Attempted synthesis of Regadenoson and Cangrelor by Aglycon Swapping Editing Reaction (ASER)

A THESIS

SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT OF THE DEGREE OF

Master of Science

by

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2026

Under the Supervision of

Prof Srinivas Hotha

Dedicated to

My late Grandfather

Certificate

This is to certify that this dissertation entitled “Synthesis of Regadenoson and Cangrelor by Aglycon Swapping Editing Reaction (ASER)” 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 Maitry Taliya under the supervision of “Prof. Srinivas Hotha, Department of Chemistry” during the academic year 2025-2026

Date: 6th April 2026

Pune (MH), India

Supervisor’s Signature

Declaration

I hereby declare that the work presented in this thesis, entitled "**Attempted synthesis of Regadenoson and Cangrelor by Aglycon Swapping Editing Reaction (ASER)**" is the result of original investigations carried out by me at the Department of Chemistry, Indian Institute of Science Education and Research (IISER), Pune, under the guidance of Prof. Srinivas Hotha.

I confirm that this submission represents my own ideas expressed in my own words. Wherever the ideas or work of others have been included, I have adequately cited and referenced the original sources. I have strictly adhered to the principles of academic honesty and integrity, ensuring that no data, ideas, or facts have been misrepresented, fabricated, or falsified.

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Finally, I declare that this body of work has not been submitted, in whole or in part, to any other institution or university for the award of any other degree or diploma.

Date: 23 March, 2026

Pune (MH), India

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ABBREVIATIONS

Å: Angstrom

Ac: Acetate

Bn: Benzyl

cat.: Catalytic

$CDCl_3$: Chloroform-d

$CHCl_3$: Chloroform

AgOTf: Silver trifluoromethanesulfonate

DCM: Dichloromethane

DEPT: Distortion less Enhancement by Polarization Transfer

DMAP: 4-Dimethyl aminopyridine

DMF: N, N'-Dimethyl formamide

DMAP N, N- Dimethyl aminopyridine

Eq.: Equivalents

Et_3N: Triethyl amine

Et_2O: Diethyl Ether

EtOAc: Ethyl Acetate

MS: Molecular Sieves

NaH: Sodium Hydride

NMR: Nuclear Magnetic Resonance

HCl: Hydrogen chloride

TfOH Trifluoro methane sulfonic acid

NIS- N-Iodo Succinimide

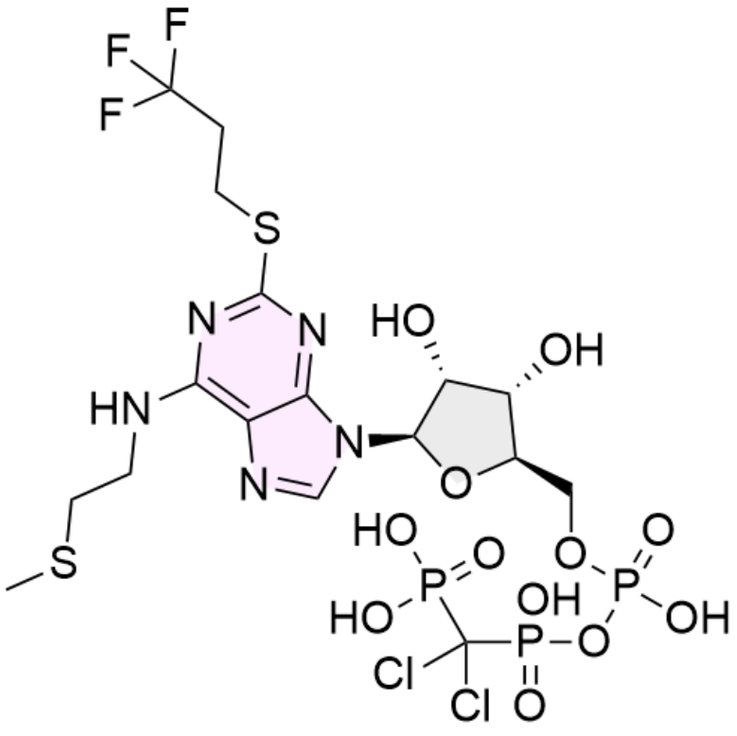
MS- Molecular Sieves

MeOH-Methanol

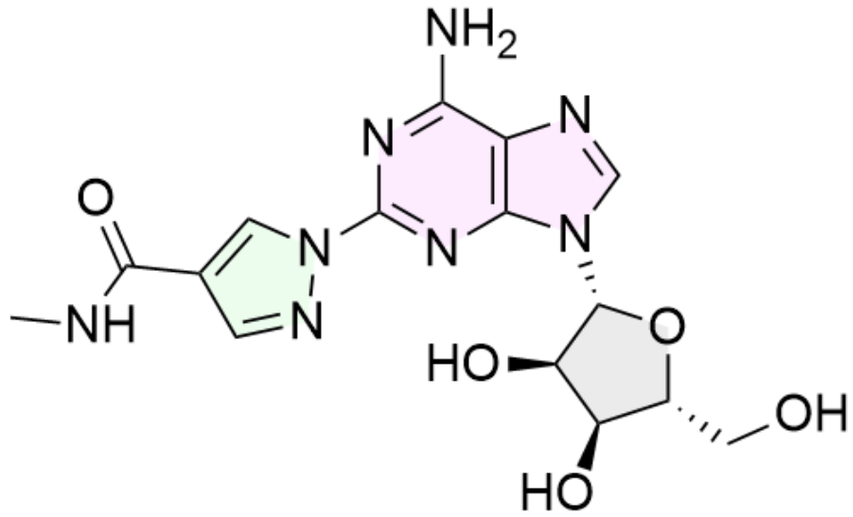
TLC Thin Layer Chromatography

Abstract

Conventional synthesis of adenosine-based drugs such as Regadenoson and Cangrelor involve multistep procedures that utilize toxic reagents, metal catalysts, and environmentally unsafe solvents. A greener and unified synthetic approach using adenosine as a renewable and naturally derived precursor is warranted. Our ASER methodology exploits the inherent functionality of adenosine, enabling selective modifications on both the purine ring and ribose framework under mild and sustainable conditions. Key transformations include regioselective substitution and coupling reactions mediated by triphenylphosphine/DIAD and sodium methoxide in methanol, eliminating the need for heavy metals and minimizing waste generation. This approach significantly improves atom economy, reduces purification steps, and operates efficiently at ambient conditions. The route not only allows the synthesis of Regadenoson and Cangrelor through a common intermediate but also offers a versatile platform for developing a broader range of adenosine-derived analogues.



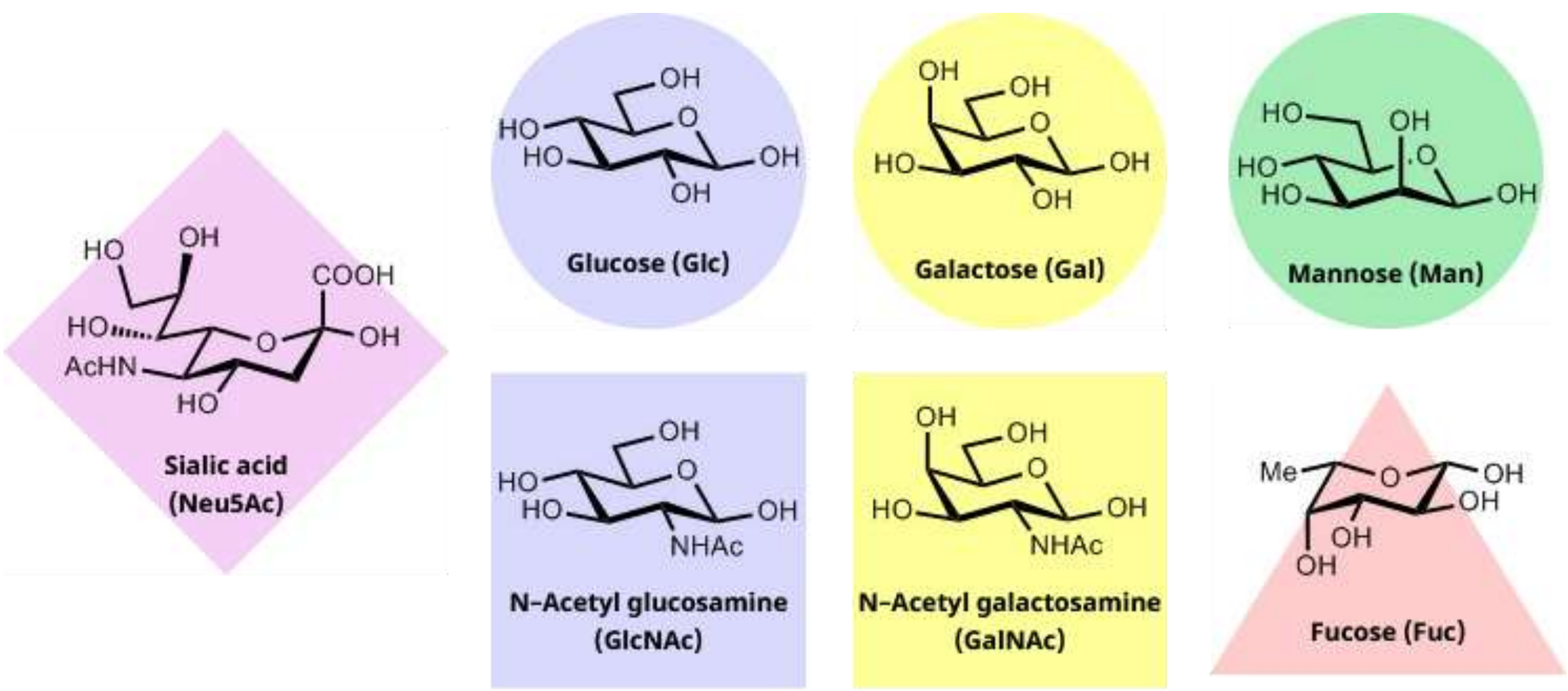
cangrelor

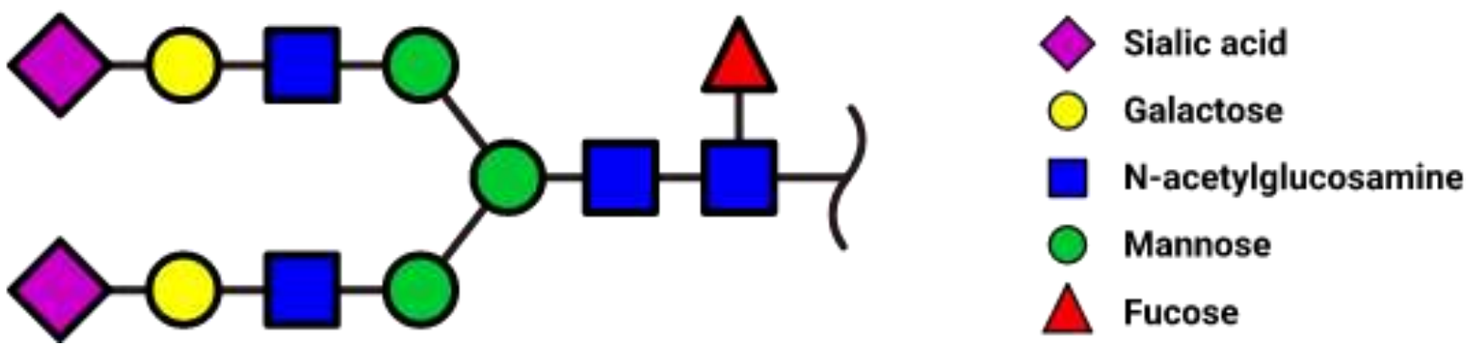


regadenoson

INTRODUCTION

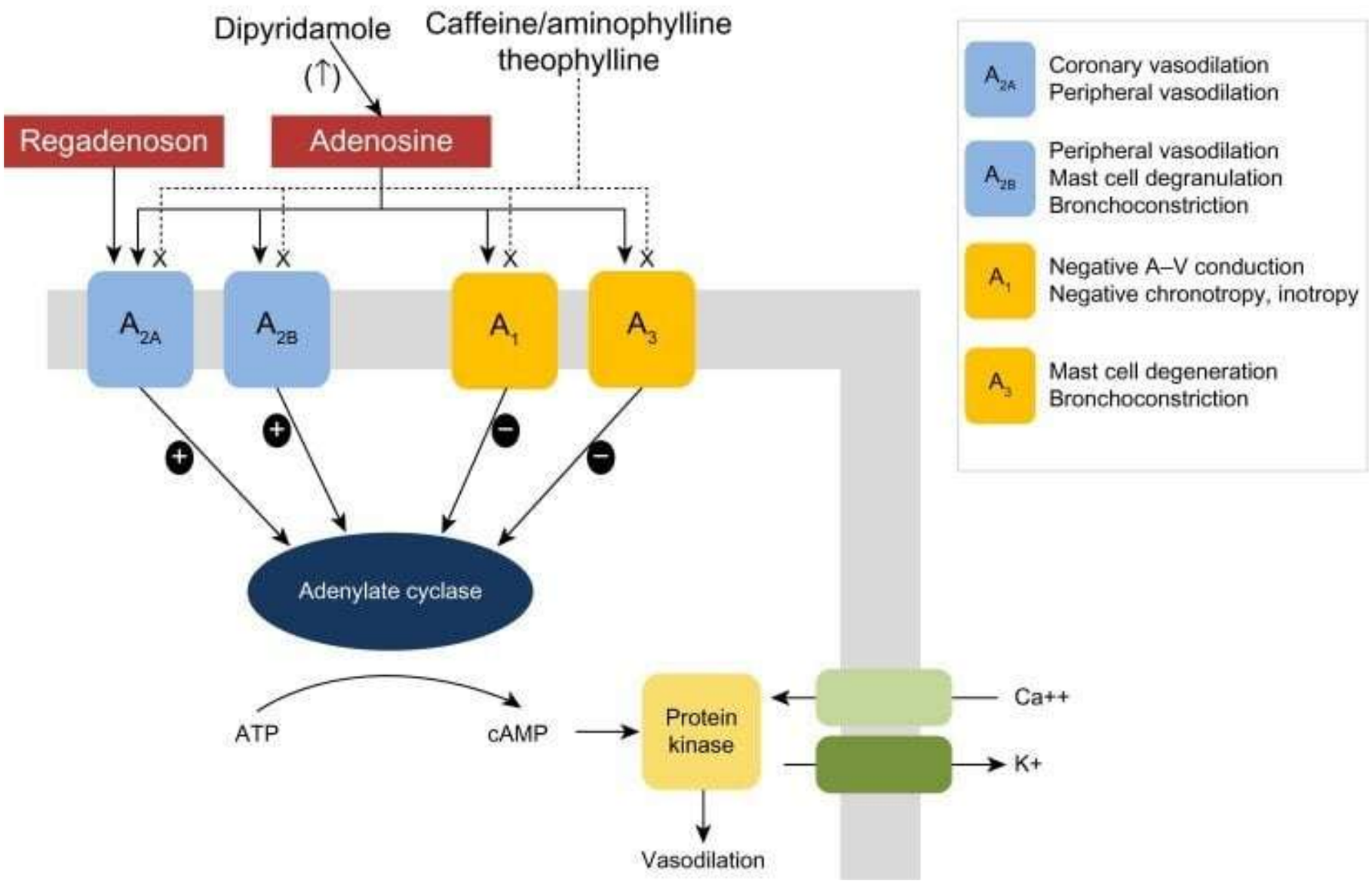
Carbohydrates and glycoconjugates function as the "third language of life," conveying vital biological information in a way that is complementary to nucleic acids and proteins. From the N-glycosidic linkages in the structure of DNA and RNA to the variety of glycan molecules on the surface of cells, carbohydrates orchestrate vital biological processes, such as cell-to-cell interactions, immune responses, and fighting off infections, such as blood types, which determine blood compatibility. Their significance is also seen in disease, such as in the progression of cancer or viral infections, which is reflected in drugs such as Cangrelor, an antiplatelet drug used to prevent blood clots, and Regadenoson, which is used to test the function of the heart. However, the complexity of glycosidic linkages, along with stereochemical issues, demands a potent synthetic approach to produce such bioactive compounds in a pure, stereo-chemically defined way.





REGADENOSON:

Regadenoson (Lexiscan) is a selective **A2A-adenosine receptor agonist** that serves as a pharmacological stress agent in radionuclide myocardial perfusion imaging (MPI). Structurally, it is an adenosine derivative modified with a **2-pyrazolyl group**, a design that grants it high affinity for the A-2A receptors in coronary arteries while minimizing impact on other adenosine receptor subtypes. By stimulating these specific receptors, Regadenoson induces rapid coronary vasodilation and increased blood flow, effectively mimicking the physiological stress of exercise for patients unable to perform physical exertion. This targeted biological mechanism provides a safer clinical profile compared to non-selective agents, reducing the risk of common side effects such as bronchoconstriction and heart block.

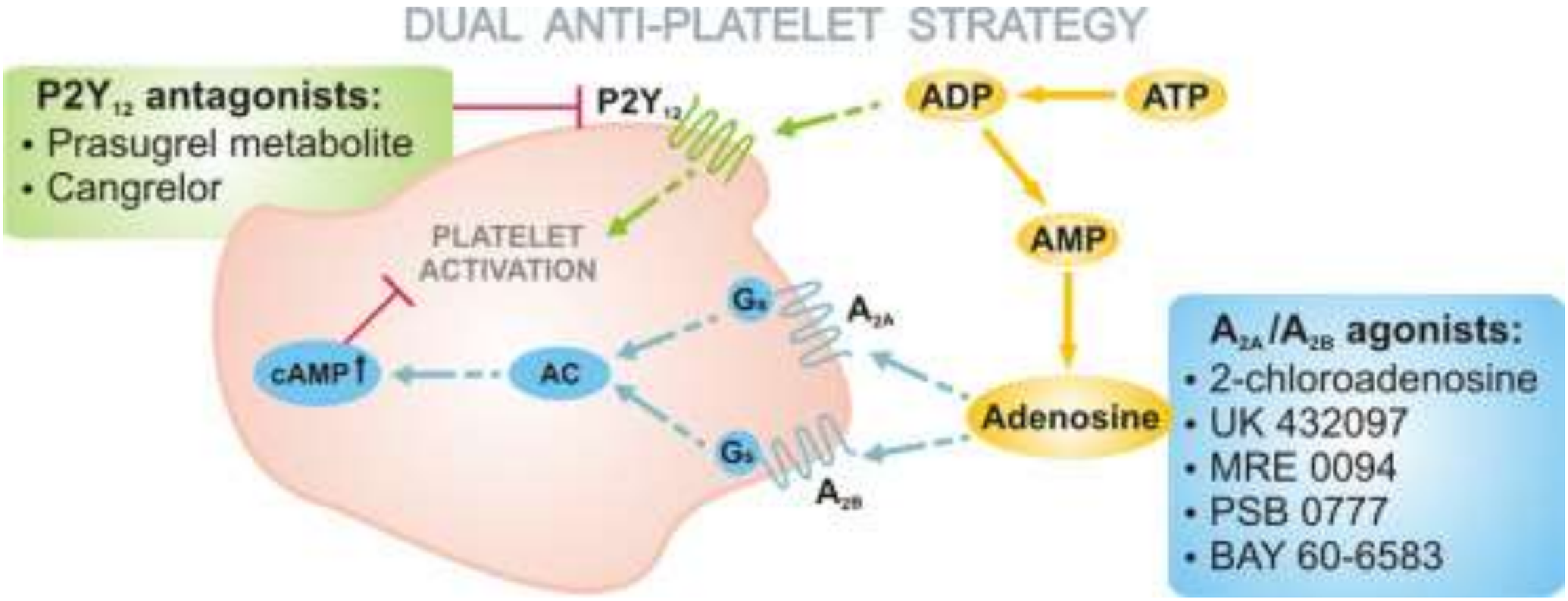


Cangrelor:

Cangrelor (marketed as Kengreal) is a high-potency, intravenous antiplatelet drug used primarily during percutaneous coronary intervention (PCI) to reduce the risk of myocardial infarction and stent thrombosis. Unlike oral antiplatelets (like Clopidogrel), Cangrelor is a direct-acting agent. Its most significant clinical advantage is its rapid onset and quick reversal (half-life of <5 minutes), allowing for precise control during surgery.

Cangrelor joins to high affinity ATP analogue which binds directly and reversibly to P2Y12 receptor. The P2Y12 receptor is a G- protein coupled receptor (GPCR) found on the surface of platelets. When Adenosine Diphosphate binds to this P2Y12 receptor it triggers a signal that leads to the stabalization of platelet aggregrates. Unlike its other members it does not require metabolic activation. It mimicks the structure of natural ligand thereby providing an immediate brake on the clotting process.

The most important characteristic of Cangrelor is its pharmacokinetic profile. If a surgeon needs a drug that works instantly but can also be turned off just as quickly if complication arises.

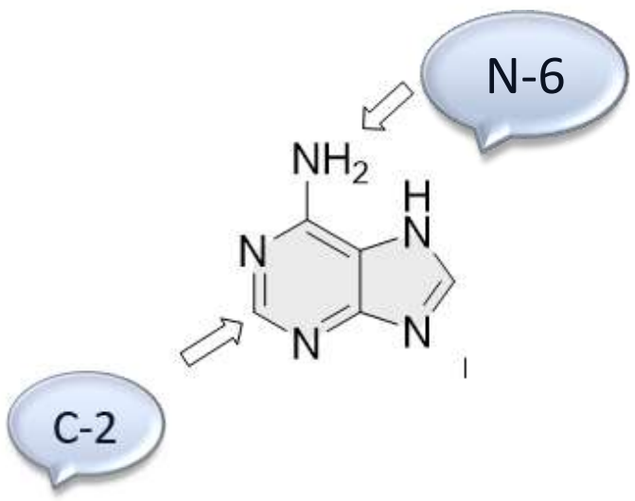


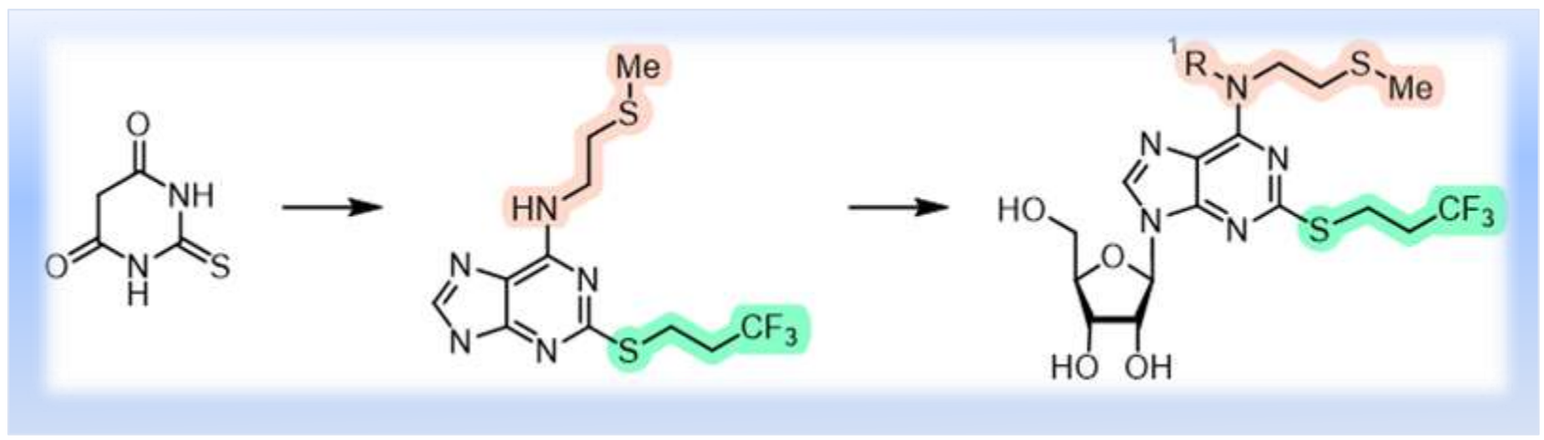
Structurally Cangrelor has a highly functionalised purine nucleoside. It has three major modifications:

1. A 2-(3,3,3-trifluoropropylthio) group on the purine ring.
2. A N-6-[2-(methylthio)ethyl] substitution.
3. A modified dichlorophosphonate triphosphate tail (prevents enzymatic hydrolysis).

While in the case of regadonoson 2-pyrazolyl functional group (1H-pyrazole-4-carboxamide) is present at the 2-position of the adenine ring.

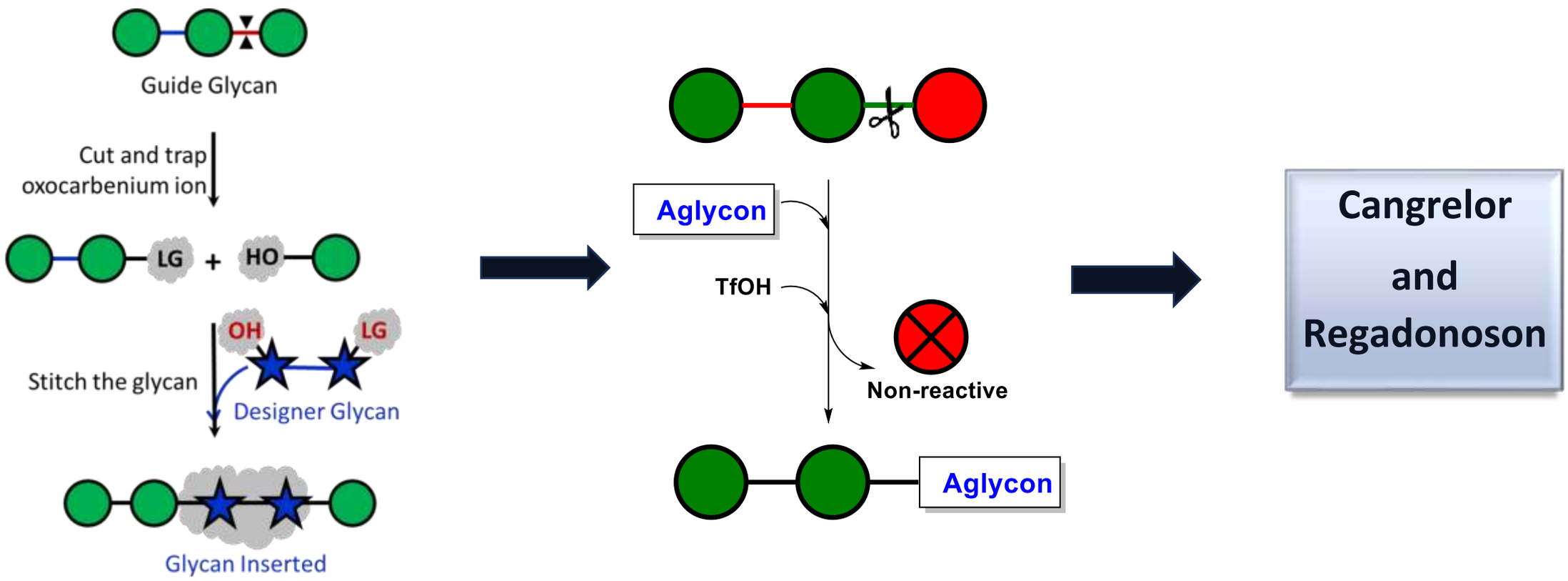
Traditional method: Modification at C-2 and N-6 position of adenine moiety





In here we rely on linear sequences and high temperature SnAr displacements. This can lead to mixtures of isomers and it build glycoside bond very early which leads that the sugar has to survive all the subsequent harsh steps.

While the traditional routes rely on linear construction of nucleoside core our work explores a more efficient and divergent strategy**: Aglycon Swapping (Nucleobase editing).** In classical approach the sugar and base had to be coupled early while the aglycon swapping allows for direct exchange or modification of the nucleobase on a pre-formed glycosyl moiety.



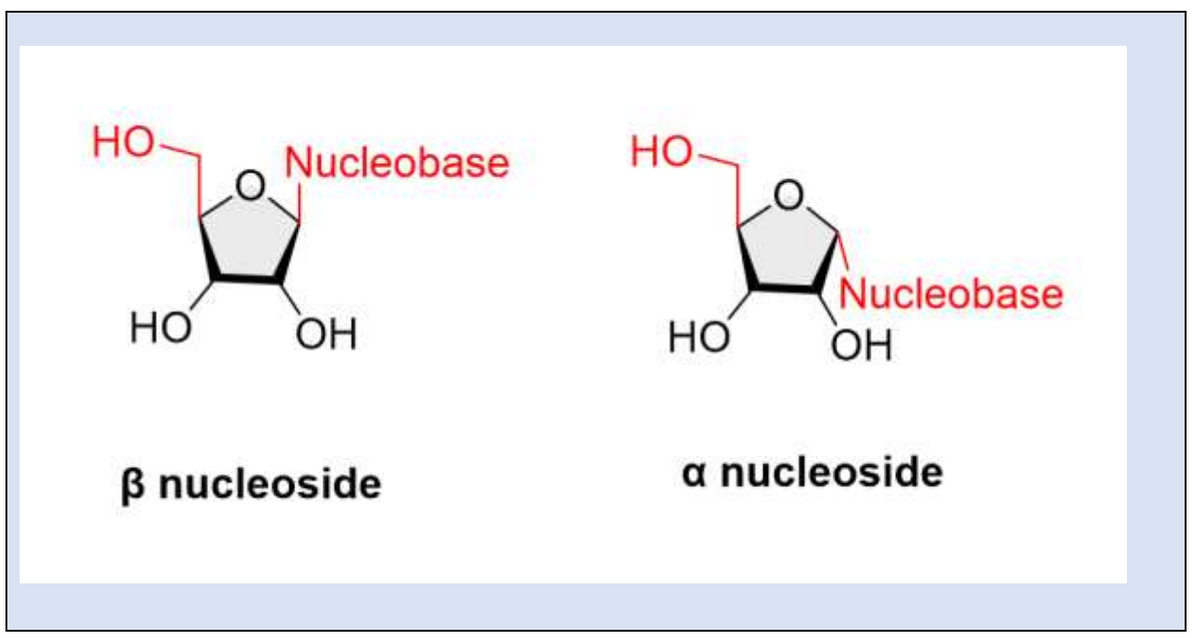
The integrity of the structure and biological activity of any nucleoside, including therapeutic drugs like Cangrelor, entirely depends on the formation of the N-glycosidic bond. This covalent bond is formed between the anomeric carbon of the ribofuranose sugar (C1) and the N-9 of the purine ring. In the context of aglycon swap, it is not only formed, but it is "edited" or "swapped" in the presence of a catalyst.

Stereoselectivity: The Challenge of the beta-Anomer

A major challenge in carbohydrate and nucleoside chemistry lies in controlling the 3D orientation of the N-glycosidic bond. There are two possible isomers, or "anomer," of nucleosides:

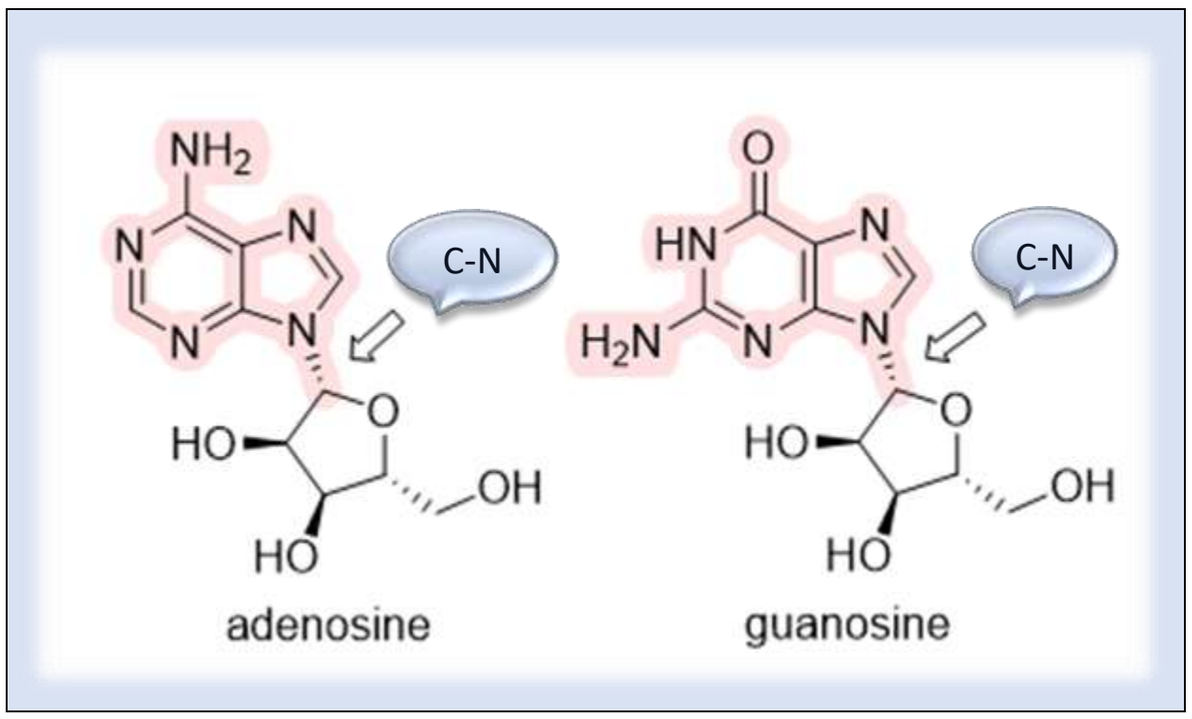
- α-anomer: The nucleobase is "down" (trans to the hydroxymethyl group of C5').
- β-anomer: The nucleobase is "up" (cis to the hydroxymethyl group of C5').

In order for drugs such as Cangrelor and Regadenoson to be effective in binding to specific receptors (P2Y12 and A2a, respectively), the beta-anomer configuration is a biological imperative. An alpha-nucleoside configuration is biologically inactive, or worse toxic**.**

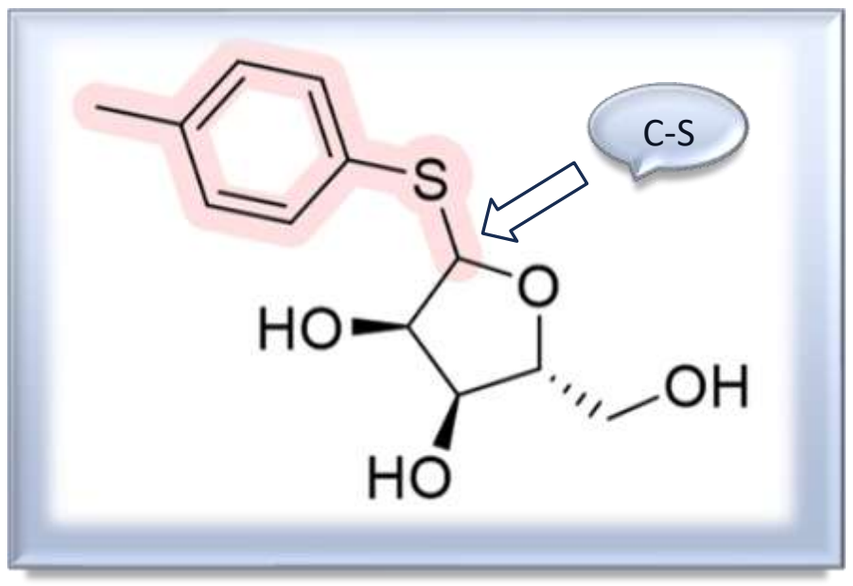


Glycosidic linkage:

A glycosidic bond is a covalent bond that connects a carbohydrate with another unit, which can be a different carbohydrate or a different kind of functional unit. The formation of a glycosidic bond occurs through a dehydration synthesis reaction between a hydroxyl group on one carbohydrate and an anomeric carbon on another carbohydrate, with a water molecule being lost in the process. The orientation of a glycosidic bond, whether it is alpha (α) or beta (β), is important for biological activity, as it determines what kind of polysaccharide will be produced—whether it will be an accessible source of energy, as with starch, or a stiff, insoluble material, as with cellulose.



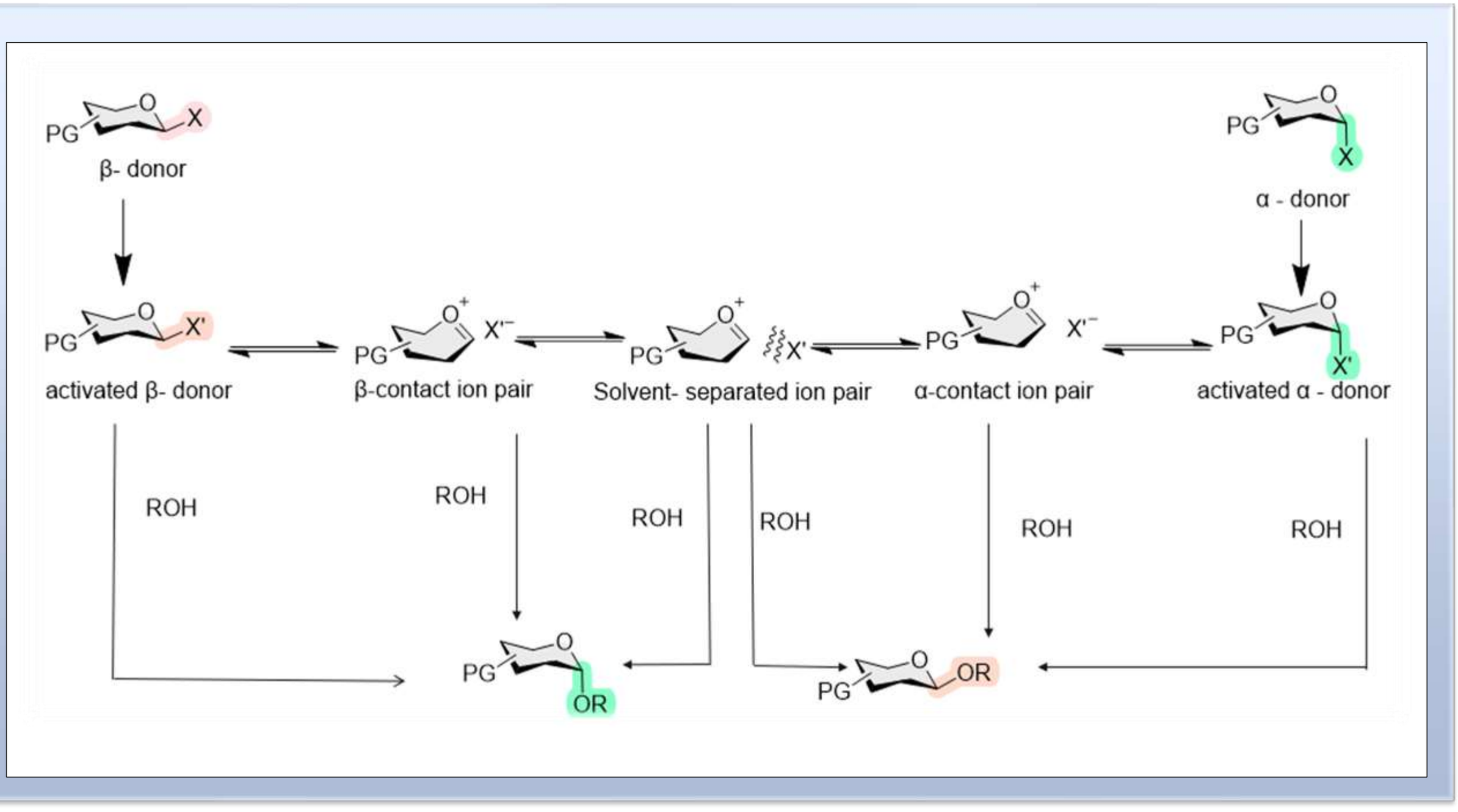
C-N Glycosidic Linkage



C-S Glycosidic Linkage

The basic principle behind chemical glycosylation reactions is quite simple: a glycosyl donor reacts with a nucleophile (ROH) and forms a glycosidic bond. The glycosyl donor, after activation, forms an oxocarbenium ion, which exists in a dynamic equilibrium of contact ion pairs and solvent-separated ion pairs. The stereochemical outcome of the glycosidic bond, whether it is alpha or beta, depends on the way the nucleophile attacks the oxocarbenium ion, and this attack can be controlled by the choice of solvent, temperature, and participating protecting groups (PG).

Introduction to Glycosylation Strategies:

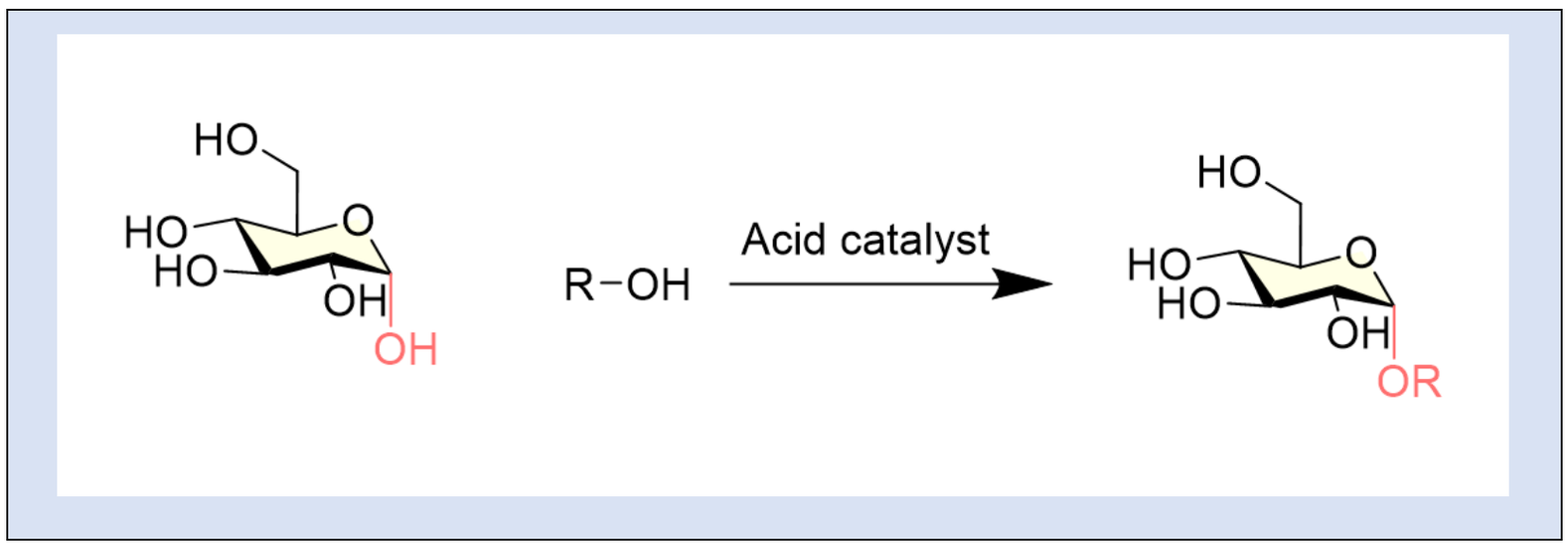


Classification of Glycosylation Methods by Activation Strategy:

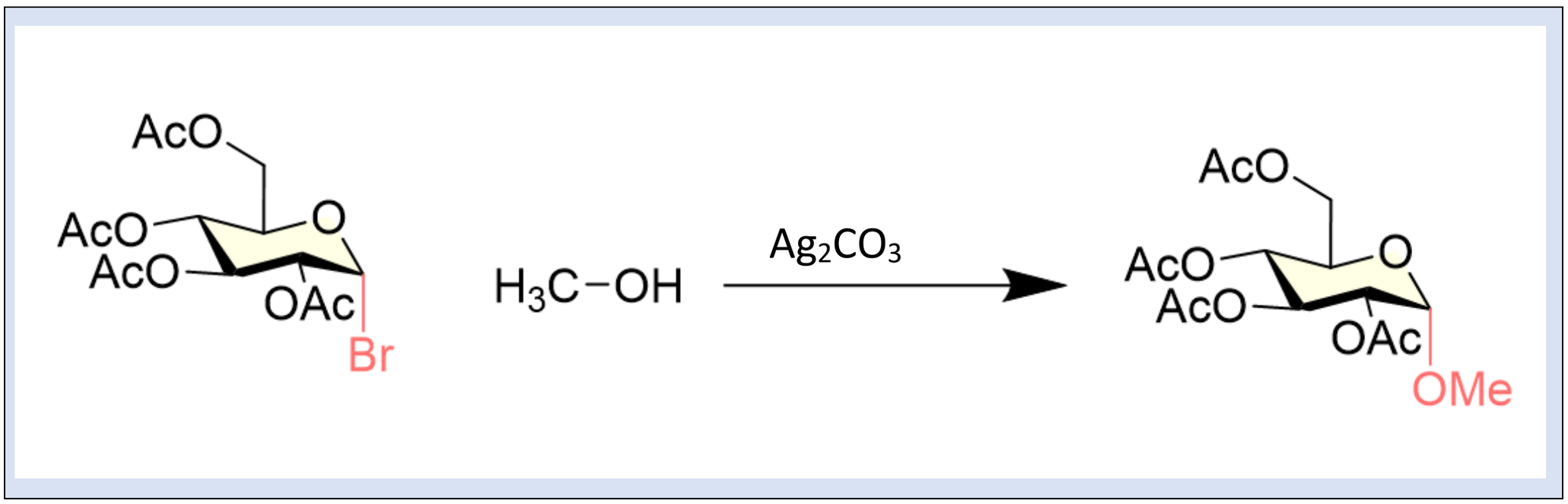
Glycosidic bond formation is not a spontaneous process. The anomeric centre is quite stable so you require the use of specific promoters or catalysts that tailor to the electronic nature of the leaving group on the glycosyl donor. This activation generally depends on the softness or hardness of the Lewis acid/electrophile and the atom which is being targeted of the donor molecule.

Earlier methods:

1.**Fischer Glycosylation**

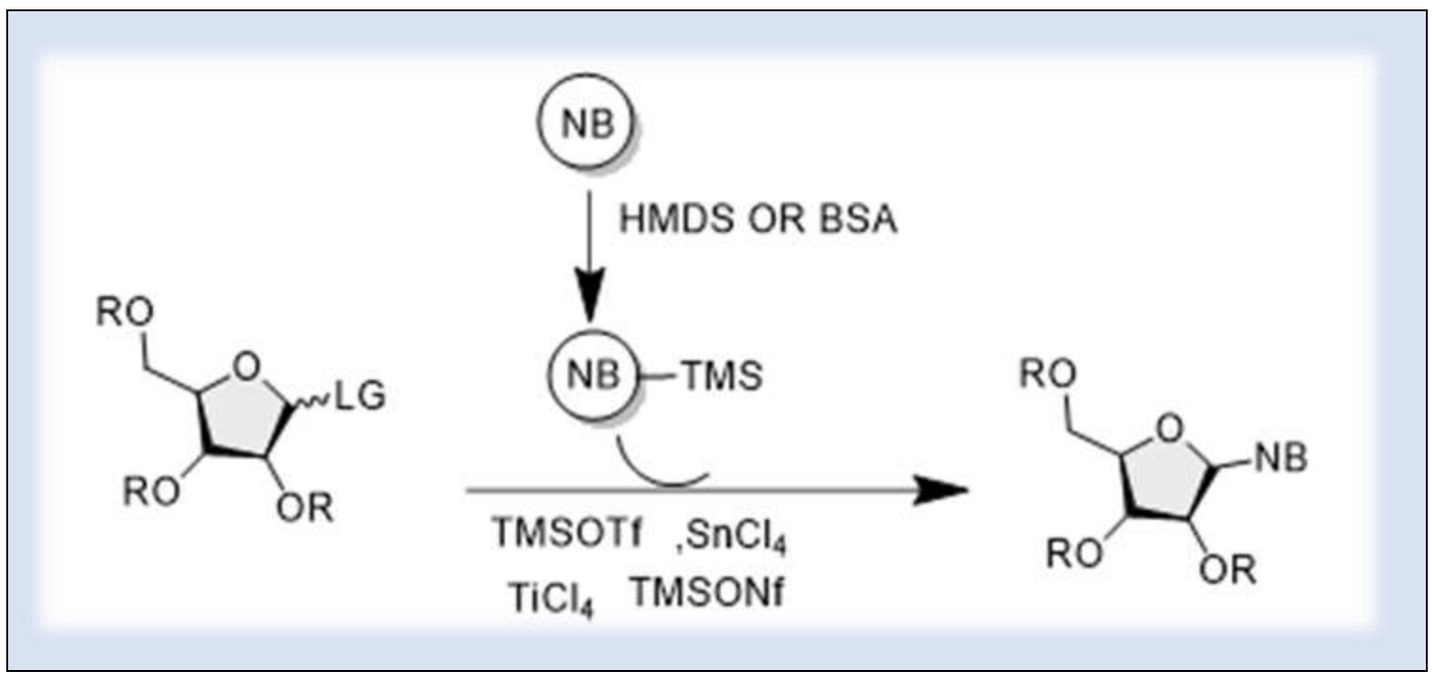


2.Koenigs–Knorr Reaction

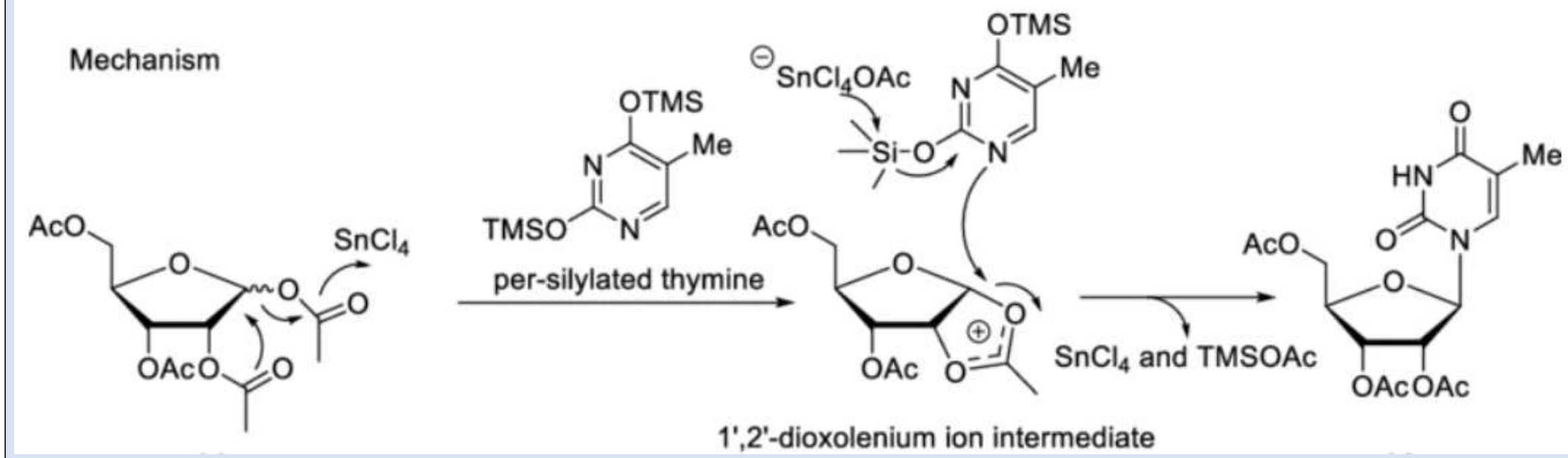


In early glycosylation procedures, acids played a crucial part either as catalysts or activating agents, or glycosyl halides were used. The Fischer Glycosylation reaction directly used sugars with alcohol, but it was not stereoselective. The Koenigs-Knorr Reaction used silver salts to activate glycosyl halides, thus introducing the donor-acceptor principle. Other procedures, including the Helferich Glycosylation reaction, used mercury salts to enhance reactivity, but they faced the same drawbacks.

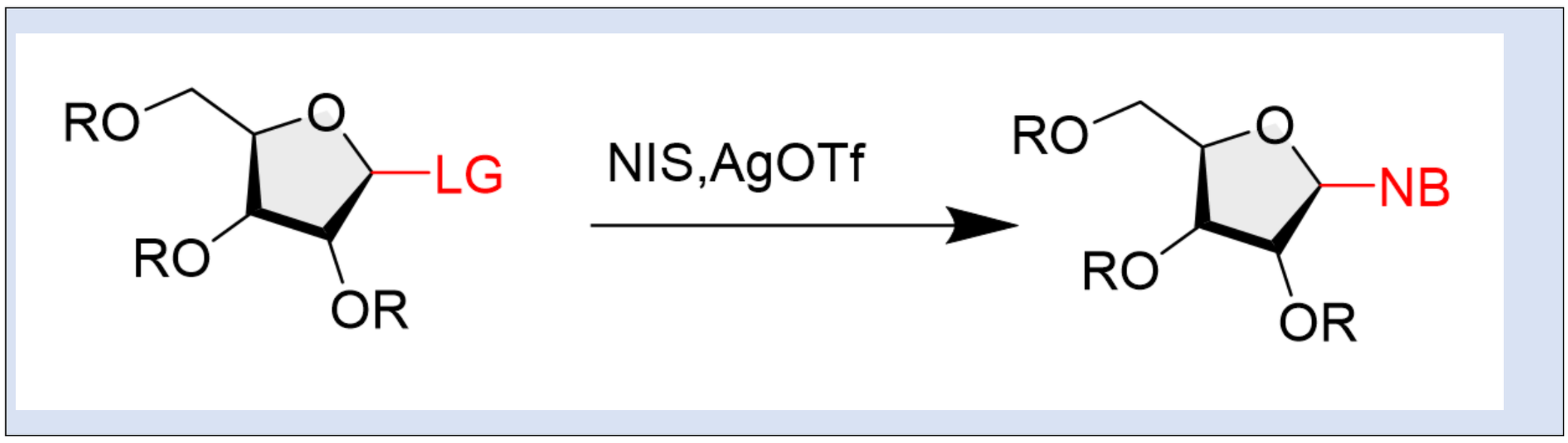
Vorbruggen Reaction:



In vorbruggen reaction the protected sugar is activated by a Lewis acid while the nucleobase is first silylated to enhance its nucleophilicity. After which the activated sugar reacts with the base to form N-glycosidic bond which gives us the beta-selectivity.

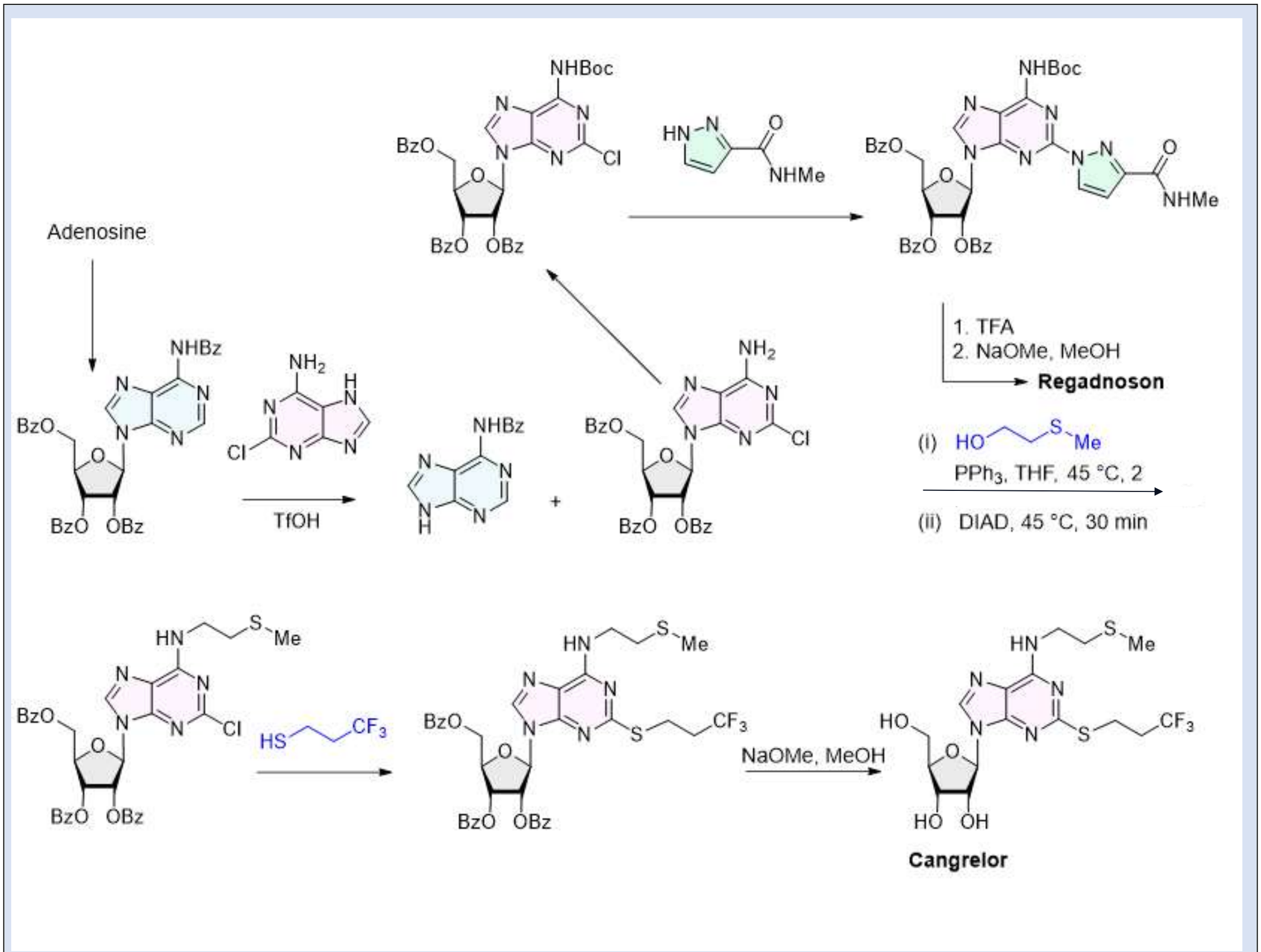


In our case the classical vorbruggen protocol is not directly employed the principle still remains similar. A thioglycoside donor is activated under mild conditions using **N-iodosuccinimide (NIS)** and **AgOTf** which generates an anomeric intermediate similar to that of Vorbruggen Glycosylation. The nucleobase then attacks this activated center to from the desired N- glycosidic linkage.

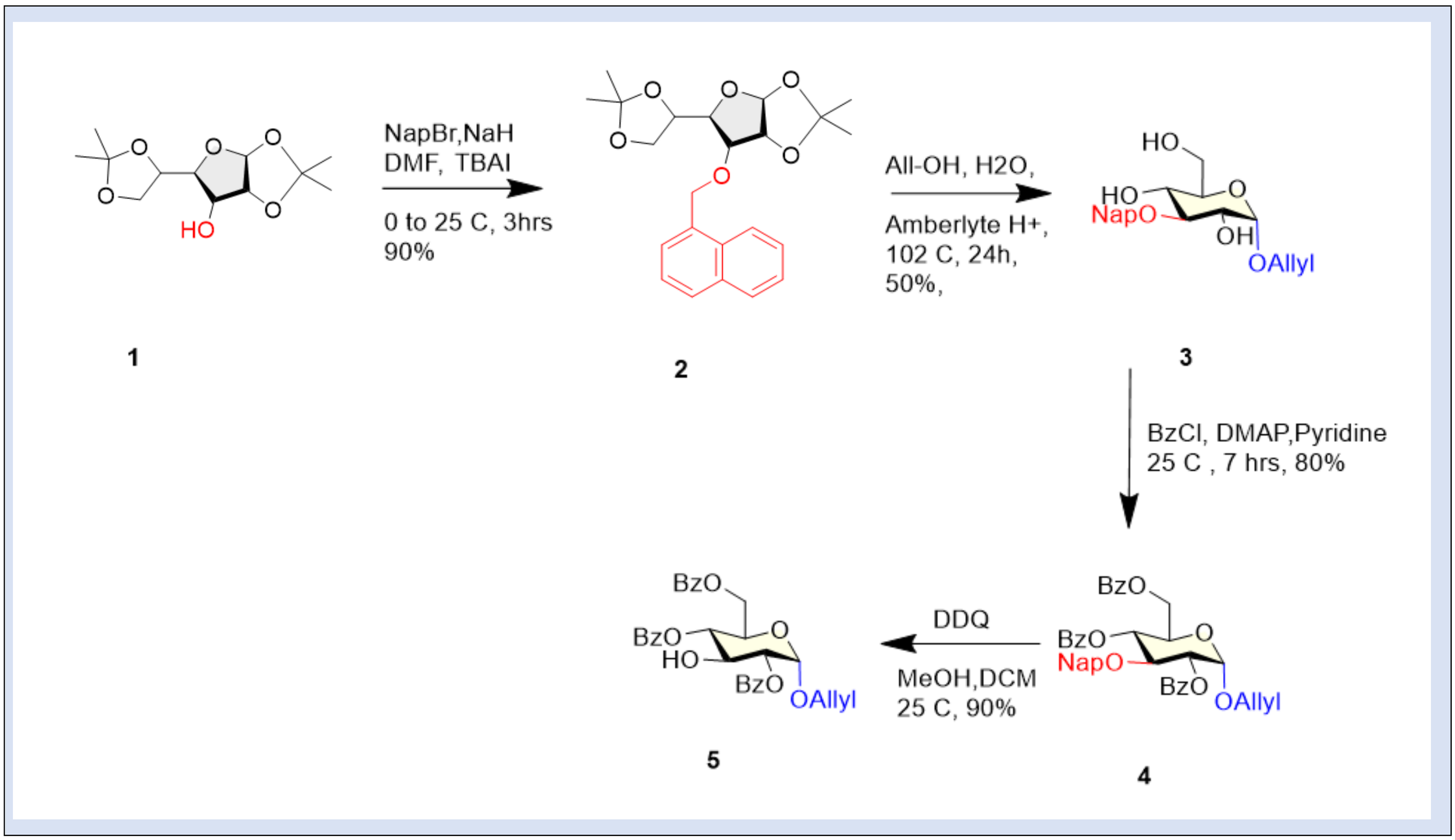


The current strategy can be viewed as a modern adaptation of Vorbrüggen glycosylation, where a more stable and tunable thioglycoside donor replaces traditional donors, allowing improved control over reactivity and reaction conditions.

RETROSYNTHESIS



Scheme for Glycosyl Acceptor:



Procedures:

2.0: Nap Protection of Diacetone D-Glucose:

To a stirred solution of Diacetone D glucose (10g, 38.42mmol, 1.0eq) in DMF, sodium hydride (1.01g, 42.26mmol, 1.1 eq) was added portion wise at 0 C under inert atmosphere. Reaction mixture was stirred for half an hour to ensure the deprotonation of the hydroxyl group. After that, 2-(bromomethyl)naphthalene (10.19g, 46.10mmol, 1.2 eq) was added slowly to the above reaction mixture. TBAI (2.84g, 7.68mmol, 0.2eq) was added as a phase transfer catalyst. Reaction mixture was stirred at room temperature for another 3 hours. After the completion of the reaction as ensured by TLC (30 % EA/Hex), the reaction mixture was quenched with ice-cold water, and the mixture was extracted using an organic solvent. Organic solvent layer was dried over sodium sulfate and evaporated on a rota. Residue was

purified using column chromatography to obtain 3-O-Naphthylmethyl protected diacetone-D-glucose as a yellow oil.

3.0: Allyl 3-O-(2-naphthylmethyl])-α/β-D-glucopyranoside

In a fresh round bottom flask, 3-O-Naphthylmethyl diacetone-D-glucose (10g, 25mmol) was taken, to which allyl alcohol (247.52ml) and Amberlyte resin (4.207g, IR-120 H+ form) and water (1ml) was added. The reaction was stirred at room temperature for 15 minutes, after which the reaction was refluxed at 104 C for 20 hours. After the reaction was over, as confirmed by TLC (70% EA/Hex), the resin was filtered and washed with MeOH. The filtrate was evaporated on a rota evaporator, and the residue was purified by silica gel chromatography to obtain a mixture of α/β Allyl 3-O-(2-naphthylmethyl])α/β-D-glucopyranoside as a white solid in 45 % quantitative yield.

4.0: Benzoylation of Allyl 3-O-(2-naphthylmethyl])-α/β-D-glucopyranoside:

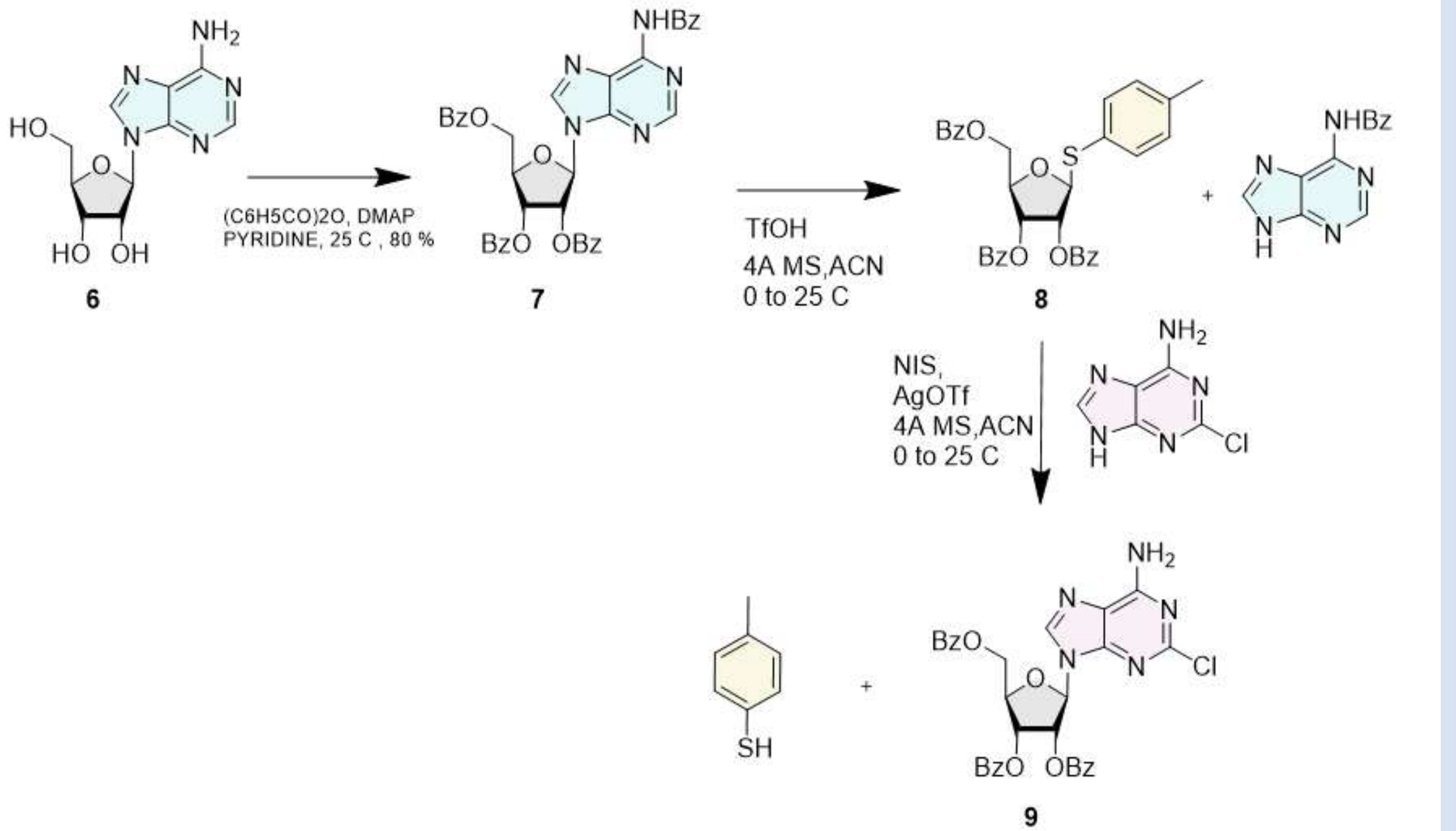
In a round bottom flask containing pyridine, Allyl 3-O-(2-Naphthylmethyl)-α/β-D-glucopyranoside (1.7g, 5.90mmol) was added, and the mixture was cooled to 0 C. Stirring was continued for 10 minutes. To the above mixture, Benzoyl Chloride (2.20ml, 18.97mmol) was added dropwise. To the above mixture, DMAP (57.94 mg, 0.474mmol) was added, and the mixture was stirred at room temperature for 5 hours under inert atmosphere. After completion of the reaction, as indicated by TLC (30% EA/Hex), the reaction mixture was quenched by adding cold water. The mixture was extracted with organic solvent. To the above mixture, 1N HCL (200ml) was used for washing. Organic solvent was extracted, dried over sodium sulphate, and evaporated using rota. To the above mixture, silica gel chromatography was used for the purification of the compound. Allyl 2,4,6-tri-O-benzoyl-3-O-(2-Naphthylmethyl})-α/β-D-glucopyranoside was obtained as white solid in 80% quantitative yield.

5.0 : Nap deprotection

To a solution of 4:1 MeOH/DCM Allyl 2,4,6-tri-O-benzoyl-3-O-(2-Naphthylmethyl})-α/β-D-glucopyranoside (400mg, 0.596mmol), DDQ (676.85mg,2.98mmol) was added. The reaction mixture was stirred for 5-6 hours and when TLC (30 % EA/Hex) indicated complete conversion, the mixture was further diluted with DCM and washed 3 times using aq

$NaHCO_3$. The combined organic layers were dried through sodium suphate, evaporated over rota and purified by silica chromatography to give (**5**) as a white solid.

Scheme for Nucleoside donor:



Procedures:

7.0: Benzoylation of adenosine:

In a round bottom flask containing pyridine, Adenosine(5g,18.71mmol) was added and stirred for 5min. Further benzoic anhydride (18.62g, 82.32mmol) and DMAP (914.3mg, 7.48mmol) was added and the reaction mixture was allowed to stir for 10 hours. After TLC (30% EA/Hex) indicates that reaction is completed ice cold water is added. Benzoylated adenosine falls out on addition of ice cold water. This is further filtered and dried under vacuum to yield pure Benzoylated Adenosine in 90 percent quantitative yield.

8.0: *S*- glycoside

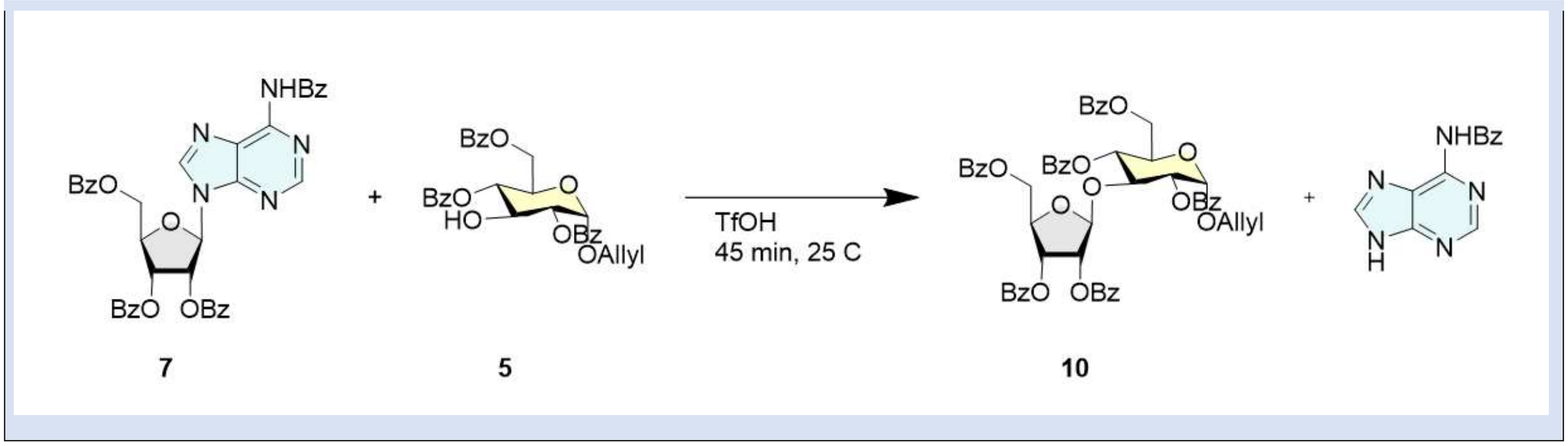
Benzoylated adenosine(500mg,0.731mmol) was taken in a dry round bottom flask and dissolved in DCM. This solution was cooled to 0 C and 4-methylbenzenethiol was added to it and stirred for 10 min. After this freshly activated molecular sieves were added to this reaction mass and this mixture was stirred for 15 mins. Triflic acid was further added to

this reaction mass and this mixture was stirred for another 45 min to 1 hour at room temperature. After TLC (10% EA/Hex) indicated completion the reaction mass was quenched with addition of triethyl amine and filtered off. The resulting filtrate is evaporated under rota and purified by using silica chromatography to give thiogylcoside.

9.0: Glycan swapping reaction

A solution of thioglycoside in dry acetonitrile was cooled to 0 C after which 2-chloroadenine followed by NIS(1.25eq) and AgOTf (0.25eq) were added and stirred for another 1 hour at room temperature. The progress of the reaction was monitored by TLC and after completion triethylamine was added to quench the reaction mass. The residue was purified by column chromatography to give N-Glycosylated product.

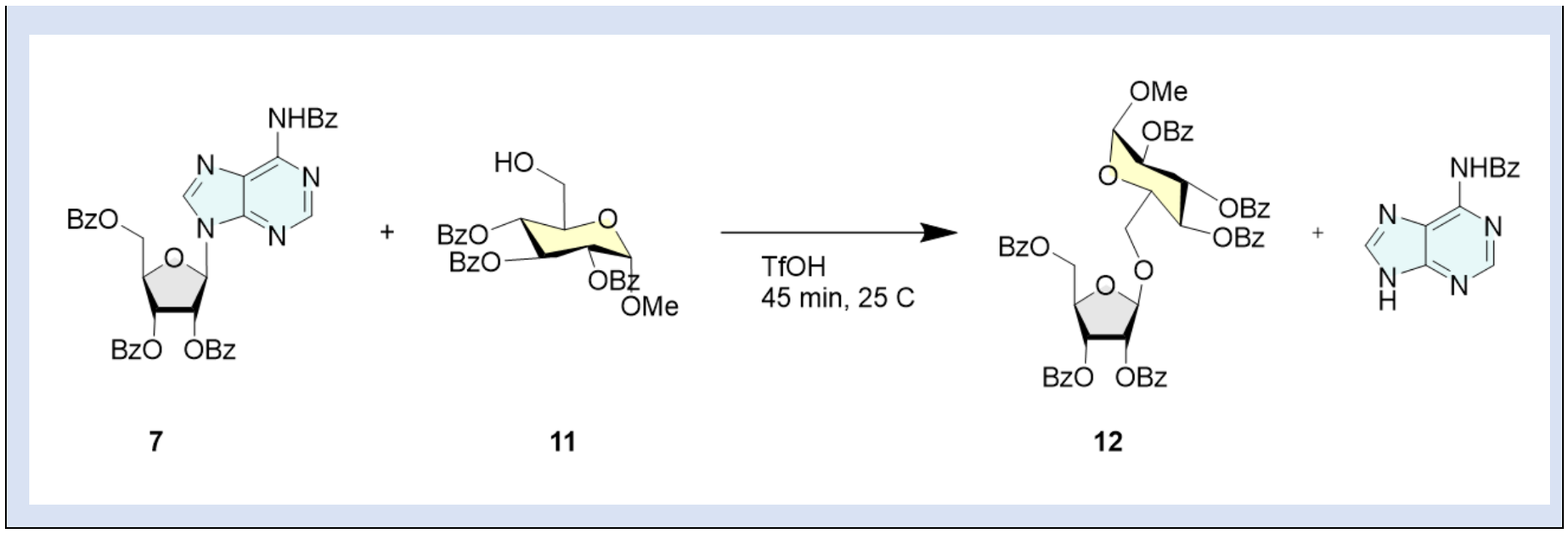
Scheme for *O*-Glycoside:



10: *O*-Glycoside from Purine nucleosides:

A dry round-bottom flask equipped with a stir bar was charged with the protected nucleoside donor **7** and glycosyl acceptor **5** in dry dichloromethane. The reaction mixture was cooled to 0 °C under an inert atmosphere. Trifluoromethanesulfonic acid (TfOH) was then added dropwise to the stirred solution and the reaction mass was allowed to stir at room temp for another 1 hour until TLC showed complete consumption of starting material. Upon completion TEA was added to quench the reaction mass and the solvent was evaporated under the rota and the residue was purified by silica gel chromatography to get the desired product.

12: Benzoyl protected *O*-glycoside:



A dry round-bottom flask equipped with a stir bar was charged with the protected nucleoside donor 7 and glycosyl acceptor 11 in dry dichloromethane. The reaction mixture was cooled to 0 °C under an inert atmosphere. Trifluoromethanesulfonic acid (TfOH) was then added dropwise to the stirred solution and the reaction mass was allowed to stir at room temp for another 1 hour until TLC showed complete consumption of starting material. Upon completion TEA was added to quench the reaction mass and the solvent was evaporated under the rota and the residue was purified by silica gel chromatography to get the desired product.

RESULTS AND DISCUSSIONS:

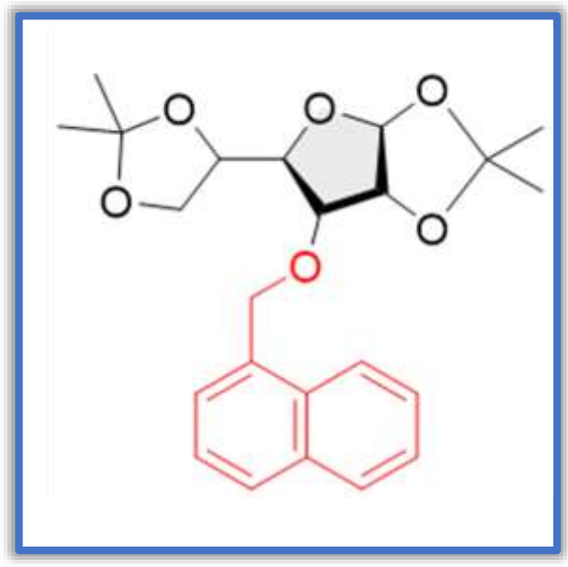
The main objective of our work was to develop a combined intermediate which could have been used for the synthesis of both Cangrelor and Regadenoson using ASER method. The main reaction of this work that is aglycan swapping reaction was carried out successfully using NIS and AgOTf. The reaction proceeded via the formation of thioglycoside intermediate which was further attacked by 2 chloroadenine to form the desired N-Glycosidic bond. The formation of this glycosylated nucleoside was confirmed by NMR however further transformations for Regadenoson and Cangrelor derivatives proved challenging as the reactions were showing low reactivity, mixture formations, and even decomposition of starting material. These Reactions might have been unsuccessful due to electronic deactivation of purine ring, steric hindrance of benzoyl protecting group and the sensitivity of N-glycosidic bond under certain conditions.

To tackle these limitations an alternate donor acceptor strategy was formed. In here a protected nucleoside donor was coupled with glycosyl acceptor under acidic activation such as triflic acid. This method resulted in successful O-glycoside products confirming the compatibility of system.

Overall we can say that the Aglycon Swapping Edition Reaction is effective strategy for the construction of N-glycosidic bond. However further functionalization of nucleobase remains a significant challenge especially in synthesis of complex drug molecules. Our work tries the bridge the gap between limitations and potential of ASER.

SPECTRAL DATA:

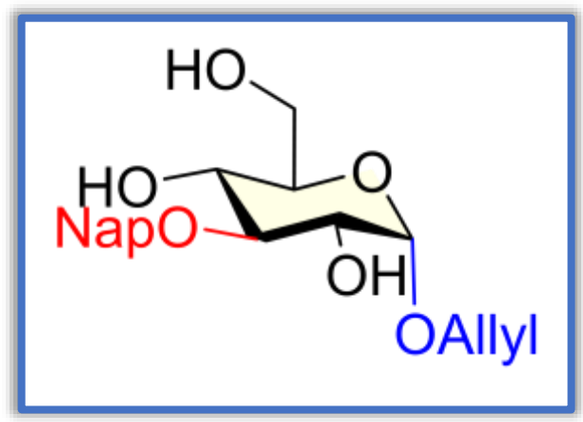
COMPOUND 2:



^{1}H NMR (401 MHz, $CDCl_3$): δ 7.90 – 7.80 (m, 4H), 7.56 – 7.45 (m, 3H), 5.96 (d, J = 3.7 Hz, 1H), 4.90 – 4.79 (m, 2H), 4.66 (d, J = 3.7 Hz, 1H), 4.46 (dt, J = 7.8, 6.0 Hz, 1H), 4.23 – 4.15 (m, 2H), 4.13 – 4.05 (m, 2H), 1.53 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 135.15, 133.30, 133.12, 128.26, 127.93, 127.76, 126.50, 126.22, 126.04, 125.69, 111.84, 109.07, 105.39, 82.74, 81.69, 81.43, 72.60, 72.45, 67.49, 26.91, 26.89, 26.32, 25.54.

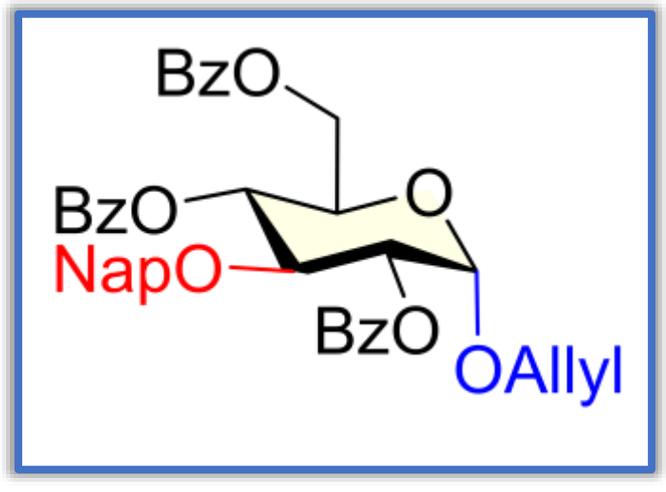
COMPOUND 3:



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 – 7.75 (m, 4H), 7.55 – 7.42 (m, 3H), 5.91 (ddt, J = 16.5, 10.7, 5.6 Hz, 1H), 5.33 (d, J = 1.7 Hz, 1H), 5.21 (dd, J = 10.6, 1.6 Hz, 1H), 4.98 – 4.88 (m, 2H), 4.76 (d, J = 11.8 Hz, 1H), 4.40 (t, J = 2.3 Hz, 1H), 4.29 – 4.20 (m, 3H), 4.11 – 3.96 (m, 2H), 3.83 (dd, J = 11.4, 3.3 Hz, 1H), 3.72 (dd, J = 11.4, 5.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 135.99, 135.89, 133.65, 133.47, 133.32, 133.05, 128.50, 128.44, 127.95, 127.75, 126.86, 126.76, 126.70, 126.44, 126.25, 126.22, 126.12, 126.06, 126.02, 125.88, 118.20, 101.99, 97.73, 83.62, 82.84, 80.39, 77.26, 75.28, 75.05, 74.79, 74.49, 72.85, 71.26, 70.59, 70.12, 68.64, 65.46, 62.47, 62.30, 60.46, 29.72, 14.20.

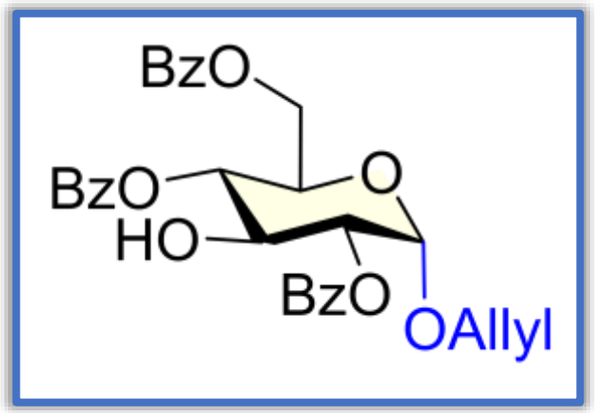
COMPUND 4:



^{1}H NMR (401 MHz, $CDCl_3$): δ 8.11 – 7.92 (m, 6H), 7.62 – 7.32 (m, 15H), 7.10 (dd, J = 8.4, 1.7 Hz, 1H), 5.76 (dddd, J = 16.9, 10.9, 6.4, 4.8 Hz, 1H), 5.60 (t, J = 9.4 Hz, 1H), 5.47 (dd, J = 9.1, 7.8 Hz, 1H), 5.17 (dq, J = 17.3, 1.7 Hz, 1H), 5.11 – 5.05 (m, 1H), 4.82 – 4.70 (m, 3H), 4.59 (dd, J = 12.0, 3.3 Hz, 1H), 4.42 (dd, J = 12.0, 5.5 Hz, 1H), 4.31 (ddt, J = 13.3, 4.9, 1.6 Hz, 1H), 4.17 – 4.06 (m, 2H), 3.99 (ddd, J = 9.4, 5.6, 3.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.08, 164.99, 134.74, 133.48, 133.43, 133.21, 133.09, 132.96, 132.87, 129.81, 129.77, 129.74, 129.25, 128.50, 128.44, 128.39, 128.34, 128.11, 127.75, 127.60, 126.90, 125.99, 125.86, 125.74, 117.72, 99.74, 79.48, 77.23, 74.05, 73.51, 72.12, 71.19, 69.83, 63.44.

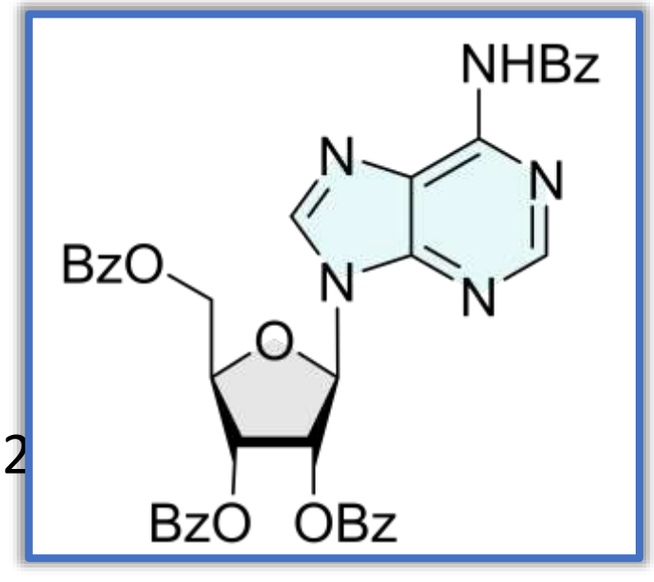
COMPOUND 5:



^{1}H NMR (401 MHz, $CDCl_3$): δ 8.09 – 7.99 (m, 6H), 7.61 – 7.51 (m, 3H), 7.49 – 7.37 (m, 6H), 5.82 (dddd, J = 17.0, 10.9, 6.3, 4.9 Hz, 1H), 5.40 (t, J = 9.5 Hz, 1H), 5.29 – 5.19 (m, 2H), 5.13 (dq, J = 10.5, 1.4 Hz, 1H), 4.78 (d, J = 7.8 Hz, 1H), 4.64 (dd, J = 12.0, 3.0 Hz, 1H), 4.46 (dd, J = 12.0, 5.6 Hz, 1H), 4.34 (ddt, J = 13.1, 5.0, 1.6 Hz, 1H), 4.21 – 4.11 (m, 2H), 4.10 – 3.88 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.28, 166.13, 133.60, 133.45, 133.42, 133.19, 129.94, 129.74, 129.52, 129.10, 128.51, 128.45, 128.40, 117.90, 99.49, 74.89, 74.08, 72.40, 71.94, 70.04, 63.43.

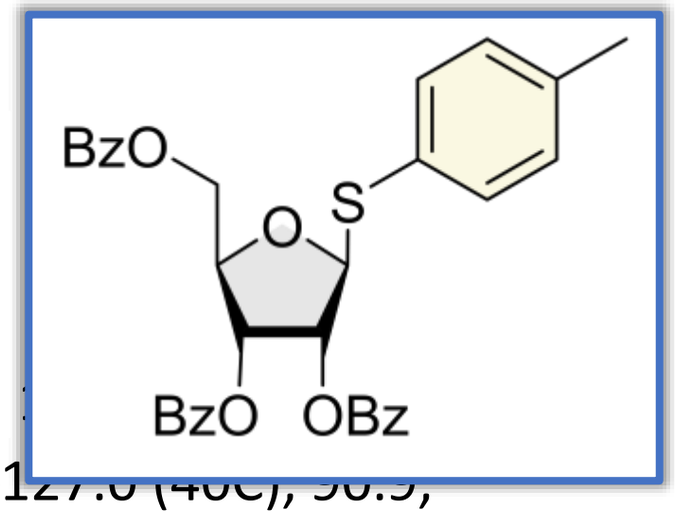
COMPOUND 7:



^{1}H NMR (401 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.66 (s, 1H), 8.22 (s, 1H), 8.13 – 8.07 (m, 2H), 8.00 (t, J = 7.2 Hz, 4H), 7.95 – 7.90 (m, 2H), 7.60 – 7.49 (m, 4H), 7.48 – 7.31 (m, 8H), 6.51 (d, J = 5.2 Hz, 1H), 6.45 (t, J = 5.5 Hz, 1H), 6.28 (t, J = 5.3 Hz, 1H), 4.92 (dd, J = 12.1, 3.3 Hz, 1H), 4.84 (q, J = 4.1 Hz, 1H), 4.72 (dd, J = 12.2, 4.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): 129.84, 129.82, 129.74, 129.31, 128.73, 12 128.59, 128.55, 127.99, 87.10, 80.85, 73.93, 71.51, 63.58.

COMPOUND 8:

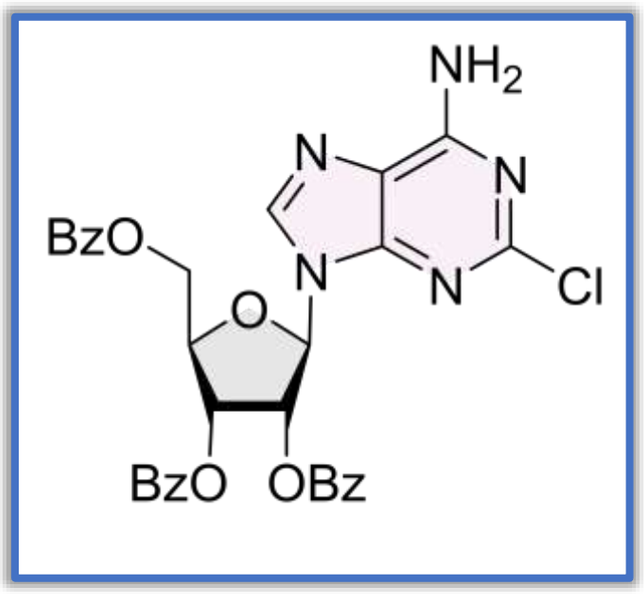


^{1}H NMR (401 MHz, $CDCl_3$): δ 8.06 – 7.78 (m, 6H), 7.53 – 7.24 (m, 11H), 7.01 (dd, J = 21.3, 7.8 Hz, 2H), 5.76 – 5.70 (m, 1H), 5.64 (t, J = 4.9 Hz, 1H), 5.56 (t, J = 5.2 Hz, 1H), 5.47 (d, J = 5.3 Hz, 1H), 4.56 (t, J = 3.1 Hz, 1H), 4.44 – 4.38 (m, 1H), 2.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): 133.5, 133.5, 133.3, 133.2, 132.7, 130.0-127.0 (10C), 90.9, 88.0, 80.4, 79.0, 74.4, 72.4, 72.2, 71.7, 64.4, 60.4, 21.2 (2C).

COMPOUND 9:

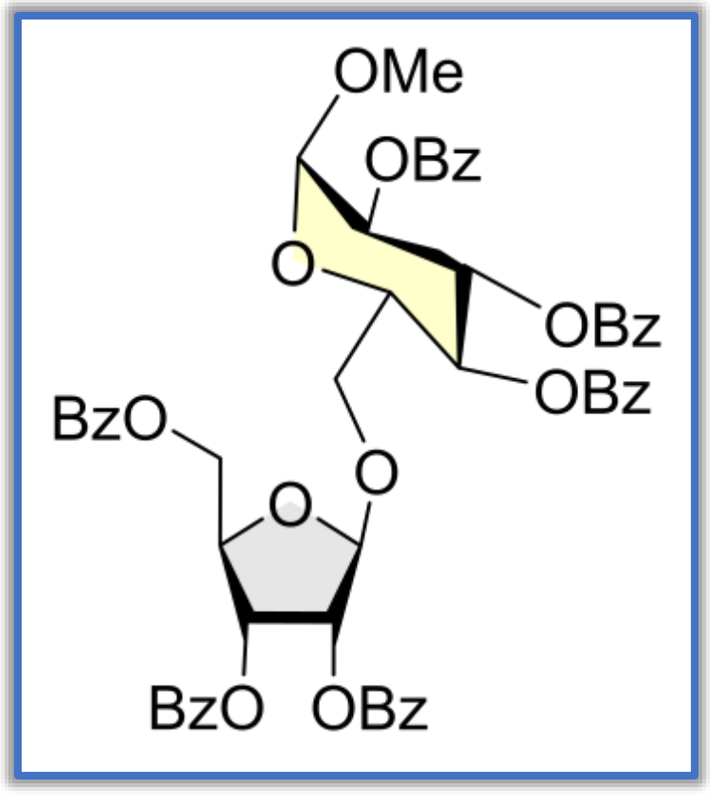
^{1}H NMR (401 MHz, $CDCl_3$): δ 8.13 – 7.86 (m, 13H), 7.63 – 7.29 (m, 19H), 6.17 – 6.12 (m, 1H), 5.91 (dd, J = 6.3, 4.9 Hz, 1H), 5.83 – 5.75 (m, 1H), 5.70 – 5.61 (m, 2H), 5.49 (dd, J = 6.4, 4.4 Hz, 1H), 4.95 – 4.53 (m, 7H).



COMPOUND 12

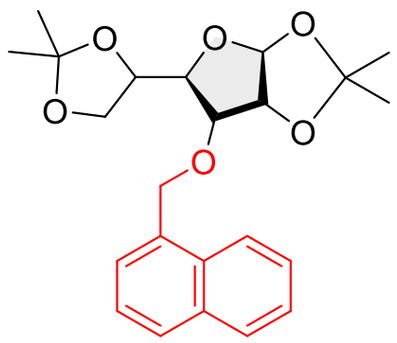
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.97 (m, 6H), 7.91 – 7.85 (m, 6H), 7.60 – 7.53 (m, 1H), 7.49 – 7.27 (m, 17H), 6.14 (t, J = 9.8 Hz, 1H), 5.88 (dd, J = 7.0, 4.8 Hz, 1H), 5.76 (d, J = 4.9 Hz, 1H), 5.52 (t, J = 9.9 Hz, 1H), 5.38 (s, 1H), 5.31 – 5.21 (m, 2H), 4.75 – 4.66 (m, 2H), 4.56 – 4.48 (m, 1H), 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).

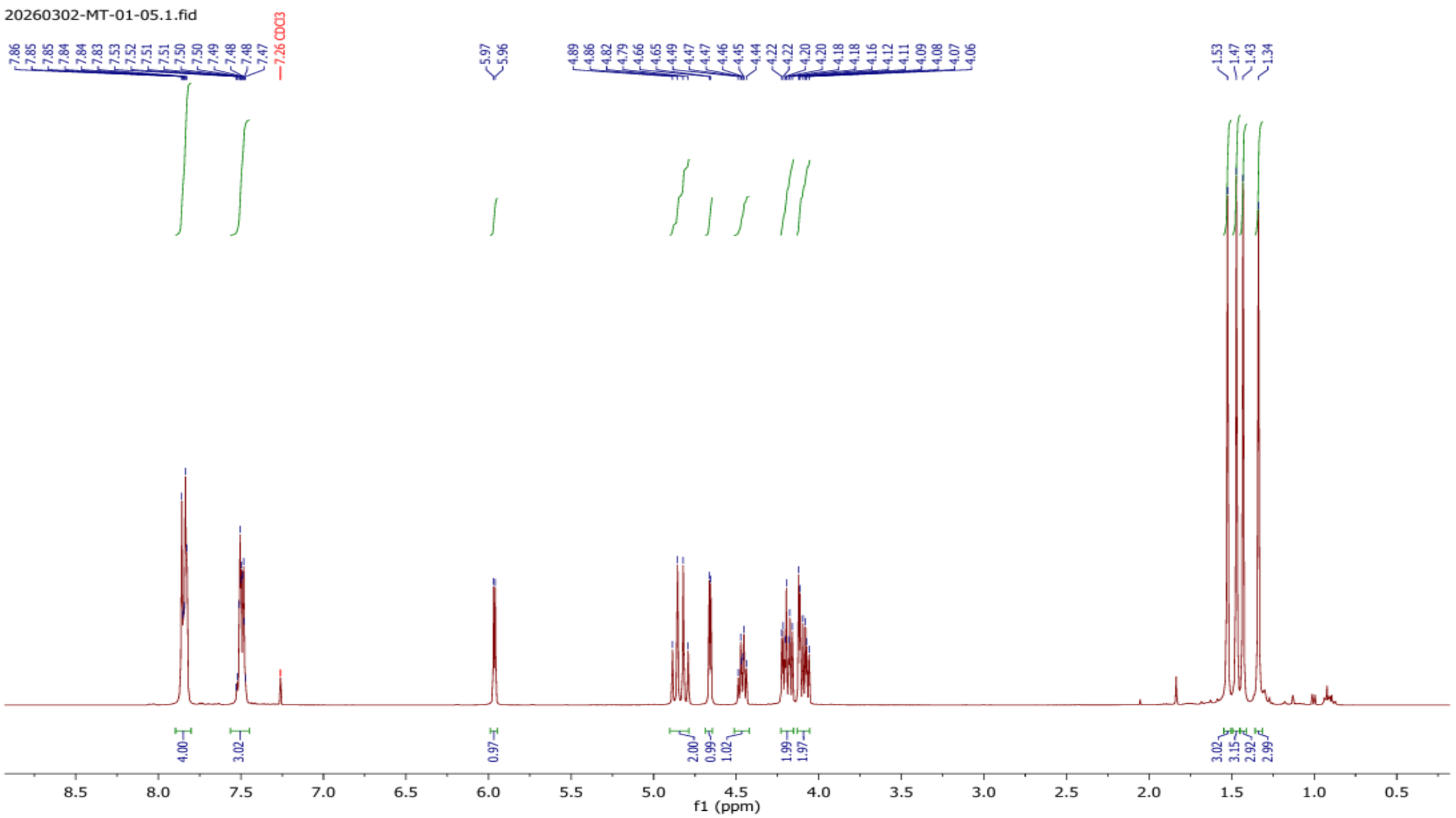
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.2, 165.9 (2C), 165.4 (2C), 165.2, 133.5, 133.4, 133.4, 133.2, 133.1, 130.0 - 129.7 (5C), 129.3, 129.2 (2C), 129.0, 128.9, 128.6-128.3 (20C), 106.3, 96.9, 79.3, 75.5, 72.4, 70.6, 69.6, 69.0, 67.1, 64.9, 55.7



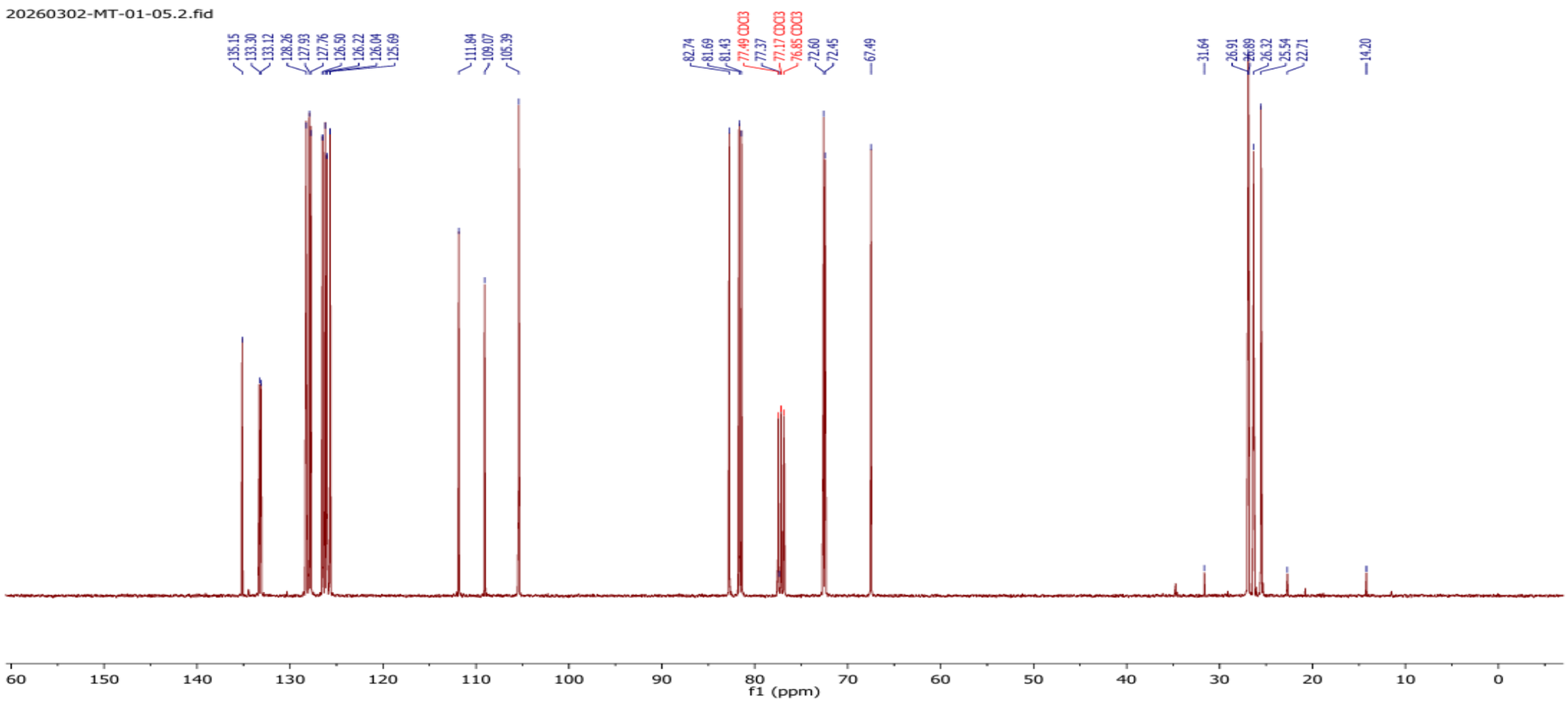
NMR SPECTRAL CHART

^{1}H NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 2:

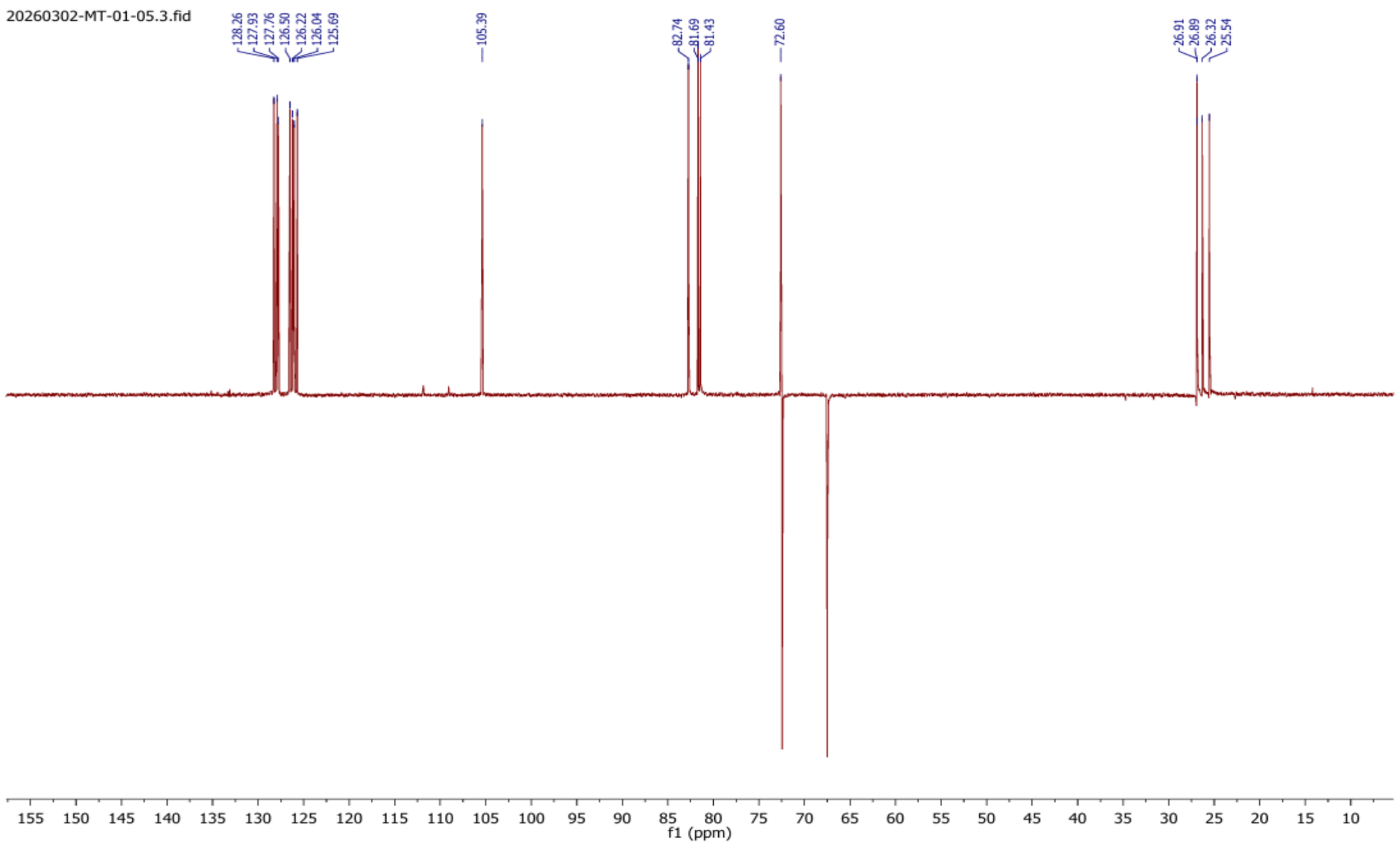




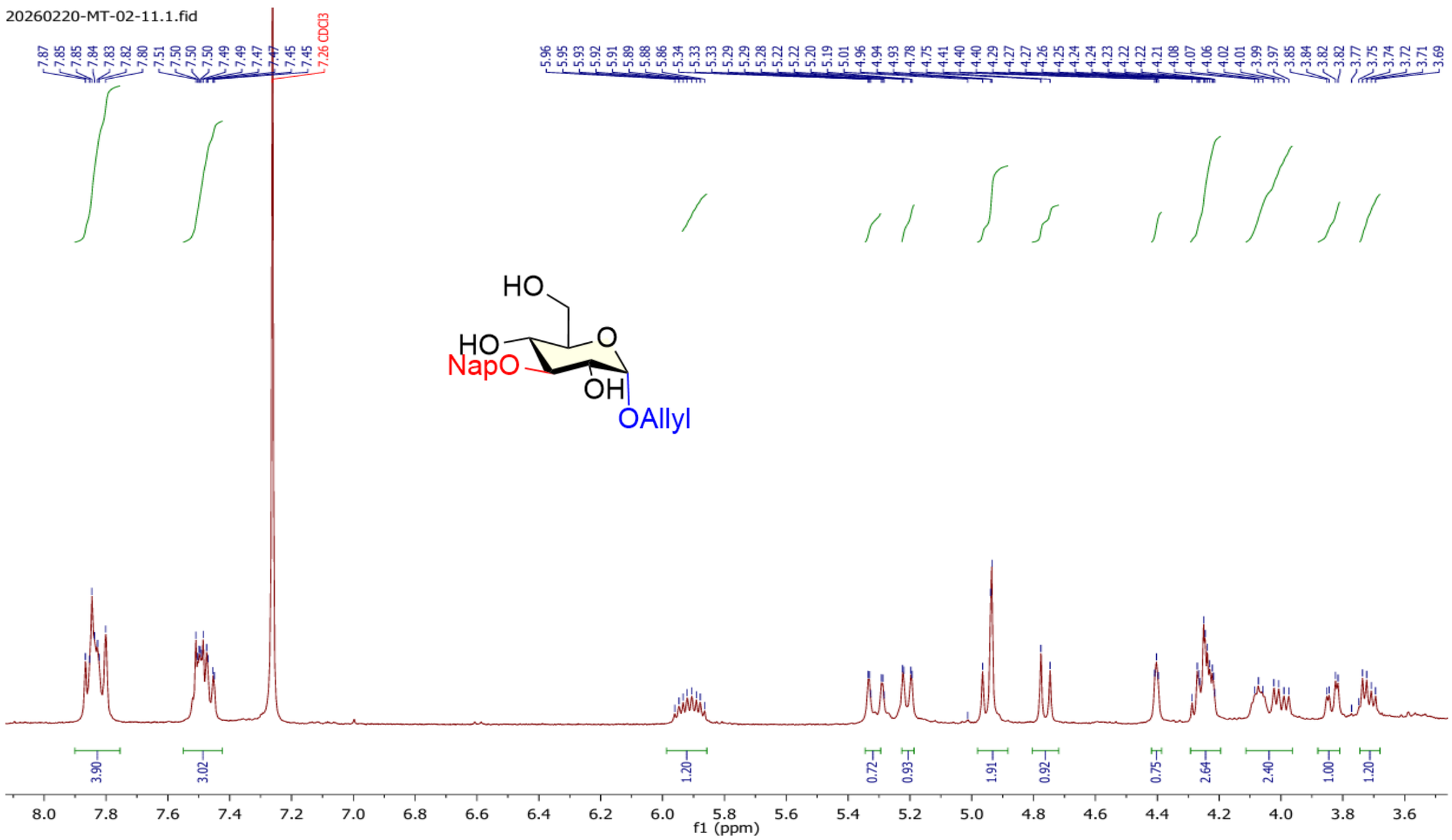
^{13}C NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 2:



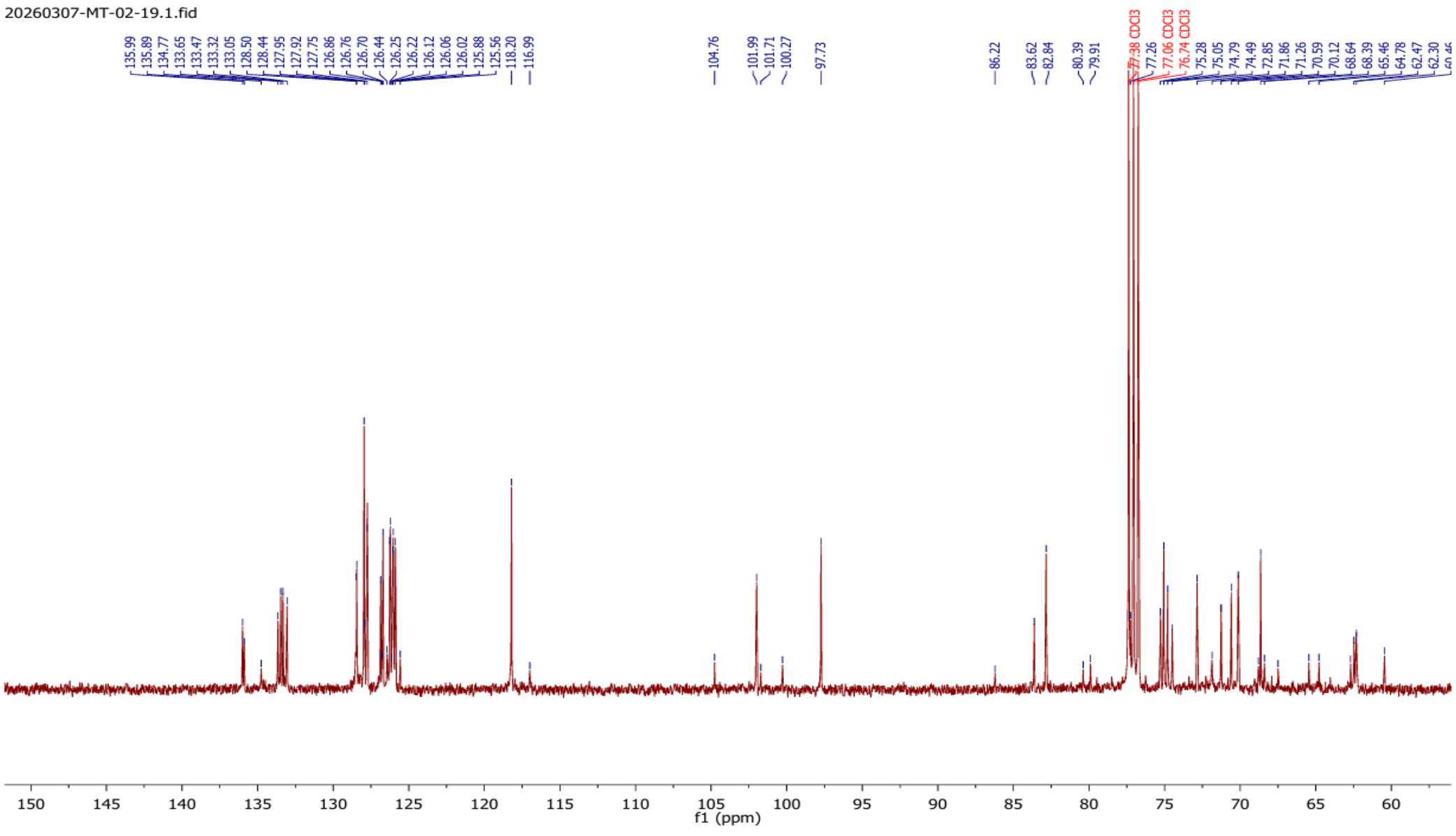
DEPT-135 NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 2:



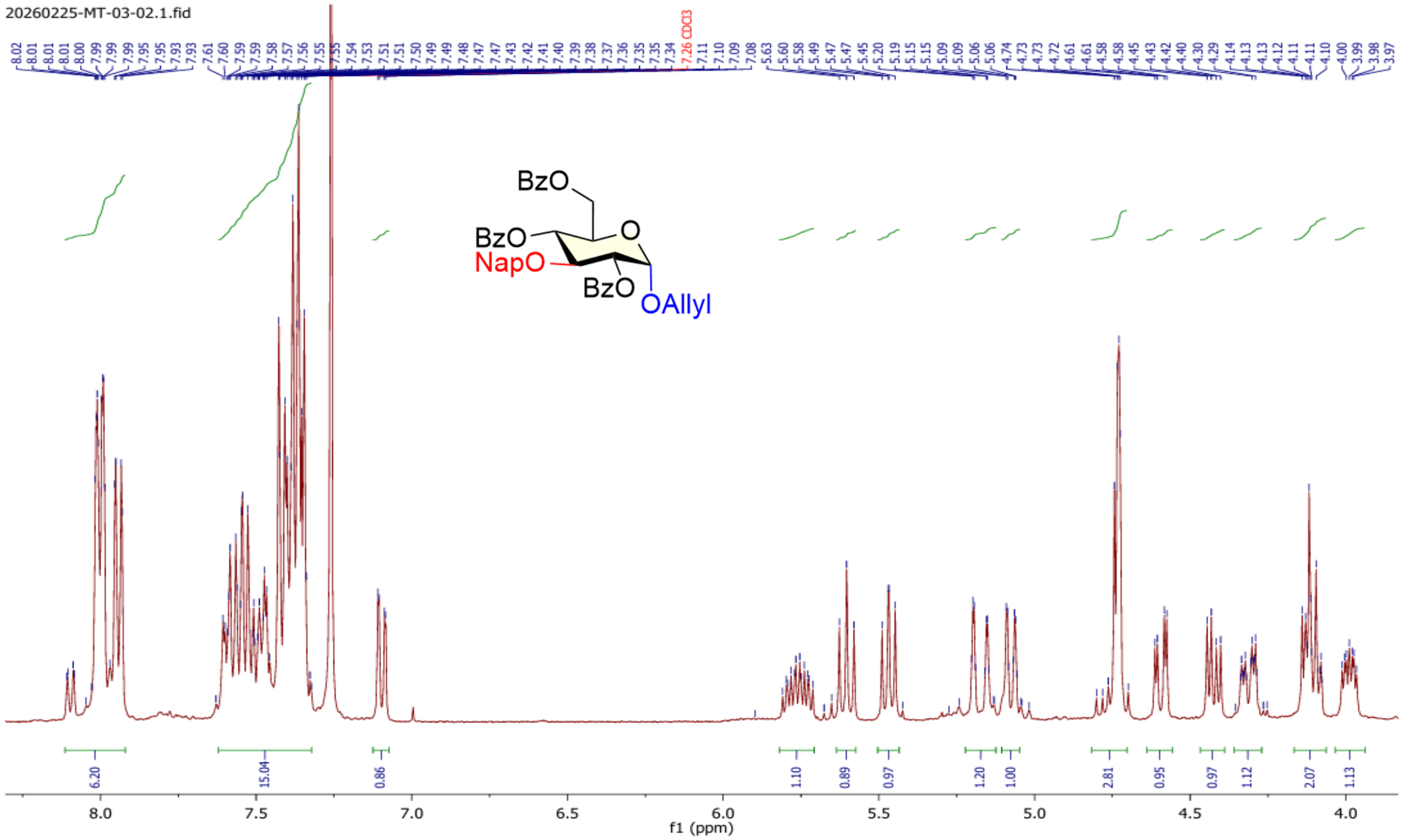
^{1}H NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 3:



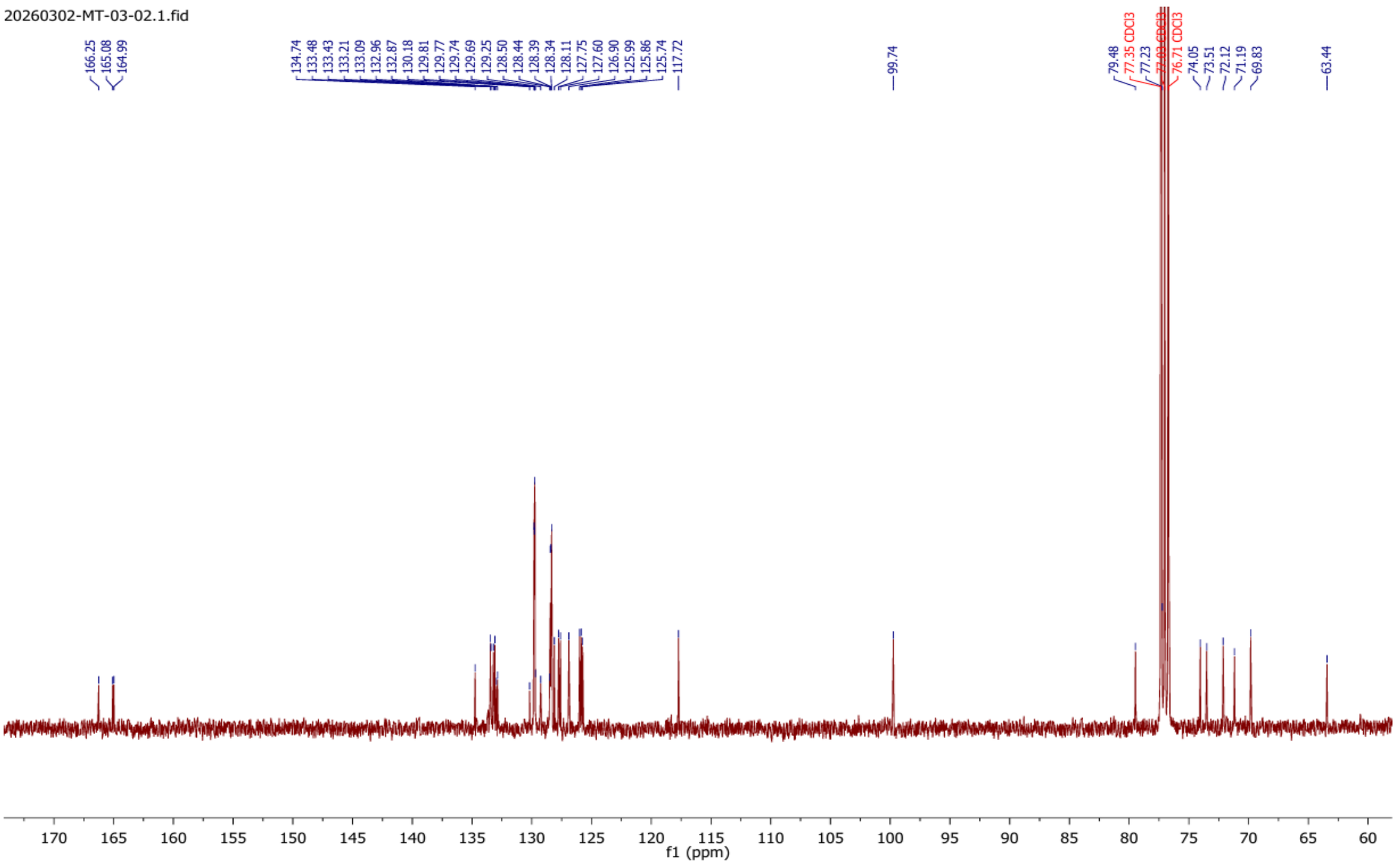
^{13}C NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 3:



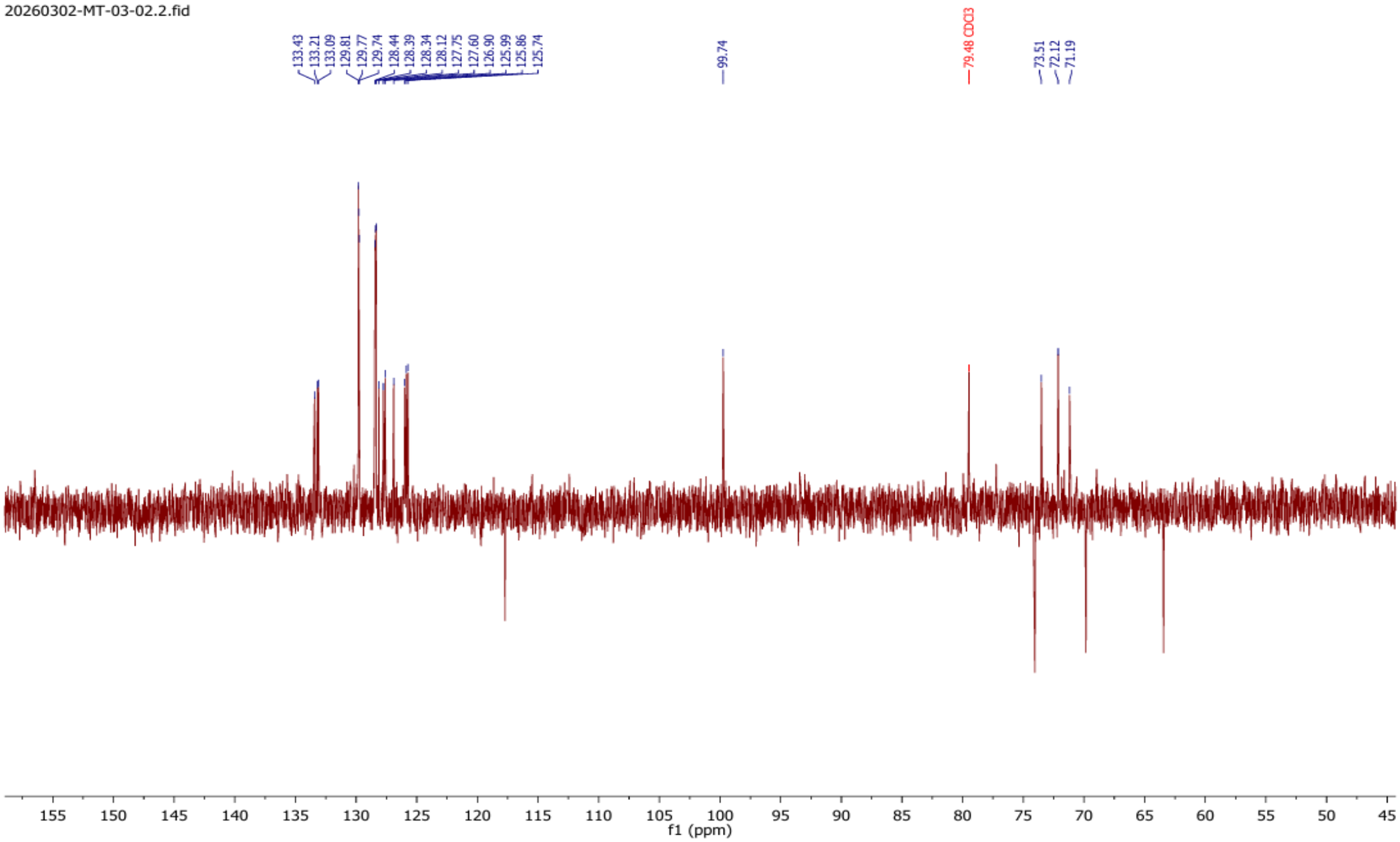
^{1}H NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 4:



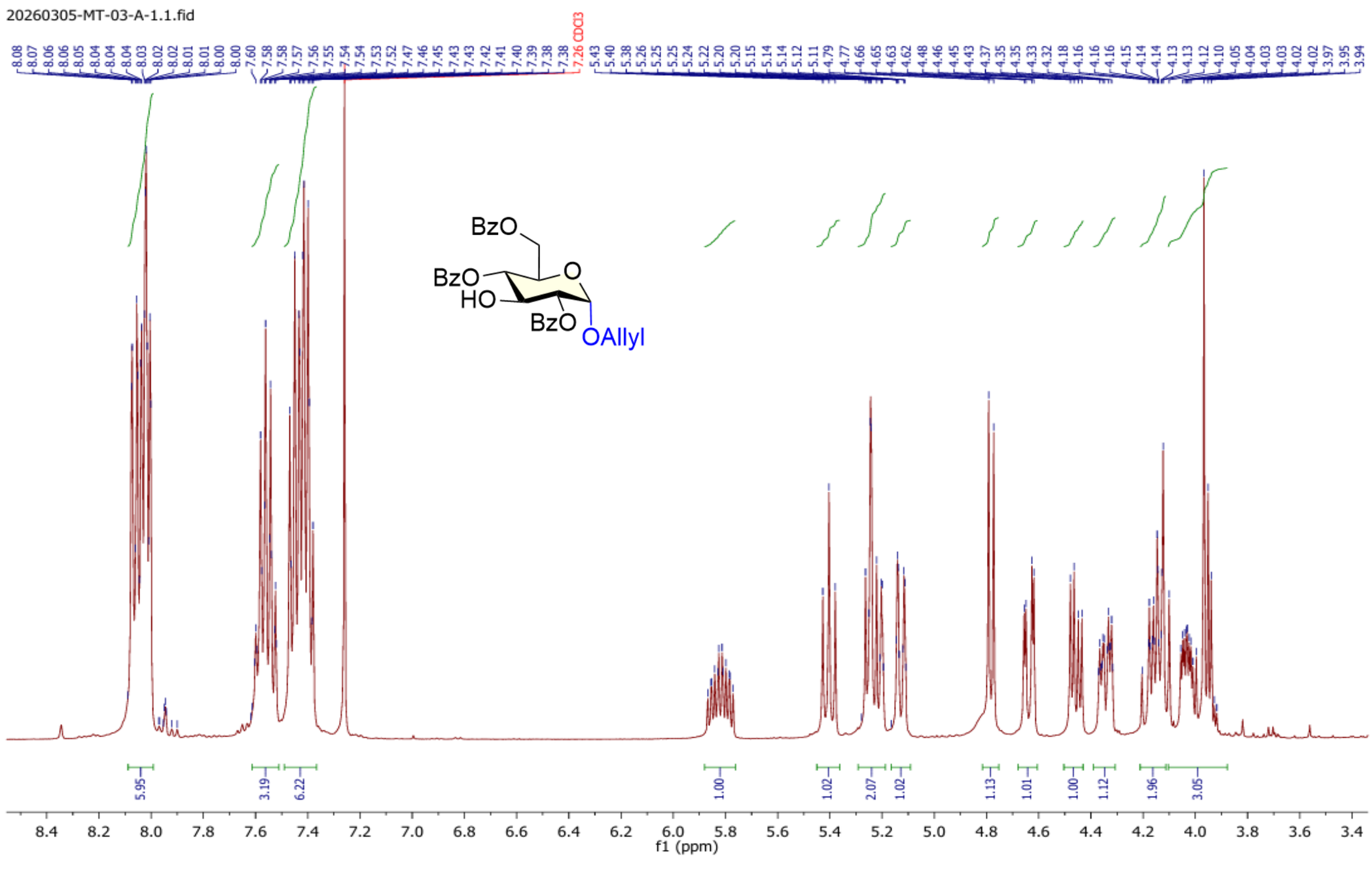
^{13}C NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 4:



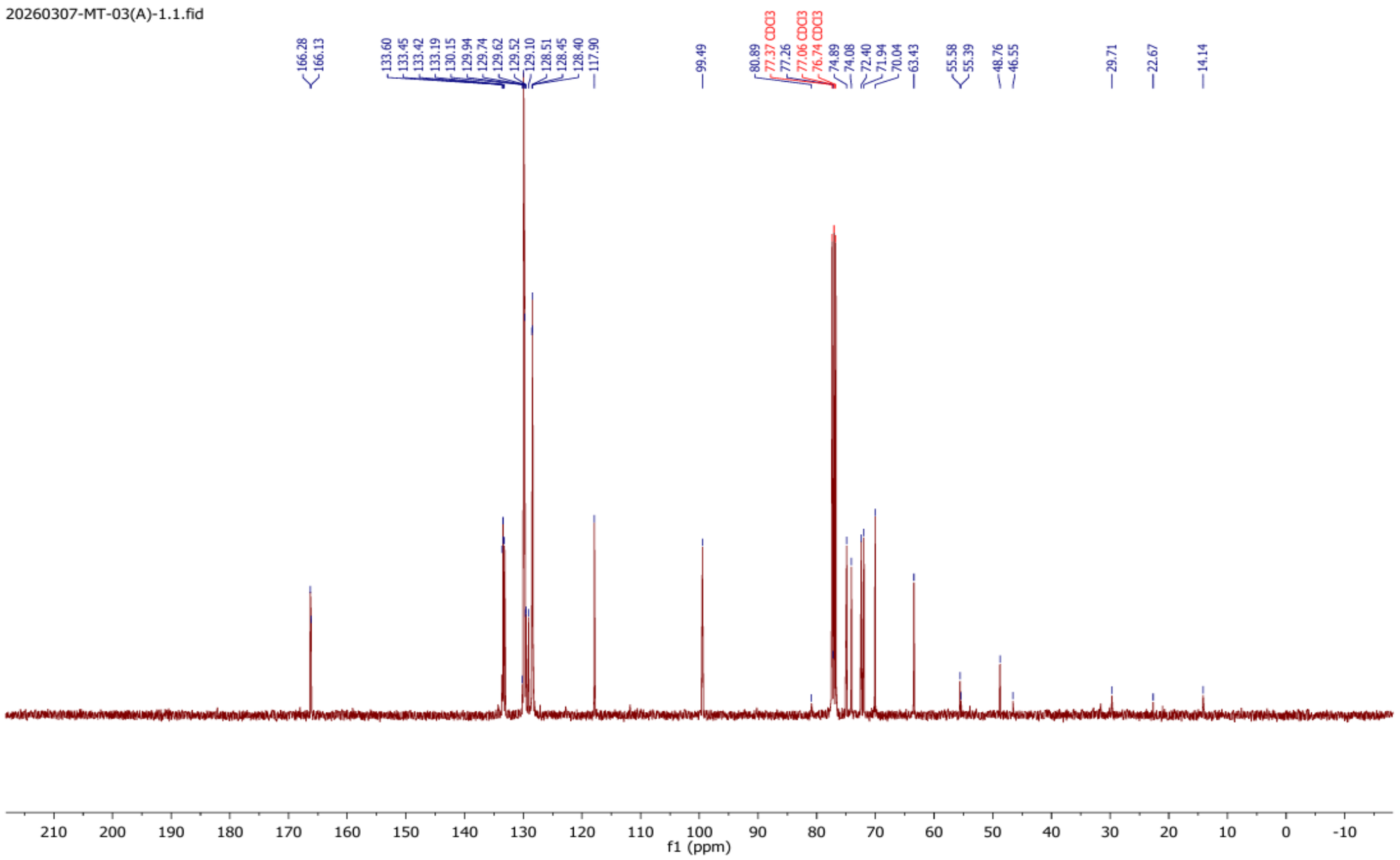
DEPT-135 NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 4:



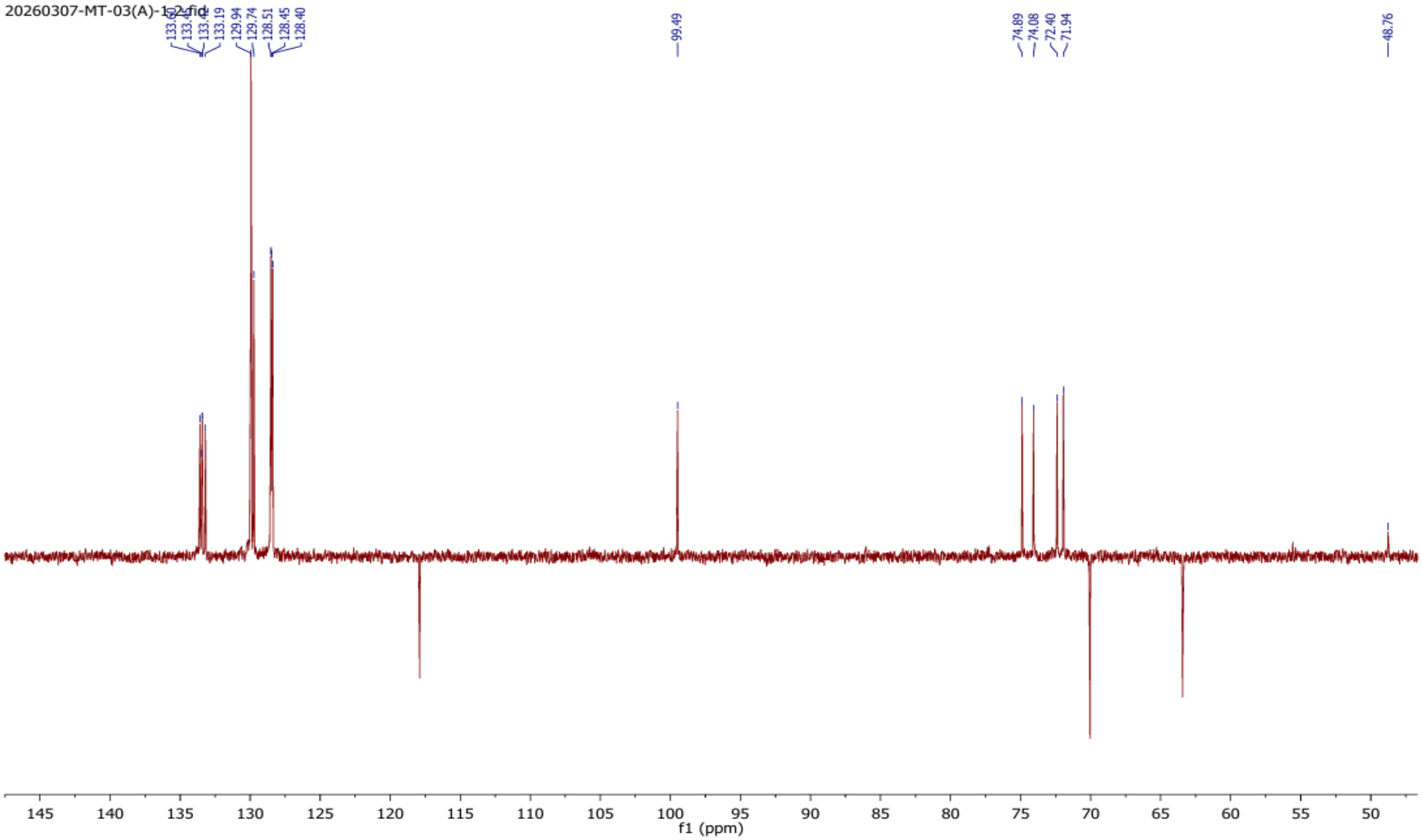
^{1}H NMR SPECTRUM (400MHz, $CDCl_3$) of Compound 5:



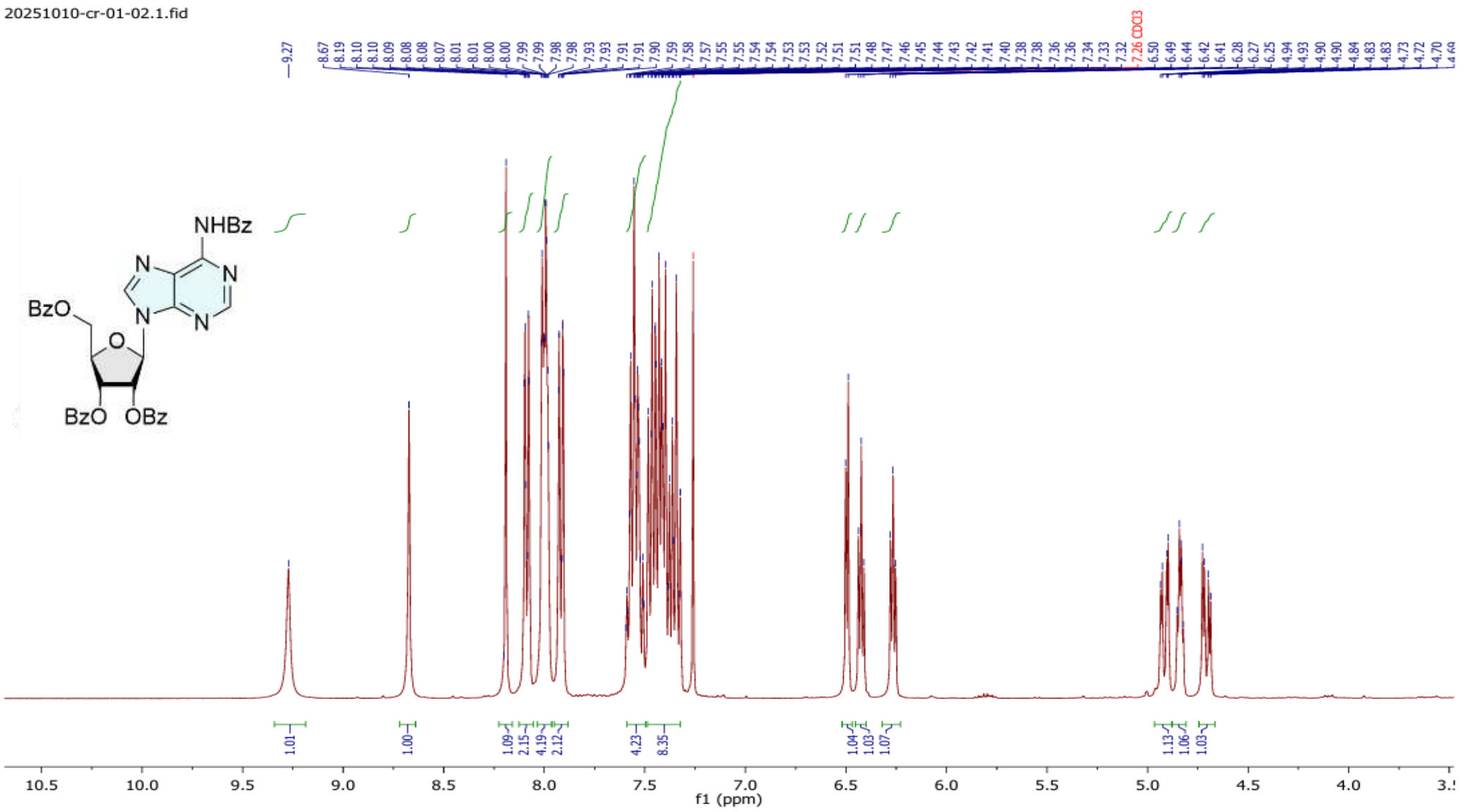
^{13}C NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 5:



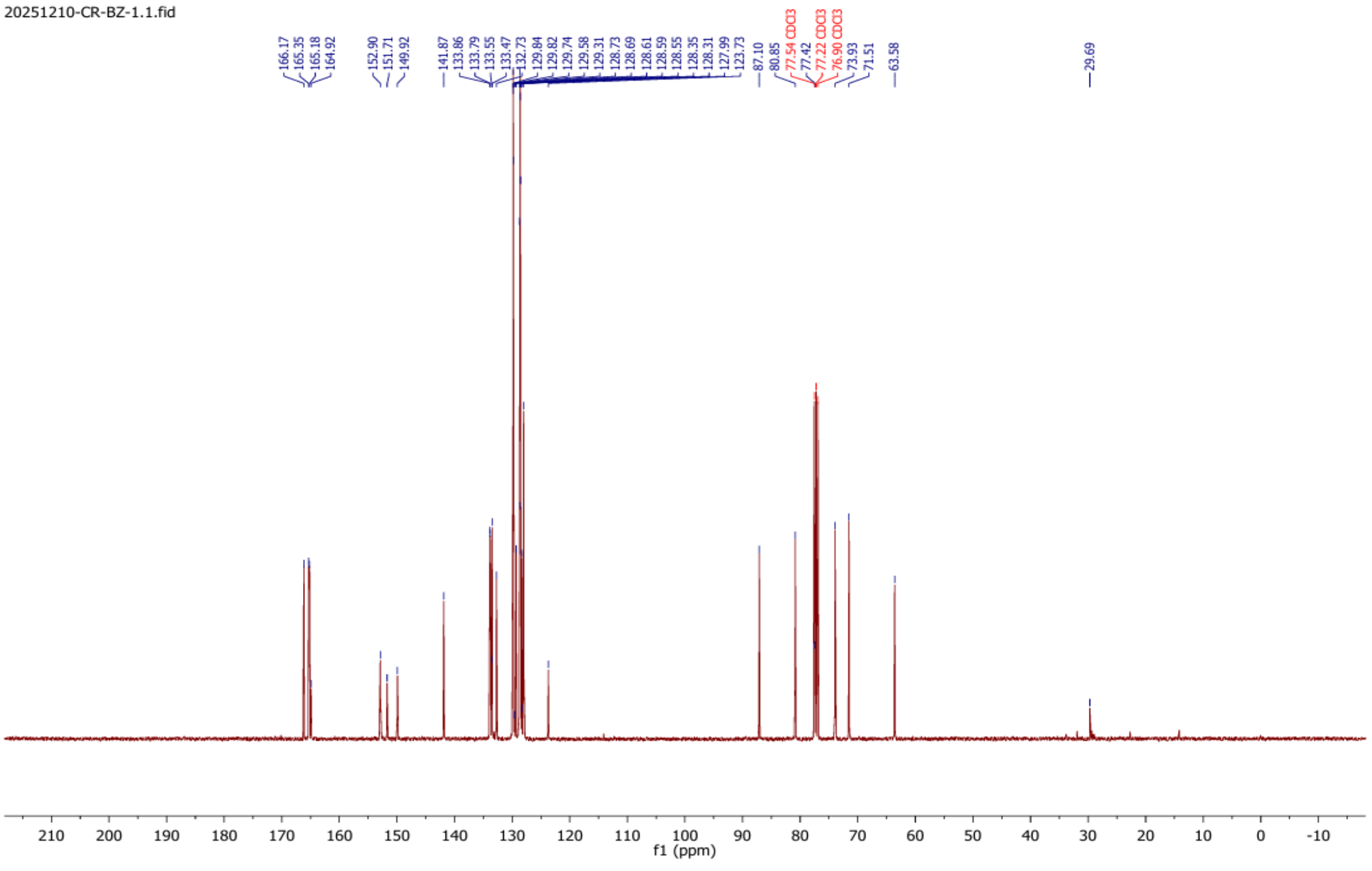
DEPT-135 NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 5:



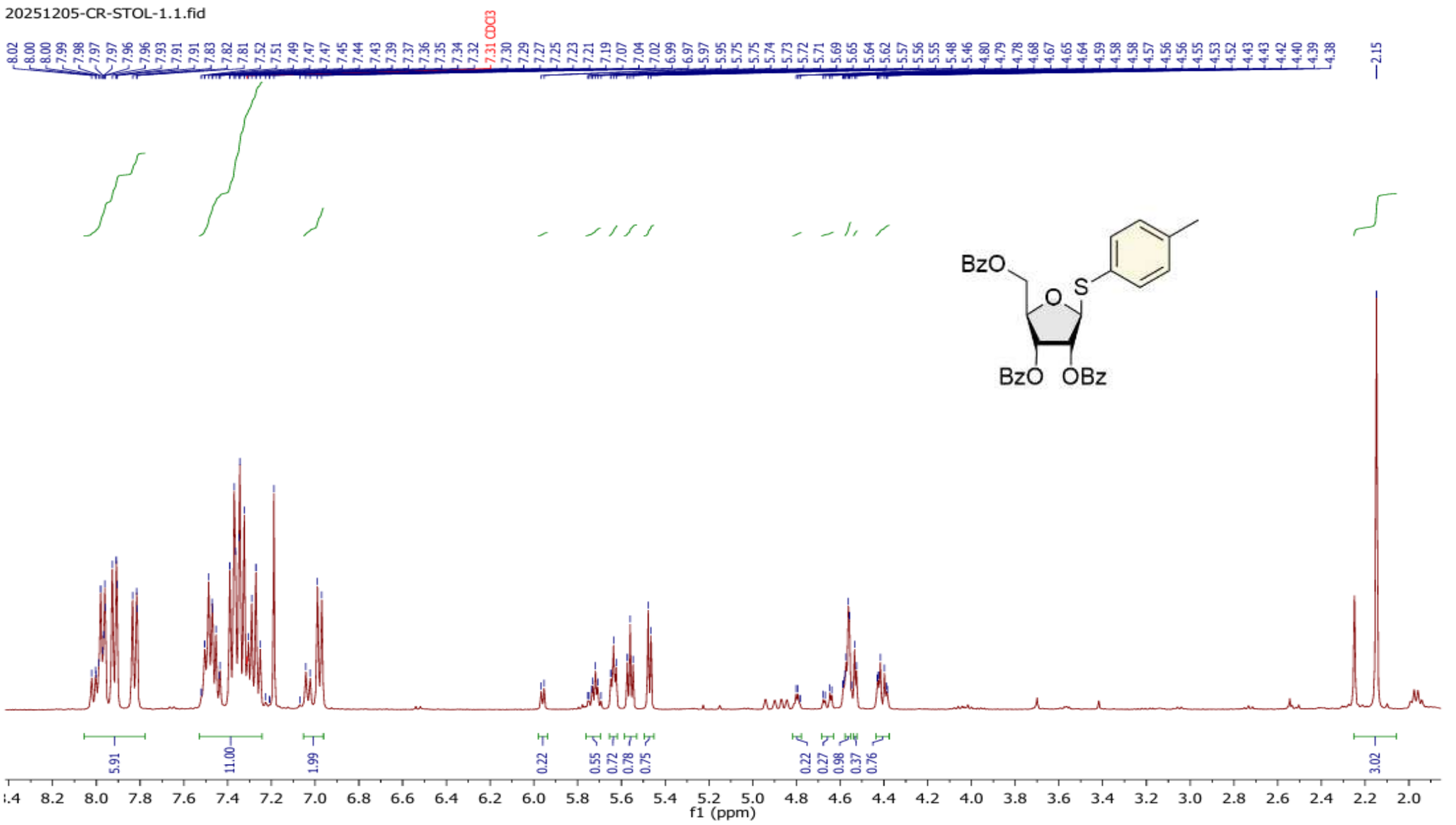
^{1}H NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 7:



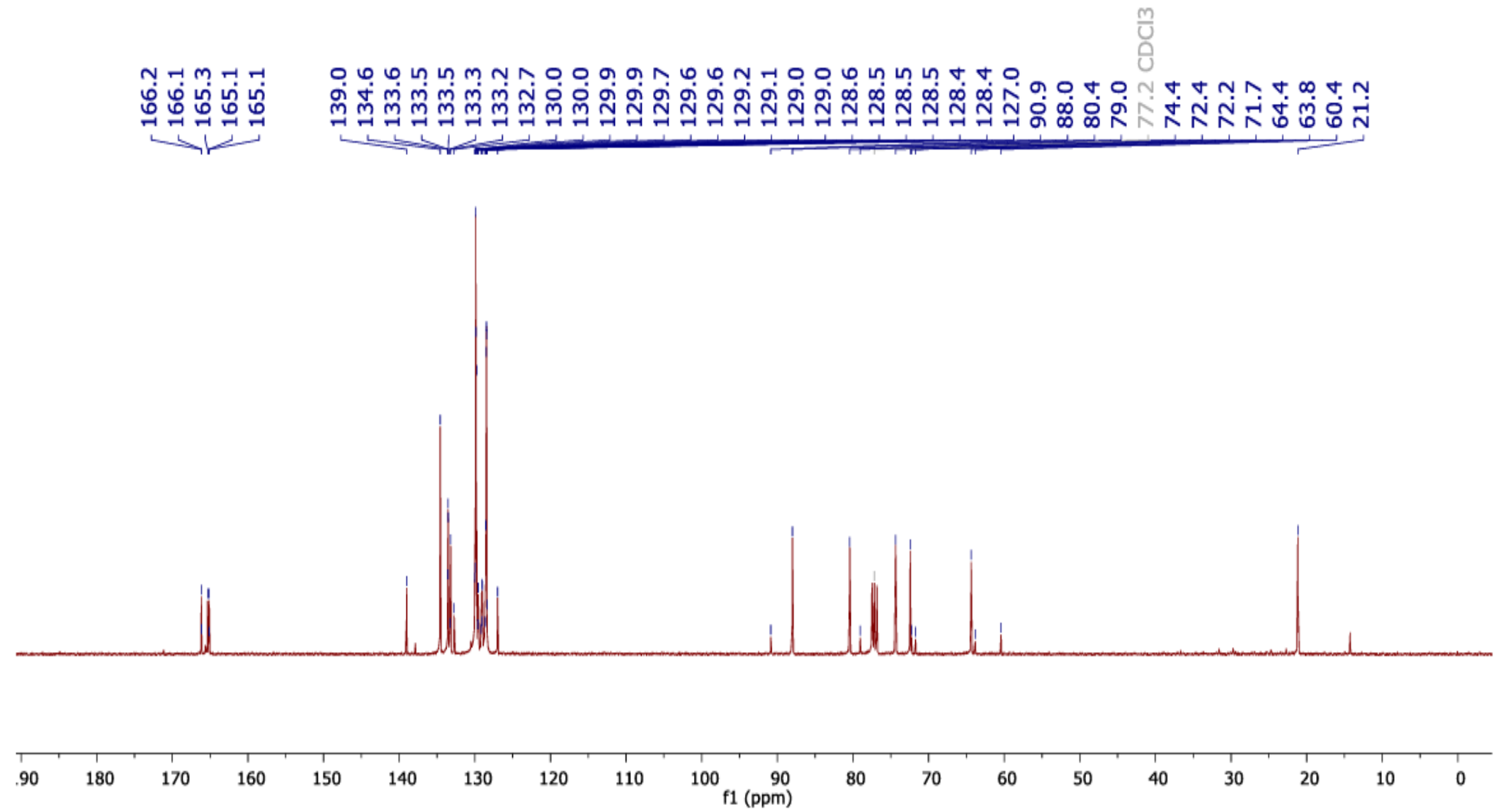
^{13}C NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 7:



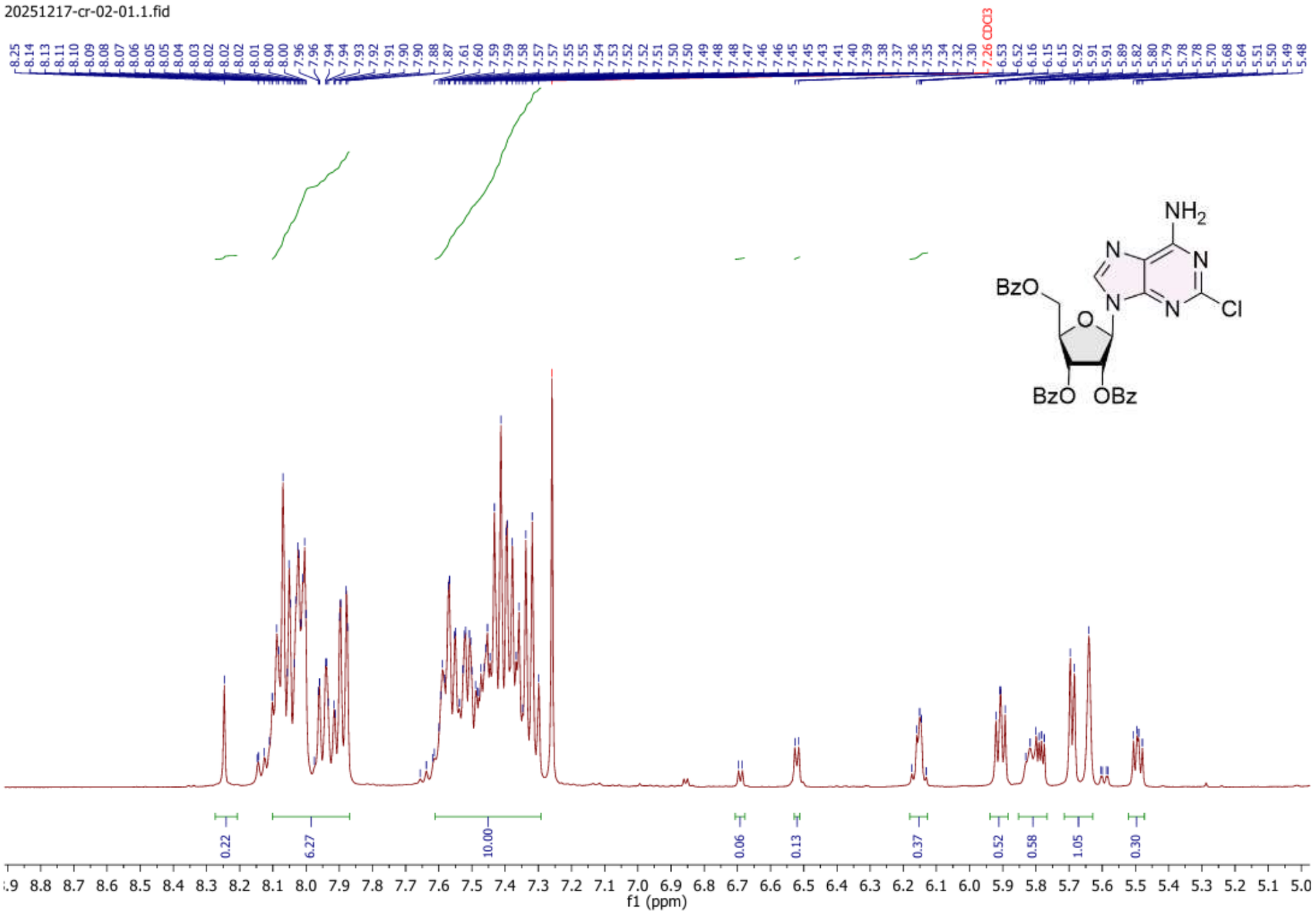
^{1}H NMR SPECTRUM (400 MHz, CDCl3) of Compound 8:



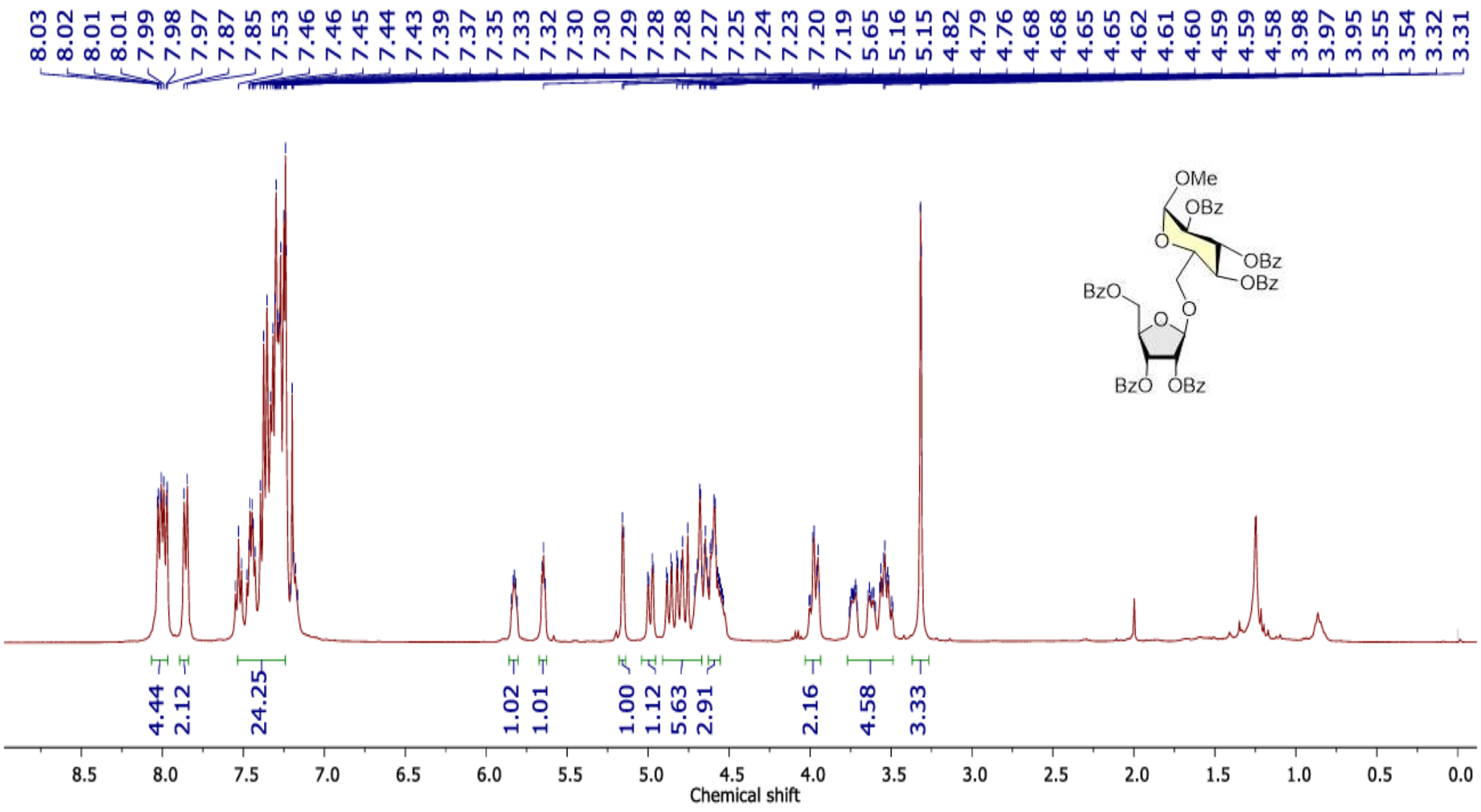
^{13}C NMR SPECTRUM (400 MHz, CDCl3) of Compound 8:



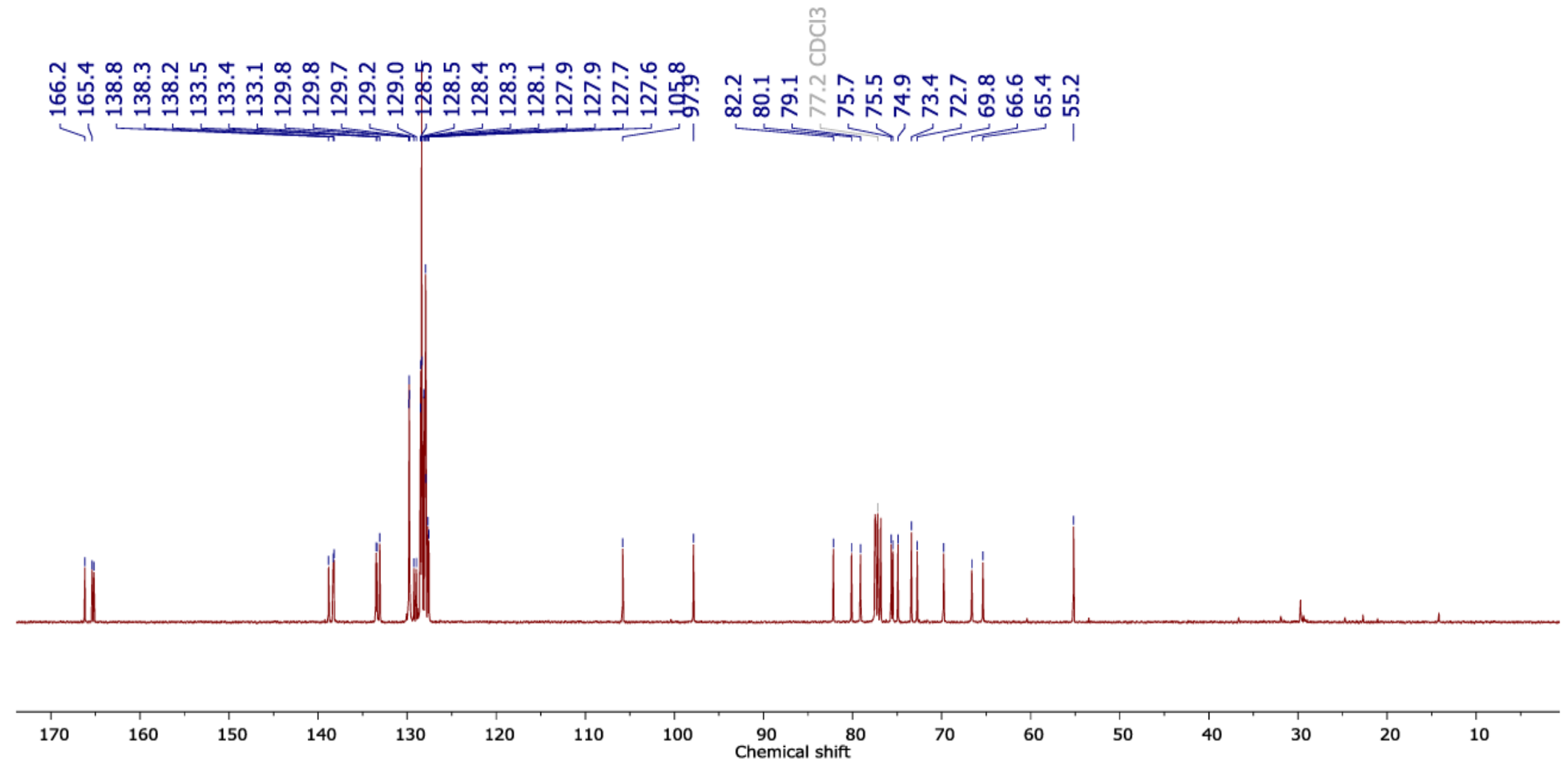
^{1}H NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 9:



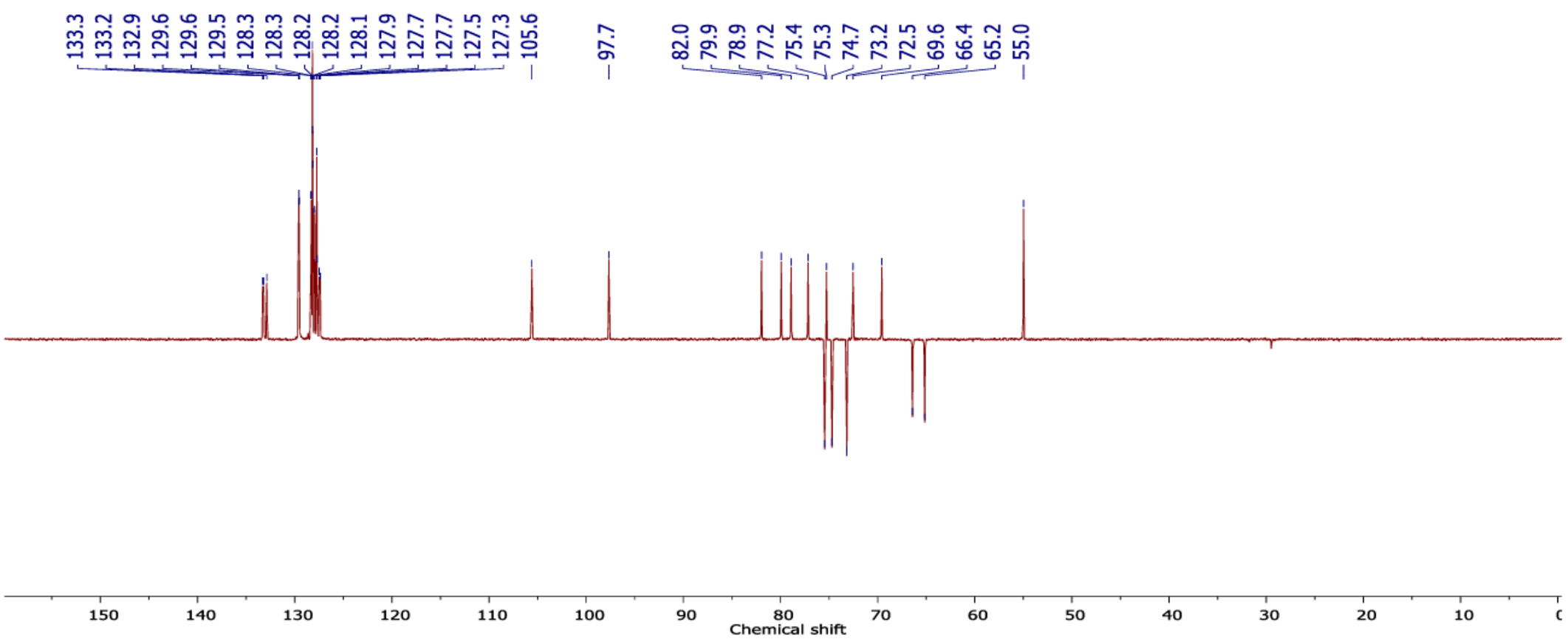
^{1}H NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 12:



^{13}C NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 12:



DEPT-135 NMR SPECTRUM (400 MHz, $CDCl_3$) of Compound 12:



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