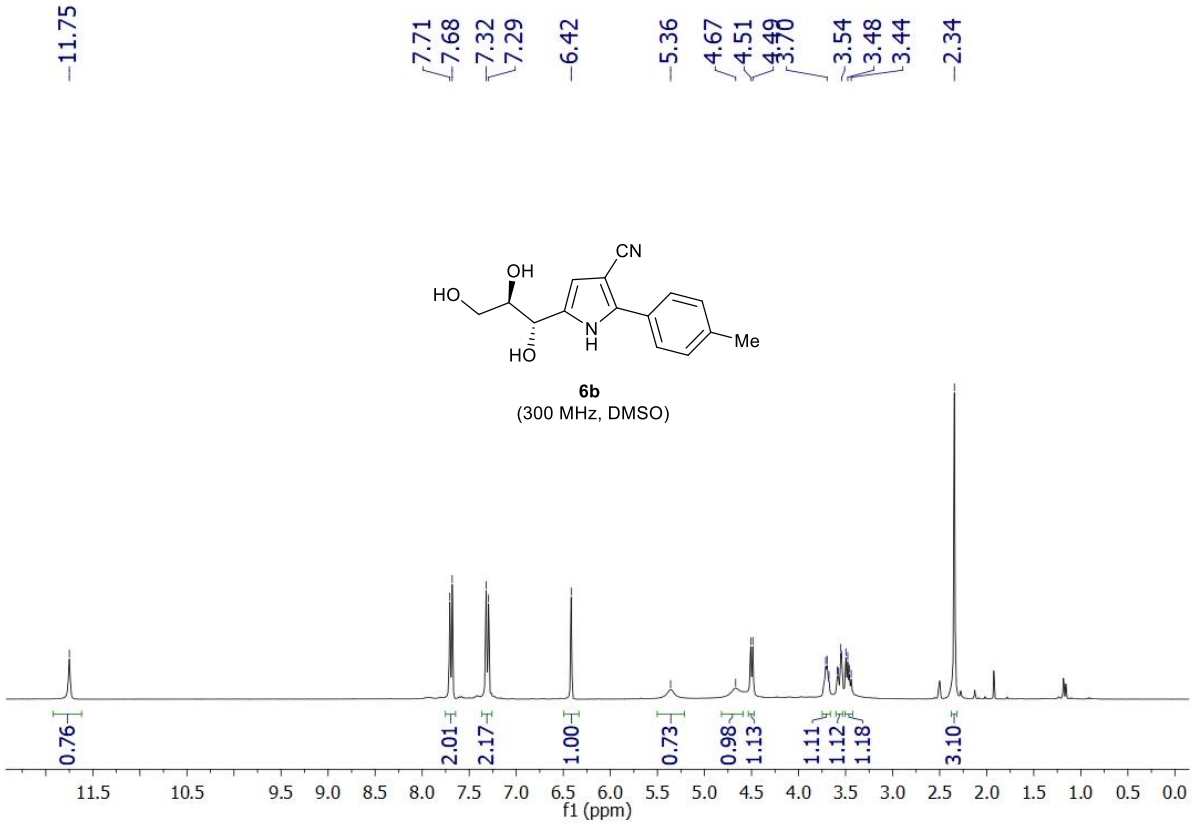


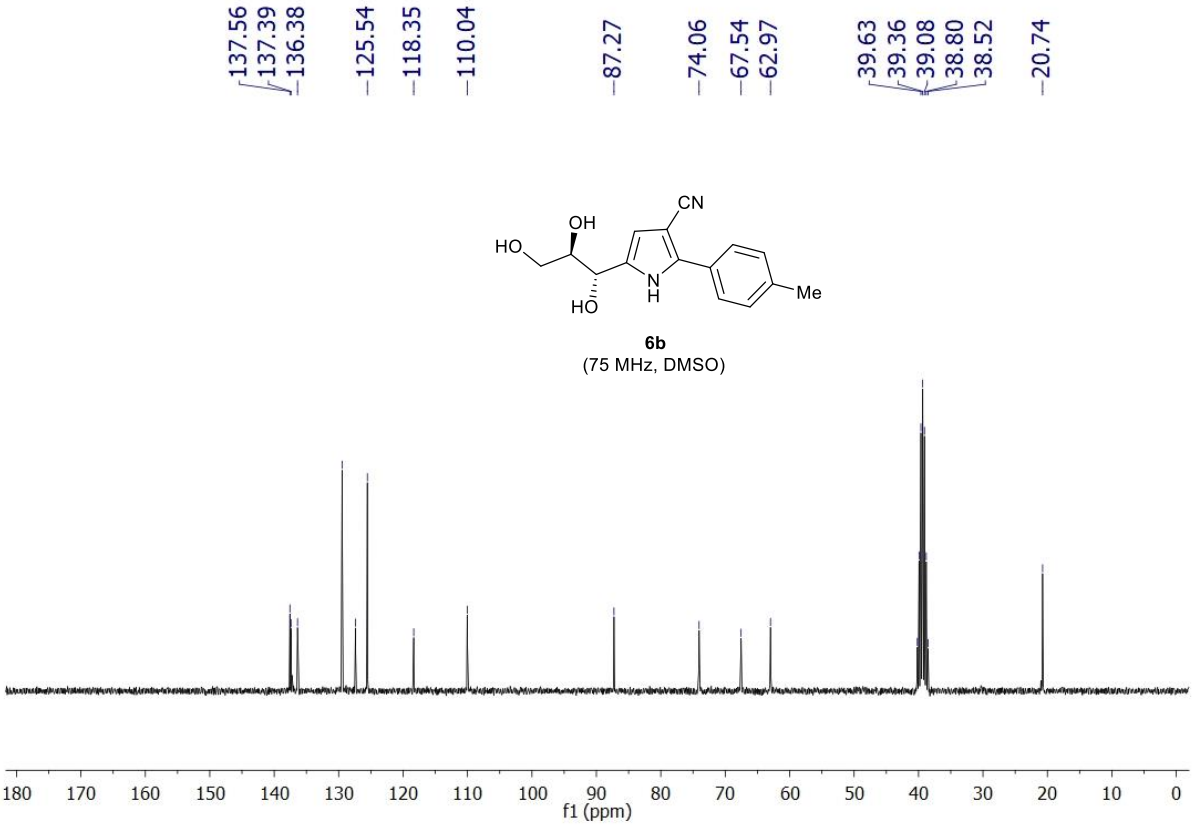
6a
(300 MHz, DMSO)



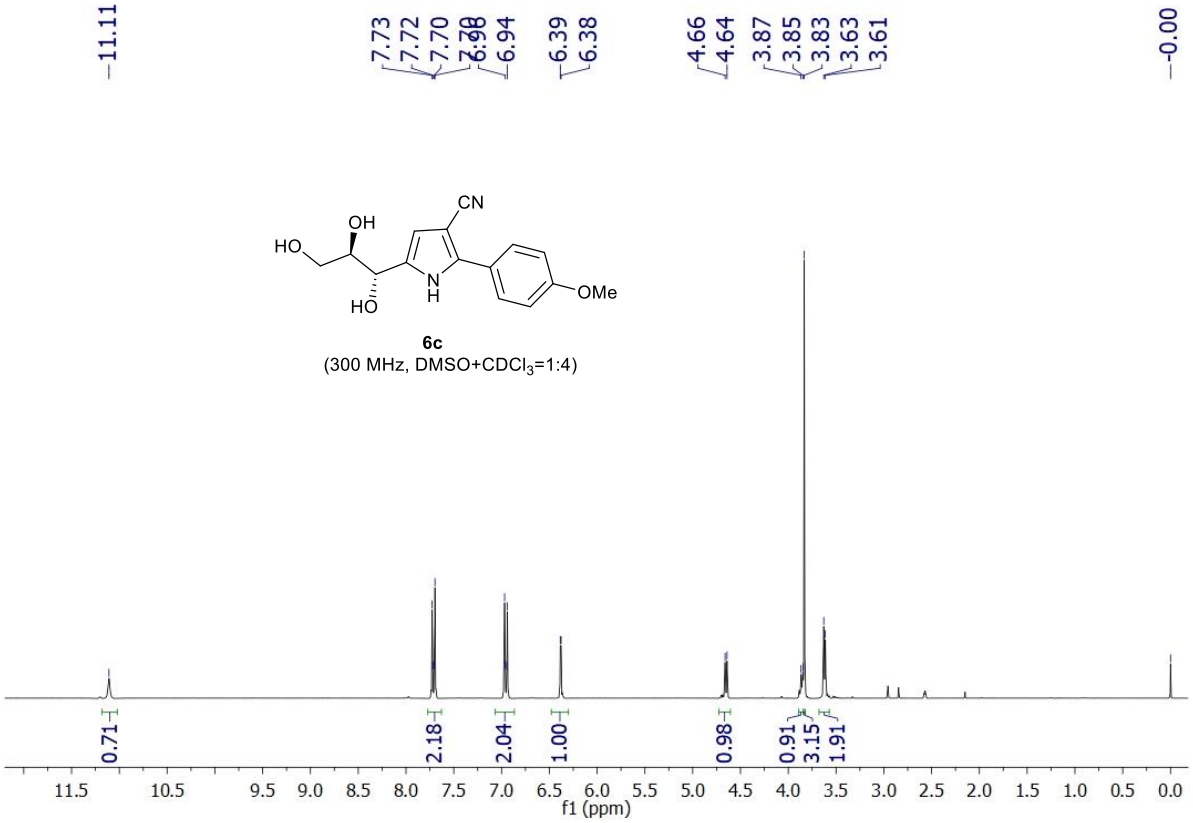
6a
(75 MHz, DMSO)

^{1}H and ^{13}C NMR spectra of **6b**

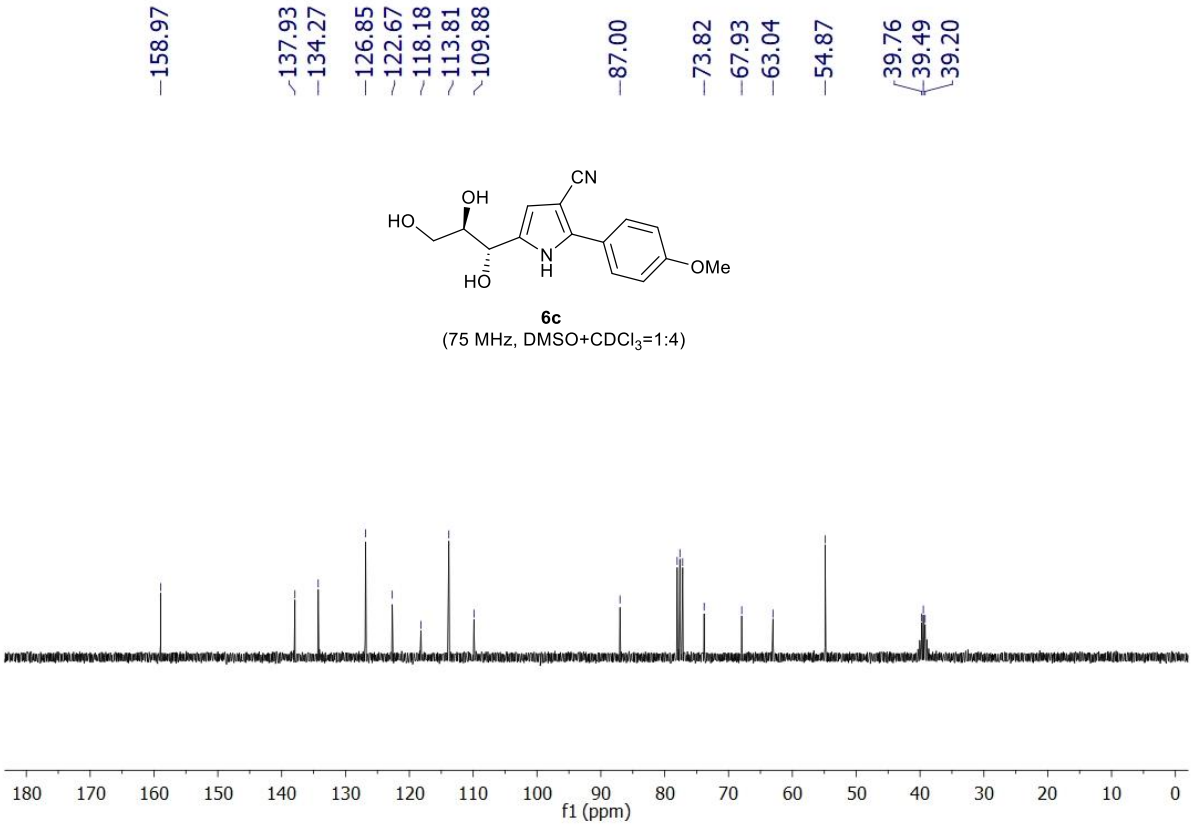




^{1}H and ^{13}C NMR spectra of **6c**

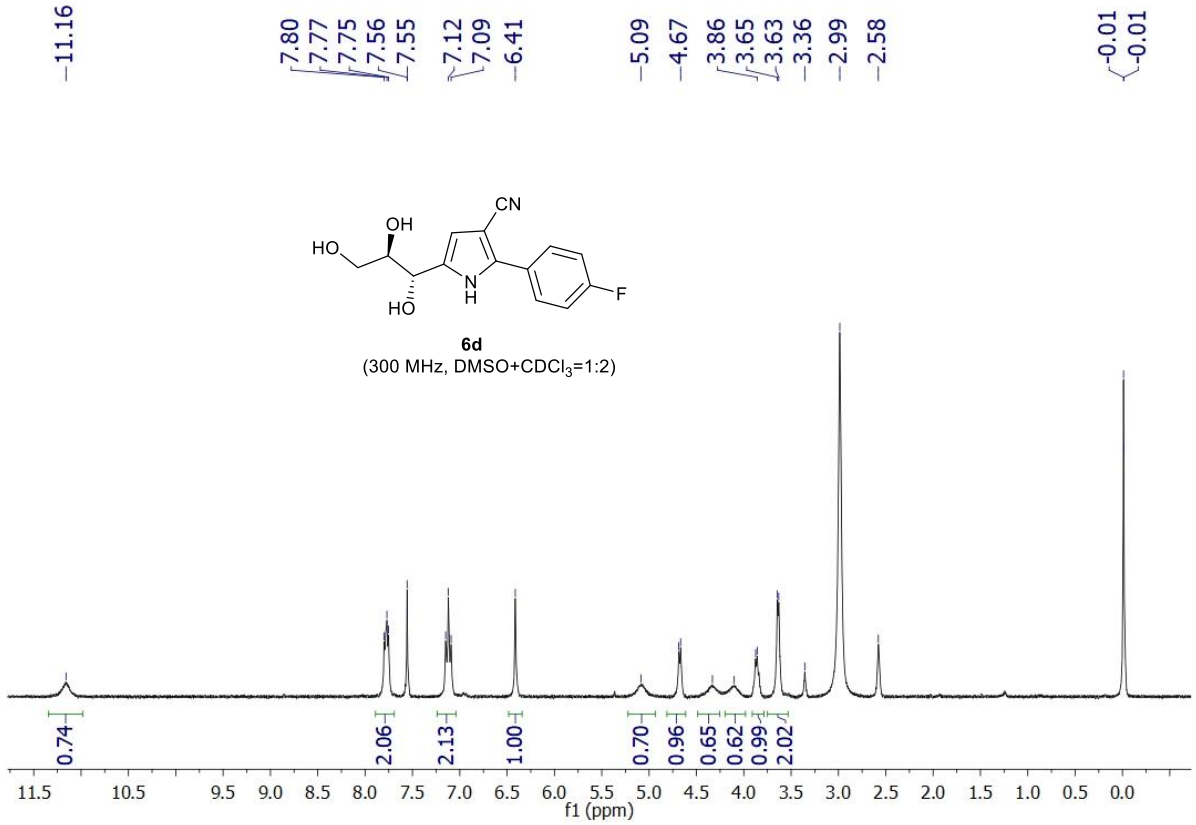


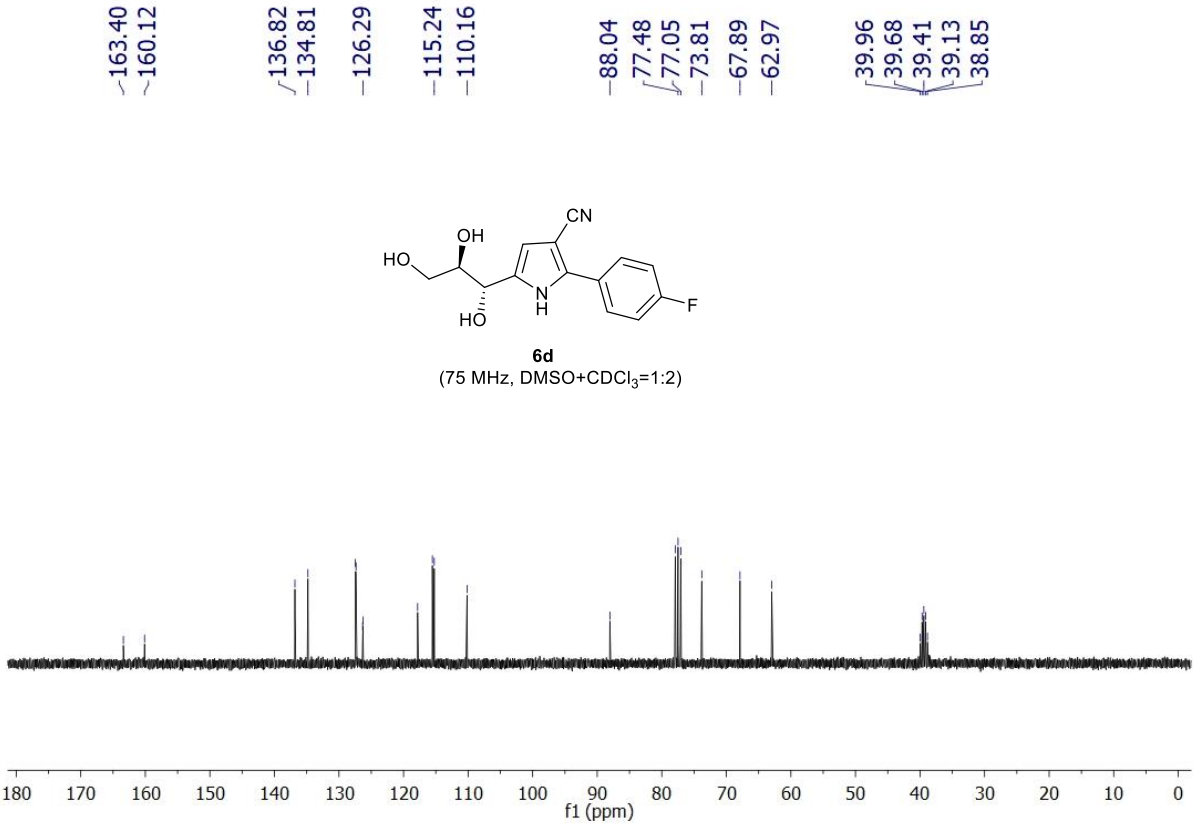
6c
(300 MHz, DMSO+$CDCl_3$=1:4)



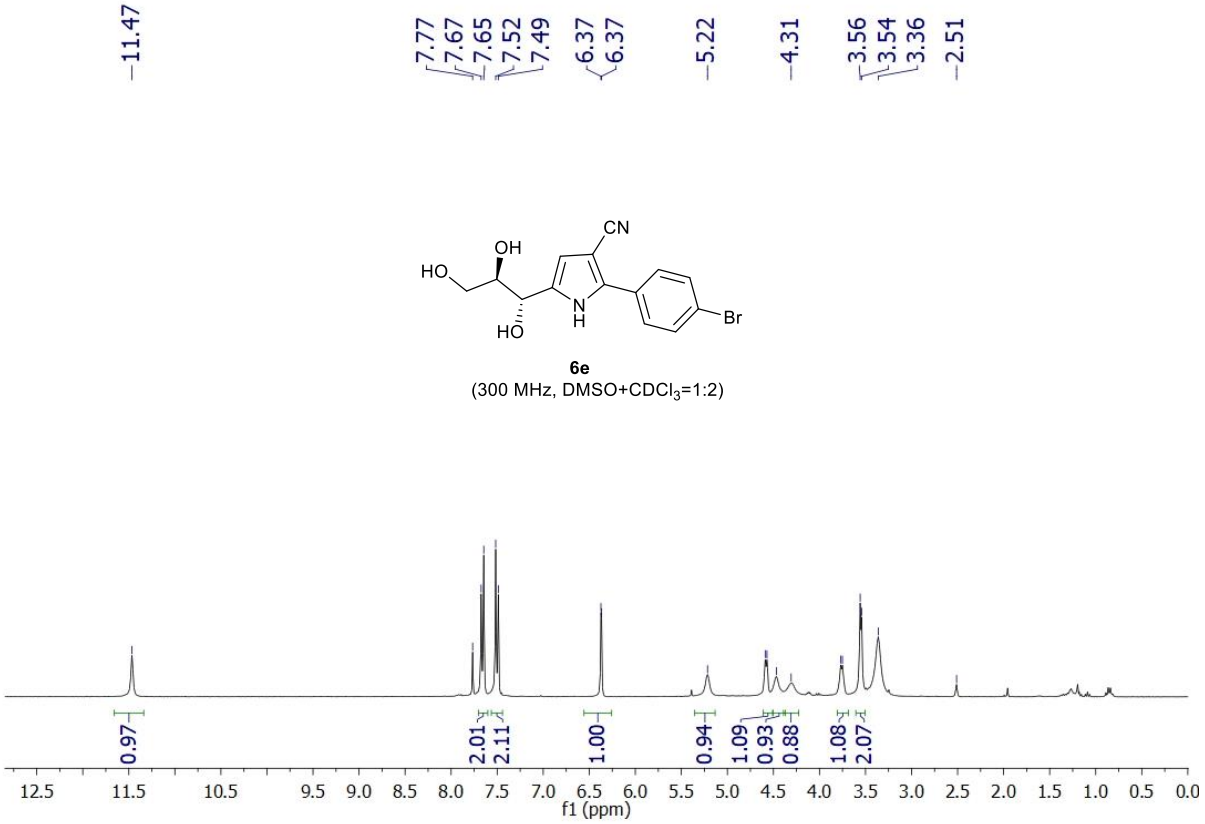
6c
(75 MHz, DMSO+$CDCl_3$=1:4)

^{1}H and ^{13}C NMR spectra of **6d**

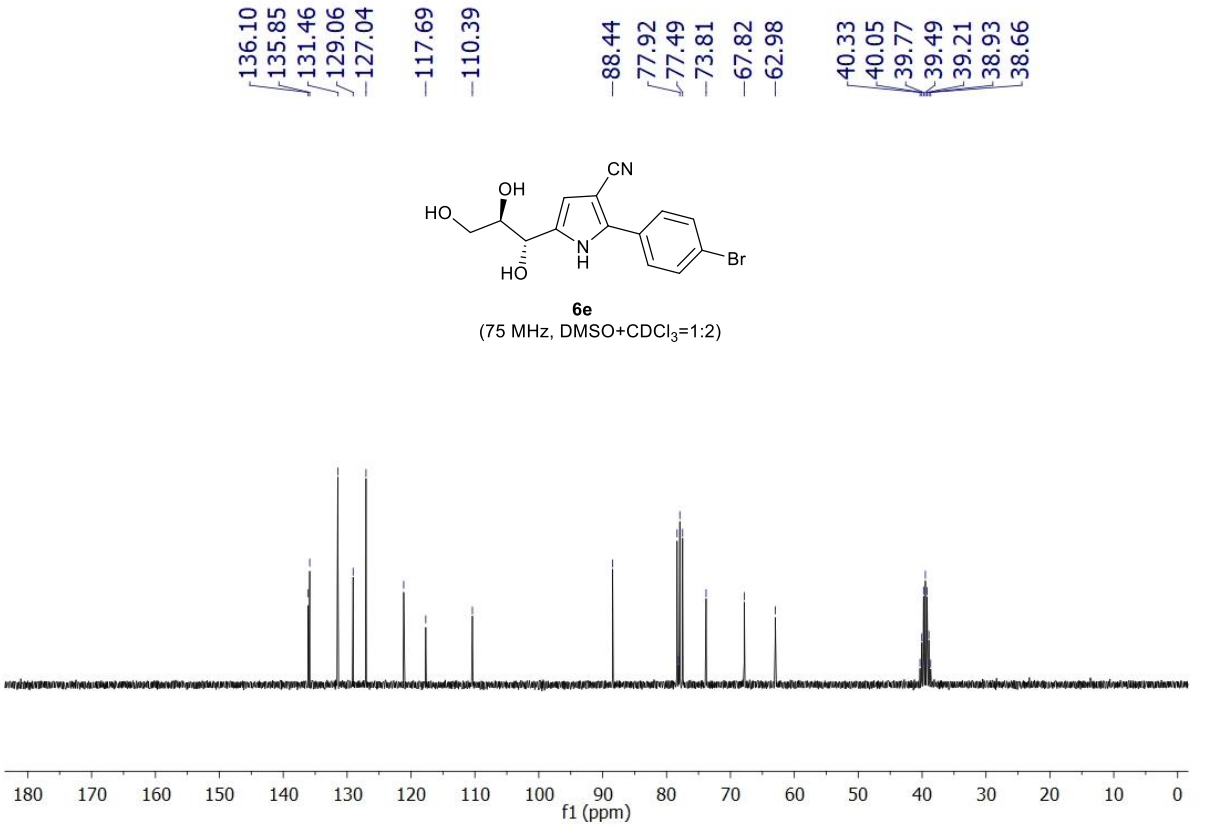




^{1}H and ^{13}C NMR spectra of **6e**

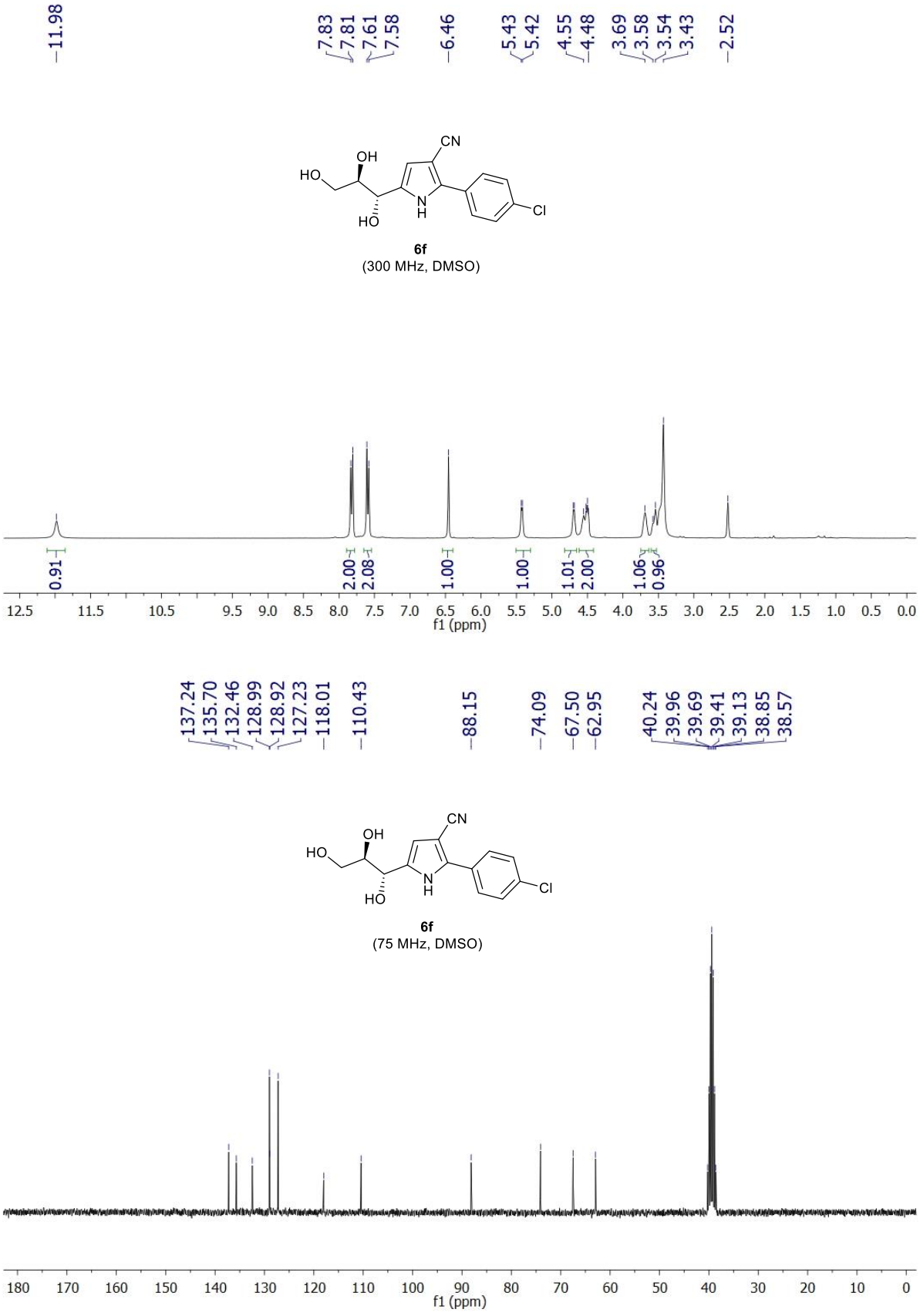


6e
(300 MHz, DMSO+$CDCl_3$=1:2)

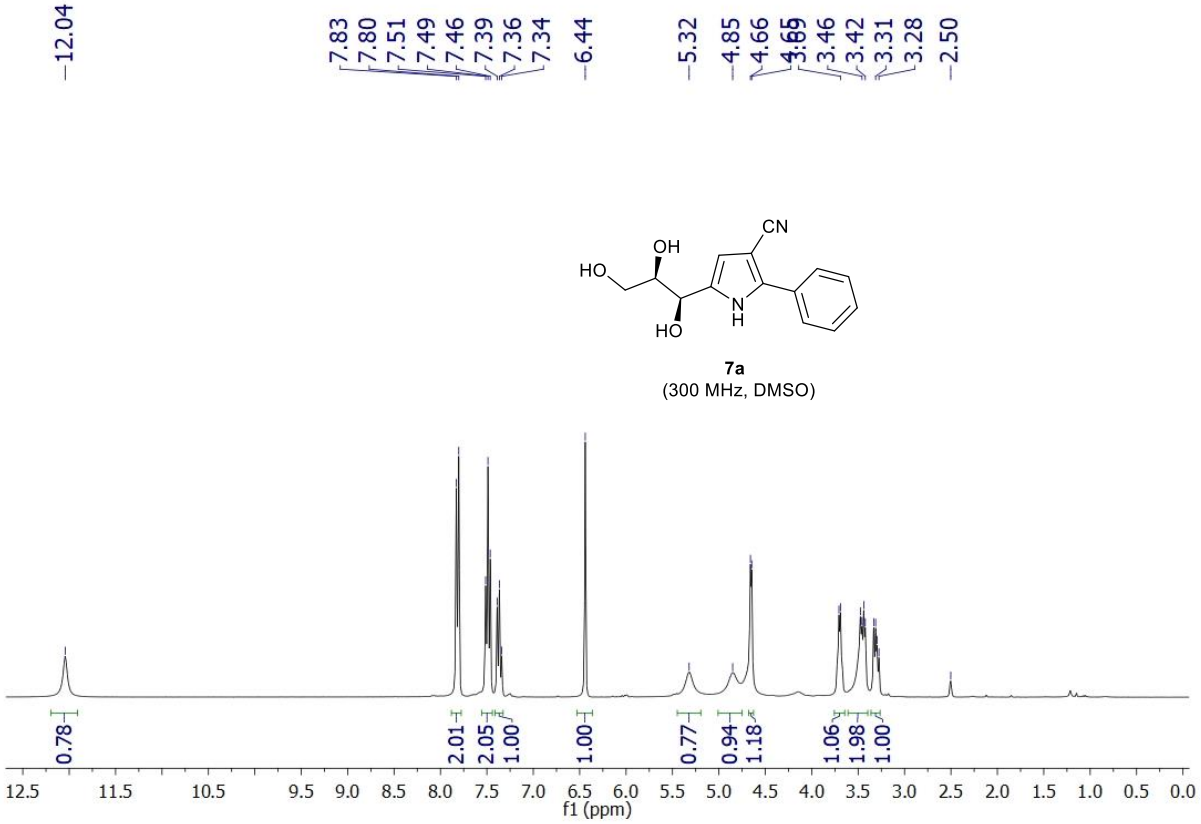


6e
(75 MHz, DMSO+$CDCl_3$=1:2)

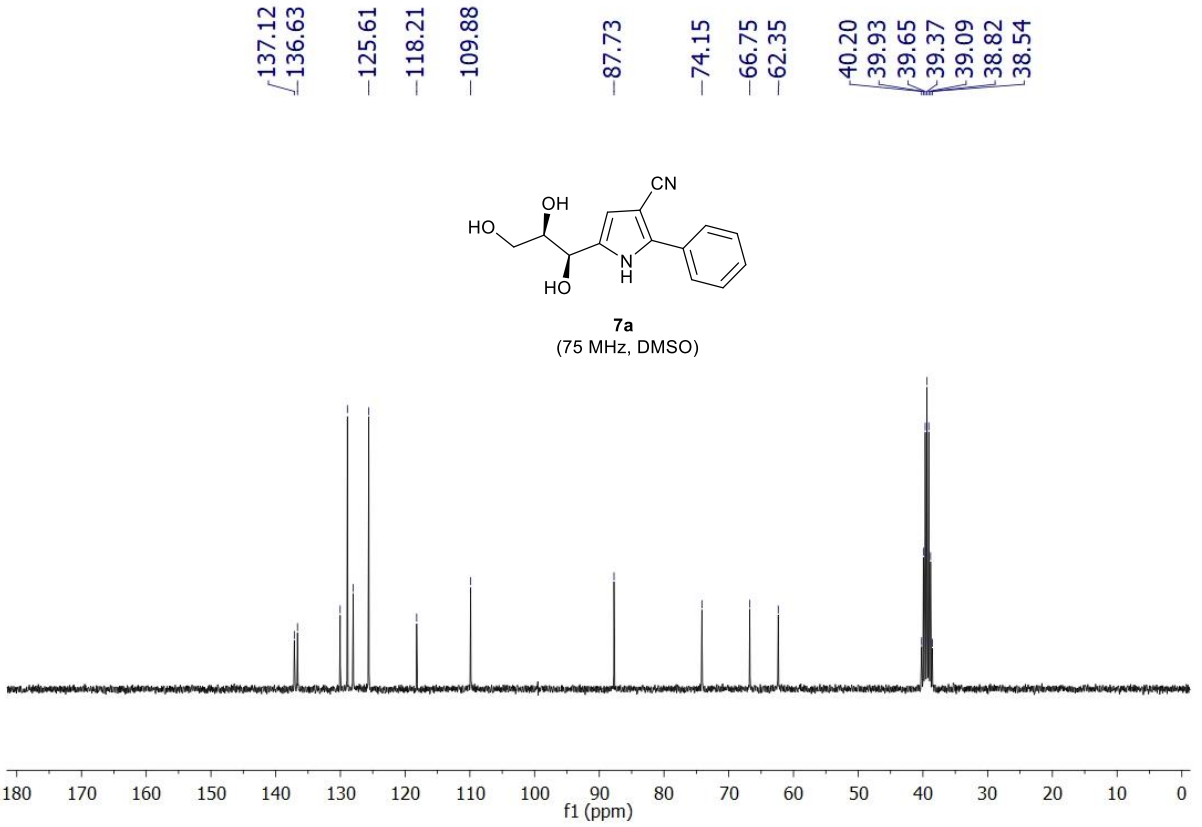
^{1}H and ^{13}C NMR spectra of **6f**



^{1}H and ^{13}C NMR spectra of **7a**

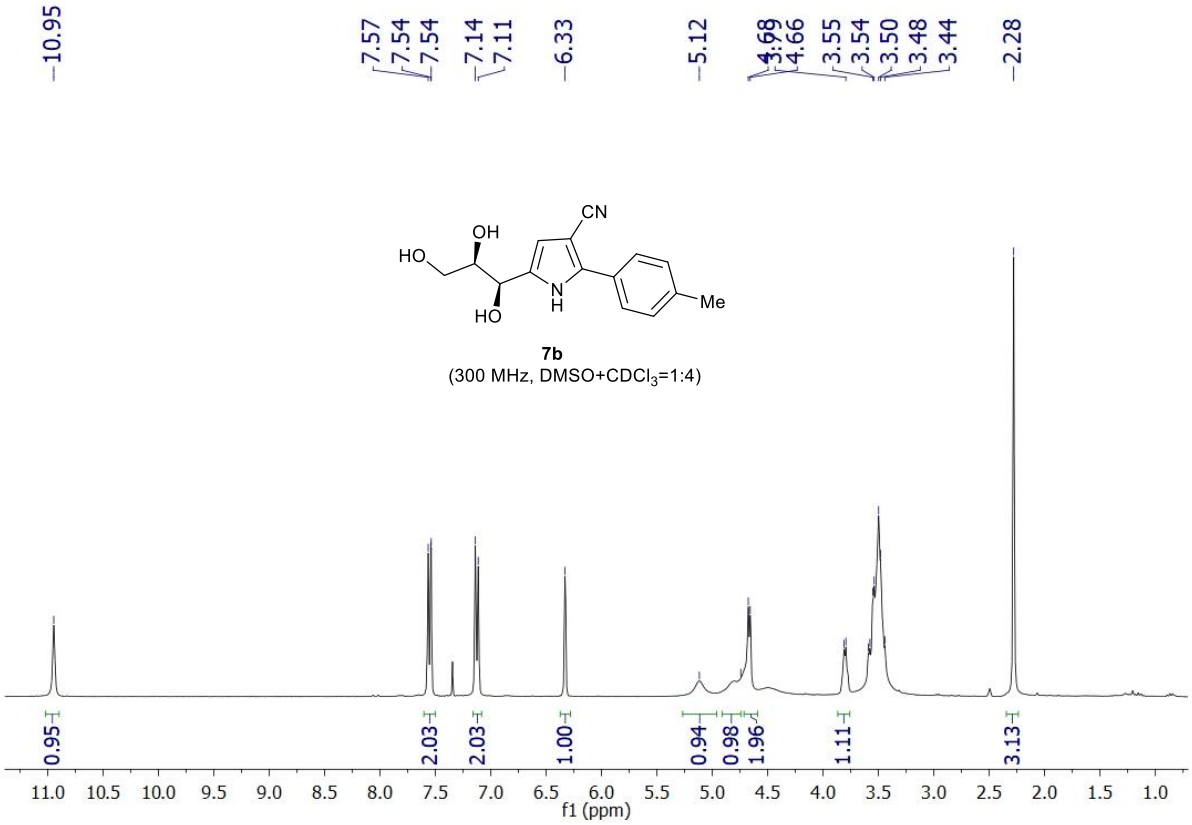


7a
(300 MHz, DMSO)

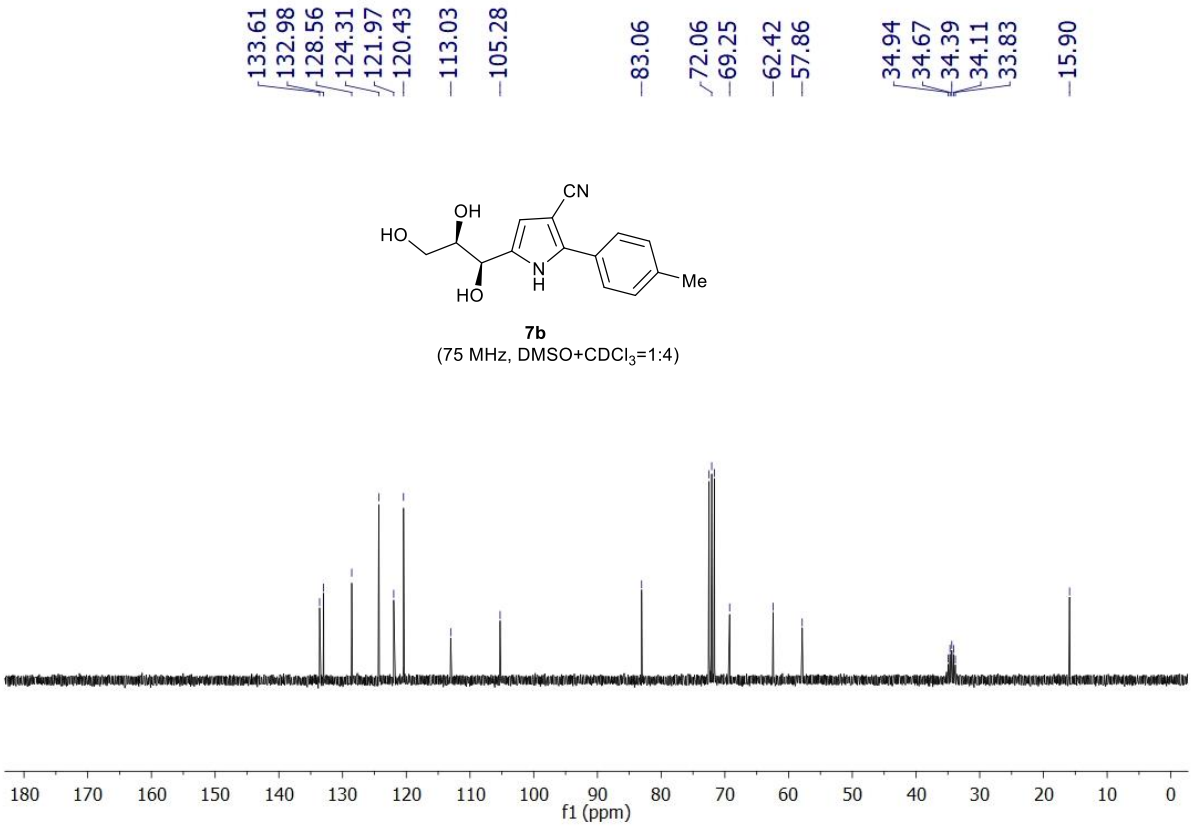


7a
(75 MHz, DMSO)

^{1}H and ^{13}C NMR spectra of **7b**

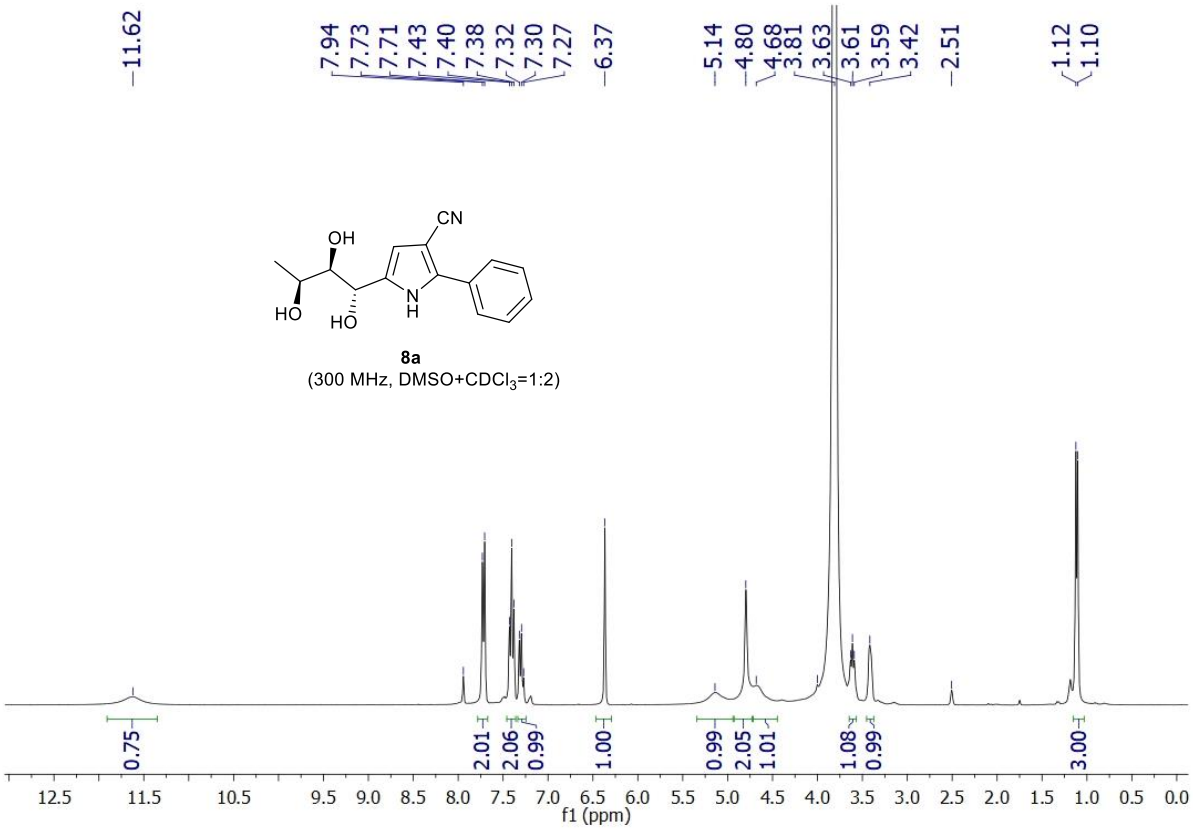


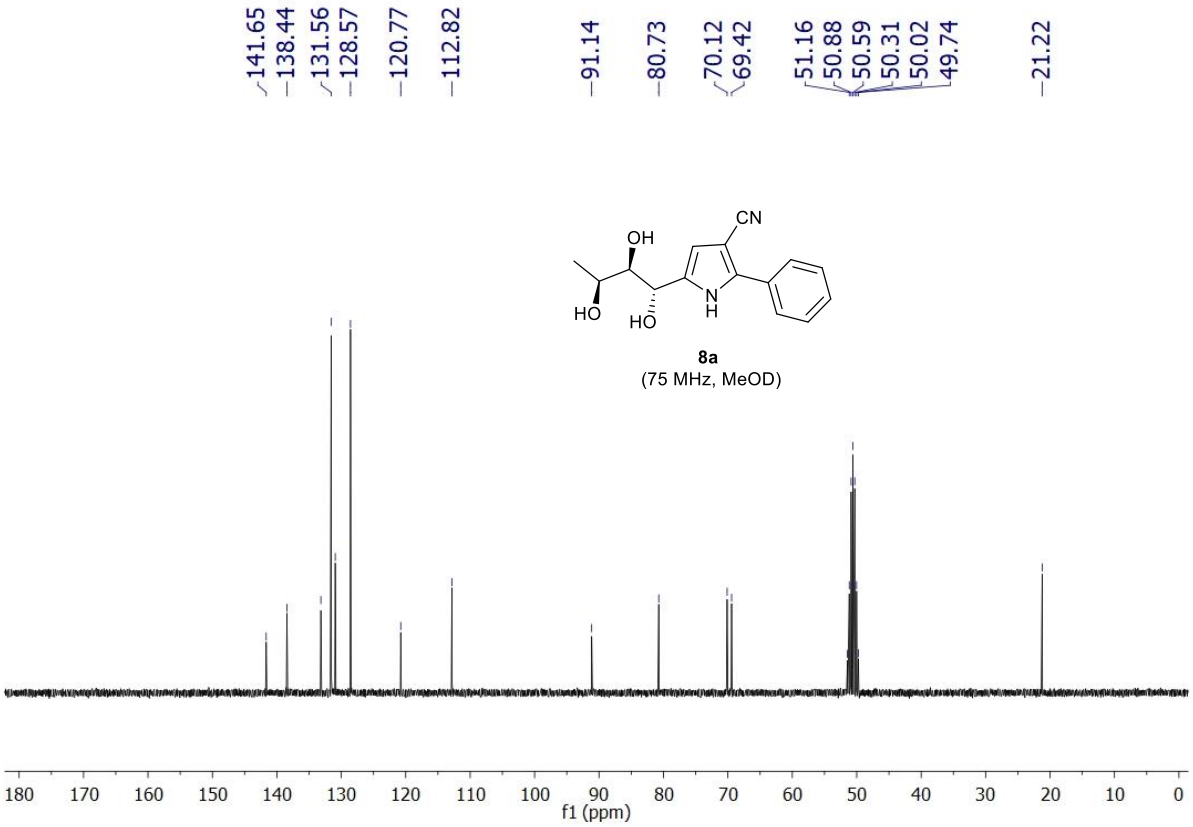
7b
(300 MHz, DMSO+$CDCl_3$=1:4)



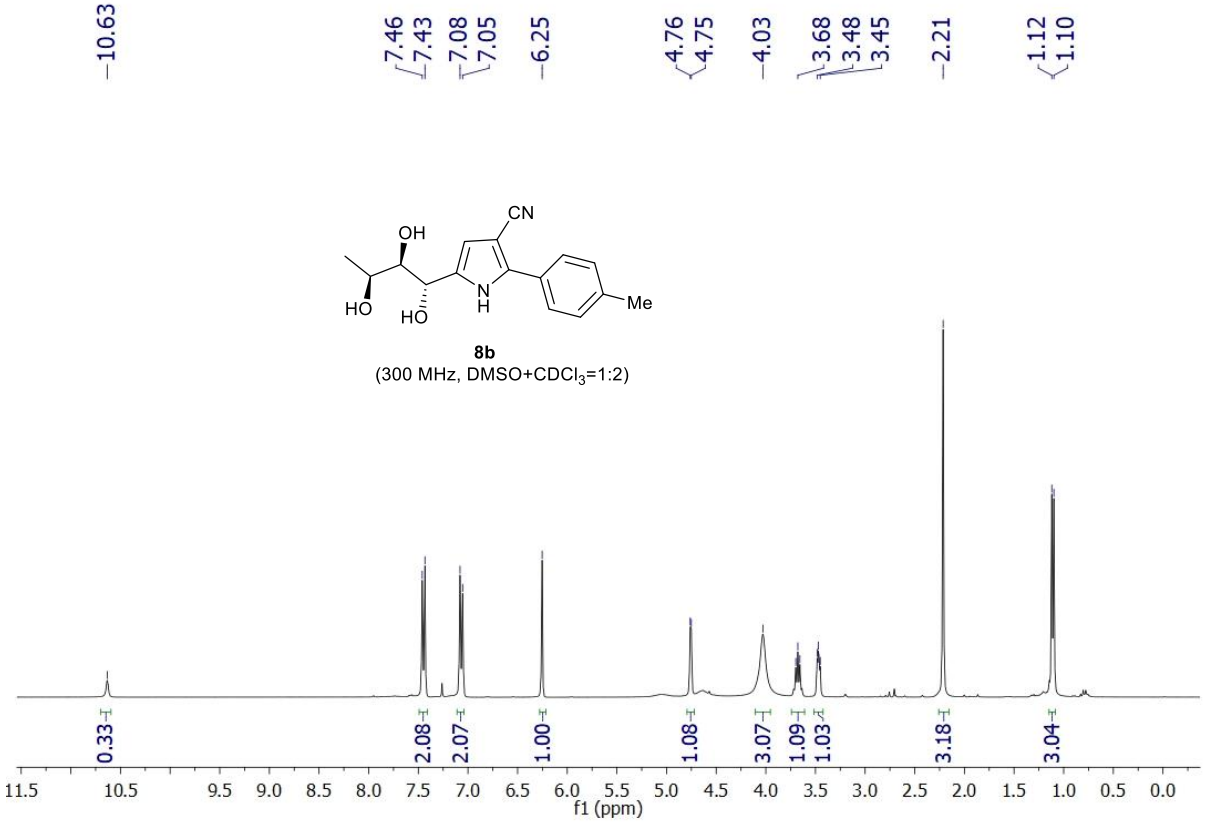
7b
(75 MHz, DMSO+$CDCl_3$=1:4)

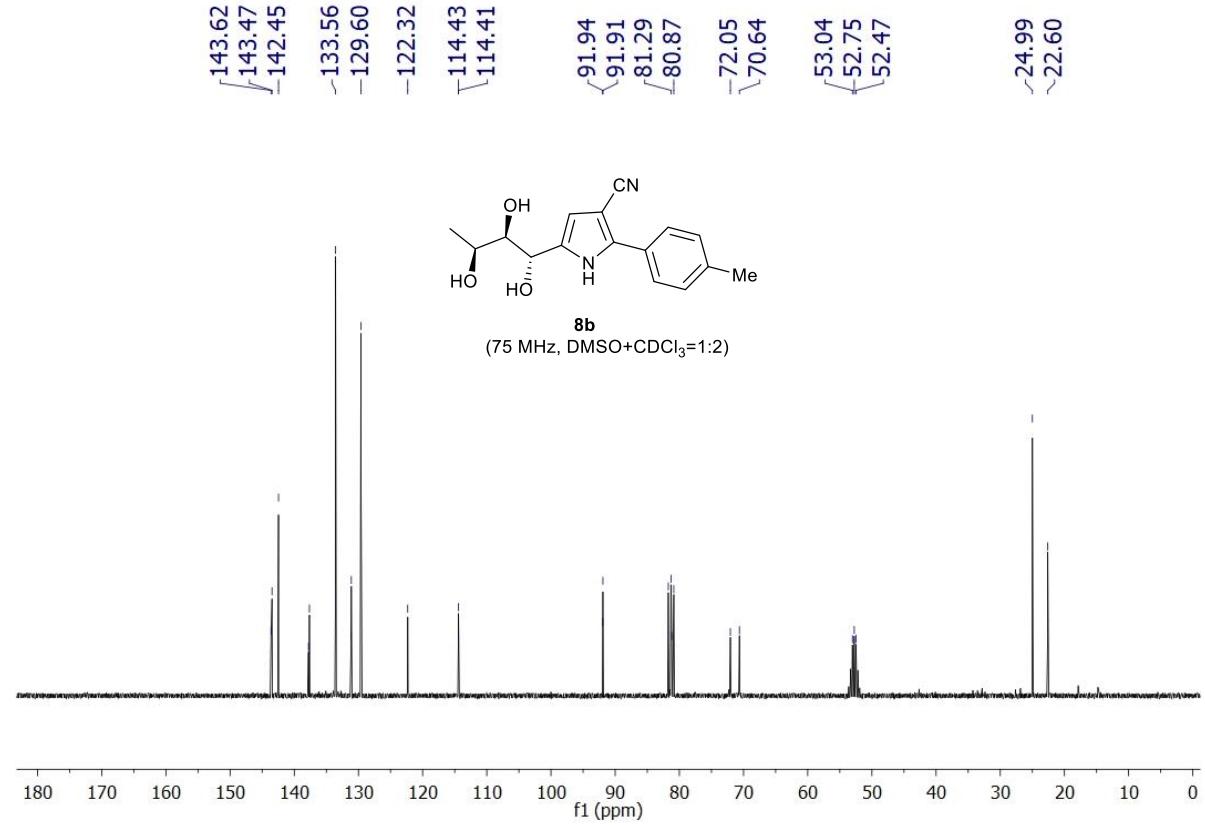
^{1}H and ^{13}C NMR spectra of **8a**



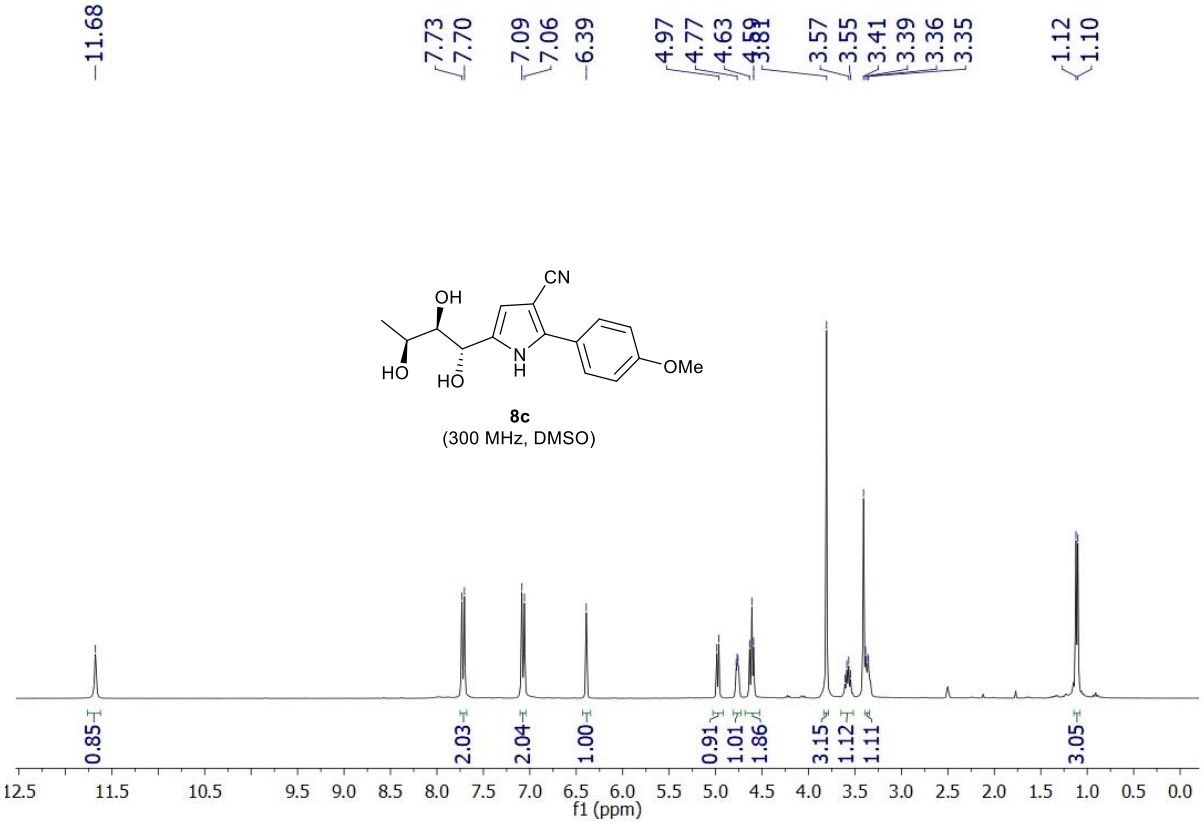


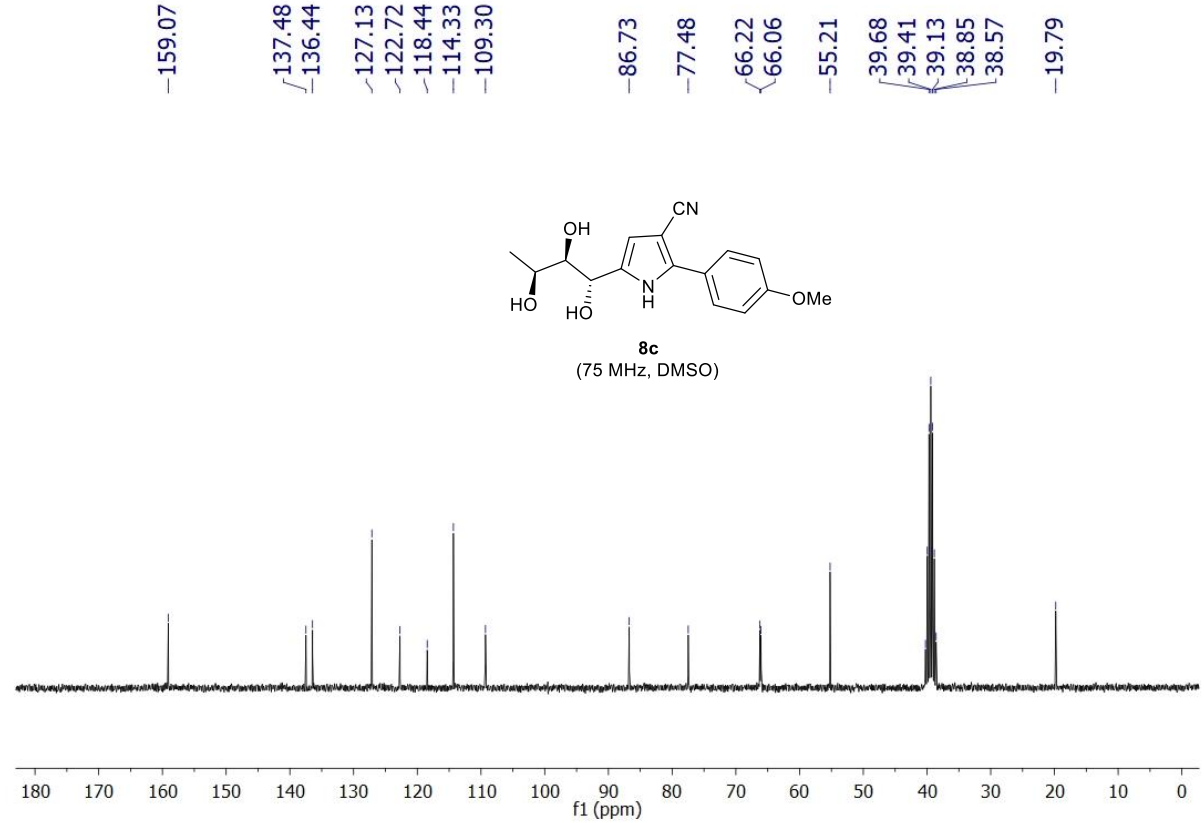
^{1}H and ^{13}C NMR spectra of **8b**



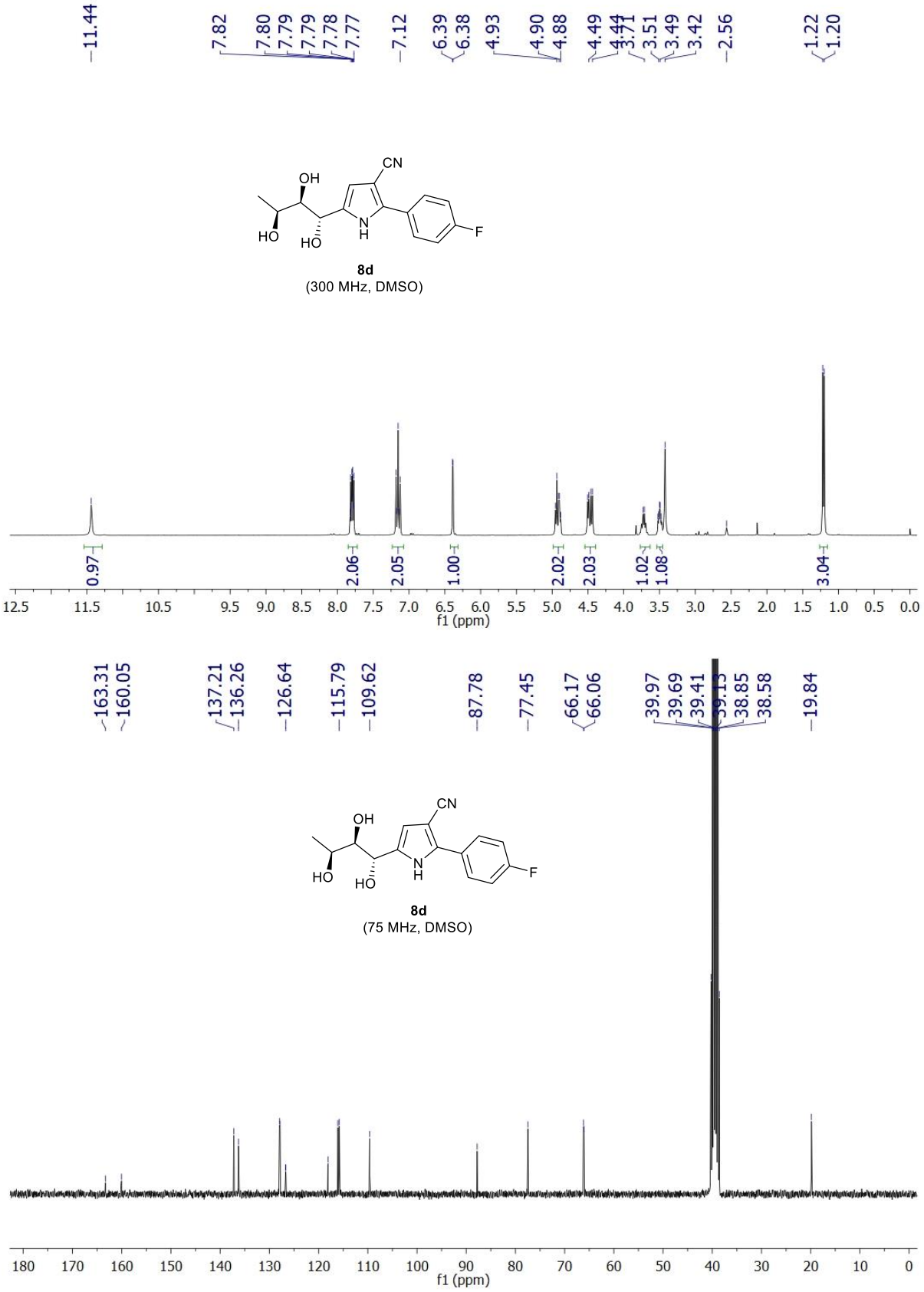


^{1}H and ^{13}C NMR spectra of **8c**

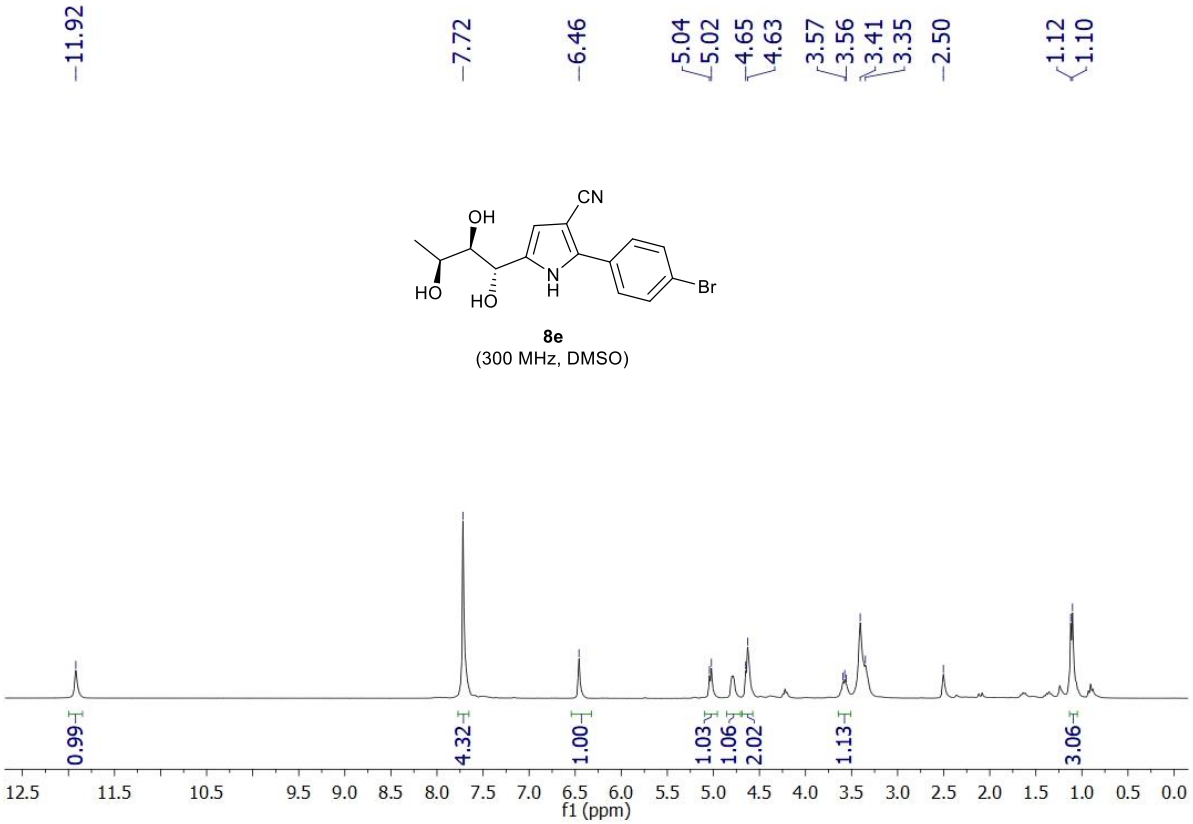




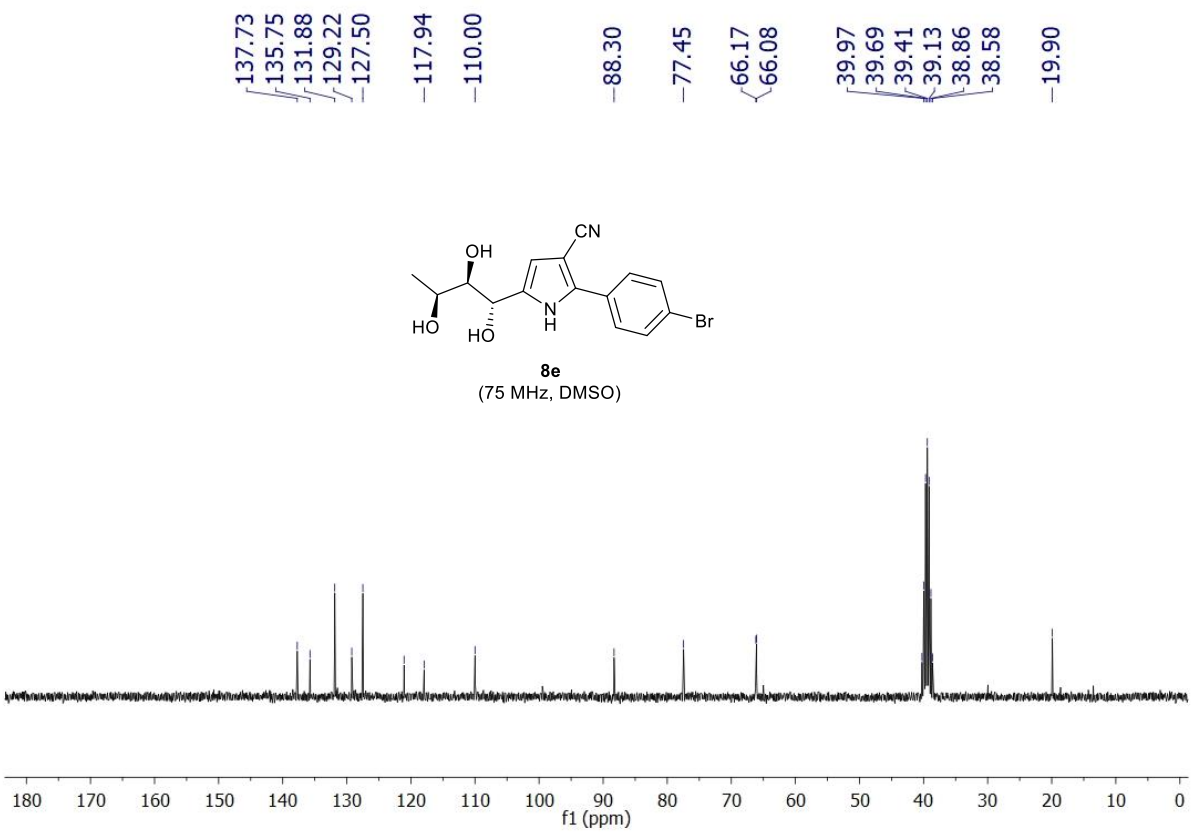
^{1}H and ^{13}C NMR spectra of **8d**



^{1}H and ^{13}C NMR spectra of **8e**

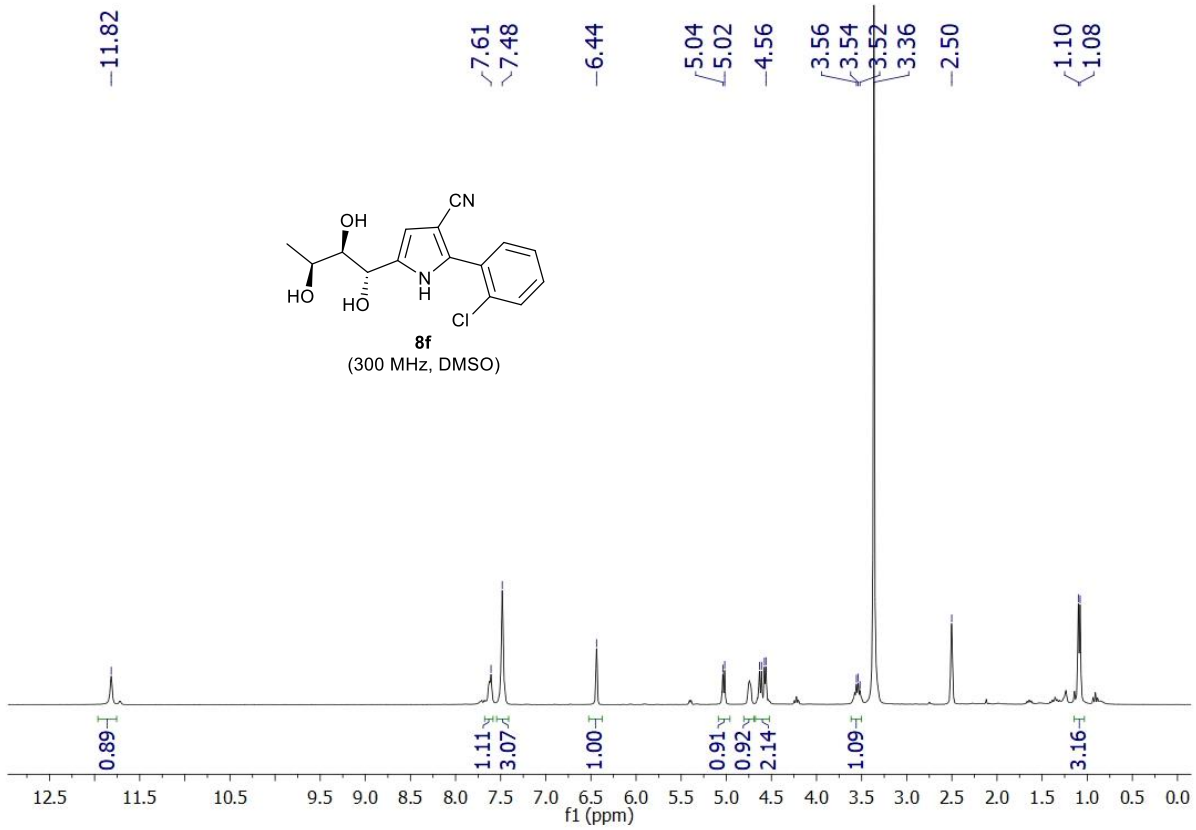


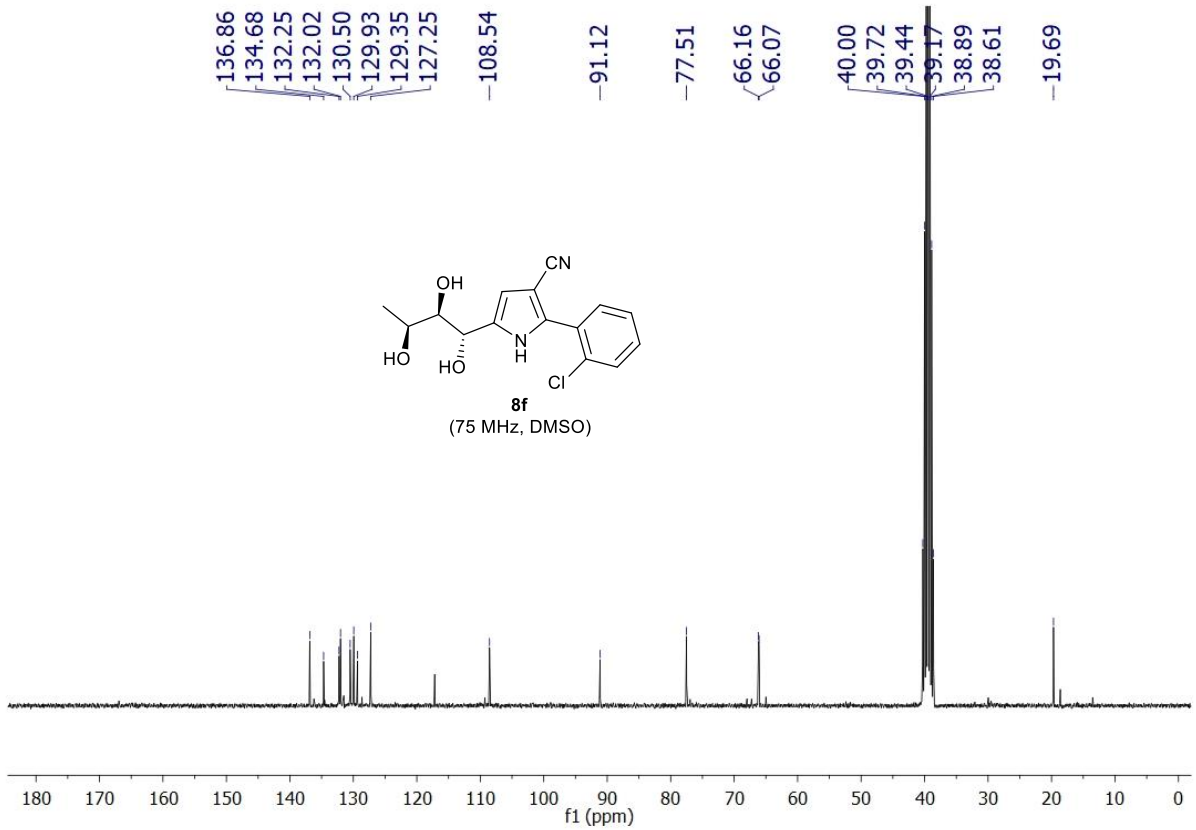
8e
(300 MHz, DMSO)



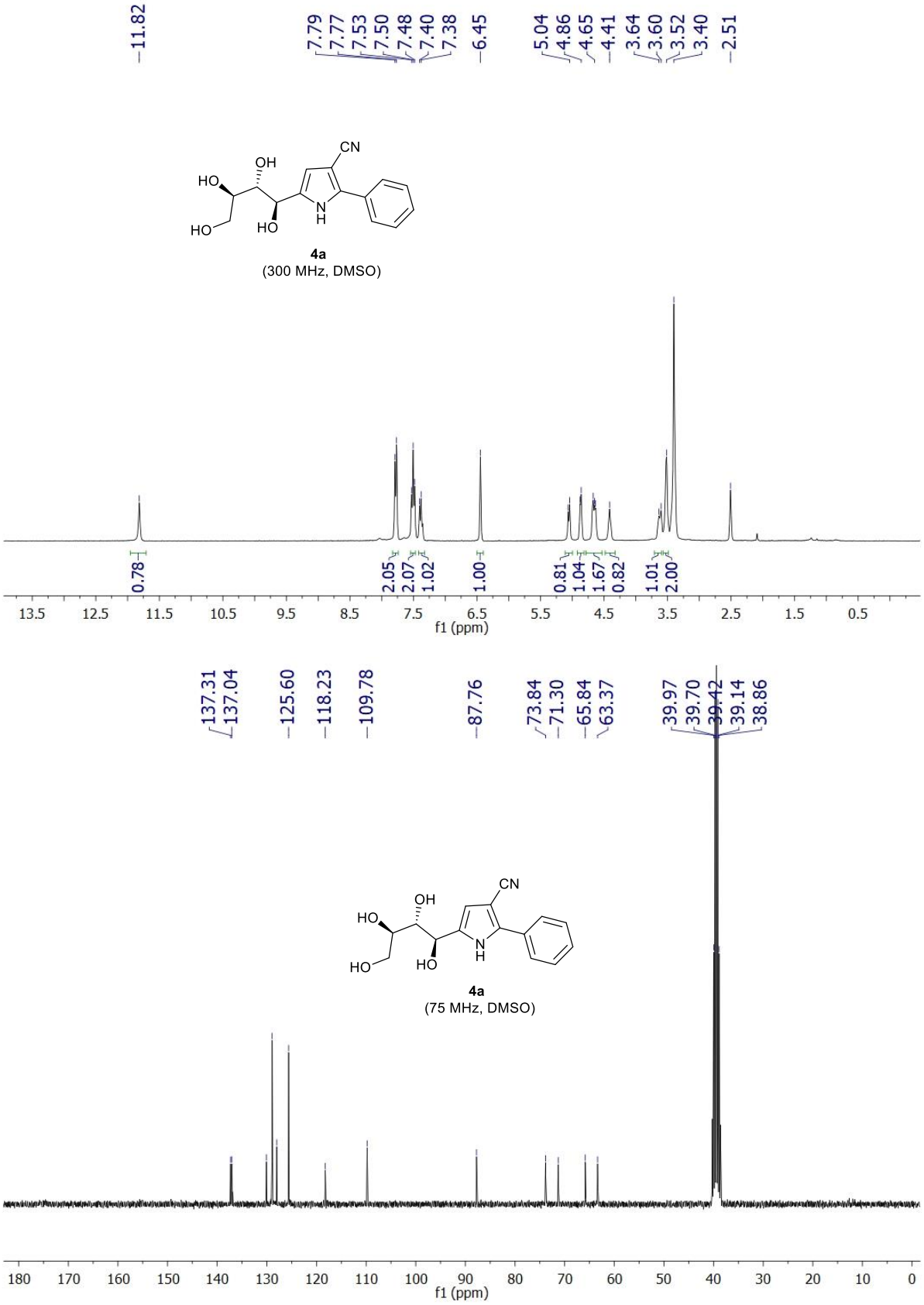
8e
(75 MHz, DMSO)

^{1}H and ^{13}C NMR spectra of **8f**

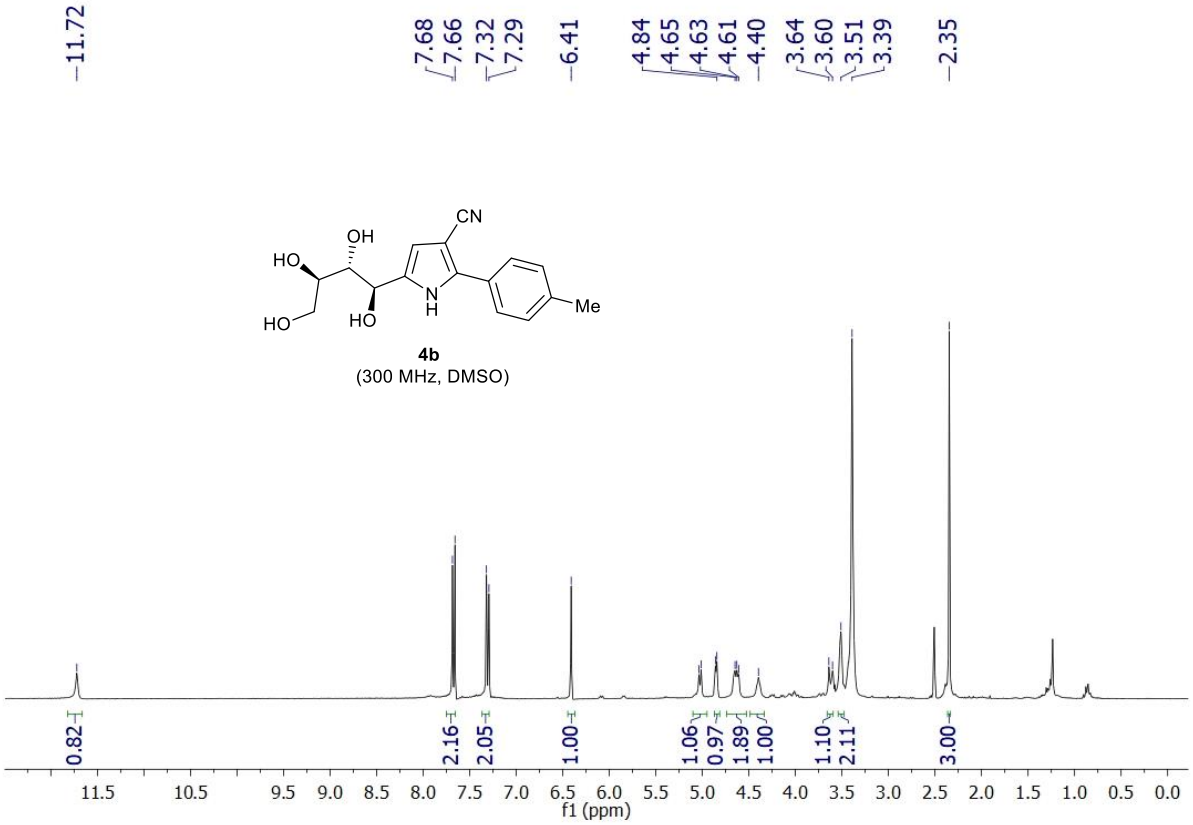


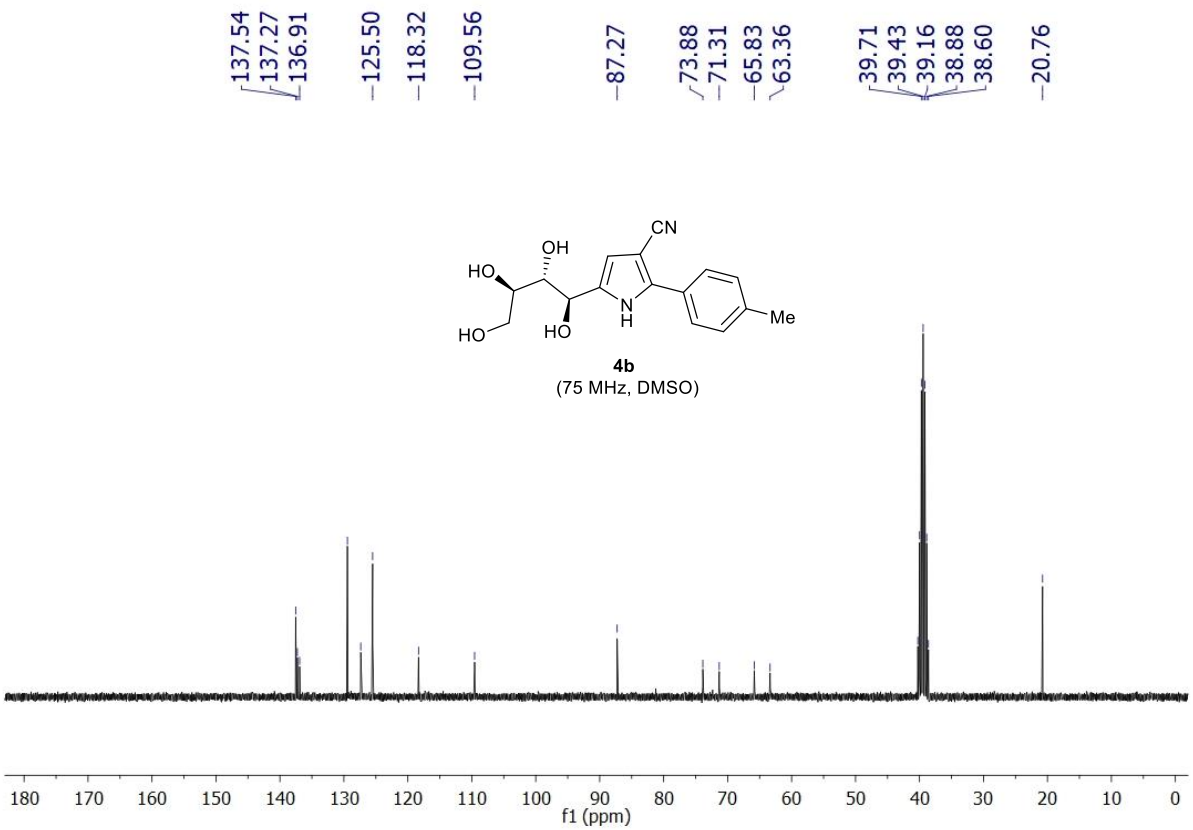


^{1}H and ^{13}C NMR spectra of **4a**

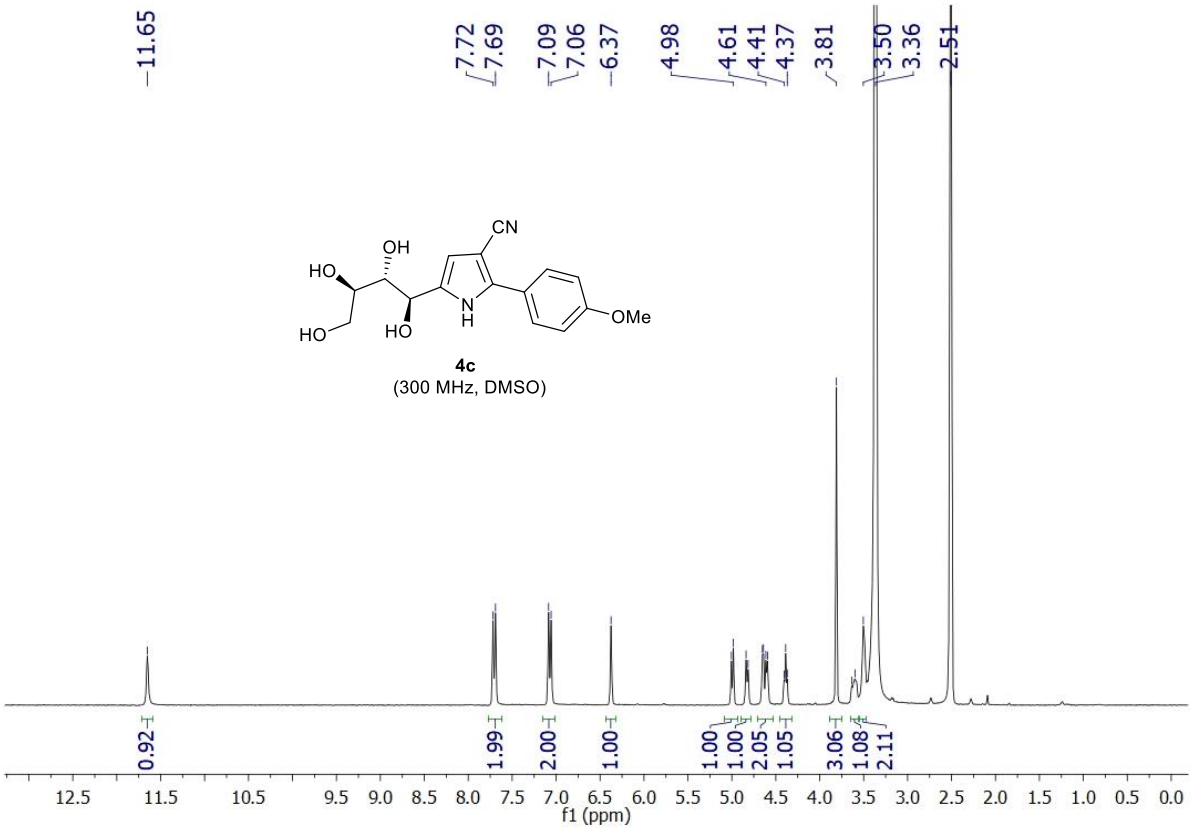


^{1}H and ^{13}C NMR spectra of **4b**

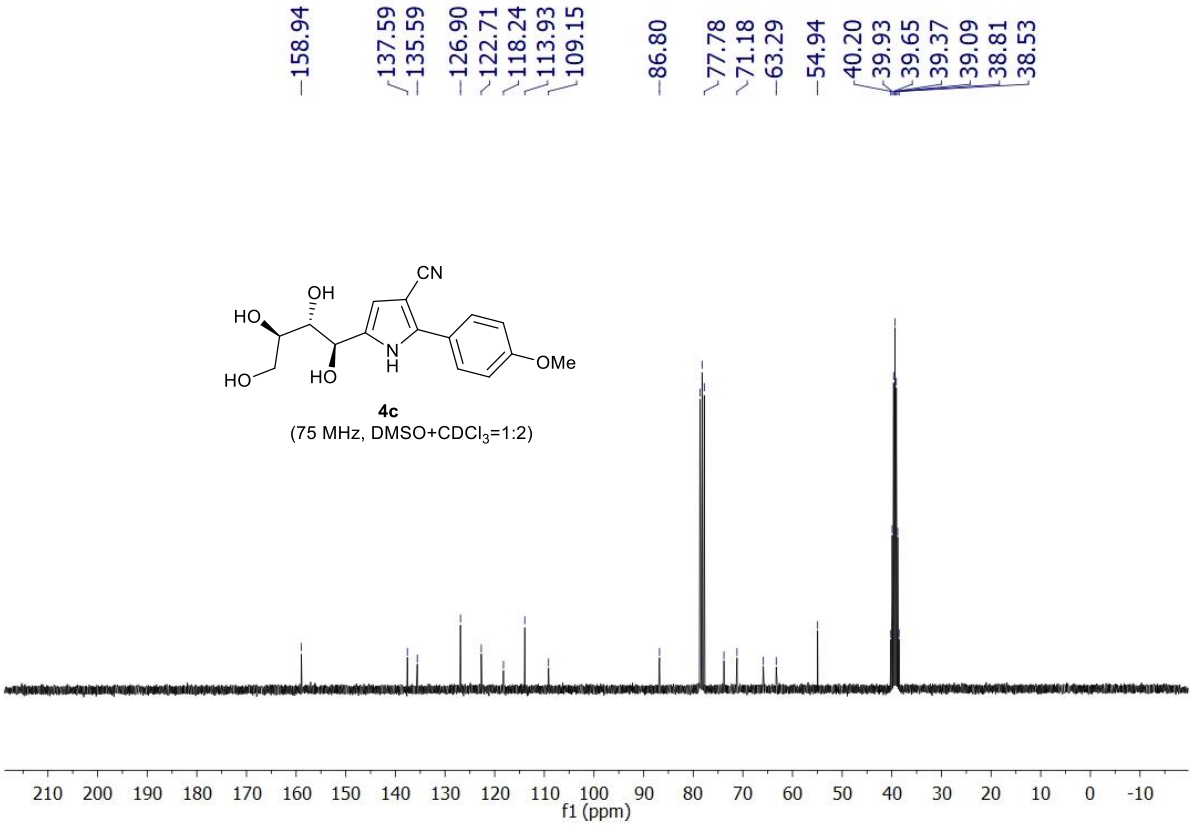




^{1}H and ^{13}C NMR spectra of **4c**

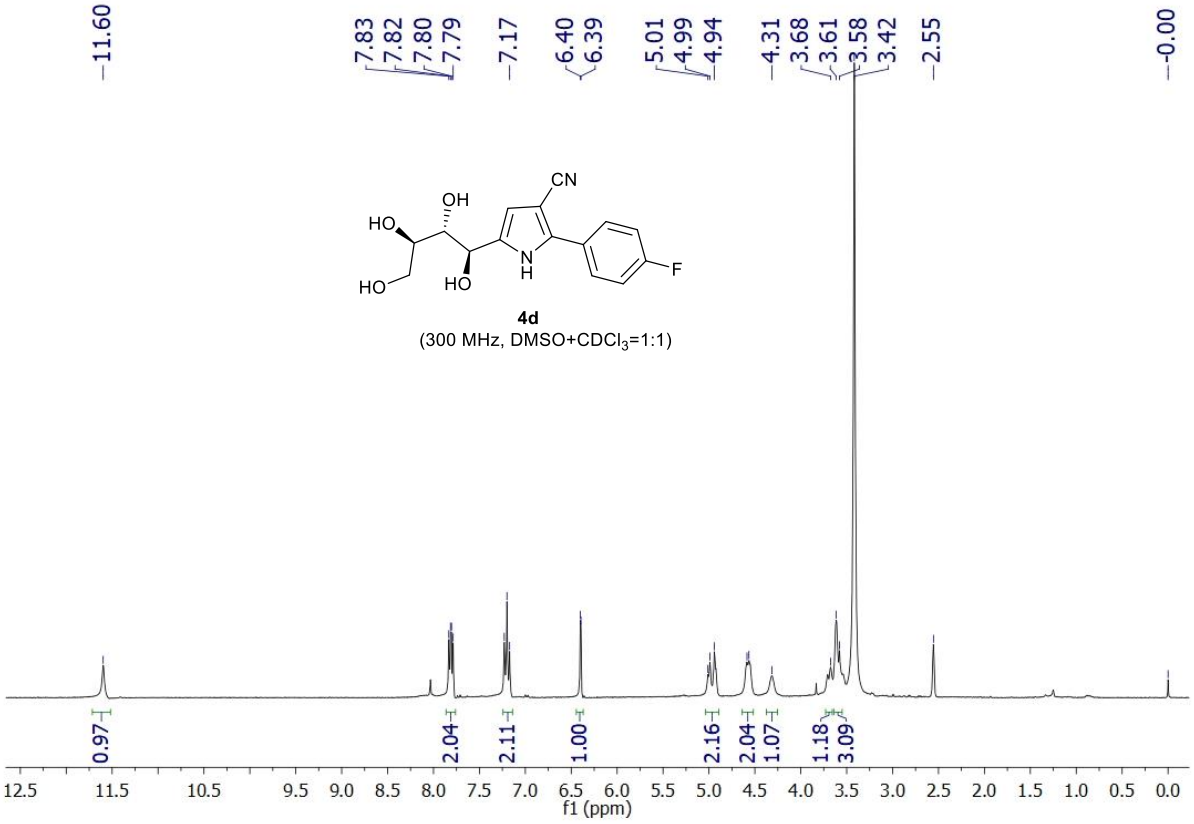


4c
(300 MHz, DMSO)

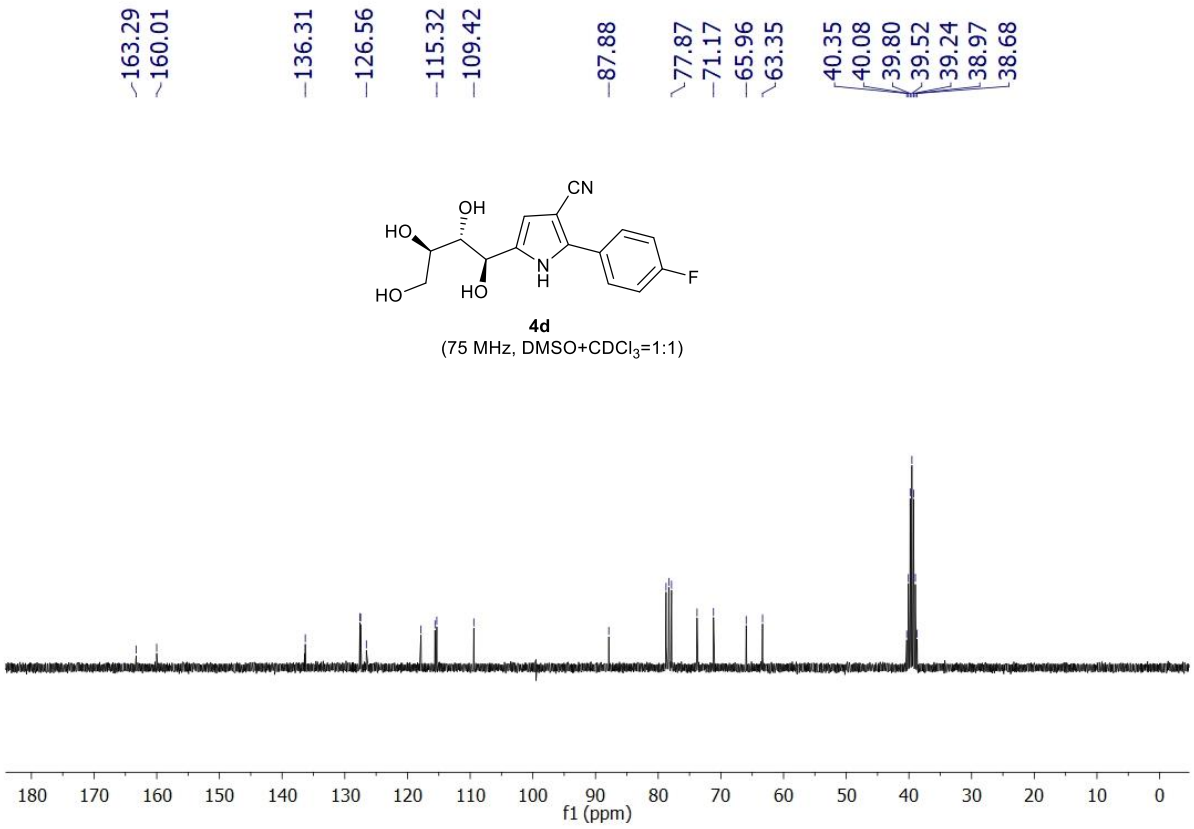


4c
(75 MHz, DMSO+$CDCl_3$=1:2)

^{1}H and ^{13}C NMR spectra of **4d**

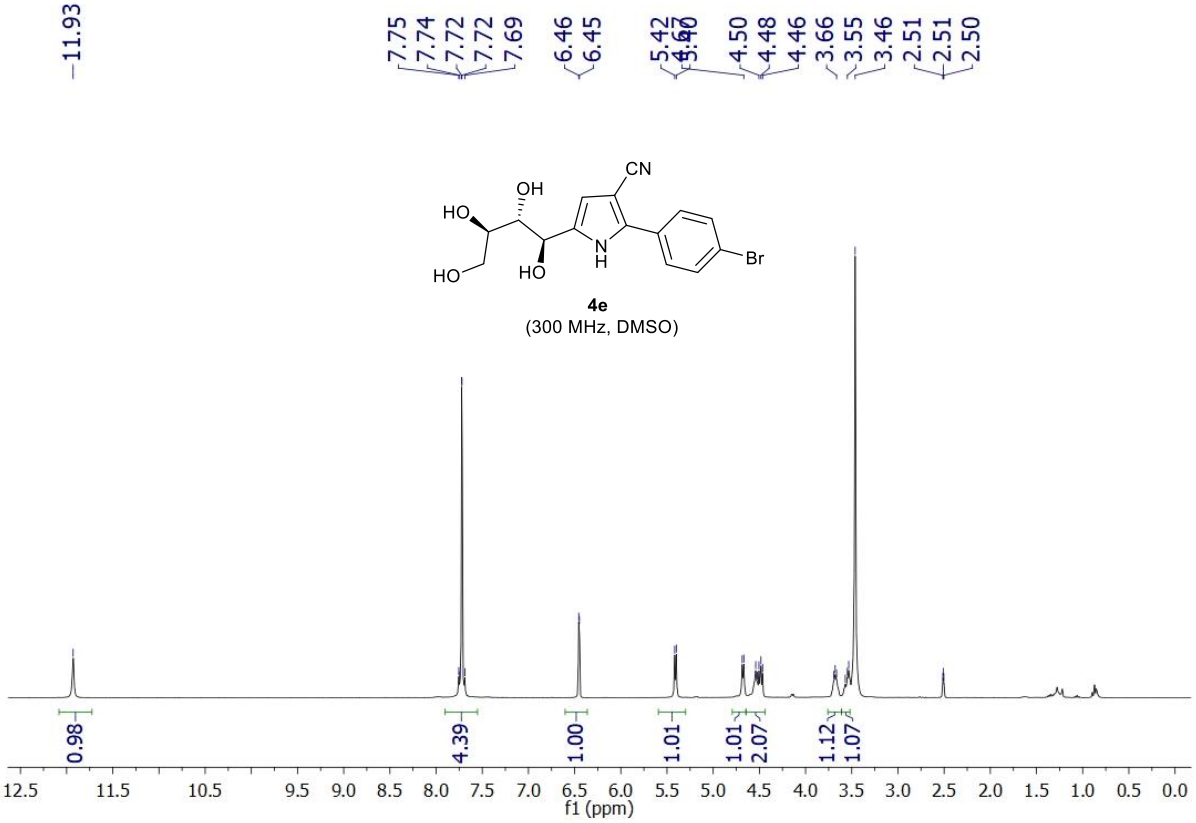


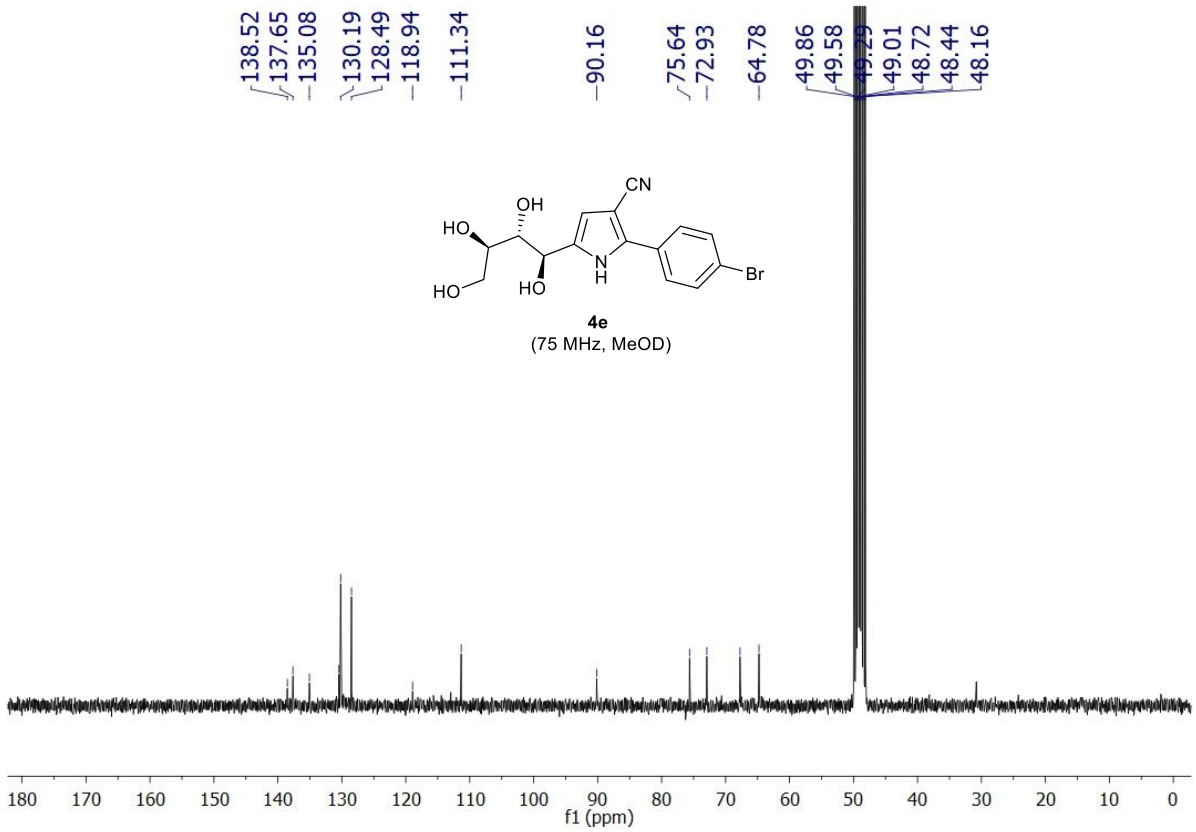
4d
(300 MHz, DMSO+$CDCl_3$=1:1)



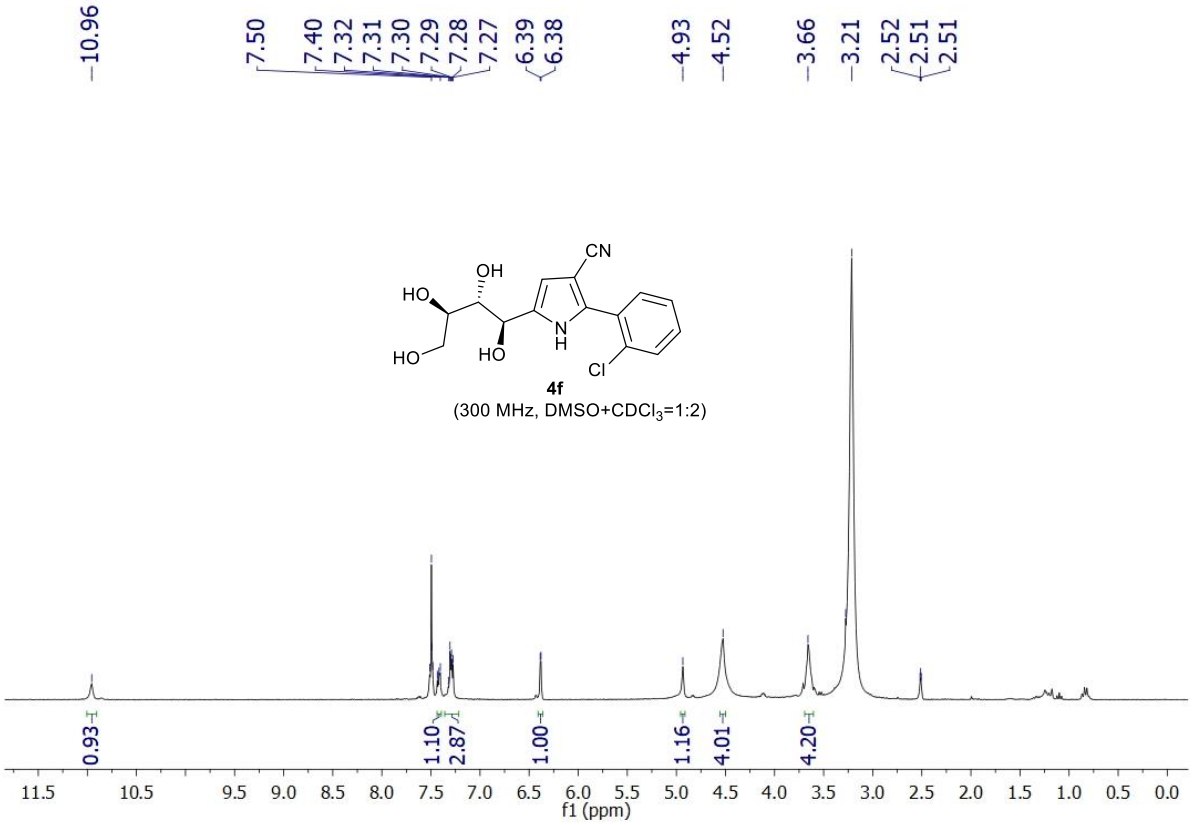
4d
(75 MHz, DMSO+$CDCl_3$=1:1)

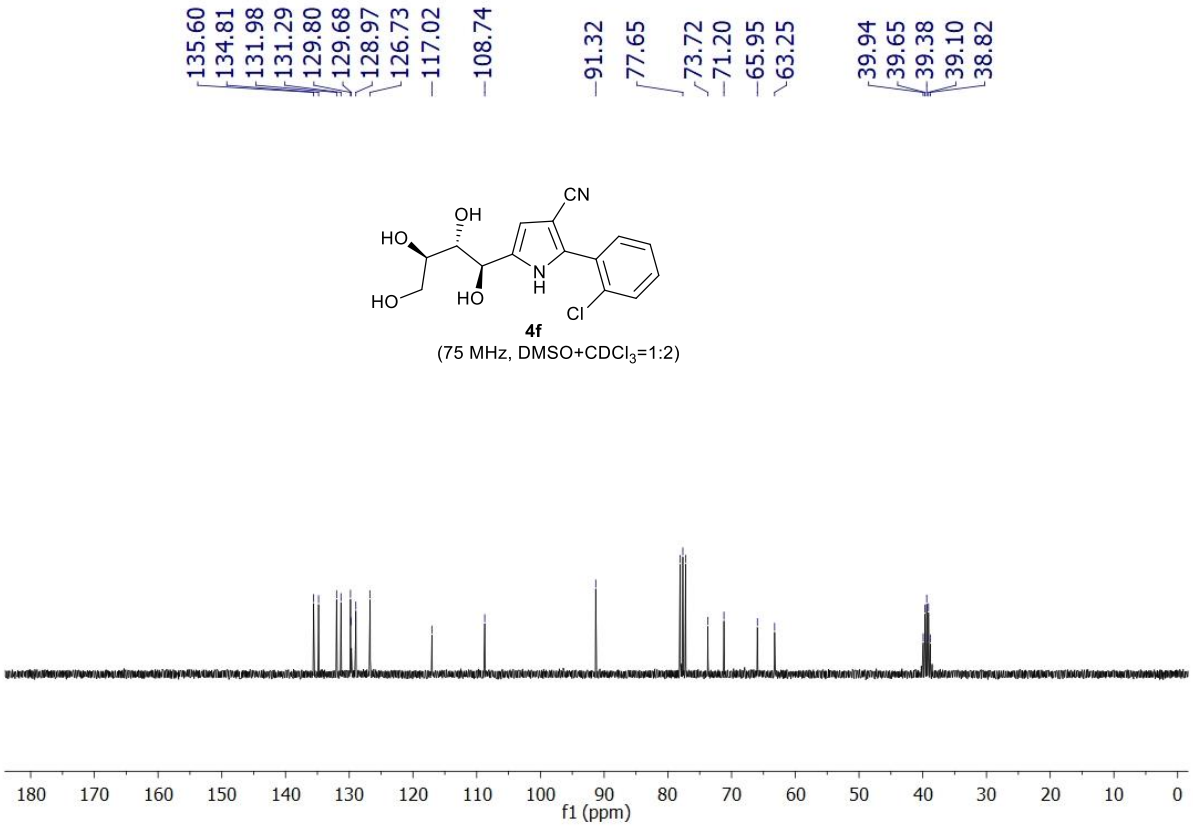
^{1}H and ^{13}C NMR spectra of **4e**



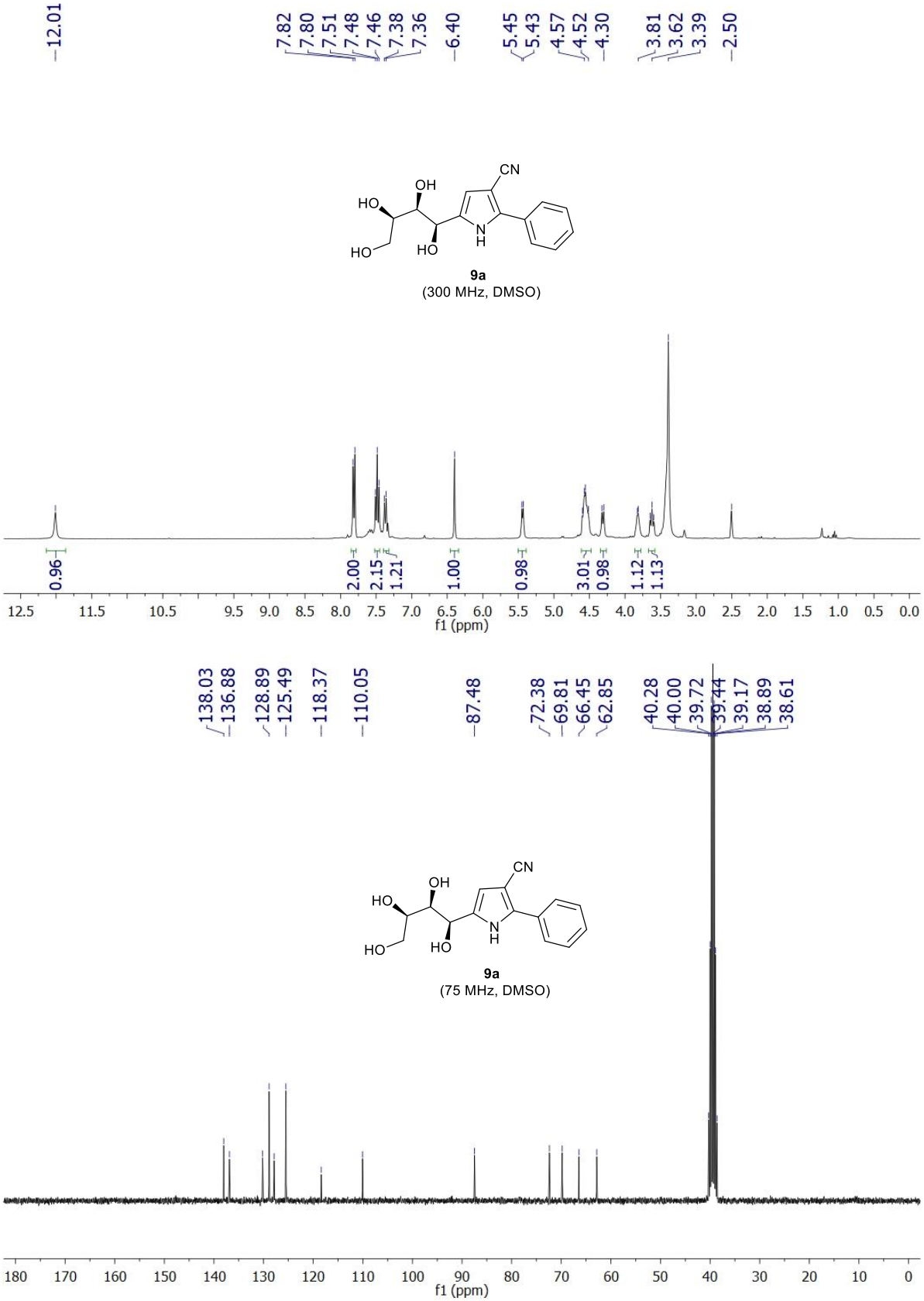


^{1}H and ^{13}C NMR spectra of **4f**

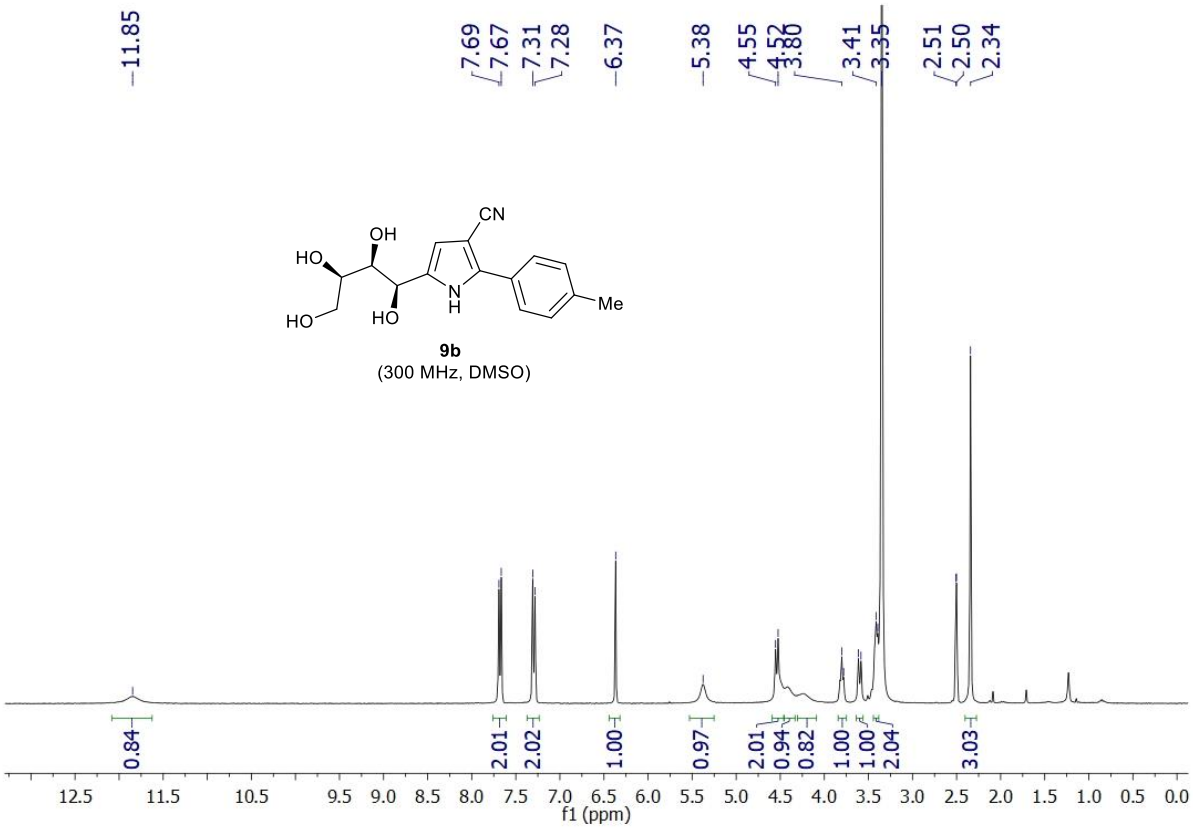


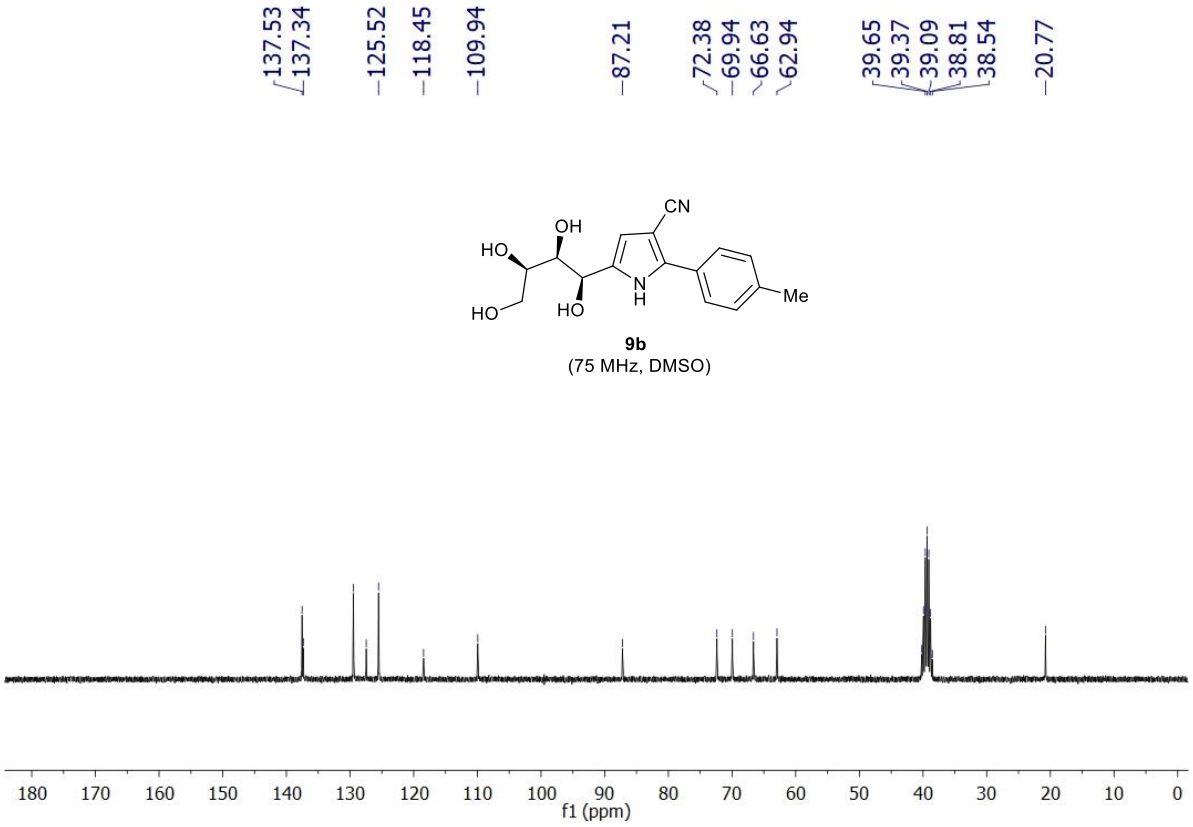


^{1}H and ^{13}C NMR spectra of **9a**

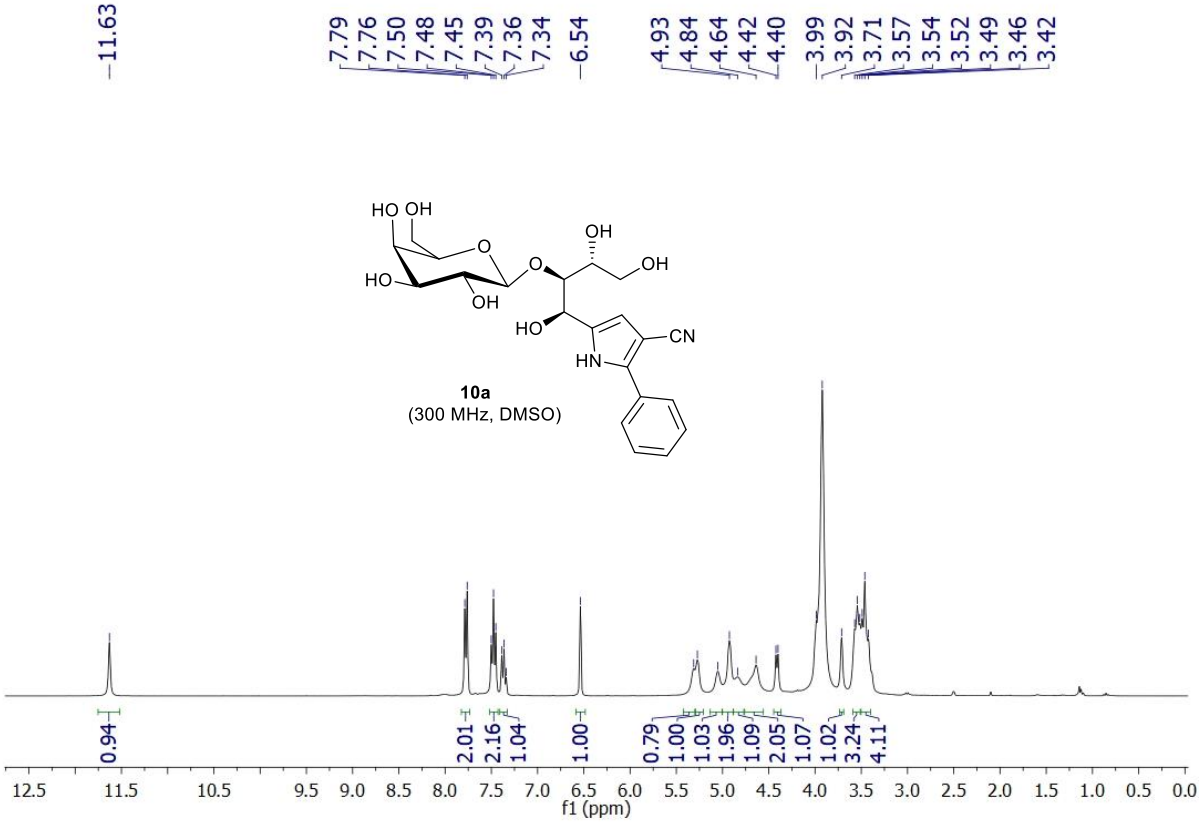


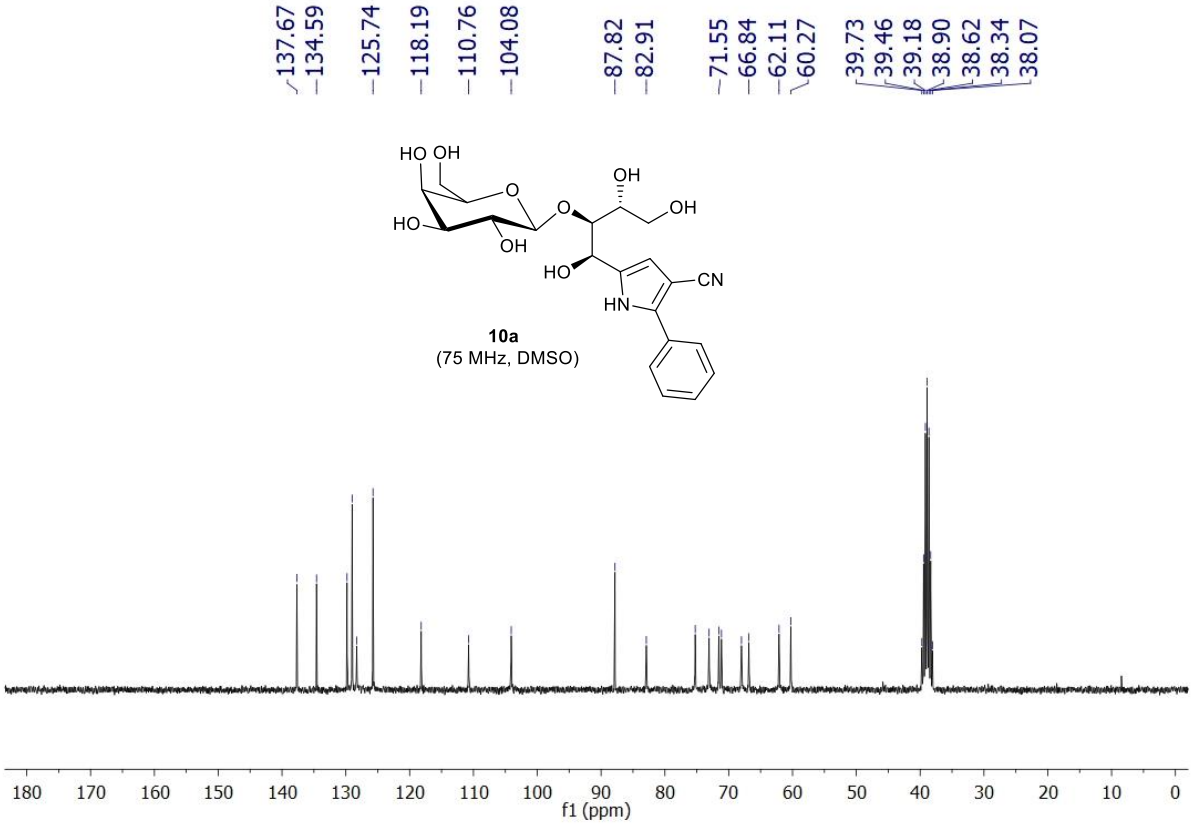
^{1}H and ^{13}C NMR spectra of **9b**



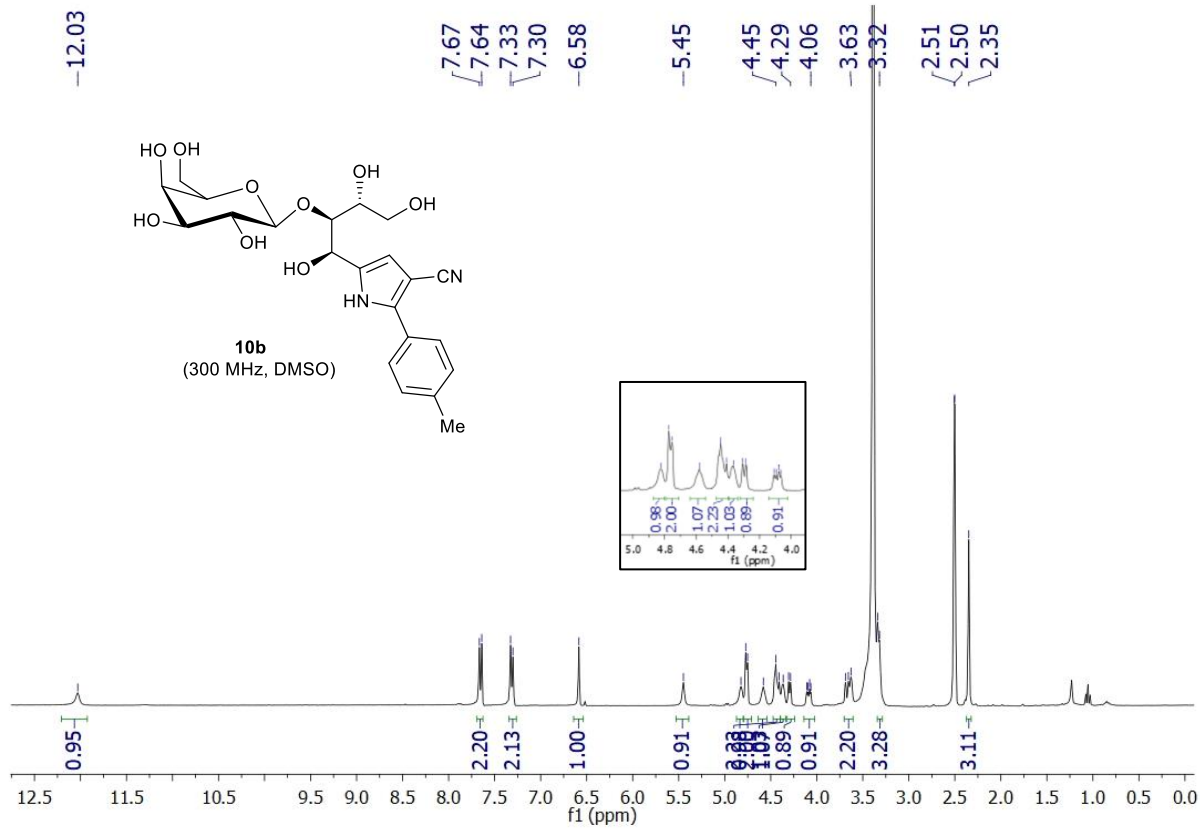


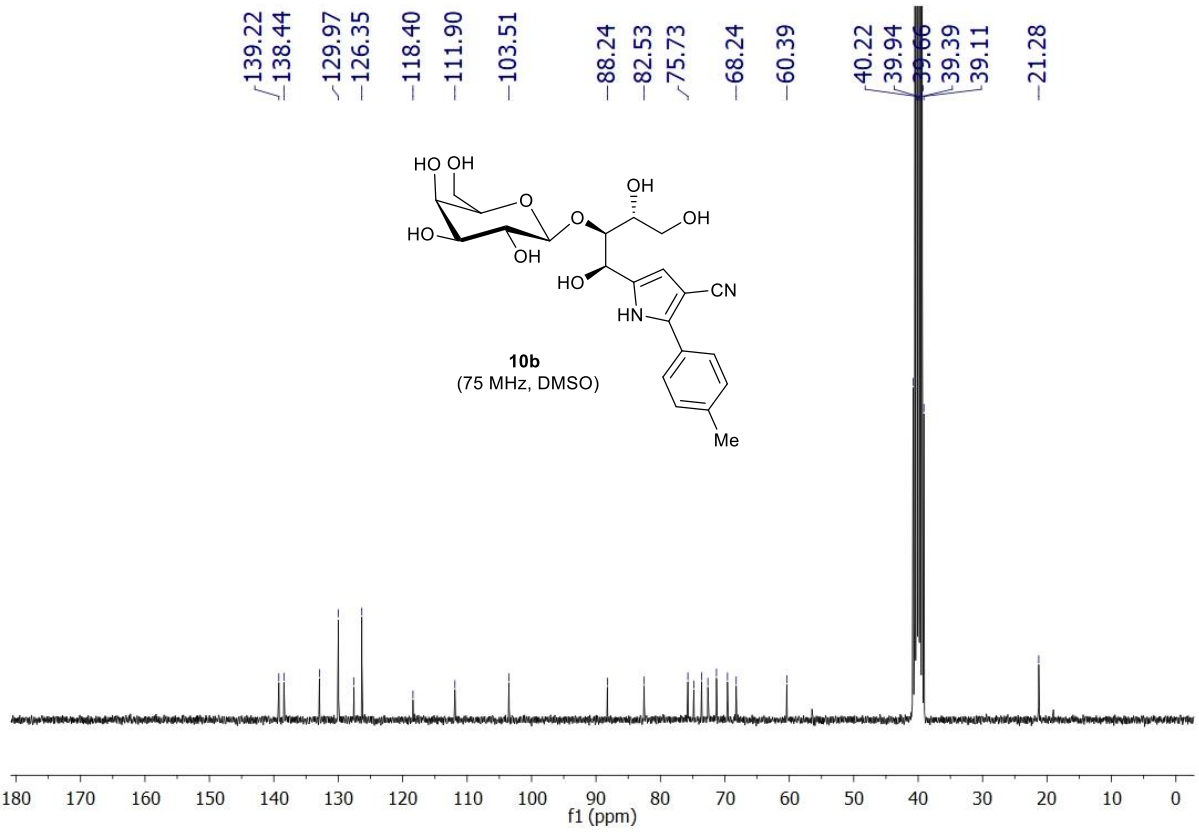
^{1}H and ^{13}C NMR spectra of **10a**



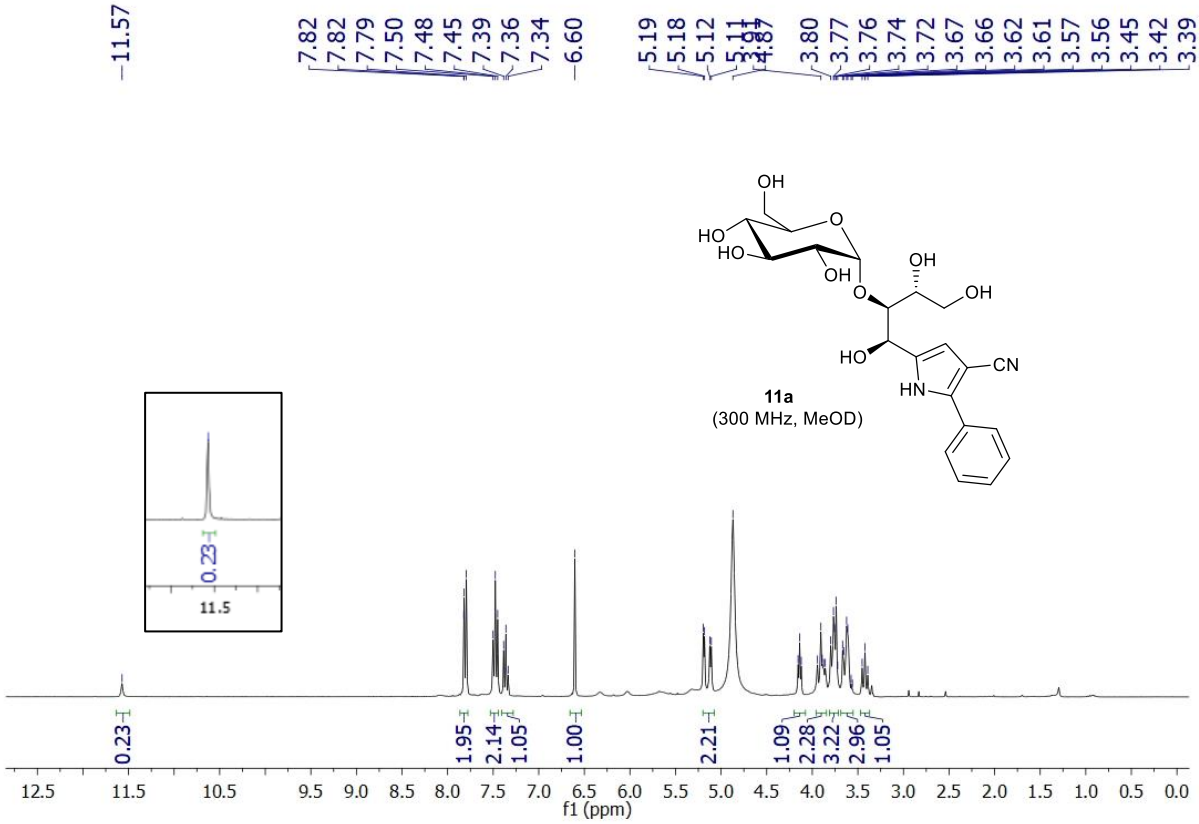


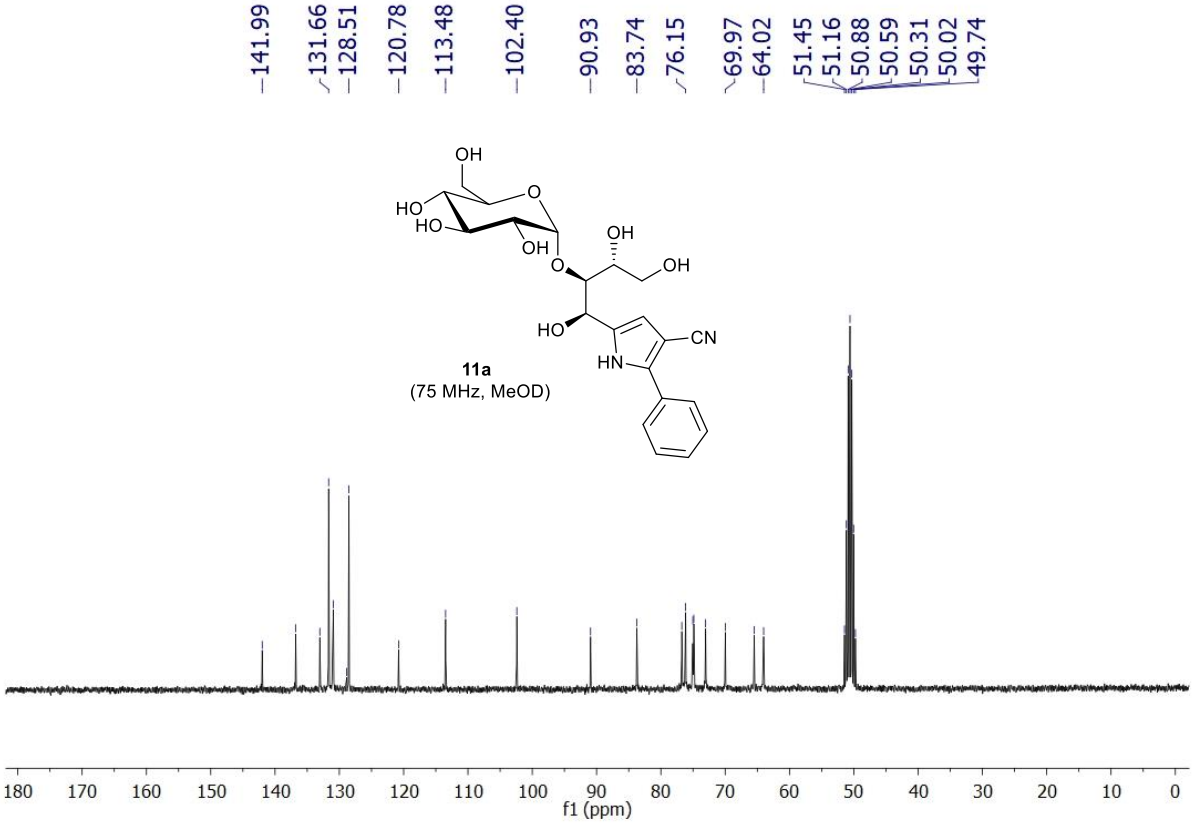
^{1}H and ^{13}C NMR spectra of **10b**



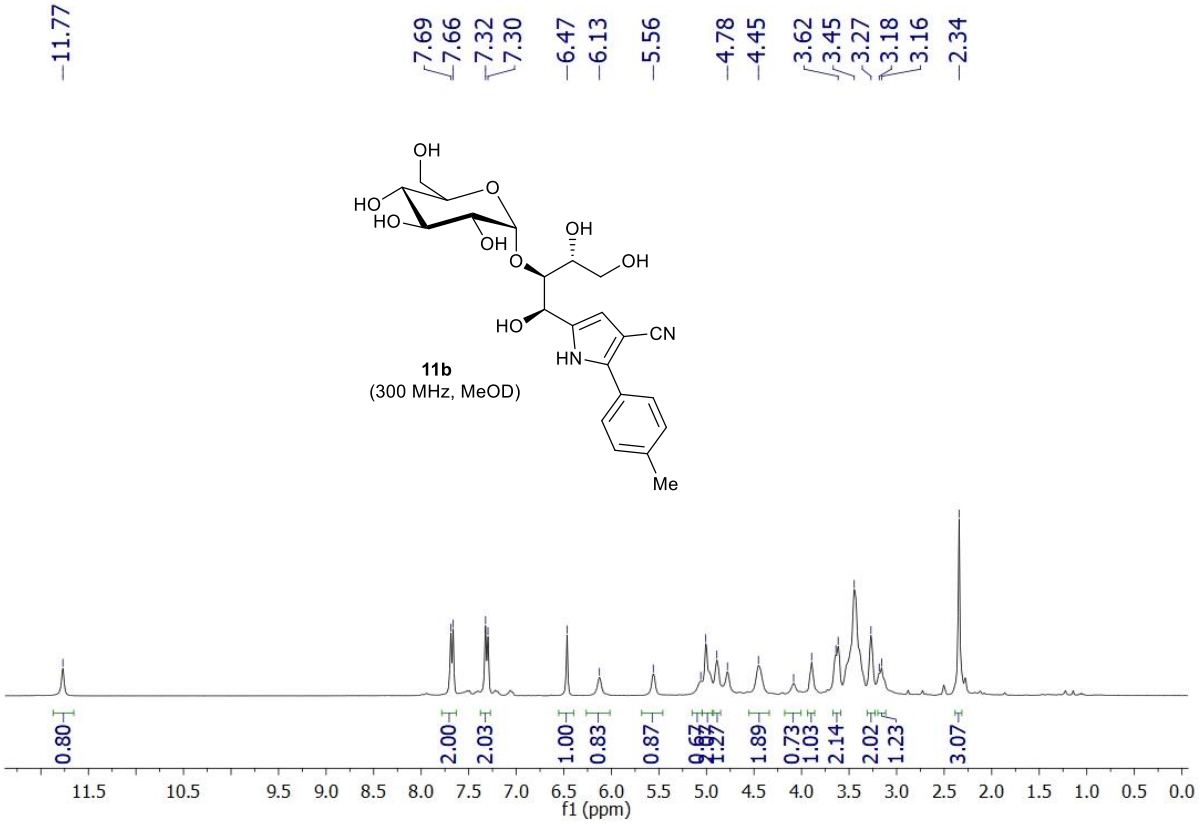


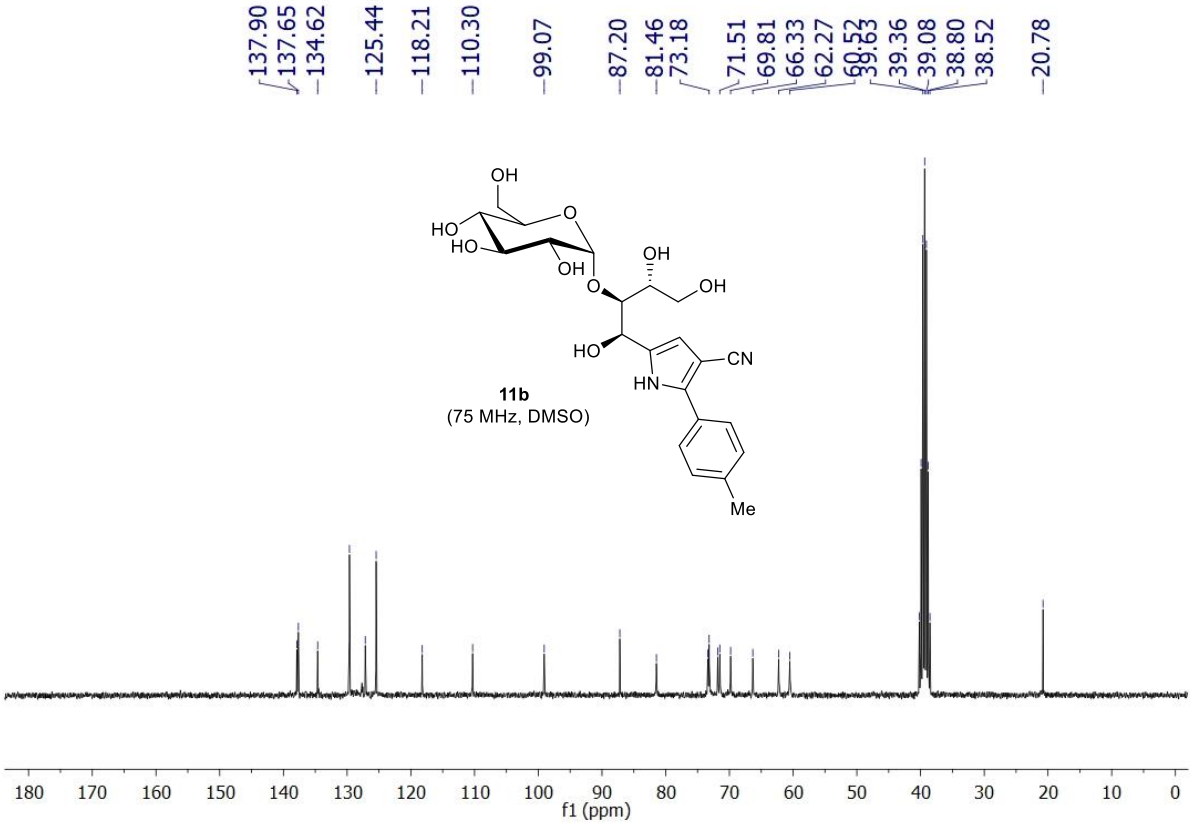
^{1}H and ^{13}C NMR spectra of **11a**



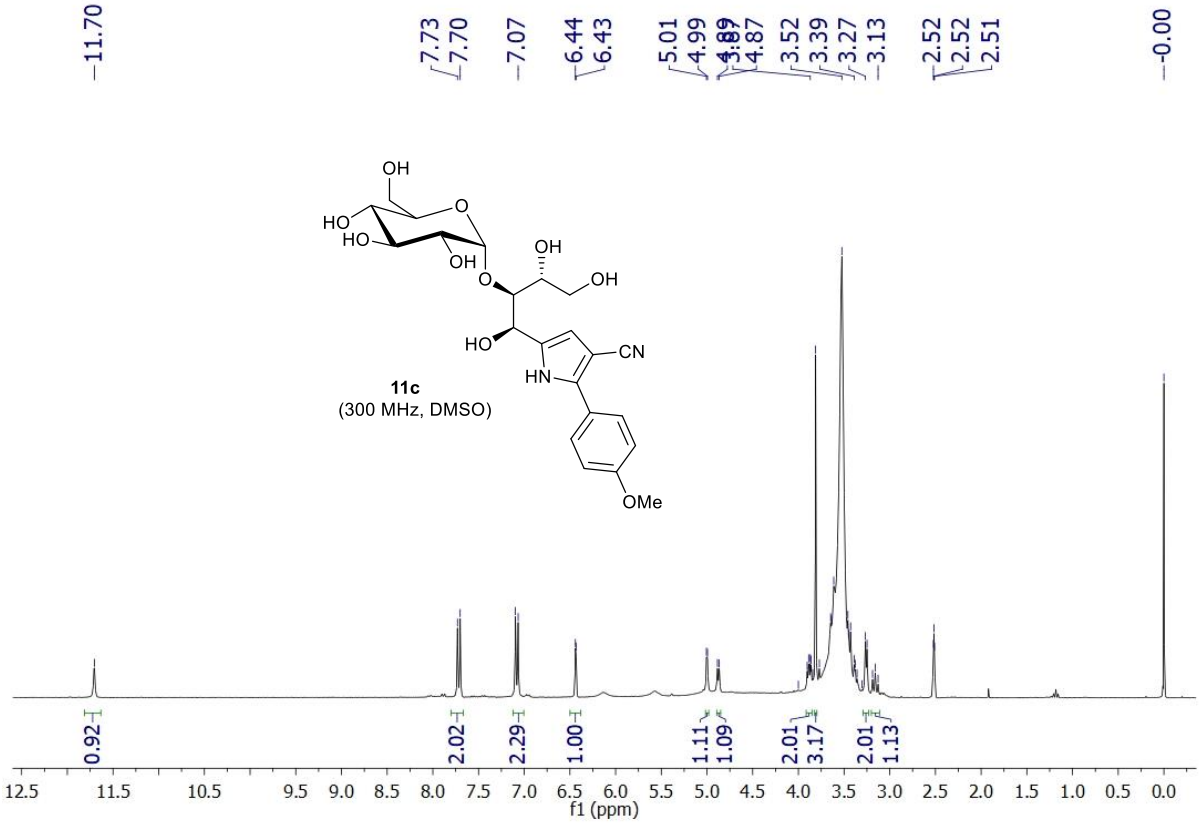


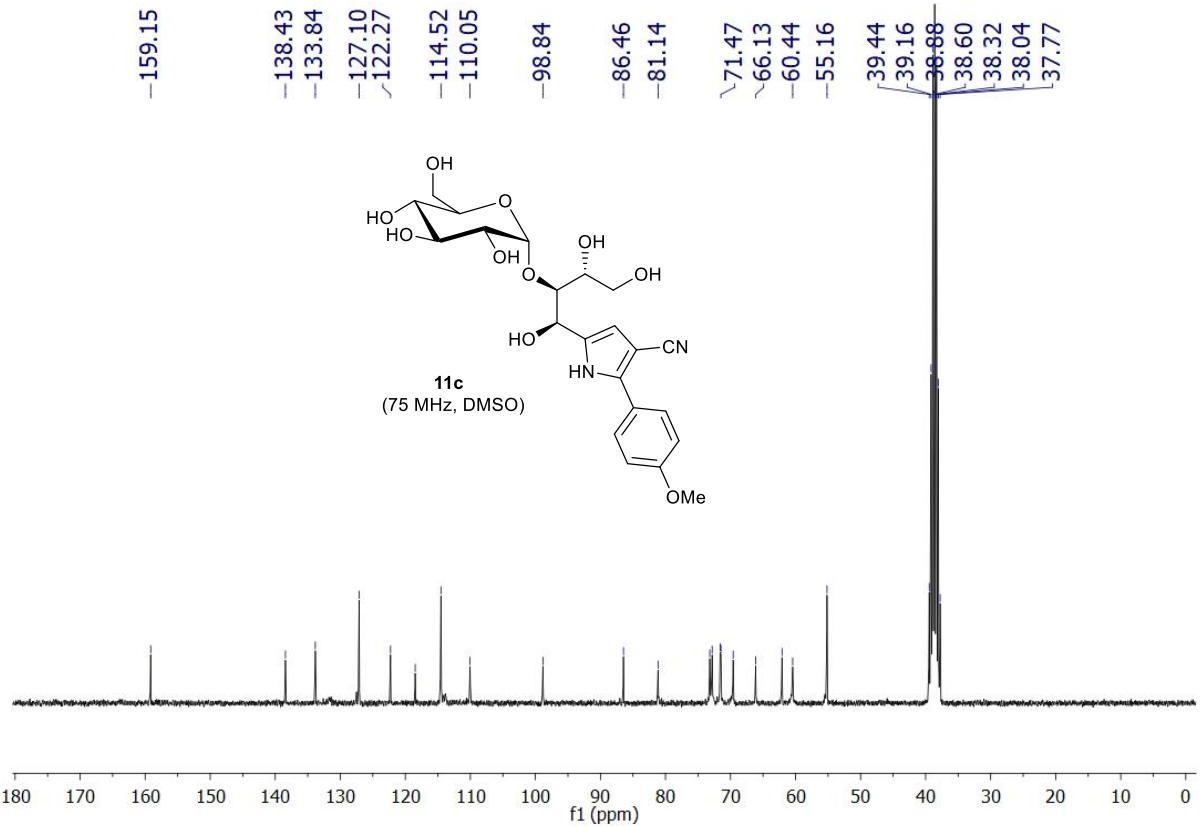
^{1}H and ^{13}C NMR spectra of **11b**



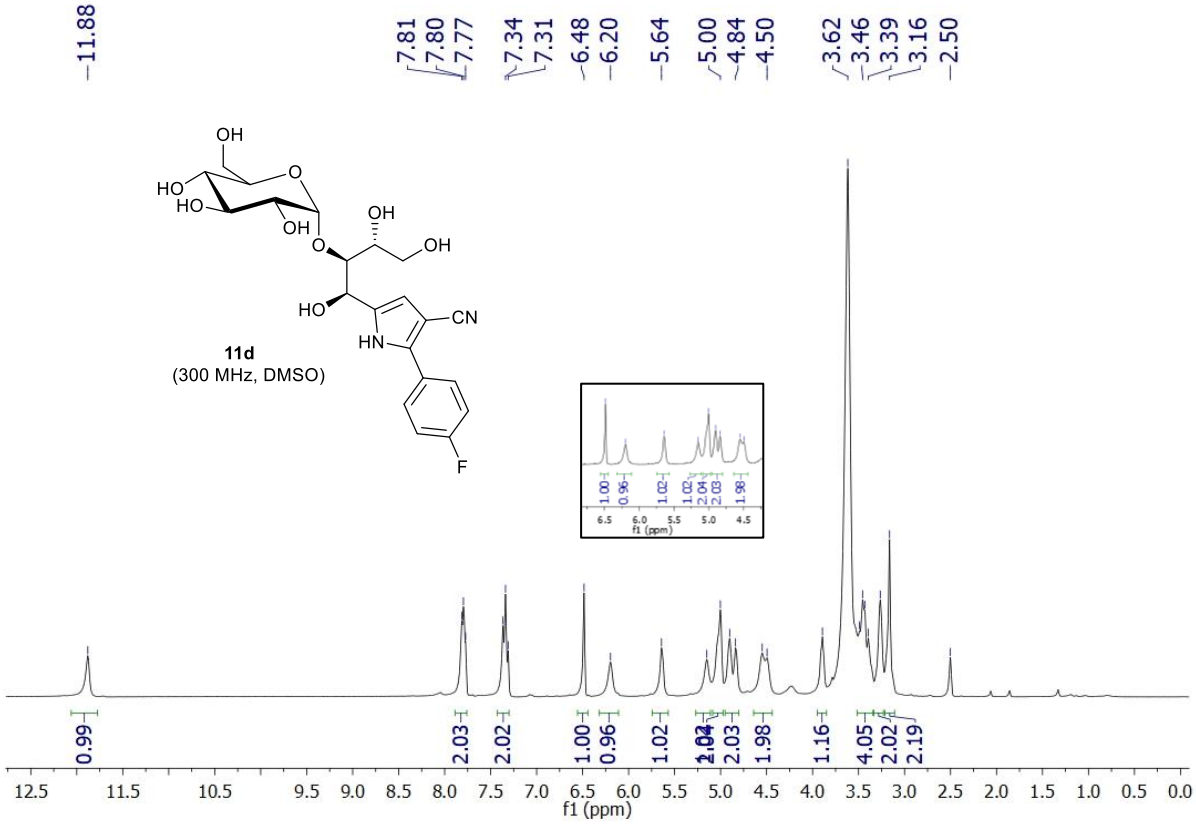


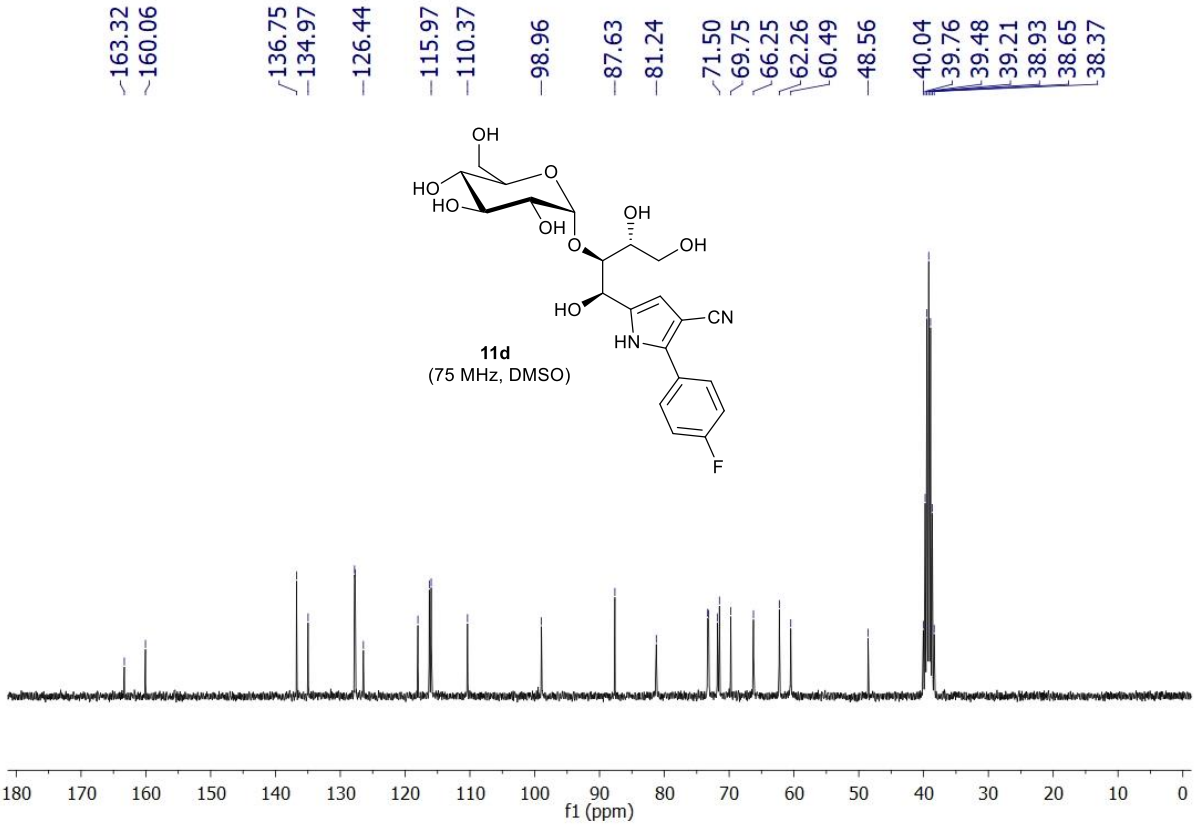
^{1}H and ^{13}C NMR spectra of **11c**



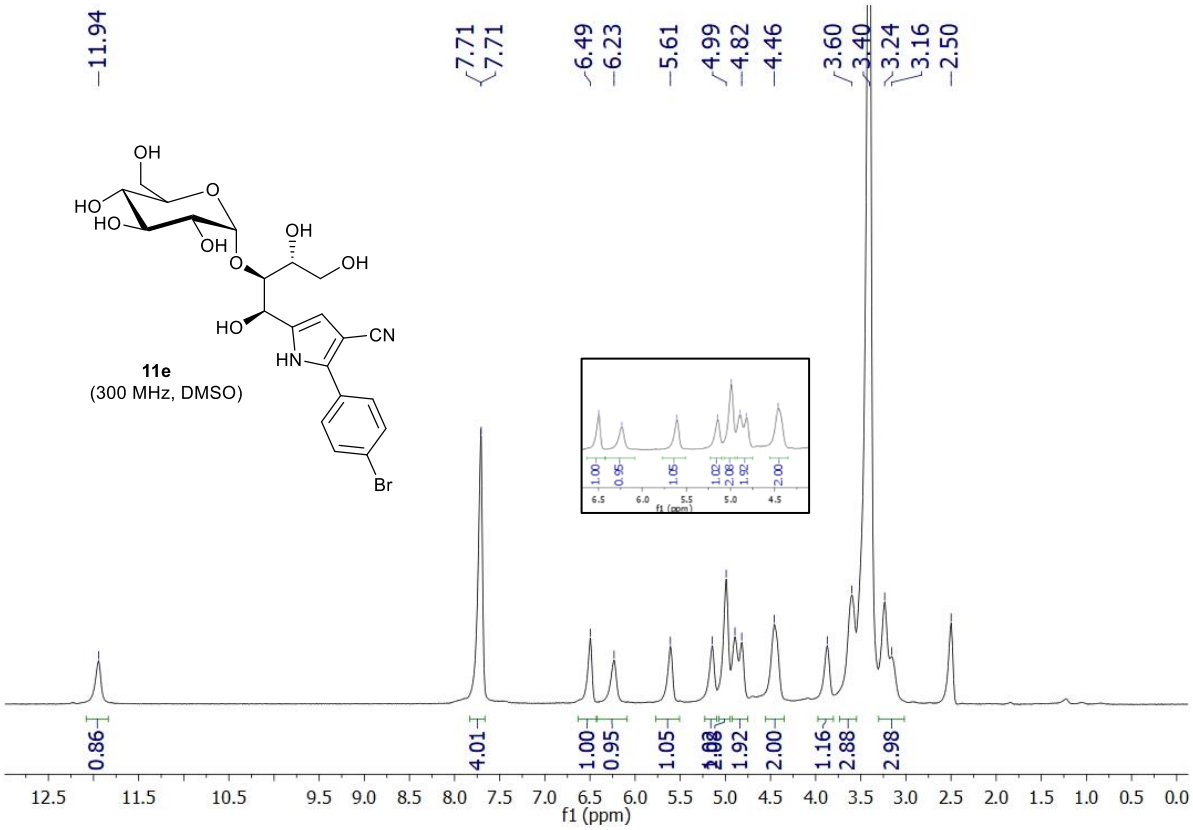


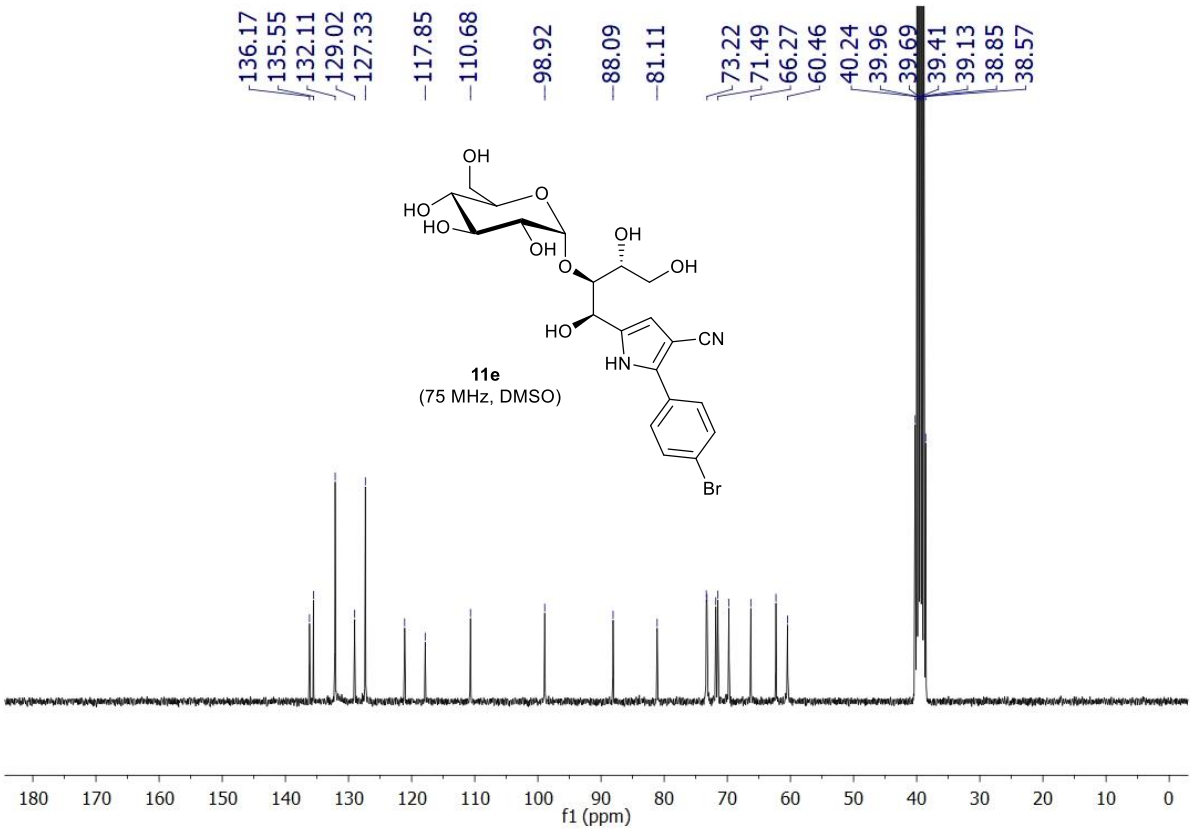
^{1}H and ^{13}C NMR spectra of **11d**



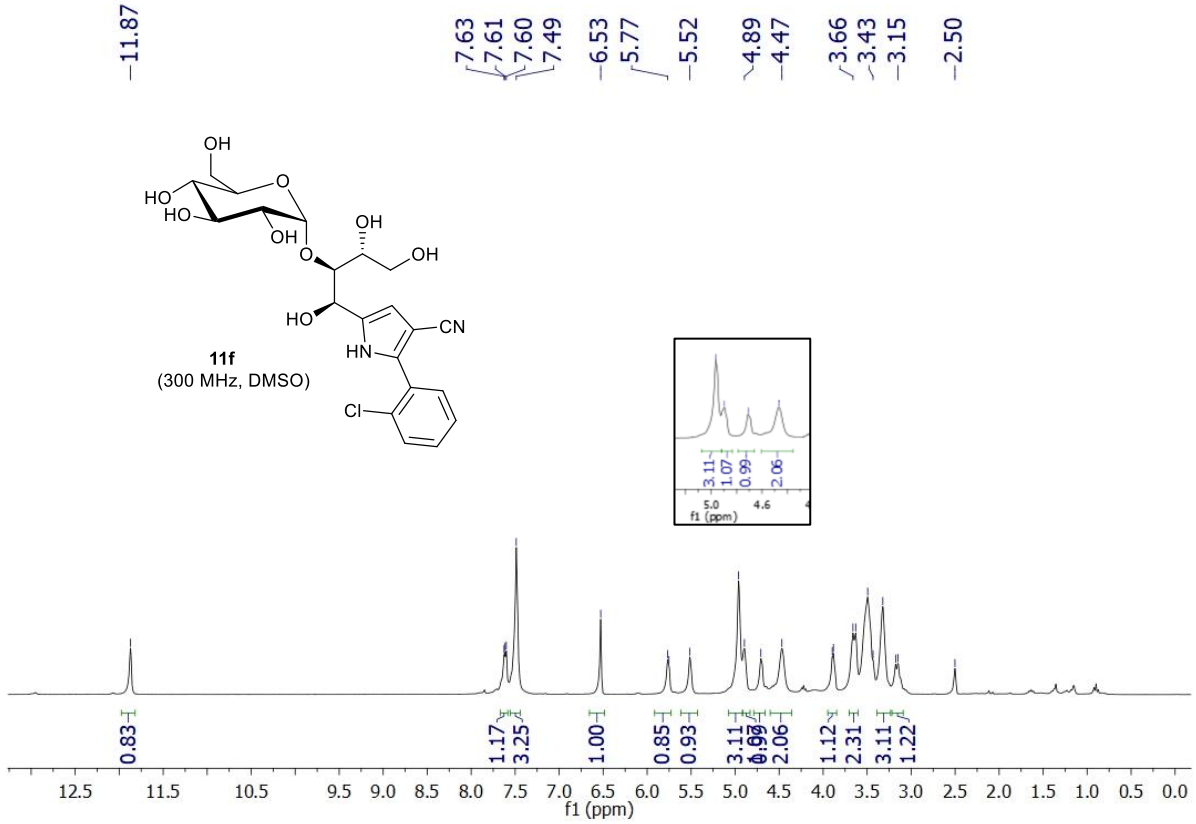


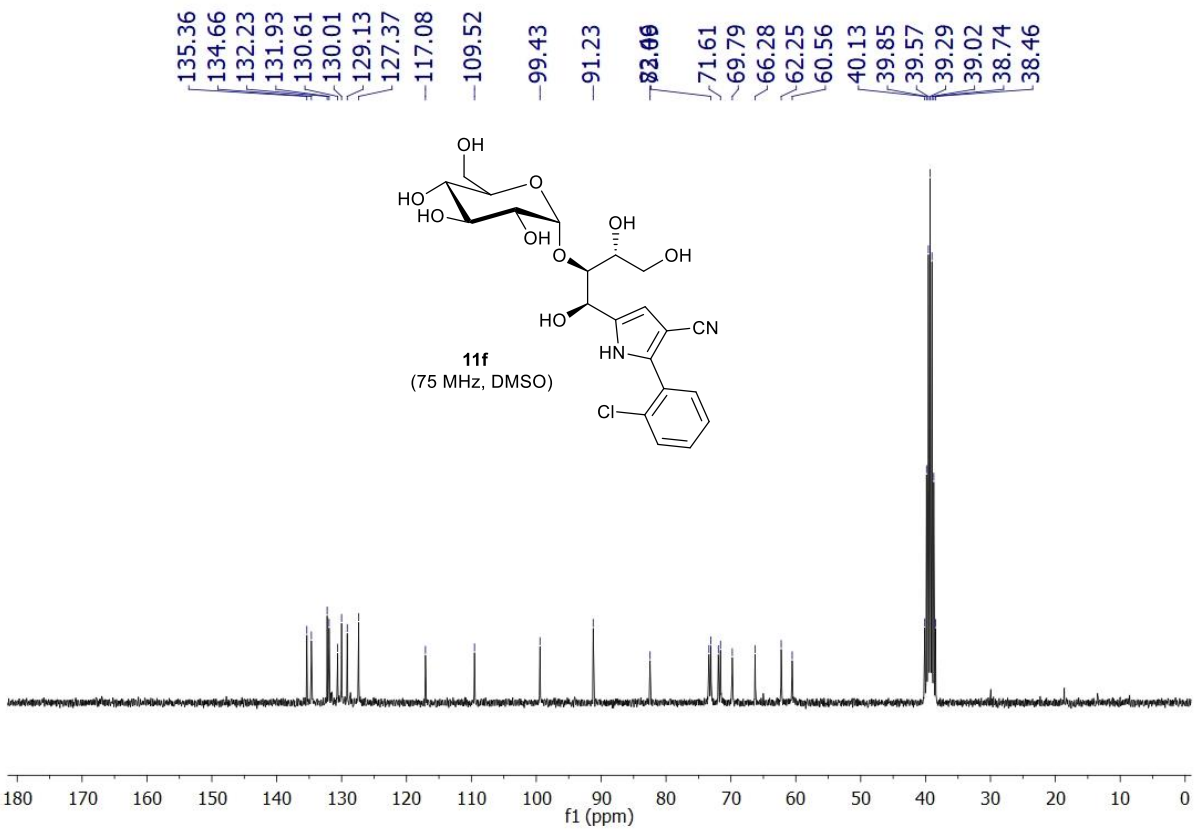
^{1}H and ^{13}C NMR spectra of **11e**



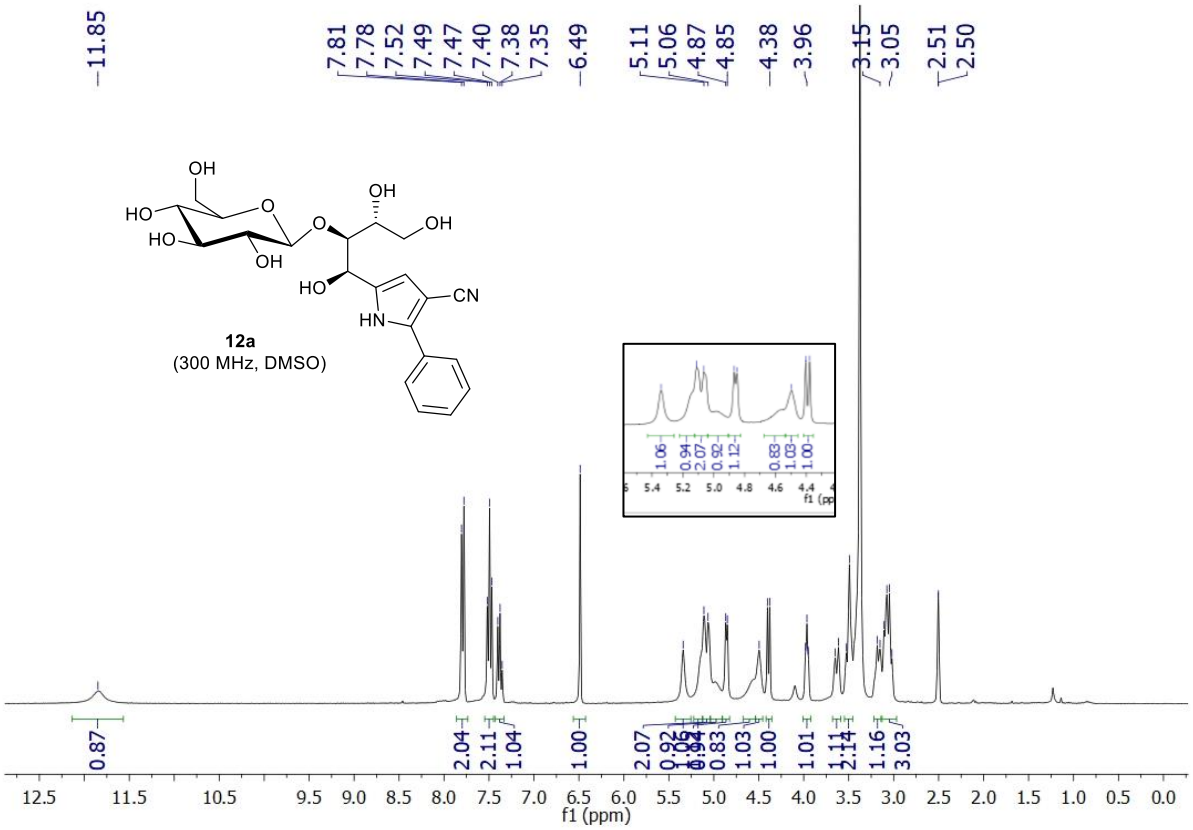


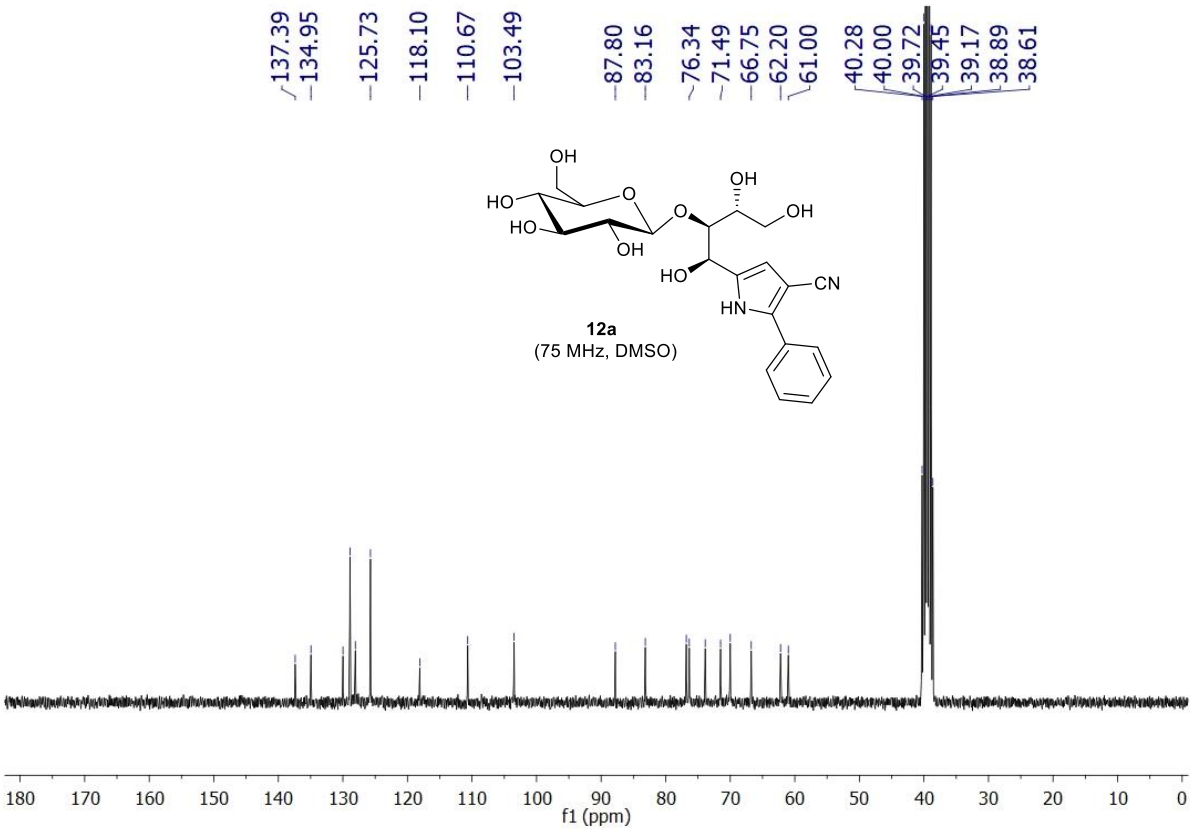
^{1}H and ^{13}C NMR spectra of **11f**



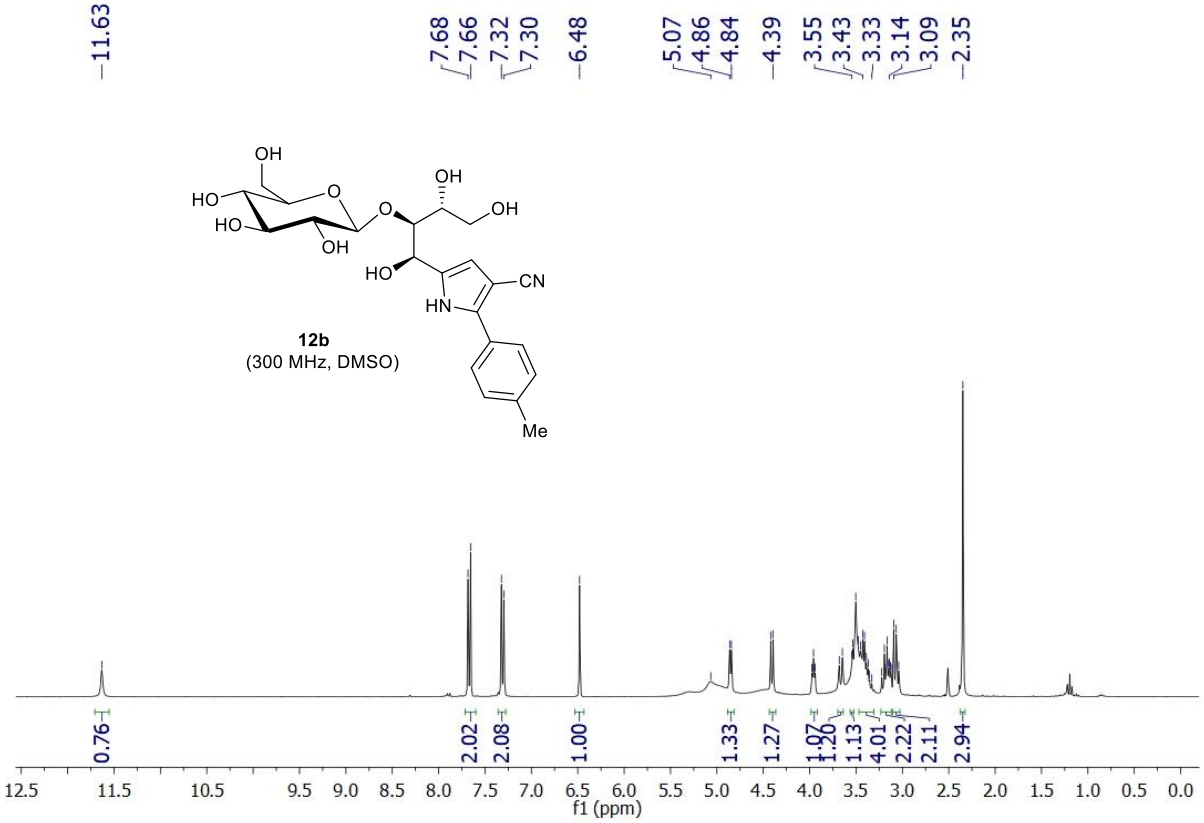


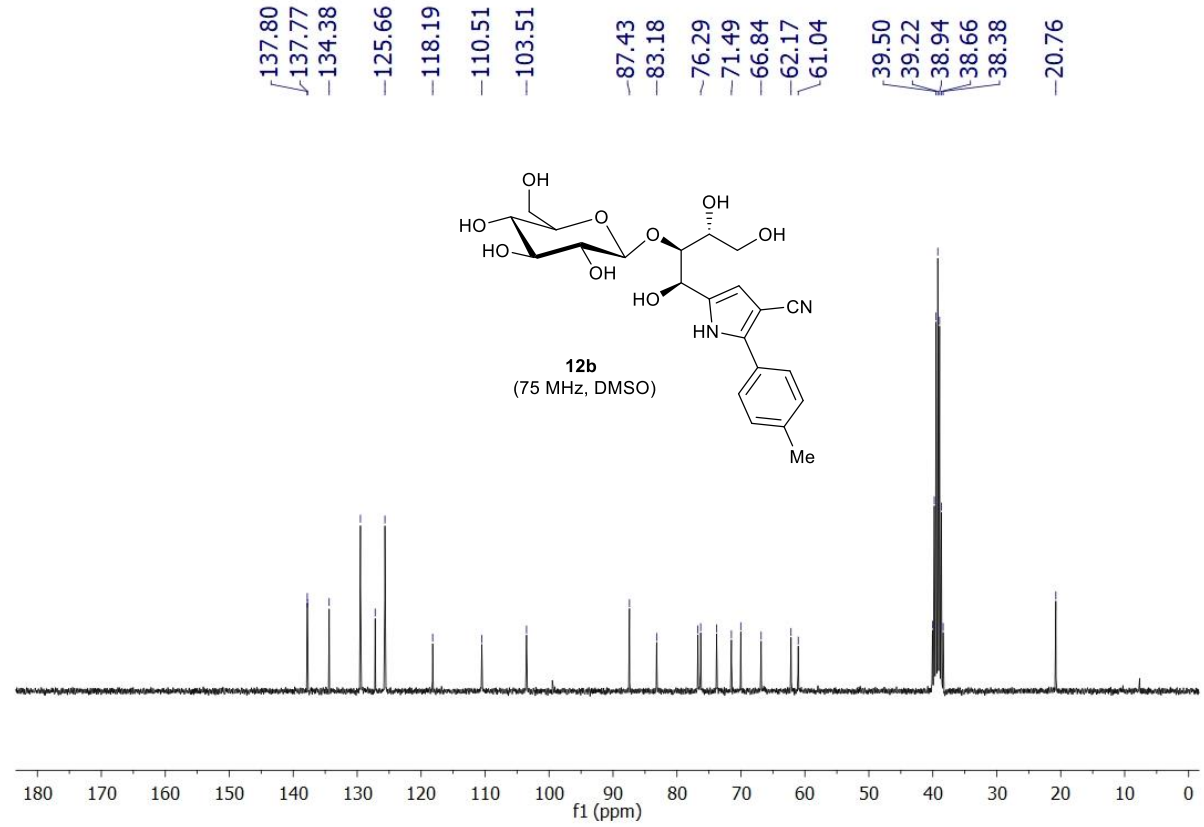
^{1}H and ^{13}C NMR spectra of **12a**



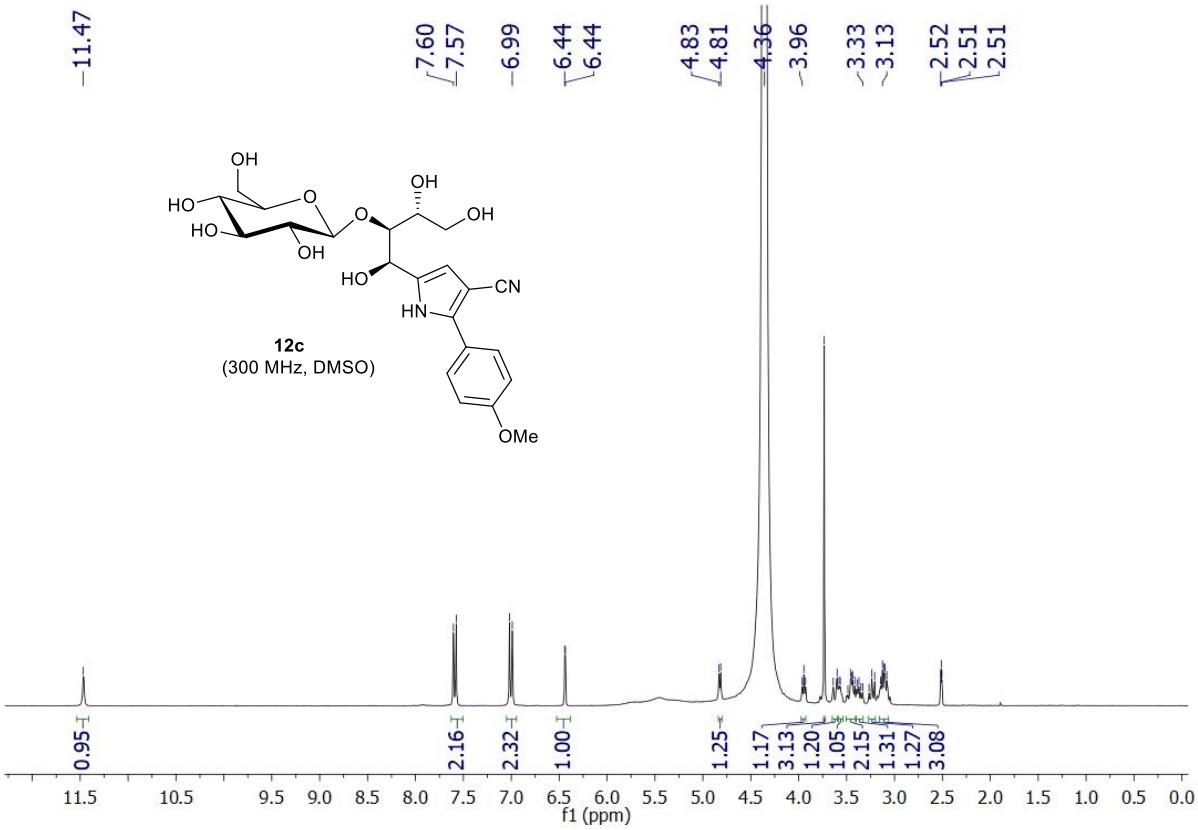


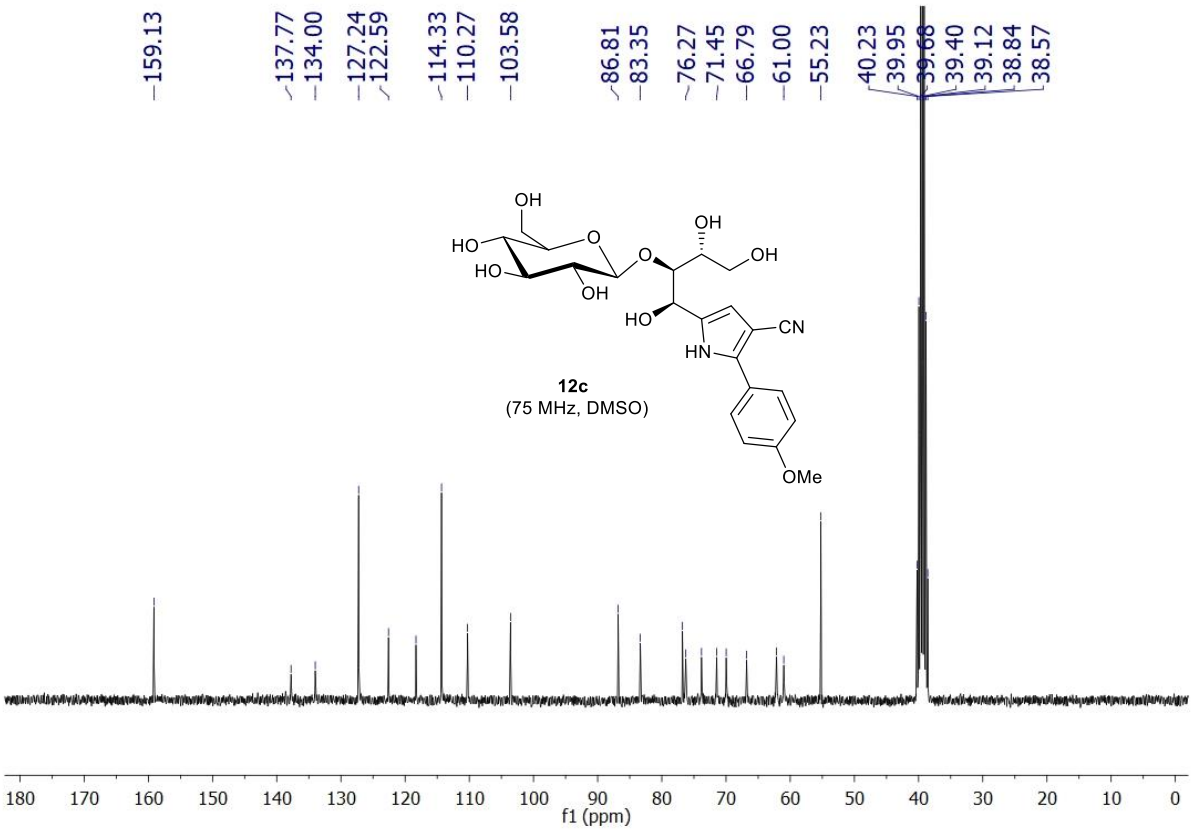
^{1}H and ^{13}C NMR spectra of **12b**



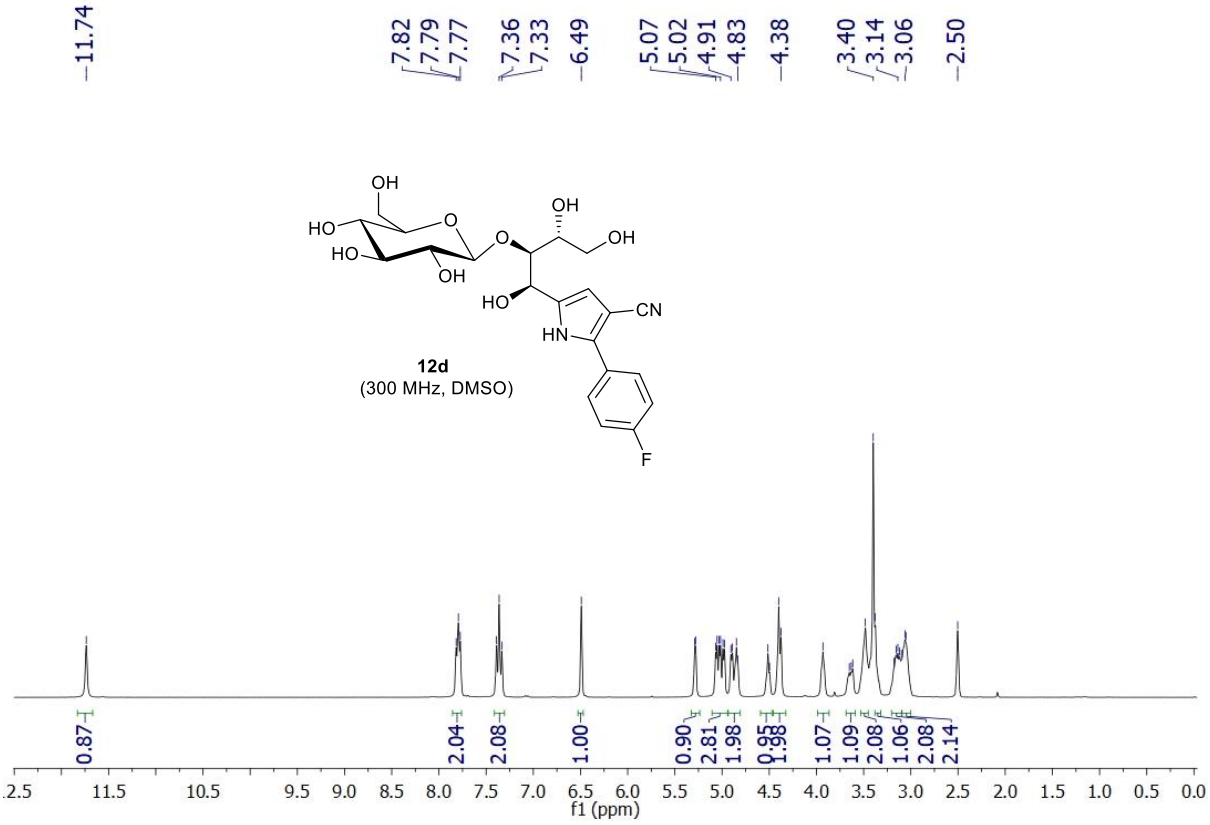


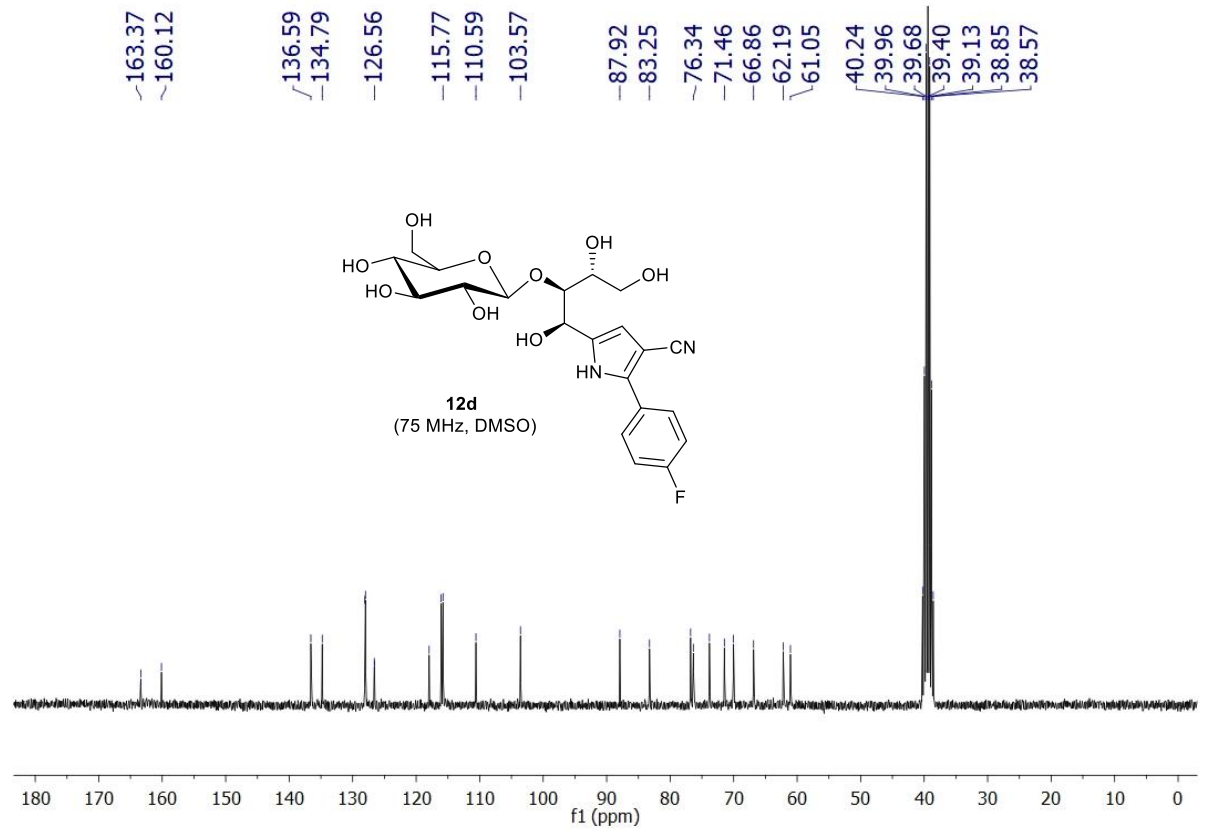
^{1}H and ^{13}C NMR spectra of **12c**



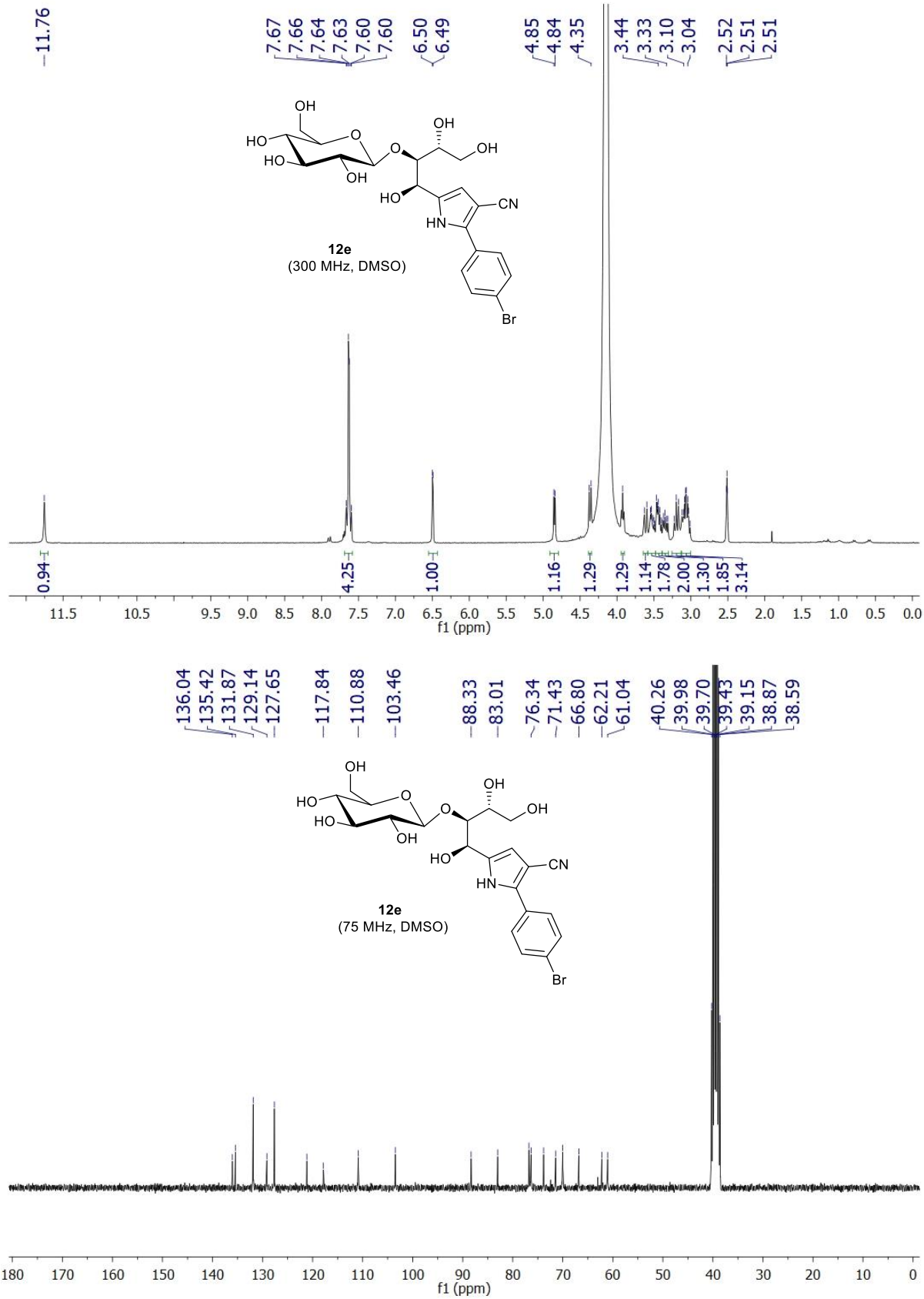


^{1}H and ^{13}C NMR spectra of **12d**

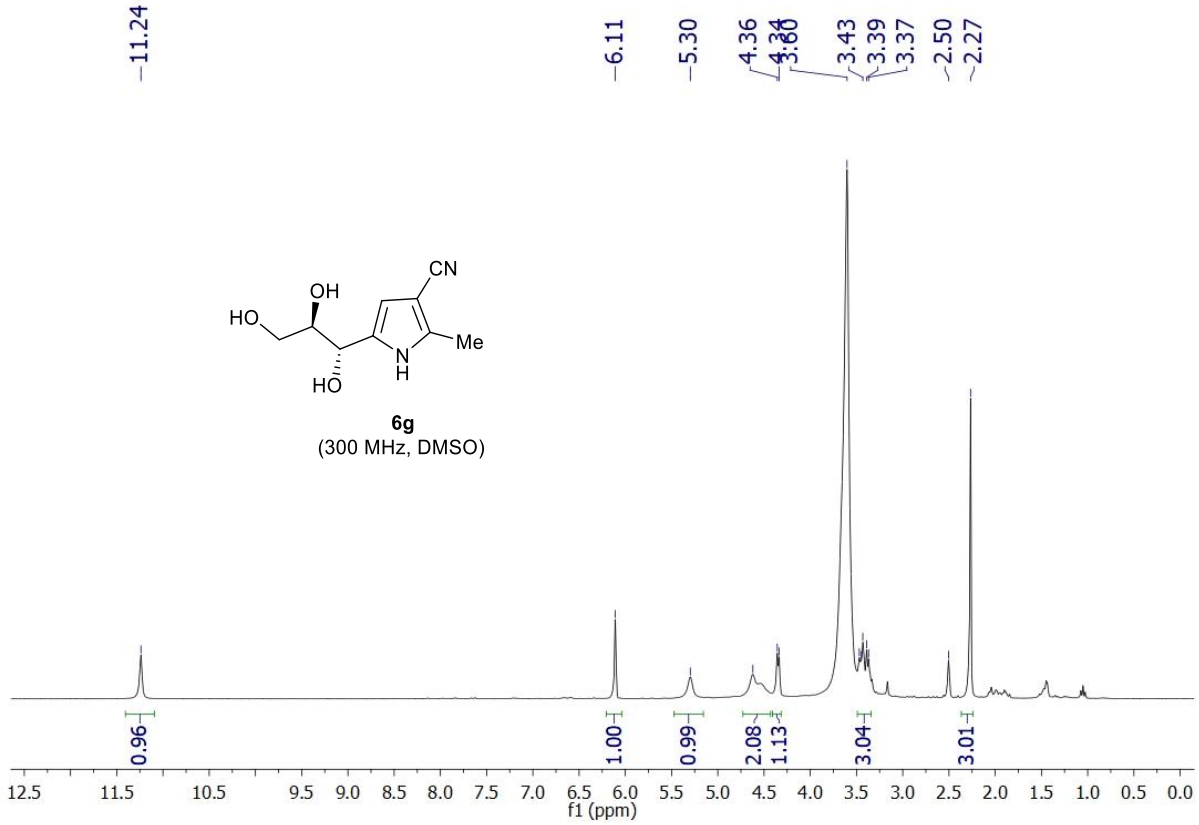


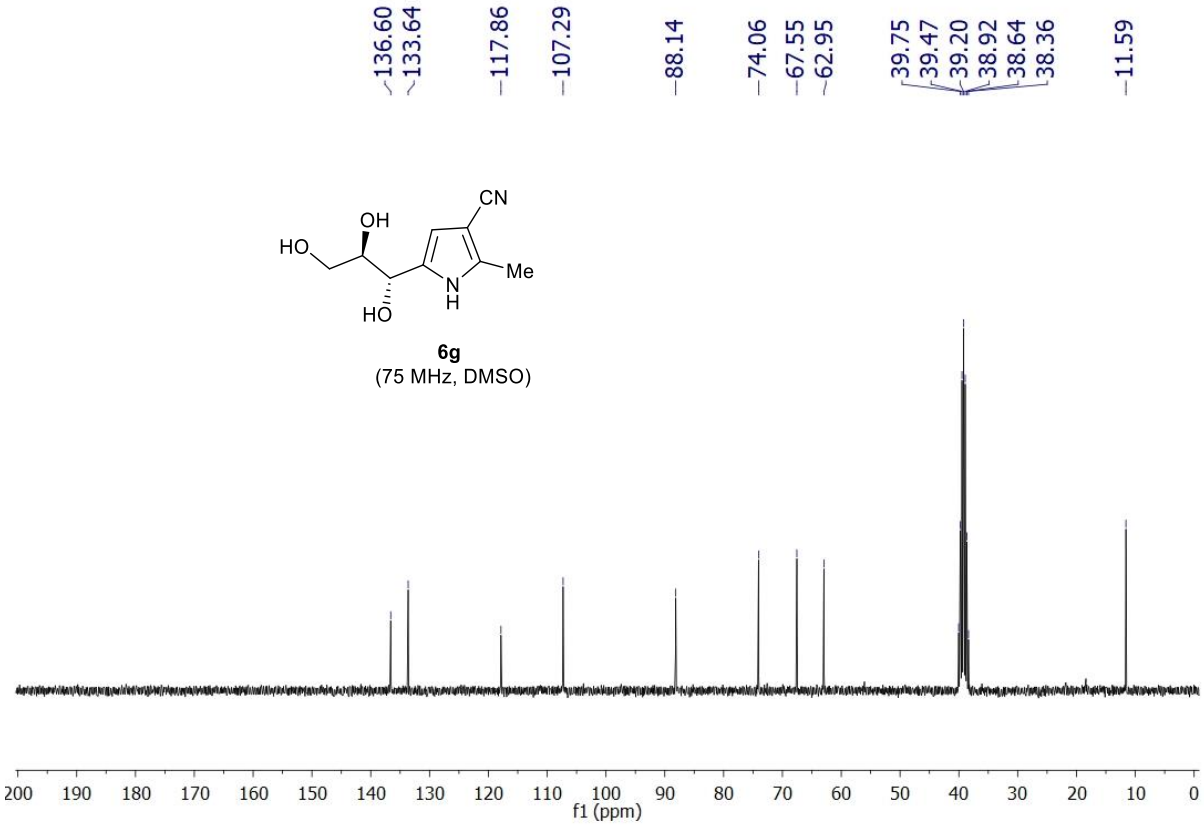


^{1}H and ^{13}C NMR spectra of **12e**

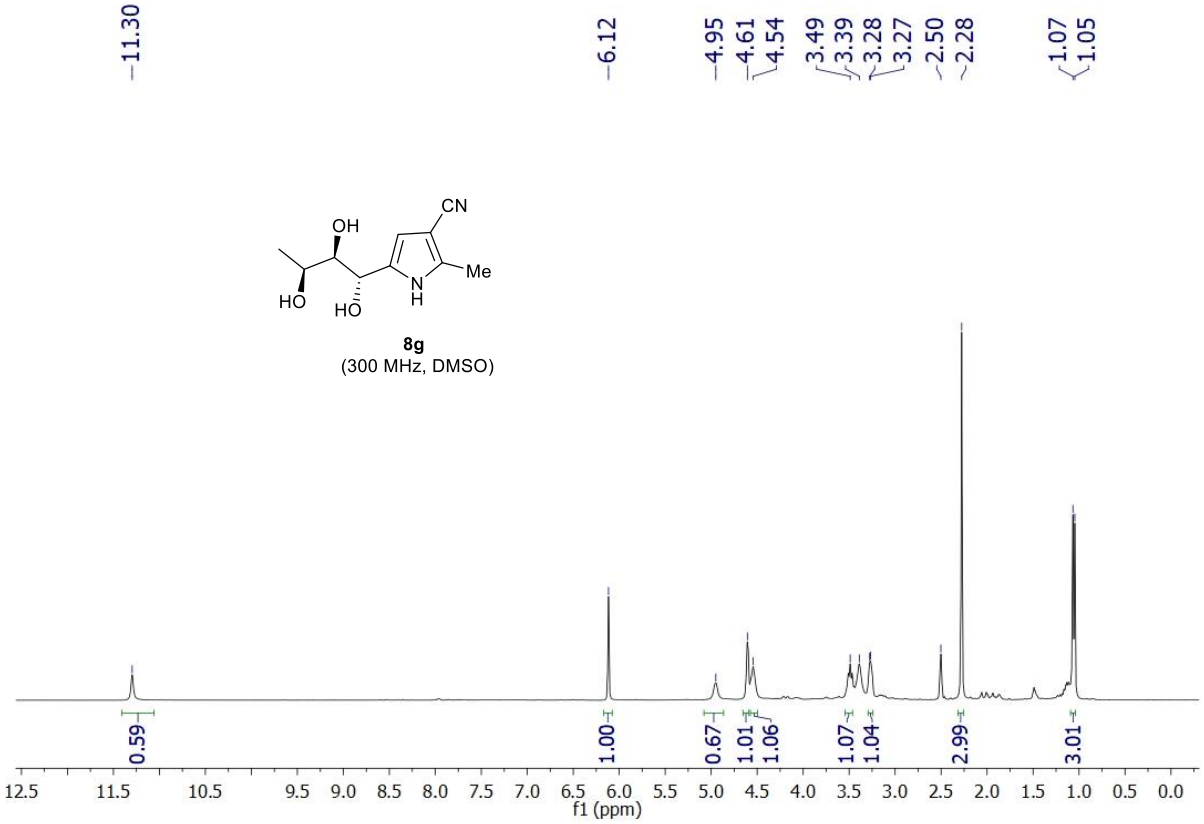


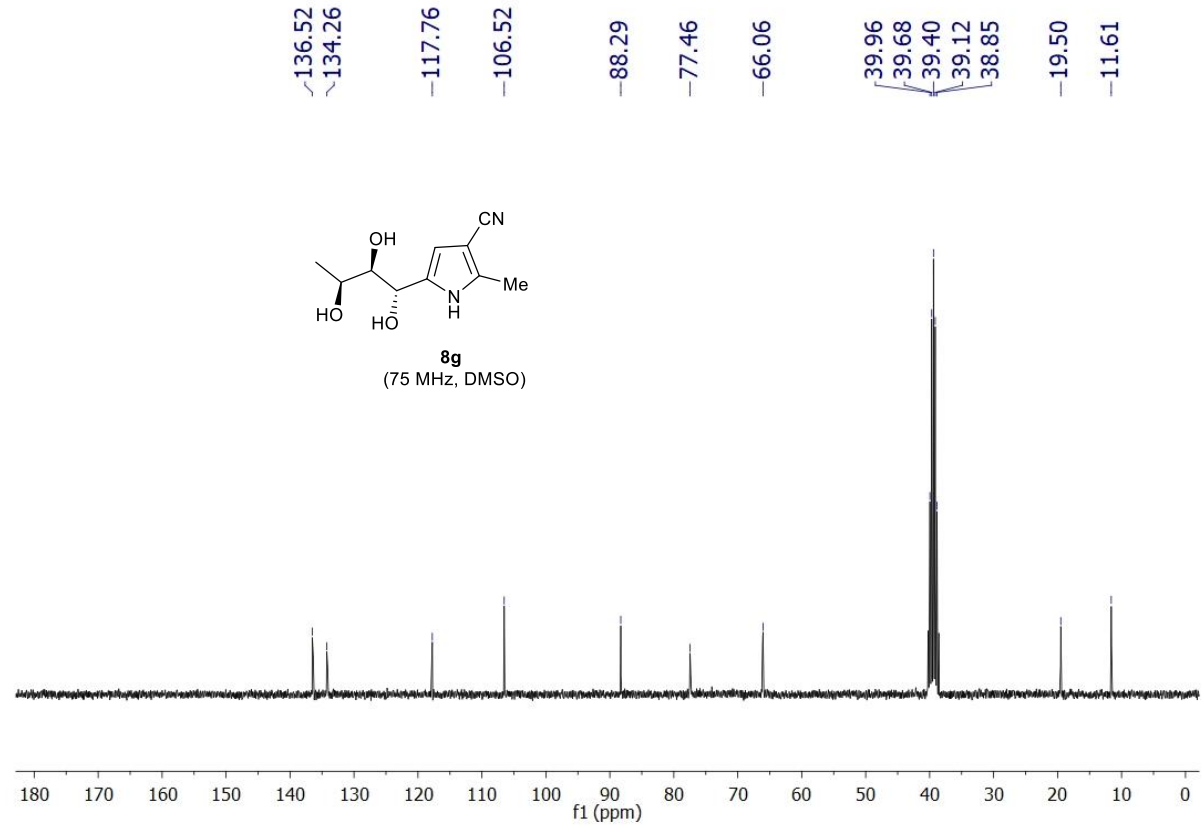
^{1}H and ^{13}C NMR spectra of **6g**



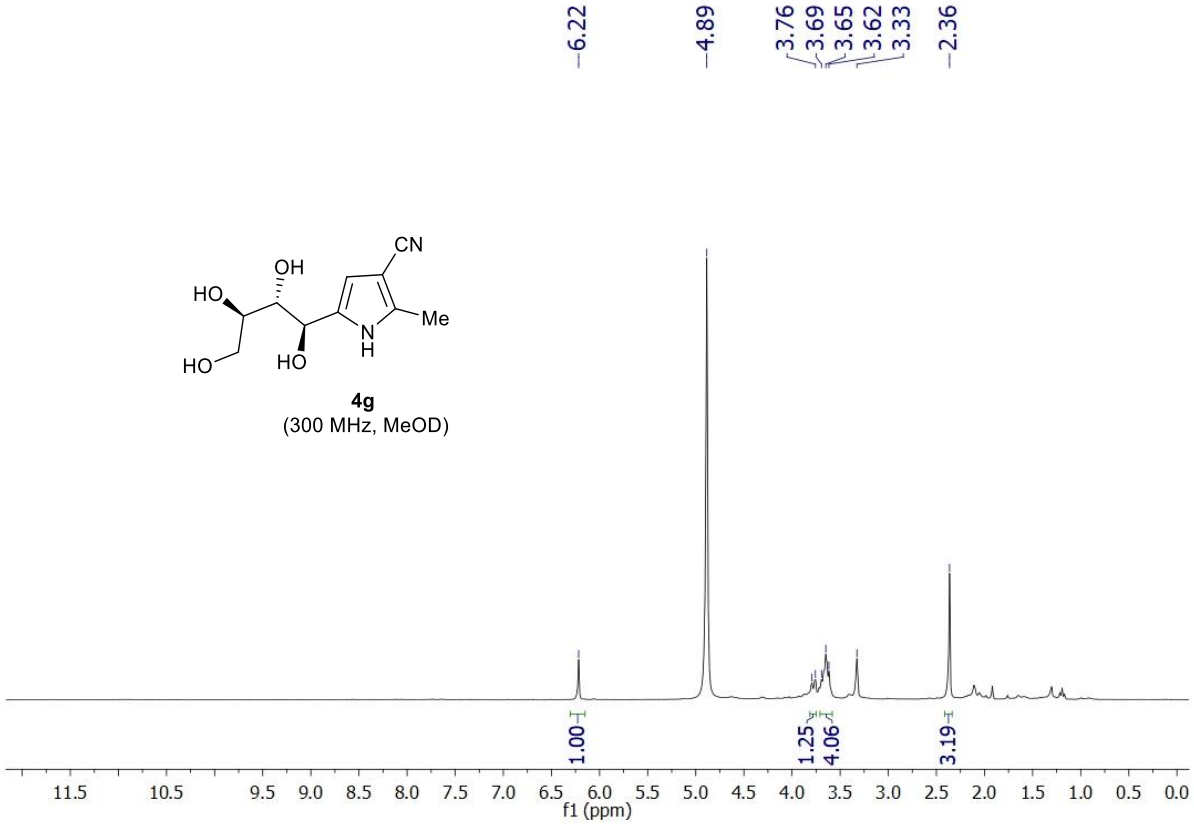


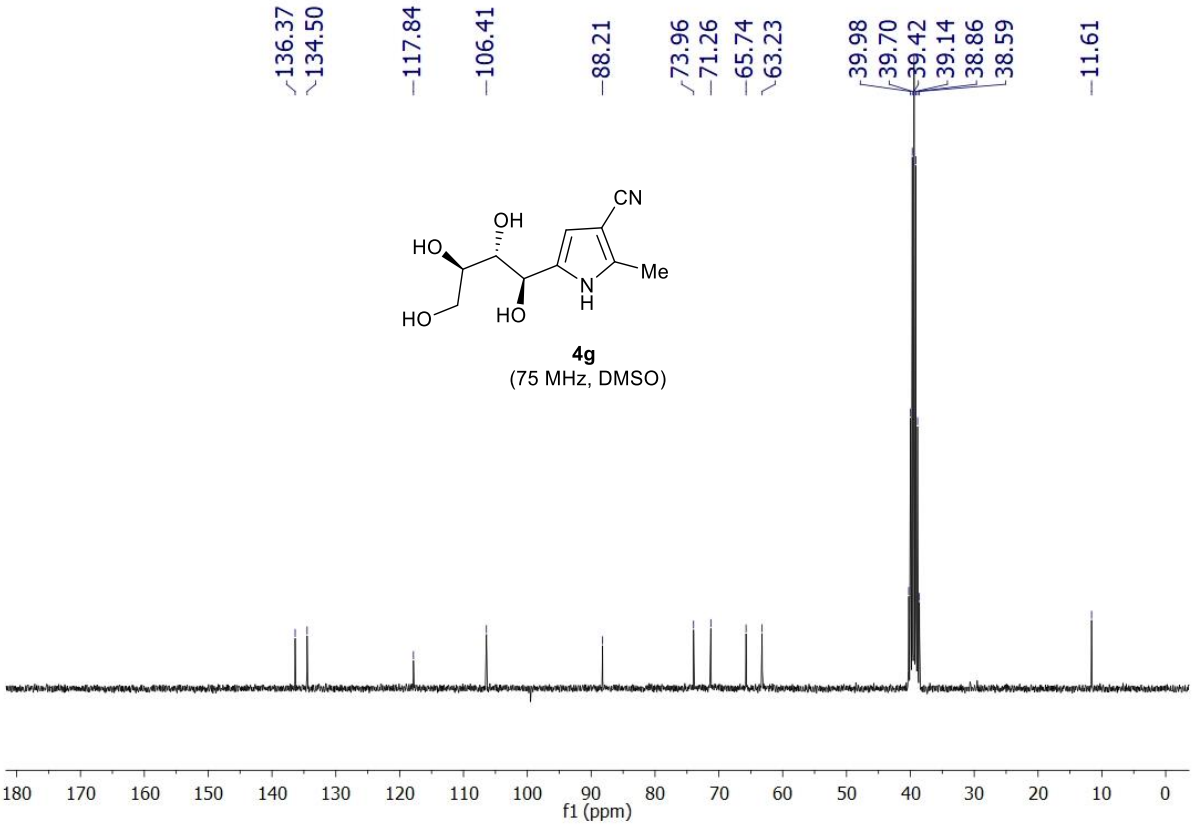
^{1}H and ^{13}C NMR spectra of **8g**



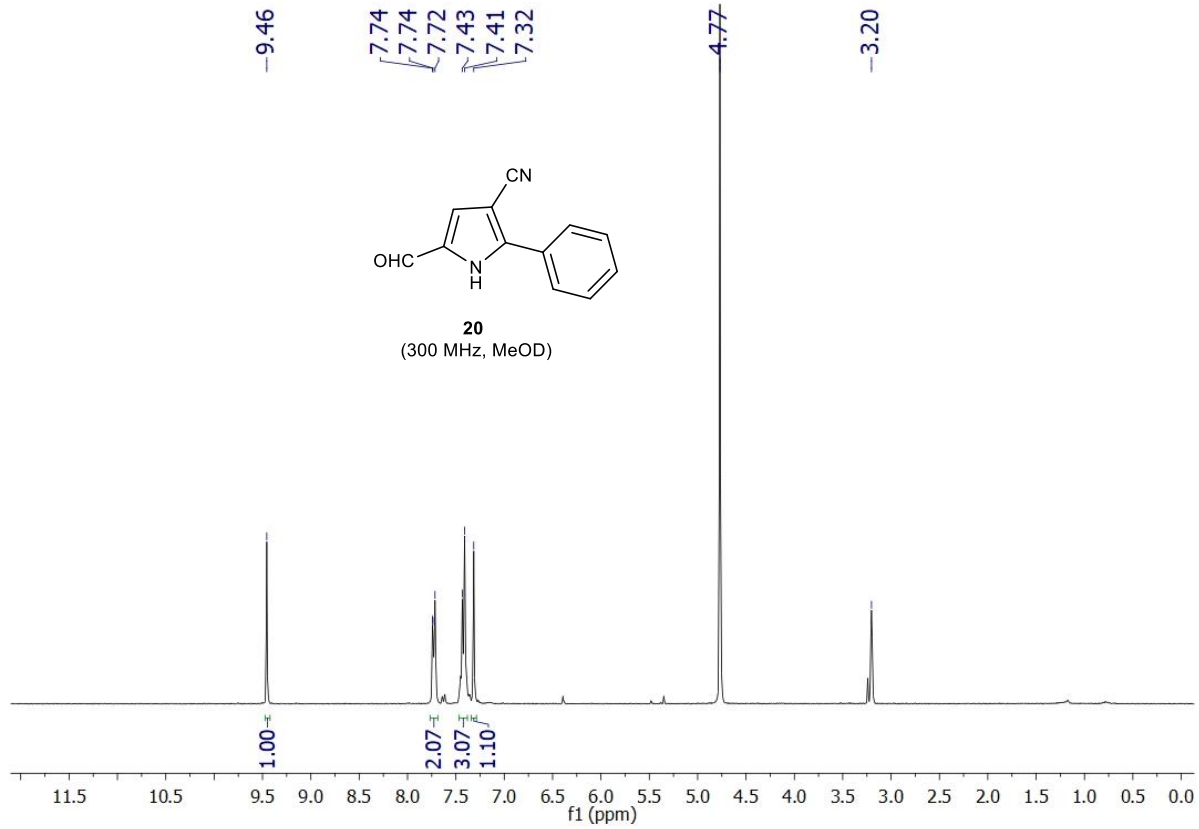


^{1}H and ^{13}C NMR spectra of **4g**

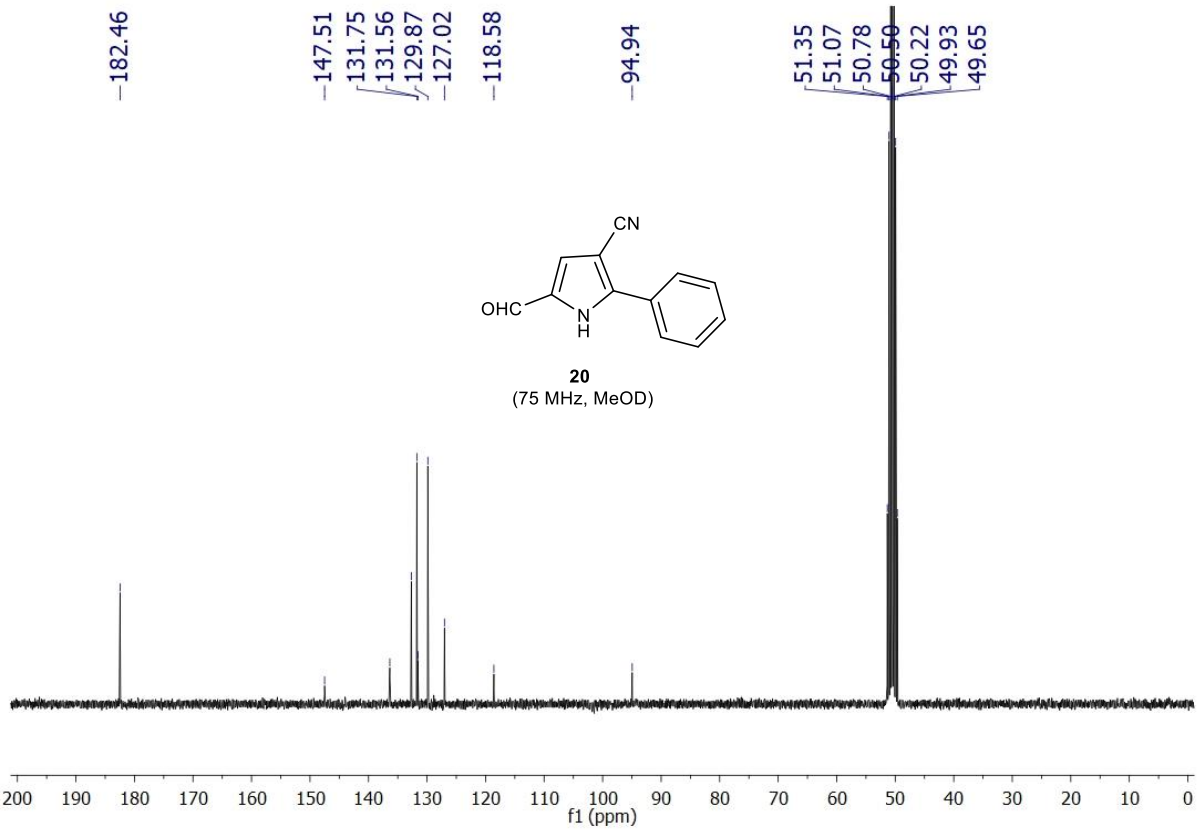




^{1}H and ^{13}C NMR spectra of **20**

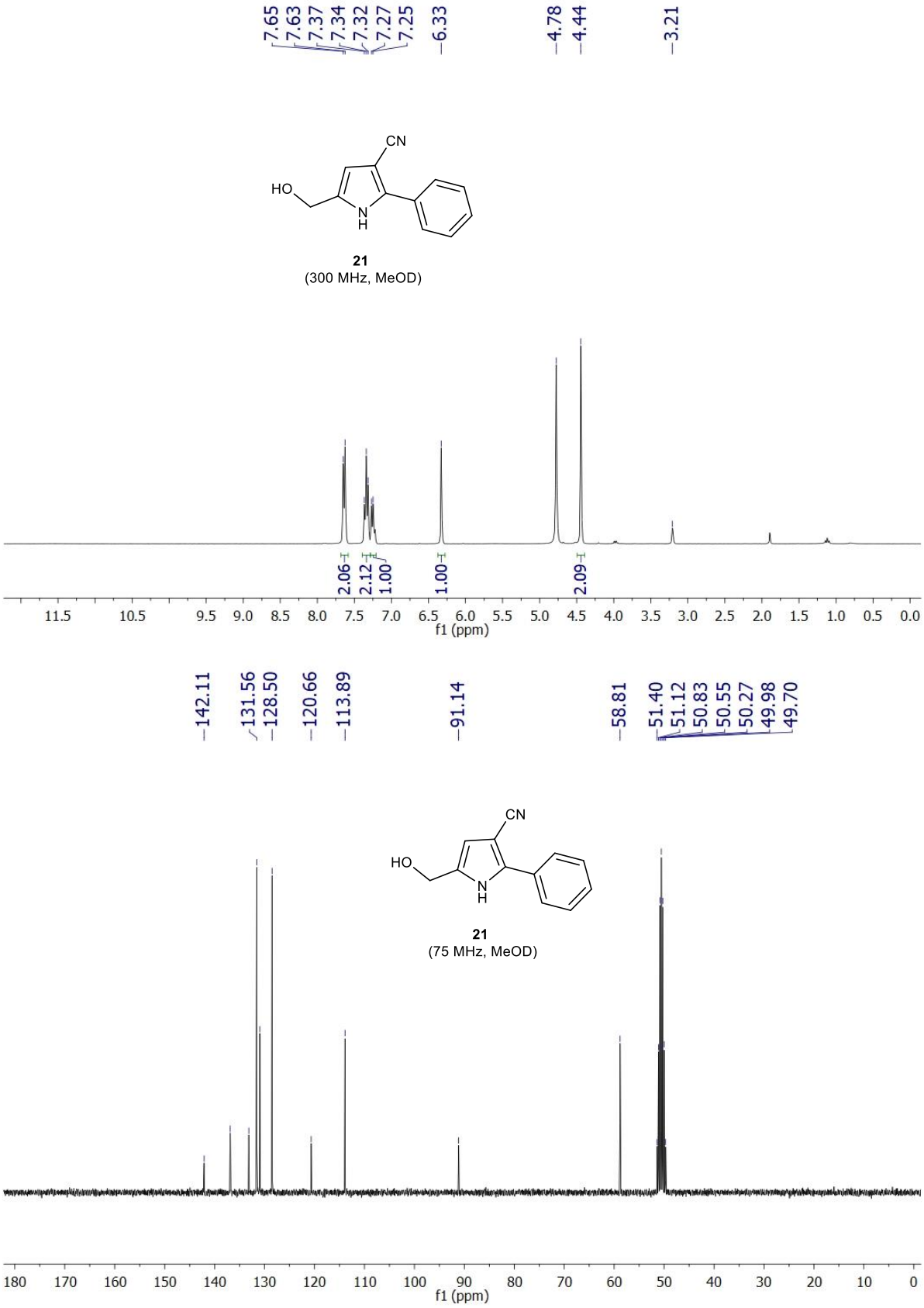


20
(300 MHz, MeOD)

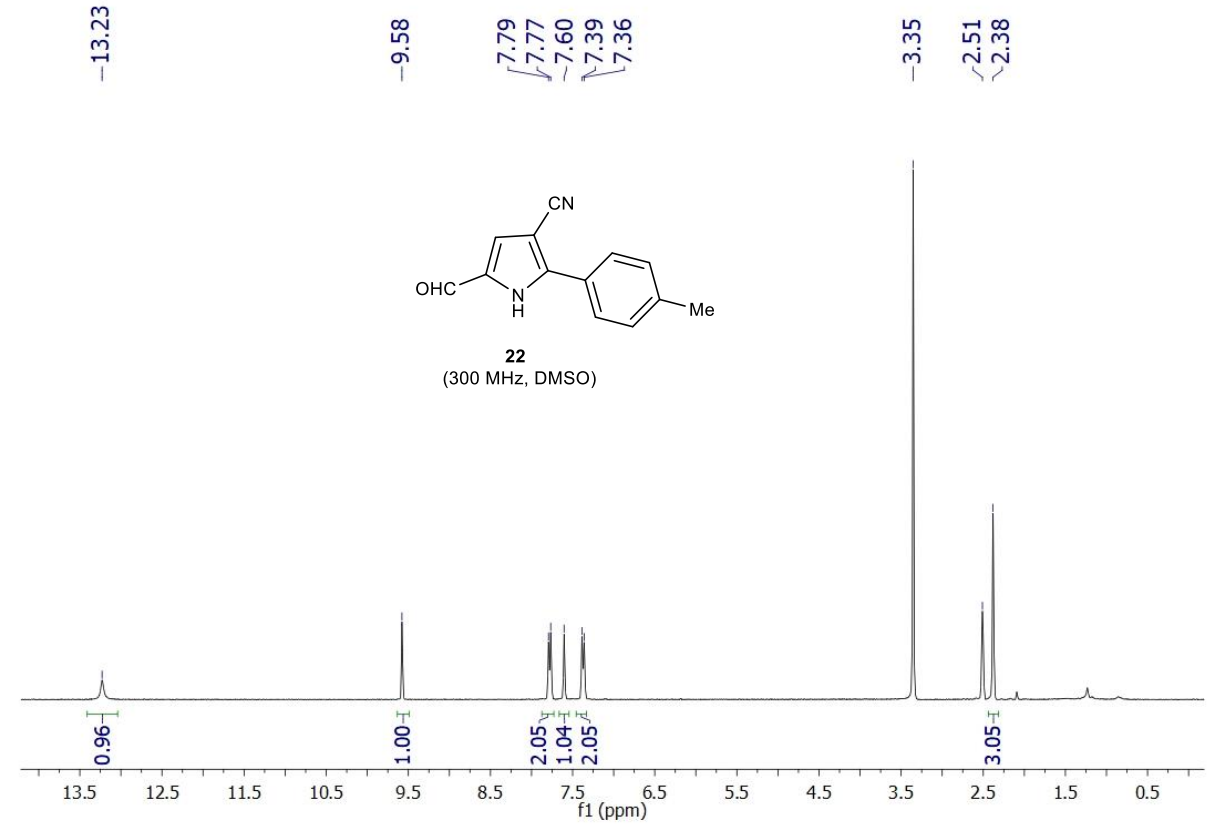


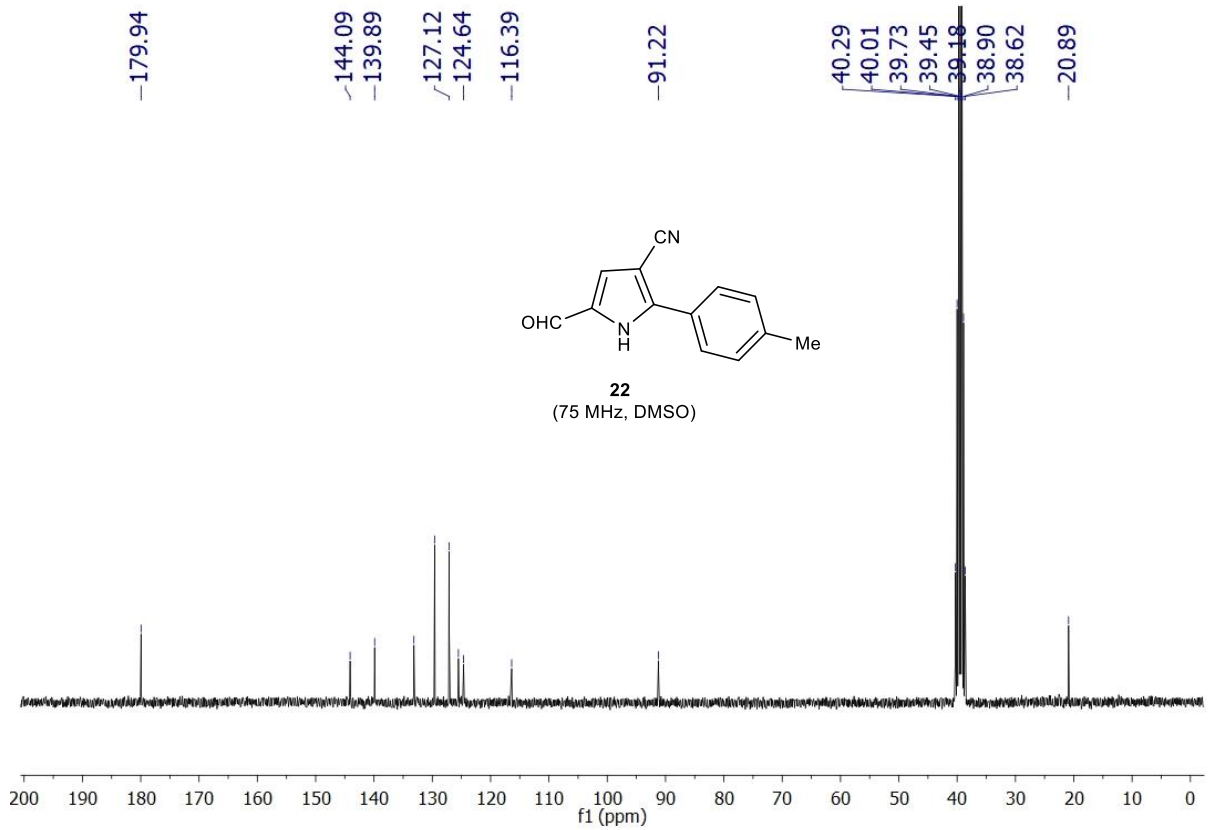
20
(75 MHz, MeOD)

^{1}H and ^{13}C NMR spectra of **21**

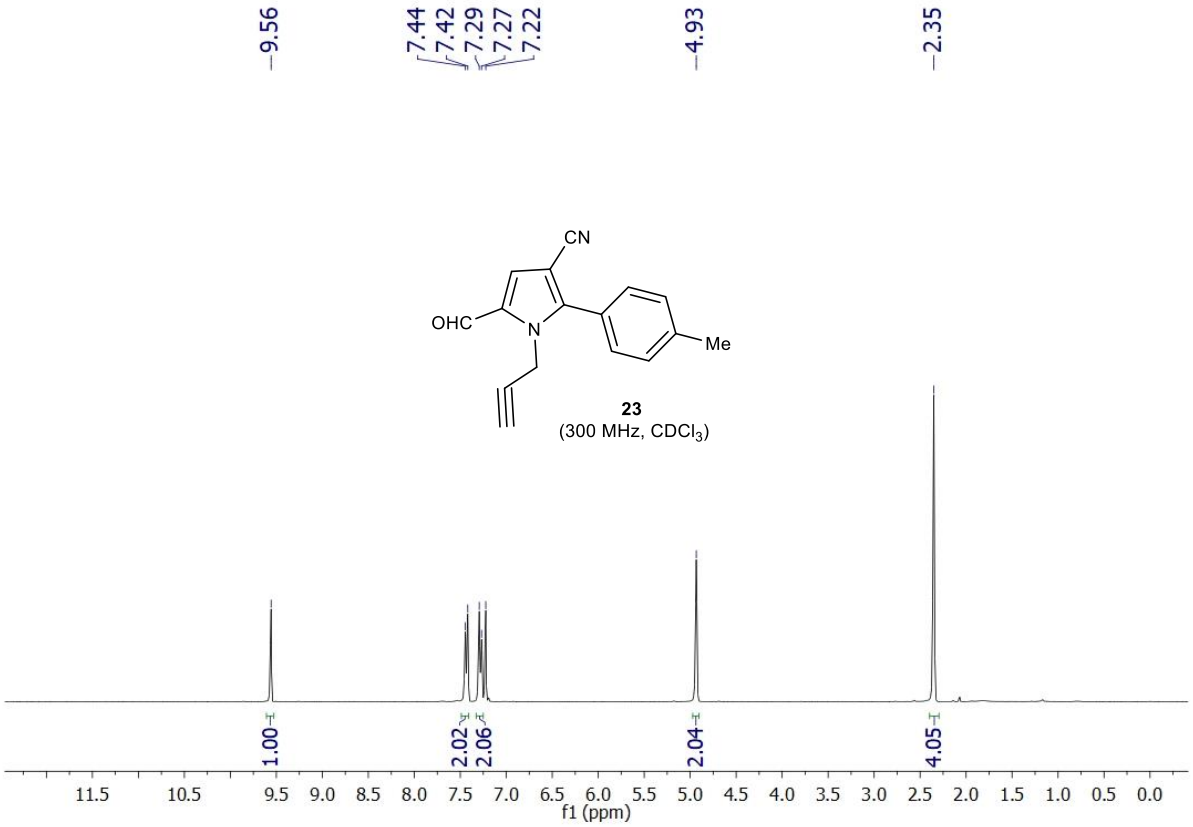


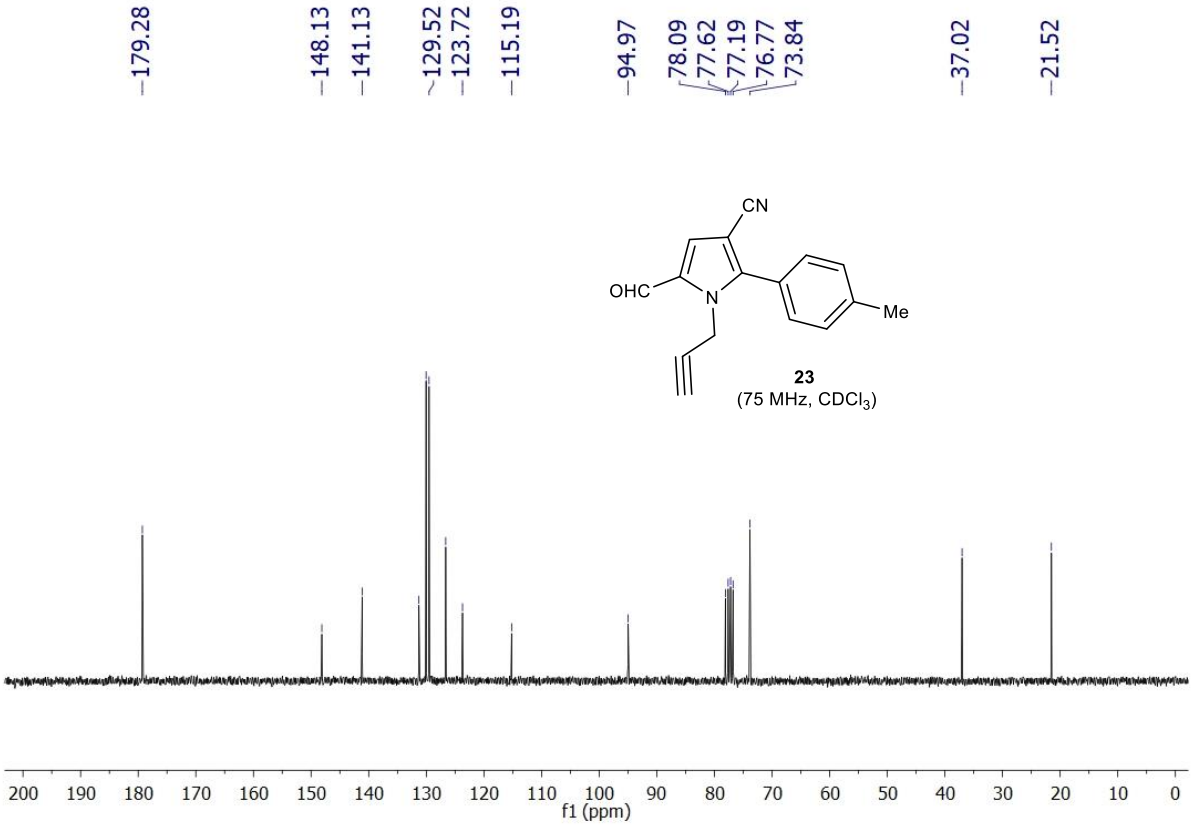
^{1}H and ^{13}C NMR spectra of **22**



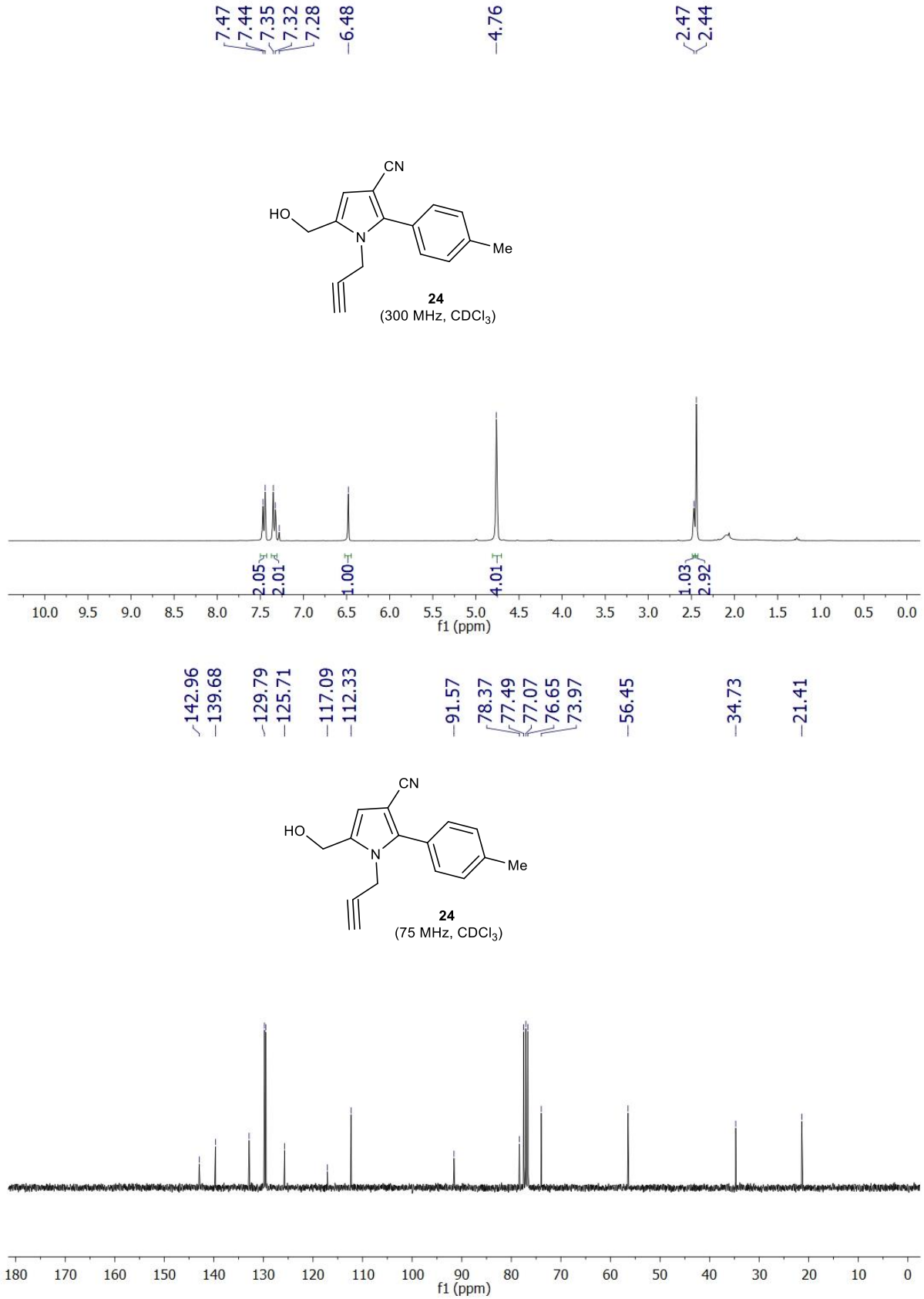


^{1}H and ^{13}C NMR spectra of **23**

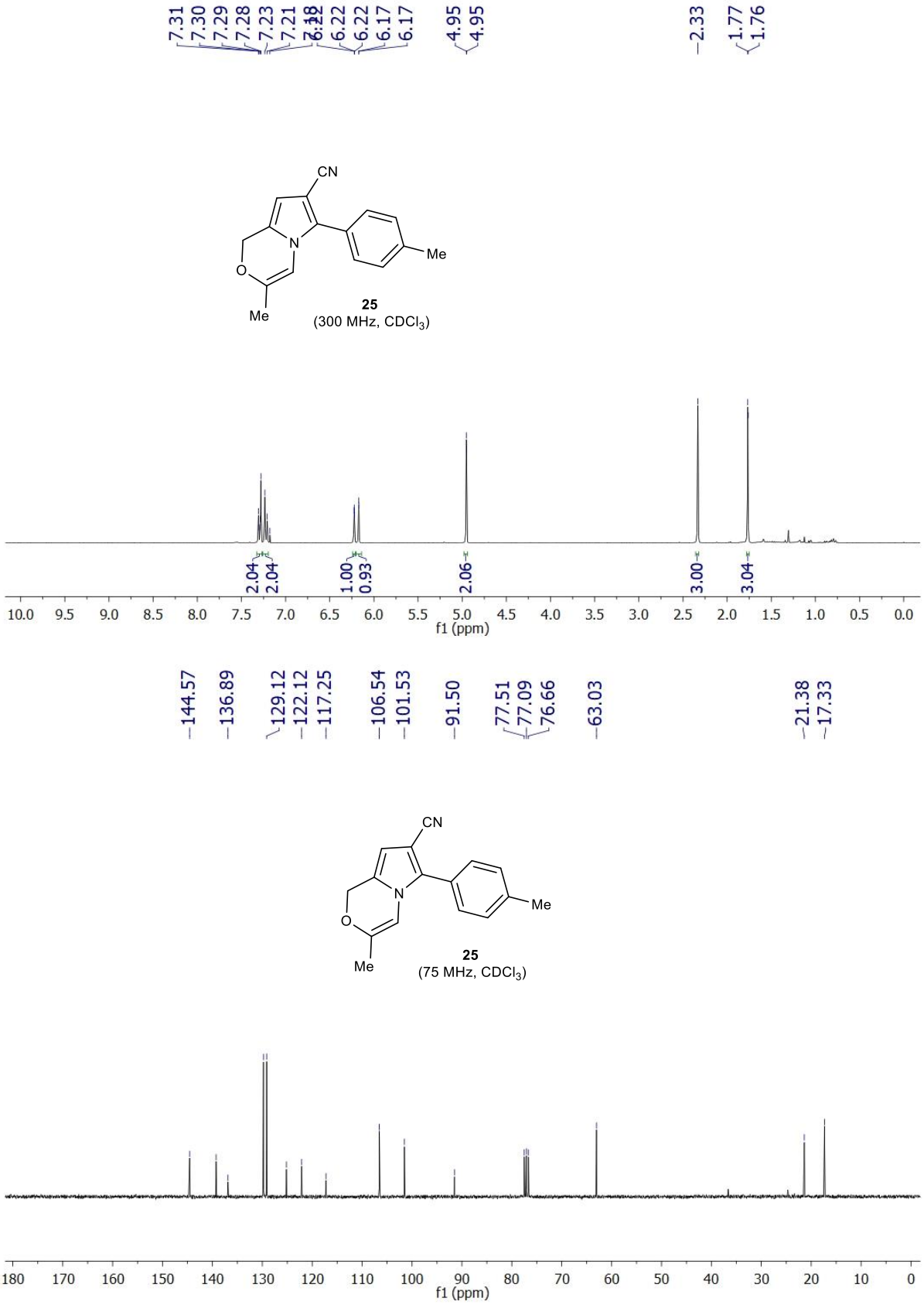




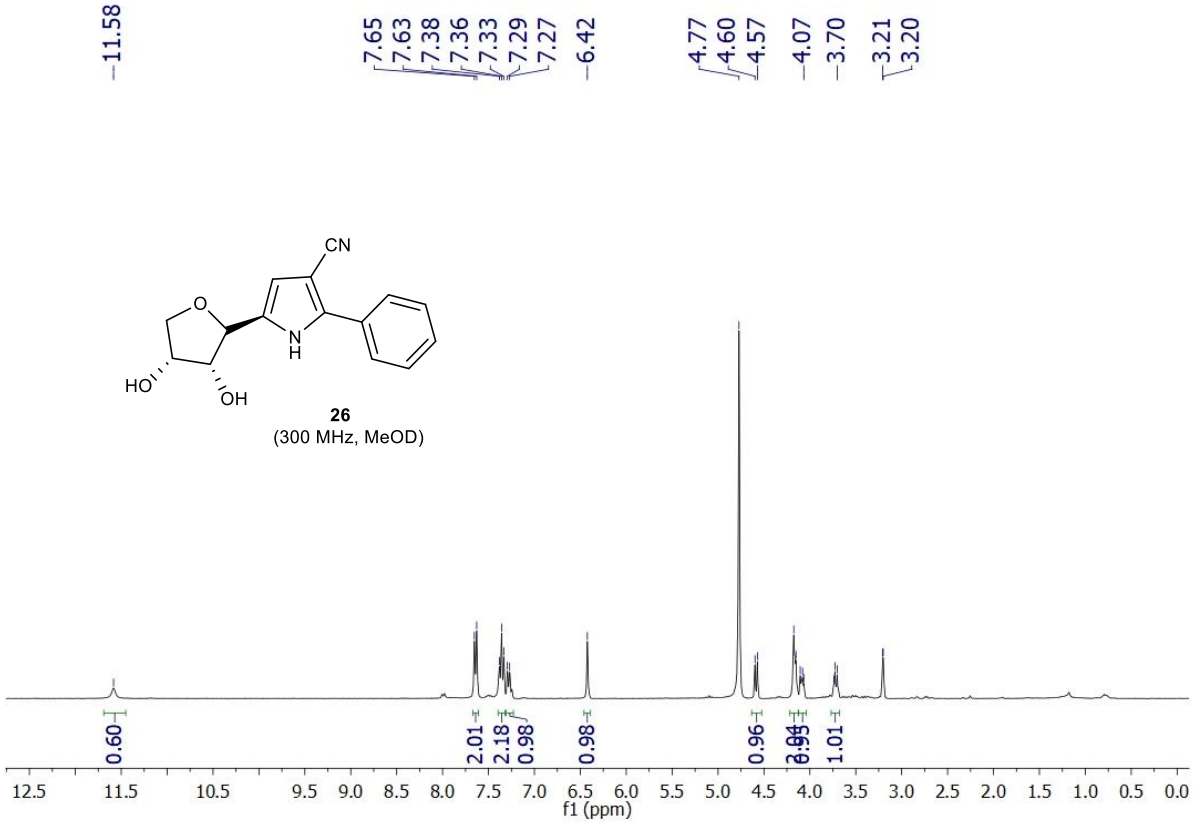
^{1}H and ^{13}C NMR spectra of **24**

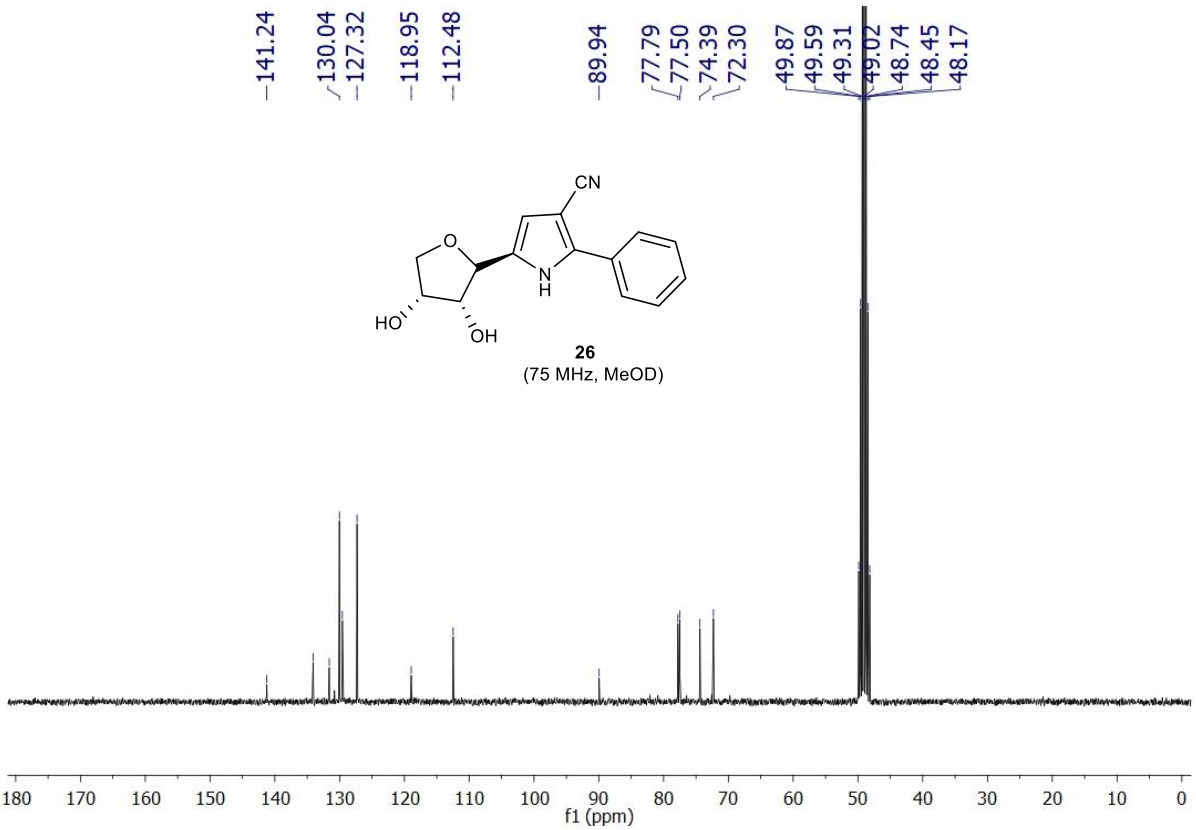


^{1}H and ^{13}C NMR spectra of **25**

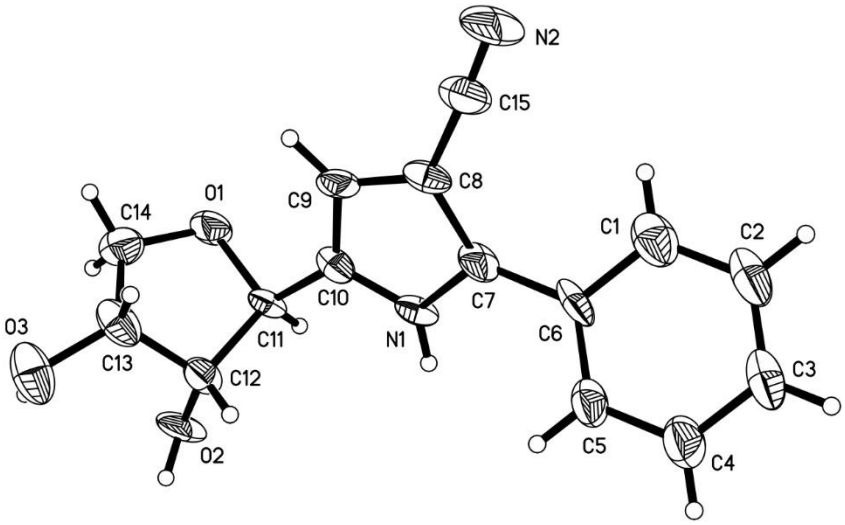


^{1}H and ^{13}C NMR spectra of **26**





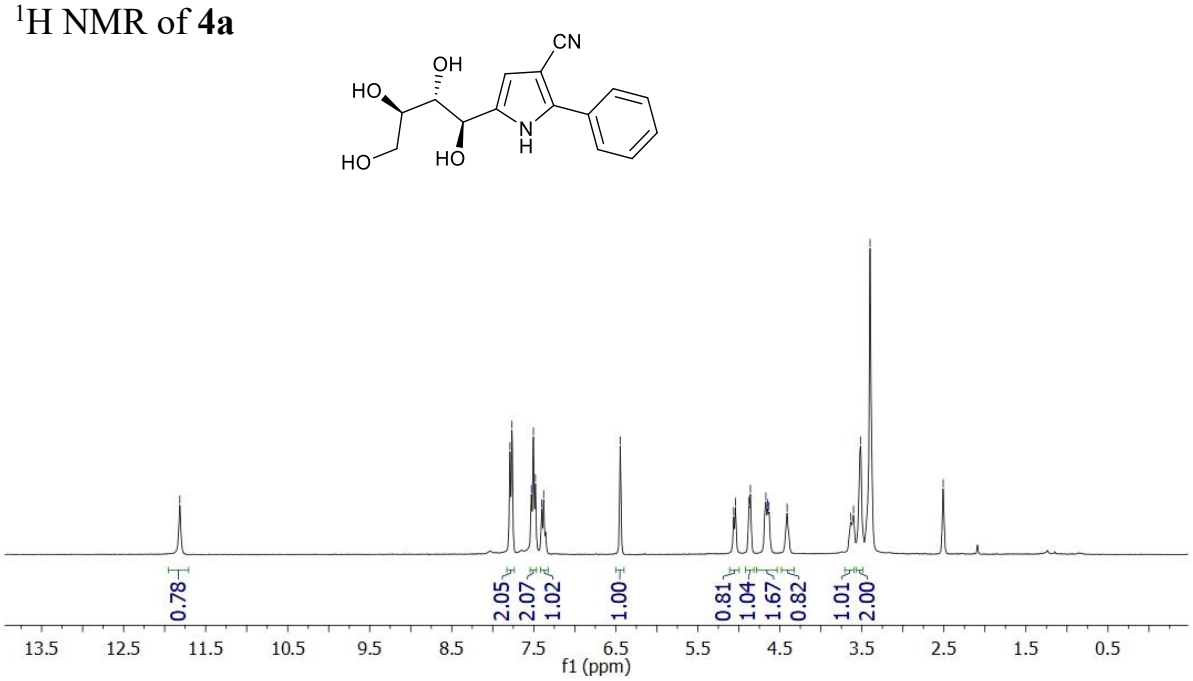
1.2 Single-crystal X-ray Diffraction of 26



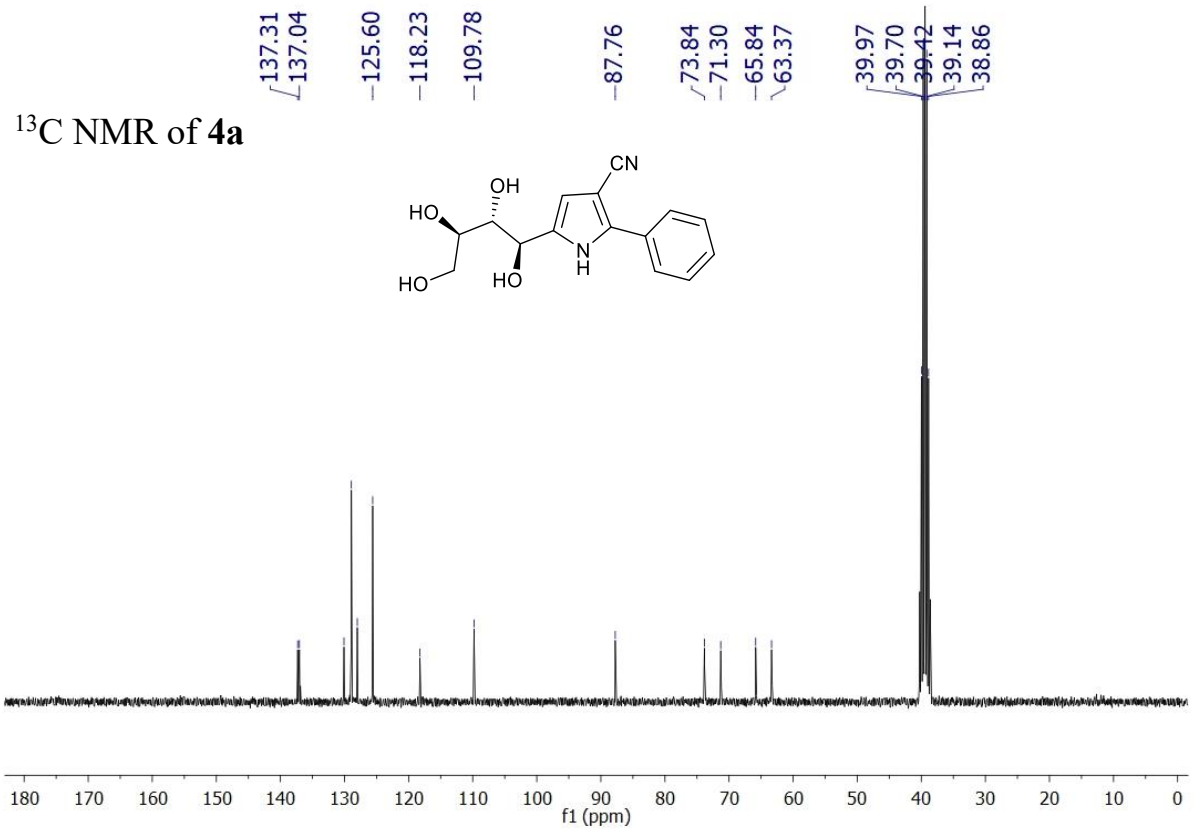
CCDC 2045898 can be obtained free of charge from the Cambridge crystallographic data centre via www.ccdc.cam.ac.uk/data_request/cif.

1.3 NMR characterization of compound 4a

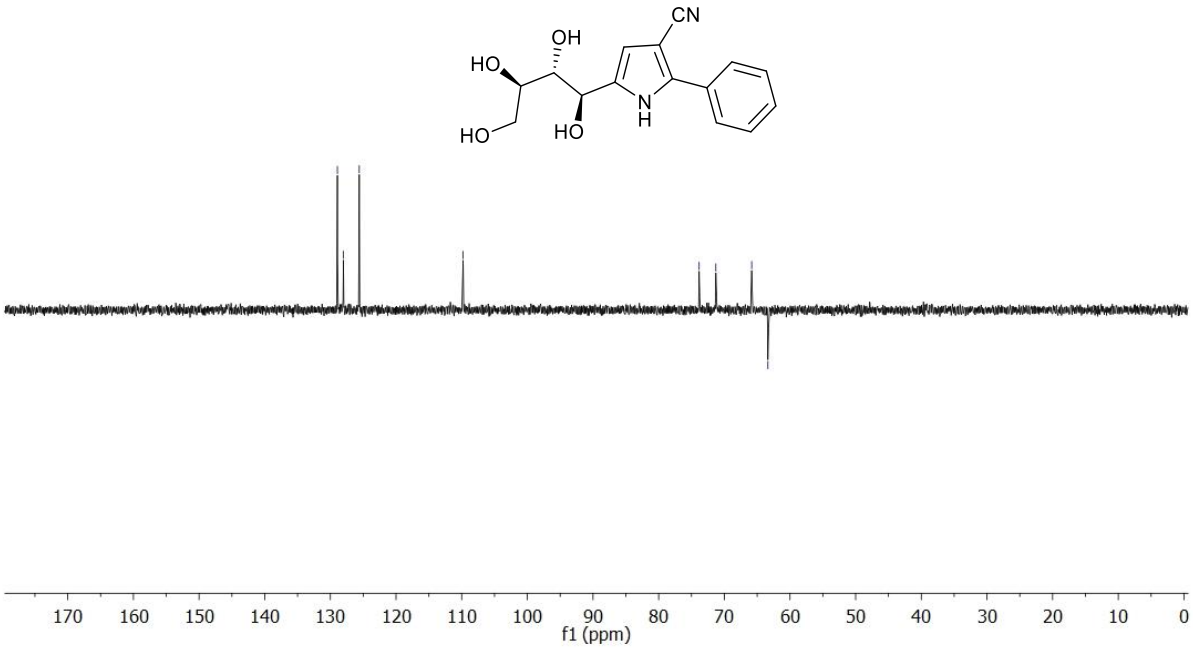
^{1}H NMR of **4a**



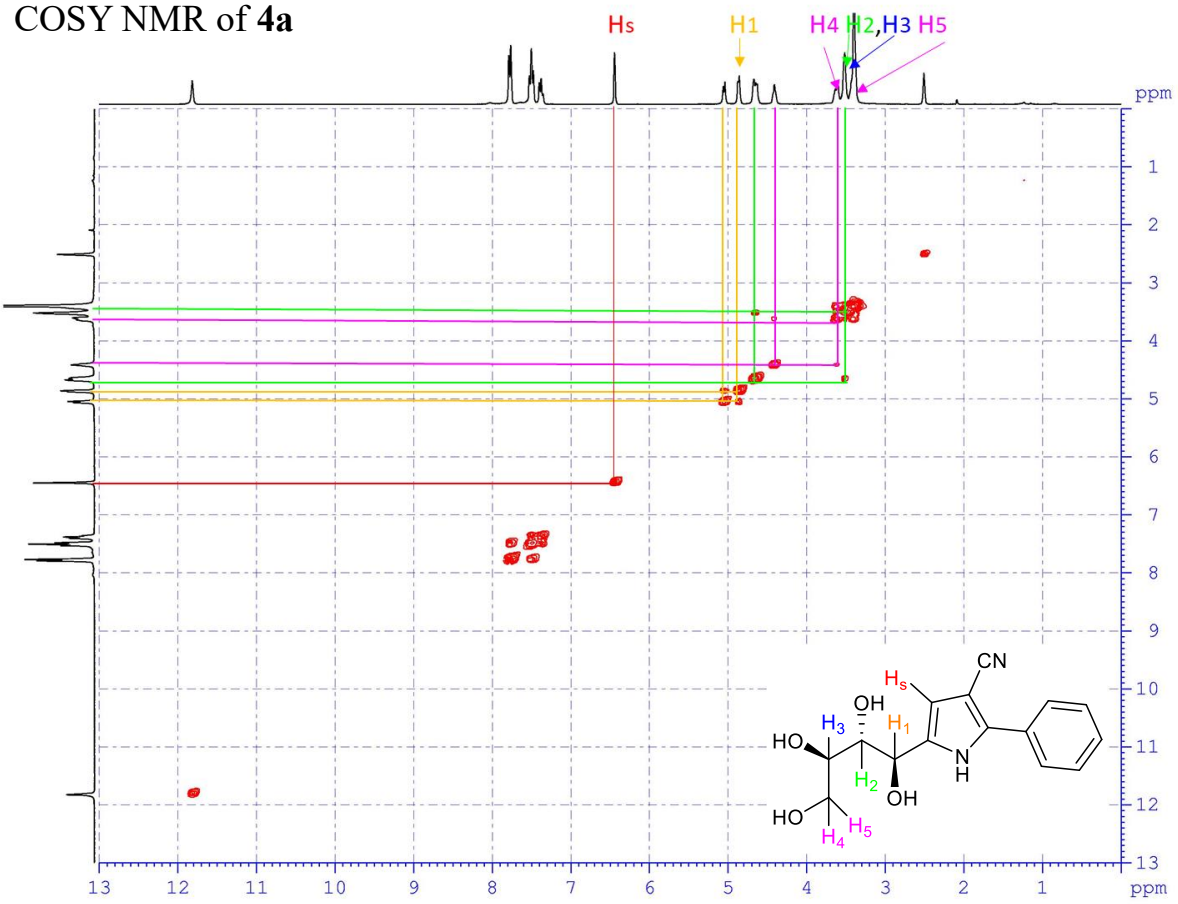
^{13}C NMR of **4a**



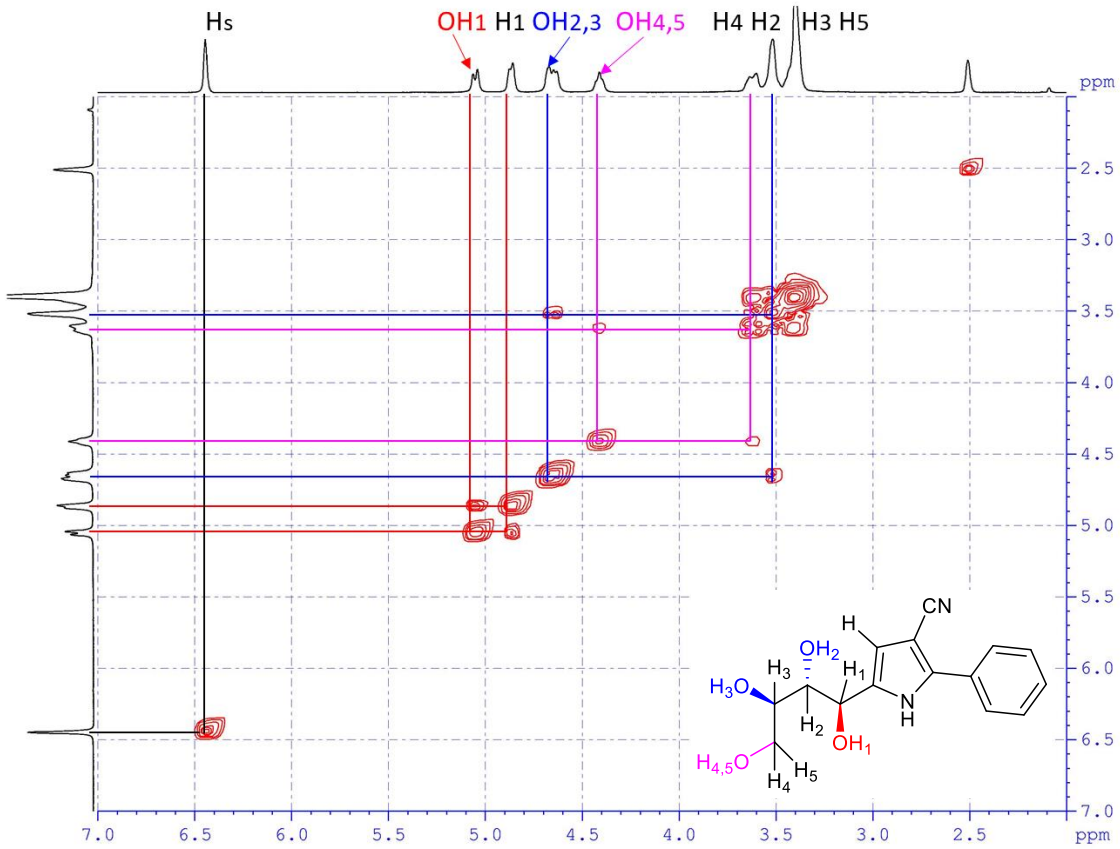
DEPT135 NMR of **4a**



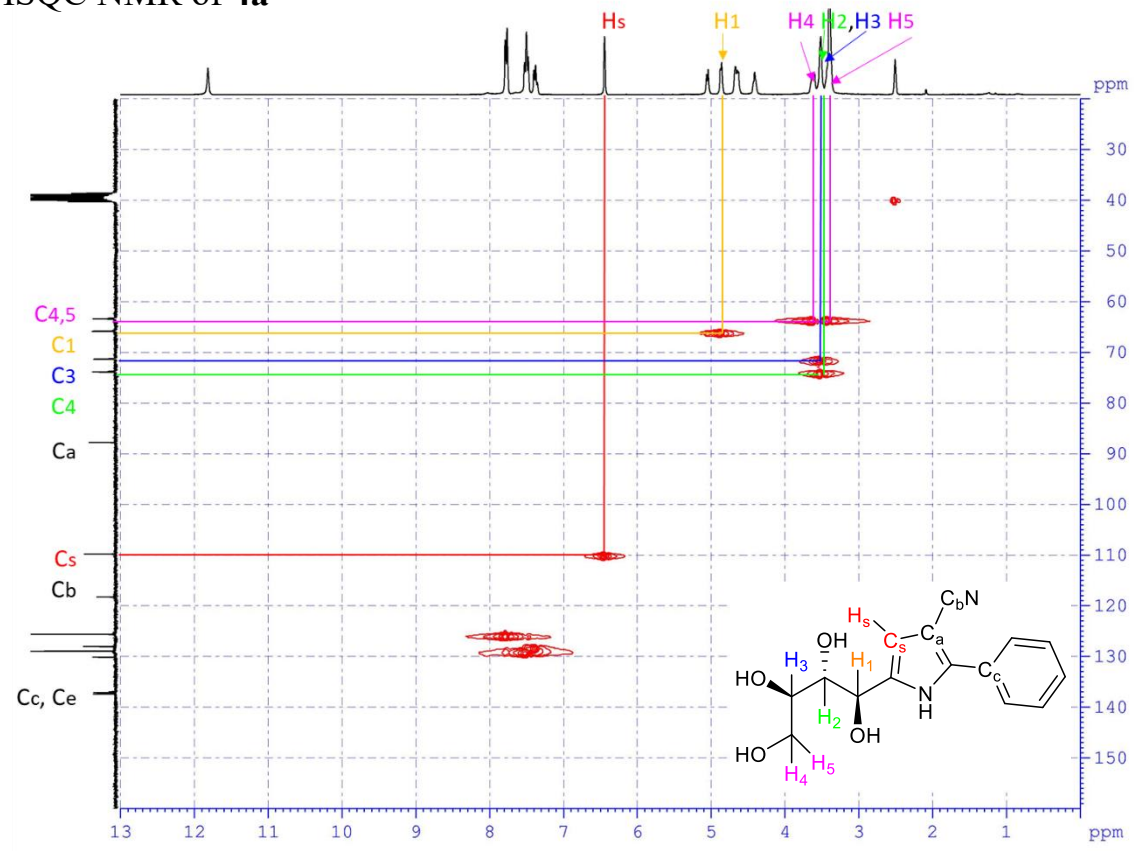
COSY NMR of **4a**



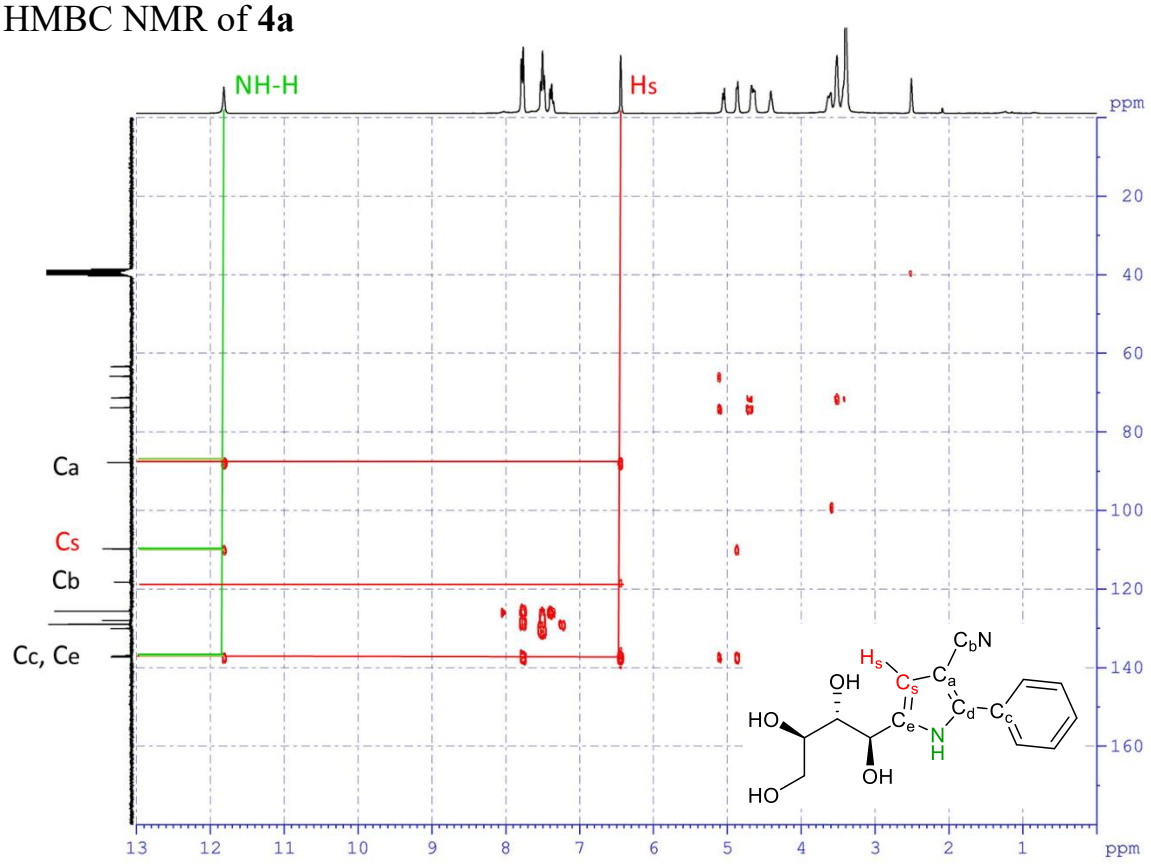
COSY NMR of **4a** (expanded)



HSQC NMR of **4a**



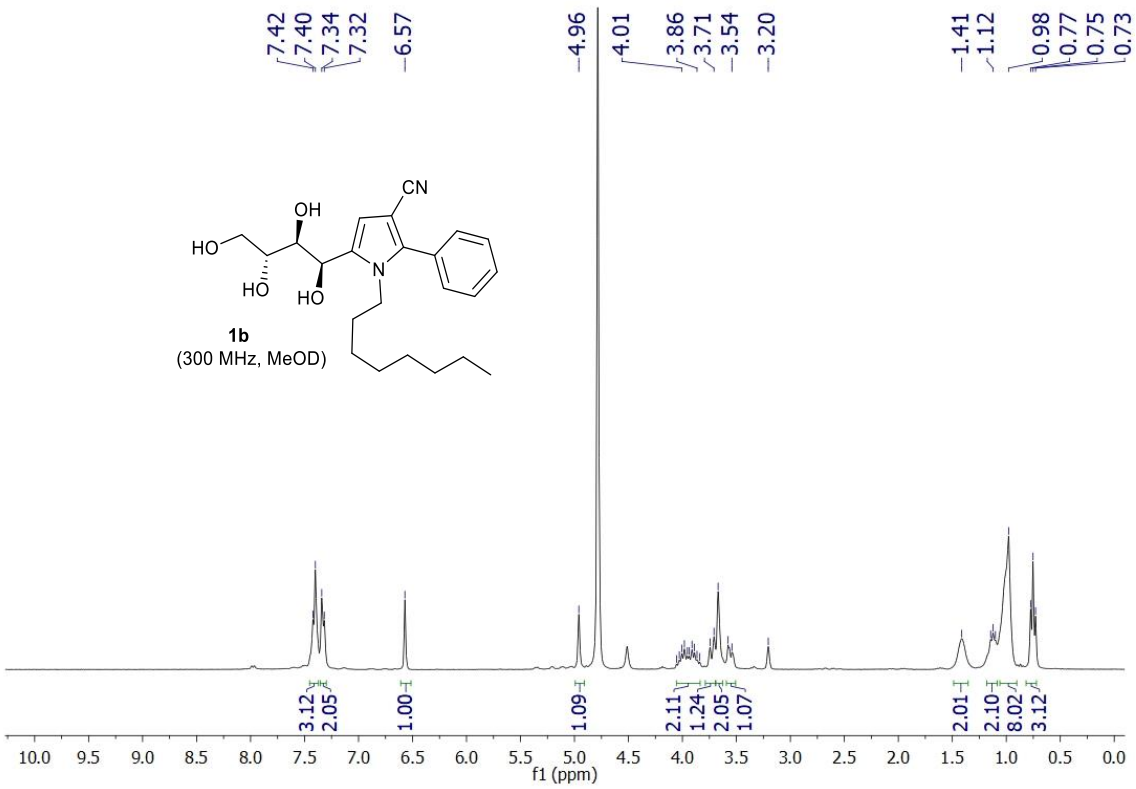
HMBC NMR of **4a**

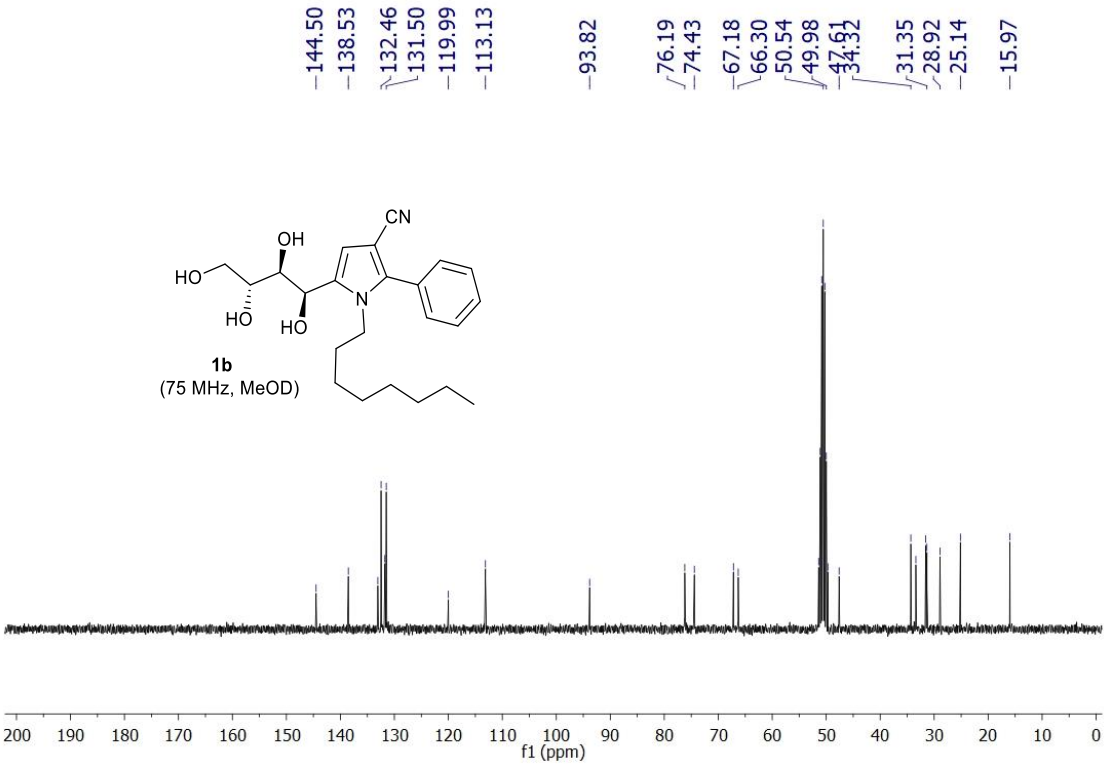


2. Supporting Information for Chapter 3

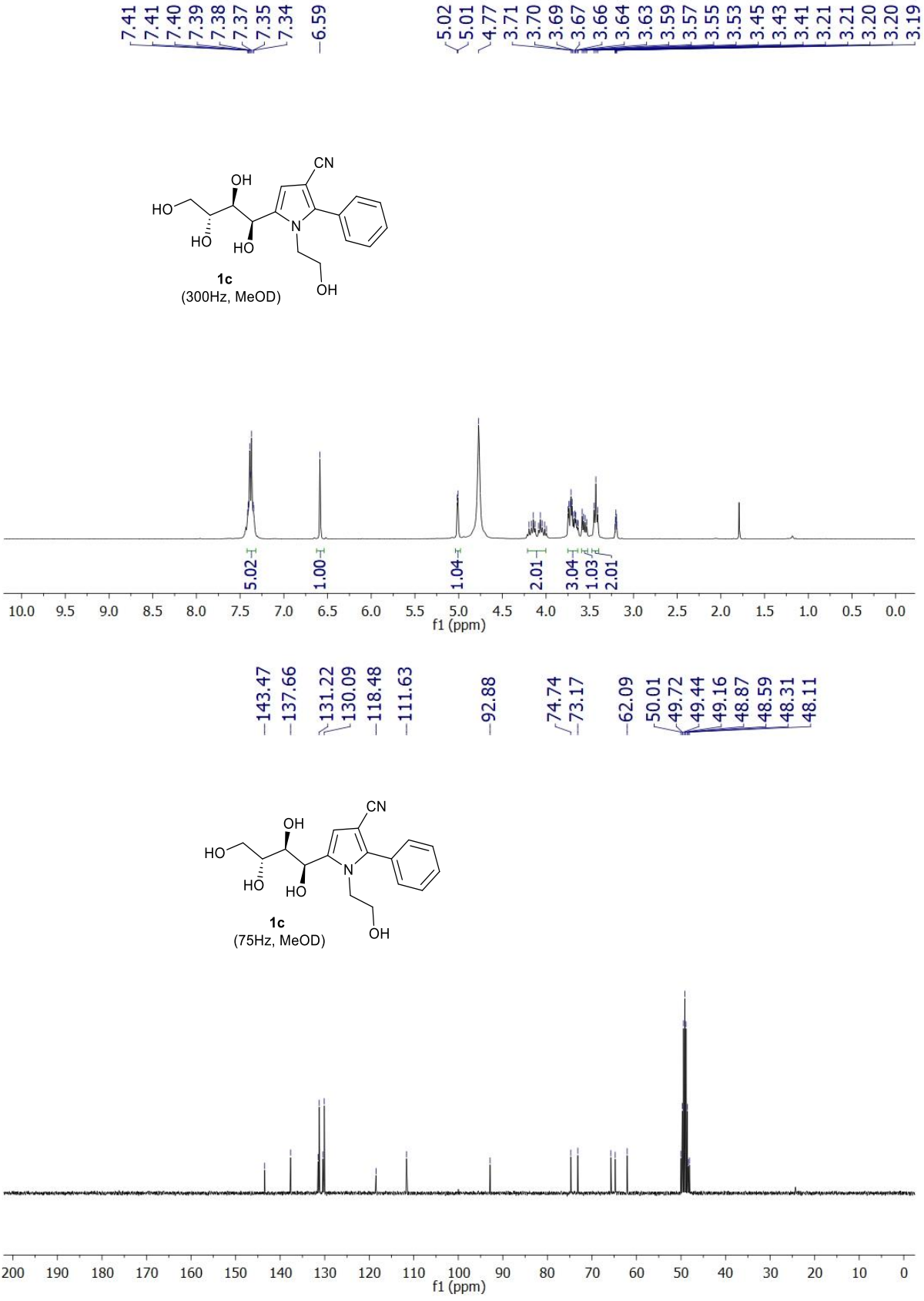
2.1 1H and 13C NMR spectra for 2,3,5-substituted pyrroles

1-Octyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

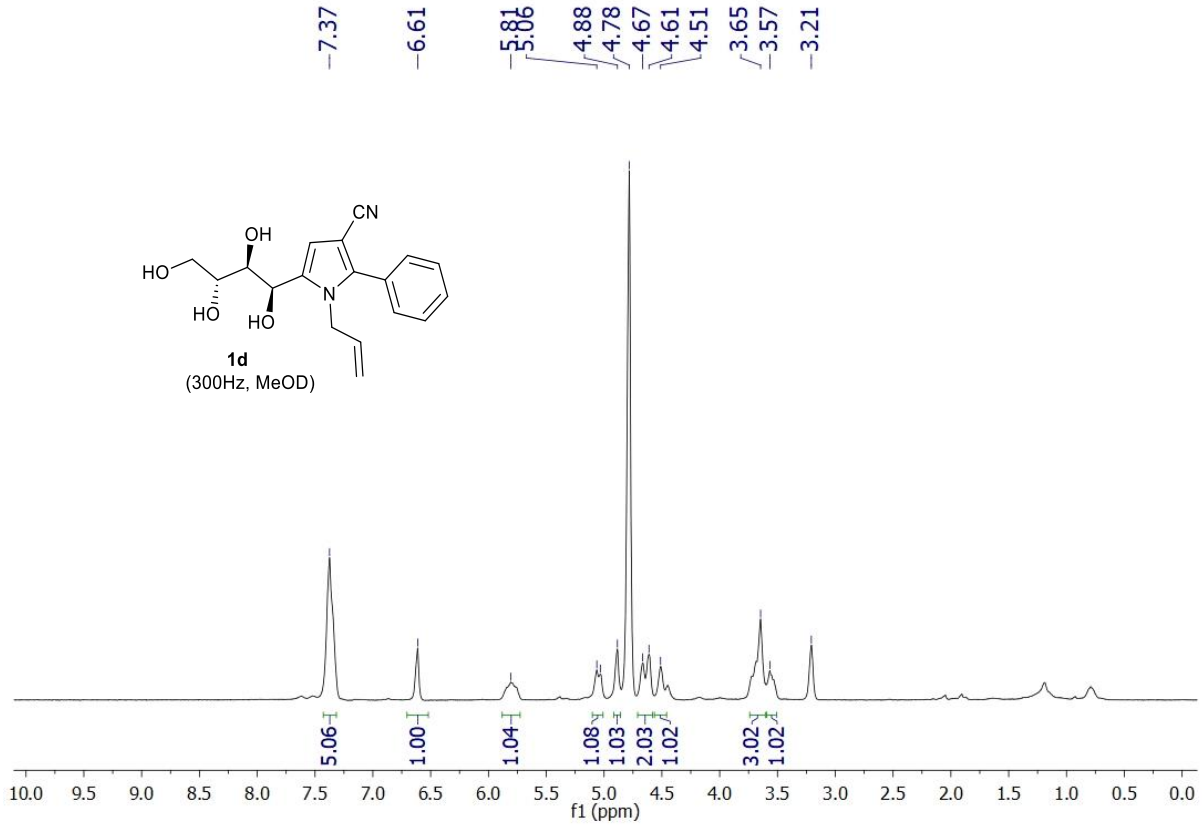


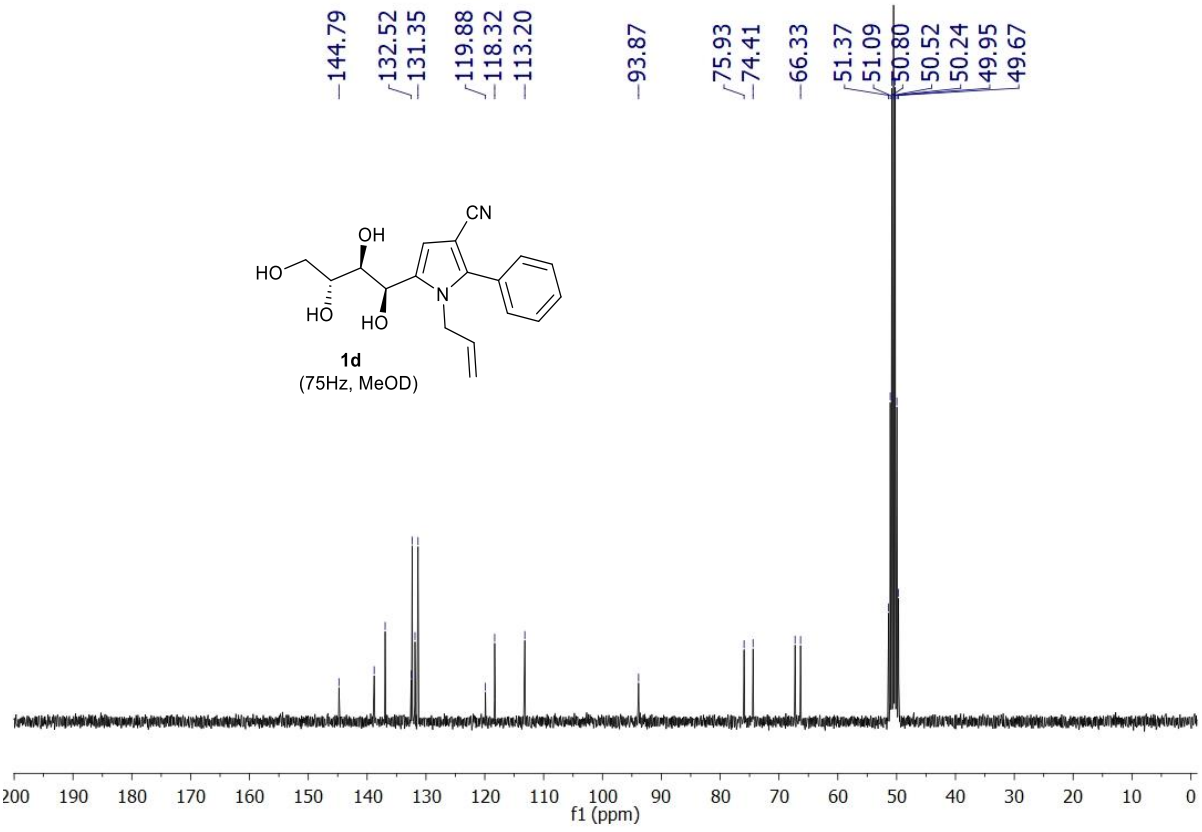


1-(2-Hydroxyethyl)-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

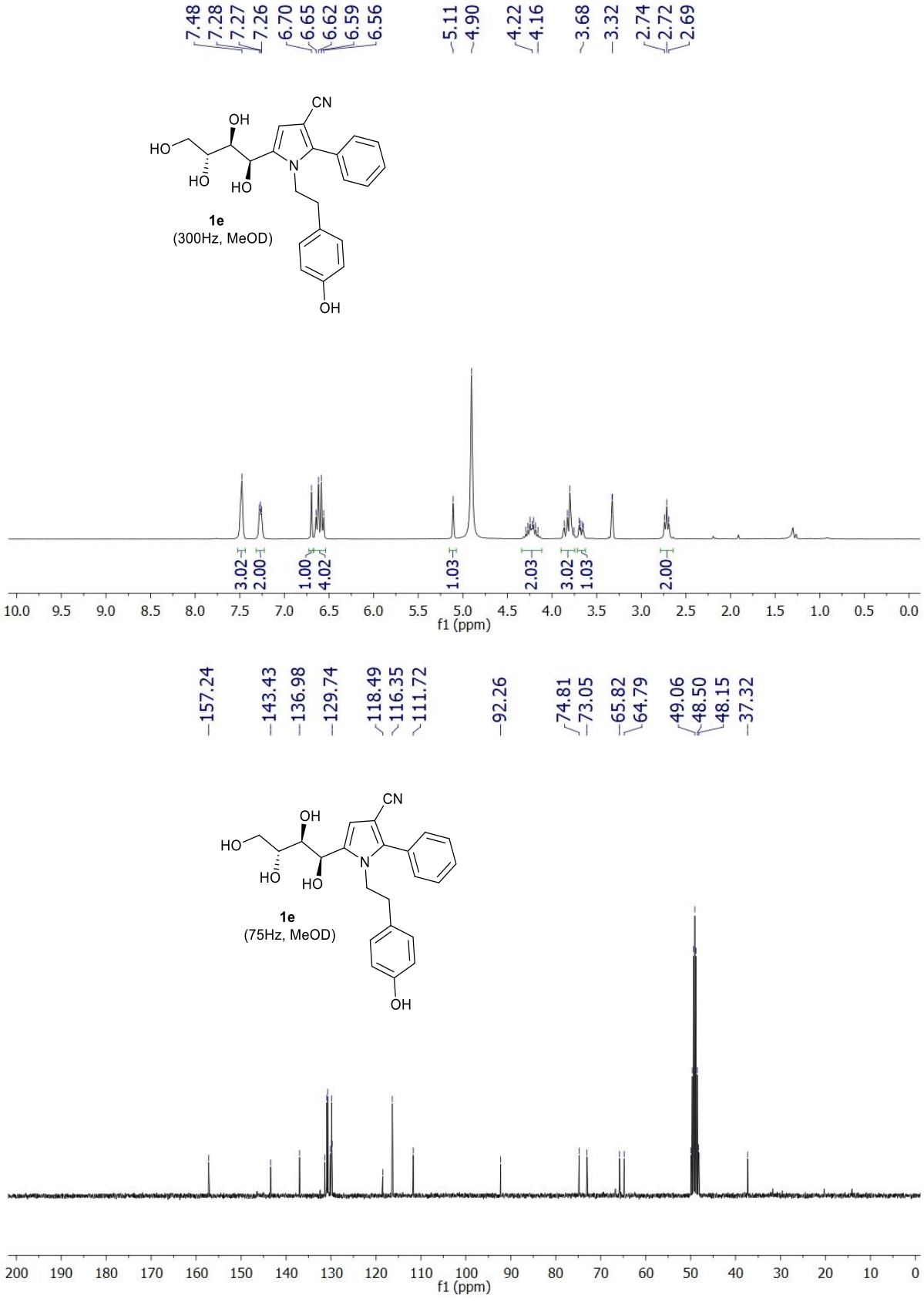


1-Allyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

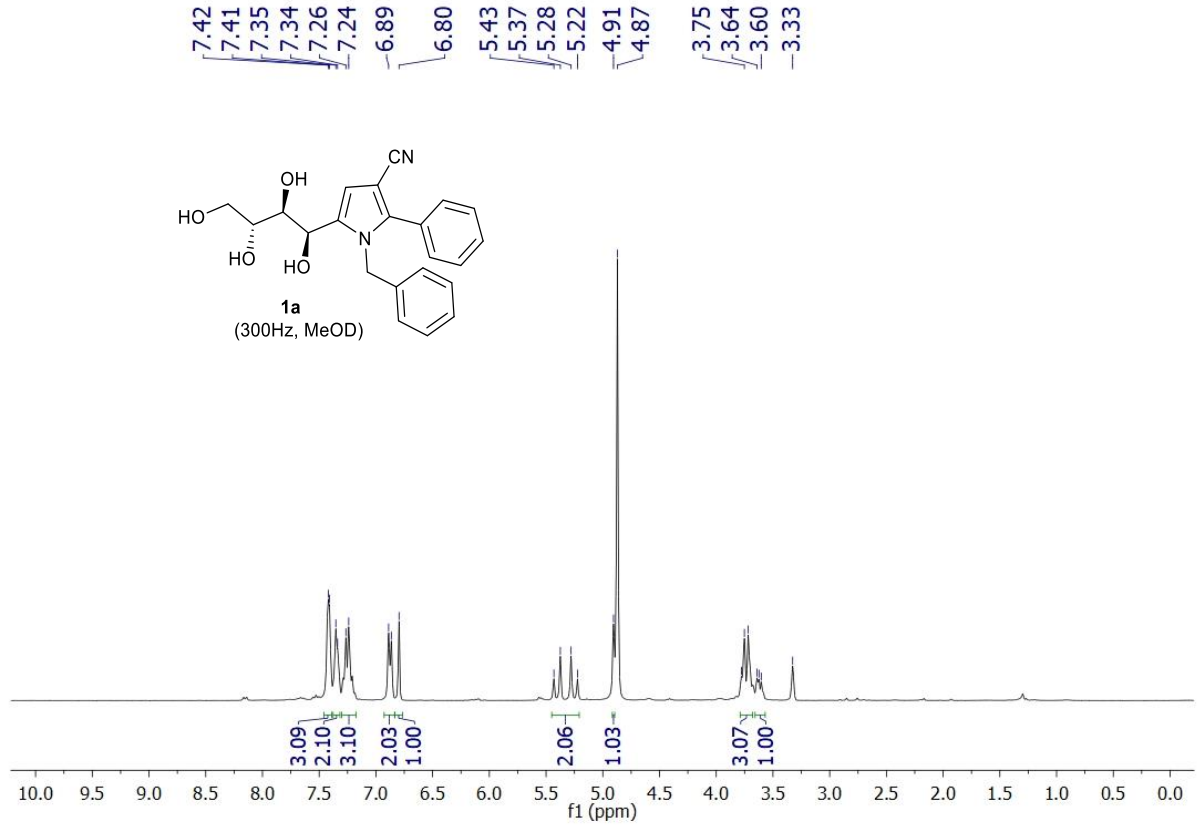


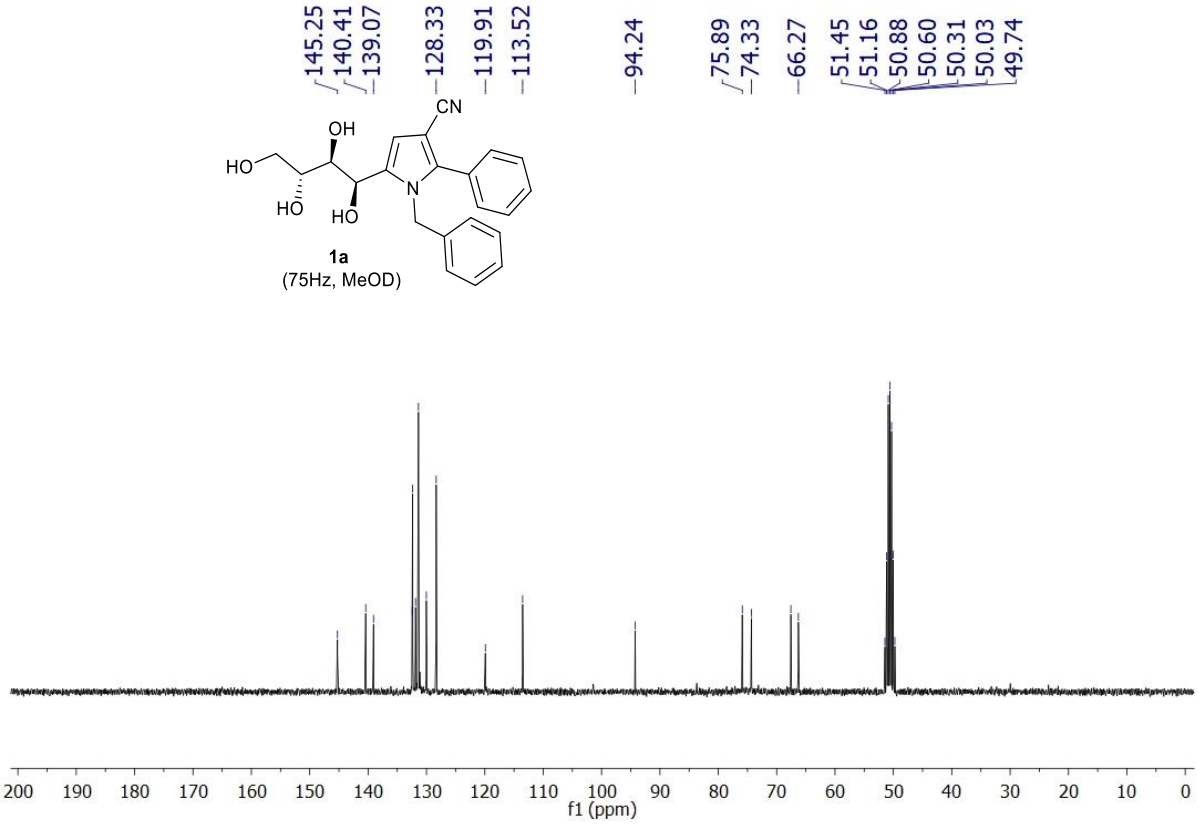


1-(4-Hydroxyphenethyl)-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

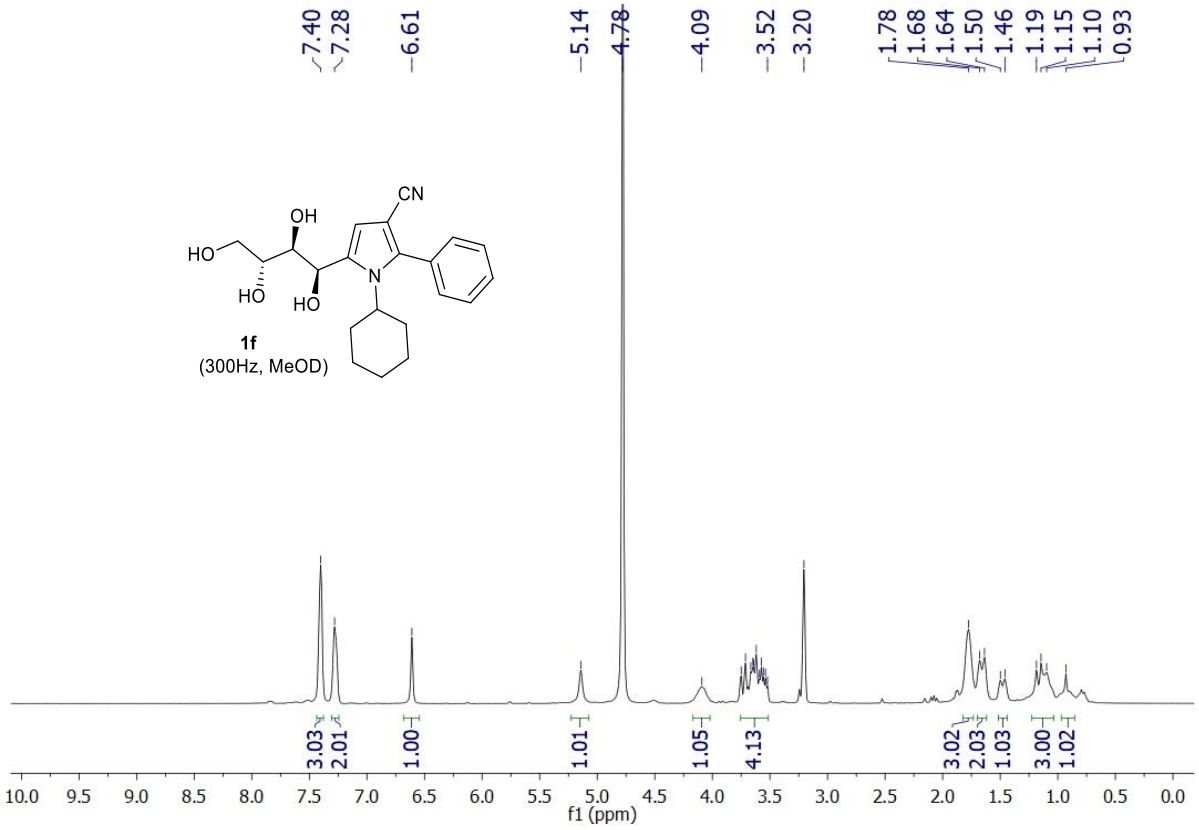


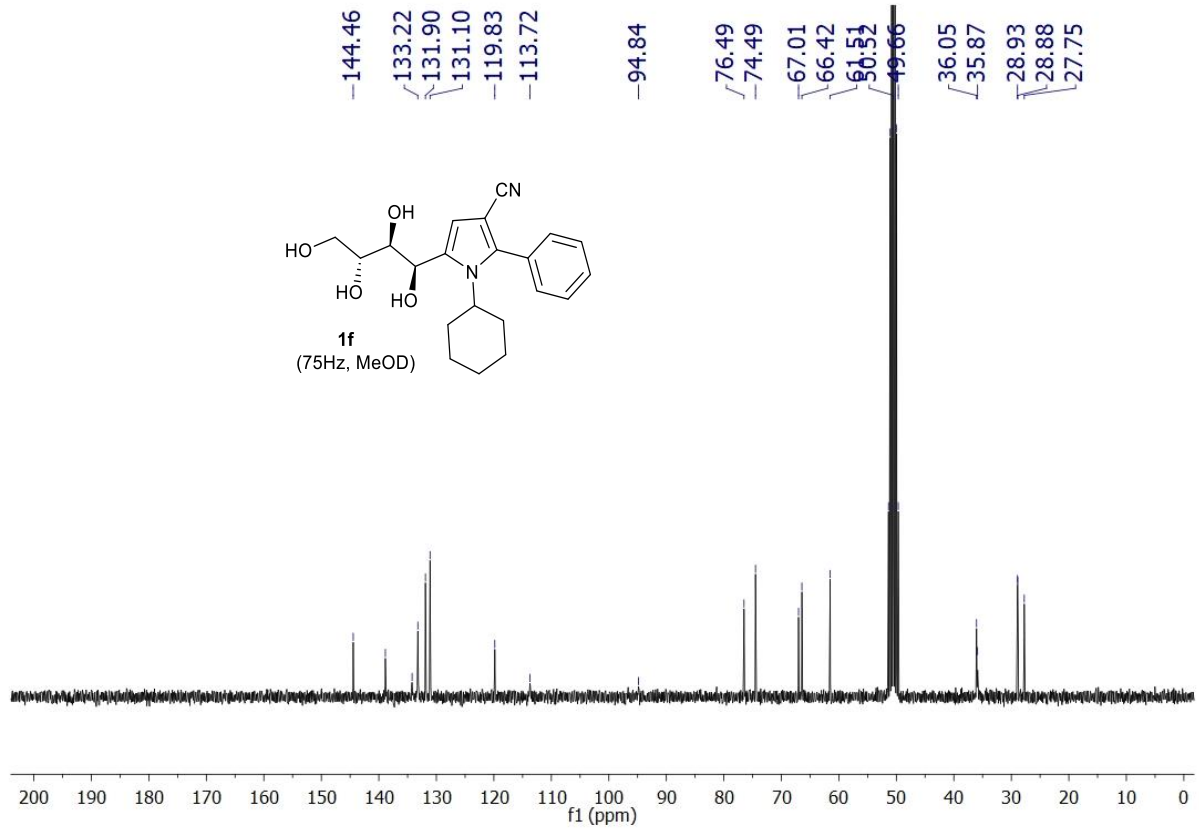
1-Benzyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



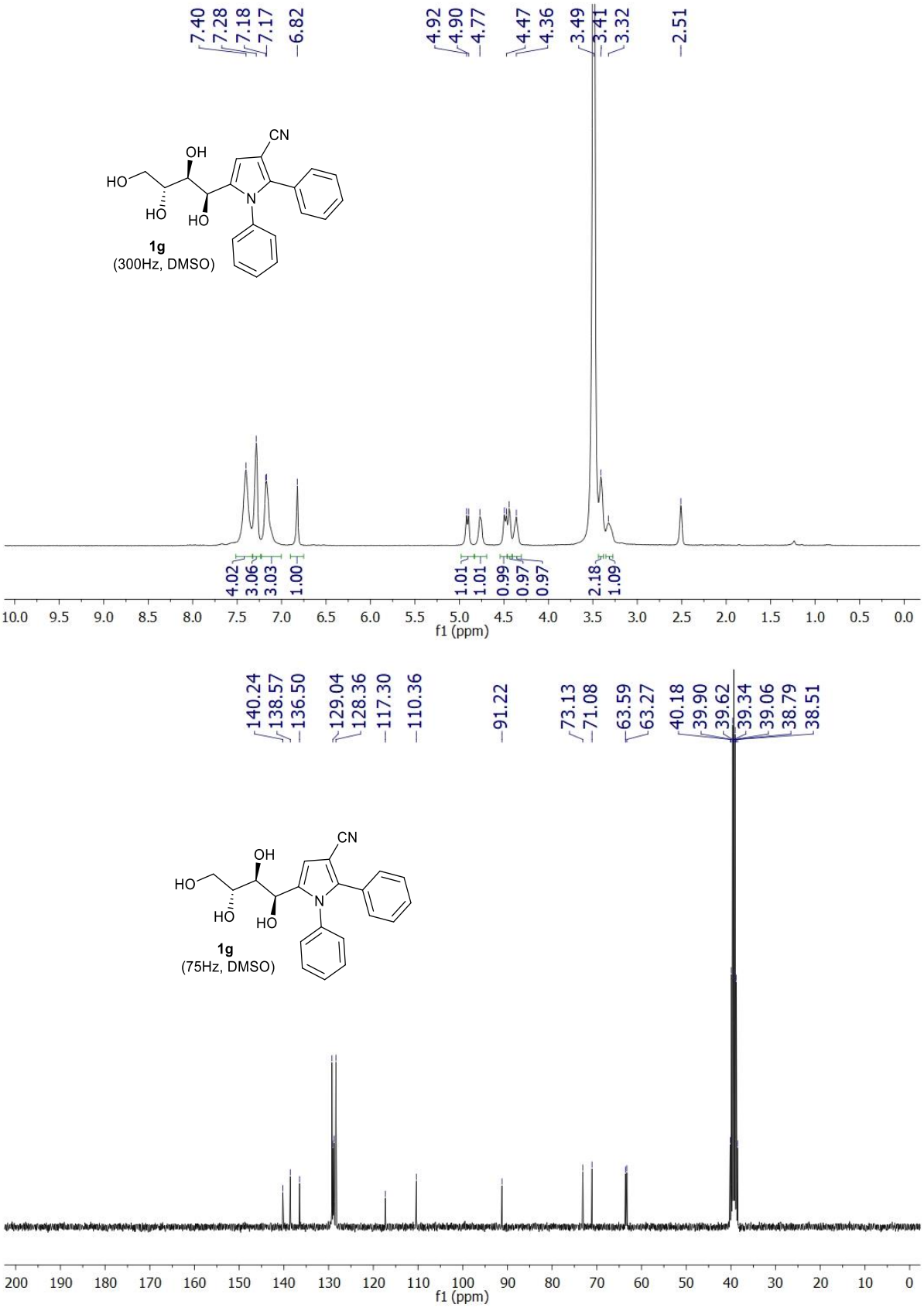


1-Cyclohexyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

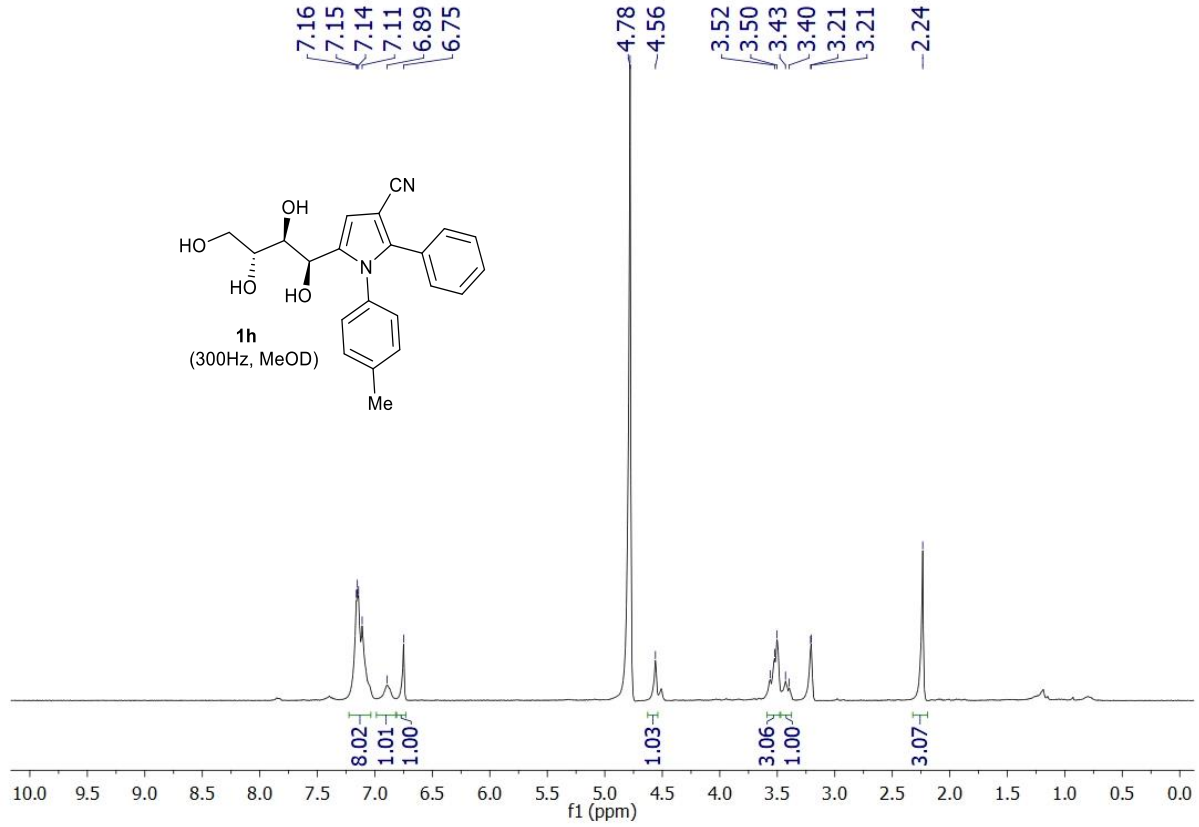


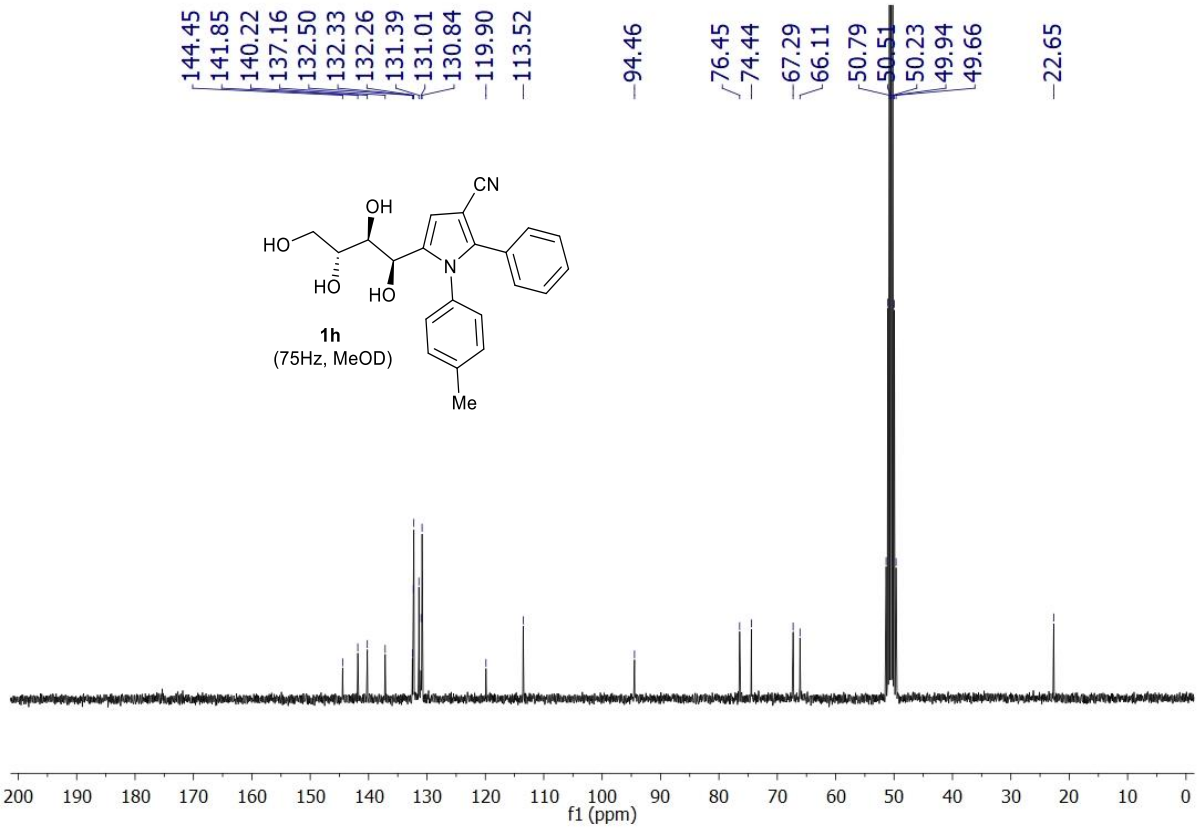


1,2-Diphenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

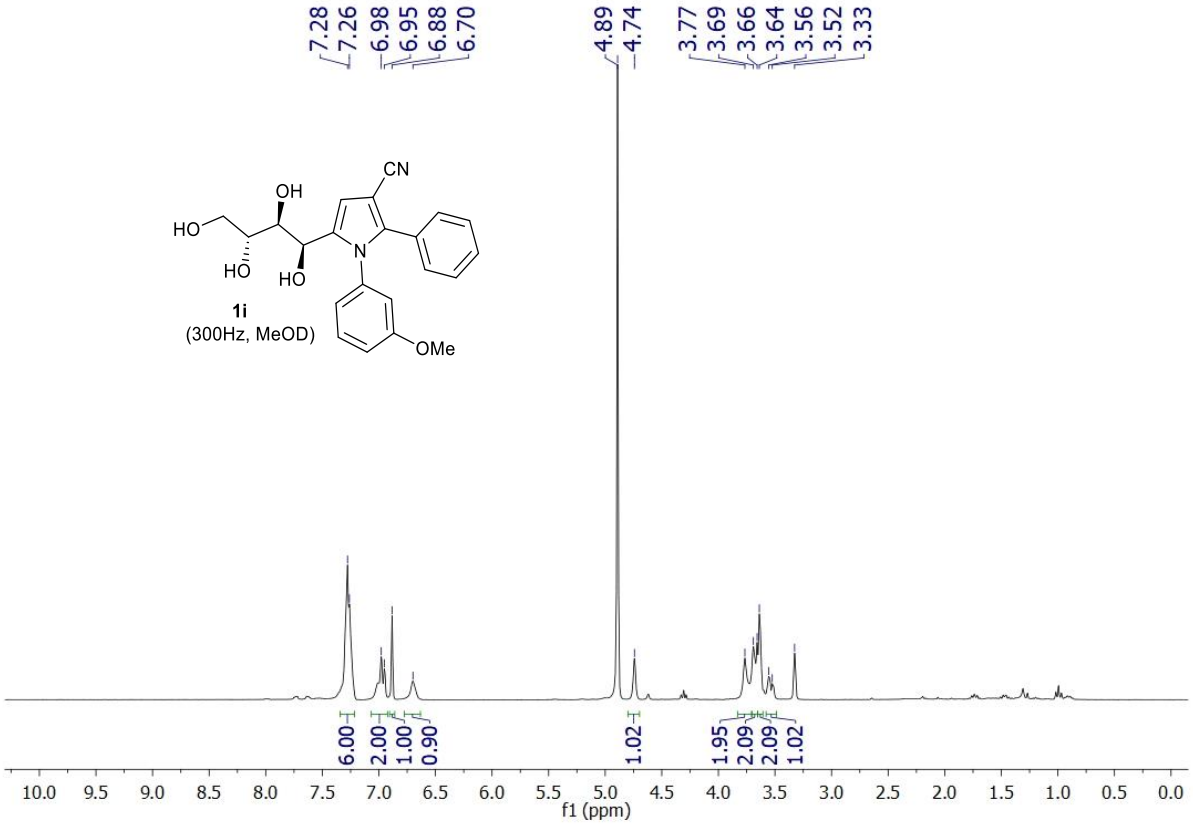


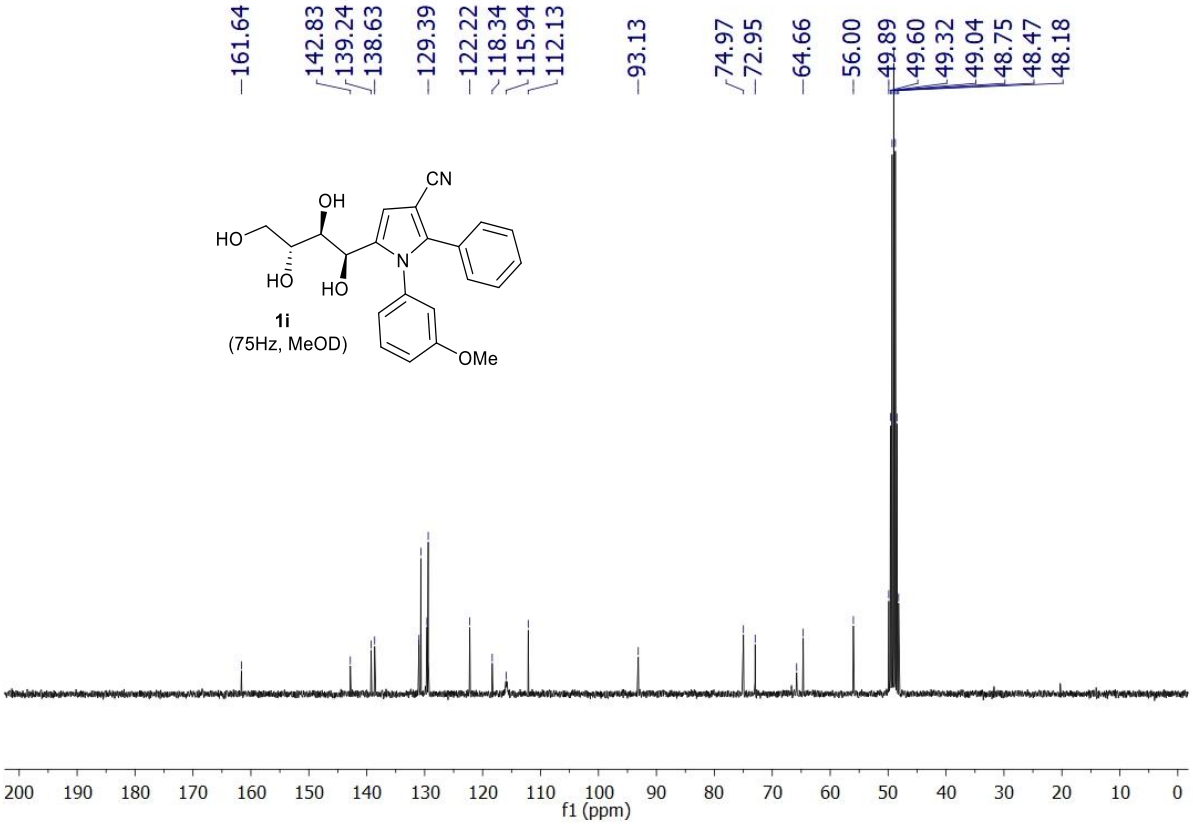
2-Phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1-(*p*-tolyl)-1*H*-pyrrole-3-carbonitrile



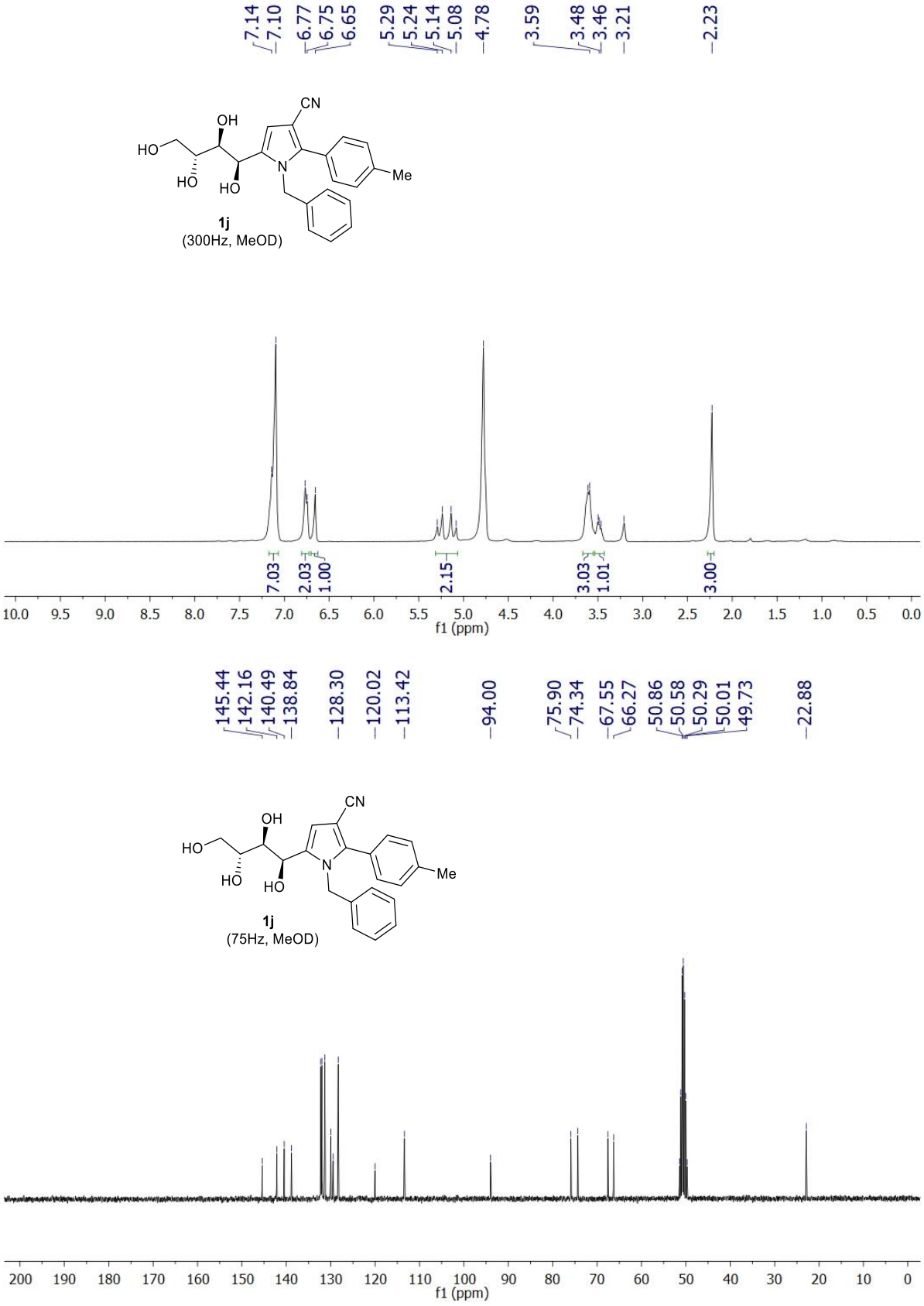


1-(3-Methoxyphenyl)-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

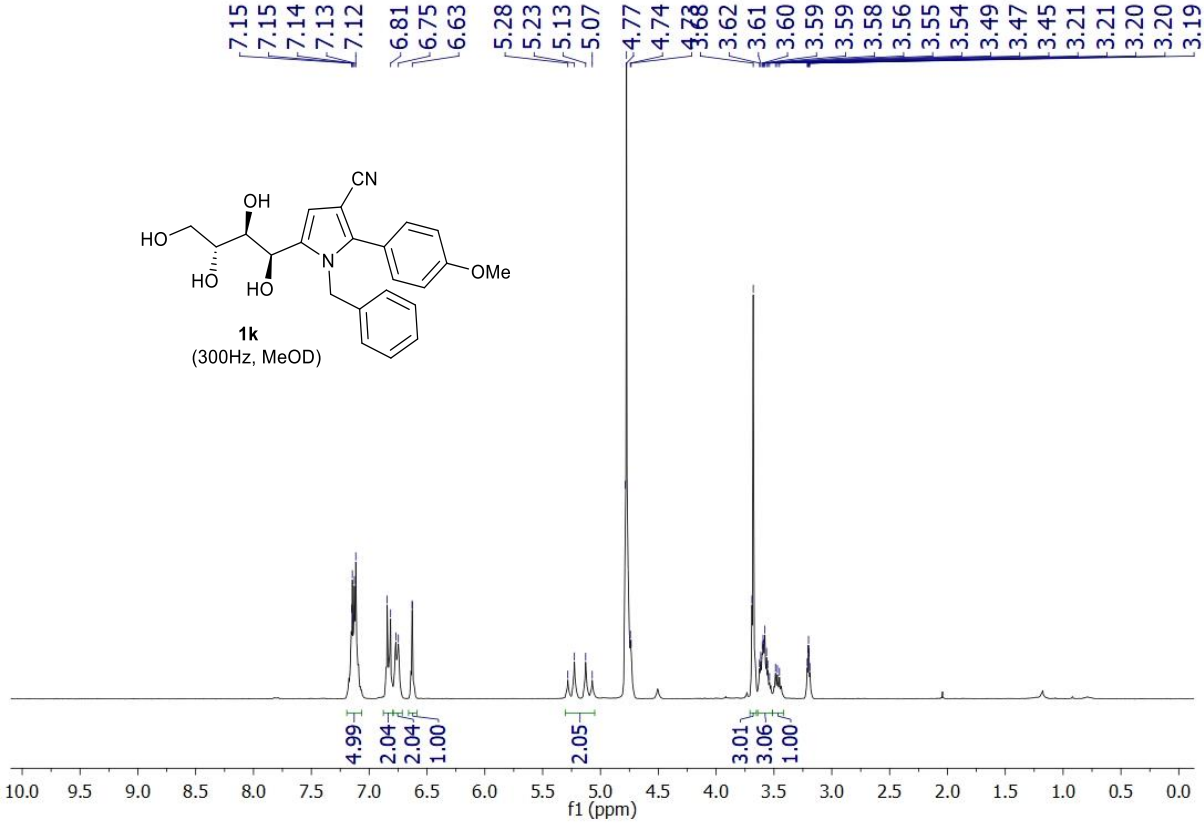


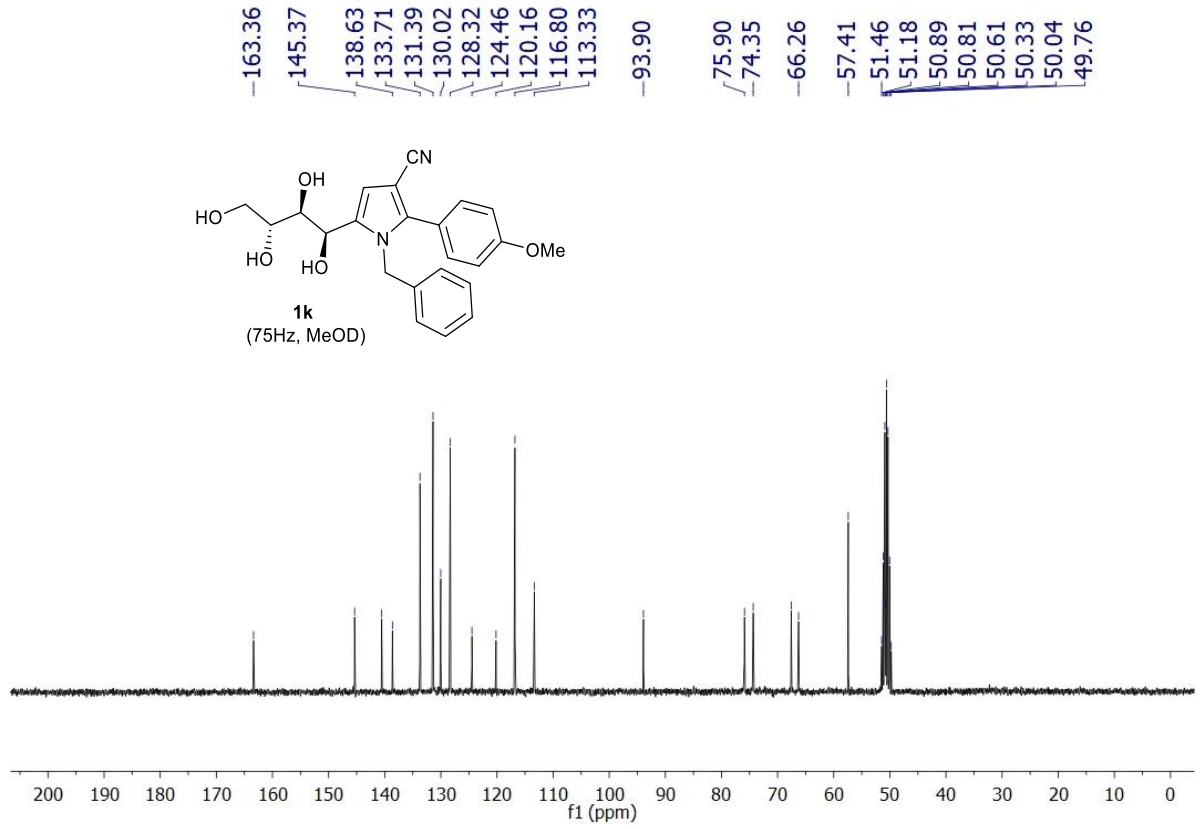


1-Benzyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-2-(*p*-tolyl)-1*H*-pyrrole-3-carbonitrile

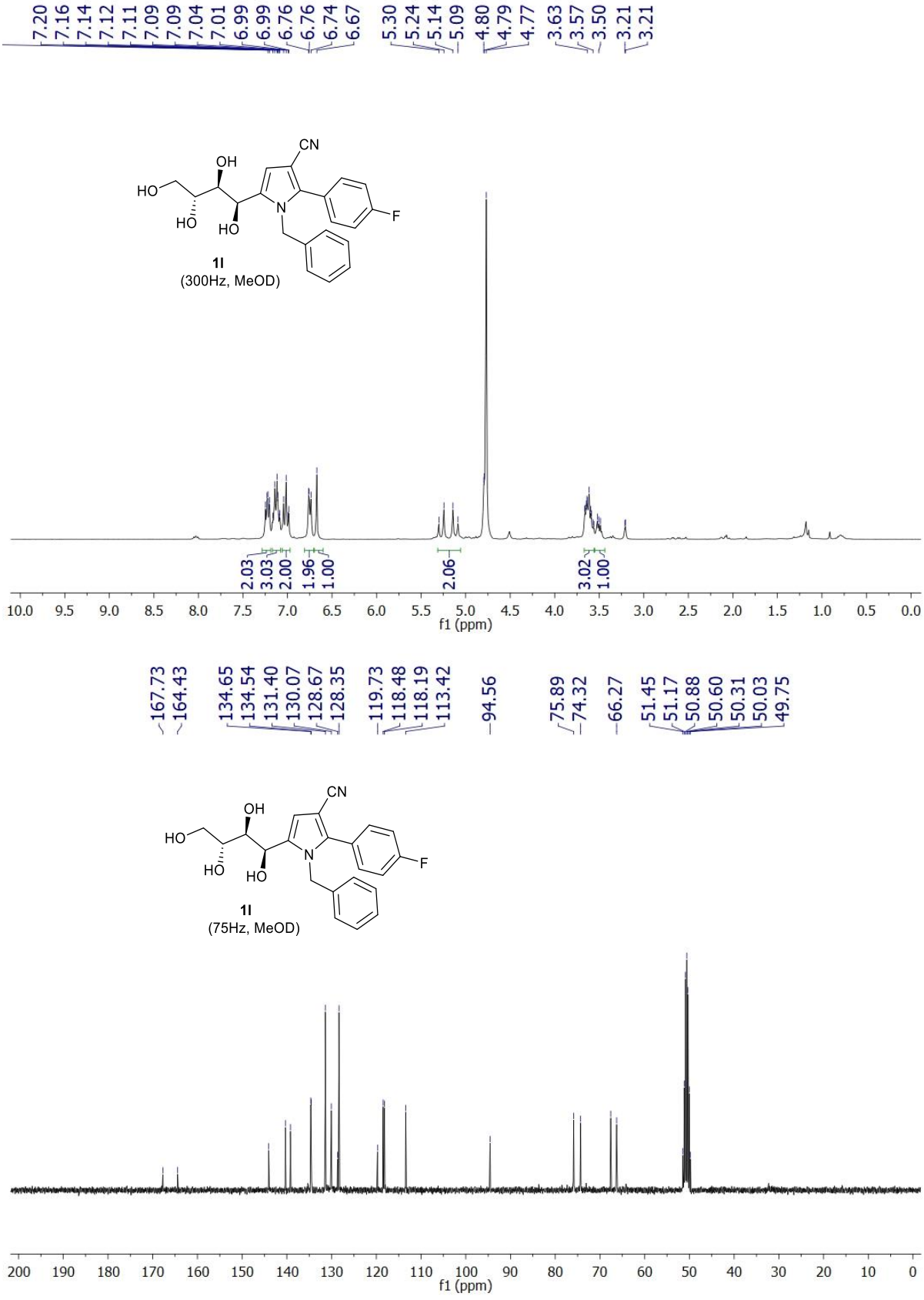


1-Benzyl-2-(4-methoxyphenyl)-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile





1-Benzyl-2-(4-fluorophenyl)-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



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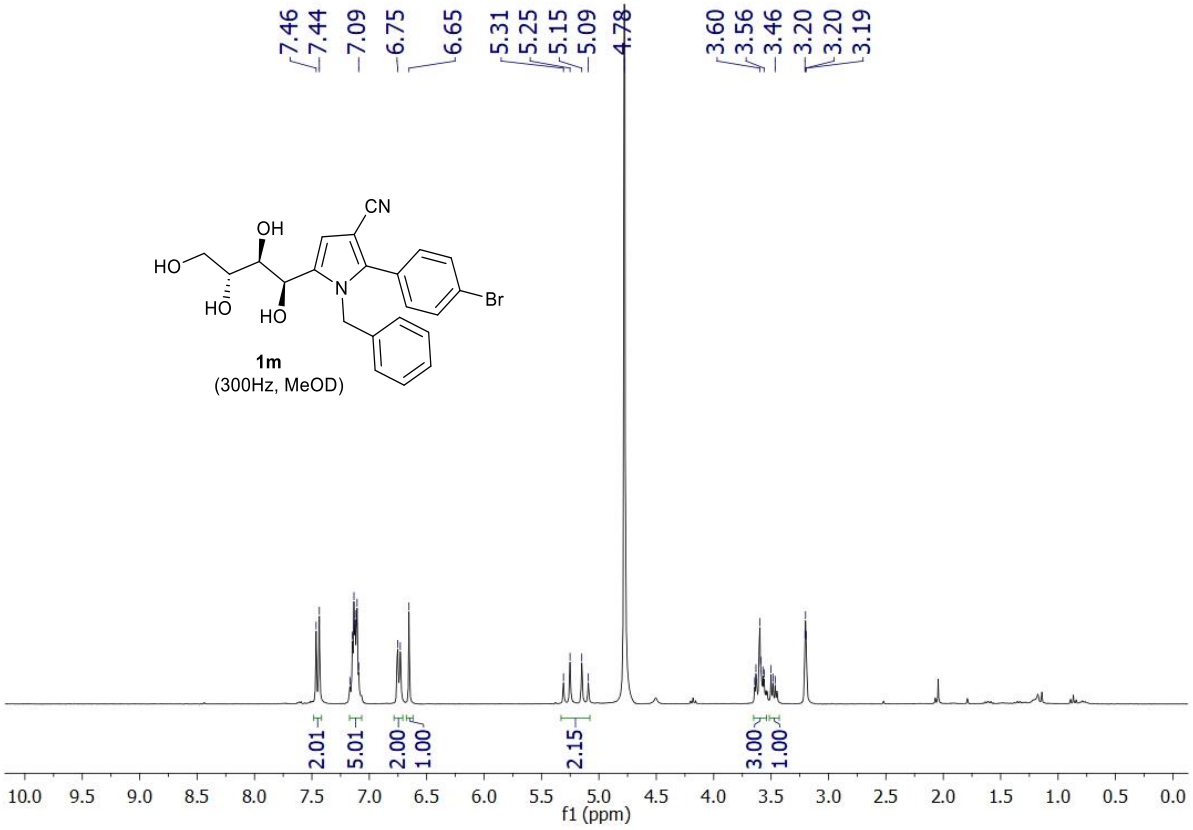
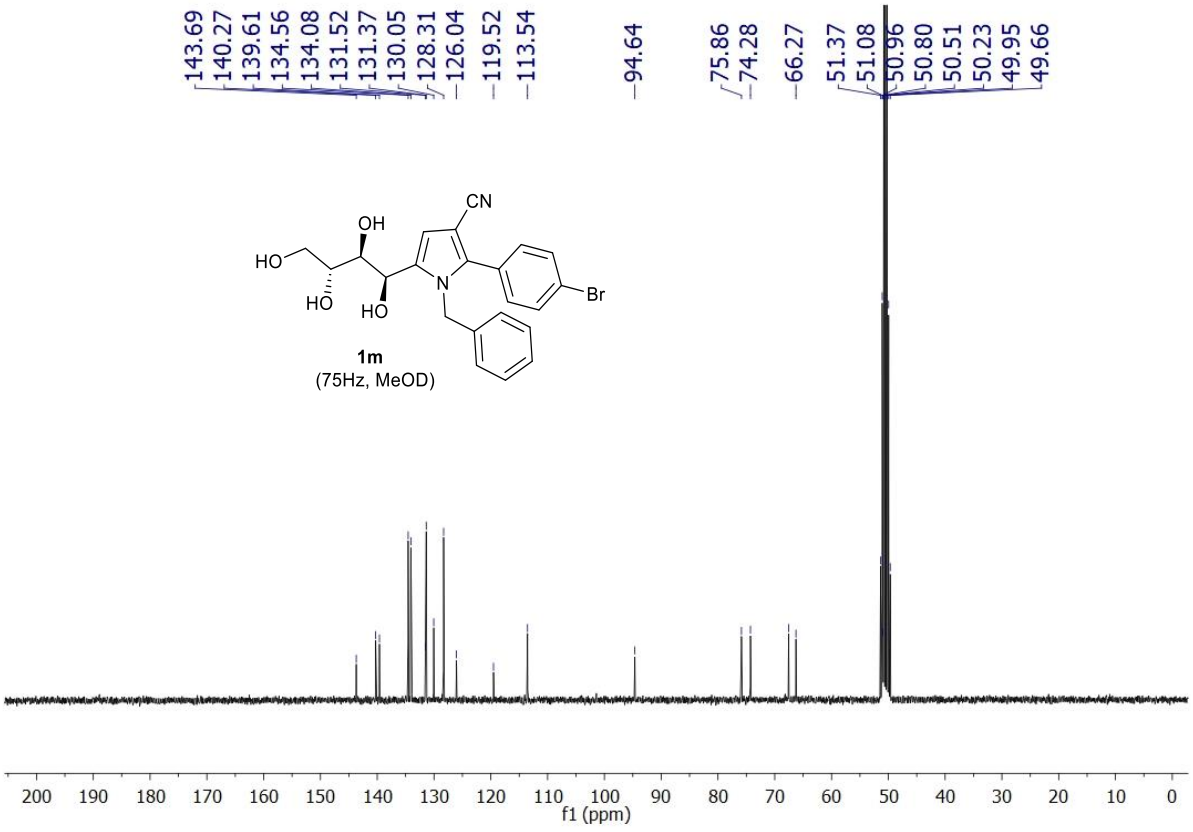
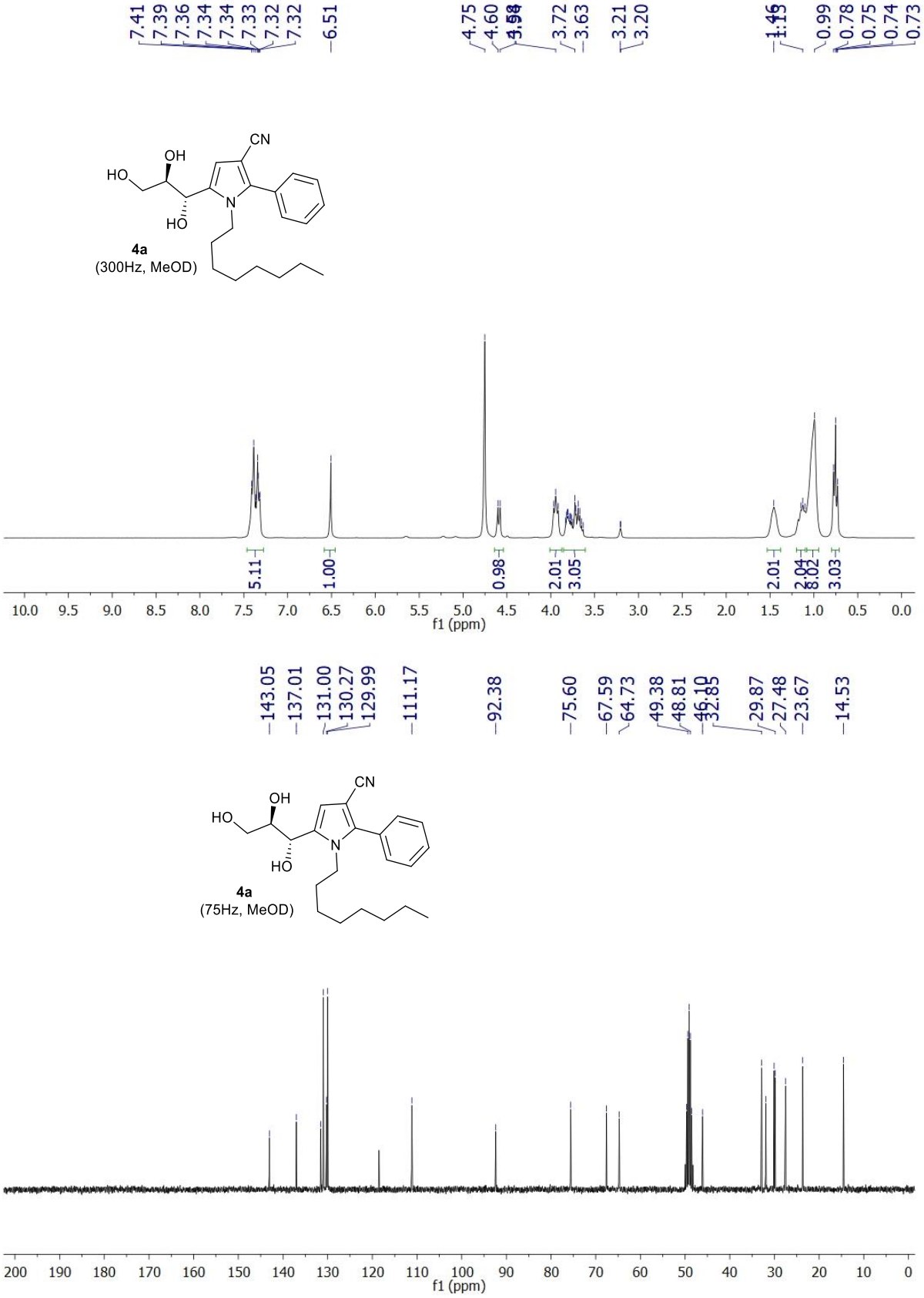
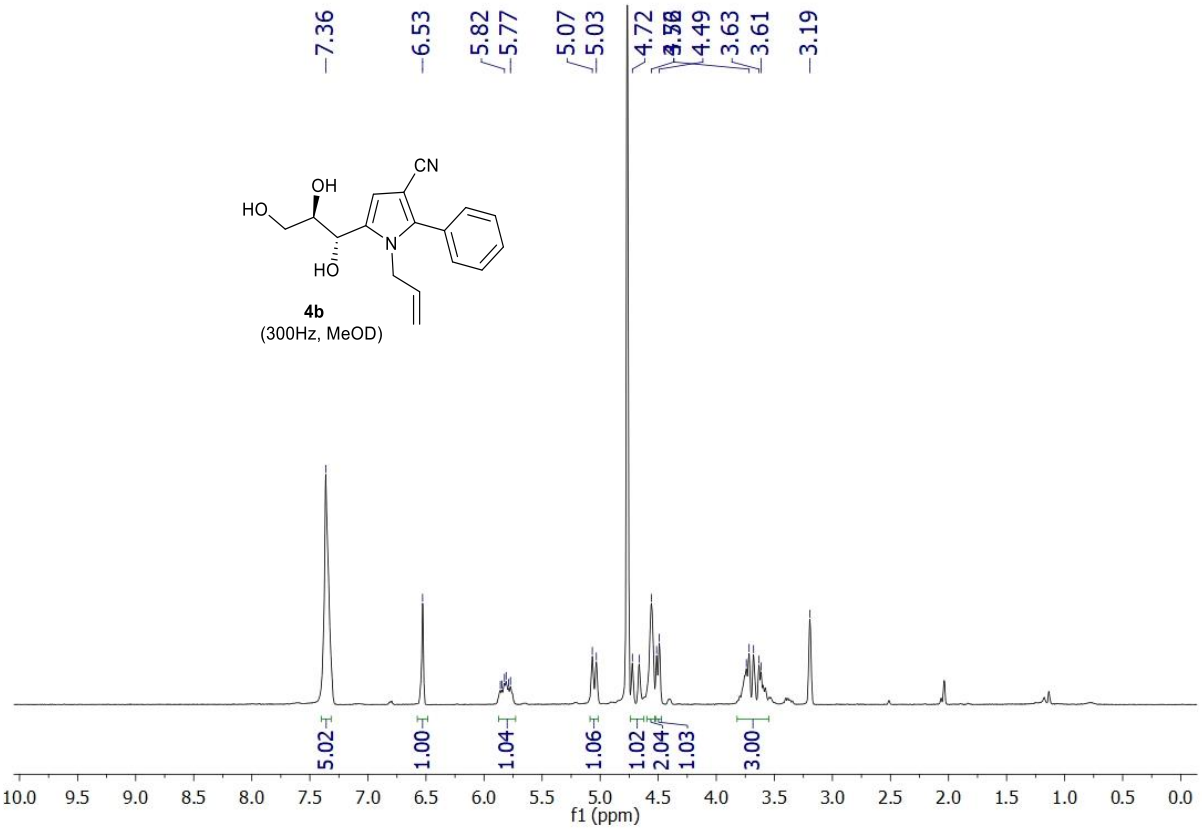


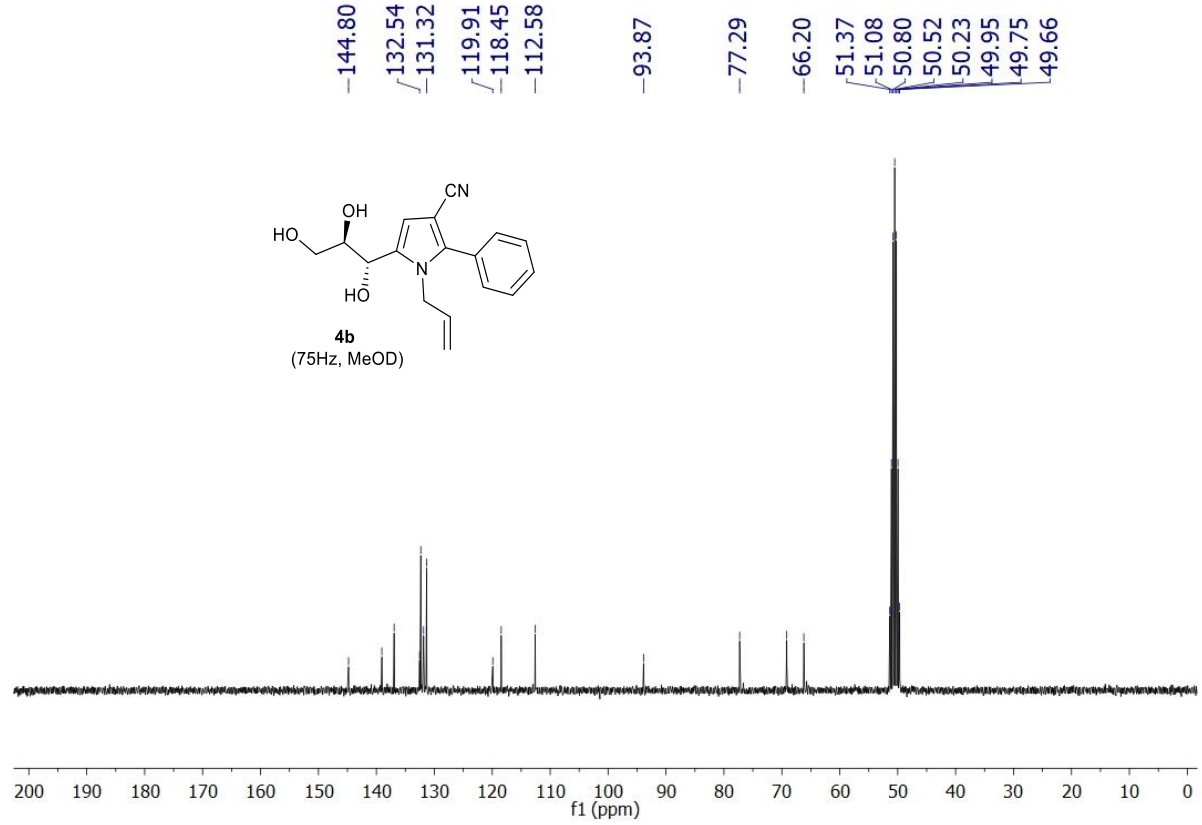


1-Octyl-2-phenyl-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile

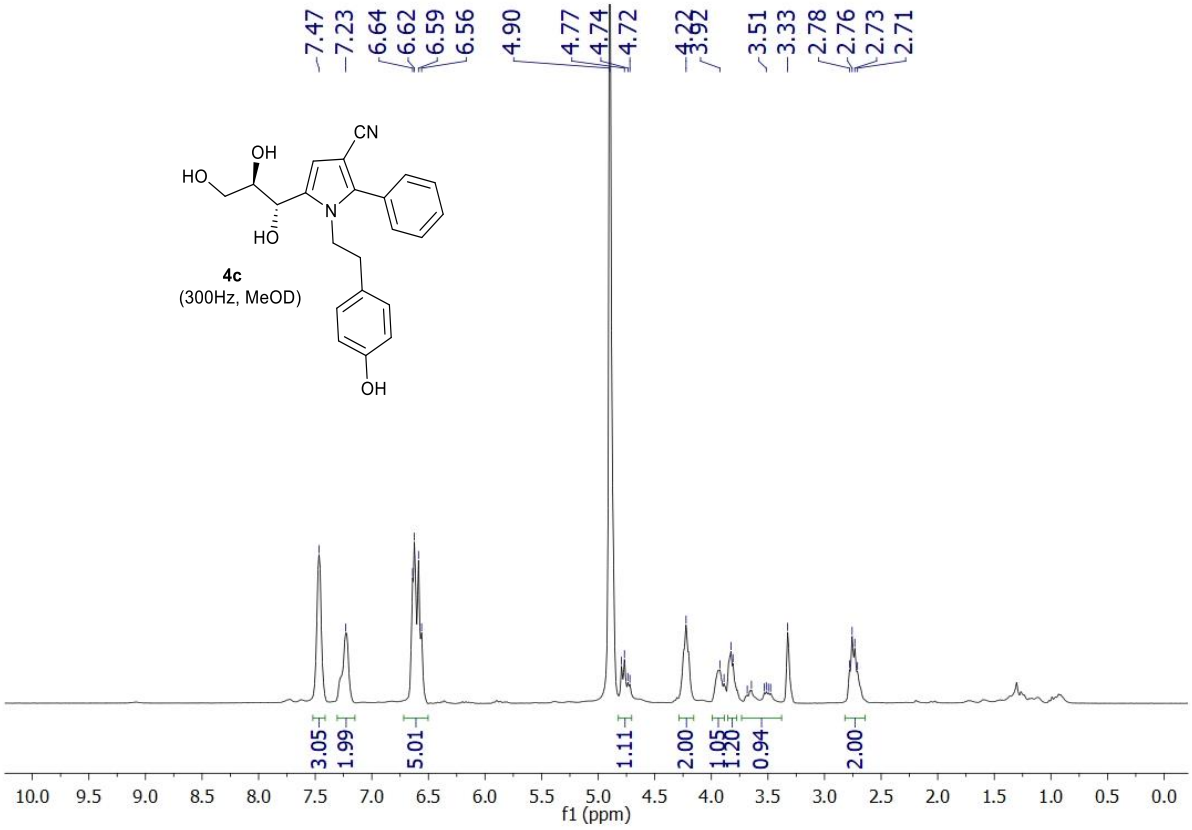


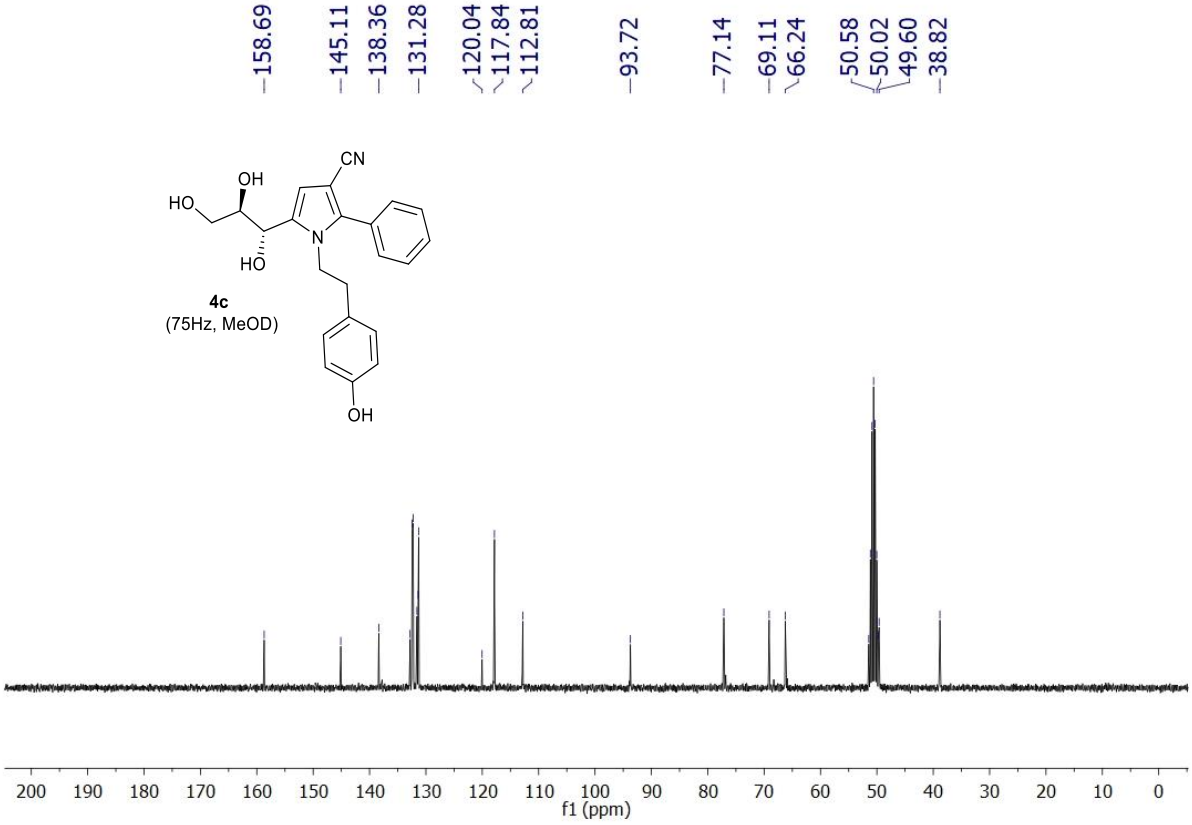
1-Allyl-2-phenyl-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



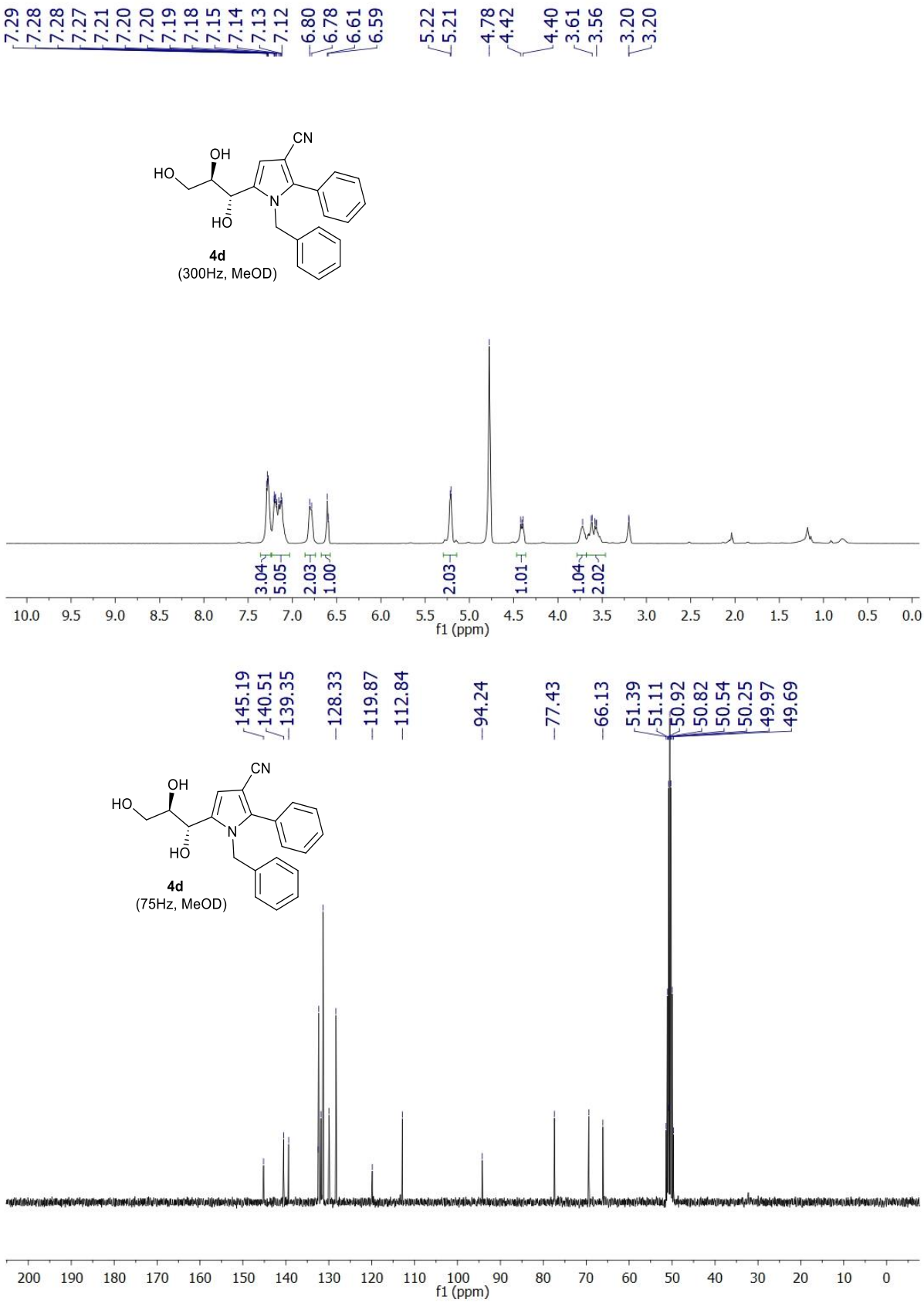


1-(4-Hydroxyphenethyl)-2-phenyl-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile

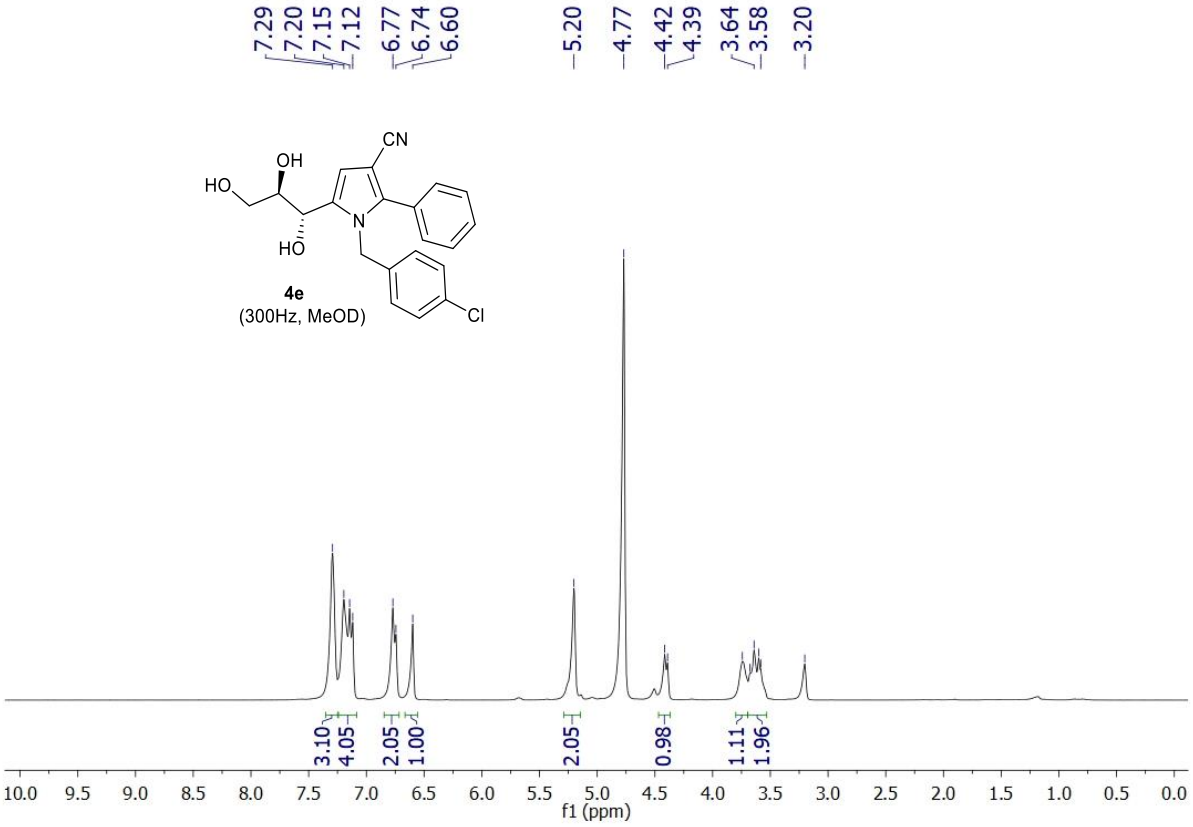


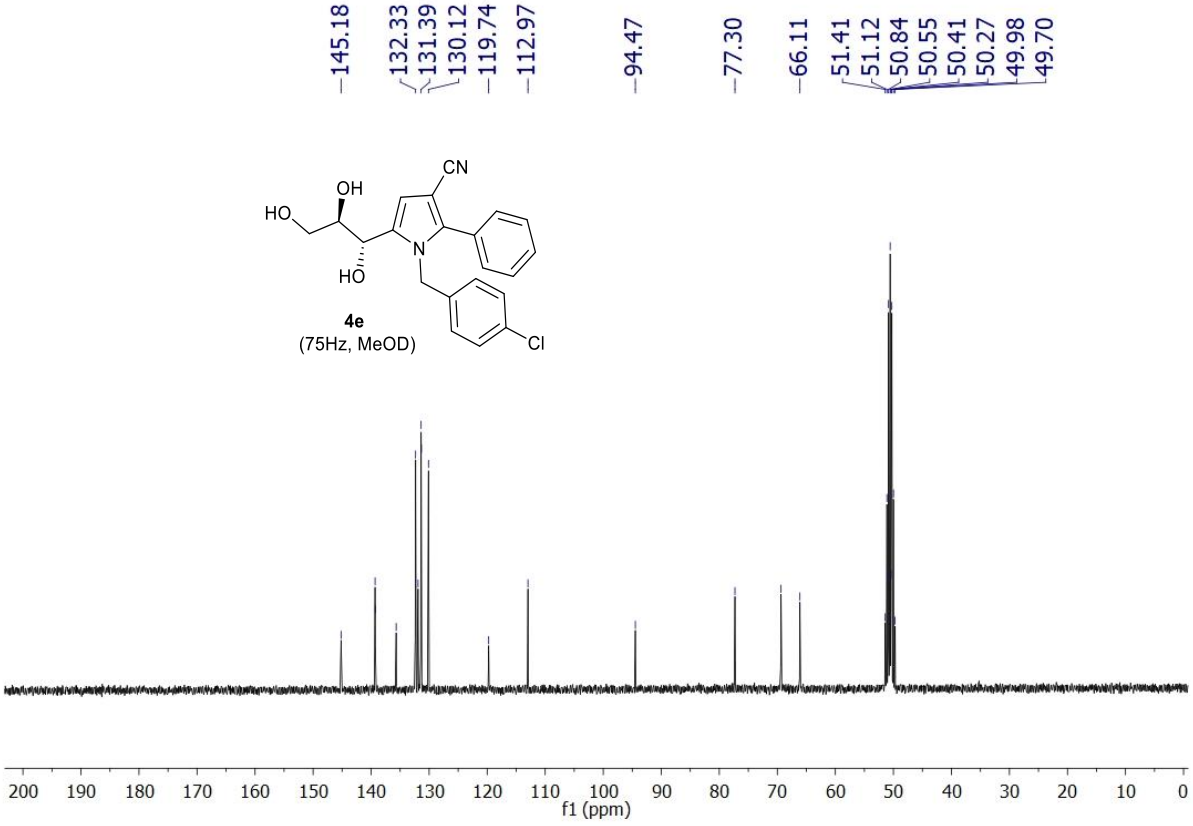


1-Benzyl-2-phenyl-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile

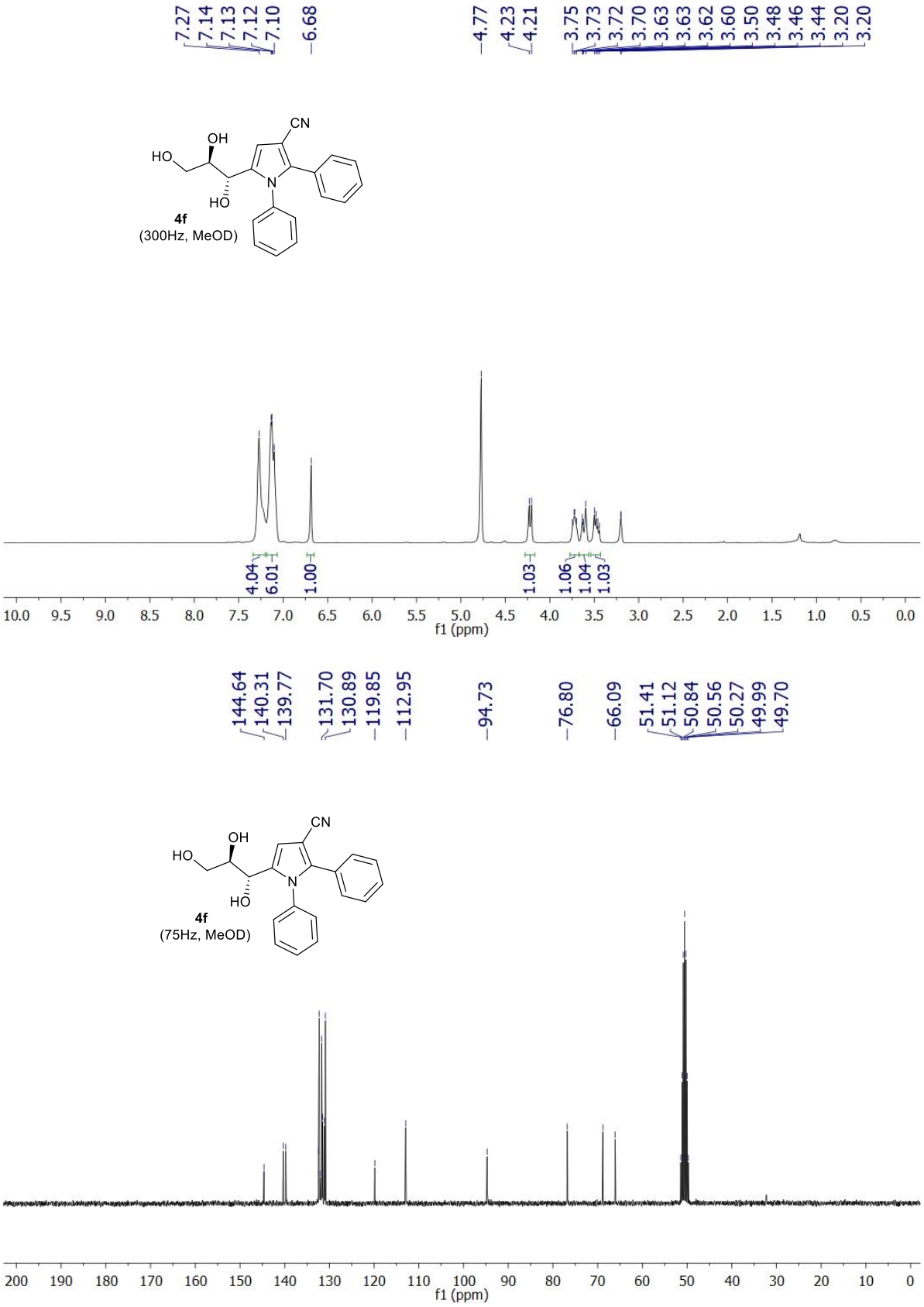


1-(4-Chlorobenzyl)-2-phenyl-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile

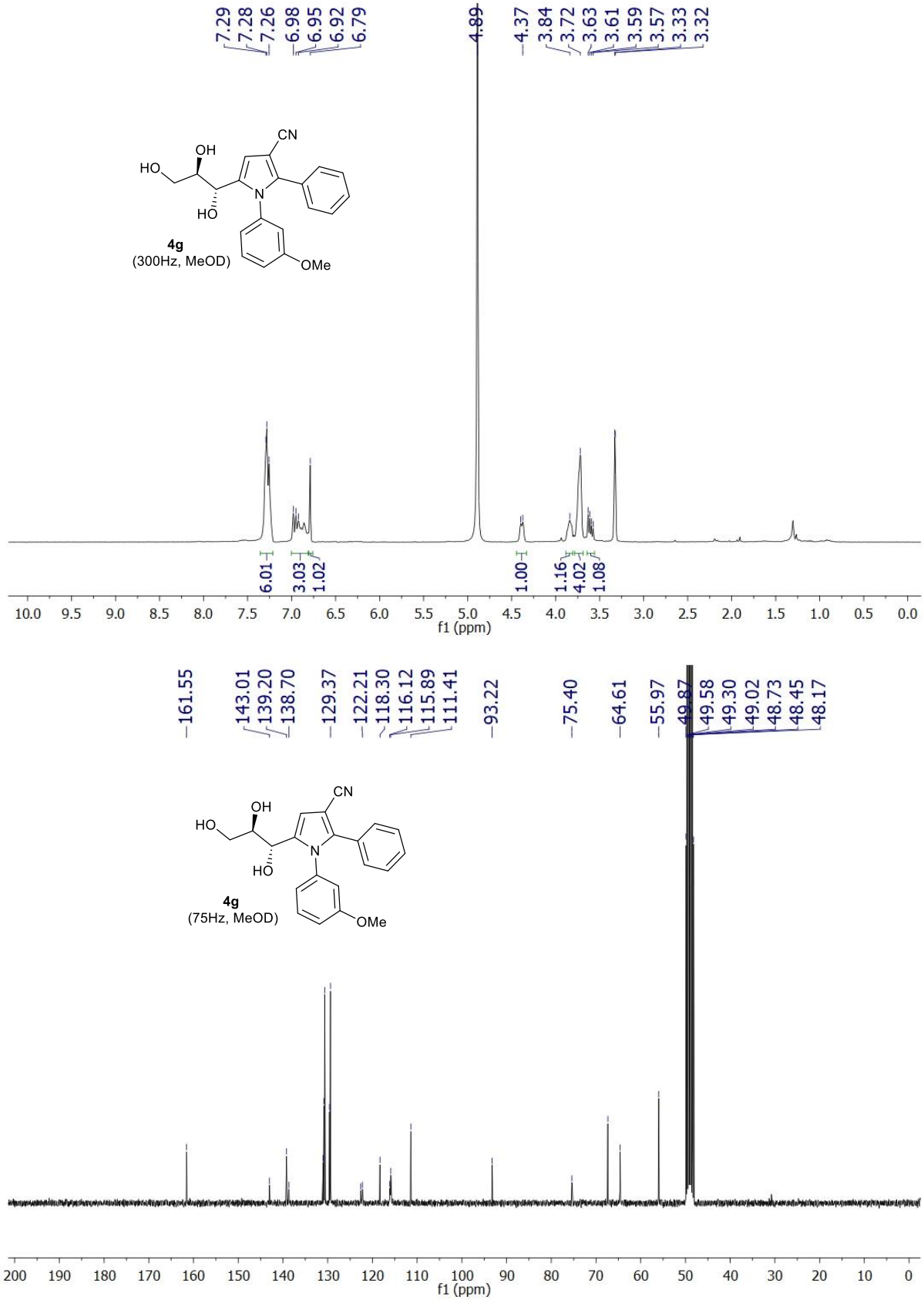




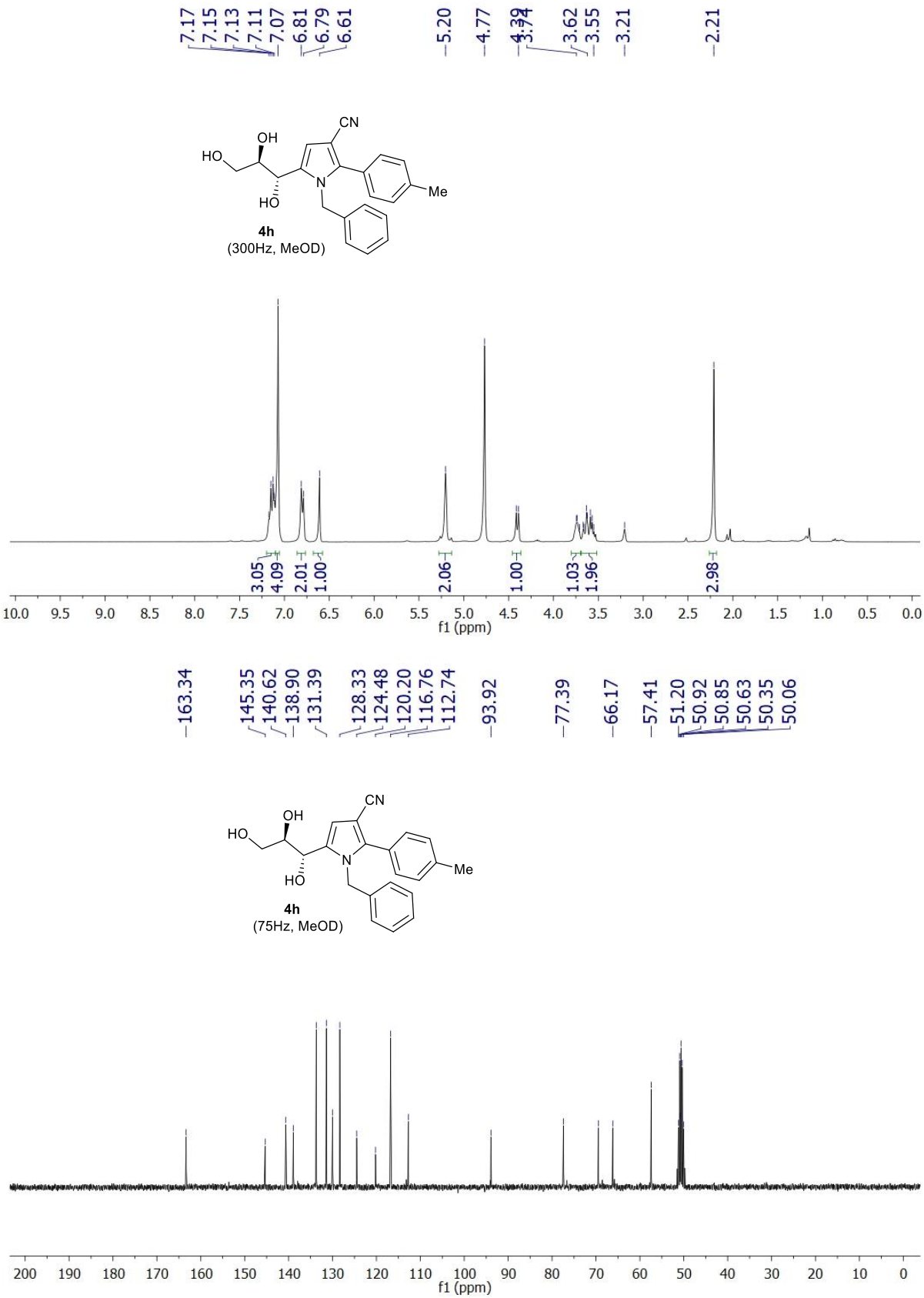
1,2-Diphenyl-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



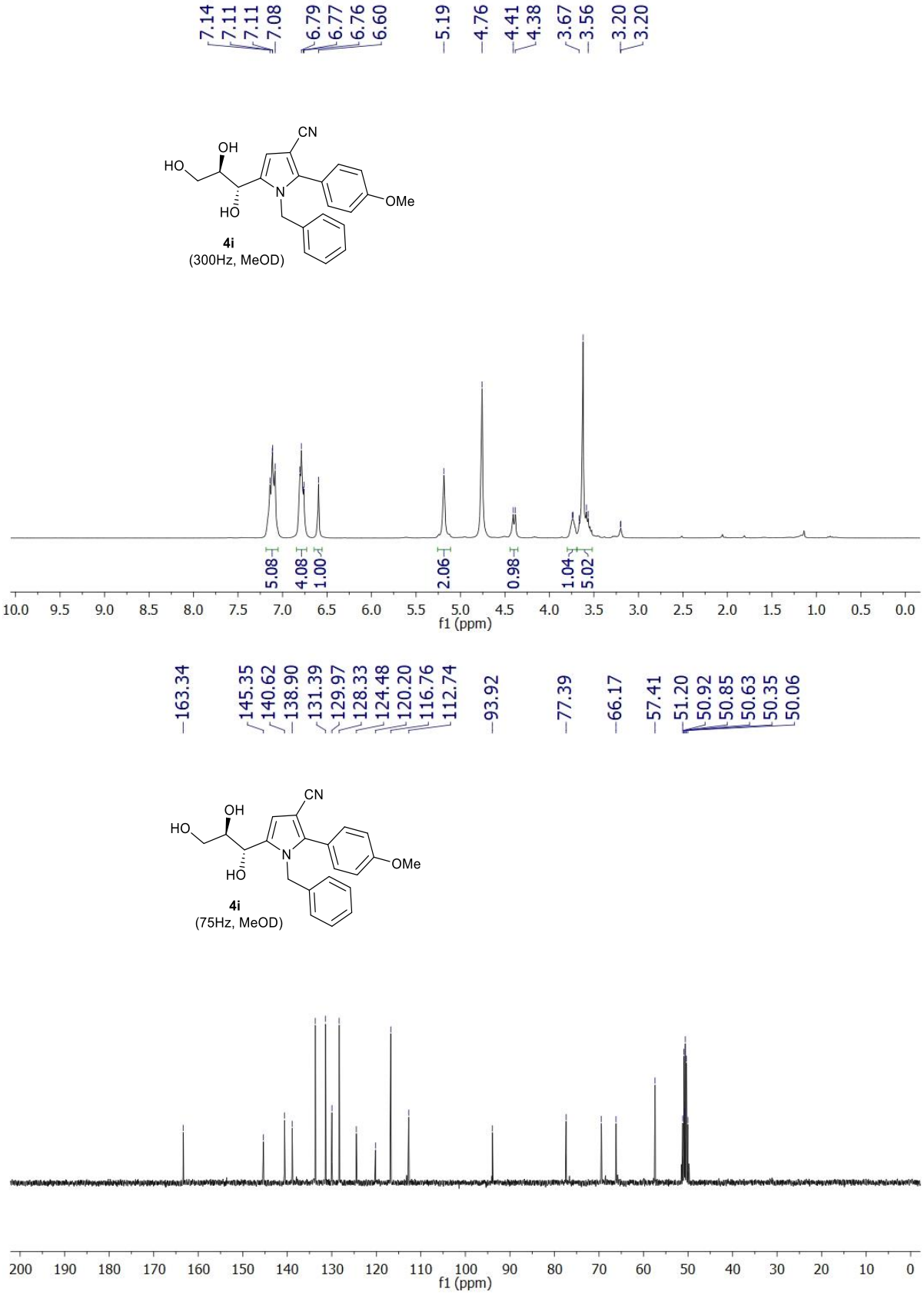
1-(3-Methoxyphenyl)-2-phenyl-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



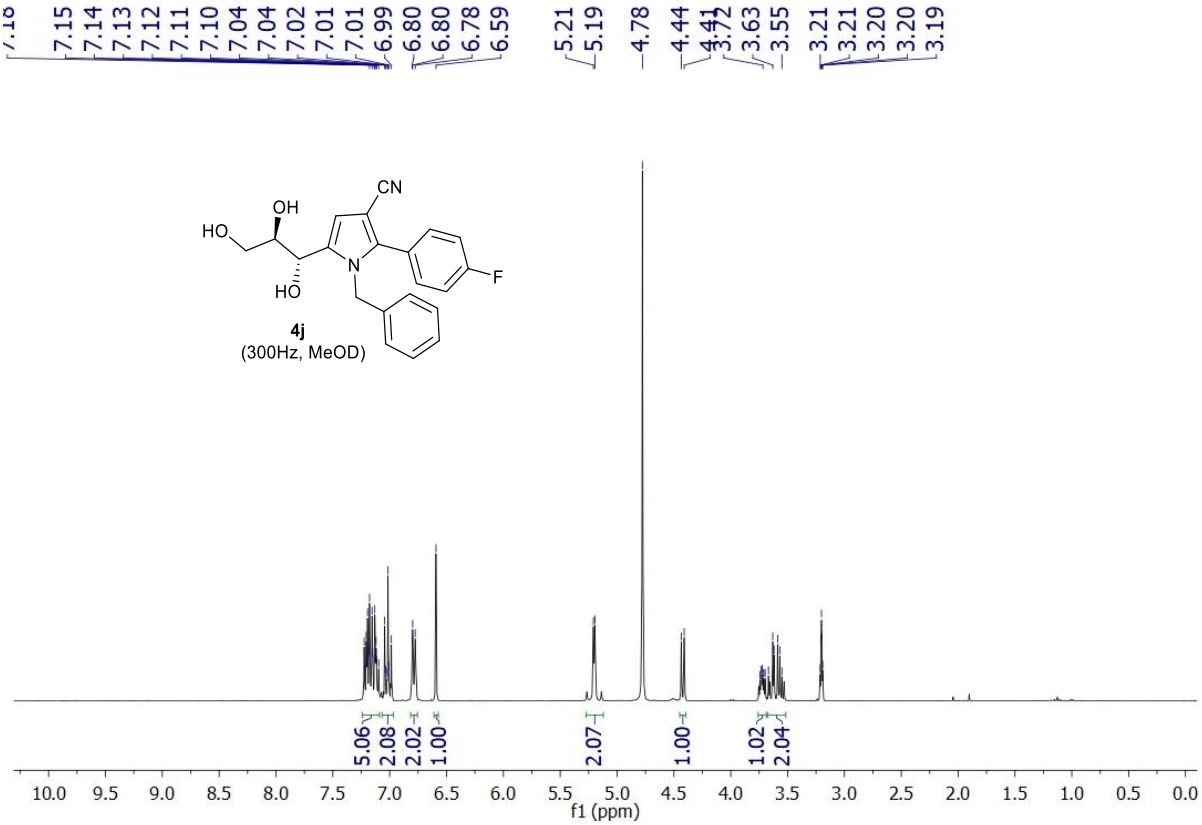
1-Benzyl-2-(*p*-tolyl)-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile

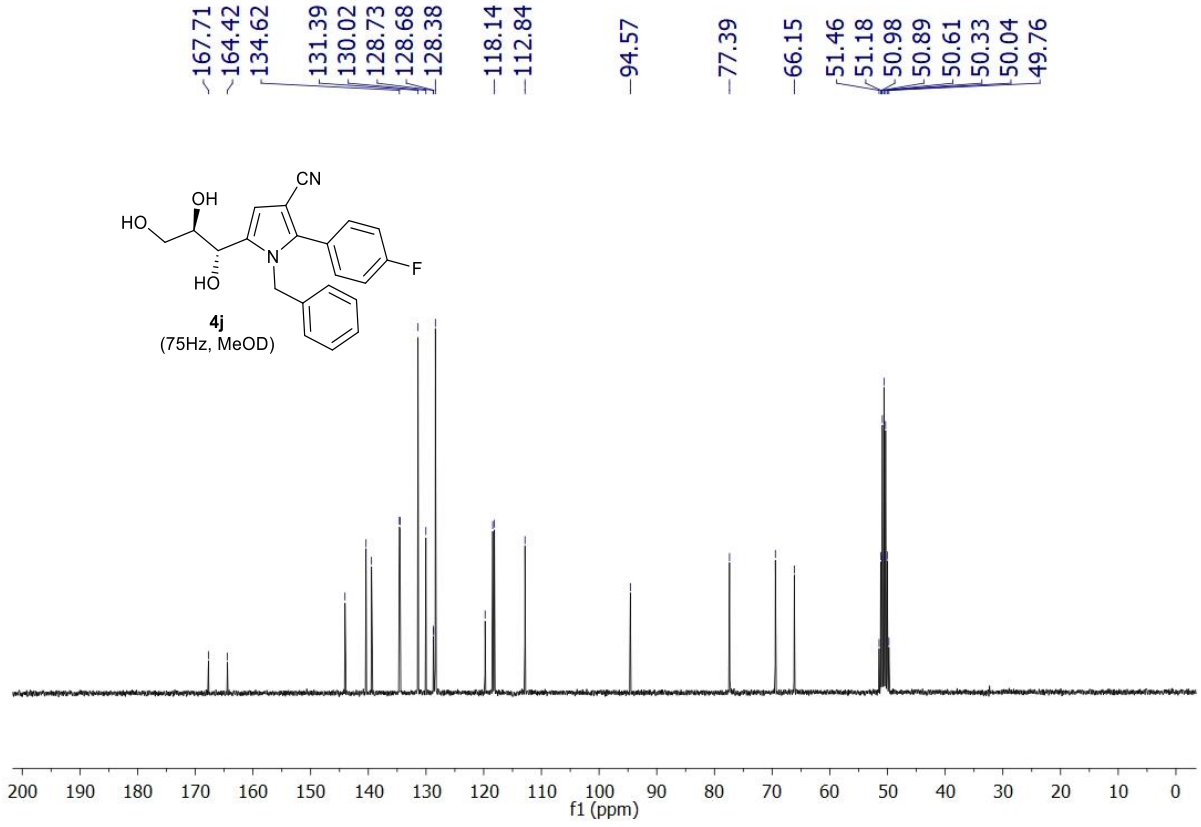


1-Benzyl-2-(4-methoxyphenyl)-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile

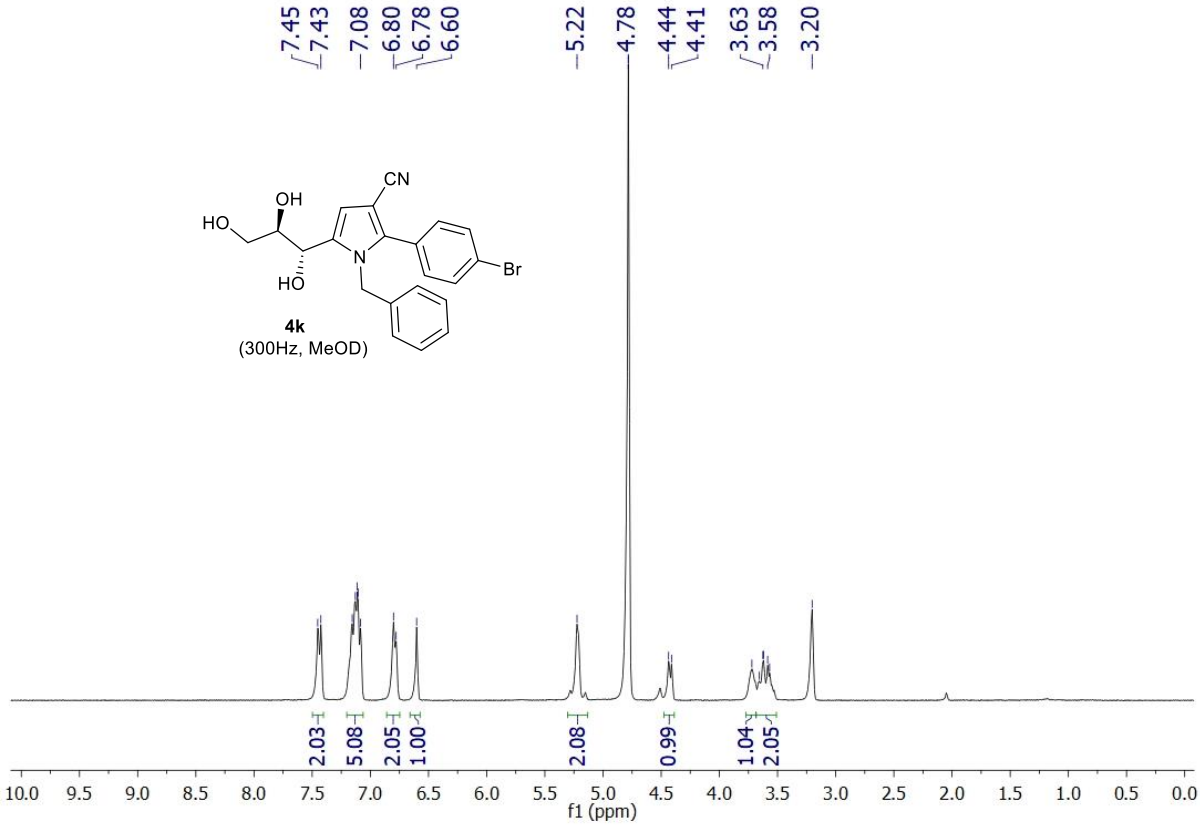


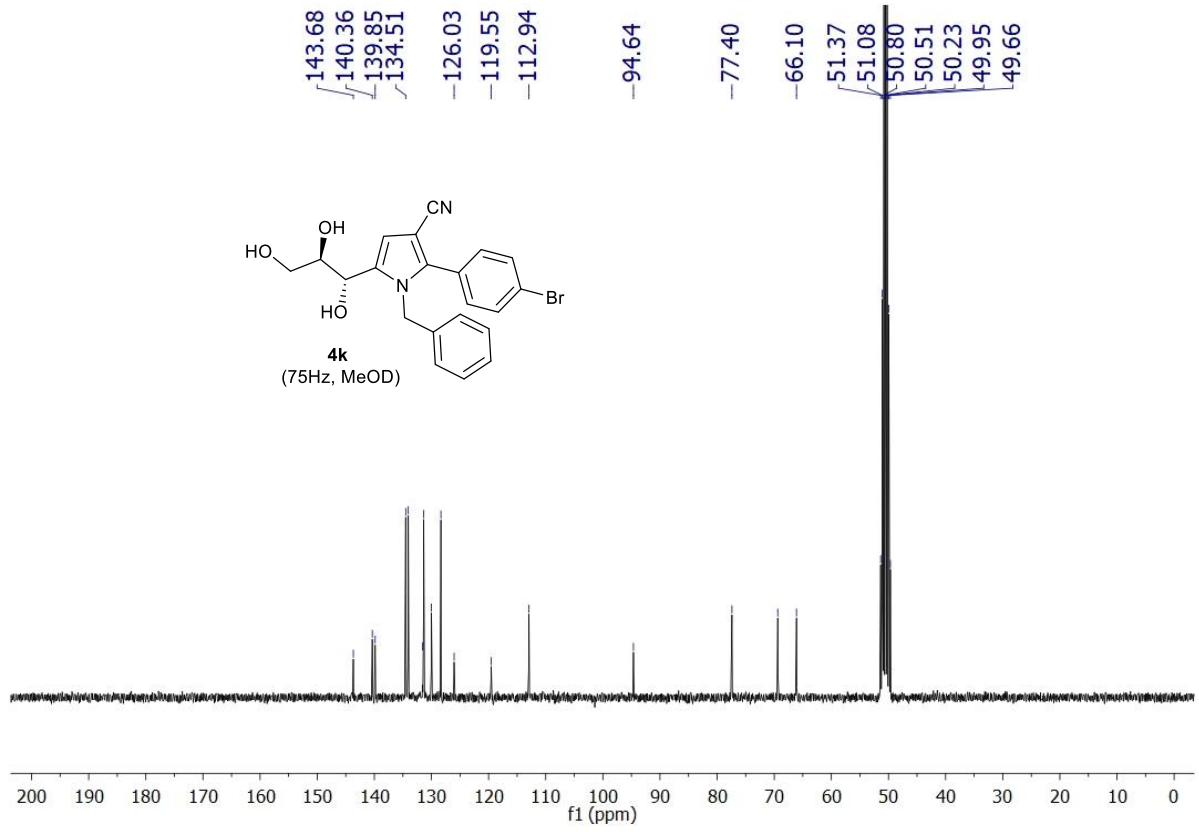
1-Benzyl-2-(4-fluorophenyl)-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



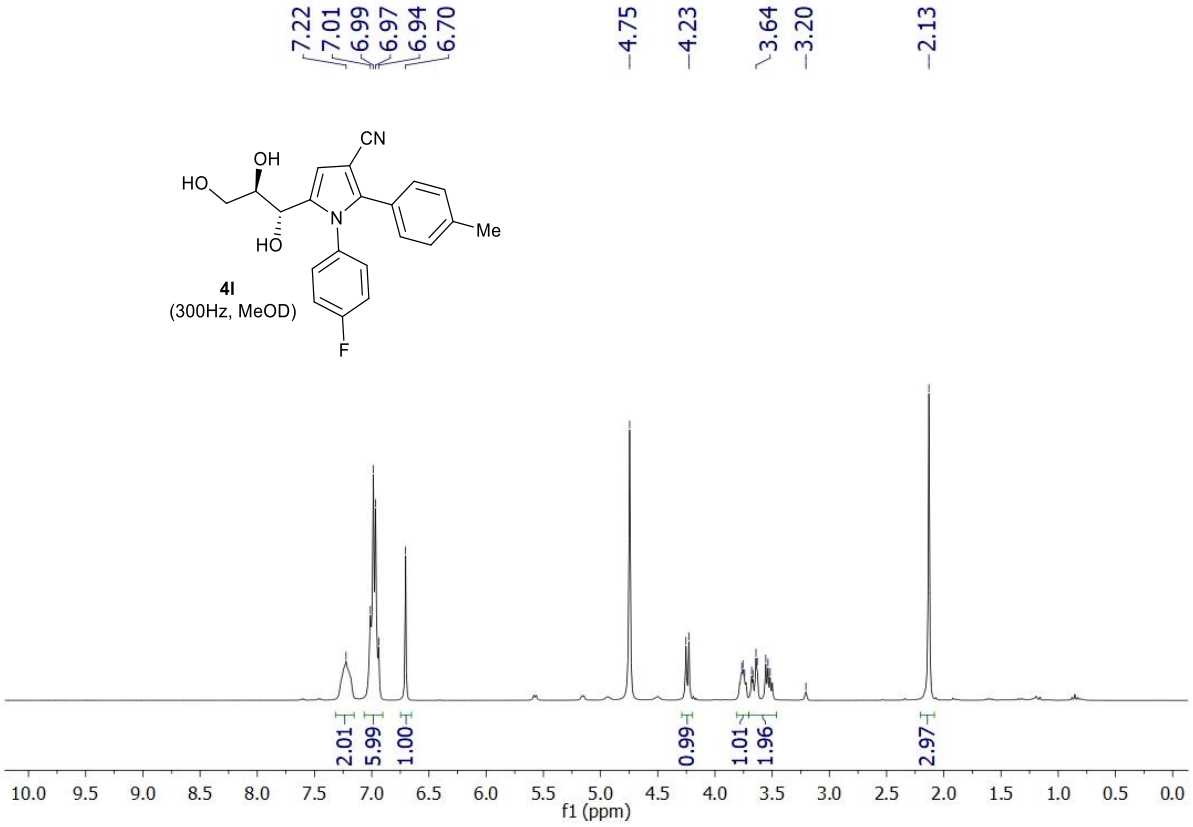


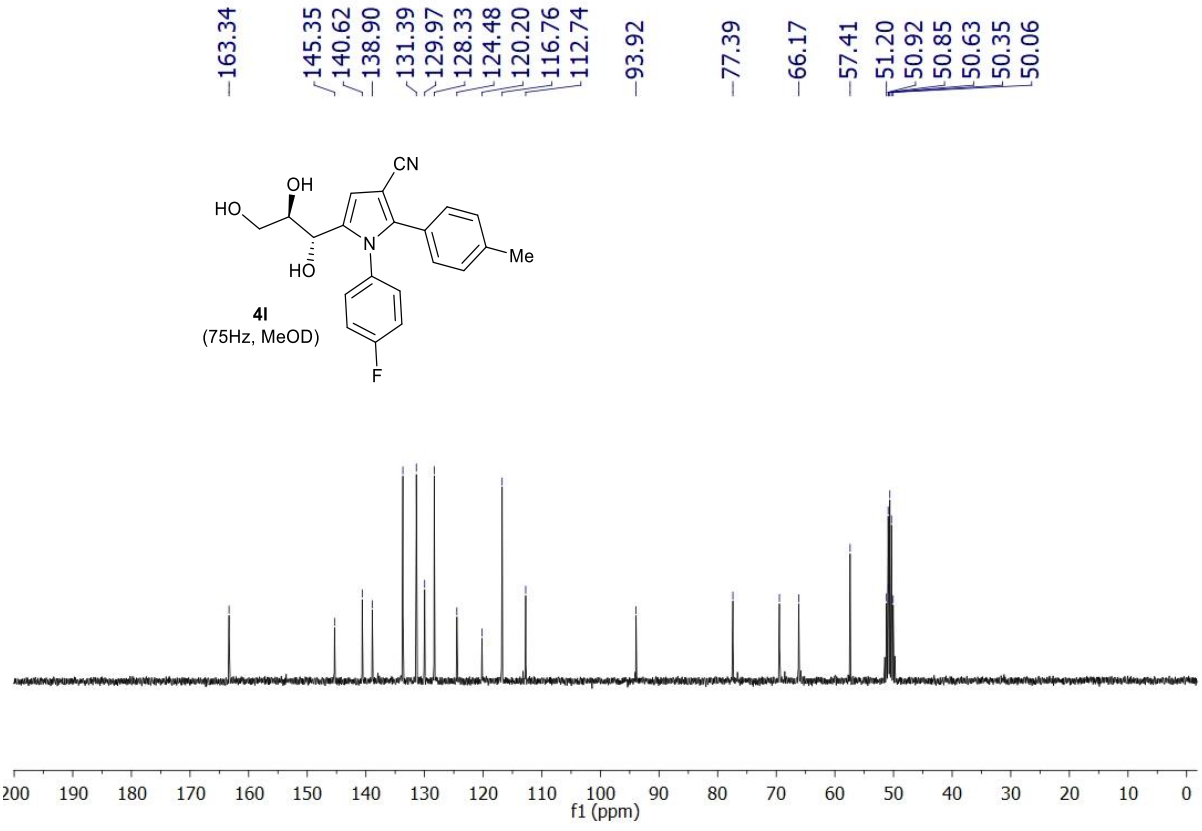
1-Benzyl-2-(4-bromophenyl)-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



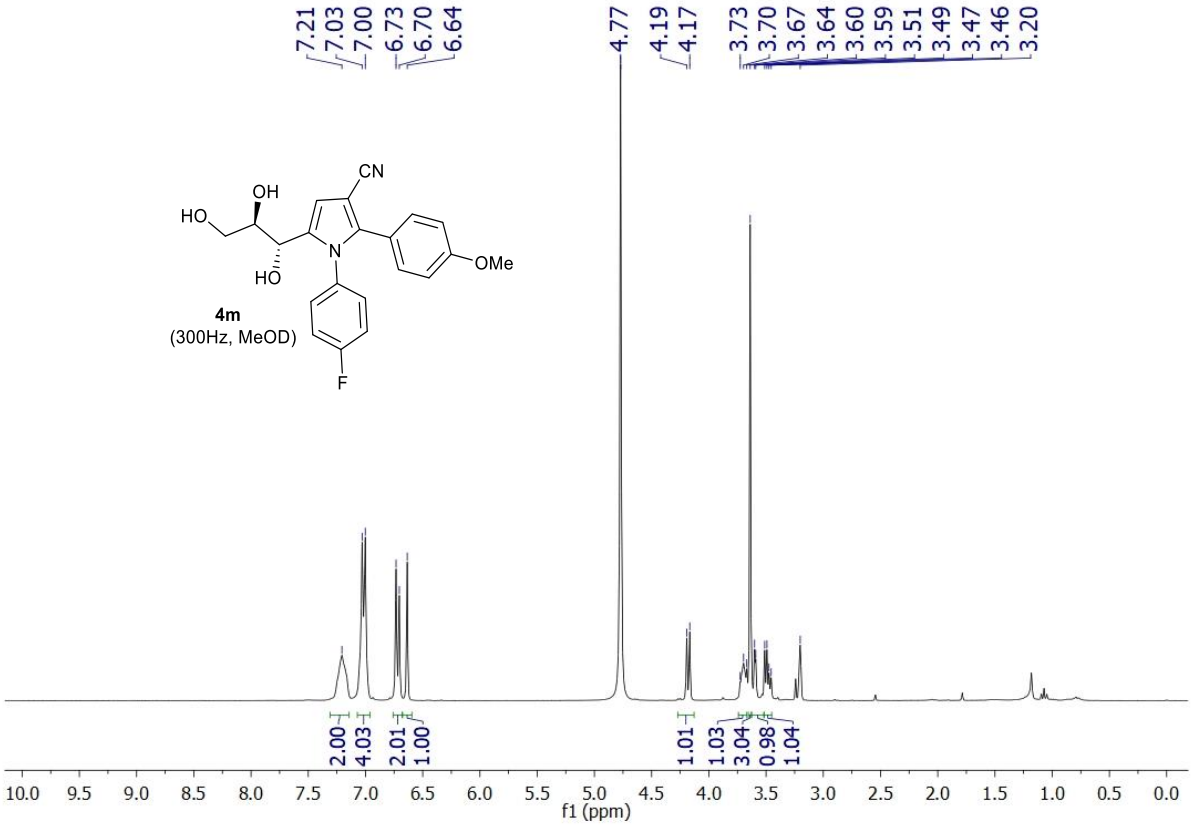


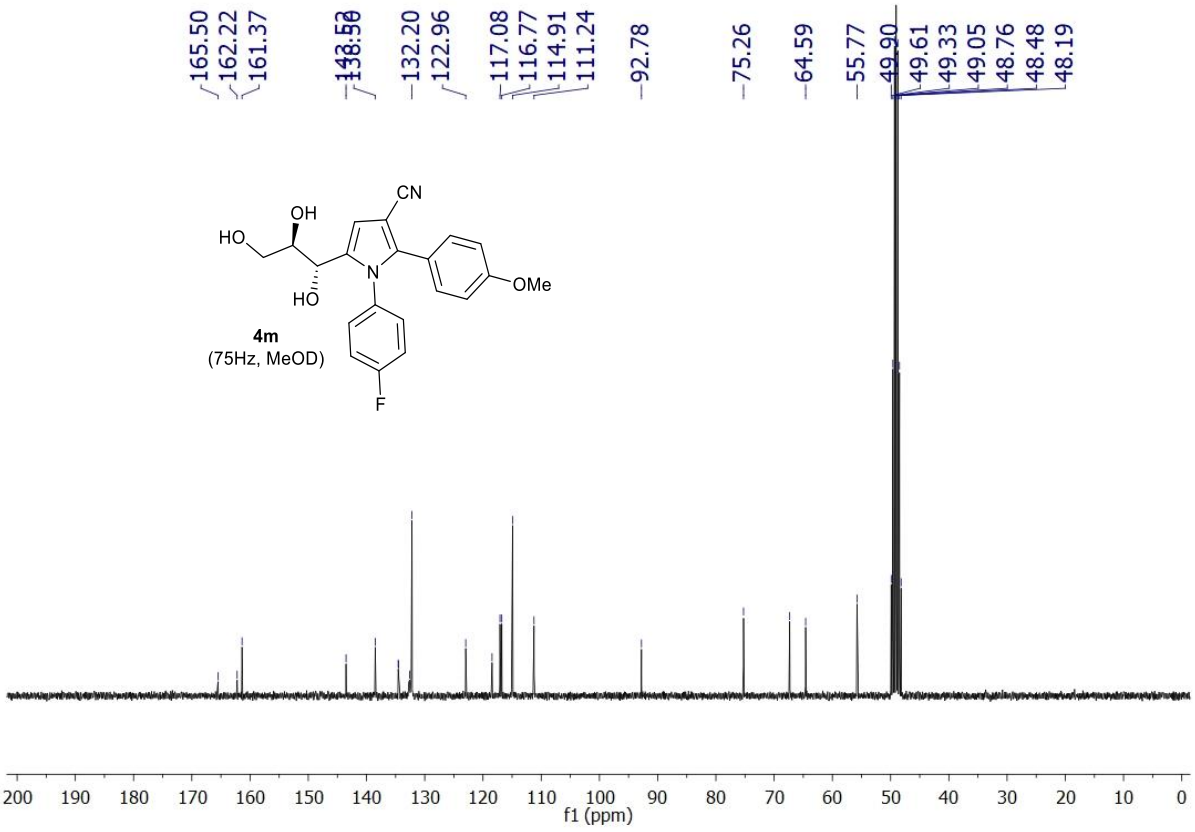
1-(4-Fluorophenyl)-2-(*p*-tolyl)-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



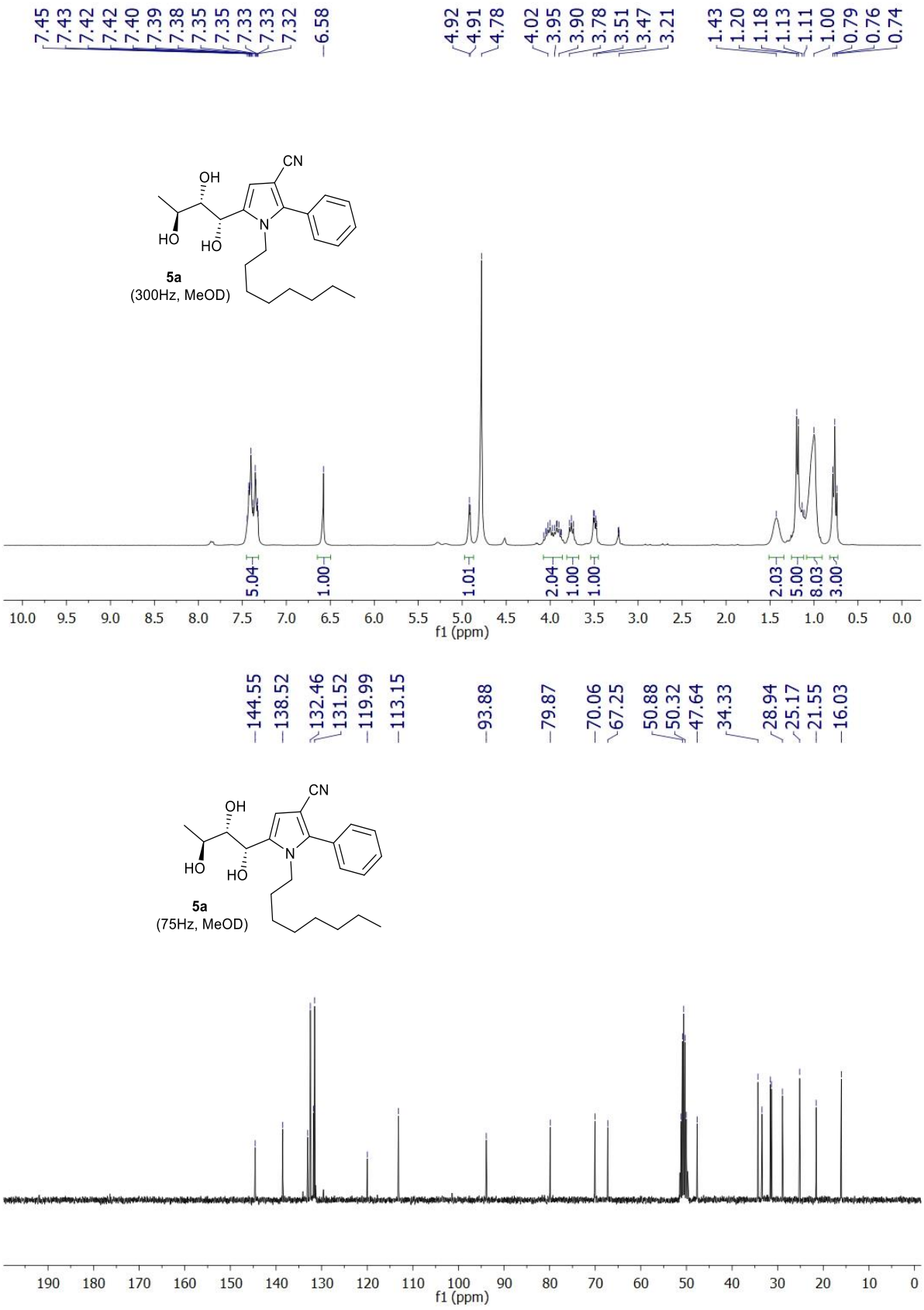


1-(4-Fluorophenyl)-2-(4-methoxyphenyl)-5-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile

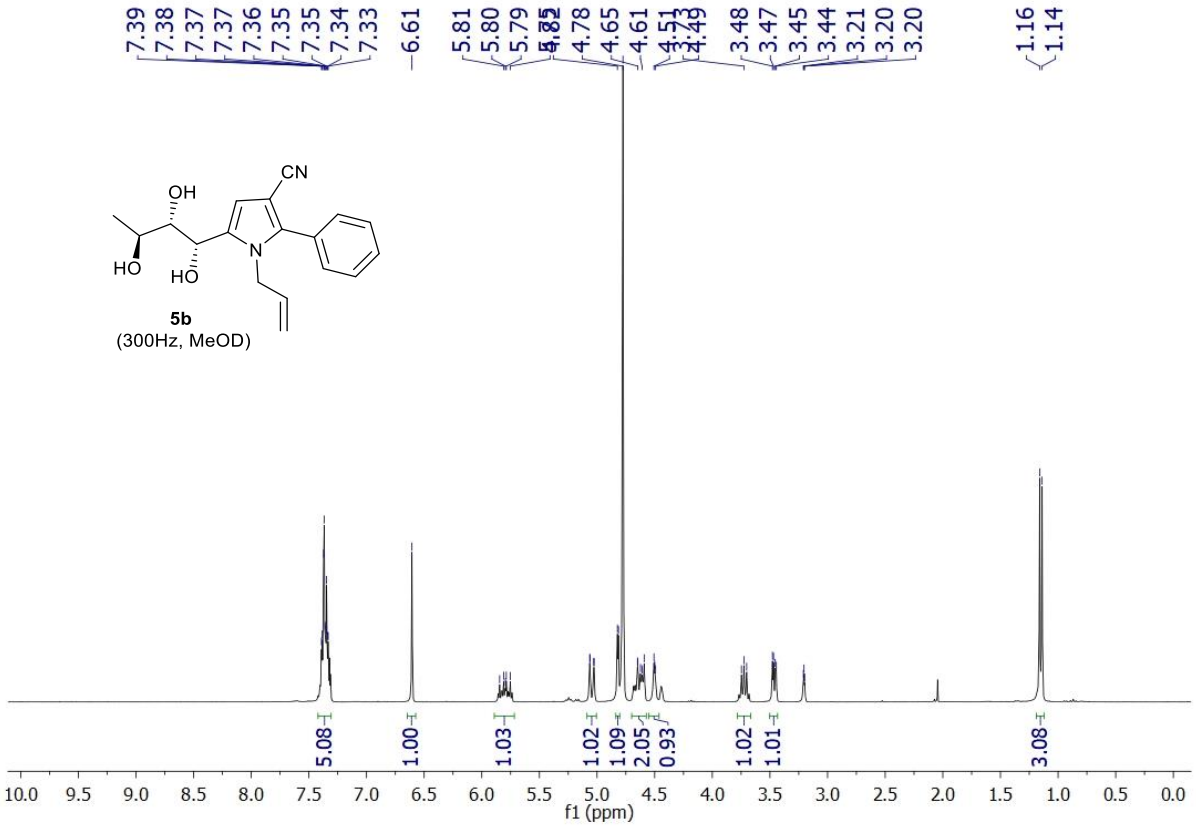


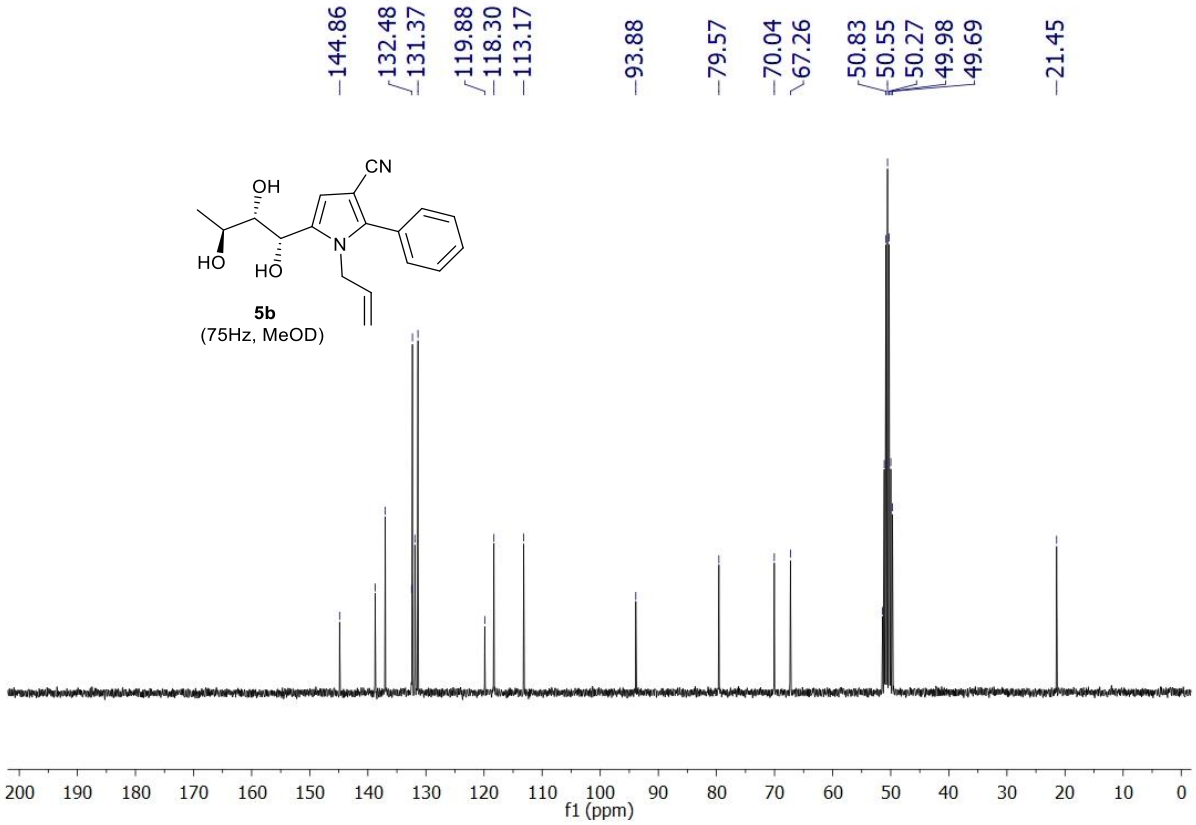


1-Octyl-2-phenyl-5-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile

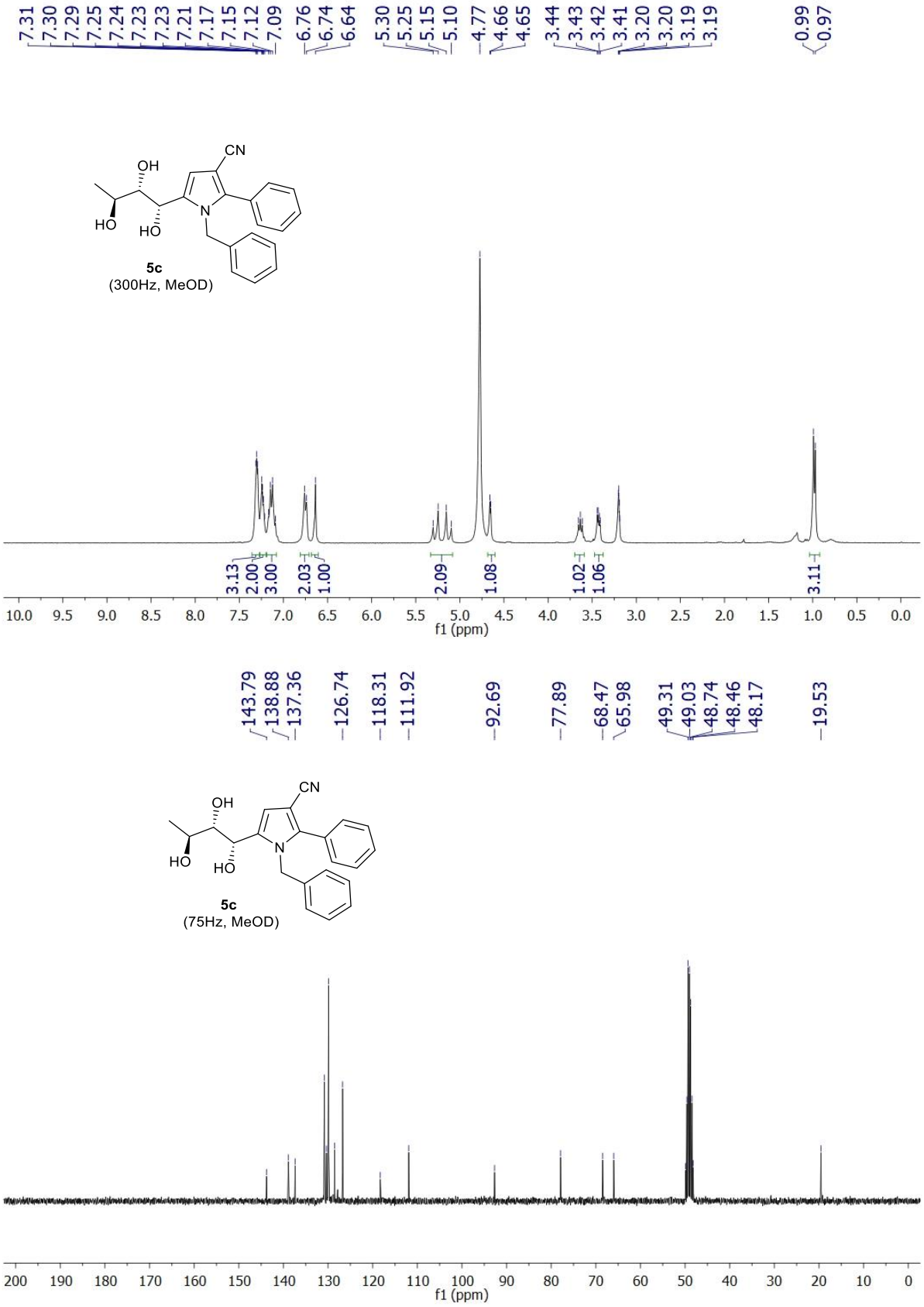


1-Allyl-2-phenyl-5-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile

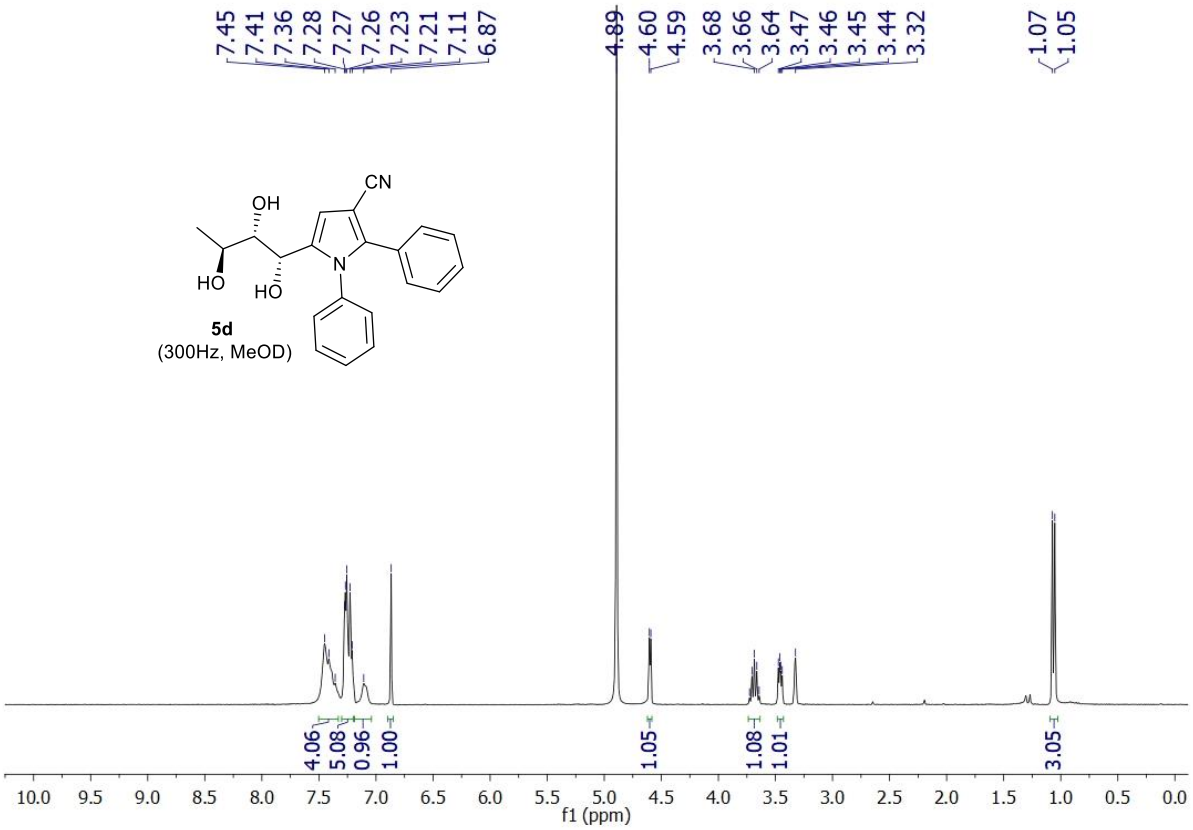


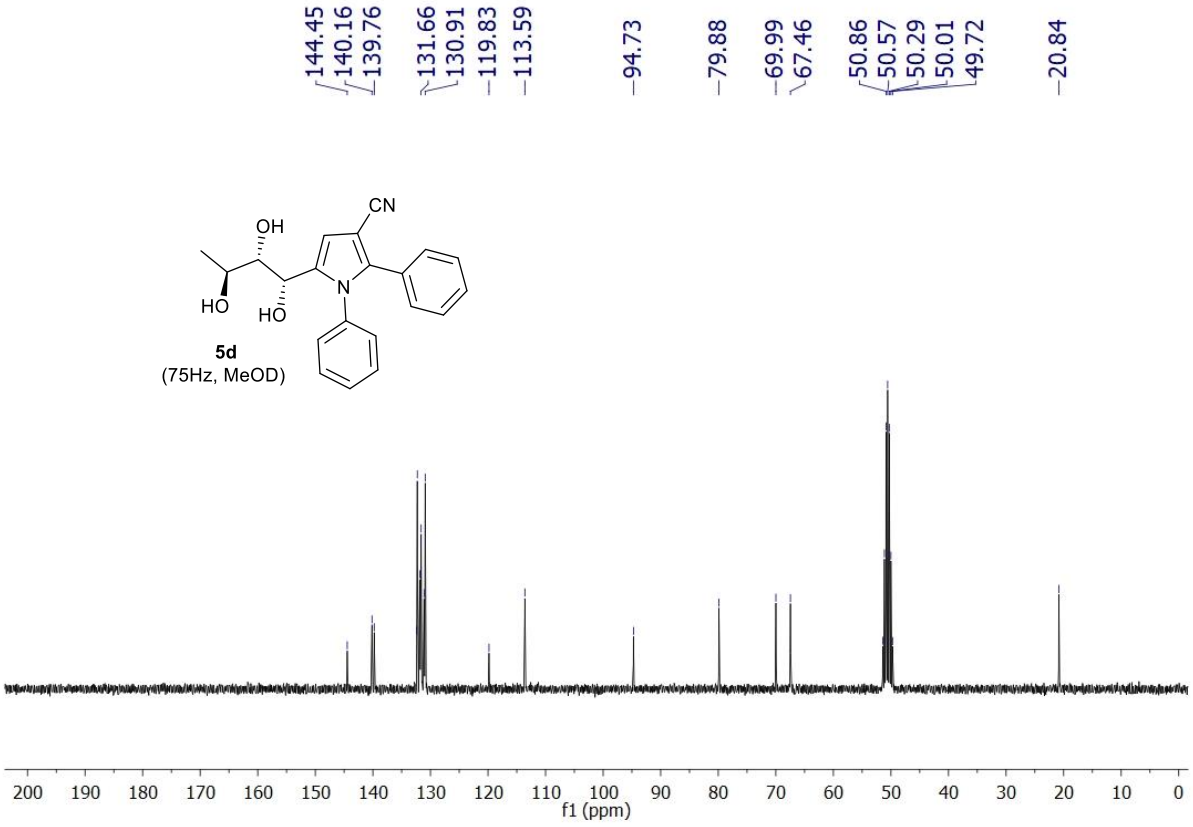


1-Benzyl-2-phenyl-5-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile

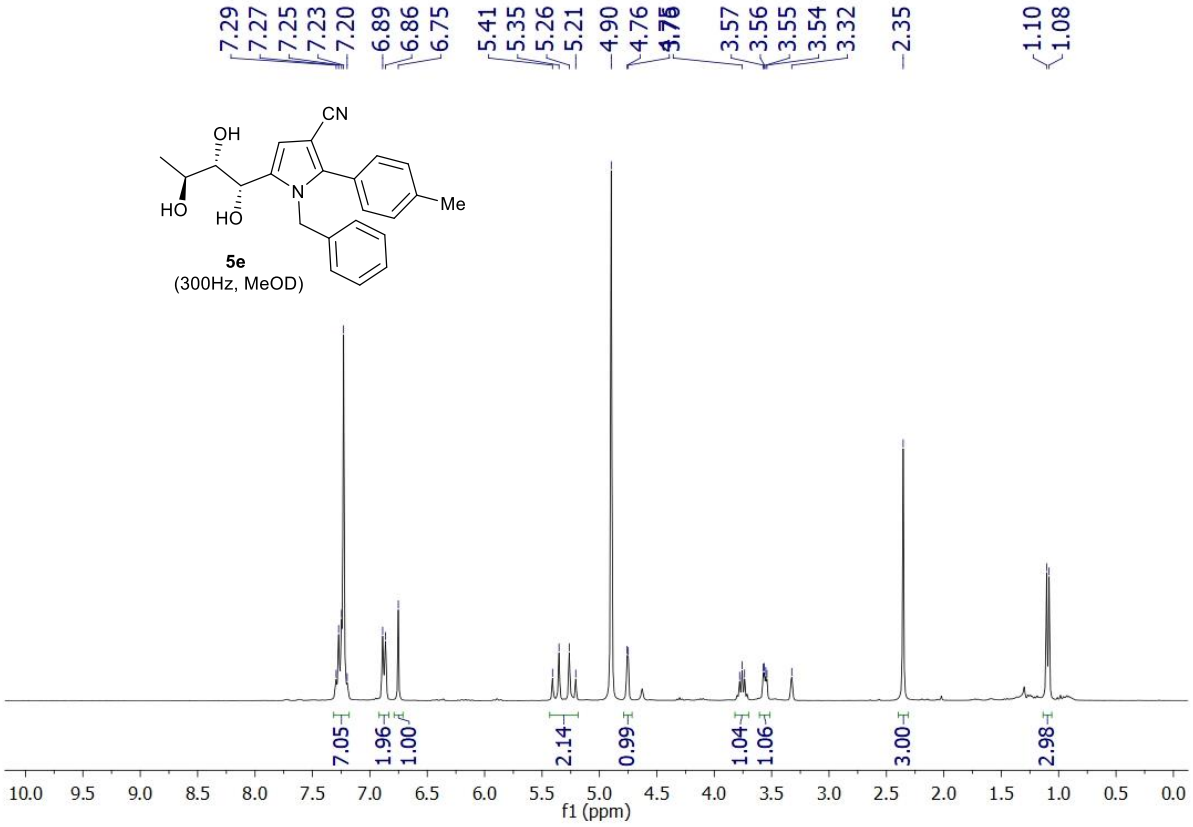


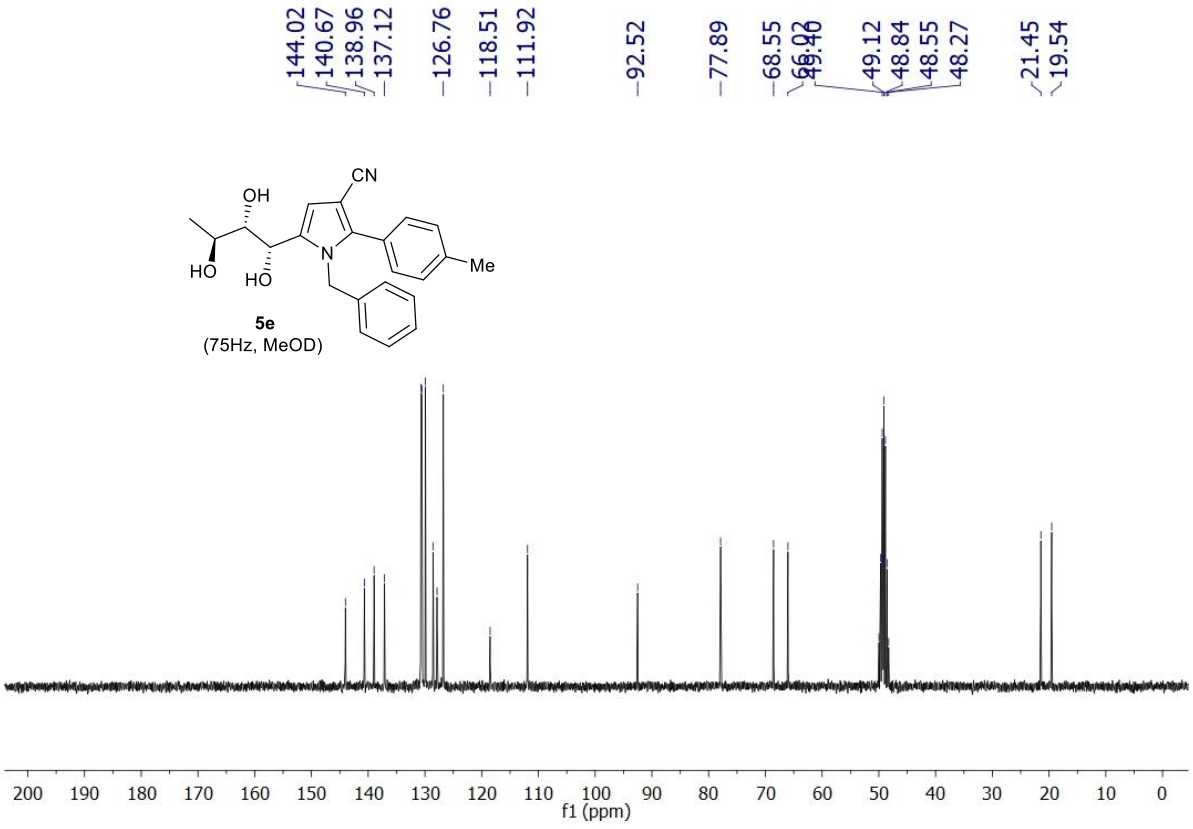
1,2-Diphenyl-5-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile



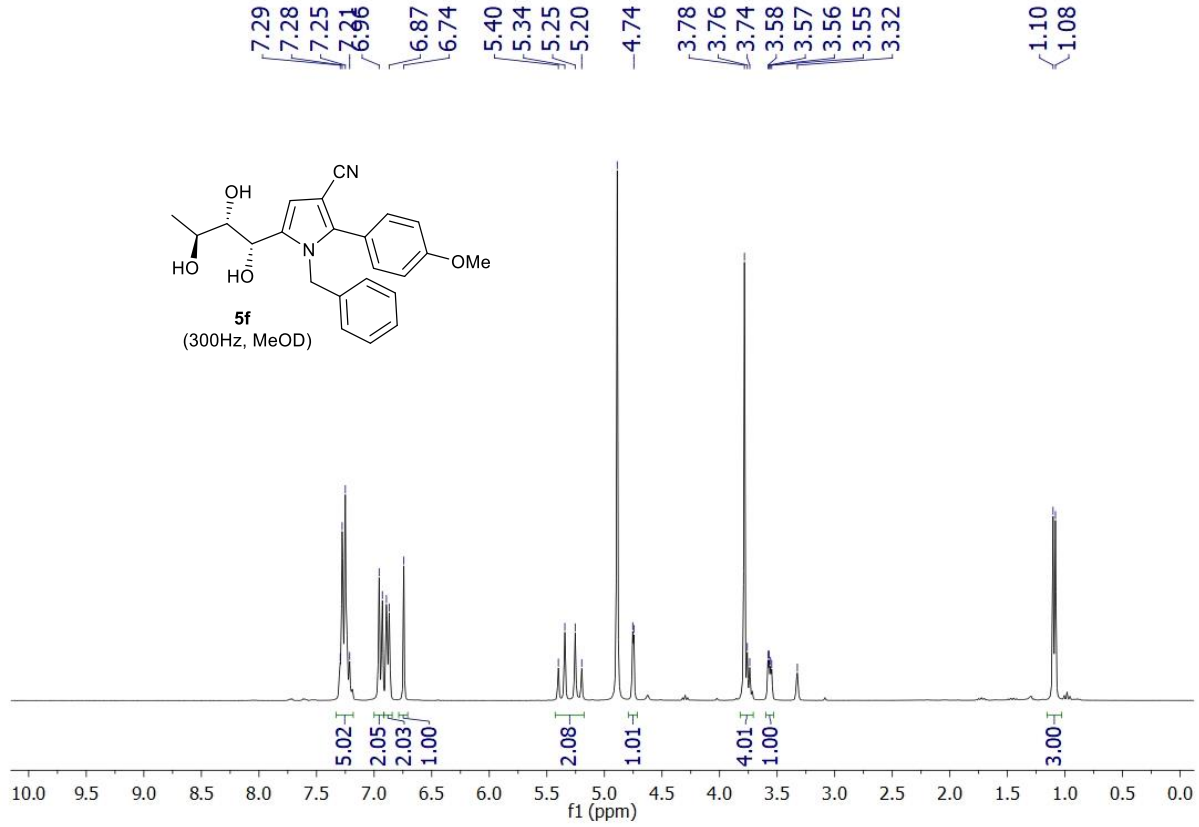


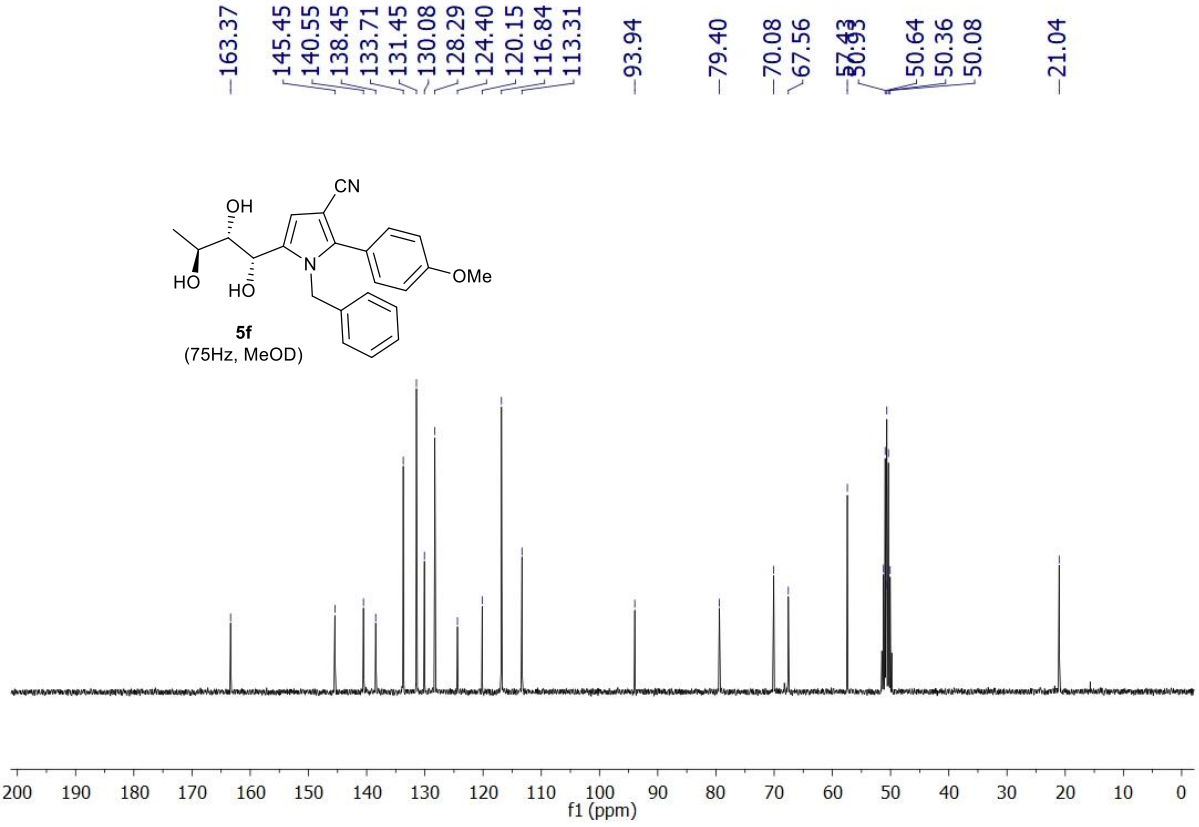
1-Benzyl-2-(*p*-tolyl)-5-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile



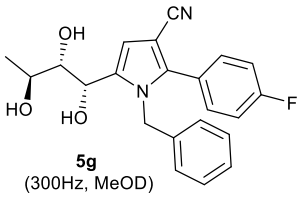


1-Benzyl-2-(4-methoxyphenyl)-5-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile

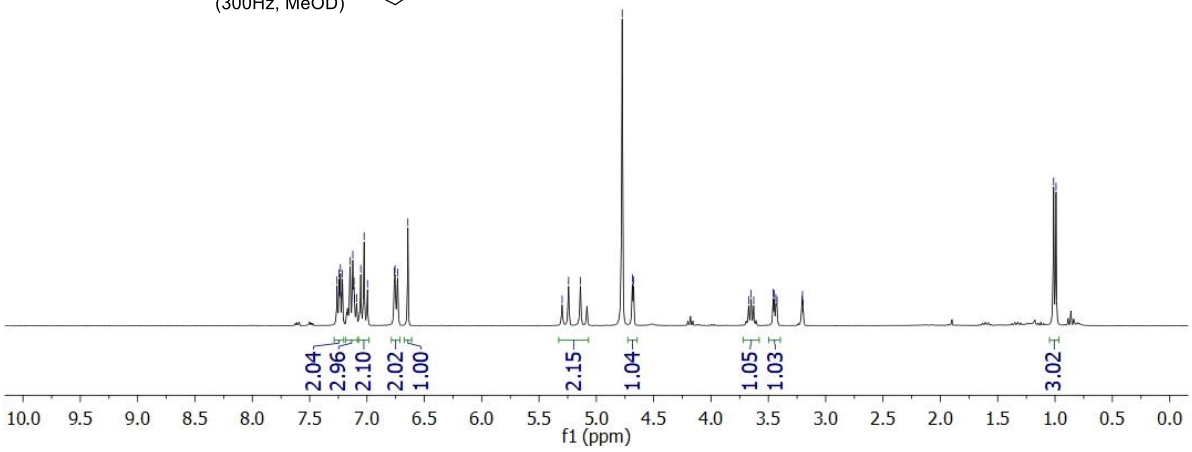


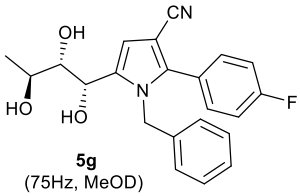


1-Benzyl-2-(4-fluorophenyl)-5-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile



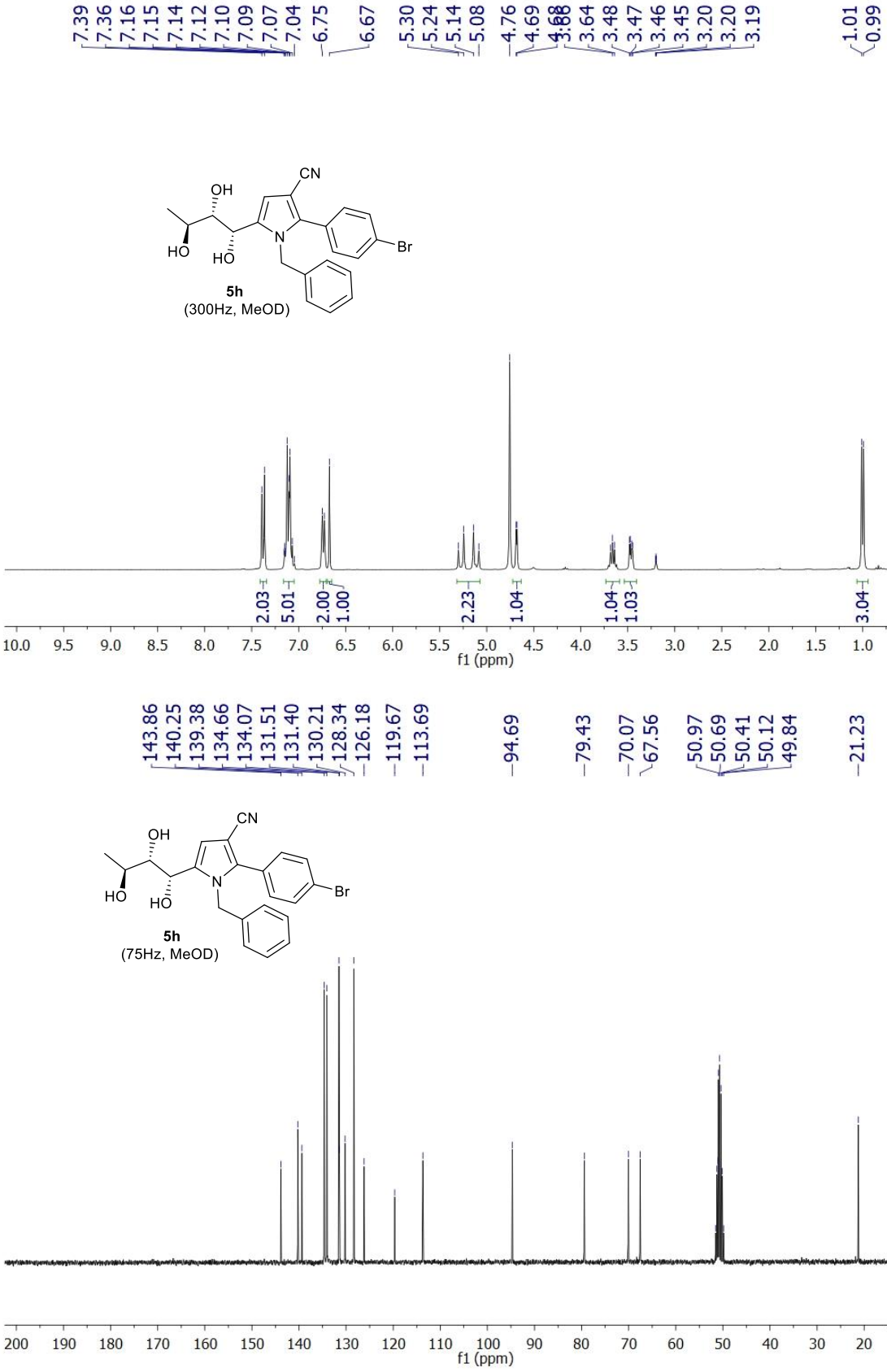
5g
(300Hz, MeOD)



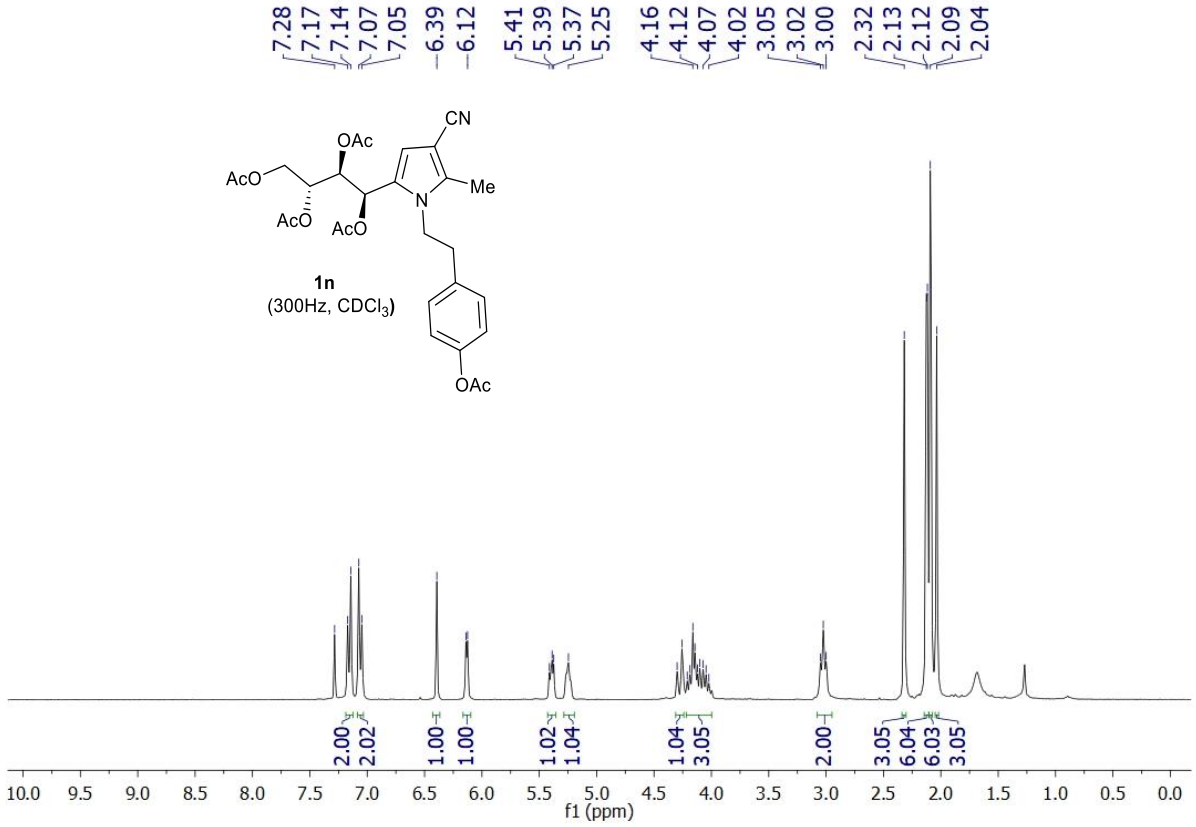


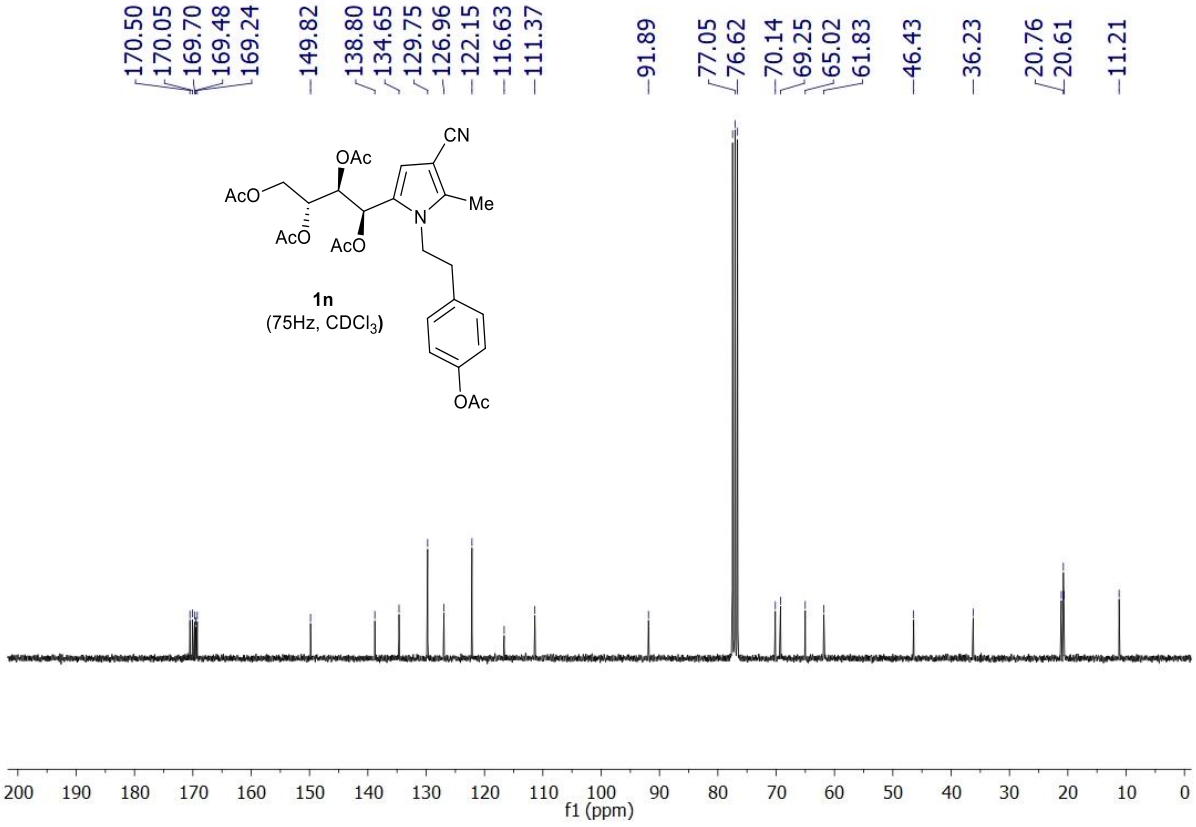
5g
(75Hz, MeOD)

1-Benzyl-2-(4-bromophenyl)-5-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile

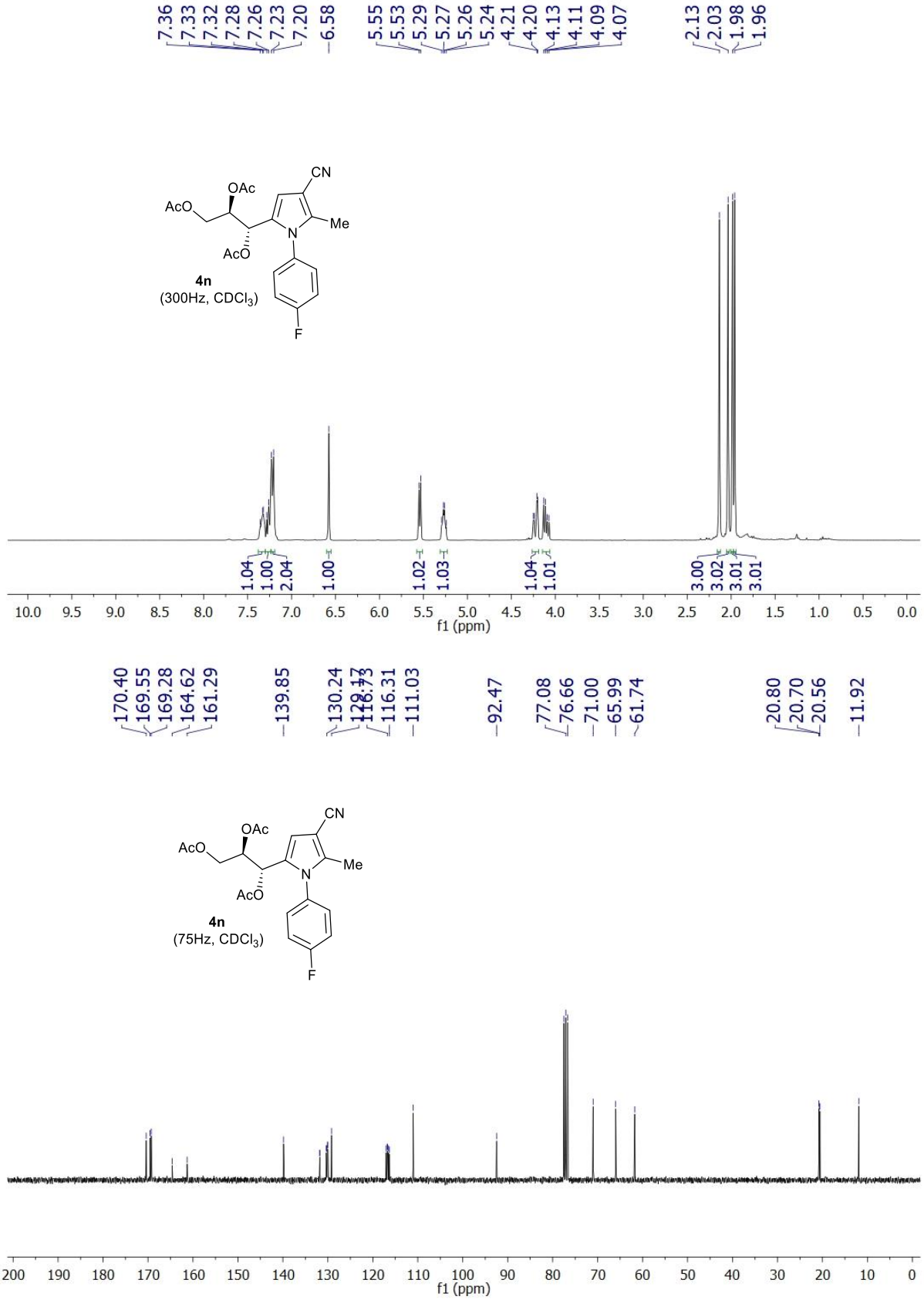


(1*R*,2*S*,3*R*)-1-(1-(4-acetoxyphenethyl)-4-cyano-5-methyl-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate

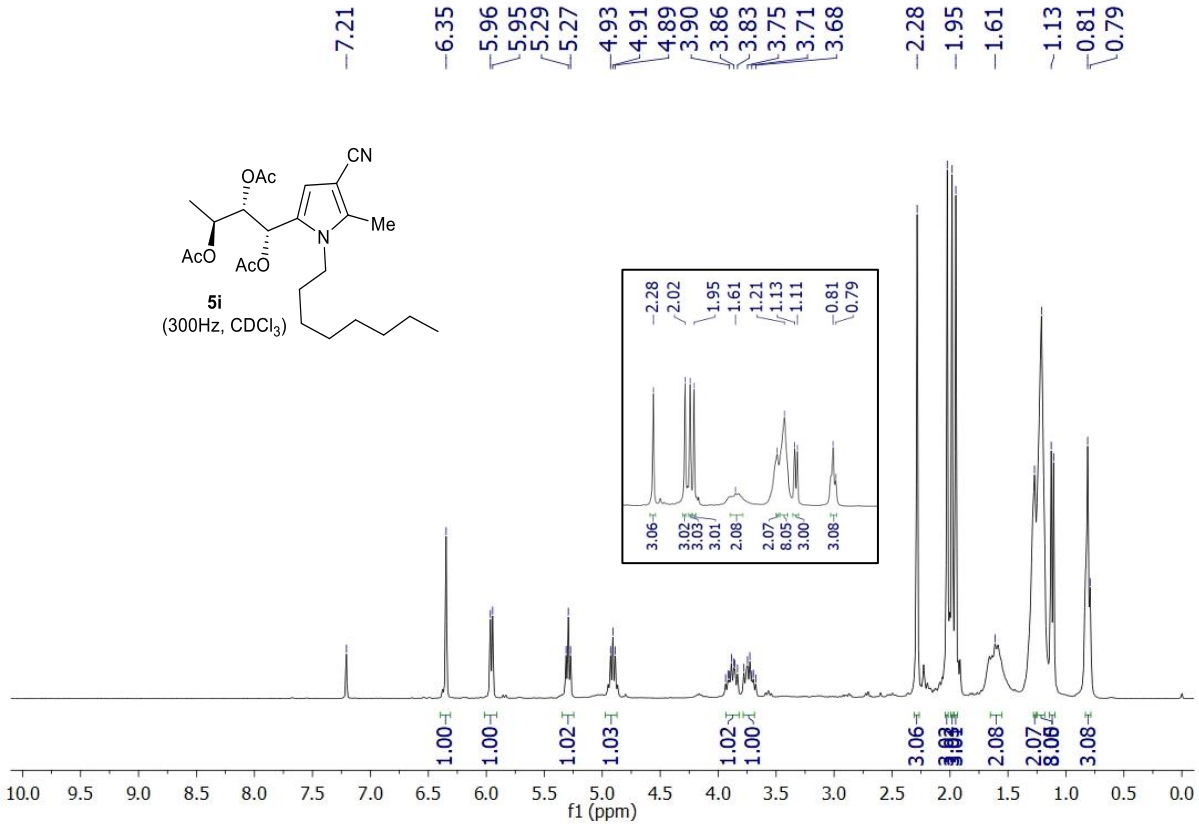


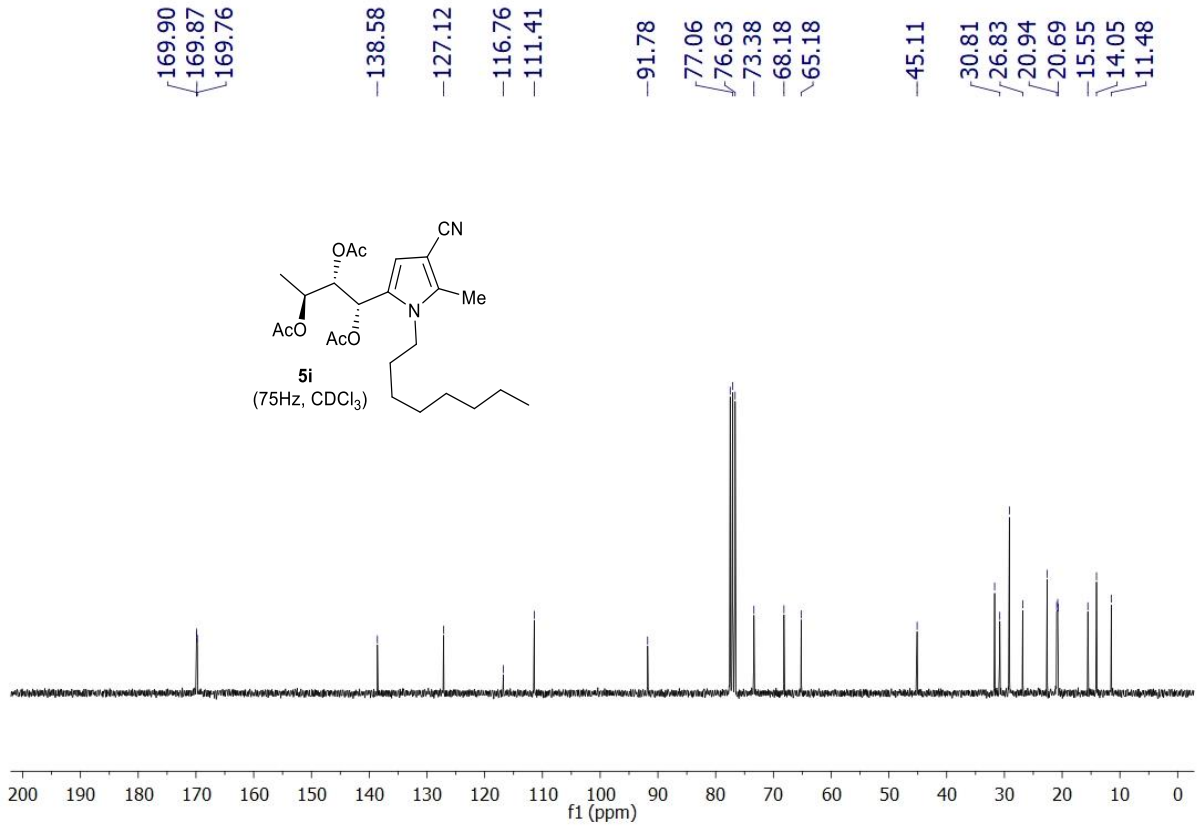


(1*S*,2*R*)-1-(4-cyano-1-(4-fluorophenyl)-5-methyl-1*H*-pyrrol-2-yl)propane-1,2,3-triyl triacetate



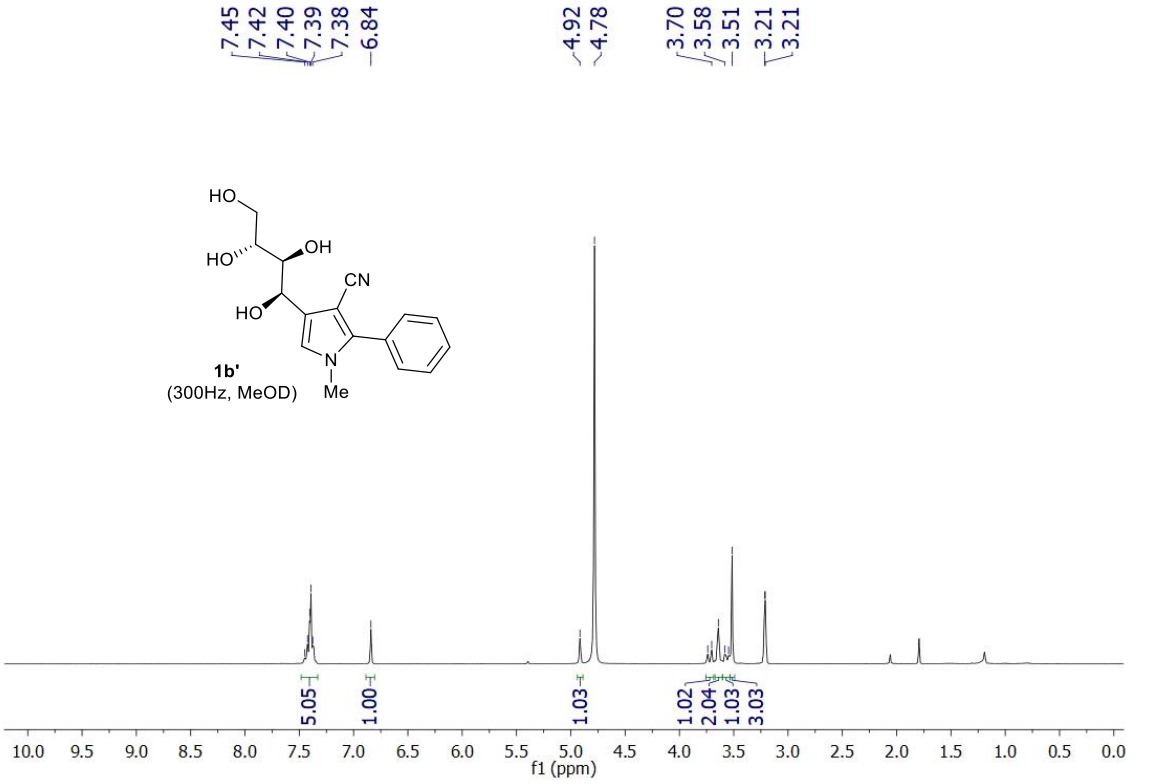
(1*S*,2*S*,3*S*)-1-(4-cyano-5-methyl-1-octyl-1*H*-pyrrol-2-yl)butane-1,2,3-triyl triacetate

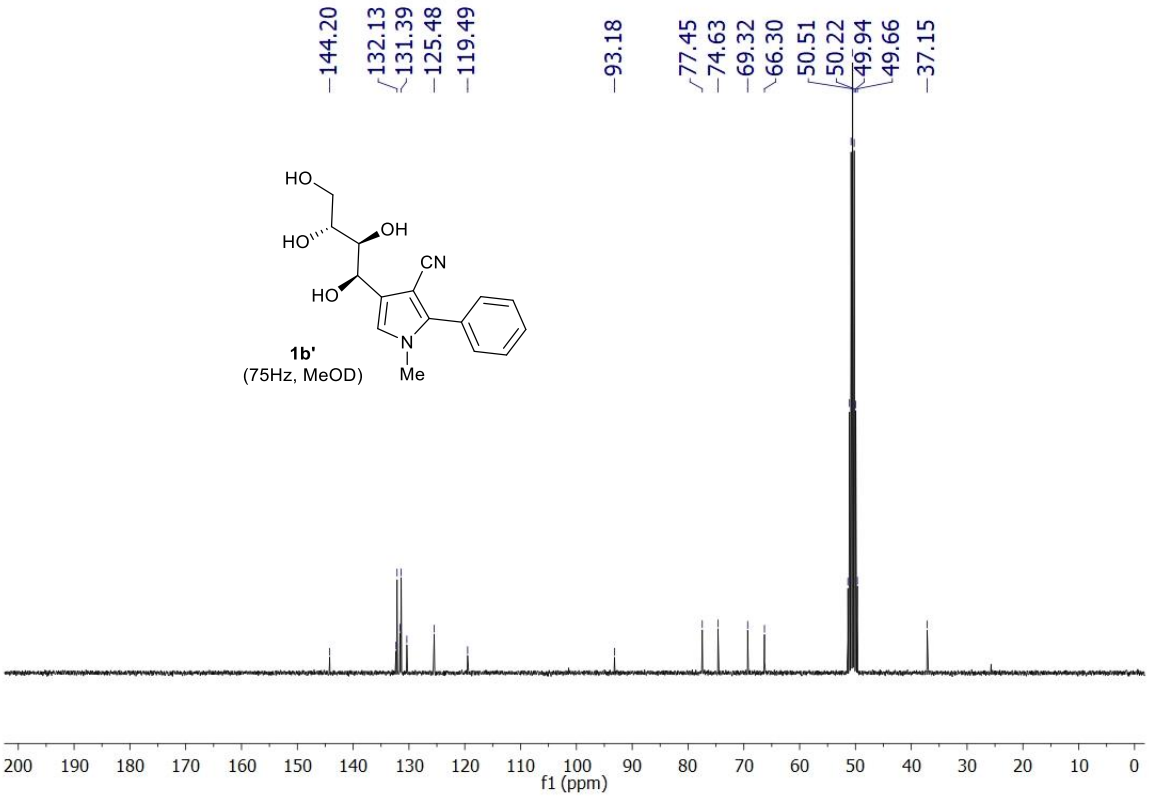




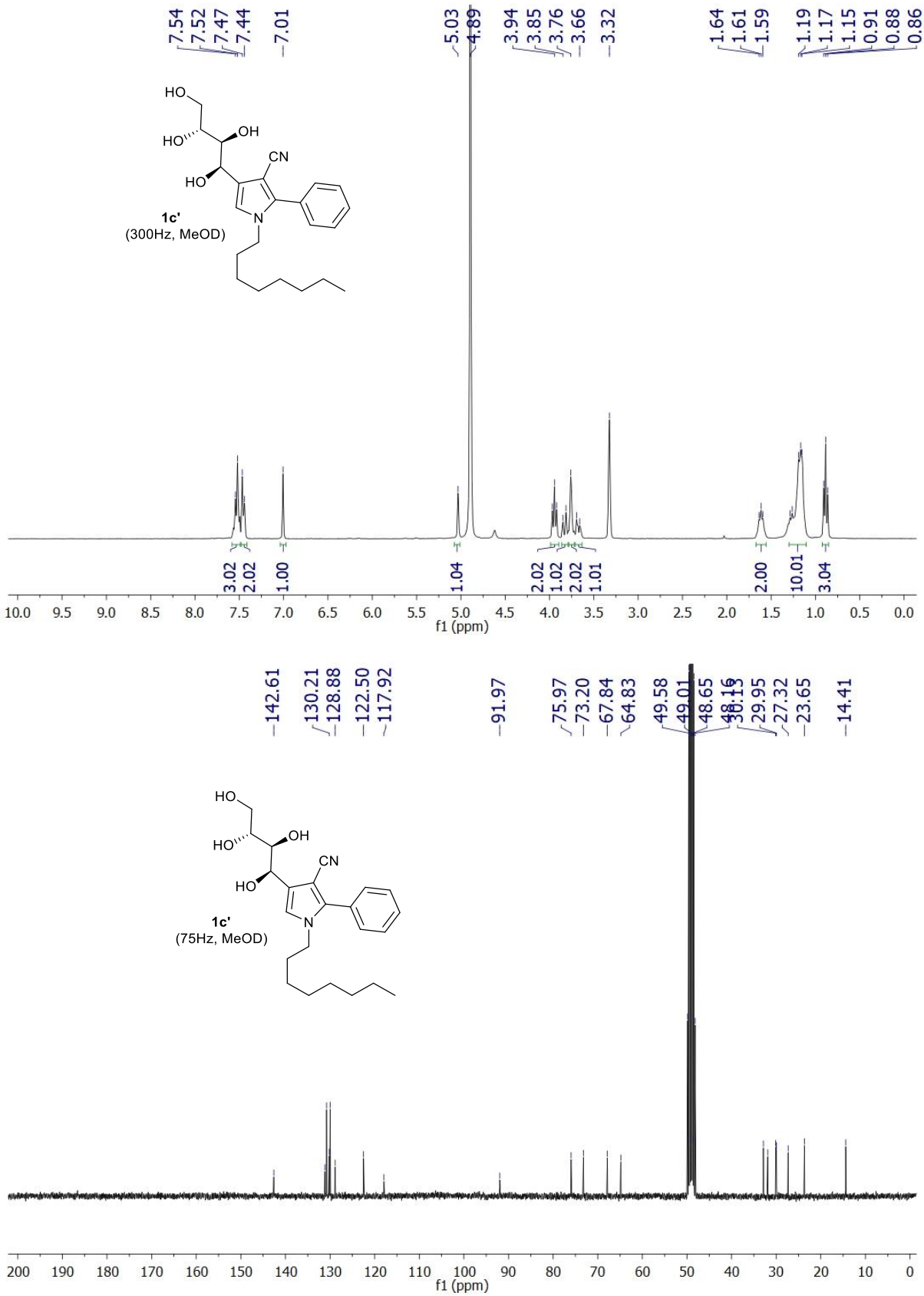
2.2 ^{1}H and ^{13}C NMR spectra for 2,3,4-substituted pyrroles

1-Methyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

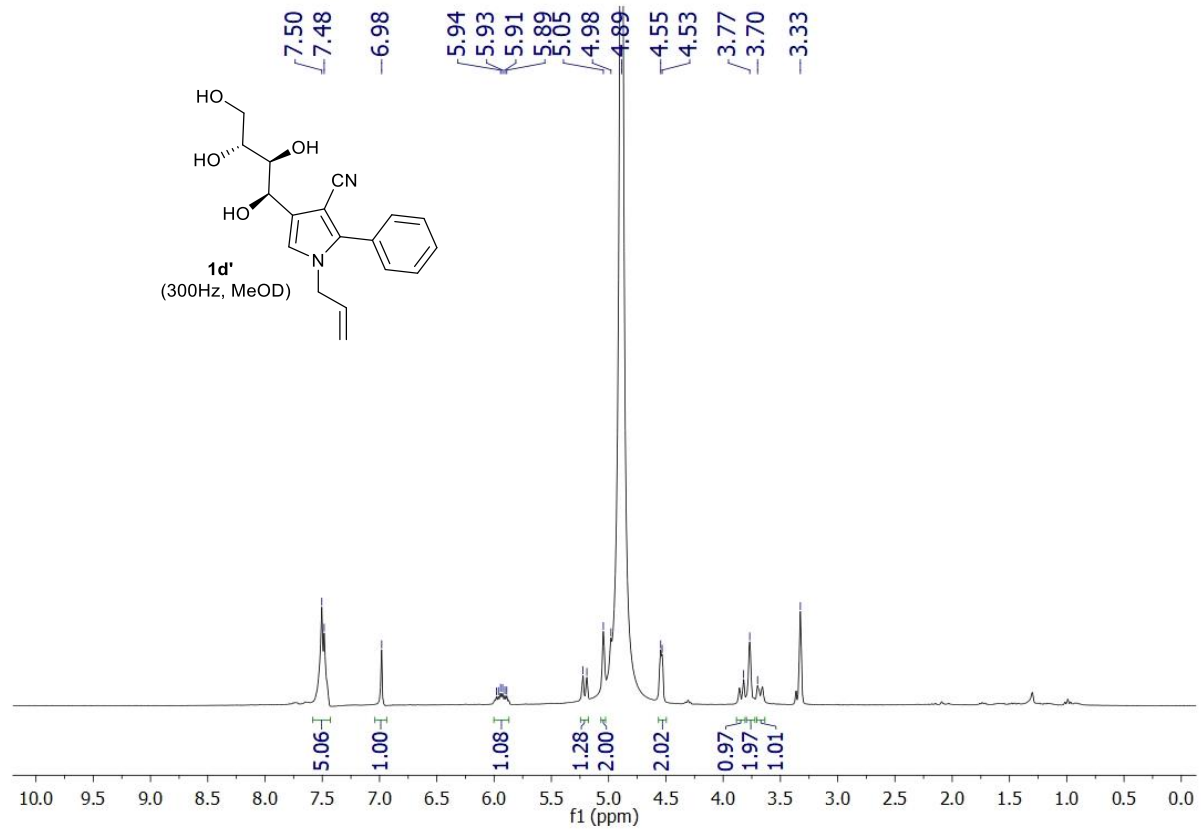


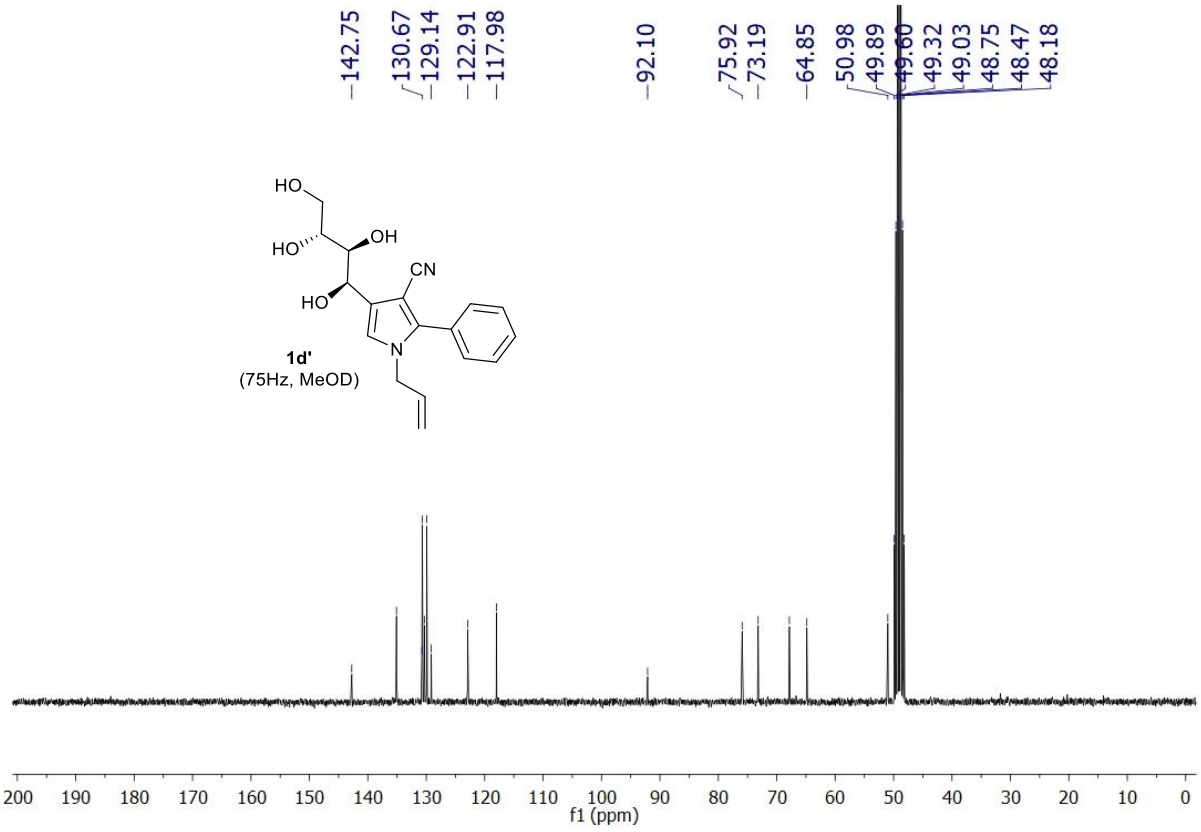


1-Octyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

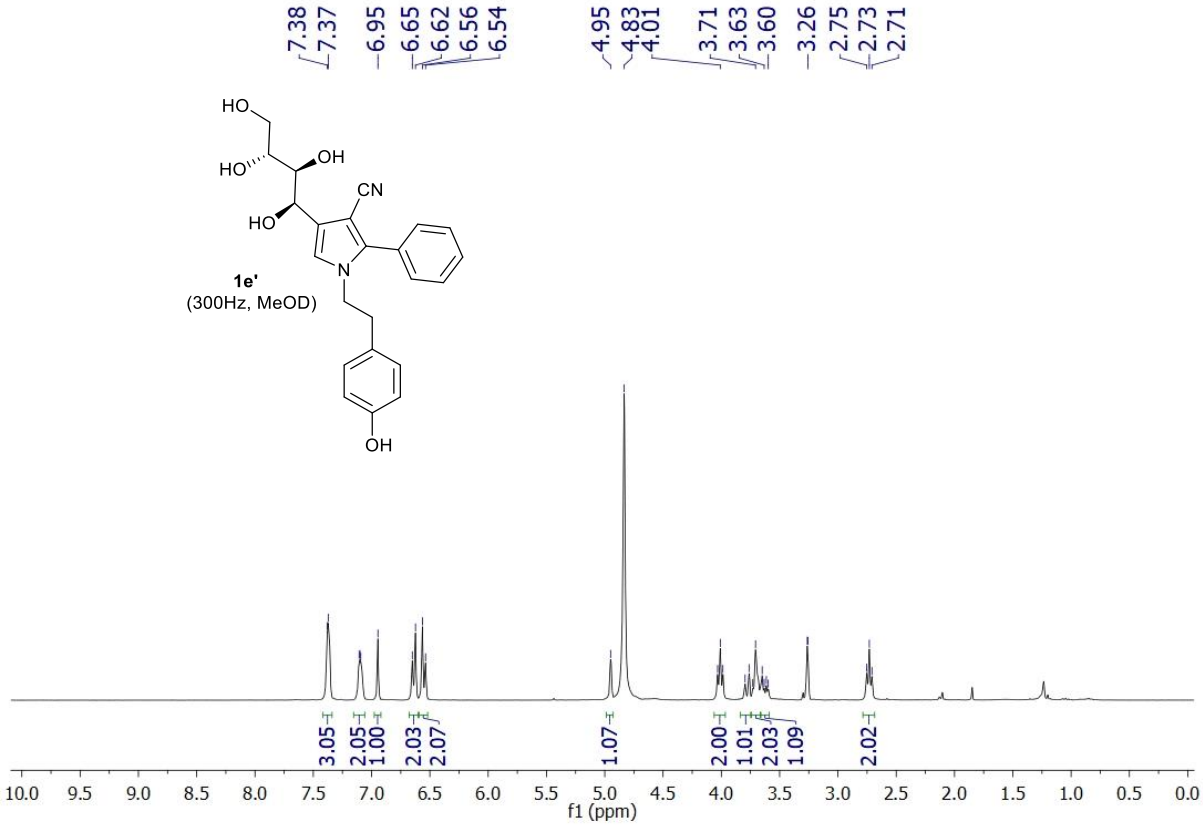


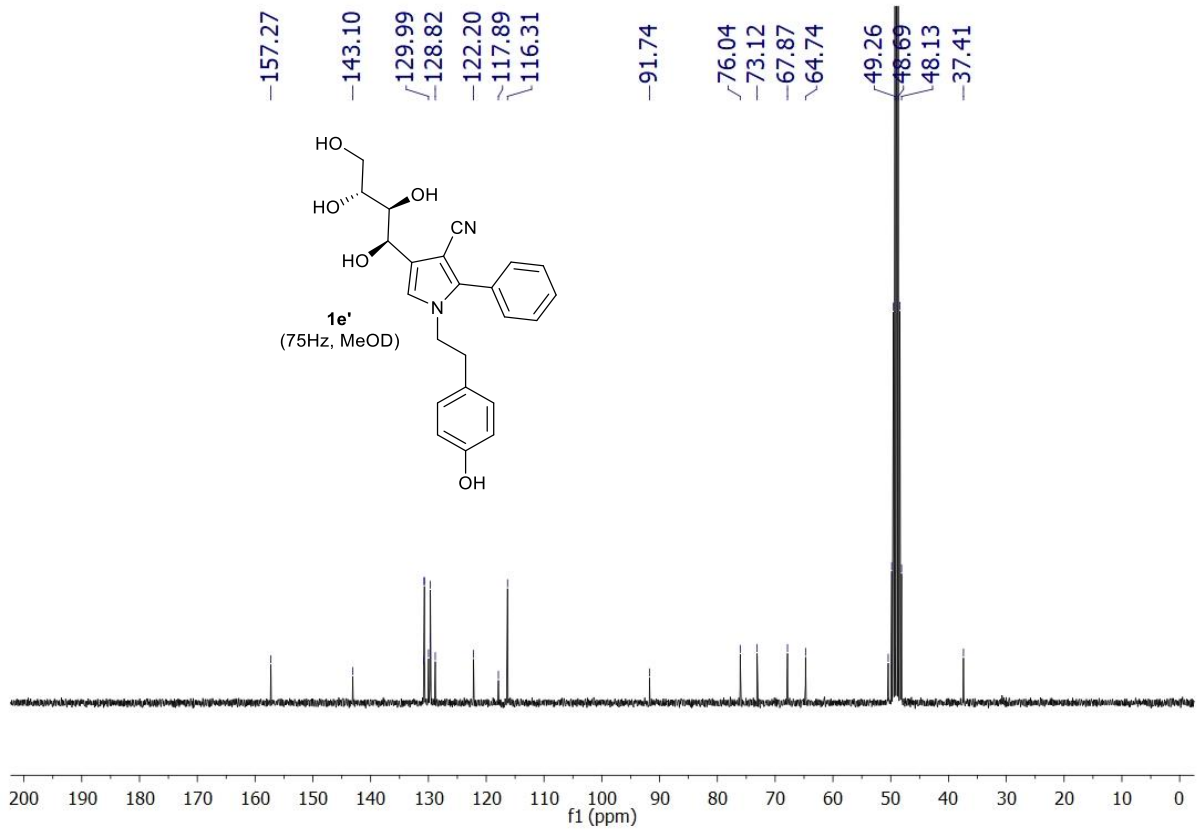
1-Allyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



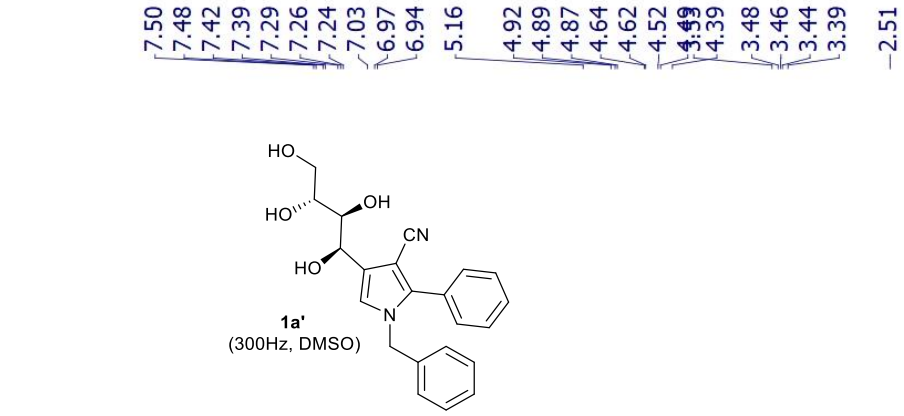


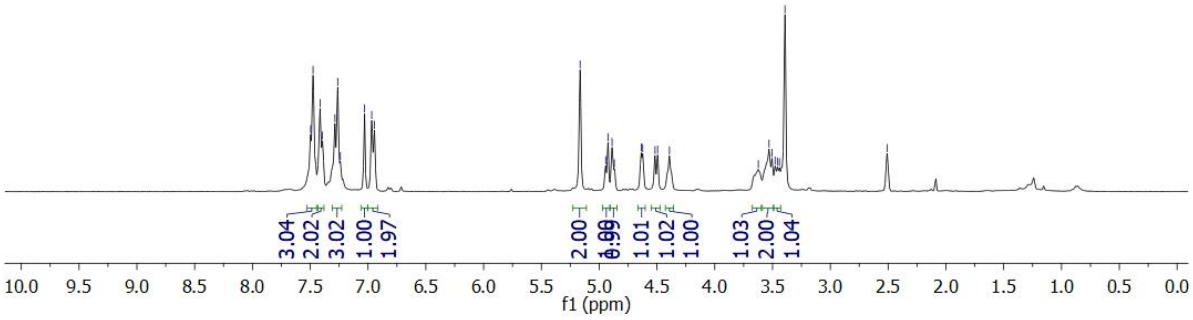
1-(4-Hydroxyphenethyl)-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

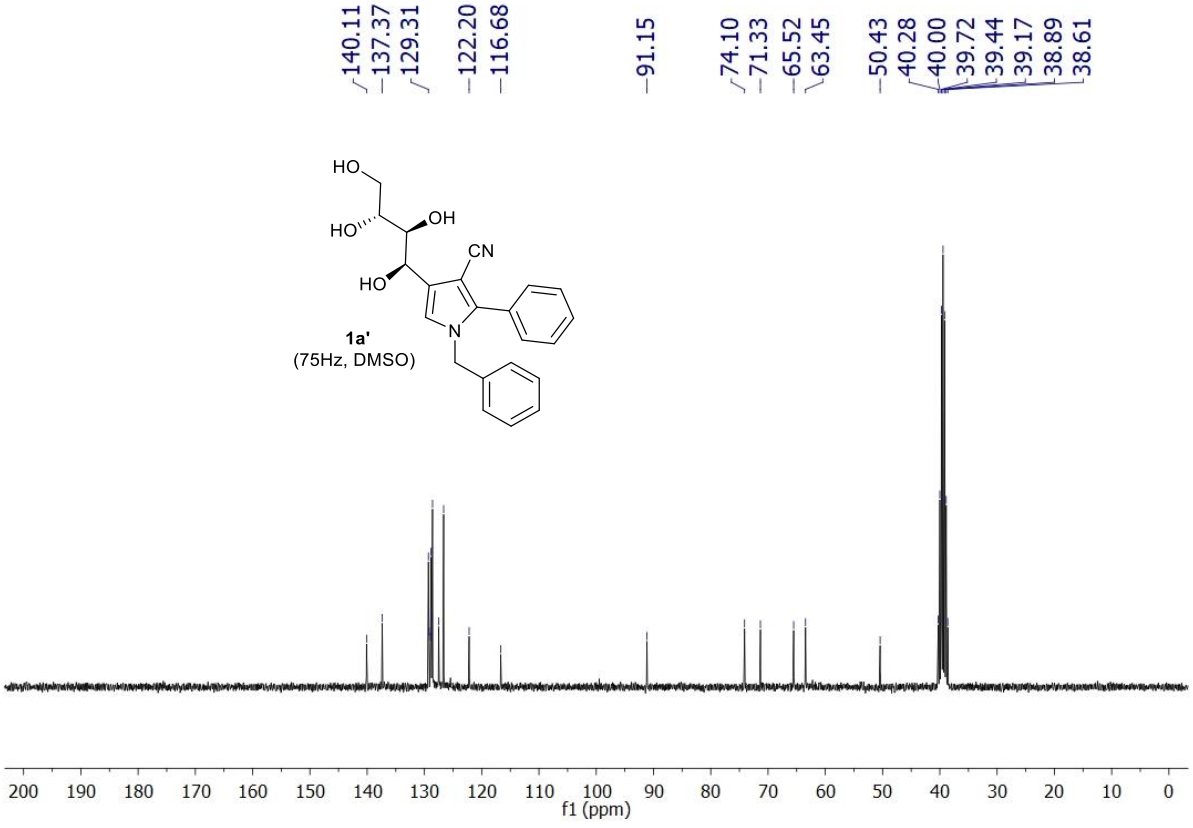




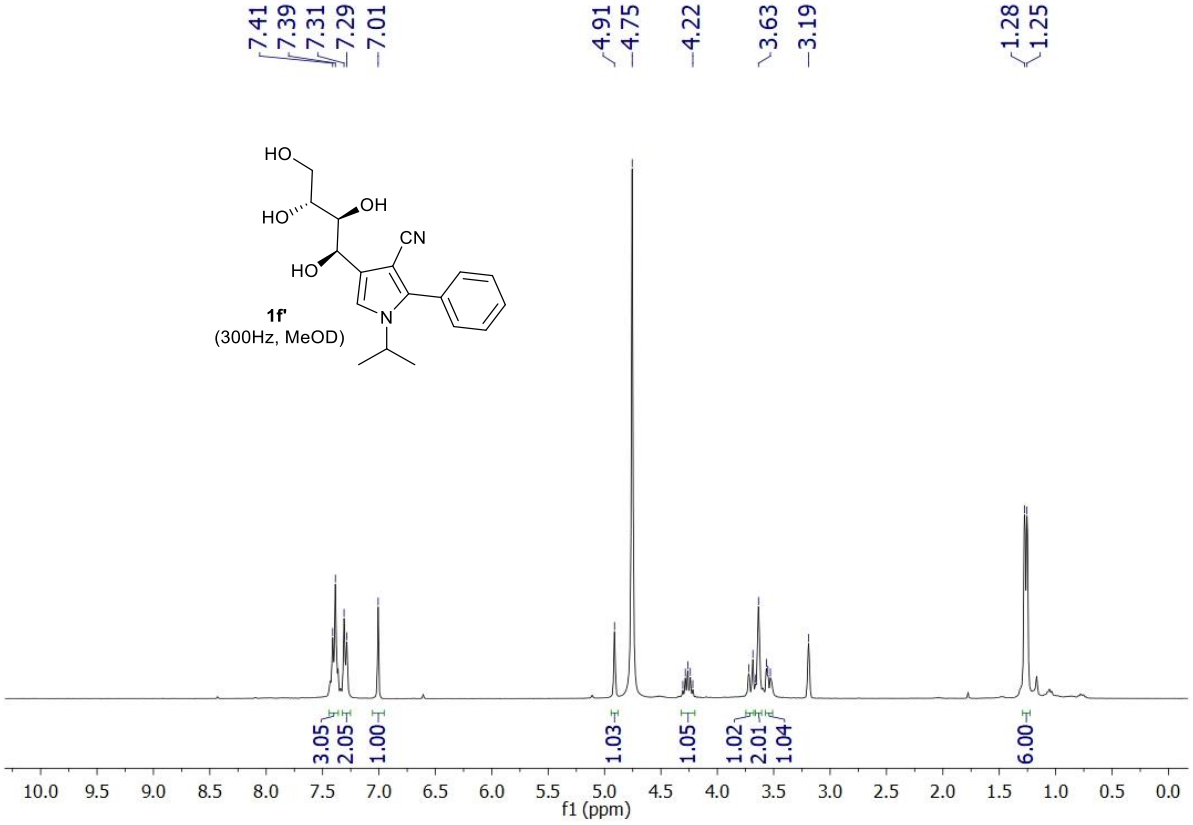
1-Benzyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

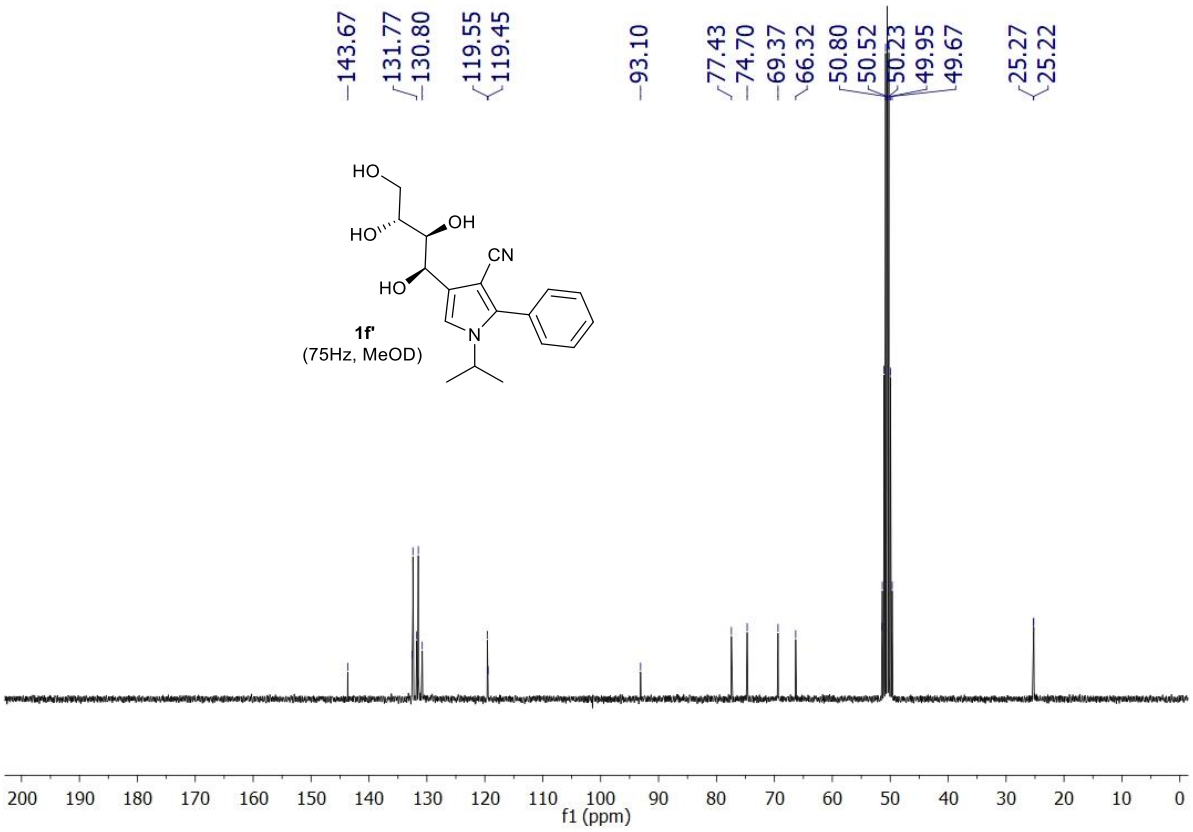




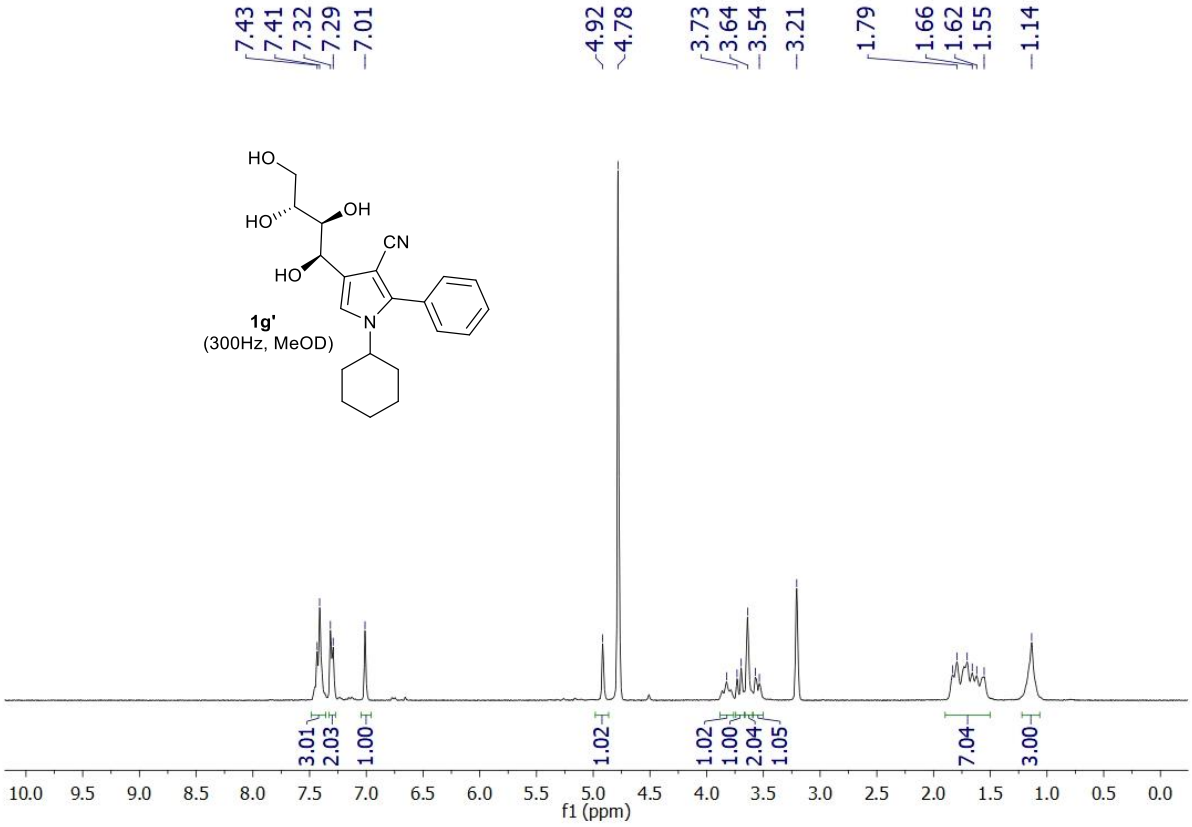


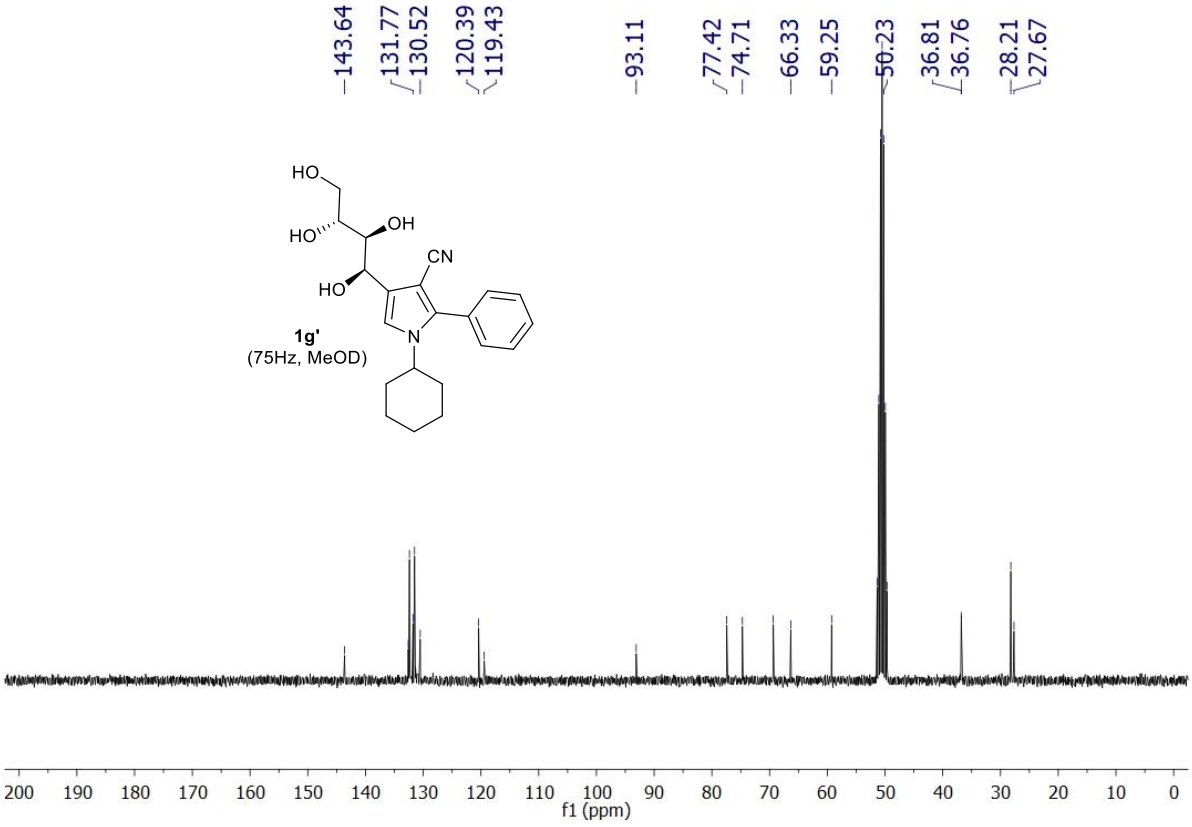
1-Isopropyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



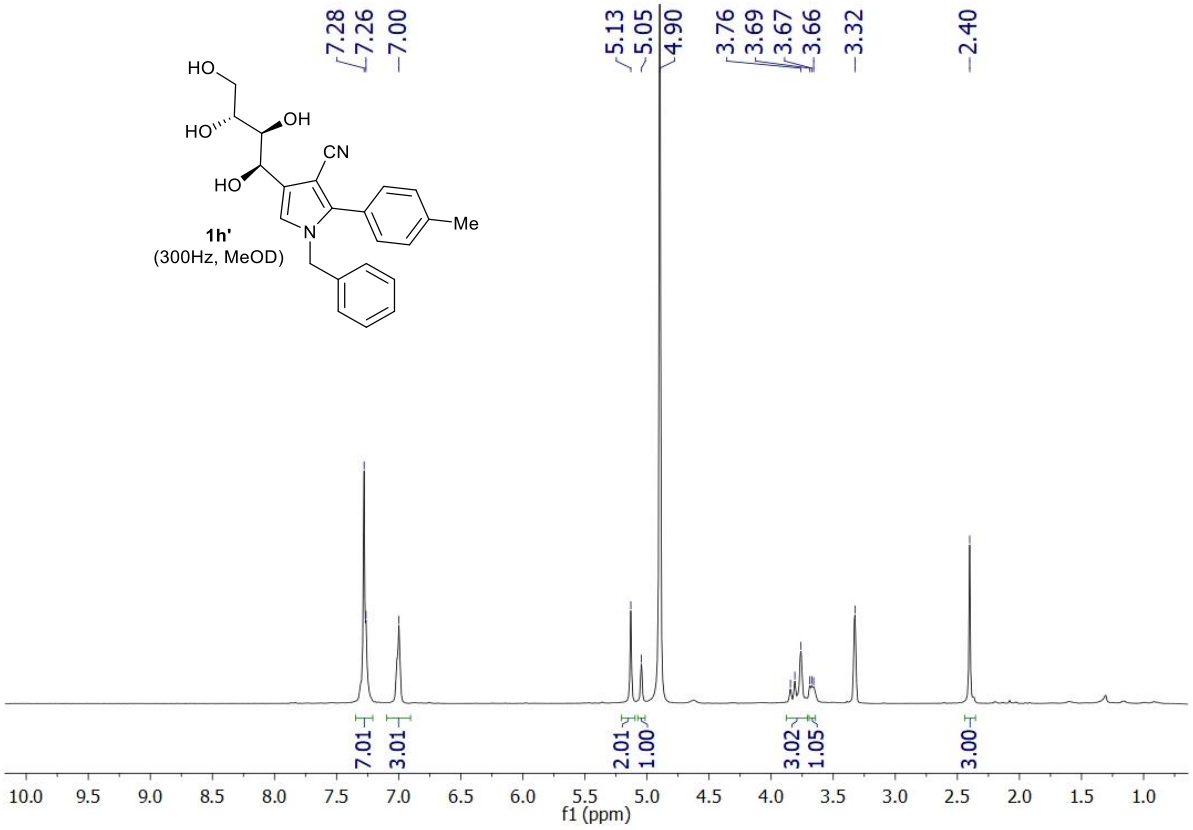


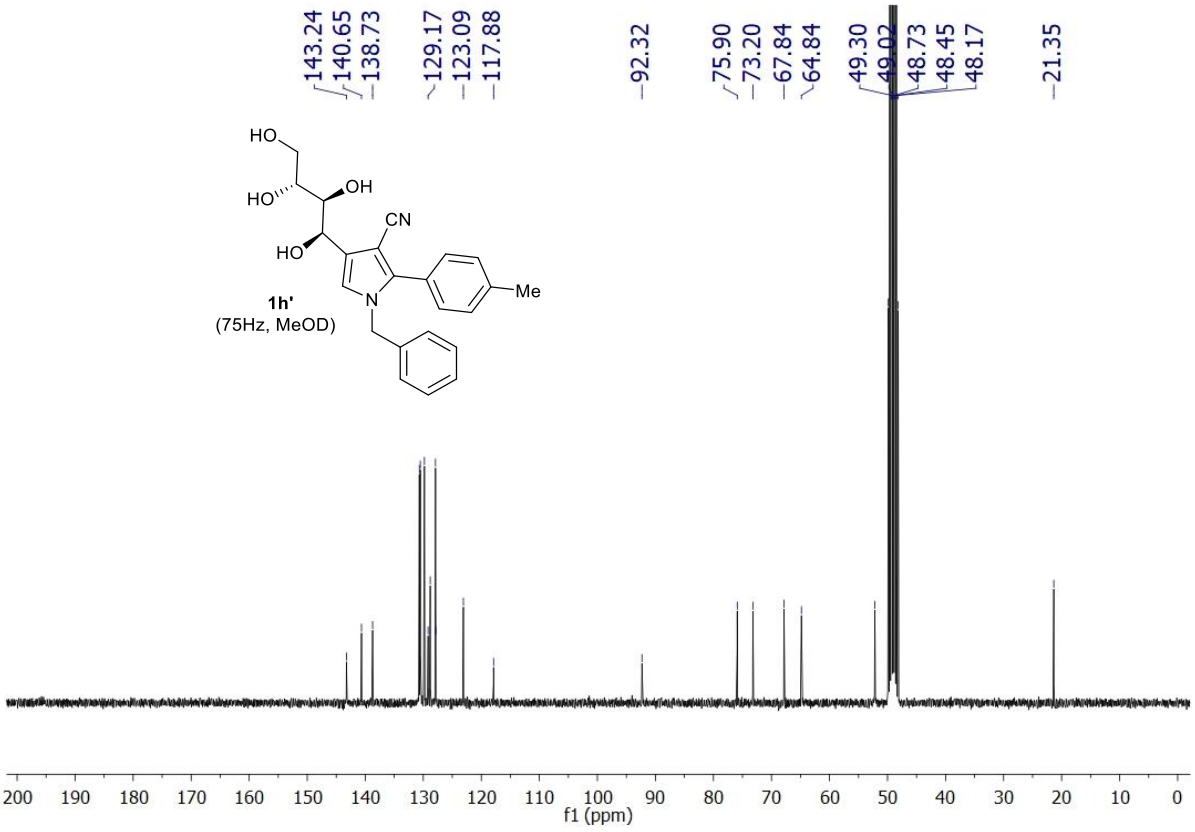
1-Cyclohexyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



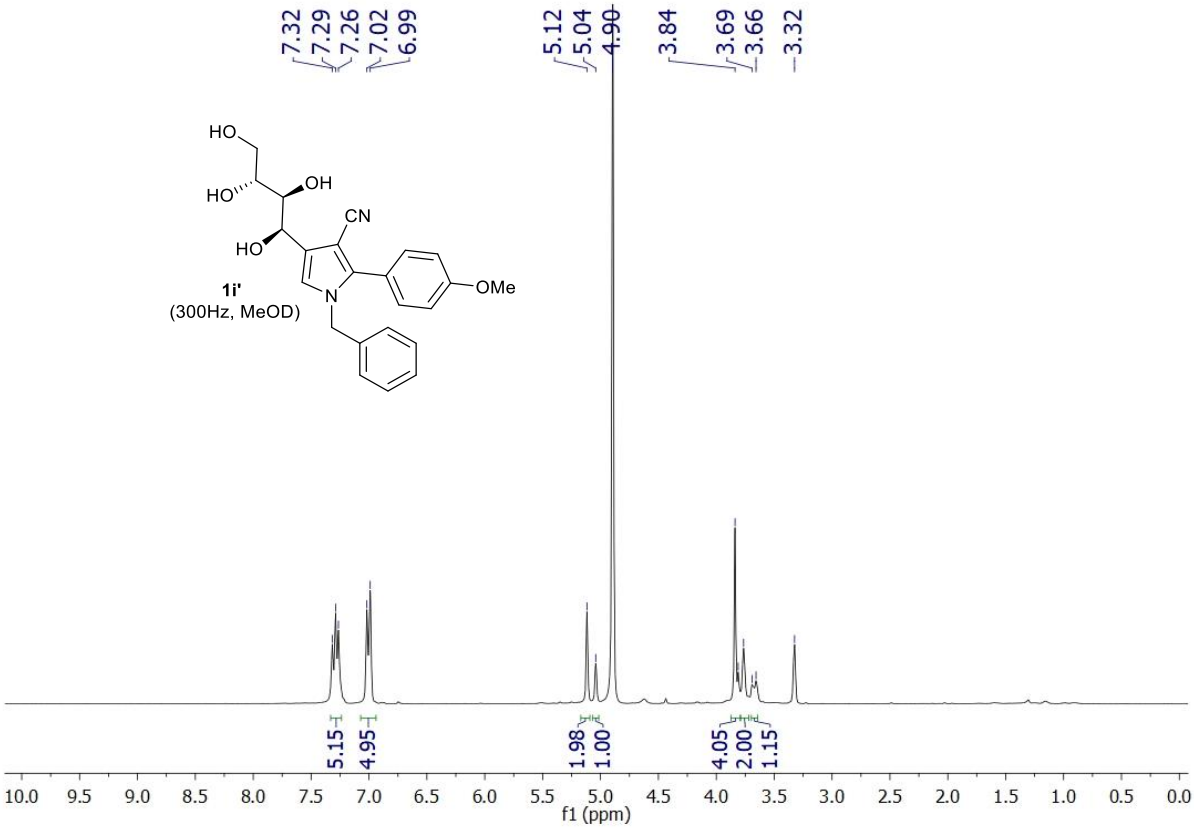


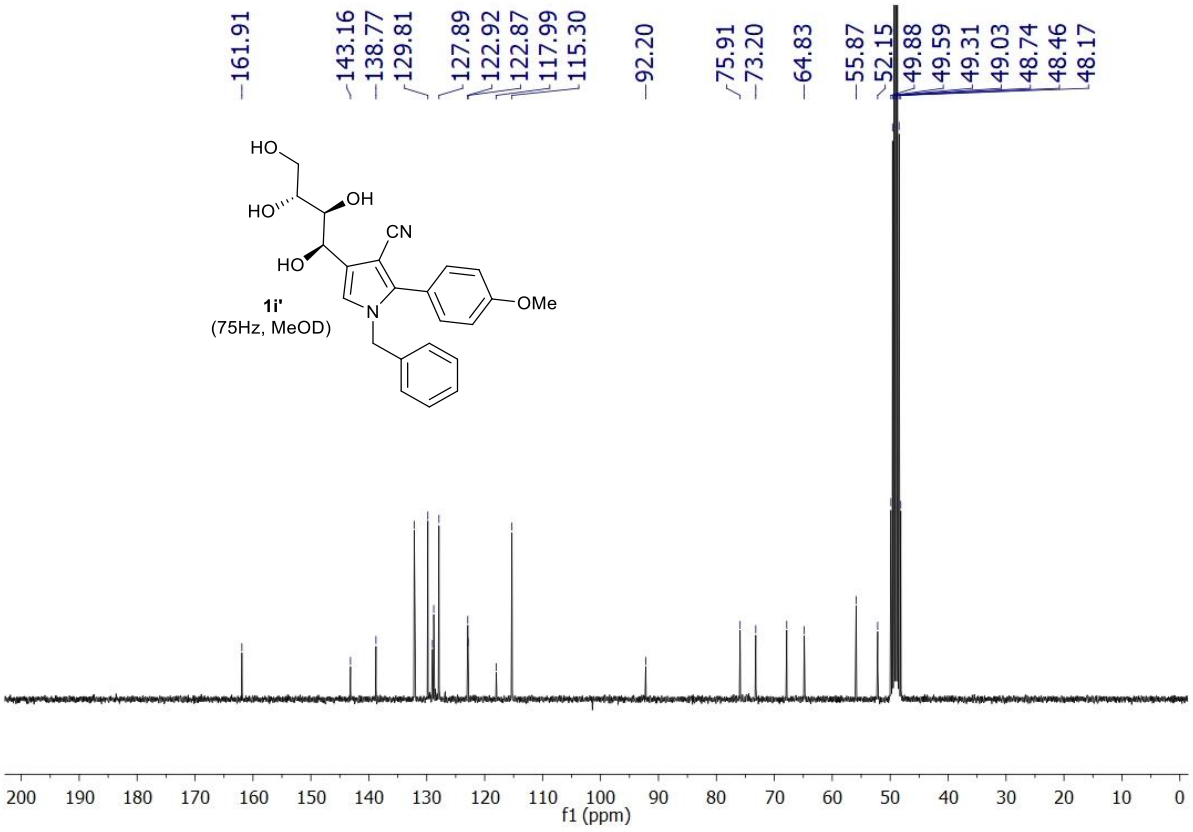
1-Benzyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-2-(*p*-tolyl)-1*H*-pyrrole-3-carbonitrile



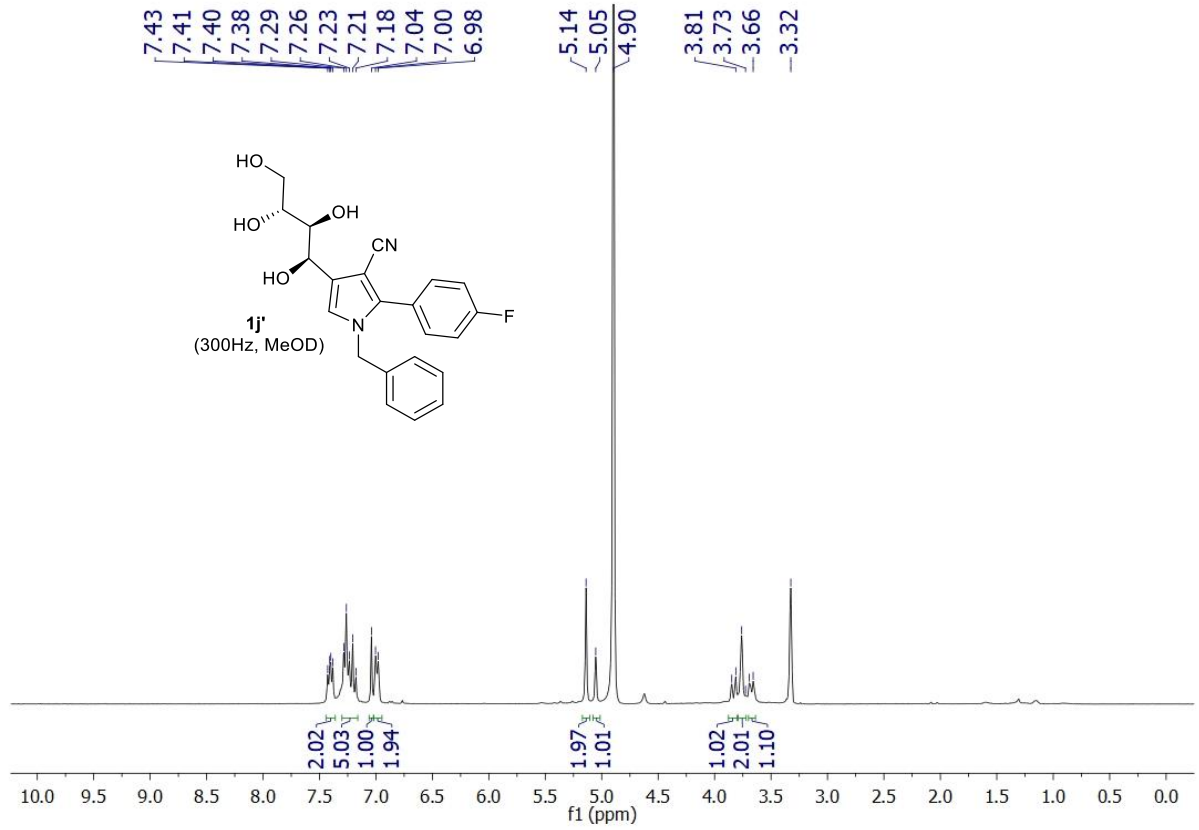


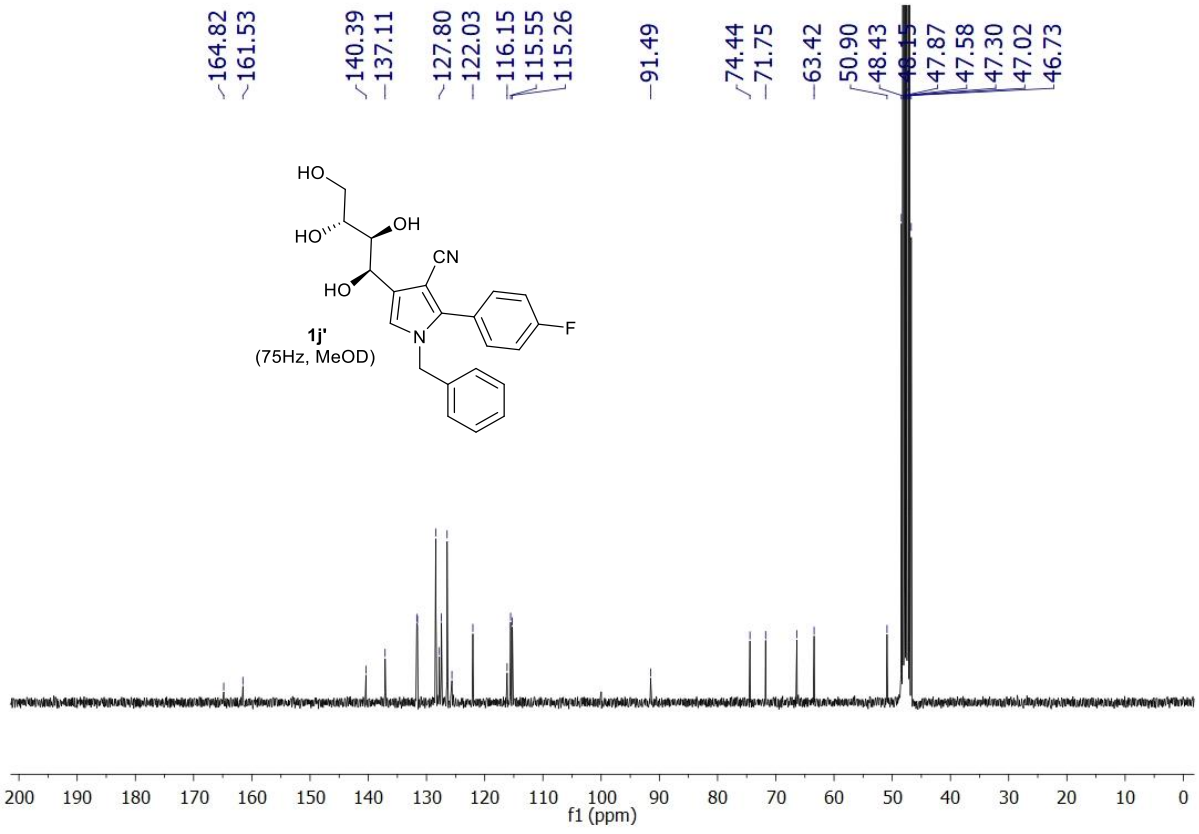
1-Benzyl-2-(4-methoxyphenyl)-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



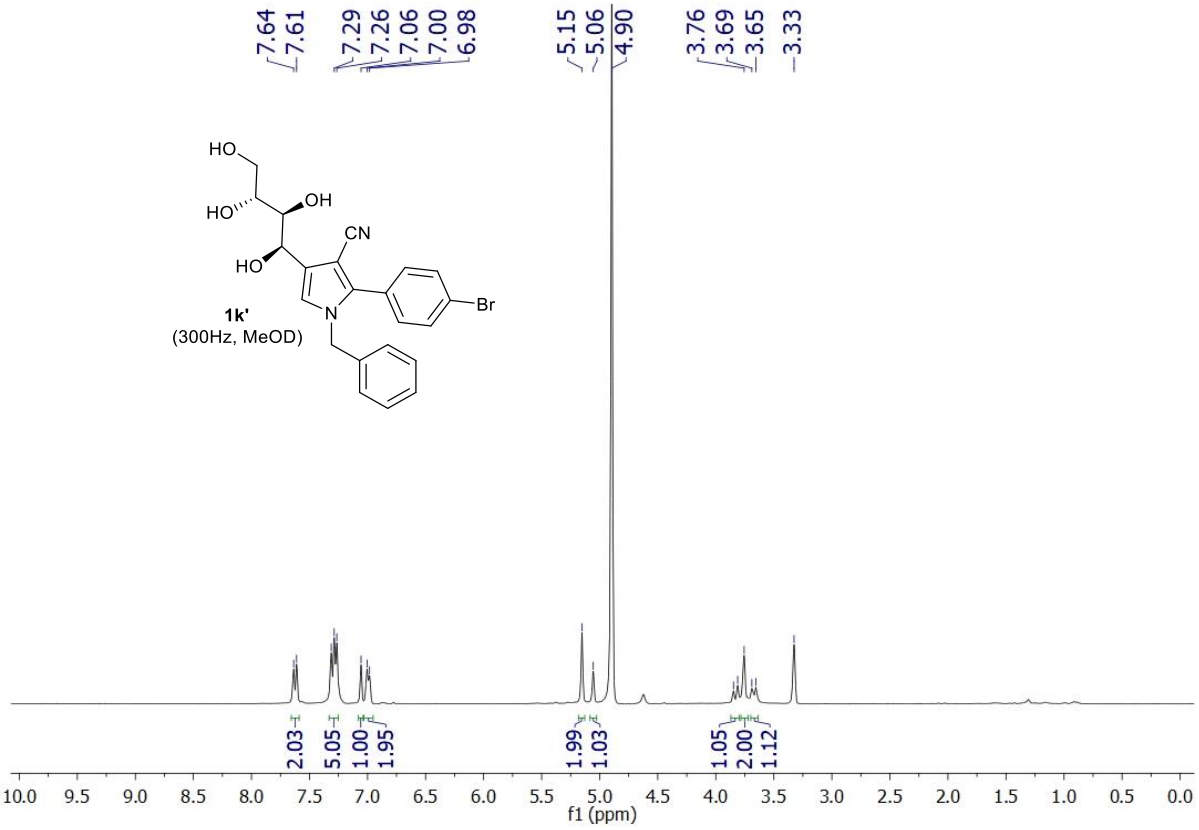


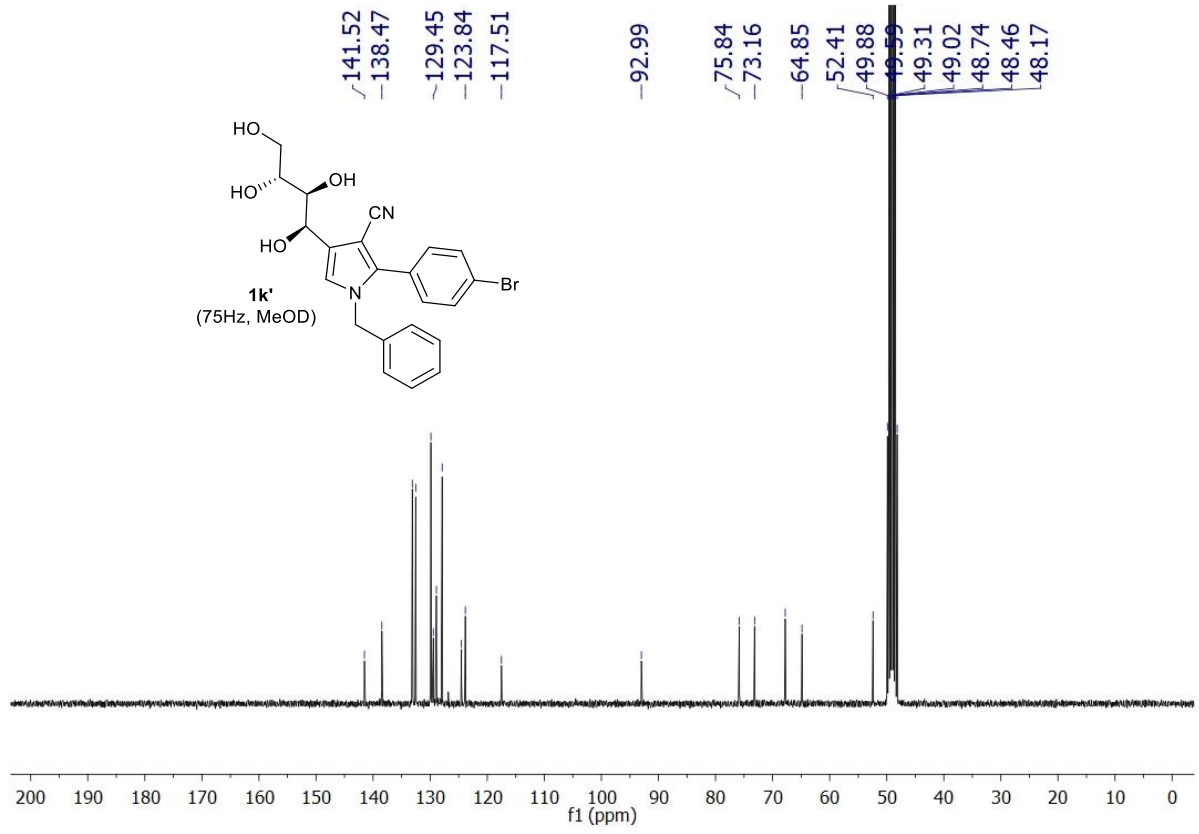
1-Benzyl-2-(4-fluorophenyl)-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



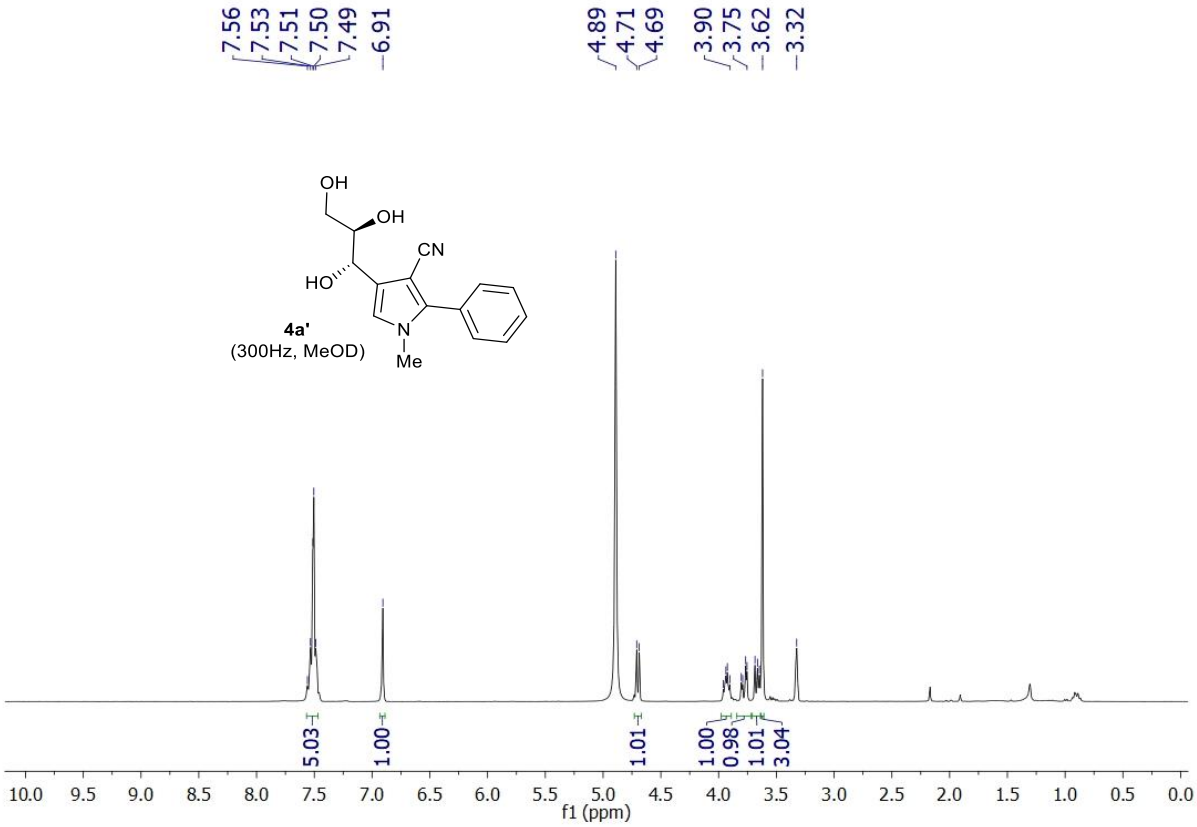


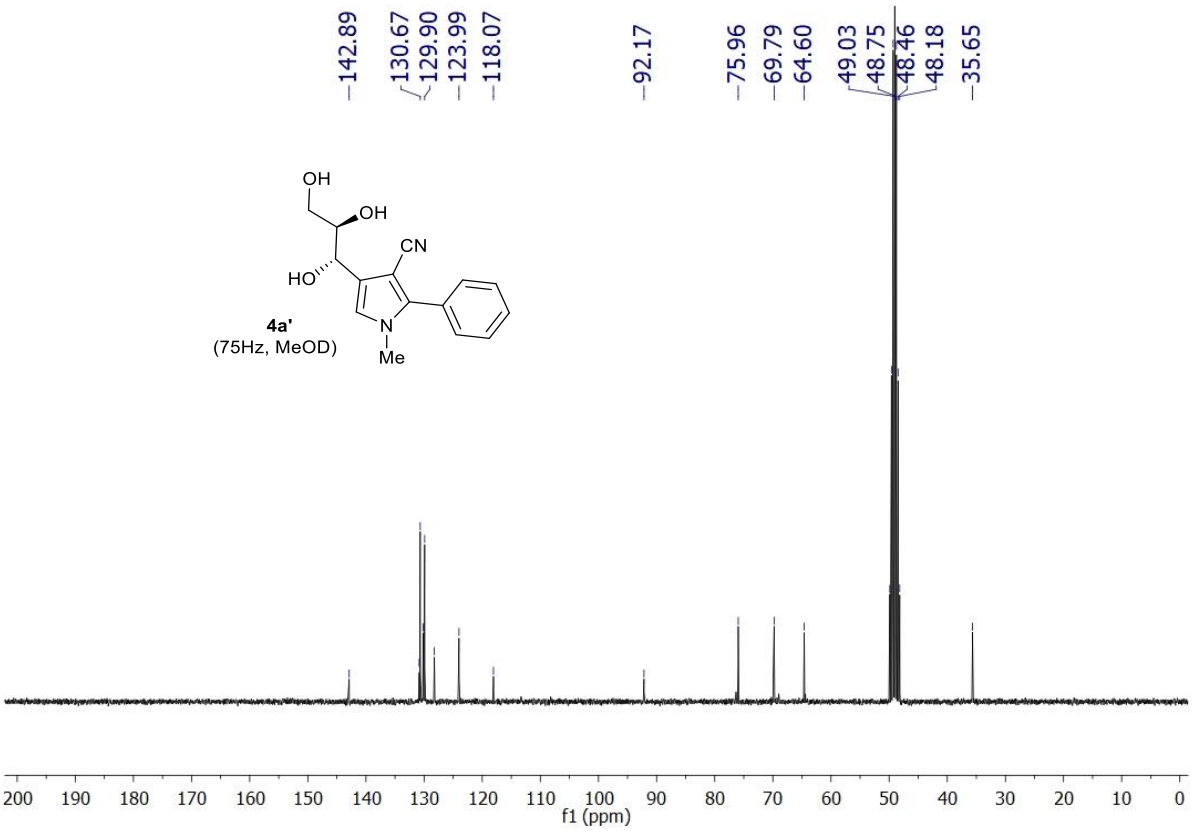
1-Benzyl-2-(4-bromophenyl)-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



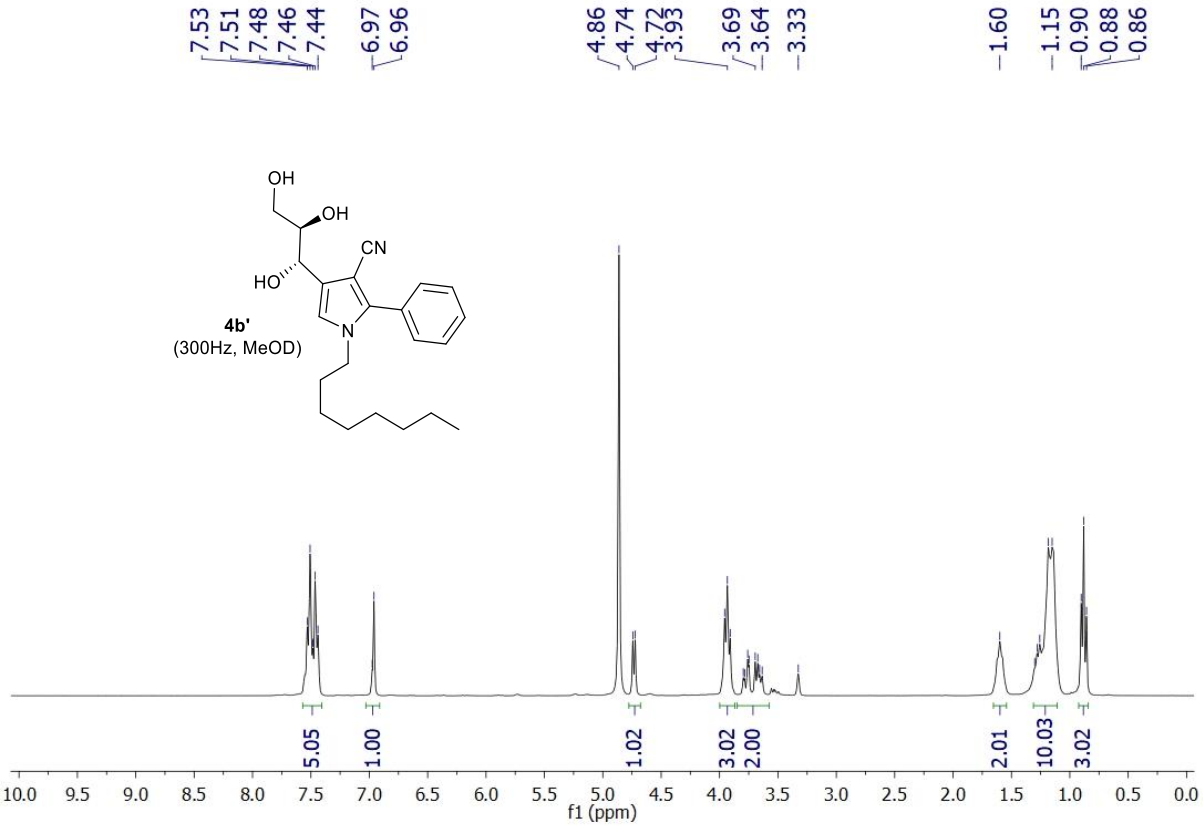


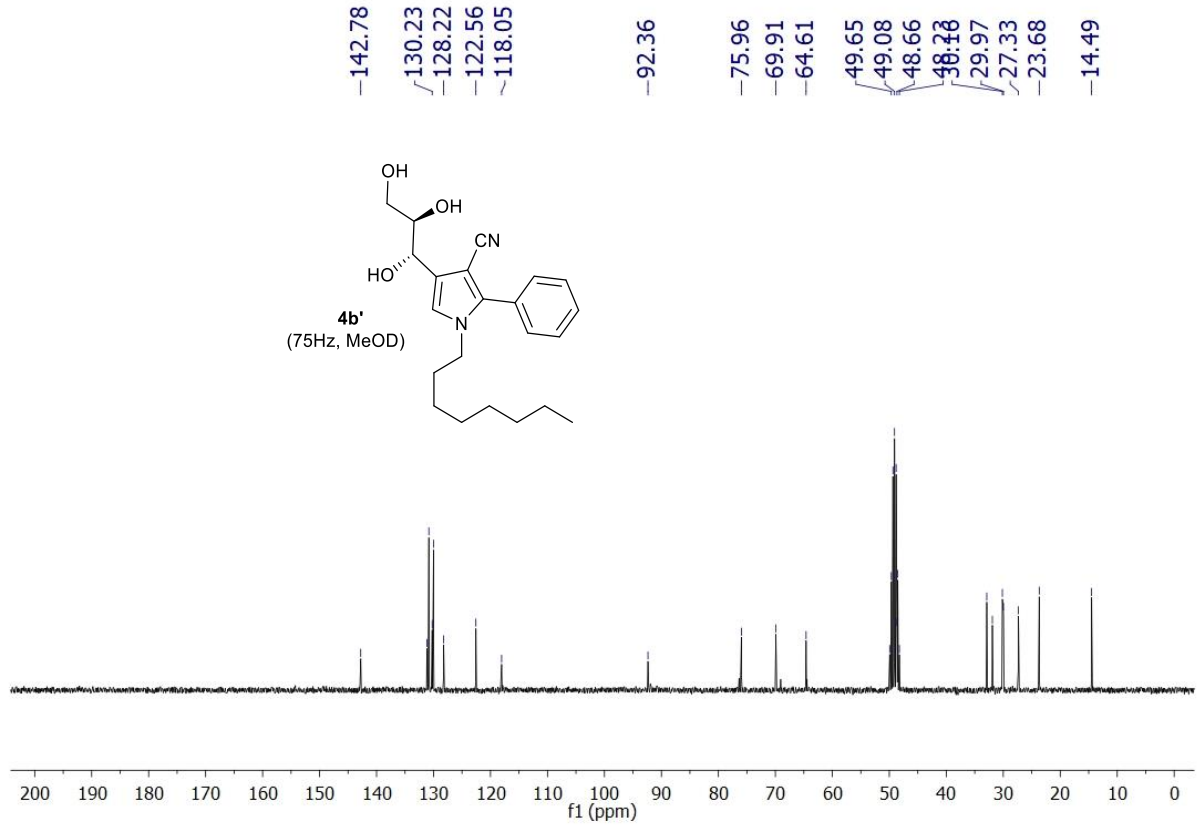
1-Methyl-2-phenyl-4-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



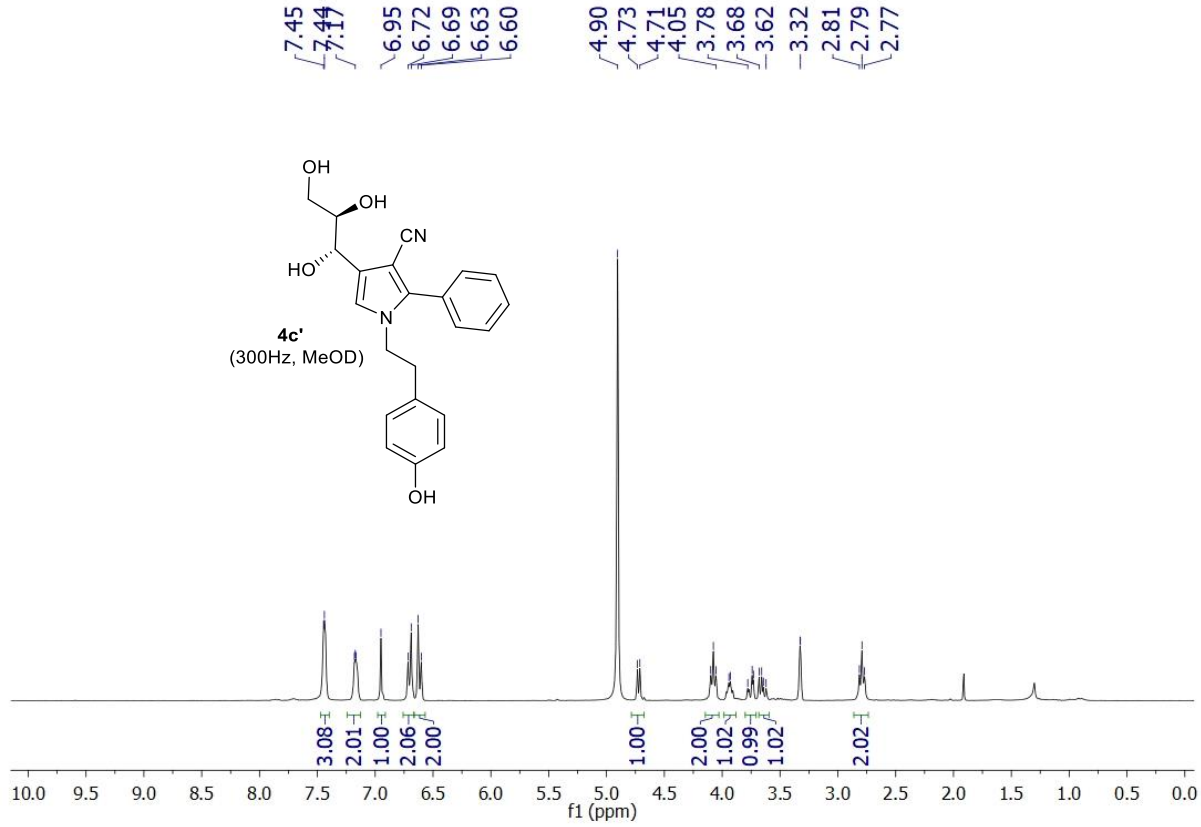


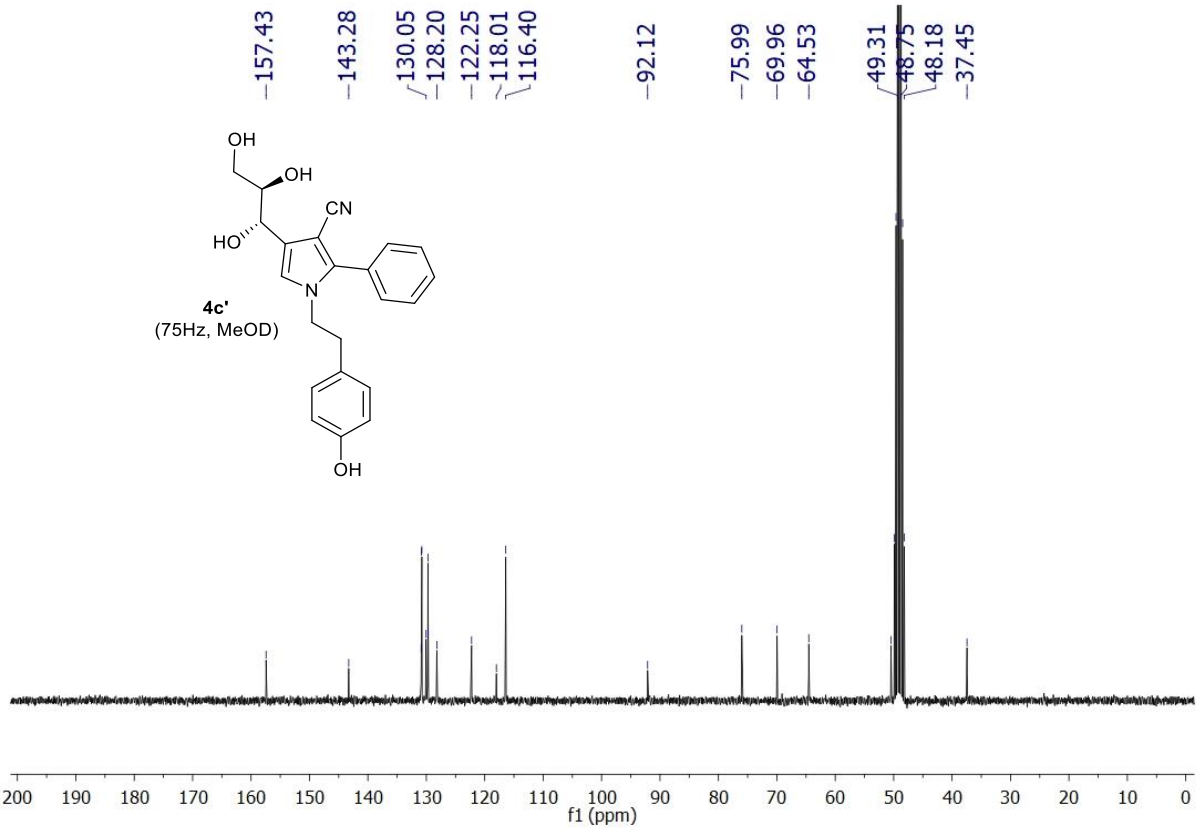
1-Octyl-2-phenyl-4-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



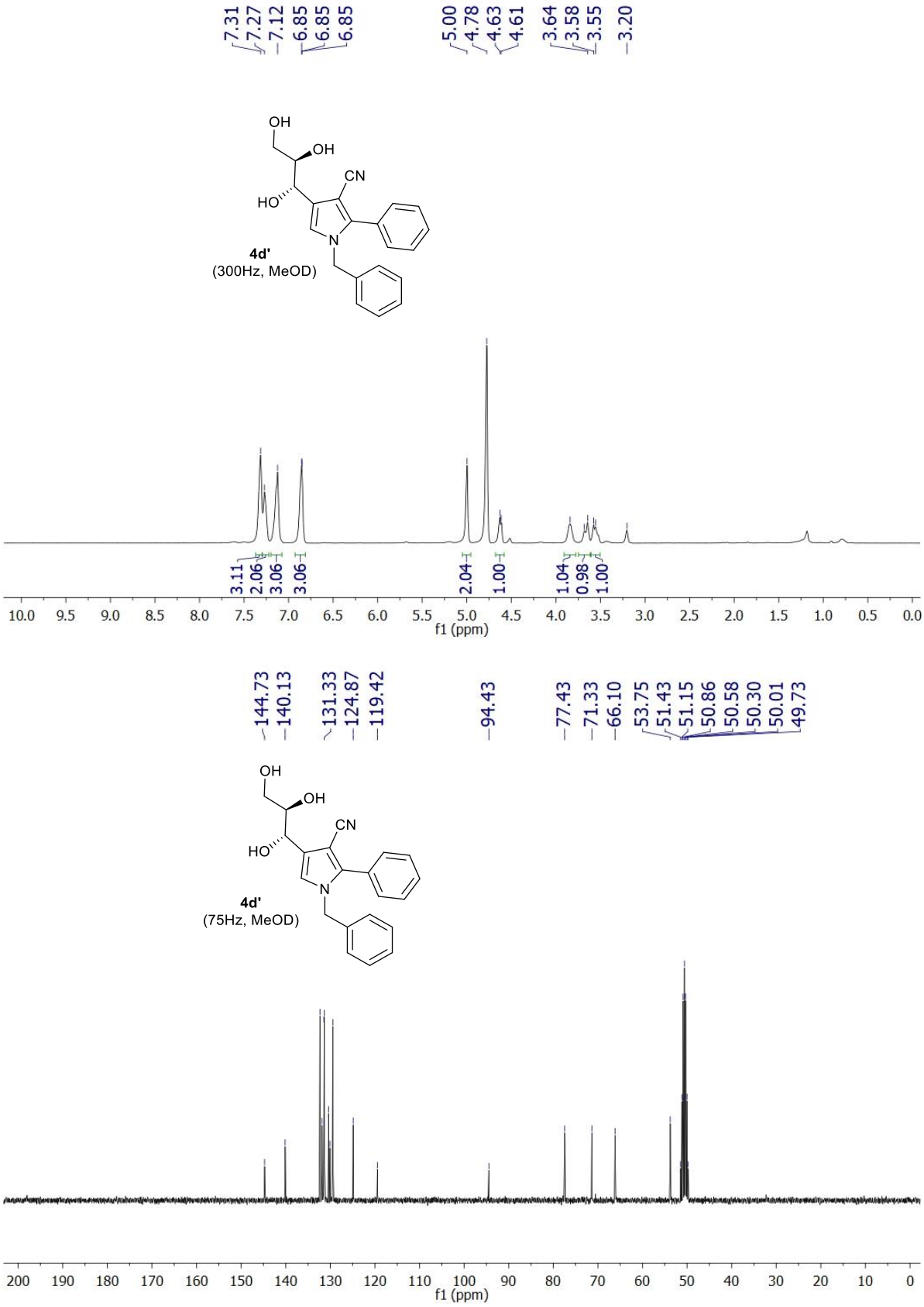


1-(4-Hydroxyphenethyl)-2-phenyl-4-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



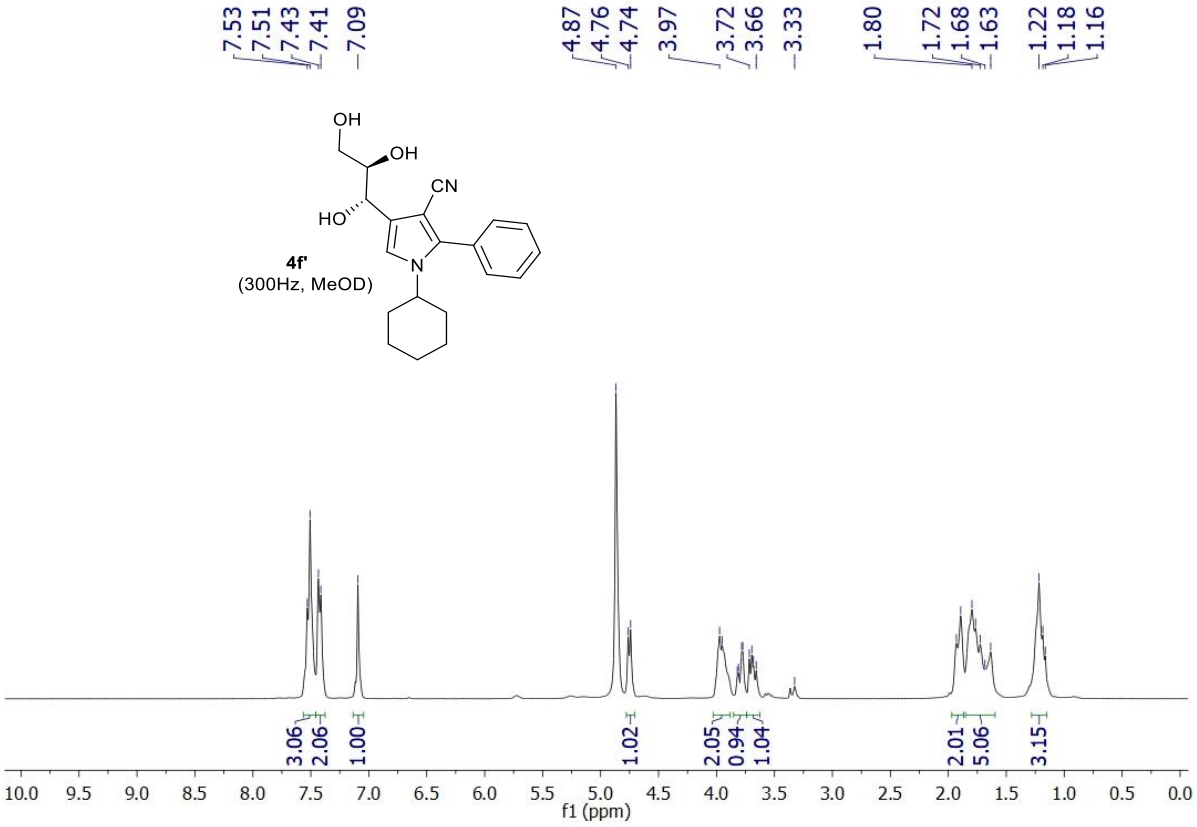


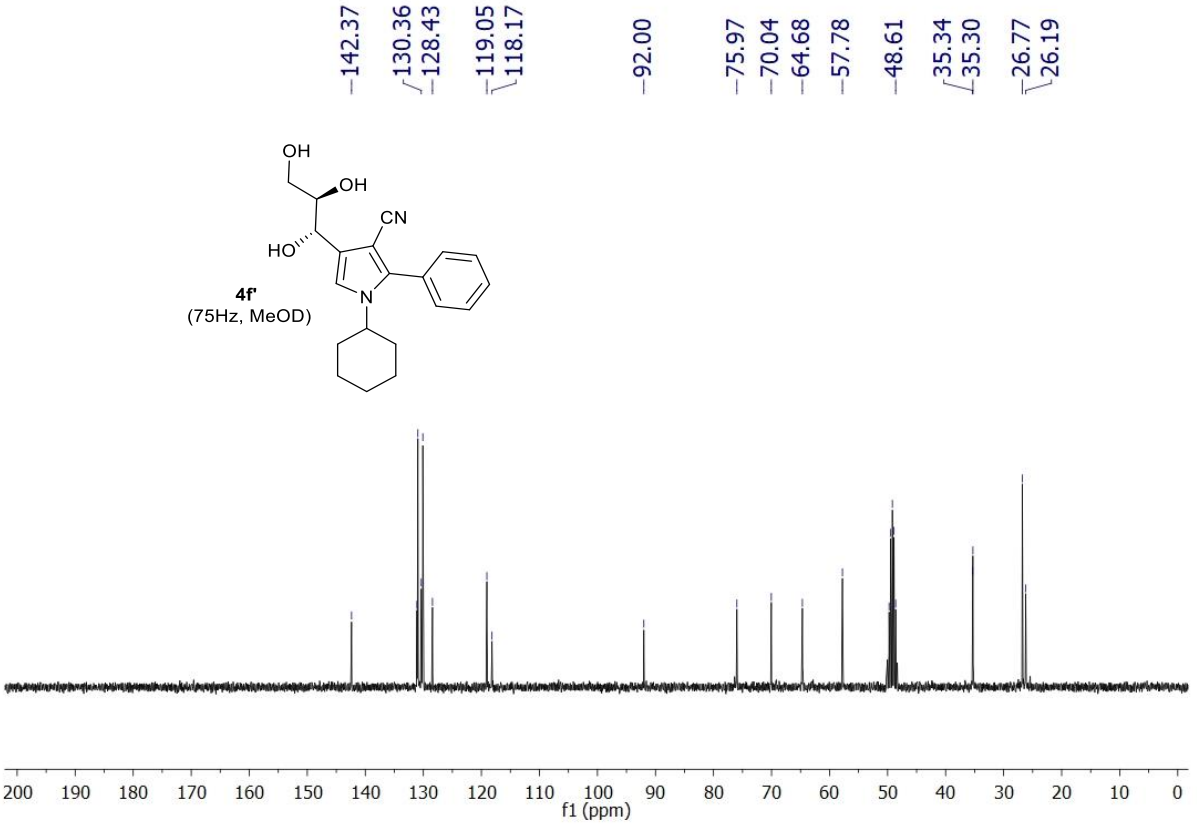
1-Benzyl-2-phenyl-4-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



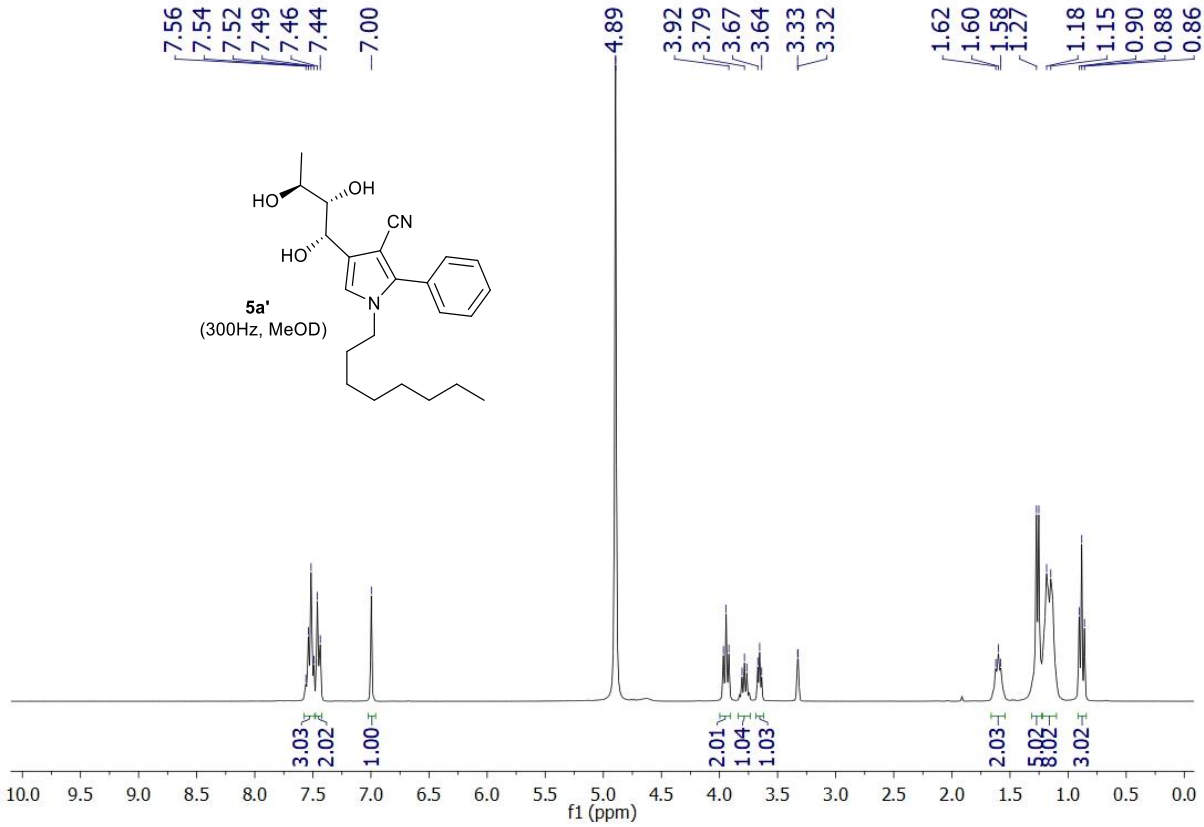
1-Isopropyl-2-phenyl-4-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile

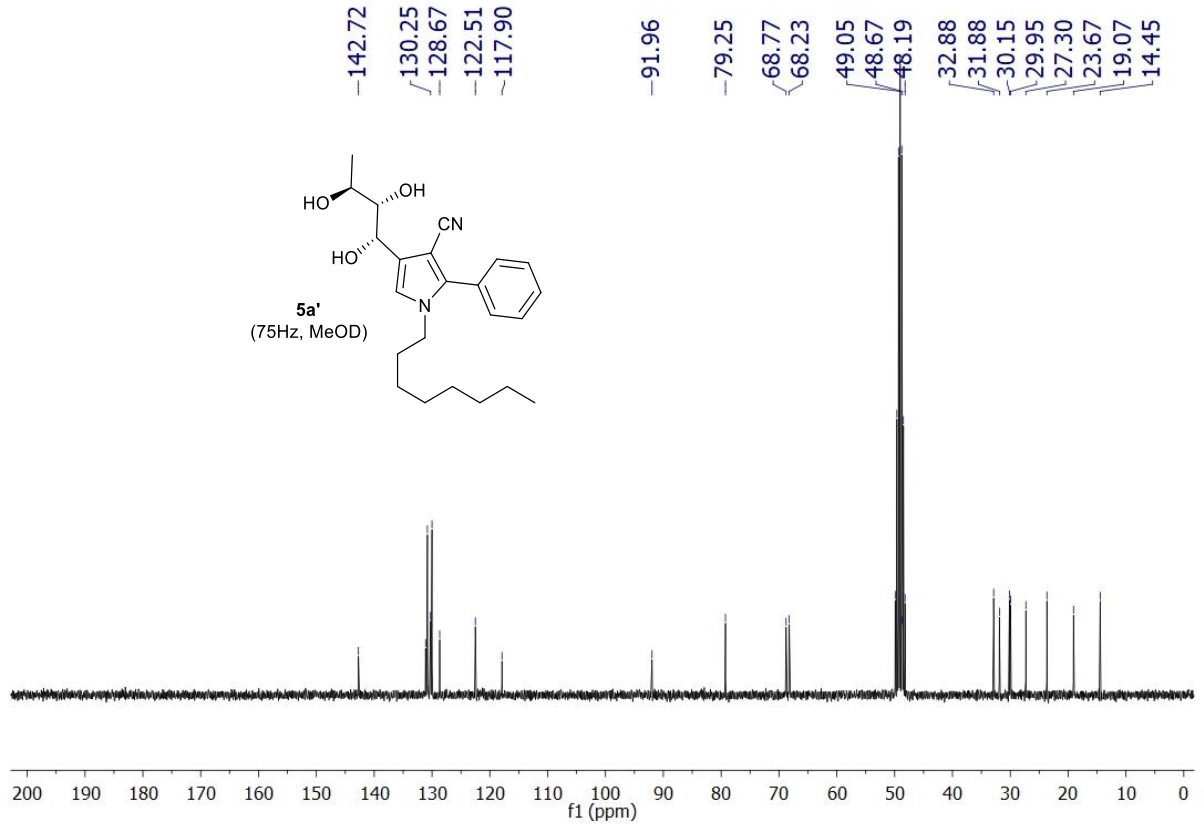
1-Cyclohexyl-2-phenyl-4-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



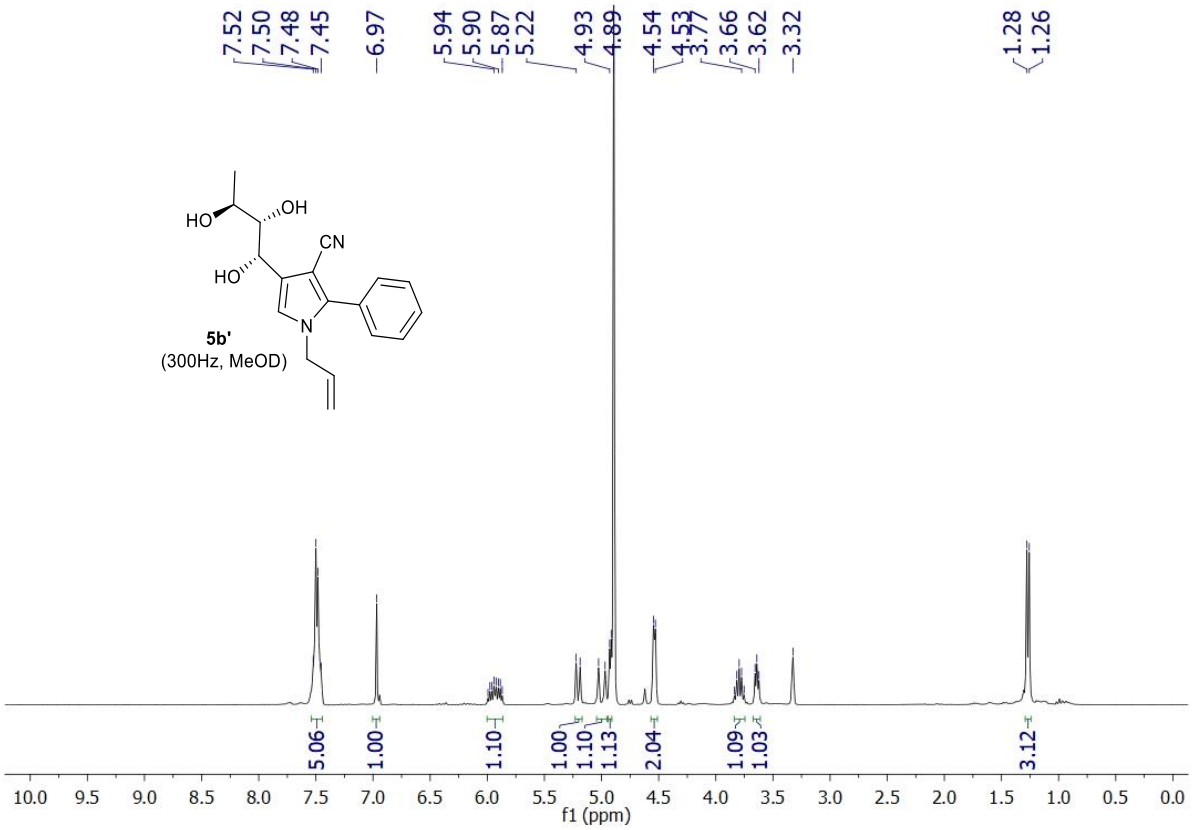


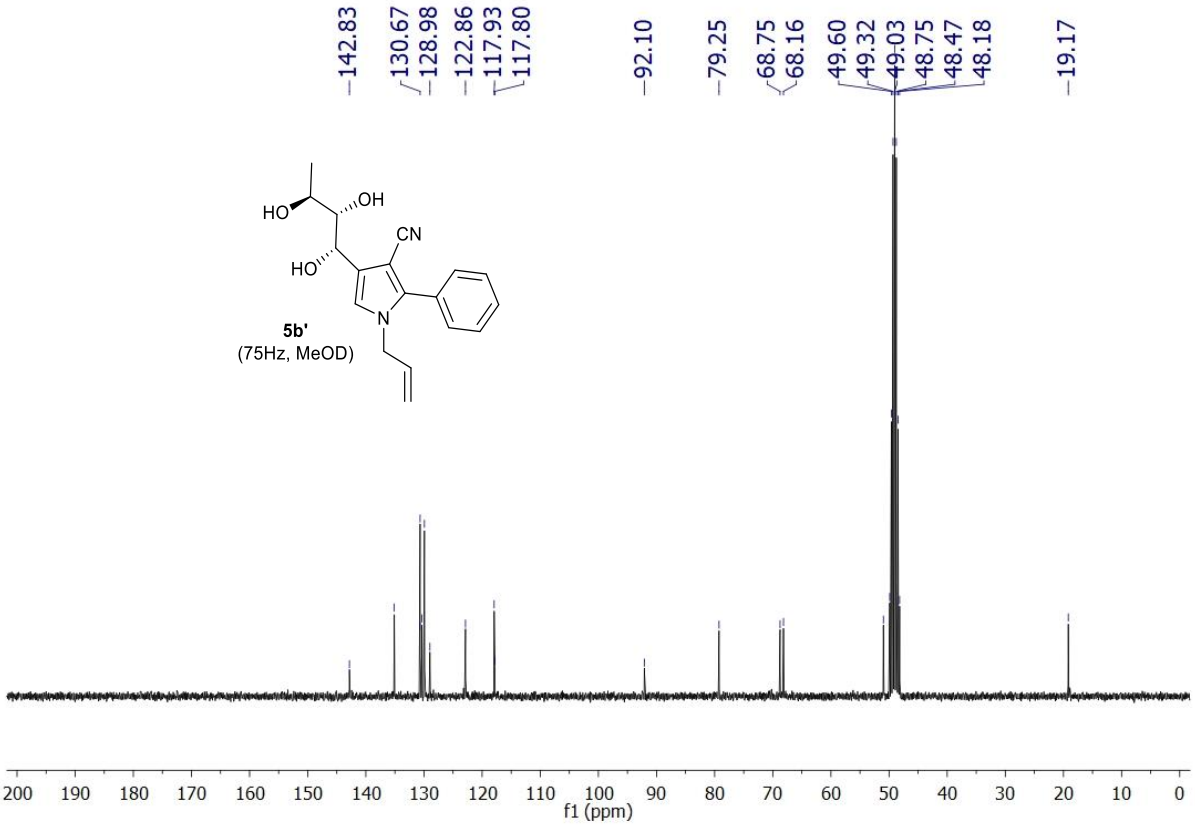
1-Octyl-2-phenyl-4-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile



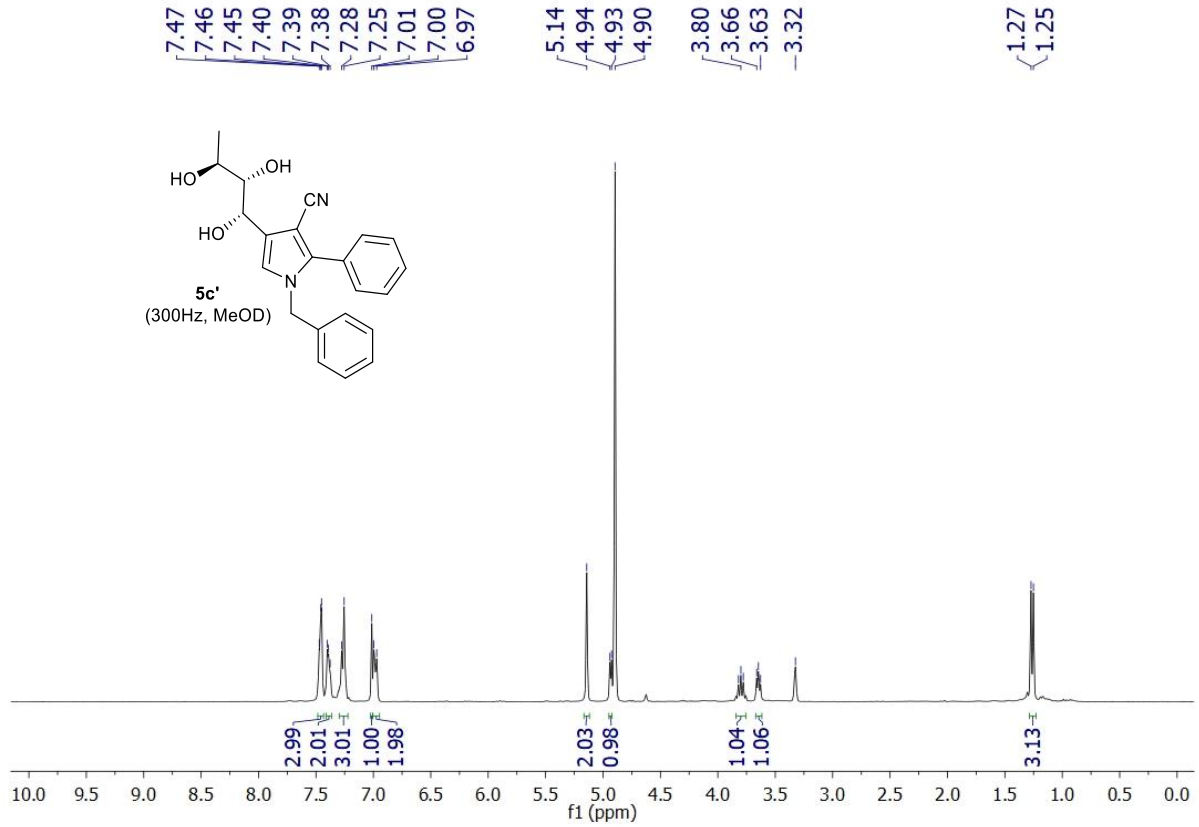


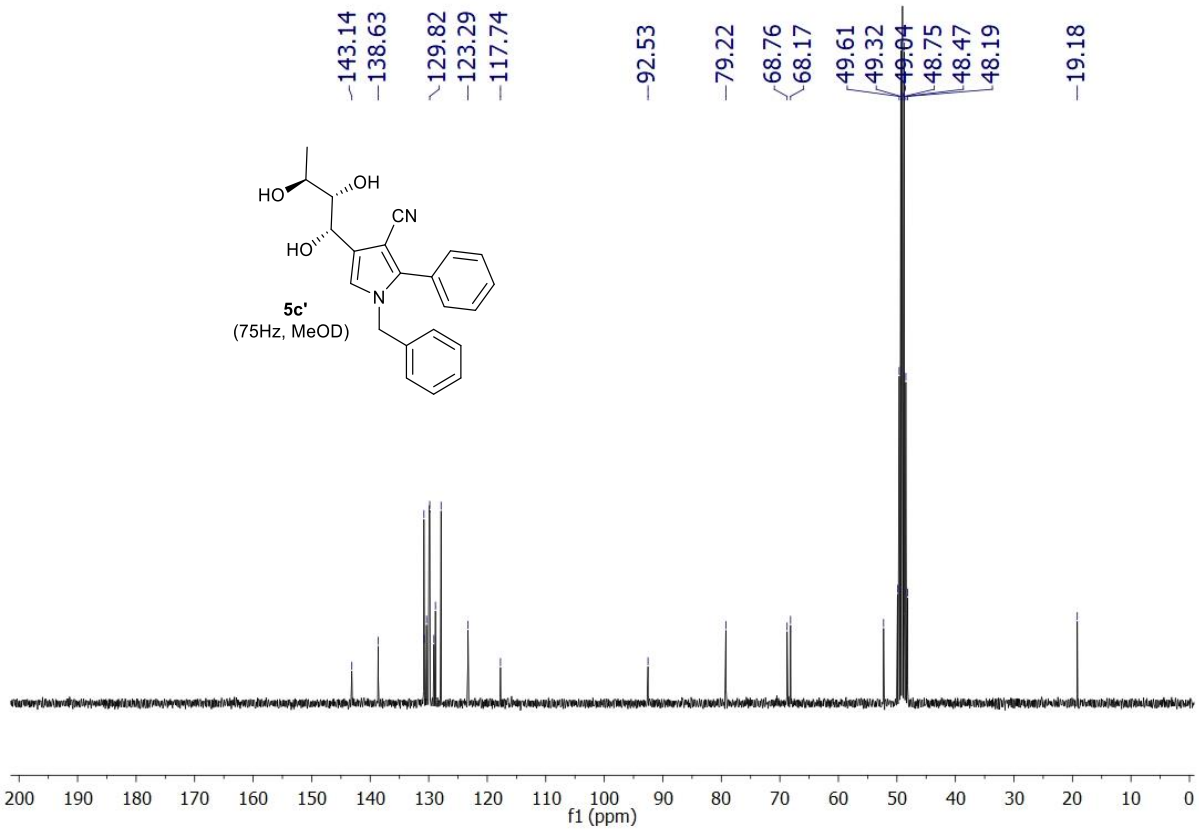
1-Allyl-2-phenyl-4-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile



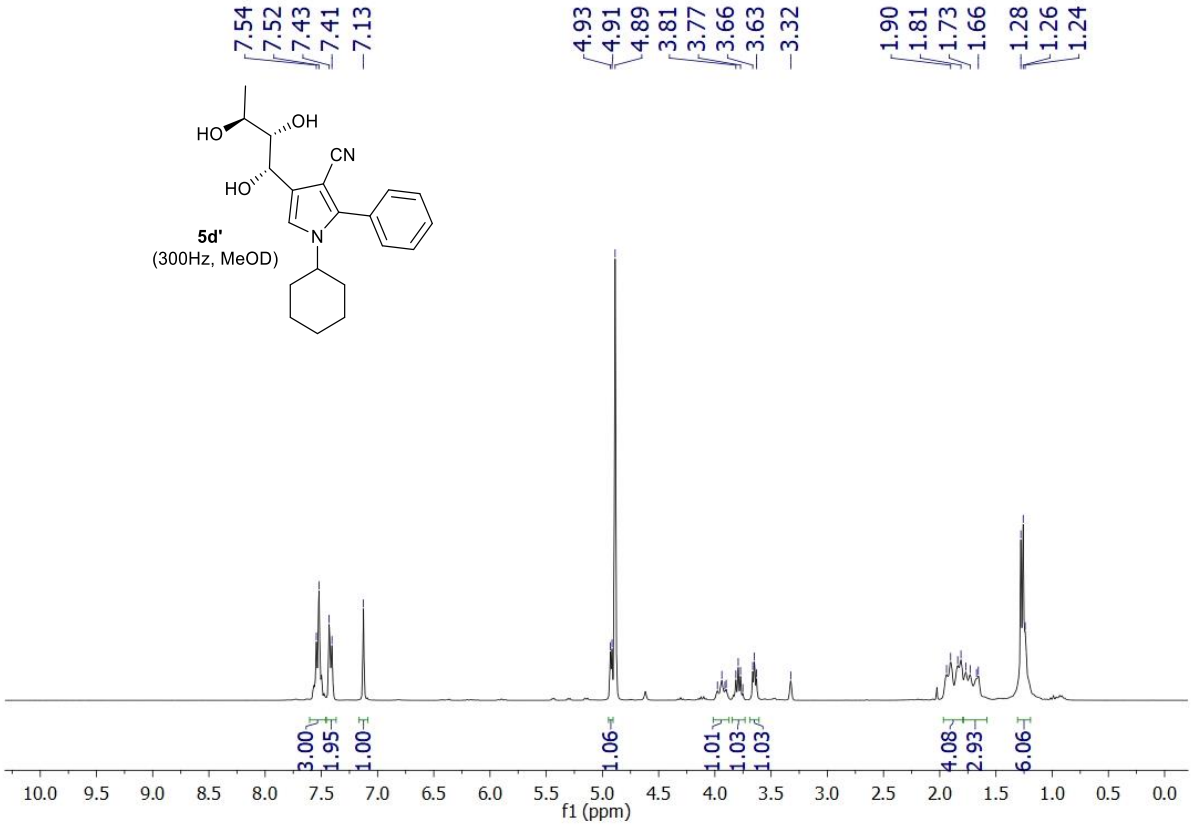


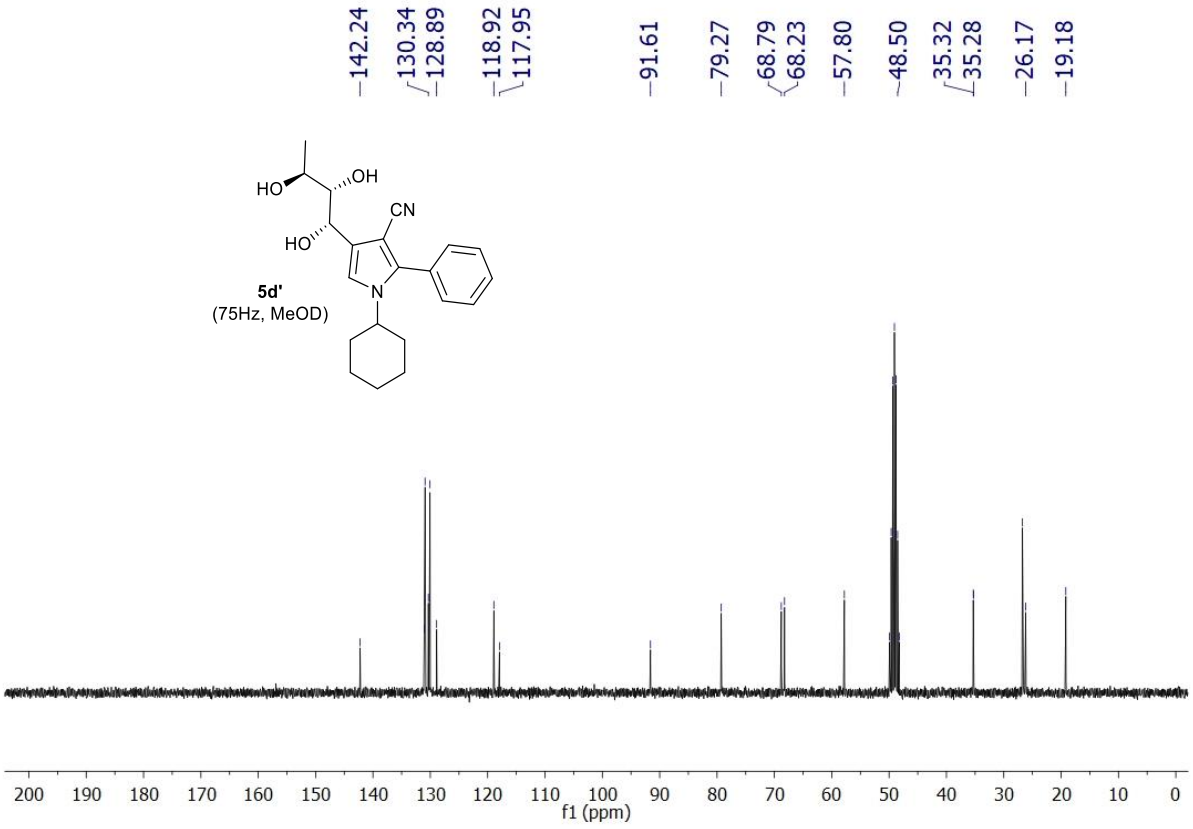
1-Benzyl-2-phenyl-4-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile



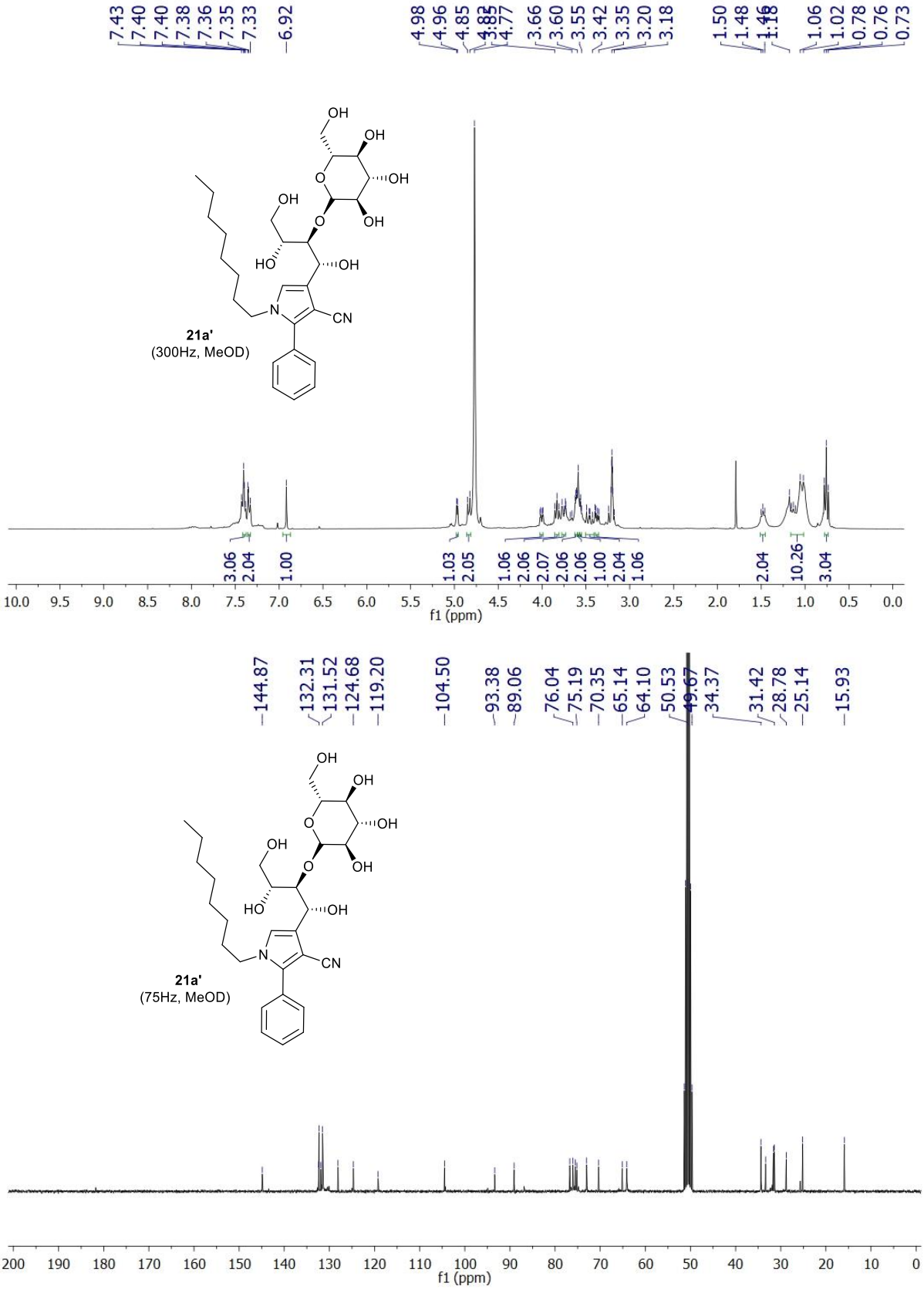


1-Cyclohexyl-2-phenyl-4-((1*S*,2*S*,3*S*)-1,2,3-trihydroxybutyl)-1*H*-pyrrole-3-carbonitrile

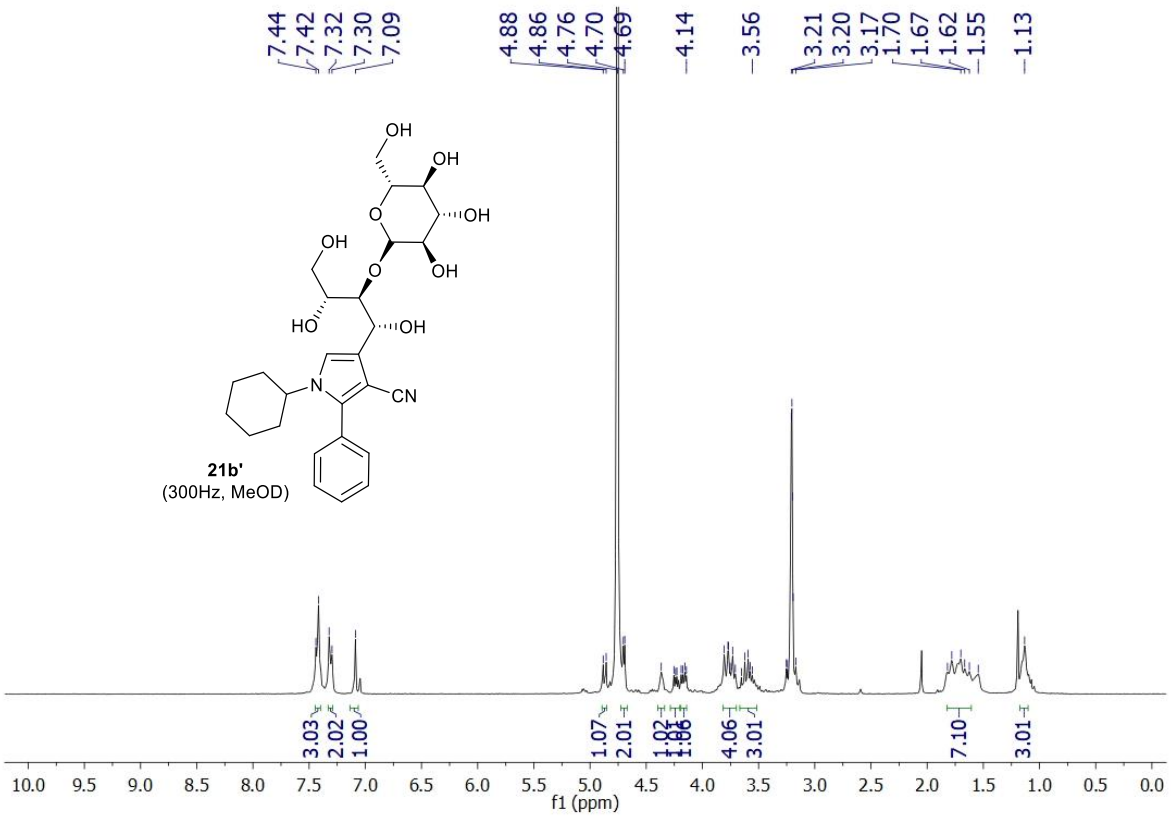


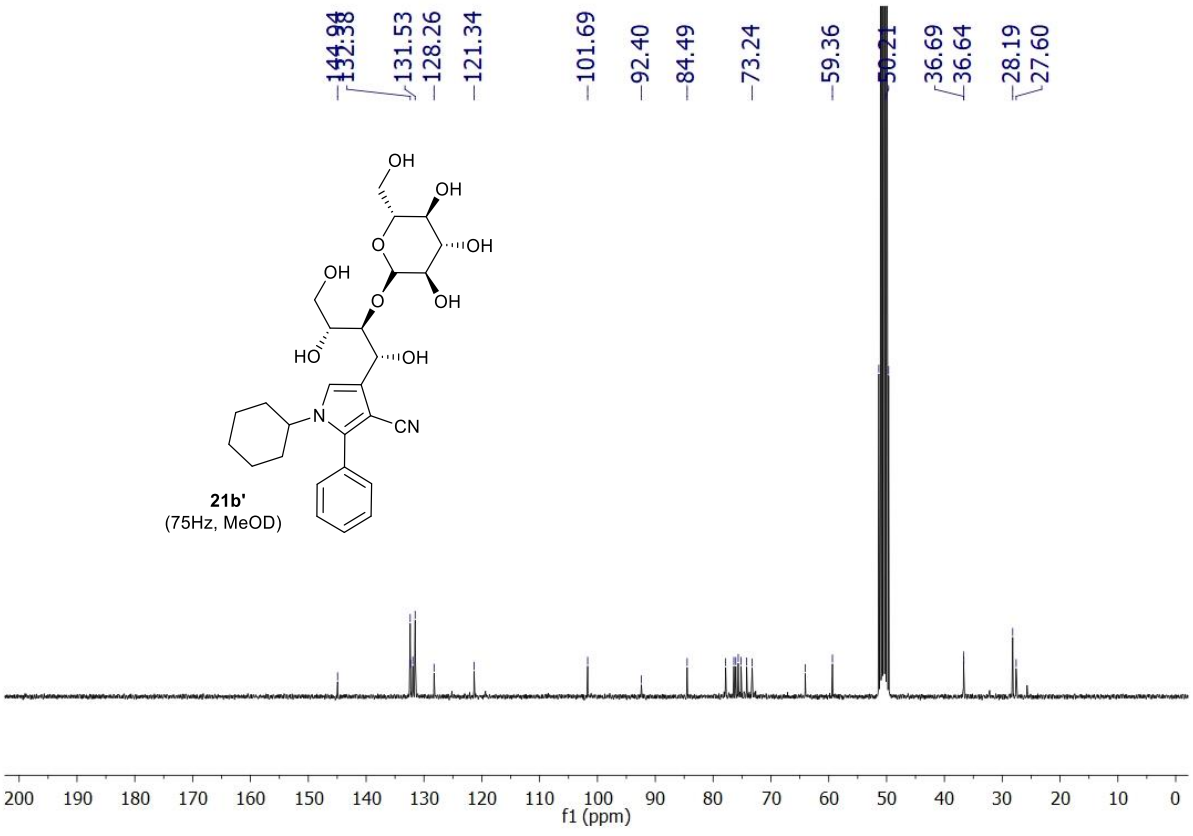


1-Octyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,3,4-trihydroxy-2-(((2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)butyl)-1*H*-pyrrole-3-carbonitrile

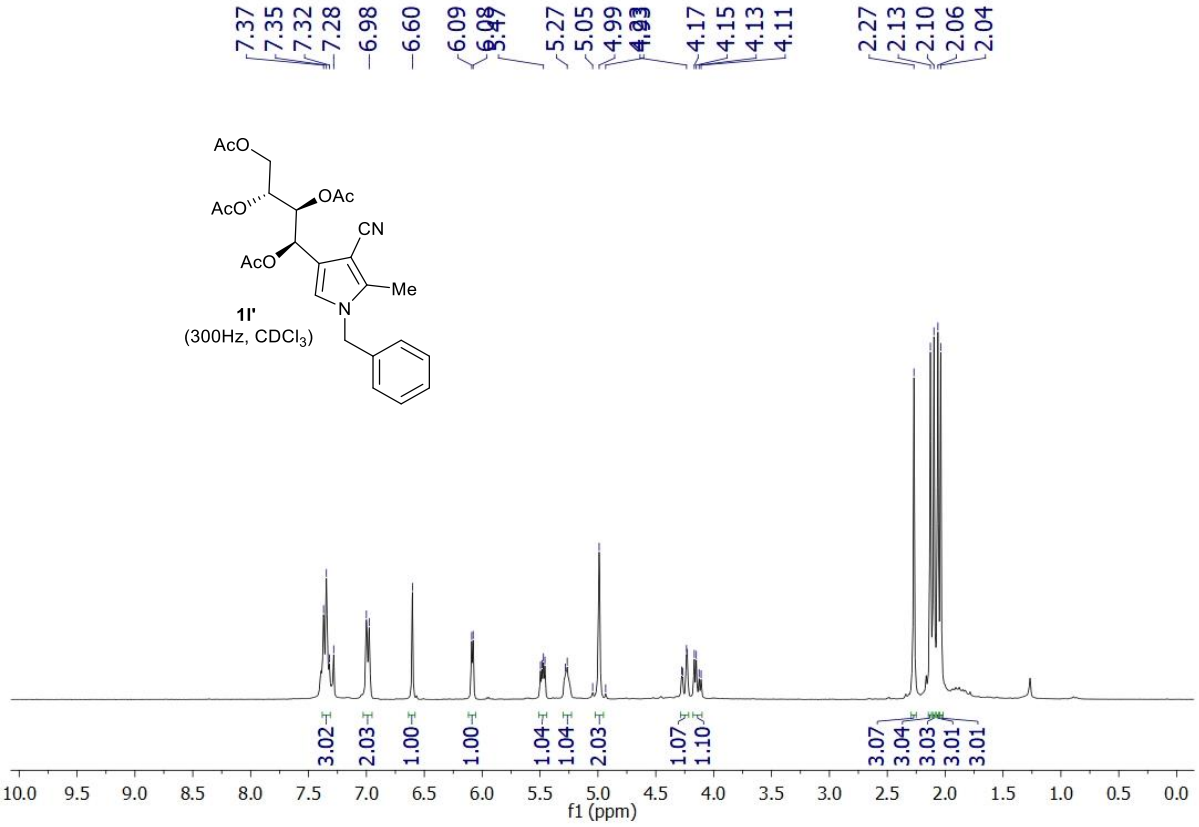


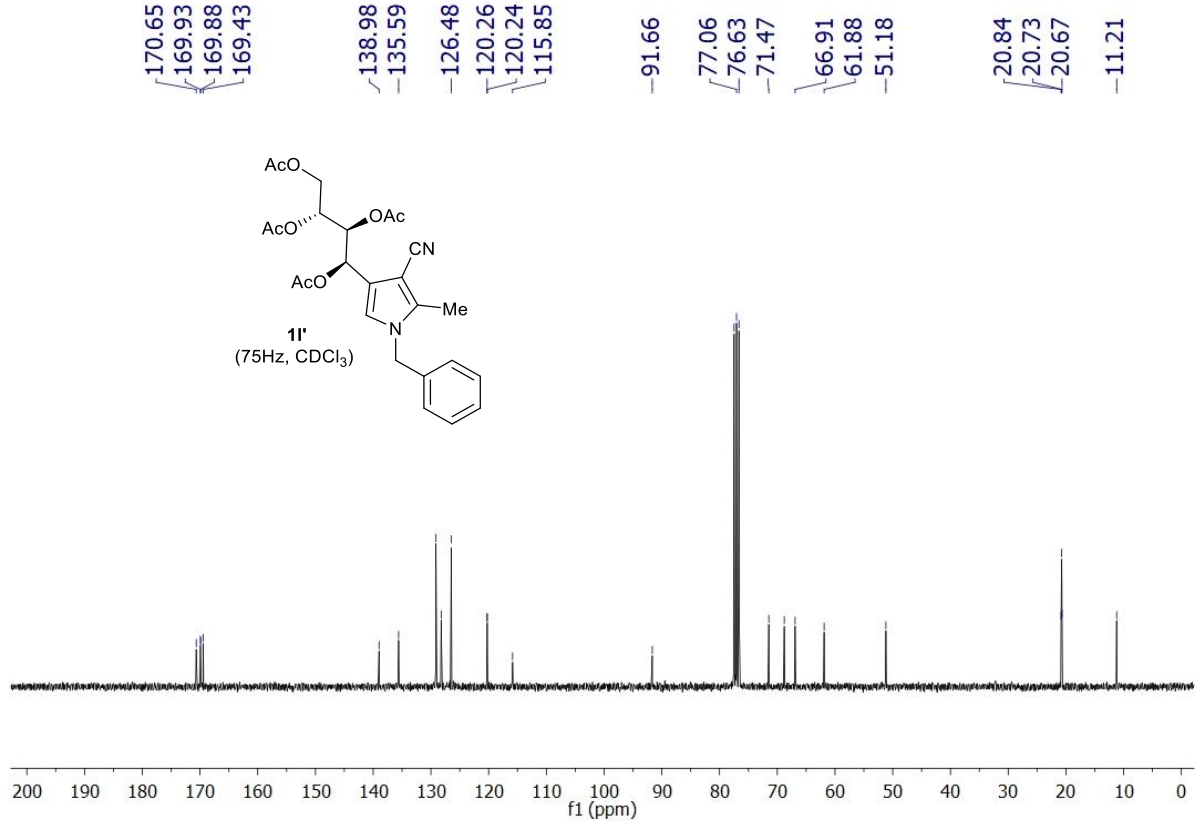
1-Cyclohexyl-2-phenyl-4-((1*R*,2*S*,3*R*)-1,3,4-trihydroxy-2-(((2*R*,3*S*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)butyl)-1*H*-pyrrole-3-carbonitrile



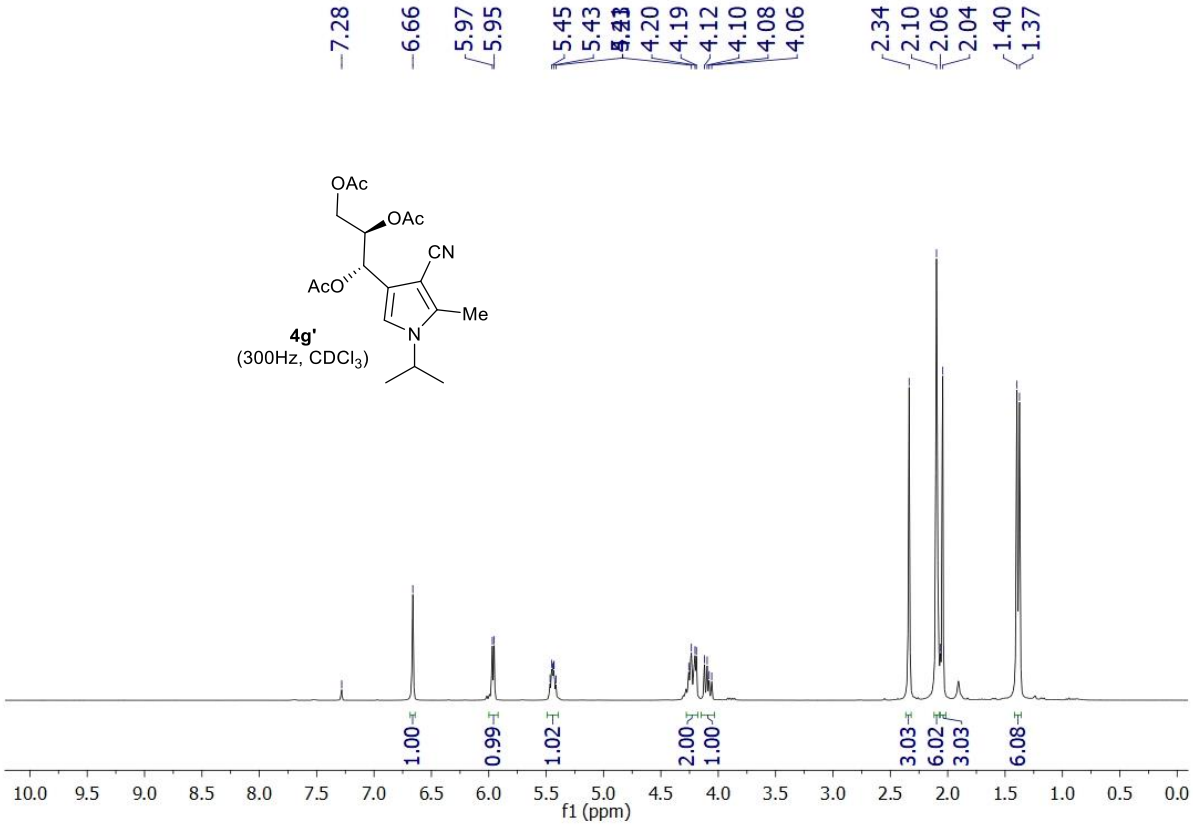


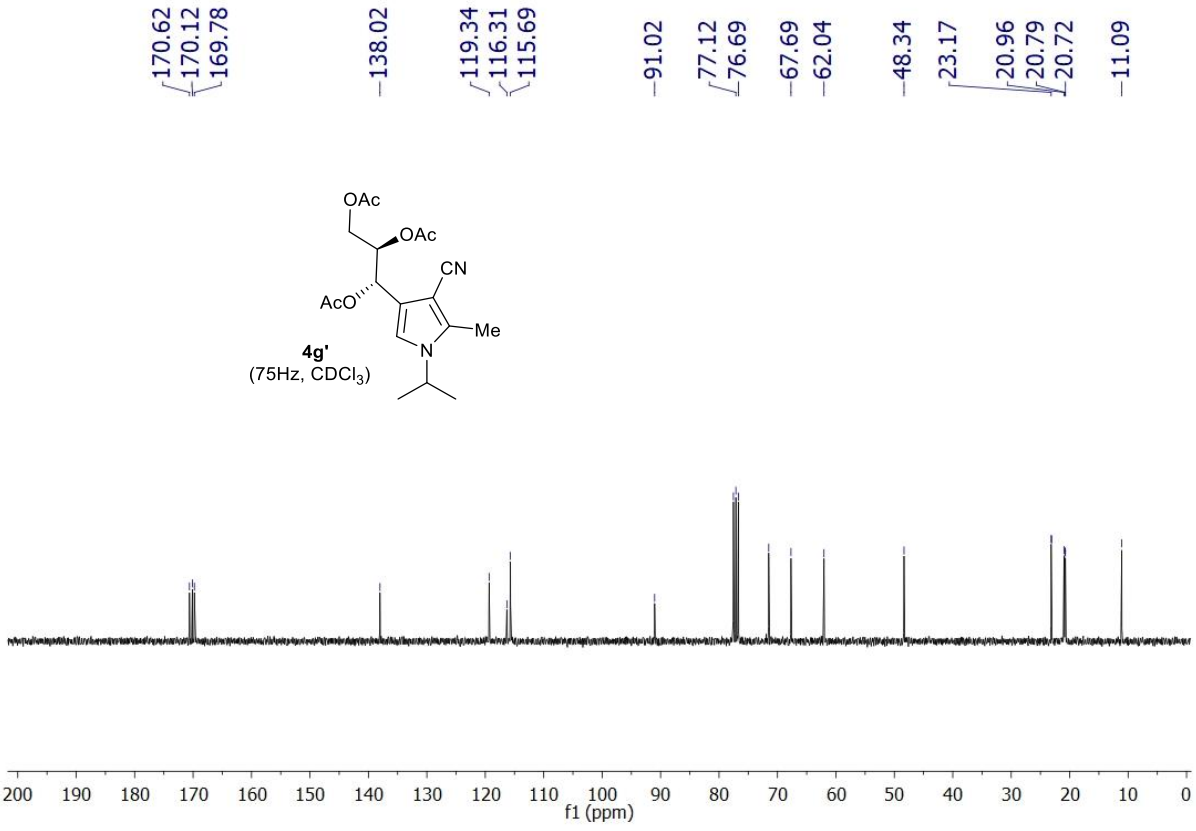
(1*R*,2*S*,3*R*)-1-(1-Benzyl-4-cyano-5-methyl-1*H*-pyrrol-3-yl)butane-1,2,3,4-tetrayl tetraacetate



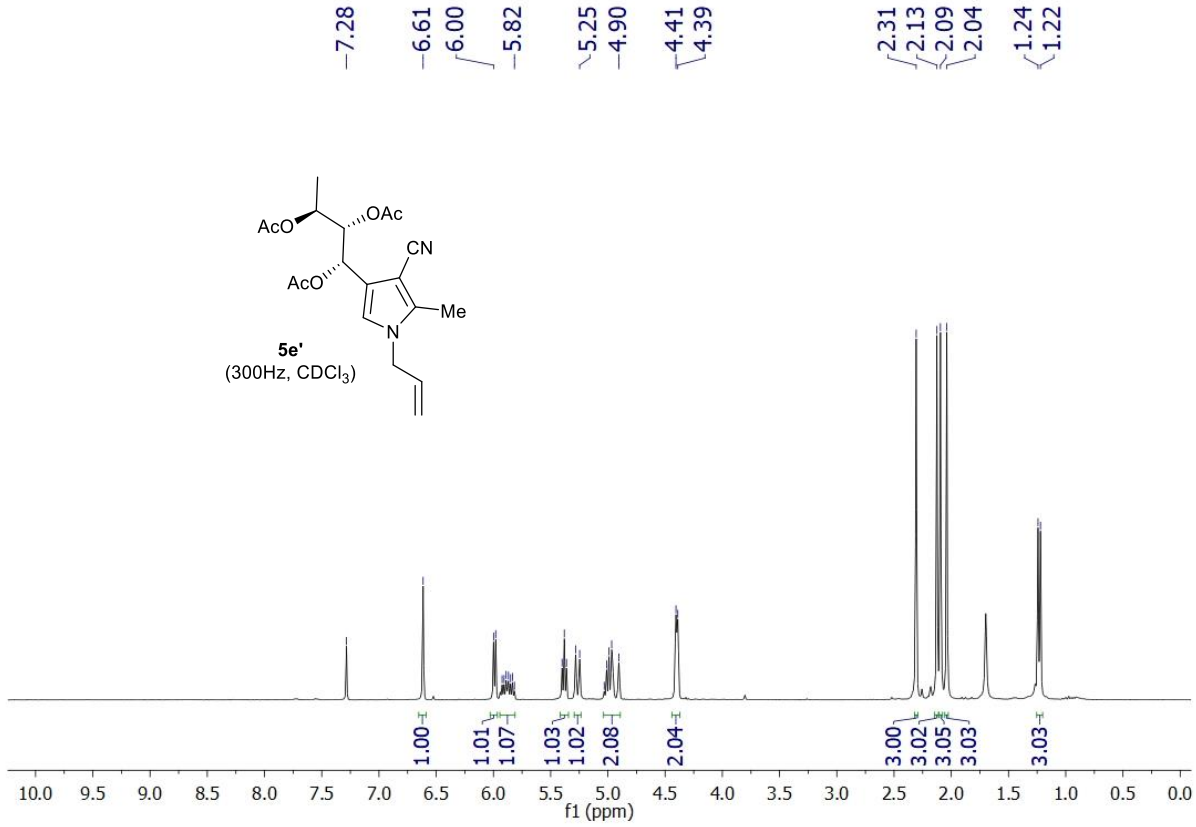


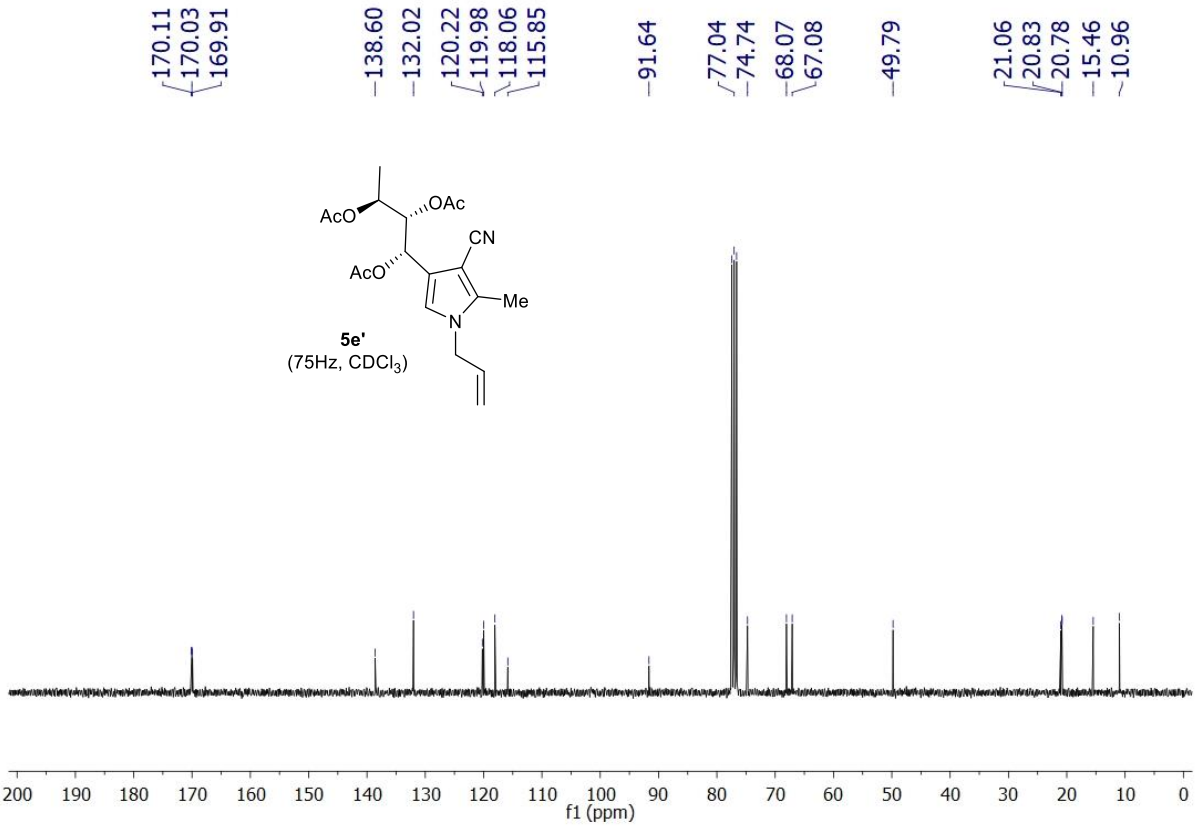
(1*S*,2*R*)-1-(4-Cyano-1-isopropyl-5-methyl-1*H*-pyrrol-3-yl)propane-1,2,3-triyl triacetate



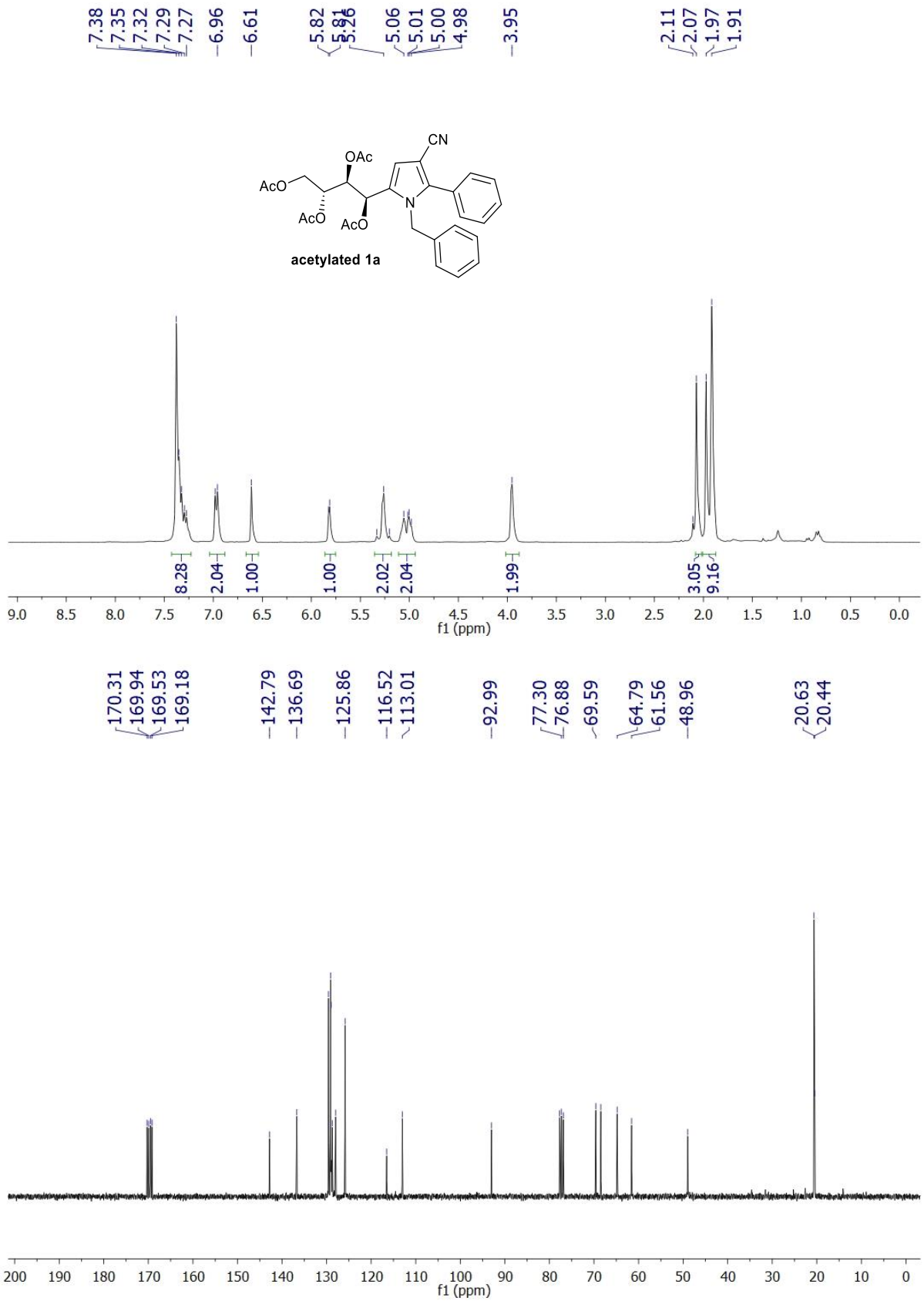


(1*S*,2*S*,3*S*)-1-(1-allyl-4-cyano-5-methyl-1*H*-pyrrol-3-yl)butane-1,2,3-triyl triacetate

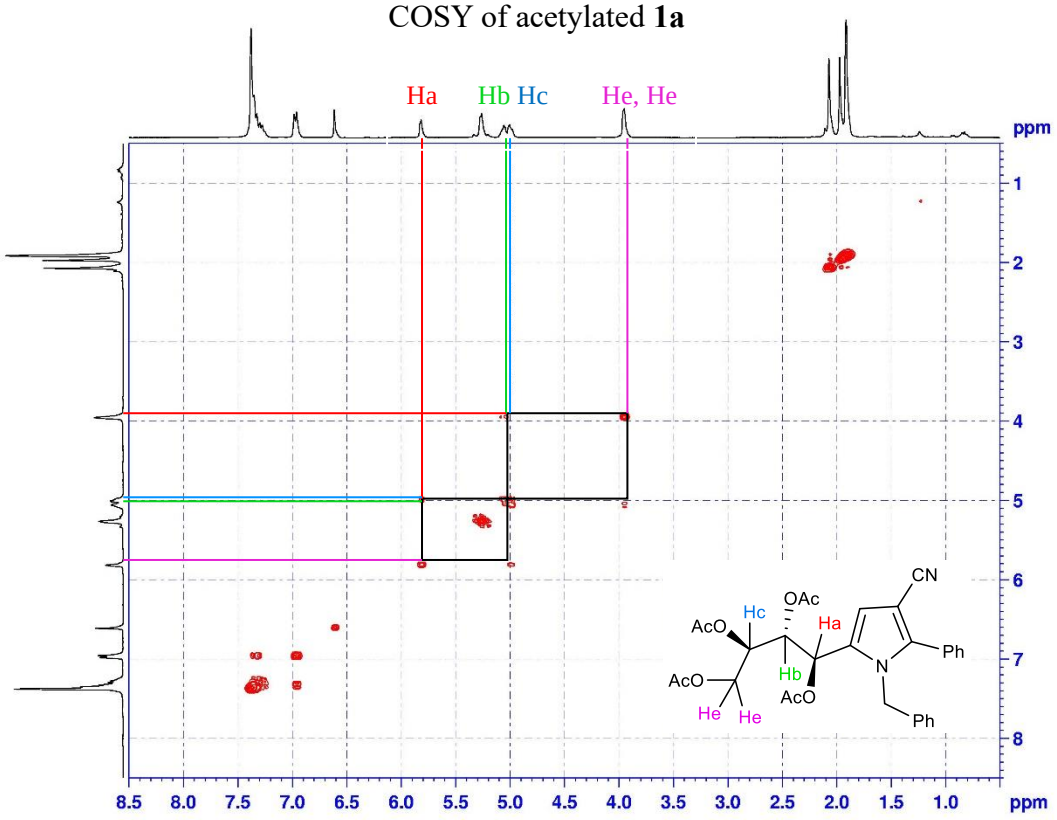




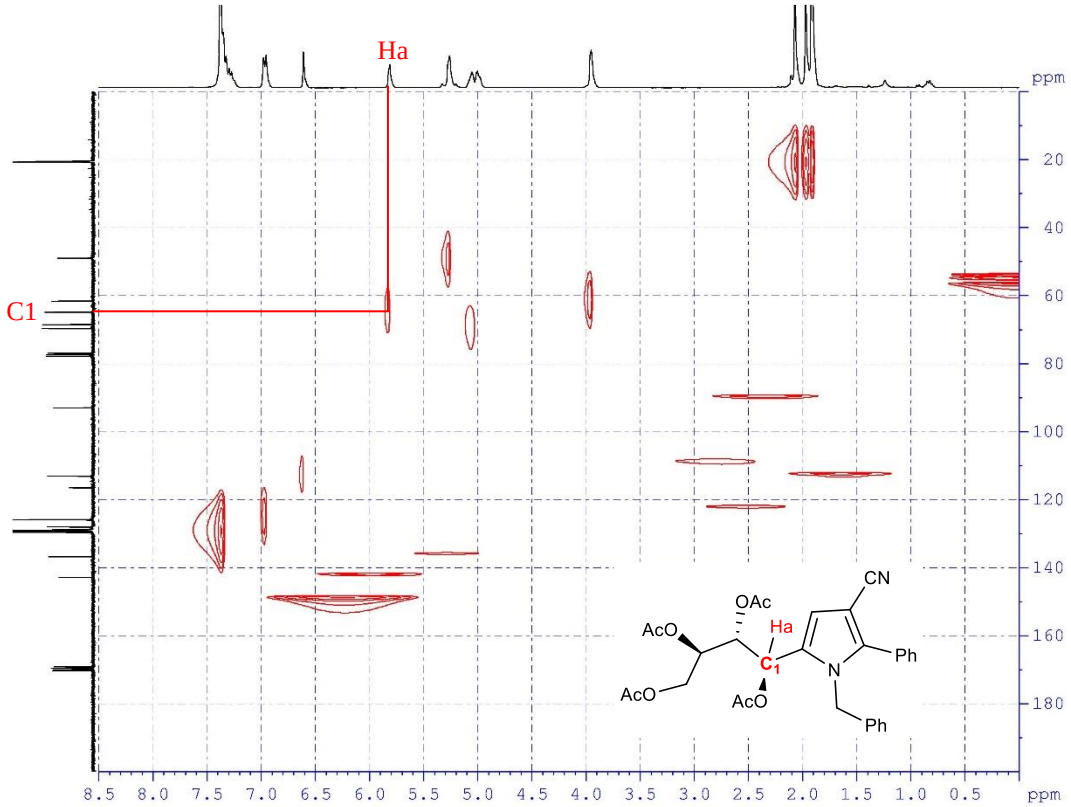
2.3 2D-NMR spectra for acetylated product 1a



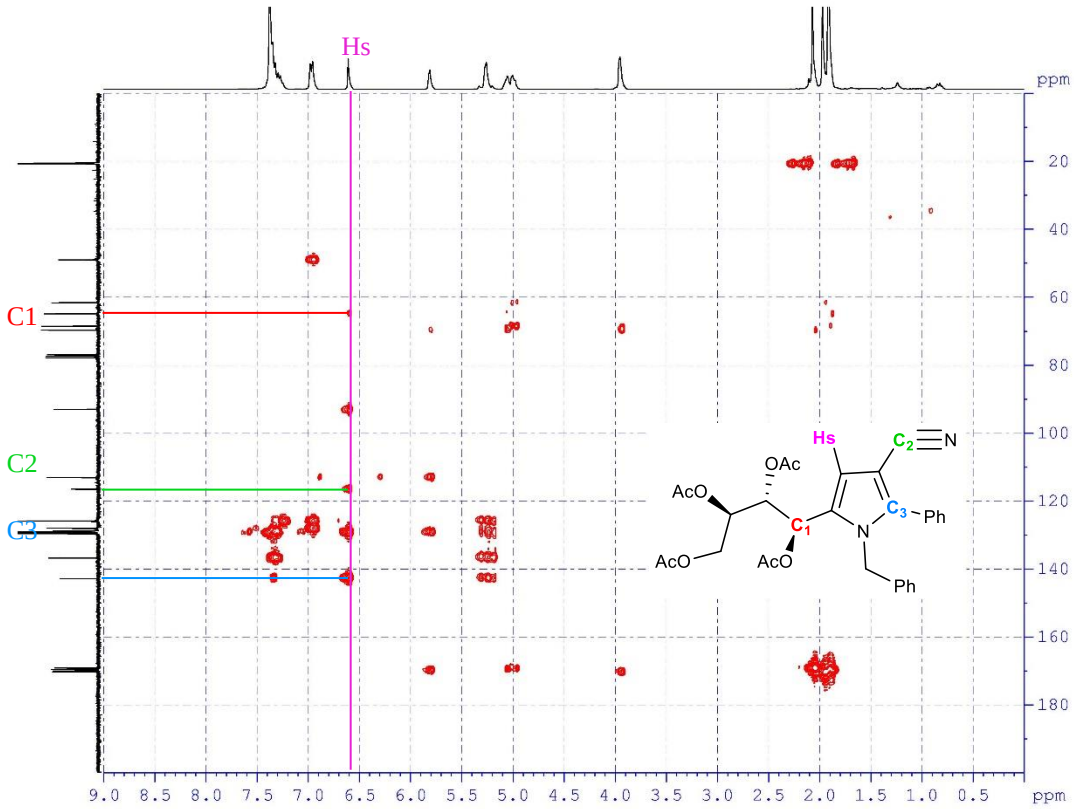
COSY of acetylated **1a**



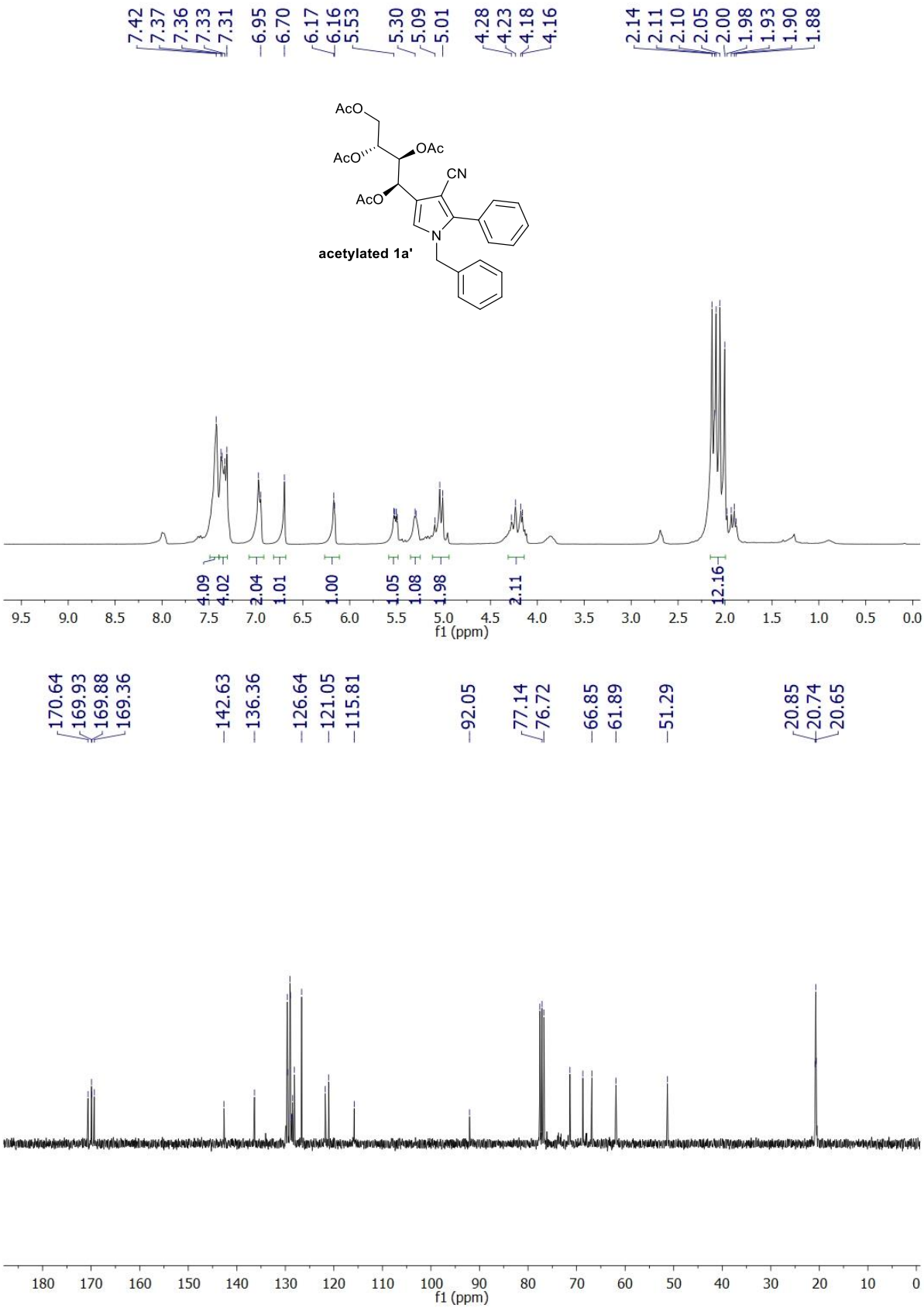
HSQC of acetylated **1a**



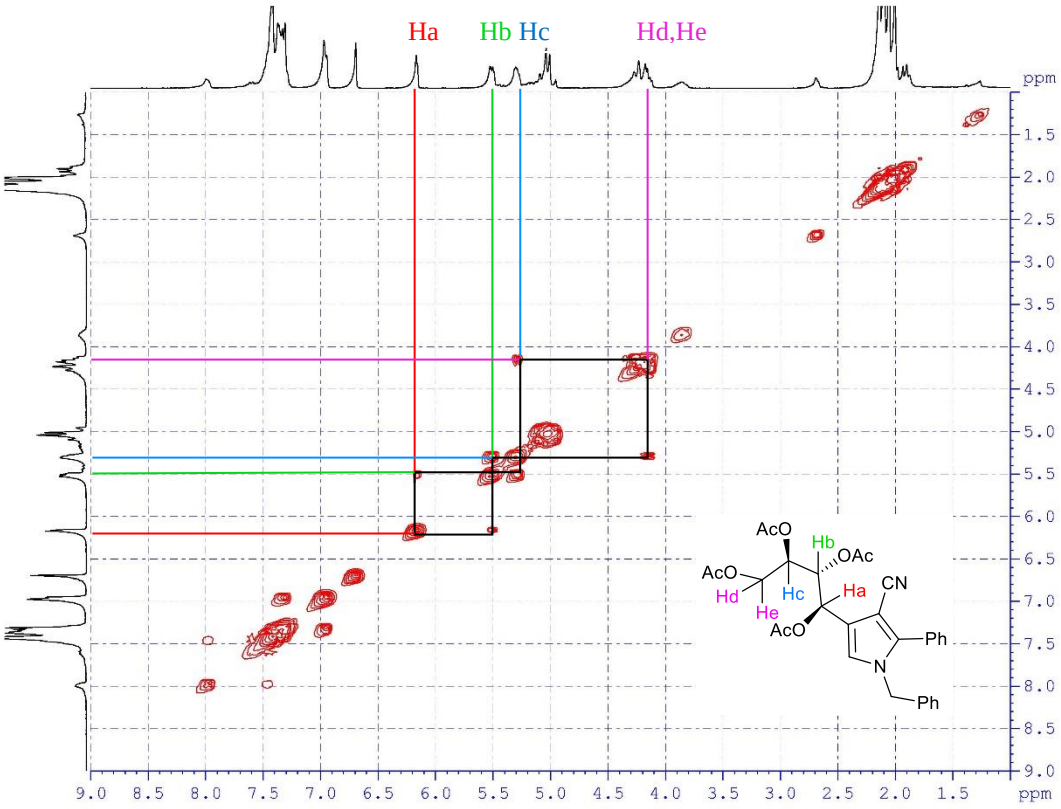
HMBC of acetylated **1a**



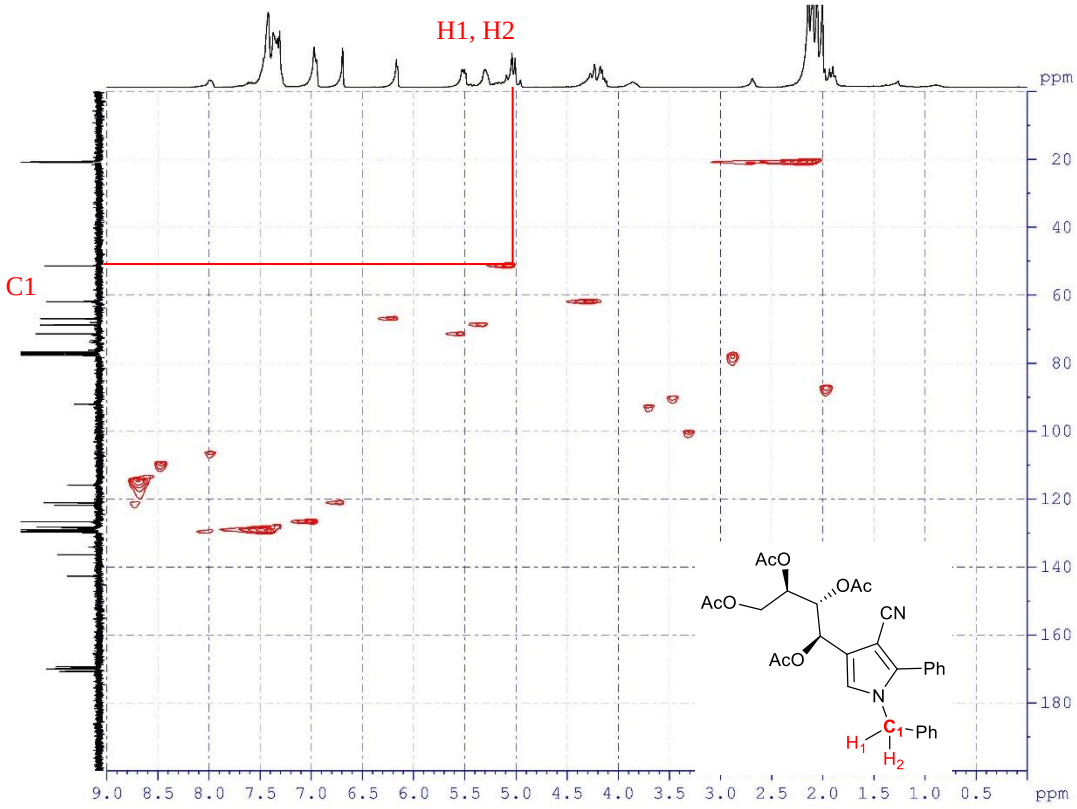
2.4 2D-NMR spectra for acetylated product 1a’



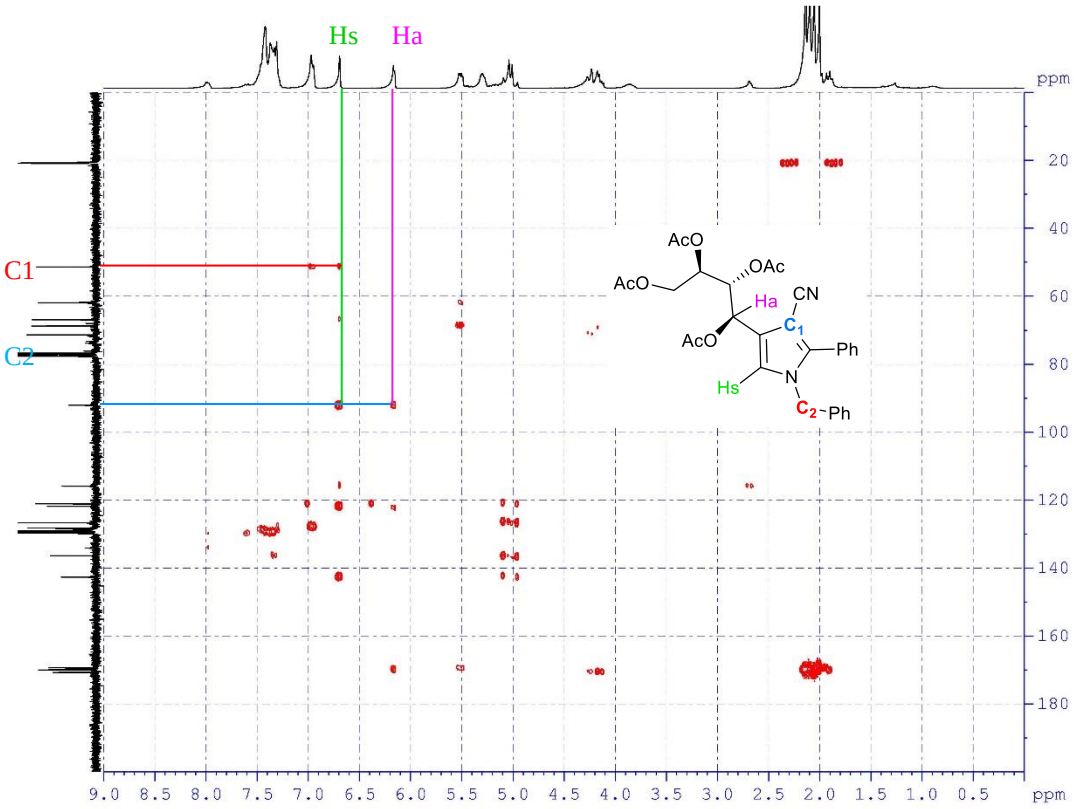
COSY of acetylated **1a'**



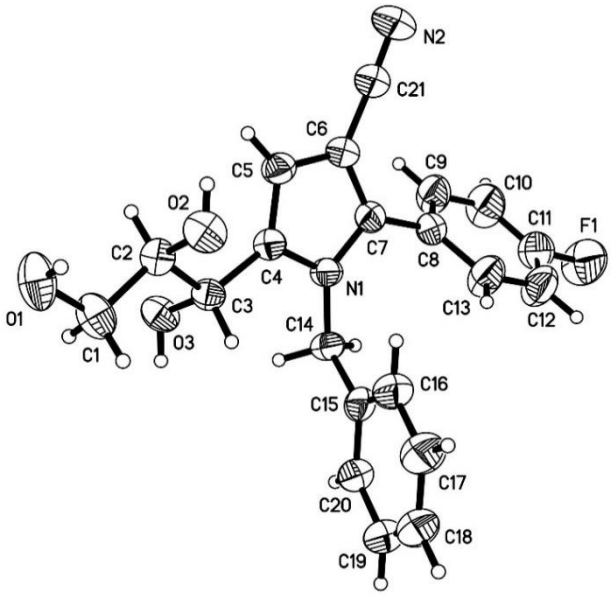
HSQC of acetylated **1a'**

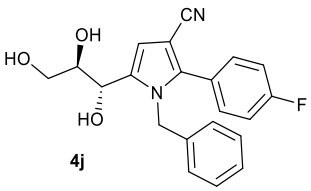


HMBC of acetylated **1a'**

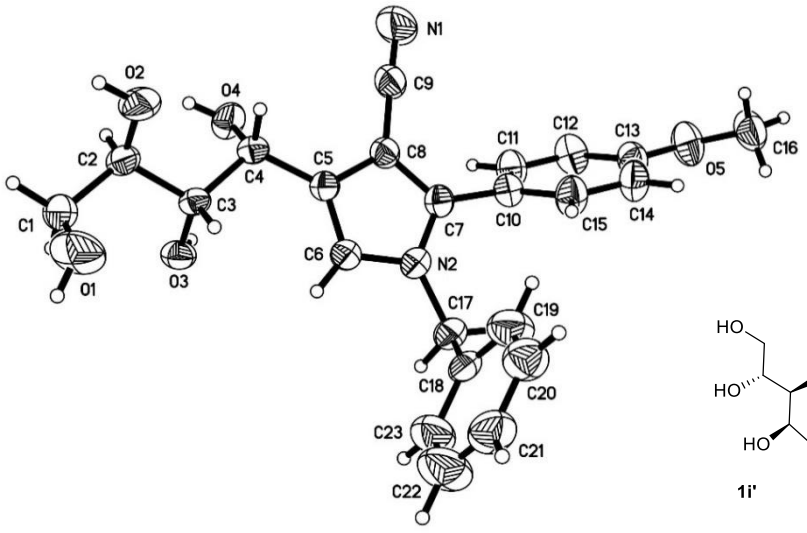


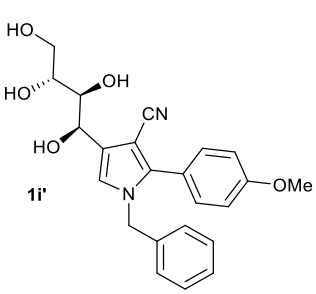
2.5 Single-crystal X-ray spectra of product 4j (CCDC 2053919)





2.6 Single-crystal X-ray spectra of product 1i' (CCDC 2053920)

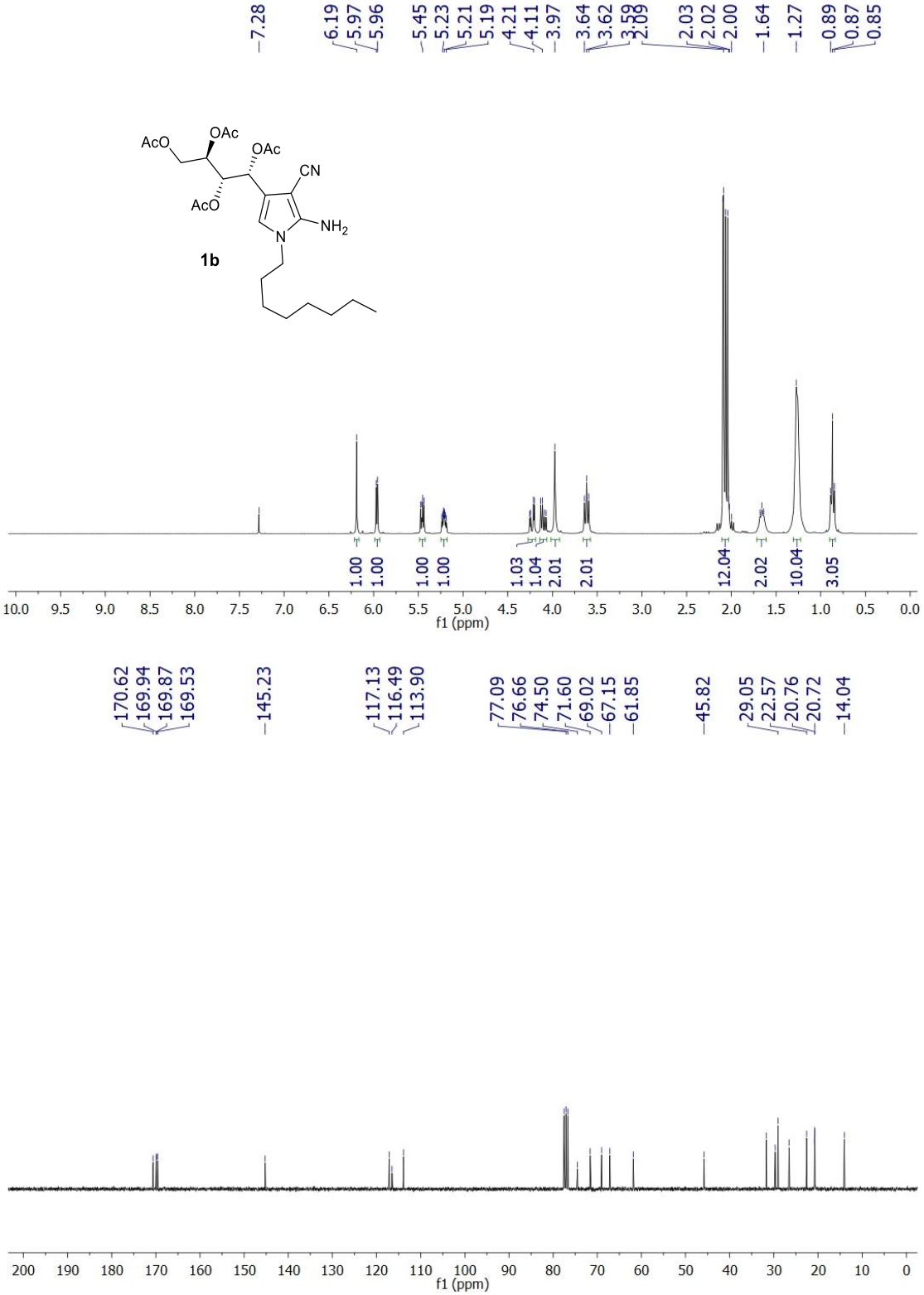




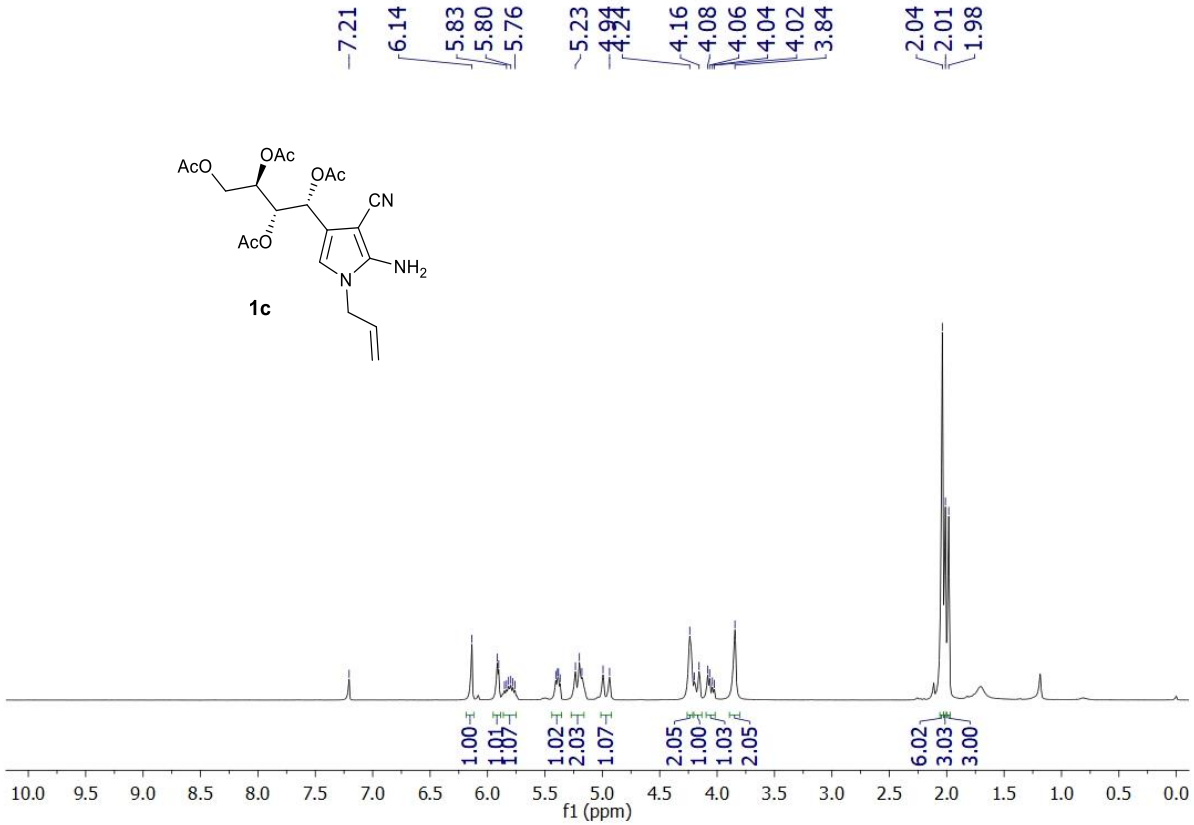
3. Supporting Information for Chapter 4

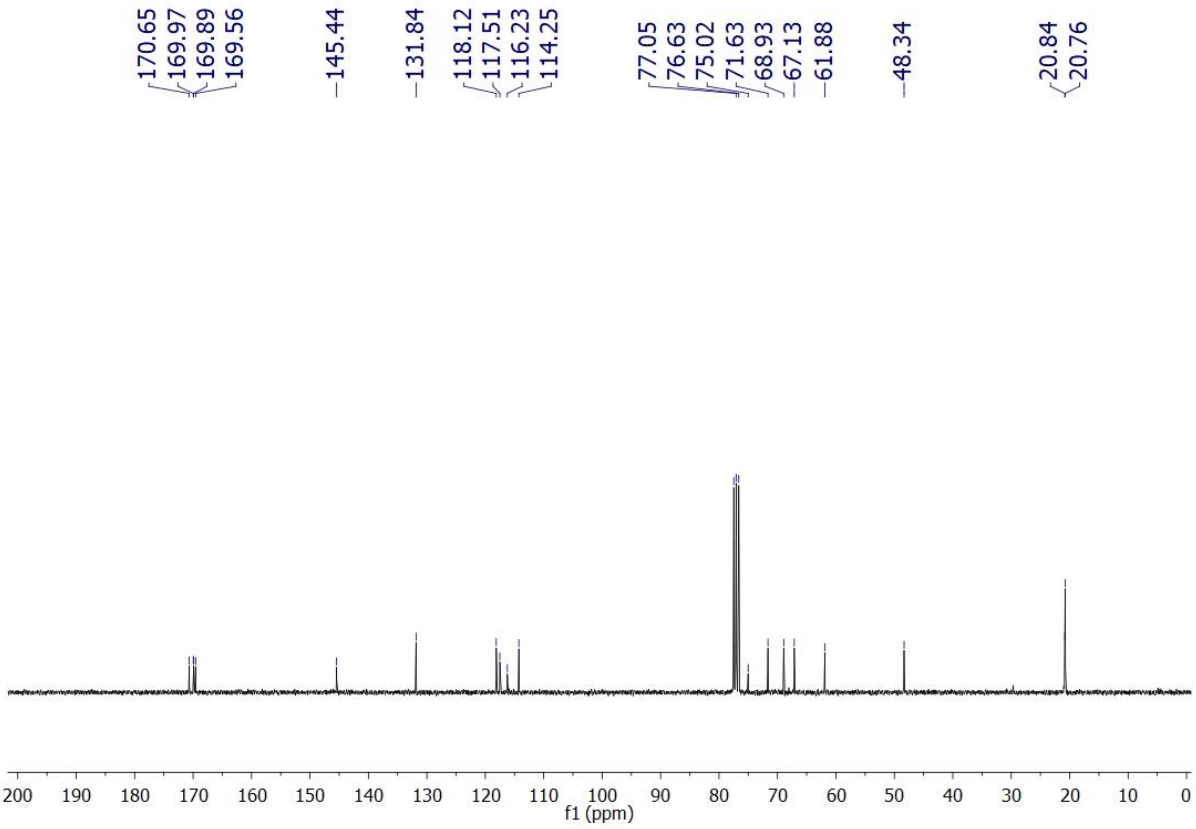
3.1 ^{1}H NMR, ^{13}C NMR and DEPT135 NMR spectra

(1*R*,2*S*,3*R*)-1-(5-Amino-4-cyano-1-octyl-1*H*-pyrrol-3-yl)butane-1,2,3,4-tetrayl tetraacetate

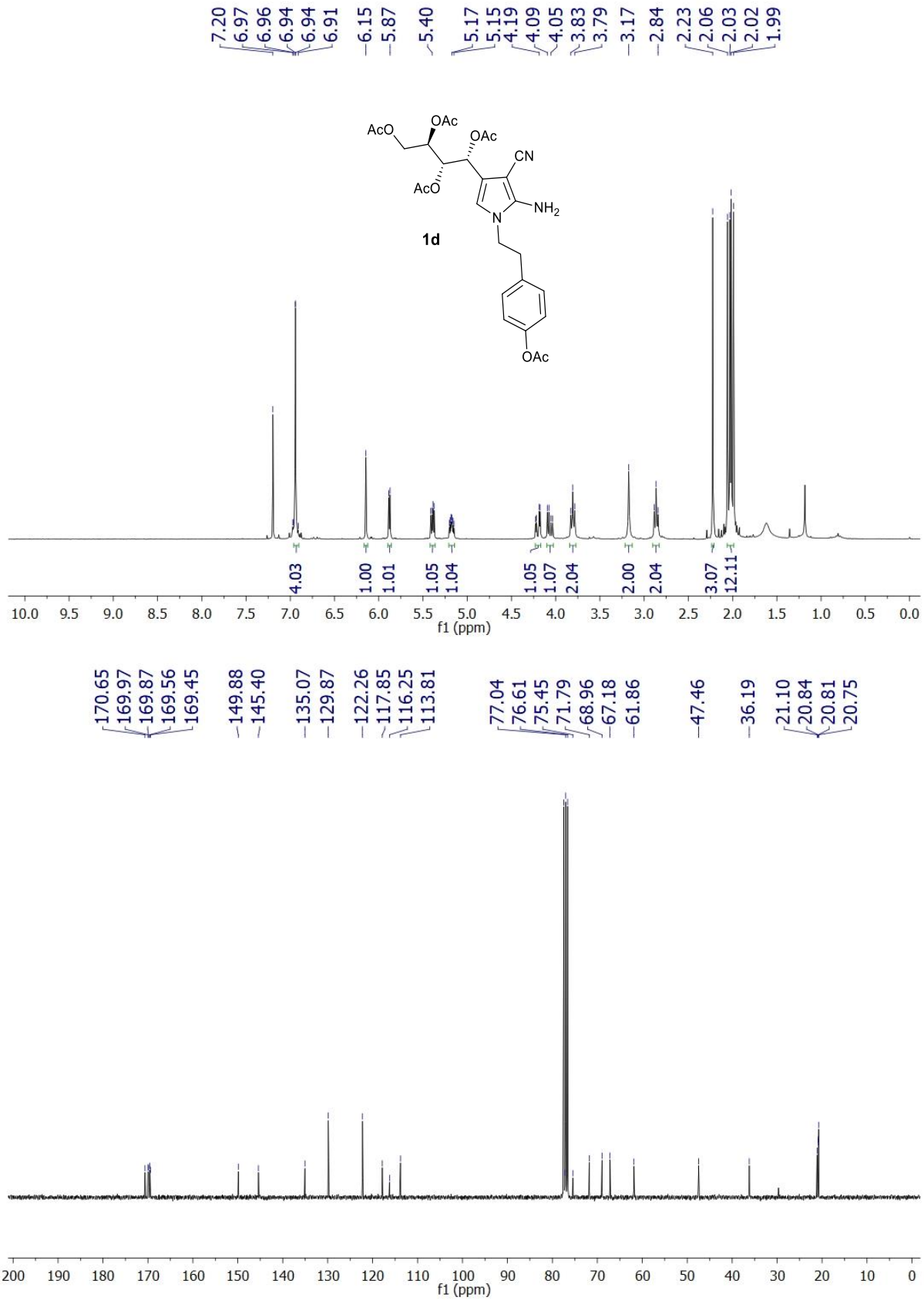


(1*R*,2*S*,3*R*)-1-(1-Allyl-5-amino-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate

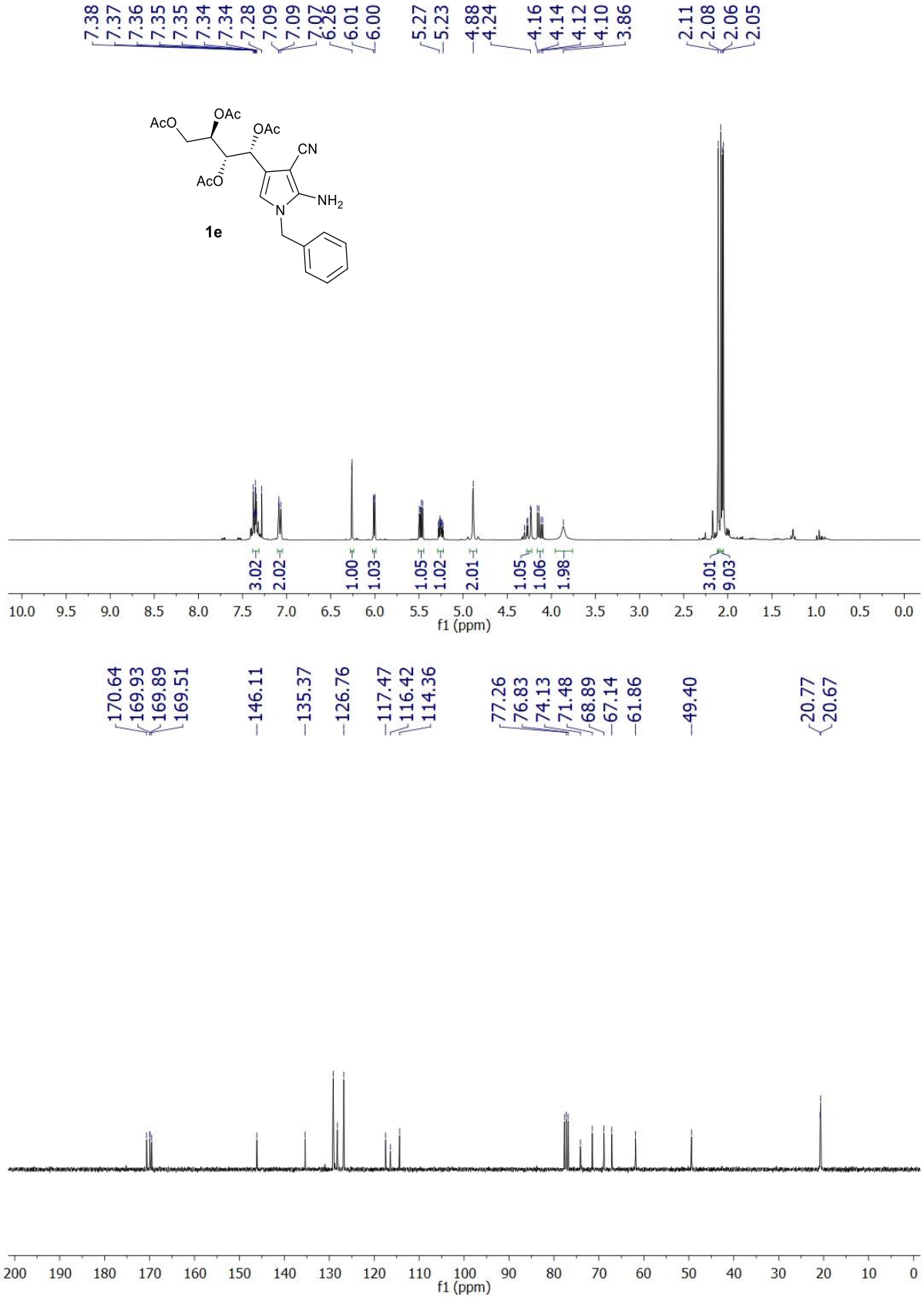




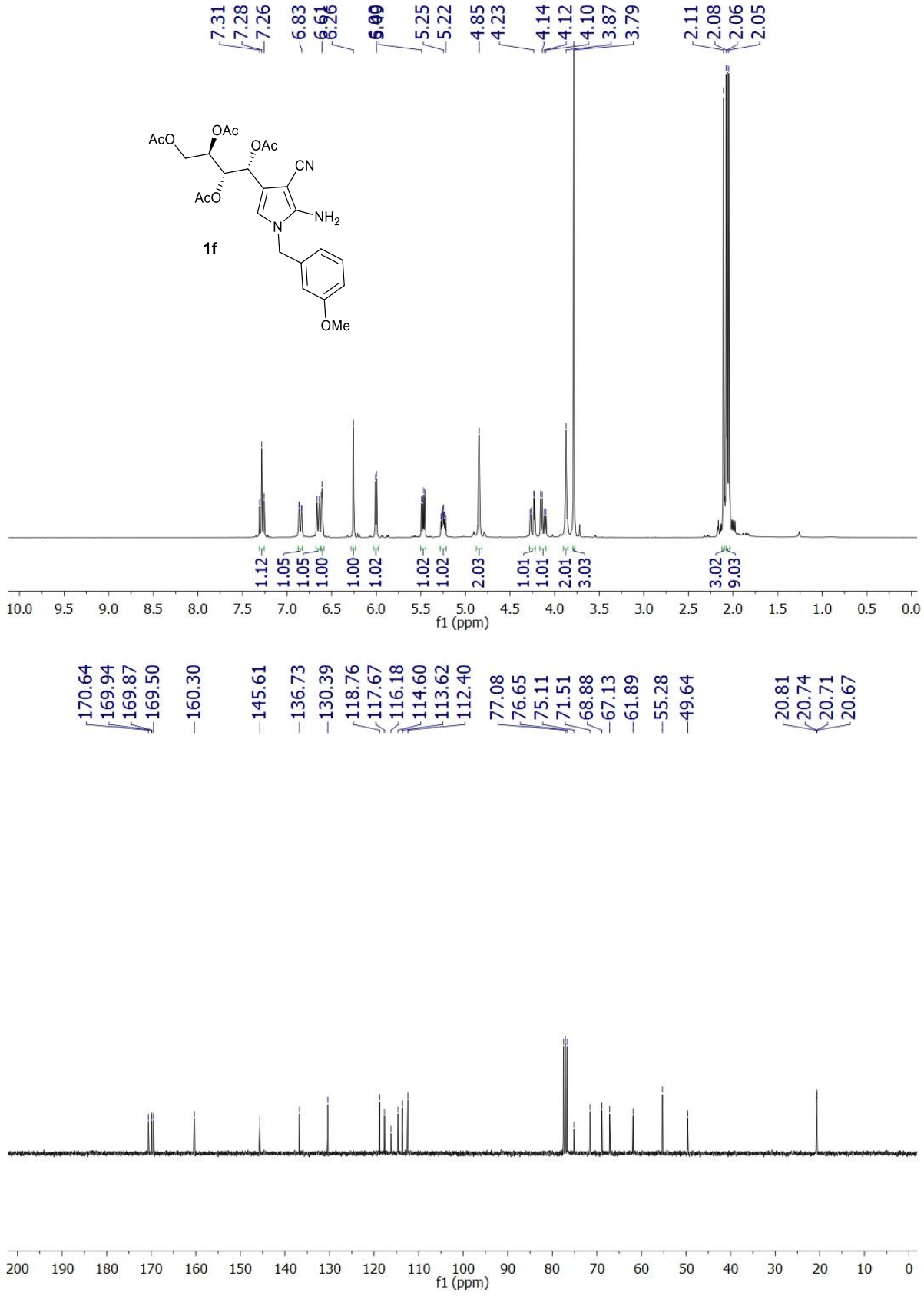
(1*R*,2*S*,3*R*)-1-(1-(4-Acetoxyphenethyl)-5-amino-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate



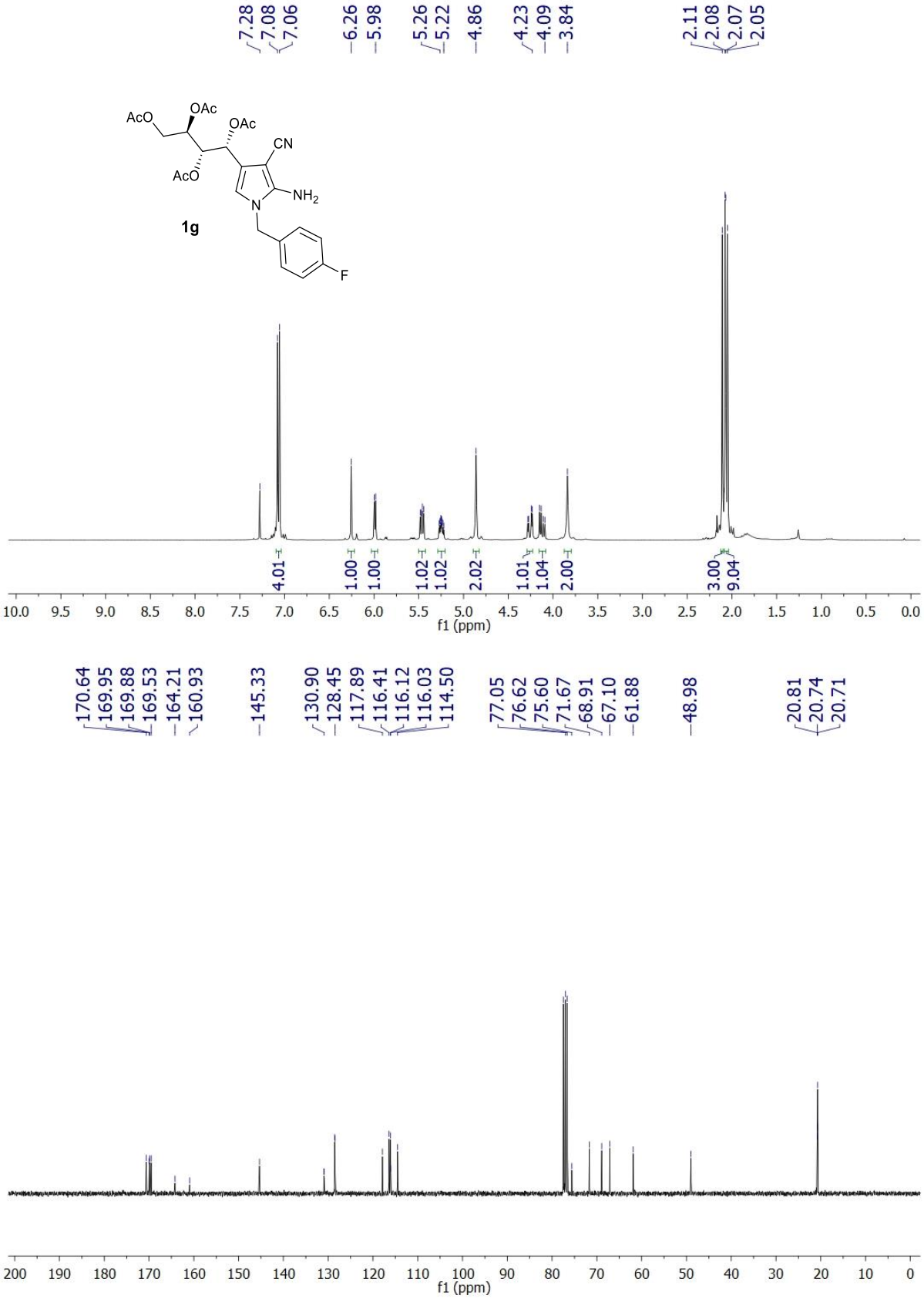
(1*R*,2*S*,3*R*)-1-(5-Amino-1-benzyl-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate



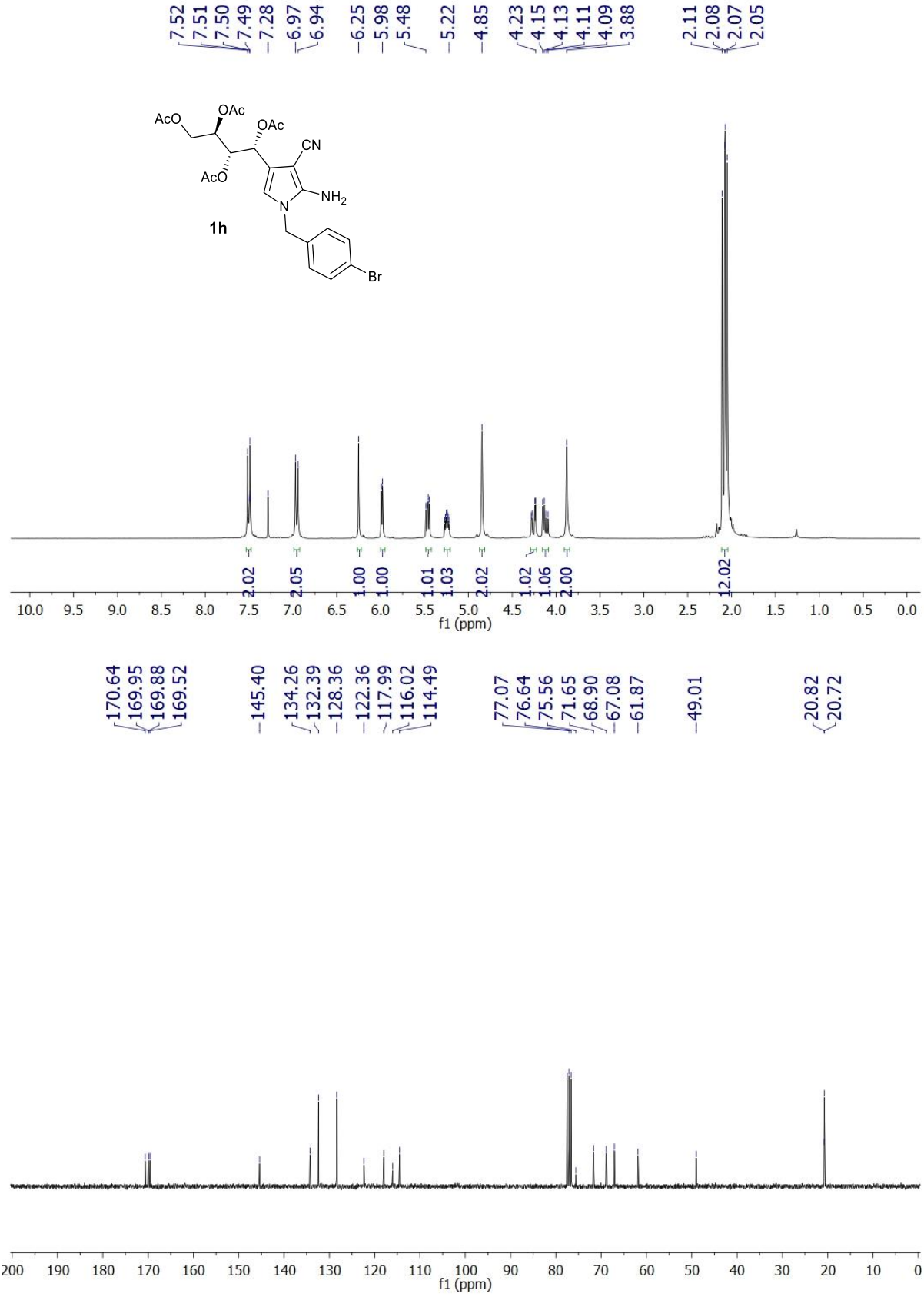
(1*R*,2*S*,3*R*)-1-(5-Amino-4-cyano-1-(3-methoxybenzyl)-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate



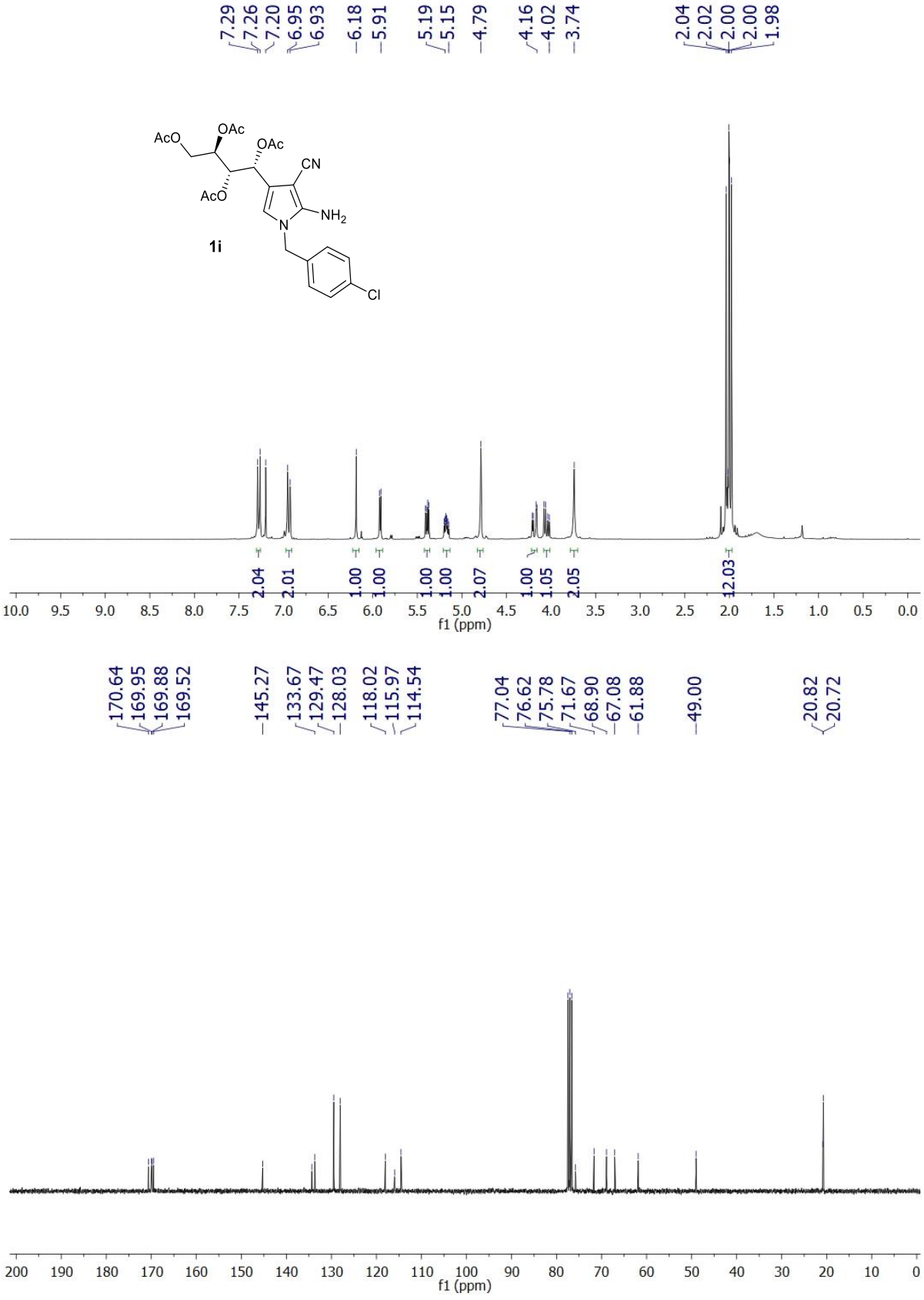
(1*R*,2*S*,3*R*)-1-(5-Amino-4-cyano-1-(4-fluorobenzyl)-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate



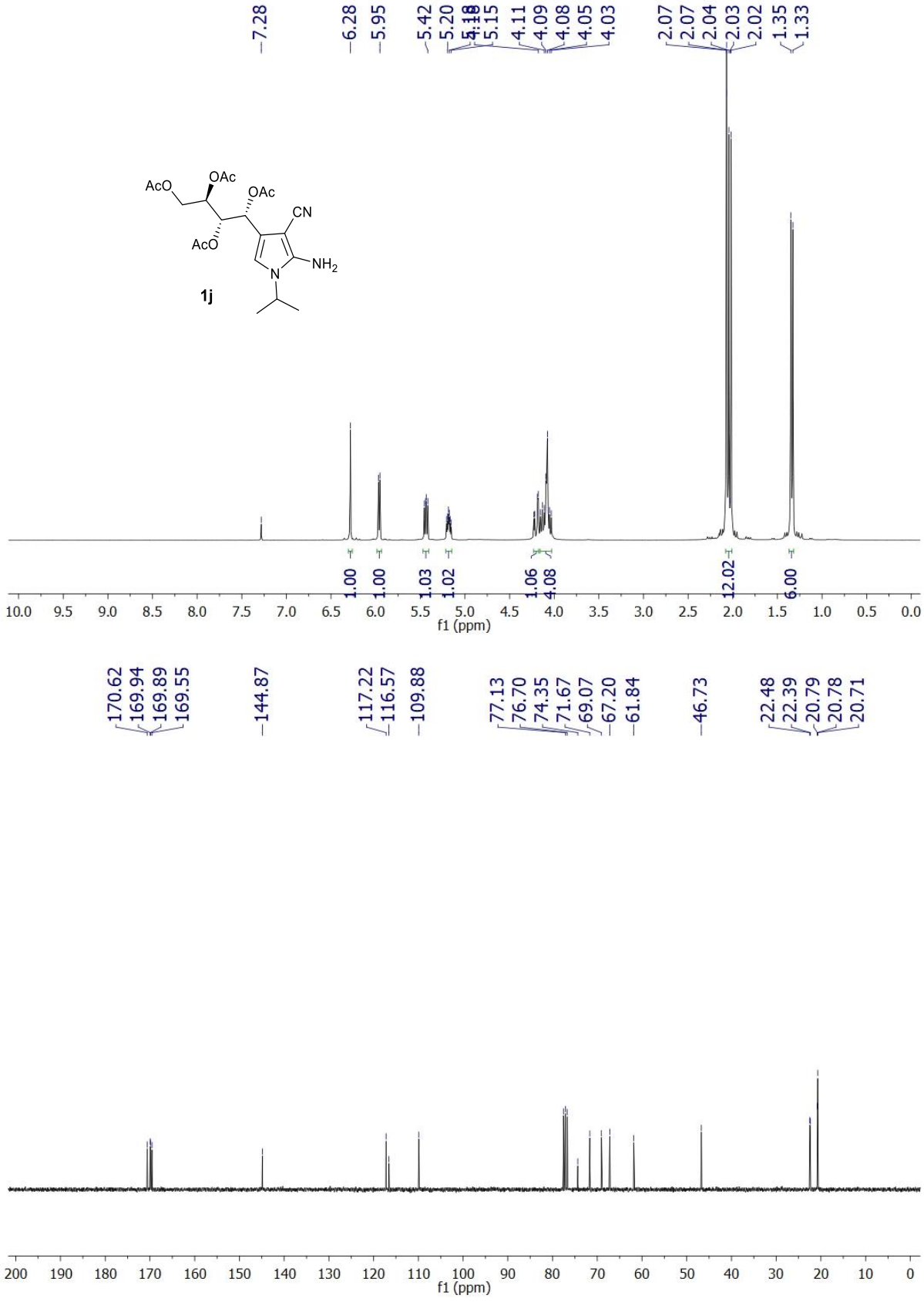
(1*R*,2*S*,3*R*)-1-(5-Amino-1-(4-bromobenzyl)-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate



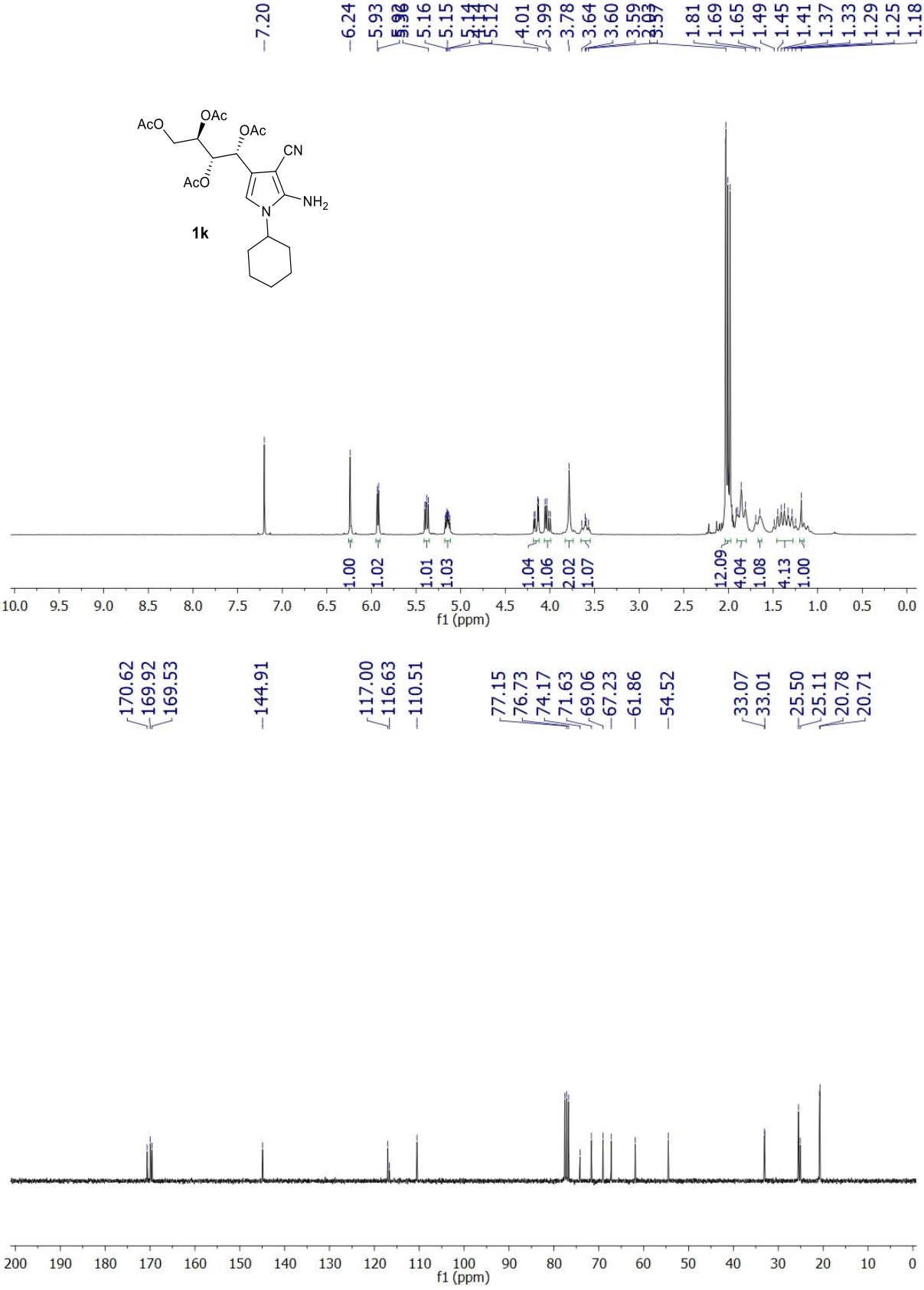
(1*R*,2*S*,3*R*)-1-(5-Amino-1-(4-chlorobenzyl)-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate



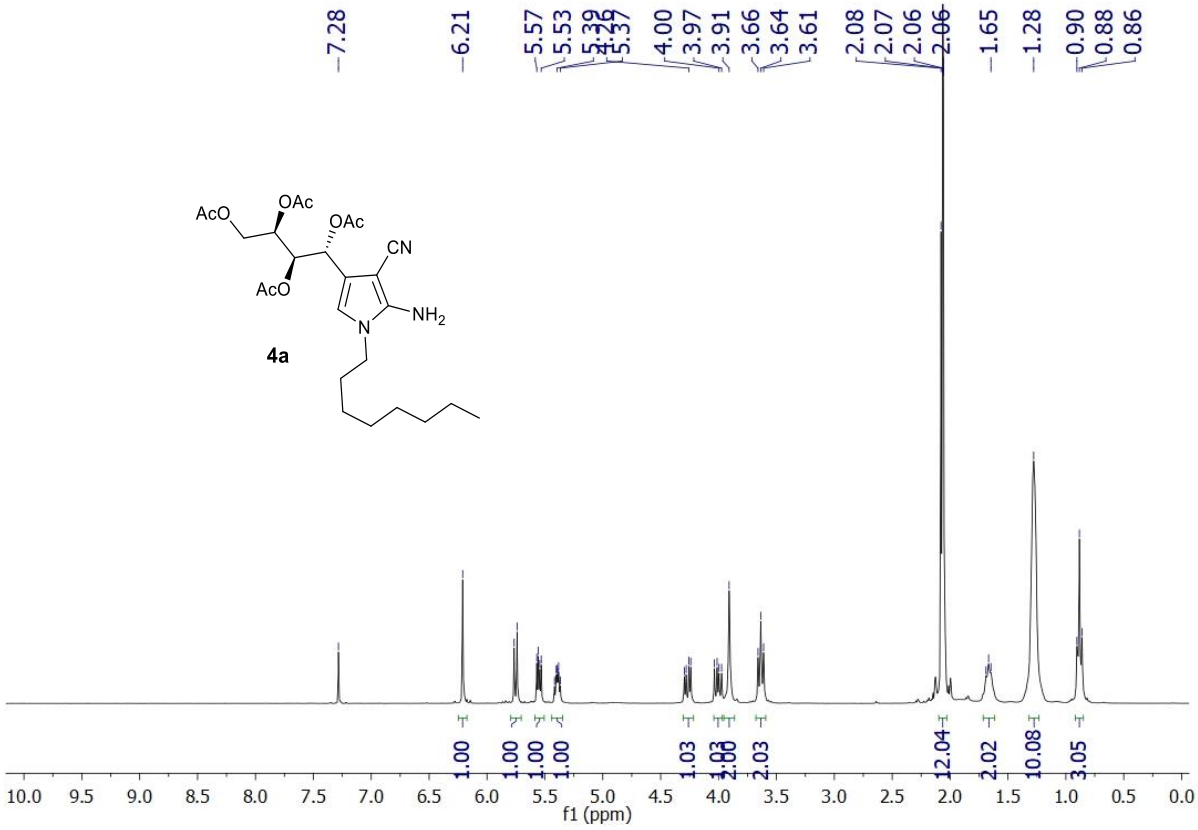
(1*R*,2*S*,3*R*)-1-(5-Amino-4-cyano-1-isopropyl-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate

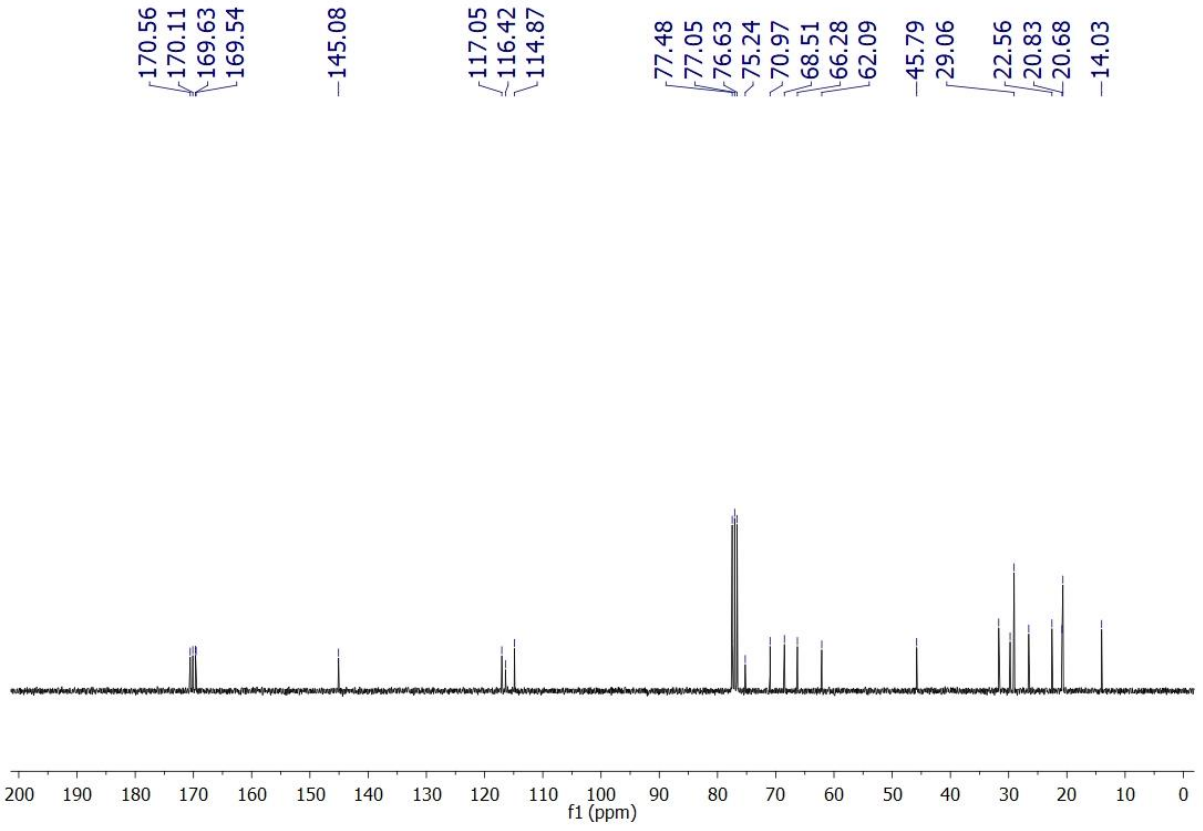


(1*S*,2*R*,3*R*)-1-(5-Amino-4-cyano-1-cyclohexyl-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate

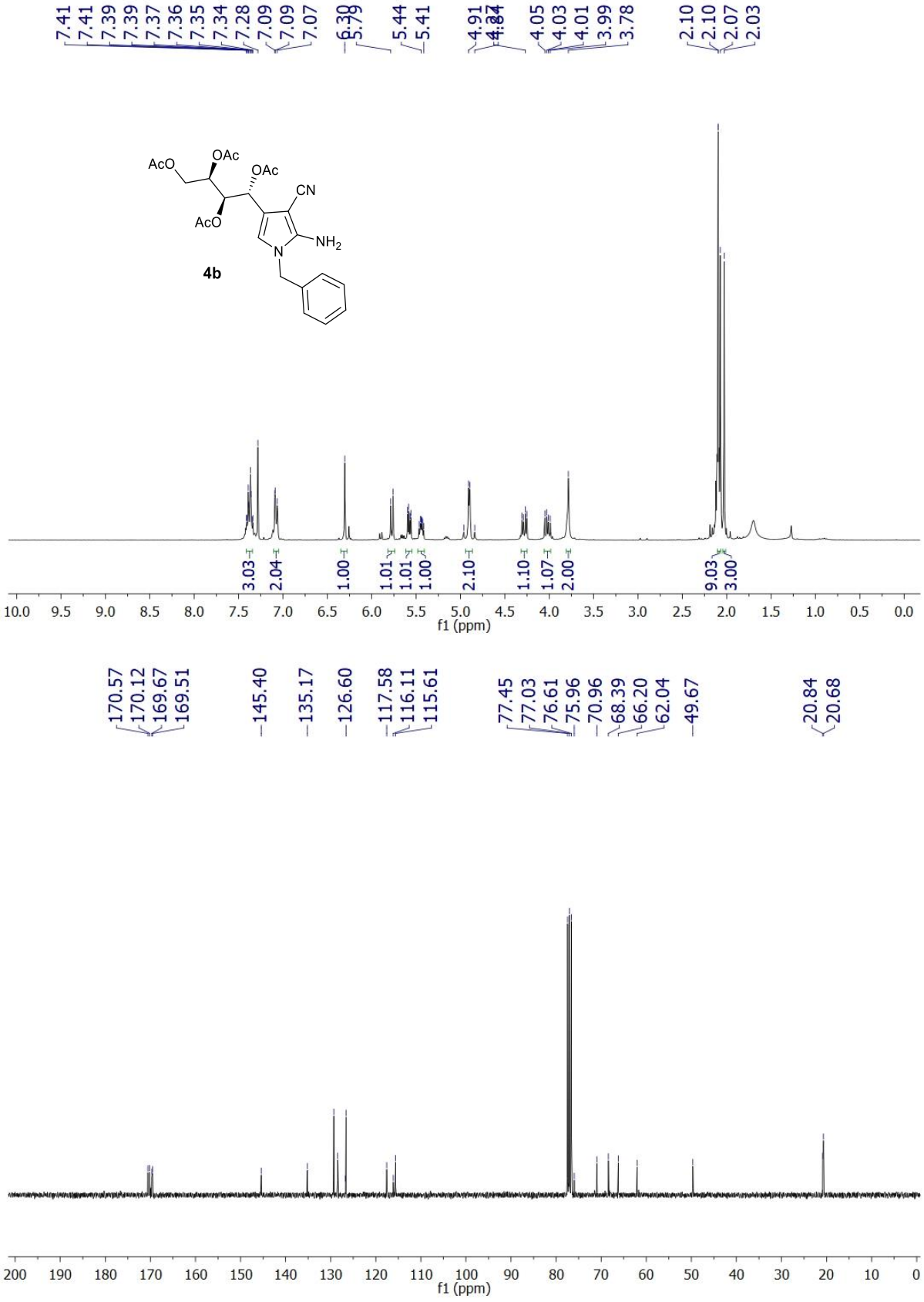


(1*R*,2*R*,3*R*)-1-(5-Amino-4-cyano-1-octyl-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate

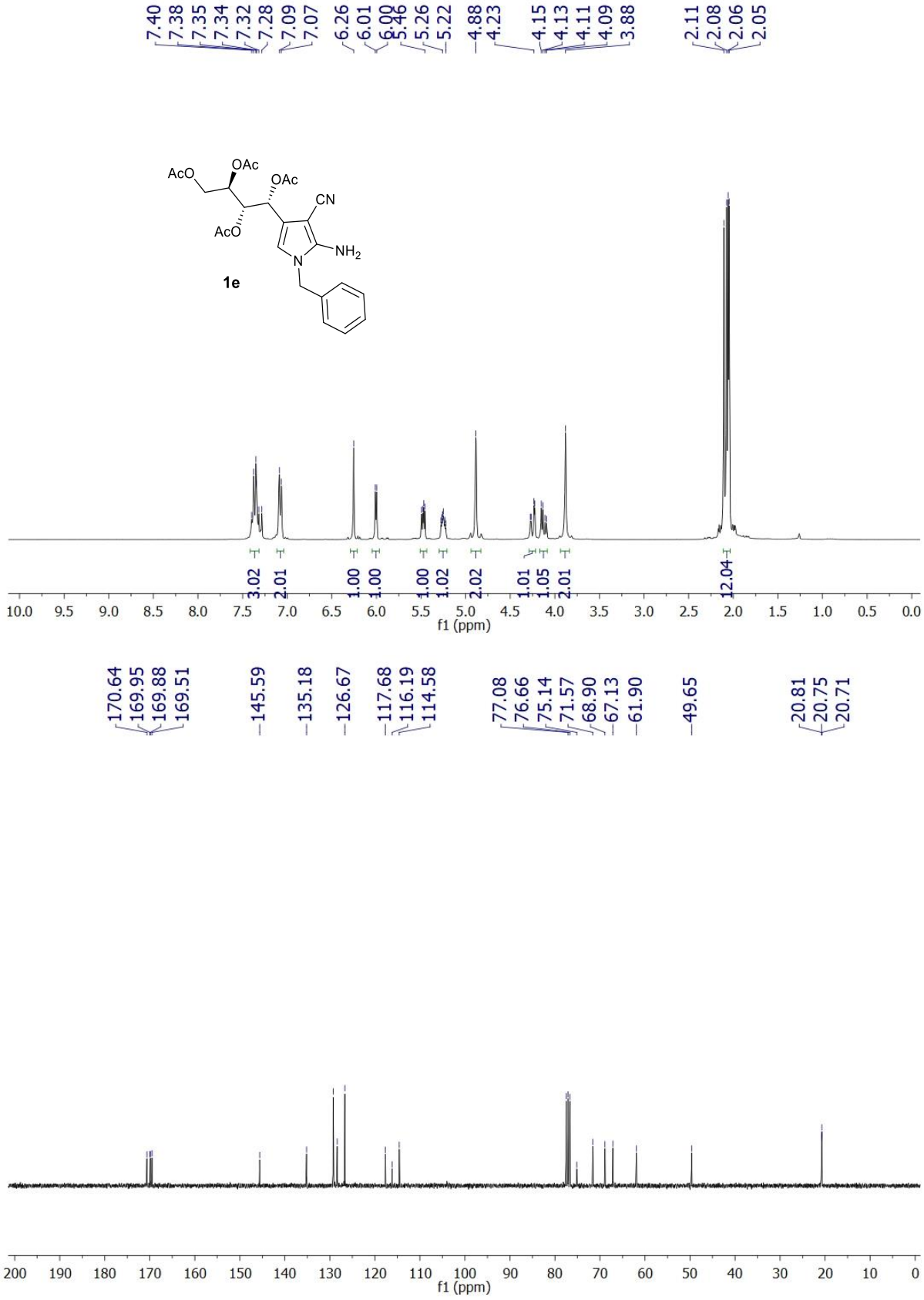




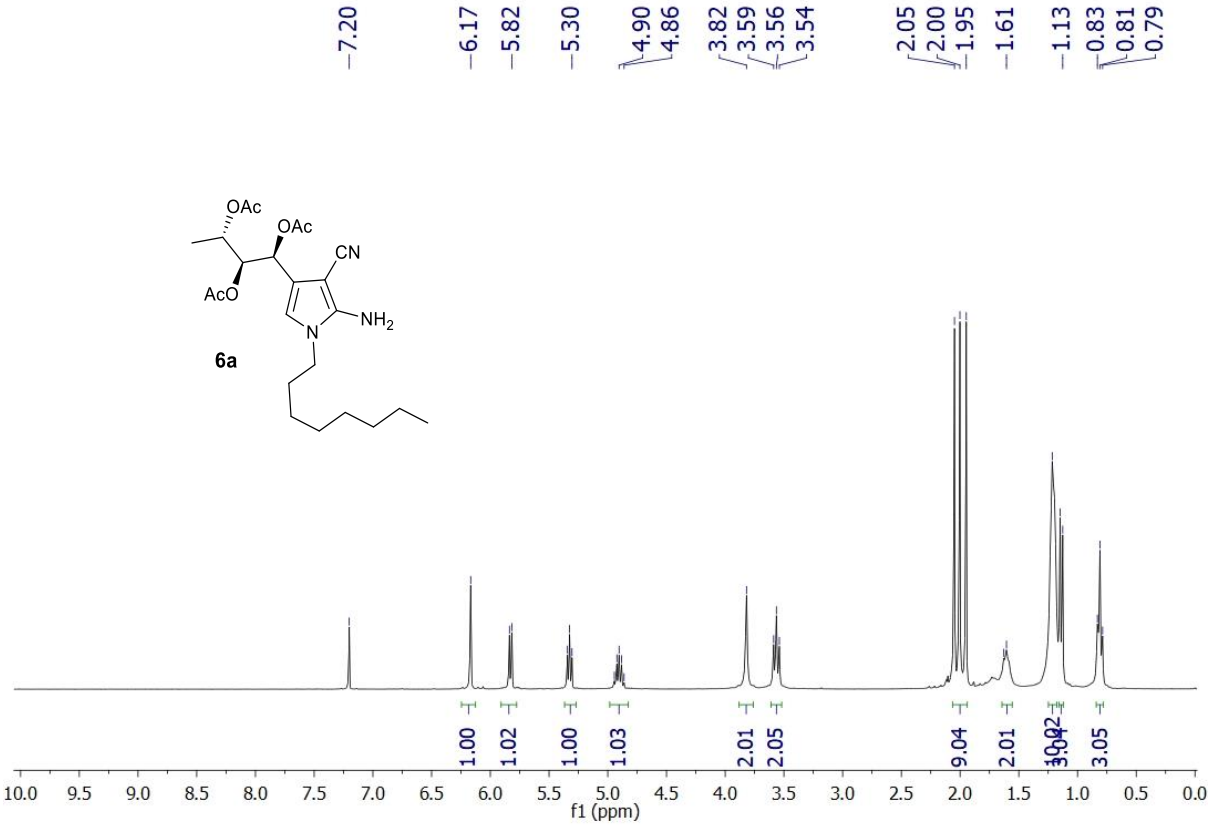
(1*R*,2*R*,3*R*)-1-(5-Amino-1-benzyl-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate

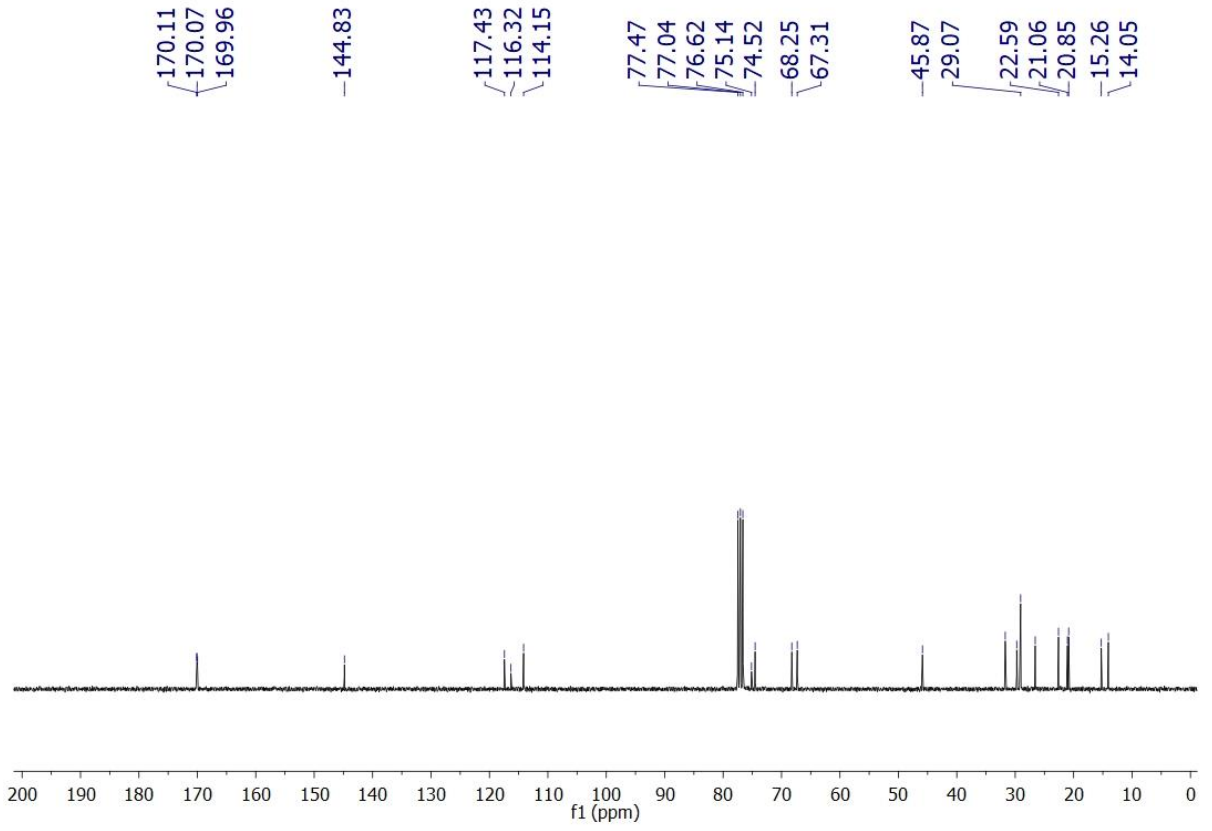


(1*R*,2*S*,3*R*)-1-(5-Amino-1-benzyl-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3,4-tetrayl tetraacetate

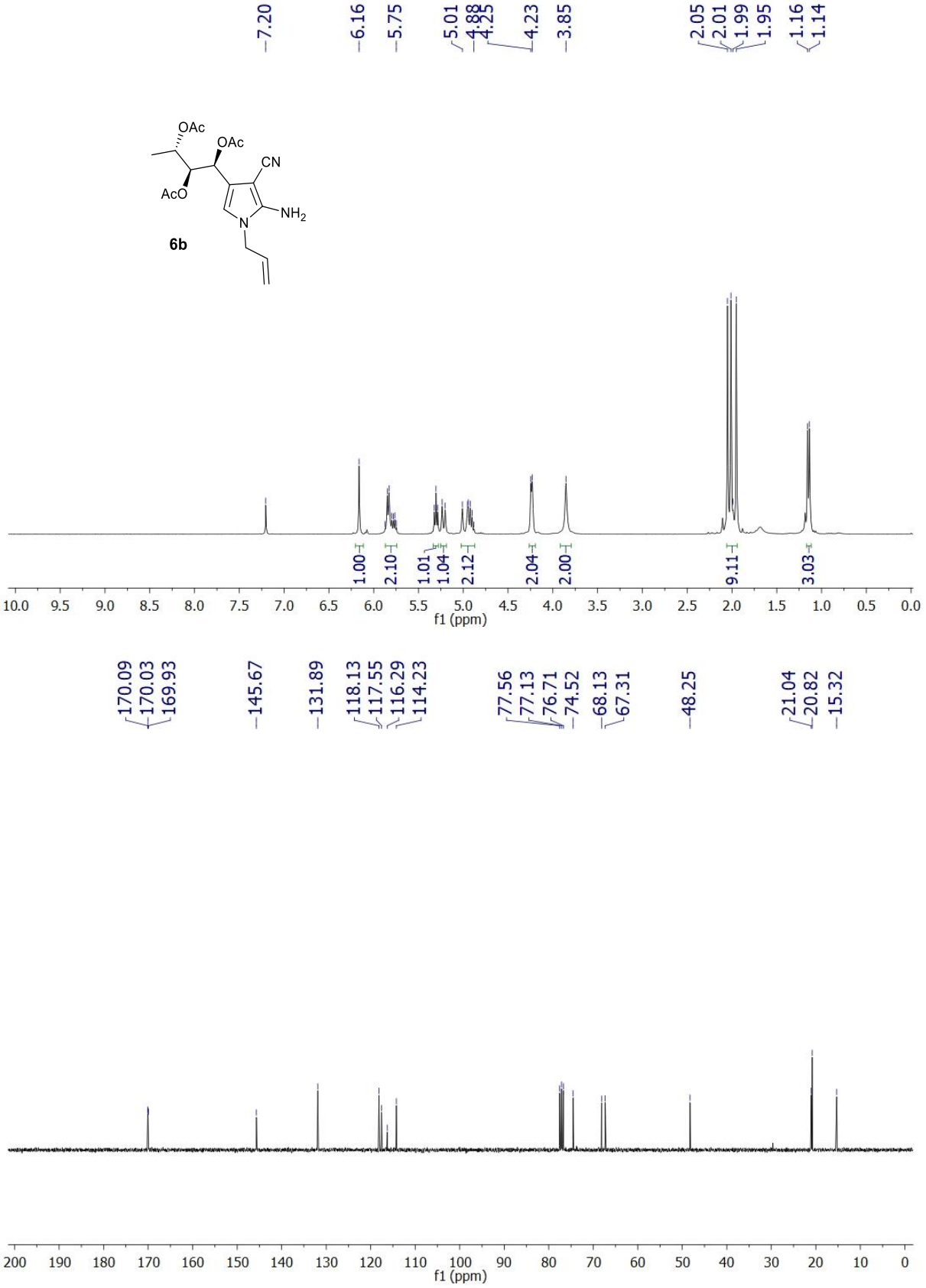


(1*S*,2*S*,3*S*)-1-(5-Amino-4-cyano-1-octyl-1*H*-pyrrol-2-yl)butane-1,2,3-triyl triacetate

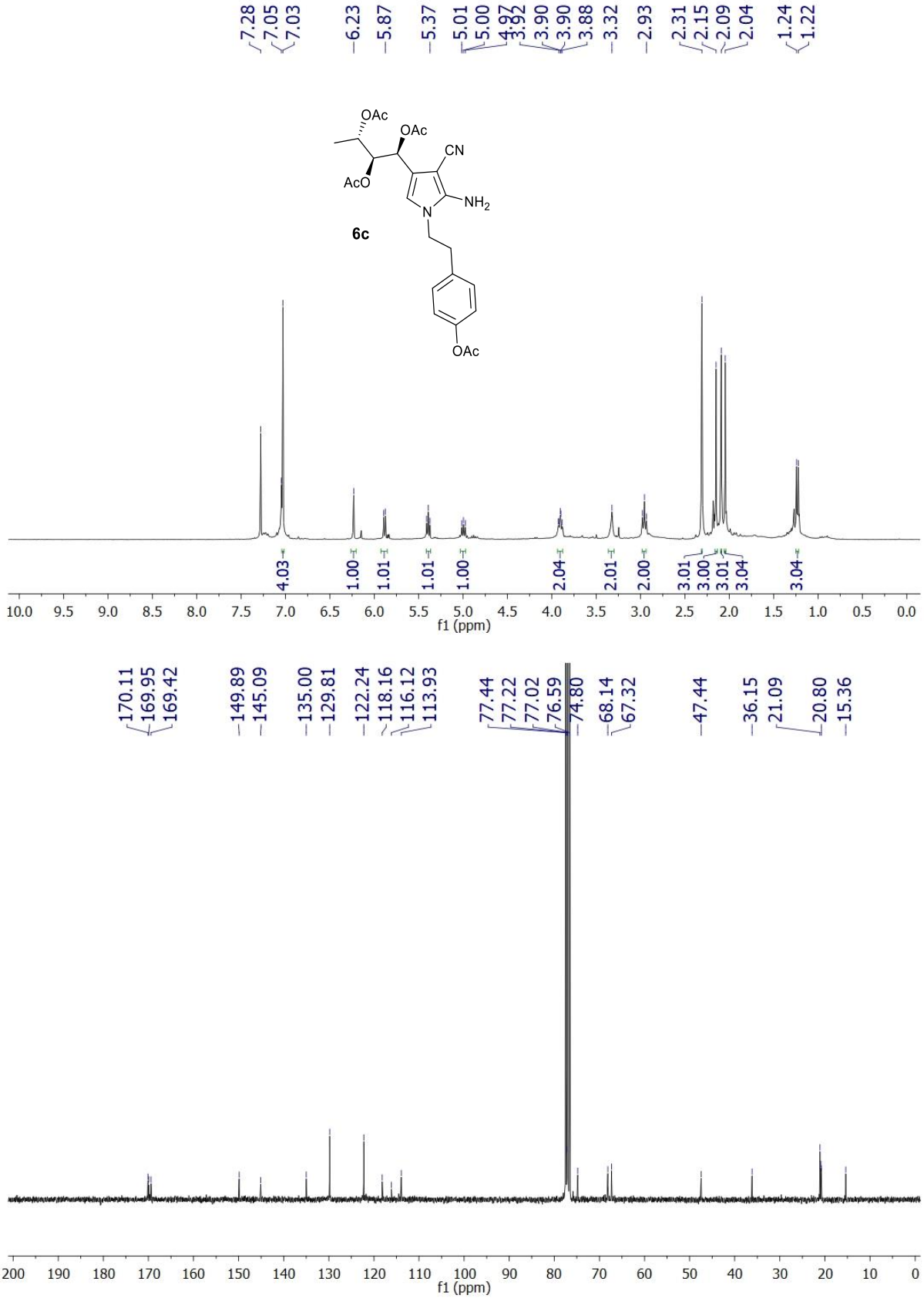




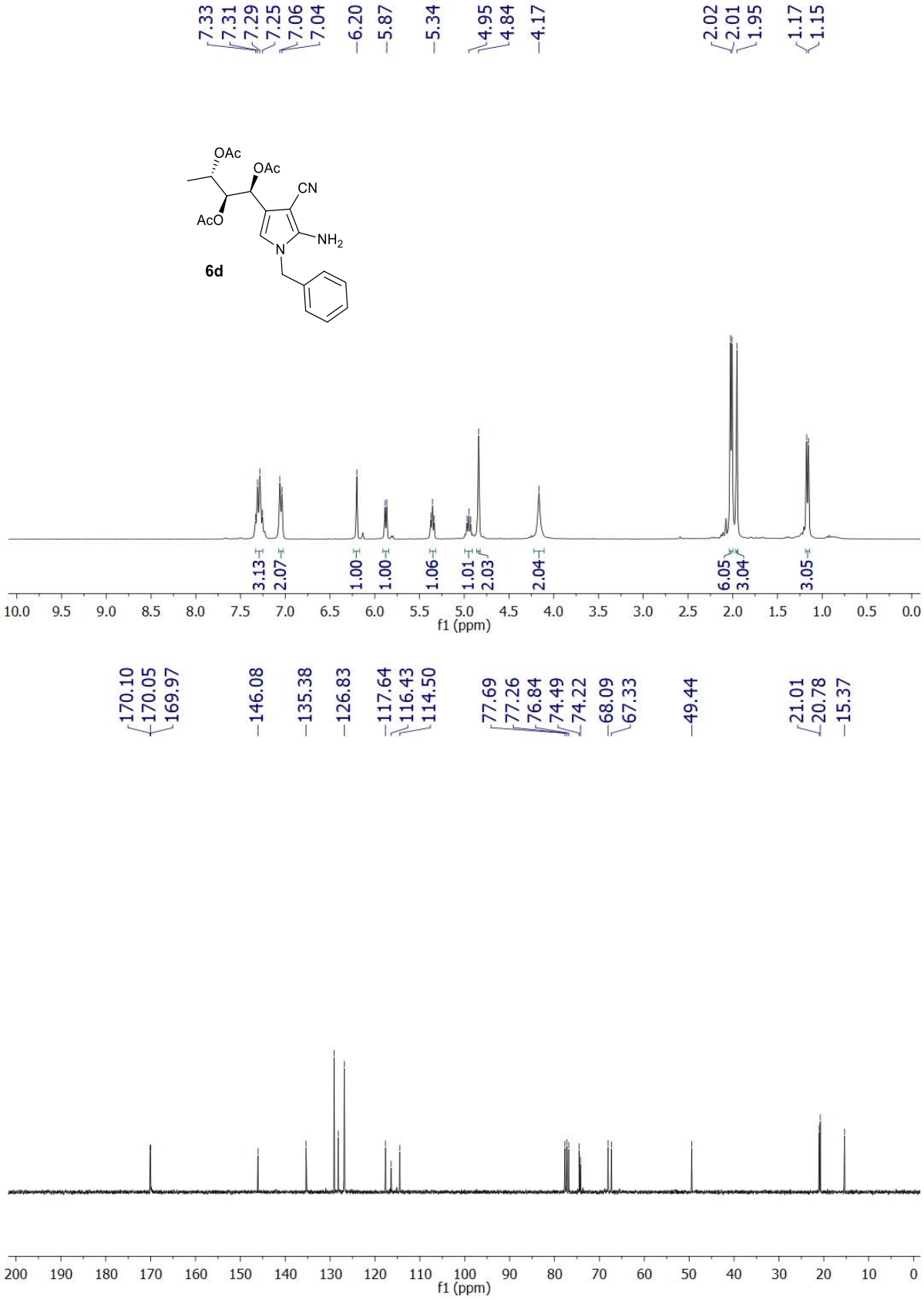
(1*S*,2*S*,3*S*)-1-(1-Allyl-5-amino-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3-triyl triacetate



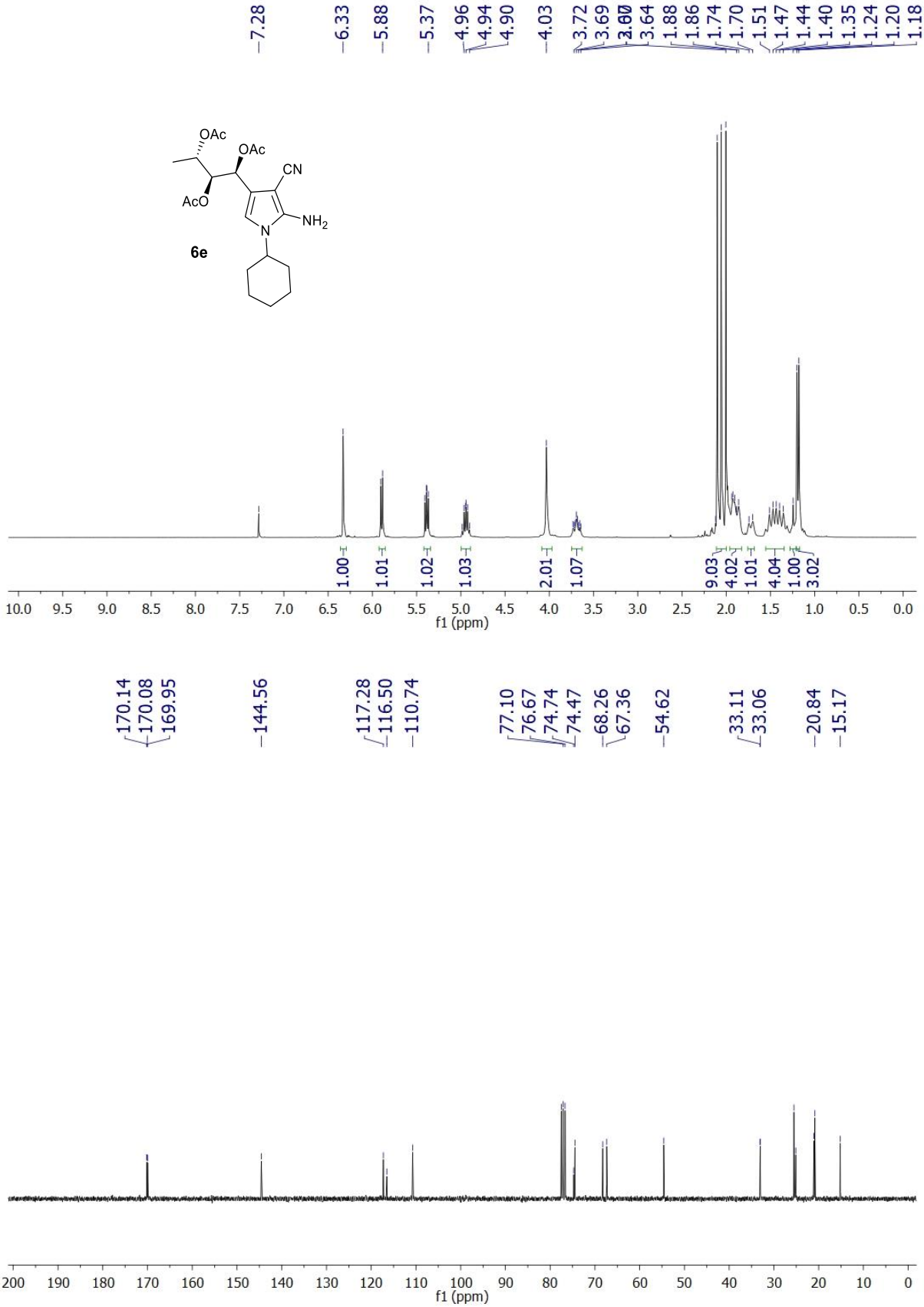
(1*S*,2*S*,3*S*)-1-(1-(4-Acetoxyphenethyl)-5-amino-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3-triyl triacetate



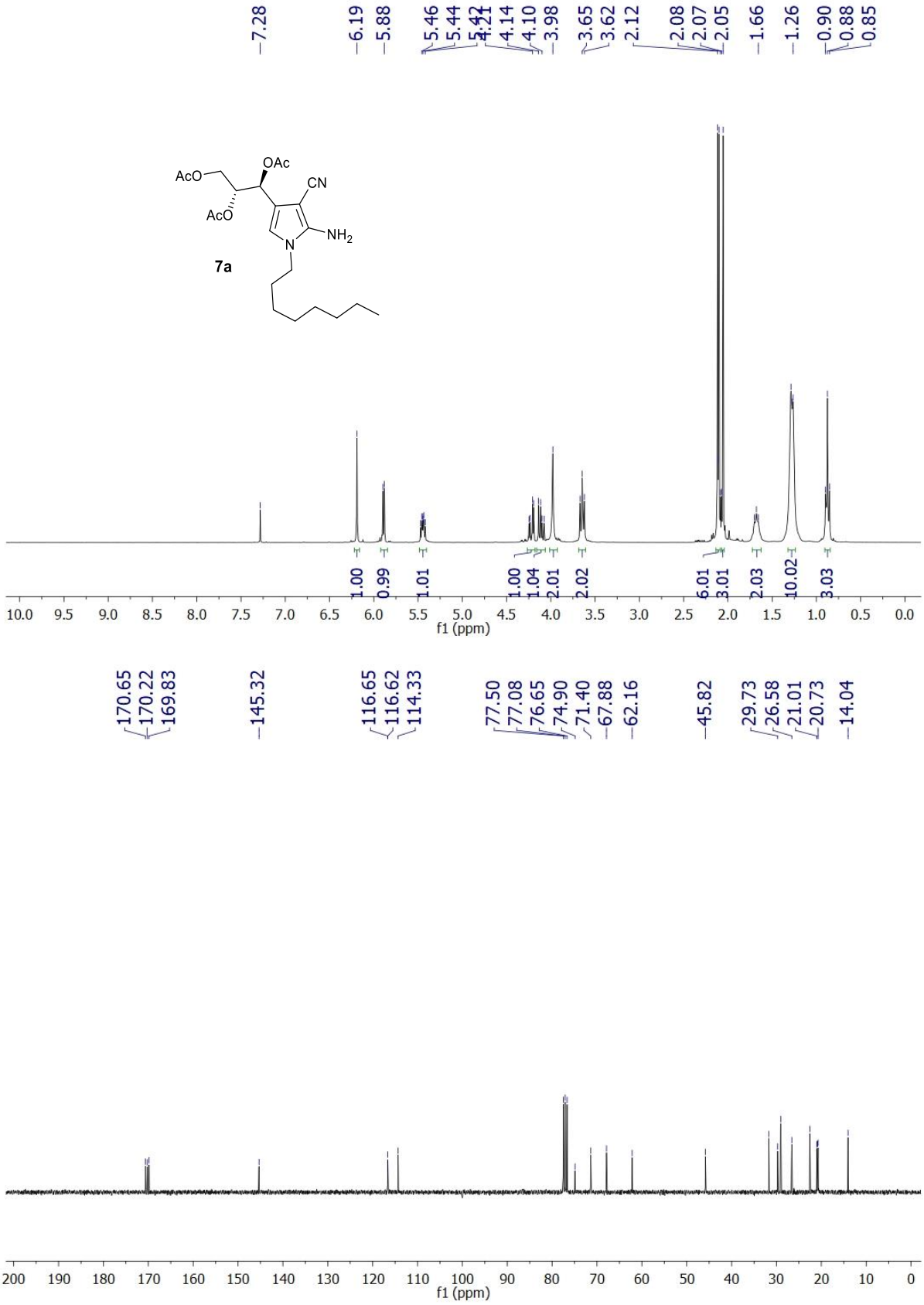
(1*S*,2*S*,3*S*)-1-(5-Amino-1-benzyl-4-cyano-1*H*-pyrrol-2-yl)butane-1,2,3-triyl triacetate



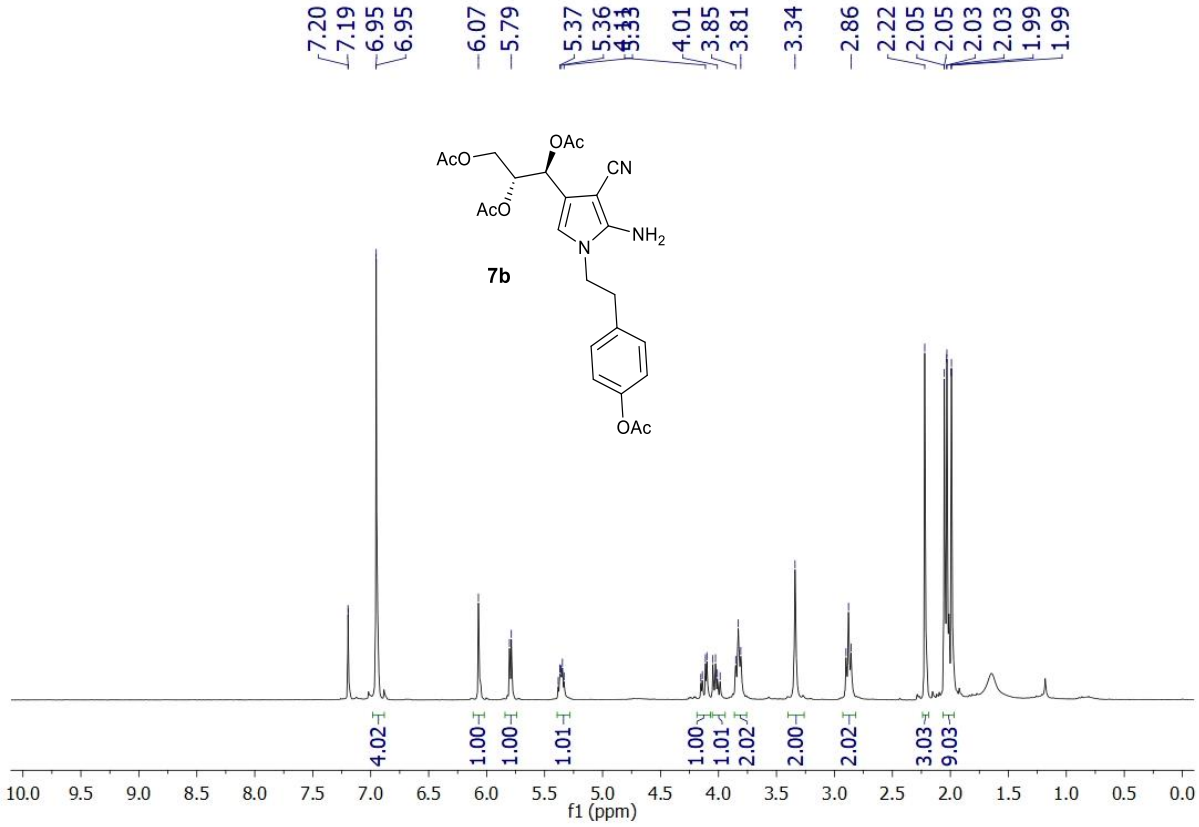
(1*S*,2*S*,3*S*)-1-(5-Amino-4-cyano-1-cyclohexyl-1*H*-pyrrol-2-yl)butane-1,2,3-triyl triacetate

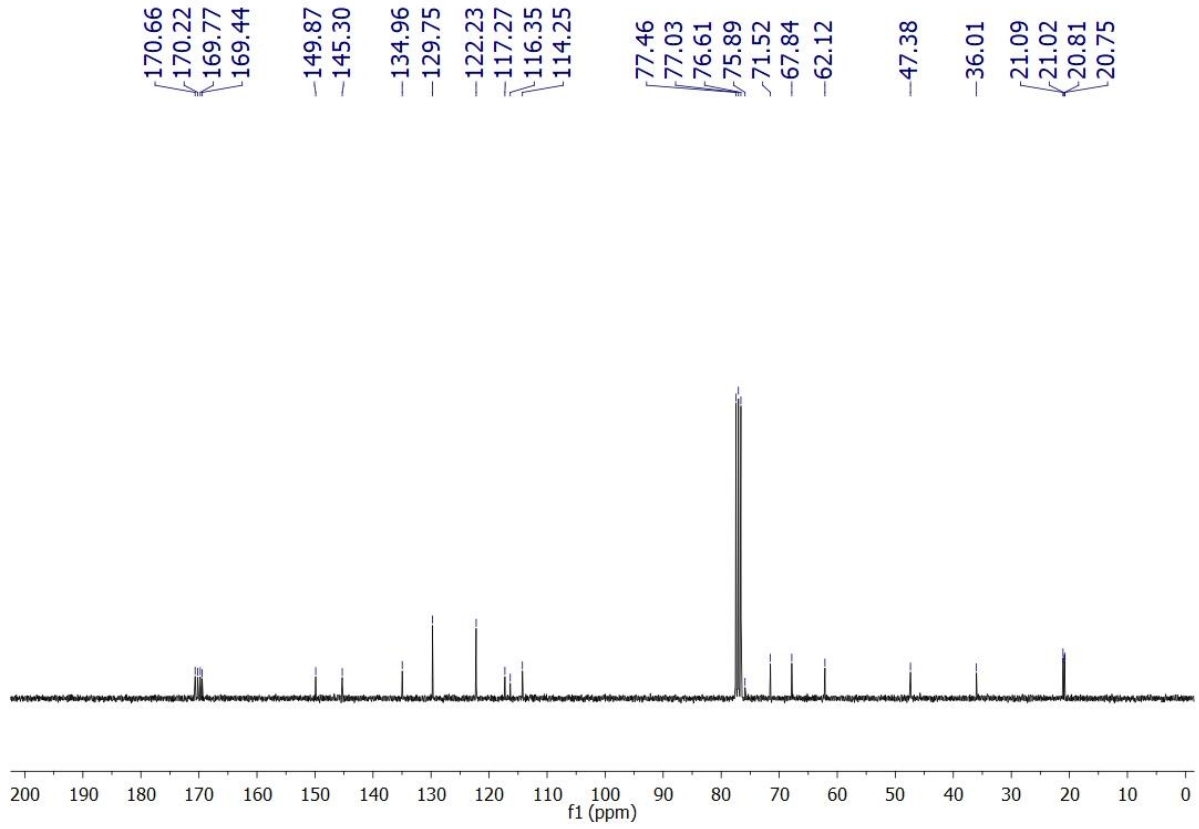


(1*S*,2*R*)-1-(5-Amino-4-cyano-1-octyl-1*H*-pyrrol-2-yl)propane-1,2,3-triyl triacetate

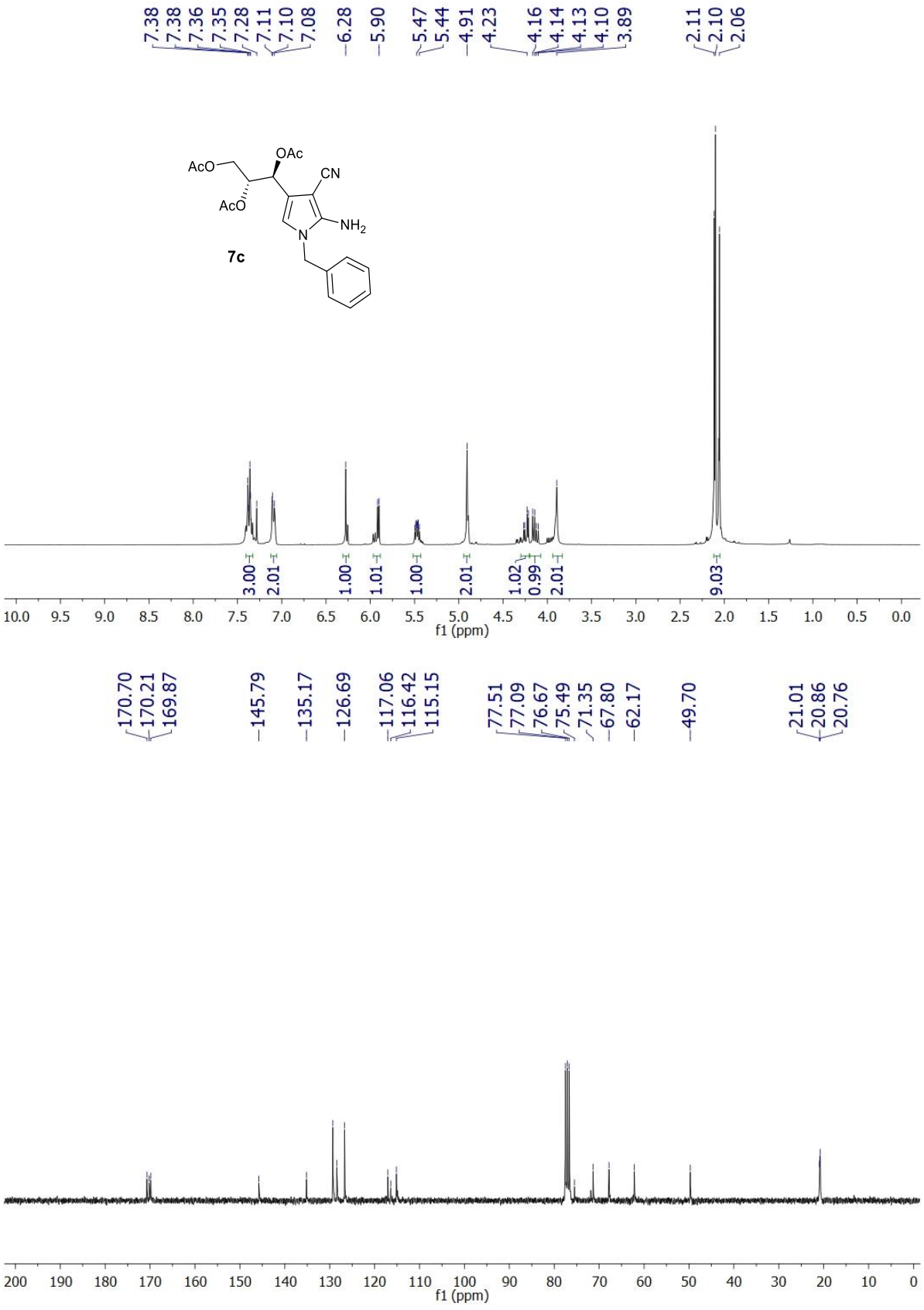


(1*S*,2*R*)-1-(1-(4-Acetoxyphenethyl)-5-amino-4-cyano-1*H*-pyrrol-2-yl)propane-1,2,3-triyl triacetate

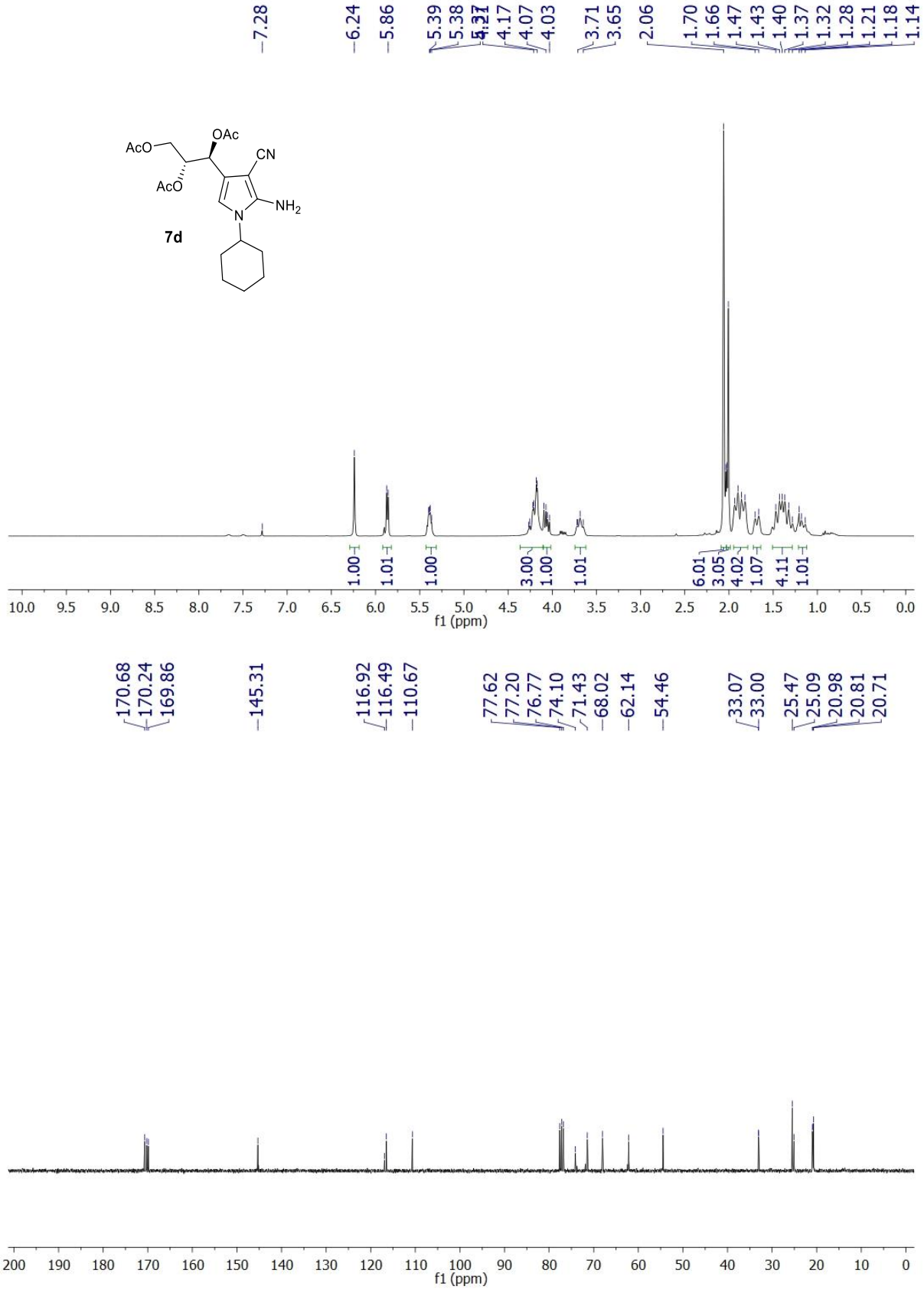




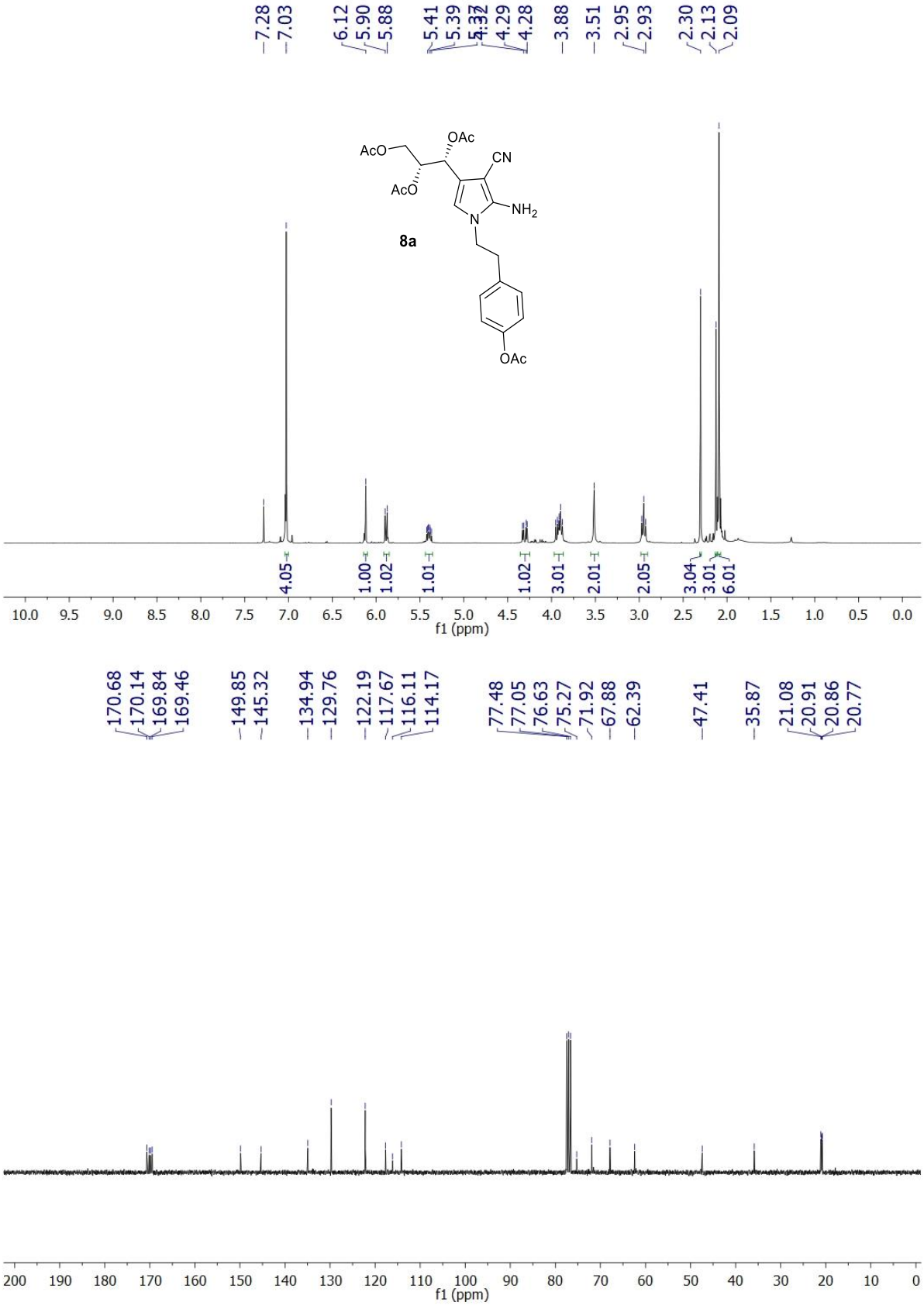
(1*S*,2*R*)-1-(5-Amino-1-benzyl-4-cyano-1*H*-pyrrol-2-yl)propane-1,2,3-triyl triacetate



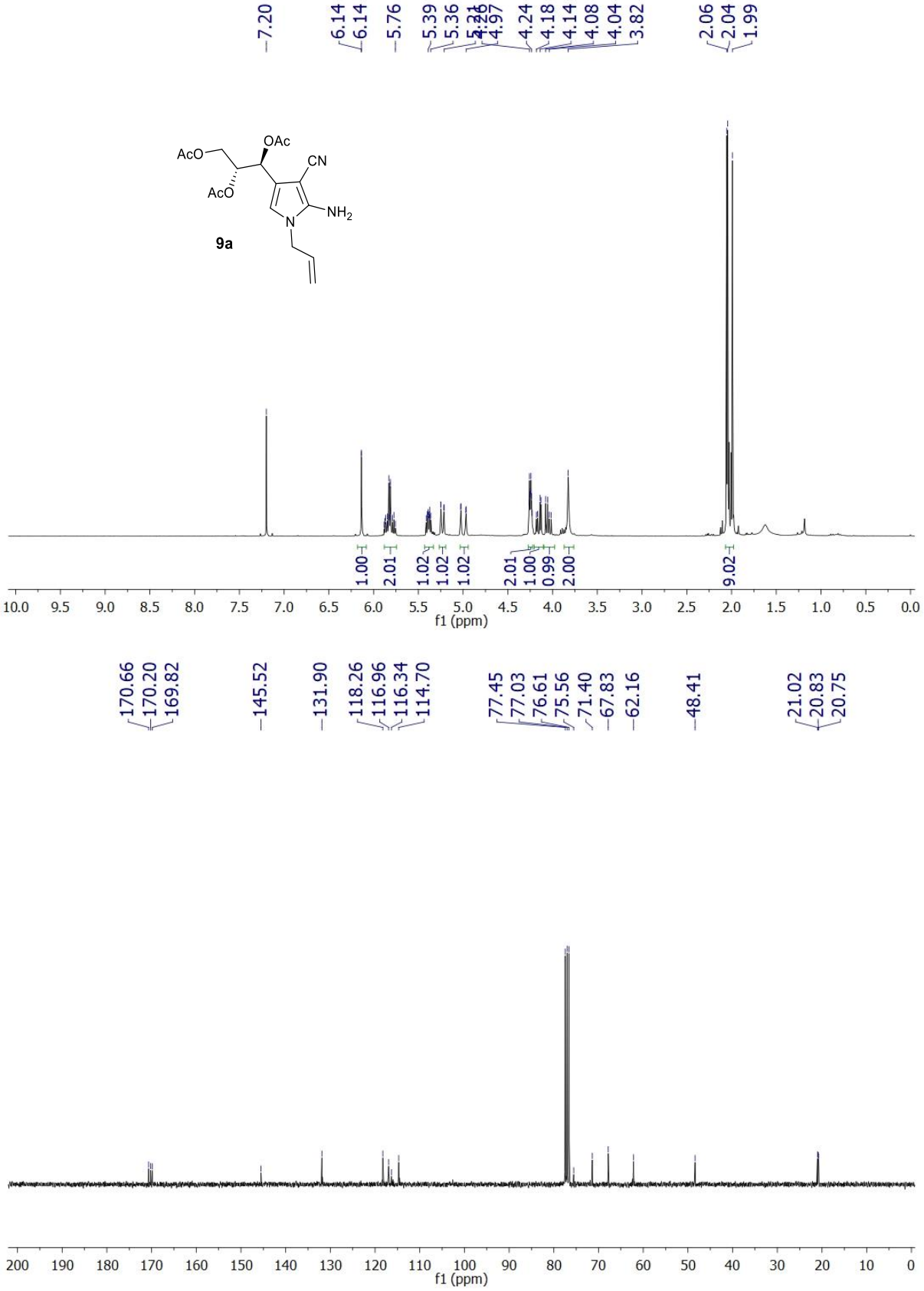
(1*S*,2*R*)-1-(5-Amino-4-cyano-1-cyclohexyl-1*H*-pyrrol-2-yl)propane-1,2,3-triyl triacetate



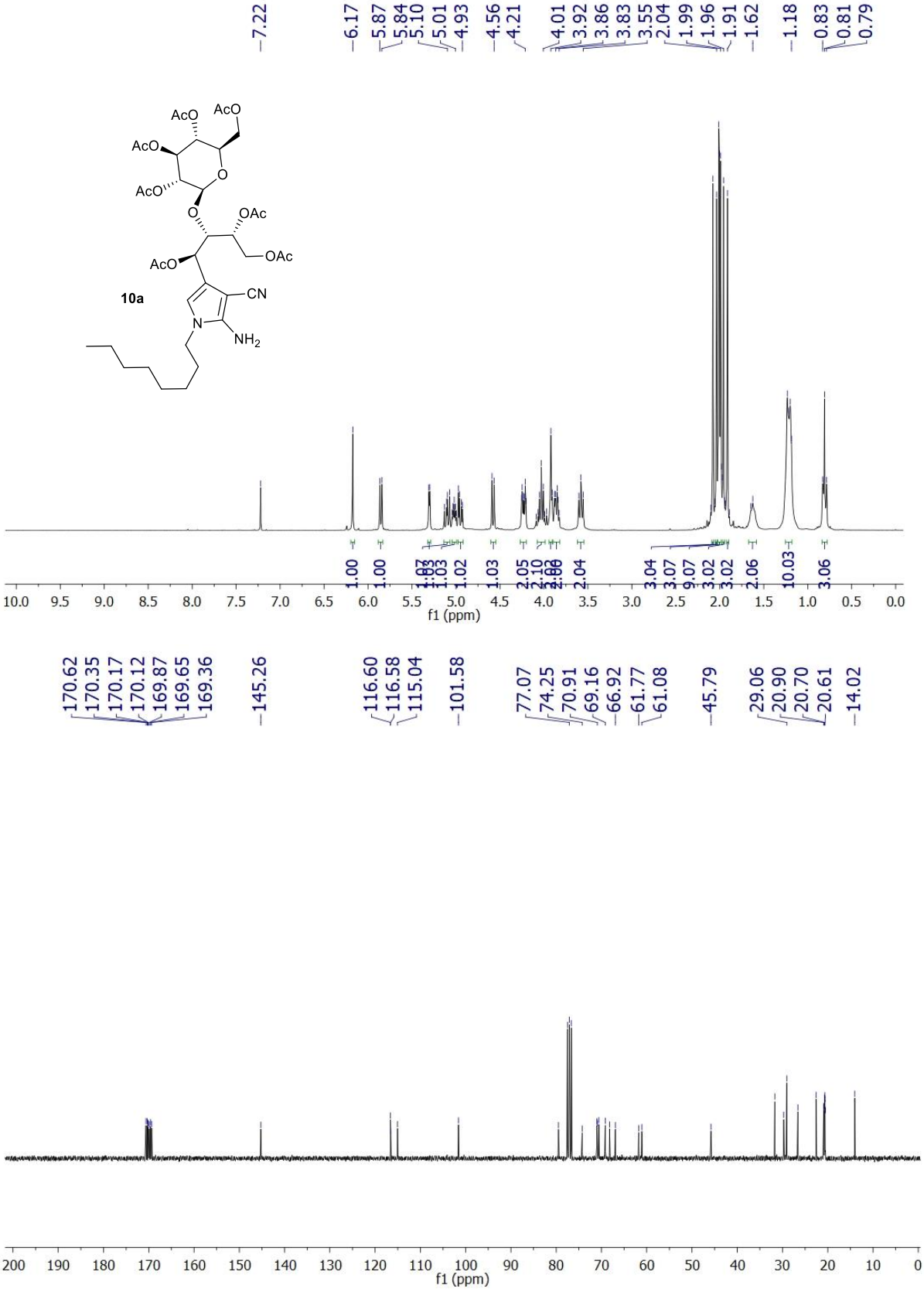
(1*R*,2*R*)-1-(1-(4-Acetoxyphenethyl)-5-amino-4-cyano-1*H*-pyrrol-2-yl)propane-1,2,3-triyl triacetate



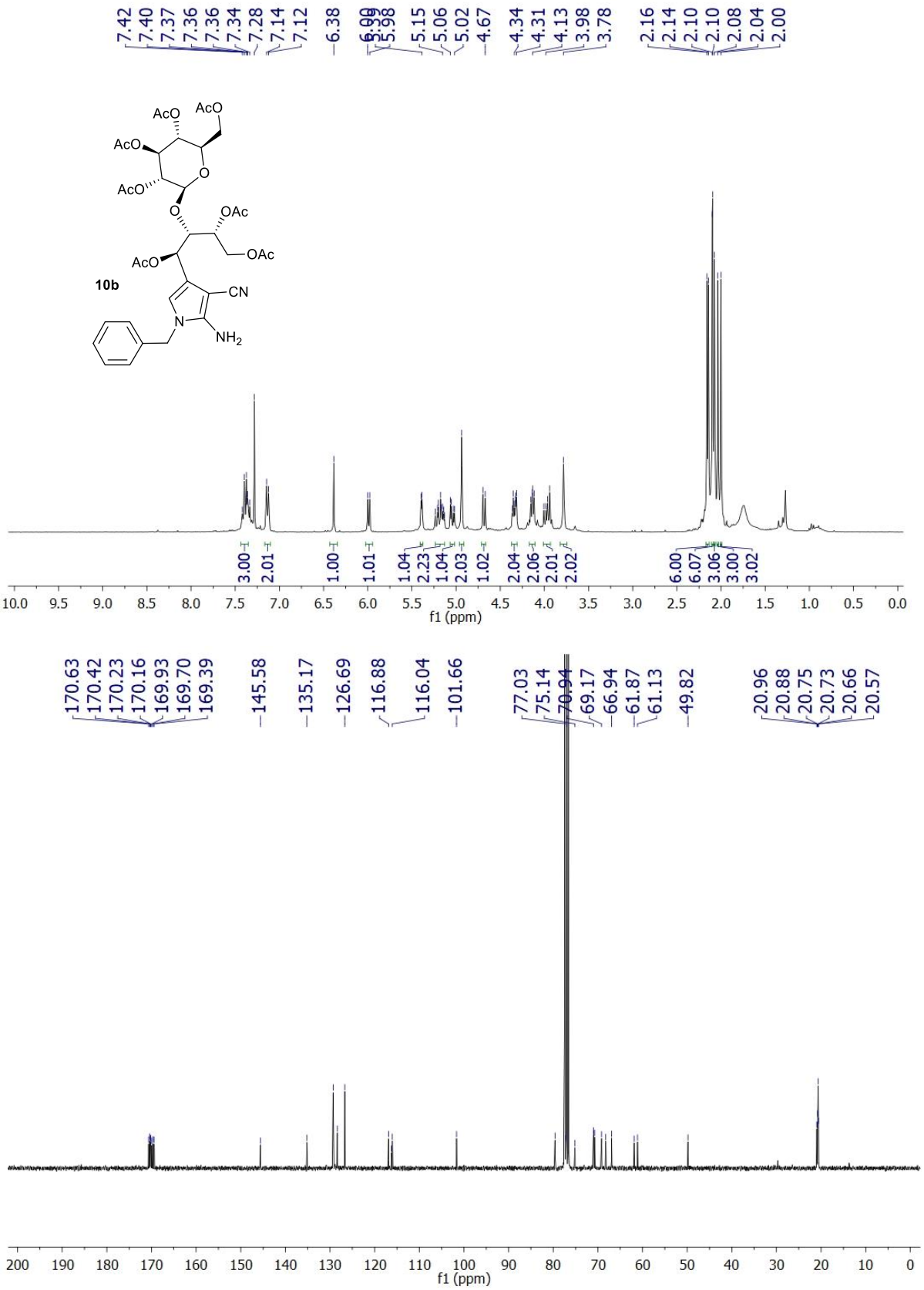
(1*S*,2*R*)-1-(1-Allyl-5-amino-4-cyano-1*H*-pyrrol-2-yl)propane-1,2,3-triyl triacetate



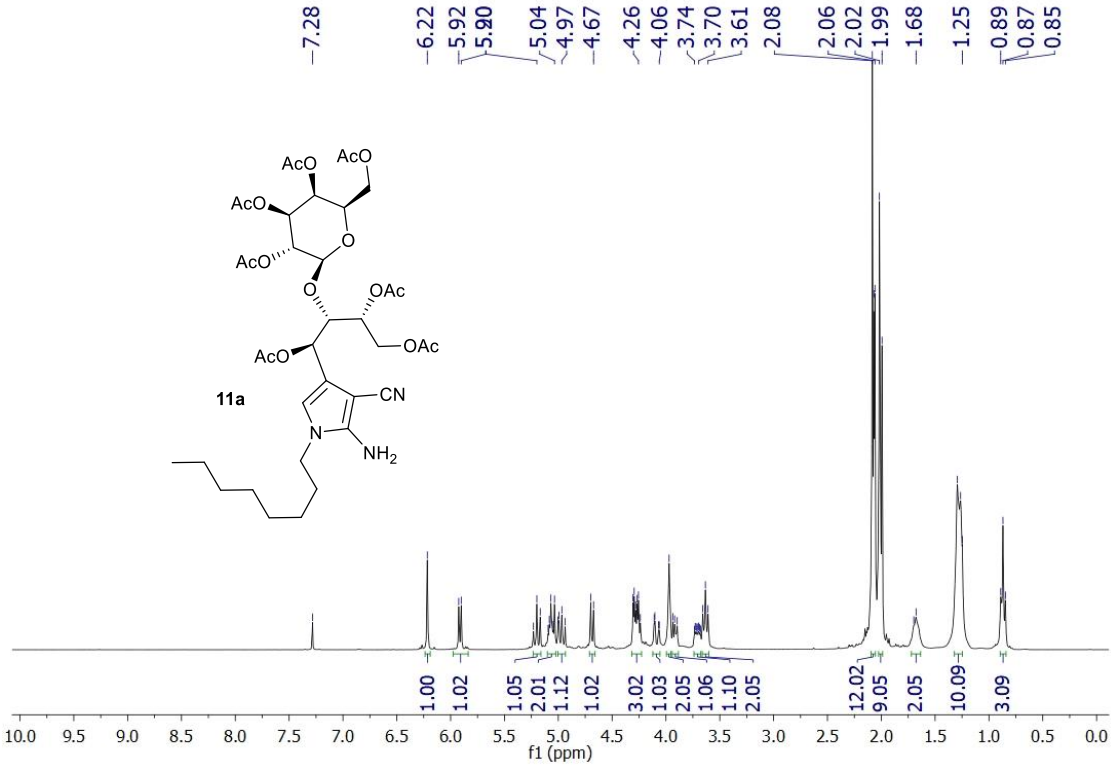
(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-(((1*R*,2*S*,3*R*)-1,3,4-triacetoxy-1-(5-amino-4-cyano-1-octyl-1*H*-pyrrol-2-yl)butan-2-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate

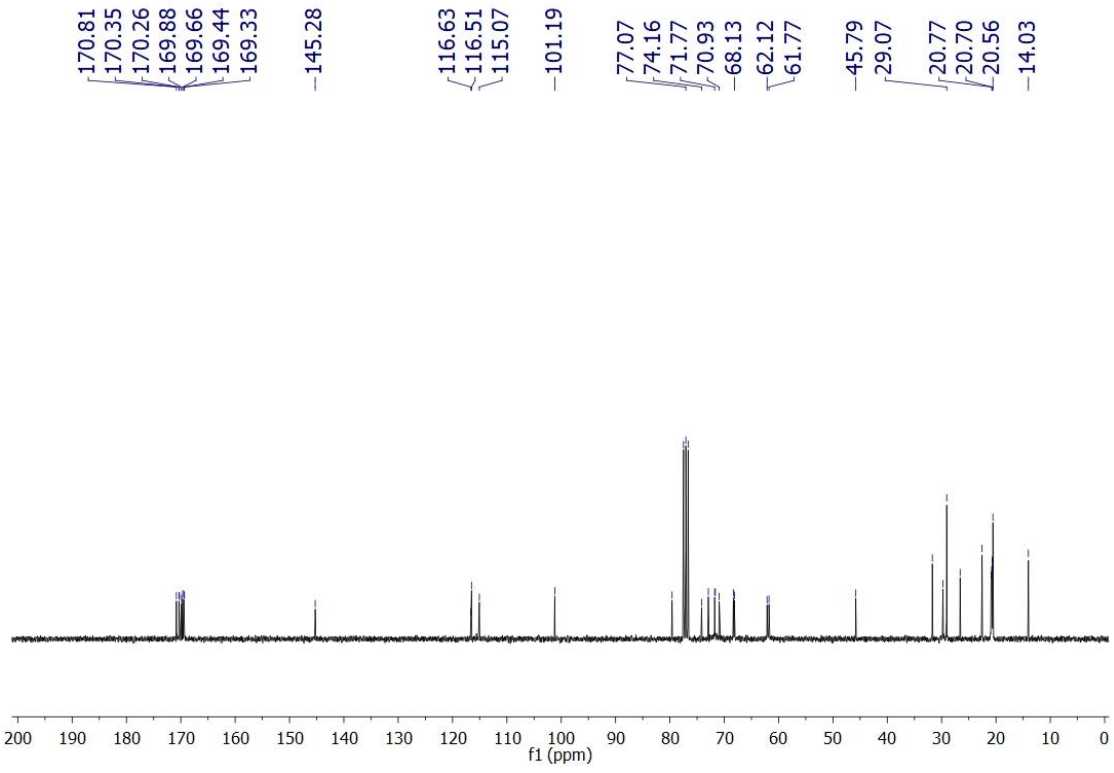


(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-(((1*R*,2*S*,3*R*)-1,3,4-triacetoxy-1-(5-amino-1-benzyl-4-cyano-1*H*-pyrrol-3-yl)butan-2-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate

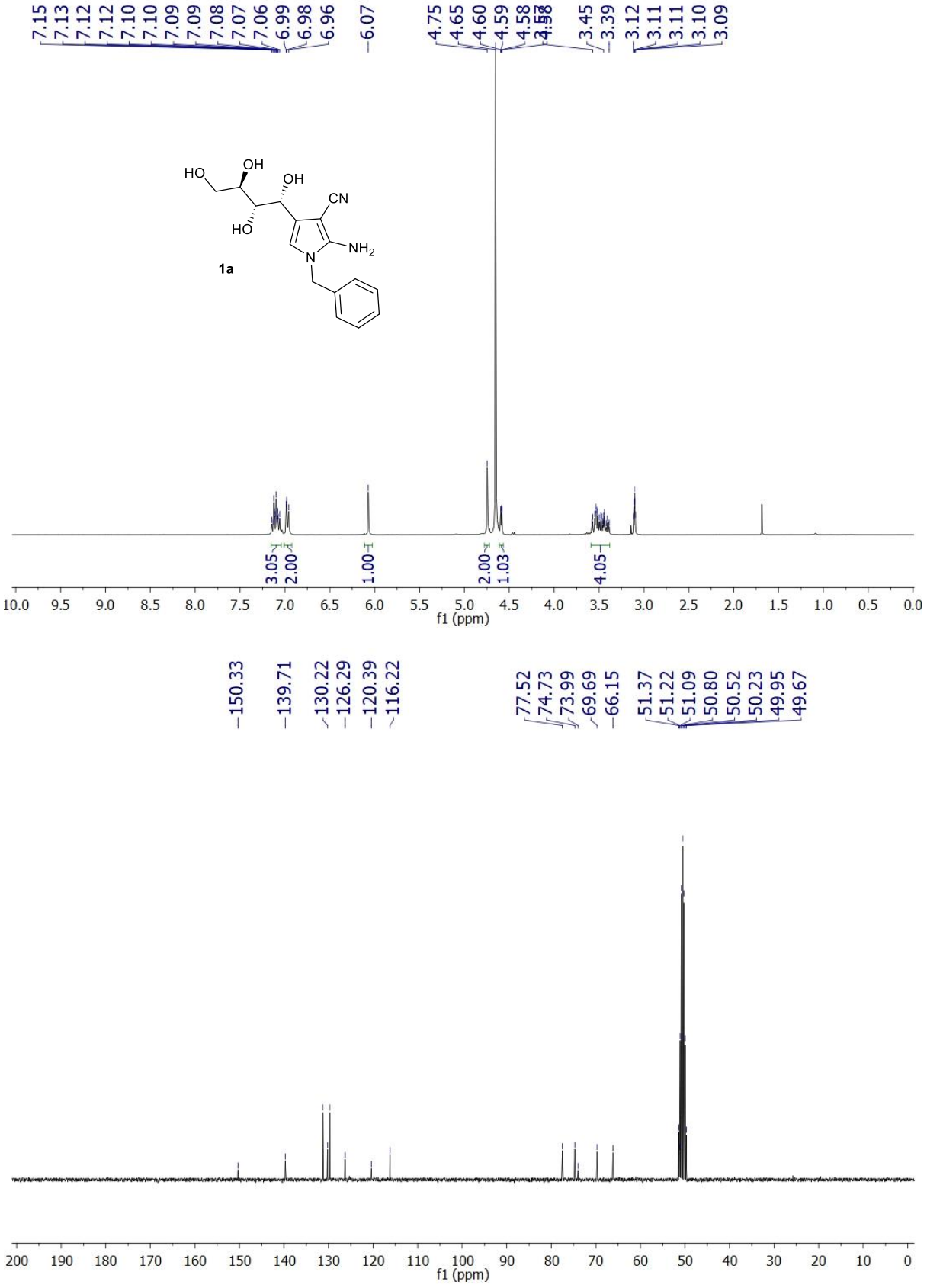


(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-(((1*R*,2*S*,3*R*)-1,3,4-triacetoxy-1-(5-amino-4-cyano-1-octyl-1*H*-pyrrol-3-yl)butan-2-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate

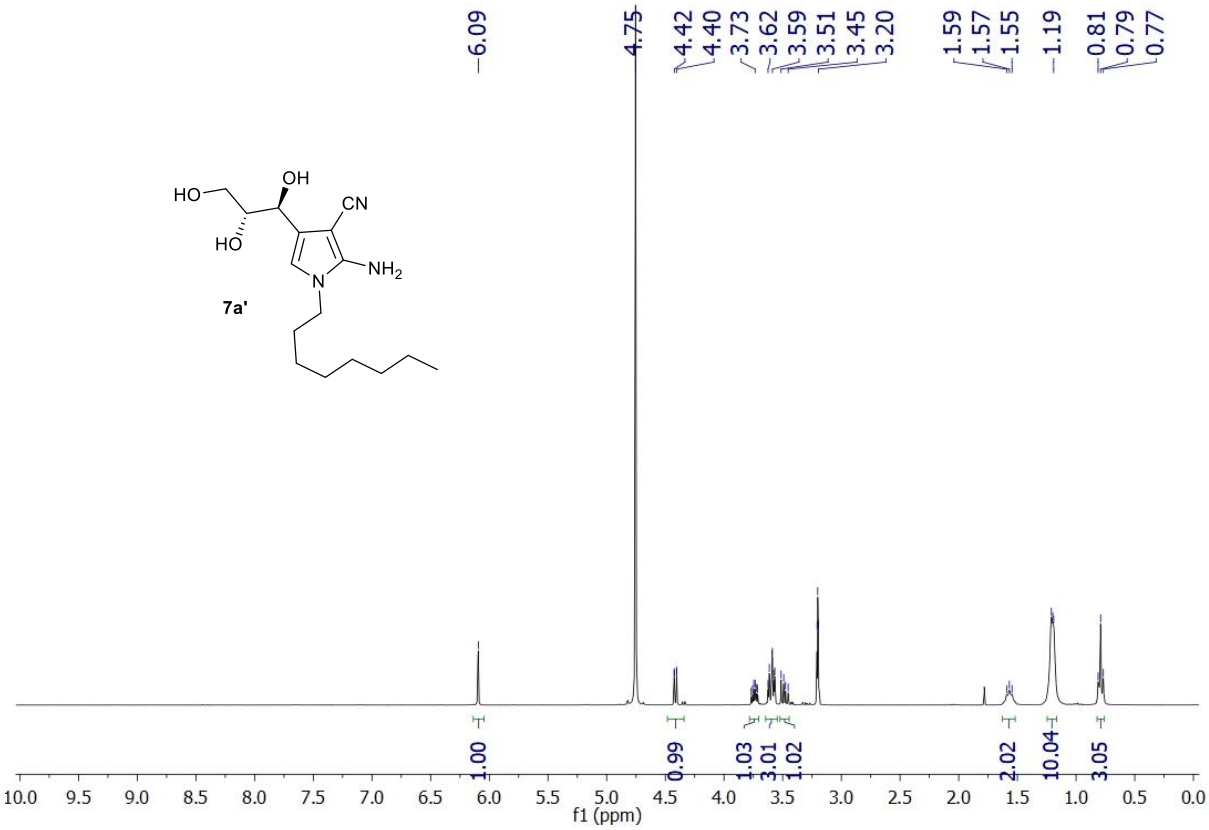


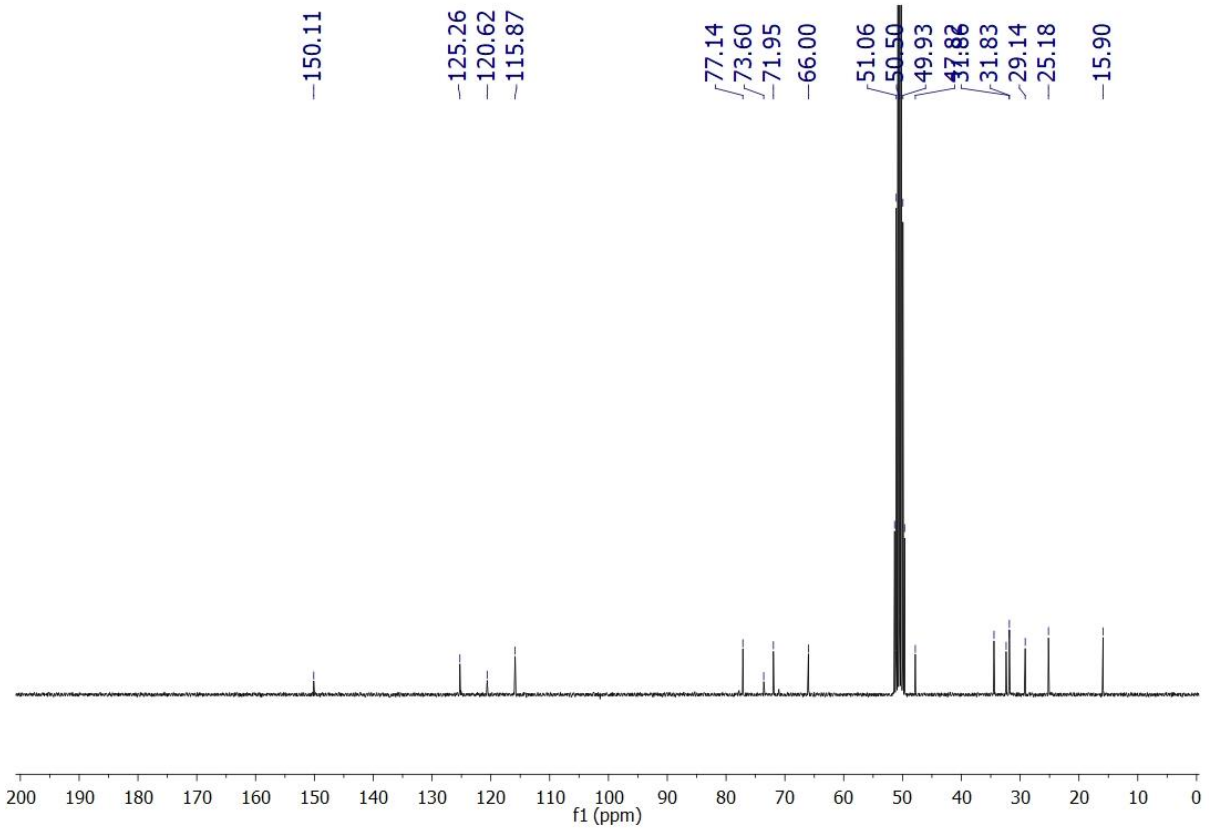


2-Amino-1-benzyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

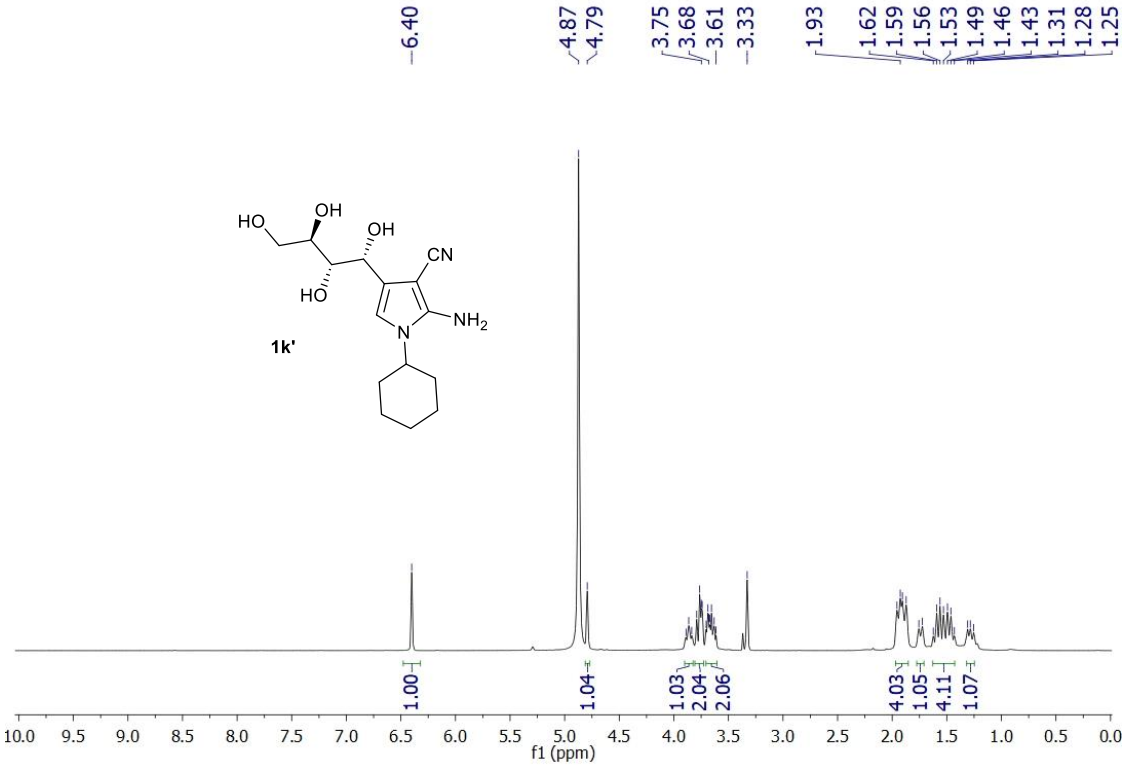


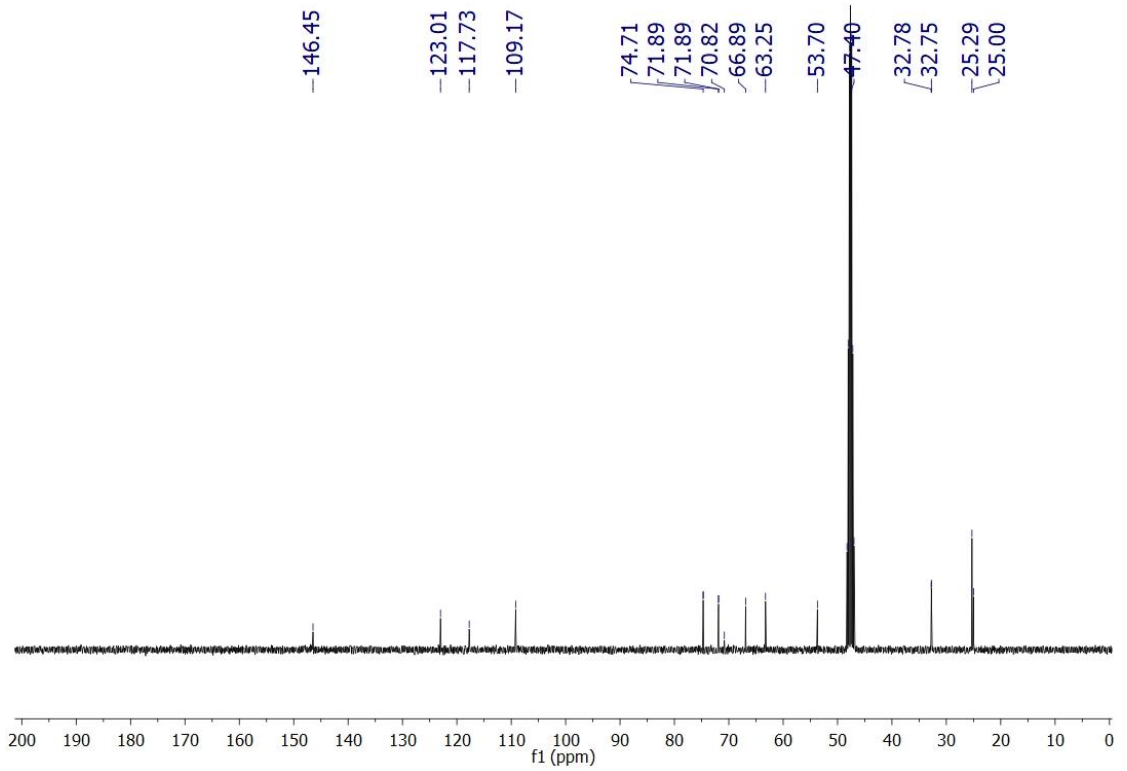
2-Amino-1-octyl-4-((1*S*,2*R*)-1,2,3-trihydroxypropyl)-1*H*-pyrrole-3-carbonitrile



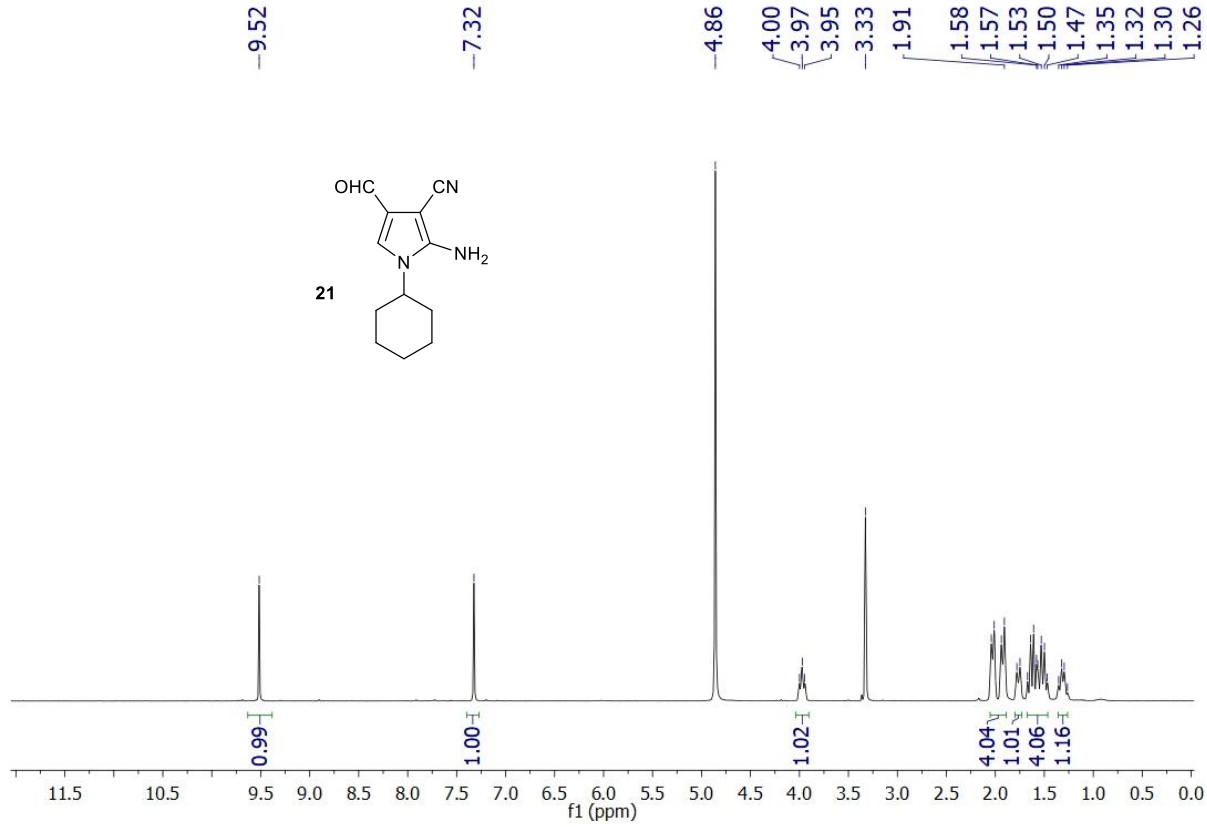


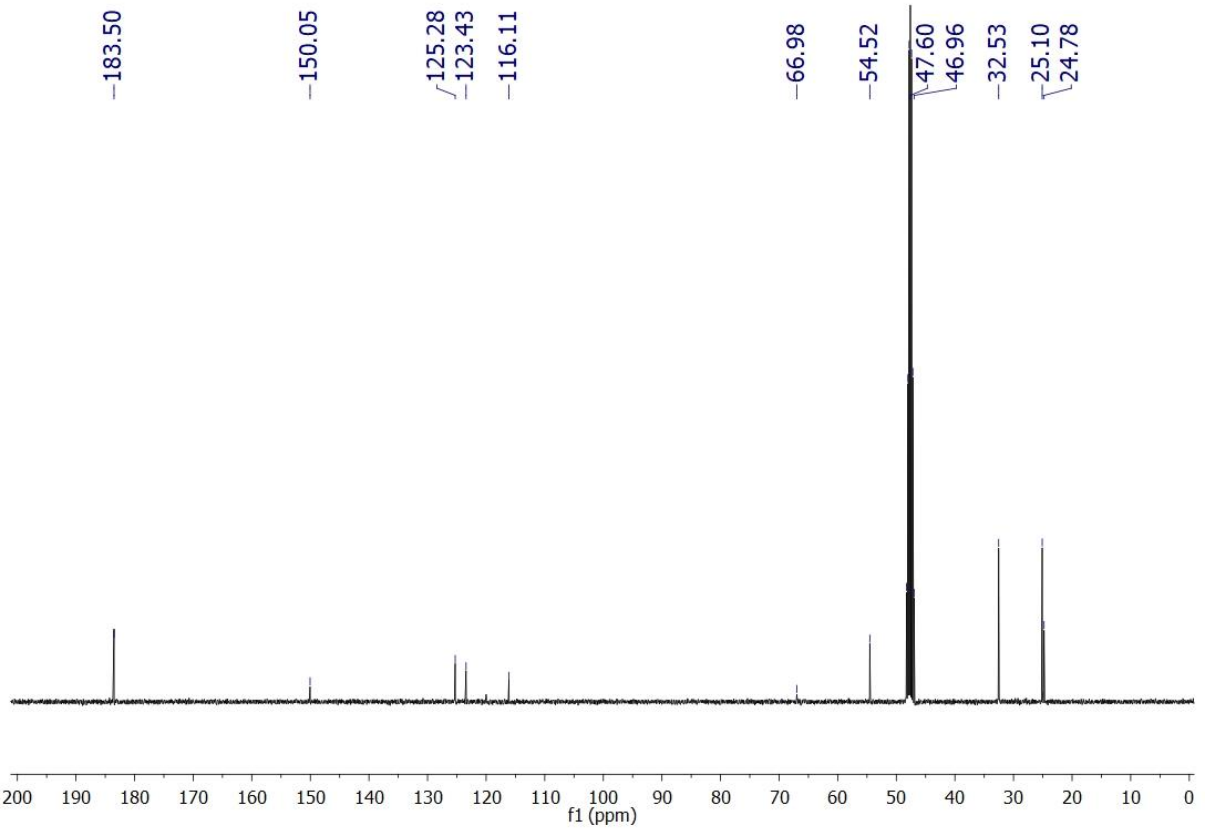
2-Amino-1-cyclohexyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



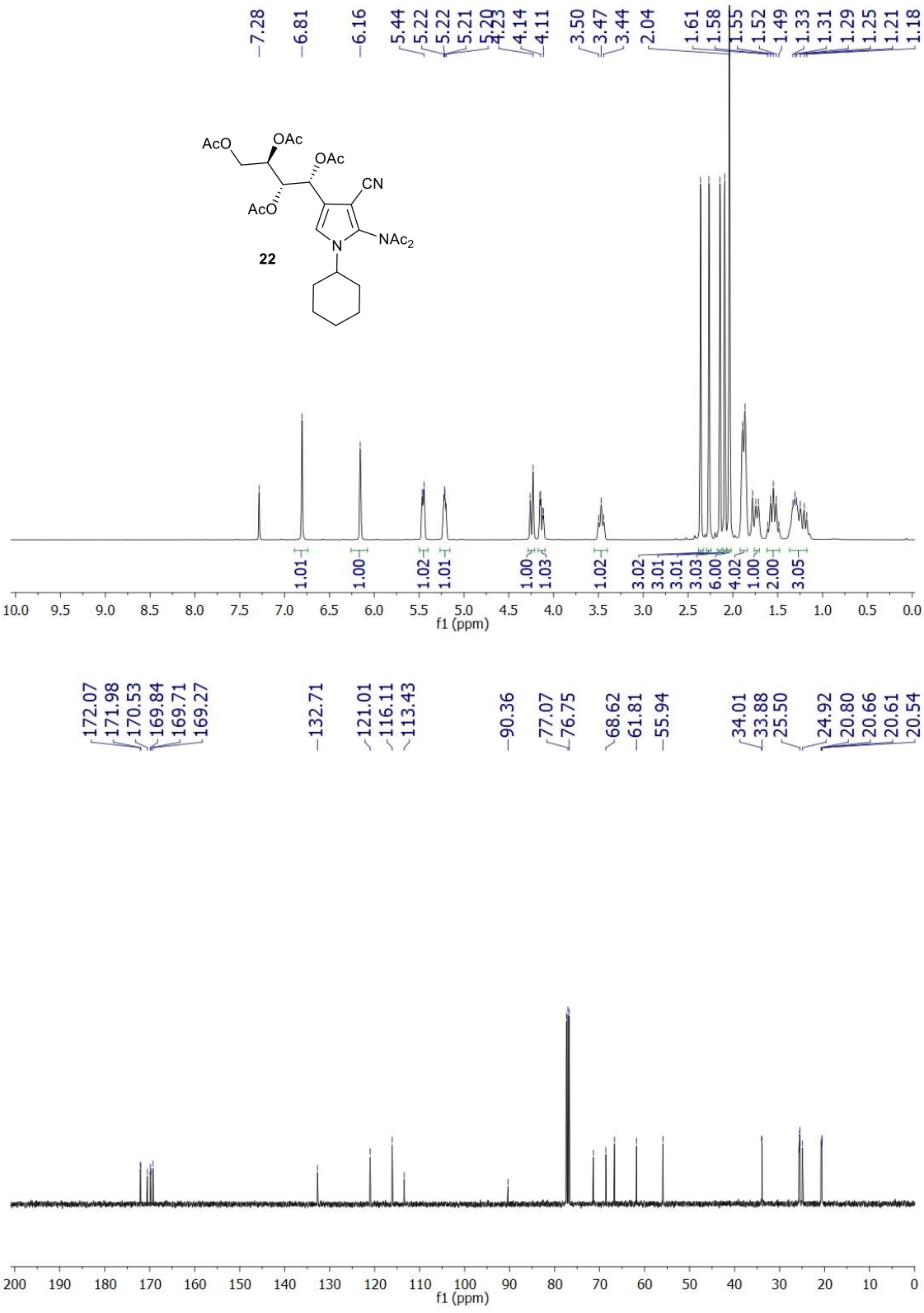


2-Amino-1-cyclohexyl-4-formyl-1*H*-pyrrole-3-carbonitrile

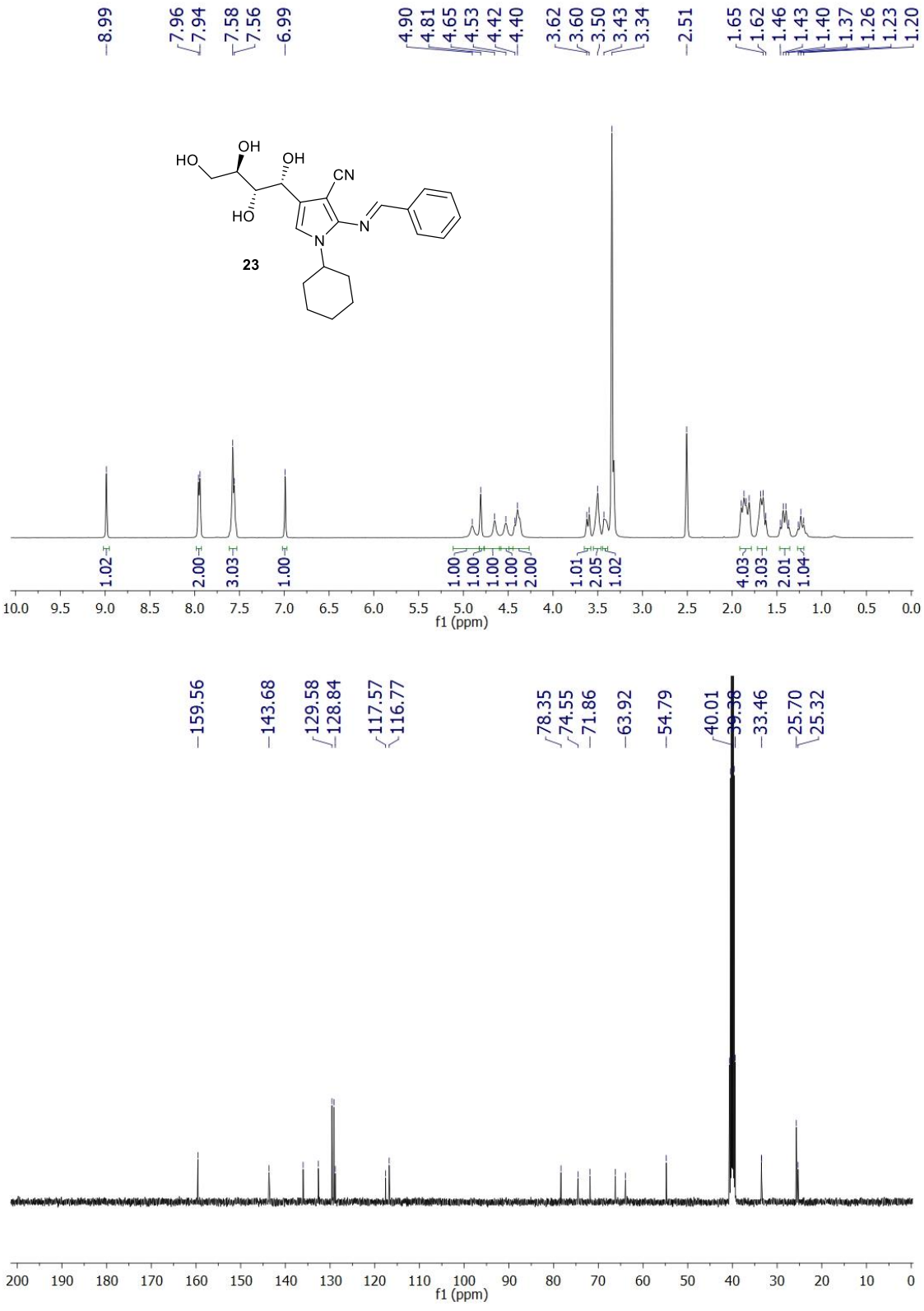




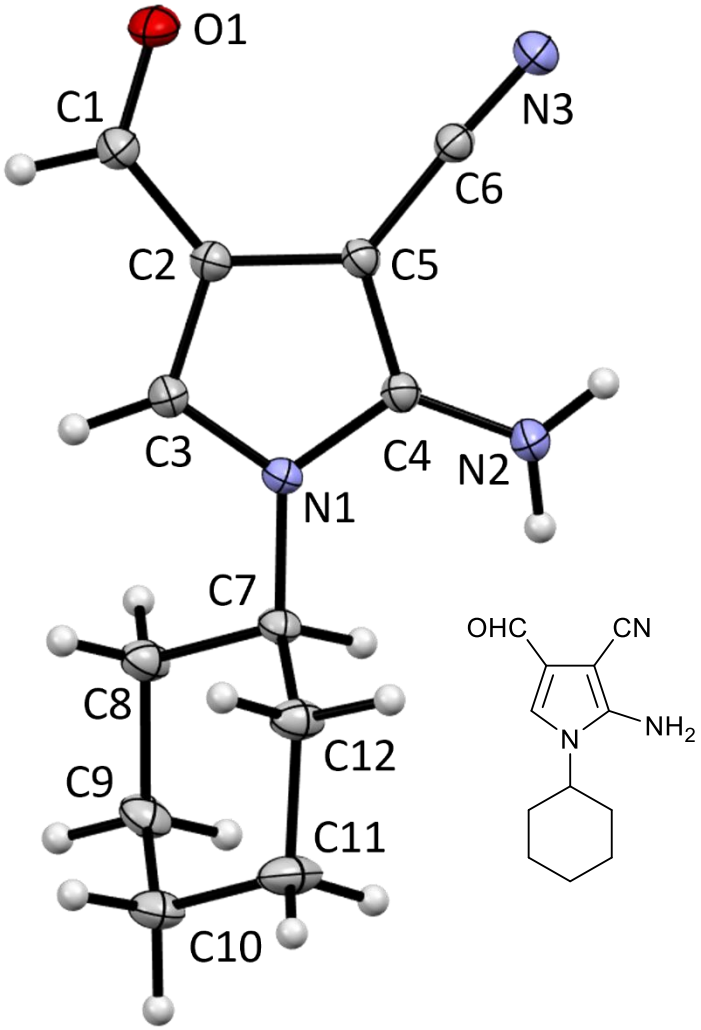
(1*R*,2*S*,3*R*)-1-(5-(*N*-Acetylacetamido)-4-cyano-1-cyclohexyl-1*H*-pyrrol-3-yl)butane-1,2,3,4-tetrayl tetraacetate



2-(((*E*)-Benzylidene)amino)-1-cyclohexyl-4-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



3.2 Single-crystal XRD of pyrrole 21



(displacement elliposoids are drawn at the 50% probability level).

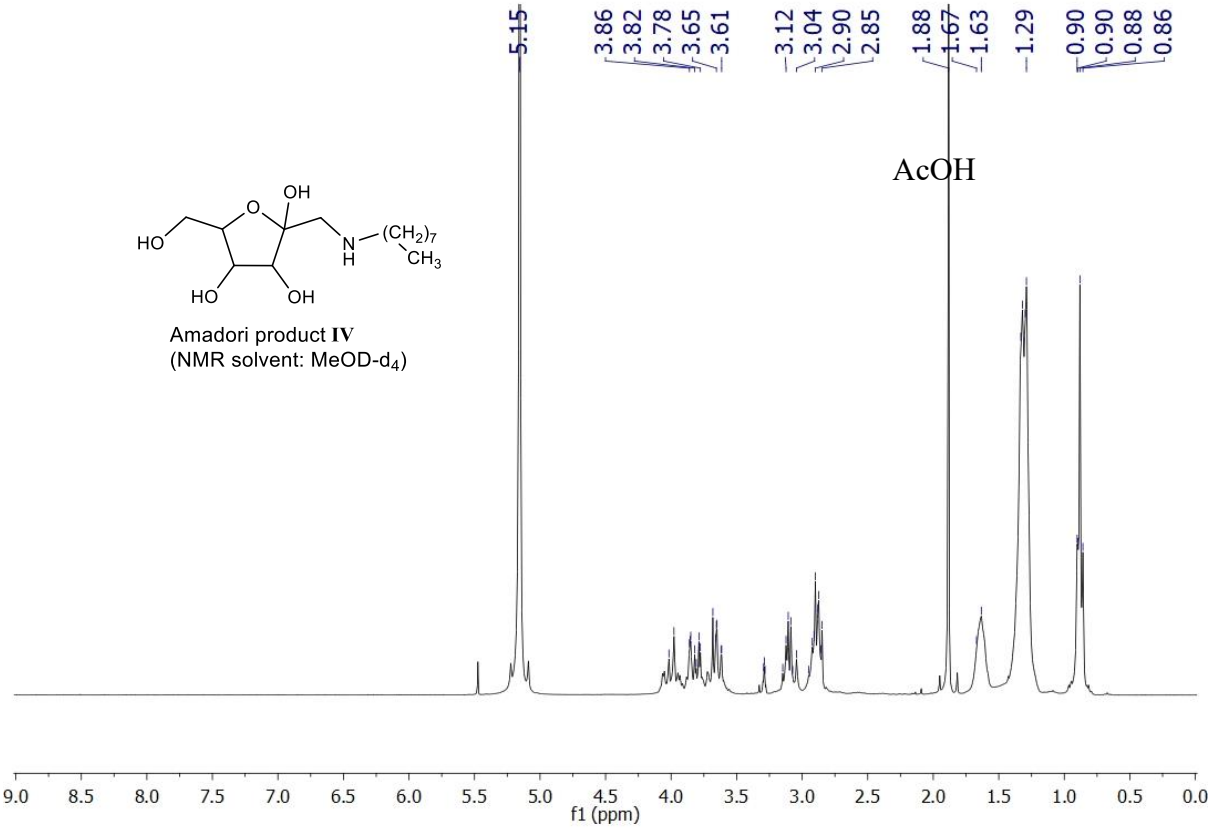
CCDC Deposition number: 2154828

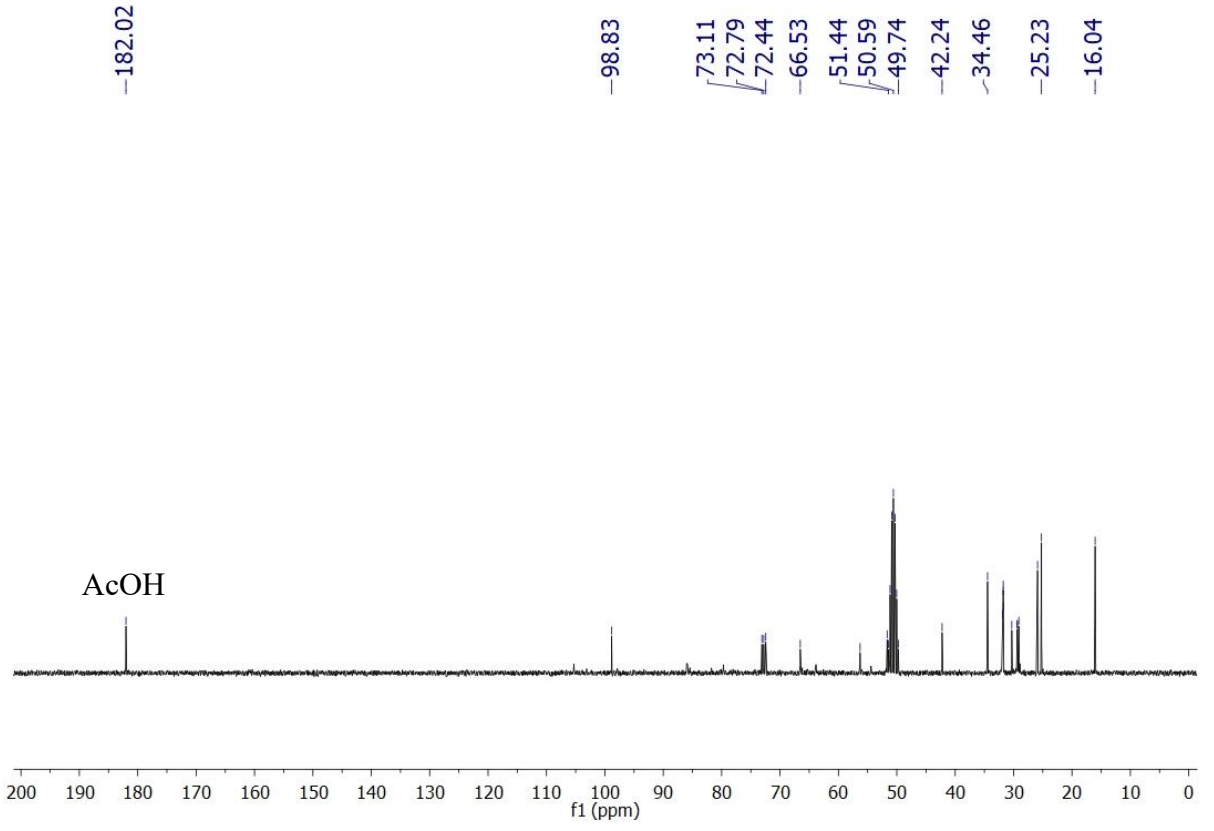
DOI: 10.5517/ccdc.csd.cc2bb8lk

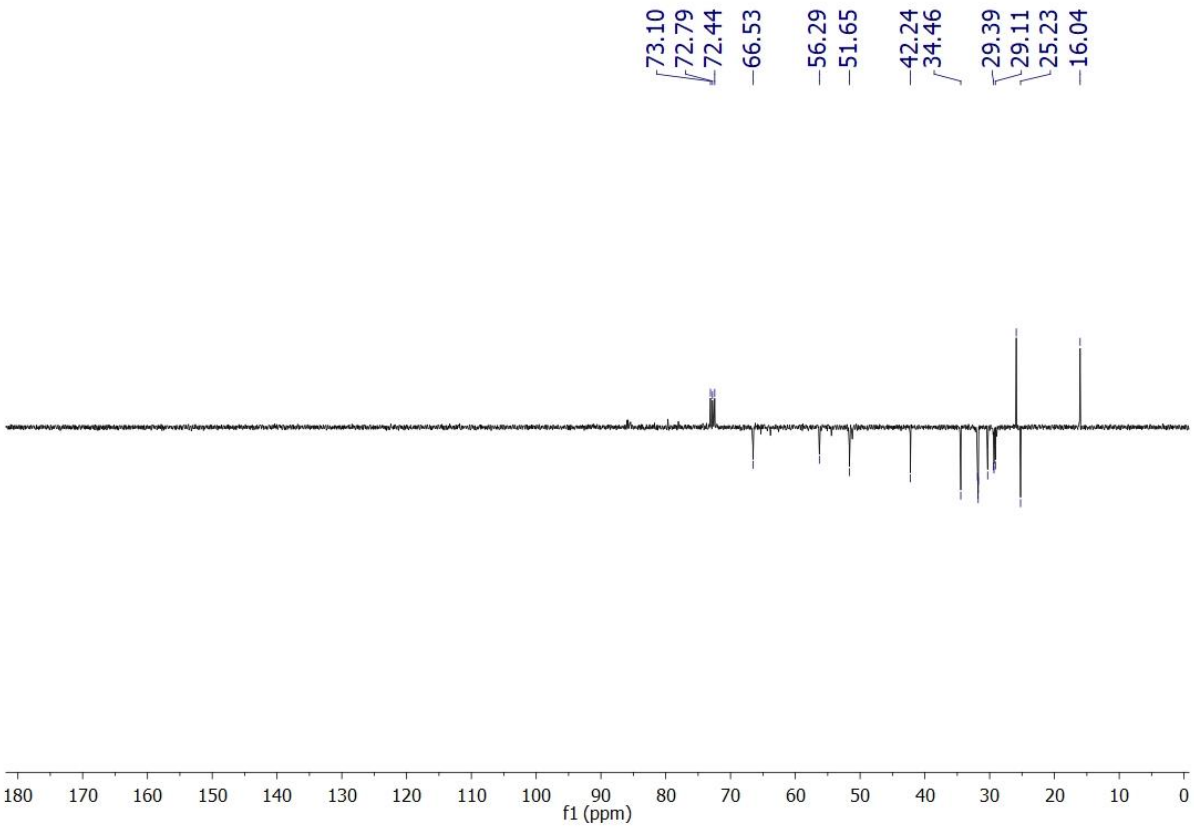
Table 3.1: Crystal data and structure refinement for product **21** (CCDC 2154828)

Empirical formula	$C_{12}H_{15}N_3O$
Formula weight	217.27
Temperature	100(2) K
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 9.4347(6) Å a= 91.358(3)°. b = 10.7636(6) Å b= 103.513(3)°. c = 11.5827(7) Å g = 94.048(3)°.
Volume	1139.84(12) $Å^3$
Z	4
Density (calculated)	1.266 Mg/m^3
F(000)	464
Reflections collected	41188
Independent reflections	12251 [R(int) = 0.1031]
Max. and min. transmission	0.9830 and 0.9770
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0719, wR2 = 0.1488
R indices (all data)	R1 = 0.1642, wR2 = 0.1821

3.3 1H NMR, 13C NMR and 13C DEPT135 NMR spectra of intermediate IV (with AcOH)

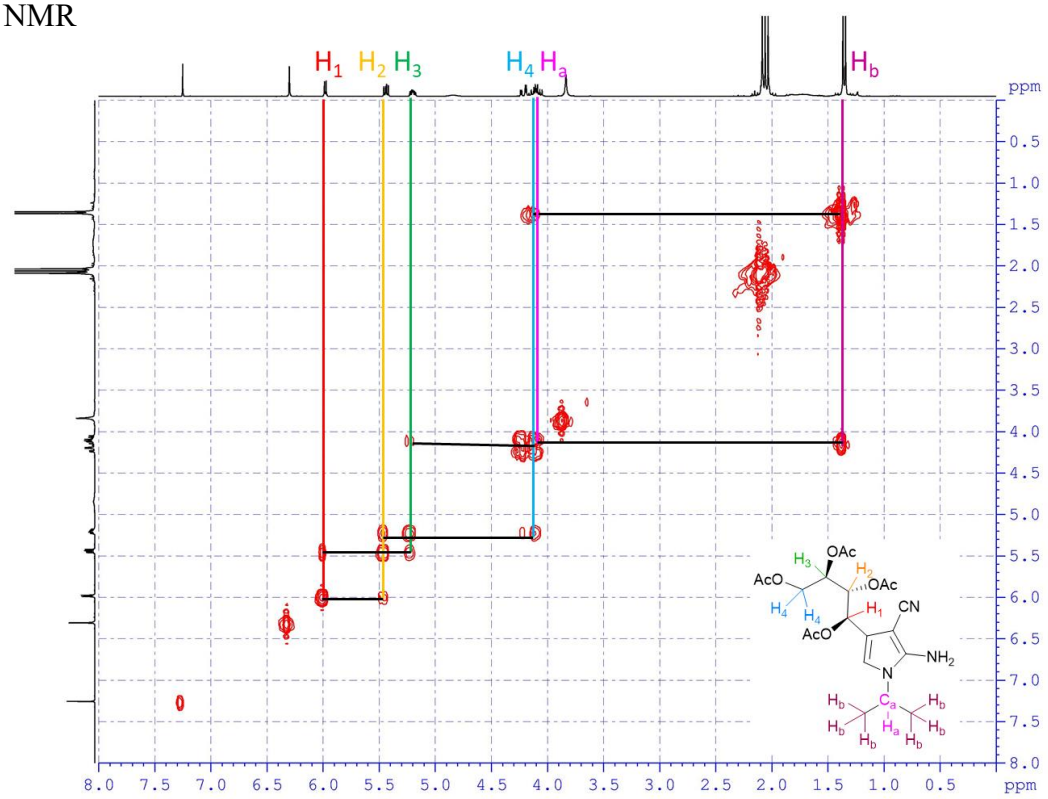




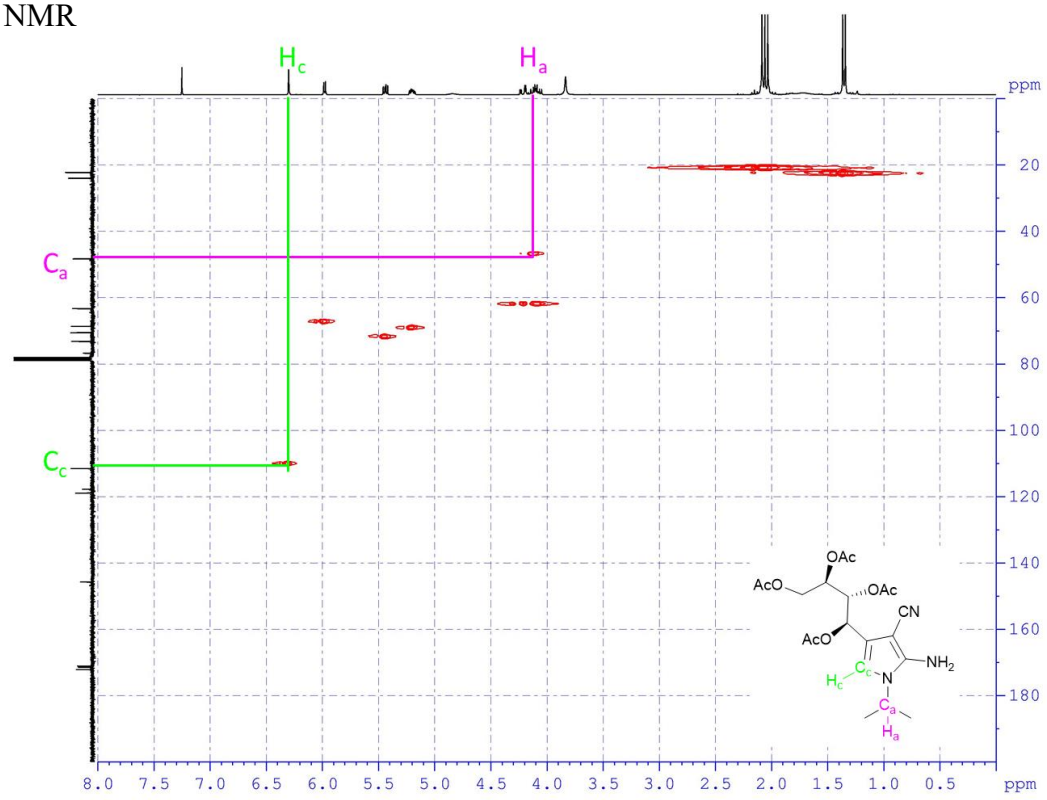

73.10
72.79
72.44
66.53
56.29
51.65
42.24
34.46
29.39
29.11
25.23
16.04
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

3.5 2D-NMR spectra for product 1j

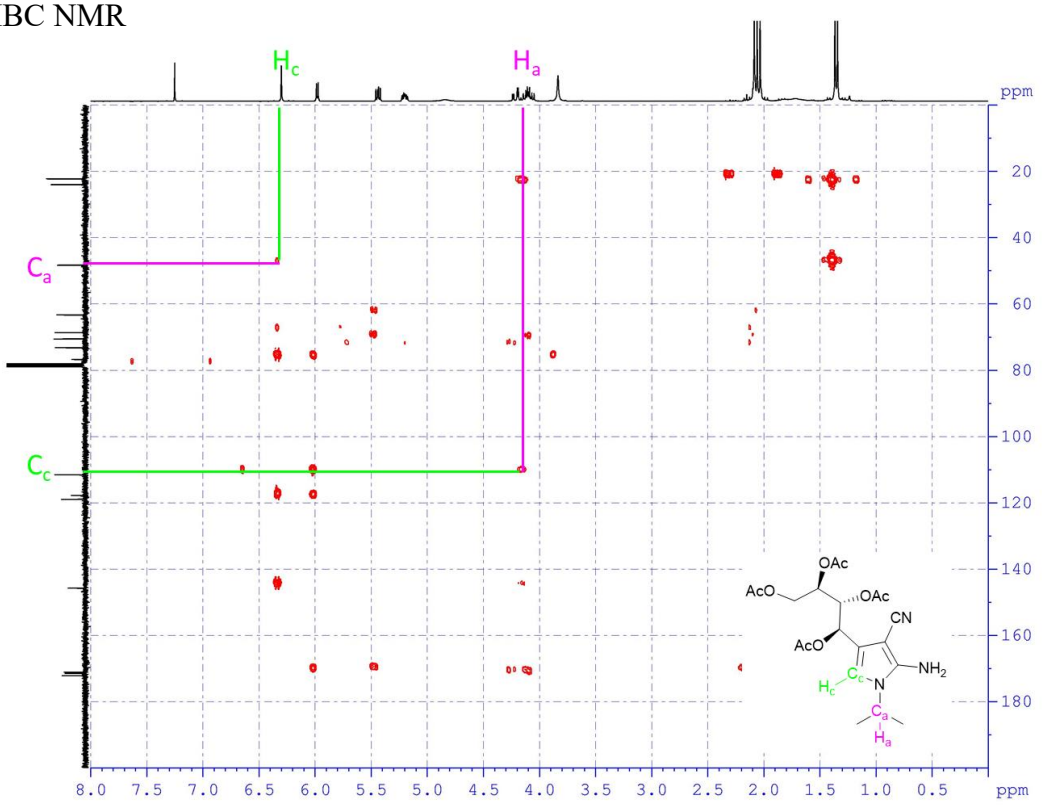
COSY NMR



HSQC NMR

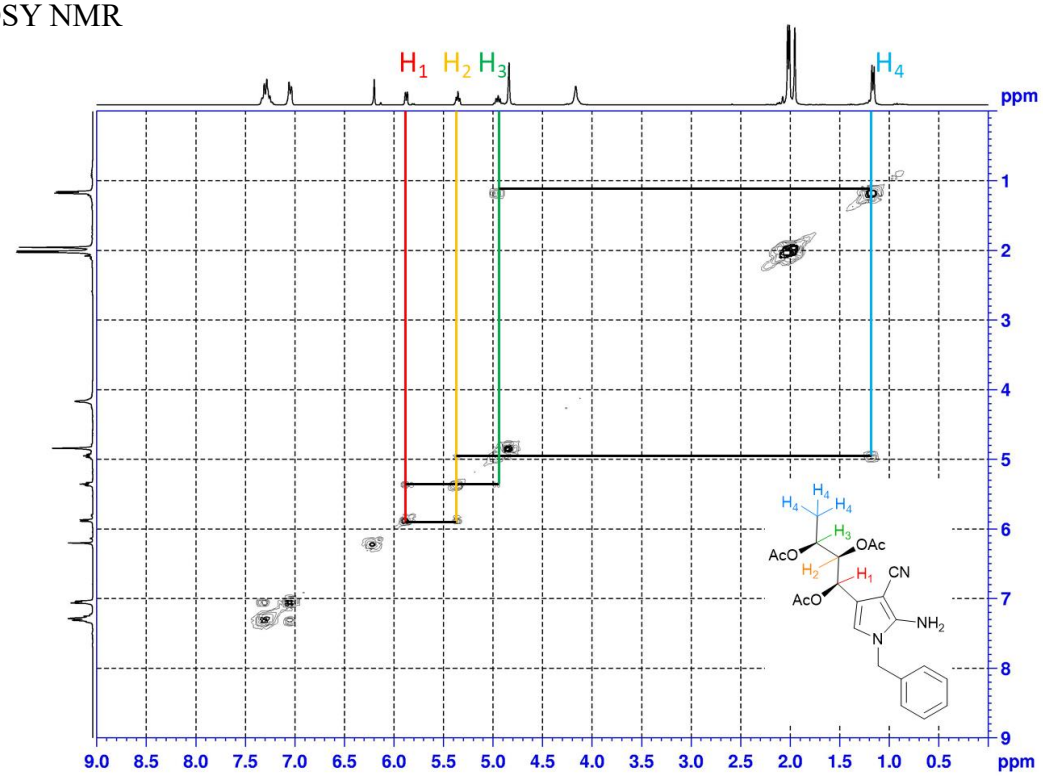


HMBC NMR

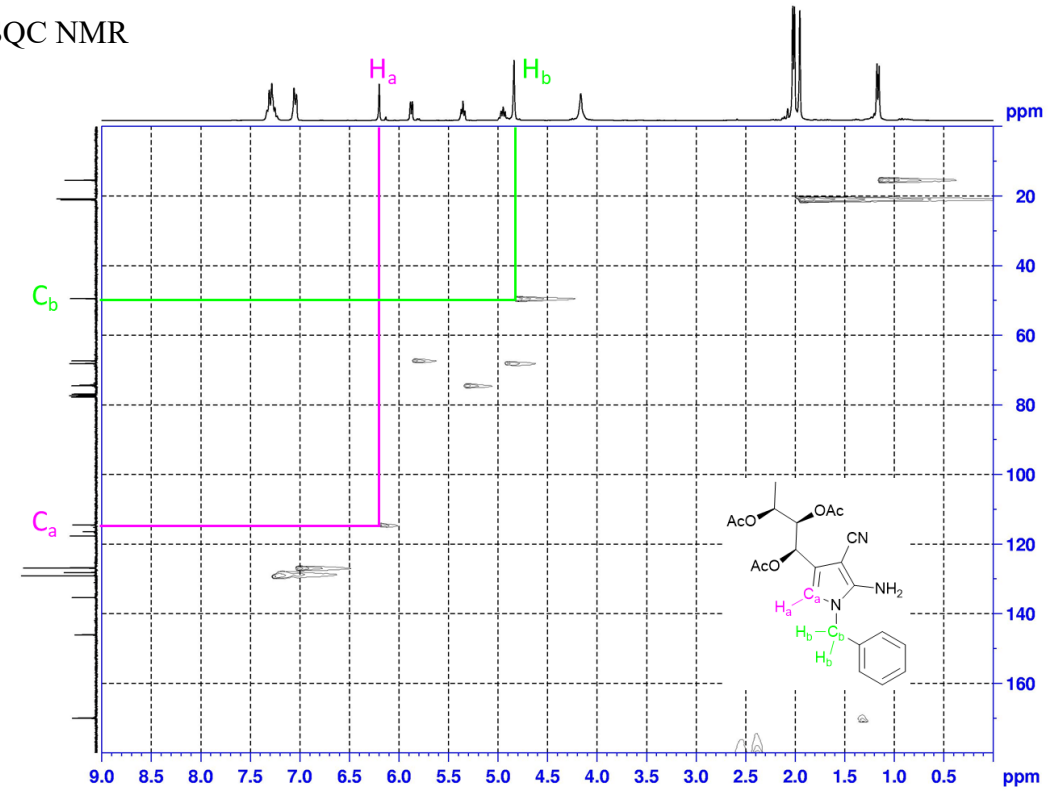

Hc
Ha
Ca
Cc
ppm
20
40
60
80
100
120
140
160
180
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm
OAc
AcO
OAc
CN
AcO
NH2
Hc
Cc
N
Ca
Ha

3.6 2D-NMR spectra for product 6d

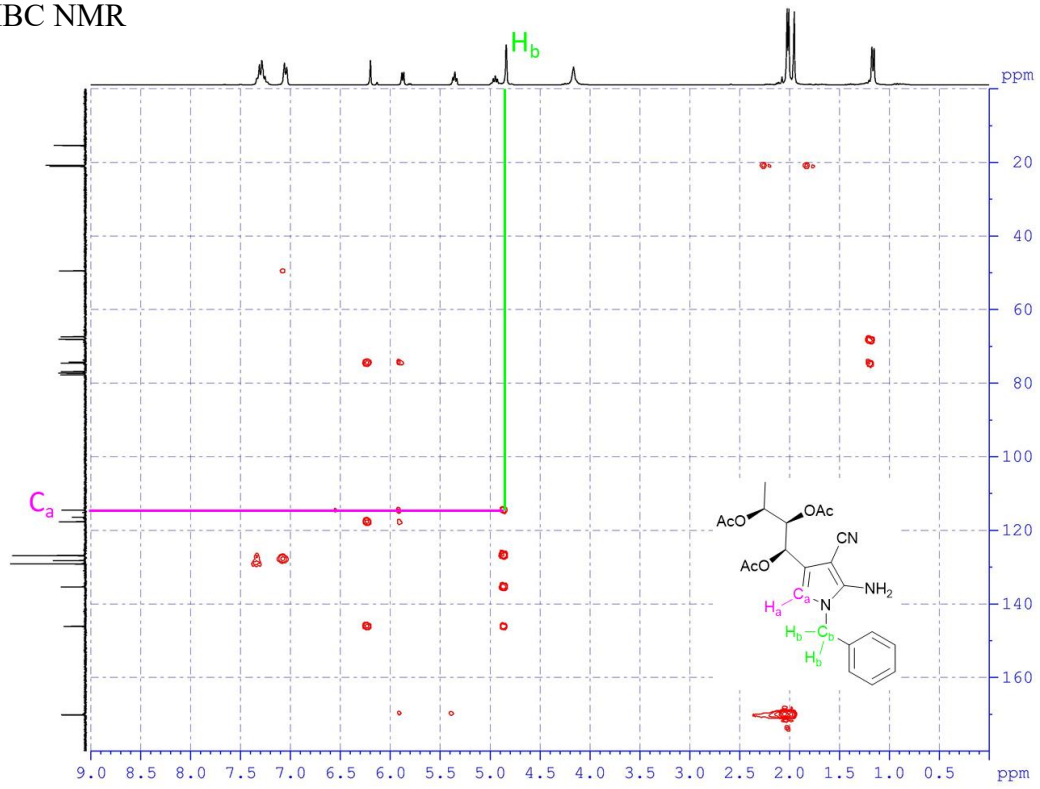
COSY NMR



HSQC NMR

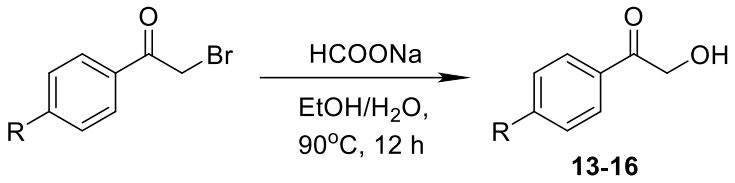


HMBC NMR


Hb
Ca
ppm
20
40
60
80
100
120
140
160
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm
AcO
OAc
AcO
CN
NH2
Ha
Ca
N
Hb
Cb
Hb

4. Supporting Information for Chapter 5

4.1 General Procedure 1: Preparation of substituted phenacyl alcohol 13-16



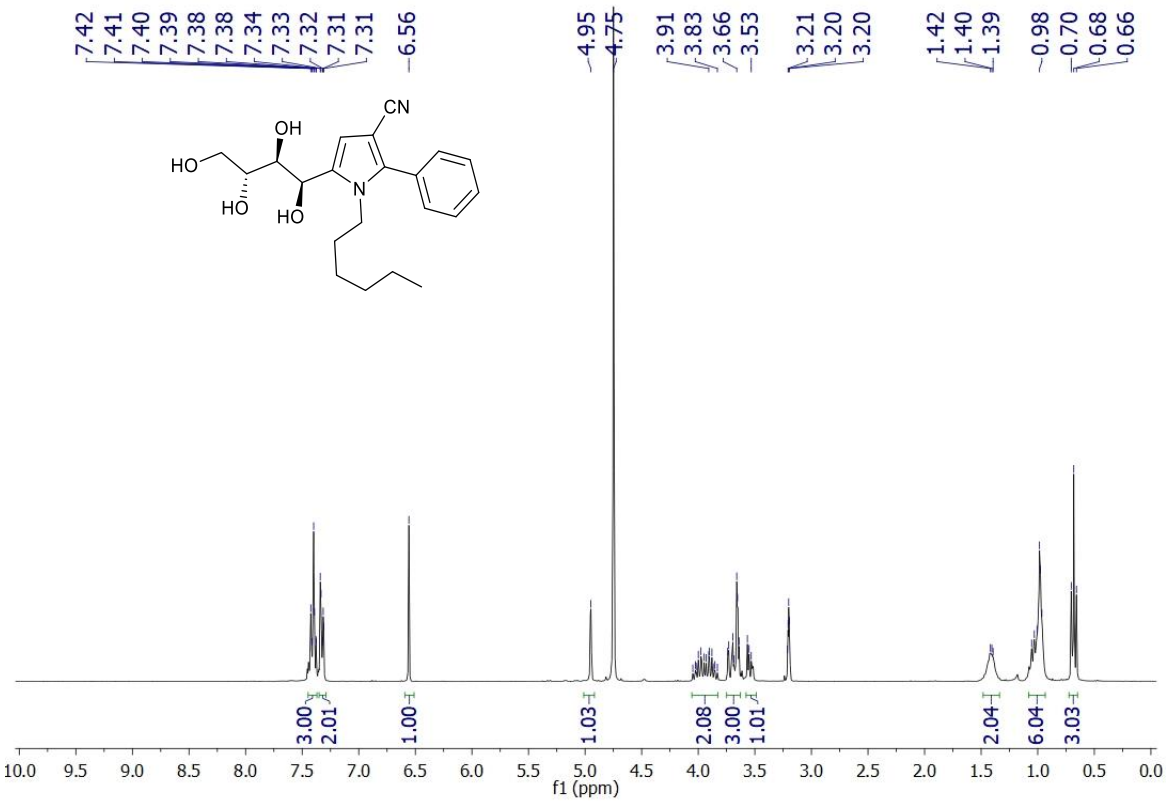
13-16

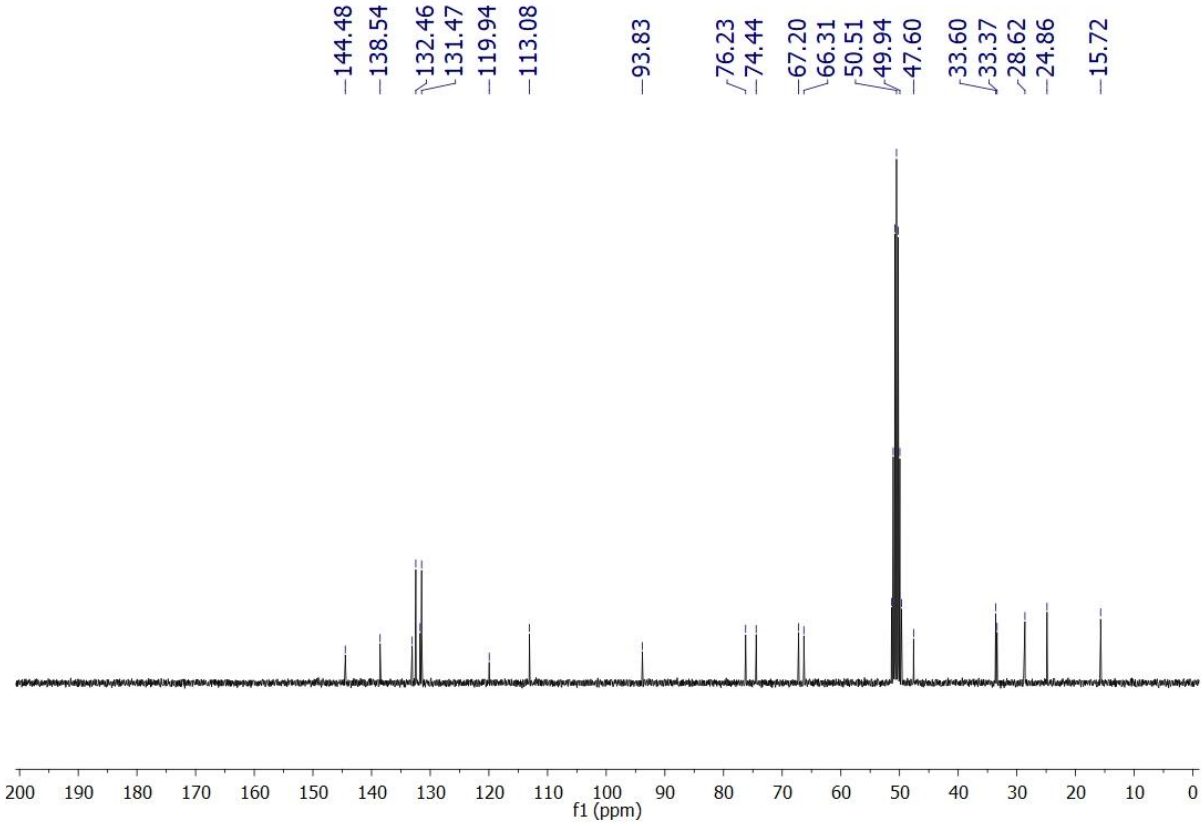
R = H, Me, OMe, F, Cl

A mixture of the phenacyl bromide (20 mmol) and sodium formate (16 mmol) was stirred in ethanol/water (30 mL, EtOH: H_2O = 9:1) at 90 ^oC for 12 hours. Upon completion of the reaction (TLC), the mixture was cooled to room temperature and ethanol was evaporated under reduced pressure. The resulting concentrated mixture was diluted with water (8 mL) and extracted using ethyl acetate (10 mL X 3 times). The organic layers were dried over Mg_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residual compound was purified using column chromatography using EtOAc/Hexane mixture (1:4). This general procedure was used to prepare for phenacyl alcohol **13-16**.

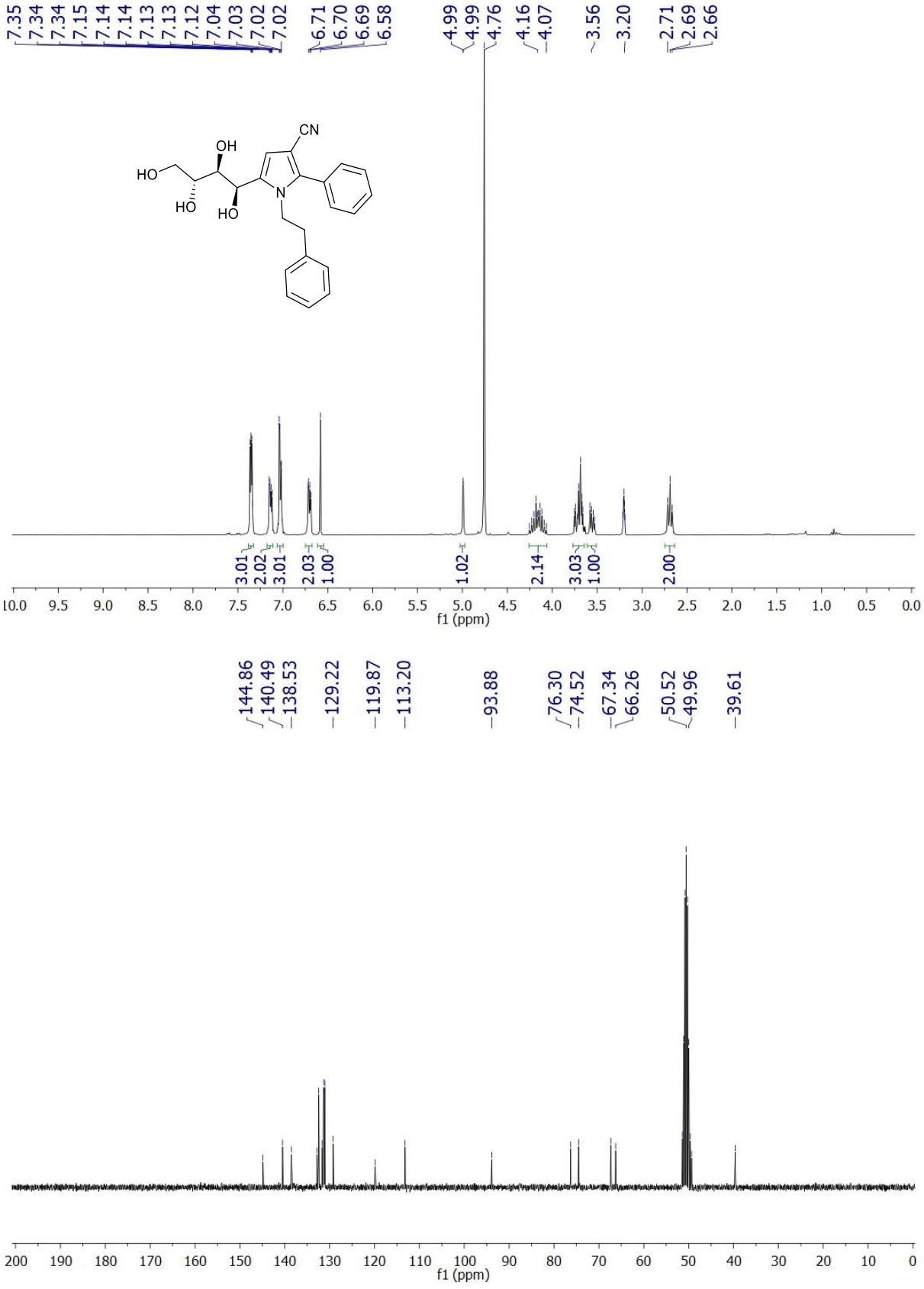
4.2 ^{1}H NMR and ^{13}C NMR spectra

1-Hexyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

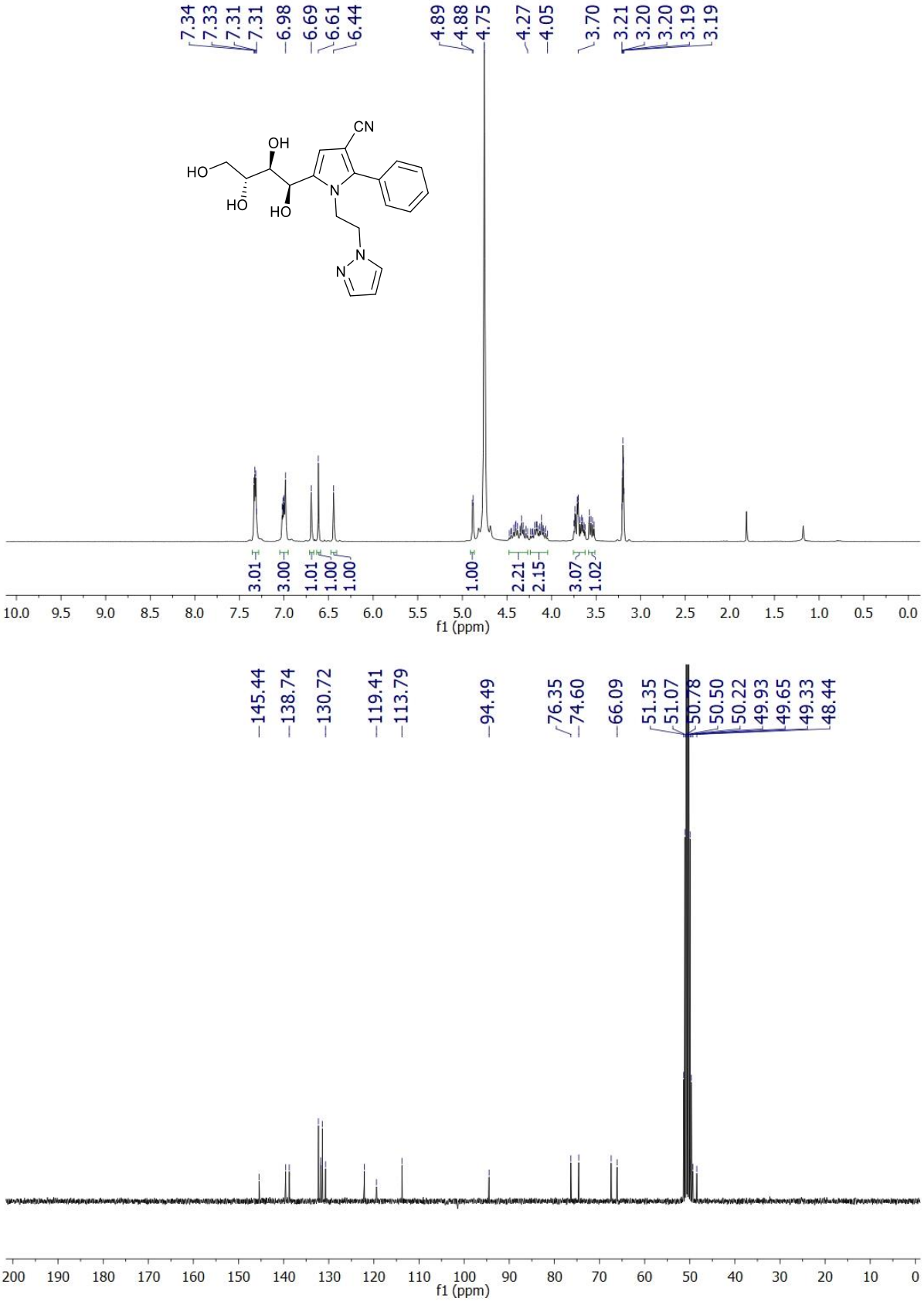




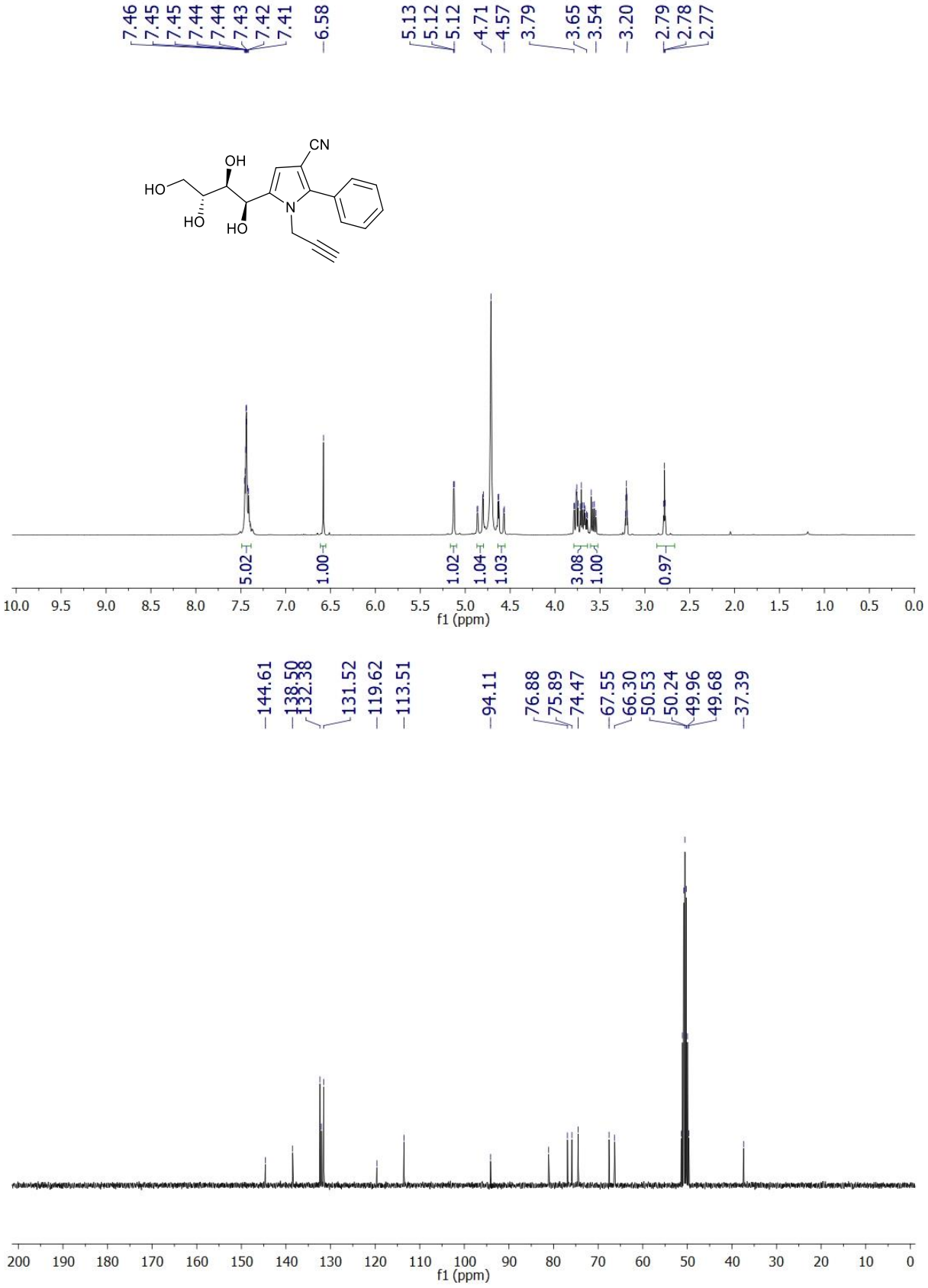
1-Phenethyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



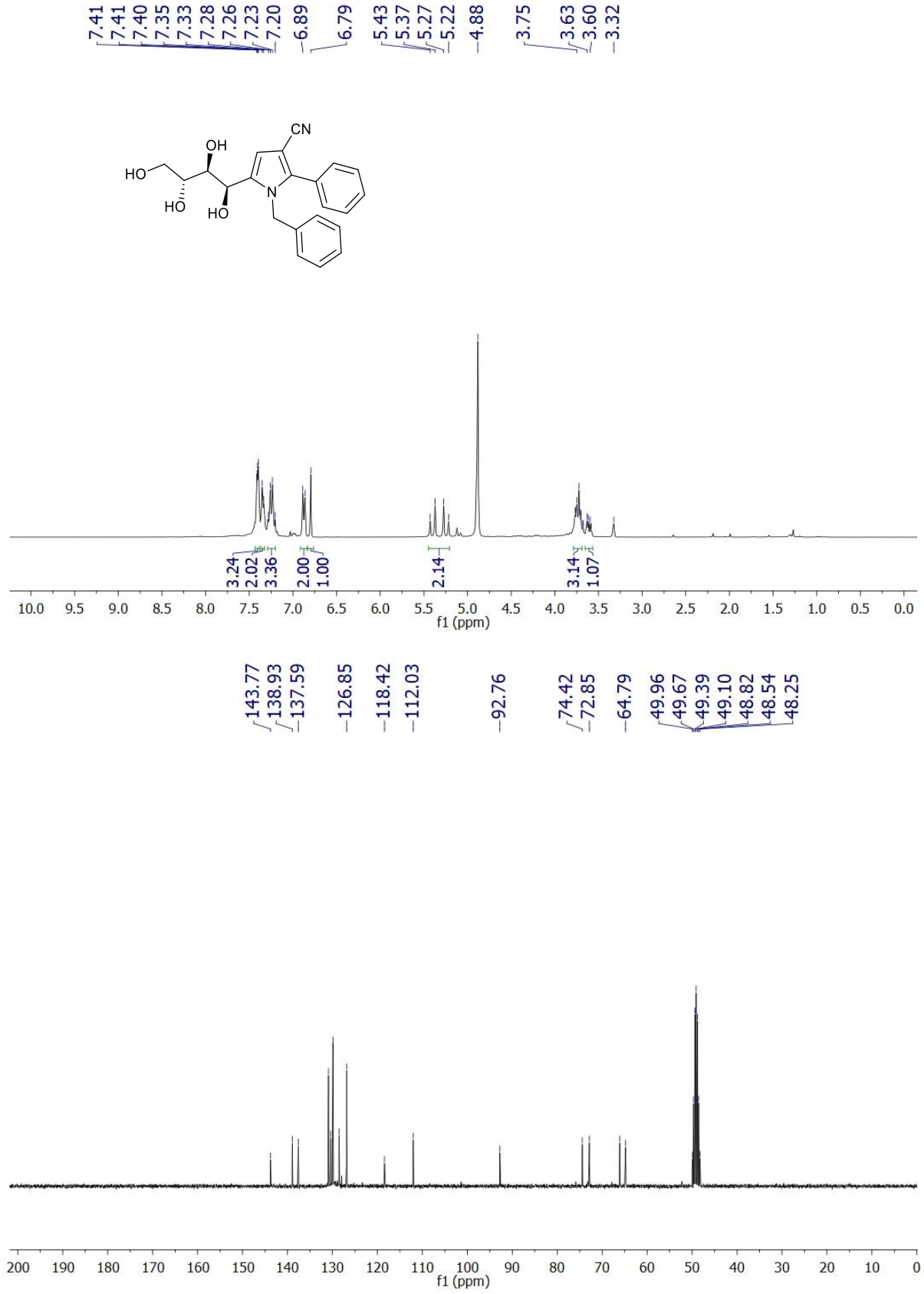
1-(2-(1*H*-Imidazol-1-yl)ethyl)-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



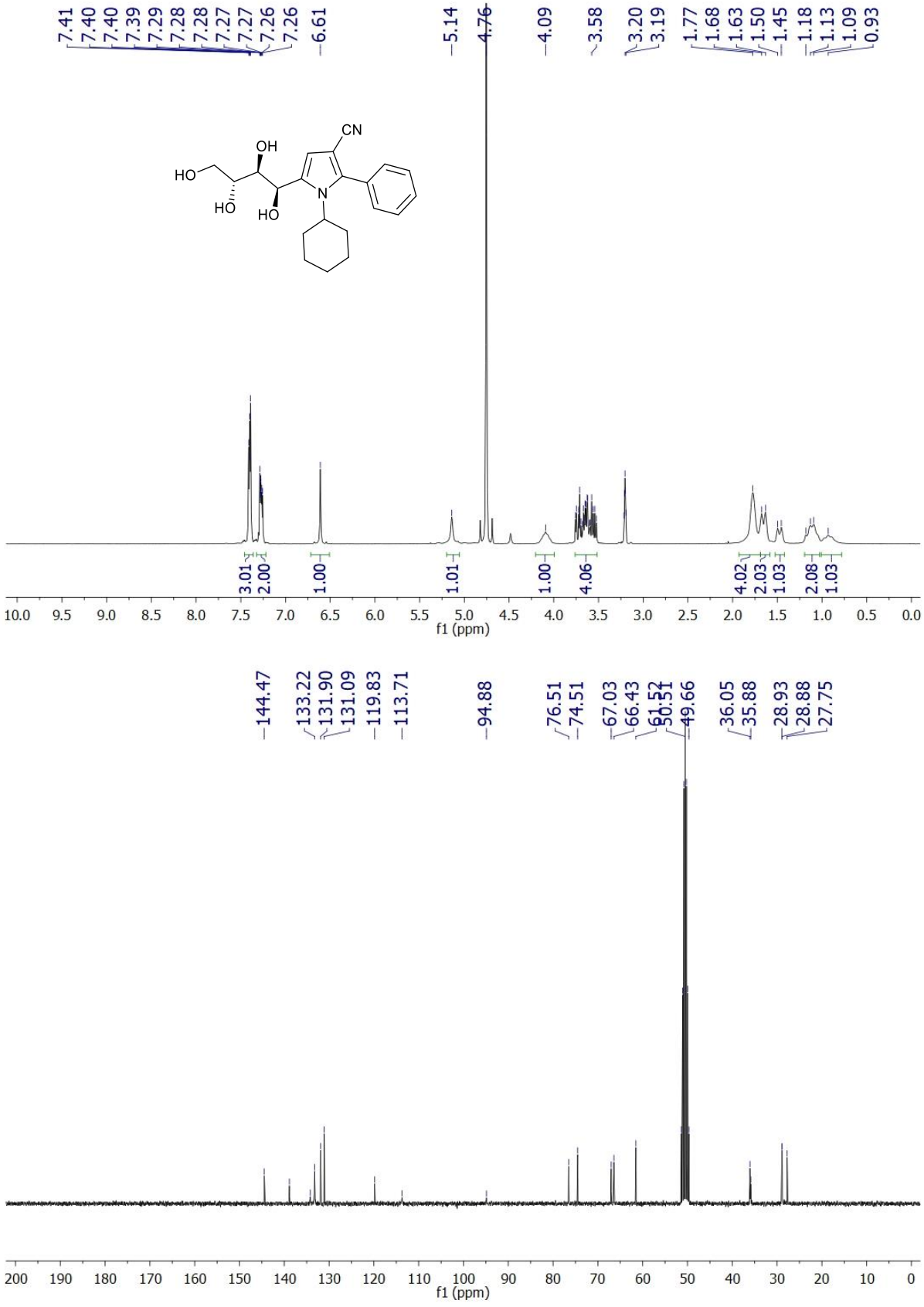
2-Phenyl-1-(prop-2-yn-1-yl)-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



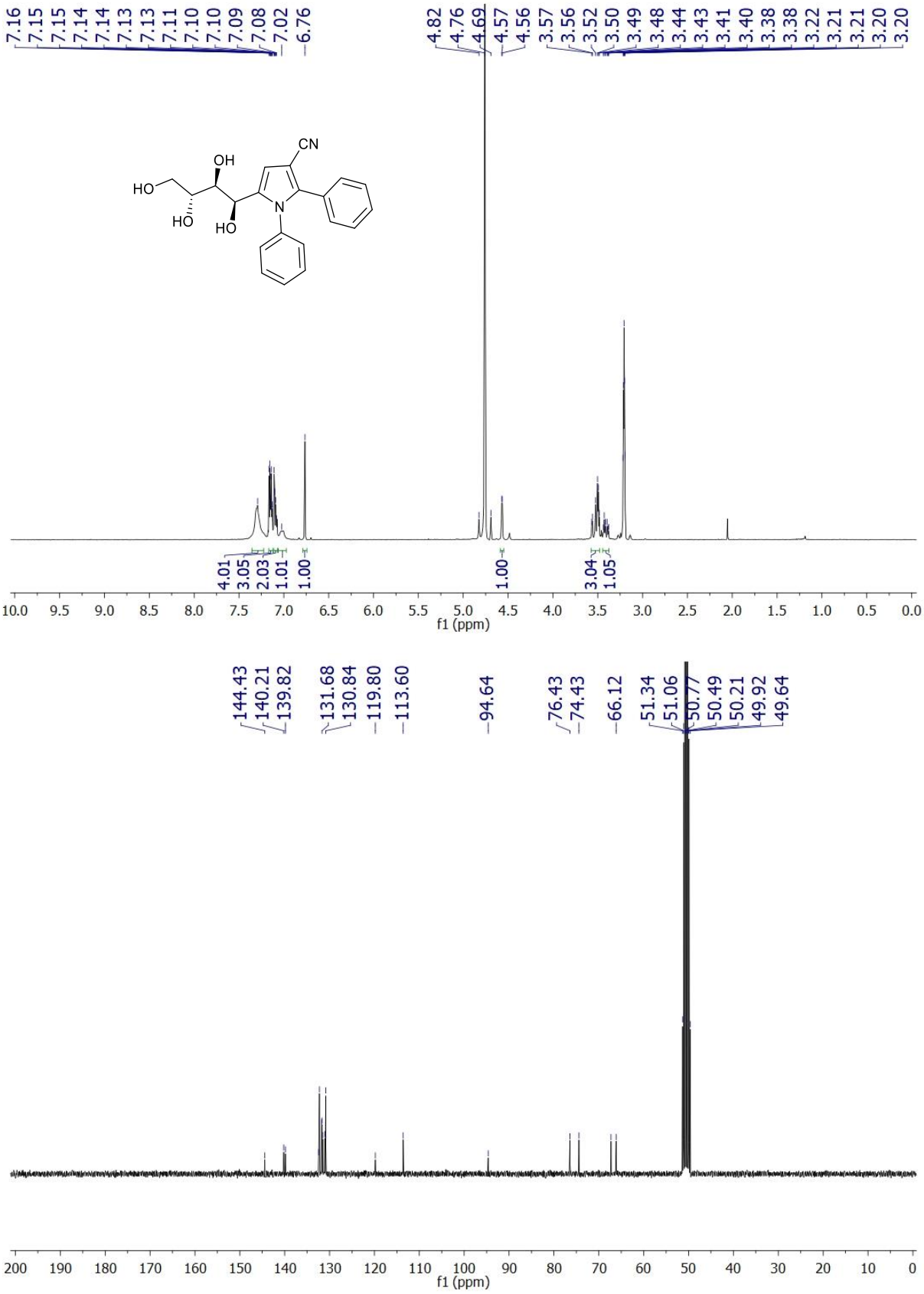
1-Benzyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



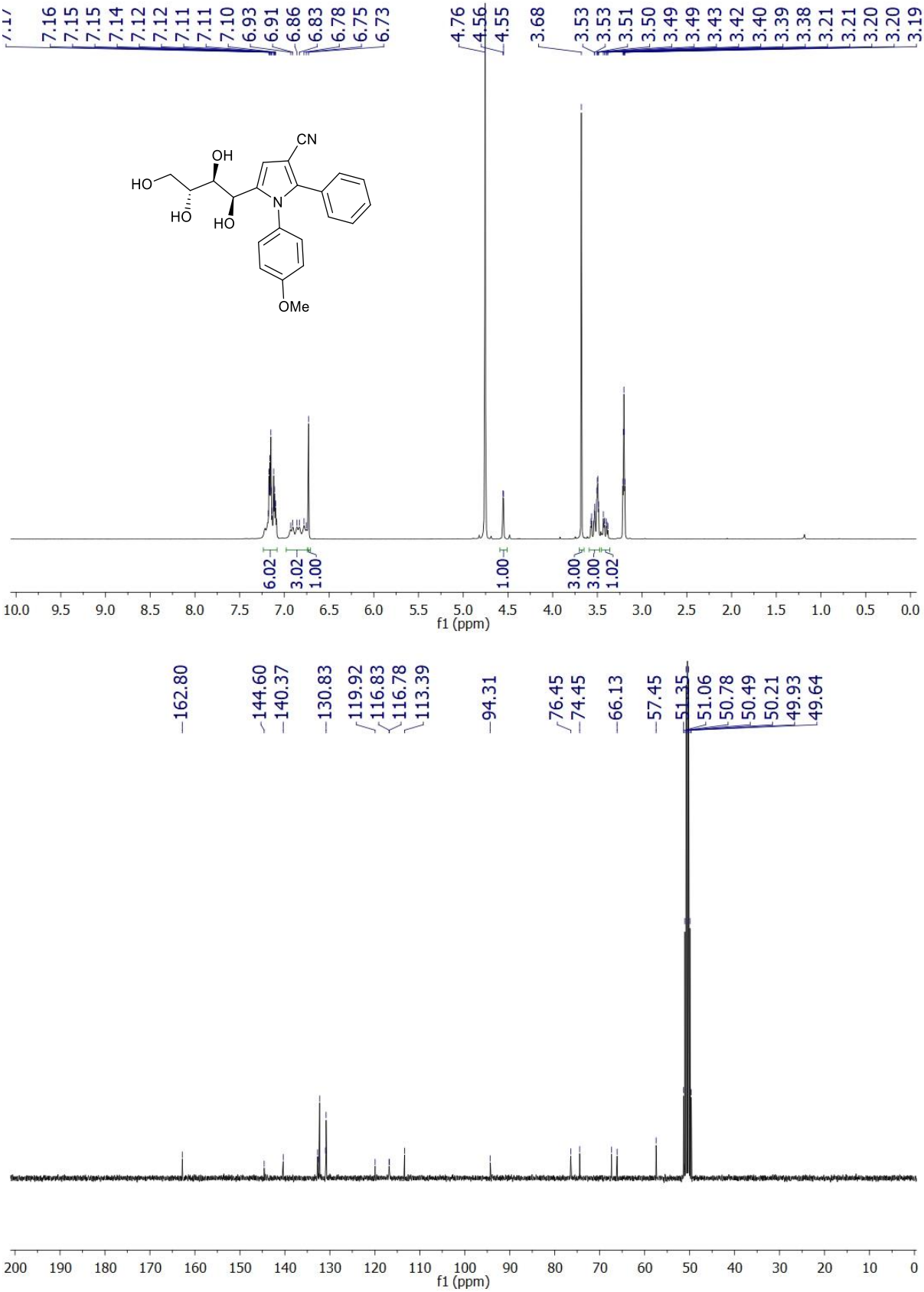
1-Cyclohexyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile



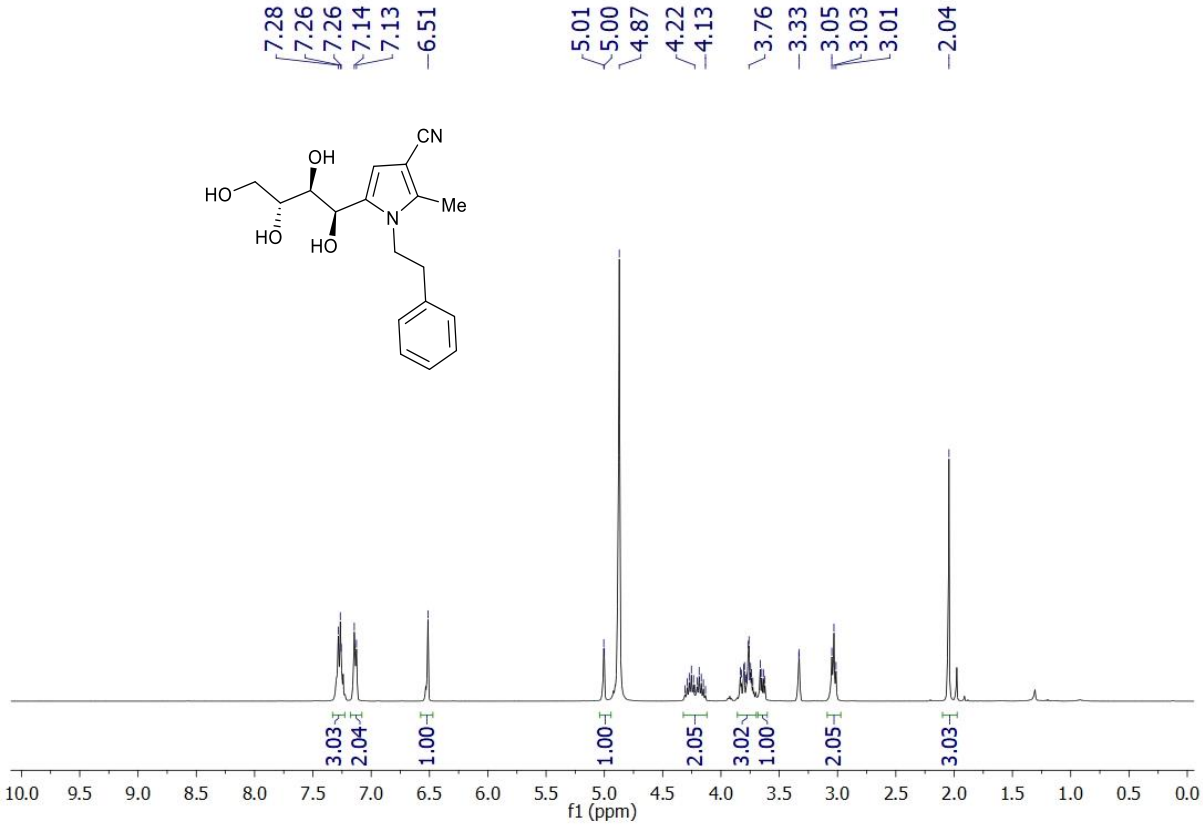
1,2-Diphenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

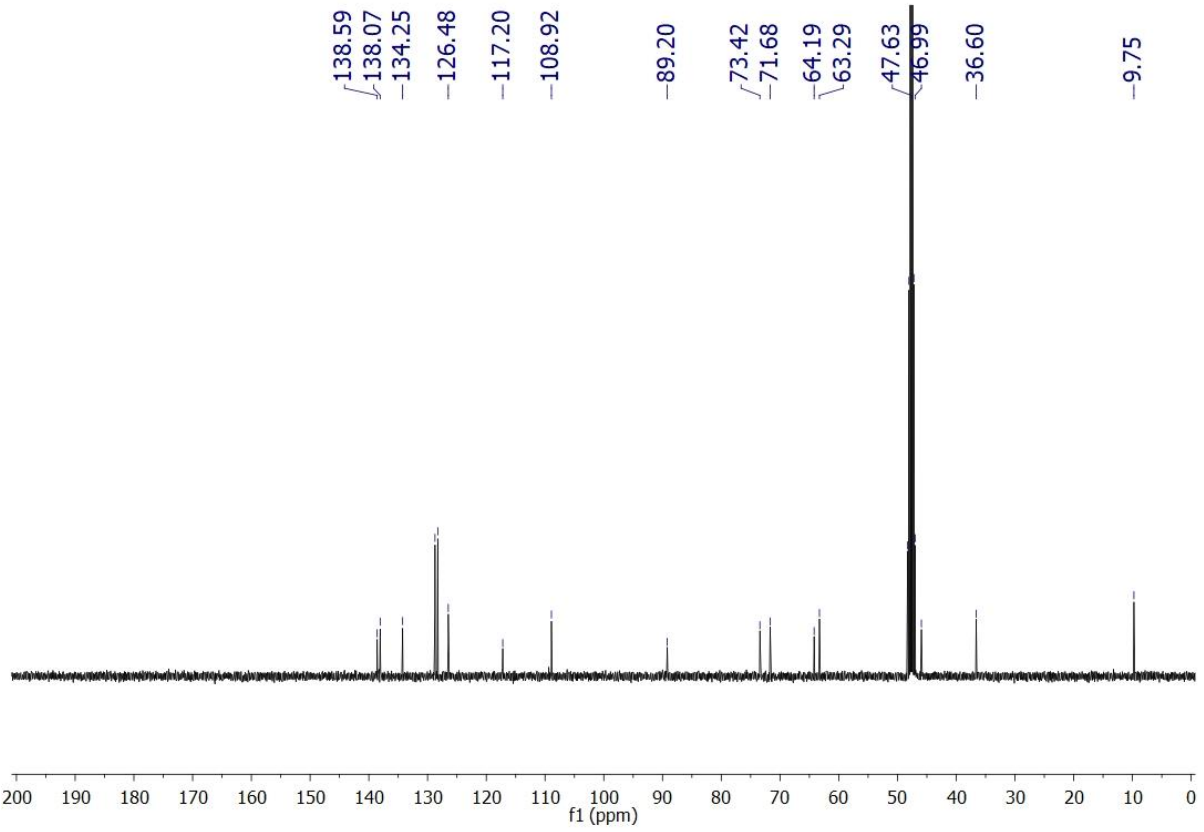


1-(4-Methoxyphenyl)-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

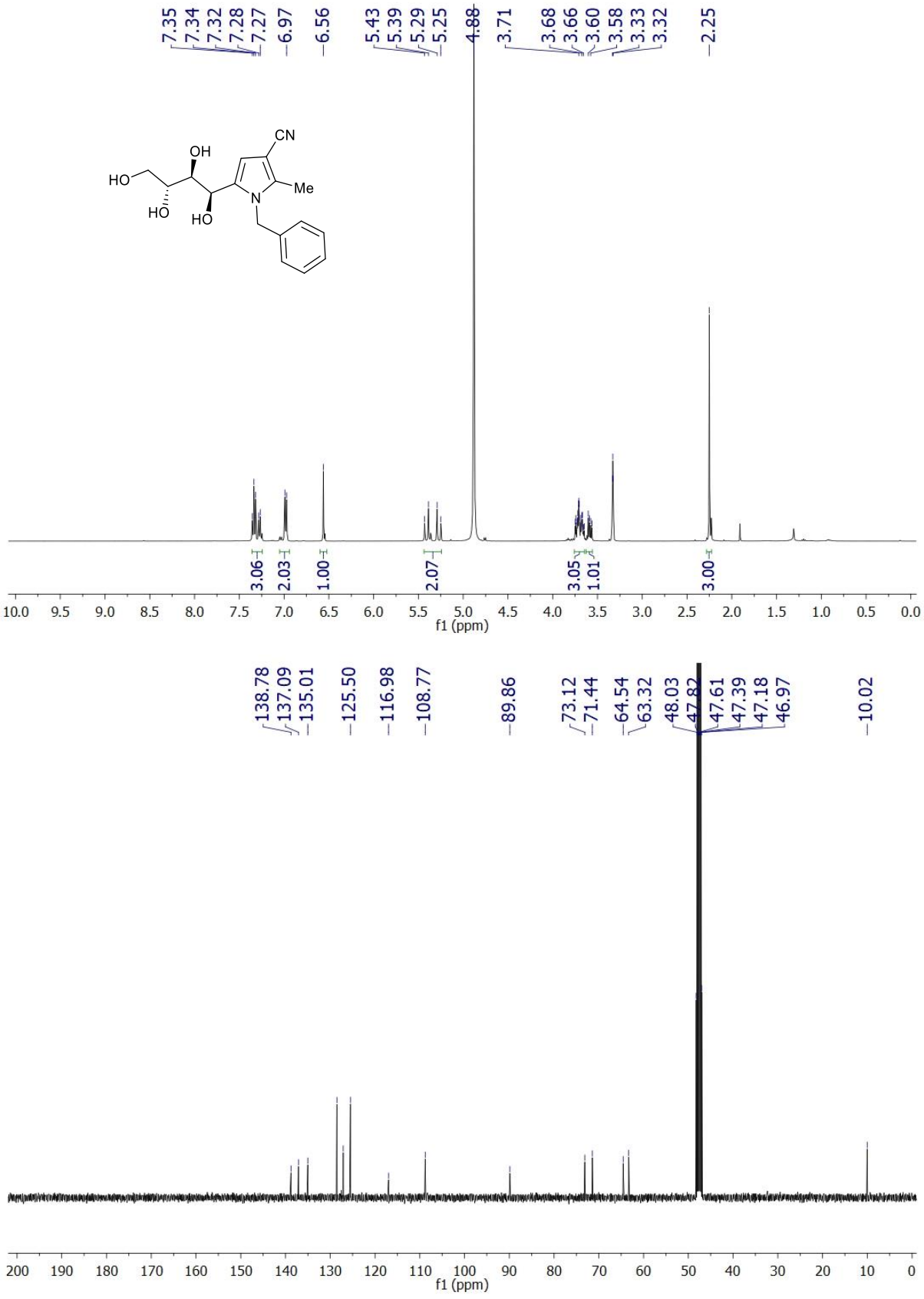


2-Methyl-1-phenethyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

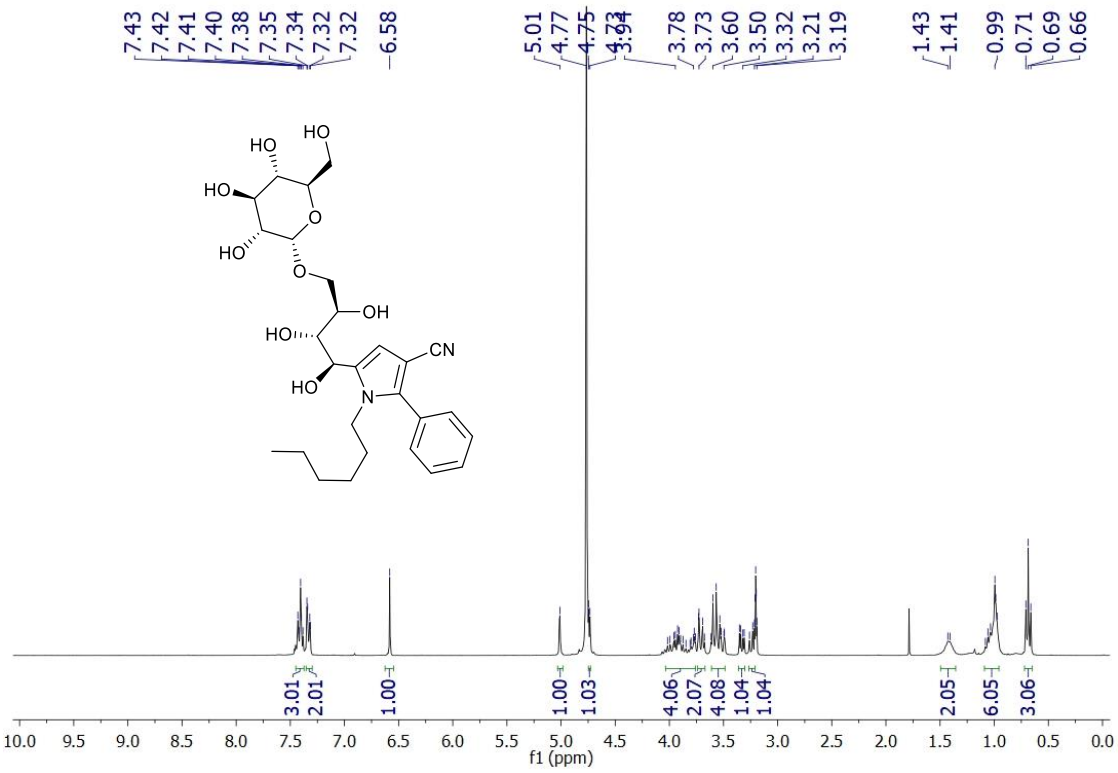


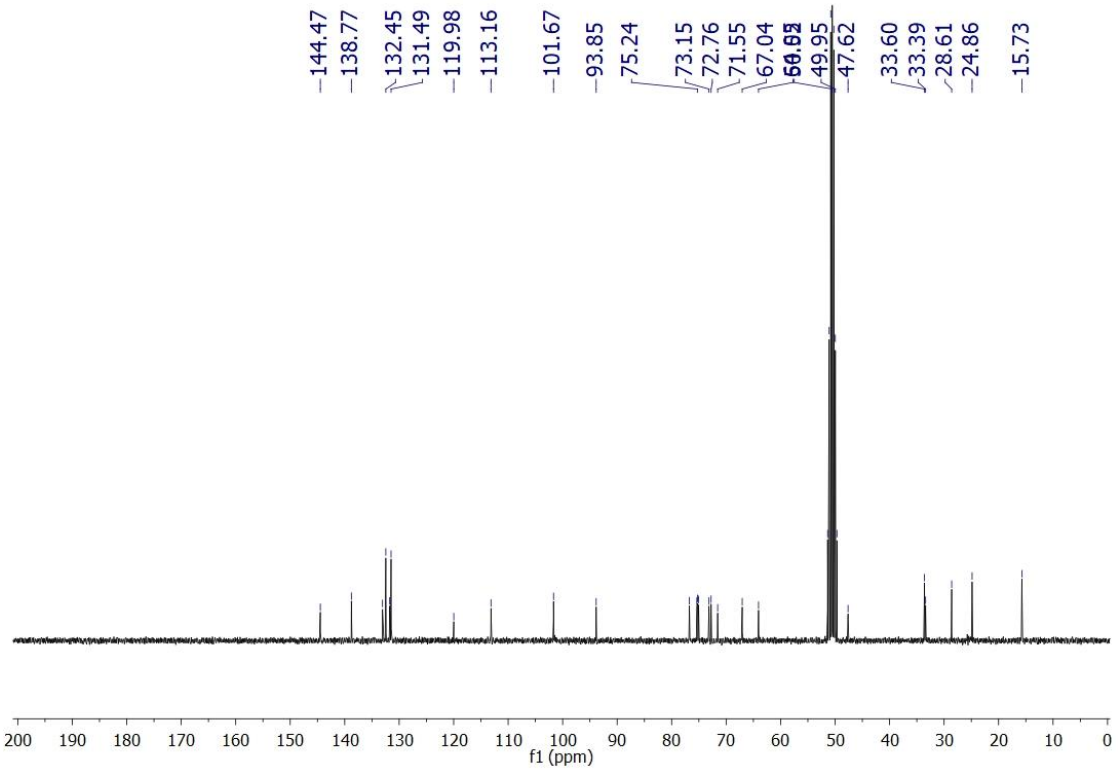


1-Benzyl-2-methyl-5-((1*R*,2*S*,3*R*)-1,2,3,4-tetrahydroxybutyl)-1*H*-pyrrole-3-carbonitrile

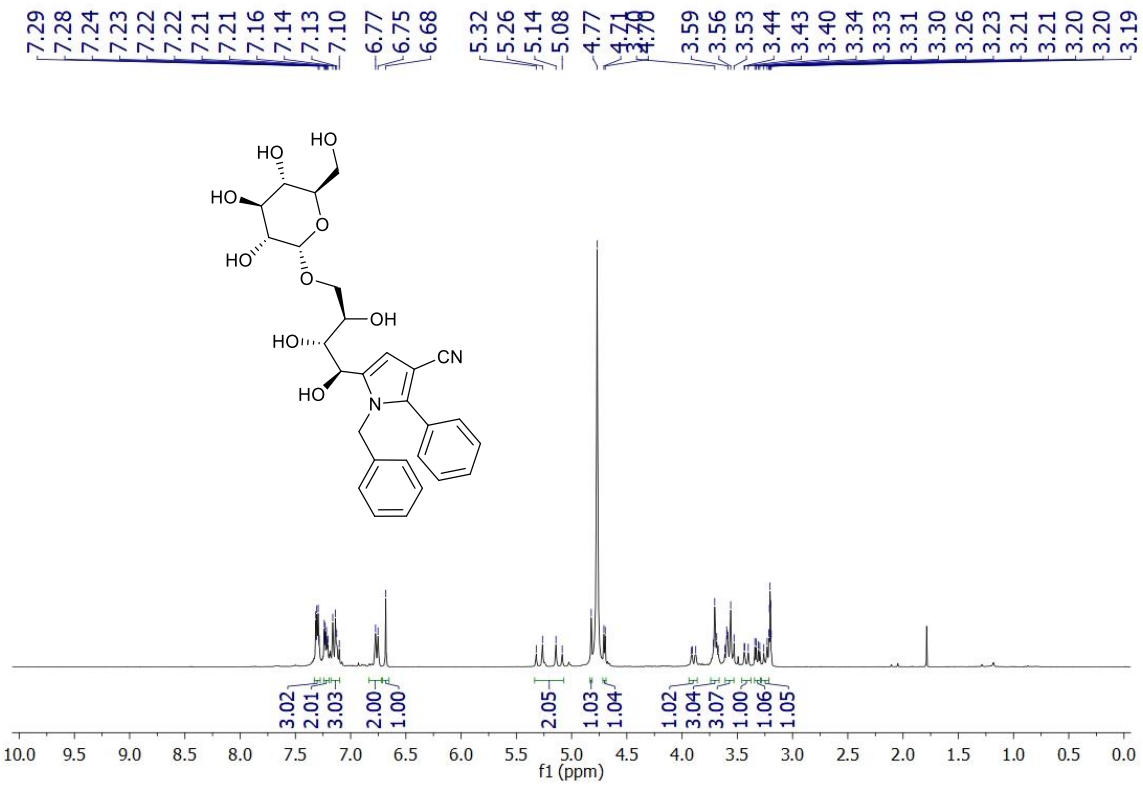


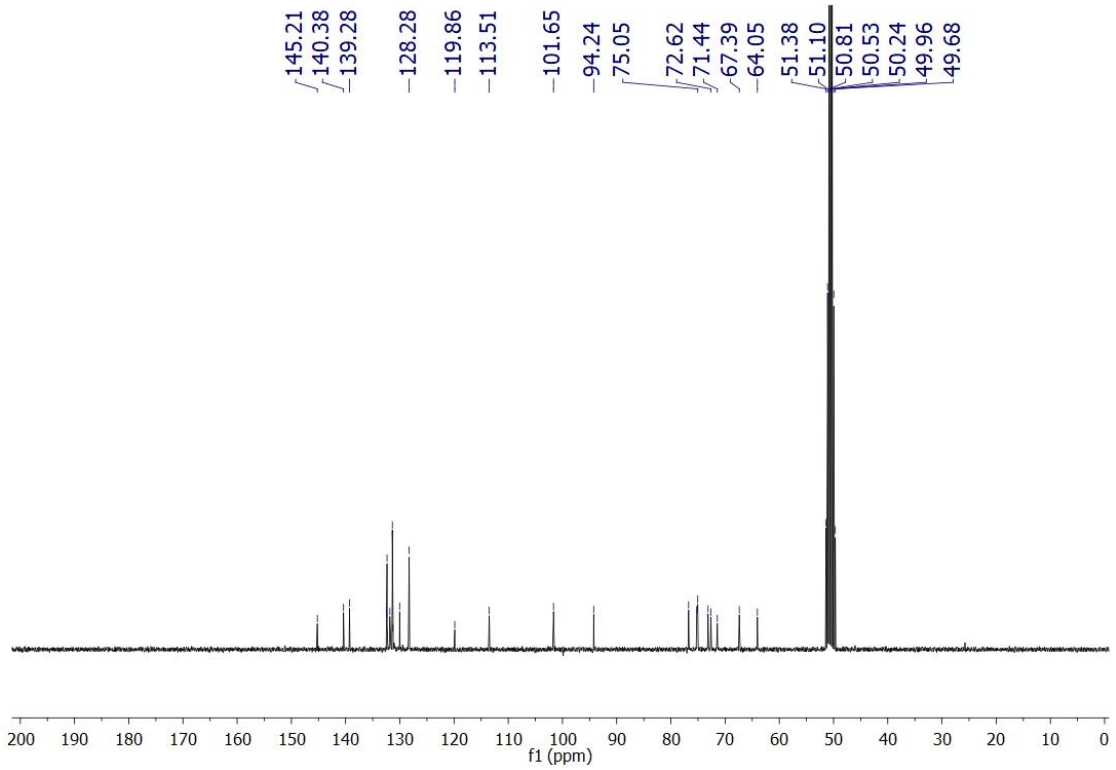
1-Hexyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3-trihydroxy-4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)butyl)-1*H*-pyrrole-3-carbonitrile



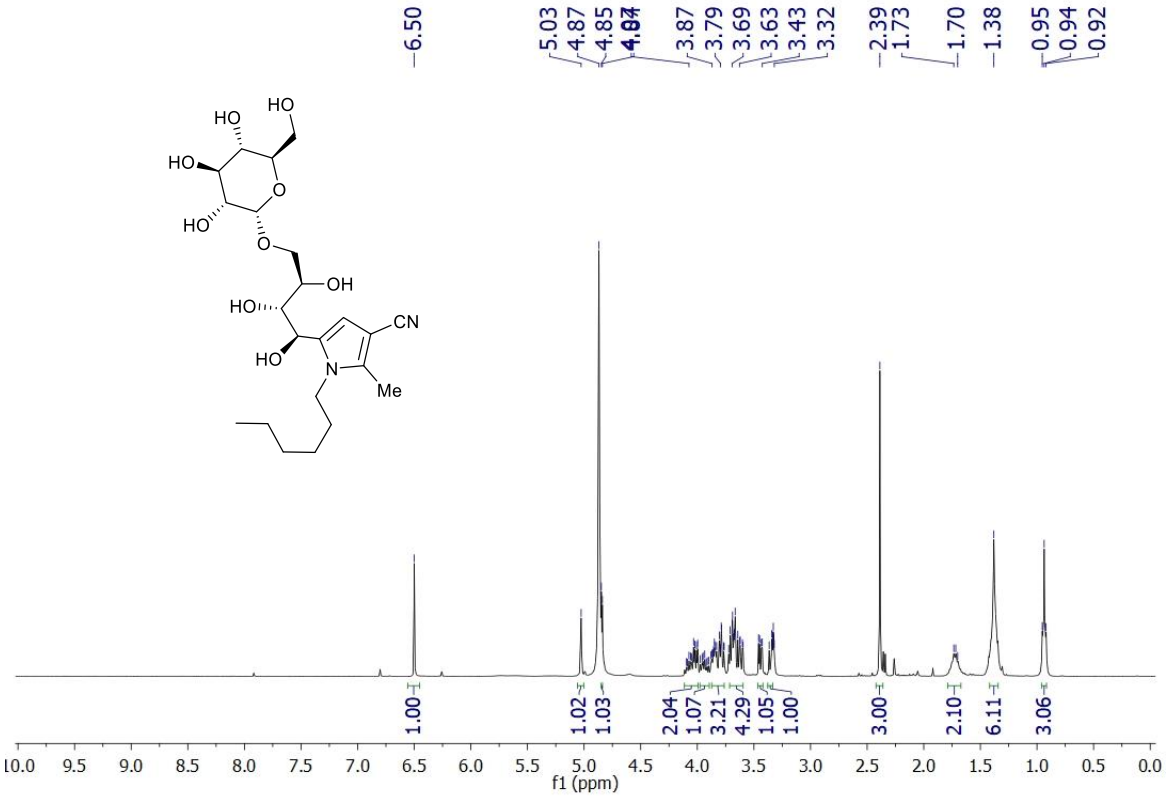


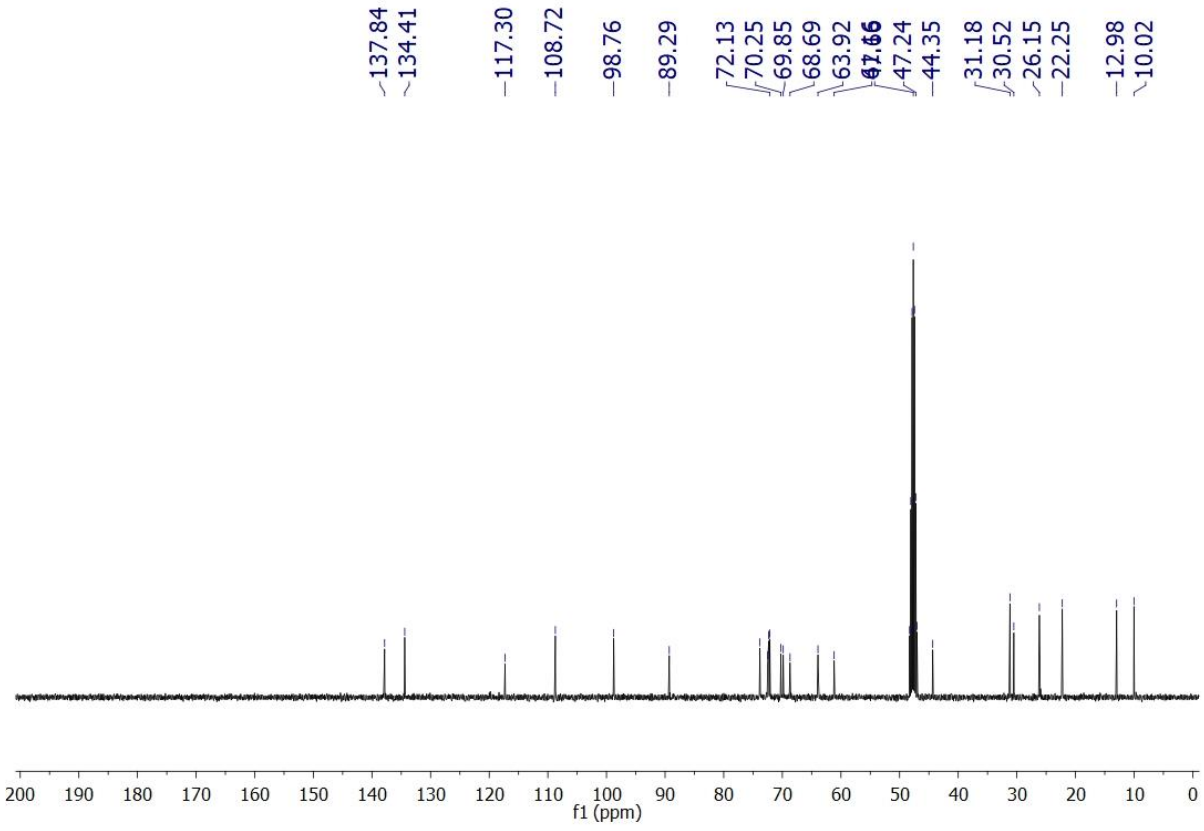
1-Benzyl-2-phenyl-5-((1*R*,2*S*,3*R*)-1,2,3-trihydroxy-4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)butyl)-1*H*-pyrrole-3-carbonitrile



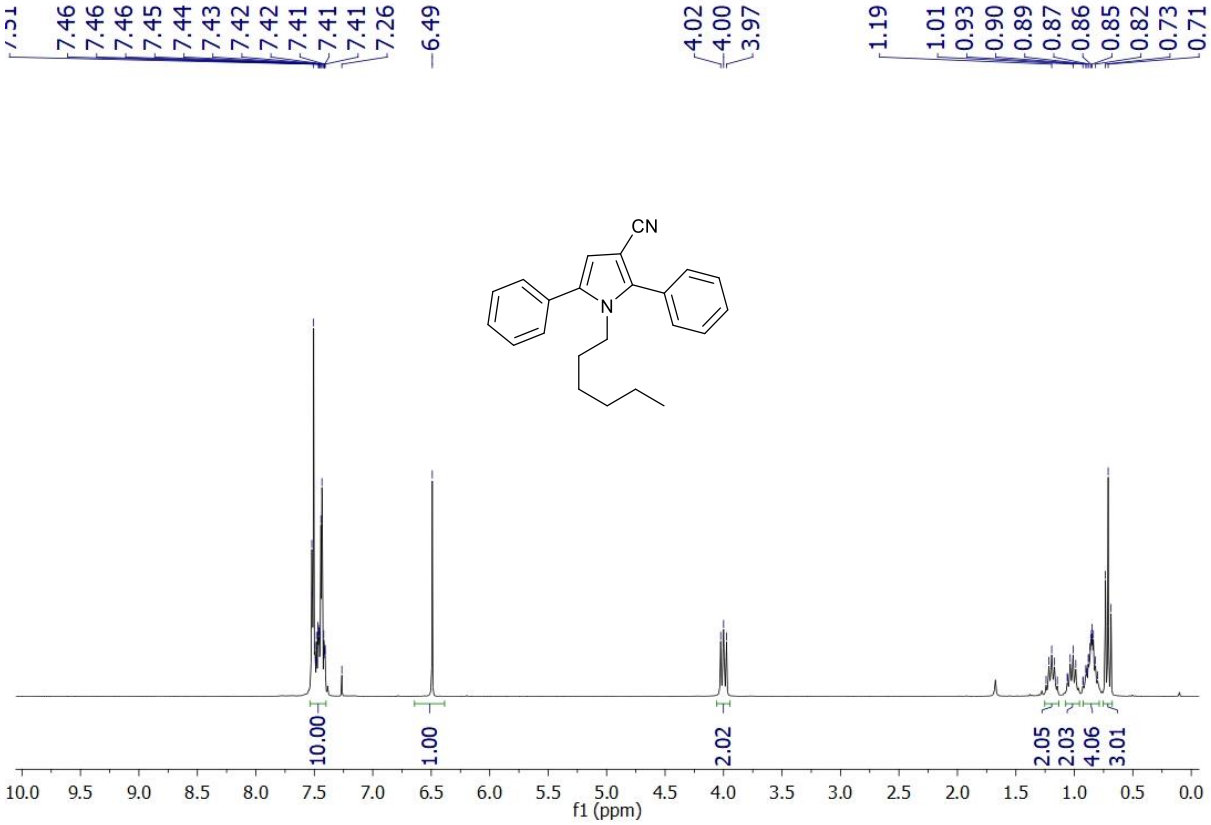


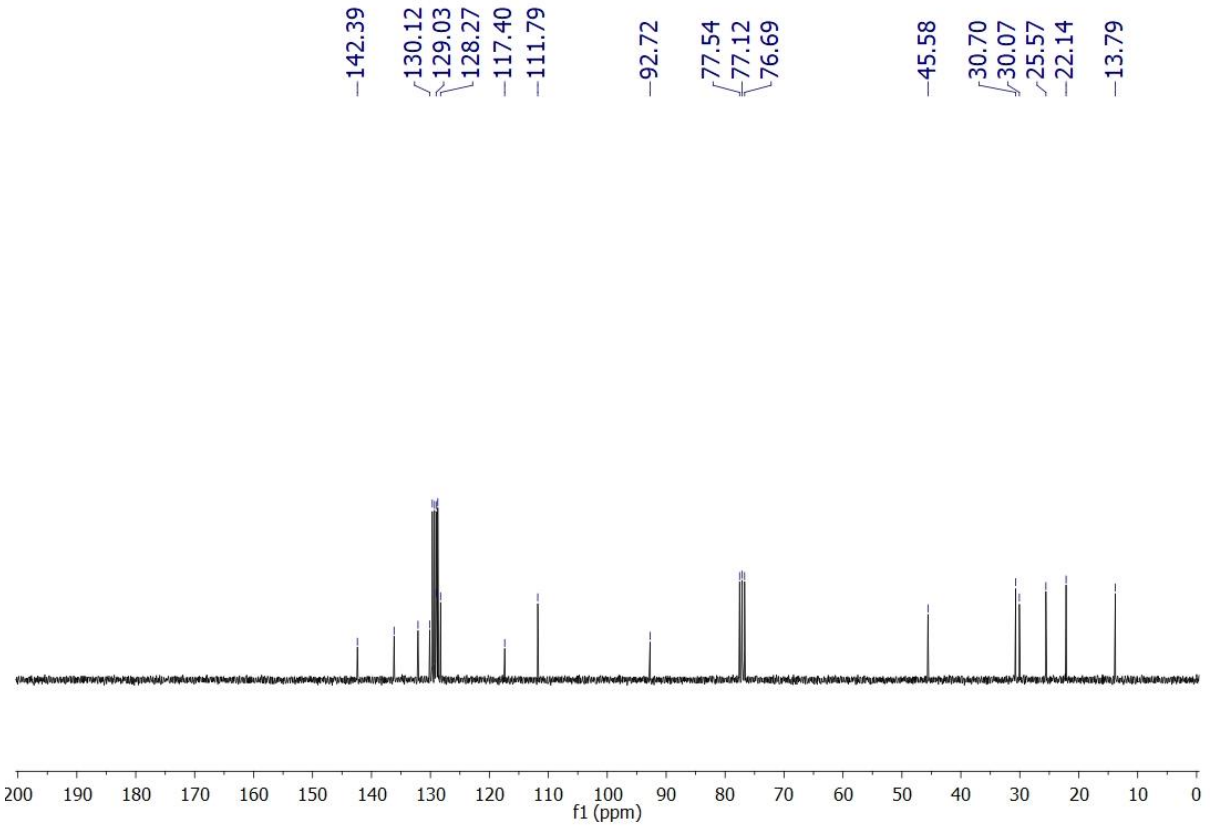
1-Hexyl-2-methyl-5-((1*R*,2*S*,3*R*)-1,2,3-trihydroxy-4-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)butyl)-1*H*-pyrrole-3-carbonitrile



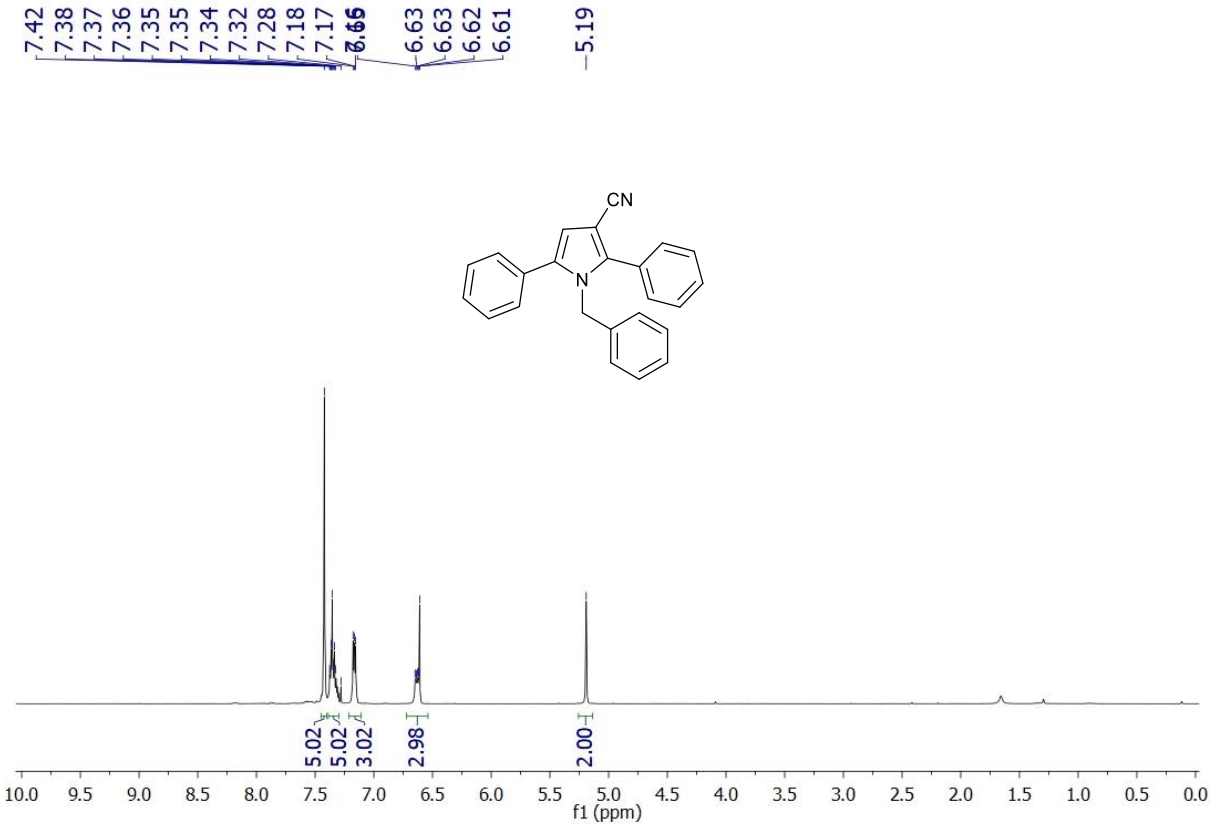


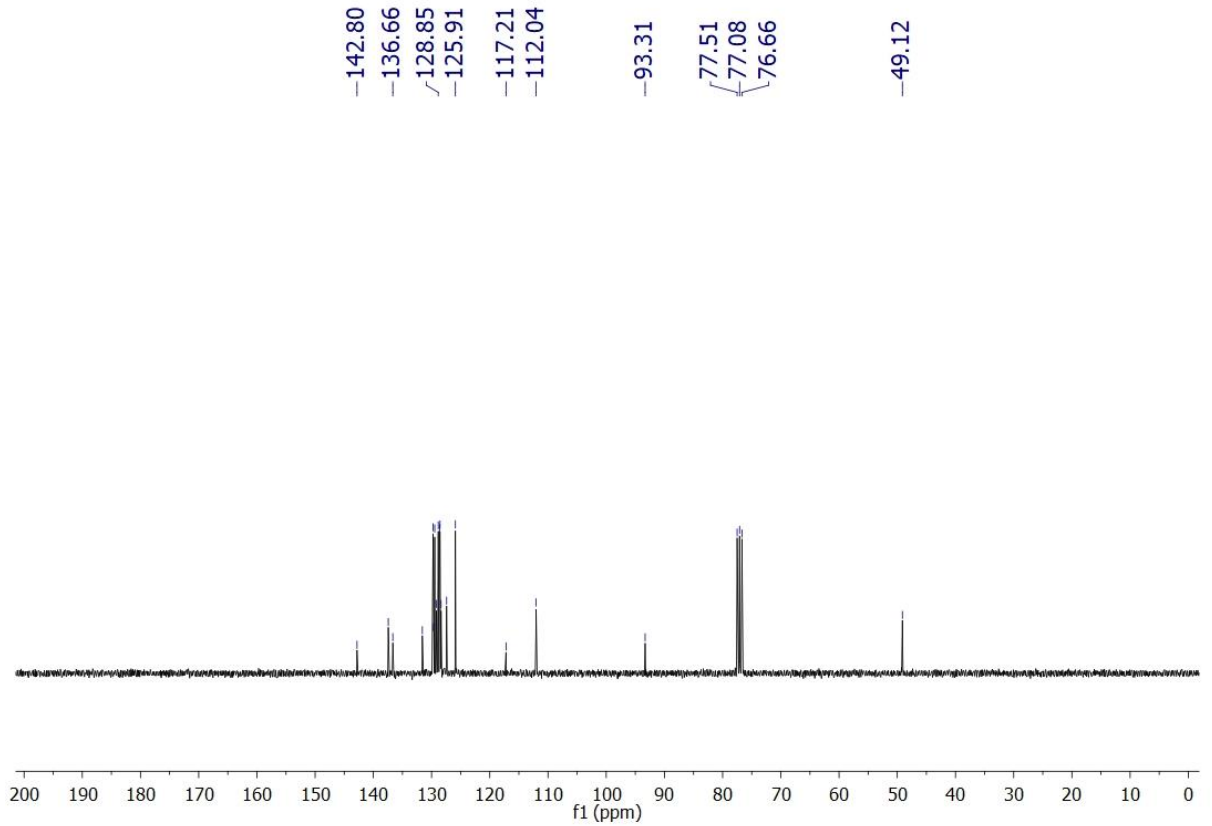
1-Hexyl-2,5-diphenyl-1*H*-pyrrole-3-carbonitrile



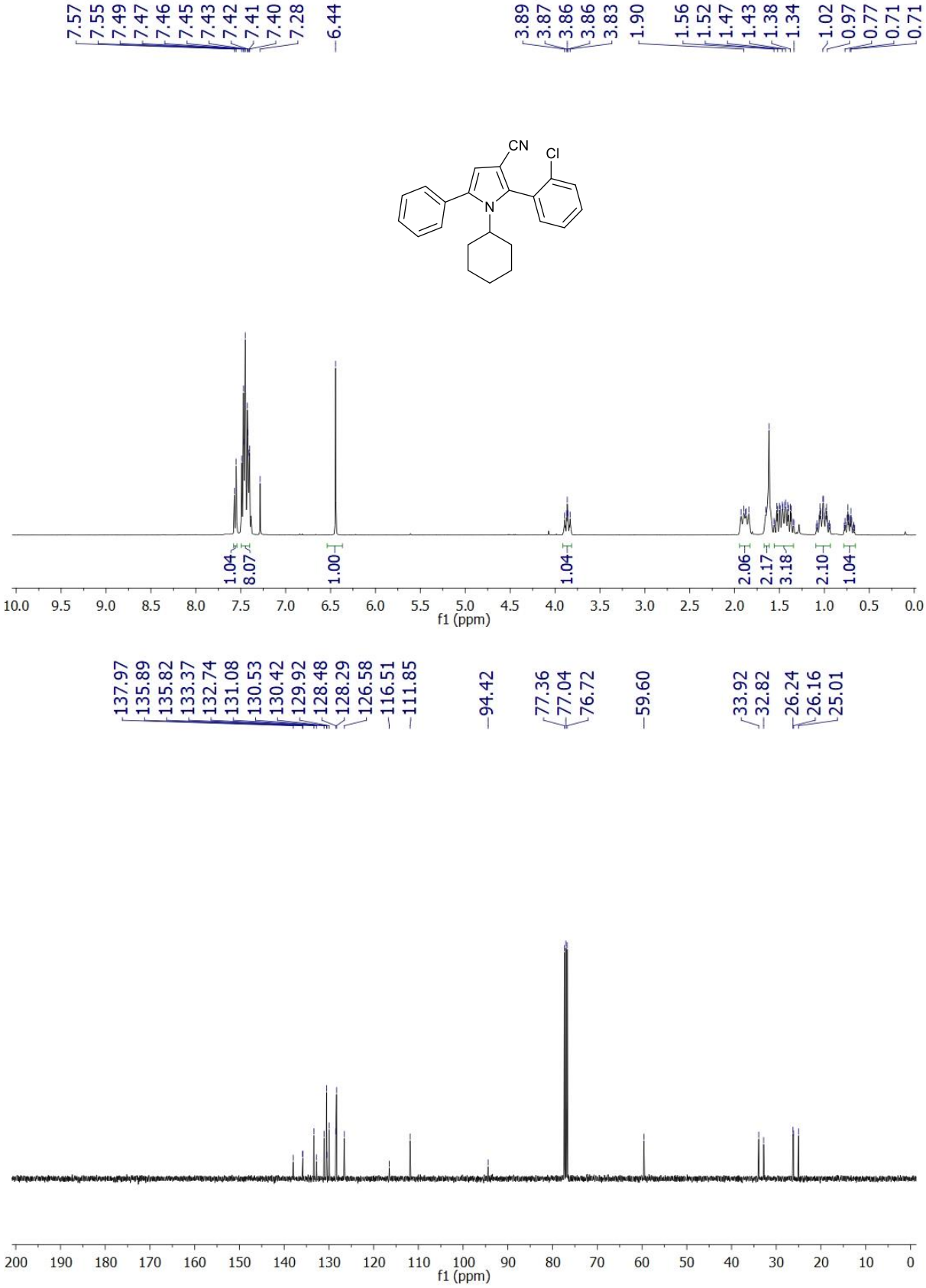


1-Benzyl-2,5-diphenyl-1*H*-pyrrole-3-carbonitrile

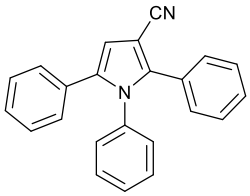


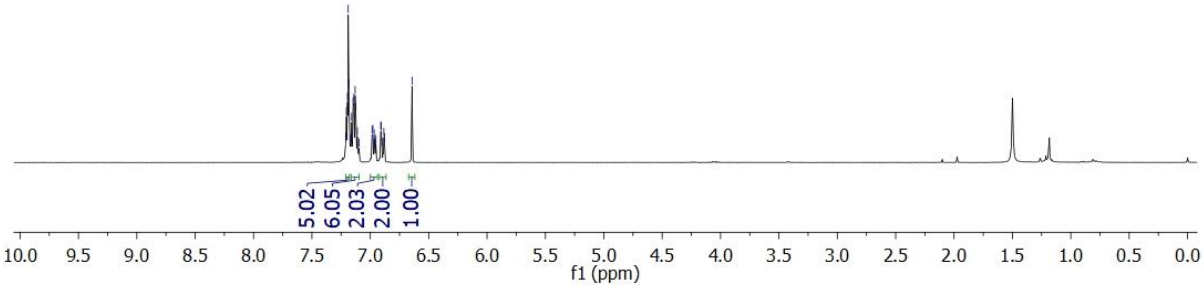


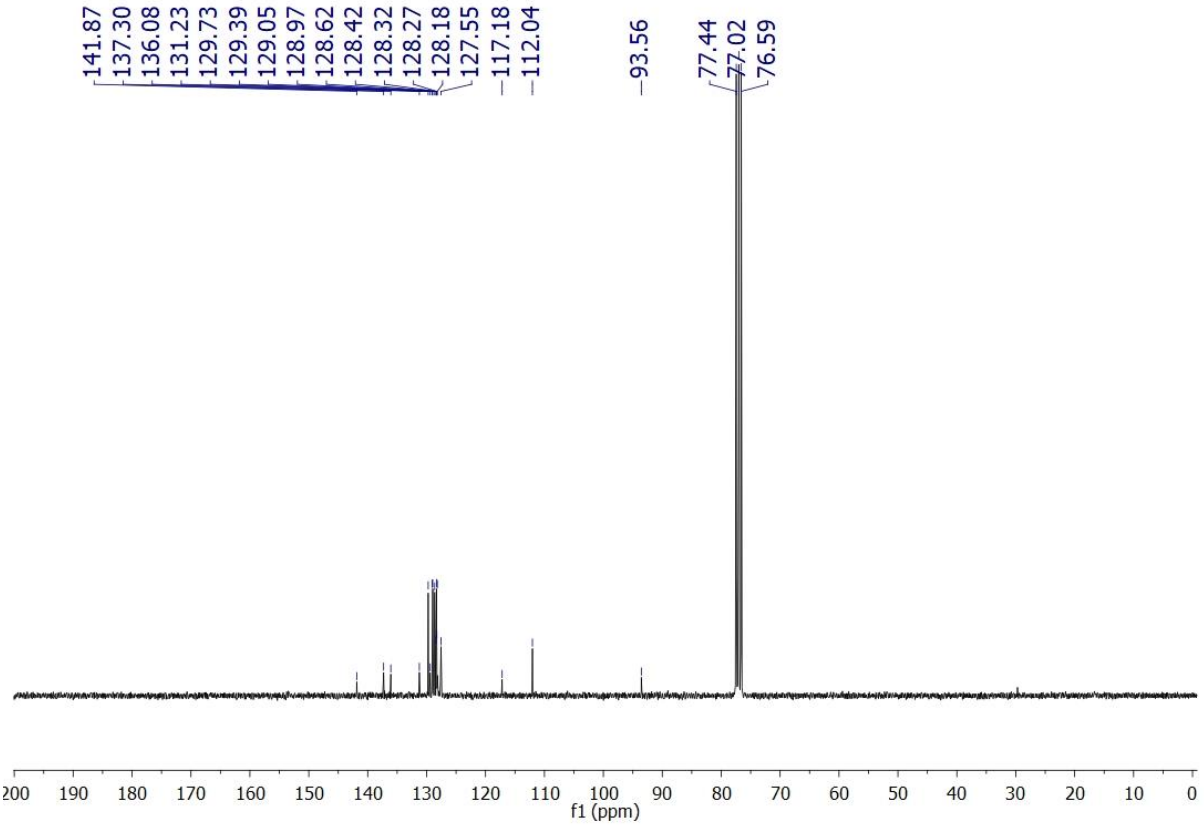
2-(2-Chlorophenyl)-1-cyclohexyl-5-phenyl-1*H*-pyrrole-3-carbonitrile



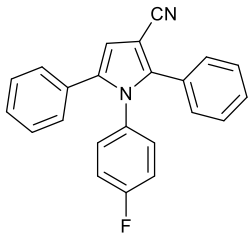
1,2,5-Triphenyl-1*H*-pyrrole-3-carbonitrile

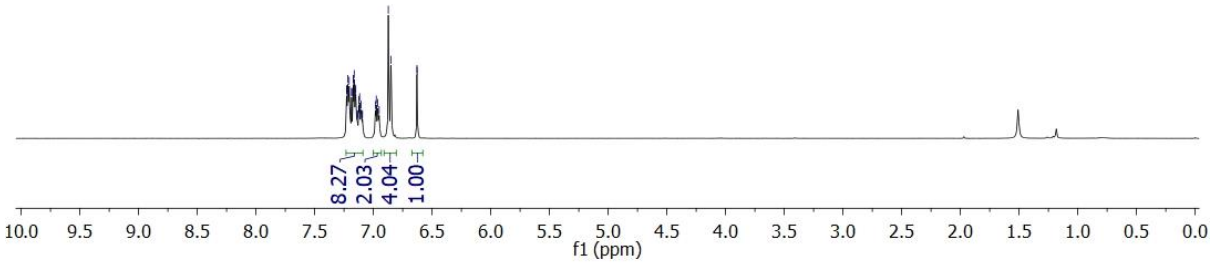


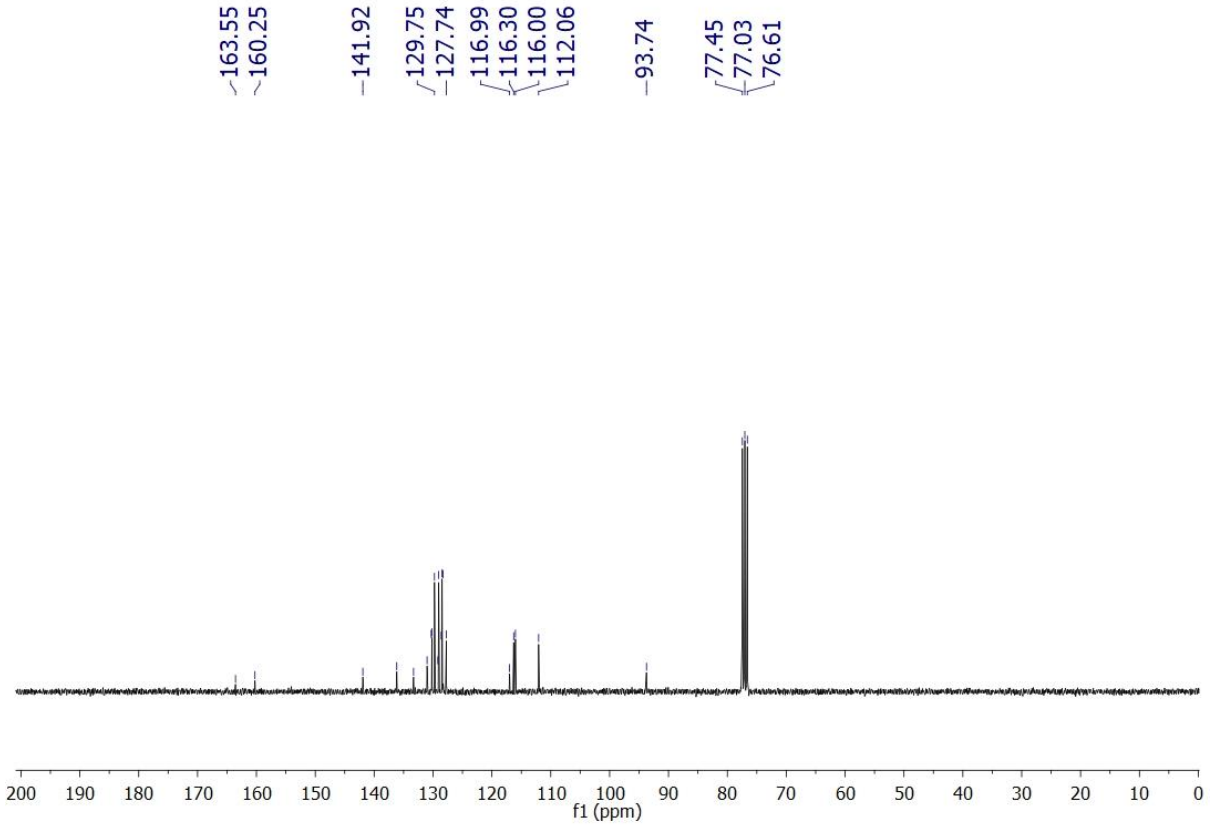




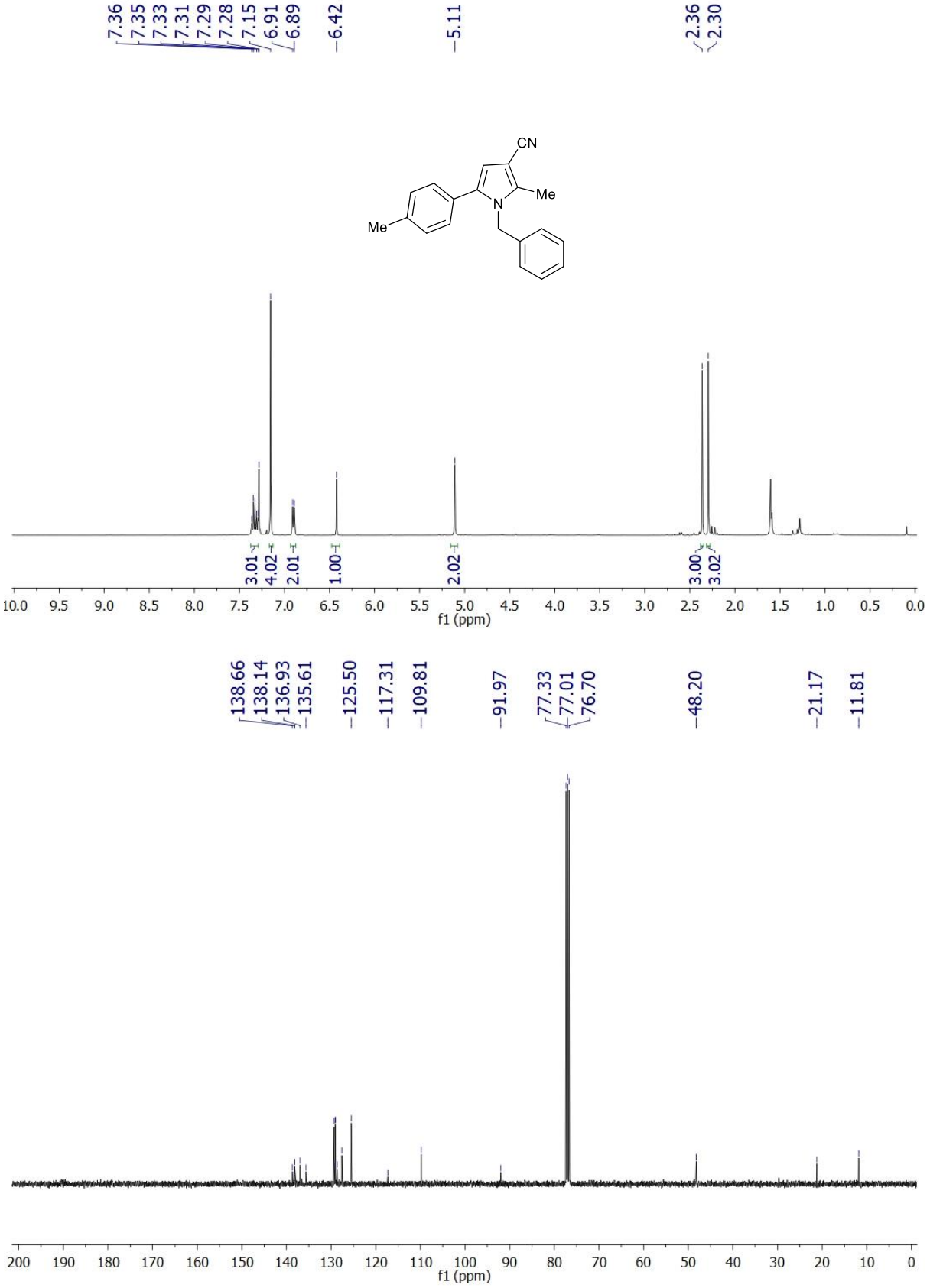
1-(4-Fluorophenyl)-2,5-diphenyl-1*H*-pyrrole-3-carbonitrile



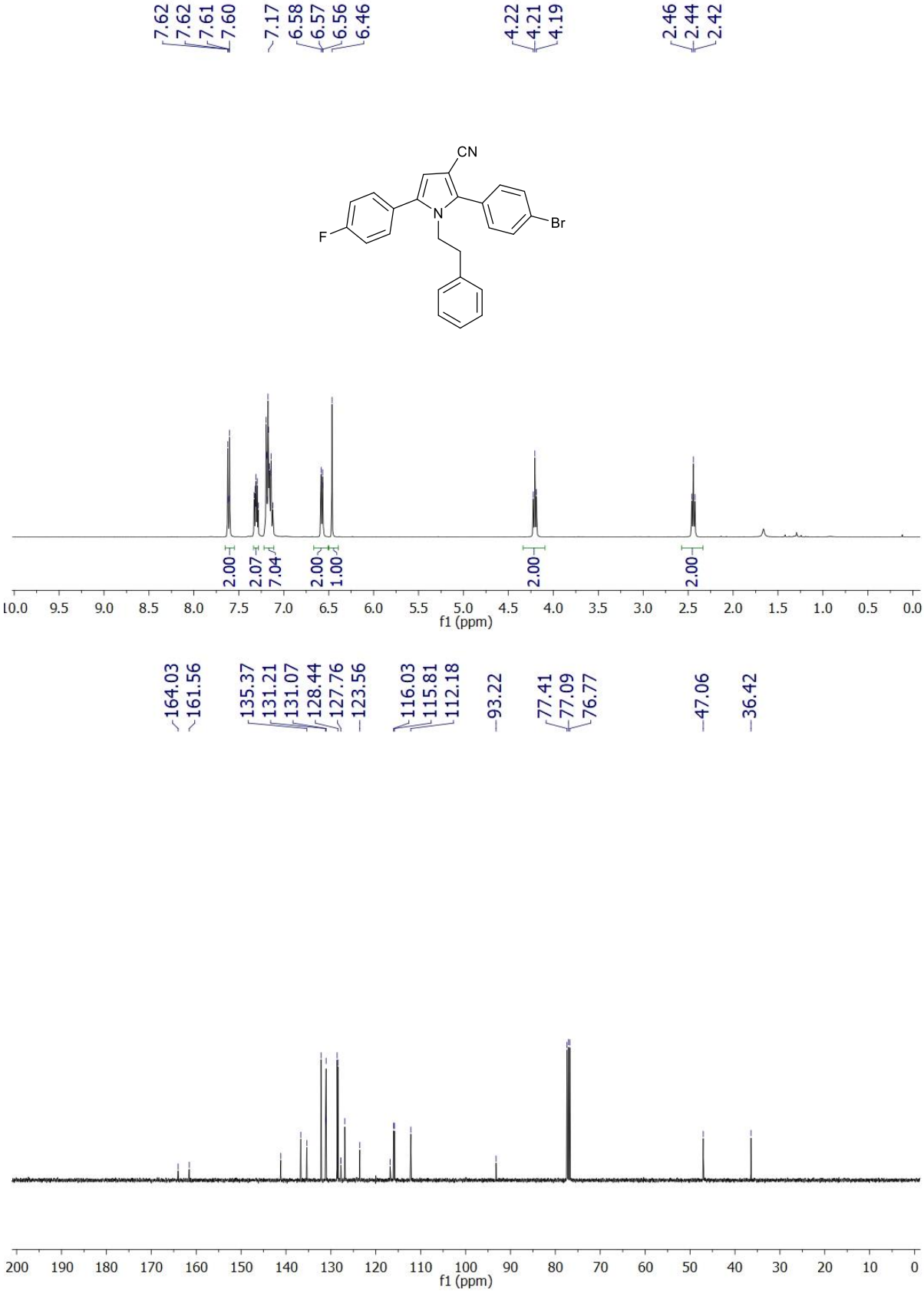




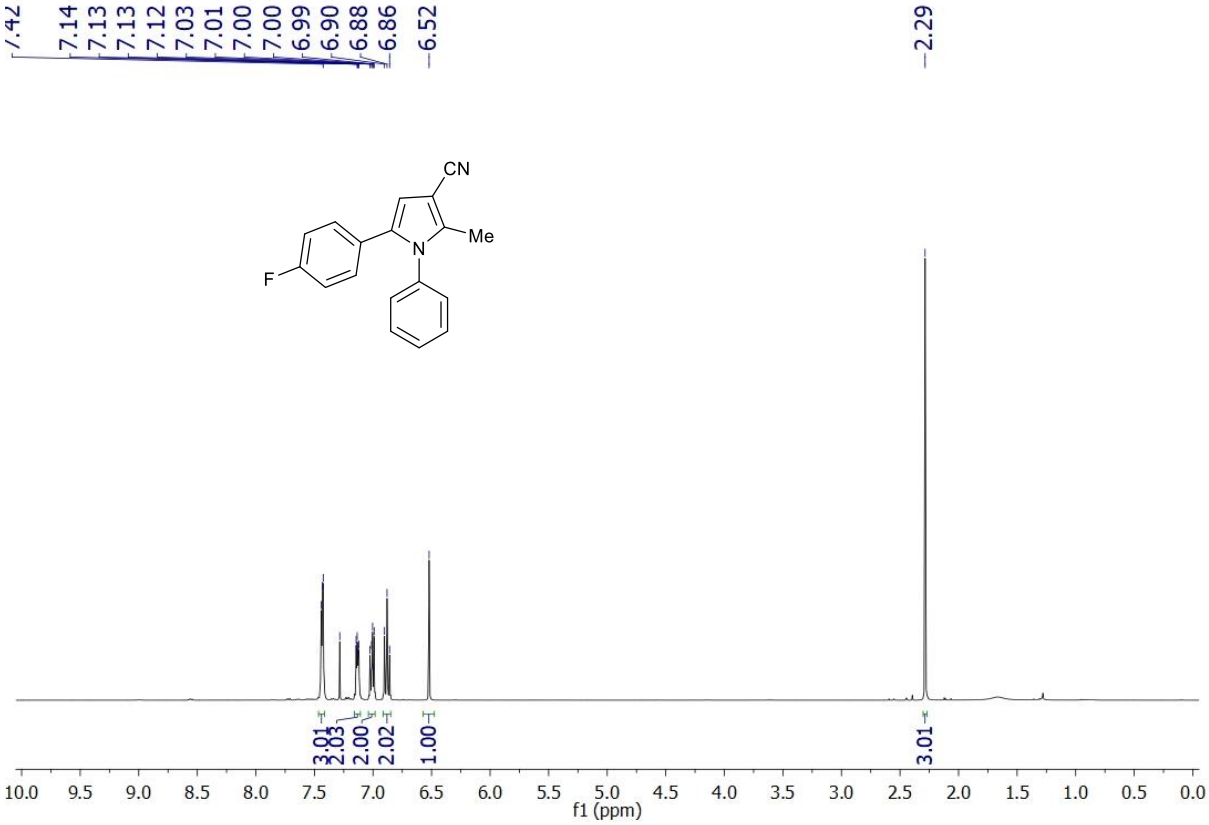
1-Benzyl-2-methyl-5-(p-tolyl)-1*H*-pyrrole-3-carbonitrile

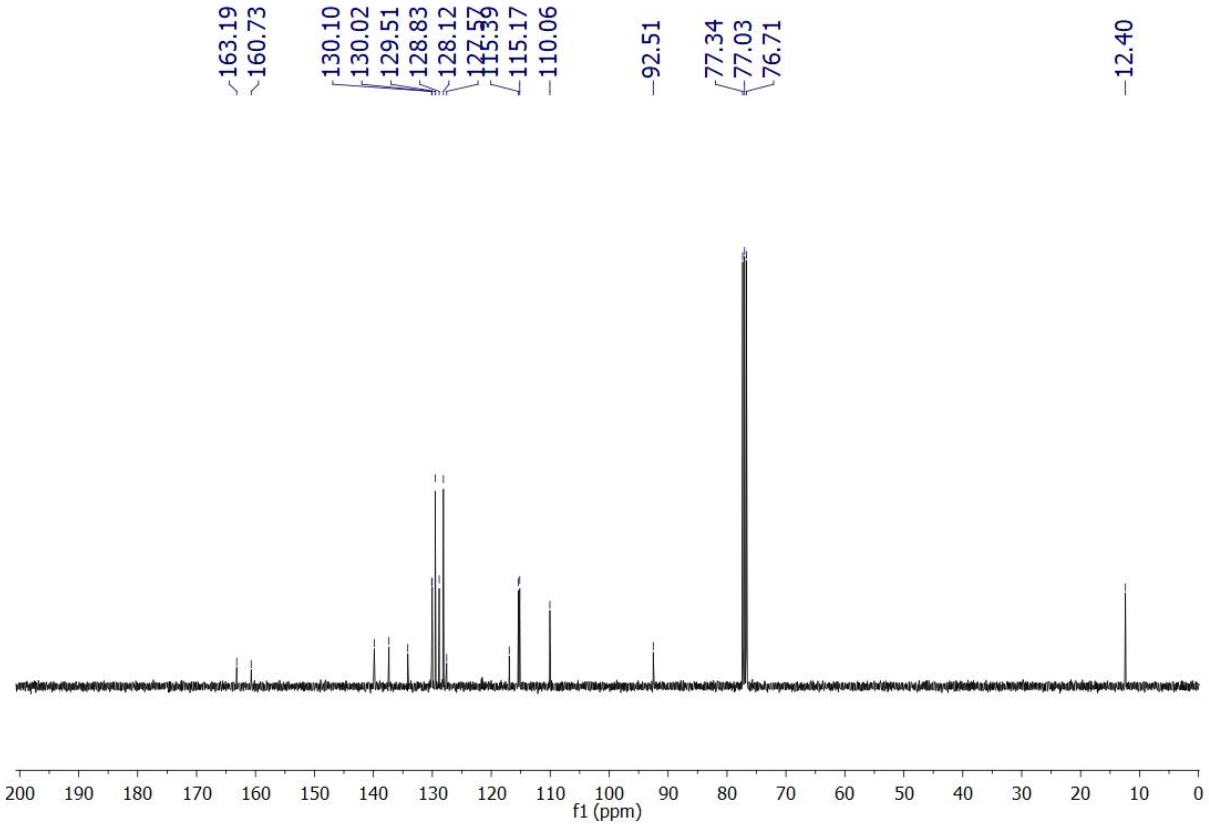


2-(4-Bromophenyl)-5-(4-fluorophenyl)-1-phenethyl-1*H*-pyrrole-3-carbonitrile

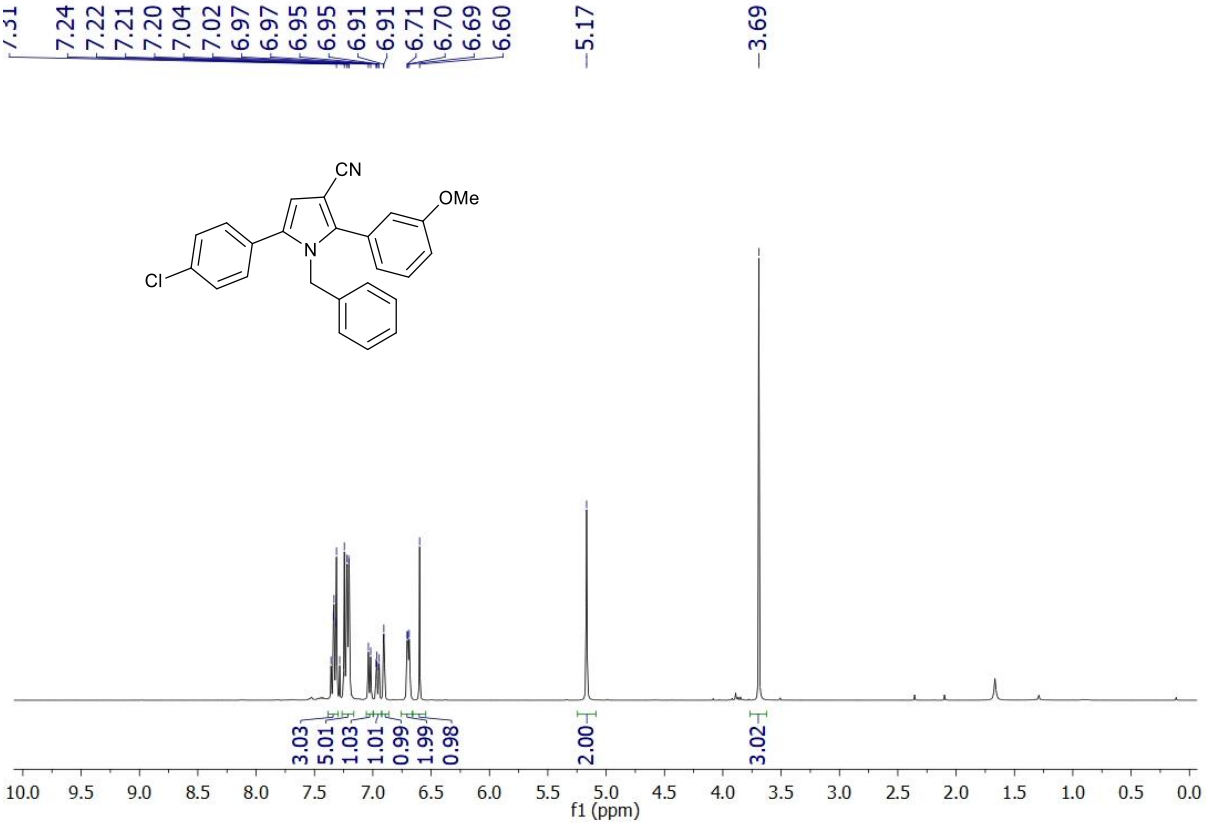


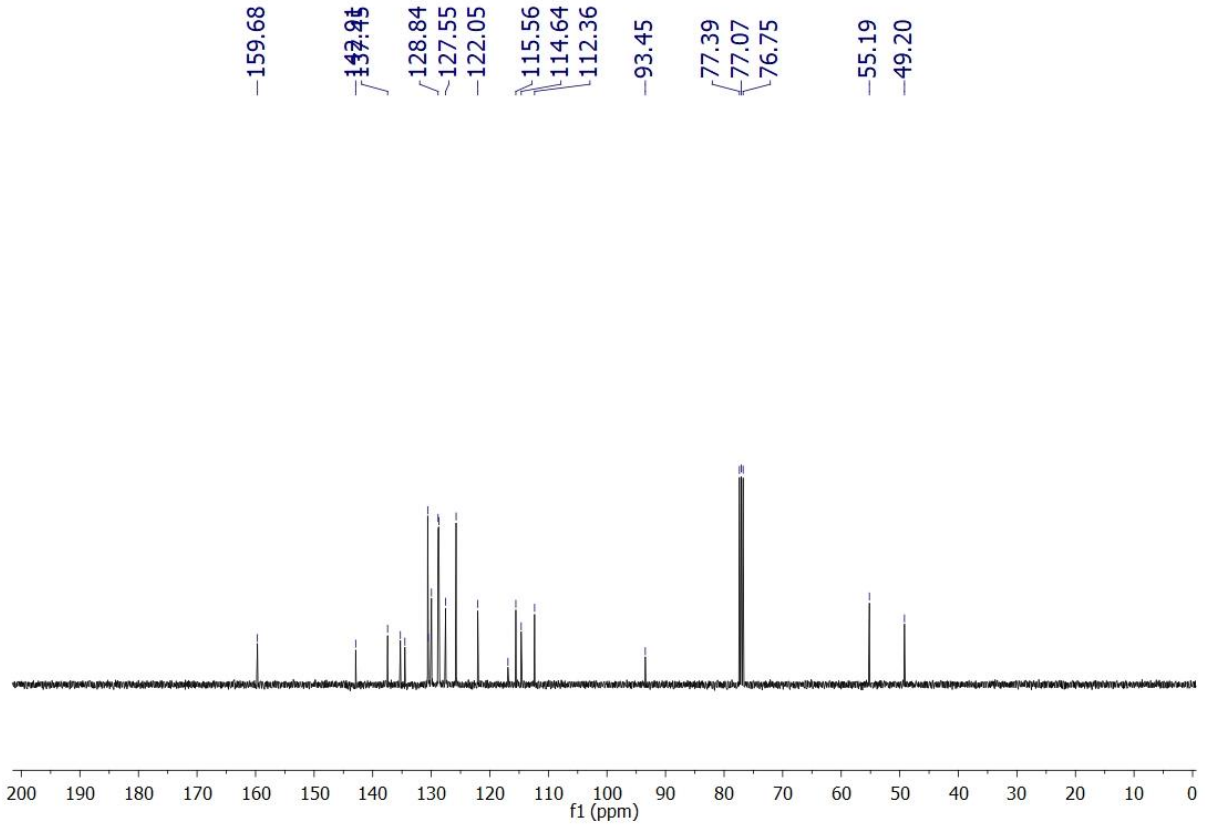
5-(4-Fluorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carbonitrile



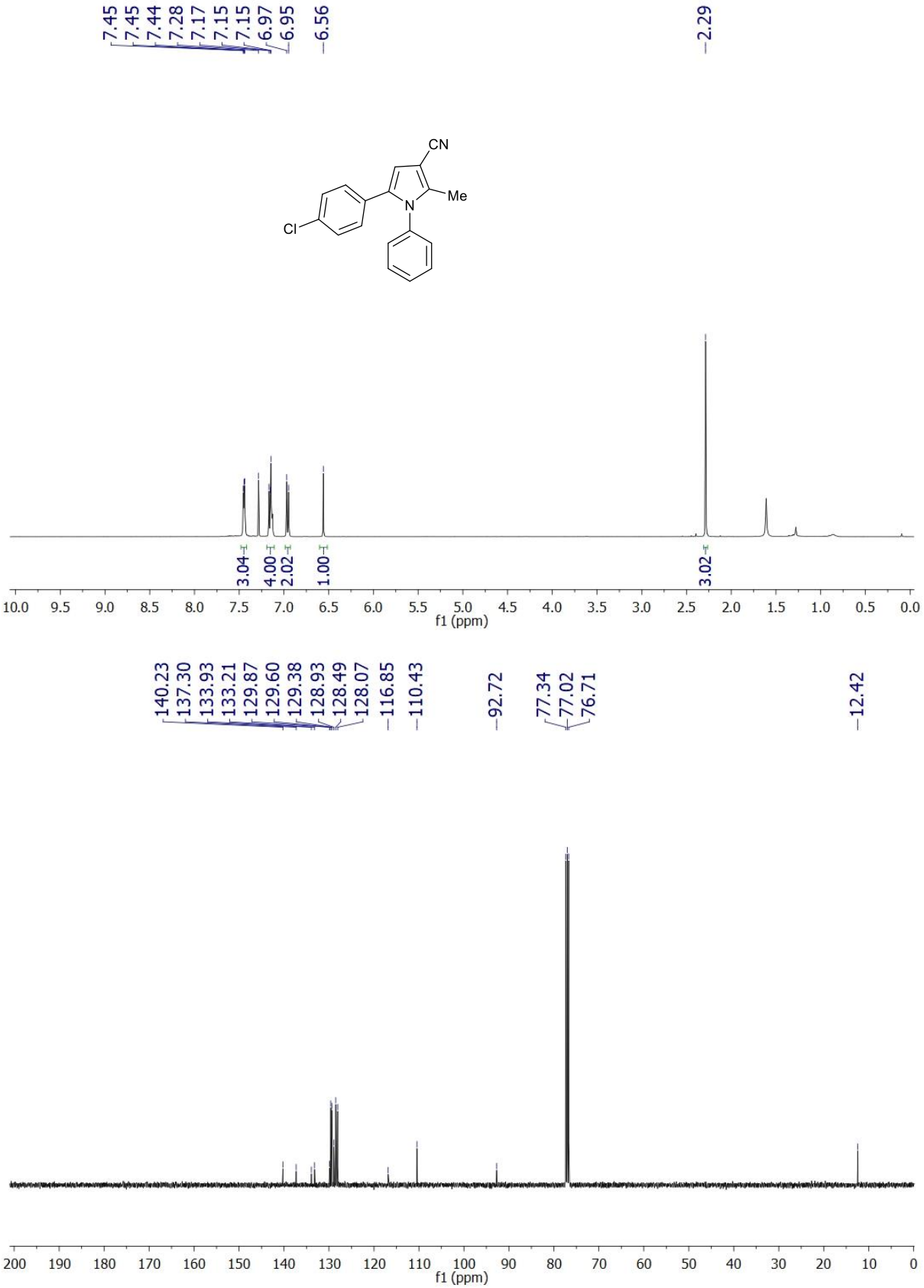


1-Benzyl-5-(4-chlorophenyl)-2-(3-methoxyphenyl)-1*H*-pyrrole-3-carbonitrile

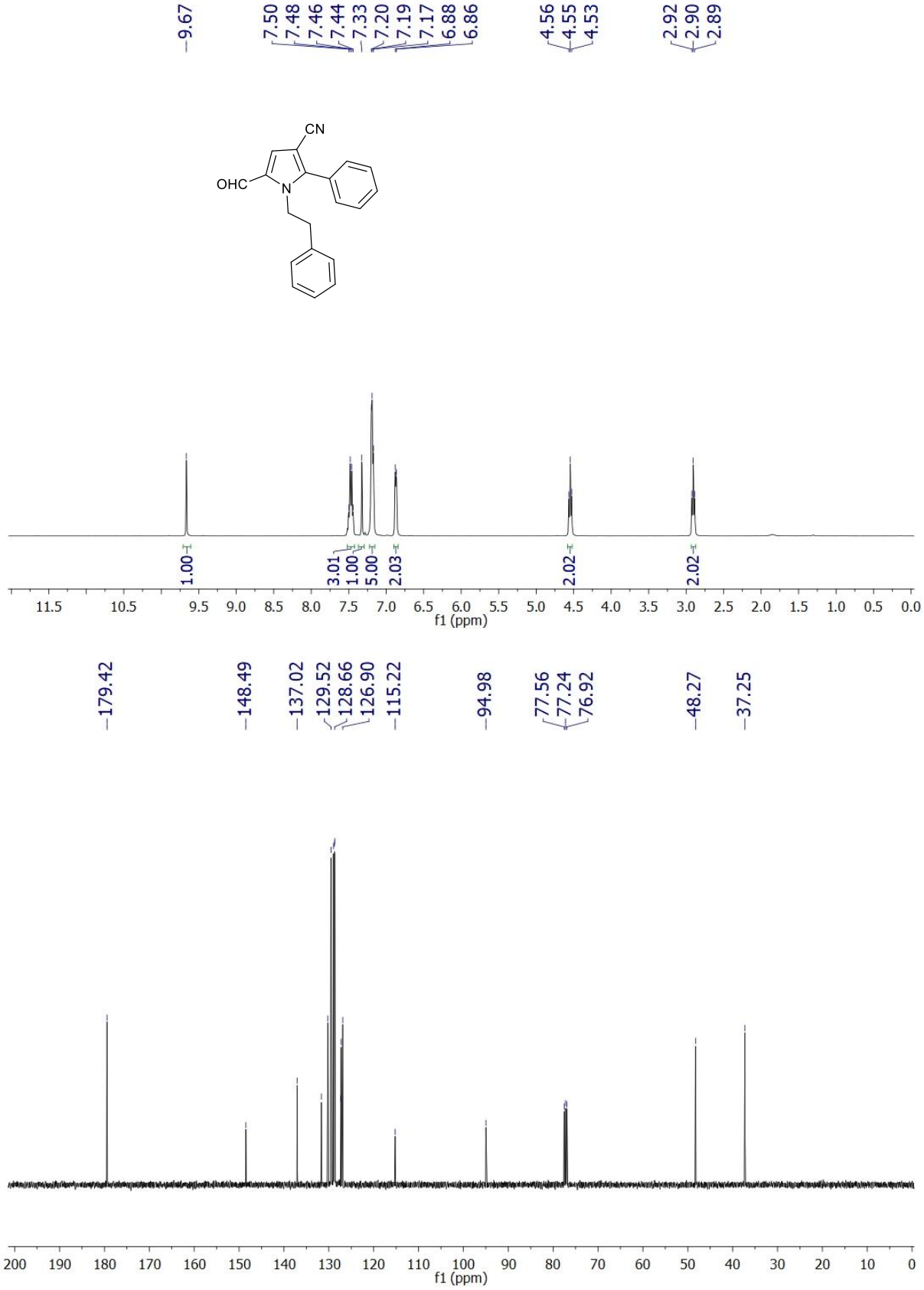




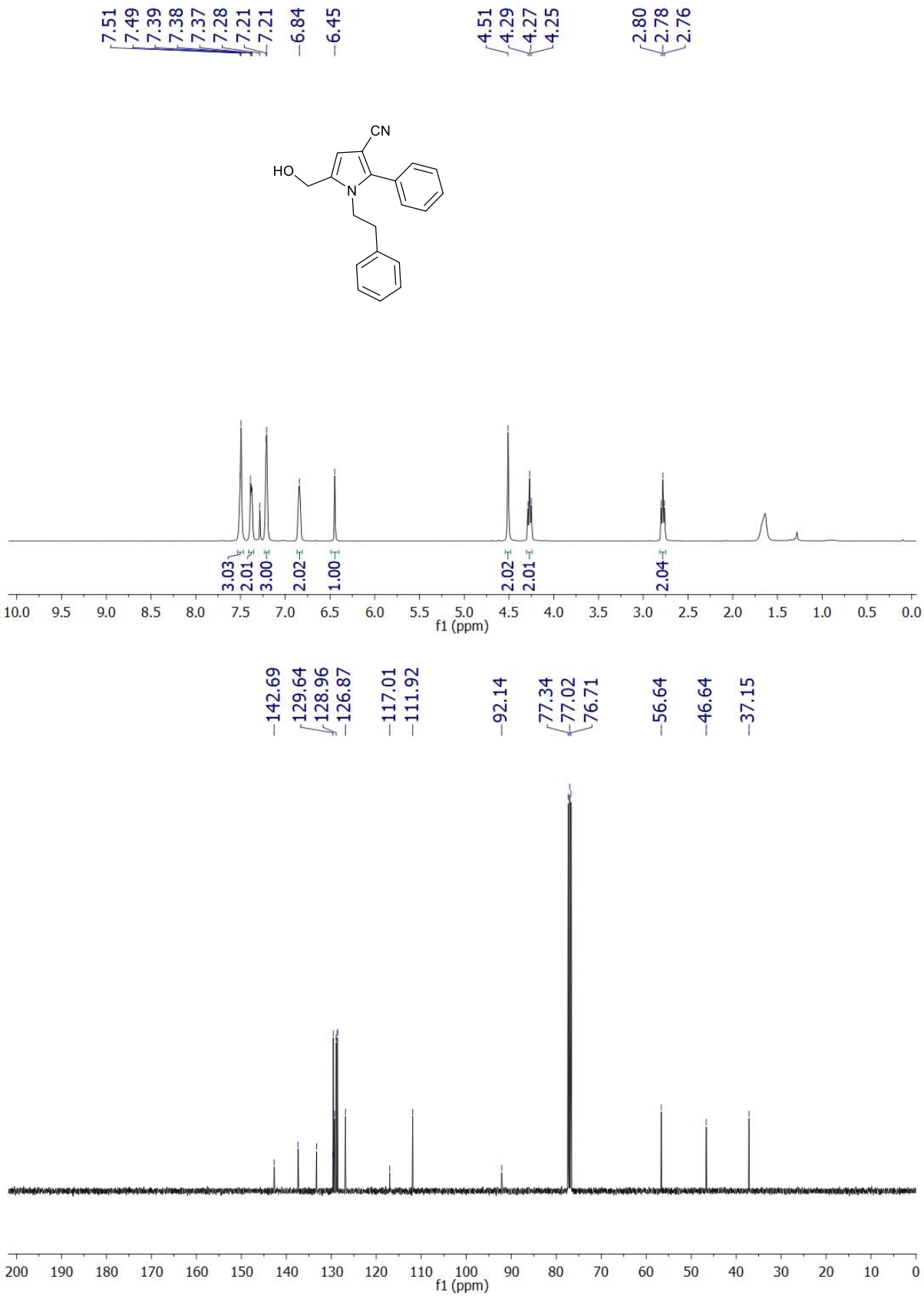
5-(4-Chlorophenyl)-2-methyl-1-phenyl-1*H*-pyrrole-3-carbonitrile



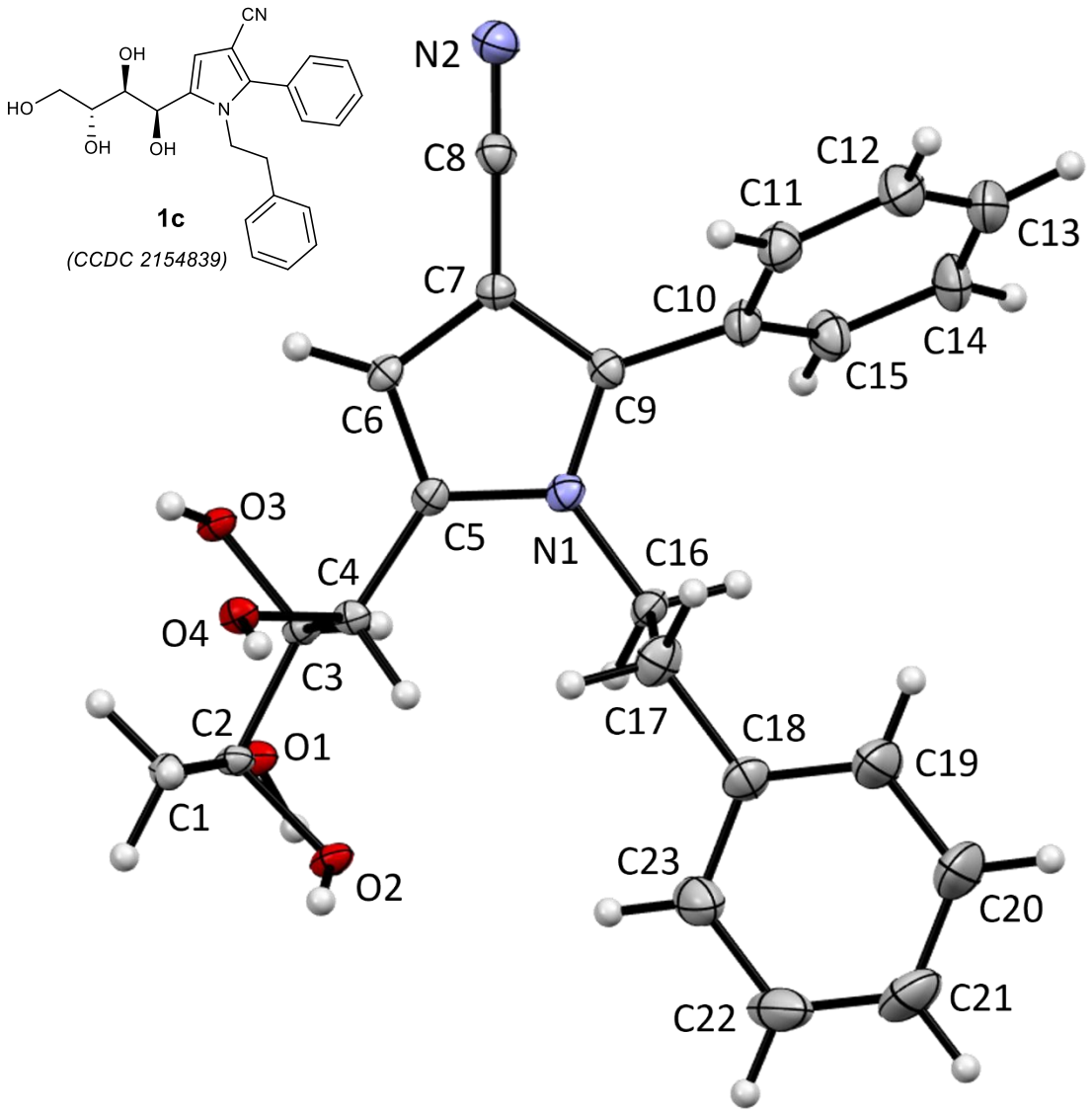
5-Formyl-1-phenethyl-2-phenyl-1*H*-pyrrole-3-carbonitrile



5-(Hydroxymethyl)-1-phenethyl-2-phenyl-1*H*-pyrrole-3-carbonitrile



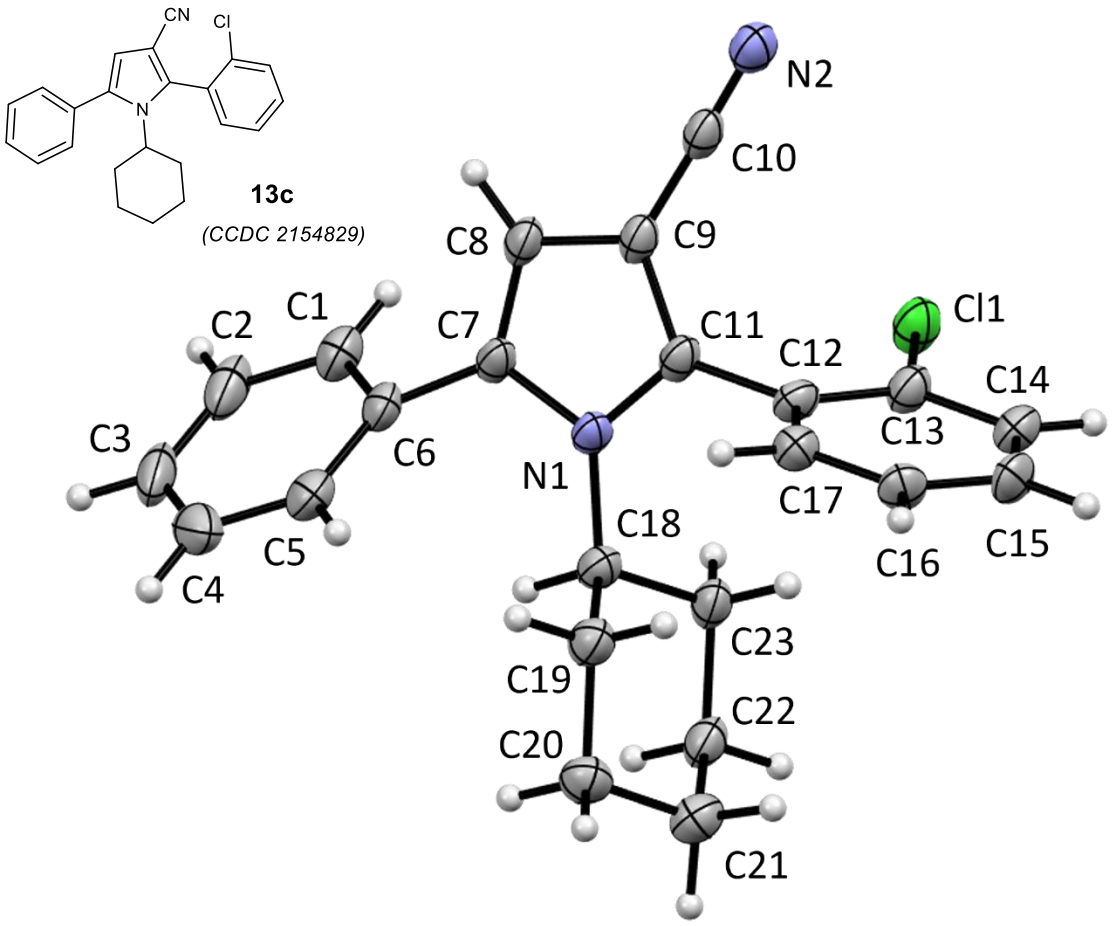
4.3 Single-crystal X-ray and crystal parameters of pyrroles 1c and 13c



(displacement ellipsoids are drawn at the 50% probability level).

Table 4.1: Crystal data and structure refinement for product **1c** (CCDC 2154839)

Empirical formula	C23 H21 Cl N2
Formula weight	360.87
Temperature	100(2) K
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 6.817(2) Å a= 85.965(9)°. b = 10.051(3) Å b= 82.295(9)°. c = 13.998(4) Å g = 86.642(8)°.
Volume	946.9(5) $Å^3$
Z	2
Density (calculated)	1.266 Mg/m^3
F(000)	380
Reflections collected	11937
Independent reflections	3622 [R(int) = 0.1102]
Max. and min. transmission	1.00 and 0.52
Goodness-of-fit on F^2	1.120
Final R indices [I>2sigma(I)]	R1 = 0.0877, wR2 = 0.1689
R indices (all data)	R1 = 0.1546, wR2 = 0.1965



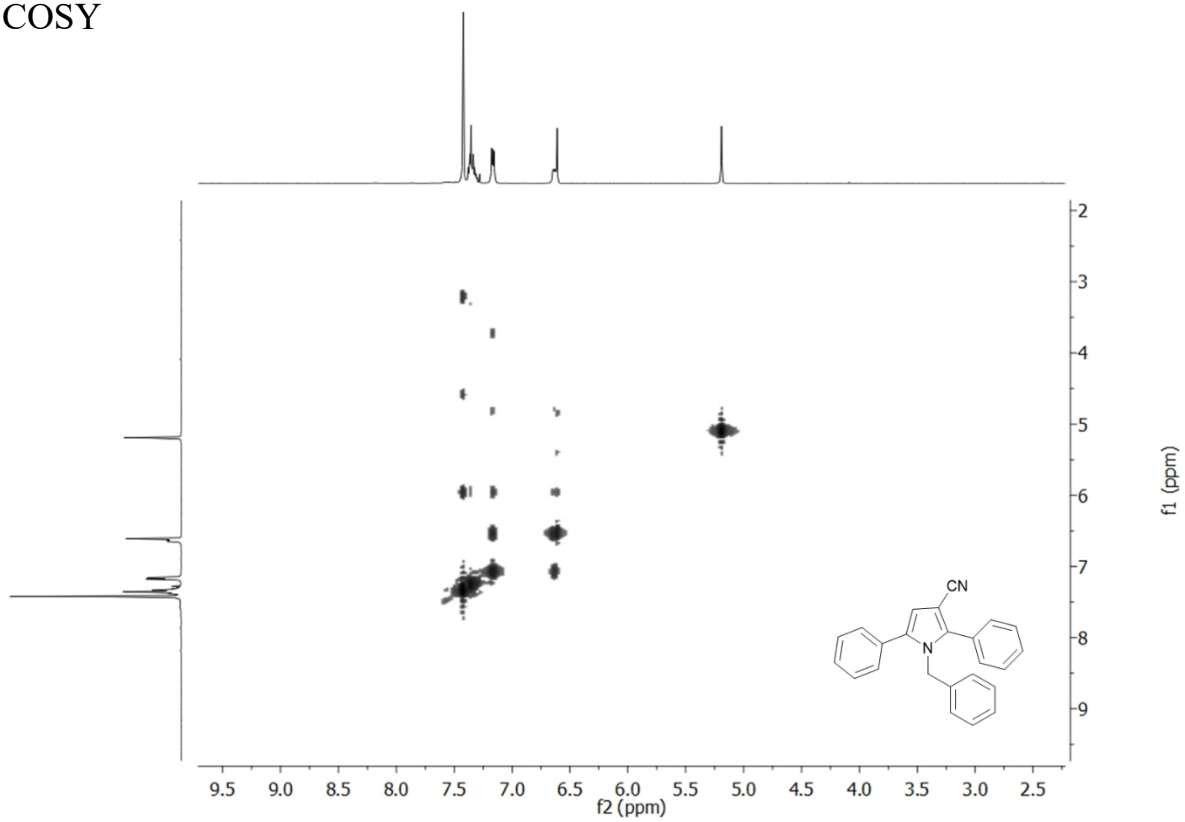
(displacement ellipsoids are drawn at the 50% probability level).

Table 4.2: Crystal data and structure refinement for product **13c** (CCDC 2154829)

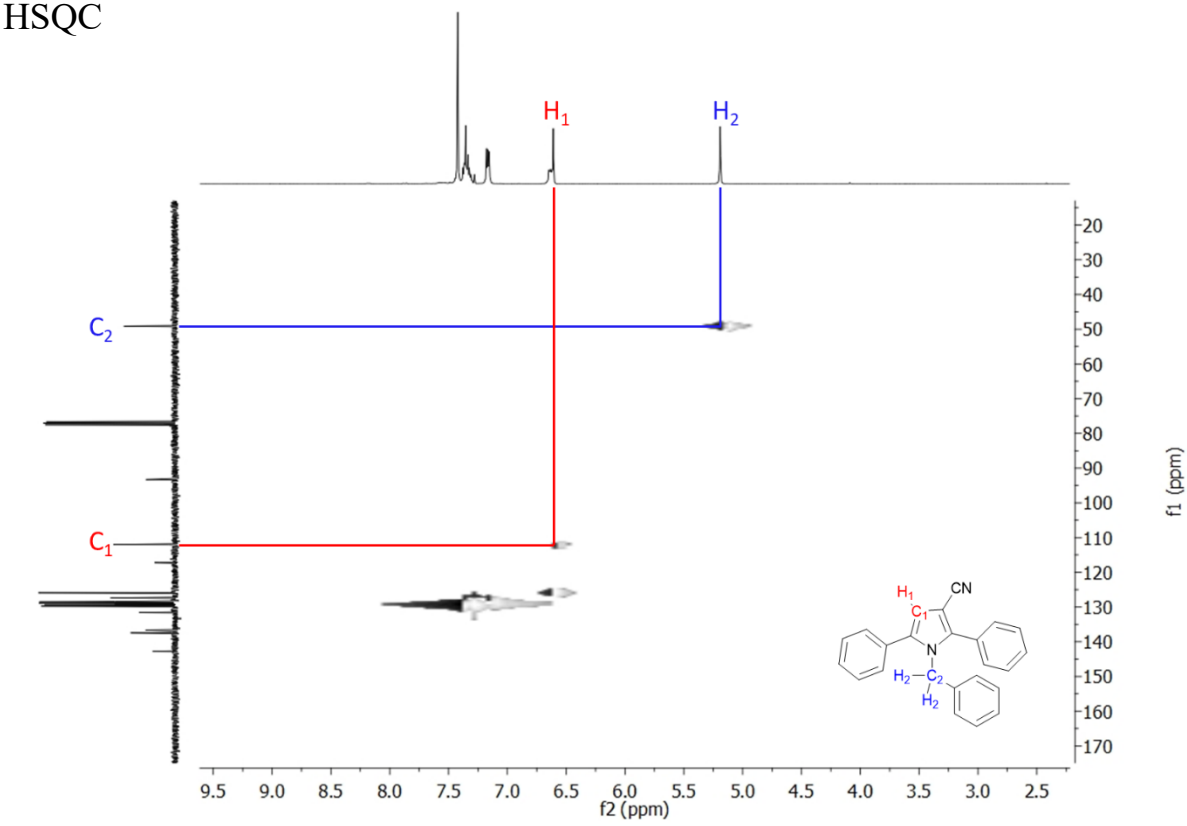
Empirical formula	C23 H24 N2 O4
Formula weight	392.44
Temperature	100(2) K
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.5794(9) Å a= 78.127(4)°. b = 12.2157(13) Å b= 83.884(4)°. c = 17.948(2) Å g = 89.967(4)°.
Volume	2043.1(4) $Å^3$
Z	4
Density (calculated)	1.276 Mg/m^3
F(000)	832
Reflections collected	159527
Independent reflections	29865 [R(int) = 0.0785]
Max. and min. transmission	0.99 and 0.88
Goodness-of-fit on F^2	1.098
Final R indices [I>2sigma(I)]	R1 = 0.0852, wR2 = 0.2133
R indices (all data)	R1 = 0.1186, wR2 = 0.2370

4.4 2D NMR of product 13b

COSY



HSQC



HMBC