SYNTHESIS OF NOVEL *N*-GLYCOSIDE ANALOGS OF D-GALACTOSE.

By

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Submitted in Partial Fulfillment of the Requirements

For the Degree of

Masters of Science in the

Chemistry Program

YOUNGSTOWN STATE UNIVERSITY

December, 2018

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Dr. Salvatore A. Sanders, Dean of Graduate Studies Date

Thesis Abstract

Galactosyl triazoles have shown potential as drug candidates and, as a consequence, the synthesis of these carbohydrate-based mimitics by the use of a modified form of click chemistry was studied.

A successful synthesis of twelve disubstituted galactosyl 1,2,3- triazoles, with yields of 70-100%, were obtained which offer a potential tool for therapeutic development.

ACKNOWLEDGEMENT

Today marks a memorable day as I write this note of appreciation after a two-year intensive work. It has been a time of great learning in the science arena amidst moments of joy and challenges that have given me the chance to reflect upon the people who have contributed in making my dream a reality again.

To my first thanks goes to God Almighty for granting me the strength and good health to the accomplishment of my goal and completing my studies. Secondly, I am sincerely grateful to my project advisor, Dr. Peter Norris for his immense encouragement and contributions towards the completion of my thesis in the last two years.

I am equally thankful to my committee members; Dr. John Jackson and Dr. Sherri Lovelace-Cameron for the guidance in bringing out the best in me during the cause of my studies. And to my colleagues, LaLama, Torres and Bernard I am heartily thankful for the time and help you gave me during my research work.

I will not forget my wonderful Mother by thanking her for the support she has been continuously supporting me both spiritually and physically throughout all these two years of survival.

Finally, to the Youngstown State University, I am thankful for the opportunity you gave me to pursue my dream, not forgetting the department chair Dr. Timothy Wagner, and Tim Styranec for your safety tips which have impacted a lot on me.

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INTRODUCTION TO CARBOHYDRATES

Carbohydrates, proteins, nucleic acids, as well as lipids, have been discovered to perform pivotal roles in living systems. These macromolecules are referred to as "biologically active" molecules due to the fact that some of the subgroups contain essential parts or functional groups that enable them to play their role in a living system. Generally, carbohydrates such as polysaccharides or glycoconjugates occur widely in nature and perform useful functions such as being metabolites in both animals and plants, and in the storage of energy. In recent times, polysaccharides have been found to perform other biological processes in defense of the immune system, cell growth, and other functions like cell adhesion and signal transduction.[1]

Elemental analysis revealed that most carbohydrate molecules are composed of atoms of carbon, hydrogen, and oxygen. Carbohydrates are further sub-divided into monosaccharides and a prime example is galactose. Sucrose on the other hand can be classified under disaccharide, maltose being another example. Polysaccharides e.g. raffinose and oligosaccharides are other classes. Monosaccharide has been identified as the simplest unit of carbohydrate. They can best be described as an aldehyde or ketone, which can be identified as colorless, crystalline and water-soluble and with a somewhat sweet taste. Monosaccharides can also be classified as aldoses, containing aldehyde functional groups and ketoses; those with ketone groups. In terms of their number of carbons, monosaccharides with three carbon atoms may be referred to as trioses, those with four as tetroses, then pentoses, hexoses, etc.[2]

THE CHEMISTRY OF D- GALACTOSE

Lactose, which is a disaccharide, consists of D-galactose and another simple sugar, D-glucose. Since D-galactose contains six carbons and an aldehyde functional group it is classified as an aldohexose. It is also one of the reducing sugars among the monosaccharide family. Galactose can be in the D or L configuration as shown in **Figure 1**, however the D-form is predominantly seen in lactose, cerebrosides, gangliosides, and mucoproteins.[3]

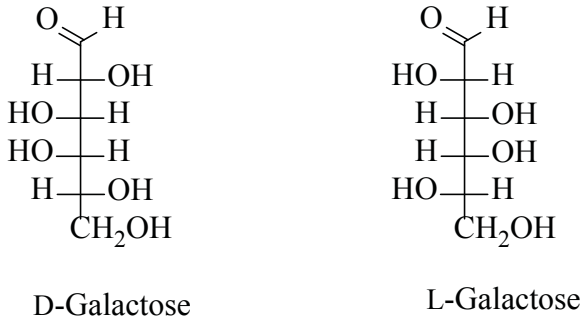


Figure 1: Structure of D-galactose and L-galactose.

Since galactose contains an aldehyde functional group, it can be found in an open form or in a ring form. When the open-chain form cyclizes, the carbon of the carbonyl group, which is also referred to as the *anomeric* carbon, will become a chiral center capable of two configurations. The anomeric carbon contains an oxygen bonded to another carbon and a hydroxyl group; this results in hemiacetal formation. A six-membered ring with oxygen as one of its constituents is referred to as a *pyranose* while the five-membered version is a *furanose*. During the process of ring formation in galactose, four possible isomers are observed, two of which are pyranoses and the other two furanoses. The five-membered galactosyl sugar has been found in the fungi kingdom, prokaryotes, Protoctista and certain higher chordate immune lectins.[3] When galactose is cyclized, the hydroxyl group at the anomeric carbon can be at the equatorial or axial position. These two anomers

are called the *alpha* or *beta* forms. In **Figure 2**, it can be seen that the beta-hydroxyl group is upwards (equatorial) and the alpha hydroxyl group is downwards (axial) in the pyranose and the furanose forms.[4]

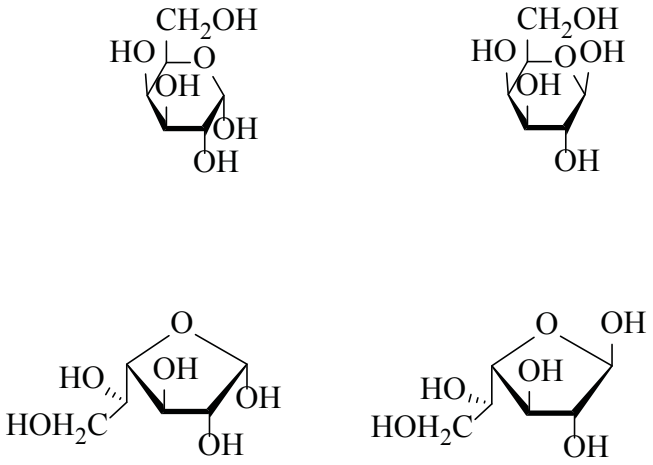


Figure 2: Cyclic forms of D-galactose.

Conformational analysis of ring compounds suggests that most six-membered structures, galactose included, are usually strain-free, especially if it is in the chair form. The six-membered rings called the pyranoses usually adopt chair conformations in the same manner as cyclohexane, and have bond angles approximately the same as that of a tetrahedral carbon atom. This means there are two possible main chair conformations for each anomer of D-glucose. Glucose and galactose have a similar structural formula, however, the only difference is observed at the C-4 carbon. At the C-4 carbon in glucose, the hydroxyl group in the equatorial position while in galactose the hydroxyl group is in the axial position. The conformation in which the largest substituents are in equatorial positions will generally be favored over the more crowded, higher energy axial positions.

This conformation with $^4C_1$ is usually considered to be the most stable chair as it will reduce the number of diaxial interactions as seen in **Figure 3**.[5]

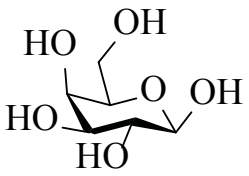


Figure 3: $^4C_1$ Chair form of β-D-galactose.

Most nutrients are daily requirements for healthy living and also for the development of essential chemicals or metabolites needed by the body. Galactose, on the other hand, is not one of those essential nutrients. It can easily be synthesized by the human body, with glucose as its precursor. In terms of energy provision, when galactose is ingested in diverse forms into the body, it is broken down into glucose which provides approximately 4.1 kCal per gram.[5] Galactose can conjugate itself or can conjugate to other molecules like glucose to form lactose, or to lipids to form glycolipids, or to proteins to make glycoproteins.

AMINO SUGARS

Amino sugars are sugar molecules in which a hydroxyl group has been replaced with an amine or acetamido group. Amino sugars and their derivatives occur in various forms in nature (**Figure 4**). Some of the most common examples are *N*-acetyl derivatives such as *N*-acetyl-aspartylglutamic acid, which is found in cell walls of bacteria. 2-Acetamido-2-deoxy-D-galacturonic acid is an example of a bacterial virus-antigen found in *Escherichia coli*.[6] On the other hand, polysaccharide sequences can contain 2-amino-2-deoxy-D-mannouronic acid that can identify itself in the bacterial cell.

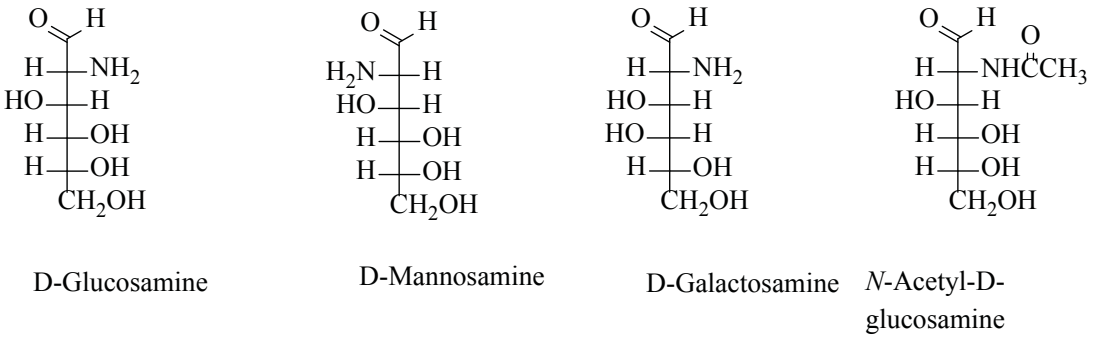


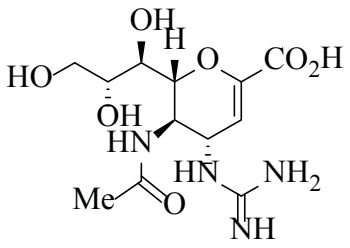
Figure 4: Common amino sugars.

Amino sugars can be generally synthesized from commercially available simple sugars including galactose, which plays an important role in this research, glucose, and glucosamine as well as diacetone glucose. For this to be achieved, it requires an introduction of amino and carboxylic functional groups. Azide and nitromethane, which are amino-functional group precursors are inserted and afterward a reduction process is performed with selectivity oxidizing the primary alcohol hence leading to the formation of the carboxylic functional group or similarly by the Wittig reaction, followed by a hydration reaction.[7]

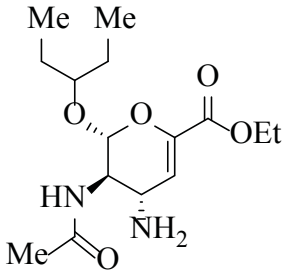
CLICK CHEMISTRY FOR THERAPY IN CARBOHYDRATES.

Over the past years, carbohydrates have been known to perform various functions in humans and other living organisms. But more importantly in the cell-surface glycan, that has the ability to interact with substances that can detect proteins to bind with. A classic example is the carbohydrate recognition proteins (CRPs). This protein-carbohydrate detection mechanism has offered the various biological activities; an example of this is in human fertilization.[8-11] Some carbohydrate detection proteins shown on pathogens have the ability to seize well-functioning carbohydrates in the cells of

humans causing the invasion of pathogens.[12-13] Consequently, carbohydrates have become a great potential carrier for the recognition and treatment of various disease-causing organisms such as bacteria and viruses.[14]



Zanamivir



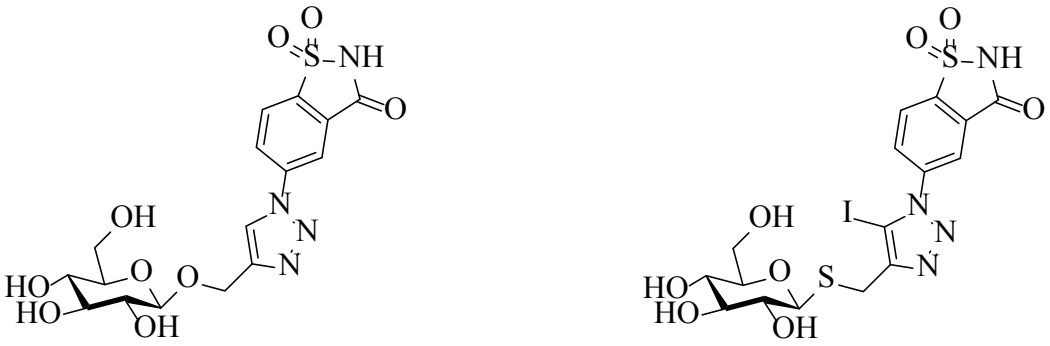
Oseltamivir

Figure 5: Compounds for the treatment of influenza.

The structures in (**Figure 5)** above, are examples of alternative drugs for the treatment of certain viruses causing disease. Even though there has been a great contribution to the advancement of carbohydrate chemistry, there has been the need to improve on the methods of developing drugs on disease-causing organisms. The introduction of "click chemistry" developed by Sharpless and Meldal has presented the chance in solving this problem.[15-16] Admittedly, with a continuous improvement in both click chemistry and thiolene reaction.[17]

1. Treatment of cancer.

Carbohydrate-based drugs such as Triazolyl produced by click chemistry have been used as an alternative cancer treatment drug. The survival of cancer cells in humans is as a result of the enzyme carbonic anhydrase activity that is brought about through hydration of carbon dioxide to bicarbonate. The development of the drug that can prevent the activity of carbonic anhydrase produced in the body can be a remedy for the treatment of cancer. Such as the CA IX (inhibition enzyme) as shown in (**Figure 6)**.[18]



I,4-disubstituted triazole 1,4 & 1,5-disubstituted triazole

Figure 6: Examples of CA IX inhibitor enzymes

Another example of a cancer treatment drug synthesized through click chemistry is the triazolyl glycocoumarin derivative heat shock protein (Hsp-90**)** as shown in **(Figure 7)**.[19]

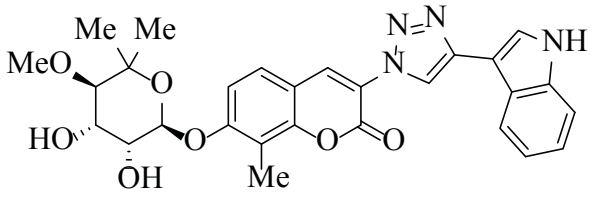


Figure 7: Part of protein derivative Hsp-90.

1. **Antimicrobial and antiviral activity**.

For most infections brought about by disease-causing organisms, their activities depend on the uppermost part of the proteins with the pericellular matrix of the human cells. In view of this, click chemistry has been employed to enhance the successful synthetic route for the production of antiviral and antimicrobial drugs. There has been the development of some sialic acid derivatives including Zanamivir and Oseltamivir drugs structures to inhibit the class of glycosidase called neuraminidase.[20,21] The structure can be seen in (**Figure 8)** below.

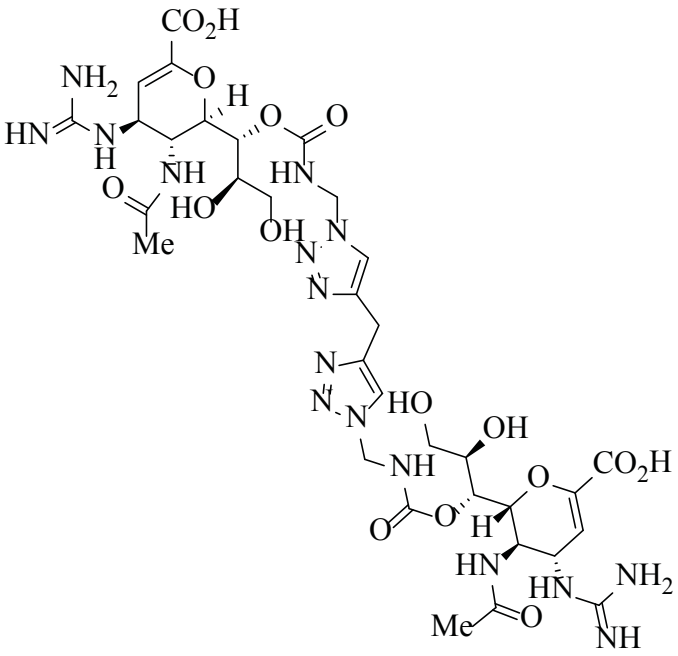


Figure 8: A modified drug for respiratory tract infection.

Some other modified sialic acid derivatives as shown in (**Figure 9)** have proved effective towards the treatment of children suffering from diseases such as the respiratory tract infection.[22] Other strategies employed in click carbohydrate chemistry have been used for the treatment of protozoal infections, for example, the "Chagas-disease" prevalent in central and South America.[23,24]

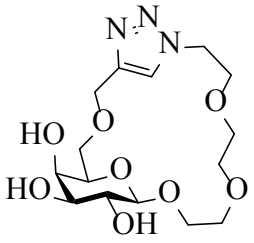


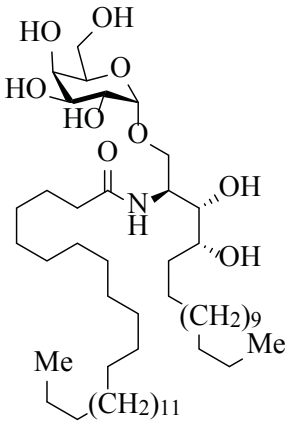
Figure 9: Synthetic molecule that can be used to treat Trypanosoma Cruzi.

2. Glycosidase and glycosyltransferase inhibitors.

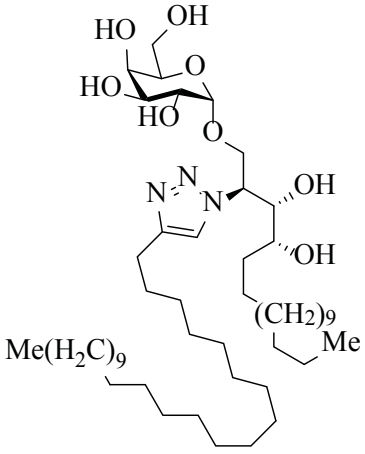
Apart from their role in causing infections, glycosidases and glycosyltransferases are involved in other disease-causing activities, for example, Gaucher's disease (GD), a disorder resulting from the mutation in lysosome storage, leading to a malfunction in glucocerebrosidase (GCase), which eventually breaks down glucosylceramide.[25,26] The use of click chemistry in iminosugars contributed to a low functioning activity towards GCase.[25,26]

3. Immunostimulating activity.

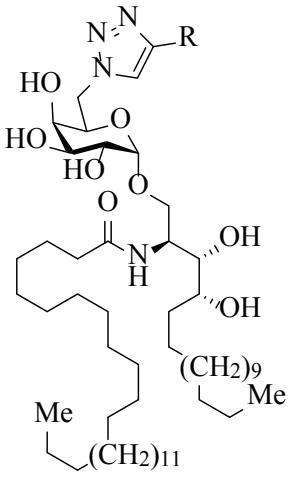
More efforts have been put into the development of carbohydrate-based library immune response agents. The involvement of click chemistry has contributed to activation of the release of the receptor cells such as natural killer T (NKT), which is usually shown in the form of T cell receptor (TCR) and a natural killer cell receptor. These cells will, later on, help to identify the antigen present. There are three steps involved with the click modification of the immunostimulating agents. These steps are; ceramide (Cer), galactose (Gal) and oligomerization modification, as shown in (**Figure 10)**.[27,28]



α-GalCer



Cer-Modified



Gal-Modified

Figure 10: Immunostimulating agents.

The modification of the click chemistry derivative triazolyl product from the α-GalCer helps to improve the stimulation of cytokines that will fight effectively the cancerous cells in the body.[29] Moreover, click chemistry over the recent years has been used in the formulation of several vaccines with carbohydrate sources which have played a vital role in the activation of antigens that are less active in the release of cytokines that can fight the cancerous cells.[30,31]

CARBOHYDRATE CLICK CHEMISTRY AND DIAGNOSTICS

Click chemistry has made it possible for the development of glycoprobes useful in the detection of disease-causing organisms due to the selectivity of the triazolyl products that function with carbohydrates at target sites of the pathogens.[32] Click chemistry has given room for the development of glycol-nanoparticle diagnostic tools widely used in modern laboratories. In addition to that, electrochemically-active glycoprobes have shown promise in the development of diagnostic tools.

PREPARATION OF ALKYNES

The reaction of cycloalkynes with an organic azide is a process not influenced by other factors or conditions and comes out as a clear and interesting organic chemical process which involves changes in fundamental forms. Without the influence of external conditions, a stable product called a triazole is obtained in the shortest time possible through the given cycloaddition of cycloalkyne with an organic azide. This latter reaction has gained grounds as a viable chemical tool and finds its use in both academia and

industry. The reaction occurs in a highly strained, medium-sized cyclic alkyne; cyclooctyne to be precise. The formation and chemical reactivity of cyclic alkynes are described with special attention given to the usefulness of cycloalkynes. Cycloaddition is completed when organic azide is reacted with an alkyne and the reaction proceeds to form a stable triazole.[33]

TRIAZOLES

A triazole is basically a five-membered ring with two carbon atoms connected to three nitrogen atoms. As a result of that, triazoles are considered as examples of heterocyclic compounds. They have the parent molecular formula, $C_2H_3N_3$. Even though they have the same molecular formula, they differ in the arrangement of the atoms. There are two sets of isomers that differ in the relative positions of the three nitrogen atoms. Each of these has two tautomers that differs by which nitrogen has a hydrogen bonded to it as indicated in (**Figure 11)**.[34]

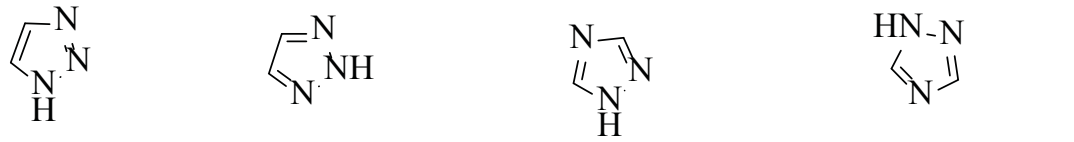
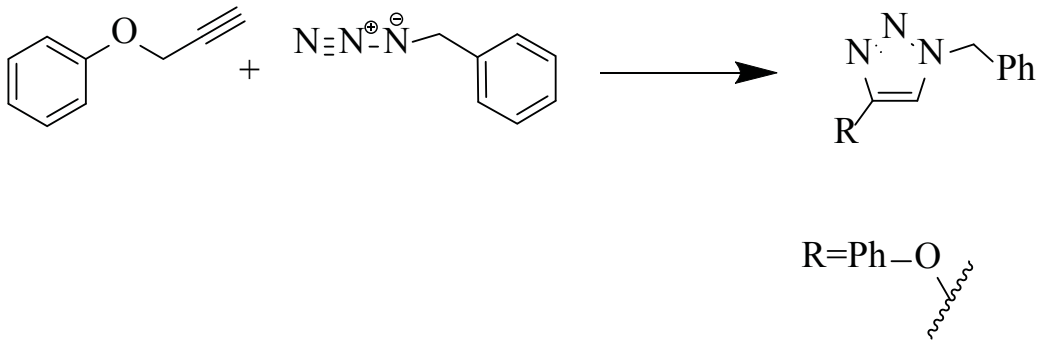


Figure 11: Examples of triazoles and acids.

TRIAZOLES IN CHEMICAL SYNTHESIS

Both internal and terminal alkynes have been utilized in the presence of azide to synthesize triazoles. A typical example is the Azide-Alkyne Huisgen Cycloaddition, which is a 1,3-dipolar cycloaddition between an azide and a terminal or internal alkyne to

give a 1,2,3-triazole. The greatest pioneer of this type of reaction was Rolf Huisgen; he was the first to understand the scope of this type of chemical synthesis.[6] However, K. Barry Sharpless has referred to this cycloaddition as "the cream of the crop" of click chemistry.[7] A typical example of a click reaction is shown in (**Scheme 1)**.[34]



Scheme 1: Chemical synthesis of a typical 1,2,3-triazole.

Gregory et.al expanded the reaction by treating azide with an alkyne to yield the final product triazole composing of 1,4 and 1,5-triazoles at 98 °C in 18 hours.[35] However, due to the lack of reactivity, and sometimes possible side elimination reactions of olefins, the usual 1,3-cycloaddition between an azide 1,3-dipole and an alkene as dipolarophiles has been given less attention. With the use of non-metal cycloadditions, some success has been found in the reaction of dipolarophiles that are electron-deficient olefins and alkynes.[36] These 1,3-dipolar molecules, due to their stability in an optimized reaction condition, are most preferred.

COPPER-CATALYZED AZIDE-ALKYNE CYCLOADDITION (CuAAC)

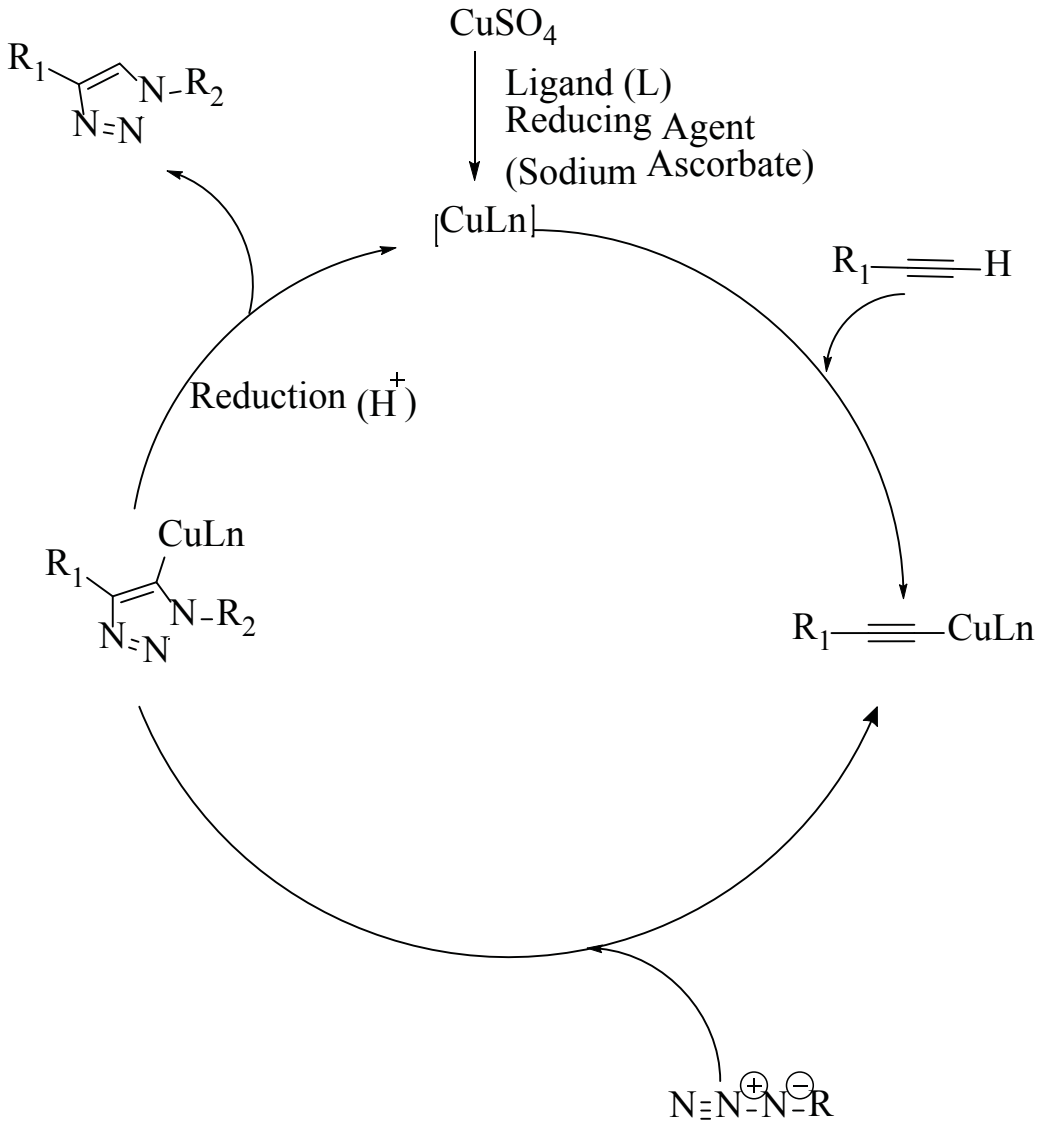
The 1,3-dipolar cycloaddition proposed by Huisgen can now be carried out to produce triazoles under the influence of a catalyst, copper (I) in particular, and this is

referred to as the copper-catalyzed azide-alkyne cycloaddition (CuAAC).[37,38] The reaction leading to the formation of the 1,3-dipolar triazole can be relatively slow and thus the incorporation of a catalyst helps to speed up the reaction, which also allows its occurrence in aqueous media. The introduction of click chemistry presents an advantage in the synthetic route while the Huisgen route seems to be deficient. Also with click chemistry, an increased yield of pure material is associated with the 1,4-disubstituted 1,2,3-triazole, the only regioisomer obtained with the copper-catalyzed azide-alkyne (CuAAC) reaction.

Whiles triazoles formed using this approach are not dependent on substituents attached to reactants, both electronic and steric effects affect the product formed in the reaction.[39] In click chemistry, the most active form of copper, Cu(I) is used, which is obtained from the reduction of copper (II) salts when reducing agents such as ascorbate is utilized in a wider range. Also depending on the area of application, both Cu(0) and Cu(II) can be used when the reaction conditions have been optimized to suit the biological or chemical environment.[40]

MECHANISM OF THE CuAAC.

In the recent past, several studies have been carried out and reports have been subsequently produced to suggest a plausible scheme for the formation of CuAAC as illustrated by the (**Scheme 2)** below. The active Cu(I) acetylide is the first step in the reaction mechanism and is obtained from the reaction of Cu(I) and alkyne in the presence of a base. This goes through a series of intermediates to form the Cu(I) triazolides that is further broken down to give the final product which is the 1,4-disubstituted 1,2,3-triazole.[41-43]



Scheme 2. Proposed mechanism of copper (I) catalysis.

ACCELERATION OF CLICK CHEMISTRY.

Addition of a ligand. Many other ligands may be introduced to modify the active Cu(I) species, thus accelerating the cycloaddition route by chelating the catalyst.[44]

Addition of base. The addition of a suitable base in click chemistry reactions results in an increased yield with Cu(I) salt with little or no effect when Cu(II) salt is used. As a consequence, the formation of a triazole is dependent on the use of amine bases, even-though a catalyst may be involved. Conversely, the absence of the base could be used to produce an alternative Cu(I) complex through ultrasonication.[44]

COPPER-FREE CLICK CHEMISTRY

Azide-alkyne cycloadditions have a number of important roles, which includes their application in biological reactions and material science, however, due to the toxicity of copper ions in living organisms, reactions which occur within the organisms are limited with this application.[45] Despite the challenges in developing metal-free click reactions, some strides by Bertozzi and co-workers has resulted in a proposed alternative route free from transition metals by the use of kinetics for the synthesis of enzyme inhibitors, particularly strained cyclooctynes that have the ability to decrease the reaction potential without metal catalyst.[46] Recent discoveries include compounds such as oxanobornadienes proposed by Cornelissen et al. and dibenzocyclooctynes formulated by Boon et al.[47,48] Wittig and Huisgen have proposed aryne addition to azides in the past and, under mild reaction conditions, some azides can be added using a fluoride-promoted ortho-elimination.[49]

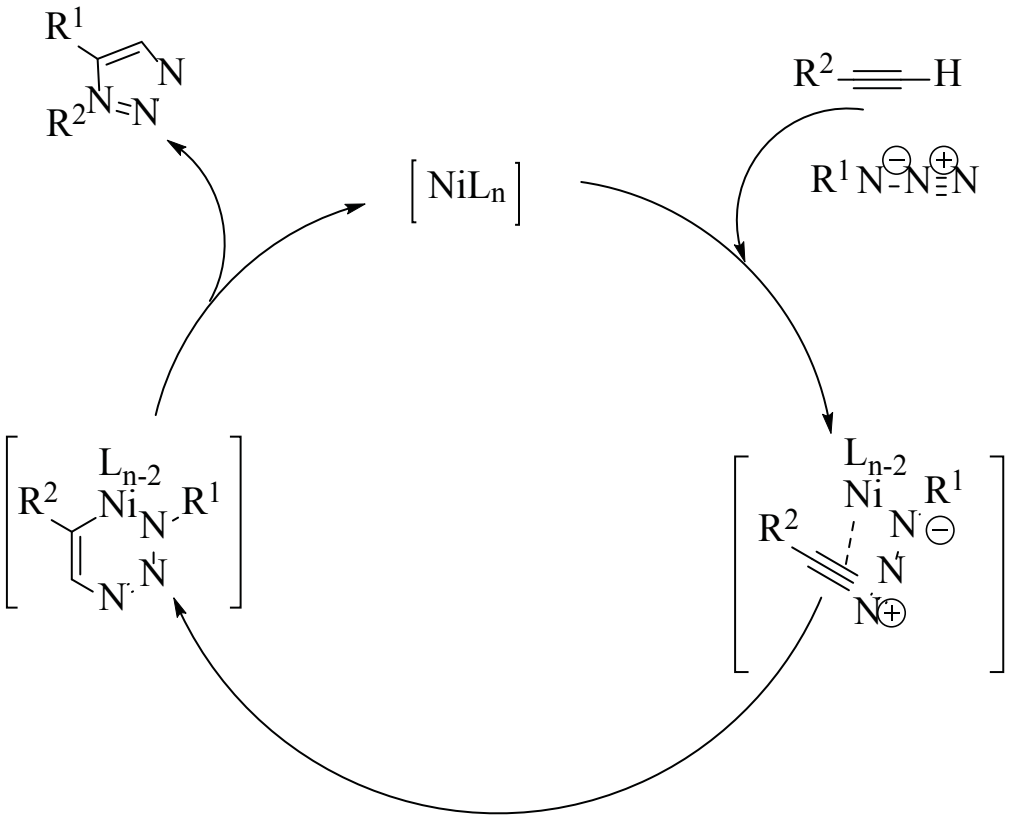
In addition, due to the toxicity of copper as one of the transition metal in click chemistry, the need for an improved synthetic pathway for the formation of triazoles has been proposed. This includes the reaction between an alkyne and an azide in the presence of copper sulphate-pentahydrate or ascorbic acid catalyst system, with the use of water as a solvent at an elevated temperature of about 60 °C.

SYNTHESIS OF 1, 5-DISUBSTITUTED 1,2,3-TRIAZOLES

The synthesis of 1,5-disubstituted triazoles has become an important part of synthetic chemistry since it was discovered. This is because one of the most important problems in carbon-heteroatom bond forming processes is regiochemistry. Huisgen 1,3-dipolar cycloaddition, which utilizes organic azides and alkynes in the formation of carbon- heteroatom bond is one of the most important reaction processes that requires a high level of regiochemical control.[50,51] It has been observed by many researchers that, thermal cycloaddition shows high activation barriers and poor regioselectivity at high temperatures, however, fast and regioselective products of 1,4-disubstituted analogs has been achieved through copper-catalyzed azide-alkyne cycloaddition (CuAAC) since it was initially reported by Sharpless and Meldal.[52] Also due to their chemical stability, aromaticity and pharmacologically role, CuAAC reactions of 1,4-disubstittuted 1,2,3-trizoles have found its uses in medicinal chemistry, material science and even chemical biology.[50]

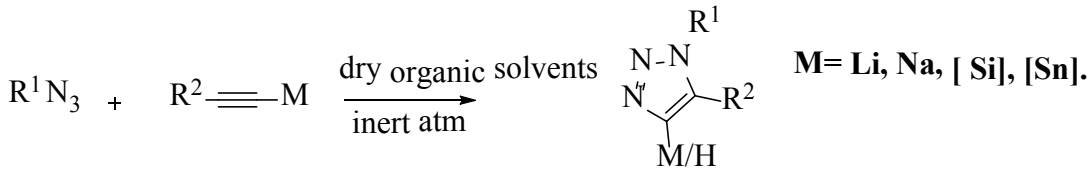
Based on the CuAAC approach, other complimentary schemes have been developed by other groups which utilize other transition metals such as Ruthenium and

Nickel in the synthesis of 1,5-disubstituted 1,2,3-trizoles. It has also been realized to be associated with favorable reaction conditions and wide range of substrates can also be used. [53] The development of the 1,5-disubstituted synthetic route has become complementary to click chemistry as illustrated by (**Schemes 3)** below.

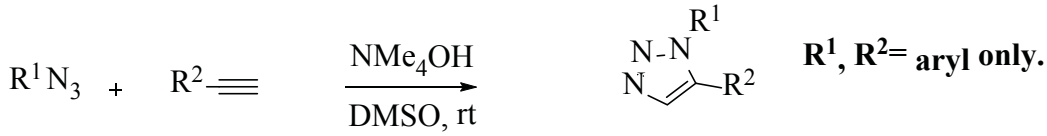


Scheme 3. The synthetic route for 1,5-disubstituted triazole.

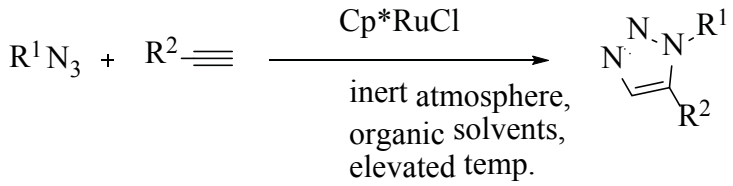
Other studies in the contribution of the preparation of 1,5-disubstituted triazoles have been done by Kwok et al., whereby a metal-free approach was utilized.[54] Also a metal acetylide has also been shown to be a useful reagents in the synthesis of triazoles with their reaction with organic azide (**Equation 1**).



Equation 1: Metal acetylide approach



Equation 2: Metal-free approach



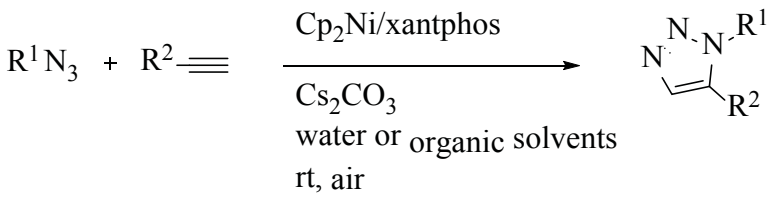
Equation 3: The RuAAC approach.

Equation 1,2,3: Approaches of 1,4 and 1,5-disubstituted triazoles.

Fokin, Jia and coworkers also gave a report in which they noted that 1,5-disubstituted triazole products could be obtained from Ruthenium-catalyzed azide-alkyne cycloadditions and reaction was possible in an inert condition.[55,59,60] The ruthenium catalyzed azide-alkyne route is considered to be responsive in water and in the presence of air; it also occurs at a higher temperature. This condition has contributed to the limitation in the use of this route in biological research as it presents toxicity issues in patients.[56,60,61]

A much-improved Nickel-catalyzed azide-alkyne cycloaddition (NiAAC) in ambient conditions for 1,5-disubstituted triazole was introduced as a remedy to the problem.[57] A benzyl azide and phenylacetylene were treated together in the presence of a nickel catalyst and the ligand xantphos at room temperature without an effort to exclude air and moisture. The desired product, that is, the 1,5-disubstituted triazole was obtained in yields of (80-95%) and to purify this compound, flash column chromatography was utilized. In terms of changing the xantphos with other ligands (P or N), no catalytic activities were observed while xantphos was absent; in the absence of xantphos also, zero percent of 1,5-disubstituted triazole product was recorded. It was however suggested that the bite angle can sometimes influence the determination of the reactivity of the nickel catalyzed azide-alkyne cycloaddition.[58]

Among the various bases that have been used in this type of reactions in the synthesis of 1,5-disubstituted trizoles, Cs_2CO_3 have been shown to be a promising base. Even though solvents like DCM and, DMF can be used, water is considered to be flexible in the production of 1,5-disubstituted triazoles. Due to the poor solubility of nickel (Cp_2Ni/ xantphos) reported, an aqueous suspension medium was utilized in the reaction, which led to the production of average to better-collected yields (40-75%) with an increased regioselectivity. Below (**Equation 4** and **Table 1**) shows the work down by the previous scientists.[59]



Equation 4: Synthetic route of 1,5-disubstituted triazole.

TRIALS	CHANGE IN CONDITIONS	% yield of 1,5-isomer	% yield of 1,4-isomer
1	None	94	6
2	No Cp_2Ni	0	0
3	$NiCl_2.6H_2O$ (instead of Cp_2Ni	0	0
4	Cp_2Ru (instead of Cp_2Ni)	0	0
5	No xantphos	0	0
6	DPE (instead of Xantphos)	76	9
7	No $CsCO_3$	70	10
8	Cp_2Ni (5 mol %) / Xantphos (5 mol %)	38	4
9	75 °C	55	5
10	100 °C	70	9
11	1.5 hrs	91	6
12	DMF (instead of toluene)	90	8
13	DCM (instead of toluene)	90	3
14	Water (instead of toluene)	91	6

Table 1. Yields of 1,5-disubstituted triazoles.[59]

STATEMENT OF THE PROBLEM.

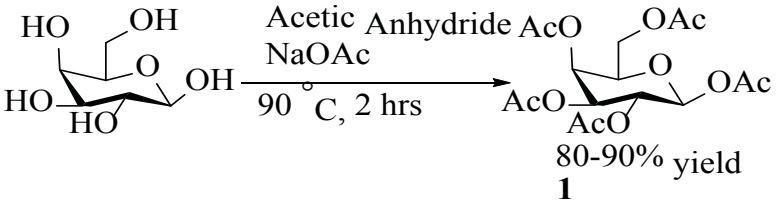
The purpose of this work was to synthesize galactosyl 1,2,3-triazole derivatives such as 1,4-disubstituted triazoles and 1,5-disubstituted triazoles. Resistant-strain microbes have become a worry to both humans and animals as they cause various kinds of diseases and 1,2,3-triazoles and their derivatives have shown potential towards the inhibition of microbial growth.

RESULTS AND DISCUSSION

The principal objective of this work was to synthesize the analogs of 1,2,3-disubstituted triazoles as possible precursors in biological applications such as drug delivery vehicles or molecules and to ensure that atom economy was utilized. The cheaply available starting materials was a consideration in carrying out this research. Hence 1,2,3,4,6-penta-*O*-acetyl-β-D-galactose was used in the production of a galactosyl azide from which other 1,2,3-triazole products were formed.

1,2,3-TRIAZOLE SYNTHESIS

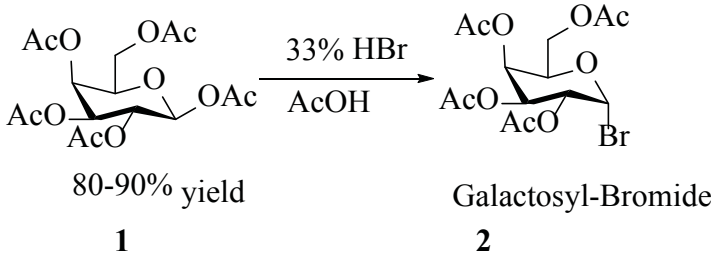
In the first step, the sugar (D-galactose) was placed in a 25 mL round bottom flask and acetic anhydride and sodium acetate were added to the flask and the reaction mixture was allowed to stir for 2 hours at a temperature of 90 °C. This was done to protect the reactive hydroxyl groups of the starting material. The reaction was stop after TLC showed total consumption of the starting material which shows a higher R_f as compared to the starting material. The crude product was extracted and then further purified by crystallization to afford **1** as a colorless crystal.



Equation 5: Synthesis of 1,2,3,4,6-penta-*O*-actyl-β-D-galactose.

The second step in the sequence as shown in (**Equation 6)**, was the treatment of 1,2,3,4,6-penta-*O*-acetylated-β-D-galactose with 33% hydrobromic acid in the presence of acetic acid to form an intermediate galactosyl bromide. The formation of this new product was through an S_N1 reaction. The burning of a new spot with a higher R_f value was indicated in the TLC which showed that the starting material had been consumed after a period of close to 3 hours.

The ^1H NMR of **2** shows that the H-1 signal has moved further downfield from 5.72 ppm to 6.62 ppm with a coupling constant of 4.06 Hz. This coupling constant is smaller than the H-1, H-2 coupling observed in compound **1.** This might explain that, the bromine is at an axial position which conforms to the anomeric effect shows by electronegative groups attached to carbons adjacent to oxygen in a ring. ^{13}C NMR also confirmed the fact that compound **2** was formed.



80-90% yield

1

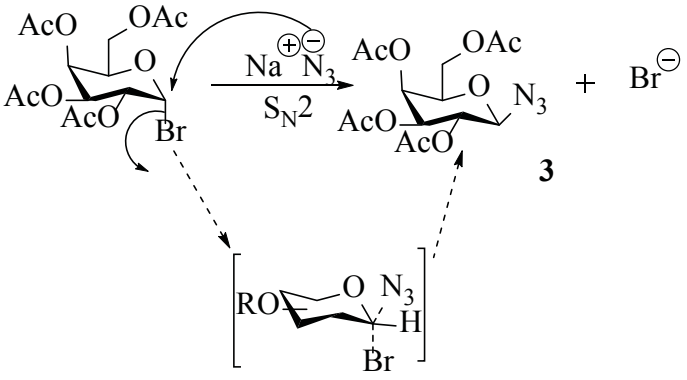
Galactosyl-Bromide

2

Equation 6. Preparation of galactosyl bromide.

The formation of β-galactosyl azide was made possible with the incorporation of bromine as a good leaving group in the reaction scheme. An acetone-water mixture in the ratio of 10:2 was used to dissolve the crude galactosyl bromide **2** and consequently sodium azide was added to the reaction mixture and allowed to stir to completion in 24 hours. The bromine in an axial position on anomeric carbon is replaced via an S_N2 route

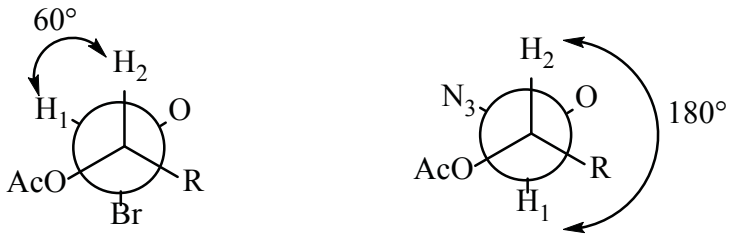
by the azide to form a new product to favor an equatorial position as indicated by the (**Scheme 4)** below.



Scheme 4. Preparation of galactosyl azide.

TLC showed a lower R_f value compared to the galactosyl bromide **2**. A 97% yield of the galactosyl azide was recovered from this reaction. Analysis of the ^{1}H NMR spectrum of compound **3** revealed that, the H-1 signal has moved further upfield from 6.62 ppm to 4.62 ppm which might be as result of the shielding nature of azido group present in compound **3**, showing the formation of the new product. This further explains that, the Bromine on compound **2** deshields H-1 proton which was at the anomeric carbon. This also caused a change in the coupling constants from the signal observed on the anomeric position where there is an increase of more than a half in value, from 4.06 Hz to 8.76 Hz. The main reason for this change in coupling constant was because of the difference in the position of protons in H1 and H2. In the galactosyl azide, they have 180º dihedral angle; with galactosyl bromide they are 60° apart from each other (gauche) which resulted in the difference in their coupling constant values as indicated in (**Figure 12)** below. ^{13}C NMR supported the formation of an azide, chemical shift observed at

170.32, (s), 170.07, (s), 169.94, (s), corresponded to carbonyl carbons in the four acetyl groups. Anomeric carbon (C-1) also shows a chemical shift at 88.31 ppm, (s) whereas peaks at 72.89 ppm, 70.74 ppm, 68.11 ppm, and 66.8 ppm represented the remaining carbons of the ring. The signal with chemical shift 61.22 ppm, (s) represented the methylene carbon while other signals at 20.63 ppm, 20.61 ppm, 20.57 ppm and 20.48 ppm supported the identity of the compound **3**. The melting point for this compound was 101-102 ºC.



2 **3**

Figure 12: Newman projections of **2** and **3** respectively.

FORMATION OF 1,4 AND 1,5-DISUBSTITUTED TRIAZOLES USING VARIOUS ALKYNES

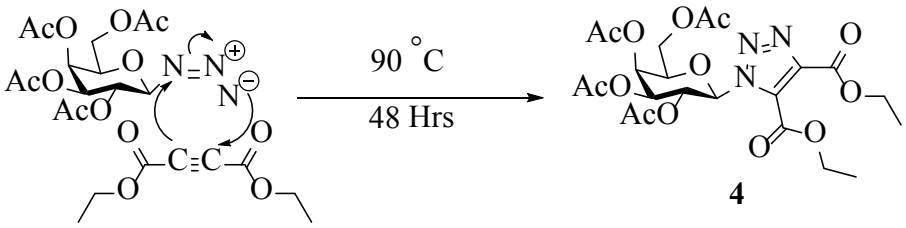
The formation of 1,4 and 1,5- disubstituted triazoles were made possible when the two compounds that is, an alkyne and an azide were reacted together under particular conditions. Herein are some of the reactions which were performed successfully in the laboratory and their procedures.

Azides have been shown to be a useful reagent in organic synthesis; they usually serve as a medium of introducing nitrogen substituent through substitution reaction with an organic halide. In click chemistry, azides have been shown to function very well due

to their stability toward water, oxygen and other reaction conditions utilize in organic synthesis. As a result of that, the galactosyl azide **3** was coupled with diverse kind of alkynes to synthesize various triazoles as shown below.

The use of diethylacetylene dicarboxylate (DEAD)

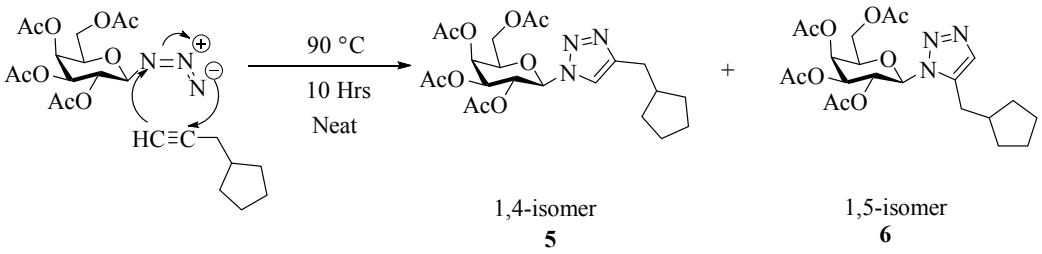
The classical method of synthesizing 1,2,3-triazole utilizes alkynes and azides at high temperature. This procedure usually produced both 1,4 and 1,5-disubstituted isomers. When diethyl acetylene dicarboxylate was allowed to react with galactosyl azide **3** according to (**Equation 7)**, a single isomer **4** was obtained. The reaction completion was indicated when a new spot with higher R_f value than that of the starting material was viewed under ultra-violet (UV) light. A shift of the anomeric proton to further downfield, from 4.62 to 6.52 ppm, was indicated by the ^{1}H NMR spectrum of compound **4**, and this could be due to the deshielding effects from the triazole. The spectrum of compound **4** also shows two new triplets at 1.33 and 1.42 ppm that represent the protons of the CH_3 groups of the dicarboxylate and two quartets at 4.21 and 4.48 ppm that represent the protons of the CH_2 groups and this further confirm the formation of the new product. ^{13}C NMR also indicated an upfield shift of carbon signal from 83.31 ppm to 13.96 ppm and 13.86 ppm for carbon of a triazole formed, other carbons observed a little bit upfield at 20.55 ppm, 20.49 ppm, 20.32 ppm and 14.14 ppm represented the methyl groups. The melting point for compound **4** was obtained as 126-127 ºC.



4

Equation 7. Preparation of a single isomer using diethyl acetylene dicarboxylate.

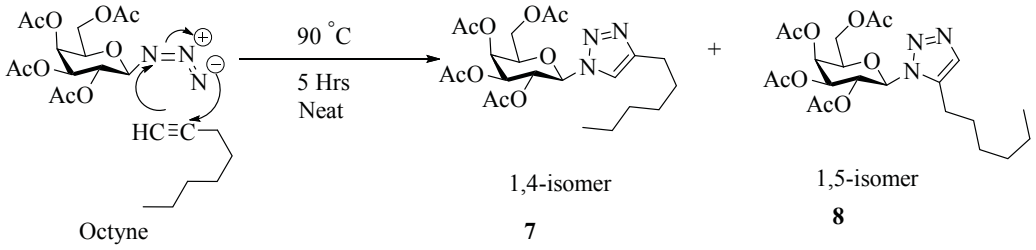
Different terminal alkynes such as 3-cyclopentyl-1-propyne, octyne and heptyne were used without any solvents in the formation of 1,4-isomer and 1,5-disubstituted triazoles. To start with, 3-cyclopentyl -1-propyne was allowed to react with galactosyl azide **3** according to (**Equation 8)**. After 24 hours, TLC showed that there was a new burning spot of higher R_f value than the starting material, indicating that a new product had been formed. The product which was in the form of a slurry was analyzed using a ^{1}H NMR and ^{13}C NMR instruments. A ^{1}H NMR spectrum of compound **5** & **6** indicated that the doublet at 4.62 ppm was totally gone and two new singlets were observed at 7.42 ppm and 7.60 ppm representing the proton presents in 1,4 and 1,5-disubstituted triazole ring. The other peaks emerging at 1.25 ppm, 1.40 ppm, and 1.80 ppm indicates the $–CH_2$ and -CH groups- of the cyclopentane portion of the product. 13C NMR also supported the statement above, the four carbon observed further upfield (20.59, ppm, (s), 20.51 ppm (s), 20.46 ppm, (s) and 20.18 ppm (s) represented methyl, the carbonyl carbons for acetyl groups indicated at 169.96 ppm, 169.92 ppm, 169.78 ppm, and 169.04 ppm, other carbons observed between 148.63 ppm to 74.02 corresponded to that of triazole isomers.



Equation 8. Synthesis of 1,4 and 1,5-triazoles using 3-cyclopentyl-1-propyne.

Using octyne

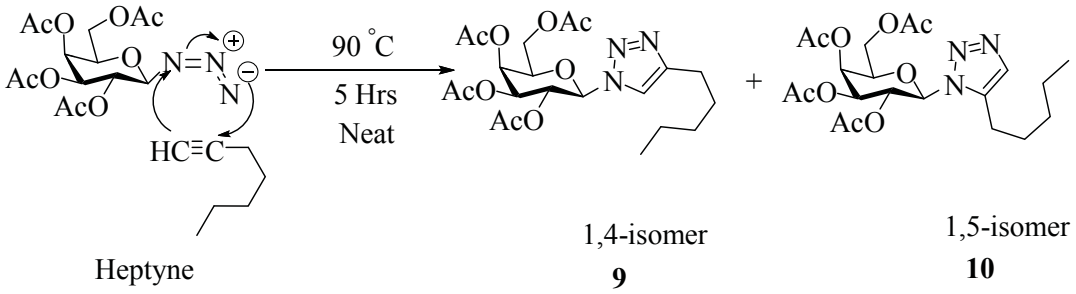
The terminal alkyne, octyne was also used to synthesize 1,4 and 1,5 disubstituted triazoles **7** and **8** according to the (**Equation 9)**. As observed in the previous spectra for the triazoles synthesized above, the doublet at 4.62 ppm was gone and two new peaks were observed giving signals at 7.42 ppm and 7.60 ppm representing the protons present in the 1,4-disubtituted isomer and 1,5-disubstituted isomer. ^{13}C NMR also supported the statement when chemical shifts at 149.20 ppm, and 118.6 ppm appeared further downfield. .The remaining protons present in the triazoles were observed further upfield between 1.60 ppm to 2.00 ppm for the methyl groups. Other chemical shifts seen further downfield represented carbons for the triazoles.



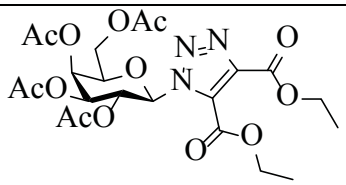
Equation 9. Synthesis of 1,4 and 1,5-triazoles using octyne.

Using heptyne

Heptyne, which is also a terminal alkyne was also used in the synthesis of the 1,4 and 1,5- isomers according (**Equation 10)**. The doublet signal at 4.62 ppm of the galactosyl azide **3** was totally gone, and two new peaks were observed at 7.42 ppm and 7.60 ppm representing the protons present in the 1,4 and 1,5-isomer. The remaining protons of the triazoles were observed further upfield between 1.60 ppm to 2.00 ppm. The table below summarizes the results obtained during the reactions of alkynes and the azide.



Equation 10. Synthesis of 1,4- and 1,5-isomers using heptyne.

Alkynes	**Reaction reagents/conditions**	**Product formed**	**% Yield**
Diethyl acetylene dicarboxylate	Heat (90 ˚C) Time (24 hours)		**94**

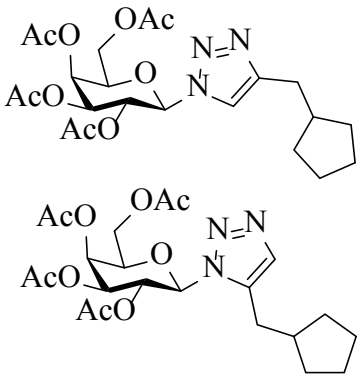
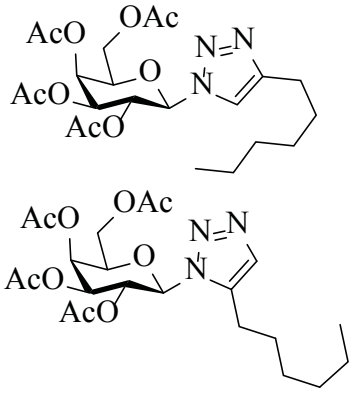
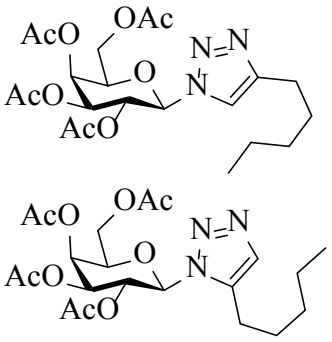
3-cyclopentyl-1-propyne	Heat (90 ˚C) Time (24 hours)		**87**
Octyne	Heat (90 ˚C) Time (24 hours)		**89**
Heptyne	Heat (90 ˚C) Time (24 hours)		**95**

Table 2. Summary of % yields for triazoles formed.

Synthesis of 1,4-disubstituted 1,2,3-triazoles.

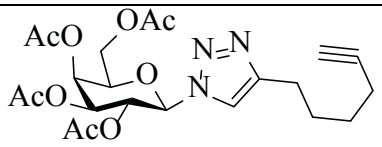
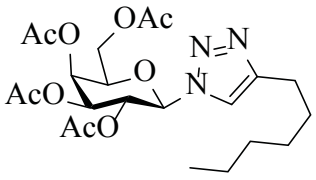
From the synthetic procedures mentioned above, that is, without the use of solvent, both the 1,4-isomer and the 1,5-isomers were produced, however, transition metal catalyzed azide-alkyne cycloadditions methods have been proven to yield only the 1,4-regioisomer products. Among these transition metals, copper (I) catalyst have been shown to improve the yield of product and also ensures the formation of only 1,4-regiosiomer. As a result, the modified method from the copper-catalyzed azide approach was used to synthesize the 1,4-regioisomer. This involve the reaction between the galactosyl azide **3** with an alkyne in the presence of copper (II) sulfate, L-ascorbic Acid, and Ethanol / water mixture. The alkynes used were phenylacetylene, octyne and 1,6-heptadiyne. The progress of these reactions were monitored by TLC where new spots with lower R_f than the starting materials were observed indicating total consumptions of the galactosyl azide **3** used.

The ^{1}H NMR spectrum of compound **5** achieved from the copper-catalyzed approach shows that, the doublet signal at 4.62 ppm corresponding to the H-1 proton of the galactosyl azide **3** was totally gone. Only one singlet signal was observed at 7.57 ppm which corresponds to the proton of the 1,4-disustituted triazole and this confirmed that, the copper catalyzed system only gives the 1,4-regioisomer.

Aromatic alkyne, phenylacetylene were also utilized in the transition metal catalyzed cycloaddition reaction that produces only one regioisomer. When compound **3** were treated with phenylacetylene according to the general procedure mentioned above

1,4-regioisomer, that is, compound **12** was formed in good yield. ^{1}H NMR Spectrum of compound **12** reveals that, the doublet signal at 4.62 ppm of the H-1 proton of the starting material was gone. Also, singlet peak at 8.01 ppm was observed. This singlet peak corresponds to the triazole proton of the 1,4-regioisomer of compound **12**. ^{13}C NMR indicated a chemical shift from 74.15 ppm to 117.80 ppm in which corresponded to C-2 and for C-1 it shifted further downfield from 86.38 ppm to 125.96 ppm to the compounds

The summary of the results obtained in the copper catalyzed cycloaddition reactions are shown in table **3**.

Alkynes	**Reaction reagents/conditions**	**Product formed**	**% Yield**
1,6-heptadiyne	$CuSO_4$, Ascorbic acid, EtOH/H_2O, 70 ºC, 1,6-heptadiyne		**97**
Octyne	$CuSO_4$, Ascorbic Acid, EtOH/H_2O, 70 ºC, octyne		**94**

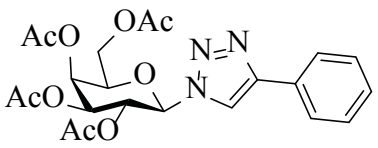
Phenylacetylene	$CuSO_4$, Ascorbic Acid, $EtOH/H_2O$, 70 ºC, phenylacetylene		**97**

Table 3. Summary of % yields of 1,4-disubstituted triazoles formed.

In our next trial, new catalytic system was used to synthesize the 1,5 regioisomer. Nickel-catalyzed Azide-alkyne cycloaddition (NiAAC) reaction was used to synthesize 1,5-disbstituted triazole with good yield as indicated in (**Table 4)**. This reaction have been shown to be a better substitute for copper catalyzed cycloaddition due to its low toxicity. When phenylacetylene was used as the alkyne and subjected to the reaction conditions indicated in (**Table 4)** below, compound **13** was obtained in good yield. TLC indicated the formation of a new spot, observed under U.V light at a lower R_f value than that of the starting material.

The ^1H NMR and COSY also gave a clear picture of the product formed as the doublet signal at 4.62 ppm of the starting material, that is compound **3** was gone. A singlet peak was observed at 7.73 ppm which corresponds to the proton of the triazole of the 1,5-regioisomer of compound **13**.

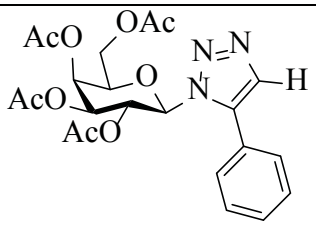
Alkynes	**Reaction reagents/conditions**	**Product formed**	**% yield**
Phenylacetylene	Cp_2Ni (10%), Xantphos (10%), Cs_2CO_3 (1mmol), 2 mL (1:1), H_2O: EtOH, Rt, 3-5 days		**84**

Table 4. Summary of % yield of 1,5-triazole.

CONCLUSION/RECOMMENDATION.

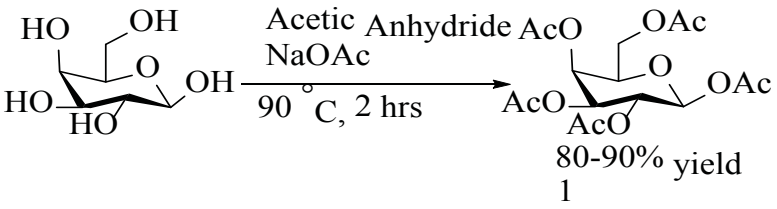
In all, fifteen galactosyl compounds were synthesized using different kinds of reaction conditions with yields ranging from 75-90%. From this piece of work, it has been shown that transition metal catalyzed cycloaddition reactions produce only one regioisomer. Under such reaction conditions, the reaction was completely regiospecific and only the 1,4-regiosiomer were formed in the case of the copper catalyzed, and 1,5-regioisomer in the case of nickel catalyzed in contrast with the mixture of regioisomer obtained under the classical thermal conditions, that is, the solventless reaction system. Given that, these triazoles can have a high potential as possible precursors in the synthesis of various antibiotics. It is therefore recommended that future works could be done to test the effectiveness of these triazoles as potential drugs in the treatment of these resistant-strain microbe.

EXPERIMENTAL

General Procedures

All reactions were monitored by thin layer chromatography (TLC) on Whatman aluminum-backed plates with diverse eluent systems. The identity of materials containing chromophores was achieved using Ultraviolet light. TLC plates were then treated with a solution of 5% sulfuric acid in ethanol and heated on a hotplate to detect carbohydrate reaction materials. Purification was achieved either by direct recrystallization or via flash column chromatography. The latter was performed with 32-63 μm, 60-Å silica gel. Nuclear Magnetic Resonance spectra were recorded on samples dissolved in $CDCl_3$ using Bruker Avance II and Avance III systems, at a frequency of 400 MHz for ^1H spectra All chemical shifts were recorded in parts per million (ppm). Signals are labelled as follows: s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), m (multiplet) and coupling constants (*J*) are measured in Hertz (Hz). COSY spectra were used to assign signals in proton spectra as needed.

Preparation of protected sugar from 1,2,3,4,6-penta-*O*-acetyl-β-D-galactose.



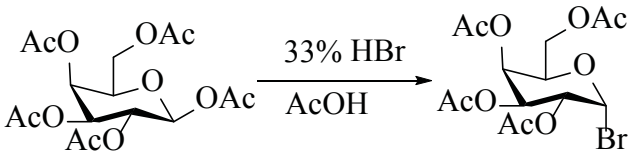
80-90% yield

1

In a 50 mL round bottom flask equipped with magnetic stir bar, D-galactose (2.5 g, 1 mmol) was dissolved in acetic anhydride (20 mL), and sodium acetate (2 g) was also added. The mixture was heated under reflux at a temperature of 90 ^{o}C for 2 hours until TLC shows total consumption of starting material. The solution was left to cool to zero degrees (0 ºC). The contents were then poured over ice-water (50 mL) slowly and left for 10-30 minutes to cool down. The product was collected by suction filtration. The penta-acetate collected were recrystallized from hot isopropanol at around 65 ºC to afford compound **1** (2.55 g, 1.00 mmol, 98%) as white crystals.

^{1}H NMR ($CDCl_3$): δ 2.01, 2.06, 2.06, 2.14, 2.18 (5s, 15H total, 4 x $COCH_3$), 4.07 (dd, 1H, H-6, *J* = 2.20, 10.12 Hz), 4.10 (dd, 1H, H-6', *J* = 4.40, 10.18), 4.16 (ddd, 1H, H-5, *J* = 2.25, 4.72. 10.15 Hz), 5.1 (dd, 1H, H-2, *J* = 3.42, 10.27 Hz), 5.35 (dd, 1H, H-3, *J* = 8.31, 10.51 Hz), 5.44 (dd, 1H, H-3, *J* = 2.69, 10.42), 5.72 (d, 1H, H-1, *J* = 8.31 Hz).

Formation of galactosyl bromide from 1, 2, 3, 4, 6-penta-*O*-acetyl-β-D-galactose.



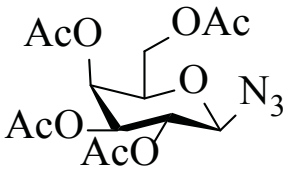
1 **2**

In a 100 mL round-bottom flask equipped with a septum, vent, and magnetic stir bar, 1,2,3,4,6-penta-*O*-acetyl-β-D-galactose (2.5 g, 1.0 mmol) was dissolved in 33% HBr in acetic acid (20 mL). The reaction mixture was stirred at room temperature for 3 hours until TLC (1:1 hexanes: ethyl acetate, product R_f = 0.31) showed complete consumption of the starting material. The mixture was then diluted with 30 mL ethyl acetate and then cooled to 0 °C. The mixture was then neutralized using 10% w/v NaOH (3 x 30 mL). The neutralization was completed using saturated sodium bicarbonate ($NaHCO_3$) (7 mL). The organic layers were separated and washed with ice-water (3x 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford **2** as a clear syrup, which was pure glycosyl bromide in (2.58 g, 1.00 mmol, 97%).

^{1}H NMR ($CDCl_3$): δ 2.03, 2.07, 2.12, 2.17, (4s, 12H total, $COCH_3$), 4.20 (dd, 1H, H-6, *J* = 1.50, 12.18 Hz), 4.28-4.37 (m, 2H, H-5, H-6'), 4.85 (dd, 1H, H-2, *J* = 4.16, 10.20 Hz), 5.17 (dd, 1H, H-3, *J* = 9.82, 9.82 Hz), 5.56 (dd, 1H, H-4, *J* = 9.64, 9.88 Hz), 6.62 (1H, H-1, *J* = 4.06 Hz)

^{13}C NMR ($CDCl_3$): δ 14.1, 31.1, 28.2, 20.1, 20.7, 20.4, 20.3, 25.1, 23.2, 74.1, 70.9, 67.5, 86.01, 133.1, 118.6.

Preparation of galactosyl azide 3 from galactosyl bromide.



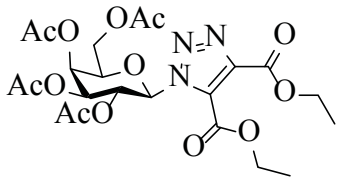
To 250 mL round-bottom flask equipped with a stir bar, galactosyl bromide (2.58 g, 1.00 mmol) and sodium azide (9.73 g, 1 mmol) were dissolved in a mixture of 140 mL (10:2) acetone: water. The mixture was allowed to stir overnight until TLC showed total consumption of the starting material. The solution was then concentrated under reduced pressure to form a slurry-like product. The organic layers were then extracted using ethyl acetate (4 x 70 mL) and dried over anhydrous magnesium sulfate. It was then concentrated again reduced pressure. The resulting residue was purified via flash column and further recrystallized using hot ethanol to give compound **3** as a white solid (2.74 g, 1.00 mmol, 94%).

^{1}H NMR ($CDCl_3$): δ 2.01, 2.08, 2.11, 2.19 (4s, 12H total, 4 x $COCH_3$), 4.04 (ddd, 1H, H-5, *J* = 2.25, 4.50, 10.14), 4.12 (dd, 1H, H-6, *J* = 1.52, 6.72 Hz), 4.19 (dd, 1H, H-6', *J* = 3.18, 6.60 Hz), 4.62 (d, 1H, H-1, *J* = 8.8 Hz), 5.06 (dd, 1H, H-2, *J* = 8.78, 10.21 Hz), 5.19 (dd, 1H, H-3, *J* = 8.8, 10.27 Hz), 5.44 (dd, 1H, H-4, *J* = 0.98, 3.42 Hz)

^{13}C NMR ($CDCl_3$): δ 20.48, 20.57, 20.61, 20.63, 61.22, 66.87, 68.11, 70.74, 72.89, 88.31, 169.32, 169.94, 170.07, 170.32.

Mp =101-102 °C

Preparation of galactosyl triazole dicarboxylate 4 from galactosyl azide 3.



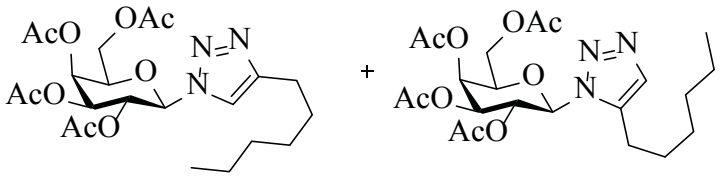
To a 50 mL round-bottom flask equipped with a stir bar, a galactosyl azide (0.77 g, 1 mmol) was dissolved in DEAD (0.32 mL, 1 mmol). The mixture was stirred under reflux set-up at a temperature of about 90 ºC for overnight until TLC showed total consumption of starting material when a new spot of a higher R_f value was noted. The mixture was concentrated under reduced pressure to form a slurry-like product. The residue was recrystallized using hot ethanol to afford the triazole **4** (0.82 g, 2.00 mmol, 94%) as pure crystals.

^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3H, $CO_2CH_2CH_3$, *J* = 7.09 Hz), 1.42 (t, 3H, $CO_2CH_2CH_3$, *J* = 7.12 Hz), 1.91, 2.02, 2.05, 2.22, (4s, 12H total, 4 x $COCH_3$), 3.34 (dd, 1H, H-6, *J* = 2.15, 12.65 Hz), 4.19 (dd, 1H, H-6' *J* = 4.76, 12.20 Hz), 4.21 (q, 2H, $CO_2CH_2CH_3$, *J* = 7.10 Hz), 4.30 (q, 2H, $CO_2CH_2CH_3$, *J* = 7.09 Hz), 4.45 (ddd, 1H, H-5, *J* = 0.92, 7.15, 16.87 Hz), 5.23 (dd, 1H, H-2, *J* = 3.12, 9.48 Hz), 5.52 (dd, 1H, H-3, *J* = 9.42, 9.42 Hz), 6.07 (dd, 1H, H-4, *J* = 8.70, 8.53 Hz), 6.52 (d, 1H, 1-H, *J* = 9.20 Hz).

^{13}C NMR ($CDCl_3$): δ 13.89, 14.14, 20.31, 20.49, 20.55, 61.07, 61.95,62.98, 63.13, 66.74, 67.27, 71.18, 74.17, 74.67, 86.15, 131.27, 139.95, 151.81, 158.19, 19.62, 168.49, 169.98, 170.08, 170.24.

Mp =126-127 °C

Preparation of triazoles 5 & 6 from galactosyl azide 3.



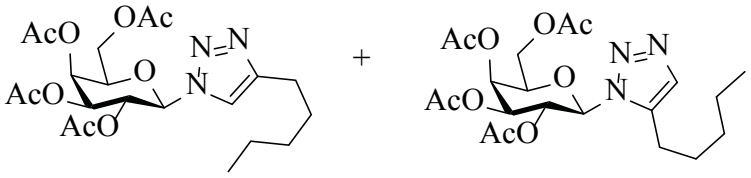
To a 25 mL round-bottom flask equipped with a stir bar, a galactosyl azide (0.38 g, 1 mmol) was dissolved in octyne (0.15 mL, 1 mmol). The mixture was stirred under reflux set-up at a temperature of about 90 ºC for overnight until TLC showed total consumption of starting material when a new spot of a higher R_f value was noted. The mixture was concentrated under reduced pressure to form a slurry-like product. The residue was recrystallized using hot ethanol to afford the triazoles **5** & **6** (0.42 g, 1.00 mmol, 89%).

^{1}H NMR ($CDCl_3$): δ 1.1-1.7 (m, 13H, triazole-C_6H_{13}), 1.88, 1.95, 2.03, 2.23 (4s, 12H total, 4 x $COCH_3$), 2.74 (dd, 1H, H-6, *J* = 7.09, 14.18), 2.88 (dd, 1H, H-6', *J* = 7.58, 19.07 Hz), 4.19 (ddd, 1H, H-5, *J* = 0.73, 7.09, 16.17 Hz), 5.26 (dd, 1H, H-4, *J* = 3.18, 10.27 Hz), 5.57 (dd, 1H, H-2, *J* = 2.45, 5.13 Hz), 5.19 (dd, 1H, H-3, *J* = 3.42, 5.87 Hz), 7.48 (s, 1H, triazole-H), 7.57 (s, 1H, triazole-H).

^{13}C NMR ($CDCl_3$): δ 14.00, 20.19, 20.45, 20.60, 22.50, 22.52, 23.22, 25.59, 28.04, 28.75,29.06, 29.12, 31.38, 31.51, 61.21, 61.26, 66.87, 66.98, 67.05, 67.82, 76.70, 77.02, 77.33, 86.18, 118.89, 133.14, 138.94, 149.17, 168.98, 169.08, 169.80, 169.93, 169.97, 170.32, 170.35, 174.5.

Mp =112-113 °C

Preparation of triazoles 7 & 8 from galactosyl azide 3.

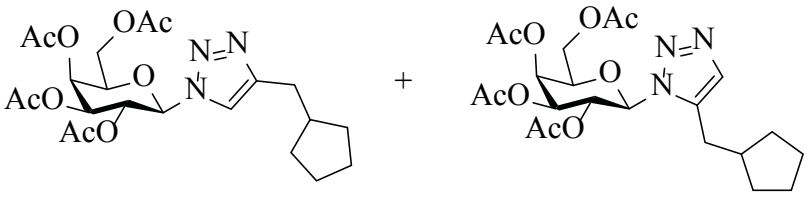


To a 50 mL round-bottom flask equipped with a stir bar, a galactosyl azide (0.38 g, 1 mmol) was dissolved in heptyne (0.16 mL, 1 mmol). The mixture was stirred under reflux set-up at a temperature of about 90 ºC for overnight until TLC showed total consumption of starting material when a new spot of a higher R_f value was noted. The mixture was concentrated under reduced pressure to form a slurry-like product triazoles **7 & 8** (0.40 g, 1.00 mmol, 94%).

^{1}H NMR ($CDCl_3$): δ 0.8-1.8 (m, 11H, triazole-C_6H_{11}), 2.04, 2.07, 2.19 2.24 (4s, 12H total, 4 x $COCH_3$), 2.74 (dd, 1H, H-6, *J* = 7.74, 15.41), 2.89 (dd, 1H, H-6', *J* = 7.71, 15.78 Hz), 4.21 (ddd, 1H, H-5, *J* = 0.78, 7.15, 16.10 Hz), 5.26 (dd, 1H, H-4, *J* = 3.42, 10.27 Hz), 5.57 (dd, 1H, H-2, *J* = 2.65, 5.02 Hz), 5.83 (dd, 1H, H-3, *J* = 3.40, 6.09 Hz), 7.48 (s, 1H, triazole-H), 7.57 (s, 1H, triazole-H).

^{13}C NMR ($CDCl_3$): δ 13.97, 20.21, 20.46, 20.61, 22.37, 25.59, 27.75, 28.86, 31.29, 31.52, 66.85, 66.96, 70.92, 73.78, 86.21, 118.84, 133.21, 149.20, 169.76, 169.93, 169.88, 170.02.

Preparation of triazole 9 & 10 from galactosyl azide 3.

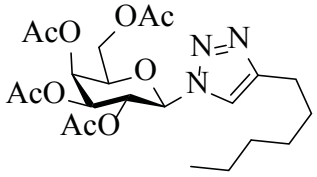


Sodium azide (0.38 g, 1 mmol) was added to a 50 mL round-bottom flask containing 3-cyclopentyl-1-propyne (0.50 mL, 1 mmol) and a stir bar under reflux set-up, the mixture were then heated up to a higher temperatures of about 90ºC. After the solution was allowed to react overnight, a TLC showed that, there was an appearance of the new spot material of higher R_f value than the staring material. Upon completion of the reaction, the ^{1}H NMR proves that indeed the new material was formed, the solution was cooled using an ice bath form a slurry-like mixture of triazole **9** & **10** in good yield (0.43 g, 1.00 mmol, 94%).

^{1}H NMR ($CDCl_3$): δ 0.9-1.9 (m, 11H, triazole-H), 1.89, 1.94, 2.04 2.06 (4s, 12H total, 4 x $COCH_3$), 2.75 (dd, 1H, H-6, *J*=7.65, 14.58), 2.86 (dd, 1H, H-6', *J*=7.65, 15.78 Hz), 4.21 (ddd, 1H, H-5, *J*=0.80, 7.20, 18.10 Hz), 5.23 (dd, 1H, H-4, *J*=3.41, 10.27 Hz), 5.58 (dd, 1H, H-2, *J*=2.65, 5.12 Hz), 5.84 (dd, 1H, H-3, *J*=3.40, 6.09 Hz), 7.49 (s, 1H, triazole-H), 7.57 (s, 1H, triazole-H).

^{13}C NMR ($CDCl_3$): δ 20.18, 20.45, 20.50, 20.58, 25.07, 25.11, 29.41, 31.62, 32.33, 32.69, 32.81, 38.60, 39.83, 61.18, 61.22, 66.94, 67.03, 67.82, 70.89, 71.07, 73.72, 74.02, 86.17, 119.17, 133.57, 138.47, 148.63, 169.04, 169.78, 169.92, 169.96, 170.33.

Preparation of triazole 5 from galactosyl azide 3.

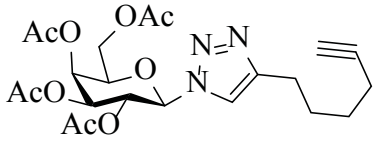


To a 50 mL round-bottom flask equipped with a stir bar, a galactosyl azide (0.38 g, 1 mmol) was dissolved in octyne (1.02 mL, 1 mmol) and 20 ml mixture of 1:1 EtOH/ H_2O. 0.15 g $CuSO_4$ and 0.2 g Ascorbic acid were also added to the reaction mixture. The resulting mixture was stirred under reflux set-up at a temperature of about 60 ^oC for 12 hours until TLC showed total consumption of starting material when a new spot of a higher R_f value was noted. The mixture was allowed to cool to 0 ^oC and then filtered. The residue obtained were washed with deionized water (50 mL x 5) and allowed to dry. The crude product was then recrystallized using hot methanol to afford the triazole **7** (0.769 g, 1.00 mmol, 94%) as pure crystals.

^1H NMR ($CDCl_3$): δ 0.8-1.8 (m, 12H, triazole-H), 1.89, 1.94, 2.04 2.06 (4s, 12H total, 4 x $COCH_3$), 2.75 (dd, 1H, H-6, *J* = 7.65, 14.58), 2.86 (dd, 1H, H-6', *J* = 7.65, 15.78 Hz), 4.21 (ddd, 1H, H-5, *J* = 0.80, 7.20, 18.10 Hz), 5.23 (dd, 1H, H-4, *J* = 3.41, 10.27 Hz), 5.58 (dd, 1H, H-2, *J* = 2.65, 5.12 Hz), 5.84 (dd, 1H, H-3, *J* = 3.40, 6.09 Hz), 7.57 (s, 1H, triazole-H).

^{13}C NMR ($CDCl_3$): δ 13.89, 14.14, 20.31, 20.49, 20.55, 61.07, 61.95,62.98, 63.13, 66.74, 67.27, 71.18, 74.17, 74.67, 86.15, 131.27, 139.95, 151.81, 158.19, 19.62, 168.49, 169.98, 170.08, 170.24.

Preparation of triazole 11 from galactosyl azide 3.

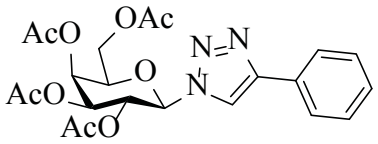


To a 50 mL round-bottom flask equipped with a stir bar, a galactosyl azide (0.38 g, 1 mmol) was dissolved in 1,6-heptadiyne (1.02 mL, 1 mmol) and 20 mL mixture of 1:1 EtOH/ H_2O. 0.15 g $CuSO_4$ and 0.2 g ascorbic acid were also added to the reaction mixture. The resulting mixture was stirred under reflux set-up at a temperature of about 60^oC for 48 hours until TLC showed total consumption of starting material when a new spot of a higher R_f value was noted. The mixture was allowed to cool to 0 ^oC and then filtered. The residue obtained were washed with deionized water (50 mL x 5) and allowed to dry. The crude product was then recrystallized using hot methanol to afford the triazole **11** (0.39 g, 1.00 mmol, 97%).

^1H NMR ($CDCl_3$): δ 0.9-1.3 (m, 6H, triazole-3(CH_2)), 1.73, 1.90, 2.03, 2.07, (4s, 12H total, 4 x $COCH_3$), (dd, 1H, H-3, *J* = 6.83, 13.45), 2.74 (dd, 2H, H-6, *J* = 7.58, 15.65), 4.21 (ddd, 1H, H-5, *J* = 0.60, 6.60, 16.20 Hz), 5.20 (dd, 1H, H-4, *J* = 2.93, 10.41 Hz), 5.60 (dd, 1H, H-2, *J* = 3.67, 6.83 Hz), 5.19 (1H,triazoles-H), 7.57 (s, 1H, triazole-H).

^{13}C NMR ($CDCl_3$): δ 17.69, 18.00, 20.20, 20.46, 20.50, 20.61, 22.01, 24.41, 26.82, 27.82, 61.19, 66.89, 66.95, 66.98,67.87, 68.91, 69.70, 70.84, 73.82, 74.04, 83.68, 86.18, 86.24, 119.28, 133.32, 147.87, 169.07, 169.75, 169.93, 170.29.

Preparation of triazole 12 from galactosyl azide 3.



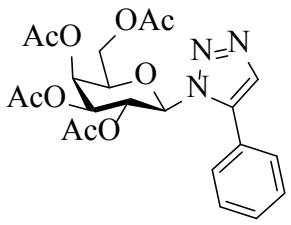
To a 50 mL round-bottom flask equipped with a stir bar, a galactosyl azide (0.38 g, 1 mmol) was dissolved in phenyl acetylene (0.41 mL, 1 mmol) and 20 ml mixture of 1:1 EtOH/ H_2O. 0.15 g $CuSO_4$ and 0.2 g ascorbic acid were also added to the reaction mixture. The resulting mixture was stirred under reflux set-up at a temperature of about 60 ^oC for 24 hours until TLC showed total consumption of starting material when a new spot of a higher R_f value was noted. The mixture was allowed to cool to 0 ^oC and then filtered. The residue obtained were washed with deionized water (50 mL x 5) and allowed to dry. The crude product was then recrystallized using hot methanol to afford the triazole **11** (0.39 g, 1.00 mmol, 97%) as pure crystals.

^1H NMR ($CDCl_3$): δ 1.93, 2.04, 2.07, 2.27 (4s, 12H total, 4 x $COCH_3$), 4.22 (ddd, 1H, H-5, *J* = 0.70, 6.70, 15.46 Hz), 5.28 (dd, 2H, H-H6, H6', *J* = 7.58, 15.65 Hz), 5.30 (dd, 1H, H-4, *J* = 3.18, 10.27 Hz), 5.60 (dd, 1H, H-3, *J* = 6.70, 12.78 Hz), 5.67 (dd, 1H, H-2, *J* = 3.73, 6.88 Hz), 5.92 (d, 1H, H-1, *J* = 9.29 Hz), 7.38(dd, 2H, Ph, *J* = 7.34, 14.67 Hz), 7.46 (dd, 2H, Ph, *J* = 7.33, 15.16 Hz), 7.88 (d, 1H, Ph, *J* = 7.58 Hz), 8.07 (s, 1H, triazole-H).

^{13}C NMR ($CDCl_3$): δ 20.25, 20.46, 20.46, 20.65, 61.21, 66.96, 67.81, 70.89, 74.14, 86.37, 117.80, 125.94, 128.51, 128.84, 130.02, 148.47, 169.14, 169.77, 169.93, 170.30

Mp =70-71 °C

GENERAL PROCEDURE FOR THE SYNTHESIS OF 1,5-DISUBSTITUTED TRIAZOLE. (Triazole 13)



In a 25 mL round bottom flask fitted with a rubber septum and a stir bar, nickelocene (0.00718 g, 0.038 mmol) was mixed with xantphos (0.1157 g, 0.2 mmol) and cesium carbonate (0.325 g, 1 mmol) in a 2 mL ratio of 1:1 water-ethyl acetate as solvents. Phenyl acetylene (0.13 mL, 1.2mmol) was also added to reaction mixture and allowed to stir at room temperature for 72- 120 hours until TLC showed total consumption starting material. A suspension that was formed over the reaction mixture was diluted with dichloromethane (DCM). The organic layer was separated and washed with distilled water and then dried over anhydrous magnesium sulfate. It was then concentrated under reduced pressure to obtain a slurry-like material. The purification process for the crude product was done by flash column chromatography on a silica gel to obtain the pure product **13** in 84%.

^{1}H NMR ($CDCl_3$): δ 1.66,1.85, 1.99, 2.03 (4s, 12H total, 4 x $COCH_3$), 4.14 (ddd, 1H, H-5, *J* = 0.74, 7.00, 14.46 Hz), 5.13 (dd, 2H, H-H6, H6', *J* = 8.01, 16.63 Hz), 5.48 (dd, 1H, H-4, *J* = 3.17, 10.27 Hz), 5.71 (dd, 1H, H-3, *J* = 7.70, 12.80 Hz), 5.67 (dd, 1H, H-2, *J* = 3.73, 6.88 Hz), 5.92 (d, 1H, H-1, *J* = 9.29 Hz), 7.29 (m, 5H, C_6H_5), 7.73 (s, 1H, triazole-H).

^{13}C NMR ($CDCl_3$): δ 20.23, 20.46, 20.57, 20.63, 61.52, 66.92, 66.93, 71.53, 73.81, 77.21, 85.05, 126.31, 128.79, 129.61, 129.88, 133.99, 139.19, 168.27, 169.95, 170.04, 170.25.

Mp =117-118℃

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APPENDIX A

NMR SPECTRA

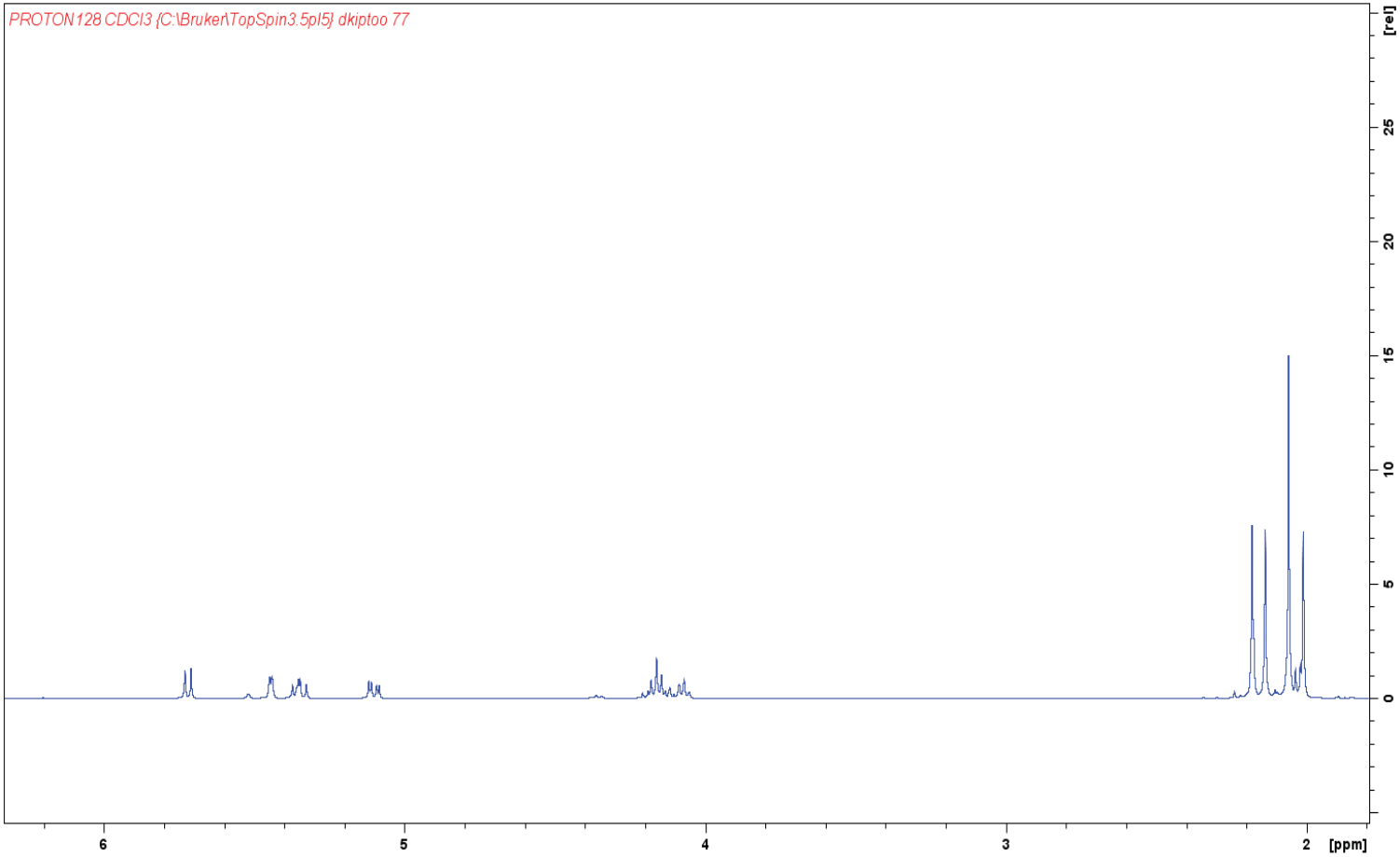

Figure 13: 400 MHz ^{1}H NMR Spectrum of β-D-Galactosepentaacetate.

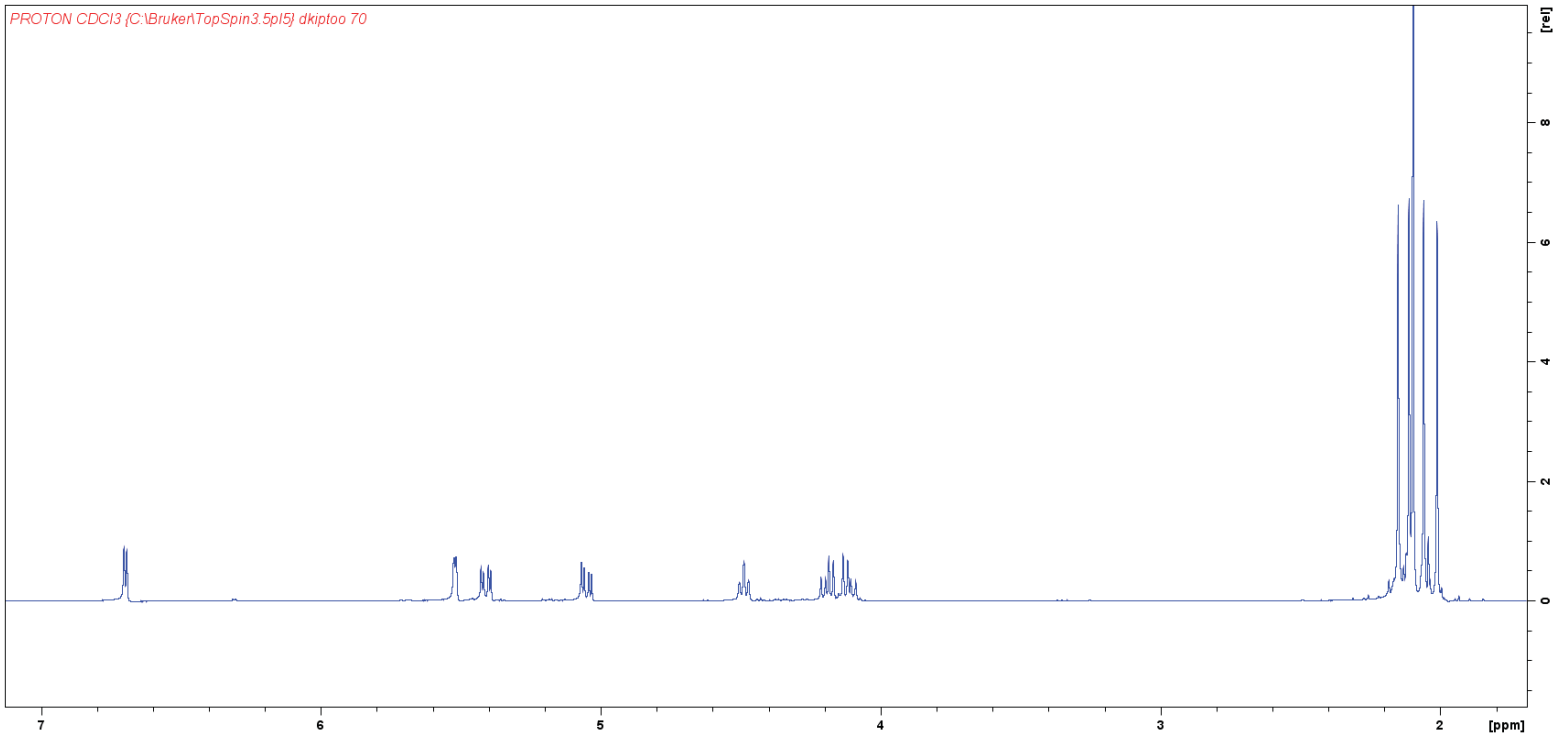

Figure 14: 400 MHz ^{1}H NMR spectrum of galactosyl bromide (**2**).

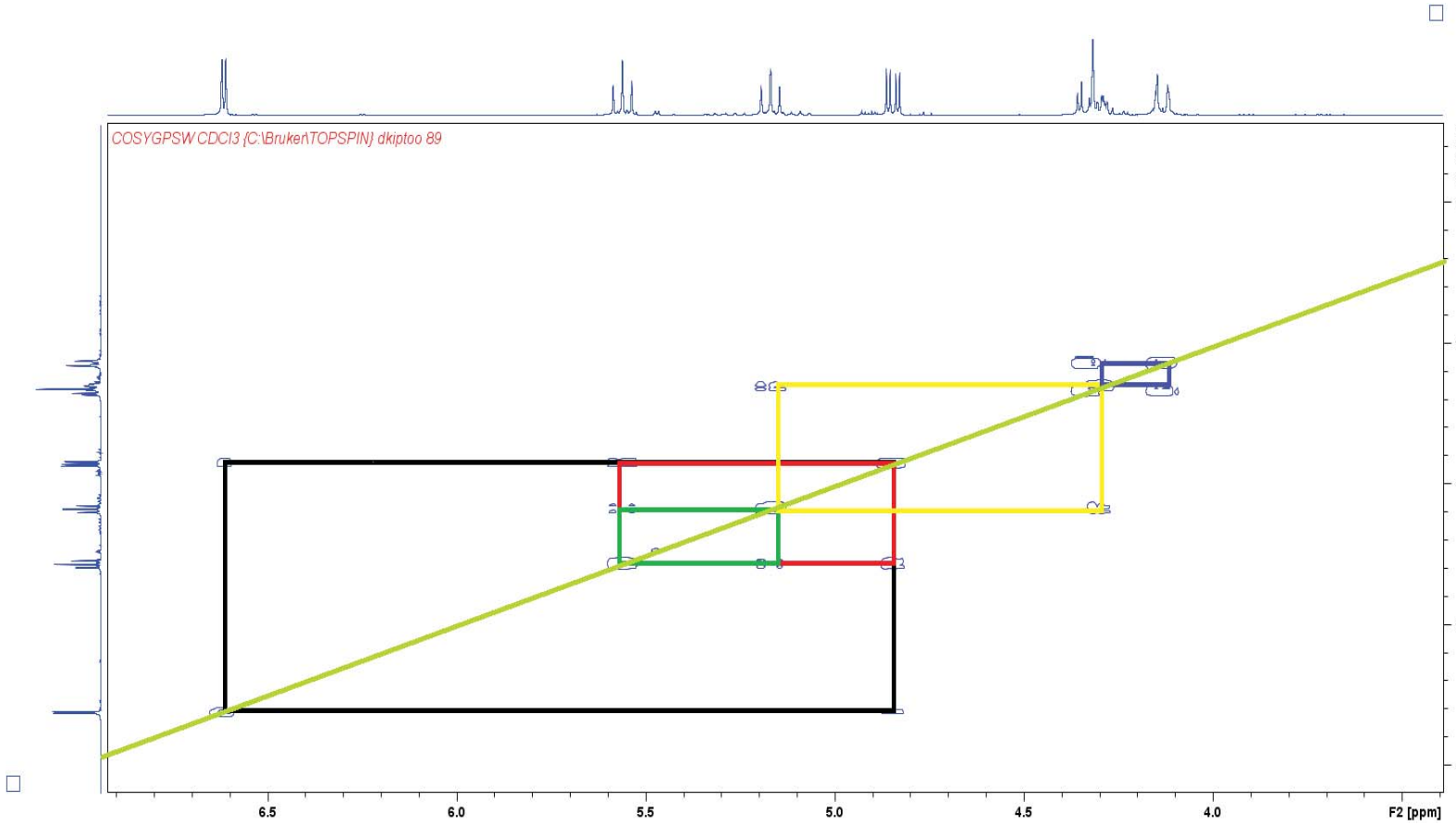

Figure 15: 400 MHz COSY NMR spectrum of galactosyl bromide (**2**).

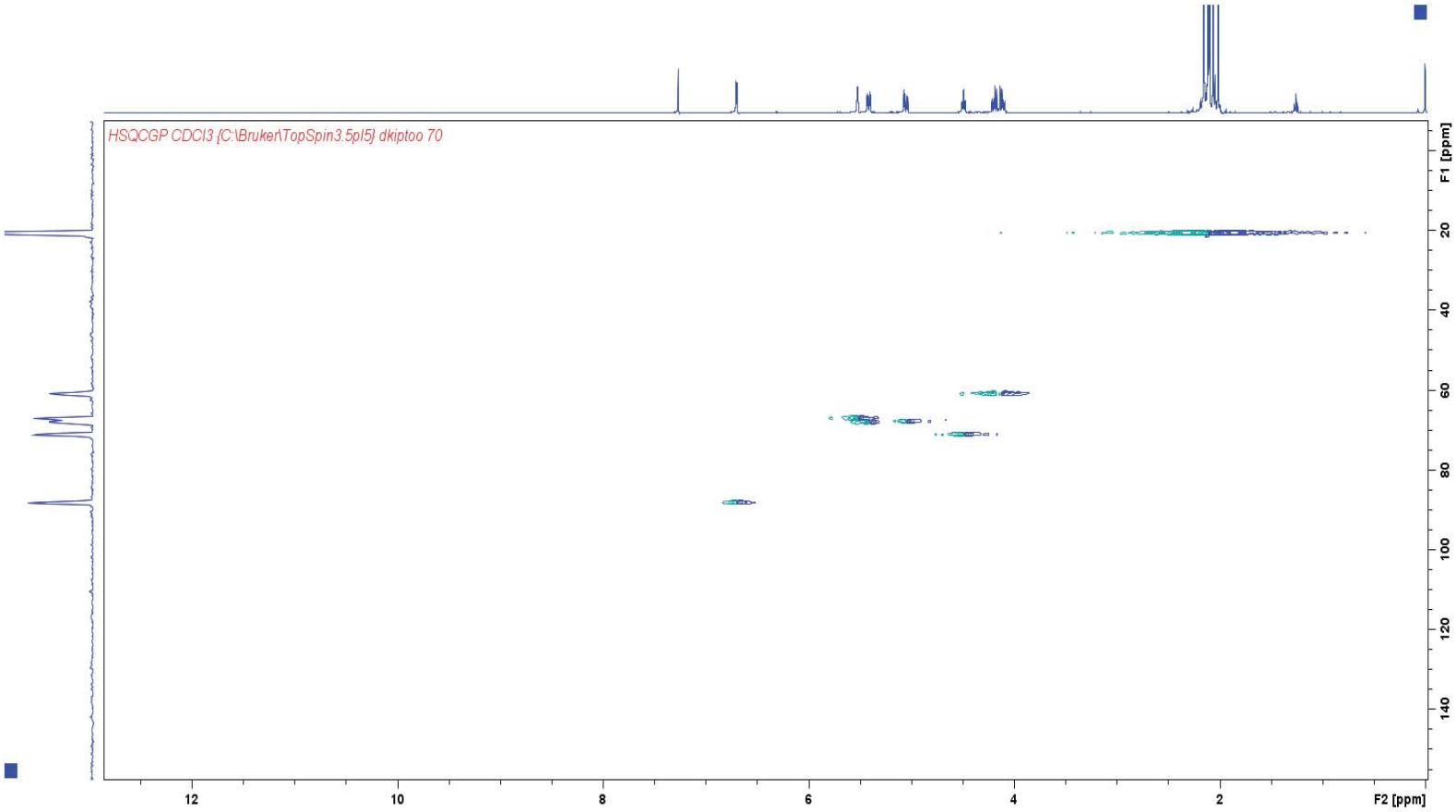

Figure 16: HSQC of galactosyl bromide (**2**).

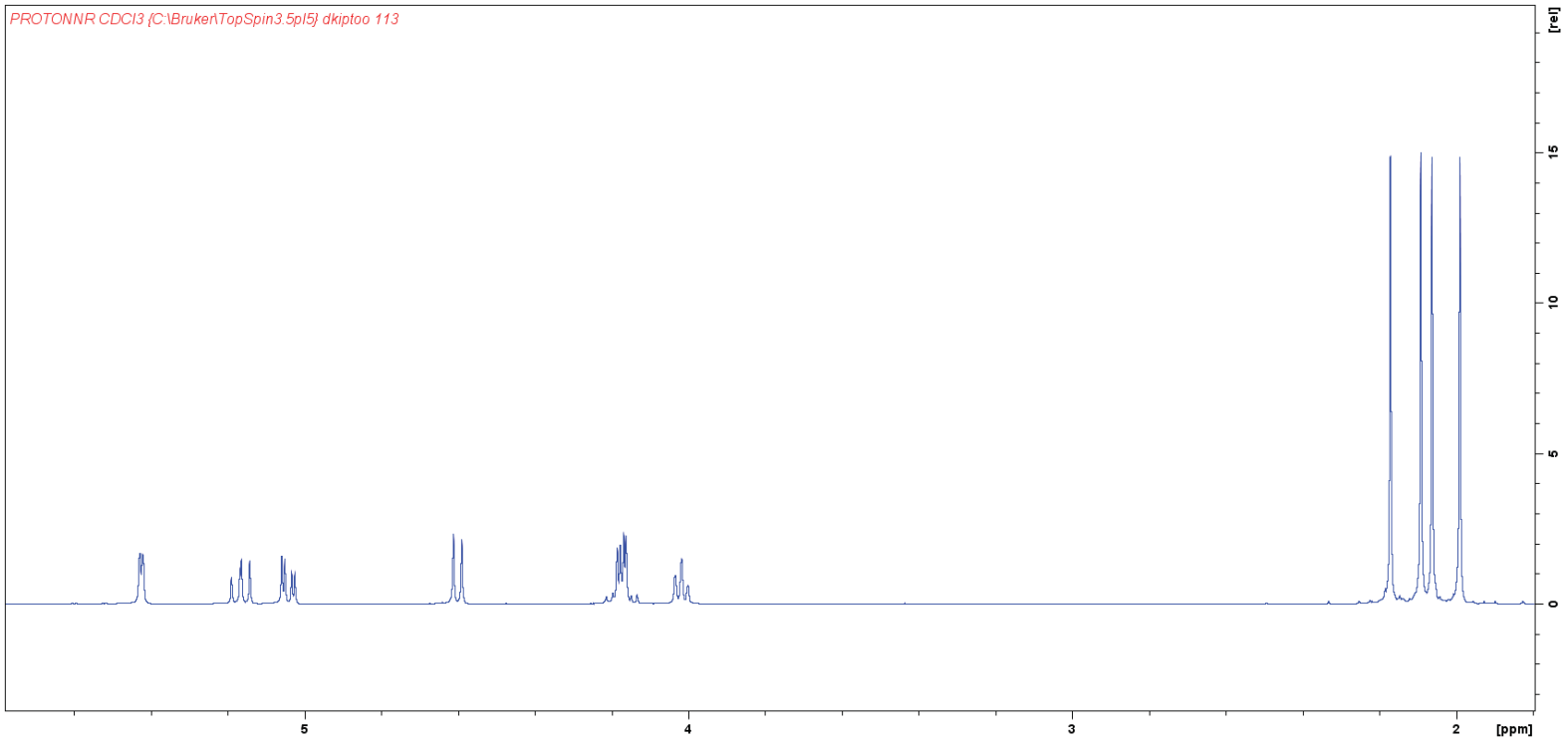

Figure 17: 400 MHz ^{1}H NMR Spectrum of galactosyl azide (**3**).

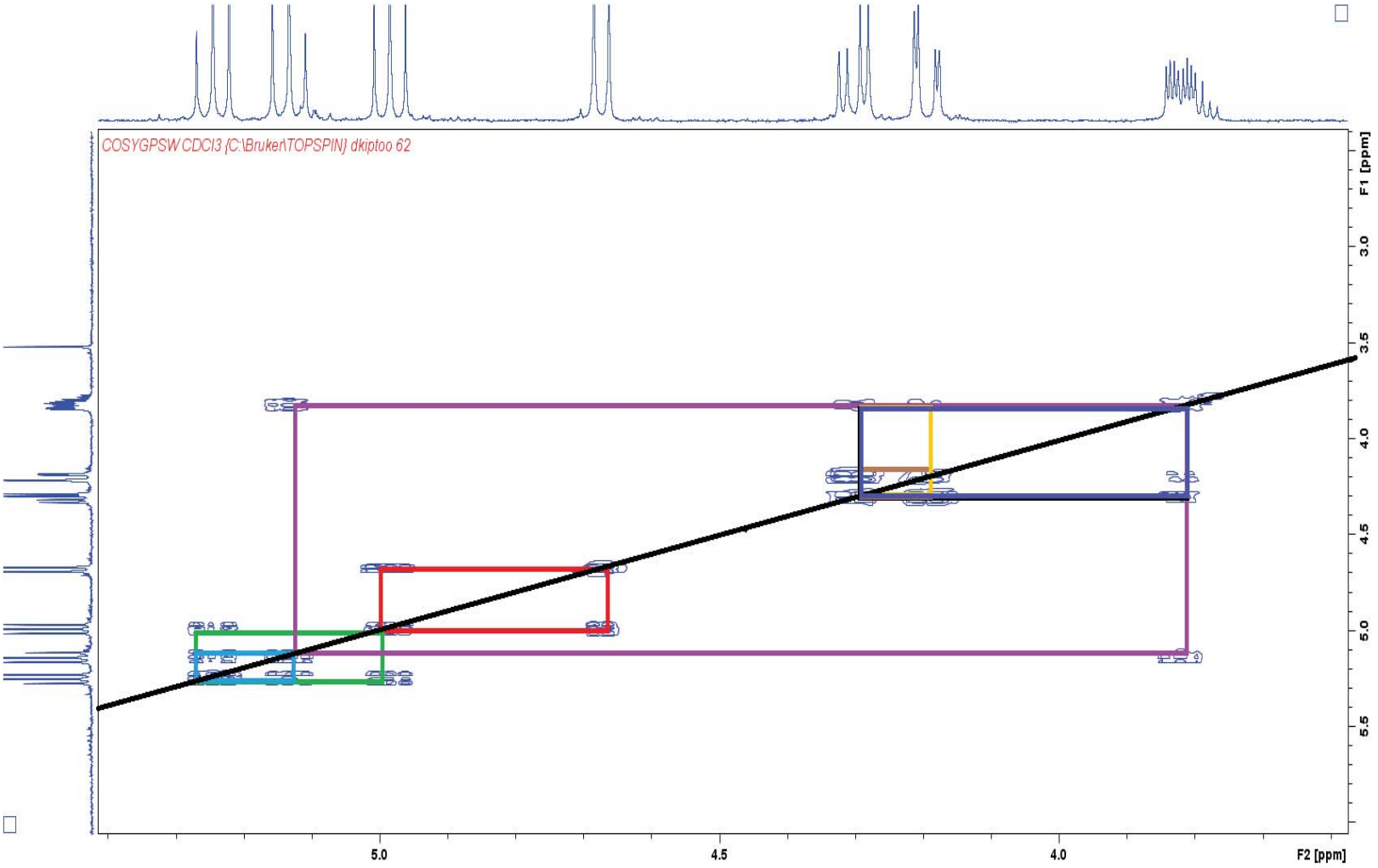

Figure 18: 400 MHz COSY of galactosyl azide (**3**).

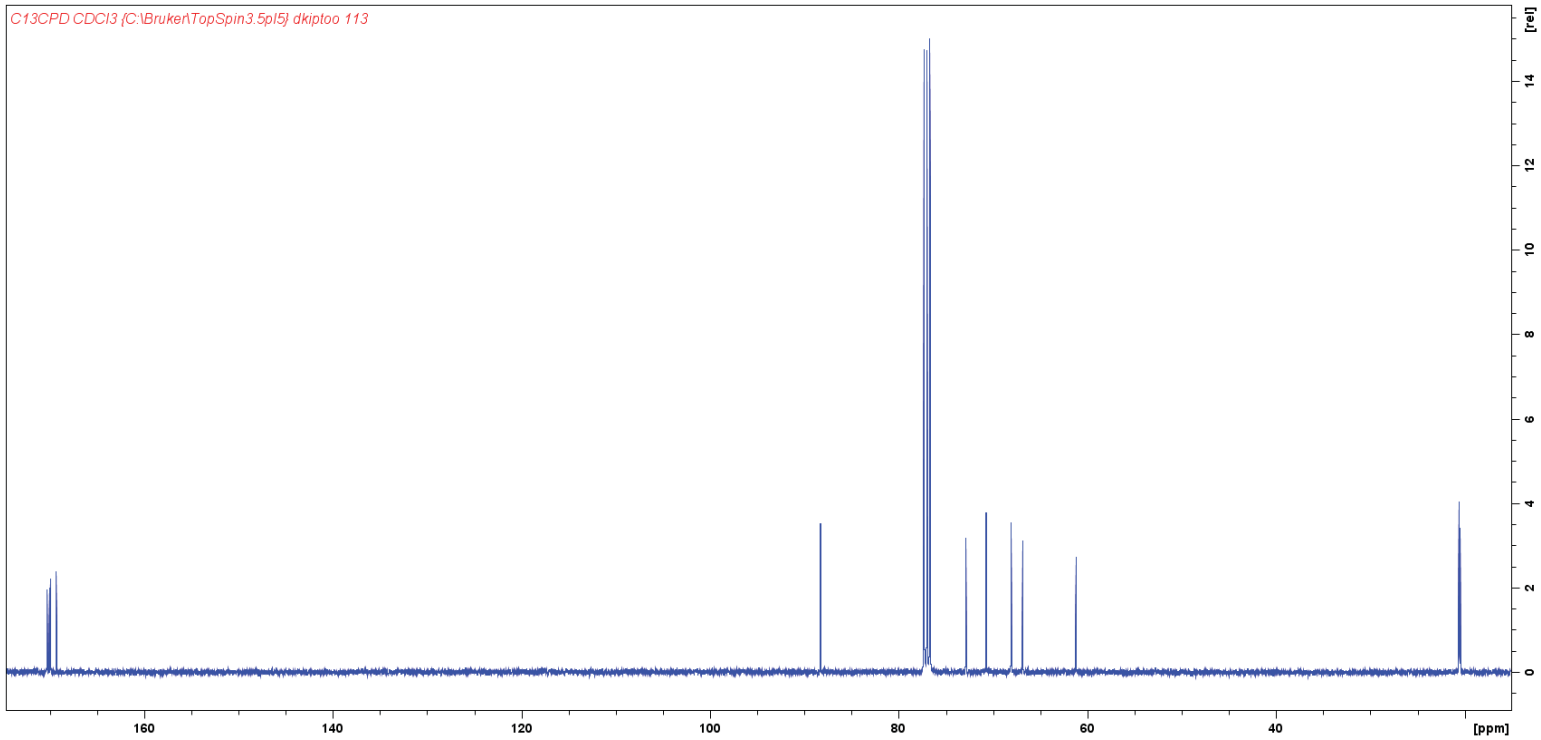

Figure 19: 100 MHz ^{13}C NMR spectrum of galactosyl azide (**3**).

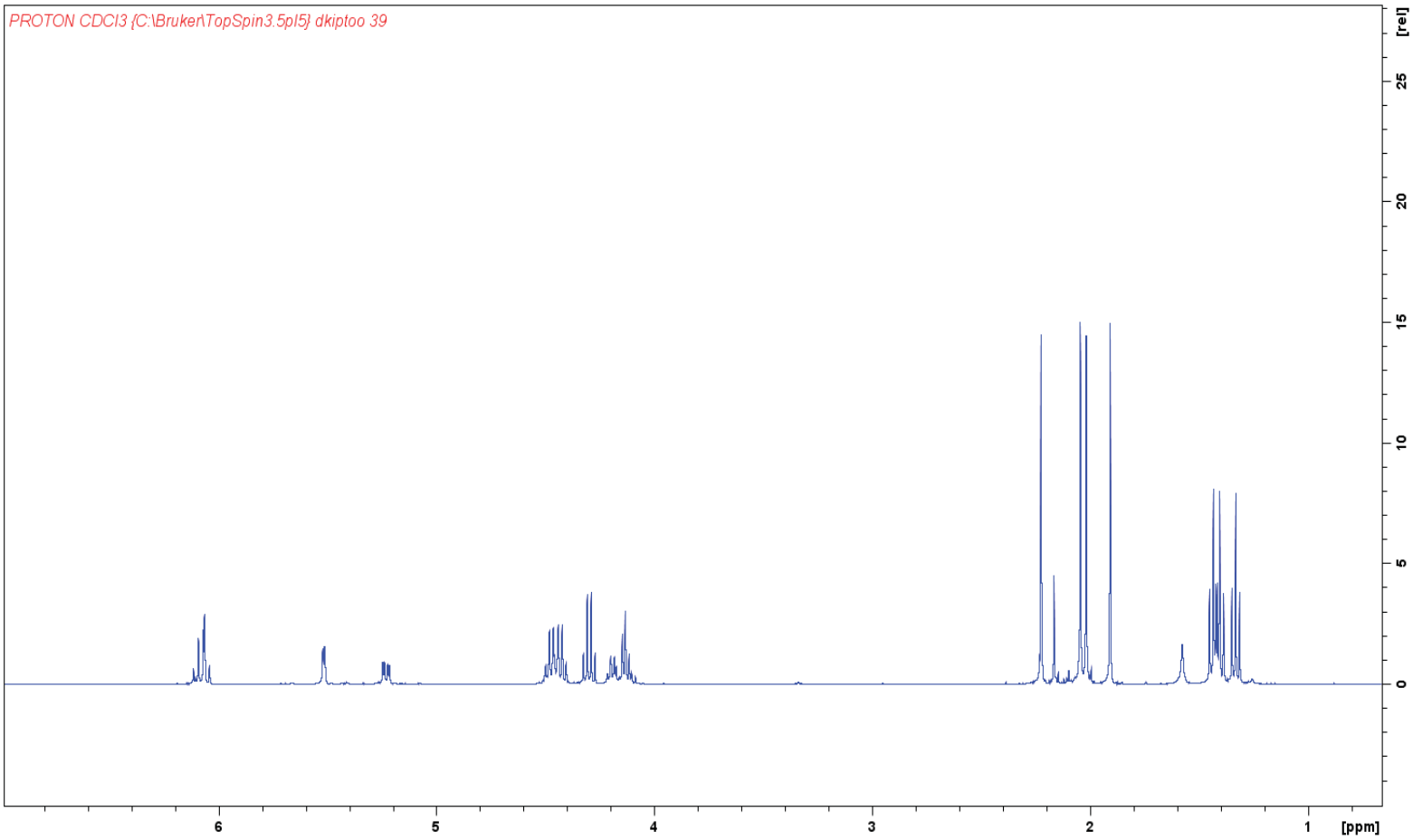

Figure 20: 400 MHz ^{1}H NMR spectrum of galactosyl triazole **4.**

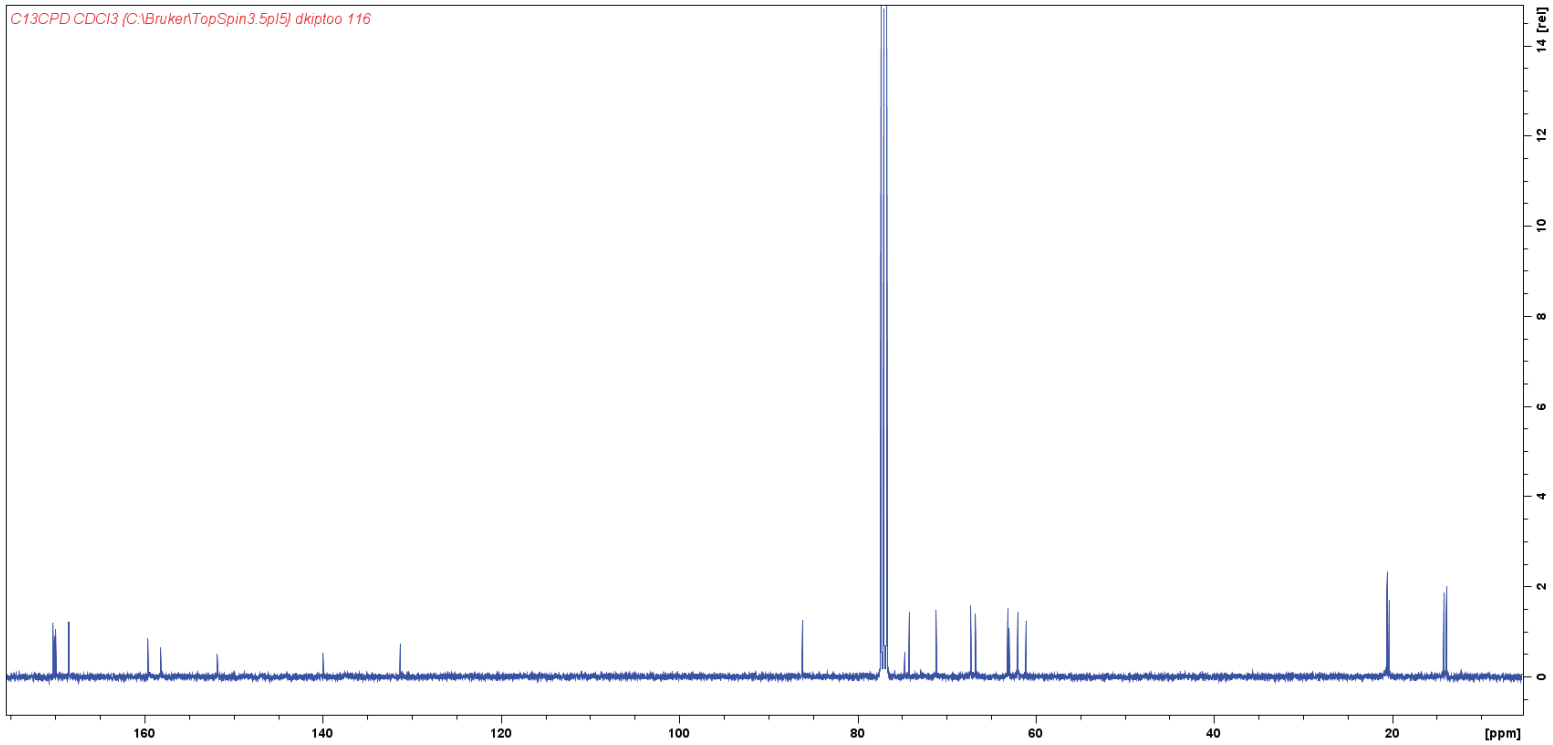

Figure 21: 100 MHz ^{13}C NMR spectrum of galactosyl triazole 4.

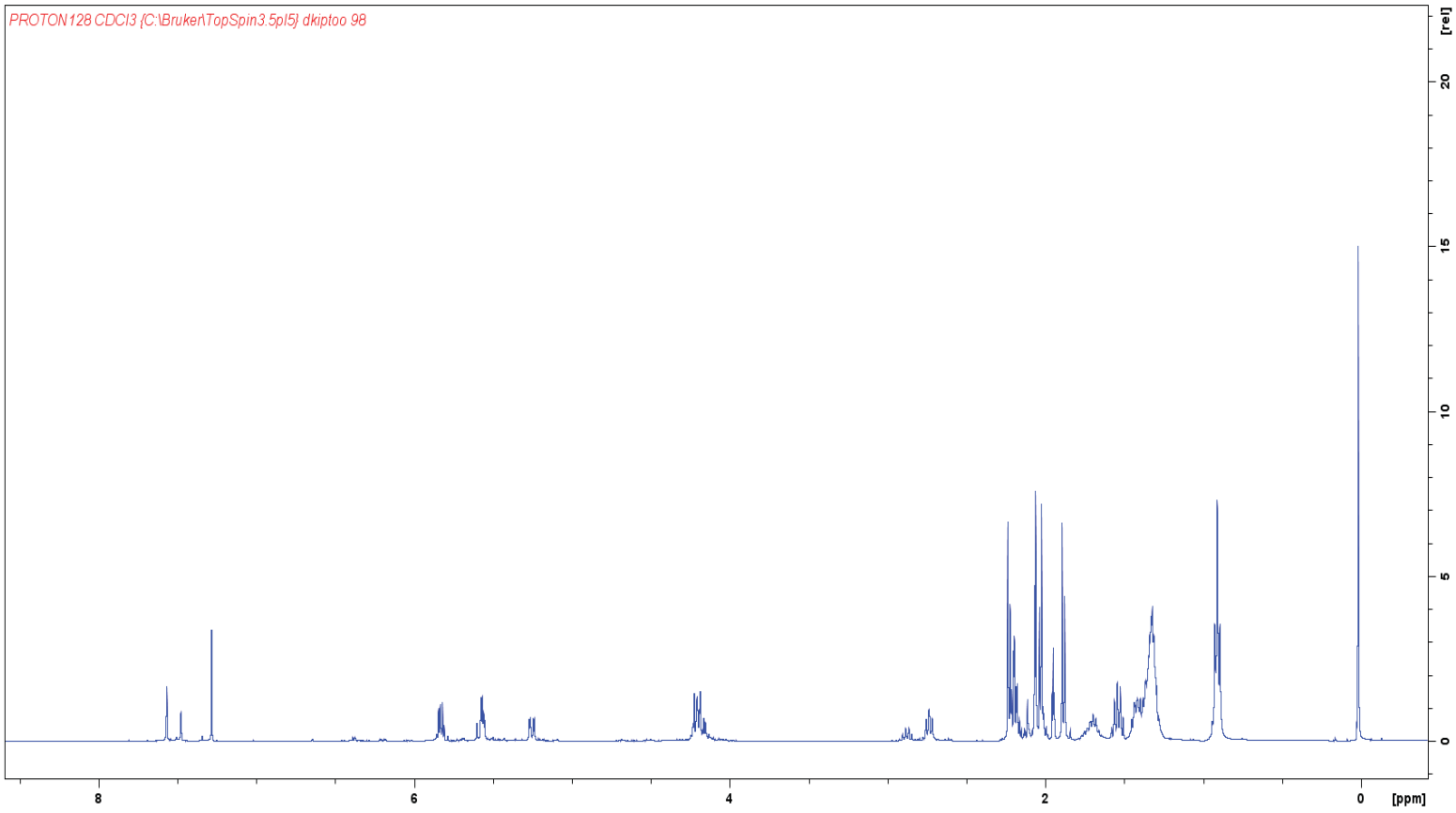

Figure 22: 400 MHz ^{1}H NMR spectrum of galactosyl triazoles **5** and **6**.

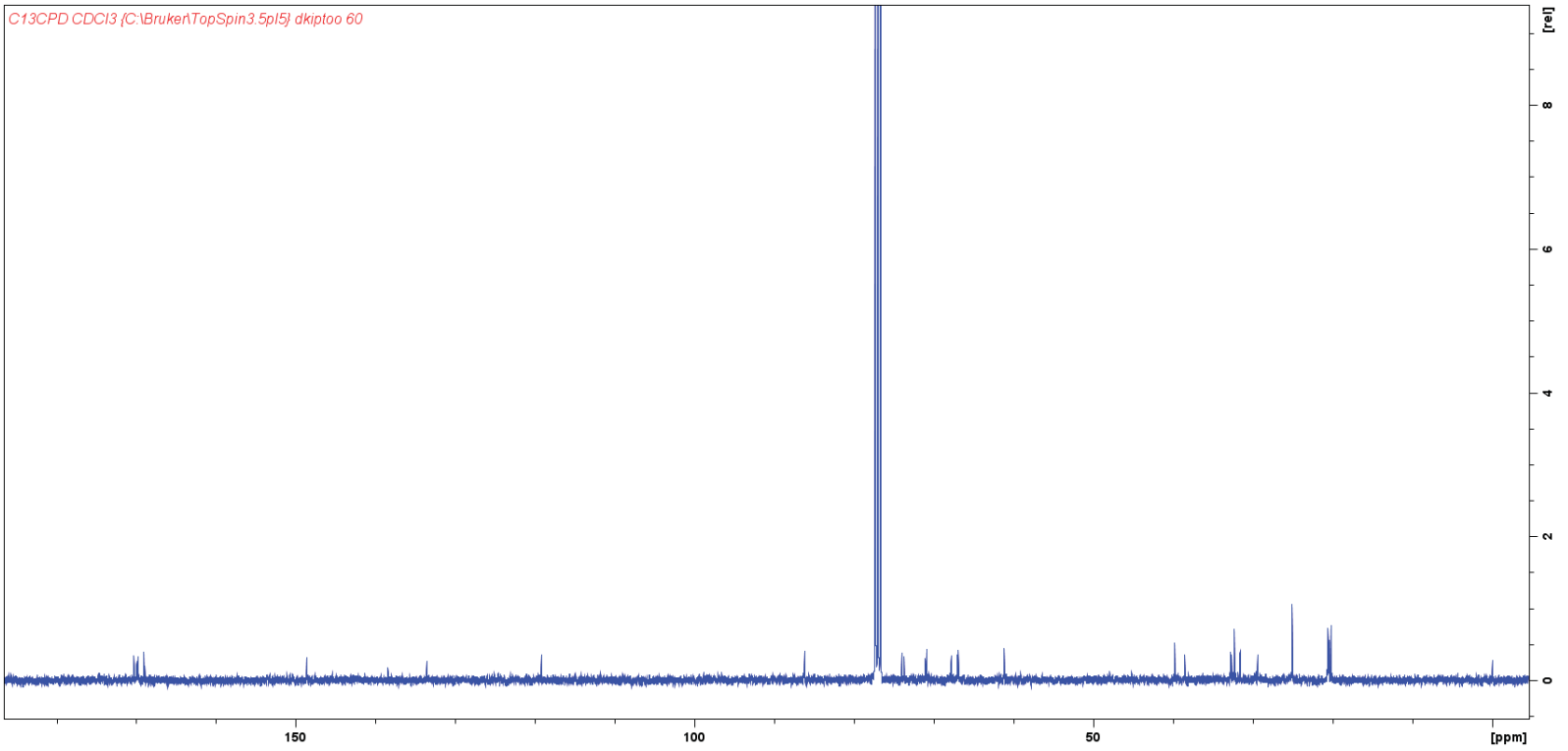

Figure 23: 100 MHz ^{13}C NMR spectrum of galactosyl triazoles **5** and **6**.

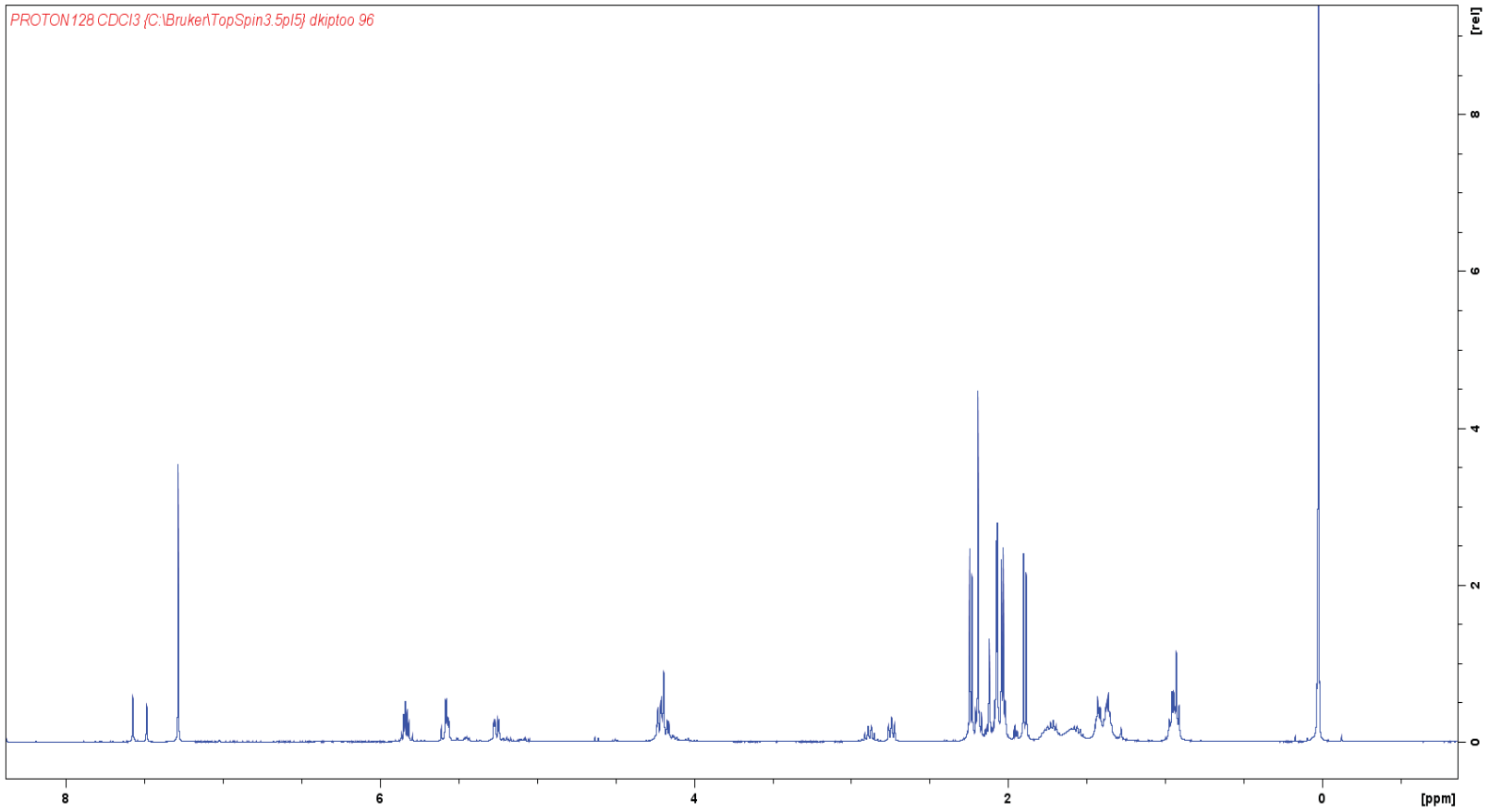

Figure 24: 400 MHz ^{1}H NMR spectrum of galactosyl triazoles **7** and **8**.

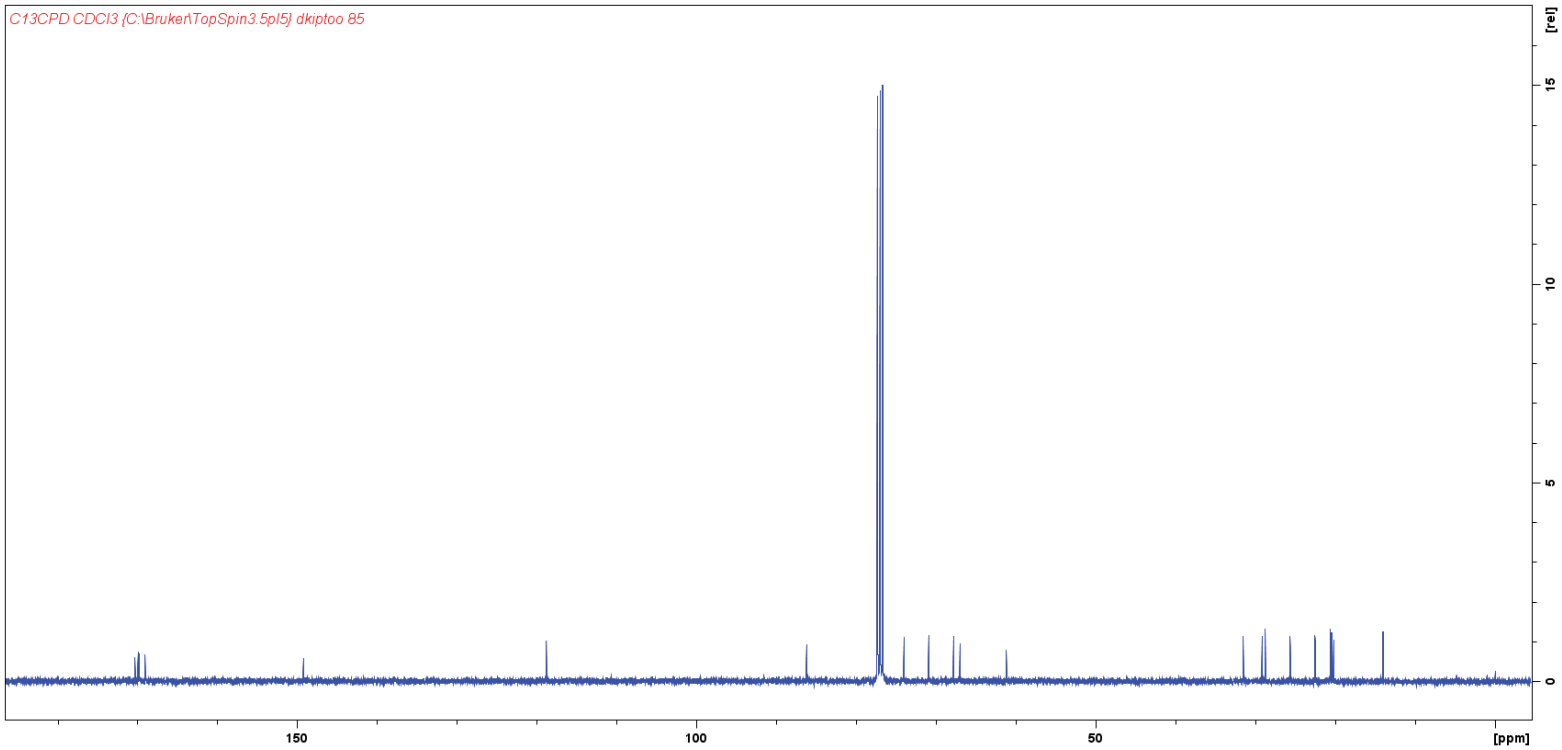

Figure 25: 100 MHz ^{13}C NMR spectrum of galactosyl triazoles **7** and **8**.

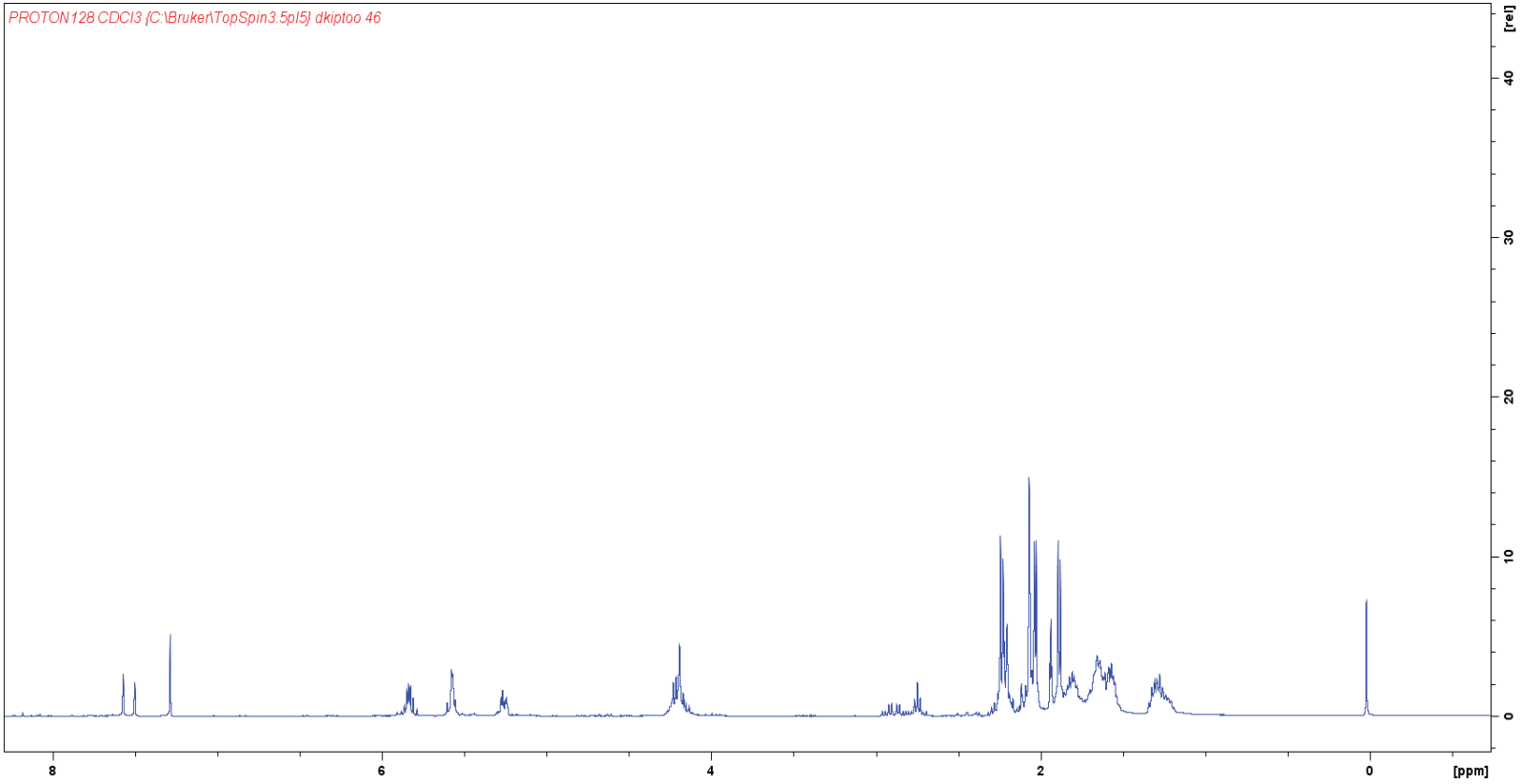

Figure 26: 400 MHz ^{1}H NMR spectrum of galactosyl triazole **9** and **10**.

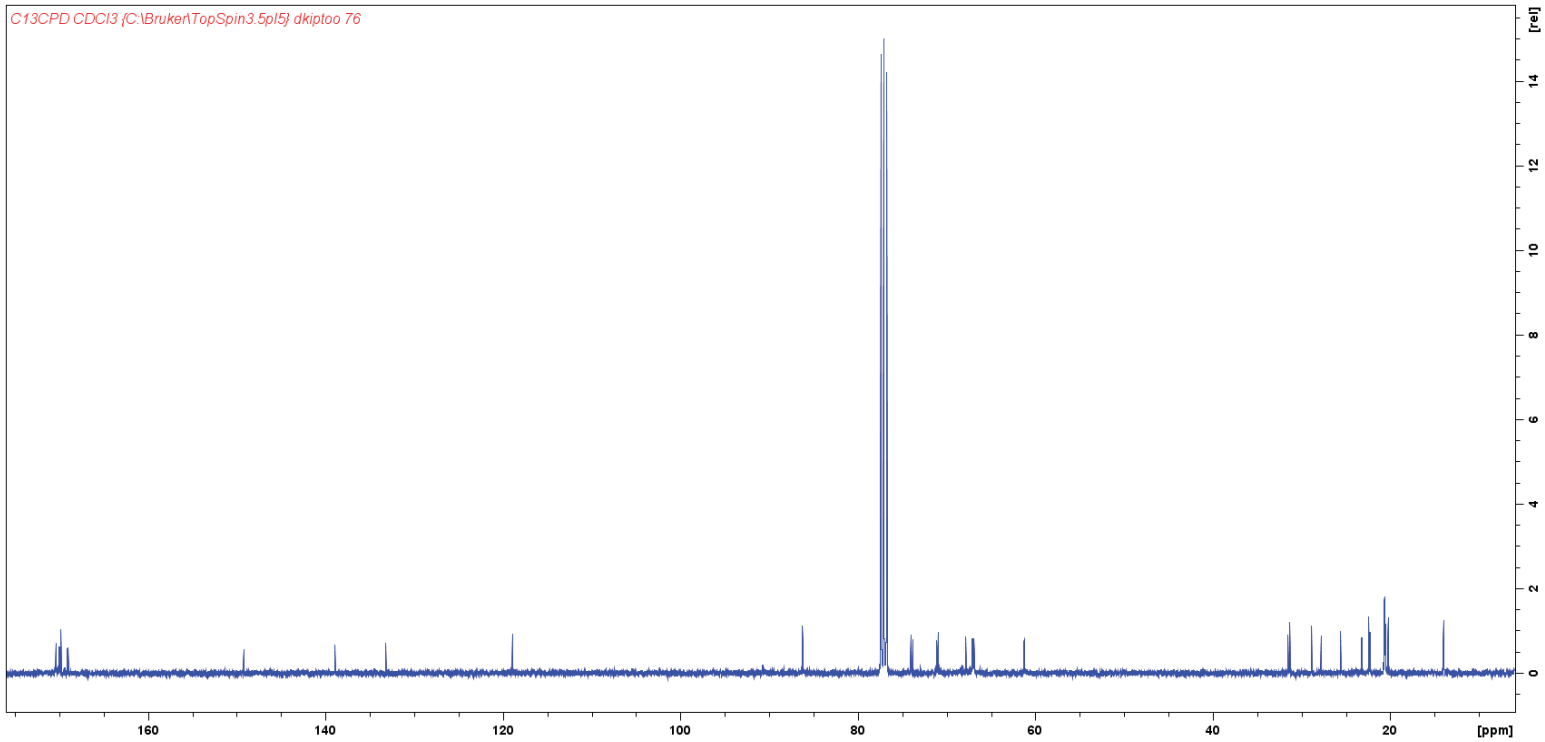

Figure 27: 100 MHz ^{13}C NMR spectrum of galactosyl triazoles **9** and **10**.

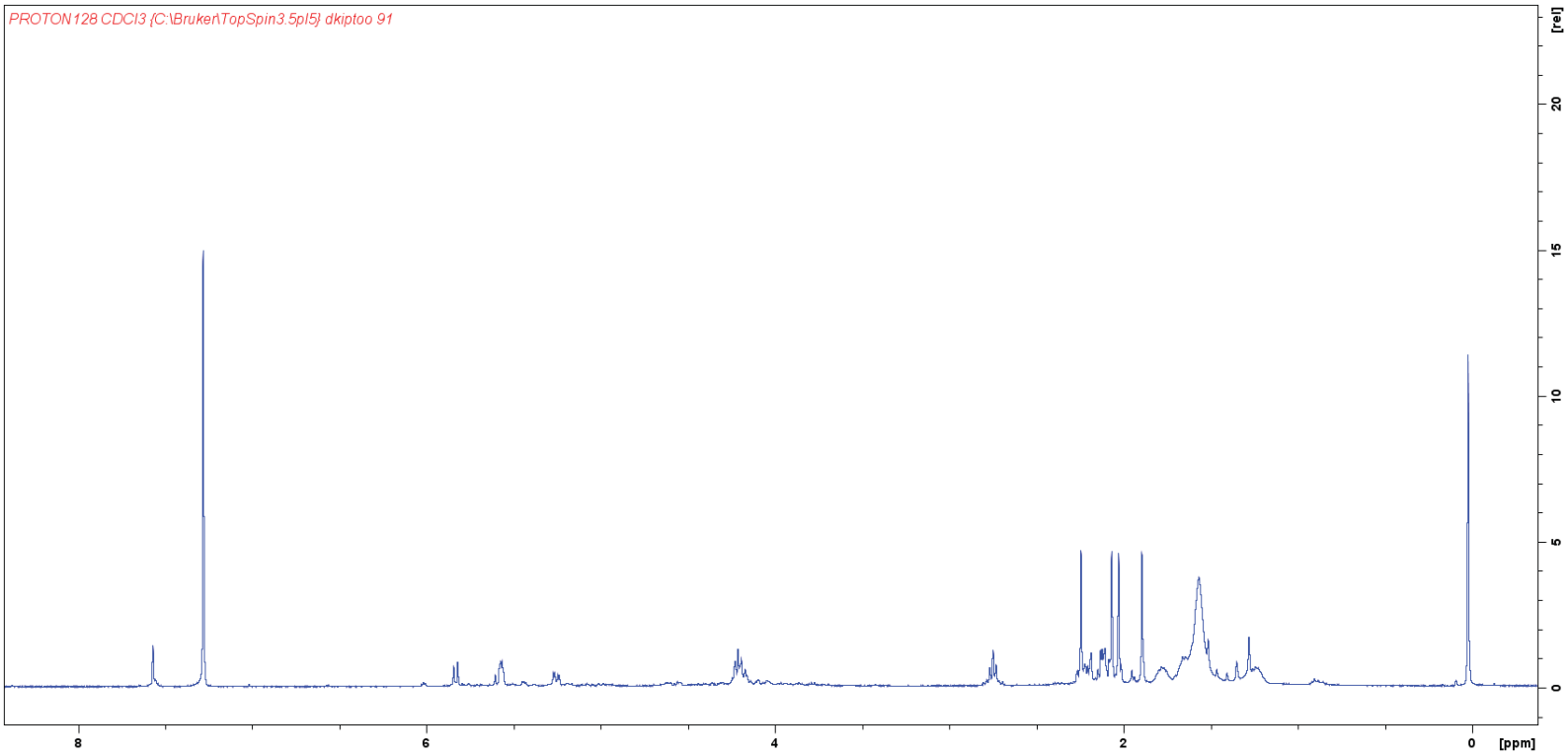

Figure 28: 400 MHz ^{1}H NMR spectrum of galactosyl triazole **11**.

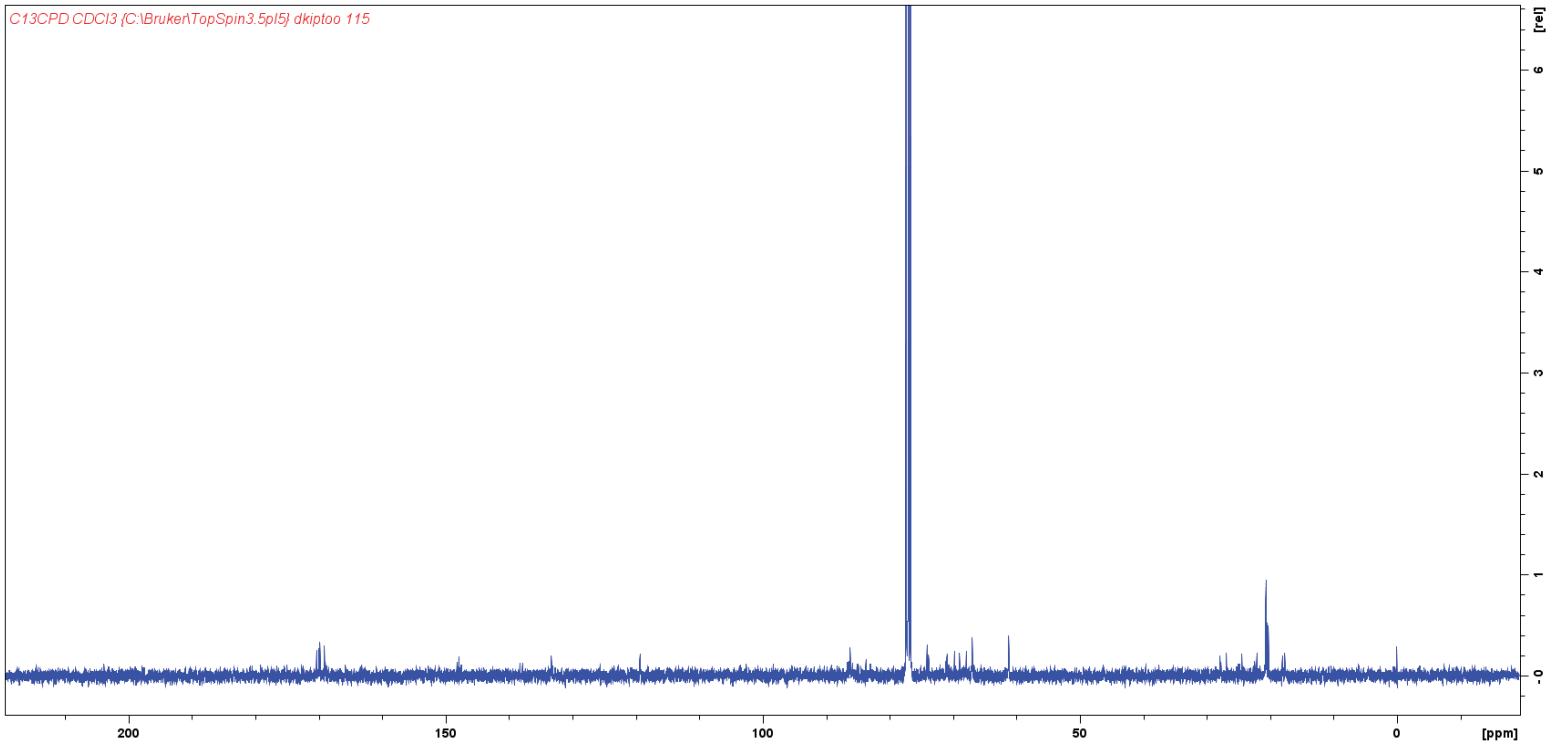

Figure 29: 100 MHz ^{13}C NMR spectrum of galactosyl triazoles **11**.

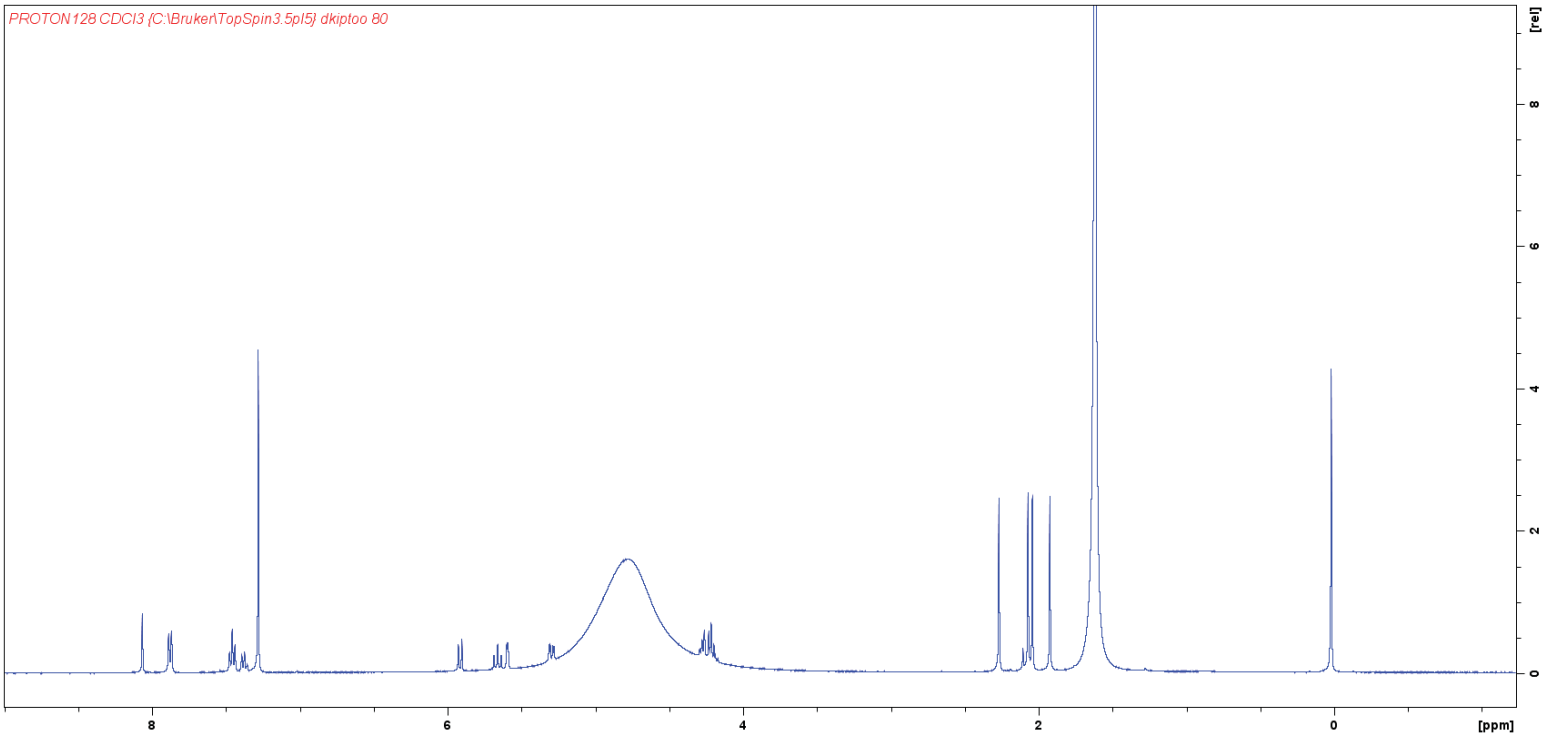

Figure 30: 400 MHz ^{1}H NMR spectrum of galactosyl triazole **12**.

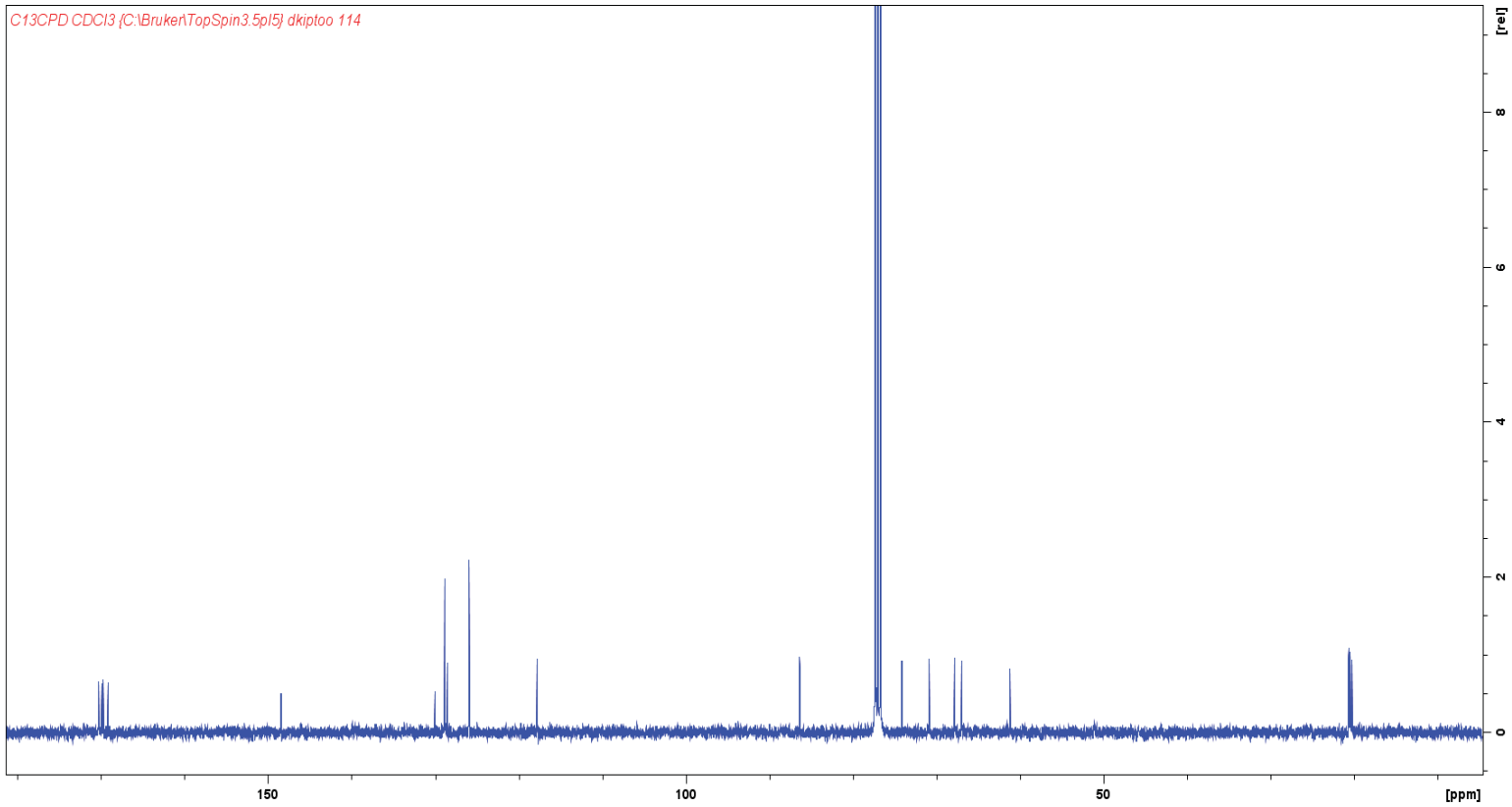

Figure 31: 100 MHz ^{13}C NMR spectrum of galactosyl triazoles **12**.

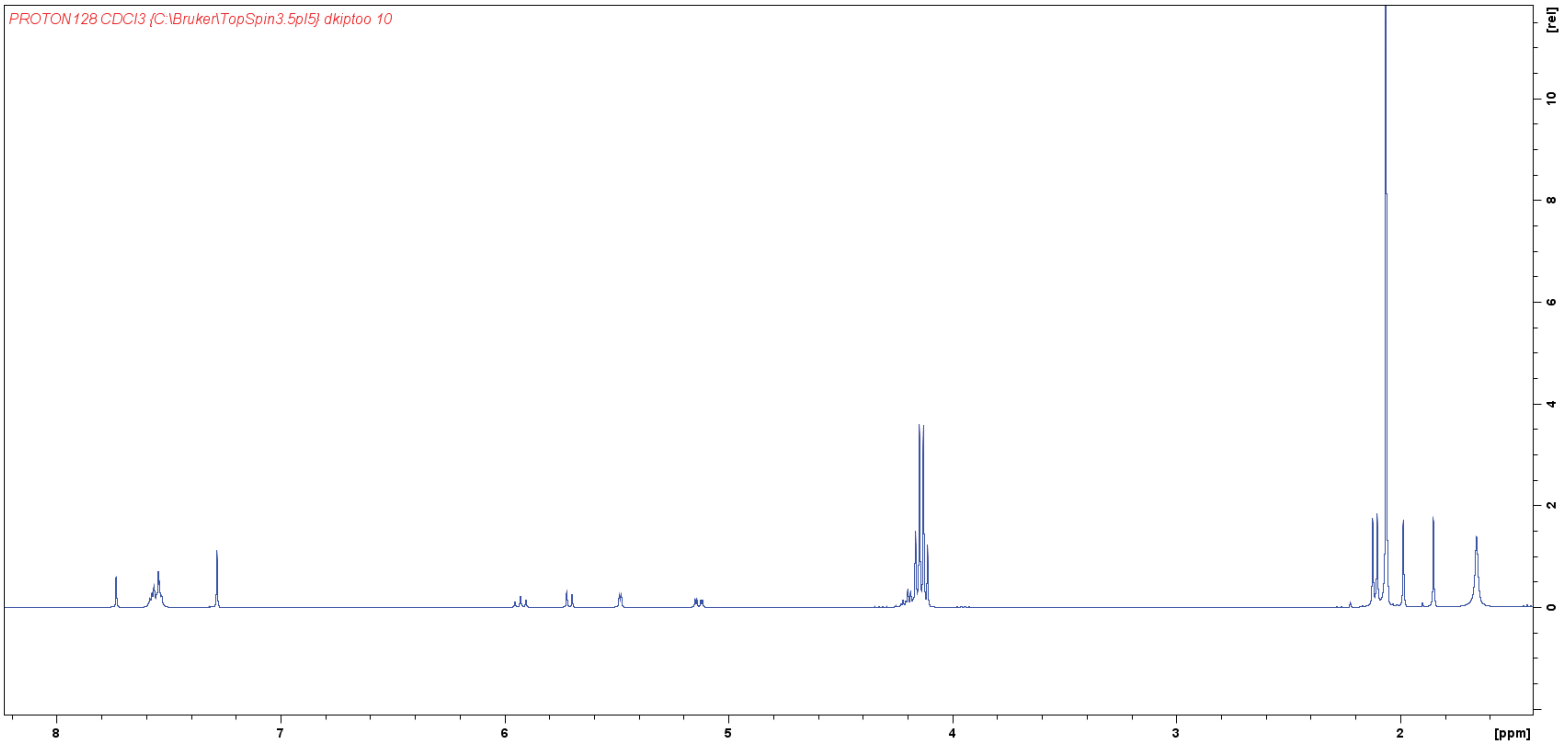

Figure 32: 400 MHz ^{1}H NMR spectrum of galactosyl triazole **13**.

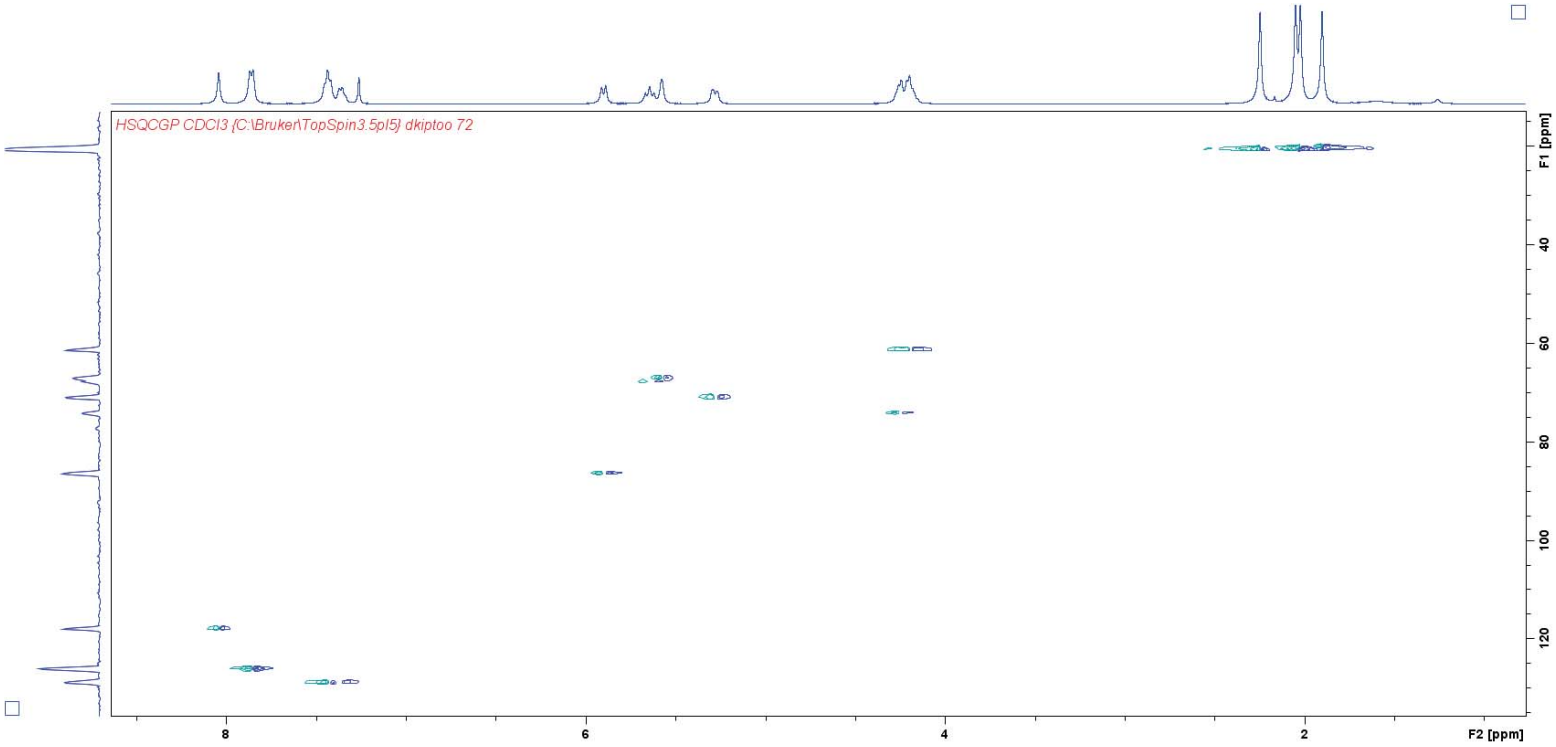

Figure 33: HSQC spectrum of galactosyl triazoles **13**.