**Synthesis of *N*-Glycosides using Azidodeoxysugars**

Monica L. Vicarel

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**Thesis Abstract**

The following work includes methods of synthesizing *N*-glycosides. The main focus is the use of azides synthesized from D-glucose and D-galactose as the precursors for the synthesis of a library of analogs that have an *N*-glycoside linkage that could potentially be tested for biological activity towards *Staphylococcus aureus* Type 5 and Type 8 capsular polysaccharides. The chemistry includes a modified Staudinger approach to be used for the synthesis of amides. Also a novel approach for the construction of 1, 2, 3-triazole-linked sugars has been studied. An investigation into one-pot conversion of non-sugar alcohols to the corresponding azides has been carried out as well as the development of chemistry mentioned above using microwave irradiation. Stereoselectivity and regiospecificity in the amide and triazole chemistry will be discussed in detail.

**Acknowledgements**

I would like to thank Youngstown State University Chemistry Department and the School of Graduate Studies for providing me the opportunity to pursue my master's degree. I would like to express my gratitude to Dr. John Jackson and Dr. Timothy Wagner for being committee members and giving suggestions when needed.

I also would like to convey my thanks to my friends and family for their support through the years, I truly appreciate it. Very special thanks to my sisters, and two brother-in-laws (Annie, Gina, Jerry and Kevin) for their encouragement and support through the years. Also thanks for giving good advice when needed. Most of all I would like to thank my Dad and Mom for their wisdom, inspiration, and most of all their unconditional love and support, what I am today is because of your efforts and dedication.

I would like to thank the past memebers of the Norris group for their guidance. I also would like to thank Basit, Julia, and Sara for their help and I want to wish them the best of luck in their future endeavors. I also would like to thank Ryan, Adam, Dobosh, and Mike for keeping things interesting in lab. I want to wish them the very best with the rest of graduate school and what they do in the future as well. Also to the whole Norris group thanks for the fun filled days.

I would like to express my gratitude to Dr. Peter Norris for his guidance, encouragement, and feedback that has helped me through the years. I would like to thank you Doc for providing me the research experience and skills that will be instrumental in achieving my professional goals. Also best of luck with your career and where ever life takes you.

**Table of Contents**

**List of Schemes**



**List of Tables**

**List of Figures**

**Introduction**

Carbohydrates are some of the most common organic molecules found in nature, the simplest examples of which are represented by the chemical formula $(C{\cdot}H_2O)_n$. Carbohydrates are a class of molecules that can participate in an assortment of processes.[1] They are associated with metabolic precursors to other biomolecules and have various biological roles. Carbohydrates are involved in cell growth, cell regulation, and cell differentiation. They are used as building blocks, biological tools, and in some cases have the potential to be drug candidates. The immunological response of the human body to inflammation is associated with carbohydrates. Carbohydrates are involved in the response to bacterial/viral infections caused by *salmonella* and *E. coli* strains. Carbohydrates also play a role in the metastasis mechanism where a tumor spreads from the primary site to other parts of the body, which is facilitated by cancer cells with carbohydrates located on their surface. These cells become viscous, which allows for them to mesh with carbohydrate-binding receptors that are accessible on the lining of the blood vessels.[2]

In addition, carbohydrates are covalently attached to an extensive assortment of other molecules. They include *glycolipids* in which the carbohydrate is linked to a lipid, and which are common components of biological membranes. Proteins that are covalently linked to carbohydrates are called *glycoproteins*. These two classes of biomolecules are generally termed *glycoconjugates* and are important components of cell walls and extracellular structures in animals, bacteria, and plants.[3] The apparent arrangements of carbohydrates on lipids and proteins along with their appearance on the surface of cells seem to be instrumental in the variety of transformations that take place

in the human body. There is a need therefore to understand the structure of carbohydrates from the simplest form known as *monosaccharides*, to the most complex *polysaccharides*. This is imperative for understanding the varied functions of carbohydrates in biological systems.

**Carbohydrate Structure and Classification**

The simplest carbohydrates are the monosaccharides or "simple" sugars. An example of a simple sugar is D-glucose (Figure 1), which is the most abundant carbohydrate in nature. It has a central role in biochemistry and is stored in the form of dimers and polymers. The most stable conformation of glucose is when the six-membered ring is closed and all the functional groups are equatorial.

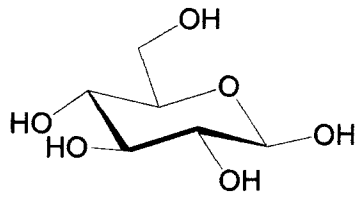
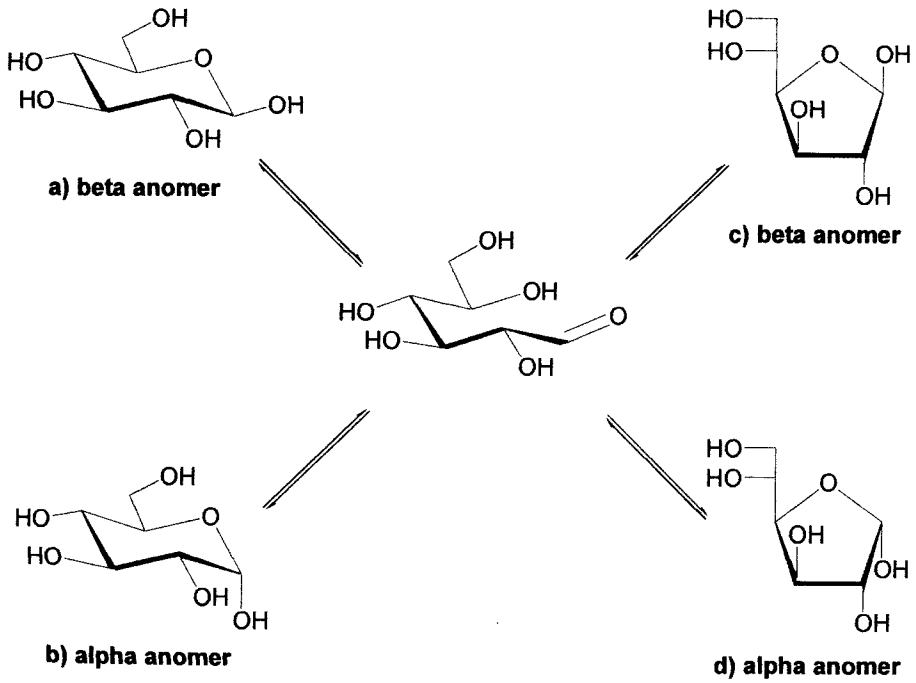



**Figure 1:** Structure of D-Glucose.

Monosaccharides are ketone and aldehyde derivatives of straight-chain polyhydroxyl alcohols containing at least three carbon atoms. They are subdivided into two classes according to the chemical nature of the carbonyl group and the number of the carbon atoms. If the carbonyl group is a ketone, the sugar is a *ketose* and if the carbonyl is an aldehyde, the sugar is an *aldose*. The smallest monosaccharides, those with three

carbon atoms, are *trioses*; the other sugars with four, five, six, and seven carbons are known as *tetroses*, *pentoses*, *hexoses*, and *heptoses* respectively.[4]

In solution monosaccharides such as D-glucose can exist in (at least) three different forms (Scheme 1). The alcohol at one end of a monosaccharide can attack the carbonyl group at the other end to form a cycle. When a six-membered ring is formed, the product of the reaction is called a *pyranose* (**a**, **b**) and after the formation of a five-membered ring, the product is called a *furanose* (**c**, **d**). There are two possible structures for the pyranose and furanose forms of monosaccharides, which are α- and β-anomers. The α and β designations are used to give the orientation of the hydroxyl group at the *anomeric* carbon relative to the $-CH_2OH$ group at carbon 5. The β designation is used when both groups are pointing in the same direction; the designation is α when these groups point in the opposite direction.




**Scheme 1:** Different forms of D-glucose in solution.

In the stereochemical nomenclature of sugars the assignment of D or L is given according to the orientation of the hydroxyl group at the first stereocenter from the bottom in the Fischer notation (Figure 2). In the example of D-galactose the hydroxyl group is on the right side of the chain and L-galactose has it on the left side.

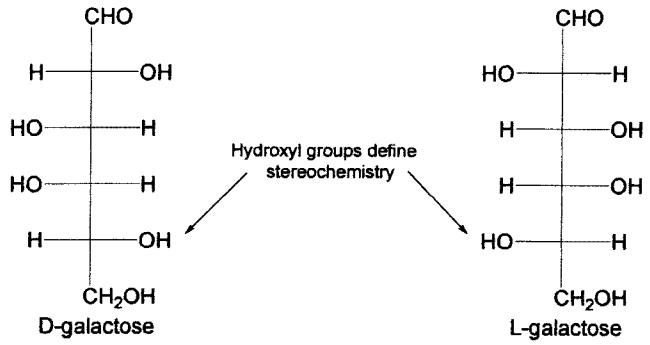



**Figure 2:** D- and L-galactose configurations.

Sugars that differ only by the configuration around one carbon atom are known as epimers of one another. D-Glucose and D-mannose are therefore epimers with respect to C2 (Figure 3).[5]

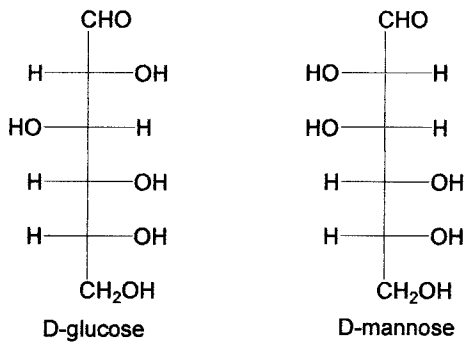



**Figure 3:** An example of epimers.

Another class of carbohydrates is disaccharides, which are formed by condensing a pair of monomer units. When one monomer unit is linked to another monomer unit the

resulting linkage is known as a glycosidic bond. An example of a disaccharide is maltose, which is a product of the enzymatic hydrolysis of starch and is the precursor to D-glucose in the digestive tract (Figure 4).[3]

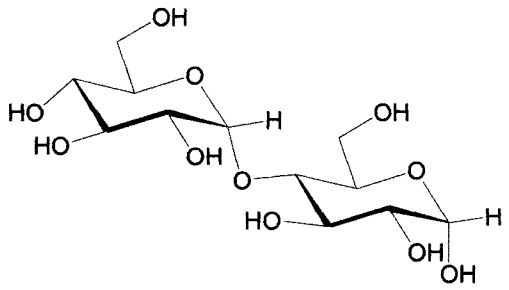



**Figure 4:** Maltose, an example of a disaccharide.

The monosaccharides and disaccharides represent only a small fraction of the total number of carbohydrates in nature. There are *oligosaccharides*, which from the Greek word *oligo,* means "a few." They consist of three to ten condensing pairs of monomer units that are also linked by glycosidic bonds.[6] The great bulk of carbohydrates in nature are known as *polysaccharides*, which typically have high molecular weights. Polysaccharides are also known as *glycans* and they have the ability to form branched structures, which differentiates these sugars from proteins and nucleic acids. These complex sugars are not only linked by glycosidic bonds but may also be linked *via* covalent bonds to amino acids, peptides, proteins, lipids, and other structures. Polysaccharides have two main functions; they serve as storage materials such as starch and glycogen (Figure 5), and give structure to cell walls for example in the form of cellulose.[7]

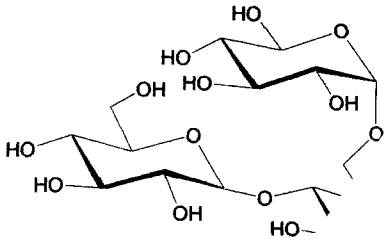


**Figure 5.**

**Glycosides**

There are numerous important types of carbohydrate derivati
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molecules play significant roles in various biological processes and medicinal development.[9] Glycosides are sugars in which the hydroxyl group at the anomeric position (of the so-called *glycosyl donor*) is substituted with a functionality (the *glycosyl acceptor*) thus forming a compound with an *–OR, -CR, -NR, -SR* linked *via* the anomeric carbon.[10] The result is glycosidic linkages, which are known as *O*-glycosides, *C*-glycosides, *N*-glycosides, and *S*-glycosides respectively. The common factor is the hydrophilic feature they introduce, which infers water solubility, selective polarity, and in appropriate situations amphiphatic character, which implies that the substance contains both polar and nonpolar regions so it is hydrophobic and hydrophilic.[9]

*S*-Glycosides are constructed when sulfur is used to replace oxygen as the glycosidic bond linkage. There are three reasons for making *S*-glycosides, the first being the relative ease of synthesis. Secondly there are well documented cases that include an analogous conformational preference about the thioglycosidic and aglyconic bonds both

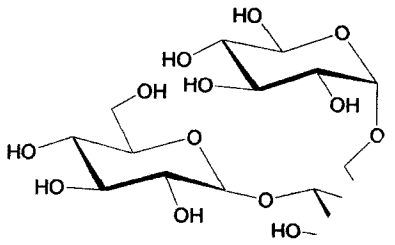

**Figure 5.**

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when complexed with a protein and in solution, and the third reason is they have less of a chance to undergo enzymatic and acid hydrolysis.[11] Bundle *et. al.* reported that *S*-linked immunogens (Figure 6), that were part of conjugate vaccines generated an antigen-specific immune response that was the same or higher than the response using *O*-linked immunogens.[11]

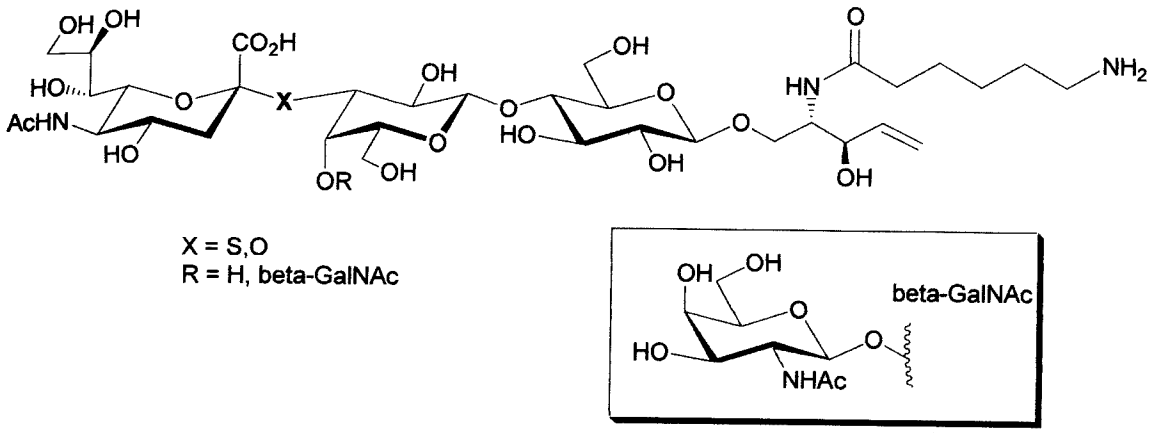



**Figure 6:** *S*- and *O*-linked synthetic carbohydrate antigens.

Another example of an *S*-glycoside with biological activity is Lincomycin, which is part of a group of related thioglycoside antibiotics that contain an amide bond. (Figure 7). This particular compound is used to combat infections that are brought about from Gram-positive bacteria and anaerobic organisms.[9]

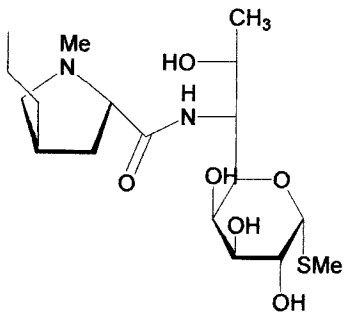



**Figure 7:** Lincomycin.

*C*-Glycosides are interesting compounds since they are stable towards acid and enzymatic hydrolysis so in turn they can be maintained in the body to fight infection or disease. Also, these glycosides do not form hydrogen bonds. It is known that *C*-glycosides mimic the overall effects of *O*-glycosides.[9] One example of a *C*-glycoside is Gilvocarcin V, which is a product of *Streptomyes griseoflavus*. It shows potent bactericidal, virucidal, cytotoxic, and antitumor activities. This compound also promotes protein-DNA cross-linking when photo-activated by nearby ultraviolet light and plays a vital role in DNA replication and transcription.[12] Another example of a *C*-glycoside is Kidamycin, which is part of the class known as Pluramycins. This particular compound has antimicrobial and antitumor activity (Figure 8).[13]

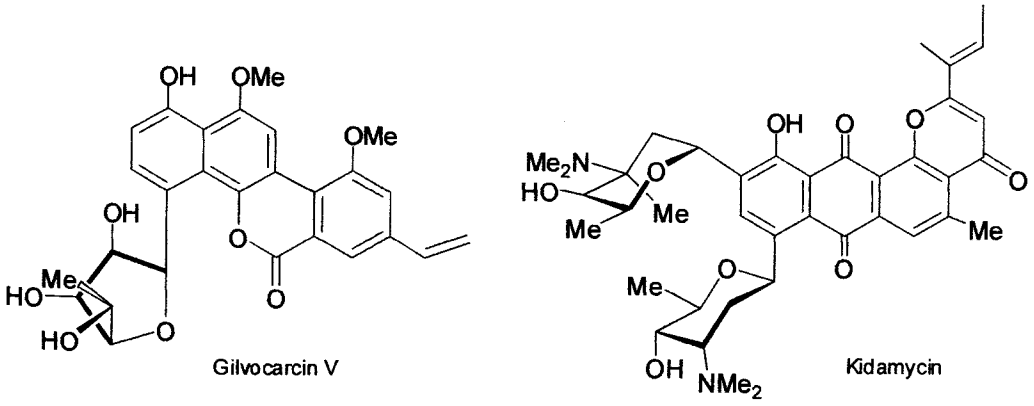



**Figure 8:** *C*-Glycoside antibiotics.

*O*-Glycosides can be found everywhere in nature from animals, plants, and bacterial sources. Some examples of *O*-glycosides that have antibiotic activity are shown in Figure 9. Erythromycin is an antibiotic used to treat many different types of bacterial infections such as *S. aureus*. Adriamycin is an anthracycline possessing anti-Gram-positive activity that is useful in fighting soft tissue sarcomas and leukemias. Another is Streptomycin, which is part of the amino glycoside family of antibiotics, with one of its uses being to treat tuberculosis.[14]

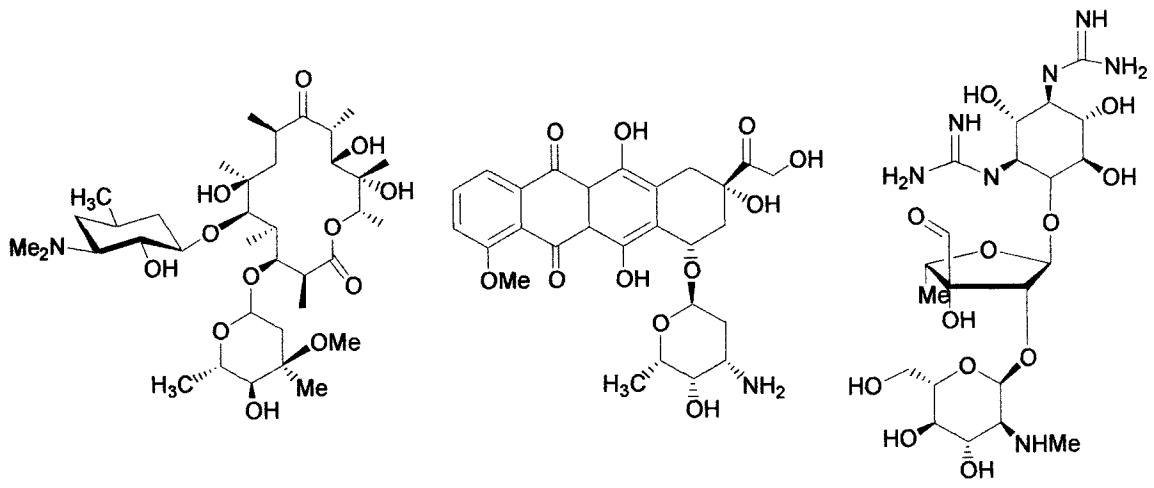
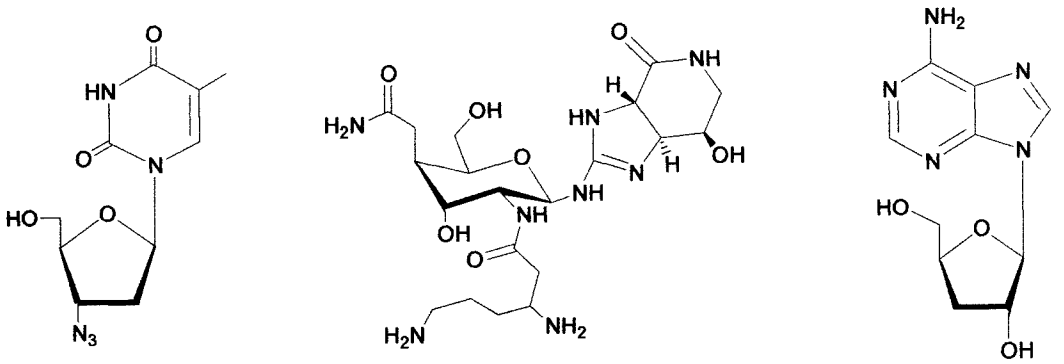



**Figure 9:** *O*-Glycoside antibiotics

*N*-Glycosides are another class of carbohydrate derivative that is studied extensively in chemistry, and include naturally occurring microbiological metabolites, nucleosides, nucleotides, and nucleic acids. As well as their important roles in RNA and DNA, nucleosides have been used as anticancer and antiviral drugs because they work

primarily by inhibiting chain elongation of nucleic acid polymers or by competitive inhibition of associated enzymes. *N*-Glycosides have been of interest because a number of these compounds have biological activity against the HIV virus; an example is azidothymidine, (AZT, Figure 10).[15] Another *N*-glycoside compound that has activity against both Gram-positive and Gram-negative organisms is Streptothricin F, which is based on the carbohydrate 2-amino-2-deoxy-D-gulose. Cordycepin, a cytotoxic agent, is an *N*-glycoside that was found to inhibit the growth of *Bacillus subtillis*, *avaim tuberclebacillus*, and Ehrlich tumor cells. Figure 10 shows these three compounds.[9]




AZT Streptothricin F Cordycepin

**Figure 10:** *N*-Glycoside antibiotics.

We are presently interested in synthesizing *N*-glycosides using glucosyl and galactosyl azides as our starting materials. The process of *N*-glycosylation inherently plays a vital role in biology and the process is crucial for the post-translational modification of proteins. One general characteristic of glycoproteins is an oligosaccharide connected to a β-glycosyl amide that is part of an Asn residue found in

the consensus sequence Asn-Xxx-Thr/Ser (Xxx is any amino acid except Pro).[16] Also, *N*-glycosides are involved in the proper folding of proteins and for the most part *N*-glycans are present but not always needed for this process to occur. [17]

The two main types of *N*-glycosides that are explored here are glycosyl amides and 1,2,3-triazoles. The reason for taking a look at *N*-glycosyl amides is due to the fact that amides are usually quite stable molecules in acidic and basic conditions. The 1,2,3-triazole compounds are appealing to many scientists since these molecules usually cannot be oxidized or reduced, which makes them useful linkers in bioorganic chemistry.[18] The process of hydrogenation and oxidation also does not have an effect on the *N*-glycosyl amides.[19] Amide- and triazole- linked carbohydrates therefore represent potentially stable mimics of *O*-glycosides.

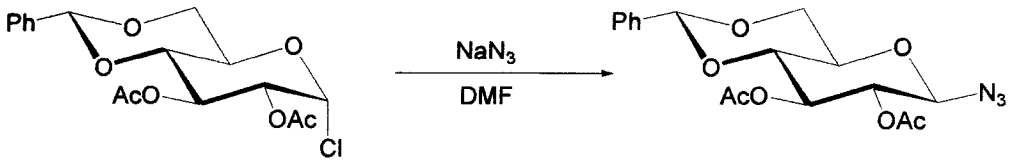
**Azide Chemistry**

Peter Grieβ discovered organic azides over 150 years ago and since that discovery a variety of methods have been applied to the synthesis and reactions of these electron-rich and versatile molecules in organic chemistry. The most modern developments in azide chemistry include applications in peptide chemistry, combinatorial chemistry, and the synthesis of heterocycles. Azide chemistry has been an essential tool in developing an assortment of reactions that have been proven useful in discovery chemistry. Some examples of these processes are cycloadditions, aza-ylide chemistry, Staudinger ligation, and even a collection of rearrangement reactions, which for example include the Curtis, Boyer-Aubé, and the Sundberg reactions. One consequence that can happen if not cautious with handling azides is that they can be explosive, due to decomposition, with

the resultant release of nitrogen. An example is sodium azide, which is used for airbag deployment in automobile accidents.[20]

There are many different preparations available for the formation of azide compounds. Some that are widely used include diazo transfer where there is an introduction of $N_2$ taking place, diazotization is also available, as is the cleavage of triazines and similar compounds.[20]

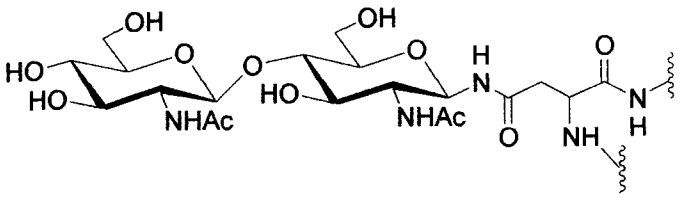
The most widely used reaction for the formation of carbohydrate-derived azide compounds, and the reaction applied in this research, is the nucleophilic displacement of a leaving group (usually from a glycosyl halide) with the introduction of nitrogen at the anomeric position (Equation 1).




**Equation 1:** Nucleophilc displacement on glycosyl chloride to form azide.

**Amide Chemistry**

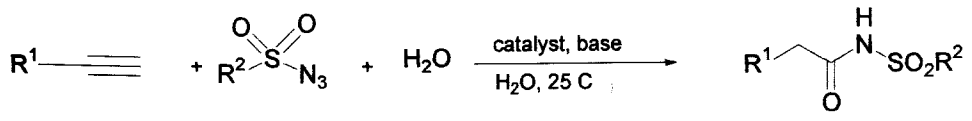
*N*-Glycosides, particularly amides, have biological relevance because they are known to be attached to other biomolecules to form glycoconjugates, for example glycoproteins.[21] Glycoproteins are attached to carbohydrates such as glucose, galactose, lactose, and sialic acid to just name a few. Figure 11 shows an example of a glycoconjugate that contains an amide linkage, which is through the side chain of aspargine.[22]



β-D-GlcNAc-(1,4)- β-D-GlcNAc-(1,*N*)-Asn

**Figure 11:** Amide-linked glycoconjugate.

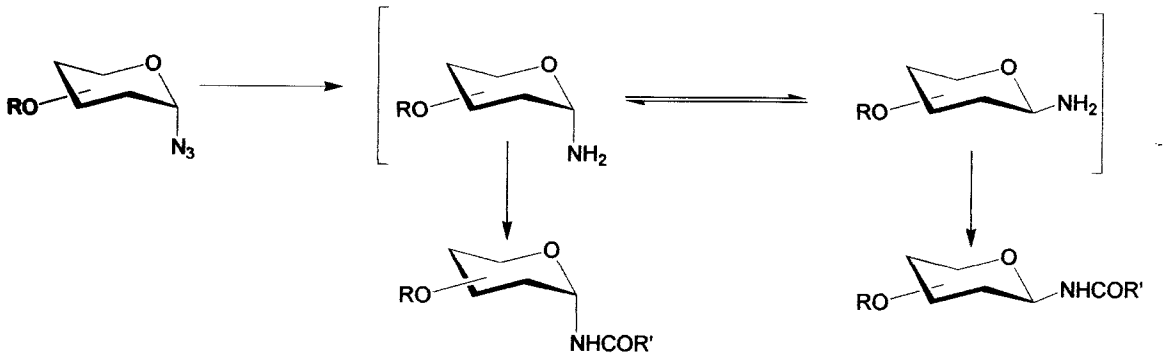
Amides are a chemical derivative that can be synthesized by a variety of methods, for example by reacting an amine with acyl chlorides, anhydrides or esters. McDonald and Danishefsky were able to form a β-azide derivative from a sulfonamide compound and then coupled it with an Asp derivative to give the corresponding amide product.[23] Cho and coworkers developed a copper-catalyzed process for the formation of amides; the reaction is regioselective and only terminal alkynes react (Equation 2). The mechanism for this procedure is not known in detail but there are two different trains of thought about how these amides are produced. The first possibility is the formation of an imidate intermediate, which then tautomerizes to give the desired amide product. The second possible pathway assumes amination takes place and converts a copperacetylide to an *N*-sulfony amide followed by the addition of water, which gives the allenamide and then the amide through tautomerization. [24]




**Equation 2:** Hydrative amide synthesis.

Two one-pot procedures for the synthesis of *N*-glycosides have been reported by Garcia-Lopez and coworkers, which features mild reaction conditions for the formation of chloroacetyl and *S*-acetylmercaptoacetyl *N*-glycosides. The azido group is reduced to the corresponding amine with the use of two different reductants, a phosphine derivative (*n*-$Bu_3P$) or a thiol derivative (1,3-propanedithiol).[25]

Problems that can occur in this chemistry include the formation of mixtures of the alpha and beta products due to the fact that the glycosyl amine derivative isomerizes (Scheme 2). The starting point is the use of a sugar-derived azido group, which gets reduced to the corresponding amine, but there are alternatives that can be used instead of amines such as glycosyl sulfoxides, glycosyl isothiocyanates, and *O*-pentenyl glycosides. Stereoselectivity continues to be a major issue in this type of process.[26]

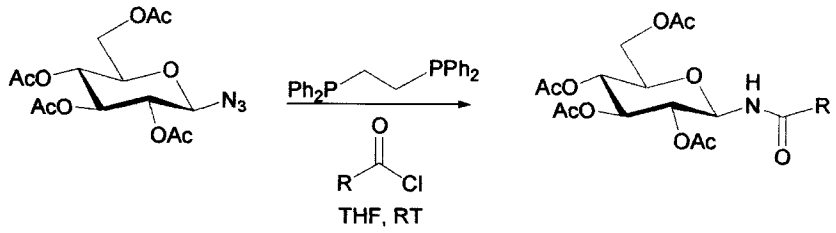



**Scheme 2:** Glycosylamine isomerization.

One of the more popular and well known routes to glycosyl amides is the Staudinger approach and its modifications. Our research on the formation of glycosyl amides takes a look at this synthesis, which uses a phosphine derivative in the reaction between an azide and acid chloride to afford the desired amide product. The modified

Staudinger synthesis has become a widely applied method for the formation of glycosyl amides. Boullanger *et al.* have applied the method using 1,2-*trans* β-glycosyl azides and reacting the sugar with acyl chlorides in the presence of triphenylphosphine at room temperature. This procedure gave the glycosyl amides in good yields and high β-stereoselectivity at the anomeric position. The same reaction was preformed on α-glycosyl azides, which led to mixtures of α- and β-glycosyl amides. The evaluation of the best solvents needed was important for optimal results. Triphenylphosphine being added late to the reaction gave the greatest yields and fastest reactions.[27]

The Norris Group has applied this modified synthesis using polymer-supported reagents but these reagents become too expensive for scaled-up reactions. The use of another phosphine derivative, 1,2-bis-(diphenylphosphino)ethane (DPPE) has been explored and gave very good results (Equation 3).[28] Libraries of glycosyl amides were made using various acid chlorides with DPPE as the phosphine derivative and the scope of this procedure was investigated in detail.




**Equation 3:** Application of DPPE in the modified Staudinger synthesis.

## 1,2,3-Triazole Chemistry

Recently there has been an increased interest in the synthesis of 1,2,3-triazoles since these compounds are important to the pharmaceutical industry. As stated before

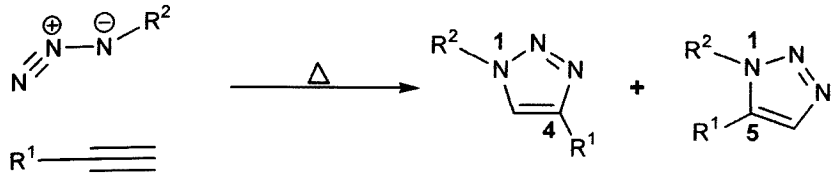
triazoles are very stable molecules and are of great interest since they are not seen in natural products and are chemically resistant to metabolic processes.[29]

Triazole derivatives are used as dyes, photostabilzers, and even for corrosive prevention of copper and copper alloys in factory environments.[30] These compounds display a variety of biological activities such as antitumor,[31] antiviral,[31] and antimicrobial.[32] 1,2,3-Triazoles also are intermediates used in the synthesis of oxazole analogs and oxazole-containing natural products. They can serve as reverse nucleosides, which in turn can be effective in stopping the HIV virus.[33] Triazoles have been known to act as β-lactamase and metalloprotease inhibitors as well as anticonvulsants.[34]

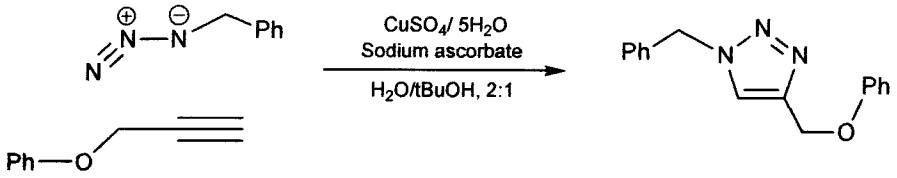
A recent growing phenomenon in chemistry has been the concept of "click reactions," which have the potential to become an important part of drug discovery. This is a new approach that can lead to optimizing or simplifying existing methods and quickly produce libraries of analogues for drug screening to find a treatment for a disease. For a reaction to be termed a click reaction, it needs to be wide in scope, easy to perform, high yielding, insensitive to water and oxygen, use readily available reagents, and feature simple reaction workup and product isolation without requiring chromatographic purification.[19]

The most recognized method for the synthesis of 1,2,3-triazoles that is also an example of a click reaction is the 1,3-dipolar cycloaddition of azides to alkynes. The major problem that arises is the control of regioselectivity in the formation of the heterocycle when the reactants are heated together under mild conditions (Equation 4). It is known through experimentation that electron-deficient alkynes are more reactive in this procedure affording the desired product more quickly and efficiently.[30]

Sharpless *et al.* reported that Cu(I) species in catalytic amounts can control the regiospecificty affording the 1,4-disubstituted 1,2,3-triazoles. The Cu(I) catalyst works better when formed *in situ* by applying the use of Cu(II) salts and reducing it with ascorbic acid (vitamin C) or sodium ascorbate as the reductant. (Equation 5).[35]

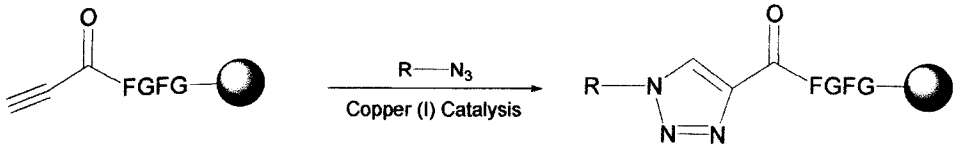


**Equation 4:** Synthesis of 1,4- and 1,5-disubstituted 1,2,3-triazoles.




**Equation 5:** Synthesis of 1,4-disubstituted 1,2,3-triazoles.

Meldal *et al.* solved the regiochemistry problem by using a copper(I) catalyst to afford 1,4-disubstituted peptidotriazoles in peptide backbones or side chains on solid support from the 1,3-dipolar cycloaddition of terminal alkynes to azides (Equation 6). The ability to control the regiospecificity of the 1,4-disubstituted 1,2,3-triazoles along with high yields and product purity allows the potential for a more diversified library of compounds that can be tested as drug candidates.[30]



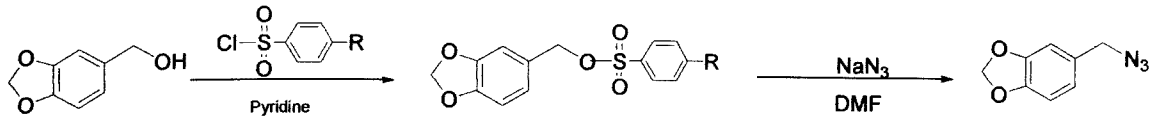

**Equation 6:** Peptidotriazoles on solid phase.

Wang and his coworkers were able to produce triazole-linked glycoconjugates and neoglycoconjugates in a one-pot synthesis using either unprotected or acetate-protected sugars in the Cu(I) catalyzed 1,3-dipolar cycloaddition of azides and alkynes.[36] This type of click reaction has become a valuable part of research when synthesizing combinatorial libraries for drug screening and will continue to be modified upon to develop medicinal therapies.

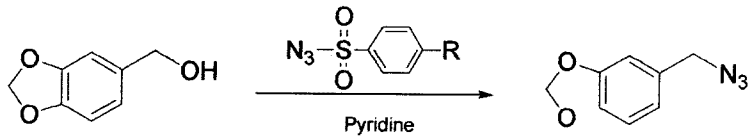
**Conversion of Non-sugar Alcohols to Non-sugar Azides**

The ability to afford specific products in a single step or one-pot procedure instead of a multi-step procedure is becoming popular since it would eliminate a lot a laborious work and would allow for the much more expedient production of more diversified compounds. An ongoing development in the Norris group is the direct conversion of a non-sugar alcohol to a non-sugar azide by applying a newly discovered one-pot procedure.

A classical reaction pathway for alcohol to azide transformation involves conversion of a primary alcohol to a tosylate intermediate, followed by the addition of the azide reagent (e.g. $NaN_3$) in a polar aprotic solvent such as DMF to give the desired azide product (Scheme 3). We have chosen to study the reaction of a primary alcohol with a sulfonyl azide in the presence of a base to give the corresponding azide (Equation 7).

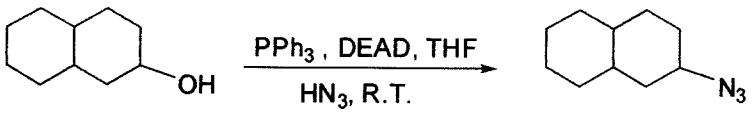



**Scheme 3:** Typical procedure for non-sugar alcohol to non-sugar azide.



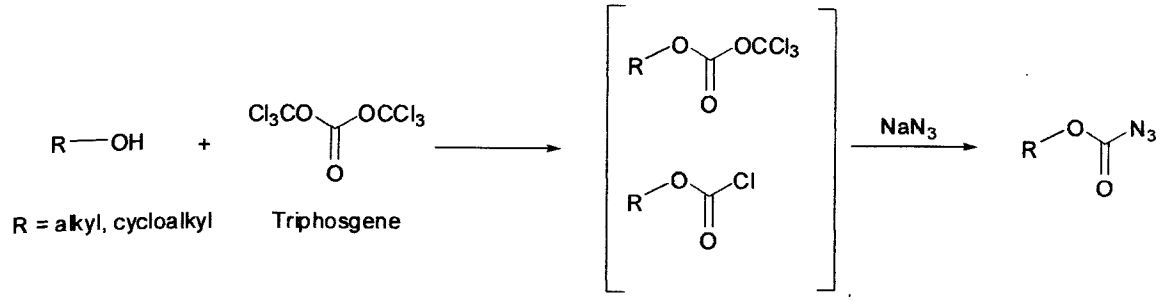

**Equation 7:** One pot procedure for non-sugar alcohol to non-sugar azide.

There are known one-pot transformations of azides from alcohols using various methods, for example employing Mitsunobu conditions where triphenylphosphine, DEAD, and an azide source in THF are used to afford the azide product (Equation 8).[37]



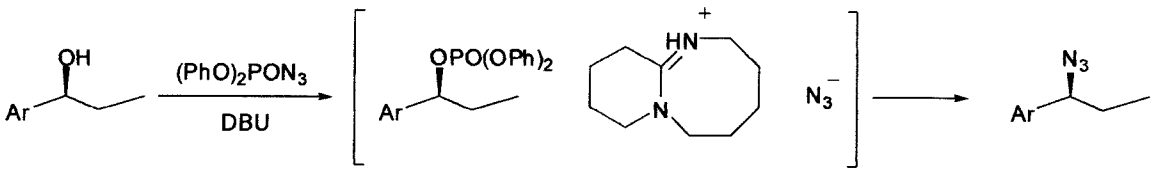

**Equation 8:** Mitsunobu conditions.

Deshmukh *et al.* used an efficient one-pot preparation of azidoformates.[38] Several chiral alcohols were reacted with triphosgene in the presence of a base, e.g. triethylamine, followed by sodium azide and the reaction was cooled at 0 °C followed by stirring at room temperature for a period of 24 hours. The reaction condition is mild, and the product is afforded in high yield with high purity (Scheme 4).[38]




**Scheme 4:** Azidoformate formation.

Thompson and coworkers discovered that Mitsunobu conditions can be avoided altogether to form azides by using DBU as a base and diphenyl phosphorazidate (DPPA) for the general transformation.[39] Mechanistically this procedure takes place through a bimolecular pathway; the first step is development of a phosphate intermediate and then the azide is formed by a $S_N2$ displacement (Scheme 5).




**Scheme 5:** Direct conversion to azide using DPPA.

A one-pot synthesis can aid in the formation of *N*-glycosides by reducing the steps it takes to afford the product. Also, this can serve as a more efficient and productive route when synthesizing an assortment of compounds that are needed for testing as potential drug candidates.

**Microwave Chemistry**

The need to introduce more environmentally safe and efficient methods has become important in synthetic chemistry over the last decade. Many have turned their attention to microwave-assisted reactions. Scientists are looking to use less hazardous materials, minimal amounts of solvent, and less energy because many still rely on the more common means of heating reactions such as oils, sand baths, water baths, and isomantles. The use of the microwave conserves energy output while the reactants and solvents are heated directly in the reaction vessel. This useful technique performs reactions at extremely high temperatures and pressures even exceeding the boiling point of the solvents being used. The fact that the reaction vessel is not involved in any transfer of heat leads to the rate of reaction being amplified.[40]

A Leukart reductive amination was studied by Loupy and coworkers and through conventional methods only a 2% yield was achieved; when microwave technology was applied the overall yield was 95%.[40] Chen and coworkers developed a method using microwave irradiation for the development of α-ketoamides as potential therapeutic agents for the treatment of such medical conditions as Alzheimer's, muscular dystrophy, and strokes.[41] Joosten *et. al.* made triazole-linked glycodendrimers with microwave-assisted synthesis using a regioselective Cu(I)-catalyzed [3+2] cycloaddition reaction.[42]

Microwave-assisted reactions increase reaction rates and yields while potentially reducing the use of hazardous materials including solvents. This technology is being applied to synthesizing amides, 1,2,3-triazoles, as well as the non-sugar azides that are discussed in this research. The Norris group is working to improve the overall synthesis of these compounds with microwave irradiation.

***Staphylococcus aureus* and Antibiotic Resistance**

The main goal of our research is to generate carbohydrate mimetics that may exhibit biological activity, particularly towards *Staphylococcus aureus*. This bacterium has been known to cause a diverse spectrum of medical conditions such as boils, pimples, and cellulitis, to more serious problems such as metastic abscesses, septic arthritis, osteomyelitis, endocarditis, and toxic shock syndrome. Interest in this bacterium comes from the increasing resistance it has developed against antibiotics. *Staphylococcus aureus* is commonly found on the skin and mucous membranes of humans.[43]

*S. aureus* is a Gram-positive bacterium, which appears as grape-like structures when viewed under a microscope. The two most common strains of *Staphylococcus aureus* that cause about 80% of the acquired infections are serotype 5 and 8. *S. aureus* develops a capsular polysaccharide (CP) around itself giving it an enhanced ability to be resistant to any treatments. This capsule is formed from three repeating sugar units comprising of *N*-acetyl-D-mannosaminuronic acid, *N*-acetyl-L-fucosamine, and *N*-acetyl-D-fucosamine.[44,45] The only distinction between type 5 and 8 is the linkages between the sugars shown in Figure 12.

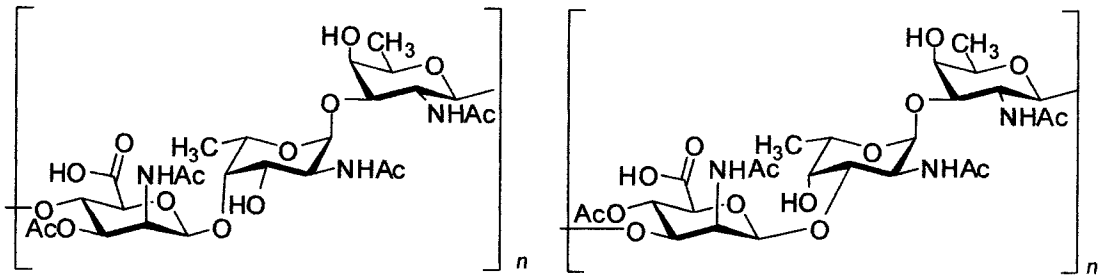



**Figure 12:** Repeat units of *S. aureus* serotype 5 & 8 capsular polysaccharides.

Today, *S. aureus* has become resistant to many commonly used antibiotics. The two best known antibiotics, methicillin and vancomycin, that were able to fight off the bacteria are now no longer useful in many casers because *staph* has developed resistant strains known as MRSA and VRSA.[43] Since *Staphylococcus aureus* bacteria are not susceptible to these treatments one can see that there is the need for some type of treatment and that the best line of defense may be to inhibit the production of the capsule and then cripple the bacterium.

**Statement of Problem**

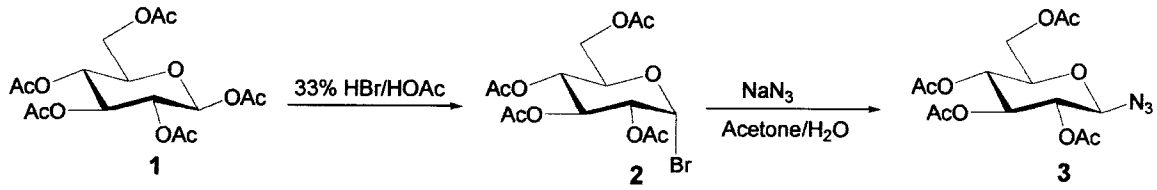
The following work describes the synthesis of *N*-glycosides using azidodeoxy sugars. Peracetylated sugars derived from D-glucose and D-galactose were chosen as starting materials. Both sugars undergo a simple $S_N1$ reaction, which results in the formation of α-glucosyl bromide and α-galactosyl bromide. Both brominated sugars then undergo an $S_N2$ reaction to give the stereospecifically *β*-glucosyl azide and *β*-galactosyl azide. The two methods investigated were a modified Staudinger approach to afford *β*-glycosyl amides and Cu(I) catalyzed 1,3-dipolar cycloaddition to form 1,4-disubstituted-1,2,3-triazoles. Also a one-pot conversion using microwave irradiation to form non-sugar azides from non-sugar alcohols was studied.

There are many disease causing bacteria that have become resistant to drug therapy are becoming a health problem. There is a growing need for new and effective treatments. *Staphylococcus aureus* is one bacterium that has developed resistant strains to the most powerful antibiotics because of a protective coating called the capsular polysaccharide, which provides protection from antibiotics. The goal of this research was to synthesize a collection of *N*-glycosides through the above mentioned approaches that may lead to sugar analogs, which could potentially inhibit the "capsule" produced by *S. aureus*.

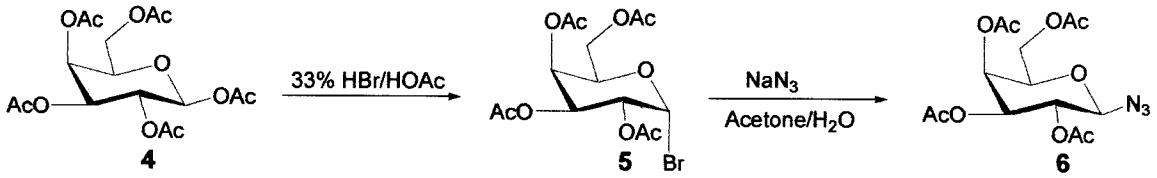
## Results and Discussion

### Synthesis of β-glucosyl and β-galactosyl azides

The focus of this research was to synthesize a collection of *N*-glycosides from readily available starting materials. The two methods used to construct the *N*-glycosides were a modified Staudinger reaction and a Cu(I)-catalyzed cycloaddition, for which the precursors are the β-glucosyl azide **3** and β-galactosyl azide **6**. We chose peracetylated D-glucose (Scheme 6) and D-galactose (Scheme 7) as our inexpensive starting materials.




**Scheme 6:** Synthesis of β-glucosyl azide **3**.




**Scheme 7:** Synthesis of β-galactosyl azide **6**.

The β-glucosyl azide **3** and β-galactosyl azide **6** were synthesized in two easy steps. The first step involves the treatment of β-D-glucose pentaacetate and β-D-galactose pentaacetate with 33% HBr in AcOH. The reactions proceed *via* an $S_N1$ pathway to afford α-glucosyl bromide **2** and α-galactosyl bromide **5**. The preferential formation of the α-anomers of the bromides is due to the anomeric effect, which only operates when

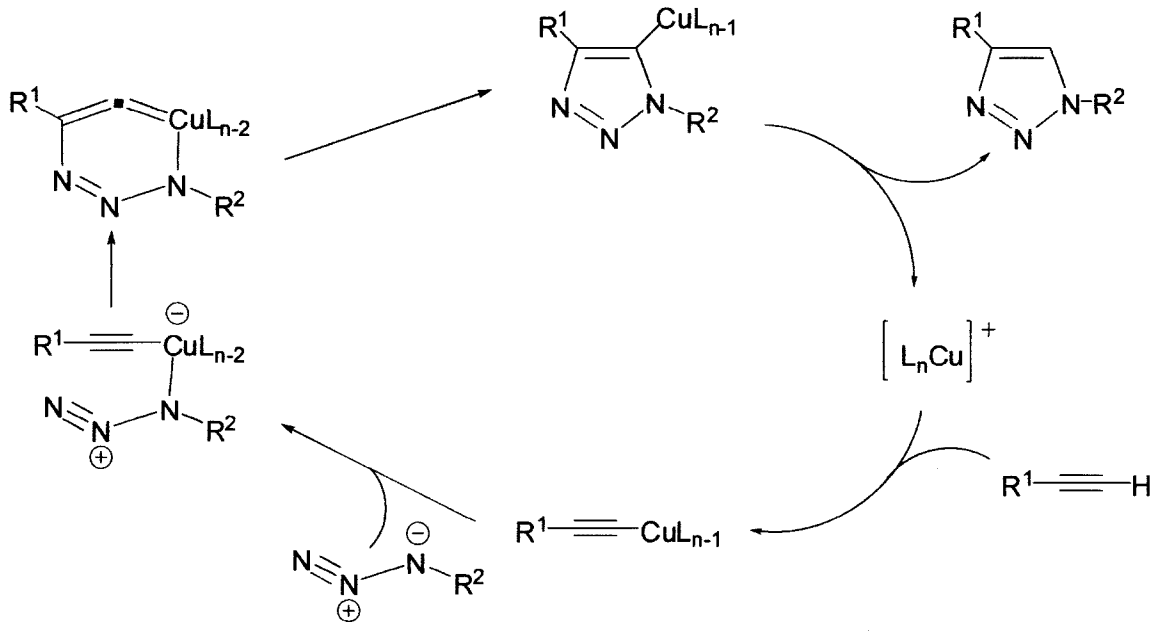
the anomeric substituent is an electronegative atom or group. The anomeric effect is the partial donation of one of the lone pairs on the endocyclic oxygen atom (*n* orbital) into the antibonding (σ*) orbital of the C-Br bond. TLC for both reactions showed the complete consumption of the starting material and the appearance of a new spot burning at a higher $R_f$ value than the acetylated starting materials. Investigation of the 1H NMR spectra of **2** and **5** showed the disappearance of the C-1 proton signal (5.70 ppm) for the starting material and the appearance of a new doublet signal at 6.60 ppm with the coupling constant for **2** being 4.02 Hz and **5** being 3.84 Hz respectively. The small coupling constants for both the α-glucosyl bromide **2** and α-galactosyl bromide **5** are an indication that the products are indeed the α-anomers.

Both α-glucosyl bromide **2** and α-galactosyl bromide **5** were reacted with sodium azide in a 5:1 acetone/water mixture, which afforded β-glycosyl azides **3** and **6** by a stereospecific $S_N2$ reaction. The completion of the reaction was indicated by TLC, which showed a new spot burning at a lower $R_f$ value than the bromide starting material in both cases. Aqueous workup was used for both reaction mixtures yielding a white solid for the β-glucosyl azide **3** and a yellow syrup for the β-galactosyl azide **6.** The products were purified by recrystallization using a minimal amount of hot methanol to give colorless crystals for both compounds **3** and **6.** Both 1H NMR spectra of **3** and **6** showed the disappearance of the doublet signal at 6.60 ppm, for H-1 of the corresponding bromide, and appearance of a new doublet signal at 4.60 ppm with the coupling constant for **3** being 8.79 Hz and for **6** 8.78 Hz, which corresponds to H-1 in each case. The large H-1 – H-2 coupling constants of both azides provide evidence for the beta configuration around

the anomeric position in each azide product. The $N_3$ group taking the place of the Br causes shielding of the anomeric proton, which moves the signal more upfield.

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

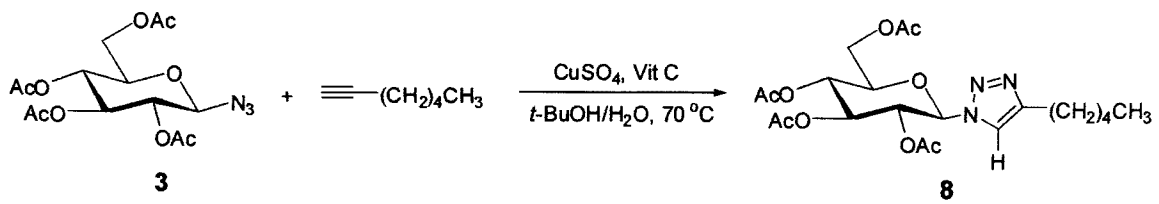
The synthesis of 1,2,3-triazoles involves reaction between an azide and alkyne and is run for a prolonged period of time at elevated temperatures. Regioselectivity remains the major issue in this cycloaddition reaction but research independently done by Sharpless and Meldal solved this problem by reporting that catalytic amounts of Cu(I) salts will give only the 1,4-disubstituted product and also increase the rate of reaction.36,37 Scheme 8 depicts the catalytic cycle for the Cu(I)-catalyzed triazole formation.




**Scheme 8**: Cu(I)-catalyzed triazole formation.

There are several advantages with this chemistry; first the formation of one isomer is possible throughout the reaction due to catalytic amounts of Cu(I) salts being used. This reaction is an example of click chemistry so product isolation is usually possible through simple filtration. The reagents used in this reaction are readily available, the reaction is easy to perform, and the product is insensitive to water and oxygen. Glycosyl azides **3** and **6** were reacted with a variety of alkynes using the $CuSO_4$/ascorbic acid system, which afforded a quick, regiospecific synthesis of 1,4-disubstituted-1,2,3-triazoles **7-22** (See Experimental Section for a complete listing). The reactions gave the products in good yields and high purity; representative examples are discussed here.

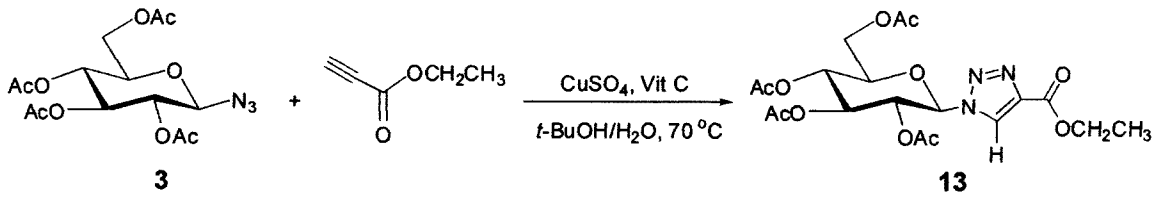
The reaction of glucosyl azide **3** with 1-heptyne afforded the triazole product **8** (Equation 9). The TLC of the reaction mixture showed a UV-active spot that burned at a lower $R_f$ value than the starting material. Investigation of the 1H NMR spectrum showed evidence of the product by indicating a singlet signal at 7.50 ppm, which corresponds to the triazole proton. Also the proton spectrum showed a triplet signal at 0.86 with a coupling constant of 6.96 Hz, which corresponds to the terminal methyl group of the alkyl chain. There are four singlets between 1.82-2.05 ppm corresponding to the 12 protons on the methyl groups of the acetates. The doublet of doublet of doublets for H-5, and the two doublet of doublets for H-6 and H-6' are present with similar chemical shifts to the azide precursor




**3** **8**

**Equation 9**: Synthesis of triazole **8** from azide **3**.

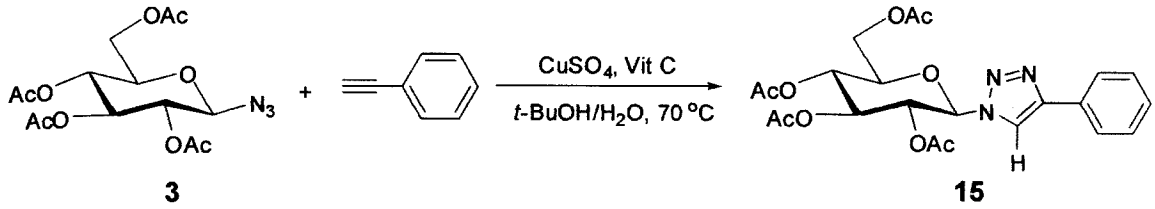
β-Glucosyl azide **3** was reacted with ethyl propiolate (Equation 10). The reaction was refluxed overnight and monitored by TLC, which showed consumption of the starting material and formation of a UV-active spot with an $R_f$ value lower than the starting material. The reaction mixture was cooled, filtered over a glass frit, and the solid was subjected to recrystallization with a minimal amount of 95% ethanol, which gave the desired product as a white solid. Analysis of the 1H NMR spectrum showed a singlet signal at 8.32 ppm, which corresponds to the triazole proton. Also a triplet signal observed at 1.40 ppm corresponds to ($CO_2CH_2C\underline{H}_3$) and the rest of the signals kept the same splitting patterns and approximate shifts as for azide **3**.




**Equation 10**: Synthesis of triazole **13** from azide **3**.

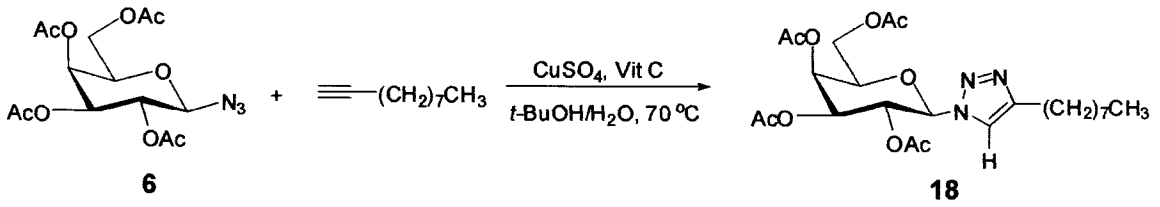
According to the typical procedure the reaction of phenylacetylene with glucosyl azide **3** afforded the triazole product **15** in highest yield (80%) (Equation 11). The reaction progress was monitored by TLC, which showed a UV-active spot that burned at a lower $R_f$ value than that of the starting material. The reaction mixture was cooled, filtered over a glass frit, and the crude product was subjected to recrystallization with 95% ethanol that afforded pure product as a white solid. The 1H NMR spectrum showed evidence of the product by indicating a singlet signal at 8.0 ppm, which corresponds to

the triazole proton and the signals that correspond to the protons of the aromatic ring were observed in the range of 7.25-7.82 ppm. The large coupling constant (9.15 Hz) for H-1 suggests that the product is indeed the β-anomer. The rest of the proton signals kept the same splitting patterns and approximate chemical shifts as in azide **3**.



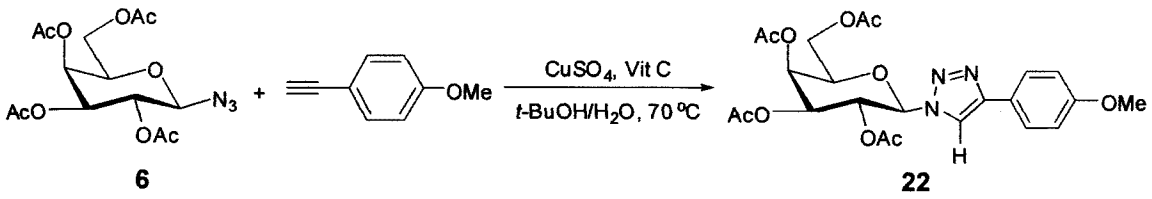

**Equation 11**: Synthesis of triazole **15** from azide **3**.

Galactosyl azide **6** was reacted with 1-decyne to afford the triazole product **18** in 80% yield (Equation 12). The analysis of the TLC showed a UV-active spot that burned at a lower $R_f$ value than that of the starting material. The 1H NMR spectrum showed the the triazole proton as a singlet signal at 7.56 ppm. The triplet signal for the terminal methyl group of the alkyl chain was observed at 0.83 ppm with a coupling constant of 6.77 Hz. Since H-1 has a large coupling constant (9.34 Hz), it is an indication that the product is indeed the β-anomer.




**Equation 12**: Synthesis of triazole **18** from **6**.

Another alkyne that was reacted with galactosyl azide **6** was 4-ethynyl anisole (Equation 13). TLC showed the appearance of a new spot, which had an $R_f$ value lower than that of the starting material. Formation of the product is evident by 1H NMR, which showed a singlet signal at 7.88 ppm, which corresponds to the triazole proton, and signals for the aromatic ring were observed in the range of 6.98-7.79 ppm. Also the proton showed a singlet signal at 3.82 Hz, which corresponds to the methyl group of 4-ethynyl anisole. The rest of the proton signals kept the same shapes and approximate chemical shifts as in azide **6**.

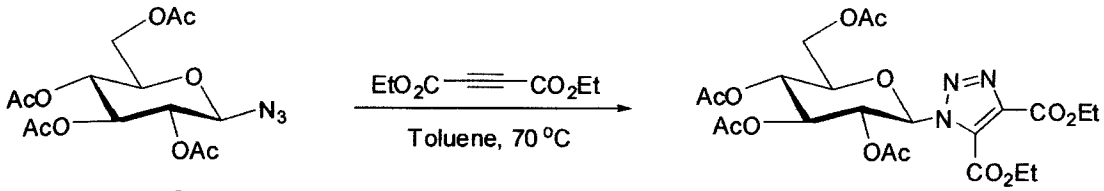



**6** **22**

**Equation 13**: Synthesis of triazole **22** from azide **6**.

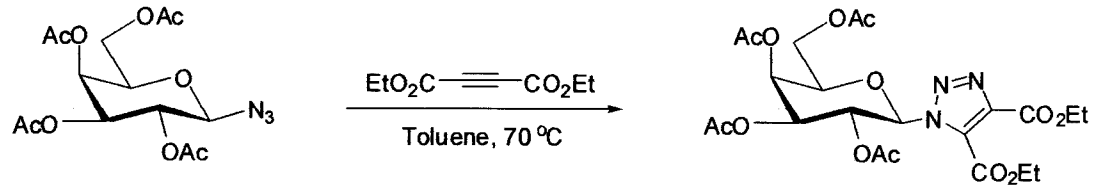
The reaction of diethylacetylene dicarboxylate with both glycosyl azides **3** and **6** was carried out in toluene without the use of any copper catalyst and the reaction gave a single isomer (**23**, Equation 14; **24** Equation 15). In each case the TLC of the reaction showed a UV-active spot that burned at an $R_f$ value lower than that of the starting material. Investigation of the 1H NMR spectra showed the appearance of a new doublet signal at 6.18 ppm for H-1 in product **23** and product **24** at 6.05 ppm indicating the formation of both triazole products and in each case the disappearance of a doublet at 4.60 ppm that corresponds to H-1 for both starting materials. The evidence for the formation of triazole **23** was obtained from the triplet signal at 1.42 ppm for

($CO_2CH_2\underline{C}H_3$) and the quartet signal at 4.39 ppm for ($CO_2\underline{C}H_2CH_3$). The formation of triazole **24** was evident with the appearance of a triplet signal at 1.42 for ($CO_2CH_2\underline{C}H_3$) and a quartet signal at 4.30 ppm for ($CO_2\underline{C}H_2CH_3$).




**3** **23**

**Equation 14**: Synthesis of triazole **23** from azide **3**.




**6** **24**

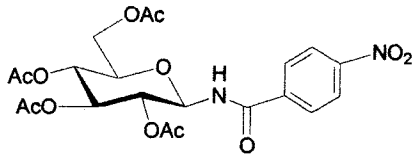
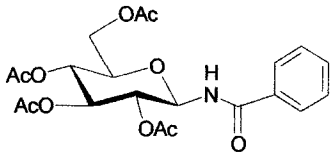
**Equation 15**: Synthesis of triazole **24** from azide **6**.

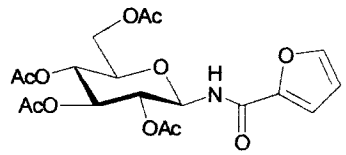
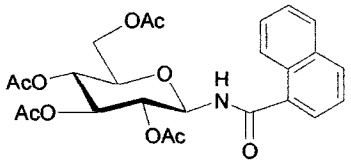
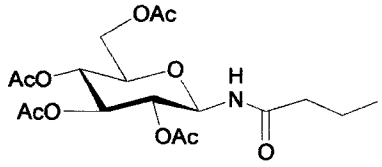
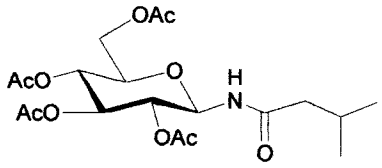
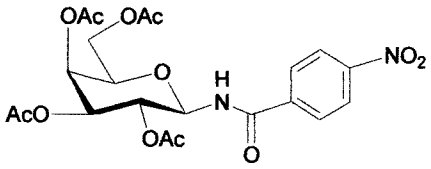
For all the glycosyl triazoles **7-24**, yields of isolated products in the 63-80% range were observed. All of the products showed clean 1H NMR spectra that were easy to interpret. The proton spectra of the products showed similar patterns, the most important being the triazole proton that was observed as a singlet in the region of 7.45-8.40 ppm. It can be concluded that the use of $CuSO_4$/ascorbic acid as a catalyst increased reaction rates and improved the product yields. Also, the use of the $CuSO_4$/ascorbic acid mixture as a catalyst only gives the 1,4-regioisomer instead of a mixture of isomers.

**Application of modified Staudinger chemistry for the synthesis of *N*-glycosyl amides**

A small collection of *N*-glycosyl amides was synthesized using different acid chlorides (Table 1). The synthesis of *N*-glycosyl amides was achieved with both the pure β-glucosyl azide **3** and β-galactosyl azide **6**. Past research within the Norris group had utilized polymer-supported triphenyphosphine in the reaction with azides and acyl chlorides to afford *N*-glycosyl amides but polymer-supported reagents are prohibitively expensive. The use of 1,2-bis(diphenylphosphino)ethane was explored for the synthesis of *N*-glycosyl amides with a good deal of success. There are advantages to using DPPE as our phosphine derivative in this type of chemistry. The first advantage is that the phosphine is a stable solid therefore it is easy to work with, secondly only 0.5 equivalents are needed in the reaction since there are two phosphines per molecule. Also, the use of DPPE over triphenyphosphine makes the elimination of the by-product bisphosphine oxide, which is very polar, easier through simple flash column chromatography.

**Table 1:** Collection of β-glycosyl amides.

| Entry | β-glycosyl amide | % yield |
|---|---|---|
| **25** |  | 80 |
| **26** |  | 61 |

| | | |
|---|---|---|
| **27** |  | 53 |
| **28** |  | 52 |
| **29** |  | 61 |
| **30** |  | 63 |
| **31** |  | 78 |
| **32** |  | 58 |

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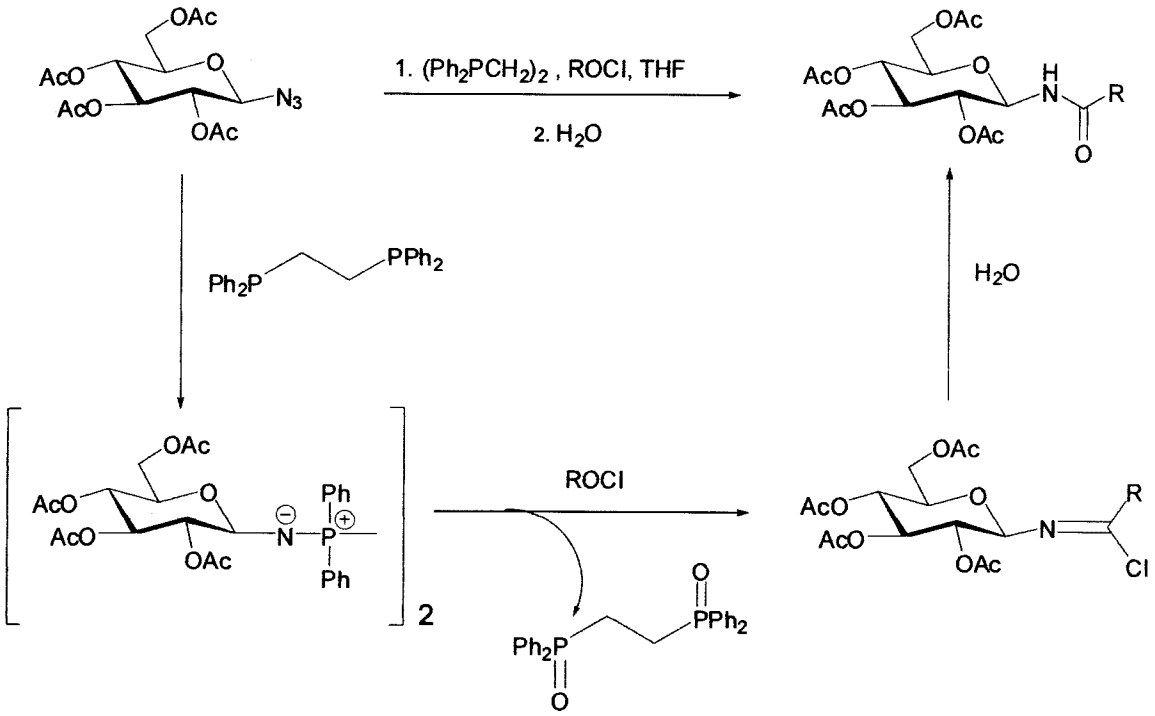
The synthesis begins between the glycosyl azide and DPPE to give the intermediate known as an aza-ylide after losing nitrogen ($-N_2$). The ylide with the nucleophilic nitrogen attacks the carbonyl carbon of the acylating agent present in the reaction and loses the bisphosphine oxide by-product through a tetrahedral intermediate. The result is the formation of the imidoyl chloride, which upon the addition of water

undergoes hydrolysis to afford the β-glycosyl amide. Scheme 9 below illustrates the reaction pathway for the modified Staudinger synthesis and the conditions applied to obtain good results.

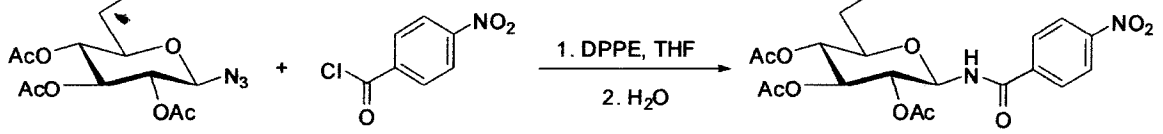



**Scheme 9:** Mechanism for the modified Staudinger reaction.

Boullanger *et al.* found that the order of the reagent addition can be important in this chemistry. It was discovered that when the acylating agent is in the reaction vessel with the azide upon the addition of the phosphine there was less anomerization of the β-ylide to the corresponding α-ylide and higher yields were also obtained with this procedure.

The synthesis of the β-glycosyl amides follow the typical procedure with either β-glucosyl azide **3** or β-galactosyl azide **6** and an acid chloride dissolved in anhydrous THF

in a flame-dried flask under nitrogen. The exclusion of water from this reaction reduces the possibility of the aza-ylide being hydrolyzed. The β-glucosyl azide **3** and *p*-nitrobenzoyl chloride (as our acylating agent) were dissolved in THF and a solution of DPPE in THF was added dropwise, the evolution of gas was seen immediately. The reaction was stirred at room temperature and monitored by TLC (1:1, hexane – ethyl acetate) after which period of time the absence of the starting material is observed with the appearance of a new spot that is quite polar and UV-active. This material was thought to be the corresponding amide. A less polar spot than the amide and azide is observed and presumably is the imidoyl chloride intermediate. The by-product bisphosphine oxide, which is a white precipitate, is seen after one and a half hours of the reaction mixture being stirred. With the addition of water (2 mL) hydrolysis of the imidoyl chloride takes place to give the desired β-glycosyl amide. The reaction mixture was reduced to remove the THF. The residue was dissolved in chloroform and washed with water after which the organic layer was reduced and the residue purified over a column of silica gel to afford pure amide **25** in 80% yield (Equation 16).




**3** **25**

**Equation 16:** Synthesis of β-glucosyl amide **25**.

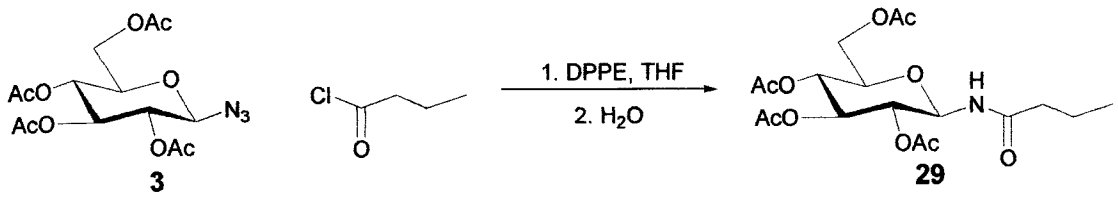
Investigation of the 1H NMR spectrum for amide **25** showed the disappearance of the doublet at 4.60 ppm, which corresponds to the anomeric proton of β-glucosyl azide **3**

and changed the signal to a triplet at 5.40 ppm due to coupling interactions between H-1 and H-2 as well as between H-1 and the proton on the amide bond. The key feature observed in β-glucosyl amide **25** is the appearance of a doublet at 7.30 ppm, which corresponds to the amide proton, and since there is a large coupling constant of 8.9 Hz the beta orientation of the non-carbohydrate portion is observed. The protons on the aromatic ring occur at 8.33 and 7.96 ppm, corresponding to the *meta-* and *ortho-* positions. Similar chemical shifts for other protons are observed with respect to β-glucosyl azide **3;** H-5 has the doublet of doublet of doublets, both doublet of doublet signals for H-6 and H-6' are present, as well as the 3 singlets for protons on the methyl groups of the acetates.

Analysis of the 13C spectrum of **25** gave the corresponding signals for the benzene ring in the range of 124.0 to 151.0 ppm. Also there is a double intensity signal present at 22.0 ppm and an overlapping signal at 21.8 ppm, which is an indication of the methyl groups of the acetate protecting groups. A signal at 166.0 ppm is found to be the carbonyl carbon of the amide and the four signals for the carbonyl carbons of the acetate groups are at 170.5 to 172.7 ppm. The low resolution mass spectrum of the product gave M(+Na) at 519.12.

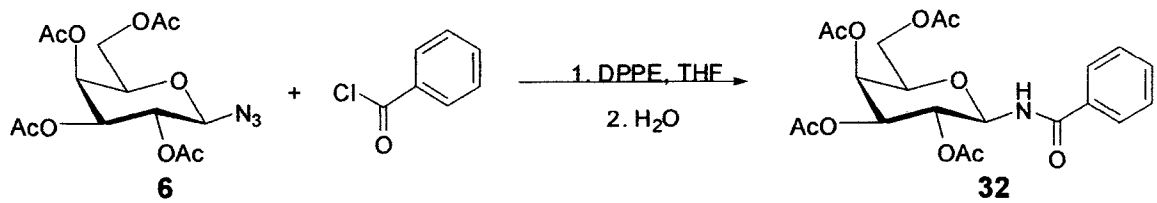
According to the typical procedure the reaction of butyryl chloride with azide **3** produced β-glyosyl amide **29** in 61% yield (Equation 17). The by-product was observed at a slower rate when compared to other derivatives, usually around 7-10 hours, which suggests the reaction is slower than with aromatic acyl chlorides, especially those with an electron-withdrawing group. The aromatic acyl chloride with an electron-withdrawing group (*p*-nitrobenzoyl chloride) should be more electrophilic since electron density is

pulled away from the carbonyl carbon making it a "more active" species. The proton NMR for amide **29** has similarities with the other β-glyosyl amides. The alkyl protons of the non-carbohydrate portion are observed at 0.90, 1.60, and 2.08 ppm. The amide proton is a doublet signal at 6.30 ppm with a large coupling constant of 9.34 Hz. Also, the large coupling constant (9.52 Hz) for H-1 suggests that the beta orientation is retained.




**Equation 17:** Synthesis of β-glycosyl amide **29**.

The reaction of the ylide with benzoyl chloride afforded the β-galactosyl amide **32** in 58% yield following the typical procedure (Equation 18). 1H NMR showed the proton of the amide at 7.04 ppm with a coupling constant of 8.97 Hz and the protons of the aromatic ring were observed in the range of 7.42-7.79 ppm. The triplet signal corresponding to H-1 was at 5.48 ppm, with a coupling constant of 9.8 Hz, is an indication that the product is indeed the β-anomer. Low resolution mass spectrometry for the product gave M(+Na) at 474.13.




**Equation 18:** Synthesis of β-glycosyl amide **32**.

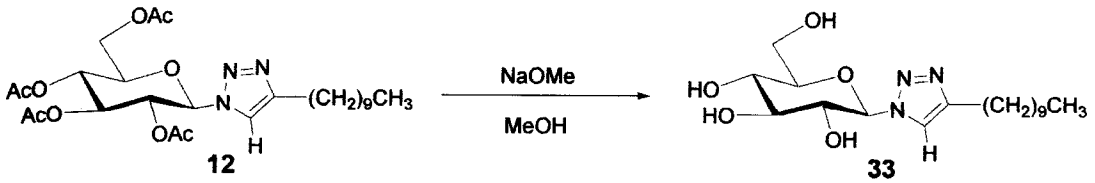
The proton NMR spectrum of the β-glycosyl amides have key similarities such as the signal for the proton of the amide is observed and the associated coupling constants suggest that the reaction is stereoselective affording only the β-anomer. Since the groups on the glucose ring are equatorial the associated protons are axial thus making the assignment of signals from coupling constants straightforward. In the galactose case the groups are equatorial at C-1, C-2, C-3, C-5, whereas the group at C-4 is axial; the protons in the β-galactosyl products are axial except H-4, which is equatorial. The signal shapes for the β-galactosyl products will differ slightly therefore from the β-glucosyl analogs.

**Synthesis of deprotected triazoles**

We are currently interested in synthesizing sugars that have the possibility to act as glycomimetics for sugars that are present in bacteria, which make up capsular polysaccharides. *Staphylococcus aureus* is one of the bacteria that produces a capsular polysaccharide around itself and is resistant to antibiotic treatment. The two serotypes that we are interested in are type 5 and type 8 because these two make up the majority of clinical isolates. There were five triazole products deprotected, to give *N*-glycosides **33-37** (See Experimental Section for full listing), and the products were sent to Dr. Diana Fagan in the Biology Department at Youngstown State University to be tested for activity against *S. aureus*.

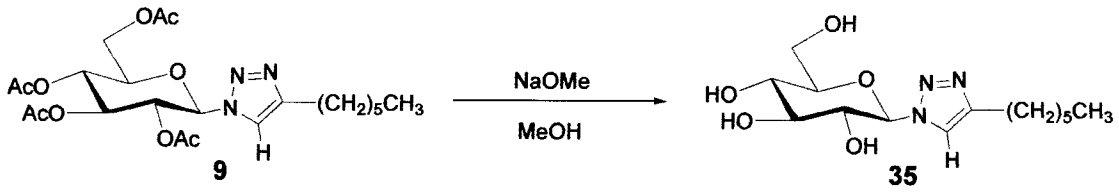
Triazole **12** (Equation 19) was dissolved in methanol and a catalytic amount of sodium was added to the solution. The reaction progress was monitored by TLC, which showed an $R_f$ value lower than that of the starting material after a four hour reaction time. The 1H NMR spectrum showed the disappearance of four singlets in the range of 1.82-2.05 ppm, which corresponds to the protons of the acetate protecting groups. Also a

singlet signal observed at 8.0 ppm corresponds to the proton on the triazole indicating the formation of the desired product.




**Equation 19:** Synthesis of deprotected product **33** from triazole **12**.

According to the typical procedure formation of product **35** was achieved in highest yield (93%) (Equation 20). TLC analysis showed an $R_f$ value lower than that of the starting material. Investigation of the 1H NMR spectrum showed the disappearance of the protons of the acetate protecting groups. The proton of the triazole was observed at 8.0 ppm indicating the formation of product **35**.




**Equation 20:** Synthesis of deprotected product **35** from triazole **9**.

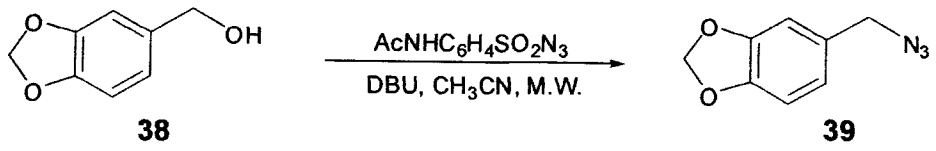
For all of the reaction products **33-37**, yields of the products in the 87-93% range were observed. It has been demonstrated that the proton NMR spectra of the deprotected products shared key similarities. The signals for the protons of the acetate protecting groups were not present and the protons of the triazoles were still observed in the 7.9-

8.28 ppm range. These compounds are currently being tested for activity against *Staphylococcus aureus* type 5 and type 8.

**One-pot Transformation of Non-sugar Alcohols to Non-sugar Azides using Microwave Irradiation**

The present research in the Norris group involves the direct conversion of a non-sugar alcohol to a non-sugar azide by applying a one-pot procedure. Also, the application of microwave heating will decrease reaction time and conserve energy. The ability to obtain a product in a single step eliminates a lot of laborious work that is involved in a multi-step procedure and gives a quicker route to a variety of compounds. The typical pathway involves a primary alcohol and reacting it with a sulfonyl chloride, to form a sulfonare ester intermediate, then the addition of sodium azide to afford the non-sugar azide by the $S_N2$ pathway. The one-pot transformation to afford the non-sugar azide involves reacting a primary alcohol with a sulfonyl azide using microwave heating.

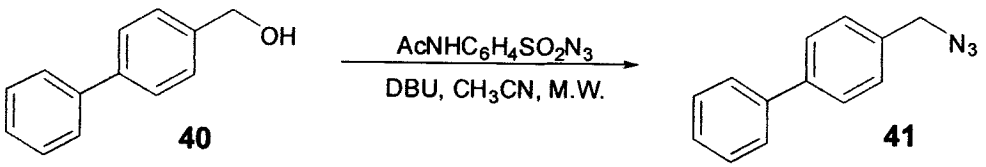
The reaction of piperonyl alcohol (**38**) with p-acetamidobenzenesulfonyl azide (*p*-ABSA) affords azide **39** in one pot (Equation 21). Progress of the reaction was monitored by TLC and after eight minutes in the microwave there was an appearance of a new spot that was UV-active, which burned at an $R_f$ value higher than that of the starting material. After an acidic workup the crude product was purified by flash column chromatography to afford pure product in a 42.8% yield. 1H NMR showed the appearance of a singlet signal at 4.21 ppm corresponding to the two protons next to the azide. Also, signals for the aryl ring protons were observed in the range of 6.77-6.80 ppm.




**38** **39**

**Equation 21:** Synthesis of compound **39** from piperonyl alcohol.

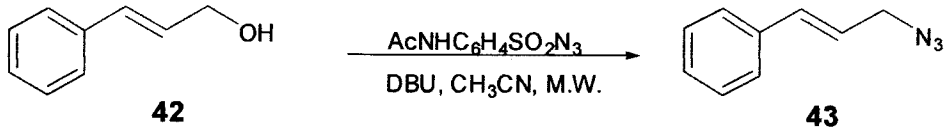
Another alcohol that was reacted was 4-biphenyl methanol with *p*-ABSA to afford product **41** in highest yield (46.5%, Equation 22). After ten minutes in the microwave TLC showed a UV-active spot that burned at a higher $R_f$ value than that of the starting material. The crude product was purified over a column of silica gel to afford pure product as a syrup. Investigation of 1H NMR spectra showed a singlet signal at 4.39 ppm, which corresponds to the protons next to the azide, and the signals for the aromatic ring protons were observed in the range of 7.39-7.61 ppm.




**40** **41**

**Equation 22:** Synthesis of compound **41** from 4-biphenyl methanol.

The reaction of cinnamyl alcohol (**42**) with *p*-ABSA affords compound **43** as a yellow syrup in a single step (Equation 23). TLC analysis showed a new UV-active spot which burned at a higher $R_f$ value than that of the starting material. The 1H NMR showed a new doublet signal at 3.94 corresponding to the protons next to the azide. The protons for the alkene were observed in the range of 6.22-6.31 ppm and the protons for the aromatic ring in the range of 7.24-7.45 ppm.




**42** **43**

**Equation 23:** Synthesis of compound **43** from cinnamyl alcohol.

The reaction occurs by an $S_N2$ displacement mechanism in 5-10 minutes, and the best conditions for this reaction are still being investigated. For example a better solvent, base, temperature, and reagent equivalents can change the overall yield since at present it is quite a low yielding reaction. Also, another parameter to change would be using a different sulfonyl azide where changing the group attached to the aromatic ring could have an effect on the reaction (Figure 13); for example, does an electron-withdrawing group or electron-donating group make a difference in the reaction? Also, will the one-pot procedure work if we use a secondary or tertiary alcohol? These questions are presently being investigated in the Norris group to find the optimal conditions for the procedure.

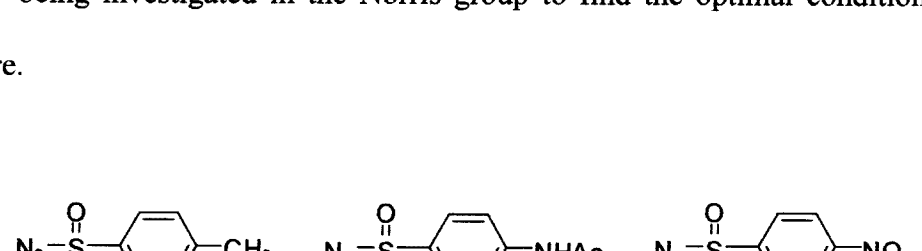


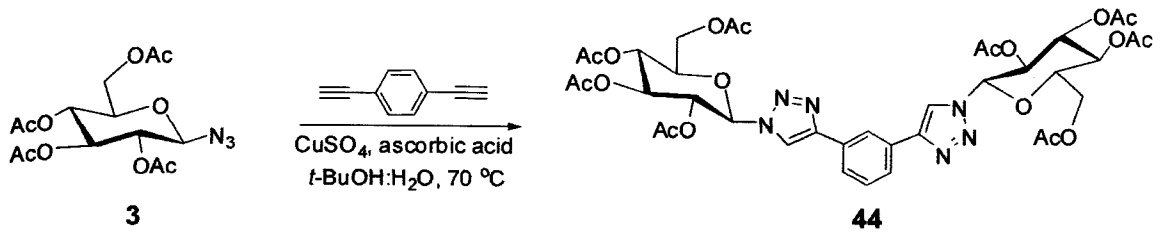

**Figure 13:** Different sulfonyl azide possibilities.

**Synthesis of divalent triazoles**

The Cu(I)-catalyzed cycloaddition reaction was used for the synthesis of two divalent compounds built from 1,3- and 1,4-diethynyl benzene. Through the use of

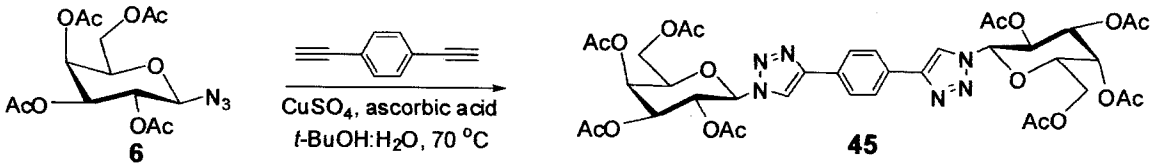
different substitution patterns around the benzene ring, the sugar ligands of the products can be directed into various orientations in space. The use of the $CuSO_4$/ascorbic acid catalyst afforded the 1,4- isomer as the only product in each case. Investigation of the 1H NMR spectra showed the retention of the β-stereochemistry due to the large coupling constants between H-1 and H-2 of the sugar rings in both cases.

The reaction using 1,3-diethynyl benzene with azide **3** produced divalent triazole **44** in 83% yield as a yellow powder (Equation 24). Two equivalents of azide **3** were needed for every one equivalent of 1,3-diethynyl benzene. The amount of catalyst used was 0.2 and 0.4 equivalents of the $CuSO_4$ and ascorbic acid and a 1:1 ratio of *t*-BuOH to $H_2O$ was used as solvent. The reaction mixture was heated to 70 °C and allowed to stir overnight. TLC showed the complete consumption of starting material and the appearance of a more polar spot that was UV-active. The reaction mixture was cooled and cold $H_2O$ was added after which the precipitate was collected over a glass frit. The resulting precipitate was washed with cold $H_2O$, which afforded the desired divalent triazole **44**. Investigation of the proton spectrum showed that the product was symmetrical. The protons of the triazole were a singlet signal observed at 8.11 ppm. The aromatic protons were observed in the range of 7.51-8.29 ppm. A doublet signal for the H-1 protons occurred at 5.95 ppm ($J$ = 9.15 Hz), the large coupling constant suggesting that the product obtained is indeed the β-anomer. The rest of the signals had the same shapes and approximate chemical shifts as azide **3**.




**Equation 24:** Synthesis of divalent triazole **44**.

A reaction was run using 1,4-diethynyl benzene under similar conditions (Equation 25). After completion and the addition of cold $H_2O$ the precipitate was filtered over a glass frit and collected as a yellow powder (85% yield). The 1H NMR spectrum of **45** showed a singlet signal at 8.09 ppm for the two protons of the triazole rings and the singlet at 7.9 ppm corresponds to the protons of the aromatic ring. The large coupling constant at H-1 (9.34 Hz) is an indication of the retention of the β-stereochemistry. 13C NMR shows the carbons of the heterocyclic and aromatic ring in the range of 119.0-148.8 ppm. Low resolution mass spectrometry found the mass of the product to be 895.5 M(+Na).



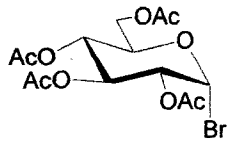

**Equation 25:** Synthesis of divalent triazole **45**.

## Experimental

### General Procedures

Rates of reactions were investigated using thin layer chromatography (TLC) on Whatman aluminum-backed plates. The TLC plates were treated with 5% sulfuric acid: 95% methanol solution followed by heating, for the indication of carbohydrate products, and *p*-anisaldehyde was used for indication of non-carbohydrate products. The products were purified by flash column chromatography utilizing 32-63 μm particle size 60-Å silica gel. A Varian Gemini 2000 nuclear magnetic resonance spectrometer was used to collect $^{1}H$ and $^{13}C$ NMR spectra at 400 MHz and 100 MHz, respectively. The solvents typically used were $CDCl_3$ and $d_6$-DMSO. The proton and carbon chemical shifts ($\delta$) were recorded in parts per million (ppm) relative to $(CH_3)_4Si$ (0.0 ppm). Splitting patterns for the NMR spectra were labeled as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet) and coupling constants ($J$) were recorded in Hertz. A Bruker Esquire-HP 1100 LC/MS was used to obtain low-resolution mass spectra.

**Preparation of 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2) from β-D-glucose pentaacetate (1).**

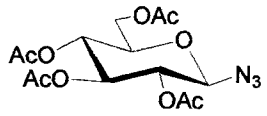



In a 250 mL round-bottom flask equipped with a magnetic stir bar and rubber septum, β-D-glucose pentaacetate (**1**, 10.0 g, 25.6 mmol) was dissolved in 33% HBr in AcOH (50 mL). The reaction mixture was allowed to stir for 2-3 hours or until TLC (2:1 hexane – ethyl acetate) showed consumption of starting material. The mixture was reduced and the residue was diluted with cold $H_2O$ (100 mL) and saturated $NaHCO_3$ (100 mL). The mixture was extracted with $CH_2Cl_2$ (3 x 50 mL) after which the combined extracts were dried over anhydrous $MgSO_4$, gravity filtered, and concentrated to afford the product as light brown syrup (8.3 g, 78% yield).

$^1$H NMR ($CDCl_3$): $\delta$ 2.01, 2.03, 2.05, 2.06 (4s, 12 H total, 4 x $COC\underline{H}_3$), 4.05 (dd, 1H, H-6, $J$ = 1.65, 12.48 Hz), 4.27-4.45 (m, 2H, H-5, H-6'), 4.81 (dd, 1H, H-2, $J$ = 4.03, 10.07 Hz), 5.11 (t, 1H, H-3, $J$ = 9.88 Hz), 5.51 (t, 1H, H-4, $J$ = 9.89 Hz), 6.60 (d, 1H, H-1, $J$ = 4.02 Hz).

$^{13}$C NMR ($CDCl_3$): $\delta$ 20.5 (double intensity), 20.6, 20.7, 60.7, 66.9, 69.9, 70.3, 71.9, 86.3, 169.0, 169.3, 169.4, 170.0.

**Preparation of 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (3) from 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2).**




In a 250 mL round-bottom flask, α-D-glucopyranosyl bromide (**2**) (12.65 g, 30.5 mmol) was dissolved in acetone (60 mL) followed by the addition of 3.0 equivalents of sodium azide (5.94 g, 91.3 mmol), which was added along with $H_2O$ (12 mL) to aid in dissolving the sodium azide. The mixture was allowed to stir overnight and monitored by TLC (1:1 hexane – ethyl acetate) to observe complete formation of the azide. The reaction mixture was reduced and the residue was partitioned between $CH_2Cl_2$ (50 mL) and $H_2O$ (75 mL). The organic layer was removed and the aqueous layers were extracted with $CH_2Cl_2$ (2 x 50 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, gravity filtered, and reduced to give a white solid. The solid was recrystallized using a minimal amount of methanol to afford colorless crystals (10.2 g, 88% yield).

$^1$H NMR ($CDCl_3$): $\delta$ 2.0, 2.03, 2.05, 2.06 (4s, 12 H total, 4x $COC\underline{H}_3$), 3.76 (ddd, 1H, H-5, $J$ = 2.38, 4.76, 10.07 Hz), 4.12 (dd, 1H, H-6, $J$ = 2.23, 12.45 Hz), 4.23 (dd, 1H, H-6', $J$ = 4.83, 12.62 Hz), 4.61 (d, 1H, H-1, $J$ = 8.79 Hz), 4.91 (dd, 1H, H-2, $J$ = 8.97, 9.52 Hz), 5.07 (dd, 1H, H-3, $J$ = 9.34, 10.07 Hz), 5.18 (dd, 1H, H-4, $J$ = 9.34, 9.52 Hz).

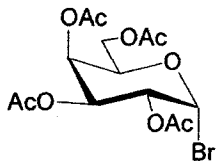
$^{13}C$ NMR ($CDCl_3$): $\delta$ 21.7 (double intensity), 21.8, 21.9, 62.7, 68.9, 71.6, 73.6, 75.0, 88.9, 170.1, 170.2, 171.0, 171.5.

*m/z* calculated : 373.3154 *m/z* found : 396.1 (+ Na)

$R_f$ = 0.46 (hexanes – ethyl acetate 1:1)

Melting point: 123-125 °C

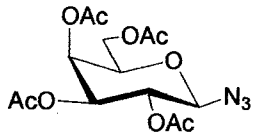
**Formation of 2,3,4,6-Tetra-*O*-acetyl-α-D-galactosyl bromide (5) from 1,2,3,4,6-penta -*O*-acetyl-β-D-galactose (4).**




In a 250 mL round-bottom flask equipped with a magnetic stir bar and rubber septum, β-D-galactose pentaacetate (8.0 g, 20.4 mmol) was dissolved in 33% HBr in AcOH (40 mL). The reaction mixture was allowed to stir for 2-3 hours at RT until TLC (2:1 hexane – ethyl acetate) showed consumption of starting material. The reaction mixture was reduced and the residue was diluted with cold $H_2O$ (100 mL) and saturated $NaHCO_3$ (100 mL). The mixture was extracted with $CH_2Cl_2$ (3 x 50 mL) after which the extracts were combined, dried over anhydrous $MgSO_4$, gravity filtered, and evaporated down to afford the product as light brown syrup (6.5 g, 77.1% yield).

$^1$H NMR ($CDCl_3$): $\delta$ 2.01, 2.03, 2.04, 2.10 (4s, 12H total, 4 x $COC\underline{H}_3$), 4.15 (dd, 1H, H-6, $J$ = 6.77, 11.35 Hz), 4.35 (dd, 1H, H-6, $J$ = 6.41, 11.35 Hz), 4.46 (m, 1H, H-5), 5.04 (dd, 1H, H-2, $J$ = 4.03, 10.80 Hz), 5.37 (dd, 1H, H-3, $J$ = 3.11, 10.61 Hz), 5.50 (d, 1H, H-4, $J$ = 3.29 Hz), 6.69 (d, 1H, H-1, $J$ = 3.84 Hz).

**Preparation of 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl azide (6) from 2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (5).**




α-D-Galactopyranosyl bromide (6.05g, 14.7 mmol) was dissolved in a 250 mL round-bottom flask using 30 mL of acetone, 3.0 equivalents of sodium azide (2.8 g, 44.1 mmol) was added along with $H_2O$ (6 mL) to aid in dissolving the sodium azide. The mixture was allowed to stir overnight at RT and monitored by TLC (1:1 hexane – ethyl acetate) to observe complete formation of the azide. The reaction mixture was reduced and the residue was partitioned between $CH_2Cl_2$ (50 mL) and $H_2O$ (75 mL). The organic layer was removed and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 50 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, gravity filtered, and reduced to give a yellow syrup. Recrystallization of the crude product using a minimal amount of methanol gave colorless crystals (4.5 g, 82 % yield).

$^1$H NMR ($CDCl_3$) : $\delta$ 1.95, 2.01, 2.07, 2.10 (4s, 12 H total, 4 x $COC\underline{H}_3$), 3.99 (m, 1H, H-5), 4.11-4.20 (m, 2H, H-6, H-6'), 4.60 (d, 1H, H-1, $J$ = 8.78 Hz), 5.02 (dd, 1H, H-2, $J$ = 3.29, 10.25 Hz), 5.21 (dd, 1H, H-3, $J$ = 8.79, 10.43 Hz), 5.40 (dd, 1H, H-4, $J$ = 1.09, 3.47 Hz).

$^{13}$C NMR ($CDCl_3$): $\delta$ 21.7 (double intensity), 21.8, 21.9, 62.3, 67.9, 69.1, 71.8, 73.9, 89.3, 170.2, 170.8, 171.0, 171.2.

$R_f$ = 0.43 (hexanes – ethyl acetate 1:1)

Melting point: 94-96 °C

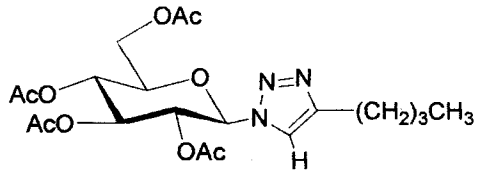
**Typical procedure for the synthesis of 1,4-disubstituted-1,2,3-triazoles *via* Cu(I)-catalyzed reactions.**

Glycosyl azide **3** or **6** (1.0 g), $CuSO_4$ (0.01 g, 0.04 mmol), ascorbic acid (0.1 g, 0.56 mmol), and alkyne (1.1 equivalents) were placed in a 100 mL three neck round-bottom flask equipped with a magnetic stir bar, thermometer, and condenser. The reactants were heated in $H_2O$ (12 mL) and *t*-BuOH (3 mL) at 60-70 °C for 6 h to overnight and monitored by TLC (1:1 hexane – ethyl acetate) to show complete consumption of starting material. The reaction mixture was allowed to cool to RT and then in an ice bath for 20 minutes. The solid was filtered over a glass frit and washed with equal parts $H_2O$ and $CH_3OH$ (10 mL) to give a white powder. The crude product was purified by recrystallization using 95% ethanol to afford product as a pure solid.

**Table 2:** 1,4-Disubstituted-1,2,3-triazoles.

| Starting material | Product | % Yield |
|---|---|---|
| **3** | **7** | 71 |
| | **8** | 72 |
| | **9** | 76 |
| | **10** | 77 |
| | **11** | 81 |
| | **12** | 78 |
| | **13** | 63 |
| | **14** | 57 |
| | **15** | 70 |
| | **16** | 65 |
| | **17** | 68 |
| **6** | **18** | 80 |
| | **19** | 76 |
| | **20** | 64 |
| | **21** | 65 |
| | **22** | 71 |

**1-Hexyne Derivative 7.**

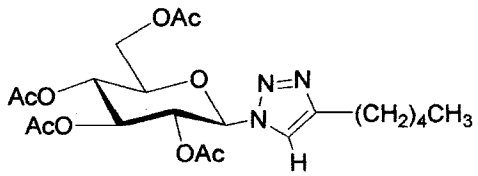



$^1$H NMR ($CDCl_3$): $\delta$ 0.90 (t, 3H, R-$(CH_2)_3C\underline{H}_3$, $J$ = 7.32 Hz), 1.20-1.40 (m, 4H), 1.58-1.70 (m, 2H), 1.84, 2.0, 2.02, 2.03 (4s, 12H total, 4 x $COCH_3$), 2.72 (t, 2H, R-$C\underline{H}_2C_2H_4$ $CH_3$, $J$ = 7.87 Hz), 3.98 (ddd, 1H, H-5, $J$ = 2.02, 5.03, 7.14 Hz), 4.16 (dd, 1H, H-6, $J$ = 2.20, 12.63 Hz), 4.28 (dd, 1H, H-6', $J$ = 4.95, 12.64 Hz), 5.18 (dd, 1H, H-2, $J$ = 9.34, 9.89 Hz), 5.39-5.51 (m, 2H, H-3, H-4), 5.82 (d,1H, H-1, $J$ = 9.15 Hz), 7.51 (s, 1H, H-triazole).

Melting point: 164-167 °C

$R_f$ = 0.21 (hexanes – ethyl acetate 1:1)

**1-Heptyne Derivative 8.**



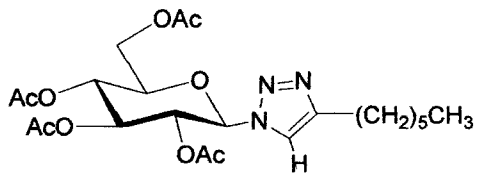

$^1$H NMR ($CDCl_3$): $\delta$ 0.86 (t, 3H, R-$(CH_2)_4C\underline{H}_3$, $J$ = 6.96 Hz), 1.25-1.38 (m, 4H), 1.58-1.72 (m, 2H), 1.82, 2.02, 2.04, 2.05 (4s, 12H total, 4 x $COCH_3$), 2.68 (t, 2H, R-$C\underline{H}_2(CH_2)_3CH_3$, $J$ = 7.59 Hz), 3.97 (ddd, 1H, H-5, $J$ = 2.02, 4.95, 6.96 Hz),

4.11 (dd, 1H, H-6, $J$ = 2.0, 12.63 Hz), 4.29 (dd, 1H, H-6', $J$ = 4.94, 12.63 Hz), 5.20 (dd, 1H, H-2, $J$ = 9.52, 10.07 Hz), 5.38-5.45 (m, 2H, H-3, H-4), 5.82 (d, 1H, H-1, $J$ = 9.15 Hz), 7.50 (s, 1H, H-triazole).

Melting point: 152-157 °C

$R_f$ = 0.22 (hexanes – ethyl acetate 1:1)

**1-Octyne Derivative 9.**

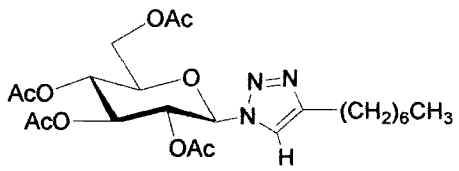



$^1$H NMR ($CDCl_3$): $\delta$ 0.83 (t, 3H, R-$(CH_2)_5C\underline{H}_3$, $J$ = 6.87 Hz), 1.23-1.40 (m, 8H), 1.58-1.70 (m, 2H), 1.83, 2.01, 2.03, 2.04 (4s, 12H total, 4 x $COCH_3$), 2.64 (t, 2H, R-$C\underline{H}_2(CH_2)_3CH_3$, $J$ = 7.61 Hz), 3.98 (m, 1H, H-5), 4.16 (dd, 1H, H-6, $J$ = 1.83, 12.45 Hz), 4.24 (dd, 1H, H-6', $J$ = 4.94, 12.63 Hz), 5.20 ( dd, 1H, H-2, $J$ = 9.35, 9.71 Hz), 5.39-5.50 (m, 2H, H-3, H-4), 5.82 (d, 1H, H-1, $J$ = 8.97 Hz), 7.45 (s, 1H, H-triazole).

Melting point: 144-148 °C

$R_f$ = 0.26 (hexanes – ethyl acetate 1:1)

**Nonyne Derivative 10.**

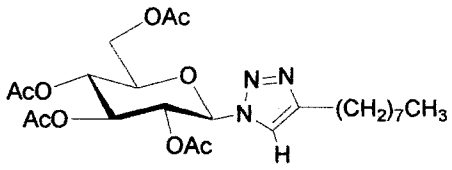



$^1$H NMR ($CDCl_3$): $\delta$ 0.85 (t, 3H, R-$(CH_2)_6C\underline{H}_3$, $J$ = 6.86 Hz), 1.25-1.45 (m, 8H), 1.50-1.70 (m, 2H), 1.82, 2.01, 2.02, 2.04 (4s, 12H total, 4 x $COCH_3$), 2.67 (t, 2H, R-$C\underline{H}_2(CH_2)_3CH_3$, $J$ = 7.60 Hz), 3.98 (m, 1H, H-5), 4.15 (dd, 1H, H-6, $J$ = 1.84, 12.45 Hz), 4.24 (dd, 1H, H-6', $J$ = 4.94, 12.45 Hz), 5.20 (dd, 1H, H-2, $J$ = 9.34, 9.70 Hz), 5.28-5.35 (m, 2H, H-3, H-4), 5.82 (d, 1H, H-1, $J$ = 8.97 Hz), 7.45 (s, 1H, H-triazole).

Melting point: 138-142 °C

$R_f$ = 0.28 (hexanes – ethyl acetate 1:1)

**Decyne Derivative 11.**



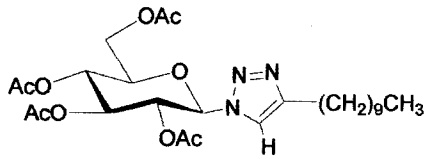

$^1$H NMR ($CDCl_3$): $\delta$ 0.85 (t, 3H, R-$(CH_2)_7C\underline{H}_3$, $J$ = 6.68 Hz), 1.24-1.40 (m, 8H), 1.50-1.75 (m, 2H), 1.82, 2.01, 2.02, 2.04 (4s, 12H total, 4 x $COCH_3$), 2.67 (t, 2H, R-$C\underline{H}_2(CH_2)_3CH_3$, $J$ = 7.59 Hz), 3.97 (m, 1H, H-5), 4.10-4.30 (m, 2H, H-6, H-6'),

5.21 (dd, 1H, H-2, $J$ = 8.89, 9.54 Hz), 5.35-5.45 (m, 2H, H-3, H-4), 5.82 (d, 1H, H-1, $J$ = 9.16), 7.45 (s, 1H, H-triazole).

Melting point: 130-132 °C

$R_f$ = 0.28 (hexanes – ethyl acetate 1:1)

**Dodecyne Derivative 12.**

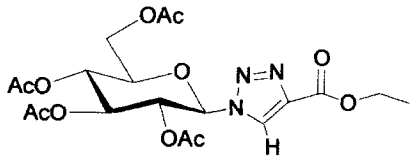



$^1$H NMR ($CDCl_3$): $\delta$ 0.84 (t, 3H, R-$(CH_2)_9C\underline{H}_3$, $J$ = 6.87 Hz), 1.21-1.39 (m, 14H), 1.60-1.85 (m, 2H), 2.01, 2.03, 2.04, 2.05 (4s, 12H total, 4 x $COCH_3$), 2.72 (t, 2H, R-$C\underline{H}_2(CH_2)_8CH_3$, $J$ = 7.69 Hz), 3.98 (m, 1H, H-5), 4.11 (dd, 1H, H-6, $J$ = 2.01, 12.45 Hz.), 5.20 (dd, 1H, H-2, $J$ = 8.70, 9.34 Hz), 5.38-5.48 (m, 2H, H-3, H-4), 5.82 (d, 1H, H-1, $J$ = 8.79 Hz.), 7.51 (s, 1H, H-triazole).

Melting point: 135-137 °C

$R_f$ = 0.32 (hexanes – ethyl acetate 1:1)

**Ethyl propiolate Derivative 13.**

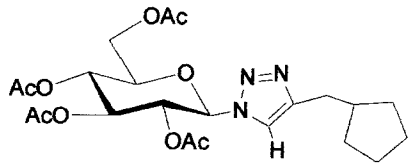



$^1$H NMR ($CDCl_3$): $\delta$ 1.40 (t, 3H, R-O-$CH_2\underline{CH_3}$, $J$ = 7.14 Hz), 1.85, 2.01, 2.03, 2.04 (4s, 12H total, 4 x $COCH_3$), 3.98 (m, 1H, H-5), 4.15 (dd, 1H, H-6, $J$ = 2.07, 12.63 Hz), 4.30 (dd, 1H, H-6', $J$ = 4.95, 12.63 Hz), 4.39 (m, 2H, R-O-$\underline{CH_2}CH_3$), 5.20 (dd, 1H, H-2, $J$ = 9.52, 9.71 Hz), 5.38 (m, 2H, H-3, H-4), 5.91 (d, 1H, H-1, $J$ = 8.98 Hz.), 8.32 (s, 1H, H-triazole).

Melting point: 162-165 °C

$R_f$ = 0.18 (hexanes – ethyl acetate 1:1)

**3-Cyclopentyl-1-propyne Derivative 14.**



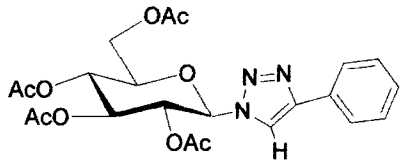

$^1$H NMR ($CDCl_3$): $\delta$ 1.17-1.90 (m, 9H), 1.82, 2.0, 2.03, 2.05 (4s, 12H total, 4 x $COCH_3$), 2.61-2.78 (m, 2H), 3.98 (m, 1H, H-5), 4.15 (dd, 1H, H-6, $J$ = 2.01, 12.63 Hz.), 4.24 (dd, 1H, H-6', $J$ = 4.95, 12.63 Hz), 5.21 (dd, 1H, H-2, $J$ = 9.34,

10.07 Hz), 5.38-5.44 (m, 2H, H-3, H-4), 5.82 (d, 1H, H-1, $J$ = 9.16 Hz), 7.50 (s, 1H, H-triazole).

Melting point: 165-167 °C

$R_f$ = 0.53 (hexanes – ethyl acetate 1:1)

**Phenylacetylene Derivative 15.**

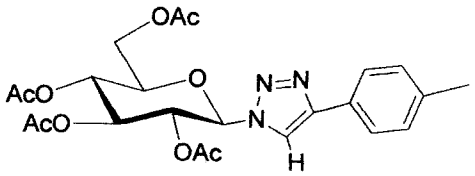



$^1$H NMR ($CDCl_3$): $\delta$ 1.88, 2.0, 2.02, 2.04 (4s, 12H total, 4 x $COCH_3$), 4.01 (m, 1H, H-5), 4.16 (dd, 1H, H-6, $J$ = 1.96, 12.91 Hz.), 4.31 (dd, 1H, H-6', $J$ = 5.13, 12.63 Hz), 5.25 (dd, 1H, H-2, $J$ = 9.34, 10.06 Hz), 5.41 (t, 1H, H-3, $J$ = 9.52 Hz), 5.50 (t, 1H, H-4, $J$ = 9.52 Hz), 5.92 (d, 1H, H-1, $J$ = 9.15 Hz), 7.25-7.82 (m, 5H, Ar-H), 8.0 (s, 1H, H-triazole).

Melting point: 198-201 °C

$R_f$ = 0.21 (hexanes – ethyl acetate 1:1)

**4-Ethynyltoluene Derivative 16.**

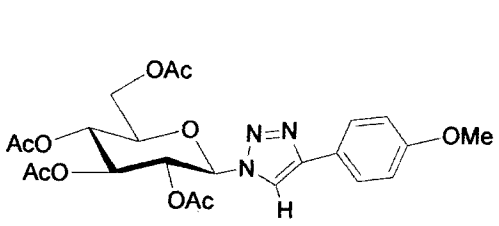



$^1$H NMR ($CDCl_3$): $\delta$ 1.85, 2.01, 2.03, 2.04 (4s, 12H total, 4 x $COCH_3$), 2.39 (s, 3H, Ar-$C\underline{H}_3$) 4.01 (ddd, 1H, H-5, $J$ = 2.01, 5.13, 7.14 Hz), 4.13 (dd, 1H, H-6, $J$ = 2.01, 12.63 Hz.), 4.30 (dd, 1H, H-6', $J$ = 4.98, 12.68 Hz), 5.22 (dd, 1H, H-2, $J$ = 9.51, 10.01 Hz), 5.41 (t, 1H, H-3, $J$ = 9.43 Hz.), 5.51 (t, 1H, H-4, $J$ = 9.52 Hz) 5.90 (d, 1H, H-1, $J$ = 9.34 Hz.), 7.20-7.78 (m, 4H, Ar-H), 7.97 (s, 1H, H-triazole).

Melting point: 218-221 °C

$R_f$ = 0.20 (hexanes – ethyl acetate 1:1)

**4-Ethynylanisole Derivative 17.**



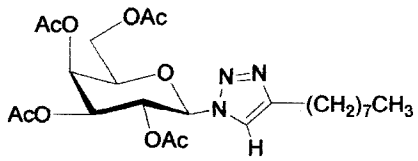

$^1$H NMR ($CDCl_3$): $\delta$ 1.88, 2.02, 2.04, 2.05 (4s, 12H total, 4 x $COCH_3$), 3.82 (s, 3H, R-$OCH_3$), 4.0 (ddd, 1H, H-5, $J$ = 2.2, 5.13, 7.33 Hz), 4.16 (dd, 1H, H-6, $J$ =

2.01, 12.63 Hz), 4.30 (dd, 1H, H-6', $J$ = 5.04, 12.73 Hz), 5.22 (dd, 1H, H-2, $J$ = 9.42, 10.07 Hz), 5.40 (t, 1H, H-3, $J$ = 9.34 Hz.), 5.50 (t, 1H, H-4, $J$ = 9.52 Hz.) 5.90 (d, 1H, H-1, $J$ = 9.33 Hz), 6.90-7.79 (m, 4H, Ar-H), 7.92 (s, 1H, H-triazole).

Melting point: 202-204 °C

$R_f$ = 0.48 (hexanes – ethyl acetate 1:1)

**Decyne Derivative 18.**

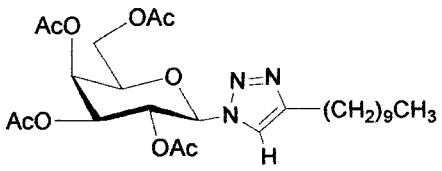



$^1$H NMR ($CDCl_3$): $\delta$ 0.83 (t, 3H, R-$(CH_2)_7C\underline{H}_3$, $J$ = 6.77 Hz), 1.20-1.39 (m, 8H), 1.60-1.73 (m, 2H), 1.89, 2.01, 2.03, 2.09 (4s, 12H total, 4 x $COCH_3$), 2.65 (t, 2H, R-$C\underline{H}_2(CH_2)_6CH_3$, $J$ = 7.50 Hz), 4.10-4.30 (m, 3H, H-5, H-6, H-6'), 5.18 (dd, 1H, H-2, $J$ = 3.11, 10.06 Hz), 5.51-5.60 (m, 2H, H-3, H-4), 5.80 (d, 1H, H-1, $J$ = 9.34 Hz), 7.56 (s, 1H, H-triazole).

Melting point: 105-107 °C

$R_f$ = 0.27 (hexanes – ethyl acetate 1:1)

**Dodecyne Derivative 19.**

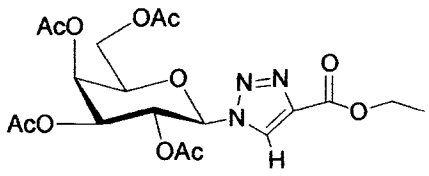



$^1$H NMR ($CDCl_3$): $\delta$ 0.84 (t, 3H, R-$(CH_2)_9C\underline{H}_3$, $J$ = 6.86 Hz), 1.20-1.40 (m, 14H), 1.61-1.75 (m, 2H), 1.90, 2.0, 2.02, 2.10 (4s, 12H total, 4 x $COCH_3$), 2.68 (t, 2H, R-$C\underline{H}_2(CH_2)_8CH_3$, $J$ = 7.68 Hz), 3.75 (m, 1H, H-5), 4.15-4.25 (m, 2H, H-6, H-6' Hz), 5.20 (dd, 1H, H-2, $J$ = 3.48, 10.26 Hz), 5.51-5.60 (m, 2H, H-3, H-4), 5.80 (d, 1H, H-1, $J$ = 9.34 Hz), 7.58 (s, 1H, H-triazole).

Melting point: 100-102 °C

$R_f$ = 0.28 (hexanes – ethyl acetate 1:1)

**Ethyl propoilate Derivative 20.**



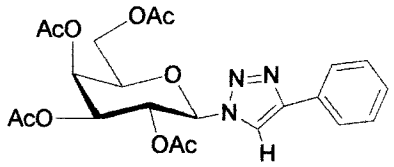

$^1$H NMR ($CDCl_3$): $\delta$ 1.39 (t, 3H, R-O-$CH_2C\underline{H}_3$, $J$ = 7.14 Hz), 1.90, 2.0, 2.03, 2.08 (4s, 12H total, 4 x $COCH_3$), 4.16 (m, 1H, H-5), 4.20-4.35 (m, 2H, H-6, H-6'),

4.40 (m, 2H, R-O-C$\underline{H_2}$CH$_3$ ), 5.23 (dd, 1H, H-2, $J$ = 3.48, 10.44 Hz.), 5.42-5.58 (m, 2H, H-3, H-4), 5.91 (d, 1H, H-1, $J$ = 9.15 Hz.), 8.39 (s, 1H, H-triazole).

Melting point: 110-112 °C

$R_f$ = 0.19 (hexanes – ethyl acetate 1:1)

**Phenylacetylene Derivative 21.**

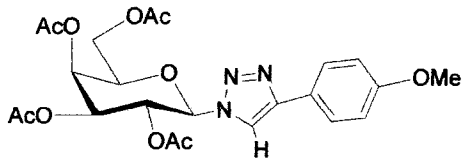



$^1$H NMR ($CDCl_3$): $\delta$ 1.95, 2.0, 2.03, 2.10 (4s, 12H total, 4 x COC$\underline{H_3}$), 3.75 (m, 1H, H-5), 4.18-4.25 (m, 2H, H-6, H-6'), 5.24 (dd, 1H, H-2, $J$ = 3.47, 10.26 Hz), 5.58 (dd, 1H, H-3, $J$ = 8.58, 10.56 Hz), 5.62 (dd, 1H, H-4, $J$ = 1.31, 3.50 Hz), 5.94 (d, 1H, H-1, $J$ = 9.34 Hz), 7.18-7.82 (m, 5H, Ar-H), 8.02 (s, 1H, H-triazole).

Melting point: 195-197 °C

$R_f$ = 0.20 (hexanes – ethyl acetate 1:1)

**4-Ethynylanisole Derivative 22.**

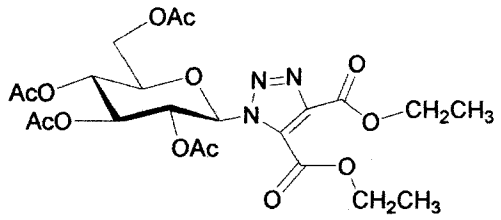



$^1$H NMR ($CDCl_3$): $\delta$ 1.89, 2.0, 2.02, 2.09 (4s, 12H total, 4 x $COCH_3$), 3.82 (s, 3H, R-$OCH_3$), 4.0 (m, 1H, H-5), 4.21-4.30 (m, 2H, H-6, H-6'), 5.24 (dd, 1H, H-2, $J$ = 3.30, 10.43 Hz), 5.57-5.62 (m, 2H, H-3, H-4), 5.87 (d, 1H, H-1, $J$ = 9.33 Hz), 6.98-7.79 (m, 4H, Ar-H), 7.88 (s, 1H, H-triazole).

Melting point: 170-172 °C

$R_f$ = 0.46 (hexanes – ethyl acetate 1:1)

**Preparation of Diethyl acetylene dicarboxylate Derivative 23.**




In a 100 mL round-bottom flask, azide **3** (1.02 g, 2.7 mmol) was dissolved in toluene (15 mL) and diethyl acetylene decarboxylate (1.56 mL) added *via* syringe. The reaction was refluxed for 6h or until TLC (1:1 hexane – ethyl acetate) showed complete

consumption of starting material. The reaction mixture was reduced and the crude product was purified by flash column chromatography to afford pure product as a crystalline solid (1.20 g, 82%).

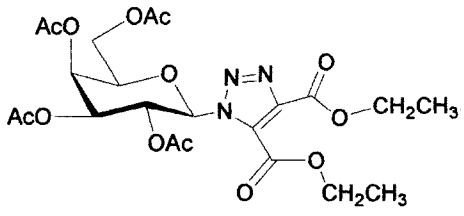
$^1$H NMR ($CDCl_3$): $\delta$ 1.38 (t, 3H, $CO_2CH_2C\underline{H}_3$, $J$ = 7.14 Hz), 1.42 (t, 3H, $CO_2CH_2C\underline{H}_3$, $J$ = 7.14 Hz), 1.85, 2.01, 2.03, 2.04 (4s, 12H total, 4 x $COCH_3$), 3.96 (ddd, 1H, H-5, $J$ = 2.2, 4.94, 10.07 Hz), 4.12 (dd, 1H, H-6, $J$ = 2.20, 12.64 Hz), 4.23 (dd, 1H, H-6', $J$ = 4.94, 12.63 Hz), 4.39 (q, 2H, R-$O_2$-$C\underline{H}_2CH_3$, $J$ = 7.14 Hz), 4.43 (q, 2H, R-$O_2$-$C\underline{H}_2CH_3$, $J$ = 7.14 Hz), 5.11 (t, 1H, H-2, $J$ = 9.88 Hz), 5.38 (t, 1H, H-3, $J$ = 9.52 Hz), 5.91 (t, 1H, H-4, $J$ = 9.34 Hz), 6.18 (d, 1H, H-1, $J$ = 9.33 Hz).

*m/z* calculated : 543.17 *m/z* found : 566.2 (+ Na)

R*f* = 0.51 (hexanes – ethyl acetate 1:1)

Melting point: 112-114 °C

**Preparation of Diethyl acetylene dicarboxylate Derivative 24.**



In a 100 mL round-bottom flask, azide **6** (1.10 g, 2.7 mmol) was dissolved in toluene (15 mL) and diethyl acetylene decarboxylate (1.76 mL) added *via* syringe. The reaction was refluxed for 6h or until TLC (1:1 hexane – ethyl acetate) showed complete consumption of starting material. The reaction mixture was reduced and the crude product was purified by flash column chromatography to afford pure product as a crystalline solid (1.07 g, 72%).

$^1$H NMR ($CDCl_3$): $\delta$ 1.38 (t, 3H, $CO_2CH_2C\underline{H}_3$, $J$ = 7.14 Hz), 1.42 (t, 3H, $CO_2CH_2C\underline{H}_3$, $J$ = 7.14 Hz), 1.81, 1.98, 2.01, 2.10 (4s, 12H total, 4 x $COCH_3$), 4.02 (m, 1H, H-5), 4.15-4.25 (m, 2H, H-6, H-6'), 4.30 (q, 2H, R-$O_2C\underline{H}_2CH_3$, $J$ = 7.14 Hz.), 4.34 (q, 2H, R-$O_2C\underline{H}_2CH_3$ , $J$ = 7.14 Hz.), 5.24 (dd, 1H, H-2, $J$ = 3.30, 9.89 Hz), 5.40 (dd, 1H, H-3, $J$ = 3.29, 6.58 Hz), 5.91 (dd, 1H, H-4, $J$ = 9.71, 9.33 Hz), 6.05 (d, 1H, H-1, $J$ = 9.33 Hz.).

*m/z* calculated : 543.17 *m/z* found : 566.2 (+ Na)

R*f* = 0.48 (hexanes – ethyl acetate 1:1)

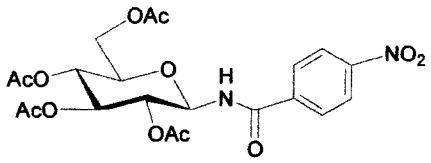
Melting point: 88-91 °C

**Typical procedure for the synthesis of *N*-glycosyl amides using the modified Staudinger reaction.**

In a flame-dried 100 mL round-bottom flask a mixture of glycosyl azide (1.0 mmol) and acylating agent (2.0 mmol) was dissolved in THF (0.1 g/mL). A solution of 1,2-bis-(diphenyphosphino)ethane (DPPE) in dry THF (0.1 g/mL) was added dropwise at

RT. The mixture was allowed to stir and monitored by TLC. When the disappearance of the ylide intermediate was observed, $H_2O$ (2 mL) was added and the mixture stirred overnight. The solvent was removed *in vacuo* and the crude residue extracted into $CH_2Cl_2$ (3 x 15 mL). The combined extracts were washed with $H_2O$ (25 mL), dried over $MgSO_4$, gravity filtered, and evaporated down and the crude product was purified over silica gel using flash column chromatography.

**Formation of amide 25 from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (3).**




Following the typical procedure amide **25** was prepared from azide **3** (1.025 g, 2.74 mmol), *p*-nitrobenzoyl chloride (1.01 g, 5.49 mmol), and DPPE (0.709 g, 1.78 mmol). The crude product was purified by flash column chromatography (1:1, hexane – ethyl acetate) and yielded pure product as colorless crystals (1.07 g, 79%).

$^1$H NMR ($CDCl_3$): $\delta$ 2.05, 2.06, 2.07, 2.10 (4s, 12H, 4 x $COCH_3$), 3.91 (ddd, 1H, H-5, $J$ = 2.01, 4.03, 10.25 Hz), 4.10 (dd, 1H, H-6, $J$ = 2.2, 12.73 Hz), 4.33 (dd, 1H, H-6', $J$ = 4.21, 12.64 Hz), 5.0 (t, 1H, H-3, $J$ = 9.70 Hz), 5.12 (t, 1H, H-4, $J$ = 9.70 Hz), 5.41 (2t overlapping, 2H, H-1, H-2, $J$ = 9.70, 9.20 Hz), 7.18 (d, 1H, N-H, $J$ = 8.9 Hz), 7.92 (d, 2H, *o*-Ar-H, $J$ = 8.79 Hz), 8.30 (d, 2H, *m*-Ar-H, $J$ = 8.97 Hz).

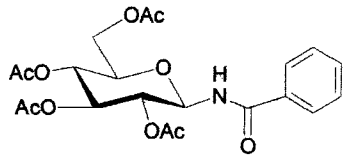
$^{13}C$ NMR ($CDCl_3$): $\delta$ 21.8, 22.0 (double intensity), 62.6, 69.1, 72.0, 73.4, 74.8, 80.1, 124.9 (double intensity), 129.5 (double intensity), 139.1, 151.0, 166.0, 170.5, 170.7, 171.5, 172.7.

*m/z* calculated: 496.13 *m/z* found: 519.23 (+ Na)

Melting point: 202-204 °C

$R_f = 0.22$

**Formation of amide 26 from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (3).**




Following the typical procedure amide **26** was prepared from azide **3** (0.721 g, 1.93 mmol), benzoyl chloride (0.65 mL, 3.82 mmol), and DPPE (0.49 g, 1.25 mmol). The crude product was purified by flash column chromatography (1:1, hexane – ethyl acetate), which yielded pure product as a crystalline solid (0.53 g, 61%).

$^1H$ NMR ($CDCl_3$): $\delta$ 2.02, 2.04, 2.05, 2.07 (4s, 12H, 4 x $COCH_3$), 3.91 (ddd, 1H, $J$ = 2.01, 4.21, 10.07 Hz), 4.09 (dd, 1H, H-6, $J$ = 2.19, 12.63 Hz), 4.32 (dd, 1H, H-6', $J$ = 4.21, 12.45 Hz), 5.06 (t, 1H, H-3, $J$ = 9.71 Hz), 5.11 (t, 1H, H-4, $J$ = 10.06 Hz), 5.39 (t, 1H, H-2, $J$ = 9.52 Hz), 5.43(t, 1H, H-1, $J$ = 9.33 Hz), 7.06 (d, 1H, N-H, $J$ = 8.97 Hz), 7.42-7.76 (m, 5H, Ar-H).

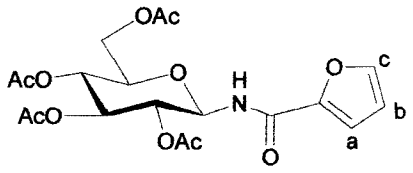
$^{13}C$ NMR ($CDCl_3$): $\delta$ 21.9 (double intensity), 22.0 (double intensity), 62.7, 69.2, 71.8, 73.6, 74.6, 80.0, 128.2, 129.7, 133.4, 133.6, 168.0, 170.5, 170.8, 171.5, 172.4.

*m/z* calculated 451.15 *m/z* found: 474.13 (+ Na)

Melting point: 186-190 °C

$R_f = 0.21$

**Formation of amide 27 from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (3).**




Following the typical procedure amide **27** was prepared from azide **3** (0.511 g, 1.36 mmol), 2-furoyl chloride (0.47 mL, 2.72 mmol), and DPPE (0.352 g, 0.88 mmol). The crude product was purified by flash column chromatography (1:2, hexane – ethyl acetate), which yielded pure product as a crystalline solid (0.342 g, 57%).

$^1H$ NMR ($CDCl_3$): $\delta$ 2.02, 2.03, 2.04, 2.07 (4s, 12H, 4 x $COCH_3$), 3.89 (ddd, 1H, H-5, $J$ = 2.01, 4.21, 10.07 Hz), 4.11 (dd, 1H, H-6, $J$ = 2.2, 12.64 Hz), 4.34 (dd, 1H, H-6', $J$ = 4.4, 12.45 Hz), 5.08 (t, 1H, H3, $J$ = 9.52 Hz), 5.13 (t, 1H, H-4, $J$ =

9.71 Hz), 5.37, 5.42 (2t overlapping, 2H, H-1, H-2, $J$ = 9.52, 9.52 Hz), 6.51 (dd, 1H, $H_b$ , $J$ = 1.83, 3.48 Hz), 7.10 (d, 1H, N-H, $J$ = 9.34 Hz), 7.17 (d, 1H, $H_a$, $J$ = 3.48 Hz), 7.48 (d, 1H, $H_c$, $J$ = 1.73 Hz).

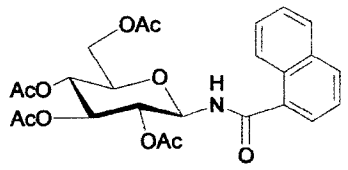
$^{13}C$ NMR ($CDCl_3$): $\delta$ 21.8, 21.9 (double intensity), 62.7, 69.2, 71.5, 73.8, 74.6, 79.0, 113.3, 117.0, 145.9, 147.5, 159.0, 170.46, 170.8, 171.5, 171.7.

*m/z* calculated 441.13 *m/z* found: 464.13 (+ Na)

Melting point: 164-166 °C

$R_f$ = 0.23

**Formation of amide 28 from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (3).**




Following the typical procedure amide **28** was prepared from azide **3** (0.491 g, 1.36 mmol), 1-naphthoyl chloride (2.72 mmol), and DPPE (0.352 g, 0.88 mmol). The crude product was purified by flash column chromatography (1:1, hexane – ethyl acetate), which yielded pure product as a white solid (0.341 g, 50%).

$^1H$ NMR ($CDCl_3$): $\delta$ 2.04, 2.05, 2.07, 2.10 (4s, 12H, 4 x $COCH_3$), 3.95 (ddd, 1H, H-5, $J$ = 2.01, 4.20, 10.07 Hz), 4.13 (dd, 1H, H-6, $J$ = 1.83, 12.27 Hz), 4.38 (dd,

1H, H-6', $J$ = 4.03, 12.63 Hz), 5.10 (t, 1H, H-2, $J$ = 9.70 Hz), 5.16 (t, 1H, H-3, $J$ = 9.80 Hz), 5.42 (t, 1H, H-4, $J$ = 9.70 Hz), 5.54 (t, 1H, H-1, $J$ = 9.15 Hz), 7.27 (d, 1H, N-H, $J$ = 9.15 Hz), 7.52-7.63 (m, 3H, Ar-H), 7.78-7.98 (m, 4H, Ar-H).

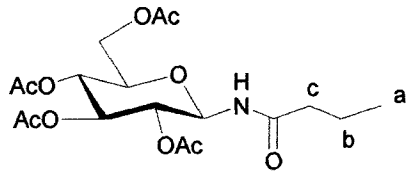
$^{13}C$ NMR ($CDCl_3$): $\delta$ 20.7 (double intensity), 20.7, 20.8, 61.6, 68.1, 70.7, 72.7, 73.6, 78.3, 124.4, 125.0, 125.05, 126.4, 127.1, 128.2, 129.8, 131.5, 132.1, 133.5, 168.9, 169.3, 169.7, 170.3, 170.6

*m/z* calculated 501.16 *m/z* found: 524.20 (+ Na)

Melting point: 162-164 °C

$R_f$ = 0.29

**Formation of amide 29 from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (3).**




Following the typical procedure amide **29** was prepared from azide **3** (0.807 g, 2.16 mmol), butyryl chloride (0.47 mL, 4.32 mmol), and DPPE (0.559 g, 1.40 mmol). The crude product was purified by flash column chromatography (100% ethyl acetate), which yielded pure product as a crystalline solid (0.562 g, 62%).

$^1$H NMR ($CDCl_3$): $\delta$ 0.90 (t, 3H, $H_a$, $J$ = 7.51 Hz), 1.60 (m, 2H, $H_b$), 2.0, 2.02, 2.04, 2.05 (4s, 12H, 4 x $COCH_3$), 2.08 (m, 2H, $H_c$), 3.83 (ddd, 1H, H-5, $J$ = 2.10, 4.39, 10.25 Hz), 4.06 (dd, 1H, H-6, $J$ = 2.0, 12.45 Hz), 4.31 (dd, 1H, H-6', $J$ = 4.4, 12.64 Hz), 4.92 (t, 1H, H-2, $J$ = 9.70 Hz), 5.06 (t, 1H, H-4, $J$ = 9.70 Hz), 5.26 (t, 1H, H-1, $J$ = 9.52 Hz), 5.28 (t, 1H, H-3, $J$ = 9.52 Hz), 6.30 (d, 1H, N-H $J$ = 9.34 Hz).

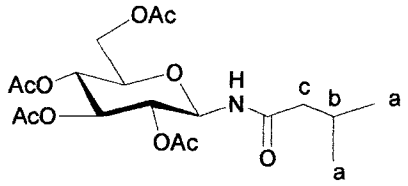
$^{13}$C NMR ($CDCl_3$): $\delta$ 14.7, 19.8, 21.82 (double intensity), 21.87, 21.9, 39.6, 62.7, 69.2, 71.6, 73.8, 74.5, 79.1, 170.4, 170.7, 171.4, 171.7, 174.1

*m/z* calculated 417.16 *m/z* found: 440.15 (+ Na)

Melting point: 116-120 °C

$R_f$ = 0.35

**Formation of amide 30 from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (3).**




Following the typical procedure amide **30** was prepared from azide **3** (0.578 g, 1.54 mmol), isovaleryl chloride (0.37 mL, 3.10 mmol), and DPPE (0.398 g, 1.0 mmol). The

crude product was purified by flash column chromatography (100% ethyl acetate), yielded pure product as a crystalline solid (0.465 g, 70%).

$^1$H NMR ($CDCl_3$): $\delta$ 0.79 (d, 3H, $H_a$, $J$ = 6.10 Hz), 0.81 (d, 3H, $H_a$, $J$ = 6.04 Hz), 1.85-2.05 (m, 2H, $H_b$, $H_c$) 1.89, 1.90, 1.92, 1.94 (4s, 12H, 4 x $COCH_3$), 3.76 (ddd, 1H, H-5, $J$ = 2.01, 4.03, 10.07 Hz), 3.95 (dd, 1H, H-6, $J$ = 2.04, 12.45 Hz), 4.22 (dd, 1H, H-6', $J$ = 4.4, 12.64 Hz), 4.84 (t, 1H, H-3, $J$ = 9.52 Hz), 4.95 (t, 1H, H-4, $J$ = 9.89 Hz), 5.19 (t, 1H, H-2, $J$ = 9.52 Hz), 5.22 (t, 1H, H-1, $J$ = 9.52 Hz), 6.62 (d, 1H, N-H, $J$ = 9.52 Hz).

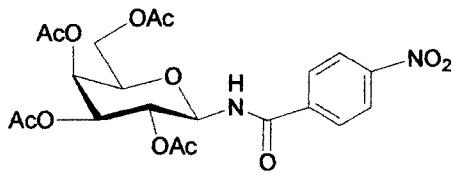
$^{13}$C NMR ($CDCl_3$): $\delta$ 21.8 (double intensity), 21.9, 23.3, 23.5, 27.1, 47.0, 62.8, 69.2, 71.6, 73.8, 74.6, 79.0, 170.4, 170.7, 171.4, 171.7, 173.6.

*m/z* calculated 431.18 *m/z* found: 454.16 (+ Na)

Melting point: 132-135 °C

$R_f$ = 0.31

**Formation of amide 31 from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide (6).**



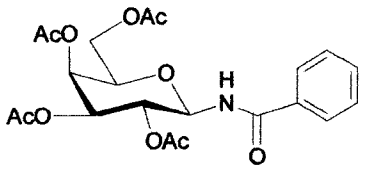
Following the typical procedure amide **31** was prepared from azide **6** (1.07 g, 2.86 mmol), *p*-nitrobenzoyl chloride (1.06 g, 5.72 mmol), and DPPE (0.74 g, 1.85 mmol). The crude product was purified by flash column chromatography (1:1, hexane – ethyl acetate), which yielded pure product as a white solid (1.14 g, 80%).

$^1$H NMR ($CDCl_3$): $\delta$ 2.01, 2.03, 2.05, 2.10 (4s, 12H, 4 x $COCH_3$), 4.05-4.15 (m, 3H, H-5, H-6, H-6'), 5.17-5.23 (m, 2H, H-3, H-4), 5.38-5.41 (2t overlapping, 2H, H-1, H-2 $J$ = 8.97, 9.20 Hz), 7.29 (d, 1H, N-H, $J$ = 8.79 Hz), 7.92 (d, 2H, *o*-Ar-H, $J$ = 8.6 Hz), 8.38 (d, 2H, *m*-Ar-H, $J$ = 8.61 Hz).

Melting point: 160-164 °C

$R_f$ = 0.24

**Formation of amide 32 from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl azide (6).**




Following the typical procedure amide **26** was prepared from azide **6** (0.462 g, 1.23 mmol), benzoyl chloride (0.42 mL, 2.46 mmol), and DPPE (0.318 g, 0.79 mmol). The crude product was purified by flash column chromatography (1:1, hexane – ethyl acetate), which yielded pure product as a white powder (0.332 g, 59%).

$^1$H NMR ($CDCl_3$): $\delta$ 2.01, 2.03, 2.04, 2.12 (4s, 12H, 4 x $COCH_3$), 4.04-4.15 (m, 3H, H-5, H-6, H-6'), 5.18-5.24 (m, 2H, H-3, H-4), 5,43 (t, 1H, H-2, $J$ = 9.70 Hz), 5.48 (t, 1H, H-1, $J$ = 9.80 Hz), 7.04 (d, 1H, N-H, $J$ = 8.97 Hz), 7.42-7.53 (m, 3H, Ar-H), 7.75-7.79 (m, 2H, Ar-H).

*m/z* calculated: 451.15 *m/z* found: 474.13 (+ Na)

Melting point: 138-140 °C

$R_f$ = 0.26

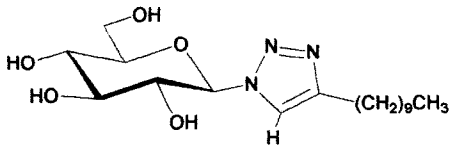
**Typical procedure for the deprotection of 1,4-disubstitued-1,2,3-triazoles.**

In an oven-dried 50 mL round-bottom flask, equipped with a magnetic stir bar and rubber septum, the 1,4-disubstitued-1,2,3-triazole (0.3 g) was dissolved in methanol (10 mL). A catalytic amount of sodium was added and the mixture was allowed to stir for 4 h at RT until TLC (100% ethyl acetate) showed complete consumption of starting material. The mixture was evaporated down to afford product as a pure solid.

**Table 3:**1,4-disubstituted-1,2,3-triazoles

| Starting Material | Product | % Yield |
|---|---|---|
| 1-Dodecyne derivative | **33** | 90 |
| 1-Decyne derivative | **34** | 92 |
| 1-Octyne derivative | **35** | 93 |
| 1-Heptyne derivative | **36** | 87 |
| 3-Cyclopentyl-1-propyne deriv. | **37** | 88 |

**Deprotected 1-dodecyne derivative 33.**



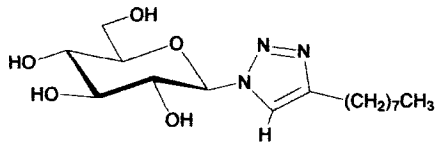

$^1$H NMR ($d_6$-DMSO): $\delta$ 0.83 (t, 3H, R-$(CH_2)_9C\underline{H}_3$, $J$ = 6.59 Hz), 1.23-1.58 (m, 14H), 2.57 (t, 2H, R-$C\underline{H}_2(CH_2)_9CH_3$, $J$ = 7.50 Hz), 3.18-3.45 (m, 3H, H-5, H-6, H-6'), 3.62-3.72 (m, 3H, H-4, H-3, H-2), 5.40 (d, 1H, H-1, $J$ = 9.15 Hz), 8.0 (s, 1H, H-triazole).

Yield: 90%

Melting point: Decomposition at 231 °C

$R_f$ = 0.15 (ethyl acetate)

**Deprotected 1-decyne derivative 34.**



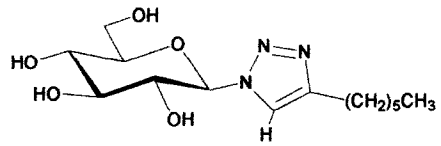

$^1$H NMR ($d_6$-DMSO): δ 0.85 (t, 3H, R-$(CH_2)_7C\underline{H}_3$, $J$ = 6.95 Hz), 1.27-1.65 (m, 12H), 2.49 (t, 2H, R-$C\underline{H}_2(CH_2)_7CH_3$, $J$ = 7.68 Hz), 3.19-3.42 (m, 3H, H-5, H-6, H-6'), 3.64-3.73 (m, 3H, H-4, H-3, H-2), 5.68 (d, 1H, H-1, $J$ = 8.97 Hz.), 8.28 (s, 1H, H-triazole).

Yield: 92%

Melting point: decomposition at 227 °C

$R_f$ = 0.19 (ethyl acetate)

**Deprotected 1-octyne derivative 35.**



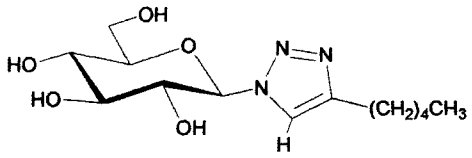

$^1$H NMR ($d_6$-DMSO): $\delta$ 0.84 (t, 3H, R-$(CH_2)_5C\underline{H}_3$, $J$ = 6.62 Hz), 1.26-1.58 (m, 8H), 2.59 (t, 2H, R-$C\underline{H}_2(CH_2)_5CH_3$, $J$ = 7.51 Hz), 3.14-3.38 (m, 3H, H-5, H-6, H-6'), 3.62-3.72 (m, 3H, H-4, H-3, H-2), 5.42 (d, 1H, H-1, $J$ = 9.15 Hz), 8.0 (s, 1H, H-triazole).

Yield: 93%

Melting point: Decomposition at 224 °C

$R_f$ = 0.16 (ethyl acetate)

**Deprotected 1-heptyne derivative 36.**



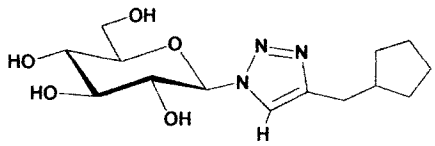

$^1$H NMR ($d_6$-DMSO): $\delta$ 0.85 (t, 3H, R-$(CH_2)_4C\underline{H_3}$, $J$ = 6.95 Hz), 1.27-1.59 (m, 6H), 2.58 (t, 2H, R-$C\underline{H_2}(CH_2)_4CH_3$, $J$ = 7.69 Hz), 3.19-3.34 (m, 3H, H-5, H-6, H-6'), 3.64-3.73 (m, 3H, H-4, H-3, H-2), 5.42 (d, 1H, H-1, $J$ = 9.34 Hz), 8.0 (s, 1H, H-triazole).

Yield: 87%

Melting point: Decomposition at 219 °C

$R_f$ = 0.21 (ethyl acetate)

**Deprotected 3-cyclopentyl-1-propyne derivative 37.**



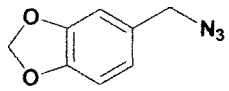

$^1$H NMR ($d_6$-DMSO): $\delta$ 1.14-1.71 (m, 9H), 3.20-3.39 (m, 3H, H-5, H-6, H-6'), 3.70-3.79 (m, 3H, H-4, H-3, H-2), 5.40 (d, 1H, H-1, $J$ = 9.33 Hz), 7.9 (s, 1H, H-triazole).

Yield: 88%

Melting point: Decomposition at 257 °C

$R_f$ = 0.18 (ethyl acetate)

**Preparation of piperonyl azide (39) from piperonyl alcohol (38).**

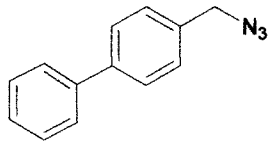


In a microwave reaction test tube, piperonyl alcohol (0.250 g, 1.64 mmol) and *p*-ABSA (0.749 g, 3.28 mmol) were dissolved in $CH_3CN$ (5 mL) followed by the addition of DBU (0.10 mL). The reaction mixture was placed in the CEM BenchMate microwave, heated at 70 °C, and monitored by TLC, which showed complete consumption of starting material after 10 minutes. The reaction mixture was reduced and the residue was partitioned between $CH_2Cl_2$ and $H_2O$ (10 mL each); the aqueous layer was extracted with $CH_2Cl_2$ (3 x 5 mL). The organic layers were combined, washed with 5% $H_2SO_4$ (3 x 10 mL), saturated $NaHCO_3$ (3 x 10 mL) and $H_2O$ (2 x 10 mL). The organic extracts were then combined, dried over $MgSO_4$, and reduced to a yellow syrup. The crude product was purified by flash column chromatography (2:1 hexane – ethyl acetate) to afford pure product as a yellow syrup (0.120 g, 42.8%).

$^1$H NMR ($CDCl_3$): $\delta$ 4.21 (s, 2H, $CH_2N_3$), 5.93 (s, 2H, $OCH_2O$), 6.77-6.80 (m, 3H, H-Ar).

$R_f$ = 0.42 (1:1 hexane – ethyl acetate)

**Preparation of 4-biphenyl methyl azide (41) from 4-biphenyl methanol (40).**

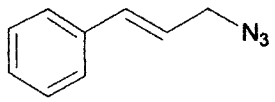



In a microwave reaction test tube, 4-bipheny methanol (0.252 g, 1.37 mmol) and *p*-ABSA (0.658 g, 2.74 mmol) were dissolved in $CH_3CN$ (5 mL) followed by the addition of DBU (0.10 mL). The reaction mixture was placed in the microwave, heated, and monitored by TLC, which showed complete consumption of starting material after 10 minutes. The reaction mixture was reduced and the residue was partitioned between $CH_2Cl_2$ and $H_2O$ (10 mL each); the aqueous layer was extracted with $CH_2Cl_2$ (3 x 5 mL). The organic layers were combined, washed with 5% $H_2SO_4$ (3 x 10 mL), saturated $NaHCO_3$ (3 x 10 mL) and $H_2O$ (2 x 10 mL). The organic extracts were combined, dried over $MgSO_4$, and reduced to a yellow syrup. The crude product was purified by flash column chromatography (2:1 hexane – ethyl acetate) to afford pure product as a yellow syrup (0.133 g, 46.5%).

$^1$H NMR ($CDCl_3$): $\delta$4.39 (s, 2H, $CH_2N_3$), 7.39-7.61 (m, 8H, H-Ar).

$R_f$= 0.46 (1:1 hexane – ethyl acetate)

**Formation of cinnamoyl azide (43) from cinnamyl alcohol (42).**

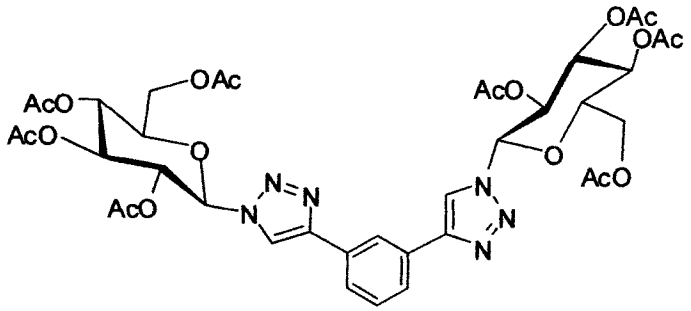



In a microwave reaction test tube, cinnamyl alcohol (0.251 g, 1.87 mmol) and *p*-ABSA (0.858 g, 3.74 mmol) were dissolved in $CH_3CN$ (5 mL) followed by the addition of DBU (0.10 mL). The reaction mixture was placed in the microwave, heated, and monitored by TLC, which showed complete consumption of starting material after 10 minutes. The reaction mixture was reduced and the residue was partitioned between $CH_2Cl_2$ and $H_2O$ (10 mL each); the aqueous layer was extracted with $CH_2Cl_2$ (3 x 5mL). The organic layers were combined, washed with 5% $H_2SO_4$ (3x 10 mL), saturated $NaHCO_3$ (3 x 10 mL) and $H_2O$ (2 x 10 mL). The organic extracts were combined, dried over $MgSO_4$, and reduced to a yellow syrup. The crude product was purified by flash column chromatography (2:1 hexane – ethyl acetate) to afford pure product as a yellow syrup (0.133 g, 44.7%).

$^1H$ NMR ($CDCl_3$): $\delta$ 3.94 (d, 2H, $CH_2N_3$), 6.22-6.31 (m, 2H, CH=), 7.24-7.45 (m, 5H, H-Ar).

$R_f$= 0.44 (1:1 hexane – ethyl acetate)

**Formation of divalent triazole 44 from 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (3).**




In a 50 mL three-neck round-bottom flask equipped with a magnetic stir bar, thermometer, and reflux condenser, glucosyl azide **3** (0.723 g, 1.93 mmol), 1,3-diethynyl benzene (0.12 mL, 0.97 mmol), $CuSO_4$ (0.105, 0.4 mmol), and ascorbic acid (0.139 g, 0.8 mmol) were suspended in a 1:1 mixture of *t*-BuOH and $H_2O$ (16 mL). The yellow suspension was allowed to stir overnight at 70 °C. Once TLC (1:1 hexane – ethyl acetate) showed consumption of starting material, the reaction was cooled and the *t*-BuOH removed *in vacuo*. Cold $H_2O$ was then added to the reaction mixture and the precipitate filtered over a glass frit to afford pure product as a yellow powder (1.42 g, 83%).

$^1$H NMR ($CDCl_3$): $\delta$ 1.89, 2.04, 2.08, 2.10 (4s, 24H, 8x $COCH_3$), 4.10 (ddd, 2H, H-5, $J$ = 2.0, 5.12, 10.25 Hz), 4.18 (dd, 2H, H-6, $J$ = 2.01, 12.82 Hz), 4.35 (dd, 2H, H-6', $J$ = 4.94, 12.63 Hz), 5.30 (t, 2H, H-2, $J$ = 10.07 Hz), 5.45 (t, 2H, H-3, $J$ = 9.52 Hz), 5.54 (t, 2H, H-4, $J$ = 9.52 Hz), 5.95 (d, 2H, H-1, $J$ = 9.15 Hz), 7.51 (t, 1H, Ar-H, $J$ = 7.68 Hz), 7.86 (dd, 2H, Ar-H, $J$ = 1.65, 7.69 Hz), 8.11 (s, 2H, H-triazole), 8.29 (t, 2H, Ar-H, $J$ = 1.65 Hz).

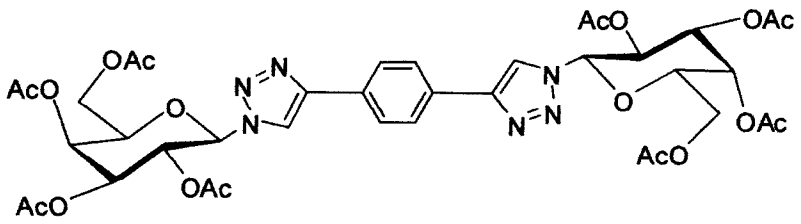
$^{13}C$ NMR ($CDCl_3$): $\delta$ 21.4, 21.8 (double intensity), 21.9, 62.7, 68.8, 71.4, 73.8, 76.1, 86.8, 119.2, 124.1, 126.8, 130.4, 131.4, 148.8, 169.9, 170.3, 170.8, 171.4.

*m/z* calculated: 872.26 *m/z* found: 895.50 (+Na)

Melting point: 132 °C

$R_f$ = 0.31 (1:1 hexane – ethyl acetate)

**Formation of divalent triazole 45 from 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl azide (6).**




In a 50 mL three-neck round-bottom flask equipped with a magnetic stir bar, thermometer, and reflux condenser, galactosyl azide **6** (0.502 g, 1.34 mmol), 1,4-diethynyl benzene (0.084 g, 0.51 mmol), $CuSO_4$ (0.105, 0.4 mmol), and ascorbic acid (0.139 g, 0.8 mmol) were suspended in a 1:1 mixture of *t*-BuOH and $H_2O$ (16 mL). The orange suspension was allowed to stir overnight at 70 °C. Once TLC (1:1 hexane – ethyl acetate) showed consumption of starting material, the reaction was cooled and the *t*-BuOH removed *in vacuo*. Cold $H_2O$ was added to the reaction mixture and the precipitate filtered over a glass frit to afford pure product as an orange powder (1.02 g, 85%).

$^{1}$H NMR ($CDCl_3$): $\delta$ 1.88, 1.99, 2.01, 2.22 (4s, 24H, 8x $COCH_3$), 4.14-4.27 (m, 6H, H-5, H-6, H-6'), 5.29 (m, 2H), 5.55 (m, 2H), 5.64 (t, 2H, $J$ = 10.07 Hz), 5.92 (d, 2H, H-1, $J$ = 9.34 Hz), 7.90 (m, 4H, Ar-H), 8.09 (s, 2H, H-triazole).

$^{13}$C NMR ($CDCl_3$): $\delta$ 21.5, 21.7, 21.93, 21.98, 62.4, 68.0, 68.9, 71.9, 75.1 87.3, 119.1, 127.3 (double intensity), 131.0, 148.8, 170.1, 170.7, 170.9, 171.2.

*m/z* calculated: 872.26 *m/z* found: 895.5 (+Na)

Melting point: decomposition at 235 °C

$R_f$ = 0.28 (1:1 hexane – ethyl acetate)

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# Appendix

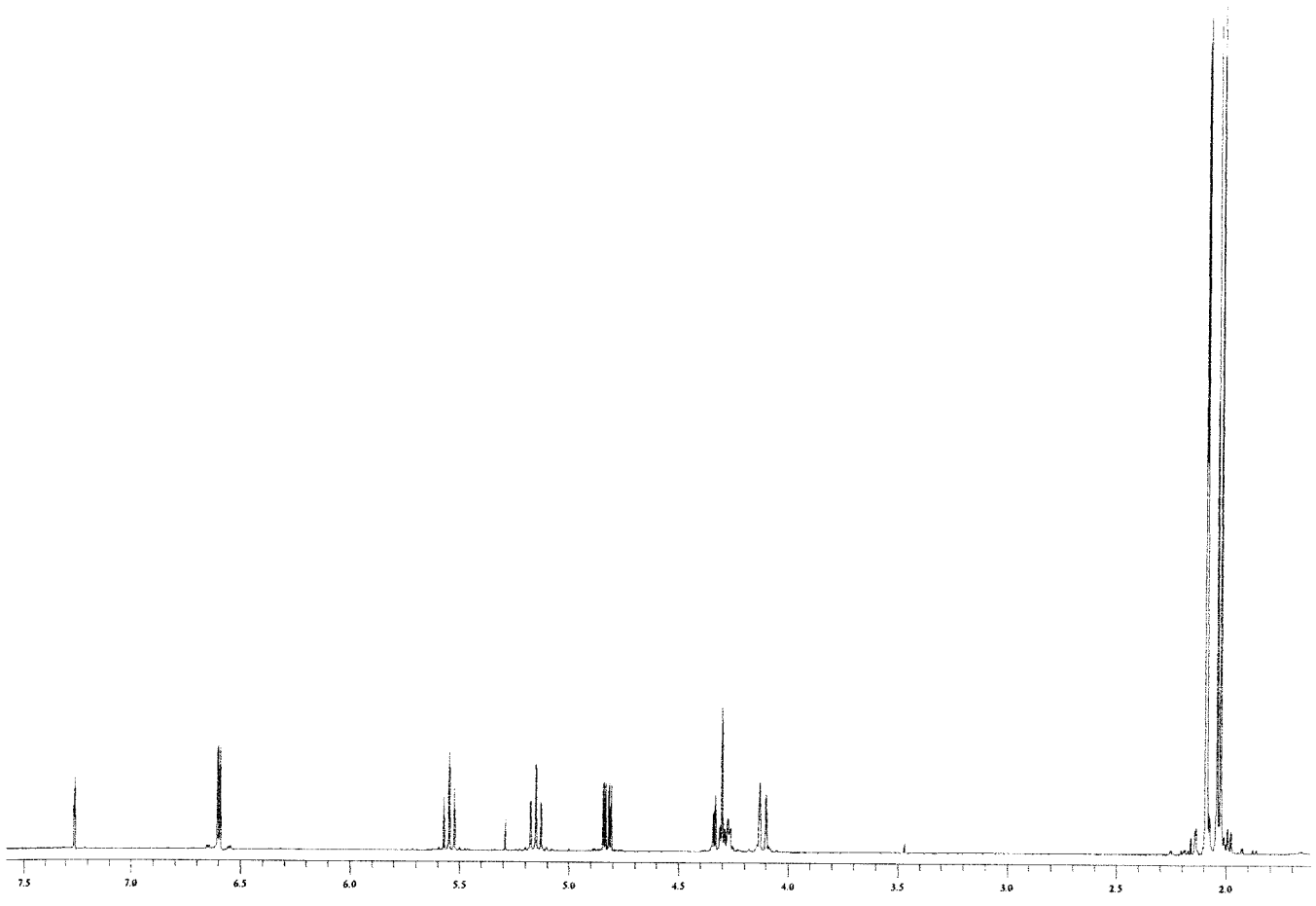


**Figure 14:** 400 MHz $^{1}$H NMR spectrum of bromide product **2**

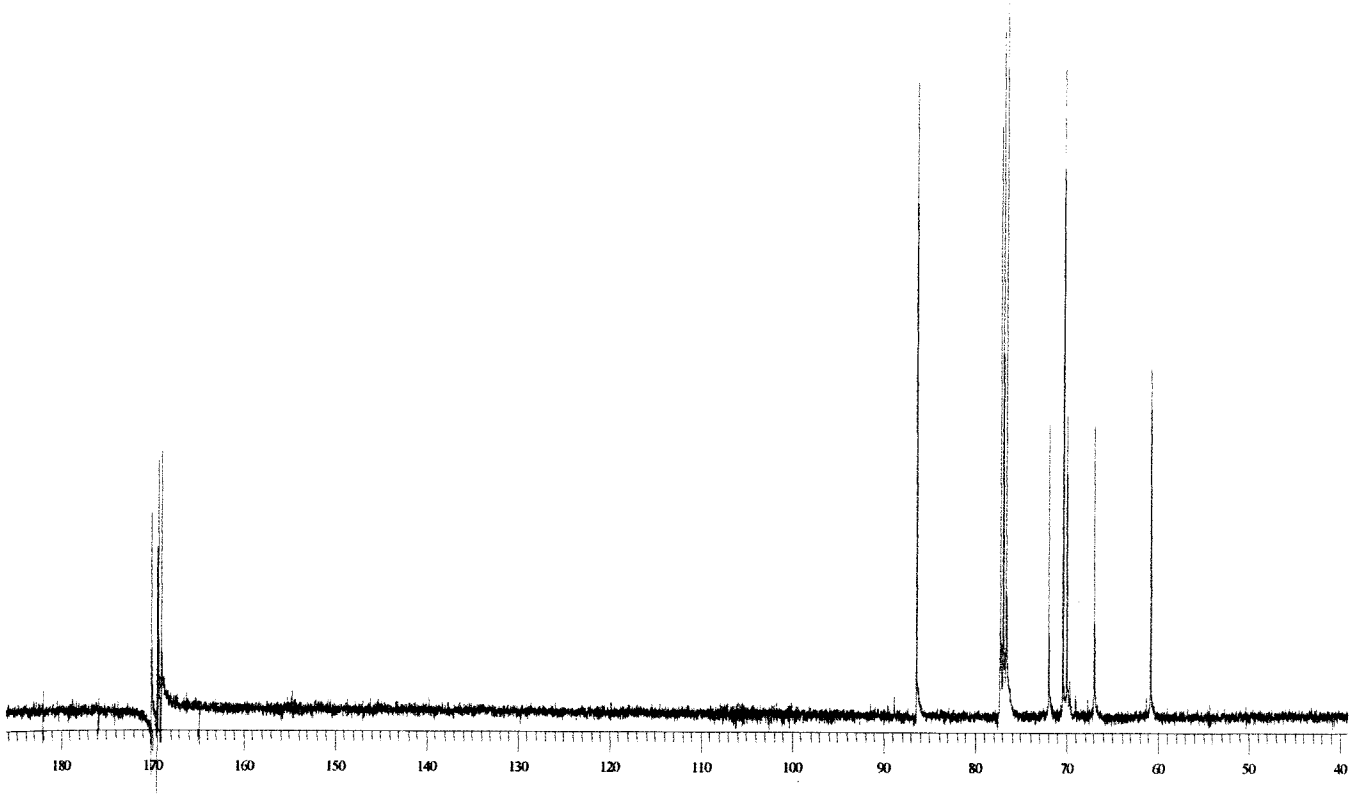


**Figure 15**: 100 MHz $^{13}C$ NMR spectrum of bromide product **2**

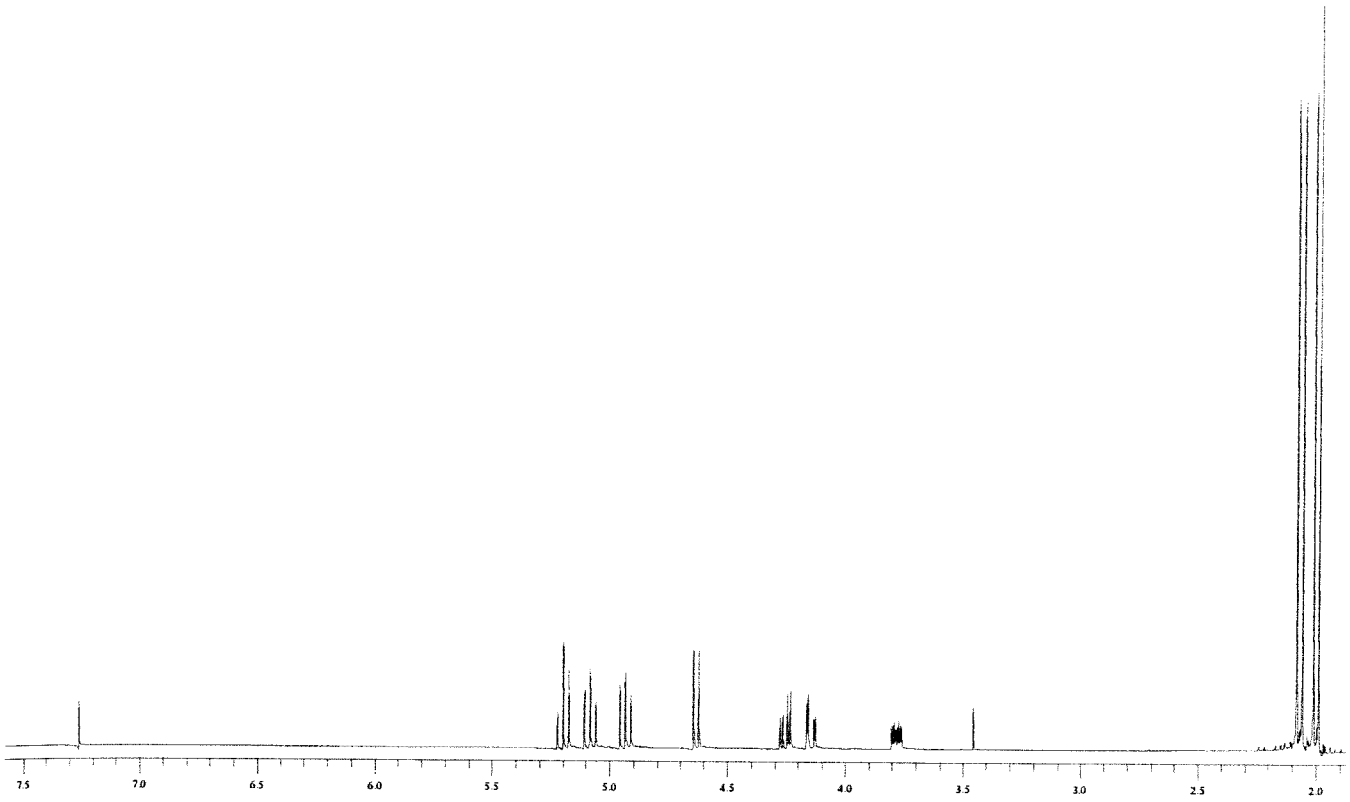


**Figure 16**: 400 MHz $^{1}$H NMR spectrum of azide **3**

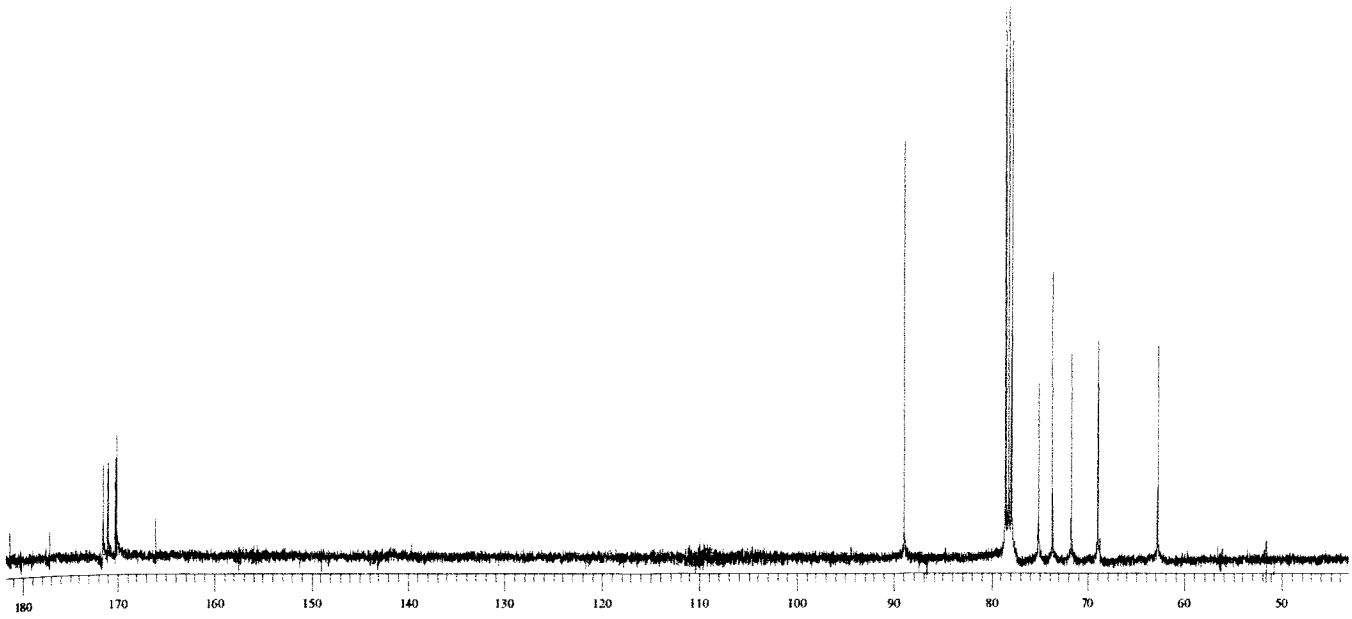


**Figure 17**: 100 MHz $^{13}C$ NMR spectrum of azide **3**

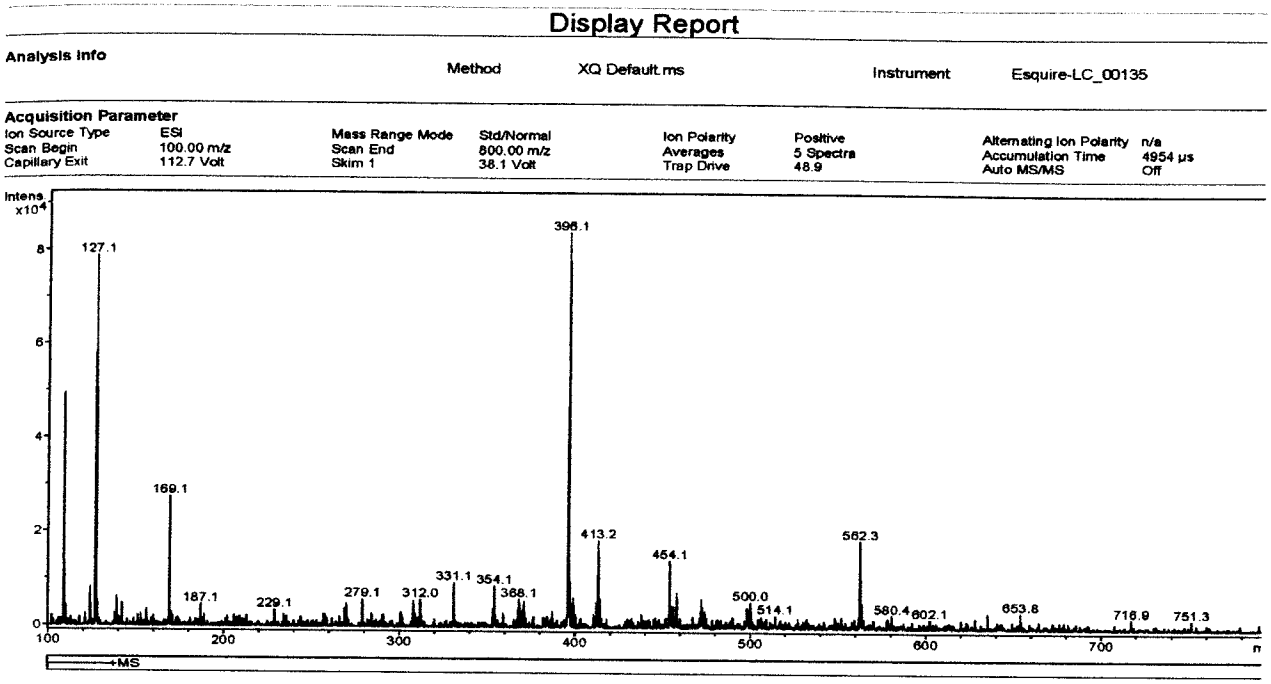


**Figure 18**: Mass Spectrum of azide product **3**

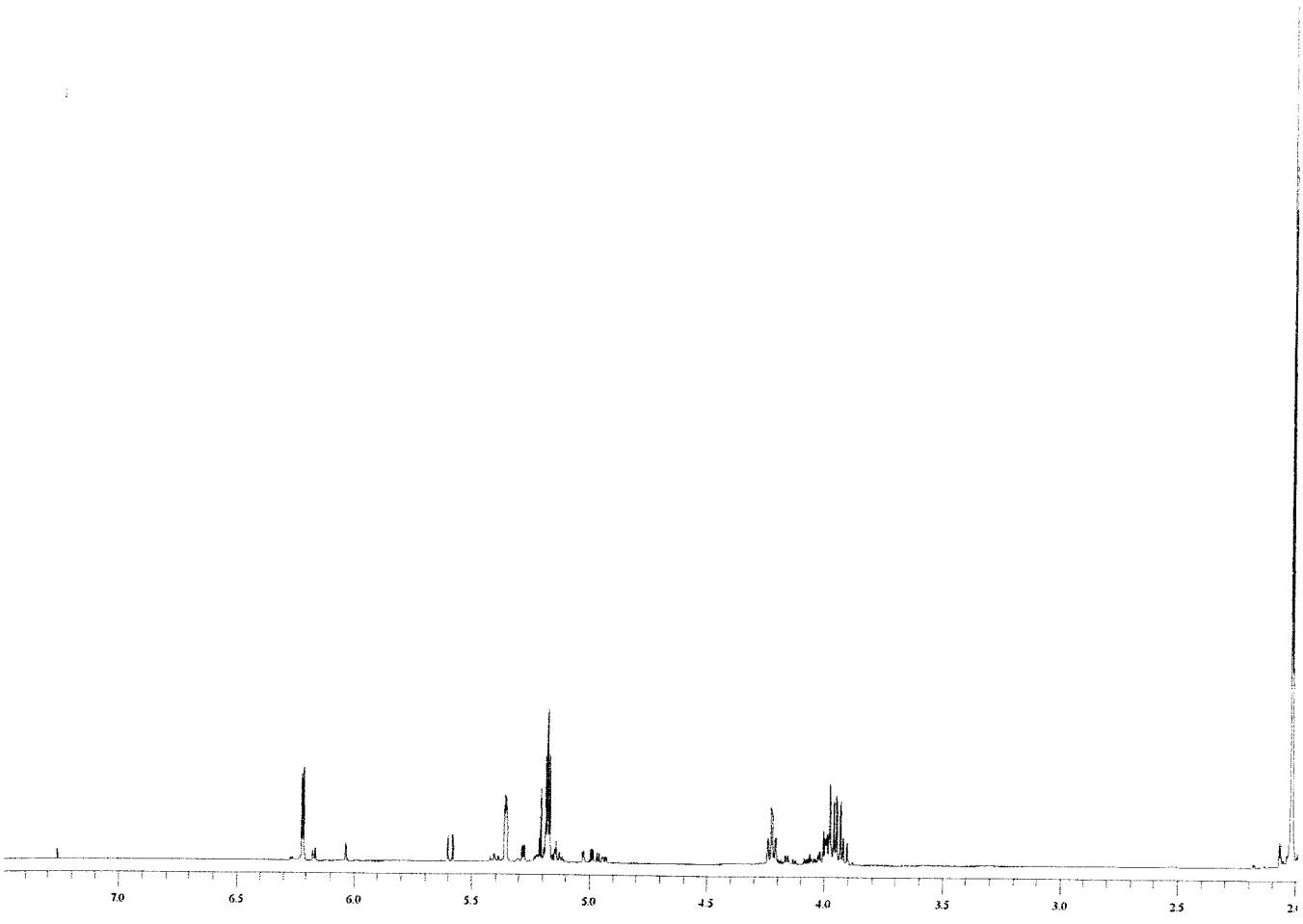


**Figure 19**: 400 MHz $^{1}$H NMR spectrum of bromide product **5**

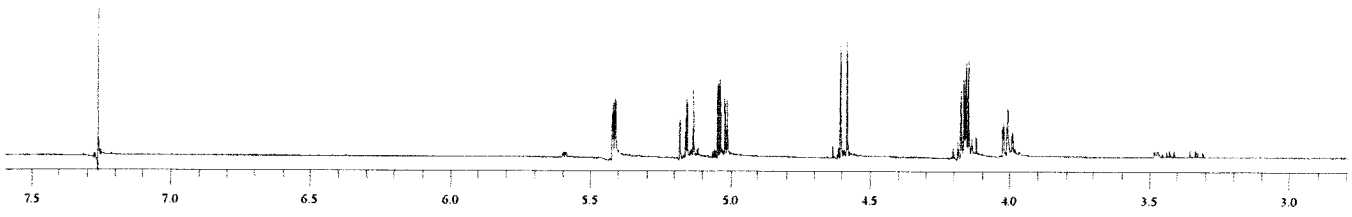


**Figure 20**: 400 MHz $^{1}$H NMR spectrum of azide product **6**

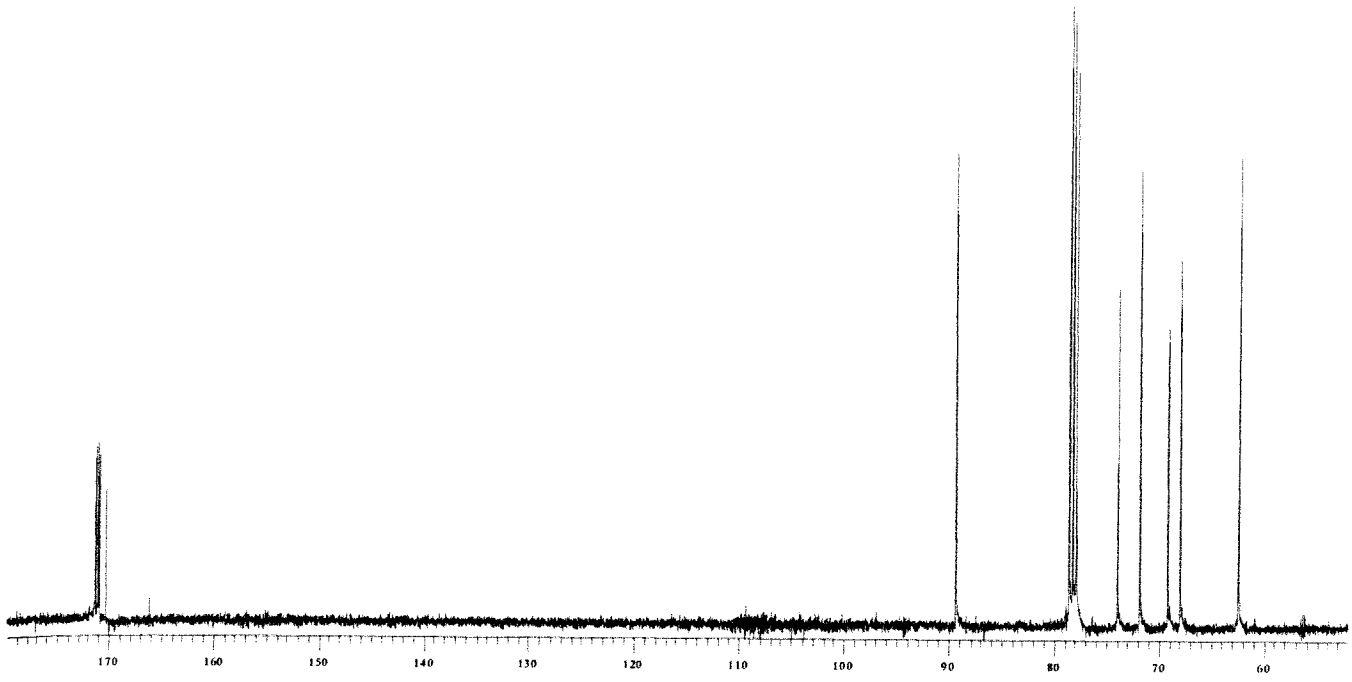


**Figure 21**: 100 MHz $^{13}C$ NMR spectrum of azide product **6**

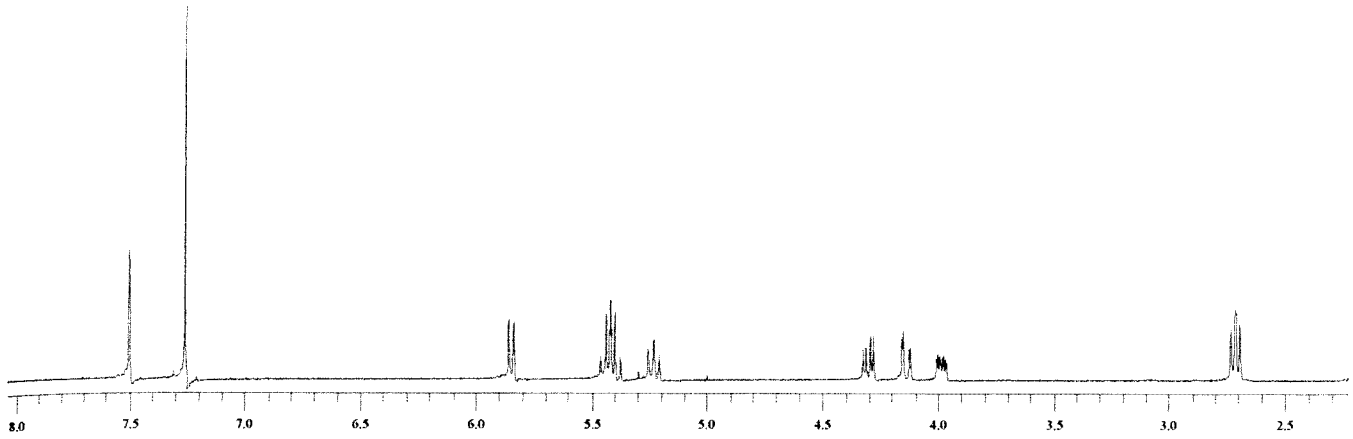


**Figure 22**: 400 MHz $^{1}$H NMR spectrum of triazole product **7**

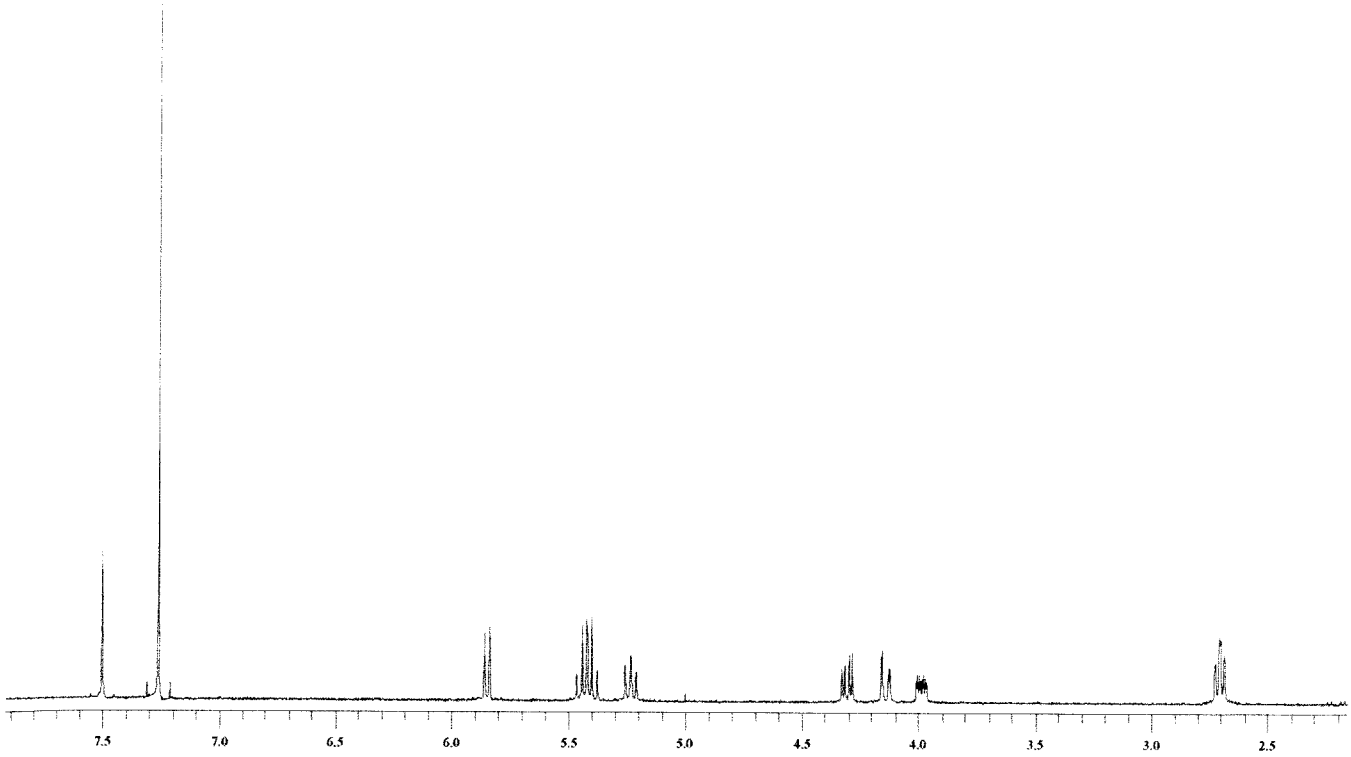


**Figure 23**: 400 MHz $^{1}$H NMR spectrum of triazole product **8**

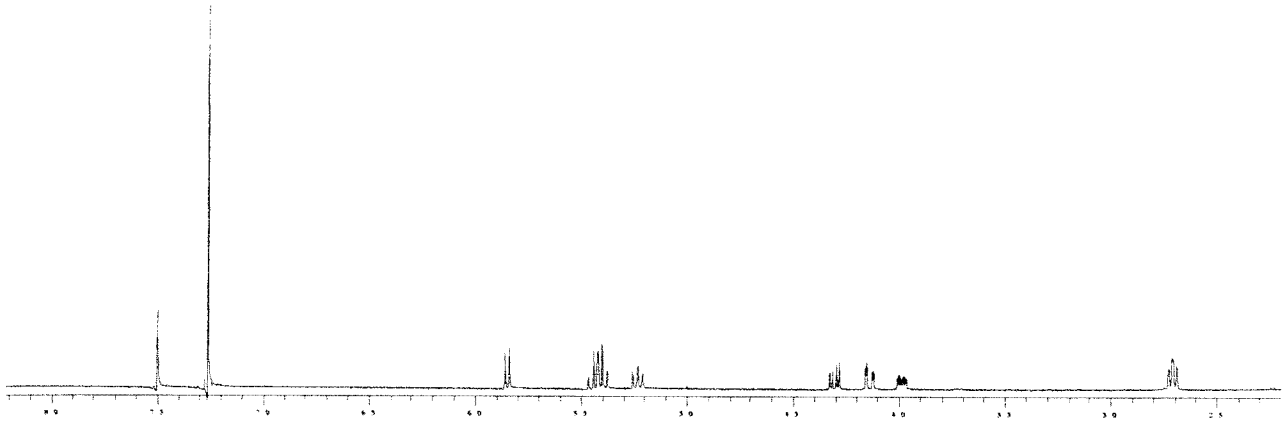

**Figure 24**: 400 MHz $^{1}$H NMR spectrum of triazole product **9**

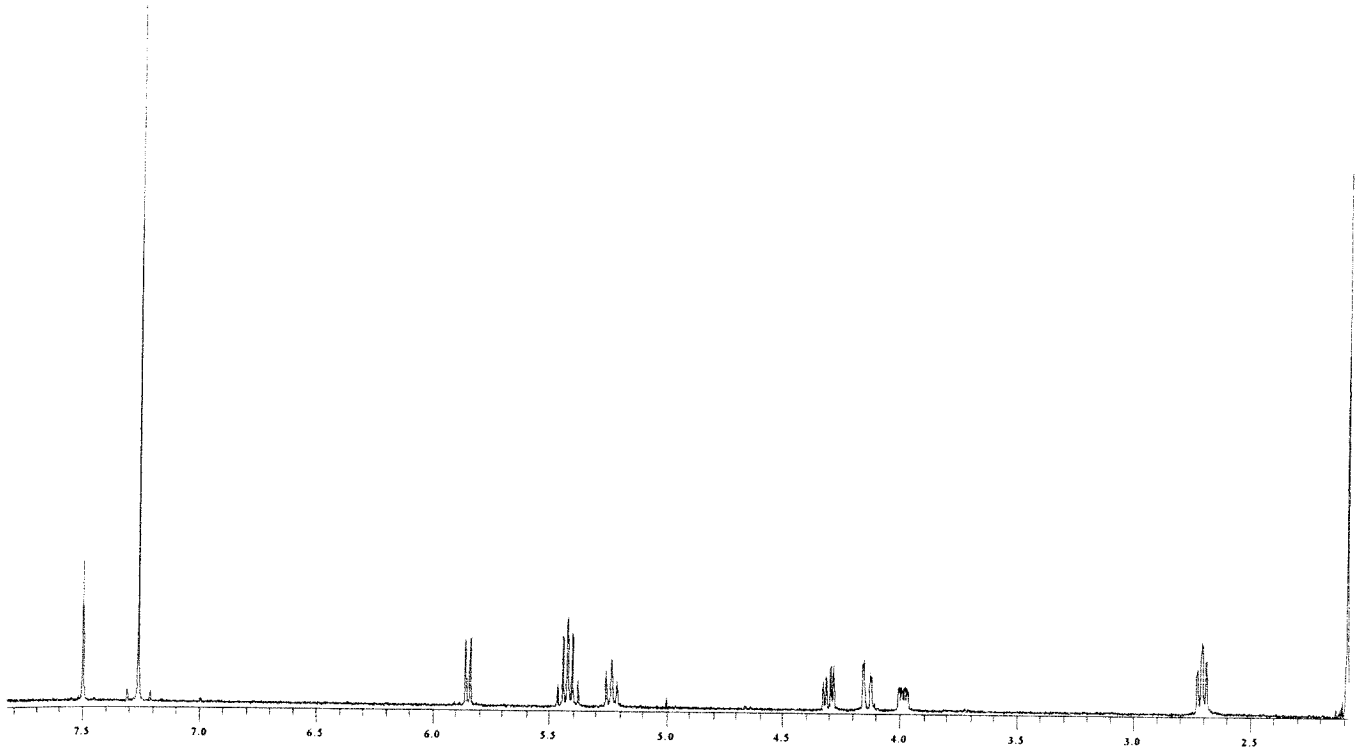


**Figure 25**: 400 MHz $^{1}$H NMR spectrum of triazole product **10**

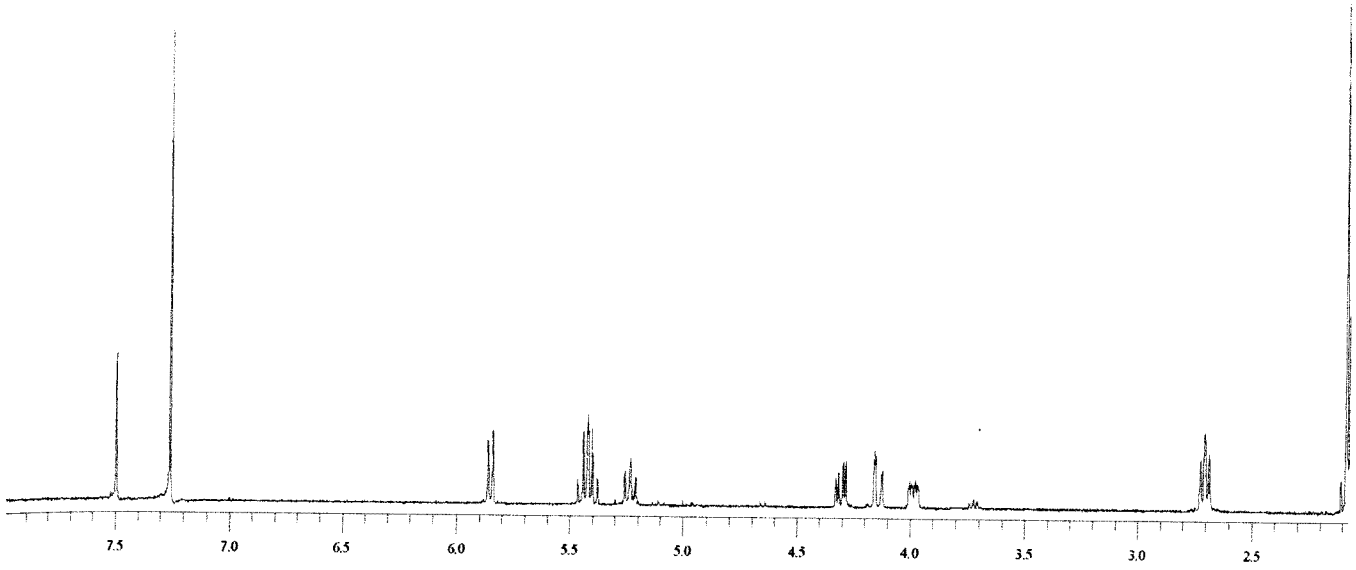


**Figure 26**: 400 MHz $^{1}$H NMR spectrum of triazole product **11**

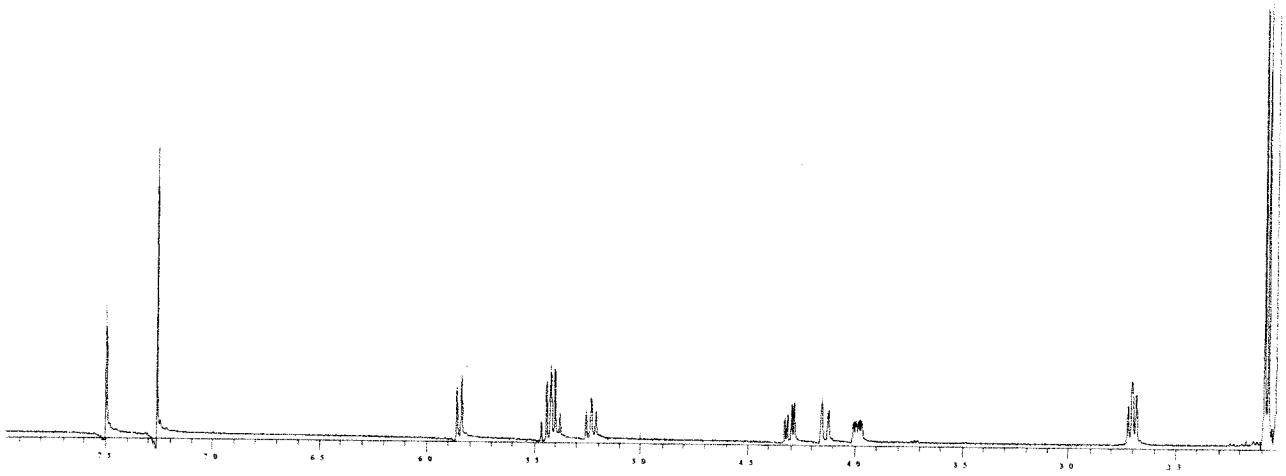

**Figure 27**: 400 MHz $^{1}$H NMR spectrum of triazole product **12**

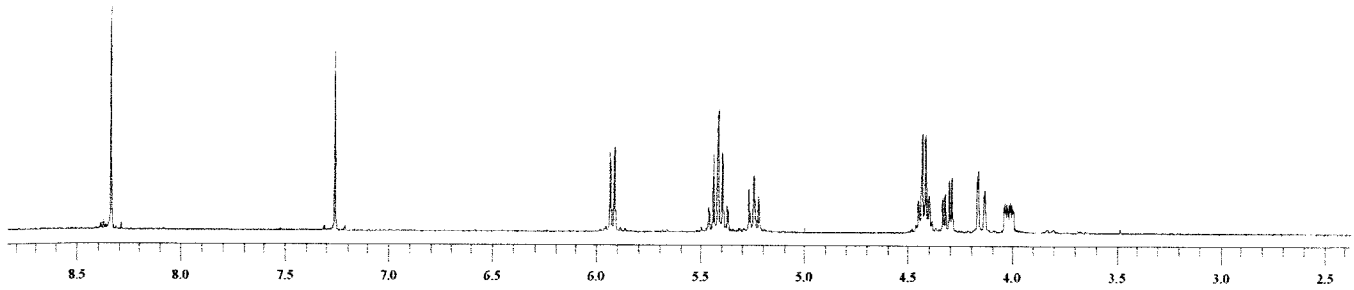


**Figure 28**: 400 MHz $^{1}$H NMR spectrum of triazole product **13**

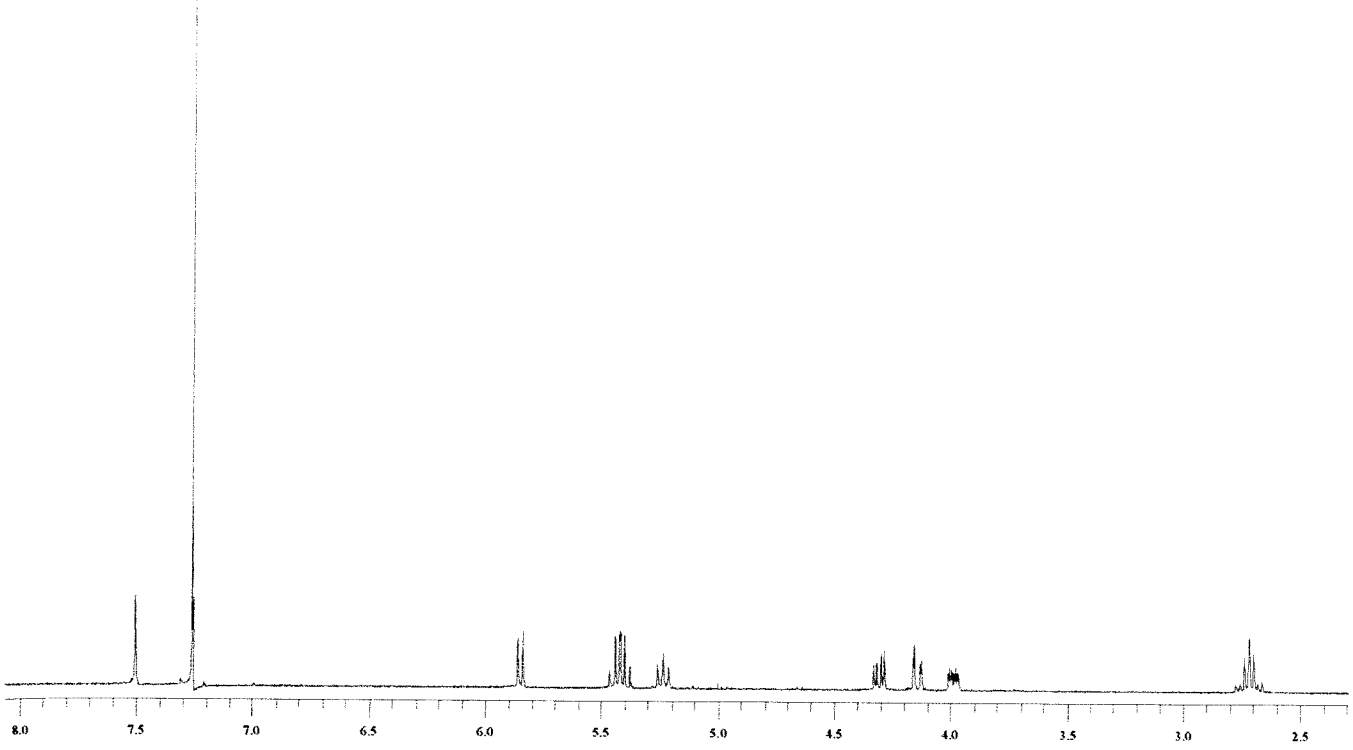


**Figure 39**: 400 MHz $^{1}$H NMR spectrum of triazole product **14**

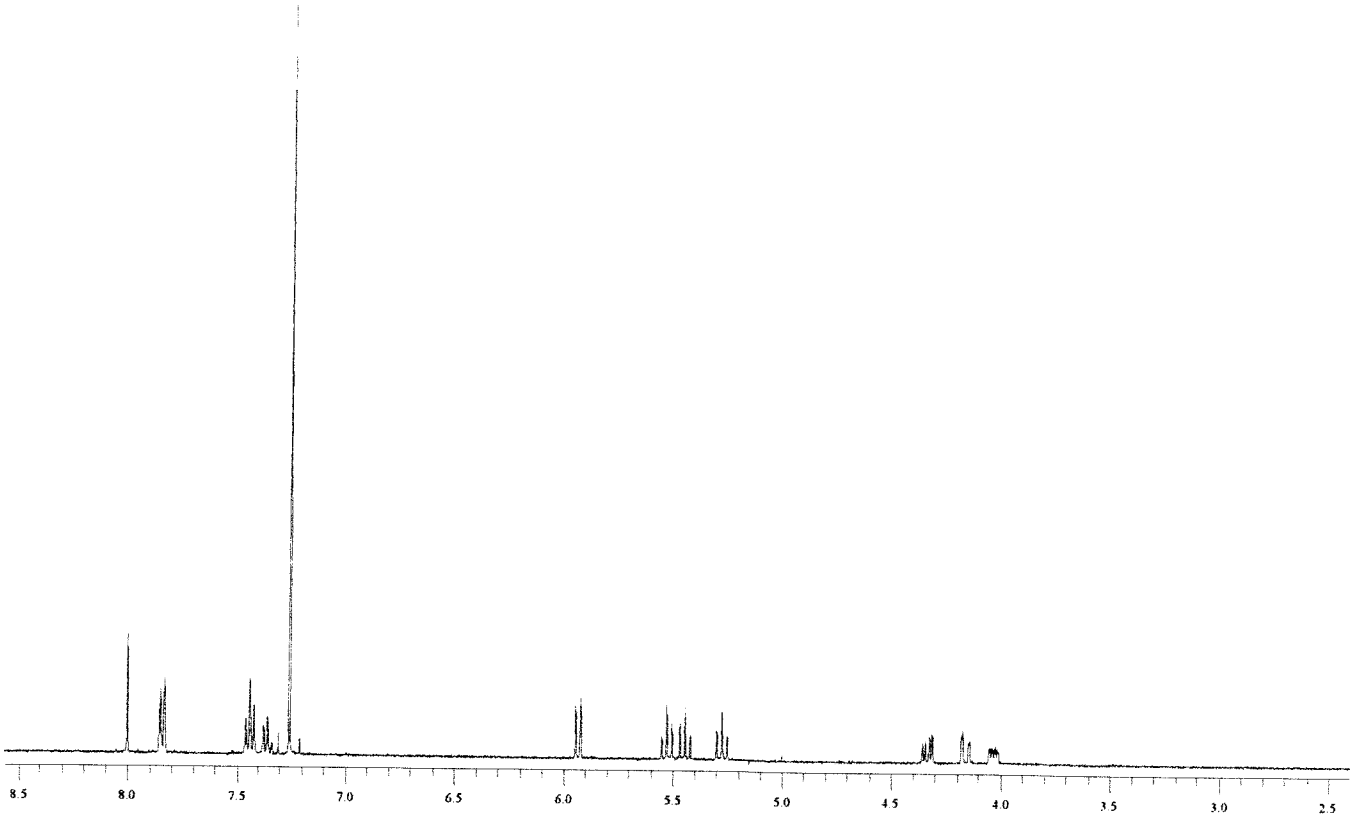


**Figure 30**: 400 MHz $^{1}$H NMR spectrum of triazole product **15**

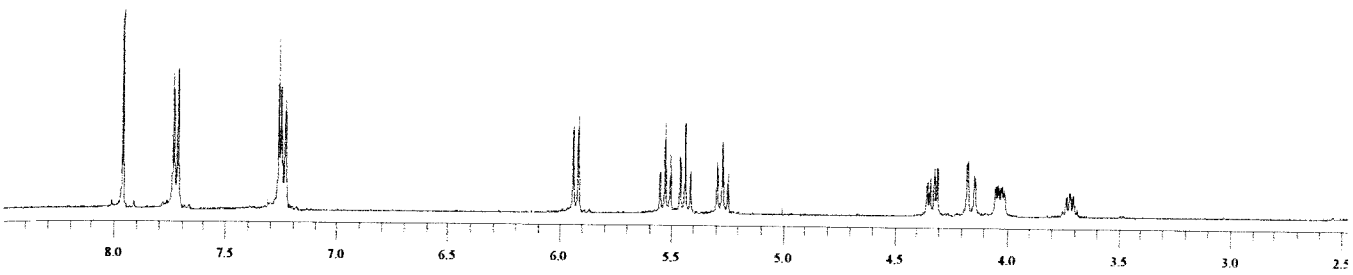


**Figure 31**: 400 MHz $^{1}$H NMR spectrum of triazole product **16**

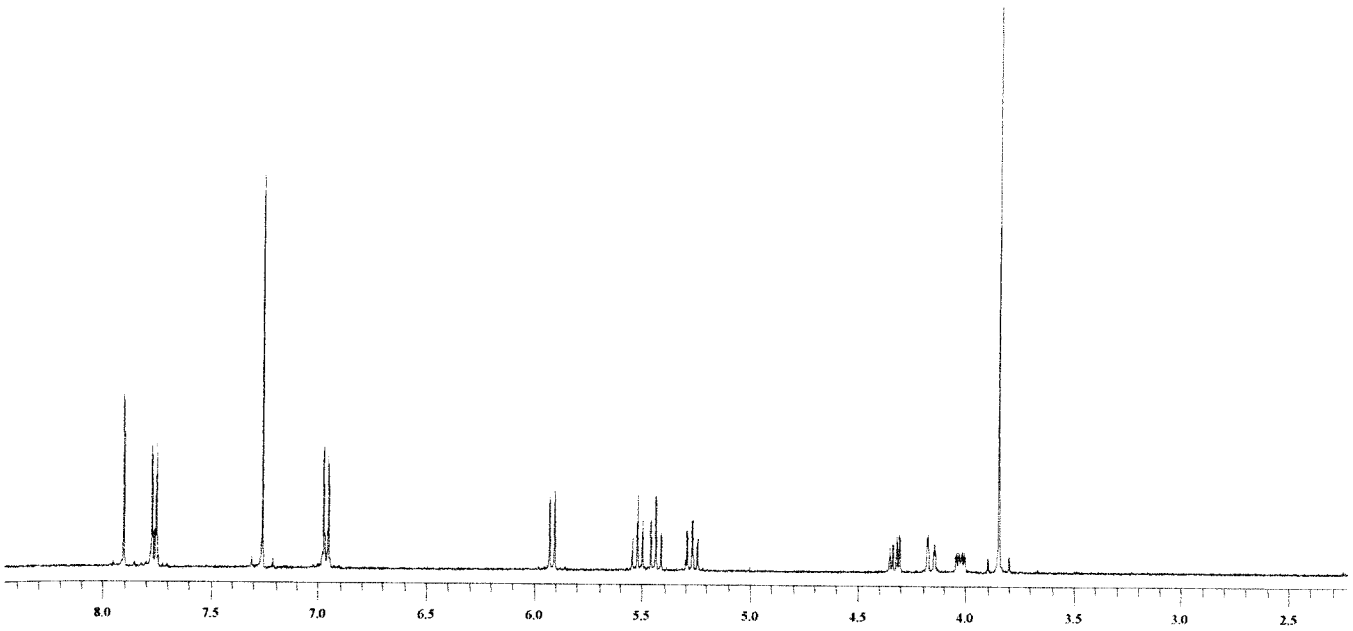


**Figure 32**: 400 MHz $^{1}$H NMR spectrum of triazole product **17**

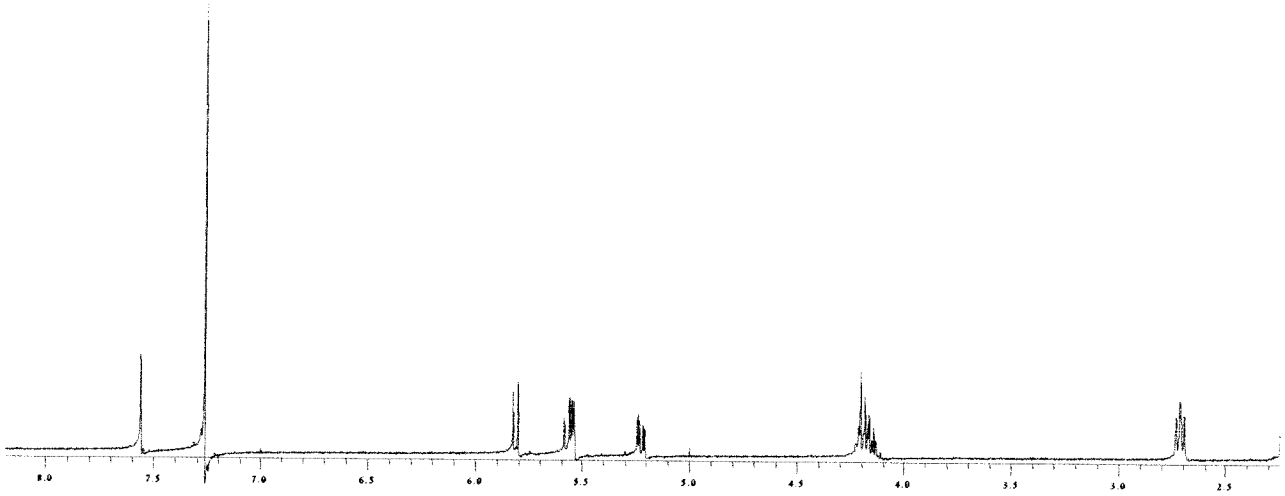


**Figure 33**: 400 MHz $^{1}$H NMR spectrum of triazole product **18**

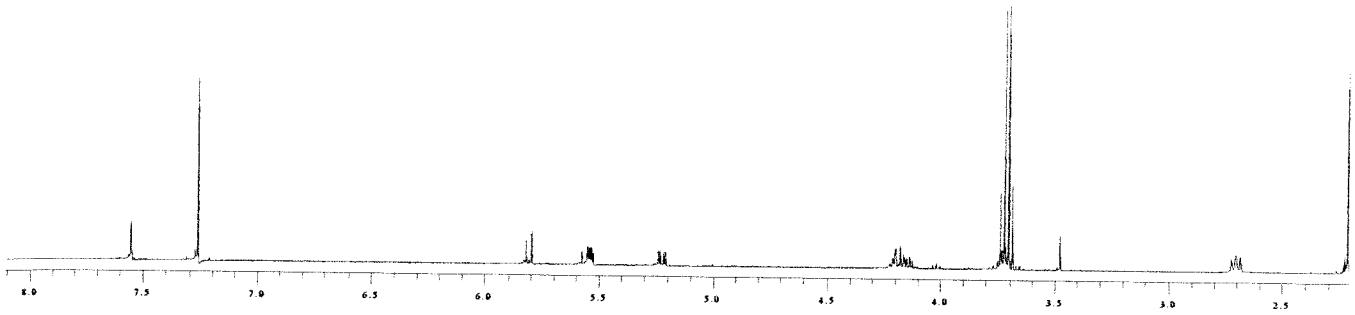


**Figure 34**: 400 MHz $^{1}$H NMR spectrum of triazole product **19**

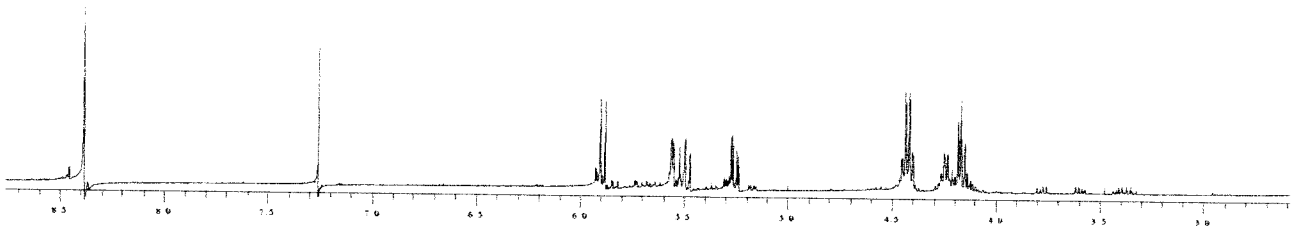

**Figure 35**: 400 MHz $^{1}$H NMR spectrum of triazole product **20**

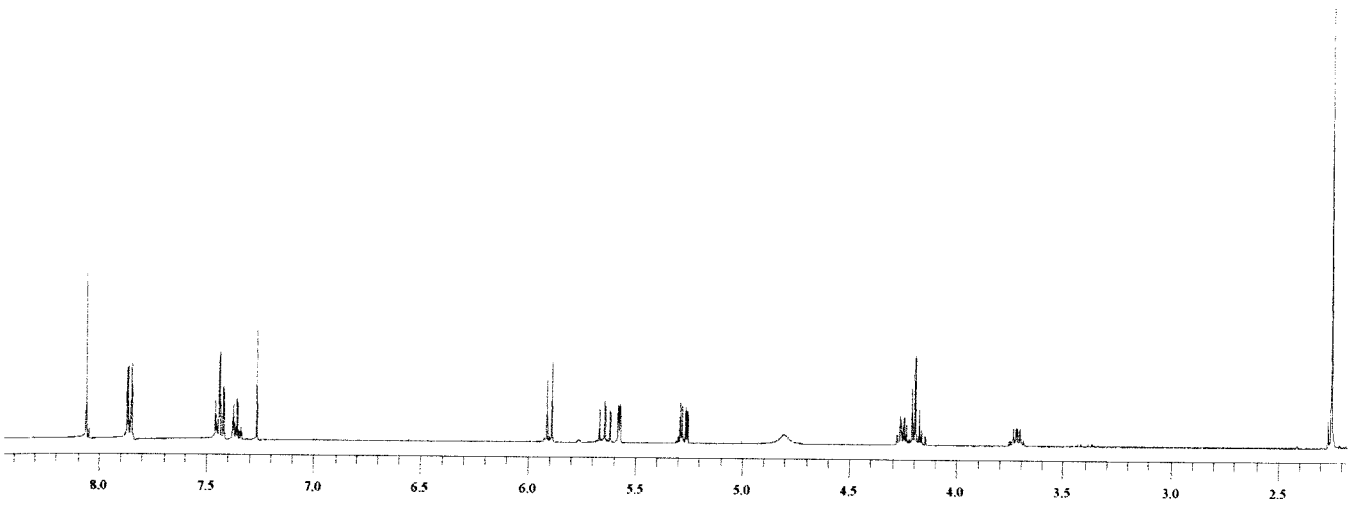


**Figure 36**: 400 MHz $^{1}$H NMR spectrum of triazole product **21**

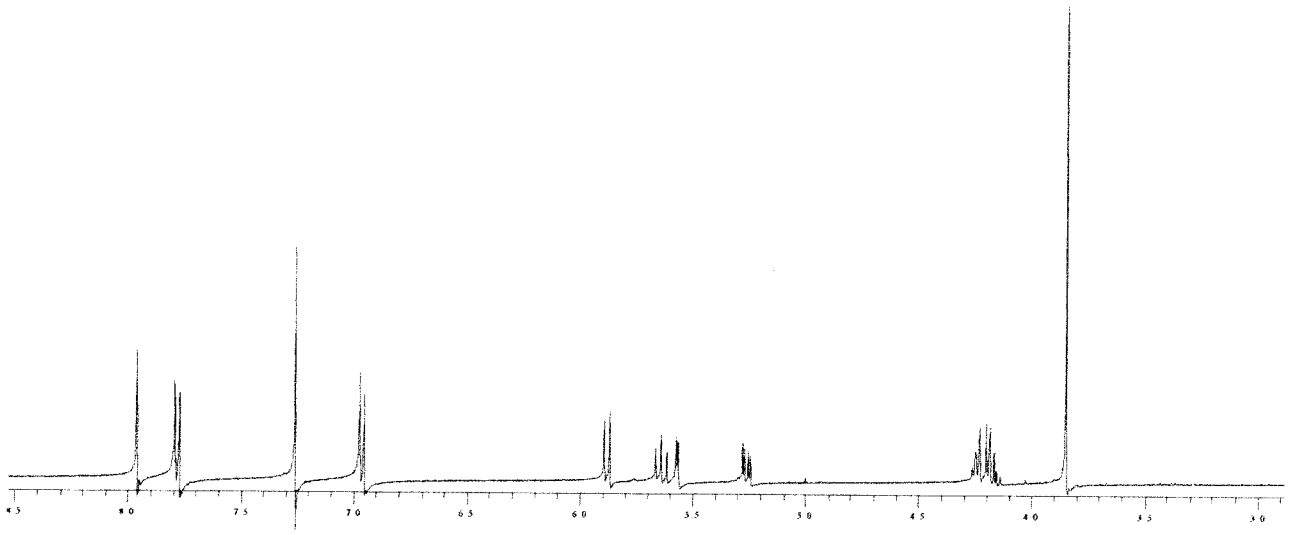

**Figure 37**: 400 MHz $^{1}$H NMR spectrum of triazole product **22**

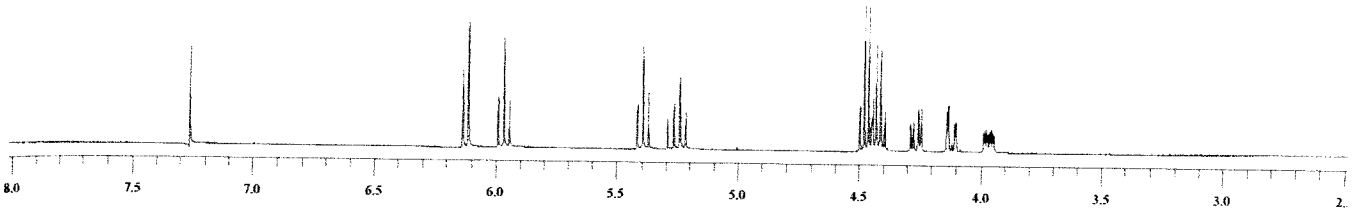


**Figure 38**: 400 MHz $^{1}$H NMR spectrum of triazole product **23**

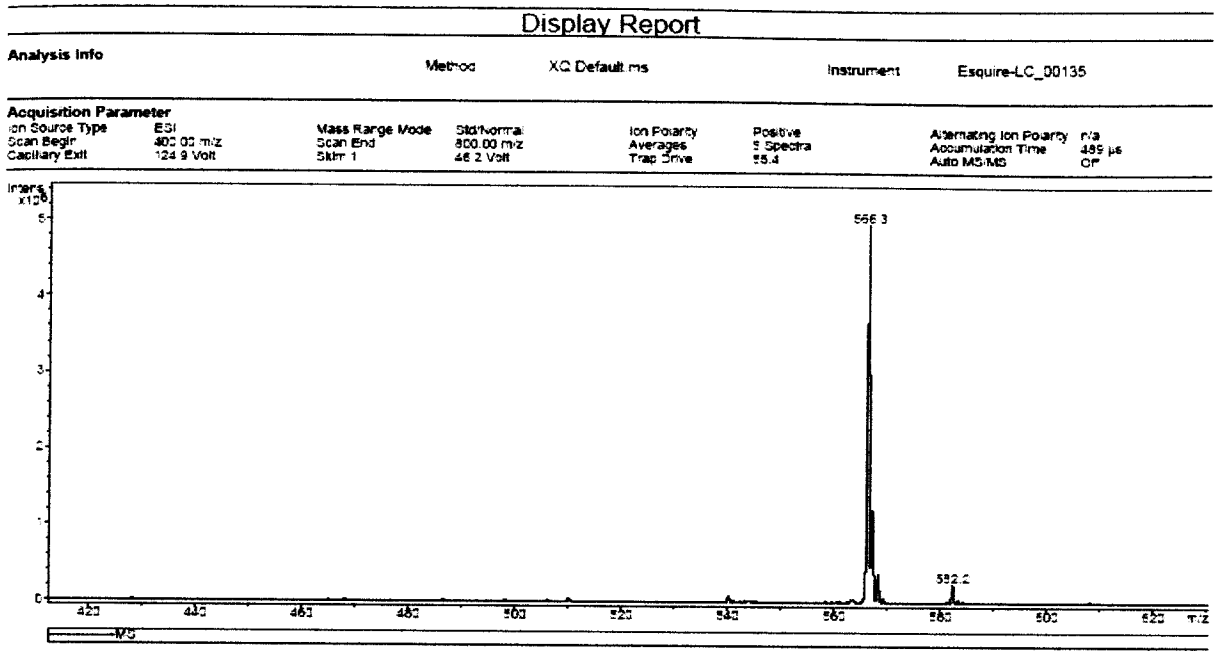


**Figure 39**: Mass spectrum of triazole product **23**

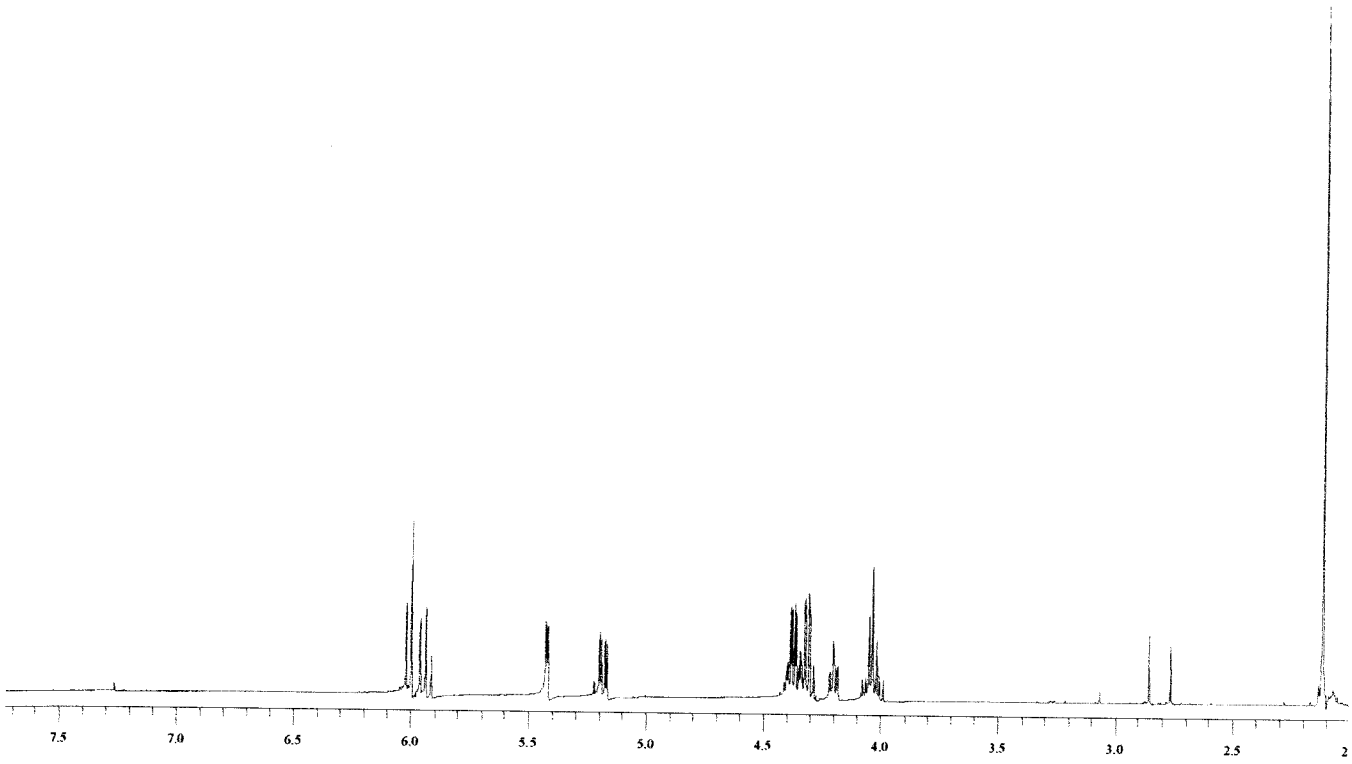


**Figure 40**: 400 MHz $^{1}$H NMR spectrum of triazole product **24**

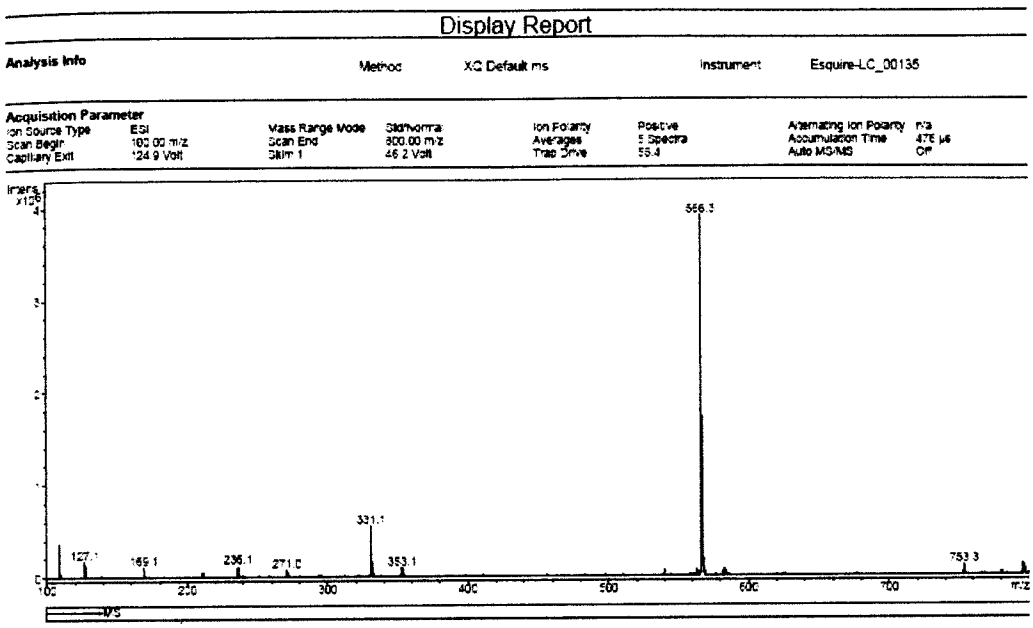


**Figure 41**: Mass spectrum of triazole product **24**

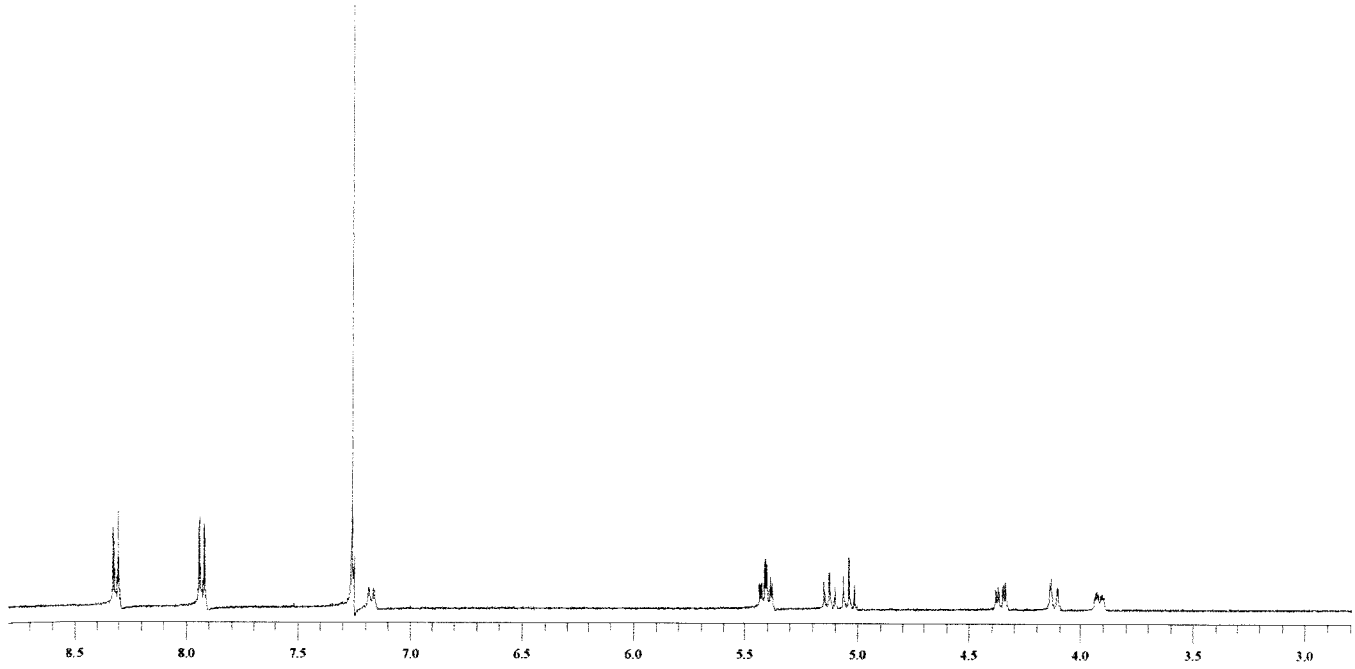


**Figure 42**: 400 MHz $^{1}$H NMR spectrum of amide product **25**

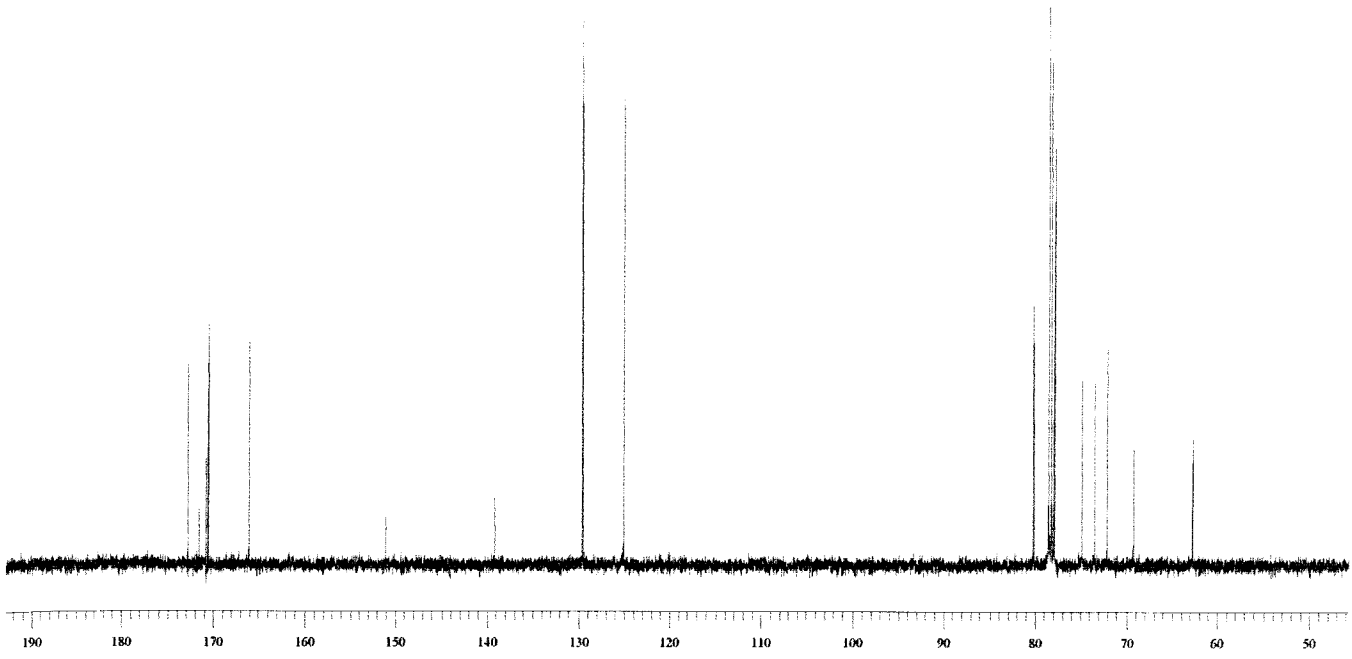


**Figure 43**: 100 MHz $^{13}C$ NMR spectrum of amide product **25**

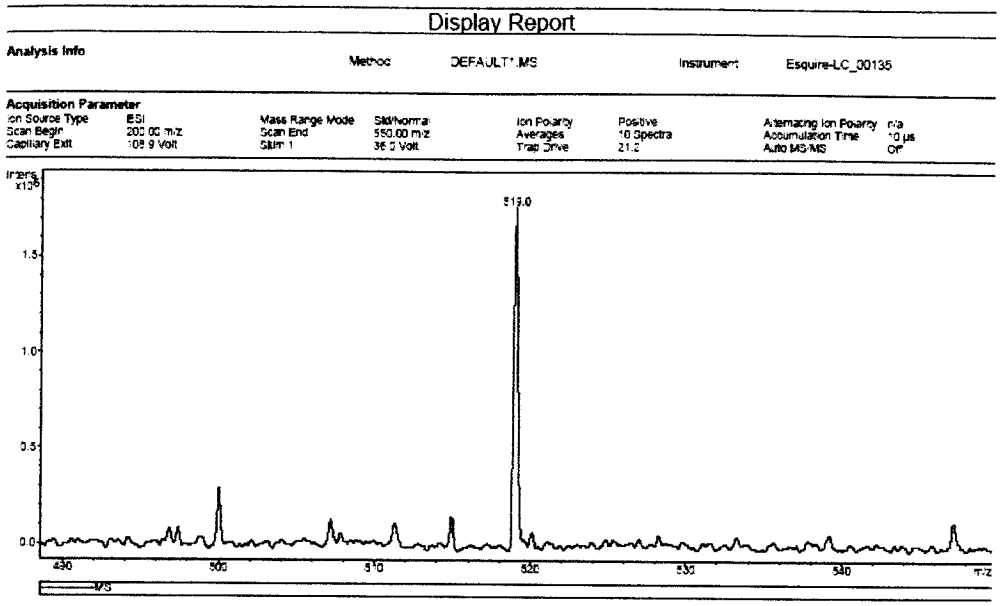


**Figure 44**: Mass spectrum of amide product **25**

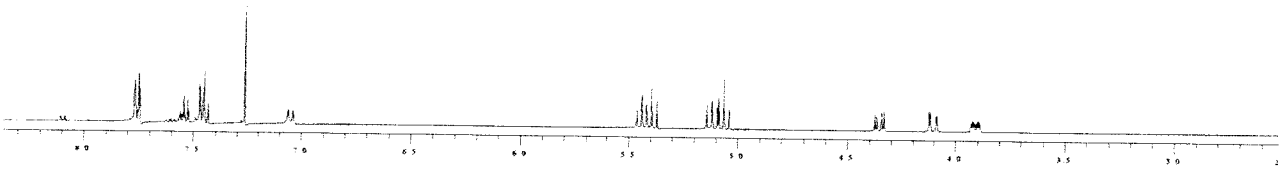

**Figure 45**: 400 MHz $^{1}$H NMR spectrum of amide product **26**

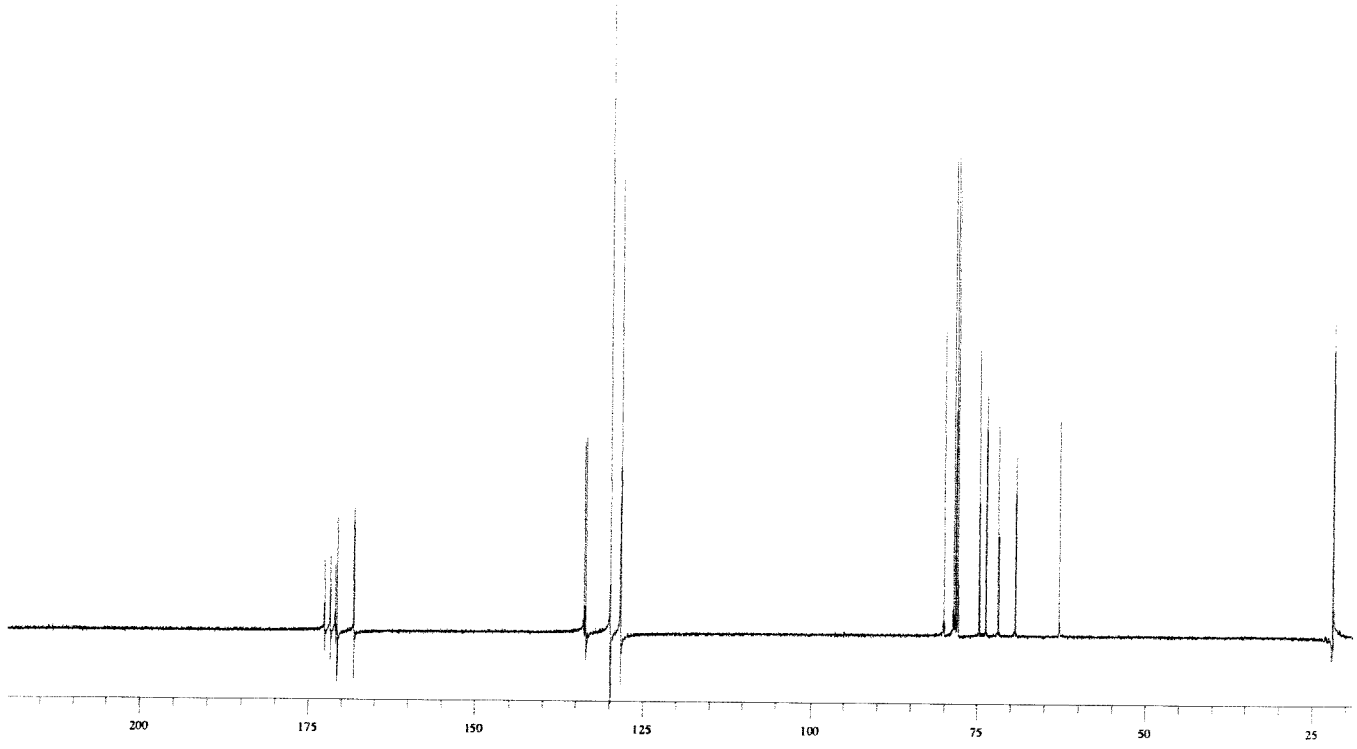


**Figure 46**: 100 MHz $^{13}C$ NMR spectrum of amide product **26**

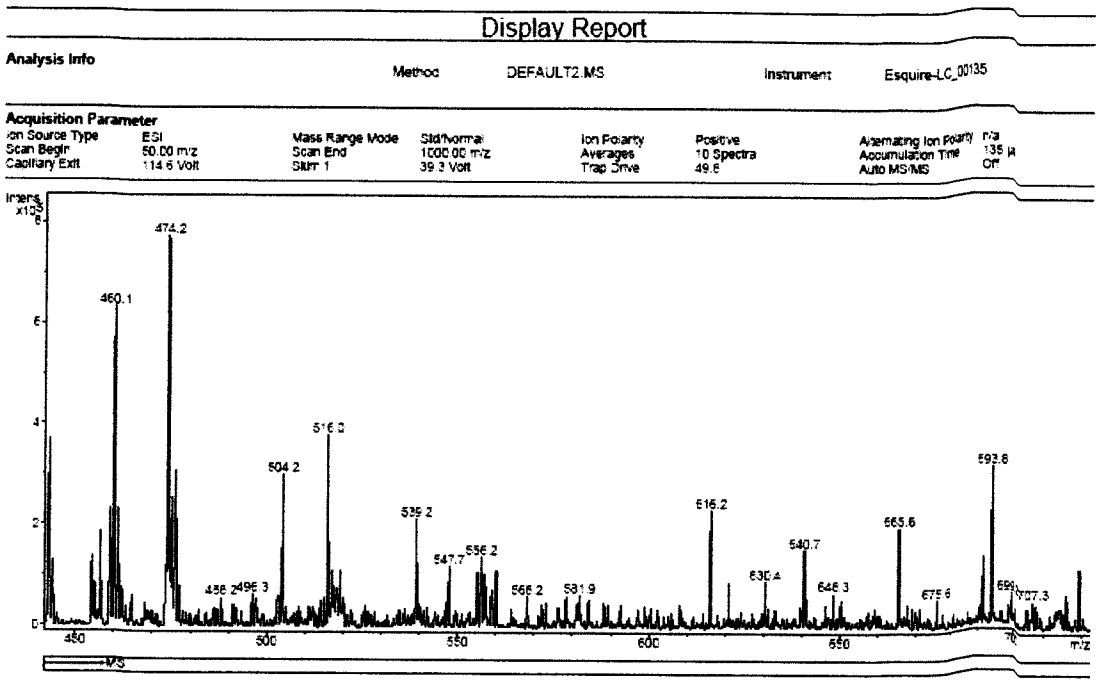


**Figure 47**: Mass spectrum of amide product **26**

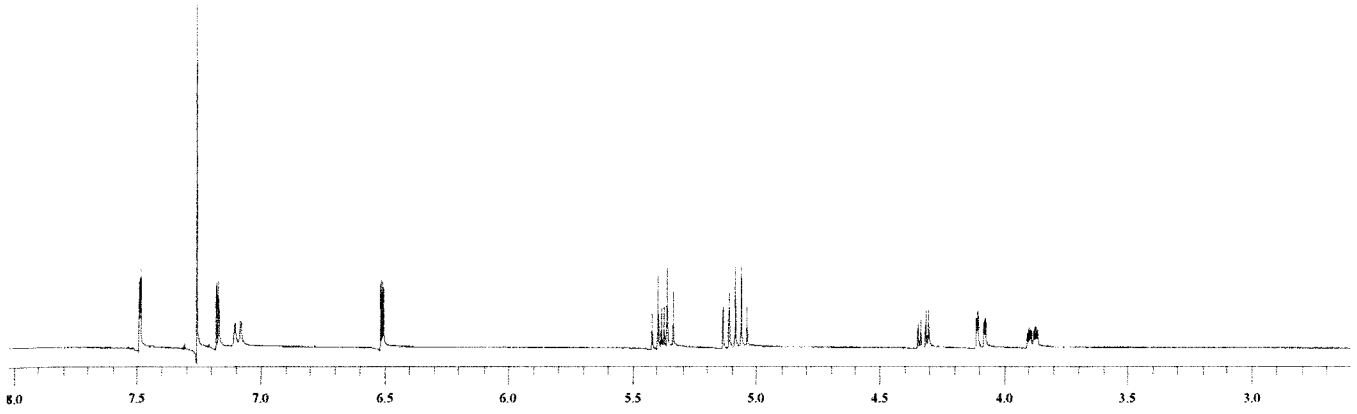


**Figure 48**: 400 MHz $^{1}$H NMR spectrum of amide product **27**

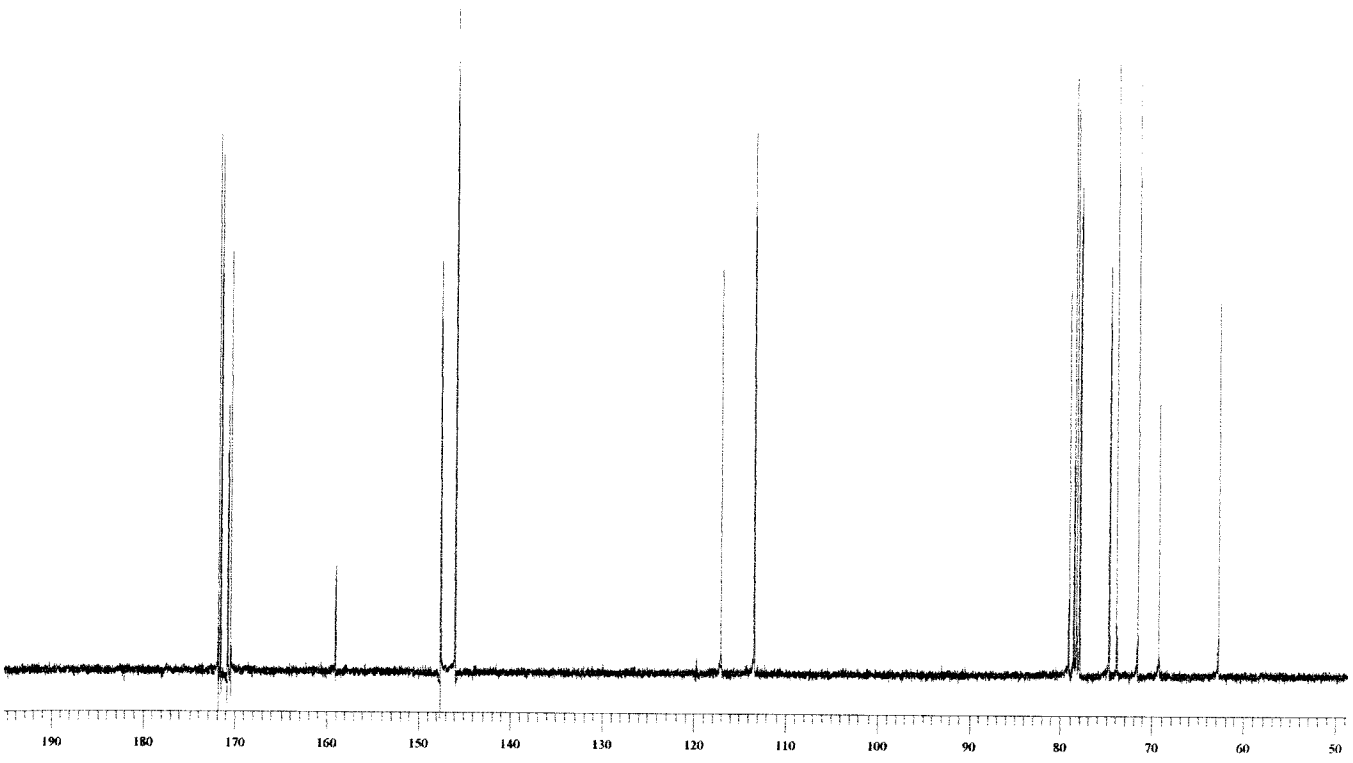


**Figure 49**: 100 MHz $^{13}C$ NMR spectrum of amide product **27**

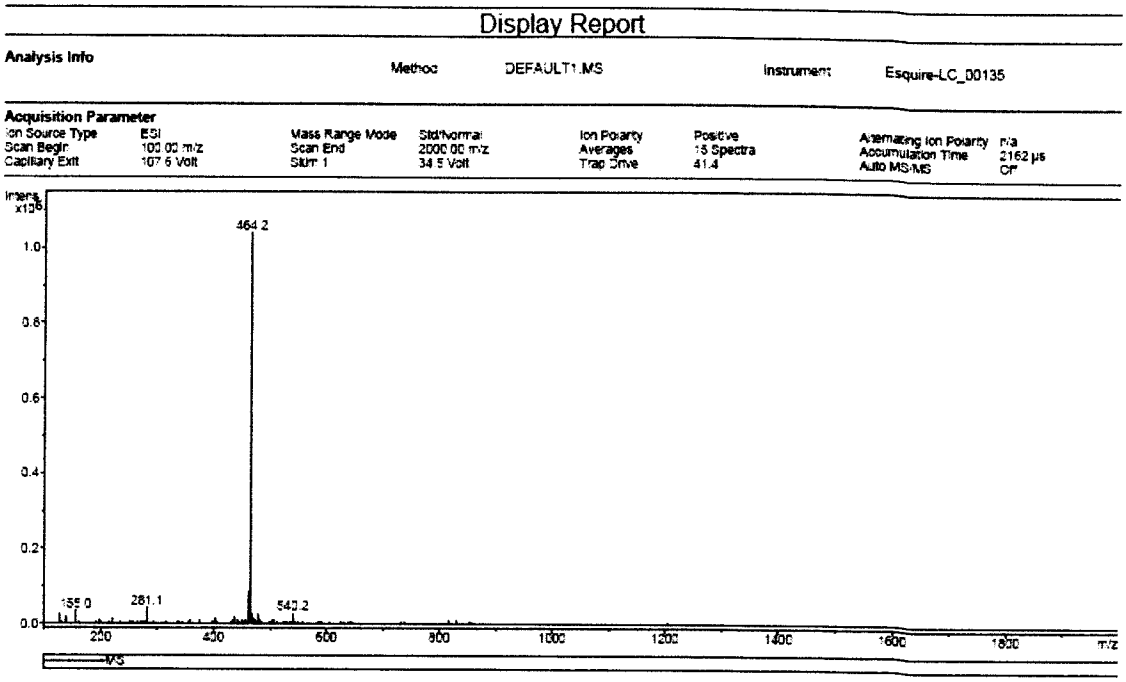


**Figure 50**: Mass spectrum of amide product **27**

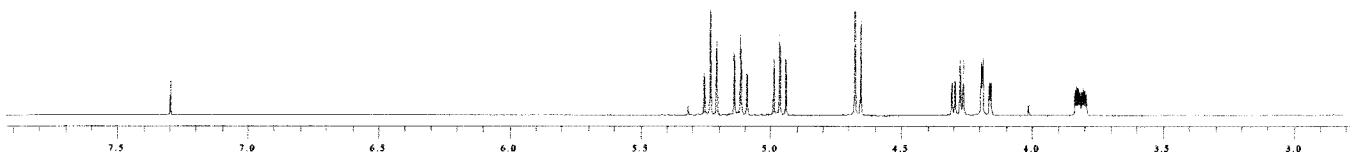


**Figure 51**: 400 MHz $^{1}$H NMR spectrum of amide product **28**

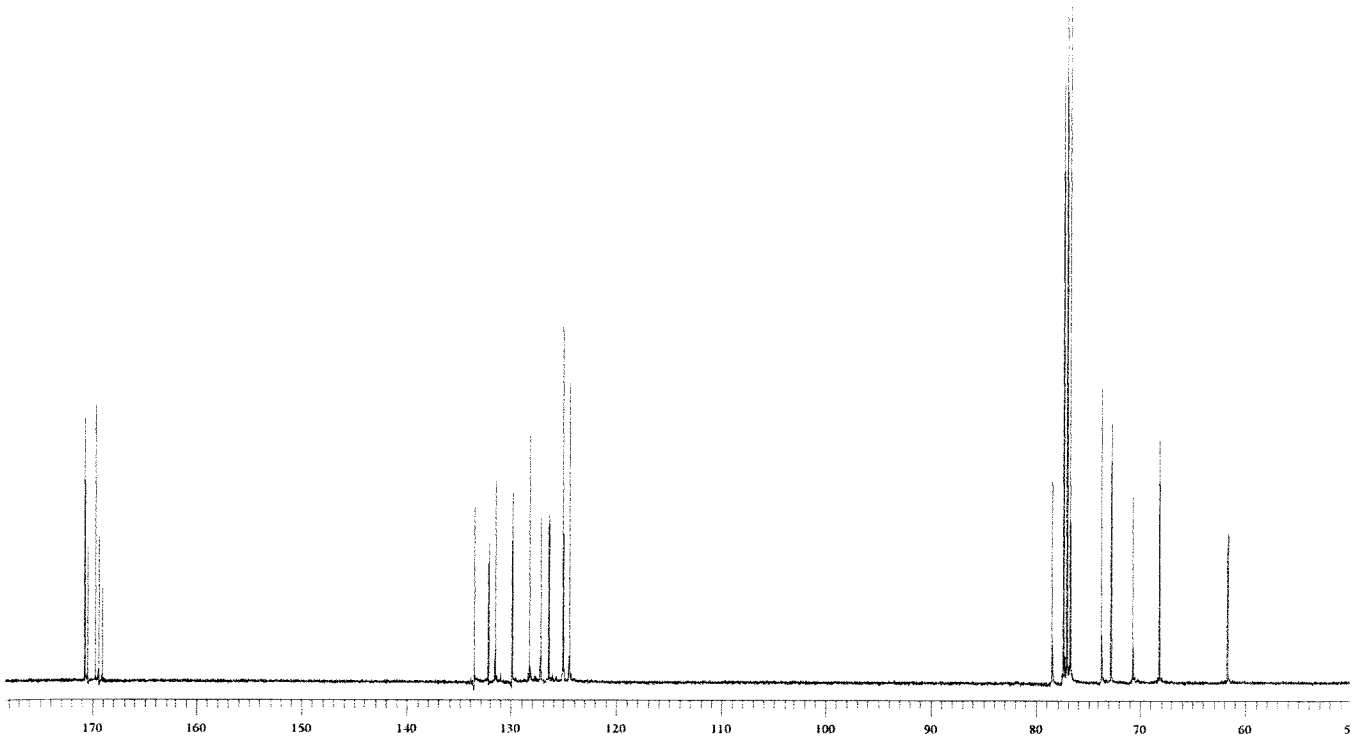


**Figure 52**: 100 MHz $^{13}C$ NMR spectrum of amide product **28**

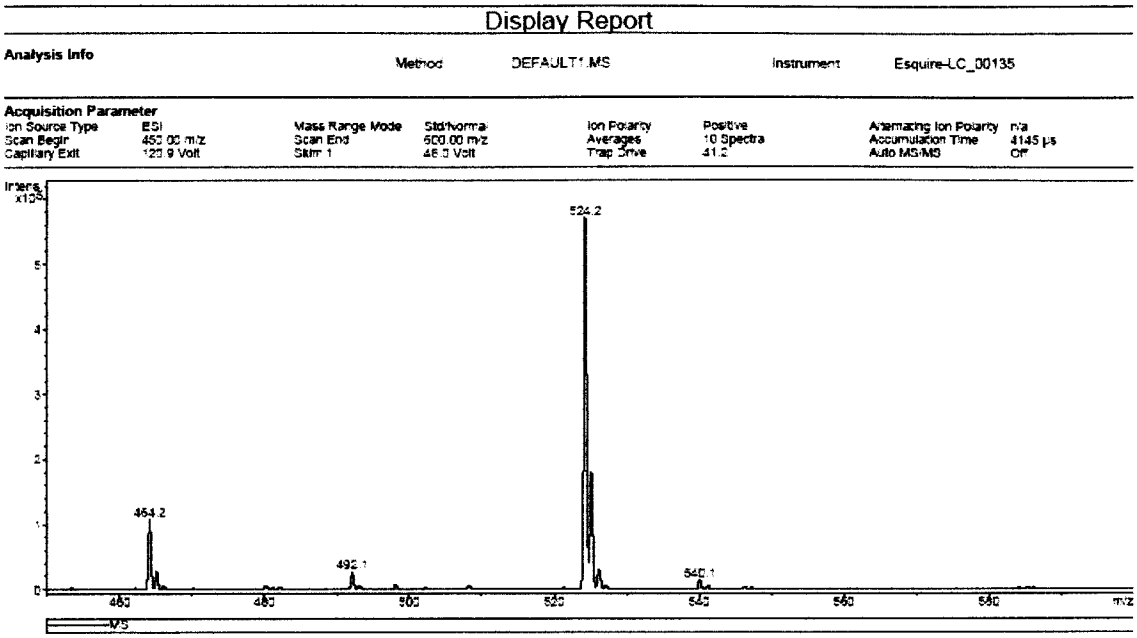


**Figure 53**: Mass spectrum of amide product **28**

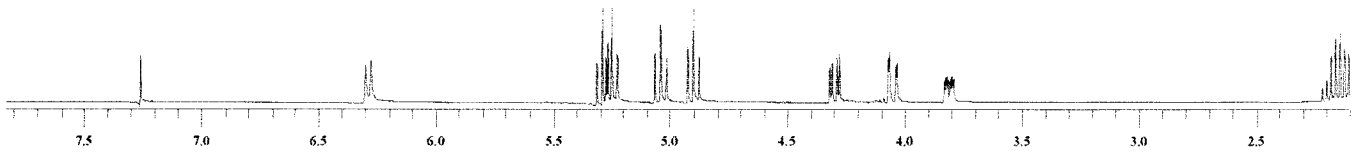


**Figure 54**: 400 MHz $^{1}$H NMR spectrum of amide product **29**

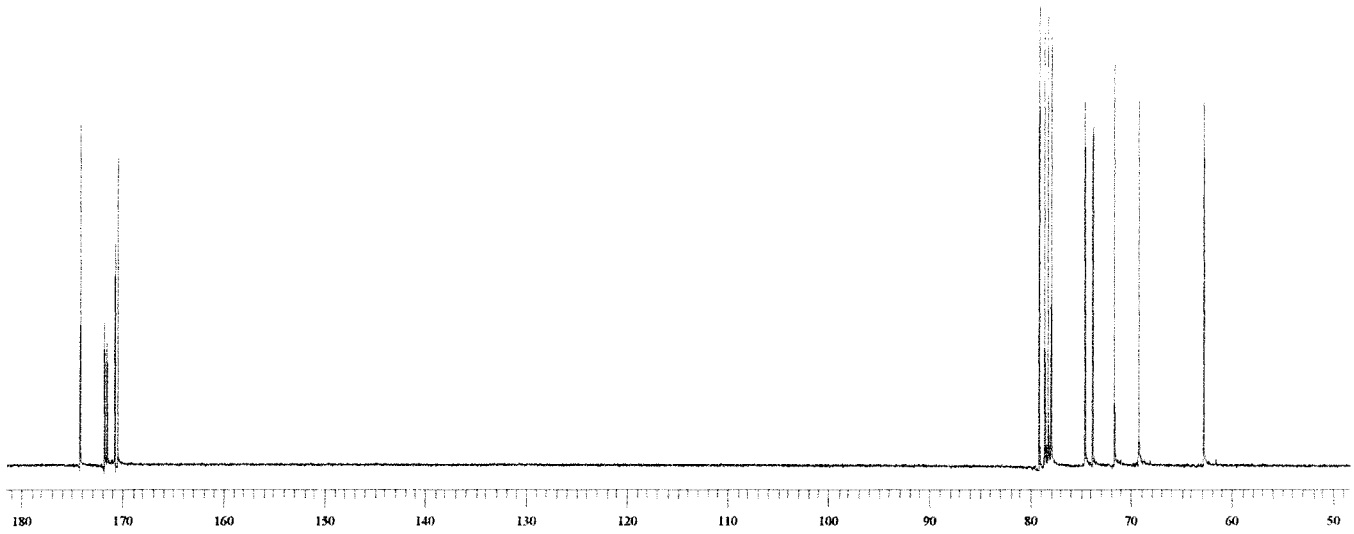


**Figure 55**: 100 MHz $^{13}C$ NMR spectrum of amide product **29**

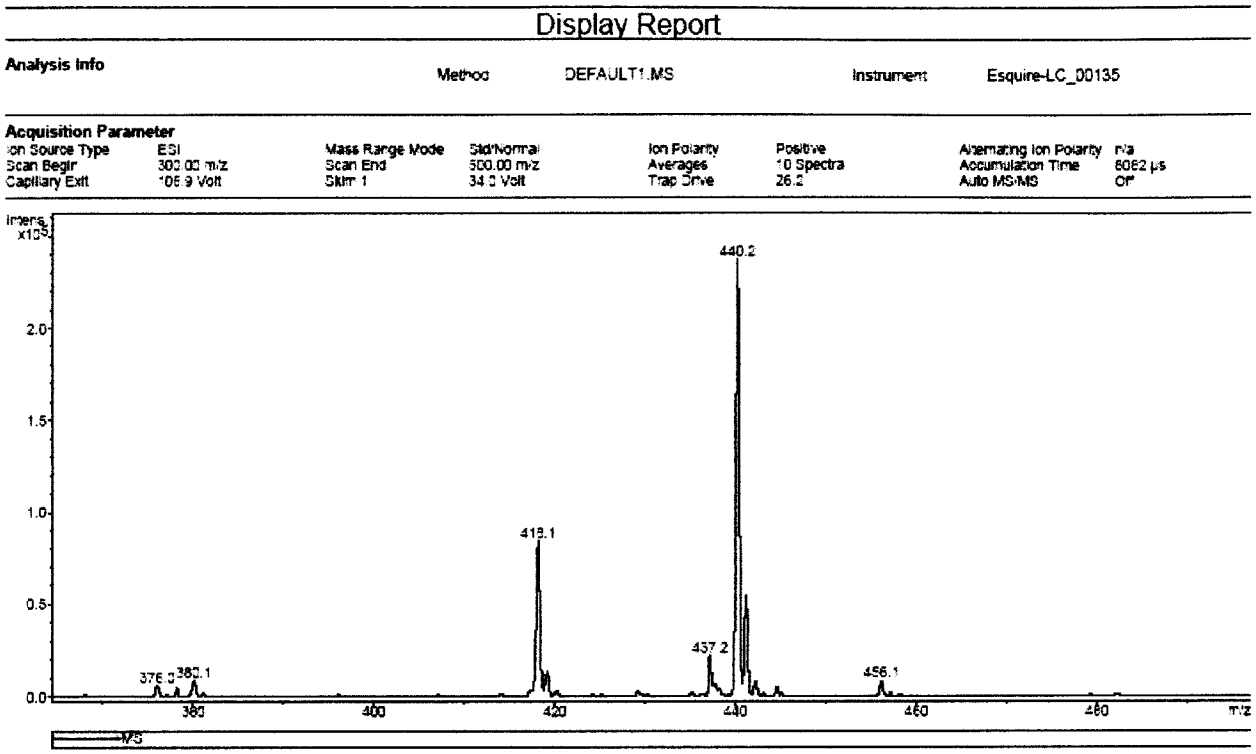


**Figure 56:** Mass spectrum of amide product **29**

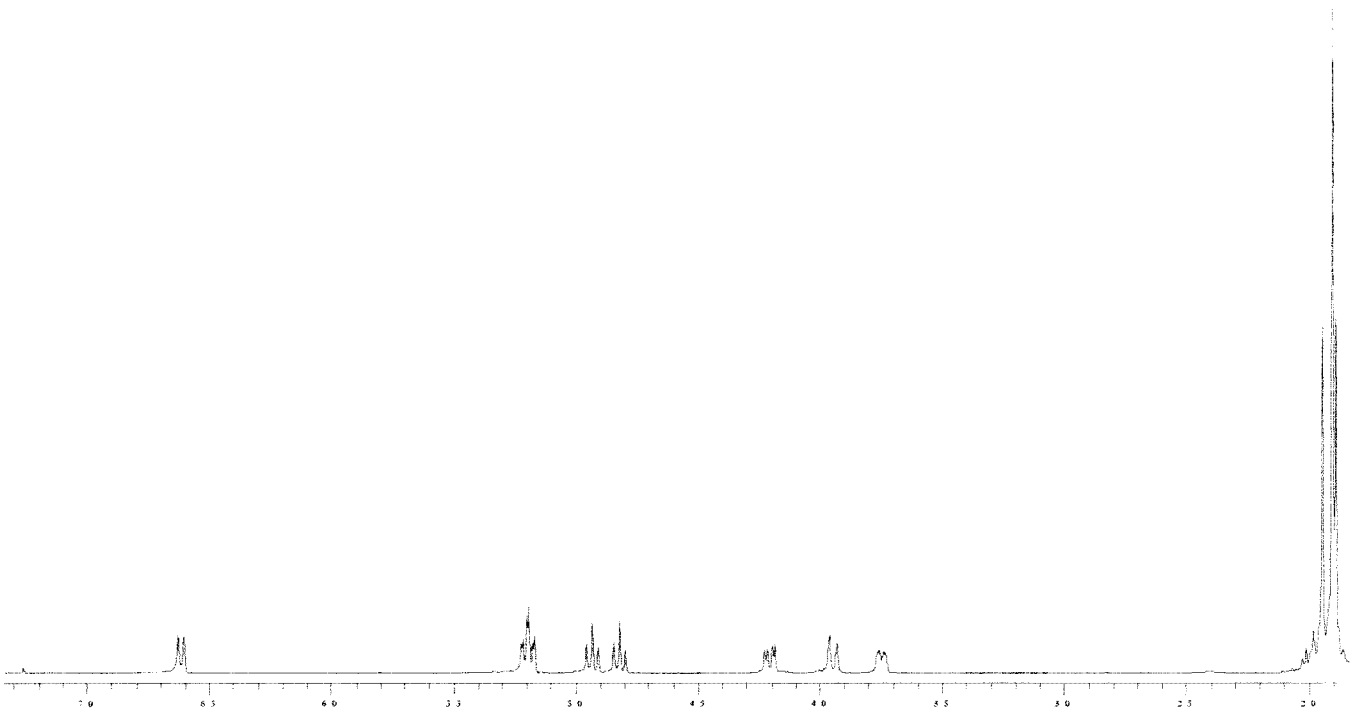

**Figure 57**: 400 MHz $^{1}$H NMR spectrum of amide product **30**

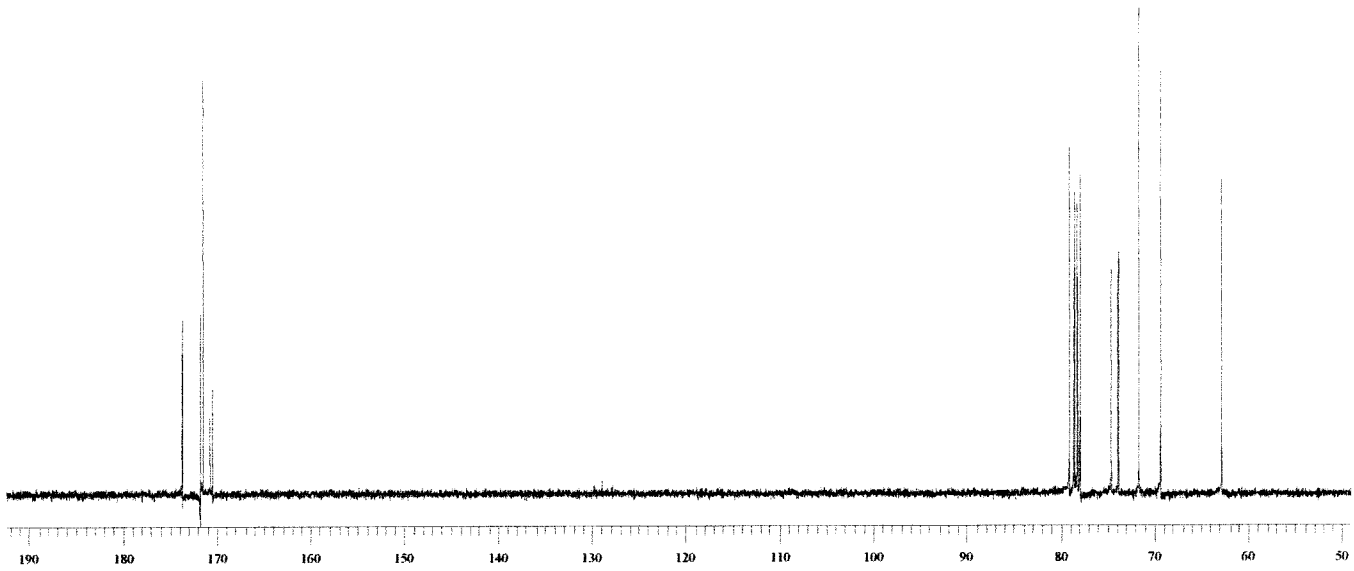


**Figure 58**: 100 MHz $^{13}C$ NMR spectrum of amide product **30**

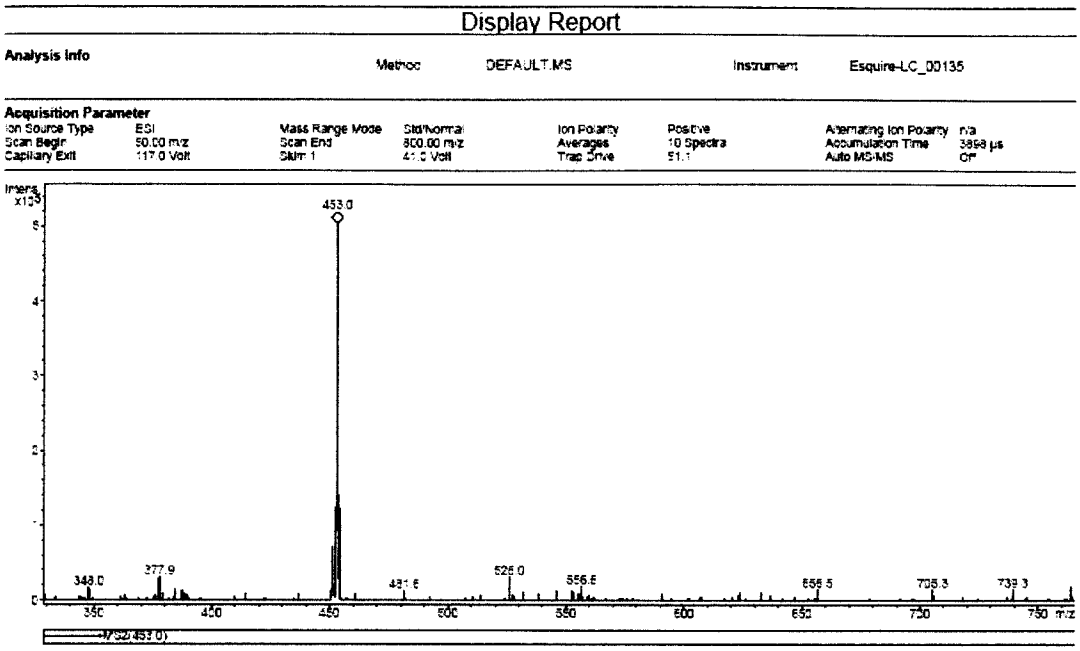


**Figure 59**: Mass spectrum of amide product **30**

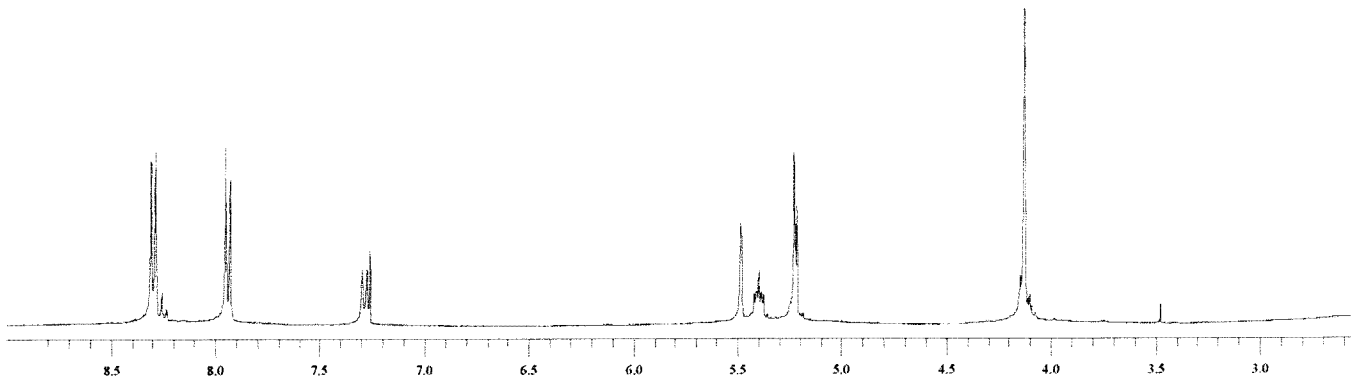


**Figure 60**: 400 MHz $^{1}$H NMR spectrum of amide product **31**

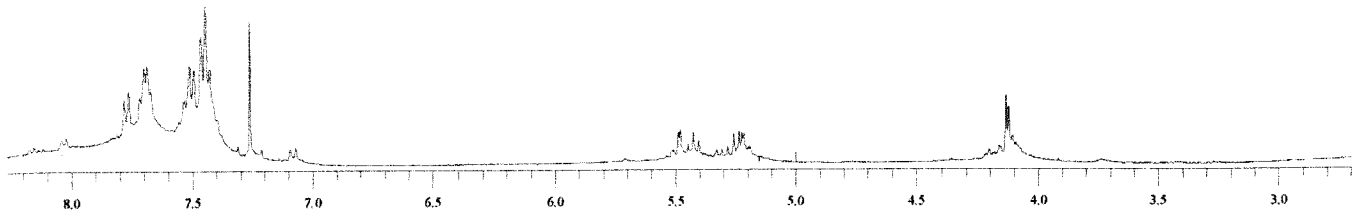


**Figure 61**: 400 MHz $^{1}$H NMR spectrum of amide product **32**

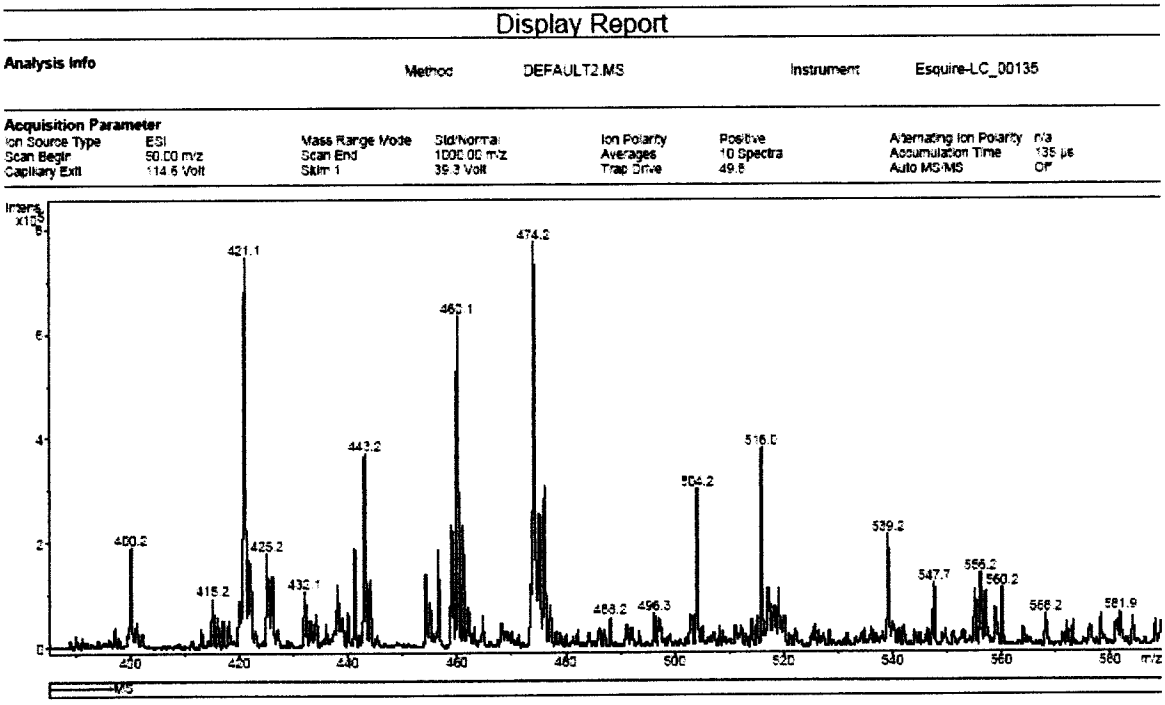


**Figure 62**: Mass spectrum of amide product **32**

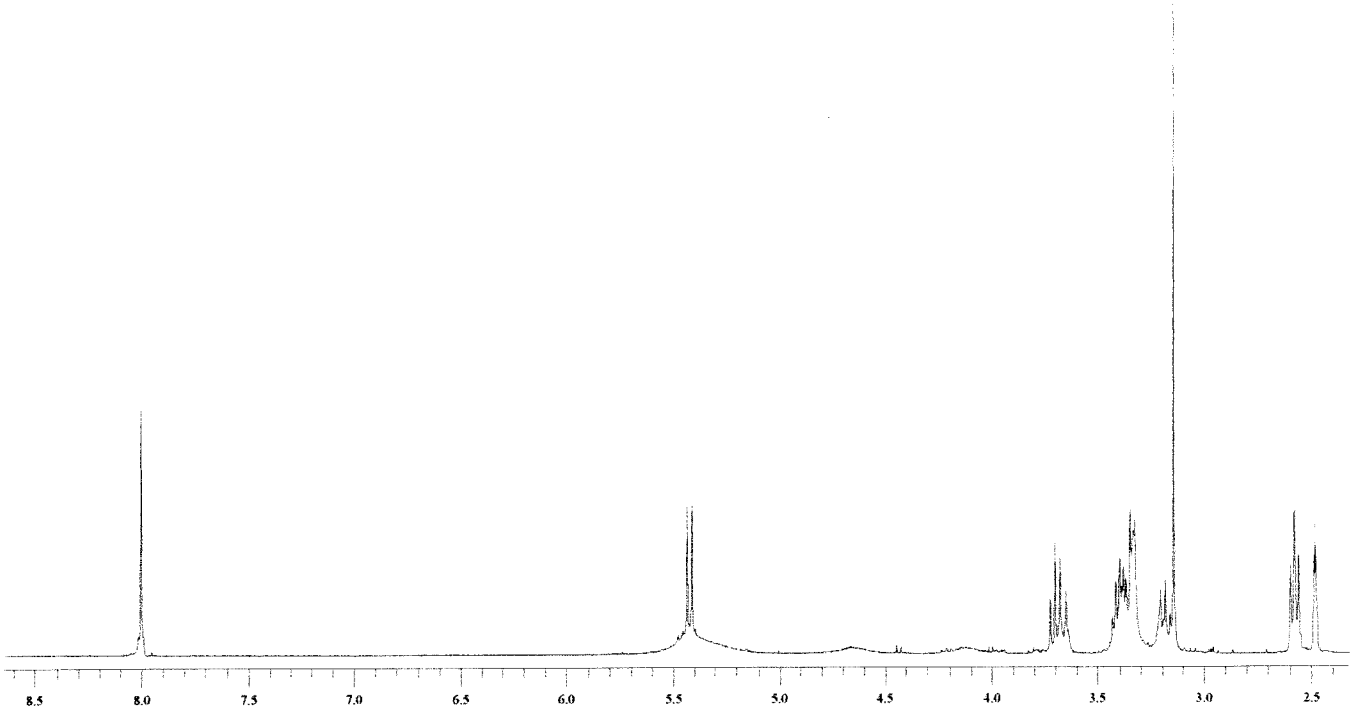


**Figure 63**: 400 MHz $^{1}$H NMR spectrum of deprotected triazole product **33**

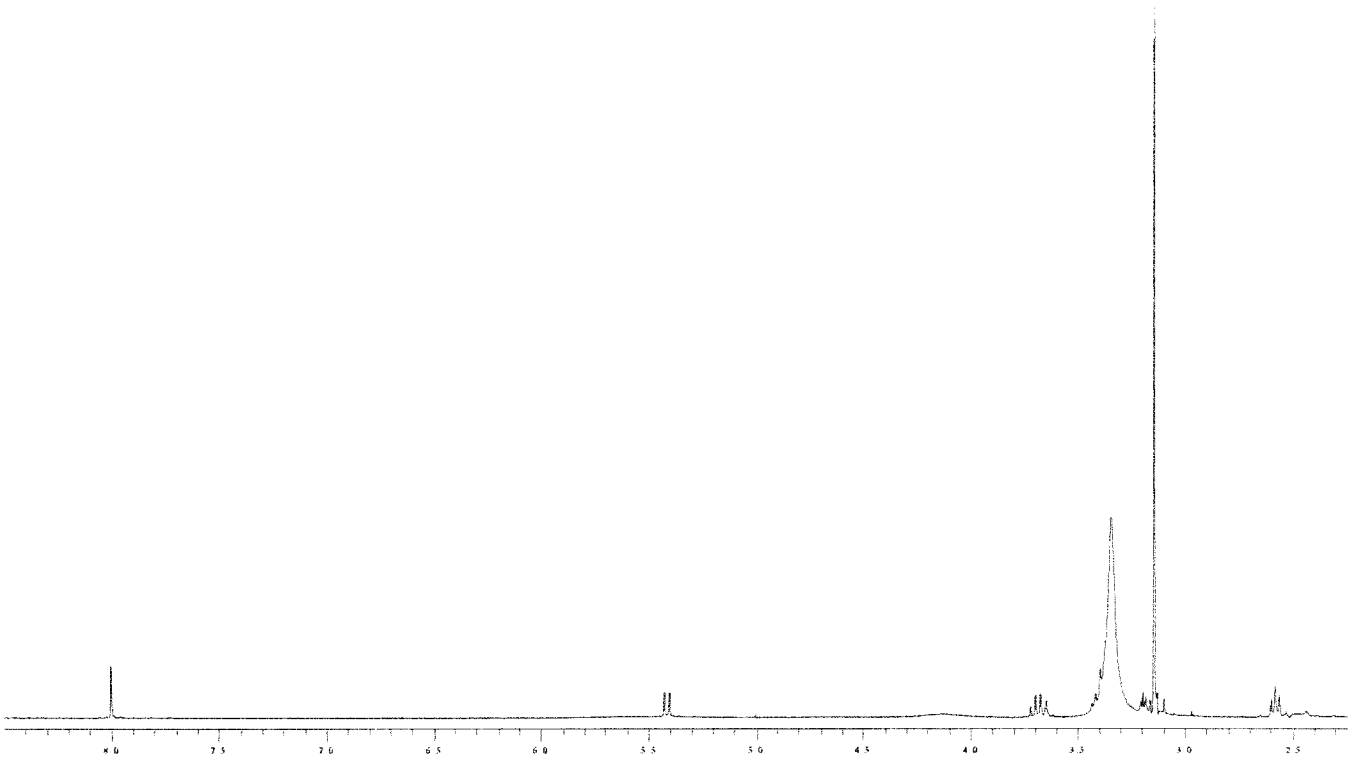

**Figure 64**: 400 MHz $^{1}$H NMR spectrum of deprotected triazole product **34**

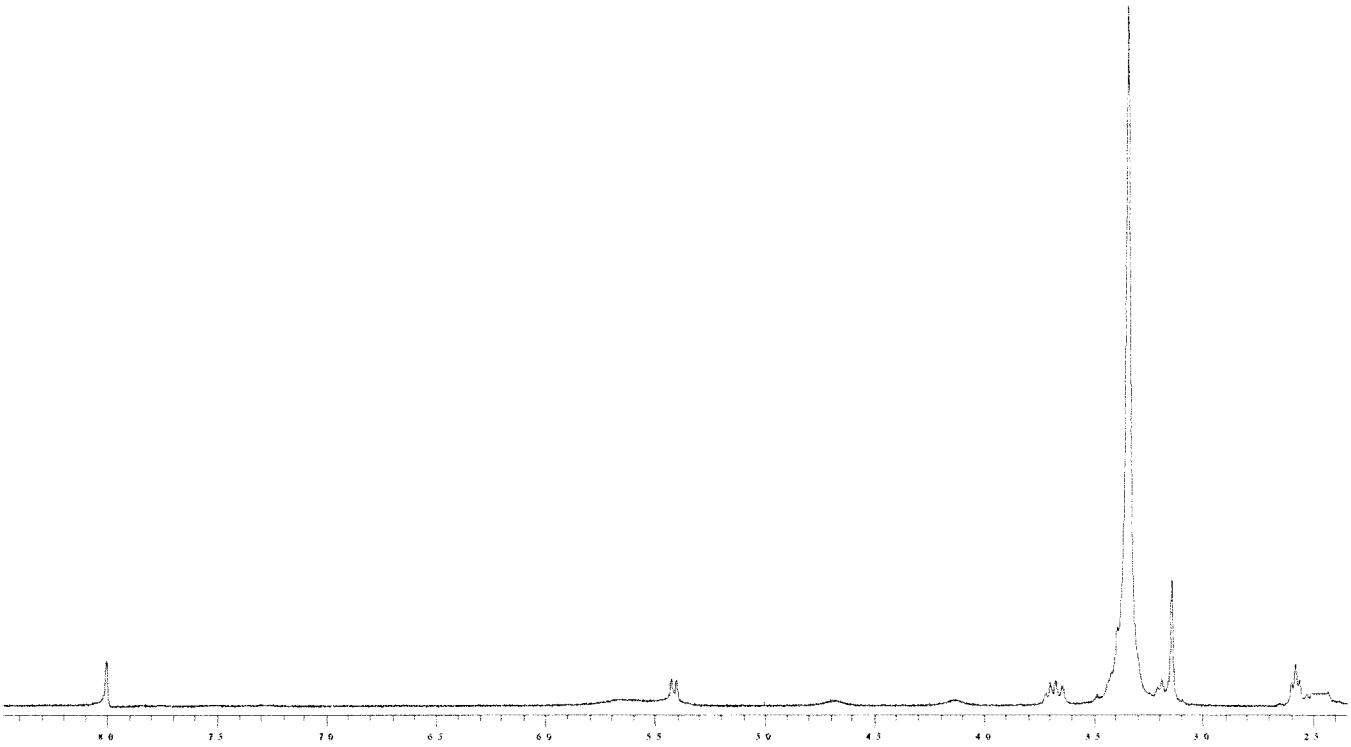

**Figure 65**: 400 MHz $^{1}$H NMR spectrum of deprotected triazole product **35**

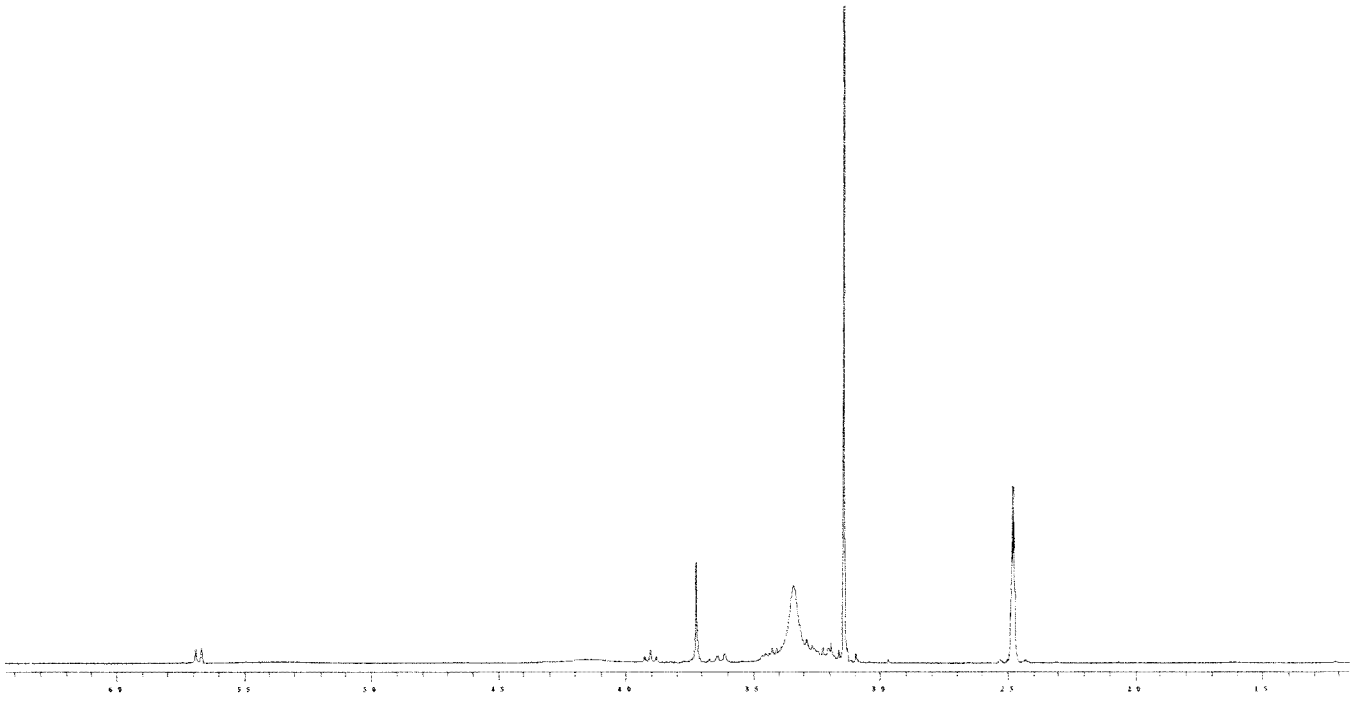

**Figure 66**: 400 MHz $^{1}$H NMR spectrum of a deprotected triazole product **36**

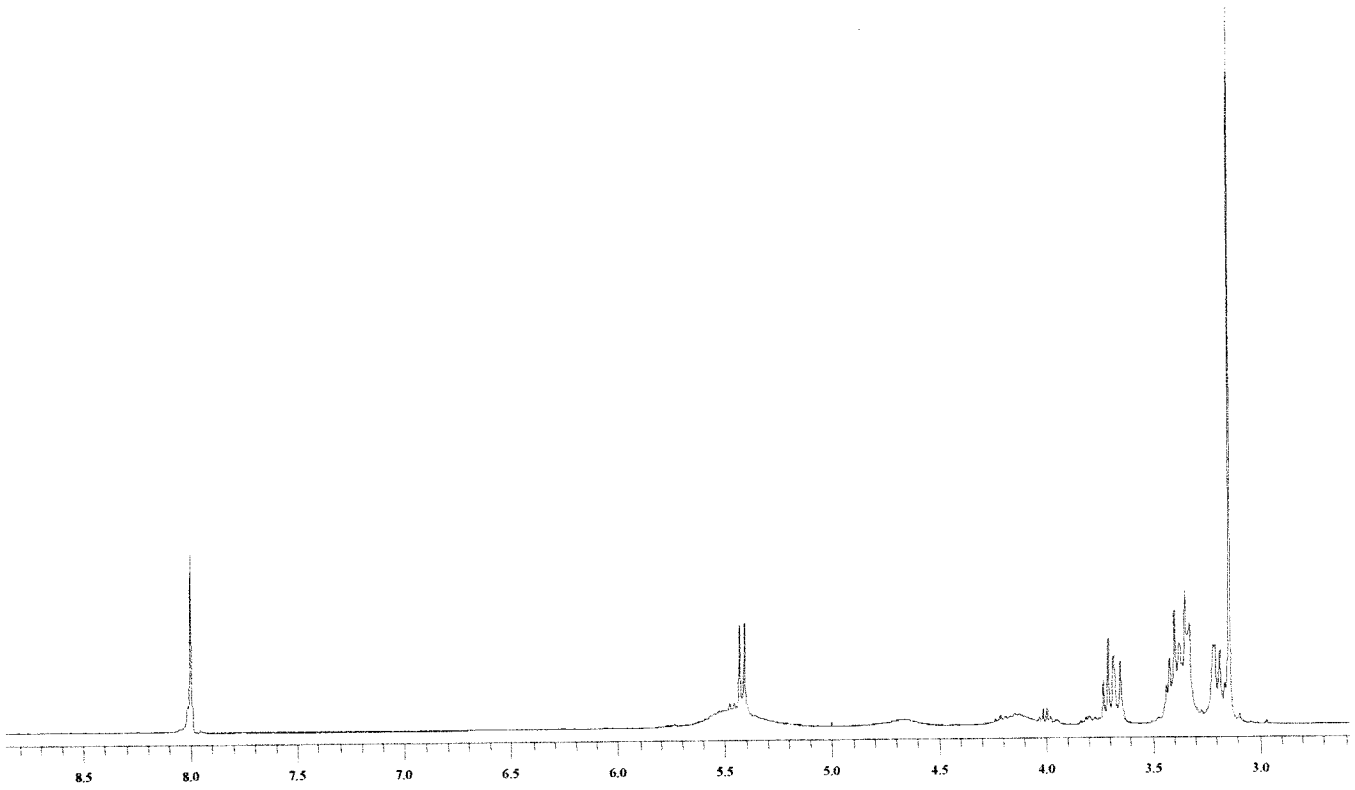


**Figure 67**: 400 MHz $^{1}$H NMR spectrum of deprotected triazole product **37**

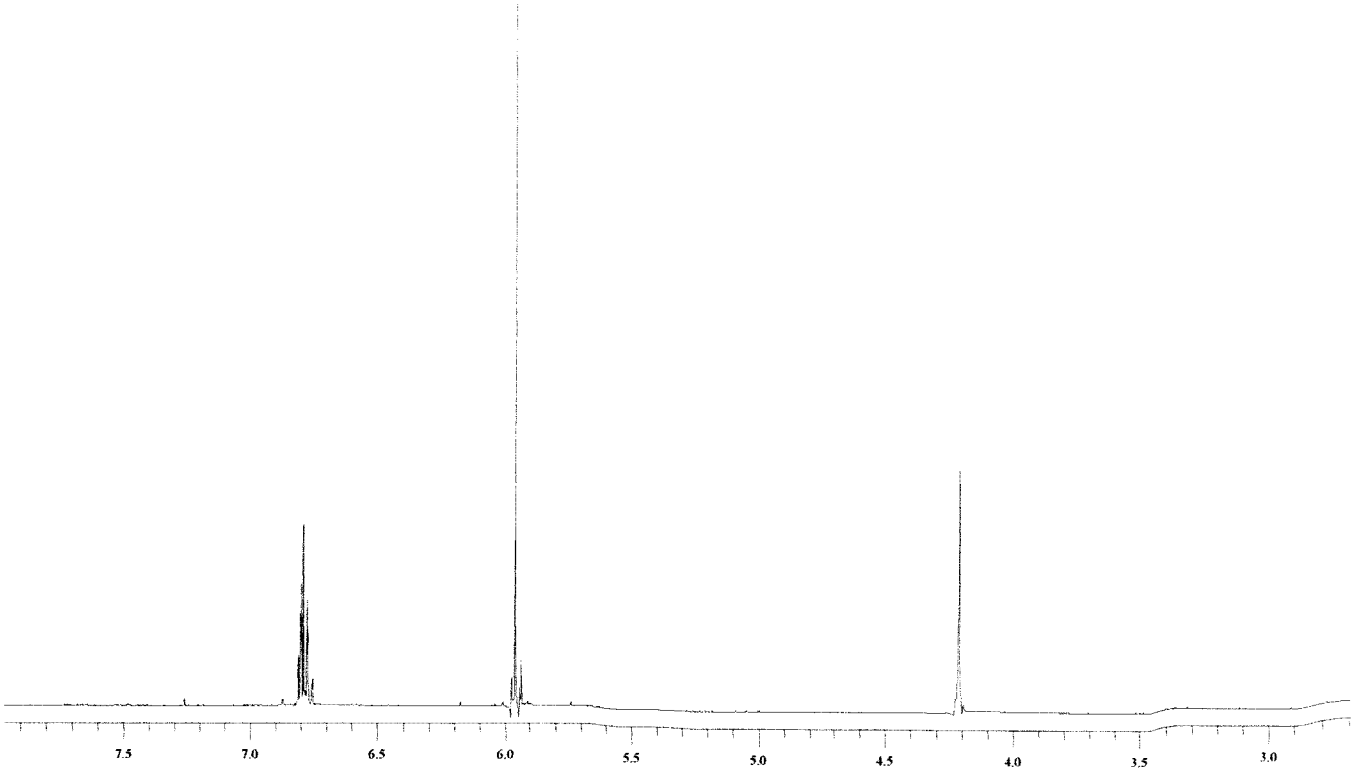


**Figure 68**: 400 MHz $^{1}$H NMR spectrum of piperonyl azide product **39**

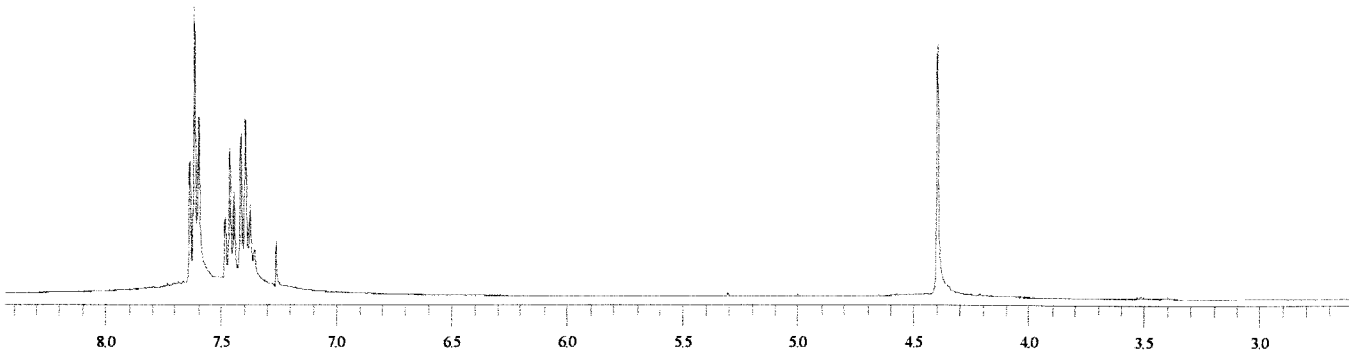


**Figure 69**: 400 MHz $^{1}$H NMR spectrum of 4-biphenyl methyl azide product **41**

**Figure 70**: 400 MHz $^{1}$H NMR spectrum of cinnamyl azide product **43**

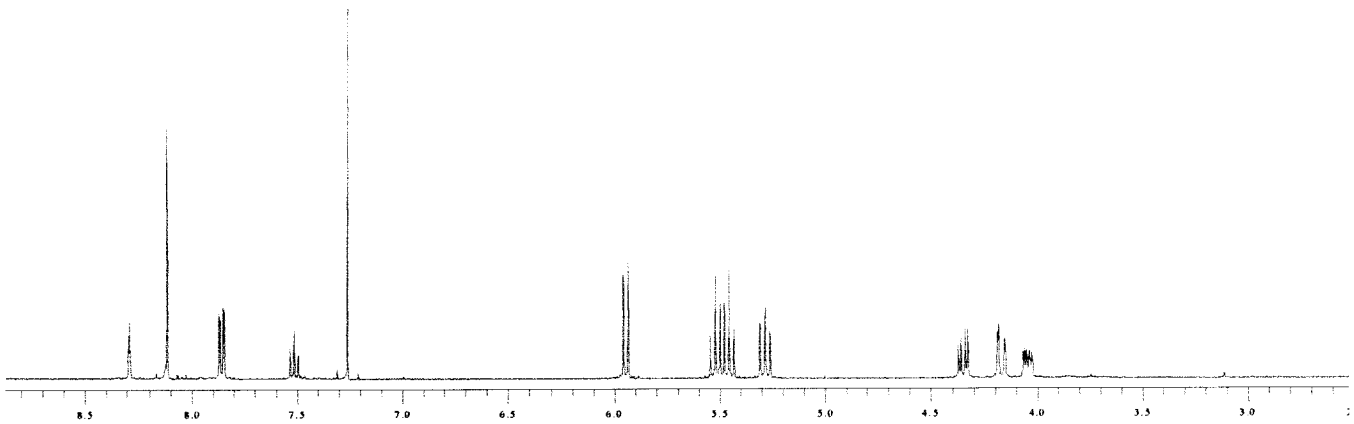


**Figure 71**: 400 MHz $^{1}$H NMR spectrum of divalent product **44**

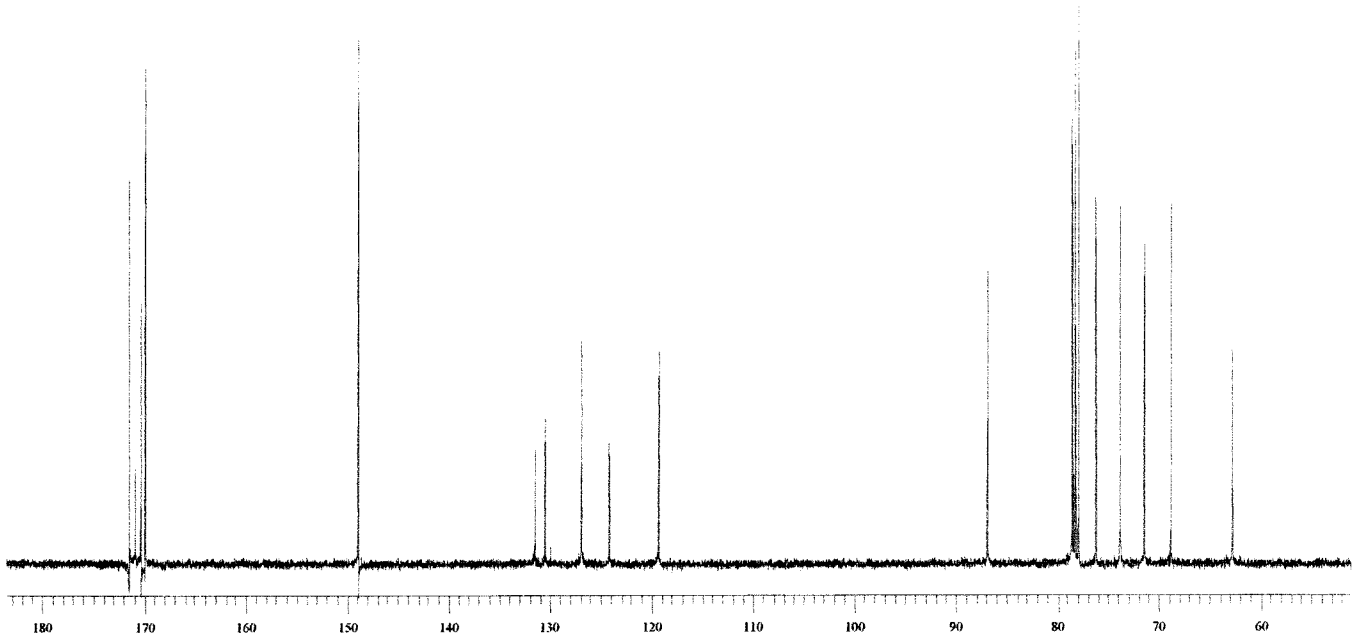


**Figure 72**: 100 MHz $^{13}C$ NMR spectrum of divalent product **44**

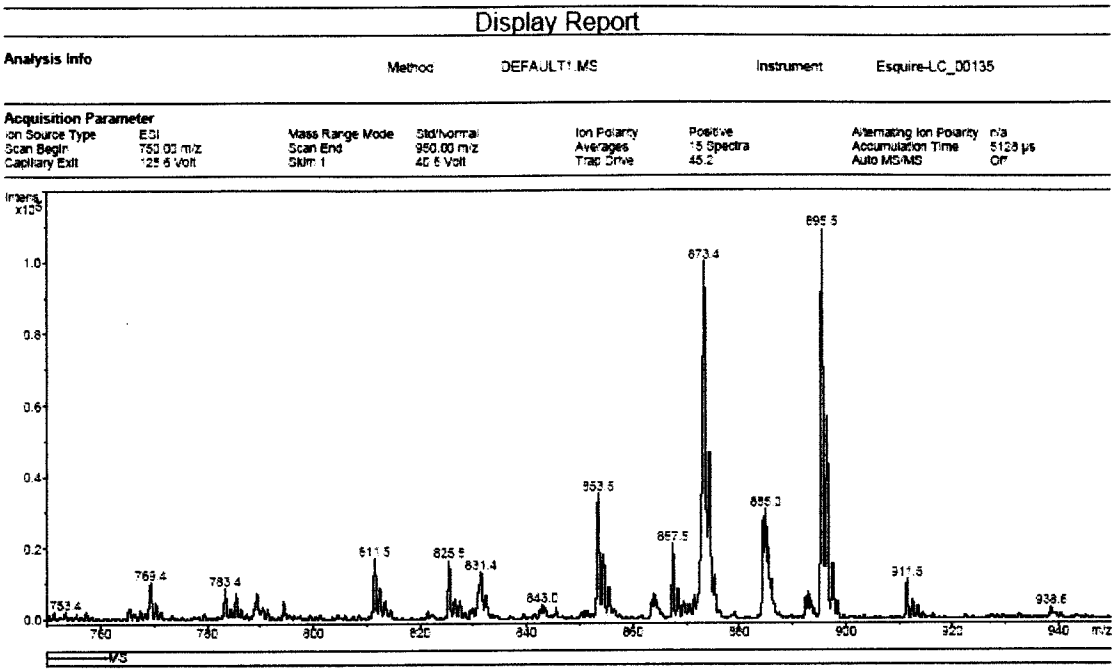


**Figure 73**: Mass spectrum of divalent product **44**

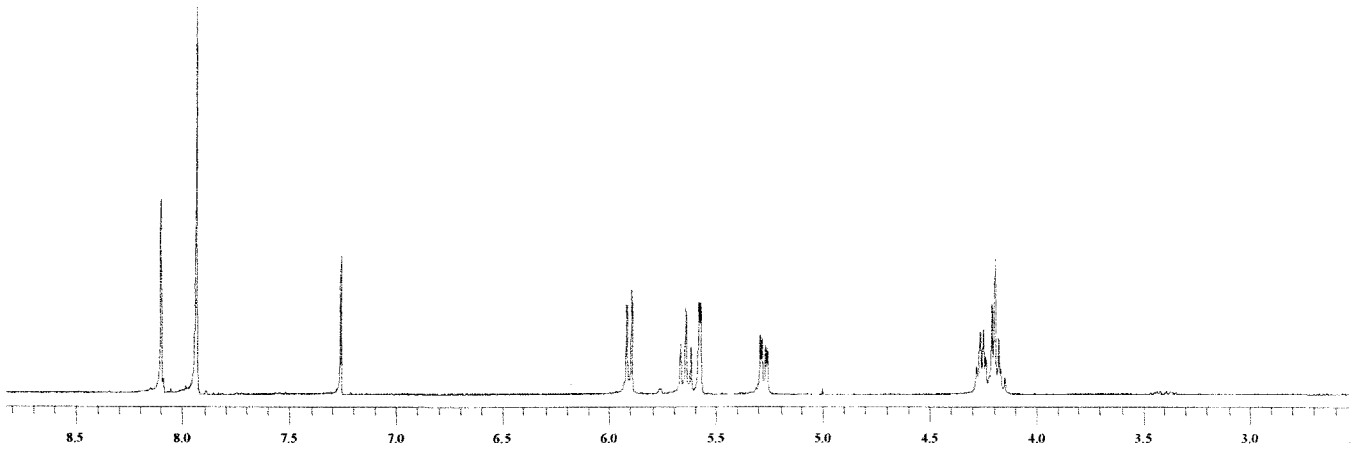


**Figure 4**: 400 MHz $^{1}$H NMR spectrum of divalent product **45**

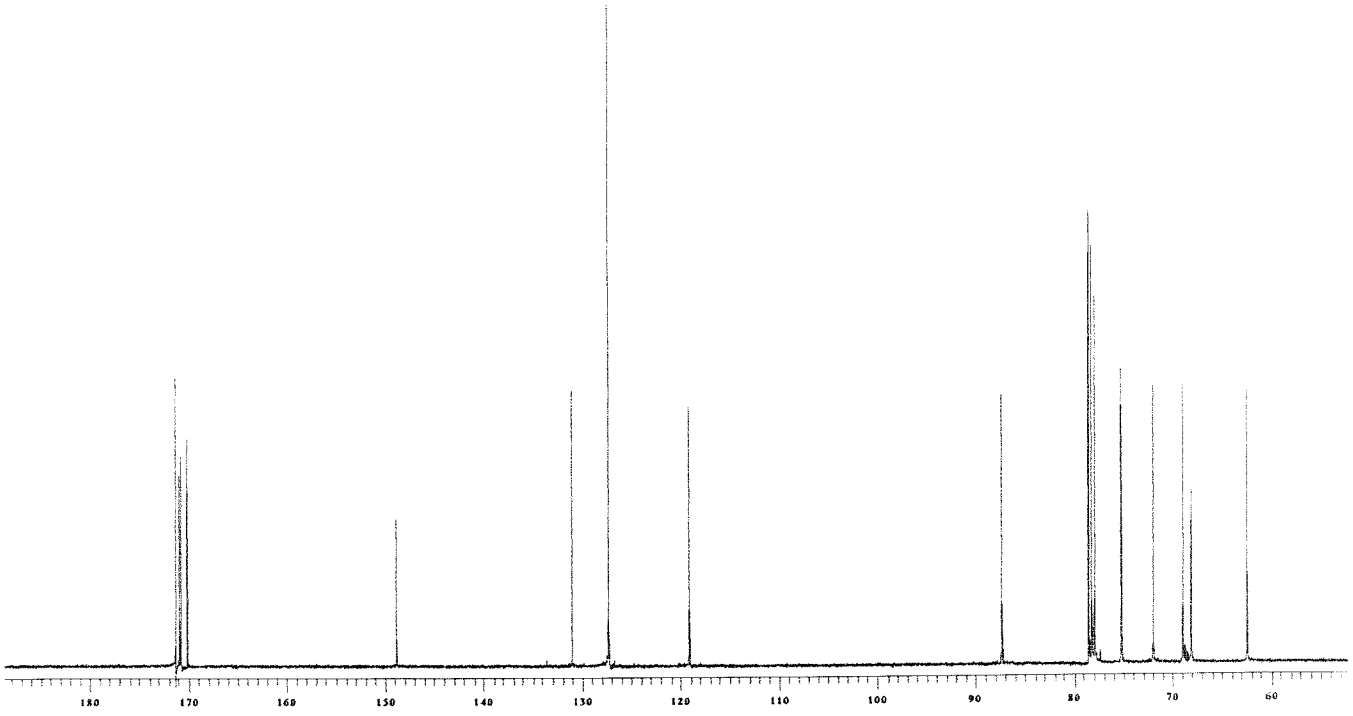


**Figure 75**: 100 MHz $^{13}C$ NMR spectrum of divalent product **45**

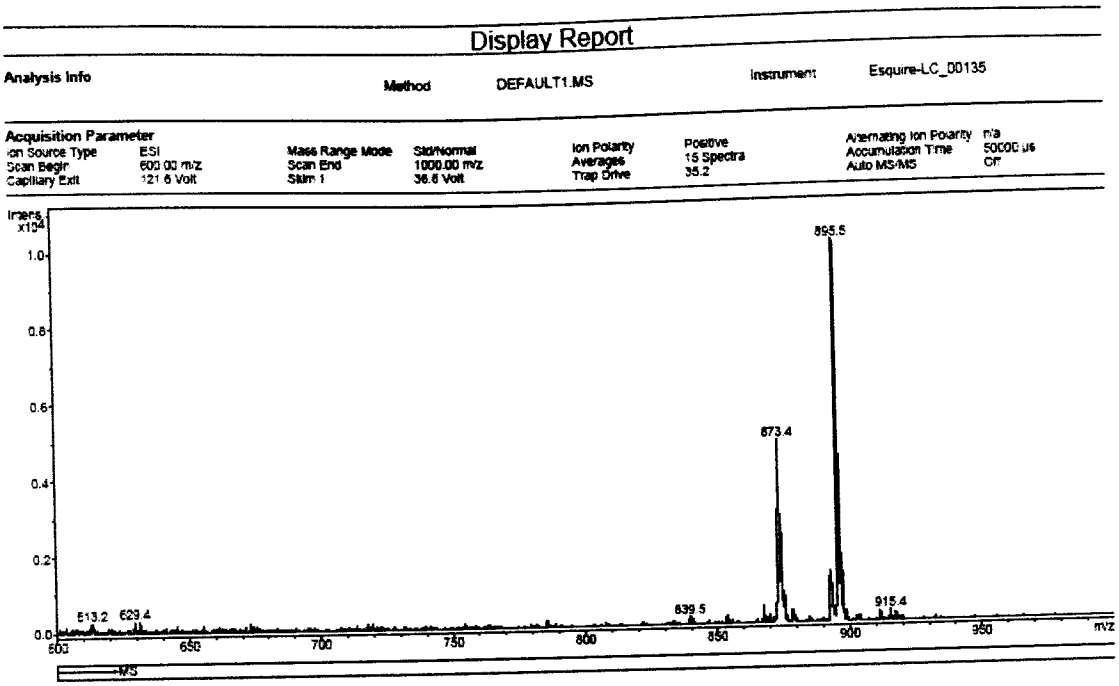


**Figure 76**: Mass spectrum of divalent product **45**