Editing of *N*-Glycans for Active Pharmaceutical Ingredients

A THESIS

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS

OF THE DEGREE OF

Master of Science

by

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2024

Under the Supervision of:
Prof. Srinivas Hotha

Dedicated to….

My Parents

Certificate

This is to certify that this dissertation entitled "***Editing of N-Glycans for Active Pharmaceutical Ingredients***" towards the partial fulfilment of the MS degree program at the Indian Institute of Science Education and Research, Pune represents study/work carried out by "Suman Kundu" under the supervision of "Prof. Srinivas Hotha, Department of Chemistry" during the academic year 2023-2024.

Date: 25 March 2024

Pune (MH), India

Srinivas Hotha

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 "**Editing of N-Glycans for Active Pharmaceutical Ingredients**" 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.

Date: 25 March 2024

Pune (MH), India

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I express my heartfelt gratitude and best wishes to all my friends and batchmates for their support, and encouragement and for making my stay here worthwhile at IISER Pune.

Above all, I would like to thank my parents for always being there with me and for their constant guidance and blessings. This small piece of work is dedicated to them.

Contents:

Abbreviations:

Å	Angstrom
Ac	Acetate
Bn	Benzyl
Bz	Benzoyl
BzCN	Benzoyl cyanide
Cat.	Catalytic
$CDCl_3$	Chloroform-*d*
$CHCl_3$	Chloroform
DCM	Dichloromethane
DEPT	Distortion less Enhancement by polarization transfer
DMAP	N, N- Dimethyl aminopyridine
DMSO	Dimethyl Suphoxide
DMF	N, N- Dimethyl formamide
Eq.	Equivalents
Et_3N	Triethyl amine
EtOAc	Ethyl acetate
gm.	Gram
HRMS	High-resolution mass spectrometry
Hz	Hertz
J	Coupling constant
MeOH	Methanol
Mg	Milligram
Min.	Minutes
MHz	Megahertz
mL	Millilitre
MS	Molecular Sieves
NIS	N-Iodo Succinimide
NMR	Nuclear Magnetic Resonance
ppm	Parts per million
rt	Room temperature
TfOH	Trifluoro methane sulfonic acid
TLC	Thin Layer Chromatography

Abstract

Analogues of nucleosides are highly significant in the realm of small molecule pharmaceuticals, serving as essential constituents in biological systems and playing a crucial role in treating cancer and viral infections as effective therapeutic agents. Synthesis of nucleosides in a cost-effective way from readily accessible starting material is still a formidable challenge, despite their widespread presence in DNA or RNA. Herein, we report the synthesis of purine and pyrimidine nucleosides using commercially available purine nucleosides through a one-step chemical transglycosylation approach. The method demonstrates effectiveness, selectivity, and wide applicability, facilitating easy synthesis of various complex *O*- *S*-, and *N*-glycosides in a streamlined fashion. Significantly, this editing strategy was further demonstrated by the syntheses of nucleoside antibiotics Ribavirin, 5-azacytidine, and Tubercidin.

Introduction:

Carbohydrates are one of the most abundant forms of biomolecules found in Nature, playing crucial roles in various living organisms. They contribute to structural integrity, participate in essential biological processes such as cell adhesion, interact with pathogens, and serve as vital components in energy storage and utilization.[1] Additionally, carbohydrates serve as fundamental building blocks for complex molecules. Diseases like cancer, hepatitis, and HIV, result from the direct involvement of carbohydrates in cellular processes. Hence, synthesizing effective resistant drugs requires a critical understanding of carbohydrates and their derivatives. Glycoconjugates[2,3] involve the covalent linkage of carbohydrates with functional groups, including proteins (glycoproteins) and lipids (glycolipids).[4] Among glycoconjugates, *N*-glycosides hold particular importance as they serve as the foundation for DNA and RNA.

N-glycosides:

N-Glycosides are compounds characterized by a carbohydrate unit attached to an aglycon through an anomeric C-N linkage. These are an essential class of carbohydrate compounds that exist in Nature and have immense importance in therapeutics. Among the notable *N*-glycosides, nucleosides stand out prominently, where a sugar moiety is covalently bonded to a nucleobase (Figure 1.1). Nucleosides play vital roles in various cellular processes, including the synthesis of DNA and RNA, enzyme regulation, and other metabolic activities.[5] While numerous naturally occurring nucleosides exist, adenosine, guanosine, cytidine, thymidine, and uridine (Figure 1.2) are the most well-known, playing essential roles in DNA, RNA, and various biological processes.

Modified nucleoside compounds hold significant importance in medicinal chemistry due to their presence in biomacromolecules and antibiotics. These substances are currently being studied for their potential to combat viruses and cancers that have become resistant to conventional treatments. Researchers are interested in nucleoside analogs, which are artificially created compounds meant to mimic natural nucleosides. These analogs can be inserted into DNA and RNA, hindering them from replicating and dividing properly.[6] They can also block key enzymes such as polymerases and kinases, which are

necessary for the functioning of viruses and human cells. In the fight against viruses like Hepatitis B virus (HBV), human immunodeficiency virus (HIV), Herpes simplex virus (HSV), Hepatitis C virus (HCV), and cytomegalovirus (CMV), modified nucleoside analogs have shown effectiveness. Overall, these modified *N*-glycosides are important in medicine because they are found in important molecules and can be used to develop new treatments for diseases.[7]

Despite the immense potential, the synthesis of *N*-glycosides has posed considerable challenges. Over the past decades, considerable efforts have been invested in developing novel synthesis methods for various *N*-linked glycosides. However, compared to the synthesis of *O*-, *S*-, and *C*-glycosides progress has been relatively limited for *N*-glycosides. The complexity arises due to the compatibility challenges between the basic nature of N-acceptors and the acidic reaction conditions typically used in glycosylation protocols. Another substantial obstacle is the poor solubility of many *N*-nucleophiles under typical organic solvents and reaction conditions. Addressing these challenges remains a focal point for advancing the synthesis of *N*-glycosides in medicinal chemistry.

Nucleoside Structure and Conformation:

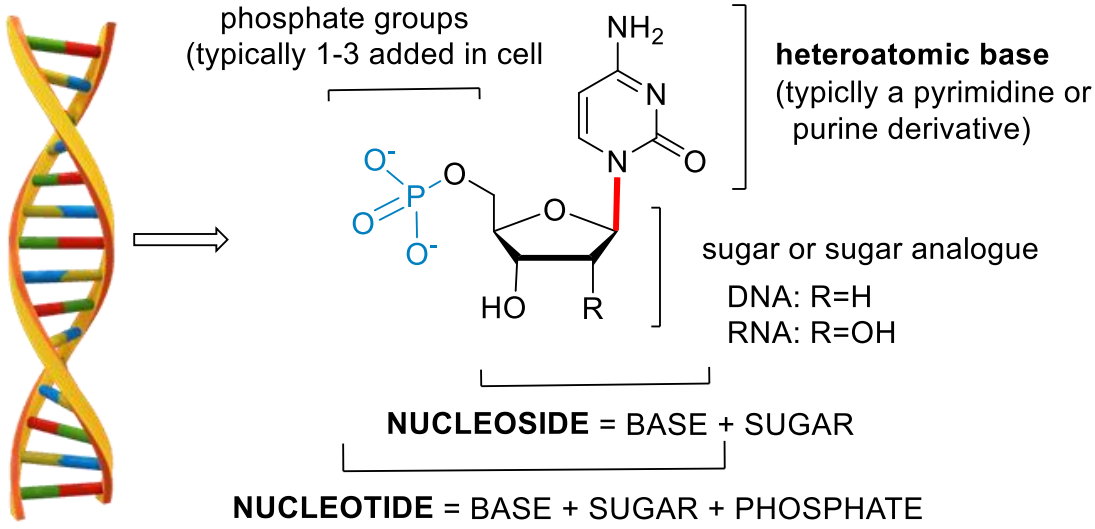


Fig. 1.1: Nucleoside Structure and Conformation

Bases commonly occurring in DNA and RNA:

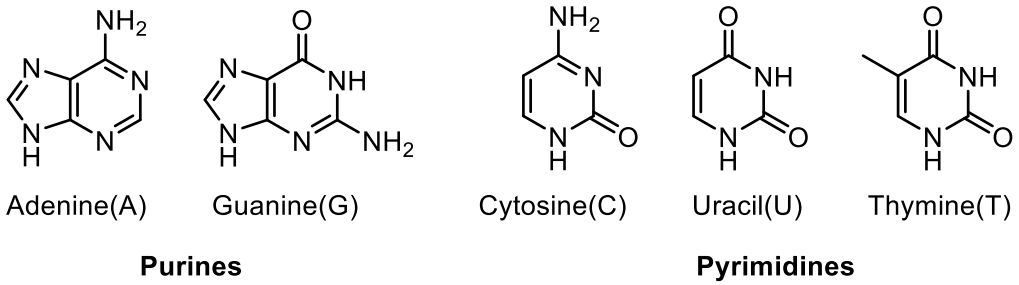


Fig. 1.2: Structures of the base pairs present in DNA and RNA

Configuration of nucleosides:

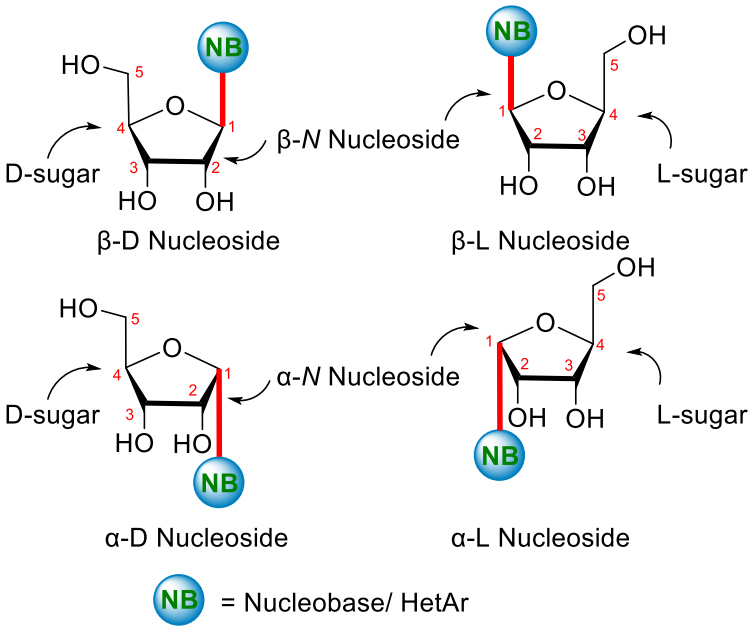
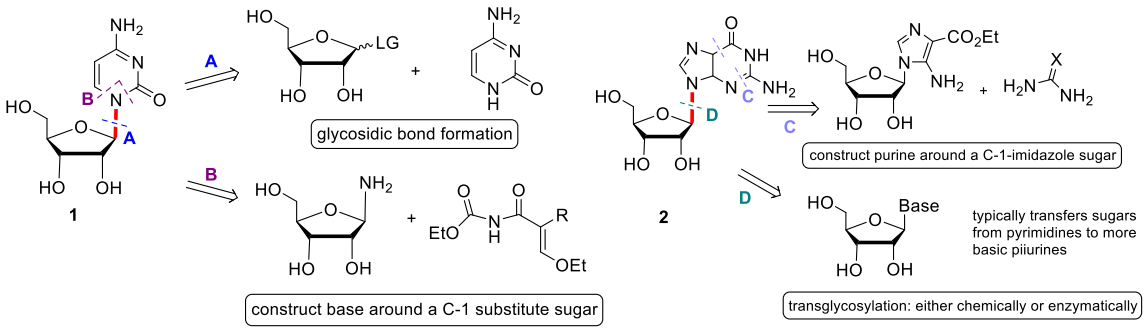


Fig. 1.3: Stereochemical Configuration of nucleosides

Approaches for the creation of *N*-glycosides:

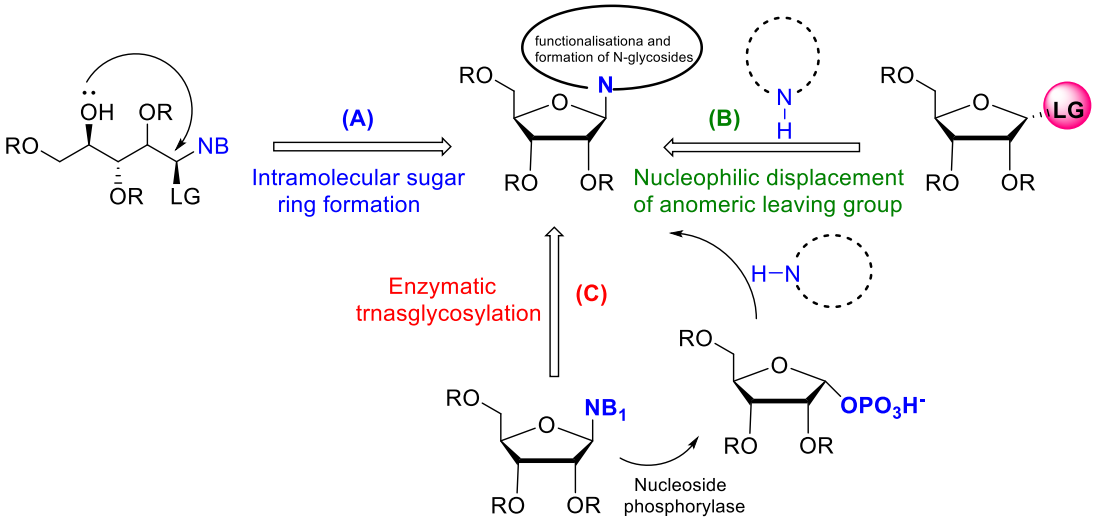
The strategies to synthesize pyrimidine-type nucleoside **1** (Scheme 1.1) can be accomplished through a standard glycosylation approach, involving the creation of an anomeric leaving group that is subsequently attached to a nucleobase-type acceptor (Scheme 1.1, A). Another viable method includes constructing the base around a C-1 substituted sugar and cyclizing it with an external partner (Scheme 1.1, B). Similar strategies can be employed for the synthesis of purine and its analogs (**2**). In this case,

purine can be formed around a C-1imidazole sugar (C), and the pathway (D) can be pursued using a conventional transglycosylation strategy (Scheme 1.1) to facilitate the transfer of base pairs for nucleoside synthesis.



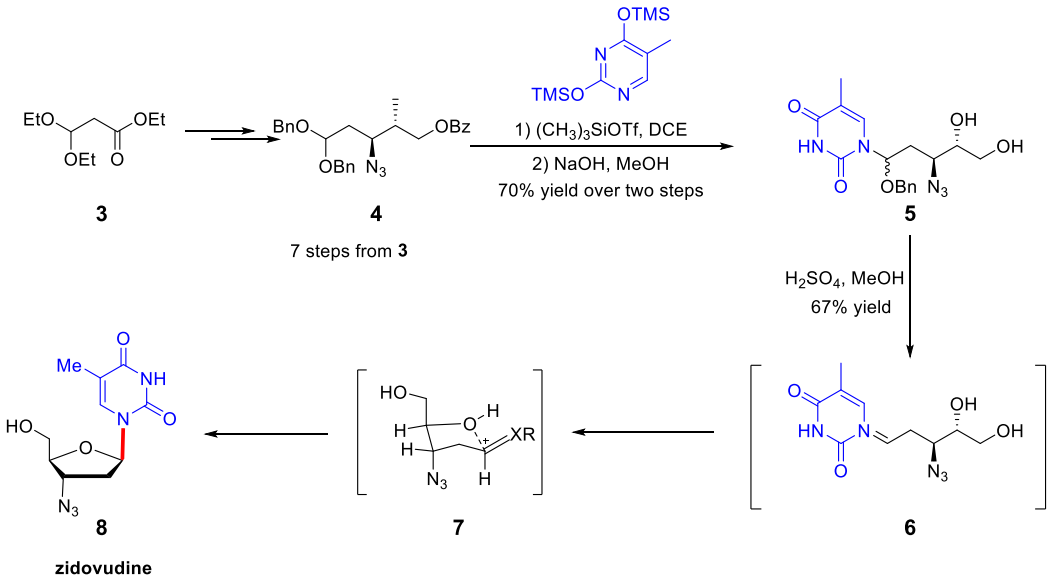
Scheme 1.1: common disconnection towards nucleosides

In the context of the *N*-functionalization of amino sugars and the creation of *N*-glycoside derivatives, there are three primary approaches (Scheme 1.2)[8]: (A) Intramolecular sugar ring formation (B)) Substitution of the leaving group bonded to the anomeric carbon of the carbohydrate moiety by a nucleophile. (C) Chemical or Enzymatic transglycosylation.



Scheme 1.2: Strategies for Nucleoside Synthesis

(A) Intramolecular sugar ring formation:

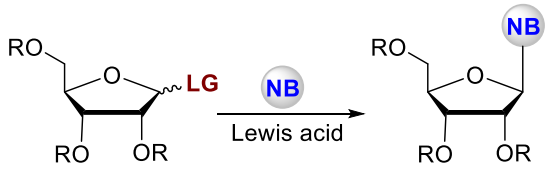


Scheme: 1.3: A method involving intramolecular cyclization utilized in the synthesis of Zidovudine [8]

Recently, notable progress has been achieved in utilizing the chiral pool of carbohydrates as starting precursors for synthesizing nucleosides with stereoselectivity via the *N*-glycosylation approach. Nonetheless, this method entails extensive synthetic steps and lacks versatility in accommodating various stereochemical substituents on the sugar ring through a single synthetic route. One potential solution to this challenge could involve exploring intramolecular sugar ring formation as an alternative strategy.[8]

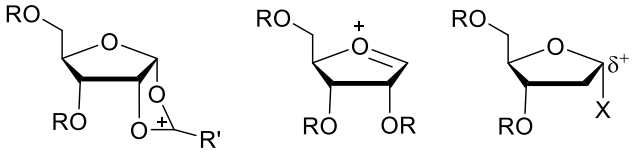
Liotta et al. pioneered a groundbreaking approach in stereoselective cyclization, exemplified the synthesis of Zidovudine (AZT), which is used to treat HIV (Scheme 1.3). They initiated their synthetic route from ethyl 3,3-diethoxypropanoate **3** and synthesized key intermediates **4** over seven synthetic steps which have two stereogenic centers. These intermediates underwent coupling with a silylated thymine base under Vorbrüggen conditions, yielding compound **5**, subsequently undergoing debenzylation. Notably, the exclusive formation of the β-anomer of Zidovudine **8** was achieved under acidic conditions via the iminium ion intermediate **7**. Although their investigation primarily focused on a single nucleoside, this pioneering approach paved the way for employing intramolecular cyclization strategies in the synthesis of diverse nucleosides.[8]

(B) Nucleophilic displacement of anomeric leaving group:



LG: leaving group, **NB**: nucleobase

Via intermediates:



Scheme: 1.4: *N*-glycosylation techniques

The synthesis of β-nucleoside analogs has traditionally involved linking the nucleobase acceptor with a protected sugar activated by a leaving group at the anomeric position. These reactions may follow various pathways, such as the formation of intermediates like 1-2 dioxolenium ion, oxocarbenium ion, or direct nucleophilic attack (Scheme 1.4).[8]

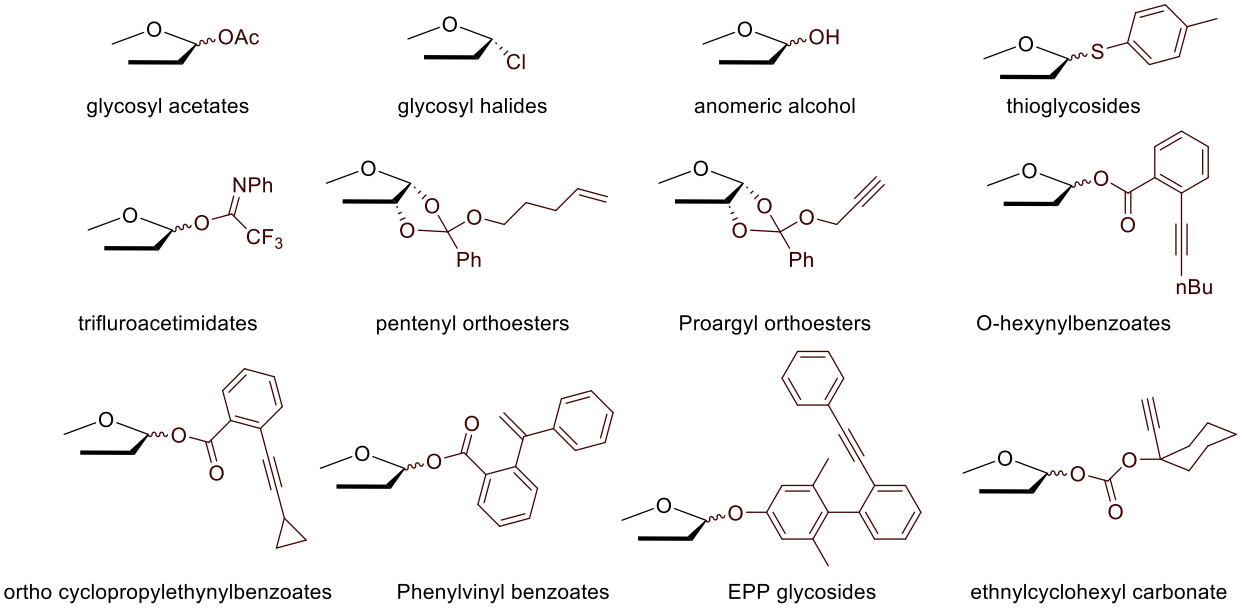


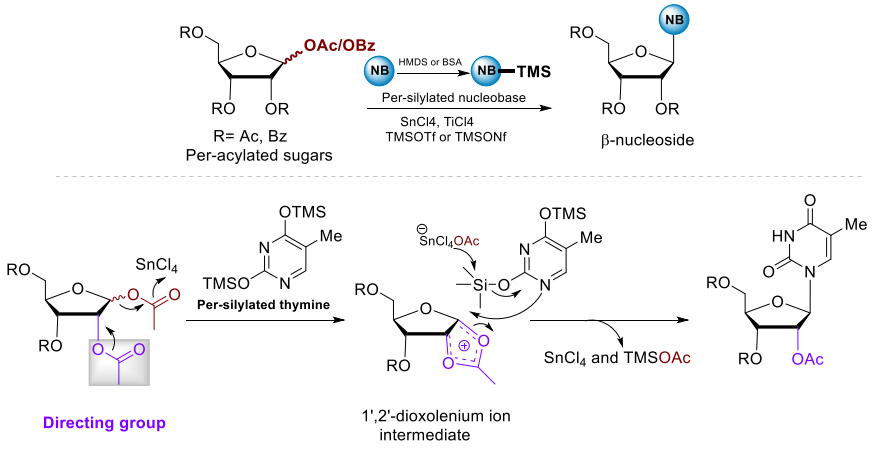
Fig. 1.4: Different types of Glycosyl donors for *N*-glycosylation

In the quest for an efficient, mild, and versatile *N*-glycosylation method, research has focused on exploring different glycosyl synthons. These synthons are designed to react with various nucleobases or per-*O*-silylated nucleobases, ultimately yielding β-

nucleosides as the major anomer. Additionally, sugar synthons can be categorized based on their anomeric leaving groups into eight types which are discussed in (Figure: 1.4).[8]

The Vorbrüggen glycosylation,[9] an enhanced version of the silyl-Hilbert-Johnson reaction[10], stands as the predominant technique for synthesizing pyrimidine, purine, and various heterocyclic nucleosides. This method employed a glycosyl acetate donor in the presence of robust Lewis acids, facilitating the reaction with a nucleobase to generate a 1',2'-dioxolenium ion intermediate (Scheme 1.5). Building upon this approach, Jamison et al. made advancements to achieve milder and more efficient synthesis process. Further, to improve the methodologies, Chen and He[11] developed a Pd-catalyzed glycosylation utilizing glycosyl chloride as the donor. This method results in the formation of β-nucleosides through an oxocarbenium ion intermediate. Subsequent modifications involved the utilization of thioglycoside donors[8] activated by (*p*-Tol)$_2$SO/Tf$_2$O. The scheme of some methods is shown as follows:

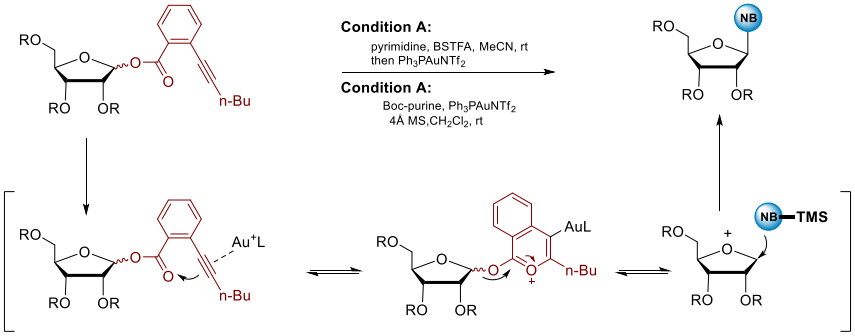
Vorbrüggen Glycosylation:



Scheme: 1.5: Mechanism of Vorbrüggen Glycosylation[9]

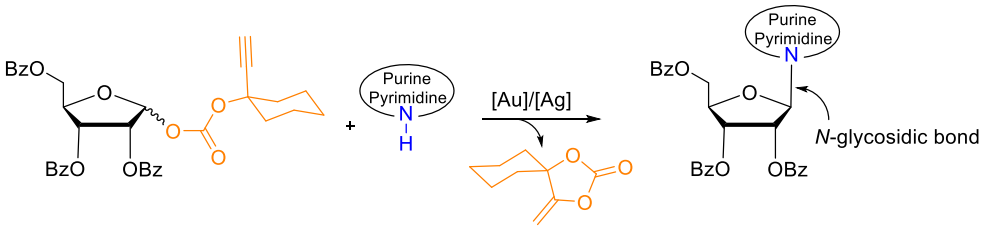
Gold -Catalysed glycosylation for the synthesis of N-glycoside

In 2011, the Yu group, employing glycosyl *o*-hexynyl benzoate as the donor activated by [$Ph_3PAuNTf_2$] reported the strategy to synthesize *N*-glycosides. This method results in the formation of a glycosyl oxocarbenium ion intermediate,[12] enabling the stereo-specific synthesis of both purine and pyrimidine nucleosides.



Scheme: 1.6: Yu Glycosylation[12], Utilizing Gold(I) as a catalyst, the process of *N*-glycosylation of pyrimidines and purines with glycosyl ortho-alkynyl benzoates.

After that, the Hotha group contributed to this field by employing gold-catalyzed activation of propargyl orthoester donors[13] for synthesizing modified pyrimidine glycosides. In 2022, the Hotha group utilized a combination of silver and gold catalysis to synthesize purine, pyrimidine, quinoline-2-one, and asparagine glycosides using alkynyl glycosyl carbonate donors. The approach employed to create different 2'-altered nucleosides and the disaccharide dipeptide component found in chloroviruses.[14]



Scheme: 1.7: Au/Ag catalyzed glycosylation by Hotha et al.

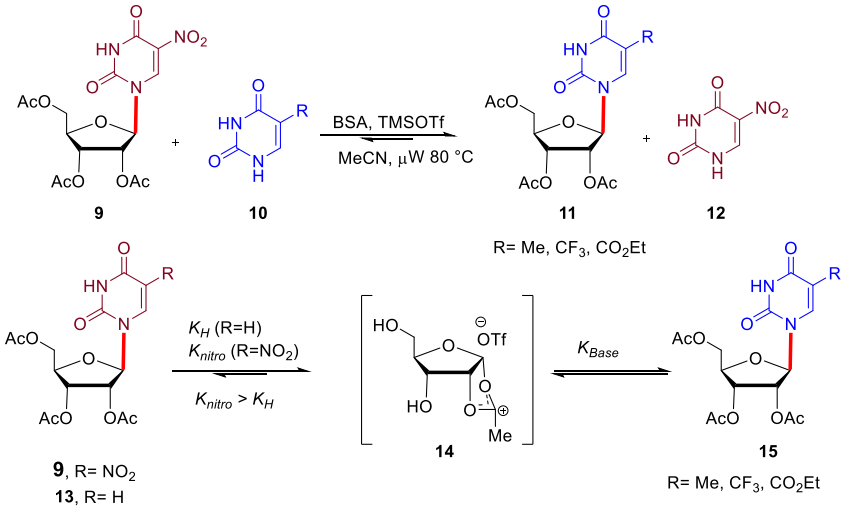
Transglycosylation:

Transglycosylation is a one-step process that has proven to be a highly efficient technique for the synthesis of nucleosides and their analogs, particularly in the late-stage

modification of nucleobases. There are two types of transglycosylations exist: a) chemical transglycosylation and b) enzymatic transglycosylation.[8]

a) Chemical transglycosylation:

In 2020, Gong et al. introduced a novel chemical method for transglycosylation, as outlined in scheme 1.8. Through their research, they found that 5-nitrouridine (9), when subjected to optimized Vorbrüggen conditions (BSA/ TMSOTf/ MeCN) with microwave irradiation, facilitates a reversible exchange of nucleobases with various 5-substituted uracils (10), resulting in moderate to high yields. The presence of the electron-withdrawing nitro-activating group enhances the leaving ability of siloxy-nitropyrimidine. The formation of a cationic intermediate (14) from 5-nitrouridine is favored due to the equilibrium constant *K*nitro being greater than K_H. Any newly introduced silylated nucleobase has the potential to engage in reversible reactions with (14), ultimately leading to the formation of a new nucleoside (15).



Scheme 1.8: Chemical transglycosylation of pyrimidine nucleosides

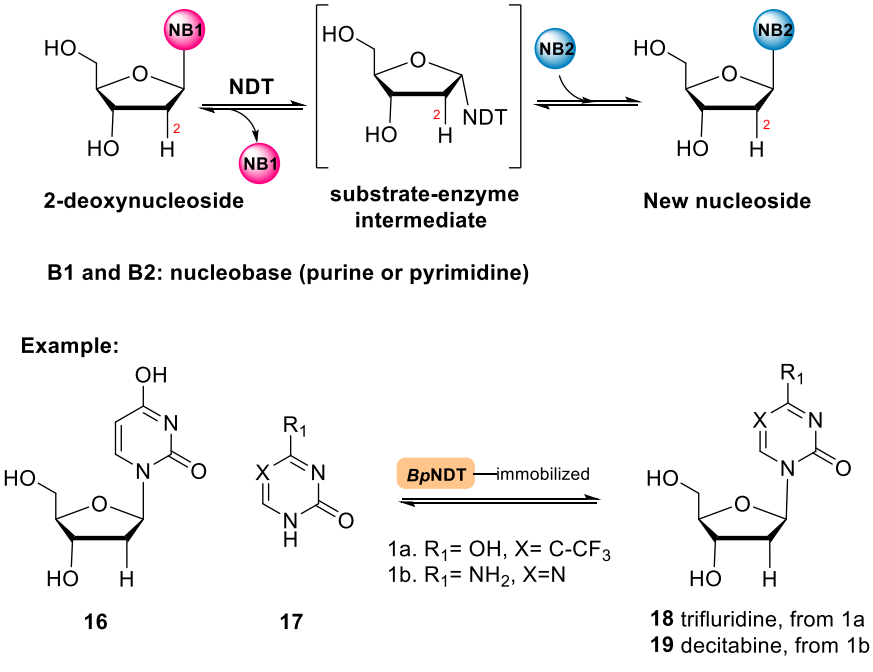
b) Transglycosylation by enzymatic pathway:

Enzymatic transglycosylation has become a pivotal technique in the synthesis of complex nucleosides, owing to its significant advancements in enzyme engineering methodologies. Techniques like directed evolution, semi-rational design, artificial synthesis, and computer-assisted design have played crucial roles in enhancing the efficiency and versatility of this approach, complementing traditional synthesis methods.

One of the key advantages of enzymatic transglycosylation lies in its kinetic control mechanism, which sets it apart from thermodynamically controlled synthesis methods. This kinetic control mechanism ensures precise regulation of reaction rates and product formation, leading to enhanced selectivity and yield. Fundamentally, enzymatic transglycosylation involves the catalytic action of enzymes on pre-existing nucleosides, serving as donors, followed by glycosylation with nucleobase acceptors. This sequential enzymatic process enables the synthesis of complex nucleosides with high precision and efficiency. Traditionally, two types of enzymes, nucleoside 2'-deoxy ribosyltransferases (NDTs) and nucleoside phosphorylases (NPs) have been employed for transglycosylation.[8]

Single enzyme transglycosylation enabled by NDT.

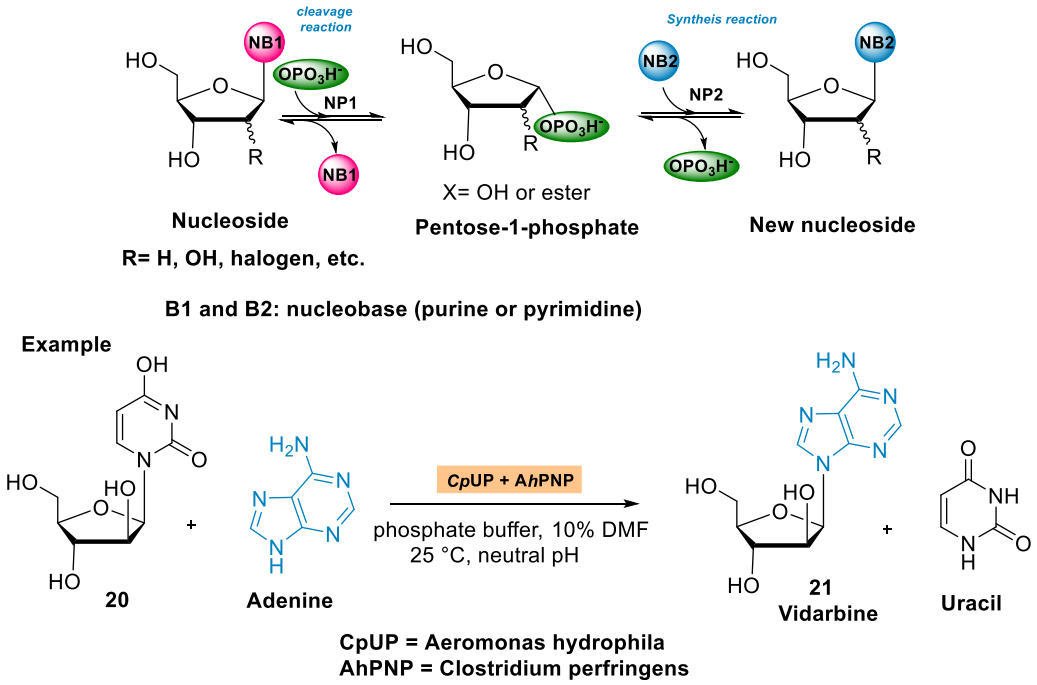
NDTs facilitate the direct exchange of 2'-deoxyribose moieties between purine and/or pyrimidine nucleosides, utilizing one nucleoside as the donor and nucleobase as the acceptor (Scheme 1.9). Based on their substrate specificity, NDTs can be categorized into NDT type I (purine NDT and PDT, responsible for purine transfers) and NDT type II (NDT, facilitating transfers between purines and/or pyrimidines).[8]



Scheme: 1.9: NDT mediated Transglycosylation

Multi-Enzyme transglycosylation enabled by NP

Nuclease phosphatases are a group of enzymes of the family of transferases that catalyze reversible cleavage of the *N*-glycosidic bond of nucleoside in the presence of an inorganic phosphatase. The drawback associated with this approach is that it can be tricky to use enzymes, which can cause operational issues.



Scheme: 1.10: NP mediated Transglycosylation

Importance of modified nucleoside in therapeutics:

Mechanism of modified nucleoside:

Modified nucleosides, when phosphorylated within cells, exhibit bioactive functions by either (1) hindering the growth of cancer cells, impeding virus replication, and disrupting various disease processes through competition with regular nucleosides, or (2) modifying the fate of function of DNA or RNA by substituting natural nucleotides with triphosphate-modified counterparts. This alteration affects aspects like base pairing, π-π stacking, or metal chelation.[15,16] Due to the crucial role of DNA and RNA replication in rapidly dividing tumor cells and viral reproduction, these modified nucleosides can serve as potential drug candidates for treating conditions such as cancer and viral infections.[16,17] Chemical

modification of nucleoside analogs can be done at the nucleobase, at different positions of the sugar ring, or at the phosphate backbone that is described below.

Modifications in nucleoside analogs:

Modified nucleosides play a crucial role in the advancements of various drug types, including (a) anticancer medications like cytarabine, azacytidine, gemcitabine, etc., (b) rheumatism drugs such as azathioprine, allopurinol, etc., (c) antiviral drugs like acyclovir, molnupiravir, etc., (d) antibiotics including trimethoprim, polyoxin J, etc., and (e) raw materials for nucleic acid drugs like DNA/RNA vaccines. In the research and development of these drugs, modifying nucleoside bases, glycosidic bonds, and sugar rings is a common strategy aimed at enhancing pharmacokinetic and pharmacodynamic properties, reducing the immunogenicity of nucleic acid drugs, and improving stability. There are primarily three categories of modified nucleoside-containing drugs: (1) sugar ring modifications; (2) unnatural base alterations; and (3) glycosidic bond connection mode changes. The subsequent types are modified drugs are shown below in Figure 1.5.

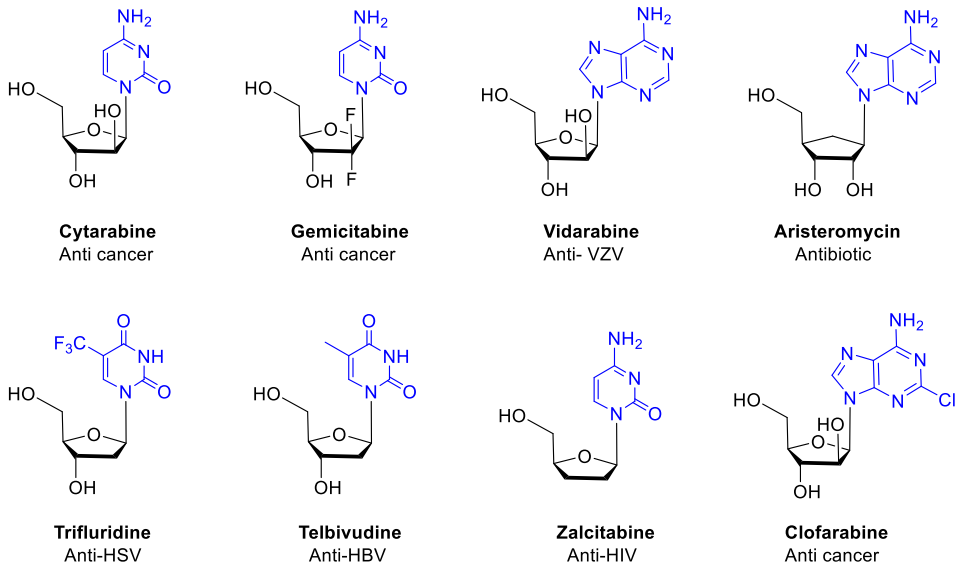


Fig. 1.5: Representative structures of modified nucleosides

Other applications:

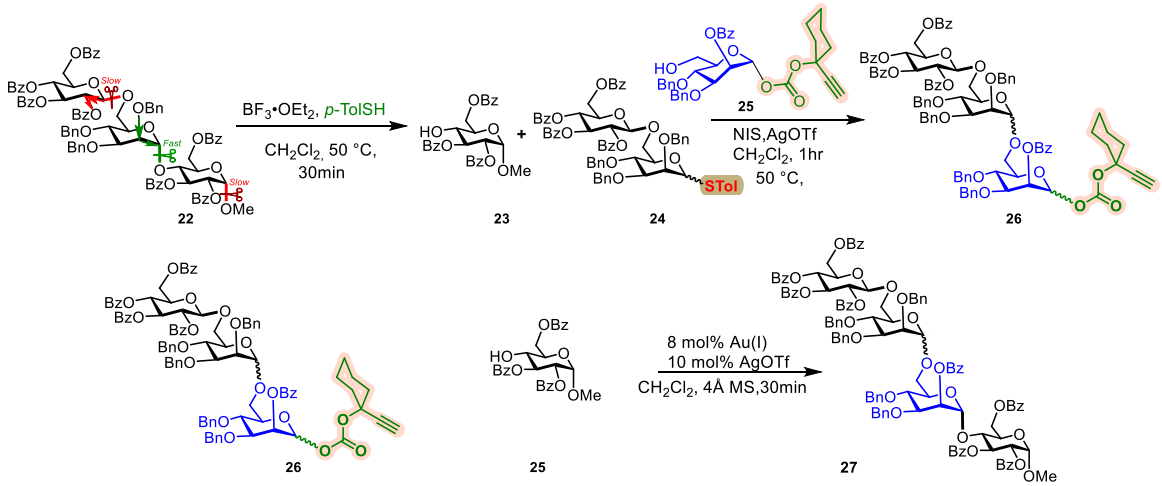
Modified nucleosides show extensive applications in disease diagnosis. By incorporating reporter groups like isotopic labels or fluorophores, or functional groups such as azide

and alkynyl, it becomes possible to achieve real-time localization and quantitative detection of nucleic acids. This approach proves valuable for investigating the structure, function, and fate of nucleic acids in physiological conditions. [18-20]

Surgical Chemical glycan editing:

Hotha group has recently developed a one-pot surgical chemical glycan editing approach where they demonstrated the ability to selectively cleave specific glycosidic bonds by leveraging subtle reactivity differences among the protective groups.

In this method, they developed a surgical strategy *Cut-Insert-Stitch-Editing Reaction* (CIStER) sequence for glycans that entails breaking an inter-glycosidic bond in a regio-specific manner, inserting a foreign glycan, and then stitching of glycosidic bonds to create a hybrid glycan by fine-tuning subtle reactivity differences.[21] This one-pot cleavage of glycosidic bond and insertion of an external aglycone unit laid the foundation of this current work which is discussed in the following section.



Scheme:1.11: Chemical glycan editing by CIStER

Statement of the goal of the project:

***Novel Synthesis of N-glycoside related drugs and API's*:**

One of the major focuses of our project is to streamline the process of synthesizing *N*-glycoside-related drugs and active pharmaceutical ingredients (APIs). Considering the limited synthetic protocols for *N*-glycosides by cost-effective processes, this project helps to find a way to simplify the synthetic processes as well as ensure efficacy and accessibility.

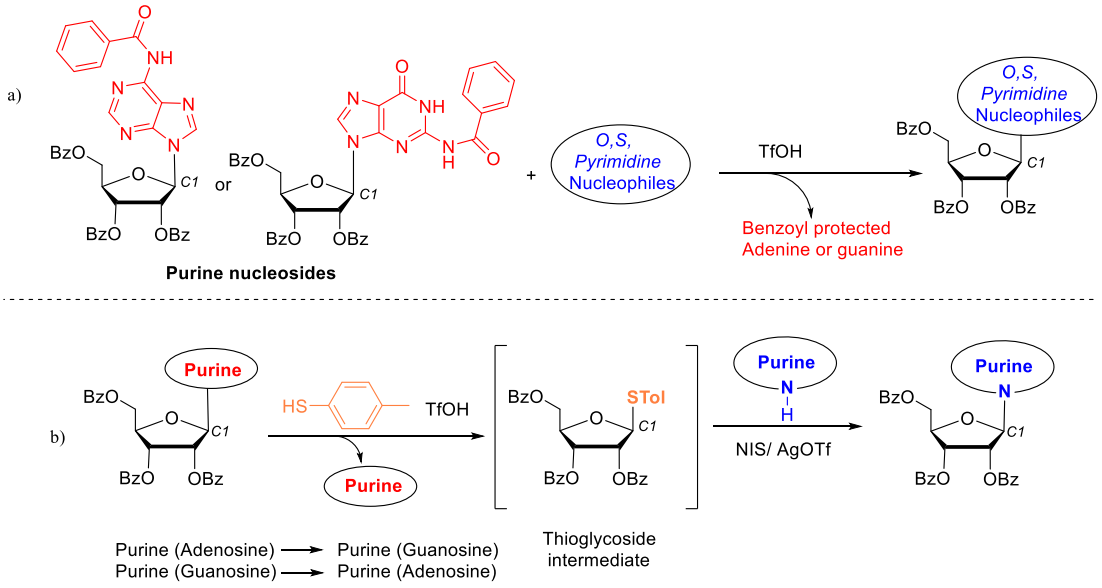
***Efficient synthesis of diverse glycosides from readily available cheap precursors*:**

Another pivotal objective of our project lies in the diversification of glycoside formation, which includes *S*-, *O*-, and *N*-glycosides. By utilizing readily available precursors, we aim to develop a synthetic protocol where a chemical transglycosylation strategy can be used to strengthen the production of glycosides.

***Chemical transglycosylation for N-glycoside diversification*:**

Additionally, this project aims to explore novel methods for the editing of glycosides, specifically, transformation between purine and pyrimidine bases. This involves the conversion of adenosine/guanosine to thymidine/cytidine/uridine (A/G→T/C/U), as well as interconversion between adenosine to guanosine (A→G). These types of base pair editing shows potential for broadening the scope of synthesis of glycoside-based compounds and their wide uses across diverse fields.

Present Work:



Scheme: 2.1: General representation of different types of glycosylation by *N*-glycan editing

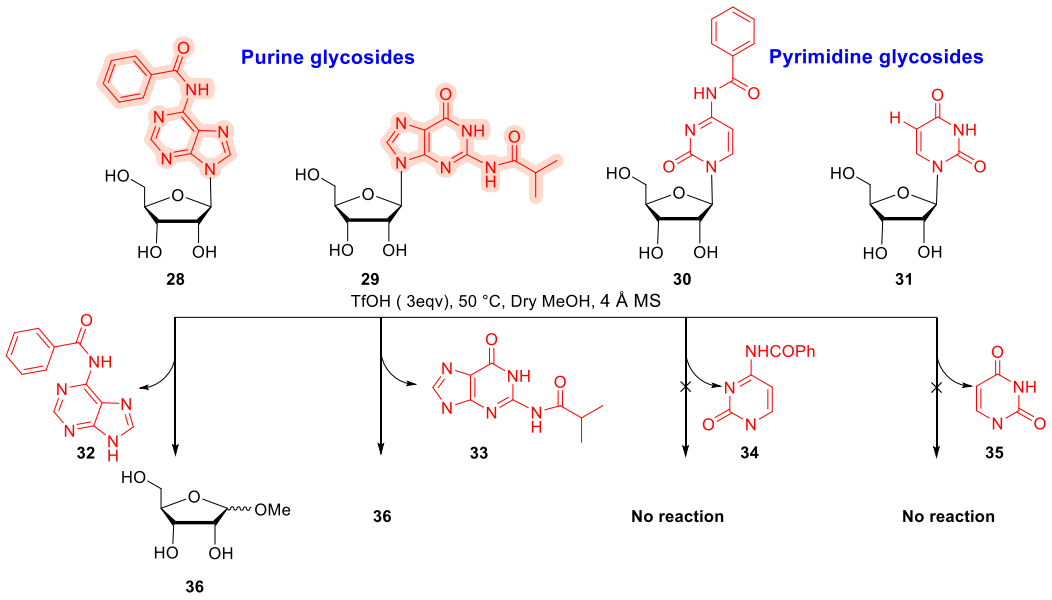
Glycan can bind to aglycones through different types of glycosidic bonds: *O*-, *S*-, *N*-, or *C*-. These are often termed O-glycosides, S-glycosides, N-glycosides, and C-glycosides, respectively.[22-24] *N*-glycosides hold particular importance as they serve as the foundational components of DNA and RNA. In these structures, the nucleobase (either purine or pyrimidine) is attached to ribofuranose via the nitrogen atom within the ring.[25]

The Vorbrüggen-modified silyl approach to the Hilbert-Johnson nucleosiadtion, utilizing anomeric 1-*O*-acyl glycosyl donors, is widely utilized in the synthesis of pyrimidine nucleosides. [26] However, this strategy may not always be acceptable for the synthesis of purine nucleosides. During nucleosidation of purine *N*-glycosides, the choice of protecting groups is often restricted due to the presence of strong Lewis acids.[27] In such instances, the conventional donor-acceptor glycosylation approach proves to be a practical method for their synthesis. Nevertheless, a significant drawback associated with this method is the lengthy steps required to synthesize the starting material. To address this limitation, enzymatic transglycosylation emerges as an effective method for generating diverse analogs of purine and pyrimidine nucleosides from a pyrimidine nucleoside.[8] Unfortunately, a direct transfer or chemical glycosylation technique to convert purine

nucleosides into pyrimidine nucleosides and base pair transformations (like Adenosine to Guanosine and vice versa) between purine glycosides has not been established.

In this study, we aimed to incorporate the conventional donor-acceptor glycosylation and chemical transglycosylation methods as tools for synthesizing *O*-, *N*-, and *S*-glycosides from readily available purine glycosides (Scheme 2.1). The subtle reactivity differences of the C-N bond in purine and pyrimidine glycosides played a crucial role, enabling the selective cleavage of the C-N bond in purine but not in pyrimidine. This method allowed the versatile synthesis of purine glycosides from purine precursors, with the reaction mediated by a single thioglycosidic intermediate. (Scheme 2.1 b).

Result and Discussions:



Scheme: 2.2: Investigation of stability of nucleosides under triflic acid conditions

We envisioned that the recently discovered chemical glycan editing approach (Scheme 1.11), employing a TfOH activator might be a potential solution for chemical transglycosylation. So, our project commenced by investigating the feasibility of cleaving the robust C-N glycosidic bond. Commercially available purine nucleosides **28** & **29** were subjected to a TfOH activator in the presence of MeOH (Scheme 2.2), which served as a nucleophile to facilitate glycosidic bond cleavage. While this strategy successfully yielded the desired product **36** with the formation of by-product **32** for purine glycosides **28** or **29**

(Scheme 2.2), the same approach applied to pyrimidine nucleosides **30** & **31**(Scheme 2.2) did not exhibit any progress in the reaction. This lack of success may be attributed to the high bond strength of the C-N bond in pyrimidine nucleosides (**30** & **31**). The course of the reaction was monitored by ^{1}H NMR spectra and the HRMS spectra of the crude reaction mixtures (Figures 2.1 & 2.2).

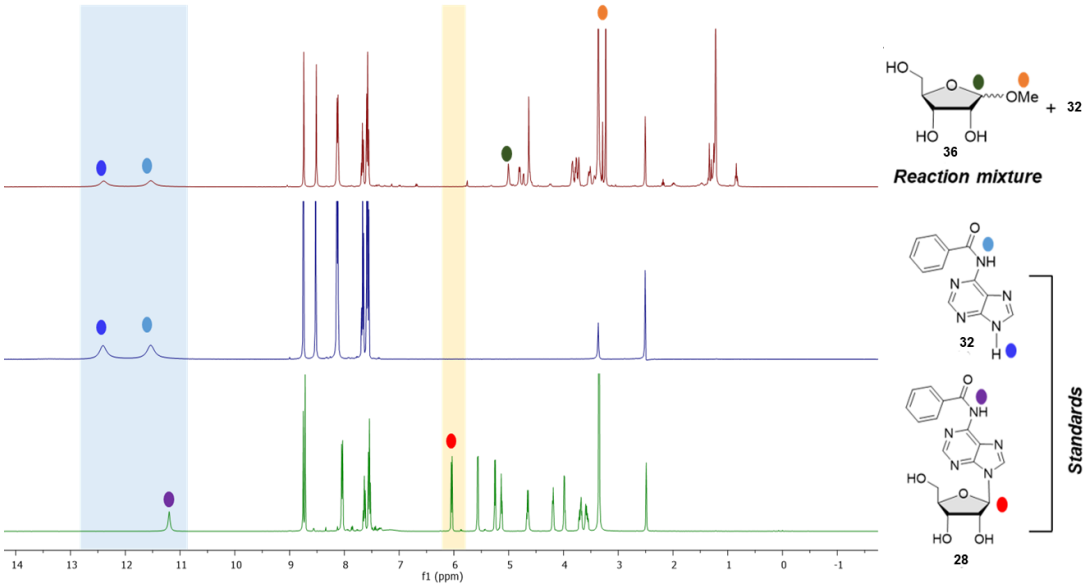


Figure 2.1: Investigation of stability of purine nucleoside (28) by ^{1}H NMR

Upon thorough investigation of the ^{1}H NMR spectra of the reaction mixture involving purine nucleosides (**28**) as the starting precursor, it became evident that there were distinct spectral features. Notably, the presence of two N-H protons in the crude reaction mixture (Fig 2.1 top panel) within the chemical shift range of 11 to 13 ppm (highlighted in blue) closely resembled the corresponding peaks in the standard compound (**32**), strongly indicating the generation of by-product **32** within the reaction mixture. Additionally, the observed shift of the anomeric C-H proton to a lower chemical shift value from 6 ppm to 5 ppm (highlighted in orange) implies the cleavage of the C-N bond and subsequent formation of the anomeric C-O bond. Furthermore, the appearance of the C-H proton associated with -OCH_3 at approximately 3.5 ppm suggests the successful formation of the desired product **36**.

The same strategy was followed for the other purine glycoside (**29**) where a similar result was obtained. However, in the case of pyrimidine nucleosides **30** & **31** the starting material remained as such.

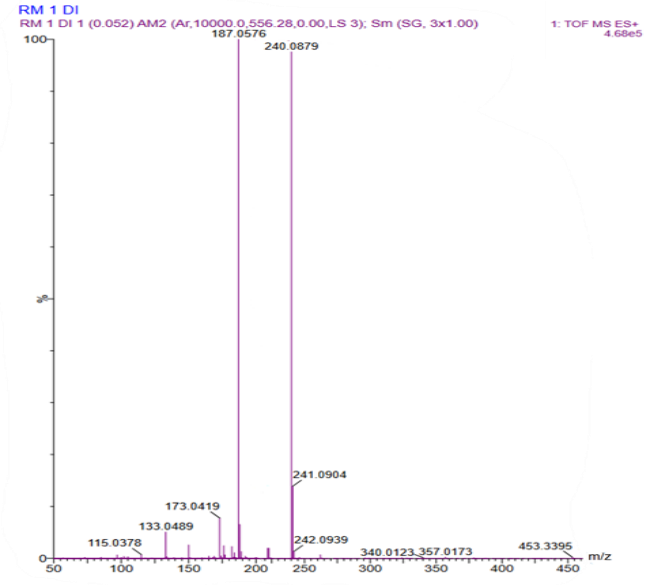
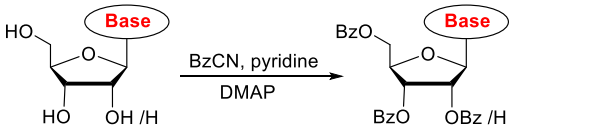


Figure 2.2: Investigation of stability of purine nucleoside (28) through HRMS

The High-Resolution Mass Spectrometry (HRMS) analysis of the reaction mixture provided additional evidence supporting the cleavage of the C-N bond within purine glycosides (**28**). This resulted in generating the desired product **36**, indicated by its molecular ion peak at m/z= 240.087. Concurrently, the appearance of a peak corresponding to by-product **32** at m/z= 187.057 verified this chemical transformation.

Reaction Optimization:

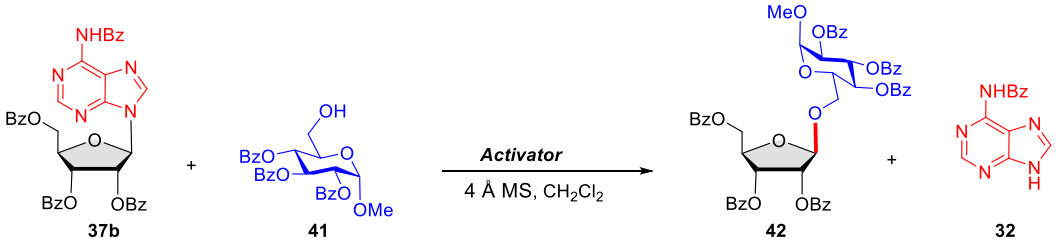


37a, B=adenine-9-yl
38a, B= guanine-9-yl
39a, B=adenine-9-yl
40a, B= guanine-9-yl

37b, B=N^6-benzoyladenine-9-yl
38b, B=N^2-benzoylguanine-9-yl
39b, B=N^6-benzoyladenine-9-yl
40b, B=N^2-benzoylguanine-9-yl

Scheme: 2.3: Benzoylation of nucleosides

To further explore the reaction outcome, and optimize the reaction under mild and catalytic levels, commercially available adenosine (**37a**) was protected with a benzoyl group as depicted in Scheme 2.3, resulting in the formation of 6-*N*-Benzoyl-9-(2',3',5'-tri-*O*-Benzoyl-β-D-ribofuranosyl) adenine (**37b**). This compound was subjected to various conditions in the presence of different activators (table 1) and acceptor (**41**) as a nucleophile (Scheme 2.4). While the glycosidic bond cleavage occurred significantly with TfOH, using only 1 equivalent at 25 °C, achieving a similar outcome was more difficult with alternative conditions (entries 4-8) (table: 1). This condition proves to be the most effective in generating diverse glycosides through the employed cut and insert editing strategy.



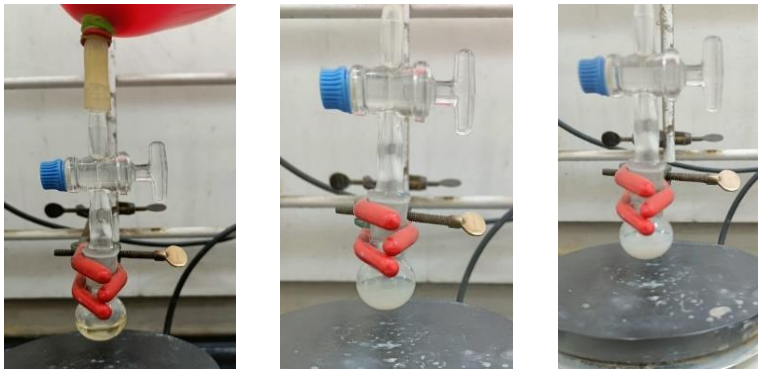
Scheme: 2.4: Reaction optimization for glycoside synthesis

Entry	Activator	Time	Temp.	Yield %
1	TfOH (3 eqv)	20min.	50 °C	96
2	TfOH (3 eqv)	30min.	25 °C	92
3	TfOH (1eqv)	45min.	25 °C	90
4	$SnCl_4$ (3eqv)	3 hrs.	25 °C	5
5	$AlCl_3$ (3eqv)	3 hrs.	25 °C	0
6	BF_3. OEt_2	3 hrs.	25 °C	15
7	Tf_2O	3 hrs.	25 °C	5
8	TMSOTf	3 hrs.	25 °C	35

Table: 1: Reaction optimization in the presence of activators

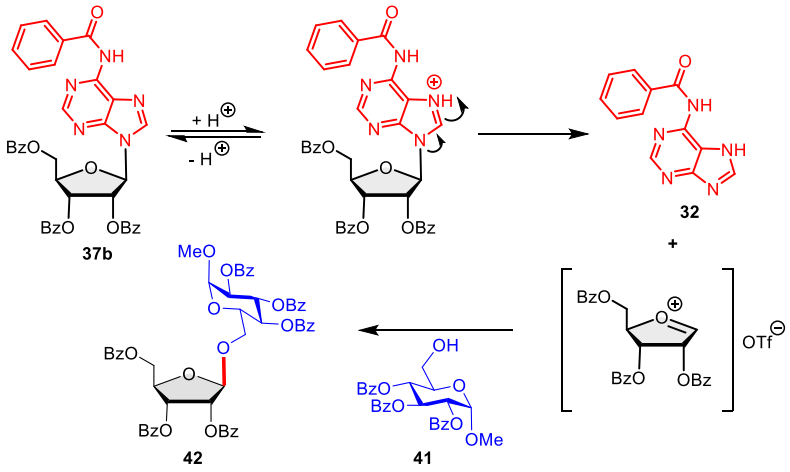
The progress of the reaction, involving the synthesis of the target product (**42**) and the by-product (**32**), was monitored using LC-MS profiling of the reaction mixture (Fig. 3.1).

Additionally, the reaction progress could be visually assessed since the by-product (**32**) rendered the reaction mixture insoluble in dichloromethane. Within approximately 30 minutes, the solution transformed into a solid, providing a concrete indication of the reaction's progress (fig. 2.3).

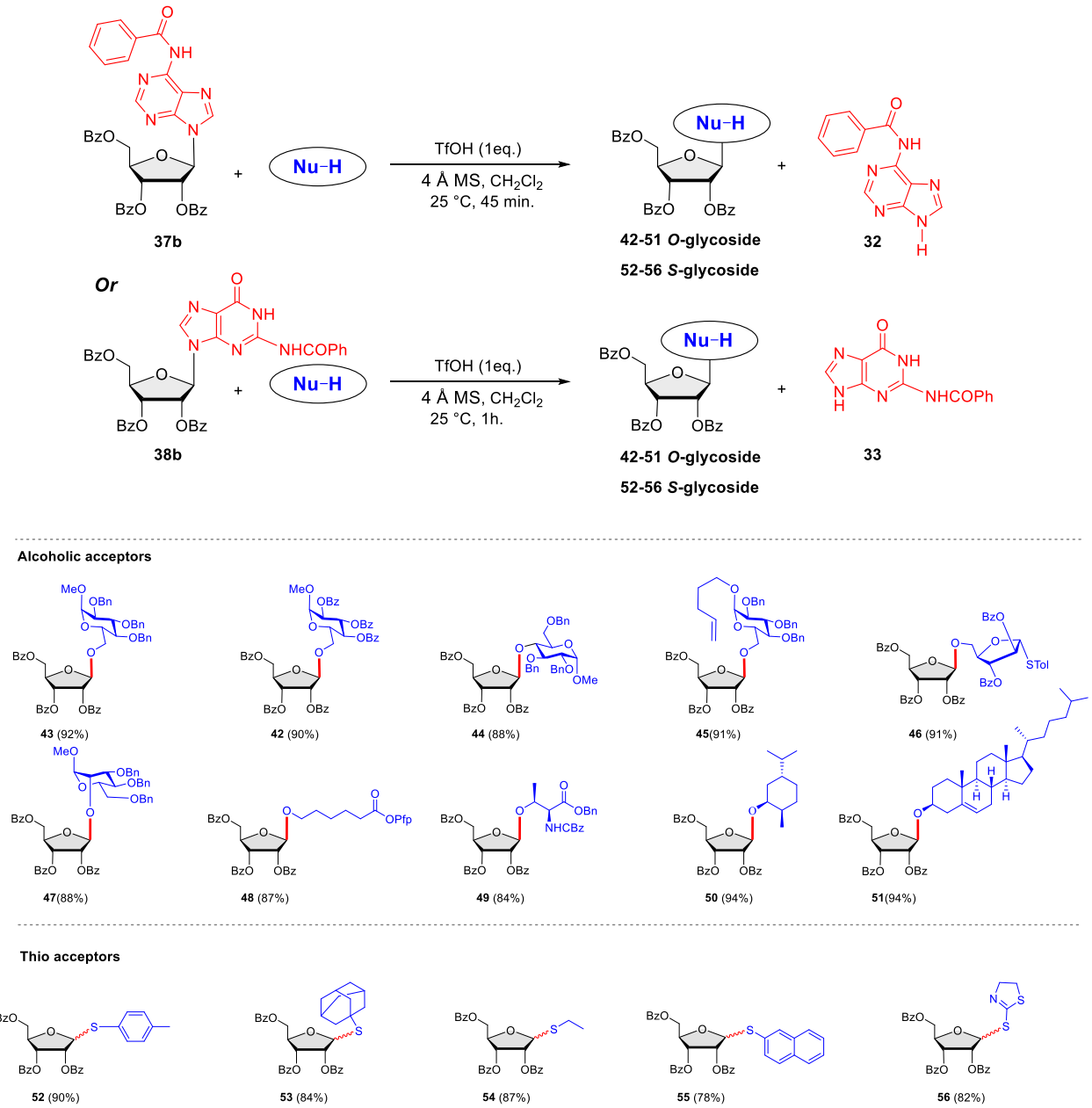


After the addition of TfOH | After 15 minutes | After 45 minutes

Fig: 2.3: Reaction progress through visual indication



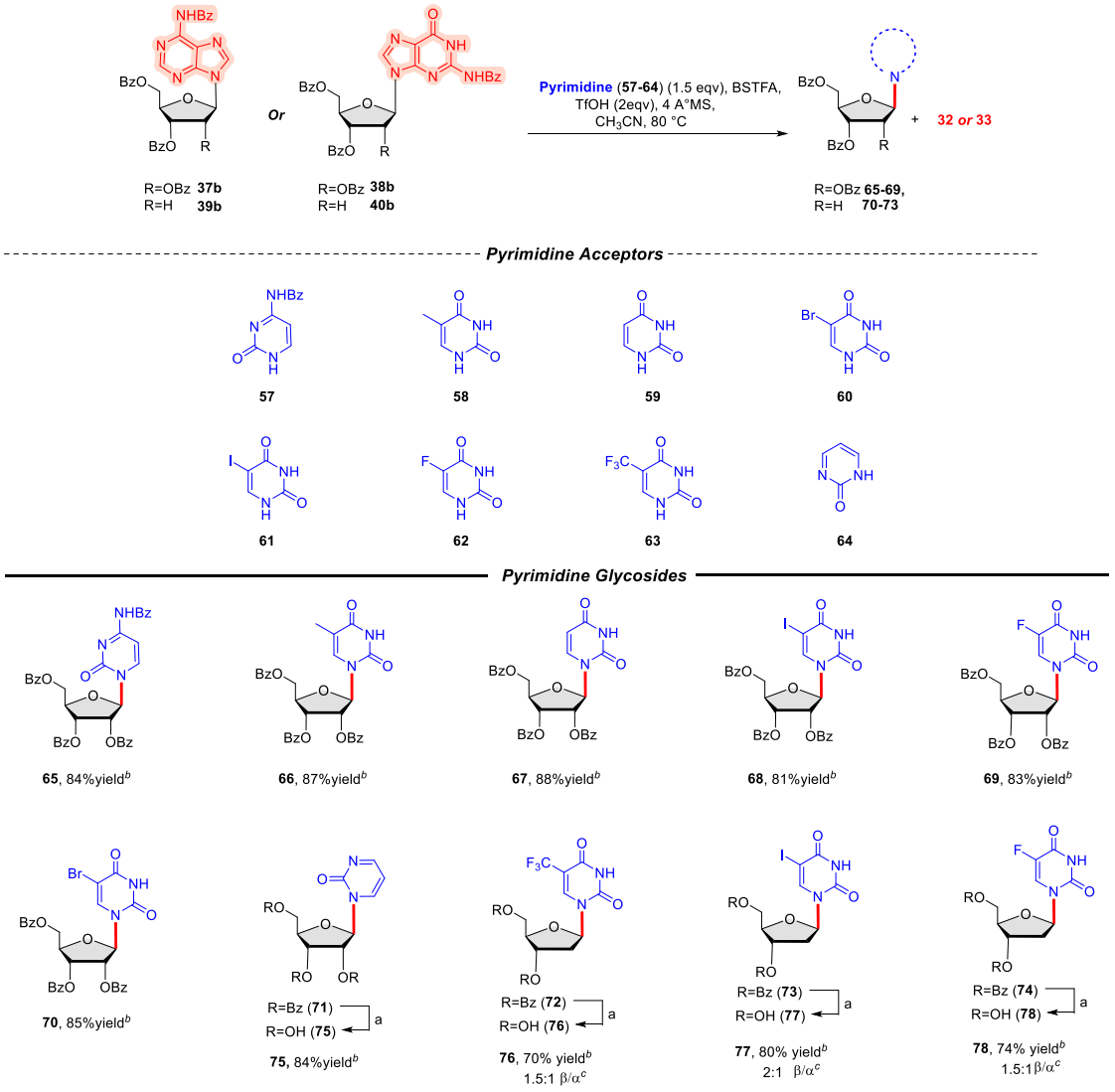
Sc**heme: 2.5: Plausible mechanism of *N*-glycan editing reaction**



Scheme: 2.6: Scope of synthesis of diverse class of *O* & *S* glycosides from purine glycosides

Under the proper optimized conditions depicted in Scheme 2.4, a variety of types of *O*- and *S*- glycosides were synthesized from the purine glycoside (**28**, or **29**), (scheme 2.6). This novel approach involved the attachment of various acceptors, including glucose-armed primary acceptors (**43**, **45**), disarmed primary acceptors (**42**), secondary acceptors (**44**), bifunctional furanose acceptors (**46**), mannose C2-OH acceptors (**47**), and different

aglycone motifs (**48-51**). This same strategy was also applied to the synthesis of various *S*-glycosides (**52-56**). Notably, this one-pot chemical glycan editing approach consistently yielded very good to excellent results across all instances, which showcases the versatility of this strategy.



Scheme: 2.7 Scope of synthesis of pyrimidine nucleosides from purine nucleoside.

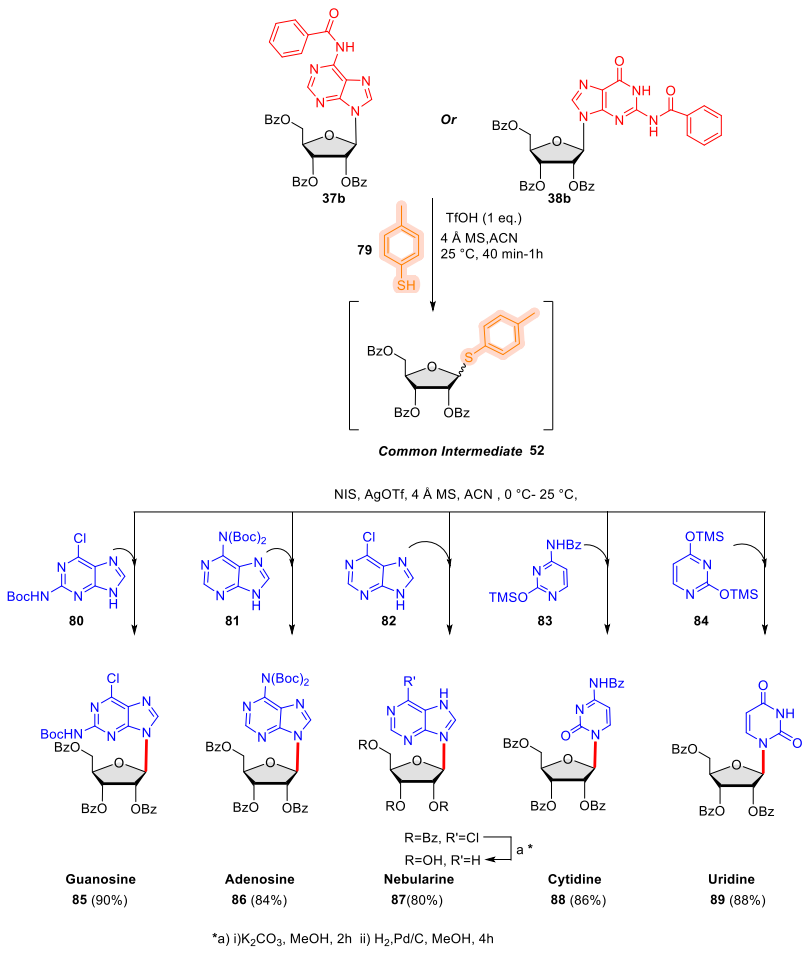
The synthesis of pyrimidine nucleosides is significant due to their applications in drug development, therapeutics, and medicinal chemistry. However, there are only certain methods to synthesize these compounds. Notably, our innovative chemical transglycosylation strategy proved to be one of the best due to its cost-effectiveness and high to excellent yield across all instances (Scheme 2.7). Since pyrimidine acceptors are

categorized as very low nucleophilic acceptors, in this case, they require relatively rigorous conditions. These were treated with 2 equivalents of triflic acid under intense heating conditions (80 °C) to achieve optimum results since the acceptors are not enough nucleophilic to facilitate the cleavage of the C-N bond to progress the reaction in a forward direction. Strategically introducing the benzoate group at the C2 position of the initial precursor (**37b** or **38b**) is crucial for achieving β-selectivity by leveraging anchimeric assistance to guide the formation of the necessary 1,2-*trans* ribofuranoside linkage.

For the shake of synthesizing pyrimidine nucleosides (scheme 2.7), compound (**37b** or **38b**) was dissolved in CH_3CN, which was treated with pyrimidine acceptors (**57**-**64**) in the presence of 2 equivalent TfOH for 1 hour. This yielded pyrimidine nucleosides (**65**-**74**) in excellent yield, accompanied by the formation of a highly polar extraction product (**32** or **33**), monitored via LC-MS profiling of the reaction mixture (fig. 3.3). The latter could be easily separated from the reaction mixture through normal silica gel column chromatography. Specifically, nucleosidation of pyrimidine often requires pretreatment of the nucleobase (**57**-**64**) with a silylating agent to render it soluble in CH_3CN.

This innovative cut-insert editing chemical transglycosylation strategy was not restricted to synthesizing the usual pyrimidine bases found in DNA or RNA (**65**-**67**). Considering the novel applications of the different nucleoside derivatives (**68**-**74**) as well as the potential medicinal implications they hold, compounds (**71**-**74**) were saponified under zemplén conditions to produce compounds (**75**-**78**).

Purine nucleosides hold ubiquitous applications due to their presence in DNA or RNA and since they are widely used as an antiviral active drug and their capability as inhibitors of key enzymes in purine metabolism. The synthesis of purine nucleoside is thus of great interest. Our novel one-pot chemical glycan editing has the potential to solve this issue. Since we have successfully synthesized the *S*-glycoside (**52**) which acts as a donor, further this was activated by using NIS/AgOTf to produce different purine and pyrimidine nucleosides in one-pot via common intermediate **52** (Scheme 2.8) in a high to excellent yield. This method is highly useful for base pair transformations like (A→G) or (G→A) and (A/G→C/T/U).

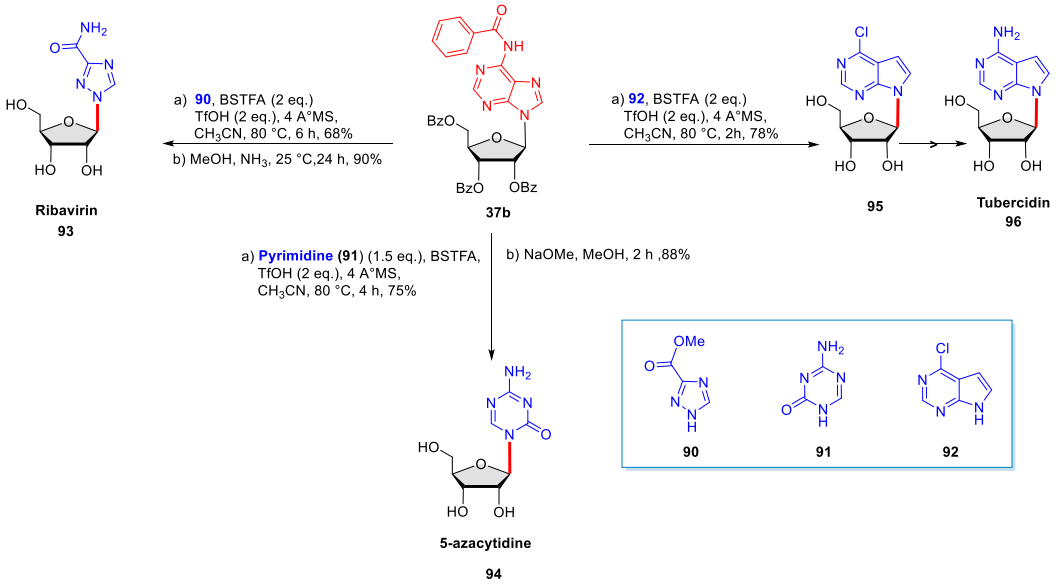


Scheme: 2.8: Interconversion between purine and pyrimidine nucleosides.

In this novel transglycosylation approach, purine nucleosides (**37b** or **38b**) (Scheme 2.8) were treated with 4-methyl benzenethiol (**79**) as a nucleophile and TfOH which acts as an activator. It formed the common thioglycoside intermediate (**52**). This was further treated with different purine or pyrimidine acceptors (**80-84**) in the presence of NIS/AgOTf under a one-pot reaction to make different nucleoside compounds (**85-89**) in excellent yields (Scheme: 2.8).

2-amino-6-chloropurine (**80**) is a common precursor for guanine glycosides which can be derived by simple acid hydrolysis of the chloropurine moiety. Adenosine nucleoside was synthesized by the treatment of adenine base (**81**) with protected guanine nucleoside (**38b**). Herein, the poor solubility of adenine in acetonitrile was overcome by introducing two BOC groups at the *N*-9 position of adenine as well as assisting in suppressing the

glycosidation through its *N*-7 position. Thus, the glycoside intermediate transglycosylation approach is highly effective since one commercially available nucleoside can assist in generating a diverse class of nucleosides easily and effectively.



Scheme: 2.9: Synthesis of nucleoside drugs.

Finally, the utility of this one-pot chemical transglycosylation strategy have been successfully demonstrated in the application to the efficient synthesis of various FDA-approved nucleoside antibiotics ribavirin, 5-azacytidine, and tubercidin (scheme: 2.9). In particular, Ribavirin **93** is an important drug against numerous viruses, majorly in the treatment of respiratory syncytial virus in pediatric patients and chronic HCV infection in both children and adults.[30] Under standard conditions for *N*-glycosylation with pyrimidines, the coupling of the acceptor (**90**) with our initial precursor (**37b**) was efficient, resulting in the formation of the nucleoside with a good yield (68%). Subsequent treatment of the nucleoside with MeOH/ NH_3 resulted in the production of nucleoside ribavirin **93** in (90%) yield.

In a similar glycosylation protocol, the coupling of the pyrimidine acceptor **91** with **37b** afforded the corresponding pyrimidine nucleoside in excellent yield (75%). In the subsequent step, the compound was deprotected with NaOMe in MeOH to afford

azacytidine **94** in (88%) yield which has a role as an antineoplastic agent and is widely used in treating myeloid Leukaemia.

Tubercidin demonstrates noteworthy effectiveness against schistosomal infections and has also been explored as a potential cancer chemotherapeutic agent. Under the optimized reaction condition the acceptor (**92**) is coupled with **37b** to afford compound **95**in (74%) yield. Further, in the subsequent step, MeOH/NH_3 treatment of the compound can afford tubercidin (**96**).

Experimental Data:

General: Reactions were carried out under ambient conditions unless otherwise indicated. Column chromatography of the crude compounds was performed on silica gel of 100-200 mesh (75- 150 µm). Products obtained as solids or syrups were dried under a high vacuum. The reactions were monitored by analytical thin layer chromatography (TLC) performed on 0.25 mm Merck silica gel plates ($60F_{254}$) under a 254nm UV lamp and stained by anisaldehyde stain.

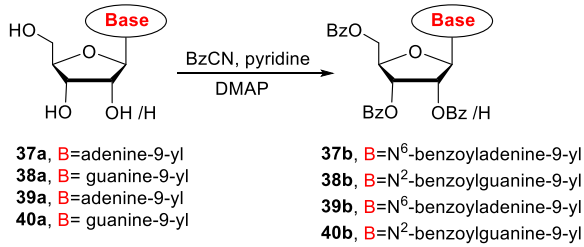
Materials: Unless otherwise noted, all the materials were obtained from commercial suppliers, Sigma-Aldrich, and used without further purification. The solvents used for LC-MS analysis were purchased from Sigma-Aldrich. 4Å molecular sieves were activated by heating at 150-200 °C under a high vacuum for 4 h before storing in a dry desiccator. Freshly distilled CH_2Cl_2 was stored over activated 4Å molecular sieves (preheated to 200-250 °C).

Instrumentation: ^{1}H and 13C NMR, spectra were recorded in $CDCl_3$, DMSO-d_6 using a Bruker 400 or 600 MHz spectrometer. ^{1}H NMR reported in parts per million (ppm) relative to tetramethylsilane and referenced to residual protium in the solvent. Spectral features are tabulated in the following order: chemical shift (δ, ppm); multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, m-complex multiplet, dt- apparent doublet of triplet, td- triplet of doublet); coupling constants (J, Hz); number of protons. High-resolution mass spectroscopy (HRMS) was performed using an ESI-TOF mass analyzer or MALDI-TOF

mass analyzer. Optical rotations were measured on a digital polarimeter at 25 °C in $CHCl_3$ solution. IR spectra were recorded on an FT-IR spectrometer.

Experimental procedures:

General procedure for benzoylation of nucleosides (37b-40b):



37a, B=adenine-9-yl
38a, B= guanine-9-yl
39a, B=adenine-9-yl
40a, B= guanine-9-yl

37b, B=N^6-benzoyladenine-9-yl
38b, B=N^2-benzoylguanine-9-yl
39b, B=N^6-benzoyladenine-9-yl
40b, B=N^2-benzoylguanine-9-yl

Nucleoside	BzCN (eq.)	Time (h)	Temp. (°C)	Yield (%)
Adenosine (**37b**)	8	7	40	90
Guanosine (**38b**)	7	7	115	92
2-*deoxy* adenosine (**39b**)	7	6	40	94
2-*deoxy* guanosine (**40b**)	6	4	115	90

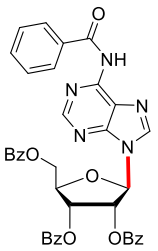
Scheme: 3.1: Benzoylation of purine nucleosides

The anhydrous compound (**37a-40a**) (1.0 eq.) was dissolved in dry pyridine (5ml, 20ml in case of **37a**, **39a** and **38a**, **40a** respectively) followed by the addition of DMAP (0.1-0.2 eq.) and BzCN (6-8 eq.). The reaction mixture was allowed to stir at 40 °C (for compounds **37a** and **39a**) and (115 °C in the case of **38a** and **40a**) until TLC analysis indicated the reaction to be completed. Upon completion, the reaction was poured over crushed ice under vigorous stirring. The precipitate was filtered under a vacuum, washed with water and petroleum ether, and dried to afford the corresponding benzoylated compounds (**37b-40b**).

(37b):

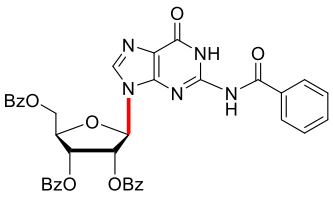
Compound **37b** was prepared from **37a** according to the abovementioned general procedure (90%, white foam). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.69 (s, 1H), 8.20 (s, 1H), 8.13 – 7.92 (m, 8H), 7.59 – 7.33 (m, 12H), 6.50 (d, *J* = 5.2 Hz, 1H), 6.43 (t,

J = 5.5 Hz, 1H), 6.27 (t, *J* = 5.3 Hz, 1H), 4.93 (dd, *J* = 12.1, 3.3 Hz, 1H), 4.88 – 4.83 (m, 1H), 4.72 (dd, *J* = 12.2, 4.3 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2, 165.4, 165.2, 164.7, 153.0, 151.7, 149.9, 141.7, 133.9, 133.8, 133.5, 132.8, 129.9 (2C), 129.8, 129.8, 129.3 (2C), 128.8 (2C), 128.7, 128.6, 128.6 (2C), 128.6 (2C), 128.3 (2C), 128.0 (4C), 123.6, 87.1, 80.9, 73.9, 71.5, 63.6.



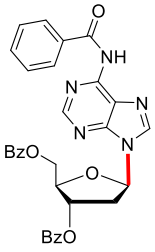
(38b):

Compound **38b** was prepared from **38a** according to the abovementioned general procedure (92%, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.03 – 11.91 (m, 1H), 9.59 (d, *J* = 4.3 Hz, 1H), 8.20 – 8.11 (m, 2H), 7.96 (td, *J* = 8.0, 1.4 Hz, 4H), 7.82 (s, 1H), 7.77 – 7.67 (m, 3H), 7.63 – 7.56 (m, 4H), 7.50 – 7.39 (m, 5H), 7.25 (d, *J* = 7.8 Hz, 2H), 6.90 (dd, *J* = 7.2, 5.0 Hz, 1H), 6.43 (dd, *J* = 5.0, 2.3 Hz, 1H), 6.19 (d, *J* = 2.3 Hz, 1H), 4.89 – 4.83 (m, 2H), 4.78 (dd, *J* = 13.2, 4.9 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 166.4, 166.1, 165.3, 155.4, 147.6, 147.1, 139.2, 134.0, 133.9, 133.9, 133.7, 131.4, 129.9, 129.8, 129.3 (2C), 129.1 (2C), 128.9, 128.8 (2C), 128.7-128.1 (10C), 122.4, 88.1, 79.4, 74.4, 70.9, 61.7.



(39b):

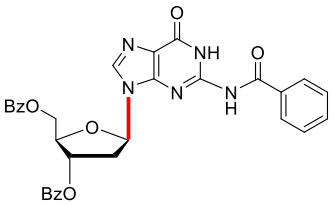
Compound **39b** was prepared from **39a** according to the abovementioned general procedure (94%, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.65 (s, 1H), 8.24 (s, 1H), 8.09 – 8.05 (m, 2H), 8.02 – 7.98 (m, 4H), 7.61 – 7.56 (m, 1H), 7.51 – 7.37 (m, 8H), 6.59 (dd, *J* = 8.1, 5.9 Hz, 1H), 4.78 (dd, *J* = 11.5, 3.8 Hz, 1H), 4.71 – 4.64 (m, 2H)4.09 (q, *J* = 7.1 Hz, 1H), 3.33 – 3.19 (m, 1H), 2.92 – 2.82 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.9, 165.7, 165.0, 152.3, 151.3, 149.7, 141.4, 133.5, 133.4, 133.2, 132.5, 132.4,129.6- 129.3 (5C), 129.2 (2C), 128.9, 128.5-127.9 (5C), 123.6, 84.9, 82.8, 75.1, 64.0, 37.2.



(40b):

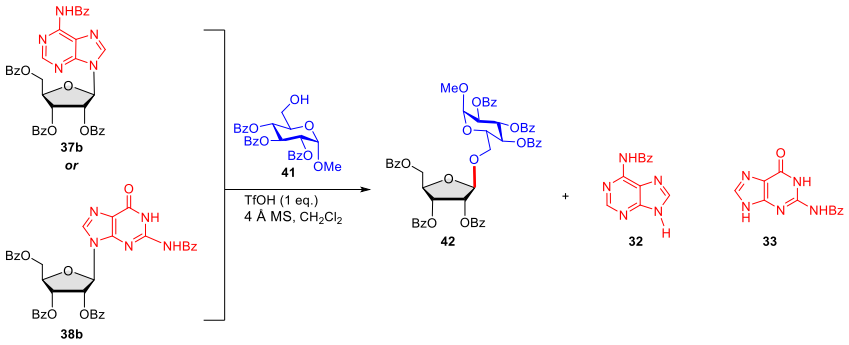
Compound **40b** was prepared from **40a** according to the abovementioned general procedure (94%, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.22 (s, 1H), 9.65 (s, 1H),

8.19 – 8.04 (m, 4H), 7.94 – 7.87 (m, 2H), 7.77 (s, 1H), 7.70 – 7.44 (m, 7H), 7.37 (t, *J* = 7.7 Hz, 2H), 6.32 (t, *J* = 6.8 Hz, 1H), 5.99 (dq, *J* = 5.8, 2.7 Hz, 1H), 5.07 (q, *J* = 7.3 Hz, 1H), 4.71 (d, *J* = 7.4 Hz, 2H), 3.26– 3.35 (1 H, m,), 2.65 –2.75 (1 H, m). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.2 (2C), 167.3, 166.3, 155.8, 147.91 (2C), 147.7, 138.9 (3C), 134.0, 130.1-130 (8C), 129.9, 129.3, 128.9 (2C), 128.4, 123.27, 86.2, 82.6, 75.2, 63.6 ,36.7



General procedure for the synthesis of O- and S-glycosides from purine nucleosides (42-56):

To a solution of purine glycosides (1 eq.) (**37b** and **38b**) in anhydrous CH_2Cl_2 (3ml), external acceptors (*O* and *S* acceptors) were added, and the reaction mixture was chilled to 0 °C for 10 min. After that freshly activated 4Å MS powder (80mg) was added under a nitrogen atmosphere and kept for vigorous stirring for another 15 min. Following this, TfOH (1 eq.) was added to this reaction mixture and allowed to stir for another 45min-1h at 25 C. The progress of the reaction was monitored by TLC analysis as well as the solidification in the reaction mixture (fig 2.3). Upon completion, Et_3N was added to quench the reaction mixture, and the solvent was removed under reduced pressure. The crude was purified by silica gel column chromatography (10-20% ethyl acetate/ hexane) to afford the compounds (**42-56**)



Scheme: 3.2: Reaction of purine glycoside (37b, 38b) with alcoholic acceptor (41) in the presence of TfOH

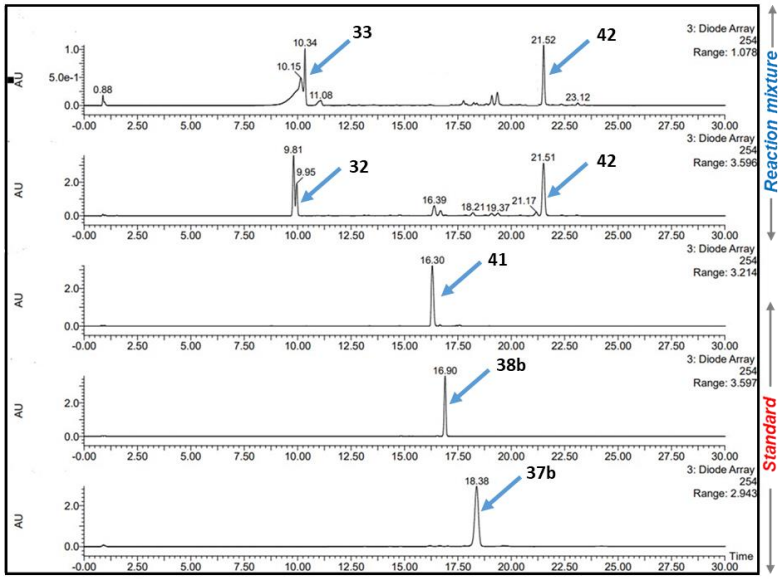
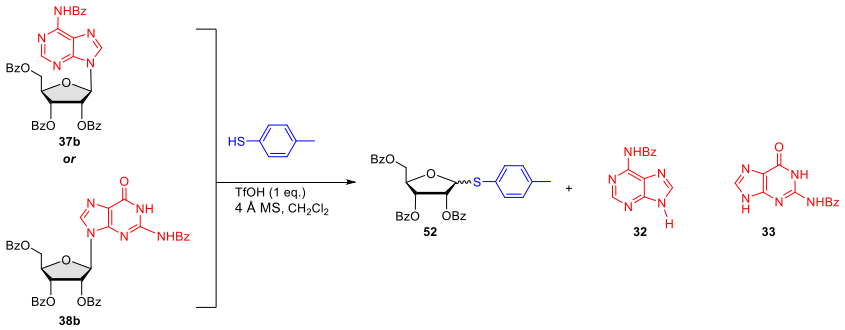


Figure 3.1: LC-MS profiling of the reaction mixture for formation of *O*-glycoside

LC-MS Conditions	Gradient		
Column: XBridge® C18 3.5 µm (4.6x50mm) Mobile Phase A: Water+ Formic acid (0.1% solution) Mobile phase B: ACN+ Formic acid (0.1% solution) Column & sample temp. 25 °C Flow rate: 0.8ml/ min. Run time: 30 min. Injection volume: 10 µL UV detection: 254nm	Time	%A	%B
	0	100	0
	5	50	50
	8	20	80
	11	10	90
	23	0	100
	24	40	60
	25	70	30
	26	100	0
	30	100	0



Scheme: 3.3: Reaction of purine glycoside (37b, 38b) with the thiotol acceptor in the presence of TfOH

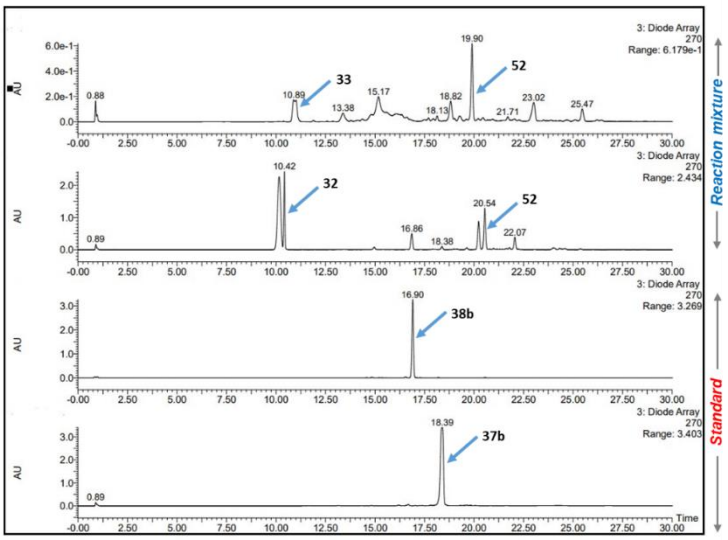
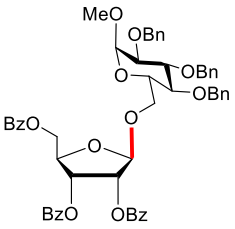


Figure 3.2: LC-MS profiling of the reaction mixture for formation of *S*-glycoside

LC-MS Conditions	Gradient		
Column: XBridge® C18 3.5 µm (4.6x50mm) Mobile Phase A: Water+ Formic acid (0.1% solution) Mobile phase B: ACN+ Formic acid (0.1% solution) Column & sample temp. 25 °C Flow rate: 0.8ml/ min. Run time: 30 min. Injection volume: 10 µL UV detection: 254nm	Time	%A	%B
	0	100	0
	5	50	50
	8	20	80
	11	10	90
	23	0	100
	24	40	60
	25	70	30
	26	100	0
	30	100	0

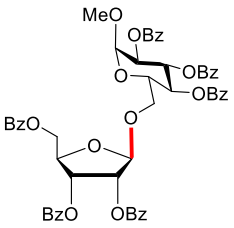
(43):



Compound **43** was prepared from **37b or 38b** according to the abovementioned general procedure (92%, viscous liquid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 – 8.05 (m, 4H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.62 – 7.33 (m, 24H), 5.91 (dt, *J* = 7.0, 4.0 Hz, 1H), 5.73 (t, *J* = 4.2 Hz, 1H), 5.24 (d, *J* = 3.0 Hz, 1H), 5.07 (dd, *J* = 11.0, 2.4 Hz, 1H), 5.00 – 4.76 (m, 6H), 4.72 – 4.64 (m, 3H), 4.07 (td, *J* = 9.4, 3.1 Hz, 2H), 3.86 – 3.57 (m, 4H), 3.40 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2, 165.4, 165.2, 138.8, 138.3, 138.2, 133.5, 133.4,

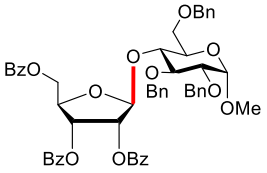
133.1, 129.8-129.7 (7C), 129.2 (2C), 129.0, 128.5, 128.5-127.6 (20C), 105.8, 97.9, 82.2, 80.1, 79.1, 75.7, 75.5, 74.9, 73.4, 72.7, 69.8, 66.6, 65.4, 55.2.

(42):



Compound **42** was prepared from **37b or 38b** according to the abovementioned general procedure (90%, white foam). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.97 (m, 6H), 7.91 – 7.85 (m, 6H), 7.60 – 7.53 (m, 1H), 7.49 – 7.27 (m, 17H), 6.14 (t, *J* = 9.8 Hz, 1H), 5.88 (dd, *J* = 7.0, 4.8 Hz, 1H), 5.76 (d, *J* = 4.9 Hz, 1H), 5.52 (t, *J* = 9.9 Hz, 1H), 5.38 (s, 1H), 5.31 – 5.21 (m, 2H), 4.75 – 4.66 (m, 2H), 4.56 – 4.48 (m, 1H), 4.25 (ddd, *J* = 10.3, 6.6, 2.3 Hz, 1H), 3.98 (dd, *J* = 11.5, 2.3 Hz, 1H), 3.75 (dd, *J* = 11.6, 6.6 Hz, 1H), 3.47 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2, 165.9 (2C), 165.4 (2C), 165.2, 133.5, 133.4, 133.4, 133.2, 133.1, 130.0 - 129.7 (5C), 129.3, 129.2 (2C), 129.0, 128.9, 128.6-128.3 (20C), 106.3, 96.9, 79.3, 75.5, 72.4, 70.6, 69.6, 69.0, 67.1, 64.9, 55.7.

(44):

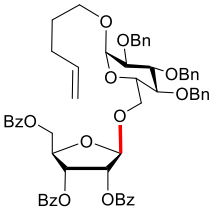


Compound **44** was prepared from **37b or 38b** according to the abovementioned general procedure (88%, thick syrup). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 – 8.00 (m, 2H), 7.95 – 7.91 (m, 2H), 7.89 – 7.85 (m, 2H), 7.53 (dt, *J* = 17.7, 7.6 Hz, 4H), 7.41 – 7.28 (m, 15H), 7.23 – 7.14 (m, 5H), 5.75 (t, *J* = 9.8 Hz ,1H), 5.64 (d, *J* = 2.0 Hz, 1H), 5.59 (dd, *J* = 4.8, 2.0 Hz, 1H), 5.02 – 4.96 (m, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.74 (d, *J* = 12.1 Hz, 1H), 4.64 – 4.53 (m, 7H), 3.97 – 3.87 (m, 2H), 3.79 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.66 (dt, *J* = 11.3, 3.3 Hz, 2H), 3.52 (dd, *J* = 9.2, 3.5 Hz, 1H), 3.35 (s, 3H). **^{13}C NMR** (101 MHz, chloroform-*d*) δ 166.2, 165.5, 165.3, 139.1, 138.3, 138.1, 133.5, 133.4, 133.1, 129.8-129.7 (7C), 129.2 (2C), 129.0, 128.5, 128.5-127.6 (20C), 106.9, 98.3, 80.7, 80.0, 78.8, 75.6, 75.5, 73.6, 73.5, 72.2, 69.6, 68.6, 64.9, 55.4.

(45):

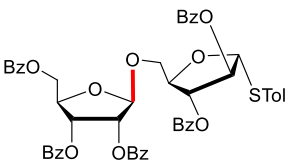
Compound **45** was prepared from **37b or 38b** according to the abovementioned general procedure (91%, thick syrup). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.97 (m, 4H), 7.89 – 7.83 (m, 2H), 7.60 – 7.40 (m, 6H), 7.37 – 7.25 (m, 18H), 5.85 – 5.73 (m, 2H), 5.63 (d, *J* = 4.9 Hz, 1H), 5.15 (s, 1H), 5.03 – 4.86 (m, 4H), 4.84 – 4.61 (m, 8H), 4.59 – 4.53 (m, 1H),

4.03 – 3.91 (m, 2H), 3.80 – 3.73 (m, 1H), 3.68 – 3.60 (m, 1H), 3.59 – 3.56 (m, 1H), 3.54 – 3.50 (m, 1H), 3.40 – 3.32 (m, 1H), 2.12 – 2.03 (m, 2H), 1.74 – 1.67 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 165.5, 165.3, 139.1, 138.5, 138.4, 138.3, 133.6-127.6 (33C), 115.0, 105.9, 96.8, 82.3, 80.5, 79.2, 75.7, 75.6, 75.1, 73.3 (2C), 72.9, 70.0, 67.6, 66.6, 65.6, 30.4, 28.7.



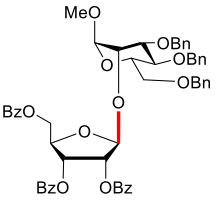
(46)

Compound **46** was prepared from **37b or 38b** according to the abovementioned general procedure (91%, white foam). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 6H), 7.88 – 7.83 (m, 2H), 7.61 – 7.53 (m, 3H), 7.49 – 7.39 (m, 8H), 7.32 – 7.26 (m, 8H), 7.06 (d, *J* = 7.9 Hz, 2H), 5.85 (t, *J* = 6.7 Hz, 1H), 5.76 (dd, *J* = 4.9, 2.0 Hz, 1H), 5.64 (d, *J* = 2.0 Hz, 1H), 5.41 (d, *J* = 1.9 Hz, 1H), 5.37 (t, *J* = 4.4, 2.1 Hz, 1H), 4.73 – 4.68 (m, 2H), 4.60 – 4.55 (m, 2H), 4.24 (q, *J* = 2.0 Hz, 1H), 4.14 – 4.08 (m, 1H), 3.94 – 3.85 (m, 1H), 2.25 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2, 166.0, 165.7, 165.3, 165.2, 137.7, 133.5, 133.3, 133.0, 132.3, 130.4, 130.0-129.8 (10C), 129.8, 129.4, 129.3 (2C), 129.1 (2C), 128.6 - 127.9 (15C), 105.8, 91.5, 87.3, 81.9, 79.3, 78.1, 75.6, 72.7, 72.0, 67.8, 65.3, 21.1.



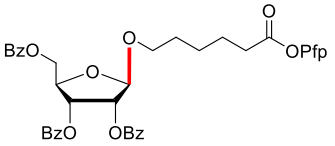
(47)

Compound **47** was prepared from **37b or 38b** according to the abovementioned general procedure (88%, white foam). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 – 7.84 (m, 6H), 7.59 – 7.27 (m, 19H), 7.25 – 7.13 (m, 5H), 5.92 – 5.82 (m, 2H), 5.74 (d, *J* = 4.8 Hz, 1H), 5.47 (s, 1H), 5.27 – 5.13 (m, 2H), 5.01 (d, *J* = 1.9 Hz, 1H), 4.84 (dd, *J* = 16.4, 11.4 Hz, 2H), 4.75 – 4.66 (m, 2H), 4.65 – 4.56 (m, 3H), 4.56 – 4.46 (m, 1H), 4.24 – 4.16 (m, 2H), 4.00 – 3.87 (m, 2H), 3.82 – 3.69 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1, 165.4, 165.3, 138.5, 138.4, 133.8, 133.6, 133.4, 133.1, 130.0-117.5 (30C), 104.6, 96.5, 79.1, 78.4, 75.9, 75.2, 75.0, 73.8, 73.5, 73.3, 72.2, 72.2, 69.3, 68.2, 66.3.



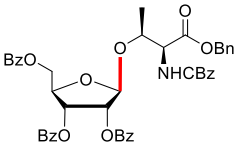
(48)

Compound **48** was prepared from **37b or 38b** according to the abovementioned general procedure (87%, yellow syrup). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 7.87 (m, 6H), 7.60 – 7.30 (m,



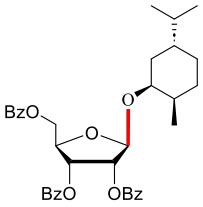
9H), 5.87 (dd, *J* = 6.6, 4.8 Hz, 1H), 5.68 (d, *J* = 4.8 Hz, 1H), 5.25 (s, 1H), 4.77 – 4.70 (m, 2H), 4.57 – 4.48 (m, 1H), 3.84 – 3.75 (m, 1H), 3.51 – 3.42 (m, 1H), 2.64 (t, *J* = 7.4 Hz, 2H), 1.79 – 1.71 (m, 2H), 1.63 – 1.56 (m, 2H), 1.49 – 1.39 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4, 166.2, 165.4, 165.3, 133.5-128.4 (24C), 105.6, 78.9, 75.6, 72.6, 68.1, 64.9, 33.2, 28.9, 25.4, 24.5.

(49)



Compound **49** was prepared from **37b or 38b** according to the abovementioned general procedure (84%, yellow syrup). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 – 7.86 (m, 6H), 7.59 – 7.36 (m, 6H), 7.36 – 7.23 (m, 13H), 5.66 (d, *J* = 9.7 Hz, 1H), 5.59 (d, *J* = 6.5 Hz, 2H), 5.34 (s, 1H), 5.28 – 5.16 (m, 2H), 5.13 – 5.05 (m, 2H), 4.65 – 4.60 (m, 1H), 4.56 (dd, *J* = 6.4, 2.3 Hz, 1H), 4.50 (d, *J* = 2.2 Hz, 1H), 4.50 – 4.46 (m, 2H), 1.31 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.3, 166.2, 165.3 (2C), 156.8, 136.3, 135.4, 133.7, 133.5, 133.3, 133.2, 129.9-128.1 (24C), 103.8, 79.1, 76.0, 74.1, 72.7, 67.6, 67.2, 65.6, 58.8, 16.8.

(50)

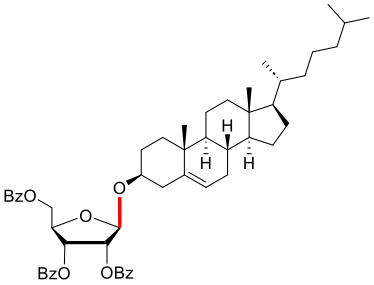


Compound **50** was prepared from **37b or 38b** according to the abovementioned general procedure (94%, yellow syrup). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.87 (m, 6H), 7.59 – 7.49 (m, 3H), 7.45 – 7.31 (m, 6H), 5.80 (dd, *J* = 7.1, 4.7 Hz, 1H), 5.61 (d, *J* = 4.8 Hz, 1H), 5.47 (s, 1H), 4.72 (td, 1H), 4.64 (dd, *J* = 11.6, 4.7 Hz, 1H), 4.52 (dd, *J* = 11.5, 6.3 Hz, 1H), 3.53 (td, *J* = 10.6, 4.2 Hz, 1H), 2.27 – 2.19 (m, 1H), 2.14 (dt, *J* = 13.2, 3.4 Hz, 1H), 1.68 – 1.62 (m, 3H), 1.27 (d, 4H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 165.5, 165.5, 133.6-128.4 (18C), 102.6, 78.2, 76.4, 73.2, 66.0, 47.9, 40.2, 34.5, 31.6, 29.8, 25.4, 23.0, 22.4, 21.1, 15.8.

(51)

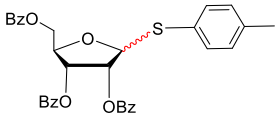
Compound **51** was prepared from **37b or 38b** according to the abovementioned general procedure (94%, yellow syrup). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.09 – 8.00 (m, 4H), 7.92 – 7.86 (m, 2H), 7.61 – 7.48 (m, 3H), 7.44 – 7.30 (m, 6H), 5.88 (dd, *J* = 6.6, 4.8 Hz,

1H), 5.64 (d, *J* = 4.8 Hz, 1H), 5.41 (s, 1H), 5.34 (dt, *J* = 4.5, 2.0 Hz, 1H), 4.75 – 4.66 (m, 2H), 4.57 – 4.49 (m, 1H), 3.63 – 3.51 (m, 1H), 2.45 – 2.34 (m, 1H), 2.29 – 2.17 (m, 1H), 2.06 – 1.75 (m, 6H), 1.60 (s, 3H), 1.53 – 1.46 (m, 3H), 1.39 – 1.32 (m, 3H), 1.26 (s, 1H), 1.19 – 0.97 (m, 11H), 0.93 (s, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.67 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2, 165.4, 165.4, 140.3-122.0 (20C), 103.9, 78.6, 78.1, 76.1, 72.7, 65.2, 56.8-23.8 (18C), 22.8, 22.6, 21.0, 19.3, 18.7, 11.9.



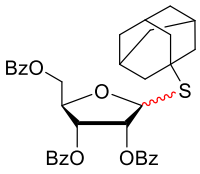
(52)

Compound **52** was prepared from **37b or 38b** according to the abovementioned general procedure (90%, white foam). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 – 7.88 (m, 6H), 7.56 – 7.31 (m, 11H), 7.04 (d, *J* = 7.7 Hz, 2H), 5.72 (t, *J* = 4.9 Hz, 1H), 5.65 (t, *J* = 5.3 Hz, 1H), 5.56 (d, *J* = 5.4 Hz, 1H), 4.65 (dd, *J* = 7.3, 3.2 Hz, 1H), 4.61 (d, *J* = 3.8 Hz, 1H), 4.51 – 4.46 (m, 1H), 2.25 (d, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 166.1, 165.3 (2C), 165.1, 165.1, 139.0, 134.6, 133.6, 133.5, 133.5, 133.3, 133.2, 132.7, 130.0-127.0 (40C), 90.9, 88.0, 80.4, 79.0, 74.4, 72.4, 72.2, 71.7, 64.4, 60.4, 21.2 (2C).



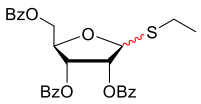
(53)

Compound **53** was prepared from **37b or 38b** according to the abovementioned general procedure (84%, white foam). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 – 7.88 (m, 6H), 7.58 – 7.29 (m, 9H), 5.85 (t, *J* = 5.3 Hz, 1H), 5.74 (dd, *J* = 4.4, 2.4 Hz, 1H), 5.72 (d, *J* = 3.8 Hz, 1H), 5.71 – 5.67 (m, 1H), 4.75 – 4.61 (m, 2H), 2.06 – 1.90 (m, 9H), 1.72 – 1.63 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 166.2, 165.7, 165.4, 165.3, 165.3, 133.5-128.4 (36C), 83.0, 82.2, 79.8, 78.4, 76.7, 73.1, 72.9, 72.1, 64.6, 64.1, 47.0, 45.9, 44.0 (7C), 36.7, 36.2 (3C), 29.9 (2C), 29.8, 29.8 (2C), 29.7, 24.8.



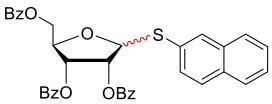
(54)

Compound **54** was prepared from **37b or 38b** according to the abovementioned general procedure (87%, thick syrup). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 – 7.98 (m, 4H), 7.96 – 7.89 (m, 2H), 7.60 – 7.49 (m, 3H), 7.47 – 7.37 (m, 4H), 7.37 – 7.31 (m, 2H), 5.90 (dd, *J* = 6.2, 4.8 Hz, 1H), 5.77 – 5.71 (m, 1H), 5.49 (d, *J* = 3.6 Hz, 1H), 4.79 – 4.55 (m, 3H), 2.81 – 2.65 (m, 2H), 1.30 (dt, *J* = 14.8, 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 166.3, 165.7, 165.4, 165.3, 165.2, 133.6-128.5 (36C), 87.3, 86.1, 79.9, 78.7, 75.6, 72.8, 72.2, 71.6, 64.4, 63.9, 25.6, 24.8, 15.3, 14.9.



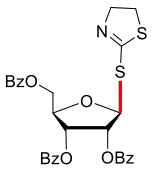
(55)

Compound **55** was prepared from **37b or 38b** according to the abovementioned general procedure (78%, white foam). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 – 7.88 (m, 7H), 7.77 – 7.30 (m, 15H), 5.80 (t, *J* = 4.8 Hz, 1H), 5.75 (t, *J* = 4.9 Hz, 1H), 5.72 (d, *J* = 5.0 Hz, 1H), 4.79 – 4.64 (m, 2H), 4.61 – 4.52 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3 (2C), 165.5 (2C), 165.2(2C), 133.7-126.4 (56C), 90.5, 88.4, 80.7 (2C), 74.9 (2C), 72.6 (2C), 64.4 (2C).



(56)

Compound **56** was prepared from **37b or 38b** according to the abovementioned general procedure (82%, white foam). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 – 7.93 (m, 6H), 7.60 – 7.51 (m, 3H), 7.48 – 7.33 (m, 6H), 6.90 (d, *J* = 6.1 Hz, 1H), 5.90 (t, *J* = 6.0 Hz, 1H), 5.84 (dd, *J* = 6.0, 3.3 Hz, 1H), 4.77 (q, *J* = 3.3 Hz, 1H), 4.68 (d, *J* = 3.3 Hz, 1H), 4.66 (d, *J* = 3.5 Hz, 1H), 4.40 – 4.31 (m, 1H), 4.21 – 4.12 (m, 1H), 3.44 – 3.34 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1, 165.5, 164.8, 164.0, 133.7-87.0 (19C), 80.7, 71.8, 71.6, 64.3, 63.8, 35.4.

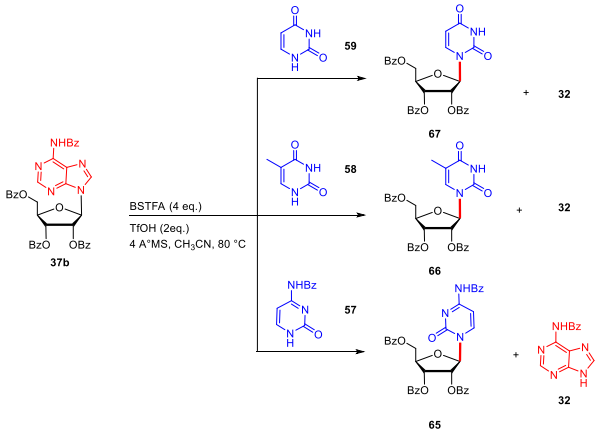


General procedures for the synthesis of pyrimidine nucleosides from purine nucleosides (65-74):

BSTFA (4.0 eq.) was added to a stirred suspension of acceptor **57-64** (2 eq.) in dry CH_3CN under a nitrogen atmosphere. After that, the mixture was stirred at 50 °C for 30 mins, this solution was added to a solution of purine nucleosides (**37b-38b**) (1.0 eq.) and activated 4Å MS (4.0 g/mmol) in dry CH_3CN, which has been refluxed at 80 °C under nitrogen

atmosphere. After the completion of the reaction (monitored by TLC and LC-MS), Et_3N was added to quench the reaction and then the solvent was removed under reduced pressure. The resulting residue was purified by silica gel column chromatography (40-50% ethyl acetate/hexane) to afford the pyrimidine nucleosides (**65-74**).

Reaction Monitoring by LC-MS Analysis:



Scheme 3.4: Reaction of Adenosine (37b) with Cytosine (57), Thymine (58), and uracil (59) in the presence of TfOH

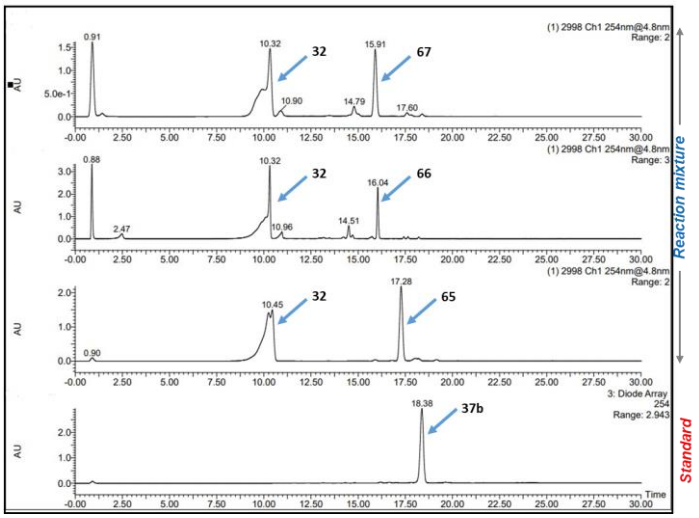
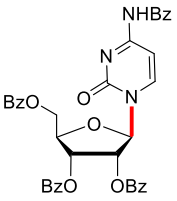


Figure 3.3: LC-MS profiling of the reaction mixture for formation of *N*-glycoside

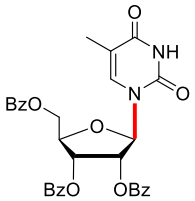
LC-MS Conditions	Gradient		
Column: XBridge® C18 3.5 µm (4.6x50mm) Mobile Phase A: Water+ Formic acid (0.1% solution) Mobile phase B: ACN+ Formic acid (0.1% solution) Column & sample temp. 25 °C Flow rate: 0.8ml/ min. Run time: 30 min. Injection volume: 10 µL UV detection: 254nm	Time	%A	%B
	0	100	0
	5	50	50
	8	20	80
	11	10	90
	23	0	100
	24	40	60
	25	70	30
	26	100	0
	30	100	0

(65):



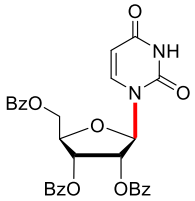
Compound **65** was prepared from **37b or 38b** according to the abovementioned general procedure (84%, white solid). **^{1}H NMR** (400 MHz, CDCl3) δ 8.83 (br s, 1H), 8.11 (d, J = 7.7 Hz, 2H), 8.01–7.87 (m, 7H), 7.66–7.47 (m, 9H), 7.36 (t, J = 7.6 Hz, 4H), 6.46 (d, J = 4.4 Hz, 1H), 5.96- 5.79 (m, 2H), 4.92–4.68 (m, 3H).

(66):



Compound **66** was prepared from **37b or 38b** according to the abovementioned general procedure (87%, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.18 – 8.11 (m, 2H), 8.01 – 7.92 (m, 4H), 7.64 – 7.47 (m, 5H), 7.43 – 7.34 (m, 4H), 7.16 (s, 1H), 6.43 (d, *J* = 6.3 Hz, 1H), 5.92 (dd, *J* = 6.0, 3.7 Hz, 1H), 5.76 (t, *J* = 6.2 Hz, 1H), 4.89 (dd, *J* = 12.1, 2.6 Hz, 1H), 4.73 – 4.62 (m, 2H), 1.60 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.0, 165.4 (2C), 163.6, 150.5, 134.9, 133.8, 130.0 (2C), 129.9 (2C), 129.7 (3C), 129.2, 128.9- 128.6 (8C), 128.4, 112.2, 87.0, 80.6, 73.4, 71.4, 64.0, 12.1.

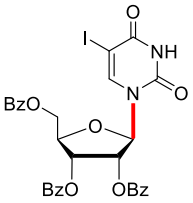
(67):



Compound **67** was prepared from **37b or 38b** according to the abovementioned general procedure (88%, white solid). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.07 (br s, 1H), 8.10 (d, J = 7.8 Hz, 2H), 7.98 (d, J = 7.8 Hz, 2H), 7.94 (d, J = 7.8 Hz, 2H), 7.54 (m, 5H), 7.38 (m, 5H), 6.32 (d, J =

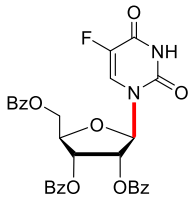
5.5 Hz, 1H), 5.89 (t, J = 5.3 Hz, 1H), 5.76 (t, J = 5.8 Hz, 1H), 5.62 (dd, J = 8.2, 2.0 Hz, 1H), 4.84 (dd, J = 12.1, 2.7 Hz, 1H), 4.72 (dd, J = 6.9, 3.9 Hz, 1H), 4.67 (dd, J = 12.2, 3.9 Hz, 1H). **^{13}C NMR** (101 MHz, CDCl3) δ 166.1, 165.4, 165.4, 163.5, 150.4, 140.0, 133.8-133.6 (3C), 129.9-129.7 (4C), 129.3, 128.7, 128.6, 128.6-128.4 (8C), 103.4, 88.4, 80.4, 73.9, 71.2, 63.9.

(68):



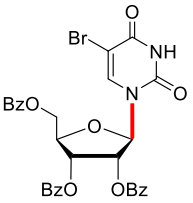
Compound **68** was prepared from **37b or 38b** according to the abovementioned general procedure (81%, white solid). **^{1}H NMR** (400 MHz, Chloroform-d) δ 9.55 (s, 1H), 8.15 – 8.10 (m, 2H), 8.01 – 7.96 (m, 2H), 7.95 – 7.90 (m, 2H), 7.86 (s, 1H), 7.62 – 7.54 (m, 2H), 7.52 – 7.48 (m, 2H), 7.42 – 7.32 (m, 5H), 6.36 (d, J = 6.0 Hz, 1H), 5.91 (dd, J = 6.0, 3.6 Hz, 1H), 5.77 (t, J = 6.0 Hz, 1H), 4.85 – 4.79 (m, 1H), 4.76 – 4.70 (m, 2H); **^{13}C NMR** (101 MHz, CDCl3) δ 166.2, 165.4, 165.4, 159.9, 150.1, 144.2, 133.9, 133.8, 133.7, 130.0 (2C), 129.9 (2C), 129.8 (2C), 129.2 (2C), 129.0 -128.6 (6C), 128.3, 87.8, 81.0, 73.9, 71.4, 70.0, 64.0.

(69):



Compound **69** was prepared from **37b or 38b** according to the abovementioned general procedure (83%, white solid). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.23 (d, J = 6.8 Hz, 1H), 8.06–7.96 (m, 2H), 7.89 (d, J = 7.7 Hz, 4H), 7.72–7.58 (m, 3H), 7.55–7.39 (m, 6H), 6.19 (d, J = 3.4 Hz, 1H), 5.93 (m, 2H), 4.73 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 165.9, 165.7, 165.0, 157.49 (d, ^{3}JC-F = 26.2 Hz), 149.5, 140.63 (d, ^{2}JC-F = 231.6 Hz), 133.9, 133.8, 133.7, 130.2 (2C), 129.9 (2C), 129.9 (2C), 129.7 (2C), 128.9-128.6 (6C), 128.4, 126.4 (d, ^{3}JC-F = 35.2 Hz), 89.3, 79.3, 73.5, 70.7, 64.1.

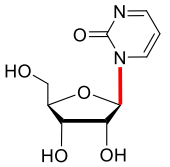
(70):



Compound **70** was prepared from **37b** or **38b** according to the above-mentioned general procedure (85%, white solid). **^{1}H NMR** (400 MHz, CDCl3) δ 9.90 (s, 1H), 8.13 – 7.91 (m, 6H), 7.79 (s, 1H), 7.59 – 7.33 (m, 9H), 6.37 (d, J = 5.8 Hz, 1H), 5.91 (t, J = 5.0 Hz, 1H), 5.78 (t, J = 6.0 Hz, 1H), 4.87 – 4.68 (m, 3H); **^{13}C NMR** (101 MHz, CDCl3) δ 166.2, 165.4, 165.4, 159.1, 149.8,

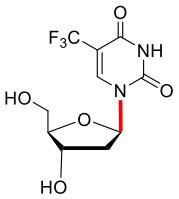
139.1, 133.9, 133.8, 133.7, 130.2 (2C), 129.9 (2C), 129.9 (2C), 129.7 (2C), 128.9-128.6 (6C), 128.4, 98.2, 88.0, 80.9, 73.9, 71.3, 63.8.

(75):



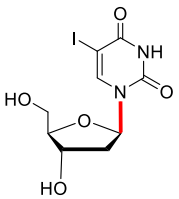
Compound **71** was synthesized from purine nucleoside **37b** or **38b** according to the general above-mentioned procedure. (84% yield). Next, a solution of **71** (200 mg, 0.371 mmol) in 3 ml CH_3OH was slowly added to NaOMe (24mg, 0.442 mmol) at room temperature. The solution was stirred for another 2 h under the same temperature. Then it was quenched with Amberlite IR 120 H^+. The solid resin was filtered, and the filtrate was concentrated in vacuo and purified by silica gel column chromatography (CH_2Cl_2/CH_3OH =10/1) affording compound **75** as a white solid. (86 % overall isolated yield). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.67 – 8.61 (m, 2H), 6.55 (dd, J = 6.7, 4.1 Hz, 1H), 5.82 (d, J = 2.1 Hz, 1H), 5.65 (d, J = 4.7 Hz, 1H), 5.28 (t, J = 5.0 Hz, 1H), 5.11 (dd, J = 4.6, 1.2 Hz, 1H), 4.07 – 3.99 (m, 3H), 3.89 – 3.80 (m, 1H), 3.73 – 3.63 (m, 1H); **^{13}C NMR** (101 MHz, DMSO-d_6) δ 166.6, 155.4, 145.0, 104.3, 91.2, 84.6, 75.1, 68.7, 60.0.

(76):



Compound **72** was prepared from **37b or 38b** according to the abovementioned general procedure. Then it was deprotected by NaOMe/CH_3OH to afford compound **76** (70%, white solid).**^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.82 (br s, 1 H), 8.72 (s, 1 H), 6.08 (t, J = 6.4 Hz, 1 H), 5.31 (br s, 1 H), 5.24 (br s, 1 H), 4.25 (s, 1 H), 3.83 (dd, J = 2.8, 6.0 Hz, 1 H), 3.65 (d, J = 11.6 Hz, 1 H), 3.58 (d, J = 12.0 Hz, 1 H), 2.20 (t, J = 5.6 Hz, 2 H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 159.5, 150.0, 142.8 (q, $^3J_{C-F}$ = 5.8Hz), 124.5 (q, J_{C-F} = 268.8Hz), 103.3 ($^2J_{C-F}$ = 32.9 Hz), 88.1, 85.9, 69.8, 60.7, 41.1.

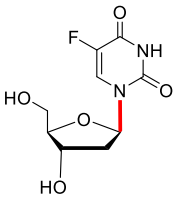
(77):



Compound **77** was prepared from **37b or 38b** according to the abovementioned general procedure. Then it was deprotected by NaOMe/CH_3OH to afford compound **77** (80%, white solid). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.78 (s, 1H), 6.47 (t, *J* = 6.5 Hz, 1H), 5.62 (d, *J*

= 4.2 Hz, 1H), 5.52 (t, *J* = 4.8 Hz, 1H), 4.62 (p, *J* = 4.1 Hz, 1H), 4.17 (q, *J* = 3.3 Hz, 1H), 4.04 – 3.91 (m, 2H), 2.55 – 2.45 (m, 2H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 160.9, 150.5, 145.5, 87.9, 85.1, 70.4, 69.7, 61.2, 40.6.

(78):

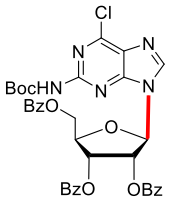


Compound **78** was prepared from **37b or 38b** according to the abovementioned general procedure. Then it was deprotected by NaOMe/CH_3OH to afford compound **78** (74%, white solid). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.79 (br s, 1 H), 8.21 (d, J = 7.6 Hz, 1 H), 6.12 (t, J = 6.4 Hz, 1 H), 5.27–5.17 (m, 2 H), 4.24 (d, J = 3.2 Hz, 1 H), 3.78 (dd, J = 3.2, 6.0 Hz, 1 H), 3.61 (dd, J = 3.2, 12.0 Hz, 1 H), 3.56 (dd, J = 3.2, 12.0 Hz, 1 H), 2.10 (dd, J = 4.8, 6.4 Hz, 2 H). **^{13}C NMR** (101 MHz, DMSO) δ 157.4 (d, $^3J_{C\text{-}F}$ = 26.1Hz), 149.4, 140.3 (d, $^2J_{C\text{-}F}$ = 229.8 Hz) ,125.1 (d, $^3J_{C\text{-}F}$ = 34.4 Hz), 87.9, 85.0, 70.6, 61.5, 40.4.

General procedure for the synthesis of purine and pyrimidine nucleoside via thioglycoside intermediate (85-89)

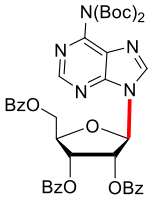
To a solution of purine glycosides (1 eq.) (**37b** and **38b**) in anhydrous acetonitrile (3ml), external acceptors (*S* acceptors) was added, and the reaction mixture was chilled to 0 °C for 10 min. After that freshly activated 4Å MS powder (80mg) was added under a nitrogen atmosphere and kept for vigorous stirring for another 15 min. Following this, TfOH (1 eq.) was added to this reaction mixture and allowed to stir for another 45min-1h at 25 °C. After that, in the same reaction mixture NIS (1.25 eq.) and AgOTf (0.25 eq.) were added at 0 °C and allowed to stir for another 45min-1h at 0 °C - 25 °C. The progress of the reaction was monitored by TLC analysis. Upon completion, Et_3N was added to quench the reaction mixture, and the solvent was removed under reduced pressure. The crude was purified by silica gel column chromatography (40-50% ethyl acetate/ hexane) to afford the compounds (**85-89**)

(85):



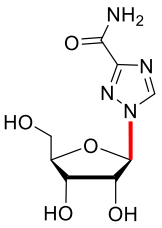
Compound **85** was prepared from **37b or 38b** according to the abovementioned general procedure (90%, white solid). The analytical data was matched with the previous reports.[14]

(86):



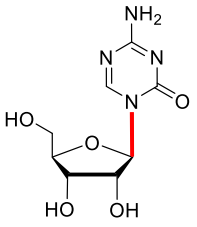
Compound **86** was prepared from **37b or 38b** according to the abovementioned general procedure (84%, white solid). The analytical data was matched with the previous reports.[14]

(93):



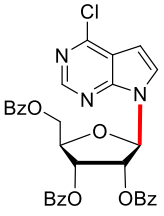
Compound **93** was prepared from **37b** according to the general procedure for the synthesis of pyrimidine nucleosides from purine nucleosides (90%, white solid). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 7.83 (s, 1H), 7.62 (s, 1H), 5.81 (d, *J* = 3.9 Hz, 1H), 5.57 (d, *J* = 5.6 Hz, 1H), 5.19 (d, *J* = 5.5 Hz, 1H), 4.92 (t, *J* = 5.5 Hz, 1H), 4.35 (q, *J* = 4.7 Hz, 1H), 4.14 (q, *J* = 5.1 Hz, 1H), 3.95 (q, *J* = 4.7 Hz, 1H), 3.63 (dt, *J* = 11.9, 4.6 Hz, 1H), 3.50 (dt, *J* = 11.8, 5.0 Hz, 1H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 160.5, 157.3, 145.1, 91.8, 85.5, 74.5, 70.0, 61.3.

(94):



Compound **94** was prepared from **37b** according to the general procedure for the synthesis of pyrimidine nucleosides from purine nucleosides (88%, white solid). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.57 – 7.49 (m, 2H), 5.67 (d, *J* = 3.8 Hz, 1H), 5.50 – 4.94 (m, 3H), 4.08 (dd, *J* = 4.9, 3.9 Hz, 1H), 4.01 (t, *J* = 5.3 Hz, 1H), 3.85 (dt, *J* = 5.8, 3.0 Hz, 1H), 3.69 (dd, *J* = 12.2, 3.0 Hz, 1H), 3.56 (dd, *J* = 12.2, 3.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 156.8, 153.8, 89.8, 84.8, 74.4, 69.4, 60.6.

(95):



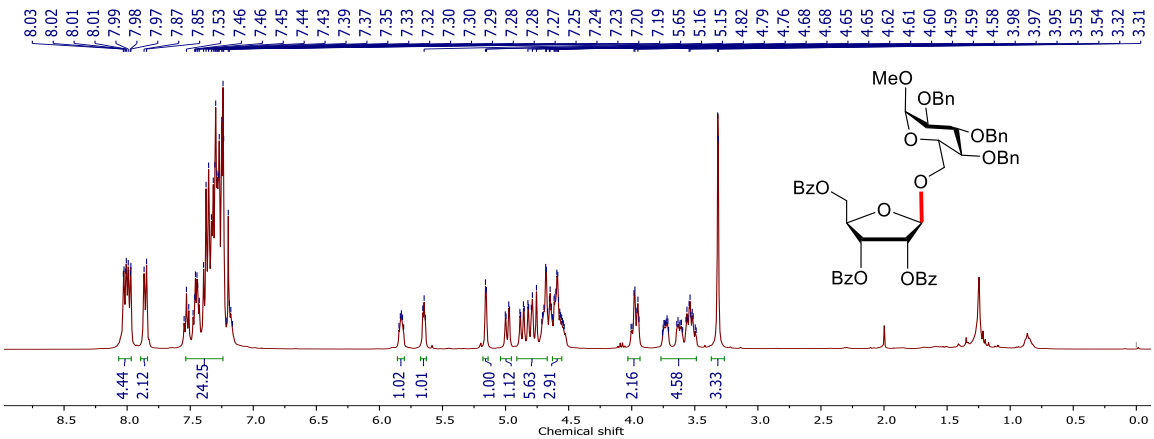
Compound 95 was prepared from **37b** according to the general procedure for the synthesis of pyrimidine nucleosides from purine nucleosides (78%, white solid). The analytical data was matched with the previous reports.[28]

Conclusions

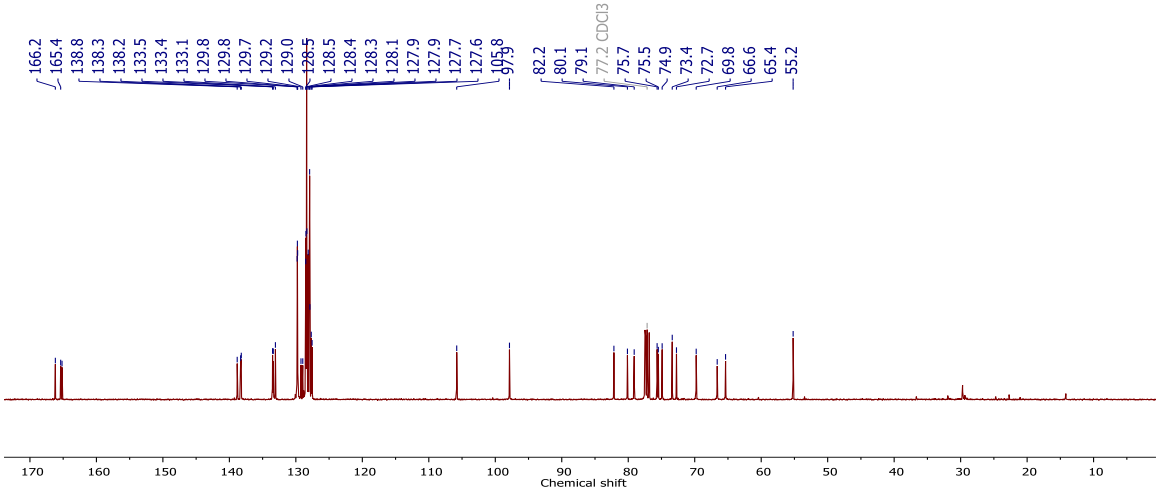
In summary, a groundbreaking unified direct one-pot method has been discovered for the chemical modification of readily available and cost-effective purine nucleosides. This innovative approach facilitates the transformation of purine nucleosides into pyrimidine nucleosides, broadening the scope to include A/G- T/C/U bases. Moreover, the synthesis of various *O*-, *S*-, and *N*-, glycosides has been achieved with remarkable efficiency, yielding high to excellent yields. The utilization of thioglycoside intermediate has streamlined the process, offering a versatile strategy for synthesizing a diverse array of purine and pyrimidine nucleosides. Importantly, this editing strategy extends its utility beyond nucleoside synthesis, demonstrating its effectiveness in the straightforward synthesis of several FDA-approved drugs. This advancement holds significant promise for accelerating drug discovery and development processes through its accessible and efficient synthetic protocol.

NMR Spectral chart:

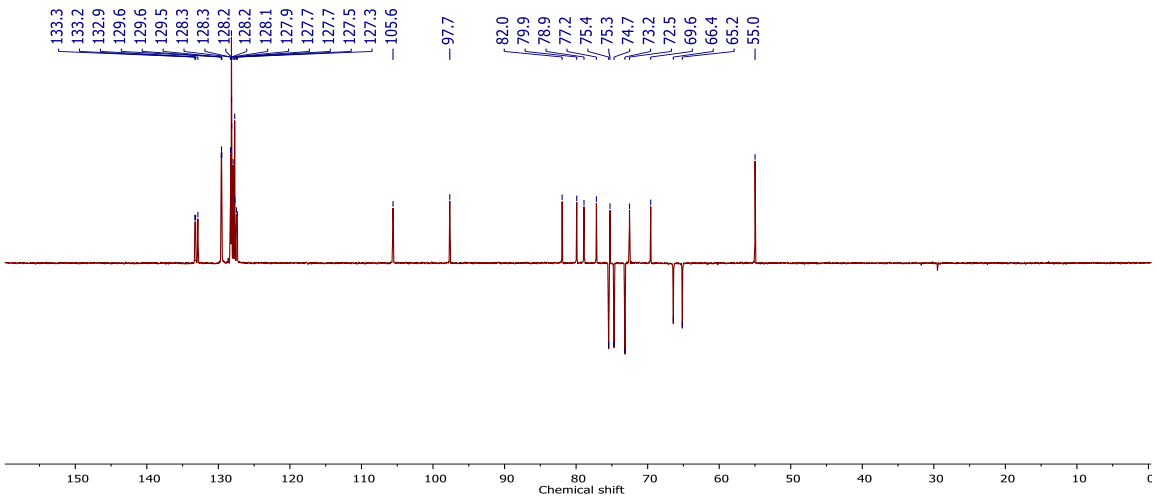
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 43:



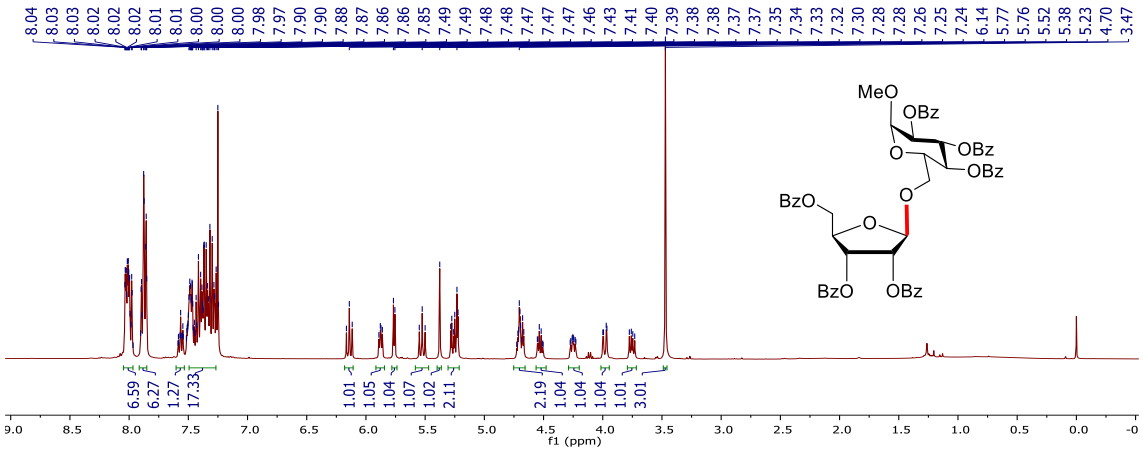
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 43



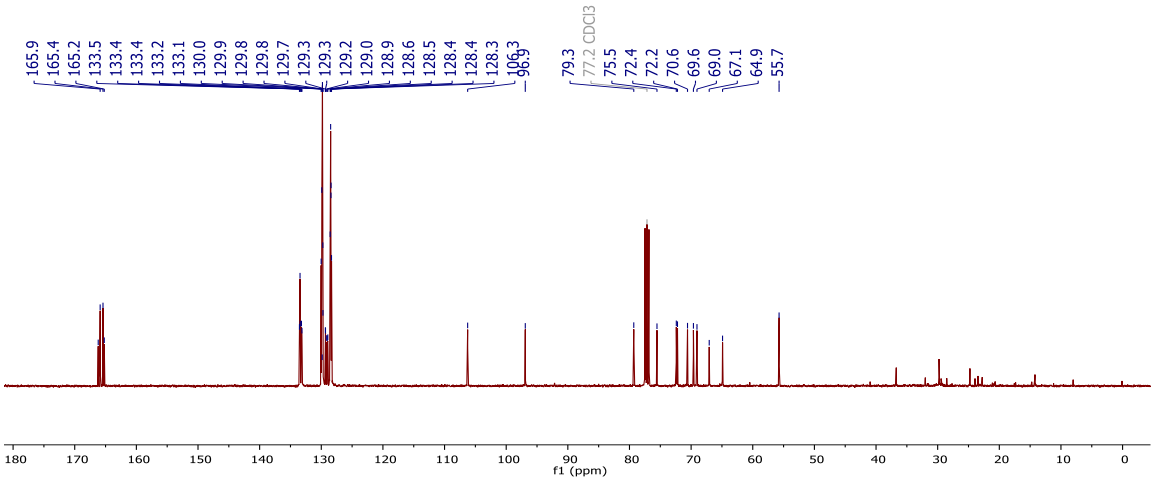
DEPT-135 NMR Spectrum (100 MHz, CDCl3) of Compound 43



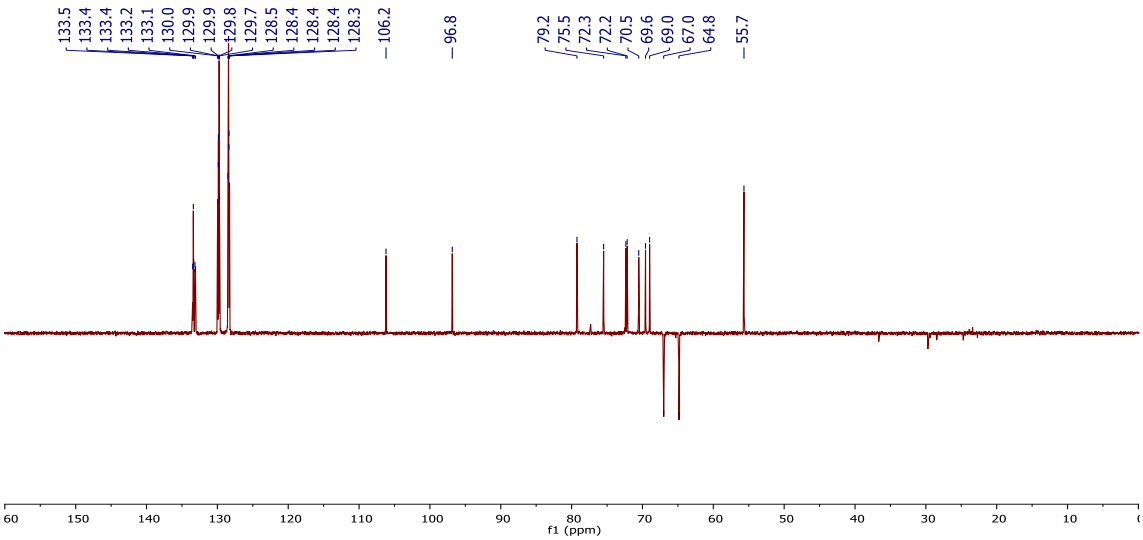
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 42:



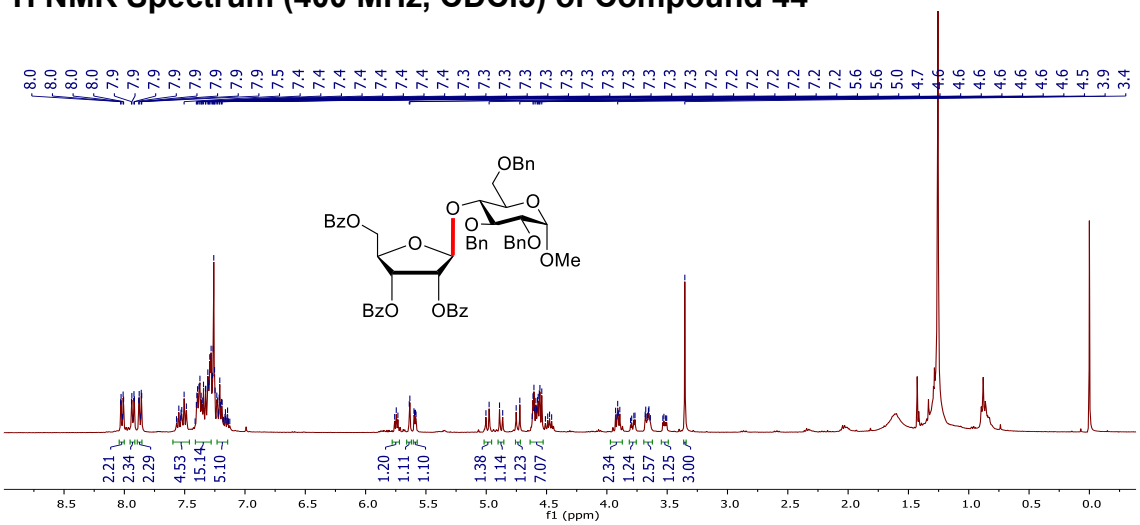
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 42



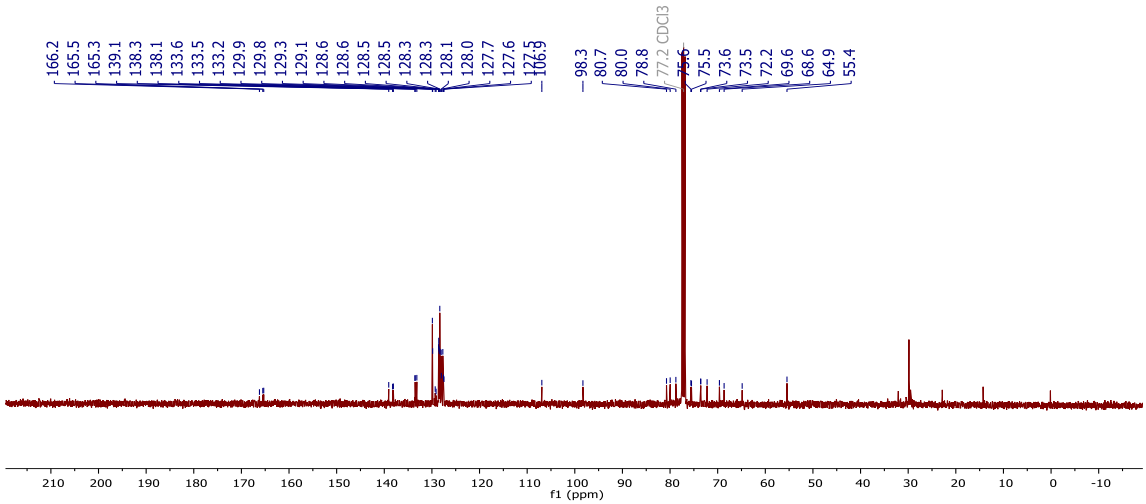
DEPT-135 NMR Spectrum (100 MHz, CDCl3) of Compound 42



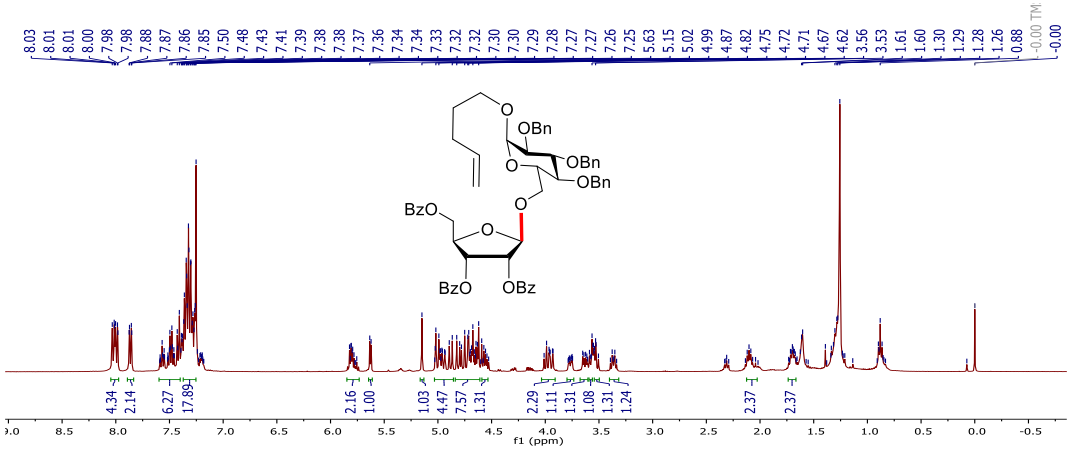
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 44



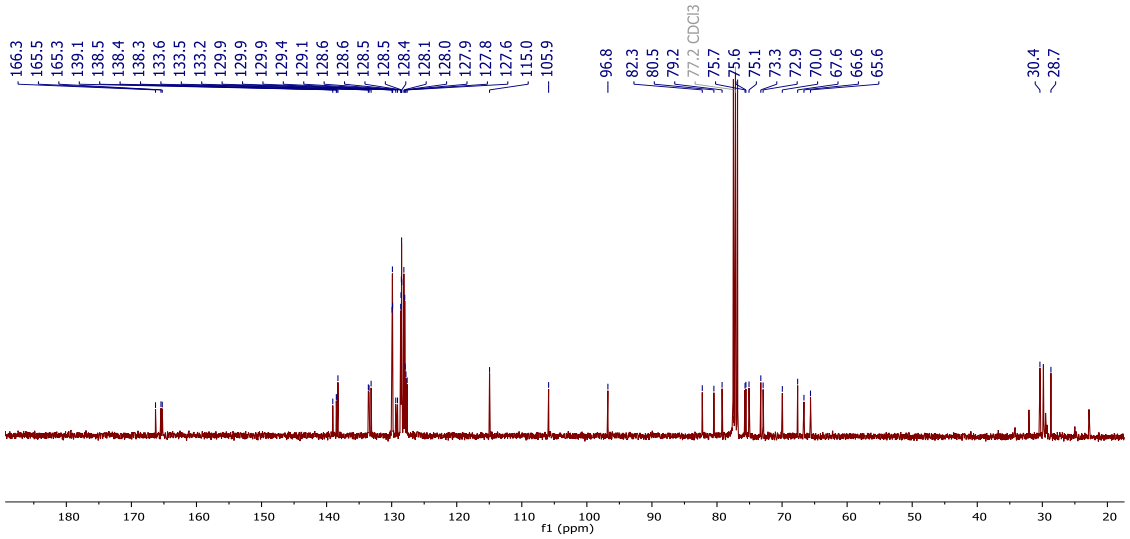
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 44



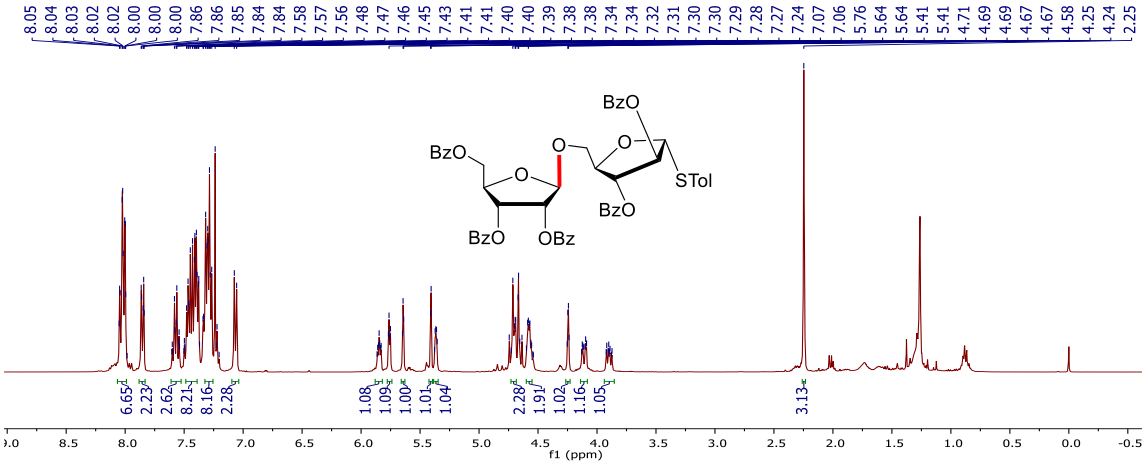
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 45



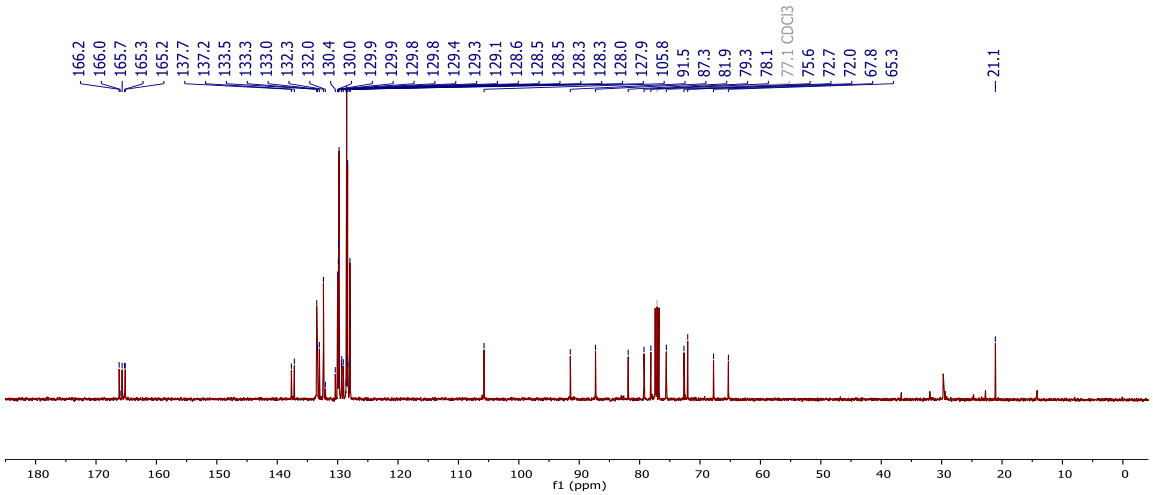
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 45



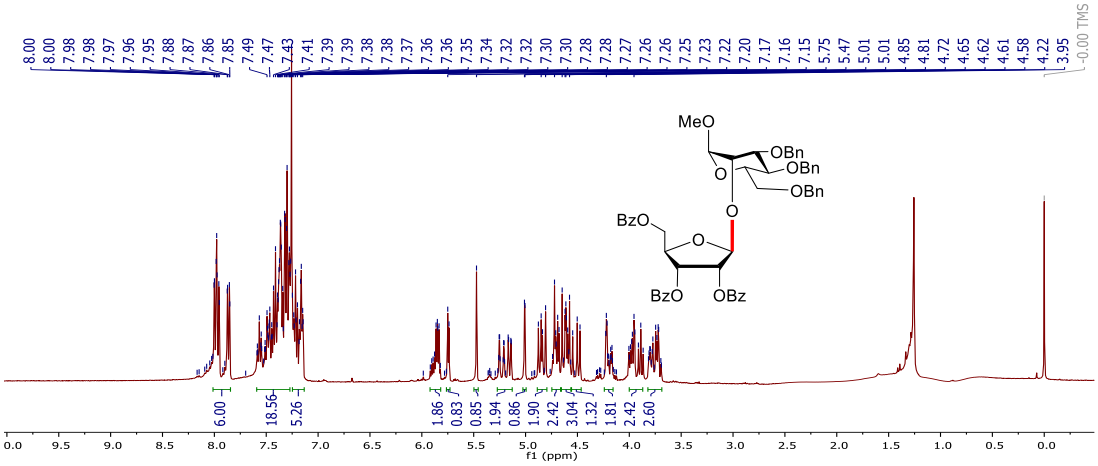
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 46



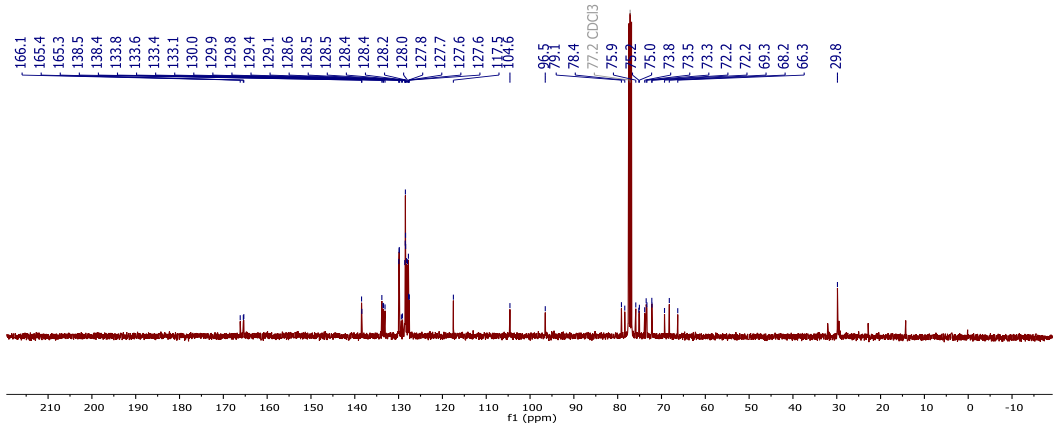
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 46



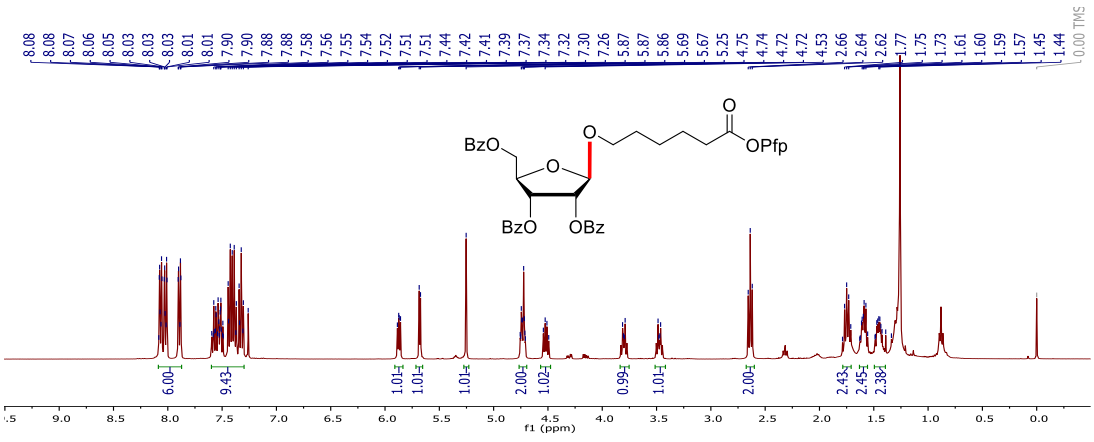
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 47



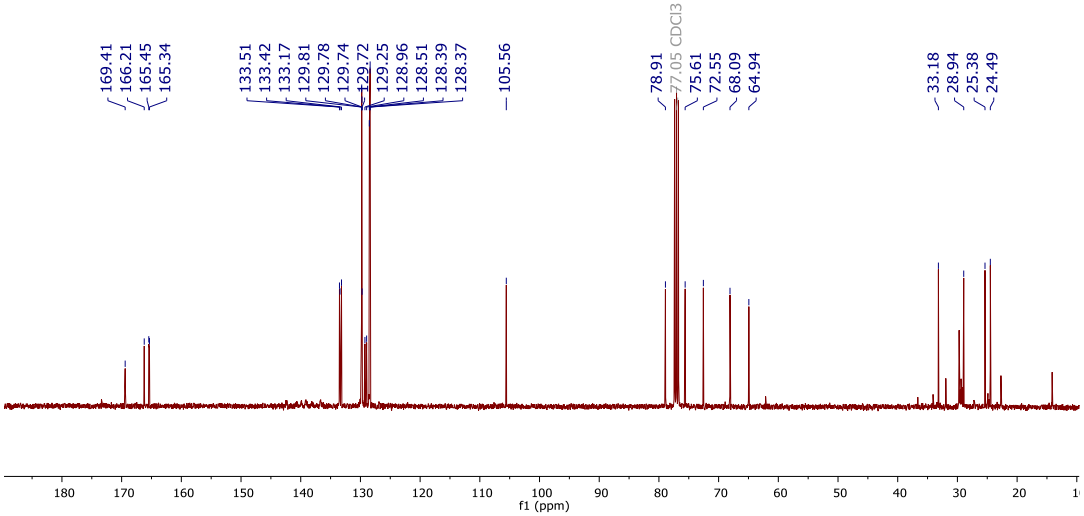
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 47



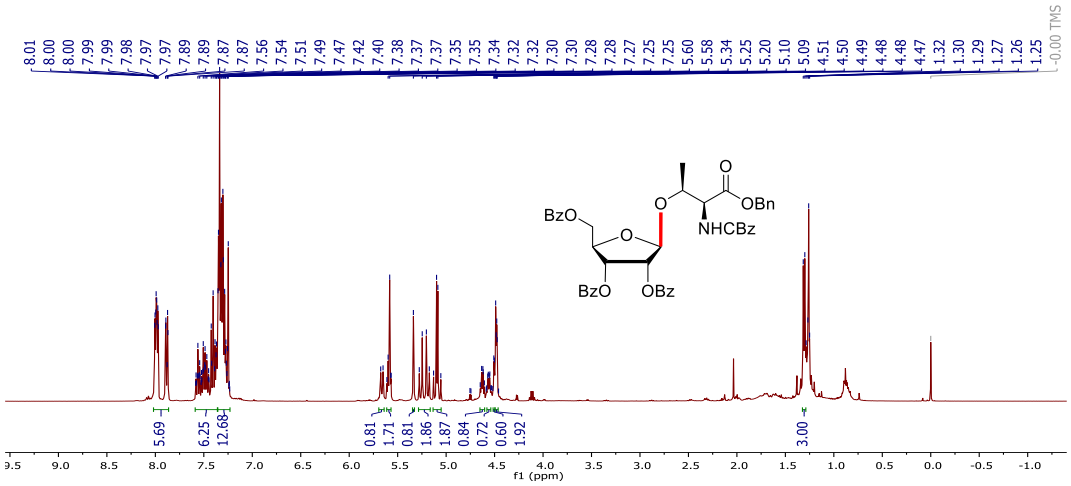
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 48



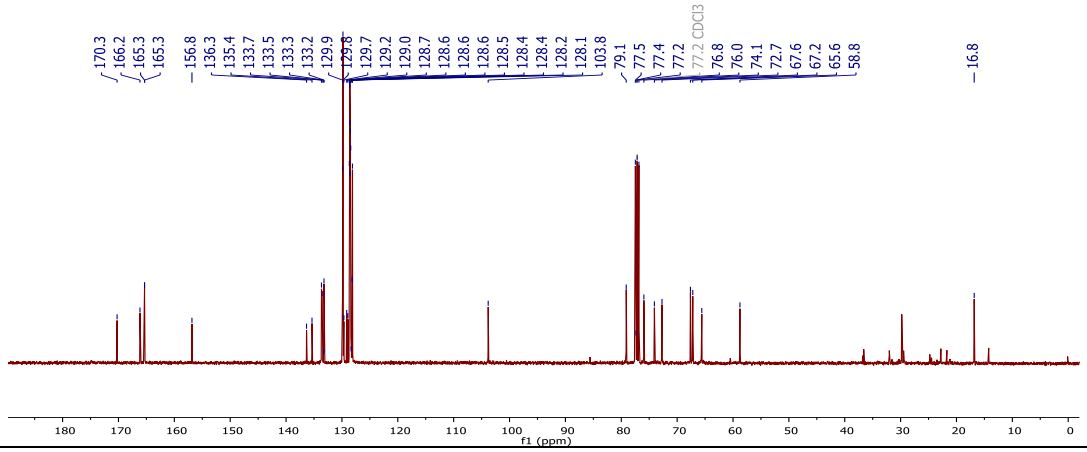
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 48



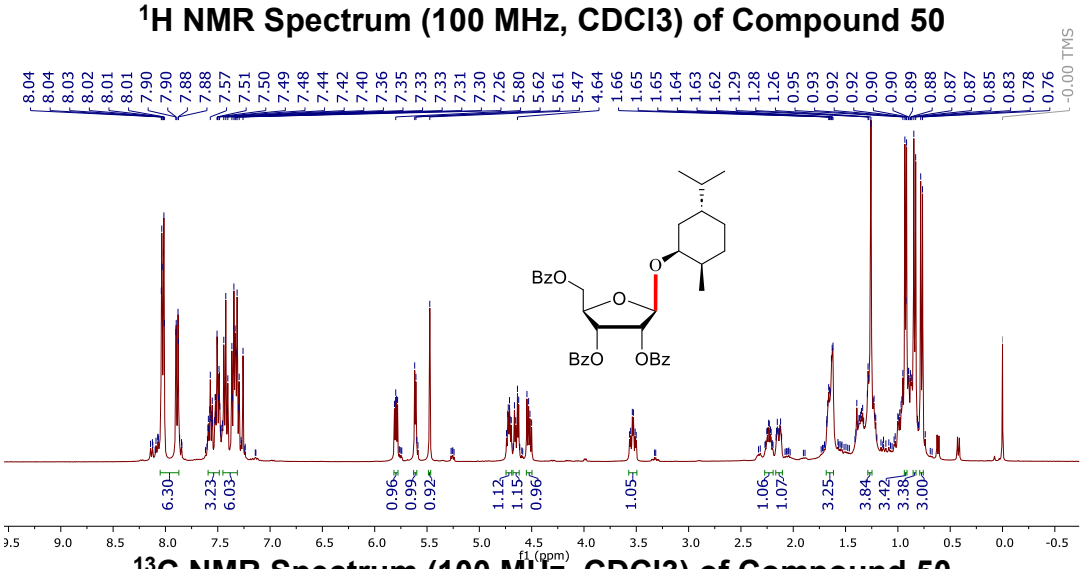
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 49



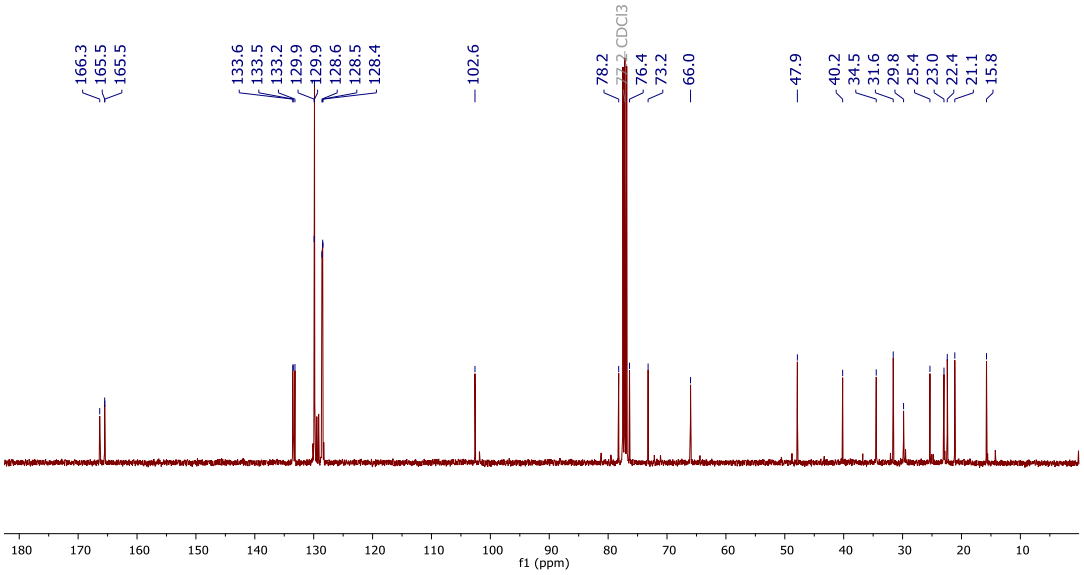
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 49



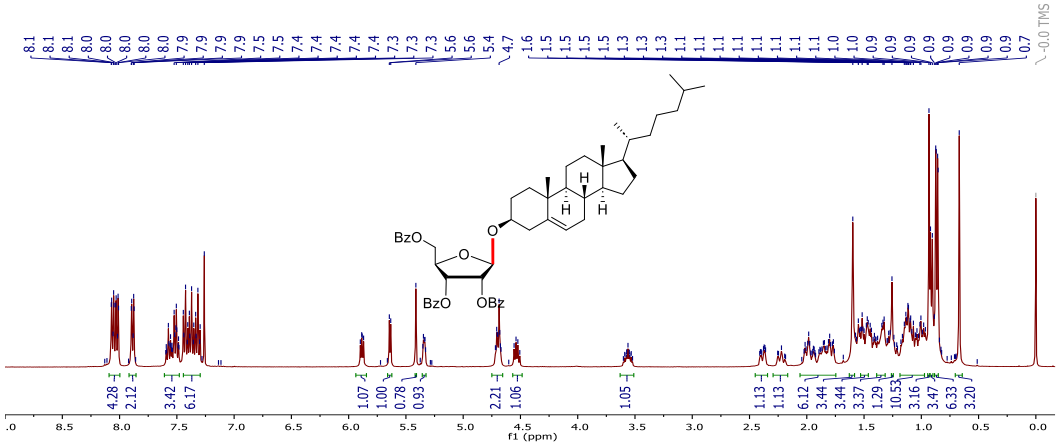
^{1}H NMR Spectrum (100 MHz, CDCl3) of Compound 50



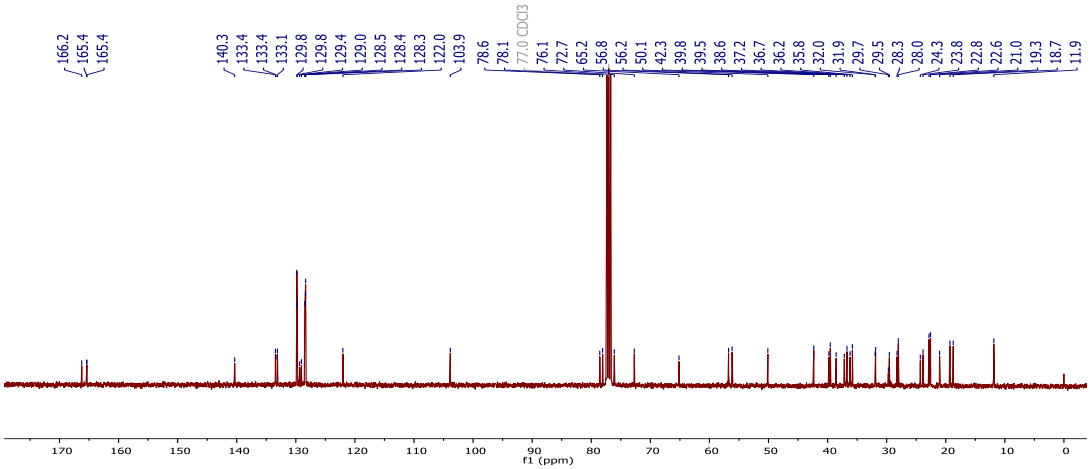
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 50



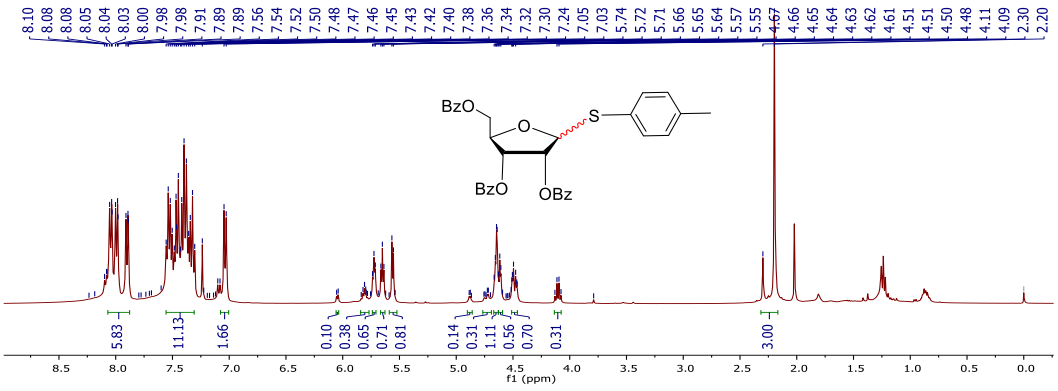
^{1}H NMR Spectrum (100 MHz, CDCl3) of Compound 51



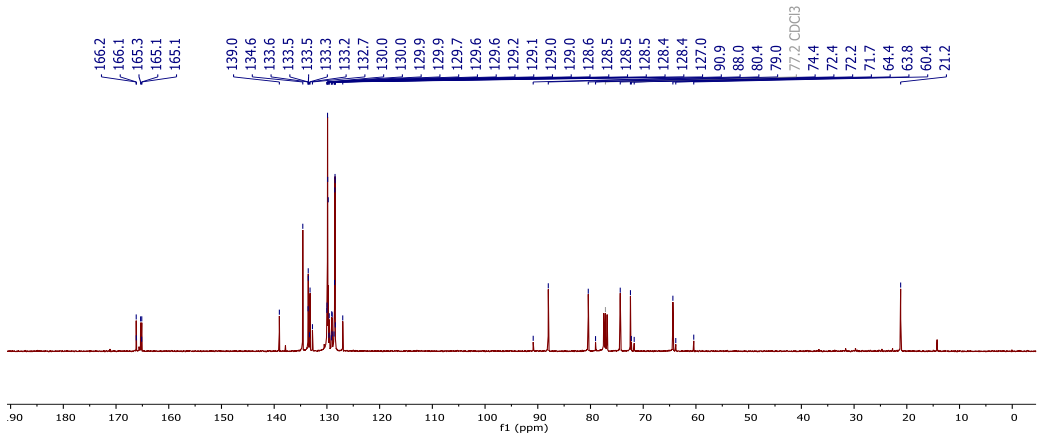
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 51



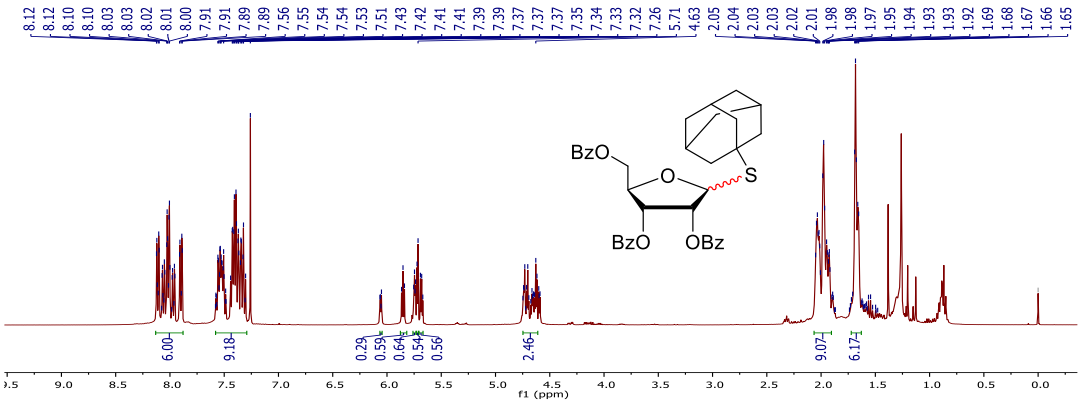
^{1}H NMR Spectrum (100 MHz, CDCl3) of Compound 52



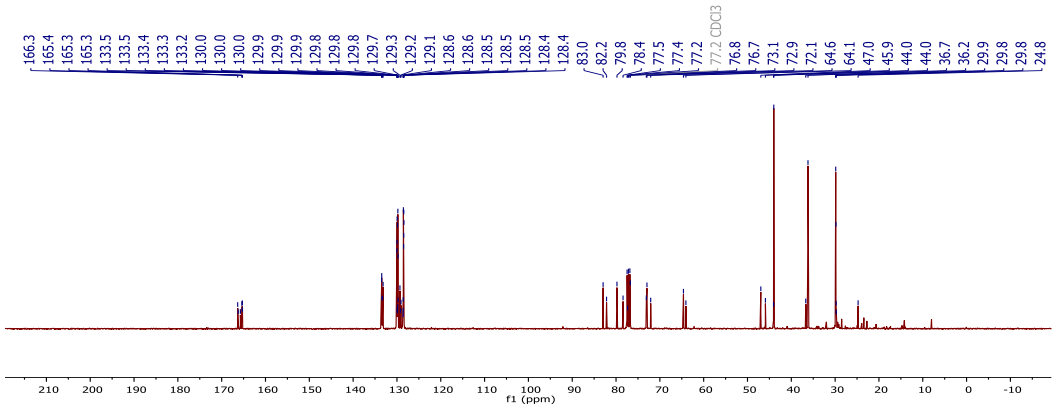
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 52



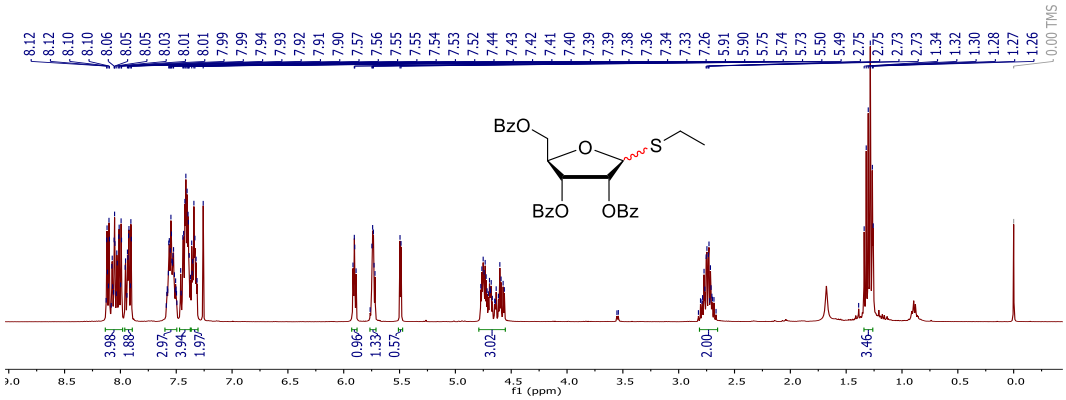
^{1}H NMR Spectrum (100 MHz, CDCl3) of Compound 53



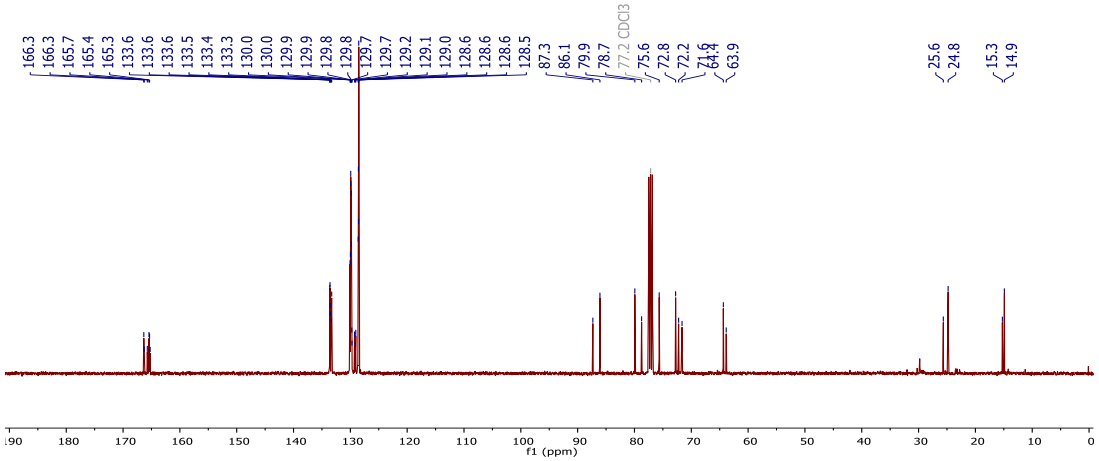
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 53



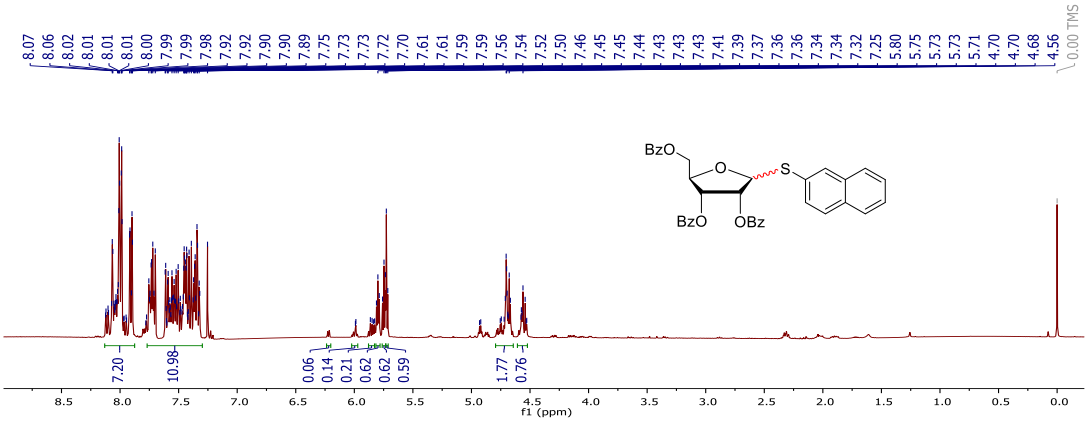
^{1}H NMR Spectrum (100 MHz, CDCl3) of Compound 54



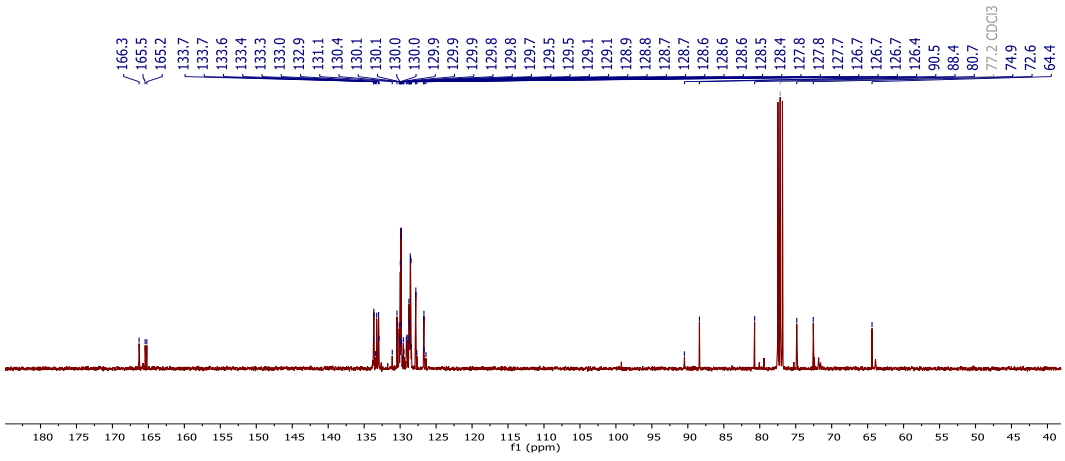
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 54



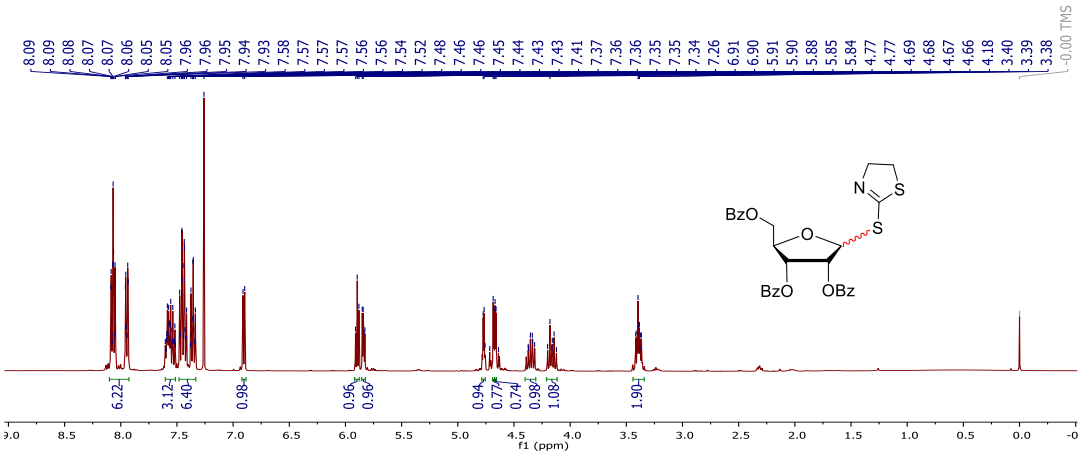
^{1}H NMR Spectrum (100 MHz, CDCl3) of Compound 55



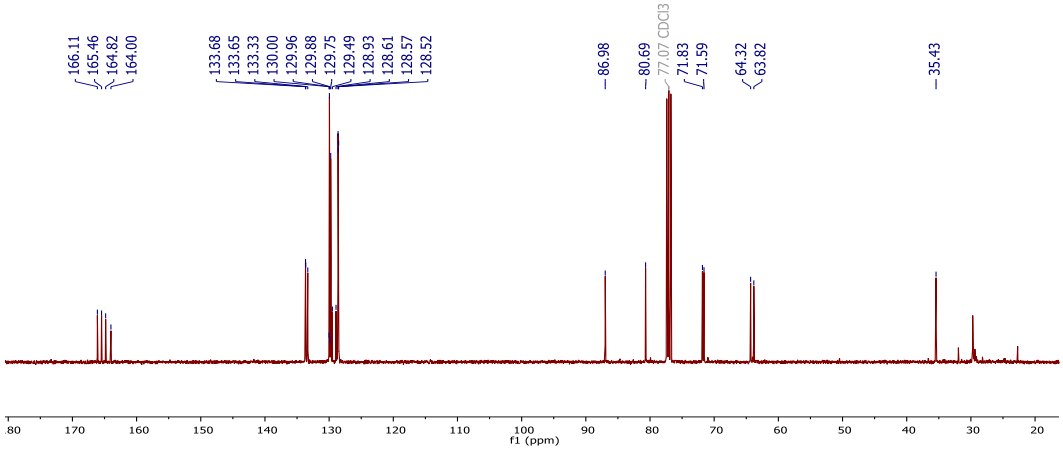
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 55



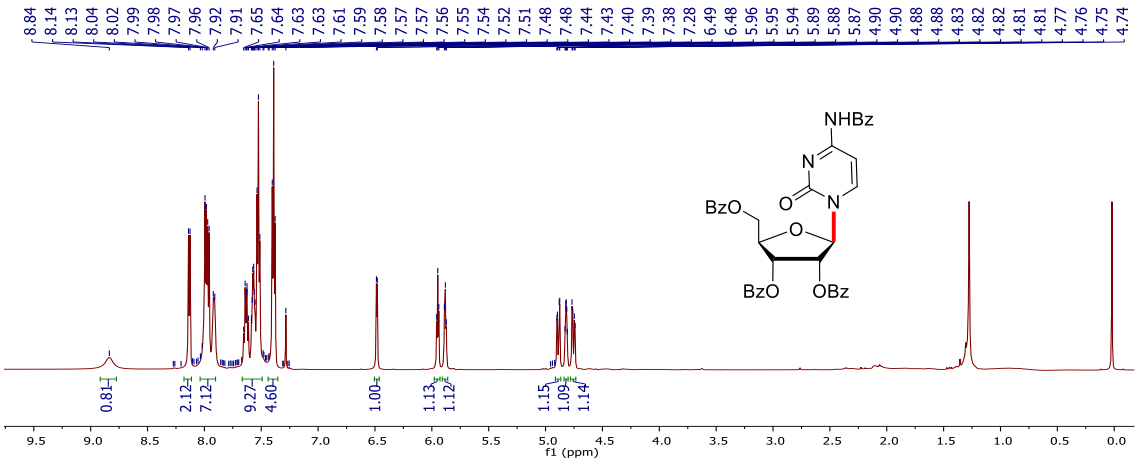
^{1}H NMR Spectrum (100 MHz, CDCl3) of Compound 56



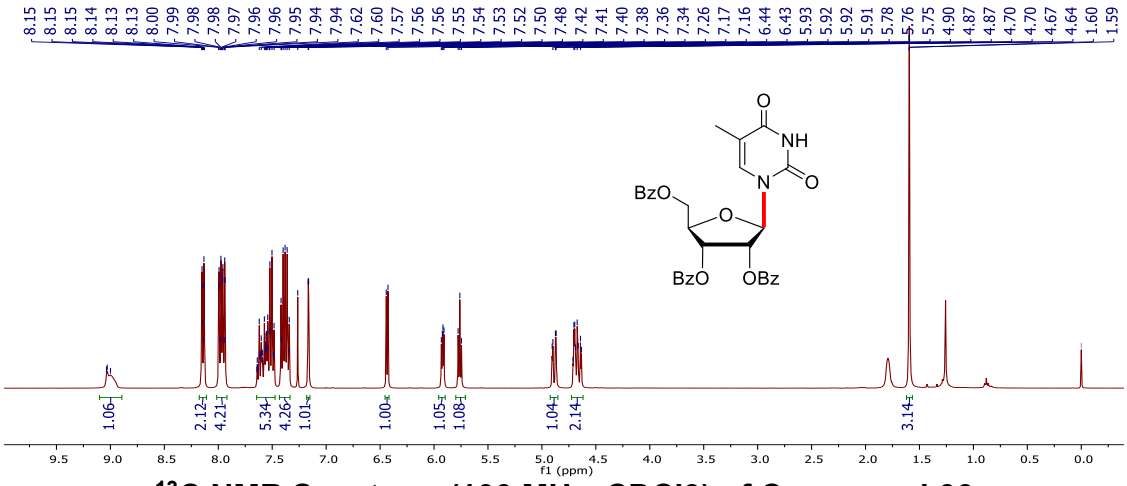
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 56



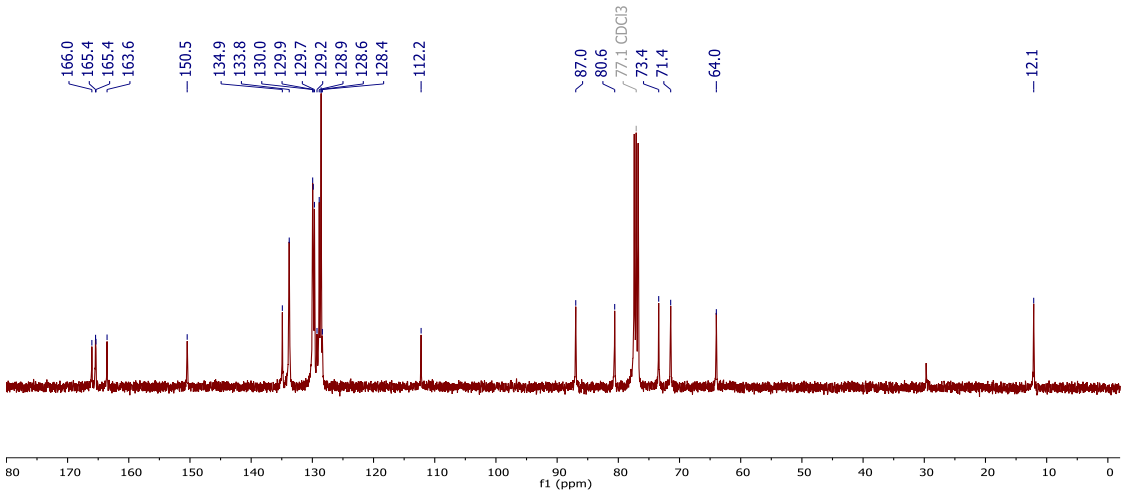
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 65



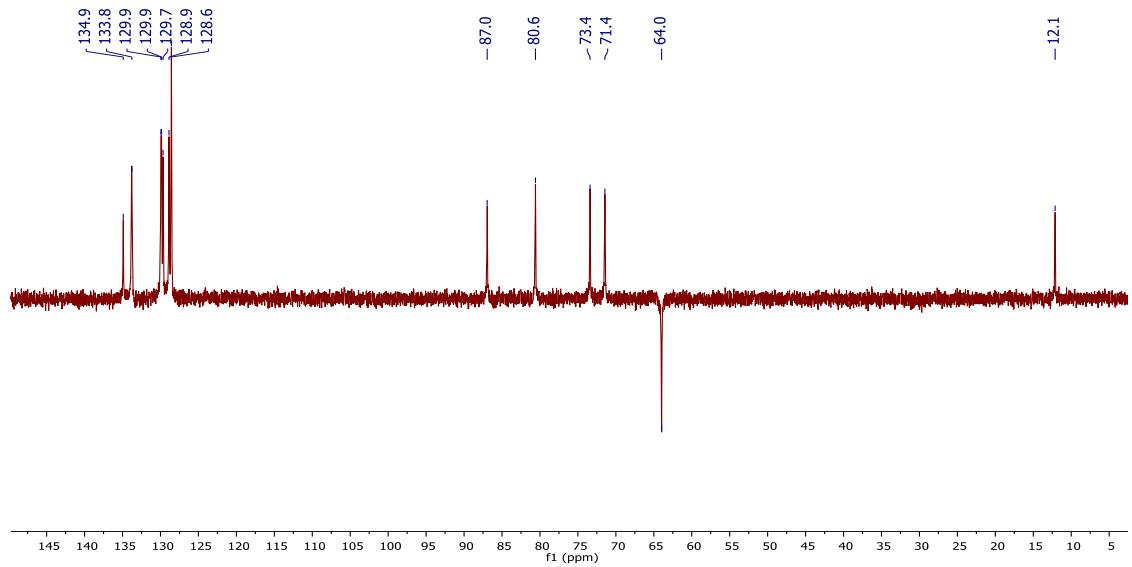
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 66



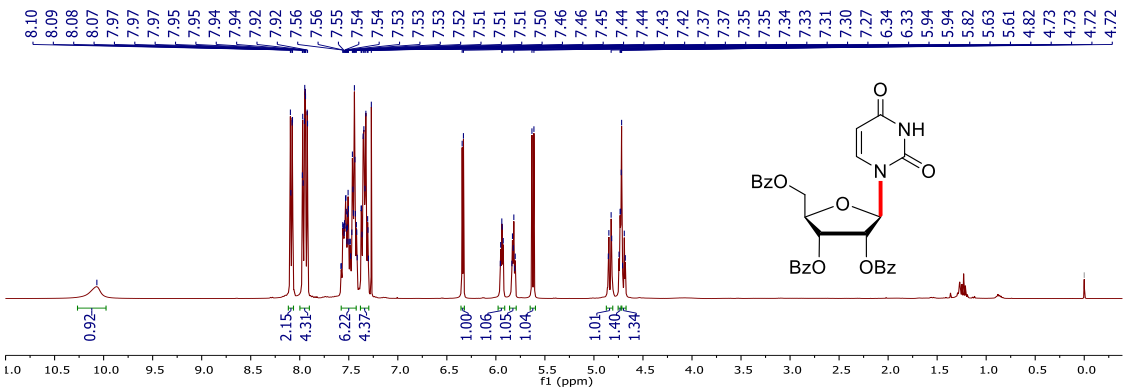
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 66



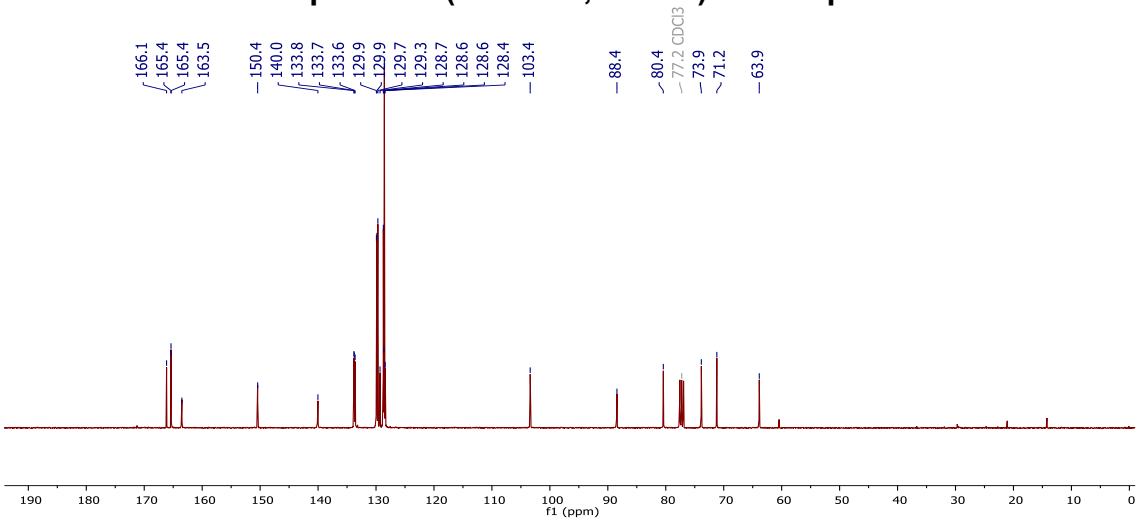
DEPT-135 NMR Spectrum (100 MHz, CDCl3) of Compound 66



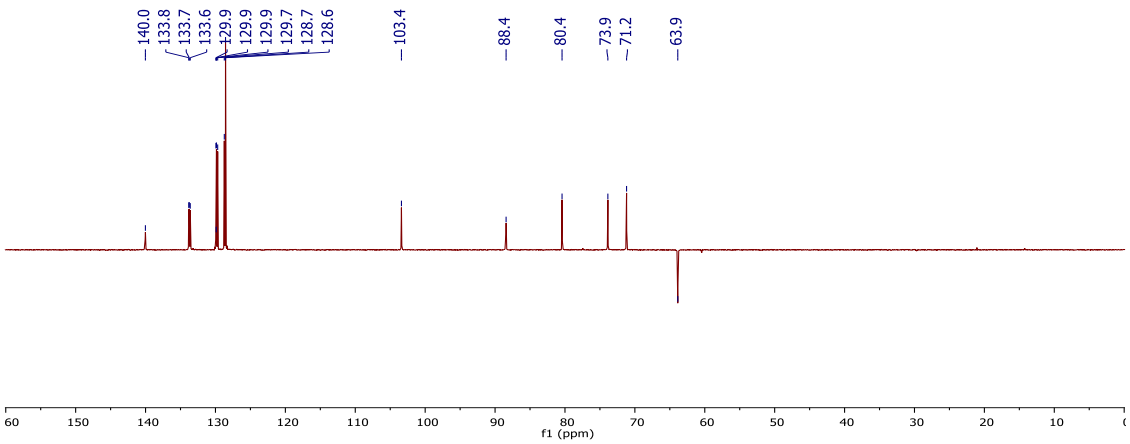
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 67



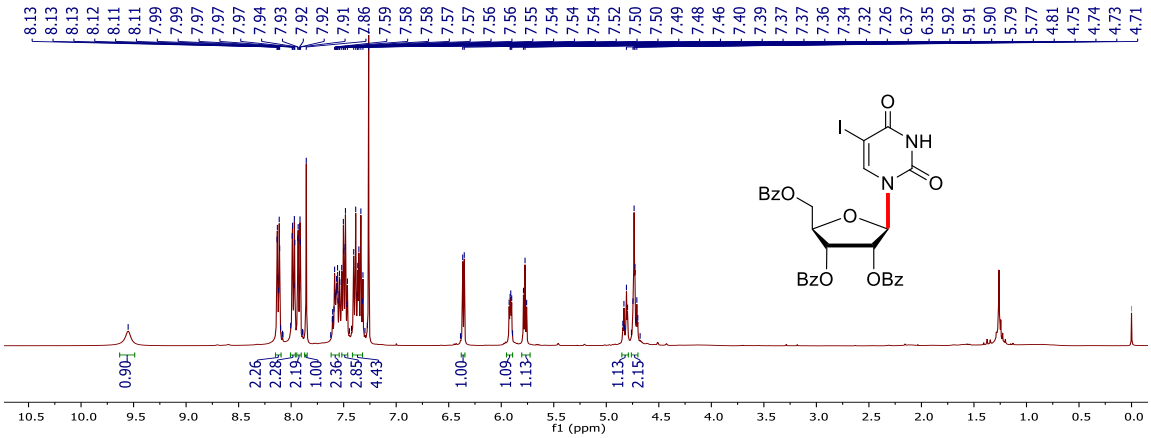
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 67



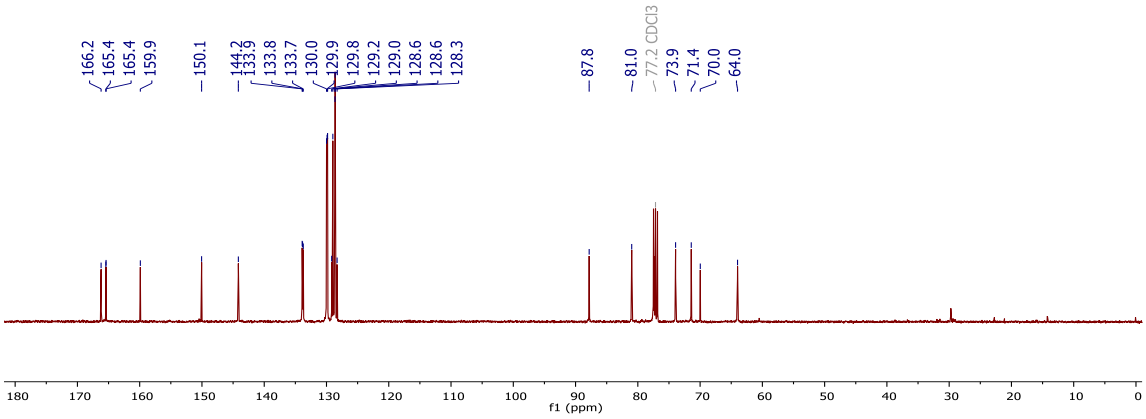
DEPT-135 NMR Spectrum (100 MHz, CDCl3) of Compound 67



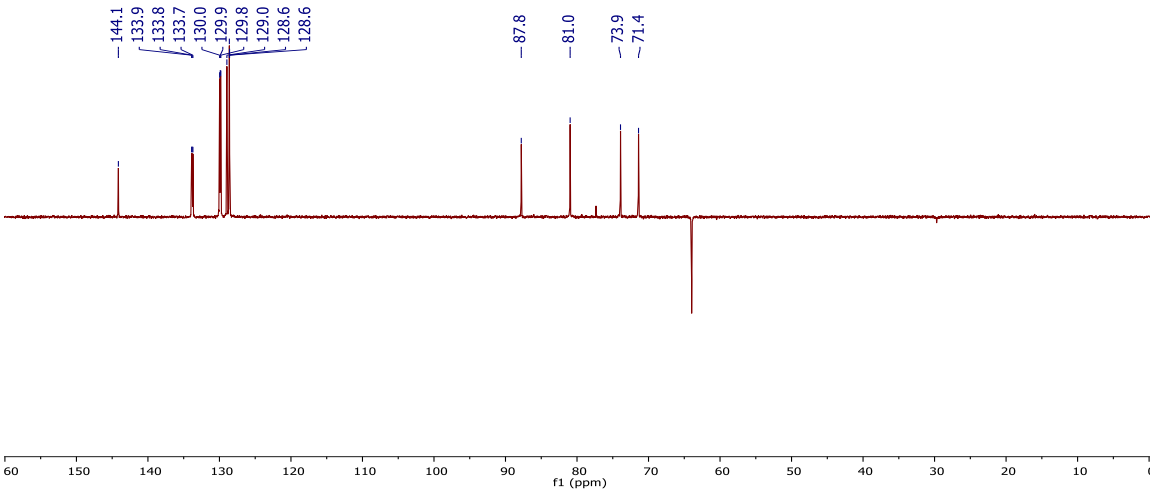
^{1}H NMR Spectrum (400 MHz, CDCl3) of Compound 68



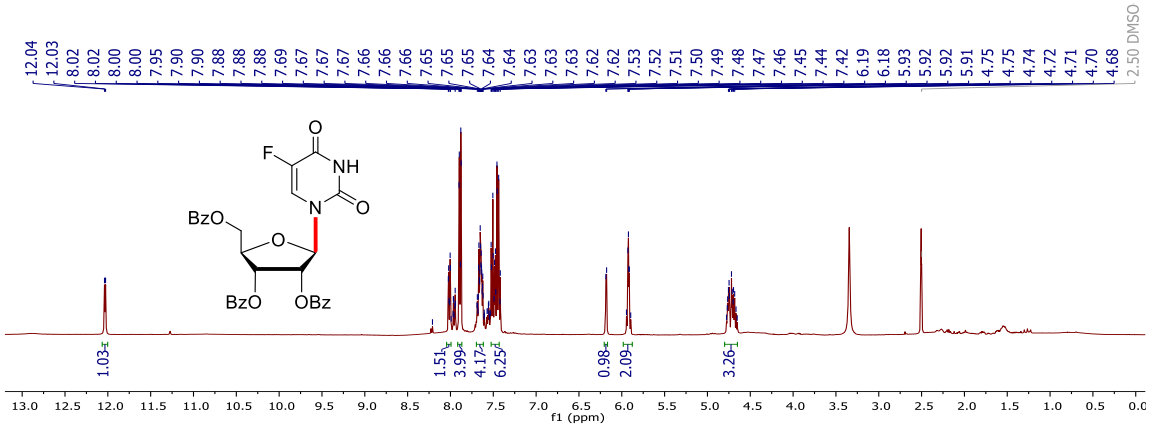
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 68



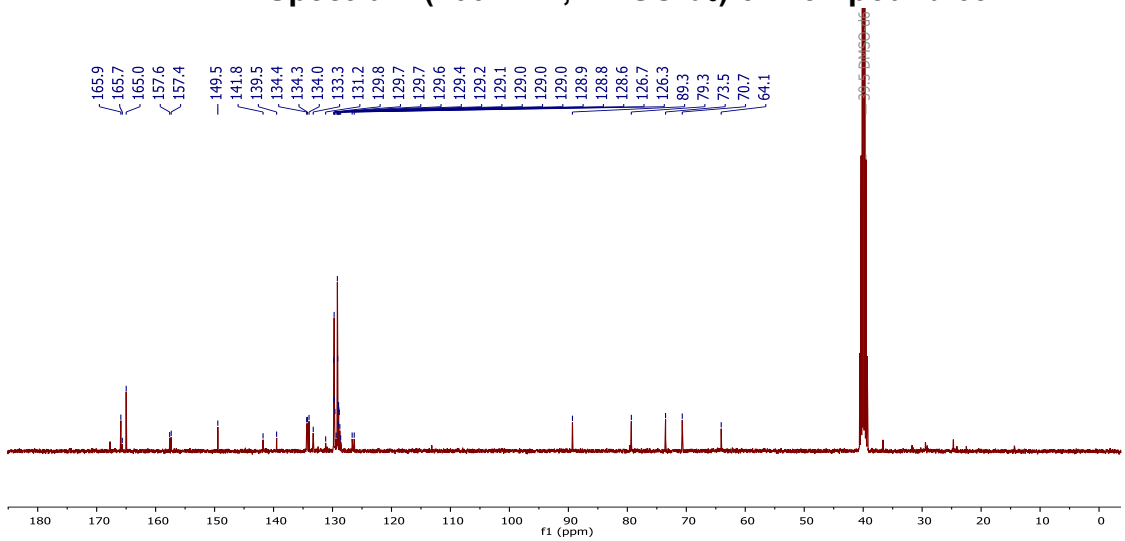
DEPT-135 NMR Spectrum (100 MHz, CDCl3) of Compound 68



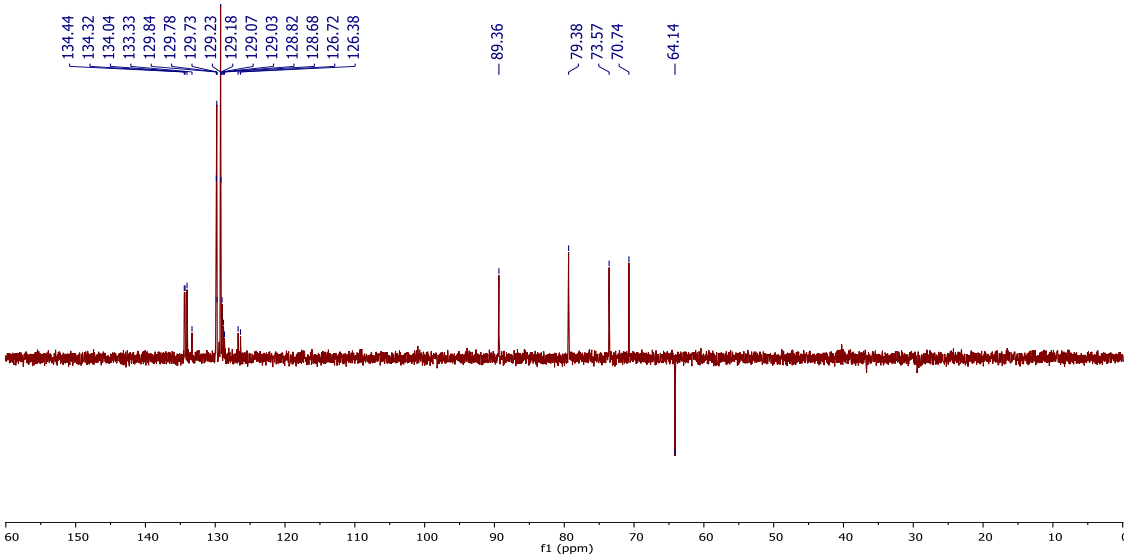
^{1}H NMR Spectrum (400 MHz, DMSO-d$_6$) of Compound 69



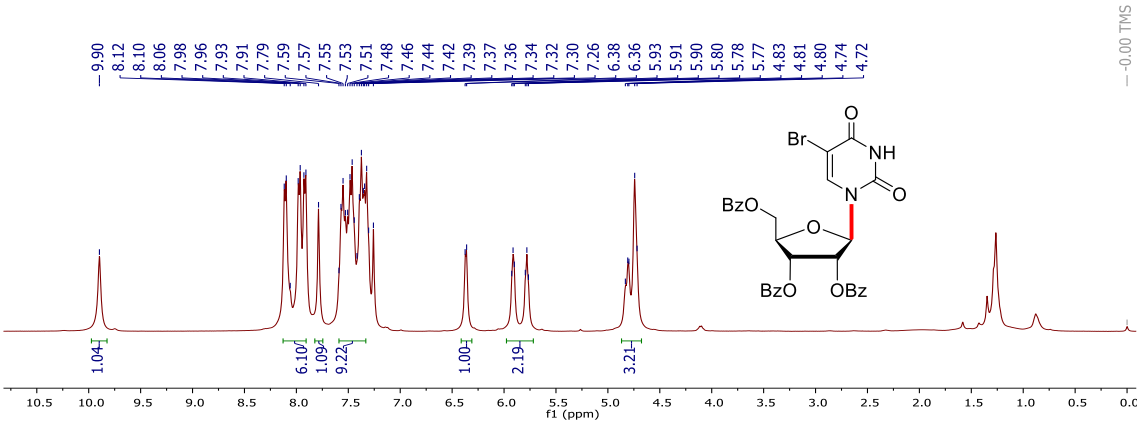
^{13}C NMR Spectrum (100 MHz, DMSO-d$_6$) of Compound 69



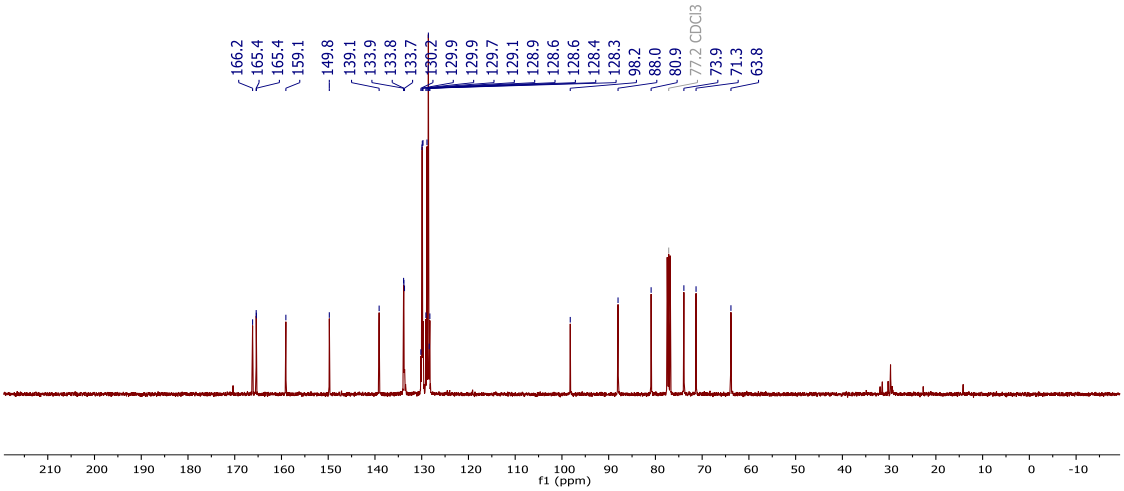
DEPT-135 NMR Spectrum (100 MHz, DMSO-d$_6$) of Compound 69



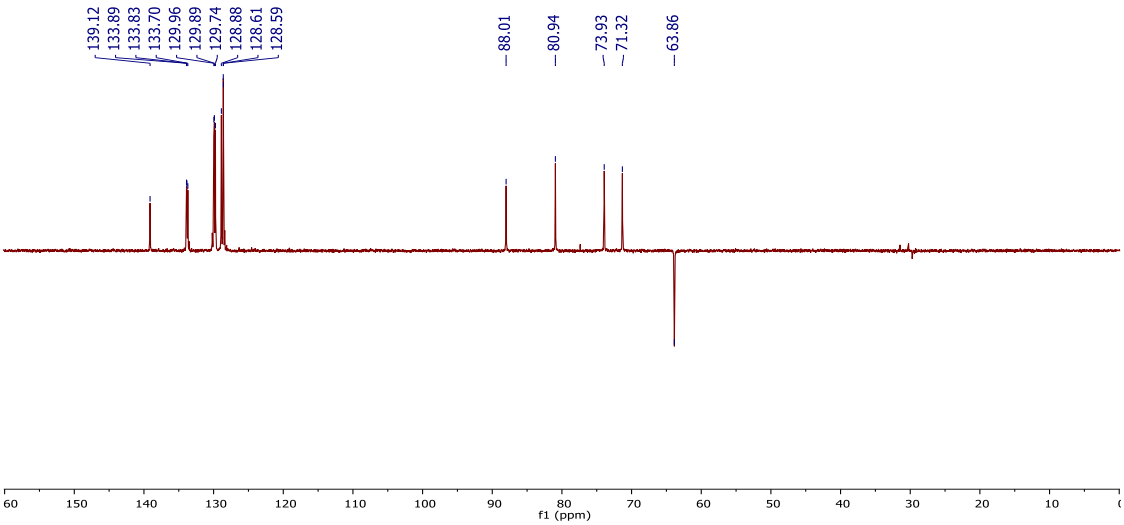
^{1}H NMR Spectrum (400 MHz, $CDCl_3$) of Compound 70



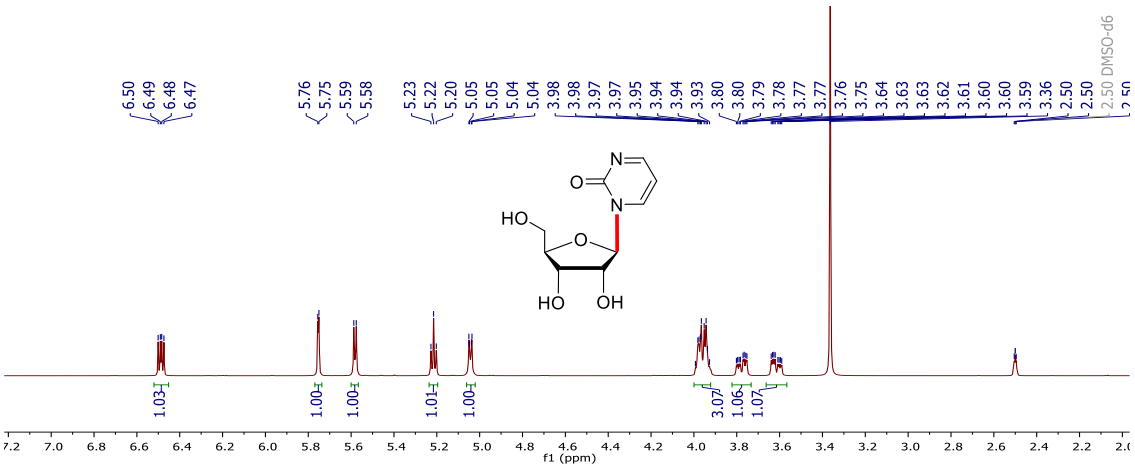
^{13}C NMR Spectrum (100 MHz, CDCl3) of Compound 70



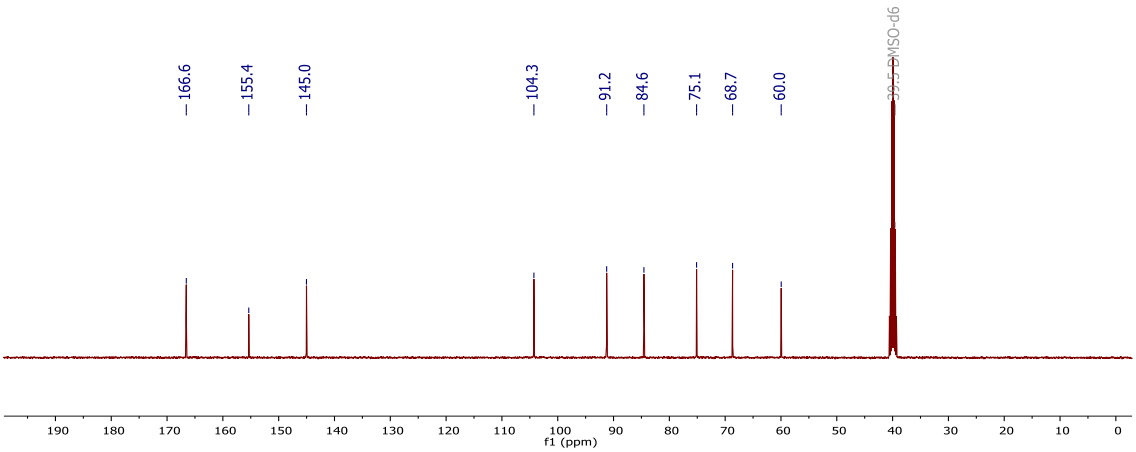
DEPT-135 NMR Spectrum (100 MHz, CDCl3) of Compound 70



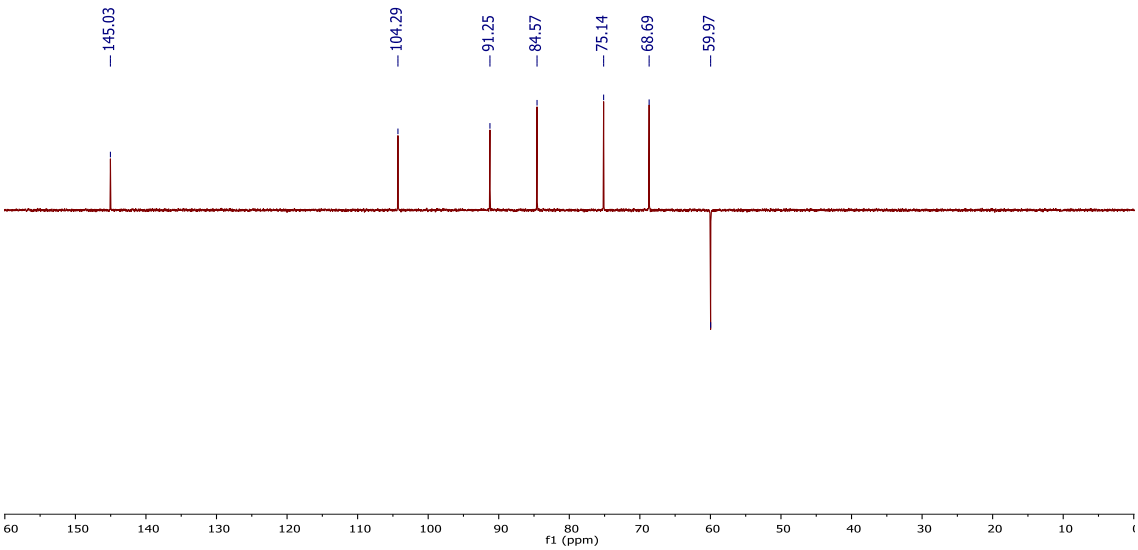
^{1}H NMR Spectrum (400 MHz, DMSO-d_6) of Compound 75



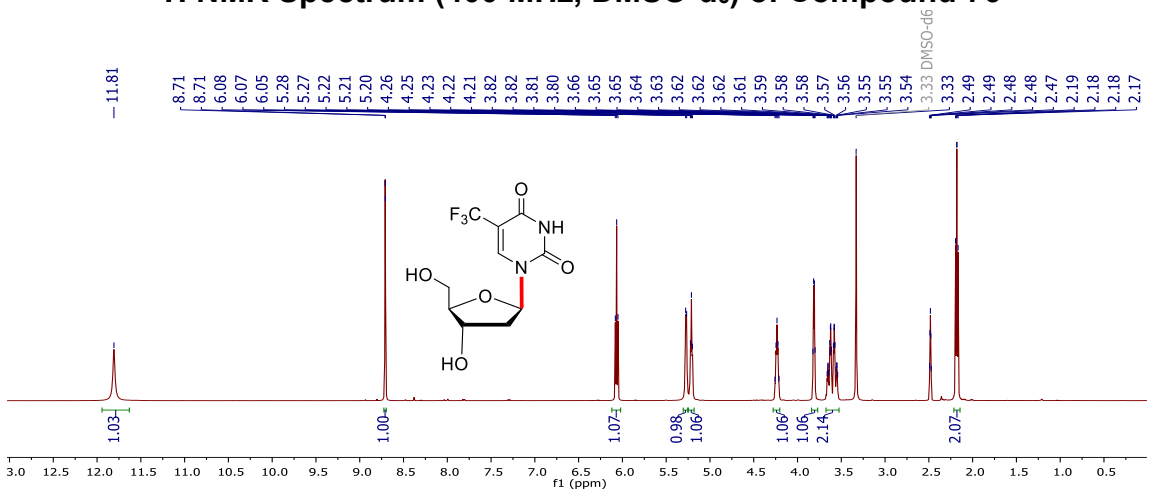
^{13}C NMR Spectrum (100 MHz, DMSO-d_6) of Compound 75



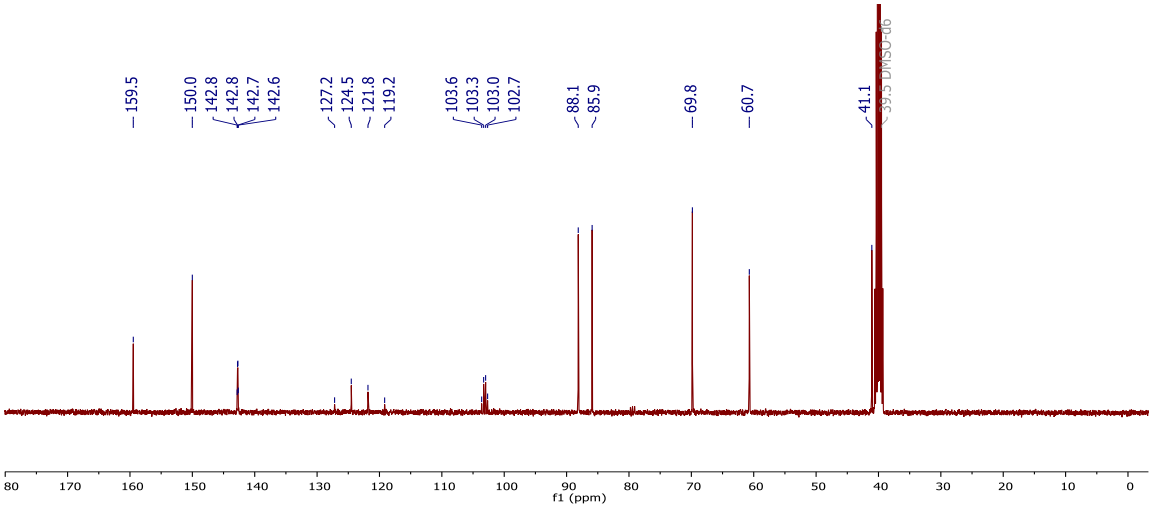
DEPT-135 NMR Spectrum (100 MHz, DMSO-d_6) of Compound 75



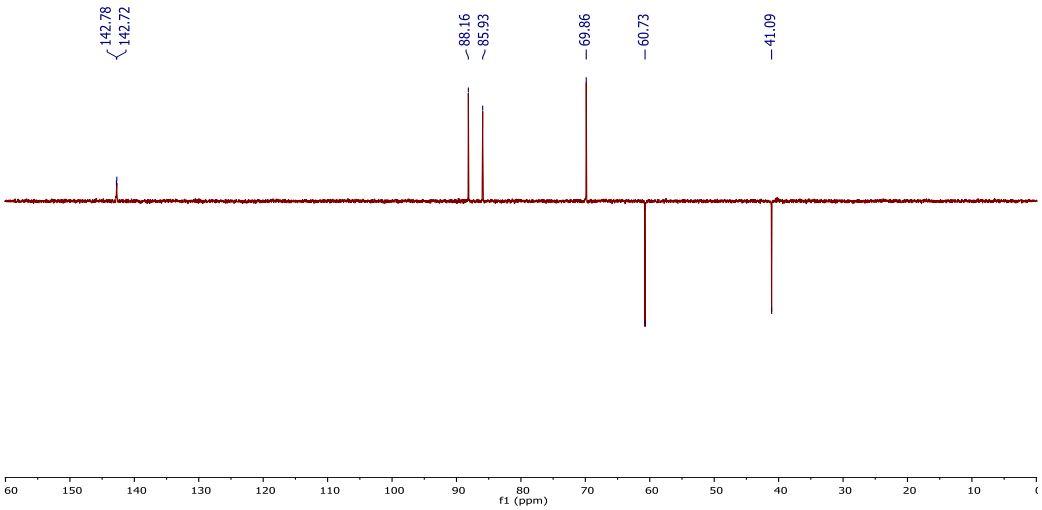
^{1}H NMR Spectrum (400 MHz, DMSO-d$_6$) of Compound 76



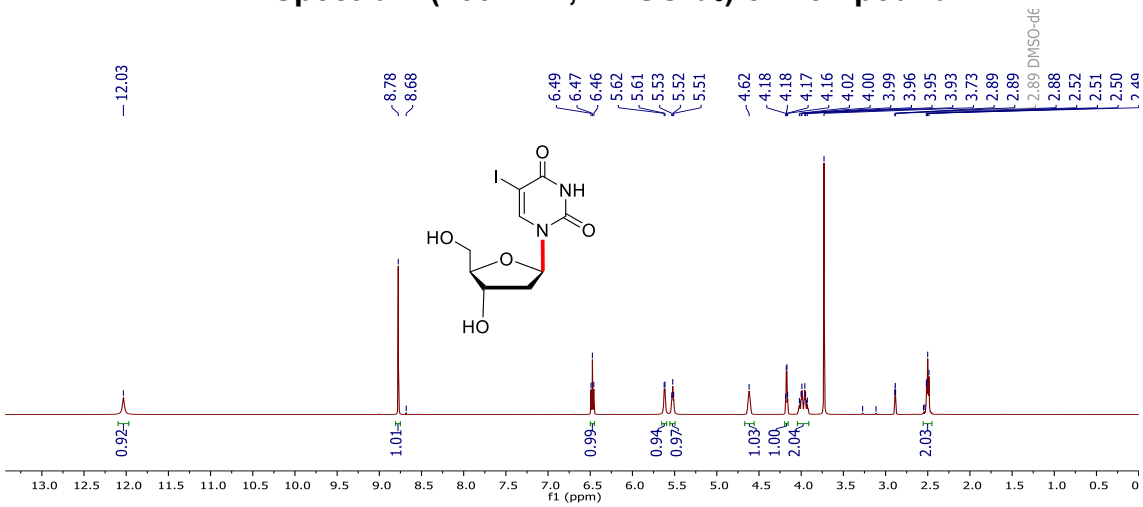
^{13}C NMR Spectrum (100 MHz, DMSO-d$_6$) of Compound 76



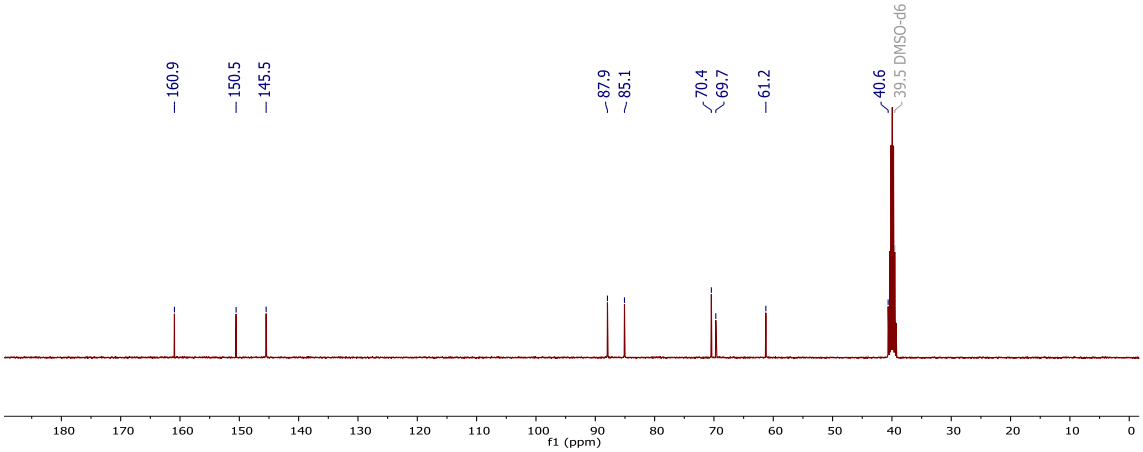
DEPT-135 NMR Spectrum (100 MHz, DMSO-d$_6$) of Compound 76



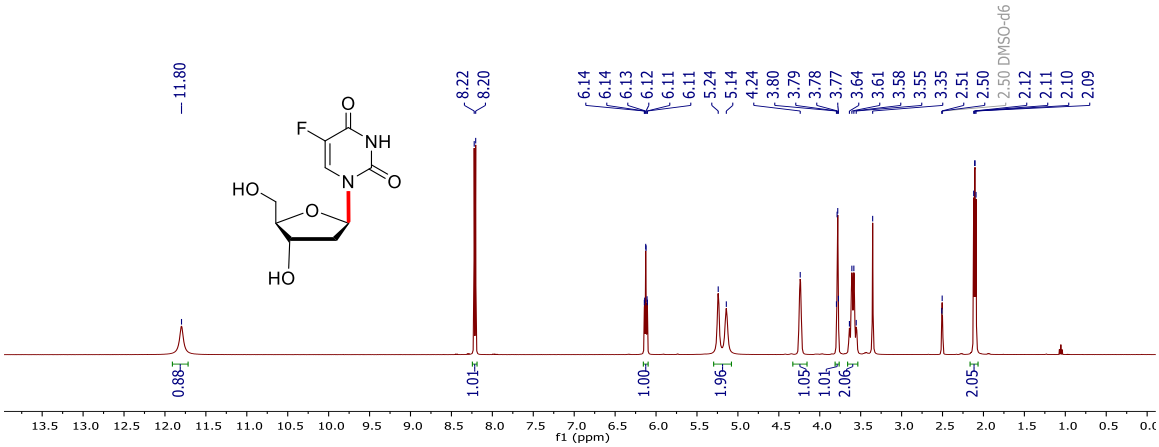
^{1}H NMR Spectrum (400 MHz, DMSO-d$_6$) of Compound 77



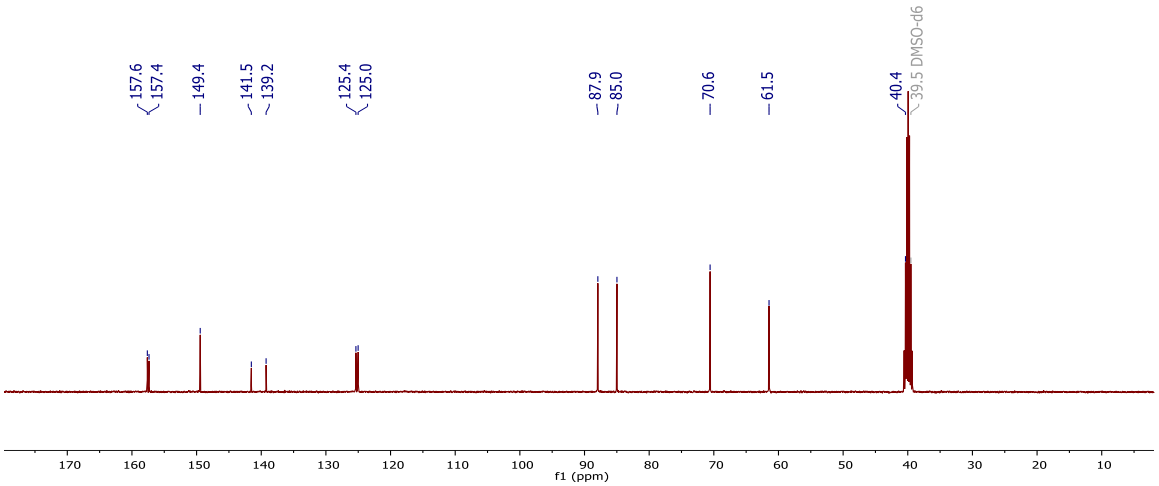
^{13}C NMR Spectrum (100 MHz, DMSO-d$_6$) of Compound 77



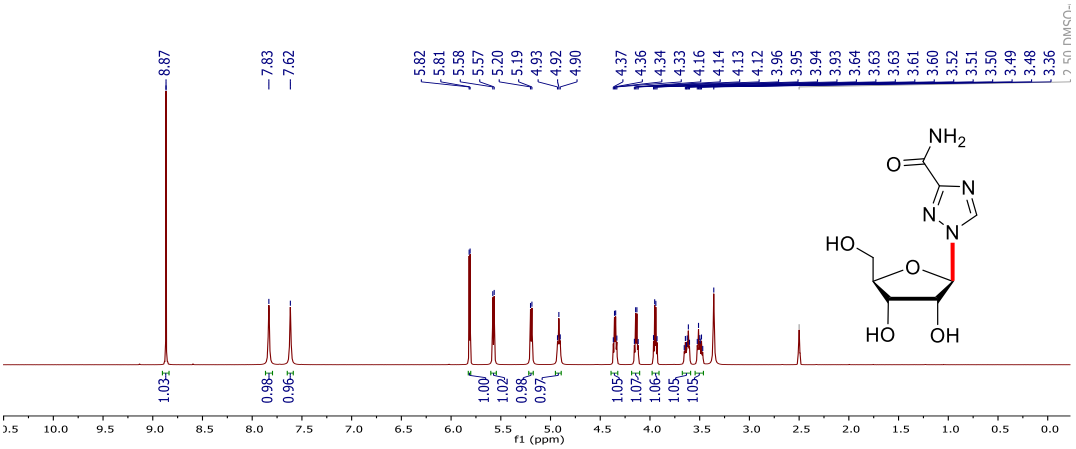
^{1}H NMR Spectrum (400 MHz, DMSO-d$_6$) of Compound 78



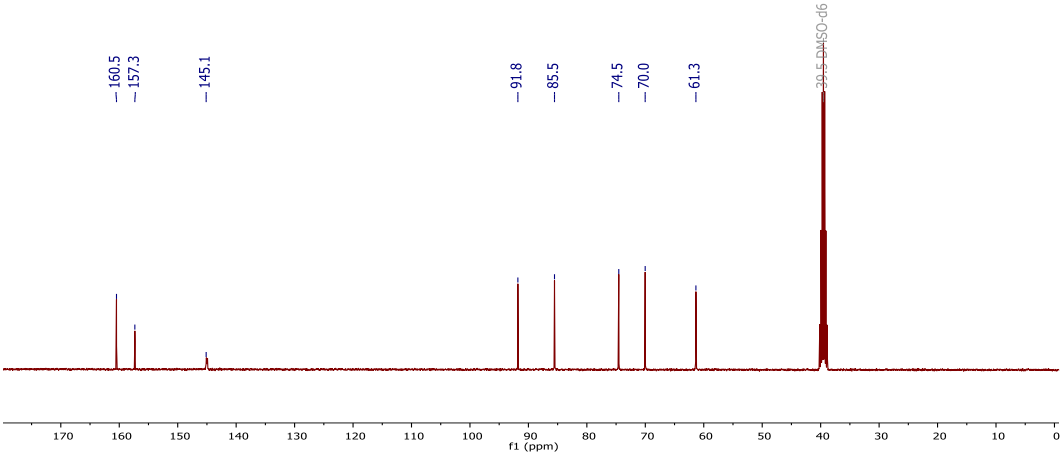
^{13}C NMR Spectrum (100 MHz, DMSO-d$_6$) of Compound 78



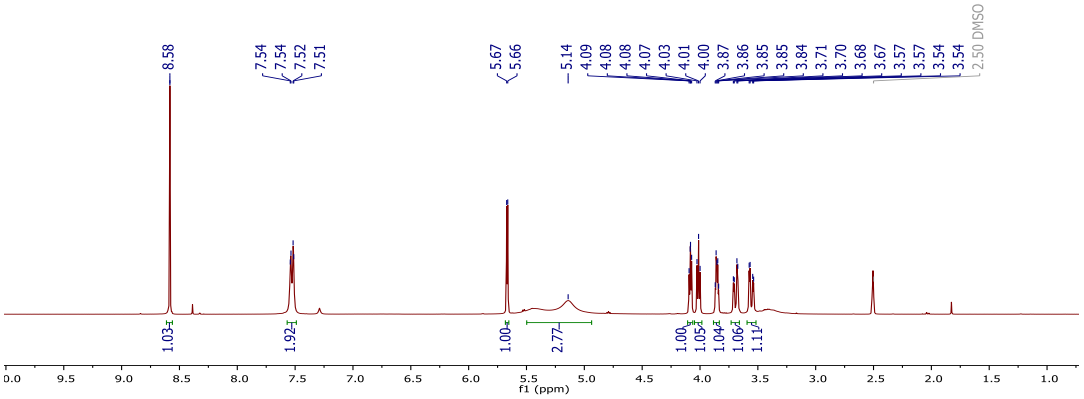
^{1}H NMR Spectrum (400 MHz, DMSO-d$_6$) of Compound 93



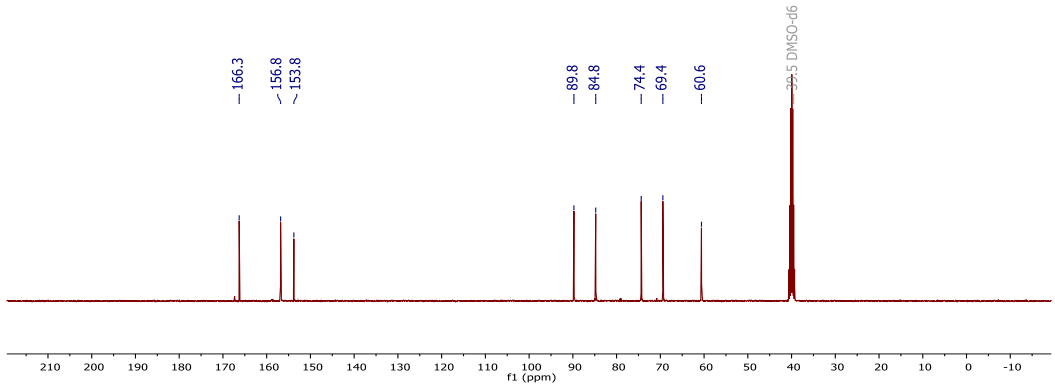
^{13}C NMR Spectrum (100 MHz, DMSO-d$_6$) of Compound 93



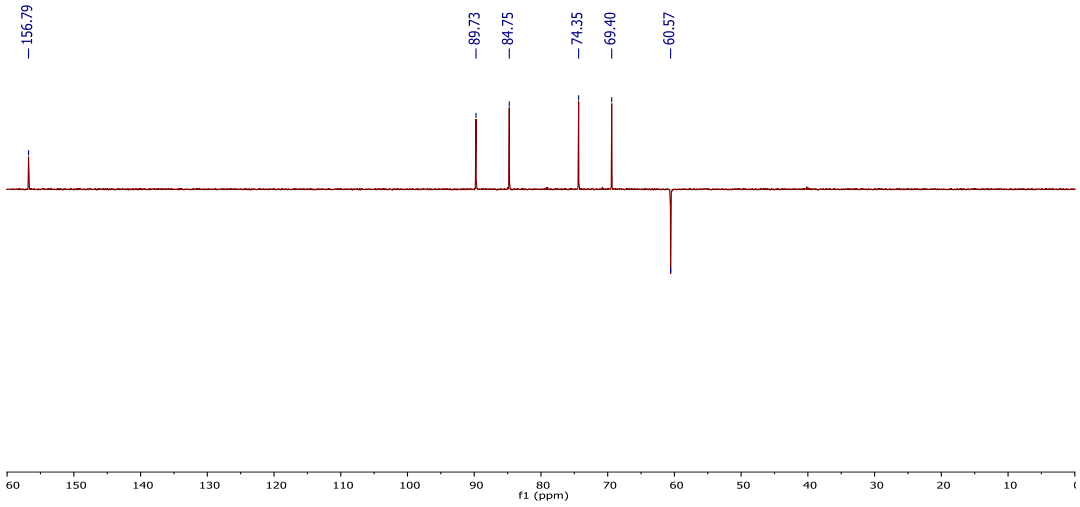
^{1}H NMR Spectrum (400 MHz, DMSO-d_6) of Compound 94



^{13}C NMR Spectrum (100 MHz, DMSO-d_6) of Compound 94



DEPT-135 NMR Spectrum (100 MHz, DMSO-d_6) of Compound 94



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