[Au]/[Ag] Catalyzed Synthesis of Benzyl Ethers, *N*-glycosides and Molnupiravir

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BY

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CERTIFICATE

Certified that, the work incorporated in the thesis entitled, "***[Au]/[Ag] Catalyzed Synthesis of Benzyl Ethers, N-glycosides and Molnupiravir***" submitted by Saptashwa Chakraborty was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other University or institution.

Date: 19th November 2022

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Declaration

I declare that the written submission of my thesis represents my ideas in my own words. I have adequately cited and referenced the sources where others' ideas have been included. I also declare that I have adhered to all academic honesty and integrity principles and have not misrepresented, fabricated, or falsified any idea/data/fact/source in my submission. I understand that the above violation might result in disciplinary action taken by the Institute and can also evoke penal action from the seeds that have not been properly cited or from whom proper permission has not been taken when needed. I hereby declare that the matter embodied in the report entitled **"[Au]/[Ag] Catalysed Synthesis of Benzyl Ethers, *N*-glycosides and Molnupiravir"** are the results of the investigations carried out by me at the Department of Chemistry, IISER Pune, under the supervision of Prof. Srinivas Hotha and the same has not been submitted elsewhere for any other degree.

Saptashwa Chakraborty

Date: 19/11/2022 **Saptashwa Chakraborty**

20152027

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General Remarks

- NMR spectra were recorded on Bruker-400 MHz, JEOL ECX 400, Bruker 500 MHz, Bruker-600 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in ppm units downfield to TMS.
- High resolution mass spectroscopy (HRMS) was performed on Waters Synapt G2 and Maldi-TOF.
- Low resolution mass spectroscopy (LRMS) was performed on Waters Acquity UPLC-MS (H Class).
- IR spectra were recorded on Perkin-Elmer 1310 and Perkin-Elmer 1600 FT-IR spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured on a JASCO P-1020 or Rudolph polarimeter.
- All reactions were monitored by Thin-Layer Chromatography carried out on precoated Merck silica plates (F254, 0.25 mm thickness); compounds were visualized by UV light or by staining with anisaldehyde spray.
- All reactions were carried out under nitrogen or argon atmosphere with dry freshly prepared solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically homogenous materials unless otherwise stated.
- All evaporators were carried out under reduced pressure on Buchi and Heildoph rotary evaporators below 45 °C unless otherwise specified.
- Silica gel (100-200) and (230-400) mesh were used for column chromatography.
- All gold and transition metal salts were purchased from multinational commercial vendors.
- Materials were obtained from commercial suppliers and were used without further purification.
- Scheme, Figure and Compound numbers in abstract and individual chapters are different.

Abbreviations

Å – Angstrom
Ac – Acetate
AcBr – Acetyl bromide
AcCl – Acetyl chloride
AcOH – Acetic acid
Ac_2O – Acetic anhydride
AG – Arabinogalactan
Ara*f* – arabinofuranosyl/arabinofuranoside
Bn – Benzyl
BnBr – Benzyl bromide
Boc – *t*-butylcarbonyl
BSTFA – N,O-Bis(trimethylsilyl)trifluoroacetamide
Bu_2SnO – Dibutyltin oxide
Bz – Benzoyl
BzCl – Benzoyl chloride
Calcd – Calculated
Cbz – Carbobenzoxy
cat. – Catalytic
$CDCl_3$ – Chloroform-D
$CHCl_3$ – Chloroform
COSY–Homonuclear Correlation Spectroscopy
DDQ – 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DCM – Dichloromethane
DCE – Dichloroethane
DEPT – Distortion less Enhancement by Polarization Transfer
DIPEA – *N,N′*-Diisopropylethylamine
DIC – *N,N′*-Diisopropylcarbodiimide
DMAP – *N,N′*-Dimethylaminopyridine
DMF – *N,N′*-Dimethyl formamide
DMSO-d_6 – Dimethyl sulfoxide (deuterated)
D_2O – Deuterium oxide
δ – delta (in ppm)
eq. – equivalents
Et_3N – Triethyl amine
Et_2O – Diethylether
EDC– 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc – Ethyl acetate
Et_3SiH – Triethylsilane
g – gram
Gal*f* – galactofuranosyl / galactofuranoside
h – hour
HOAt – 1-Hydroxy-7-azabenzotriazole
HMBC– Heteronuclear Multiple Bond Correlation Spectroscopy
HRMS – High-Resolution Mass Spectrometry
HSQC– Heteronuclear Single Quantum Correlation Spectroscopy
Hz – Hertz
Im. – Imidazole
IR – Infrared
J – coupling constant
Kg – Kilogram
Lev – Levulinoate
M – Molar
Man*p* – mannopyranosyl / mannopyranoside
MeI – Methyl Iodide
MeOD – Methanol-D4
mg – milligram
min. – minutes
MHz – Megahertz
mL – millilitre
mmol – millimolar
MS – Molecular sieves
Mtb – Mycobacterium tuberculosis
NaH – Sodium hydride
NAP – N-bromomethyl naphthalene
NGP – Neighbouring group participation
NIS – N-Iodosuccinimide
NMR – Nuclear Magnetic Resonance
NNGP – Non-neighbouring group participation
PMB – p-Methoxy benzyl
PMBCl – p-Methoxy benzyl chloride
Py – Pyridine
PTSA, TsOH – *p*-Toluene sulfonic acid
ppm – parts per million
Rib*f* – ribofuranoside / ribofuranosyl
rt – room temperature
sat. – saturated
Tb – tuberculosis
TBAI – tetra-n-Butyl ammonium iodide
TBDMS – *t*-Butyldimethylsilyl
TBDMSCl – *t*-Butyldimethylchloride
TBDPS – *t*-Butyldiphenylsilyl
TBDPSCl – *t*-Butyldiphenylsilylchloride
TCA – Trichloroacetimidate
TfOH – trifluoromethanesulfonic acid
TFA – Triflouroacetic acid
THF – Tetrahydrofuran
TLC – Thin Layer Chromatography
TMSOTf – Trimethylsilyl trifluoromethanesulfonate
µg – microgram

Abbreviations

μmol – micromolar
μL – microliter
xyl*p* –Xylopyranoside

Synopsis

The thesis entitled, "***[Au]/[Ag] Catalysed Synthesis of Benzyl Ethers, N-glycosides and Molnupiravir***" is divided into four chapters. In chapter 1, a brief overview on glycosylation methods, stereoselective glycoconjugate synthesis and their importance in therapeutics are described. Chapter 2 focuses on describing development of a novel Au/Ag catalytic mild etherification method and its strategic application in one-pot orthogonal protecting group installation. Chapter 3 delineates discovery of a unified catalytic glycosylation reaction for synthesizing various *N*-glycosides. An oxidation-reduction reaction sequence for furnishing C2' modified nucleosides and synthesis of a disaccharide-dipeptide moiety from chlorovirus ATCV-1 have also been explained. Chapter 4 describes about identifying the shortest chemical route for the synthesis of antiviral drug Molnupiravir.

Chapter 1: Glycosylation, Glycoconjugates, and Their Importance in Therapeutics

Glycoconjugates are widely distributed on cell surfaces and secreted fluids in the form of polysaccharides, glycoproteins, and glycolipids or proteoglycans. They play crucial role in a plethora of biological processes such as cell-cell recognition, viral and bacterial infection, inflammation, tumor metastasis, metabolism, etc. However, accessing naturally available glycoconjugates in their pure form is tremendously challenging due to the micro-heterogeneous nature of the biomacromolecules. This particular problem has stalled the progress in understanding the role of glycans and glycoconjugates in living organisms whereas the central paradigm of many revolutionary discoveries in molecular biology focused on *Central Dogma*. In this context, chemical and chemo-enzymatic syntheses of glycans are of great importance as pure glycoconjugates with well-determined structures can be obtained by these methods. Stereoselective synthesis of glycoconjugates is still a very challenging task despite the first successful chemical glycosylation being reported more than a century back. In the last few decades, development of various glycosyl donors, mild catalytic activation methods as well as biomimetic chemo-enzymatic processes have been reported in the literature. Recently discovered gold-catalyzed glycosylation reaction opened up scopes for synthesizing otherwise difficult glycosides by exploiting its milder activation condition and excellent multi-facet compatibility. Therapeutics' importance of glycoconjugates is well recognized and applied successfully in masses. Many carbohydrate-based drugs and vaccines are either in the final phases of clinical trials or already in

medical use to cure diseases. A recently developed Au-Ag catalyzed activation of 1-alkynyl carbonate donor could solve many existing issues in the field of synthetic carbohydrate chemistry which is explored thoroughly in the following chapters.

Chapter 2: [Au]/[Ag] Catalyzed Activation of Novel Shelf-stable Reagents for Etherification

Chemical synthesis of oligosaccharides and glycoconjugates uses many protecting groups that can be installed or removed without affecting other functional groups that are already present. Benzyl ethers are one of the most commonly used protecting groups in synthetic carbohydrate chemistry as it stabilizes the oxycarbenium ion in the transition state and can be subjected to hydrogenolysis under neutral condition. Installation of benzyl ether often invokes strong basic conditions that might be detrimental to other protecting groups such as esters and carbamates. To overcome this

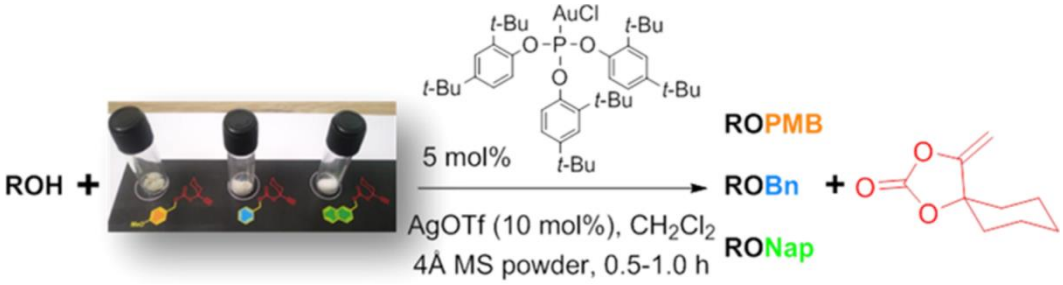


Figure 2.1. Synthesis of Benzyl, PMB, and Nap-ethers using novel shelf-stable reagents

problem, chemists have discovered many acid-catalyzed activation methods using benzyl trichloroacetimidate, BnOTf, Dudley's reagent for etherification. However, these reagents are moisture sensitive, not shelf-stable, and do not work well on carbohydrate hydroxyl groups. Hence, a new mild efficient method for etherification using stable reagents is highly desirable. Taking a cue from the silver-assisted gold-catalyzed glycosylation, a new catalytic method has been identified that enables protection of hydroxyl groups as benzyl, p-methoxybenzyl, or naphthylenemethyl ethers using easily accessible and stable carbonate reagent. The method has been tested on a wide range of substrates that includes primary and secondary hydroxyl groups of saccharide unit bearing various protecting groups, menthol, cholesterol, serine etc. The often-utilized olefins and benzoates, as well as benzylidene-, silyl-, Troc-, and Fmoc-protecting groups

do not get affected during the newly identified protocol. Regioselective protection and one-pot installation of benzyl and *p*-methoxybenzyl ethers are demonstrated thoroughly in this chapter.

Chapter 3: Unified, Direct, and Catalytic Syntheses of *N*-glycosides

N-glycosides are compounds having a carbohydrate unit attached to an aglycone through a C-N bond linkage at the reducing end instead of a hydrolyzable C-O bond. Synthesis of *N*-glycosides from stable glycosyl donors in a catalytic fashion is still challenging as its complexities revolve around the nature of the leaving group, non-similar reactivity of different carbohydrate units, and solubility issue of the nucleophiles though they exist ubiquitously in DNA, RNA, glycoproteins, etc. Many *N*-glycoside drugs are in the market that are used to cure viral infection, bacterial infection and cancer. Vorbrüggen nucleosidation is the most common and widely used glycosylation reaction for pyrimidine glycoside synthesis whereas Yu glycosidation for purine

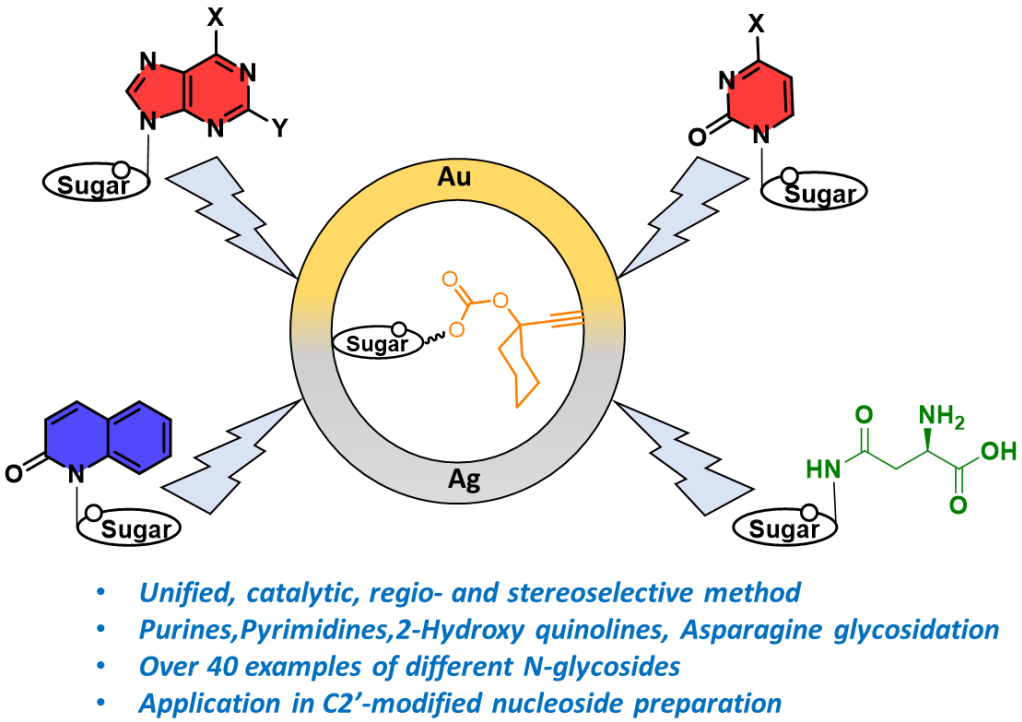


Figure 3.1. Catalytic syntheses of various important *N*-glycosides

glycoside synthesis has been recognized as a benchmark in the field. Takahashi first demonstrated the direct attachment of asparagine to a saccharide unit through its amide –$CONH_2$. Albeit limited success in synthesizing crucial *N*-glycosides, there is no unified prevalent method for all kinds of

N-glycoside synthesis through direct nucleophilic addition. Here in this chapter, silver-assisted gold-catalyzed activation of alkynyl glycosyl carbonate donors has been explained to be versatile for the synthesis of purine and pyrimidine nucleosides, asparagine-glycosides and quinolin-2-one *N*-glycosides. Thus synthesized nucleosides were subjected to the oxidation-reduction sequence for the conversion of Rib*f*- to Ara*f*- nucleosides giving access to otherwise difficult nucleosides. Furthermore, the protocol is demonstrated to be suitable for the synthesis of 2'-modified nucleosides in a facile manner. Direct attachment of asparagine containing dipeptide to the glucopyranose and subsequent extrapolation to afford the dipeptide disaccharide unit of chloroviruses is yet another facet of this endeavor.

Chapter 4: Developing the Shortest Chemical Synthetic Route for Antiviral Drug Molnupiravir

Molnupiravir or EIDD-2801 is an *N*-hydroxy cytidine prodrug that was discovered at Emory University as a potential anti-influenza drug candidate. After the emergence of the global COVID-19 pandemic, this drug was under clinical trial as a therapeutic candidate against Sars-Cov-2 virus and eventually cleared phase 3 clinical trial. It was found that this particular drug has an advantage over Remdisivir as Molnupiravir can be administered orally. Recently, this N4-D-β-hydroxycytidine (NHC) analog has been approved as an antiviral drug for treating covid-19 infected adult patients who are at risk of progressing to hospitalization. The patented route for

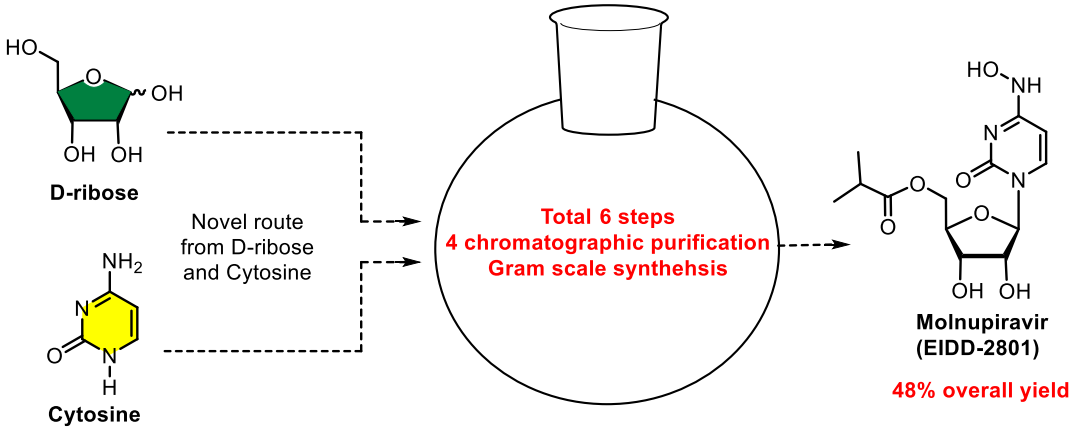


Figure 4.1. Developing shortest chemical route for Molnupiravir synthesis

the drug by Merck and Ridgeback Biotherapeutics consists of 10 steps and less than 10% overall yield. Later on, a few chemical and chemo-enzymatic synthetic methods are reported where intermediate nucleoside or expensive enzymes have been used. Taking a cue from the excellent *N*-glycosidation protocol that was developed in our lab recently, we could successfully synthesize this drug molecule in just 6 steps starting from commodity cheap chemical D-ribose and cytosine with 48% overall yield. The whole synthetic route involves just four chromatographic purifications and is applied in gram-scale synthesis.

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Chapter 1: Glycosylation, Glycoconjugates and Their Importance in Therapeutics

Chapter 1

1.1. Introduction to an early history of carbohydrates:

One of the most prevalent and widely distributed chemical substances on our planet is carbohydrates. Carbohydrates comprise most of the earthly biomass that is made up of plant tissues.[1] When life began to emerge on Earth during the prebiotic era, carbohydrates were essential in establishing a direct connection between solar energy and chemical energy through photosynthesis.[2] Plants and many microorganisms store carbohydrates as a source of chemical energy.[3] Through respiration, non-photosynthesizing organisms utilize this chemical energy (glycolysis)[4] for their survival and evolution. Additionally, carbohydrates are frequently used as molecular building blocks in plants (cellulose), arthropods(chitins), and the cell walls of a wide range of species, from simple single cells to extremely complex multicellular ones.[5] Apart from their role as a major source of energy for living organisms, carbohydrates are rarely present in Nature as a monomer (monosaccharide); rather they serve as building blocks for more complex molecules *viz*. glycoconjugates.

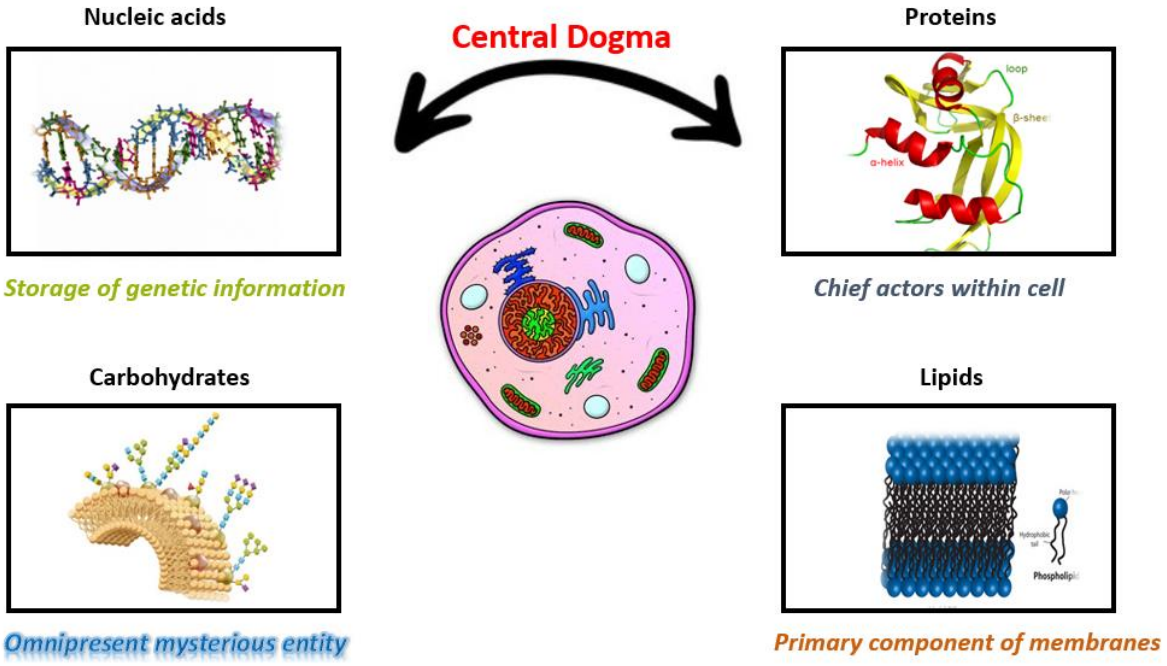


Fig. 1.1: Four major biomacromolecules of life

Glycoconjugates[6,7] have myriad roles in organisms but they were often overlooked due to their complex structures and intricate functions. The biological utilities of carbohydrates are prominent in simple to complex organisms that require the interaction between cells and extracellular matrix.[8] Between the four major biomacromolecules that build a living cell (essentially nucleic acids, proteins, lipids, and carbohydrates), the biochemical importance of carbohydrates was unclear till Leloir's discovery of the metabolic pathways of sucrose[9] and biosynthesis of glycans.[10] During many revolutionary discoveries of molecular biology in 1970, the central paradigm of research was focused on the *Central Dogma* (**Fig 1.1**).[11] The ability to control one class of molecules based on the knowledge of another, its template-based accuracy, the patterns of sequence homology and relatedness that predict function and show evolutionary linkages are what give this concept its significance. Along with this well-established hypothesis about the flow of biological information from DNA to RNA to protein, discoveries of many essential tools like sequencing[12] and editing genomes[13] skyrocketed the research in protein and nucleic acids. In parallel, successful discoveries on the importance of lipids[14] (as a major component of membranes) and other small molecule metabolites were made.[15] Carbohydrates remained an omnipresent mysterious entities in biological science because of the inherent complexity of their structures, the inability to identify

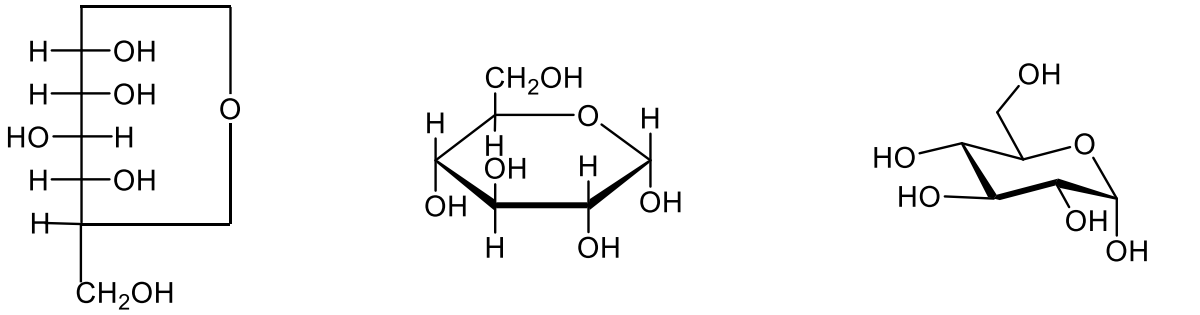


Fig. 1.2: Different conformational representations of α-D-glucose

their sequences, and, the fact that their biosynthesis is non-templated.[16] However, the chemistry of carbohydrates has been a conspicuous matter since the 18th century[17] when an unknown sugar was isolated from honey, grapes, and starch that was different from sucrose. Later on, Jean Dumas named this unknown sugar as 'glucose'. The early definition of carbohydrates was known to be

compounds that are polyhydroxy aldehydes or polyhydroxy ketones or substances that on acidic or enzymatic hydrolysis produce polyhydroxy aldehydes or polyhydroxy ketones.[18] In the late 19th century, after the successful finding of stereoisomerism for tetrahedral carbon by Le Bel and Vant Hoff, Emil Fischer discovered the structure of glucose for the first time although the actual conformation at *C*5 position was determined almost after sixty years with the help of X-ray crystallography. Meanwhile, Heidi and Heinz proposed that the cyclic structure of glucose molecules can be present in the solution with two different optical rotations.[19] Haworth's demonstration of the ring conformation of carbohydrates was pioneering work on stereochemistry and conformation of carbohydrate molecules (**Fig 1.2**).[20] Odd Hassel and Richard Barton demonstrated that the pyranose ring takes on a non-planar shape when glucose is present in chair form with axial and equatorial hydrogen atoms, after the previous findings by Fischer and Haworth on the characteristics and conformation of glucose. The complex reaction of attaching a sugar unit to another moiety was termed the 'glycosylation reaction'. In 1988, Richard Dwek first coined the term 'glycobiology' which then became a new frontier in molecular biology research with the perspective of understanding the cellular and molecular biology of glycans. Eventually, glycobiology has become one of the rapidly growing fields with broad applicability to a wide range of biomedical, biotechnological, and fundamental research fields.[21]

1.2. A Brief description of Glycosylation:

Glycosylation is often described as a process by which carbohydrate molecules are covalently attached to a target macromolecule, typically proteins or lipids.[22] This process is considered to be one of the most ubiquitous, heterogeneous, non-templated, and stereo-chemically complex post-translational modification that has many important structural and biophysical roles.[23,24] Installation of glycans via glycosylation reaction on different bio-macromolecules has a huge impact on various biological processes such as fertilization, viral replication, parasitic infection, cell growth, cell-cell adhesion, inflammation, and so on.[25] Glycosylation is highly sensitive to alterations in cellular function, and abnormal glycosylation can be related to the cause of a number of diseases including cancer and rheumatoid arthritis. In a prokaryotic cell, glycosylation reaction takes place at the interface of the cytoplasmic membrane and cytoplasm or in the periplasm whereas, in a eukaryotic cell, the process occurs in the endoplasmic reticulum, Golgi apparatus and sometimes

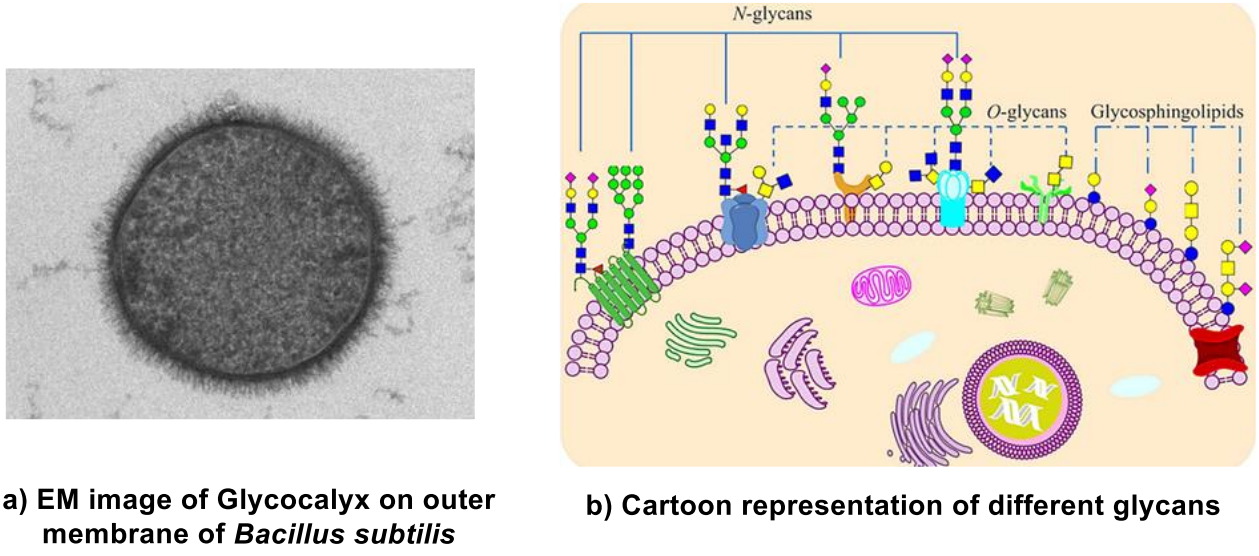
in nucleus and cytosol.[26] Though carbohydrates can be present in the cell without being attached to any other molecules, the majority of the glycans are generally attached to either protein (glycoprotein) or lipid (glycolipid). During glycosylation, an oligosaccharide is attached through a nitrogen atom of an asparagine side chain or an oxygen atom of a serine/threonine residue.[23] *C*-glycosylation is a less common form of glycosylation that occurs on tyrosine or tryptophan residue. *S*-linked glycosylation occurs through a sulphur atom on cysteine or methionine residue whereas *C*-mannosylation happens through *C–C* linkage formation at the *C2* position of tryptophan.[27] Millions of years of biological evolution have selected and optimized the enzymes that are responsible for glycosylation in cells and these enzymes are categorized under the name glycosyltransferases, glycosidases and glycosynthases.[28] In this site-specific and stereoselective reaction, a new covalent bond forms between a glycosyl donor and a glycosyl acceptor. In living organisms, majorly a limited set of donor glycosides; conspicuously the *Leloir* donor glycosides are used and the nature of the glycosyltransferases determines whether glycosylation occurs with *retention* or *inversion* of configuration at the anomeric center. The complete understanding and mechanisms used by glycosyltransferases are not resolved yet and are the subject of intense research.[29]

1.3. Major types of glycosylation and their importance:

In this section, major classes of glycosylation found in natural systems (**Fig 1.3**) and their importance will be discussed.

1.3.1. *N-linked glycosylation:*[30,31] In this process, *N*-acetylglucosamine is attached to the *N* atom of an asparagine side chain via a β-1*N* linkage. Generally in these asparagine-linked glycoconjugates, a core $GlcNAc_2$ mannose $(Man)_3$ is present that might get elaborated and modified further. This addition and modification generally include galactosylation, fucosylation, GlcNAcylation, and sialylation. Though *N*-glycosylation is very common in eukaryotes and archaea but rarely found in bacteria. Biosynthesis of *N*-linked glycans takes place via three major steps. i) Synthesis of a lipid precursor in which a branched oligosaccharide is attached to Dolicol phosphate (Dol-P) on the cytoplasmic side of ER, ii) *En block* transfer of the precursor oligosaccharide to protein and subsequent addition and trimming as a part of quality control process in the lumen of ER and finally iii) processing of the oligosaccharide in Golgi apparatus.[32]

N-linked glycans have important intrinsic and extrinsic functions such as providing structural components to the cell wall and ECM, modulation of protein properties (solubility and stability), trafficking of glycoproteins, and mediation of cell-cell signaling.



a) EM image of Glycocalyx on outer membrane of *Bacillus subtilis*

b) Cartoon representation of different glycans

Fig. 1.3: Electronic microscope image and cartoon representation of glycans[33,34]

1.3.2. *O-linked glycosylation:*[35–37] *O*-glycosylation is a post-translational modification in which glycosylation happens on the amino acids having free hydroxyl functional groups, usually serine and threonine. In prokaryotes, this process occurs in the cytoplasm whilst for a eukaryotic cell, it takes place in the endoplasmic reticulum, Golgi apparatus, and occasionally in the cytoplasm. Different types of *O*-glycosylation linkages include *O*-GlcNAc, *O*-GalNAc, *O*-Gal, *O*-Man, *O*-Fuc, *O*-Glu, many glycosaminoglycans (GAGs) and lipids. After the protein is folded, the addition of GalNAc from a precursor molecule takes place on serine/threonine residue via the action of an enzyme called GalNAc tranferase in the Golgi apparatus. *O*-GalNAc sugars play a major role in immune response, fertilization and protection against invading pathogens. GlcNAc addition to the serine or threonine occurs on cytoplasmic and nuclear proteins and this is the first example of glycosylation that does not occur on secretor proteins. *O*-GlcNAc modification competes with phosphorylation at the same amino acids residue which suggests the complexity of these modifications and regulatory circuits. O-GlcNAcylation has a major role in enhancing the Warburg effect, a change in cancer cell metabolism which favors their growth. Glycosaminoglycans are long linear polysaccharide chains attached to the protein to form proteoglycans. These

polysaccharides consist of a repeating unit of amino sugar and a uronic acid or galactose. Based on their core disaccharide structure GAGs are classified into four categories which are Heparin/Heparan sulfate (HSGAGs), Chondroitin/Dermatan sulfate (CSGAGs), Hyaluronic Acid (HA), and Keratan Sulfate (KS). GAGs are crucial in the formation of the glycocalyx and as these classes of molecules are highly polar and hydrophilic, they have their role in the body as lubricants and shock absorbers.

1.3.3. *Glypiation*:[38,39] In this kind of special glycosylation, protein is attached to the lipid anchor via glycan chain to form GPI (glycosylphosphatidylinositol) anchor. It is a common post-translational modification that localizes protein to the cell membrane. GPI anchor is well observed in surface glycoproteins in eukaryotes and archaea. A phosphoethanolamine linker part of GPI binds to the *C*-terminus of a particular target protein whereas the phospholipid tail present in the glycan core structure anchors the protein to the membrane. GPI anchors have vast functional diversity which includes cell adhesion, signal transduction, and immune recognition.

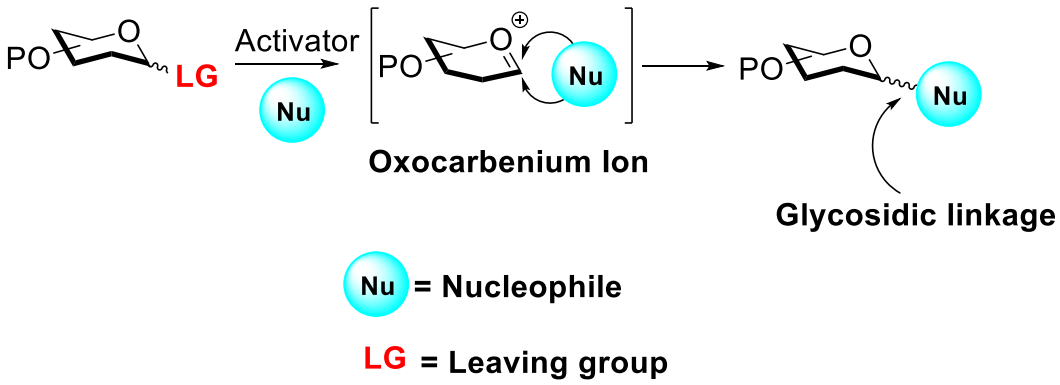
Apart from these examples, *C*-mannosylation[40] (where a mannose sugar is added to a tryptophan residue via a *C*-*C* bond) and phosphoserine glycosylation[41] are also observed in the living organisms.

For a better and thorough understanding of the roles of glycans and to expand their scope for biomedical research, pure glycans with well-determined structures are necessary. Unlike nucleic acids and proteins, which are easily attained in a homogeneous form using polymerase chain reaction (PCR), purification, and recombinant technologies, glycans present in biological systems are heterogeneous. Hence, it is often a daunting and cumbersome task to isolate pure glycans from the natural systems in good quantity.[25] In this context, chemical syntheses of oligosaccharides and glycoconjugates have become relevant by which homologous glycans in their purest form can be obtained in larger quantities.

1.4. Chemical Glycosylation:

A chemical glycosylation reaction can be described as a nucleophilic displacement of a leaving group attached to the anomeric carbon of a glycosyl donor via the action of certain promoters (Lewis acids, Brønsted acids, neutral reagents, inorganic salts etc).[42] After the leaving group is

displaced, an oxocarbenium ion intermediate forms that is attacked by a glycosyl acceptor (nucleophile) to form a new glycosidic bond (**Scheme 1.1**).

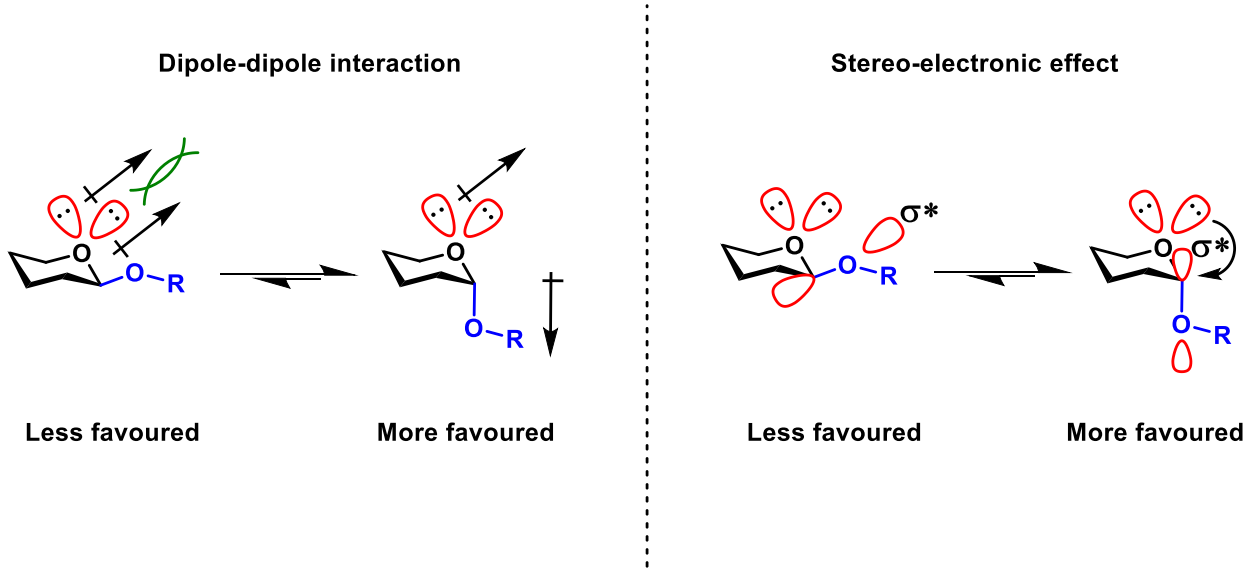


Scheme 1.1: General representation of chemical glycosylation reaction

The biggest challenge of this chemical reaction is attaining the right stereoselectivity of the formed glycosidic bond. The very first chemical glycosylation reaction was performed by Michael where aryl glycosides were synthesized from glycosyl halide in 1879.[43] Later on, Emil Fischer successfully synthesized alkyl glycosides from hemiacetals.[44] Following their lead, Koenigs and Knorr came up with a more controlled and general glycosylation procedure using glycosyl halide as a donor and Ag_2CO_3 as an activator.[45] Since then, many new methodologies have been developed to date focusing on the stereochemical outcome and efficiency of the glycosylation reaction which will be discussed later in this chapter.

1.5. Factors that control Chemical Glycosylation:

1.5.1 *Anomeric effect:* The most stable conformer of a cyclohexane system is the one having chair conformation and all the substituents in the equatorial position. This concept is only applicable to the 1-hydroxy sugar moieties where β-conformer is more stable via intramolecular hydrogen bonding with *O*-5 ring oxygen. When this hydroxyl group at *C*1 position is replaced by OR/SR/ halides or any other polar group, it prefers the axial conformation at the anomeric center. This phenomenon was first observed by Edward[46] and later named as anomeric effect by Lemieux.[47] It can be explained by the dipole-dipole interaction where two dipoles of the heteroatoms are partially aligned in the equatorial configuration, therefore repelling each other whereas in the axial configuration, the opposite orientation of the dipoles stabilizes the system.



Scheme 1.2: Anomeric effect

The molecular orbital theory explains that the axial configuration is stabilized by the hyperconjugation of the nonbonding ring oxygen lone pair electron to the antibonding orbital of the C-X bond at the anomeric position to make it the thermodynamically stable (**Scheme 1.2**). It is worth mentioning that as the glycosylation reaction is irreversible in nature, the role of the anomeric effect is often reduced and other factors that control the orientation of the formed glycosidic bond come to the forefront of the discussion.[48]

1.5.2. *Structure of glycosyl donors and acceptors:*[49,50] As in the majority of the cases glycosylation reaction proceeds through a unimolecular S_N1 mechanism; the orientation of the leaving group present in the glycosyl donor is of lesser importance since an oxocarbenium intermediate forms. If the reaction proceeds via a bimolecular S_N2 mechanism, an inversion of stereoconfiguration is observed at the anomeric center. In that case, glycosyl donors with 1,2-cis configuration gives 1,2-trans glycosidic linkage and vice-versa. This is well observed in cases of glycosyl halide activation via an insoluble catalyst, α-imidates in the presence of BF_3-Et_2O at low temperature and 1,2-anhydro sugars as glycosyl donors. On the contrary, 1,2-trans oriented glycosyl donor such as glycosyl thiocyanate, β-glucosyl halide or in-situ generated glycosyl triflate specifically afforded 1,2-cis linkages.

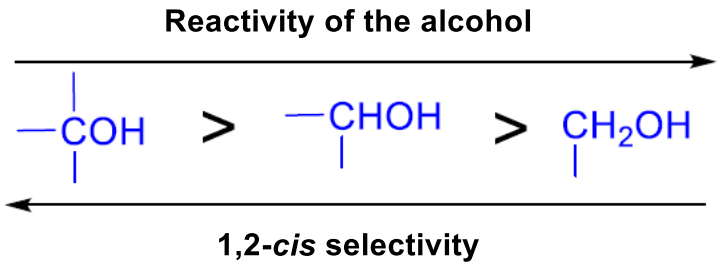
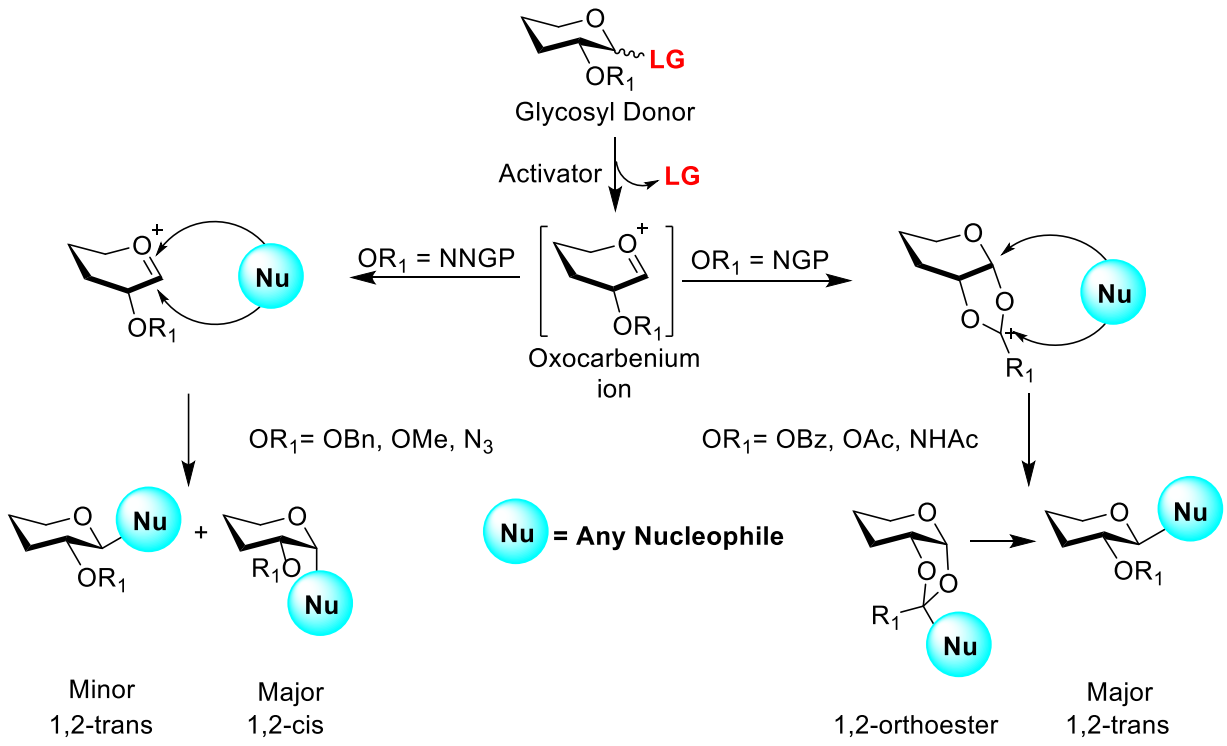


Fig. 1.4: Reactivity and selectivity order of alcohols

1,2- cis selectivity outcome is inversely correlated to the reactivity of the hydroxyl group in the glycosyl acceptor.[51] Primary hydroxyl group is a stronger nucleophile compared to the secondary hydroxyl group (**Fig 1.4**) and thus it is more difficult to control the reaction which results in poor α:β selectivity.[52] This principle is evident in case of the synthesis of glycopeptide as well where the secondary hydroxyl group of threonine gives better α-selectivity than primary hydroxyl group of serine when glycosylated with particular glycosyl donor (trichloroacetimidate, 2-azido-2-deoxy galactosyl bromide). In very few cases, primary hydroxyl group gives better α-selectivity over secondary hydroxyl group. This can be portrayed as an indirect evident that glycosylation reaction proceeds through partial bimolecular mechanism.[53]

1.5.3. *Protecting groups:* Chemical synthesis of oligosaccharides still profoundly depends on the regioselective protection/deprotection of the hydroxyl groups at mono or polysaccharide level. Often, the glycosyl donor and the acceptor are protected to reduce undesirable competition among similarly reactive alcohols.[54] Though in the beginning, protecting groups were used to temporarily mask similar reactive sites, it was soon understood that the intrinsic properties of the protecting groups could hugely affect the outcome of a glycosylation reaction. The neighboring group participation concept is widely used in synthetic carbohydrate chemistry and the effect is most powerful when the substituent is at the *C*2 position of a glycosyl donor. Synthesis of 1,2- *trans* glycosidic linkage is easily achieved by installing an ester group at the *C*2 position as it stabilizes the oxocarbenium ion by forming an acyloxonium ion. This prevents the nucleophilic attack from one particular side, thus forming pure 1,2- *trans* linkage (**Scheme 1.3**). Furthermore, it was also observed that steric bulk can also play a crucial role in the stereochemical outcome of glycosylation reaction. In 1988, Fraser-Reid *et al*. described a new method, the armed-disarmed concept to

explain the properties of various protecting groups.[55] It was observed that the installation of ester-type protecting groups strongly reduced the reactivity of *n*-pentenyl glycosyl donor compared to other kinds of protecting groups.[56] Increased electron-withdrawing effect of the ester groups can reduce the electron density and hence, the nucleophilicity of the leaving group to make the glycosyl donor less reactive. The electron-withdrawing effect can also destabilize the formed oxocarbenium ion. These donors were named disarmed donors. On the other hand, armed glycosyl donors are equipped with ether protecting groups that increase the reactivity of the donor. Taking cue from this concept, Ley *et al.* developed a method where glycosyl donor and acceptor can be tuned accordingly to their reactivity. Later on, Wong et al devised a mathematical approach for the reactivity of glycosyl donors and acceptors by assigning relative reactivity values (RRV) for a large number of compounds.[57] While working with an *S*-benzoxazolyl glycosyl donors,

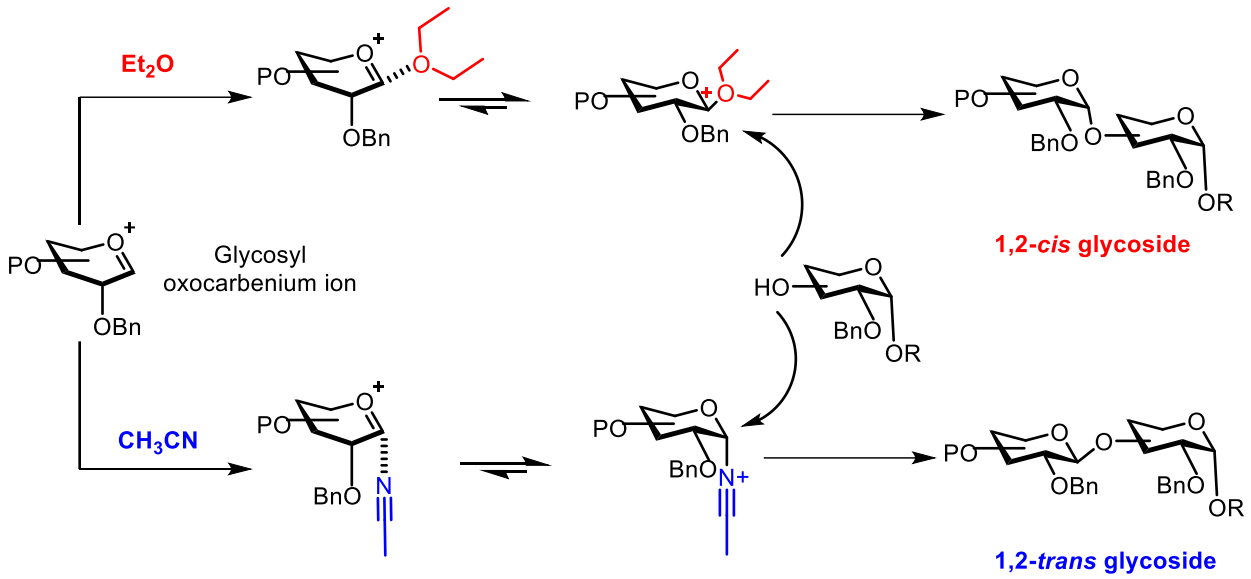


Scheme 1.3: Effect of protecting groups on the stereochemical outcome of the glycosylation reaction

Demchenko *et al.* observed that a donor having participating ester group at the *C2* position and electron donating groups at other remaining positions is more reactive than its armed (per-*O*-benzylated) donor counterpart. These types of donors were named superarmed donors and this altered reactivity was rationalized by considering *O2*-*O5* cooperating effect.[58,59] Though the effect of the remote substituents is of minimum importance, there is strong evidence that substitution at *C*6 position can have a great influence on the stereochemical outcome of glycosylation. It has been discovered that *C*6 substituent with steric bulkiness or having strong electron withdrawing properties are helpful for synthesizing 1,2-cis glucosylation. Similarly, there are many pieces of evidence where remote participation of protecting groups are sufficiently strong while the participating groups reside at *C4* or *C3* at the sugar ring. Cyclic acetal protecting group can induce a torsional effect which might affect the stereochemistry at the anomeric center.[60–62]

1.5.4. *Reaction Conditions:*

1.5.4.1. *Solvent effect:*[63–65] Apart from the dissolution of glycosyl substrate and reagents in a glycosylation reaction, many physical properties *viz.* dielectric constant, donicity number, molecular dipole, and Lewis basicity of the used solvent are taken into consideration. Till date, majority of the glyosylation reactions share a similar reaction mechanism of Koenigs-Knorr type glycosylation where the formed glycosyl oxocarbenium ion is assisted with a counter ion as an ion pair. This ion pair can exist as a close contact ion pair (CCIP), a solvent-separated ion pair (SSIP) or a covalent glycosyl adduct. The stability of these charged intermediate is hugely affected by the nature of the solvent. Solvent participation in glycosylation reaction can be explained by two proposed general hypotheses. The *solvent coordinated hypothesis* explains that the solvent molecule gets coordinated with oxocarbenium ion preferentially on one side of the ring so that the incoming nucleophile can attack only from one side. From quantum mechanical calculation and solvent dynamic simulation studies by Hunenberger and Sato, another hypothesis called *conformation and counterion distribution hypothesis* came to relevance. This hypothesis discusses about oxocarbenium ion attaining different conformations based on the nature of the solvent which eventually affects the stereochemical outcome. Most glycosylation reaction work in a particular temperature range and solvents for those reactions are chosen based on the melting point/boiling point of the solvent. Through charge separation between *O*-5 and β-*O*-1, polar solvents like acetonitrile, DMF, etc. favor the synthesis of 1,2-trans glycosides, whereas non-polar solvents like



Scheme 1.4: Solvent effect on glycosylation reaction

dichloromethane,1,2-dichloroethane, nitroethane, or toluene produce 1,2-cis glycosides. However, some solvents, like acetonitrile and diethyl ether interact with the oxocarbenium ion and favourably form 1,2-trans or 1,2-cis glycosides in C-2 non-participation protected glycosyl donors (**Scheme 1.4**). Usage of binary or quaternary solvent system is also widely used in glycosylation reaction. In weakly polar solvents like dioxane, and Et_2O, solvation of the ion pair is poor and they are considered non-dissociating solvents. CCIP intermediates are more stabilized in nondissociating solvents compared to dissociating solvents like nitromethane and acetonitrile. Depending on the dielectric constant, polarity , and electron pair donating capacity the solvents used in glycosylation can be classified into i) polar and non-coordinating (nitromethane, dichloromethane), ii) weakly polar and non-coordinating (benzene,toluene), iii) polar and coordinating (acetonitrile) and iv) weakly polar and coordinating (ethers) solvents.

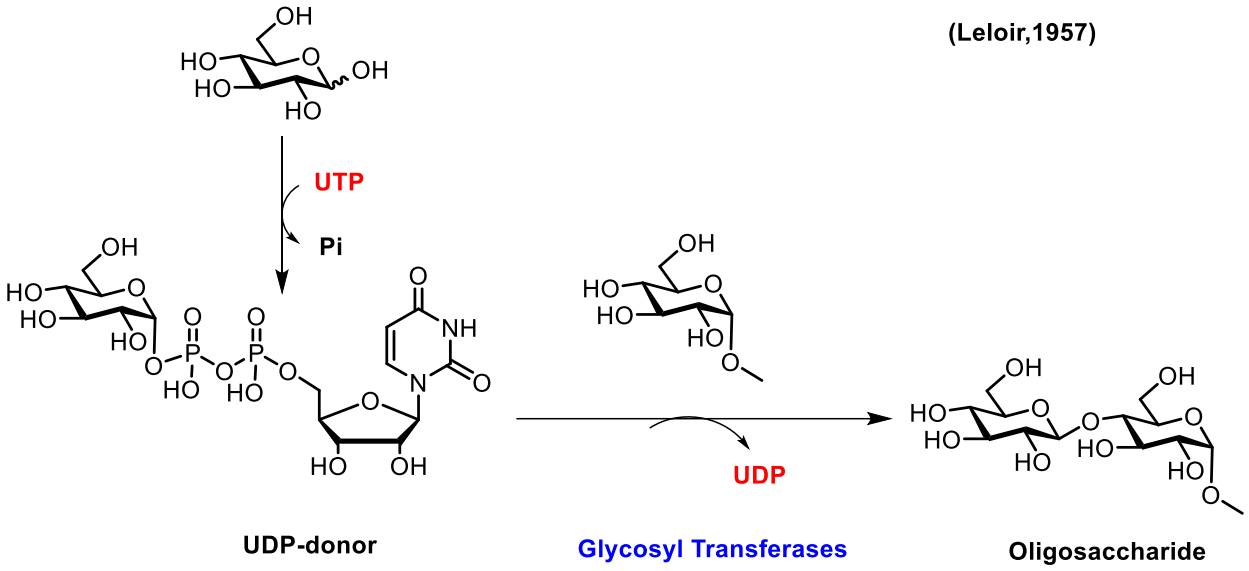
1.5.4.2. *Effect of promoter:*[66,67] To achieve 1,2-cis glycosylation, milder activating conditions are preferable. For example, halide ion-catalyzed reaction gives the best result for glycosylation with glycosyl halide. Thioglycosides perform better when activated through a mild agent, such as iodonium dicollidine perchlorate (IDCP). Trichloroacetimidates are best initiated with the acidic catalysts, such as trimethylsilyl trifluoromethanesulfonate (TMSOTf) or triflouromethanesulfonic acid (TfOH). The presence of various additives in the system can also influence the

stereoselectivity; one remarkable example is the addition of perchlorate ion in order to achieve 1,2 cis selectivity.

Along with these, pressure, temperature, presence of chiral auxiliary protecting group, presence of glycosyl acceptor tethering group, and addition of exogenous nucleophilic additive can also influence the outcome of glycosylation reaction.[68,69]

1.6. Enzymatic Glycosylation:

Glycosylation in living organisms is governed by several enzymes that perform this intricate reaction in a stereo- and regioselective manner.[70] Majorly, glycosylation occurs at the ER and Golgi with various enzymes viz, glycosidase, glycosynthase, and glycosyl transferases. In 1957, Luis F. Leloir first discovered glycosyl transferases responsible for the biosynthesis of oligosaccharides using sugar nucleotides as glycosyl donors. Later, this class of glycosyl transferases was named 'Leloir Enzymes' (**Scheme 1.5**).[71] Another class of glycosyl transferases that are commonly known as 'non-Leloir' enzymes works on sugar phosphate substrates. On the other hand, glycosidases and glycosynthases use nitrophenyl glycosides and glycosyl halides as glycosyl donors, respectively. As glycosylation reaction that involves enzymes can proceed without protecting group manipulation, scientists have been exploring it thoroughly as an alternative to chemical glycosylation. Enzymatic oligosaccharide synthesis relies on two fundamentally different approaches; i) rigorous usage of glycosyltransferases and ii) the application of glycosyl hydrolases.[70] Often enzymes perform glycosylation using building blocks or intermediates made via chemical transformation. A combination of both these methods is popularly known as chemoenzymatic process.[72] Lindhardt and Liu first demonstrated an efficient and scalable chemoenzymatic synthesis of low molecular weight heparins.[73] An automation platform for enzymatic oligosaccharide synthesis on solid support has been reported recently by Boons and co-workers that helps overcome the stumbling block for the enzymatic process by developing a regeneration strategy of the sugar nucleotides.[74,75] Even though enzymes furnish products with high substrate specificity and selectivity, the preparative scale application of those enzymes is often impeded by their inherent instability, poor availability in Nature, and difficulties in isolation.



Scheme 1.5: Mechanism of Glycosylation reaction by Glycosyltransferases

However, the emergence of cloning technology and directed evolution-inspired protein engineering have shown great promise in developing enzymes with high stability and enhanced catalytic activity.

1.7. Different glycosidic linkages:[76]

Diversity in structures of oligosaccharides and glycoconjugates owes to the various possible linkages and attachment of aglycone through different atoms to the reducing end of the sugar. Based on the relative orientation of two vicinal functional groups attached to the C*1* and C*2* positions, glycosidic linkages are classified majorly into two types viz. *1,2-cis* and 1,2-*trans* linkages. If both the groups are co-planar, then it is considered a 1,2-*cis* linkage and if they are non-coplanar, then the linkage is called a 1,2-*trans* linkage. When there is an absence of any functional group at the *C*2 position of a saccharide unit (*2-Deoxy* sugars), the assignment of the linkage solely depends on the orientation of the functional group at the reducing end (**Fig. 1.5**). Synthesis of 1,2- *cis* linkage is far more challenging compared to 1,2-*trans* linkage as the latter relies on a well-developed anchimeric assistance strategy. The presence of a non-participating group at the *C*2 position generally leads to the formation of 1,2-*cis* product majorly along with the

formation of 1,2-*trans* product although the most stable conformation of the intermediate oxocarbenium ion plays a huge role in stereoselectivity. It is often a daunting task to separate this mixture of formed anomers by chromatographic purification, hence, efforts have been made to develop methodologies that predominantly give exclusive1,2-*cis* products. Hindsgaul group

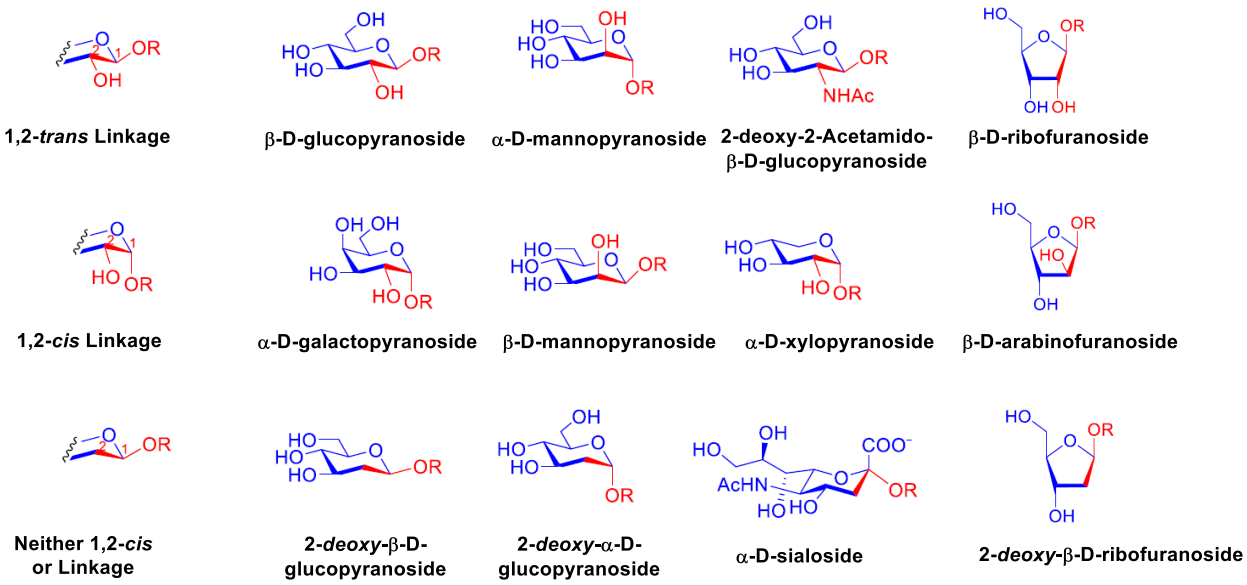
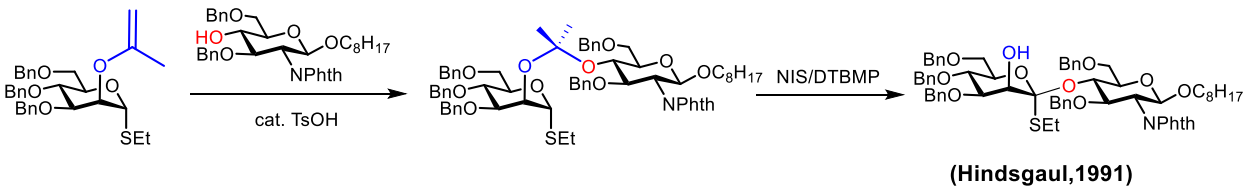


Fig 1.5: Different glycosidic linkages

first reported intramolecular aglycone delivery (IAD) strategy to make pure 1,2-*cis* mannopyranside (**Scheme 1.6**).[77] Boons group introduced a chiral auxiliary protecting group ((1S)-phenyl-2-(phenylsulfanyl) ethyl) at the C2 position of glycosyl donor to synthesize selective 1,2-*cis* glycoside. Kim *et al* established the use of remote participation from *C*3 and C4 carbon for 1,2-*cis* selectivity.[78] Epimerization of C2-Hydroxyl group by performing oxidation followed by stereoselective reduction was acclaimed as a pioneering work by Hotha group (furanosides)[79]

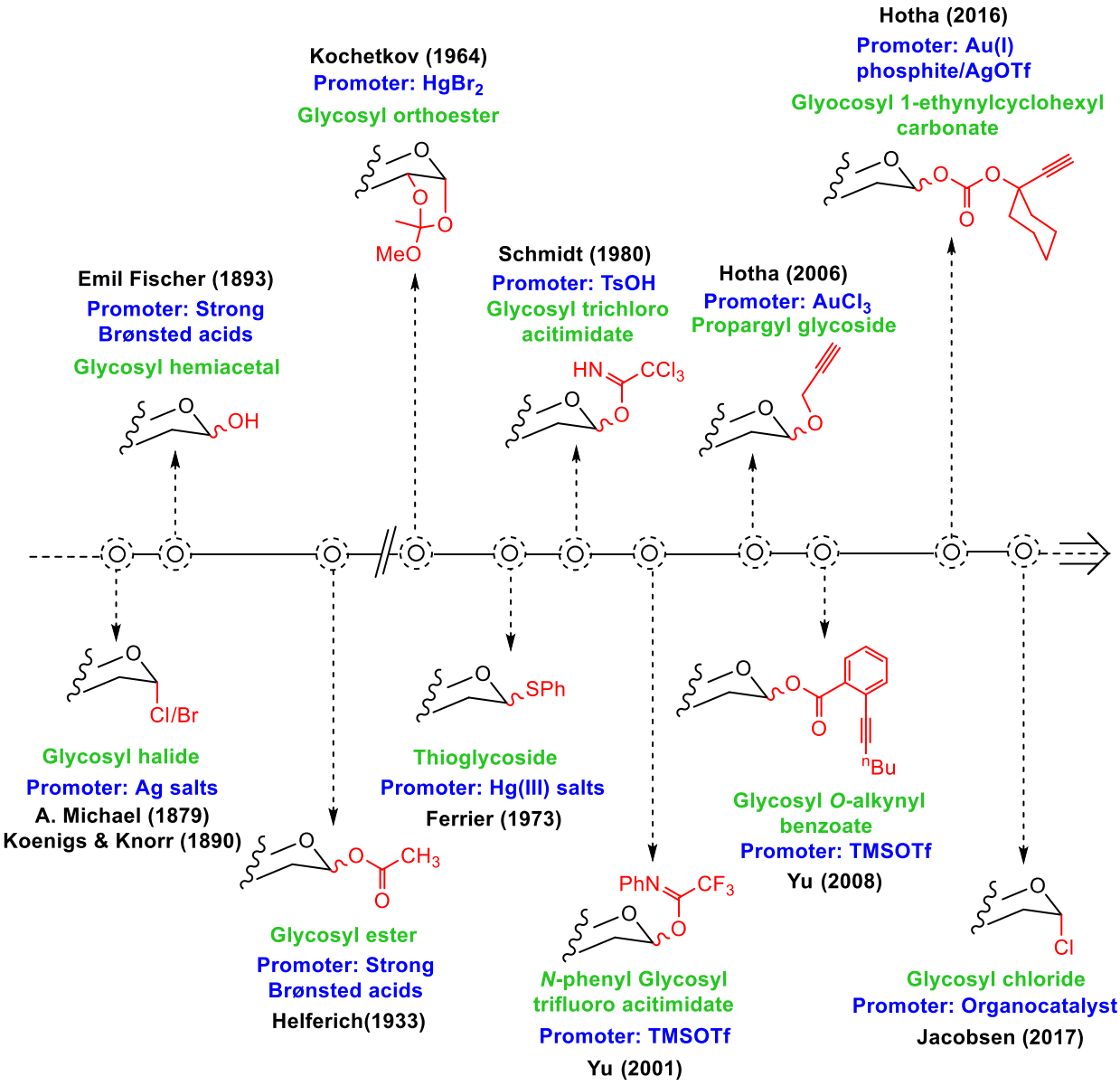


Scheme 1.6: Intramolecular aglycon delivery (IAD) for 1,2-*cis* mannoside

and Garegg group (pyranosides)[68] to achieve otherwise challenging 1,2-cis glycosides.

1.8. Development of Glycosyl Donor chemistry:

As discussed in the earlier section, glycosyl donor upon activation donates a glycosyl moiety to an acceptor that supposedly has a nucleophilic character. An anomeric glycosyl chloride was first



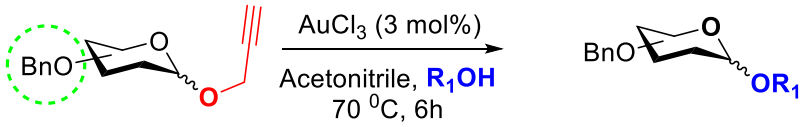
Scheme 1.7: Chronological development of glycosyl donors

used as a glycosyl donor by Michael.[43] Later on, Koenigs and Knorr[45] described the activation of glycosyl bromide and chloride with insoluble silver salts (Ag_2O, Ag_2CO_3) for glycosylation. This method was considered the earliest method to synthesize 1,2-*trans* glycosidic linkage. Helferich and Weiss modified the existing method by using heavy metal salts (HgO, $HgCl_2$, etc) for activation.[80] Emil Fischer developed a glycosylation method that uses strong Brønsted acids to activate hemiacetals.[44] Contemporarily, Helferich reported the usage of anomeric esters as glycosyl donors under strong acidic condition.[81] Ogawa and co-workers came up with TMSOTf as an efficient catalytic system for glycosyl acetate.[82] In 1964, Kochetkov[83] discovered that 1,2-glycosyl orthoesters can undergo glycosylation reaction in presence of catalytic amount of $HgBr_2$.[84] Glycosyl fluoride was thoroughly explored for different glycosylations by Mukaiyama and co-workers.[85] While the activators used by Mukaiyama group were essentially $SnCl_2$ and $AgClO_4$, fine-tuning of the reaction conditions was developed by Nicolaou and Noyori by introducing TMSOTf as an activator for glycosyl fluoride donors.[86] In the early 1980s, the advancement in the methodology of glycosylation revolved around developing mild promoter systems. Danishefsky and co-workers developed a highly efficient protocol for glycosylation by activating 1,2 anhydro sugar with $ZnCl_2$. Sinäy first reported glycosyl imidate donor for the synthesis of various glycosides wherein stoichiometric quantity of TsOH was used for the activation.[87] Later, Schmidt modified the leaving group attached to the anomeric center by introducing the trichloroacetimidate group.[88] This newly developed donor could be activated by catalytic amount of Lewis acid and gained critical acclaim as this donor solved many existing problems regarding glycoconjugate and oligosaccharide syntheses. Recently, another modified version of imidate donor namely trifluoroacetimidate and *N*-phenyl trifluoroacetimidate was developed by Yu.[89,90] This modified imidate donor is the most stable in its class and could be activated with a milder catalytic condition. The concept of using thioglycoside as glycosyl donor was first implemented by Ferrier and Lonn developed a different mode of activation for thioglycosides.[91] Mukaiyama reported the first-ever catalytic activation for thioglycosides using trityl tetrakis(pentafluorophenyl) borate (20 mol%) and sodium periodate.[85] Bert Fraser-Reid introduced glycosyl *n*-pentenyl donor in the late 1980s.[56,92] This donor could be activated by halogenation (with NBS, NIS, I_2, IDCP) of the double bond and Brønsted acids, which causes cyclization and the release of the tetra-hydro furfuryl iodide to produce an active oxocarbenium

species. Subsequent nucleophilic attack leads to the formation of glycosides. Very recently Jacobsen reported the activation of glycosyl halides using macrocyclic bis-thiourea based organocatalysts (**Scheme 1.7**).[93] Ever since the report of the first glycosylation, advancements in the field of developing new glycosyl donors have been evident in the last century. However, only *S*-aryl and trichoroacetimidate/*N*-phenyl trifluoro acetimidate donors are well recognized for the synthesis of oligosaccharides and glycoconjugates to date. The aforementioned donors have many limitations regarding stability, reaction output, and yields that open the scope for the development of 'universal glycosyl donor'.

1.9. Gold catalysis in glycosylation:

The majority of gold-catalyzed reactions involve +1 and +3 oxidation states of Au as Au(0) is inert in nature. Fukuda and Ukimoto made a significant advancement in the field of homogeneous gold catalyst-mediated reaction by demonstrating the Au(III) salt-mediated nucleophilic addition of alcohol onto alkyne to synthesize ketal.[94] Gold catalyzed synthesis of arenes is another pioneering work reported by Hashmi's group.[95] Although the usage of transition metals like Pd(II), Ni(II), Rh(II), Ti(IV), Cu(II), etc for glycosylation was prevalent, the application of gold catalysis in glycoside synthesis was completely unknown. Taking a cue from Au(III) catalyzed Ferrier-type reaction with 3-*O*-propargyl derivative, Hotha and Kashyap reported activation of anomeric propargyl glycosyl donor with catalytic $AuCl_3$ for the first time in 2006.[96] This new method of glycosylation encouraged other carbohydrate chemists to explore and further improve the scope of gold catalysis in glycosylation reactions. Reports of $AuCl_3$ mediated activation of alkyne functionality containing 2,2-dimethylbut-3-ynyl thioglycosides from the Zhu group[97] and glycosyl propargyl 1,2- orthoester donor for 1,2-*trans* glycosylation from the Hotha group[79,98] are considered significant advancements in the field. Later, Hotha and Kayastha identified that 1-ethynylcyclohexanyl glycoside donors are much more reactive than propargyl glycosides as the former could be activated at room temperature using $AuCl_3$ and AgOTf as a co-catalyst.[99] Vankar *et al.* could successfully activate long-known trichloroacetimade donor with Au(III) salts.[100] Yu group discovered *O*-hexynylbenzoates glycosyl donors that get activated in presence of $Ph_3PAuOTf$ or $Ph_3PAuNTf_2$ to furnish various glycosides and saccharide unit containing natural products.[101,102] Mishra and co-workers could successfully establish a very mild Au(I)/Ag(I) co-

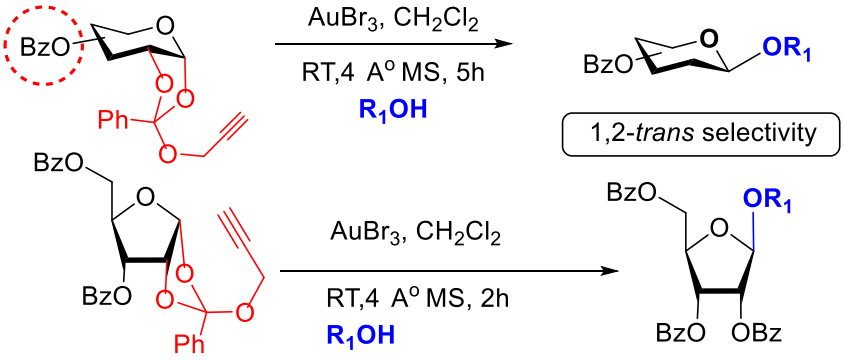


(Hotha, 2006)

R_1OH = Aliphatic, Alicyclic, Steroidal, Sugar alcohol

Armed system

a) First report of gold ($AuCl_3$) catalyzed glycosylation using propargyl donor

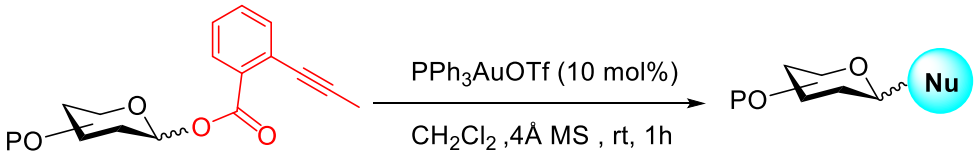


(Hotha, 2007,2013)

R_1OH = Aliphatic, Alicyclic, Steroidal, Sugar alcohol

Disarmed system

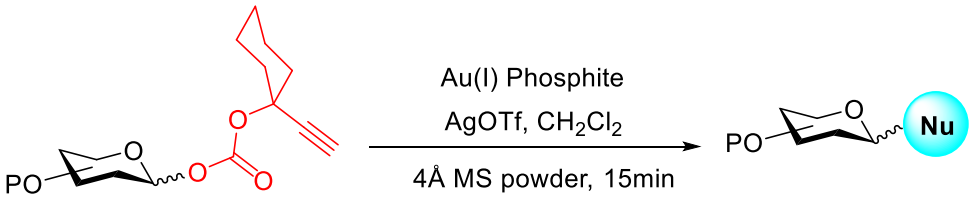
b) $AuBr_3$ catalyzed glycosylation using propargyl orthoester donor



(Yu, 2008)

Armed & Disarmed system Nu **= O.N,C nucleophile**

c) Au(I) catalyzed activation of *O*-alkynyl benzoate donor



(Hotha, 2016)

Armed & Disarmed system Nu **= O.N,C nucleophile**

d) Au/Ag catalyzed glycosylation using 1-ethynyl cyclohexyl carbonate donor

Scheme 1.8: Milestone discoveries in Au-catalyzed glycosylation reaction

catalyzed glycosylation method using 1-ethynylcyclohexyl glycosyl carbonate donor.[103] Au(I) catalyzed glycosylation method are milder compared to traditional glycosylation methods where the usage of strong Lewis acid or Brønsted acid activators are frequent. Hence, these relatively new methods are gaining attention as the syntheses of many otherwise difficult glycosides could be efficiently performed by exploiting salient features of gold catalysis.

1.10. Synthesis and importance of different glycosides:

The structures of glycoconjugates are complex and they inherently encode specific biological information. Therefore, in order to understand the function of natural glycoconjugates in various biological processes, synthetic approaches for the creation of well-defined scaffolds are required.[104] Additionally, the development of new polymeric materials with distinctive features and improved functions depends greatly on the molecular design and synthesis of glycoconjugates using biomimetic approaches.[70] Although *O*-glycosides are the majority in numbers regarding possible structures and presence in Nature, glycosylation can happen through *N*, *C*, *S*, *P* -atoms and rarely through *N*-*O* or *O*-*N* to form diverse glycoconjugates.[105] However, syntheses of *O*-glycosides have been studied for over a century and there are already many well-established methods to acquire *O*-glycosides.[49] Compared to nucleophiles containing heteroatoms other than oxygen, hydroxyl functional groups are better nucleophiles which is an advantage to making *C*-*O* linkages at the reducing end of the sugar. *N*-glycosides are present in DNA, RNA, and Glycoproteins naturally whereas a plethora of modified N-glycosides has immense importance as therapeutics.[106] Poor nucleophilicity and solubility issues of *N*-acceptors are reasons for not having many well-established methodologies available to synthesize *N*-glycosides (more details in *Chapter 3*). On the other hand, *C*-glycosides are inert to glycosidase and hydrolases which makes them potential therapeutic candidates. Sometimes, *C*-glycoside mimetic exhibit much higher anti-proliferative activity over its native *O*-glycoside congeners. Advancement in the transition metal-catalyzed *C*-*H* activation reactions made the synthesis of *C*-aryl glycosides and 1,2-*cis* C-glycosides convenient. Rearrangements, condensation, and glycosylation reactions are among other methods to obtain *C*-glycosides.[107] Thioglycosides have been widely used as stable glycosyl donors[108] whereas thiosialosides are important hydrolytically stable Neu5Ac analogs that have emerged as potential inhibitors for Neu5Ac recognizing proteins.[109]

1.11. Importance of synthetic carbohydrate-based moieties in therapeutics:

Apart from the conventional usage of naturally occurring carbohydrate-based therapeutic agents namely Alginic acid, Hyaluronic acid, Fucoidan, Mannitol etc, there has been a continuous effort to develop purely synthetic carbohydrate-based therapeutics.[110] A fully synthetic compound has

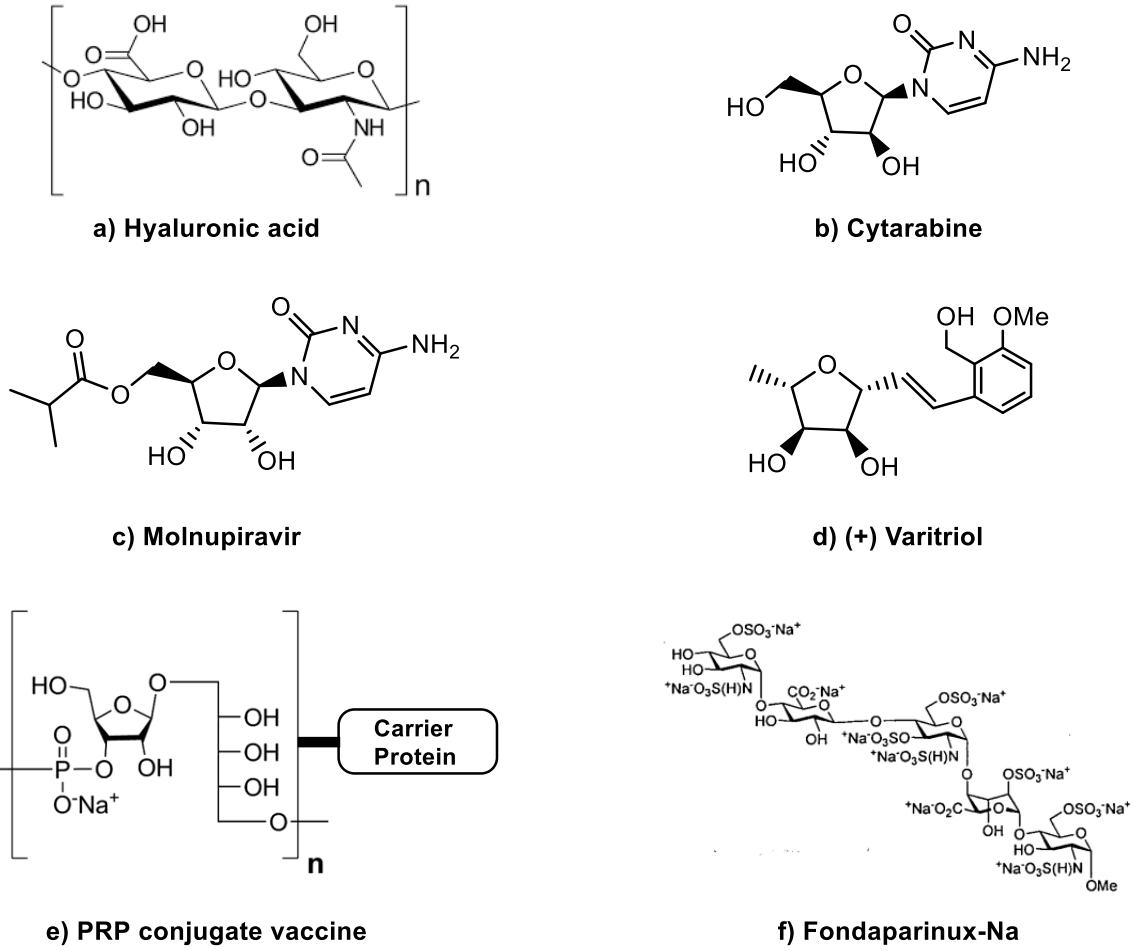


Fig. 1.6: Examples of carbohydrates in therapeutics

the benefit of being ultra-pure, of known well-determined structure, and it has no risk associated with unwanted side effects or pathogenic infection from animal sources. Successful chemoenzymatic syntheses of selectin inhibitor Sialyl Lewis^X,[111,112] anticoagulant Heparinoids,[113] and glycomimetic bimosiamose[114] have allowed conducting structure-activity relationships related experiments in many biological processes. Recombinant therapeutic proteins are often tweaked by a carbohydrate portion that increases the activity and improves its half-life in the body.

Glycosylation on recombinant erythropoietin or superoxide dismutase has succeeded significantly in this particular field of research. Novel chemical synthetic routes have immensely helped in developing anticoagulant Fondaparinux (Arixtra)[115] or Idraparinux[116] in large quantities in its purest form. Advancement in the synthesis of various *C*-glycosides and nucleosides has improved the scope of developing novel glycomimetics. Gliflozins (anti-diabetic)[117], Varitriol (anti-tumor), and Ambruticine (anti-fungal)[118] are approved drugs with *C*-glycosidic linkages whereas there are currently more than 30 FDA-approved modified nucleoside drugs available for the treatment of many antiviral diseases and cancer (**Fig. 1.6**)[119].

1.12. Promising 1-ethynylcyclohexyl glycosyl carbonate donor:

After almost ten years of efforts in fine-tuning the reaction conditions since the first report of gold-catalyzed glycosylation from Hotha group, Mishra *et al.* came up with a mild, easily scalable, catalytic, and fast glycosylation method using shelf-stable glycosyl 1-ethynylcyclohexyl carbonate donor and Au(I) phosphite and AgOTf as co-catalysts.[103] This new donor has shown promise in synthesizing various glycoconjugates and oligosaccharides. *O*-glycosylation reaction takes 15 minutes for completion at room temperature with this newly developed method. Synthetic carbohydrate chemists' toolbox now has a variety of glycosyl donors that can be used to create monosaccharides and disaccharides. However, only a few glycosyl donors have so far been used in the synthesis of higher oligosaccharides and complex glycosides. The first oligosaccharide synthesis reported by using this method was a tridecasaccharide reminiscent of lipoarabinomannan from *M. tuberculosis* cell wall. Eventually, 21-mer arabinomannan[120] and arabinogalactan[121] fragments found in *M. tuberculosis* cell wall were synthesized proficiently. Recently synthesis of a more complex branched glycan fragment present in chlorovirus ATCV-1 was successfully accomplished by Hotha group.[122] High glycosylation yields even in higher oligosaccharide couplings is another advantage of using this alkynyl carbonate donor chemistry. Development on syntheses of challenging 1,2- cis linkages of glucose and galactose unit using this new glycosyl donor have been studied thoroughly. Application of this donor is found in developing a successful shortest synthetic route for core pentasaccharide of the life-saving drug Fondaparinux.[123] This donor has also been used in developing a novel solid-phase synthesis method for making oligosaccharides in a much shorter time.[124] Promising results in oligosaccharide syntheses and

being a relatively milder method compared to the traditional glycosyl donors have already brought this donor into the limelight although there is scope in developing this method for synthesizing otherwise difficult glycosides and glycoconjugates. Importance of glycosyl alkynyl carbonate donor in the synthesis of various glycosides and the properties of 1-ethynylcyclohexyl carbonate moiety as a leaving group will be discussed thoroughly in the following chapters of this thesis.

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Chapter 2: [Au]/[Ag] Catalyzed Activation of Novel Shelf-stable Reagents for Etherification

2.1. Introduction

Carbohydrates are the heaviest functionalized class of biomolecules found in Nature. The availability of the hydroxyl moiety present in carbohydrates is unrivaled by any other type of natural product[1] as Nature utilizes this diverse possibility for creating structural versatility. Regio- and stereoselective access of these hydroxyl groups is critical in synthesizing oligosaccharides and glycoconjugates. Enzymes, which are highly functional group specific, help synthesize oligosaccharides naturally.[2] Glycosyltransferase, majorly a single-pass transmembrane protein possessing a quaternary structure, can position the carbohydrate in the active site with the help of its inherent topological machinery for the benefit of the synthesis (**Fig. 2.1**).[3,4]

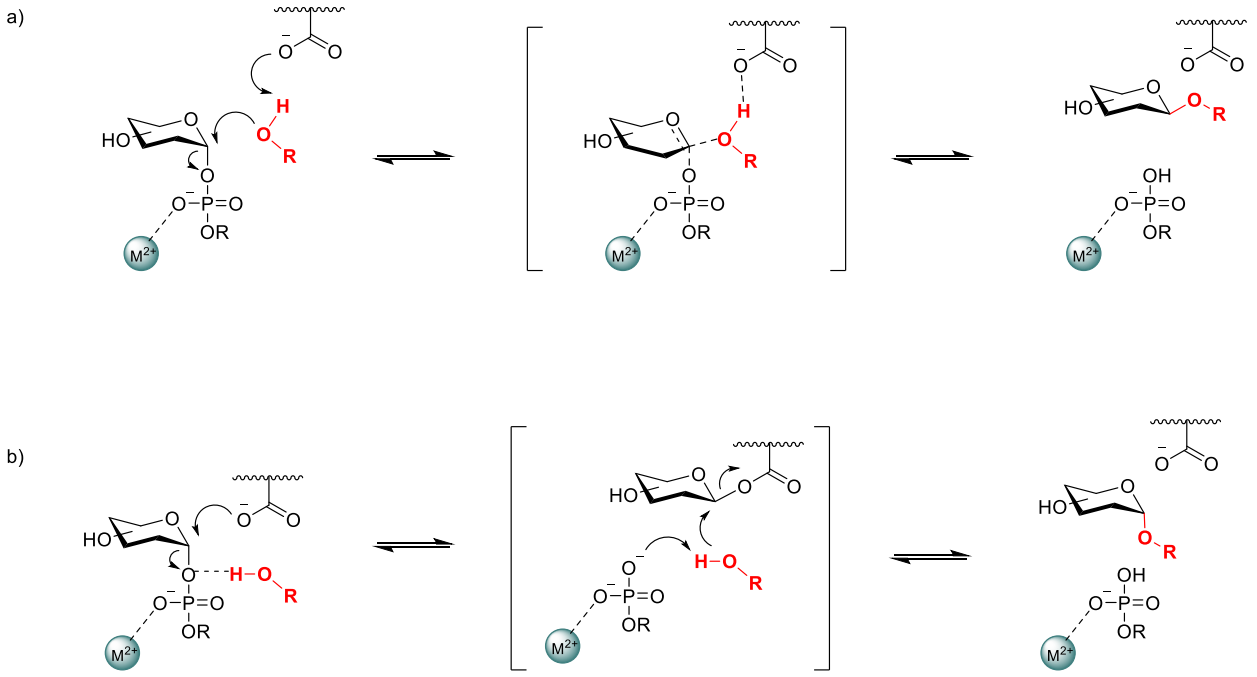


Figure 2.1: Mechanism of inverting (a) and retaining (b) glycosyl transferase reaction in enzyme pocket

As a result, only one specific reaction in a particular hydroxyl group can be enabled, and thus the enzyme also offers functional group protection not by forming any covalent bond but by using various non-covalent interactions in the active site. However, conversely, chemical

synthesis of oligosaccharides still profoundly depends on the regioselective protection/deprotection of the hydroxyl groups at mono or polysaccharide level.[5,6] Chemical glycosidation is a condensation reaction involving a glycosyl donor and an acceptor, which will be repeatedly utilized while synthesizing oligosaccharides. Chemical synthesis of oligosaccharides is still a daunting task as regioselectivity among multiple reactive alcohols is highly demanding.[7] Often, the glycosyl donor and the acceptor are protected to reduce undesirable competition among similarly reactive alcohols. Glycosyl donors are prepared in a fully protected form with a leaving group at the *C*-1 position. In contrast, the acceptor (ROH) is synthesized in such a way that a lone hydroxyl group is left to undergo glycosylation.

A facile synthesis of large and branched oligosaccharides generally exploits protection and deprotection strategies on demand[8]. For regioselective carbohydrate protection, evaluation of the distinctness of the present functional moieties is critical. The difference in reactivity of the functional moieties is majorly governed by the factors like steric effects, electronic effects, and stereoelectronic effects viz. thermodynamic/kinetic anomeric effect, exoanomeric effect etc.[9] Alcohols which are in **i)** Primary, secondary or anomeric position, **ii)** axial or equatorial position (especially in all the pyranosides), **iii)** the presence of 1,2-*cis*-, 1,3-*cis*- diol or diequatorial 1,2-*trans*- diol (as they interact with bifunctional protecting group or chelating metal ion) can behave significantly different under diverse reaction conditions. Owing to its steric reason, primary alcohol group present on a carbohydrate molecule is the most reactive one.[10] It's easier to block this primary hydroxyl group site selectively by using bulky protecting group. Anomeric hydroxyl group distinguishes itself from all other secondary alcohols as it holds hemiacetal functionality. Also, the anomeric alcohol proton is of the lowest *pKa* value amongst all the hydroxyl groups as it is a part of hemiacetal functionality (**Fig 2.2**). Thus, it can easily undergo a chemoselective reaction that uses basic conditions.[11] Contrariwise, the anomeric hydroxyl group is least reactive in all the secondary alcohols on a carbohydrate ring when exposed to an acidic condition. It has also been observed that the axial secondary hydroxyl group is less reactive than the equatorial one.[12] A huge number of protecting groups and strategies for installation/uninstallation over the years were developed and documented.[13,14]

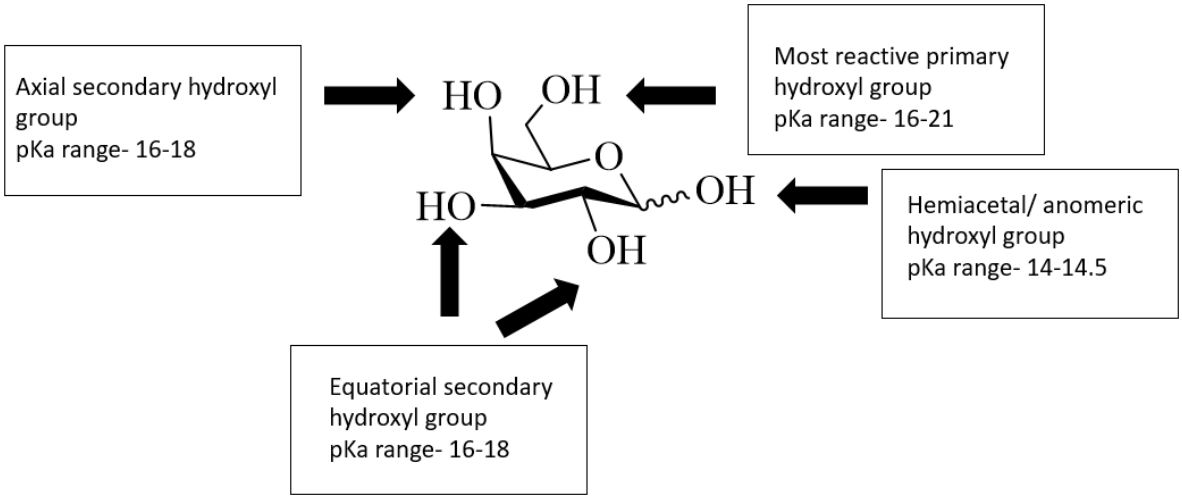


Figure 2.2: Different hydroxyl groups on a pyranose ring

Protecting groups have a massive influence on the reactivity of a carbohydrate synthon.[15] Protecting groups which are electron-withdrawing (disarmed), can deactivate a glycosyl donor by destabilizing the partially formed positive charge at the anomeric center of the donor when activated whereas benzyl ether carrying carbohydrate donor (armed) synthon behaves in a completely opposite manner. Prof. Fraser-Reid had thoroughly exploited and theorized this armed-disarmed concept for the very first time in carbohydrate chemistry.[16] Chemical syntheses of oligosaccharides and glycosides call utilization of many protecting groups that can be installed or deprotected without affecting other functional groups existing in the molecule. This necessity fueled the discovery of various protecting groups over the last century. Some of the naturally occurring oligosaccharides (cyclodextrins, glycosaminoglycans) demand a unique strategy in protecting group chemistry to synthesize them due to the structural rigidity and orientation of the hydroxyl groups (which often experience strong intramolecular hydrogen bonding), protecting group strategies for cyclodextrins are somewhat intractable compared to the solution phase.[17] The importance of the orthogonal protecting groups in monosaccharide building blocks is exceptionally high in the case of solid-phase oligosaccharide synthesis as removal of the side product is a formidable task that may lead to the formation of deletion sequences or undesired stereoisomers until the very end of the synthesis.[6] Tedious protecting group manipulations to synthesize

orthogonally protected building blocks demand hectic chromatographic purification, which can be avoided by using covalently attached purification labels (FTags[18], ITags[19]). With the help of these tags, purification can be possible just by extraction in a suitable solvent for which that particular tag has an affinity. These tags can also act as temporary protecting groups as well.

2.2. Common protecting groups in carbohydrate chemistry

During the course of the discoveries of different reactivity of hydroxyl groups and different protecting groups, so many useful terms for cataloging those protecting groups have also been created such as i) permanent vs. temporary[20] ii) armed vs. disarmed[21] iii) participating vs. non-participating[22] iv) orthogonal vs. non-orthogonal[23] v) cyclic vs. acyclic[15] and many more. A few commonly used protecting groups and their functions in carbohydrate synthesis are described below:

2.2.1. *Silyl ethers*:[24,25] Silyl ethers the most commonly used protecting groups in synthetic carbohydrate chemistry as either temporary or permanent protecting groups (TBDPS, TBDMS) in synthetic carbohydrate chemistry. The bulkier size of TBDPS (tert-butyl diphenyl silane) protecting group is often used to protect primary hydroxyl groups selectively over secondary hydroxyl groups. Protection of free hydroxyl groups of carbohydrate molecules with silyl ethers are routinely carried out using TBDPS-/TBDMS- chloride or triflate and mild base such as imidazole in solvents like DMF or THF. Silyl ethers are non-participating type protecting groups but they can influence the stereoselective outcome of the glycosylation reaction because of their large size. There are reports of cyclic silyl protecting groups such as di-*tert* butylsilylene (DTBS) which can restrict the sugar ring in a particular conformation thus leading to a stereoselective glycosidic linkage. Deprotection of silyl ethers is performed using a fluoride anion source such as HF.Py complex or TBAF salt.

2.2.2. *Esters*:[26] Esters are routinely used as protecting groups in synthetic carbohydrate chemistry. Among them, the most commonly used benzoate, acetate, levulinate, pivolate. Although ester groups are electron withdrawing in nature which thereby destabilize thus formed oxacarbenium ion if they are next to the anomeric center, they can control stereoselectivity through neighboring group participation. Presence of an ester group at the *C*-2 position can give rise to 1,2-*trans* stereoselectivity at the anomeric center. Neighboring group participation through the distal ester groups from *C*-3 or *C*-6 position is also reported.[27] Free hydroxyl groups are protected as esters

either by base mediated esterification or under neutral conditions using coupling reagents whereas deprotection of esters are done using bases like sodium methoxide or potassium carbonate that is known as saponification in general organic chemistry or Zemplén deacylation in synthetic carbohydrate chemistry.

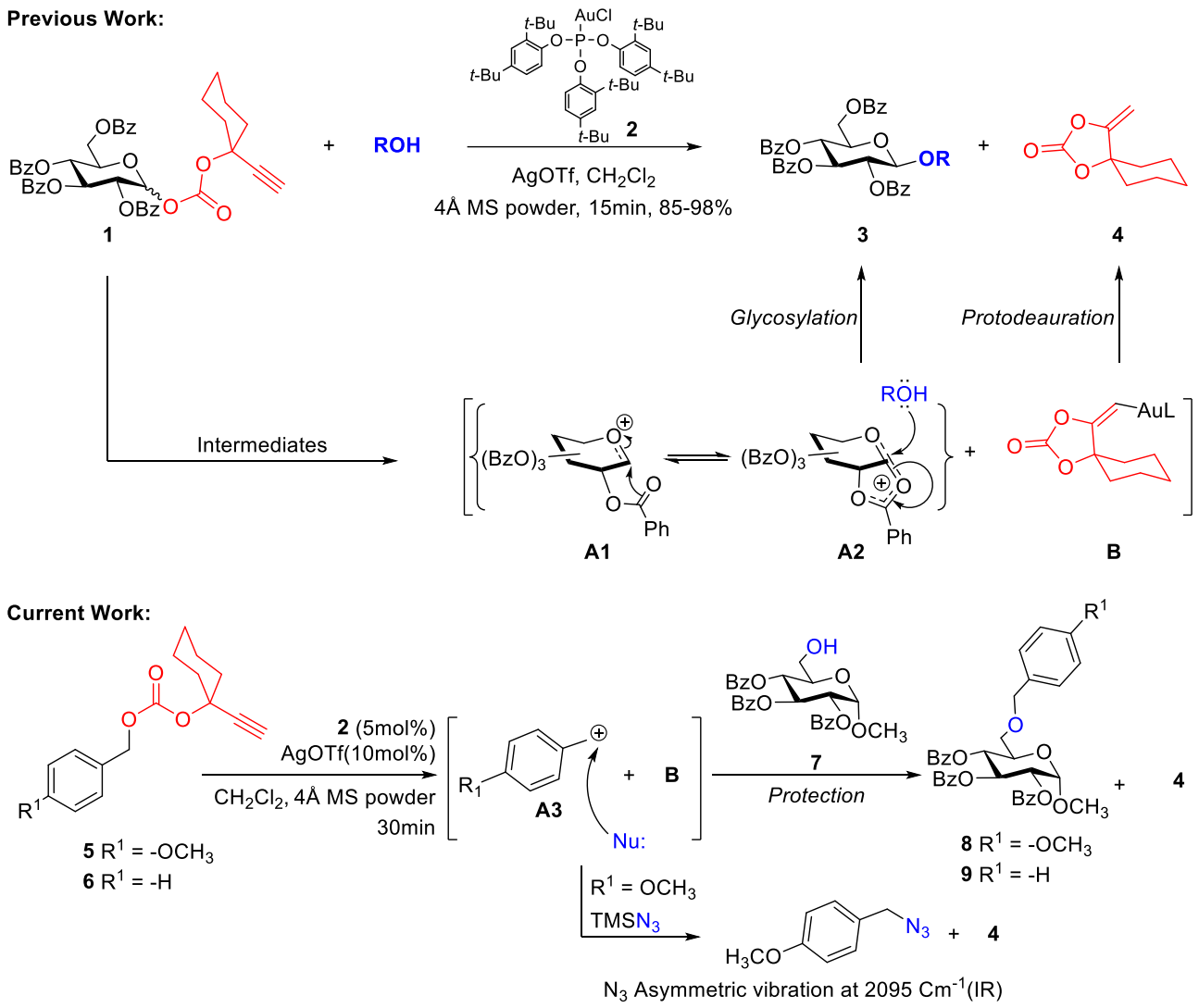
2.2.3. *Acetals and ketals*: Commonly used acetal linkages in carbohydrate chemistry are benzylidene and acetonide groups which generally protect two hydroxyl groups at a time and lock the sugar ring in a particular conformation.[28] Conformational restriction can control the stereochemical chemical outcome of the reaction that was beautifully demonstrated by Crich group who in a seminal work demonstrated conformation using 4,6-benzylidene protection in mannosyl triflate can result in stereoselective formation of β-mannosides easily.[29,30] Acetal groups can be deprotected in the presence of Brøsted acids and protic solvents.

2.2.4. *Carbonates, Carbamates and Oxzolidinone*:[31] Carbonates and oxazolidinones are again used as conformation constraining protecting groups to achieve desired selectivity. Oxazolidinone[32] are important for the synthesis of α-2-amino-2-*deoxy*-glucopyranosides and α-sialosides. Among those, Cbz group can give rise to 1,2-*trans* glycosidic linkage from a *C*2 position. Troc is a very common $-NH_2$ protecting group for aminosugars which also helps in getting 1,2-*trans* linkages.[33]

2.2.5. *Ethers*: Ethers such as benzyl, *p*-OMe benzyl, naphthyl and trityl ethers are used as either permanent or temporary protecting groups in carbohydrate syntheses. All these groups have electron-donating properties and hence they can stabilize the intermediate oxocarbenium ion.[34] Benzylation of alcohols affords benzyl ethers is one of the most celebrated reactions which many oligosaccharide syntheses utilize. Frequently, benzylations are conducted under NaH/DMF/benzyl halides that are strongly alkaline and hence, base-labile protecting groups will also get affected[35]. Later introduced BnOTf[36] permits benzylation under neutral conditions whereas benzyl trichloroacetimidates[37] enable syntheses of benzyl ethers under acid catalysis using catalytic amount of TfOH. However, moisture sensitivity and instability of BnOTf and benzyl trichloroacetamidates are the major limitations of these two methods. Therefore, installation of benzylic ethers under mild catalytic conditions that provide excellent yields will be highly rewarding[38–40].

2.3. Current work:

Recently introduced glycosyl (1-ethynylcyclohexyl) carbonates (e.g. **1** in **scheme 2.1**) were identified as glycosyl donors due to the synergistic catalytic action of Au-phosphite (**2**) and AgOTf to afford the syntheses of glycosides **3** with the extrusion of a spirocyclic carbonate **4**. The reaction was postulated to undergo through the activation of alkyne by the [Au]/[Ag]-catalytic system resulting in the formation of a carbocation at the *C*-1 position extruding the Au-alkylidene **B**.[41] Thus formed carbocation at the anomeric is highly stabilized due to the formation of the oxocarbenium ion intermediate **A1** which will be in equilibrium with the trioxolenium ion intermediate **A2**. Attack of the aglycon ROH led to glycosides and the protodeauration resulted in the formation of the spirocyclic carbonate **4**. Push of electrons from the *exo*-cyclic oxygen is envisaged as one of the possible factors for the stabilization of the carbocation at the anomeric position. In this scenario, we hypothesized that the benzylic carbonates shall also undergo similar reaction to afford benzylic cation **A3** releasing the intermediate **B** and thus formed benzylic cation shall be available for the attack of nucleophiles. To verify our hypothesis, benzylic carbonates **5** and **6** were respectively prepared from commercially available 4-methoxy benzyl alcohol and benzyl alcohol in excellent yields using easily accessible and stable 1-ethynylcyclohexyl (4-nitrophenyl) carbonate.[9] A model reaction was carried out between glucose-derived alcohol **7** and the carbonate **5** in the presence of 4Å MS powder, 5 mol% each of Au-phosphite (**2**) and AgOTf at 25 ºC to obtain corresponding PMB-ether **8** in 95% yield and the cyclic carbonate **4**. Similar reaction with benzyl (1-ethynylcyclohexyl) carbonate **6** with alcohol **7** afforded the benzyl protected monosaccharide **9** in 84% yield. Gratifyingly, the benzoate esters were found to be intact during the reaction, the reaction was complete in 30min and more importantly, the benzylic carbonate is noticed to be very stable. Formation of the benzylic cation **A3** was established by conducting the reaction with the $TMSN_3$ instead of alcohol **7** to afford the 4-methoxy benzyl azide and the cyclic carbonate **4**. Azide formation was confirmed by the characteristic N_3 asymmetric vibration at 2095 cm^{-1}.[42] A plausible mechanism can be advanced based on the literature precedence though a thorough mechanistic investigation is pending.[41] *p*-Methoxy benzyl carbonate **5** can be activated either by the *in situ* formed LAuOTf to give intermediate **A4** or by the sub-stoichiometric [Au,Ag] clusters to give intermediate **A5**. Intermediates **A4** and **A5** undergo 1,5-*exo*-dig cyclization giving the earlier postulated alkylidene intermediate **B** releasing the much desired benzylic carbocation **A6** that shall



Scheme 2.1: Benzylic (1-ethynylcyclohexyl) carbonates for the synthesis of benzylic ethers

be attacked by the alcohol **7** to give PMB-ether **8** releasing a proton that facilitates the protodeauration to give the cyclic carbonate **4**[43,44]. Encouraged by the identification of the new benzylation protocol, we further targeted the application of this method for the synthesis of benzyl ethers to understand the substrate scope. Accordingly, it has been noticed that olefins do not get affected under these experimental conditions as evident while perform reactions on alcohols **10**[45], **12**[46],**14**[47] to obtain corresponding PMB-ethers **11**,**13**,**15**. Noticeably, the Troc-protection on the glucosamine derivative **12** and the silyl ethers in compounds **12** and **13** were stable for these conditions. In addition, the current procedure is suitable for installation of benzyl ethers on alcohols which are alicylic (e.g. menthol **16**), steroidal (e.g. cholesterol **18**), amino acid

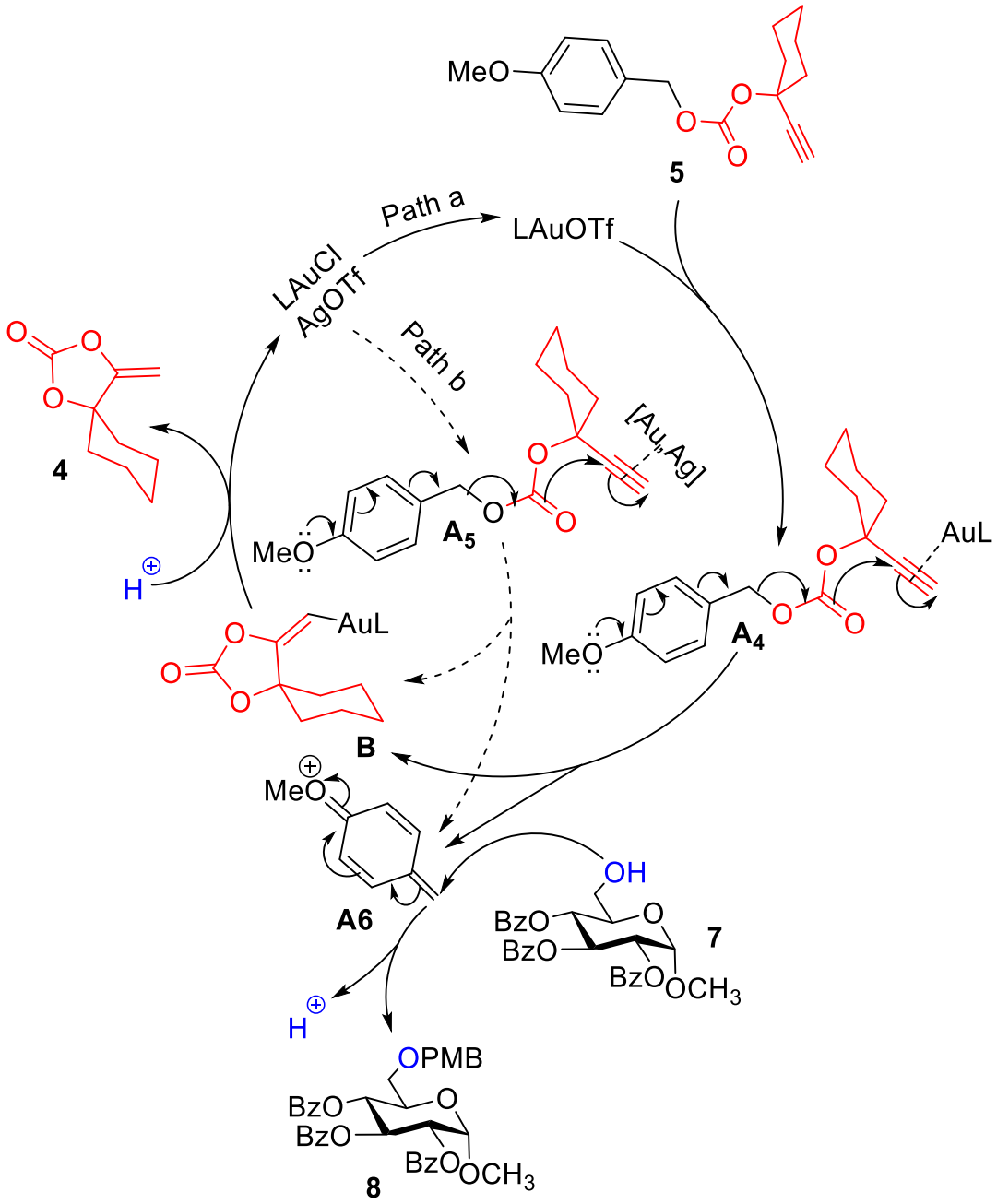
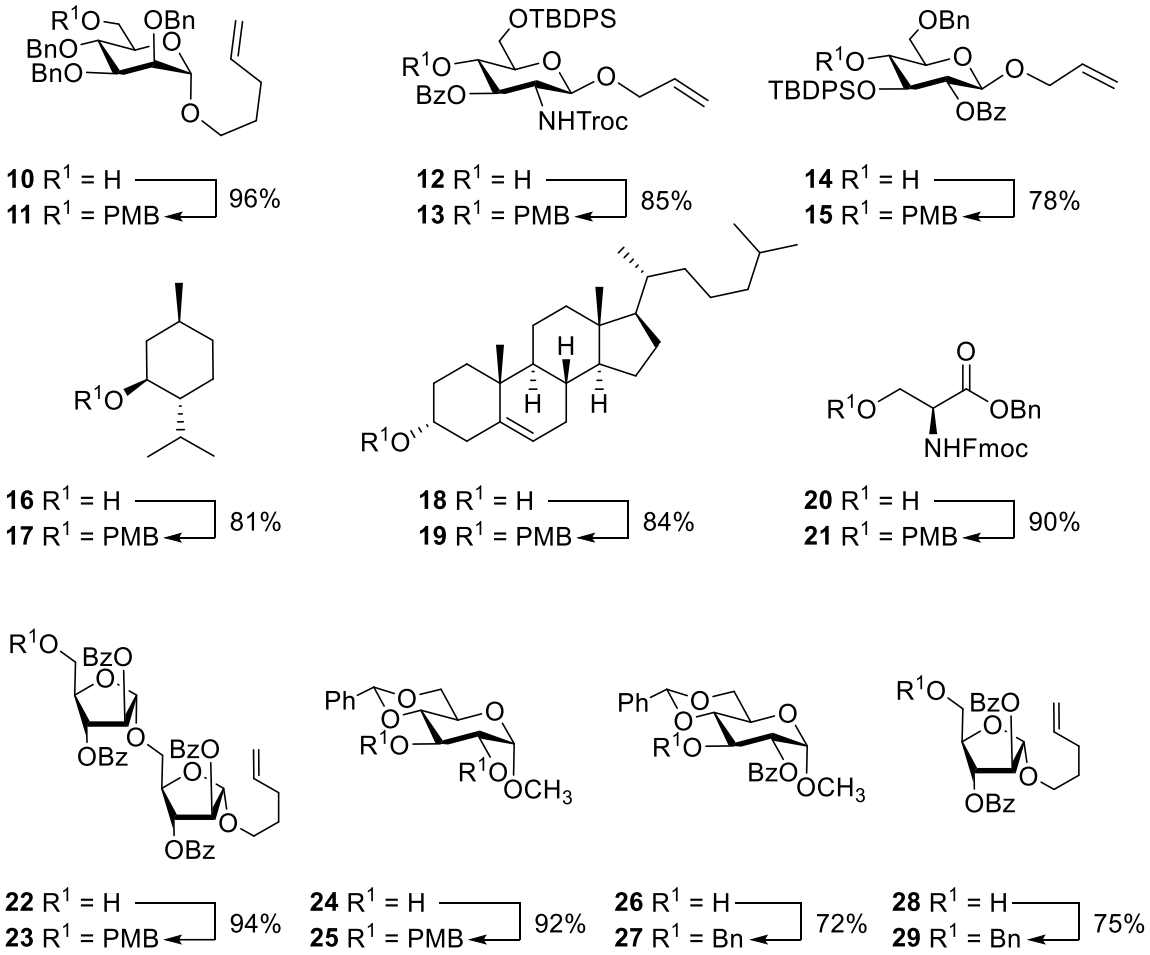


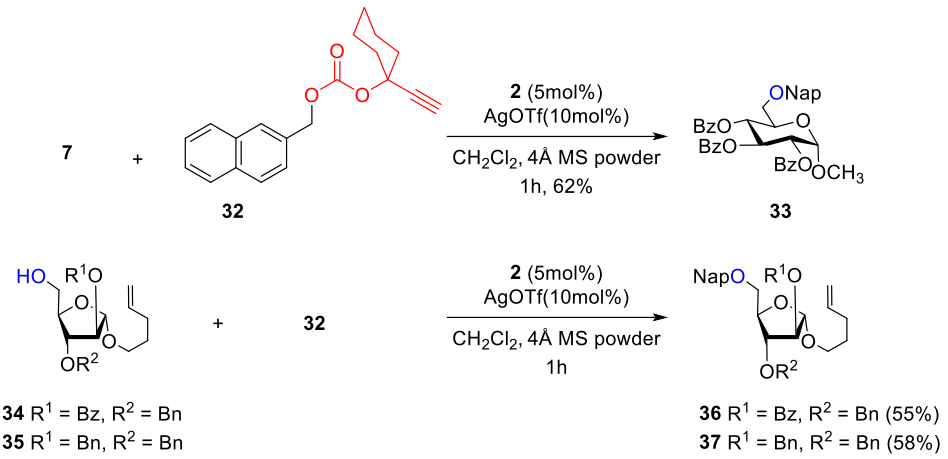
Figure 2.3: Plausible mechanistic pathway

(e.g. serine **20**[48]) to afford respectively PMB-ethers **17**, **19** and **21** in very high yields. Furthermore, the reaction is found to be suitable for installation of PMB ethers or benzyl ethers on disaccharide (e.g. **22**[49]), benzylidene glucoside (e.g **24**, **26**[50]) and furanoside **28** to give respective ethers **23**,**25**,**27**,**29 (Scheme 2.2).**



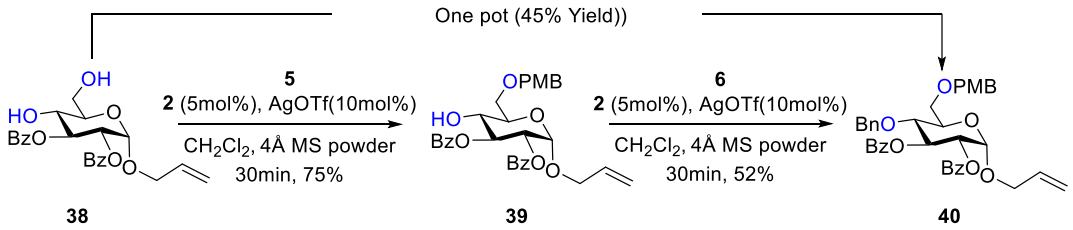
Scheme 2.2: Substrate Scope

Another benzyl ether in the form of Nap-ethers gained momentum as their deprotection conditions are orthogonal to the benzyl ethers.[10] In view of this, alcohol **7** was treated with Nap-carbonate **32** in the presence of catalytic quantities of Au-phosphite (**2**) and AgOTf in CH_2Cl_2 to notice formation of Nap-ether **33** in 62% yield. Similarly, arabinofuranosyl alcohols **34** and **35** reacted with carbonate **32** to afford desired Nap-ethers **36** and **37** in 55% and 58% yield respectively **(Scheme 2.3).** 1º-Alcohols are better nucleophiles than 2º-alcohols and as a consequence, the attack of the nucleophile on the benzylic cation shall also follow the same trend. Hence, easily accessible allyl glucoside **38** possessing both primary and secondary alcohols was subjected to the benzylation



Scheme 2.3: Synthesis of Nap-ethers

conditions using PMB-carbonate **5** in the presence of catalyst **2** and AgOTf in CH_2Cl_2 to notice formation of the C6-PMB blocked glucoside **39** in 75% yield. In continuation, the PMB ether **39** was subjected to identical conditions with Bn-carbonate **6** to afford the benzyl ether **40** in 52% of isolated yield. All the reaction conditions are identical except the substrates and hence, a one pot conversion of diol **38** to compound **40** was envisioned so that the purification is minimized and overall pot-economy shall improve as a result. Accordingly, the two independent reactions are conducted one after the other in one pot without isolating the intermediate compound **39** to obtain the final compound **40** in 45% over all isolated yield (**Scheme 2.4**).



Scheme 2.4: Orthogonal and One-pot introduction of PMB and Bn ethers

To summarize, a new method for the installation of benzyl-, 4-methoxy benzyl- and Nap- ethers has been identified taking cue from the [Au]/[Ag]-catalyzed alkynyl carbonate glycosylation chemistry. These conditions are mild enough to synthesize benzyl ethers bearing olefins, silyl

ethers, Troc-, Fmoc, benzyl esters, benzoates, and benzylidenes. The mechanism was postulated to be similar to that of the alkynyl glycosyl carbonate glycosidation. One pot installation of PMB and benzyl ethers is yet another new feature of this recently developed method.

2.4. Experimental data:

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification.1-Ethynylcyclohexanol, *p*-nitrophenyl chloroformate and all metal salts were purchased from Sigma-Aldrich. Unless otherwise reported all reactions were performed under nitrogen atmosphere. Removal of the solvent *in vacuo* refers to distillation using a rotary evaporator attached to an efficient vacuum pump. Products obtained as solids or syrups were dried under high vacuum. Analytical thin-layer chromatography was performed on pre-coated silica plates (F_{254}, 0.25 mm thickness); compounds were visualized by UV light or by staining with anisaldehyde spray.

IR spectra were recorded on a AT-IR spectrometer. NMR spectra were recorded either on a 400 or a 600 MHz with $CDCl_3$ as the solvent and TMS as the internal standard. High resolution mass spectroscopy (HRMS) was performed using an ESI-TOF mass analyser. Low resolution mass spectroscopy (LRMS) was performed on UPLC-MS with SWADESI-TLC interface.

1-Ethynylcyclohexyl (4-methoxybenzyl) carbonate (**5**): DMAP (2.65g, 21.71mmol) was added to a CH_2Cl_2 (20 mL) solution of p-methoxybenzyl alcohol (1.77 mL, 14.48 mmol) and stirred for 30 minutes. 1-Ethynylcyclohexyl 4-nitrophenyl carbonate (5.03 g, 17.37mmol) was added in three portions (3x1.7 g) in 30 min intervals. The reaction mixture was stirred for 3 h, concentrated *in vacuo* to obtain the crude residue that was purified by silica gel column chromatography using 5% ethyl acetate-hexane as mobile phase to obtain compound **5** (3.97 g, 95% yield) as a white crystalline solid.

1-Ethynylcyclohexyl (benzyl) carbonate (**6**): DMAP (2.03 g, 16.65 mmol) was added to a CH_2Cl_2 (15 mL) solution of benzyl alcohol (1.13 mL, 11.10 mmol) and stirred for 30 minutes. 1-Ethynylcyclohexyl 4-nitrophenyl carbonate (3.85 g, 13.32 mmol) was added in three portions (3x1.3 g) in 30 min intervals. The reaction mixture was stirred for 3 h, concentrated *in vacuo* to obtain the crude residue that was purified by silica gel column chromatography using 2% ethyl

acetate-hexane as mobile phase to obtain compound **6** (2.7 g, 94% yield) as a white crystalline solid.

1-Ethynylcyclohexyl (napthalen-2-yl methyl) carbonate (**32**): DMAP (1.16 g, 16.65 mmol) was added to a CH_2Cl_2 (10 mL) solution of 2-napthalenemethanol (1.0g, 6.32 mmol) and stirred for 30 minutes. 1-Ethynylcyclohexyl 4-nitrophenyl carbonate (2.19 g, 7.6 mmol) was added in three portions (3x700mg) in 30 min intervals. The reaction mixture was stirred for 3 h, concentrated *in vacuo* to obtain the crude residue that was purified by silica gel column chromatography using 2% ethyl acetate-hexane as mobile phase to obtain compound **32** (2.7 g, 94% yield) as a white amorphous solid.

Procedure for 1-(azidomethyl)-4-methoxybenzene synthesis (**C**): A solution of carbonate **5** (50 mg, 1 eq) in CH_2Cl_2 (2 mL) was treated with excess trimethylsilyl azide (250 mg) and freshly activated 4Å molecular sieves powder, stirred for 15 mins. Gold-phosphite catalyst **20** (7.62 mg, 0.05 eq) and AgOTf (6.68 mg, 0.15 eq.) were added and stirred for 1 h. Preparative TLC was performed to avoid compound loss due to the highly volatile nature of azide **22**.

General procedure of the gold-catalysed PMB-ether preparation: To a solution of alcohol (**7, 10, 12, 14, 16, 18, 20, 22, or 24**) (1.0 eq) and the carbonate **5** (1.0 eq. per –OH group) in anhydrous CH_2Cl_2 (3 mL/100 mg of alcohol) was added freshly activated 4Å MS powder (30 mg/mL) and stirred for 20 minutes under nitrogen atmosphere. To the reaction mixture at 25 ^oC, gold-phosphite **2** (5 mol%) and AgOTf (10 mol%) were added and stirred for 30 minutes. At the end of the reaction as adjudged by the TLC examination, the reaction mixture was passed through a bed of celite and the filtrate was concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase.This procedure was adopted for the synthesis of compounds **8**, **11**, **13**, **15**, **17**, **19**, **21**,**23**, and **25**).

General procedure of the gold-catalysed Benzyl ether preparation: To a solution of alcohol (**7, 26** or **28**) (1.0 eq) and the carbonate **6** (1.2 eq. per –OH group) in anhydrous CH_2Cl_2 (3 mL/100 mg of alcohol) was added freshly activated 4Å MS powder (30 mg/mL) and stirred for 20 minutes under nitrogen atmosphere. To the reaction mixture at 25^oC, gold-phosphite **2** (5 mol%) and AgOTf (10 mol%) were added and stirred for 1 h. At the end of the reaction as adjudged by the TLC examination, the reaction mixture was passed through a bed of celite and the filtrate was

concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase. This procedure was adopted for the synthesis of compounds **9**, **27** and **29**.

General procedure of the gold catalysed Nap-ether preparation: Alcohol (**7, 30** or **31**) (1.0 eq) was dissolved in anhydrous CH_2Cl_2 (3 mL/ 100 mg alcohol) and freshly activated 4Å MS powder (30 mg/mL) was added and stirred for 15 min. Gold-phosphite **2** (5 mol%) and AgOTf (10 mol%) were added to the reaction mixture under nitrogen atmosphere. A solution of carbonate **32** (1.5 eq per –OH group) in Dry CH_2Cl_2 was added dropwise and slowly and stirred for 1 h at 25^oC. At the end of the reaction as adjudged by the TLC examination, the reaction mixture was passed through a bed of celite and the filtrate was concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase.This procedure was adopted for the synthesis of compounds **33**, **36** and **37**.

Procedure for selective primary PMB-ether protection: Alcohol (**35**) (170 mg, 0.4 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL/100mg alcohol, to maintain the higher dilution percentage) and freshly activated was added and stirred for 20 min. Gold phosphite **2** (10 mol%) and AgOTf (10 mol%) were added to the reaction mixture under nitrogen atmosphere. A solution of carbonate 5 (0.3 eq, 38mg) in 0.5 mL of dry CH_2Cl_2 was added dropwise and slowly at 0 ^oC and this process was repeated for three more times with addition of 150 mg of carbonate **5** (1.2 eq, 0.52 mmol) in total and stirred for 30 more minutes at 0 ^0C. At the end of the reaction as adjudged by the TLC examination, the reaction mixture was passed through a bed of celite and the filtrate was concentrated *in vacuo* to get a residue that was purified by silica gel column chromatography using ethyl acetate:hexane (8:92) as mobile phase to obtain compound **36** as a sticky solid. (134mg, 75% yield).

Procedure for one-pot synthesis of PMB and Bn-ethers: Selective PMB protection was performed on alcohol **35** (120 mg) by following previously explained method. In the same pot, Gold-phosphite **2** (5 mol%) and AgOTf (10 mol%) were added afterwards. Next, a solution of carbonate **6** (2 eq dissolved in 1 ml of dry CH_2Cl_2) were added in a slow dropwise manner under inert atmosphere. The progress of the reaction was monitored by TLC examination, after the completion of the reaction, the mixture was passed through a bed of celite and the filtrate was concentrated *in vacuo*

to obtain a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase obtaining compound **37** in an overall yield of 45% (50mg).

2.5. Characterization data:

1-Ethynylcyclohexyl 4-methoxybenzyl carbonate (**5**): White crystalline solid, mp (ºC): 57, IR (cm^{-1}, $CHCl_3$): 3264, 2938, 2860,1746,1447,1269, 1077, 911, 730, 578; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.20 – 1.37 (ddq, J = 13.7, 9.3, 4.7 Hz, 1H), 1.45 – 1.55 (m, 1H), 1.54 – 1.73 (m, 4H), 1.77 – 1.91 (dt, J = 10.5, 4.0 Hz, 2H), 2.16 (dt, J = 10.5, 4.0 Hz, 2H), 2.62 (s, 1H), 3.77 (s, 3H), 5.07 (s, 2H), 6.83 – 6.88 (m, 2H), 7.28 – 7.33 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.60, 22.61, 25.05, 36.91, 36.92, 55.34, 69.20, 74.94, 77.56, 83.12, 114.00, 114.00, 127.50, 130.43, 130.43, 152.90, 159.90; HRMS (ESI-MS): m/z calcd for $[C_{17}H_{20}O_4Na]^+$: 311.1259; Found: 311.1262.

1-Ethynylcyclohexyl benzyl carbonate (**6**): Crystalline solid, mp (ºC): 61; IR (cm^{-1}, $CHCl_3$): 3266, 2932, 2861, 1746, 1514, 1448,1231, 1077, 971, 788, 555; ^1H NMR (400.31 MHz, $CDCl_3$): δ 1.31 (ddq, J = 13.7, 9.3, 4.7 Hz, 1H), 1.46 – 1.58 (m, 1H), 1.57 – 1.74 (m, 4H), 1.86 (dt, J = 10.5, 4.0 Hz, 2H), 2.18 (dt, J = 10.5, 4.0 Hz, 2H), 2.63 (s, 1H), 5.15 (s, 2H), 6.89 – 7.75 (m, 5H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.6, 22.6, 25.1, 36.9, 36.9, 69.3, 75.0, 77.7, 83.1, 128.5, 128.5, 128.5, 128.6, 128.5, 135.4, 152.9; HRMS (ESI-MS): m/z calcd for $[C_{16}H_{18}O_3Na]^+$: 281.1154; Found: 281.1151.

1-(azidomethyl)-4-methoxybenzene (**C**): Liquid; IR (cm^{-1}, $CHCl_3$): 2922,2851,2095 (N_3),1611,1513,1461; ^1H NMR (400.31 MHz, $CDCl_3$): δ 3.84 (s, 3H), 4.29 (s, 2H), 6.94 (d, J = 8.7 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H); HRMS (ESI-MS): m/z calcd for $[C_8H_9N_3ONa]^+$: 186.0643; Found: 186.0638.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(*p*-methoxybenzyl) α-D-glucopyranoside (**8**): Eluent for purification: 15% ethyl acetate in *n*-hexane; yield 117 mg from 100 mg of compound **7** (95%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.5): +68.9º; IR (cm^{-1}, $CHCl_3$): 2925, 2852, 1727, 1512, 1451, 1366, 1249, 1098, 1033, 754, 707; ^1H NMR (400.31 MHz, $CDCl_3$). δ 3.50 (s, 3H), 3.62 – 3.71 (m, 2H), 3.75 (s, 3H), 4.25 (ddd, *J* = 10.2, 4.5, 2.9 Hz, 1H), 4.44 – 4.58 (m, 2H), 5.26 – 5.34 (m, 2H), 5.68

(t, *J* = 9.9 Hz, 1H), 6.15 (t, *J* = 9.6 Hz, 1H), 6.74 – 6.80 (m, 2H), 7.20 – 7.26 (m, 2H), 7.27 – 7.35 (m, 2H), 7.36 – 7.48 (m, 5H), 7.50 – 7.57 (m, 2H), 7.87 – 8.03 (m, 6H).^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.2, 55.6, 68.1, 68.9, 69.5, 70.7, 72.2, 73.3, 97.0, 113.7, 113.7, 128.3, 128.3, 128.3, 128.3, 128.4, 128.4, 129.1, 129.2, 129.3, 129.5, 129.5, 129.7, 129.7, 129.7, 129.8, 129.8, 129.9, 129.9, 133.0, 133.2, 133.3, 159.1, 165.2, 165.8, 165.8.HRMS (ESI-MS): m/z calcd for $[C_{36}H_{34}O_{10}Na]^+$: 649.2050 Found: 649.2059.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-benzyl α-D-glucopyranoside (**9**): Eluent for purification: 15% ethyl acetate in *n*-hexane; yield 150 mg from 147 mg of compound **8** (84%); Thick syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 0.5): +37.6º; IR (cm^{-1}, $CHCl_3$): 3890, 3738, 2924, 2857, 1730, 1600, 1452, 1366, 1273, 1173, 1042, 917, 710 ; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.34 (s, 3H), 3.54 (t, *J* = 3.8 Hz, 2H), 4.10 (dt, *J* = 7.6, 4.5 Hz, 1H), 4.42 (dd, *J* = 12.0, 10.2 Hz, 2H), 5.08 – 5.19 (m, 2H), 5.52 (t, *J* = 9.9 Hz, 1H), 6.00 (t, *J* = 9.5 Hz, 1H), 7.02 – 7.18 (m, 7H), 7.19 – 7.30 (m, 5H), 7.35 – 7.39 (m, 2H), 7.73 – 7.78 (m, 4H), 7.84 – 7.85 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.7, 68.7, 69.0, 69.6, 70.7, 72.2, 73.8, 97.1, 127.7, 127.8, 127.8, 128.3, 128.3, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 129.2, 129.2, 129.4, 129.8, 129.8, 129.9, 129.9, 130.0, 130.0, 133.1, 133.3, 133.4, 137.7, 165.3, 165.9, 165.9; HRMS (ESI-MS): m/z calcd for $[C_{35}H_{32}O_9Na]^+$: 619.1944; Found: 619.1940.

Pent-4-enyl 2,3,4-tri-*O*-benzyl-6-*O*-(*p*-methoxybenzyl) α-D-mannopyranoside (**11**): Eluent for purification: 15% ethyl acetate in *n*-hexane; yield 177 mg from 150 mg of compound **10** (96%); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 0.9): +10.2º; IR (cm^{-1}, $CHCl_3$): 2925, 1738, 1738, 1610, 1511, 1453, 1365, 1216, 1096, 910, 818, 697; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.65 (q, *J* = 6.9 Hz, 2H), 2.09 (q, *J* = 6.7 Hz, 2H), 3.40 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.68 – 3.74 (m, 2H), 3.76 – 3.82 (m, 6H), 3.93 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.99 – 4.04 (m, 1H), 4.49 (d, *J* = 3.7 Hz, 1H), 4.52 (d, *J* = 2.7 Hz, 1H), 4.63 – 4.66 (m, 3H), 4.73 -4.80 (m, 2H), 4.89 (s, 1H), 4.90 (d, *J* = 10.6 Hz, 1H), 4.93 – 5.07 (m, 2H), 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 6.84 – 6.87 (m, 2H), 7.13 – 7.21 (m, 2H), 7.26 – 7.36 (m, 10H), 7.36 – 7.44 (m, 5H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 28.7, 30.4, 55.3, 67.0, 68.9, 71.9, 72.3, 72.7, 73.1, 74.9, 75.1, 75.3, 80.4, 98.0, 113.8, 113.8, 115.0, 127.7, 127.7, 127.7, 127.8, 127.8, 128.0, 128.0, 128.1, 128.1, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 129.6, 129.6, 130.6, 138.2, 138.6, 138.6, 138.7, 159.2; HRMS (ESI-MS): m/z calcd for $[C_{40}H_{46}O_7Na]^+$: 661.3141; Found: 661.3146.

Allyl 2-*deoxy*-2-(((2,2,2-trichloroethoxy)carbonyl)amino)-3-*O*-benzoyl-4-*O*-(*p*-methoxybenzyl)-6-*O*-(*tert*-butyldiphenylsilyl) β-D-glucopyranoside (**13**): Eluent for purification: 20% ethyl acetate in *n*-hexane; yield 136 mg from 143 mg of compound **12** (85%); Yellow syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +30.8º; IR (cm^{-1}, $CHCl_3$): 2933, 1738, 1516, 1367, 1216, 1105, 1036, 707 ; ^{1}H NMR(400.31 MHz, $CDCl_3$). δ 1.16 (s, 9H), 3.72 (s, 3H), 3.88 (ddd, *J* = 9.9, 3.8, 2.0 Hz, 1H), 3.93 – 4.00 (m, 3H), 4.04 (ddt, *J* = 12.8, 6.4, 1.3 Hz, 1H), 4.17 – 4.26 (m, 2H), 4.50 – 4.59 (m, 3H), 4.73 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 3.6 Hz, 1H), 5.24 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.44 (d, *J* = 10.1 Hz, 1H), 5.67 (dd, *J* = 10.8, 9.1 Hz, 1H), 5.92 (dddd, *J* = 17.0, 10.4, 6.4, 5.3 Hz, 1H), 6.64 – 6.67 (m, 2H), 6.94 – 6.99 (m, 2H), 7.41 – 7.50 (m, 8H), 7.57 – 7.63 (m, 1H), 7.78 (m, 4H), 8.06 – 8.11 (m, 2H).^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.4, 26.9, 26.9, 26.9, 54.6, 55.1, 62.6, 68.2, 72.1, 74.1, 74.3, 74.6, 75.7, 95.3, 96.3, 113.7, 118.2, 127.6, 127.6, 127.8, 127.8, 128.4, 128.4, 129.6, 129.7, 129.7, 129.7, 129.7, 129.7, 129.7, 129.9, 129.9, 133.1, 133.2, 133.4, 133.6, 135.7, 135.7, 135.9, 135.9, 154.4, 159.2, 166.4.HRMS (ESI-MS): m/z calcd for $[C_{43}H_{48}O_9NCl_3SiNa]^+$: 878.2062 Found: 878.2059.

Allyl 2-*O*-benzoyl-3-*O*-*tert*-butyldiphenylsilyl-4-O-(*p*-methoxybenzyl)-6-*O*-benzyl β-D-glucopyranoside (**15**): Eluent for purification: 15% ethyl acetate in *n*-hexane; yield 80 mg from 74 mg of compound **14** (78%); Solid, mp (ºC): 172; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +104.6º; IR (cm^{-1}, $CHCl_3$): 2929, 2858,1726, 1610, 1513, 1454, 1367, 1246, 1160, 1105, 927, 822, 741, 610 ; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 0.95 (s, 9H), 3.70 – 3.80 (m, 2H), 3.82 – 3.87 (m, 5H), 3.88 – 3.93 (m, 1H), 4.01 – 4.08 (m, 1H), 4.48 (d, *J* = 10.6 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.64 – 4.74 (m, 2H), 4.80 (d, *J* = 10.6 Hz, 1H), 4.97 (dt, *J* = 10.5, 1.3 Hz, 1H), 5.01 – 5.10 (m, 2H), 5.13 (dd, *J* = 3.9, 1.3 Hz, 1H), 5.64 (ddt, *J* = 16.0, 10.4, 5.2 Hz, 1H), 6.75 – 6.90 (m, 2H), 6.93 – 7.03 (m, 2H), 7.10-7.17 (m, 2H), 7.18 – 7.26 (m, 3H), 7.31 – 7.38 (m, 4H), 7.39 – 7.51 (m, 7H), 7.53-7.63 (m, 2H), 7.70-7.81 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.6, 26.8, 26.8, 26.8, 55.3, 68.0, 68.7, 70.0, 73.5, 73.6, 73.7, 74.7, 78.9, 94.9, 113.6, 113.6, 116.5, 127.2, 127.2, 127.5, 127.5, 127.6, 127.6, 127.8, 128.0, 128.0, 128.5, 128.5, 129.0, 129.0, 129.1, 129.5, 129.7, 129.7, 129.7, 130.6, 132.4, 133.4, 133.6, 133.9, 135.3, 135.3, 136.0, 136.0, 138.0, 159.0, 165.9; HRMS (ESI-MS): m/z calcd for $[C_{47}H_{52}O_8SiNa]^+$: 795.3329; Found: 795.3332.

1-((((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)-4-methoxybenzene (**17**): Eluent for purification: 10% ethyl acetate in *n*-hexane; yield 78 mg from 55 mg of compound **16** (81%);

Liquid; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -74.5; IR (cm^{-1}, $CHCl_3$): 3882,2951, 2922, 2865, 1739, 1612, 1513, 1456, 1369, 1246, 1040, 820, 591; ^{1}H NMR (400.31 MHz, $CDCl_3$) δ 0.70 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 1H), 0.89 (s, 3H), 0.92 (s, 3H), 0.94 – 0.98 (m, 1H), 1.26 (s, 3H), 1.59 – 1.67 (m, 2H), 2.22 (d, *J* = 46.8 Hz, 2H), 3.11 – 3.18 (m, 1H), 3.79 (s, 3H), 4.33 (d, *J* = 11.1 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 6.86 (d, *J* = 6.6 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H).^{13}C NMR (100.67 MHz, $CDCl_3$): δ 16.0, 21.0, 22.4, 23.2, 25.5, 31.6, 34.6, 40.3, 48.3, 55.2, 70.0, 76.7, 77.0, 77.3, 78.4, 113.7, 113.7, 129.3, 129.3, 131.2, 159.0..HRMS (ESI-MS): m/z calcd for $[C_{18}H_{28}O_2Na]^+$: 299.1987 Found: 299.1992.

O-(*p*-methoxybenzyl)cholesterol (**19**): Eluent for purification: 10% ethyl acetate in *n*-hexane; yield 220 mg from 200 mg of compound **18** (84%); Pale brown solid, mp (ºC): 110; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -16.3º; IR (cm^{-1}, $CHCl_3$): 2937, 2861, 1737, 1512, 1459, 1369, 1245, 1099, 1035, 818, 526; ^{1}H NMR (400.31 MHz, $CDCl_3$). δ 0.71 (s, 3H), 0.87 – 0.98 (m, 10H), 1.04 (s, 3H), 1.13 (dtd, *J* = 21.4, 11.6, 11.1, 5.7 Hz, 7H), 1.27 – 1.43 (m, 6H), 1.46 – 1.64 (m, 7H), 1.82 – 2.10 (m, 5H), 2.29 (ddd, *J* = 13.5, 11.0, 2.8 Hz, 1H), 2.44 (ddd, *J* = 13.3, 4.8, 2.3 Hz, 1H), 3.29 (tt, *J* = 11.2, 4.5 Hz, 1H), 3.82 (s, 3H), 4.52 (s, 2H), 5.37 (dt, *J* = 5.5, 1.9 Hz, 1H), 6.88 – 6.93 (m, 2H), 7.27 – 7.33 (m, 2H)^{13}C NMR (100.67 MHz, $CDCl_3$): δ 11.9, 18.8, 19.4, 21.1, 22.6, 22.9, 23.9, 24.3, 28.0, 28.3, 28.5, 31.9, 32.0, 35.8, 36.2, 36.9, 37.3, 39.2, 39.5, 39.8, 42.3, 50.2, 55.3, 56.2, 56.8, 69.6, 78.3, 113.8, 113.8, 121.5, 129.2, 129.2, 131.2, 141.0, 159.0.HRMS (ESI-MS): m/z calcd for $[C_{35}H_{32}O_9Na]^+$: 529.4022 Found: 529.4023.

Benzyl *N*-(((9H-fluoren-9-yl)methoxy)carbonyl)-*O*-(*p*-methoxybenzyl)-L-serinate (**21**): Eluent for purification: 25% ethyl acetate in *n*-hexane; yield 140 mg from 105 mg of compound **20** (90%); Yellow solid; mp (ºC): 98.5; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -0.1º; IR (cm^{-1}, $CHCl_3$): 3441, 3208, 2953, 1728, 1513, 1452, 1364, 1297, 1243, 1036, 744, 528 ; ^{1}H NMR (400.31 MHz, $CDCl_3$). δ 3.76 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.82 (s, 3H), 3.97 (dt, *J* = 9.6, 2.9 Hz, 1H), 4.29 (t, *J* = 7.3 Hz, 1H), 4.46 (m, 4H), 5.18 – 5.33 (m, 2H), 5.81 – 5.93 (m, 1H), 6.90 (dd, *J* = 8.7, 2.6 Hz, 2H), 7.21 (dd, *J* = 8.6, 2.6 Hz, 2H), 7.33 – 7.41 (m, 7H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.68 (dt, *J* = 7.7, 3.9 Hz, 2H), 7.82 (d, *J* = 7.6 Hz, 2H).^{13}C NMR (100.67 MHz, $CDCl_3$): δ 47.2, 54.6, 55.3, 67.3, 69.5, 73.0, 113.9, 113.9, 120.0, 120.0, 125.2, 125.3, 127.1, 127.2, 127.8, 127.8, 128.2, 128.2, 128.4, 128.4, 128.6, 128.6, 129.4, 129.4, 129.5, 135.4, 141.3, 141.3, 143.8, 144.0, 156.1, 159.4, 170.4 HRMS (ESI-MS): m/z calcd for $[C33H31O_6NNa]^+$: 560.2049 Found: 560.2051.

4-pentenyl-2,3-di-*O*-benzoyl-5-*O*-[2,3-di-*O*-benzoyl-5-*O*-(*p*-methoxybenzyl)-α-D-arabinofuranosyl]-α-D-arabinofuranoside (**23**): Eluent for purification: 20% ethyl acetate in *n*-hexane; yield 270 mg from 250 mg of compound **22** (94%); Yellow solid; mp (ºC): 168; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +0.4º; IR (cm^{-1}, $CHCl_3$): 3888, 3828, 3393, 2927, 1724, 1605, 1258, 1176, 1107, 1032, 914, 711, 525 ; ^{1}H NMR (400.31 MHz, $CDCl_3$) δ 1.73 – 1.82 (m, 2H), 2.16 – 2.23 (m, 2H), 3.54 (dt, *J* = 9.5, 6.1 Hz, 1H), 3.78 (s, 3H), 3.79 – 3.91 (m, 3H), 3.96 (dd, *J* = 11.1, 3.1 Hz, 1H), 4.24 (dd, *J* = 11.2, 4.6 Hz, 1H), 4.49 (td, *J* = 4.7, 3.0 Hz, 1H), 4.59 – 4.66 (m, 3H), 4.98 (ddt, *J* = 10.2, 2.2, 1.3 Hz, 1H), 5.03 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.23 (s, 1H), 5.45 (s, 1H), 5.50 – 5.54 (m, 2H), 5.62 (d, *J* = 1.2 Hz, 1H), 5.64 – 5.67 (m, 1H), 5.84 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 6.78 – 6.86 (m, 2H), 7.26 – 7.34 (m, 4H), 7.38 – 7.54 (m, 8H), 7.56 – 7.63 (m, 2H), 7.94 – 8.11 (m, 8H).^{113}C NMR (100.67 MHz, $CDCl_3$): δ 28.7, 30.3, 55.2, 66.2, 66.6, 69.2, 73.2, 77.7, 77.7, 81.5, 81.7, 81.8, 82.5, 105.6, 105.9, 113.7, 113.7, 114.9, 128.2, 128.2, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 129.0, 129.2, 129.2, 129.3, 129.3, 129.3, 129.8, 129.8, 129.8, 129.8, 129.8, 129.8, 129.9, 129.9, 130.0, 133.1, 133.3, 133.3, 133.4, 138.1, 159.1, 165.1, 165.4, 165.6, 165.7.HRMS (ESI-MS): m/z calcd for $[C_{51}H_{50}O_{14}Na]^+$: 909.3098 Found: 909.3094.

Methyl 2,3-di-*O*-(*p*-methoxybenzyl)-4,6-*O*-benzylidene α-D-glucopyranoside (**25**): Eluent for purification: 15% ethyl acetate in *n*-hexane; yield 85 mg from 50 mg of compound **24** (92%); Thick syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 0.5): +44.9º, IR (cm^{-1}, $CHCl_3$): 3070, 2890, 1682, 1533, 1450, 1265, 1216, 1090, 917, 839 ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.38 (s, 3H), 3.51 (dd, J = 9.3, 3.7 Hz, 1H), 3.57 (t, J = 9.4 Hz, 1H), 3.69 (t, J = 10.2 Hz, 1H), 3.78 (s, 3H), 3.78 (t, J = 10.2 Hz, 1H), 3.79 (s, 3H), 4.00 (t, J = 9.3 Hz, 1H), 4.25 (dd, J = 10.0, 4.7 Hz, 1H), 4.53 (d, J = 3.7 Hz, 1H), 4.62 (d, J = 11.9 Hz, 1H), 4.72 – 4.86 (m, 3H), 5.53 (s, 1H), 6.73 – 6.99 (m, 4H), 7.20 – 7.34 (m, 4H), 7.37 (d, J = 7.0 Hz, 3H), 7.46 – 7.53 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.2, 55.3, 55.3, 62.4, 69.1, 73.4, 75.0, 78.3, 78.7, 82.1, 99.3, 101.3, 113.7, 113.7, 113.8, 113.8, 126.1, 126.1, 128.2, 128.2, 128.9, 129.7, 129.7, 129.8, 129.8, 130.3, 130.9, 137.5, 159.2, 159.4; HRMS (ESI-MS): m/z calcd for $[C_{30}H_{34}O_8Na]^+$: 545.2151; Found: 545.2147.

Methyl 2-*O*-benzoyl-3-*O*-benzyl-4,6-*O*-benzylidene α-D-glucopyranoside (**27**): Eluent for purification: 20% ethyl acetate in *n*-hexane; yield 221 mg from 250 mg of compound **26** (72%); White solid; mp (ºC): 136; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +128.2º; IR (cm^{-1}, $CHCl_3$): 3020, 2923, 1722, 1271, 1214, 1098, 996, 745, 668, 580 ; ^{1}H NMR (400.31 MHz, $CDCl_3$) δ 3.42 (s, 3H), 3.85 (q, *J* =

9.7, 9.2 Hz, 2H), 3.97 (td, *J* = 9.8, 4.6 Hz, 1H), 4.25 (t, *J* = 9.3 Hz, 1H), 4.38 (dd, *J* = 10.1, 4.6 Hz, 1H), 4.79 – 4.95 (m, 2H), 5.11 (d, *J* = 3.8 Hz, 1H), 5.16 (ddd, *J* = 9.5, 3.8, 0.8 Hz, 1H), 5.67 (s, 1H), 7.19 – 7.25 (m, 3H), 7.26 – 7.30 (m, 2H), 7.41 – 7.52 (m, 5H), 7.54 – 7.59 (m, 2H), 7.60 – 7.66 (m, 1H), 8.07 – 8.11 (m, 2H).^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.4, 62.4, 69.0, 73.6, 74.8, 75.8, 82.3, 98.0, 101.4, 126.1, 126.1, 127.6, 128.0, 128.0, 128.3, 128.3, 128.3, 128.3, 128.4, 128.4, 129.0, 129.7, 130.0, 130.0, 133.3, 137.4, 138.2, 166.0. HRMS (ESI-MS): m/z calcd for $[C_{35}H_{32}O_9Na]^+$: 499.1733 Found: 499.1739.

4-pentenyl 2,3-di-*O*-benzoyl-5-*O*-benzyl α-D-arabinofuranoside (**29**): Eluent for purification: 15% ethyl acetate in *n*-hexane; yield 92 mg from 100 mg of compound **28** (75%); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -18.8º; IR (cm^{-1}, $CHCl_3$): 2927, 1725, 1600, 1451, 1362, 1264, 1108,1067, 1029, 710 ; ^{1}H NMR (400.31 MHz, $CDCl_3$) δ 1.70 – 1.80 (m, 2H), 2.14 – 2.24 (m, 2H), 3.55 (dt, *J* = 9.5, 6.2 Hz, 1H), 3.78 – 3.85 (m, 1H), 3.85 – 3.95 (m, 2H), 4.43 – 4.50 (m, 1H), 4.67 (s, 2H), 4.97 (ddd, *J* = 10.1, 2.0, 1.1 Hz, 1H), 5.02 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.26 (s, 1H), 5.48 (d, *J* = 1.3 Hz, 1H), 5.52 (d, *J* = 4.8 Hz, 1H), 5.83 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 7.24 – 7.32 (m, 3H), 7.34 – 7.42 (m, 4H), 7.42 – 7.48 (m, 2H), 7.53 – 7.61 (m, 2H), 7.97 – 8.03 (m, 2H), 8.06 – 8.10 (m, 2H).^{13}C NMR (100.67 MHz, $CDCl_3$): 28.9, 30.4, 66.8, 69.9, 73.8, 77.9, 81.9, 82.4, 105.8, 115.0, 127.7, 127.8, 127.8, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 129.3, 129.5, 130.0, 130.0, 130.0, 130.0, 133.5, 133.5, 138.1, 138.2, 165.5, 165.9. HRMS (ESI-MS): m/z calcd for $[C_{31}H_{32}O_7Na]^+$: 539.2046 Found: 539.2045.

1-ethynylcyclohexyl (naphthalen-2-ylmethyl) carbonate (**32**): White amorphous solid; mp (ºC): 60.7; IR (cm^{-1}, $CHCl_3$): 3290, 2940, 2863, 1770, 1593, 1493, 1268, 1206, 1008, 771; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 1.23 – 1.40 (m, 1H), 1.49 – 1.58 (m, 1H), 1.59 – 1.75 (m, 4H), 1.82 – 1.93 (m, 2H), 2.15 – 2.24 (m, 2H), 2.64 (d, *J* = 1.4 Hz, 1H), 5.32 (s, 2H), 7.44 – 7.54 (m, 3H), 7.80 – 7.89 (m, 4H).; ^{13}C NMR (100.67 MHz, $CDCl_3$): 22.6, 22.7, 25.1, 36.9, 36.9, 69.5, 75.0, 77.8, 83.1, 126.0, 126.4, 126.4, 127.7, 127.8, 128.2, 128.5, 132.8, 133.3, 133.3, 152.9.; HRMS (ESI-MS): m/z calcd for $[C_{39}H_{34}O_9Na]^+$: 308.1412; Found: 308.1412.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(naphthalene-2-ylmethyl) α-D-glucopyranoside (**33**): Eluent for purification: 12% ethyl acetate in *n*-hexane; yield 119 mg from 150 mg of compound **7** (62%); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +55.9º; IR (cm^{-1}, $CHCl_3$): 2924, 2855, 1728, 1600, 1452, 1366, 1269, 1171, 1100, 1041, 974, 857, 756, 711; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 3.53 (s, 3H), 3.78 (t, *J* =

3.8 Hz, 2H), 4.31 (dt, *J* = 7.6, 4.5 Hz, 1H), 4.77 (dd, *J* = 12.0, 10.2 Hz, 2H), 5.32 – 5.39 (m, 2H), 5.75 (t, *J* = 9.9 Hz, 1H), 6.20 (t, *J* = 9.5 Hz, 1H), 7.31 – 7.55 (m, 12H), 7.73 – 7.80 (m, 4H), 7.90 – 7.94 (m, 4H), 8.03 – 8.04 (m, 2H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.6, 68.6, 68.9, 69.6, 70.7, 72.2, 73.8, 97.1, 125.8, 125.8, 126.0, 126.7, 127.7, 127.9, 128.2, 128.3, 128.3, 128.3, 128.3, 128.4, 128.4, 129.1, 129.1, 129.3, 129.7, 129.7, 129.7, 129.7, 130.0, 130.0, 133.0, 133.1, 133.2, 133.2, 133.4, 135.1, 165.3, 165.9, 165.9; HRMS (ESI-MS): m/z calcd for $[C_{39}H_{34}O_9Na]^+$: 669.2101; Found: 669.2097.

4-pentenyl 2-*O*-benzoyl-3-O-benzyl-5-*O*-naphthalene-2-ylmethyl α-D-arabinofuranoside (**36**): Eluent for purification: 15% ethyl acetate in *n*-hexane; yield 74 mg from 100 mg of compound **34** (55%); Liquid; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +51.3º; IR (cm^{-1}, $CHCl_3$): 3019, 2923, 2858, 1816, 1723, 1453, 1264, 1215, 1106, 816, 746, 669 ; ^{1}H NMR (400.31 MHz, $CDCl_3$). δ 1.69 – 1.79 (m, 2H), 2.11 – 2.21 (m, 2H), 3.51 (dt, *J* = 9.7, 6.4 Hz, 1H), 3.64 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.72 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.79 (dt, *J* = 9.7, 6.6 Hz, 1H), 4.03 (d, *J* = 5.5 Hz, 1H), 4.35 (td, *J* = 5.3, 3.7 Hz, 1H), 4.58 (d, *J* = 12.1 Hz, 2H), 4.71 (q, *J* = 12.2 Hz, 1H), 4.80 (d, *J* = 12.1 Hz, 1H), 4.96 (ddd, *J* = 11.4, 2.2, 1.3 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.18 (s, 1H), 5.38 (d, *J* = 1.4 Hz, 1H), 5.83 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 7.19 – 7.27 (m, 3H), 7.28 – 7.33 (m, 4H), 7.38 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.44 – 7.53 (m, 3H), 7.71 – 7.76 (m, 3H), 7.79 – 7.83 (m, 1H), 7.92 – 7.97 (m, 2H).^{13}C NMR (100.67 MHz, $CDCl_3$): δ 28.8, 30.3, 67.0, 69.5, 72.3, 73.6, 82.1, 82.1, 83.5, 106.2, 114.9, 125.8, 126.0, 126.2, 126.6, 127.8, 127.8, 128.0, 128.0, 128.0, 128.2, 128.4, 128.4, 128.5, 128.5, 129.5, 129.8, 129.8, 133.1, 133.3, 133.4, 135.5, 137.8, 138.3, 165.6.HRMS (ESI-MS): m/z calcd for $[C_{35}H_{36}O_6Na]^+$: 575.2410 Found: 575.2411.

4-pentenyl 2,3-di-*O*-benzyl-5-*O*-naphthalene-2-ylmethyl α-D-arabinofuranoside (**37**): Eluent for purification: 12% ethyl acetate in *n*-hexane; yield 86 mg from 73 mg of compound **35** (58%); Liquid; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 0.5): +39.6º; IR (cm^{-1}, $CHCl_3$): 2923, 2863, 1738, 1366, 1213, 1099, 909, 744, 699; ^{1}H NMR (400.31 MHz, $CDCl_3$) δ 1.71 – 1.79 (m, 2H), 2.14 – 2.23 (m, 2H), 3.48 (qd, *J* = 6.6, 3.3 Hz, 1H), 3.71 (tdd, *J* = 10.9, 8.4, 4.5 Hz, 2H), 3.81 (dtd, *J* = 9.8, 6.5, 3.3 Hz, 1H), 4.00 (dt, *J* = 6.9, 3.5 Hz, 1H), 4.08 (dd, *J* = 3.4, 1.5 Hz, 1H), 4.25 – 4.32 (m, 1H), 4.50 – 4.57 (m, 2H), 4.61 (dd, *J* = 11.9, 3.3 Hz, 2H), 4.78 (t, *J* = 3.6 Hz, 2H), 5.02 (dq, *J* = 10.3, 1.5 Hz, 1H), 5.05 – 5.13 (m, 2H), 5.88 (dqd, *J* = 16.9, 6.7, 3.4 Hz, 1H), 7.28 (tq, *J* = 7.5, 3.9, 3.1 Hz, 5H), 7.37 (d, *J* = 3.1 Hz, 5H), 7.51 (ddd, *J* = 8.9, 5.2, 2.3 Hz, 3H), 7.80 – 7.90 (m, 4H)..^{13}C NMR (100.67 MHz,

$CDCl_3$): δ 28.8, 30.4, 67.0, 69.8, 72.0, 72.2, 73.5, 80.5, 83.6, 88.5, 106.2, 114.9, 125.9, 125.9, 126.1, 126.6, 127.7, 127.7, 127.8, 127.8, 127.9, 127.9, 127.9, 127.9, 128.2, 128.3, 128.3, 128.5, 128.5, 133.0, 133.3, 135.6, 137.6, 137.9, 138.3. HRMS (ESI-MS): m/z calcd for $[C_{35}H_{38}O_5Na]^+$: 561.2617 Found: 561.2620.

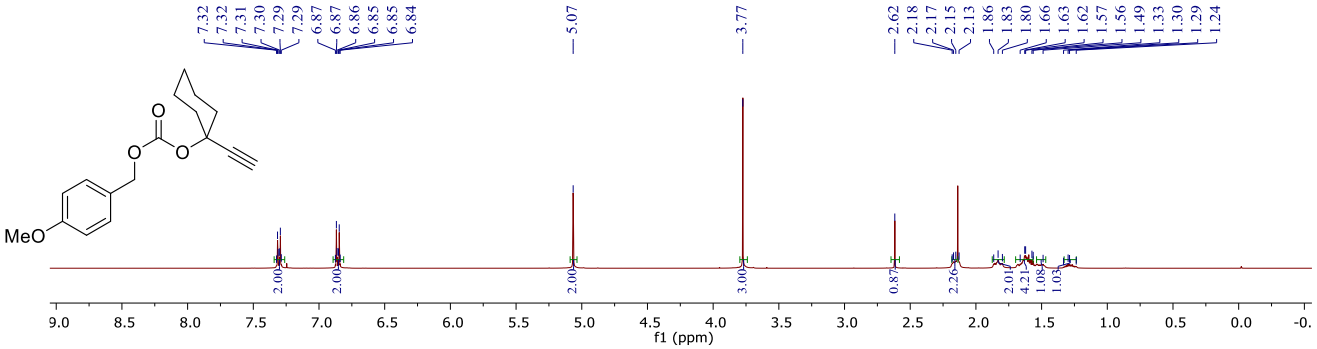
Allyl 2,3,-di-*O*-benzoyl-6-*O*-(*p*-methoxybenzyl) α-D-glucopyranoside (**39**): white solid, mp (ºC): 155; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +140.6º; IR (cm^{-1}, $CHCl_3$): 3497, 2922, 1725, 1609, 1513, 1453, 1275, 1103, 1037, 712, 562; ^{1}H NMR (400.31 MHz, $CDCl_3$). δ 3.23 (s, 1H), 3.75 – 3.89 (m, 5H), 3.97 – 4.11 (m, 3H), 4.27 (ddt, *J* = 13.3, 5.1, 1.6 Hz, 1H), 4.59 (q, *J* = 11.7 Hz, 2H), 5.16 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.28 – 5.36 (m, 3H), 5.80 – 5.84 (m, 1H), 5.85 – 5.92 (m, 1H), 6.89 – 6.95 (m, 2H), 7.28 – 7.34 (m, 2H), 7.35 – 7.41 (m, 4H), 7.49 – 7.55 (m, 2H), 7.99 – 8.03 (m, 4H).^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.3, 68.6, 69.2, 70.5, 70.6, 71.4, 73.4, 74.1, 76.8, 77.1, 77.4, 95.3, 113.9, 113.9, 117.6, 128.4, 128.4, 128.4, 128.4, 129.2, 129.4, 129.4, 129.8, 129.9, 129.9, 129.9, 129.9, 129.9, 133.3, 133.3, 133.5, 159.3, 166.0, 167.2.HRMS (ESI-MS): m/z calcd for $[C_{31}H_{32}O_9Na]^+$: 571.1944 Found: 571.1945.

Allyl 2,3,-di-*O*-benzoyl-4-O-benzyl-6-*O*-(*p*-methoxybenzyl) α-D-glucopyranoside (**40**): Thick syrup $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +164.4º; IR (cm^{-1}, $CHCl_3$): 2966, 1725, 1615, 1508, 1480, 1134, 1037, 712, 533; ^{1}H NMR (400.31 MHz, $CDCl_3$). δ 3.70 – 3.74 (m, 1H), 3.82 (s, 2H), 3.85 (dd, *J* = 10.8, 2.7 Hz, 1H), 4.00 – 4.06 (m, 3H), 4.23 (ddt, *J* = 13.2, 5.1, 1.6 Hz, 1H), 4.44 – 4.56 (m, 3H), 4.68 (d, *J* = 11.7 Hz, 1H), 5.13 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.22 (dd, *J* = 10.2, 3.7 Hz, 1H), 5.29 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.32 (d, *J* = 3.8 Hz, 1H), 5.80 – 5.87 (m, 1H), 6.04 – 6.09 (m, 1H), 6.90 – 6.93 (m, 2H), 7.03 (dd, *J* = 6.6, 2.8 Hz, 2H), 7.13 – 7.18 (m, 3H), 7.28 (s, 1H), 7.32 – 7.36 (m, 2H), 7.37 – 7.40 (m, 3H), 7.49 – 7.53 (m, 2H), 7.97 – 8.00 (m, 4H).^{13}C NMR (100.67 MHz, $CDCl_3$): δ 55.3, 67.7, 68.5,

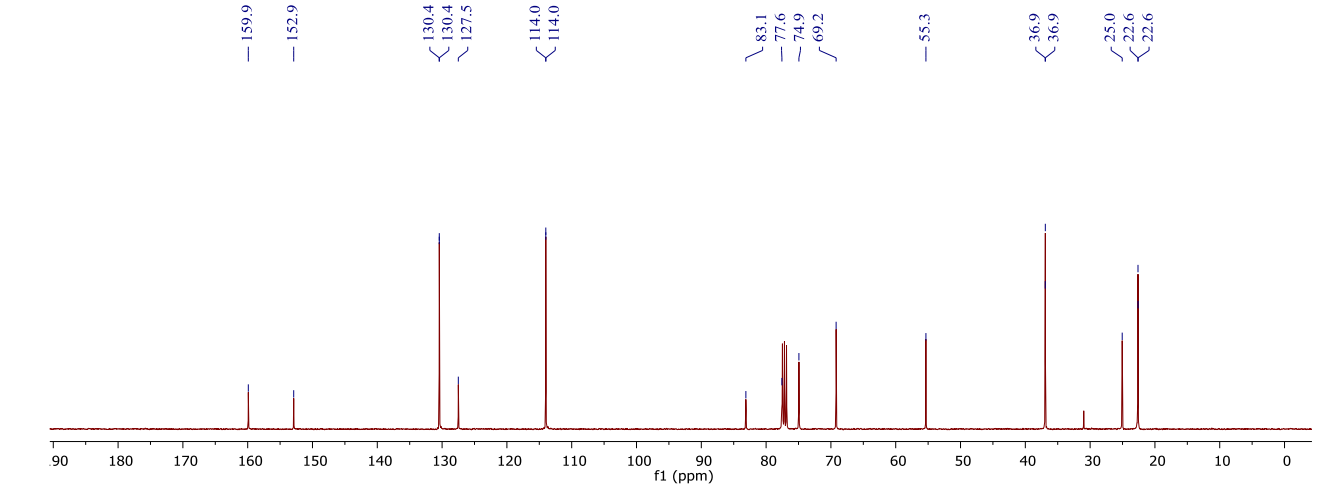
70.3, 72.2, 72.8, 73.3, 74.7, 76.0, 95.3, 113.9, 113.9, 117.5, 127.7, 127.7, 128.0, 128.0, 128.2, 128.2, 128.3, 128.3, 128.4, 128.4, 129.3, 129.7, 129.7, 129.8, 129.8, 129.9, 129.9, 133.0, 133.2, 133.5, 137.5, 139.3, 159.4, 165.7, 166.0.HRMS (ESI-MS): m/z calcd for $[C_{38}H_{38}O_9Na]^+$: 661.2414 Found: 661.2412.

2.6. NMR Spectral chart

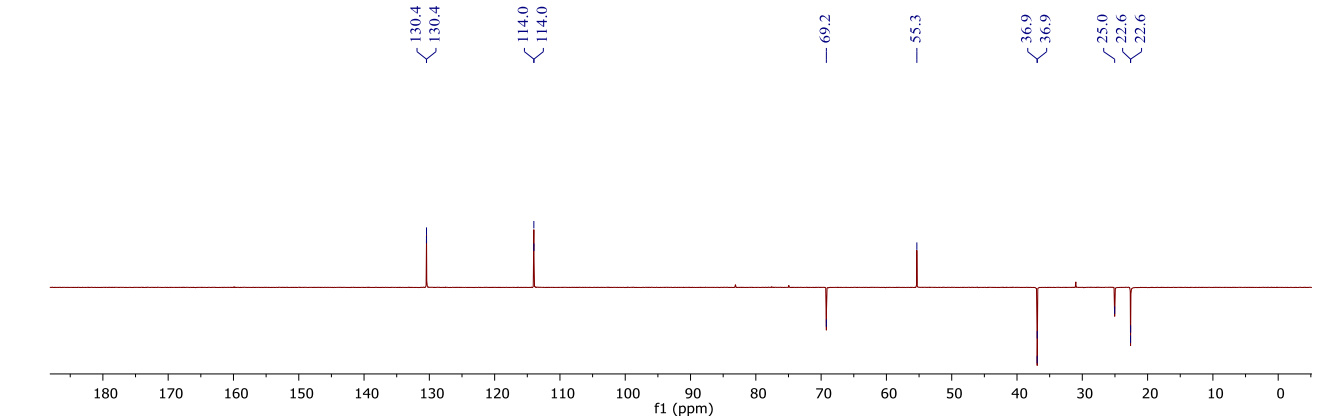
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 5



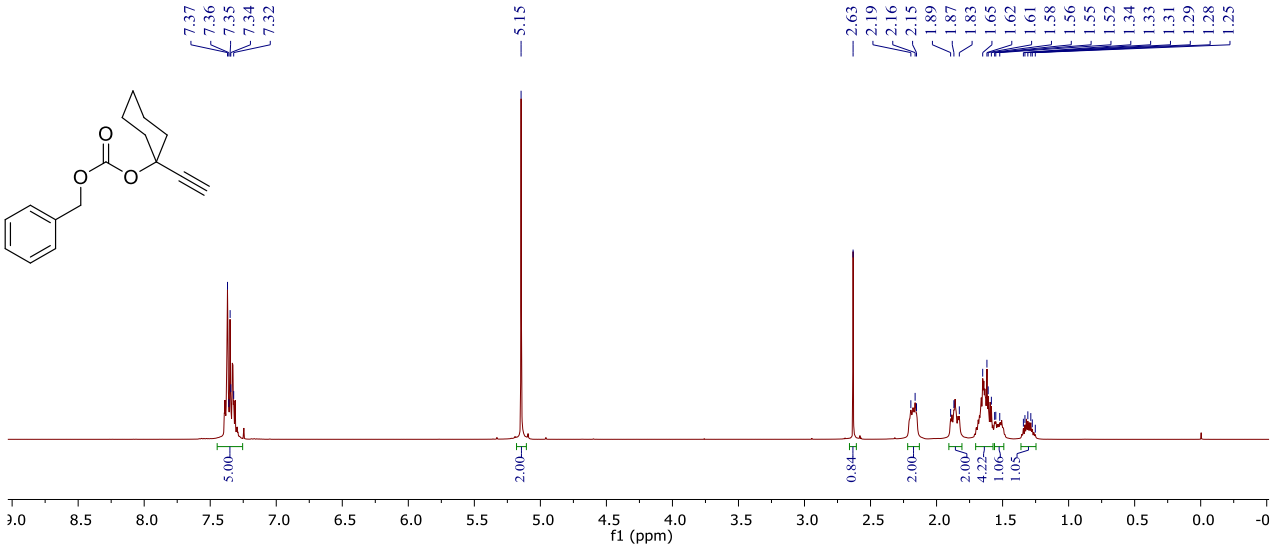
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 5



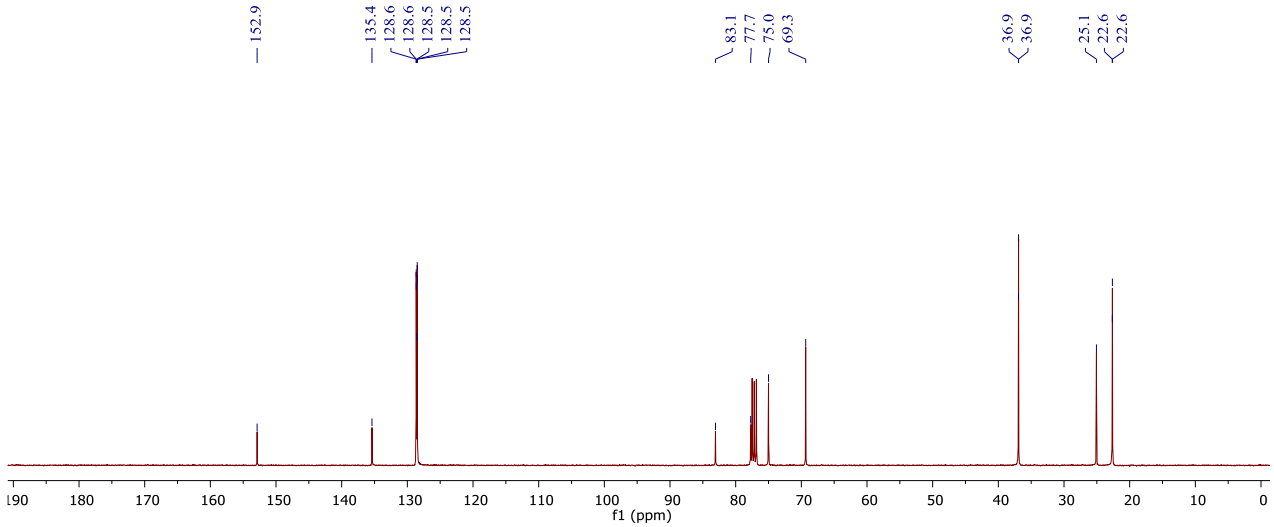
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 5



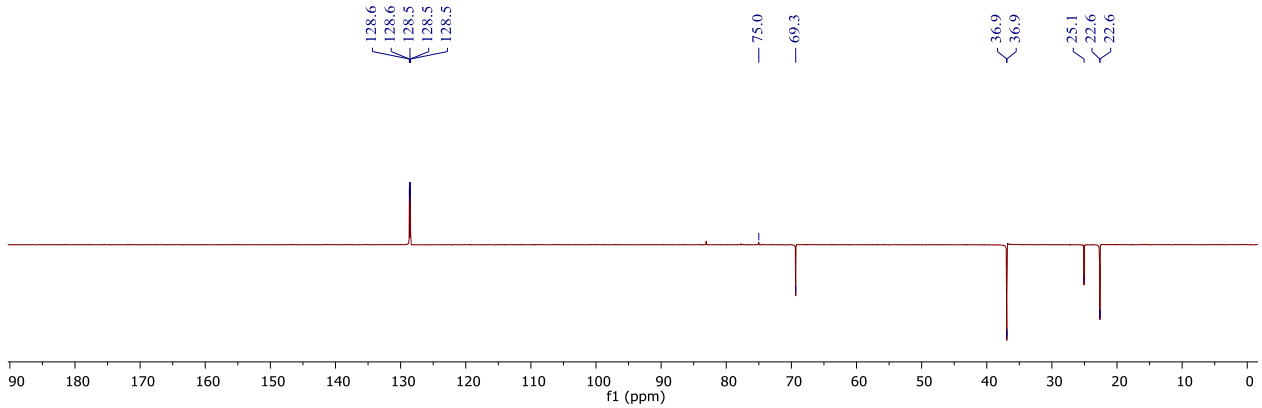
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 6



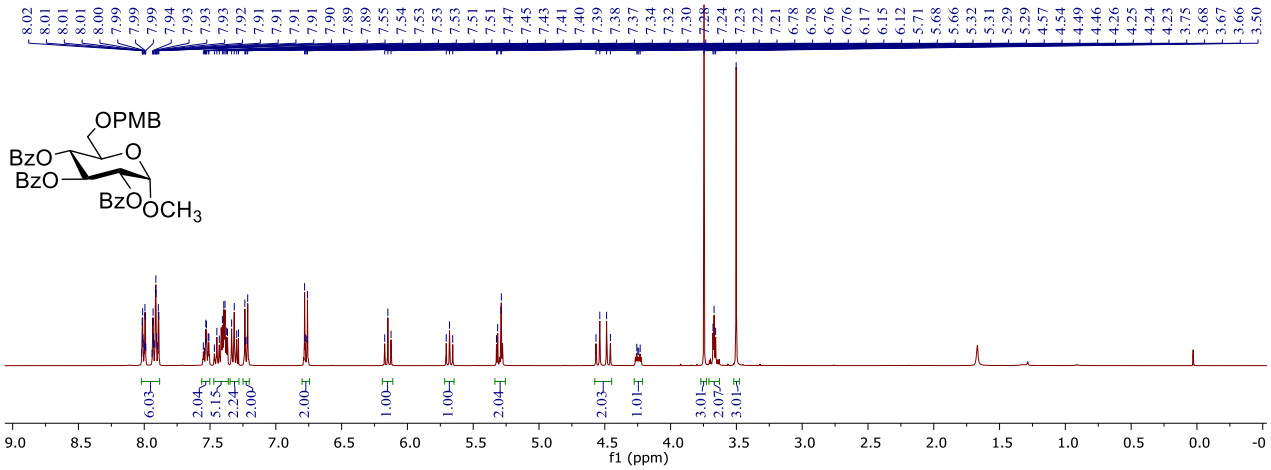
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 6



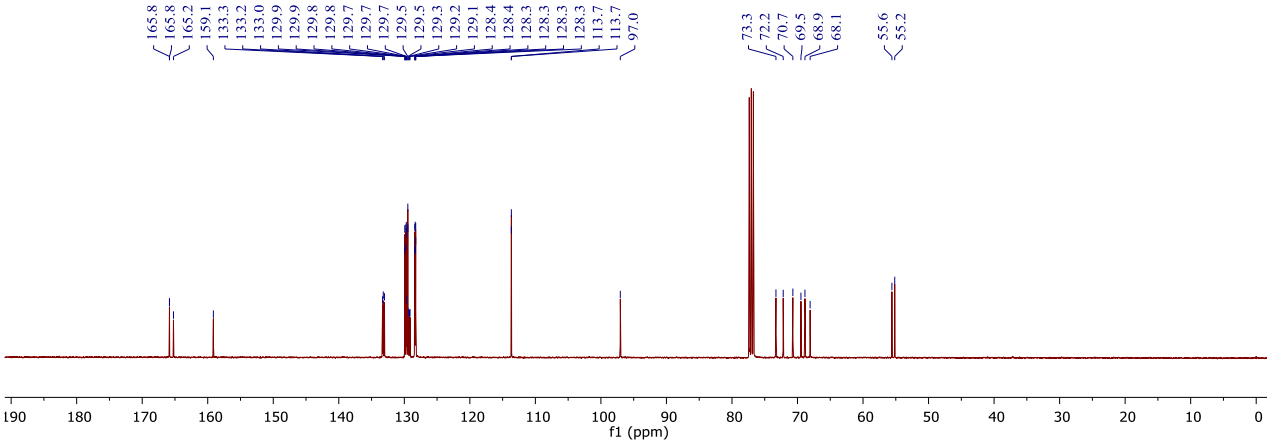
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 6



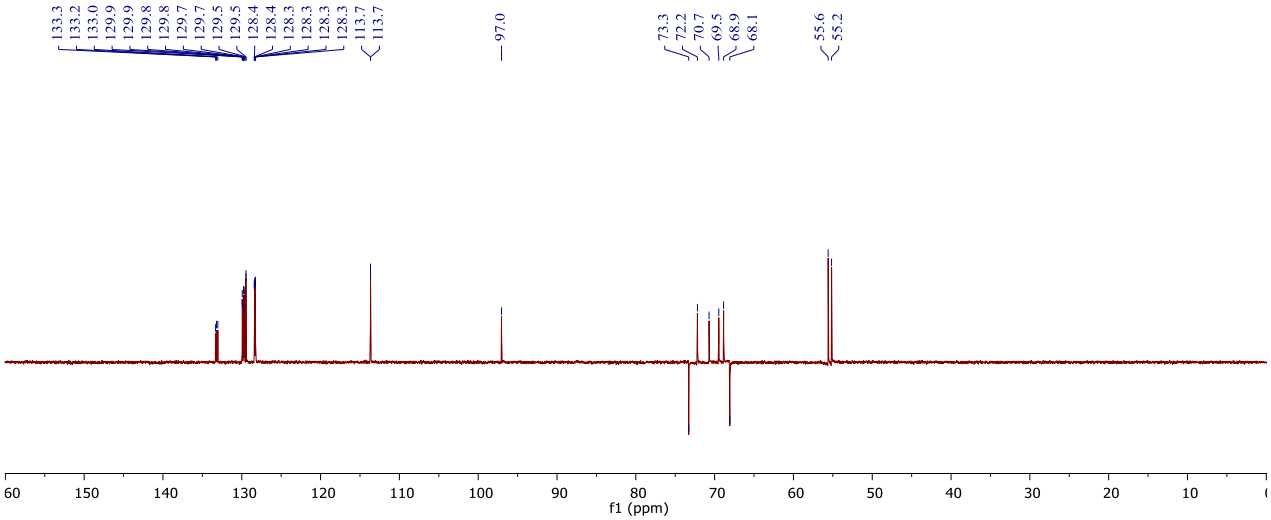
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 8



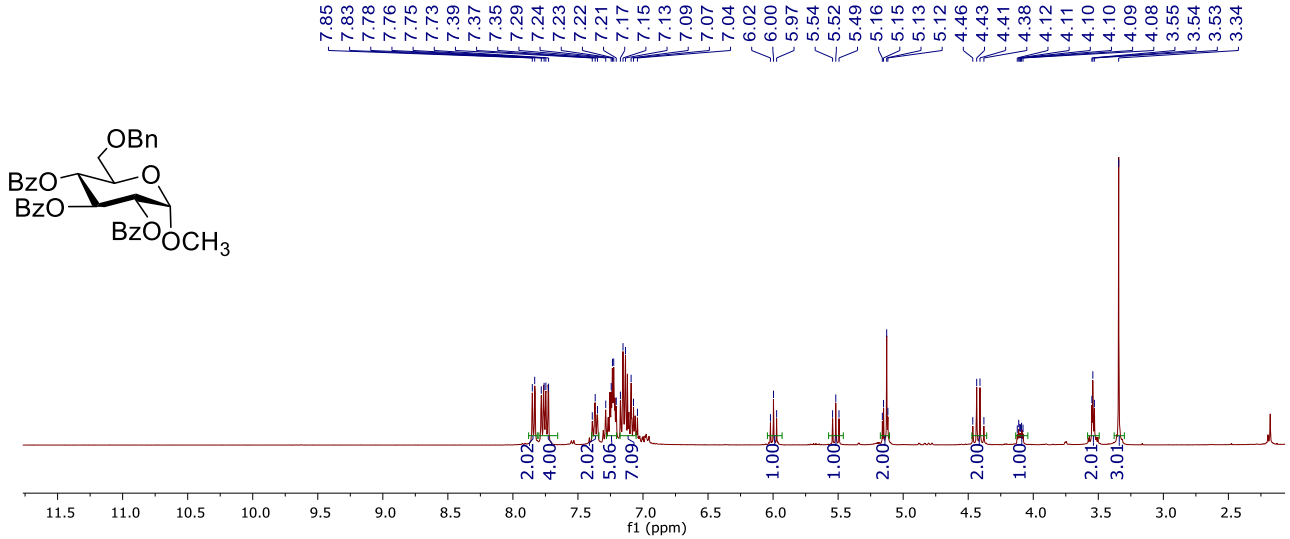
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 8



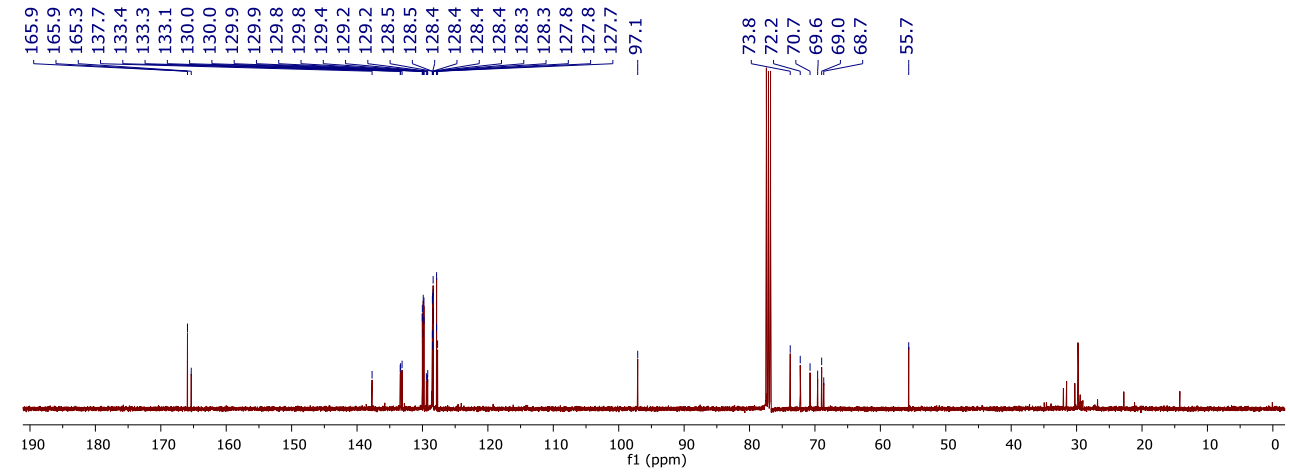
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 8



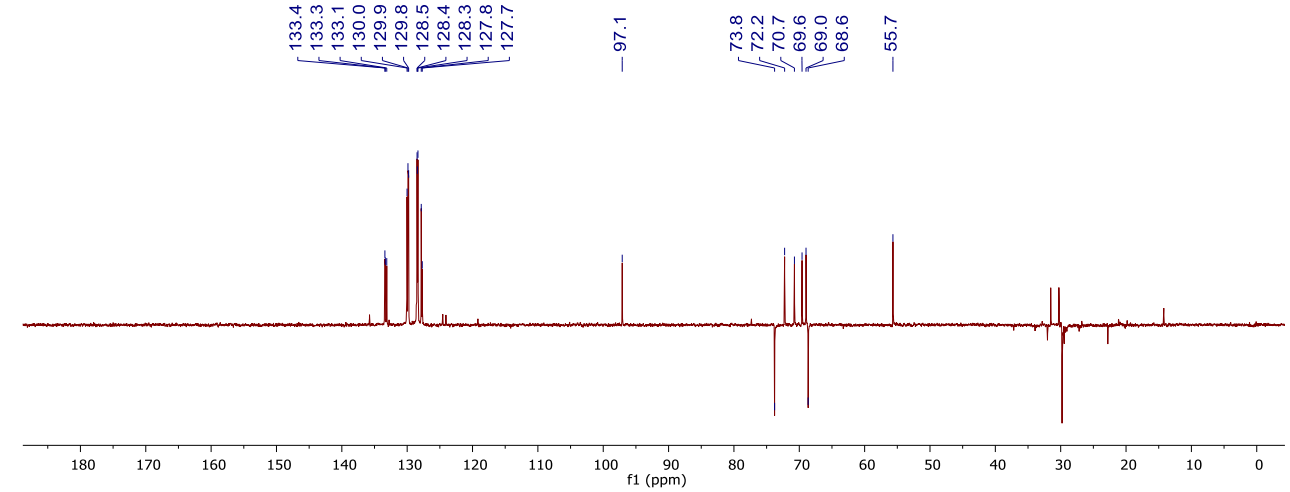
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 9



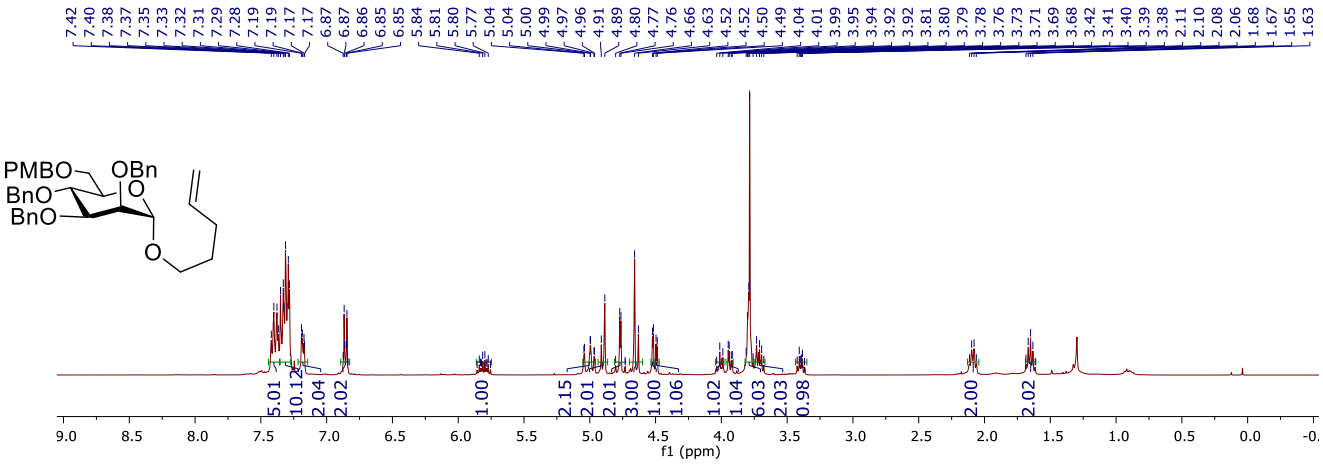
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 9



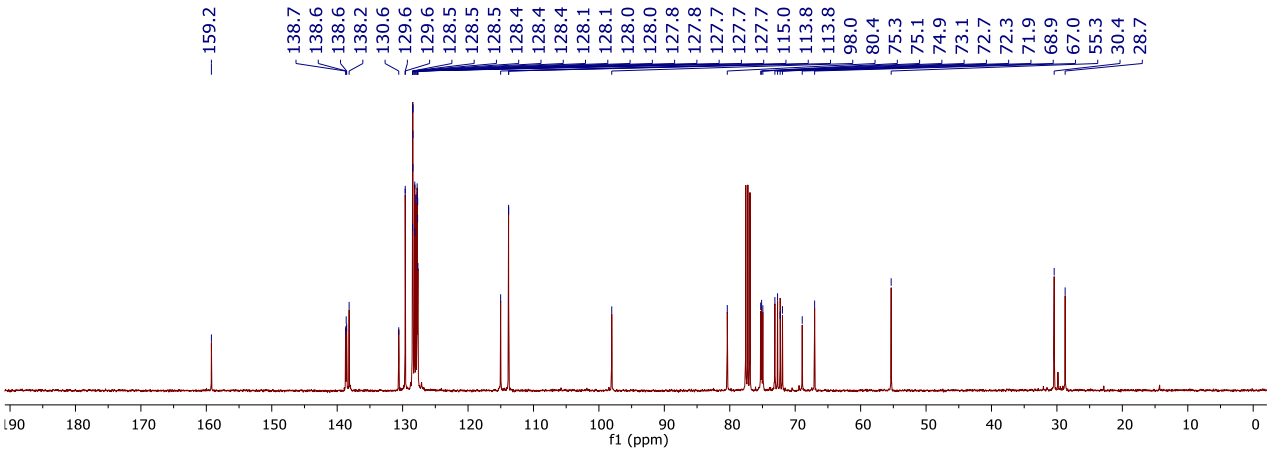
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 9



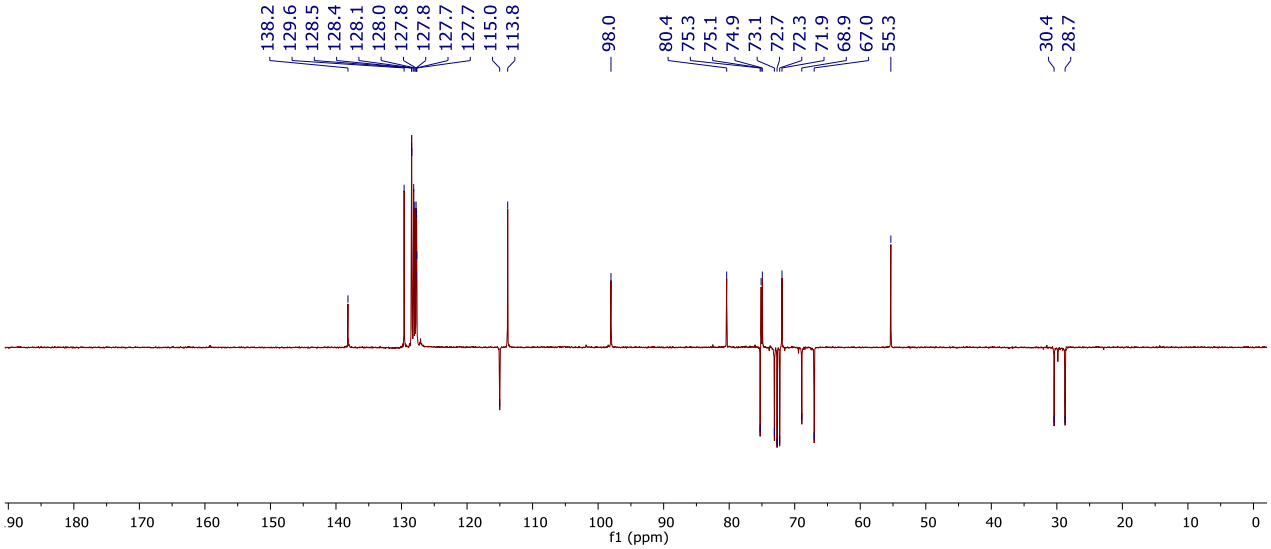
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 11



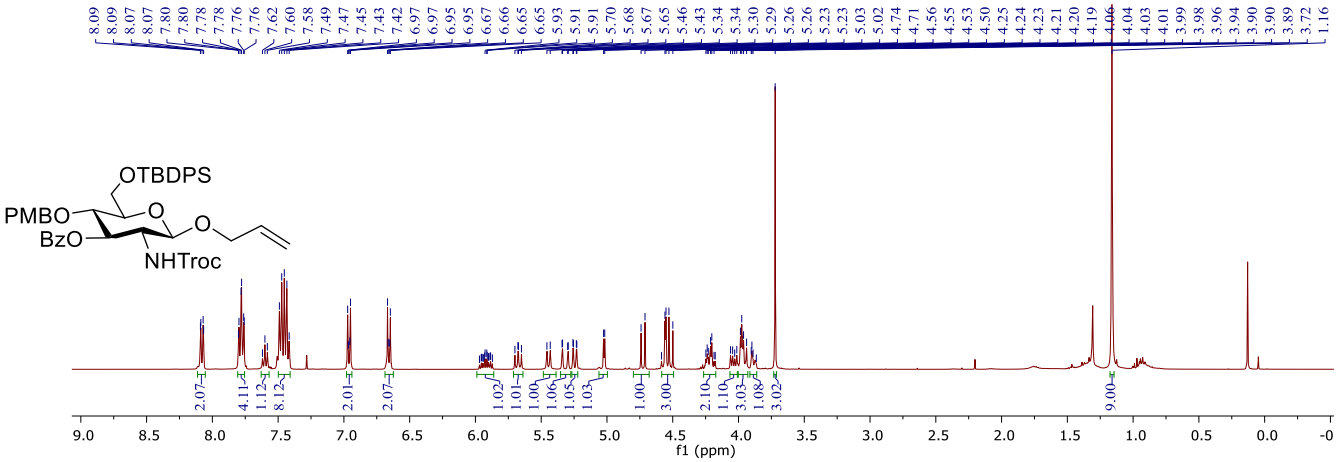
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 11



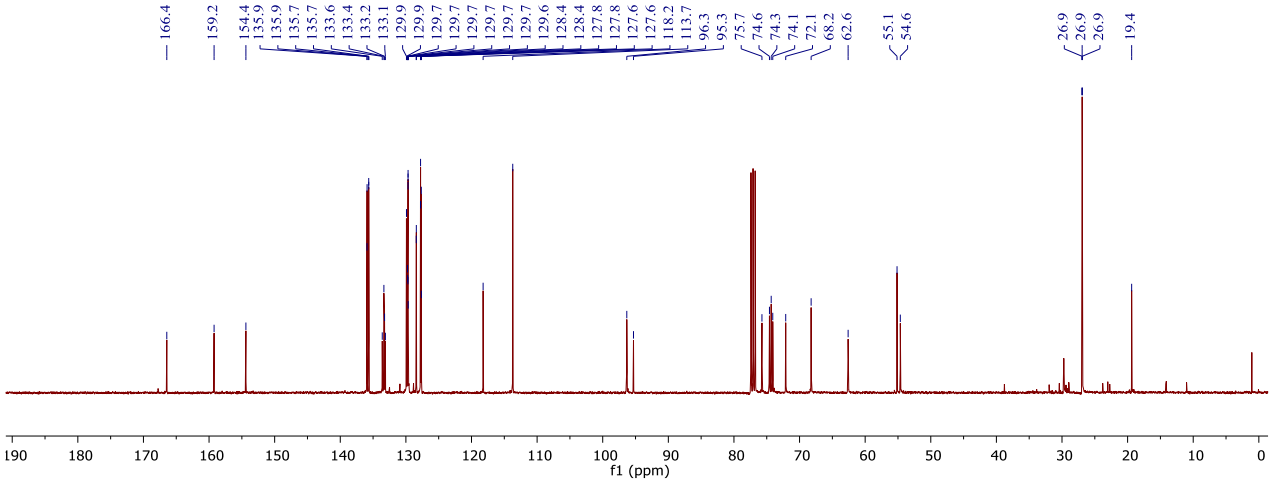
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 11



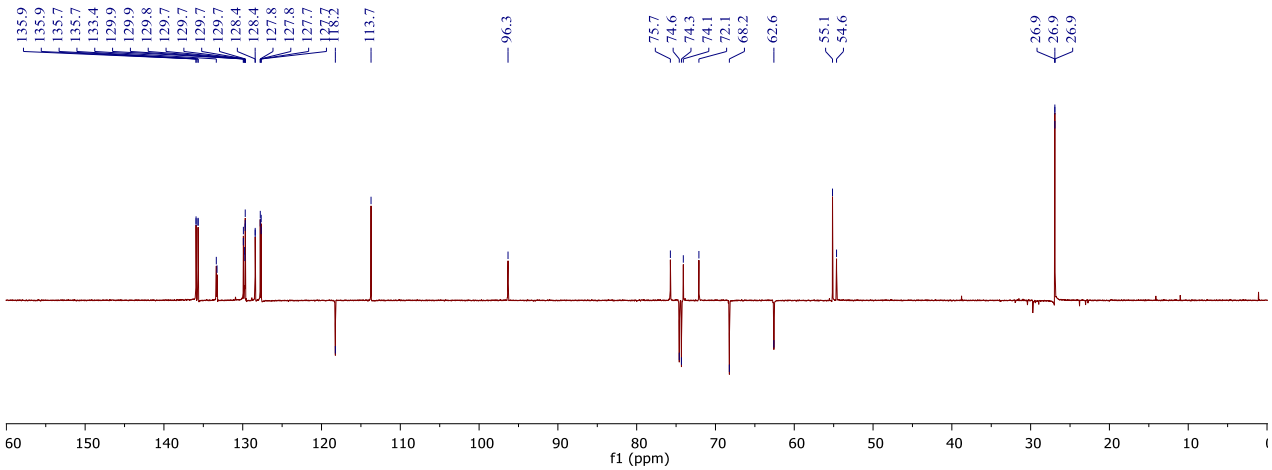
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 13



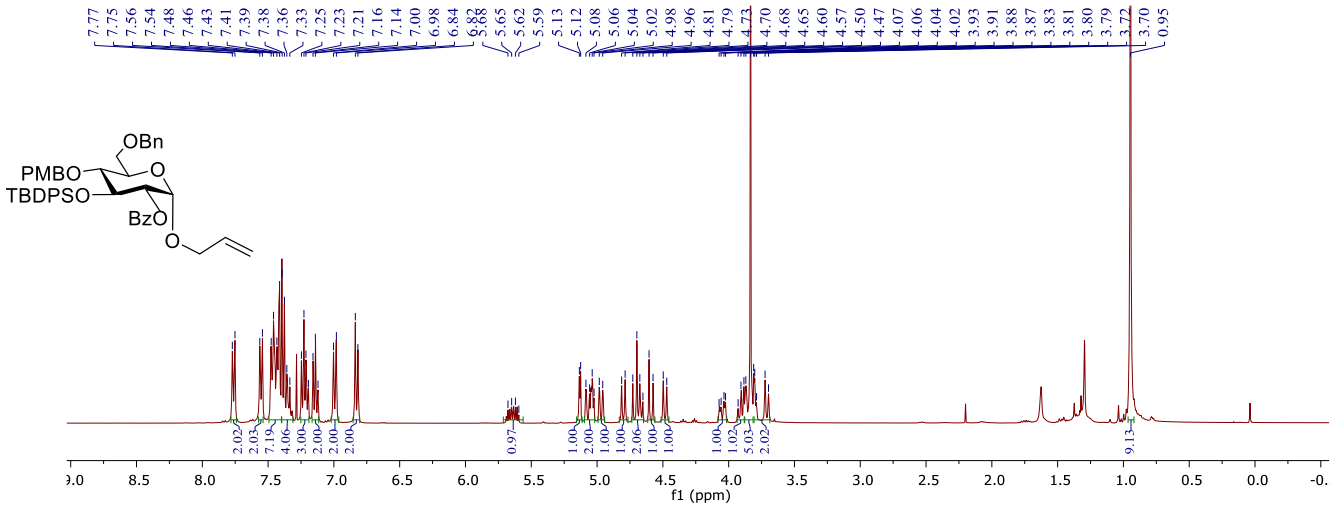
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 13



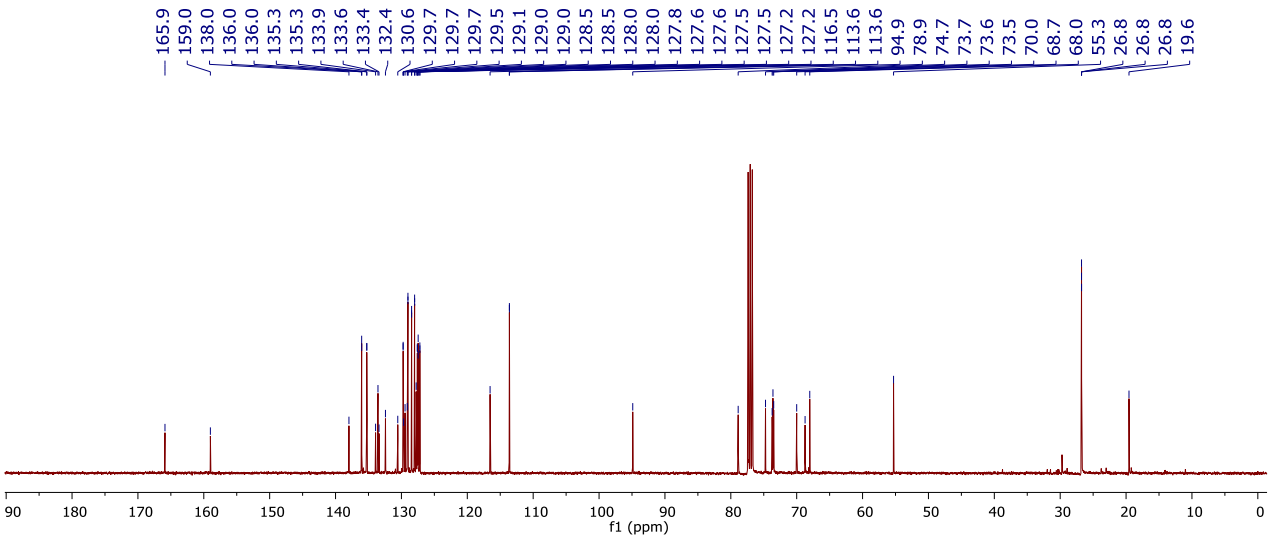
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 13



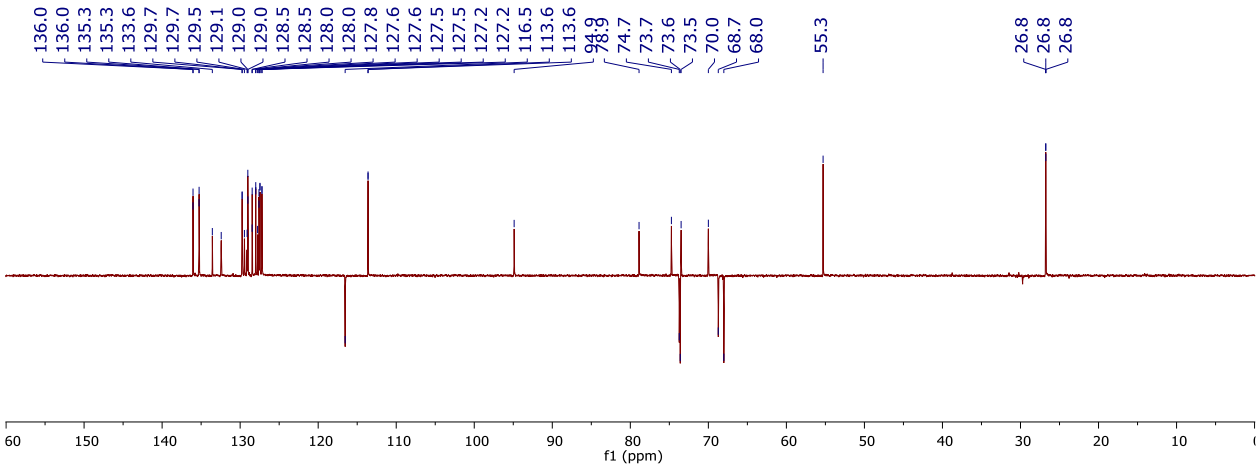
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 15



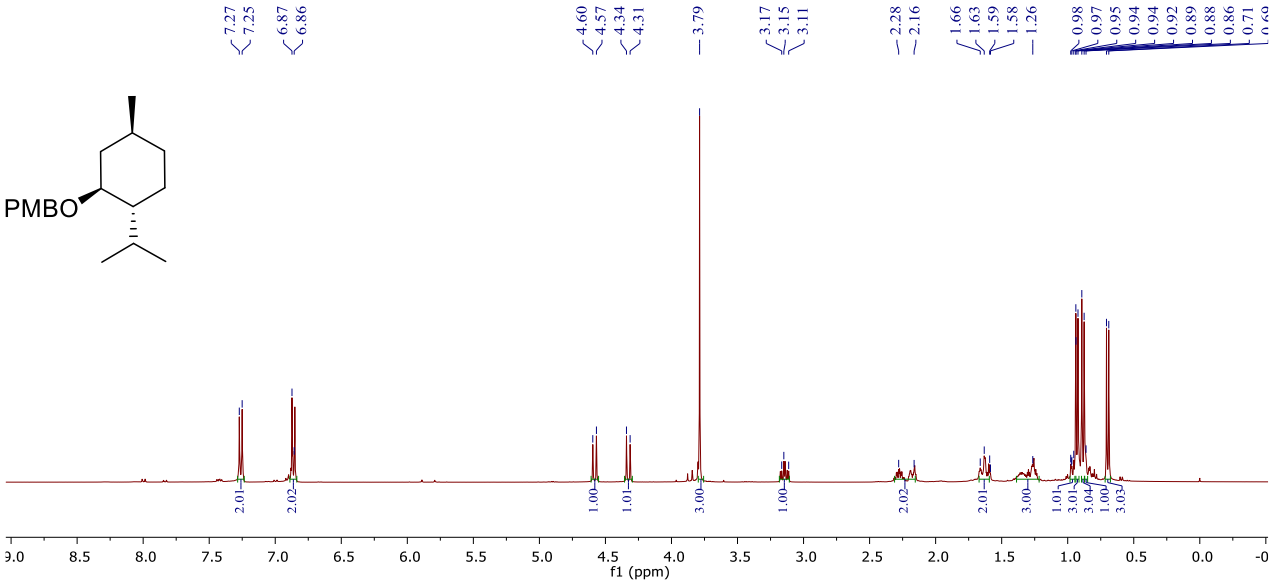
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 15



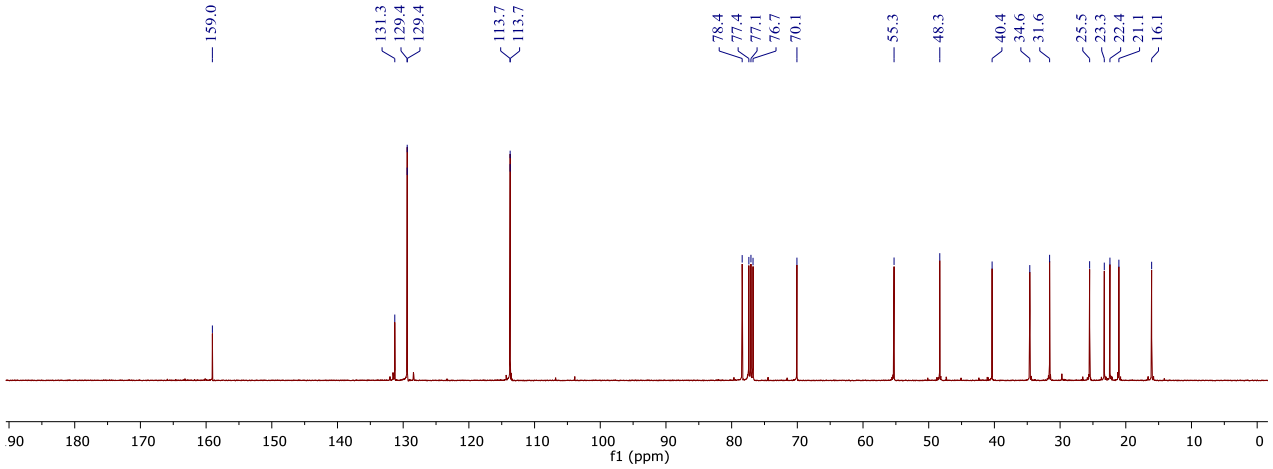
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 15



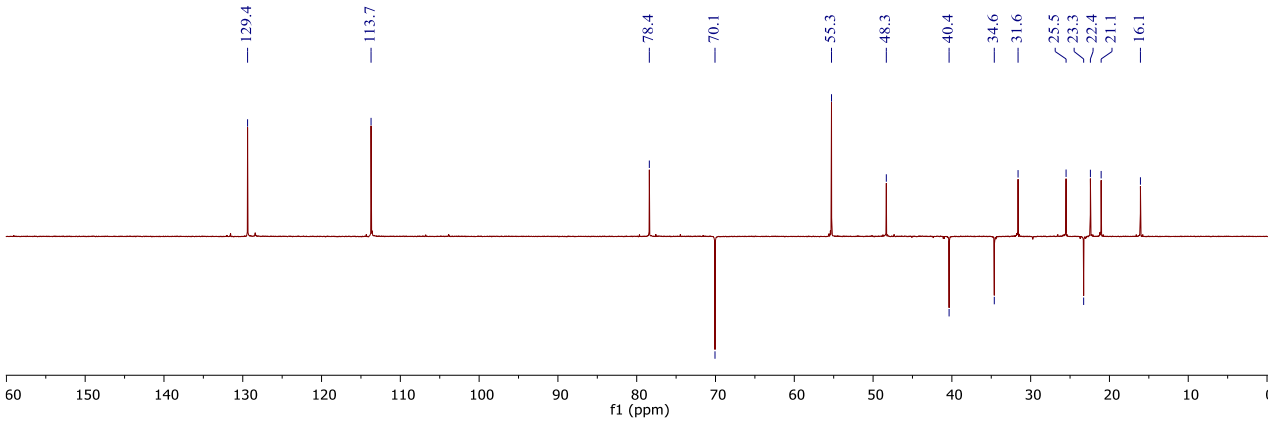
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 17



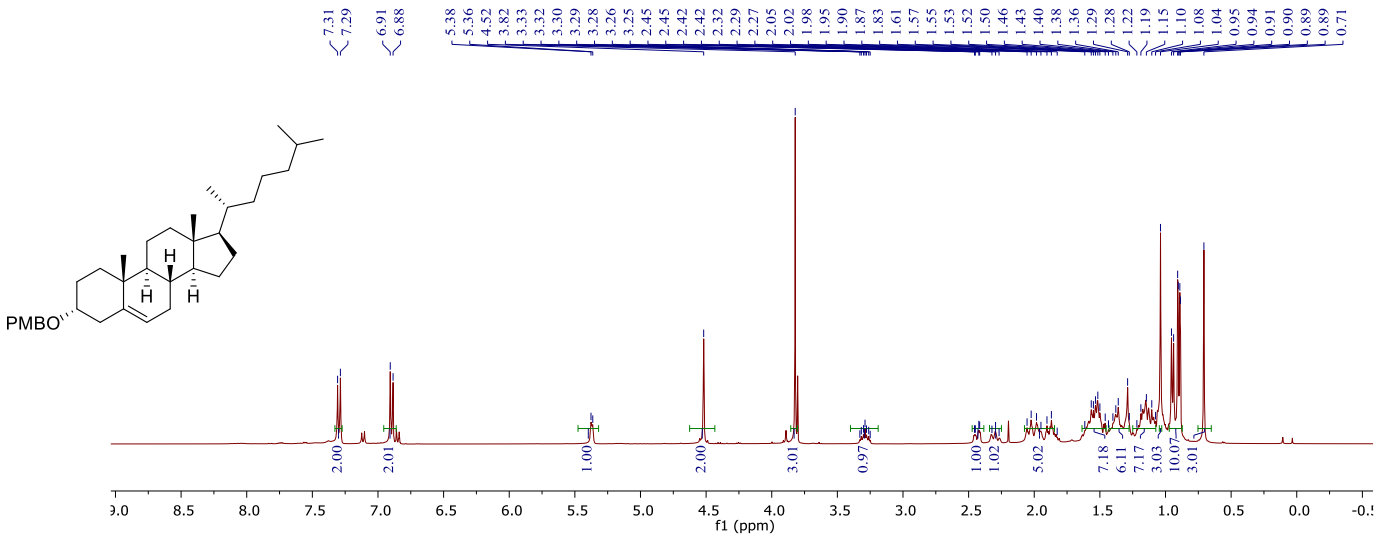
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 17



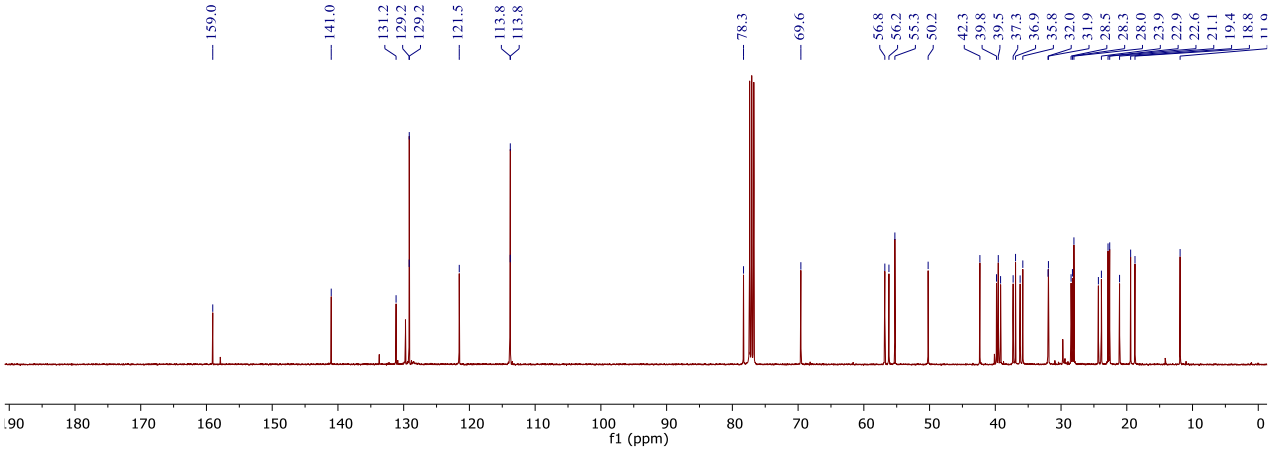
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 17



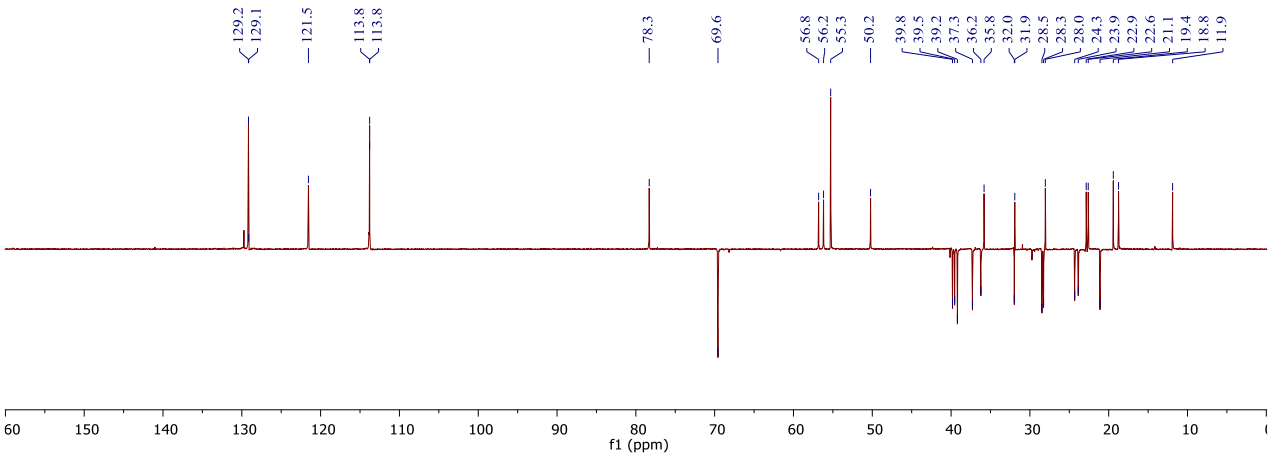
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 19



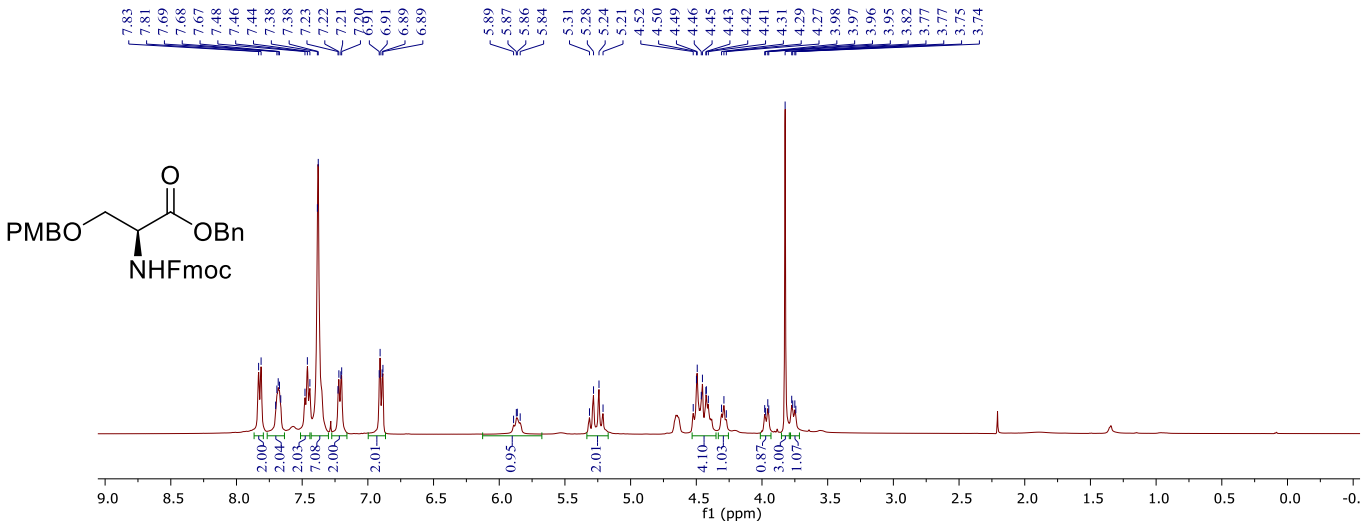
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 19



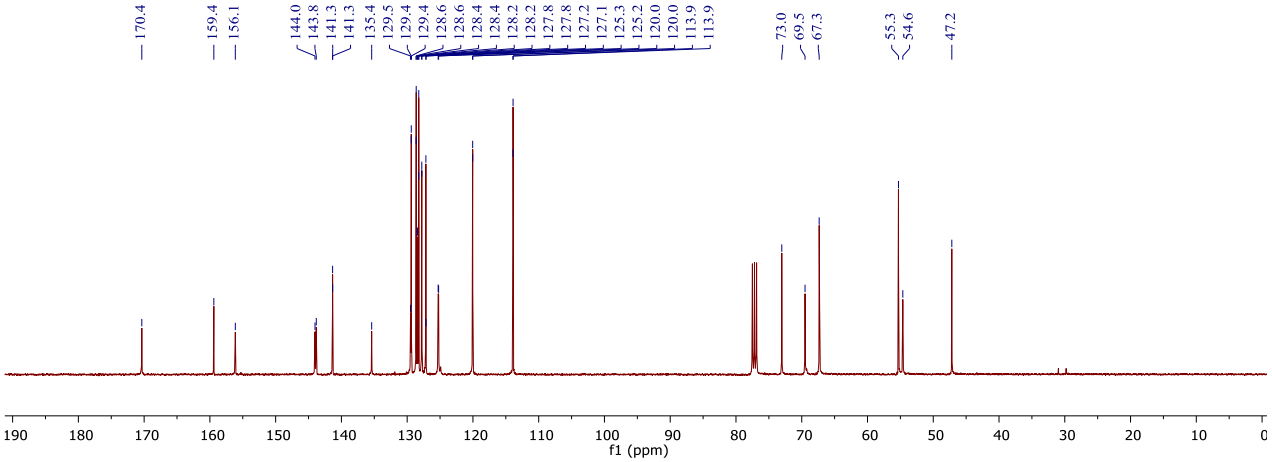
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 19



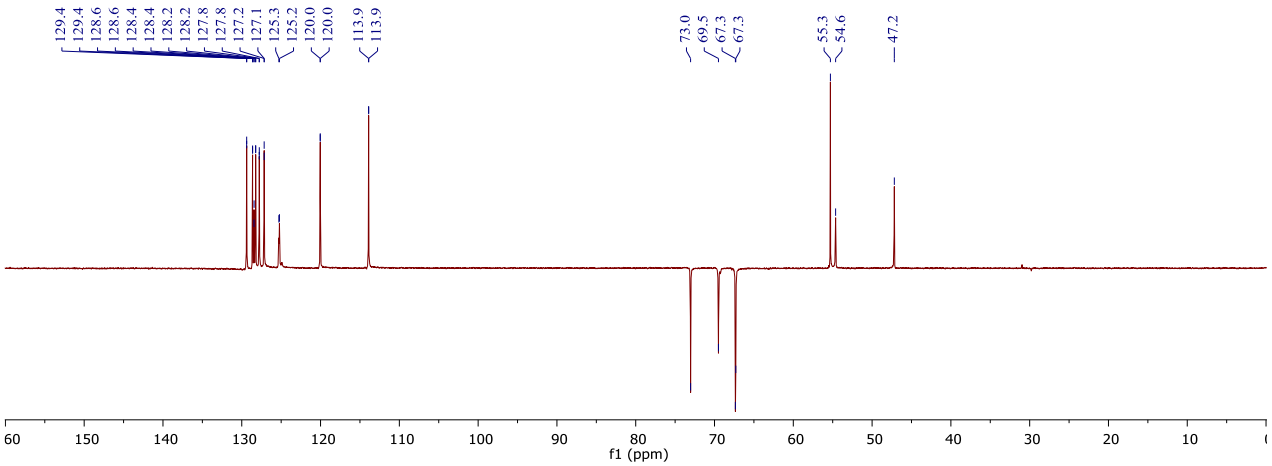
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 21



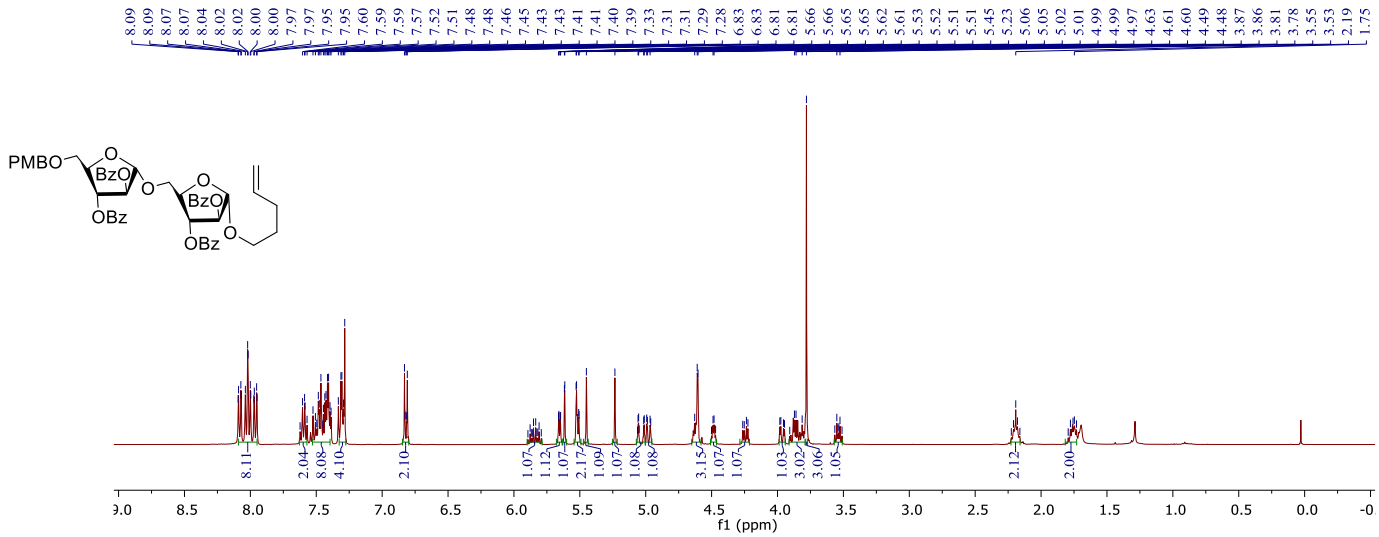
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 21



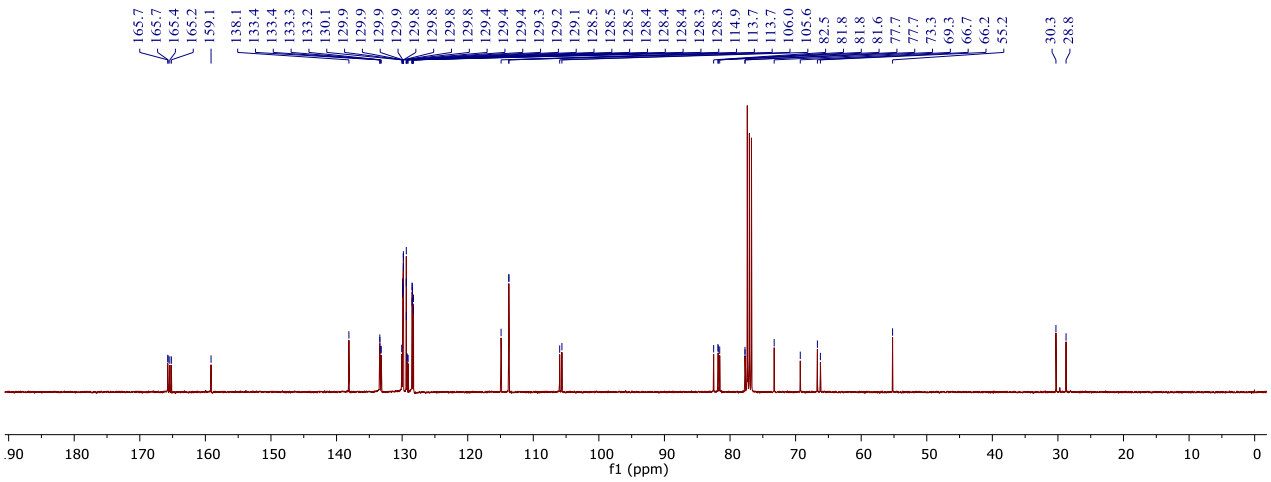
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 21



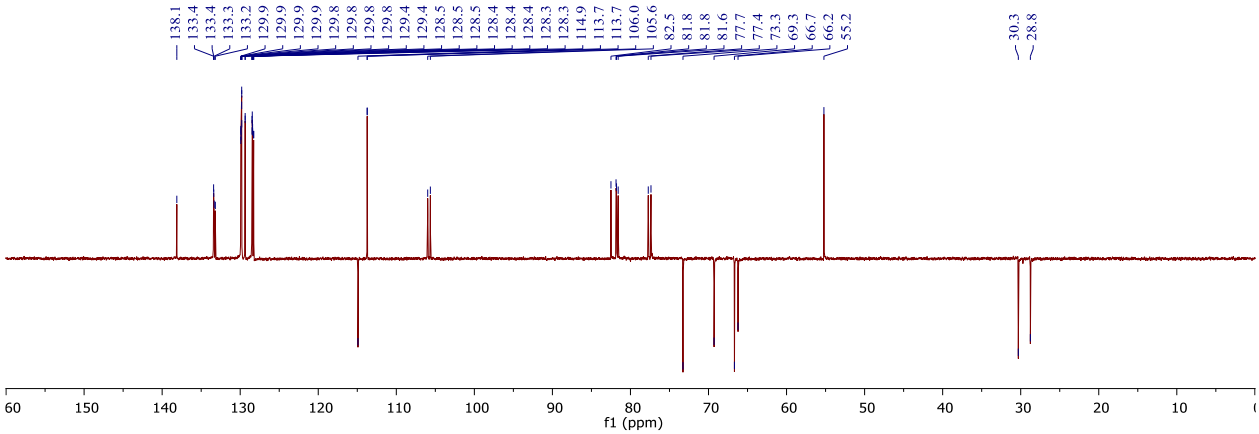
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 23



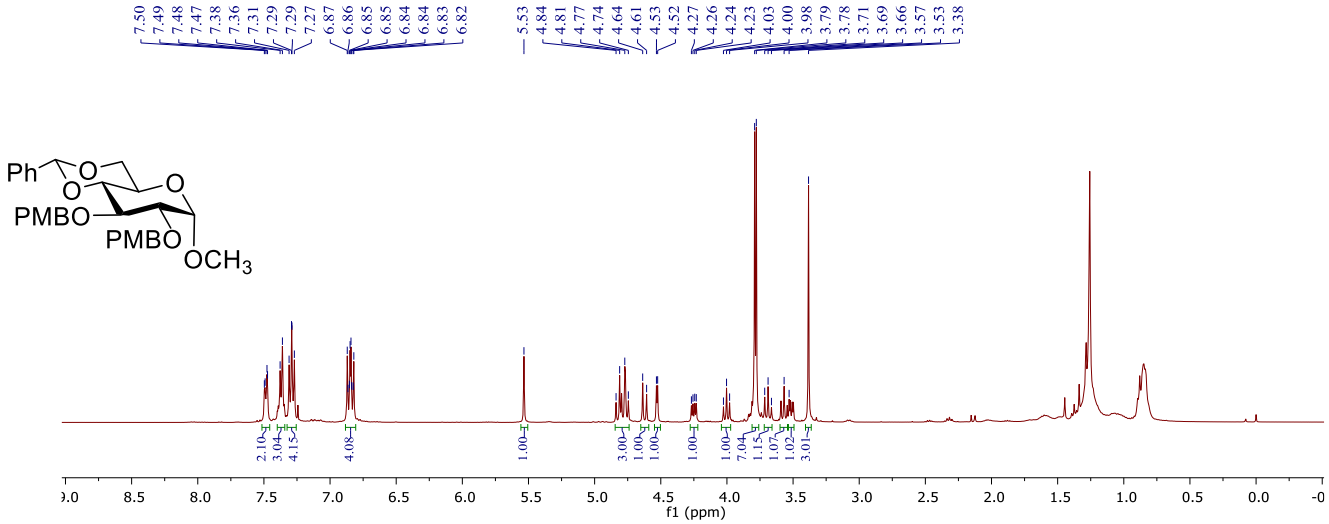
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 23



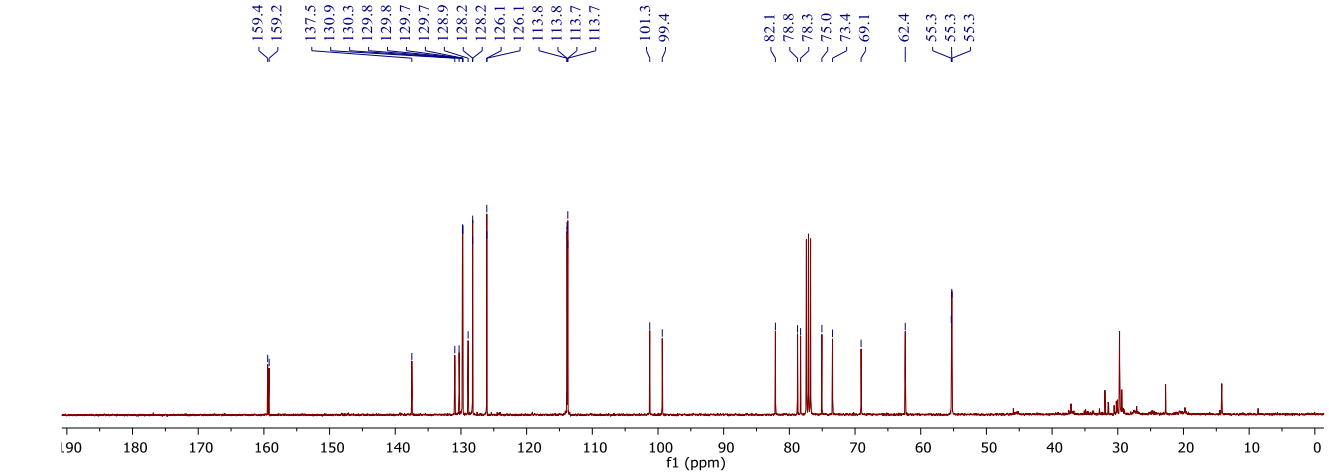
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 23



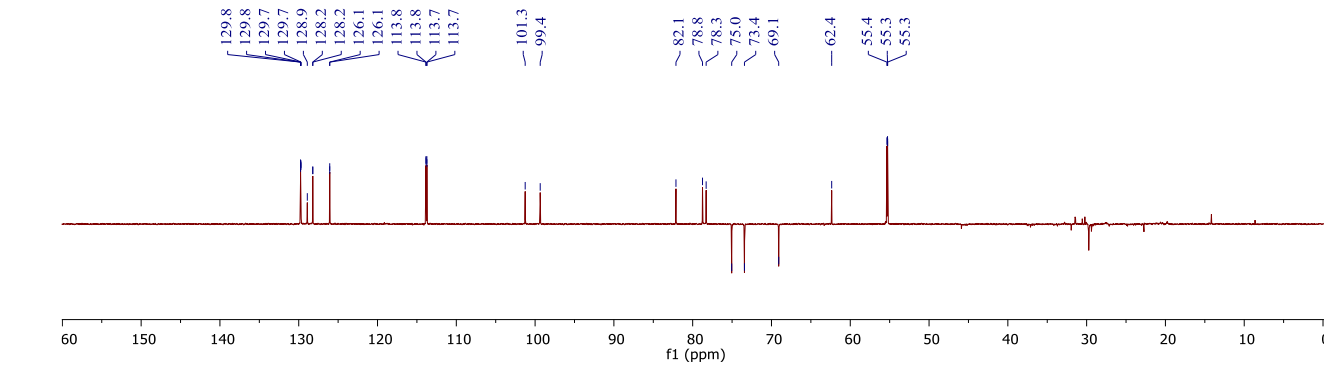
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 25



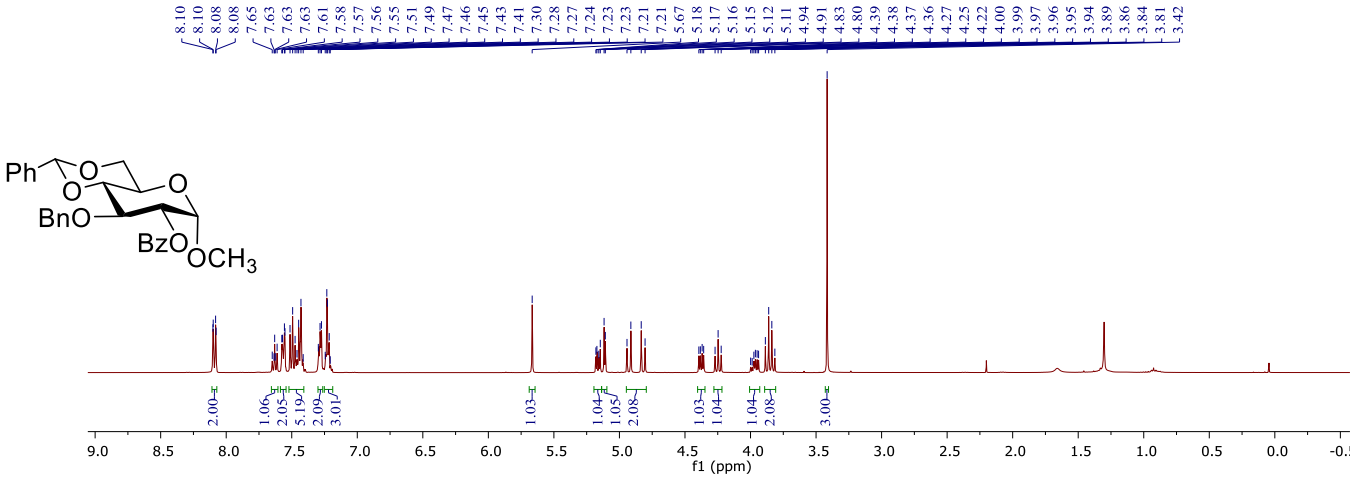
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 25



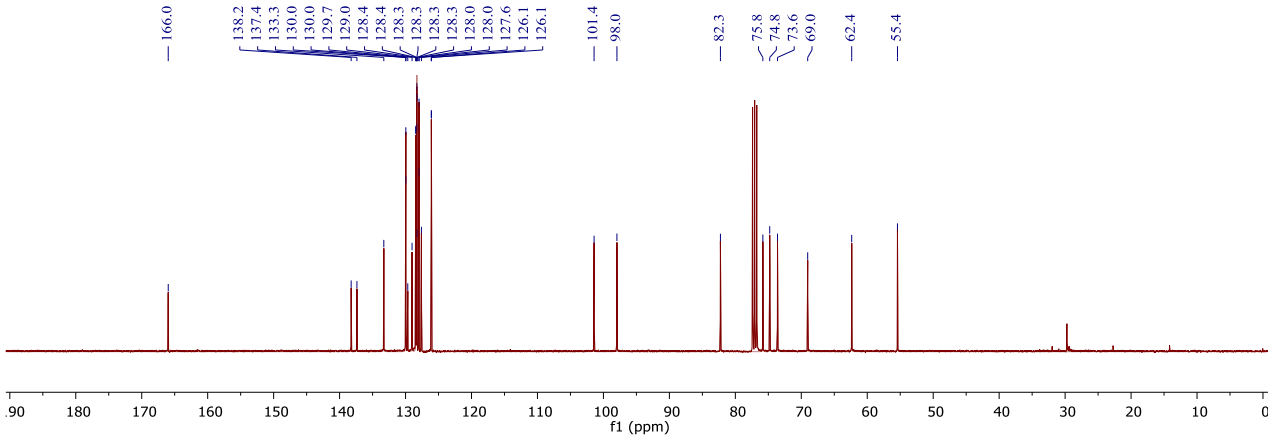
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 25



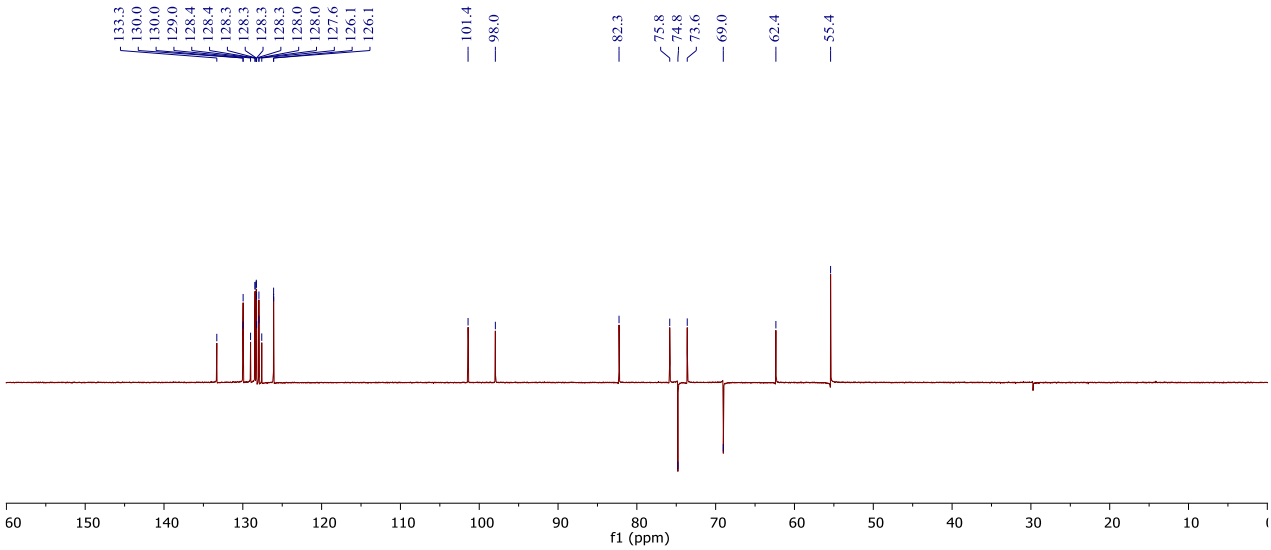
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 27



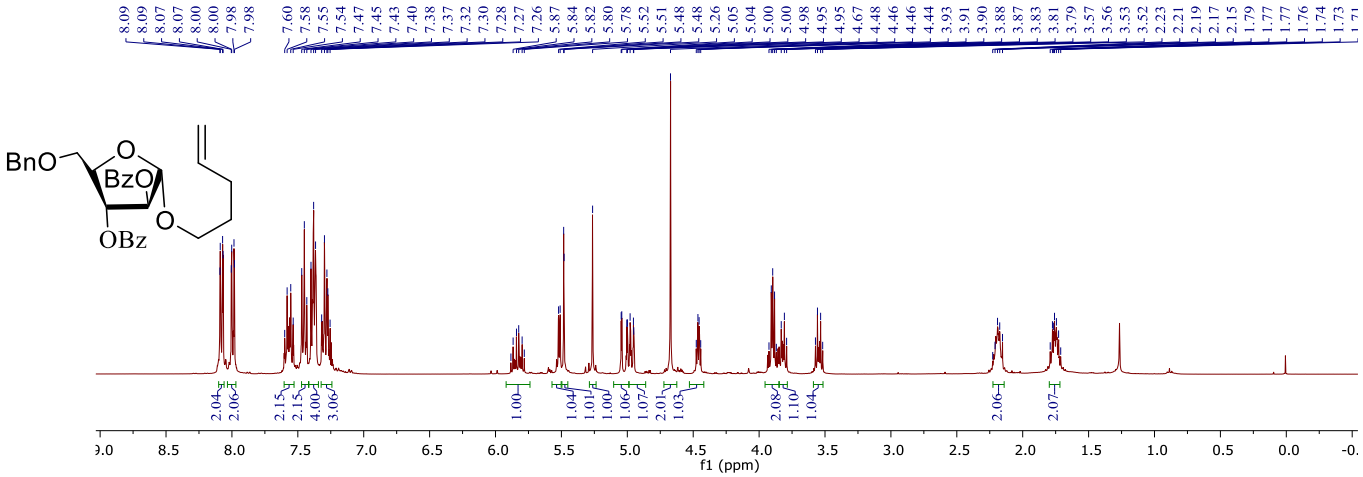
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 27



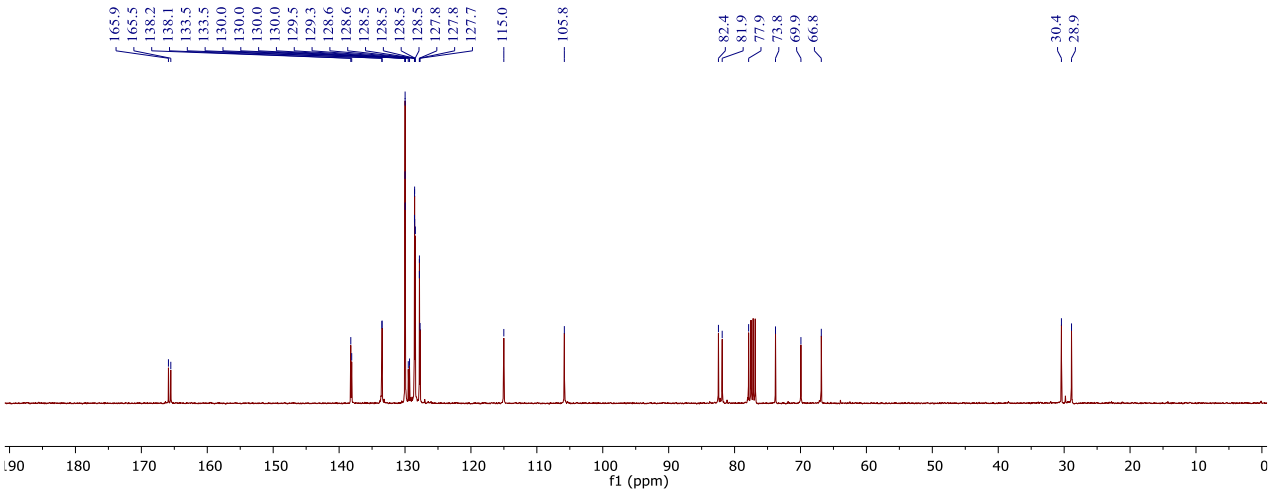
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 27



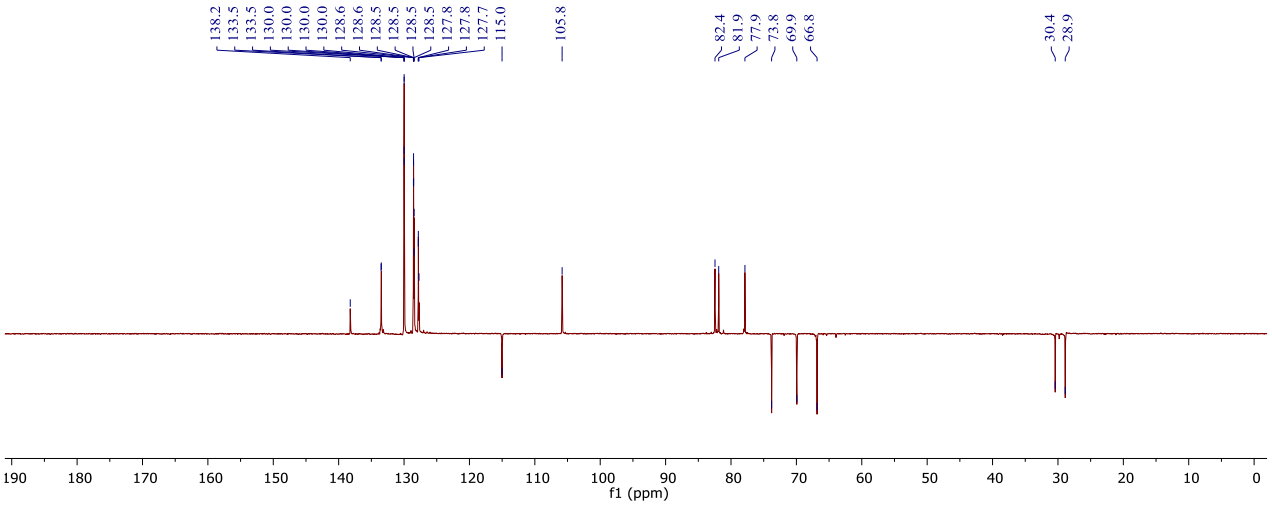
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 29



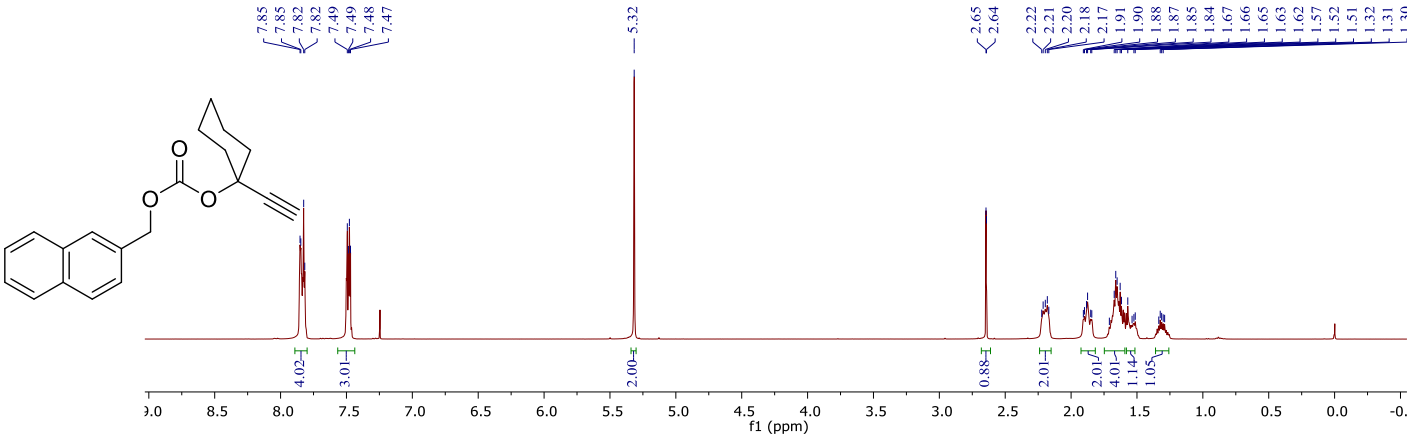
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 29



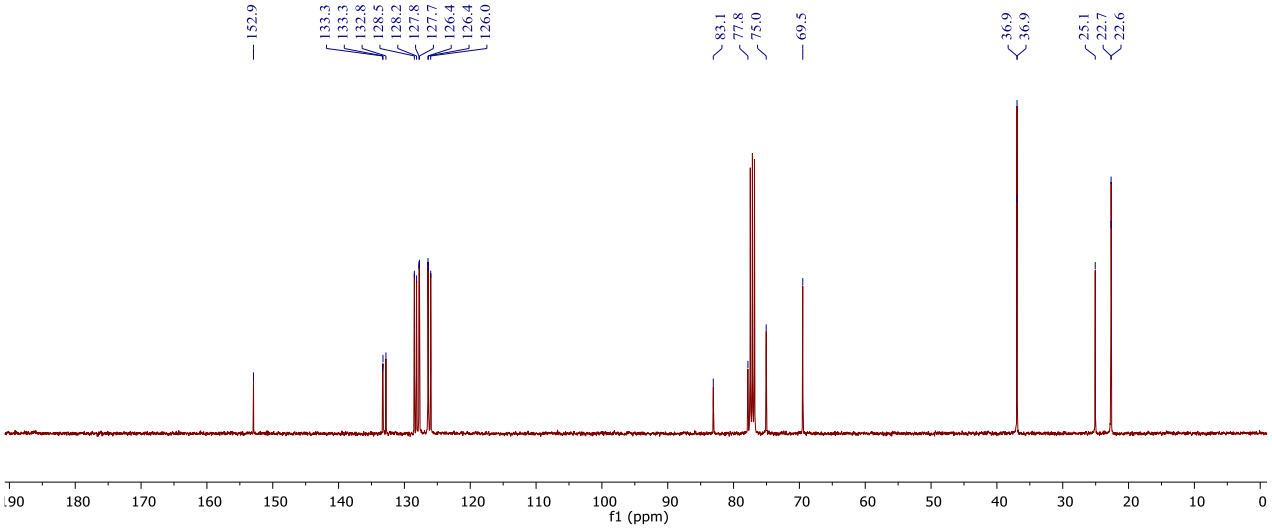
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 29



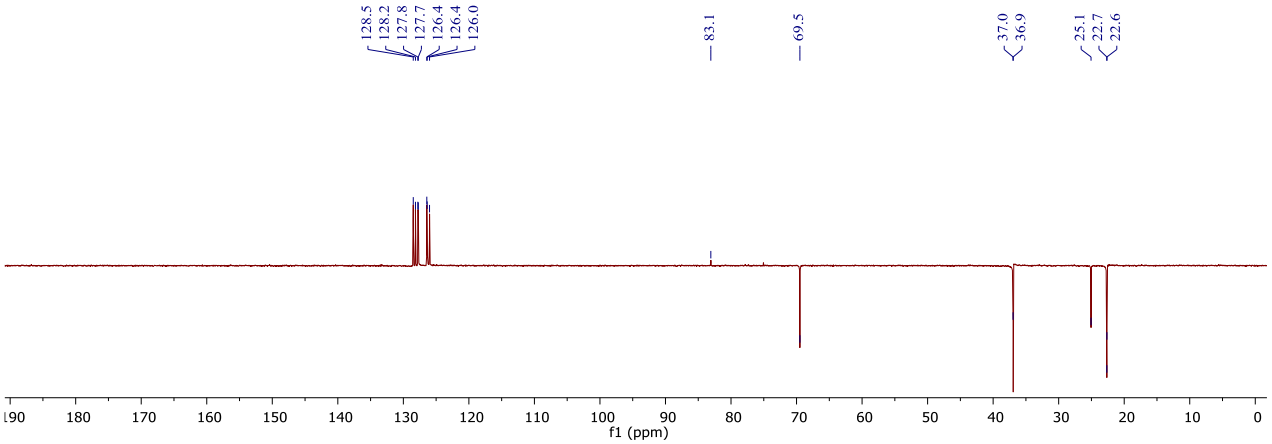
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 32



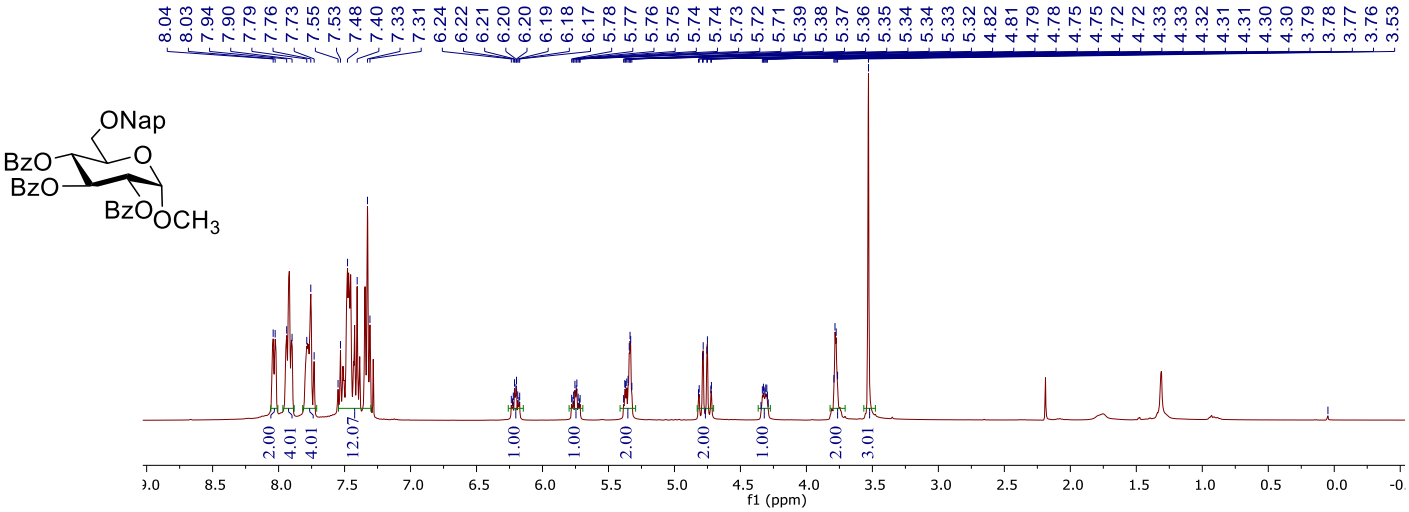
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 32



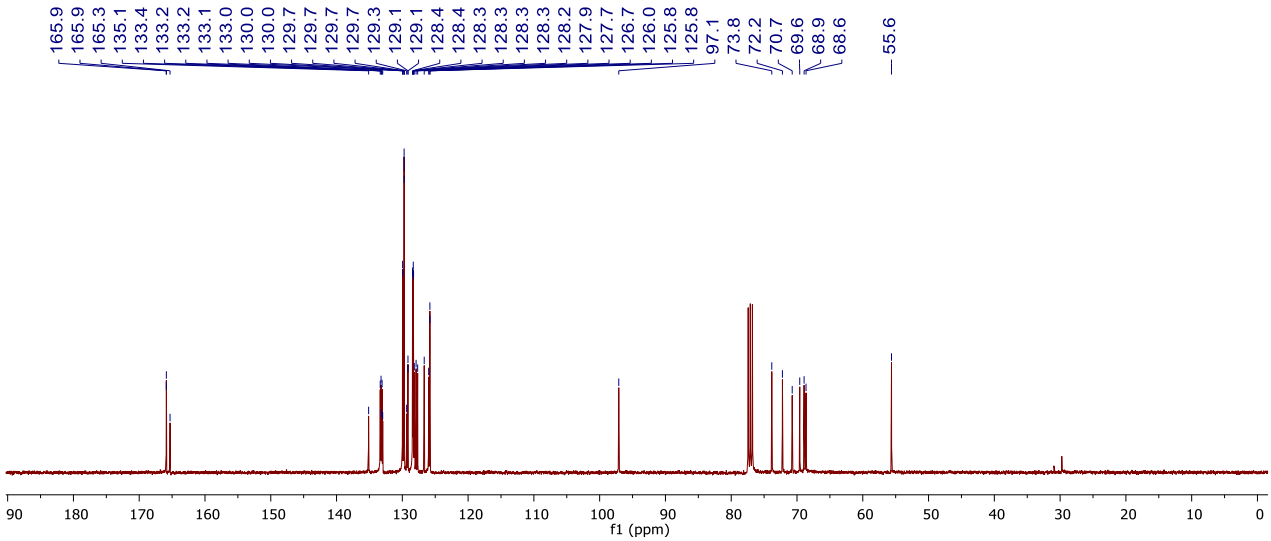
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 32



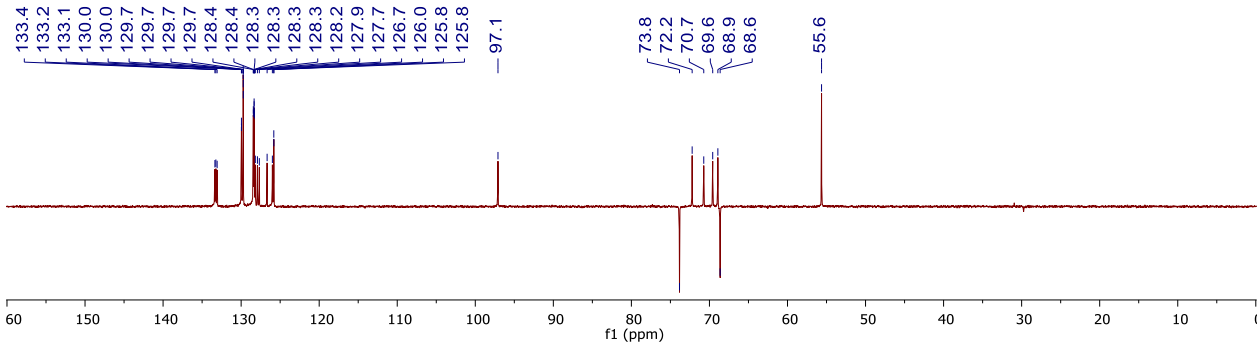
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 33



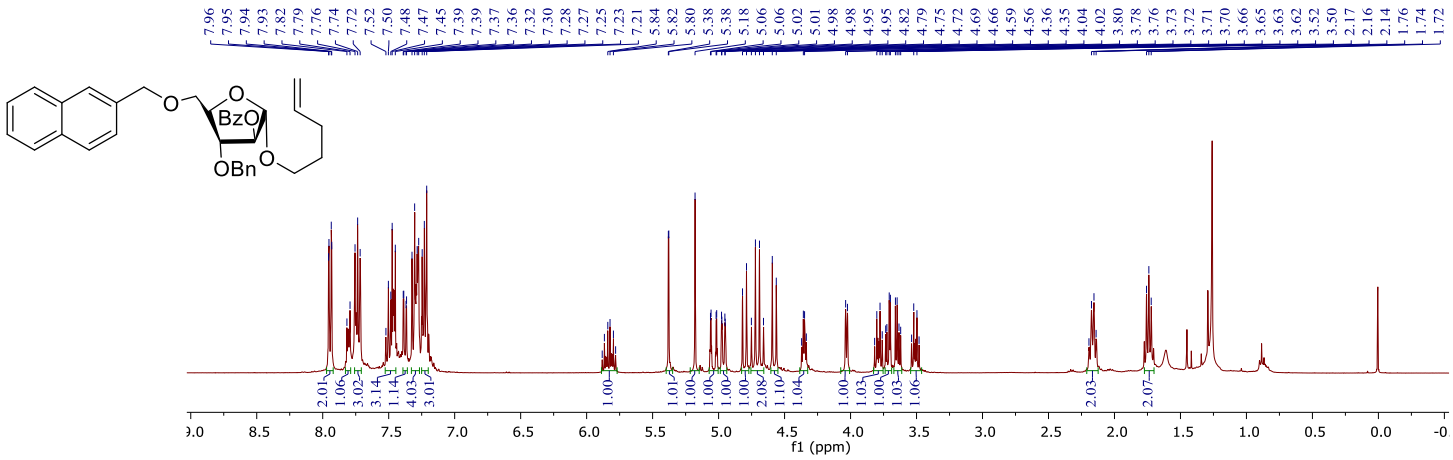
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 33



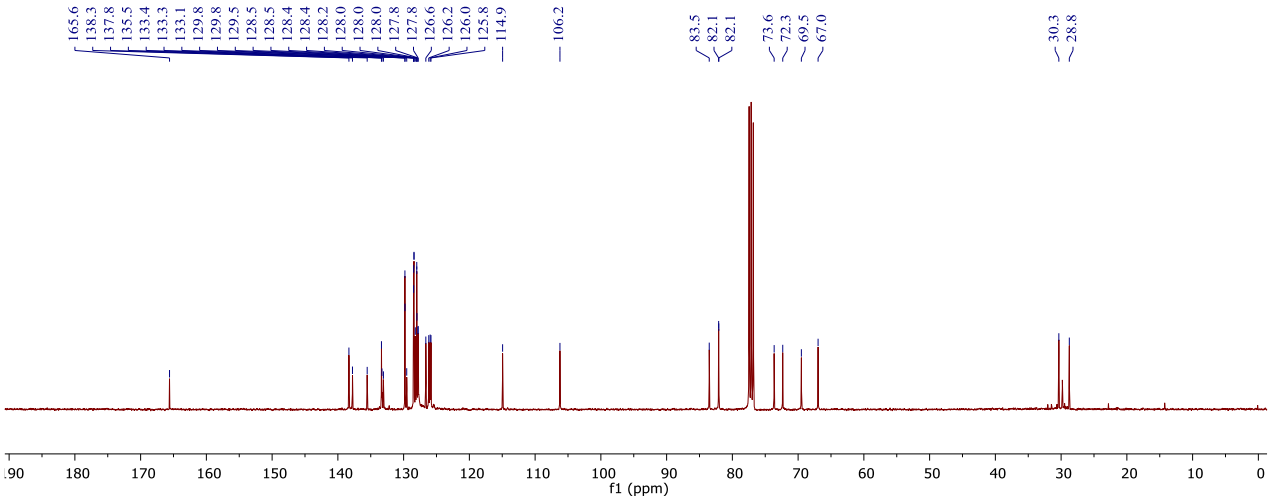
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 33



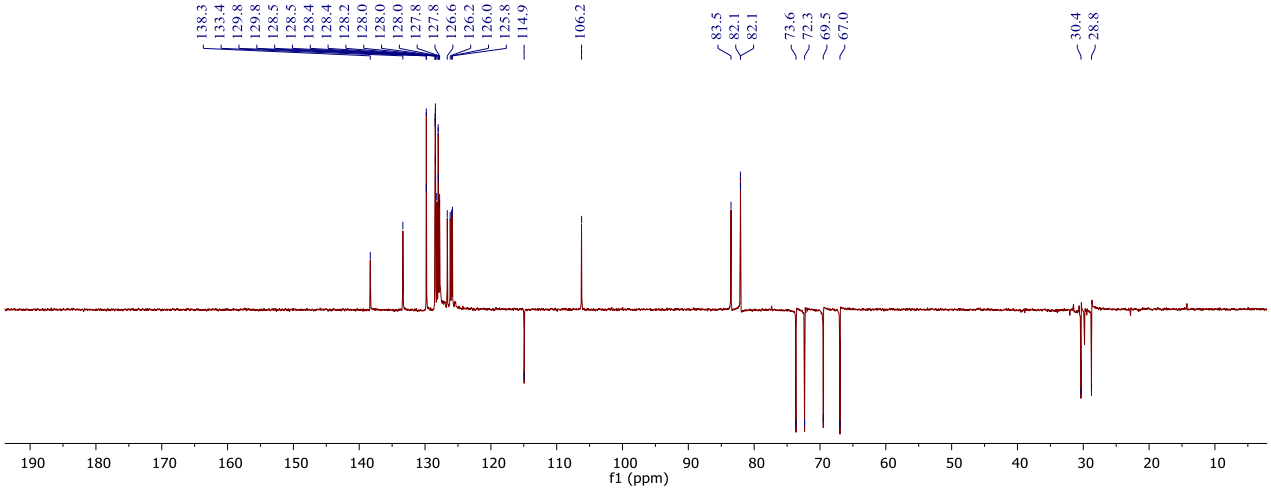
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 36



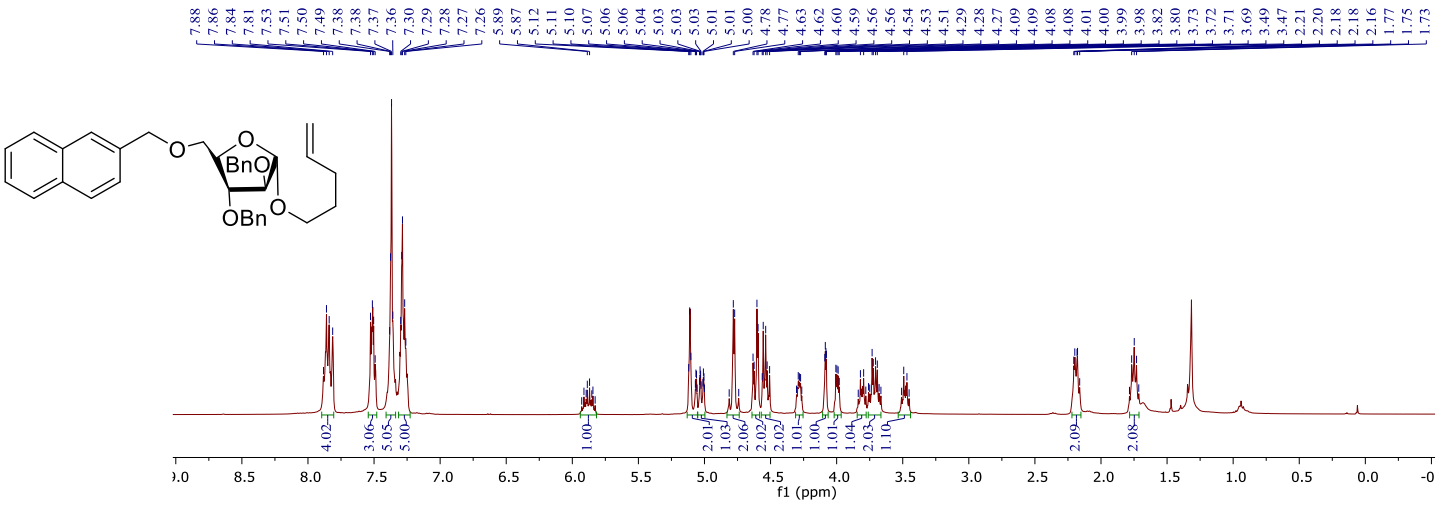
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 36



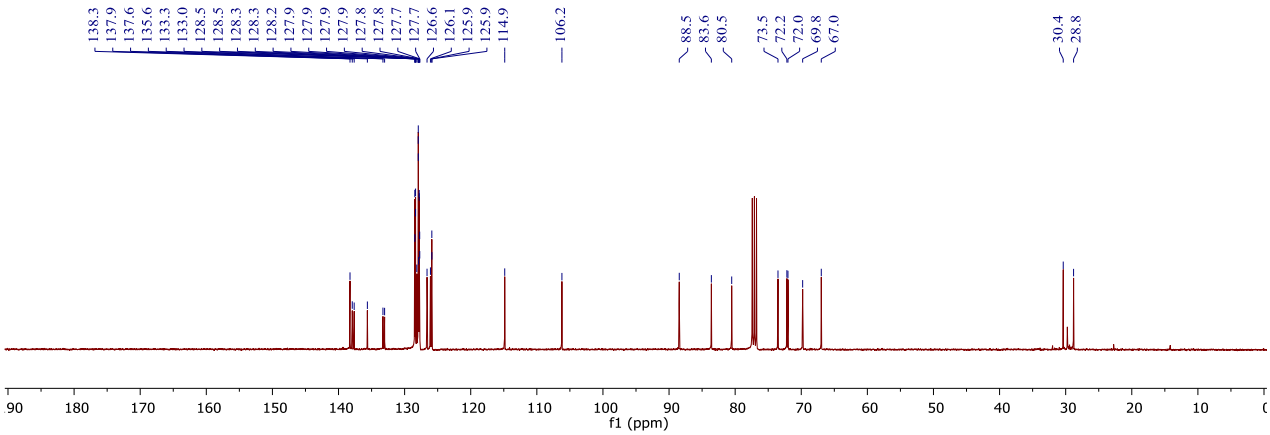
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 36



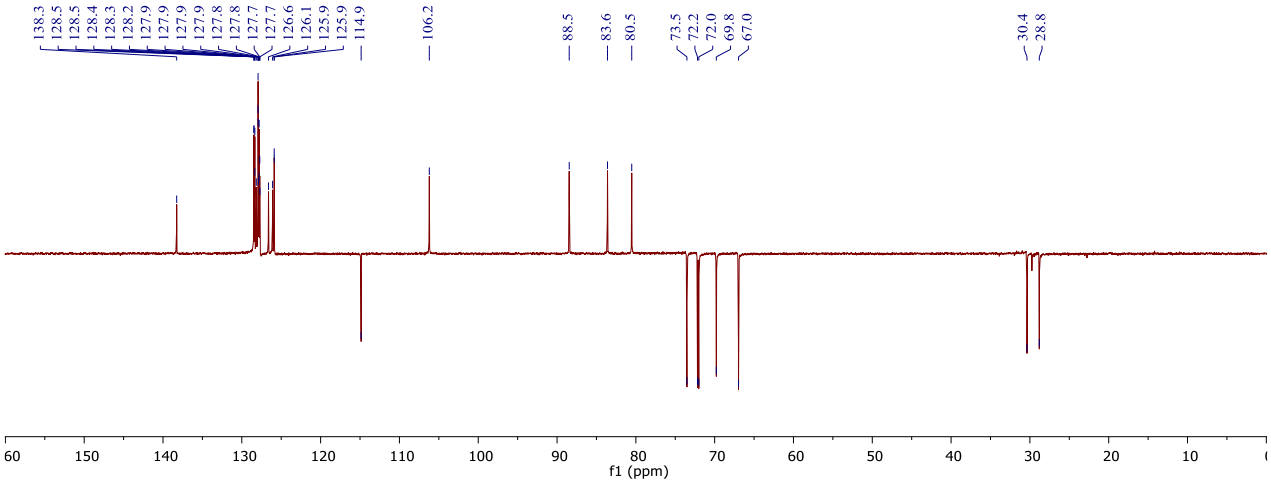
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 37



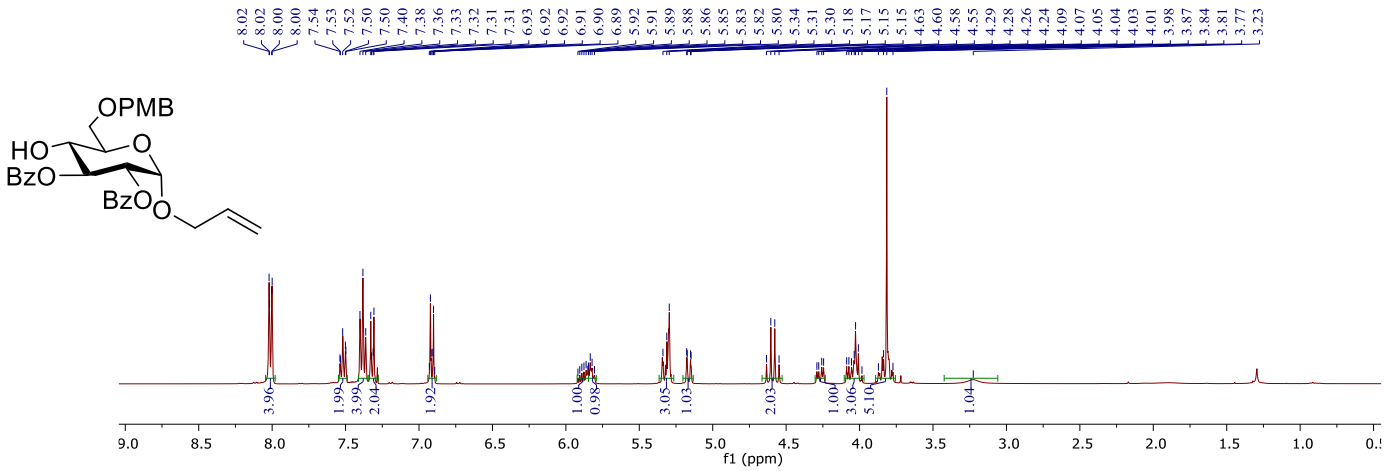
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 37



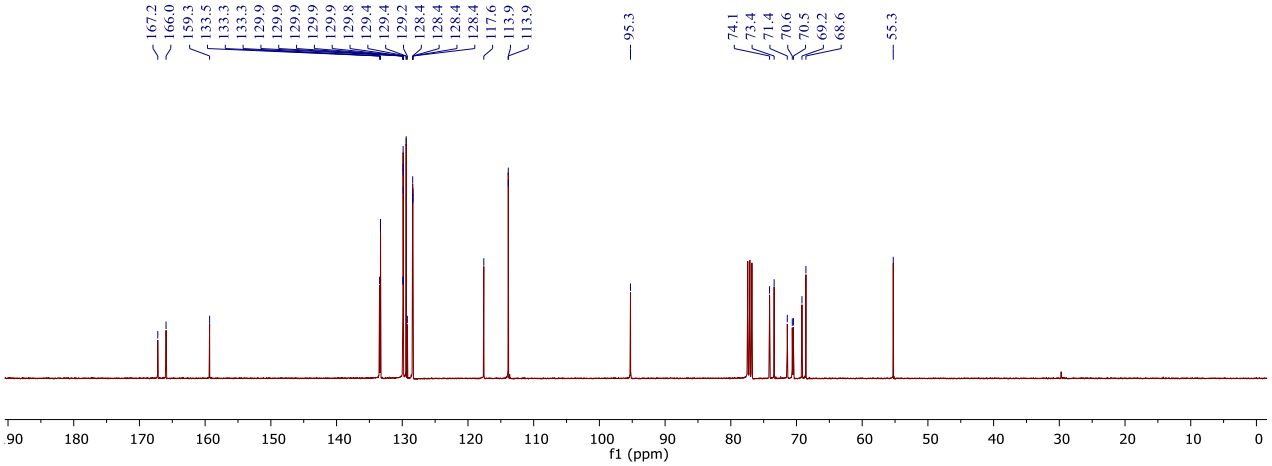
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 37



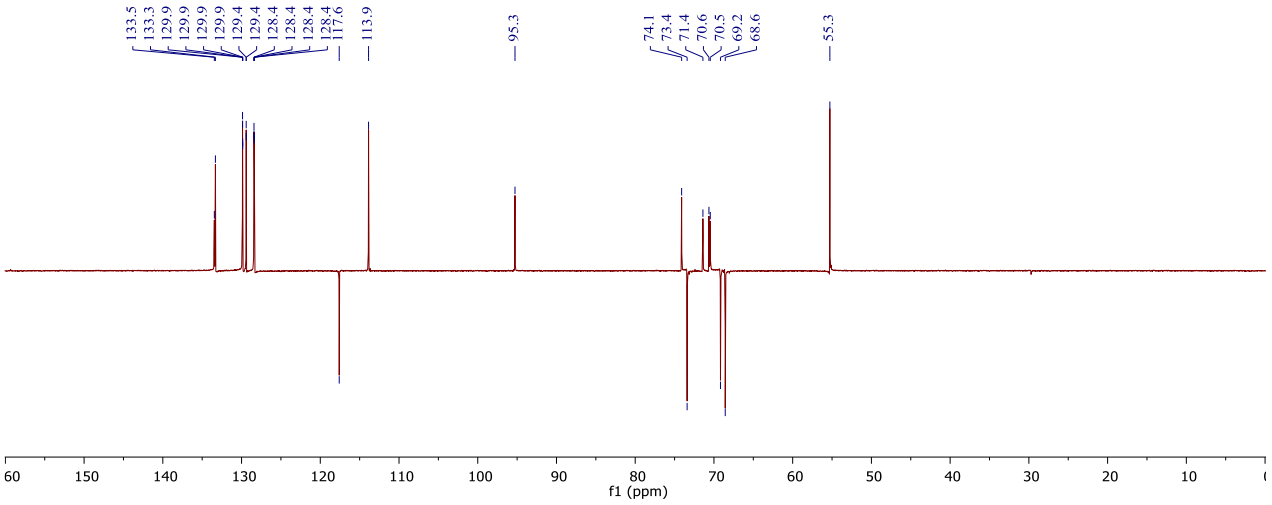
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 39



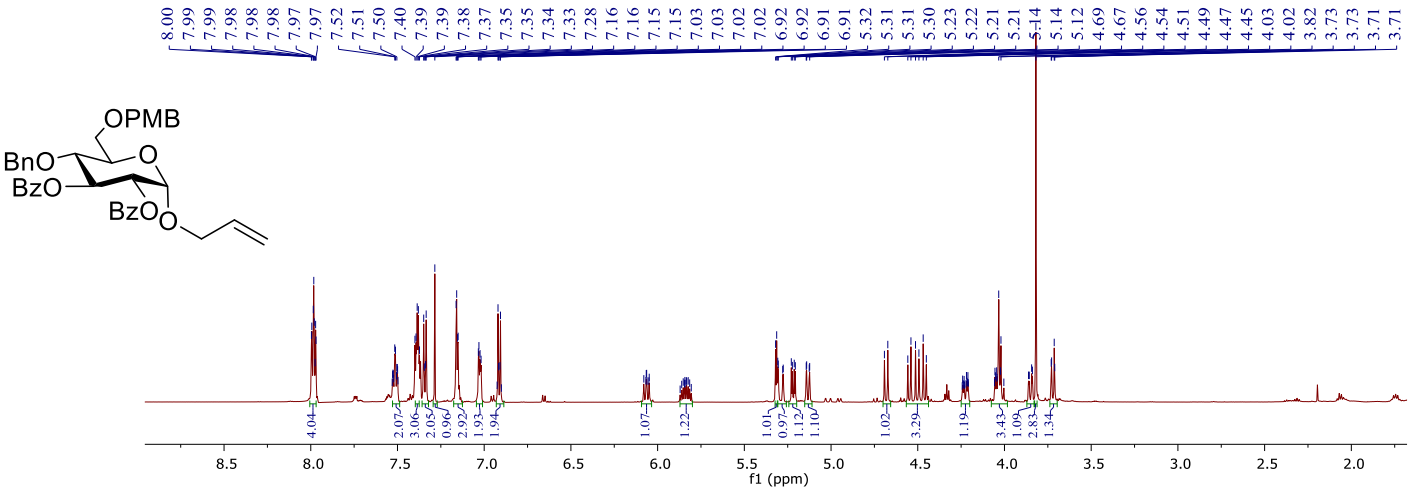
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 39



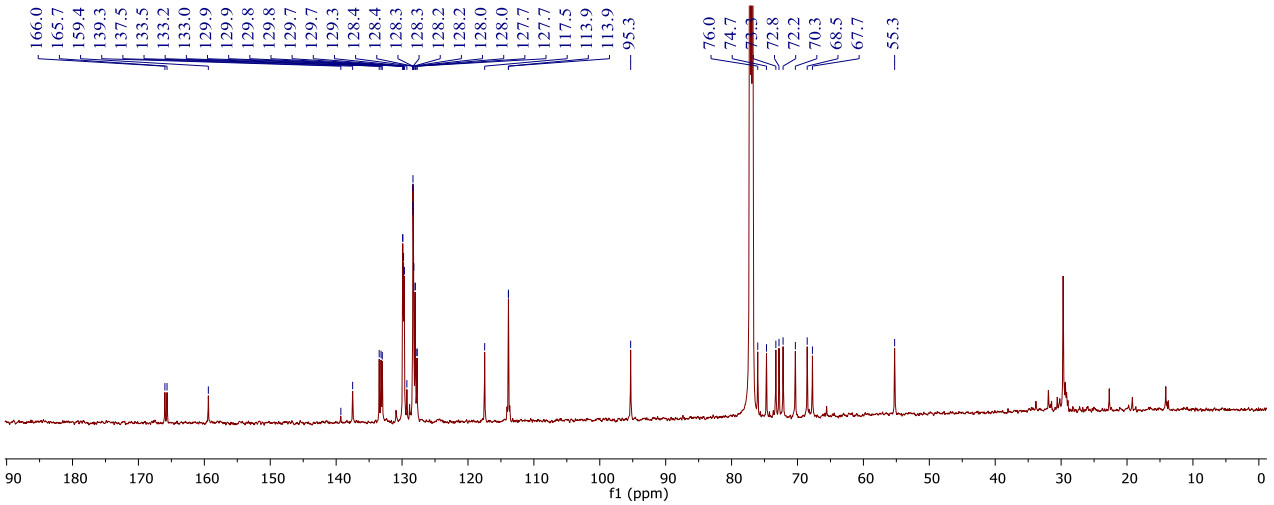
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 39



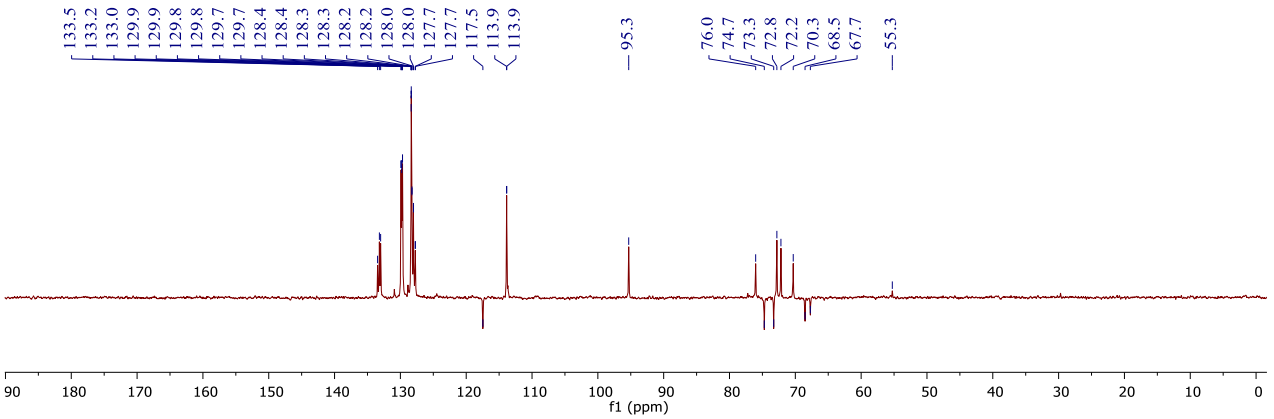
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound 40



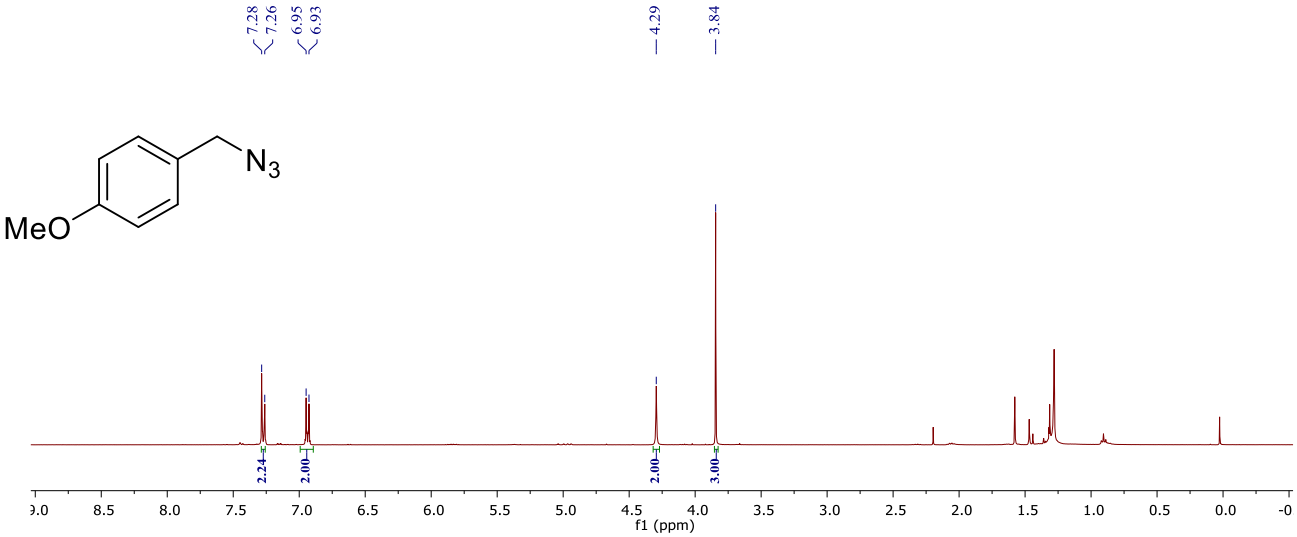
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 40



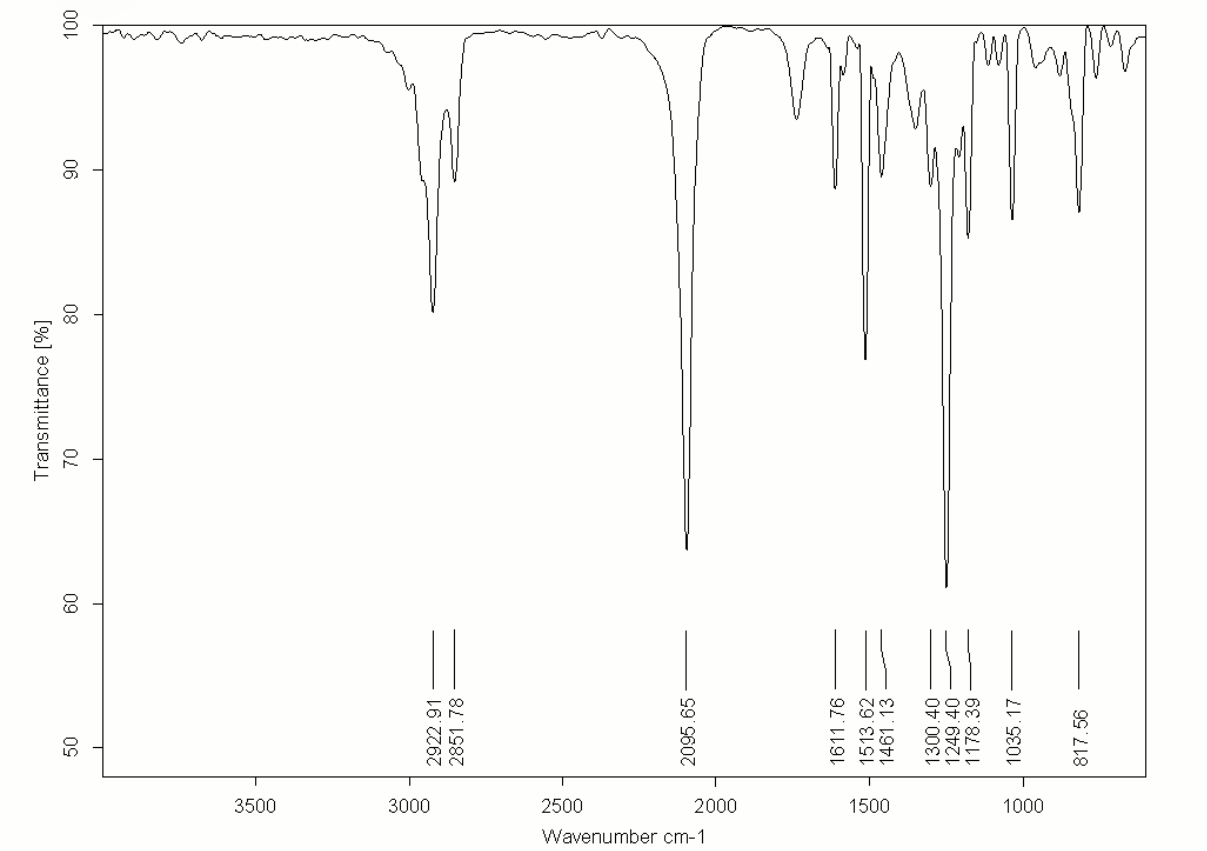
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound 40



^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound C



IR Spectrum of Compound C



2.7. References:

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Chapter 3: Unified, Direct, and Catalytic Syntheses of N-glycosides

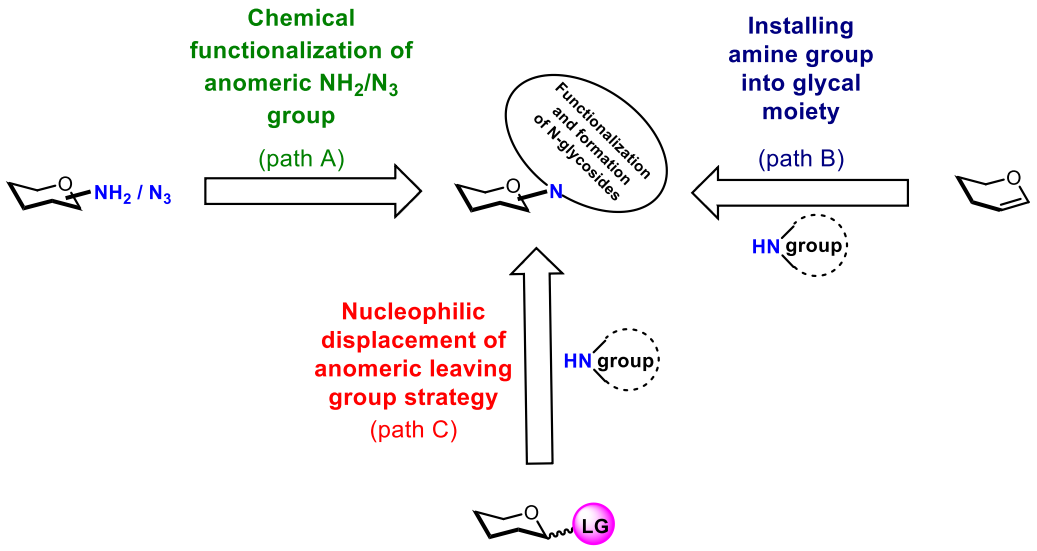
Chapter 3

3.1. Introduction

N-glycosides are compounds having a carbohydrate unit attached to an aglycone through a *C*-*N* bond linkage at the reducing end instead of a hydrolyzable *C*-*O* bond.[1] These are an essential class of carbohydrate compounds that exist in Nature and have immense importance in therapeutics. Arguably, the most well-known *N*-glycosides are nucleosides which are fundamental building blocks for DNA and RNA. The synthesis of nucleosides has been a constant topic of research in efforts to understand the limits and range of Watson-Crick base pairing,[2] to develop new therapeutic agents as medicines, manipulate genetic processes through antisense oligonucleotides,[3] and to understand RNA interference.[4] Another important class of *N*-glycosides is glycopeptide or glycoprotein, where a carbohydrate unit or oligosaccharide is attached to an asparagine amino acid through a β-glycosidic amide bond with γ-NH_2.[5] Protein glycosylation is one of the major post-translational modifications and glycoproteins often act as hormones, antibodies, and enzymes in living organisms.[6] Apart from these biologically existent *N*-glycosides, there are many other *N*-functional carbohydrate moieties that are present as scaffolds of natural products and have enormous scope as biochemical probes. There are examples of *N*-glycosides that have shown activities such as galactosidase inhibition[7] and glycogen phosphorylase inhibition.[8] 1-Amidosugar is another privileged *N*-glycoside unit in pharmaceuticals due to its exceptional properties such as the potential to increase bioavailability and oral absorption.[9] Usage of this moiety is progressively growing to solve existing issues in the field of drug discovery and to help in optimizing ADMET parameters. Substituted *N*-glycosides are also a treasured part of medicinal chemistry due to their constituent's occurrence in biomacromolecules and antibiotics.[10] Therefore, continuous efforts have been made in the past decades for the development of novel methods for the synthesis of various *N*-linked glycosides albeit limited success has been reported compared to the development of the syntheses of *O*- and *C*-glycosides. Synthesis of *N*-glycosides is far more challenging owing to numerous reasons that center on the complex compatibility issues between the basicity of *N*-acceptor and the acidic reaction conditions often invoked in most of the glycosylation protocols. Poor solubility of many *N*-nucleophiles in common organic solvents and reaction conditions is another major hurdle in the synthesis of *N*-glycosides.

3.2. Strategies for synthesis of *N*-glycosides

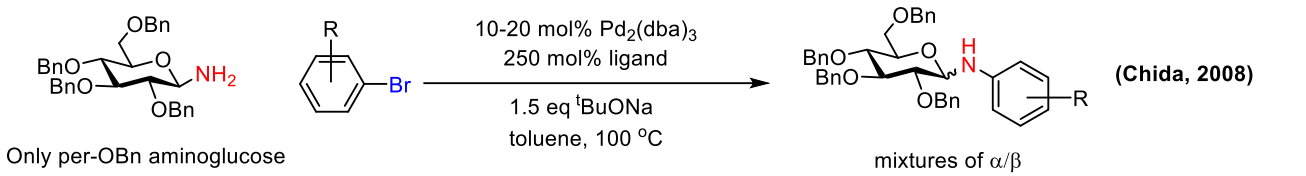
There are three major types of general strategies for the synthesis of N-glycosides preceding in the literature which are essentially i) chemical functionalization of anomeric NH_2 or N_3 group, ii) Installation of amine or substituted amine groups into the glycal moiety, and iii) nucleophilic displacement of the leaving group attached to anomeric center of the carbohydrate unit (**Scheme 3.1**).[11] These strategies will be discussed elaborately in this section.



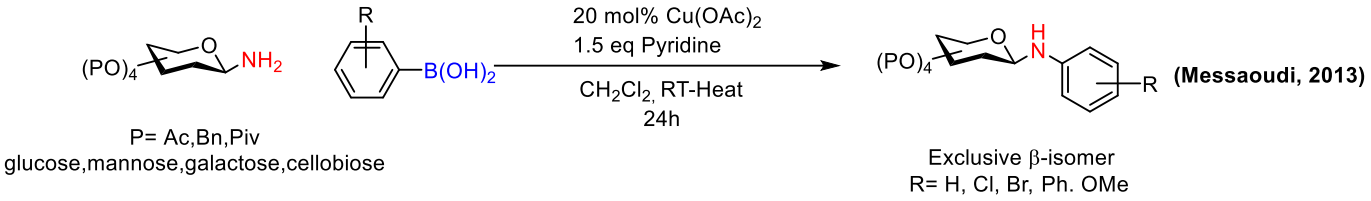
Scheme 3.1: General strategies for *N*-glycoside synthesis

i) *Chemical functionalization of anomeric NH_2 or N_3 group (path A)*: Anomeric *N*-functionalization is the most trivial method for the synthesis of *N*-glycosides where chemical modifications occur at the anomeric –NH_2 or N_3 group. Anomeric azide group can also be converted to an amine group by reduction and processed further for the synthesis of various *N*-functionalized glycosides. Bertho *et al.* first reported the synthesis of anomeric azide from per acetylated glycosyl bromide using NaN_3 and DMF at an elevated temperature back in 1930.[12] Later on, many catalytic processes have been developed to synthesize glycosyl anomeric azides namely S_N2 displacement of sulfonates (tosylate, mesylate and triflate) or by using a Lewis acid catalyst ($ZnCl_2$, $FeCl_3$, $In(OTf)_3$, $SnCl_4$ etc.) and $TMSN_3$ as a nucleophile.[13,14] *N*-Arylation of glycosyl amines is a gateway for developing many *N*-heterocyclic glycoconjugates. First-time production of heteroaryl and aryl *N*-glycosides was reported by Chida *et al.* in 2008 *via* performing a $Pd_2(dba)_3$ catalyzed Buchwald-Hartwig *N*-arylation reaction.[15] To overcome the restricted substrate scope and increase the desired β-anomer,

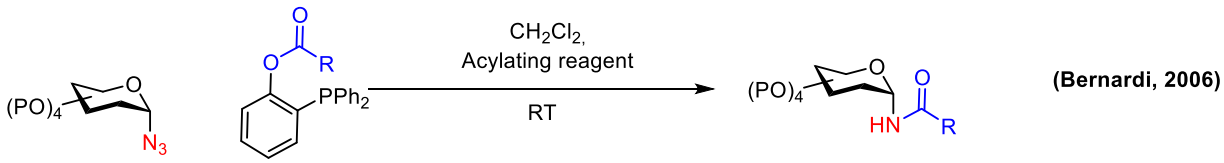
Messaoudi group developed method for *N*-arylation of glycosamine using various aryl boronic acids and Cu-catalysis in 2013.[16]



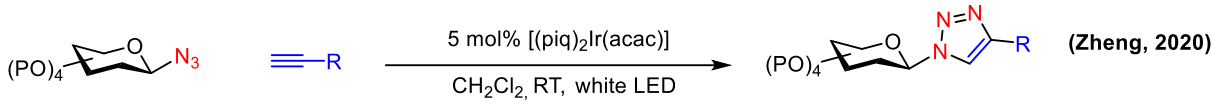
a) Pd catalysed Buchwald-Hartwig *N*-arylation reaction



b) Cu catalysed *N*-arylation with arylboronic acids



c) Traceless Staudinger ligation of glycosyl azide with phsophines



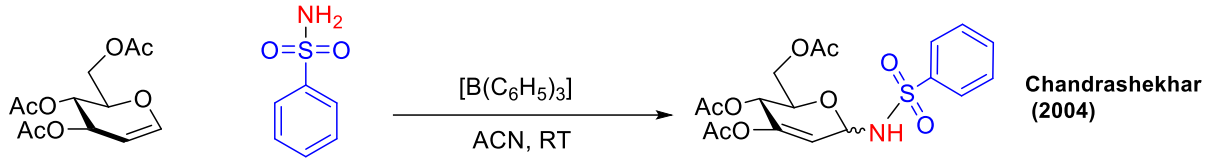
d) Photocatalysed glycosyl azide-alkyne cycloaddition

Scheme 3.2: *N*-Glycoside by chemical functionalization of anomeric NH_2/N_3

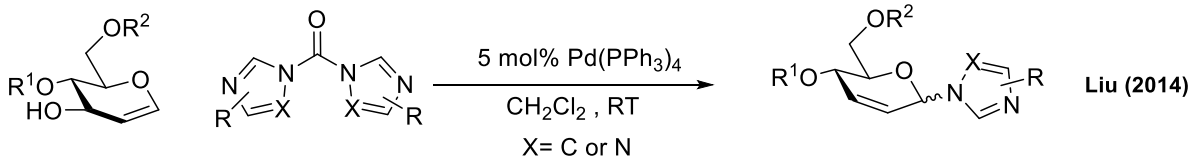
Many research groups have reported expedient syntheses of glycosyl amides starting from either anomeric amine or azide group.[17,18] Staudinger condensation reaction of glycosyl azides and carboxylic acids is one of the pioneering reactions for synthesizing glycosyl amides.[19] The same group has also reported intramolecular Pd-catalysed *N*-arylation reaction for the synthesis of 1-amido sugars but the method deals with the formation of *E*/*Z*- as well as α/β– isomers as there is no direct control at the anomeric center to get exclusive β-isomer. Catalytic hydrogenation of glycosyl azide results in the formation of amines. A sequential coupling reaction of acid analogues

with those of amine counterparts is another technique to form glycosidic amide linkage but rapid anomerization of glycosyl amine to its most stable β-isomer gives rise to only β-glycosyl isomer. Anomeric azide group containing carbohydrate units are essential synthetic precursors for the synthesis of triazolyl glycoconjugates.[20,21] 1,2,3- triazole glycosides have been successfully synthesized using Cu(I) catalyzed cycloaddition reaction and metal-free organocatalysis mediated cycloaddition reactions. Misra group has reported novel synthesis of 1,4,5-trisubstituted glycosyl-1,2,3-triazole derivatives using cycloaddition between glycosyl azide and enolate of active esters and ketones.[22] Photocatalyzed cycloaddition of glycosyl azide-alkyne has been reported by Zhang *et al* in 2020 to synthesize 1,4-disubstituted triazole (**Scheme 3.2**).[21]

ii) *Installation of amine or substituted amine groups into glycal moiety (path B):* Glycals are one of the most important chiral building blocks in glycoconjugate synthesis. Ferrier type glycosylation reaction involving nitrogen center nucleophiles has been established as an important method for synthesizing *N*-linked glycoconjugates since the beginning of the millennium.[23] In 2003, Collinas *et al*. observed [PPh_3•HBr] catalyzed sulfonamide glycosylation with benzylated glucals.[24,25] Later on, Chandrashekhar group reported [$B(C_6H_5)_3$]-catalyst mediated Ferrier type glycosylation of sulfonamides with acetylated glucal to obtain 2,3-unsaturated sulfonamide *N*-glycosides.[26] Bin bia *et al* discovered the usage of $Tm(OTf)_3$ to synthesize *N*-sulfonyl 2,3-unsaturated *N*-glucosides.[27] A one-pot Pd-catalyzed carbamation, decarboxylation and allylation reaction sequence on glycal



a) Lewis acid catalyzed Ferrier type glycosylation of sulfonamide

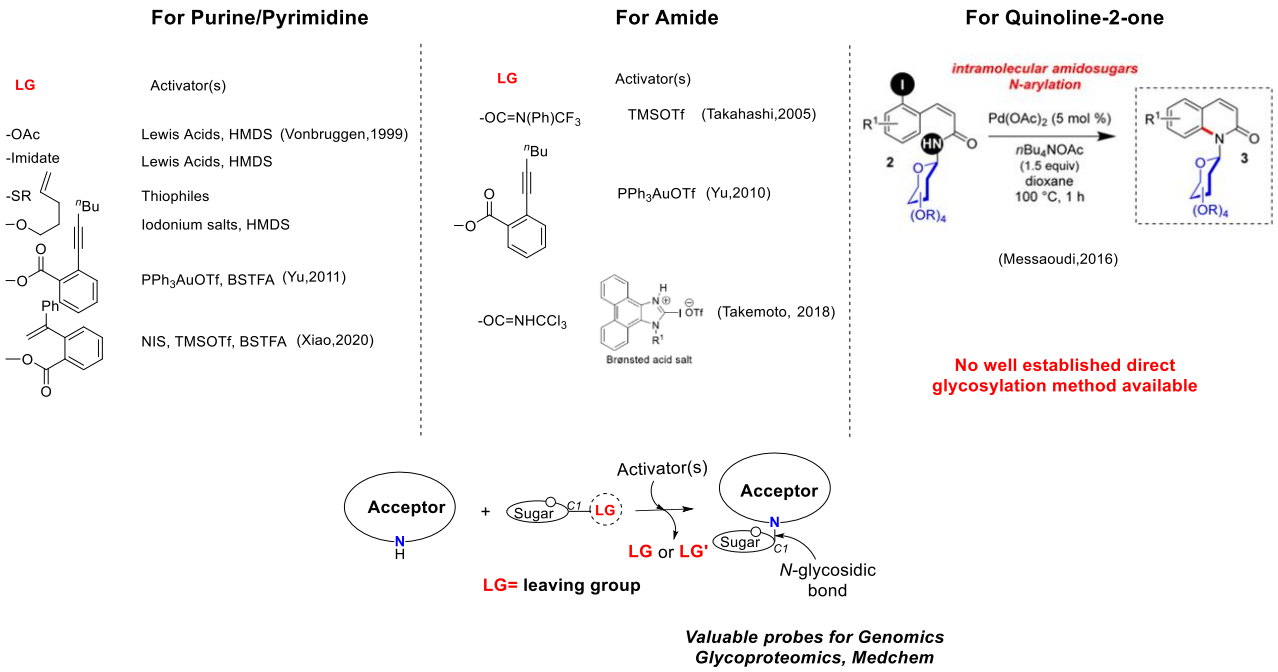


b) Pd catalyzed 2,3 unsaturated β-N-glycosyl imidazole synthesis

Scheme 3.3: Direct attachment of *N*-acceptor into glycal donor

donors was materialized by Liu group in 2014 (**Scheme 3.3**).[28] The method could successfully make various β-*N*-glycosyl imidazole analogues in high yields. Recently, Zhang group has come up with synthetic methodologies involving Pd-catalysts to furnish various amines, amides, imidazole, benzimidazoles and substituted heterocycle glycoconjugates from glycal donors.[29]

iii) *Nucleophilic displacement of leaving group attached to anomeric center of sugars (path C):* Apparently, though this method might appear as the most straightforward one, it has its complexities revolving around the nature of the leaving group, non-similar reactivity of different carbohydrate units and solubility issue of the nucleophiles. Owing to all the difficulties related to



Scheme 3.4: Selected previous approaches for the synthesis of important *N*-glycosides via direct glycosylation method

the stereoselective synthesis of *N*-glycosides, only a few catalytic approaches are reported to date. Pyrimidine glycosylation was first reported by Hilbert and Johnson using 2,4-dialkoxy pyrimidine and per-*O*-acetylated glucosyl bromide in 1970.[30] Vonbrüggen pioneered the modification of the

classic Hilbert-Johnson nucleosidation by exploiting labile trimethyl silyl-protected pyrimidine acceptors and stoichiometric amount of strong Lewis acids.[31] Harsh reaction conditions of these methods restricted the choices of substrate scope especially when the coupling partner is poorly nucleophilic (e.g. purines). Careful designing of the leaving group attached to the anomeric center could enable nucleosidation under mild conditions. However, only limited successful reports using privileged *O*-glycosyl donors *viz.* glycosyl halides,[32] imidates,[33,34] *n*-pentenyl glycosides,[35] glycosyl phosphates and thioglycosides[36] have been registered. Yu group has developed novel regio- and stereoselective method for purine and pyrimidine glycosylation using stable glycosyl alkynyl benzoate donor and catalytic [PPh_3AuNTf_2].[37] This method solved many existing issues related to nucleosidation type reaction and exerted *N*-glycosylation in high yield with a wide range of substrate scope. In our group, gold catalyzed activation of propargyl orthoester donor was explored thoroughly for synthesizing modified pyrimidine glycosides by Rao, Nishanth and Hotha.[38] *N*-Glycoside synthesis using *O*-1-(phenylvinyl)-benzoate donor was reported from Xiao group.[39] A novel self-promoted stereoselective *N*-glycosylation method using nosylcarbamates, tosylcarbamates, and sulfonamide as acceptors and TCA donor was recently reported.[40] Direct glycosylation of amides through the nitrogen center is one of the most challenging and difficult approaches owning to poor nucleophilicity of amide –$CONH_2$. Takahashi first reported the direct *N*-glycosylation of asparagine using *N*-phenyl trifluoroacetimidate glycosyl donor in nitromethane solvent.[41] Recently, Takemoto group has discovered a thiourea/halogen bond donor co-catalytic system for direct *N*-functionalization of amides (**Scheme 3.4**).[42]

3.3. Importance of modified nucleoside in therapeutics

Modified nucleoside compounds are considered as one of the versatile classes of drugs that display multiple modes of action and different mechanisms for potential indication.[43] Nucleosides and nucleotide analogs are synthetic and chemically modified compounds that are developed mostly to imitate the physiological counterparts of nucleotides.[44] Since the initial approval of cytarabine back in 1969 by the FDA for the treatment of acute myeloid leukemia, there are currently more than 25 approved modified nucleotide analogs that are used as drugs for the treatment of various life-threatening diseases such as cancer and viral infections (**Figure 3.2**).[45–47] A large variety of

modified nucleoside drugs with promising biological activities are made since the past thirty years to cure viral infection caused by human cytomegalovirus (HCMV), human immunodeficiency virus type 1 (HIV-1), varicella zoster virus (VZV), herpes simplex virus (HSV) and human hepatitis C virus (HCV). All these compounds have the potential to exploit cellular mechanisms and they subsequently get assimilated into DNA or RNA to hinder viral replication process.[48–51] Nucleoside and nucleotide analogues can also inhibit a wide range of human and viral enzymes such as polymerases, kinases, ribonucleotide reductase, methyl transferases and so on.[52,53] Chemical modification of nucleoside analogs can be done at the nucleobase, at different positions of the sugar ring or at the phosphate backbone that are described below;

i) *Nucleobase modification*:[54,55] Nucleobase modification of nucleotides have immense potential to affect the stabilizing interaction between two strands of DNA or RNA. Azotation, halogenation, and conjugation at the *N* center of bases[56] are arguably the most common modifications that prevail.

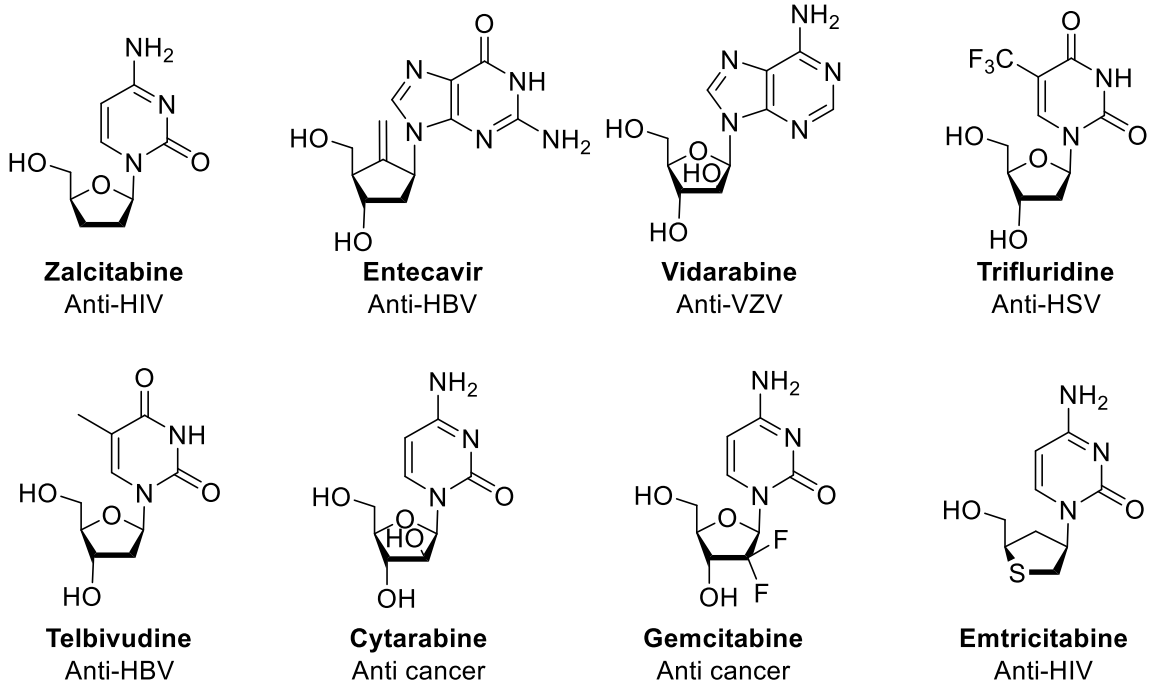
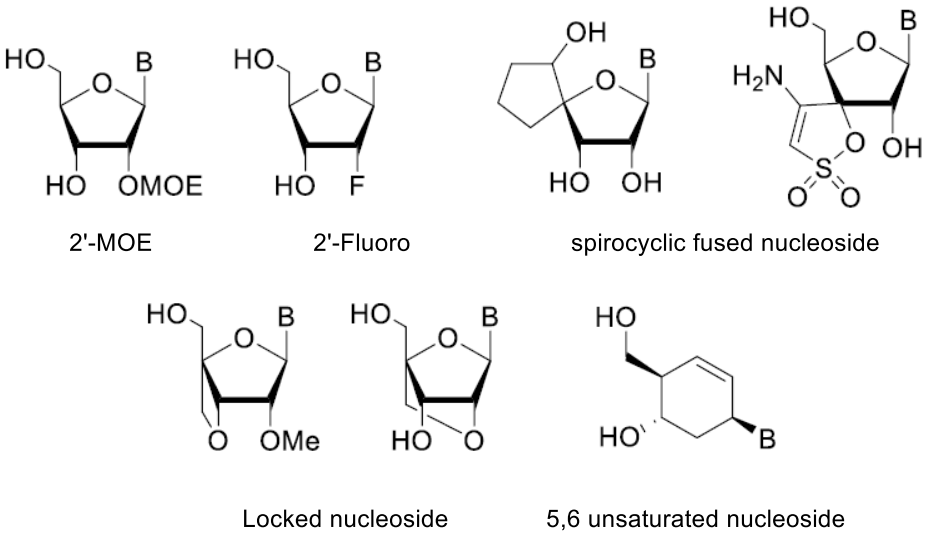


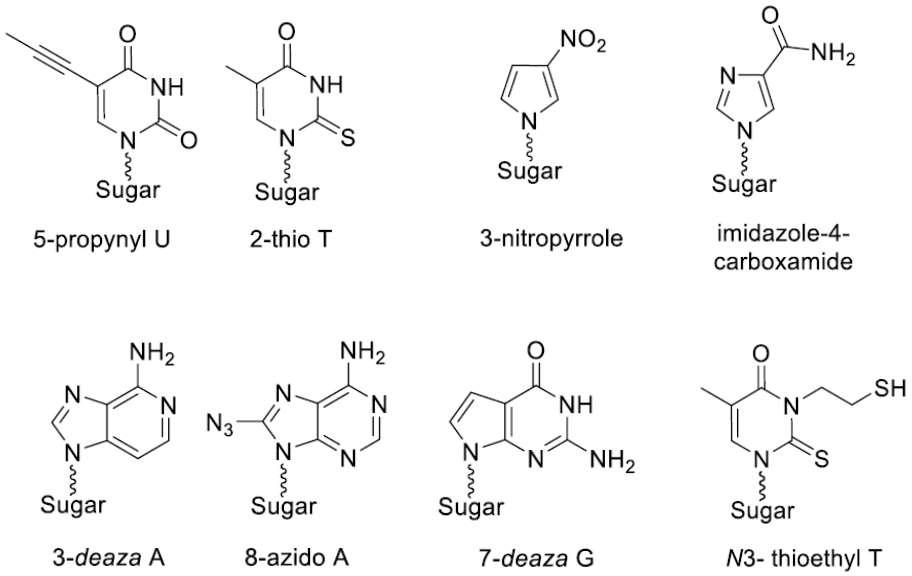
Figure 3.2: Representative structures of nucleoside-based drugs

Expanded nucleobases featured with conjugated systems or phenyl rings can enhance π-π stacking interactions between two base pairs. The most alluring sites for base modifications are *N*6 and *N*7 positions of purines and *N*4 and *N*5 positions of pyrimidines as these sites located in the major groove are exposed to the solvent. Successful introduction of azide and alkyne functional groups at nucleobases paved the way for performing 1,3 dipolar azide-alkyne cycloaddition reaction (Click reaction) for further modification.[56]

ii) *Sugar ring modification*:[57–59] To develop novel nucleoside analogs, reports of modification at the sugar ring of the nucleotide by replacing native *O or H* atoms with non-traditional hetero atoms like fluorine, nitrogen, sulfur, selenium, or carbon are found in the preceding literature. The fact that 2' –OH group is a distinguishing feature between DNA and RNA has led to investigating the biological activities of compounds having different moieties attached to the 2' position other than hydroxyl groups. Reactions including halogenation at different positions, alkylation of hydroxyl groups, ring opening, hydroxylation or dehydroxylation are performed on the sugar ring in order to furnish the desired modification. Inversion of the stereocenters of the saccharide unit can lead to many unnatural nucleosides (For e.g. *L-deoxy* ribose nucleosides). Modification with the installation of fused ring at different positions of the sugar or spirocyclic nucleosides[60] are found to alter cytotoxicity and anomerization (**Figure 3.3**). Locked nucleic acids (LNA)[61,62] are a class of oligonucleotide that comprises of one or more nucleotide units attached to a conformationally fixed bridged methylene group containing unit. LNAs can be useful antisense agents as C3'-endo (β-D-LNA) or C2'-endo (α-L-LNA) conformers increase thermal stability, stabilizes duplex structure and decoys the transcription factor. Modified nucleic acids offer various benefits for many biotechnological applications and can be helpful in solving issues related to first generation nucleoside therapeutics. Converting furanosyl ribose sugar ring to a hexose ring can inhibit enzyme machinery due to the increased ring size. Often, the synthetic routes are cumbersome and getting desired β-selectivity is a major issue especially when the sugar ring modification at *C*2' position are done prior to *N*-glycosylation reaction.



a) Sugar modified nucleosides



b) Nucleobase modified nucleosides

Figure 3.3: Representative structures of modified nucleosides a) Sugar-modified nucleosides b) Nucleobase-modified nucleosides

iii) *Backbone modification:*[63–65] Backbone modification can be done by replacing *P-O* bonds by *P-N* bonds and protecting the phosphate group hydroxyls with more polar groups. The alteration in structure of the phosphodiester linkage or the whole backbone (peptide nucleic acids) have been reported by many research groups.[66,67]

However, despite the successful syntheses of many antiviral drugs, continuous efforts in the development of better synthetic methods and discovering new antiviral agents are absolutely necessary to tackle problems in antiviral chemotherapy such as poor oral availability, the emergence of resistant viral strains and long-term toxicity issues.

3.4. Current work:

Glycoconjugates can be visualized as glycan moieties attached to a protein as in glycoproteins, and lipids as in glycolipids through a glycosidic linkage etc.[68] Glycans can be attached to the aglycons through a *O*-, *N*-, *S*- or *C*- glycosidic bond and they are usually referred to as *O*-glycoside, *N*-glycoside, thioglycoside or *C*-glycoside respectively.[40,69,70] Among these, *N*-glycosides occupy a special position as they are present in DNA/RNA wherein a nucleobase (purine or pyrimidine) is glycosylated to a ribofuranose through the ring nitrogen.[71] Besides, many proteins are post-translationally glycosylated through asparagine amides; apart from this, some *N*-linked glycosides are explored as small molecule inhibitors (**Figure 3.4**). Several decades of research culminated in the development of facile glycosylation protocols for the synthesis of *O*- and *C*- glycosides.[72–76] Although similar, synthesis of *N*-glycosides is far more challenging owing to the numerous reasons that center around the complex compatibility issues between the basicity of *N*-nucleophiles and the acidic reaction conditions often invoked in most of the glycosylation protocols.[37]

Vorbrüggen-modified silyl version of the Hilbert-Johnson nucleosidation from anomeric 1-*O*-acyl glycosyl donors is one of the most popular methods for the synthesis of pyrimidine nucleosides;[31] however, it is not always applicable for the synthesis of purine and asparagine glycosides. The use of strong Lewis acids while performing this nucleosidation often limits the choice of protecting groups while synthesizing purine N-glycosides.[77] Catalytic activation of *o*-alkynyl benzoates using [$Ph_3PAuNTf_2$],[37] O-(1-phenylvinyl) benzoates[39] under NIS/TMSOTf or propargyl orthoesters[38] by $AuBr_3$ are recent improvements for the original Vorbrüggen conditions. Yu glycosidation of purine bases is a significant benchmark in developing catalytic and regioselective purine glycoside synthesis. Synthesis of amide glycosides are routinely performed by chemical functionalization of N_3, NH_2 or glycals.[78] Besides, the synthesis of asparagine glycosides by nucleophilic displacement of anomeric OH is challenging and rarely investigated;

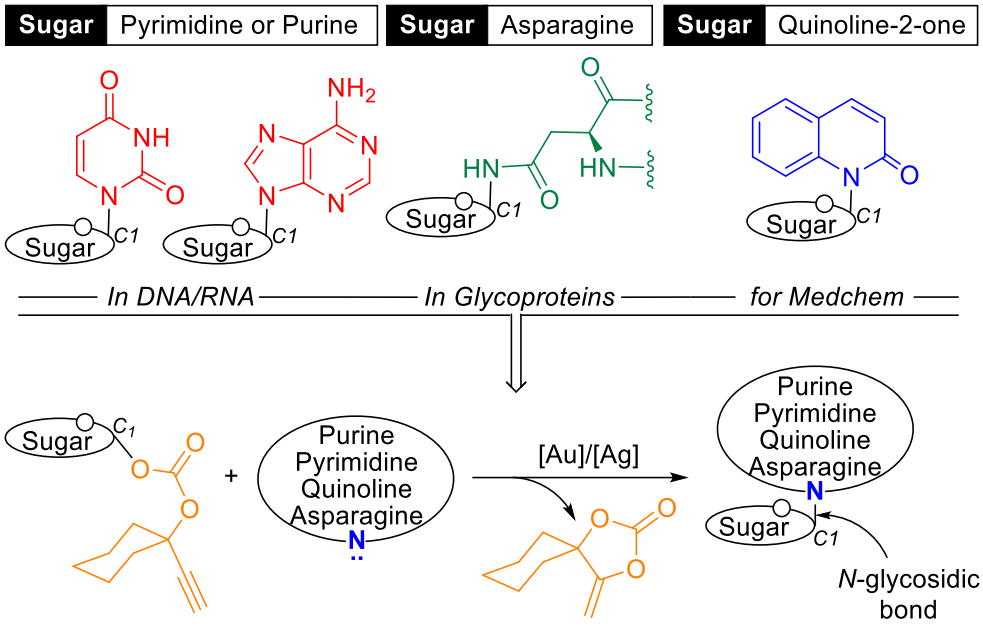
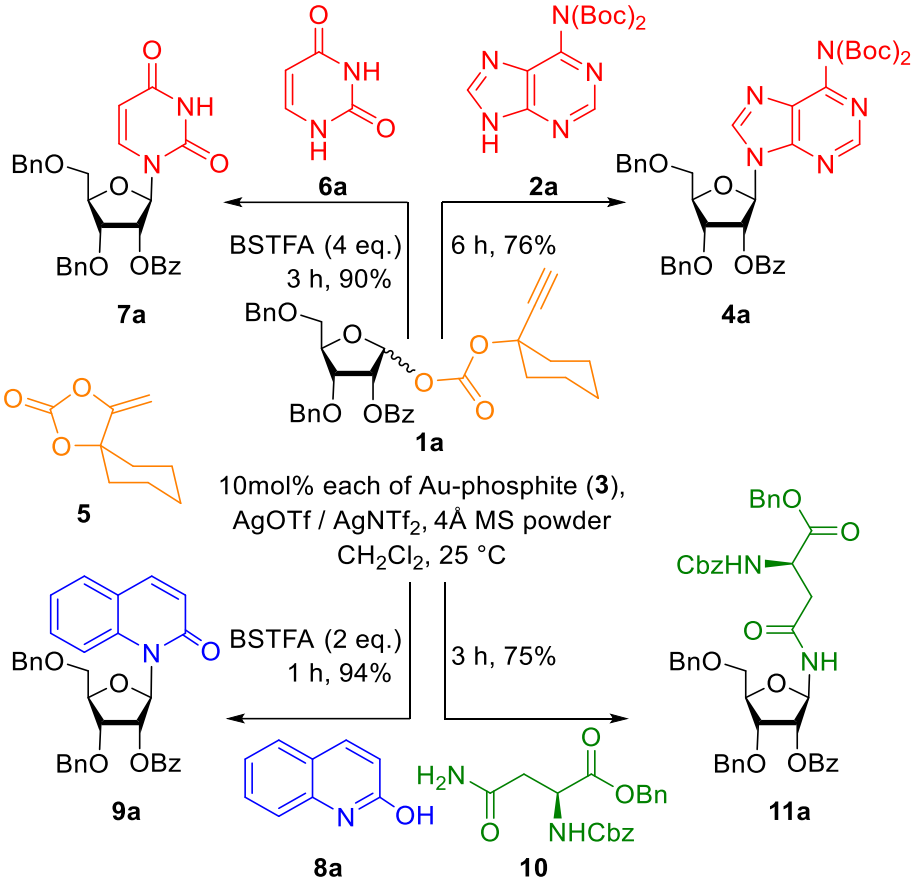


Figure 3.4: General representation of the Synthesis of *N*-Glycosides

direct glycosidation of asparagine is cumbersome.[41,42,79] Quinoline-2-one glycosides were reported through the intramolecular *N*-arylation using Pd-catalysis albeit forming other possible isomers.[80] A unified and direct method for the synthesis of all *N*-glycosides under catalytic, mild conditions and in high yields from shelf stable molecules will augment the development of novel therapeutics, diagnostics and also enhance our current understanding of their biological roles.

We envisioned that the recently discovered ethynylcyclohexyl glycosyl carbonate donors[81] might offer a unique solution towards the synthesis of all these *N*-glycosides under catalytic and mild conditions from shelf stable donors (**Figure 3.4**). Accordingly, the journey commenced with the synthesis of easily accessible ethynylcyclohexyl ribofuranosyl donor **1a** from D-ribose. The strategic installation of benzoate at C2 position in donor **1a** is significant as it would impart anchimeric assistance to direct the formation of the required 1,2-*trans* ribofuranosidic linkage,[82] increases its reactivity,[83,84] and paves the way to C-2' modified nucleosides as well. Donor **1a** in CH_2Cl_2 was treated with adenine derivative 2a in presence of 10 mol% each of



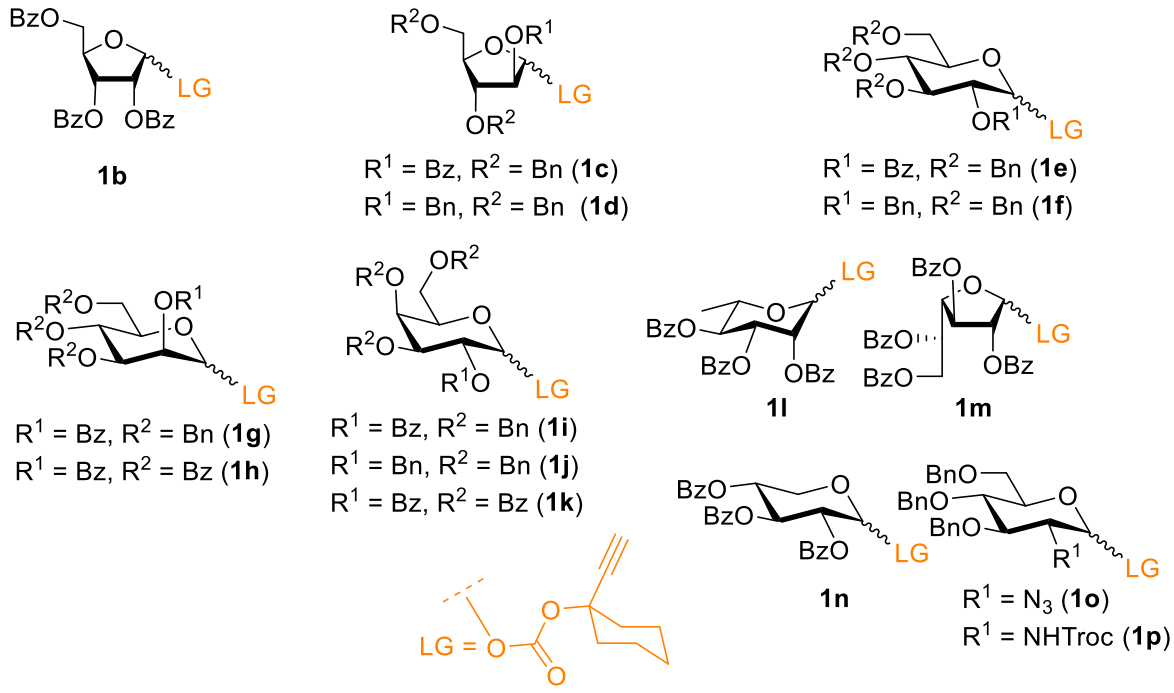
Scheme 3.5: Synthesis of *N*-Glycosides by Silver Assisted Gold-catalysed Glycosidation of Alkynyl Carbonates.

BSTFA: *N,O*-Bis(trimethylsilyl)trifluoro acetamide. Au-phosphite: Chloro [tris(2,4-di-tert-butylphenyl)phosphite] gold. Cbz: Benzyloxycarbonyl. Boc: *tert*-butoxycarbonyl

chloro[tris(2,4-di-*tert*-butylphenyl)phosphite]gold (**3**) and $AgNTf_2$ for 6 h to afford adenosine **4a** in 76% yield along with the formation of the non-polar extrusion product **5** that could be easily removed from the reaction mixture by simple silica gel chromatography. Herein, the poor solubility of adenosine in CH_2Cl_2 is circumvented by placing two Boc-groups at the N10-position of adenine as well as assisted in suppressing the glycosidation through its N9-position.[37,85] However, nucleosidation of pyrimidine often requires a pretreatment of the nucleobase with a silylating agent and binary solvent mixture containing CH_3CN and CH_2Cl_2.[38] In continuation of establishing the unified method for *N*-glycosylation, commercially available uracil (**6a**) in CH_2Cl_2 was stirred at

100 °C in presence of four molar equivalents of BSTFA in a pressure tube until the solution became clear. The clear solution of silylated derivative of uracil was treated with donor **1a**, 10 mol% each of Au-phosphite (**3**) and $AgNTf_2$ to afford protected uridine **7a** in 90% yield (Scheme 1). Successful *N*-glycosylation with silylated pyrimidine acceptor inspired us to synthesize 1-amido sugars using 2-hydroxy quinolines. Similarly, silylation followed by *N*-glycosidation of the commercially available 2-hydroxyquinoline **8a** furnished the medicinally important quinolin-2-

List of glycosyl donors



List of glycosyl acceptors

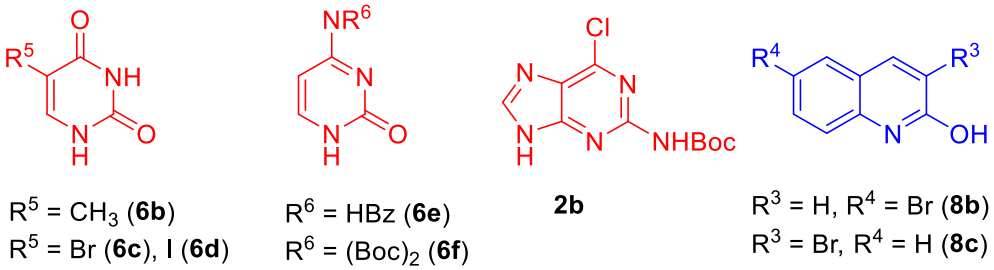
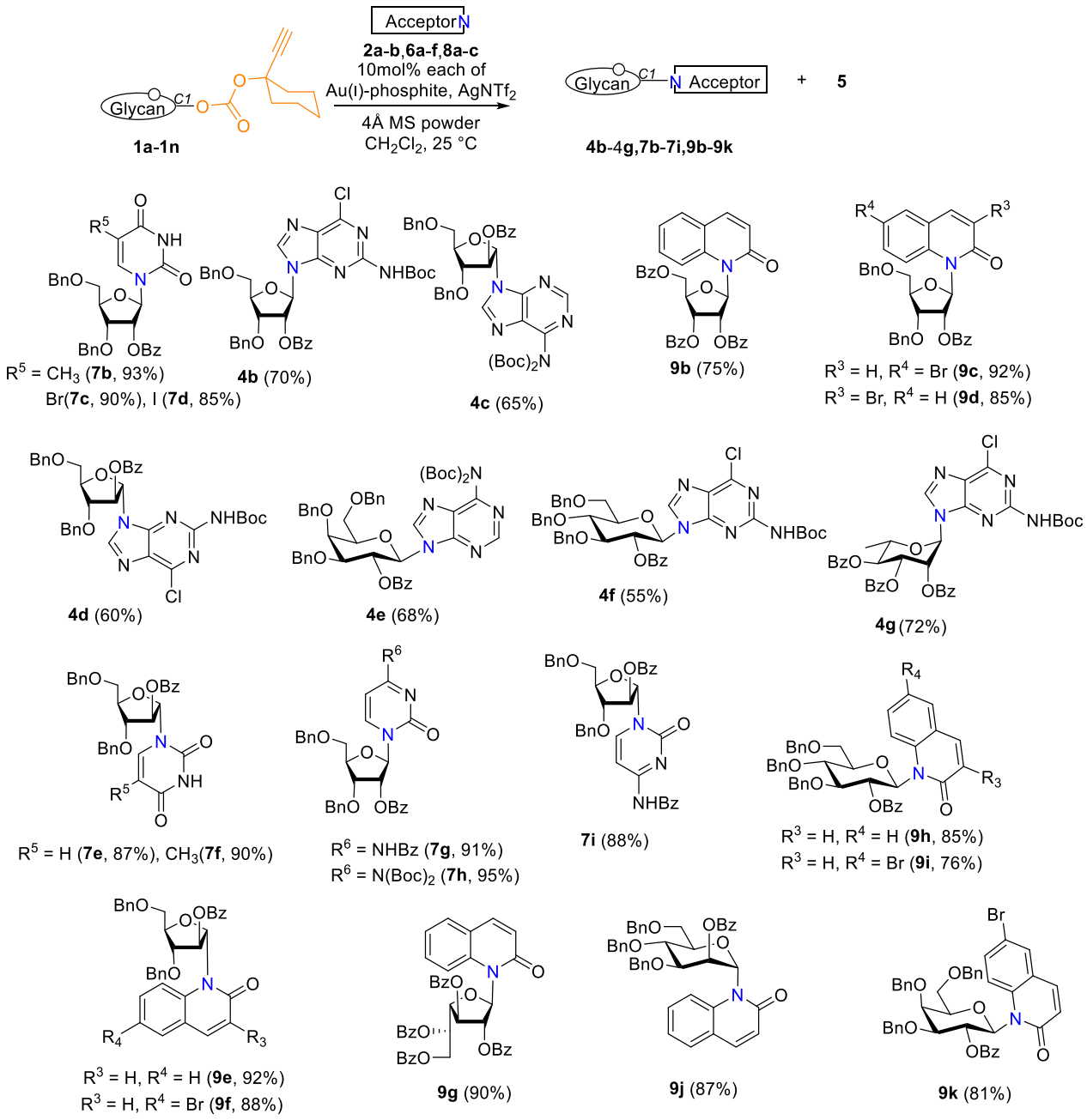


Chart 3.1: List of glycosyl donors and acceptors

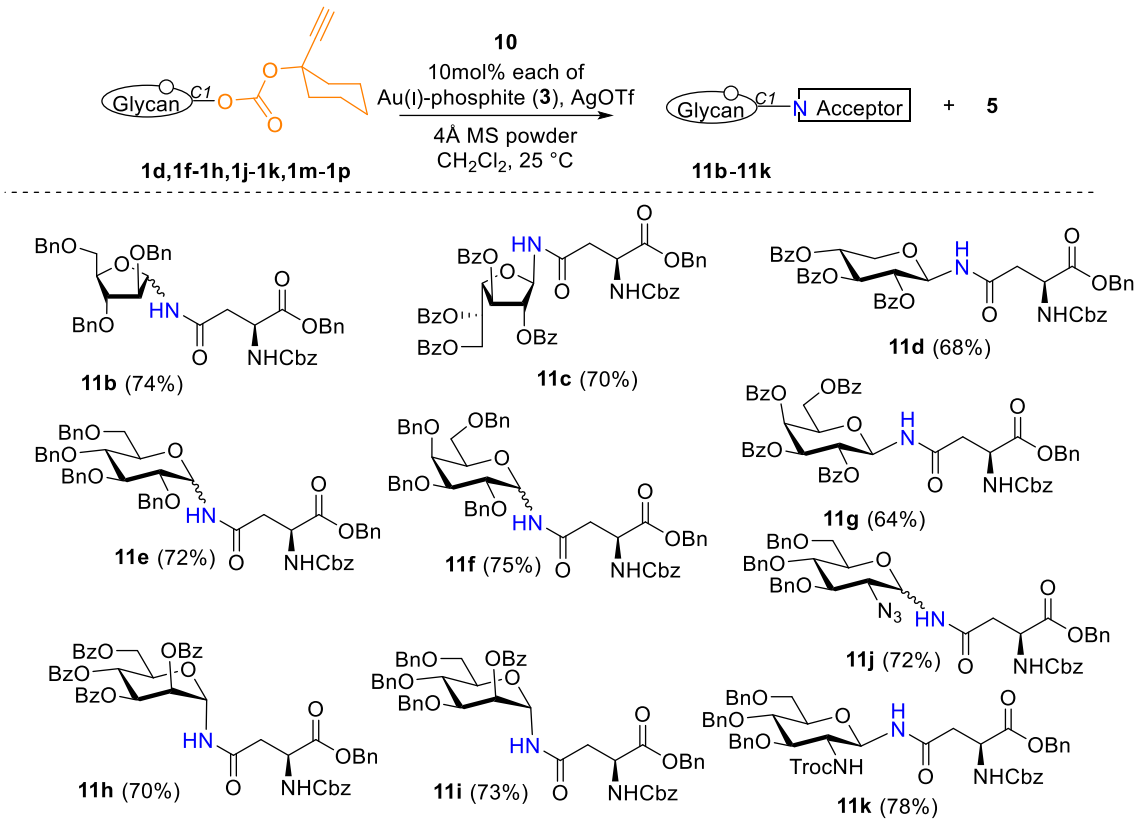
one derivative **9a** in 1 h that was otherwise synthesized in a multi-step endeavor invoking intramolecular *N*-arylation using Palladium catalysis.[80] Proteins often undergo post-translational modification through the asparagines at the γ-position forming a β-glycosidic bond in order to form matured glycoproteins.[5] The direct chemical glycosidation of asparagine derivatives is challenging due to the poor nucleophilicity of the nitrogen of the amide. To our delight, gold catalyzed glycosidation is found to be suitable for the direct attachment of the asparagine derivative **6a** emulating the biosynthetic machinery for the *N*-glycoprotein syntheses. The protected asparagine Cbz.Asn.OBn (**10**) produced the *N*-linked asparagine ribofuranoside **11a** in 75% yield within 3 h directly without any formation of the 1,6-anhydro sugar[79] or the orthoamides.[42] Identification of these silver-assisted gold-catalyzed *N*-glycosidation conditions for the model ribofuranosides **1a** → **4a**,**7a**, **9a**, **11a** (**Scheme 3.5**) motivated us to investigate the scope of these glycosidation conditions for the synthesis of a range of *N*-glycosides.

We have identified glycosyl acceptors (**2a-b**,**6a-6f**,**8a-c**) and synthesized a panel of glycosyl donors comprising furanosides (**1b-d**, **1m**), pyranosides (**1e-1l**, **1n 1o-1p**) (**Chart 3.1**). We were delighted to observe that furanosyl carbonates of D-Rib*f*- (**1a**,**1b**), D-Ara*f*- (**1c**,**1d**), D-Gal*f*-(**1m**) smoothly underwent the *N*-glycosidation with nucleobases **2b**, **6b-6e** providing corresponding nucleosides (**7b-7i**, **4b-4d**) in very good yields. Besides furanosyl carbonates, pyranosyl donors D-Glu*p*- (**1e**,**1f**), D-Man*p*-(**1g-h**), D-Gal*p* (**1j-1k**), L-Rha*p*- (**1l**), and D-GluN*p*- (**1o**, **1p**) also produced nucleosides **4e-4g** in high yields. Presence of the bis-Boc protecting group on the *N*4 position (**6f**) improved the solubility as well as avoided the use of silylating reagent BSTFA affording the nucleoside **7h**. Gratifyingly, identified conditions afforded quinolin-2-one *N*-glycosides (**9b-9k**) by reacting with corresponding glycosyl donors (**1a-1c**,**1e**,**1g**,**1i**,**1m**) and 2-hydroxy quinolines (**8a-c**) (**Scheme 3.6**). 2-amino-6-chloro purine glycosides are precursor for guanine glycosides that can be derived by simple acid hydrolysis of chloropurine moiety. Successful syntheses of these nucleosides show the significance of silver assisted gold catalyzed N-glycosidation protocol for the syntheses of purines pyrimidines and quinolone-2-one glycosides utilizing furanosyl and pyranosyl donors of pentoses and hexoses.



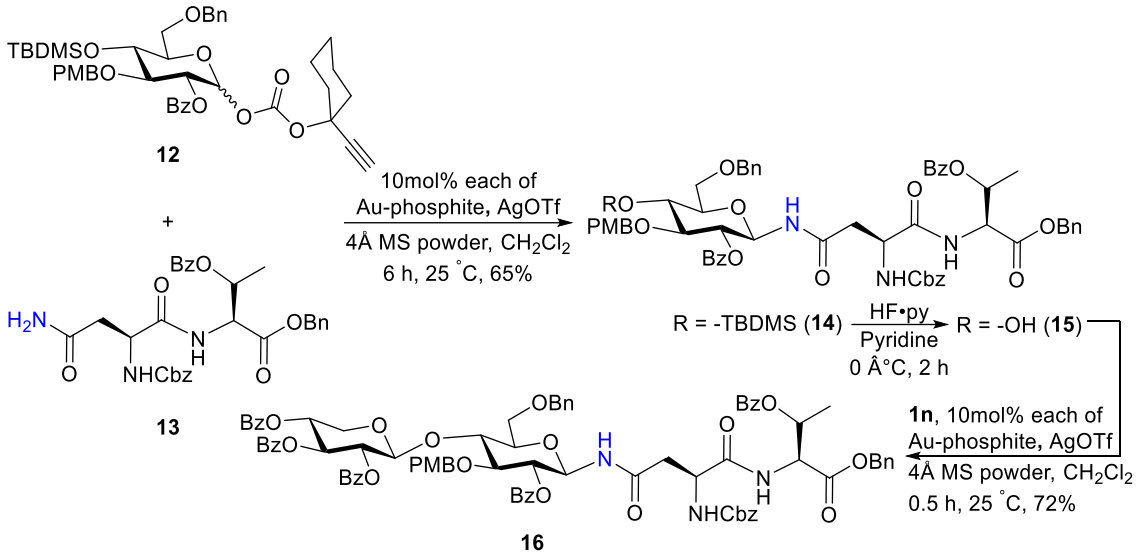
Scheme 3.6: Substrate scope for purine pyrimidine and quinolone-2-one glycosides

Next, we changed our attention to the substrate scope of the asparagination. Direct glycosidation of asparagine derivative (**10**) afforded *N*-glycosides (**11b-11k**) from the select panel of alkynyl carbonates **1a-1p**. The *N*-glycosidation occurred with complete 1,2-*trans* diastereoselectivity (e.g.



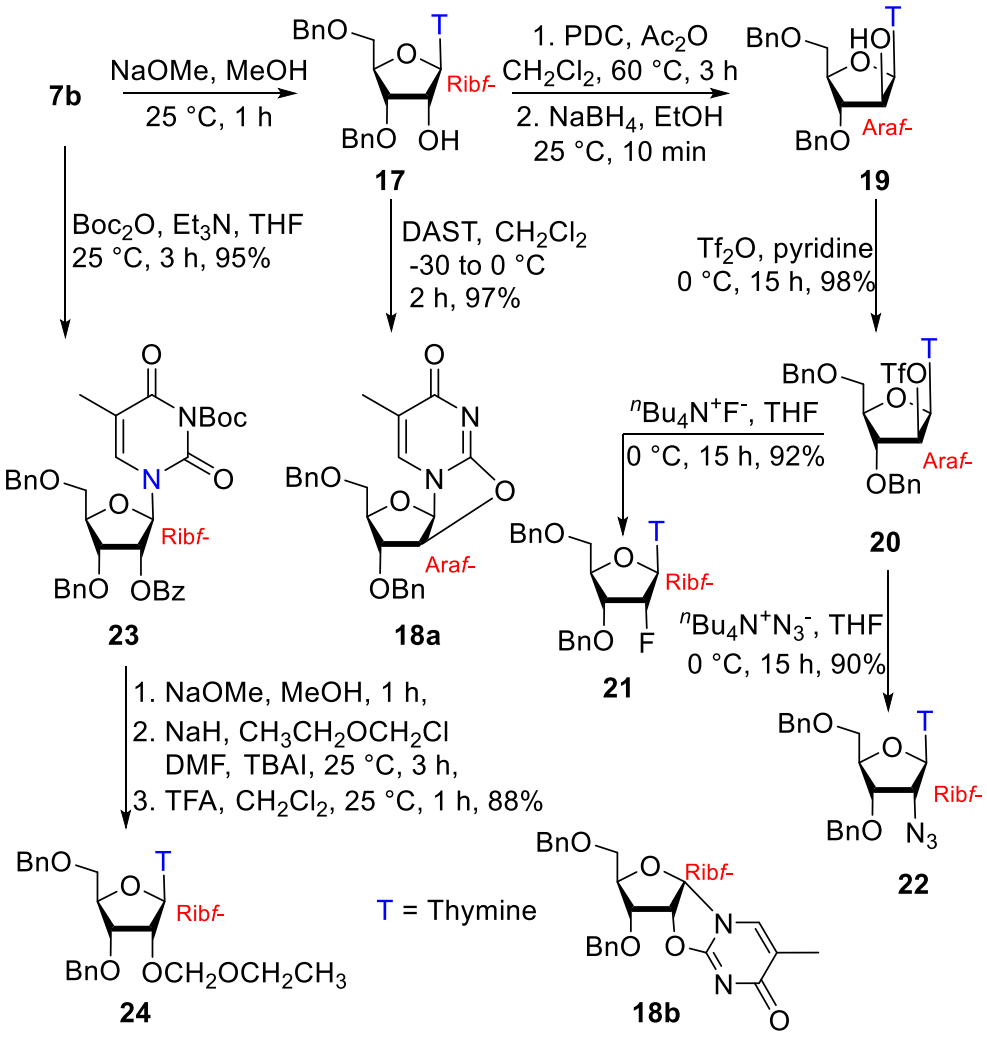
Scheme 3.7: Substrate scope for asparagine glycosides

11c, **11d**, **11g-11i**,**11k**) when the glycosyl donor was poised with a C2-ester moiety through the neighboring group participation whereas those substrates that do not have esters resulted in anomeric mixture of *N*-glycosides with major α-isomer (**Scheme 3.7**). The utility of the direct *N*-asparagination method was verified by the synthesis of the dipeptide disaccharide reminiscent of the molecule present in chloroviruses.[86,87] Accordingly, the designer glycosyl carbonate donor **12** containing four orthogonally cleavable protecting groups was treated with CbzNT(OBz)Bn (**13**) and 10 mol% each of gold phosphite **3** and AgOTf in CH_2Cl_2 for 6 h at 25 ºC to obtain the gluco-asparaginate **14** in 65%. Further, the silyl deprotection of glycoconjugate **14** with HF•py followed by the treatment with the D-Xyl*p* carbonate donor **1n** successfully afforded the glycopeptide **16** in 72% yield (**Scheme 3.8**) which was otherwise reported to be difficult by direct *N*-asparagination.[88]



Scheme 3.8: Synthesis of disaccharide dipeptide moiety through the direct attachment of CbzNT(OBz)Bn

In parallel, thymidine **7b** was investigated for the synthesis of C-2' modified furanosides as it is strategically equipped with orthogonally hydrolysable benzoate at the C-2' position. C-2' Modified nucleosides are important API intermediates since they can be utilized as building blocks for the synthesis of *Si*-RNA-based therapeutics and antiviral drugs.[55] Saponification under Zemplén deacylation conditions using NaOMe, MeOH occurred smoothly to give alcohol **17** which was treated with fluorinating agent DAST in CH_2Cl_2 with a wish to obtain C-2' 2-*deoxy*-2-fluoro-Ara*f*- derivative. To our surprise, the reaction resulted in the formation of the tricylic nucleoside **18a**; the same set of reactions starting from Ara*f*-derivative **1c** produced the similar tricyclic nucleoside **18b**.[89] Formation of the tricyclic derivatives **18a** and **18b** can be explained due to the intramolecular S_N2 attack of nucleobase-amide onto the activated 2'-OH by DAST. To circumvent this problem, we invoked our earlier studies on the conversion of D-Rib*f*- to D-Ara*f*-glycosides through oxidation and reduction sequence.[90,91] Accordingly, oxidation of the compound **17** was performed using PDC/Ac_2O in 3 h and reduced with $NaBH_4$ in EtOH to convert D-Rib*f*-compound **17** to D-Ara*f*- derivative **19** easily. Further, the lone hydroxyl group at the C-2' position was transformed into triflate **20** using Tf_2O/pyridine in 98% yield.



Scheme 3.9: Synthesis of 2'-modified nucleoside derivatives

The triflate **20** was split into two portions, the first portion was treated with ^{n}-Bu$_4$N$^+$F$^-$ in THF to obtain the C2'-*deoxy*-C2'-fluoro thymidine **21** and the second portion was treated with ^{n}-Bu$_4$N$^+$N$_3^-$ to afford the C2'-*deoxy*-C2'-azido thymidine **22** in 90% yield (**Scheme 3.9**).[89]

2'-O-Alkylated nucleosides are well known for their excellent medicinal potential in the Si-RNA therapeutics.[92] Alkylation of the thymidine **17** using NaH and MOMCl resulted in alkylation at 2'- and N3 position which necessitated us to initiate the N3-protection of the thymidine **7b** using Boc$_2$O, Et$_3$N in THF at 25 ºC in 95% yield. Next, saponification of compound **23** under Zemplén conditions and subsequent protection with commercially available 2'-*O*-(2-Methoxyethyl)-Cl

produced the 2'-*O*-MOE protected thymidine which upon deprotection of the Boc-protecting group using TFA afforded the 2'-MOE protected thymidine **24** in 88% overall yield.

In conclusion, A unified, direct and catalytic method for the *N*-glycosidation using [Au]/[Ag]-catalysts was identified and demonstrated with a panel of glycosyl donors and purines, pyrimidines, 2-hydroxyquinolines, protected asparagines as glycosyl acceptors. The N-glycosidations are clean, high yielding and occur at ambient temperatures. Presence of acyl moieties at the C-2 position ensured the neighboring group participation to impart the 1,2-*trans* selectivity in the glycosidation step. Glycosidation of bis-Boc protected cytosine was affected without the need of additional silylating reagent. Catalytic synthesis of 1-amido sugar derivatives through the direct N-glycosidation was investigated. The utility of this protocol was demonstrated by the synthesis of the disaccharide dipeptide unit present in the cell membrane of chloroviruses. Direct access to the C2'-modified nucleoside derivatives through oxidation followed reduction is accomplished. Conversion of Rib*f*- thymidine to the Ara*f*- thymidine and further S_N2 displacement with fluorinating agent or the azide afforded 2'-*deoxy* 2-fluoro and 2-azido thymidines. Synthesis of natural and unnatural nucleosides is currently underway.

3.5. Experimental data:

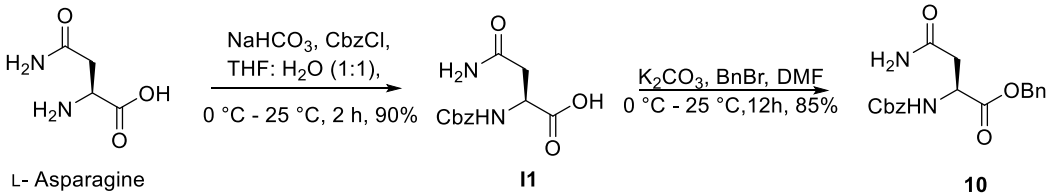
General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. 1-Ethynylcyclohexanol, *p*-nitrophenyl chloroformate, purine and pyrimidine bases, 2-hydroxy quinolines and all metal salts were purchased from Sigma-Aldrich. Unless otherwise reported all reactions were performed under Nitrogen atmosphere. Removal of solvent *in vacuo* refers to the distillation using a rotary evaporator attached to an efficient vacuum pump. Products obtained as solids or syrups were dried under high vacuum. Analytical thin-layer chromatography was performed on pre-coated silica plates (F_{254}, 0.25 mm thickness); compounds were visualized by UV light or by staining with anisaldehyde spray. IR spectra were recorded on a FT-IR spectrometer. NMR spectra were recorded either on a 400 or a 600 MHz with $CDCl_3$ or DMSO or CD_3OD as the solvent and TMS as the internal standard. High resolution mass spectroscopy (HRMS) was performed using an ESI-TOF mass analyzer. Low

resolution mass spectroscopy (LRMS) was performed on UPLC-MS with SWADESI-TLC interface.

General procedure for silylation of 2-hydroxy quinoline derivative(s): To a dispersed solution of **8a-8c** (1 mmol) in dry CH_2Cl_2 (3 mL), 3 mmol of BSTFA was added and stirred at room temperature for 1-2 h till the solution became clear. This solution was further used for glycosylation.

General procedure for silylation of pyrimidine derivative(s): Commercially available pyrimidine bases (**6a-e**) (1.0 mmol) were suspended in dry CH_2Cl_2 and BSTFA (6 mmol) was added in a sealed tube and tightly capped. The dispersed solution was heated at 100 °C till the solution became clear. Then the solution was cooled to room temperature and was further used for glycosylation.

Synthesis of protected L-asparagine amino acid **10***:* To a rapidly stirring aqueous solution of asparagine (1 mmol), $NaHCO_3$ (3 mmol) was added and stirred for 10 min at 25 °C. A solution of CbzCl (1.5 mmol) in THF was added dropwise into the reaction mixture at 0 °C and gradually warmed to 25 °C. After the complete consumption of the amine, the reaction mixture was neutralized with aqueous 1*N* HCl solution and extracted with ethyl acetate (3x25 mL). The organic layer was then concentrated *in vacuo* and purified by silica gel column chromatography (CH_2Cl_2/MeOH) to obtain the desired compound **I1** as a white solid.



Scheme SI.1: Synthesis of asparagine glycosyl acceptor

Next, Cbz protected asparagine **I1** (1mmol) was dissolved in DMF and K_2CO_3 (3 mmol.) was added, the reaction mixture was cooled to 0 °C and stirred for 10 min. Benzyl bromide (1.1 mmol) was added slowly and stirred for 12 h at room temperature. After the complete conversion of the starting material, ice cold brine solution was added, extracted with EtOAc (3x25 mL), the combined organic layers were concentrated *in vacuo* and the resulting residue was purified by flash silica gel column chromatography (dichloromethane/methanol) to obtain the desired protected asparagine **10** as white solid.

Synthesis of Ethynylcyclohexyl Glycosyl Carbonate Donors **1a-1p***:* To a solution of corresponding hemiacetal (1.0 mmol) in anhydrous CH_2Cl_2 (10 mL/1 g of hemiacetal), ethynylcyclohexyl (4-nitrophenyl) carbonate (1.2 mmol) and DMAP (1.1 mmol) were added and the reaction mixture was stirred at 25 °C for 3 h. After complete consumption of the starting hemiacetal, the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (ethyl acetate/hexane as mobile phase) to obtain ethynylcyclohexyl glycosyl carbonate donors in more than 90% yield.

General procedure for the synthesis of pyrimidine glycosides **7a-7i:** To a solution of silylated pyrimidine (1.1 mmol) in anhydrous CH_2Cl_2 (10 mL), glycosyl carbonate donor was added (1.0 mmol). Next, freshly activated 4Å MS powder (30 mg/mL) was added and stirred for 20 min under nitrogen atmosphere, gold-phosphite (**3**) (10 mol%) and $AgNTf_2$ (10 mol%) were added and stirred at 25 °C. After 6 h as adjudged by TLC analysis, the reaction mixture was passed through a bed of Celite® and the filtrate was concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase.

General procedure for the synthesis of purine glycosides **4a-4g:** Freshly activated 4Å MS powder (30 mg/mL) was added to a solution containing glycosyl carbonate donor (1.0 mmol) and freshly synthesized protected purine base (1.1 mmol) in anhydrous CH_2Cl_2 (10 mL) and stirred under nitrogen atmosphere. After 20 min, gold-phosphite **3** (10 mol%) and $AgNTf_2$ (10 mol%) were added to the reaction mixture at 25 °C and stirred for 8 h. At the end of the reaction, as monitored by the TLC examination, the reaction mixture was filtered through a bed of Celite® and the filtrate was concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase.

General procedure for quinolin-2-one glycosides **9a-9k***:* Glycosyl carbonate donor (1.0 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL). In parallel, a solution of silylated 2-hydroxy quinoline (1.1 mmol) in anhydrous CH_2Cl_2 (5 mL) was freshly prepared and cannulated into the glycosyl donor solution. Next, freshly activated 4Å MS powder (30 mg/mL) was added into it and stirred for 20 minutes under nitrogen atmosphere. Gold-phosphite **3** (10 mol%) and $AgNTf_2$ (10 mol%) were added to the reaction mixture at 25 °C and stirred for 1 hr. At the end of the reaction as adjudged by the TLC examination, the reaction mixture was passed through a bed of celite and the

filtrate was concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase.

General procedure for the synthesis of asparagine glycosides **11a-11k***:* Asparagine derivative **10** (1.1 mmol) was added to a stirring solution of glycosyl carbonate donor (1.0 mmol) in dry CH_2Cl_2. Freshly activated 4Å MS powder (30 mg/mL) was then added and allowed to stir for 20 minutes under nitrogen atmosphere. Gold-phosphite **3** (10 mol%) and AgOTf (10 mol%) were added to the reaction mixture at 25 °C and stirred for 8 h. At the end of the reaction as adjudged by the TLC examination, the reaction mixture was filtered through a bed of Celite®, and the filtrate was concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase.

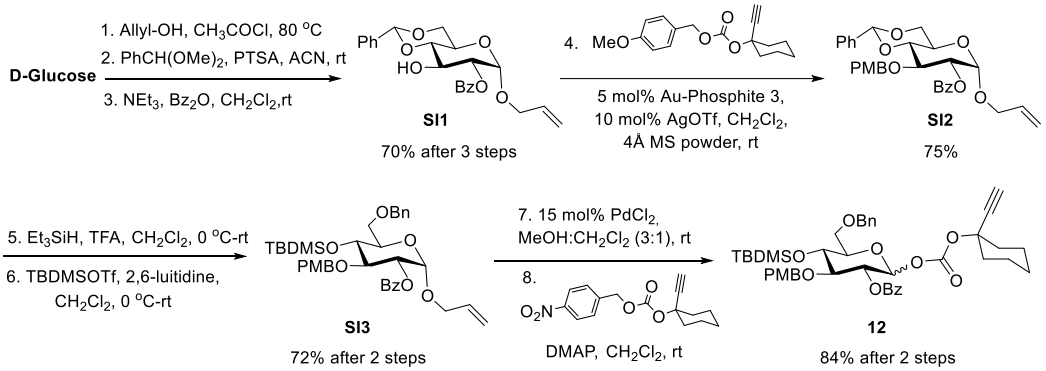
Compound number	Preparation and characterization reference
Hemiacetals of **1b,1d,1f,1j,1k,1l,1m,1n** and corresponding carbonate donors	B. Mishra, M. Neralkar, S. Hotha, *Angew. Chem. Int. Ed.* **2016**, *55*, 7786-7791
Hemiacetals of **1a-c, 1e, 1g,1i**	S. A. Thadke, B. Mishra, S. Hotha, *Org. Lett.* **2013**, *15*, 2466-2469.
Hemiacetals of **1o**	E. D. Goddard-Borger, R. V. Stick *Org. Lett.* 2007, 9, 19, 3797–3800
Hemiacetals of **1p**	S. Izumi, Y. Kobayashi, Y. Takemoto *Angew. Chem. Int Ed.* **2020**, *59*, 14054-14059.
2a,2b	Q. Zhang, J. Sun, Y. Zhu, F. Zhang, B. Yu, *Angew. Chem. Int. Ed.* **2011**, *50*, 4933-4936
6f	M. G. Gupta, B. R. Madhanagopal, K. N. Ganesh, *J. Org. Chem.* **2021**, *86*, 414-428
I1	A. Saha, S. Panda, D. Manna, *Chem. Commun.* **2016**, *52*, 9438-9441

General procedure for saponification: To a solution of the benzoate/acetate (1.0 mmol) in anhydrous CH_2Cl_2/MeOH (4 mL, 1:1), 1M NaOMe in MeOH (0.3 mmol per benzoate/acetate)

was added and the reaction mixture was stirred at 25 °C for 3 h. After complete consumption of the starting material, Amberlite® IR 120 (H^+) [1.0 g/mol] was added to the reaction mixture for neutralization. The solid resin was filtered off and the filtrate was concentrated *in vacuo*, the crude residue was purified by silica gel column chromatography to obtain the alcohol.

Synthesis of compound **12***:*

Procedure for the synthesis of compound **12***:*



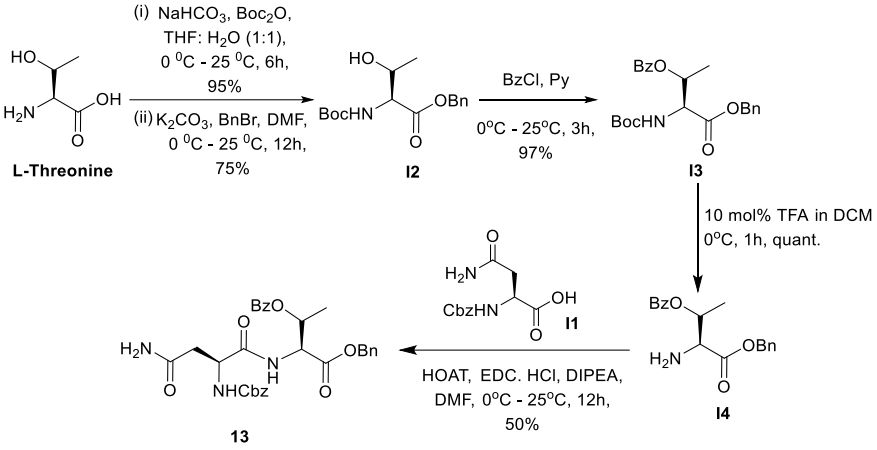
Scheme SI.2: Synthesis of glycosyl donor 12

Number	**Procedures for reference**
Step 1, 2	S. Pasari, S. Manmode, G. Walke, S. Hotha, *Chem. Eur. J.* **2018**, *24*, 1128
Step 3	X.-A. Lun, C.-H. Chou, C.-C. Wang, S.-C. Hung, *Synlett* **2003**, *9*, 1364
Step 4[93]	S. Chakraborty, B. Mishra, M. Neralkar, S. Hotha *J. Org. Chem.* **2019**, *84*, 6604
Step 5	M. Sakagami, H. Hamana, *Tetrahedron Lett.* **2000**, *41*, 5547
Step 6	G. Walke, N. Kasdekar, Y. Sutar, S. Hotha, *Communications Chem.* **2021**, 4:15
Step 7, 8	B. Mishra, M. Neralkar, S. Hotha, *Angew. Chem. Int. Ed.* **2016**, *55*, 7786

Synthesis of Di-peptide **13*:***

A) Synthesis of L-threonine derivative **I4***:* To a rapidly stirring aqueous solution of L-threonine (1 mmol), $NaHCO_3$ (3 mmol) was added at 25 °C and stirred for 10 min. A solution of Boc_2O (1.5 mmol) in THF was then added dropwise into the reaction mixture at 0 °C and gradually warmed

up to 25 °C. After the complete consumption of the amine, the reaction mixture was neutralized by adding an aqueous solution of 1*N* HCl and extracted with ethyl acetate (3x25 mL). The organic layer was concentrated *in vacuo* and purified by silica gel column chromatography (CH_2Cl_2/MeOH) to obtain the desired compound as a white solid in 95% isolated yield.



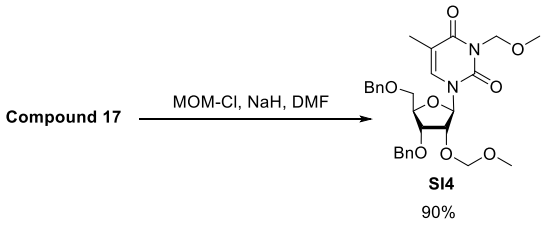
Scheme SI.3: Synthesis of di-peptide 13

Next, the Boc protected L-threonine was redissolved in DMF (10 mL) and K_2CO_3 (3 mmol) was added, the reaction mixture was cooled down to 0 °C and stirred for 10 min. Benzyl bromide (1.2 mmol) was added slowly and stirred for 12 h at room temperature. After the complete consumption of the starting material, ice cold brine solution was added into the reaction mixture and extracted with EtOAc (3x25 mL). The combined organic layers were concentrated *in vacuo* and purified by flash silica gel chromatography (*n*-hexane/EtOAc) to obtain the desired protected L-threonine **I2** as a white solid with 75% yield.

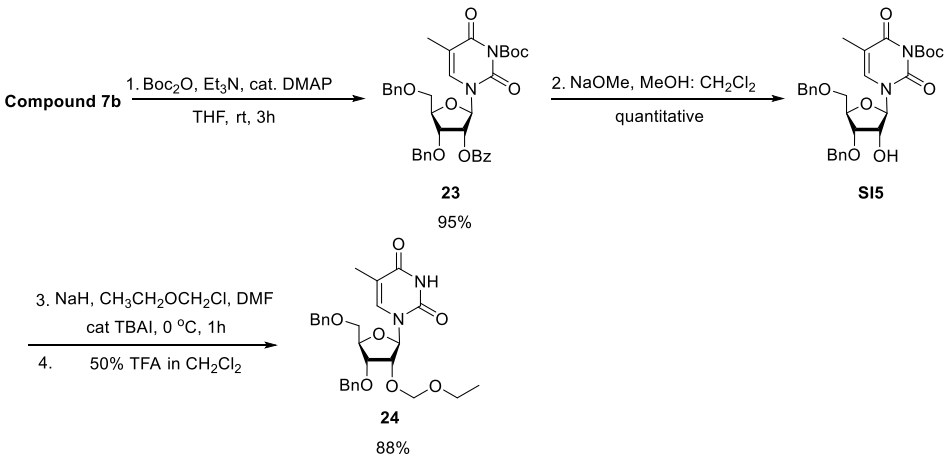
Finally, the free –OH group of the protected L-threonine **I2** was saponified by dissolving the compound in anhydrous pyridine, followed by dropwise addition of BzCl (1.2 mmol) at 0 °C and warming the reaction mixture to 25 °C with continuous stirring. After completion of the reaction, the reaction mixture was neutralised by adding aqueous 1*N* HCl solution and extracted with dichloromethane (3x25 mL). The combined organic layers were concentrated *in vacuo* and purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain the desired compound **I3** as a white solid in 97% isolated yield.

B) Di-peptide synthesis **13***:* To a solution of compound **I3** (1 mmol) in anhydrous CH_2Cl_2, 10 mol% TFA in anhydrous CH_2Cl_2 was added slowly at 0 °C and the reaction mixture was stirred for 1 h. The reaction mixture was was concentrated *in vacuo* and the resulting residue was directly

used in the next step without further purification. The residue was redissolved in anhydrous DMF, diisopropyethylamine (5 mmol), EDCI.HCl (2 mmol) and HOAt (1.5 mmol) were added sequentially at 0 ºC under nitrogen atmosphere. After 30 min, L-threonine compound **I4** in anhydrous DMF was added drop wise to the reaction mixture at 0 ºC. The reaction mixture was gradually warmed up to 25 °C and stirred for 12 h, ice cold brine solution was added to the reaction mixture and extracted with EtOAc (3x25 mL) and washed with aqueous 1*N* HCl solution, sat. aq. $NaHCO_3$ solution and water sequentially. EtOAc layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the resulting crude residue was purified by silica gel column chromatography (*n*-hexane/EtOAc) to obtain the desired di-peptide **13**.



Di-alkylation of compound 17



Mono-*O*-alkylation of compound 17

Scheme SI.4: Synthesis of mono-*O*-alkylated and Di-alkylated derivatives of 7b

Oxidation-Reduction method for synthesis of compound **19** *from* **17***:* To a stirring solution of compound **17** (1 mmol) in anhydrous CH_2Cl_2 (5 mL), pyridinium dichromate (0.7 mmol) and acetic anhydride (3.3 mmol) were added and the reaction mixture was refluxed at 60 °C. After the complete consumption of starting material as adjudged by TLC analysis (~3 h), the reaction mixture was quickly passed through a bed of silica gel, the filtrate was evaporated *in vacuo* to

obtain corresponding 2-ulose derivative as a white solid which was directly used in the next step without further purification.

The crude 2-ulose residue was redissolved in EtOH/EtOAc (2:1) and cooled to 0 °C. $NaBH_4$ (1.2 mmol) was added portion-wise and stirred at 0 °C for 30 min. Excess sodium borohydride was quenched with AcOH and the volatile solvents were evaporated *in vacuo*. The crude residue was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase to obtain the epimerized alcohol **19** in quantitative yield.

Synthesis of compound **21** *&* **22***:* To a stirring solution of compound **20** in THF (1 mmol), tetrabutylammonium fluoride (1.5 mmol) (for **21**) or tetrabutylammonium azide (1.5 mmol) (for **22**) was added and stirred at 0 °C. After the completion of the reaction (~15 h), the reaction mixture was concentrated i*n vacuo* and the crude residue was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase.

Synthesis of compound **24*:*** Treatment of compound **17** (1 mmol) with chloromethyl methyl ether (2 mmol) and NaH (1.5 mmol) in DMF (5 mL) resulted in the undesired dialkylated compound **SI4**. To circumvent this problem, N3- position of **7b** was protected with Boc group followed by deprotection of the benzoyl group was performed to obtain compound **SI5.**

To a stirring DMF solution of **SI5** (1mmol) prepared *vide supra* NaH was added (1.1 mmol) at 0 °C, chloromethyl ethyl ether (1.5 mmol) and catalytic TBAI were added to the reaction mixture. After the complete consumption of starting material as adjudged by TLC analysis, the reaction mixture was concentrated *in vacuo* and was extracted in EtOAc. The organic layer was washed with brine solution and concentrated under diminished pressure. The crude residue was redissolved in anhydrous CH_2Cl_2 and treated with 50% TFA solution. After the completion of the reaction, the mixture was concentrated *in vacuo* and washed with saturated $NaHCO_3$ solution. The crude residue was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase to obtain **24** in 88% yield.

4.6. Confirmation of anomeric configuration of *N*-glycosides and donors:

2D NMR explanation for glycosyl donors **1e**,**1g**,**1i**,**1l:** *C*1 and *H*1 of the corresponding donors were identified by HSQC spectra analysis. *H*1 for donor **1e** was detected at δ 6.34 ppm and *C*1 for donor **1e** was detected at δ 93.4 ppm. $^1J_{C\text{-}H}$ coupling constant of 184 Hz confirms the α-anomeric

linkage of the glucosyl carbonate donor **1e**. Similarly, the $^{1}J_{C-H}$ coupling constant values of **1g** (180 Hz), **1i** (172 Hz), and **1l** (180 Hz) confirms the α anomeric linkage of the respective carbonate donors.

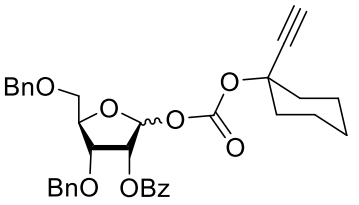
2D NMR explanation for *N*-furanosyl glycosides**:** *C*1 and *H*1 of the corresponding *N-furanosyl glycosides* were identified by COSY, HMBC, and HSQC spectra analysis. 1,2-*trans* linkages of both ribofuranosyl and arabinofuranosyl N-glycosides were confirmed by low J_{H1-H2} coupling constants in ^{1}H NMR which are in parity with the reported values found in the literature (*Journal of Biomolecular NMR* **2016**, *64*, 291-305 and *Angew. Chem. Int. Ed.* **2011**, *50*, 4933-4936). Unexpected 2D-NOESY correlations between H-1 and H-2,3, which may be due to the puckering of the sugar ring (B. V. Rao, S. Manmode, S. Hotha, *J. Org. Chem.* **2015**, *80*, 1499-1505). However, similar trends in $^{1}J_{C-H}$ values derived from coupled HSQC NMRs (172 Hz for **4a** and **4c**, 184 Hz for **7g** and 180 Hz for **7i**, 164 Hz for **9a** and **9e**) confirms the 1,2-*trans* linkages.

2D NMR explanation for *N*-pyranosyl glycosides**:** *C*1 and *H*1 of the corresponding *N-pyranosyl glycoside* were identified by COSY, HMBC, and HSQC spectra analysis. Anomeric configurations are confirmed by $^{1}J_{C-H}$ values (e.g. 164 Hz for **4f** confirms β-linkage whereas 168 Hz for **4g** confirms α-linkage, 164 Hz for **9h** confirms-β linkage, 168 Hz for **9j** confirms α-linkage at the anomeric center).

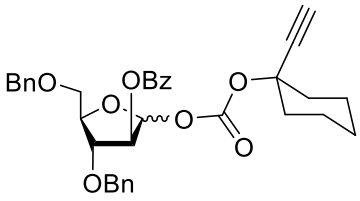
2D NMR explanation for asparagine glycosides: *C*1 and *H*1 of the corresponding *N*-pyranosyl glycosides were identified by COSY, HMBC, and HSQC spectra analysis. Broadening of the *H*1 happens because of the coupling with both *H*2 and the amide-NH from the aglycon. However, the anomeric configurations have been elucidated by $^{1}J_{C-H}$ values derived from coupled HSQC NMRs. (168 Hz for **11e** and **11i** confirms the α-linkage, 174 Hz for **11h** confirms the α-linkage, 160 Hz for **11d** and 156 Hz for **11g** confirms the β-linkage at the anomeric center).

3.7. Characterization Data:

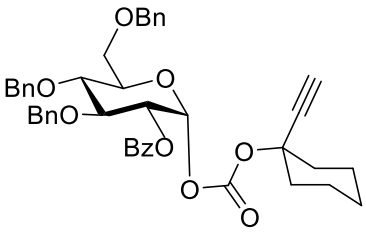
1-O-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,5-di-*O*-benzyl α/β-D-ribofuranoside (**1a** α:β: 5:1): Syrup, IR (cm^{-1}, $CHCl_3$): 3281, 2936, 2862, 1758, 1726, 1600, 1451,1268, 1238, 1010, 910, 786, 730, 704; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (dt, *J* = 8.5, 1.7 Hz, 2H), 7.59 – 7.53 (m, 1H), 7.46 – 7.40 (m, 2H), 7.35 – 7.20 (m, 10H), 6.46 – 6.20 (m, 1H), 5.64 – 5.38 (m, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.62 – 4.51 (m, 2H), 4.51 – 4.41 (m, 2H), 4.39 – 4.24 (m, 1H), 3.74 – 3.43 (m, 2H), 2.55 (s, 1H), 2.27 – 2.09 (m, 2H), 1.88 – 1.76 (m, 2H), 1.68 – 1.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 22.6, 22.6, 22.6, 25.0, 25.0, 36.5, 36.6, 36.8, 37.0, 69.1, 69.6, 72.1, 73.1, 73.2, 73.5, 73.6, 74.0, 75.0, 75.3, 75.4, 76.8, 77.8, 78.4, 82.1, 82.6, 82.8, 84.2, 98.0, 101.5, 127.6, 127.6, 127.6, 127.6, 127.7, 127.8, 127.8, 127.9, 128.0, 128.0, 128.0, 128.0, 128.3, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 129.4, 129.4, 130.0, 130.0, 130.1, 130.2, 133.3, 133.5, 137.3, 137.8, 137.8, 138.3, 150.9, 151.6, 165.4, 165.6 (α□β isomers). HRMS (ESI-MS): m/z calcd for $C_{35}H_{36}O_8$ $[M+H]^+$: 585.2488 Found: 585.2493.



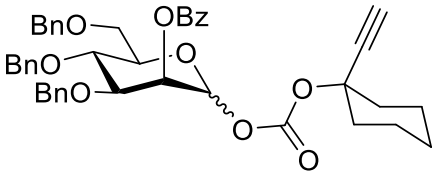
1-O-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,5-di-*O*-benzyl α/β-D-arabinofuranoside (**1c** α/β: 2:1): Syrup, IR (cm^{-1}, $CHCl_3$): 3282, 2938, 2862, 1758, 1722, 1610, 1448,1268, 1240, 1008, 914, 786, 730, 704, 568; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 – 7.94 (m, 2H), 7.60 – 7.53 (m, 1H), 7.42 – 7.22 (m, 12H), 6.41 – 6.27 (m, 1H), 5.57 – 5.51 (m, 1H), 4.90 – 4.65 (m, 1H), 4.65 – 4.53 (m, 2H), 4.53 – 4.47 (m, 2H), 4.33 – 4.11 (m, 1H), 3.71 – 3.59 (m, 2H), 2.48 (s, 1H), 2.28 – 1.97 (m, 2H), 1.89 (ddt, *J* = 12.9, 9.9, 3.8 Hz, 2H), 1.74 – 1.44 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 22.6, 22.6, 22.7, 24.9, 25.0, 36.5, 36.7, 36.7, 36.9, 68.9, 71.0, 72.3, 72.4, 73.5, 73.6, 75.0, 75.4, 77.9, 78.0, 78.3, 80.2, 81.2, 81.5, 82.5, 82.7, 82.8, 84.5, 97.2, 102.8, 127.7, 127.7, 127.7, 127.7, 127.7, 127.7, 127.7, 127.8, 127.9, 127.9, 128.0, 128.0, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.6, 128.6, 128.6, 128.6, 129.1, 129.2, 129.9, 129.9, 130.1, 130.1, 133.5, 133.6, 137.5, 137.6, 137.9, 138.0, 150.9, 151.3, 165.2, 165.5. (both isomers). HRMS (ESI-MS): m/z calcd for $C_{35}H_{36}O_8$ $[M+H]^+$: 585.2488 Found: 585.2498.



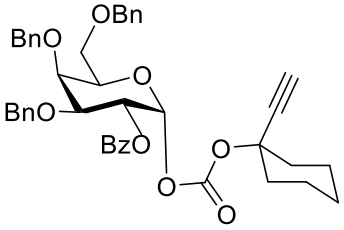
1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,4,6-tri-*O*-benzyl α-D-glucopyranoside (**1e**): White crystalline solid, mp (ºC): 101.2, $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +73.6; IR (cm^{-1}, $CHCl_3$): 3289, 3031, 2935, 2862,1761,1728,1601,1495,1452,1362, 1274,1237,1155 , 850, 745; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 – 7.98 (m, 2H), 7.53 (ddt, *J* = 8.9, 7.0, 1.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.37 – 7.23 (m, 10H), 7.23 – 7.17 (m, 5H), 6.35 (d, *J* = 3.6 Hz, 1H), 5.34 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.87 – 4.79 (m, 3H), 4.64 – 4.50 (m, 3H), 4.24 (t, *J* = 9.5 Hz, 1H), 4.06 (ddd, *J* = 10.2, 3.5, 1.9 Hz, 1H), 3.89 (t, *J* = 9.6 Hz, 1H), 3.79 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.71 (dd, *J* = 11.1, 2.0 Hz, 1H), 2.37 (s, 1H), 2.06 (dt, *J* = 11.7, 5.8 Hz,, 2H), 1.79-1.82 (m, 2H), 1.68 – 1.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 22.6, 25.0, 36.7, 36.7, 68.1, 72.5, 73.5, 73.6, 75.2, 75.3, 75.6, 77.2, 78.3, 79.9, 82.6, 93.5, 127.8, 127.8, 127.9, 127.9, 127.9, 127.9, 128.0, 128.0, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 129.5, 130.0, 130.0, 130.0, 133.3, 137.9, 138.0, 138.1, 151.0, 165.5. HRMS (ESI-MS): m/z calcd for $C_{43}H_{44}O_9$ $[M+H]^+$: 705.3064 Found: 705.3071.



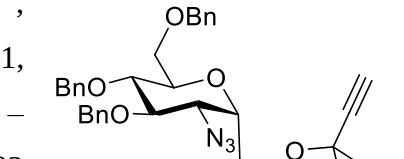
1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,4,6-tri-*O*-benzyl α/β-D-mannopyranoside (**1g** α/β: 2.3:1.0): White crystalline solid, mp (ºC): 95.8, IR (cm^{-1}, $CHCl_3$): 3290, 3035, 2935, 2862,1760, 1730, 1610, 1490, 1458, 1362, 1274,1095, 1009, 897, 740; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15-8.06 (m, 2H), 7.63 (m, 1H), 7.37 – 7.20 (m, 17H), 6.17 – 5.91 (m, 1H), 5.72 (s, 1H), 4.90 – 4.73 (m, 3H), 4.61 – 4.53 (m, 3H), 4.21 – 3.79 (m, 5H), 2.62 (d, *J* = 2.7 Hz, 1H), 2.14 – 1.43 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 22.5, 22.6, 22.6, 24.9, 24.9, 36.6, 36.6, 36.8, 36.9, 67.7, 67.8, 68.6, 68.7, 71.5, 71.8, 73.5, 73.5, 73.5, 73.6, 73.7, 74.0, 75.4, 75.4, 75.5, 75.5, 76.4, 77.9, 78.5, 78.7, 80.1, 82.5, 94.1, 94.4, 127.5, 127.6, 127.6, 127.6, 127.6, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.0, 128.0, 128.0, 128.1, 128.1, 128.1, 128.1, 128.2, 128.2, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 129.6, 129.9, 130.1, 130.1, 130.2, 130.2, 133.2, 133.4, 137.4, 137.8, 138.2, 138.3, 138.5, 138.5, 150.4, 151.1, 165.4, 165.7; HRMS (ESI-MS): m/z calcd for $C_{43}H_{44}O_9$ $[M+H]^+$: 705.3064 Found: 705.3065.



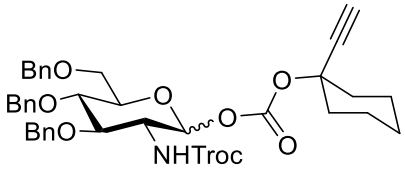
1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,4,6-tri-*O*-benzyl α-D-galactopyranoside (**1i**): White crystalline solid, mp (ºC): 97.6; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +28.2; IR (cm^{-1}, $CHCl_3$): 3290, 3024, 2942, 2855, 1760, 1726, 1604, 1495, 1452, 1362, 1274, 1155, 1095, 1015, 897; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.41 – 7.27 (m, 11H), 7.23 – 7.18 (m, 4H), 5.84 (dd, *J* = 9.9, 8.3 Hz, 1H), 5.72 (d, *J* = 8.3 Hz, 1H), 5.04 (d, *J* = 11.4 Hz, 1H), 4.68 (dd, *J* = 11.9, 8.2 Hz, 2H), 4.54 – 4.45 (m, 3H), 4.10 (d, *J* = 2.8 Hz, 1H), 3.82 (t, *J* = 6.5 Hz, 1H), 3.78 – 3.72 (m, 2H), 3.70 (dd, *J* = 9.1, 6.0 Hz, 1H), 2.42 (s, 1H), 2.02 (ddt, *J* = 42.1, 11.2, 5.3 Hz, 2H), 1.89 – 1.69 (m, 2H), 1.68 – 1.31 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 22.4, 24.9, 36.5, 36.7, 68.2, 71.0, 72.0, 72.4, 73.7, 74.7, 74.8, 75.0, 78.3, 79.8, 82.6, 95.9, 127.8, 127.8, 127.9, 128.0, 128.1, 128.1, 128.3, 128.3, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 128.6, 130.0, 130.1, 130.1, 130.1, 133.2, 137.5, 137.9, 138.5, 151.4, 165.3; HRMS (ESI-MS): m/z calcd for $C_{43}H_{44}O_9$ $[M+H]^+$: 705.3064 Found: 705.3061.



1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-deoxy-2-azido,3,4,6-tri-*O*-benzyl α-D-glucopyranoside (**1o**): Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +1.8; IR (cm^{-1}, $CHCl_3$): 3264, 2938, 2860, 2098, 1746, 1728, 1447,1269, 1077, 911, 730, 578; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.36 (m, 4H), 7.35 – 7.30 (m, 9H), 7.18 (dt, *J* = 6.9, 2.3 Hz, 2H), 5.38 – 5.33 (m, 1H), 4.92 – 4.87 (m, 2H), 4.81 (dd, *J* = 10.8, 2.2 Hz, 1H), 4.67 – 4.52 (m, 3H), 3.82 – 3.75 (m, 3H), 3.62 – 3.52 (m, 3H), 2.66 (d, *J* = 2.1 Hz, 1H), 2.22 – 2.14 (m, 2H), 1.98 – 1.91 (m, 2H), 1.68-1.43 (m, 6H);^{13}C NMR (100 MHz, $CDCl_3$): δ 22.6, 22.6, 25.0, 36.7, 36.9, 65.0, 67.9, 73.6, 75.2, 75.5, 75.9, 76.0, 77.3, 78.9, 82.5, 83.3, 96.0, 127.8, 128.0, 128.0, 128.1, 128.1, 128.2, 128.2, 128.3, 128.3, 128.5, 128.5, 128.6, 128.6, 128.6, 128.7, 137.7, 137.9, 138.0, 151.; HRMS (ESI-MS): m/z calcd for $C_{36}H_{39}N_3O_7$ $[M+H]^+$: 626.2866 Found: 626.2860.

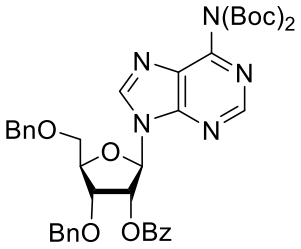


1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*deoxy*-2-(((2,2,2-trichloroethoxy)carbonyl)amino)-3,4,6-tri-*O*-benzyl α/β-D-glucopyranoside (**1p**α/β : 3:1) Syrup; IR (cm^{-1}, $CHCl_3$): 3290, 3024, 2942, 2855, 1743, 1726, 1604, 1510, 1452, 1371, 1274, 1088, 1011, 890; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 – 7.24 (m, 13H), 7.18 (tt, *J* = 4.4, 2.2 Hz,



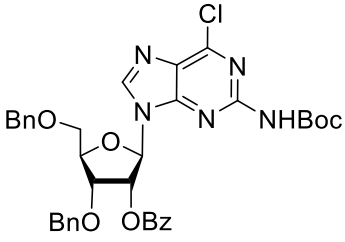
2H), 6.05 (d, *J* = 3.6 Hz, 1H), 4.99 – 4.86 (m, 1H), 4.86 – 4.76 (m, 2H), 4.72 (dd, *J* = 11.3, 6.0 Hz, 1H), 4.70 – 4.46 (m, 4H), 4.13 (td, *J* = 10.0, 3.6 Hz, 1H), 3.97 – 3.62 (m, 5H), 2.61 (d, *J* = 4.7 Hz, 1H), 2.14 (dt, *J* = 18.1, 5.7 Hz, 2H), 1.87 (q, *J* = 10.1 Hz, 2H), 1.70 – 1.51 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 22.5, 22.5, 22.5, 24.9, 24.9, 36.5, 36.6, 36.8, 36.9, 54.2, 54.2, 67.9, 68.2, 73.2, 73.5, 73.5, 73.6, 74.7, 74.8, 75.2, 75.2, 75.2, 75.3, 75.4, 75.7, 77.6, 77.7, 78.5, 78.6, 79.2, 79.5, 82.5, 82.5, 95.0, 95.1, 95.3, 95.3, 127.7, 127.7, 127.9, 127.9, 127.9, 127.9, 127.9, 127.9, 127.9, 127.9, 127.9, 128.0, 128.0, 128.0, 128.1, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 137.8, 137.8, 137.8, 137.9, 137.9, 137.9, 150.8, 151.3, 153.9, 154.1(α□β isomers). HRMS (ESI-MS): m/z calcd for $C_{39}H_{42}Cl_3NO_9$ $[M+Na]^+$: 774.2003 Found: 774.2016.

N,*N*-Di-*t*-butoxycarbonyl-9-(2-*O*-benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)adenine (**4a**): 137 mg isolated from 150 mg (**1a**) (76% isolated yield); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -11; IR (cm^{-1}, $CHCl_3$): 2980, 1789, 1728, 1600, 1497, 1353, 1277, 1214; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.50 (s, 1H), 8.12 – 7.94 (m, 2H), 7.72 – 7.52 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.40 – 7.29 (m, 5H), 7.28 – 7.18 (m, 5H), 6.53 (d, *J* = 3.7 Hz, 1H), 5.95 (dd, *J* = 4.9, 3.7 Hz, 1H), 4.69 – 4.62 (m, 2H), 4.62 – 4.51 (m, 2H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.44 (dd, *J* = 5.8, 2.9 Hz, 1H), 3.85 (dd, *J* = 10.8, 2.6 Hz, 1H), 3.61 (dd, *J* = 10.8, 3.2 Hz, 1H), 1.45 (s, 18H);



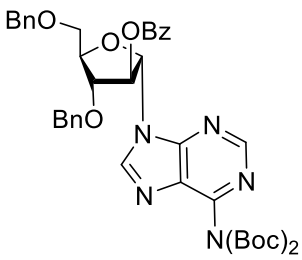
^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 27.8, 27.8, 27.8, 27.8, 27.8, 68.5, 73.3, 73.6, 75.3, 76.2, 82.4, 83.8, 83.9, 87.1, 127.9, 127.9, 128.1, 128.1, 128.1, 128.1, 128.4, 128.4, 128.5, 128.5, 128.6, 128.6, 129.0, 129.2, 130.0, 130.0, 133.6, 137.1, 137.3, 143.4, 150.4, 150.5, 150.5, 152.2, 152.8, 165.4; HRMS (ESI-MS): m/z calcd for $C_{41}H_{45}N_5O_9$ $[M+Na]^+$: 774.3115; Found: 774.3117.

2-*t*-Butoxycarbonylamino-6-chloro-9-(2-*O*-benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)purine (**4b**): 122 mg isolated from 150 mg (**1a**) (70% isolated yield); Syrup, $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +44.4; IR (cm^{-1}, $CHCl_3$): 3338, 2925, 2860,1724, 1610, 1552, 1510, 1222, 1155, 937, 840; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.08 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.61 (s, 1H), 7.49 – 7.31 (m, 8H), 7.14-7.26 (m, 5H), 6.79 (d, *J* = 3.2 Hz, 1H), 5.79 (dd, *J* = 4.8, 3.2 Hz, 1H), 4.64 (dd, *J* = 14.4, 11.7 Hz, 2H), 4.56 – 4.46 (m, 2H), 4.41 – 4.31 (m, 2H), 3.91 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.56 (dd, *J* = 10.9, 2.0 Hz, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz,

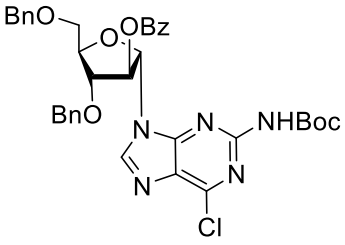


$CDCl_3$): δ 28.2, 28.2, 28.2, 67.5, 73.4, 73.6, 75.4, 76.3, 81.6, 82.6, 88.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.2, 128.4, 128.4, 128.4, 128.6, 128.6, 128.7, 128.7, 128.8, 129.9, 129.9, 133.7, 136.9, 137.0, 143.0, 147.6, 150.3, 152.8, 163.7, 165.1; HRMS (ESI-MS): m/z calcd for $C_{36}H_{36}ClN_5O_7$ $[M+H]^+$: 686.2382; Found: 686.2387.

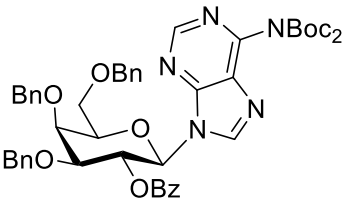
N,*N*-Di-*t*-butoxycarbonyl-9-(2-*O*-benzoyl-3,5-di-O-benzyl-α-D-arabinofuranosyl)adenine (**4c**): 124 mg isolated from 150 mg (**1c**) (65% isolated yield); Syrup, $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +27.6; IR (cm^{-1}, $CHCl_3$): 2986, 1795, 1720, 1611, 1510, 1373, 1353, 1282, 1220; ^1H NMR (400 MHz, $CDCl_3$): δ 8.89 (s, 1H), 8.53 (s, 1H), 7.98 (dt, *J* = 7.2, 1.3 Hz, 2H), 7.64 (s, 1H), 7.48 – 7.44 (m, 2H), 7.30 (tdd, *J* = 6.2, 2.9, 1.7 Hz, 10H), 6.59 (d, *J* = 1.6 Hz, 1H), 6.05 (t, *J* = 1.7 Hz, 1H), 4.80 – 4.69 (m, 3H), 4.58 (s, 2H), 4.39 (dd, *J* = 3.7, 1.8 Hz, 1H), 3.70 (qd, *J* = 10.5, 5.2 Hz, 2H), 1.47 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 27.8, 27.8, 27.8, 27.8, 27.8, 69.1, 72.6, 73.6, 80.8, 82.6, 83.8, 83.9, 85.3, 88.3, 127.7, 127.7, 127.9, 128.0, 128.0, 128.2, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.6, 128.9, 129.9, 129.9, 133.8, 136.7, 137.5, 143.5, 150.3, 150.4, 152.3, 152.3, 153.0, 165.2; HRMS (ESI-MS): m/z calcd for $C_{41}H_{45}N_5O_9$ $[M+Na]^+$: 774.3115; Found: 774.3122.



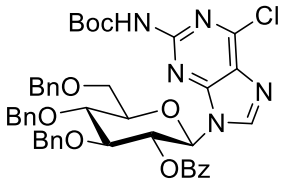
2-*t*-Butoxycarbonylamino-6-chloro-9-(2-*O*-benzoyl- 3,5-di-*O*-benzyl-α-D-arabinofuranosyl)purine (**4d**): 110 mg isolated from 150 mg (**1c**) (60% isolated yield); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +26.8; IR (cm^{-1}, $CHCl_3$): 3345, 2918, 2880,1788, 1738, 1605, 1540, 1231, 1148, 937, 850, 776; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.11 (s, 1H), 7.88 (d, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.22 (s, 10H), 6.47 (s, 1H), 5.96 (s, 1H), 4.74 (dd, *J* = 10.0, 4.0 Hz, 2H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.52 (s, 2H), 4.35 – 4.30 (m, 1H), 3.65 (tt, *J* = 10.5, 5.1 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 28.2, 28.3, 69.2, 72.6, 73.6, 80.8, 81.6, 82.8, 85.4, 88.6, 127.8, 127.8, 127.9, 127.9, 127.9, 127.9, 128.2, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.7, 129.9, 129.9, 133.9, 136.8, 137.6, 142.9, 150.2, 151.4, 152.3, 152.6, 165.2; HRMS (ESI-MS): m/z calcd for $C_{36}H_{36}ClN_5O_7$ $[M+H]^+$: 686.2382; Found: 686.2390.



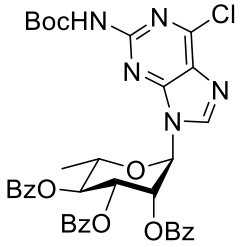
N,*N*-Di-^{t}butoxycarbonyl-9-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl) adenine (**4e**): 126 mg isolated from 150 mg (**1i**) (68% isolated yield); Syrup, $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +18.3; IR (cm^{-1}, $CHCl_3$): 3120, 2990, 1810, 1772, 1665, 1510, 1450, 1373, 1280, 1220, 1155, 1095, 692; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.45 (s, 1H), 7.79 – 7.72 (m, 2H), 7.52 – 7.48 (m, 1H), 7.40 – 7.28 (m, 15H), 7.20 – 7.17 (m, 2H), 6.12 (t, *J* = 9.6 Hz, 1H), 5.98 (d, *J* = 9.4 Hz, 1H), 5.37 (t, *J* = 4.6 Hz, 1H), 5.07 (d, *J* = 11.4 Hz, 1H), 4.70 (dd, *J* = 11.8, 4.4 Hz, 2H), 4.57 (d, *J* = 12.3 Hz, 1H), 4.53 – 4.45 (m, 2H), 4.02 – 3.91 (m, 2H), 3.68 (dd, *J* = 6.4, 4.4 Hz, 2H), 1.31 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 28.1, 28.1, 28.1, 28.1, 28.1, 68.1, 71.3, 72.1, 72.8, 73.7, 75.0, 76.9, 79.8, 80.9, 82.2, 82.2, 127.8, 127.8, 127.9, 127.9, 128.0, 128.0, 128.0, 128.0, 128.0, 128.3, 128.3, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 129.7, 129.7, 133.4, 137.1, 137.4, 138.1, 140.7, 149.5, 149.8, 150.7, 150.8, 153.1, 165.1; HRMS (ESI-MS): m/z calcd for $C_{49}H_{53}N_5O_{10}$ $[M+Na]^+$: 894.3690; Found: 894.3698.



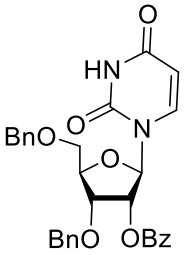
2-^{t}Butoxycarbonylamino-6-chloro-9-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)purine (**4f**): 95 mg isolated from 150 mg (**1e**) (55% isolated yield); Yellow solid, mp (ºC): 88.5; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +66.4; IR (cm^{-1}, $CHCl_3$): 2924, 1727, 1606, 1574, 1451, 1411, 1323, 1262, 1144, 1092; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.59 (s, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.36 – 7.20 (m, 12H), 7.11 (d, *J* = 5.9 Hz, 5H), 5.96 (d, *J* = 9.5 Hz, 1H), 5.69 (t, *J* = 9.2 Hz, 1H), 4.88 (d, *J* = 10.9 Hz, 1H), 4.79 (d, *J* = 11.1 Hz, 1H), 4.73 – 4.61 (m, 2H), 4.61 – 4.47 (m, 2H), 4.09 (t, *J* = 9.0 Hz, 1H), 4.00 (t, *J* = 9.2 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.83 – 3.68 (m, 2H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3, 28.3, 28.4, 68.2, 73.3, 73.6, 75.3, 75.5, 77.4, 78.3, 81.0, 81.8, 82.8, 127.5, 127.9, 127.9, 127.9, 127.9, 127.9, 128.0, 128.0, 128.1, 128.1, 128.1, 128.4, 128.4, 128.4, 128.5, 128.6, 128.6, 128.6, 128.6, 130.0, 130.0, 133.6, 137.5, 137.8, 137.8, 142.2, 150.2, 151.4, 152.6, 152.8, 165.0; HRMS (ESI-MS): m/z calcd for $C_{44}H_{44}ClN_5O_8$ $[M+H]^+$: 806.2957; Found: 806.2960.



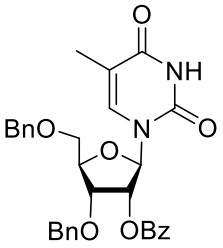
2-^{t}-Butoxycarbonylamino-6-chloro-9-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)purine (**4g**): 120 mg isolated from 150 mg (**1l**) (72% isolated yield); Pale yellow solid; mp (ºC): 143.6; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +26.2; IR (cm^{-1}, $CHCl_3$): 2978, 1726, 1573, 1513, 1451, 1367, 1252, 919, 876; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 – 8.19 (m, 2H), 8.00 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 8.2 Hz, 2H), 7.94 (d, *J* = 7.3 Hz, 2H), 7.59 – 7.47 (m, 3H), 7.47 – 7.33 (m, 6H), 6.69 (t, *J* = 3.6 Hz, 1H), 6.37 (dd, *J* = 8.0, 3.6 Hz, 1H), 6.29 (d, *J* = 3.4 Hz, 1H), 5.69 (t, *J* = 7.9 Hz, 1H), 4.27 – 4.19 (m, 1H), 1.49 (s, 9H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 28.2, 28.2, 28.2, 69.2, 70.4, 71.3, 71.6, 81.5, 81.5, 127.8, 128.6, 128.6, 128.6, 128.6, 128.6, 128.7, 128.7, 129.0, 129.0, 130.0, 130.0, 130.0, 130.0, 130.0, 130.0, 133.6, 133.7, 133.9, 143.4, 150.1, 152.1, 152.5, 153.0, 165.3, 165.5, 165.6; HRMS (ESI-MS): m/z calcd for $C_{37}H_{34}ClN_5O_9$ $[M+H]^+$: 728.2123; Found: 728.2128.



1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)uracil (**7a**): 182 mg isolated from 200 mg (**1a**) (90% isolated yield); Syrup, $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +52.6; IR (cm^{-1}, $CHCl_3$): 3019, 2325, 1694,1623, 1347, 1316, 1263, 1087, 927, 730; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.09 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.35 (dd, *J* = 12.7, 6.3 Hz, 3H), 7.29 – 7.21 (m, 7H), 6.32 (d, *J* = 3.8 Hz, 1H), 5.57 (q, *J* = 3.8 Hz, 1H), 5.38 (d, *J* = 8.1 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 8.7 Hz, 3H), 4.39 (t, *J* = 6.2 Hz, 1H), 4.32 (d, *J* = 4.7 Hz, 1H), 3.93 – 3.85 (m, 1H), 3.60 (d, *J* = 12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.7, 73.3, 73.8, 75.1, 75.9, 82.3, 88.0, 102.5, 128.1, 128.1, 128.2, 128.2, 128.2, 128.2, 128.4, 128.5, 128.5, 128.6, 128.8, 128.8, 129.2, 130.1, 130.1, 133.6, 137.3, 137.3, 140.4, 150.5, 164.0, 165.6; HRMS (ESI-MS): m/z calcd for $C_{30}H_{28}N_2O_7$ $[M+Na]^+$:551.1794; Found: 551.1798.

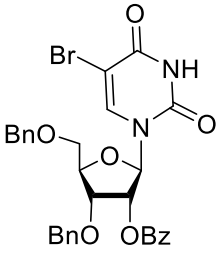


1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)thymine (**7b**): 171 mg isolated from 200 mg (**1a**) (93% isolated yield); Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +16.6; IR (cm^{-1}, $CHCl_3$): 3019, 2355, 1704,1623, 1356, 1305, 1293, 1107, 935, 742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.12 – 8.06 (m, 2H), 7.60 – 7.53 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.37 – 7.28 (m, 5H), 7.21-7.26 (m, 5H), 6.35 (d, *J* = 4.5 Hz, 1H), 5.58 (t, *J* = 4.7 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.58 – 4.50 (m, 2H), 4.50 –

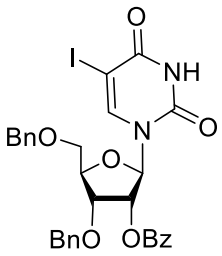


4.41 (m, 2H), 4.31 (d, *J* = 5.2 Hz, 1H), 3.88 (d, *J* = 10.8 Hz, 1H), 3.59 (d, *J* = 13.1 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2, 69.0, 73.3, 73.7, 75.1, 76.2, 82.3, 87.6, 111.3, 127.8, 127.8, 128.1, 128.1, 128.1, 128.2, 128.5, 128.5, 128.6, 128.6, 128.8, 128.8, 129.2, 130.1, 130.1, 133.6, 135.9, 137.4, 137.4, 150.6, 164.2, 165.7; HRMS (ESI-MS): m/z calcd for $C_{31}H_{30}N_2O_7$ $[M+H]^+$: 543.2131; Found: 543.2134.

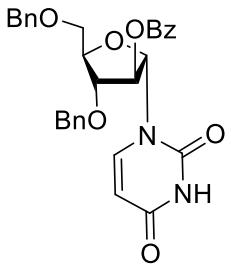
5-Bromo-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)uracil (**7c**): 140 mg isolated from 150 mg (**1a**) (90% isolated yield); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -5.2; IR (cm^{-1}, $CHCl_3$): 3019, 2338, 1696,1627,1439, 1352, 1329, 1054, 915; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.06 (d, *J* = 7.7 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.29 (m, 7H), 7.24 – 7.14 (m, 5H), 6.28 (d, *J* = 3.9 Hz, 1H), 5.61 (q, *J* = 4.2, 3.7 Hz, 1H), 4.63 (dd, *J* = 11.8, 4.3 Hz, 2H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.47 – 4.37 (m, 2H), 4.31 (d, *J* = 5.5 Hz, 1H), 3.89 – 3.79 (m, 1H), 3.51 (d, *J* = 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.0, 73.3, 73.6, 75.2, 75.9, 82.6, 88.0, 97.2, 128.0, 128.1, 128.1, 128.1, 128.1, 128.2, 128.4, 128.5, 128.6, 128.6, 128.7, 128.7, 129.1, 130.1, 130.1, 133.6, 137.1, 137.2, 139.8, 149.8, 159.2, 165.5; HRMS (ESI-MS): m/z calcd for $C_{30}H_{27}BrN_2O_7$ $[M+H]^+$:607.1080; Found: 607.1091.



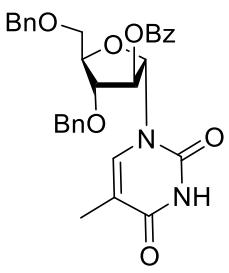
5-Iodo-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)uracil (**7d**): 188 mg isolated from 200 mg (**1a**) (85% isolated yield); Syrup, $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -21.4; IR (cm^{-1}, $CHCl_3$): 3064, 1689, 1608, 1356, 1318, 1268, 1025, 776; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.12 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.50 – 7.35 (m, 7H), 7.29 – 7.21 (m, 5H), 6.33 (d, *J* = 3.8 Hz, 1H), 5.68 (q, *J* = 4.1 Hz, 1H), 4.77 – 4.59 (m, 3H), 4.47 (dd, *J* = 8.4, 5.7 Hz, 2H), 4.36 (d, *J* = 5.7 Hz, 1H), 3.94 – 3.84 (m, 1H), 3.61 – 3.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.8, 68.7, 73.3, 73.6, 75.2, 75.9, 82.5, 88.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.2, 128.4, 128.5, 128.6, 128.8, 128.8, 129.1, 130.1, 130.1, 133.6, 137.2, 137.2, 145.0, 150.1, 160.3, 165.5; HRMS (ESI-MS): m/z calcd for $C_{30}H_{27}IN_2O_7$ $[M+H]^+$:655.0941; Found: 655.0949.



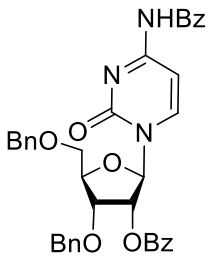
1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-α-D-arabinofuranosyl)uracil (**7e**): 153 mg isolated from 200 mg (**1c**) (87% isolated yield); Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +11; IR (cm^{-1}, $CHCl_3$): 3022, 2335, 1694,1623, 1348, 1316, 1268, 1087, 927, 730; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.2 (s, 1H), 7.95 (d, *J* = 7.7 Hz, 2H), 7.58 (d, *J* = 7.9 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.29 (dd, *J* = 15.7, 8.8 Hz, 10H), 6.30 (d, *J* = 2.1 Hz, 1H), 5.71 (d, *J* = 8.2 Hz, 1H), 5.68 – 5.58 (m, 1H), 4.79 (d, *J* = 11.9 Hz, 1H), 4.77 – 4.65 (m, 2H), 4.61 – 4.51 (m, 2H), 4.25 (s, 1H), 3.63 (ddd, *J* = 35.5, 10.2, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.2, 72.2, 73.4, 80.6, 82.2, 85.8, 90.4, 102.3, 127.7, 127.7, 127.9, 128.0, 128.0, 128.2, 128.5, 128.5, 128.6, 128.6, 128.6, 128.8, 129.9, 129.9, 133.7, 136.9, 137.5, 137.5, 140.4, 150.5, 163.9, 164.0; HRMS (ESI-MS): m/z calcd for $C_{30}H_{28}N_2O_7$ $[M+Na]^+$:551.1794; Found: 551.1794.



1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-α-D-arabinofuranosyl)thymine (**7f**): 166 mg isolated from 200 mg (**1c**) (90% isolated yield); Syrup, $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +17; IR (cm^{-1}, $CHCl_3$): 3029, 2358, 1704,1623, 1356, 1309, 1293, 1127, 935, 742, 578; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 7.99 – 7.93 (m, 2H), 7.64 – 7.58 (m, 1H), 7.48 – 7.42 (m, 3H), 7.36 – 7.26 (m, 10H), 6.36 (d, *J* = 2.1 Hz, 1H), 5.63 (s, 1H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.74 (dt, *J* = 8.2, 4.1 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.62 – 4.54 (m, 2H), 4.26 (s, 1H), 3.68 (dd, *J* = 10.1, 5.9 Hz, 1H), 3.60 (dd, *J* = 10.1, 6.2 Hz, 1H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5, 69.2, 72.2, 73.5, 80.8, 82.5, 85.4, 89.9, 110.9, 127.8, 127.8, 127.9, 127.9, 127.9, 128.2, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.8, 129.9, 129.9, 133.7, 136.2, 136.9, 137.5, 150.5, 164.2, 165.2; HRMS (ESI-MS): m/z calcd for $C_{31}H_{30}N_2O_7$ $[M+H]^+$: 543.2131; Found: 543.2131.

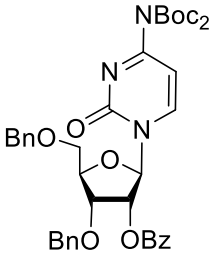


N^4-benzoyl-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)cytosine (**7g**): 148 mg isolated from 150 mg (**1a**) (91% isolated yield); Syrup, $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +81.6; IR (cm^{-1}, $CHCl_3$): 2997, 2850,1746,1547,1255, 1137, 917, 757, 567; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (s, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.08 (d, *J* = 7.7 Hz, 2H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.56 (q, *J* = 7.8 Hz, 2H), 7.48-7.41 (m, 7H), 7.31-7.23 (m, 8H), 6.23 (s, 1H), 5.82 (s, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.46 (d, *J* = 11.3 Hz, 1H), 4.42 (s, 1H), 4.37 (s, 2H), 3.99 (d, *J* = 10.9 Hz, 1H), 3.65 (d, *J* = 10.8 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 67.2, 73.2, 73.6, 74.4, 74.7,

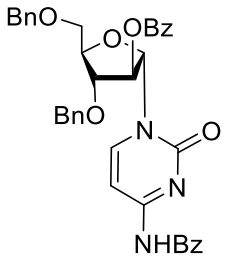


81.7, 89.8, 97.1, 127.8, 128.0, 128.0, 128.0, 128.1, 128.1, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.7, 128.7, 128.9, 128.9, 129.2, 130.0, 130.0, 133.1, 133.5, 137.1, 137.2, 145.1, 155.2, 162.7, 165.3, 165.4; HRMS (ESI-MS): m/z calcd for $C_{37}H_{33}N_3O_7$ $[M+Na]^+$: 654.2216; Found: 654.2223.

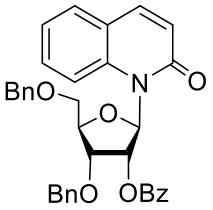
N,*N*-Di-*tert*-butoxycarbonyl-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)cytosine (**7h**): 177 mg isolated from 150 mg (**1a**) (95% isolated yield); White solid, mp (ºC): 113.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +81.6; IR (cm^{-1}, $CHCl_3$): 3054, 2938, 2822,1742, 1735, 1443,1269, 1077, 765, 672; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 7.6 Hz, 1H), 8.15 – 8.05 (m, 2H), 7.61 – 7.53 (m, 1H), 7.46 – 7.31 (m, 5H), 7.35-7.19 (m, 7H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.17 (d, *J* = 1.6 Hz, 1H), 5.72 (dd, *J* = 4.4, 1.6 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.43 – 4.26 (m, 4H), 3.77 (m, 2H), 1.56 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 27.7, 27.7, 27.7, 27.7, 27.7, 67.3, 73.3, 73.5, 74.5, 74.6, 81.6, 84.9, 85.0, 90.2, 96.1,127.9, 128.0, 128.0, 128.2, 128.2, 128.2, 128.4, 128.4, 128.4, 128.5, 128.6, 128.7, 129.5, 129.9, 130.0, 133.3, 137.2, 137.3, 144.2, 149.5, 149.6, 154.1, 162.6, 165.1; HRMS (ESI-MS): m/z calcd for $C_{40}H_{45}N_3O_{10}$ $[M+H]^+$: 728.3183; Found: 728.3185.



N^4-benzoyl-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-α-D-arabinofuranosyl)cytosine (**7i**): 138 mg isolated from 150 mg (**1c**) (88% isolated yield); Syrup, $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -1.6; IR (cm^{-1}, $CHCl_3$): 2991, 2848,1746,1547,1255, 1137, 917, 757, 678; ^1H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 7.98-7.42 (d, *J* = 7.6 Hz, 10H), 7.40-7.23 (m, 12H), 6.32 (s, 1H), 5.68 (s, 1H), 4.80 – 4.75 (m, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.55 – 4.45 (m, 2H), 4.11 (s, 1H), 3.65 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.50 (dd, *J* = 10.0, 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.5, 72.0, 73.5, 80.0, 82.1, 87.3, 92.3, 96.4, 127.5, 127.8, 127.8, 127.8, 128.0, 128.0, 128.0, 128.1, 128.5, 128.5, 128.6, 128.6, 128.6, 128.7, 128.7, 129.0, 129.1, 129.1, 129.9, 129.9, 133.2, 133.7, 136.9, 137.4, 145.0, 154.9, 162.8, 165.1, 165.1; HRMS (ESI-MS): m/z calcd for $C_{37}H_{33}N_3O_7$ $[M+Na]^+$: 654.2216; Found: 654.2216.

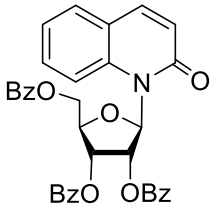


1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-□-D-ribofuranosyl)quinolin-2-one (**9a**): 136 mg isolated from 150 mg (**1a**) (94% isolated yield); Syrup, $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +19.8; IR (cm^{-1}, $CHCl_3$): 3032,

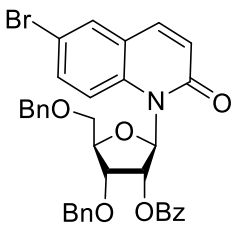


2663, 1716, 1660, 1493, 1447,1268, 1097, 1026; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 9.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.39-7.30 (m, 6H), 7.28 – 7.21 (m, 5H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.73 (s, 1H), 6.61 (d, *J* = 9.5 Hz, 1H), 6.26 (dd, *J* = 5.5, 2.6 Hz, 1H), 4.88 (t, *J* = 7.9 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 8.4 Hz, 3H), 4.37 (t, *J* = 6.5 Hz, 1H), 3.84 (dd, *J* = 10.7, 2.0 Hz, 1H), 3.69 (dd, *J* = 10.7, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.8, 73.3, 73.6, 73.9, 76.7, 81.7, 89.1, 115.2, 121.3, 122.0, 123.0, 127.8, 128.0, 128.0, 128.0, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 129.2, 129.7, 130.0, 130.0, 130.8, 133.5, 137.7, 138.1, 139.1, 140.7, 162.5, 166.0; HRMS (ESI-MS): m/z calcd for $C_{35}H_{31}NO_6$ $[M+Na]^+$: 584.2049; Found: 584.2043.

1-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)quinolin-2-one (**9b**): 108 mg isolated from 150 mg (**1b**) (75% isolated yield); White solid; mp (ºC): 87.2; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -54.6; IR (cm^{-1}, $CHCl_3$): 3045, 2668, 1716, 1704, 1690, 1493, 1447,1258, 1097, 1034, 867; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 – 8.14 (m, 4H), 7.96 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.65 (dd, *J* = 12.7, 9.3 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.54-7.48 (m, 6H), 7.39 – 7.33 (m, 4H), 7.22 (q, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 4.7 Hz, 1H), 6.73 – 6.66 (m, 2H), 6.06 (t, *J* = 5.3 Hz, 1H), 5.19 (q, *J* = 3.9 Hz, 1H), 4.86 – 4.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.0, 79.5, 79.8, 82.2, 89.6, 114.6, 121.5, 122.0, 123.0, 128.6, 128.6, 128.6, 128.6, 128.7, 128.7, 128.9, 129.2, 129.6, 129.8, 130.0, 130.0, 130.0, 130.0, 130.1, 130.1, 130.7, 133.3, 133.7, 133.8, 138.9, 140.9, 163.1, 165.9, 166.1, 166.4; HRMS (ESI-MS): m/z calcd for $C_{35}H_{27}NO_8$ $[M+H]^+$: 590.1815; Found: 590.1823.

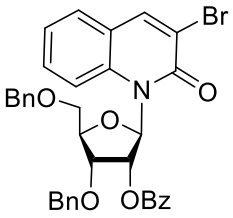


6-Bromo-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)quinolin-2-one (**9c**): 151 mg isolated from 150 mg (**1a**) (92% isolated yield); Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +19.6; IR (cm^{-1}, $CHCl_3$): 3031, 2864, 1720, 1660, 1599, 1560, 1495, 1452, 1093, 947; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.07 (m, 2H), 7.65 – 7.57 (m, 3H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.42 – 7.35 (m, 5H), 7.32-7.28 (m, 4H), 7.27 – 7.23 (m, 1H), 6.83 – 6.73 (m, 1H), 6.66 (d, *J* = 9.5 Hz, 1H), 6.17 – 6.06 (m, 1H), 5.29 (s, 1H), 4.83 (td, *J* = 7.4, 6.9, 2.3 Hz, 1H), 4.71 (dd, *J* = 11.5, 1.8 Hz, 1H), 4.59 – 4.50 (m, 3H), 4.36 (tq, *J* = 4.5, 2.2 Hz, 1H), 3.87 (dt, *J* = 10.8,

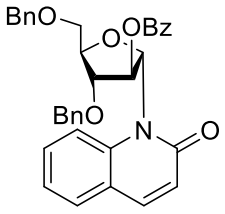


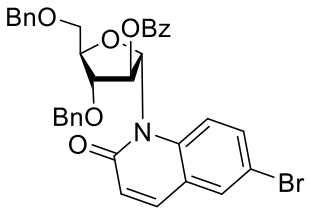
2.2 Hz, 1H), 3.67 (ddd, *J* = 11.0, 4.9, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.3, 72.8, 73.6, 73.8, 76.1, 81.8, 88.5, 115.7, 117.3, 122.8, 123.0, 127.9, 128.0, 128.0, 128.0, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 129.5, 129.9, 129.9, 131.1, 133.3, 133.5, 137.6, 137.6, 137.9, 139.3, 162.1, 166.0; HRMS (ESI-MS): m/z calcd for $C_{35}H_{30}BrNO_6$ $[M+H]^+$: 640.1335; Found: 640.1343.

3-Bromo-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)quinolin-2-one (**9d**): 128 mg isolated from 150 mg (**1a**) (85% isolated yield); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +4.6; IR (cm^{-1}, $CHCl_3$): 3034, 2868, 1720, 1660, 1599, 1560, 1495, 1452, 1089, 942, 737; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 – 8.08 (m, 3H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.48 (dd, *J* = 9.7, 7.9 Hz, 3H), 7.45 – 7.41 (m, 1H), 7.39-7.35 (m, 4H), 7.33 – 7.28 (m, 1H), 7.27-7.22 (m, 6H), 6.61 (d, *J* = 2.8 Hz, 1H), 6.27 (dd, *J* = 6.4, 2.7 Hz, 1H), 4.92 (dd, *J* = 8.3, 6.4 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.59 – 4.54 (m, 3H), 4.41 (ddd, *J* = 8.3, 6.0, 2.2 Hz, 1H), 3.87 (dd, *J* = 10.8, 2.3 Hz, 1H), 3.77 (dd, *J* = 10.8, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.0, 73.5, 73.5, 73.8, 77.1, 81.8, 90.6, 115.1, 117.4, 121.0, 123.5, 127.7, 127.9, 127.9, 127.9, 128.2, 128.2, 128.3, 128.3, 128.4, 128.4, 128.4, 128.5, 128.5, 129.5, 129.9, 129.9, 131.0, 133.4, 137.6, 137.9, 138.6, 142.2, 158.3, 165.9; HRMS (ESI-MS): m/z calcd for $C_{35}H_{30}BrNO_6$ $[M+H]^+$: 640.1335; Found: 640.1340.

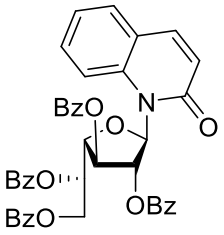


1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-α-D-arabinofuranosyl)quinolin-2-one (**9e**): 132 mg isolated from 150 mg (**1c**) (92% isolated yield); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +33.4; IR (cm^{-1}, $CHCl_3$): 3032, 2663, 1718, 1662, 1498, 1450, 1268, 1097, 1026, 977, 876; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 9.5 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.51 (d, *J* = 9.1 Hz, 1H), 7.43 – 7.31 (m, 12H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 5.5 Hz, 1H), 6.64 (d, *J* = 9.5 Hz, 1H), 6.45 (dd, *J* = 5.5, 3.5 Hz, 1H), 5.24 (s, 1H), 4.88 – 4.81 (m, 2H), 4.71 – 4.63 (m, 3H), 4.62 – 4.59 (m, 1H), 3.86 – 3.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.0, 72.4, 73.8, 79.5, 83.0, 84.2, 88.5, 115.7, 121.5, 121.7, 122.8, 127.9, 128.0, 128.0, 128.0, 128.1, 128.1, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 129.3, 129.3, 130.0, 130.0, 130.5, 133.5, 137.7, 138.0, 138.3, 140.6, 163.0, 165.8; HRMS (ESI-MS): m/z calcd for $C_{35}H_{31}NO_6$ $[M+Na]^+$: 584.2049; Found: 584.2053.





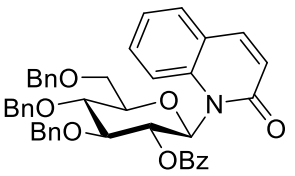
6-Bromo-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-α-D-arabinofuranosyl)quinolin-2-one (**9f**): 146 mg isolated from 150 mg (**1c**) (88% isolated yield); Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +46.4; IR (cm^{-1}, $CHCl_3$): 3034, 2874, 1710, 1668, 1605, 1564, 1495, 1452, 1089, 942, 737, 588; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.7 Hz, 2H), 7.69 (d, *J* = 9.1 Hz, 1H), 7.62 (d, *J* = 2.3 Hz, 1H), 7.57 – 7.30 (m, 15H), 7.05 (d, *J* = 5.5 Hz, 1H), 6.62 (d, *J* = 9.5 Hz, 1H), 6.27 (t, *J* = 4.4 Hz, 1H), 4.79 (d, *J* = 11.8 Hz, 1H), 4.74 (q, *J* = 4.4 Hz, 1H), 4.68 – 4.57 (m, 3H), 4.53 (t, *J* = 3.9 Hz, 1H), 3.75 (qd, *J* = 10.6, 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.8, 72.3, 73.8, 79.4, 82.9, 84.0, 88.5, 115.5, 117.5, 122.9, 123.0, 127.8, 127.9, 127.9, 128.0, 128.0, 128.1, 128.1, 128.5, 128.5, 128.5, 128.5, 128.6, 129.0, 129.9, 129.9, 131.2, 133.1, 133.5, 137.1, 137.4, 137.8, 139.2, 162.4, 165.7; HRMS (ESI-MS): m/z calcd for $C_{35}H_{30}BrNO_6$ $[M+H]^+$: 640.1335; Found: 640.1338.



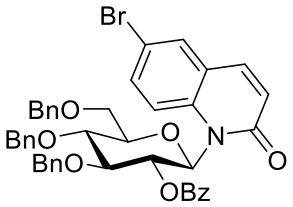
1-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)quinolin-2-one (**9g**): 128 mg isolated from 150 mg (**1m**) (90% isolated yield); White solid; mp (ºC): 94.7; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +37.2; IR (cm^{-1}, $CHCl_3$): 3065, 1722, 1661, 1595, 1493, 1452,1262, 1176, 1025, 988; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.1 Hz, 2H), 8.19 (d, *J* = 7.4 Hz, 2H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.73-7.40 (m, 15H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 2H), 6.70 (d, *J* = 9.5 Hz, 1H), 6.59 (dt, *J* = 5.0, 2.2 Hz, 1H), 6.21 (d, *J* = 11.7 Hz, 1H), 5.97 (d, *J* = 9.2 Hz, 1H), 5.20 – 5.14 (m, 1H), 4.79 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.5, 72.2, 79.2, 80.4, 83.0, 89.5, 115.0, 121.6, 121.8, 123.1, 128.4, 128.4, 128.5, 128.5, 128.6, 128.7, 128.7, 128.7, 128.8, 129.1, 129.3, 129.7, 129.7, 129.8, 129.8, 129.9, 129.9, 130.1, 130.1, 130.4, 130.4, 130.6, 133.2, 133.4, 133.6, 133.8, 138.4, 140.9, 163.1, 165.8, 165.8, 166.1, 166.2; HRMS (ESI-MS): m/z calcd for $C_{43}H_{33}NO_{10}$ $[M+H]^+$: 724.2183; Found: 724.2185.

1-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)quinolin-2-one (**9h**): 165 mg isolated from 200 mg (**1e**) (85% isolated yield); Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +12.2; IR (cm^{-1}, $CHCl_3$): 3030, 2869,1727, 1660, 1594, 1497, 1453, 1361, 1096; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.54 – 7.28 (m, 16H), 7.26 – 7.10 (m, 6H), 7.02 (d, *J* = 9.9 Hz, 2H), 6.44 (d, *J* = 9.4 Hz, 1H), 6.20 (t, *J* = 9.4 Hz, 1H), 4.98 (d, *J* = 10.9 Hz, 1H), 4.80 (dd,

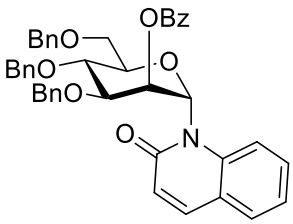
J = 21.0, 11.0 Hz, 2H), 4.73 – 4.61 (m, 2H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.20 (dt, *J* = 46.3, 9.3 Hz, 2H), 3.99 (dd, *J* = 10.9, 2.9 Hz, 1H), 3.87 (dd, *J* = 28.4, 10.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.3, 70.5, 73.4, 75.4, 75.6, 77.5, 78.3, 81.0, 83.9, 117.5, 120.5, 121.3, 123.1, 127.5, 127.5, 127.7, 127.9, 128.1, 128.2, 128.2, 128.2, 128.2, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.7, 129.2, 129.3, 129.9, 129.9, 130.4, 133.3, 137.7, 137.9, 138.1, 138.4, 140.9, 162.7, 165.0; HRMS (ESI-MS): m/z calcd for $C_{43}H_{39}NO_7$ [M+Na]$^+$: 704.2624; Found: 704.2622.



6-Bromo-1-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl) quinolin-2-one (**9i**): 123 mg isolated from 150 mg (**1e**) (76% isolated yield); Syrup; [α]$^{25}_D$ ($CHCl_3$, *c* 1.0): -28.8; IR (cm^{-1}, $CHCl_3$): 3037, 2870,1727, 1660, 1594, 1497, 1453, 1369, 1156, 1099, 747, 598; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 9.7, 5.3 Hz, 1H), 7.88 (t, *J* = 6.7 Hz, 2H), 7.64 – 7.17 (m, 20H), 7.06 – 6.95 (m, 1H), 6.47 (dd, *J* = 9.6, 1.9 Hz, 1H), 6.31 – 5.87 (m, 1H), 5.30 (d, *J* = 2.2 Hz, 1H), 5.01 (dd, *J* = 10.9, 4.5 Hz, 1H), 4.80 (dtd, *J* = 32.5, 10.9, 4.1 Hz, 3H), 4.67 – 4.52 (m, 2H), 4.20 (dtd, *J* = 35.9, 8.8, 4.5 Hz, 2H), 4.05 – 3.81 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.2, 70.4, 73.4, 75.4, 75.5, 77.2, 78.1, 80.8, 83.6, 115.9, 119.2, 121.6, 122.8, 127.5, 127.5, 127.8, 127.8, 128.0, 128.1, 128.1, 128.1, 128.1, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 129.0, 129.8, 129.8, 131.2, 133.1, 133.3, 136.8, 137.6, 138.0, 138.2, 139.5, 162.1, 165.0; HRMS (ESI-MS): m/z calcd for $C_{43}H_{38}BrNO_7$ [M+Na]$^+$: 782.1729; Found: 782.1738.

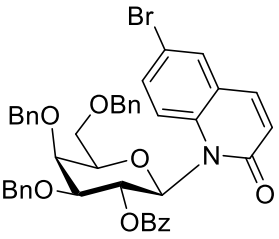


1-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)quinolin-2-one (**9j**): 172 mg isolated from 200 mg (**1g**) (87% isolated yield); Syrup; [α]$^{25}_D$ ($CHCl_3$, *c* 1.0): +11; IR (cm^{-1}, $CHCl_3$): 3031, 2863,1730, 1661, 1599, 1497, 1458, 1363, 1096, 987; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.57 – 7.52 (m, 1H), 7.52 – 7.48 (m, 2H), 7.48 – 7.42 (m, 4H), 7.43 – 7.38 (m, 4H), 7.37 (d, *J* = 3.2 Hz, 1H), 7.35 (s, 3H), 7.33 – 7.27 (m, 2H), 7.26 – 7.17 (m, 5H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 10.6 Hz, 1H), 6.37 (d, *J* = 9.8 Hz, 1H), 4.73 (s, 2H), 4.71 – 4.62 (m, 2H), 4.62 – 4.52 (m, 4H), 4.19 (t, *J* = 8.7 Hz, 1H), 4.05 – 3.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.3, 67.9, 72.0, 73.6, 73.7, 73.9, 74.9, 76.9, 77.0, 117.7, 121.0, 121.3, 122.7, 127.8, 127.9, 127.9, 127.9, 127.9, 128.0, 128.0, 128.0, 128.1, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.7, 128.7, 129.0, 129.4, 130.0, 130.0, 130.3, 133.4, 137.7, 137.8, 138.2,

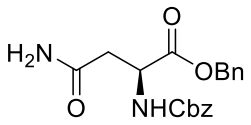


138.3, 140.6, 162.9, 165.3; HRMS (ESI-MS): m/z calcd for $C_{43}H_{39}NO_7$ $[M+Na]^+$: 704.2624; Found: 704.2630.

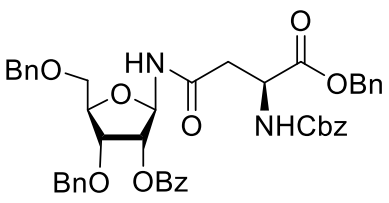
6-Bromo-1-(2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glalactopyranosyl)quinolin-2-one (**9k**): 134 mg isolated from 150 mg (**1i**) (81% isolated yield); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -38.6; IR (cm^{-1}, $CHCl_3$): 3031, 2879,1734, 1642, 1594, 1497, 1453, 1361, 1096, 879; ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 5.1 Hz, 1H), 7.94 – 7.85 (m, 2H), 7.53 (d, *J* = 14.6 Hz, 2H), 7.50 – 7.40 (m, 6H), 7.40 – 7.33 (m, 7H), 7.27 – 7.15 (m, 6H), 6.93 – 6.83 (m, 1H), 6.49 – 6.39 (m, 2H), 5.20 (dd, *J* = 10.6, 3.2 Hz, 1H), 4.77 (dd, *J* = 12.2, 2.1 Hz, 1H), 4.68-4.62 (m, 2H), 4.60 – 4.39 (m, 2H), 4.29 (s, 1H), 4.05 – 3.94 (m, 2H), 3.83 – 3.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.9, 69.1, 72.1, 72.9, 73.8, 75.0, 75.9, 80.7, 80.8, 115.9, 119.9, 121.5, 122.7, 127.7, 127.8, 128.0, 128.1, 128.2, 128.2, 128.2, 128.2, 128.2, 128.2, 128.5, 128.5, 128.6, 128.6, 128.7, 128.7, 128.7, 128.7, 129.4, 129.9, 129.9, 130.9, 133.2, 136.9, 137.6, 137.7, 138.5, 139.7, 162.2, 165.4; HRMS (ESI-MS): m/z calcd for $C_{43}H_{38}BrNO_7$ $[M+Na]^+$: 782.1729; Found: 782.1732.



N-(Benzyloxycarbonyl)-L-asparagine benzyl ester (**10**): White solid; mp (ºC): 134.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -18.4; IR (cm^{-1}, $CHCl_3$): 3162, 1735, 1478, 1432, 1267, 988, 907, 672; ^1H NMR (400 MHz, DMSO-d_6): δ 7.70 (d, *J* = 8.2 Hz, 1H), 7.43 – 7.28 (m, 11H), 6.98 (s, 1H), 5.13 (s, 1H), 5.08 – 5.01 (m, 2H), 4.52 (td, *J* = 7.9, 5.6 Hz, 1H), 2.63 (dd, *J* = 15.6, 5.6 Hz, 1H), 2.52 (dd, *J* = 15.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 46.1, 60.2, 75.0, 75.5, 137.1, 137.1, 137.2, 137.2, 137.3, 137.5, 137.8, 137.8, 137.9, 137.9, 145.4, 146.3, 165.4, 180.3, 181.1; HRMS (ESI-MS): m/z calcd for $C_{19}H_{20}N_2O_5$ $[M+Na]^+$: 379.1270; Found: 379.1281.

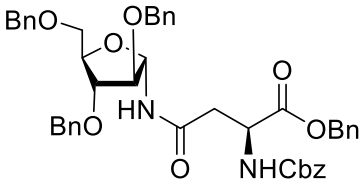


N^2-((Benzyloxycarbonyl))-N^4-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)-L-asparagine benzyl ester (**11a**): 148 mg isolated from 150 mg (**1a**) (75% isolated yield); White solid; mp (°C): 88.1, $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +32.4; IR (cm^{-1}, $CHCl_3$): 3348, 3032, 2931,1721, 1500, 1453,1267, 1211, 1119, 1067, 914; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.35 – 7.23 (m, 20H), 6.77 (d, *J* = 9.6 Hz, 1H), 6.08 (dd, *J* = 9.5, 5.2 Hz, 1H), 5.96 (d, *J* = 8.6 Hz, 1H), 5.39 (t, *J* = 5.0 Hz, 1H), 5.20 – 4.98 (m, 5H), 4.59 – 4.50 (m,

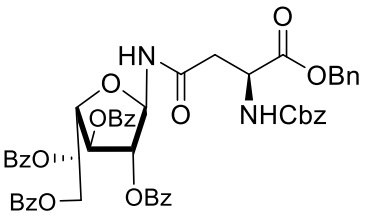


4H), 4.28 (dd, *J* = 8.1, 4.1 Hz, 2H), 3.49 (t, *J* = 3.7 Hz, 2H), 2.99 (dd, *J* = 16.5, 4.5 Hz, 1H), 2.71 (dd, *J* = 16.4, 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.0, 50.7, 67.1, 67.6, 69.8, 71.5, 73.0, 73.7, 77.8, 78.8, 81.6, 127.8, 127.8, 127.9, 127.9, 127.9, 128.0, 128.0, 128.2, 128.2, 128.3, 128.3, 128.4, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.7, 128.7, 129.2, 129.9 , 129.9, 130.2, 133.7, 135.4, 136.2, 137.2, 137.8, 156.3, 165.5, 170.0, 170.8; HRMS (ESI-MS): m/z calcd for $C_{45}H_{44}N_2O_{10}$ $[M+Na]^+$: 795.2894; Found: 795.2901.

N^2-(Benzyloxycarbonyl)-*N*^{4}-(2,3,5-tri-*O*-Benzyl-α-D-arabinofuranosyl)-L-asparagine benzyl ester (**11b**): 145 mg isolated from 150 mg (**1d**) (74% isolated yield); White solid; mp (ºC): 103.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +12.2; IR (cm^{-1}, $CHCl_3$): 3020,1720,1499,1214, 744, 668; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.28 (m, 25H), 6.69 – 6.65 (m, 1H), 6.08 – 6.05 (m, 1H), 5.86 (dd, *J* = 8.8, 4.3 Hz, 1H), 5.20 – 5.10 (m, 4H), 4.66 – 4.56 (m, 3H), 4.54 – 4.44 (m, 4H), 4.14 – 4.12 (m, 1H), 4.08 – 4.03 (m, 2H), 3.64 – 3.53 (m, 2H), 2.67 (dd, *J* = 15.6, 5.6 Hz, 1H), 2.42 (dd, *J* = 15.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.4, 50.6, 66.9, 67.3, 69.8, 72.0, 72.4, 73.6, 79.4, 80.5, 80.9, 82.6, 127.8, 127.8, 127.9, 127.9, 128.0, 128.0, 128.0, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.2, 128.2, 128.2, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 135.6, 136.4, 137.1, 137.5, 137.7, 156.2, 169.7, 171.0; HRMS (ESI-MS): m/z calcd for $C_{45}H_{46}N_2O_9$ $[M+Na]^+$: 759.3282; Found: 759.3280.

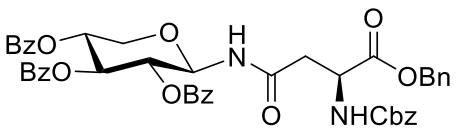


N^2-(Benzyloxycarbonyl)-*N*^{4}-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)-L-asparagine benzyl ester (**11c**): 87 mg isolated from 100 mg (**1m**) (70% isolated yield); Brown solid, mp (ºC): 88; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +11.6; IR (cm^{-1}, $CHCl_3$): 3019, 2868,1726,1243,1269, 1117, 740, 678; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.5 Hz, 2H), 8.02 (d, *J* = 7.5 Hz, 2H), 7.96 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 2H), 7.58-7.51 (m, 4H), 7.42-7.22 (m, 18H), 7.19 (d, *J* = 7.0 Hz, 1H), 6.27 – 6.09 (m, 2H), 6.07 – 5.98 (m, 1H), 5.78 – 5.66 (m, 2H), 5.22 – 5.07 (m, 4H), 4.82 – 4.64 (m, 4H), 2.96 (dd, *J* = 18.4, 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.0, 50.8, 63.5, 67.1, 67.5, 71.3, 78.5, 80.3, 81.3, 84.4, 127.9, 128.0, 128.1, 128.1, 128.3, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5,

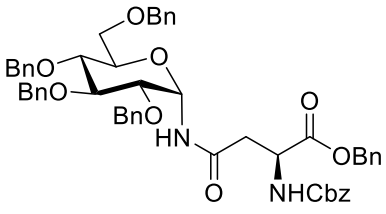


128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.7, 128.7, 129.3, 129.5, 129.7, 129.9, 129.9, 130.0, 133.1, 133.4, 133.5, 133.8, 135.3, 136.2, 156.3, 165.6, 165.7, 165.8, 166.2, 170.1, 170.9; HRMS (ESI-MS): m/z calcd for $C_{53}H_{46}N_2O_{14}$ $[M+H]^+$: 935.3027; Found: 935.3039.

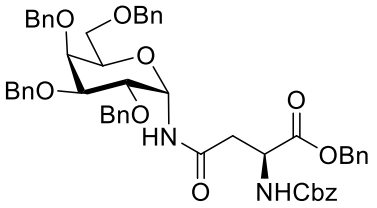
N^2-(Benzyloxycarbonyl)-*N*^{4}-(2,3,4-tri-*O*-Benzoyl-β-D-xylopyranosyl)-L-asparagine benzyl ester (**11d**): 88 mg isolated from 100 mg (**1n**) (68% isolated yield); White solid; mp (ºC): 105.4; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +37.5; IR (cm^{-1}, $CHCl_3$): 3021,1726,1488,1269, 1107, 943, 753, 589; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.7 Hz, 4H), 7.91 (d, *J* = 7.3 Hz, 2H), 7.57 – 7.36 (m, 8H), 7.34 – 7.18 (m, 11H), 6.96 (s, 1H), 6.00 (t, *J* = 9.4 Hz, 2H), 5.48 – 5.30 (m, 3H), 5.09 (s, 2H), 5.03 (d, *J* = 12.3 Hz, 1H), 4.87 (d, *J* = 12.3 Hz, 1H), 4.67 – 4.57 (m, 1H), 4.38 (dd, *J* = 11.5, 5.6 Hz, 1H), 3.68 (t, *J* = 11.0 Hz, 1H), 2.86 (dd, *J* = 16.4, 4.3 Hz, 2H); (100 MHz, $CDCl_3$): δ 37.9, 50.6, 64.8, 67.0, 67.2, 69.8, 71.5, 72.5, 79.2, 128.0, 128.1, 128.2, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.8, 128.9, 129.7, 129.7, 129.8, 129.9, 129.9, 129.9, 130.0, 130.0, 130.1, 133.4, 133.6, 133.8, 135.2, 136.2, 156.1, 165.5, 165.6, 166.9, 170.6, 170.7; HRMS (ESI-MS): m/z calcd for $C_{45}H_{40}N_2O_{12}$ $[M+H]^+$: 801.2659; Found: 801.2661.



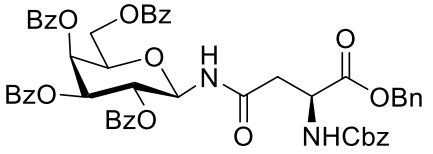
N^2-(Benzyloxycarbonyl)-*N*^{4}-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-L-asparagine benzyl ester (**11e**): 134 mg isolated from 150 mg (**1f**) (72% isolated yield); White solid; mp (ºC): 117.3; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +40.4; IR (cm^{-1}, $CHCl_3$): 3020,1726, 1217, 1065, 741, 668; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.28 (m, 29H), 7.19 – 7.18 (m, 2H), 6.66 (s, 1H), 6.14 (s, 1H), 5.80 (s, 1H), 5.20 (dd, *J* = 10.2, 9.3 Hz, 2H), 5.12 (dd, *J* = 12.0, 10.0 Hz, 2H), 4.96 (d, *J*=10.4, 1H), 4.84 (d, *J*=10.7 Hz, 2H), 4.65 (d, *J*=10.7 Hz, 1H), 4.62 (s, 2H), 4.56 (d, *J*=10.7 Hz, 1H), 4.48 (d, *J*=12.1 Hz, 1H), 3.87 – 3.62 (m, 6H), 3.03 (dd, *J* = 15.6, 5.6 Hz, 1H), 2.85 (dd, *J* = 15.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.1, 51.0, 67.1, 67.6, 68.3, 71.3, 72.7, 73.6, 74.9, 75.0, 75.5, 77.0, 77.6, 81.9, 127.7, 127.8, 127.8, 127.8, 127.9, 128.0, 128.0, 128.0, 128.0, 128.1, 128.1, 128.2, 128.2, 128.2, 128.2, 128.2, 128.3, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 135.3, 136.2, 137.2, 138.0, 138.1, 138.5, 156.3, 170.8, 170.9; HRMS (ESI-MS): m/z calcd for $C_{53}H_{54}N_2O_{10}$ $[M+Na]^+$: 901.3676; Found: 901.3688.



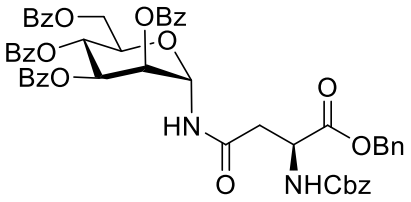
N^2-(Benzyloxycarbonyl)-N^4-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-L-asparagine benzyl ester (**11f**): 140 mg isolated from 150 mg (**1j**) (75% isolated yield); White solid; mp (ºC): 107.9; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +29.8; IR (cm^{-1}, $CHCl_3$): 3018,1722, 1217, 1071, 736, 668; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.12 (m, 31H), 6.59 – 6.58 (m, 1H), 6.12 (s, 1H), 5.78 – 5.77 (m, 1H), 5.19 – 5.04 (m, 4H), 4.82 (d, *J*=11.4, 1H), 4.71 (s, 2H), 4.62 (d, *J*=11.8 Hz, 2H), 4.56 (d, *J*=9.4 Hz, 1H), 4.51 (d, *J*=11.4 Hz, 1H), 4.42 (d, *J*=11.8 Hz, 1H), 4.08 – 3.91 (m, 3H), 3.68 – 3.54 (m, 3H), 2.96 (dd, *J* = 15.6, 5.6 Hz, 1H), 2.72 (dd, *J* = 15.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.0, 51.0, 67.1, 67.6, 67.9, 71.6, 73.0, 73.2, 73.6, 73.9, 74.3, 74.4, 75.2, 77.9, 127.6, 127.6, 127.8, 127.8, 128.1, 128.1, 128.1, 128.1, 128.2, 128.2, 128.2, 128.2, 128.2, 128.2, 128.2, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.7, 128.7, 128.7, 128.7, 128.7, 135.5, 136.3, 137.7, 138.2, 138.4, 138.5, 156.4, 170.8, 171.0; HRMS (ESI-MS): m/z calcd for $C_{53}H_{54}N_2O_{10}$ $[M+Na]^+$: 901.3676; Found: 901.3684.



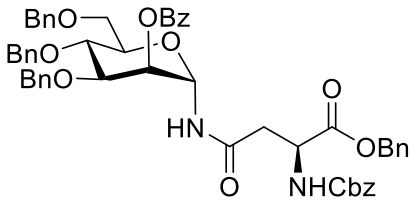
N^2-(Benzyloxycarbonyl)-N^4-(2,3,4,6-tetra-*O*-Benzoyl-β-D-galactopyranosyl)-L-asparagine benzyl ester (**11g**): 160 mg isolated from 200 mg (**1k**) (64% isolated yield); White solid; mp (ºC): 103.2; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +72.2; IR (cm^{-1}, $CHCl_3$): 1726,1498, 1344, 1287, 1125, 943, 741, 676; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 7.8 Hz, 2H), 8.02 (d, *J* = 7.4 Hz, 2H), 7.95 (d, *J* = 7.4 Hz, 2H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.40 (m, 10H), 7.36 – 7.29 (m, 11H), 7.19 – 7.16 (m, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.13 – 6.00 (m, 2H), 5.87 – 5.78 (m, 1H), 5.67 (s, 1H), 5.67 – 5.56 (m, 1H), 5.01 – 4.80 (m, 2H), 4.73 (d, *J* = 9.6 Hz, 1H), 4.63 (dd, *J* = 10.3, 5.7 Hz, 2H), 4.42 (dq, *J* = 17.0, 6.2 Hz, 2H), 3.01 – 2.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9, 50.5, 61.8, 67.0, 67.2, 68.3, 69.5, 71.5, 73.0, 78.9, 128.0, 128.0, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.7, 129.0, 129.0, 129.3, 129.3, 129.7, 129.7, 129.8, 129.8, 129.9, 129.9, 130.0, 130.0, 133.3, 133.4, 133.7, 133.8, 135.2, 136.2, 156.1, 165.4, 165.4, 166.0, 167.0, 170.5, 170.5; HRMS (ESI-MS): m/z calcd for $C_{53}H_{46}N_2O_{14}$ $[M+Na]^+$: 957.2847; Found: 957.2850.



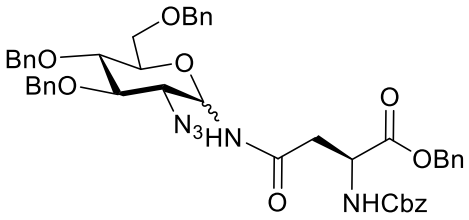
N^2-(Benzyloxycarbonyl)-*N*^{4}-(2,3,4,6-tetra-*O*-Benzoyl-α-D-mannopyranosyl)-L-asparagine benzyl ester (**11h**): 175 mg isolated from 200 mg (**1h**) (70% isolated yield); White crystalline solid; mp (ºC): 92; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -15.6; IR (cm^{-1}, $CHCl_3$): 1726,1510, 1339, 1287, 1115, 949, 742, 676, 597; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 7.7 Hz, 2H), 7.80 (d, *J* = 11.3 Hz, 2H), 7.74 – 7.46 (m, 4H), 7.40-7.34 (m, 5H), 7.32-7.22 (m, 13H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.21 (s, 1H), 6.11 (t, *J* = 8.1 Hz, 1H), 5.98 (s, 2H), 5.83 (s, 1H), 5.26 – 5.05 (m, 4H), 4.80 (s, 1H), 4.72 – 4.53 (m, 2H), 4.50 (s, 1H), 3.17 – 2.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.2, 50.9, 62.7, 66.9, 67.2, 67.5, 69.8, 70.3, 70.6, 76.2, 128.0, 128.0, 128.0, 128.0, 128.1, 128.1, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.7, 129.0, 129.6, 129.6, 129.8, 129.8, 129.8, 129.8, 129.9, 130.0, 130.0, 133.0, 133.4, 133.7, 133.8, 135.3, 136.1, 156.5, 165.1, 165.5, 166.2, 166.5, 170.4, 171.0; HRMS (ESI-MS): m/z calcd for $C_{53}H_{46}N_2O_{14}$ $[M+Na]^+$: 957.2847; Found: 957.2853.



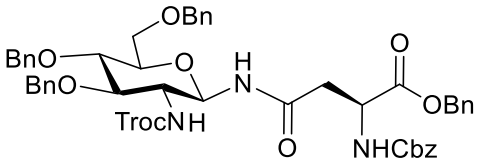
N^2-(Benzyloxycarbonyl)-*N*^{4}-(2-*O*-Benzoyl-3,4,6-tri-*O*-Benzyl-α-D-mannopyranosyl)-L-asparagine benzyl ester (**11i**): 137 mg isolated from 150 mg (**1g**) (73% isolated yield); Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): -3.6; IR (cm^{-1}, $CHCl_3$): 3076, 2931, 2875,1750,1448,1237, 1077, 987, 738; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 6.9 Hz, 2H), 7.63 – 7.55 (m, 1H), 7.48-7.40 (m, 8H), 7.37-7.31 (m, 12H), 7.29-7.25 (m, *J* = 8.9 Hz, 7H), 7.21-7.23 (br-s, 1H), 6.24 – 6.10 (m, 1H), 5.93 – 5.74 (m, 1H), 5.73 – 5.52 (m, 1H), 5.23 – 5.06 (m, 4H), 4.92 – 4.70 (m, 3H), 4.70 – 4.45 (m, 5H), 4.12 – 4.02 (m, 2H), 3.95 – 3.80 (m, 2H), 2.87 (dd, *J* = 67.4, 16.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.1, 50.9, 67.1, 67.6, 68.8, 69.4, 72.1, 73.5, 73.9, 74.1, 74.3, 75.3, 77.0, 127.6, 127.6, 127.6, 127.7, 127.8, 127.9, 128.0, 128.0, 128.1, 128.1, 128.1, 128.2, 128.2, 128.2, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 129.6, 130.0, 130.0, 133.4, 135.3, 136.2, 137.7, 138.0, 138.4, 156.4, 165.9, 170.1, 171.0; HRMS (ESI-MS): m/z calcd for $C_{53}H_{52}N_2O_{11}$ $[M+H]^+$: 893.3649; Found: 893.3660.



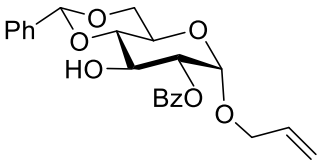
N^2-(Benzyloxycarbonyl)-*N*^{4}-(2-*deoxy*-2-azido-3,4,6-tri-*O*-benzyl α/β-D-glucopyranosyl)-L-asparagine benzyl ester (**11j**): 93 mg isolated from 100 mg (**1o**) (72% isolated yield α/β: 2:1); Syrup; IR (cm^{-1}, $CHCl_3$): 3316, 3031, 2924, 2105,1736,1288, 1212, 1062, 911, 730, 578; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.26 (m, 25H), 7.13 (d, *J* = 3.8 Hz, 1H), 6.61 – 6.45 (m, 1H), 6.05 (d, *J* = 9.3 Hz, 1H), 5.71 (dd, *J* = 7.6, 5.3 Hz, 1H), 5.14 – 5.06 (m, 3H), 4.86 – 4.75 (m, 3H), 4.60 – 4.47 (m, 3H), 4.41 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.81 – 3.56 (m, 6H), 3.50 – 3.30 (m, 1H), 2.99 – 2.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.9, 38.3, 50.7, 50.9, 62.1, 62.1, 65.4, 67.0, 67.2, 67.6, 68.0, 68.1, 72.0, 73.6, 73.6, 73.6, 74.9, 75.0, 75.4, 75.5, 75.7, 76.7, 77.5, 78.3, 81.3, 84.1, 127.8, 127.8, 127.8, 127.8, 127.8, 127.9, 127.9, 127.9, 128.0, 128.0, 128.0, 128.0, 128.0, 128.0, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.1, 128.2, 128.2, 128.2, 128.2, 128.2, 128.2, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 135.2, 135.3, 136.1, 136.2, 137.5, 137.6, 137.6, 137.8, 137.8, 137.9, 156.3, 156.3, 170.2, 170.5, 170.7, 170.8 (α/β isomers); HRMS (ESI-MS): m/z calcd for $C_{46}H_{47}N_5O_9$ $[M+H]^+$: 814.3452; Found: 814.3460.



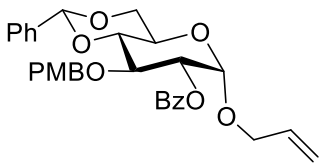
N^2-(Benzyloxycarbonyl)-*N*^{4}-(2-*deoxy*-2-(((2,2,2-trichloroethoxy)carbonyl)amino)-3,4,6-tri-*O*-benzyl β-D-glucopyranosyl)-L-asparagine benzyl ester (**11k**): 145 mg isolated from 150 mg (**1p**) (78% isolated yield); Syrup, $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +25.2; IR (cm^{-1}, $CHCl_3$): 3302, 3032, 2918, 1709, 1666, 1537, 1453,1266,1062; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 3H), 7.34 – 7.26 (m, 22H), 7.18 (d, *J* = 2.7 Hz, 1H), 5.99 (d, *J* = 8.9 Hz, 1H), 5.14 – 5.04 (m, 4H), 4.84 (d, *J* = 11.8 Hz, 1H), 4.78 - 4.72 (m, 3H), 4.68 – 4.55 (m, 5H), 4.49 – 4.41 (m, 2H), 3.81 – 3.68 (m, 3H), 3.61 – 3.53 (m, 1H), 3.49 – 3.31 (m, 2H), 2.75 (ddd, *J* = 71.5, 16.5, 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.8, 50.6, 55.6, 67.1, 67.3, 68.0, 73.7, 74.6, 74.8, 75.1, 76.6, 78.4, 80.1, 80.1, 95.4, 127.9, 128.1, 128.1, 128.1, 128.1, 128.2, 128.2, 128.2, 128.2, 128.3, 128.3, 128.5, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.6, 128.7, 128.7, 129.0, 129.1, 135.6, 136.3, 137.5, 137.7, 137.8, 156.0, 156.2, 170.7, 170.9; HRMS (ESI-MS): m/z calcd for $C_{49}H_{50}Cl_3N_3O_{11}$ $[M+H]^+$: 962.2589; Found: 962.2990.



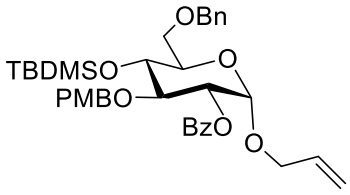
Allyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**SI1**): syrup $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +111.4; IR (cm^{-1}, $CHCl_3$): 2867,1716,1453, 1358, 1272, 1152, 1095, 1030, 578; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.59 – 7.55 (m, 1H), 7.53 – 7.49 (m, 2H), 7.47 – 7.42 (m, 2H), 7.42 – 7.38 (m, 1H), 7.36 (q, *J* = 2.9 Hz, 2H), 5.86 – 5.76 (m, 1H), 5.55 (s, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.21 (d, *J* = 3.8 Hz, 1H), 5.14 (dq, *J* = 10.5, 1.3 Hz, 1H), 5.05 (dd, *J* = 9.7, 3.8 Hz, 1H), 4.37 (t, *J* = 9.5 Hz, 1H), 4.30 (dd, *J* = 10.2, 4.9 Hz, 1H), 4.19 (ddt, *J* = 13.2, 5.1, 1.5 Hz, 1H), 4.02 – 3.97 (m, 1H), 3.97 – 3.93 (m, 1H), 3.77 (t, *J* = 10.3 Hz, 1H), 3.61 (t, *J* = 9.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.4, 68.8, 68.9, 69.0, 74.1, 81.6, 96.0, 102.1, 117.8, 126.4, 126.4, 128.5, 128.5, 128.5, 128.6, 129.4, 129.6, 130.0, 130.0, 133.5, 133.5, 137.1, 166.3; HRMS (ESI-MS): m/z calcd for $C_{23}H_{24}O_7$ $[M+H]^+$: 413.1600 Found: 413.1610.



Allyl 2-*O*-benzoyl-3-O-(4-methoxybenzyl)-4,6-*O*-benzylidene-α-D-glucopyranoside (**SI2**): Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +101.2; IR (cm^{-1}, $CHCl_3$): 2925,1719,1612, 1513, 1452, 1271, 1177, 1095, 1036; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 – 8.01 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.43 – 7.38 (m, 3H), 7.19 – 7.13 (m, 2H), 6.74 – 6.66 (m, 2H), 5.80 (ddt, *J* = 16.3, 10.8, 5.5 Hz, 1H), 5.62 (s, 1H), 5.25 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.20 (d, *J* = 3.9 Hz, 1H), 5.14 – 5.09 (m, 2H), 4.84 – 4.68 (m, 2H), 4.32 (dd, *J* = 10.2, 4.9 Hz, 1H), 4.25 – 4.20 (m, 1H), 4.20 – 4.15 (m, 1H), 4.03 – 3.95 (m, 2H), 3.83 – 3.77 (m, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 62.7, 68.8, 69.0, 73.5, 74.6, 75.6, 82.3, 96.2, 101.4, 113.7, 113.7, 117.8, 126.2, 126.2, 128.4, 128.4, 128.5, 128.5, 129.1, 129.7, 129.7, 129.8, 130.0, 130.0, 130.5, 133.4, 133.5, 137.5, 159.2, 166.0; HRMS (ESI-MS): m/z calcd for $C_{31}H_{32}O_8$ $[M+H]^+$: 533.2175 Found: 533.2175.

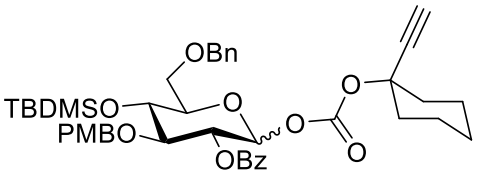


Allyl 2-*O*-benzoyl-3-*O*-(4-methoxybenzyl)-4-*O*-(*t*butyldimethylsilyl)-6-*O*-benzyl-α-D-glucopyranoside (**SI3**): Syrup; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +152.2; IR (cm^{-1}, $CHCl_3$): 2928, 2856, 1722, 1613, 1585, 1514, 1452, 1359,1331,1250, 995; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 – 7.97 (m, 2H), 7.56 – 7.51 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.37 – 7.30 (m, 4H), 7.28 (dd, *J* = 5.8, 3.0 Hz, 1H), 7.08 – 7.03 (m, 2H), 6.68 – 6.63 (m, 2H), 5.89 – 5.79 (m, 1H), 5.26 (dt, *J* = 17.1, 1.7 Hz, 1H), 5.16 (d, *J* = 3.8 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.73 (d, *J* = 10.7 Hz, 1H), 4.66 (d, *J* = 2.1 Hz,

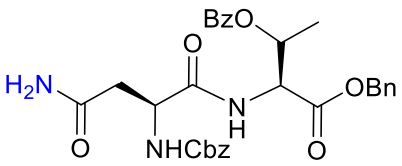


1H), 4.63 (d, *J* = 3.5 Hz, 1H), 4.54 (d, *J* = 12.3 Hz, 1H), 4.22 (ddt, *J* = 13.4, 5.0, 1.6 Hz, 1H), 4.04 – 3.97 (m, 2H), 3.87 (ddd, *J* = 9.9, 5.4, 2.1 Hz, 1H), 3.77 – 3.73 (m, 1H), 3.71 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.69 (s, 3H), 3.66 (dd, *J* = 10.6, 5.5 Hz, 1H), 0.85 (s, 9H), 0.00 (d, *J* = 4.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.7, -3.6, 18.1, 26.1, 26.1, 26.4, 55.2, 68.4, 69.2, 71.2, 71.9, 73.4, 74.5, 74.8, 80.2, 95.4, 113.5, 113.6, 117.3, 127.6, 127.6, 128.4, 128.4, 128.5, 128.5, 129.0, 129.0, 129.8, 129.8, 129.9, 130.6, 133.2, 133.9, 137.2, 138.3, 158.8, 165.9; HRMS (ESI-MS): m/z calcd for $C_{37}H_{48}O_8Si$ $[M+Na]^+$: 671.3016 Found: 671.3014.

1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)- 2-*O*-benzoyl-3-*O*-(4-methoxybenzyl)-4-*O*-(^{t}butyldimethylsilyl)-6-*O*-benzyl-αβ-D-glucopyranoside (**12** α/β: 2:1); Syrup, IR (cm^{-1}, $CHCl_3$): 2928, 2856, 1764, 1732, 1611, 1513, 1454, 1363,1337,1243,1026, 912; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.90 (m, 2H), 7.55 – 7.25 (m, 8H), 7.06 – 7.01 (m, 2H), 6.67 – 6.60 (m, 2H), 6.39 – 5.66 (m, 1H), 5.37 – 5.27 (m, 1H), 4.75 – 4.50 (m, 4H), 4.02 – 3.82 (m, 1H), 3.82 – 3.59 (m, 7H), 2.35 (d, *J* = 8.1 Hz, 1H), 2.09 – 1.74 (m, 3H), 1.68 – 1.35 (m, 7H), 0.84 (d, *J* = 6.0 Hz, 9H), 0.00 (d, *J* = 5.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.9, -4.7, -3.7, -3.6, 18.1, 18.1, 22.2, 22.4, 22.7, 22.7, 24.9, 25.0, 26.0, 26.0, 26.0, 26.0, 26.0, 26.1, 36.3, 36.7, 36.7, 36.8, 55.2, 55.2, 68.5, 68.8, 70.4, 70.7, 73.0, 73.1, 73.5, 73.5, 74.7, 74.8, 74.9, 75.2, 77.8, 77.9, 78.3, 78.5, 82.4, 82.5, 82.6, 82.7, 93.5, 95.5, 113.5, 113.5, 113.6, 113.6, 127.6, 127.7, 127.7, 127.7, 127.7, 127.7, 127.8, 127.8, 128.3, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 129.0, 129.0, 129.4, 129.4, 129.5, 129.6, 129.9, 130.0, 130.0, 130.0, 133.2, 133.2, 138.1, 138.2, 151.1, 151.2, 158.9, 159.0, 165.1, 165.4 (α□β isomers); HRMS (ESI-MS): m/z calcd for $C_{43}H_{54}O_{10}Si$ $[M+Na]^+$: 781.3384 Found: 781.3390.

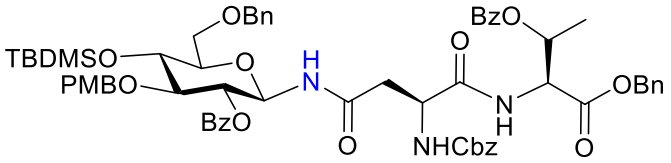


CbzNT(OBz)Bn Dipeptide (**13**): mp (ºC): 170.0; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -5.7; IR (cm^{-1}, $CHCl_3$): 3200, 3055, 2940, 1730, 1410, 1230, 1017, 933, 712; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (d, *J* = 8.9 Hz, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 8.07 – 8.00 (m, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.56 – 7.44 (m, 3H), 7.41 (s, 1H), 7.35 – 7.29 (m, 5H), 7.26 – 7.14 (m, 5H), 7.00 (s, 1H), 5.56 (qd, *J* = 6.3, 3.0 Hz, 1H), 5.09 (dd, *J* = 28.1, 12.6 Hz, 2H), 4.99 (d, *J* = 5.6 Hz, 1H), 4.86 (dd, *J* = 9.0, 2.9 Hz, 1H), 3.68 (d, *J* = 6.1 Hz, 1H), 2.60 (dd, *J* = 15.8, 5.6 Hz, 1H), 2.52 – 2.48 (m, 1H),1.29 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.9, 37.5,

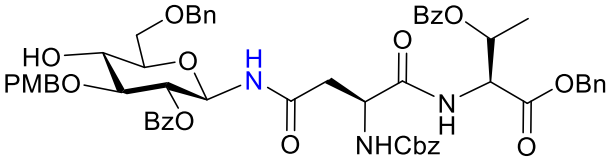


43.9, 49.8, 55.8, 65.9, 66.9, 71.0, 128.1, 128.1, 128.1, 128.2, 128.4, 128.7, 128.7, 128.8, 128.8, 129.0, 129.8, 130.1, 130.1, 133.9, 136.0, 137.4, 156.9, 165.2, 169.7, 169.7, 172.0, 172.4; HRMS (ESI-MS): m/z calcd for $C_{30}H_{31}N_3O_8$ $[M+Na]^+$: 584.2009; Found: 584.2017.

Compound **14**: Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +166.5; IR (cm^{-1}, $CHCl_3$): 3436, 2929, 2857,1723, 1611, 1514, 1456,1362, 1077, 996, 927; ^1H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.7 Hz, 2H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 6.8 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.35 – 7.26 (m, 14H), 7.20 (s, 1H), 7.01 (d, *J* = 8.2 Hz, 2H), 6.65 (d, *J* = 8.1 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H), 5.56 (d, *J* = 6.9 Hz, 1H), 5.24 (t, *J* = 9.1 Hz, 1H), 5.14 (t, *J* = 9.3 Hz, 1H), 5.08 – 5.03 (m, 3H), 4.66 (s, 2H), 4.57 (q, *J* = 8.5, 5.0 Hz, 2H), 4.50 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 9.3 Hz, 1H), 3.80 (t, *J* = 8.8 Hz, 1H), 3.77 – 3.65 (m, 5H), 3.61 – 3.54 (m, 2H), 3.43 – 3.33 (m, 1H), 2.72 (dd, *J* = 15.3, 3.2 Hz, 1H), 2.47 (dd, *J* = 16.1, 6.3 Hz, 1H), 1.14 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (151MHz, $CDCl_3$) δ -4.9, -3.7, 16.7, 18.0, 25.9, 25.9, 26.0, 37.2, 51.1, 55.1, 55.7, 67.1, 67.5, 68.5, 70.6, 70.9, 73.3, 73.8, 74.8, 78.0, 78.1, 83.6, 113.5, 113.5, 127.6, 127.6, 127.6, 127.7, 128.0, 128.0, 128.0, 128.2, 128.3, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.6, 128.9, 128.9, 128.9, 129.0, 129.3, 129.7, 129.8, 129.9, 130.0, 130.0, 133.1, 133.4, 135.1, 136.1, 138.0, 156.2, 158.9, 165.1, 166.7, 169.0, 171.0, 172.0; HRMS (ESI-MS): m/z calcd for $C_{64}H_{73}N_3O_{15}Si$ $[M+Na]^+$: 1174.4709 Found: 1174.4716.

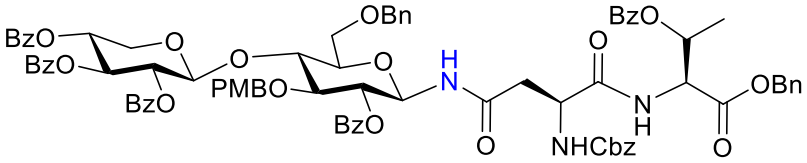


Compound **15**: syrup, $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +80.4; IR (cm^{-1}, $CHCl_3$): 3438, 2929, 2860,1728, 1614, 1514, 1367, 1078, 996, ,678; ^1H NMR (600 MHz, $CDCl_3$) δ 8.1-7.92 (m, 4H), 7.56 – 7.49 (m, 3H), 7.40-7.36 (m, 4H), 7.33 – 7.21 (m, 14H), 7.2 (m,1H), 7.12 – 7.07 (m, 2H), 6.77 (t, *J* = 6.8 Hz, 1H), 6.74 – 6.64 (m, 2H), 6.41 (d, *J* = 8.1 Hz, 1H), 5.61 – 5.42 (m, 1H), 5.20 (t, *J* = 9.1 Hz, 1H), 5.10 – 5.03 (m, 2H), 5.03 – 5.00 (m, 2H), 4.73 – 4.63 (m, 2H), 4.55 (t, *J* = 9.5 Hz, 2H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.42 – 4.36 (m, 1H), 3.80 (t, *J* = 9.3 Hz, 1H), 3.72 (s, 3H), 3.68 – 3.59 (m, 2H), 3.49 – 3.41 (m, 1H), 2.88 – 2.77 (m, 1H), 2.70 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.50 (dd, *J* = 16.0, 6.2 Hz, 1H), 1.88 (d, *J* = 15.2 Hz, 2H), 1.08 (d, *J* = 6.5 Hz, 3H).; ^{13}C NMR (151 MHz,

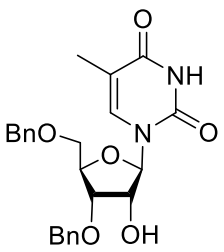


$CDCl_3$) δ 16.6, 37.0, 51.2, 55.2, 55.7, 67.1, 67.5, 69.5, 71.0, 71.8, 73.0, 73.7, 74.7, 75.6, 78.3, 82.0, 113.9, 114.0, 127.8, 127.8, 127.8, 127.9, 128.0, 128.0, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.7, 128.8, 129.0, 129.4, 129.7, 129.7, 129.7, 129.7, 129.9, 129.9, 130.0, 130.1, 133.2, 133.5, 135.1, 136.1, 137.6, 156.3, 159.4, 165.1, 166.8, 169.1, 171.0, 172.0.HRMS (ESI-MS): m/z calcd for $C_{58}H_{59}N_3O_{15}$ $[M+Na]^+$: 1060.3844 Found: 1060.3846.

Compound **16**: Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +8.4; IR (cm^{-1}, $CHCl_3$): 3494, 3346, 2928, 1727,1453,1265, 1096, 1069, 918 ; ^1H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.8 Hz, 2H), 7.98 – 7.90 (m, 8H), 7.65 – 7.54 (m, 4H), 7.50 (dd, *J* = 17.3, 7.7 Hz, 4H), 7.47 – 7.44 (m, 6H), 7.36 - 7.25 (m, 17H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 7.9 Hz, 1H), 5.65 (dd, *J* = 10.6, 8.0 Hz, 1H), 5.60 – 5.54 (m, 1H), 5.45 (dd, *J* = 9.6, 7.5 Hz, 1H), 5.35 (dt, *J* = 9.4, 4.8 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 5.09 – 4.93 (m, 6H), 4.90 (d, *J* = 10.3 Hz, 1H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.68 (dd, *J* = 11.1, 9.0 Hz, 2H), 4.63 – 4.59 (m, 1H), 4.47 (d, *J* = 9.4 Hz, 1H), 4.34 (d, *J* = 11.9 Hz, 1H), 4.29 (dd, *J* = 11.8, 5.4 Hz, 1H), 4.17 (t, *J* = 9.4 Hz, 1H), 3.76 (s, 3H), 3.55 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.32 (d, *J* = 10.8 Hz, 1H), 3.26 (dd, *J* = 11.9, 9.8 Hz, 1H), 3.05 (d, *J* = 9.9 Hz, 1H), 2.72 (dd, *J* = 16.2, 3.8 Hz, 1H), 2.39 (dd, *J* = 16.3, 6.7 Hz, 1H), 1.15 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 16.8, 37.3, 50.9, 55.2, 55.8, 62.5, 67.1, 67.1, 67.5, 70.0, 70.8, 71.8, 72.2, 72.7, 73.6, 75.2, 75.9, 76.0, 78.2, 80.2, 100.5, 113.7, 113.7, 128.0, 128.0, 128.1, 128.2, 128.2, 128.3, 128.3, 128.3, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 128.6, 128.6, 128.7, 128.7, 128.8, 128.8, 129.0, 129.1, 129.2, 129.6, 129.9, 130.0, 130.0, 130.1, 130.1, 133.0, 133.3, 133.4, 133.5, 133.6, 135.1, 136.1, 137.7, 156.1, 159.3, 164.9, 165.0, 165.5, 165.6, 166.7, 169.0, 170.9, 172.0; HRMS (ESI-MS): m/z calcd for $C_{84}H_{79}N_3O_{22}$ $[M+Na]^+$: 1504.5053 Found: 1504.5056.

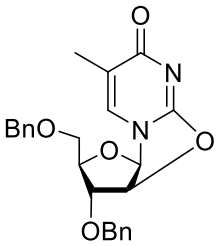


1-(3,5-di-*O*-benzyl-β-D-ribofuranosyl)thymine (**17**): $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): -13.8; IR (cm^{-1}, $CHCl_3$): 3264, 2938, 2860,1746,1447,1269, 1077, 911, 730, 578; ^1H NMR (400 MHz, $CDCl_3$): δ 10.11 (s, 1H), 7.59 (s, 1H), 7.40-7.34 (m, 5H), 7.35 – 7.30 (m, 3H), 7.30 – 7.26 (m, 2H), 6.03 (d, *J* = 4.0 Hz, 1H), 4.79 (dd, *J* = 12.0, 2.1 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.60 – 4.49 (m,

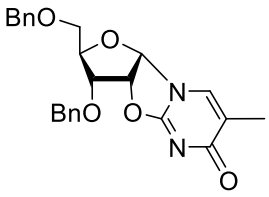


2H), 4.39 (t, *J* = 4.6 Hz, 1H), 4.32 (dt, *J* = 4.9, 2.3 Hz, 1H), 4.16 (t, *J* = 5.0 Hz, 1H), 3.87 (dd, *J* = 10.9, 2.4 Hz, 1H), 3.60 (dd, *J* = 10.8, 2.2 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0, 69.2, 72.5, 73.6, 74.0, 76.6, 81.5, 89.8, 110.9, 127.7, 127.7, 128.0, 128.0, 128.0, 128.1, 128.5, 128.5, 128.6, 128.6, 135.8, 137.4, 137.4, 151.1, 164.2; HRMS (ESI-MS): m/z calcd for $C_{24}H_{26}N_2O_6$ $[M+Na]^+$: 461.1689; Found: 461.1692.

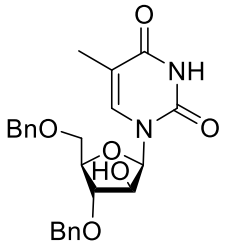
2,2'-Anhydro-1-(3,5-di-*O*-benzyl-β-D-arabinofuranosyl)thymine (**18a**): (90% isolated yield); $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +76.4; IR (cm^{-1}, $CHCl_3$): 3020, 2344, 1704, 1360, 1305, 1298, 1122, 935, 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 8H), 7.24 – 7.13 (m, 3H), 6.21 (d, *J* = 5.9 Hz, 1H), 5.29 (d, *J* = 5.9 Hz, 1H), 4.67 – 4.55 (m, 2H), 4.46 – 4.36 (m, 2H), 4.29 (d, *J* = 12.4 Hz, 2H), 3.30 (qd, *J* = 10.4, 4.2 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 68.8, 72.4, 73.6, 83.7, 85.8, 86.3, 90.8, 119.0, 128.0, 128.0, 128.0, 128.2, 128.2, 128.4, 128.5, 128.5, 128.7, 128.7, 130.3, 136.2, 136.9, 159.7, 172.6; HRMS (ESI-MS): m/z calcd for $C_{24}H_{24}N_2O_5$ $[M+H]^+$: 421.1763; Found: 421.1766.



2,2'-Anhydro-1-(3,5-di-*O*-benzyl-α-D-ribofuranosyl)thymine (**18b**): (82% isolated yield); Syrup; $[\alpha]^{25}_D$ (MeOH, *c* 1.0): -30.9; IR (cm^{-1}, MeOH): 3024, 2338,1706,1447,1269, 1077, 911, 730,; ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.64 (s, 1H), 7.37 – 7.20 (m, 10H), 6.25 (d, *J* = 5.3 Hz, 1H), 5.41 (t, *J* = 5.3 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.56 – 4.44 (m, 2H), 4.17 (dd, *J* = 8.8, 5.3 Hz, 1H), 3.86 (ddd, *J* = 8.8, 4.4, 2.1 Hz, 1H), 3.74 (dd, *J* = 11.5, 2.2 Hz, 1H), 3.61 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.33 (p, *J* = 1.6 Hz, 1H), 1.94 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, Methanol-d_4): δ 12.5, 67.6, 72.4, 73.1, 76.7, 78.8, 79.8, 90.2, 118.1, 127.5, 127.6, 127.6, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.2, 132.8, 137.2, 137.8, 161.0, 174.0; HRMS (ESI-MS): m/z calcd for $C_{24}H_{24}N_2O_5$ $[M+H]^+$: 421.1763; Found: 421.1763.

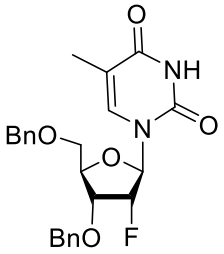


1-(3,5-di-*O*-benzyl-β-D-arabinofuranosyl)thymine (**19**):147 mg isolated from 150 mg (**17**) (quantitative yield); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +110; IR (cm^{-1}, $CHCl_3$): 3267, 2942, 2864,174650,1447,1269, 1077, 911, 733, 578; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.61 (s, 1H), 7.53 (s, 1H), 7.42-7.36 (m, 10H), 6.20 (d, *J* = 3.9 Hz, 1H), 4.92 – 4.76 (m, 2H), 4.67 (d, *J* = 18.4 Hz, 2H), 4.60 (d, *J* = 11.9 Hz, 2H), 4.22 (q, *J* = 4.2 Hz, 1H), 4.05 (dd, *J* = 3.8, 2.2 Hz, 1H), 3.80 (dd, *J* = 10.5,

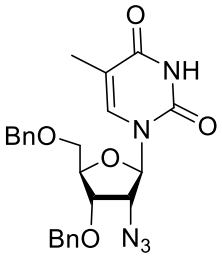


3.7 Hz, 1H), 3.73 (dd, *J* = 10.6, 4.8 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 69.6, 71.8, 73.5, 73.7, 81.5, 83.6, 86.7, 108.4, 127.9, 127.9, 127.9, 128.0, 128.0, 128.1, 128.5, 128.5, 128.6, 128.6, 137.4, 137.5, 138.6, 150.8, 165.3; HRMS (ESI-MS): m/z calcd for $C_{24}H_{26}N_2O_6$ $[M+Na]^+$: 461.1689; Found: 461.1695.

1-(2-*deoxy*-2-fluoro-3,5-di-*O*-benzyl-β-D-ribofuranosyl)thymine (**21**): 91 mg isolated from 100 mg (**17**) (92% isolated yield); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +40.6; IR (cm^{-1}, $CHCl_3$): 2938, 2833,1760,1486,1273, 1077, 921, 736; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.54 (s, 1H), 7.37 – 7.21 (m, 10H), 6.05 (d, *J* = 18.0 Hz, 1H), 5.12-4.96 (m, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.57 – 4.47 (m, 3H), 4.29 (d, *J* = 6.9 Hz, 1H), 4.21 (ddd, *J* = 14.5, 7.6, 3.7 Hz, 1H), 3.93 (dd, *J* = 11.1, 1.6 Hz, 1H), 3.66 (dd, *J* = 11.1, 2.2 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.0, 68.0, 72.9, 73.7, 74.6, 74.7, 81.1, 88.4, 88.7, 90.7, 92.6, 111.0, 127.9, 127.9, 128.0, 128.0, 128.3, 128.4, 128.7, 128.7, 128.7, 128.7, 135.8, 137.1, 137.3, 150.0, 163.6; HRMS (ESI-MS): m/z calcd for $C_{24}H_{25}FN_2O_5$ $[M+H]^+$: 441.1826; Found: 441.1827.

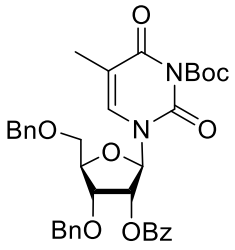


1-(2-*deoxy*-2-azido-3,5-di-*O*-benzyl-β-D-ribofuranosyl)thymine (**22**): 95 mg isolated from 100 mg (**17**) (90% isolated yield) syrup, $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +1.8; IR (cm^{-1}, $CHCl_3$): 2938, 2833, 2098, 1766,1486,1279, 1077, 921, 736, 681; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.53 (d, *J* = 1.4 Hz, 1H), 7.40-7.32 (m, 8H), 7.25 (s, 1H), 7.24 – 7.20 (m, 2H), 6.06 (d, *J* = 5.0 Hz, 1H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.55 – 4.49 (m, 2H), 4.27 – 4.22 (m, 2H), 3.85 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.55 (dd, *J* = 11.0, 1.8 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2, 64.4, 68.8, 73.1, 73.8, 77.4, 82.0, 87.1, 111.1, 127.8, 127.8, 128.0, 128.0, 128.4, 128.5, 128.8, 128.8, 128.8, 128.8, 135.1, 136.8, 137.1, 150.1, 163.3; HRMS (ESI-MS): m/z calcd for $C_{24}H_{25}N_5O_5$ $[M+H]^+$: 464.1934; Found: 464.1930.

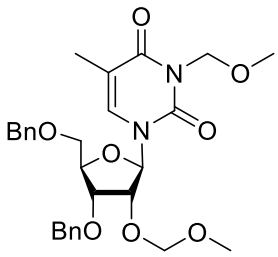


3-*tert*-Butoxycarbonyl-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)thymine (**23**): (95% isolated yield); Colourless solid; mp (ºC): 97; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +32.8; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.3 Hz, 2H), 7.63 – 7.55 (m, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.32 (dd, *J* =

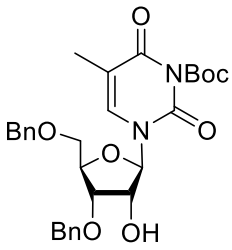
11.2, 6.2 Hz, 3H), 7.24 (dd, *J* = 6.9, 2.9 Hz, 7H), 6.28 (d, *J* = 3.7 Hz, 1H), 5.61 (t, *J* = 4.3 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.56 – 4.43 (m, 3H), 4.39 (t, *J* = 5.4 Hz, 1H), 4.29 (d, *J* = 5.9 Hz, 1H), 3.90 (d, *J* = 12.9 Hz, 1H), 3.59 (d, *J* = 12.8 Hz, 1H), 1.57 (s, 9H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 27.5, 27.5, 27.5, 68.5, 73.3, 73.7, 74.9, 75.7, 82.2, 86.8, 88.0, 110.8, 127.8, 127.8, 128.1, 128.1, 128.2, 128.2, 128.5, 128.5, 128.6, 128.6, 128.8, 128.8, 129.2, 130.1, 130.1, 133.6, 135.1, 137.3, 137.3, 147.9, 148.5, 161.4, 165.6; HRMS (ESI-MS): m/z calcd for $C_{36}H_{38}N_2O_9$ $[M+Na]^+$: 665.2475; Found: 665.2487.



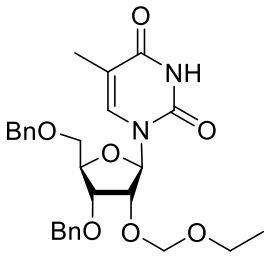
3-methoxymethyl-1-(2-*O*-*m*ethoxymethyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)thymine (**SI4**): 90% isolated yield; Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +78.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.35 – 7.30 (m, 8H), 7.22 (dd, *J* = 7.4, 2.1 Hz, 2H), 5.99 (d, *J* = 2.2 Hz, 1H), 5.40 – 5.33 (m, 2H), 5.01 (d, *J* = 6.7 Hz, 1H), 4.79 – 4.72 (m, 2H), 4.55 – 4.48 (m, 3H), 4.33 – 4.29 (m, 2H), 4.14 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.96 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.66 (dd, *J* = 11.1, 2.0 Hz, 1H), 3.42 (d, *J* = 3.0 Hz, 6H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6, 56.1, 57.8, 68.0, 72.0, 72.4, 73.6, 74.7, 77.2, 81.1, 89.4, 95.9, 109.8, 127.7, 127.7, 127.7, 127.7, 128.1, 128.1, 128.5, 128.5, 128.6, 128.6, 134.5, 137.3, 137.4, 150.9, 163.5; HRMS (ESI-MS): m/z calcd for $C_{28}H_{34}N_2O_8$ $[M+H]^+$: 527.2393; Found: 527.2402.



3-*tert*-Butoxycarbonyl-1-(3,5-di-*O*-benzyl-β-D-ribofuranosyl)thymine (**SI5**): (Quantitative yield); Syrup; $[\alpha]^{25}_D$ ($CHCl_3$, *c* 1.0): +43.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 1.3 Hz, 1H), 7.44-7.32 (m, 8H), 7.27 (dd, *J* = 7.8, 1.9 Hz, 2H), 5.97 (d, *J* = 4.7 Hz, 1H), 4.69 – 4.60 (m, 2H), 4.58 – 4.51 (m, 2H), 4.34 – 4.29 (m, 1H), 4.27 (dt, *J* = 4.5, 2.3 Hz, 1H), 4.16 (t, *J* = 4.8 Hz, 1H), 3.86 (dd, *J* = 10.7, 2.5 Hz, 1H), 3.58 (dd, *J* = 10.8, 2.2 Hz, 1H), 2.99 (s, 1H), 1.61 (s, 9H), 1.57 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 27.3, 27.4, 27.5, 69.3, 72.8, 73.7, 73.9, 77.2, 81.3, 86.7, 89.7, 110.6, 127.6, 127.6, 128.0, 128.0, 128.2, 128.5, 128.7, 128.7, 128.7, 128.7, 135.1, 136.7, 137.2, 147.9, 148.8, 161.3; HRMS (ESI-MS): m/z calcd for $C_{29}H_{34}N_2O_8$ $[M+Na]^+$: 561.2213; Found: 561.2219.

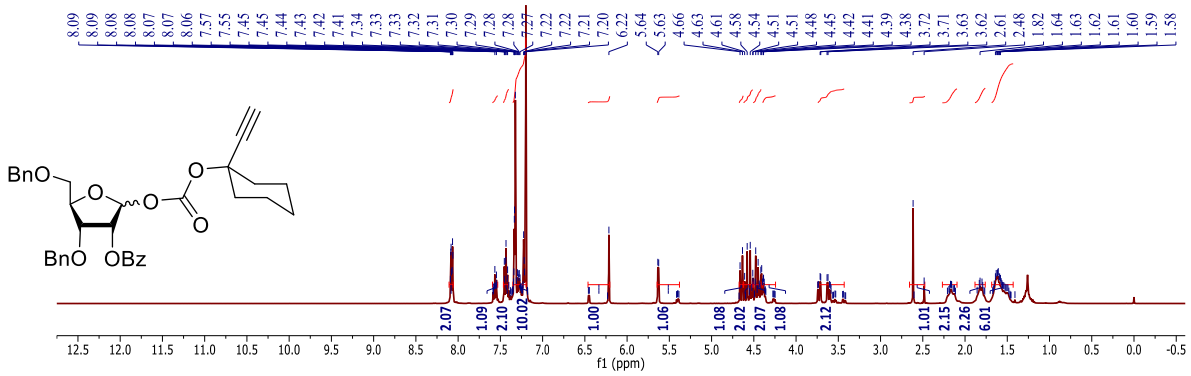


1-(2-*O*-ethoxymethyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)thymine (**24**): $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +91.9; IR (cm^{-1}, $CHCl_3$): 3274, 2908, 2865,1746, 1714, 1454,1269, 1077, 918, 841; ^1H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.69 (d, *J* = 1.4 Hz, 1H), 7.37 – 7.23 (m, 10H), 5.97 (d, *J* = 2.0 Hz, 1H), 4.73 (d, *J* = 11.8 Hz, 1H), 4.59 – 4.49 (m, 3H), 4.31 (dt, *J* = 7.6, 2.1 Hz, 1H), 4.12 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.05 (dd, *J* = 4.9, 2.1 Hz, 1H), 3.95 (ddd, *J* = 11.5, 5.8, 2.0 Hz, 2H), 3.83 (ddd, *J* = 11.3, 5.9, 3.7 Hz, 1H), 3.67 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.59 (dt, *J* = 5.0, 3.4 Hz, 2H), 3.36 (s, 3H), 1.46 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9, 59.0, 68.0, 69.8, 72.2, 72.3, 73.6, 74.5, 81.2, 81.3, 88.5, 110.3, 127.7, 127.7, 127.9, 127.9, 128.0, 128.1, 128.5, 128.5, 128.6, 128.6, 135.9, 137.4, 137.5, 150.1, 163.9; HRMS (ESI-MS): m/z calcd for $C_{27}H_{32}N_2O_7$ $[M+H]^+$: 497.2288; Found: 497.2288.

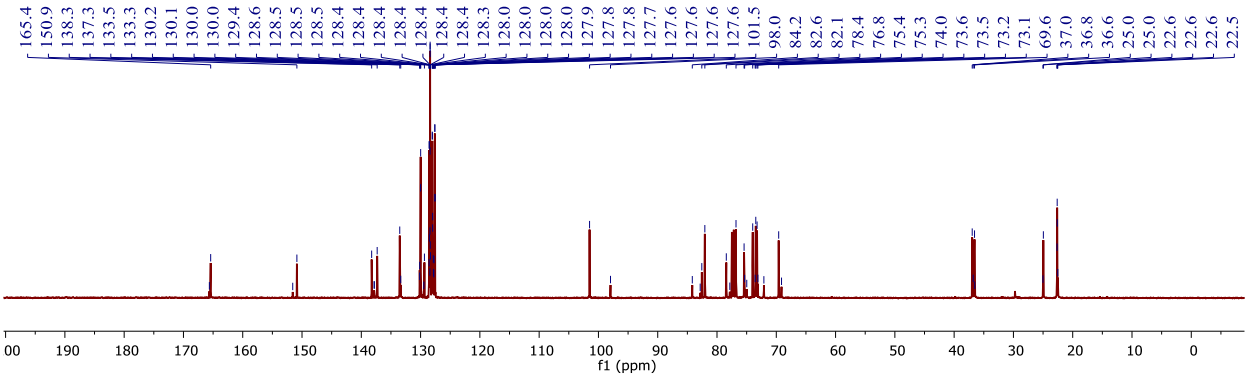


3.8. NMR Spectral Chart:

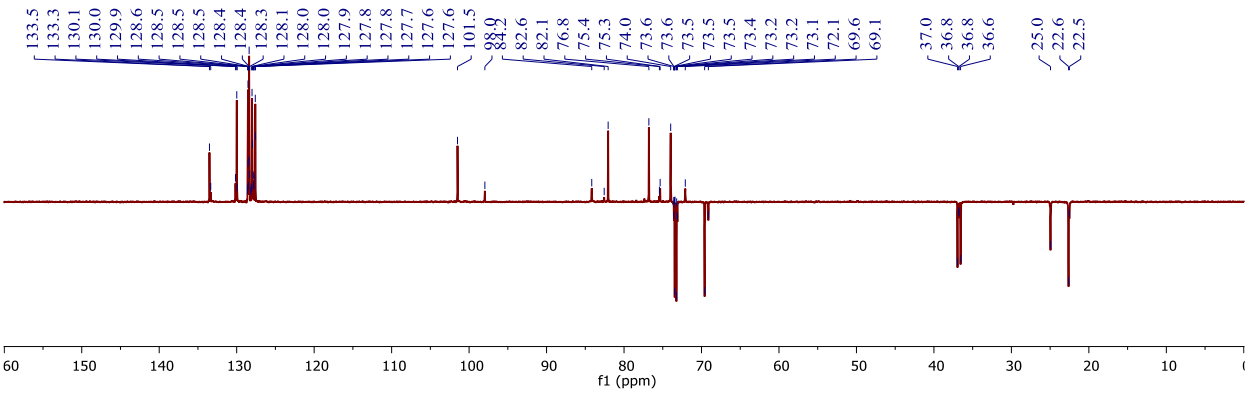
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **1a**



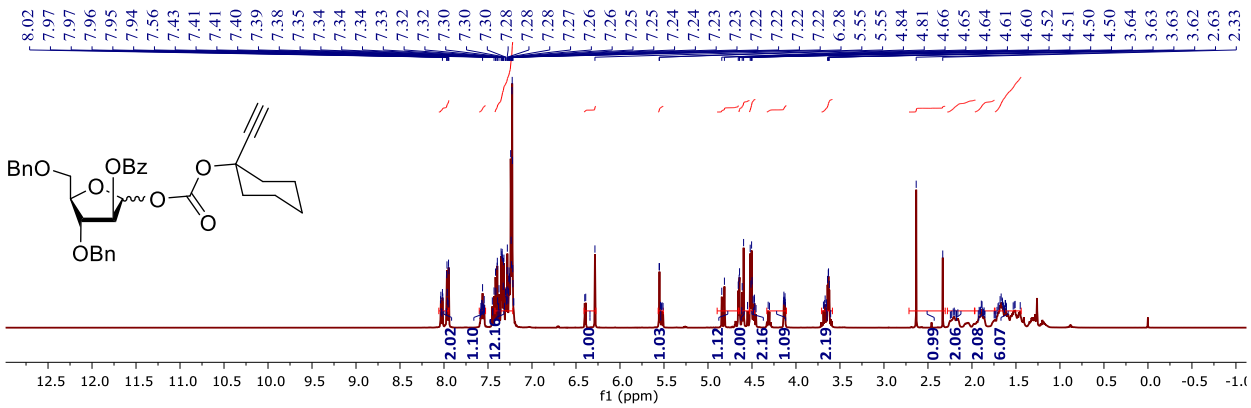
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1a**



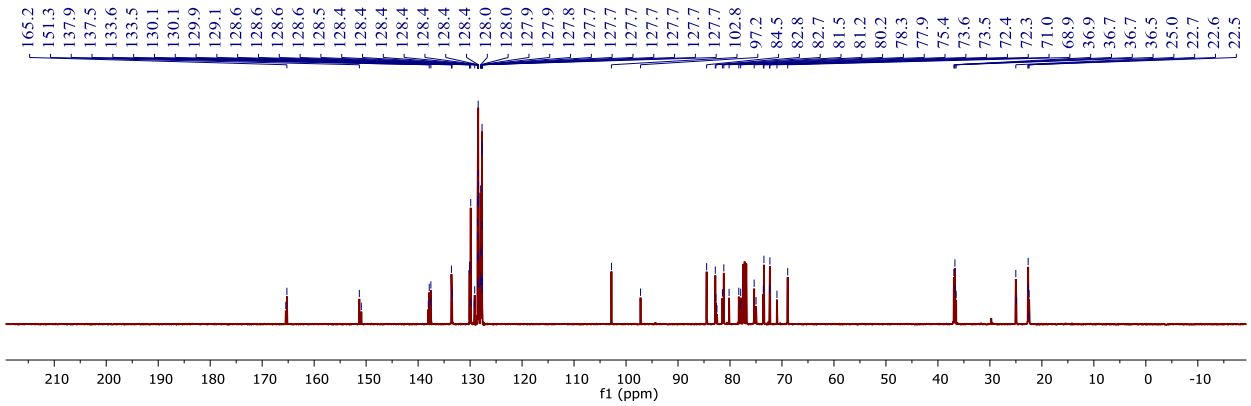
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1a**



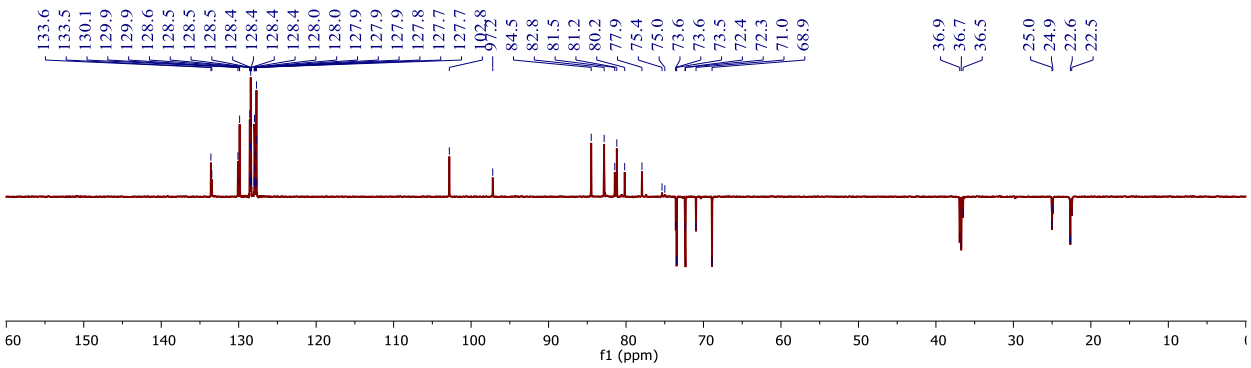
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **1c**



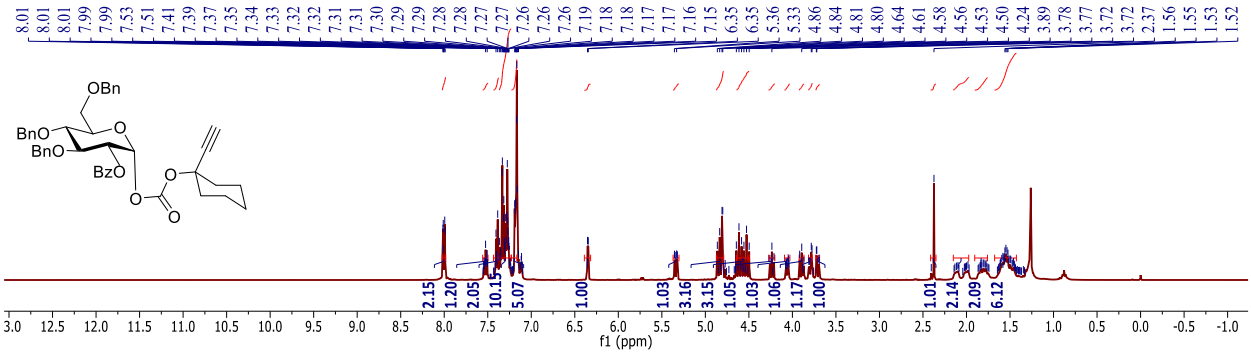
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1c**



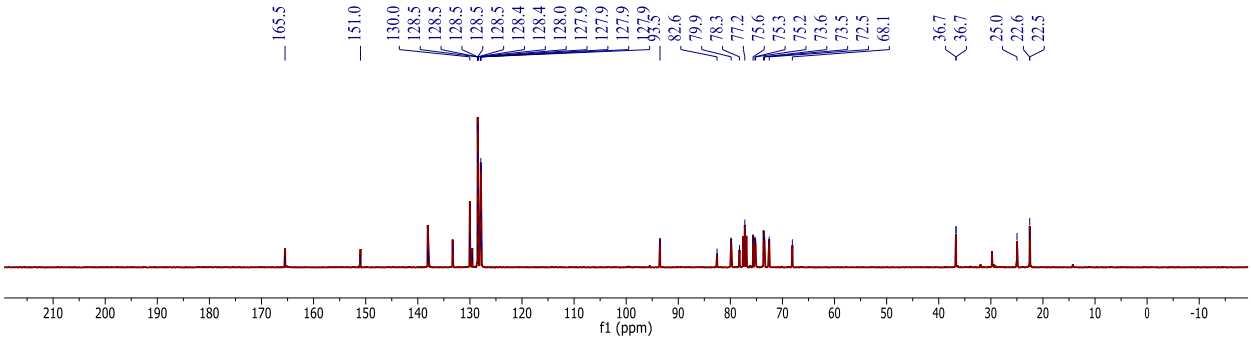
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1c**



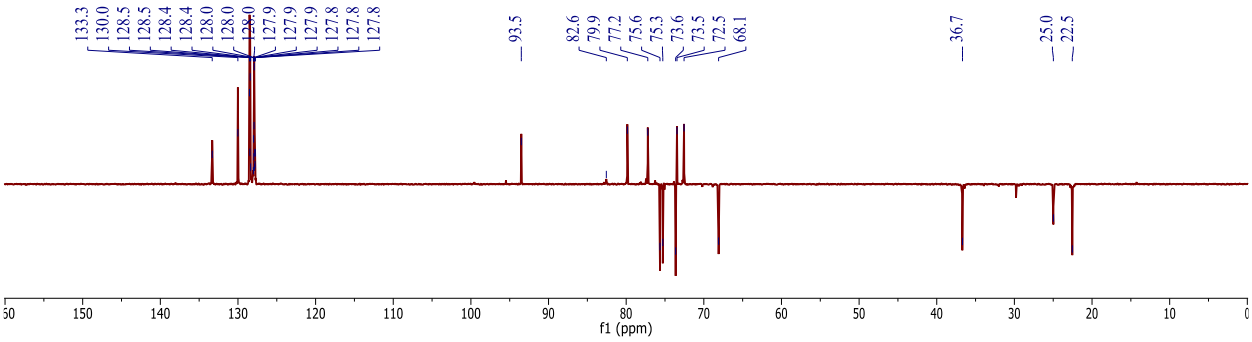
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **1e**



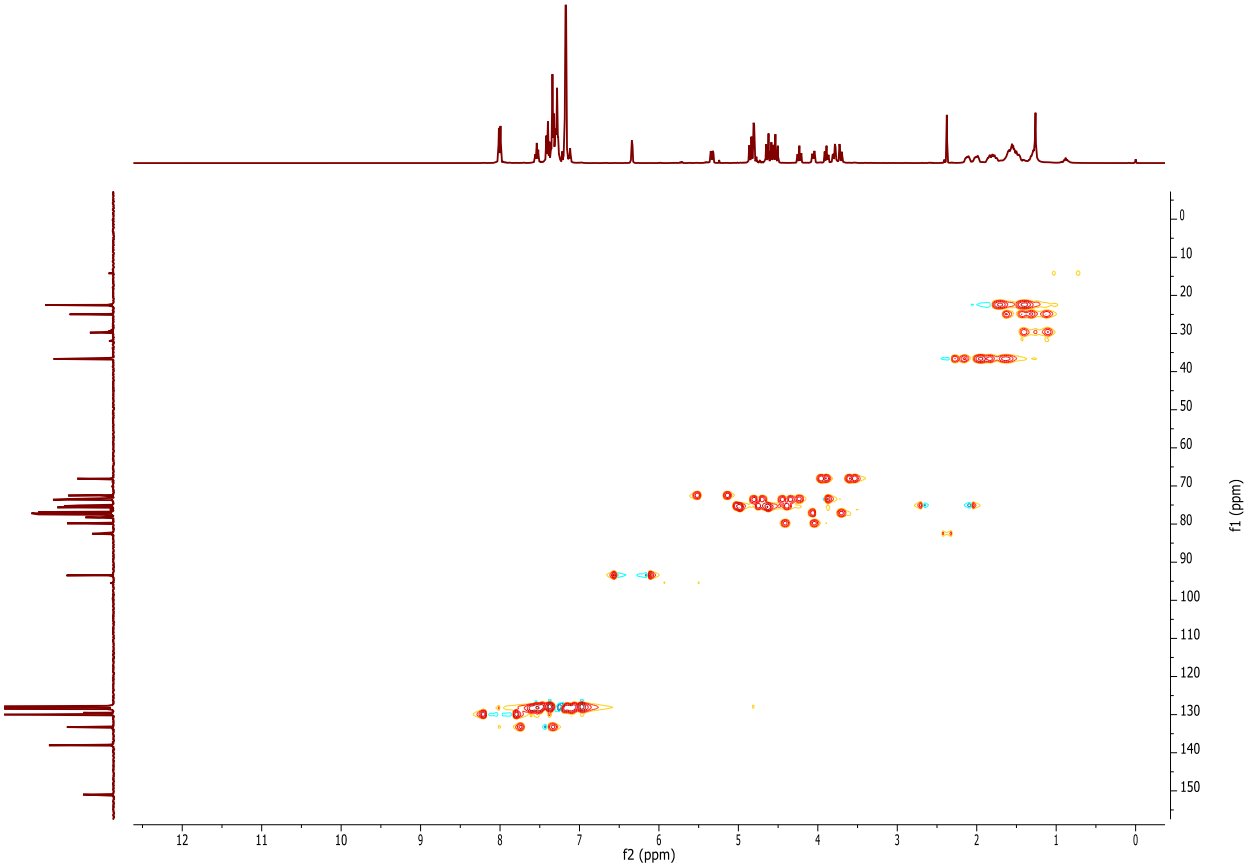
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1e**



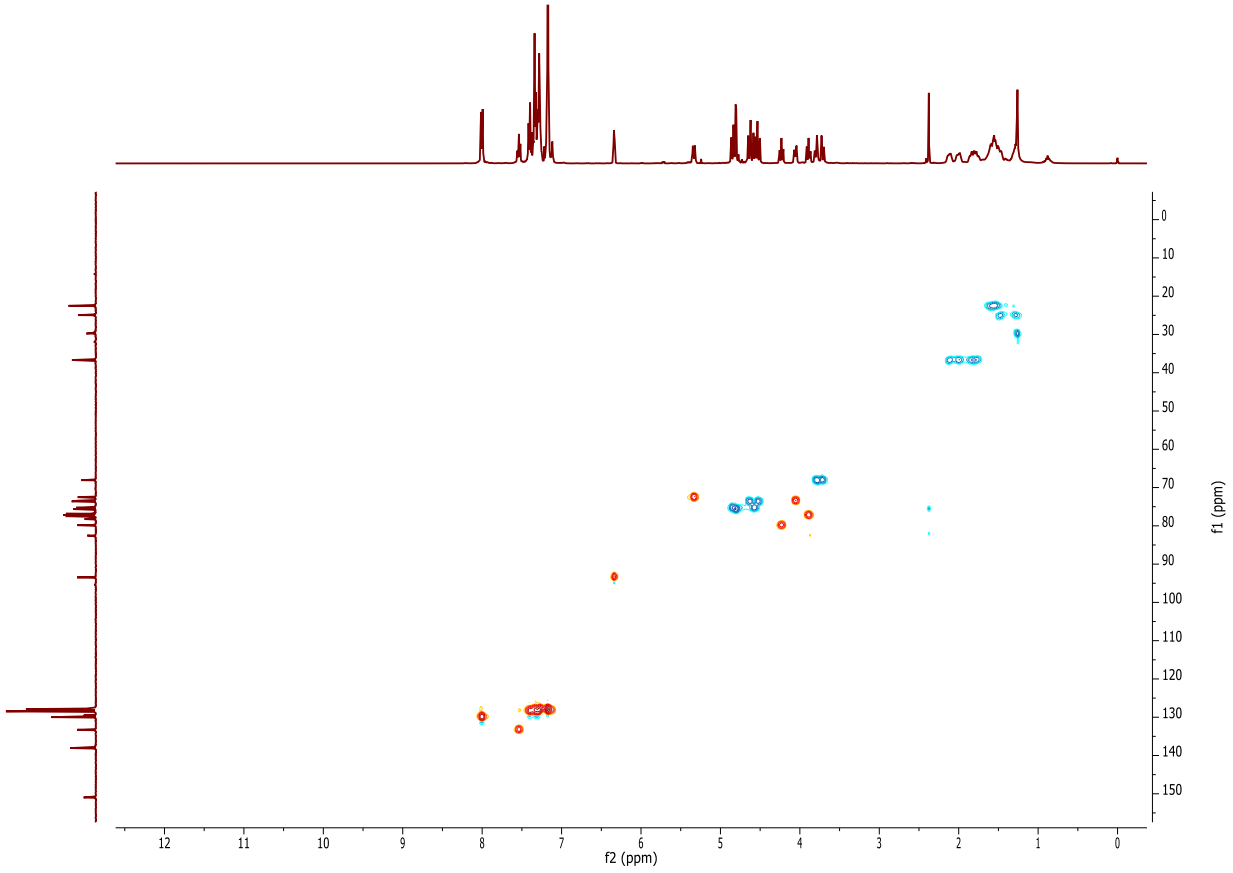
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1e**



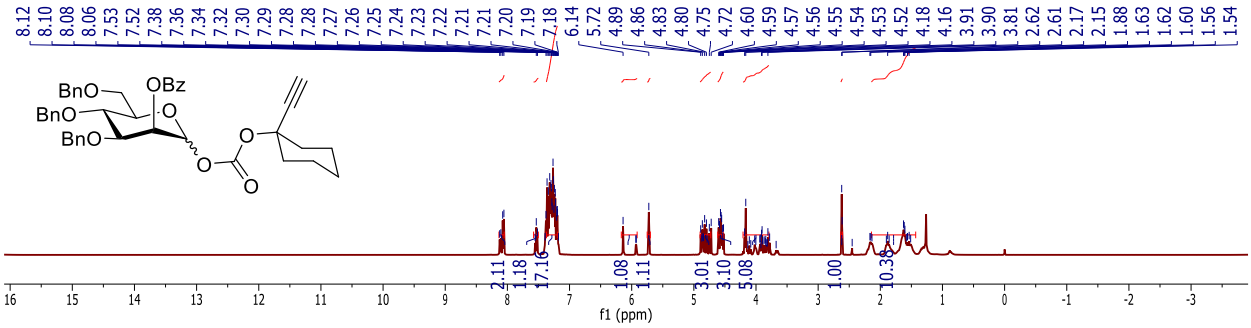
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **1e**



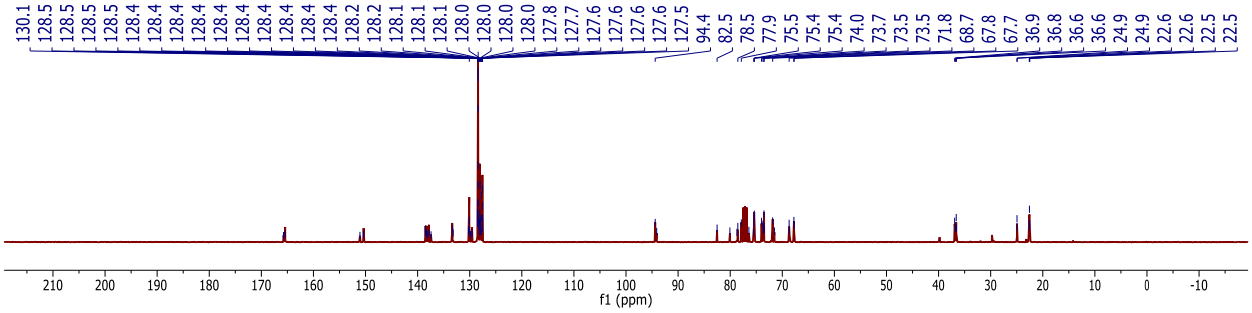
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **1e**



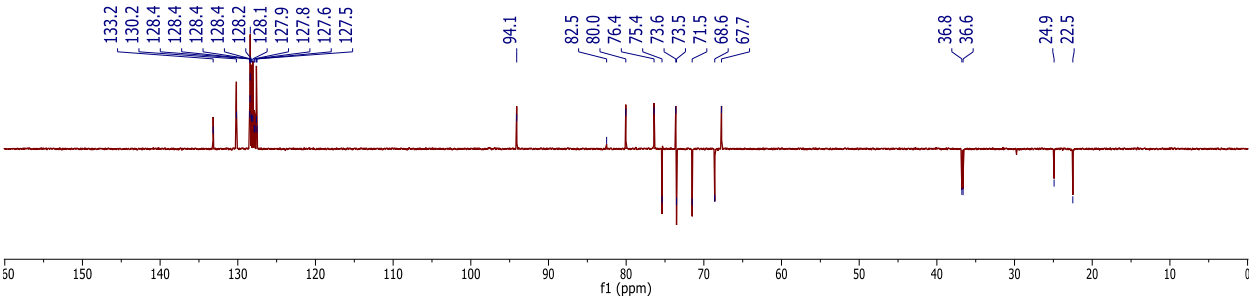
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **1g**



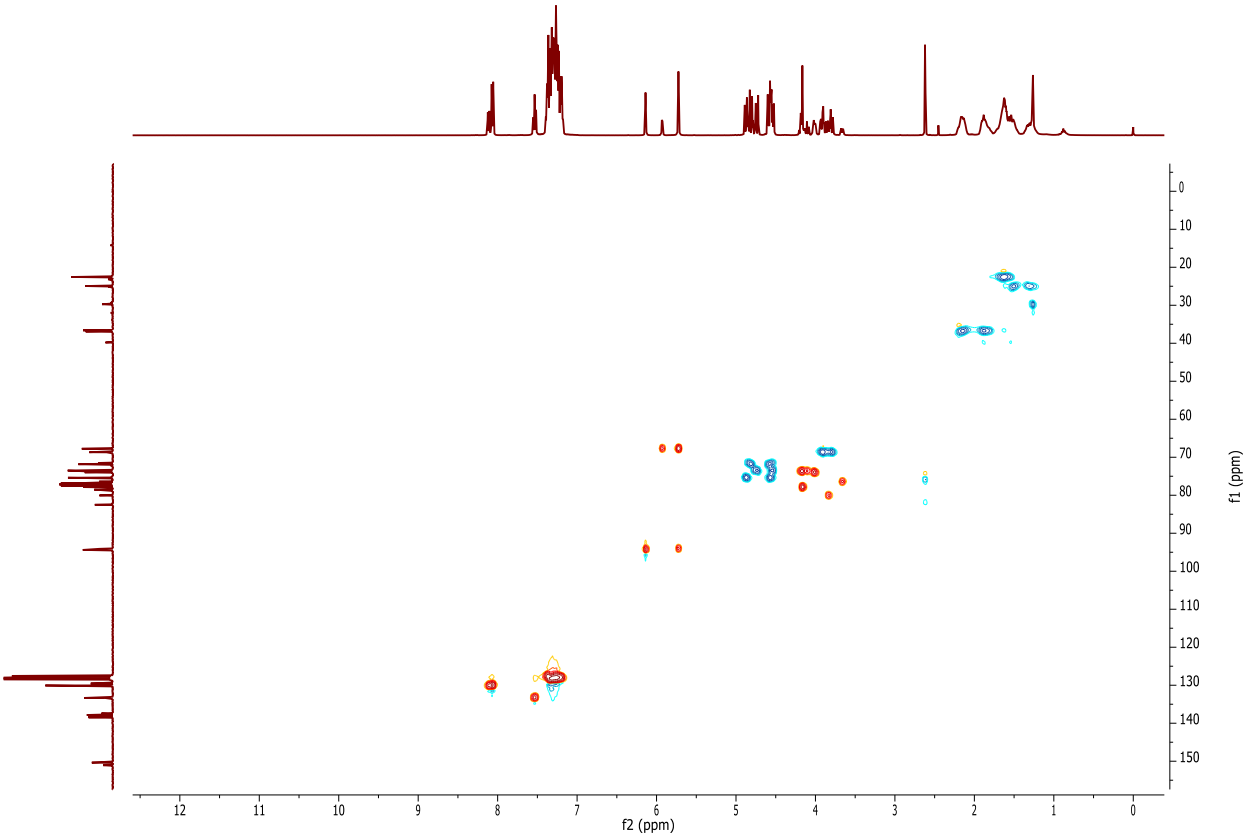
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1g**



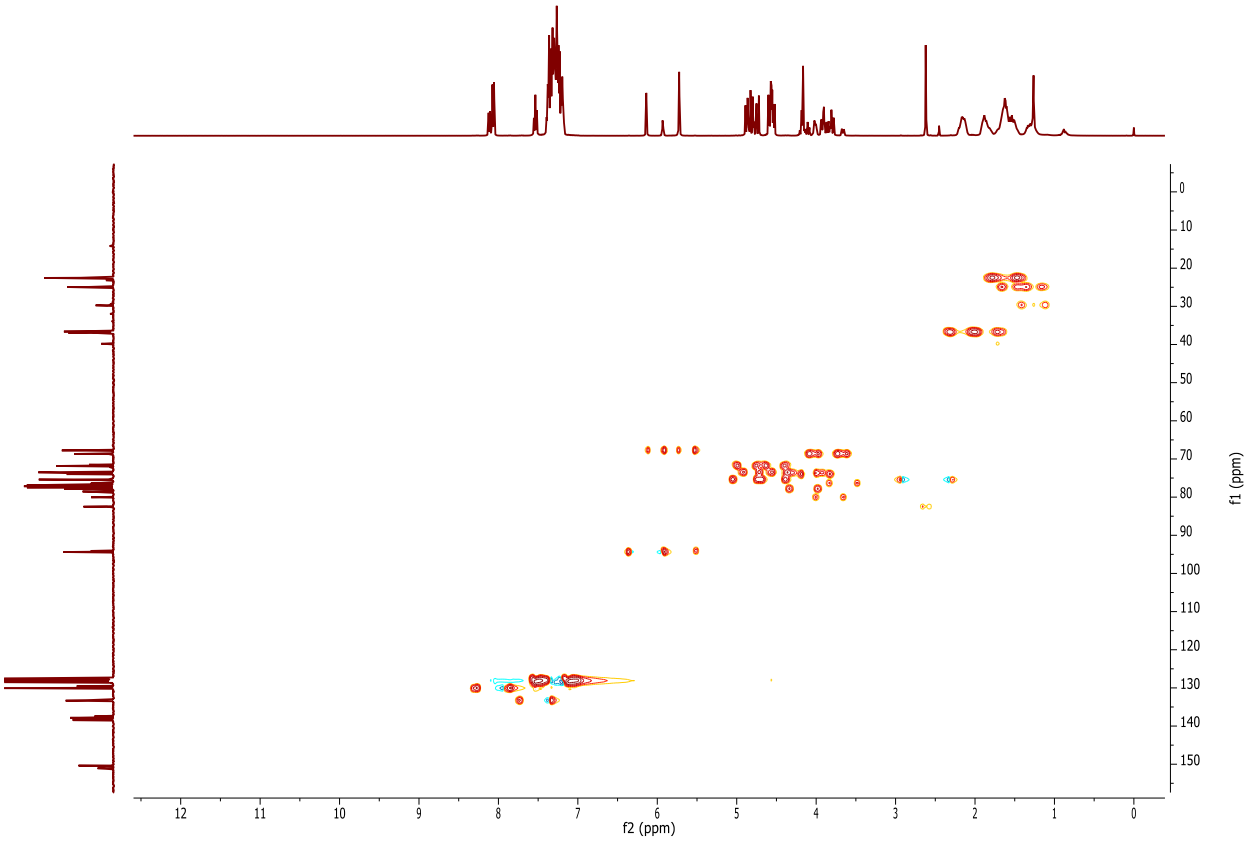
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1g**



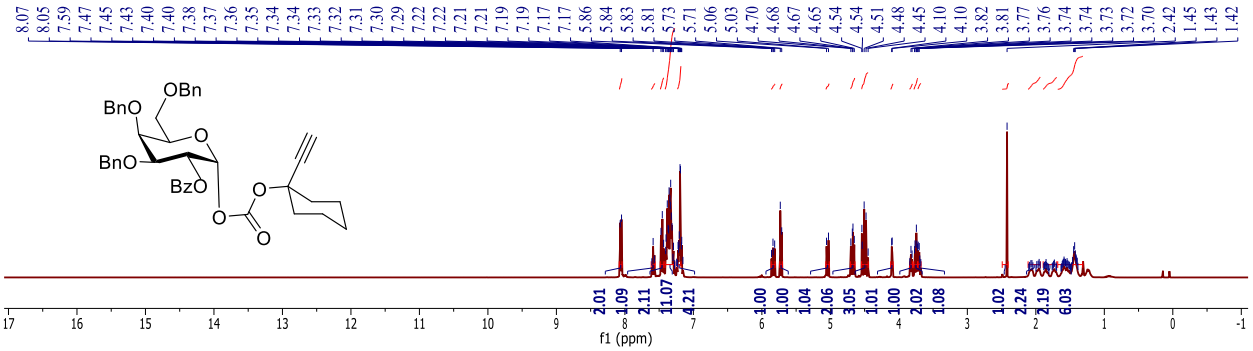
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **1g**



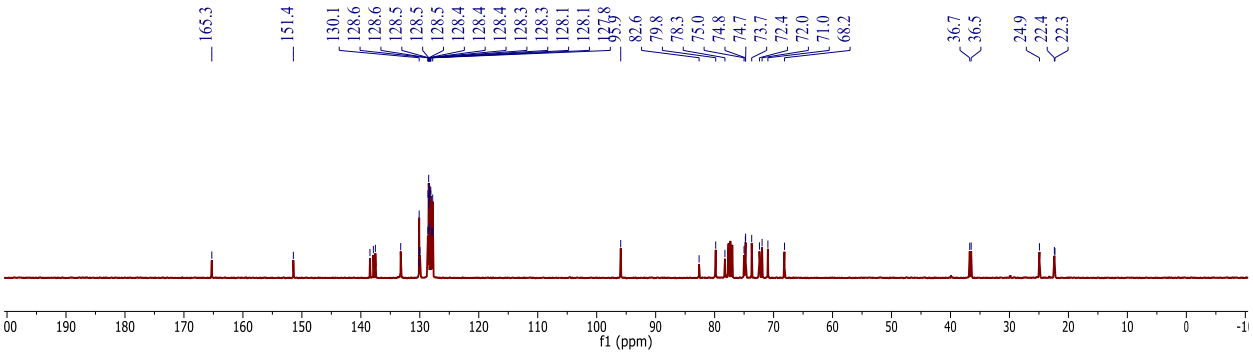
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **1g**



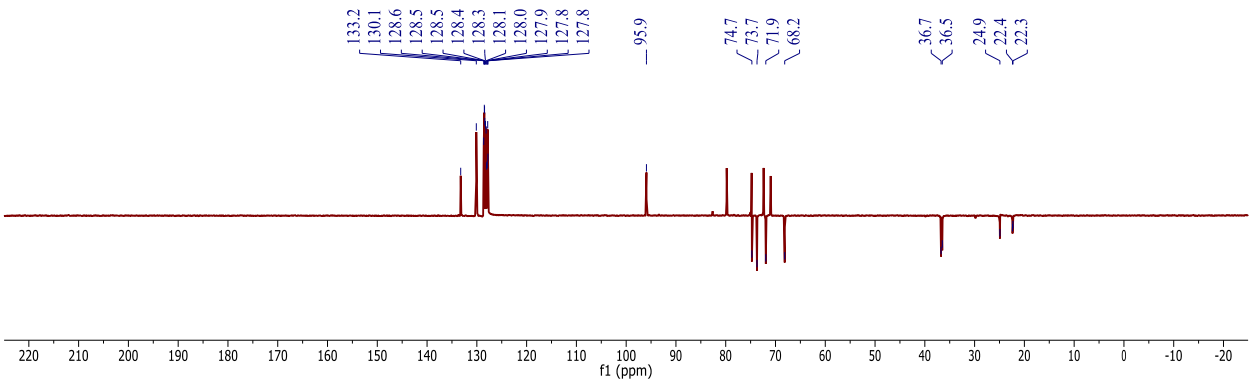
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **1i**



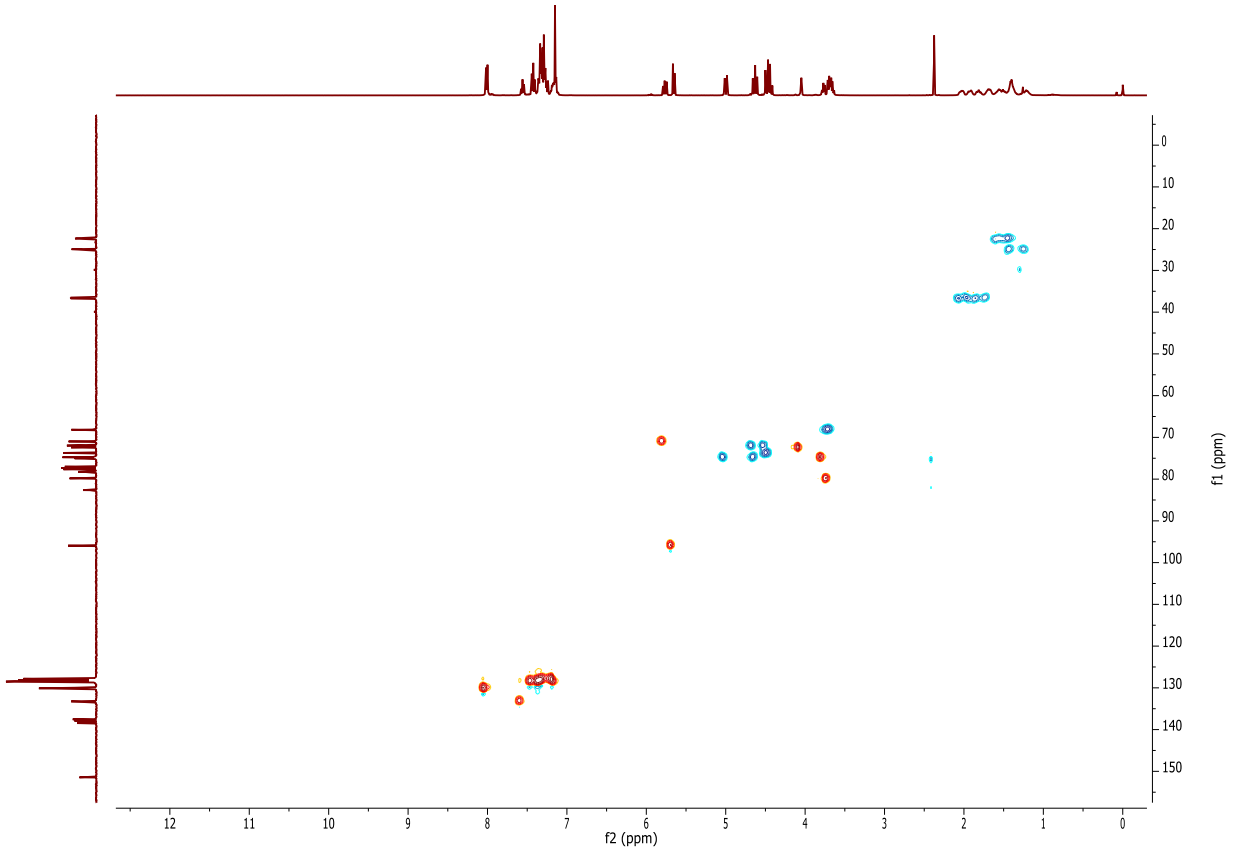
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1i**



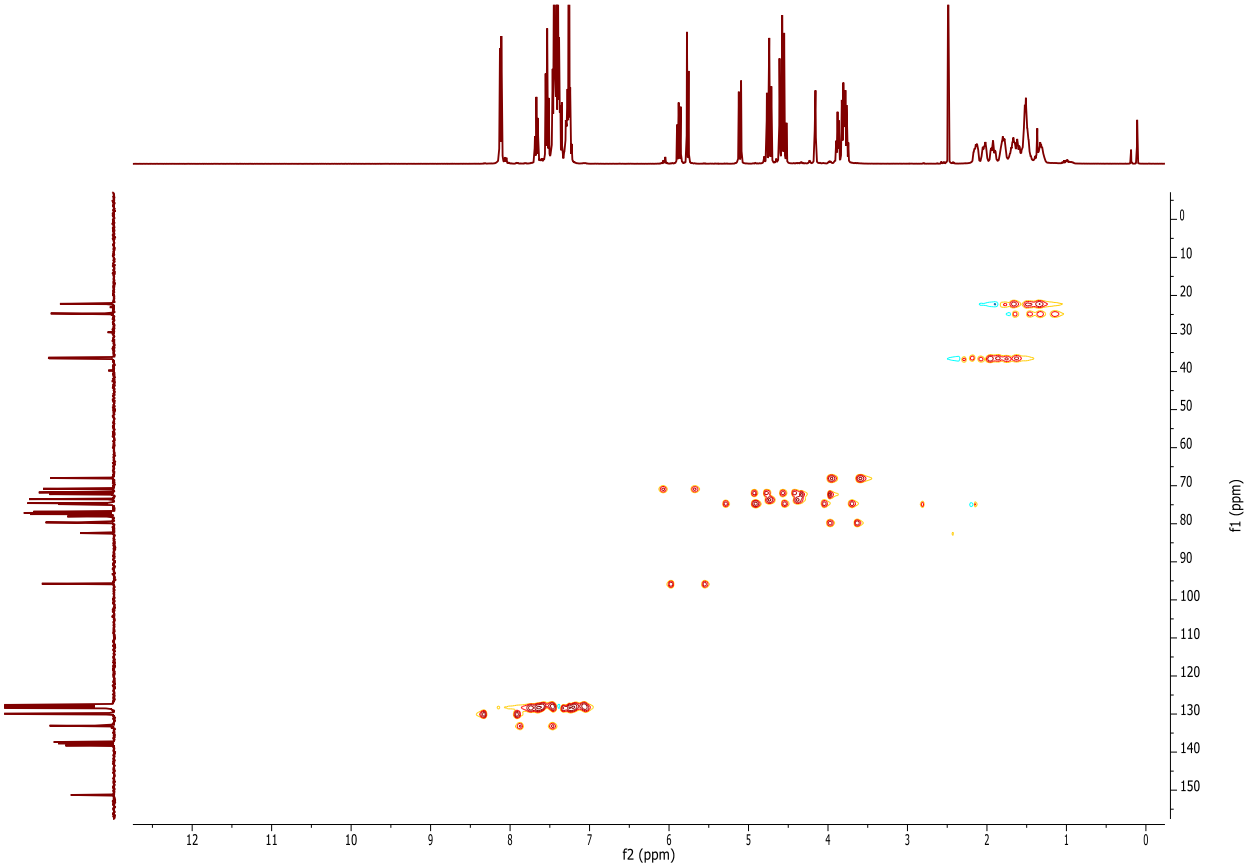
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1i**



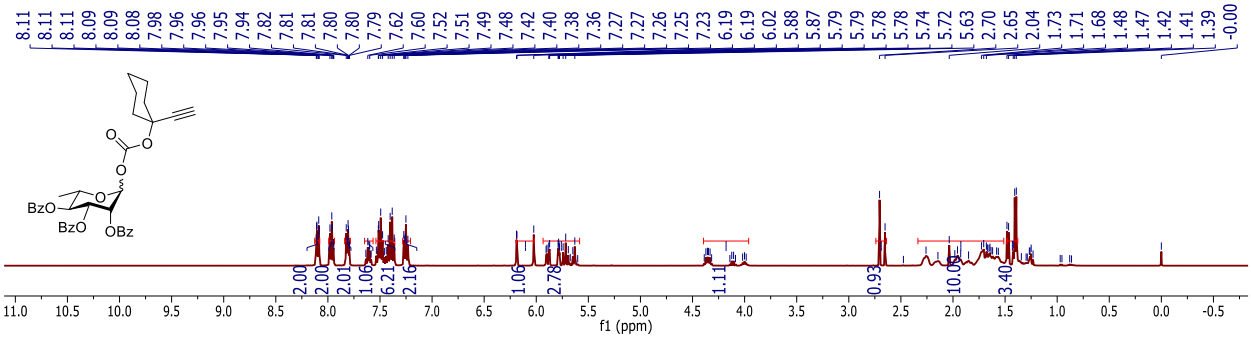
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **1i**



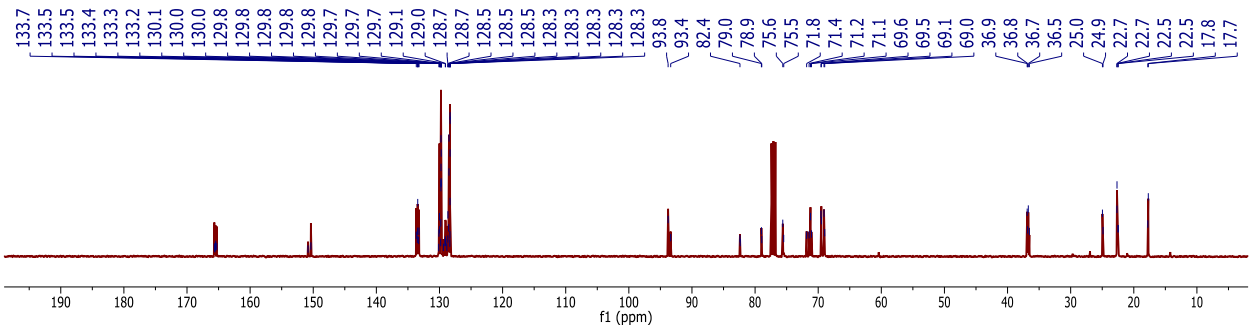
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **1i**



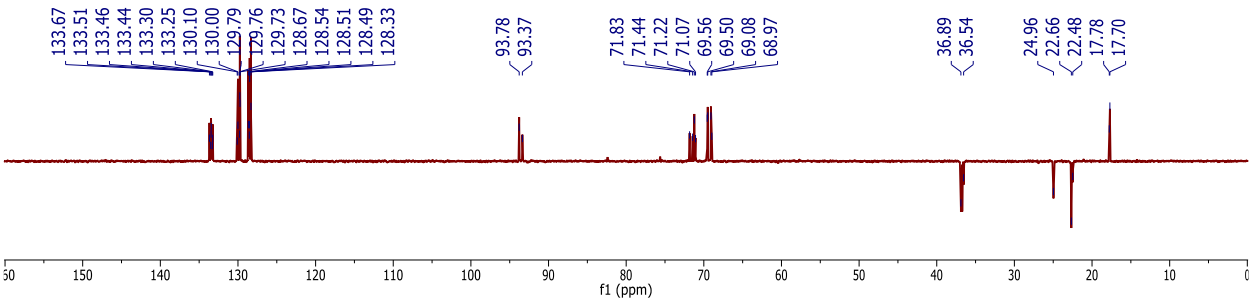
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **1l**



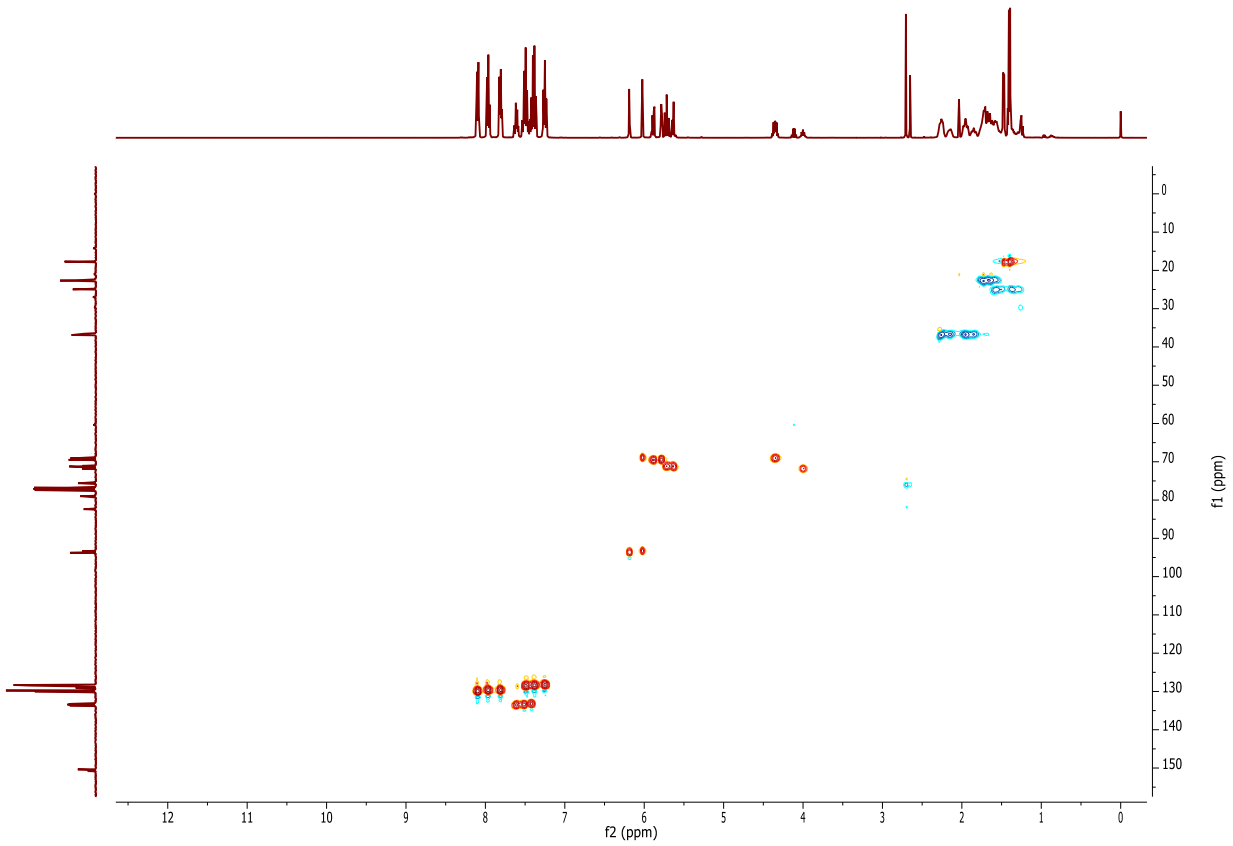
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1l**



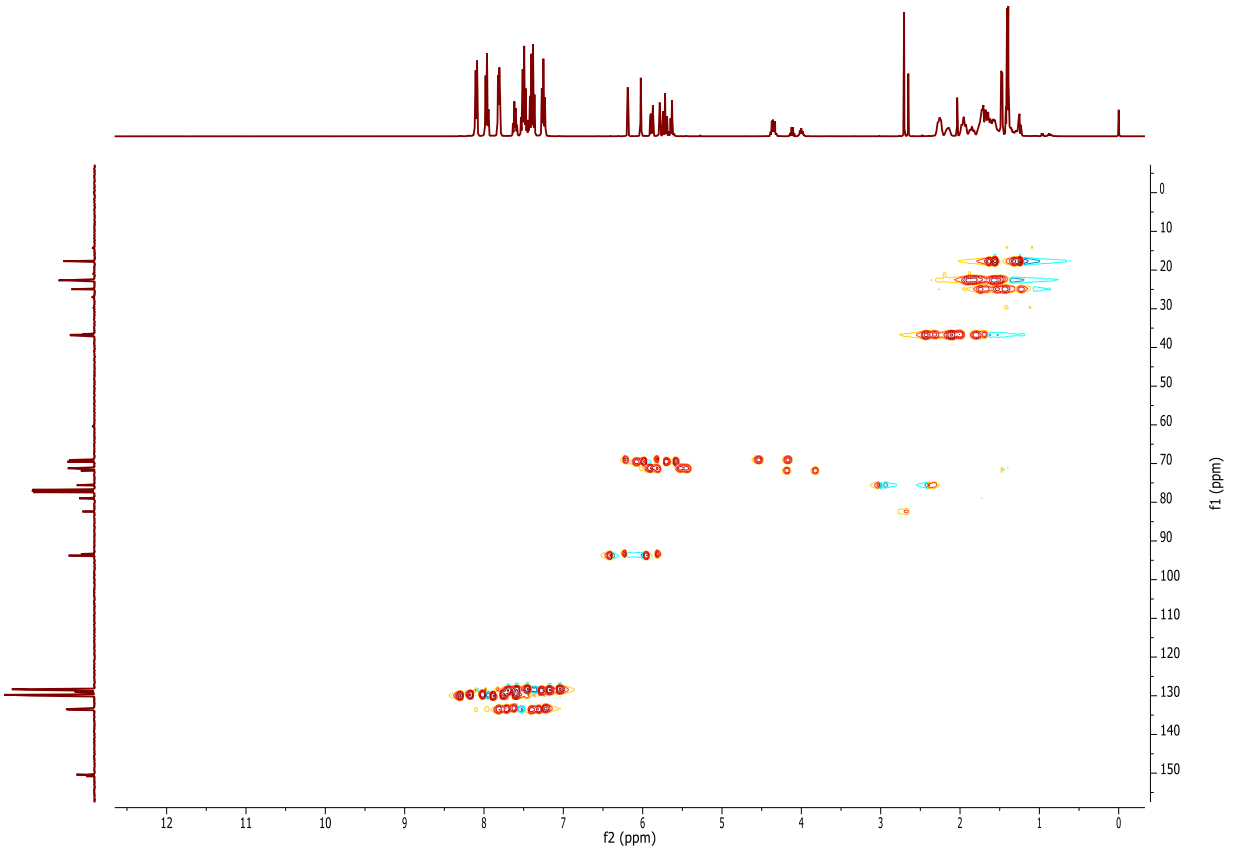
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1l**



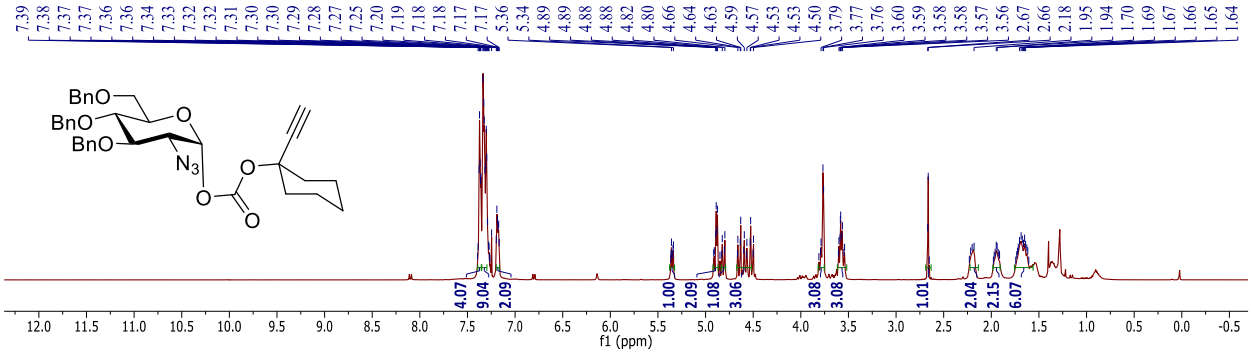
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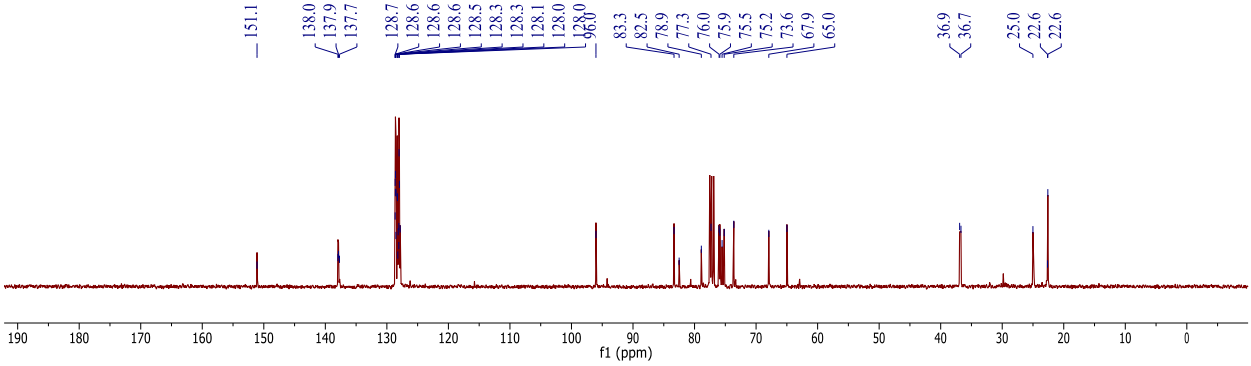
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **1l**



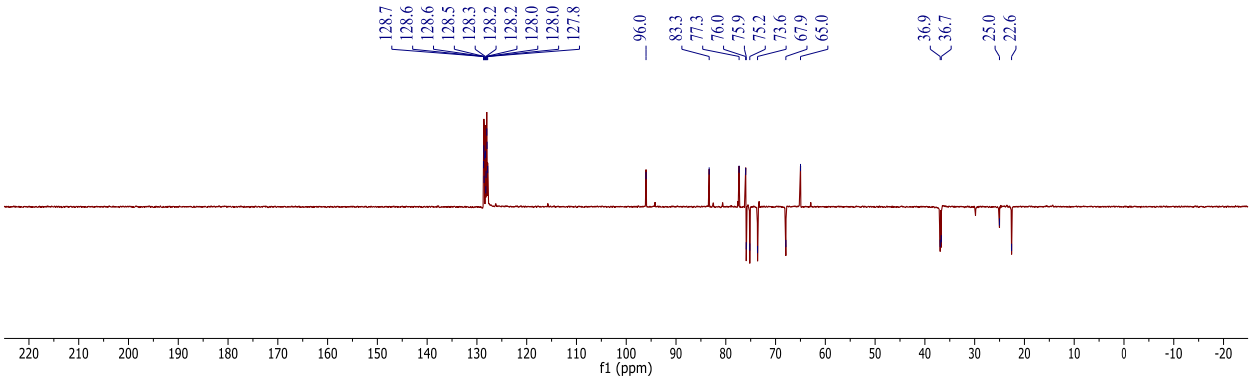
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **1o**



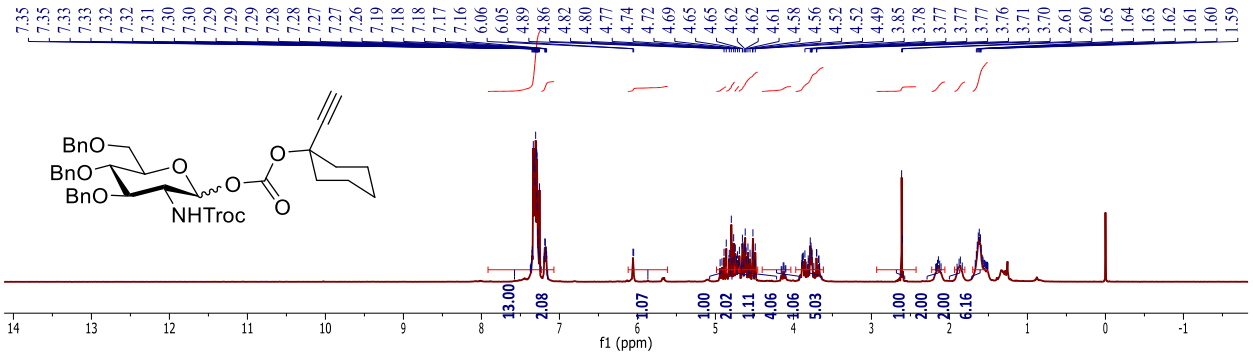
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1o**



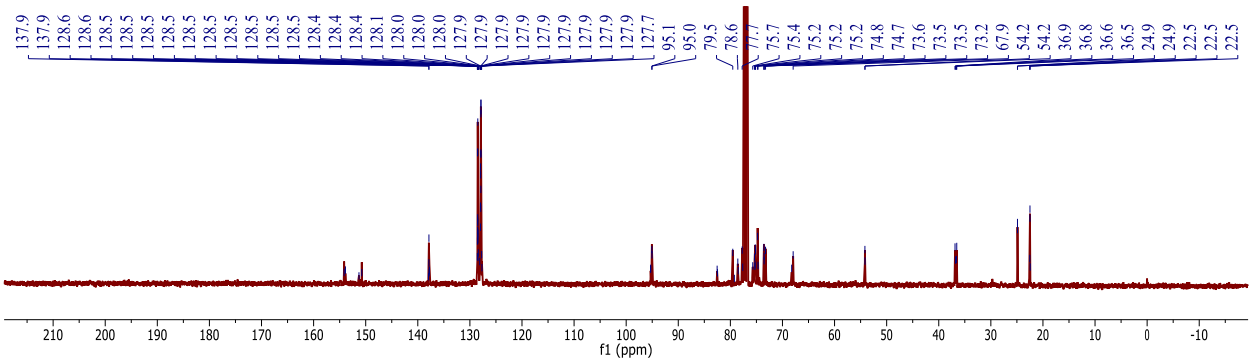
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1o**



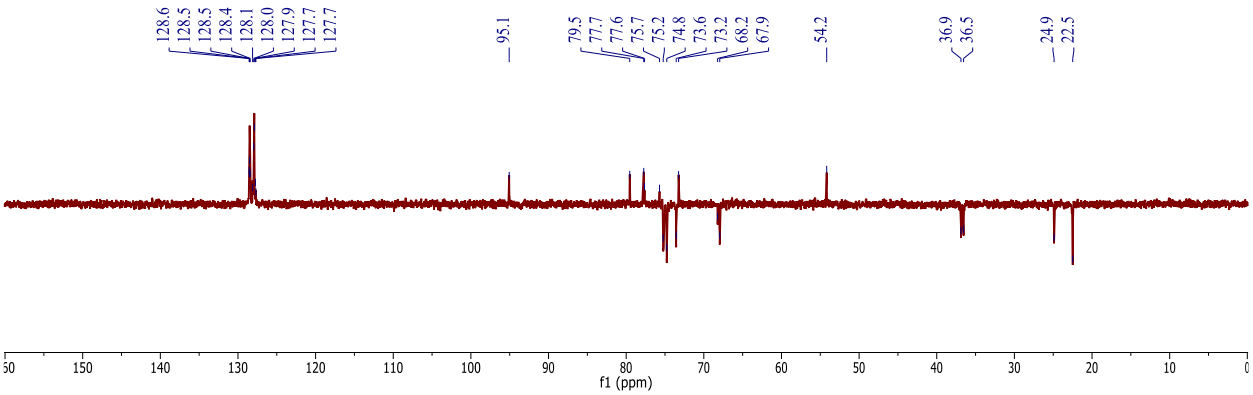
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **1p**



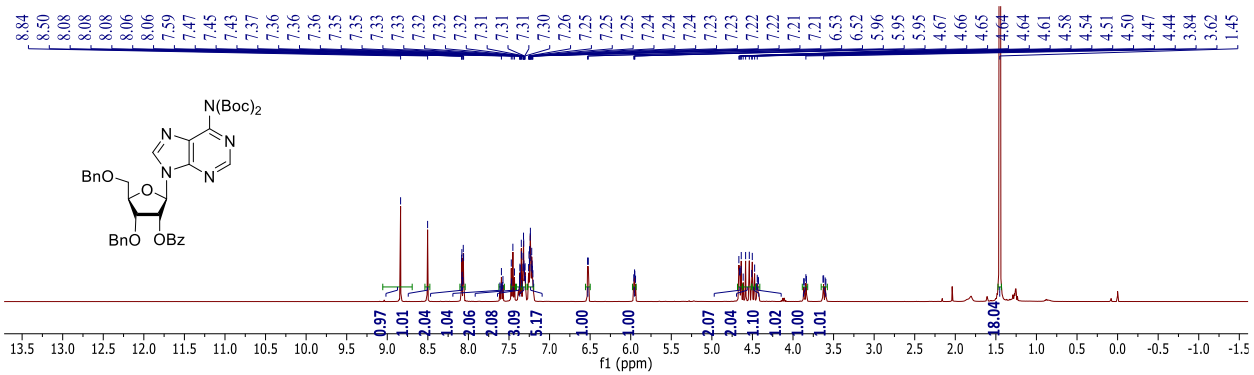
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1p**



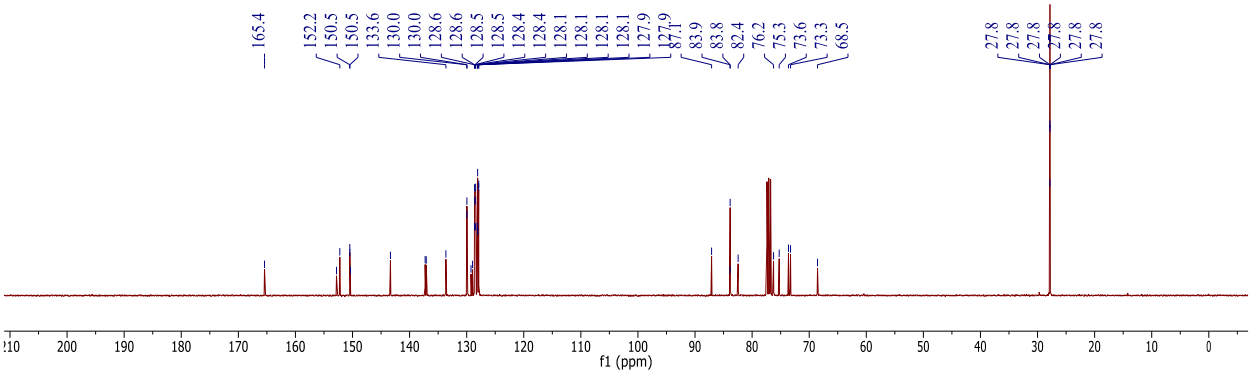
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **1p**



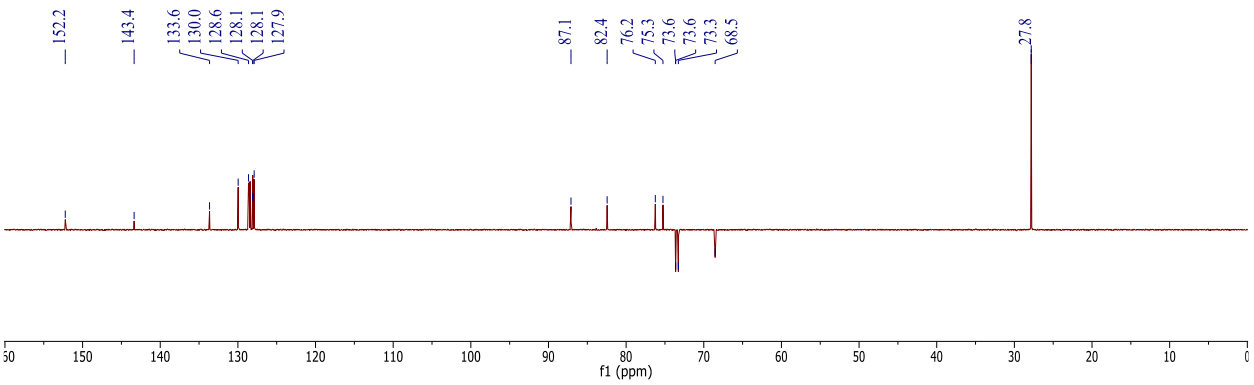
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4a**



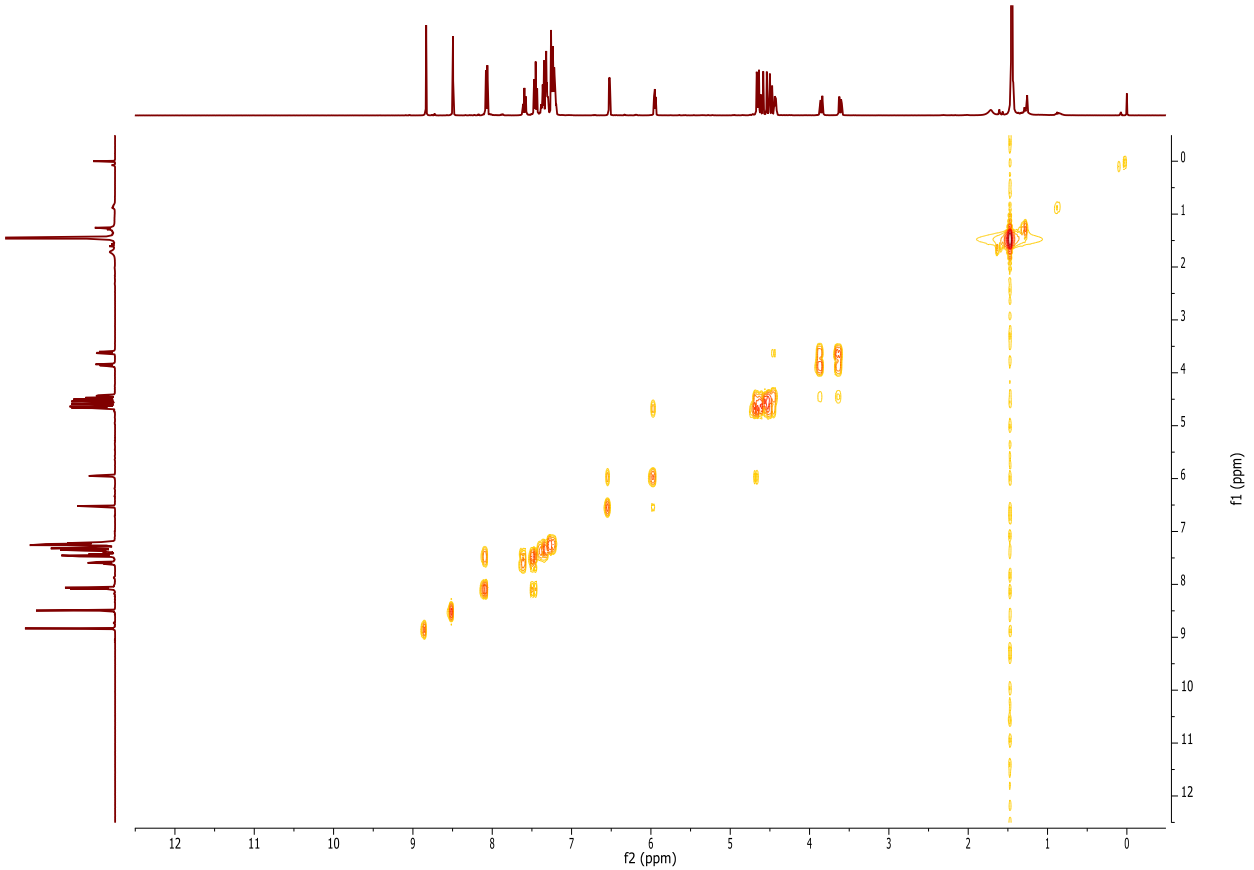
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4a**



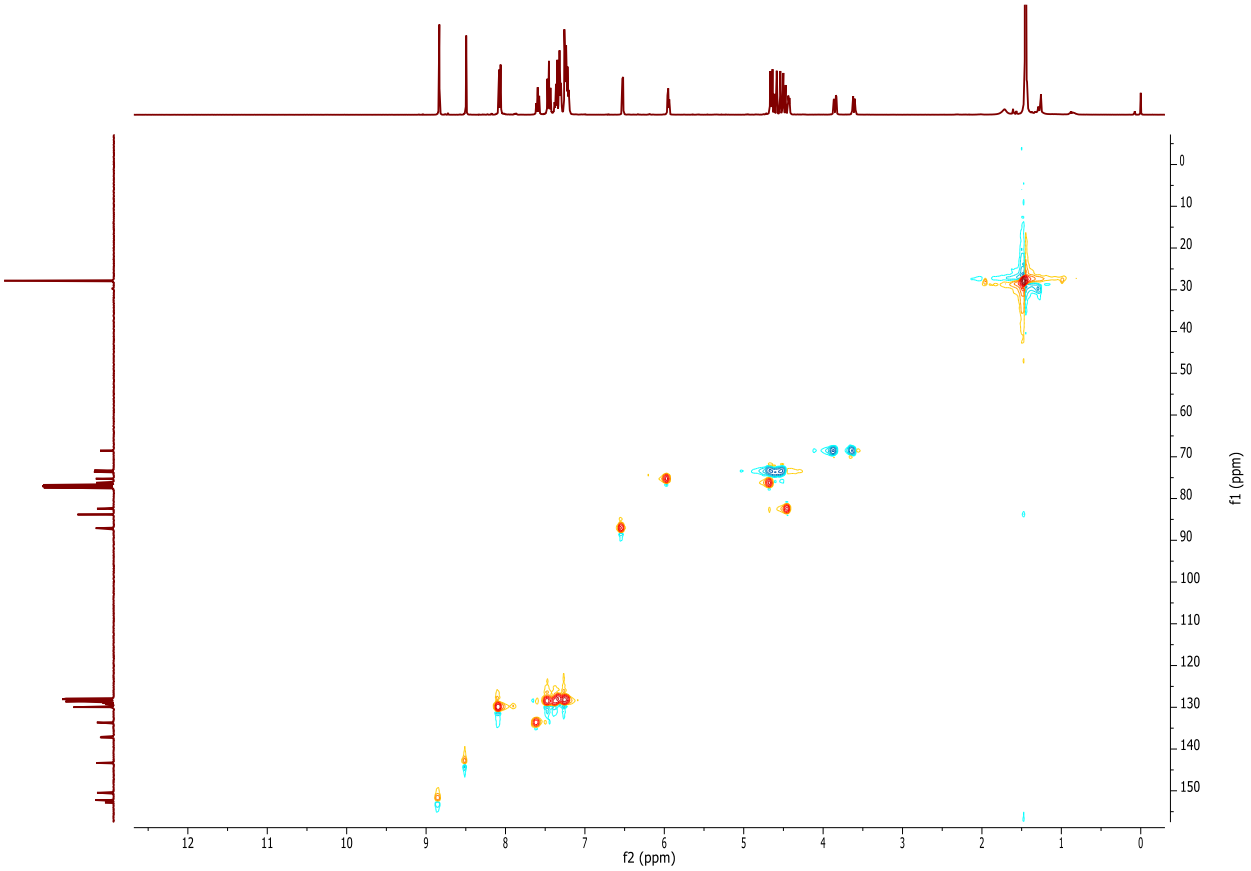
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4a**



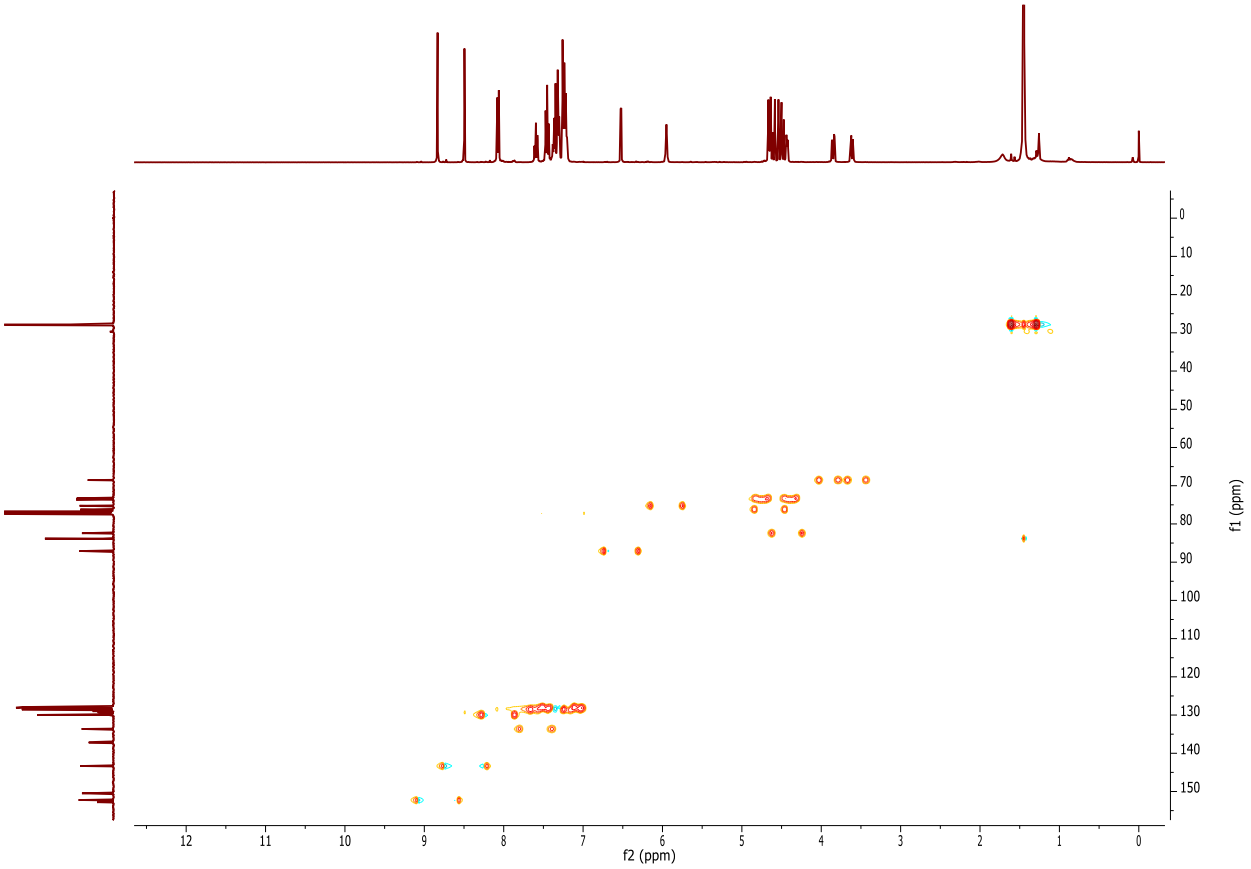
^{1}H-^{1}H COSY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4a**



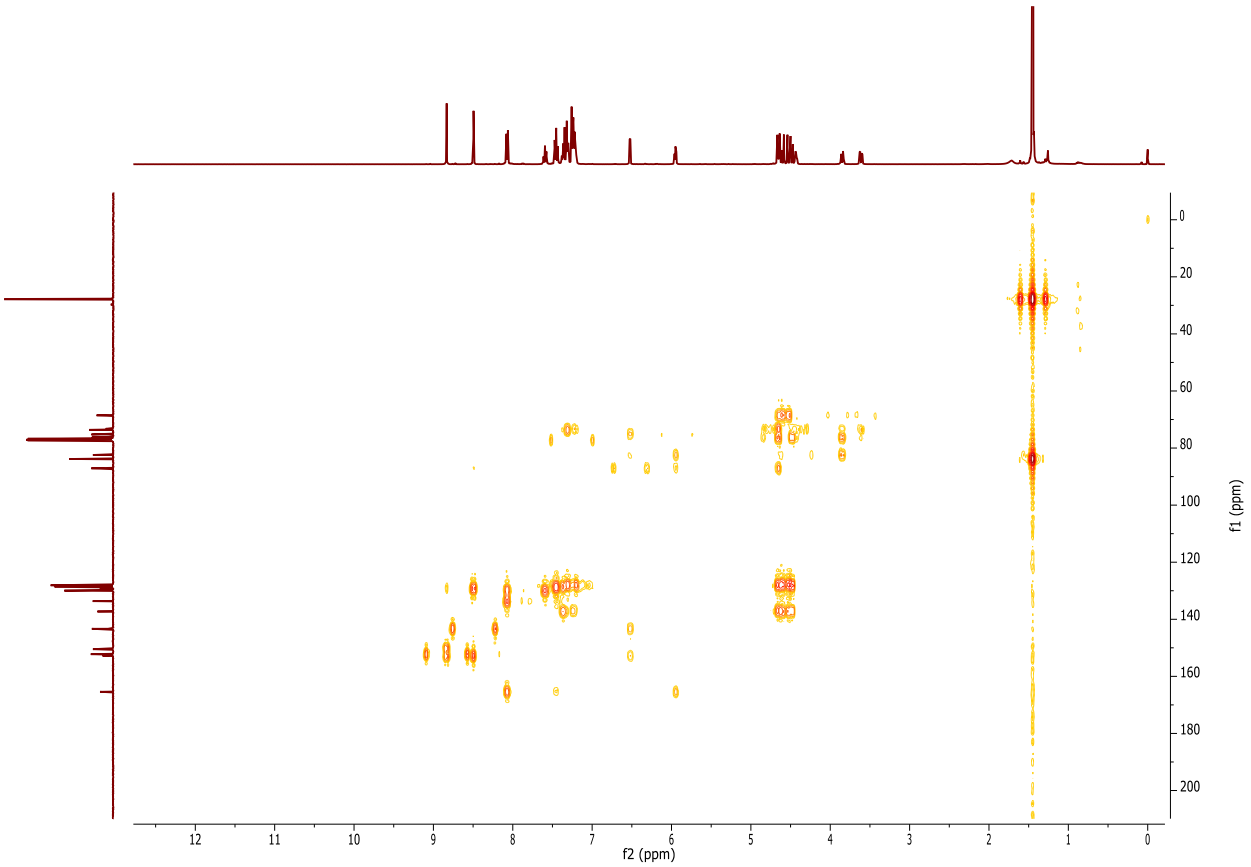
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4a**



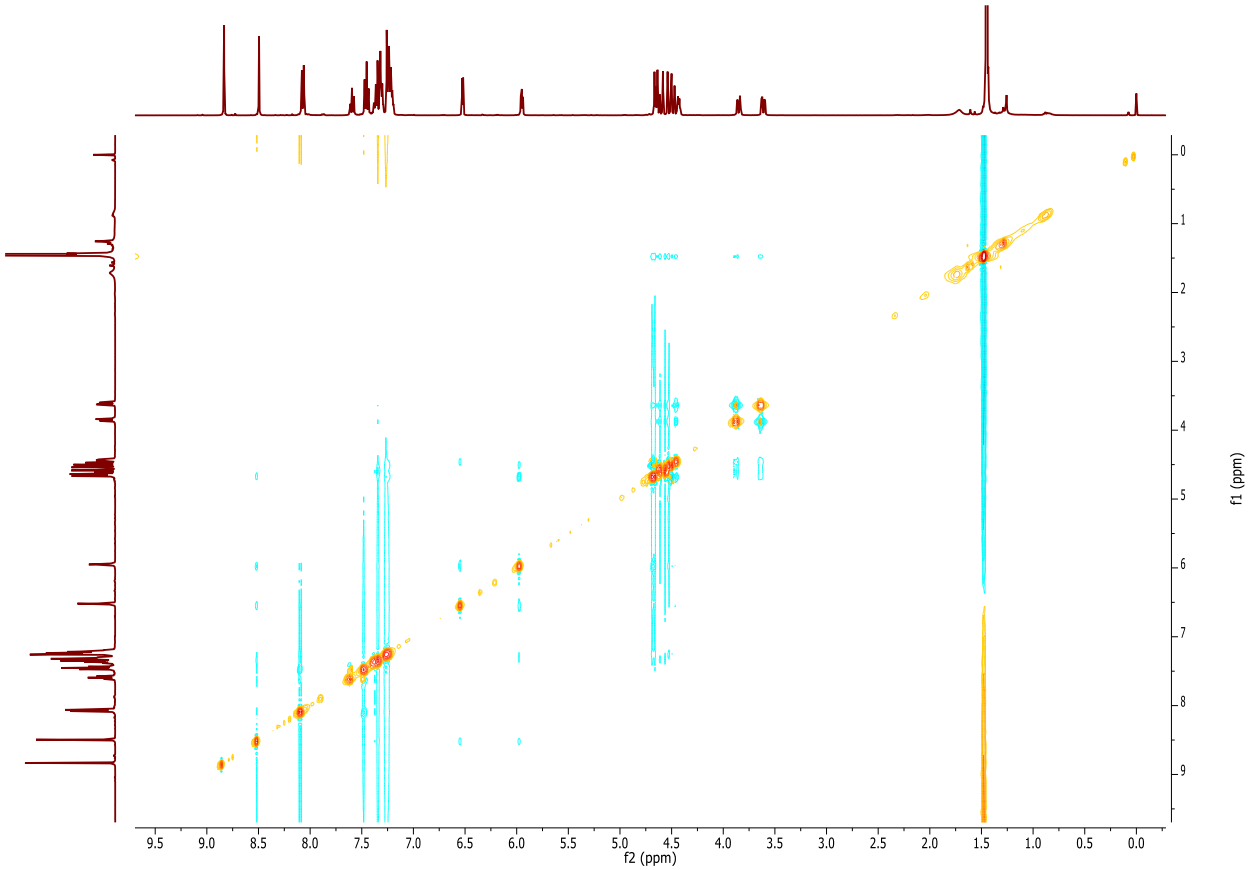
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4a**



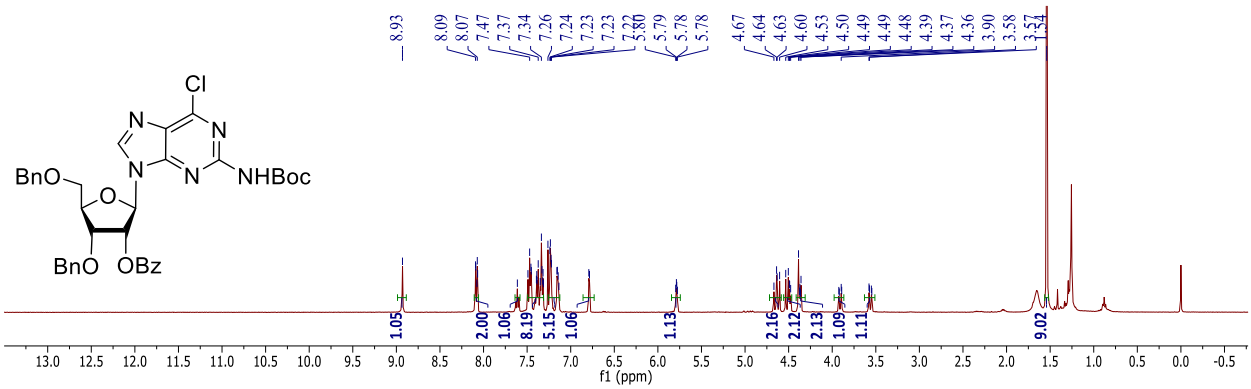
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4a**



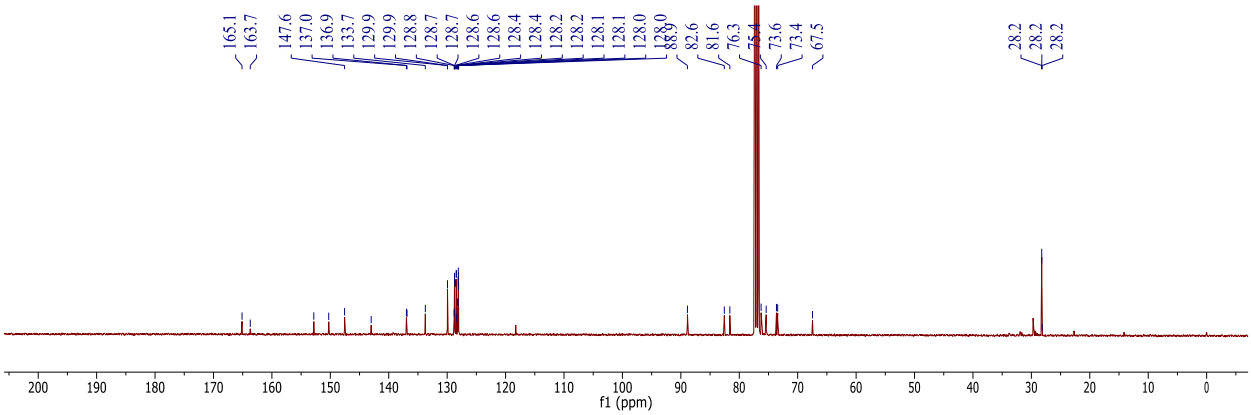
^{1}H-^{1}H NOESY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4a**



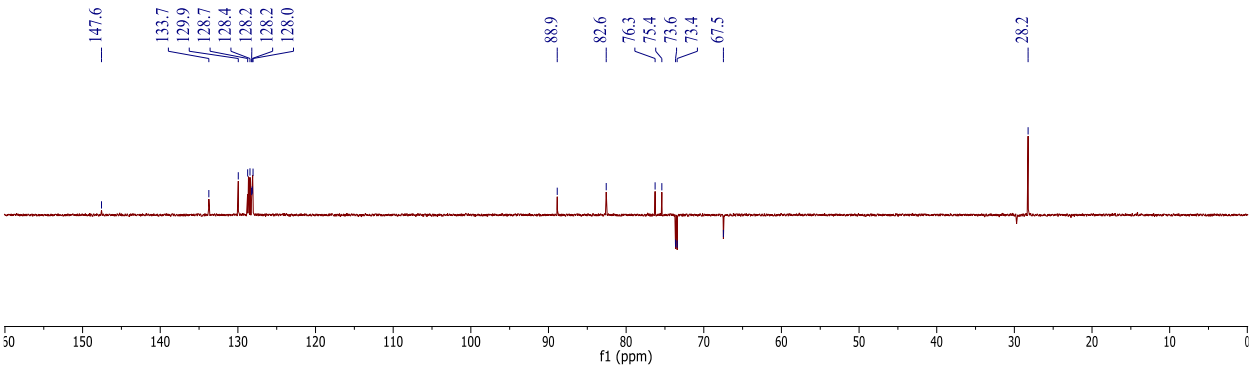
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4b**



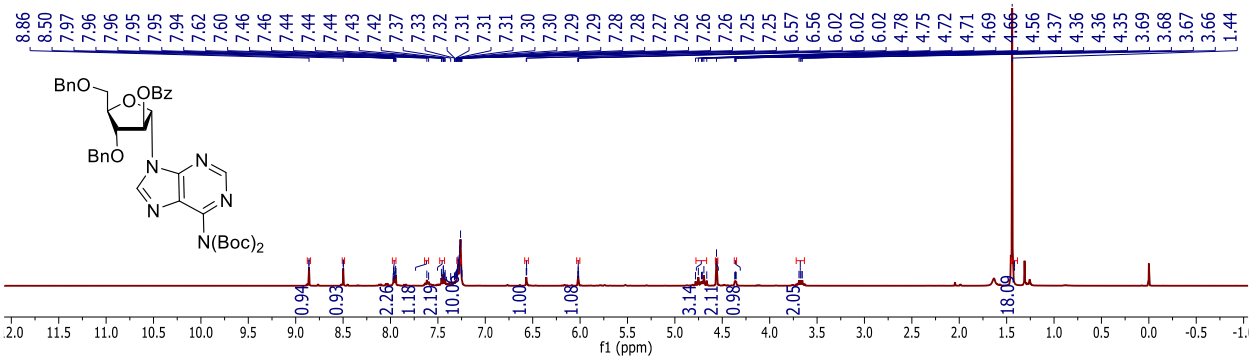
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4b**



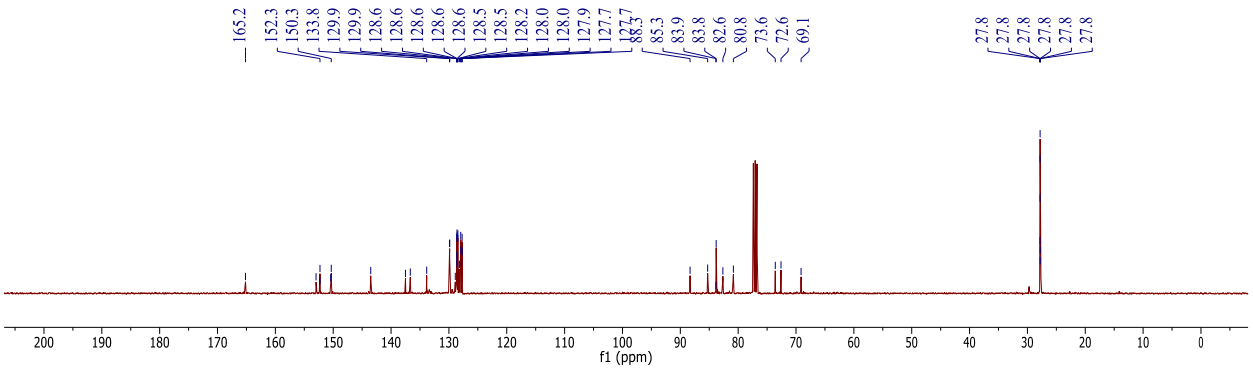
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4b**



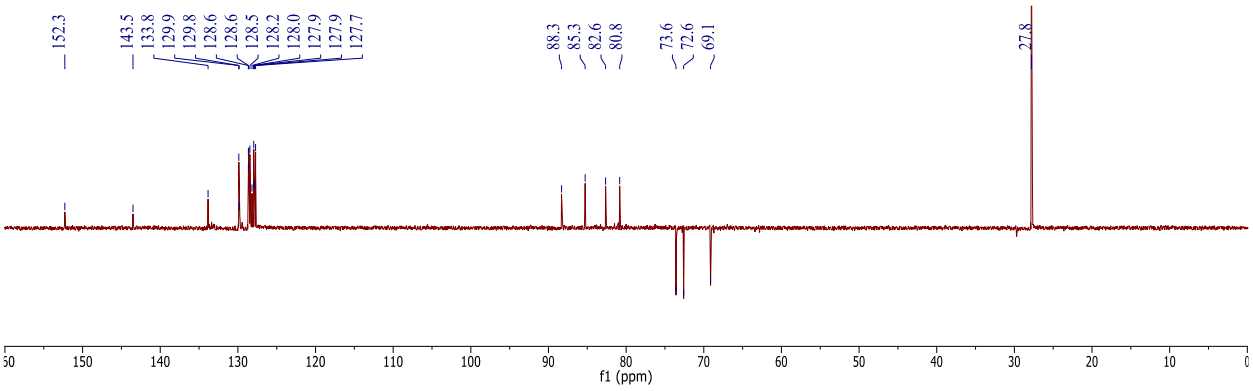
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4c**



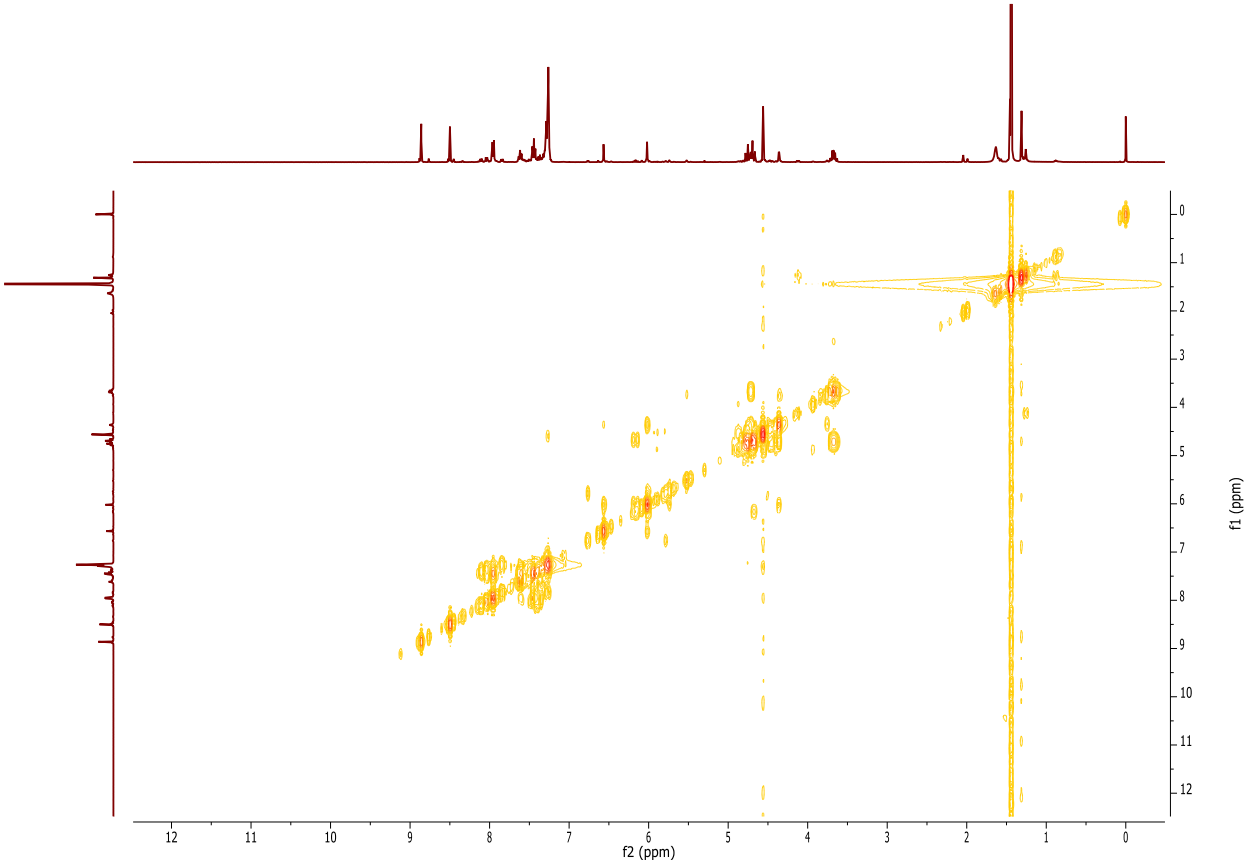
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4c**



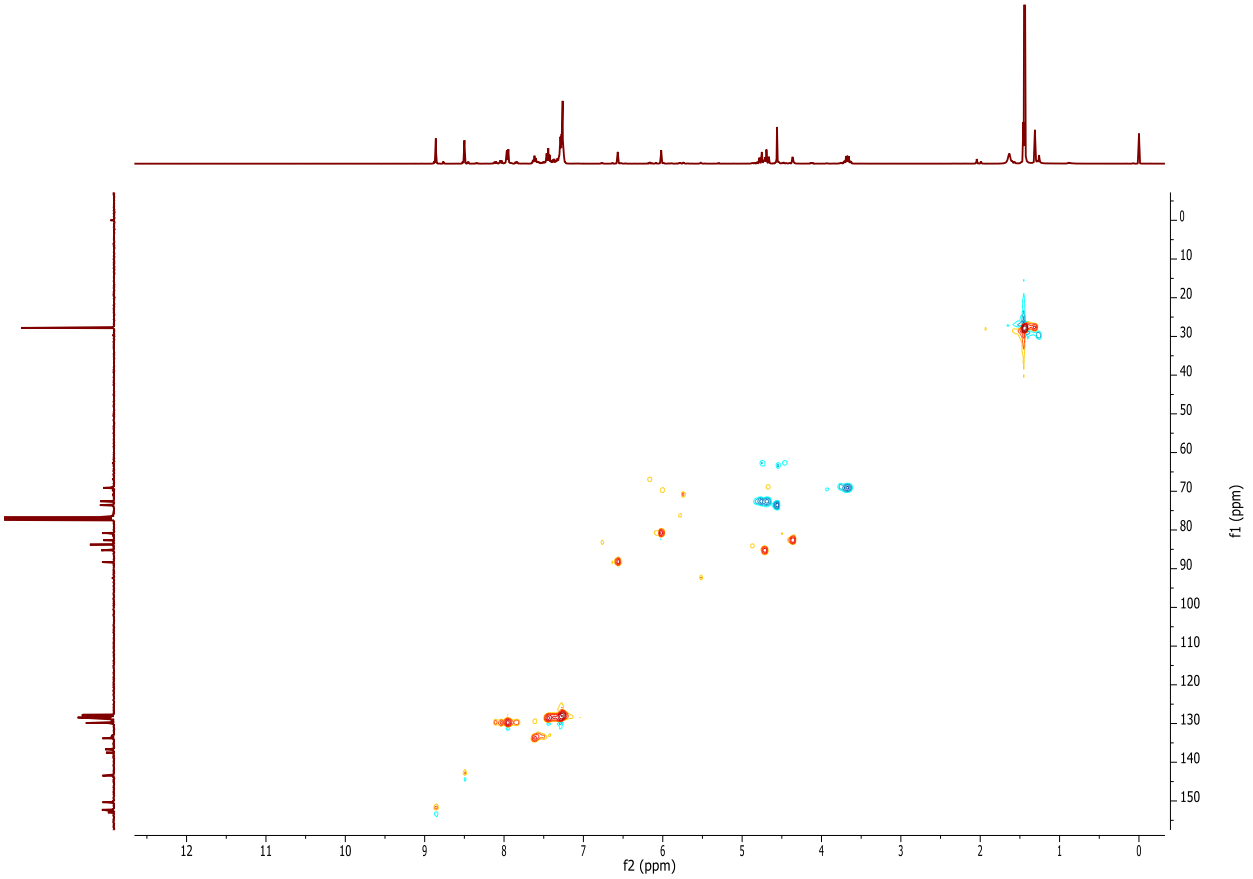
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4c**



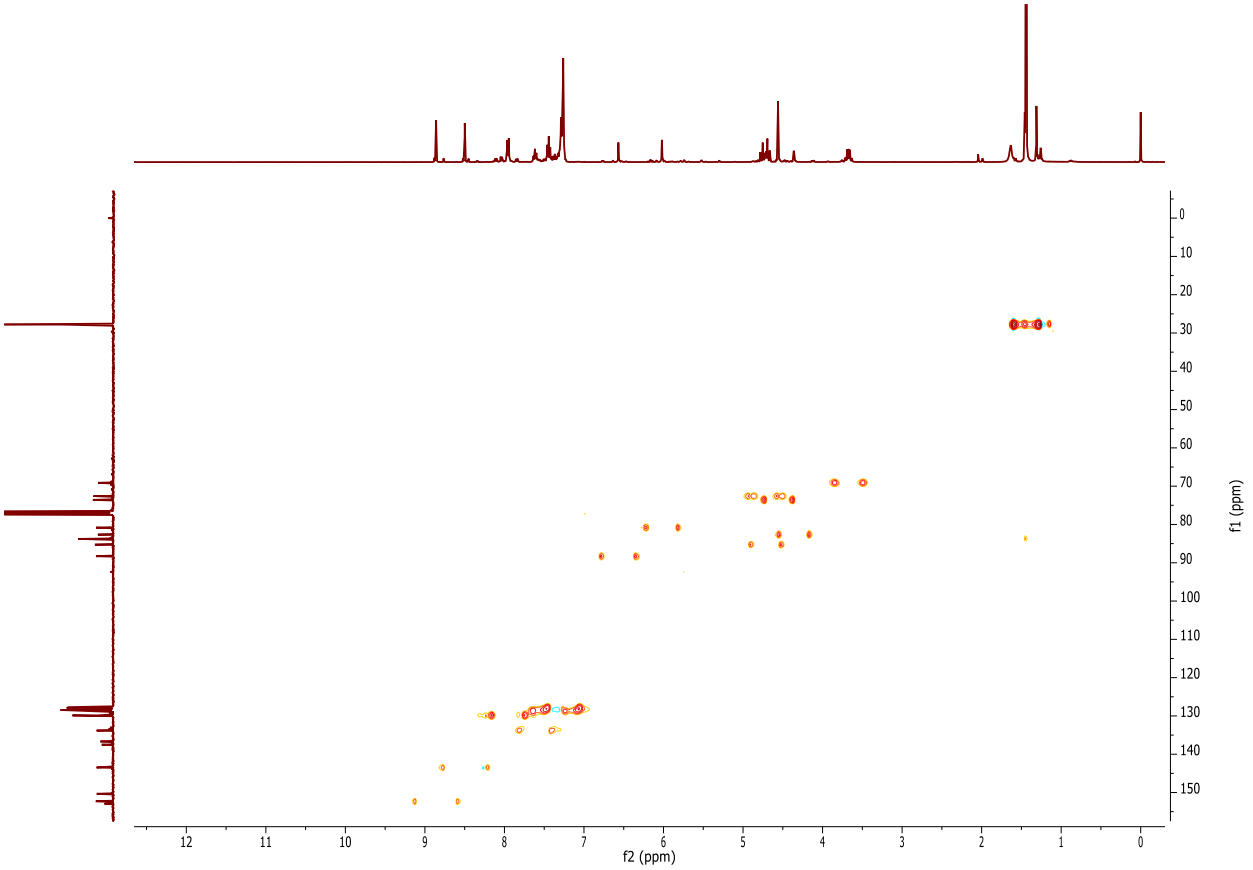
^{1}H-^{1}H COSY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4c**



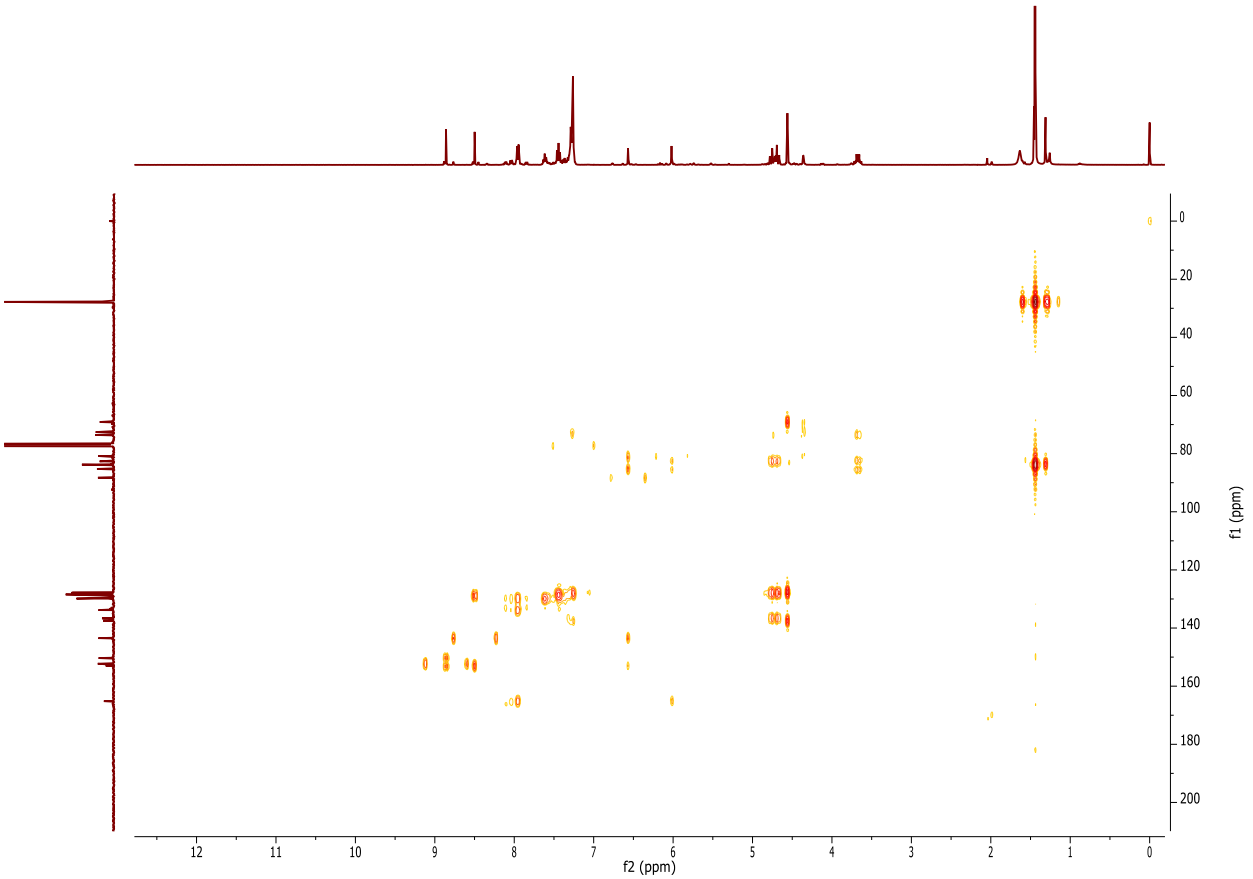
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4c**



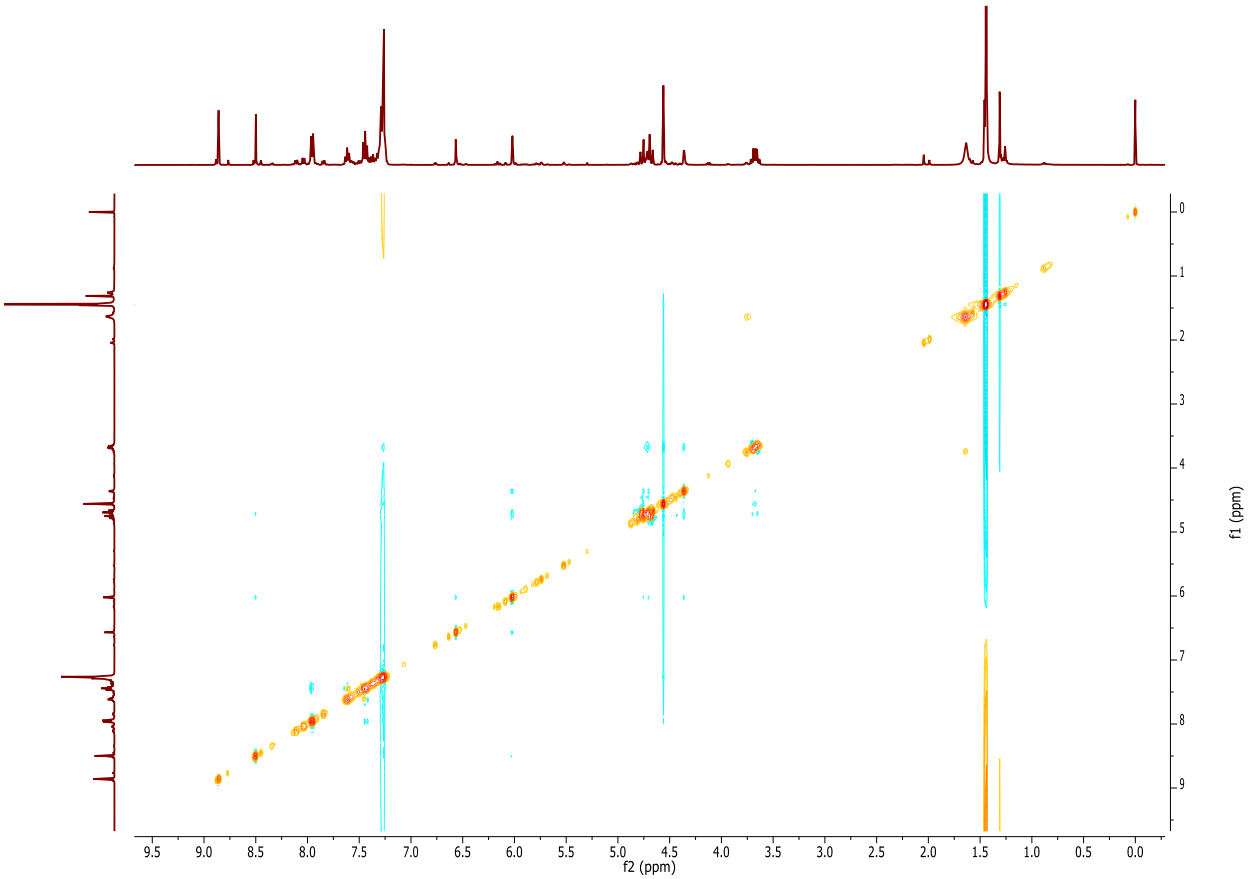
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4c**



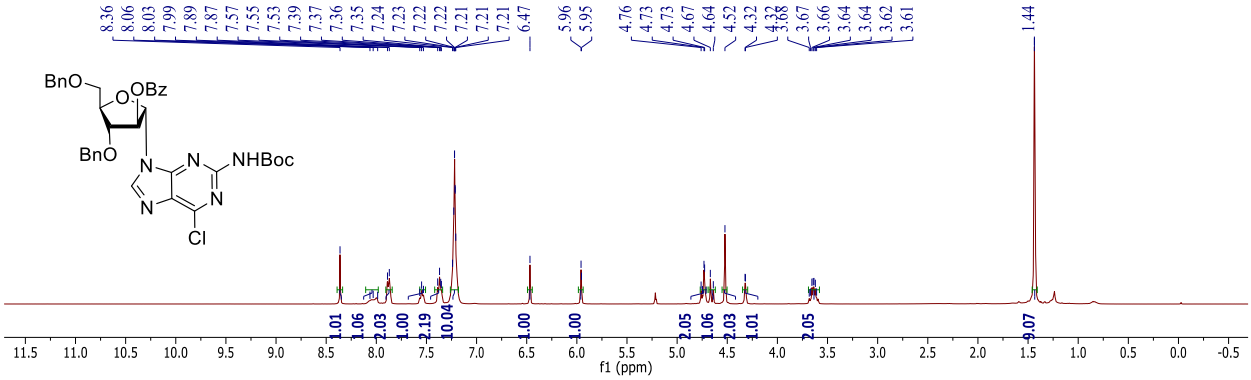
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4c**



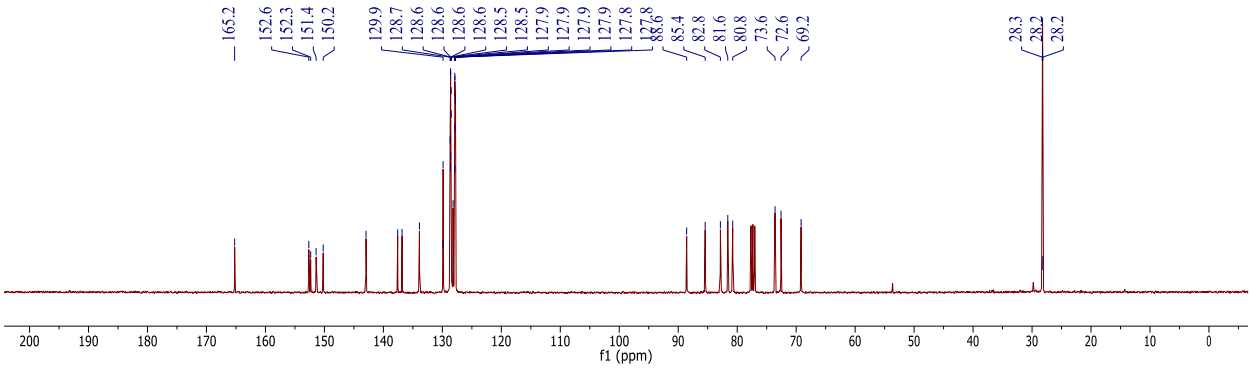
^{1}H-^{1}H NOESY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4c**



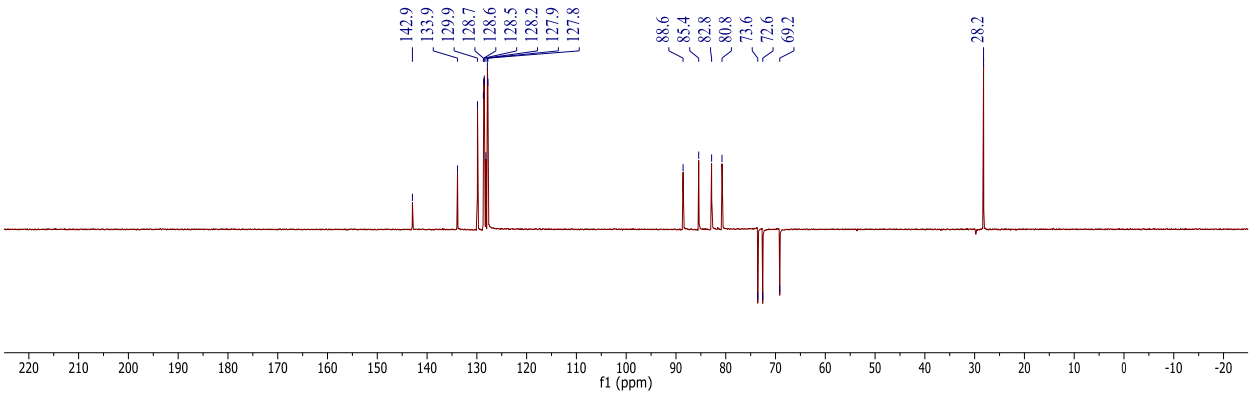
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4d**



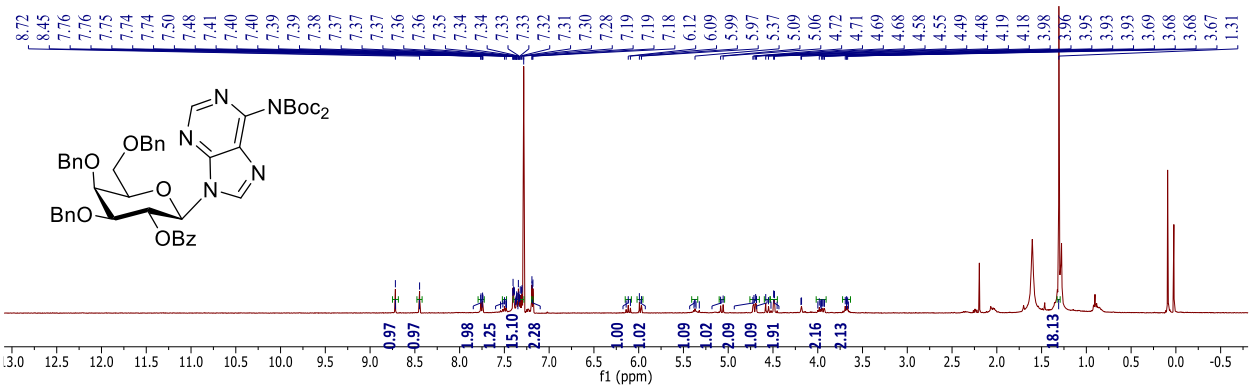
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4d**



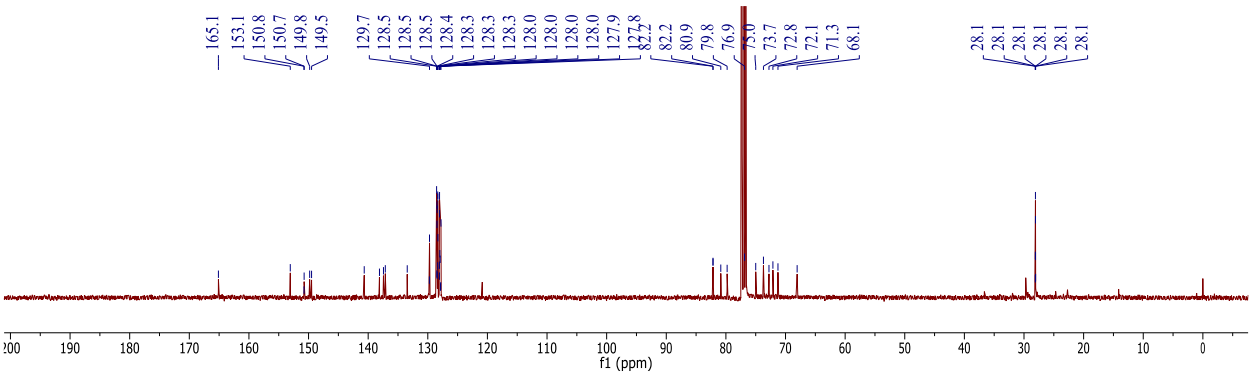
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4d**



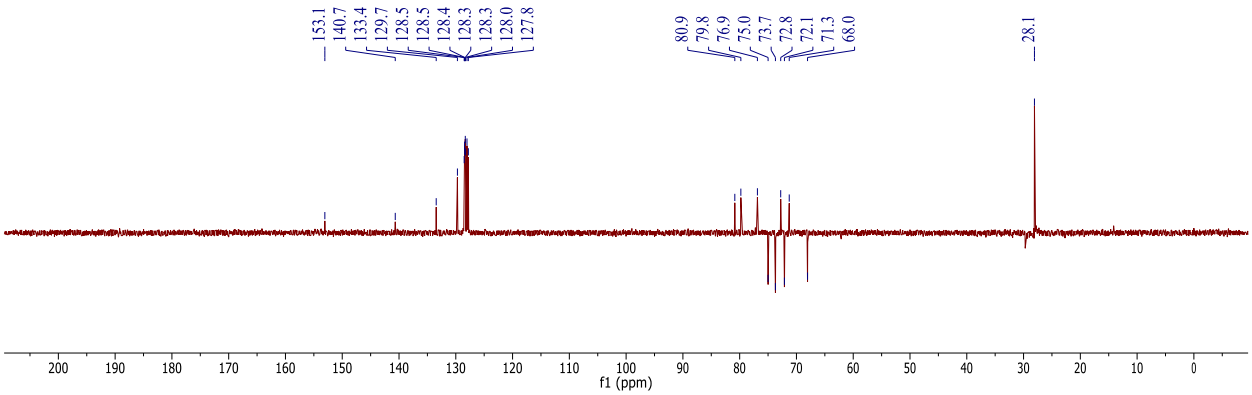
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4e**



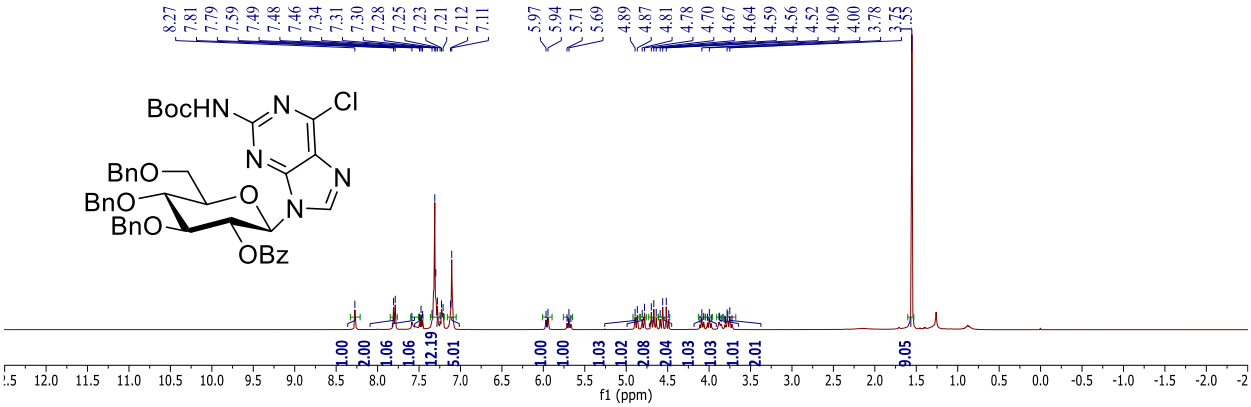
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4e**



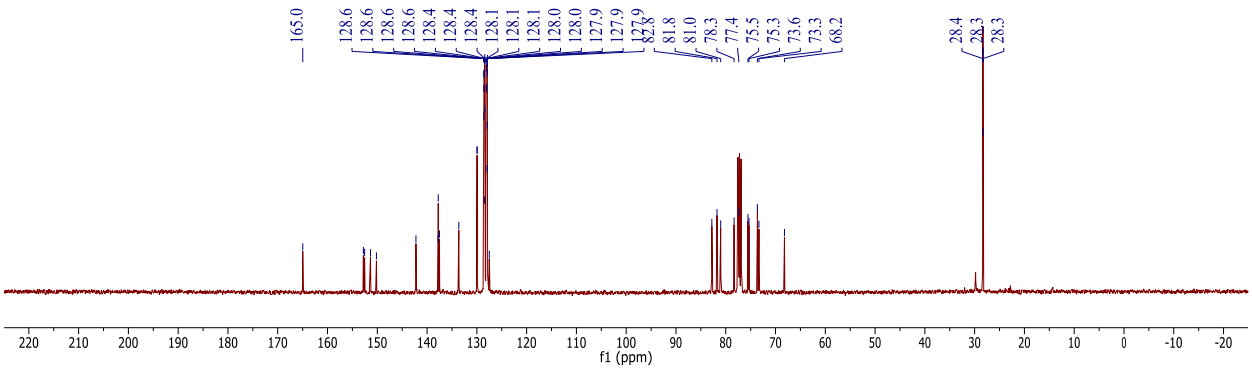
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4e**



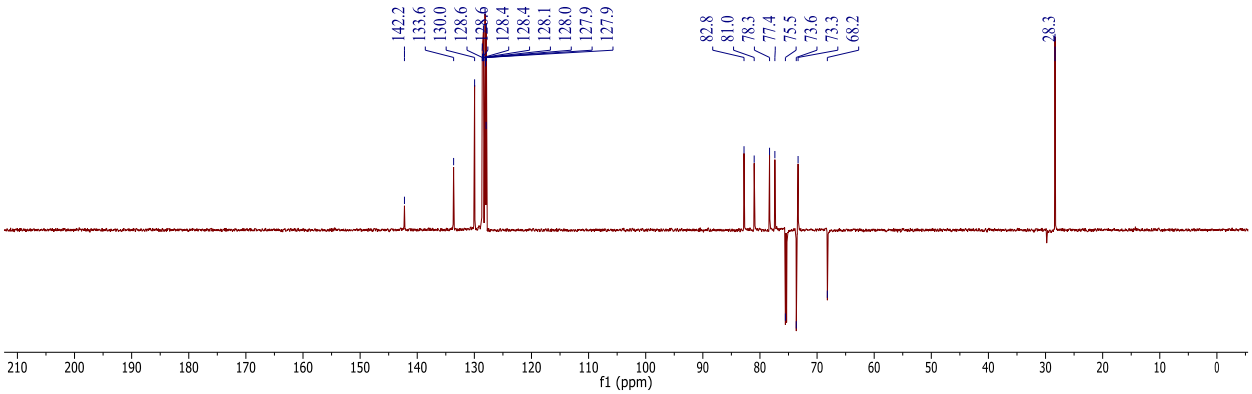
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4f**



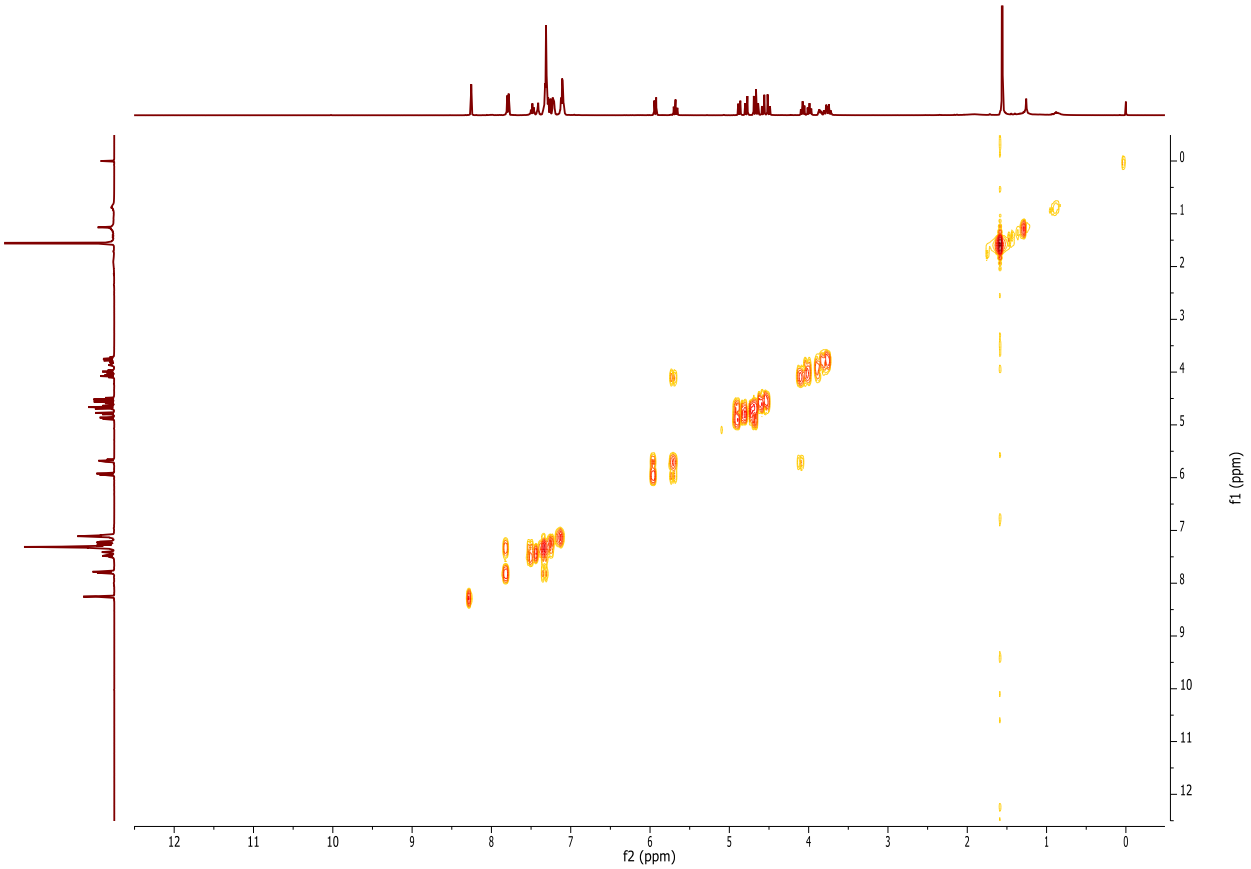
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4f**



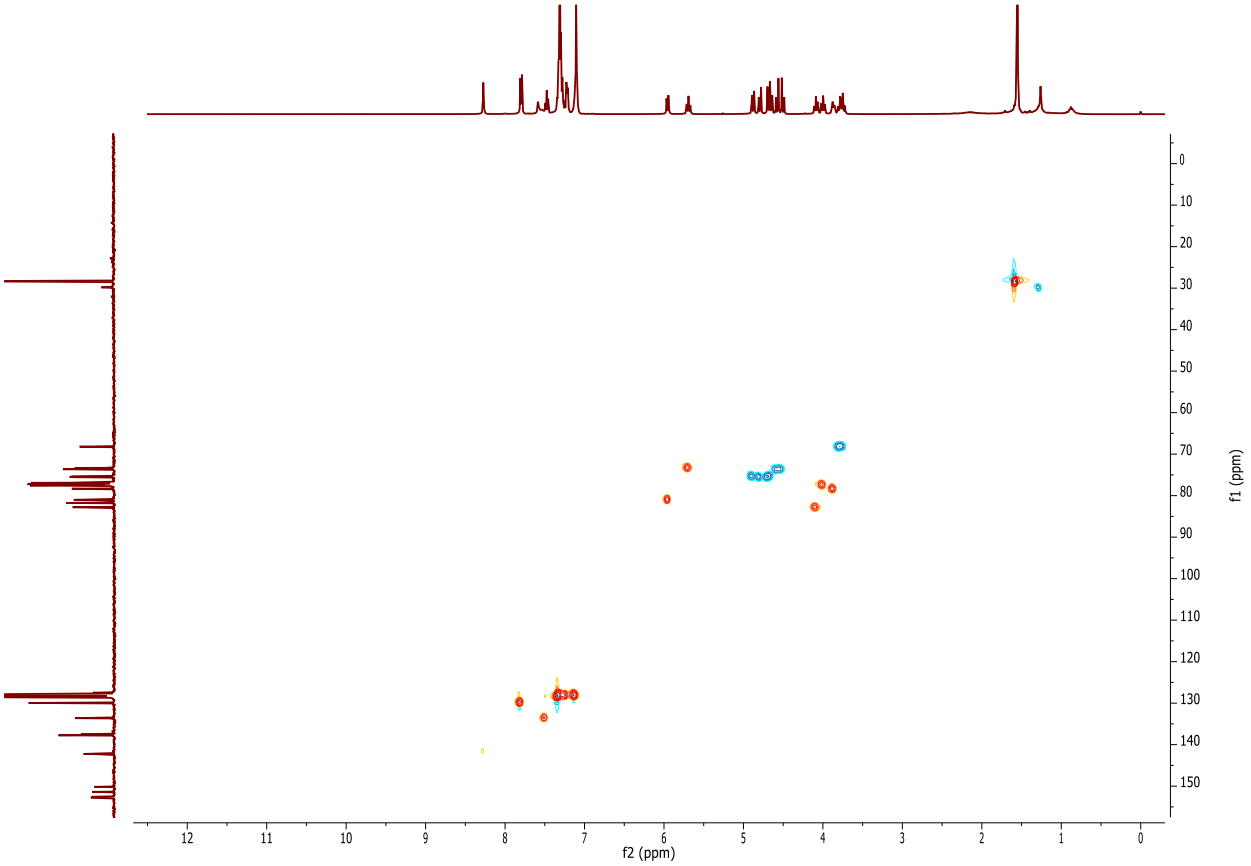
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4f**



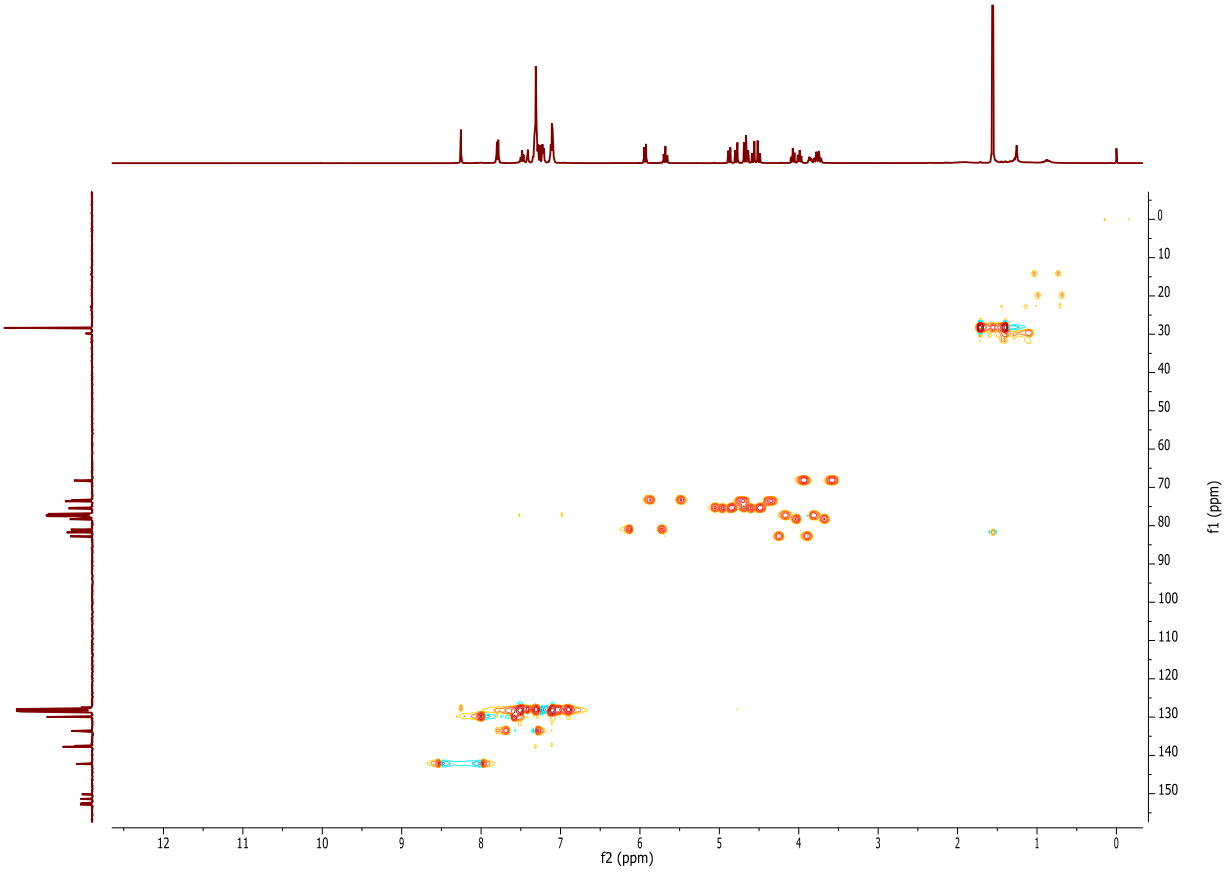
^{1}H-^{1}H COSY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4f**



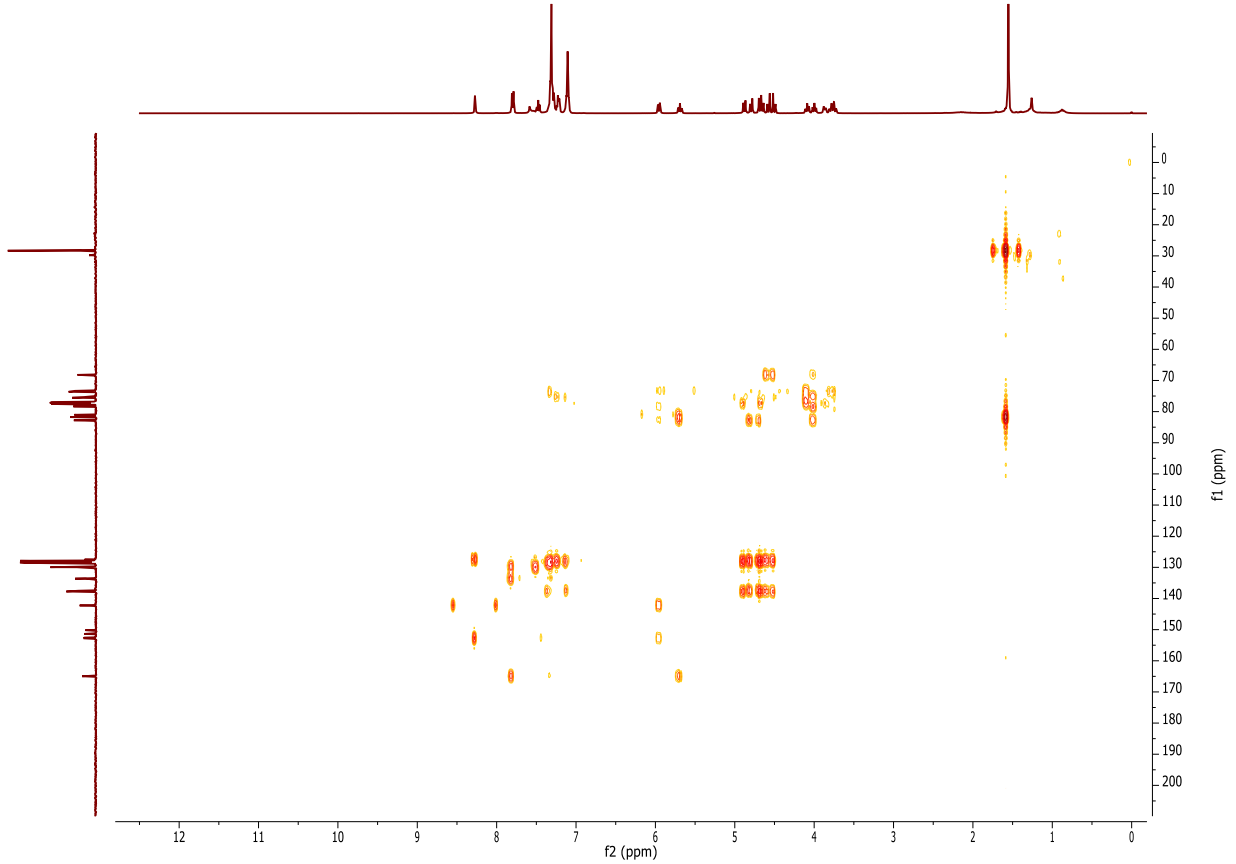
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4f**



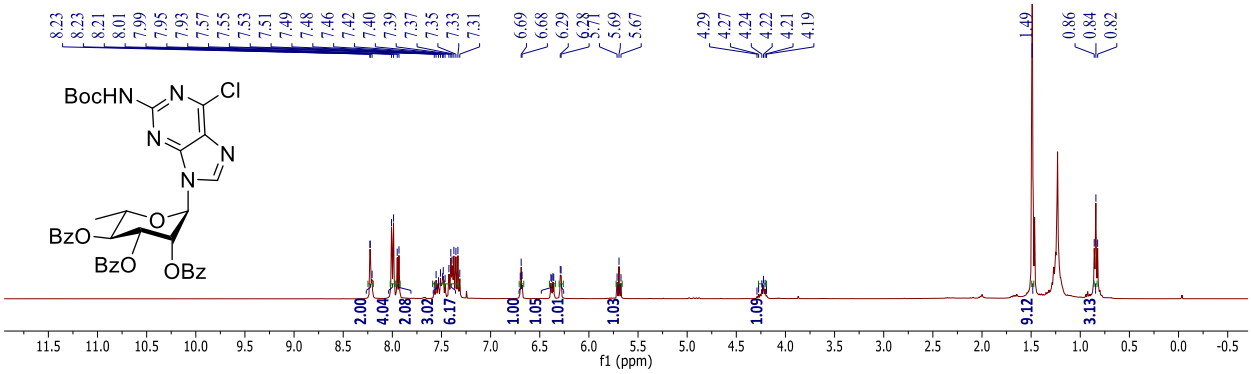
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4f**



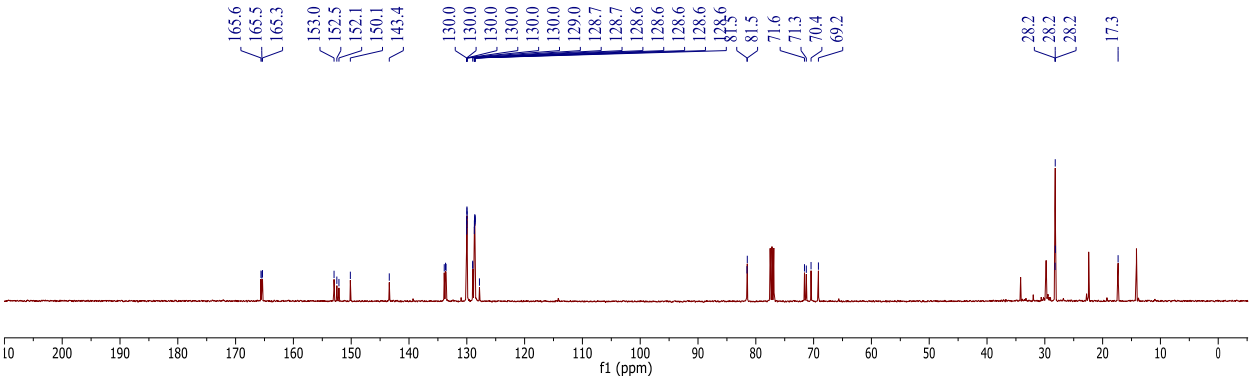
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4f**



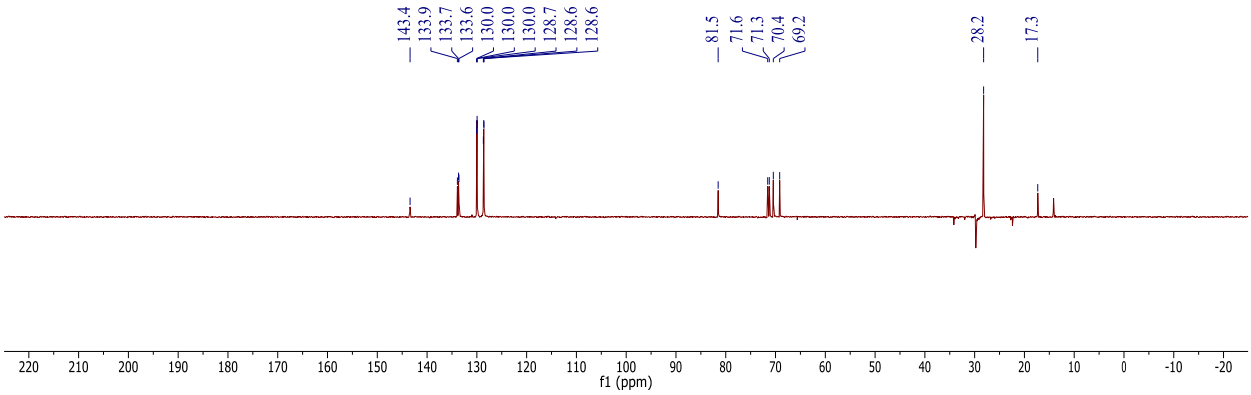
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **4g**



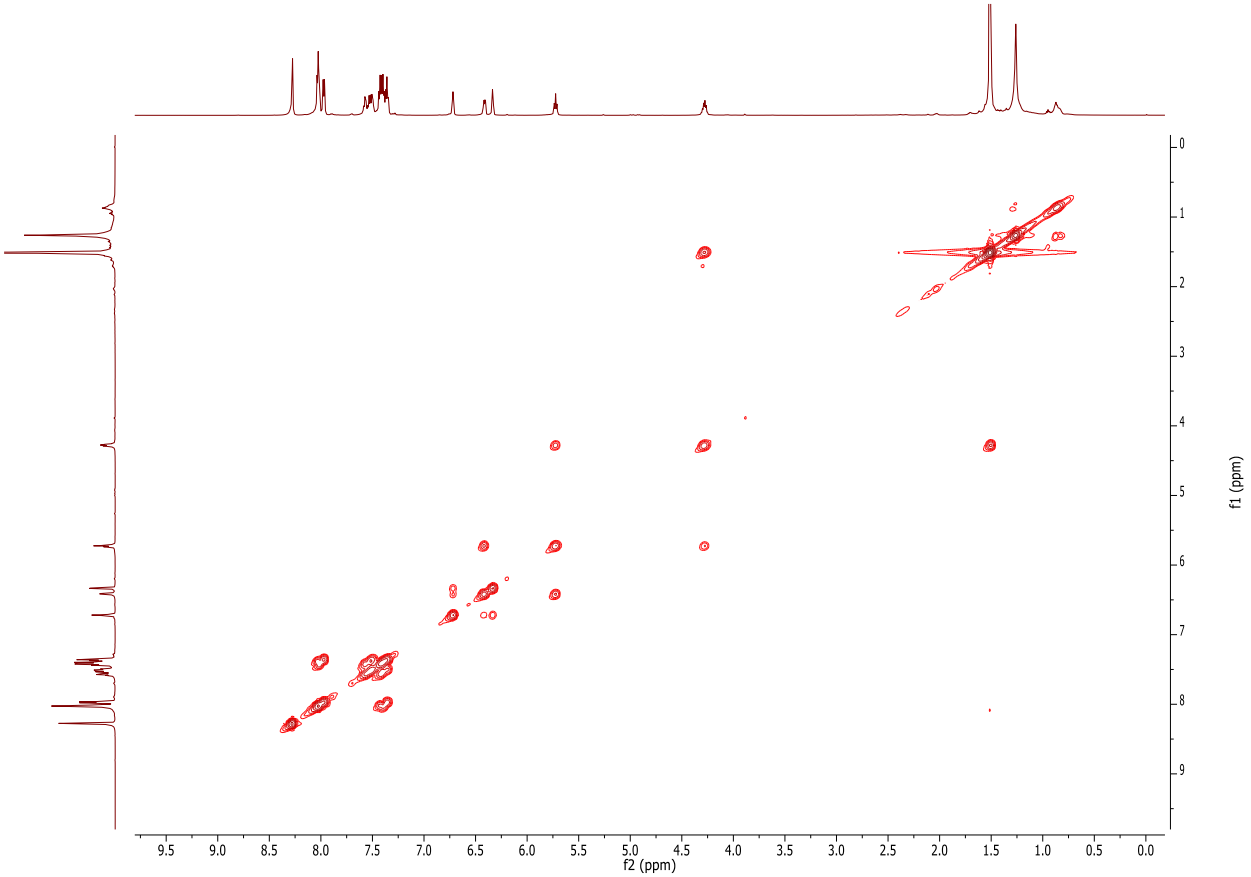
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4g**



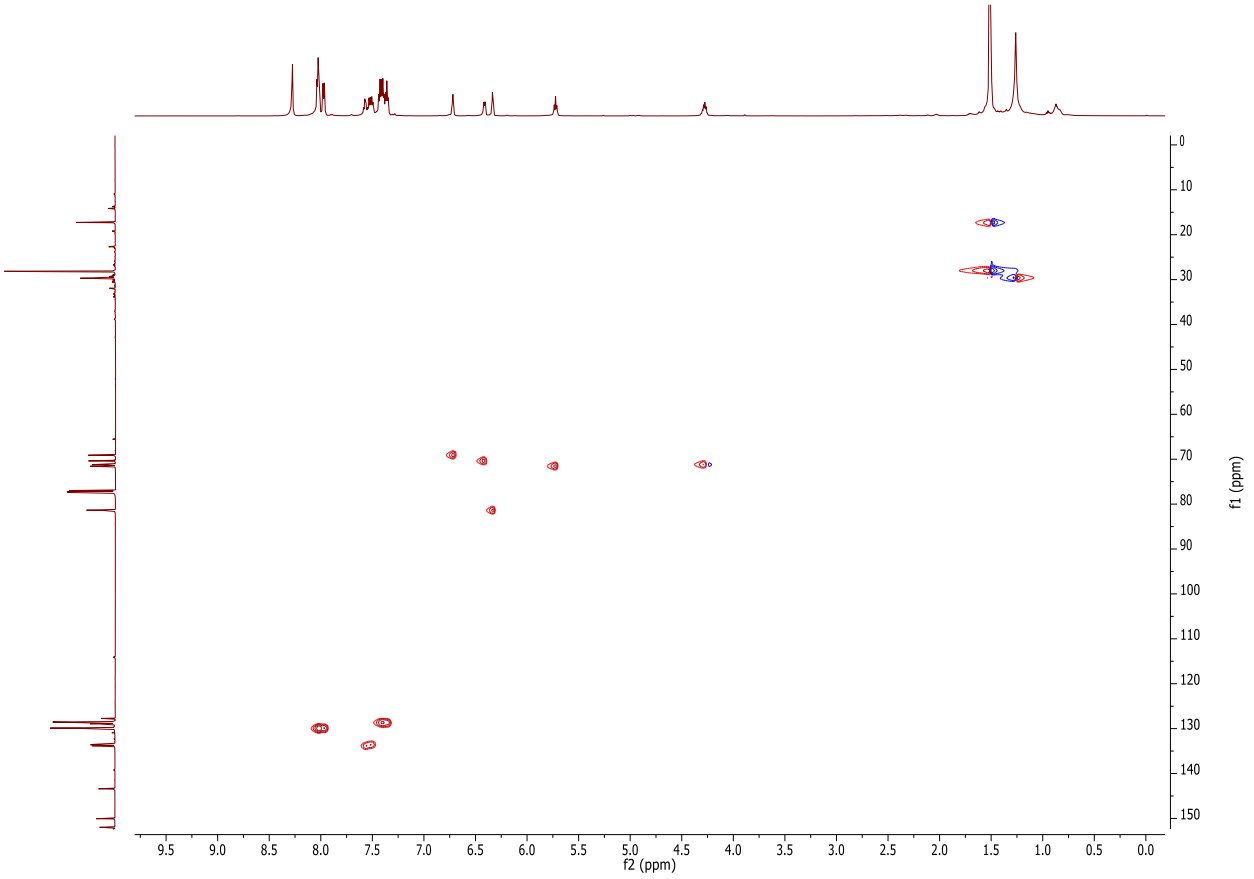
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **4g**



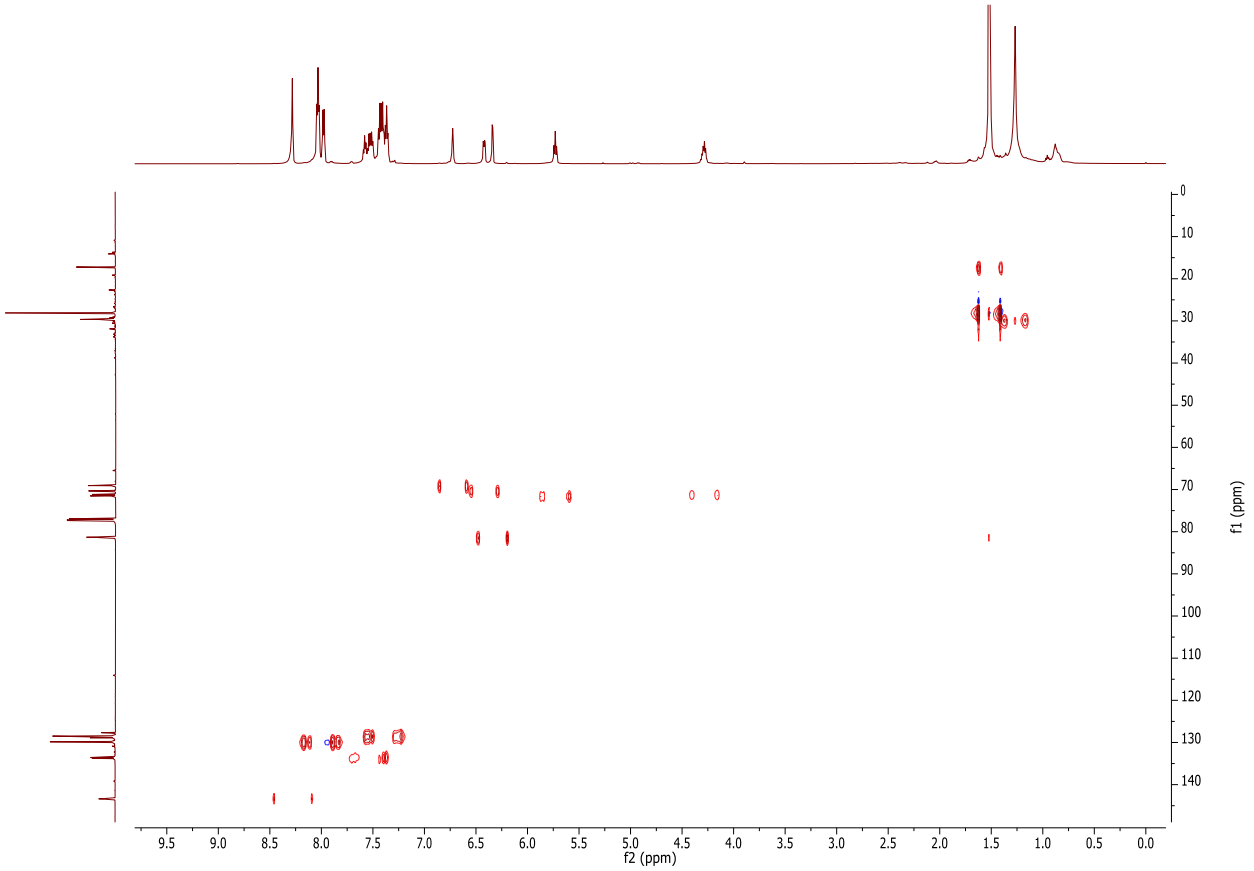
^{1}H-^{1}H COSY NMR Spectrum (600 MHz, $CDCl_3$) of Compound **4g**



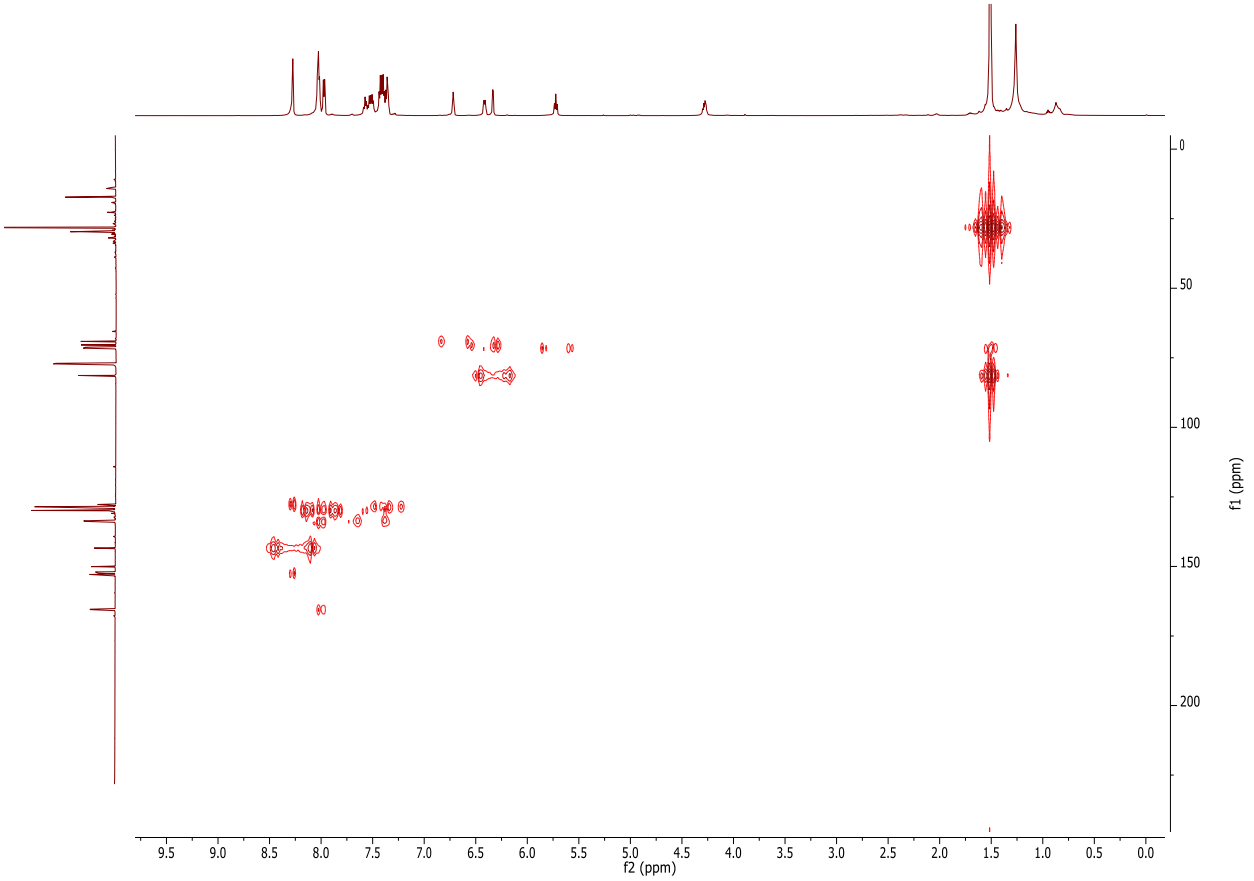
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **4g**



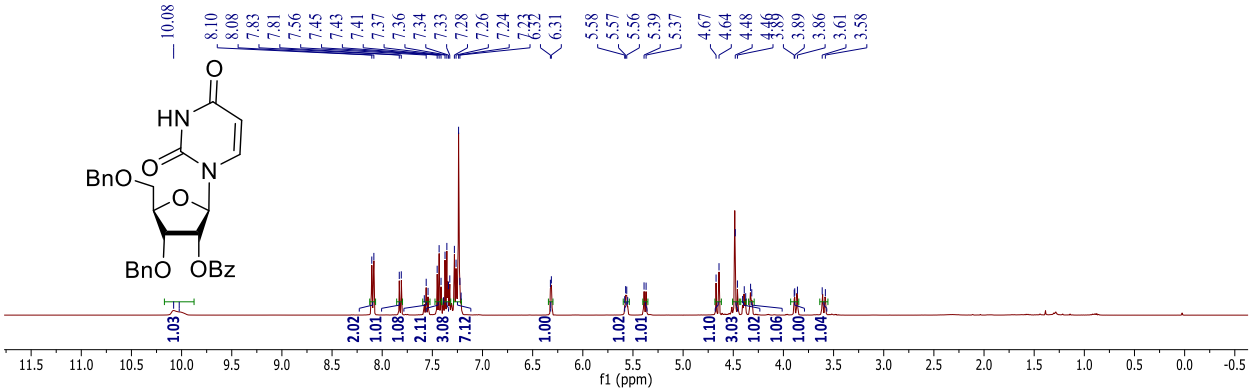
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **4g**



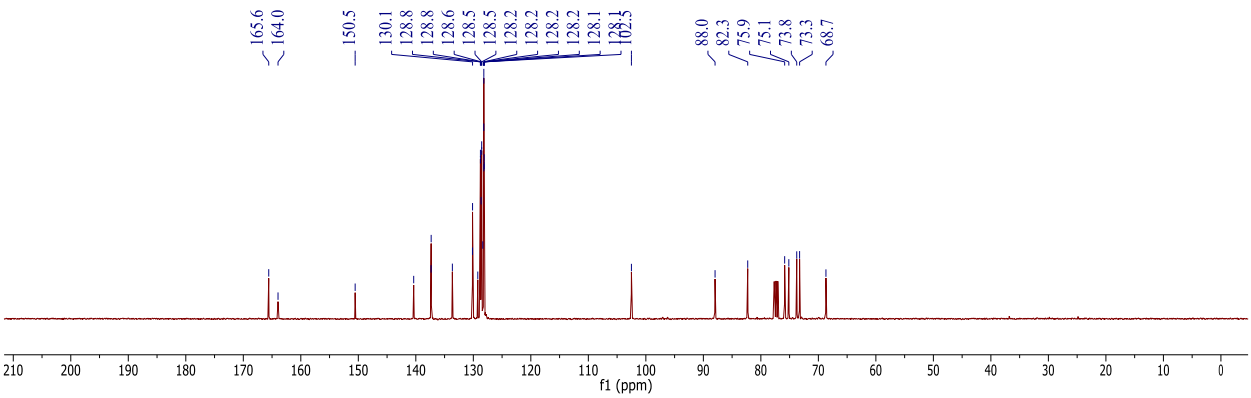
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **4g**



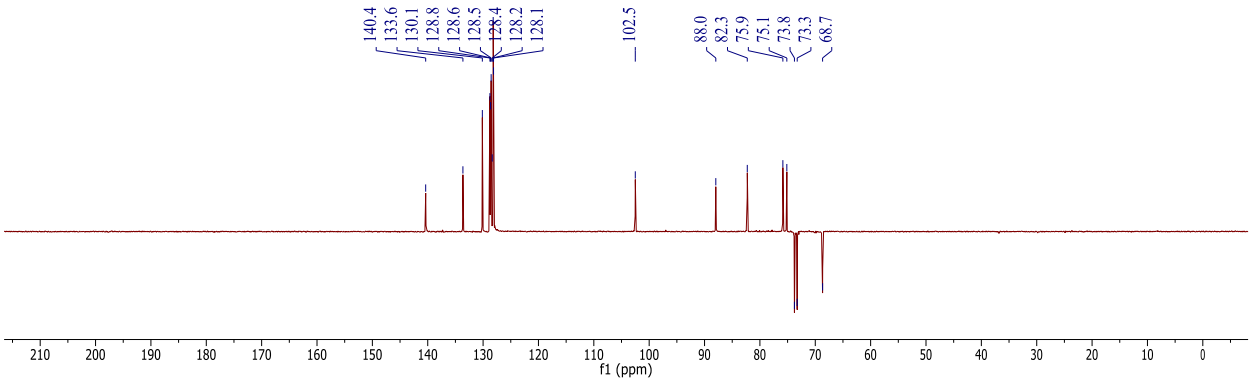
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7a**



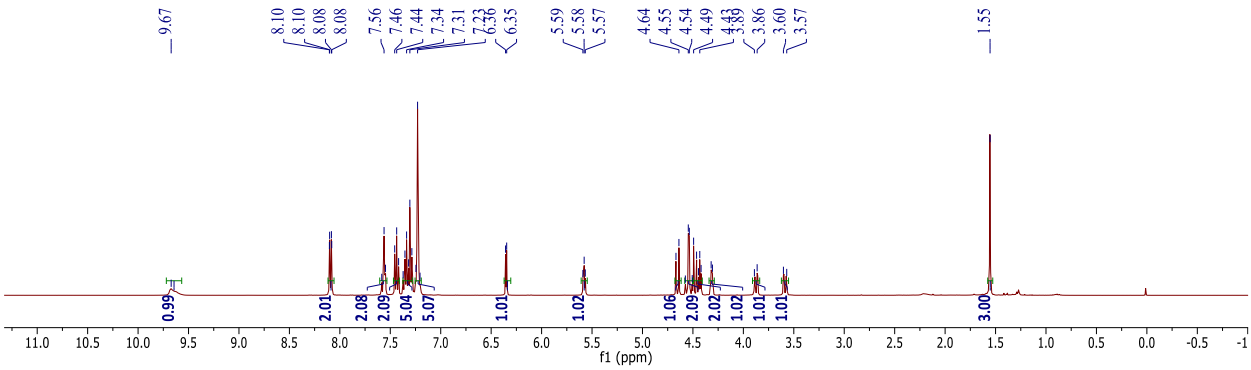
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7a**

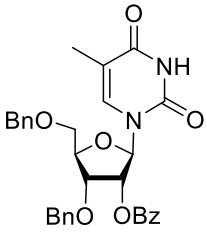


DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7a**

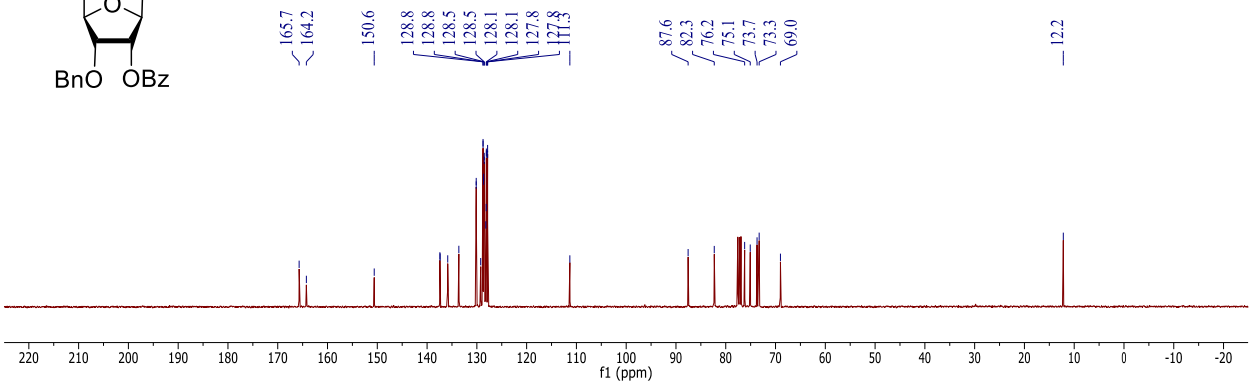


^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7b**

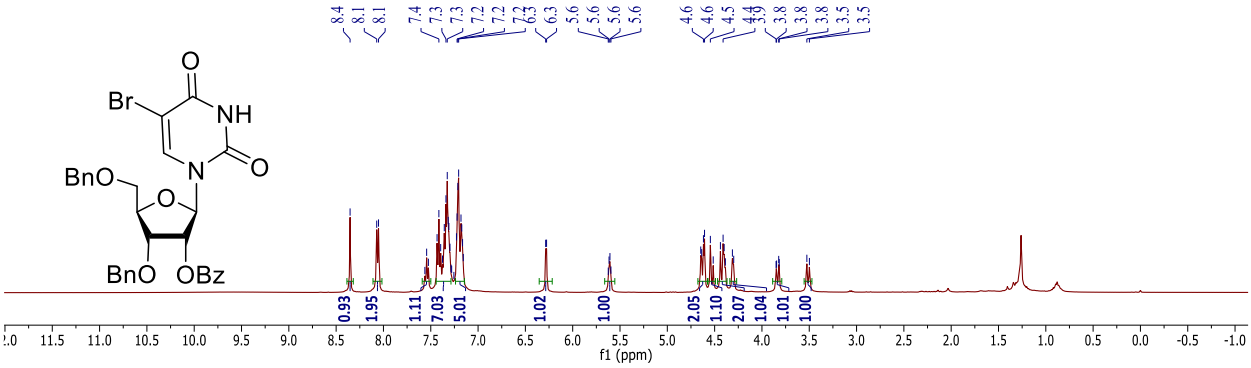




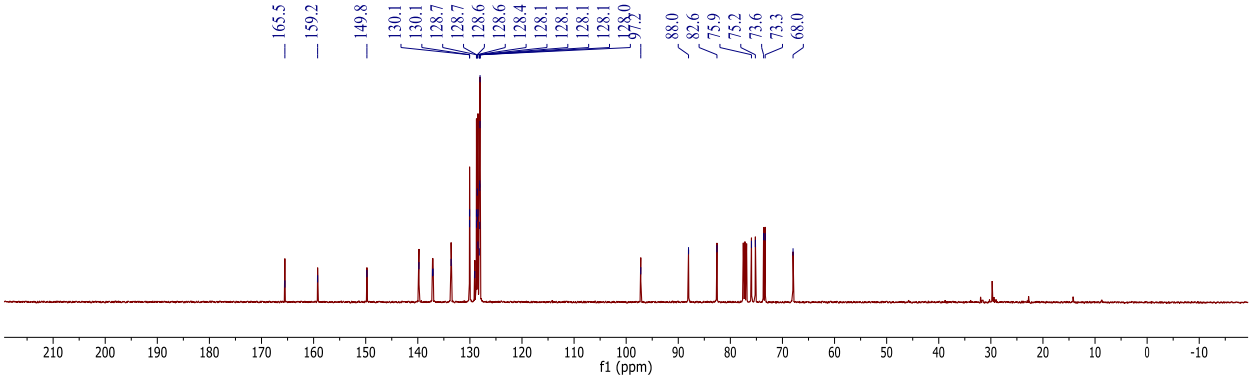
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7b**



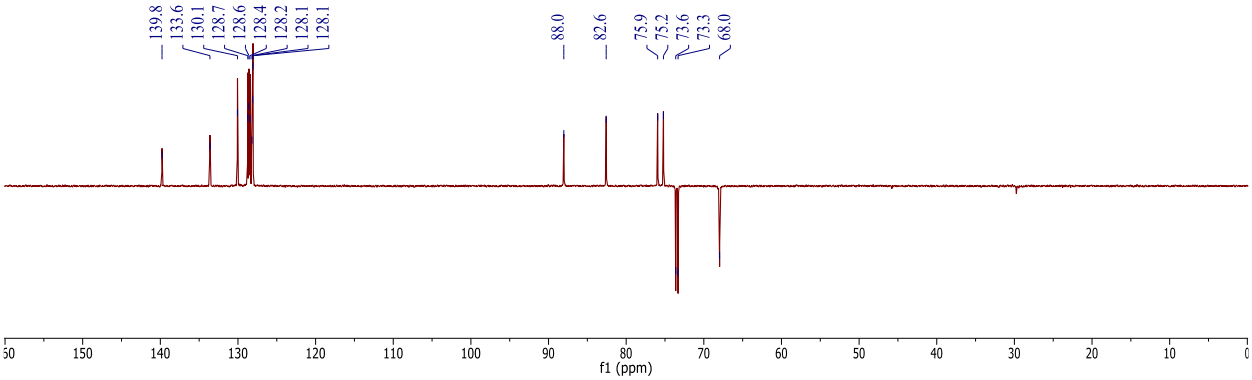
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7c**



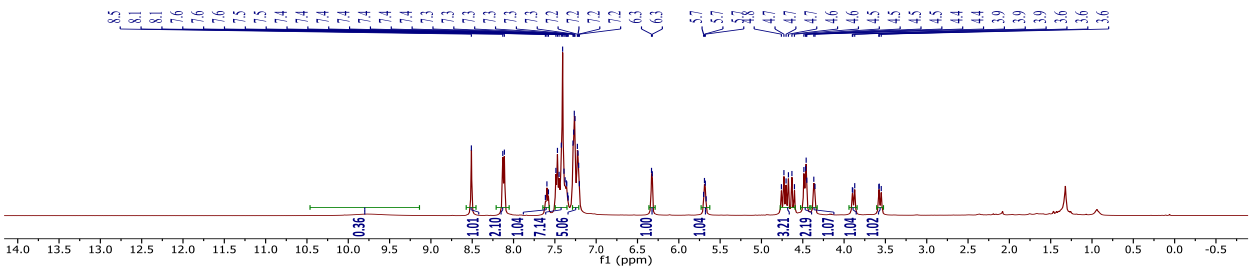
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7c**



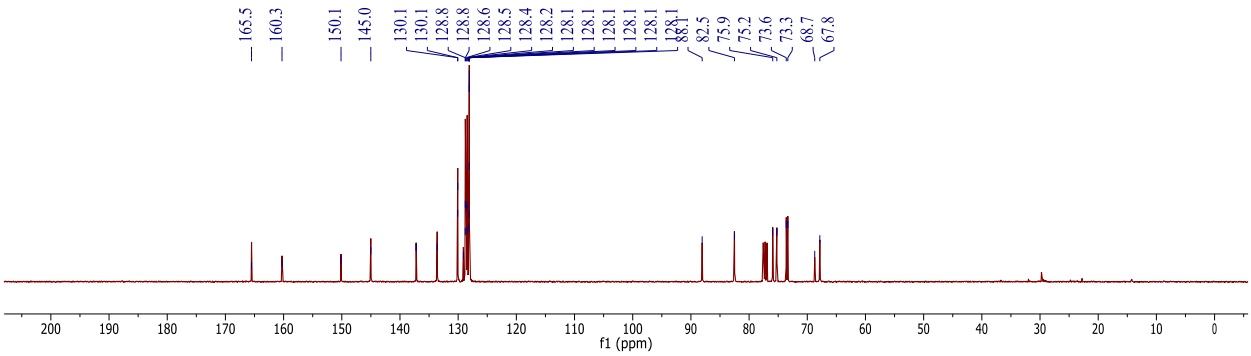
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7c**



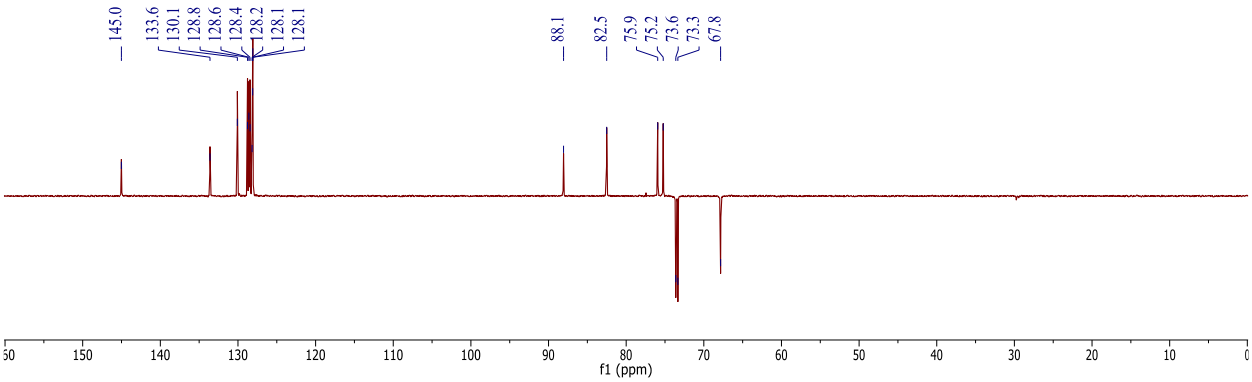
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7d**



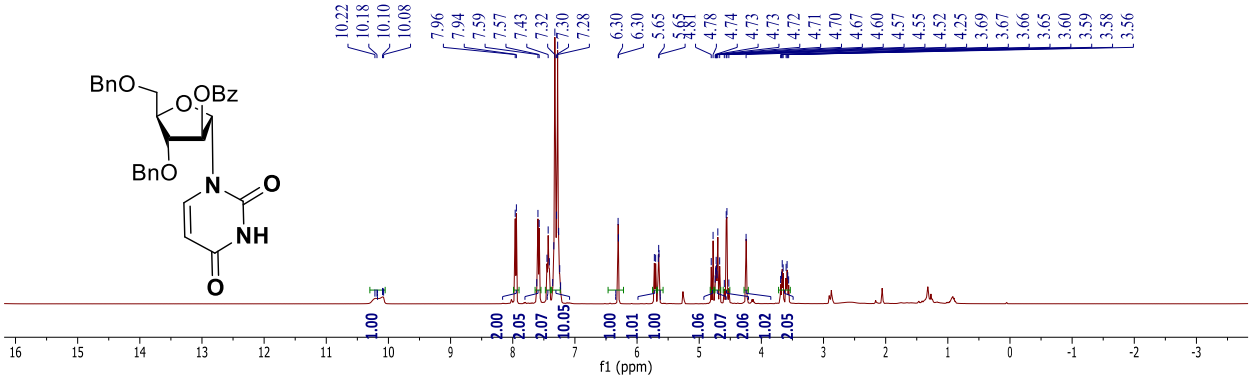
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7d**



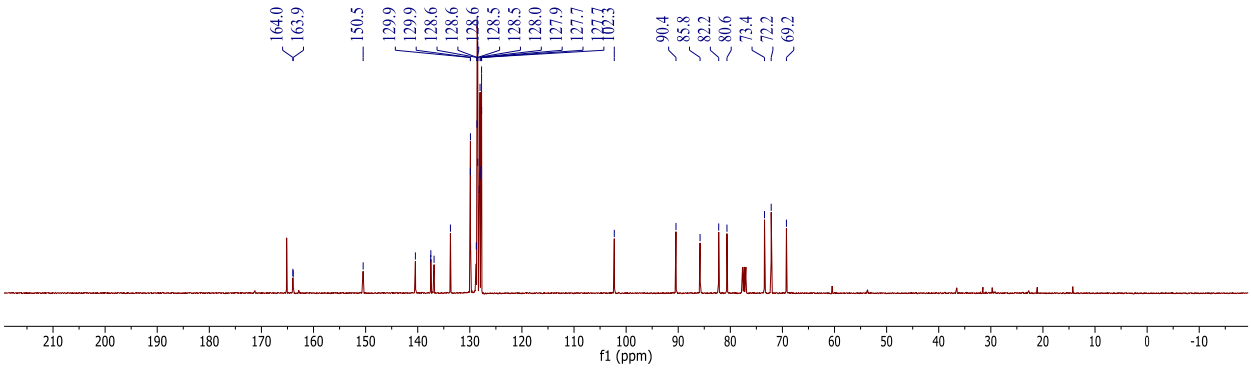
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7d**



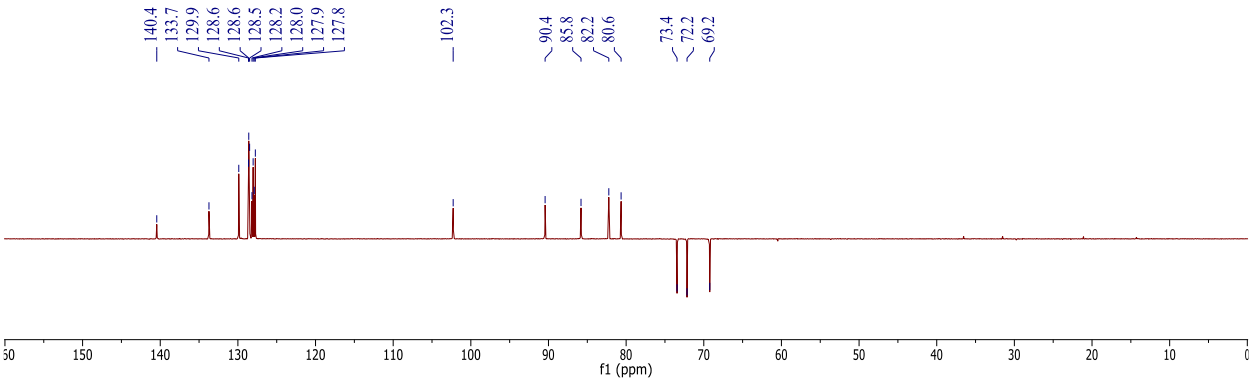
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7e**



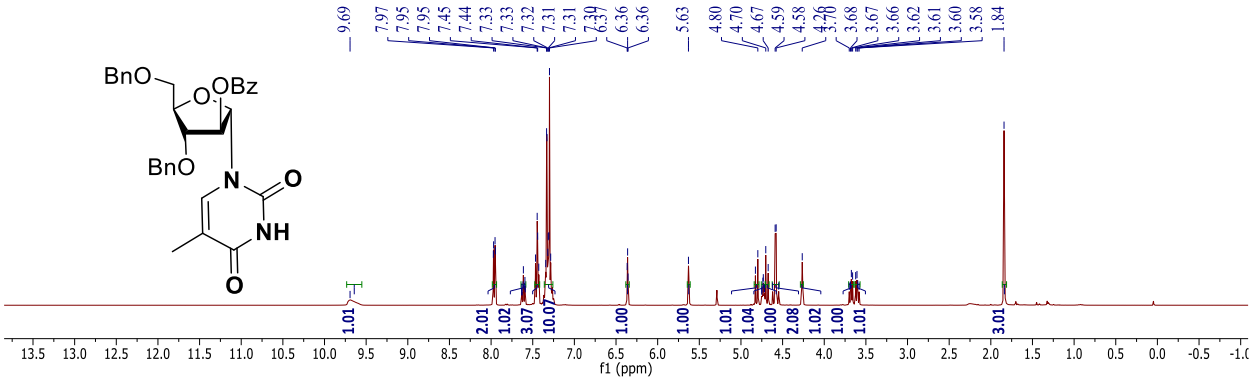
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7e**



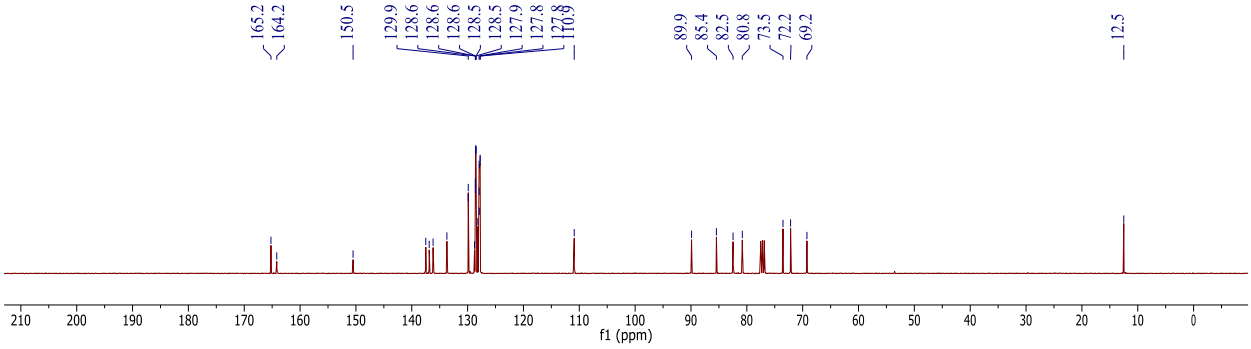
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7e**



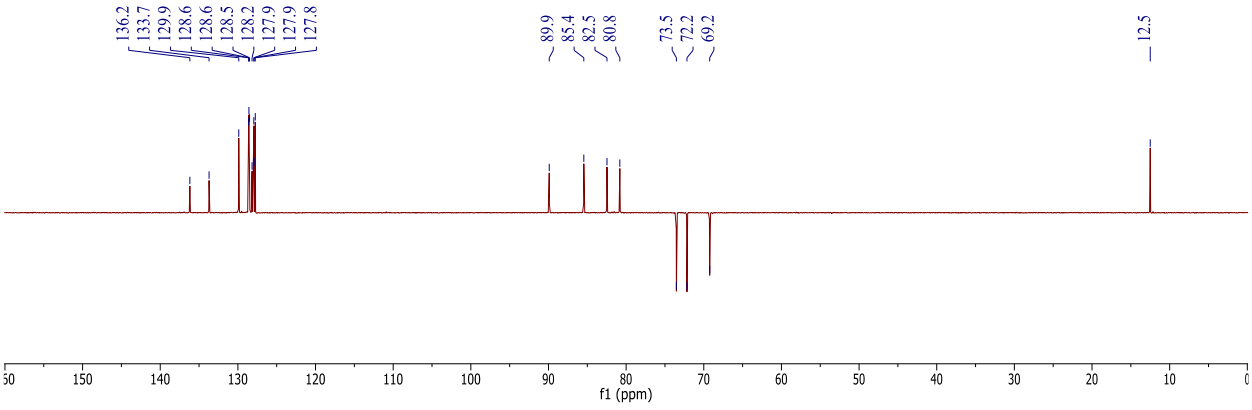
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7f**



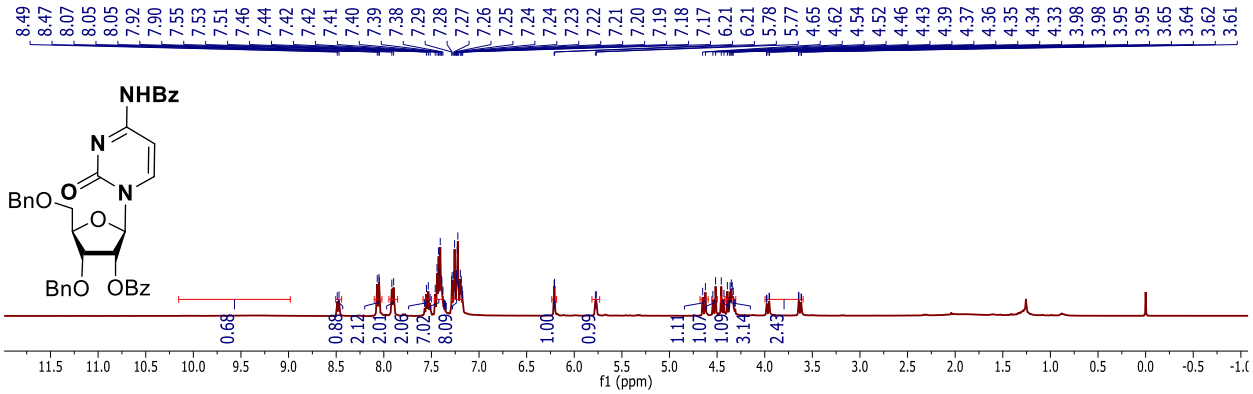
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7f**



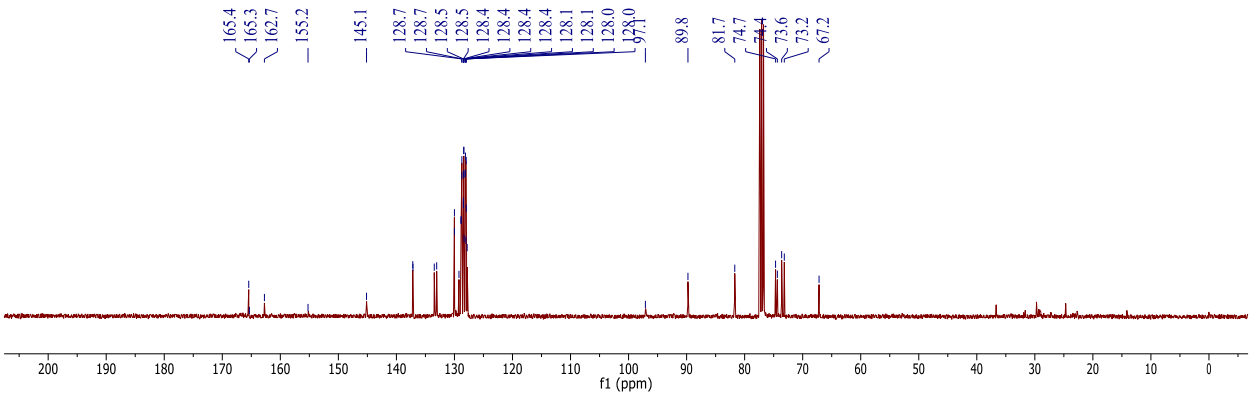
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7f**



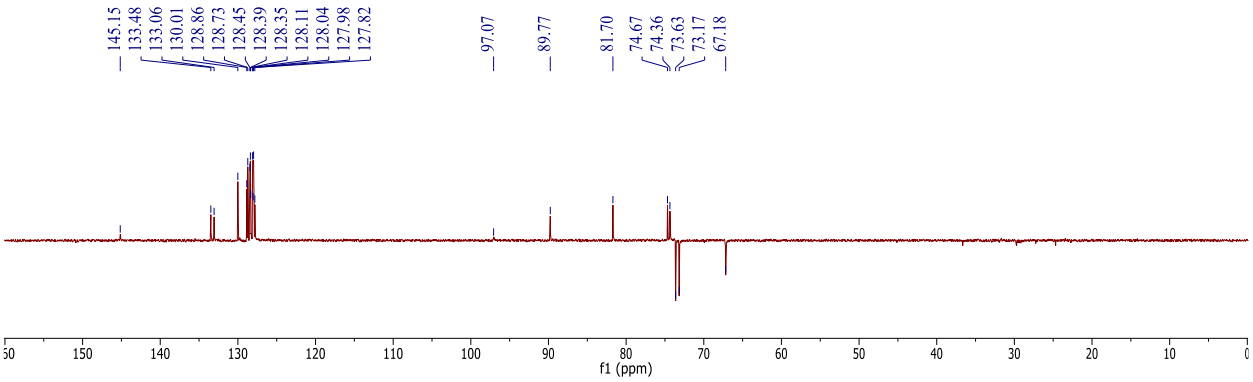
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7g**



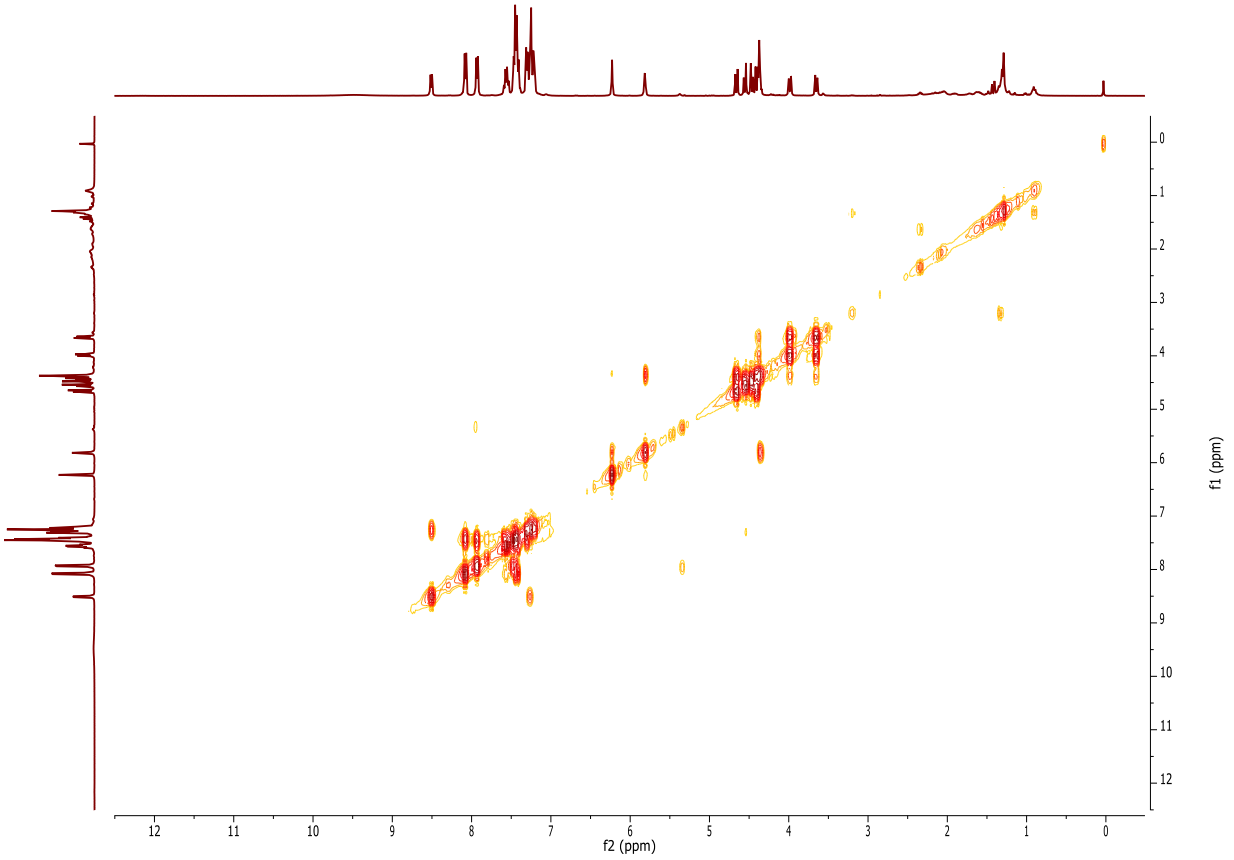
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7g**



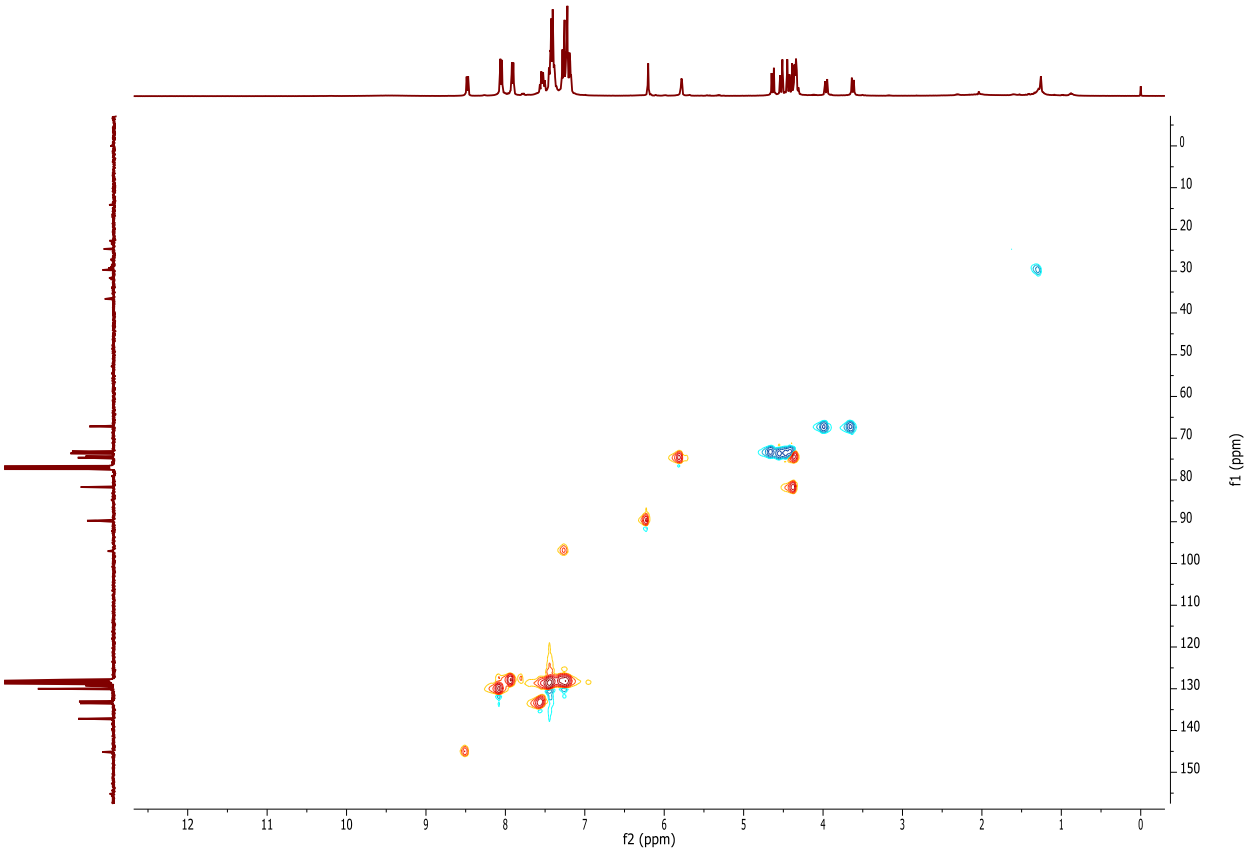
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7g**



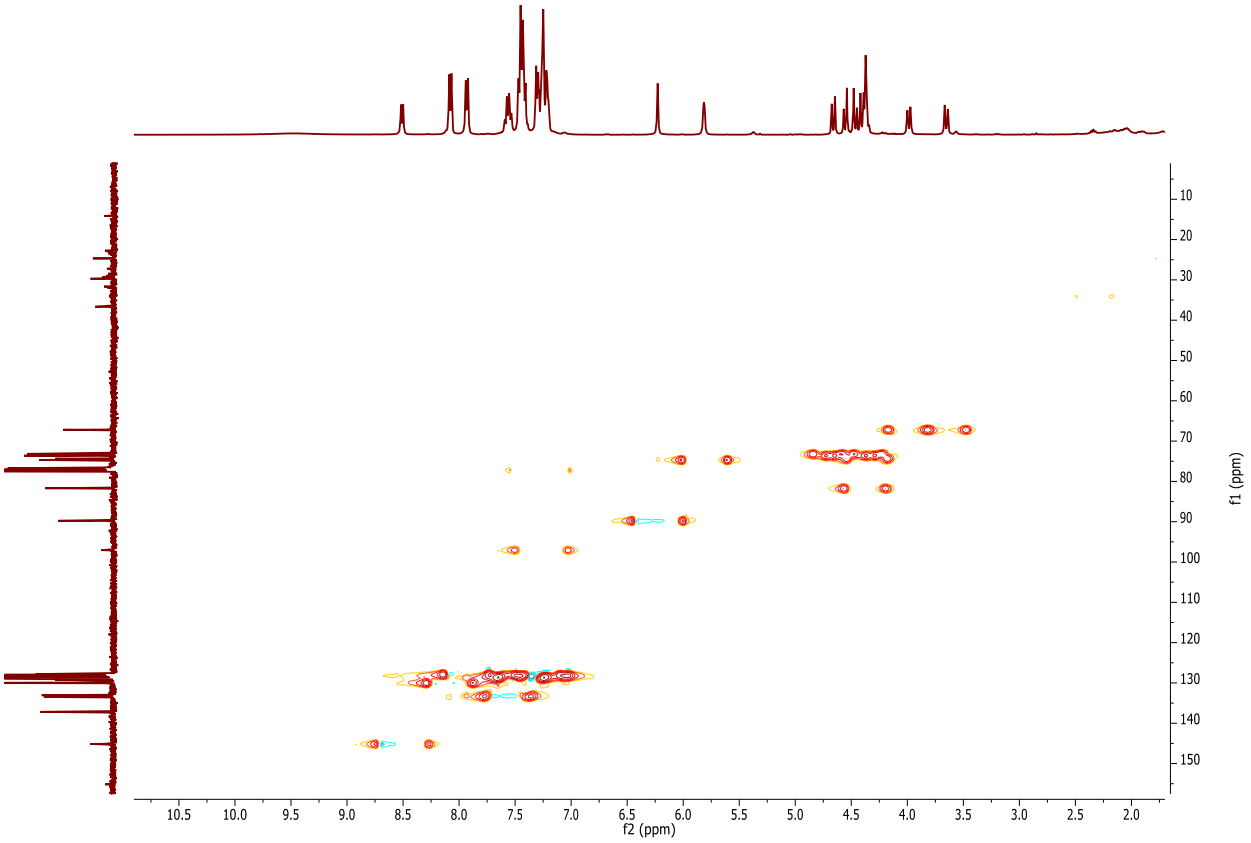
^{1}H-^{1}H COSY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7g**



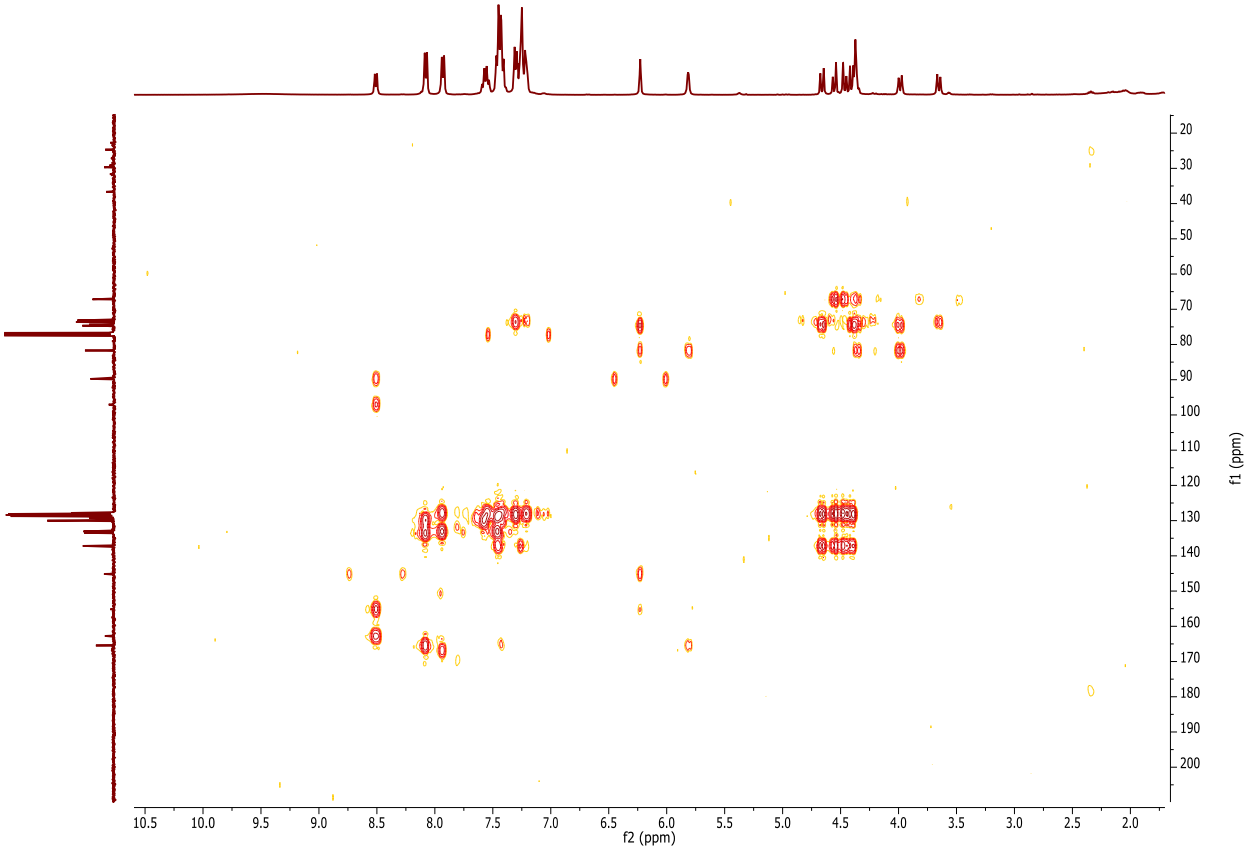
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **7g**



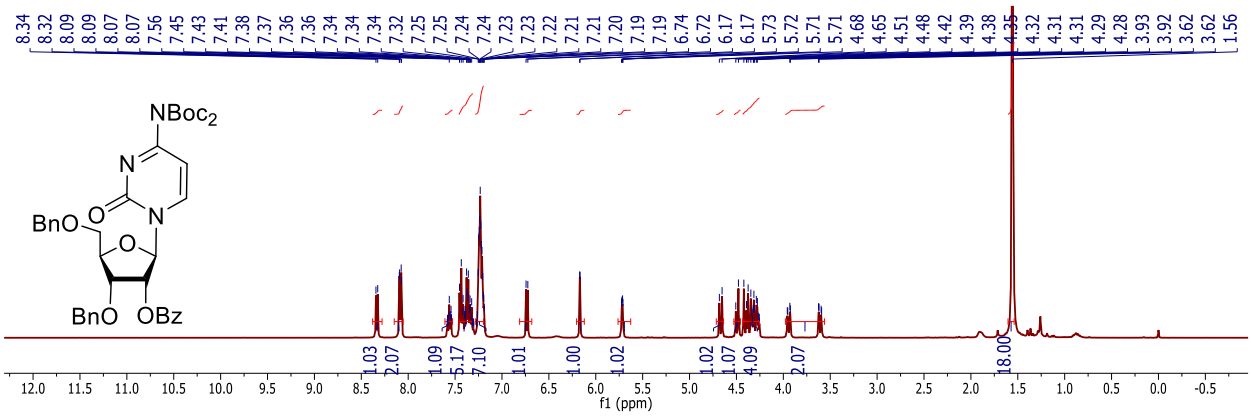
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **7g**



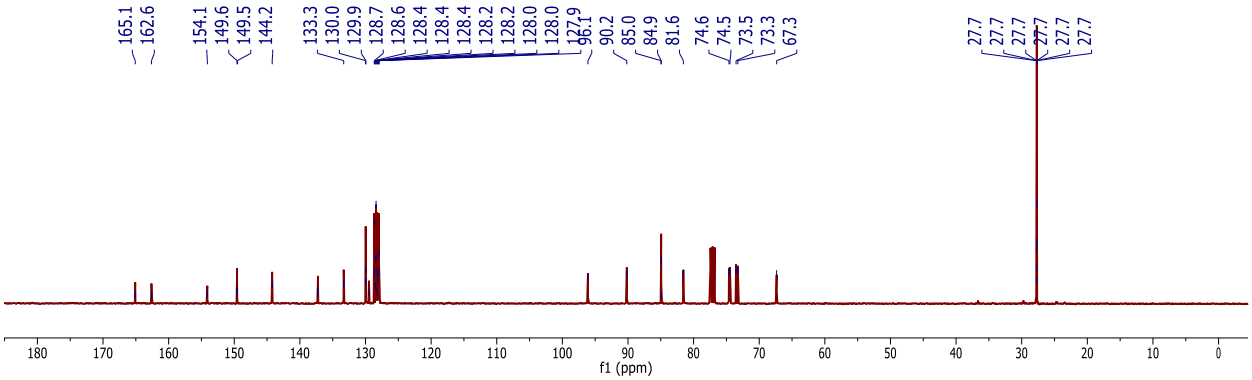
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **7g**



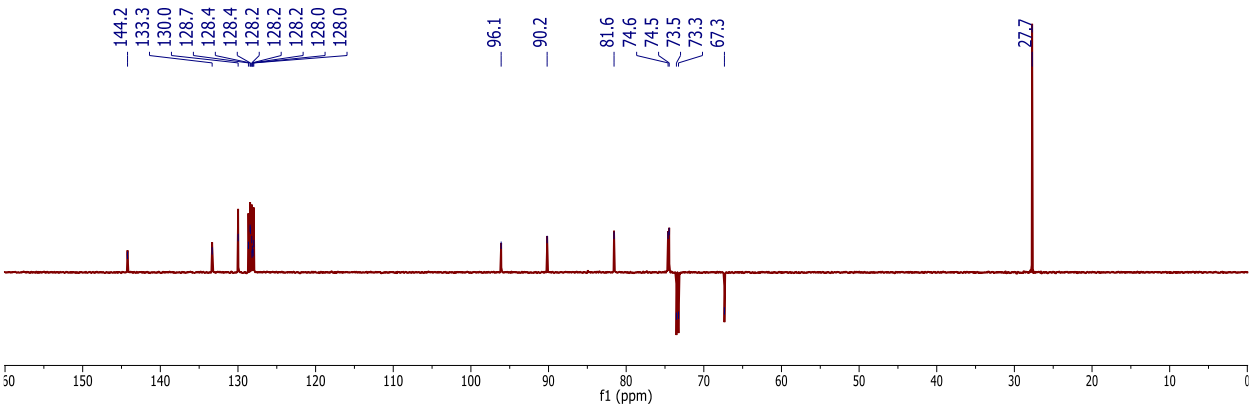
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7h**



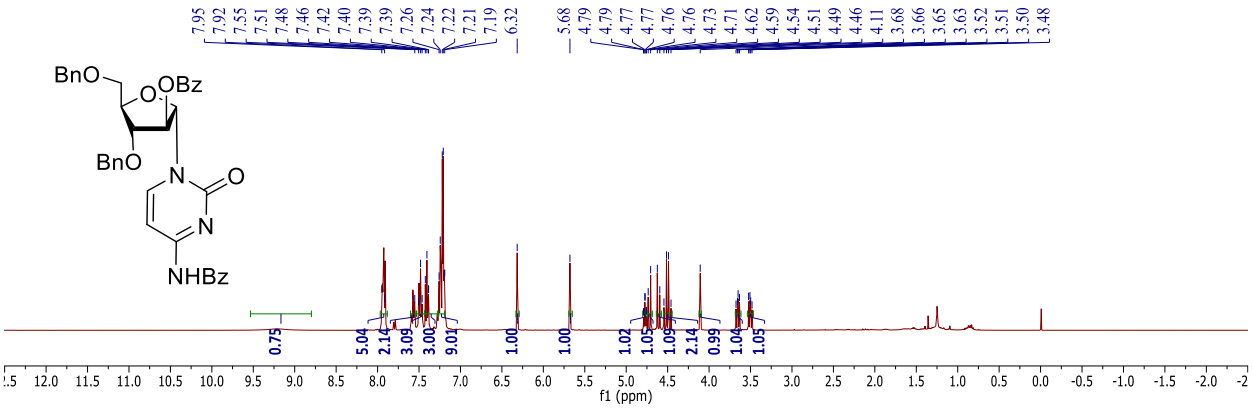
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7h**



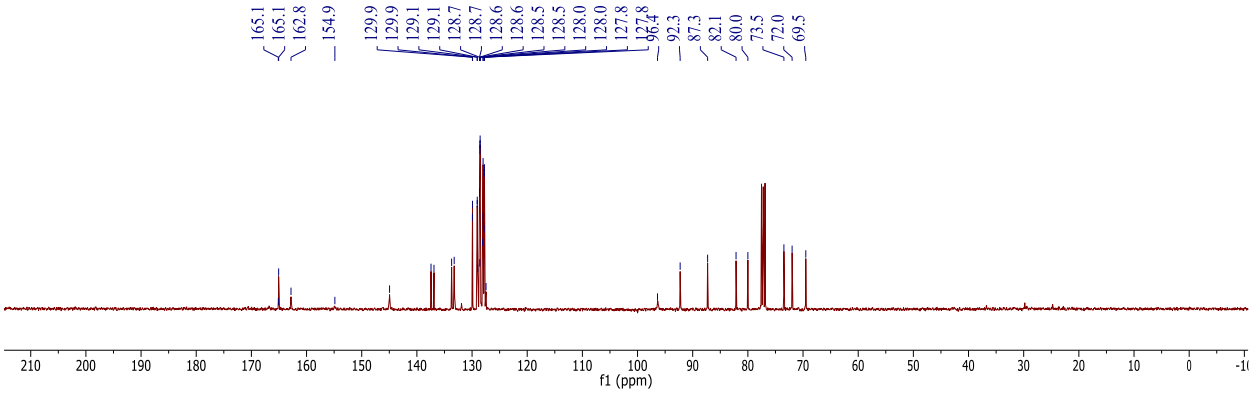
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7h**



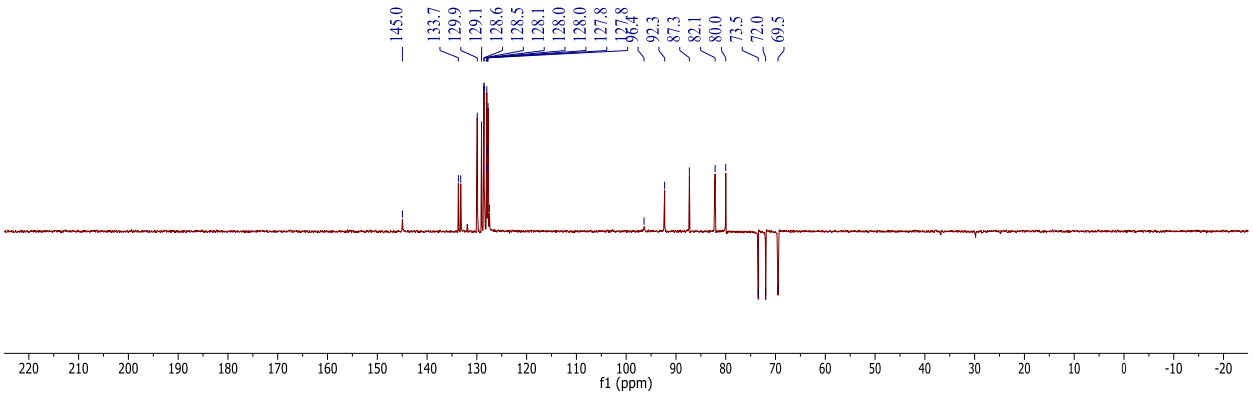
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **7i**



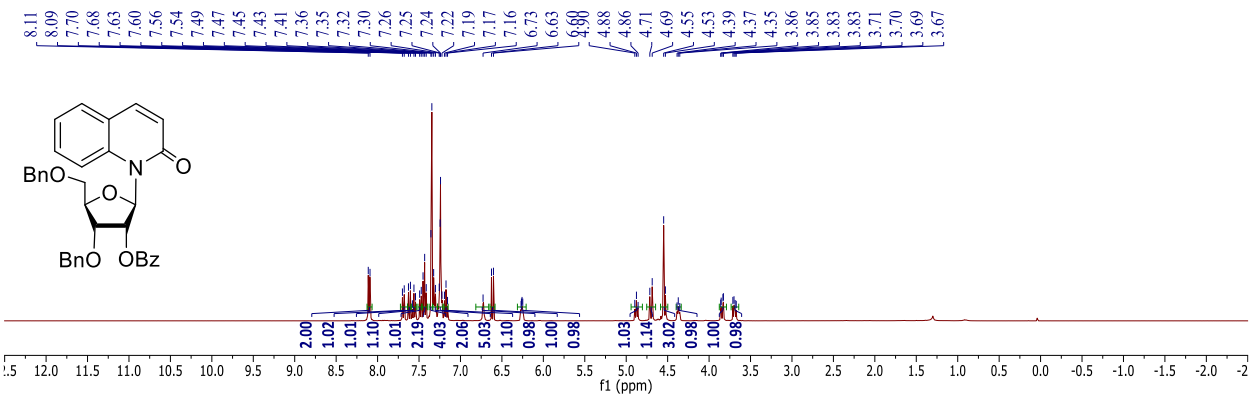
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7i**



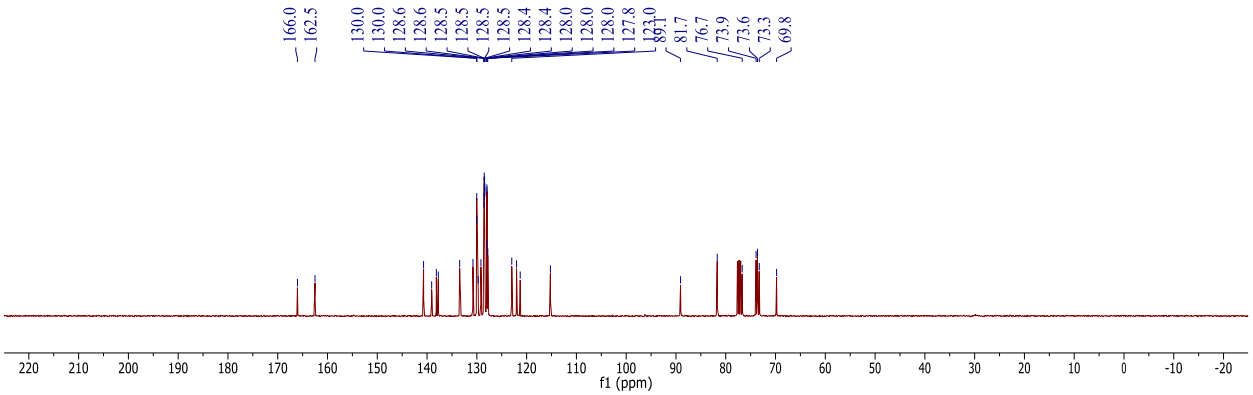
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **7i**



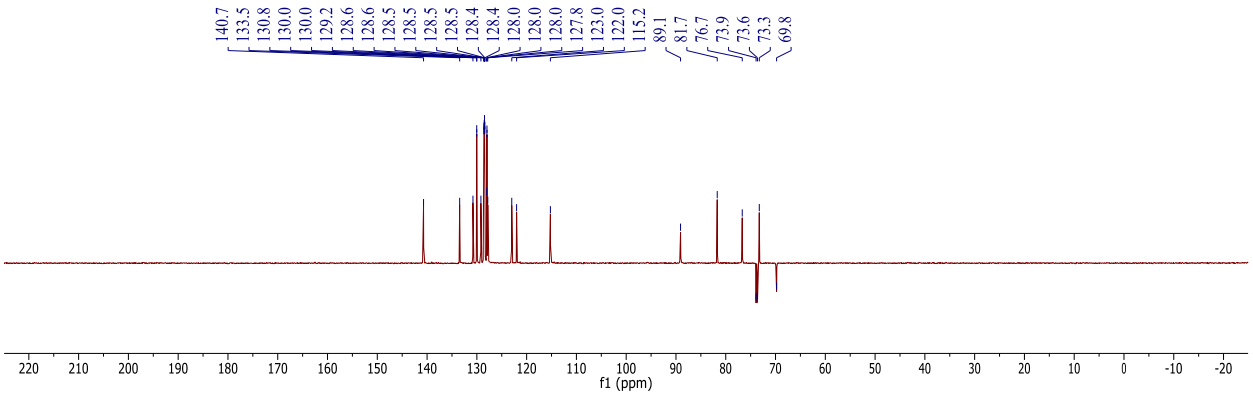
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9a**



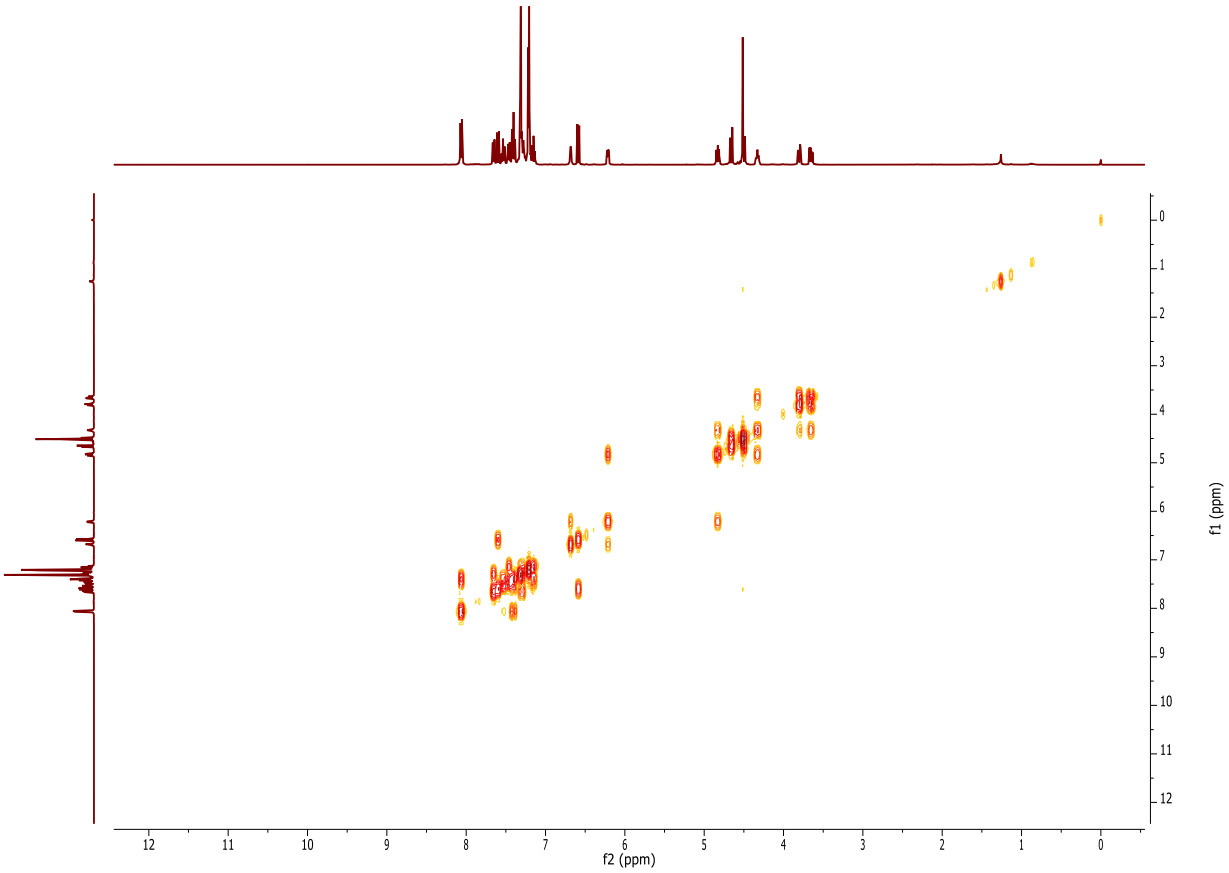
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9a**



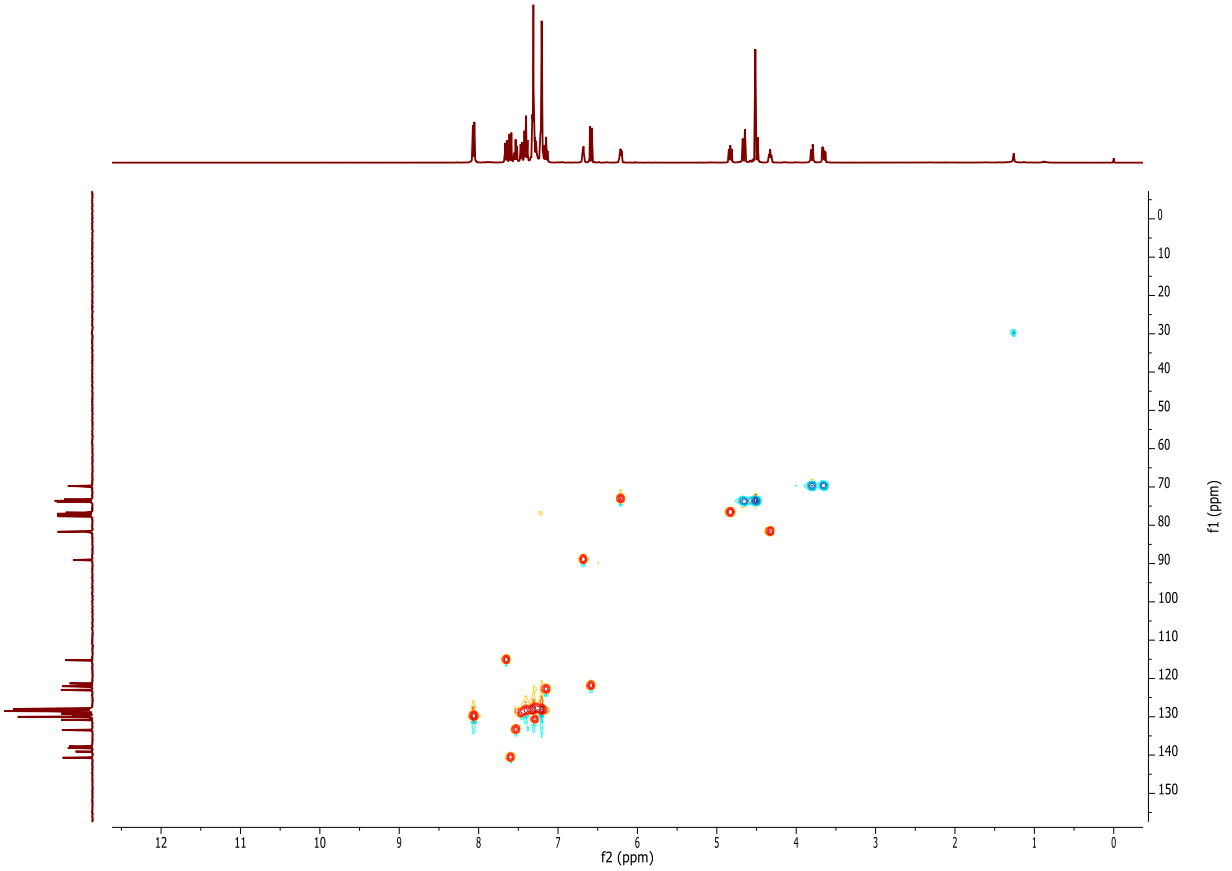
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9a**



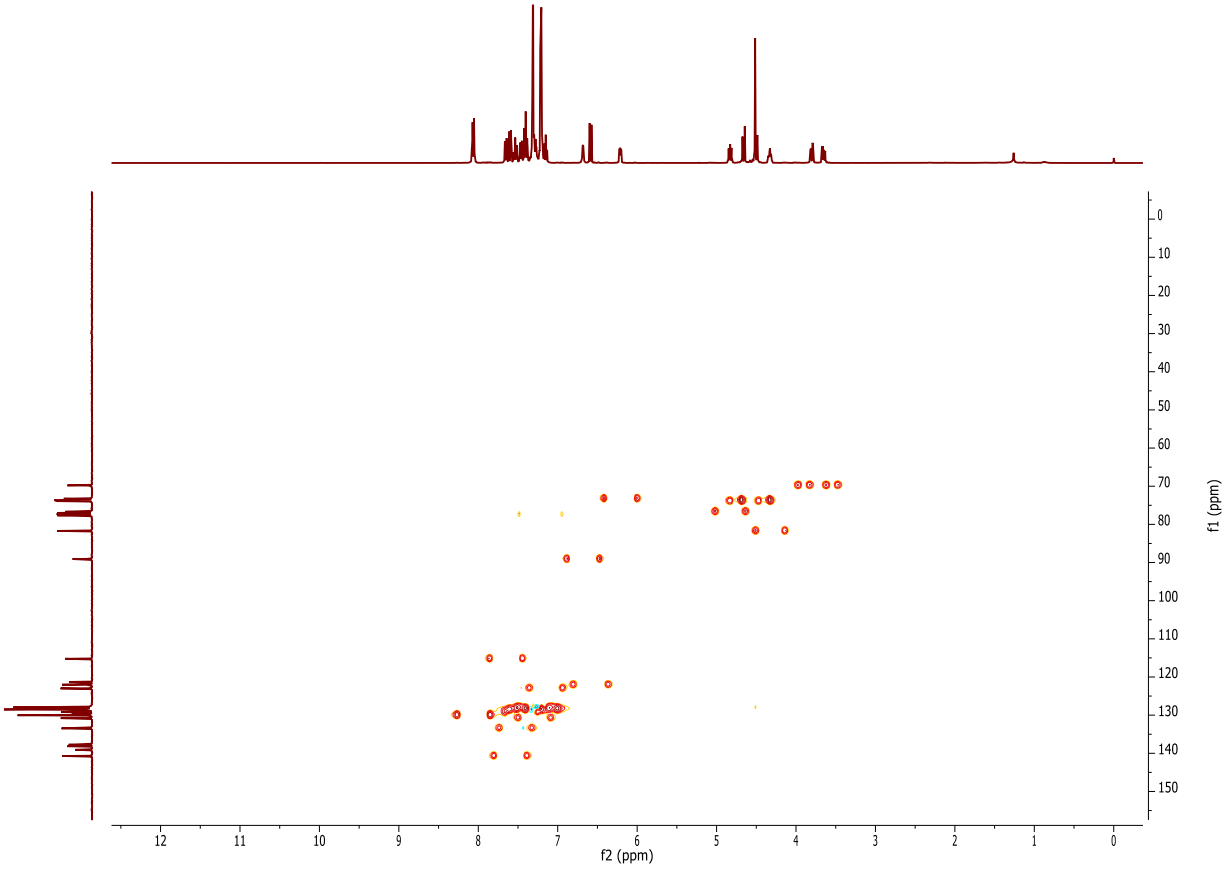
^{1}H-^{1}H COSY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9a**



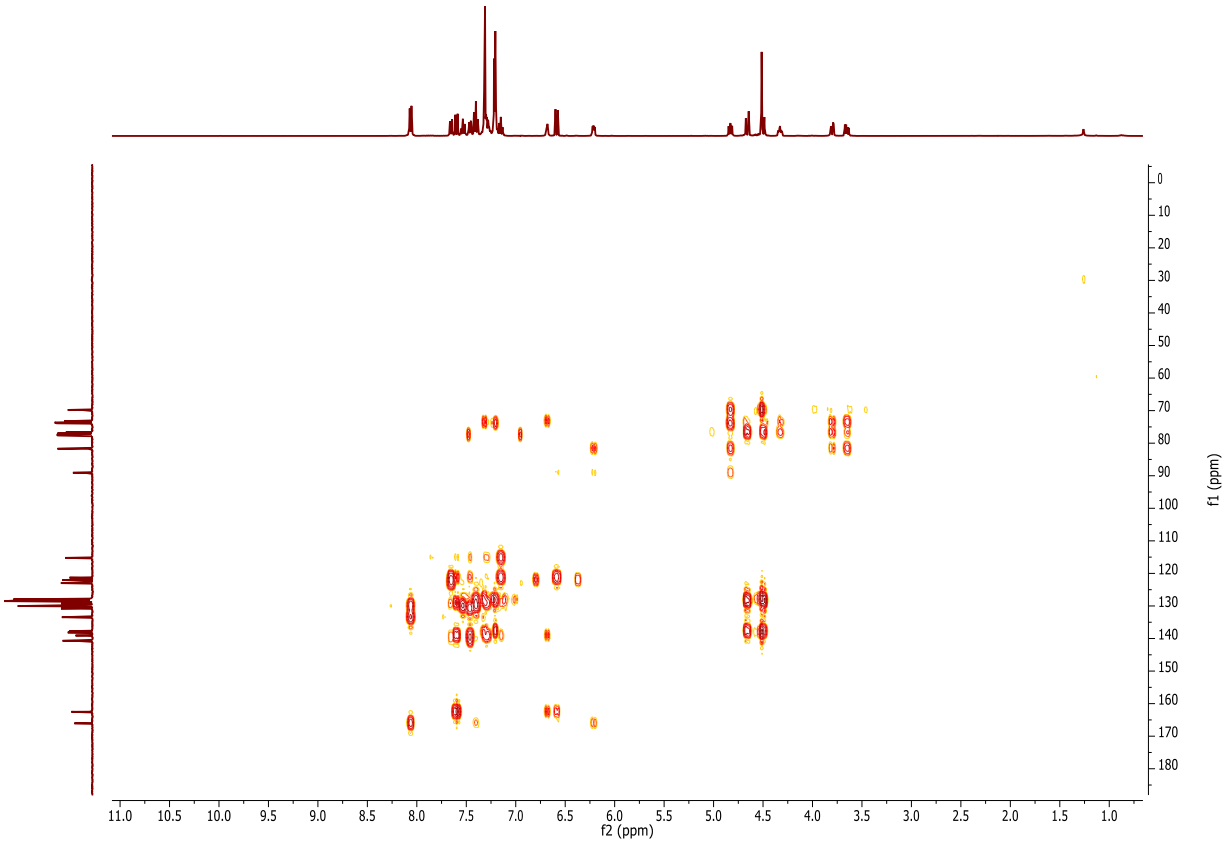
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9a**



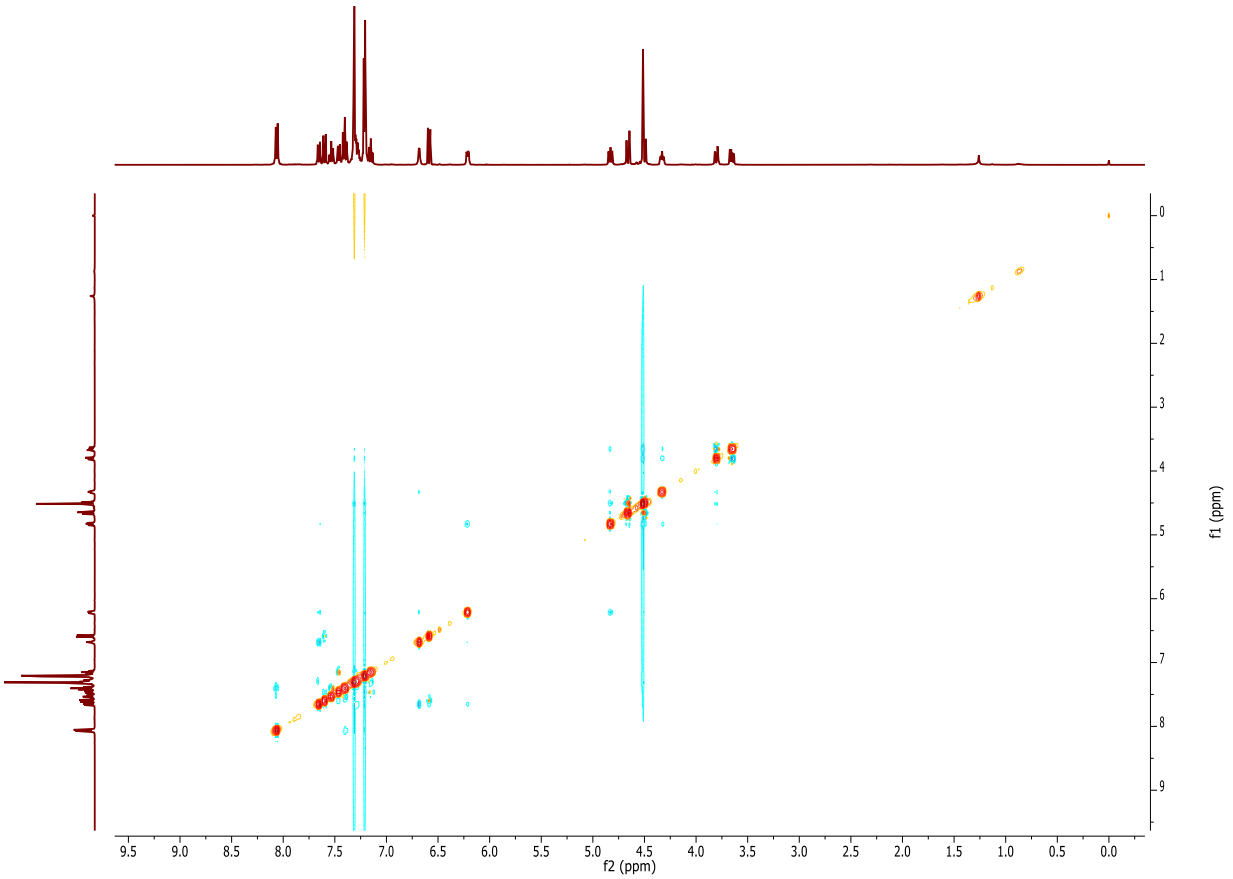
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9a**



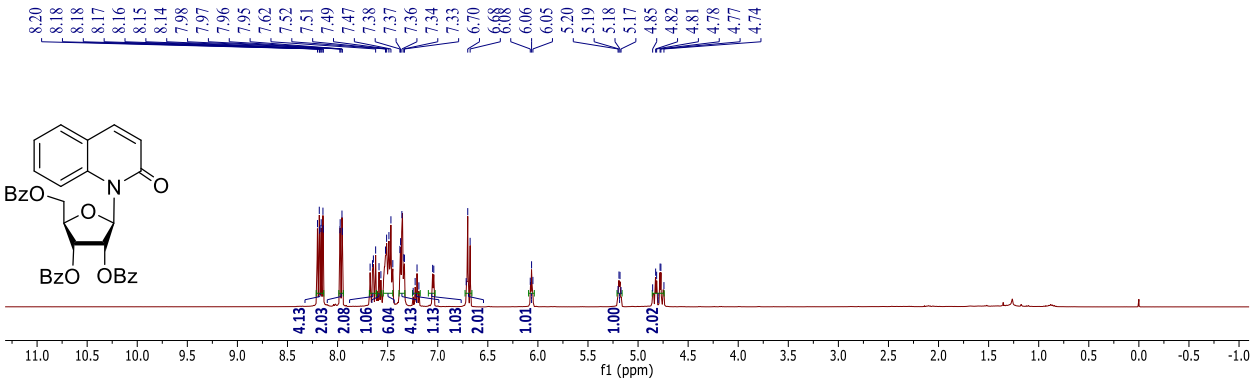
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9a**



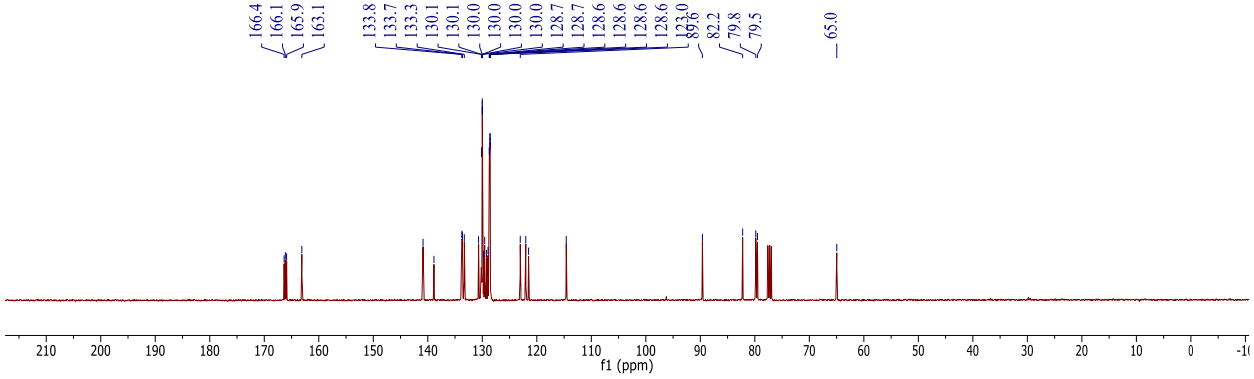
^{1}H-^{1}H NOESY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9a**



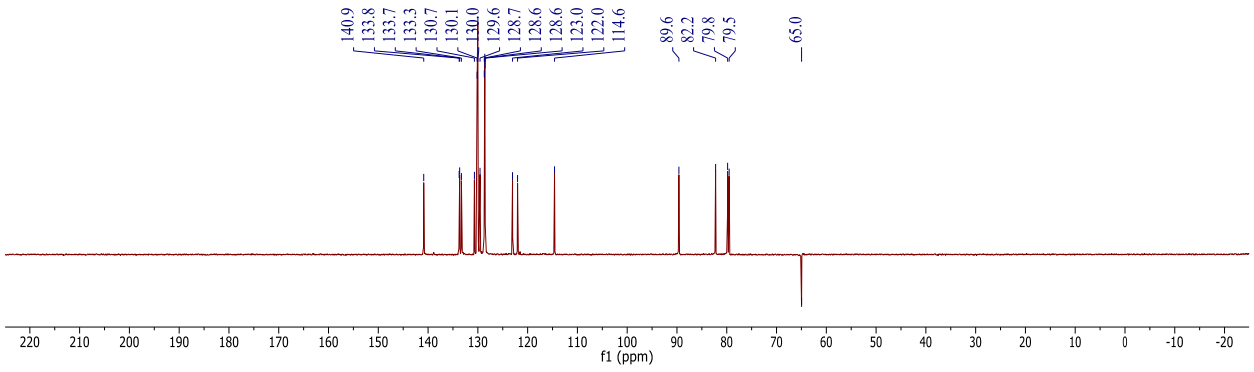
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9b**



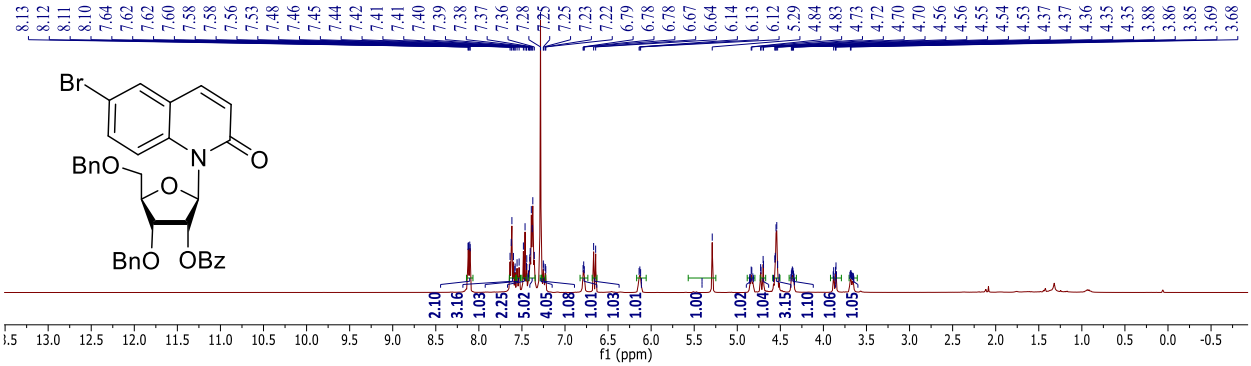
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9b**



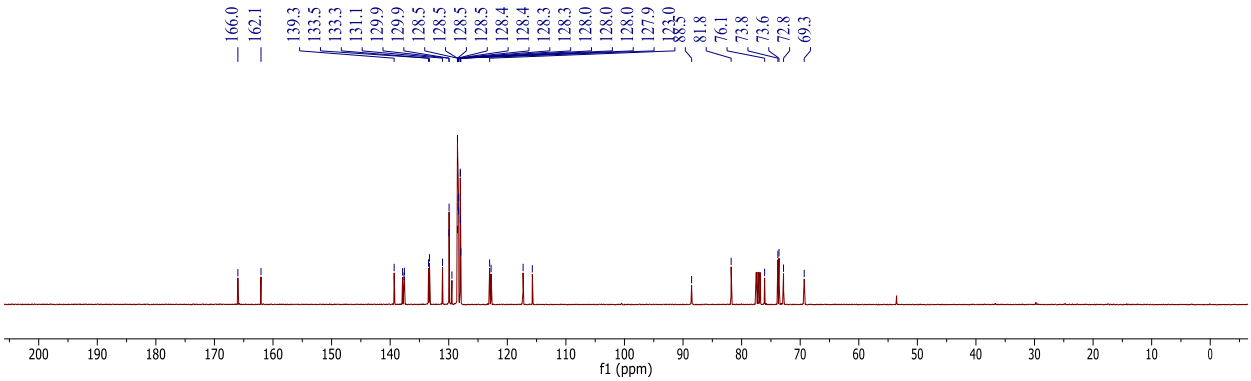
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9b**



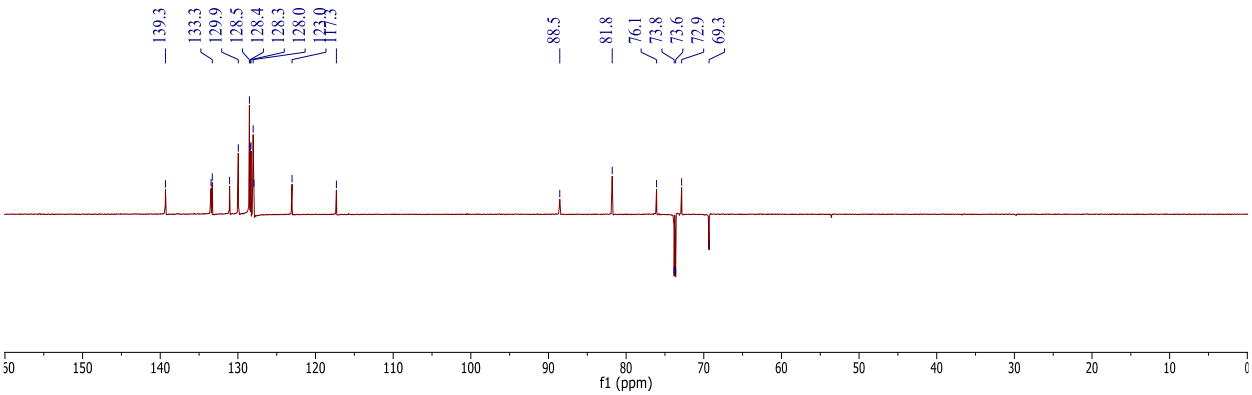
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9c**



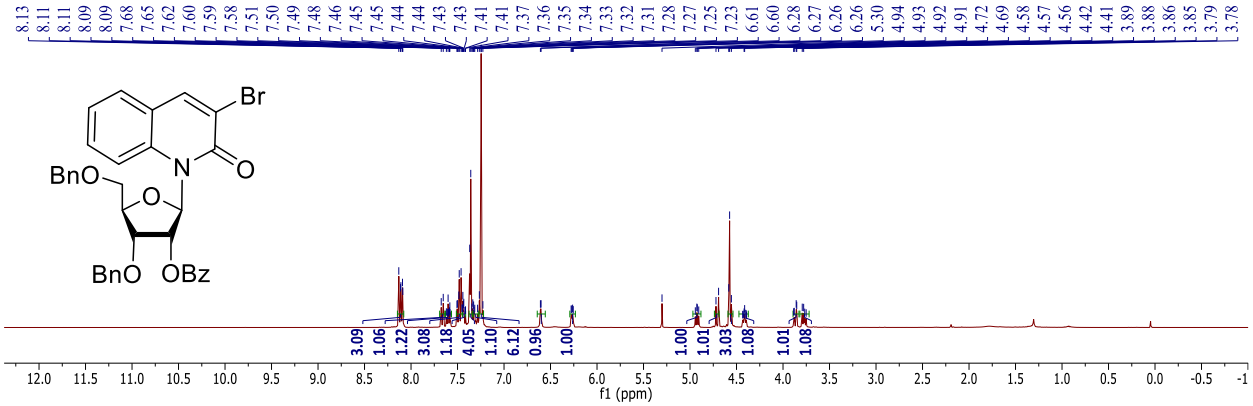
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9c**



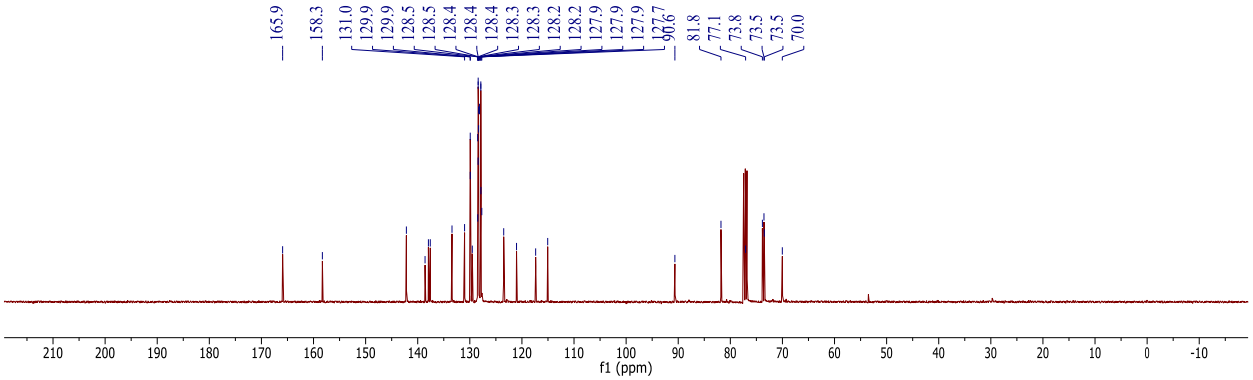
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9c**



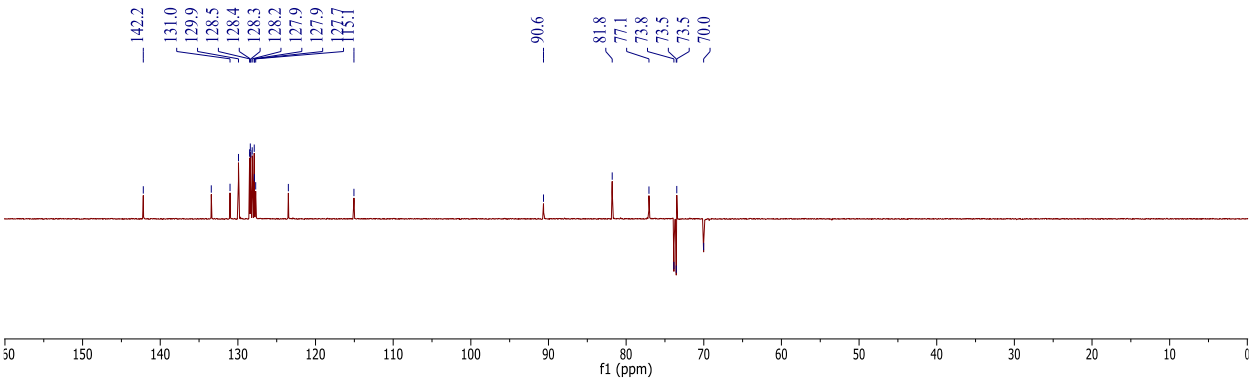
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9d**



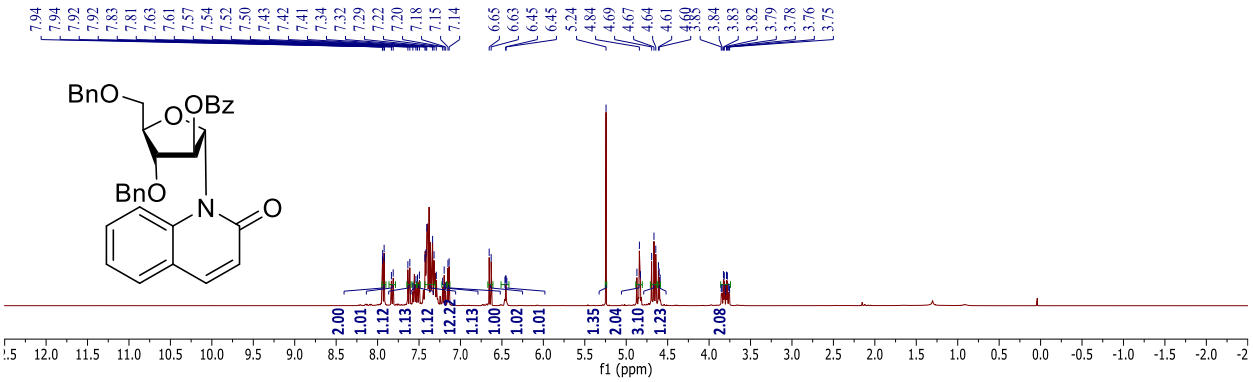
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9d**



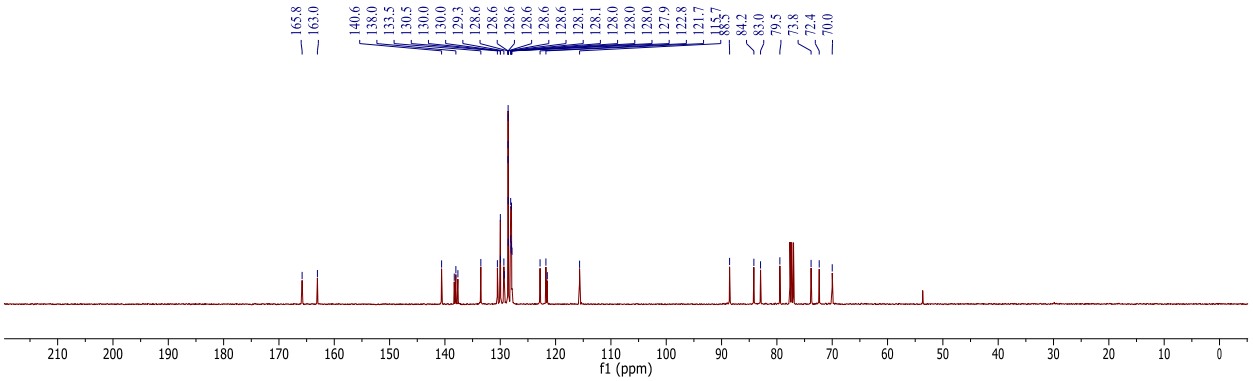
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9d**



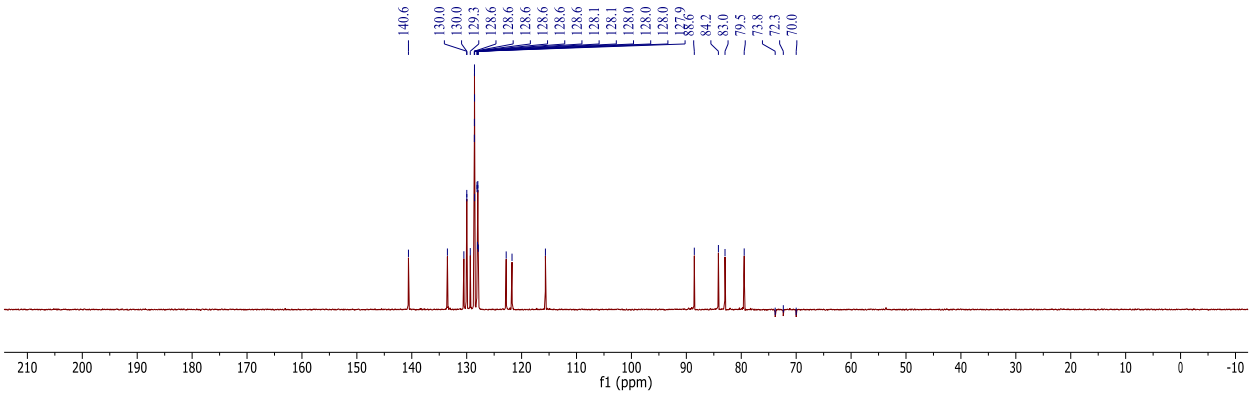
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9e**



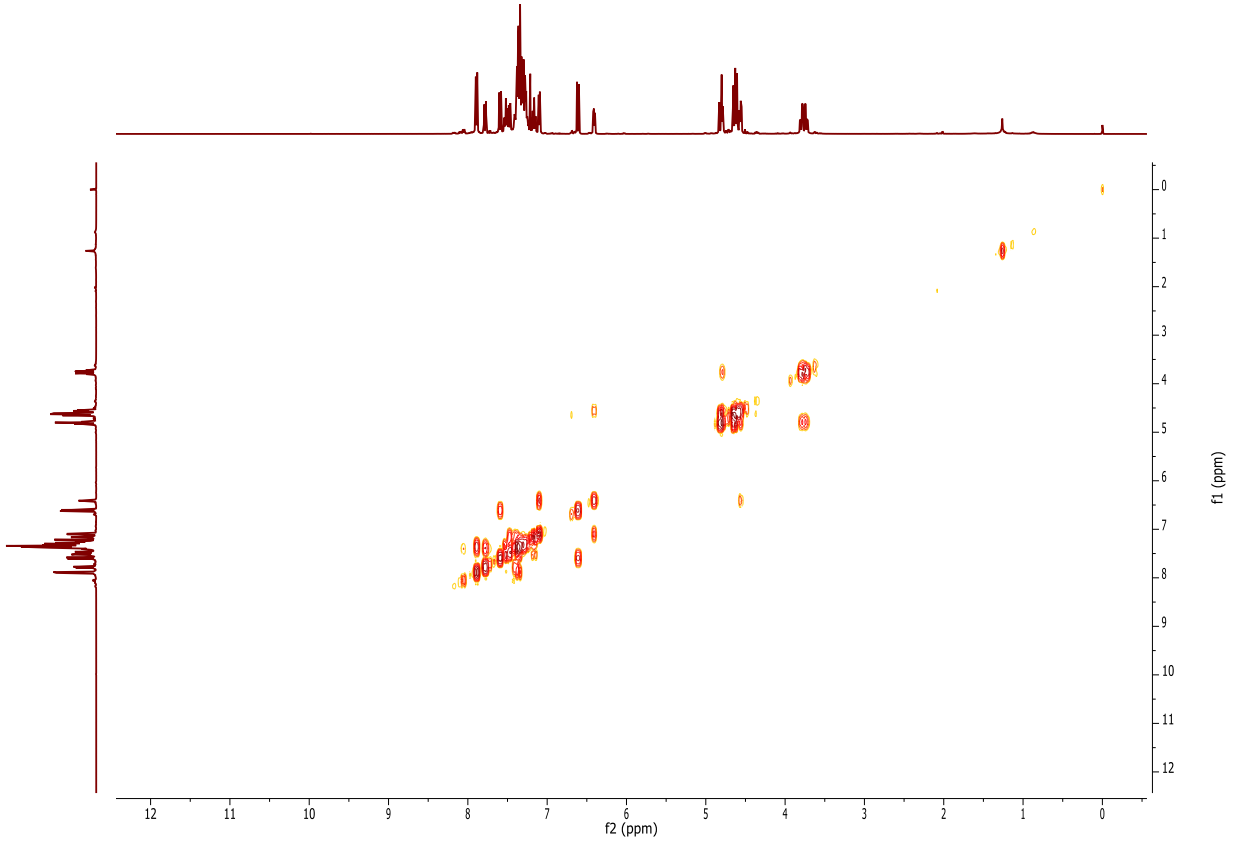
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9e**



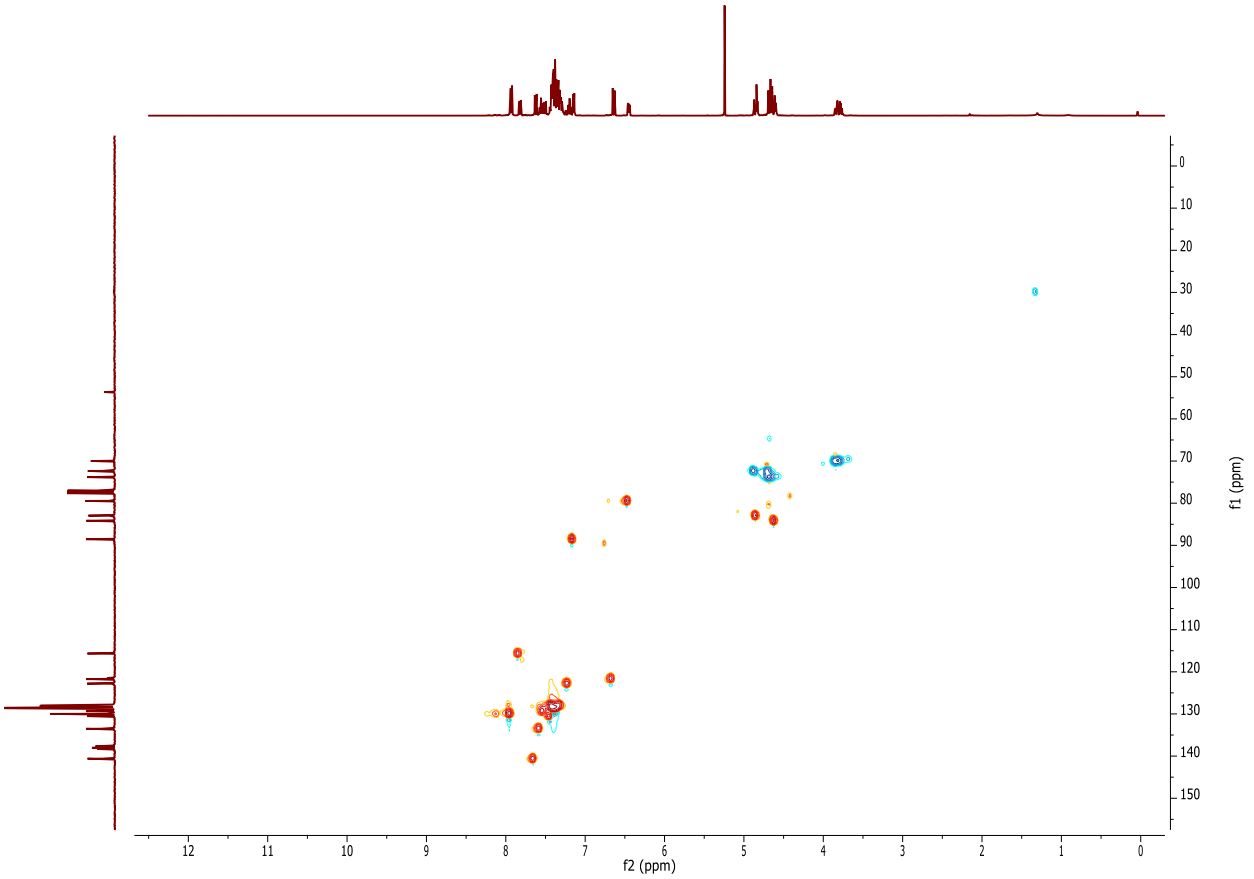
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9e**



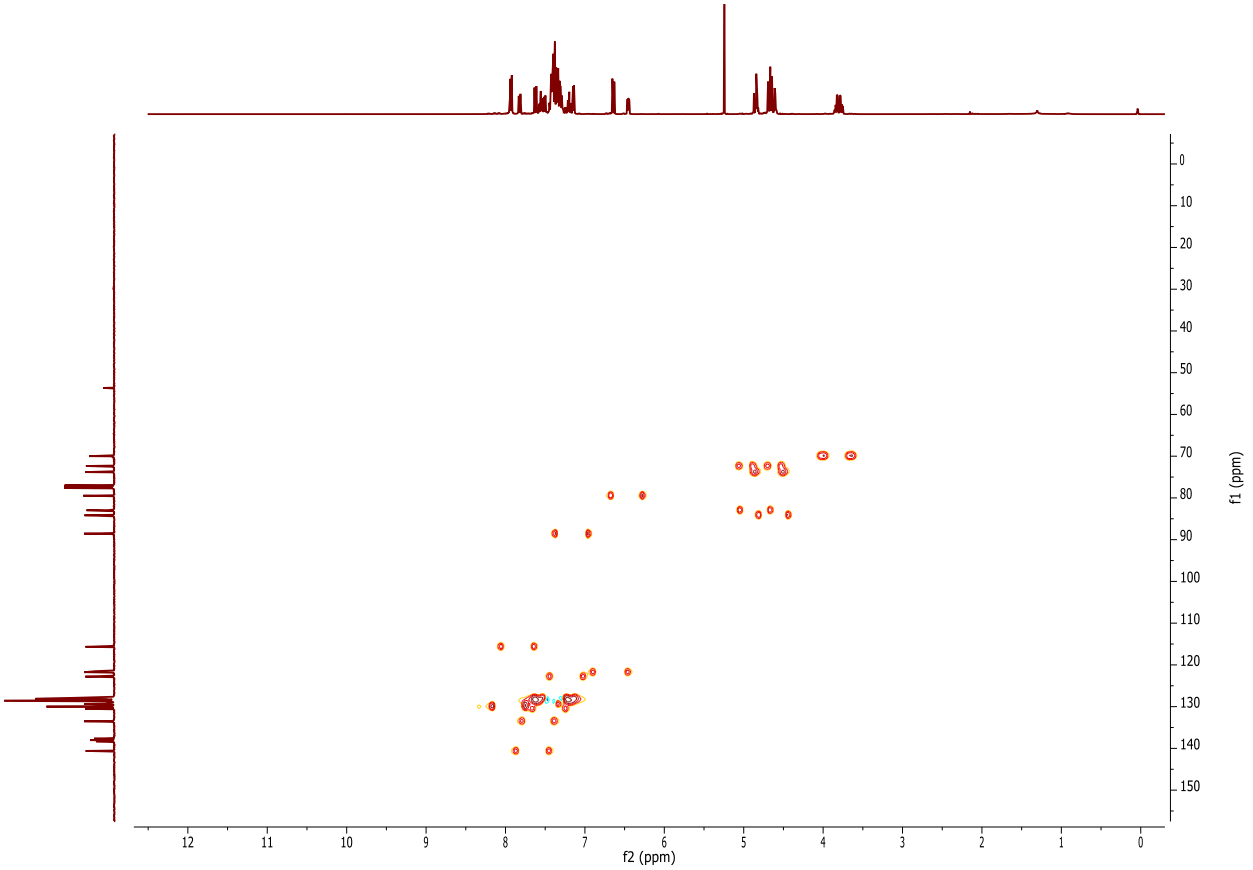
^{1}H-^{1}H COSY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9e**



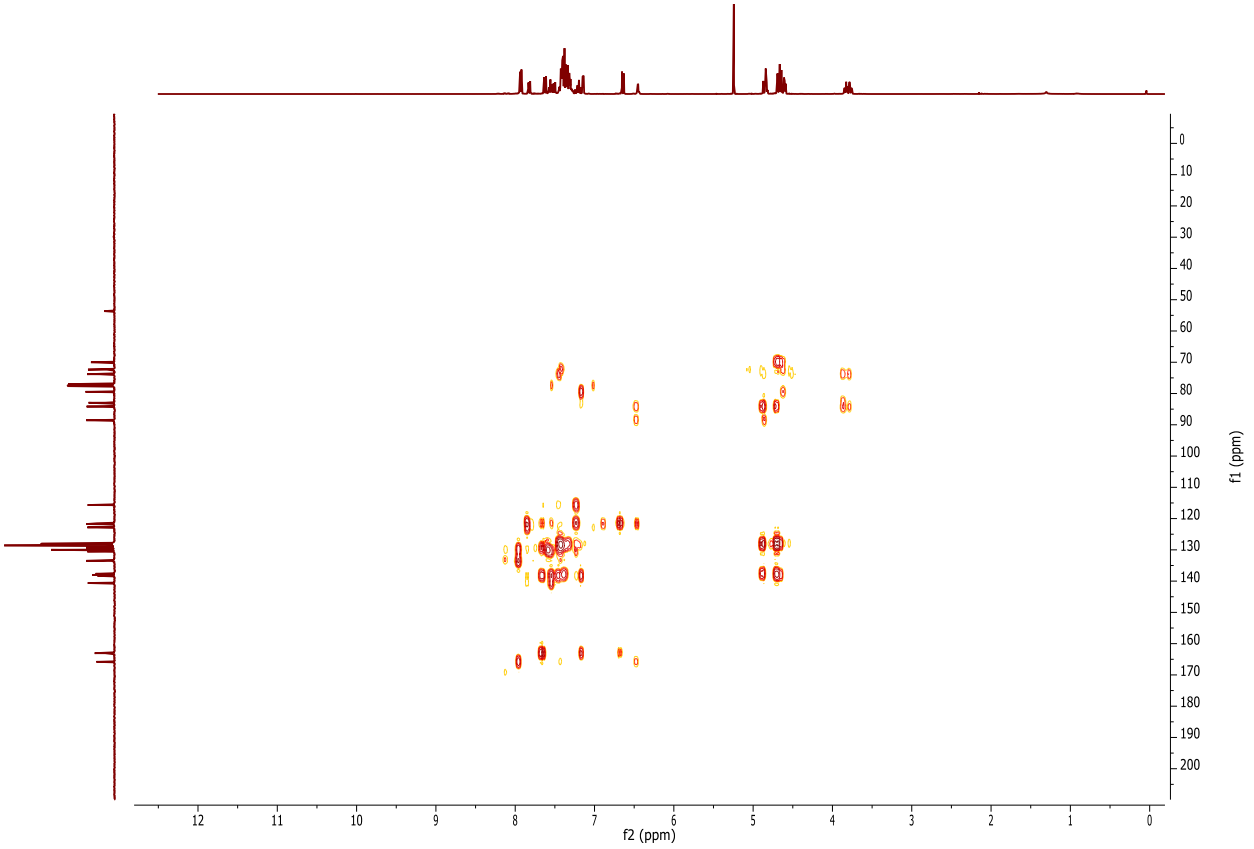
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9e**



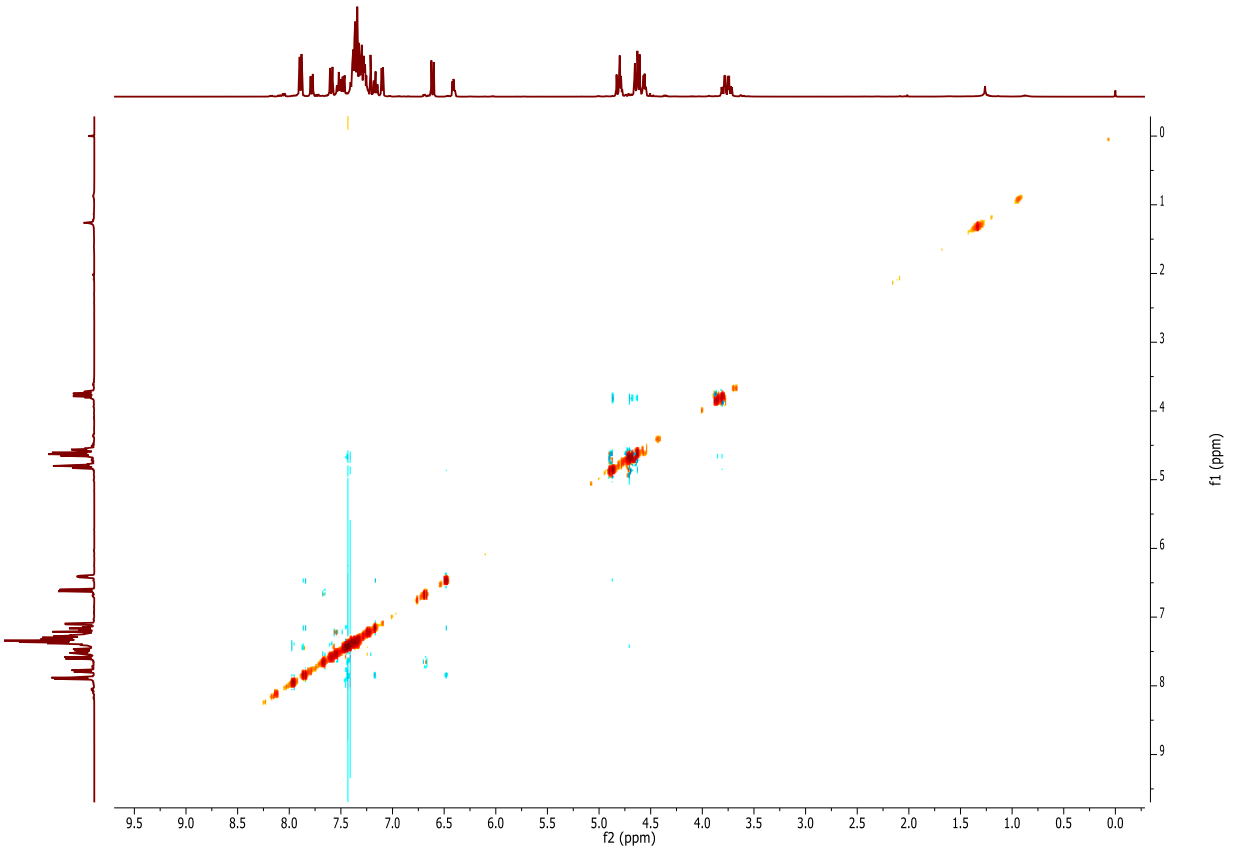
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9e**



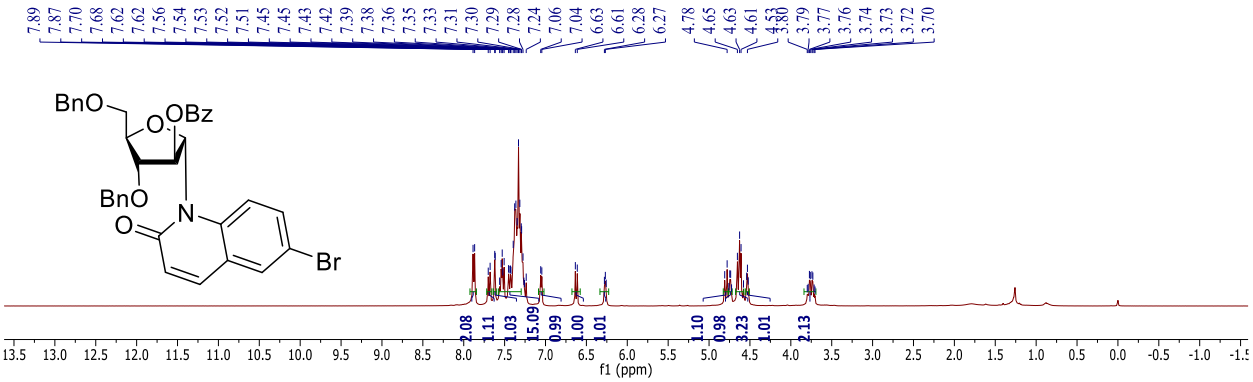
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9e**



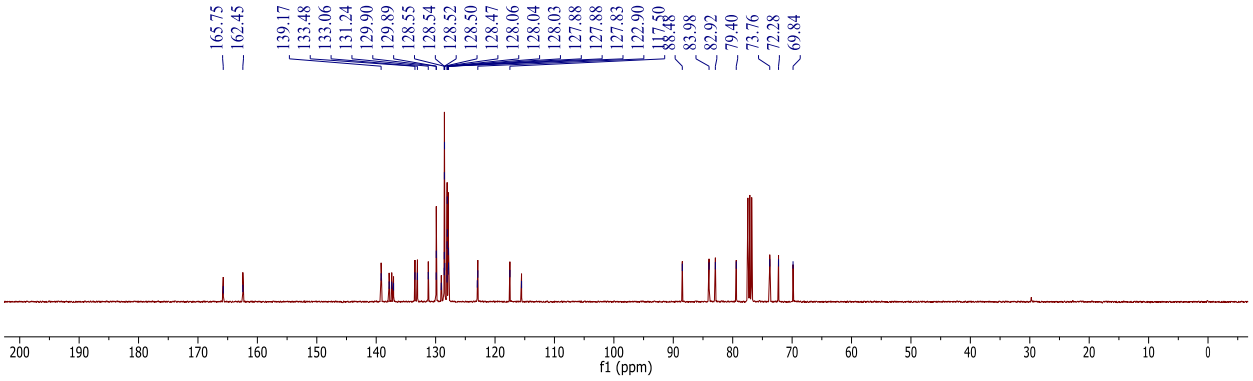
^{1}H-^{1}H NOESY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9e**



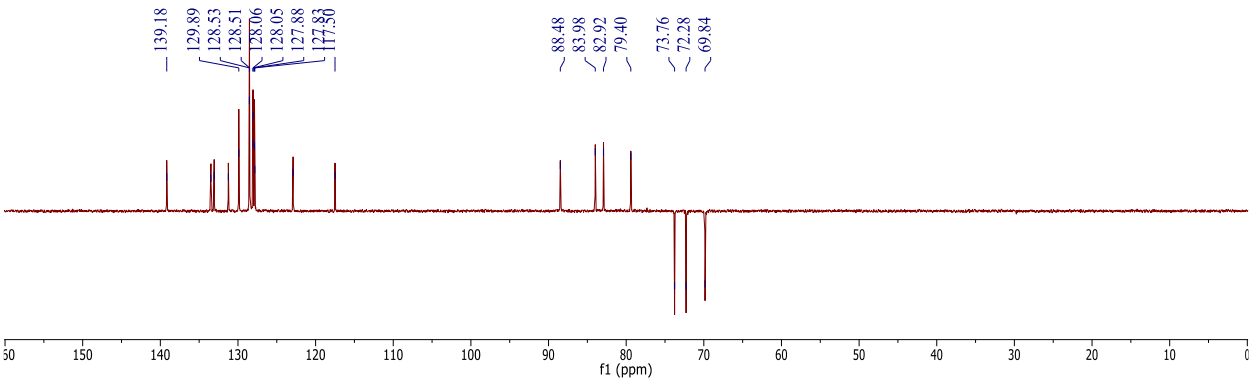
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9f**



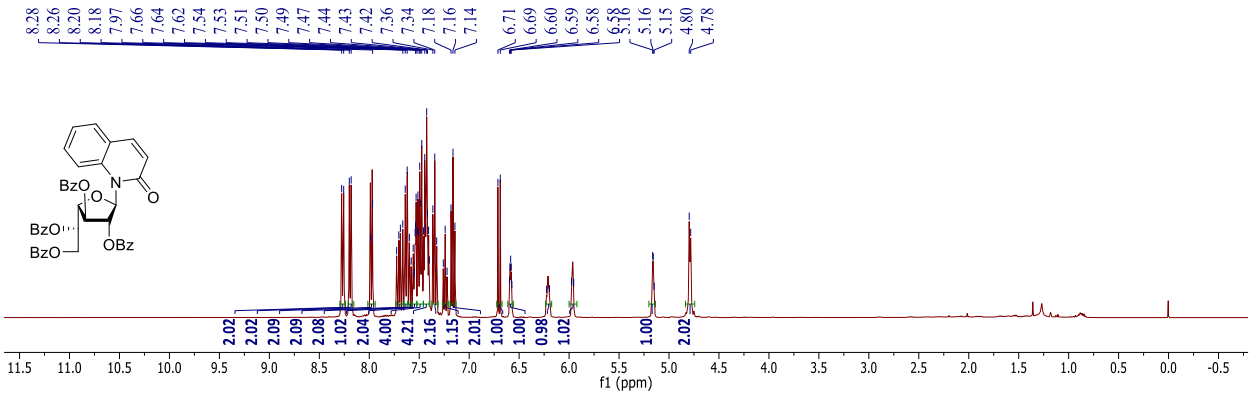
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9f**



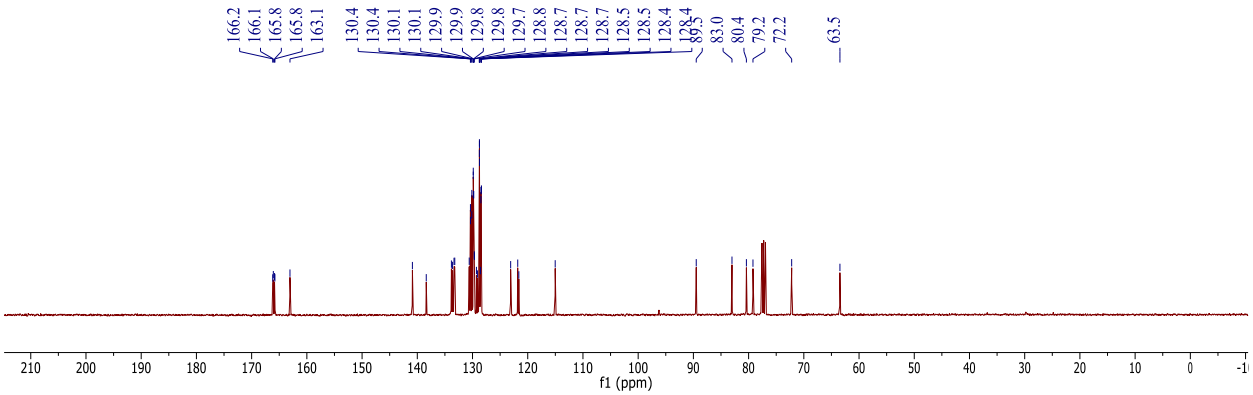
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9f**



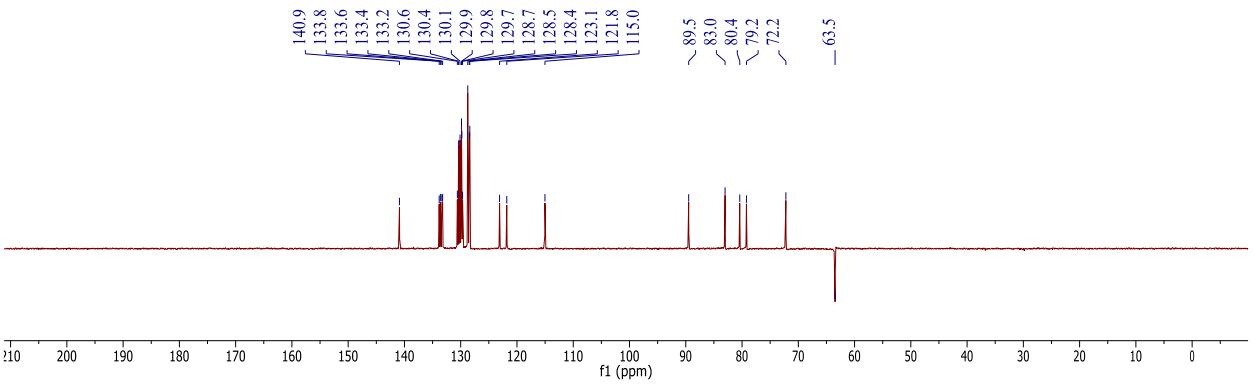
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9g**



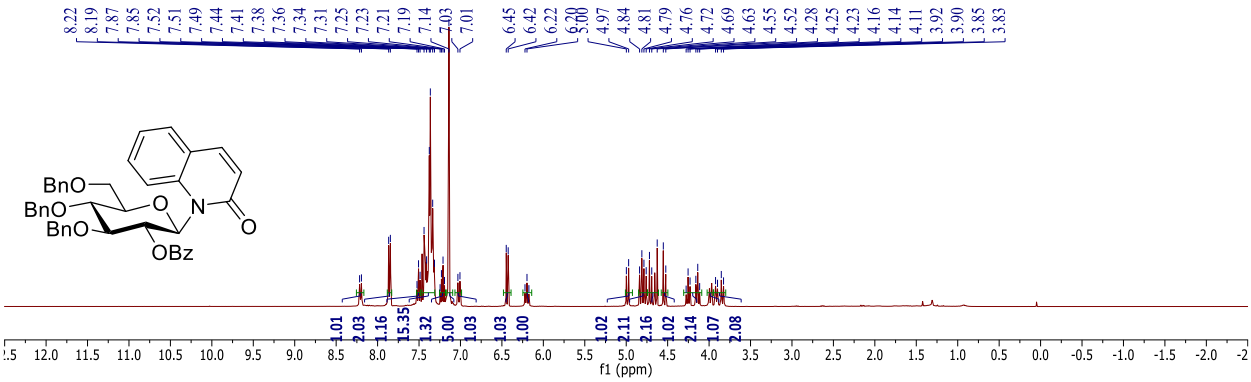
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9g**



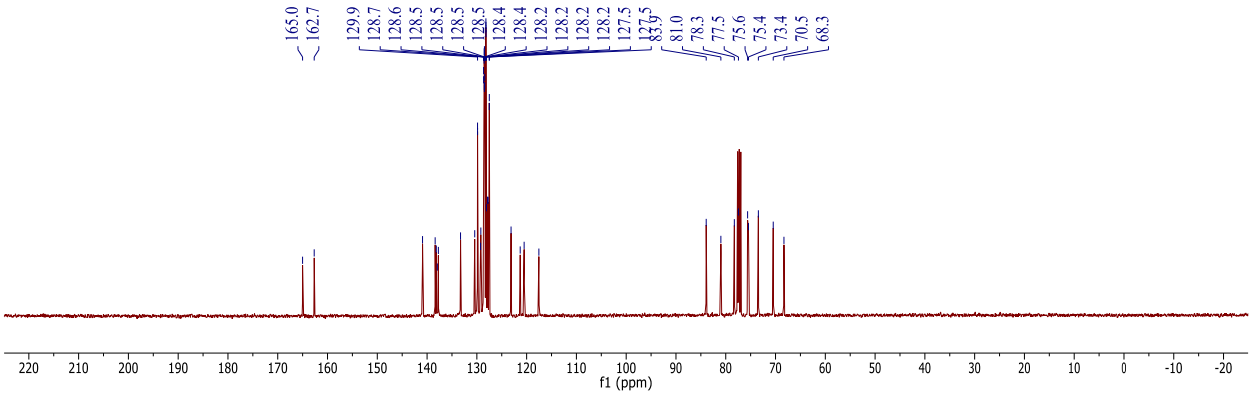
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9g**



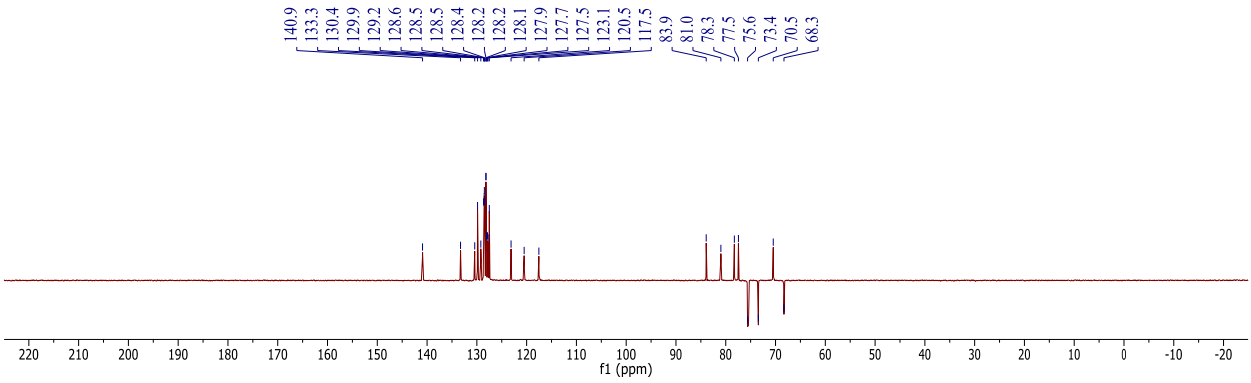
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9h**



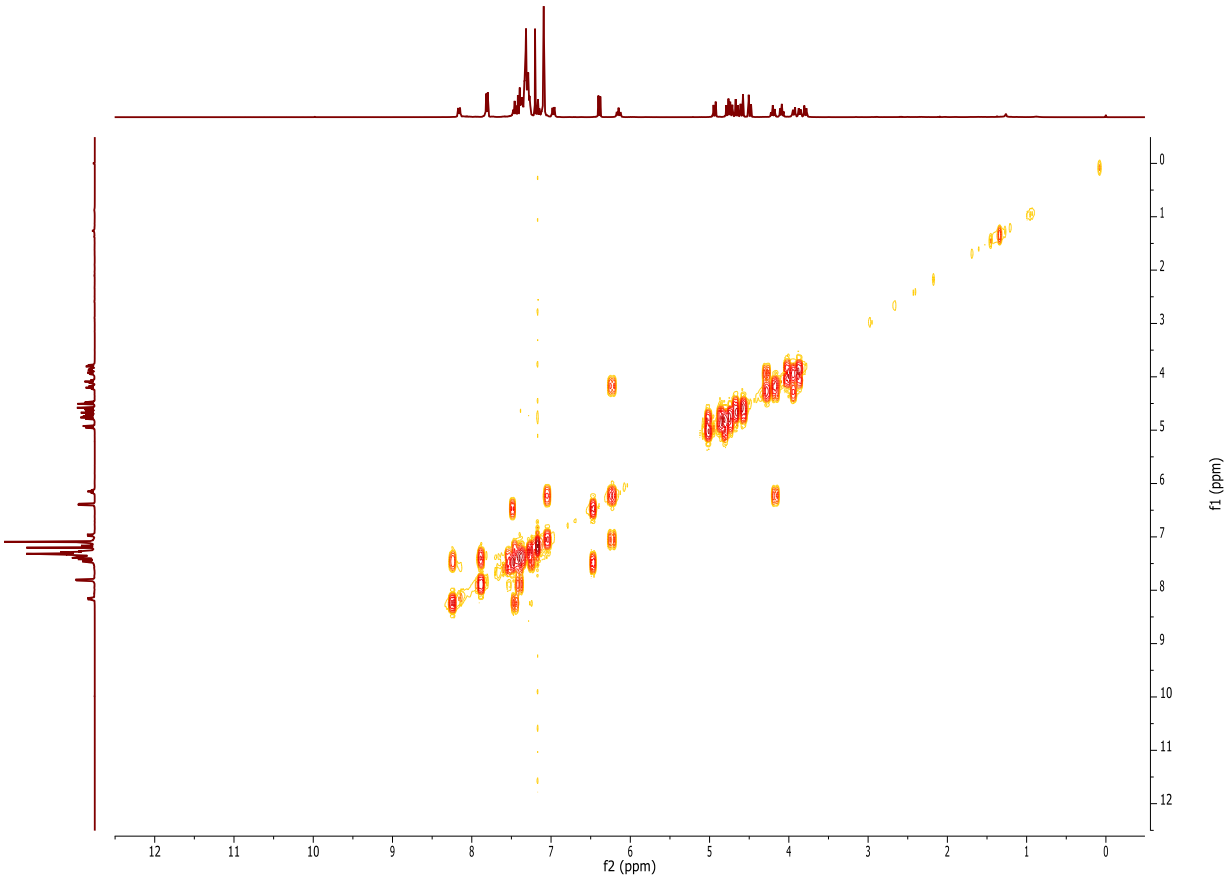
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9h**



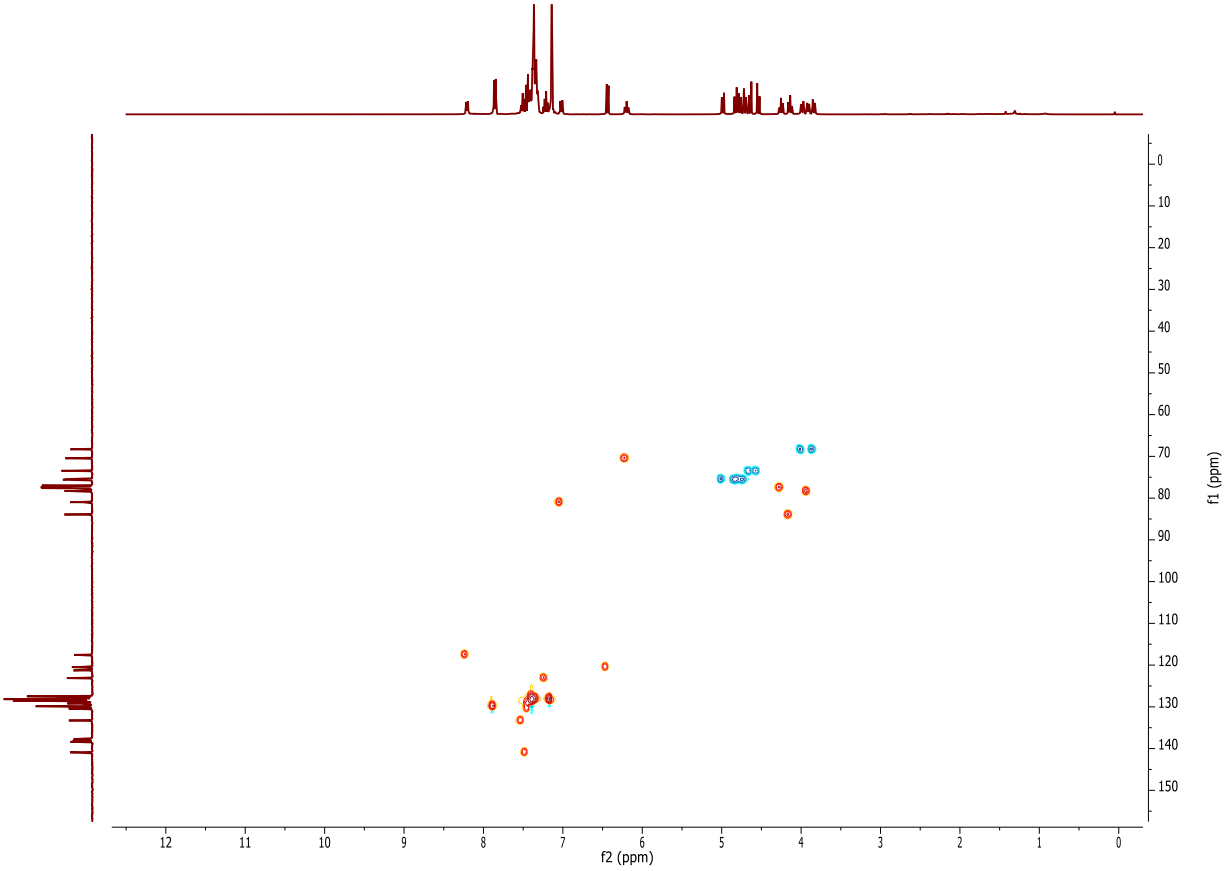
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9h**



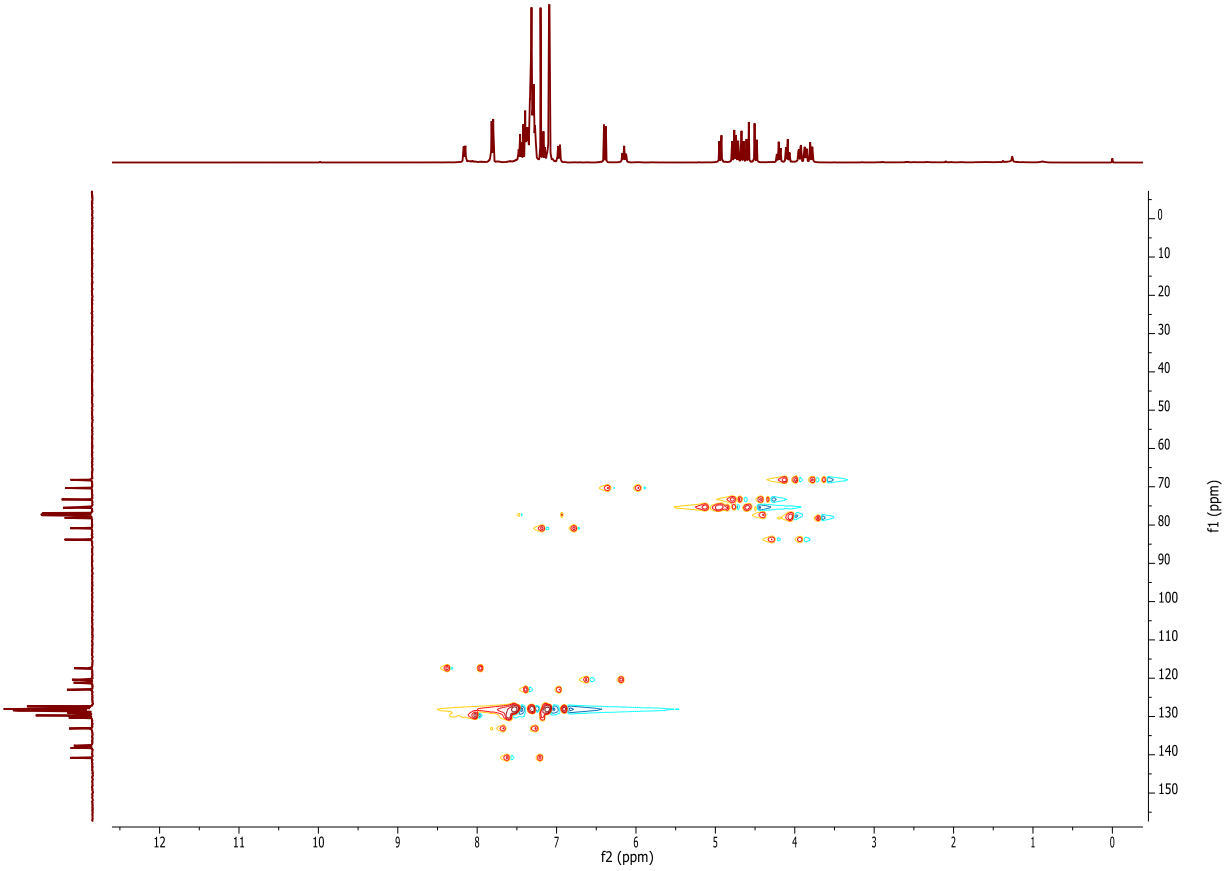
^{1}H-^{1}H COSY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9h**



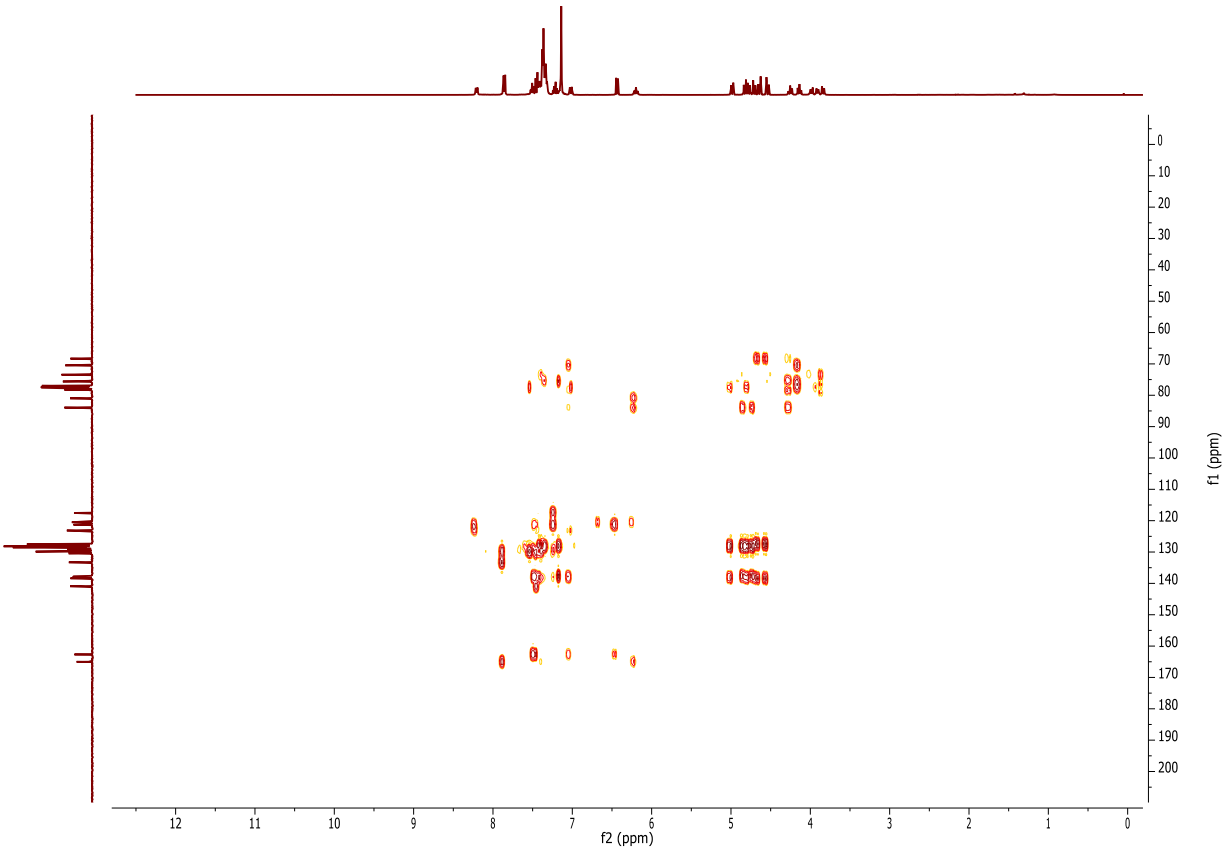
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9h**



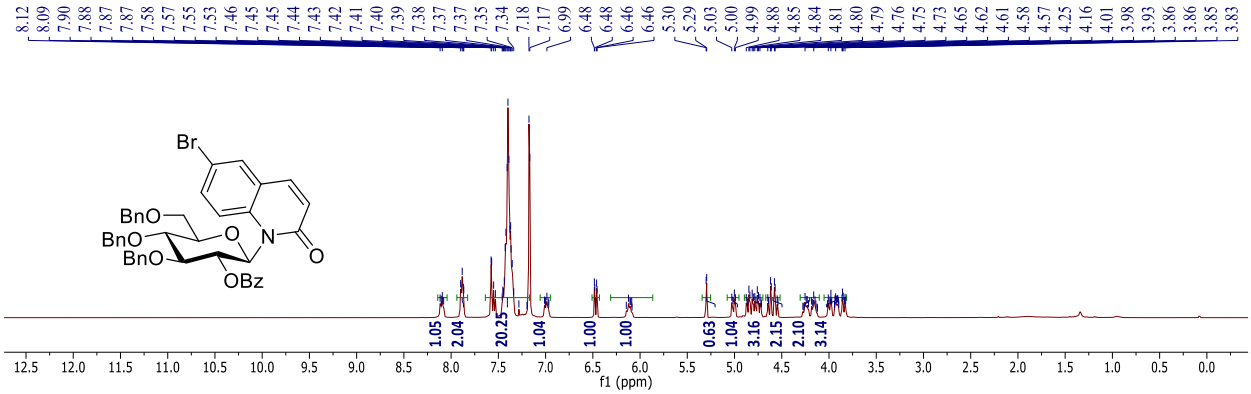
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9h**



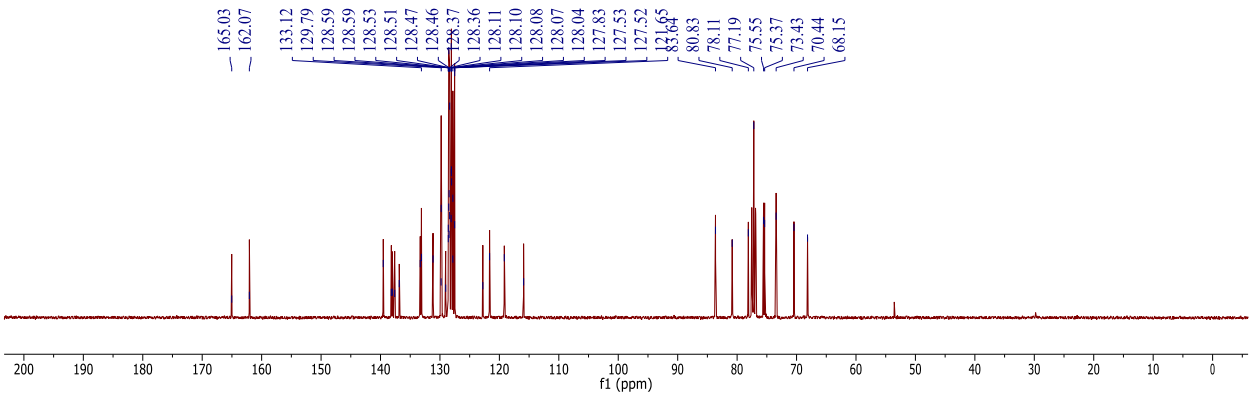
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9h**



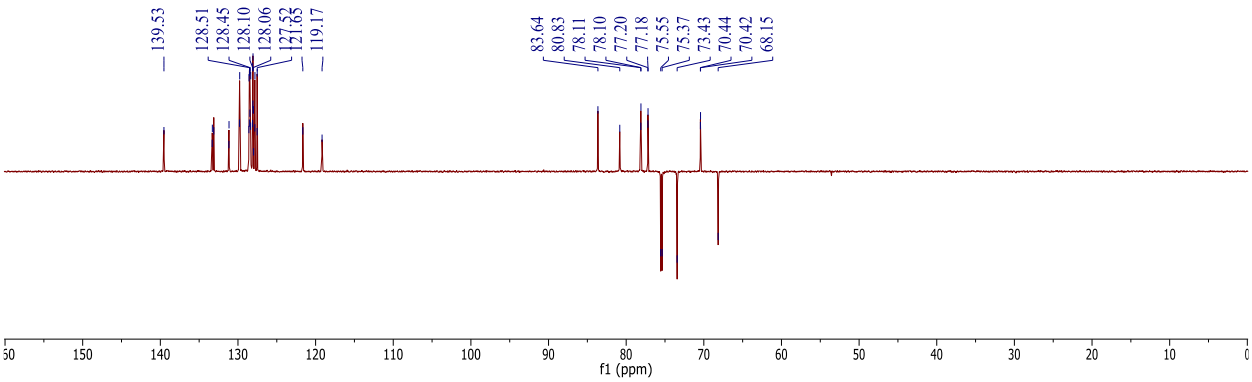
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9i**



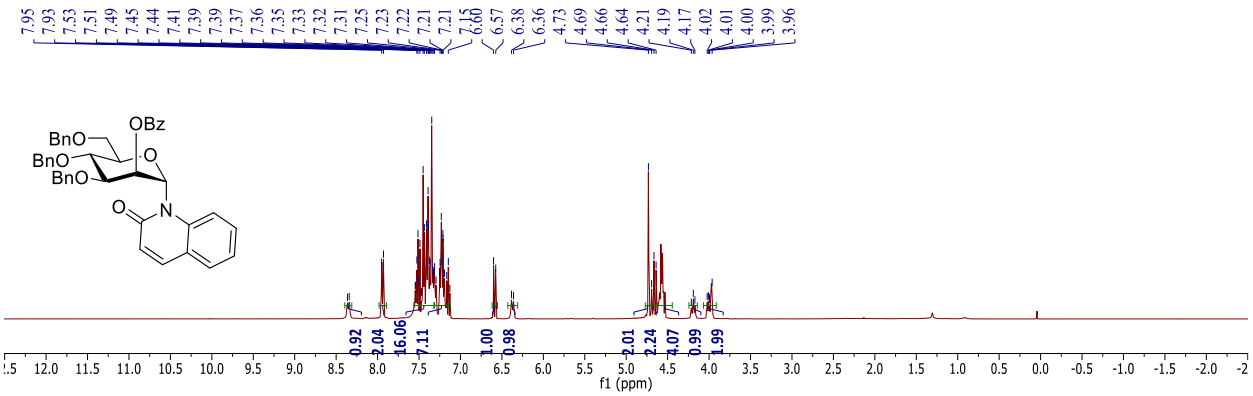
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9i**



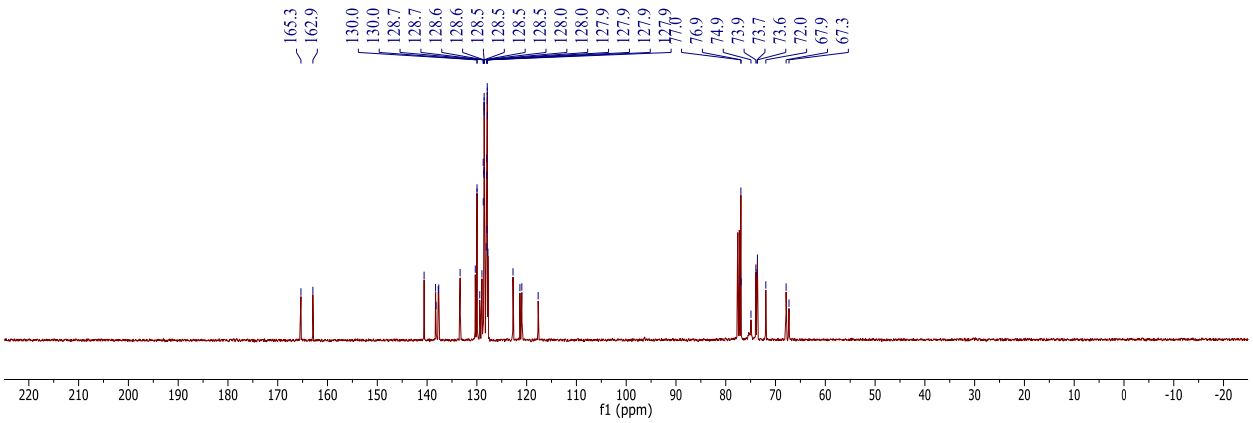
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9i**



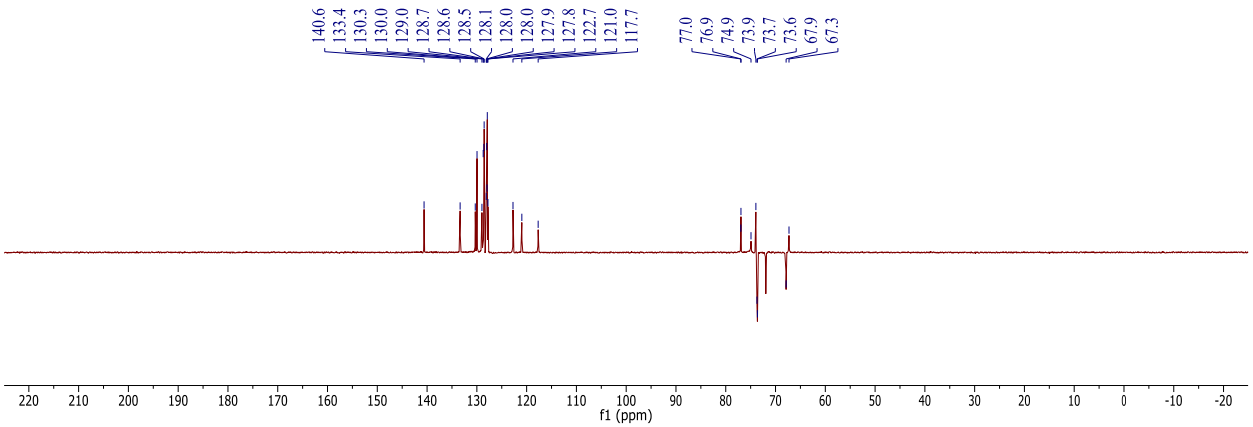
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9j**



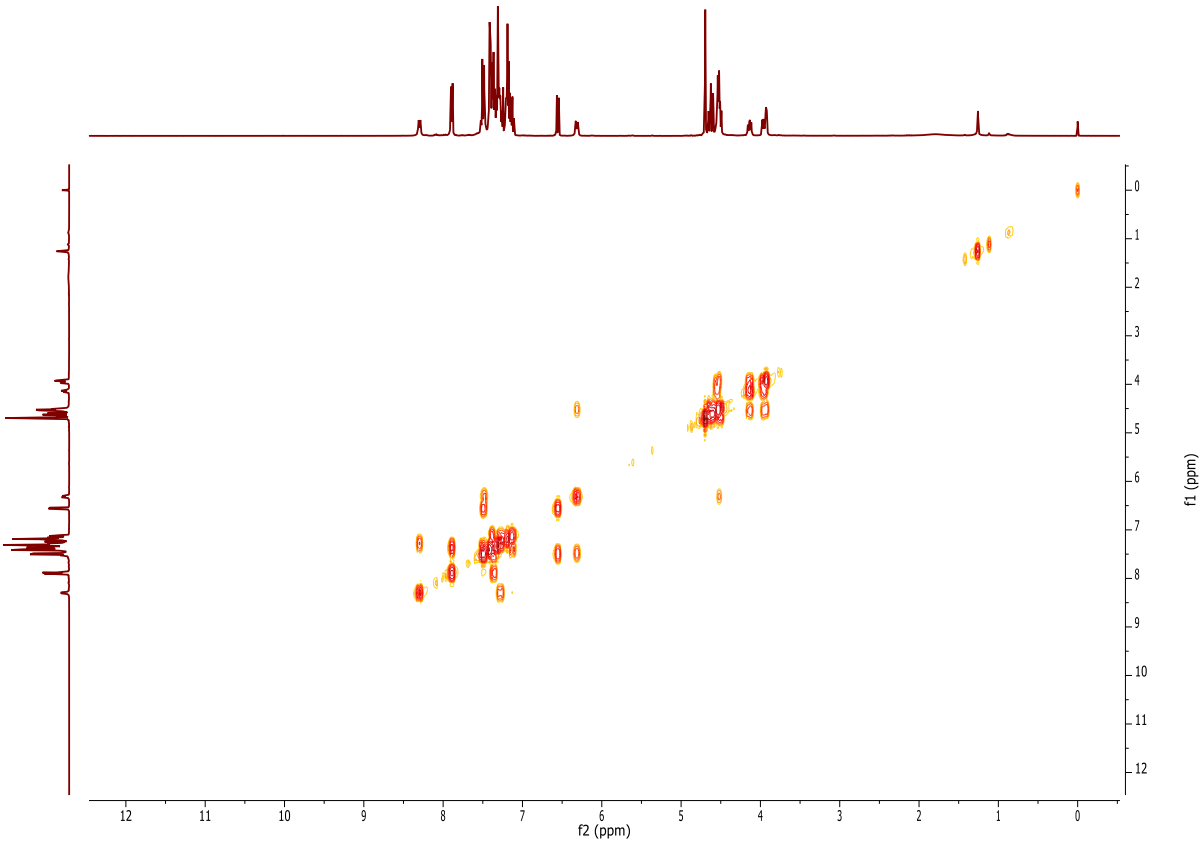
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9j**



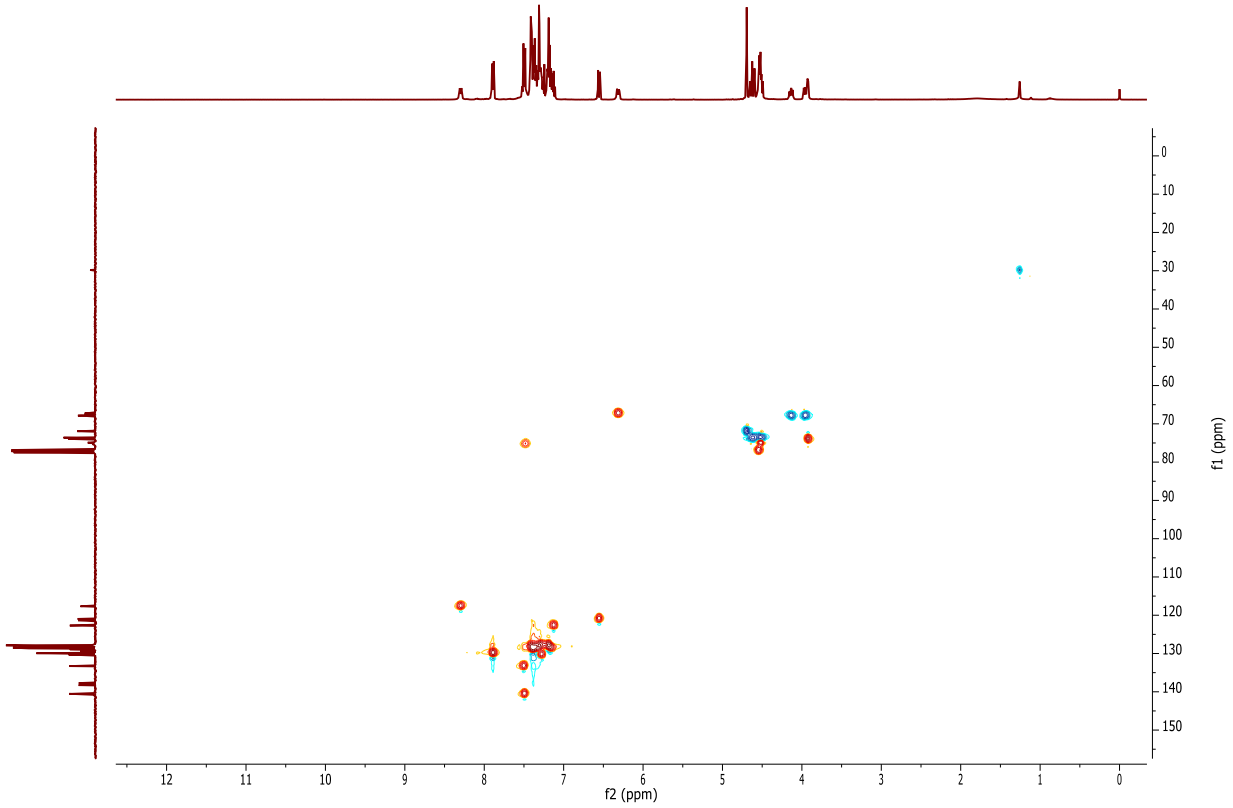
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9j**



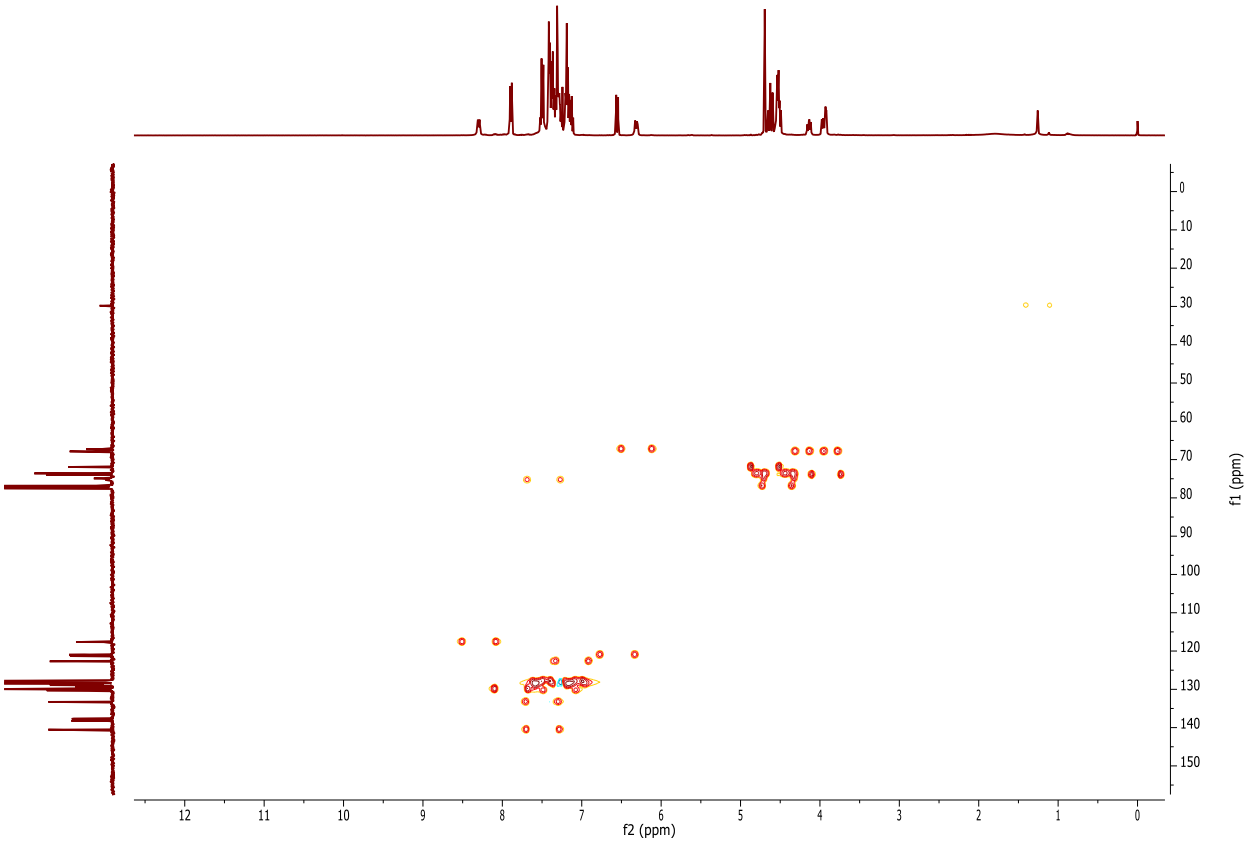
^{1}H-^{1}H COSY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9j**



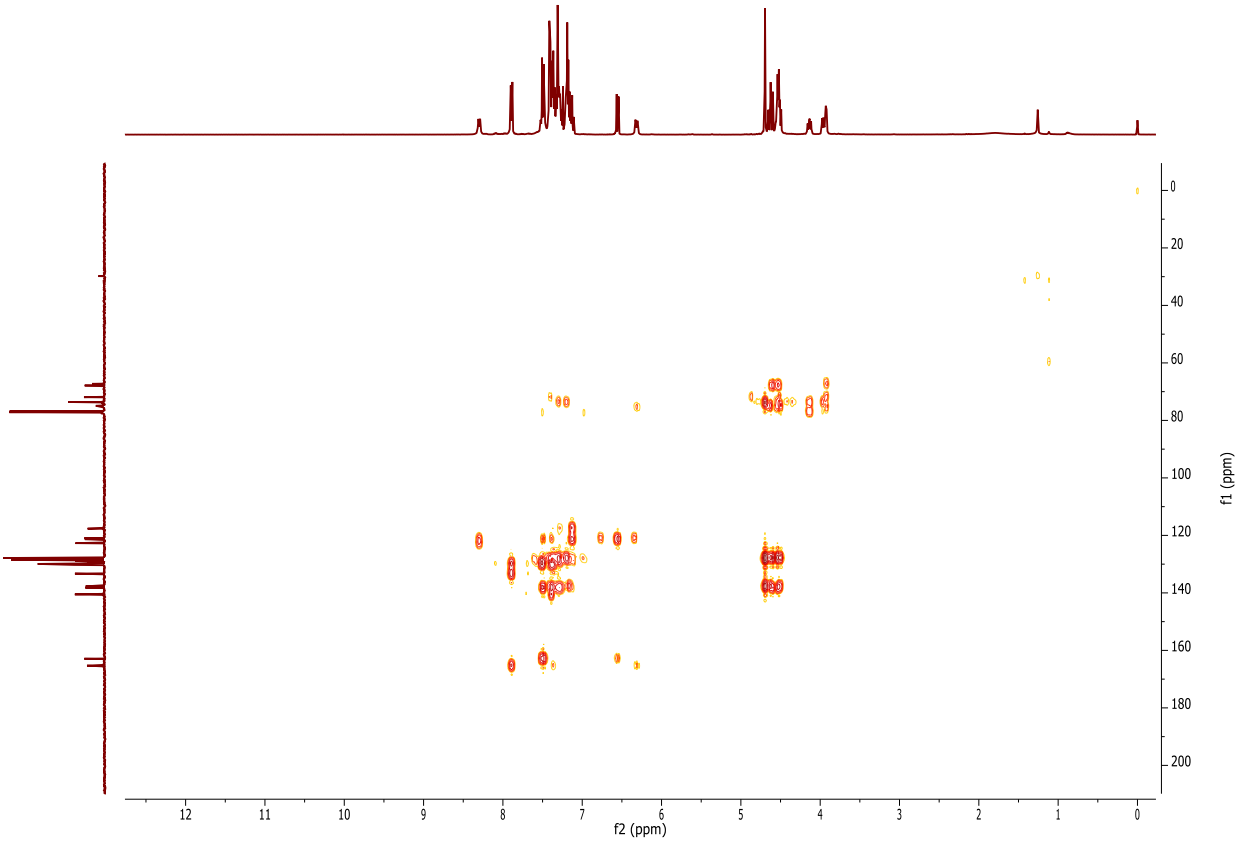
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9j**



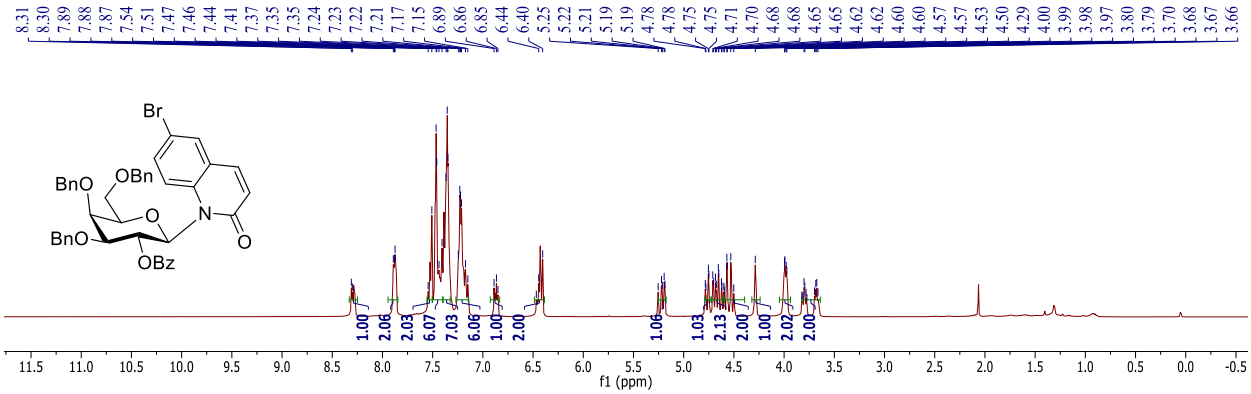
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9j**



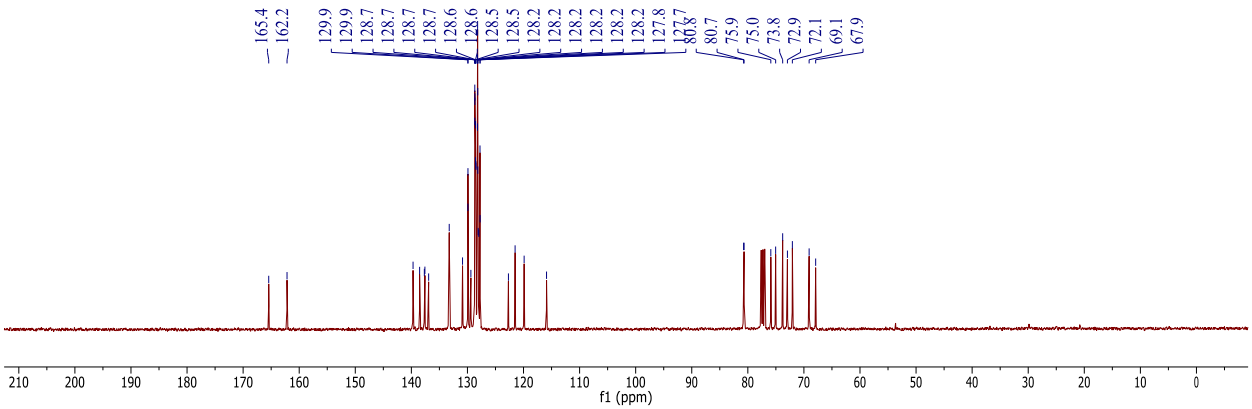
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **9j**



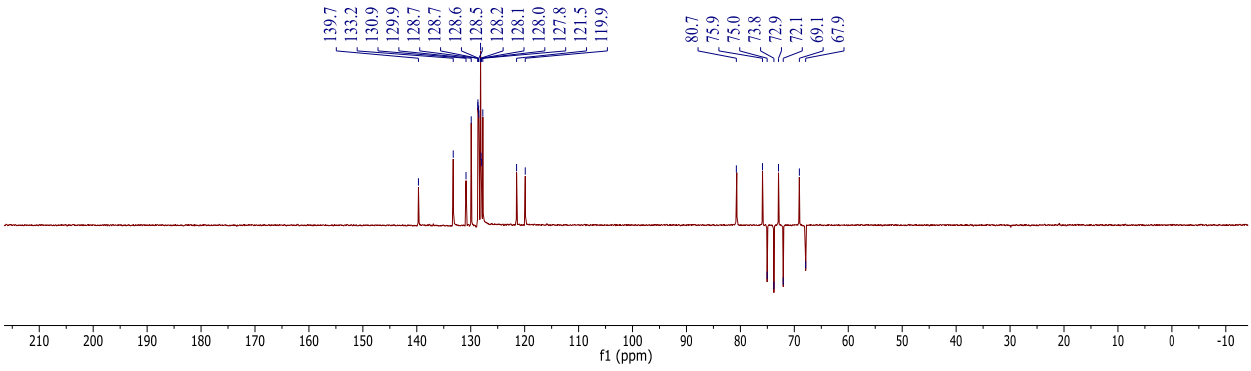
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **9k**



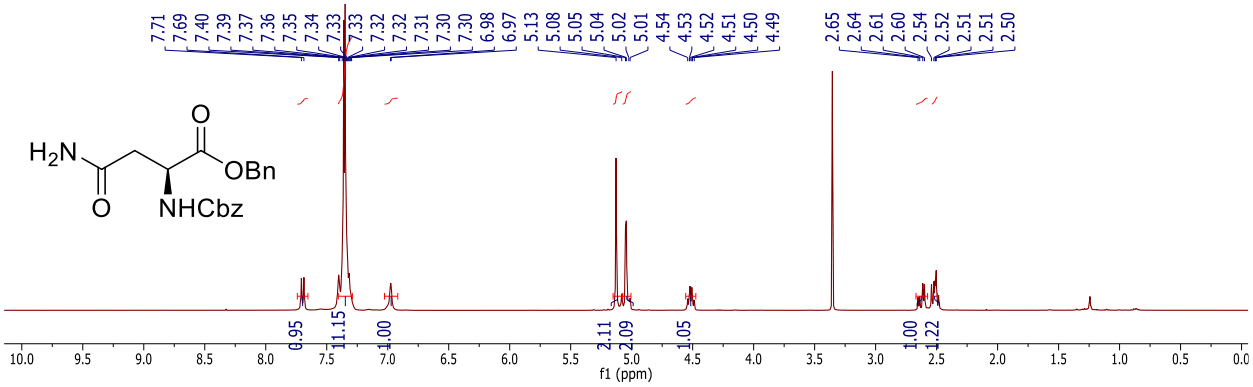
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9k**



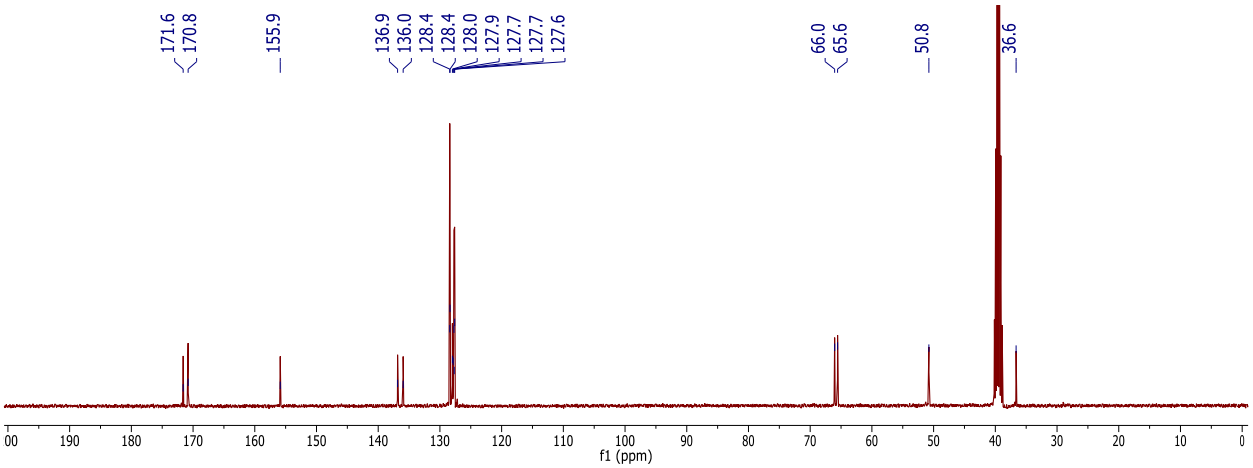
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **9k**



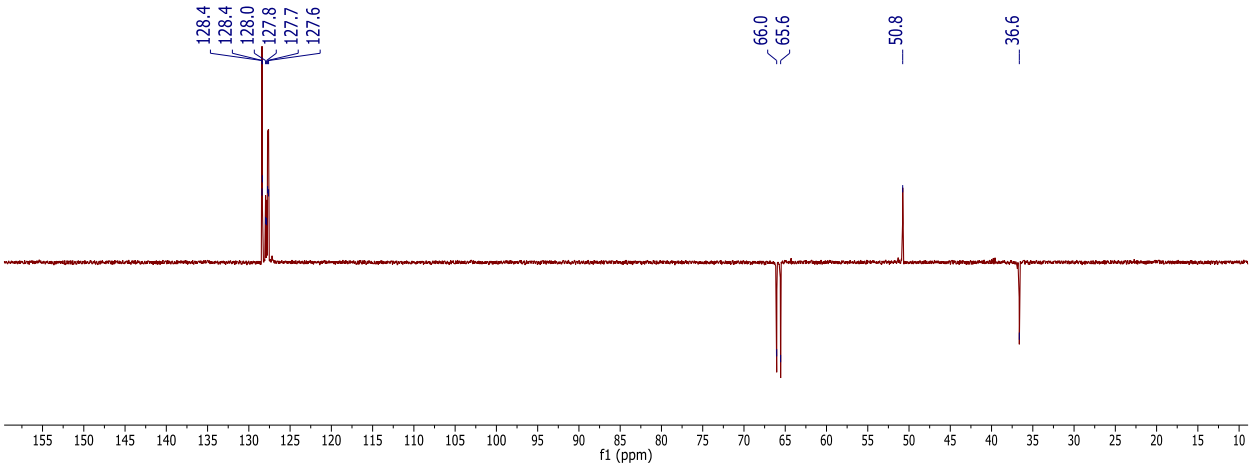
^{1}H NMR Spectrum (400.31 MHz, DMSO-d_6) of Compound **10**



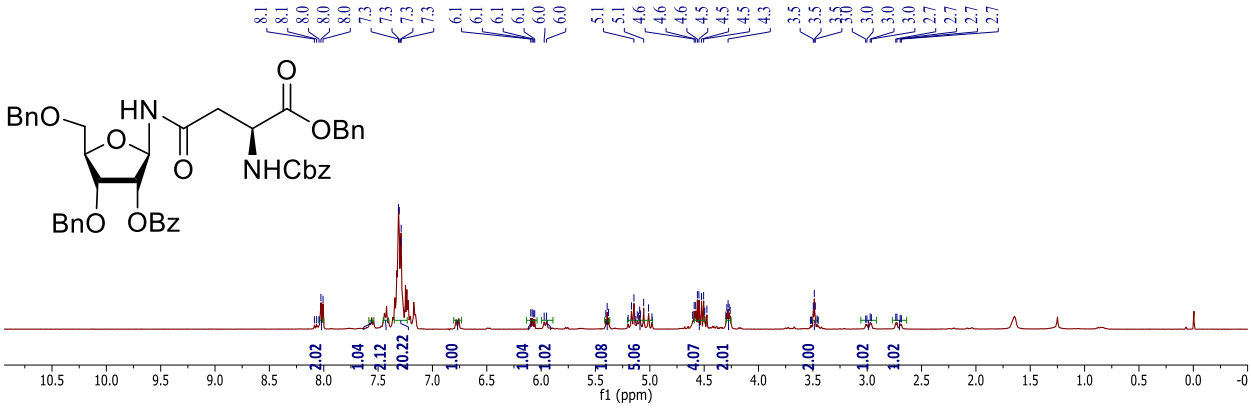
^{13}C NMR Spectrum (100 MHz, DMSO-d_6) of Compound **10**



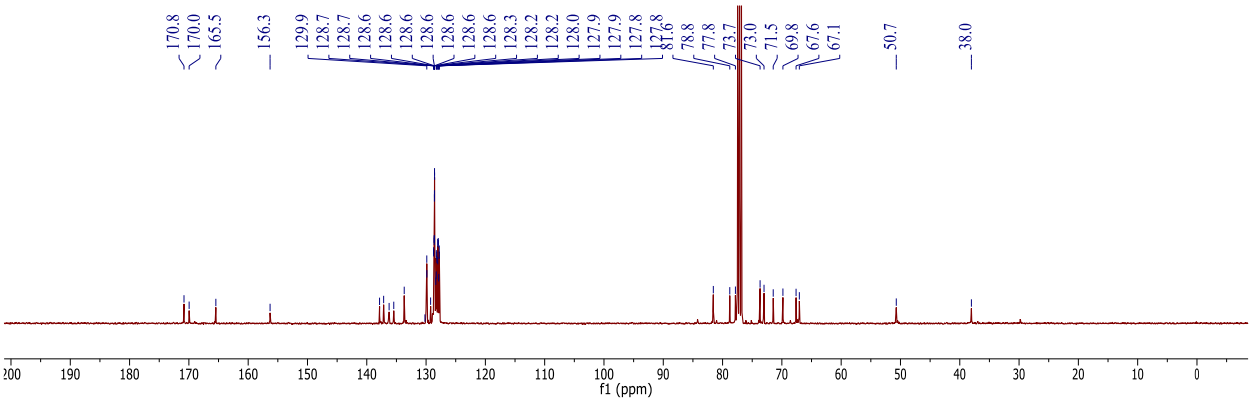
DEPT-135 NMR Spectrum (100 MHz, DMSO-d_6) of Compound **10**



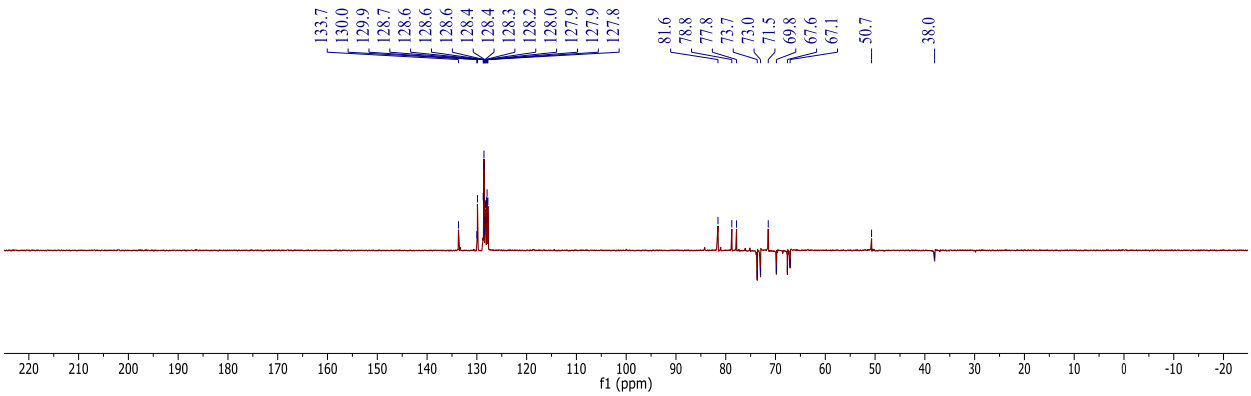
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **11a**



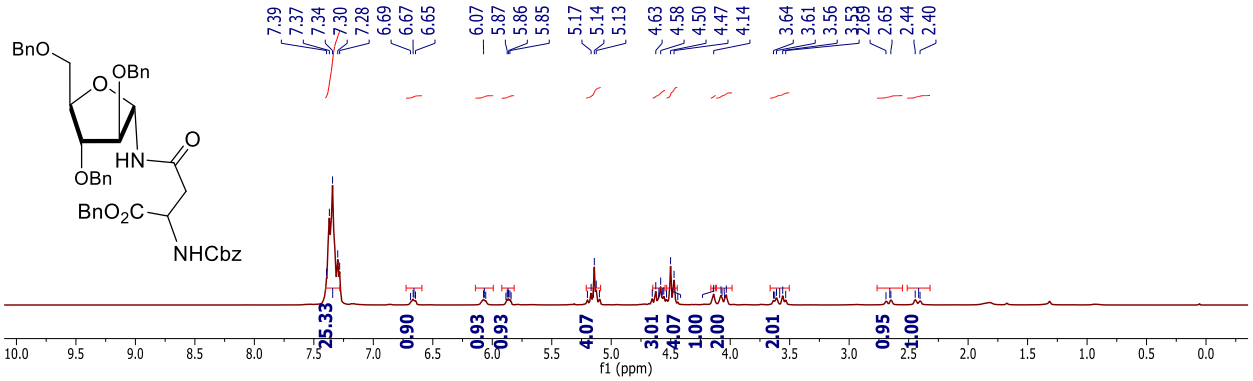
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11a**



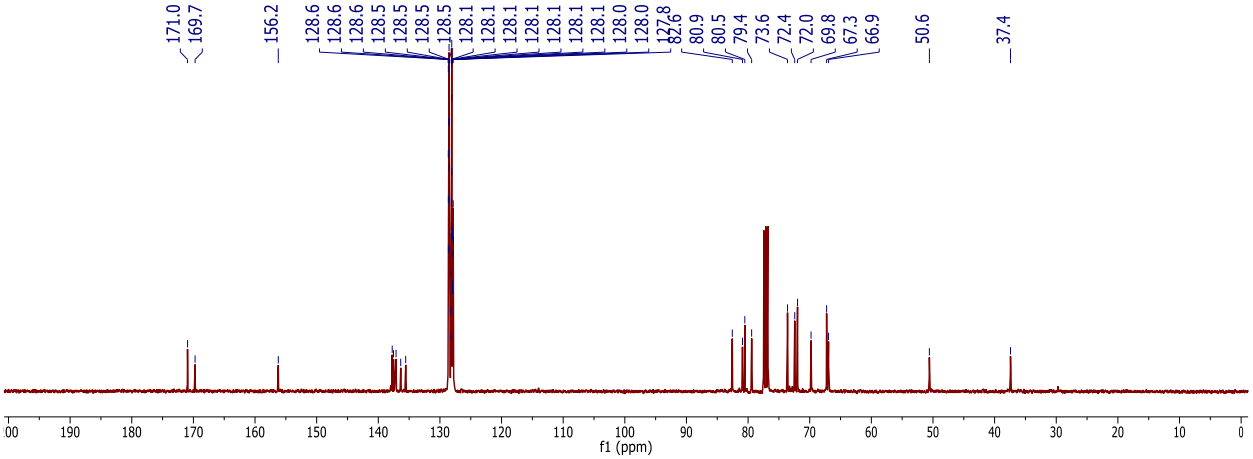
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11a**



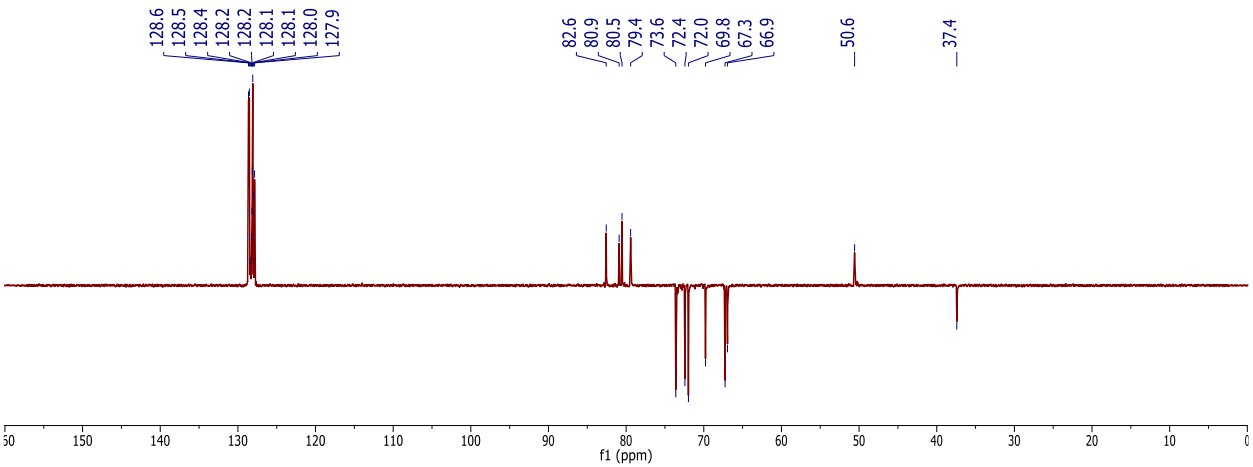
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **11b**



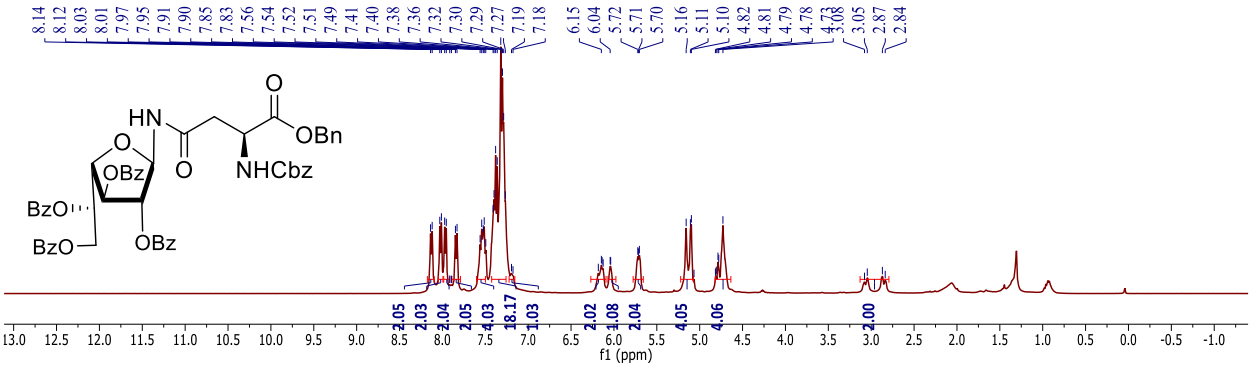
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11b**



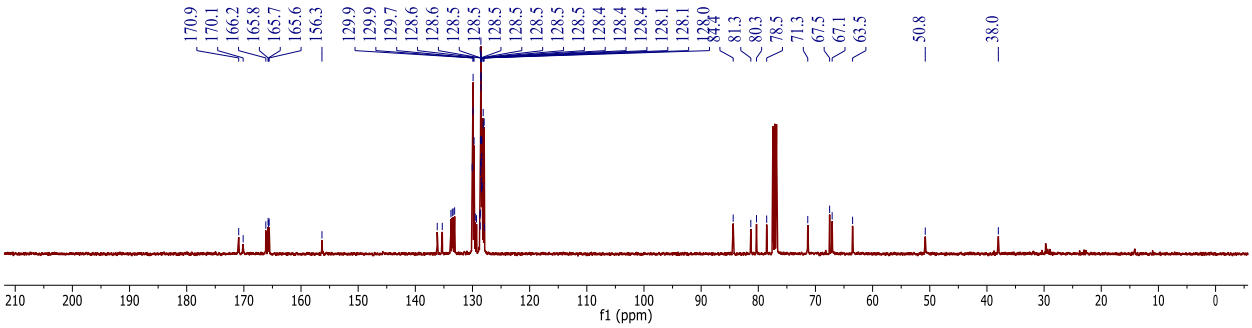
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11b**



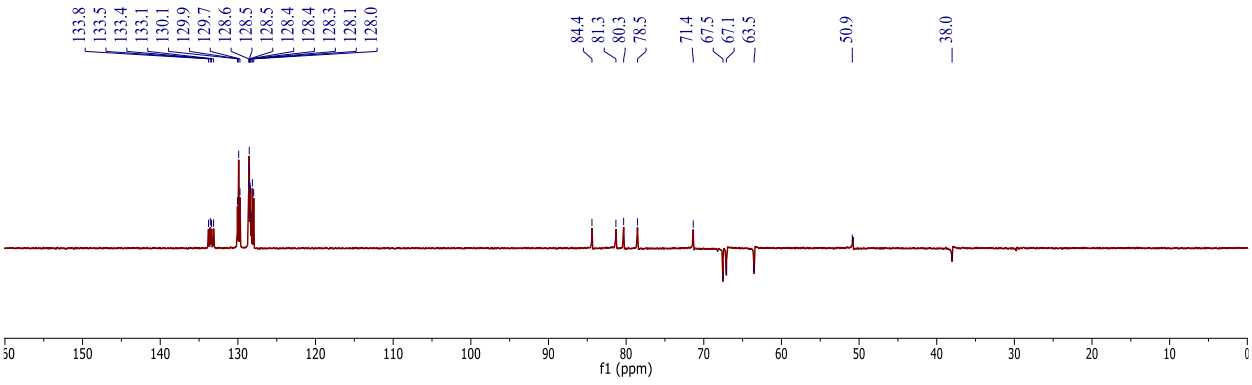
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **11c**



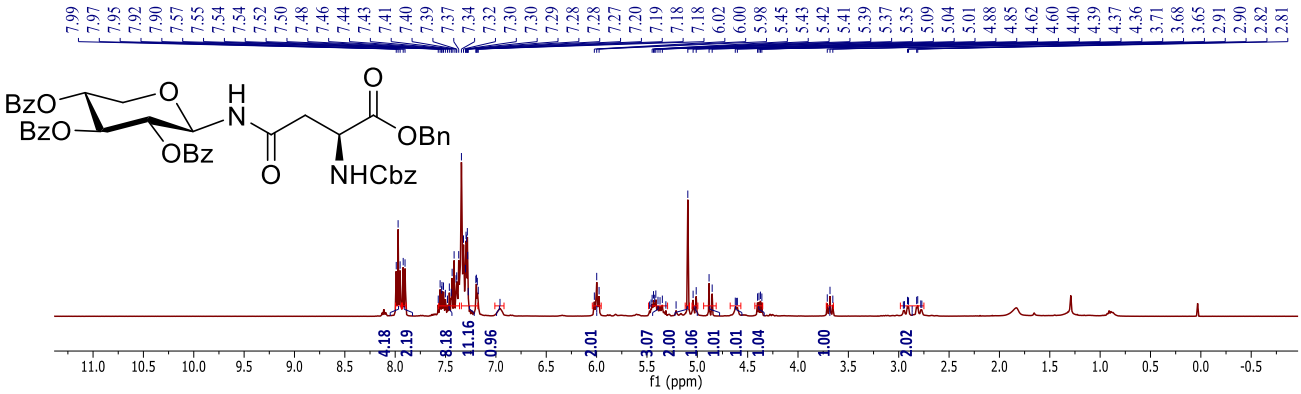
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11c**



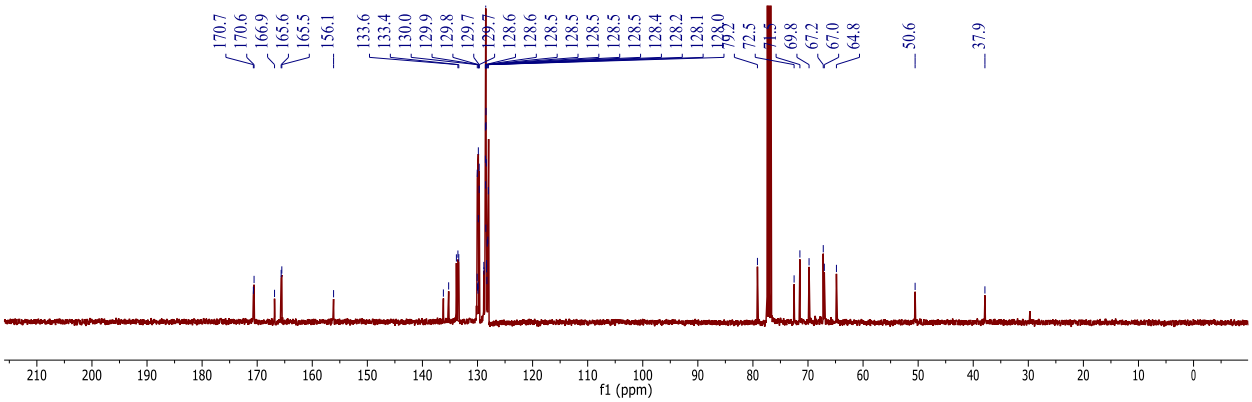
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11c**



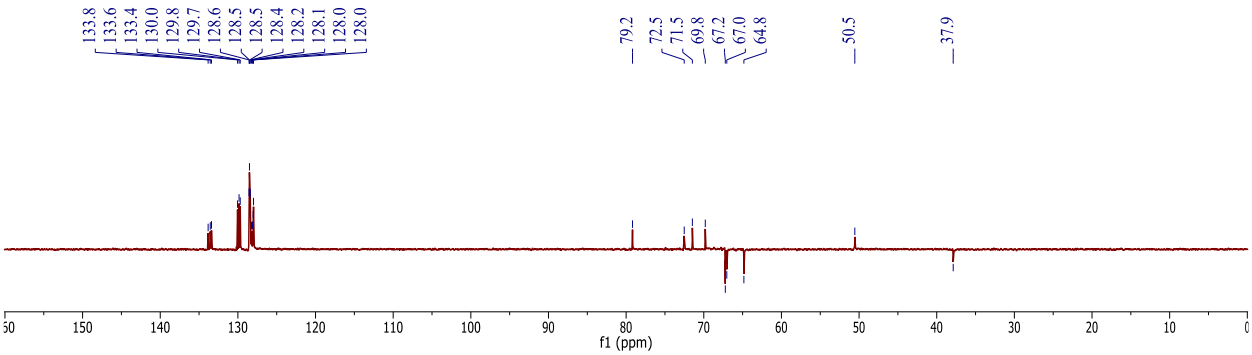
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **11d**



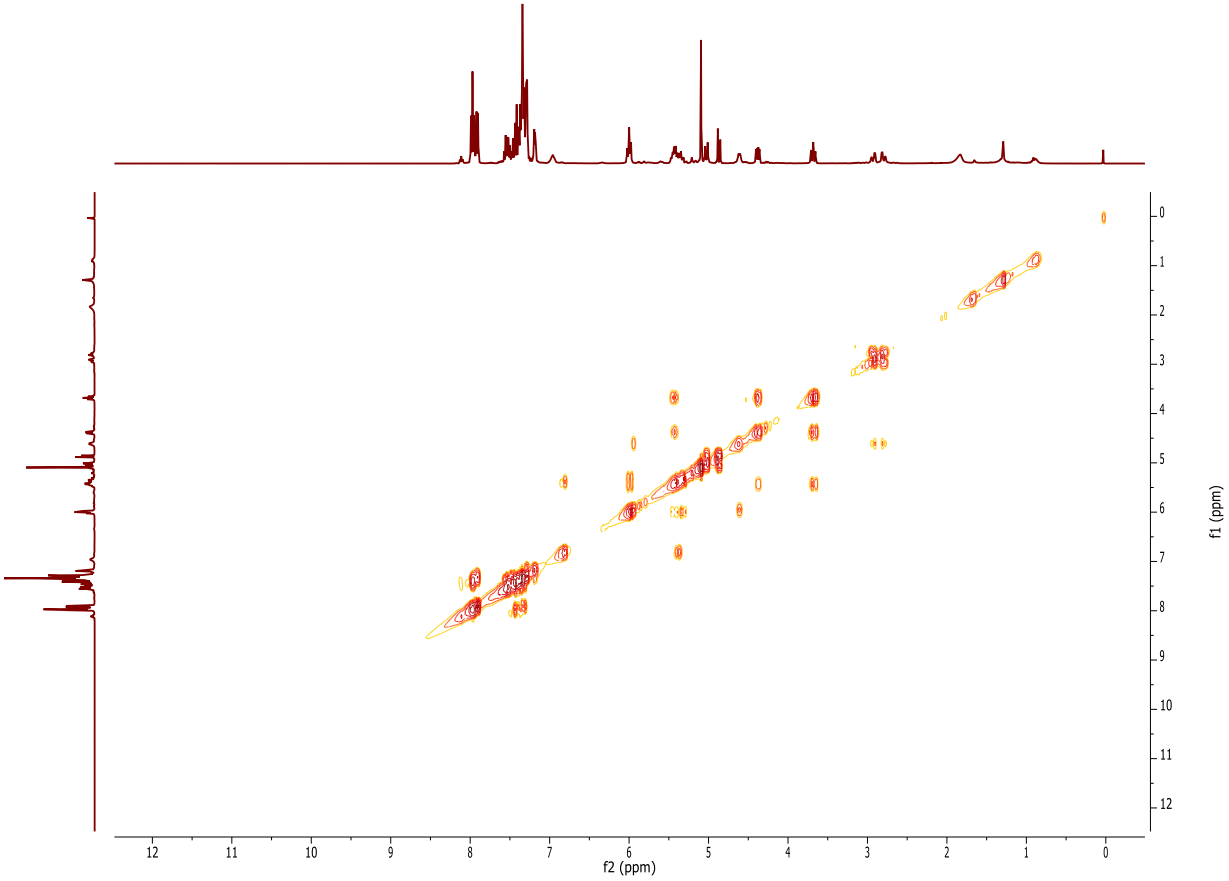
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11d**



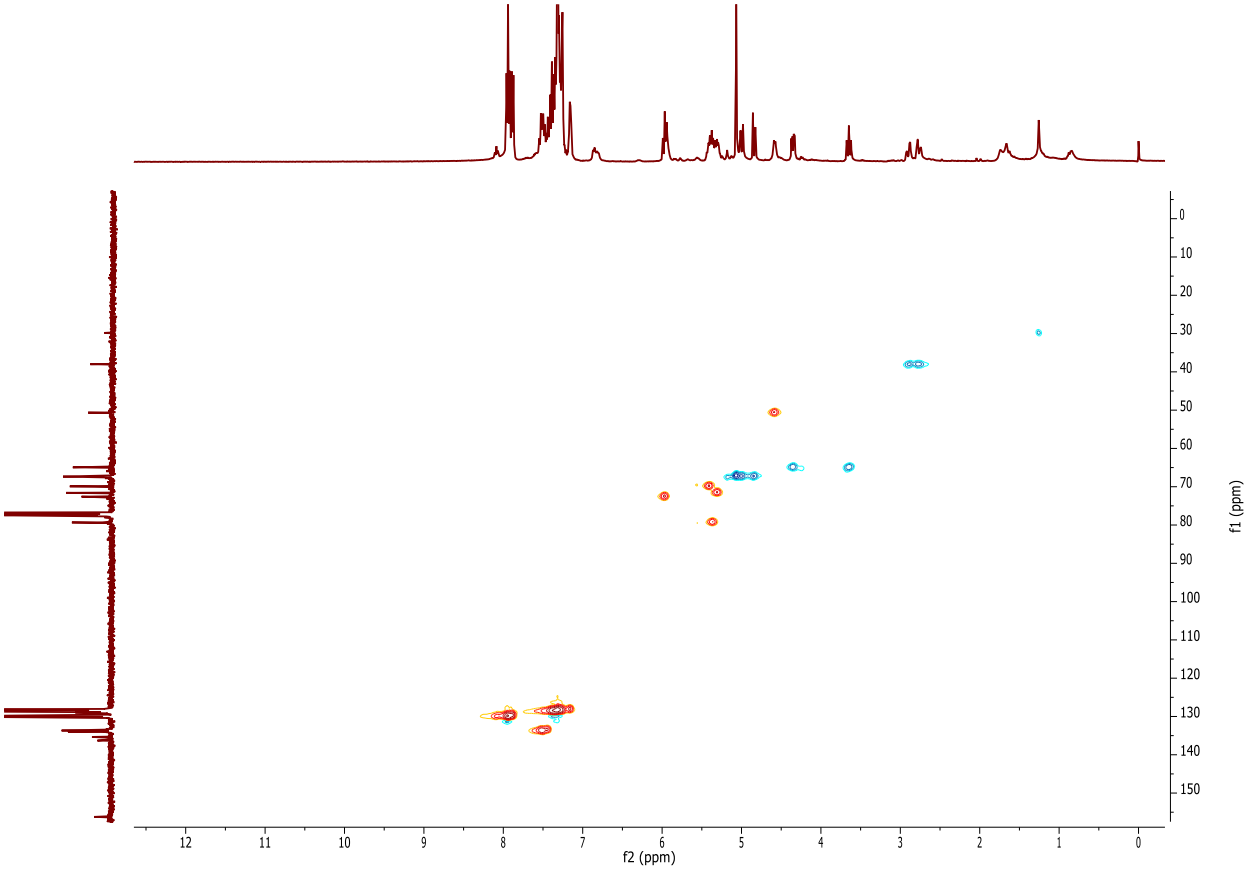
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11d**



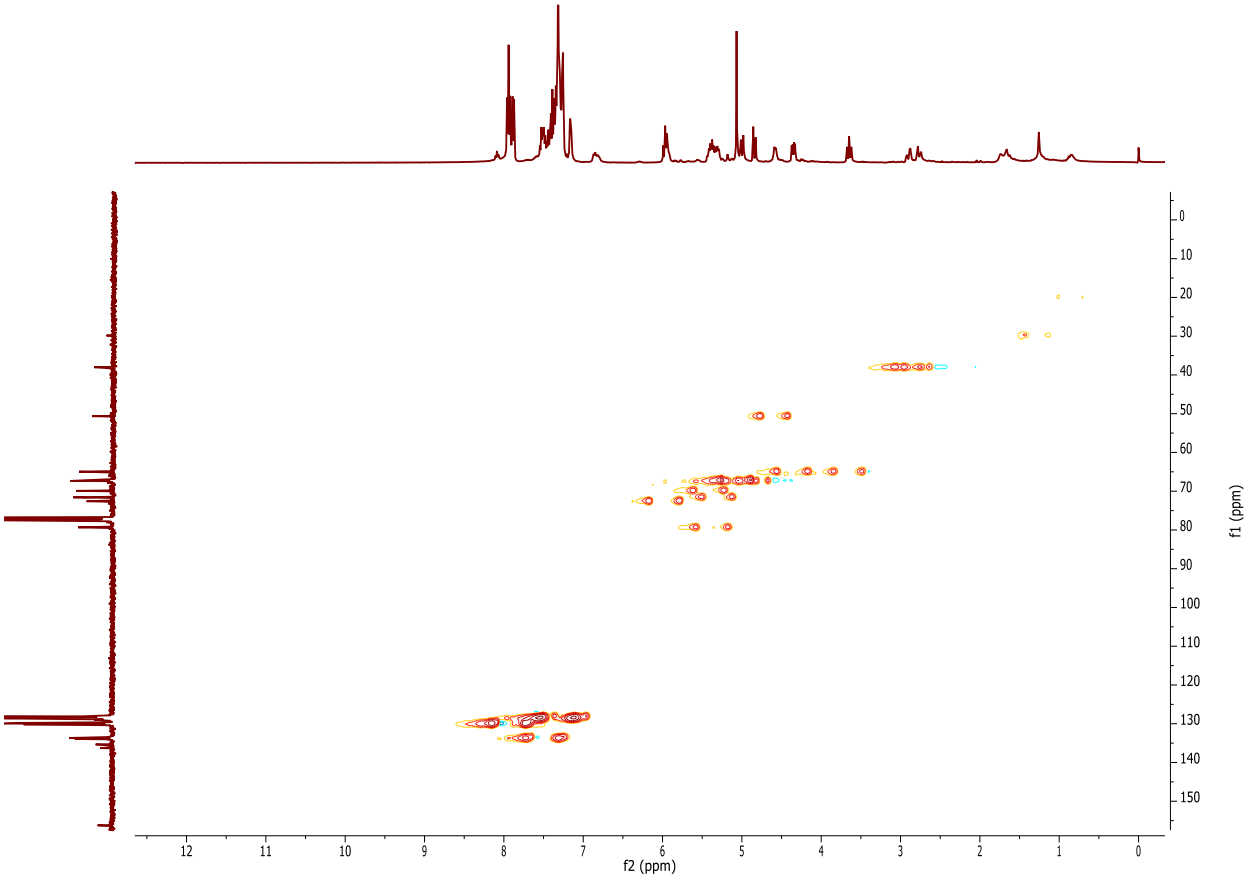
^{1}H-^{1}H COSY NMR Spectrum (600 MHz, $CDCl_3$) of Compound **11d**



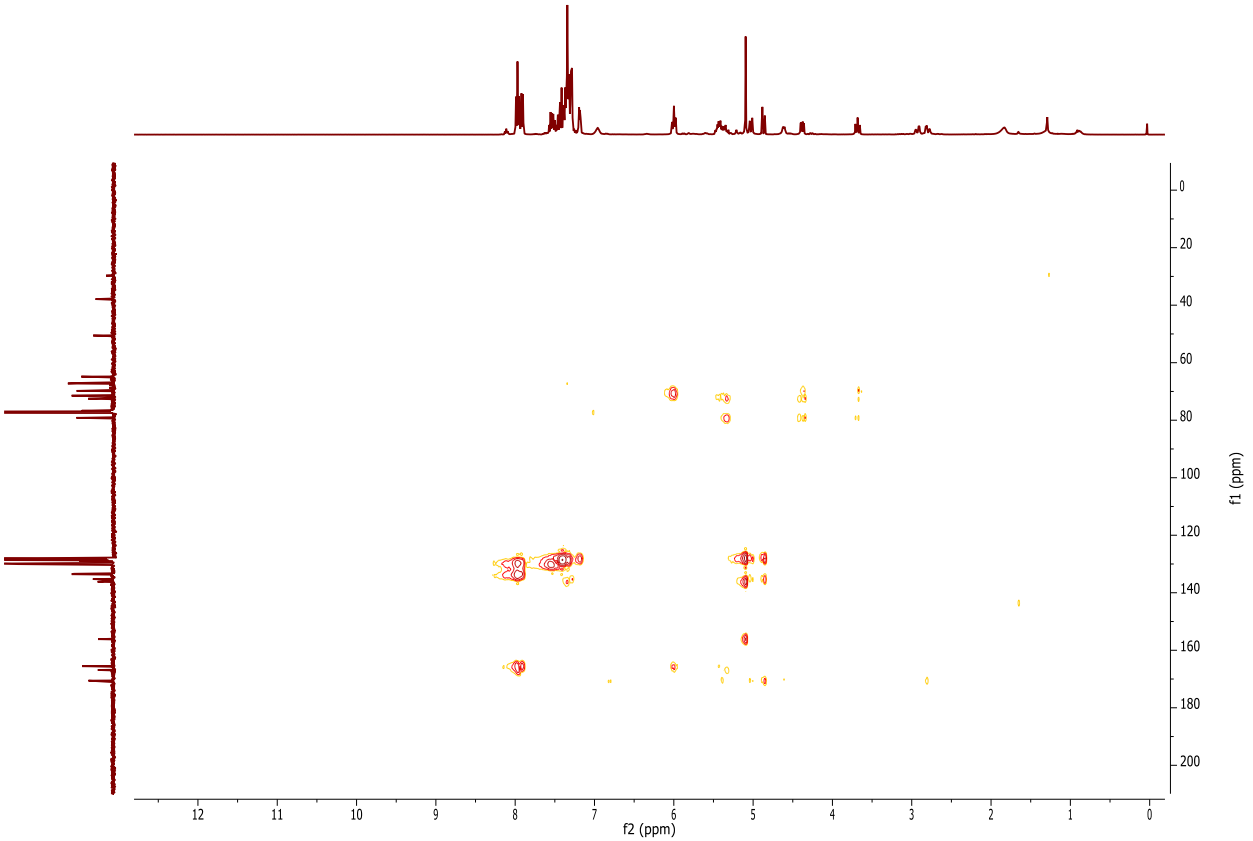
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11d**



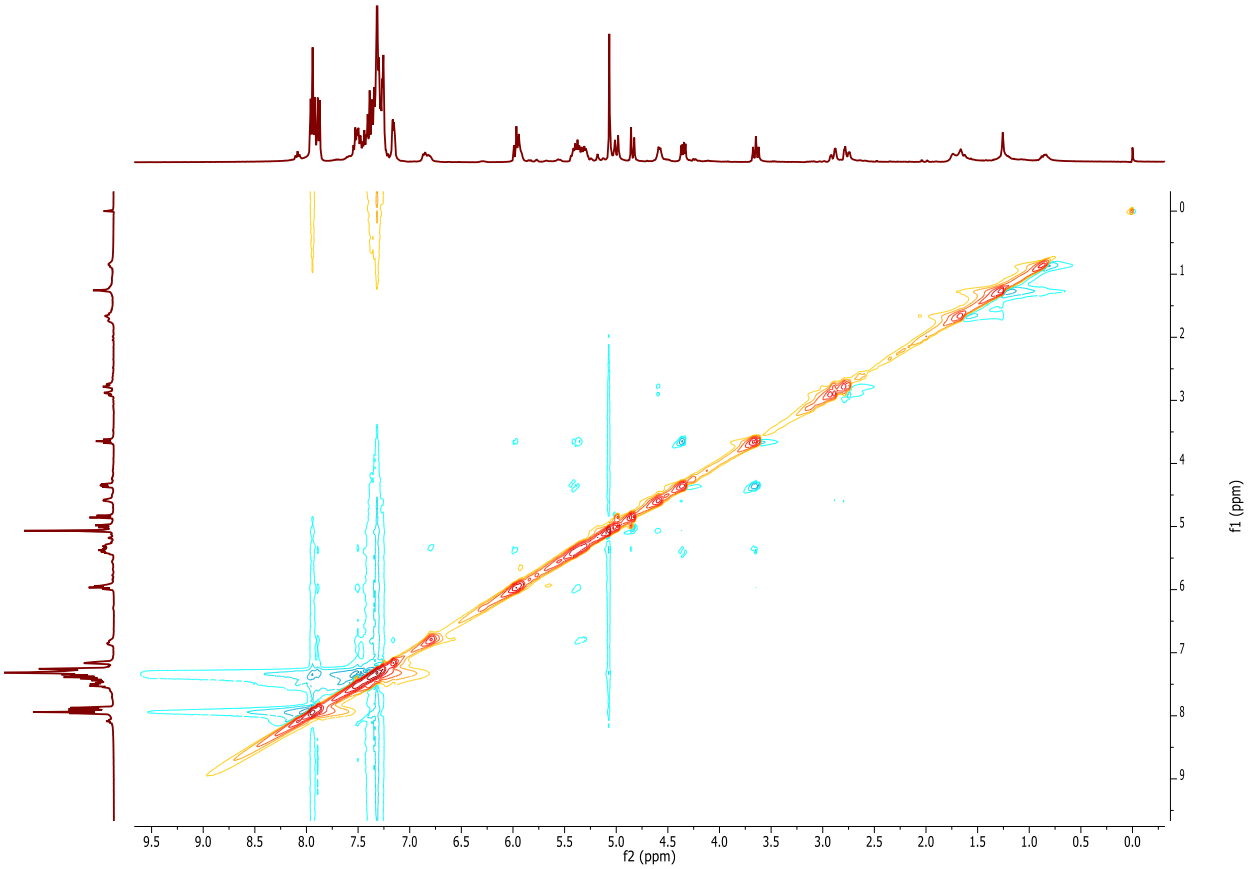
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11d**



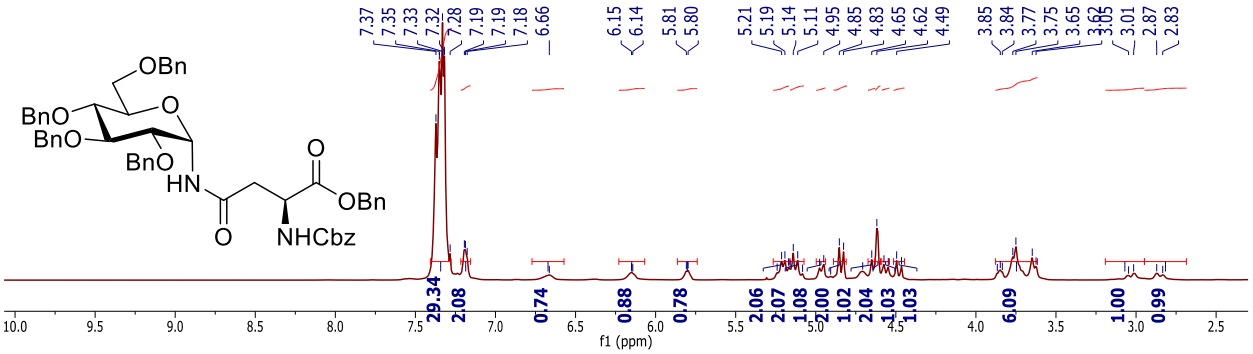
^{1}H-^{13}C HMBC NMR Spectrum (400 MHz, 100 MHz, $CDCl_3$) of Compound **11d**



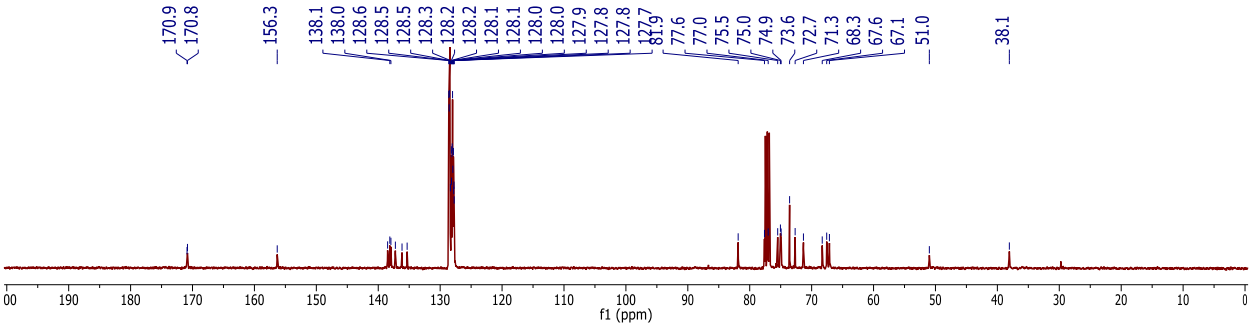
^{1}H-^{1}H NOESY NMR Spectrum (600 MHz, $CDCl_3$) of Compound **11d**



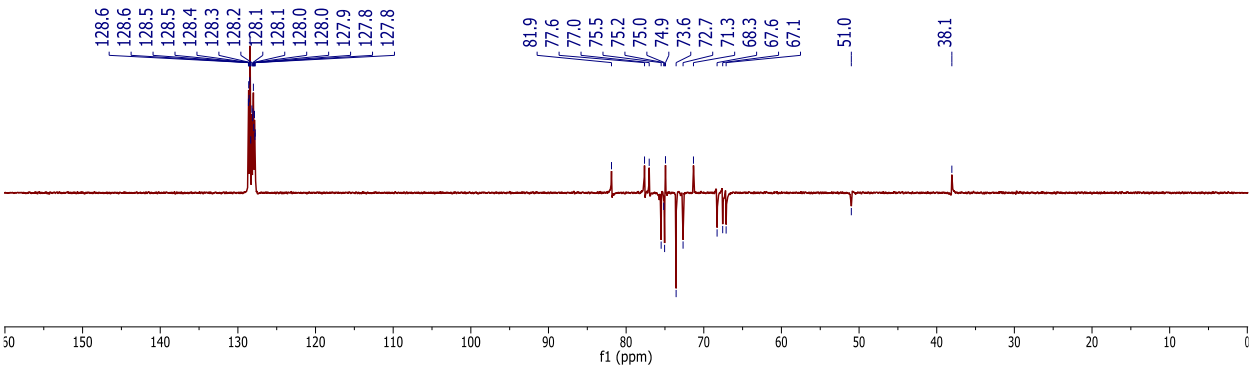
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **11e**



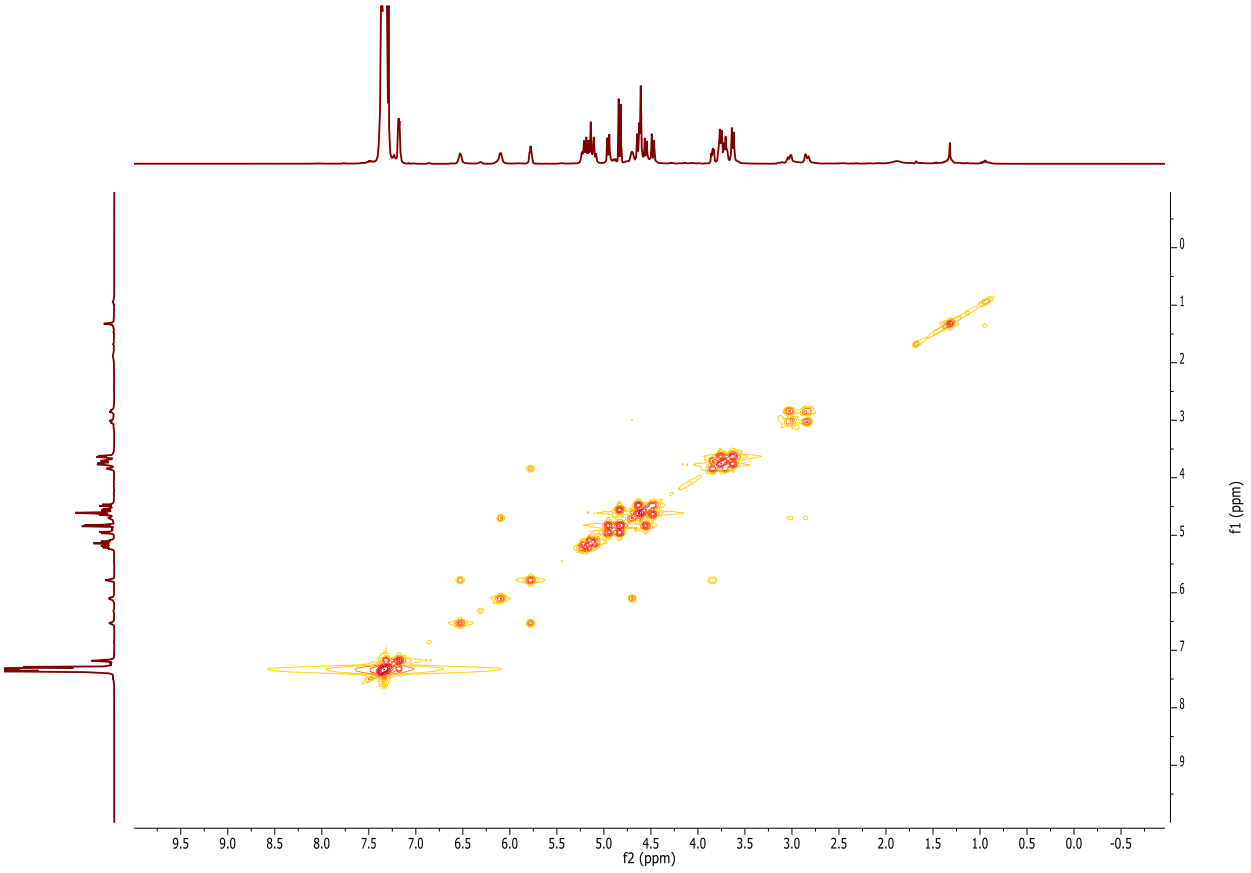
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11e**



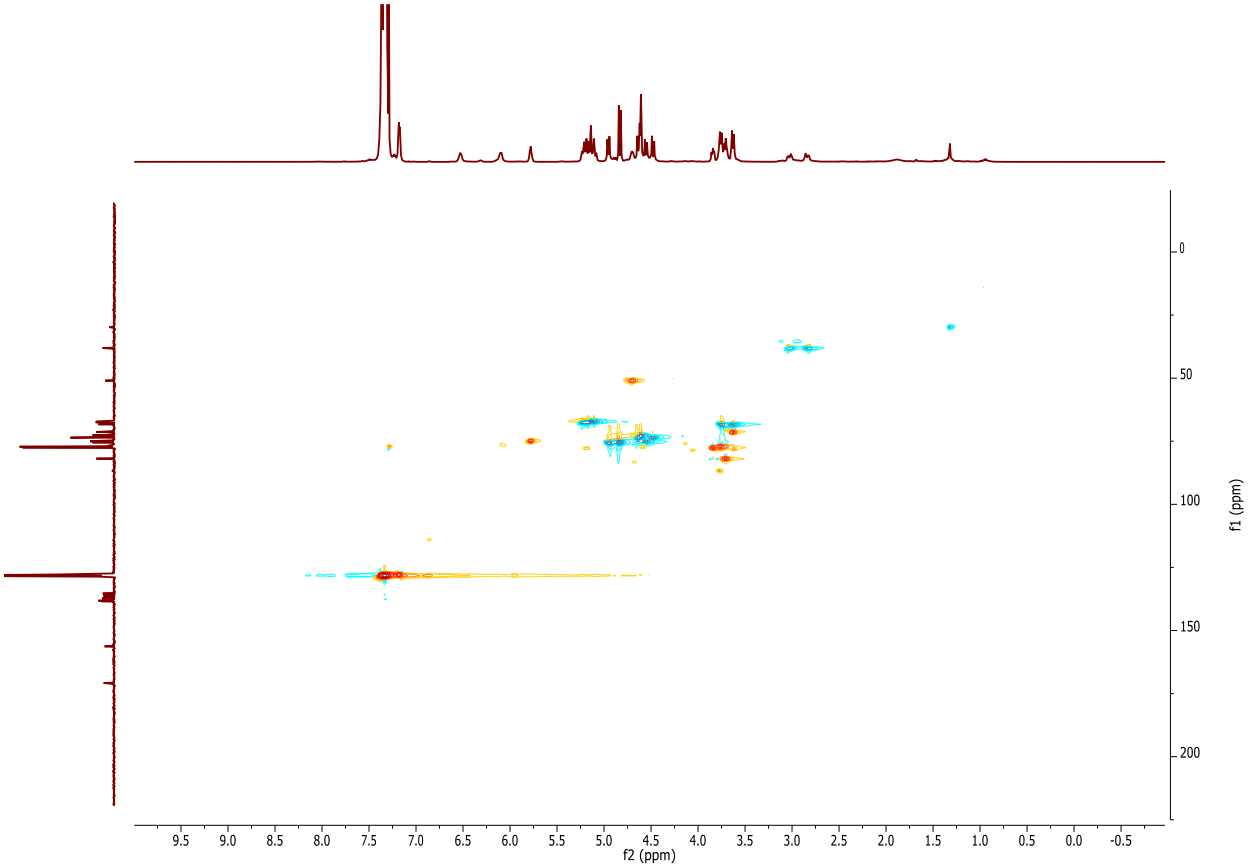
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11e**



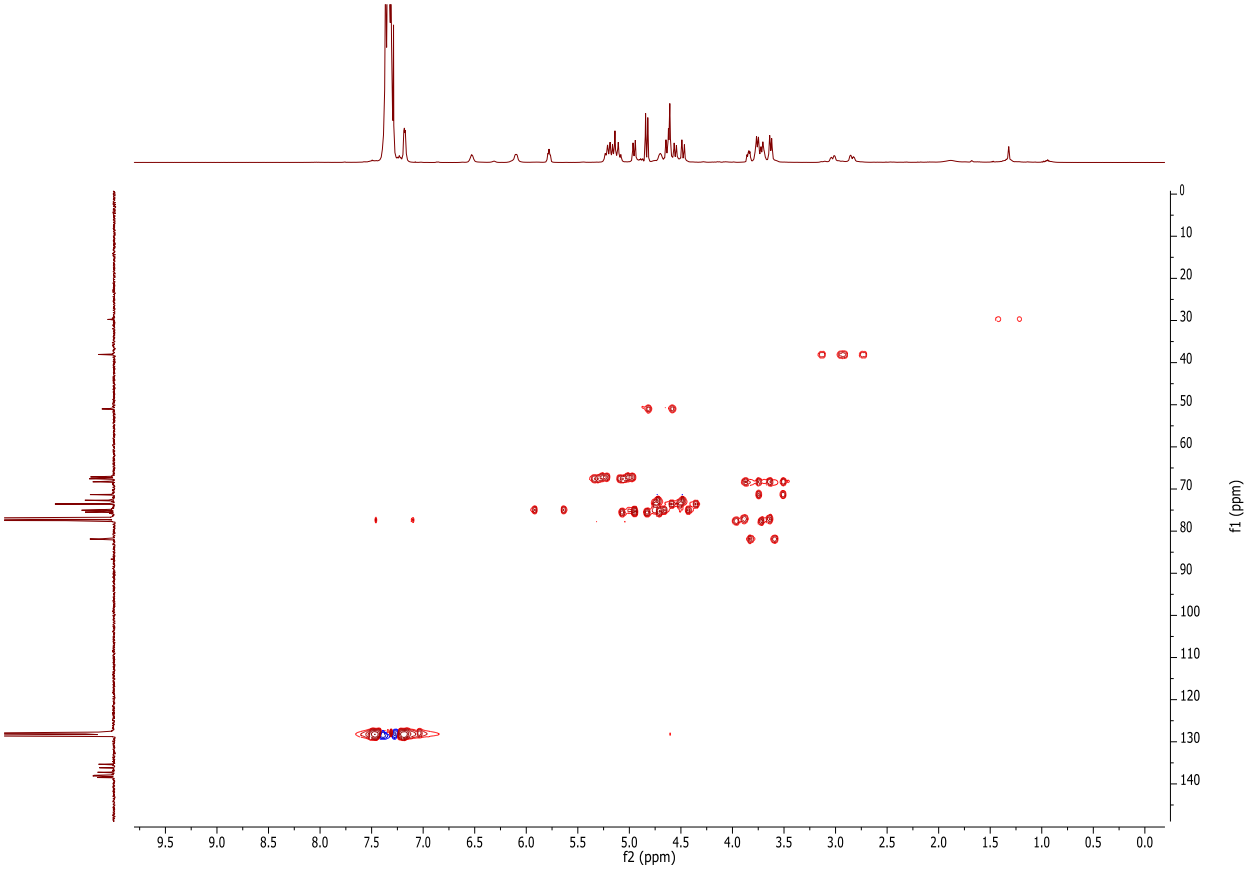
^{1}H-^{1}H COSY NMR Spectrum (400 MHz, $CDCl_3$) of Compound **11e**



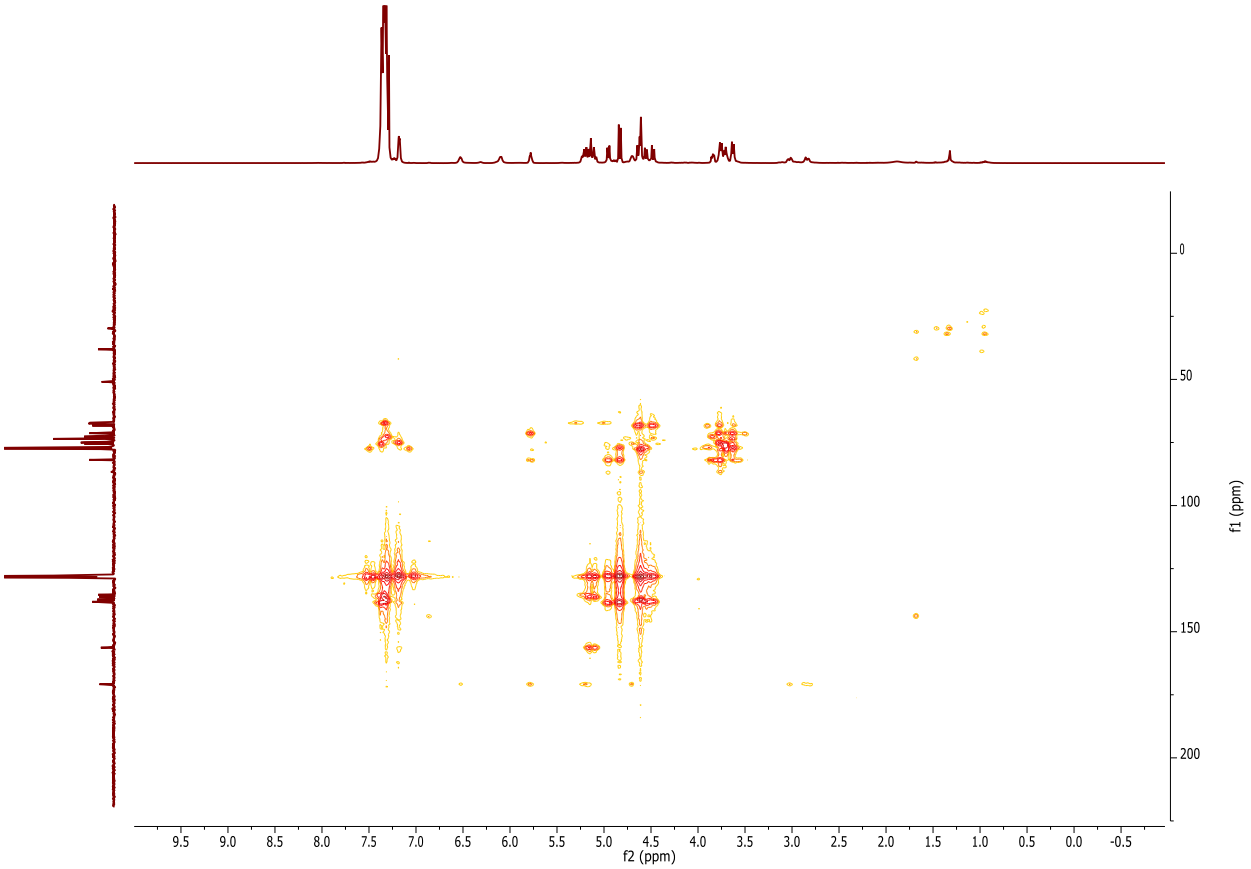
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11e**



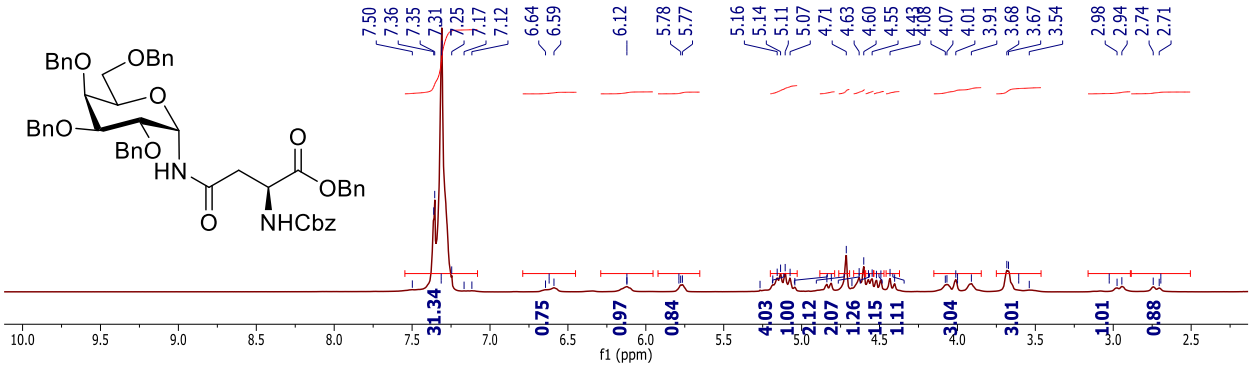
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11e**



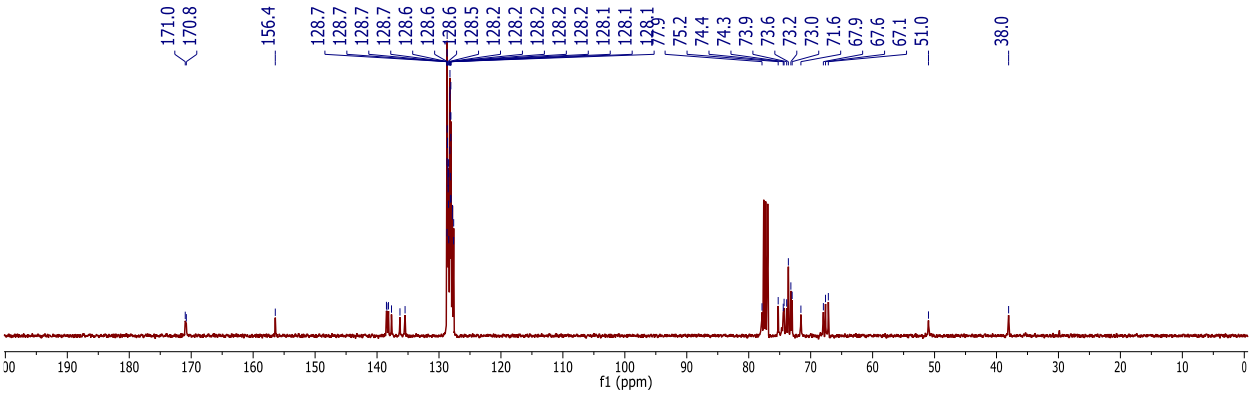
^{1}H-^{13}C HMBC NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11e**



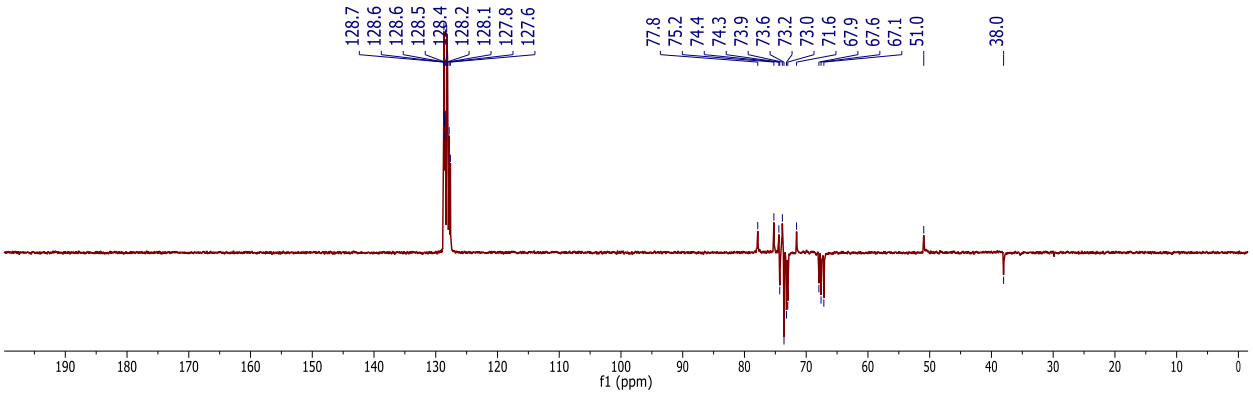
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **11f**



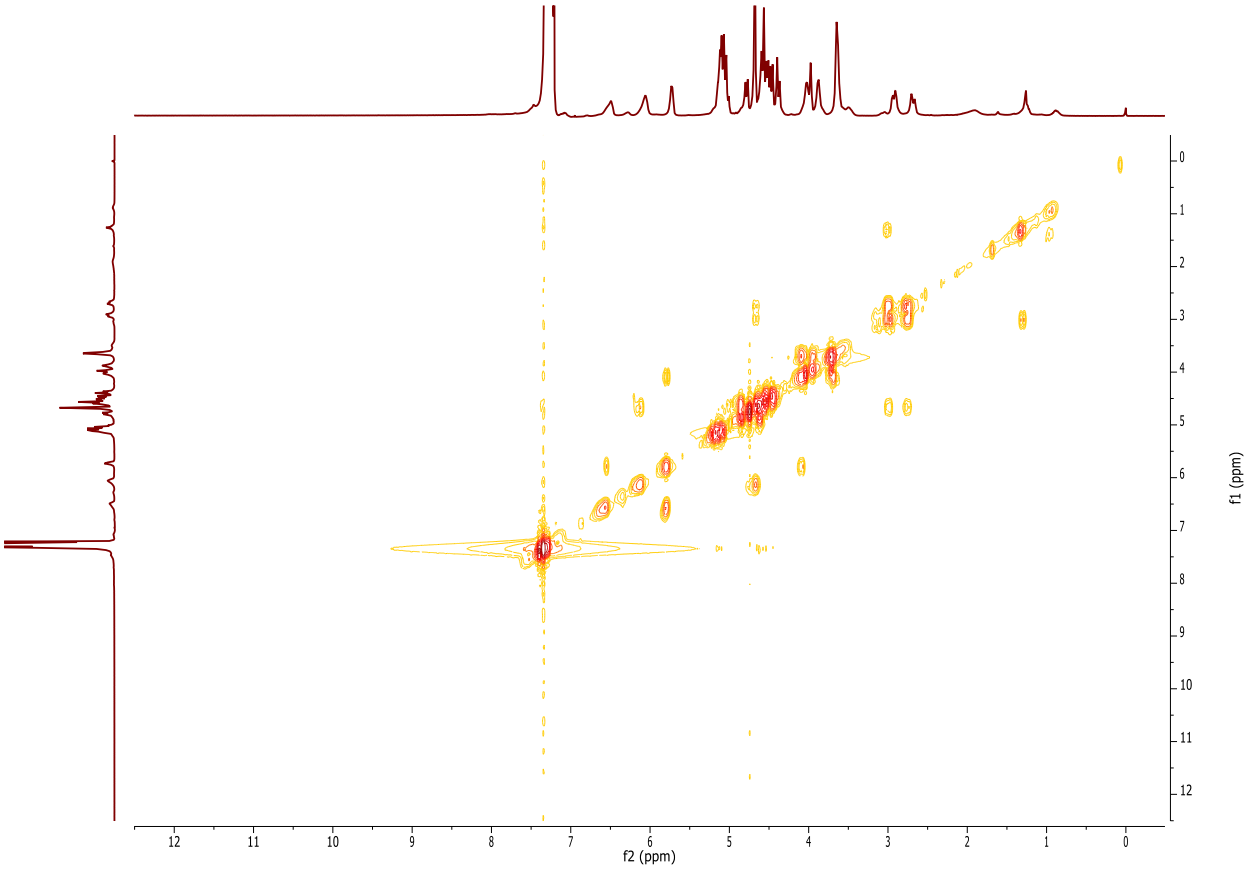
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11f**



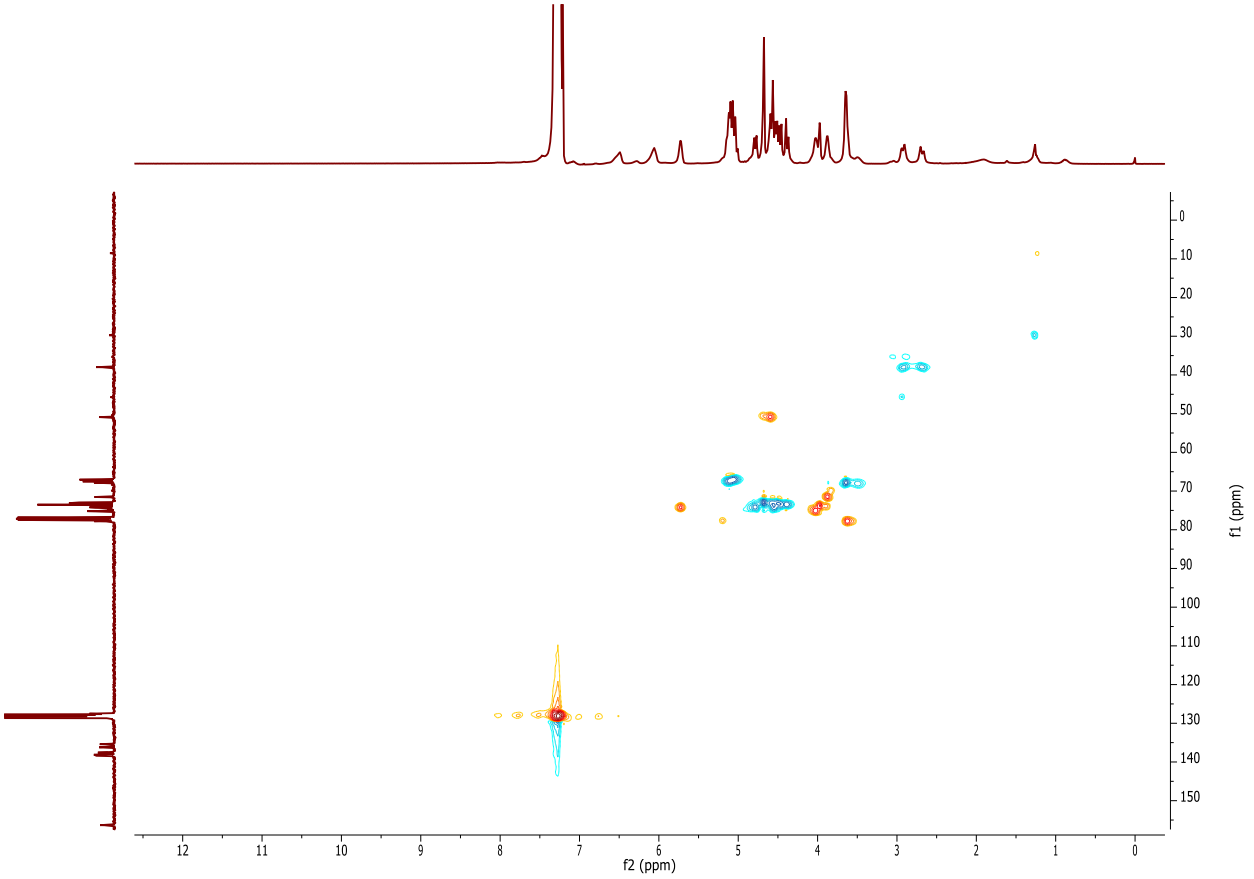
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11f**



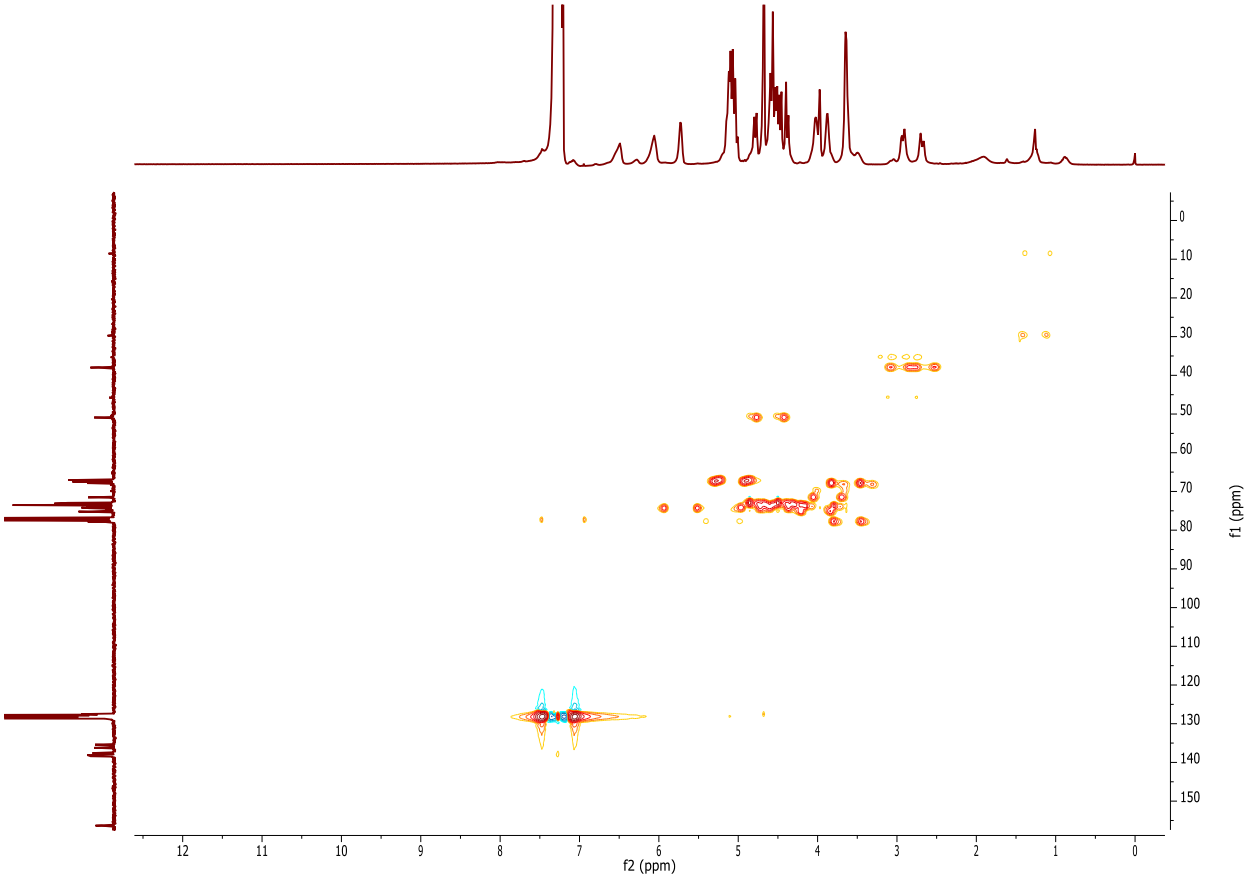
^{1}H-^{1}H COSY NMR Spectrum (600 MHz, $CDCl_3$) of Compound **11f**



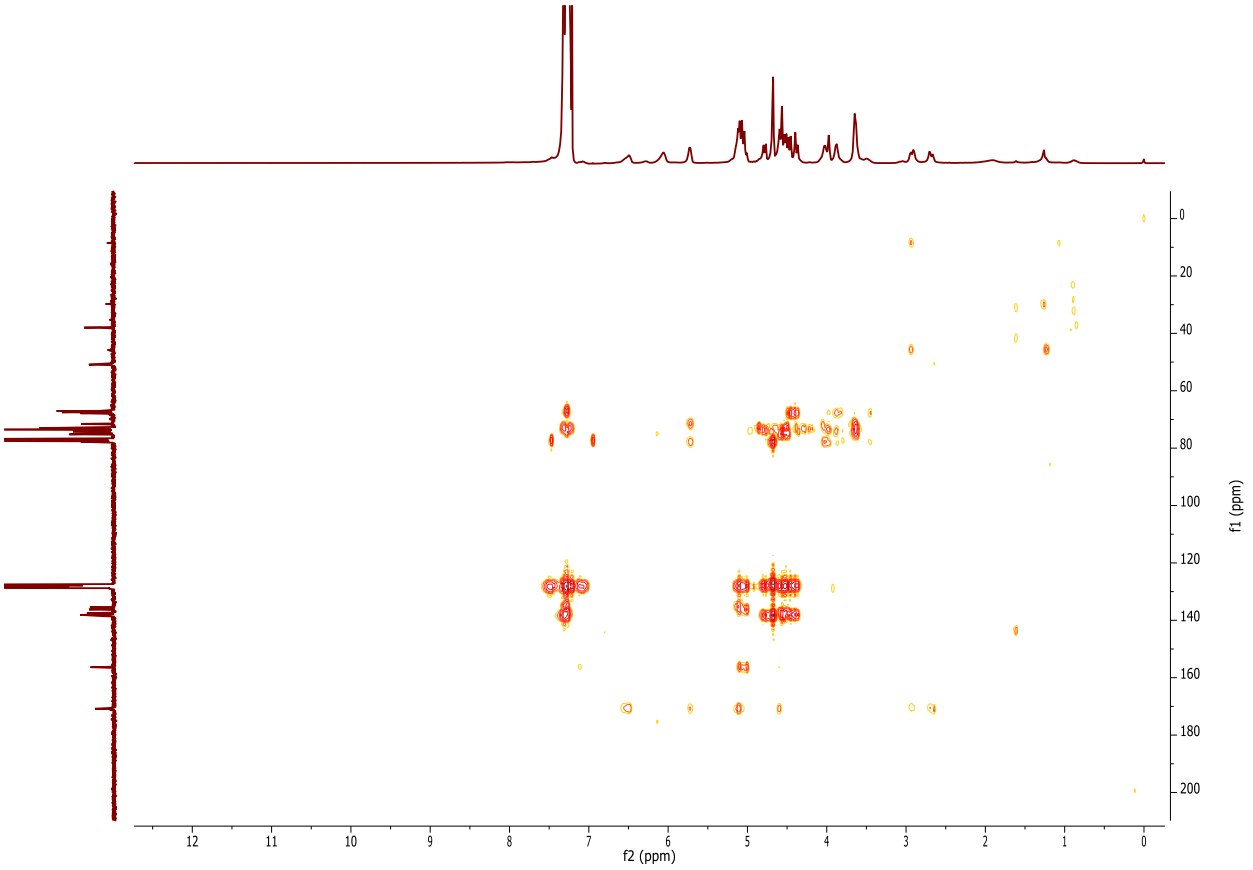
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11f**



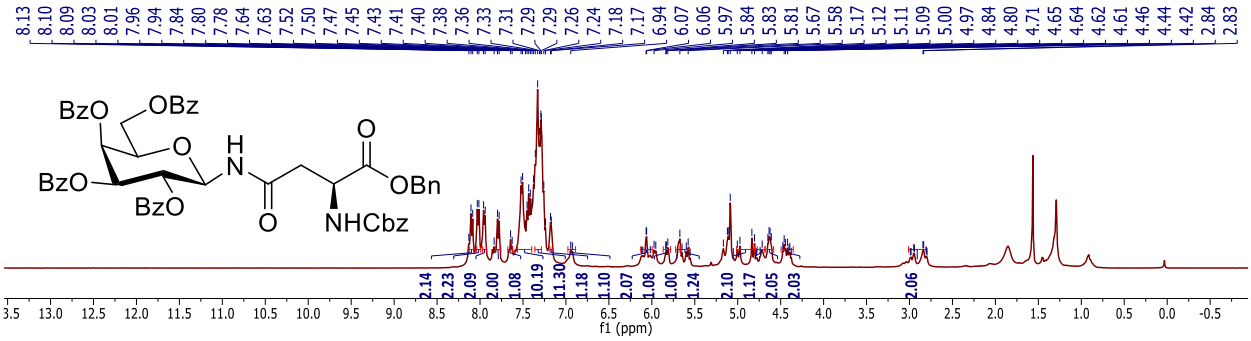
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11f**



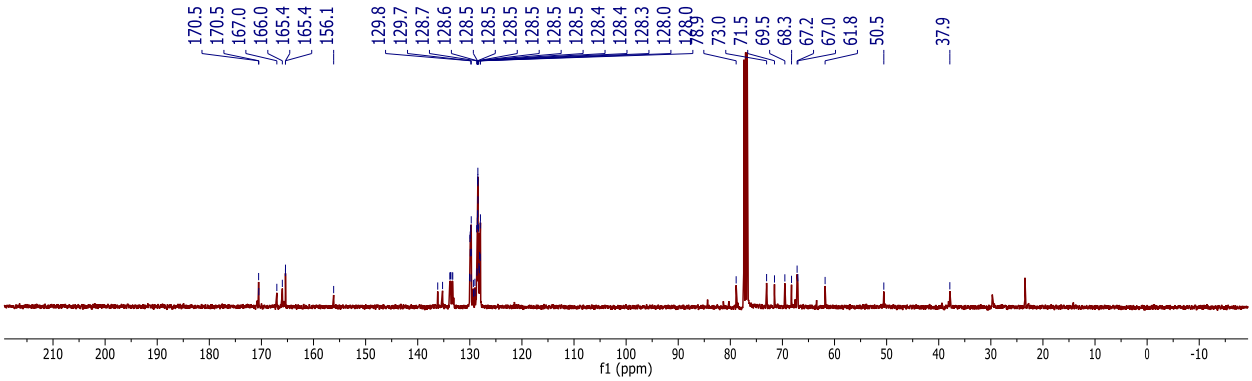
^{1}H-^{13}C HMBC NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11f**



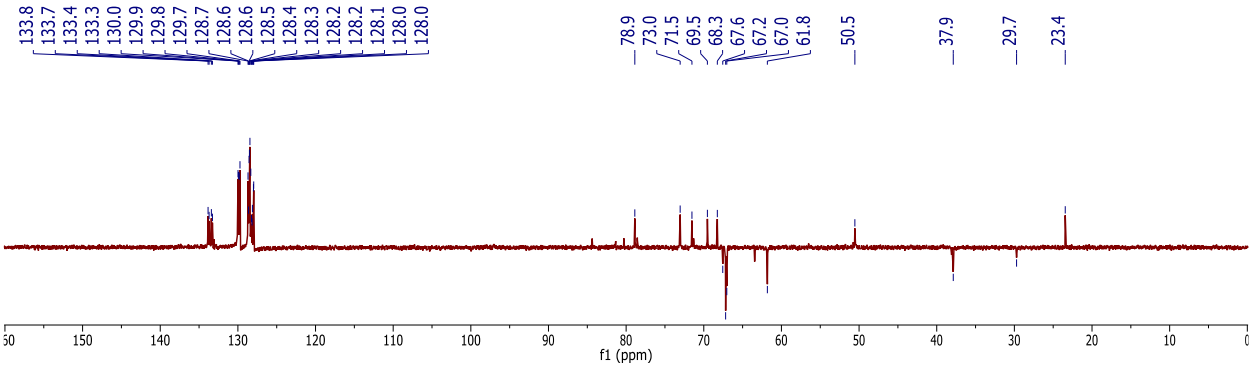
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **11g**



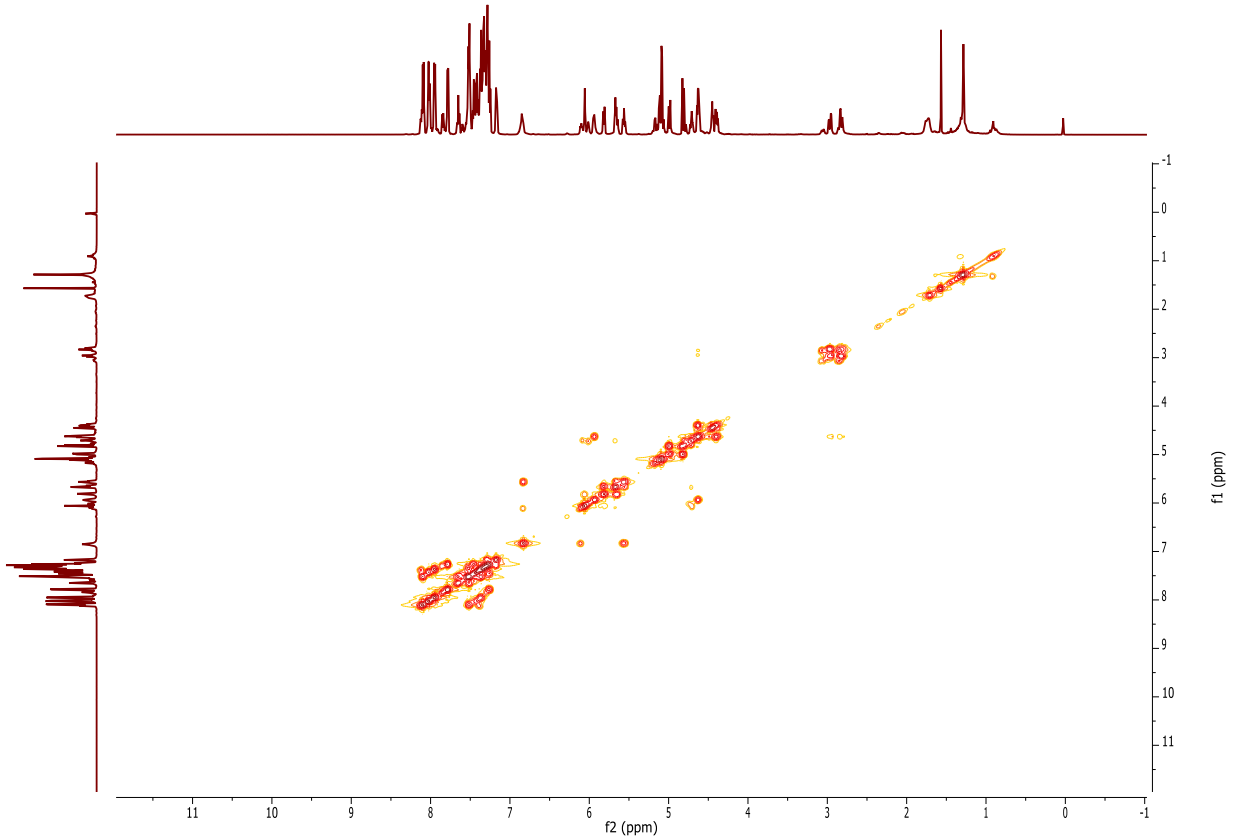
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11g**



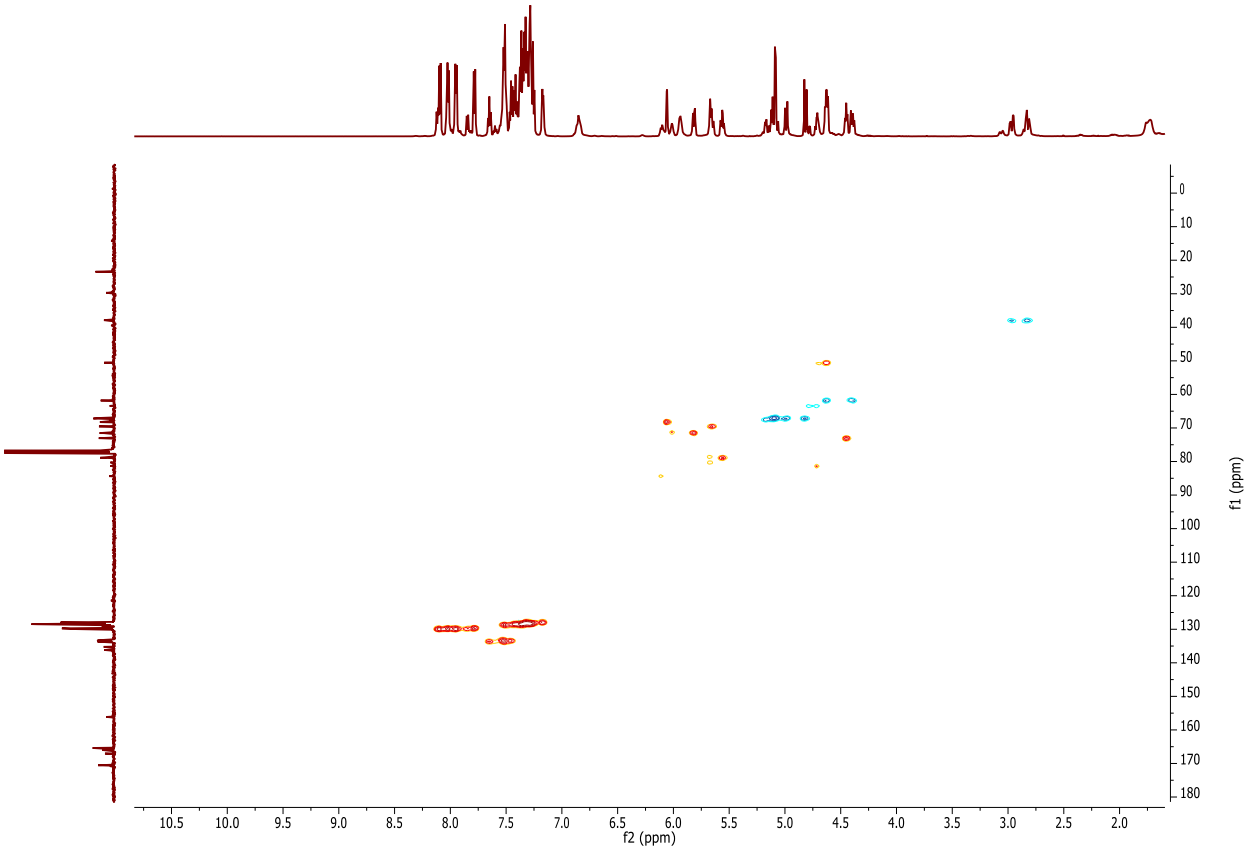
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11g**



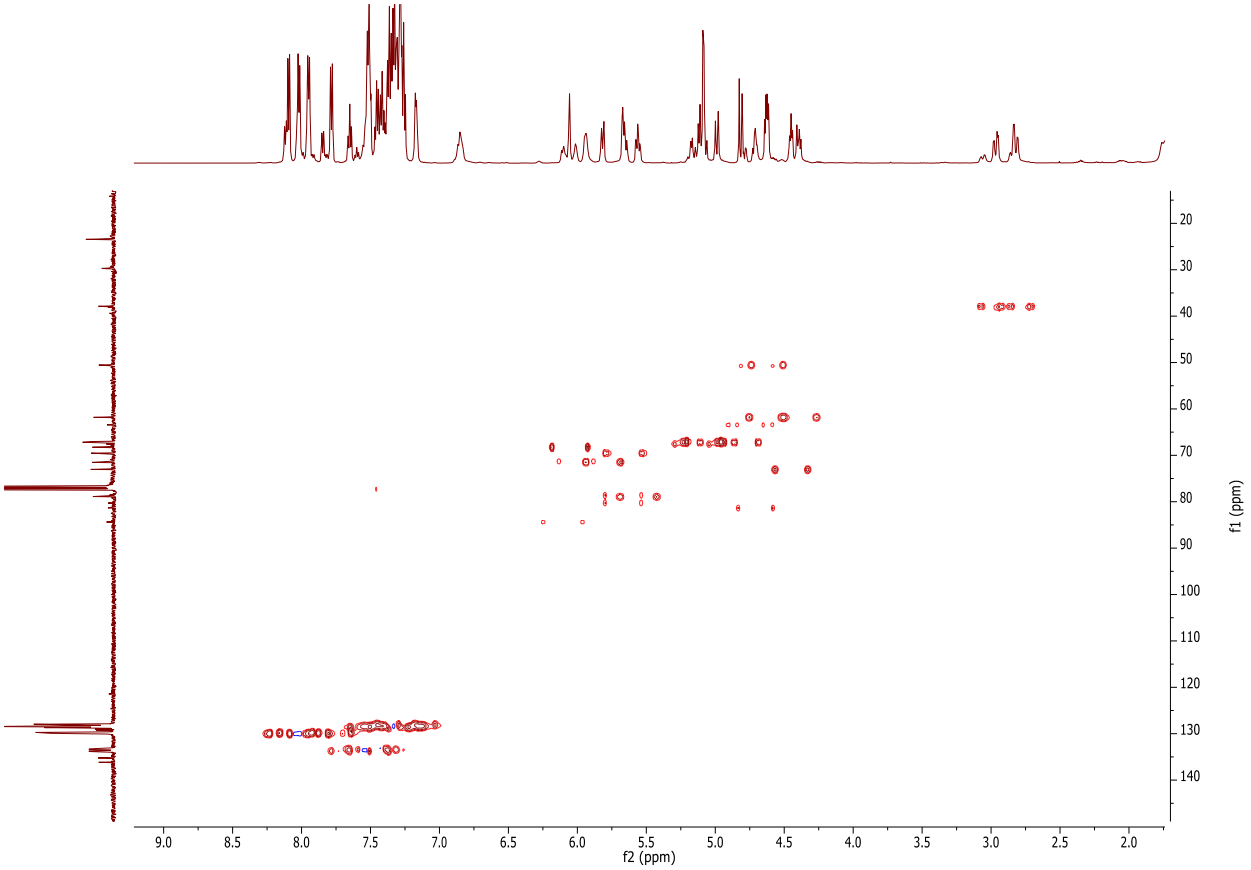
^{1}H-^{1}H COSY NMR Spectrum (600 MHz, $CDCl_3$) of Compound **11g**



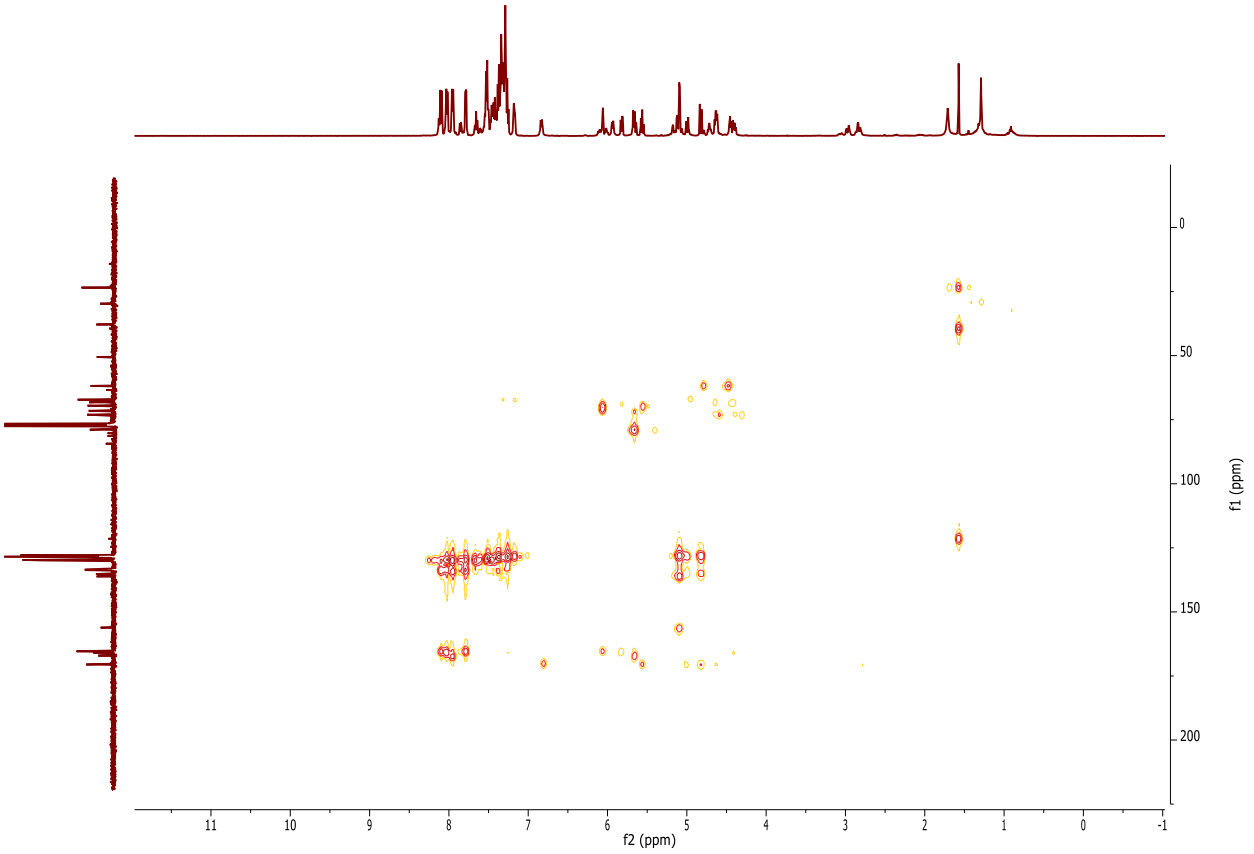
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11g**



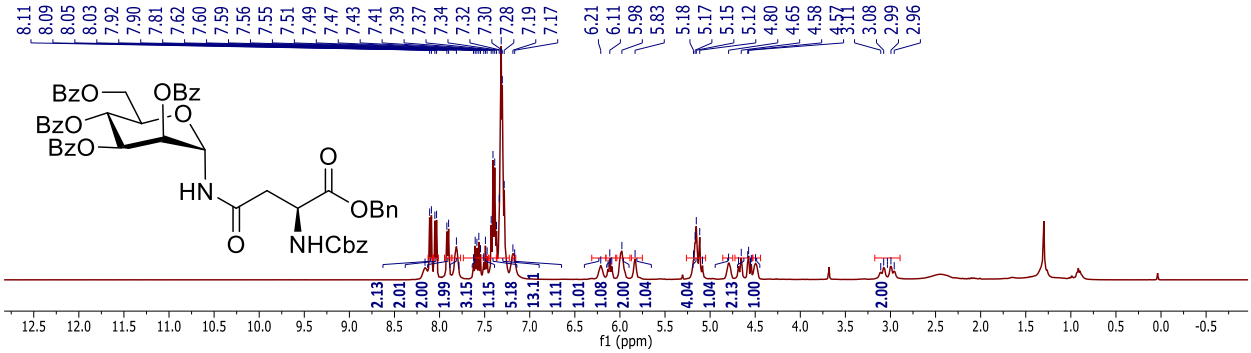
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11g**



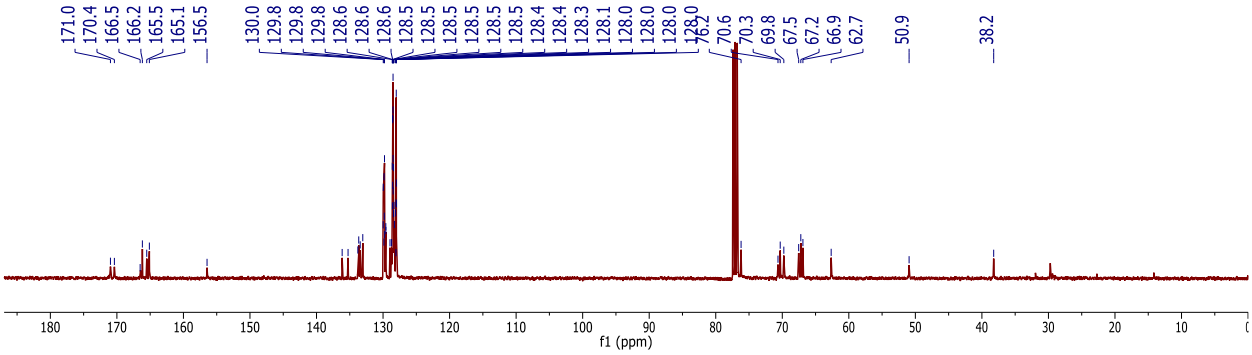
^{1}H-^{13}C HMBC NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11g**



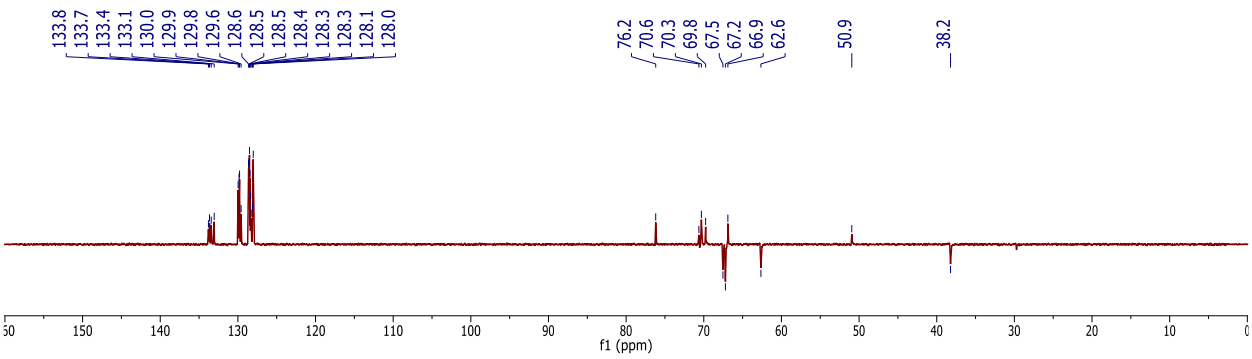
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **11h**



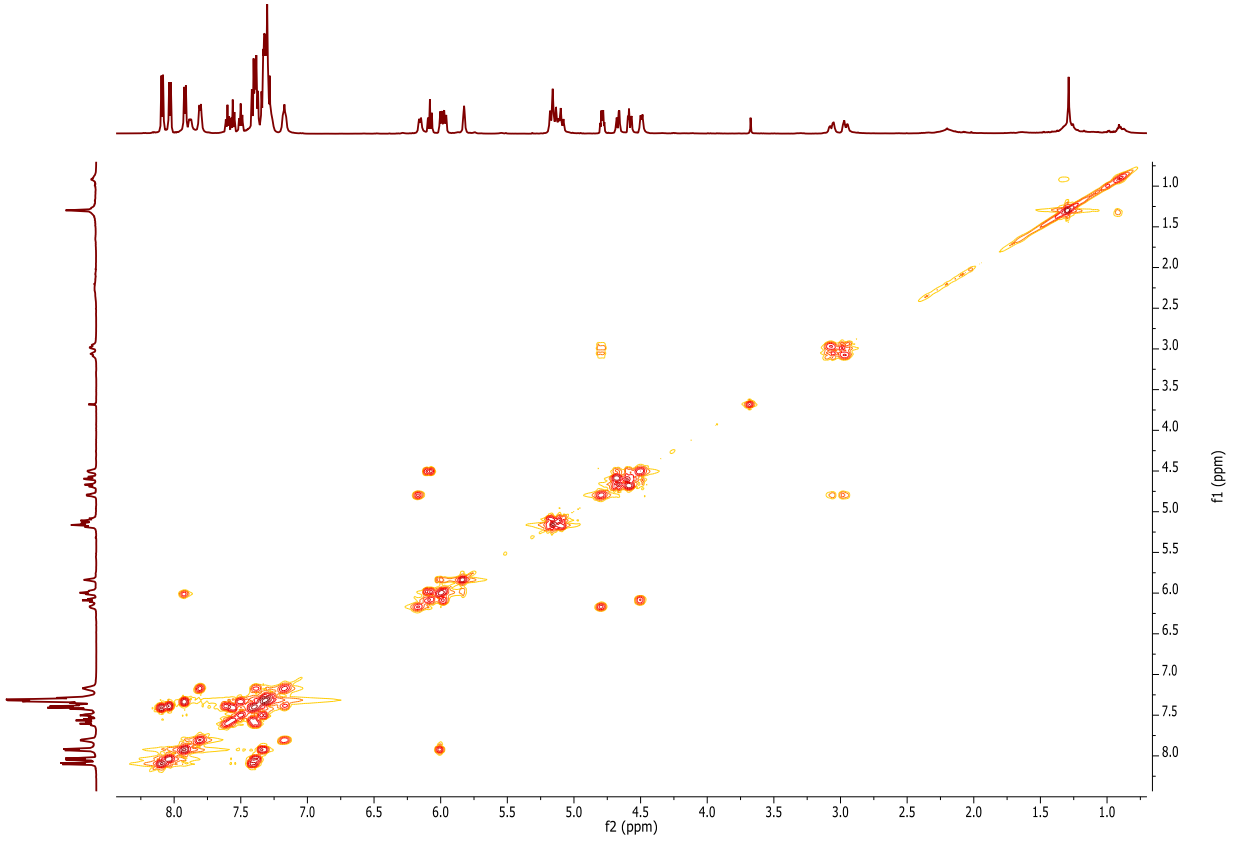
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11h**



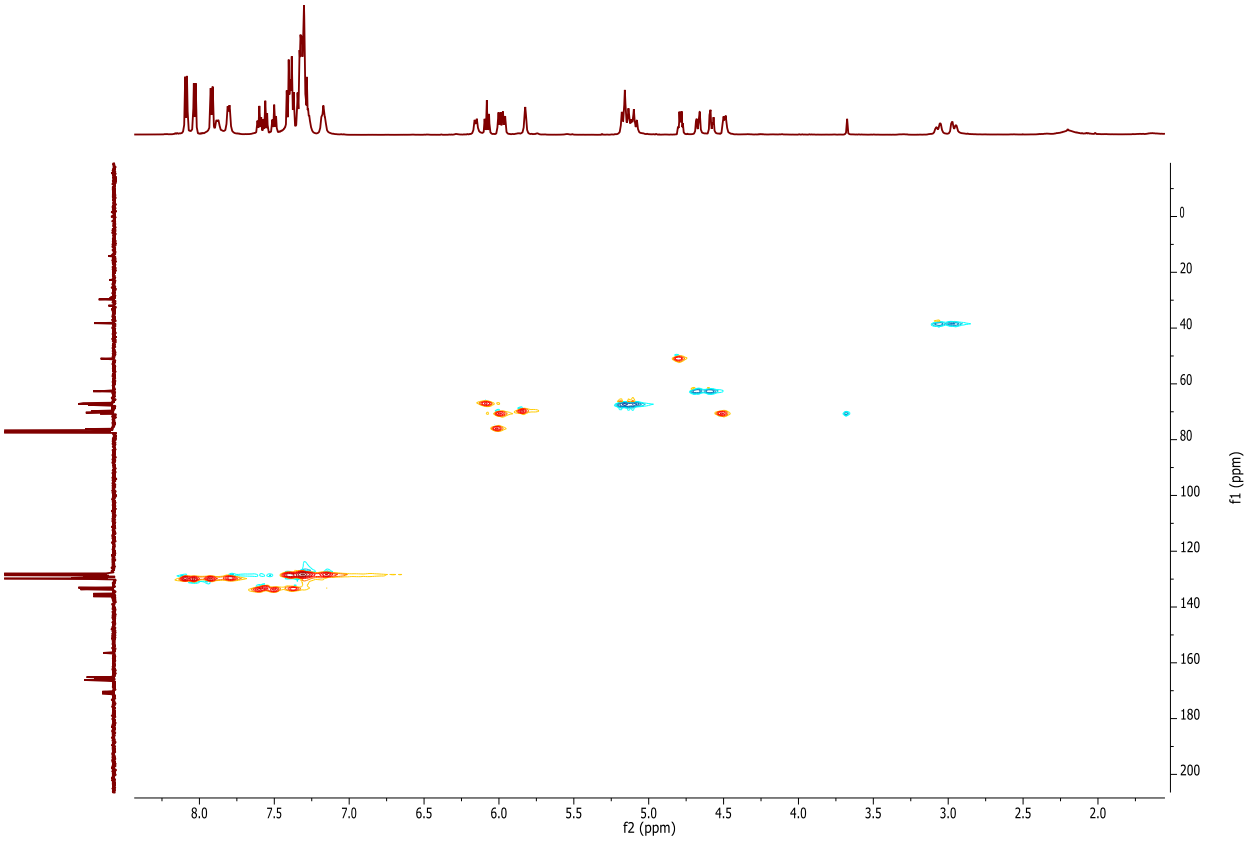
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11h**



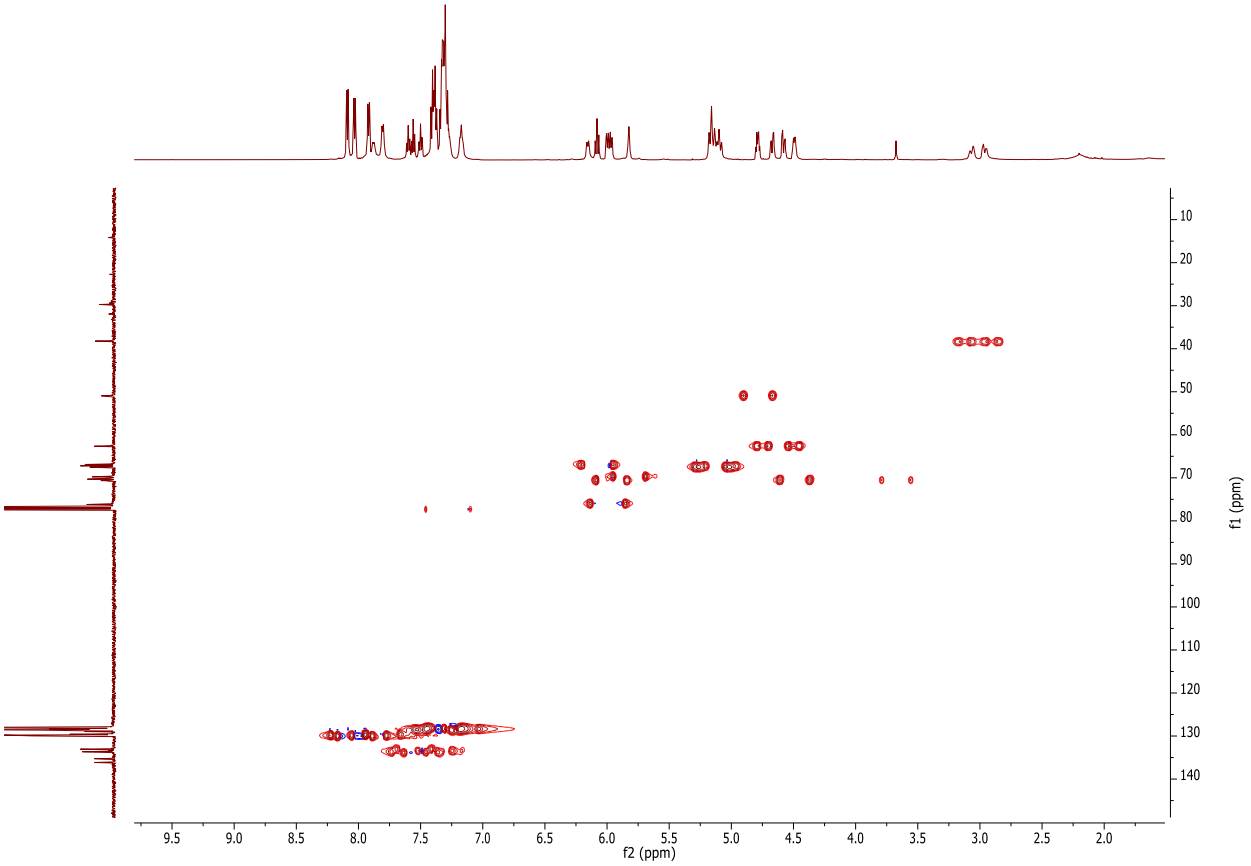
^{1}H-^{1}H COSY NMR Spectrum (600 MHz, $CDCl_3$) of Compound **11h**



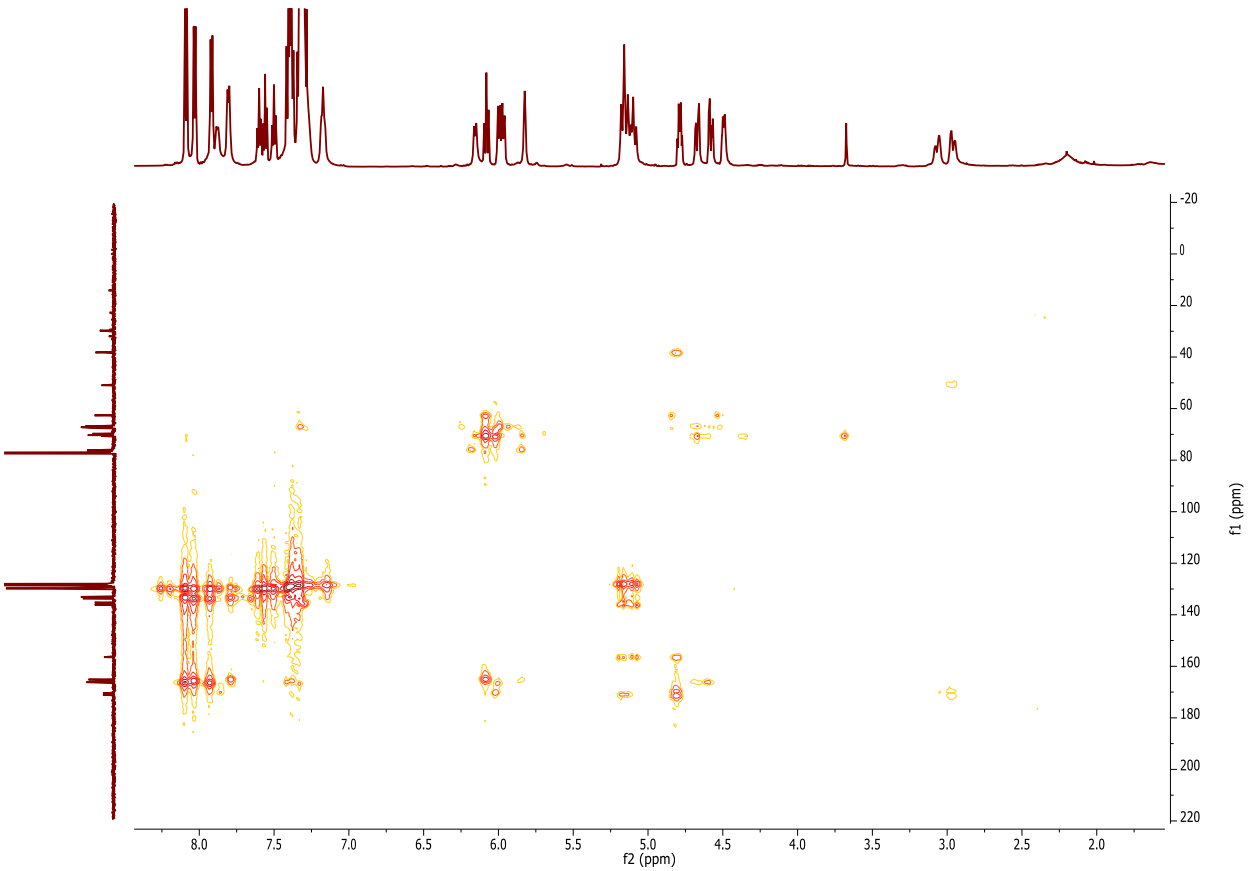
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11h**



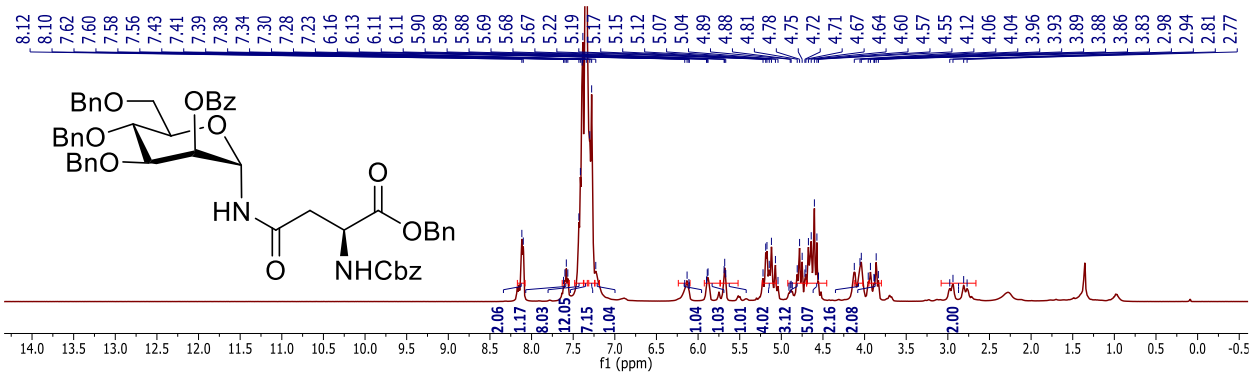
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11h**



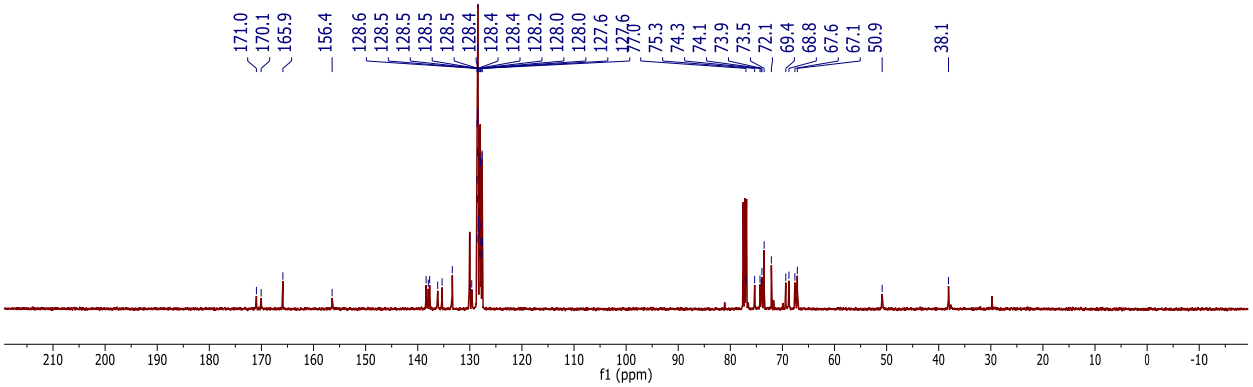
^{1}H-^{13}C HMBC NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11h**



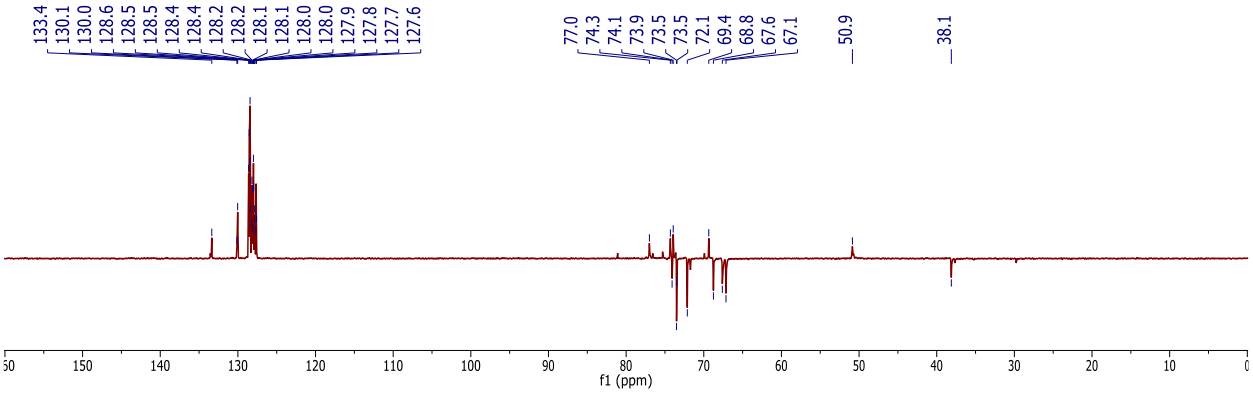
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **11i**



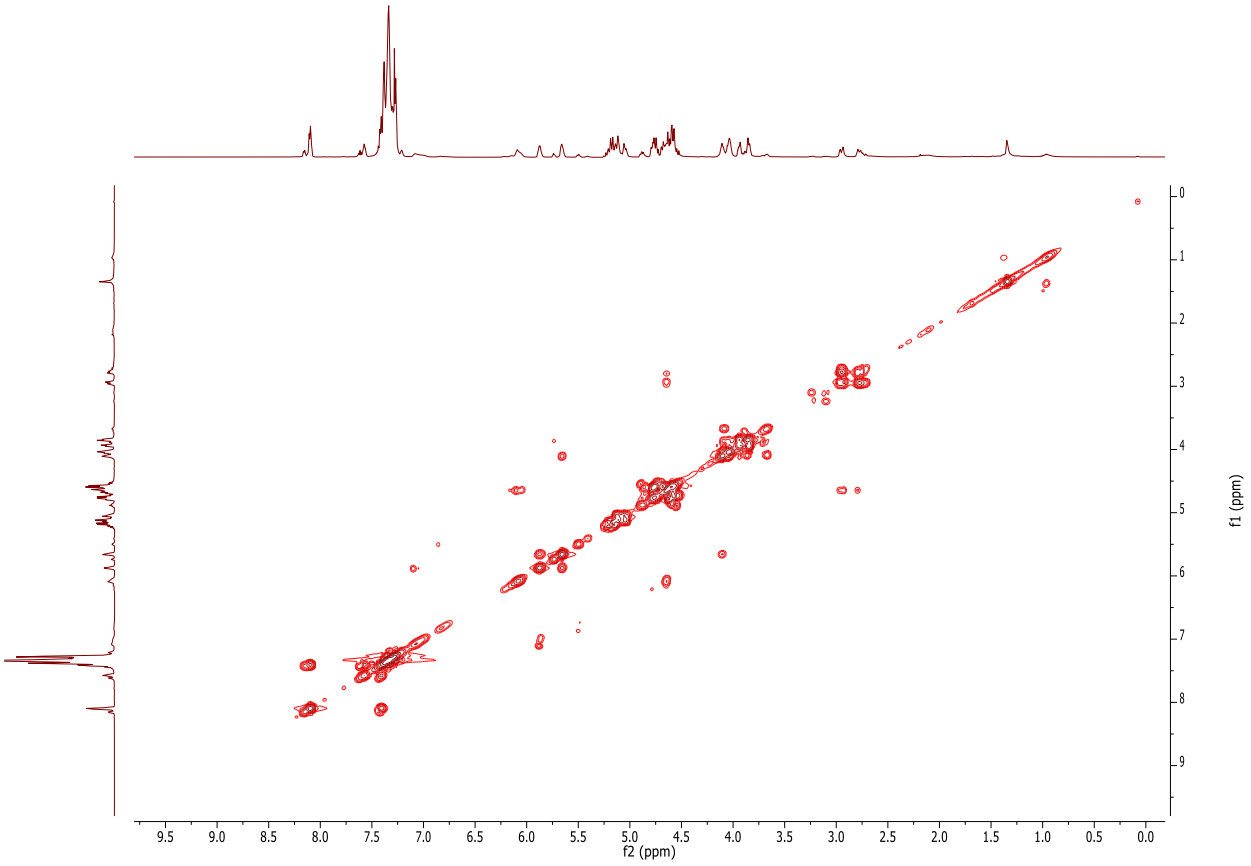
NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11i**



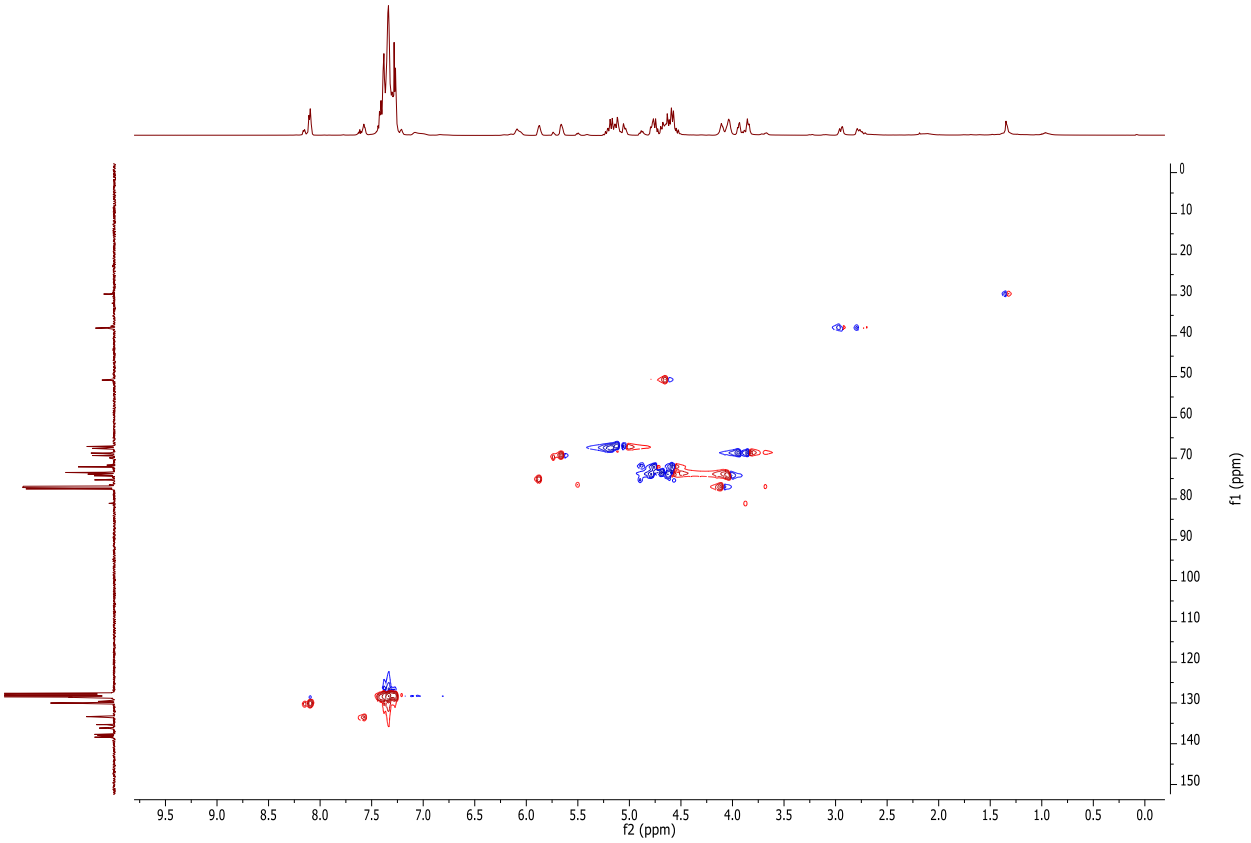
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11i**



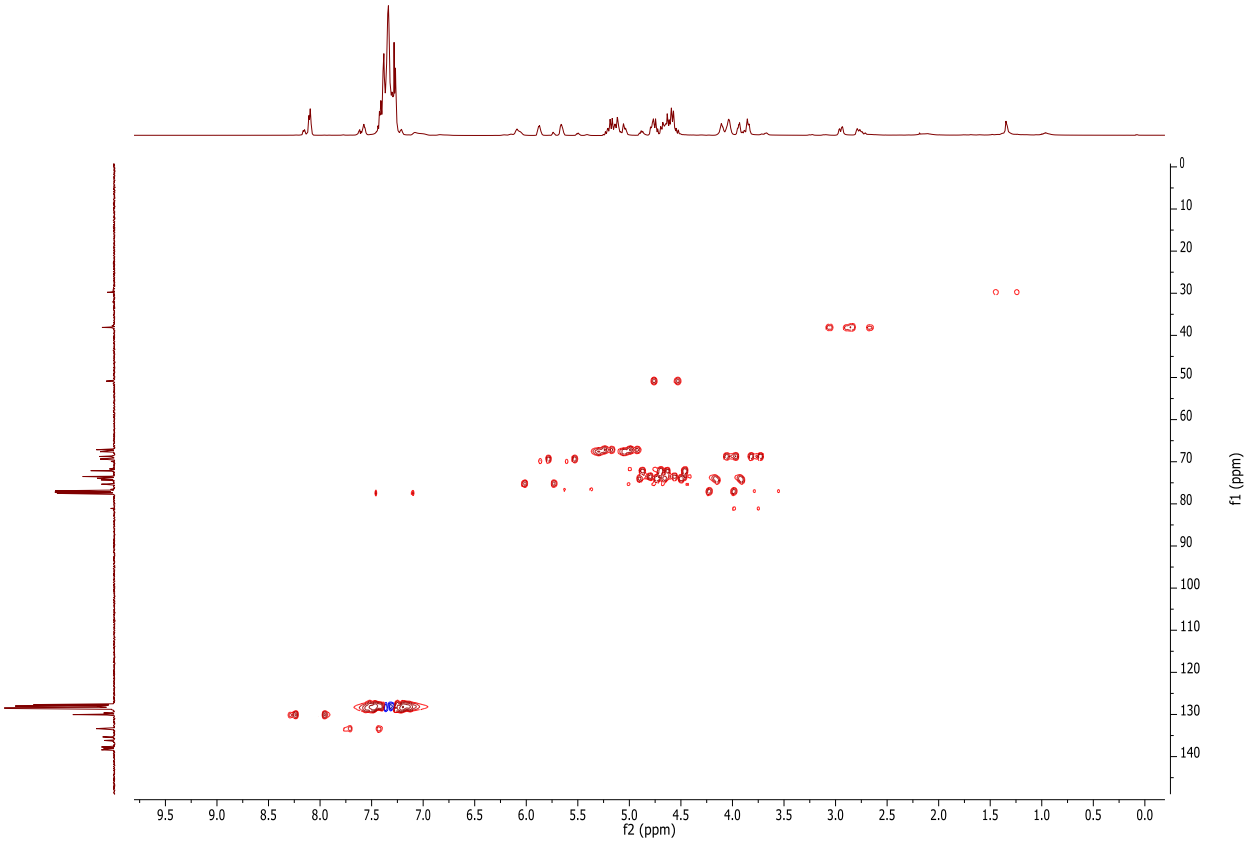
^{1}H-^{1}H COSY NMR Spectrum (600 MHz, $CDCl_3$) of Compound **11i**



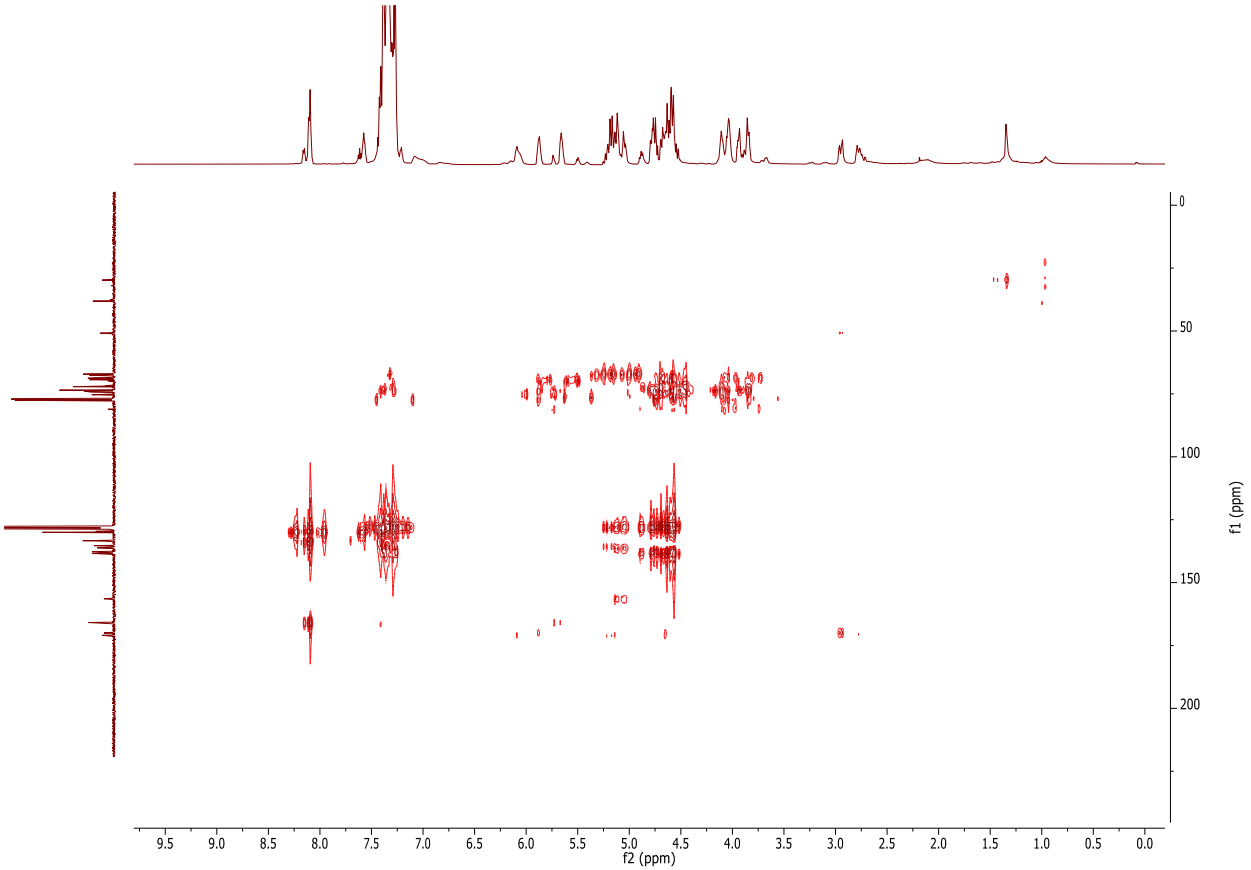
^{1}H-^{13}C HSQC (multiplicity edited) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11i**



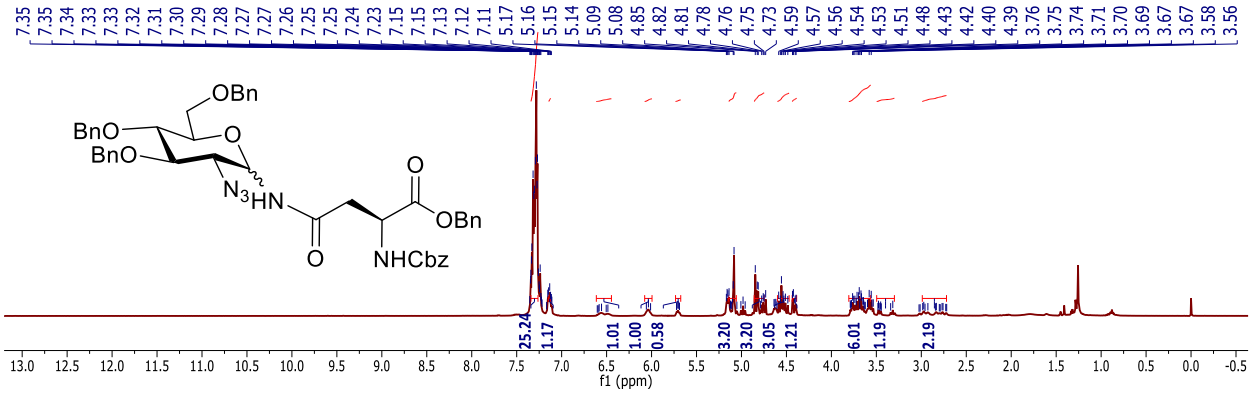
^{1}H-^{13}C HSQC (^{13}C coupled in ^{1}H direction) NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11i**



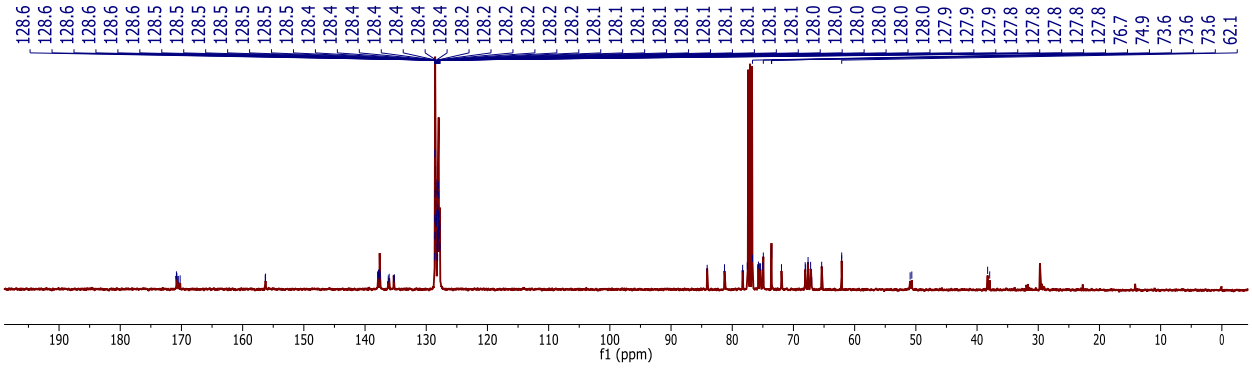
^{1}H-^{13}C HMBC NMR Spectrum (600 MHz, 151 MHz, $CDCl_3$) of Compound **11i**



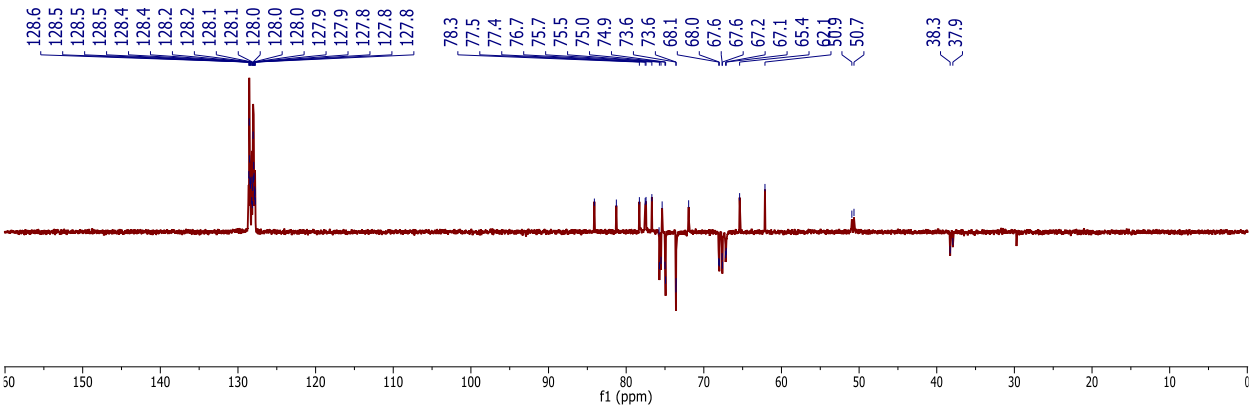
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **11j**



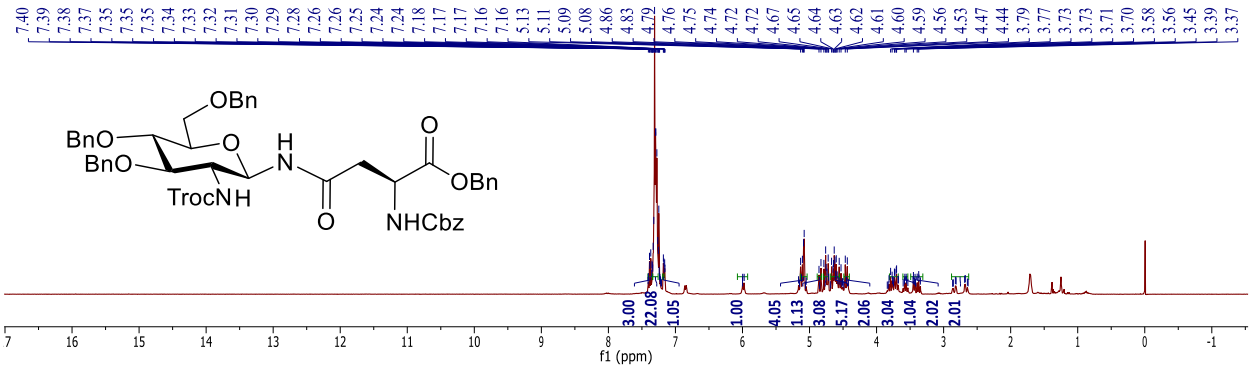
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11j**



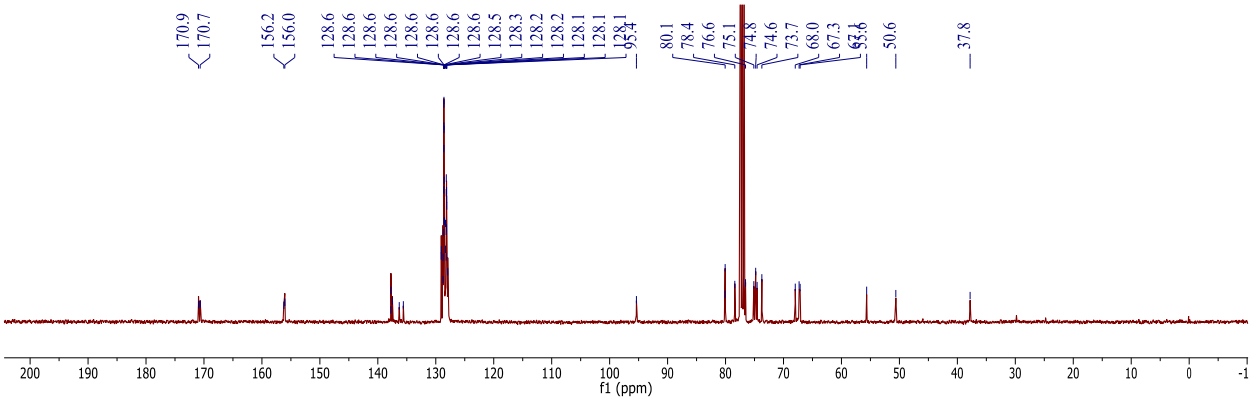
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11j**



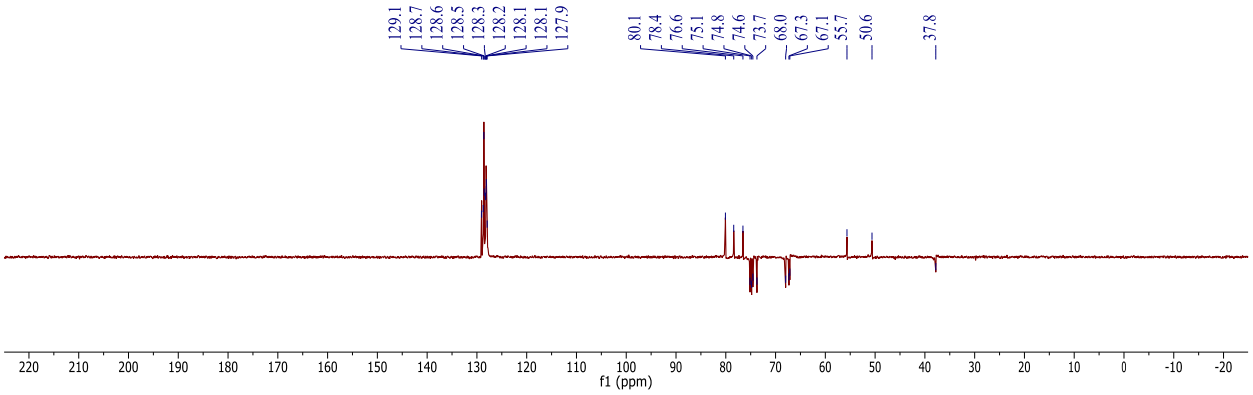
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **11k**



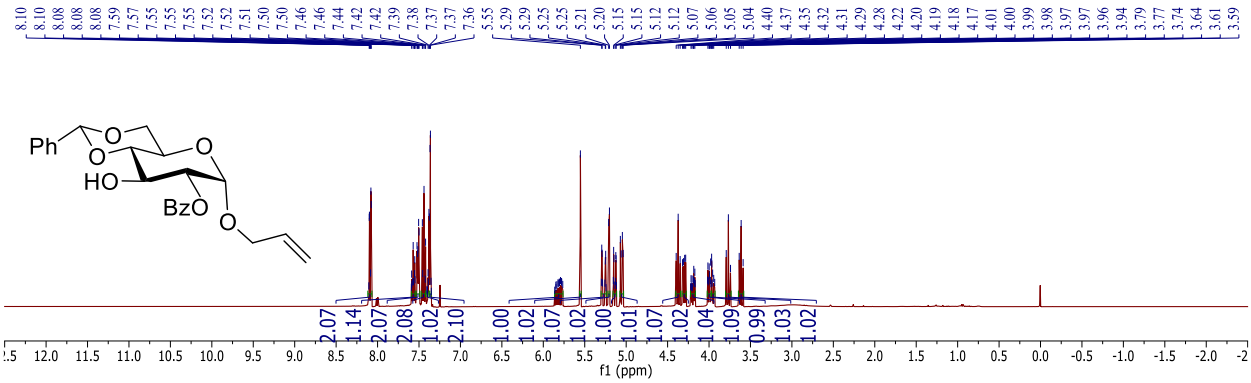
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11k**



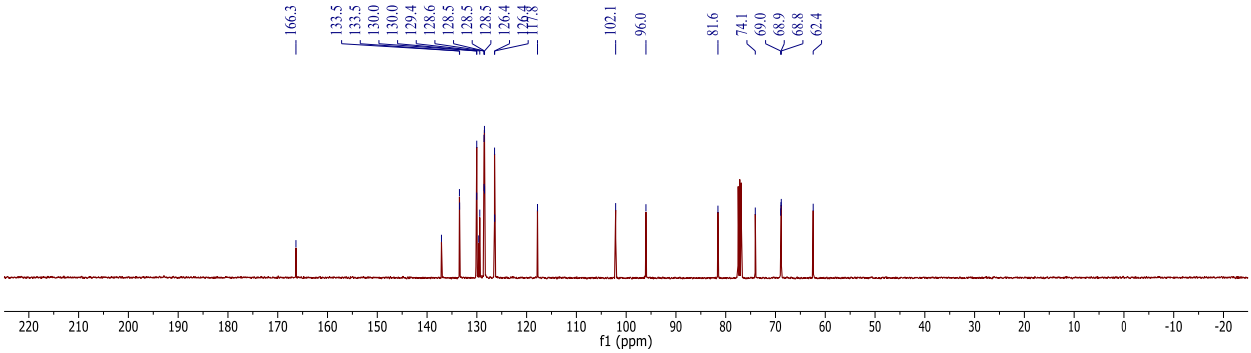
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **11k**



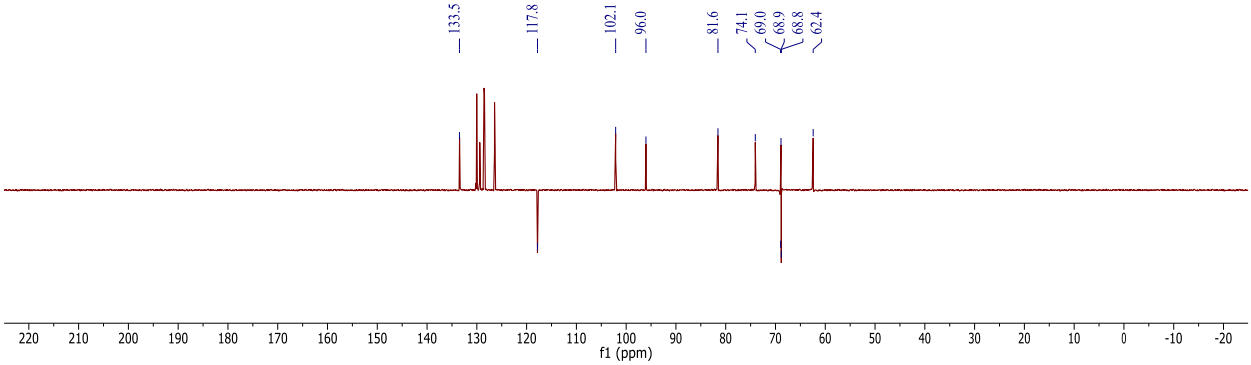
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **SI1**



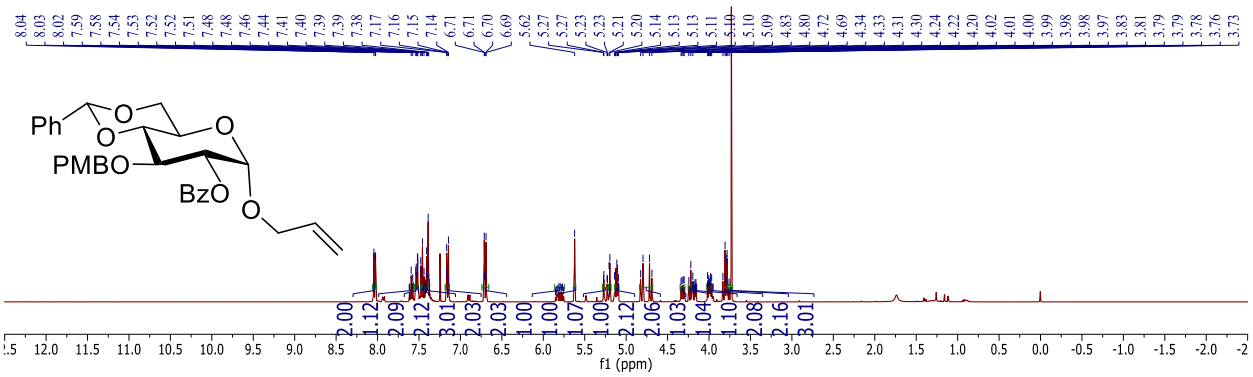
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **SI1**



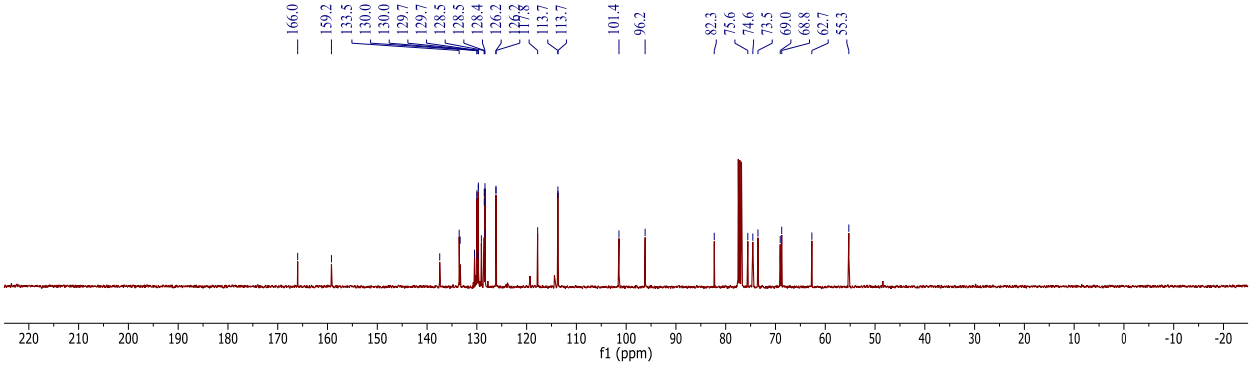
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **SI1**



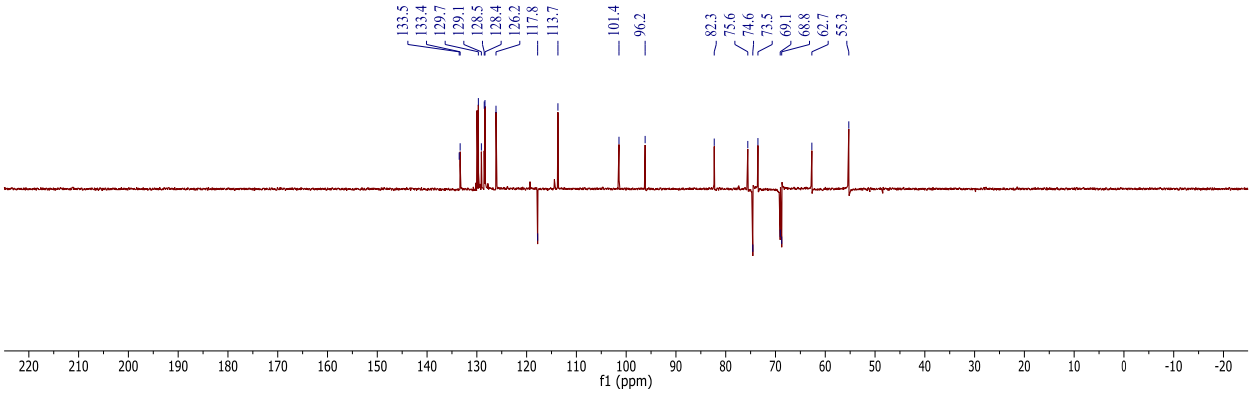
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **SI2**



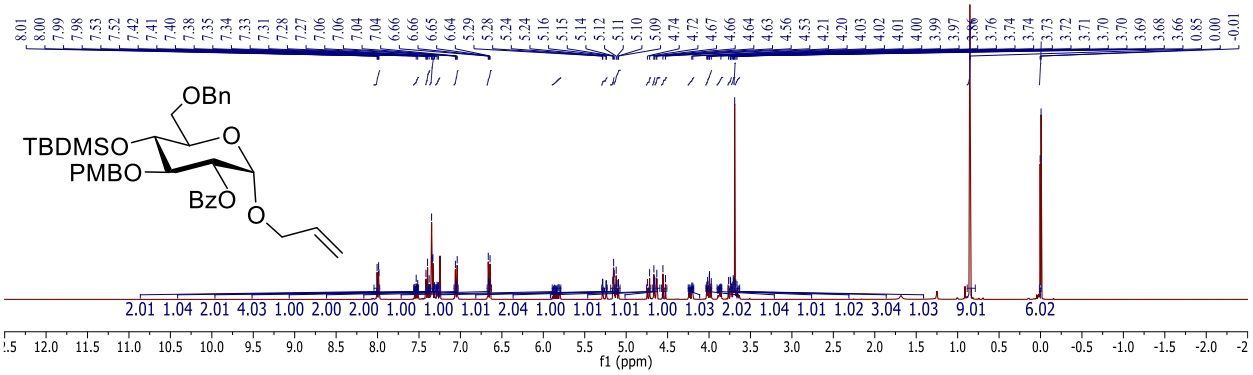
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **SI2**



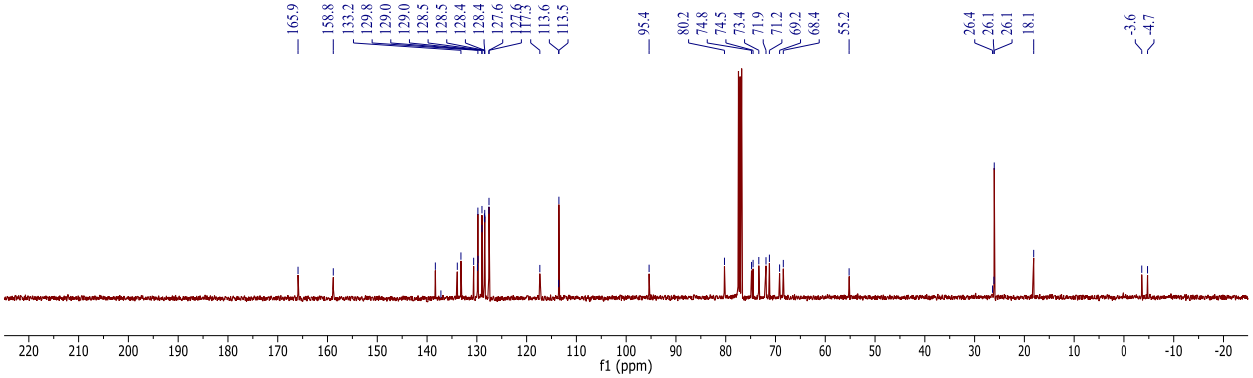
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **SI2**



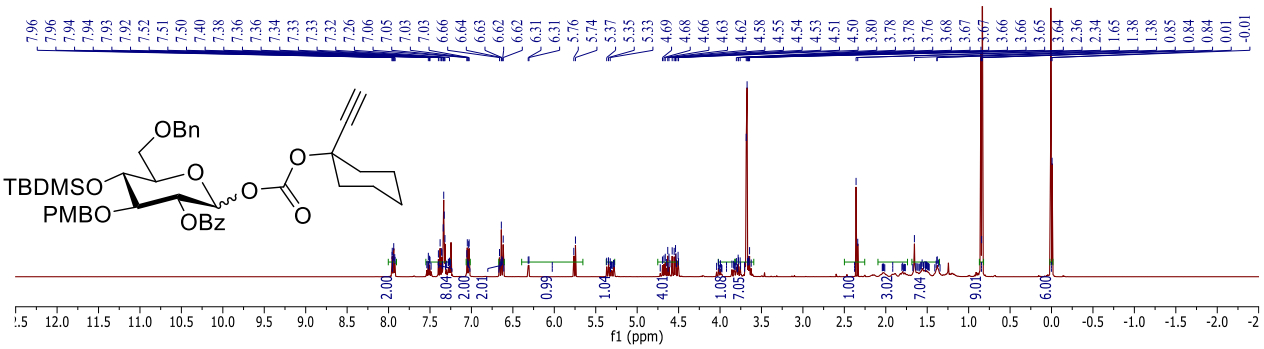
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **SI3**



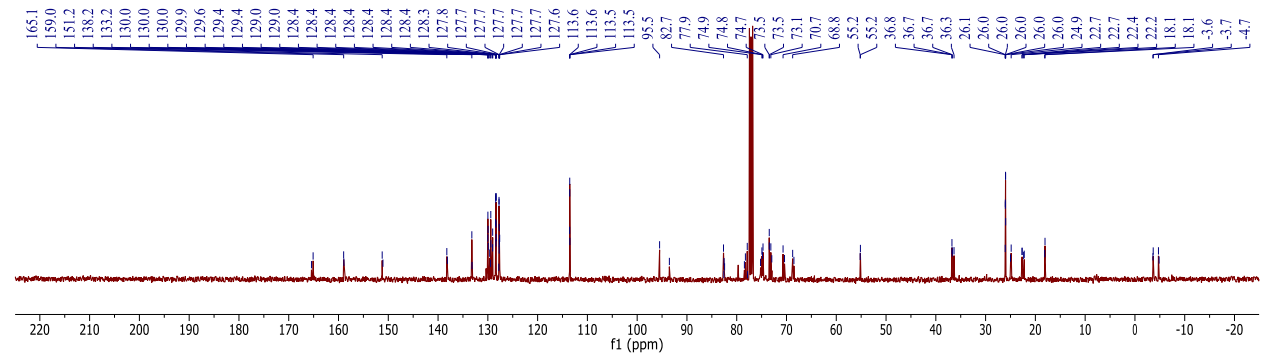
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **SI3**



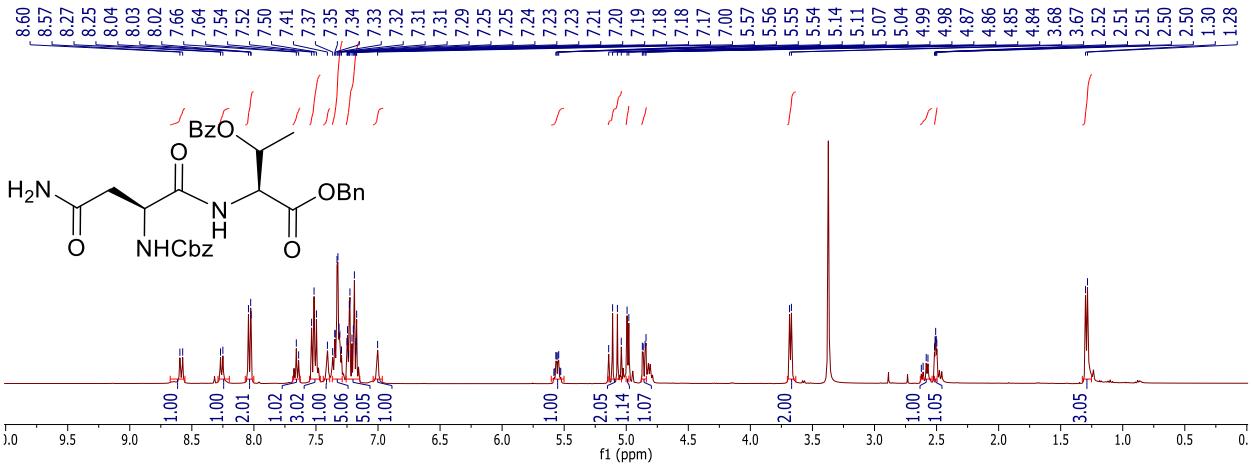
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **12**



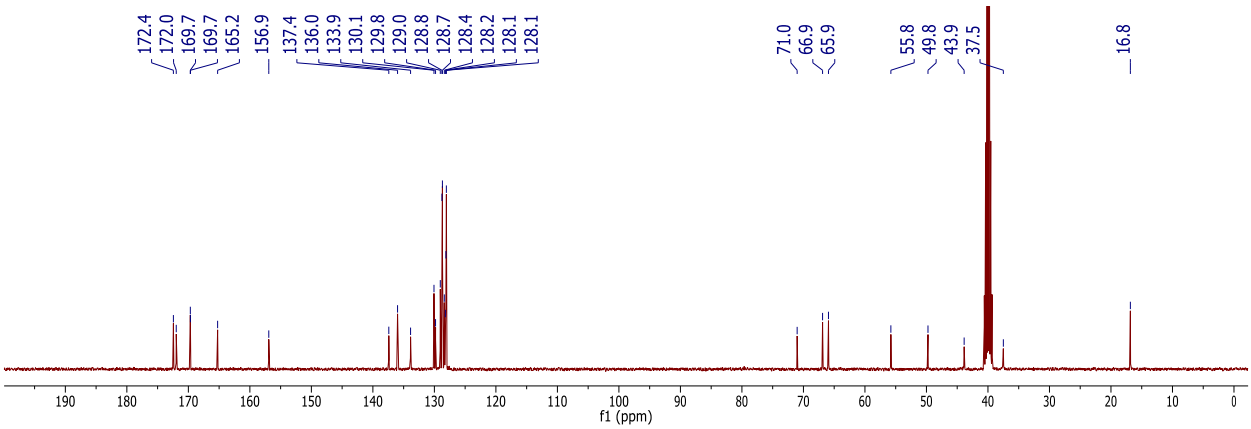
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **12**



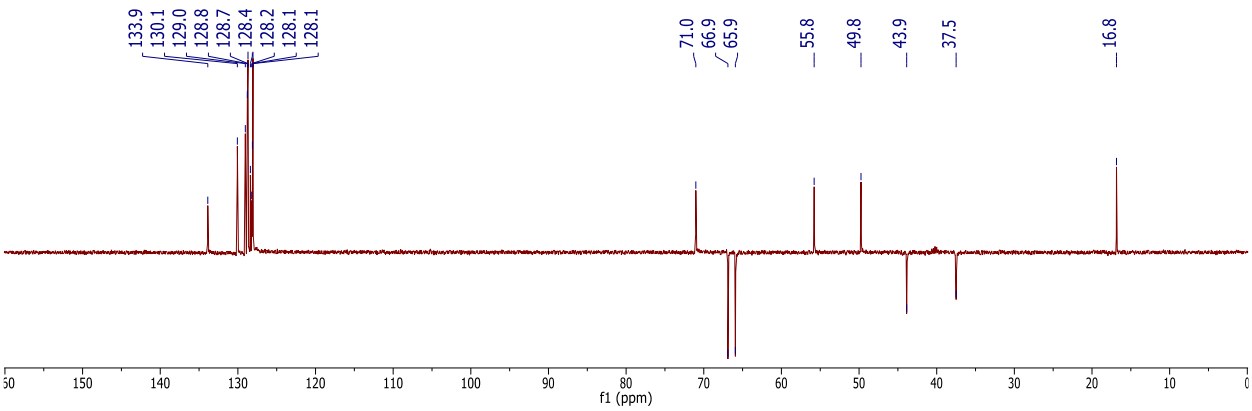
^{1}H NMR Spectrum (400.31 MHz, DMSO-d_6) of compound **13**



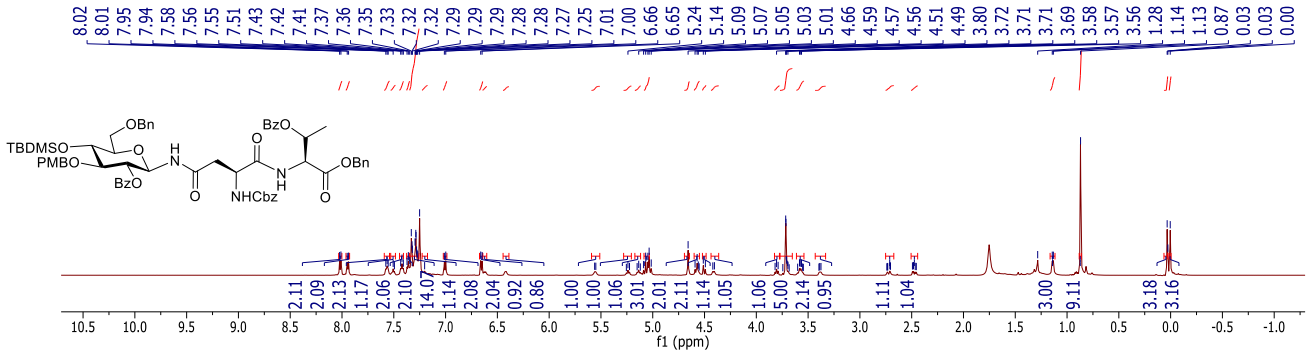
^{13}C NMR Spectrum (100 MHz, DMSO-d_6) of compound **13**



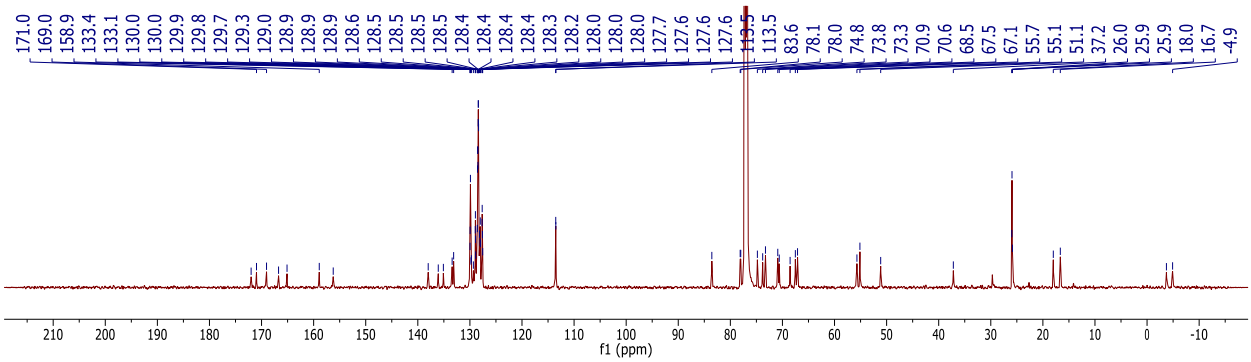
DEPT-135 NMR Spectrum (100MHz, DMSO-d_6) of compound **13**



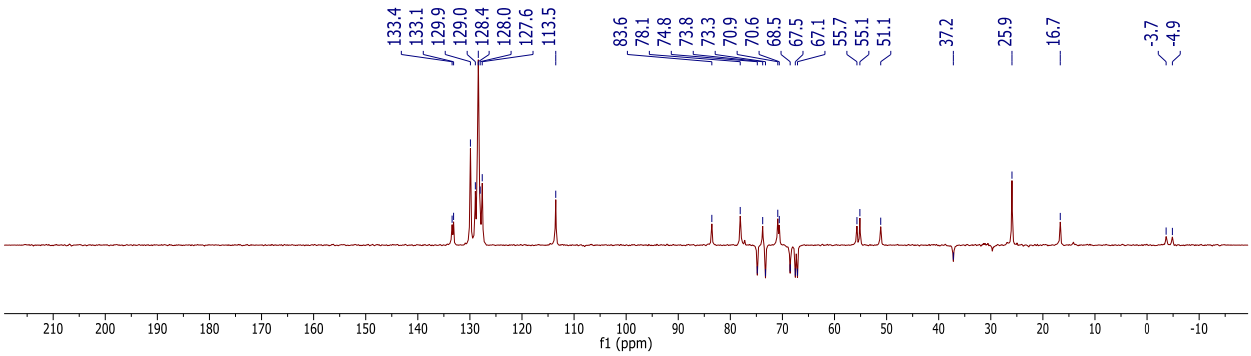
^{1}H NMR Spectrum (600 MHz, $CDCl_3$) of Compound **14**



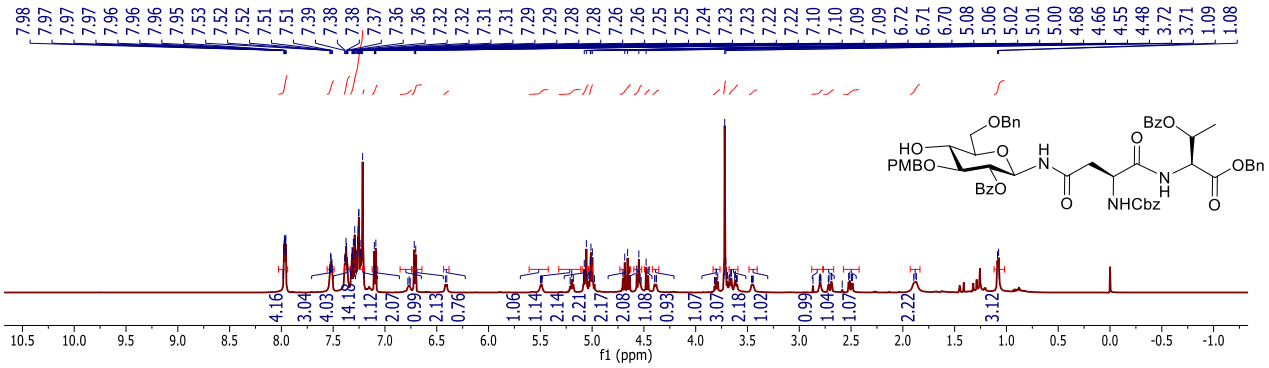
^{13}C NMR Spectrum (151 MHz, $CDCl_3$) of Compound **14**



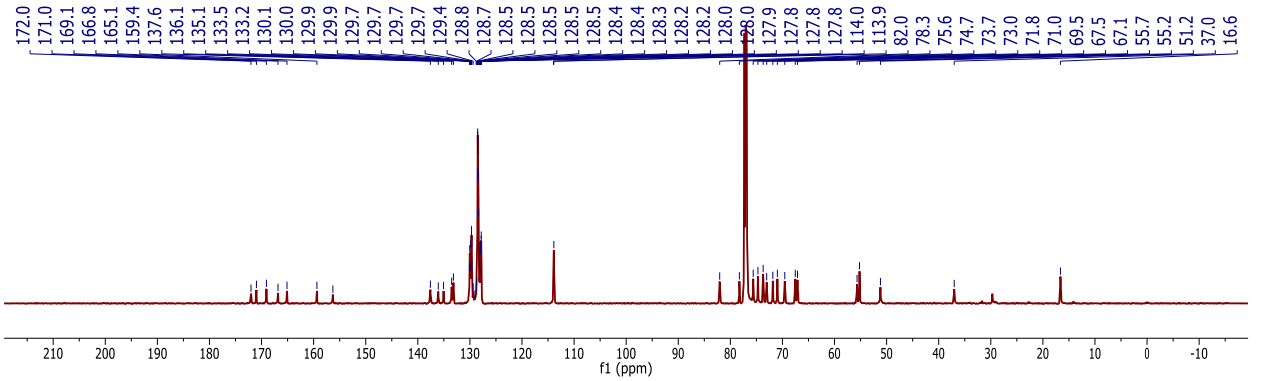
DEPT-135 NMR Spectrum (151 MHz, $CDCl_3$) of Compound **14**



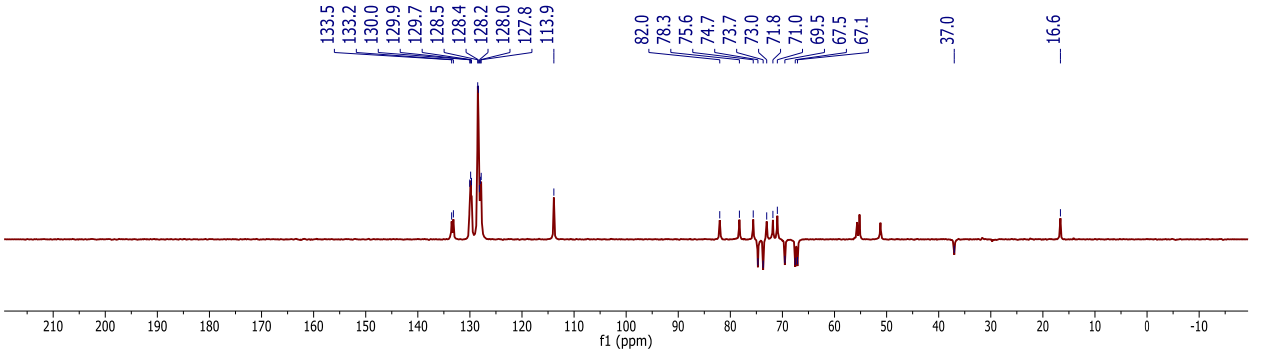
^{1}H NMR Spectrum (600 MHz, $CDCl_3$) of Compound **15**



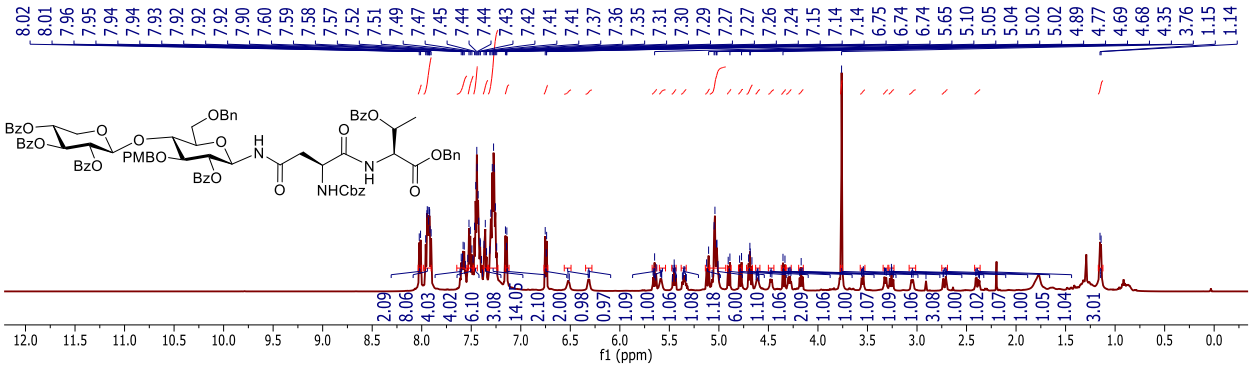
^{13}C NMR Spectrum (151 MHz, $CDCl_3$) of Compound **15**



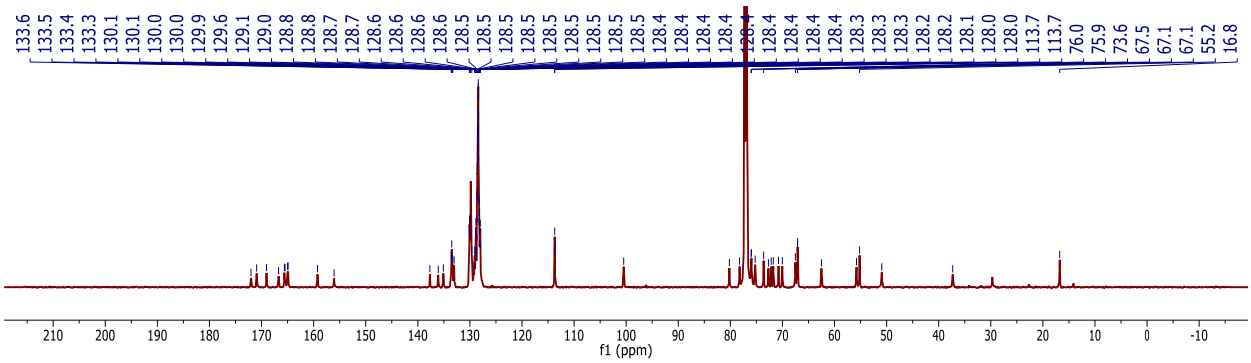
DEPT-135 NMR Spectrum (151 MHz, $CDCl_3$) of Compound **15**



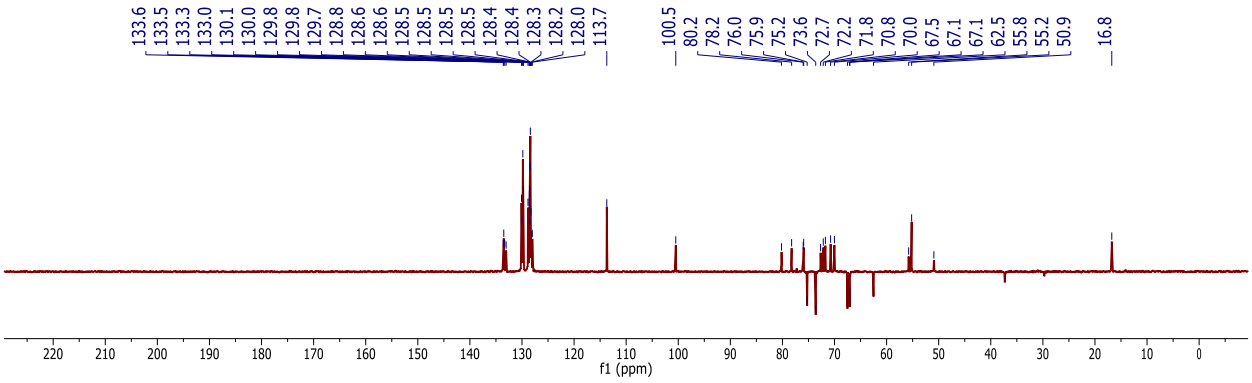
^{1}H NMR Spectrum (600 MHz, $CDCl_3$) of Compound **16**



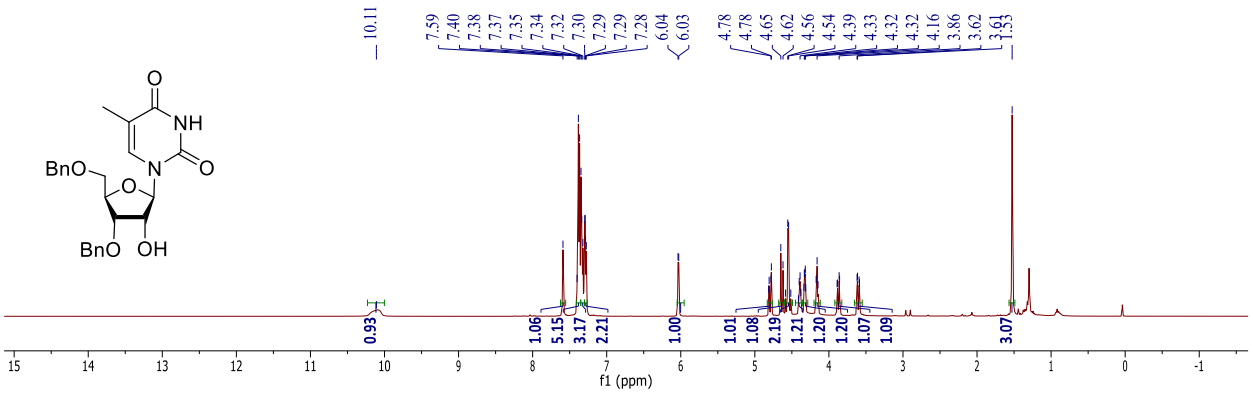
^{13}C NMR Spectrum (151 MHz, $CDCl_3$) of Compound **16**



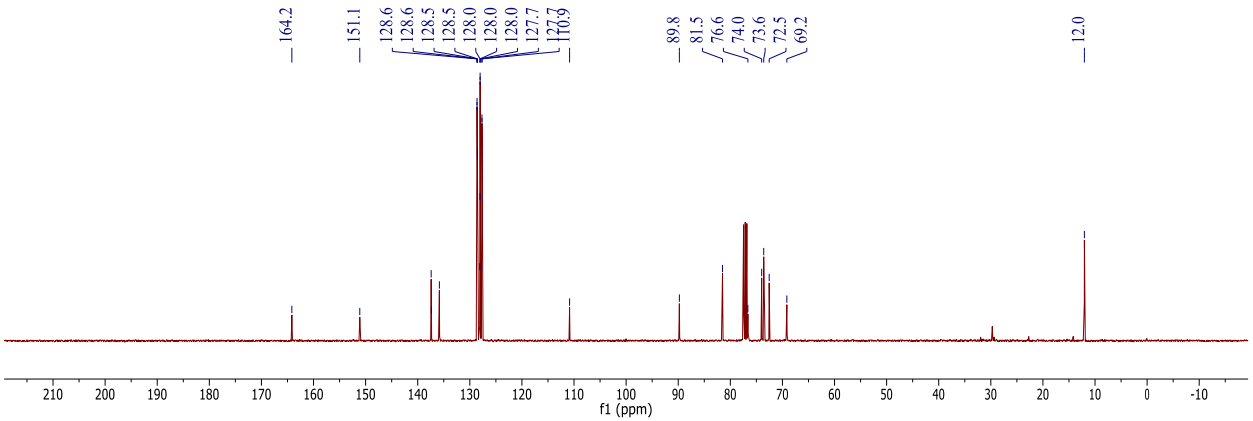
DEPT-135 NMR Spectrum (151 MHz, $CDCl_3$) of Compound **16**



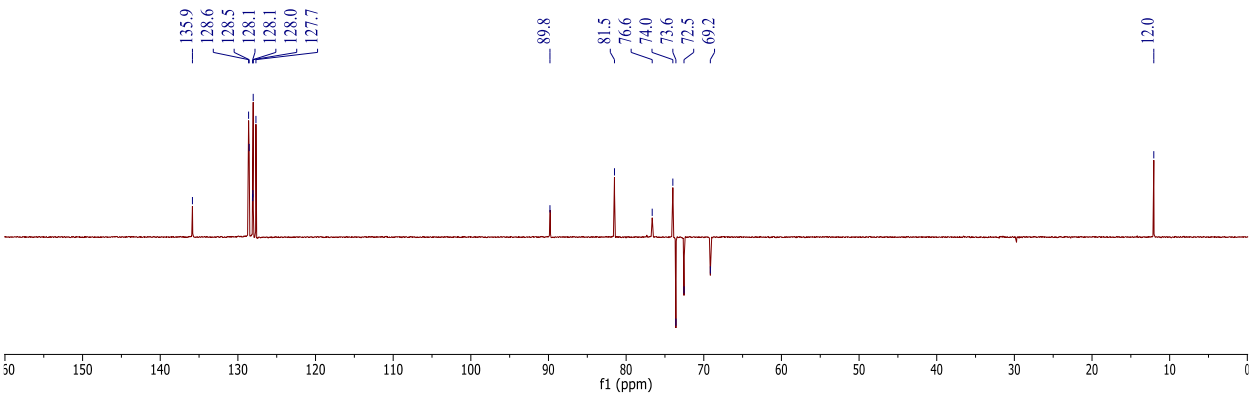
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **17**



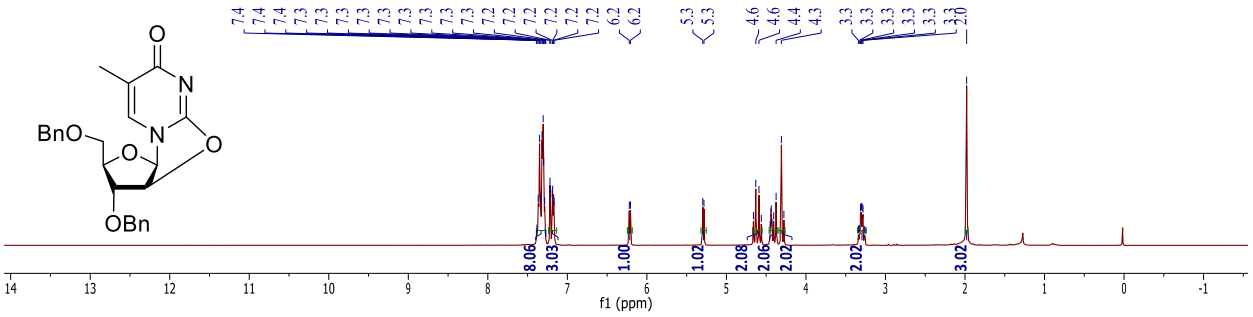
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **17**



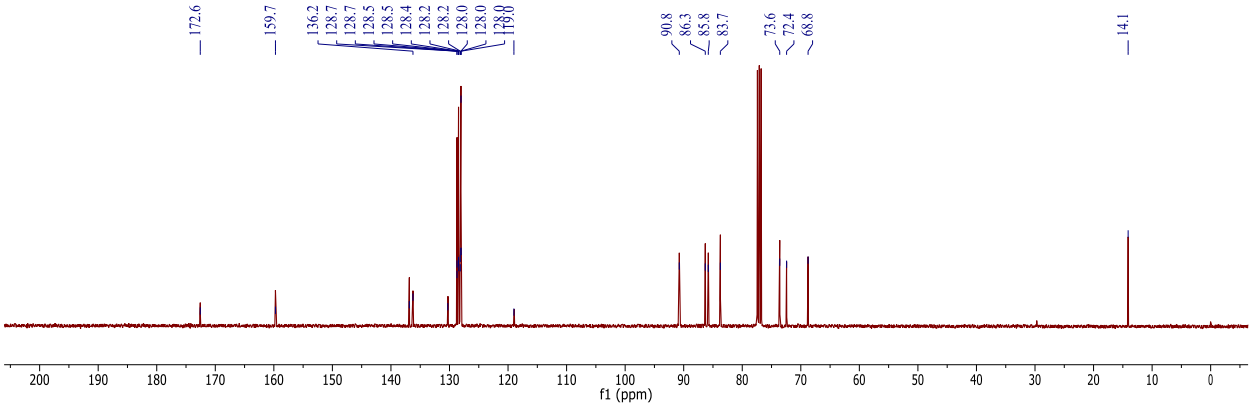
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **17**



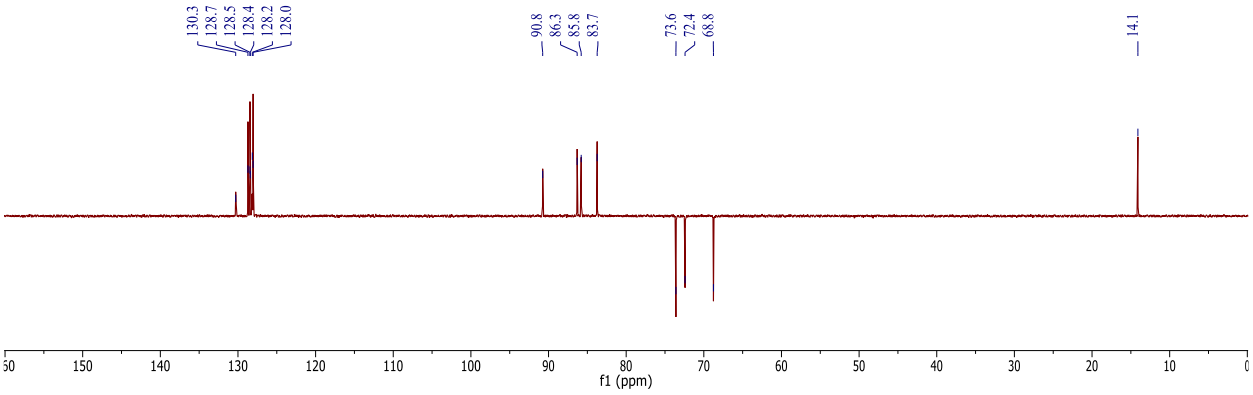
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **18a**



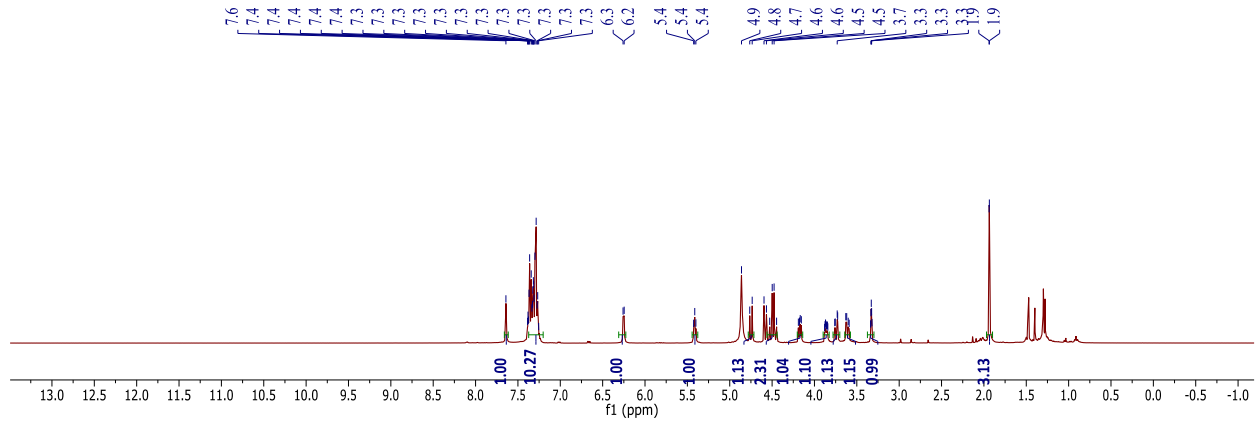
^{13}C NMR Spectrum (400 MHz, $CDCl_3$) of Compound **18a**



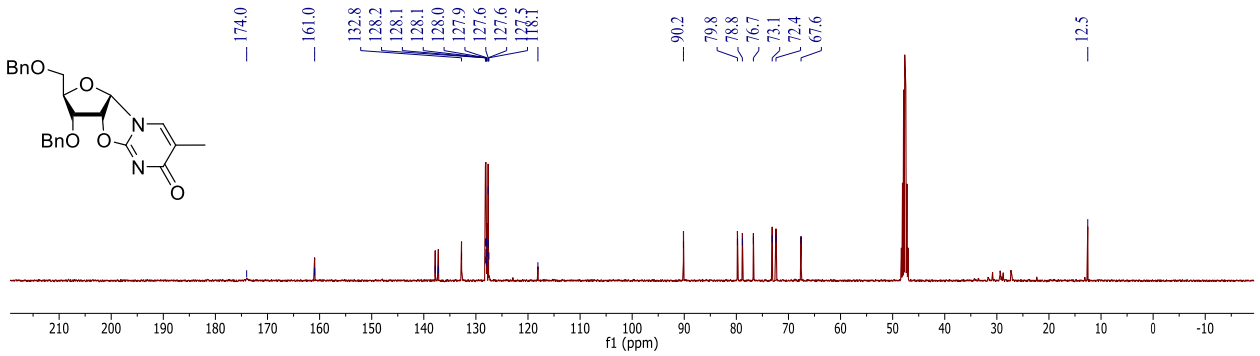
DEPT-135 NMR Spectrum (400 MHz, $CDCl_3$) of Compound **18a**



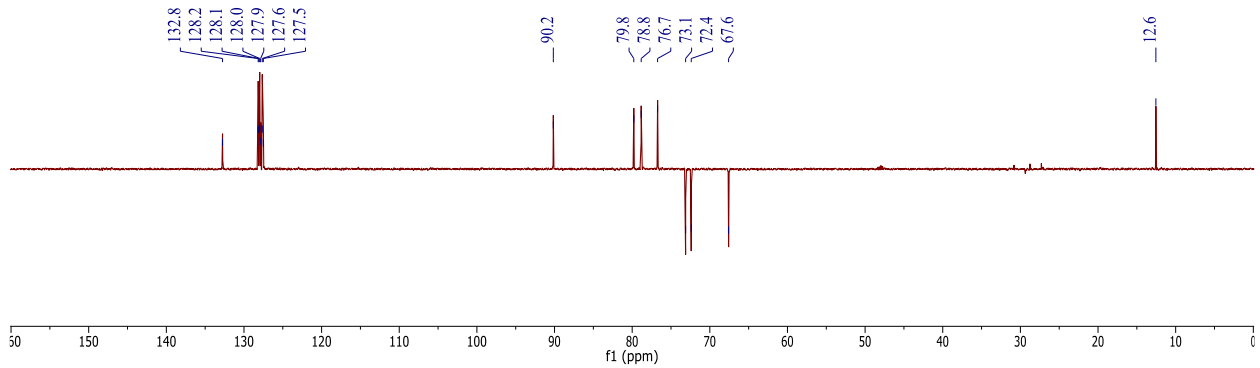
^{1}H NMR Spectrum (400 MHz, Methanol-d_4) of Compound **18b**



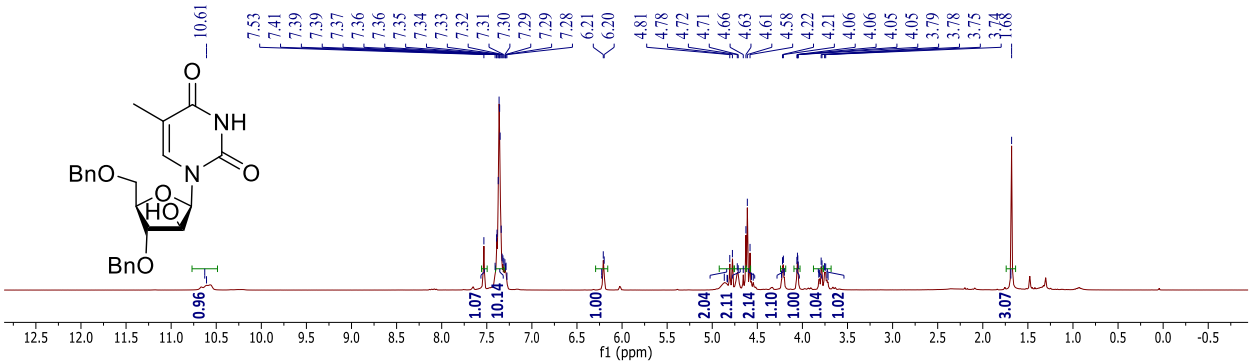
^{13}C NMR Spectrum (100 MHz, Methanol-d_4) of Compound **18b**



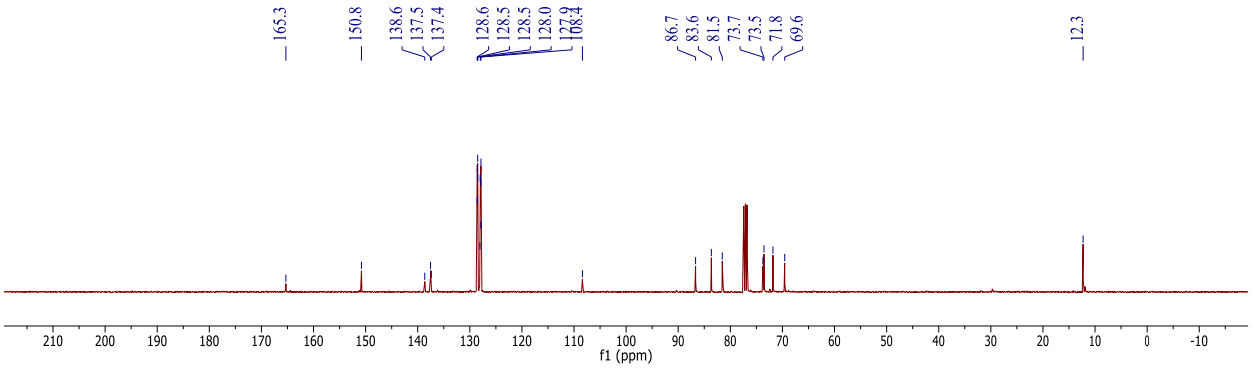
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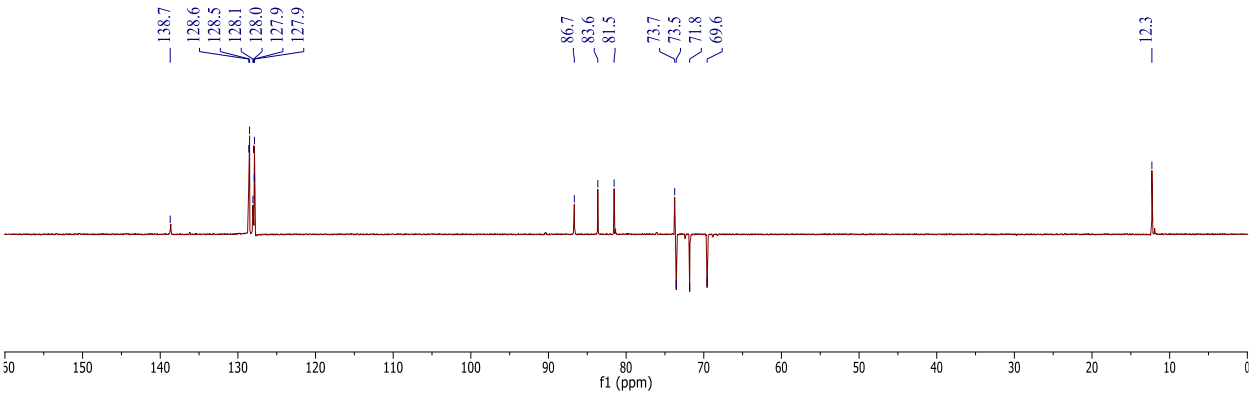
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **19**



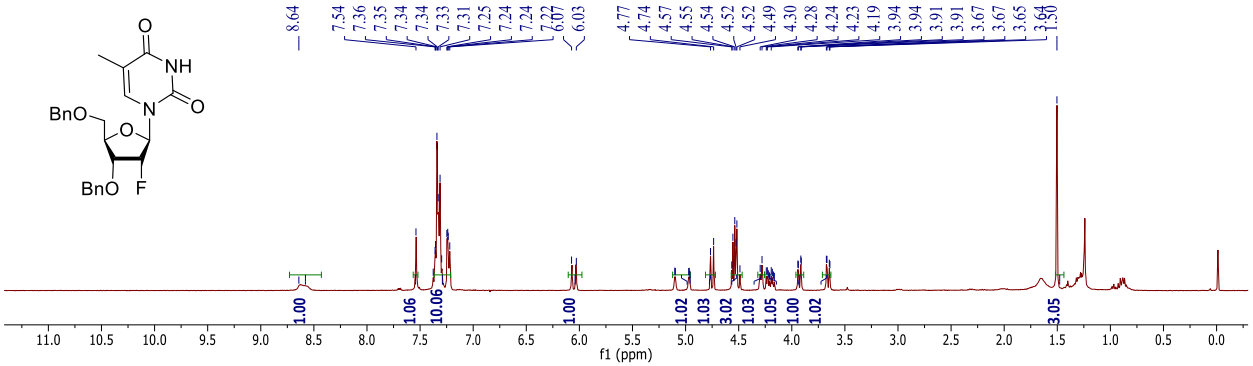
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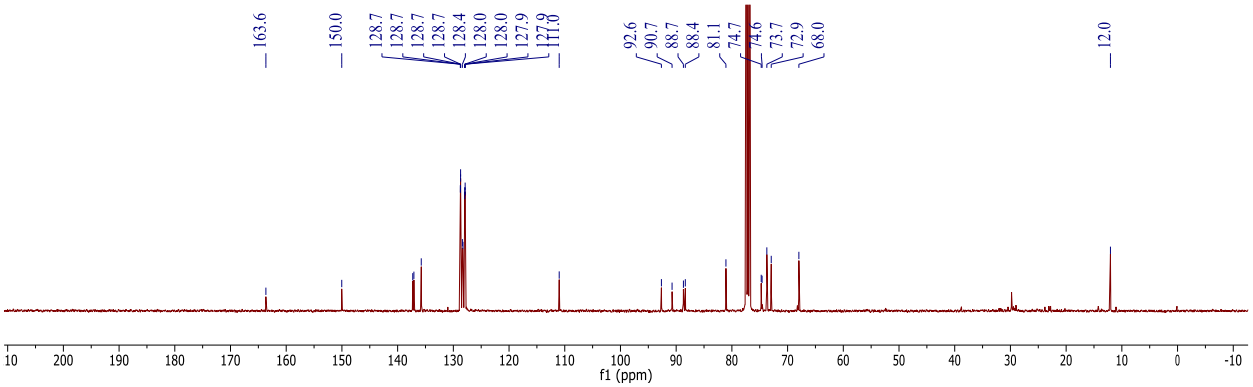
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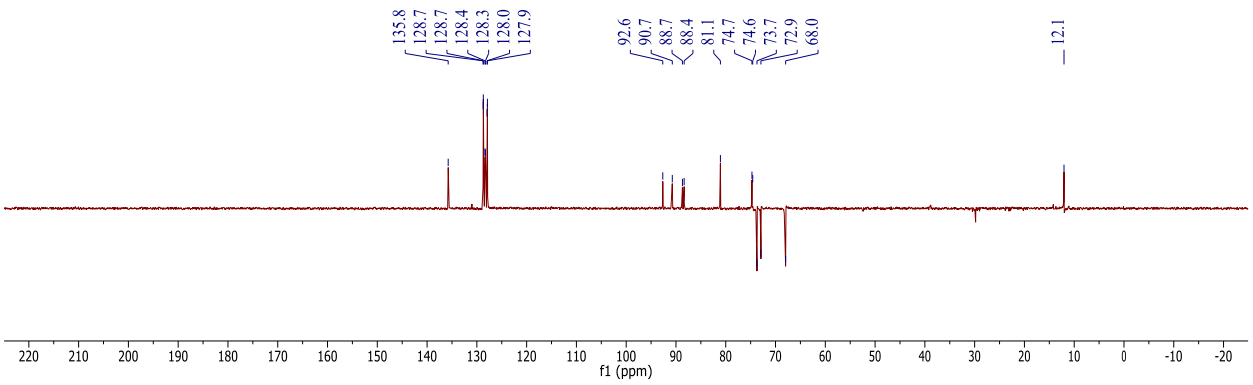
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **21**



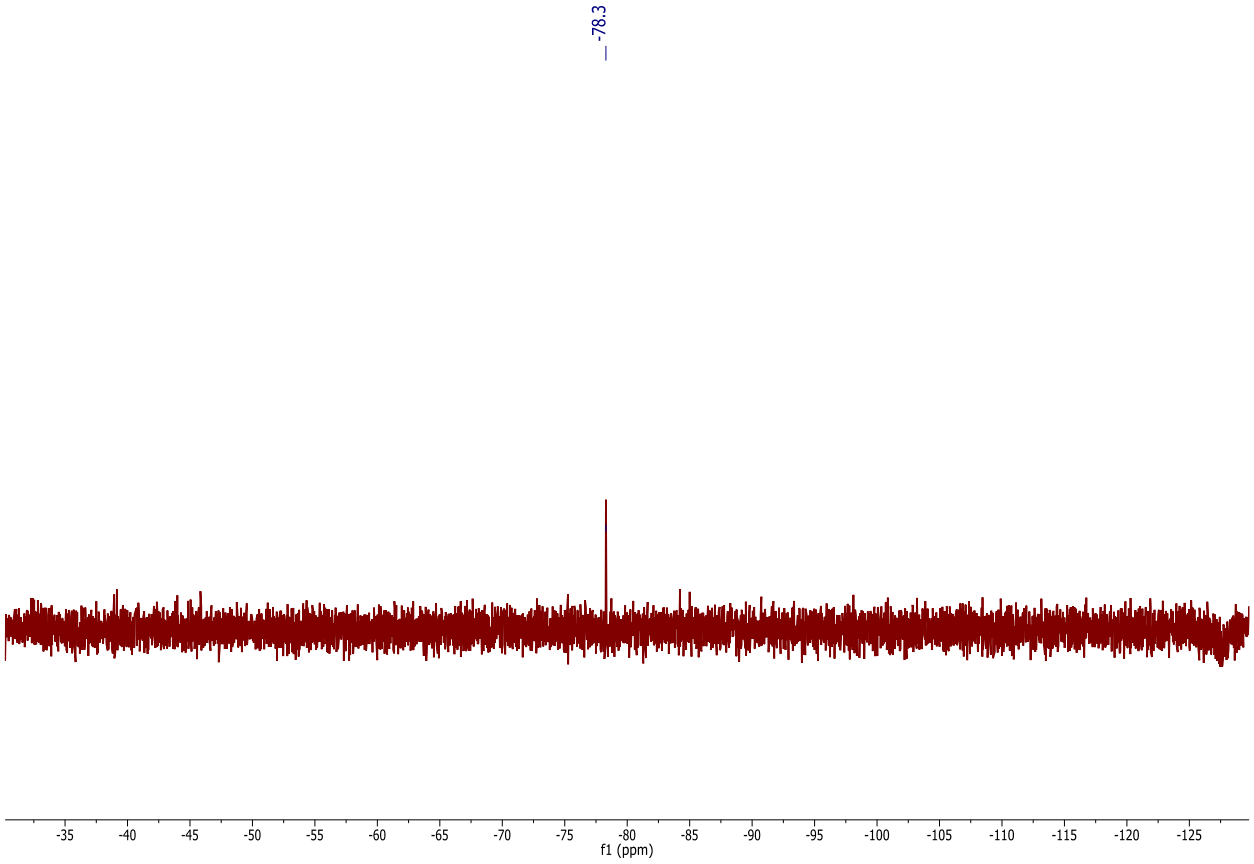
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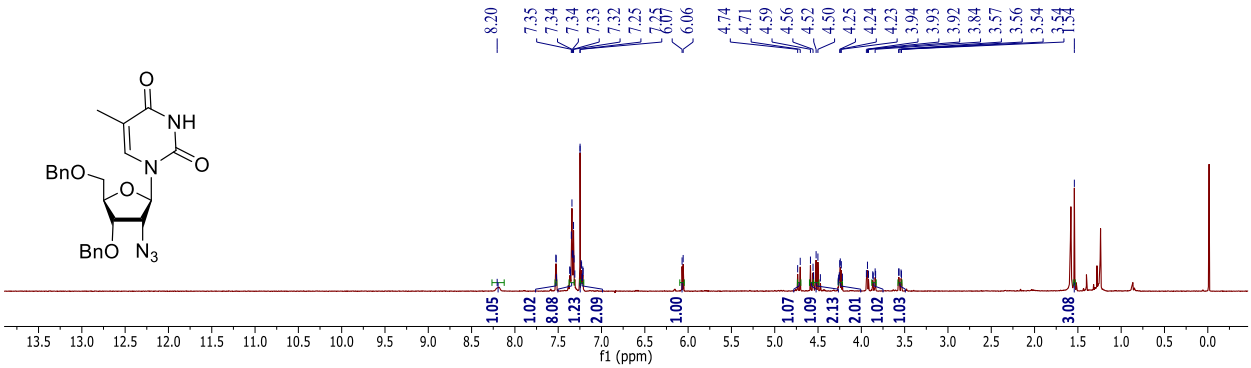
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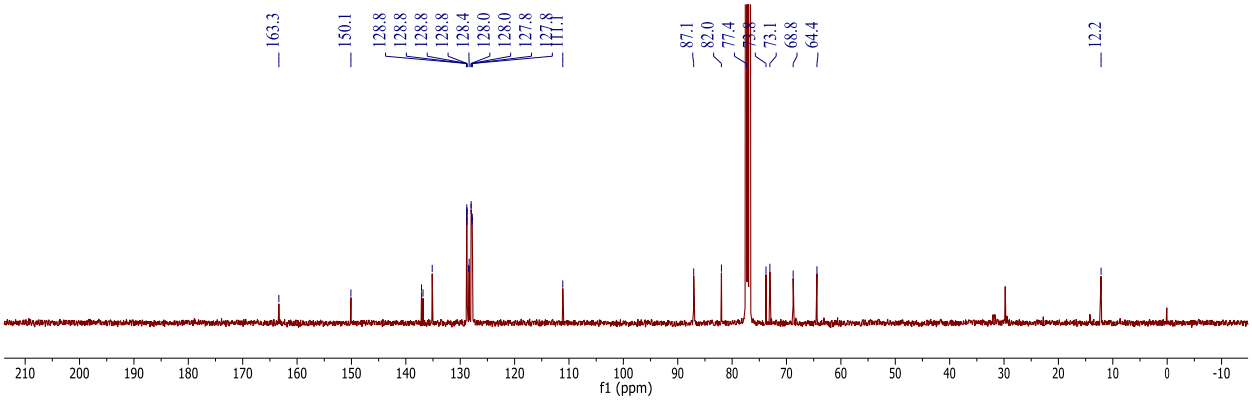
^{19}F NMR Spectrum (500 MHz, $CDCl_3$) of Compound **21**



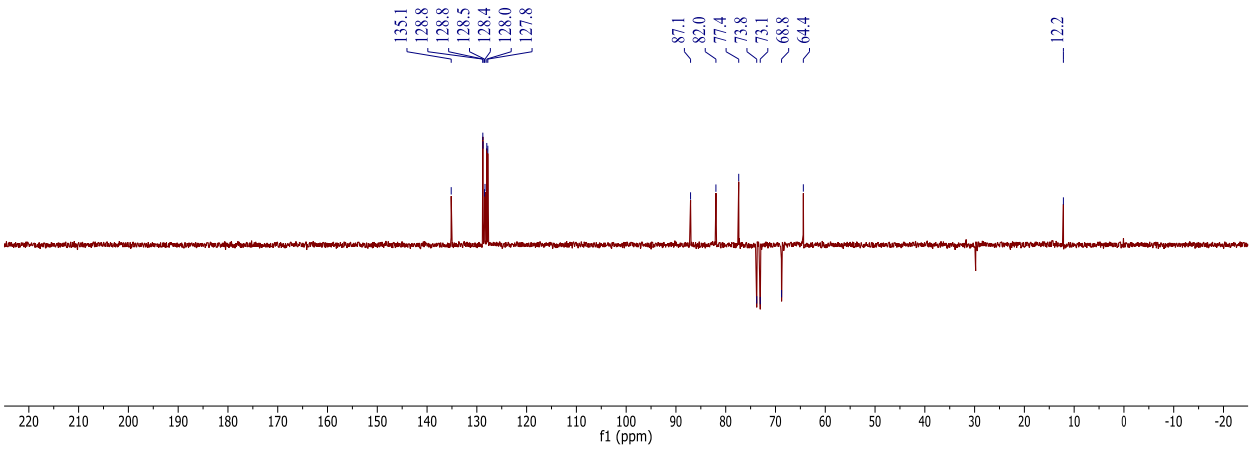
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **22**



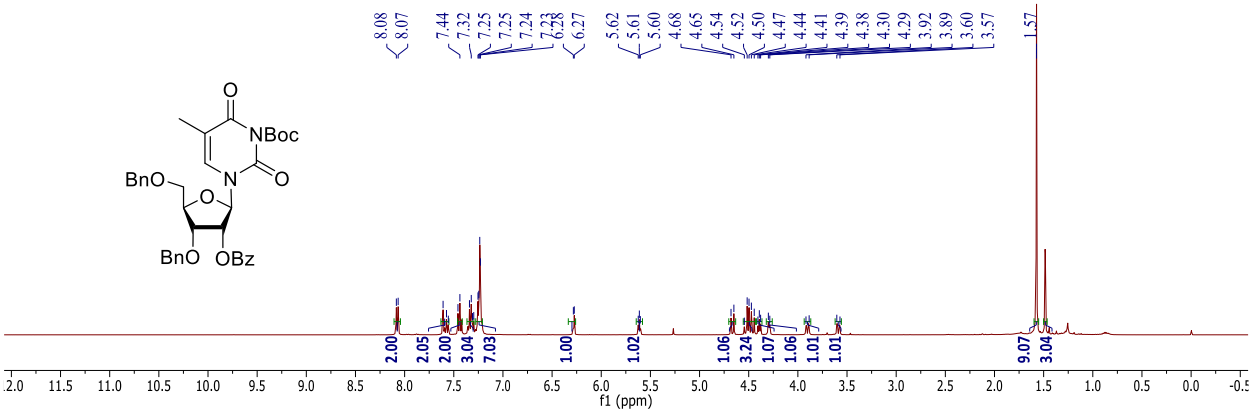
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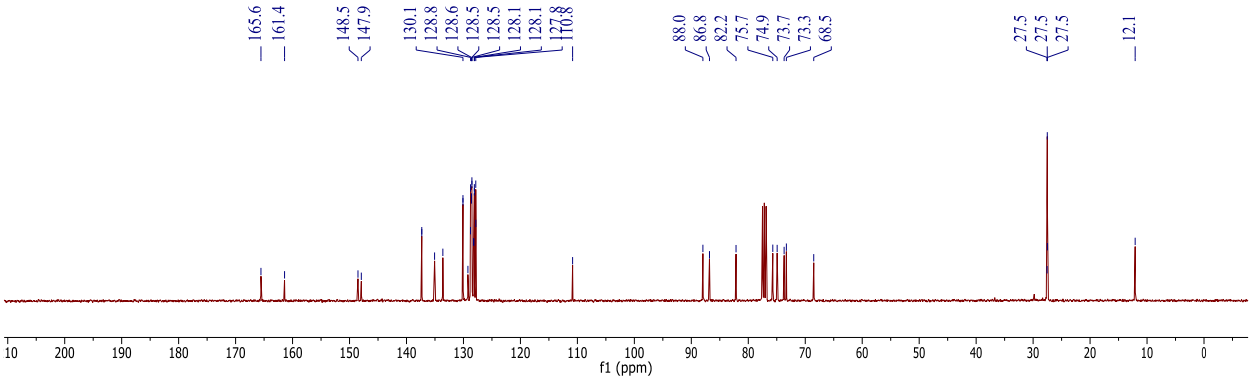
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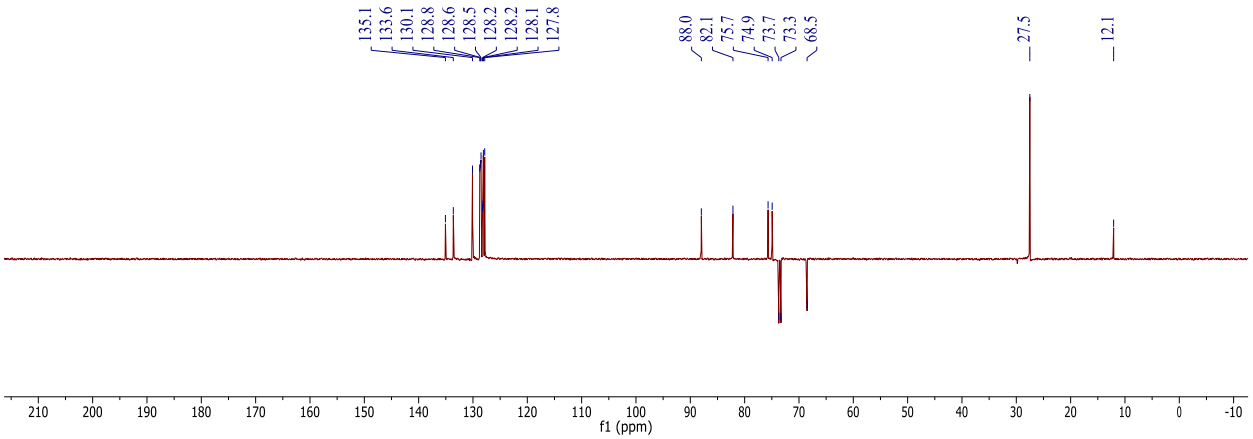
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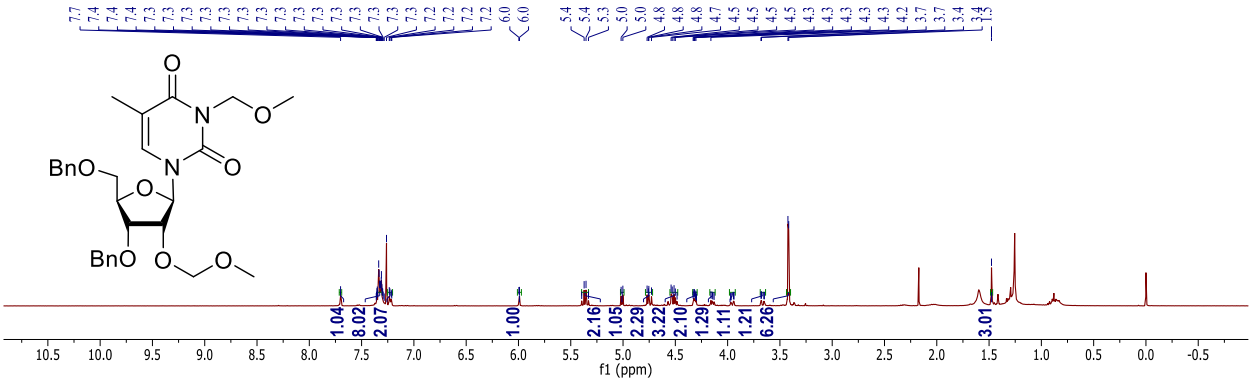
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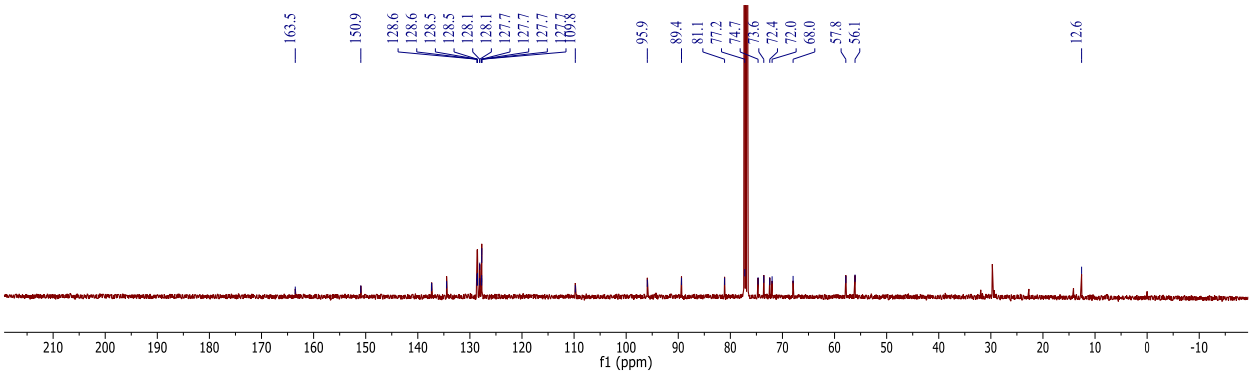
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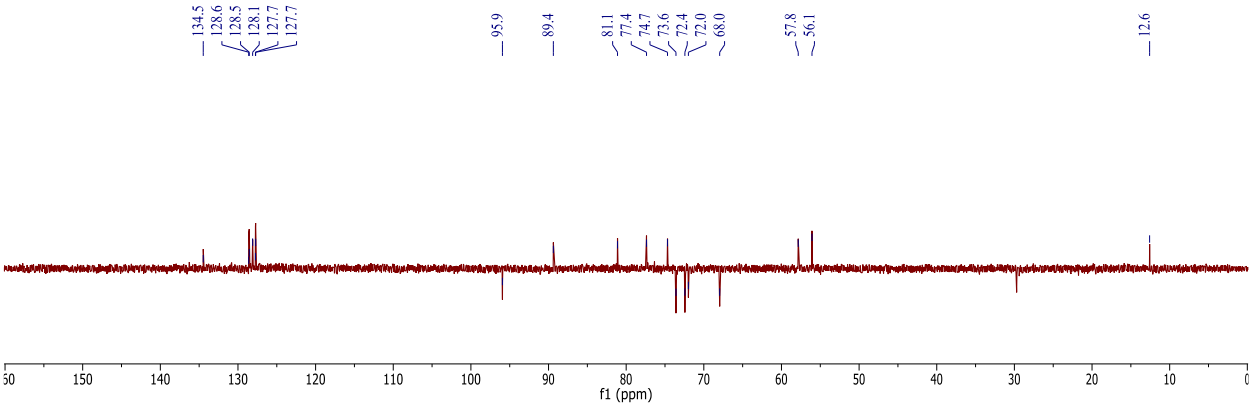
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **SI4**



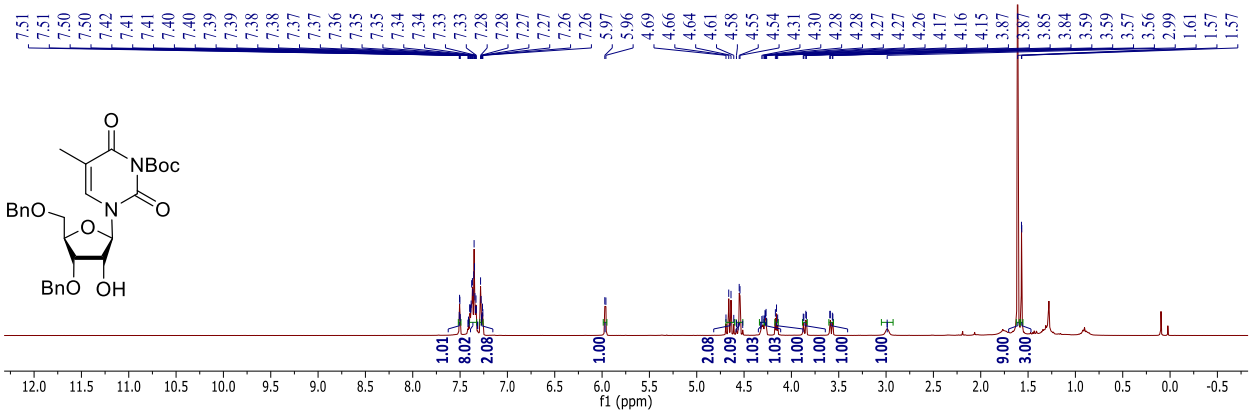
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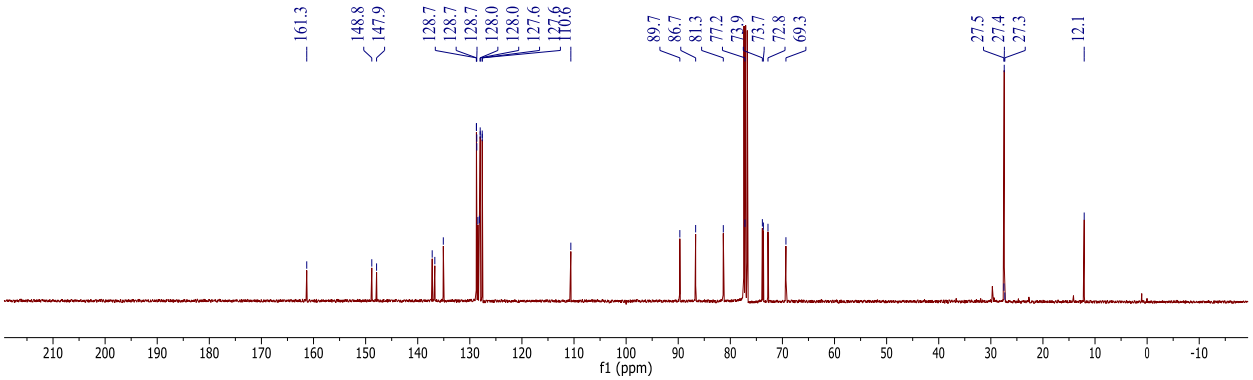
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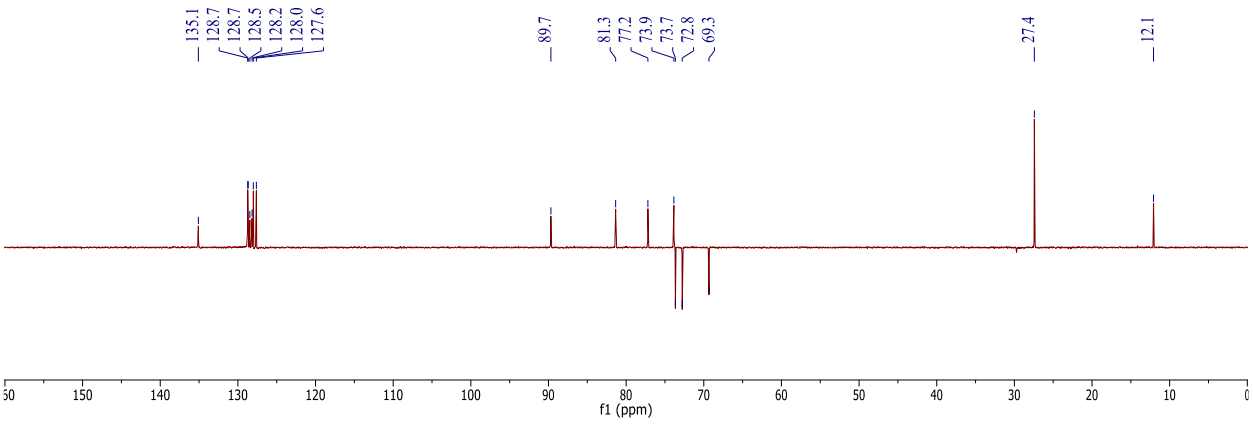
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **SI5**



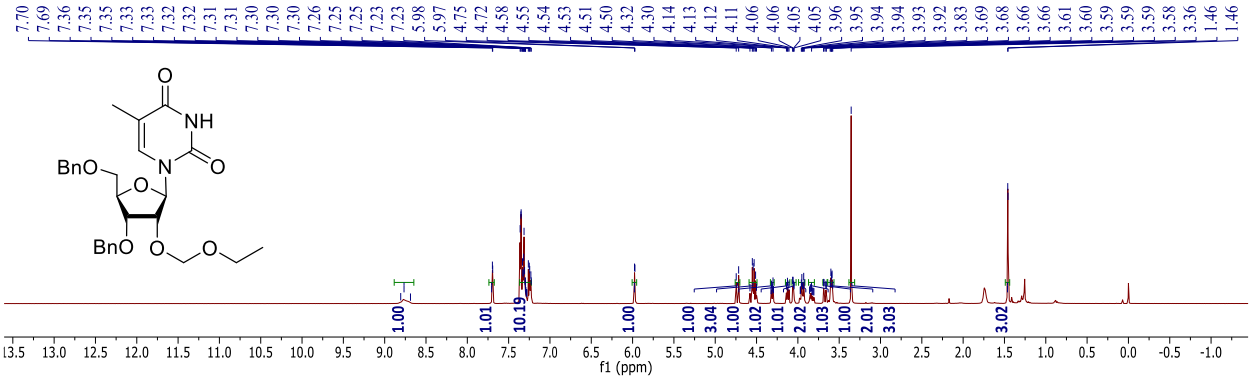
^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **SI5**



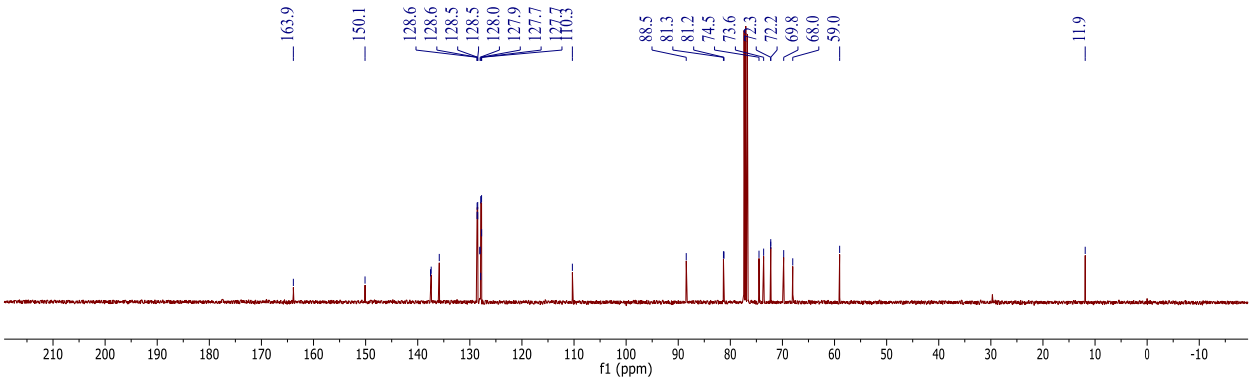
DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **SI5**



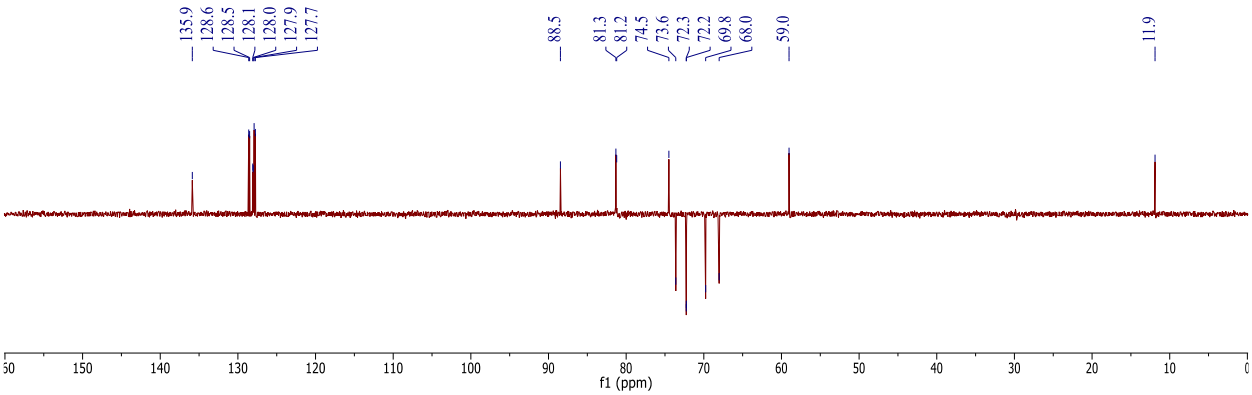
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound **24**



^{13}C NMR Spectrum (100 MHz, $CDCl_3$) of Compound **24**



DEPT-135 NMR Spectrum (100 MHz, $CDCl_3$) of Compound **24**



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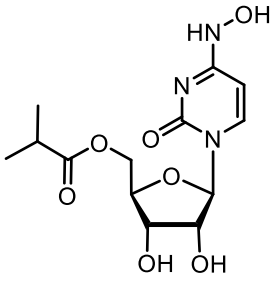
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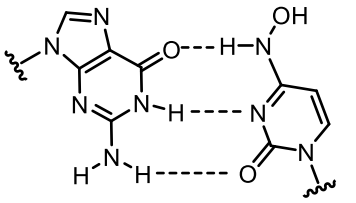
Chapter 4: Developing the Shortest Chemical Synthetic Route for Antiviral Drug Molnupiravir

4.1. Introduction:

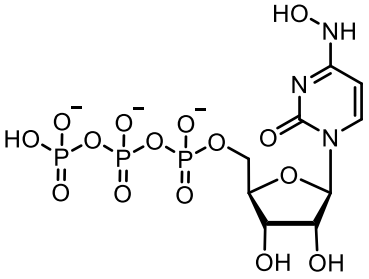
The ongoing COVID-19 pandemic has posed a significant threat to people's lives, public health and impacted the economy worldwide. More than 6 million people are dead and over half a billion have been infected worldwide by the SARS-CoV-2 virus.[1] Since the start of the global pandemic created by this virus, there has been a continuous quest to develop novel antiviral agents to tackle this health crisis.[2] The COVID-19 pandemic has highlighted the lack of readily available antiviral agents and the dire need for developing economic processes to efficiently manufacture antiviral drugs on a large scale. Although the development of vaccines against this lethal virus promises a long-term solution, there are concerns regarding the mutation of the virus to escape acquired immunity.[3,4] Hence, it is equally essential to identify novel antiviral agents to treat COVID-19 infection and develop rapid and efficient synthetic routes to produce medicines from readily available commercial reagents.



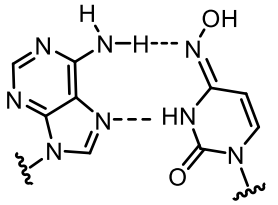
a) Chemical Structure of Molnupiravir



Guanine Imino-M



b) Active form of Molnupiravir used by RdRp enzyme of SARS-CoV-2 virus



Adenine Amino-M

c) Strong H-bonding with A and G in the template strand

Figure 4.1: Chemical structure of Molnupiravir and its active form

Molnupiravir or EIDD-2801 is a ribonucleoside prodrug that was first developed as an anti-influenza drug at Emory University in 2018.[5] Recently, this N^4-D-β-hydroxycytidine (NHC) analog has been approved as an antiviral drug for treating covid-19 infected adult patients who are at risk of progressing to hospitalization.[6] Molnupiravir has its advantage over alternative therapies (e.g. Remdisivir, which is administered intravenously)[7] because of its structural simplicities, wide range of antiviral activities, and oral availability. Unlike many antiviral drugs which stall viral replication by targeting RNA polymerases and terminating chain elongation, Molnupiravir acts as a mutagenizing agent that can initiate error catastrophe by introducing point mutation.[8] The active form of Molnupiravir, essentially the NHC triphosphate is readily taken up instead of UTP or CTP by the RNA dependent RNA polymerase enzyme of the virus during the chain elongation process. The imino form and the amino form of active Molnupiravir can form strong hydrogen bonds with Adenine and Guanine in the template strand respectively (**Figure 4.1**), which eventually leads to a mutated RNA product. In this way, Molnupiravir can escape the exonucleolytic proofreading mechanism of SARS-Cov-2 virus and induce mutagenesis successfully to stop viral replication. The success of this drug in treating covid infected patients outside of hospitalization has called for the development of cost-effective novel routes for synthesizing this active pharmaceutical ingredient (API).

5.2. Previous methods for synthesizing Molnupiravir:

The synthesis of this important antiviral drug was first executed in 2018 at the Emory University. Many chemical and chemoenzymatic synthetic routes have been developed since then especially after the API was selected for trial as a treatment for Covid-19 infection.[9] The majority of the synthetic routes generally used the intermediate nucleoside, *viz*. either uridine or cytidine although the synthesis of those intermediates are accomplished by multistep reactions whereas there are only two reports that use nucleobase and ribose as starting materials (**Fig. 4.2**). In this section, the previously established routes are elaborated under two sub-sections as follows,

i) Chemical synthesis: The first synthetic route reported by Emory University is comprised of five steps starting from Uridine with unclear yields, unoptimized reaction conditions and 17% overall yield[5]. Merck Co. in collaboration with Ridgeback Biotherapeutics has patented a 10-step route starting from ribose and uracil, although the overall yield of the process is less than 10%.[10]

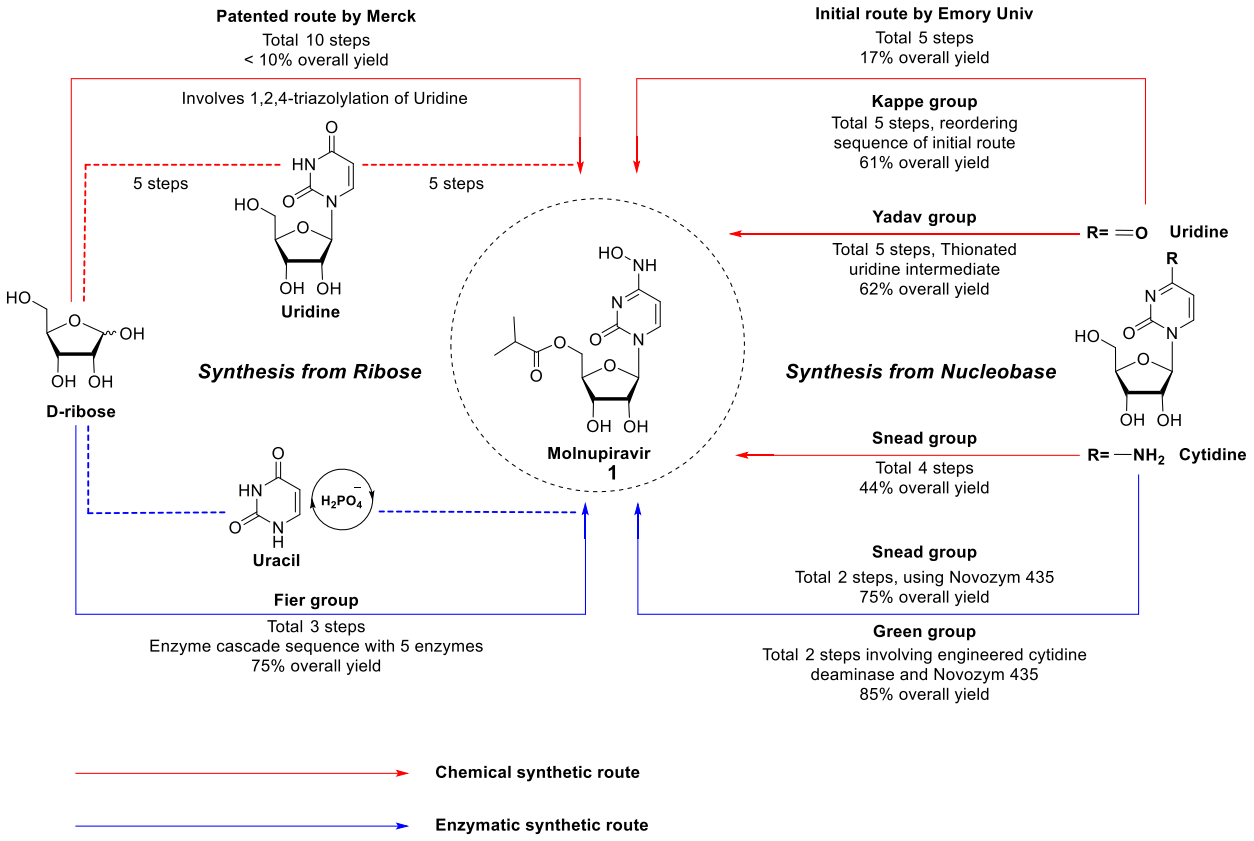
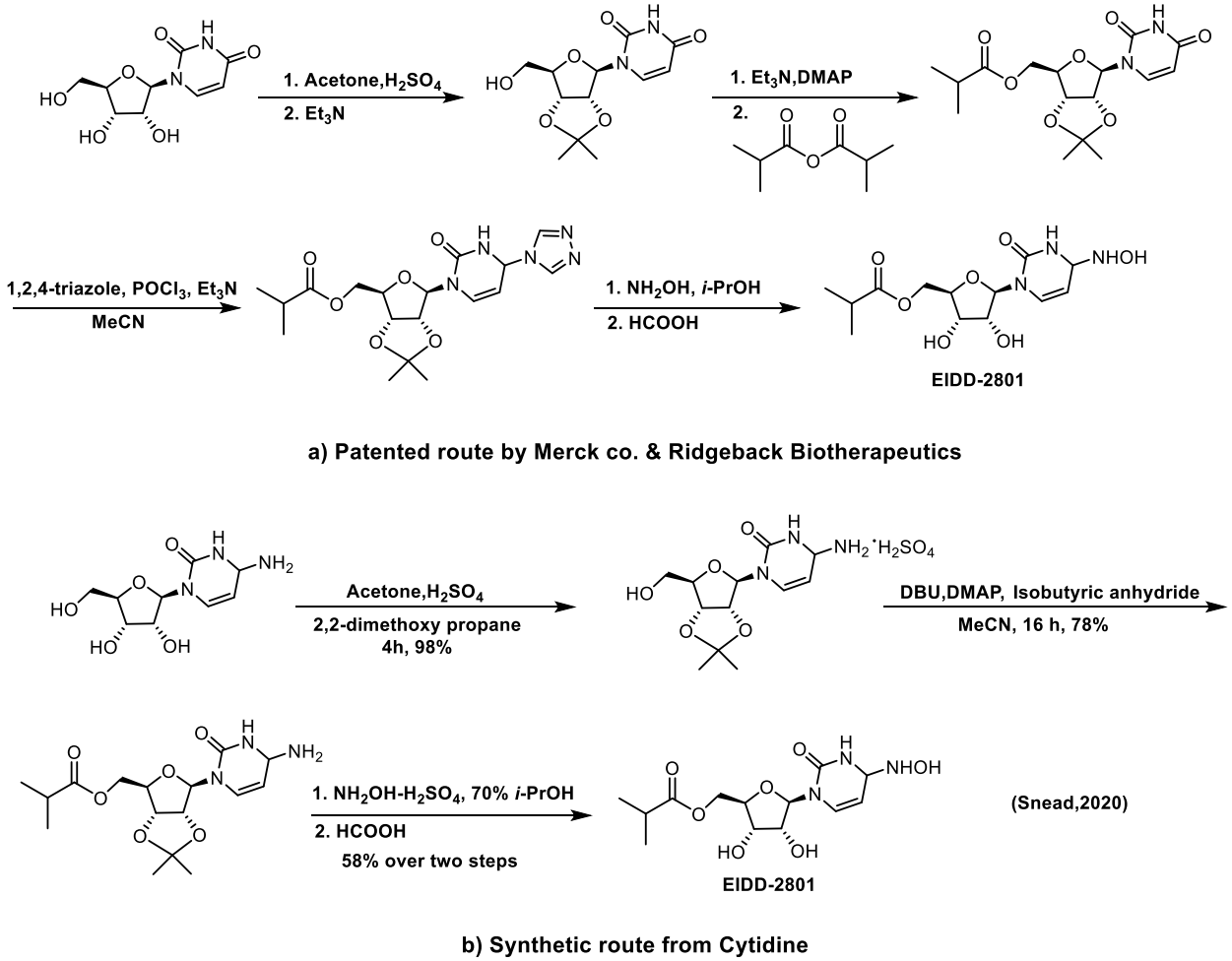


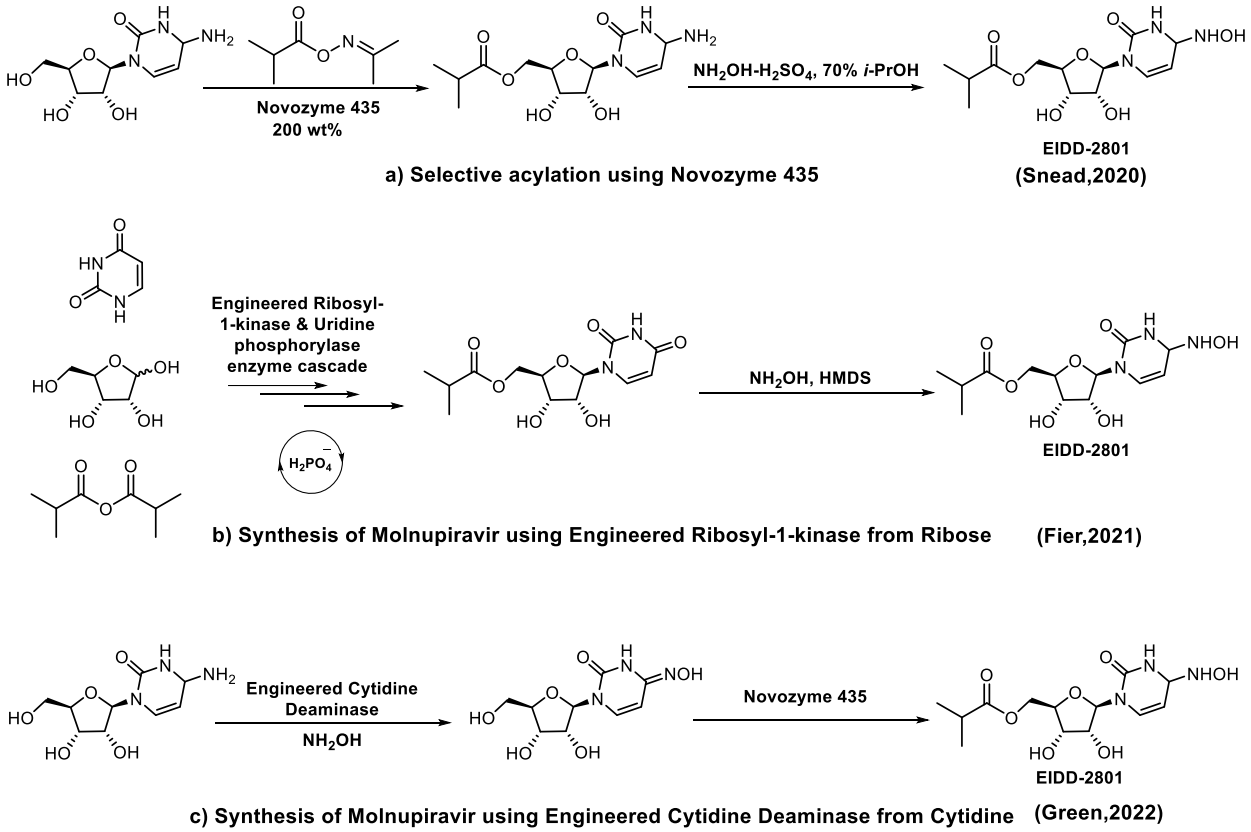
Figure 4.2: Previous synthetic routes for Molnupiravir

The main disadvantage in the aforementioned synthetic routes is very poor yield in the triazole coupling step to convert uracil moiety into *N*-hydroxy cytosine. Kappe group could successfully solve that problem just by reordering the reaction sequences and developing a continuous flow method in the acetonide deprotection step.[11] Later on, Snead group reported a 3-step conversion of Molnupiravir from Cytidine with an improved yield of 44% (**Scheme 4.1**).[12] A short route for the gram-scale synthesis of the drug through the formation of a thionated Uridine intermediate was reported by Yadav group.[13] Shen group has introduced *N*,*N*-dimethyl formamide-dimethyl acetal (DMF-DMA) protecting group in order to perform site-specific esterification efficiently to produce the drug in 70% yield without chromatographic purification.[14]



Scheme 4.1: Chemical synthesis of Molnupiravir from Uridine and Cytidine

ii) Chemo-enzymatic synthesis: Snead group developed the first use of an enzyme in a two-step synthetic route of Molnupiravir that consists of esterification and hydroxamination of Cytidine.[15] They could efficaciously acylate the primary hydroxyl group of ribose by using Novozyme 435 which indeed eliminates the need for protecting groups. An engineered ribosyl-1-kinase and uridine phosphorylase enzymes were used by Fier group to streamline the synthesis of the API starting from ribose and uracil[16] (**Scheme 4.2**). These enzymes were arrayed with a pyruvate-oxidase-enabled phosphate recycling strategy to get the antiviral drug in a 7-fold higher yield and this newly established method is almost 70% shorter compared to the initial route. Recently Green group reported a biocatalytic process for the production of Molnupiravir using an engineered ribosyl kinase enzyme that performs more than 85000 turnovers in less than 3 hours.[17]

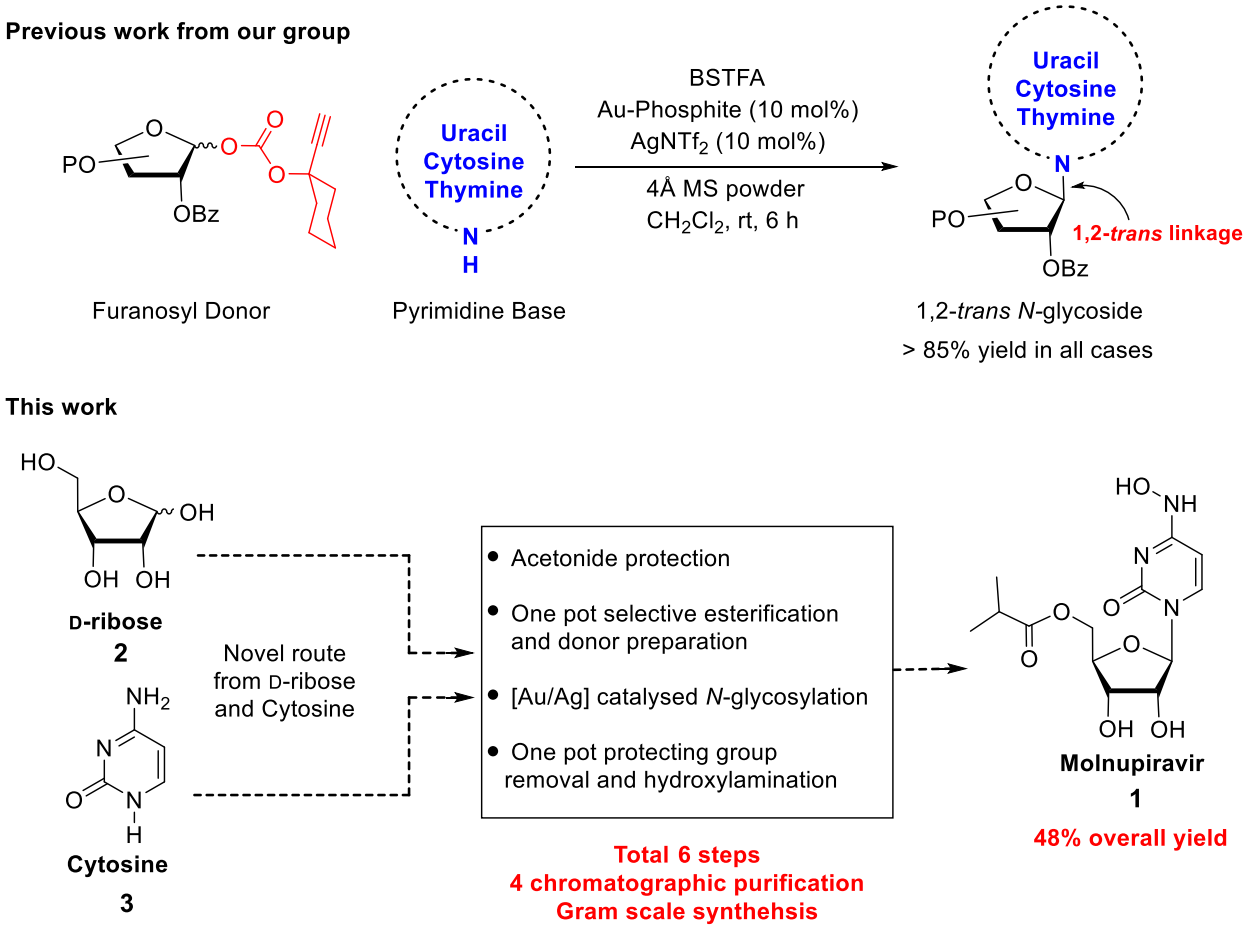


Scheme 4.2: Chemo-enzymatic synthesis of Molnupiravir

Though advancement has taken place with enzymatic synthesis of Molnupiravir but the high cost of those enzymes is a major setback for cost-effective synthesis. Developed chemical routes have mostly used intermediate nucleoside which indeed is prepared in multiple steps from simpler building blocks. Although scientists are currently working on developing robust large scale manufacturing routes[18–20], there is scope for chemists to develop novel routes for synthesizing this antiviral drug from simple building blocks in minimum steps.

4.3. Current work:

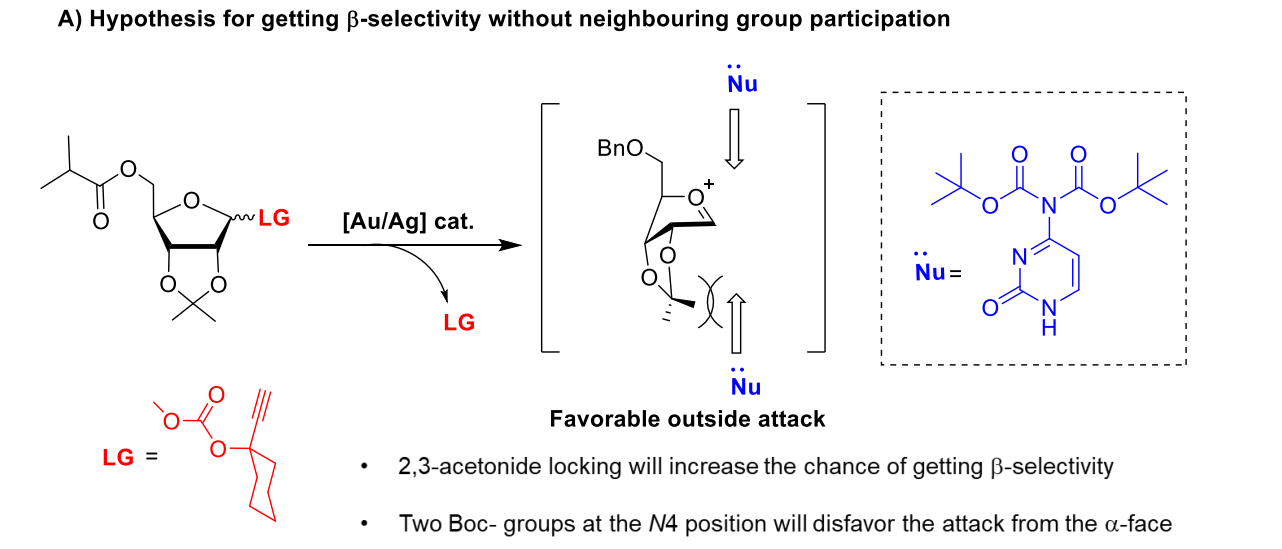
Previously a novel method for the synthesis of various *N*-glycosides was reported by our group. The glycosylation condition is catalytic and mild, hence it has its own advantages over conventional methods for coupling many *N*-acceptors equipped with various protecting groups. The newly developed mild glycosylation method enables strategic implementation of protecting groups that help in increasing the solubility of the sparingly soluble nucleobases as well as improve

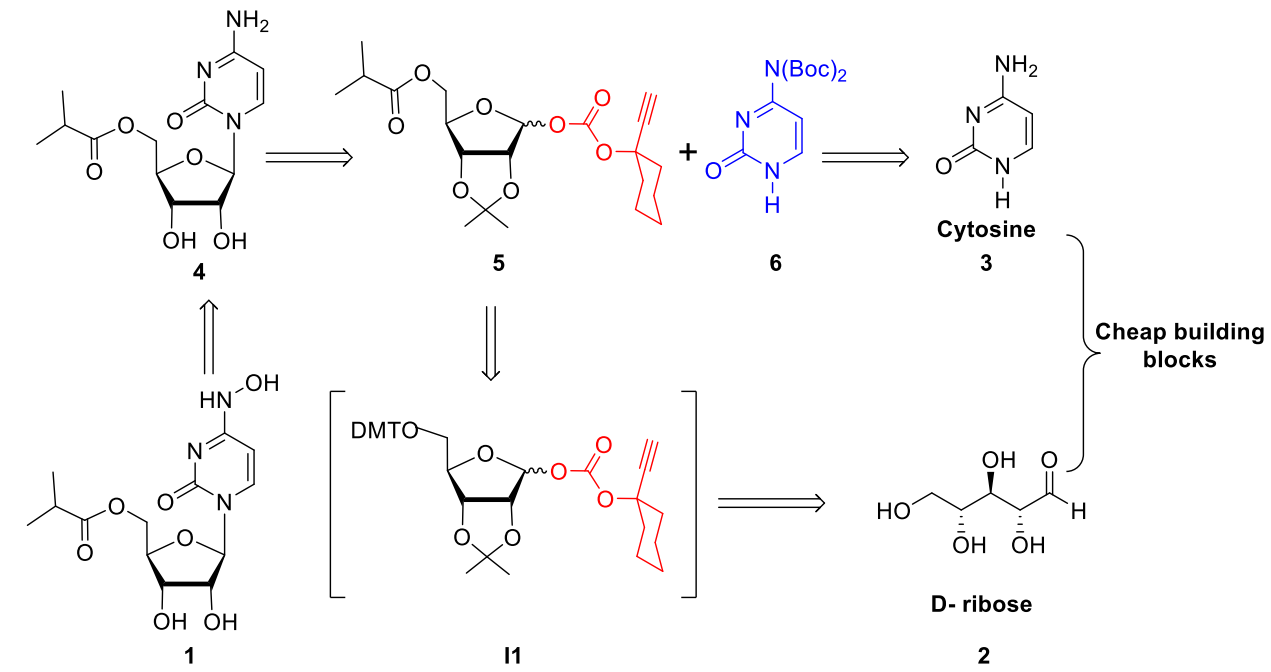


Scheme 4.3: Novel route for the synthesis of Molnupiravir

regioselectivity (*see chapter 3*). Successful glycosylation protocol of nucleobases inspired us to synthesize Molnupiravir, an *N*-hydroxy cytidine prodrug in minimum steps. We chose ribofuranosyl donor and Cytosine as the nucleobase acceptor instead of the conventionally used Uracil to avoid complex triazolylation step that is required to synthesize the prodrug. Instead of using commercially available N^4-Bz Cytosine, we decided to protect the N^4 amine group of much cheaper Cytosine with bis-Boc group to increase the solubility of the nucleobase.[21] This strategy would also avoid the deacylation of N^4-Bz group in the final stages of the synthesis as the primary hydroxyl group of the prodrug is equipped with an isopropyl ester group. To minimize the overall number of steps, the implementation of an ester group at the C2 position of the ribofuranosyl donor

was bypassed. To attain the desired β-stereoselectivity at the anomeric center without neighboring group participation, installation of acetonide group at the C2 and C3 positions was envisioned.





Scheme 4.4: A) Hypothesis of getting β-selectivity and B) Retrosynthesis of Molnupiravir

Although ribofuranosyl cation prefers 1,3-cis or inside attack of nucleophile, but here, the locked conformation of the ribofuranosyl cation at the transition state would favor an unnatural outside

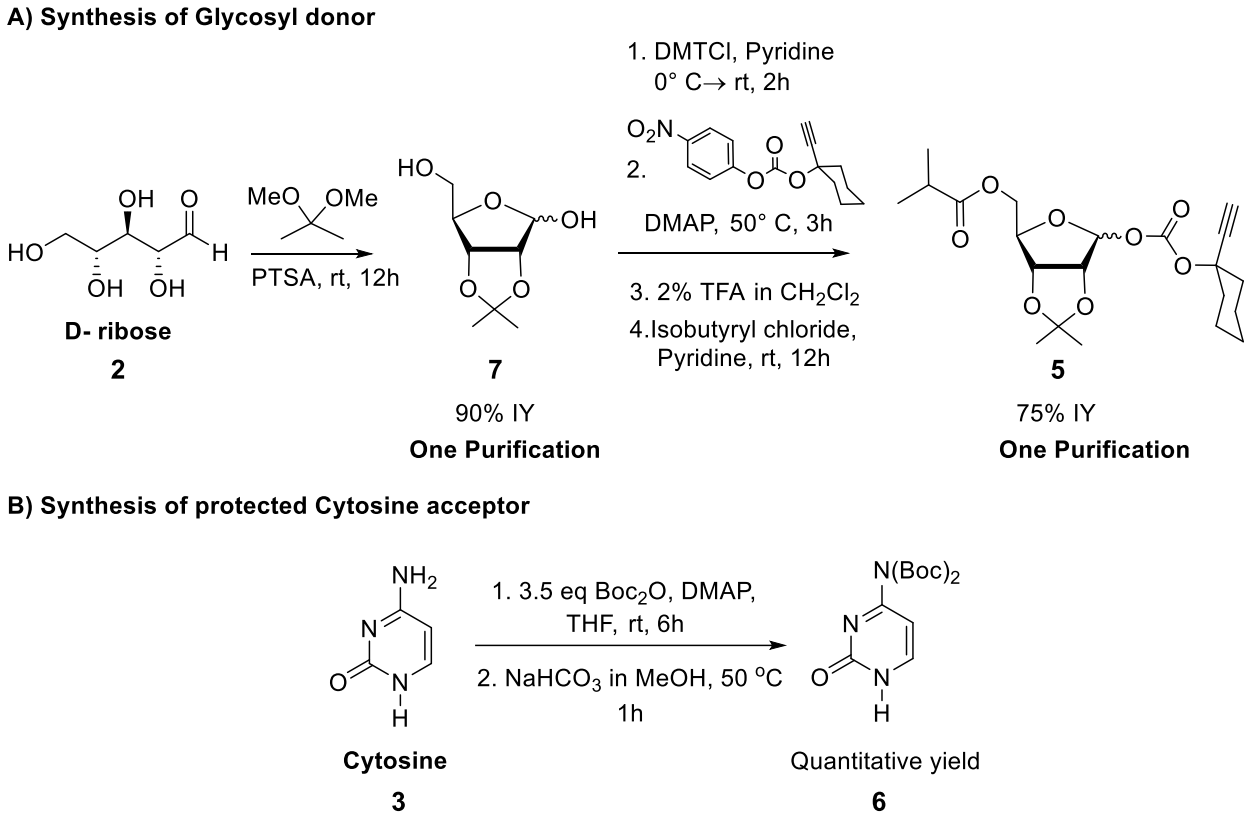
attack of the nucleophile as the inside face is sterically hindered, thus increasing the chance to get higher β- selectivity.[22] Two bulky Boc groups at the N^4 position will also favor attack from the outside face.

4.3.1. Retrosynthesis:

Retrosynthesis of the antiviral drug Molnupiravir **1** was exercised to accomplish the synthesis in minimum steps and in a convergent way. Target molecule **1** could be obtained by hydroxylamination at the N^4 position of compound **4.** Compound **4** is a partially deprotected Cytidine analogue that can be synthesized by coupling glycosyl donor **5** and acceptor **6**. Glycosyl donor **5** could be derived by deprotection of DMT group of intermediate compound **I1** that can be produced by multiple one pot reaction starting from cheap commodity chemical D-ribose **2**. Selective one pot temporary DMT protection of primary hydroxyl group followed by anomeric ethynyl cyclohexyl propargyl carbonate group installation would give intermediate compound **I1** that can be used for synthesizing the glycosyl donor. On the other hand, glycosyl acceptor **6** can be prepared from another cheap commodity chemical Cytosine in a sequential two step reaction.

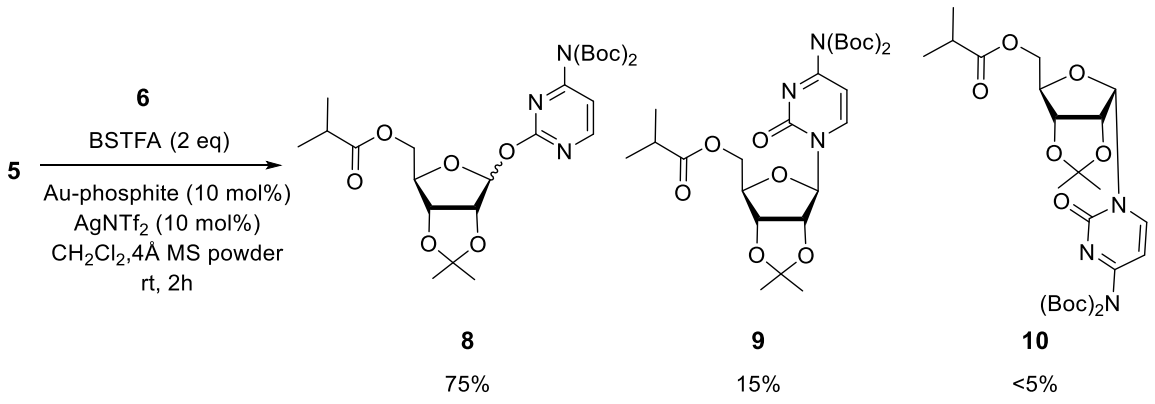
4.3.2. Syntheses of building blocks 5 and 6:

Synthesis of glycosyl donor **5** started from D-ribose. Anomeric allyl or pentenyl protection to lock the sugar ring in its furanoside form were not successful as considerable amount of ribopyranoside was formed along with the furanoside which eventually leads to overall yield loss. So we decided to protect 2,3 acetonide of D-ribose with 2,2-dimethoxy propane and PTSA. In this way ribofuranoside **7** was formed in 90% yield and very less amount of ribopyranoside was detected. Next, compound **7** was subjected to temporary primary hydroxyl group protection with dimethyl trityl chloride (DMTCl) in pyridine. Being a bulky group, the primary hydroxyl group selectively got protected. The free anomeric hydroxyl group was then converted to ethynyl cyclohexyl propargyl donor in the same pot. Later, the acid labile DMT group was cleaved by using 3% trifluoroacetic acid and esterification with isobutyryl ester was performed in the same pot. After three sequential reactions, the donor **5** was isolated in 75% overall yield after one purification. For glycosyl acceptor **6**, commercially available cytosine **3** was protected with tris-Boc group, while two Boc groups reside at the N4 position and third Boc group at the N1 position.



Scheme 4.5: Syntheses of glycosyl donor and acceptor

In the same pot, selectively N1 Boc group was cleaved to get the desired compound **6** using sodium

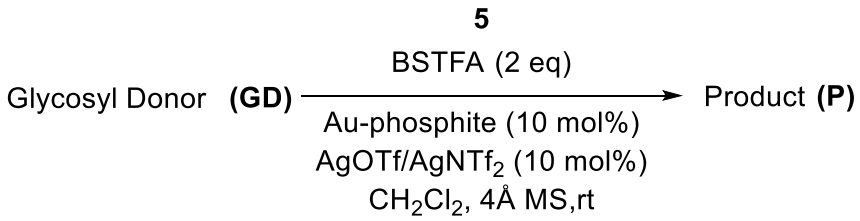


Scheme 4.6: Optimization of glycosylation

bicarbonate in methanol.

4.3.3. Optimization of glycosylation:

After the successful synthesis of donor **5** and acceptor **6**, these two compounds were subjected to *N*-glycosylation reaction by following previously optimized conditions with Au phosphite and



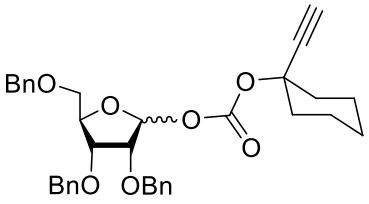
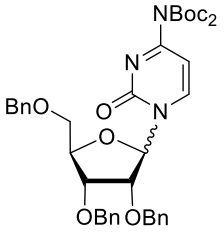
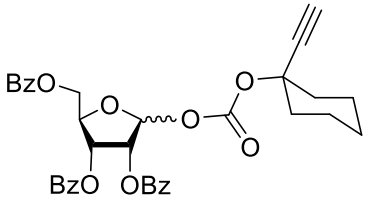
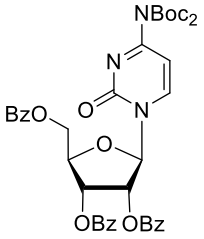
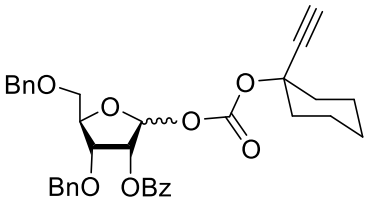
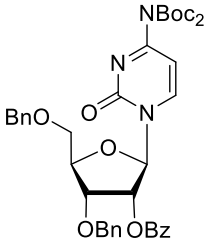
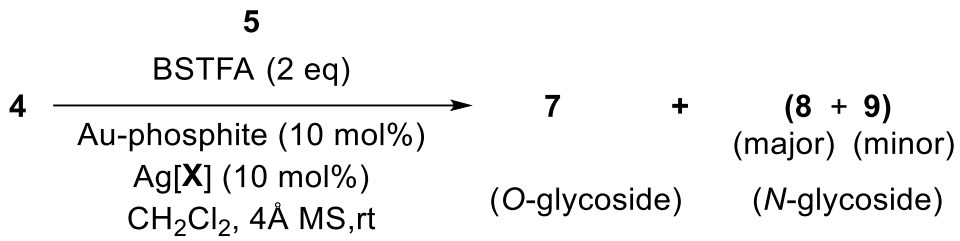
Entry	Glycosyl Donor (**GD**)	Ag Catalyst	Product (**P**)
1a.	 **GD 1**	**AgOTf**	 **P1** (α:β:1:1)
1b.		**$AgNTf_2$**	
2a.	 **GD 2**	**AgOTf**	 **P2**
2b.		**$AgNTf_2$**	
3a.	 **GD 3**	**AgOTf**	 **P3**
3b.		**$AgNTf_2$**	

Table 4.1: Screening of different ribofuranosyl donor for *N*-glycosylation reaction

$AgNTf_2$ co-catalysts. Surprisingly, we found that majorly *O*-glycosidic product has formed and less than 20% *N*-glycosidic product was detected. Compound **8** was characterized through ^{1}H and ^{13}C NMR spectral analysis. Anomeric carbon was identified at δ 97.8 ppm and 104.5 ppm for two isomers that clearly indicated the *O*-glycoside formation. In our previous work, no such observation was found when the corresponding glycosyl donors are of armed, disarmed, and, superarmed nature and $AgNTf_2$ and AgOTf as silver co-catalysts. We envisioned that the stability of the oxacarbenium ion and counter anion present in the reaction mixture have a significant role in the outcome of the glycosylation. A series of glycosyl donor *viz*, armed ribofuranosyl donor **GD1**, disarmed ribofuranosyl donor **GD2** and superarmed ribofuranosyl donor **GD3** were synthesized and subjected to glycosylation reaction with **6**, Au-phosphite, and either $AgNTf_2$ or AgOTf as silver co-catalysts. In all the cases exclusive *N*-glycosidic product **P1, P2,** and, **P3** were observed. No *O*-glycosylated product was detected in any of the glycosyl donors that was used (**Table 4.1**). Next, we changed our attention to screen the role of counter anions that essentially



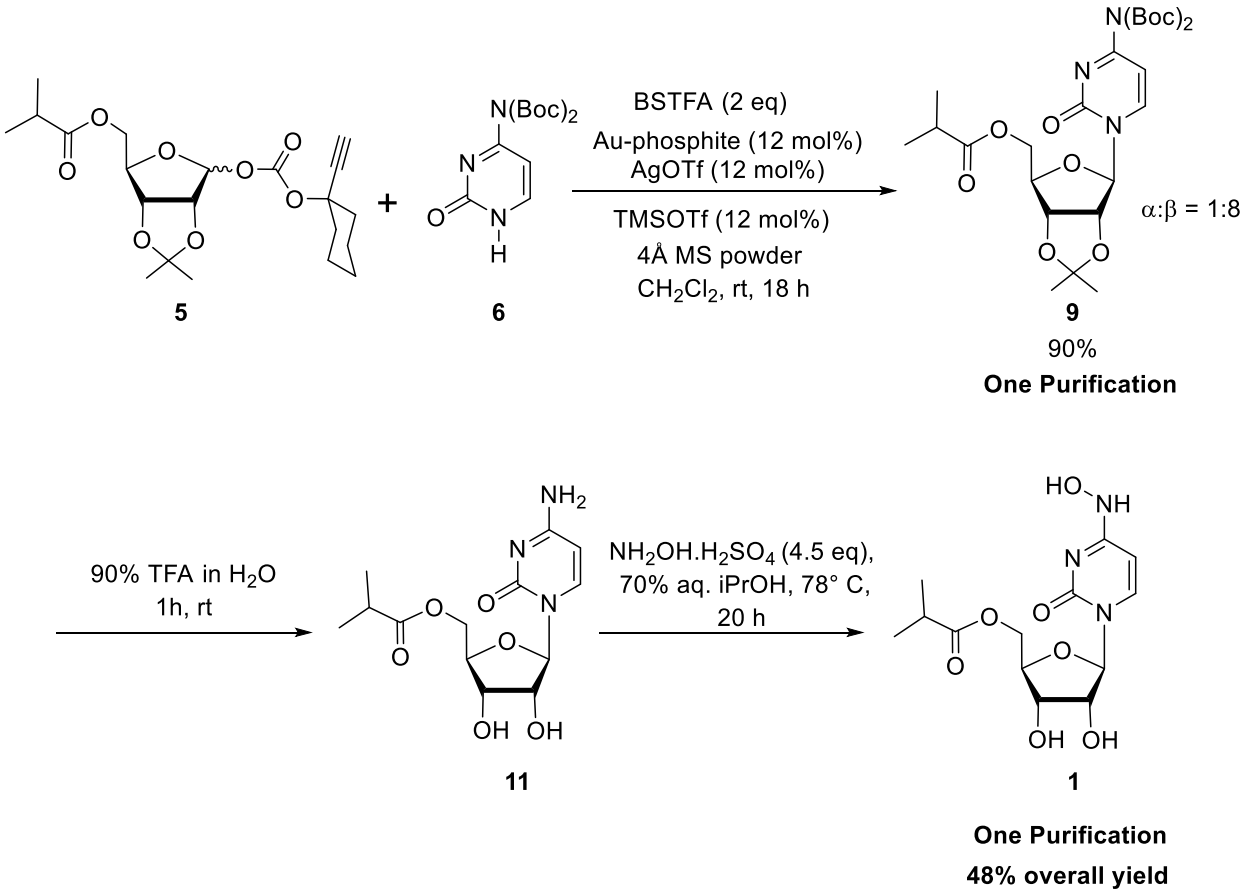
Entry	Counter anion (X^-)	Solvent	*O*- glycoside	*N*-glycoside
1	NTf_2	Dichloromethane	> 75%	< 20%
2	BF_4	Dichloromethane	> 80%	< 10%
3	OCH_3	Dichloromethane	No reaction	
4	OCF_3	Dichloromethane	No reaction	
5	SbF_6	Dichloromethane	> 80%	< 10%
6	OTf	Dichloromethane	Not detected	Exclusive product.

Table 4.2: Screening of different counter anions for *N*-glycosylation reaction

comes from the silver catalyst. A series of Ag(I) catalysts with different counter anions were screened for the glycosylation reaction. Counter anions with dispersed negative charge produced *O*-glycoside as a major product with a small amount of *N*-glycoside (NTf_2, SbF_6, BF_4) whereas the reaction didn't initiate in the cases of acetate or trifluoroacetate counter anion. Exclusive *N*-glycosidic product was identified with AgOTf as the co-catalyst (**Table 4.2**). The glycosylation yield was successfully increased up to 90% when TMSOTf was used as an additive.

4.3.4. Synthesis of Molnupiravir:

The best-optimized condition for the *N*-glycosylation reaction was 12 mol% of each Au-phosphite and AgOTf catalysts along with 12 mol% of TMSOTf as additive. Mild glycosylation condition



Scheme 4.7: Completion of synthesis

afforded nucleosidation with acetonide protected ribofuranosyl donor and bis-Boc protected adenine to furnish the desired β isomer in 88% yield along with 12% of the corresponding α isomer. After the successful synthesis of the protected cytidine analog, both Boc and acetonide groups were successfully cleaved off in a single step by using TFA solution to get compound **11** in quantitative yield. Next hydroxylamination at the N4 position was performed to get the desired *N*-hydroxy cytidine prodrug **1**. The NMR and mass spectroscopy data were in accordance with the previously reported values with anomeric proton identified at δ 6.02 ppm with a doublet (*J*=3.9 Hz*)* and anomeric C was identified at δ 85.5 ppm. In conclusion, we have successfully synthesized Molnupiravir in just six steps and using four chromatographic purification from commodity chemical D-ribose and cytosine. The overall yield of the newly discovered synthetic route is 48%.

4.4. Experimental Data:

*General Methods***.** Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification.1-Ethynylcyclohexanol, *p*-nitrophenyl chloroformate, Cytosine and all metal salts were purchased from Sigma-Aldrich. Unless otherwise reported all reactions were performed under nitrogen atmosphere. Removal of the solvent *in vacuo* refers to distillation using a rotary evaporator attached to an efficient vacuum pump. Products obtained as solids or syrups were dried under high vacuum. Analytical thin-layer chromatography was performed on pre-coated silica plates (F_{254}, 0.25 mm thickness); compounds were visualized by UV light or by staining with anisaldehyde spray.

IR spectra were recorded on a AT-IR spectrometer. NMR spectra were recorded either on a 400 or a 600 MHz with $CDCl_3$, MeOD, or DMSO-*d*6 as the solvent and TMS as the internal standard. High-resolution mass spectroscopy (HRMS) was performed using an ESI-TOF mass analyzer. Low-resolution mass spectroscopy (LRMS) was performed on UPLC-MS with SWADESI-TLC interface.

General procedure for 2,3-acetonide protection: To a stirring solution of commercially available D-ribose (1 mmol) in dry acetone, 2,2-dimethoxy propane (1.5 mmol) and PTSA (0.5 mmol) were added and stirred for 12 h at ambient temparaure. After the completion of the reaction as adjudged by TLC, the reaction mixture was concentrated *in vacuo* and washed with sat. sodium bicarbonate

solution. Next, the crude was purified by silica gel column chromatography with EtOAc/Hexane mobile phase. (Adapted for the synthesis of compound **7**)

*General procedure for preparation of glycosyl carbonate donor **5**:* A solution of compound **7** (1 mmol) in anhydrous pyridine was charged with DMT-Cl (1 mmol) at 0 °C and stirred for 2 h. After the consumption of the starting material as adjudged by TLC analysis, the reaction mixture was concentrated *in vacuo* and the trace solvent was removed under high vacuum. The crude was re-dissolved in anhydrous CH_2Cl_2 and DMAP (1.1 mmol) and ethynylcyclohexyl (4-nitrophenyl) carbonate (1.1 mmol) prepared *vide supra* were added to it. The reaction mixture was refluxed at 50 °C for 3 h and after the complete consumption of starting material, the solvent was evaporated under reduced pressure and washed with sat. aqueous ammonium hydroxide solution. Next, the crude was subjected to primary DMT deprotection. The crude was dissolved in CH_2Cl_2 and 2% TFA solution (1mL/g) was added and stirred at ambient temperature for 30 min. After the completion of the deprotection reaction, the solvent was evaporated and the crude was washed with sat. aqueous sodium bicarbonate solution and extracted in CH_2Cl_2, dried over Na_2SO_4 and concentrated. Next, the crude was redissolved in anhydrous pyridine and charged with isobutyryl chloride (1.1 mmol) at 0 °C and cat. DMAP. The reaction mixture was stirred for 12 h at ambient temperature. After the completion of the reaction, the solvent was evaporated and the crude was extracted in EtOAc and subjected to silica gel column chromatographic purification to get glycosyl donor **5** in 75% overall yield.

*General procedure for preparation of glycosyl acceptor **6**:* Into a stirring suspension of commercially available cytosine (1 mmol) in anhydrous THF, Boc-anhydride (3.5 mmol) and DMAP (0.5 mmol) were added and stirred for 6 h at room temperature. The solvent was evaporated *in vacuo* and the crude was dissolved in MeOH and saturated aq. $NaHCO_3$ was added. The turbid solution was stirred for 1 h at 50°C. After evaporation of MeOH, water was added to the suspension, and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and evaporated to give pure **6** as a white solid.

General procedure for glycosylation: Bis-Boc protected cytosine **6** prepared *vide supra* (1.0 mmol) was suspended in dry CH_2Cl_2 and BSTFA (2.5 mmol) was added in a round bottom flask and stirred till the solution became clear. To this solution of silylated pyrimidine (1.1 mmol) in anhydrous CH_2Cl_2 (6 mL), glycosyl carbonate donor **5** was added (1.0 mmol). Next, freshly

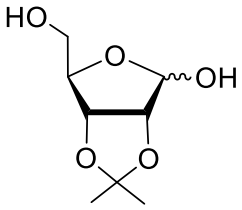
activated 4Å MS powder (30 mg/mL) was added and stirred for 20 min under nitrogen atmosphere, gold-phosphite (**3**) (12 mol%), AgOTf (12 mol%) and TMSOTf (12 mol%) were added and stirred at 25 °C. After 18 h as adjudged by TLC analysis, the reaction mixture was passed through a bed of Celite® and the filtrate was concentrated *in vacuo* to obtain a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as mobile phase to obtain desired glycoside **9** in 80% yield.

General procedure for acetonide and Boc deprotection: Compound **9** was treated with 90% aqueous TFA solution (1ml/100mg) and stirred for 1 h at ambient temperature. After the completion of the deprotection as adjudged by TLC analysis, the reaction mixture was concentrated and redissolved in ethyl acetated and washed with aq. sat. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and evaporated to give pure **11** in quantitative yield.

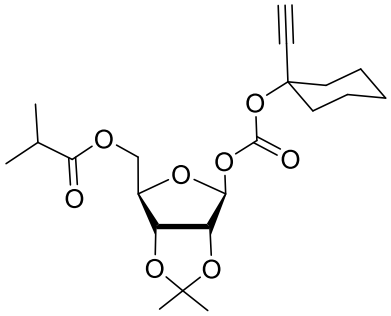
General procedure for N4 hydroxylamination: Compound **11** (1mmol) was suspended in 70% aq. isopropanol and hydroxylamine sufate (4.5 mmol) was added into it and stirred for 20h at 78 °C. After the complete consumption of starting material, the reaction mixture was concentrated and purified by silica gel column chromatography to give compound **1.**

4.5. Characterization Data:

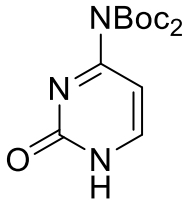
2,3-*O*-Isopropylidene-β-D-ribofuranoside [α:β (0.11:1)] (**7**); syrup, ^{1}H NMR (400.31 MHz, $CDCl_3$) δ 5.44 (d, *J* = 6.2 Hz, 1H), 5.41 – 5.34 (m, 2H), 4.78 (dd, *J* = 6.0, 1.0 Hz, 1H), 4.69 (dd, *J* = 6.6, 2.3 Hz, 1H), 4.62 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.54 (d, *J* = 5.9 Hz, 1H), 4.38 – 4. 34 (m, 1H), 4.24 (d, *J* = 9.4 Hz, 1H), 4.17 – 4.08 (m, 2H), 3.75 – 3.56 (m, 5H), 1.54 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 114.3, 112.3, 102.8, 97.1, 87.7, 86.8, 81.7, 81.6, 81.2, 79.5, 63.6, 63.3, 26.4, 26.2, 24.8, 24.8. HRMS (ESI-MS): m/z calcd for $C_8H_{14}O_5$ $[M+Na]^+$: 213.0710;Found: 212.9877



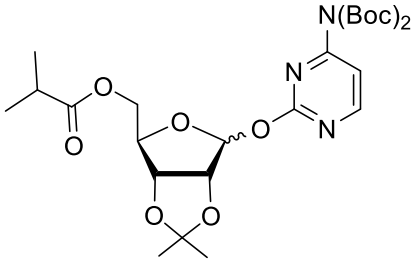
1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)- 5-*O*-Isobutyryl-2,3-*O*-Isopropylidene-β-D-ribofuranoside (**5**); syrup, ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 6.12 (s, 1H), 4.78 (d, *J* = 5.9 Hz, 1H), 4.73 (dd, *J* = 6.0, 1.1 Hz, 1H), 4.47 (td, *J* = 6.4, 1.1 Hz, 1H), 4.19 – 4.07 (m, 2H), 2.63 (s, 1H), 2.61 – 2.53 (m, 1H), 2.24 – 2.06 (m, 1H), 1.93 – 1.78 (m, 2H), 1.69 – 1.56 (m, 5H), 1.49 (s, 3H), 1.38 – 1.27 (m, 4H), 1.19 (d, *J* = 1.1 Hz, 3H), 1.17 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 176.7, 151.0, 113.4, 104.9, 85.8, 85.2, 82.7, 81.7, 78.3, 75.3, 64.1, 37.1, 36.5, 34.0, 26.6, 25.2, 25.0, 22.6, 22.6, 19.1, 19.1. $C_{21}H_{30}O_8$ $[M+H]^+$: 411.2019;Found: 411.2028.



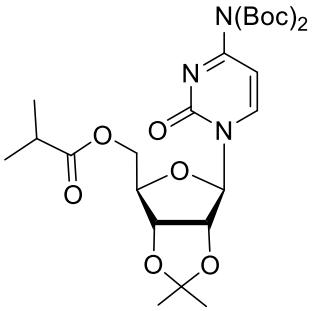
Bis-Boc-cytosine**(6)**:White solid, mp (ºC): 315, ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 13.08 (s, 1H), 7.79 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.06 (dd, *J* = 7.1, 1.4 Hz, 1H), 1.51 (s, 18H).; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 27.7, 27.8, 27.8, 27.8, 27.8, 27.8, 85.0, 85.0, 96.9, 146.3, 149.5, 149.6, 158.6, 163.7.; HRMS (ESI-MS): m/z calcd for $C_{14}H_{21}N_3O_5$ $[M+H]^+$: 312.1559; Found: 312.1560.



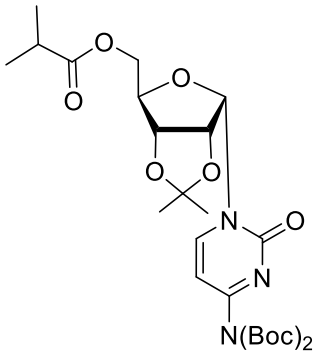
N,*N*-Di-*tert*-butoxycarbonyl-1-*O*-(5-*O*-Isobutyryl-2,3-*O*-Isopropylidene ribofuranosyl)cytosine **(**α:β : 1:1**)** (**8**): syrup, ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 8.44 – 8.38 (m, 1H), 7.45 – 7.35 (m, 1H), 6.49 – 6.45 (m, 1H), 4.94 – 4.84 (m, 1H), 4.83 – 4.42 (m, 2H), 4.34 – 4.18 (m, 1H), 4.16 (dd, *J* = 7.0, 1.7 Hz, 1H), 2.57 (dp, *J* = 16.8, 7.0 Hz, 1H), 1.61 – 1.50 (m, 21H), 1.37 – 1.34 (m, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.13 (ddd, *J* = 7.0, 4.1, 0.8 Hz, 3H).; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.0, 19.0, 19.0, 19.1, 25.3, 25.9, 26.0, 26.6, 27.7, 27.7, 27.8, 27.8, 27.8, 27.8, 27.8, 27.8, 27.8, 27.8, 27.9, 33.9, 34.0, 63.9, 64.0, 80.5, 80.9, 80.9, 82.1, 84.4, 84.5, 84.7, 84.7, 85.2, 85.3, 97.8, 104.5, 106.4, 106.4, 113.1, 116.2, 149.9, 149.9, 149.9, 150.0, 159.8, 159.8, 159.9, 160.1, 162.6, 163.1, 176.5, 176.7.; HRMS (ESI-MS): m/z calcd for $C_{26}H_{39}N_3O_{10}$ $[M+H]^+$: 554.2714; Found: 554.2717.



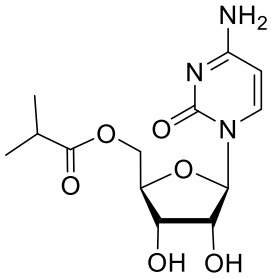
N,*N*-Di-*tert*-butoxycarbonyl-1-(2,3-*O*-Isopropylidene-5-*O*-isobutyryl-β-D-ribofuranosyl)cytosine (**9**): $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 0.7): +23.6;^{1}H NMR (400.31 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.22 (d, *J* = 4.0 Hz, 1H), 5.02 (dd, *J* = 5.9, 4.0 Hz, 1H), 4.76 (dd, *J* = 6.0, 0.9 Hz, 1H), 4.56 (t, *J* = 3.4 Hz, 1H), 4.26 – 4.17 (m, 2H), 2.60 (p, *J* = 7.0 Hz, 1H), 1.54 (s, 18H), 1.36 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H).; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.0, 19.1, 24.2, 26.0, 27.7, 27.8, 27.8, 27.8, 27.8, 27.8, 34.0, 65.2, 77.4, 79.1, 81.2, 81.7, 85.0, 85.0, 87.9, 95.1, 113.4, 144.5, 149.7, 149.7, 154.1, 162.5, 176.5.; HRMS (ESI-MS): m/z calcd for $C_{26}H_{39}N_3O_{10}$ $[M+H]^+$: 554.2714; Found: 554.2714.



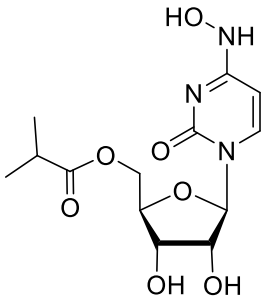
N,*N*-Di-*tert*-butoxycarbonyl-1-(2,3-*O*-Isopropylidene-5-*O*-isobutyryl-α-D-ribofuranosyl)cytosine(**10**): syrup,^{1}H NMR (400.31 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.6 Hz, 1H), 7.07 (dd, *J* = 7.5, 0.7 Hz, 1H), 5.61 (d, *J* = 1.5 Hz, 1H), 5.08 – 5.03 (m, 1H), 4.84 (dd, *J* = 6.3, 3.8 Hz, 1H), 4.43 – 4.34 (m, 2H), 4.32 – 4.25 (m, 1H), 2.51 (pd, *J* = 7.0, 0.7 Hz, 1H), 1.62 (s, 3H), 1.54 (s, 18H), 1.32 (s, 3H), 1.13 (ddd, *J* = 7.0, 1.7, 0.7 Hz, 6H).; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 19.0, 19.1, 25.3, 27.2, 27.6, 27.7, 27.8, 27.8, 27.8, 27.8, 33.9, 64.4, 81.6, 85.2, 85.3, 85.3, 86.7, 96.1, 97.2, 114.2, 145.7, 149.4, 149.5, 154.0, 163.0, 176.7.; HRMS (ESI-MS): m/z calcd for $C_{26}H_{39}N_3O_{10}$ $[M+H]^+$: 554.2714; Found: 554.2719.



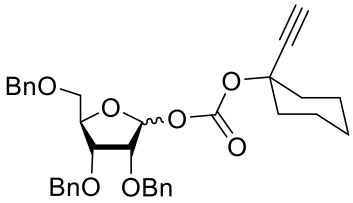
N,*N*-Di-*tert*-butoxycarbonyl-1-(2,3-*O*-Isopropylidene-5-*O*-isobutyryl-α-D-ribofuranosyl)cytosine(**11**):^{1}H NMR (400.31 MHz, DMSO-d6) δ 7.50 (d, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 73.1 Hz, 2H), 6.04 (d, *J* = 3.1 Hz, 1H), 5.71 (d, *J* = 7.4 Hz, 1H), 5.39 (dd, *J* = 58.9, 5.2 Hz, 2H), 4.32 (dd, *J* = 12.0, 2.4 Hz, 1H), 4.18 – 4.12 (m, 1H), 4.06 (q, *J* = 7.2, 6.7 Hz, 3H), 2.51 (s, 1H), 1.10 (d, *J* = 6.8 Hz, 6H).; ^{13}C NMR (100.67 MHz, DMSO-d6): δ 19.2, 19.3, 33.6, 64.0, 70.3, 71.6, 80.0, 86.1, 93.1, 143.5, 155.7, 166.1, 176.5.; HRMS (ESI-MS): m/z calcd for $C_{13}H_{19}N_3O_6$ $[M+Na]^+$: 336.1172; Found: 336.1178.



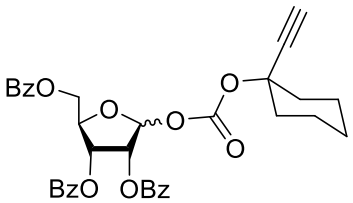
5'-*O*-isobutyryl *N4*-hydroxy cytidine or Molnupiravir (**1**):^{1}H NMR(400.31 MHz, Methanol-d4) δ 7.00 (d, *J* = 8.3 Hz, 1H), 6.02 (d, *J* = 3.9 Hz, 1H), 5.51 (d, *J* = 8.3 Hz, 1H), 4.35 (dd, *J* = 12.0, 2.7 Hz, 1H), 4.28 – 4.19 (m, 2H), 4.17 – 4.08 (m, 2H), 2.59 (p, *J* = 7.0 Hz, 1H), 1.16 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100.67 MHz, Methanol-d4) δ 18.0, 18.0, 33.8, 63.6, 71.1, 71.2, 80.4, 85.5, 95.8, 132.7, 145.5, 150.3, 177.1.; HRMS (ESI-MS): m/z calcd for $C_{13}H_{19}N_3O_7$ $[M+H]^+$: 330.1301; Found: 330.1312.



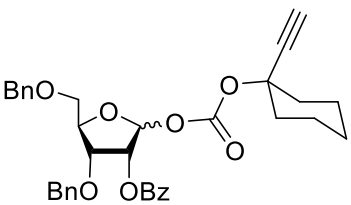
1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,5-tri-*O*-benzyl α/β-D-ribofuranoside (**GD 1**): syrup; ^{1}H NMR (400.31 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 15H), 6.22 – 6.10 (m, 1H), 4.86 – 4.39 (m, 7H), 4.37 – 4.14 (m, 1H), 4.03 – 3.91 (m, 1H), 3.74 – 3.40 (m, 2H), 2.59 (d, *J* = 13.6 Hz, 1H), 2.16-1.28 (m, 10H). ^{13}C NMR (100.67 MHz, CDCl3) δ 22.6, 22.6, 25.0, 36.5, 37.0, 69.9, 72.2, 72.5, 73.4, 75.2, 77.0, 78.1, 78.8, 81.9, 82.7, 101.7, 127.5, 127.6, 127.6, 127.8, 127.8, 127.9, 128.0, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.5, 137.4, 137.6, 138.4, 151.2. HRMS (ESI-MS): m/z calcd for $C_{35}H_{38}O_7$ $[M+H]^+$: 571.2696 Found: 571.2710.



1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2,3,5-tri-*O*-benzoyl α/β-D-ribofuranoside (**GD 2**) : syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.08 (m, 2H), 8.05 – 7.98 (m, 2H), 7.87 (dt, *J* = 8.4, 1.7 Hz, 2H), 7.60 – 7.33 (m, 9H), 6.34 (s, 1H), 5.96 (dd, *J* = 7.1, 4.9 Hz, 1H), 5.89 – 5.82 (m, 1H), 4.87 – 4.73 (m, 2H), 4.55 (dd, *J* = 12.1, 4.4 Hz, 1H), 2.63 (s, 1H), 2.18 – 1.55 (m, 10H). ^{13}C NMR (100.67 MHz, $CDCl_3$) δ 22.6, 22.6, 24.9, 36.4, 36.9, 63.8, 71.2, 75.0, 75.4, 78.7, 80.1, 101.2, 128.4, 128.4, 128.4, 128.4, 128.4, 128.6, 128.6, 128.7, 128.8, 129.6, 129.8, 129.8, 129.9, 129.9, 129.9, 129.9, 133.1, 133.5, 133.7, 150.8, 165.0, 165.3, 166.2. HRMS (ESI-MS): m/z calcd for $C_{35}H_{32}O_{10}$ $[M+H]^+$: 613.2074 Found: 613.2086.

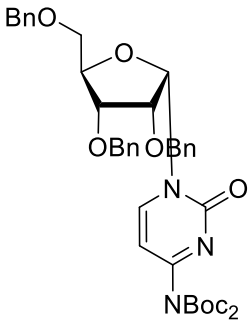


1-*O*-(((1-ethynylcyclohexyl)oxy)carbonyl)-2-*O*-benzoyl-3,5-di-*O*-benzyl α/β-D-ribofuranoside (α□β□: 5:1) (**GD 3**): Syrup, IR (cm^{-1}, $CHCl_3$): 3281, 2936, 2862, 1758, 1726, 1600, 1451,1268, 1238, 1010, 910, 786, 730, 704; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 8.08 (dt, *J* = 8.5, 1.7 Hz, 2H), 7.59 – 7.53 (m, 1H), 7.46 – 7.40 (m, 2H), 7.35 – 7.20 (m, 10H), 6.46 – 6.20

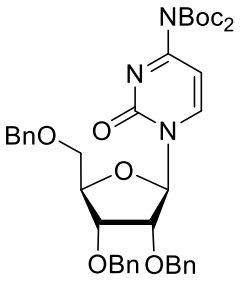


(m, 1H), 5.64 – 5.38 (m, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.62 – 4.51 (m, 2H), 4.51 – 4.41 (m, 2H), 4.39 – 4.24 (m, 1H), 3.74 – 3.43 (m, 2H), 2.55 (s, 1H), 2.27 – 2.09 (m, 2H), 1.88 – 1.76 (m, 2H), 1.68 – 1.43 (m, 6H); ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 22.5, 22.6, 22.6, 22.6, 25.0, 25.0, 36.5, 36.6, 36.8, 37.0, 69.1, 69.6, 72.1, 73.1, 73.2, 73.5, 73.6, 74.0, 75.0, 75.3, 75.4, 76.8, 77.8, 78.4, 82.1, 82.6, 82.8, 84.2, 98.0, 101.5, 127.6, 127.6, 127.6, 127.6, 127.7, 127.8, 127.8, 127.9, 128.0, 128.0, 128.0, 128.0, 128.3, 128.4, 128.4, 128.4, 128.4, 128.4, 128.4, 128.5, 128.5, 128.5, 128.6, 129.4, 129.4, 130.0, 130.0, 130.1, 130.2, 133.3, 133.5, 137.3, 137.8, 137.8, 138.3, 150.9, 151.6, 165.4, 165.6 (α□β isomers). HRMS (ESI-MS): m/z calcd for $C_{35}H_{36}O_8$ $[M+H]^+$: 585.2488 Found: 585.2493.

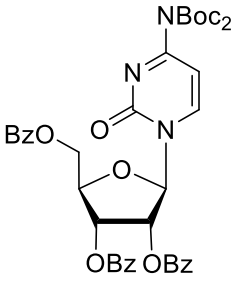
N,*N*-Di-*tert*-butoxycarbonyl-1-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)cytosine (**P1 α**): syrup; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 8.48 (d, *J* = 7.6 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.36 – 7.25 (m, 13H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.01 (s, 1H), 4.96 (dd, *J* = 72.9, 12.2 Hz, 2H), 4.52 – 4.38 (m, 4H), 4.18 (d, *J* = 11.8 Hz, 1H), 4.07 (d, *J* = 4.6 Hz, 1H), 4.00 – 3.94 (m, 2H), 3.69 (dd, *J* = 11.1, 1.8 Hz, 1H), 1.56 (s, 18H).; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 27.8, 27.8, 27.8, 27.8, 27.8, 27.9, 67.0, 71.7, 72.2, 73.4, 73.6, 78.7, 81.1, 84.9, 84.9, 90.1, 96.0, 127.8, 127.9, 127.9, 128.0, 128.0, 128.1, 128.2, 128.4, 128.4, 128.5, 128.5, 128.6, 128.6, 128.7, 128.7, 137.4, 137.5, 137.9, 144.4, 149.7, 149.7, 154.5, 162.6.; HRMS (ESI-MS): m/z calcd for $C_{40}H_{47}N_3O_9$ $[M+H]^+$: 714.3319; Found: 714.3321.



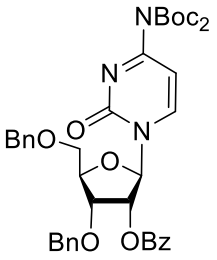
N,*N*-Di-*tert*-butoxycarbonyl-1-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)cytosine (**P1 β**): syrup; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.31 – 7.23 (m, 15H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.28 (d, *J* = 3.8 Hz, 1H), 4.53 – 4.38 (m, 8H), 4.10 (dd, *J* = 7.6, 4.3 Hz, 1H), 3.68 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.51 (dd, *J* = 11.0, 4.0 Hz, 1H), 1.55 (s, 18H).; ^{13}C NMR (100.67 MHz, $CDCl_3$): 29.7, 29.7, 29.8, 29.8, 29.8, 29.9, 69.3, 72.9, 73.6, 74.1, 75.9, 78.0, 81.2, 84.9, 84.9, 87.1, 95.8, 127.7, 127.9, 128.0, 128.0, 128.0, 128.1, 128.2, 128.2, 128.2, 128.5, 128.5, 128.5, 128.5, 128.6, 128.6, 137.3, 137.3, 137.8, 145.6, 149.6, 149.7, 154.7, 162.6.; HRMS (ESI-MS): m/z calcd for $C_{40}H_{47}N_3O_9$ $[M+H]^+$: 714.3319; Found: 714.3328.



N,*N*-Di-*tert*-butoxycarbonyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)cytosine (**P2**): White solid, mp (ºC): 121; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +66.7; ^{1}H NMR (400.31 MHz, $CDCl_3$): δ 8.10 – 8.05 (m, 2H), 7.96 – 7.89 (m, 4H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.57 – 7.43 (m, 5H), 7.36 – 7.30 (m, 4H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.26 (d, *J* = 3.9 Hz, 1H), 5.91 (t, *J* = 5.9 Hz, 1H), 5.83 (dd, *J* = 5.9, 4.0 Hz, 1H), 4.82 (dd, *J* = 12.0, 2.9 Hz, 1H), 4.75 (ddd, *J* = 6.2, 4.3, 2.8 Hz, 1H), 4.69 (dd, *J* = 12.0, 4.3 Hz, 1H), 1.54 (s, 18H).; ^{13}C NMR (100.67 MHz, $CDCl_3$): δ 27.7, 27.8, 27.8, 27.8, 27.8, 27.8, 63.8, 71.0, 74.9, 80.5, 85.2, 85.3, 90.9, 96.9, 128.5, 128.5, 128.6, 128.6, 128.7, 128.7, 128.8, 128.8, 129.4, 129.8, 129.8, 129.9, 130.0, 130.0, 130.1, 133.6, 133.7, 133.7, 143.8, 149.4, 149.4, 154.0, 162.8, 165.3, 165.3, 166.3.; HRMS (ESI-MS): m/z calcd for $C_{40}H_{41}N_3O_{12}$ $[M+H]^+$: 756.2768; Found: 756.2768.

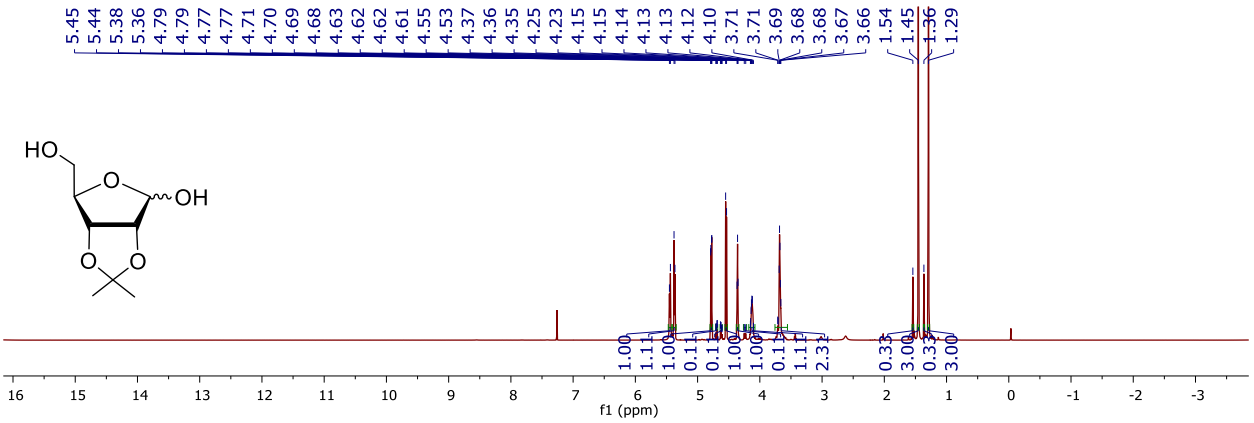


N,*N*-Di-*tert*-butoxycarbonyl-1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)cytosine (**P3**): White solid, mp (ºC): 113.4; $[\alpha]^{25}_{D}$ ($CHCl_3$, *c* 1.0): +81.6; IR (cm^{-1}, $CHCl_3$): 3054, 2938, 2822,1742, 1735, 1443,1269, 1077, 765, 672; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 7.6 Hz, 1H), 8.15 – 8.05 (m, 2H), 7.61 – 7.53 (m, 1H), 7.46 – 7.31 (m, 5H), 7.35-7.19 (m, 7H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.17 (d, *J* = 1.6 Hz, 1H), 5.72 (dd, *J* = 4.4, 1.6 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.43 – 4.26 (m, 4H), 3.77 (m, 2H), 1.56 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 27.7, 27.7, 27.7, 27.7, 27.7, 67.3, 73.3, 73.5, 74.5, 74.6, 81.6, 84.9, 85.0, 90.2, 96.1,127.9, 128.0, 128.0, 128.2, 128.2, 128.2, 128.4, 128.4, 128.4, 128.5, 128.6, 128.7, 129.5, 129.9, 130.0, 133.3, 137.2, 137.3, 144.2, 149.5, 149.6, 154.1, 162.6, 165.1; HRMS (ESI-MS): m/z calcd for $C_{40}H_{45}N_3O_{10}$ $[M+H]^+$: 728.3183; Found: 728.3185.

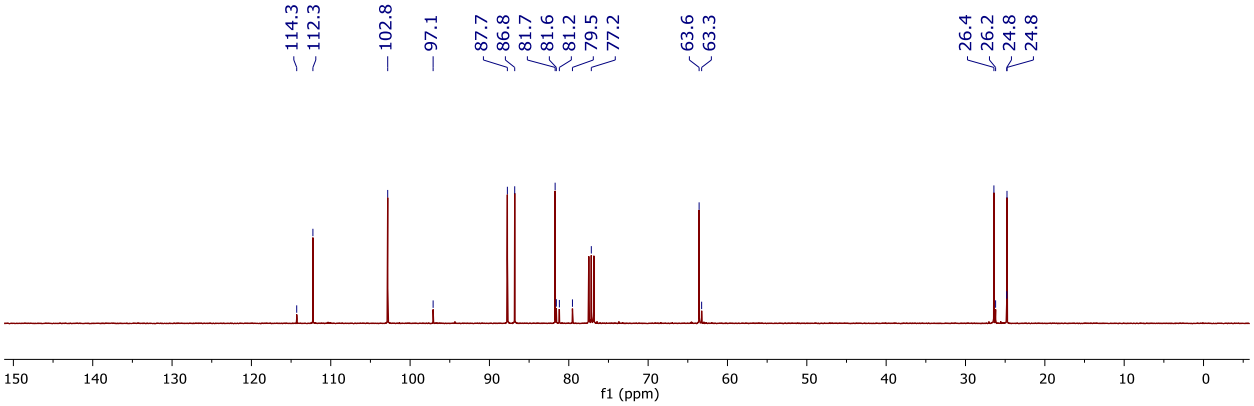


4.6. NMR spectra chart:

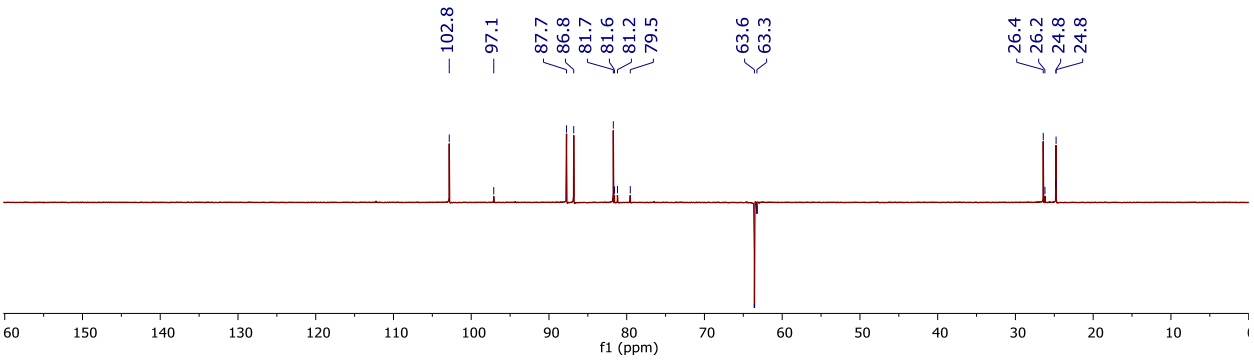
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **7**



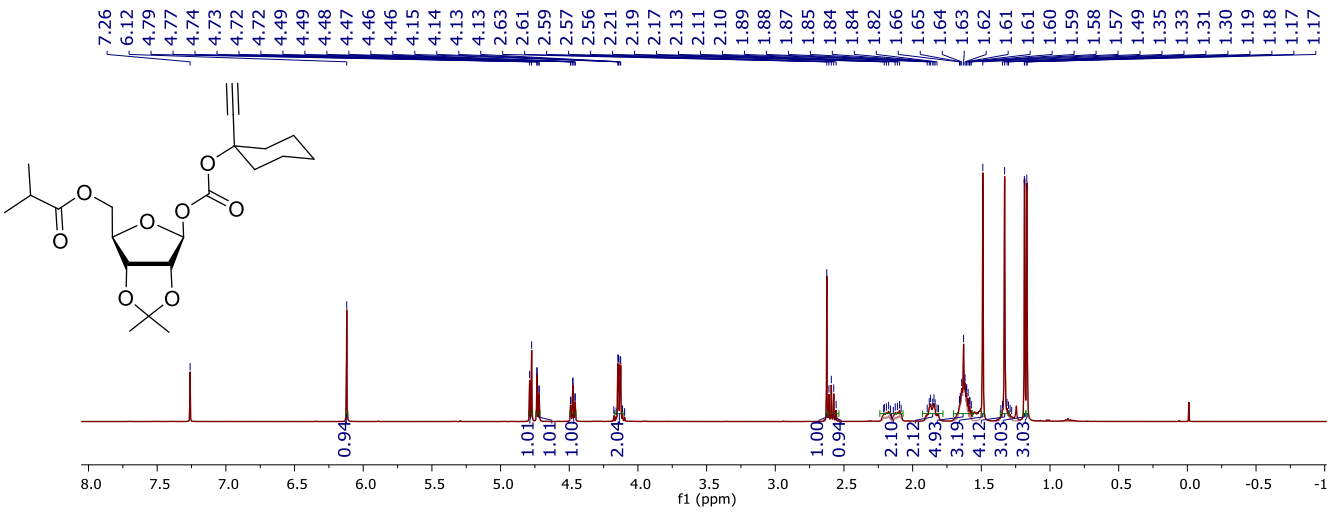
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **7**



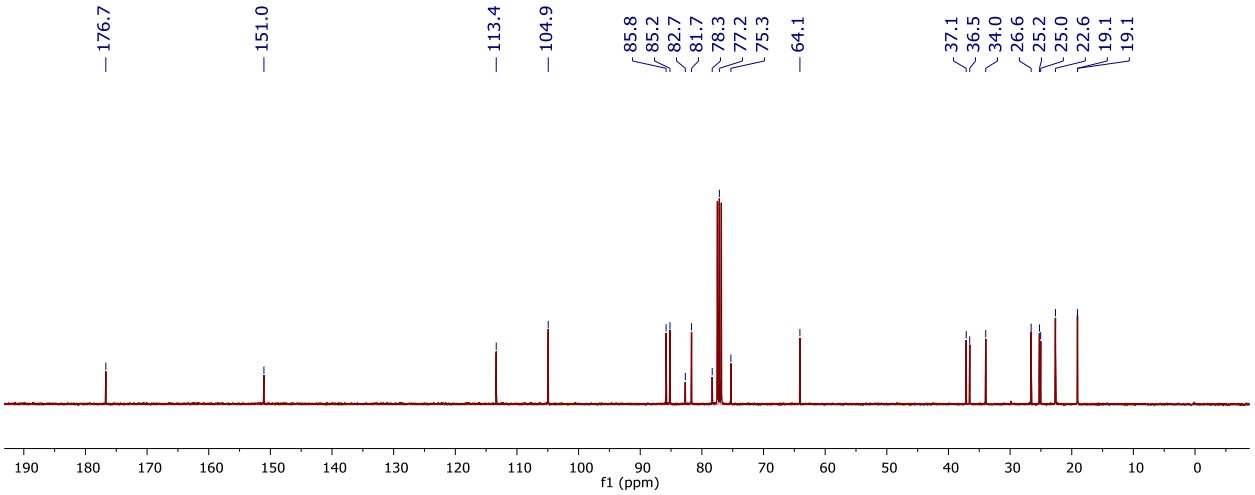
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **7**



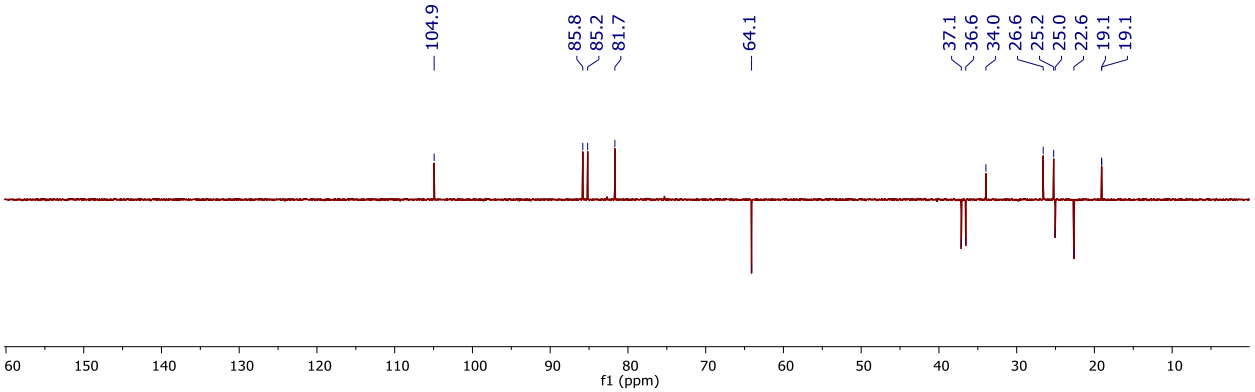
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **5**



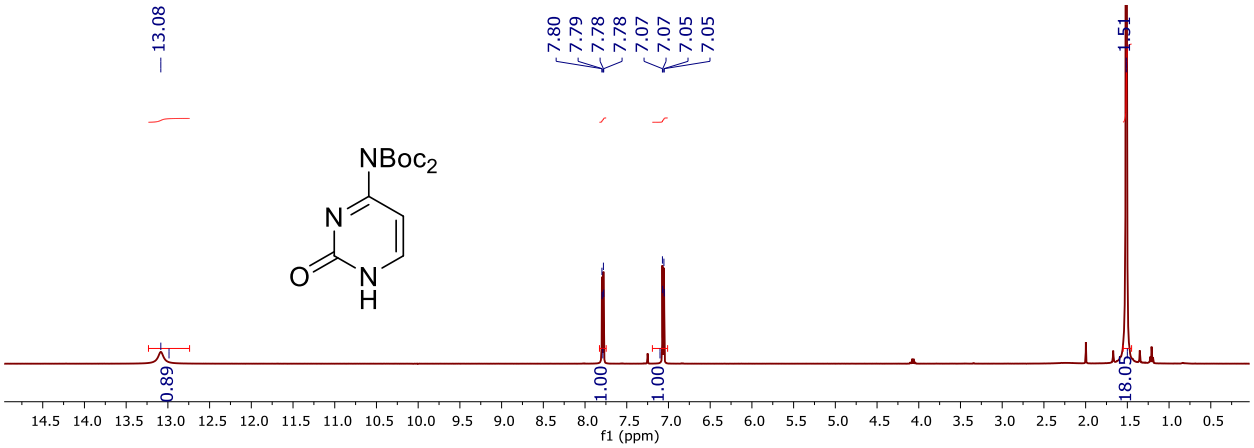
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **5**



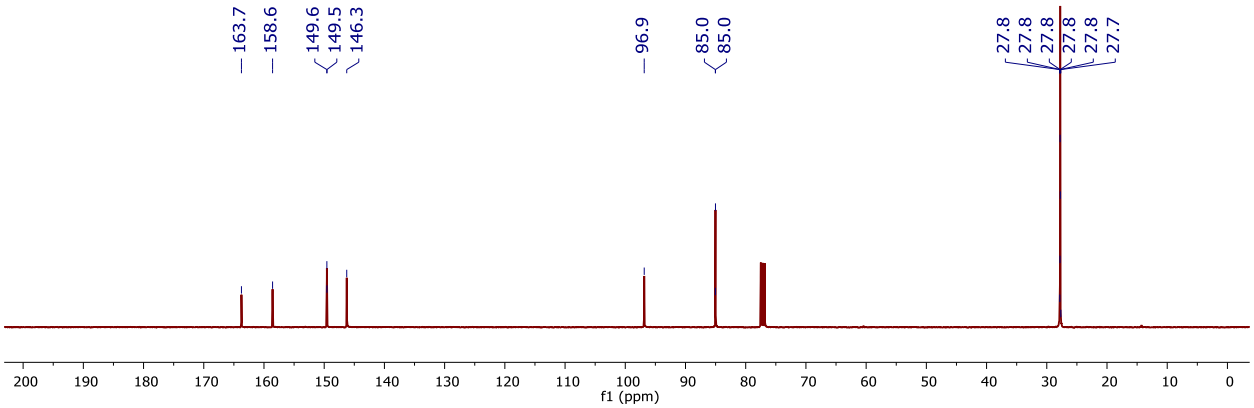
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **5**



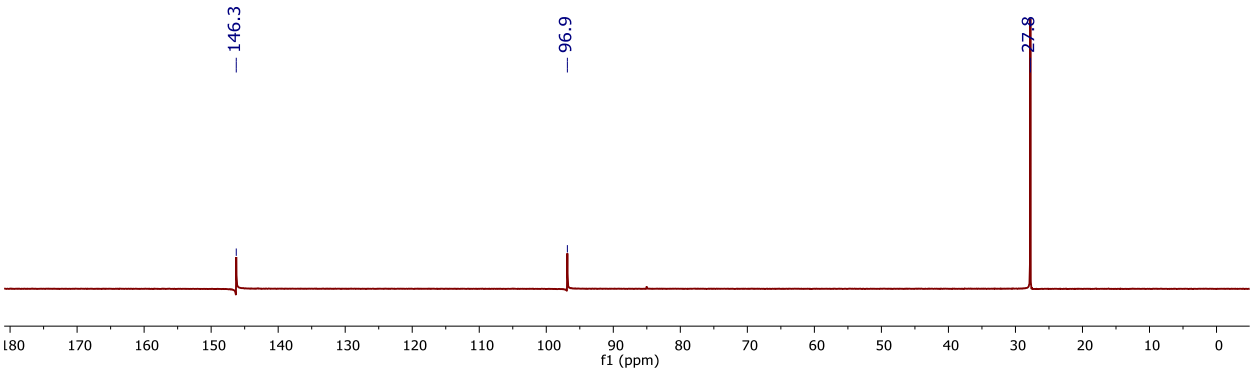
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **6**



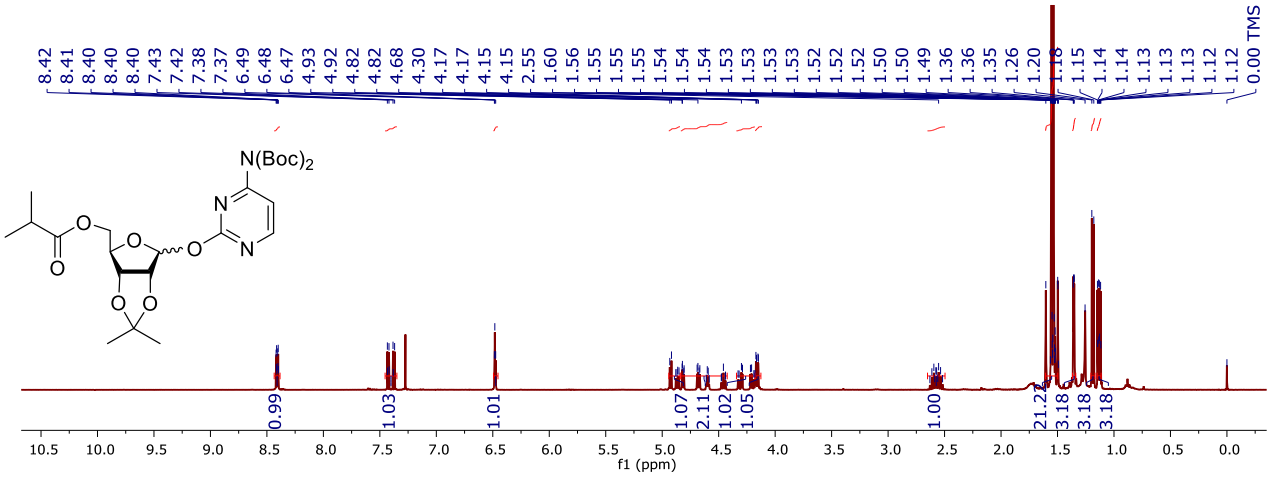
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **6**



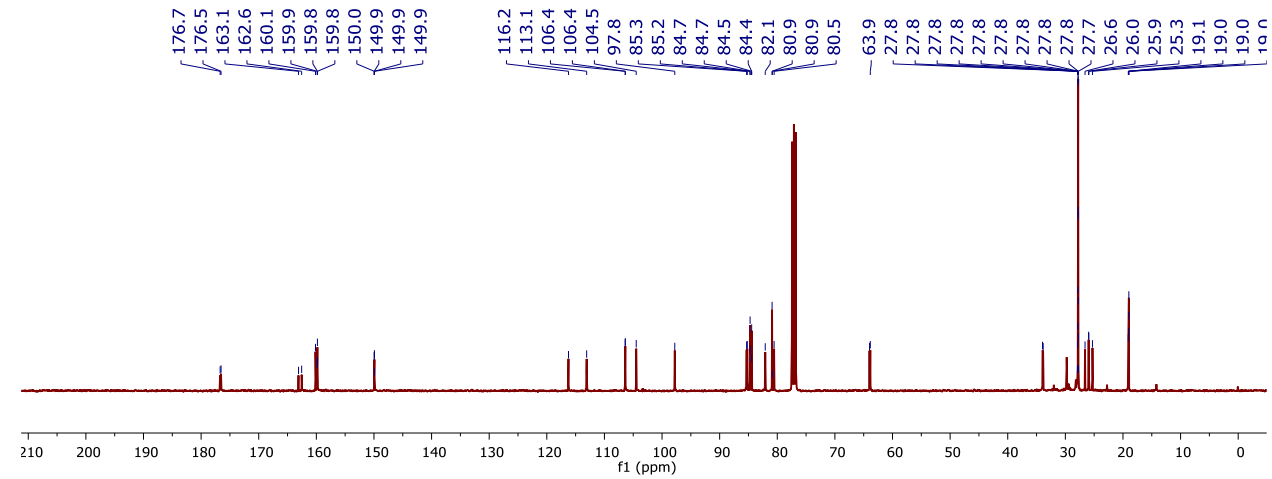
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **6**



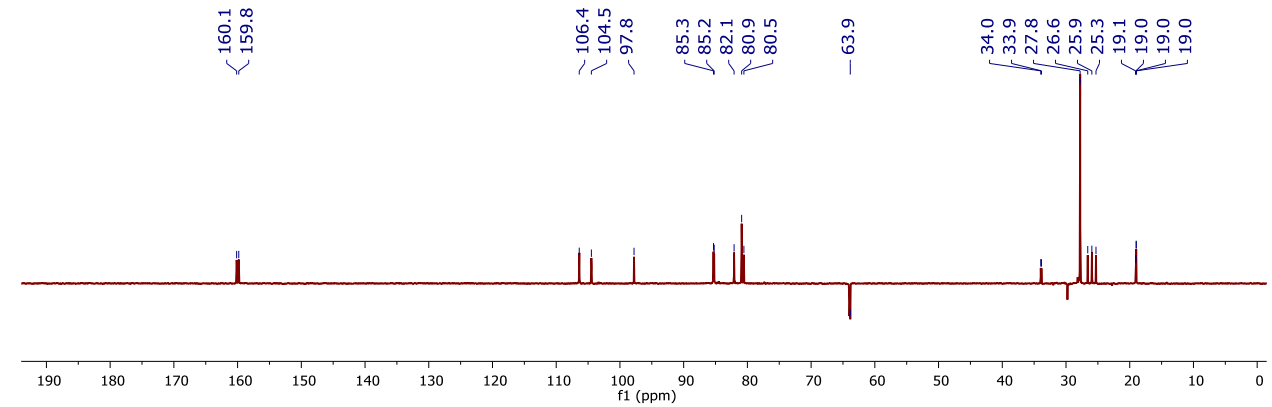
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **8**



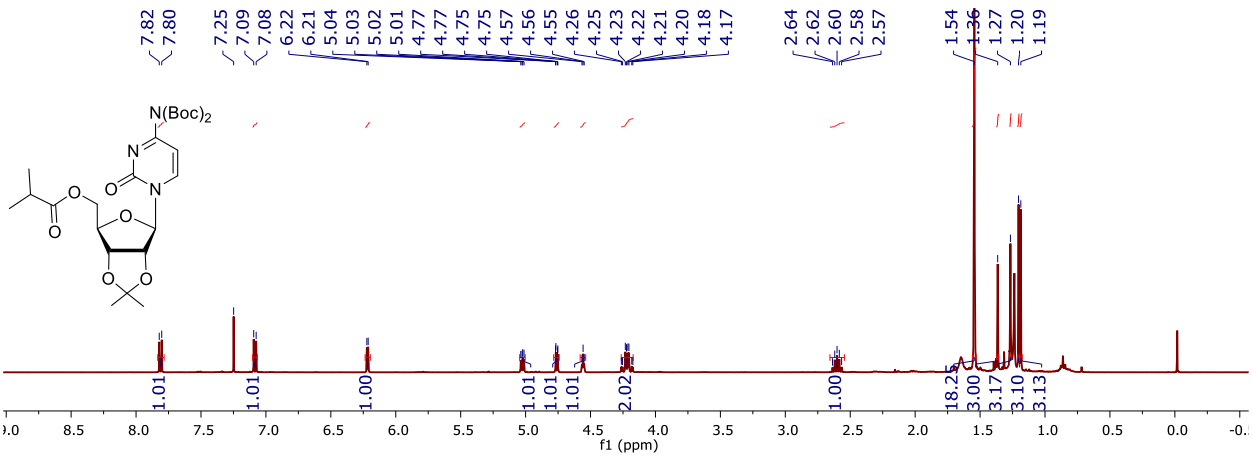
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **8**



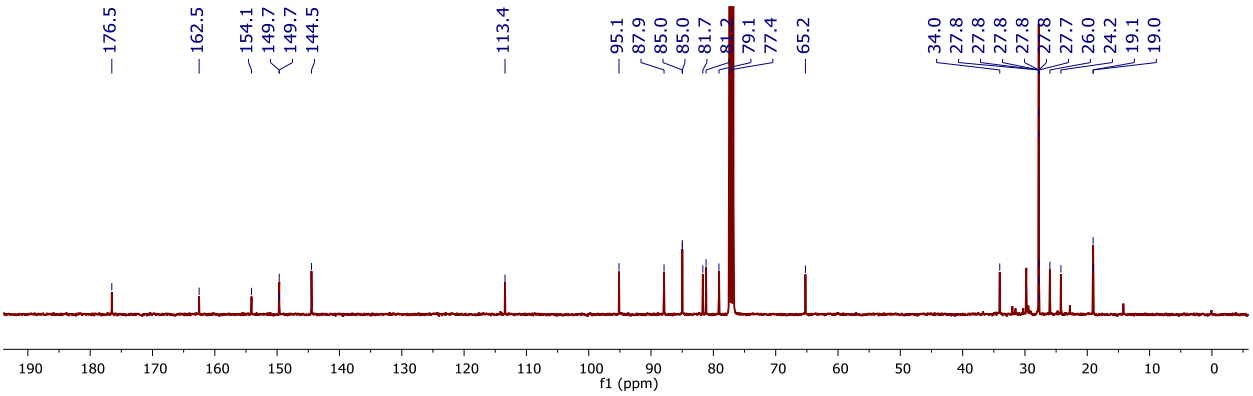
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **8**



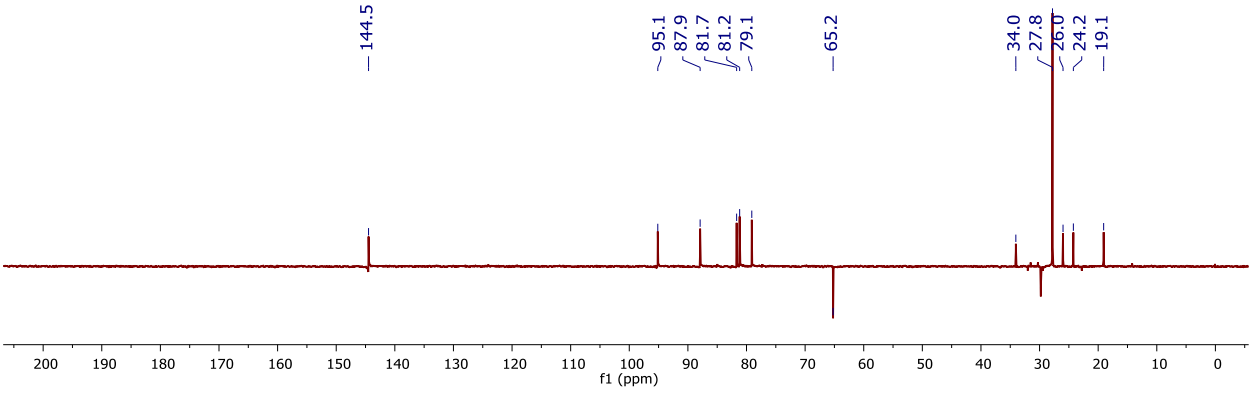
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **9**



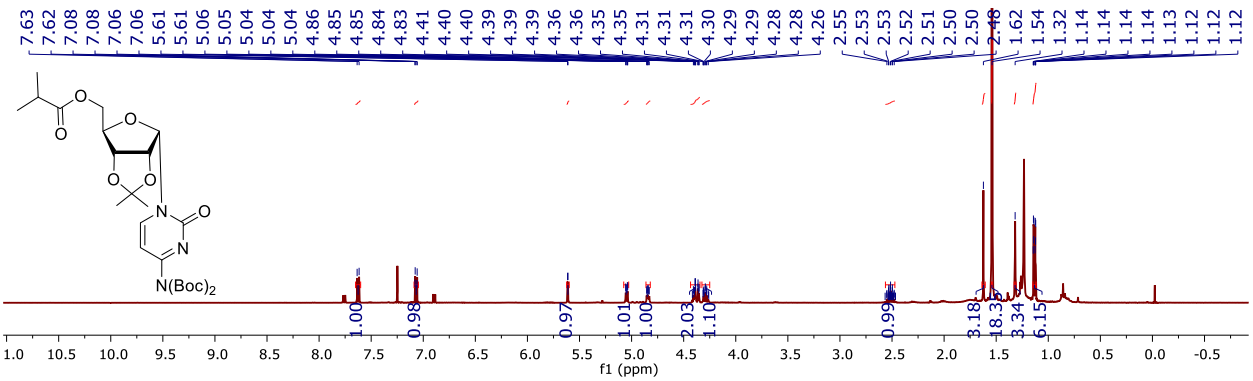
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **9**



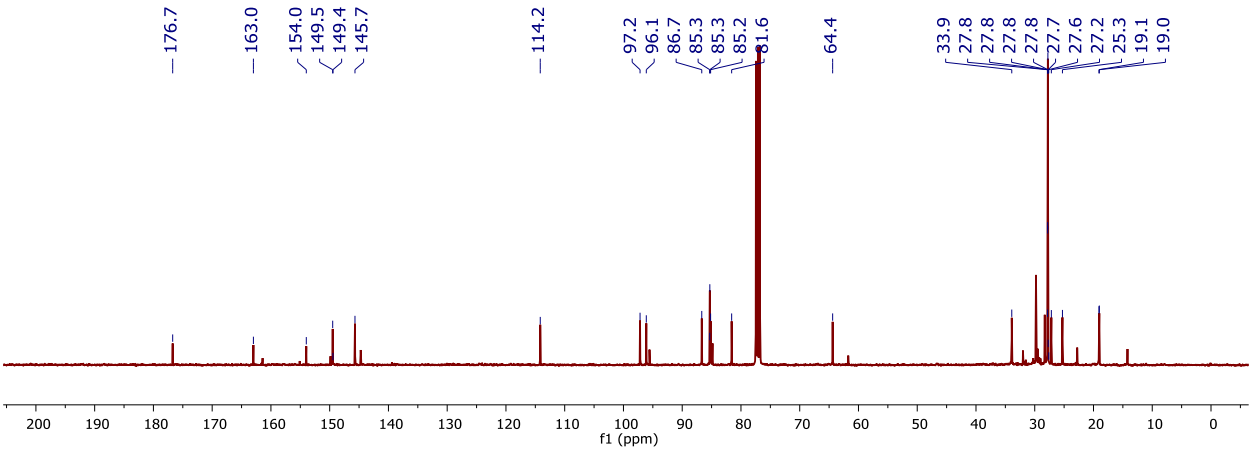
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **9**



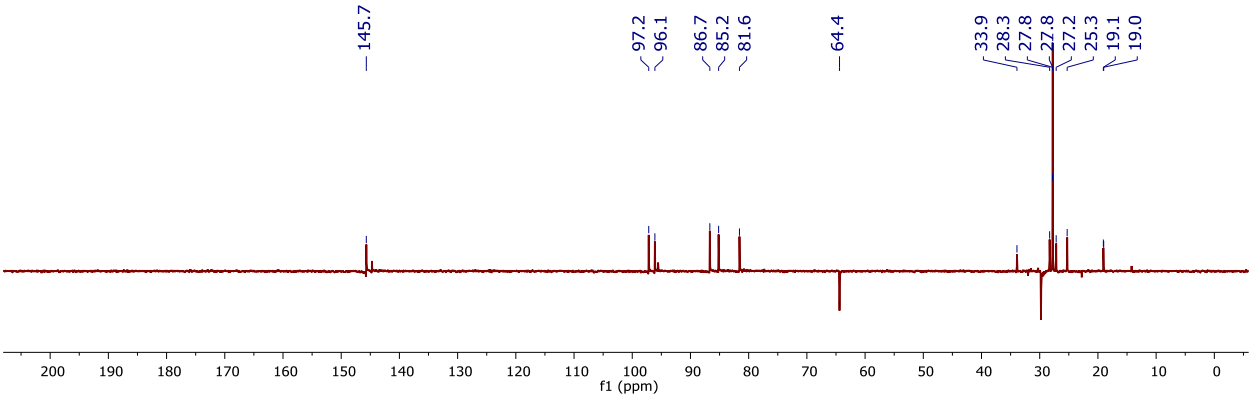
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **10**



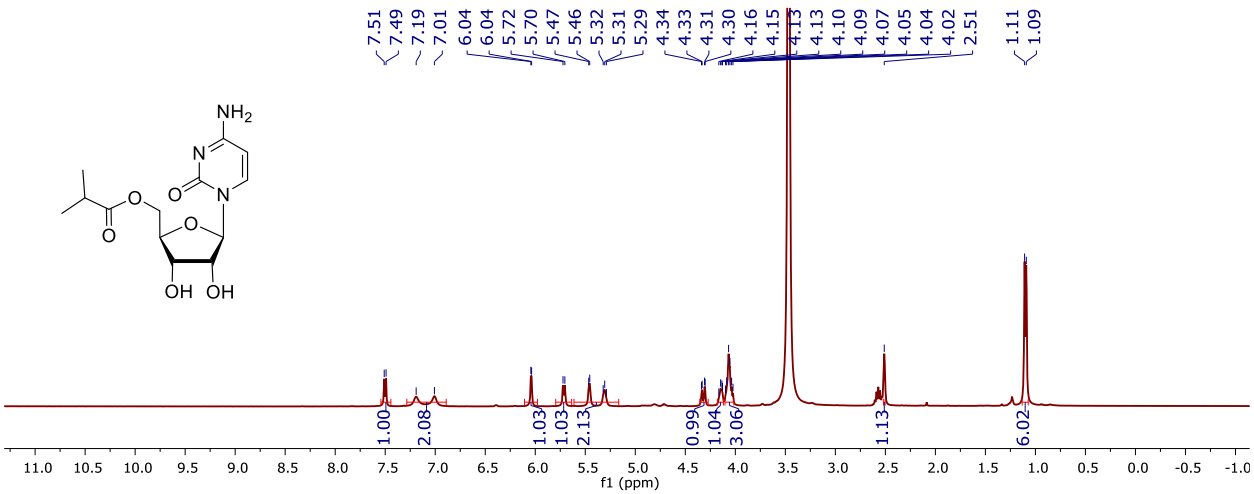
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **10**



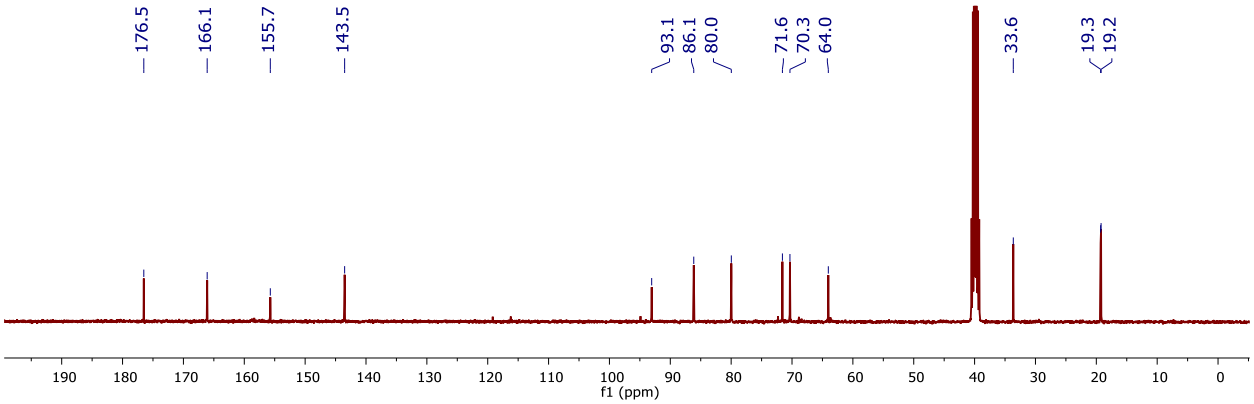
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **10**



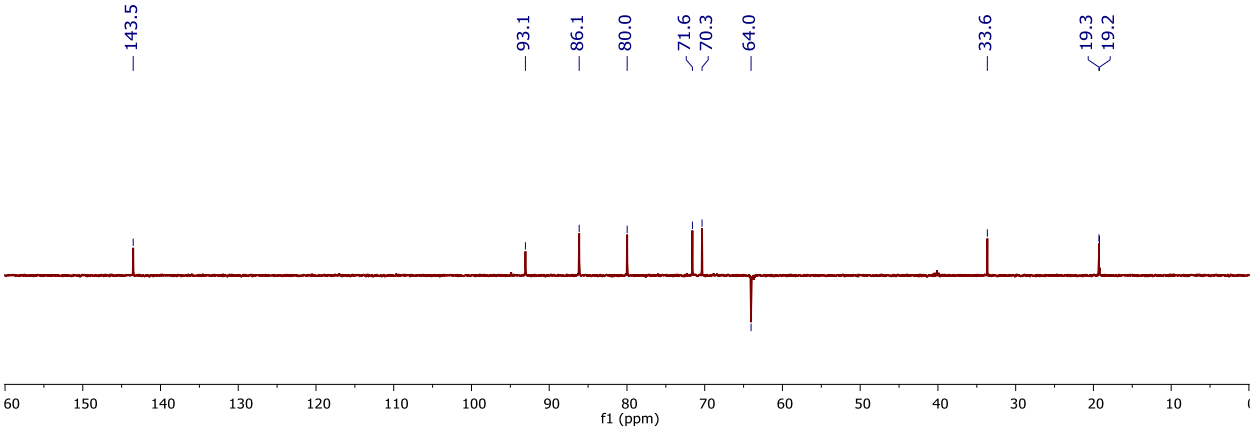
^{1}H NMR Spectrum (400.31 MHz, DMSO-*d6*) of Compound **11**



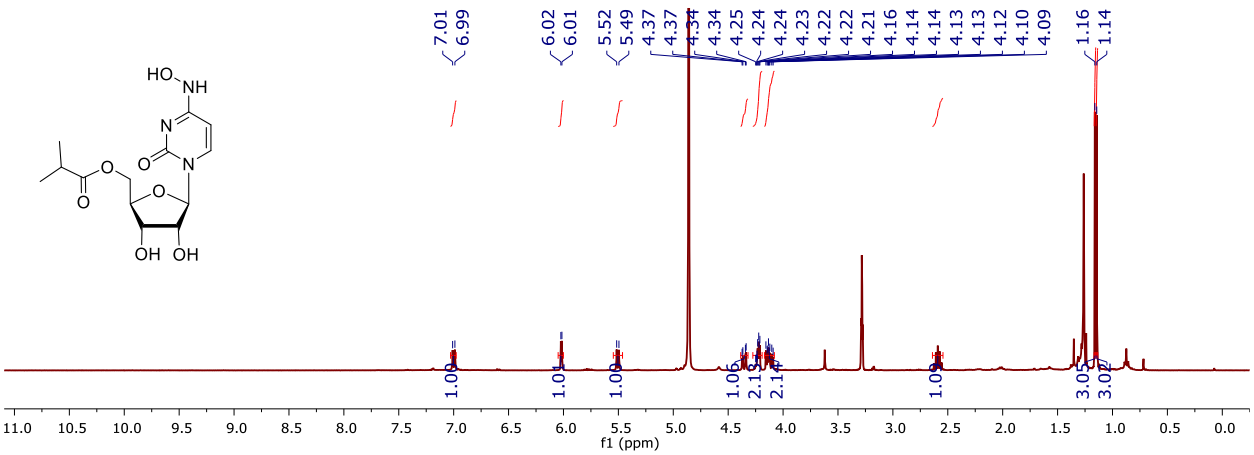
^{13}C NMR Spectrum (100.67 MHz, DMSO-*d6*) of Compound **11**



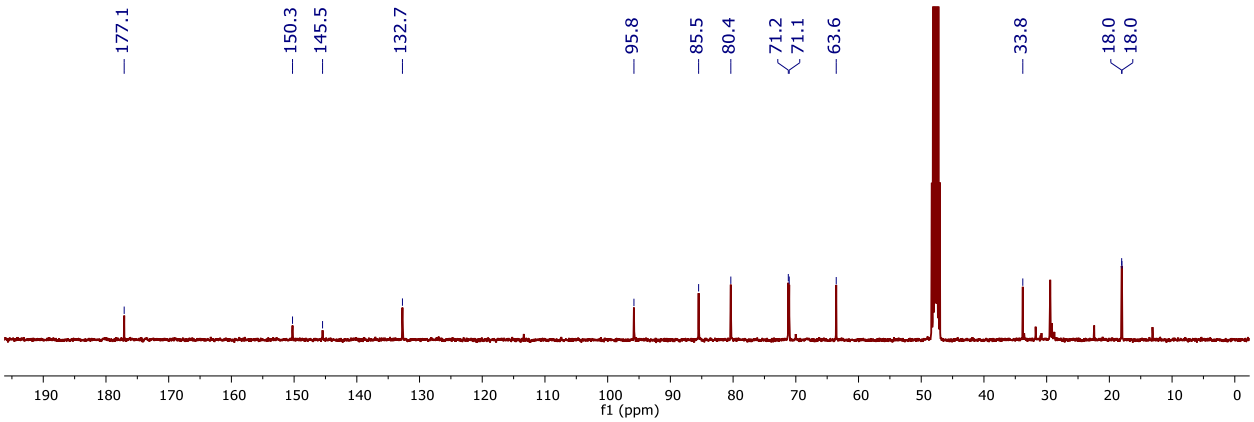
DEPT-135 NMR Spectrum (100.67 MHz, DMSO-*d6*) of Compound **11**



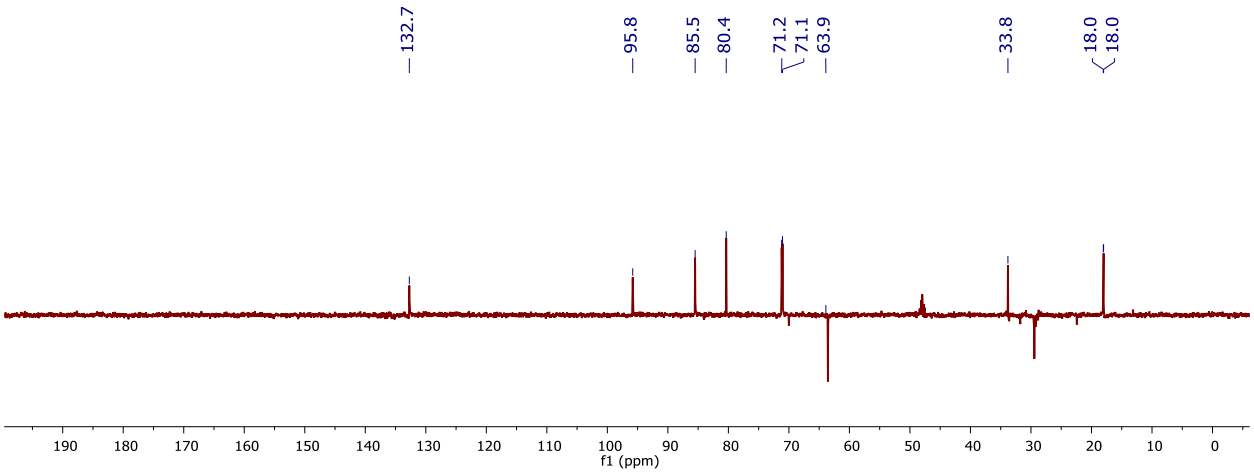
^{1}H NMR Spectrum (400.31 MHz, MeOH-*d4*) of Compound **1**



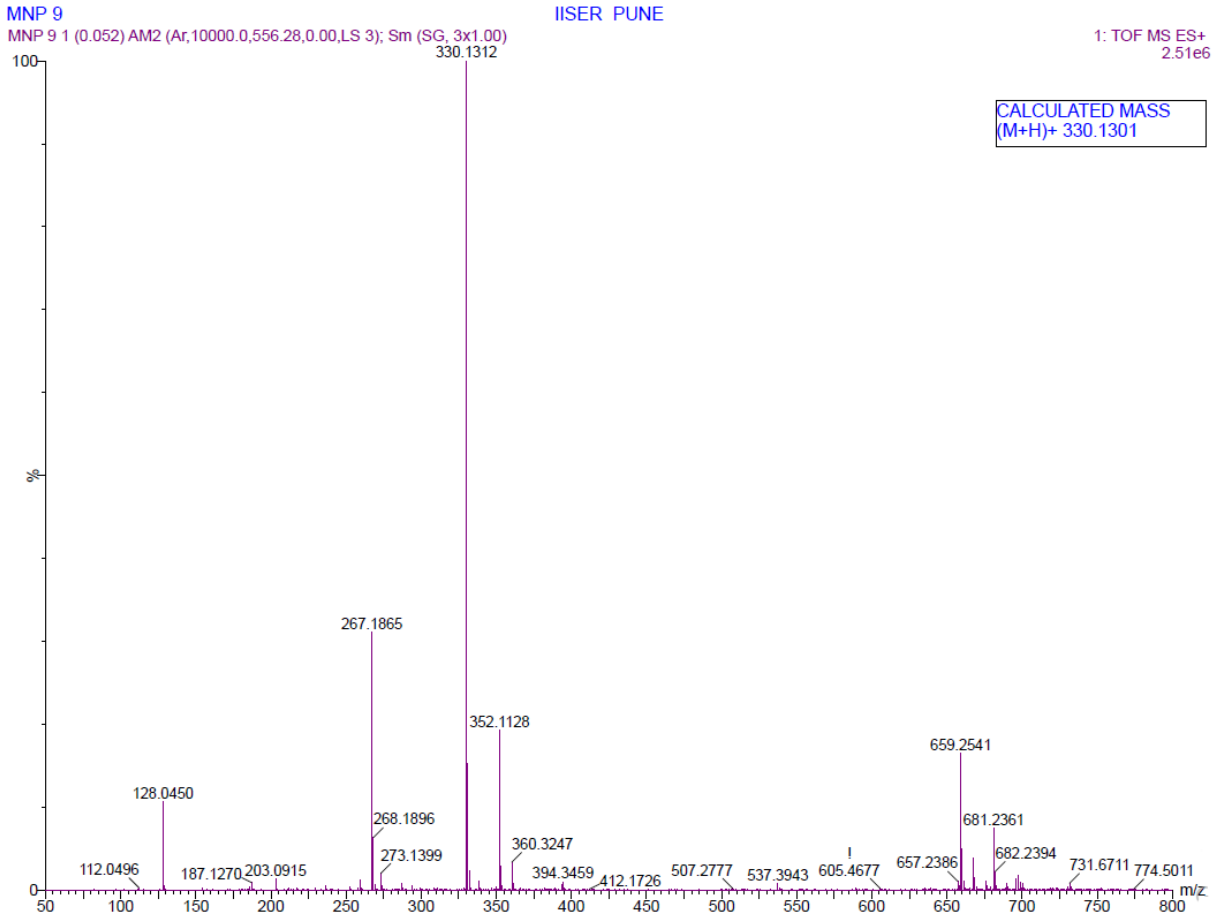
^{13}C NMR Spectrum (100.67 MHz, MeOH-*d4*) of Compound **1**



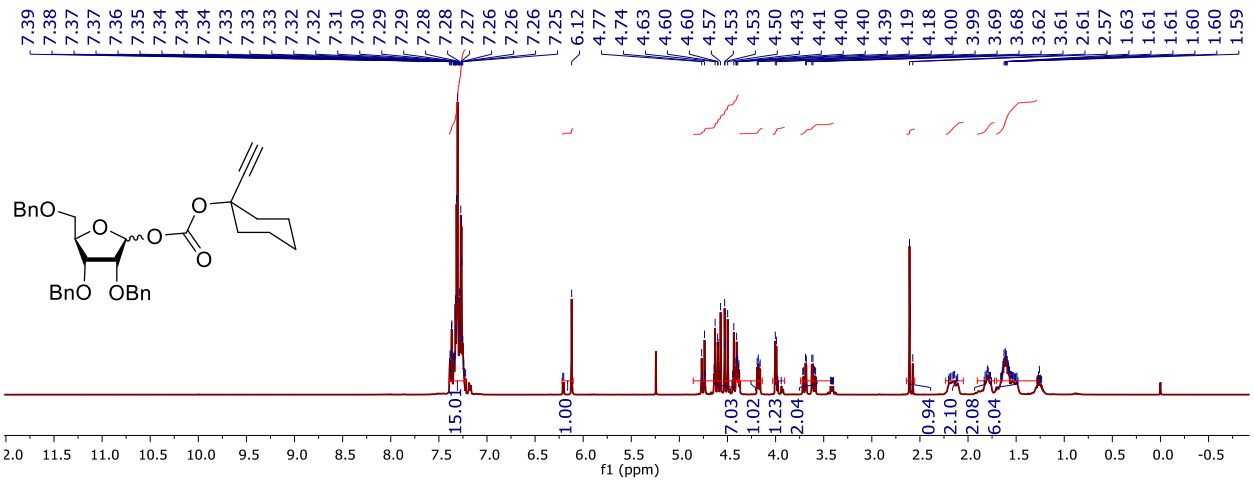
DEPT-135 NMR Spectrum (100.67 MHz, MeOH-*d4*) of Compound **1**



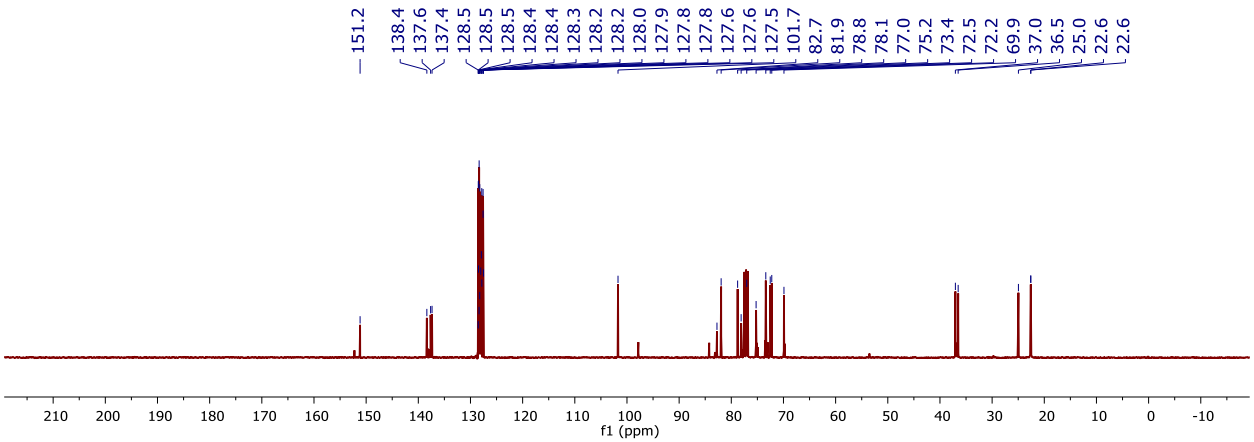
HRMS Spectrum of Compound **1**



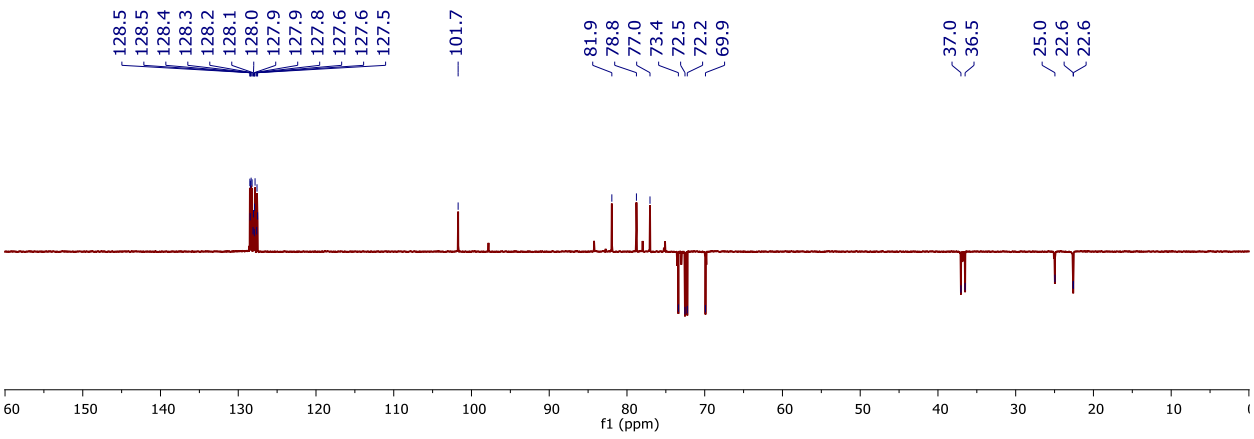
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **GD 1**



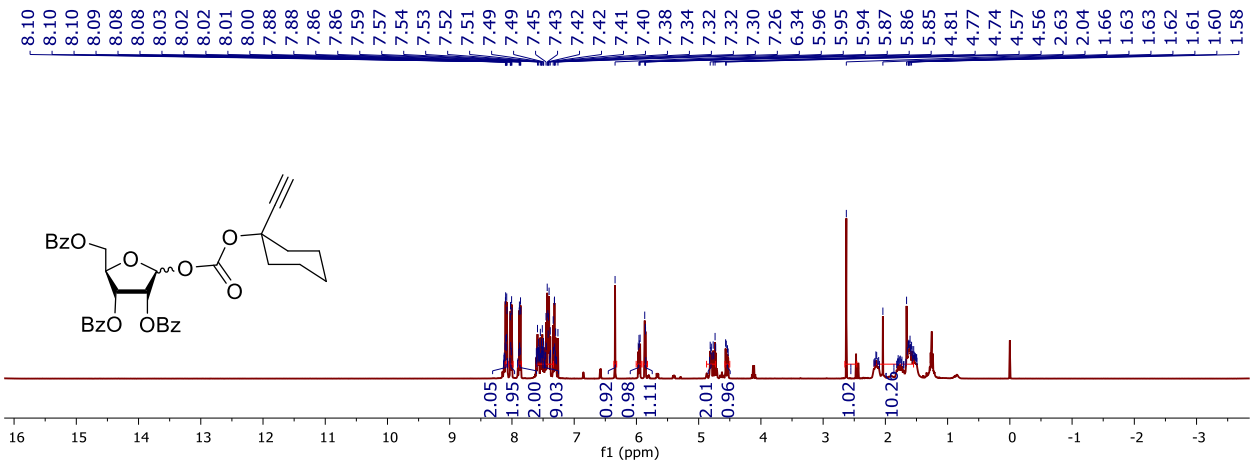
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **GD 1**



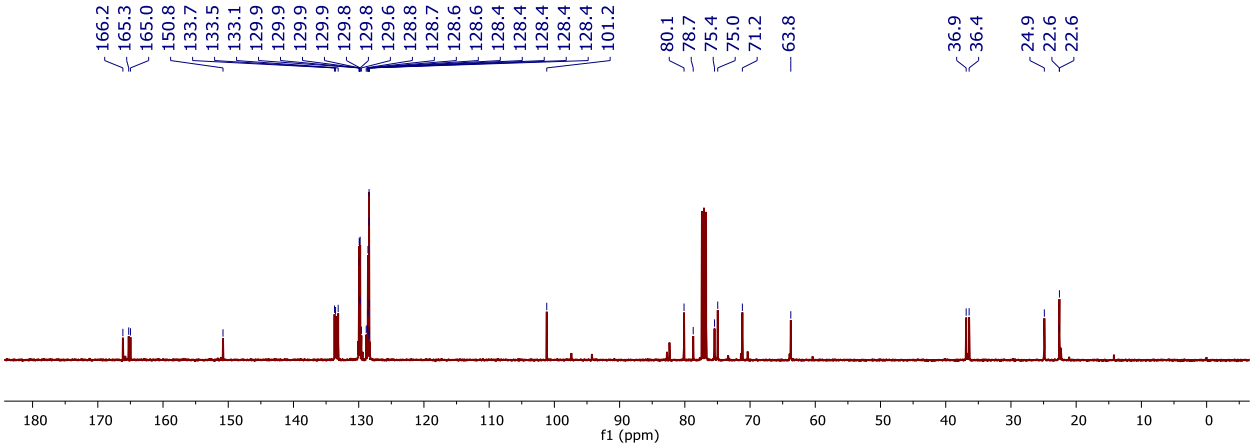
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **GD 1**



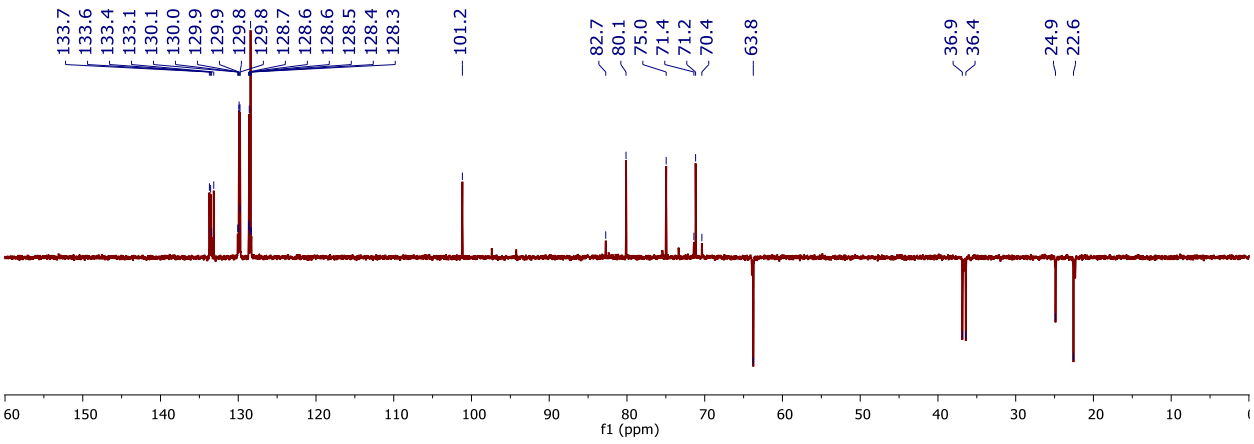
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **GD 2**



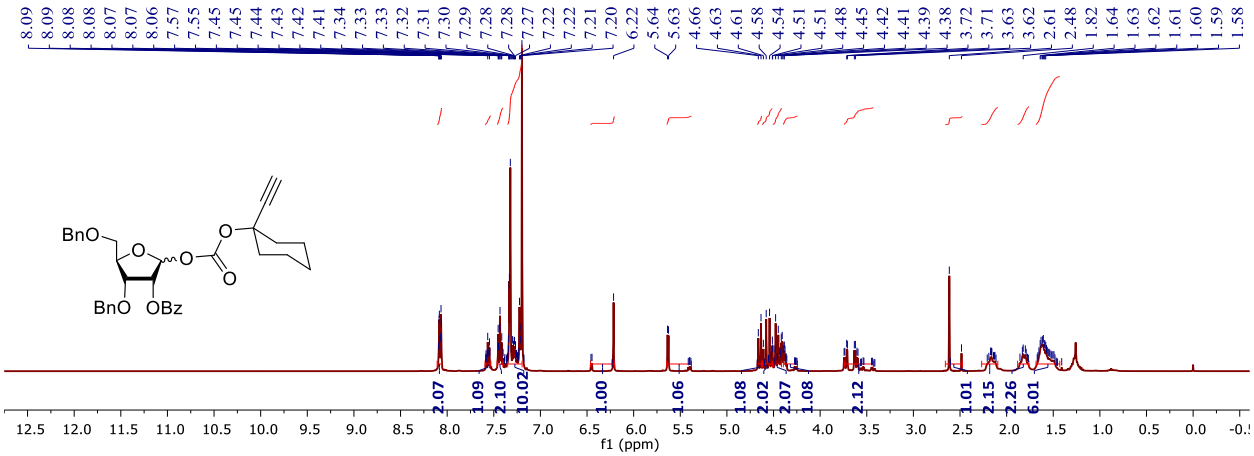
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **GD 2**



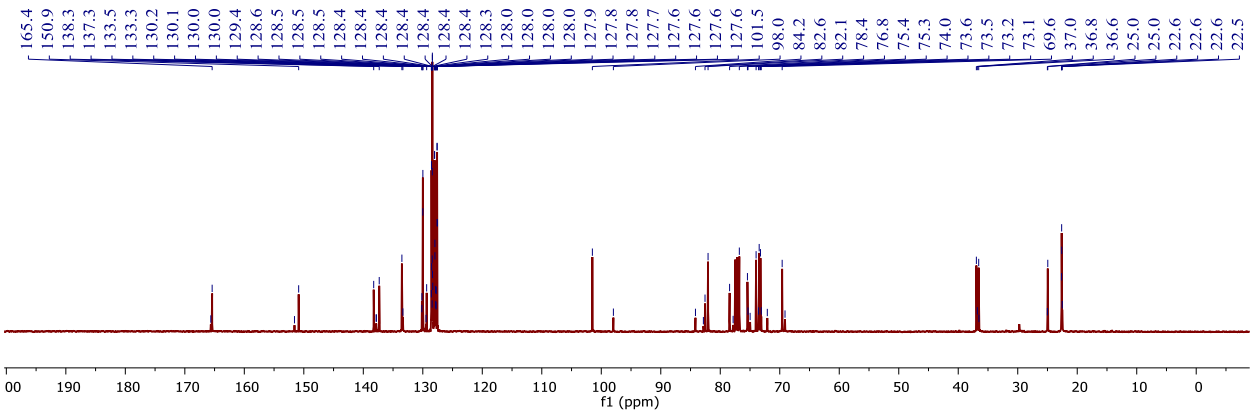
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **GD 2**



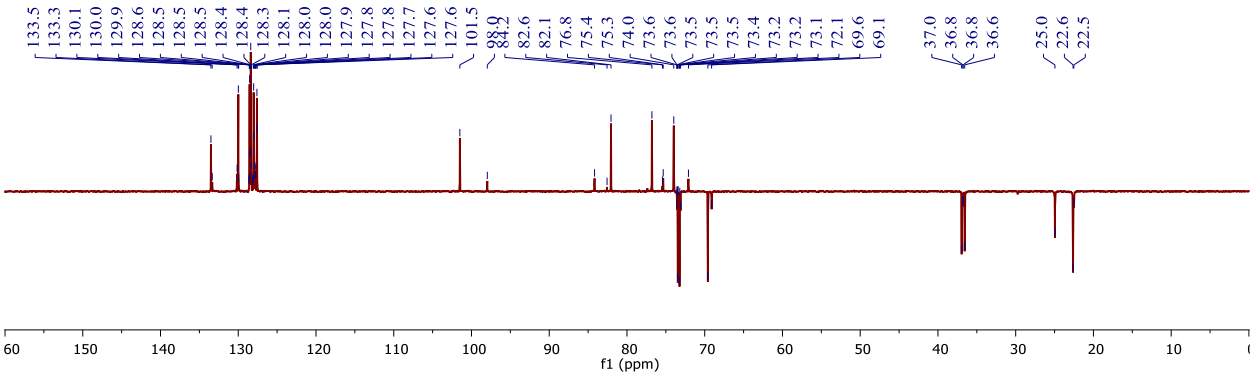
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **GD 3**



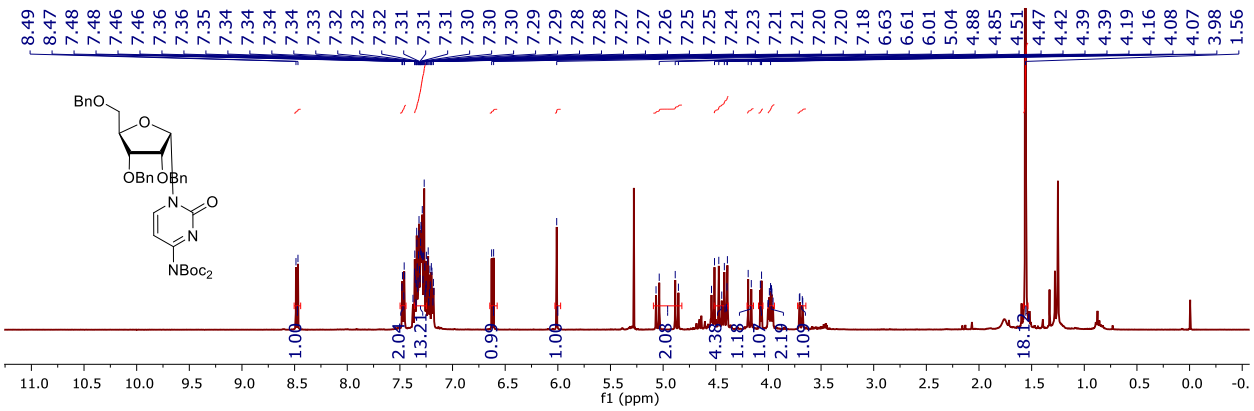
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **GD 3**



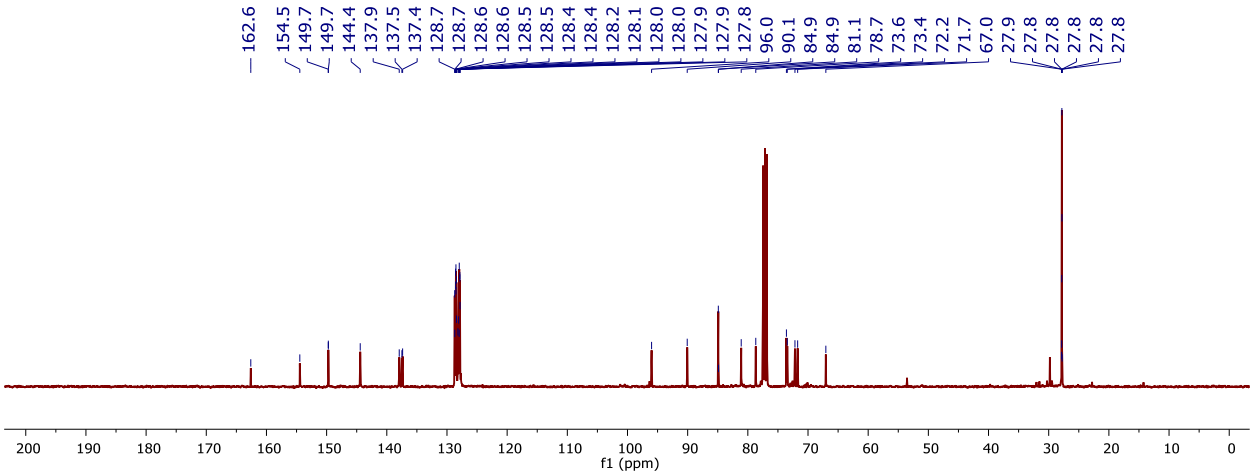
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **GD 3**



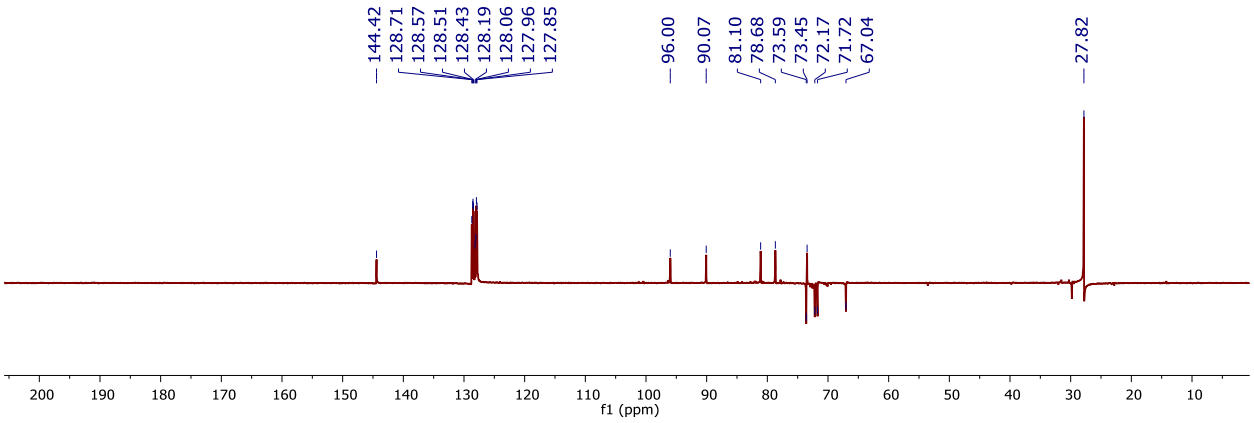
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **P1 α**



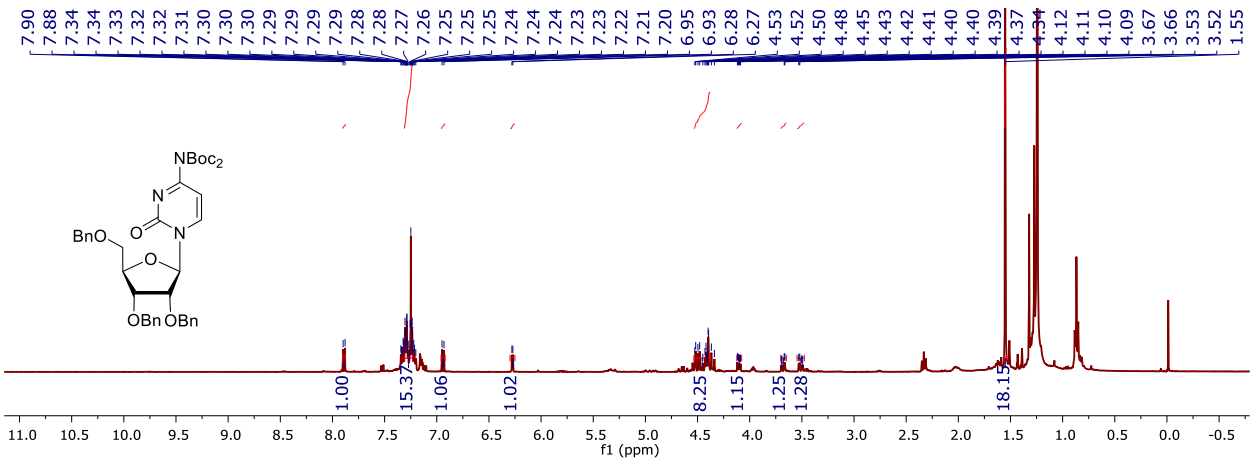
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **P1 α**



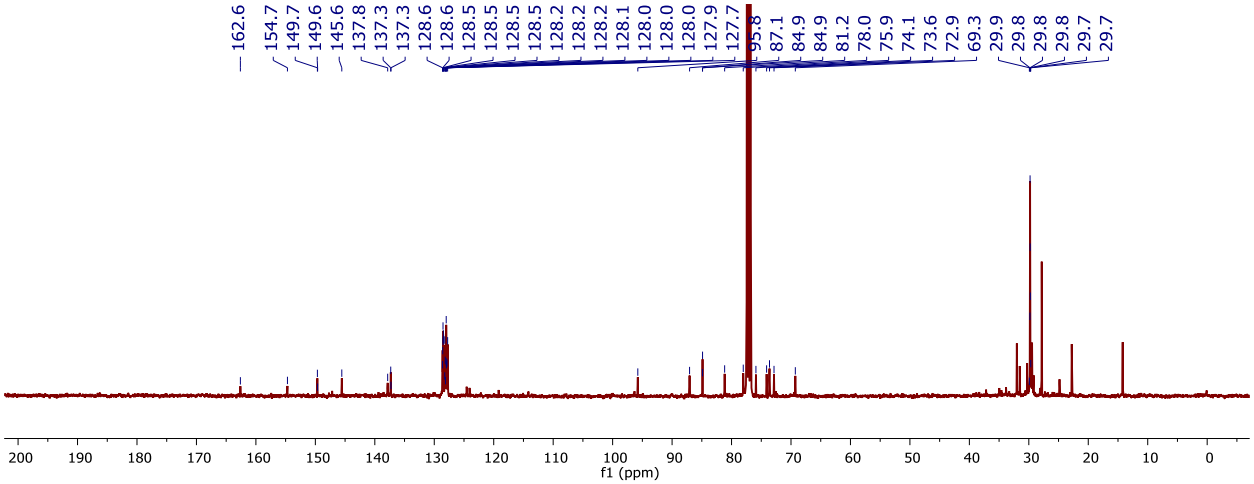
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **P1 α**



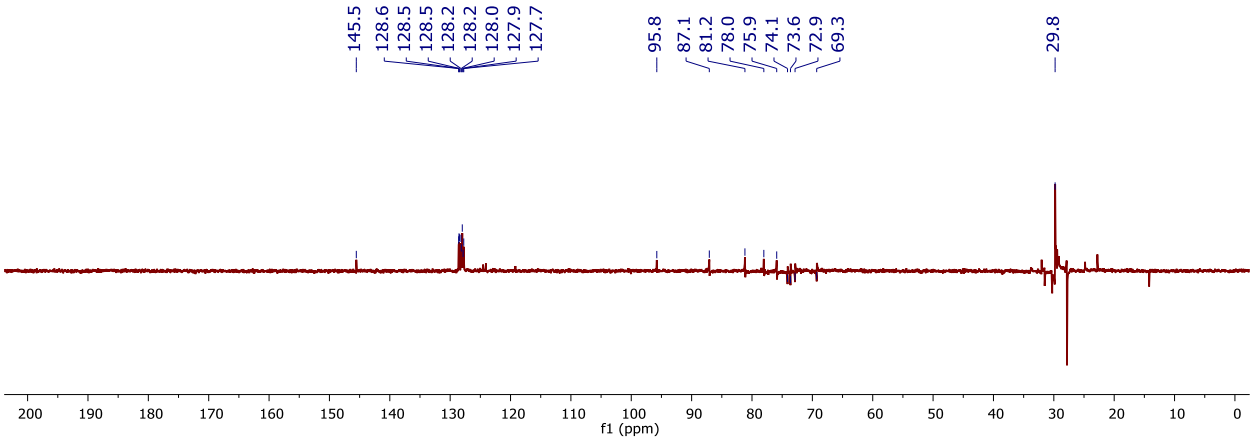
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **P1 β**



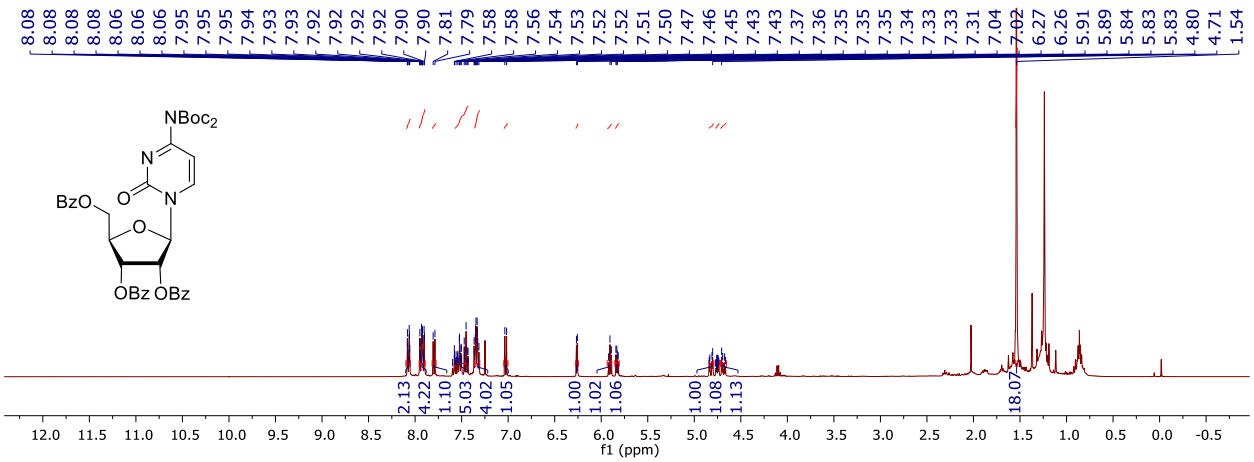
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **P1 β**



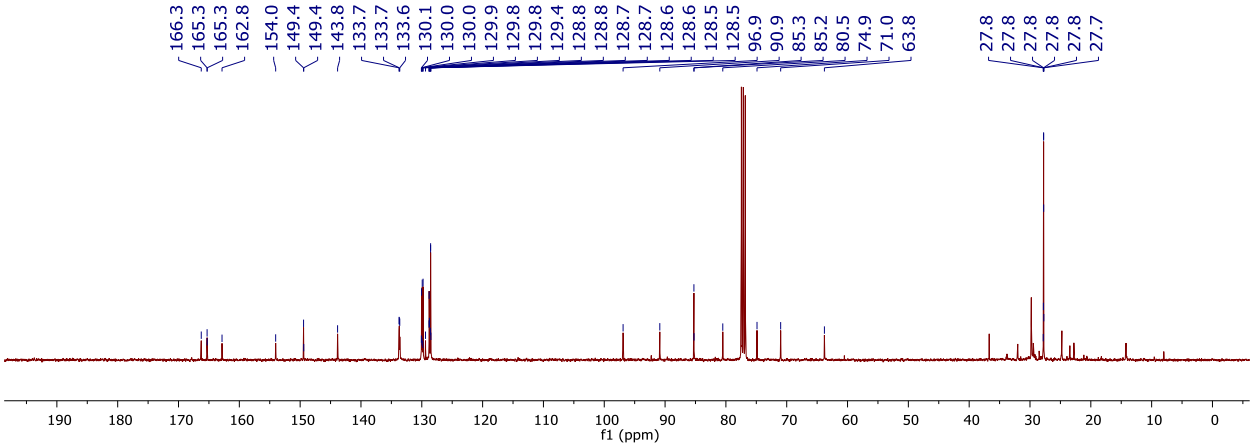
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **P1 β**



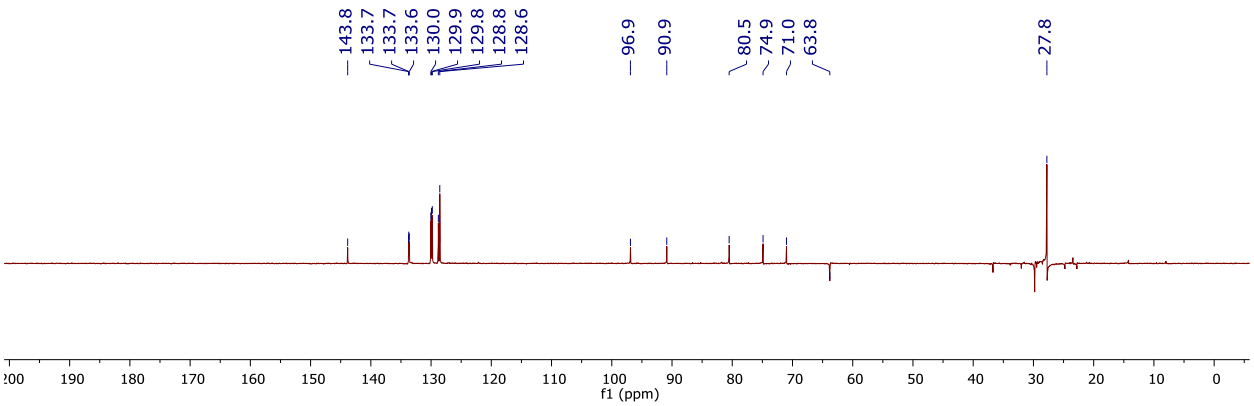
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **P2**



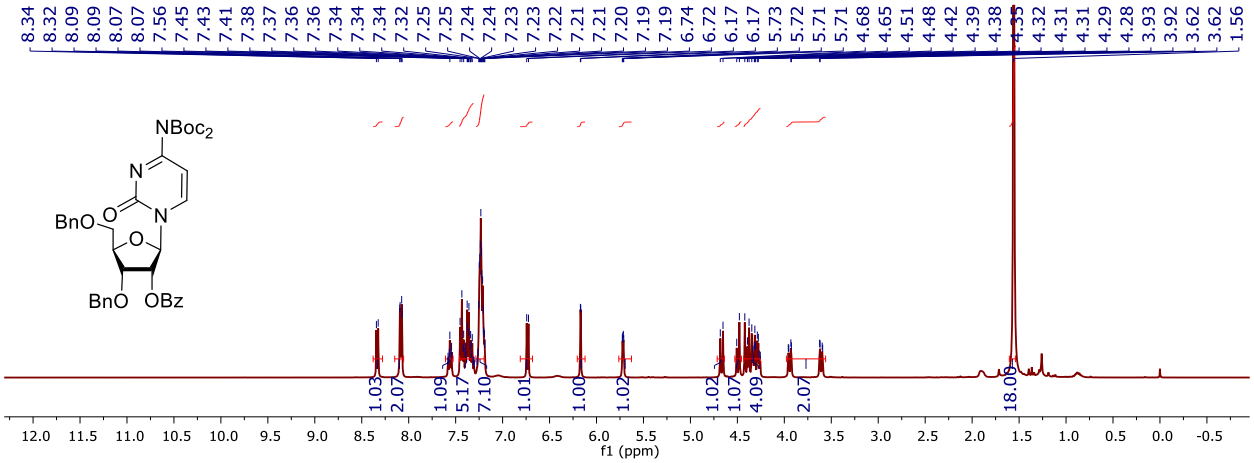
^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **P2**



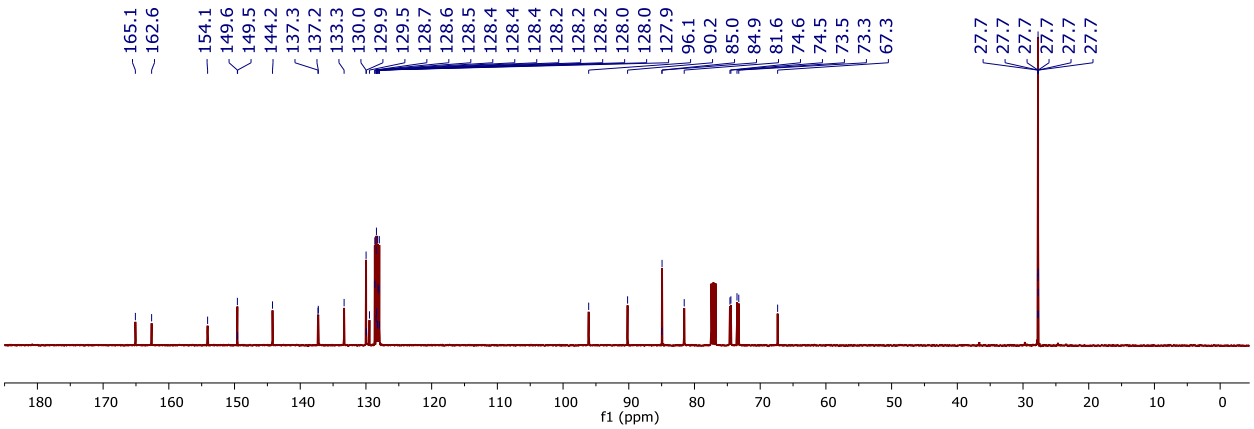
DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **P2**



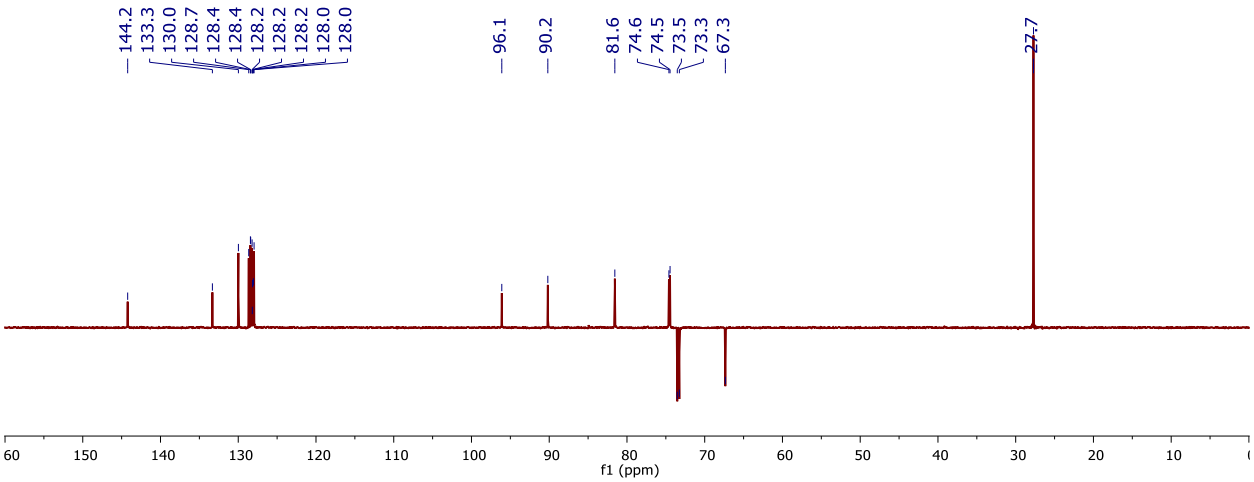
^{1}H NMR Spectrum (400.31 MHz, $CDCl_3$) of Compound **P3**



^{13}C NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **P3**



DEPT-135 NMR Spectrum (100.67 MHz, $CDCl_3$) of Compound **P3**



4.7. References:

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List of Publications

1. Stable Benzylic (1-Ethynylcyclohexanyl)carbonates Protect Hydroxyl Moieties by the Synergistic Action of [Au]/[Ag] Catalytic System, Saptashwa Chakraborty, Bijoyananda Mishra, Mahesh Neralkar and Srinivas Hotha*, *J. Org. Chem.* **2019**, *84*, 6604−6611

2. Synthesis of the hyper-branched core tetrasaccharide motif of chloroviruses, Bijoyananda Mishra, Sujit Manmode, Gulab Walke, Saptashwa Chakraborty, Mahesh Neralkar and Srinivas Hotha*, *Org. Biomol. Chem*., **2021**,*19*, 1315-1328

3. Glycosylation in the green chemistry era, Sujit Manmode, Saptashwa Chakraborty, Yogesh Sutar, Madhuri Vangala and Srinivas Hotha*, In *Carbohydrate Chemistry*, **2021**, pp. 131-156, (Book Chapter)

4. Saptashwa Chakraborty, Bijoyananda Mishra, Pratim Das, Sandip Pasari, and Srinivas Hotha* Synthesis of N-glycosides by Silver Assisted Gold Catalysis. *Angew. Chem Int. Ed.* (just accepted) (https://doi.org/10.1002/anie.202214167)

5. Saptashwa Chakraborty, Daksh Telang, Bijoyananda Mishra, and Srinivas Hotha* [Au]/[Ag]-Catalysed Glycosidation of Glycosyl Alkynyl Carbonate Donors for the synthesis of *C*-glycosides (Manuscript under preparation)

6. Saptashwa Chakraborty, Yogesh Sutar, Jayshree Rajput and Srinivas Hotha* Establishing shortest chemical route for the synthesis of Molnupiravir from Ribose and Cytosine (Manuscript communicated)

7. Saptashwa Chakraborty, Bijoyananda Mishra, and Srinivas Hotha* Convergent total synthesis of Branched High-Mannan oligosaccharide fragment present in *T. acidophilum*, using Glycosyl Alkynyl Carbonate Donors (work is under progress)

8. Saptashwa Chakraborty, Pratim Das, Bodhayan Biswas, Bijoyananda Mishra, and Srinivas Hotha* Expedient synthesis of Tridecasaccharide motif present on HIV envelope trimer GP-41 (work is under progress)