รายงานวิจัยฉบับสมบูรณ์

โครงการ
การเตรียมสาร amino-triazoleglycosidesชนิดใหม่
ด้วยวิธีที่ง่ายเพื่อตรวจสอบฤทธิ์ต้านมะเร็ง

Preparation of new amino-triazoles glycosides by simple method
for evaluation of anticancer activity

รุ่งนภา แซ่เอ็งและคณะ

โครงการวิจัยประเภทงบประมาณเงินรายได้
จากเงินอุดหนุนรัฐบาล (งบประมาณแผ่นดิน)
ประจำปีงบประมาณ 2561
มหาวิทยาลัยบูรพา

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28 กุมภาพันธ์ 2562

กิตติกรรมประกาศ

งานวิจัยนี้ได้รับทุนสนับสนุนการวิจัยจากงบประมาณเงินรายได้จากเงินอุดหนุนรัฐบาล
(งบประมาณแผ่นดิน) ประจำปีงบประมาณพ.ศ. 2561 มหาวิทยาลัยบูรพา
ผ่านสำนักงานคณะกรรมการการวิจัยแห่งชาติเลขที่สัญญา82/2561

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คำนำ

โครงการวิจัย “การเตรียมสาร amino-triazoleglycosidesชนิดใหม่ด้วยวิธีที่ง่ายเพื่อตรวจสอบฤทธิ์ต้านมะเร็ง” ได้รับการสนับสนุนทุนการวิจัยงบประมาณแผ่นดินประจำปีงบประมาณ 2561 มหาวิทยาลัยบูรพา รายงานการวิจัยฉบับนี้เสนอรายละเอียดของการวิจัยซึ่งประกอบด้วยบทนำที่เสนอผลงานวิจัยที่เกี่ยวข้อง ผลการทดลองวิจัย การอภิปรายสรุปผล และการตรวจสอบโครงสร้างของสาร

การวิจัย “การเตรียมสาร amino-triazoleglycosidesชนิดใหม่ด้วยวิธีที่ง่ายเพื่อตรวจสอบฤทธิ์ต้านมะเร็ง”สำเร็จลุล่วงไปด้วยดีโดยผู้วิจัยต้องขอขอบคุณทีมวิจัยซึ่งประกอบด้วยที่ปรึกษาโครงการศ.ดร. อภิชาต สุขสำราญคณะวิทยาศาสตร์ มหาวิทยาลัยรามคำแหง ศ.ดร. ภาวิณีปิยะจตุรวัฒน์มหาวิทยาลัยมหิดล ผู้ร่วมโครงการดร. อุทัยวรรณศิริอ่อนรวมทั้งนิสิตปริญญาเอก สาขาวิชาเคมี นางสาววราภรณ์ สุขจริตรักษ์งานวิจัยนี้ได้รับการสนับสนุนจากภาควิชาเคมี คณะวิทยาศาสตร์และทุนเรียนดีวิทยาศาสตร์แห่งประเทศไทย

ผศ. ดร. รุ่งนภา แซ่เอ็ง
อาจารย์ประจำภาควิชาเคมี คณะวิทยาศาสตร์
หัวหน้าโครงการวิจัย

บทคัดย่อ

ไกลโคไซด์เป็นสารที่มีประโยชน์ในธรรมชาติและได้รับการยอมรับว่าเป็นสารสำคัญและเป็นสารตั้งต้นเพื่อสังเคราะห์ผลิตภัณฑ์ธรรมชาติที่มีฤทธิ์ทางชีวภาพ สำหรับสารอนุพันธ์1,2,3-triazoles และสารประกอบเอมีนมีบทบาทสำคัญในการสังเคราะห์สารอินทรีย์เนื่องจากใช้เป็นสารสังเคราะห์สำหรับการผลิตยา เคมีภัณฑ์และสารออกฤทธิ์ทางชีวภาพ เพื่อรวมสารทั้งสามกลุ่มนี้ในโมเลกุลเดียวกัน งานวิจัยนี้จึงได้พัฒนาการสังเคราะห์สารamino triazole glycosideผ่านการทำปฏิกิริยาสองขั้นตอนในหนึ่งหม้อปฏิกิริยาโดยวิธี*N*-alkylation ของอนุพันธ์ของ amine กับ propargyl bromide เพื่อให้ propargylamineในขั้นตอนแรกตามมาด้วยปฏิกิริยา 'click' กับ azido-glycoside โดยใช้CuIในน้ำ ได้สารผลิตภัณฑ์amino-triazole glycosides ที่ให้ผลผลิตปานกลางถึงดี สารที่ได้จากการสังเคราะห์จะถูกนำไปศึกษาฤทธิ์ต้านเซลล์มะเร็ง

Abstract

Glycosides are utility in nature and recognized as key substances using as starting materials in the synthesis of biologically active natural products. Their synthesis has received much attention for organic chemist in recent year. 1,2,3-Triazole andamines derivatives play an important role in organic synthesis due to their wide use as synthetic intermediates for the production of pharmacophores, fine chemicals and bioactive compounds. To combine these three classes of compounds in the same molecule, we developed a convenient and efficient method for synthesis of amino triazole glycoside derivatives *via* one-pot two steps reaction. The *N*-alkylation of amine derivatives with propargyl bromide to give propargylamine was performed in the first step subsequently followed by a ‘click’ reaction with various azido-glycoside in the presence of CuI in aqueous solution to provide amino-triazole glycosides in moderate to good yield. The synthetic compounds will be further screening for their anticancer activity.

Chapter 1 Introduction and Literature reviews

Introduction

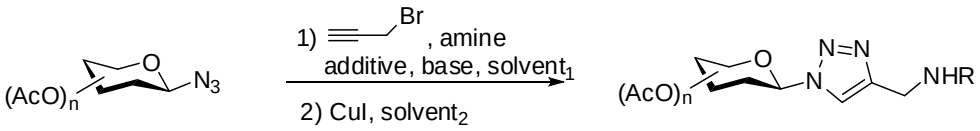
Carbohydrates in the form of glycosides and glycoconjugates play important roles in many biological processes. Many carbohydrate-containing complex natural compounds are found in nature as important biological substances (Narayanaperumal et al, 2012) such asamygdalin (vitamin B17) and salicin (anti-inflammatory agent in the human body). Current definition is that "the carbohydrates" are a much large family of compounds, comprising monosaccharide, oligosaccharide and polysaccharide. Carbohydrate can also be covalently linked to other biopolymers, such as lipids and proteins (Boons and Hale, 2000). Carbohydrates are useful intermediates in the synthesis of complex oligosaccharides and natural products. In addition, they exist as oligo- and polysaccharides or included in aglycon structures as glycol-derivatives with roles in a broad range of biological processes (Filice and Palomo, 2012).

Amine in general are one of most common structural features of naturally and unnatural synthetic targets. Amine and their derivatives are the most widely and effective in biologically active compounds and used throughout the chemical industry (Salvatore, Nagle, & Jung, 2002; Singh,Kavala, Samal& Patel, 2007).

In addition, 1,2,3-triazoles, classic nitrogen heterocyclic compounds, are used in pharmaceuticals, agrochemicals, dyes and photographic materials.1,2,3-triazoles have found wide range of application and biological activities such as anti-HIV (Silva et al., 2009), antimicrobial (Banday et al., 2012; Sumangala et al., 2010), antibiotics (Agalave et al., 2011), anticancer (Salmon et al., 2012) and α-glucosidase inhibition (Ferreira et al., 2010; Senger et al., 2012).The popularity of 1,2,3-triazoles is largely driven by their facile and modular synthesis via click chemistry. Click chemistry was established by Sharpless and co-worker in 2001, which is addressing as a set of powerful, highly reliable,and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries. This reaction is wide in scopeof chemistry, including organic,medicinal, materials, surface, polymer chemistry and chemical biology (Sokolova and Nenajdenko, 2013). Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has become the prime example of click reactions and thatmoreimportantly, many applications thereof not only aimed to linktwo units together but also to synthesize the triazole moiety in the complex molecules (Schulzeab and Schubert, 2014).

Since carbohydrate, amine and triazole structure were previously reported for pharmaceutical properties, therefore, this work was aimed to combine all of these fragments together and synthesize of amino-triazoleglycosidederivatives for further investigation of their biological activity.

In this work, we will develop a new synthetic methodologyfor the synthesis of amino-triazoleglycoside from various sugar derivatives. All synthetic analogues will be further study for biological activity. 1-azido-acetoxyglycosides will be prepared and used as starting molecules. The *N*-alkylation and click reaction for the synthesis of amino triazole-glycoside derivatives from commercial available amine were carried out*via* one-pot reaction procedure.



1 **2**

Scheme 1.1 The one-pot synthesis of amino triazole-glycosides from carbohydrate derivatives

Literature reviews

Carbohydrates are the most abundant group of natural compounds commonly referred to sugars and starches. The monosaccharides of the most importance in nutrition are glucose, fructose, and galactose. These carbohydrates are widely distributes in food which also found in some vegetable, and fruit, honey, corn, syrup, and molasses (Kretchmer& Hollenbeck, 2000). Their glycoconjugates, are involved in important functions, as cell-cell recognition and communication, inflammation, immunological response, bacterial and viral infection, tumorigenesis and metastasis (Kumar,Seenivasan, Kumar V., &Das, 2011)

Furthermore, carbohydrates linked to a heterocyclic moiety are important for bioactivity displaya significant influenceto the pharmacokinetics, drug targeting and mechanism of action (Kamenecka et al., 2009). Similarly, N-heterocyclic compounds, [1,2,3]-triazoles are used as a linker with various active functional moiety to improve the abilityto drugs discoveryand exhibit wide range of bioactivities (Brak et a., 2010).

1,2,3-Triazoles are potential targets for drug discoveryas they exhibit a broad spectrum of biological properties and many efforts have been made to optimize methods for their preparation. The most popular method for construction of 1,2,3-triazoles frameworks is the click reaction or 1,3-dipolar Huisgen-cycloaddition reaction of azide with alkynes. Therefore, it is desirable to develop a new, convenient and efficient synthetic approach for the formation of triazoles (Liang et al., 2005).

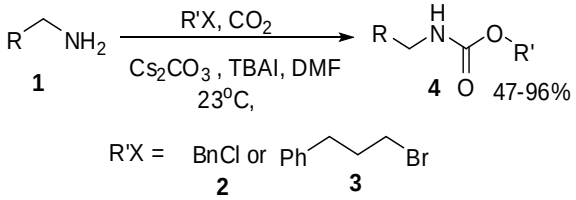
Amines have long been employed as robust and versatile synthons due to their high stability and easy chemical elaboration as dyes, color pigments, electrolytes, stabilizers, and synthons for pharmaceuticals, agricultural chemicals, herbicides, polymers, and functionalized materials, etc.(Cheng et al., 2014). In particular, propargly amines as key intermediates for the synthesis of various important building blocks. One of the most frequently used procedures for the preparation of propargyl amines is the *N*-alkylation of primary and secondary amines with alkyl halides in the presence of a base.The review of selected examples of various reactions using in this work is presented as follow.

2.1 The examples of preparation of amine derivatives by *N*-Alkylation

The *N*-alkylation of amines is important reaction in preparation of amine derivatives. There are a lot of applications in the field of pharmaceuticals, agriculture, popular in drug development and useful synthetic intermediates.

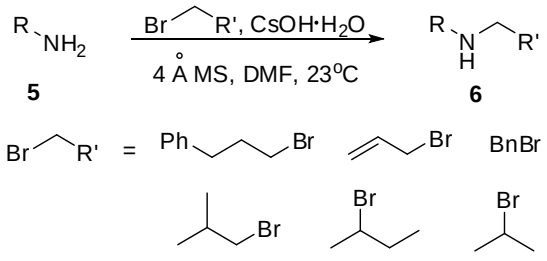
Salvatore, Shin, Nagle and Jung (2001) reported the synthesis of carbamates derivatives **4** in the present of three-components coupling which was performed using

aliphatic, aromatic and heterocyclic amines contain electron donating and electron withdrawing group**1**, carbon dioxide and reactive and unreactive halides **2** or **3** by applying a similar procedure to carbonylation protocol. The reaction mixture was saturated with CO_2 in the presence of Cs_2CO_3 at room temperature in DMF as solvent. Tetrabutylammonium (TBAI) was found to be a crucial additive in averting direct N-alkylations and overalkylation of the produced carbamate. (Scheme **2.1**)



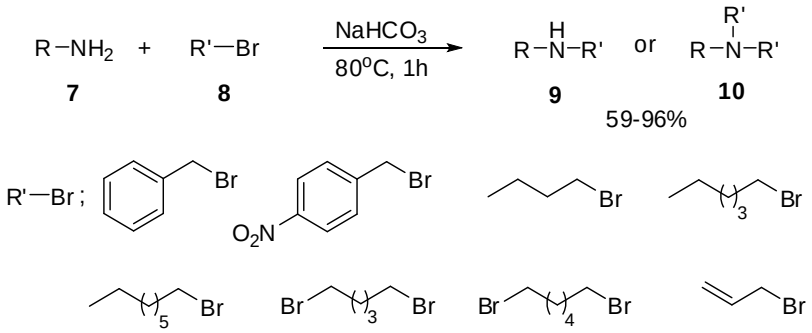
Scheme 2.1 Synthesis of carbamates derivatives **4**.

Salvatore, Shin, Nagle and Jung (2002) showed that the method using cesium hydroxide for the chemoselective*N*-alkylation of primary amines **5**, afforded secondary amines predominantly or exclusively. Observed selectivities between mono- and dialkylations were typically on the order of 9:1 or higher chemoselectivity is "cesium effect". Reaction of amines united with various bromideproduced the derivatives amines **6**in the presence of high yield using powdered dry 4 Å molecular sieves in anhydrous DMF. It was found that the inclusion molecular sieves accelerated the alkylation as well as improved the selectivity and yield of the secondary amine. This methodology proves to be a general protocol for the syntheses of various secondary amines, offering a wide variety of applications(Scheme **2.2**).



Scheme 2.2*N*-alkylation of amines **2.15**.

Singh, Kavala, Samal and Patel (2007) showed that the synthesis of secondary and tertiary amines **9** or **10**by direct *N*-alkylation of primary or secondary amines **7** with various benzylic halides or aliphatic halides **8** in an aqueous medium in the presence of a mild inorganic base such as $NaHCO_3$ and sodium dodecyl sulfate, the product were obtained in excellent yields. The advantage of this method is scalability, the absence of quaternary ammonium salt formation and operationally convenient conditions. (Scheme **2.3**)

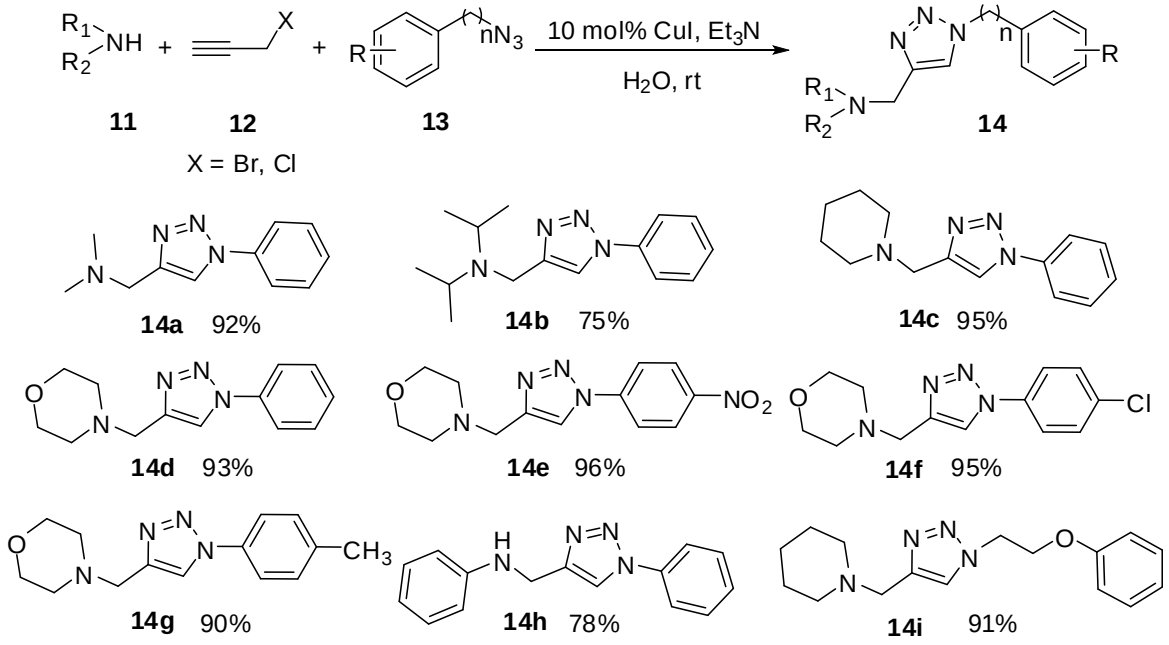


Scheme 2.3 Synthesis of secondary and tertiary amines **9** or **10**.

2.2 The examples of 1,4-disubstituted-1,2,3-triazoles formations by click chemistry

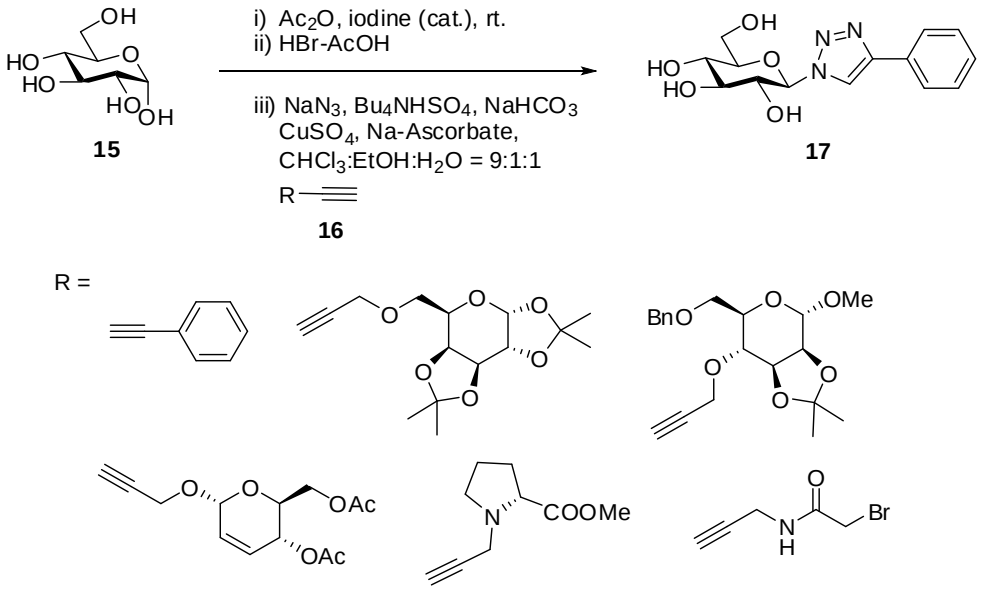
1,2,3-triazole derivatives, classic nitrogen heterocyclic compounds have found application and biological activities such as agricultural, pharmaceutical, material, anti-HIV and anticancer. Several methodologies were then investigated to control the regioselectivity and to improve the reaction conditions for the formation of 1,2,3-triazoles. The copper catalyzed azide alkyne cycloaddition reaction (abbreviated to Cu-AAC) or click chemistry is the well documented, with several published reviews describing the different catalysts and ligands used, including the mechanistic aspects.

Yan, Zhao, Fan, Liu and Liang (2005) reported the synthesis of (1-substituted-1H-1,2,3-triazol-4-ylmethyl)-dialkylamines derivatives **14a-i** in the present of one-pot reaction of amines **11**, propargyl halides **12**, azides**13** and Cu(I) in water at room temperature. The substrates variety of substituents aromatic, benzyl and aliphatic with electron-withdrowing and electron-donation group were employed for this study. Twenty examples of triazole amine derivatives were afforded in 70-98% yield using this one pot procedure. Some examples are shown in Scheme **2.4**.



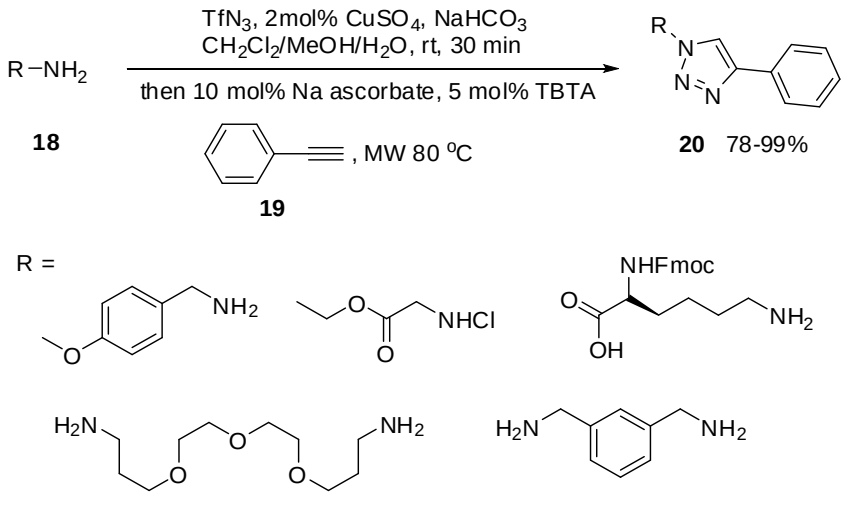
Scheme 2.4 Synthesis of (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines**14a-h**.

Chittaboina,Xie and Wang (2005) reported the highly efficient one-pot four steps synthesis of 1,2,3-triazole-linked glycoconjugates using unprotected saccharide **15**with acetic anhydride and trace amount of iodine, followed by brominolysis of anomeric acetate and subsequent azide conversion followed by click reaction with alkyne**16** in the presence of Cu(I) as a catalyst to give 1,2,3-triazoles-linked glycoconjugate**17** in excellent yield. By executing several reaction steps in a single pot and purifying only at the final stage, this procedure excludes the isolation of all the intermadiates including labile glycosyl bromides, which significantly reduces the reaction time and improves the overall yield (Scheme **2.5**).



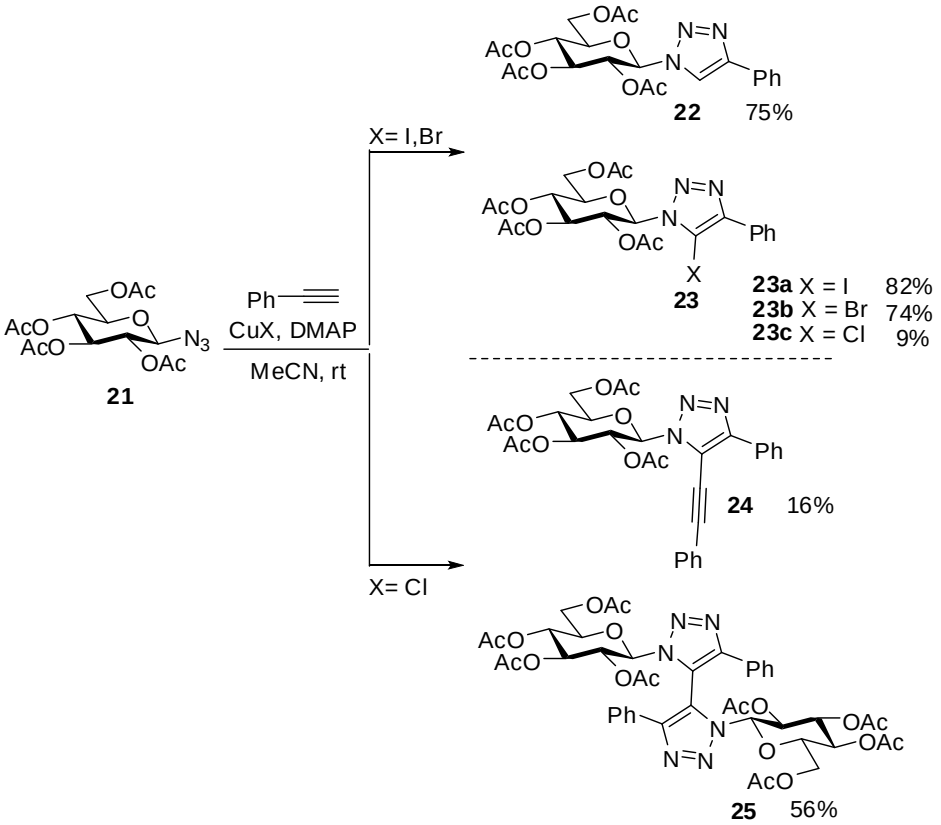
Scheme 2.5 Synthesis of 1,2,3-triazole-linked glycoconjugates**17**.

Beckmann and Wittmann (2007) reported the synthesis of 1,4-Disubstituted 1,2,3-triazoles **20** using amines **18** and alkyne **19**by one-pot reaction of Cu(II)-catalyzed diazo transfer at ambient temperature using sodium bicarbonate as base and Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition by heating to 80^{O}C with microwave irradiation for avoiding the isolation of the azide intermediates to obtain high yield of products within reasonable reaction times. (Scheme **2.6**)



Scheme 2.6 Synthesis of 1,4-Disubstituted 1,2,3-triazoles **20**.

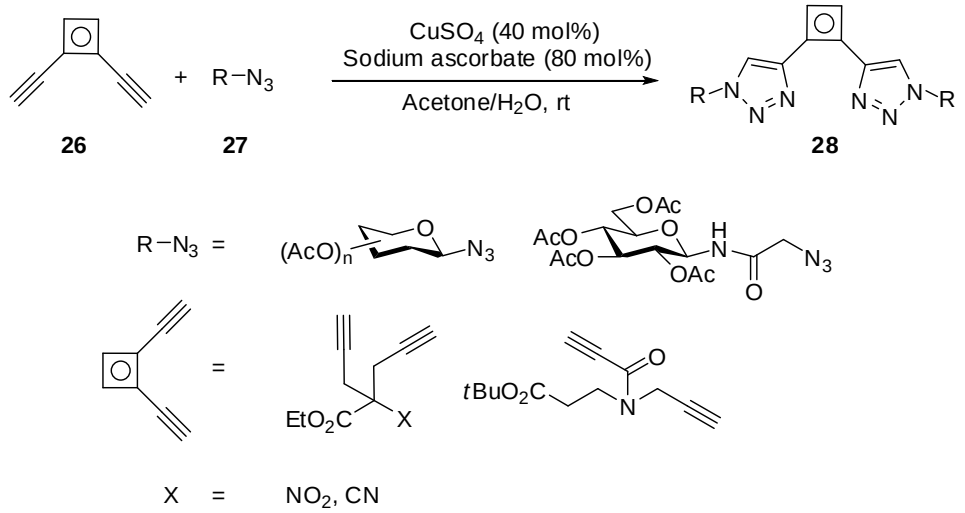
Goyard, Praly and vidal (2012) reported the synthesis of 5-halogenated 1,2,3-triazole under smooth condition using Cu(I)-halides (i.e., CuI, CuBr and CuCl), alkyne and DMAP to carry out the 1,3-dipolar cycloaddition and halogenation in one-pot reaction to obtain compound **24** (16% yield) and **25** (56% yield) in the presence of CuCl. Formation of the 5-proto-triazole **22** (75% yield) as a single product when using 0.1 equiv of CuI. The presence of iodinated derivative **23a**(82% yield) could be detected when using larger amounts of CuI. The 5-brominated 1,2,3-triazoles **23b**(74% yield) were prepared from excess CuBr 2 equiv. The introduction of a chlorine atom at the 5-position of the triazole ring of **23c** was more difficult and product was isolated in only 9% yield. The methodology reported herein appears as a valuable, no additiveand high yields. (Scheme **2.7**)



Scheme 2.7 Azide-alkyne 1,3-dipolar cycloaddition using of Cu(I)-halides and their corresponding 1,2,3-triazoles.

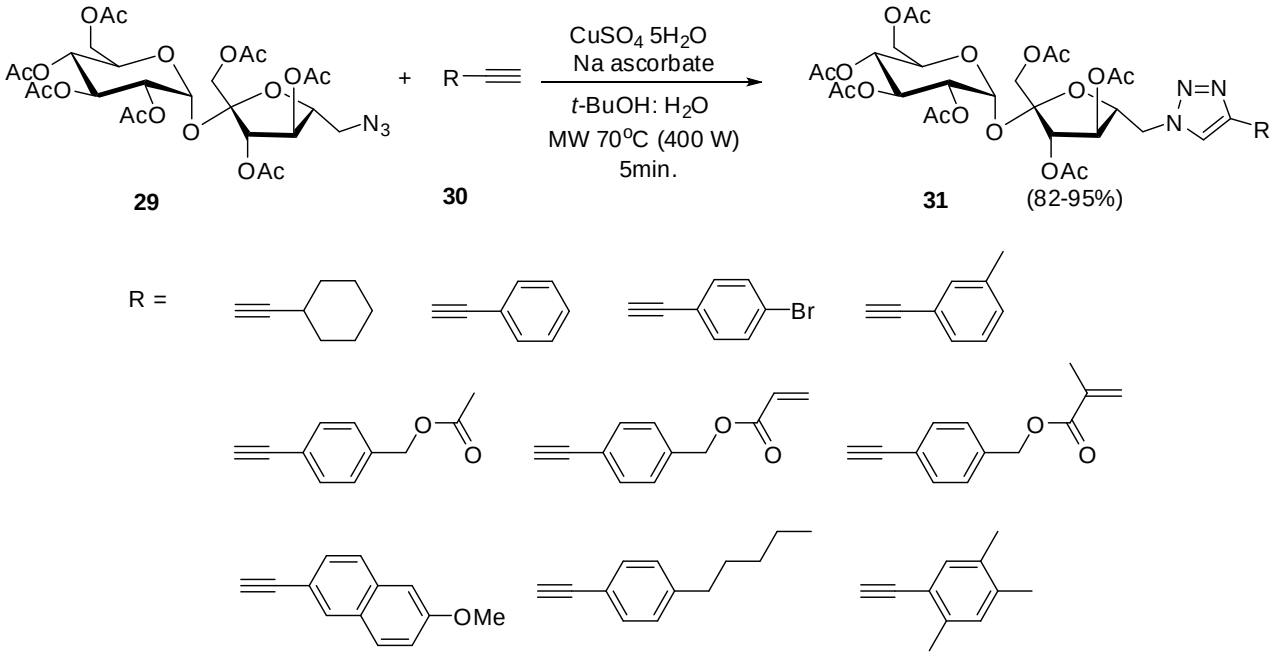
Sahoo, Singhamahapatra, Kumar and Loganathan (2013) reported the synthesis of triazole-linked divalent glycopeptide mimics **28**with conceptually new divalent linkers. The alkyne-functionalized divalent building block was used for the Cu(I)-catalyst [3+2] cycloadditionreacton with per-*O*-acetylated glycosylazides or azidoacetamide to synthesize the triazole-linked divalent glycoconjugates with different linkers. The dialkyne-

functionalized building blocks can be used for the synthesis of unsymmerical divalent compounds by sequential click reaction with different sugar azides and azidoaceamides. The peptide-based divalent glycoconjugates with two chemically non-equivalent triazolering have higher conformational flexibility and will be useful for biological analysis(Scheme **2.8**).



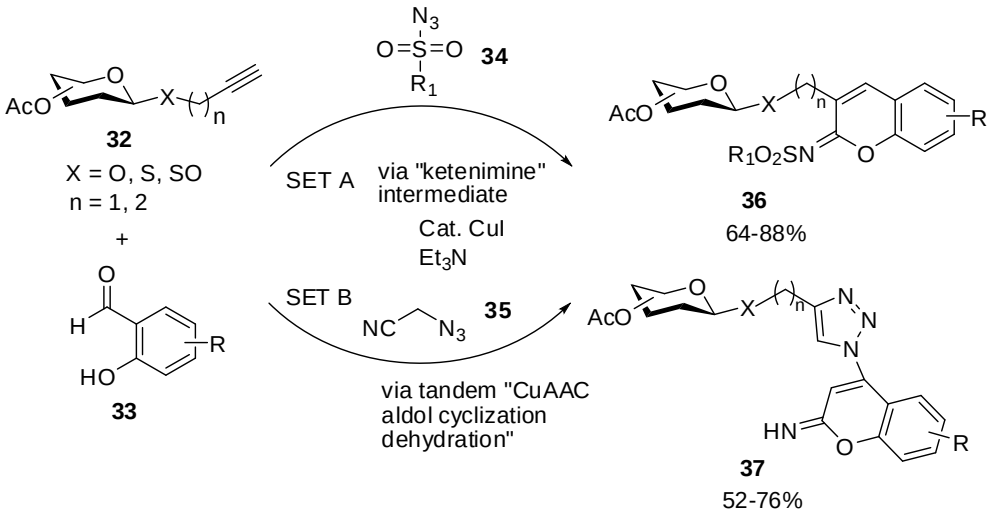
Scheme 2.8 Synthesis of triazole-linked divalent glycoamino acid mimics**28**.

Potewar, Petrova and Barros (2013)reported the click reaction of 1,2,3-triazole-sucrose derived **29**with various alkynes **30** in the presence of$CuSO_4$•$5H_2O$ catalyst, sodium ascorbate in *tert*-BuOH/H_2O (1:1) at 70^{o}Cusing microwave assisted to give 1-4-phenyl-1,2,3-triazole **31** in excellent yields in short reaction times (Scheme **2.9**).



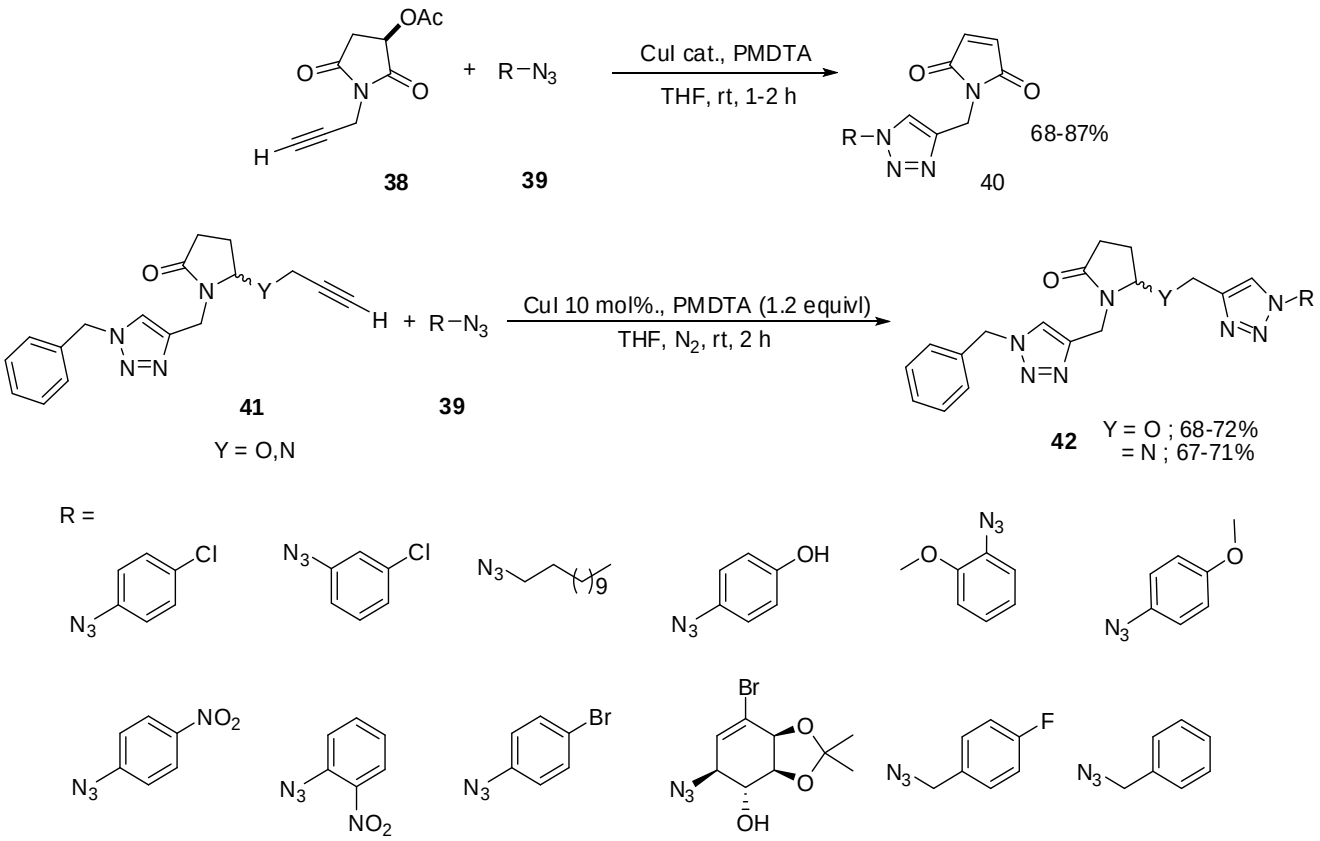
Scheme 2.9 Synthesis of 1-4-phenyl-1,2,3-triazole **31**.

Mandal (2014) reported the synthesis of glycosyl-iminocoumarins**36** in one-pot reaction fromsulfonylazides and salicylaldehydes in presence of CuI and triethlamine*via*ketenimine intermediate. Similarly, reaction of propargyl glycoside with slicylaldehyde and sulfonylazidegaveglycosyl 3-triazolyl-2-iminocoumarin derivative**37** in one-pot three component condensation via copper-catalyzed Huisgencycloaddition reaction. The method has been achieved to give product in good yields(Scheme **2.10**).



Scheme 2.10 Synthesis of glycosylated iminocoumarin**36**and 3-triazolyl-2-iminocounarinderivative**37**

Stefani, Ferreira, Ali and Pementa (2014) reported the synthesis offunctionalized*N*-triazolylmaleimides**40**and *N*-triazolyl-5-triazolyl pyrrolinones**42** in two steps one-pot elimination and click reaction. The reactions of *N*-propargyl imide with aromatic and alkyl azides were promoted by CuI using PMDTA as base and tetradydrofuran as a solvent at room temperatrue.The reaction was investigated with a variety of organic azides such as aromatic and non-aromatic organic azides which contained of electron-withdrawing and electron-donating to obtain products in moderate to good yields(Scheme **2.11**).

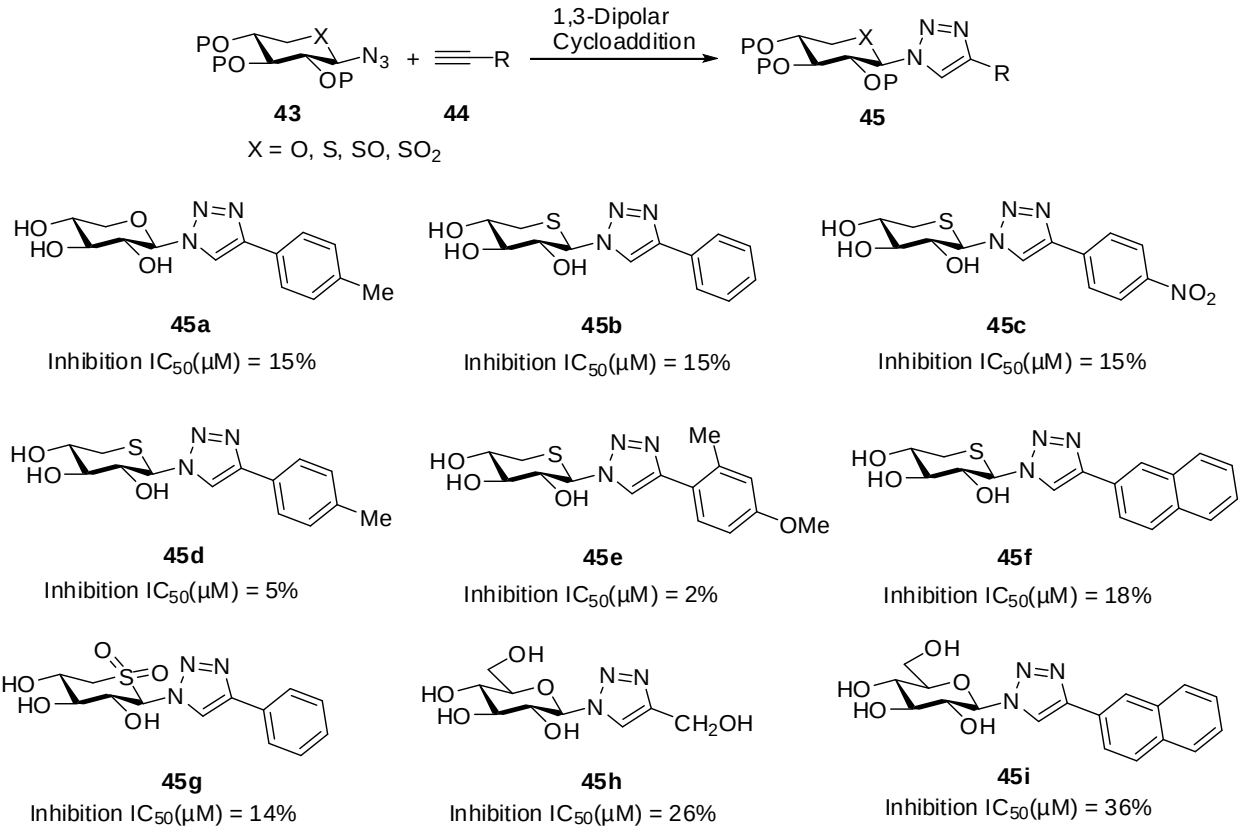


Scheme 2.11 Synthesis of *N*-tirazolylmaleimides**40**and *N*-triazolyl-5-triazolyl pyrrolinones**42**.

2.3 Application of 1,2,3-triazole compounds in medicinal chemistry.

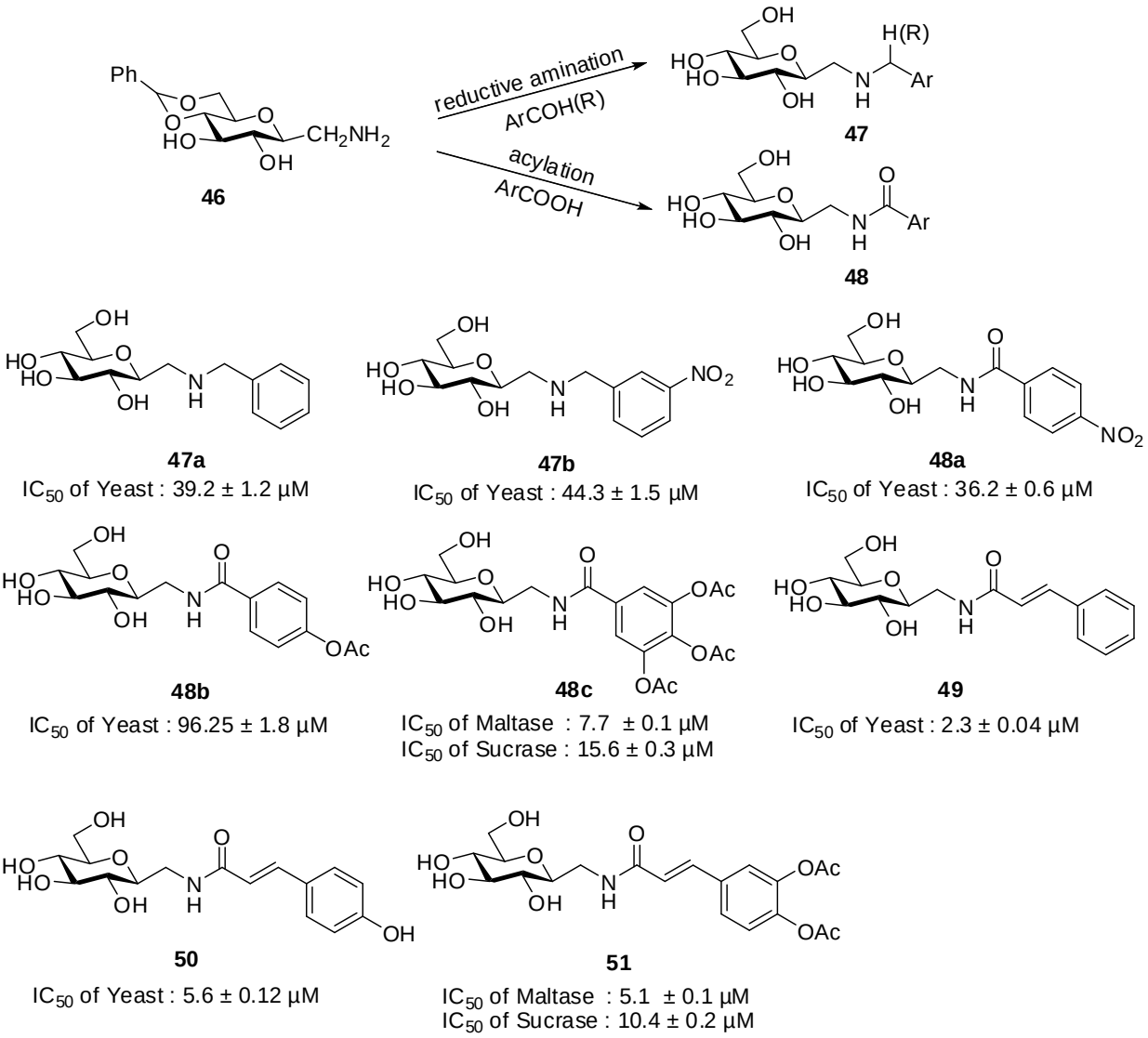
Since the click reaction was established, there has been an explosive growth in publications describing a wealth of application of this practical and sensible chemical approach particularly to medicinal chemistry. Hence, we reviewed some efforts of new classes of biological active compounds having 1,2,3-triazole moiety linked sugar analogues as important building blocks used as antibacterial agent, pharmaceutical intermediates, anti-hyperglycemic, α-glucosidase inhibitors.

Goyard, Baron, Skourti, Chajistamatiou, Docsa,Gergely, Chrysina, Praly and Vidal (2012) reported the synthesis of 1,2,3-triazoles from xylosyl and 5-thioxylosyl azides. The reaction was coupled by Cu(I)-catalyzed of alkynes to the corresponding D-xylopyranosylazide. Oxidation of the sulfur atom afforded the sulfoxide and sulfone analogues in good yields. Deacetylation led to product which was evaluated as RMGP*b* inhibitors. Compared to glucose-based analogues, sulfoxide and sulfone analogues appeared to be much weaker inhibitors of glycogen phosphorylase, as the absence of a hydroxymethyl group weakens their binding at the enzyme active site(Scheme **2.12**).



Scheme 2.12 Synthesis of 1,2,3-triazoles from xylosyl and 5-thioxylosyl azides derivative **45a-i**.

Bian, Fan, Ke, Luan, Zhao and Zeng (2013) reported the synthesis of*N*-substituted 1-amino methyl-β-D-glucopyranoside derivatives which were prepared from aminomethyl-4-6-*O*-benzylidene-β-D-glucopyranoside intermediate through reductive amination or acylation. These sugar mimetics were found to be α-glycosidase inhibitors from yeast and rat intestine (maltase and sucrase) with IC_{50}values covering a wide range from 2.3 μM to 2.0 μM in assay. Compound **50** and **51** were identified as the most potent inhibitors for yeast α-glucosidase of maltase and sucrase. The results suggest that the amino-methyl-β-D-glucopyranoside moiety can mimic the substates of α-glucosidase in the enzyme catalytic site leading to competitive enzyme inhibition. (Scheme **2.13**)



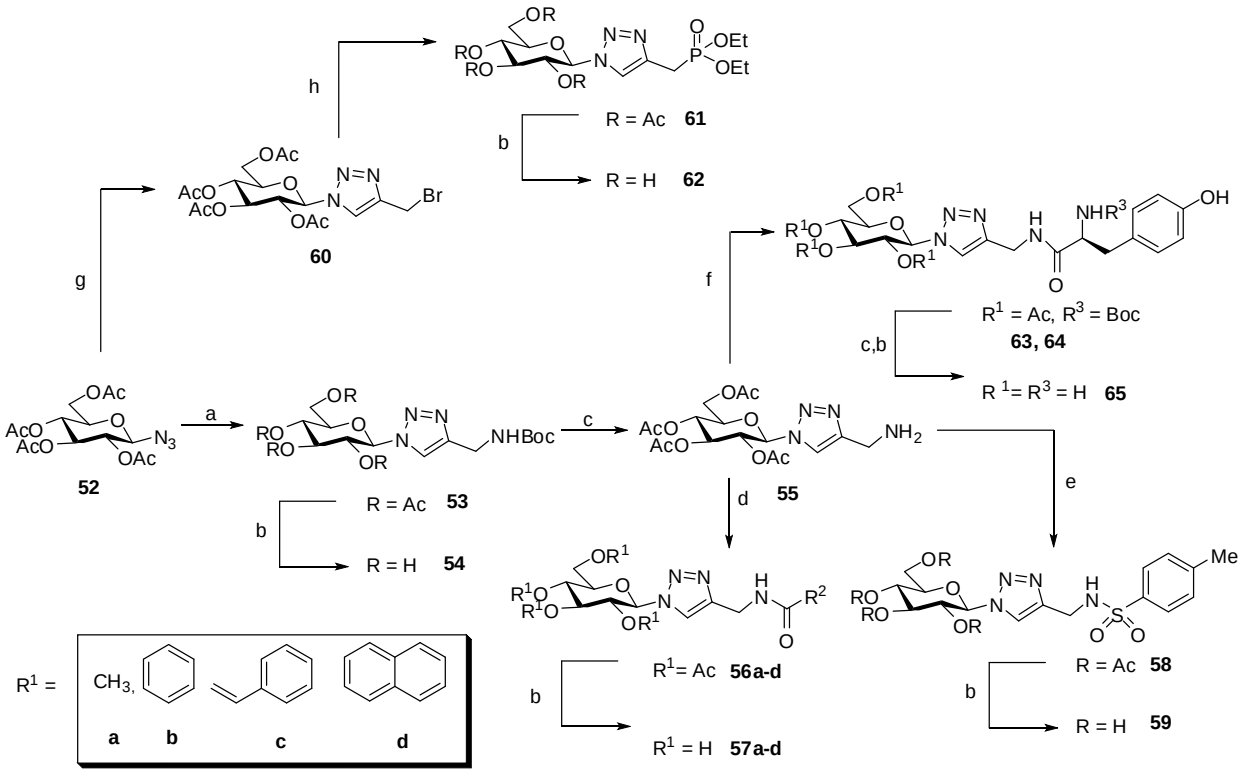
Scheme 2.13 Synthesis of N-substituted 1-amino methyl-β-D-glucopyranoside derivatives**.**

Goyard, Docsa, Gergely, Praly and Vidal (2015) reported the synthesis of4-amidomethyl-1-glucose-1,2,3-triazole derivatives via cycloaddition of Boc-propagylamide with peracetylatedglucosylazide and studies their potential of glycogen phosphorylase inhibitors toward this enzyme. The eight inhibitor candidates have been assayed *in vitro* for their inhibitory toward RMGP*b* as shown in Table1. Compound **54** showed the best inhibitor (IC_{50} = 620 µM) which unexpectedly slightly better than the 2-naphthylamido substituted analogue **57d** (IC_{50} = 650 µM). The evaluation of eight GP inhibitor candidates highlighted that the structural design was limited to only a small series of 4-amidomethyl-1-glucose-1,2,3-triazoles while several other structural moieties (sulfamido, amino acid or phosphonate) proved detrimental. To surprise, the inhibitory properties of the Boc-amine protected

intermediate **55** were the best in this study although with an IC_{50} value in the high μM range. (scheme **2.14**)

Table1 Enzyme kinetic studies of the eight inhibitor candidate against RMGP*b*.

Inhibitor	IC50 (μM)
54	620
57a	40% inhibition at 5000
57b	1400
57c	2100
57d	650
59	30% inhibition at 5000
65	No inhibition at 5000
62	No inhibition at 5000



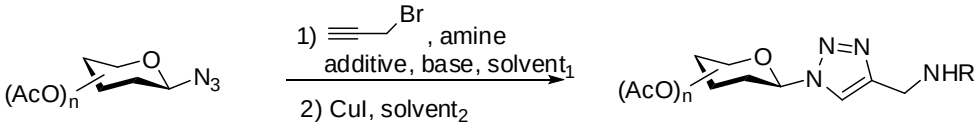
reagent and condition : (a) $HC{\equiv}CCH_2NHBoc$, CuI, *i*$PrNEt_2$, DMF, 70°C, 4h ; (b) MeONa, MeOH, rt, 16h ; (c) CH_2Cl_2/TFA (10:1),rt, 4h (d) R^2COCl, Et_3N, CH_2Cl_2, rt, 4h ; (e) TsCl, Et_3N, CH_2Cl_2, rt, 4h ; (f) BocTyrOH, EDCI, HOBt, CH_2Cl_2/DMF (2:1), -10°C (g) $HC{\equiv}CCH_2Br$, $CuSO_4$, sodium ascorbate, *t*$BuOH/H_2O$ (1:1), rt, 16h ; (h) $P(OEt)_3$, 140°C, 1h

Scheme 2.14 Synthesis of 4-amidomethyl-1-glucose-1,2,3-triazole derivatives.

According to the bioactivities of amine, glycoside and triazole, this project was aimed to studythe efficient methodology for the synthesis of amino-triazoleglycosidederivatives.Thepurposeof our researchwas attempt to simplify by one-pot reactionas a safe, convenient and environmentally benign for eliminating the need for work-up and product isolation between successive synthetic steps.All synthetic analogues will be further study for biological activity

Chapter 2: Results and Discussions

In this work, we developed new synthetic methodologyfor the synthesis of amino-triazoleglycoside from 1-Azido-β-D-sugar via one-pot two steps reaction. The one-pot of *N*-alkylation and click reaction from commercial available amine was carried out.The*N*-alkylation of amine derivatives with propargyl bromide to give propargylamine was performed in the first step subsequently followed by a 'click' reaction with various azido-glycosides in the presence of CuI in aqueous solution to provide amino-triazole glycosides.



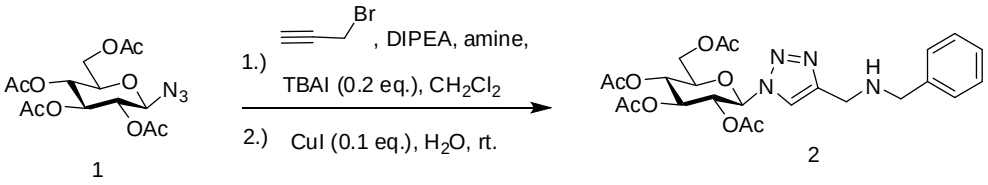
1 **2**

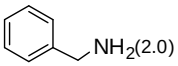
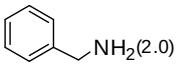
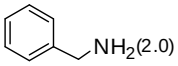
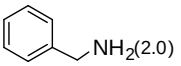
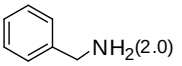
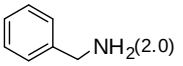
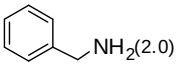
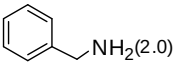
Scheme 2.1 The one-pot synthesis of amino triazole-glycoside from carbohydrate derivatives

To validate the strategy and investigation the condition for one pot synthesis of amino glycoside **2**, the reaction of glycosylazide with benzylamine followed by click reaction was examined as a model reaction under various conditions(Table 1). The starting material, azido-glucopyranoside 1 was easily prepared in high yield (85%) from the reaction of D-glucose pentaacetatewithtrimethylsilylazide ($TMSN_3$) at room temperature. The optimaization reaction was carried out by frist*N*-propargylation of benzylamine with propargylbromidein the first step using DIPEA as base, with addition of TBAI as an additive followed by Huisgen 1,3-Dipolar Cycloaddition or copper (I) -catalyzed alkyne-azidecycloaddition (CuAAC) in second step.

When the reaction was conducted in THF, no reaction was occurred (entry 1). Low yields of product were observed when stirring the reaction in 1:1 mixture of water and THF and the mixture of water and CH_3CN. As shown in entries 2 and 3, the productswere afforded in 10% and 9% respectively. Mixture of solvents H_2O:MeOH, H_2O:*t*-BUOH, H_2O:DMF, H_2O:CH_2Cl_2 and CH_2Cl_2 were investigated and were failed to obtain the product.

Table 1 Optimization conditions for one pot synthesis of amino glycoside **2**



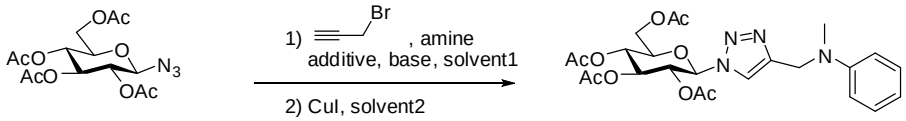
Entry	alkyne (eq.)	base (eq.)	amine (eq.)	T_1/T_2 (h)	solvent	yield
1	2.0	3.0		overnight	THF	-
2	2.0	3.0		1/23	THF:H_2O (1:1)	10 %
3	2.0	3.0		1/23	CH_3CN:H_2O (1:1)	9 %
4	2.0	3.0		1/3	MeOH:H_2O (1:1)	-
5	2.0	3.0		1/3	*t*-BuOH:H_2O (1:1)	-
6	2.0	3.0		1/3	DMF:H_2O (1:1)	-
7	2.0	3.0		1/23	CH_2Cl_2	-
8	2.0	3.0		1/3	CH_2Cl_2:H_2O (1:1)	-

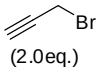
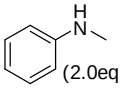
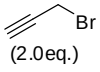
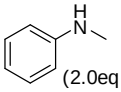
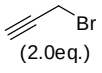
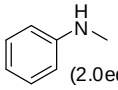
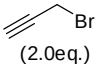
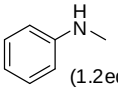
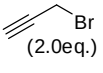
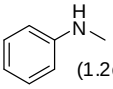
Next, we investigated the reaction of glycosylazideand*N*-methylaniline as the model system for screening a variety of reaction parameters. As shown in Table 2, when the reaction was proceed in 2:1 mixture of water and dichloromethane and Et_3N was used as bases, no product was observedafter stirring the reaction overnight (entry 1). The product was obtained in 52% yield in entry 2 when the reaction time was decreased to 11 h. These results are probably due to the decomposition of product in long reaction time.

To improve the yield of product, DIPEA and K_2CO_3 were employed as base together with additive such as TBAI and KI. In the presence of DIPEA and TBAI, the desired product was obtained in good yields (entries 3 and 4). Using K_2CO_3as base in the present of KI as additives (entry 5), the reaction was carried out in 2:1 mixture of water and acetonitrile,

offering the greatest product in 92% yield. The conditions in entries 4 and 5 were employed as optimized conditions for synthesis a series of amino triazole glycoside.

Table 2 Optimization conditions for one pot synthesis of amino glycoside **2**



Entry	alkyne	amine	base	additive	solvent 1/2	Time 1/2(h)	yields[c](%)
1	 (2.0eq.)	 (2.0eq.)	Et_3N (2.0eq.)	-	CH_2Cl_2/H_2O	overnight	trace
2	 (2.0eq.)	 (2.0eq.)	Et_3N (1.0eq.)	-	CH_2Cl_2/H_2O	1/10	52%
3[d]	 (2.0eq.)	 (2.0eq.)	DIPEA (1.0eq.)	TBAI (0.2eq.)	CH_2Cl_2/H_2O	1/24	54%
4[d]	 (2.0eq.)	 (1.2eq.)	DIPEA (1.0eq.)	TBAI (0.2eq.)	CH_2Cl_2/H_2O	1/24	74%
5[c,*]	 (2.0eq.)	 (1.2eq.)	K_2CO_3 (1.0eq.)	KI (0.2eq.)	CH_3CN/H_2O	1/3	92%

[c] is isolated yields
[d] is recovery yields
* is in N-alkylation reaction have tempurature to 70^{o}C

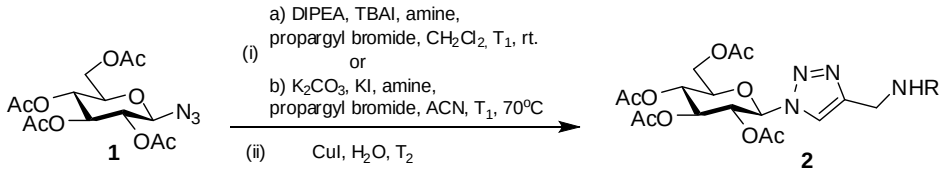
Under the optimized conditions in hand, a number of substrates were investigated (Table 3). D-glucosyl-azide was employed as starting material to perform click reaction with *in situ* generation of substituted amine. We examined the scope of D-glucosylazide and variety of substituents aromatic amine, aliphatic and heterocyclic amine. Both heterocyclic amine such as pyrrolidine and morpholine were reacted with propargyl bromide in the presence of DIPEA and TBAI to afford the N-alkylated compounds in 1 h and followed by click reaction to obtain the triazoleglycosides (entries 1-2).Morpholine provided an excellent yield of product whilepyrrolidinegave good yield under the present reaction conditions.

Aniline derivatives provided the desired products in excellent yields under the condition b using K_2CO_3 as base in the present of KI as additives (entry 5). The reaction of *N*-butyl aniline gave 87% and *N*-methyl aniline provided 92%yields when the reactions were proceed in 2:1 mixture of water and acetonitrile. Moreover, this methodology could also be extended to primary and secondary aliphatic amine (entries 5-7) led to the products in

moderate yields. Using secondary aliphatic amines, the reaction was completed in 24 h in the click step (entries 5 and 7).

1-Naphthylamine could readily employed in this reactions condition, affording the desired products in 74%yield after performing *N*-alkylation step for 24 h followed by click reaction for 3 h (entry 8). The halogen substitutedfluoro-, and bromo-aniline, which are useful for synthetic diversification, were proceed in the same condition and well tolerated in this reaction (entries 9-11) affording the product in good yields.

Table 3 Synthesis of amino triazole-D-glucopyranoside derivatives**2**



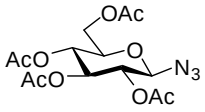
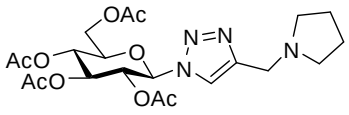
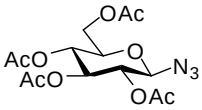
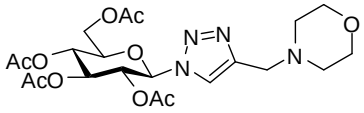
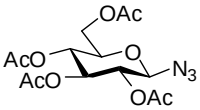
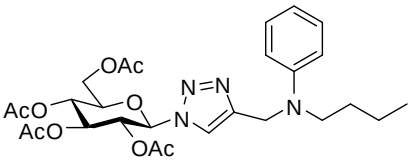
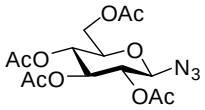
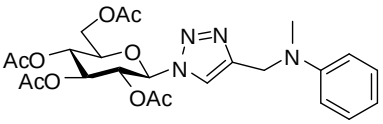
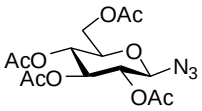
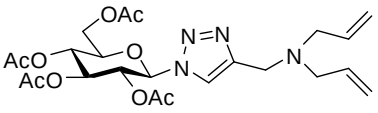
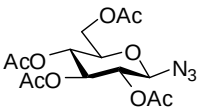
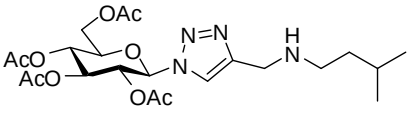
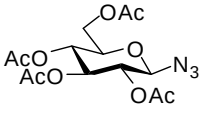
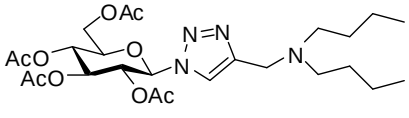
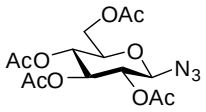
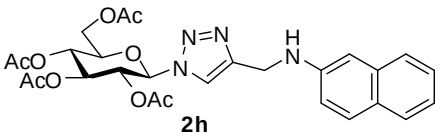
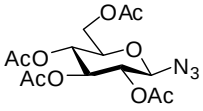
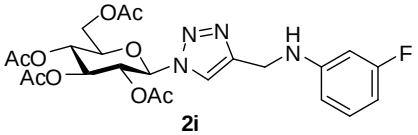
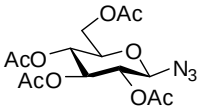
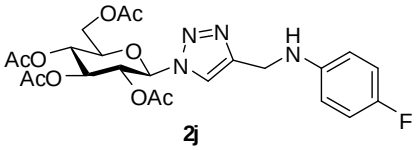
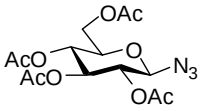
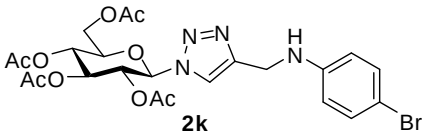
Entry	Glycosyl azide	Product	Time(h)	Yield(%)
1[a]		 **2a**	1/7	54
2[a]		 **2b**	1/3	96
3[b]		 **2c**	1/15	87
4[b]		 **2d**	1/3	92
5[b]		 **2e**	1/24	58
6[b]		 **2f**	2/2	51
7[b]		 **2g**	1/24	48

Table 3 (Continued)

Entry	Glycosyl azide	Product	Time(h)	Yield(%)
8[(b)]		 **2h**	24/3	74
9[(b)]		 **2i**	24/3	78
10[(b)]		 **2j**	24/3	78
11[(b)]		 **2k**	24/3	73

Next, we examined the scope of our finding methodology to employ D-galactosyl-azide as starting material(Table 4). The reaction conditions are compatible with amine derivatives as previous results in Table 3. Under the optimized conditions, D-galactosyl-azide was performed click reaction with *in situ* generation of substituted amine. We examined the scope of variety of substituents aromatic amine, aliphatic and heterocyclic amine.

Morpholine was reacted with propargyl bromide in the presence of DIPEA and TBAI to afford the *N*-alkylated compounds in 3 h and followed by click reaction for 3 h to obtain triazole glycoside in 90%yield (entries 1).

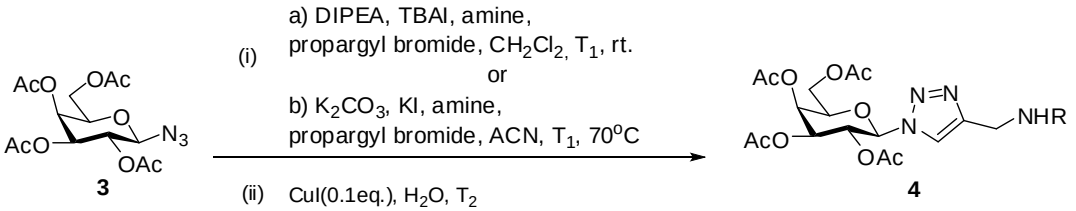
Pyrrolidine was reacted with propargyl bromide in the same condition as entry 1 to afford the *N*-alkylated compounds in 1 h and followed by click reaction for 7 h to obtain the triazole glycoside in moderate yield (entry 2).

Secondary aliphatic amine provided the desired products in good yields under the condition b using K_2CO_3 as base in the present of KI as additives (entries 3-4). When the reactions were proceed in 2:1 mixture of water and acetonitrile, dibutyl amine gave 68% and diallyl amine provided 75%yields. These reactions take 24 h to complete *N*-alkylation due to the steric hindrance of substituted groups and the click reaction was completed in 6 h.

Fluoro-anilines, which were carried out in the same condition (entries 5-6) affording the product in 75% for *m*-fluoro-aniline and 48% yield for *p*-fluoro-aniline.Bromo-aniline gave good yield of product by using the condition using DIPEA and TBAI (entry 7).

1-Naphthylamine was proceed N-alkylation step using K_2CO_3as base in the present of KI as additives followed by click reaction affording the desired products in fair yield after performing *N*-alkylation step for 24 h followed by click reaction for 3 h (entry 8). The reaction of *N*-methylaniline in this one pot methodology gave excellent yield proving the efficiency of this methodology.

Table 4 Synthesis of amino triazole-D-galactopyranoside derivatives**4**



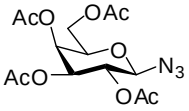
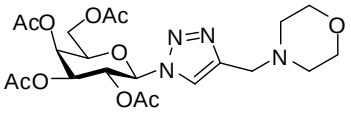
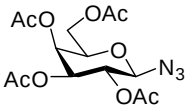
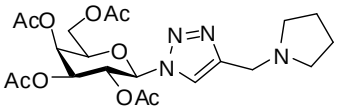
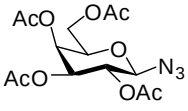
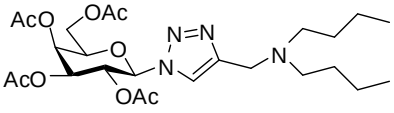
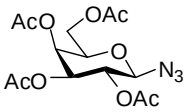
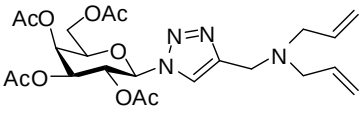
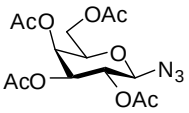
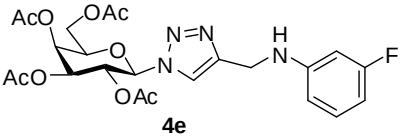
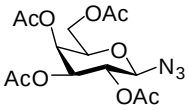
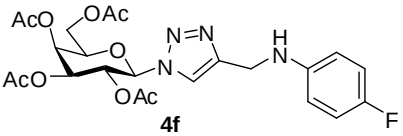
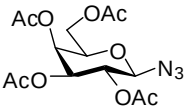
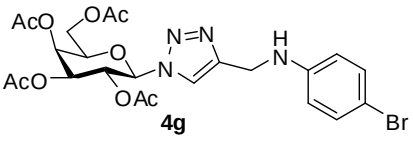
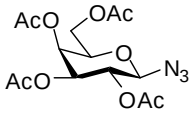
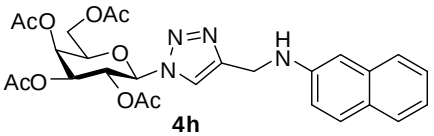
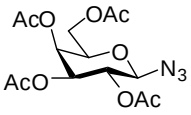
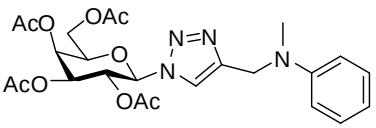
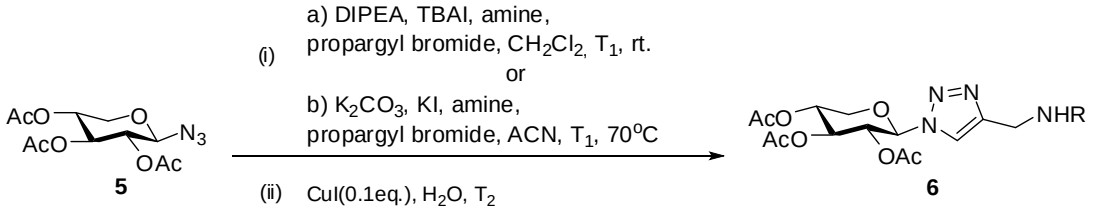
Entry	Glycosyl azide	Product	Time(h)	Yield(%)
1(a)		 **4a**	3/3	90
2(a)		 **4b**	1/7	51
3(b)		 **4c**	24/6	68
4(b)		 **4d**	24/6	75
5(b)		 **4e**	17/3	75
6(b)		 **4f**	17/3	48
7(a)		 **4g**	24/3	71

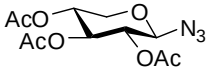
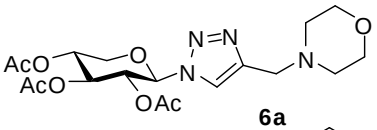
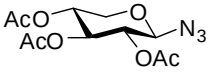
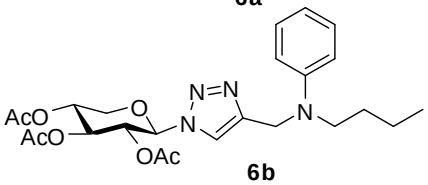
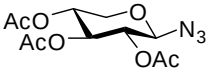
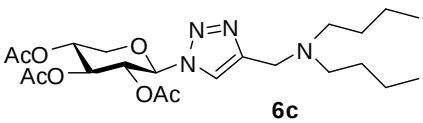
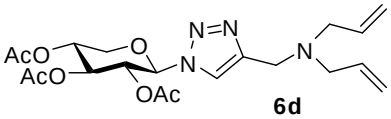
Table 4 (Continued)

Entry	Glycosyl azide	Product	Time(h)	Yield(%)
8(b)		 **4h**	24/3	48
9(b)		 **4i**	3/6	95

With the optimized conditions, we employed D-xylosyl-azide as starting material to perform one pot reaction for synthesis of amino triazole-D-xylopyranoside(Table 5). D-xylosyl-azide was reacted smoothly with *in situ* generation of substituted amine via click reaction. We examined the scope of substituents aromatic amine, aliphatic and heterocyclic amine.

Table 5 Synthesis of amino triazole-D-xylopyranoside derivatives **6**

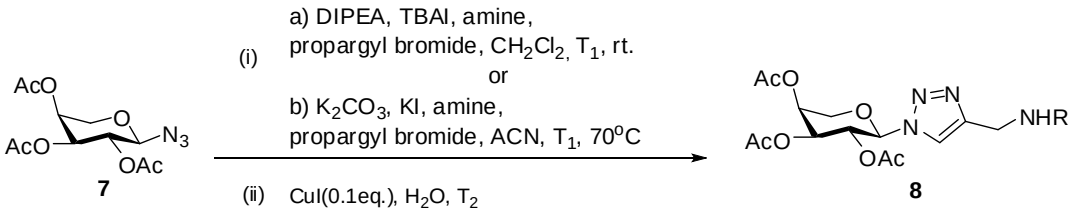


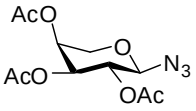
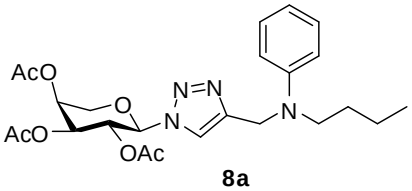
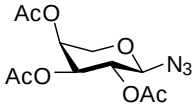
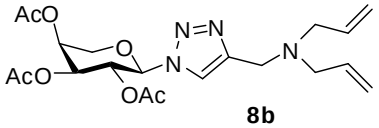
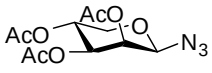
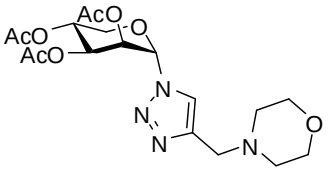
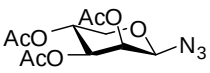
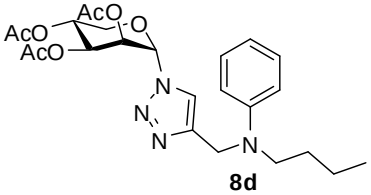
Entry	Glycosyl azide	Product	Time(h)	Yield(%)
1(a)		 **6a**	3/2	48
2(b)		 **6b**	3/15	88
3(b)		 **6c**	5/6	76
4(b)		 **6d**	5/6	76

Morpholine was reacted with propargyl bromide in the presence of DIPEA and TBAI to afford the *N*-alkylated compounds in 3 h and followed by click reaction for 2 h to obtain amino triazole-D-xylopyranoside**6a** in 48%yield (entries 1, Table 5).

Secondary aliphatic amine provided the desired products in good yields under the condition b using K_2CO_3 as base in the present of KI as additives (entries 3-4). These reactions take 3-5 h to complete *N*-alkylation and the click reaction was completed in 6-15 h. affording the products **6b**-**6d** in high yield.

Table 6 Synthesis of amino triazole-D-arabinopyranoside derivatives**8**

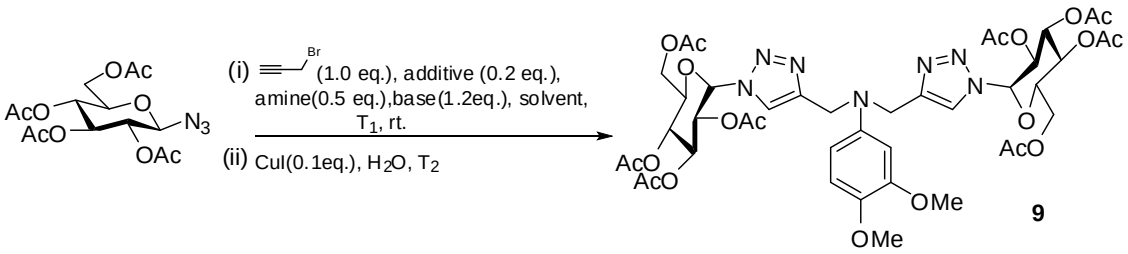


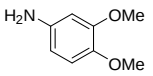
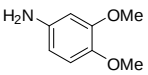
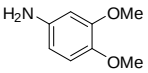
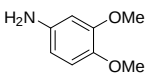
Entry	Glycosyl azide	Product	Time(h)	Yield(%)
1(b)		 **8a**	4/2	55
2(b))		 **8b**	5 /10	51
3(b)		 **8c**	5/3	72
4(b)		 **8d**	5/3	51

Further investigation our methodolody, we employed D-arabinosyl-azide as starting material to perform one pot reaction for synthesis of amino triazole-D-arabinopyranoside(Table 6). D-arabinosyl-azide was reacted smoothly with *in situ* generation of substituted amine via click reaction. We examined the scope of substituents aromatic amine, aliphatic and heterocyclic amine.

Morpholine and secondary aliphatic amines were reacted smoothly with azide providing the desired products in good yields under the condition b using K_2CO_3 as base in the present of KI as additives (entries 1-4, Table 6). These reactions take 4-5 h to complete *N*-alkylation and the click reaction was completed in 2-10 h. affording the products **8a-8d**.

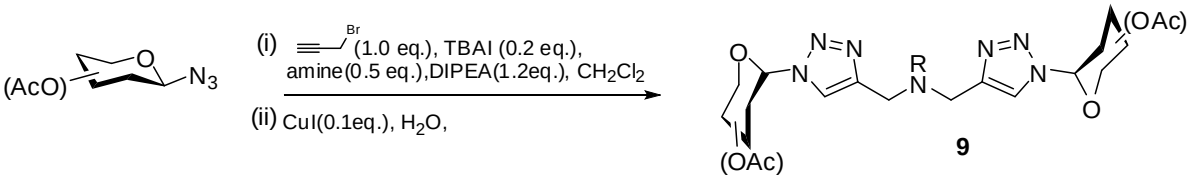
Table 7Optimization of one-Pot Synthesis of amino bistrizaoleglycoside

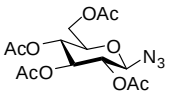
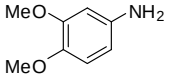
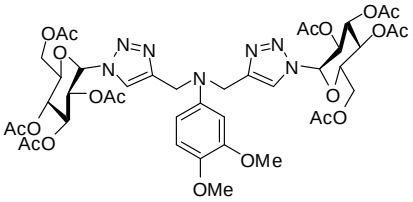
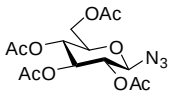
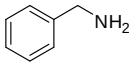
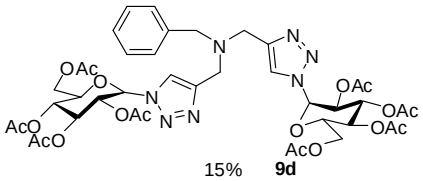


Entry	Base	Amine	Additive	Solvent	Time(h)	%Yield
1	$NaHCO_3$		-	CH_2Cl_2:H_2O	3h/24h	23%
2	NaOH		-	CH_2Cl_2:H_2O	3h/24h	-
3	KOH			CH_2Cl_2:H_2O	3h/24h	-
4	DIPEA		TBAI	CH_2Cl_2:H_2O	3h/24h	27%

With the successful results of our one pot methodology, we further study the synthesis of amino bistriazole glycoside by reaction of glycosylazide and dimethoxyaniline. As shown in Table 7, when the reaction was proceed using $NaHCO_3$ or DIPEA as bases, designed product was observed after stirring the reaction one day (entries 1 and 4). The reactions were performed in dichloromethane and water.

Table 8One-Pot Synthesis of amino bistrizaoleglycoside

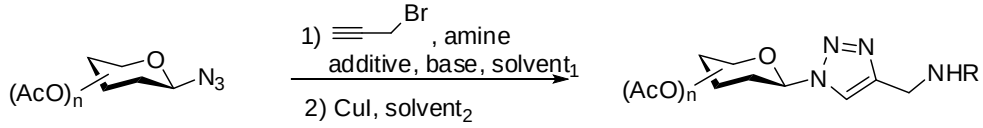


Entry	Sugar	Amine	Time(h)	Desired product
1			3/24	 27% 9a
2			6/24	 15% 9d

Under the optimized conditions in hand, D-glucosyl-azide was employed as starting material to perform click reaction with *in situ* generation of dimethoxy aniline and benzyl amine. Both amines were reacted with propargyl bromide in the presence of DIPEA and TBAI to afford the *N*-alkylated compounds and followed by click reaction to obtain the bistriazoleglycosides in low yields sue to the steric hindrance of products (entries 1-2).

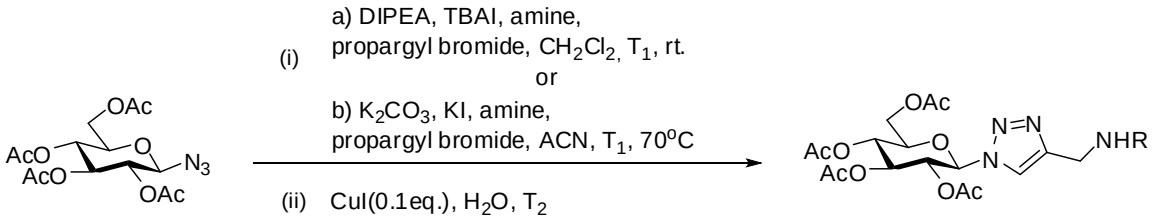
Chapter 3Conclusion

In this work, we have developed new and convenient synthetic methodologyfor the synthesis of amino-triazoleglycoside from various 1-Azido-β-glycosideand amines using one-pot two steps procedure. Thefirst step *N*-alkylation of amine derivatives with propargyl bromide to give propargylamine was performed subsequently followed by a 'click' reaction with azido-glycosides in the presence of CuI in aqueous solution to provide amino-triazole glycosides.



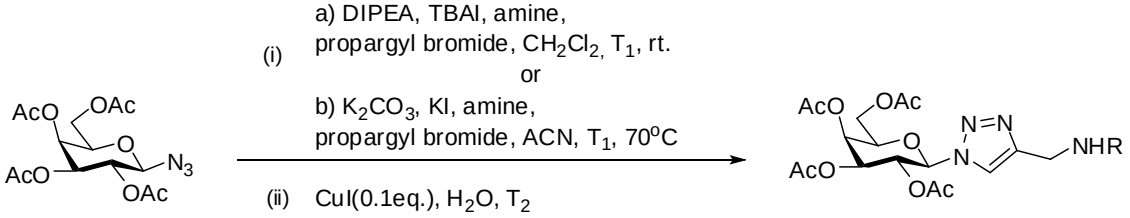
1 **2**

We studied and investigated the best conditions for *in situ* generation of substituted amine by *N*-alkylationwhich followed by click reaction. The two optimized conditions were found by using DIPEA and TBAI in dichloromethane:water as solvent system and K_2CO_3 and KI in 2:1 mixture of water and acetonitrile.

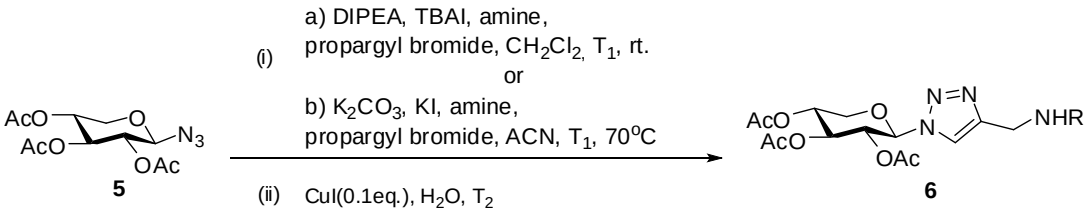


Eleven new analogues of desired amino triazoleglucopyranosideswere prepared in fair to excellent yields using the one pot procedure.

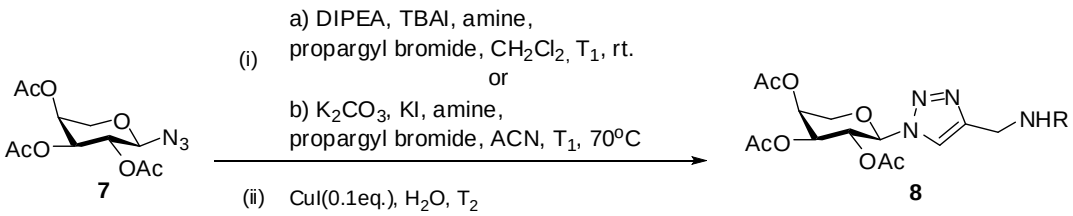
Moreover, we employed the optimized conditions for synthesis of amino triazolegalctosides. Nineanalogueswere obtained in fair to excellent yields proving the efficiency of our methodology.



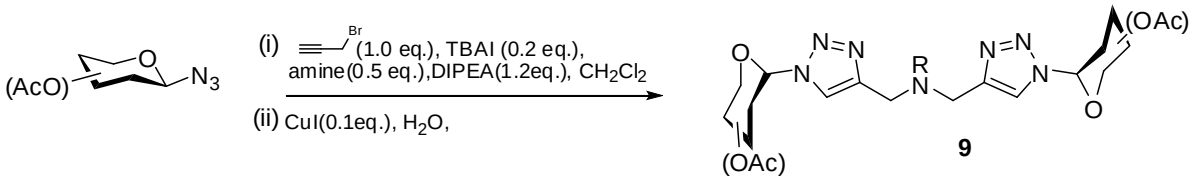
Further investigation our procedure, we employed D-xylosyl-azide as starting material to perform one pot reaction for synthesis of amino triazole-D-xylopyranoside.D-xylosyl-azide was reacted smoothly with *in situ* generation of substituted amine via click reaction.



We employed D-arabinosyl-azide as starting material to prove our one pot reaction. D-arabinosyl-azide was reacted smoothly with *in situ* generation of substituted amine via click reaction to obtain amino triazole-D-arabinopyranoside in good yield.



Proving the generality of our procedure, we further study the synthesis of amino bistriazole glycoside by reaction of glycosylazide and dimethoxyaniline. The reaction was proceeded to obtain the desired product.



Chapter 4 Experimental Procedures

Synthesis of amino triazole-glycoside (General Procedure A)

Following the general procedure B, morpholine was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 0:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 0:1 as eluent) to give product **2b** as a white solid (96%). R_f = 0.12 (*n*-hexane/EtOAc 0:1).

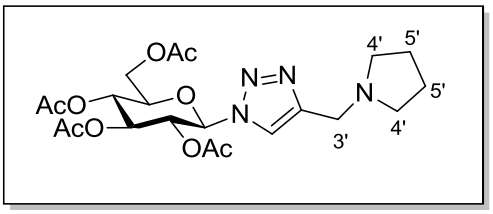


Figure 2 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)- 4-(pyrrolidin-1-ylmethyl)-1,2,3-triazole

Following the general procedure A, N-methylaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (CH_2Cl_2/MeOH 9:1 as eluent) to give product **2a** as a brown solid (54%) (R_f = 0.27 (CH_2Cl_2/MeOH 9:1)

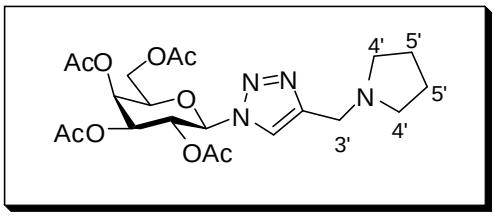


Figure 3 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)- 4-(pyrrolidin-1-ylmethyl)-1,2,3-triazole

Following the general procedure A, N-methylaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (CH_2Cl_2/MeOH 9:1 as eluent) to give product **4b** as a brown solid (51%) (R_f = 0.27 (CH_2Cl_2/MeOH 9:1)

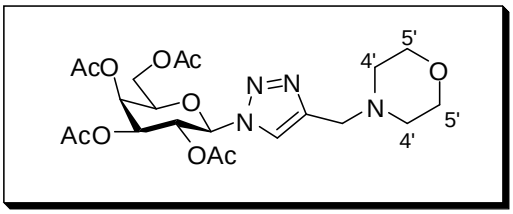


Figure 4 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)- 4-(morpholinomethyl)-1,2,3-triazole.

Following the general procedure A, morpholine was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 0:1 as eluent) to give product **4a** as a white solid (90%). R_f = 0.15 (*n*-hexane/EtOAc 0:1).

Synthesis of amino triaole-glycoside (General Procedure B)

Following the general procedure B, di-n-butylamine was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 9:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 7:3 as eluent) to give product **2g** as a white solid (48%) (R_f = 0.15 (*n*-hexane/EtOAc 7:3).

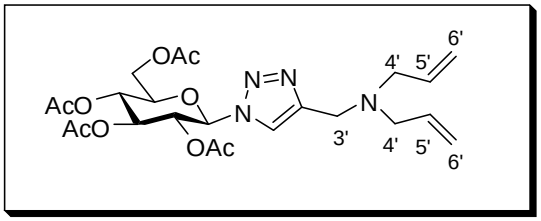


Figure 6 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-(diallylamino)methyl-1,2,3-triazole

Following the general procedure B, diallylamine was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 9:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 7:3 as eluent) to give product **2e** as a white solid (58%) (R_f = 0.12 (*n*-hexane/EtOAc 7:3).

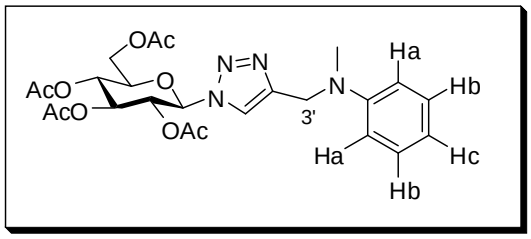


Figure 7 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)- 4-(methylphenylamino)-1,2,3-triazole

Following the general procedure B, N-methylaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 7:3 as eluent) to give product **2d** as a white solid (95%) (R_f = 0.10 (*n*-hexane/EtOAc 7:3)

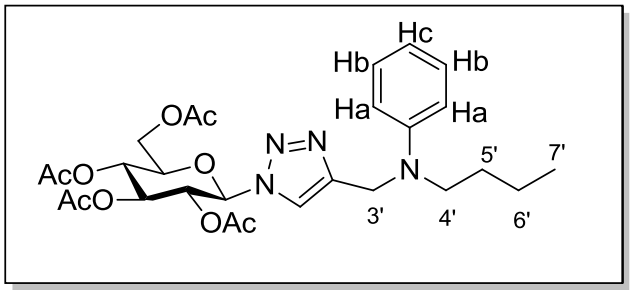


Figure 8 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)- 4-(butyl(phenyl)amino)-1,2,3-triazole

Following the general procedure B, N-n-butylaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **2c** as a brown solid (87%) (R_f = 0.17 (*n*-hexane/EtOAc 3:2)

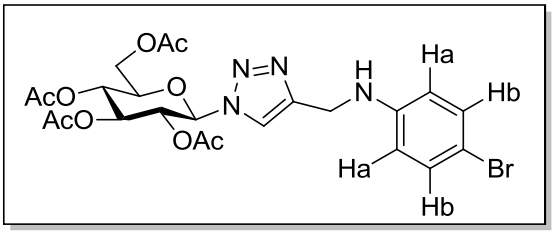


Figure 9 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)- 4-(4-bromophenylamino)-1,2,3-triazole

Following the general procedure B, 4-bromoaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 4:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **2h** as a yellow solid (73%) (R_f = 0.097 (*n*-hexane/EtOAc 3:2)

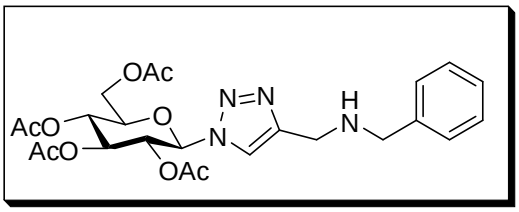


Figure 10 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-((benzylamino)methyl)-1,2,3-triazole

Following the general procedure B, benzylamine was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 4:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 1:4 as eluent) to give product **2** as a yellow solid (58%) (R_f = 0.50 (*n*-hexane/EtOAc 1:4)

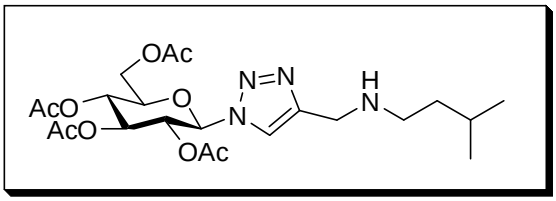


Figure 11 Structure of 1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)- 4-((isopentylamino)methyl)-1,2,3-triazole

Following the general procedure B, 1-amino-3-methyl butane was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 4:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:7 as eluent) to give product **2f** as a yellow solid (51%) (R_f = 0.42 (*n*-hexane/EtOAc 3:7)

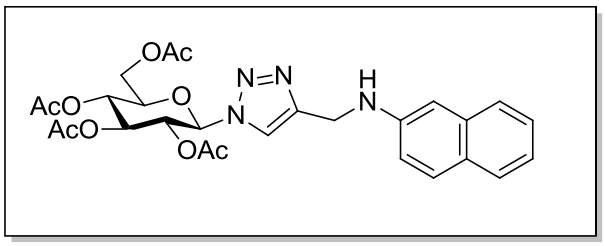


Figure 12 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)- 4-(naphthalen-2-ylamino)-1,2,3-triazole

Following the general procedure B, 1-naphthylamine was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 4:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:7 as eluent) to give product **2h**as a brown solid in 74% yield; R_f = 0.12 (*n*-hexane/EtOAc 3:7)

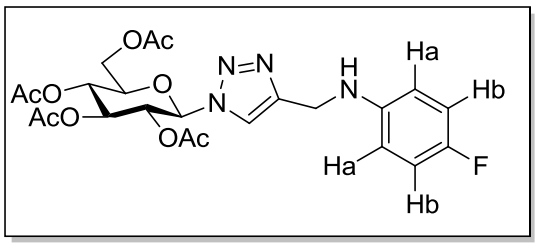


Figure 13 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)- 4-(4-fluorophenylamino)-1,2,3-triazole

Following the general procedure B, 4-fluoroaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:7 as eluent) to give product **2j**as a brown solid in 78% yield; R_f = 0.10 (*n*-hexane/EtOAc 3:7)

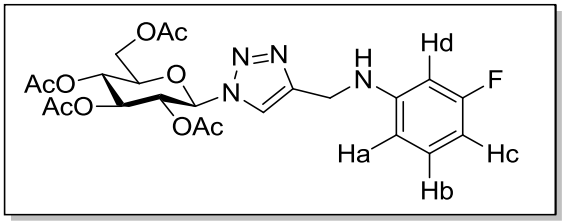


Figure 14 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)- 4-(3-fluorophenylamino)-1,2,3-triazole

Following the general procedure B, 2-fluoroaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **2i** as a brown solid (78%) (R_f = 0.12 ((*n*-hexane/EtOAc 3:2)

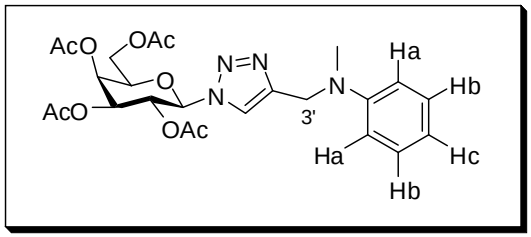


Figure 15 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)- 4-(pyrrolidin-1-ylmethyl)-1,2,3-triazole

Following the general procedure B, N-methylaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2as eluent) to give product **4i** as a brown solid (95%) (R_f = 0.15 (*n*-hexane/EtOAc 3:2)

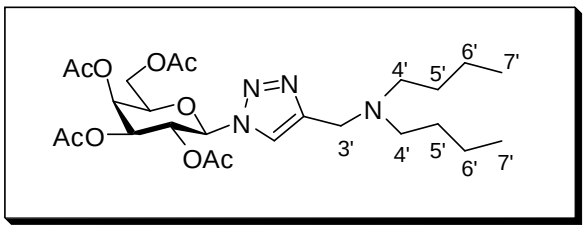


Figure 16 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)- 4-(dibutylamino)-1,2,3-triazole

Following the general procedure B, di-n-butylamine was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 9:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **4c** as a yellow solid (68%) (R_f = 0.15 (*n*-hexane/EtOAc 3:2).

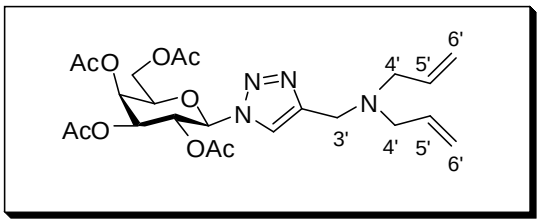


Figure 17 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)- 4-(diallylamino)-1,2,3-triazole

Following the general procedure B, diallylamine was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 9:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **4d** as a brown solid (75%) (R_f = 0.17 (*n*-hexane/EtOAc 3:2).

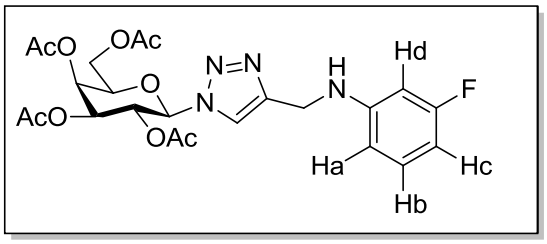


Figure 18 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-4-(3-fluorophenylamino)-1,2,3-triazole

Following the general procedure B, 2-fluoroaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **4e** as a brown solid (75%) (R_f = 0.15 ((*n*-hexane/EtOAc 3:2)

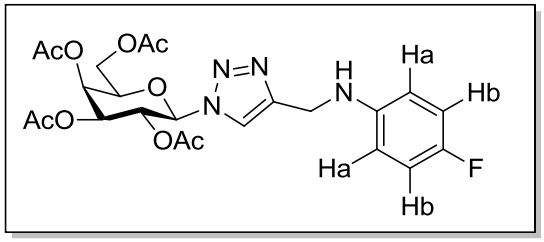


Figure 19 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-4-(4-fluorophenylamino)-1,2,3-triazole

Following the general procedure B, 4-fluoroaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **4f**as a yellow solid in 48% yield; R_f = 0.04 (*n*-hexane/EtOAc 3:2)

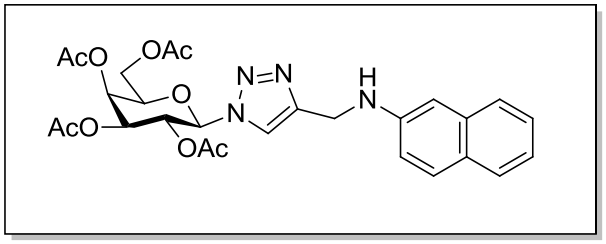


Figure 20 Structure of 1-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)- 4-(naphthalen-2-ylamino)-1,2,3-triazole

Following the general procedure B, 1-naphthylamine was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 4:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:7 as eluent) to give product **4h**as a brown solid in 48% yield; R_f = 0.09 (*n*-hexane/EtOAc 1:3).

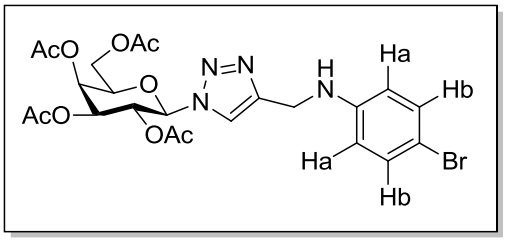


Figure 21 Structure of 1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)- 4-(4-bromophenylamino)-1,2,3-triazole

Following the general procedure B, 4-bromoaniline was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 4:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 1:1 as eluent) to give product **4g** as a yellow solid (71%) (R_f = 0.25 (*n*-hexane/EtOAc 1:1).

Following the general procedure B, 4-bromoaniline (0.052 mL) was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 4:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 1:1 as eluent) to give product **2** as a yellow solid (71%) (R_f = 0.25 (*n*-hexane/EtOAc 1:1).

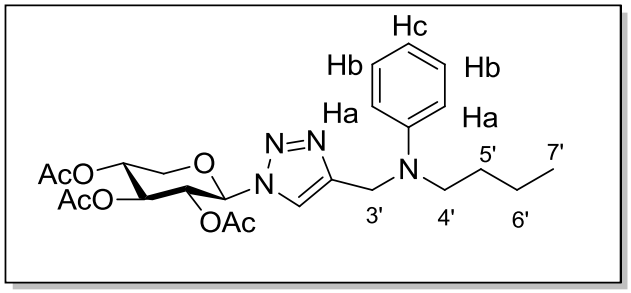


Figure 3 Structure of 1-(2,3,4,6-Tri-*O*-acetyl-β-D-xylopyranosyl)- 4-(butyl(phenyl)amino)-1,2,3-triazole

Following the general procedure B, N-n-butylaniline (0.064 mL) was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **2** as a brown solid (88%) (R_f = 0.24 (*n*-hexane/EtOAc 3:2).

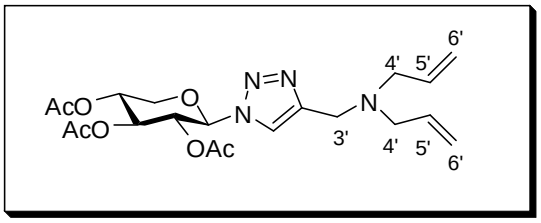


Figure 3 Structure of 1-(2,3,4-Tri-O-acetyl-β-D-xylopyranosyl)- 4-(diallylamino)-1,2,3-triazole

Following the general procedure B, diallylamine (0.049 mL) was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 9:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **2** as a white solid (76%) (R_f = 0.14 (*n*-hexane/EtOAc 3:2).

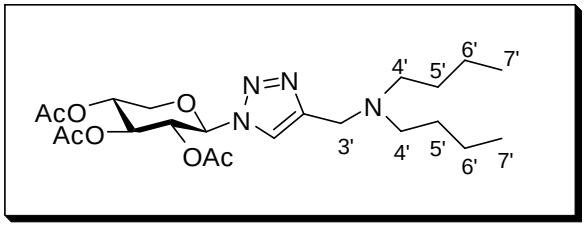


Figure 2 Structure of 1-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)- 4-(dibutylamino)-1,2,3-triazole

Following the general procedure B, di-n-butylamine (0.067 mL) was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 9:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **2** as a white solid (76%) (R_f = 0.14 (*n*-hexane/EtOAc 3:2).

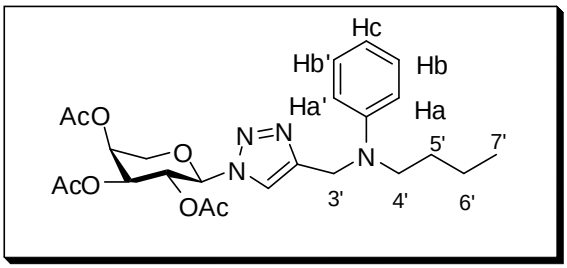


Figure 3 Structure of 1-(2,3,4-Tri-*O*-acetyl-β-L-arabinopyranosyl)- 4-(butyl(phenyl)amino)-1,2,3-triazole

Following the general procedure B, N-n-butylaniline (0.064 mL) was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 7:3 as eluent) to give product **2** as a brown solid (55%) (R_f = 0.24 (*n*-hexane/EtOAc 7:3).

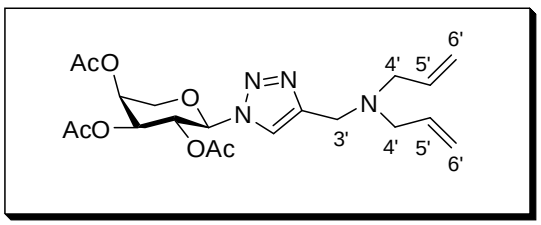


Figure 3 Structure of 1-(2,3,4-Tri-O-acetyl-β-L-arabinopyranosyl)- 4-(diallylamino)-1,2,3-triazole

Following the general procedure B, diallylamine (0.049 mL) was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 9:1. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 1:1 as eluent) to give product **2** as a brown solid (51%) (R_f = 0.07 (*n*-hexane/EtOAc 1:1).

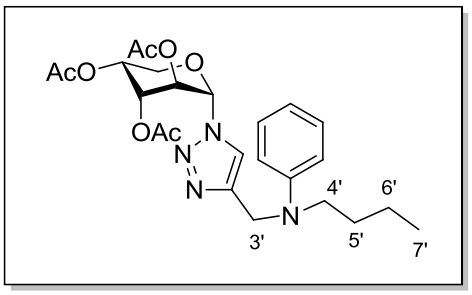


Figure 3 Structure of 1-(2,3,4-Tri-*O*-acetyl-α-D-arabinopyranosyl)- 4-((butyl(phenyl)amino))-1,2,3-triazole

Following the general procedure B, N-n-butylaniline (0.064 mL) was employed. The solvent system for monitoring the reaction by TLC is *n*-hexane/EtOAc 3:2. The crude compound was purified by siliga gel column chromatography (*n*-hexane/EtOAc 3:2 as eluent) to give product **2** as a brown solid (51%) (R_f = 0.17 (*n*-hexane/EtOAc 3:2).

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Output / Outcome

ผลงานที่ขอจดสิทธิบัตรการประดิษฐ์ จำนวน 1 เรื่อง

สารอนุพันธ์อะมิโน-ไตรอะโซล ไกลโคไซด์ชนิดใหม่ (New amino-triazole glycoside derivatives) เลขที่คำขอ 1801002074 วันที่ 4 เม.ย. 2561

ผลงานที่อยู่ในระหว่างเตรียม manuscript ส่งวารสารนานาชาติ European Journal of Organic Chemistry

Waraporn Sutcharitruk, Uthaiwan Sirion, and Rungnapha Saeeng* “One Pot Synthesis of Amino-triazole-glycoside”

การนำเสนอผลงานวิจัยแบบโปสเตอร์ในงานประชุมระดับนานาชาติ

1. Waraporn Sutcharitruk and Rungnapha Saeeng* Synthesis of Amino-triazole-glycoside, Scientific Frontiers in Natural Product Based Drugs Conference, July 6-7, 2017,Department of Pharmacology, National University of Singapore, Singapore

การนำเสนอผลงานวิจัยแบบโปสเตอร์ในงานประชุมระดับชาติ

1. Waraporn Sutcharitruk, Uthaiwan Sirion, and Rungnapha Saeeng* Synthesis of Amino-triazole-galactoside, Science RESEARCH conference 9th, May 25-26, 2017, Department of Science, Burapha University of Thailand.

การผลิตบัณฑิต

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