Design of selective ligands for conjugate drug targeting to human serum albumin (HSA) through cysteine-34 and β-D-galactopyranoside inhibitors towards galectins

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Abstract

Design of selective ligands for conjugate drug targeting to human serum albumin (HSA) through cysteine-34 and β-D-galactopyranoside inhibitors towards galectins

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Concordia University, 2011

Galectins are a large family of 15 structurally related β-D-galactopyranoside recognizing proteins. In mammals, they play a crucial role in the control of cell differentiation, proliferation, activation, metastasis and apoptosis of immune cells. Moreover, galectins have recently shown their role in HIV-1 biology by stabilizing the viral adhesion and augmentation in virus replication. Consequently, access to potent and selective inhibitors of galectins is highly desirable as tools for detailed evaluation of galectin function and activities at the cellular level and they would constitute lead compounds for the development of galectin blocking drugs. Natural ligands have low affinities and being too polar would not pass through the cell membrane. To circumvent the above issues we have logically designed and synthesized stable *C*-galactoside triazole derivatives. Some of these compounds exhibit IC_{50} values of 2.5 mM against Galectin-3. To further improve their efficacy, we have designed and synthesized *S*-galactosides, *C*-lactosides, *S*-lactosides and LacNAc derivatives with a hydrophobic pharmacophoric part i.e. substituted triazole moiety through a peptide link at the anomeric position that can balance the partition coefficient to cross cell membranes and increase the *in vivo* stability. Biological evaluations of these compounds are in progress.

Peptides are well known for recognizing and activating specific receptors. Peptidase quickly intercepts and cleaves to transform them in to biologically inactive fragments that are further cleared by the kidneys. As a consequence peptides have a short half-life and brief duration of activity, such issues preclude them from being developed in to commercialized drugs. To overcome such issues taking advantage of the characteristic nature of HSA to accumulate in tumour tissues is exploited for transport and to increase the bioavailability. We have designed and synthesized hetero trifunctional linkers (maleimido, vinylsulphonamide and acrylamide) with a Michael acceptor on one side to conjugate with the HSA through cysteine-34, and a carboxylic acid and alkyne functionality on the other side to couple peptide based drugs and to install a better triazole derivative functionality to fit the linker in the hydrophobic binding pocket of cysteine-34. The relative reactivities of these linkers were evaluated using cysteine under physiological conditions with time, the maleimido derivative found to be the fastest reacting Michael acceptor (less than 10 min) and the vinyl sulfonamide which reacts completely within 45 min. The acrylamide functionality did not react at all under physiological conditions, requiring the pH to be raised to 8.5 for reaction to occur. Theses three linkers are under further evaluation to react with HSA under physiological conditions using HPLC and MS-FAB characterization.

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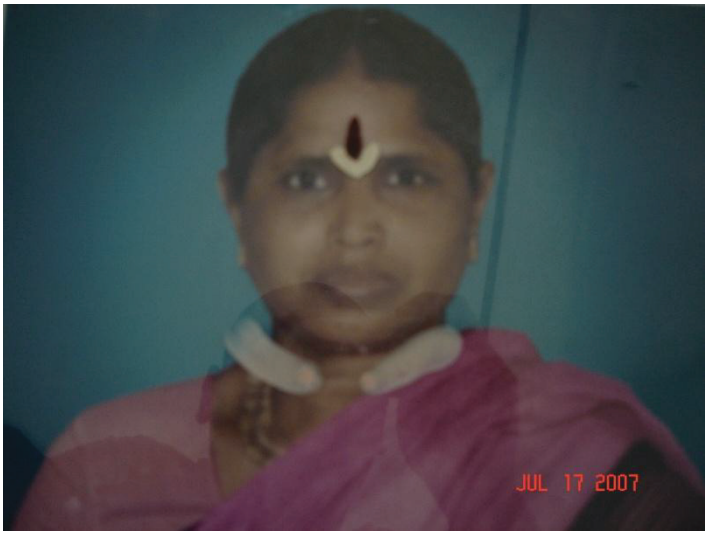
Dedication



Late. Smt. Annamaneni Chandrakala Devi

To my parents

And

To my late aunt. Smt. Chandrakala Devi

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List of Schemes

List of abbreviations

Å	Angstrom
α	Alpha
Abs	Absorbance
Ac	Acetyl
Asc.ac.	Ascorbic acid
Ac_2O	Acetic anhydride
AcCl	Acetyl chloride
ACN	Acetonitrile
Acm	Acetamidomethyl
AIBN	*N,N*'-Azobisisobutyronitrile
AIDS	Acquired Immuno Deficiency Syndrome
AllBr	Allyl bromide
APT	Attached Proton Test
Arg	Arginine
arom.	Aromatic
Asp	Aspartate
Asn	Asparagine
ATP	Adenosine-5'-TriPhosphate
ATPase	Adenosine-5'-TriPhosphatase

B

β	Beta
BAIB	Bisacetoxyiodobenzene
$BF_3.(Et_2O)_2$	Boron trifluoride etherate
Bn	Benzyl
BnBr	Benzyl bromide
Boc	*tert*- ButoxyCarbonyl
BOP	Benzotriazol-1-yloxytris (dimethylamino) phosphonium hexafluorophosphate

BSP	1-Benzenesulfinyl piperidine
^{t}BuOH	*tert*-Butanol
^{t}Bu	*tert*-Butyl
$Bu_2Sn(OMe)_2$	Dibutyltin dimethoxide
Bu_2SnO	Dibutyltin oxide
Bu_3SnH	Tributyltin hydride
BzCl	Benzoyl chloride
Bz	Benzoyl

C

c	Concentration (g/100 mL)
C	Carbon
C_q	Quaternary Carbon
c-AMP	Adenosine monophosphate cyclic
CAN	Ceric Ammonium Nitrate
CD4 or 8	Cluster of Differentiation 4 or 8
CDI	1,1'-Carbonyl-diimidazole
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
CH_3CN	Acetonitrile
cm	Centimetre
COSY	COrrelated SpectroscopY
CuI	Copper iodide
$CuSO_4$	Copper sulfate
Cys	Cysteine

D

d	Deuterium
DCC	Dicylohexylcarbodiimide
DCU	Dicyclohexylurea

DCM	Dichloromethane
DBU	1,8-Diazabicylo[5.4.0]undec-7-ene
DDQ	Dichlorodicyanoquinone
decomp.	Decomposition
DEPT	Distortionless Enhancement by Polarization Transfer
DIPCDI	Diisopropylcarbodiimide
DIPEA	*N,N′*-diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMP	2,2-Dimethoxypropane
DMSO	Dimethylsulfoxide
DMTST	Dimethyl (methylthio) sulfonium trifluoromethan sulfonate
DNA	Deoxyribonucleic acid
DTNB	5, 5'-Dithiobis (2-nitrobenzoic acid)

E

ε	Epsilon
EDCI	1-Ethyl-3-(3-(dimethylaminopropyle) carbodiimide
EDT	Ethanedithiol
ELLA	**E**nzyme **L**inked **L**ectin **A**ssays
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EPS	Exopolysaccharide
eq.	Equivalent
ER	Endoplasmic
Et_3N	Triethylamine

F

Fmoc	Fluorenyl-MethOxy-Carbonyl

G

Gal*p*	D-Galactopyranoside
Glc	D-Glucose
GlcNAc	*N*-Acetyl-D-glucosamine
GlcNPhth	*N*-Phtalimido-D-glucose
Glc*p*A	Glucuronic acid
Gln	Glutamine
Glu	Glutamate

H

H	Hydrogen
H_2	Dihydrogen
h	Hour
HAUT	(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBF_4	Hydrogen tetrafluoroborate
HBr	Hydrogen Bromide
HBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate
HCl	Hydrochloric acid
HCTU	2-(6-Chloro-1-H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium Hexafluorophosphate
HETCOR	Heteronuclear Chemical Shift Correlation
HF	Hydrogen Fluoride
His	Histidine
HOBt	1-Hydroxybenzatriazole
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSL	Homoserine lactone

HSQC	Heteronuclear Single Quantum Correlation

I

I_2	Iodine
IC_{50}	Inhibition Concentration required for 50% inhibition
IDCP	Iodonium dicollidine perchlorate
Ig	Immunoglobuline
Im	Imidazole
IR	Infrared
ITC	Isothermal Titration Calorimetry
ivDde	(4,4-Dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl

K

K_a	Affinity constant
Kcal/mol	Kilocalorie per mole
KJ/mol	Kilojoule per mole
K_d	Dissociation Constant
K_2CO_3	Potassium bicarbonate

L

LC-MS-TOF	Liquid Chromatography Mass Spectrometry Time Of Flight
LiOH	Lithium hydroxide
Litt.	Litterature
Le^a	Lewis a
Le^x	Lewis x
Lev	Levulinate
LPS	Lipopolysaccharide
Lys	Lysine

M

M	Molarity; concentration (mol/L)
mCPBA	*m*-Chloroperoxybenzoic ccide
Me	Methyl
MeI	Methyl iodide
Me_2EtN	*N,N*-dimethylethylamine
MeOH	Methanol
MeOTf	Methyltrifluoromethanesulfonate
Mg	Magnesium
mg	Milligram
MHz	MegaHertz
min	Minute
mL	Millilitre
mmol	Millimole
Mmt	*p*-Methoxyphenyldiphenylmethyl
MOE	Modelling Orbital Electronic
MP	Methoxyphenyl
Mpe	3-Methyl-pent-3-yle
Ms	Mesylate
MS (ESI)	Mass Spectrometry (electrospray)
MsCl	Mesylate chloride
m/z	Mass/charge

N

NaCl	Sodium Chloride
$NaCNBH_3$	Sodium Cyanoborohydride
NaH	Sodium Hydride
$NaHCO_3$	Sodium bicarbonate
NaN_3	Sodium Azide
NaOMe	Sodium Methoxide

Na_2CO_3	Sodium Carbonate
Na_2SO_4	Sodium Sulfate
NBS	*N*-Bromosuccinimide
NBD	Nucleotide Binding Domain
NH_4Cl	Ammonium Chloride
NIS	*N*-Iodosuccinimide
nm	Nanometre
nM	Nanomolar
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effet
Nsu	*N*-Succinimide

P

Pbf	2,2,4,6,7-Pentamethyldihydrobenzofuran-5-sulfonyl
Pd^o	Palladium zero
Pd/C	Palladium on charcoal
$Pd(OH)_2/C$	Palladium dihydroxide on charcoal
$Pd^o(PPh_3)_4$	Palladium tetrakis-triphenylphosphine
PEG	(poly) ethylene glycol
Pf	Point of fusion
Pfp	Pentafluorophenyle
Ph	Phenyl
Ph_2SO	Diphenylsulfonic anhydride
PhSH	Thiophenol
Phth	Phthalimido
Pmc	2,2,5,7,8-Pentamethylchroman-6-sulfonyl
PMB	*para*-Methoxybenzyl
PPh_3	Triphenylphosphine
ppm	parts per million
*p*TsOH	*p*-Toluenesulfonic acid
PyBOP	Benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphonium

	hexafluorophosphate

Q

QS	Quorum sensing

R

R*f*	Retardation factor
Rha*p*	Rhamnopyranoside
RP	Reverse Phase
rpm	Rotation per minute
RT	Room temperature

S

Ser	Serine
S_N	Substitution nucleophilic

T

TBAI	Tetrabutylammonium Iodide
Tamis mol.	Tamis molecular
TBAHS	Tetrabutylammonium hydrogensulfate
TBAF	Tetrabutyl ammonium Fluoride
TBDPSiCl	*tert*-Butyldiphenylsilyl chloride
TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
TCR	T Cell Receptor
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxide
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonic anhydride

TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TISOTf	Triisopropylsilyl trifluoromethanesulfonate
TLC	Thin Layer Chromatography
TMSBr	Trimethylsilyl bromide
Thr	Threonine
TIS	Triisopropylsilane
$TMSN_3$	Trimethylsilyl Azide
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TNBS	2,4,6-Trinitrobenzensulfonic acid
TNTU	*O*-(Bycyclo[2.2.1]hept-5-ene-2,3-dicarboximido)-*N,N,N'.N'*-Tetramethyluronium tetrafluoroborate
Trp	Tryptophane
Trt	Trityl
TSTU	*N,N,N',N'*-Tetramethyl-*O*-(*N*-succinimidyl)uronium tetrafluoroborate
Tyr	Tyrosine

U

µL	Microlitre
µM	Micromolar
UV	Ultraviolet

Z

$ZnCl_2$	Zinc Chloride

Chapter 1
Introduction

1.1 Introduction to glycobiology

"Glycobiology" A new frontier of molecular biology opened to develop new technologies to explore structure and function of "glycans". The word "glycobiology" was first coined in 1980 to recognize the union of two traditional disciplines carbohydrate chemistry and biochemistry. Defined in the broad view, glycobiology is the study of the structure, biosynthesis, biology and evolution of saccharides. Glycoconjugates are formed when they are attached to the proteins or lipids. Glycoconjugates are mainly categorized as two types 1) "glycolipids" glycoconjugates attached to lipids or 2)"glycoproteins" glycoconjugates attached to proteins either through nitrogen (*N*-linked) or oxygen atom (*O*-linked)[1].

1.1.1 Glycolipids

Glycans are attached to the head group of lipids, the lipid portion of glycolipid embedded in the membrane bilayer and fall into two structural categories. Glycolipids built on ceramide are known as glycosphingolipids. Ceramide is formed between a fatty acid with the long chain amino alcohol sphingisine by an amide linkage. Glycosphingolipids function like membrane glyco protein in the presence of potential recognition markers involved in cell-cell interactions. Glycosphingolipids also function in the organization of specialized membrane domain. In contrast, glycophospholipids built on a phosphatidylglycerol core provide a mechanism for anchoring proteins to the cell

surface. Glycosphingolipids are further divided into two main groups known as galactosphingolipids or glucosphingolipids respectively based on whether the first sugar attached to sphingosine is galactose or glucose.[2]

1.1.2 Glycoproteins

Glycoproteins are the proteins covalently attached to carbohydrates such as glucose, galactose, lactose, fucose, sialic acid, *N*-acetylglucosamine, *N*-acetylgalactosamine, etc. Depending on the linkage between the carbohydrates with the protein, glycoproteins are divided in to two groups 1) *O*-linked glycoproteins, which are linked to carbohydrates trough the hydroxyl group of serine, threonine or hydroxylysine. 2) *N*-linked glycoproteins in which the protein is linked to carbohydrate through the amide group of asparagines (Figure 1).

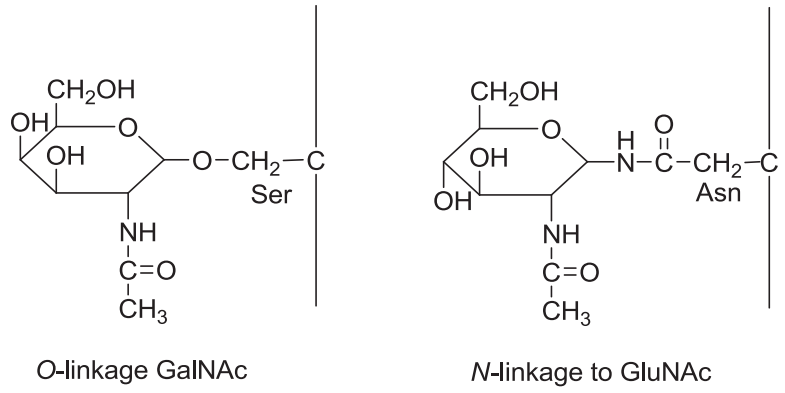


Figure 1. *O*-linked glycoproteins and *N*-linked glycoproteins

1.1.3 Carbohydrate binding proteins (CBPs)

Excluding glycan-specific antibodies, it is possible to classify CBPs into two individual groups. 1) Lectins, Most lectins are members of families with "carbohydrate recognition domains" (CRD) that apparently evolved from shared ancestrial genes, often retaining specific features of primary amino acid sequence or three dimensional structure. Lecitns were discovered more than 100 years ago, found from the microbial world to humans 2) Glycosaminoglycan-binding proteins.

1.2 Introduction to galectins

Lectins are carbohydrate binding proteins that can recognize various glycoconjugates on the cell surface and extra cellular matrices. Lectins have many functions ranging from mediation of cell adhesion and the promotion of cell-cell interactions to the recognition of pathogens. Animal lectins are grouped into several families.[3, 4, 5] Galectins is one family among them, which are defined by their ability to recognize β-galactosides and by their consensus amino acid sequences.[6,7] The study of galectins is one of the most attractive areas for biologists and chemists and the results for the word "galectin" in Scifinder Scholar reveals a steady increase in the number of papers published per year (Figure 2). New galectins and their biological roles have been discovered over the years. There are 15 mammalian galectins found so far and most of them are implicated in the pathology of various diseases. The number of publications on galectin-1 and galectin-3 are growing remarkably, the number itself tells of their implications in various diseases. One of the most interesting implications of galectins is

their intriguing roles in cancer biology, they are involved in every step of cancer processes right from neoplastic transformation to angiogenesis. Moreover, galectins have recently shown their role in HIV-1 biology by playing a very initial and pivotal role in virion adhesion to the host cell.

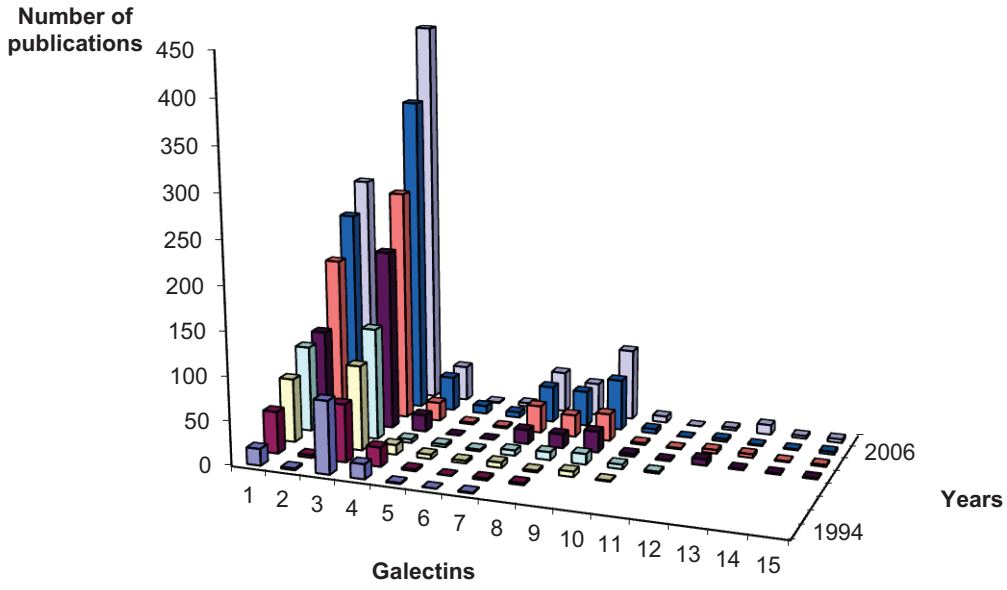
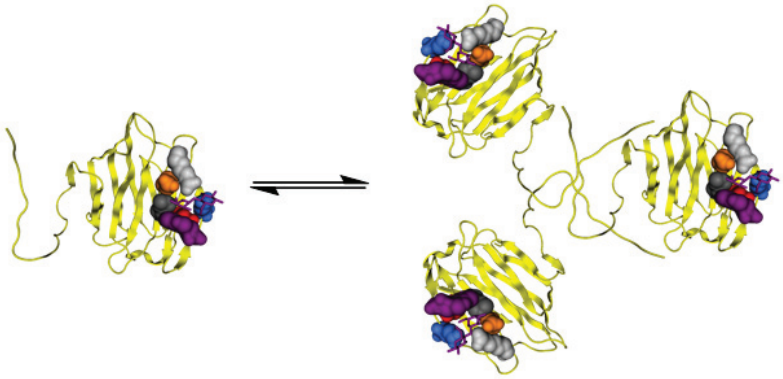


Figure 2. Scifinder Scholar data in terms of number of papers published per year per galectin

All galectins contain a conserved carbohydrate recognition domain (CRDs) of about 130 amino acids, and these are responsible for the carbohydrate binding.[8] To date 15 mammalian galectins have been identified, which can be subdivided into those that have one CRD (Gal-1,2,5,7,10,11,13,14 and 15) and those that have two CRDs (Gal-4,6,8,9,12). Galectin-3, a one CRD containing galectin, is unique and contains unusual tandem repeats of short amino acid stretches fused onto the CRD.[9,10,11,12]

a) Galectins with one CRD; Proto-type: Galectins-1, 2, 5, 7, 10, 11, 13, 14, 15

b) Galectin with one CRD and a proline-glycine rich peptide; Chimera-type: Galectin-3



c) Galectins with a tandem of two distinct CRD; Tandem-repeat-type: Galectins-4, 6, 8, 9, 12

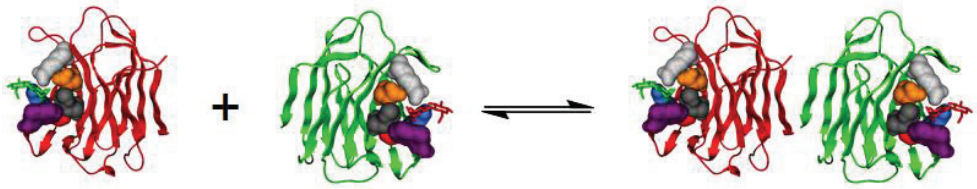


Figure 3. Schematic representation based on X-ray and spectroscopic analysis of various types of galectins: a) galectins with one CRD with possibilities of dimerization; b) galectins with one CRD with possibilities of oligomerization through their proline-glycine rich peptide tail and c) galectins with a tandem of two distinct CRD.

Many galectins are either bivalent or multivalent with respect to their carbohydrate binding activities and are shown in Figure 3. Distribution of some galectins is restricted to specific tissues and some are widely distributed in many tissues. The modulation in expression of galectins is strongly regulated by development, differentiation and under different physiological and pathological conditions.[13] Interestingly, the expression of galectins is altered in tumor cells compared with the normal counter parts.[14] Though there is some conflicting data on the expression of galectins under different pathological conditions, most of the recent data shows that galectins are elevated in neoplastic transformation with some exceptions like colon cancer.[15] Expression of certain types of galectins is specific to certain types of cancers.[12] Galectin-1 is over expressed in breast carcinoma,[16] high grade bladder carcinomas,[17, 18] bladder[19] and thyroid cancer.[20] In contrast, studies have shown that galectin-1 decrease expression in neck cancer.[21] Galectin-3 is over expressed in thyroid,[22] central nervous system,[23] head and neck squamous cell carcinoma,[24] stomach,[25] pancreas,[26] bladder[27] and renal carcinoma.[28] Galectin-3 was also found down regulated in colon cancer[12] and in urological cancers.[29]

Although there is little experimental biological evidence, qualitatively many groups have shown that galectins have important functions in several aspects of cancer biology like regulation of tumor development and growth, including tumor transformation, angiogenesis, metastasis, apoptosis and cell-cycle progression.9 Moreover, galectins seem to play an important role in HIV-1 biology by helping in

attachment of virion to host cell.[30,31] Herein, a brief implication of galectin into the biology world before a review on the galectin inhibitors.

1.2.1 Role of galectins in tumour transformation and survival

Anchoring RAS proteins to membranes are crucial to activate downstream signaling molecules RAF1 and extracellular signal-regulated kinase (ERK) for transformation of a normal cell into a neoplastic cell. Under normal conditions it is not possible for RAS proteins to anchor to the membrane for an increase in the downstream signalization transformation. Indeed, galectin-1 and galectin-3 could act as anchoring partners, thus helping in tumor transformation. Kloog *et al*. have shown that over expression of galectin-1 and galectin-3 in tumor cells increased the tumor transformation. Inhibition of galectin-1 using antisense RNA suppressed the transformation induced by this protein.[32,33] The mechanisms by which galectins are involved in cell transformation are not yet fully understood.

1.2.2 Role of galectins in apoptosis

Galectins are a family of apoptosis regulating proteins. The study of apoptosis regulation has been demonstrated mainly by using two different approaches. In the first approach, the recombinant galectins were exogenously added to cells, including tumor cells, and were shown to induce apoptosis, probably by binding to cell surface glycoconjugates. The second approach was the study of tumor cells transfected with a cDNA encoding for an individual galectin and its anti-apoptotic activities was clearly demonstrated in a variety of tumor cell types exposed to diverse apoptotic stimuli.[8,34] It

has been clearly demonstrated by different groups that regulation of apoptosis depends on the localization of galectins.[35] Extra cellular galectin-1 and galectin-9 and intracellular galectin-12 and galectin-7 are shown to be proapoptotic.[36, 37] On the other hand, apoptotic regulation of galectin-3 depends on its localization and it has been shown to be anti-apoptotic in cytoplasm[38] and proapoptotic in nucleus. Although galectin-3 is proapoptotic intranucleously, this galectin is phosphorylated by casein kinase at Serine-6 and translocate in to the cytoplasm.[39] Phosphorylation of Serine-6 is compulsory to translocate galectin-3 from the nucleus to the cytoplasm and by mutating Serine-6 into alanine or glutamic acid, the phosphorylation is not possible and galectin-3 remained in the nucleus.[40,41] The anti-apoptotic activity of galectin-3 is not yet completely understood, but this lectin translocates from the cytosol to the mitochondria along with another interacting partner and an anti-apoptotic protein (Bcl-2), which is very close to galectin-3 in sequence similarity. Both proteins have a *N*-terminal end rich in proline, glycine and alanine and contain very specific amino acids at the *C*-terminal end (Asp, Try, Gly, Arg). These amino acids are very critical for Bcl-2 regarding its anti-apoptotic functions.[36,42] This sequence is highly conserved in galectin-3 and important for the carbohydrate binding activities. Under normal conditions following exposure to apoptotic stimuli, the mitochondrial membrane potential will alter and release proapoptotic proteins by opening the mitochondrial pores, like cytochrome-*C*, SMAC or DIABLO and begin the apoptosis process. Galectin-3 with its interacting partner Bcl-2 translocate onto the mitochondrial membrane and doesn't allow alteration in membrane potential of

mitochondria to release proapoptotic proteins, thereby preventing apoptosis by arresting the mitochondrial pathway of apoptosis (Figure 4).[37]

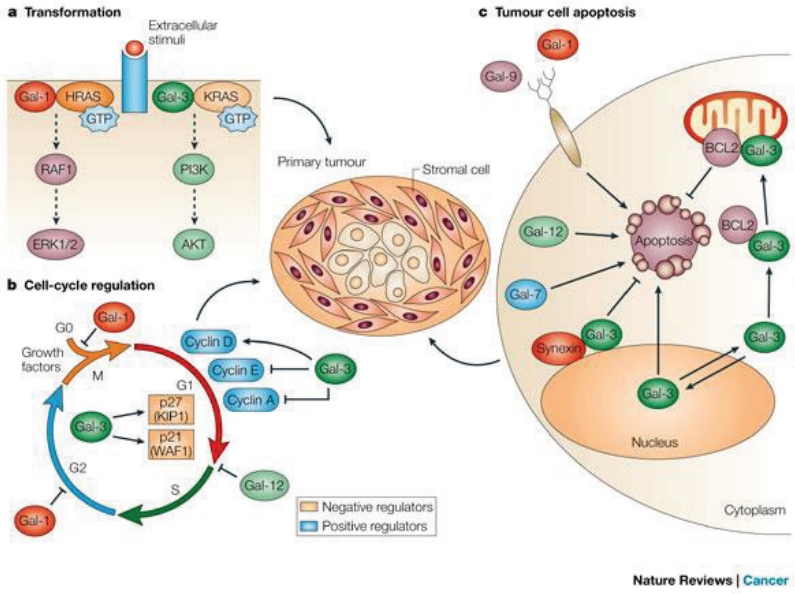


Figure 4. Role of galectins in neoplastic transformation and arrest of the mitochondrial pathway of apoptosis9

1.2.3 Role of galectins in tumor metastasis

Metastasis is a complex multi process of spreading secondary tumors in the body. Cells from primary tumor have to disintegrate intravasate into transport media (blood/lymph vessels), travel to distal places, extravasate and find a suitable site for proliferation. Galectins were shown to facilitate the above complicated process. Galectins that are released by tumor cells might interfere with the adhesion of adjacent cells either by interacting between two cells or by interacting with integrins which are responsible for the cell adhesion.[43,44,45] cells The thus liberated from primary tumor intravasate and

transports to preferable distal places where they can proliferate. Galectin-3 induces intravasation and spread exogenously on the surface of tumor cells.[46] Finally, galectins do have a role in connecting the new tumor to the blood vessels for nutrients supply. For example, galectin-3 has angiogenic activity *in vitro* by migrating to the endothelial cells. Angiogenic activity of galectin-3 is proved by over expression of this lectin in breast carcinoma cells. Galectin-3 seems to provide abundant blood capillaries around the tumor in which galectin-3 was over expressed compared to control (Figure 5).[45]

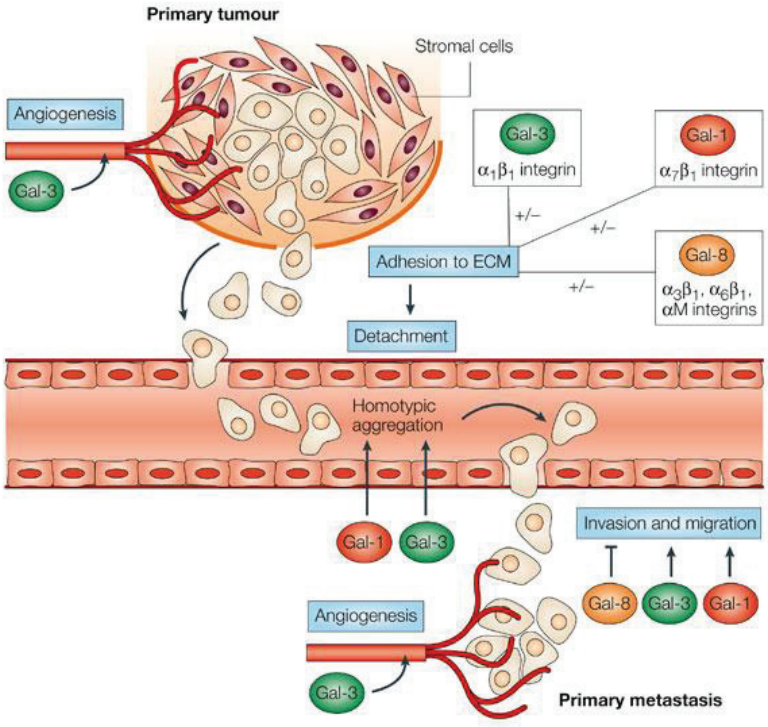


Figure 5. Role of galectins in metastasis9

1.2.4 Role of galectins in tumor immune response evasion

Recent studies indicated that some galectins released by the tumor might help to evade the immune surveillance.[47] Galectin-1 is the most extensively studied galectin among other galectins in context of regulation of immune response and this lectin induces the apoptosis on activated T-cells[48] when added exogenously to T-cells *in vitro*. Galectin-3 can also induce T-cell apoptosis[49] and can restrict T-cell receptor initiated signal transduction by forming multivalent complexes with glycans present on the T-cell receptor.[50] Addition of galectin-3 to human eosinophils produced a selective inhibition of IL5 transcription, which led to the reduction of immune response. Such inhibition of IL5 transcription was reversed by incubating the natural galectin inhibitor lactose.[48] Galectin-2 and galectin-9 can also shown to induce T-cell apoptosis.[51, 52, 53]

1.2.5 Galectins and HIV-1

HIV primarily infects vital cells in the human immune system such as helper T cells (specifically $CD4^+$ T cells), macrophages and dendritic cells.[54] HIV type 1 (HIV-1) infection is a dynamic process involving 3 steps: adhesion, infusion, and integration.[55] In the literature it has been proposed that various types of modulators mediating the adhesion process between primary cellular receptor CD4 and virus encoded external envelope gp 120.[56]

Galectin-1 is shown to have a role in HIV-1 establishment in humans initiated by attaching the virion to the target cell surface. The event of infection relies on the interaction of the external envelope gp120 subunit with cellular receptor CD4.[30] Under

physiological conditions binding of external envelope gp120 of the virus to cellular receptor CD4 is not that strong[57] and this finding will open the door to the question what are all the other factors or proteins helping in the early and important event (adhesion) of HIV type-1 infection. Sachiko Sato *et al*. have clearly shown the role of galectin-1 in virus attachment to host cell,[30] using LuSIV reporter cells. They have conducted experiments with galectin-1 and galectin-3, with and without galectin antagonist (lactose) to cross confirm the role of galectins in cell adhesion. The dose dependent increase in infectivity was observed only for galectin-1 but not with galectin-3.

Galectin-1 promotes HIV-1 infectivity in monocyte-derived macrophages (MDMs) by stabilizing the viral adhesion and augmentation in virus replication was dose dependent manners. The fusion inhibitors T-20 and TAK779 remained effective at reducing infection even in the presence of galectin-1, thus showing participation in the early stage of infection prior to fusion. The above results show that galectin-1 facilitates HIV-1 infection in monocyte derived macrophages by promoting adsorption.[31] An interesting contrast was found between galectin-1 and galectin-3[30,31] and this could be explained due to the slight differences in the structure of carbohydrate recognition domain and ligand specificity (CRD).[58]

Chapter 2

Galectin ligands

Globally, there are 2 classes of galectin inhibitors (Figure 6). The first class being the natural glycoconjugates having a terminal galactosides residue and the second group being synthetic inhibitors. The later one can be subdivided into three categories: those that posses *i*) anomeric modification on the galactoside residue; *ii*) 3'-modification on the galactoside residue, and *iii*) multivalent galactosilated molecules.

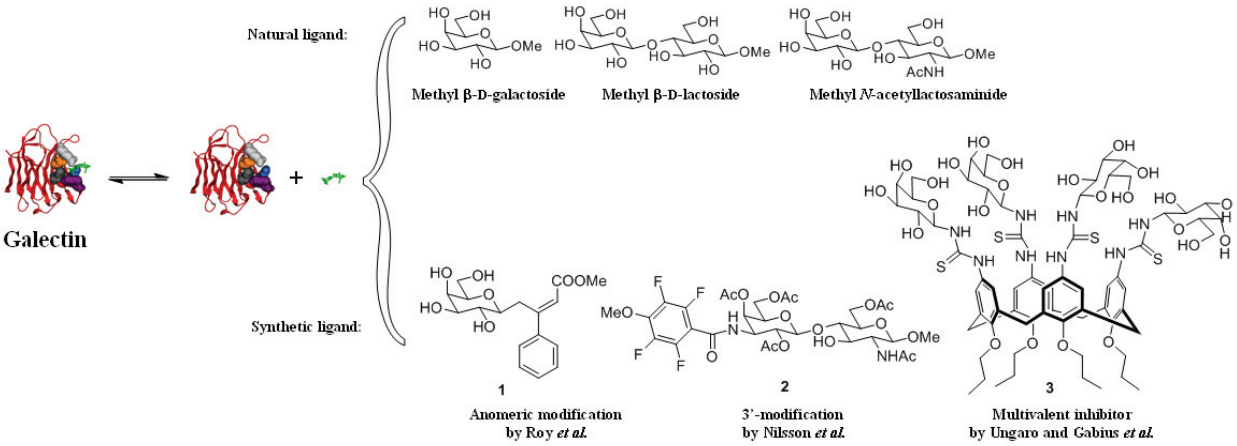


Figure 6. Possible ligands that can bind to the galectin family. Naturally occurring and synthetic ligands for galectins: Anomeric modification made by Roy *et al.*[71], 3'-modification made by Nilsson *et al.*[81] and multivalent inhibitor made by Ungaro and Gabius *et al.*[59]

2.1 Natural ligands for galectins

There are numerous naturally occurring compounds that have been screened for their association with various galectins.[60] Some examples are presented in Table 1.

Table 1. Natural ligands for various galectins.

Entry	Galectin	Ligand/Highlights	Reference
1	3	Myelin-associated glycoprotein, tenascin-C and -R/ No binding to collagen I.	61
2	3	Poly-*N*-acetyllactosamine/ Present on colon cancer mucin.	62
3	3	Lactosyl, paraglobosyl, gangliosyl and neolactohexaosyl oligosaccharides/ Made by a strain that is highly infectious for the male urethra: *Neisseria gonorrhoeae.*	63
4	3	Mycobacterial mycolic acids/ Major constituents of *Mycobacterium tuberculosis* can inhibit the lectin self-association but not its carbohydrate-binding abilities.	64
5	1-5, 7	Multivalent glycoprotein asialofetuin/ Enhanced affinity for a specific ligand through a clustering mechanism.	65
6	3	*O*-antigen side-chain of *Helicobacter pylori* lipopolysaccharides/ Promotes adhesion of *H. pylori* to gastric epithelial cells and may enhance colonization of the host.	66
7	3	Mgat5-modified *N*-glycans/ Regulates fibronectin matrix remodeling in tumor cells.	67
8	1	Thomsen-Friedenreich antigen on trophoblast cells/ Gal-1 is localized at the border between fetal trophoblast and maternal stroma.	68
9	3	Pectic Polysaccharides from dietary sources/ Reduction of tumor cell invasiveness.	69

The exact role of the galectins is not fully understood but analysis of natural ligands helps their biological comprehension. Furthermore, the synthesis of non-natural ligands provides interesting tools to help understand the complexity of all the biological implication of galectins.

2.2 Synthetic ligands

As explained in the Introduction to galectins, in mammals galectins play a pivotal role in the control of cell differentiation, proliferation, activation, metastasis and apoptosis of immune cells. Moreover, galectins have recently shown their role in HIV-1 biology by stabilizing the viral adhesion and it was shown that the augmentation in virus replication was dose dependent. Naturally occurring carbohydrate ligands like methyl β-D-galactoside, methyl β-D-lactoside and methyl-β-D-*N*-acetyllactosamine have low affinities and are too polar (low partition coefficients) to pass through the cell membranes. Consequently, access to potent and selective inhibitors of galectin are highly desirable tools for detailed evaluation of galectin function and activities at cellular level. In addition they would constitute lead compounds for the development of galectin blocking drugs. Synthetic ligands reported until recently were reviewed under 4 different categories 1) Anomeric modification 2) 2'-modification 3) 3'-modification and 4) multivalent inhibitors.

2.2.1 Anomerically modified galectin inhibitors

Subsite-D is one of the binding sites of galectins, which extend towards the anomeric position. Subsite-D is a widely explored binding site of galectins. The highest

number of compounds was made by manipulating the anomeric position of galactose, lactose and *N*-acetyl lactosamine (LacNAc) to find a highest affinity compound, compared to any other position targeting other binding subsites.

Table 2. Anomerically modified galectin inhibitors and their potencies (literature)

Entry	Compd. No	Potency	Galectin	Reference
1	**2.1**	0.18, 2.2 mM(Kd)	7, 8N	70
2	**2.2**	1.8, 0.14 mM(Kd)	3, 8N	70
3	**2.3**	180 μM (Kd)	3	71, 72
4	**2.4**	5 mM (IC_{50})	1,3	73
5	**2.5**	5 mM (IC_{50})	1, 3	74
6	**2.6**	0.313 mM (IC_{50})	1	74
7	**2.7**	2.5 mM (IC_{50})	1, 3	74
8	**2.8**	5 mM (IC_{50})	1, 3	74
9	**2.9**	0.08,0.625 mM (IC_{50})	1, 3	73
10	**2.10**	0.04,0.313 mM (IC_{50})	1, 3	75
11	**2.11**	0.313 mM (IC_{50})	1, 3	73
12	**2.12**	120 μM (Kd)	1, 4N, 4C, 8N	76

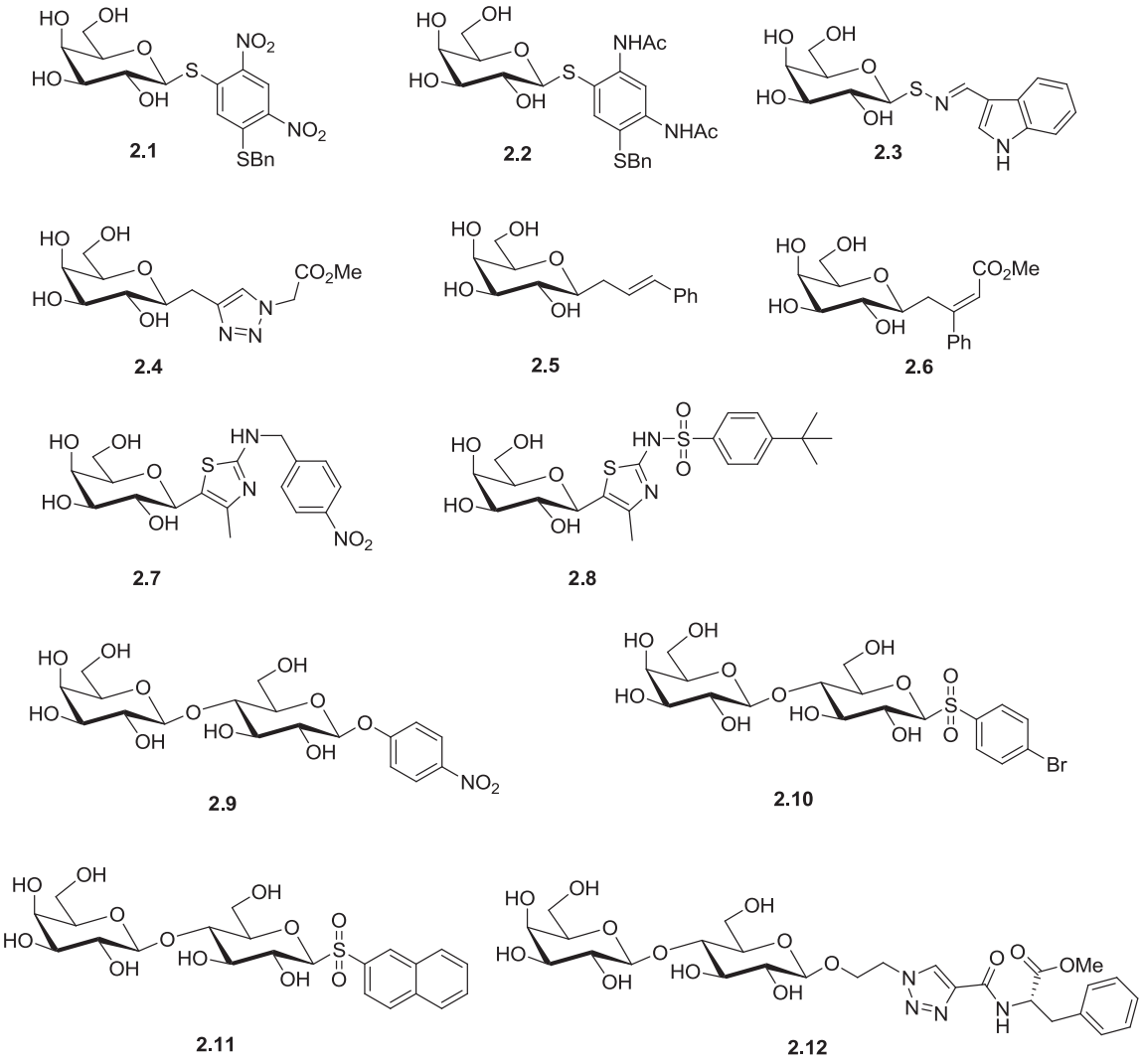


Figure 7. Anomerically modified galectin inhibitors

2.2.2 2'-position modified galectin inhibitors

Hindsgaul *et al.* explored the *N*- and 2' position of *N*-acetyllactosamine (LacNAc) and derivatized two different libraries of compounds. 1) Compounds with different aryl pharmacophores on the amine functionality of glucosamine and with a long *O*-alkyl group on the anomeric position. Selective protection of amine group using TrocCl was

very useful to synthesize analogs selectively. 2) Compounds with different pharmacophores at the 2'-position of galactose were synthesized by removal of the acetate protecting group. Screening libraries of *N*-and 2'-derivatized type I disaccharides with the FAC/MS technique revealed these candidates had an enhanced affinity for galectin-3. The best result was obtained with the *N*-naphthoyl derivative **2.13** (10.6 μM), (Kd) which showed a 7-fold increased affinity compared to the parent LacNAc compound (Kd) 73.3 μM.[77]

Nilsson et al synthesized a library of 8 compounds by exploring the 2-*O*-position on methyl lactose molecule. The ester derivatives were tested for binding to galectin-1, -3, -7, -8N, and -9N by using a fluorescence-polarisation assay. All the ester derivatives showed greatly increased affinity for galectin-1 and -3, as compared to the parent methyl β-lactoside, presumably because of additional beneficial interactions between the ester π-systems and the arginine guanidinium groups. The best inhibitors of the library are **2.16** (2.5±0.5 μM for Gal-3) **2.15** (Kd 4.4±3.6μM for gal-1), and **2.17** (2.2±0.5 μM for Gal-3).[78]

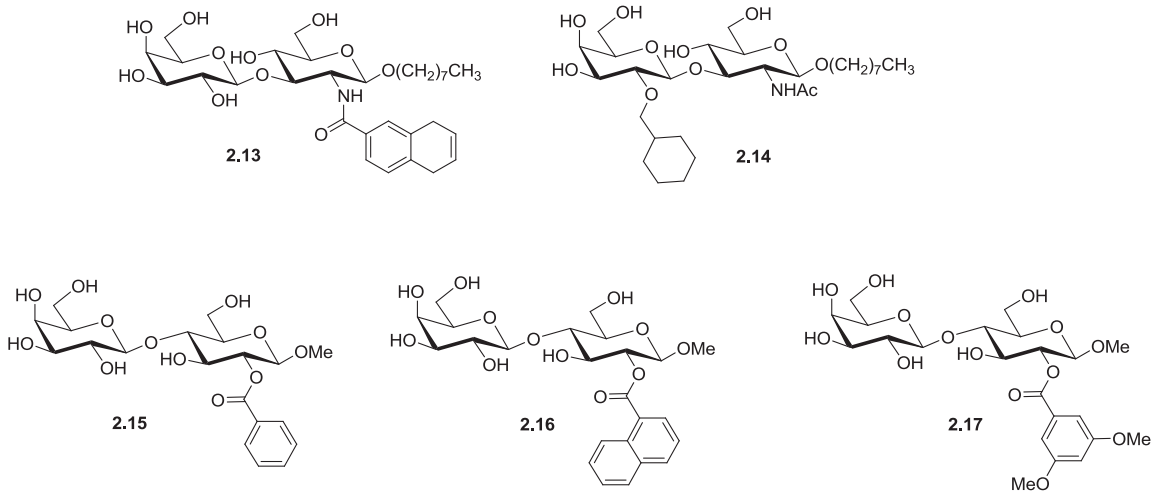


Figure 8. 2, 2'-Modified galectin inhibitors

2.2.3 3'-position modified galectin inhibitors

The crystal structure of LacNAc with Galectin-3 complex shows a possible extended binding groove close to OH-3 (Gal) Figure 9. This binding groove has been exploited in the design of high-affinity inhibitors through synthesis of 3'-benzamido derivatives of LacNAc from a 3-azido-3-deoxy galactose precursor.[79] The crystal structure shows that the side chain of Arg144 stacks against the aromatic moiety of the inhibitor, an interaction made possible by a reorientation of the side chain relative to that seen in the LacNAc complex. Based on these structures, a large number of 3'-position modified inhibitors of galectin were synthesized (figure 10).

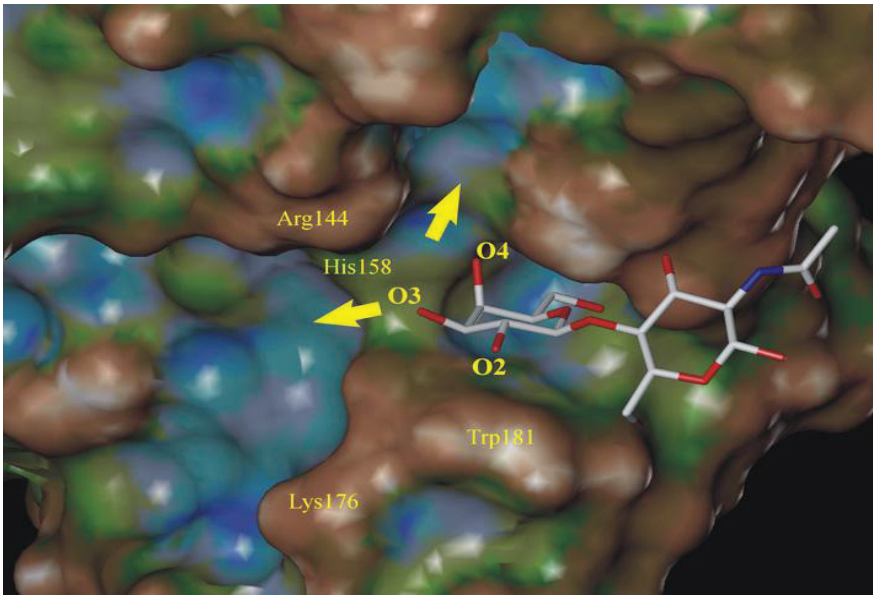


Figure 9. Crystal structure of Galectin-3 with LacNAc showing a possible extended binding groove close to OH-3(Gal)

Table 3. 3'-position modified galectin inhibitors and their potencies (literature)

Entry	Compd No	Potency	Galectin	Reference
1	2.18	107 μM(Kd)	3	80
2	2.19	1.25, 5.0 mM (Kd)	1, 3	73
3	2.20	>5	1, 3	73
4	2.21	4.4 μM(Kd)	3	81
5	2.22	15 μM(Kd)	3	82
6	2.23	0.74 mM(Kd)	7	83
7	2.24	0.39 mM(Kd)	7	83

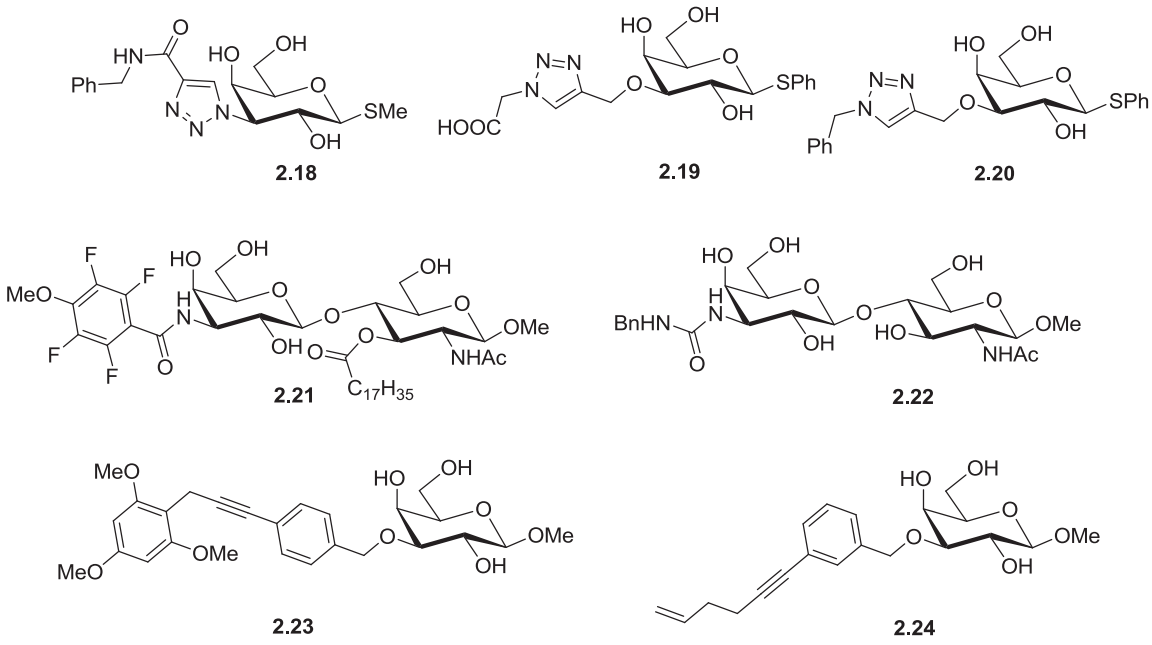


Figure 10. 3'-position modified galectin inhibitors

2.2.4 Multivalent inhibitors

Several mechanisms like intramolecular chelate effects and intermolecular aggregative process may operate to enhance the relative potency of multivalent inhibitors. Several research groups have exploited the idea of using multivalency compounds to find high affinity galectin inhibitors. The stronger cluster effect was seen with the divalent compound **2.30** against galectin-3.

Table 4. Multivalent inhibitors of galectins and their potencies

Entry	Compound No.	Potency	Galectin	Reference
1	2.25	0.3 mM (IC_{50})	1 and 3	73
2	2.26	5 mM and >5 mM (IC_{50})	1 and 3	73
3	2.27	2.5 and >5 mM (IC_{50})	1 and 3	73
4	2.28	0.3 and 0.16 mM (IC_{50})	1 and 3	73
5	2.29	30.8 μM (IC_{50})	3	84
6	2.30	33 nM (Kd)	3	85
7	2.31	0.3, 0.16 mM (IC_{50})	1 and 3	74
8	2.32	0.6, 0.3 mM (IC_{50})	1 and 3	74
9	2.33	0.3, 0.16 mM (IC_{50})	1 and 3	74
10	2.34	>5, 2.5 mM (IC_{50})	1 and 3	74
11	2.35	7.4, 17 μM (Kd)	1 and 3	86

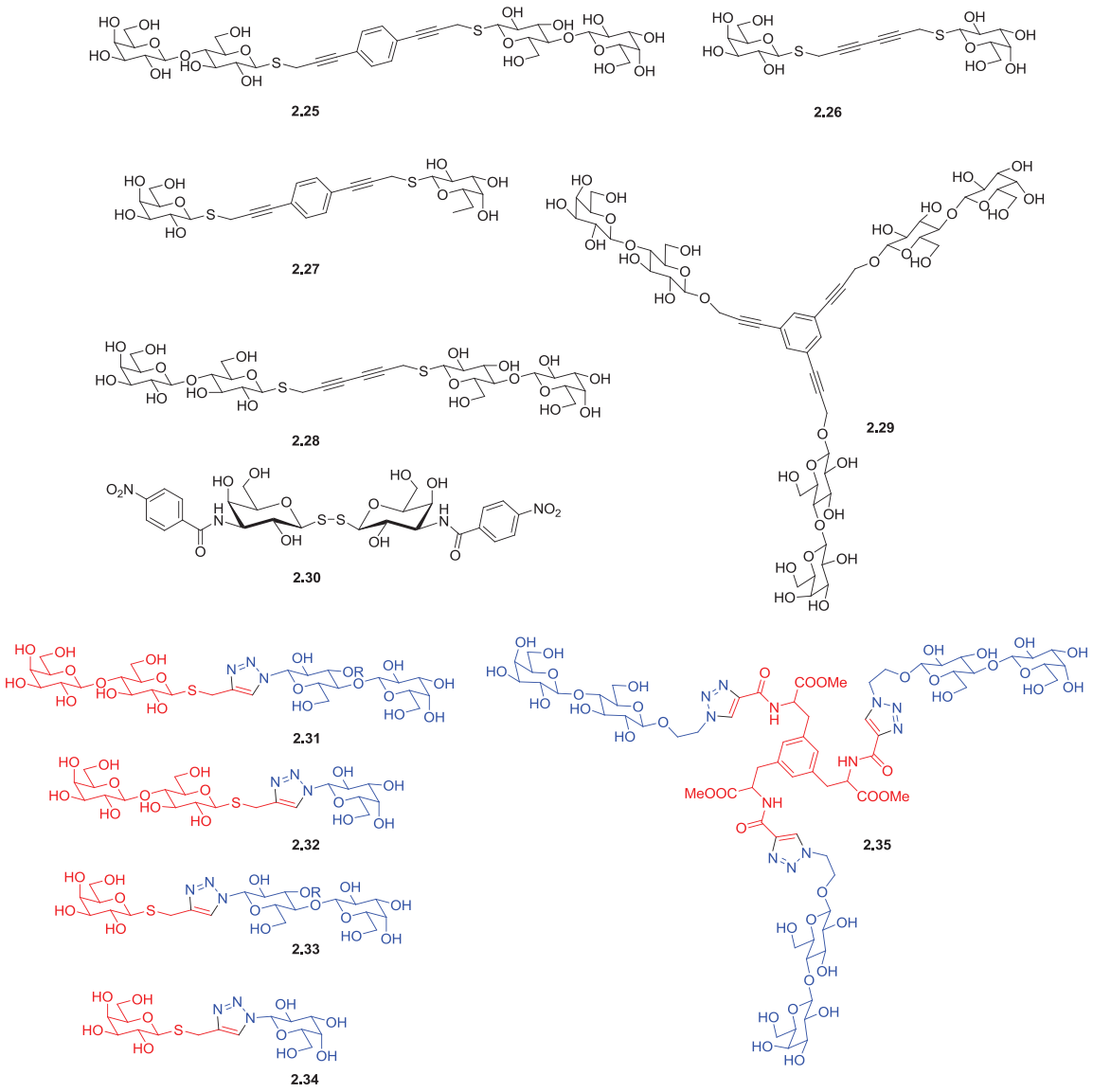


Figure 11. Multivalent inhibitors of galectins

2.3 Rational strategies for the synthesis of galectin inhibitors

The amino acids which provide interaction with carbohydrate ligands are highly conserved throughout all family members. The eight amino acids of human galectin-3 (hGal-3) CRD are Arg144, His158, Asn160, Arg162, Glu165, Asn174, Trp181 and Glu184. All the interactions between the amino acids of carbohydrate recognition domain (CRD) and ligands can be understood by crystallographic analyses of various galectins and ligands (Figure 12). First of all, only three water molecules are present in the galectin-3 CRD (2NMN) without any ligand (Figure 12a). A first molecule of water interacts with His158, Asn160, and Arg162. A second water molecule interacts with Asn174 and Glu184 and finally, the last one with Arg162 and Glu184. Interestingly, the positions of these water molecules are very close in the space where the 1-OH, 4'-OH and 6'-OH of the lactose residue are making hydrogen bonds.[87] When complexed to lactose (2NN8), the majority of the interactions are formed between sub site *C* and residues His158, Asn160, Arg162, Trp181 and Arg144 (Figure 12b). Sub-site *C* sits on a tryptophan "greasy floor" by making favorable hydrophobic interactions with C-3, C-4 and C-5. These stacking interactions are made from galactoside C-H bonds with proximity of the π orbitals of the aromatic residue.[88] Axial 4'OH has the possibility to make hydrogen bonds directly with His158, Asn160, Arg162 and indirectly with Arg144 by the intermediary of a water molecule. All these polar and hydrophobic interactions described above are the key to differentiate β-galactosides from other natural sugars like β-glucosides and α-mannosides. However, Nilsson and co-workers showed some cases

where synthetic β-mannosides substituted at the C1 position can have a better affinity than β-galactosides with hGal-3 and hGal-9N.[89] If 3'-OH and 4'-OH are not found in equatorial and axial conformation respectively, then galectins affinity and selectivity to β-galactosides will be decreased or suppressed. The 6'-OH group is forming direct hydrogen bonding with Arg174 and Glu184 in sub-site C. Also, the 3'-OH group interacts indirectly with Arg144 *via* a water molecule. The endocyclic oxygen is forming direct hydrogen bonds with Arg162. No important interaction is observed with the 2'-OH and the glycosidic oxygen. For the sub-site D, the 3-OH group is forming direct hydrogen bonds with Arg162 and Glu184. Because of the interactions with sub-site D, this explains the selectivity to β-galactosides and no selectivity to α-galactosides. Also the 2-OH and 6-OH groups are forming indirect hydrogen bonding with Glu165 and Glu184 respectively *via* a water molecule. No important interaction is observed with 1-OH and endocyclic oxygen.

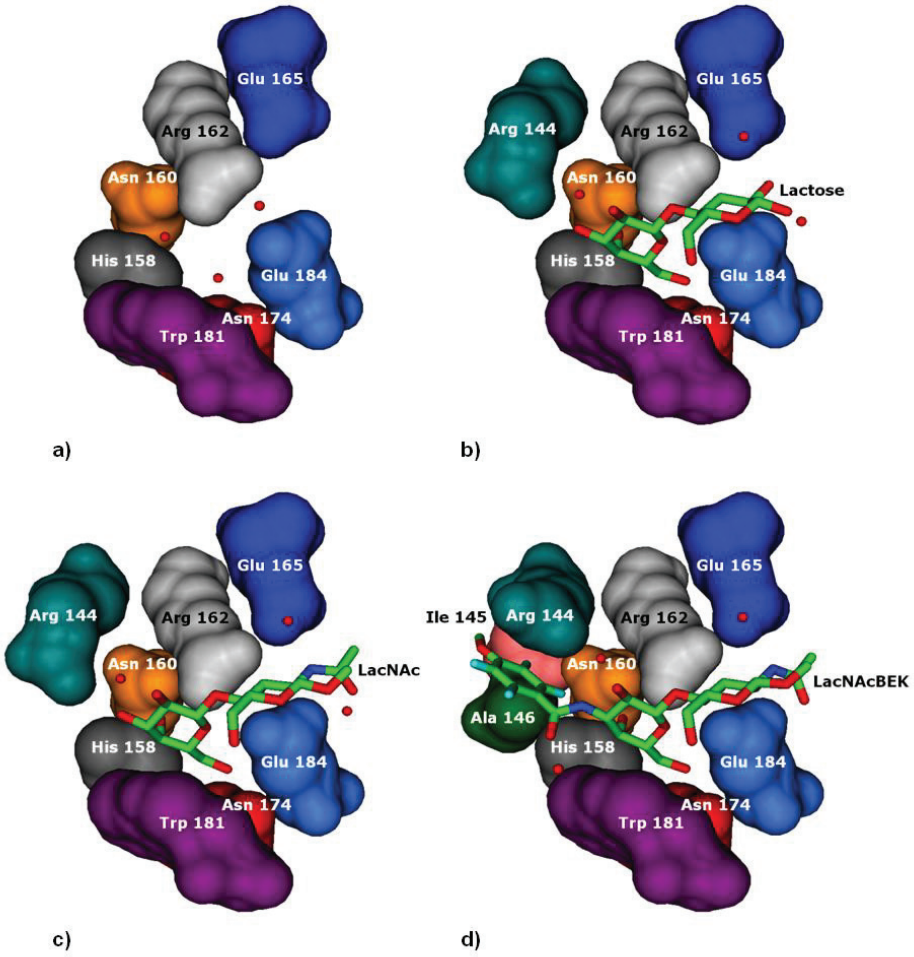


Figure 12. Comparison of the architecture of the interaction site obtained from available crystallographic X-ray for galectin-3 with various ligands: a) ligand free (2NMN); b) lactose (2NN8); c) LacNAc (1KJL); d) LacNAcBEK (1KJR). The color of each amino acid is used to depict structurally equivalent substitution.

Interactions are almost the same when lactose is replaced by LacNAc (1KJL), except for the *N*-acetyl moiety that is making indirect hydrogen bonding with Glu165. In the case of LacNAcBEK (1KJR), interactions are very similar of those observed with

lactose and LacNAc, but not for the subsite B. Foremost, carbonyl and N-H of the amide group are forming indirect hydrogen bonding with Arg144 and Trp181, both with intermediary of water. Second, as described in earlier papers, 4-methoxy-2,3,5,6-tetrafluorobenzamido moiety is forming π-cation interaction with Arg144. Finally two more amino acids Ile145 and Ala146 are participating by making hydrophobic interactions with subsite B.[90]

By studying the CRDs of some human galectins complexed to lactose many similarities and few differences were found (Figure 13). First, no important interaction is observed in subunit C with the glycosidic oxygen, 2'-OH, 1-OH, and in subunit D with the endocyclic oxygen and 6-OH. Except for subunit D it is only the glycosidic oxygen in hGal-3 that makes indirect hydrogen bonds with Arg44. Second, the main interactions are totally conserved and include hydrophobic interactions with tryptophan, direct hydrogen bonds with histidine, asparagine and arginine, except for the 4'-OH where it is forming indirect hydrogen bonding to Asn63. In some cases, additional interactions were observed between the 4'-OH and a water molecule or an arginine (directly or indirectly). The endocyclic oxygen and 6'-OH are all conserved, except for hGal-2 endocyclic oxygen where there is no important interaction. There is a conserved interaction for 3-OH, except for hGal-2 where an additional hydrogen bonding with an arginine is found and also for hGal-9N where glutamic acid is replaced by arginine. Third, 3'-OH and 2-OH interactions are variable, in some cases there is no interaction with certain human galectin. When interaction is present, 3'-OH is forming an indirect hydrogen bonds with

glutamine or asparagine. If interactions are not absent, there is direct hydrogen bonding between 2-OH and an arginine or indirect interaction with a glutamine. Moreover, Nilsson and co-workers showed some cases where β-talosides can have a better affinity than β-galactosides with hGal-4C and hGal-8N.[91] Molecular modeling studies shows that in hGal-8N axial 2'-OH interacts directly with Arg52 compared to equatorial 2'-OH that has no interaction. Because of the similarities between hGal-8N and hGal-7, molecular modeling shows also that axial 2'-OH interacts directly with Arg53 in hGal-7. In addition, six amino acids that interact directly or indirectly with a β-galactoside ligand are always conserved in the sequence alignment throughout the galectins family. A first set of three residues are spaced with two residues: His, Asn and Arg. The second set is spaced with seven and three residues respectively: Asn, Trp and Glu. A variable distance from nine to thirteen residues is observed between two sets of amino acids. Other residues included in the CRD are not necessarily conserved. Some of them are found before the first set: Arg144 (hGal-3), Arg44 (hGal-9N), Arg52 and Gln54 (hGal-8N). Others are found after the second set: Arg87 (hGal-9N), Arg70 and Arg120 (hGal-2). In some cases, they are included between the two sets: His52 (hGal-1) and Glu165 (hGal-3). The unique exception is hGal-7 where only the conserved six amino acids are present, no other variable residues are found as is the case for other galectins.

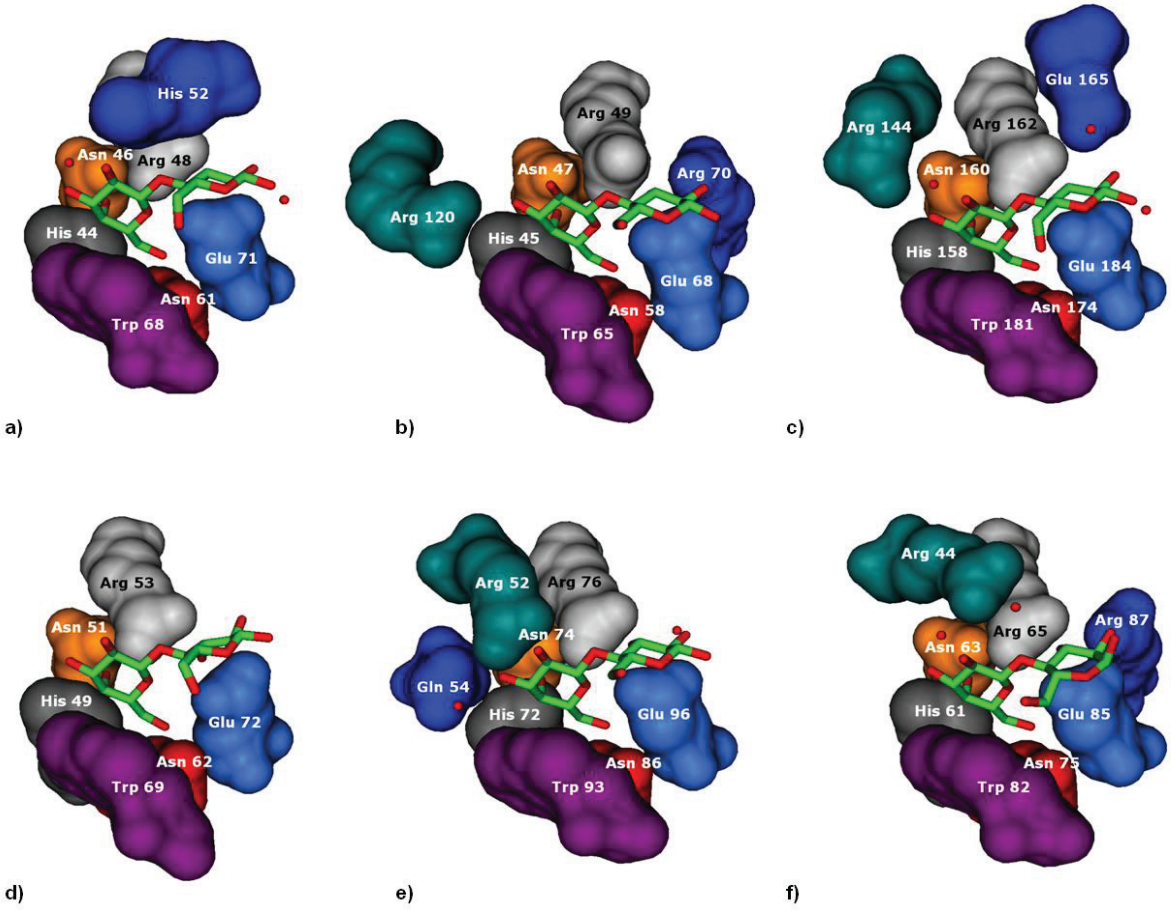


Figure 13. Comparison of the architecture of the interaction site obtained from available crystallographic X-ray for various human galectins complexed to lactose: a) hGal-1 (1GZW); b) hGal-2 (1HLC); c) hGal-3 (2NN8); d) hGal-7 (4GAL); e) hGal-8N (2YXS); f) hGal-9N (2EAK). Color of each amino acid is used to depict structurally equivalent substitution.

Chapter 3

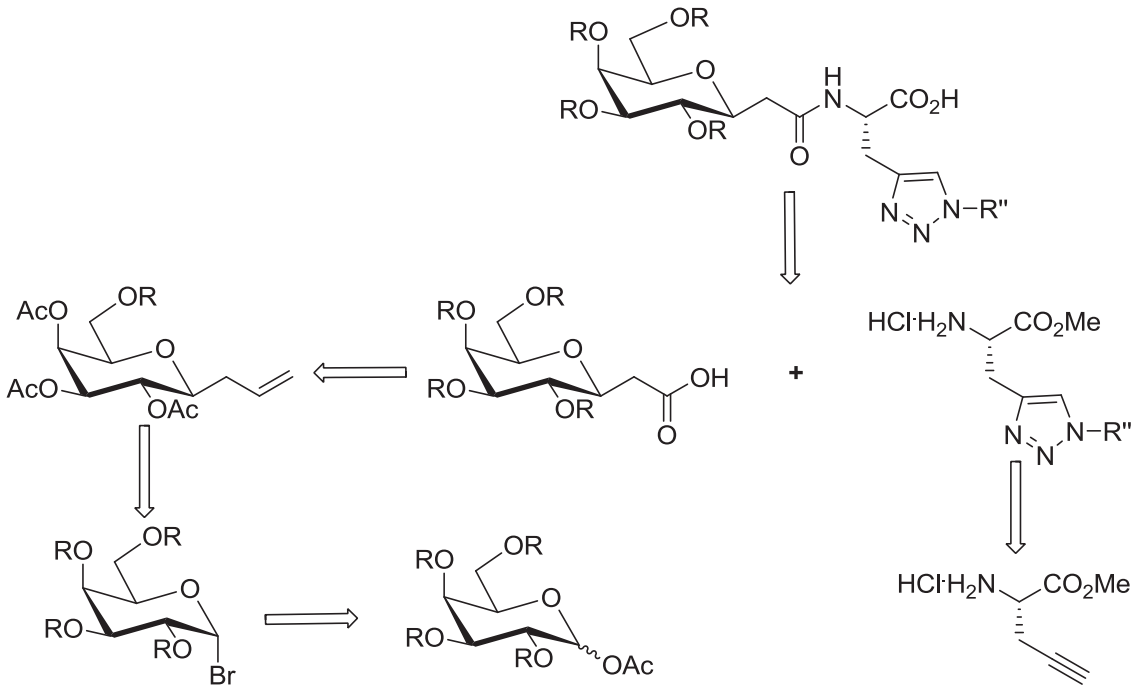
3.1 Synthesis of potential inhibitors of galectins

3.1.1 Retrosynthetic analysis of *C*-galactopeptidomimetics

C-galactopeptidomimetics possess a peptide bond that connects the glycan with the aglycan pharmacophore, hence the need to prepare the *C*-galactose acid and triazole amino acid. Galactose acid can be synthesized from β-*C*-allylgalactose by employing classical ozonolysis to produce an aldehyde followed by oxidation to an acid. *C*-Glycosides are important precursors toward stable and biologically active glycomimetics. Amongst these, *C*-allyl galactosides represent powerful and versatile precursors toward other functionalities, and as key intermediates in several natural product syntheses.

C-Allyl glycosides can be prepared from glycosyl halides, anomeric acetates, methyl glycosides, and even sugar lactones using a wide range of procedures.[92] Some of the most common and practical methods involve treating sugar lactones with excess allylmagnesium bromide, followed by reduction of the ensuing tertiary alcohol with silanes and a Lewis acid (Kishi's procedure),[93] allylation using allyl trimethylsilane and Lewis acids such as BF_3 etherate or TMSOTf (Sakurai reaction),[94] epoxide opening with organometallic reagents,[95] and by radical allylation of glycosyl halides using allyl stannanes or sulfones (Keck allylation).[96] However, most protocols provide anomeric mixtures of the desired *C*-allyl glycosides that are not always readily separable. Although there many methods of preparation of *C*-allyl glycosides, the desired β-configuration can be made by the procedure described by Wong and coworkers,[97] which improves the

stereoselectivity of the formation of the β-glycoside. Thus, peracetylated *C*-allyl β-D-galactopyranoside can be obtained in a stereoselective fashion. Aminoacid triazole can be synthesized from the alkyne precursor L-propargylglycine (L-pra) using the regio selective 1, 3 dipolar cyclo addition reaction (click chemistry) discovered by Prof. K. Barry Sharpless (Scheme 1).

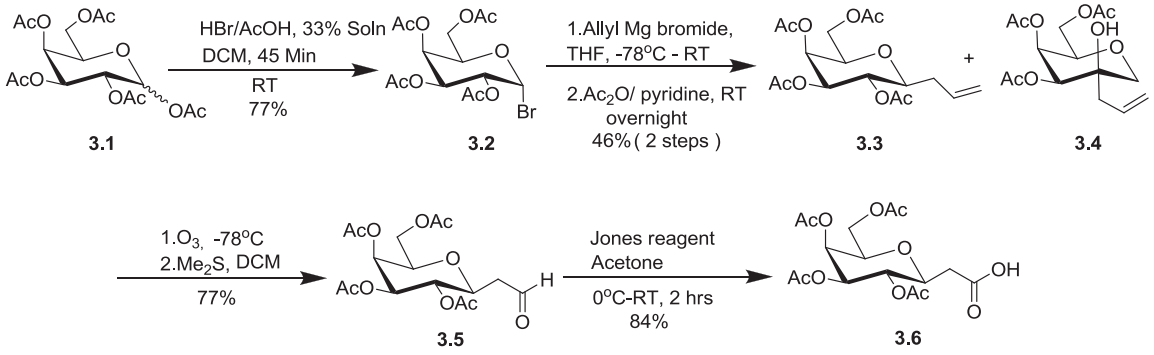


Scheme 1. Retrosynthetic analysis of C-galactopeptidomimetics

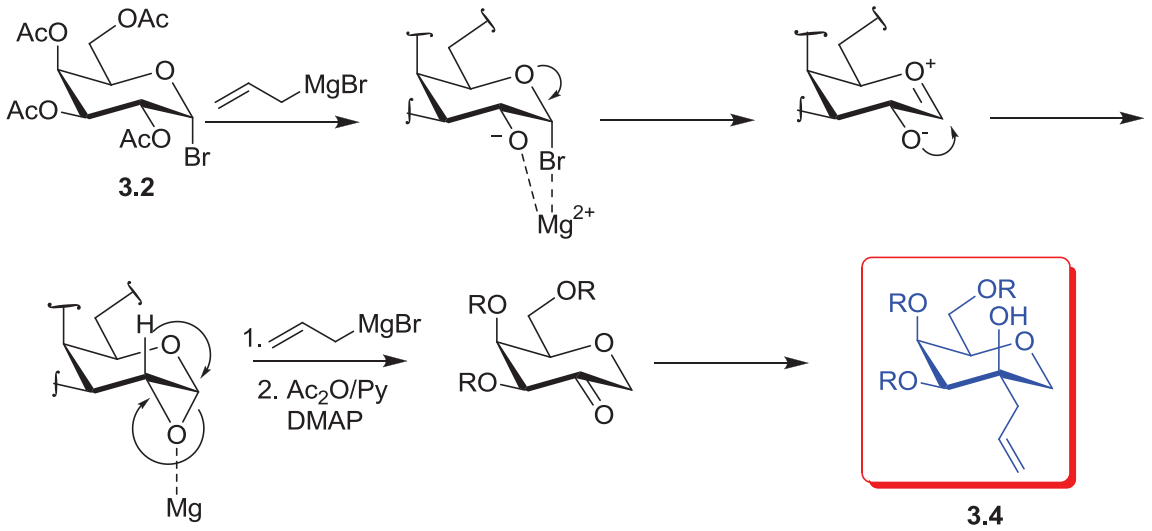
3.1.2 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl ethanoic acid (3.6)

The synthesis of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl ethanoic acid (**3.6**) was initiated by bromination of known per-acetylated galactose (**3.1**) using HBr/AcOH to get c (**3.2**) in a stereoselective fashion by the formation of an oxonium intermediate followed by nucleophilic attack by bromide, although bromide attacks the oxonium intermediate

from both α and β faces and leading to both anomers, the β anomer will get epimerized to the α anomer because of the lower energy of the α and β anomers (5 Kcal/mol).[98] This is followed by Grignard reaction on the bromogalactose (**3.2**) to obtain 3-(tetra-*O*-acetyl-β-D-galactopyranosyl)-1-propene (**3.3**) in a stereoselective fashion from α-bromo-2,3,4,6-tetra-*O*-acetyl-galactose (**3.2**) using excess allyl magnesium bromide (10 eq) in S_N^2 fashion followed by an aqueous workup and re-*O*-acetylation (Scheme 2). Concomitantly, *C*-2-allylated anhydro sugar (**3.4**) was also obtained as side product in 21% yield. The formation of (**3.4**) presumably arises from a 1,2-epoxide intermediate, followed by the formation of a 2-keto intermediate through a 1,2-hydride shift, and then allylation (Scheme 3). The stereochemistry of **3.4**, arising from a 2-keto intermediate has been unambiguously determined by X-Ray data.[97] Upon standard ozonolysis reaction on *C*-allyl galactose (**3.3**) aldehyde (**3.5**) was obtained. Oxidation of aldehyde (**3.5**) using $CrO_3.H_2SO_4$ in acetone (Jones oxidation) gave 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl ethanoic acid (**3.6**).



Scheme 2. Synthesis of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl ethanoic acid



Scheme 3. Proposed mechanism for the formation of impurity (3.4)

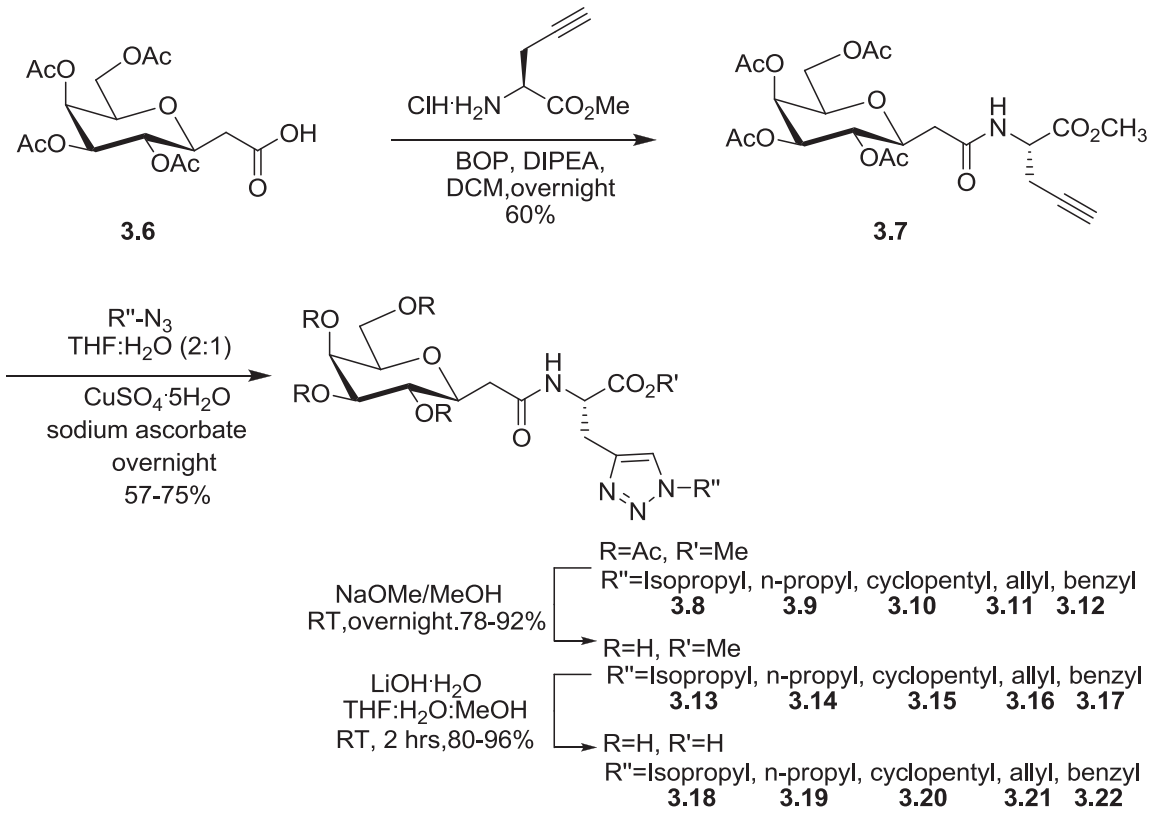
3.1.3 Synthesis of L-propargylglycine methyl ester HCl.

L-propargyl glycine methyl ester HCl synthesis is shown in scheme 32.

3.1.4 Synthesis of *C*-galactopeptidomimetics

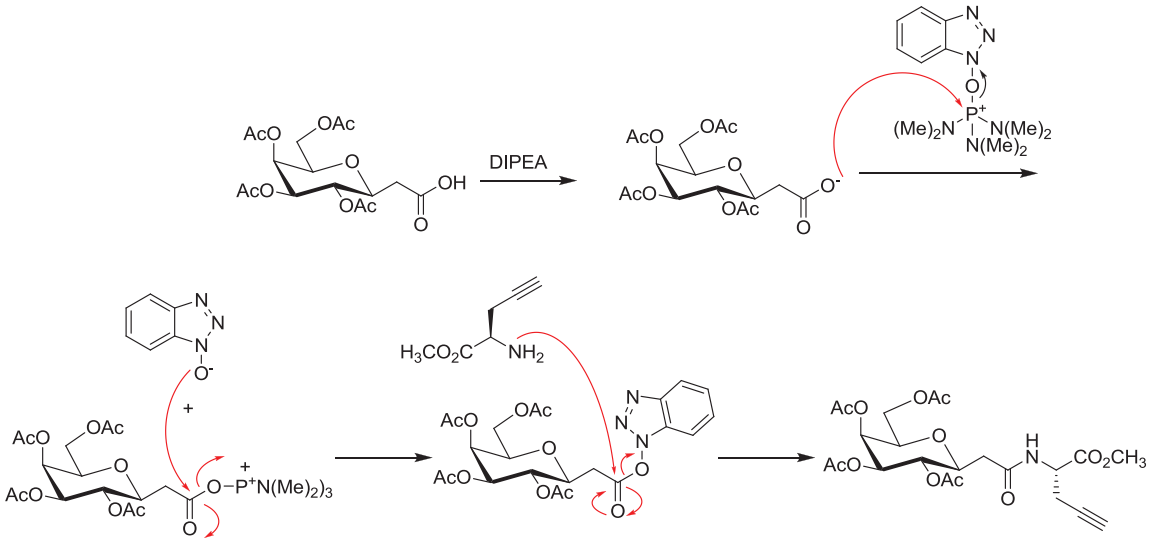
Peptide coupling reaction is employed to couple the galactose acid (**3.6**) and amino acid with pre alkyne installed functionality (6.7) (Scheme.32) [99] to further build the pharmacophoric part. A series of coupling reagents were tried for peptide coupling including DCC (Dicyclohexylcarbodiimide), EDC·HCl (1-Ethyl-3-(3-dimethylamino propyl) carbodiimide hydrochloride) and DIPC (Diisopropylcarbodiimide) (Figure 14), but none of these traditional coupling reagents worked or produced the product with very poor yields. After this series of trials, the peptide coupling reaction finally worked well with the BOP reagent and DIPEA as a base in THF to obtain compound (**3.7**) (Scheme 4). With an alkyne functionality installed on key intermediate (**3.7**), a library of triazole

compounds synthesized by employing the regio selective 1,3-dipolar cyclo addition reaction (click chemistry) using $CuSO_4.5H_2O$ as Cu (II) source, sodium ascorbate as reducing agent and various azides. The yields of click chemistry reactions were good to excellent. Thus a small library of triazole compounds (**3.8-3.12**) were synthesized. Deprotection of *O*-acetylated sugar was performed using NaOMe/MeOH (Dry) to methyl ester derivatives (**3.13-3.17**). Finally methyl ester hydrolysis using $LiOH.H_2O$ in the $THF:H_2O$:MeOH (3:1:2) solvent mixture gave final compounds (**3.18 - 3.22**) in excellent yields (Scheme 5).



Scheme 4. Synthesis of *C*-galactopeptidomimetics

The BOP coupling reaction is initiated by abstracting the proton on the acid by DIPEA, then the caboxylate anion attacks the electron deficient phosphonium ion of BOP reagent to initiate the peptide coupling mechanism by releasing benzotriazol-1-yl-oxide. Thus released benzotriazol-1-yl-oxide anion will attack carbonyl carbon to activate the carbonyl carbon for the amide bond formation by the amino acid. The mechanism of coupling in the presence of BOP is shown in scheme 5.



Scheme 5. Arrow pushing mechanism for peptide coupling reaction using BOP reagent

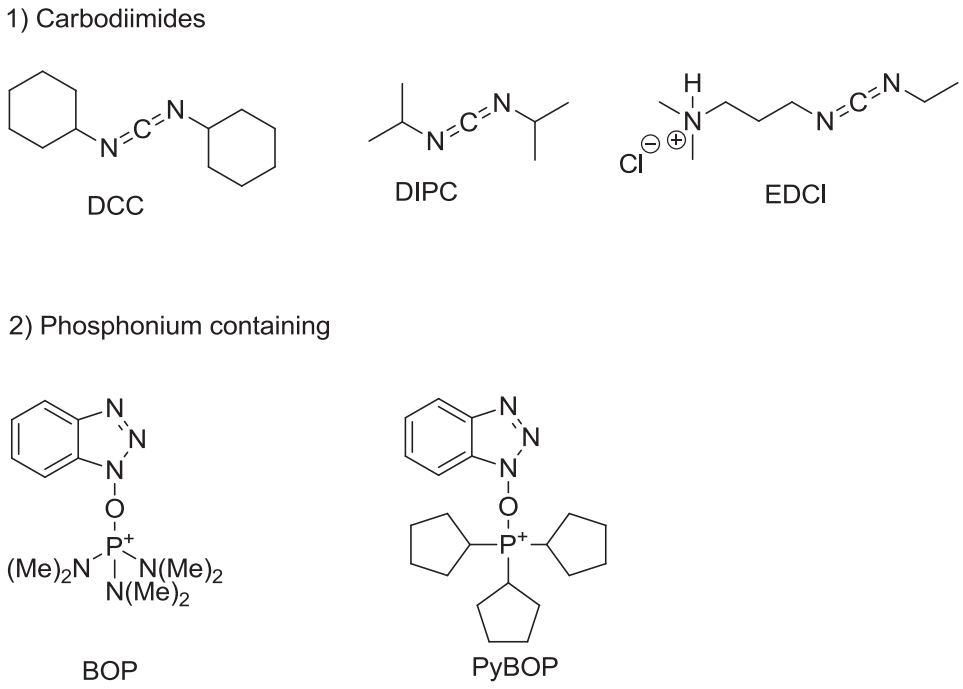
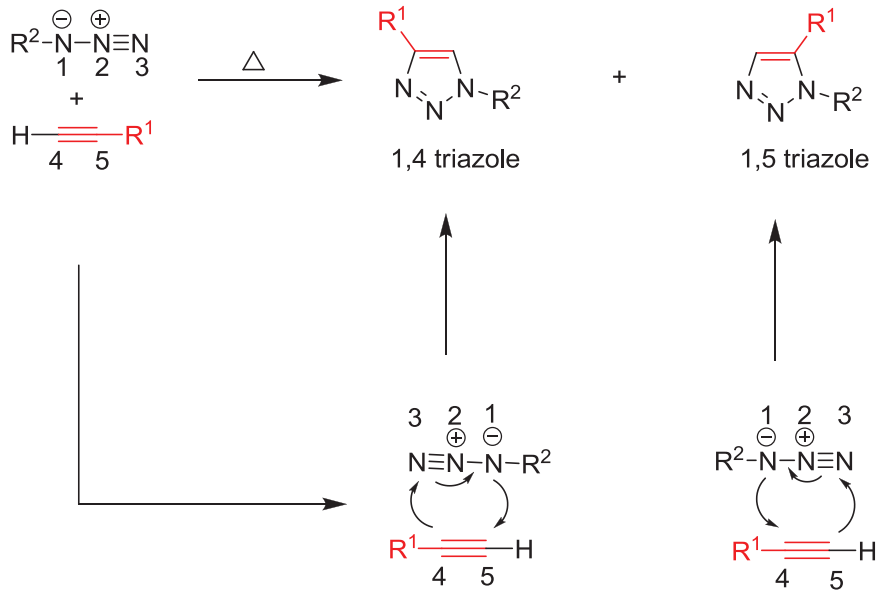


Figure 14. Peptide coupling reagents

3.1.5 The Huisgen 1,3-dipolar cycloaddition

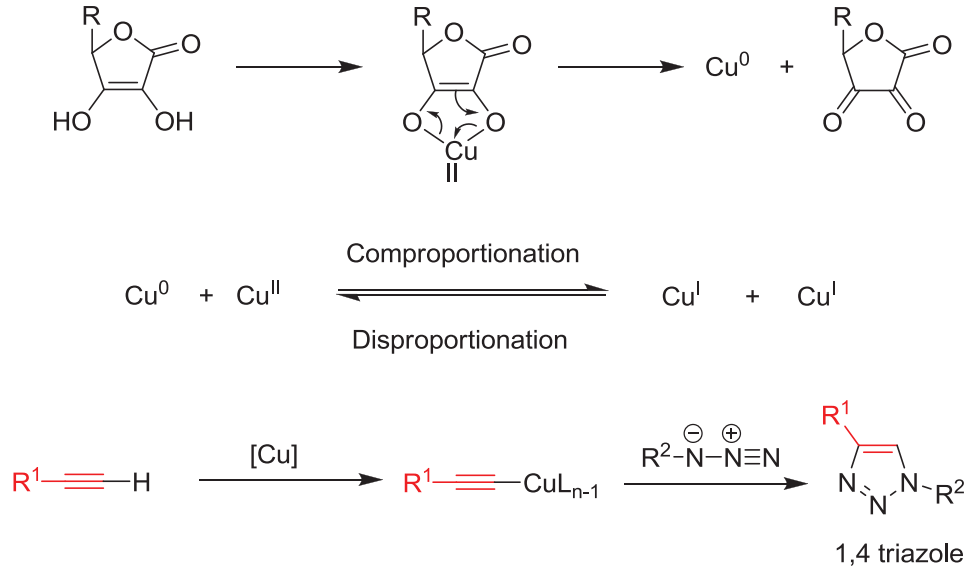
The Huisgen cycloaddition is the reaction of dipolarophile (alkyne) and 1,3-dipole compound (azide) under thermal conditions leading to the formation of 1,4 and 1,5 triazoles without any selectivity (Scheme 6).



Scheme 6. Huisgen 1,3-dipolar cycloaddition under thermal conditions

Although Huisgen's 1,3-dipolar cycloaddition is a powerful tool to construct biologically important triazole compounds using alkynes and azides, formation of both 1,4 and 1,5-triazole regioisomers was the drawback of the reaction. In contrast to the Huisgen's 1,3-dipolar cycloaddition, Click chemistry became very popular for it's capacity to control the regioselectivity in 1,3-dipolar cyclo addition. Cu (I) is the key for the regioselectivity. A copper compound, for example $CuSO_4$, exists in +2 oxidation state. The required Cu (I) is generated in situ adding a reducing agent like sodium ascorbate to reduce the Cu (II) species to Cu (I) via Cu (0) by comproportionation and disproportionation for the formation of Cu acetylide intermediate the champion of regioselectivity (Scheme 7). Where solubility is an issue copper halides can be used in

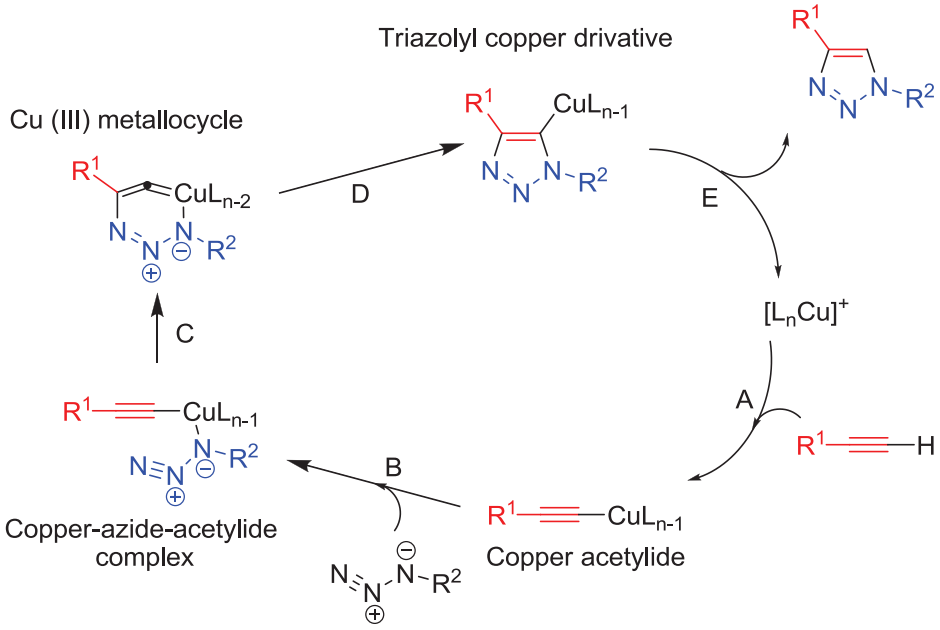
combination with amines like triethylamine (TEA) and diisopropylethylamine (DIPEA) used as reducing agent.



Scheme 7. In situ generation of Cu (I) and copper acetylide formation

The click chemistry catalytic cycle starts by the formation of copper acetylide formation via π-complex using Cu (I) species generated in situ as shown in Scheme 8. One of the ligands on the Cu (I) will be replaced by the alkyne. Click chemistry works without the need for ligands. However the presence of ligands will help in obtaining pure products without many impurities by preventing the Cu (I) interactions and leading to degradation and oxidation of Cu (I) to Cu (II). Thus obtained copper acetylide metal centre coordinates with the lone pair electrons on nitrogen of the azide to form a copper-azide-acetylide complex formation by replacing one more ligand. This is the key step in the 1,3-dipolar cycloaddition reaction using copper catalyst. Regiospecificity is attributed to

the metal coordination with the electron rich nitrogen of the azide. Metal coordination is the contrast to the Huisgen's 1,3-dipolar cycloaddition under thermal conditions to obtain 1,4 and 1,5 triazoles. In the next step the distal nitrogen attack the C-2 carbon of the acetylide to form a Cu (III) metallocycle, which undergoes ring contraction to form triazolyl copper derivative followed by protonation to complete the catalytic cycle. The source of proton being the hydrogen pulled off from the alkyne in the initial step of catalytic cycle. The catalyst ligand complex is regenerated for further reaction cycles[100].

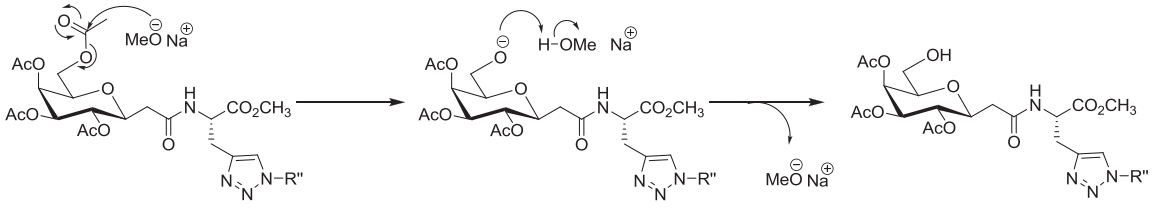


Scheme 8. Stepwise click chemistry mechanism

3.1.6 Catalytic Zemplén deacylation

Deacetylation of compounds 3.8-3.12 were carried out under the Zemplen conditions (NaOMe/MeOH), emphasizing the use of sodium methoxide in methanol. Methoxide nucleophile attacks the δ+ carbonyl carbon to generate alkoxide anion, which

abstracts the proton from methanol and regenerates the sodium methoxide to participate in the catalytic cycle. No further purification is necessary because the methoxide was neutralized using H^+ resin. $NaOCH_3$ is better over the NaOH because it is catalytic and with acetate protecting group the product is methylacetate which is volatile and can removed from the product easily up on evaporation (scheme 9).



Scheme 9. Catalytic Zemplén deacylation reaction mechanism

3.2 Biological results

All compounds and controls (lactose and galactose) were tested by inhibition of hemagglutination assay at a concentration of 1 μM of both galectins. Hemagglutination assays were performed using red blood cells, type *O*, fixed with 3% glutaraldehyde-0.0025% NaN_3 in PBS[101,102] to confer both lectins equal relative affinities. Table 5 show inhibitory properties and relative activities of our derivatives toward Gal-1 and Gal-3. The inhibitory potencies varied from inactive to moderately active. Compound **3.17** is the best among the library with a IC_{50} of 2.5 mM (20 times better than galactose), indicating that the phenyl group close to the anomeric position increases the affinity toward Gal-3 over, Gal-1; Methyl ester analogue **3.17** is more potent over its free acid analogue **3.22** in-line with the importance of the log *P* value to cross the cell membrane. With regard to

the analogue **3.22** it might become very hydrophilic with two open water soluble functionalities, which might hinder the penetration of the molecule through the cell membrane. Where as in the case of analogue **3.17** it is tightly balanced between hydrophobic and hydrophilic properties with open free sugar on one side and with closed amino acid on the other side. It is important to note that compound **3.17** is not only the most promising candidate against galectin-3, being less selective against Gal-1. Although compound **3.17** is 20 times more potent than the parent molecule galactose it is not a very potent molecule. Another reason for the above compounds being less efficient is in solution the assays the present work described involve inhibition of hemagglutination which are known to usually require higher concentrations of compound. Although compound **3.17** is not a very potent molecule it would be a good candidate for further development in the loop process of lead optimization in the drug discovery process.

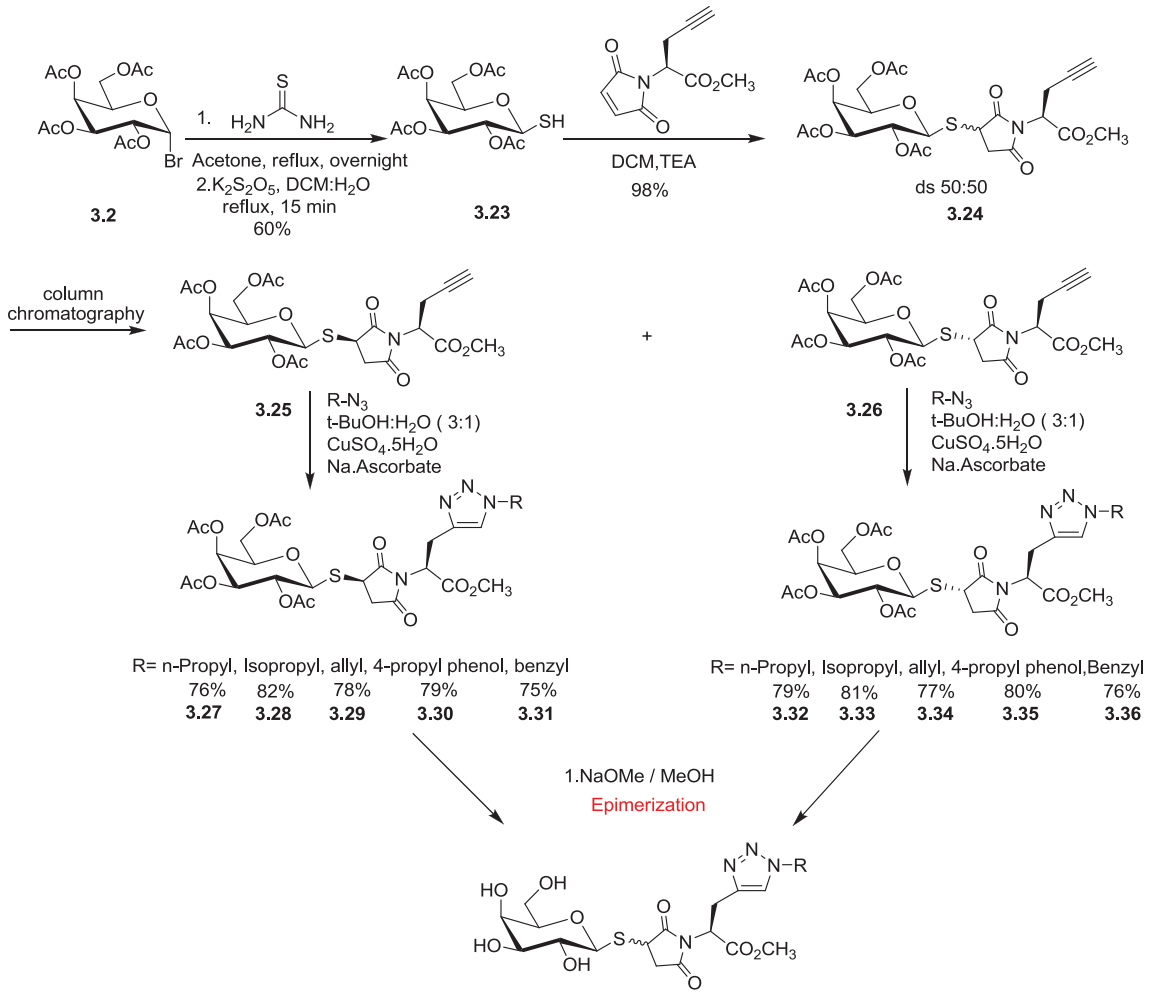
Table 5. Inhibitory properties and relative activity of compounds 3.14-3.23 against Gal-1 and -3

Compound#	Inhibitory properties (mM)		Relative activity	
	Galectin-1	Galectin-3	Galectin-1	Galectin-3
Galactose	50	50	1	1
Lactose	0.8	0.8	1	1
3.13	>5	5	<10	10
3.14	>5	>5	<10	<10
3.15	5	5	10	10
3.16	5	5	10	10
3.17	5	2.5	10	20
3.18	>5	>5	<10	<10
3.19	>5	>5	<10	<10
3.20	>5	>5	<10	<10
3.21	>5	5	<10	10
3.22	>5	>5	<10	<10

3.3 Synthesis of 1st generation *S*-galactosides

First generation *S*-galactosides synthesis was initiated from the α-bromo-2,3,4,6-tetracetyl-galactose (**3.2**) by nucleophilic substitution reaction with thiourea to obtain the isothiouronium salt intermediate, which is hydrolyzed by potassiumpyrosulfate ($K_2S_2O_5$) to obtain 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactose (**3.23**) in stereo selective fashion.[103] Stereo selectivity can be attributed to the acetate protecting group, which will block the α-face completely by anchimeric assistance. Michael addition of thiogalactoside to the maleimidopropargylglycine (Scheme 10) resulted in the 50:50 distereomeric mixture of

thiogalactoside (**3.24**). Diastereomers (**3.25** and **3.26**) were separated using column chromatography. Both the diasteromers were used to build the triazole pharmacophoric part using various azides employing the regio selective 1,3 dipolar cyclo addition reaction (click chemistry) using $CuSO_4.5H_2O$ as Cu(II) source, and sodium ascorbate as reducing agent to generate Cu(I). Deprotection of final *O*-acetylated thio galactosides using NaOMe/MeOH (Dry) lead to the epimerization of newly formed chiral centre during Michael addition (Scheme 10). When de *O*-acetylation in acidic condition using HCl/MeOH as well epimerization took place. A neutral method using KCN/MeOH known to be very good for acid and base sensitive compounds[104] was attempted but failed to deprotect the sugar without epimerization. The possible reason for the epimerization could be that the chiral centre being at α to carbonyl group is responding to nucleophile irrespective to the pH conditions of the reaction.



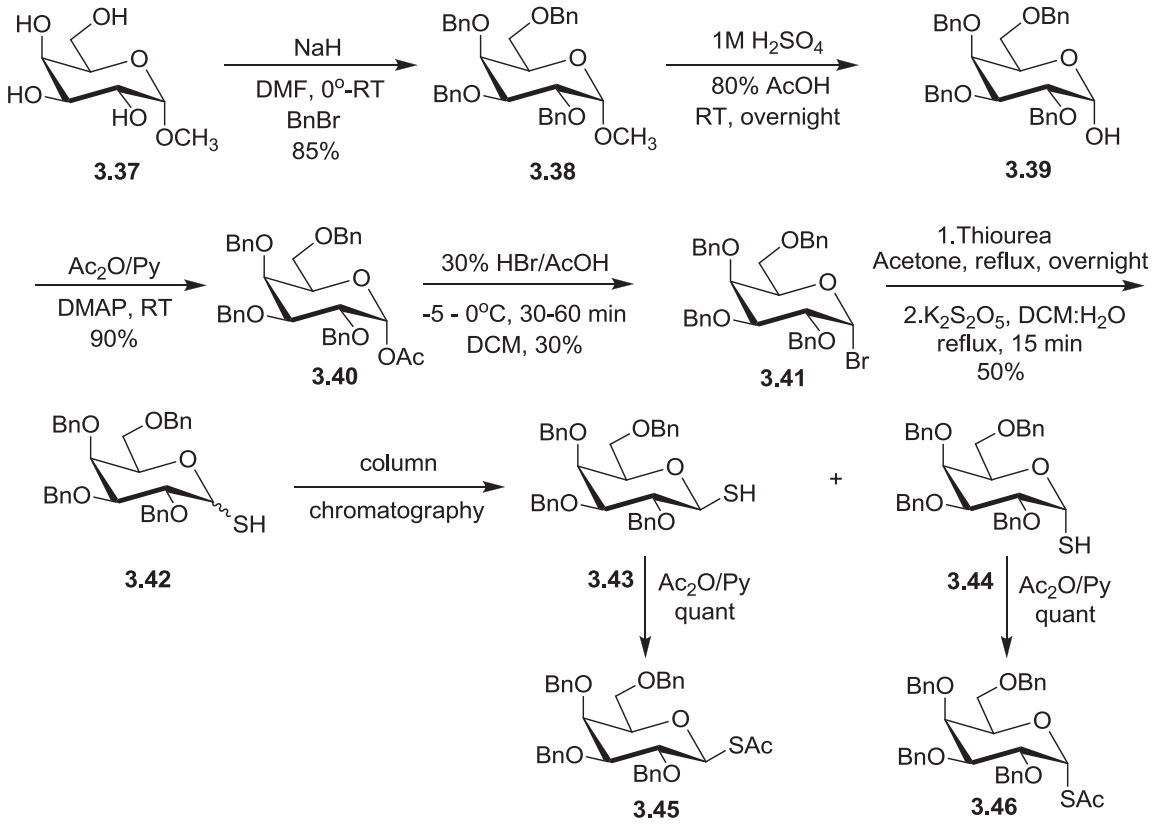
Scheme 10. Synthesis of 1st generation *S*-galactosides

As discussed above hydrolysis conditions were very sensitive to the chiral centre that epimerized in every attempt made to deprotect the acetate protecting groups. To avoid this it was planned to change the protecting groups to benzyl as this protecting group can be deprotected using Pd/C under H_2 pressure. There is a known limitation to the benzyl protecting group in that it is hard to deprotect when there is sulfur atom in the molecule. Knowing this problem the benzyl protecting group was chosen because there was enough

evidence that catalytic transfer hydrogenation can be used to cleave benzyl ethers in some compounds that contain sulfur, a poison for hydrogenolysis catalysts.[105]

Thus we started the synthesis of benzyl ether protecting group version of 1st generation S-galactosides with the protection of free hydroxyl groups of α-methyl galactose (**3.37**) to obtain 2,3,4,6 tetra-*O*-benzyl-α-methyl galactose (**3.38**). Methyl galactose was subjected to demethylation using 1M H_2SO_4 and 80% acetic acid to liberate the free hydroxyl group and then convert into an acetate group (**3.40**), using Ac_2O/Py. Having an acetate group installed in anomeric position, bromination is carried out using HBr/AcOH to get α-bromo-2,3,4,6-tetra-*O*-benzyl galactose (**3.41**) in a stereo selective fashion by the formation of an oxonium intermediate followed by nucleophilic attack by bromide, to have a better leaving group for nucleophilic substitution reaction by thiourea. However the benzyl protecting groups were removed by HBr/AcOH in a very unusual way at room temperature. The same reaction was carried out at -5-0^{o}C found no or minimum deprotection of benzyl protecting group but some of anomeric acetate group hydrolysis was observed to get 2,3,4,6-tetra-*O*-benzyl galactose matching with the reference compound on TLC along the desired product bromo galactose (**3.41**). Nucleophilic substitution reaction of thiourea on bromogalactose to obtain the isothiouronium salt followed by mild hydrolysis with potassium pyrosulfate in dichloromethane and water mixture at 40^{o}C for about 15-20 min to obtain the mixture of α and β 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactose (**3.42**) with the β isomer as the major product (Scheme 11). Both the isomers β (**3.43**) and α (**3.44**) were separated on column chromatography and

we acetylated the thiol to see the anomeric proton as a doublet to establish coupling constant. In the ^{1}H NMR spectrum of α-isomer (**3.46**) the coupling constant of H1 and H2 ($J_{1,2}$) was found to be 5.22 Hz, as expected, H-1 proton of the α-isomer (**3.46**) found to more deshielded (6.2δ**)** than the β-isomer (**3.45**) and the α-isomer (**3.46**) found to be less polar on the TLC compared to the β-isomer (**3.45**). For the β-isomer the coupling constant of H1 and H2 found to be 10.16 Hz which is larger in agreement with the theoretical value, unlike the α-isomer H-1 of β-isomer is more shielded (5.13 δ) and more polar (Figure 15).



Scheme 11. Synthesis of 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactose (3.43)

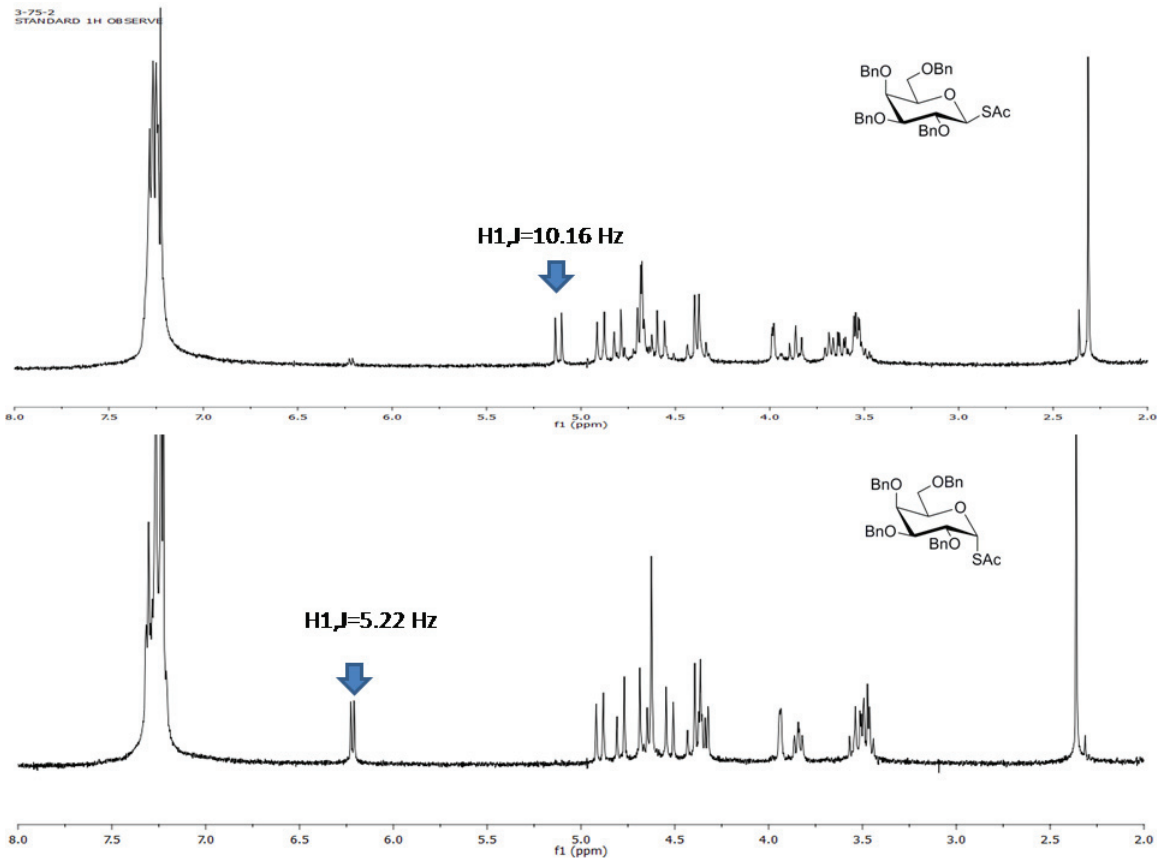
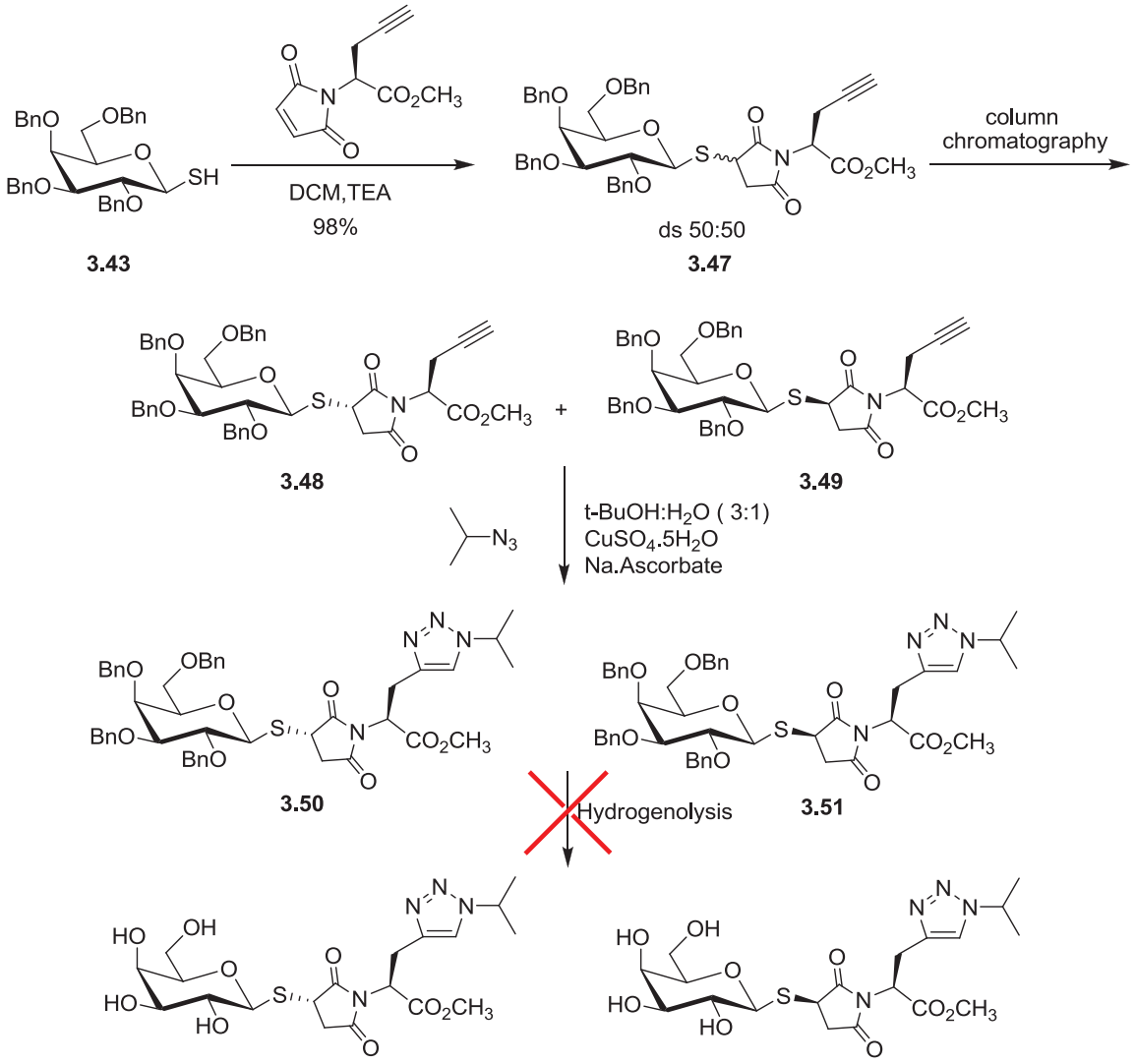


Figure 15. ^{1}H NMR spectrum showing the coupling constant and chemical shift differences of β and α anomers of 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactose

Michael addition of 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactose (**3.43**) on the maliemido propargyl glycine methyl ester HCl (Scheme 12) obtained S-galactoside (**3.47**) in a very good yield with a 50:50 diastereomeric mixture. Both the diastereomers were separated on column chromatography and we initially performed click chemistry as discussed above with only isopropyl azide to check the deprotection of benzyl protecting groups, before building the library of compounds. Hydrogenolysis of benzyl protecting groups were tried using transfer hydrogenation method Pd/C in methanol with cyclohexene as the hydrogen source. However this

method did not work, even after adding the new fresh catalyst by filtering the old one after each reaction. All the reagents and conditions attempted are listed in the Table 6.



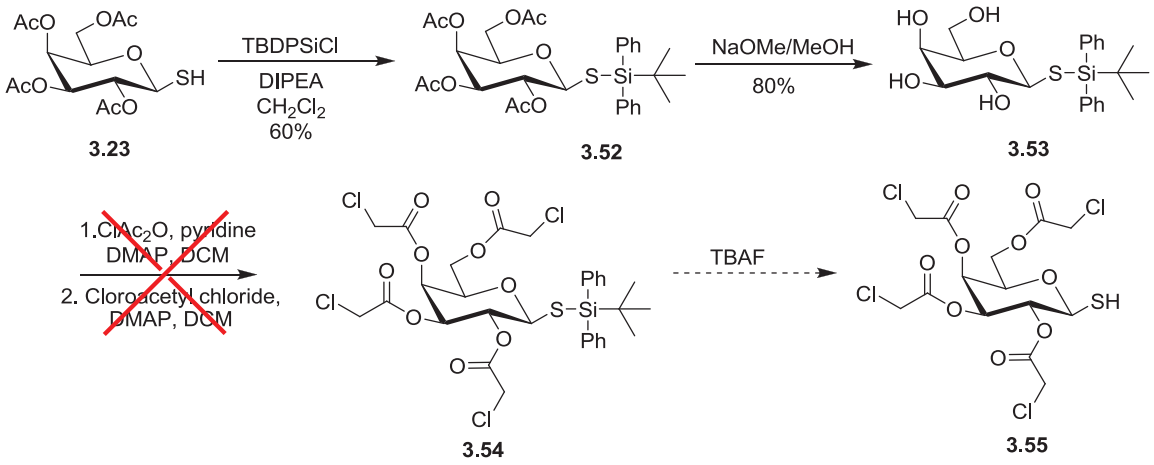
Scheme 12. Synthesis of 1st generation *S*-galactosides

Table 6. List of reagents and conditions used for hydrogenolysis

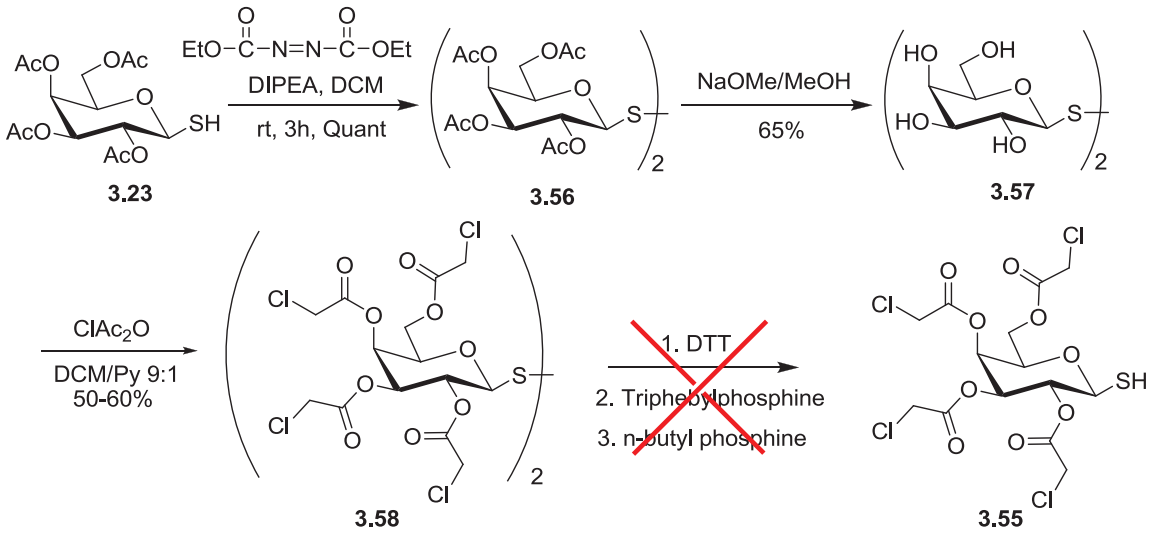
Entry	Reagents	condition	yield
1.	10%Pd/C cyclohexene MeOH	reflux, 1-24 hrs	No reaction
2.	10%Pd/C H_2, MeOH	RT, 1-2 days	No reaction
3.	10%Pd/C H_2, MeOH,1drop HCl	RT, 1-2 days	No reaction
4.	10%Pd/C H_2, EtOH	RT, 1-2 days	No reaction
5.	10%Pd/C H_2, EtOH, 1drop HCl	RT, 1-2 days	No reaction
6.	10%Pd/C H_2, EtOAc	RT, 1-2 days	No reaction
7.	10%Pd/C H_2, EtOAC, 1drop HCl	RT, 1-2 days	No reaction
8.	20%PdOH/C H_2, MeOH	RT, 1-2 days	decomposed

Having two methods failed in the deprotection of the *S*-galactosides, "**PROTECTIVE GROUPS in ORAGNIC SYNTHESIS**" by W. Green was searched for a protecting group that can be removed under mild neutral conditions. The chloroacetyl protecting group was chosen as it can bear all the reactions performed on this molecule and can be removed in aqueous pyridine at room temperature. To make sure that aqueous pyridine will not epimerize the *S*-galactoside, aqueous pyridine was added to compound **3.25** prepared in Scheme 10 and stirred at room temperature for two days and analyzed by NMR, which revealed that the stereochemistry was intact without any epimerization. The target of this strategy was to make 2,3,4,6-tetra-*O*-chloroacetyl-1-thio-β-D-galactose for

Michael addition on maleimidopropargyl glycine and follow above mentioned click chemistry and deprotection. Starting with the protection of the thiol functional group of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactose (**3.23**) with *tert*-Butyl(chloro)diphenylsilane and deprotection of acetate protecting groups with NaOMe/MeOH to obtain free sugar. Protection of the hydroxyl groups with chloroaceticanhydride/ pyridine and catalytic DMAP like classical acetylation reaction somehow this reaction did not work. Chloroacetylchloride in pyridine with catalytic DMAP was also attempted but this reaction also did not work (Scheme 13). So the self protection strategy of the thiol functional group was adapted (Scheme 14) by dimerization, protecting group exchange with chloroacetyl group and cleavage of the disulfide using classical disulfide reduction[106] to obtain 2,3,4,6-tetra-*O*-chlorocetyl-1-thio-β-D-galactose (**3.55**). 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactose (**3.23**) in presence of diethylazidodicarboxylate (DEAD) and catalytic amount of Hunig's base dimerized in a quantitative yield.[107] The dimer (**3.56**) was deprotected under Zemplén conditions to obtain free sugar (**3.57**) and protected with chloroacetyl group using the same conditions used in Scheme 13 to obtain (**3.58**). It is noteworthy that chloroacetylation worked well on galactose thiol dimer whereas it did not work in Scheme 13 in presence of TBDPSi protecting group on thiol. Unfortunately disulfide reduction was not successful employing 1) Dithiothritol (DTT) 2) Triphenylphosphine and 3) *n*-Butylphosphine.



Scheme 13. Synthesis of 2,3,4,6-tetra-*O*-chloroacetyl-1-thio-β-D-thiogalactose

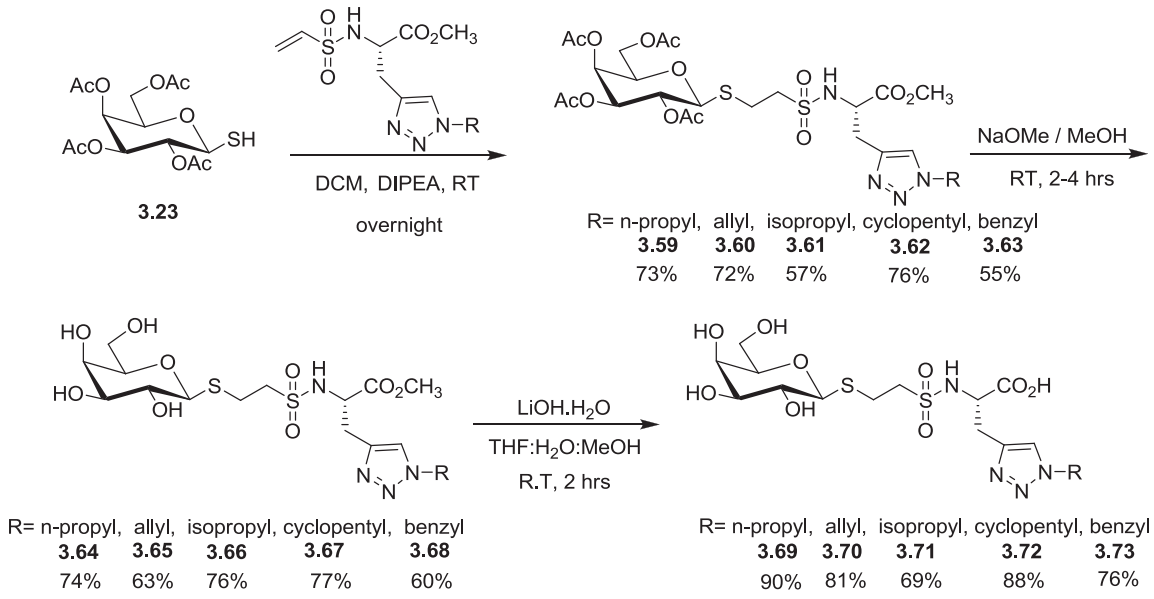


Scheme 14. Synthesis of 2,3,4,6-tetra-*O*-chloroacetyl-1-thio-β-D-thiogalactose using self protecting strategy

3.4 Synthesis of *S*-galactosulfonamides

The synthesis of *S*-galactosulfonamides was started by 1,4-addition of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactose (**3.23**) (Scheme 15) on vinylsulfonamides (**6.26-630**) using Hunig's base in DCM at room temperature to obtain 2,3,4,6-tetra-*O*-acetyl-β-D-*S*-

galactosulfonamides **3.59-3.63** in a good to excellent yields. Keeping the more potent biological results of methyl ester compounds of *C*-galactosides compared to the acid derivatives (Table 5) *S*-galactosulfonamides were also deprotected using NaOMe/MeOH (Dry) to afford the methyl ester derivatives (**3.64-3.68**). Finally methyl ester hydrolysis using LiOH.H_2O in the THF:H_2O:MeOH (3:1:2) solvent mixture at R.T in about 2 hrs gave final compounds (**3.69-3.73**) in excellent yields (70-90%) (Scheme 15).

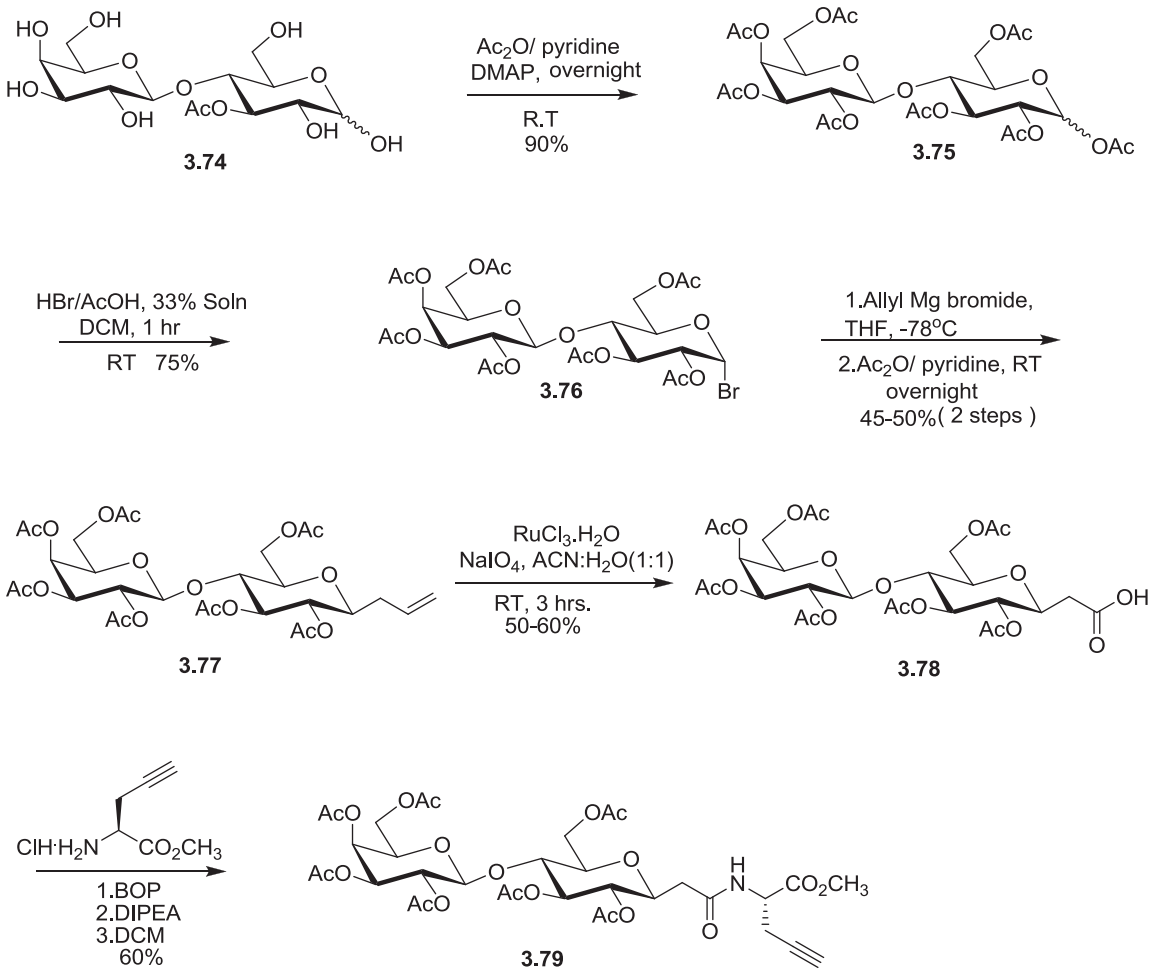


Scheme 15. Synthesis of *S*-Galactosulfonamides

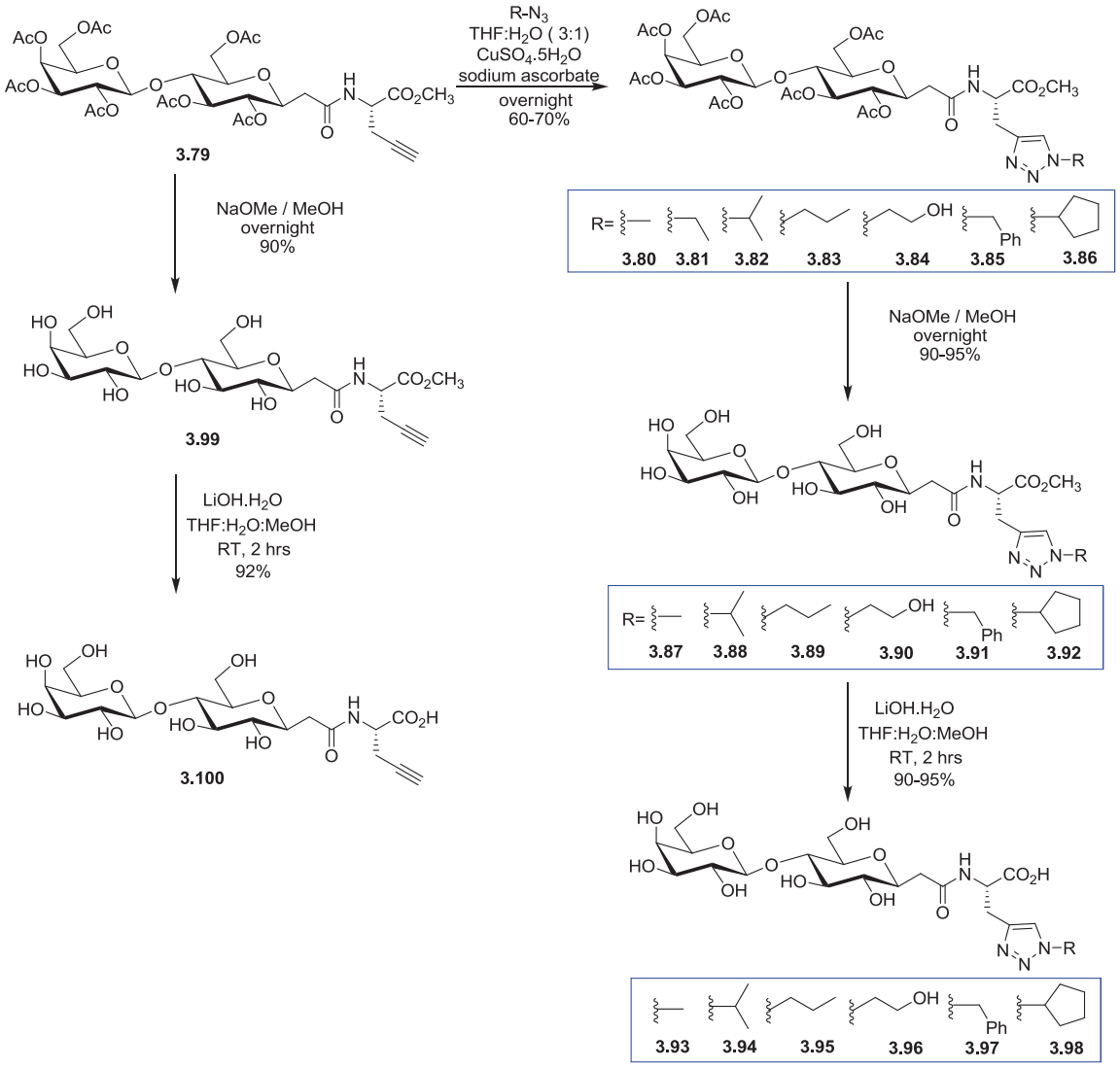
3.5 Synthesis of *C*-lactopeptidomimetics

C-lactopeptidomimetics synthesis was initiated by protecting the lactose (**3.74**) with acetate protecting groups in a very classical way using acetic anhydride in pyridine to obtain lactose octaacettate (**3.75**) in an excellent yield. Bromination of lactose octaacetate using 33% HBr/AcOH to get bromolactose (**3.76**) in a stereoselective fashion as

described in Scheme 2. Grignard reaction on the bromolactose using excess allyl magnesium bromide followed by an aqueous workup and re-*O*-acetylation gave 3-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyrano syl)-1-propene (**3.77**) obtained in a stereo selective fashion. Oxidative cleavage of β-C-allyl lactose by $RuCl_3/NaIO_4$ in ACN:H_2O mixture to 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl ethanoic acid (**3.78)** (Scheme 16) directly in a single step[108] in contrast to scheme 2 where alkene is ozonolized to aldehyde and then oxidised to acid using the Jones reagent. Peptide coupling reaction between lactose acid and L-propragylglycine methyl ester hydrochloride **6.7** (scheme 32) using BOP (Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate) peptide coupling reagent was performed to get *N*-(methyl propargyl-L-glycine)1'-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl)-acetamide (**3.79**). The triazole pharmacophoric part was built using regio selective 1,3 dipolar cyclo addition reaction (click chemistry) with $CuSO_4{\cdot}5H_2O$ as Cu(II) source and sodium ascorbate as reducing agent to obtain a library of compounds (**3.80-3.86**) *O*-acetyl deprotection carried out using Zemplén deacetylation (catalytic NaOMe/DryMeOH) followed by work-up by adding H^+ resin, to obtain methyl ester derivatives (**3.87-3.92**). Finally methyl ester hydrolysis was performed using $LiOH.H_2O$ in the THF:H_2O:MeOH (3:1:2) solvent mixture gave final compounds (**3.93-3.98**) in excellent yields (Scheme 17).



Scheme 16. Synthesis of *C*-lactopeptidomimetics

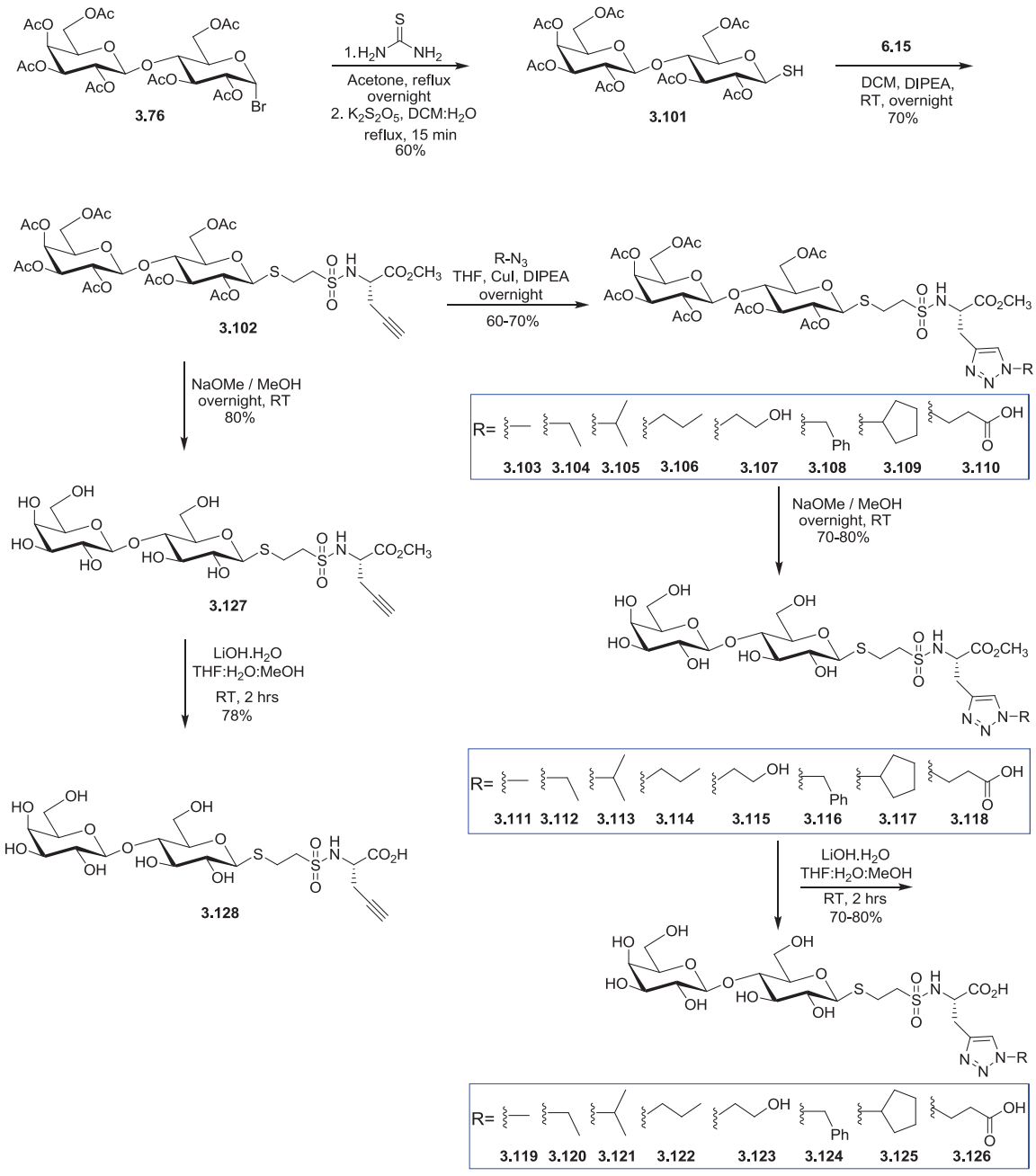


Scheme 17. Synthesis of triazole derivatives of *C*-lactopeptidomimetics

3.6 Synthesis of *S*-lactosulfonamides

S-lactosulfonamides synthesis was initiated by nucleophilic substitution reaction with thiourea on the bromolactose (**3.76**) to obtain the isothiouronium salt intermediate, which is hydrolyzed by potassiumpyrosulfate ($K_2S_2O_5$) to obtain 2,3,4,6-tetra-*O*-acetyl-

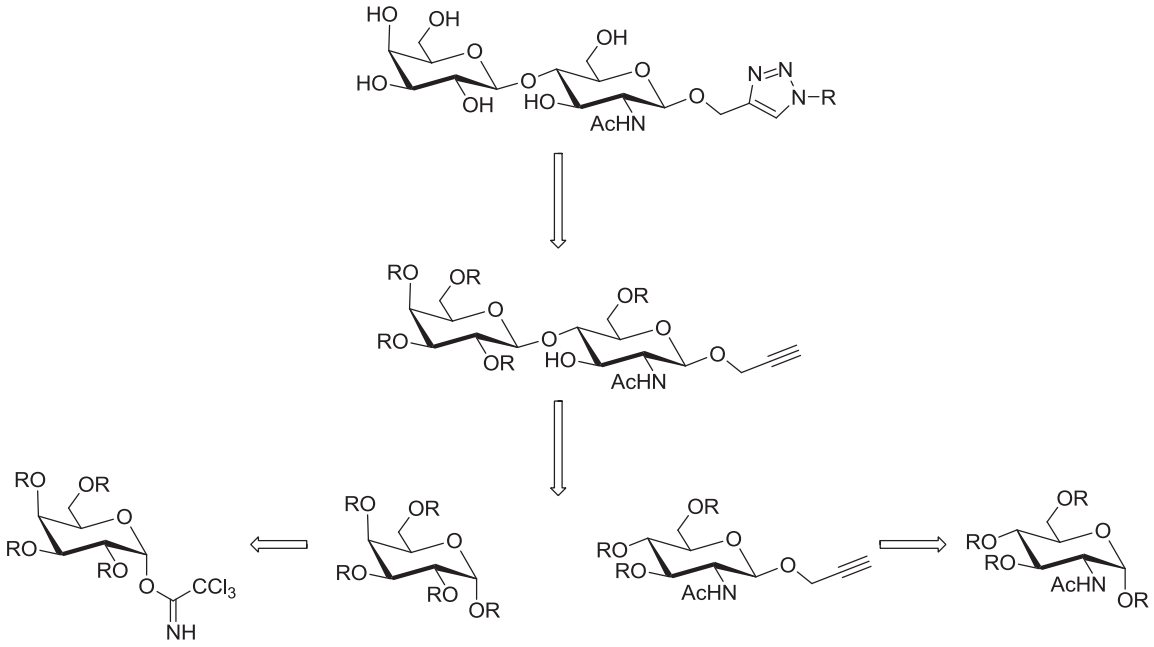
1-thio-β-D-galactopyranosyl(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (**3.101**) in a stereoselective fashion in the same way explained for the galactose thiol chemistry shown in Scheme 10. 1,4-addition of β-lactose thiol on the vinyl sulfonamide **6.15** (scheme 36), resulted in the β-lactose vinyl sulfonamide (**3.102**) in a decent yield. With an alkyne functionality installed "click chemistry" was performed on lactose sulfonamide using THF:H_2O (3:1) and *t*-BuOH:H_2O (3:1) mixed solvent system conditions, although reaction is moving forward to some extent towards triazole formation, it is not going to completion of reaction (about 25% starting material left un reacted) and TLC of the reaction mixture shows many side products, which is very unusual behavior of click chemistry. Usually when analyzing click chemistry reactions by TLC the only major product is observed with one or two other faint spot visualized on the plate. Having observed an incomplete reaction and numerous impurities formed in the above solvent system and reagents, non aqueous (dry) conditions were adopted for "click chemistry" by performing reaction in dry DCM using CuI as Cu(I) source and DIPEA. Under these conditions the reaction was observed to proceed to completion, with reduced impurities formed to produce the triazole library (**3.103-3.110**) in good yield. The *O*-acetylated *S*-lactosulfonamides were deprotected using NaOMe/MeOH (Dry) to produce methyl ester derivatives (**3.111-3.118**). Finally methyl ester hydrolysis using LiOH.H_2O in the THF:H_2O:MeOH (3:1:2) solvent mixture at R.T in about 2 hrs gave final compounds (**3.119-3.126**) in excellent yields (Scheme 18).



Scheme 18. Synthesis of *S*-lactosulfonamides

3.7 Synthesis of Lac NAc triazoles

The disaccharide LacNAc triazole has a β (1→4) glycosidic link between galactose and glucose which is the key step in the synthesis of LacNAc triazole disaccharide. The β (1→4) glycosidic link can be achieved by glycosylation reaction between two building blocks 1) Galactose moiety as a donor (trichloroacetamidate) which can be synthesized from per-acetylated galactose by selectively deprotecting the anomeric acetate. 2) N-acetyl glucosamine acceptor, although there are many ways and methods of glycosylation there are issues with reactivity of the secondary hydroxyl group at C-4 of a hexapyranose with a $^{1}C_{4}$ conformation rendering it particularly unreactive when the remaining hydroxyl groups are acetylated. However there is one regioselective open glycosylation method with more than one hydroxyl groups free.[109] Acetyl protecting groups would be appropriate keeping the stereochemistry requirements on glucose acceptor. The β-*O*-propargyl configuration can be achieved by anchimeric assistance during the glycosidation reaction by propargyl alcohol. For the galactose donor the acetyl protecting group is also appropriate in terms of selective deprotection of anomeric acetate and the formaton of trichloroacetamidate, although DBU needs to be used to block the β-face to obtain the α-configuration exclusively, instead of using two differerent protecting groups also increasing the synthesis by 4 steps (Scheme 19).

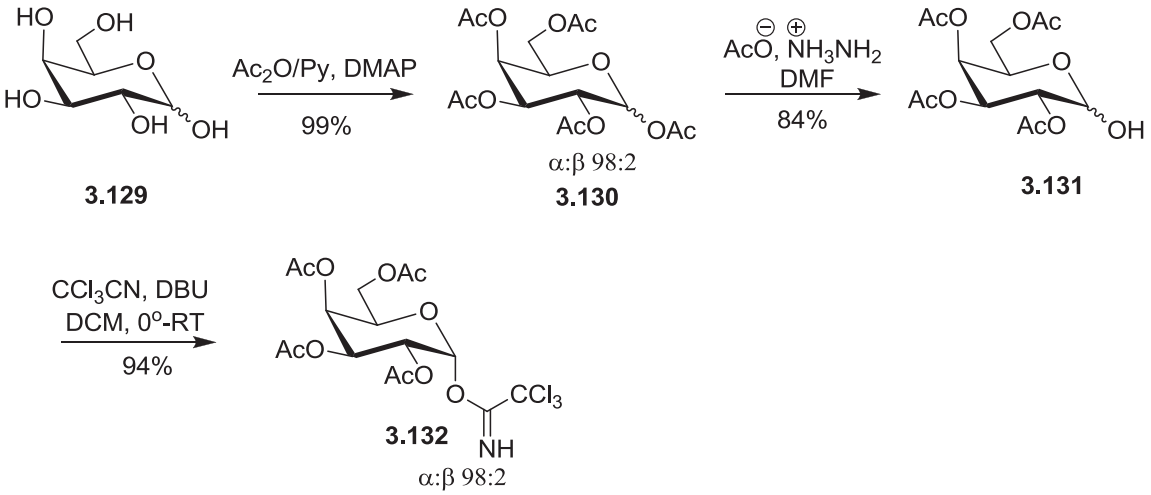


Scheme 19. Retrosynthetic analysis of LacNAc triazole disaccharide

3.7.1 Synthesis of O-(2,3,4,6-tetra-*O*-acetyl-D-galactopyraranosyl)-trichloroacetamidate donor

According to the retrosynthetic analysis described in Scheme 19, D-galactopyranoside donor synthesis begins with a classical acetylation reaction under basic conditions, in the presence of acetic anhydride, pyridine and DMAP as a catalyst (method of Behrend).[110] The acetylation is quasi-quantitative, producing the penta-acetylated product **3.130** from D-galactopyranose (**3.129**) as a mixture of anomers. At room temperature, the thermodynamic effect is dominant and the anomeric effect is also responsible for the majority of the α product. However this mixture of anomers is generally not a problem for the following stages of the synthesis. Selective deprotection of the anomeric acetate of per-acytlated galactose (**3.130**) was realized by the Schmidt

hydrazine acetate in the DMF to obtain hemiacetal (**3.131)**.[111,112] The selectivity of the reagent for the anomeric acetate is explained by its biggest sensitivity towards a nucleophilic attack on the anomeric position relative to the other other positions. The last step is to convert the anomeric alcohol into trichloroacetimidate in dichloromethane by using the trichloroacetonitrile in the presence of DBU.

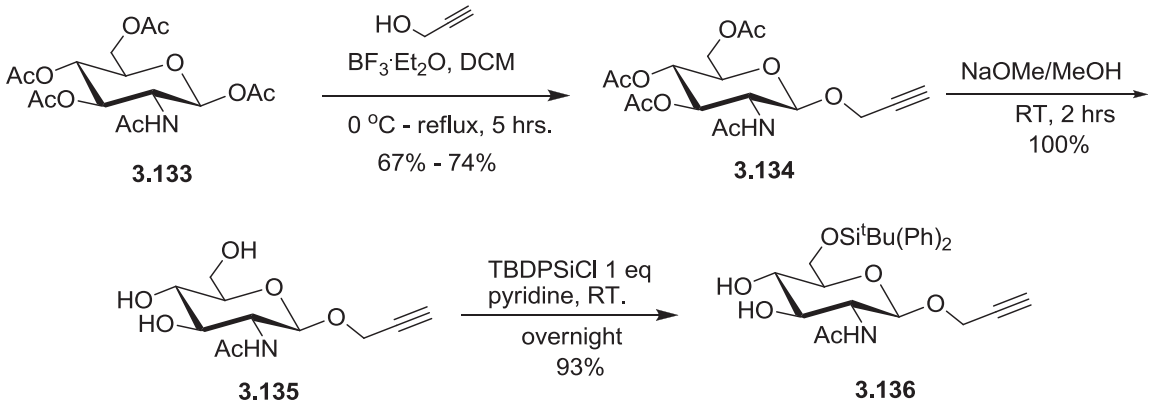


Scheme 20. Synthesis of D-galactoside trichloroacetamidate donor

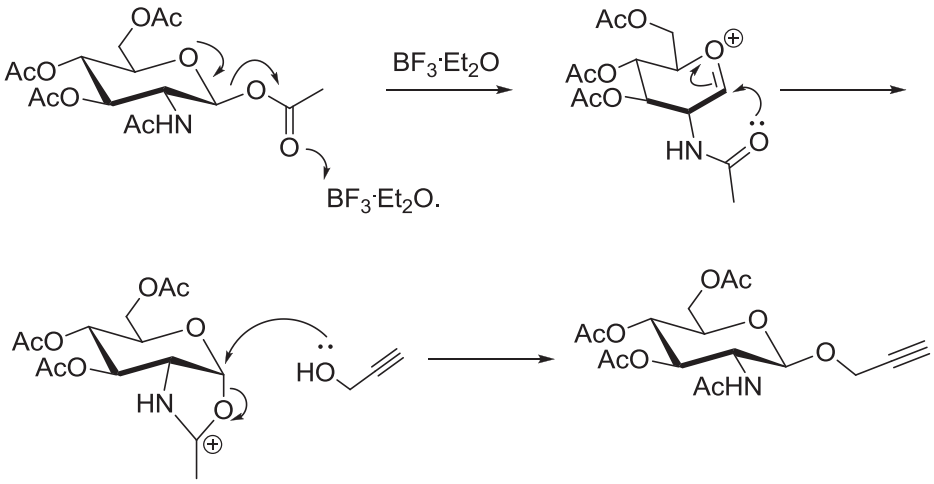
3.7.2 Synthesis of D-GlcNAc acceptor

As illustrated in the Scheme 21, acceptor **3.136** can be synthesized in a stereoselective fashion from β-D-glucopyranoside **3.133.** This final product can be obtained by synergy between anomeric and anchimeric effects. Anchimeric assistance explains the role of the participating functional group on the position 2. After activation by a Lewis acid and intramolecular elimination of acetic acid, a free lone pair of electrons on the oxygen of the acetate function at position 2 participates in anchimeric assistance at

the anomeric position during the transition state oxonium to form an oxocarbenium. Consequently the acetoxycarbenium undergoes nucleophilic attack during the glycosidation (glycosydation is the installation of an aglycone) by propargyl alcohol. Since one of the faces assisted by the position 2, the nucleophilic attack will take place only on the β side, because of steric hinderance. This phenomenon of anchimeric participation influences the result of a glycosylation towards the preferred β configuration (Scheme 22). This step is followed by removal of the acetate groups under Zemplén conditions to liberate the hydroxyl groups. The 6-OH group is then regioselectively protected using 1 equivalent of *tert*-butyldiphenylsilyl chloride to prepare acceptor **3.136**.



Scheme 21. Synthesis of β-D-GlcNAc acceptor

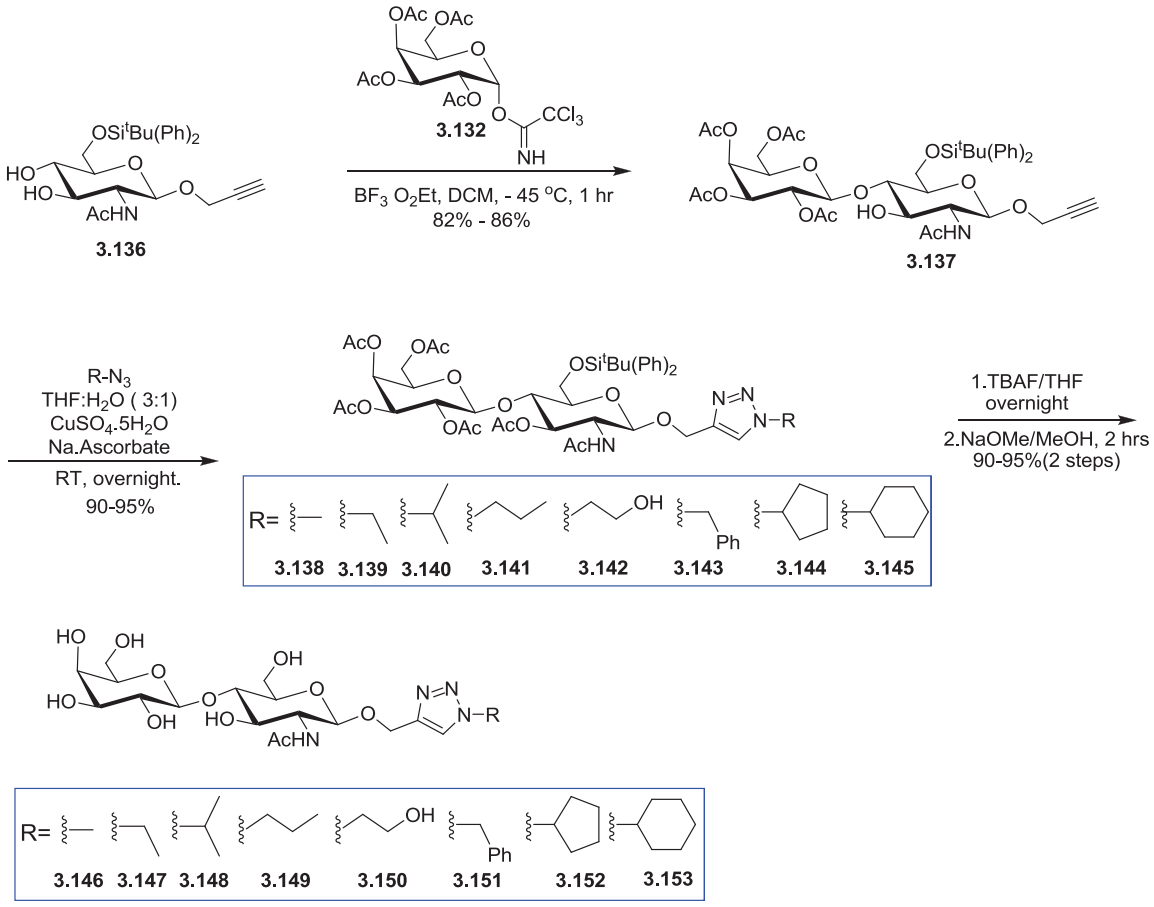


Scheme 22. Anchimeric assistance during the glycosidation

3.7.3 Regiospecific glycosylation towards the synthesis of *N*-acetyllactosamine

An efficient regiospecific glycosylation between donor trichloroacetamidate **3.132** and acceptor **3.136** which is bearing two free hydroxyl groups as acceptors using $BF_3{\cdot}Et_2O$ as a promoter to obtain β (1→4) linked disaccharide (**3.137**) was attempted. The secondary hydroxyl group at C-4 of a hexapyranose with a $^1C_4$ conformation was particularly unreactive when the remaining hydroxyl groups were acetylated.[113] However the unreactivity problem was improved by protecting the hydroxyl functionalties as benzyl groups compared to its acyl counterparts under similar glycosilation conditions.[114] However this procedure involves tedious multiple protection and deprotection steps. To overcome such drawbacks a new strategy has been developed to use lightly protected acceptors that has hydroxyl group unprotected, especially near the glycosylation site. This open glycosylation in which one hydroxyl group preferentially glycosilated in the presence of other free hydroxyl groups is achieved by using bulky protecting groups such

as 6-*O*-benzyl or 6-*O*-pivaloyl and 6-*O*-*tert*-butyldiphenylsilyl on the 6-OH group.[115,116] Regioselectivity is attributed to the bulky 6-*O*-tert-butyldiphenylsilyl group. The very bulky protecting group could cover the top side (3, 5-*cis*) of OH-3 of the acceptor and block the approach of the glycosyl donor.[109] With an alkyne functionality installed on key intermediate (**3.137**) using regiospecific glycosylation, a library of compounds was synthesized by employing the regioselective 1,3 dipolar cyclo addition reaction (click chemistry) using $CuSO_4 \cdot 5H_2O$ as Cu(II) source, sodium ascorbate as reducing agent and various azides to obtain triazole products **3.138 - 3.145**. The yields of click chemistry reactions were good to excellent. Followed by deprotection of 6-*O*-tert-butyldiphenylsilyl group and acyl groups using TBAF and NaOMe respectively to obtain final compounds **3.146 - 3.153** in excellent yields (Scheme 23). Residual TBAF was always left in the final product and appeared in the NMR spectrums, resulting in isolation of the final products as an oil. Even column chromatography was not able to separate the residual TBAF from the product. Mixed resin (acid+base) wash removed the residual TBAF.



Scheme 23. Synthesis of LacNAc triazoles through regiospecific glycosylation

Chapter 4

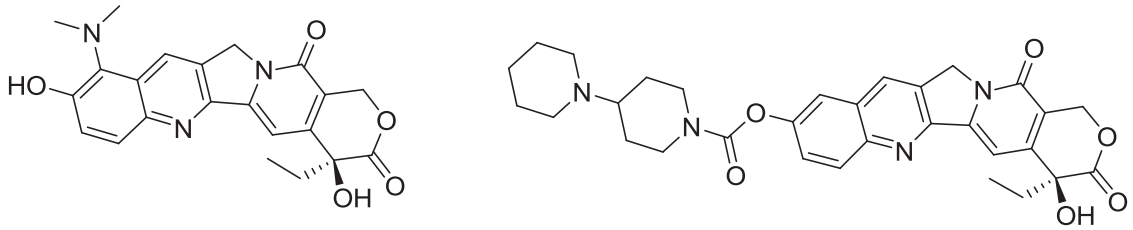
Camptothecin Anti-cancer pro-drug using galactoside war-head for cell delivery

4.1 Introduction

Camptothecin, a pentacyclic alkaloid with a novel ring system isolated from Camptotheca acuminata (Nyssaceae) stem wood by Wall and co-workers, has shown to have an anti tumor activity against the mouse leukemia L1210 system.[117] The compound has a pentacyclic ring system with an asymmetric center in ring E with a configuration of *S* at C20. The pentacyclic ring system includes a pyrrolo [3, 4-*b*] quinoline moiety (rings A, B, and C), a conjugated pyridine (ring D), and a six-membered lactone (ring E) with an R-hydroxyl group. Isolated natural camptothecin itself is not water soluble for biological tests, therefore water soluble sodium carboxylate salt was used in clinical trials. However this salt was devoid of anticancer activity and produced severe toxicity. Insolubility, instability and toxicity led to the discontinuation of phase II clinical trials. However camptothecin's efficacy to inhibit the topoisomerase I[118,119,120] revived interest in comptothecin. Ever since camptothecin found to be a topoisomerase I inhibitor, different groups tried to minimise the drawbacks of camptothecin insolubility, instability and toxicity. The sodium carboxylate salt of camptothecin exhibited 1/10th the potency of camptothecin, which suggests that the E ring lactone is crucial for the potency of camptothecin. Camptothecin is modified on rings A and B to prepare Topotecan and Irinotecan (Figure 16) both of which are available commercially. For the improvement of

lactone ring stability, esters were prepared in an analogous manner.[121] β-cyclodextrin camptothecin conjugates were found to be superior tumor growth inhibitors over the parent camptothecin, and it was observed that a short course of treatment with the polymer conjugates gives long-term control of tumor growth that does not occur with either CPT or irinotecan because of controlled release of camptothecin.[122] A folate mediated camptothecin prodrug was synthesized using a hydrophilic peptide spacer linked to folate via a releasable disulfide carbonate linker. The conjugate was found to possess high affinity for folate receptor-expressing cells with 10 nM inhibition against human KB cells.[123] Water-soluble poly-(L-glutamic acid)-Gly-camptothecin conjugates enhance camptothecin stability and efficacy *in vivo*.[124] Acoustically active nanoemulsions for camptothecin encapsulation were used to circumvent the parent camptothecin problems with nanoemulsions prepared using liquid perfluorocarbons and coconut oil. Ultrasound was effective on the droplets, thus releasing the bioactive drug at specific sites.[125] New prodrugs of CPT were synthesized, based on a carbamate linkage between the 20-hydroxy group of CPT and a linker designed to be enzymatically removed by either Penicillin-G-Amidase or catalytic antibody 38C2. Cell growth inhibition assays showed an up-to-2250-fold difference in toxicity between the prodrugs and the active drug and a significant increase in toxicity was also observed.[126] Polyester-drug graft copolymer conjugates were made by click cycloaddition of azide-functionalized camptothecin derivatives with alkyne-functionalized aliphatic polyesters. Further grafting of residual alkyne groups with azide-terminated poly (ethylene oxide) gave a water-

soluble polyester-camptothecin conjugate. Control over PEGylation and drug loading, inherent to the graft copolymer design, opens versatile routes to new materials with potential utility in polymer therapeutics.[127]



Topotecan Irinotecan

Figure 16. Commercial camptothecin analogs

In our strategy to address the limited bioavailability[128,129,130] and to improve the pharmacokinetic properties of the parent drug, an ester at the C-20-OH group was introduced using a hydrolytically stable *C*-galactoside residue. This modification can also increase the steric hindrance around the carbonyl group of the E-ring, thus eliminating the intramolecular hydrogen bonding and, consequently increase the key lactone ring stability in vivo which is a key feature of camptothecin to be potent. The choice for the galactoside is based on the observation that cancer cells over-express a family of galactoside binding proteins called galectins.

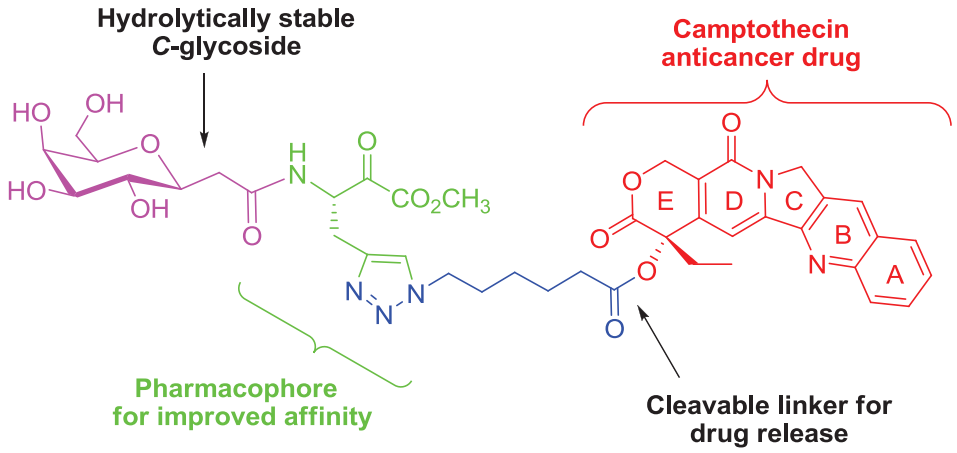
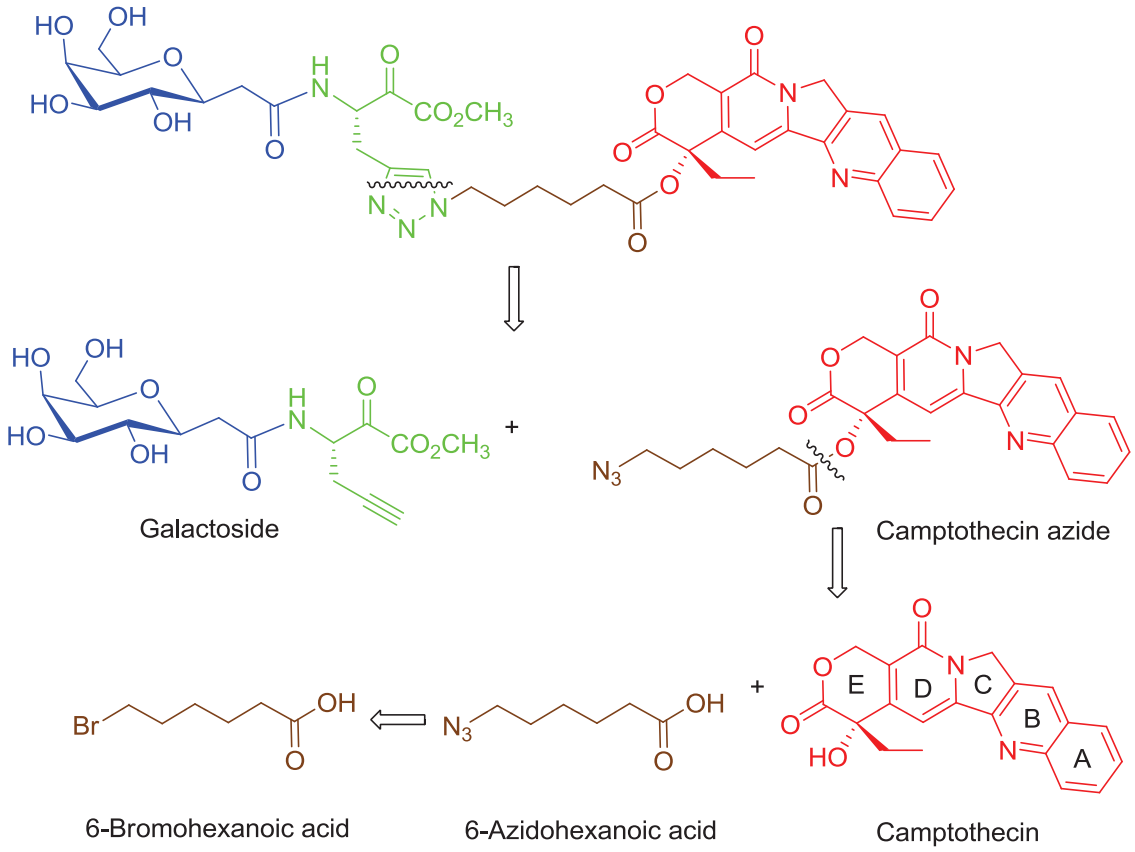


Figure 17. Strategic representation of camptothecin prodrug

4.2 Retrosynthetic analysis of Camptothecin prodrug

The above proposed galactoside prodrug of camptothecin was envisioned to connect an unprotected galactoside synthon with a camptothecin azide using regio selective 1,3 dipolar cyclo addition reaction (click chemistry) to obtain the final compound to avoid camptothecin ester hydrolysis during deprotection of final compound. Aqueous solvent conditions of click chemistry (THF:H_2O 3:1) are very much in favor of dissolving the unprotected galactoside and camptothecin azide. The Camptothecin azide can be constructed using an esterification reaction between 6-azidohexanoic acid and camptothecin.[129] 6-azidohexanoic acid can be synthesized from 6-bromohexanoic acid by a nucleophilic substitution reaction.



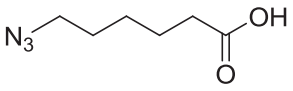
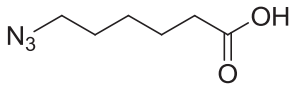
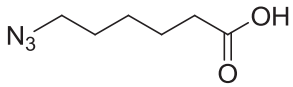
Scheme 24. Retrosynthetic analysis of galactoside camptothecin prodrug

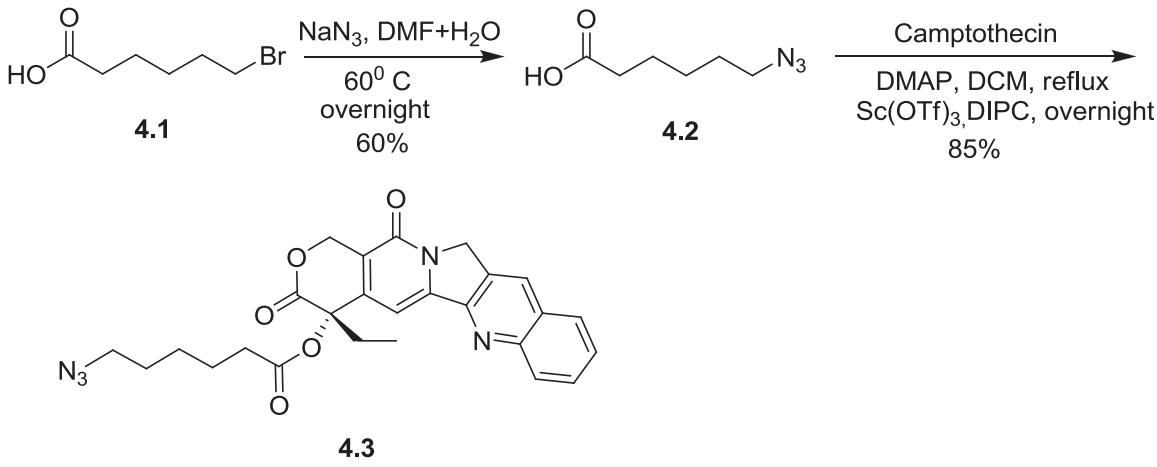
4.2.1 Camptothecin azide

Camptothecin azide was initiated by preparation of 6-azidohexanoic acid (**4.2**) from 6-bromohexanoic acid (**4.1**) using sodium azide in DMF:H_2O (1:1) mixture, employing a nucleophilic substitution reaction. The 6-azidohexanoic acid then undergoes an esterification reaction at the C-20-OH of camptothecin to give the camptothecin azide (**4.3**). To couple the 6-azidohexanoic azide with camptothecin at the C-20-OH group, a number of various conditions were attempted (Entry 1) (Table 7) but did not work even upon extensive reaction times.[129] A classical esterification reaction was attempted using

the anhydride of 6-azidohexanoic acid in pyridine with a catalytic amount of pyridine was not successful either. $Sc(OTf)_3$ was investigated to activate the alcohol of camptothecin as shown in entry 3[131] at room temperature, however the Camptothecin did not solubilize. Finally, with higher temperatures shown in Entry 4 (Table 7) the esterification proceeded (Scheme 25).

Table 7. Optimization of esterification reaction on camptothecin

Entry	Reagents	Conditions	% Yield
1.	 DCC/DMAP/CH_2Cl_2	RT, 1-4 days	No reaction
2.	$(R_2CO)_2O$/Py/DMAP R=$CH_2(CH_2)_4N_3$	RT, 1-4 days	No reaction
3.	 DIPC/$Sc(OTf)_3$/DMAP CH_2Cl_2	RT, 1-4 days	No reaction
4.	 DIPC/$Sc(OTf)_3$/DMAP CH_2Cl_2	Reflux, 12 hrs	85%

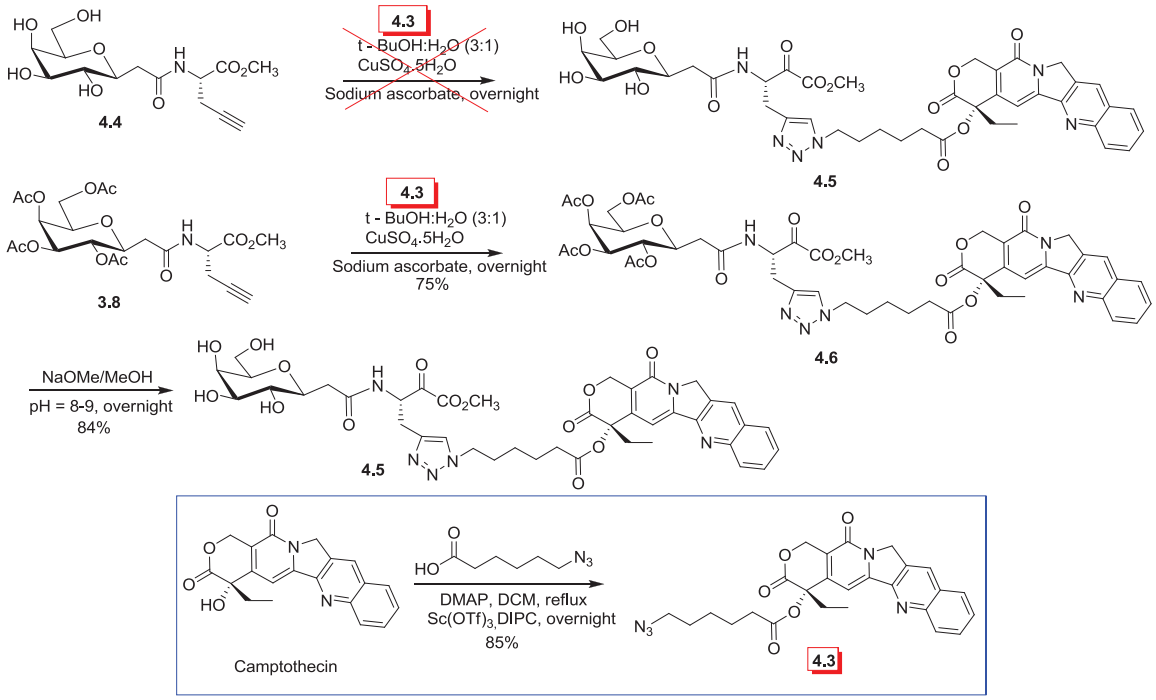


Scheme 25. Synthesis of camptothecin azide

4.2.2 Synthesis of camptothecin prodrug

Having galactoside (**4.4**) with the alkyne functionality installed and deprotected, the copper catalyzed 1,3 dipolar cycloaddition (click chemistry) was carried out using $CuSO_4 \cdot 5H_2O$ as a Cu(II) source and sodium ascorbate as a reducing agent with camptothecin azide to obtain the final camptothecin prodrug (**4.5**). Unfortunately the click chemistry did not work for unknown reasons although all the reagents and reactants were dissolved in the solvent system chosen. Having trouble with the click chemistry using unprotected galactoside, the protected galactoside was used instead to successfully obtain the galactoside protected camptothecin prodrug under the same conditions as above in 75% yield. The final challenge involved deprotection of the acetate groups in the presence of the ester linkage between camptothecin and galactoside. In a few trials strictly controlling pH between 7-9 and taking the advantage of sterically bulky *tert*-butyl

ester (stable under neutral and basic conditions) of camptothecin the acetates groups were successfully deprotected to obtain the camptothecin anticancer prodrug **4.5** (Scheme 26).



Scheme 26. Synthesis of camptothecin prodrug

Chapter 5

Diastereoselective 1, 4 - addition on *C*-allyl galactose using Evan's chiral auxiliary

5.1 Introduction

In recent years glycosides have become very popular in medicinal chemistry research for their specificity and efficacy to modulate the activity of various proteins involved in disease states. *O*-linked glycosylation is the classical approach for building a pharmacophore on the glycosides because of the convenience of well established glycosylation methodology. Although it is very convenient and easy to build pharmacophores on a sugar molecule using *O*-glycosylation, the resulting molecules are very susceptible for *in vivo* degradation, rendering them biologically inactive. This basic problem of *in vivo* stability stops them from being developed further into potent commercial drugs. With a special emphasis on galectins and their biological roles from cell transformation to metastasis as described in the Introduction, it is very critical to build hydrolytically stable galactosides with a stereo specific pharmacophores on the reducing end to fill up the binding pocket (Figure 18) to obtain good selectivity.[132]

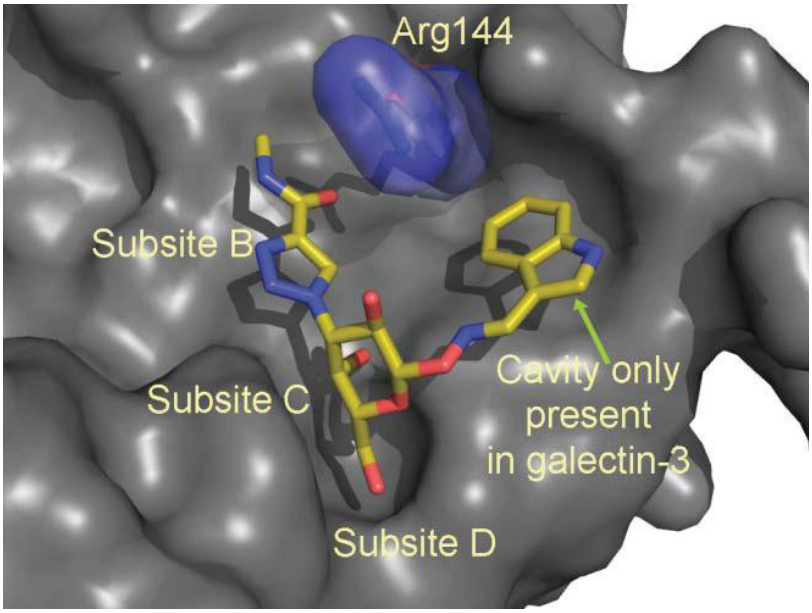


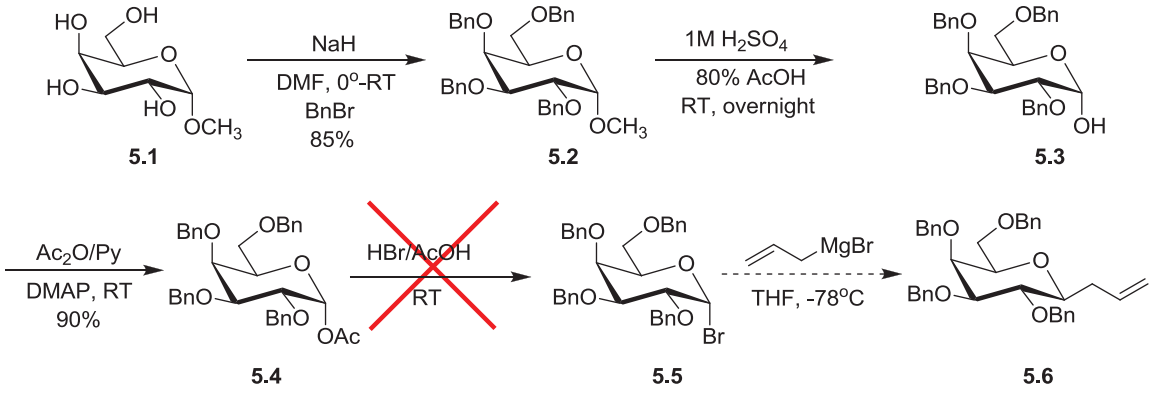
Figure 18. Hydrophobic binding pocket extended towards reducing end in galectin-3 X-ray crystal structure

C-Allyl-β-D-galactose is one potential galactoside that can serve as platform to build pharmacophores on the reducing end. To install the pharmacophores in a diastereoslective fashion we have envisioned a way to obtain a diastereoselective 1,4 addition using the Evans chiral auxiliary.

5.2 Synthesis

β-*C*-allyl galactose was proected with benzyl groups to allow for Grignard reagents to be used in 1,4 additions. Thus synthesis started with the protection of free hydroxyl groups of α-methyl galactose to obtain 2,3,4,6-*tetra*-*O*-benzyl-α-methyl galactose (**5.2**). Methyl galactose was subjected to demethylation using 1M H_2SO_4 and 80% acetic acid to liberate free hydroxyl group which is then converted into an acetate

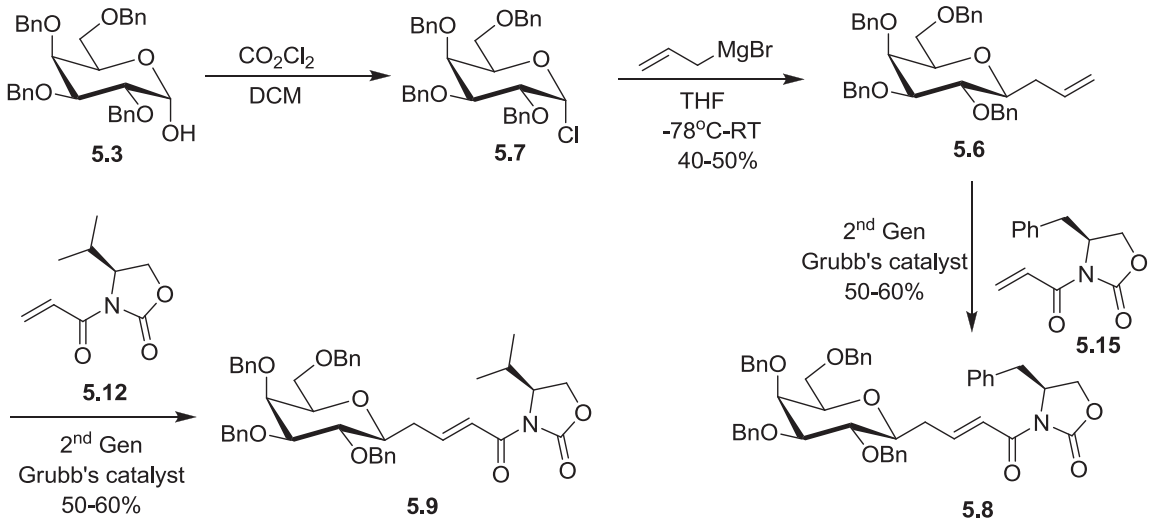
group, by acylaion in a classical way using Ac_2O/Py. Having the acetate group installed at the anomeric position[133], bromination is carried out using HBr/AcOH to get α- bromo-2,3,4,6-tetrabenzyl-galactose (**5.5**) in a stereoselective fashion by the formation of an oxonium intermediate followed by nucleophilic attack by bromide. However the benzyl protecting groups were removed by HBr/AcOH in a very unusual way at room temperature. Although benzyl groups were tolerated at lower temperature as described in scheme 11 the yield was considerably low.



Scheme 27. Synthesis of 3-(Tetra-*O*-benzyl-β-D-galactopyranosyl)-1-propene

The final steps of the synthesis of 3-(Tetra-*O*-benzyl-β-D-galactopyranosyl)-1-propene (**5.6**) (Scheme 27) required alteration due to the unusual deprotection of benzyl protecting groups by HBr/AcOH. In a revised approach 2,3,4,6-tetra-*O*-benzyl galactose (**5.3**) was transformed into 2,3,4,6-tetra-*O*-benzyl-α-chlorogalactose (**5.7**) using oxalylchloride in dichloromethane. A Grignard reaction was carried out on compound **5.7** using allyl magnesium bromide to obtain selectively the β anomer in S_N^2 fashion to obtain 3-(Tetra-*O*-benzyl-β-D-galactopyranosyl)1-propene (**5.6**)[134]. The allylation reaction yields were

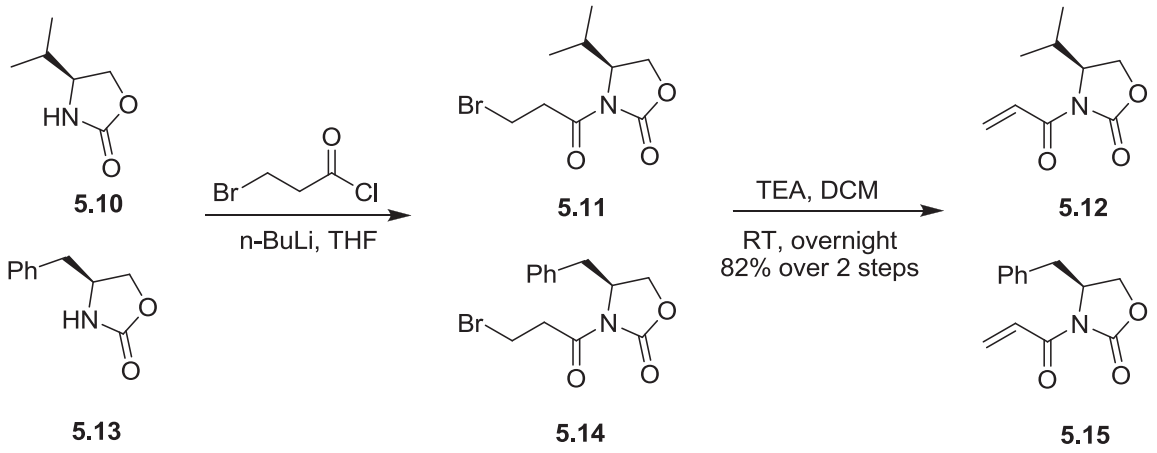
expected to be far better on benzylated starting material than the acetylated version as the acetyl protecting groups were removed by the by Grignard reagent and 1,2 hydride shift leading to *C*-2-allylated anhydro sugar (**3.4**) in 21% yield (Scheme 3). Modest yields for the Grignard reaction on 2,3,4,6-tetra-*O*-benzyl-α-chloro galactose (**5.7**) can be attributed to poor leaving ability of chloro group compared to bromo group. Then the *C*-allyl galactose was subjected to olefin cross metathesis with *N*-acryloyl-(S)-4-benzyl-2-oxazolidinone (**5.15**) and *N*-acryloyl-(S)-4-isopropyl-2-oxazolidinone (**5.12**) using Grubb's 2nd generation catalyst to obtain **5.8** and **5.9** in modest yields (scheme 28).



Scheme 28.Synthesis of isopropyl and benzyl oxazolidinone bearing *C*-allyl galactoside

The chiral auxiliaries *N*-acryloyl (S)-4-benzyl-2-oxazolidinone (**5.15**) and *N*-acryloyl (S)-4-isopropyl-2-oxazolidinone (**5.12**) were synthesized from (S)-4-benzyl-2-oxazolidinone (**5.10**) and (S)-4-isopropyl-2-oxazolidinone (**5.13**) by treating with n-BuLi and 3-bromo

propionyl chloride to obtain *N*-3-bromopropionyl oxazolidinones (**5.11** and **5.14**) followed by triethylamine induced elimination of HBr gave final compounds (**5.12**) and (**5.15**) in very good yields (Scheme 29). Attempts to use triethylamine as base to couple 3-bromopropionyl chloride and *insitu* dehydrobromination failed to deliver the final product. Triethylamine failed to abstract the NH proton of oxazolidinone due to the higher pKa value (20.5) of NH proton on the oxazolidinone.[135]

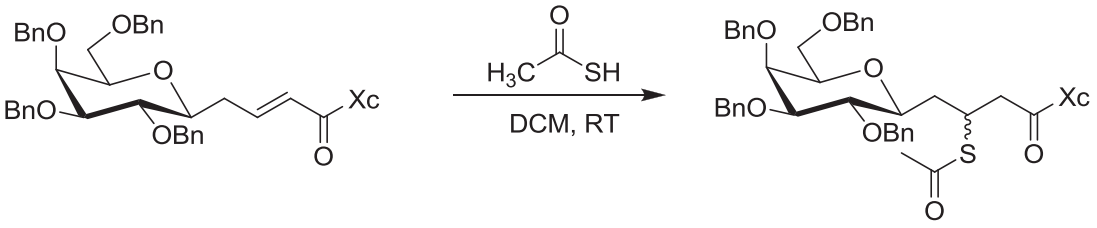


Scheme 29. Synthesis of *N*-acryloyl isopropyl and benzyl oxazolidinones

5.2.1 Primary Screening of chiral auxiliaries

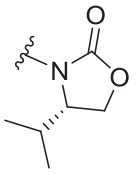
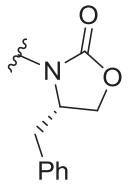
The above prepared *C*-galactoside with isopropyloxazolidinone (**5.9**) was examined for the efficacy of the chiral auxiliary to control diastereoselective 1,4-addition using simple thioacetic acid, to obtain a thioacetate compound (Scheme 30). Thioacetate was chosen for the primary testing considering that the diastereotopic protons of an acetate group will show up as a singlet and the peaks would be resolved by ^{1}H-NMR to enable quantification of the diastereoselectivity by integrating the two singlets

corresponding to two diastereomers. As postulated on *C*-galactoside (**5.9**) 1, 4 addition of thioacetic acid in presence of triethylamine proceeded with good yields, with almost no selectivity (ds 60:40) (Figure 19). Then keeping the bulky benzyl group (S)-4-benzyl-2-oxazolidinone (**5.15**) in view another *C*-galactoside was synthesized with (S)-4-benzyl-2-oxazolidinone (**5.8**) as a chiral auxiliary and performed the 1,4-addition using the thioacetic acid under similar conditions as above. Diastereoselectivity is modestly improved showing the influence of bulky benzyl group (Table 8). Although the benzyl group of oxazolidinone is completely blocking one of the faces to the nucleophile (Figure 20), the selectivity was not up to the expectations. The poor selectivity could be due to rotation of the chiral auxiliary around the single bond between carbonyl carbon and nitrogen atom of oxazolidinone in solution as shown in the Figure 20.



Scheme 30. 1,4-Addition using thioacetic acid for the primary screening of auxiliaries

Table 8. Diastereoselectivity

Compd No	Chiral auxiliary(Xc)	Nucleophile	Conditions	%yields	ds
5.16		CH_3COSH	CH_2Cl_2, rt, 2hrs	77%	60 : 40
5.17		CH_3COSH	CH_2Cl_2, rt, 2hrs	85%	70 : 30

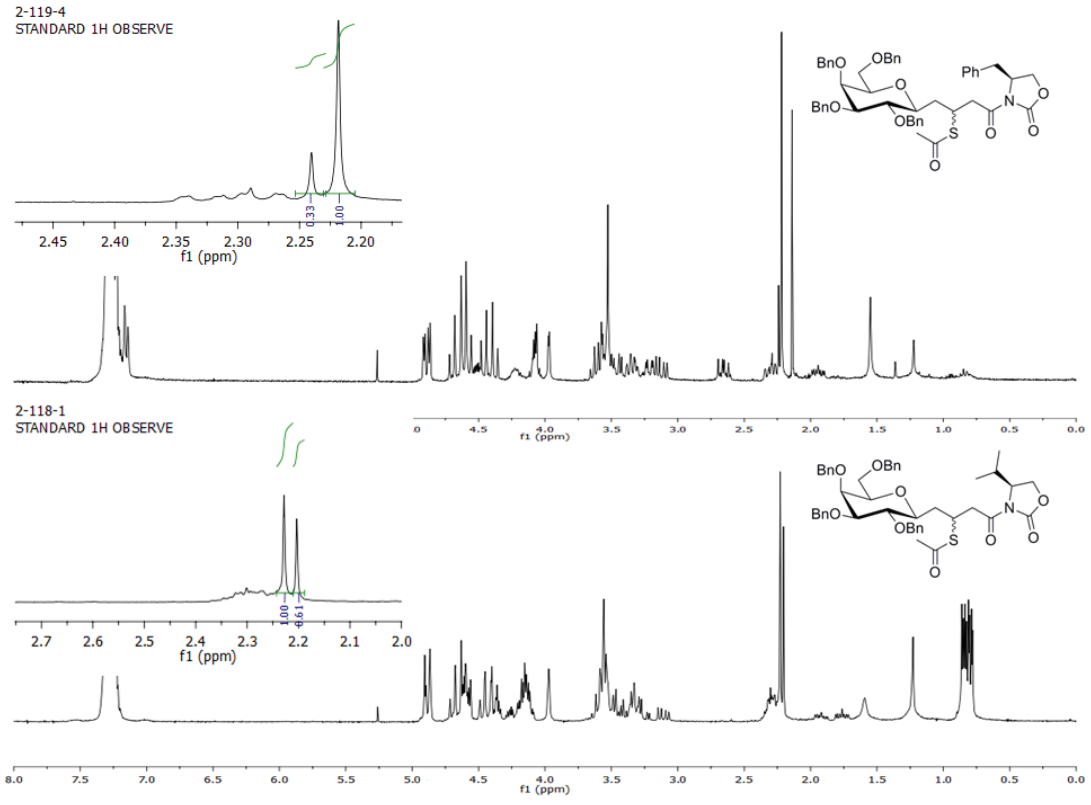


Figure 19. Quantification of diastereoselectivity using methyl singlet peak of thioacetate

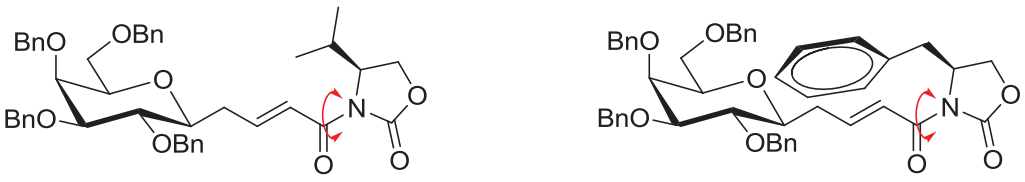


Figure 20. Possible rotation of chiral auxiliary

5.3 Diastereoselective 1,4-addition with chelation control

The diastereoselectivity was not optimum in the primary screening of the chiral auxiliaries using 1,4-addition of thioacetic acid, for the most probable reason of rotation of the chiral auxiliary. To enhance diastereoselectivity it is important to avoid the rotation of the chiral auxiliary of the amide bond and to keep the auxiliary in such a position to direct the nucleophile completely to one face by blocking the opposite face approach. It was decided to use chelation control employing a Grignard reagent to create an enolate intermediate in which a metal coordinates both the oxygens of the oxazolidinone carbonyl and the acryloyl carbonyl like locking with two hands to increase the conformation population (Figure 21)[136]. Initial attempts of 1,4-addition on galactoside (**5.9**) using EtMgBr, CuBr.DMS in THF at -78^{o}C revealed that the reaction was completed in 1 hr with little side product in a 77% yield. Initially the ratio was approximately determined by integrating the newly generated stereogenic centre proton (Figure 22), since this proton couples with six protons on the adjacent carbons it was difficult to determine the ratio of diastereomers exactly obtained in 1,4-addition. To establish the exact ratio of diastereomers without any ambiguity a HPLC technique was used. It was found to be 60:40 by HPLC analysis (Figure 23). The probable reason could

be the isopropyl handle on the chiral auxiliary is not covering one face completely. The same reaction was then attempted under the same conditions with the galactoside having a benzyloxazolidinone chiral auxiliary (**5.8**). The reaction worked well with 85% yield and with very good stereo control. The diastereomeric ratio was unambiguously determined by ^{1}H NMR (Figure 22) and HPLC (Figure 24) to be 97:3. HPLC and NMR spectrums were recorded on the crude product to avoid any diastereomer separation on flash column chromatography.

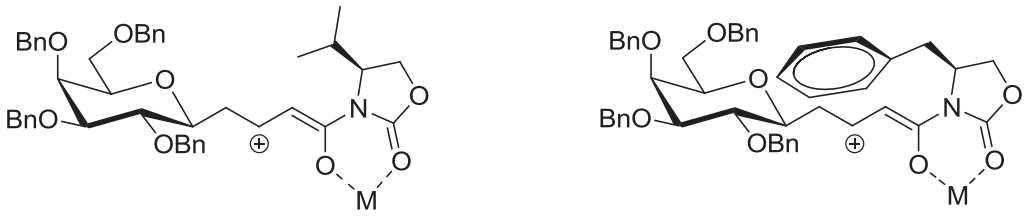
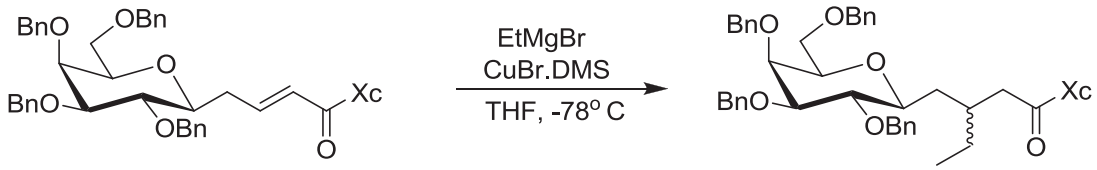
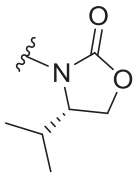
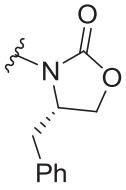


Figure 21. Possible enolate intermediates with chelation control for diastereoselectivity



Scheme 31. Diastereoselective 1,4-addition using cuprates

Table 9. Optimization of chiral auxiliaries

Compd No.	Chiral auxiliary(Xc)	Nucleophile	Conditions	%yields	ds
5.18		EtMgBr CuBr.DMS	THF, -78°C 1 hr	77%	60 : 40
5.19		EtMgBr CuBr.DMS	THF, -78°C 1 hr	85%	97 : 3

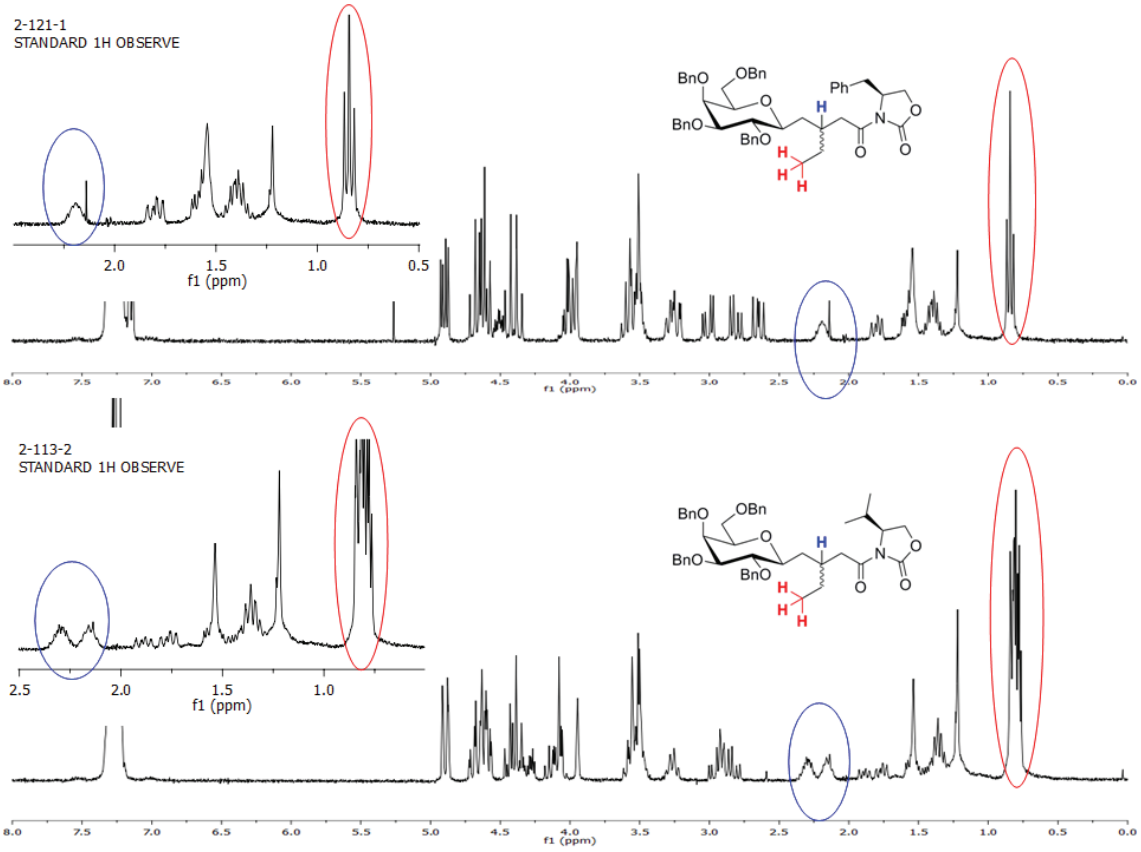
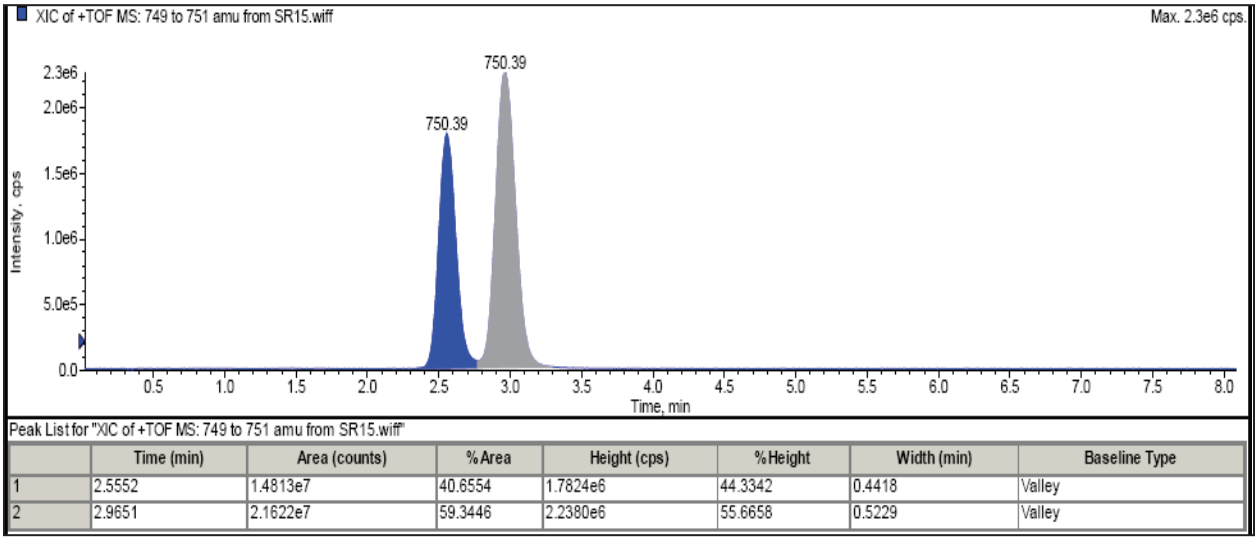


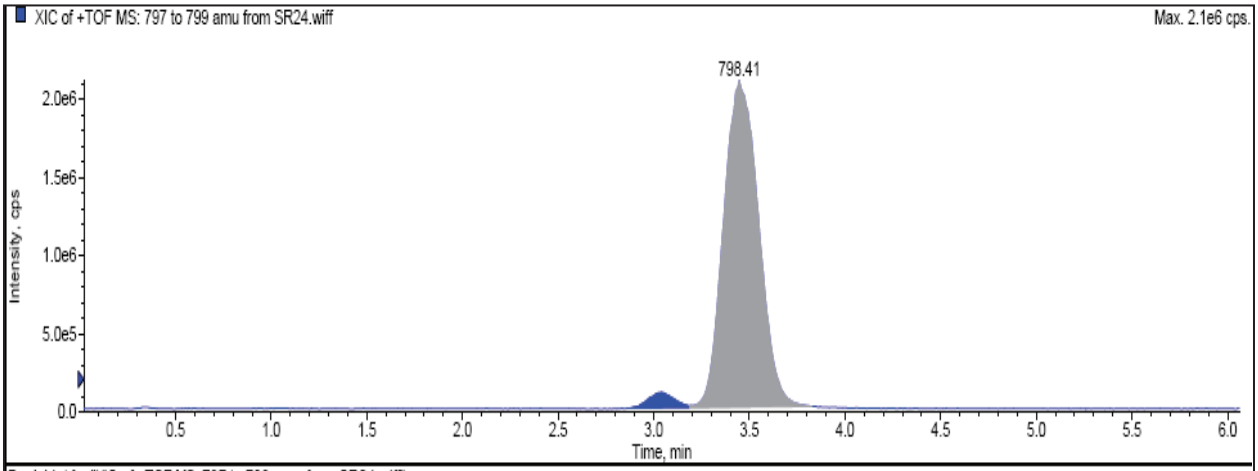
Figure 22. Quantification of diastereoselectivity using ^{1}H NMR



Peak List for "XIC of +TOF MS: 749 to 751 amu from SR15.wiff"

	Time (min)	Area (counts)	% Area	Height (cps)	% Height	Width (min)	Baseline Type
1	2.5552	1.4813e7	40.6554	1.7824e6	44.3342	0.4418	Valley
2	2.9651	2.1622e7	59.3446	2.2380e6	55.6658	0.5229	Valley

Figure 23.Quantification of diastereoselectivity using HPLC on isopropyloxazilidinone chiral auxiliary



Peak List for "XIC of +TOF MS: 797 to 799 amu from SR24.wiff"

	Time (min)	Area (counts)	% Area	Height (cps)	% Height	Width (min)	Baseline Type
1	3.0400	9.0874e5	3.3316	9.7792e4	4.4760	0.3155	Valley
2	3.4472	2.6368e7	96.6684	2.0870e6	95.5240	0.6401	Valley

Figure 24. Quantification of diastereoselectivity using HPLC analysis on benzyloxazilidinone chiral auxiliary

Chapter 6

Design of selective ligands for conjugate drug targeting to human serum albumin (HSA) through cysteine-34

6.1 Introduction

Peptides are well known for recognizing and activating specific receptors within the body. Peptidase enzyme quickly intercepts and cleaves the peptides, transforming them in to biologically inactive fragments that are further cleared by the kidneys. As a consequence peptides have a short half-life typically less than 5 min. This brief duration of activity, exclude them from being developed into commercialized drugs. The objective of the project is to design a way to circumvent the bioavailability and transportation issues of the peptide based drugs. Human serum albumin (HSA) is monomeric protein of 585 residues having a molecular weight of 66,449 Da. It is the chief circulating protein in the blood stream with an approximate concentration of 35 -50 mg/ml.[137] It has three structurally similar α- helical domains I-III which are further divided in to sub domains A and B.[138] It possesses a unique free thiol residue at cysteine-34[139] (Figure 25) which is used as a platform technology that involves *in vivo* drug conjugation through maleimdo-drug conjugation. It is known that HSA accumulates in tumor tissues[140,141] due to an enhanced vascular permeability of tumor blood vessels for circulating macromolecules combined with a lack of lymphatic drainage in the tumor tissue.[142] Under normal physiological conditions, oleates and palmitates account for almost 70% of free fatty acid in the blood. In many diseases, such as diabetes mellitus and bacterial infections, the fatty

acid levels increases dramatically. Under those conditions HSA undergoes favorable conformational change (allosteric) in drug binding sites I and II. Indeed this drug binding mechanism is now being exploited as an alternative targeting strategy whereby hybrid molecules such as Ibuprofen-anti-sense nucleotide conjugates are used for cancer therapy.[143]

The drug binding site in domain II is found at a distance of 32.5 Å from cysteine-34 buried in domain I, while it is 25.5 Å away from Trp-214 also found in domain II.[143] Additionally, fluorescence emission spectra of acrylodan, a cysteine-specific fluorescence probe, have been used to study the microenvironment surrounding Cysteine -34 following exposure to oleate and ionic quenchers. The study also clearly revealed that there were electrostatic attractive forces involved, thus demonstrating that upon binding to hydrophobic residues, the cysteine-34 site becomes more accessible and that it is surrounded by charged amino acids.[144] These observations were further substantiated by the increased binding of thiol-containing drugs in the presence of fatty acids.

The above information point towards the feasibility of modulating the reactivity of Cys-34 in the presence of fatty acids by a favourable conformational change (allosteric). The DAC (Drug Affinity Complex) strategy can be further improved by having a thiol-reactive species, such as maleimido derivatives, vinyl sulphonamides and acrylamides possessing charged amino acids in their vicinity. We designed and synthesized linkers (maleimide, vinyl sulphonamide and acrylamide Figure 27) with Michael acceptors on one side to conjugate with the HSA and carboxylic acid and alkyne

functionality on the other side to couple peptide based drugs and to install a better triazole derivative functionality (Figure 26). It is known that conjugated peptides have greater *in vivo* stability.[145,146] By conjugating the peptide based drugs to HSA trough the above ligands (Figure 27) it is possible to circumvent the degradation problems presented at the beginning. The relative reactivities of thiol reacting species were tested using simple model thiol (Cysteine) under physiological conditions, Maleimido derivatives were found to be the fastest reacting Michael acceptor (less than 10 min), followed by vinylsulfonamide reacting completely in 45 min. Whereas acrylamide functionality did not react at all under physiological conditions, in the later case the pH had to be raised to 8.5 for reaction to occur. Three ligands are under further evaluation by reacting with HSA to be in real physiological conditions using HPLC (kinetic data), and MS-FAB characterization to assess their reactivity. This concept can be applied to other drugs that need to be delivered to a cancer site either by coupling to a carboxylic acid through a peptide link or using click chemistry between an alkyne functionality and azide.

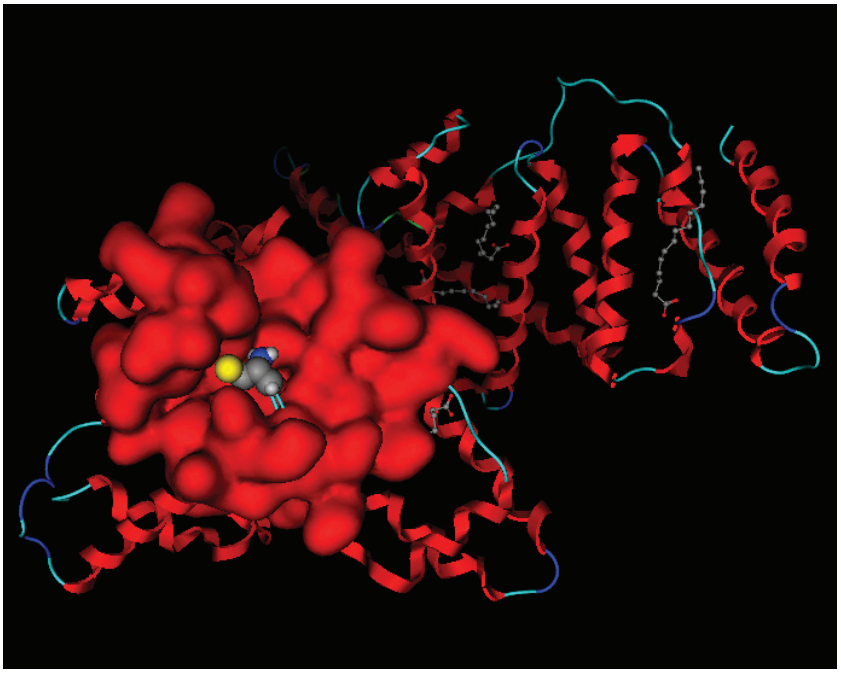


Figure 25. Free thiol residue at cysteine-34 in human serum albumin crystal structure after favorable conformational change upon binding to excess fatty acids.

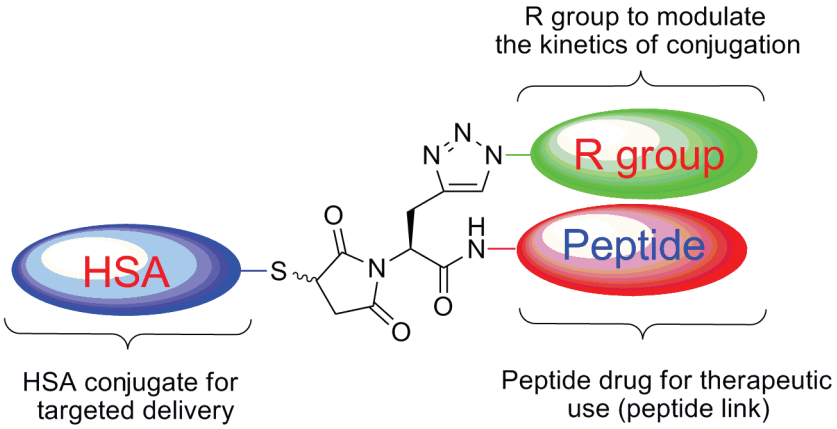


Figure 26. Strategic representation of HSA conjugation

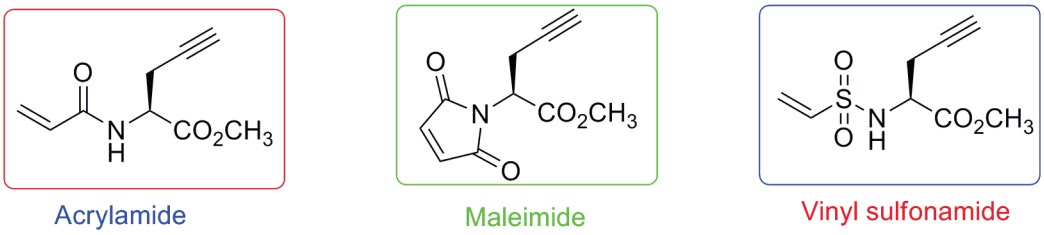
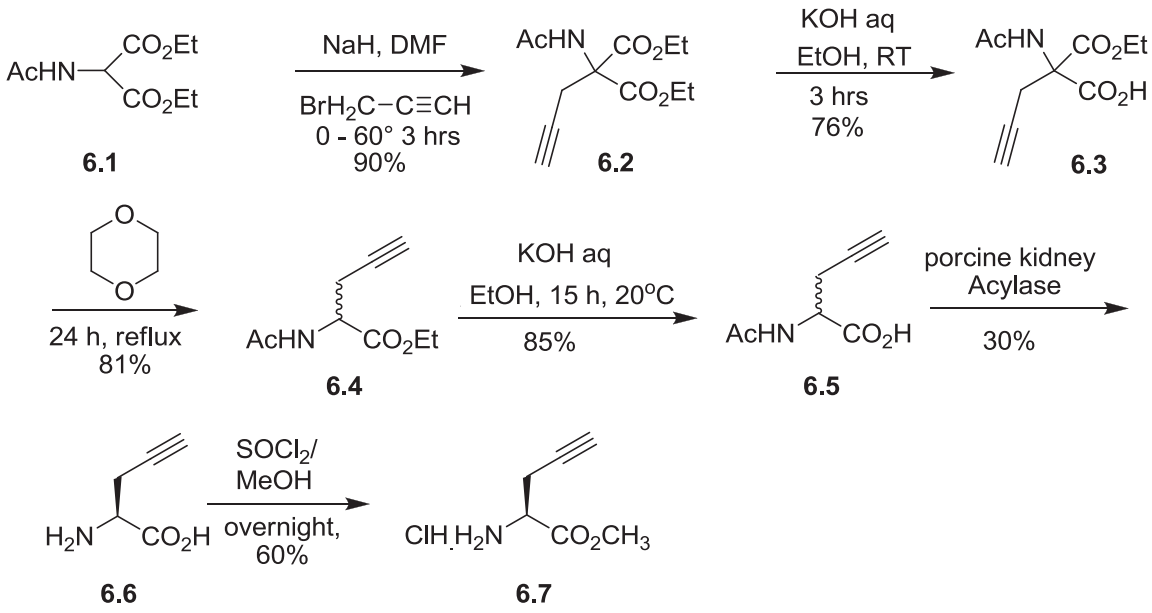


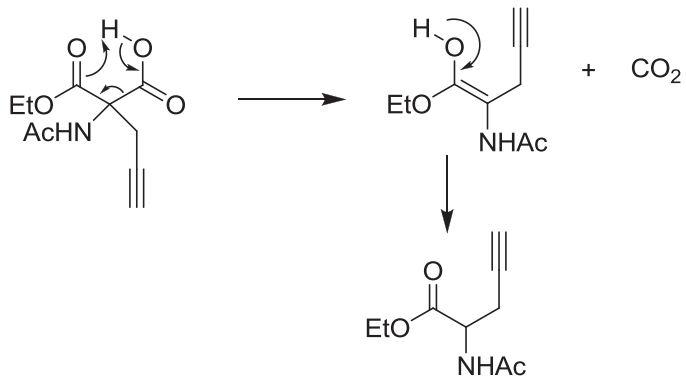
Figure 27. Linkers designed for conjugate drug targeting to Human Serum Albumin (HSA)

6.2 Synthesis of L-propargyl glycine (L-Pra)

L-Propargyl glycine is synthesized stereoselectively starting with the condensation of the sodium salt of diethylacetamidomalonate and propargyl bromide to obtain propargyl diethyl acetamido propargyl malonate (**6.2**). This compound was converted to monoethyl acetamidopropargylglycine (**6.3**) by hydrolysis of one of the ethyl esters selectively using 1 eq base. This was followed by β-keto decarboxylation by the formation cyclic transition state to protonate carbonyl functionality with O-H and C-C vleavage to release CO_2 and formation of π bond to obtain an enol ether (Scheme 33) which will quickly rearrange to form D,L-*N*-acetyl-propargylglycine (**6.4**). Finally L-propargylglycine (**6.6**) was obtained by ethyl ester hydrolysis and stereospecific hydrolysis of the acetamide group using porcine kidney acylase[147]. L-propargyl glycine is converted into it's methyl ester hydrochloride salt (**6.7**) to prepare the linkers (Figure 27).



Scheme 32. Synthesis of L-propargyl glycine

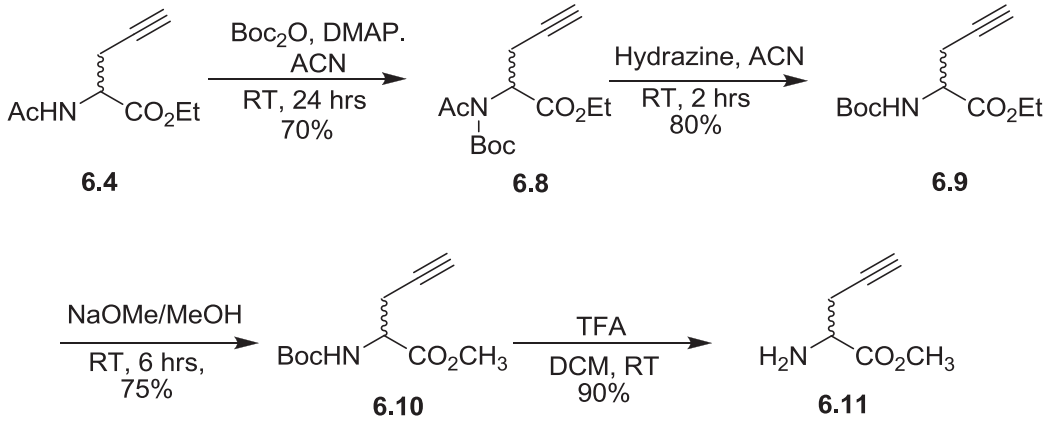


Scheme 33. β-Ketoacid decarboxylation mechanism

6.3 Synthesis of D, L-propargyl glycine

It is important to prove that the purity of L-propargyl glycine obtained by stereospecific hydrolysis of D,L-mixture unambiguously. To prove the purity it was planned to

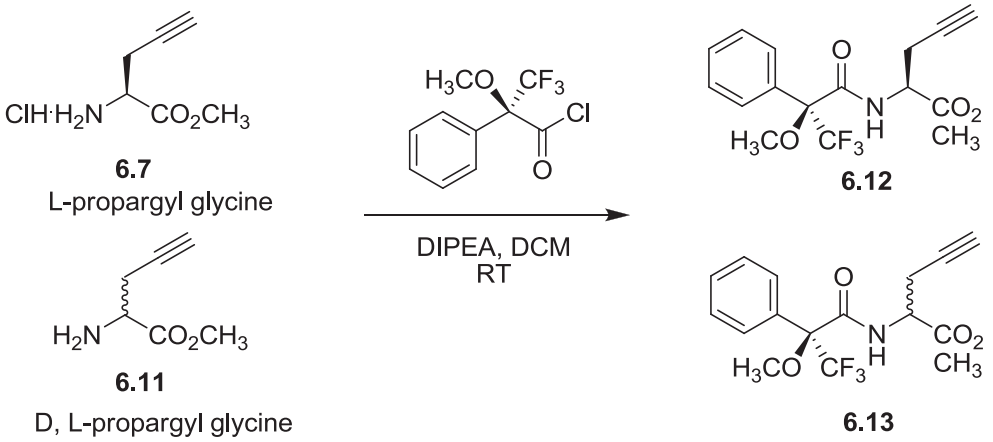
introduce another chiral centre to create the diastereotopic protons. To compare the purity experiments of L-propargyl glycine it was planned to synthesize the D,L-propargyl glycine. To prepare D,L-propargyl glycine it is necessary to hydrolyze the acetamide bond of **6.4** which requires very harsh conditions such as refluxing in HCl solution[148]. Hence a much smoother route was chosen by activating the amide by introducing the Boc group prior to hydrolysis to obtain (**6.8**)[149]. Selective hydrolysis of the amide using hydrazine in acetonitrile leaves *N*-Boc-protected D,L-propargyl glycine ethyl ester (**6.9**)[150]. Transesterification reaction using NaOMe on (**6.9**) gave *N*-Boc-protected D,L-propargyl glycine ethyl ester (**6.10**). Finally *N*-Boc-protecting group was successfully deprotected using trifluoroacetic acid at room temperature in an excellent yield.



Scheme 34. Synthesis of D, L-propargyl glycine

6.4 Purity of the L-propargyl glycine.

D and L-propargyl glycines are enantiomers, having the same physical and chemical properties, they are indistinguishable using NMR. In order to distinguish both enantiomers another chiral centre must be introduced such as preparation of a derivative using Mosher's acid chloride to make the protons diastereotopic. Since the diasteroisomers are chemically and physically distinguishable they are separable and measurable using ^{1}H NMR. To establish the purity of the L-propargyl glycine obtained from enzymatic hydrolysis of acetamide, the Mosher amides **6.12** and **6.13** of L-propargyl glycine and D,L-propargyl glycine were synthesized to compare (Scheme 35).



Scheme 35. Synthesis of Mosher amides of L-Propargyl glycine and D, L- Propargyl glycine

As expected the ^{1}H NMR specrtum of Mosher amide of L-propargyl glycine has one set of peaks representing the presence of single isomer (L-propargyl glycine). The Mosher amide of D, L-propargyl glycine clearly showed two sets of peaks representing the presence of racemic mixture in 1:1 ratio (Figure 28).

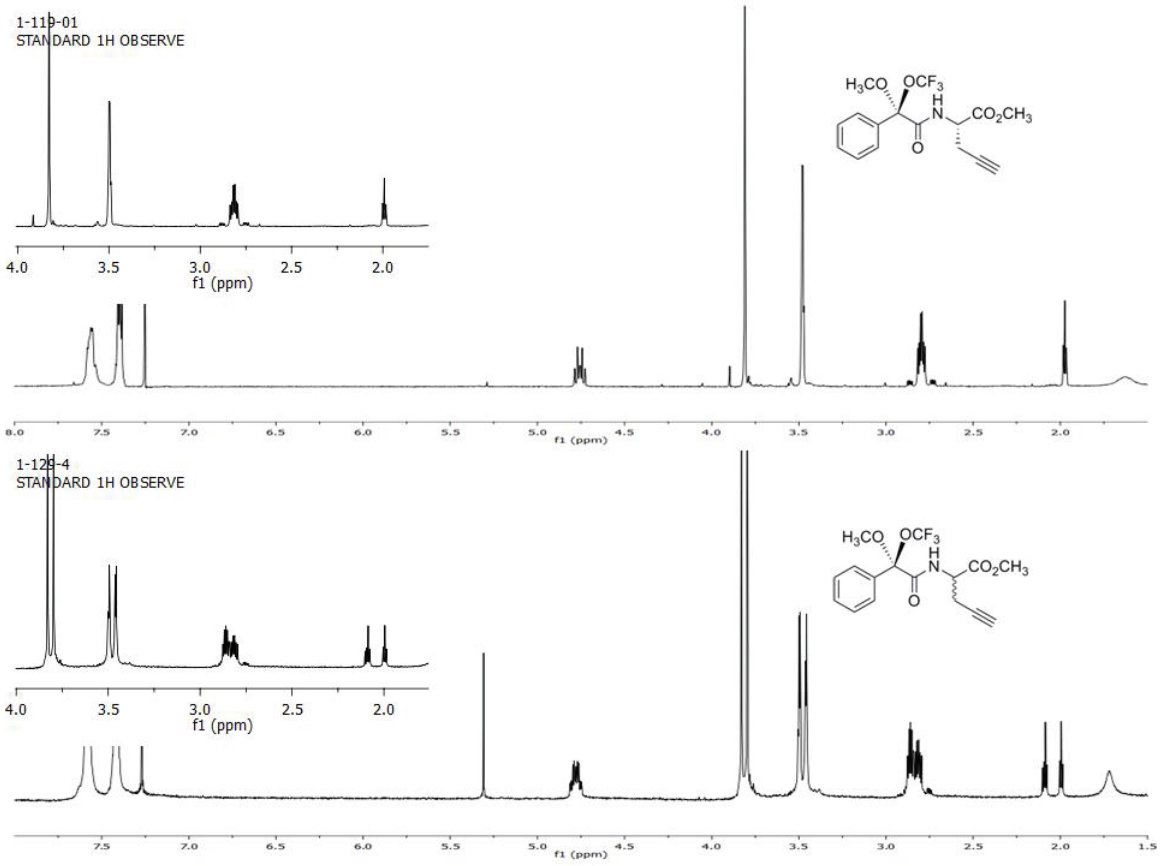
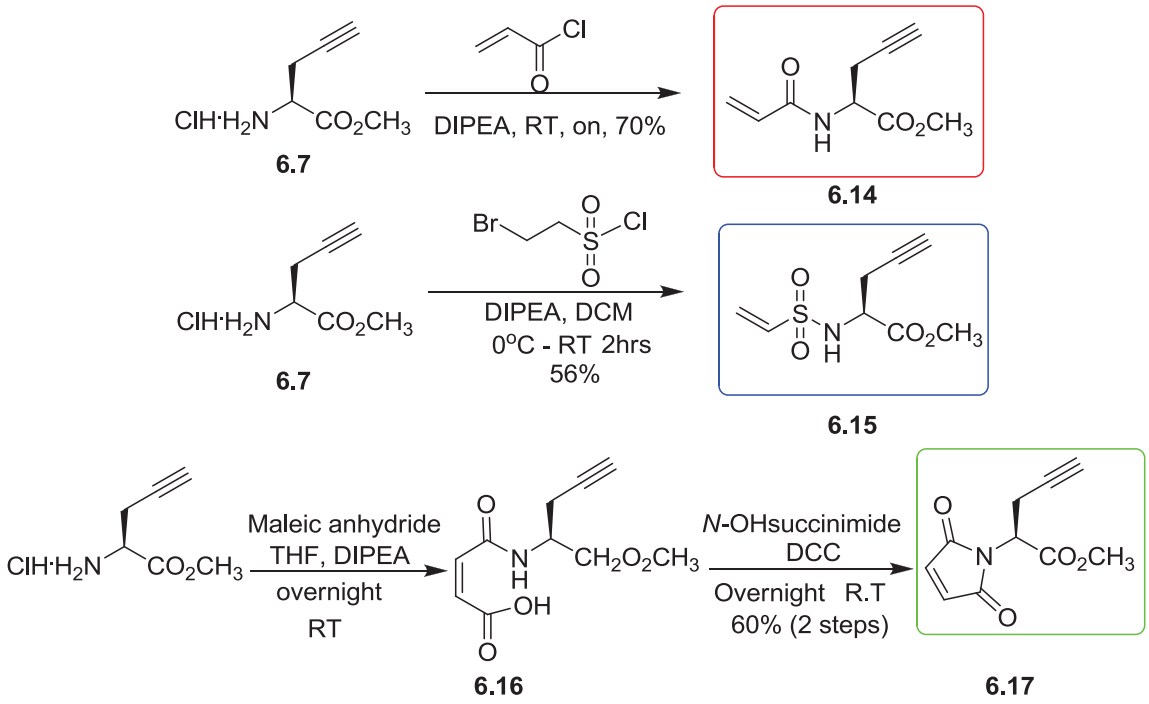


Figure 28. ^{1}H NMR of Mosher amide of L-propargyl glycine and D,L-propargyl glycine.

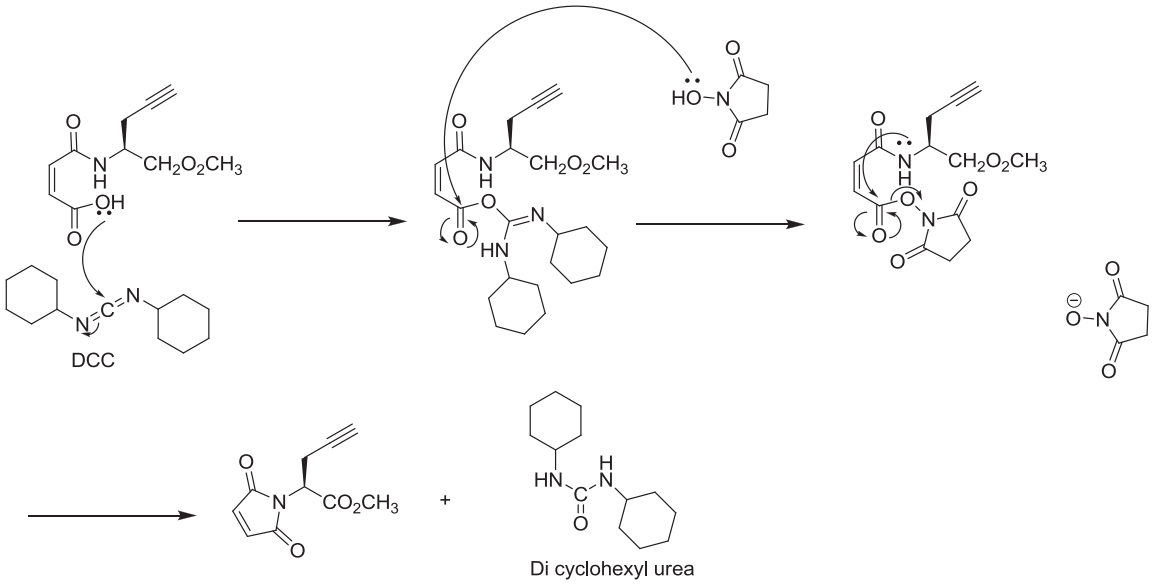
6.5 Synthesis of linkers

As mentioned in the introduction potential peptide drug candidates will be conjugated to HSA through linkers. Basically the linkers possess a thiol reacting group, and a carboxylic acid group to couple with potential peptide drug candidates. Another functionality on the linker is an alkyne group to attain a hydrophobic residue to modulate the kinetics of conjugation. The latter two steps (peptide coupling and click chemistry) were carried out in the laboratory and can be modulated any way to success. The

conjugation of peptide through the linker to HSA is the most important step in which conjuagtion must complete quickly at physiological conditions before the peptide is degraded by peptidase. Hence three types of linkers with a thiol reacting Micheal acceptor were designed and synthesized namely 1) acrylamide 2) vinyl sulfonamide 3) Maleimide. Acrylamide is synthesized from L-proargyl glycine methyl ester HCl **6.7** and acryloyl chloride in presence of base. Vinylsulfonamide is synthesized by reacting L-proargyl glycine methyl ester HCl **6.7** with 2-bromo ethanesulfonyl chloride using 3 eq of base. Maleimide is synthesized by an addition reaction between L-proargyl glycine methyl ester HCl **6.7** (Scheme 36) and maleic anhydride followed by a peptide coupling reaction as shown in the mechanism (Scheme 37).



Scheme 36. Synthesis of acrylamide, vinylsulfonamide and maleimide linkers

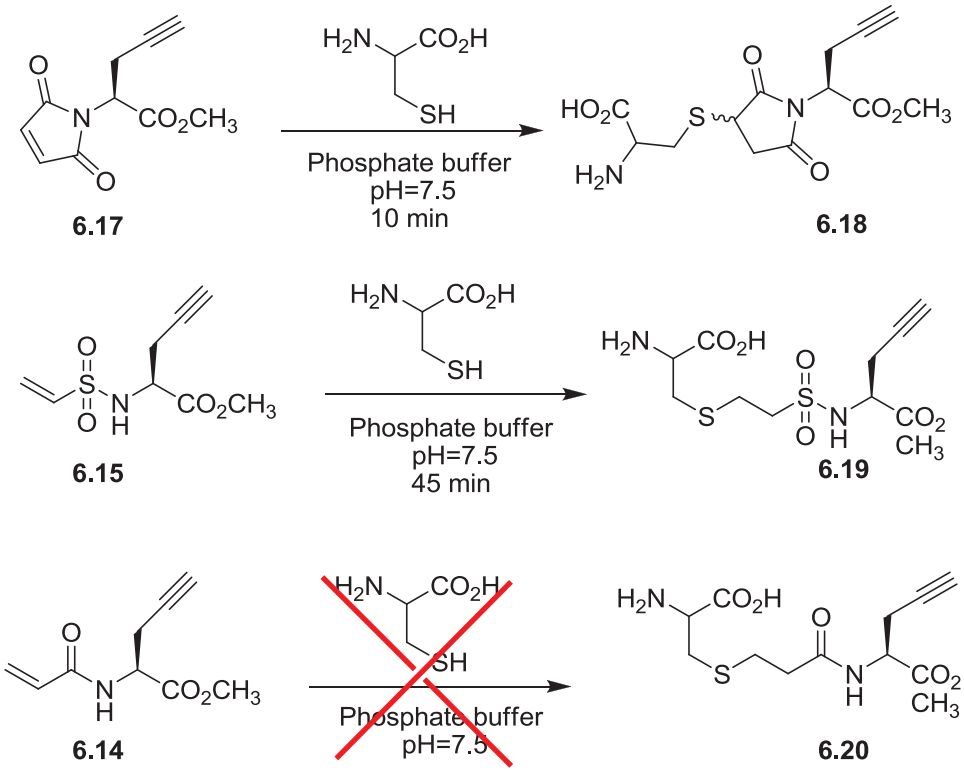


Scheme 37. Peptide coupling mechanism using DCC coupling reagent and *N*-Hydroxysuccinimide.

6.6 Reactivity

Having synthesized three kinds of linkers, the linkers were screened primarily to their reactivity towards simple thiol i.e. cysteine in physiological pH conditions, to have an approximate idea about their thiophilicity. In three round bottom flasks, the three linkers and cysteine (excess) were dissolved in phosphate buffer (pH 7.5) stirred and monitored by TLC at 10 min intervals. The maleimide linker was found to be the fastest linker by completely reacting with cysteine in under 10 min. Vinyl sulfonamide was found to be the second fastest reacting linker undergoing complete reaction in 45 min. The acryl amide did not react at all under physiological pH, and it was necessary to raise the pH to 8-8.5 for the reaction to occur (Scheme 38).

The two linkers underwent further evaluation by reacting with HSA under physiological conditions using HPLC (kinetic data) and MS-FAB characterization to monitor their reactivity with HSA with internal standards. The above concept can be applied to other drugs that need to be delivered to cancer sites either by coupling to the carboxylic acid through a peptide linkage or using click chemistry on the alkyne functionality using azide.



Scheme 38. Differential reactivity of linkers with model thiol

6.6.1 Triazole Analogs to better fit in HSA

The study also clearly revealed that there were electrostatic attractive forces involved, thus demonstrating that upon binding to hydrophobic residues, the cysteine-34

site becomes more accessible and that it is surrounded by charged amino acids.[144] A molecular model with maleimide in the binding pocket also showed a hydrophobic pocket (Figure 29). Using the third hetero alkyne functionality a small library of triazole derivatives (**6.21-6.30**) of maleimide and vinyl sulfonamides were prepared. Different azides with different length and size were used to build triazole library of compounds using the regio selective 1,3 dipolar cycloaddition reaction. Once the underivatized linkers (Figure 27) are studied for their kinetics of conjugation using human serum albumin (HSA), this library of compounds (Scheme 39) will be evaluated for the competitive conjugation against simple linkers.

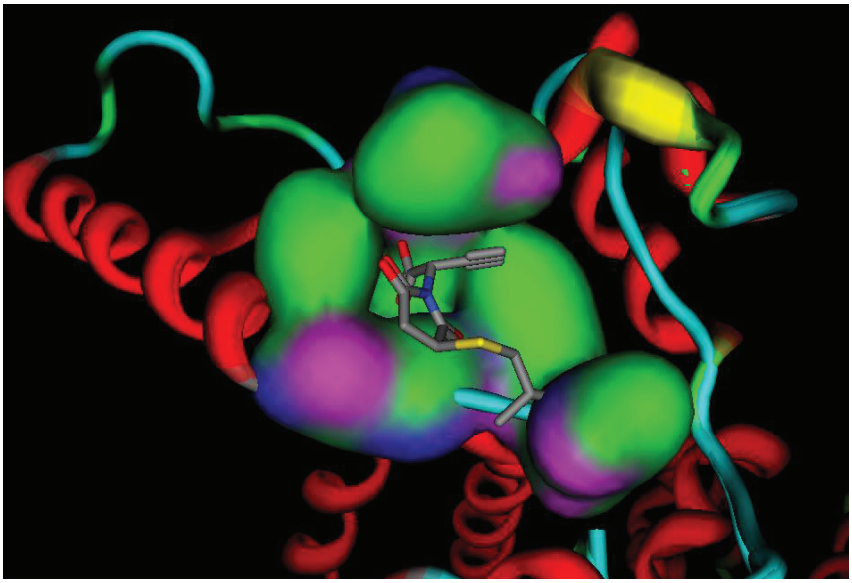
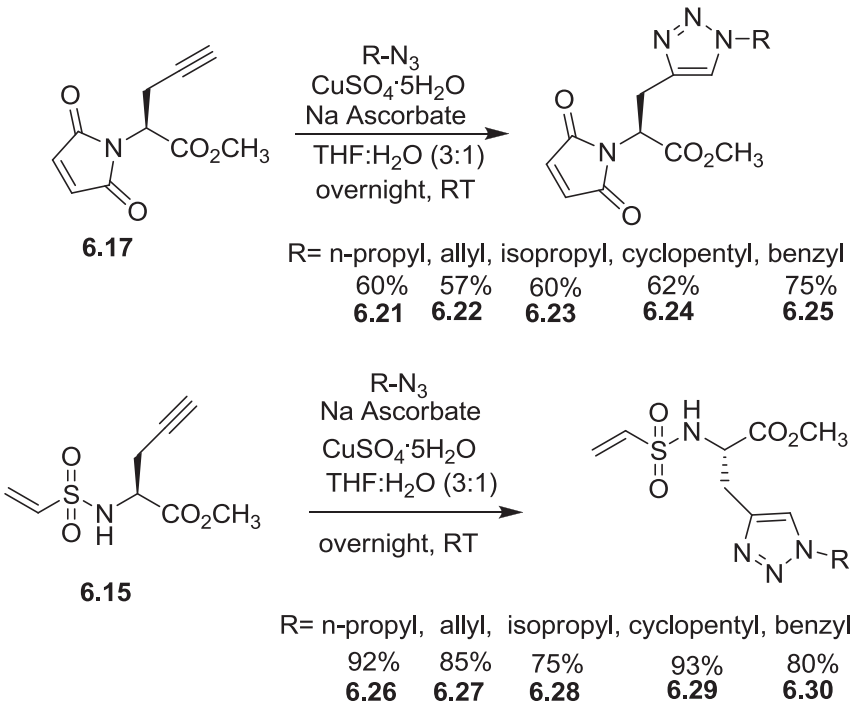


Figure 29. Hydrophobic binding pocket close to alkyne group



Scheme 39. Synthesis of triazole analogs of maleimide and vinyl sulfonamide linkers

Chapter 7

Conclusions

1. Triazole pharmacophores bearing *C*-galactopeptidomimetics were successfully synthesized using Grignard reaction, peptide coupling reaction and regio selective 1,3 dipolar cyclo addition reaction (click chemistry). All compounds and controls (lactose and galactose) were tested by inhibition of hemagglutination assay at a concentration of 1 μM of both galectins. Compound **3.17** is the best among the library with a IC_{50} of 2.5 mM (20 times better than galactose), indicating that the phenyl group close to the anomeric position increases the affinity towards Galectin-3 over Galectin-1. Methyl ester compound **3.17** found to be more potent than the free acid compound **3.22** perhaps due to balanced log P values. However this molecule needs to be further developed for better potency.

2. Synthesis of 1st generation S-galactosides using various protecting groups including acetyl, benzyl, and chloroacetyl were unsuccessful in keeping the chiral centre intact on the maleimido ring. α and β isomers of benzylated galactose thiol were isolated and the stereochemistry established using coupling constants of H1 and H2 of their acetylated derivatives.

3. *S*-galactosulfonamides using Michael addition of thiogalactoside on triazole derivatives of vinyl sulphonamides was successfully synthesized. This library of compounds under biological tests for their efficacy to inhibit galectin-1 and -3.

4. *C*-lactopeptidomimetics with a similar pharmacophores to *C*-galactopeptidomimetics were successfully synthesized to compare the disaccharide effect. In this scheme in contrast to *C*-galactopeptidomimetics lactose acid was generated directly from *C*-allyl lactose using $NaIO_4$ instead of ozonolysis followed by oxidation to acid. These *C*-lactopeptidomimetics are under biological tests for their efficacy to inhibit galectin-1 and -3.

5. *S*-lactosulfonamides with a similar pharmacophores on *S*-galactosulfonamides were successfully synthesized to compare the disaccharide effect. These *S*-lactosulfonamides are under biological tests for their efficacy to inhibit galectin-1 and -3.

6. LacNAc triazoles were successfully synthesized by regioselective glycosylation reaction between donor D-galactoside trichloroacetamidate and propargyl glucose acceptor and click chemistry. LacNAc triazoles are under evaluation to see if there is any synergic effect of triazole pharmacophore and *N*-acetyl group of LacNAc.

7. Camptothecin anti-cancer prodrug was successfully synthesized through complicated esterification of the 3^o alcohol with 6-azidohexanoic acid using $Sc(OTf)_3$. $Sc(OTf)_3$ may coordinate with the acyl pyridinium intermediate to produce highly reactive species. Acetylated galactose selectively deprotected in presence of 3^o camptothecin ester with tight control of pH of NaOMe. Camptothecin anti cancer prodrug is readily water soluble which is a key physical property of prodrug over the parent camptothecin to reduce the toxicity of the drug. The prodrug is under

biological evaluation for efficacy and toxicological studies in comparison to the parent camptothecin.

8. Chiral auxiliaries for diastereoselective 1,4-addition using alkyl cuprates were successfully synthesized and screened. Benzyl oxazolidinone found to be the best chiral auxiliary on *C*-allyl galactose for diastereoselective 1,4-addition with ds 97:3. Diastereoselectivity was primarily established using ^{1}H NMR and finally unambiguously using HPLC.

9. Three hetero tri functional ligands to conjugate peptide based anti cancer drug candidates and other biologically active molecules to human serum albumin (HSA) for improved bioavailability and pharmacokinetic properties of peptide based drug candidates were successfully synthesized. Primary screening of ligands was completed using model thiol (Cysteine) to evaluate the best Michael acceptor. Maliemide found to be the fastest reacting Michael acceptor by reacting completely in less than 10 minutes, vinyl sulfonamide stood in second place by completely reacting in 45 minutes. The acryl amide did not react at all under physiological pH, requiring pH 8-8.5 for the reaction to occur. The linkers maliemide and vinyl sulphonamides are under further evaluation to react with HSA under physiological conditions using HPLC (kinetic data) and MS-FAB characterization to monitor their reactivity with HSA with internal standards.

Chapter 8

Experimental

The nomenclature used in this thesis was adapted from "International Union of Pure and Applied Chemistry and International Union of Biochemistry and Molecular Biology (1997) Nomenclature of carbohydrates, *J. Carbohydr. Chem*., 16, 1191-1280.

8.1 General

8.1.1 Solvents

Solvents were distilled[151] as described below and stored on molecular sieves, on potassium hydroxide or calcium hydride. Dichloromethane was distilled over phosphorus pentoxide (P_2O_5). The pyridine was distilled over potassium hydroxide. Toluene was distilled over calcium hydride. THF was distilled over sodium / benzophenone and ether on lithium aluminum hydride. DMF was distilled over ninhydrin and stored over molecular sieves. Acetone was dried over calcium sulfate. Methanol is distilled over metallic sodium and stored over molecular sieves. During the stages of glycosidation and glycosylation, the solvents used were freshly distilled. The solvents used for chromatography were of ACS grade and were not distilled before use. The solvents are evaporated under reduced pressure (water pump).

8.1.2 Chromatography

The progress of reactions was followed by thin layer chromatography (TLC) plates of silica gel (Merck 60 F254) using appropriate eluents systems. The visualization

of molecules was performed different methods depending on the class of compounds and functional groups present in the molecule 1) By irradiation under UV light (λ = 254 nm). 2) By soaking in specific mixed acid (sulfuric acid/methanol/water: 5/45/45 v/v/v) 3) By oxidizing solution of molybdate (prepared from 25 g of ammonium molybdate and 10 g of ceric sulfate dissolved in 900 ml of water and 100 mL of concentrated sulfuric acid, followed by heating to 300° C.4) By soaking in $KMnO_4$ solution (prepared by mixing equal quantities of 1% $KMnO_4$ solution and 2% Na_2CO_3 soultion). The rapid chromatographic separations were performed under pressure of compressed air on a column of silica gel (Silica-P Flash Silica Gel, Silicycle) with the eluent indicated.

8.1.3 Physico-chemical analysis

8.1.3.1 General

The optical rotations were measured on a JASCO Polarimeter P-1010 and are recorded at the corresponding temperature. The lyophilization is done on a device Freeze Mobile 24 (Virtis). The nominal mass measurements are performed on an LC-MSD instrument and accurate mass measurements by high resolution mass spectrometry were performed on an LC-MSD-TOF instrument (liquid chromatography mass spectrometry time of flight) model 6210 Agilent Technologies by the Laboratory of Mass Spectrometry, University of Montreal in electrospray ionization (ESI) and the Laboratory "Analytical for organic molecules" of the University of Quebec at Montreal. The source used in the TOF-MS is electrospray in positive mode with the condition of the source (capillary 4000V for scanning; gas temperature to 350^{o} C; gas flow to 12 L / min sprayed

at 35 PSI) and, with the condition of MS (shredders to 100V; skimmer to 60V). A volume of 1 µL was injected using a mobile phase of ACN/H_2O 50% with 0.1% formic acid. The elemental analysis is performed by Elementary Analysis Laboratory at the University of Montreal.

8.1.3.2 Nuclear Magnetic Resonance spectroscopy (NMR)

The Nuclear Magnetic Resonance (NMR) spectra of proton (^1H) and carbon (^{13}C) were recorded with Varian-Gemini apparatus 2000 or Varian Innova-AS600. The ^1H spectra were recorded at a frequency of 300 MHz or 600 MHz and those of ^{13}C at 75 MHz or 150 MHz

The chemical shifts (δ) were expressed in parts per million (ppm) relative to tetramethylsilane and $CDCl_3$ internal references and solvents. Coupling constants (J) were measured in Hz. Notations used for describing spectra is as follows: s (singlet), sb (broad singlet), d (doublet), dd (doublet of doublet), m (multiplet), Harom. (aromatic protons), Cq (quaternary carbon) and Carom. (aromatic carbon).

For related compounds, the samples are analyzed after lyophilization in D_2O 99.9%. The measurements were performed in heavy water, ≥ 99.97%. The reference is used then the peak of residual water in proton spectra (calibrated by the equation δ = 5,051-0.0111T, where T is the temperature at the time of the acquisition. Acetone is used for the reference for ^{13}C spectrum (internal: methyl signal of acetone adjusted to δ = 29.8 ppm).[152]

For the protected compounds and / or the compounds soluble in chloroform, $CDCl_3$ signal is used as the reference. The signal for proton spectra calibrated to $\delta = 7.27$ ppm at whatever the temperature spectrum recorded. The central line of the $CDCl_3$ signal was calibrated for the ^{13}C spectra ($\delta = 77.0$ ppm). Bidimensional experiments, homo or heteronuclear are calibrated by analogy with the corresponding to one dimension spectrum

The protons were assigned using the correlation of two-dimensional homonuclear chemical shift type COSY (Correlated Spectroscopy) experiments. While the assignment of carbon is complemented by experiments like DEPT (Distortionless Enhancement by Polarization Transfer) which allows to differentiate quaternary carbons and secondary carbons linked to an odd number of protons (primary and tertiary carbons), APT (Attached Proton Test) which can identify the carbon linked to an even and odd number of protons and the correlation of chemical shift heteronuclear two-dimensional inverse type HETCOR (Heteronuclear Chemical Shift Correlation) to highlight two types of nuclei with different coupling between them more or less strong.

8.2 General protocols

8.2.1 General procedure for Click chemistry using $CuSO_4 \cdot 5H_2O$ (THF+H_2O)

A solution of azide (0.12 mmol), propargyl β-D-galactopyranoside (0.1 mmol), $CuSO_4 \cdot 5H_2O$ (10%) and sodium ascorbate (20%) were dissolved in a 1:1 mixture of tetrahydrofuran and water. After 12 hrs of the reaction time, reaction mixture was concentrated to remove THF and extracted with EtOAc/DCM. The organic layer washed

with satd. NH_4Cl solution (3 x 10 mL) and brine (3 x 10 mL), dried over $MgSO_4$ and concentrated to give the crude triazole product which is then purified by column chromatography.

8.2.2 General procedure for Click chemistry using $CuSO_4{\cdot}5H_2O$ (t-BuOH+H_2O)

A solution of azide (0.12 mmol), propargyl β-D-galactopyranoside (0.1 mmol), $CuSO_4{\cdot}5H_2O$ (10% wt mol) and sodium ascorbate (20% wt mol) were dissolved in a 1:1 mixture of water and t-BuOH. After 12 hrs of reaction time reaction mixture concentrated to remove THF and extracted with EtOAc/DCM. Organic layer washed with satd. NH_4Cl solution (3 x 10 mL) and brine (3 x 10 mL), dried over $MgSO_4$ and concentrated to crude triazole product purified by column chromatography.

8.2.3 General procedure for Click chemistry using CuI

To the solution of azide (0.12 mmol) and propargyl β-D-galactopyranoside (0.1 mmol) in dry THF was added *N*,*N*-diisopropylethylamine (DIPEA) (0.2 mmol,) and CuI (0.01 mmol). The reaction mixture was then allowed to stir at room temperature for 12 h. After solvent evaporation, the crude product was dissolved with ethyl acetate, washed with NH_4Cl solution (3 x 10 mL) and brine (3 x 10 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator. The residue was purified by column chromatography.

8.2.4 De-*O*-acetylation using sodium methoxide (Zemeplén)

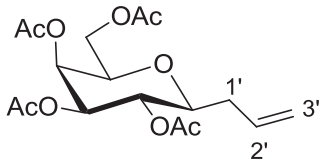
The compound is dissolved in dry MeOH (0.1M), or directly in the solution of sodium methoxide in distilled methanol (pH 10). A catalytic amount of (generally 0.1 equivalent) sodium methoxide is added, maintaining the solution at pH 9-10, and the

mixture was stirred at room temperature under nitrogen atmosphere. When the deprotection is complete, the solution is neutralized by the resin Amberlite IR-120 (H^+), filtered and concentrated. If necessary, the product was purified by column chromatography on silica gel.

8.2.5 Standard saponification procedure with LiOH solution (1M, THF:MeOH:H_2O = 3 :2 : 1)

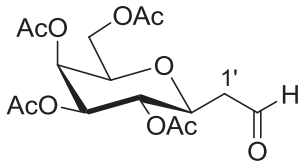
The compound is dissolved in a mixture MeOH/H_2O/THF 8:4:12 (v/v/v). LiOH/H_2O solution (1M, 1.2 eq) was added and the mixture was stirred at room temperature. When the deprotection is complete, the solution is neutralized by the resin Amberlite IR-120 (H^+), filtered, concentrated, then re-dissolved in water and lyophilized to obtain solid final product. If necessary, the product was purified by column chromatography on silica gel.

3-(Tetra-*O*-acetyl-β-D-Galactopyranosyl)-1-propene (3.3)



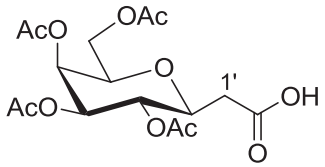
Allyl magnesium bromide (31.4 mL of a 1 M soln in ether) was added to solution of 2,3,4,6-tetra-*O*-cetyl-α-bromo-D-galactose **3.2** (1.29 g, 3.1 mmol) in THF (15 ml) at -78°C. The mixture was warmed up to 23° C within 0.5 h, then poured into H_2O (60 mL). Glacial acetic acid (6 mL) was added to dissolve the magnesium salts and the mixture was shaken with Et_2O until two separate layers were observed. Aqueous layer was evaporated to dryness and the residue was stirred overnight with Ac_2O (30 mL), pyridine (30 mL) and a catalytic amount of DMAP. After removal of the solvent , the remaining oil was diluted with EtOAc, washed with 1 M HCl soln, water, brine and dried over $MgSO_4$, The concentrated crude product was purified by silica gel column chromatography (hexane:EtOAc 3:1) to afford the compound **3.3** (538 mg, 1.4 mmol). $\mathbf{R_f}$ 0.81 (EtOAc/Hexane 6.5:3.5); $[\alpha]_D^{22}$ + 4.82 (*c* 1.0, CH_2Cl_2); **^{1}H NMR**(300 MHz, $CDCl_3$): δ5.86-5.73 (m, 1H, H-2'), 5.39 (dd, *J* = 1.0, 3.4 Hz, 1H, H-4), 5.12-4.95 (m, 4H, H-2,3 and H3'), 4.14-3.99 (m, 2H, H-6_a, 6_b), 3.83 (td, *J* = 1.0, 6.7 Hz, 1H, H-5), 3.44 (td *J* = 5.9, 10.1 Hz, 1H, H-1), 2.34-2.22 (m, 2H, H-1'), 2.12 (s, 3H), 2.02 (s, 6H), 1.94 (s,3H), all OAc. **^{13}C NMR** (75 MHz, $CDCl_3$): δ170.24, 170.14, 170.04, 169.56, 133.20, 117.26, 77.69, 74.05, 72.16, 69.21, 67.70, 61.50, 35.95, 20.67-20.46 ppm. **MS (ESI)** calcd for $C_{17}H_{24}O_9$ + $[H]^+$: 373.14, found 373.1.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl ethanaldehyde (3.5)



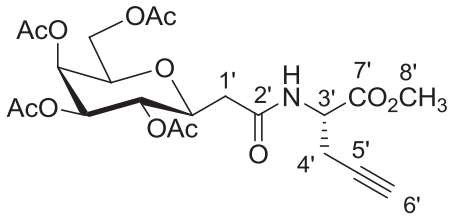
Compound **3.3** (1.3 g, 3.4 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL) and cooled to -78°C. Ozone was bubbled through the solution until no starting material was left (approximately 1 hr). The mixture was deozonized by bubbling nitrogen gas through the solution until it was clear. 5 mL of dimethyl sulfide was added and allowed the reaction mixture to obtain RT and stirred overnight. Rotary evaporated the reaction mixture and flashed the crude product by column chromatography using 10-20% of EtOAc in Hexane to obtain aldehyde **3.5** (1.006 g, 2.6 mmol); $\mathbf{R}_f$ 0.43 (EtOAc/Hexane 6.5:3.5); $[\alpha]_D^{22}$ + 14.66 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 9.75 (t, *J* = 1.8 Hz, 1H, -C(0)H), 5.46 (dd, 1H, *J* = 0.93, 3.3 Hz, 1H, H-4), 5.18 – 5.10 (m, 1H, H-2), 5.08 (dd, *J* = 10.1, 3.3 Hz 1H, H-3), 4.11- 4.05 (m, 2H, H-6_a, H-6_b), 4.02 – 3.97 (m, 1H, H-1), 3.95 (dd, *J* = 7.11, 10.6 Hz, 1H, H-5), 2.78 (ddd, *J* = 8.2,16.9Hz, 1.8Hz, 1H,CH_aH_b), 2.60 (ddd, *J* = 3.7, 1.6Hz, 1H, CHaHb), 2.18,2.05,2.04,2.00 (4S,3H each,-C(O)CH_3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 198.69, 170.80-170.01 (4C), 74.45, 73.42, 71.84, 68.95, 67.65, 61.70, 45.59, 20.75 (4C); **MS (ESI)** calcd for $C_{16}H_{22}O_{10}$+ $[H]^+$: 375.33, found 375.3.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl ethanoic acid (3.6)



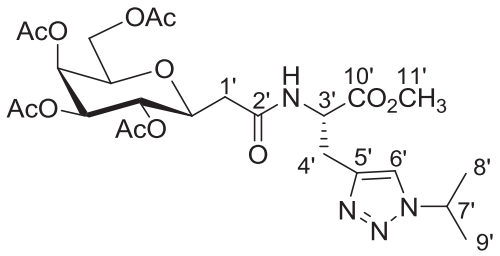
To a solution of compound **3.5** (1.013 g, 2.7 mmol) in acetone 2 mL of $CrO_3{\cdot}H_2SO_4$ was added drop wise at 0^oC and stirred for 1.5 hrs, then 10 mL of Isopropyl alcohol was added the reaction mixture concentrated to half and a small amount of 0.1 N HCl added then extracted with EtOAc. The organic layers were combined and washed with water, brine and dried over $MgSO_4$ and concentrated to dry to obtain **3.6** (0.89 g, 2.2 mmol). $\mathbf{R_f}$ 0.31 Streak (CH_2Cl_2/Methanol 9.5:0.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 5.48 (dd, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 0.9 Hz, 1H, H-4), 5.17 (dd, $J_{1,2} = J_{2,3}$ = 10.0Hz. 1H, H-2), 5.08 (dd, J = 10.1, 3.2 Hz, 1H, H-3), 4.15-4.10 (m, 2H, H-6a, H-6b), 3.96-3.90 (m, 2H, H-1, H-5), 2.70-2.56 (m, 2H, CHaHb), 2.16, 2.14, 2.11, 2.02 (4sing, 3H each, -C(O)CH_3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171-170 (5C), 74.67, 74.22, 71.55, 68.73, 67.19, 60.97, 36.82, 21.39-21.10 (4C); **MS (ESI)** calcd for $C_{16}H_{22}O_{11}$ + (H^+): 391.11, found 391.1.

Compound 3.7



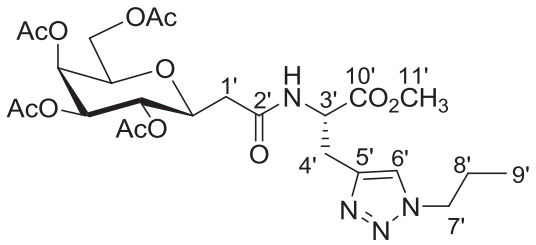
To a solution of compound **3.6** (0.89 g, 2.2 mmol), L-propargyl glycine methyl ester HCl (0.559 g, 3.4 mmol) and BOP reagent (1.21 g, 2.7 mmol) in dry THF under nitrogen atmosphere was added DIPEA (1.0 g, 7.9 mmol) drop wise and reaction mixture left to stir overnight. The reaction mixture oncentrated and then dissolved in CH_2Cl_2 and washed with 1M $KHSO_4$, $NaHCO_3$ and brine solution and dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography using 10-30% EtOAc in Hexanes to obtain **3.7** (0.608 g, 1.3 mmol); $\mathbf{R}_f$ 0.39 (EtOAc/Hexane 6.5:3.5); $[\alpha]_D^{22}$ + 56 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 6.9 (d, 1H, NH), 5.36 (d *J* = 3.3, 1H, H-4), 5.05 (dd, *J* = 10.1, 3.3 Hz, H-2, 2H, H-3), 4.84 - 4.71 (m, 1H, H-3'), 4.24 - 4.04 (m, 2H, H-6_a,H-6_b), 3.96 (dd, *J* = 7.9, 6.7 Hz, 1H, H-5), 3.92 - 3.85 (m, 1H, H-1), 3.71 (s, 3H, H-8'), 2.84 - 2.76 (m, 2H, H-4'), 2.54 - 2.46 (m, 2H, H-1'), 2.07, 1.97, 1.94, 1.89 (4S,3H each,-C(O)CH_3), 2.02-2.00 (m, 1H, H-6'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ170.67, 170.55-170.62 (O<u>C</u>OCH_3, C=O), 169.24, 78.61, 75.39, 74.40, 71.90, 68.70, 67.69, 61.55, 52.88, 50.79, 38.90, 22.43, 20.84-20.68 (OCO<u>C</u>H_3); **MS (ESI)**calcd for $C_{22}H_{29}NO_{12}$ + $[H]^+$: 500.16, found 500.1.

Compound 3.8



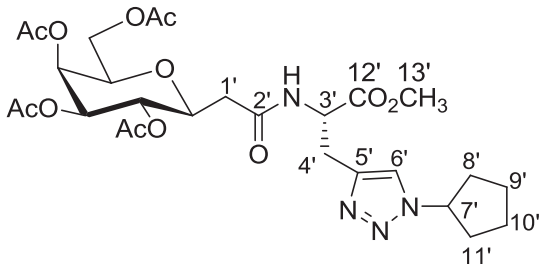
To a solution of compound **3.7** (0.166 g, 332 μmol) in THF:H_2O (3:1.5) 4.5 mL, isopropyl azide (0.056 g, 664 μmol) $CuSO_4.5H_2O$ (0.0122 g 20%) and sodium ascorbate (0.0263 g, 40%) were added and after 12h of reaction time following the general procedure (**7.2.1**) described above, β-D-galactopyranoside **3.8** (0.145 g, 249 μmol) was obtained. $\mathbf{R}_f$ 0.21 (EtOAc/Hexane 7.5:2.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.35(s, 1H, H- 6'), 7.2 (d, 1H, *J* = 8.79 Hz, NH), 5.45 (d, *J* = 2.9 Hz, 1H, H-4), 5.11-5.05 (m, 2H, H-2, H-3), 4.9-4.88 (m, 1H, H-3'), 4.81-4.72 (m, 1H, H-7'), 4.06-4.01 (m, 3H, H-5, H-6a,6b), 3.93-3.86 (m, 1H, H-1), 3.69 (s, 3H, H-11'), 3.24-3.22 (m, 2H, H-4'), 2.46-2.45 (m, 2H, H-1'), 2.13, 2.03, 1.99, 1.97 (4s, 3H each,-C(O)CH3), 1.55 (dd, *J* = 1.09, 5.76 Hz, 6H, H-8', H-9'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.49, 170.52, 170.44, 170.29,170.05 (OCOCH3, C=O), 169.37, 142.64, 119.69, 75.26 , 74.32, 72.09, 68.77, 67.73, 61.36, 53.13, 52.66, 51.96, 38.92, 27.93, 23.13-20.847 (OCOCH3), 20.787; **MS (ESI)** calcd for $C_{25}H_{36}N_4O_{12}$ + $[H]^+$: 585.23, found 585.3.

Compound 3.09



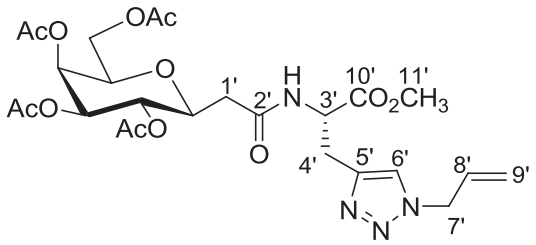
To a solution of compound **3.7** (0.15 g, 300 μmol) in THF:H_2O (3:1.5) 4.5 mL, n-propyl azide (0.051 g, 600 μmol) $CuSO_4.5H_2O$ (0.015 g 20%) and sodium ascorbate (0.024 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-galactopyranoside **3.9** (0.128g, 219 μmol) was obtained. **Rf** 0.25 (EtOAc/Hexane 7.5:2.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.28 (s, 1H, H-6'), 7.13 (d, *J* = 7.96 Hz, 1H, NH), 5.40 (d, *J* = 2.47 Hz, 1H, H-4), 5.10-4.97 (m, 2H, H-2, H-3), 4.86-4.84 (m, 1H, H-3'), 4.23 (t, *J* = 7.14Hz, 1H, H-7'), 4.06-3.96 (m, 3H, H-5, H-6a, H-6b), 3.90-3.86 (m, 1H, H-1), 3.65 (s, 3H, H-11'), 3.20-3.17 (m, 2H, H-4'), 2.44-2.40 (m, 2H, H-1'), 2.09, 1.99, 1.92, 1.90 (4S, 3 H each,-C(O)CH3), 1.87-1.77 (m, 2H, H-8'), 0.88 (t, *J* = 7.41Hz, 3H, H-9'); **^{13}C NMR ($CDCl_3$, 75 MHz):** δ171.46, 170.53, 170.44, 170.29, 170.06 (OCOCH3, C=O), 169.35, 142.81, 122.06, 75.26, 74.33, 72.08, 68.76, 67.73, 61.37, 52.69, 52.06, 51.98, 38.93, 27.89, 23.13, 20.94-20.787 (4C,OCOCH3), 11.18; **MS (ESI)** calcd for $C_{25}H_{36}N_4O_{12}$ + $[H]^+$: 585.23, found 585.3.

Compound 3.10



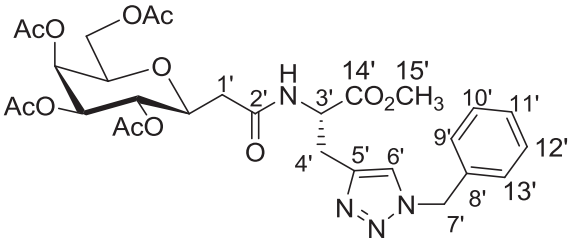
To a solution of compound **3.7** (0.15 g, 300 μmol) in THF:H_2O (3:1.5) 4.5 mL, cyclopentyl azide (0.066 g, 600 μmol) $CuSO_4.5H_2O$ (0.011 g 20%) and sodium ascorbate (0.024 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-galactopyranoside **3.10** (0.119 g, 195 μmol) was obtained; $\mathbf{R}_f$ 0.27 (EtOAc/Hexane 7.5:2.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.28 (s, 1H, H-6'), 7.16 (d, *J* = 7.96 Hz, 1H, NH), 5.40 (dd, *J* = 0.82, 3.29 Hz, 1H, H-4), 5.06-5.00 (m, 2H, H-2, H-3), 4.86-4.82 (m, 2H, H-3', H-7'), 4.06-3.96 (m, 3H, H-5, H-6a,6b), 3.88-3.81 (m, 1H, H-1), 3.65 (s, 3H, H-13'), 3.18-3.14 (m, 2H, H-4'), 2.43-2.40 (m, 2H, H-1'), 2.17 (m, 2H, H-8'), 2.08, 1.98, 1.94, 1.92 (4x, 3 H each,-C(O)CH_3), 1.85 - 1.80 (m, 4H, H-9', H-10'), 1.72-1.70 (m, 2H, H-11'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.49, 170.50-170.04 ($OCOCH_3$, C=O), 169.36, 142.67, 120.72, 75.25, 74.32, 72.09, 68.77, 67.73, 61.98, 61.36, 52.66, 51.94, 38.92, 33.54, 27.90, 24.21, 20.93-20.78 (4C, $OCOCH_3$); **MS (ESI)** calcd for $C_{27}H_{38}N_4O_{12}$ + $[H]^+$: 611.24, found 611.3.

Compound 3.11



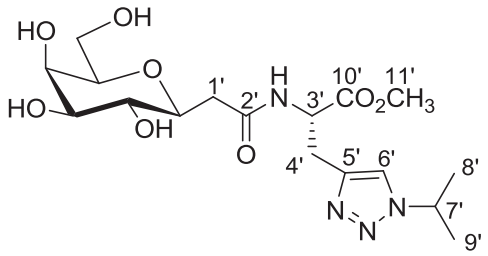
To a solution of compound **3.7** (0.15 g, 300 μmol) in THF:H_2O (3:1.5) 4.5 mL, allyl azide (50 mg, 600 μmol) $CuSO_4.5H_2O$ (15 mg 20%) and sodium ascorbate (24 mg, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-galactopyranoside **3.11** (99 mg, 171 μmol) was obtained; $\mathbf{R}_f$ 0.62 (CH_2Cl_2/MeOH 9.5 : 0.5); $[\alpha]_D^{22}$ + 10.08 (c 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.35 (s, 1H, H- 6'), 7.2 (d, *J* = 8.79 Hz, 1H, NH), 6.01-5.85 (m, 1H, H-8'), 5.45 (d, *J* = 3.02 Hz, 1H, H-4), 5.27 (dd, *J* = 10.16, 10.98 Hz, 2H, H-9'), 5.07-5.00 (m, 2H, H-2, H-3), 4.91-4.81 (m, 3H, H-3',H-7'), 4.00-3.96 (m, 3H, H-5, H-6a,6b), 3.95-3.90 (m, 1H, H-1), 3.66 (S, 3H, H-11'), 3.21 (Brs, 2H, H-4') 2.44-2.41 (m, 2H, H-1'), 2.09-1.92 (4s, 3H each,-C(O)CH3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.40, 170.52-170.05 (OCOCH3, C=O), 169.36, 143.06, 131.39, 122.14, 120.34, 75.25, 74.30, 72.04, 68.72, 67.71, 61.35, 52.87, 52.73, 51.94, 38.90, 27.83, 20.95-20.79 (OCOCH3); **MS (ESI)** calcd for $C_{25}H_{34}N_4O_{12}$ + $[H]^+$: 583.57, found 583.4.

Compound 3.12



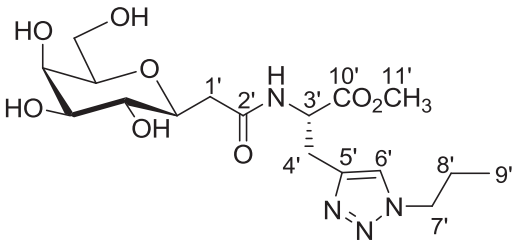
To a solution of compound **3.7** (0.166 g, 330 μmol) in THF: H_2O (3: 1.5) 4.5 mL, benzyl azide (0.088 g, 664 μmol) $CuSO_4.5H_2O$ (0.0122 g 20%) and sodium ascorbate (0.026 g, 40%) were added and after 12 hrs of reaction time following the general procedure described above, β-D-galactopyranoside **3.12** (0.130 g, 0.088 g, 205 μmol) was obtained. **R_f** 0.67 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{22}$ - 5.32 (*c* 0.1, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.34 - 7.32 (m, 3H, H-6 and aryl-H), 7.22 - 7.18 (m, 3H, Aryl-H), 7.10 (d, *J* = 7.96 Hz, 1H, NH), 5.38 (dd, *J* = 1.09, 3.29 Hz, 1H, H-4), 5.06 - 4.96 (m, 2H, H-2, H-3), 4.85 - 4.82 (m, 1H, H-3'), 4.03 - 3.98 (m, 2H, H-6a, H-6b), 3.89 - 3.81(m, 2H, H-5, H-1), 3.61 (s, 3H, H-15'), 3.16 (d, *J* = 5.22 Hz, 2H, H-4'), 2.43 - 2.39 (m, 2H, H-1'), 2.10, 2.00, 1.97, 1.93 (4s, 3H each,-C(O)CH3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.38, 170.51, 170.41, 170.26, 170.02 (OCOCH3, C=O), 169.30, 143.35, 134.88, 129.32-128.16 (Aryl-C), 122.12, 75.25, 74.32, 72.03, 68.75, 67.73, 61.37, 54.27, 52.65, 51.95, 38.92, 27.95, 20.95, 20.85, 20.79 (4C, OCOCH3); **MS (ESI)** calcd for $C_{29}H_{36}N_4O_{12}$ + $[H]^+$: 633.23, found 633.3.

Compound 3.13



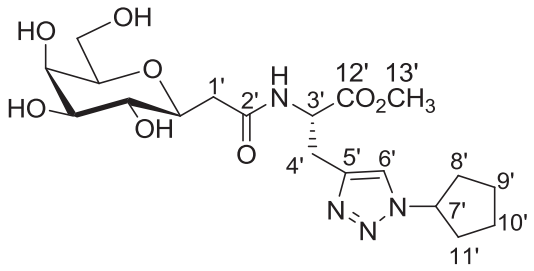
To a solution of compound **3.8** (0.046 g, 78 μmol) in 3 mL of dry methanol, 1M NaOMe solution added until the reaction mixture reached pH of 9-10, within 4 hrs of reaction time following the general procedure (**7.2.4**) described above to obtain deprotected β-D-galactopyranoside **3.13** (22 mg, 53 μmol); $\mathbf{R}_f$ 0.20 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{24}$ + 28.64 (*c* 1.0, CH_3OH); **^{1}H NMR** (CD_3OD, 300 MHz): δ 7.72 (s, 1H, H-6'), 4.63 - 4.59 (m, 1H, Hz, H-3'), 4.22 – 4.19 (m, 1H, H-7'), 3.61 (bs, 1H, H-4), 3.61 (s, 3H, H-11'), 3.55 - 3.52 (m, 1H), 3.38 - 3.35 (m, 1H), 3.32 - 3.27 (m, 2H), 3.20 - 3.17 (m, 2H), 3.12 - 3.05 (m, 1H), 2.62 (dd, 1H), 0.80 (d, *J* = 6.7 Hz, 6H, H-8', H-9'); **^{13}C NMR** (CD_3OD, 75 MHz): δ 173.87, 172.77, 143.84, 124.79, 80.39, 78.51, 76.13, 72.07, 70.92, 62.85, 53.66, 53.04, 52.96, 39.72, 28.54, 22.07; **MS** (**ESI)** calcd for $C_{17}H_{28}N_4O_8$ + $[H]^+$: 417.19, found 417.3.

Compound 3.14



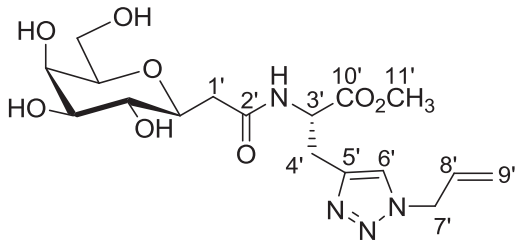
To a solution of compound **3.9** (0.101 g, 172 μmol) in 3 mL of dry methanol 1M NaOMe solution added until the reaction mixture reached pH of 9-10, within 4 hrs of reaction time following the general procedure (**7.2.4**) described above to obtain the deprotected β-D-galactopyranoside **3.14** (57 mg, 138 μmol); $\mathbf{R}_f$ 0.24 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{24}$ - 7.56 (*c* 0.5, CH_3OH); **^{1}H NMR** (CD_3OD, 300 MHz): δ 7.71 (s, 1H, H-6'), 4.63 (t, *J* = 5.41 Hz, 1H, H-3'), 4.22 (t, *J* = 7.41 Hz, 2H, H-7'), 3.60 (bs, 1H, H-4), 3.60 (s, 3H, H-11), 3.55 - 3.52 (m, 1H), 3.38 - 3.35 (m, 1H), 3.32 - 3.27 (m, 2H), 3.20 - 3.17 (m, 2H), 3.12 - 3.05 (m, 1H), 2.62 (dd, *J* = 2.19, 12.63 Hz, 1H), 2.23 - 2.28 (m, 2H, H-8'), 0.80 (t, 3H, *J* = 7.41 Hz, H-9'); **^{13}C NMR** (CD_3OD, 75 MHz): δ 173.85, 172.75, 143.82, 124.77, 80.37, 78.48, 76.11, 72.05, 70.90, 62.83, 53.64, 53.02, 52.94, 39.70, 28.52, 24.67, 11.22; **MS (ESI)** calcd for $C_{17}H_{28}N_4O_8$ + $[H]^+$: 417.19, found 417.2.

Compound 3.15



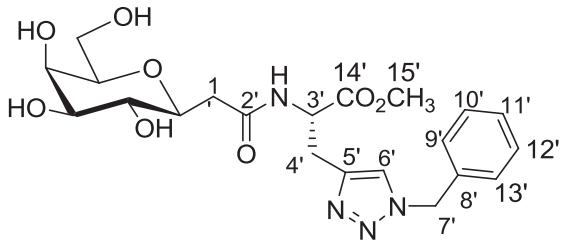
To a solution of compound **3.10** (0.087 g, 142 mmol) in 3 mL of dry methanol 1M NaOMe solution added until the reaction mixture reached pH of 9-10, within 4 hrs of reaction time following the general procedure (**7.2.4**) described above to obtain the deprotected β-D-galactopyranoside **3.15** (58 mg, 131 μmol); $\mathbf{R}_f$ 0.21 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{24}$ + 19.31 (*c* 1.0, CH_3OH); **^{1}H NMR** (CD_3OD, 300 MHz): δ 7.71 (s, 1H, H-6'), 4.87 - 4.82 (m, 1H, H-7'), 4.66 - 4.62 (m, 1H, H-3'), 3.61 (d, *J* = 1.64 Hz, 1H, H-4), 3.61 (s, 3H, H-13'), 3.56 - 3.52 (m, 1H), 3.38 - 3.34 (m, 1H), 3.31 - 3.31 (m, 2H), 3.20 - 3.18 (m, 2H), 3.10 - 3.04 (m, 1H), 2.62 (dd, *J* = 2.19, 16.48 Hz, 1H), 2.41 - 2.33 (m, 1H, H-1), 2.11 - 2.10 (m, 2H, cyclopentyl-CH_2), 1.95 - 1.89 (m, 2H, cyclopentyl-CH_2), 1.80 - 1.75 (m, 2H, cyclopentyl-CH_2), 1.67-1.63 (m, 2H,cyclopentyl-CH_2); **^{13}C NMR** (CD_3OD, 75 MHz): δ173.83, 172.82, 143.76, 123.39, 80.34, 78.46, 76.11, 72.04, 70.85, 63.33, 62.77, 53.65, 52.93, 39.67, 34.24, 28.57, 25.04; **MS** (**ESI)** calcd for $C_{19}H_{30}N_4O_8$ + $[H]^+$: 443.20, found 443.3.

Compound 3.16



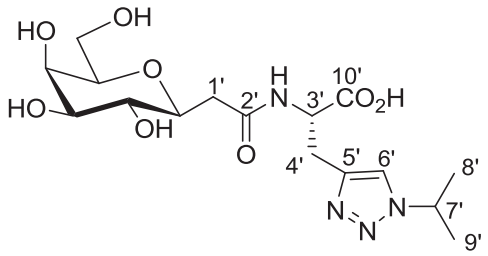
To a solution of compound **3.11** (0.131 g, 225 μmol) in 3 mL of dry methanol, 1M NaOMe solution added until the reaction mixture reached pH of 9-10, within 4 hrs of reaction time following the general procedure (**7.2.4**) described above to obtain deprotected β-D-galactopyranoside **3.16** (73 mg, 175 μmol); $\mathbf{R}_f$ 0.22 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{24}$ + 19.71 (*c* 1.0, CH_3OH); **^{1}H NMR** (CD_3OD, 300 MHz): δ 8.24 (d, *J* = 7.69Hz, 1H, NH), 7.68 (s, 1H, H-6'), 5.95 - 5.90 (m, 1H, H-8'), 5.14 (qd, *J* = 1.3, 10.43 Hz, 2H, H-9'), 5.03 - 4.95 (m, 2H, H-7'), 4.63 - 4.75 (m, 1H, H-3'), 3.68 (dd, *J* = 0.82, 1.92 Hz, 1H, H-4), 3.60 (s, 3H, H-11'), 3.57 - 3.48 (m, 1H), 3.39 - 3.34 (m, 1H), 3.3 - 3.30 (m, 1H), 3.19 - 3.17 (m, 1H), 3.12 - 3.00 (m, 2H) 2.16 - 2.59 (m, 1H), 2.31 (dd, *J* = 14.8, 8.9 Hz, 1H, H-1); **^{13}C NMR** (CD_3OD, 75 MHz): δ 173.80, 172.77, 144.12, 132.27, 124.67, 119.66, 80.25, 78.38, 76.02, 72.06, 70.81, 62.74, 53.60, 53.47, 52.97, 39.64, 28.51; **MS (ESI)** calcd for $C_{17}H_{26}N_4O_8$ + $[H]^+$: 415.17, found 415.3.

Compound 3.17



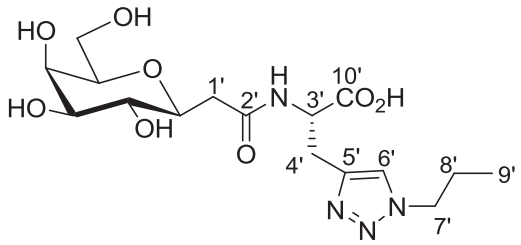
To a solution of compound **3.12** (0.100 g, 158 μmol) in 3 mL of dry methanol, 1M NaOMe solution is added until the reaction mixture reached pH of 9-10, within 4 hrs of reaction time following the general procedure (**7.2.4**) described above to obtain deprotected β-D-galactopyranoside **3.17** (59 mg, 126 μmol). $\mathbf{R}_f$ 0.24 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{24}$ + 9.05 (*c* 1.0, CH_3OH); **^{1}H NMR** (CD_3OD, 300 MHz): δ 8.20 (d, *J* = 8.10 Hz, 1H, NH), 7.70 (s, 1H, H-6'), 7.28 - 7.17(m, 5H, Aryl-H), 5.58 - 5.48 (m, 2H, H-7'), 4.64 - 4.62 (m, 1H, H-3'), 3.61 (d, *J* = 1.64 Hz, 1H, H-4), 3.59 - 3.45 (m, 1H), 3.61 (s, 3H, H-15'), 3.56 - 3.52 (m, 2H), 3.39 - 3.30 (m, 2H), 3.28 - 3.25 (m, 2H), 3.19 - 3.05 (m, 1H), 2.62 (d, *J* = 14.97 Hz, 1H), 2.39 - 2.31 (m, 1H, H-1); **^{13}C NMR** (CD_3OD, 75 MHz): δ 173.84, 172.81, 144.44, 136.96, 130.04 - 128.97 (Aryl-C), 124.73, 80.40, 78.42, 76.02, 72.02, 70.90, 62.85, 54.81, 53.77, 52.89, 39.67, 28.56; **MS (ESI)** calcd for $C_{21}H_{28}N_4O_8$ + $[H]^+$: 465.19, found 465.3.

Compound 3.18



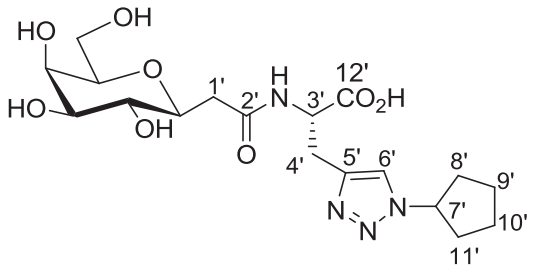
To a solution of compound **3.13** (32 mg, 76 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M soln of LiOH. (3.8 mg, 92 μmol) followed by the general saponification procedure (**7.2.5**) described above to obtain **3.18** (26 mg, 65 μmol); $\mathbf{R}_f$ 0.37 (CH_3CN/H_2O 8:2); $[\alpha]_D^{24}$ + 25.54 (*c* 1.0, H_2O); **^{1}H NMR** (D_2O, 300 MHz): δ 7.90 (s, 1H, H-6'), 4.72 - 4.63 (m, 1H, H-3'), 4.72 - 4.66 (m, 1H, H-7'), 3.93 (d, *J* = 3.29 Hz, 1H, H-4), 3.70 (d, *J* = 7.41 Hz, 1H), 3.63 - 3.48 (m, 4H), 3.44 - 3.38 (m, 1H), 3.27 - 3.14 (m, 2H), 2.76 (dd, *J* = 2.33, 15.5 Hz, 1H), 2.43 (dd, *J* = 9.33, 5.76 Hz, 1H), 1.86 - 1.81 (m, 1H), 2.62 (dd, 1H), 1.51 (d, *J* = 6.7 Hz, 6H, H-8', H-9'); **^{13}C NMR** (D_2O, 75 MHz): δ 173.98, 173.33, 142.88, 122.18, 78.71, 76.85, 74.14, 70.67, 69.26, 61.27, 67.93, 53.9, 38.49, 27.34, 22.31; **MS (ESI)** calcd for $C_{16}H_{26}N_4O_8$ + $[H]^+$: 403.17, found 403.3.

Compound 3.19



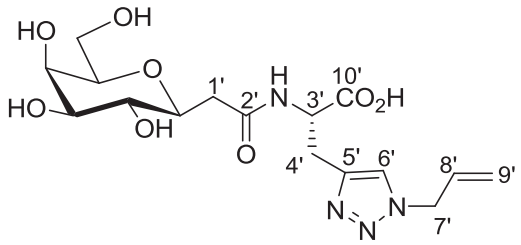
To a solution of compound **3.14** (25 mg, 60 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M soln of LiOH (3 mg, 71μmol) followed by the general saponification procedure (**7.2.5**) described above to obtain **3.19** (23 mg, 57 μmol); $\mathbf{R_f}$ 0.33 (CH_3CN/H_2O 8:2); $[\alpha]_D^{24}$ + 20.63 (*c* 1.0, H_2O); **^{1}H NMR** (D_2O, 300 MHz): δ 8.01 (s, 1H, H-6'), 4.75 - 4.71 (m, 1H, H-3'), 4.39 (t, *J* = 7.00 Hz, 2H, H-7'), 3.93 (d, *J* = 2.88 Hz, 1H, H-4), 3.65 - 3.50 (m, 4H), 3.45 - 3.36 (m, 1H), 3.32 - 3.30 (m, 1H), 2.77 (dd, *J* = 2.61, 15.10 Hz, 1H), 2.43 (dd, *J* = 5.90, 9.20, Hz, 1H) 1.95 - 1.83 (m, 2H, H-8'), 0.82 (t, *J* = 7.41 Hz, 3H, H-9'); **^{13}C NMR** (D_2O, 75 MHz): δ 173.60, 173.48, 142.06, 125.14, 78.61, 76.76, 73.99, 70.59, 69.18, 61.24, 52.78, 52.36, 38.45, 26.75, 23.12, 10.24; **MS (ESI)** calcd for $C_{16}H_{26}N_4O_8$ + $[H]^+$: 403.17, found 403.3.

Compound 3.20



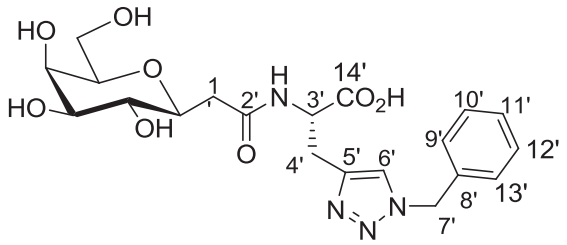
To a solution of compound **3.15** (50 mg, 113 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M soln of LiOH (5.6 mg, 135 μmol) followed by the general saponification procedure (**7.2.5**) described above to obtain **3.20** (42 mg, 99 μmol); $\mathbf{R}_f$ 0.31 (CH_3CN/H_2O 8:2); $[\alpha]_D^{24}$ + 47.22 (*c* 1.0, H_2O); **^{1}H NMR** (D_2O, 300 MHz): δ 7.98 (s, 1H, H-6'), 5.00 - 4.96 (m, 1H, H-3'), 4.37 - 4.71 (m, 1H, H-7') 3.91 (d, 1H, *J* = 3.29 Hz, H-4), 3.63 - 3.59 (m, 2H), 3.58 - 3.47 (m, 2H), 3.43 - 3.37 (m, 1H), 3.30 - 3.26 (m, 2H), 3.24 - 3.16 (m, 1H), 2.75 (d, *J* = 14.69 Hz, 1H), 2.40 (dd, 1H, *J* = 5.63, 8.92 Hz), 2.26 - 2.17 (m, 2H, cyclopentyl-CH_2), 1.97 -1.89 (m, 2H, cyclopentyl-CH_2), 1.78 - 1.67 (m, 4H, cyclopentyl-CH_2); **^{13}C NMR** (D_2O, 75 MHz): δ 173.71, 173.47, 142.09, 123.61, 78.60, 76.78, 74.01, 70.59, 69.17, 63.05, 61.20, 52.42, 38.45, 32.96, 26.88, 23.75; **MS (ESI)** calcd for $C_{18}H_{28}N_4O_8$ + $[H]^+$: 429.19, found 429.3.

Compound 3.21



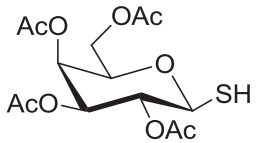
To a solution of compound **3.16** (40 mg, 96 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M soln of LiOH. (4.8 mg, 115μmol) followed by the general saponification procedure (**7.2.5**) described above to obtain **3.21** (34 mg, 86 μmol); $\mathbf{R}_f$ 0.34 (CH_3CN/H_2O 8:2); $[\alpha]_D^{24}$ - 89.11 (*c* 1.0, H_2O); **^{1}H NMR** (D_2O, 300 MHz): δ 7.94 (s, 1H, H-6'), 6.08 - 5.98 (m, 1H, H-8'), 5.32 (d, 1H, *J* = 9.88 Hz, H-9_a'), 5.16 (d, *J* = 17.03 Hz, 1H, H-9_b'), 5.01 (d, *J* = 5.90 Hz, 2H, H-7'), 4.74 - 4.72 (m, 1H, H-3'), 3.92 (t, *J* = 2.61 Hz, 1H, H-4), 3.71 - 3.68 (m,1H), 3.63 - 3.48 (m, 2H), 3.44 - 3.40 (m, 1H), 3.30 - 3.17 (m, 2H), 2.17 (d, *J* = 15.24 Hz, 1H) 2.45 - 2.36 (m, 1H); **^{13}C NMR** (D_2O, 75 MHz): δ 173.78, 173.53, 142.54, 131.27, 124.98, 119.77, 78.59, 76.75, 73.95, 70.58, 69.17, 61.21, 52.96, 52.43, 38.44, 26.87; **MS (ESI)** calcd for $C_{16}H_{24}N_4O_8$ + $[H]^+$: 401.15, found 401.3.

Compound 3.22



To a solution of compound **3.17** (50 mg, 107 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M soln of LiOH. (5.4 mg, 129 μmol) followed by the general saponification procedure (**7.2.5**) described above to obtain **3.22** (38 mg, 86 μmol); $\mathbf{R}_f$ 0.41 (CH_3CN/H_2O 8:2); $[\alpha]_D^{24}$ + 26.22 (*c* 1.0, H_2O); **^{1}H NMR** (D_2O, 300 MHz): δ 7.90 (s, 1H, H-6'), 7.44 - 7.40 (m, 3H, H_{Arom}),7.34 - 7.30 (m, 2H, H_{Arom}), 5.41 (s, 2H, H-7'), 4.58 - 4.54 (m, 1H, H-3'), 3.69 (d, *J* = 2.88 Hz, 1H, H-4), 3.49 - 3.48 (m, 1H), 3.39 - 3037 (m, 2H), 3.33 - 3.29 (m, 1H), 3.24 - 3.13 (m, 2H), 3.11 - 3.07 (m, 2H), 3.04 - 2.96 (m, 1H), 2.53 (d, *J* = 14.97 Hz, 1H), 2.23 - 2.15 (m, 1H, H-1); **^{13}C NMR** (D_2O, 75 MHz): δ 173.37, 172.97, 142.42, 134.31, 129.02-127.60 (Aryl-C), 124.21, 77.85, 76.17, 73.19, 69.91, 68.51, 60.53, 53.62, 51.78, 37.81, 26.32; **MS (ESI)** calcd for $C_{20}H_{26}N_4O_8$ + $[H]^+$: 451.17, found 451.3.

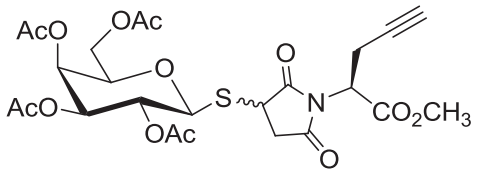
2,3,4,6-tetracetyl-1-thio-β-D-galactose 3.23



To a solution of known compound **3.2** (1.67 g, 4 mmol) in 20 ml of acetone was added thiourea (0.464 g, 6 mmol) and the reaction mixture refluxed overnight. The reaction

mixture was concentrated to obtain 2.2 g of thiouronium salt. The thiouronium salt was dissolved in 4.5 ml of water and 6.6 ml of dichloromethane to which was added $K_2S_2O_5$ (1.2 g, 5.5mmol) and refluxed for 20. The reaction mixture was allowed to cool to room temperature, both layers were separated and the organic layer was dried to obtain 1.65 g of crude thiol galactose. The crude product was purified by flash chromatography using dichloromethane alone to obtain **3.23** (0.904 g, 2.5 mmol); $\mathbf{R}_f$ 0.71 (EtOAc/Hexane 6.5:3.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ5.40 (dd, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 0.9 Hz, 1H, H-4), 5.15 (t, J = 9.9 Hz, H-2), 4.99 (dd, J = 10.1, 3.4 Hz, 1H, H-3), 4.52 (t, J = 9.8 Hz, 1H, H-1), 4.10 (d, J = 6.6 Hz, 2H, H-6a, H-6b), 2.35 (d, J = 9.9Hz, 1H, SH), 2.13, 2.06, 2.02, 1.95 (4S, 3 H each,-C(O)CH_3; **^{13}C NMR** ($CDCl_3$, 75 MHz): δ170.54, 170.33, 170.13, 170.00, ($OCOCH_3$, C=O), 79.32 (C – 5), 75.10 (C-2), 71.73 (C-3) 71.01 (C-1) 67.43 (C-6) 61.64 (C-4) 20.99 – 20.71 (4C,$OCOCH_3$); **MS (ESI)** calcd for $C_{14}H_{20}O_9S$ + $[H]^+$: 365.08, found 365.2.

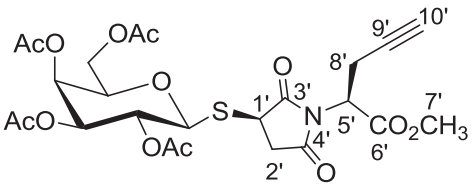
Compound 3.24



To a solution of compound **6.17** (57 mg, 0.27 mmol) and compound **3.24** (100 mg, 0.27 mmol) in CH_2Cl_2 (5mL), was added 4 drops of TEA and stirred at RT overnight. The reaction mixture concentrated on rotovap to get crude product as a 50:50 mixture of diastereomers (**3.24**). The the crude product was purified by flash chromatography

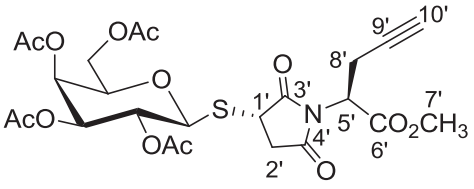
column using 5-10% EtOAc in hexane to separate both the β-D-thiogalactoyranoside diastereomers **3.25** and **3.26**

Compound 3.25



^{1}H-NMR ($CDCl_3$, 300 MHz) 5.47 (d, *J* = 3.3Hz, 1H, H-4), 5.23 (td, *J* = 7.3Hz, *J* = 19.4Hz, 1H, H-3), 5.10 (dd, *J* = 3.3Hz, J=9.5Hz, 1H, H-2), 4.92 (dd, *J* = 5.1Hz, *J* = 11.1Hz, 1H, H-1) 4.18 - 4.08 (m, 1H, H-5'), 4.01 (t, *J* = 7.0Hz, 1H, H-2'), 3.76 (s, 1H) 3.28 (dd, J = 9.4Hz, *J* = 19.0Hz, 1H, H-6) 3.17 - 2.95 (m, 1H, H-3'), 2.64 (dd, *J* = 19.0, 4.0 Hz, 1H, H-1'), 2.17, 2.06, 1.99, (3S, 12H, -(O)CH3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ175.50, 173.26, 170.09, 167.50, 82.91, 78.69, 74.77, 71.72, 71.39, 67.42, 67.33, 67.28, 61.53, 53.37, 51.19, 36.81, 35.39, 36.81, 35.39, 20.91, 20.87, 20.85, 20.74, 18.55; **MS (ESI)** calcd for for $C_{24}H_{29}NO_{13}S + [H]^+$: 572.14, found 572.1.

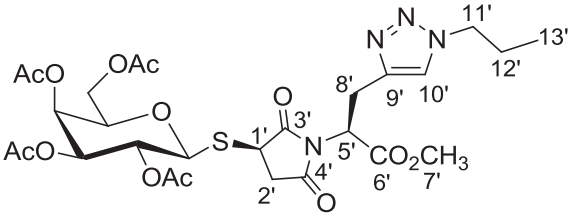
Compound 3.26.



^{1}H-NMR (300 MHz) 5.36 (d, *J* = 3.3Hz, 1H, H-4), 5.02 (d, *J* =3.3Hz, 1H, H-3), 5.03 - 4.95 (m, 1H, H-2) 4.87 (d, *J* = 9.9Hz, 1H, H-1) 4.11 - 3.99 (m, 4H, H-5',H-6,H-5) 3.92 (t, *J* = 4.6Hz, 1H, H-2') 3.75 (s, 1H, H-7') 3.20 - 2.98 (m, 1H, H-6) 3.05 (dddd, *J* = 2.7Hz, *J*

= 8.1Hz, *J* = 7.6Hz, *J* = 17.4Hz, 1H, H-1') 2.09, 2.03, 1.99, 1.92 (4s, 12H,3 H each,-C(O)CH3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.75, 170.04, 169.80, 167.24, 82.42, 78.92, 74.24, 71.34, 71.21, 67.16, 66.78, 61.48, 53.34, 51.57, 40.63, 37.85, 20.69, 20.67, 20.58, 20.52, 20.47, 18.50; **MS (ESI)** calcd for for $C_{24}H_{29}NO_{13}S + [H]^+$: 572.14, found 572.1.

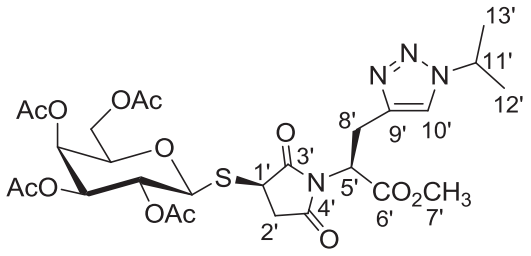
Compound 3.27



To a solution of compound **3.25** (0.050 g, 87 μmol) in THF:H_2O (3;1.5) 4.5 mL, n-propyl azide (0.015 g, 174 μmol) $CuSO_4.5H_2O$ (0.004 g 20%) and sodium ascorbate (0.007 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.27** (0.087 g, 76%) was obtained; $\mathbf{R}_f$ 0.35 (EtOAc/Hexane 7:3); $[\alpha]_D^{22}$ - 29.03 (c = 1.0 in CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.36 (s, 1H, H-10'), 5.43 (d, *J* = 3.29 Hz, 1H, H-4), 5.18 - 5.16 (m, 2H, H-2, H-3), 5.10 - 5.07 (m, 1H, H-5), 4.92 (d, *J* = 11.3, 4.0 Hz, 1H, H-5'), 4.25 (t, *J* = 7.14 Hz, 2H, H-11'), 4.12 (d, *J* = 6.04 Hz, 2H, H-6a, 6b), 4.04 - 3.98 (m, 2H, H-2'), 3.77 (s, 3H, H-7'), 3.53 - 3.47 (m, 2H, H-8'), 3.21 (dd, *J* = 9.34, 18.67 Hz, 1H, H-1), 2.55 (dd, *J* = 18.95, 4.39 Hz, 1H, H-1'), 2.15 - 1.97 (4S, 12H, 3H each, -(O)CH3), 1.89 - 1.85 (m, 2H, H-12'), 0.90 (t, *J* = 7.41 Hz, 2H, H-13'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ175.36, 173.61, 170.56, 170.38, 170.09, 170.00, 168.39, 142.77, 122.10, 82.97, 74.68, 71.80,

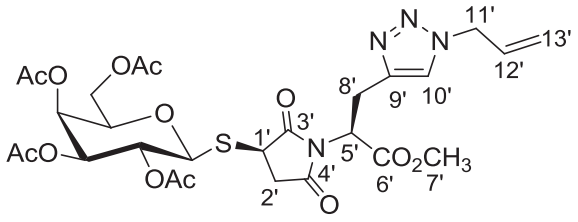
67.55, 67.34, 61.56, 53.19, 52.64, 52.02, 37.73, 35.83, 29.86, 24.26, 23.83, 20.91, 20.86, 20.84, 20.7311.13; **MS (ESI)** calcd for $C_{27}H_{36}N_4O_{13}S + [H]^+$: 657.65, found 657.3.

Compound 3.28



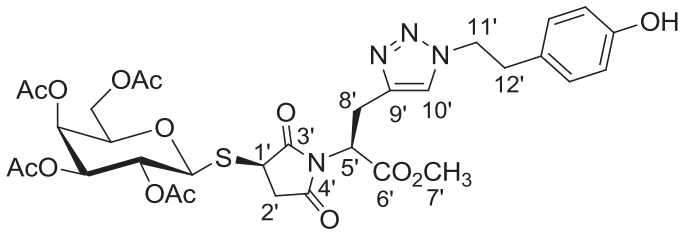
To a solution of compound **3.25** (0.050 g, 87 μmol) in THF : H_2O (3:1.5) 4.5 mL, isopropyl azide (0.015 g, 174 μmol) $CuSO_4.5H_2O$ (0.004 g 20%) and sodium ascorbate (0.007 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.28** (47 mg, 82%) was obtained; $\mathbf{R}_f$ 0.18 (EtOAc/Hexane 7:3); $[\alpha]_D^{22}$ - 25.08 (*c* = 1.0 in CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.38 (s, 1H, H-10'), 5.43 (d, *J* = 3.29 Hz, 1H, H-4), 5.18 - 5.16 (m, 2H, H-2, H-3), 5.10 - 5.07 (m, 1H, H-5), 4.91 (d, *J* = 4.0 Hz, 1H, H-5'), 4.75 - 4.71 (m, 1H, H-11'), 4.12 (d, *J* = 6.04 Hz, 2H, H-6a, 6_b), 4.05 - 3.96 (m, 2H, H-2'), 3.77 (s, 3H, H-7'), 3.53 - 3.48 (m, 2H, H-8'), 3.21 (d, *J* = 9.6 Hz, 1H, H-1), 2.55 (dd, *J* = 4.39, 18.95 Hz, 1H, H-1'), 2.15-1.97 (4S, 3H each, 12H, -(O)CH_3), 1.53 (dd, *J* = 1.92, 6.86 Hz, 6H, H-12',13'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 175.35, 173.59, 170.10, 168.43, 142.56, 131.08, 128.98, 119.74, 82.97, 74.68, 71.080, 68.33, 67.55, 67.34, 61.57, 53.20, 52.64, 37.76, 35.85, 30.53, 29.88, 29.44, 24.30, 23.91, 23.21, 20.88; ; **MS (ESI)** calcd for $C_{27}H_{36}N_4O_{13}S + [H]^+$: 657.65, found 657.21.

Compound 3.29



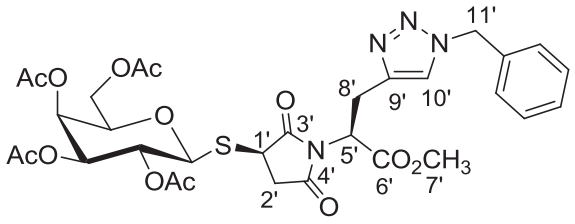
To a solution of compound **3.25** (0.050 g, 87 μmol) in THF:H_2O (3:1.5) 4.5 mL, allyl azide (0.014 g, 174 μmol) $CuSO_4.5H_2O$ (0.004 g 20%) and sodium ascorbate (0.007 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.29** (45 mg, 78%) was obtained; $\mathbf{R}_f$ 0.37 (EtOAc/Hexane 7:3); $[\alpha]_D^{22}$ - 28.25 (c = 1.0 in CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.38 (s, 1H, H-10'), 6.1 - 5.9 (m, 1H, H-12'), 5.43 (d, *J* = 0.82, 2.47 Hz, 1H, H-4), 5.32 - 5.29 (m, 2H, H-13'), 5.20 - 5.16 (m, 2H, H-2, H-3), 5.10 - 5.07 (m, 1H, H-5), 4.95 - 4.91 (m, 3H, H-11', H-5'), 4.41 (d, *J* = 7.41 Hz, 2H, H-6a,6b), 4.04 - 3.98 (m, 2H, H-2'), 3.77 (s, 3H, H-7'), 3.54 - 3.48 (m, 2H, H-8'), 3.22 (d, *J* = 9.34, 1H, H-1), 2.54 (dd, *J* = 4.39, 18.68 Hz, 1H, H-1'), 2.15 - 1.98 (4S, 12H, 3H each, -(O)CH3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ175.38, 173.63, 170.58, 170.38, 170.10, 170.01, 168.36, 143.11, 131.46, 122.15, 120.13, 82.97, 74.668, 71.80, 67.53, 67.33, 61.56, 53.22, 52.76, 52.61, 37.73, 35.83, 24.25, 20.938, 20.89, 20.85, 20.74; **MS (ESI)** calcd for $C_{27}H_{34}N_4O_{13}S$ + $[H]^+$: 655.64, found 655.19.

Compound 3.30



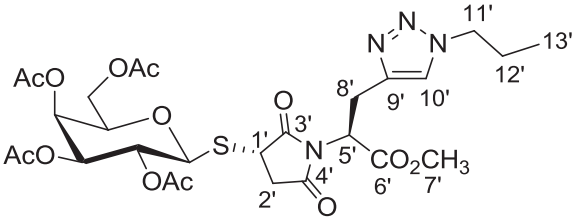
To a solution of compound **3.25** (0.050 g, 87 μmol) in THF:H_2O (3:1.5) 4.5 mL, 4-(2-azidoethyl) phenol (0.028 g, 174 μmol) $CuSO_4.5H_2O$ (0.004 g 20%) and sodium ascorbate (0.007 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.30 (**51 mg, 79%) was obtained; $\mathbf{R}_f$ 0.25 (EtOAc/Hexane 7:3); $[\alpha]_D^{22}$ - 16.7 (*c* = 1.0 in CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.13 (s, 1H, H-10'), 6.86 (d, *J* = 8.51 Hz, H-14', 2H, H_{Arom}), 6.74 (d, *J* = 6.74 Hz, H-15', 2H, H_{Arom}), 5.43 (d, *J* = 3.29 Hz, 1H, H-4), 5.18 - 5.13 (m, 2H, H-2, H-3), 5.10 - 5.09 (m, 1H, H-5), 4.95-4.80 (m, 1H, H-5'), 4.48 (t, *J* = 6.59 Hz, 2H, H-11'), 4.14 - 4.11 (m, 2H, H-6a, 6_b), 4.03 - 3.97 (m, 2H, H-2'), 3.76 (s, 3H, H-7'), 3.49 - 3.43 (m, 2H, H-8'), 3.17 (dd, *J* = 9.34, 18.68 Hz, 1H, H-1), 3.07 (t, *J* = 6.86 Hz, 2H, H-12'), 2.54 (dd, *J* = 4.39, 18.95 Hz, 1H, H-1'), 2.15 - 1.98 (4S, 12H, 3H each, -(O)CH_3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 175.33, 173.79, 170.79, 170.46, 170.19, 168.36, 155.41, 142.54, 130.00, 128.64, 122.70, 115.92, 83.07, 74.6271.79, 67.62, 67.39, 61.62, 53.52, 52.67, 52.04, 38.07, 35.95, 35.84, 24.15, 20.94, 20.89, 20.85, 20.75; **MS (ESI)** calcd for $C_{32}H_{38}N_4O_{14}S + [H]^+$: 735.72, found 735.21.

Compound 3.31



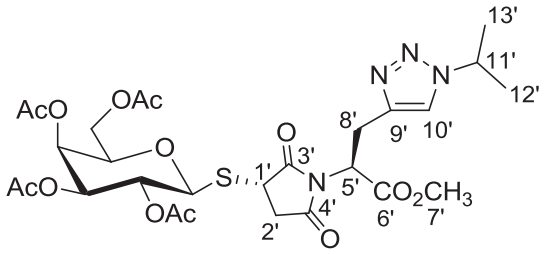
To a solution of compound **3.25** (0.050 g, 87 μmol) in THF : H_2O (3:1.5) 4.5 mL, benzyl azide (0.023 g, 174 μmol) $CuSO_4.5H_2O$ (0.004 g, 20%) and sodium ascorbate (0.007 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.31 (**51 mg, 79%) was obtained; $\mathbf{R}_f$ 0.38 (EtOAc/Hexane 7:3); $[\alpha]_D^{22}$ - 21.04 (c = 1.0 in CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.34 - 7.31 (m, 3H, H_{Arom}), 7.22 (s, 1H, H-10'), 7.17 - 7.15 (m, 2H, H_{Arom}), 5.44 -5.35 (m, 3H, H-4, H-11'), 5.14 - 5.12 (m, 2H, H-2, H-3), 5.06 - 5.04 (m, 1H, H-5), 4.95-4.80 (m, 1H, H-5'), 4.08 (d, *J* = 6.31 Hz, 2H, H-6a, 6b), 3.96 - 3.91 (m, 2H, H-2'), 3.71 (s, 3H, H-7'), 3.47 - 3.42 (m, 2H, H-8'), 3.12 (dd, *J* = 9.34, 18.68 Hz, 1H, H-1), 2.35 (dd, *J* = 4.39, 18.68 Hz, 1H, H-1'), 2.12 - 1.94 (4S, 12H, 3H each, -(O)CH3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 175.16, 173.26, 170.15, 169.86, 169.77, 168.05, 143.13, 134.73, 121.9482.68, 74.46, 71.57, 67.29, 67.10, 61.31, 54.01, 52.98, 52.31, 37.20, 35.3424.04, 20.71, 20.64, 20.52; **MS (ESI)** calcd for $C_{31}H_{36}N_4O_{13}S + [H]^+$: 705.70, found 705.21.

Compound 3.32



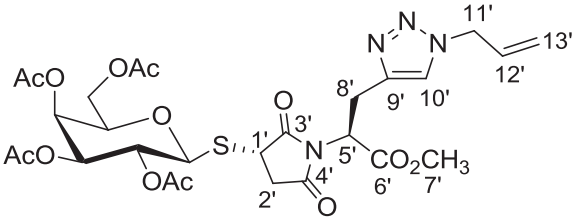
To a solution of compound **3.26** (0.050 g, 87 μmol) in THF:H_2O (3:1.5) 4.5 mL, n-propyl azide (0.015 g, 174 μmol) $CuSO_4.5H_2O$ (0.004 g 20%) and sodium ascorbate (0.007g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.32** (0.045 g, 79%) was obtained; $\mathbf{R}_f$ 0.37 (EtOAc/Hexane 7:3); $[\alpha]_D^{22}$ - 48.68° (c = 1.0 in CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.39 (s, 1H, H-10'), 5.47 - 5.44 (m, 2H, H-1', H-4), 5.14 - 5.04 (m, 2H, H-2'), 4.89 (dd, *J* = 4.12,11.26 Hz, 1H, H-5'), 4.42 - 4.39 (m, 1H, H-5), 4.30 (t, *J* = 7.37 Hz, 1H, H-11'), 4.13 (dd, $J_{3,4}$ = 5.29, $J_{3,2}$ = 11.53 Hz, 1H, H-3), 4.01 - 3.91 (m, 2H, H-6a,6b), 3.80 (s, 3H, H-7'), 3.64 (dd, *J* = 11.26, 15.10 Hz, 1H, H-2), 3.47-3.33 (m, 2H, H-8'), 3.14 (d, *J* = 9.61, Hz, 1H, H-1), 2.14-1.97 (4S, 3H each, -C(O)CH_3), 1.89 (m, 2H, H-12'), 0.90 (t, *J* = 7.41 Hz, 3H, H-13'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ174.27 (C-3'), 173.92 (C-4'), 170.54, 170.25, 169.98, 169.84 ($OCOCH_3$, C=O), 168.14 (C-6'), 142.71 (C-9'), 121.86 (C-10'), 82.43 (C-5), 73.93 (C-1), 71.20 (C-3), 67.71 (C-2), 67.08 (C-4), 62.02 (C-6), 53.10 (C-11'), 53.06 (C-5'), 51.78 (C-7'), 41.81 (C-2'), 36.91 (C-1'), 23.64 (C-8'), 23.56 (C-12'), 20.71-20.56 (4C, OCOCH3), 10.843 (C-13'); **MS (ESI)** calcd for $C_{27}H_{36}N_4O_{13}S$ + $[H]^+$: 657.65, found 657.21.

Compound 3.33



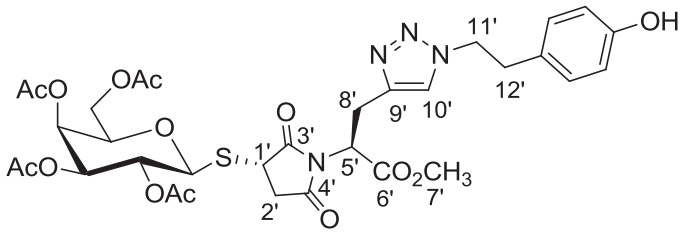
To a solution of compound **3.26** (0.050 g, 87 μmol) in THF:H_2O (3:1.5) 4.5 mL, Isopropyl azide (0.015 g, 174 μmol) $CuSO_4.5H_2O$ (0.004 g 20%) and sodium ascorbate (0.007 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.33** (0.046 g, 81%) was obtained; $\mathbf{R}_f$ 0.20 (EtOAc/Hexane 7:3); $[\alpha]_D^{22}$ – 39.49° (c = 1.0 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41 (s, 1H, H-10'), 5.45 - 5.42 (m, 2H, H-1', H-4), 5.16 - 5.12 (m, 2H, H-2'), 4.92 - 4.81 (m, 2H, H-5', H-11'), 4.43 - 4.40 (m, 1H, H-5), 4.14 (dd, $J_{3,4}$ = 4.94, $J_{3,2}$ = 11.53 Hz, 1H, H-3), 4.02 - 3.92 (m, 2H, H-6a,6b), 3.80 (s, 3H, H-7'), 3.64 (dd, J = 11.26, 15.10 Hz, 1H, H-2), 3.47 - 3.34 (m, 2H, H-8'), 3.14 (dd, J = 9.61, 18.68 Hz, 1H, H-1), 2.14 - 1.97 (4S, 3H each, -C(O)CH3), 1.54 (2d, J = 1.92, 6.86 Hz, 6H, H-12',13'); **^{13}C NMR** ($CDCl_3$, 75 MHz): 174.50 (C-3'), 174.18 (C-4'), 170.9, 170.49, 170.21, 170.09 ($OCOCH_3$, C=O), 168.41 (C-6'), 142.73 (C-9'), 119.71 (C-10'), 82.64 (C-5), 74.14 (C-1), 71.51 (C-3), 67.91 (C-2), 67.34 (C-4), 62.28 (C-6), 53.34 (C-11', C-5'), 53.17 (C-7'), 42.02 (C-2'), 37.15 (C-1'), 23.87 (C-8'), 23.15, 25.13 (C-12', 13'), 20.71-20.56 (4C, $OCOCH_3$); **MS (ESI)** calcd for $C_{27}H_{36}N_4O_{13}S$ + $[H]^+$: 657.65, found 657.21.

Compound 3.34



To a solution of compound **3.26** (0.050 g, 87 μmol) in THF:H_2O (3:1.5) 4.5 mL, allyl azide (0.015 g, 174 μmol) $CuSO_4.5H_2O$ (0.004 g, 20%) and sodium ascorbate (0.007 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.34** (0.044 g, 77%) was obtained; $\mathbf{R}_f$ 0.39 (EtOAc /Hexane 7:3); $[\alpha]_D^{22}$ –33.19° (c = 1.0 in CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.42 (s, 1H, H-10'), 6.00 - 5.94 (m, 1H, H-12'), 5.46 - 5.43 (m, 2H, H-1', H-4), 5.30 (dd, *J* = 0.82, 12.91Hz, 2H, H-13'), 5.21 - 5.11 (m, 2H, H-2'), 5.05 - 4.96 (m, 2H, H-11'), 4.93 - 4.88 (dd, *J* = 3.6, 4.12 Hz, 1H, H-5'), 4.40 - 4.38 (m, 1H, H-5), 4.14 (dd, $J_{3,4}$= 4.94, $J_{3,2}$ = 11.53 Hz, 1H, H-3), 4.01 - 3.92 (m, 2H, H-6a,6b), 3.80 (s, 3H, H-7'), 3.70 - 3.61 (m, 1H, H-2), 3.48 - 3.33 (m, 2H, H-8') 3.15 (d, *J* = 9.34, 1H, H-1), 2.14, 2.05, 2.04, 1.97 (4S, 12H, 3H each,-C(O)CH_3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 174.31(C-3'), 173.93 (C-4'), 170.55-169.90 ($OCOCH_3$, C=O), 168.11 (C-6'), 143.02 (C-9'), 131.30 (C-12'), 121.97 (C-10'), 119.83 (C-13), 82.47 (C-5), 73.97 (C-1), 71.26 (C-3), 67.70 (C-2), 67.08 (C-4), 62.02 (C-6), 53.14 (C-11'), 53.01 (C-5'), 52.53 (C-7'), 41.81 (C-2'), 36.91 (C-1'), 23.58 (C-8'), 20.58-20.56 (4C, $OCOCH_3$); **MS (ESI)** calcd for $C_{27}H_{34}N_4O_{13}S + [H]^+$: 655.64, found 655.13.

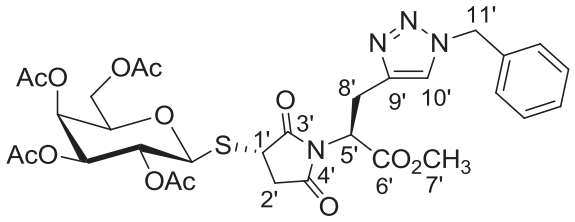
Compound 3.35



To a solution of compound **3.26** (0.063 g, 113 μmol) in THF:H_2O (3:1.5) 4.5 mL, 4-(2-azido ethyl) phenol (0.037 g, 227 μmol) $CuSO_4.5H_2O$ (0.005 g 20%) and sodium ascorbate (0.008 g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.35** (0.065 g, 80%); (0.191 g, 79%) was obtained; $\mathbf{R}_f$ 0.27 (EtOAc/Hexane 7:3); $[\alpha]_D^{22}$ – 64.45° (c = 1.0 in CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.00 (s, 1H, H-10'), 6.85 - 6.75 (m, 4H, H_{Arom}), 5.55 - 5.52 (m, 1H, H-1'), 5.44 (dd, *J* = 1.09, 3.57 Hz, 1H, H-4), 5.25-5.04 (m, 2H, H-2'), 4.80 (dd, *J* = 3.57, 11.26 Hz, 1H, H-5'), 4.65 - 4.61(m, 1H, H-5), 4.46 - 4.40 (m, 2H, H-11'), 4.14 (dd, *J* = 5.21,11.53Hz, 1H, H-3), 4.06 - 3.91(m, 2H, H-6a,6b), 3.80 (s, 3H, H-7') 3.58 (dd, *J* = 11.26, 15.10 Hz, 1H, H-2), 3.47 - 3.33 (m, 2H, H-8'), 3.15 (dd, *J* = 9.61, 18.68 Hz, 1H, H-1), 3.06 (t, *J* = 6.59 Hz, 2H, H-12'), 2.16,2.06,2.00,1.99 (4s, 12H, 3H each,-C(O)CH_3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 174.45 (C-3'), 174.07 (C-4'), 170.84, 170.40, 170.10, 169.98 (OCOCH3, C=O), 168.15 (C-6'), 154.99 (C_{Arom}), 142.73 (C-9'), 130.04 (C_{Arom}), 128.799 (C_{Arom})122.80 (C-10'), 115.64 (C_{Arom}), 82.42 (C-5), 73.94 (C-1), 71.21 (C-3), 67.87 (C-2), 67.21 (C-4), 62.14 (C-6), 53.16 (C-11', C-5'), 52.05 (C-7'), 42.95 (C-2'), 36.90 (C-1'), 29.66, 23.44 (C-8'), 23.15, 25.13 (C-12', 13'),

20.80-20.61 (4C, $OCOCH_3$); **MS (ESI)** calcd for $C_{32}H_{38}N_4O_{14}S$ + $[H]^+$: 735.21, found 735.22.

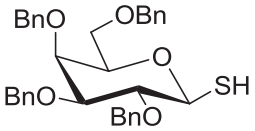
Compound 3.36



To a solution of compound **3.26** (0.050 g, 87 μmol) in THF:H_2O (3:1.5) 4.5 mL, benzyl azide (0.023 g, 174 μmol) $CuSO_4.5H_2O$ (0.004 g, 20%) and sodium ascorbate (0.007g, 40%) were added and after 12 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-thiogalactopyranoside **3.36** (0.047 g, 76%) was obtained; $\mathbf{R}_f$ 0.40 (EtOAc/Hexane 7:3); $[\alpha]_D^{22}$ – 36.06° (c = 1.0 in CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.37 - 7.34 (m, 3H, H_{Arom}), 7.31 (s, 1H, H-10'),7.24 - 7.21 (m, 2H, H_{Arom}), 5.53 - 5.44 (m, 4H, H-11', H-1', H-4), 5.20 - 5.07 (m, 2H, H-2') 4.89 (dd, *J* = 4.21, 11.53 Hz, 1H, H-5'), 4.40 - 4.39 (m, 1H, H-5), 4.14 (dd, *J* = 5.22, 11.53 Hz, 1H, H-3), 4.02 - 3.88 (m, 2H, H-6a,6b), 3.79 (s, 3H, H-7'), 3.63 (dd, *J* = 11.26, 15.10 Hz, 1H, H-2), 3.44 - 3.32 (m, 2H, H-8'), 3.11 (dd, *J* = 9.61, 18.67 Hz, 1H, H-1), 2.15, 2.06, 2.04, 1.97 (4S, 12H, 3 H each,-C(O)CH3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 174.53 (C-3'), 174.12 (C-4'), 170.78, 170.49, 170.25, 170.14 ($OCOCH_3$, C=O), 168.31 (C-6'), 142.73 (C-9'), 134. 95 (C_{Arom}), 129.28-128.21 (C_{Arom}), 122.29 (C-10'), 82.72 (C-5), 74.23 (C-1), 71.48 (C-3), 67.95 (C-2), 67.35 (C-4), 62.25 (C-6), 54.29, 53.36 (C-11', C-5'), 53.22 (C-7'), 41.98 (C-2'), 37.20

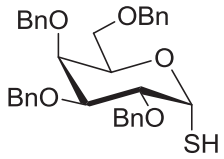
(C-1'), 23.83 (C-8'), 21.00-20.79 (4C, $OCOCH_3$); **MS (ESI)** calcd for $C_{31}H_{36}N_4O_{13}S$ + $[H]^+$: 705.70, found 705.21.

Compound 3.43



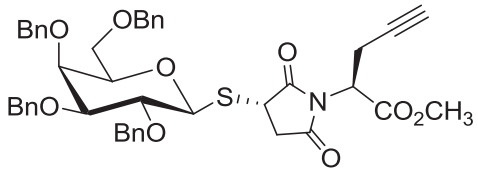
To a solution of known α-bromo galactose **3.41** (0.171 g, 283 μmol) was added 10 ml of acetone, thiourea (0.032 g, 420 μmol) and the reaction mixture refluxed overnight. The reaction mixture was rotovapped to get the thiouronium salt. The thiouronium salt was dissolved in 2.2 ml of water and 3.3 ml of dichloromethane. Then 75 mg of $K_2S_2O_5$ was added and refluxed for 20 minutes. The reaction mixture was allowed to drop to room temperature, both the aqueous and organic layers were separated and the organic layer dried to get 79 mg of crude α and β anomeric mixture thiol galactose. The crude product was purified by flash chromatography column using dichloromethane alone to obtain α (**3.43**) and β anomer (**3.43**) ; $\mathbf{R}_f$ 0.33 (Hex/EtOAc 8.0:2.0); $[\alpha]_D^{24}$ + 0.74 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 - 7.18 (m, 20H, H_{arom}), 4.88 (dd, *J* = 17.8, 7.8 Hz, 2H, $\underline{CH_2}$-Ph), 4.68 (s, 1H, $\underline{CH_2}$-Ph), 4.58 (d, *J* = 11.6 Hz, 1H, $\underline{CH_2}$-Ph), 4.46 - 4.33 (m, 3H, $\underline{CH_2}$-Ph), 3.93 (d, *J* = 2.8 Hz, 1H, H-4), 3.72 (t, *J* = 9.3 Hz, 1H, H-1), 3.58 - 3.47 (m, 5H, H-2,3,5,6,6'), 2.26 (d, *J* = 8.4 Hz, 1H, SH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.55, 138.41, 137.84, 128.37, 128.33, 128.27, 128.22, 127.85, 127.83, 127.71, 127.62, 127.52, 127.46, 79.60, 78.66, 75.80, 74.80, 74.73, 73.40, 73.24, 72.54, 70.36, 68.56; **MS (ESI)** calcd for $C_{34}H_{36}O_5S$ + $[H]^+$: 557.23, found 557.21.

Compound 3.44



R_f 0.41 (Hex : EtOAc 8.0 : 2.0); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 - 7.14 (m, 20H), 5.83 - 5.79 (m, 1H, H-1), 4.85 (d, 11.6 Hz, 2H, $\underline{CH_2}$-Ph), 4.74 - 4.51 (m, 4H, $\underline{CH_2}$-Ph), 4.42 (d, *J* = 11.9 Hz, 2H, $\underline{CH_2}$-Ph), 4.31 (t, *J* = 6.3 Hz, 1H, H-5), 4.22 (dd, *J* = 9.8, 5.3 Hz, 1H, H-2), 3.94 (d, *J* = 1.6 Hz, 1H, H-4), 3.78 (dd, *J* = 9.8, 2.8 Hz, 1H, H-3), 3.50 (d, *J* = 6.4 Hz, 2H, H-6,6'), 1.80 (d, *J* = 3.9 Hz, 1H, SH); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.53, 137.92, 128.34, 128.30, 128.24, 128.19, 127.82, 127.68, 127.59, 127.49, 127.42, 79.58, 78.63, 75.78, 74.77, 74.71, 73.37, 73.21, 72.50, 70.34, 68.54; **MS** (**ESI)** calcd for $C_{34}H_{36}O_5S + [H]^+$: 557.23, found 557.21.

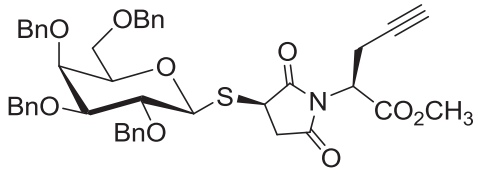
Compound 3.48



To a solution of galactose thiol **3.45** (0.1 g, 179 μmol) and L-propargyl maliemide (0.037 g, 179 μmol) in dichloromethane (5 mL) was added 2 drops of TEA and stirred at RT overnight. The reaction mixture was concentrated on rotovap and purified by flash chromatography column using 2-4% ether in toluene to get α and β-D-thiolactoyranoside mixture in almost 50:50 mixture. Both the diastereomers were separated by column chromatography. **3.48** is α isomer, **3.49** is β isomer (134 mg, 98% together); **R_f** 0.27 (Toluene/Ether 8.5:1.5); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 - 7.11 (m, 20H), 4.87 (ddd,

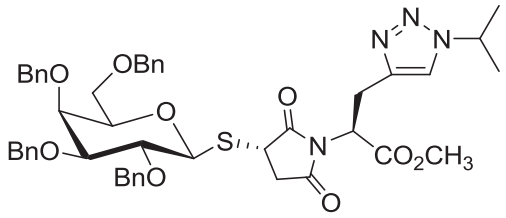
J = 24.8, 16.2, 7.8 Hz, 4H), 4.76 - 4.65 (m, 2H), 4.65 - 4.53 (m, 2H), 4.47 - 4.32 (m, 2H), 4.07 (dd, *J* = 8.3, 5.3 Hz, 1H), 3.93 (t, *J* = 9.3 Hz, 2H), 3.66 (s, 3H), 3.61 (d, *J* = 6.5 Hz, 1H), 3.58 - 3.43 (m, 4H), 3.21 - 3.07 (m, 2H), 3.06 - 2.89 (m, 2H), 1.87 (t, *J* = 2.5 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.14, 173.70, 166.94, 138.08, 137.66, 137.61, 137.26, 127.96, 127.85, 127.83, 127.78, 127.56, 127.50, 127.38, 127.27, 127.24, 127.14, 127.09, 83.16, 82.88, 78.46, 76.58, 75.13, 74.08, 72.99, 72.71, 72.04, 70.78, 67.66, 52.62, 50.76, 38.99, 37.76, 29.23, 18.26; **MS (ESI)** calcd for $C_{44}H_{45}NO_9S + [H]^+$: 764.28, found 764.23.

Compound 3.49



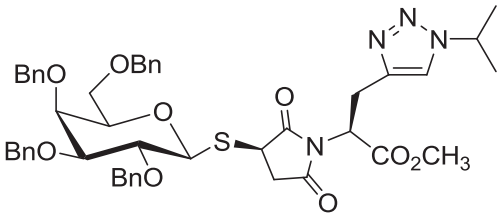
R_f 0.20 (Toluene/Ether 8.5:1.5); $[\alpha]_D^{23}$ - 17.68 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 - 7.14 (m, 20H), 5.03 (d, *J* = 9.7 Hz, 1H), 4.97 - 4.84 (m, 2H), 4.75 (d, *J* = 4.0 Hz, 2H), 4.69 (s, 2H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.47 - 4.34 (m, 2H), 4.13 (dd, *J* = 9.3, 4.0 Hz, 1H), 3.95 (d, *J* = 2.5 Hz, 1H), 3.80 (t, *J* = 9.5 Hz, 1H), 3.68 (s, 3H), 3.57 (ddd, *J* = 22.6, 15.0, 7.9 Hz, 5H), 3.25 - 3.12 (m, 1H), 2.97 (dd, *J* = 5.1, 2.6 Hz, 1H), 2.91 (dd, *J* = 5.2, 2.7 Hz, 1H), 2.67 (dd, *J* = 18.9, 4.0 Hz, 1H), 1.88 (t, *J* = 2.6 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.27, 173.81, 167.47, 138.49, 138.30, 137.89, 137.82, 128.42, 128.34, 128.30, 128.26, 127.78, 127.68, 127.66, 127.56, 127.50, 83.54, 78.95, 78.49, 75.80, 74.76, 74.69, 73.54, 73.45, 71.82, 71.19, 71.03, 69.34, 52.95, 50.74, 35.43, 35.23, 29.67, 18.56; **MS (ESI)** calcd for $C_{44}H_{45}NO_9S + [H]^+$: 764.28, found 764.23.

Compound 3.50



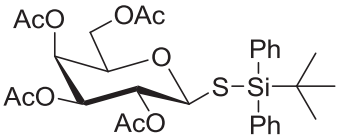
To a solution of compound **3.48** (43 mg, 56 μmol) in THF:H_2O (1:1) 2 mL, isopropyl azide (7 mg, 82 μmol) $CuSO_4.5H_2O$ (2 mg 0.2eq) and sodium ascorbate (4 mg, 0.4eq) were added and after 12h of reaction time following the general procedure described above, β-D-thio galactopyranoside **3.50** (0.033g, 70%) was obtained; $\mathbf{R_f}$ 0.12 (Toluene /Ether 8.5:1.5); $[\alpha]_D^{24}$ - 21. (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 - 7.14 (m, 20H), 5.00 - 4.87 (m, 2H), 4.81 (q, *J* = 10.4 Hz, 2H), 4.68 (d, *J* = 2.5 Hz, 2H), 4.66 - 4.60 (m, 2H), 4.60 - 4.53 (m, 1H), 4.40 (q, *J* = 11.8 Hz, 2H), 4.01 (t, *J* = 6.8 Hz, 1H), 3.95 (d, *J* = 2.3 Hz, 1H), 3.86 (t, *J* = 9.4 Hz, 1H), 3.68 (s, 3H), 3.67 - 3.53 (m, 3H), 3.52 - 3.37 (m, 3H), 3.03 (d, *J* = 6.8 Hz, 2H), 1.44 (t, *J* = 6.6 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.73, 174.30, 168.28, 142.45, 138.59, 138.19, 138.16, 137.81, 128.35, 128.32, 128.20, 128.17, 128.00, 127.91, 127.73, 127.62, 127.59, 127.50, 127.48, 119.43, 83.64, 83.46, 77.98, 76.77, 75.50, 74.52, 73.36, 73.27, 72.51, 68.06, 52.88, 52.77, 52.47, 39.74, 38.14, 24.47, 22.93, 22.82; **HRMS (ESI)** calculated for $C_{47}H_{52}N_4O_9S$ $[M + Na]^+$: 871.33472, found 871.33517.

Compound 3.51



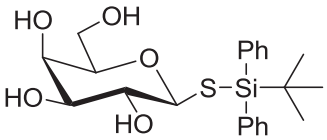
To a solution of compound **3.49** (34 mg, 44 μmol) in THF : H_2O (1:1) 2 mL, isopropyl azide (6 mg, 82 μmol) $CuSO_4.5H_2O$ (2 mg 0.2eq) and sodium ascorbate (4 mg, 0.4eq) were added and after 12h of reaction time following the general procedure described above, β-D-thio galactopyranoside **3.51** (32 mg, 70%) was obtained; $\mathbf{R_f}$ 0.1 (Toluene/Ether 8.5:1.5); $[\alpha]_D^{24}$ - 50.50 (c 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 - 7.15 (m, 1H), 5.05 - 4.85 (m, 20H), 4.76 (dd, *J* = 22.1, 10.9 Hz, 3H), 4.66 (d, *J* = 2.1 Hz, 2H), 4.64 - 4.52 (m, 2H), 4.47 - 4.28 (m, 2H), 4.04 (dd, *J* = 9.4, 4.1 Hz, 2H), 3.94 (d, *J* = 2.1 Hz, 1H), 3.77 (t, *J* = 9.4 Hz, 1H), 3.70 (s, 1H), 3.65 - 3.52 (m, 1H), 3.48 (s, 3H), 3.11 (dd, *J* = 18.9, 9.4 Hz, 4H), 2.51 (dd, *J* = 18.9, 4.1 Hz, 2H), 1.40 (t, *J* = 6.6 Hz, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.31, 173.42, 168.19, 142.08, 138.25, 137.84, 137.49, 128.24, 128.21, 128.04, 128.00, 127.98, 127.75, 127.65, 127.59, 127.50, 127.41, 127.38, 119.54, 83.66, 83.60, 77.93, 76.42, 75.03, 74.38, 73.30, 73.15, 72.52, 68.23, 52.69, 52.53, 52.15, 37.17, 35.72, 24.02, 22.71, 22.69. **HRMS (ESI)** calculated for $C_{47}H_{52}N_4O_9S$ $[M + Na]^+$: 871.33472, found 871.33366.

Compound 3.52



To the solution of compound **3.23** (0.450 g, 1.2 mmol) in DCM added TBDPSiCl (0.37 ml 1.2 eq), TEA (0.33 mL, 2 eq) and DMAP (catalytic) and stirred at RT for 1 hr and concentrated the RM under vacuum and flashed the crude product using 10-20% EtOAc in hexane to obtain pure product **3.52** (0.446g, 60%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 - 7.69 (m, 4H), 7.54 - 7.33 (m, 6H), 5.28 (t, *J* = 9.9 Hz, 1H), 5.20 (dd, *J* = 3.4, 1.0 Hz, 1H), 4.68 (dd, *J* = 10.0, 3.4 Hz, 1H), 4.01 (d, *J* = 9.8 Hz, 1H), 3.85 (dd, *J* = 11.2, 7.3 Hz, 1H), 3.67 (dd, *J* = 11.2, 6.2 Hz, 1H), 3.16 (t, *J* = 6.8 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 1.92 (s, 3H), 1.89 (s, 3H), 1.11 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.20, 170.03, 170.00, 169.38, 136.41, 136.14, 131.95, 131.67, 130.20, 130.03, 127.81, 127.50, 81.16, 73.96, 71.75, 69.57, 66.93, 60.76, 27.45, 20.75, 20.62, 20.47, 20.44, 20.22; **HRMS (ESI)** calculated for $C_{30}H_{38}N_4O_9SSi$ $[M + Na]^+$: 625.19035, found 625.18908.

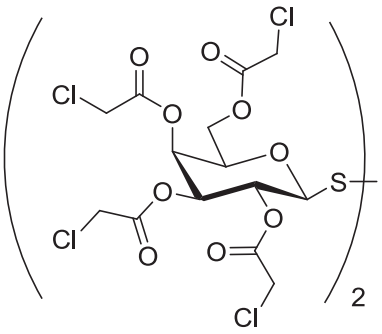
Compound 3.53



To the solution of compound **3.52** (0.1 g, 166 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**7.2.4**) to obtain deprotected β-D-S-galactopyranoside **3.53** (57 mg, 80%); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 - 7.52 (m, 4H), 7.51 - 7.24 (m,

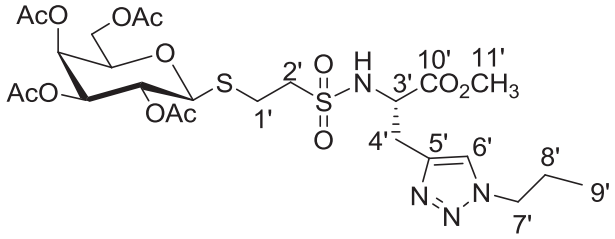
6H), 4.42 - 4.00 (m, 1H), 3.89 - 3.74 (m, 1H), 3.65 (d, *J* = 10.4 Hz, 2H), 3.46 - 3.23 (m, 1H), 2.80 (s, 1H), 2.37 - 2.16 (m, 1H), 1.15 - 0.94 (m, 9H).

Compound 3.58



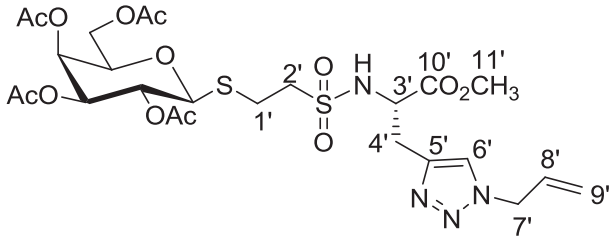
To a solution of **3.57** (0.053 g, 135 μmol) in dry DCM was added chloroacetic anhydride, (0.278 g, 1.6 mmol), DMAP, pyridine (catalytic) and stirred the reaction mixture for 12 hrs and concentrated the reaction mixture in vaccuo. Crude product purified by flash chromatography using DCM alone to obtain chloroacetylated galactosethiol dimer **3.58** (0.74 g, 55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (d, *J* = 2.7 Hz, 2H), 5.61 (s, 2H), 5.49 (dd, *J* = 9.2, 6.7 Hz, 3H), 5.31 (d, *J* = 0.6 Hz, 2H), 4.49 (t, *J* = 6.8 Hz, 2H), 4.28 (d, *J* = 6.7 Hz, 2H), 4.18 (d, *J* = 0.5 Hz, 4H), 4.17 (s, 4H), 4.07 (d, *J* = 0.5 Hz, 4H), 4.03 (d, *J* = 0.6 Hz, 4H), 4.01 (d, *J* = 0.5 Hz, 2H).

Compound 3.59



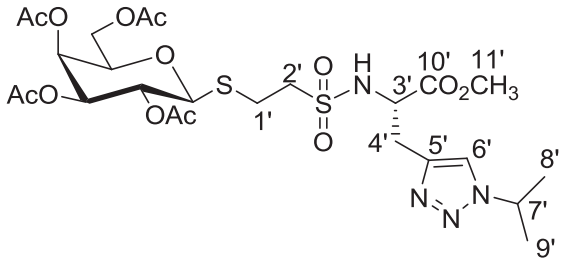
To a solution of **6.26** (24 mg, 79 μmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactoyranoside **3.23** (35 mg, 96 μmol) in CH_2Cl_2 5 mL was added 4 drops of TEA and stirred at RT overnight. The reaction mixture was concentrated on a rotovap and crude purified by flash column chromatography using 30% EtOAc in hexane to obtain β-D-thiogalactoyranoside **3.59** (38 mg, 57 μmol). $\mathbf{R}_f$ 0.26 (CH_2Cl_2/MeOH 9.5:0.5); $[\alpha]_D^{22}$ + 9.99 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.38 (s, 1H, H-6'), 5.80 (d, *J* = 8.51Hz, 1H, NH), 5.36 (d, *J* = 3.29 Hz, 1H, H-4), 5.17 (t, *J* = 9.88 Hz, 1H, H-5), 5.00 (dd, *J* = 3.29, 3.29 Hz, 1H, H-3), 4.57 (d, *J* = 9.88 Hz, 1H, H-2), 4.44 – 4.40 (m, 1H, H-3'), 4.24 (t, *J* = 7.41 Hz, 2H, H-7') 4.06 - 4.00 (m, 2H, H-6a,b), 3.94 (d, *J* = 9.8 Hz, 1H, H-1), 3.70 (s, 3H, H-11'), 3.39 - 3.31 (m, 2H, H4'), 3.23 - 3.20 (m, 2H, H-2'), 3.04 (t, *J* = 8.24 Hz, 2H, H-1'). 2.10 - 2.00 (4S, 3 H each,-C(O)CH_3), 1.86 - 1.81 (m, 2H, H-8'), 0.88 (t, *J* = 7.41 Hz, 3H, H-9'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.243, 143.91, 124.85, 88.00, 80.690, 76.21, 71.17, 70.47, 62.65, 57.13, 55.42, 53.23, 52.98, 30.18, 24.67, 11.25; **MS (ESI)** calcd for $C_{25}H_{38}N_4O_{13}S_2$ + $[H]^+$: 667.17, found 667.2.

Compound 3.60



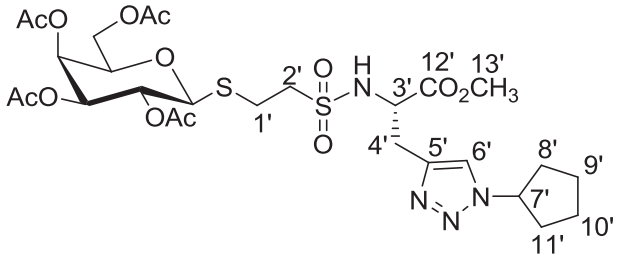
To a solution of **6.27** (20 mg, 66 μmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactoyranoside **3.23** (25.9 mg, 79 μmol) in CH_2Cl_2 5mL was added 4 drops of TEA and stirred at RT overnight. The reaction mixture was concentrated on a rotovap and crude purified by flash column chromatography using 30% EtOAc in hexane to obtain β-D-thiogalactoyranoside **3.60** (32 mg, 47.9 μmol); $\mathbf{R}_f$ 0.22 (CH_2Cl_2 /MeOH 9.5:0.5); $[\alpha]_D^{22}$ + 23.40 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.37 (s, 1H, H-6'), 5.95 – 5.90 (m, 1H, H-8') 5.71 (d, *J* = 8.51Hz, 1H, NH), 5.38 (d, *J* = 2.4 Hz, 1H, H-4), 5.30 (dd, *J* = 10.2, 1.1, Hz, 1H, H-9'), 5.19 (ddd, *J* = 0.824,9.34, 9.88 Hz, 1H, H-5), 5.01 (dd, *J* = 3.29, 3.57 Hz, 1H, H-3), 4.91 (d, *J* = 3.57 Hz, 1H, H-7'), 4.58 (d, *J* = 9.89 Hz, 1H, H-2), 4.44 - 4.40 (m, 1H, H-3'), 4.07 - 4.01 (m, 2H, H-6a,b), 3.95 (d, *J* = 9.8 Hz, 1H, H-1), 3.79 (s, 3H, H-11'), 3.39 - 3.31 (m, 2H, H4'), 3.23 - 3.21 (m, 2H, H-2'), 3.04 - 3.00 (m, 2H, H-1'). 2.11 - 1.93 (4S, 3H each,-C(O)CH_3), **^{13}C NMR** ($CDCl_3$, 75 MHz): δ171.68 (C-10'), 170.73 - 169.83 (O<u>C</u>OCH_3, C=O), 142.62 (C-5'), 131.280 (C-8'), 122.34 (C-6'), 120.527 (C-9'), 85.06 (C-1), 74.74 (C-5) 71.92 (C-2), 67.45 (C-4), 67.09 (C-3), 62.01 (C-6), 55.49 (C-3'), 54.92 (C-2'), 53.15(C-11'), 53.00 (C-7'), 29.15 (C-4'), 24.98 (C-1'), 20.99–20.78 (OCO<u>C</u>H_3); **MS** (**ESI)** calcd for $C_{25}H_{36}N_4O_{13}S_2$ + $[H]^+$: 665.17, found 665.2.

Compound 3.61



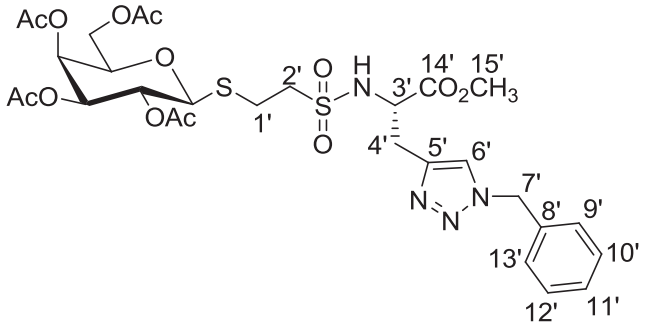
To a solution of **6.28** (16 mg, 53 μmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactoyranoside **3.23** (19.2 mg, 52 μmol) in CH_2Cl_2 5mL was added 4 drops of TEA and stirred at RT overnight. The reaction mixture was concentrated on a rotovap and crude purified by flash column chromatography using 30% EtOAc in hexane to obtain β-D-thiogalactoyranoside **3.61** (20 mg, 30 μmol). $\mathbf{R}_f$ 0.24 (CH_2Cl_2/MeOH 9.5:0.5); $[\alpha]_D^{22}$ + 41.96 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.38 (s, 1H, H-6'), 5.72 (d, *J* = 8.79Hz, 1H, NH), 5.38 (d, *J* = 2.47 Hz, 1H, H-4), 5.18 (t, *J* = 9.88 Hz, 1H, H-5), 5.01 (dd, *J* = 3.29, 3.29 Hz, 1H, H-3), 4.74 (qu, *J* = 6.86 Hz, 1H, H-7'), 4.59 (d, *J* = 9.88Hz, 1H, H-2) 4.46 – 4.40 (m, 1H, H-3'), 4.08 - 4.01 (m, 2H, H-6a,b), 3.95 (d, *J* = 9.8 Hz, 1H, H-1), 3.72 (s, 3H, H-11'), 3.41- 3.33 (m, 2H, H4'), 3.23 - 3.19 (m, 2H, H-2'), 3.06 (t, *J* = 7.41 Hz, 2H, H-1'), 2.12 - 1.94 (4S, 3 H each,-C(O)CH_3), 1.53 (d, *J* = 6.86 Hz, 6H, H-8' and 9'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.74 (C-10'), 170.74–169.81 (O<u>C</u>OCH_3, C=O), 142.12 (C-5'), 119.92 (C-6'), 85.12 (C-1), 74.74 (C-5) 71.95 (C-2), 67.48 (C-4), 67.11 (C-3), 62.03 (C-6), 55.49 (C-3'), 54.96 (C-2'), 53.15(C-11'), 29.88 (C-8'), 29.44(C-9') 25.09(C-4'), 23.18 (C-1'), 21.00–20.79 (OCO<u>C</u>H_3); **MS (ESI)** calcd for $C_{25}H_{38}N_4O_{13}S_2$ + $[H]^+$: 667.17, found 667.2.

Compound 3.62



To a solution of **6.29** (38 mg, 115 μmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactoyranoside **3.23** (50.5 mg, 138 μmol) in CH_2Cl_2 5mL was added 4 drops of TEA and stirred at RT overnight. The reaction mixture was concentrated on a rotovap and crude purified by flash column chromatography using 30% EtOAc in hexane to obtain β-D-thiogalactoyranoside **3.62** (61 mg, 88 μmol). $\mathbf{R}_f$ 0.22 (CH_2Cl_2/MeOH 9.5:0.5); $[\alpha]_D^{22}$ + 8.06 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.36 (s, 1H, H-6'), 5.77 (d, *J* = 8.51Hz, 1H, NH), 5.37 (d, *J* = 3.29 Hz, 1H, H-4), 5.17 (t, *J*=9.89 Hz, 1H, H-5), 5.04 (dd, *J* = 3.57, 3.29 Hz, 1H, H-3), 4.82 (qu, *J* = 6.04 Hz, 1H, H-7'), 4.58 (d, *J*=9.88Hz, 1H, H-2) 4.44 - 4.41 (m, 1H, H-3'), 4.08 - 4.01 (m, 2H, H-6a,b), 3.96 (d, *J* = 9.8 Hz, 1H, H-1), 3.71 (s, 3H, H-13'), 3.39 - 3.32 (m, 2H, H4'), 3.22 - 3.19 (m, 2H, H-2'), 3.04 (t, *J* = 7.41 Hz, 2H, H-1'). 2.11 - 1.69 (4m, 8H, H-8',9',10',11') 2.11 - 1.93 (4S, 3H each,-C(O)CH_3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.77 (C-12'), 170.72–169.81 (O<u>C</u>OCH_3, C=O), 142.15 (C-5'), 121.03 (C-6'), 85.10 (C-1), 74.71 (C-5) 71.93 (C-2), 67.47 (C-4), 67.12 (C-3), 62.01 (C-6), 55.51 (C-3'), 54.95 (C-2'), 53.11(C-13'), 33.54 (C-11, C-8), 29.36 (C-4'), 25.05 (C-1'), 24.20 (C-9', C-10'), 21.00 – 20.79 (OCO<u>C</u>H_3); **MS (ESI)** calcd for $C_{27}H_{40}N_4O_{13}S_2$ + $[H]^+$: 693.20, found 693.20.

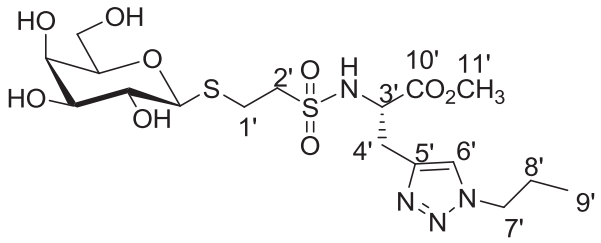
Compound 3.63



To a solution of **6.30** (25 mg, 71 μmol) and 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactoyranoside **3.23** (43 mg, 60 μmol) in CH_2Cl_2 5mL was added 4 drops of TEA and stirred at RT overnight. The reaction mixture was concentrated on a rotovap and crude purified by flash column chromatography using 30% EtOAc in hexane to obtain β-D-thiogalactoyranoside **3.63** (35 mg, 49 μmol); $\mathbf{R}_f$ 0.31 (CH_2Cl_2/MeOH 9.5:0.5); $[\alpha]_D^{22}$ + 15.29 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.31 - 7.27 (m, 3H, H-6' and H_{Arom}), 7.20 - 7.18 (m, 2H, H_{Arom}), 5.77 (d, *J* = 8.51Hz, 1H, NH), 5.37 (d, *J* = 2.47 Hz, 1H, H-4), 5.17 (t, *J* = 9.88 Hz, 1H, H-5), 5.01 (dd, *J* = 3.29, 3.29 Hz, 1H, H-3), 4.58 (d, *J* = 9.88Hz, 1H, H-2), 4.43 - 4.39 (m, 1H, H-3'), 4.06 - 4.01 (m, 2H, H-6a,b), 3.94 (d, *J* = 9.8 Hz, 1H, H-1), 3.66 (s, 3H, H-15'), 3.35 - 3.29 (m, 2H, H4'), 3.25 (t, *J* = 6.31, Hz, 2H, H-2'), 3.04 (t, *J* = 7.41 Hz, 2H, H-1'), 2.11 - 1.93 (4S, 3 H each,-C(O)CH_3); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ171.67 (C-14'), 170.73 –169.83 ($OCOCH_3$, C=O), 142.84 (C-5'), 134.99 (C-8'), 129.35 - 128.21 (C-9,10,11,12,13), 122.45 (C-6'), 85.06 (C-1), 74.74 (C-5) 71.94 (C-2), 67.48 (C-4), 67.13 (C-3), 62.01 (C-6), 55.50 (C-3'), 54.94 (C-2'), 54.38

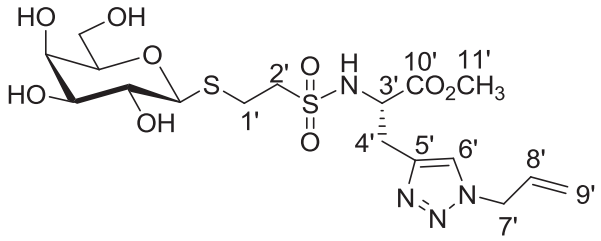
(C-7'), 53.08 (C-15'), 29.41 (C-4'), 25.00 (C-1'), 21.00 - 20.79 (OCOCH3); **MS (ESI)** calcd for $C_{29}H_{38}N_4O_{13}S_2 + [H]^+$: 715.18, found 715.20.

Compound 3.64



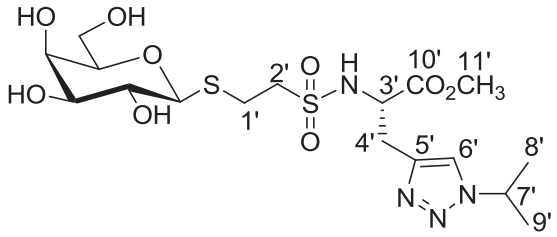
To a solution of compound **3.59** (0.038 g, 56 μmol) in 3 mL of dry methanol, 1M NaOMe solution was added until reaction mixture pH was 9-10. After 4 hrs of reaction time following the general procedure described above (**8.2.4**). The deprotected β-D-thiogalactopyranoside **3.64** (21 mg, 42 μmol) was obtained; $\mathbf{R}_f$ 0.25 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{22}$ - 9.96 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (CD_3OD, 300 MHz): δ 7.76 (s, 1H, H-6') 4.28 (t, *J* = 10.1Hz , 1H, H-7') 3.81 (d, *J* = 2.2Hz, 1H, H-4) 3.69 (s, 1H, H-11'), 3.68 - 3.61 (m,1H), 3.55 - 3.49 (m, 2H), 3.25 - 3.21 (m, 1H) 3.38 - 3.31 (m, 4H), 3.09 (t, *J* = 8.3Hz, 2H, H-2') 2.93 (t, *J* = 7.5Hz, 2H, H-1') 1.94 - 1.83 (m, 2H, H-8'), 0.85 (t, *J* = 7.4Hz, 3H, H-9'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.24, 143.91, 124.82, 88.00, 80.69, 76.21, 71.17, 70.47, 62.65, 57.13, 55.42, 53.23, 52.98, 49.85, 30.18, 24.671, 11.251; **MS (ESI)** calcd for $C_{17}H_{30}N_4O_9S_2 + [H]^+$: 499.12, found 499.1.

Compound 3.65



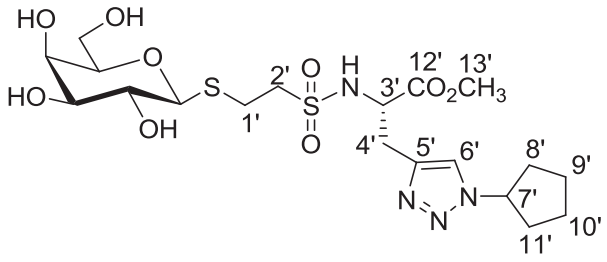
To a solution of compound **3.60** (0.032 g, 48 μmol) in 3 mL of dry methanol, 1M NaOMe solution was added until reaction mixture pH was 9-10, after 4 hrs of reaction time following the general procedure described above (**8.2.4**). The deprotected β-D-thiogalactopyranoside **3.65** (15 mg, 30 μmol) was obtained; $\mathbf{R}_f$ 0.24 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{22}$ - 1.34 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (CD_3OD, 300 MHz): δ7.37 (s, 1H, H-6'), 5.61 - 5.57 (m, 1H, H-8'), 4.82 (dd, *J* = 1.3Hz, *J* = 13.6Hz, 2H, H-9'), 4.56 (td, *J* = 1.4Hz, *J* = 5.9Hz, 1H, H-7'), 3.92 – 3.87 (m, 1H, H-3'), 3.42 (d, *J* = 2.4 Hz, 1H, H-4), 3.30 (s, 1H, H-11'), 3.24 - 3.19 (m, 1H), 3.09 - 3.04 (m, 2H) 3.01 (dd, *J* = 3.2Hz, *J* = 9.1Hz,1H), 2.94 - 2.76 (m, 4H), 2.64 (dd, *J* = 8.5Hz, *J* = 14.8Hz, 2H, H-2'), 2.51 (t, *J* = 7.8Hz, 2H, H-1'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.23, 144.19, 133.24, 124.89, 119.77, 88.03, 80.69, 76.22, 71.18, 70.48, 62.66, 57.10, 55.43, 53.59, 53.23, 30.17, 24.91; **MS (ESI)** calcd for $C_{17}H_{28}N_4O_9S_2$ + $[H]^+$: 497.55, found: 497.2.

Compound 3.66



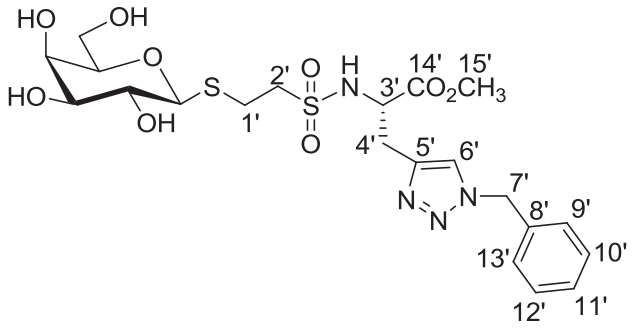
To a solution of compound **3.61** (0.020 g, 30 μmol) in 3 mL of dry methanol, 1M NaOMe solution was added until reaction mixture pH was 9-10, after 4 hrs of reaction time following the general procedure described above (**8.2.4**). The deprotected β-D-thiogalactopyranoside **3.66** (12 mg, 24 μmol) was obtained; $\mathbf{R}_f$ 0.25 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{22}$ + 23.68 (*c* 0.5, CH_2Cl_2); **^{1}H NMR** (CD_3OD, 300 MHz): δ 7.88 (s, 1H, H-6'), 4.28 (d, *J* = 9.6Hz, 1H, H-1), 4.14 - 4.28 (m, 1H, H-7'), 4.20 (dd, *J* = 4.7Hz, *J* = 8.3Hz, 1H, sugar-H), 3.95 (d, *J*=3.0Hz, 1H, H-4), 3.67(s, 3H, H-11'), 3.35 - 3.60 (m, 2H, sugar-H), 3.22 - 3.30 (m, 2H sugar-H), 3.22 (ddd, *J* = 4.5Hz, *J* = 10.5Hz, *J* = 14.5Hz, 2H, H-1'), 2.99 (dd, *J* = 7.2Hz, *J*=15.3Hz, 2H, H-2'), 2.77 (td, *J* = 5.8Hz, *J* = 9.9Hz, 1H, H-4'), 1.32 (d, *J* = 6.7Hz, 6H, H-8',9'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.43, 143.99, 122.71, 87.91, 80.71, 70.08, 62.60, 57.28, 54.77, 53.21, 30.67, 25.01, 23.14; **MS (ESI)** calcd for $C_{17}H_{30}N_4O_9S_2$ + $[H]^+$: 499.12, found 499.0.

Compound 3.67



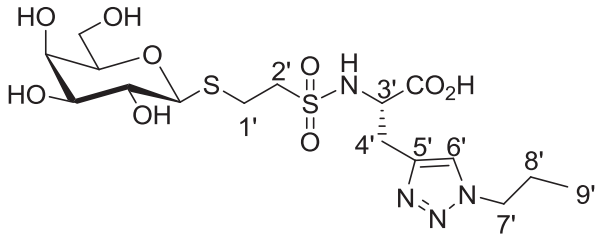
To a solution of compound **3.62** (0.059 g, 85 μmol) in 3 mL of dry methanol, 1M NaOMe solution was added until reaction mixture pH was 9-10, after 4 hrs of reaction time following the general procedure described above (**8.2.4**). The deprotected β-D-thiogalactopyranoside **3.67** (34 mg, 65 μmol) was obtained; $\mathbf{R}_f$ 0.20 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{22}$ - 12.06 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (CD_3OD, 300 MHz): δ7.39 (s, 1H, H-6'), 4.55 - 4.48 (m, 1H, H-7'), 3.95 - 3.88 (m, 1H, H-3'), 3.42 (d, *J* = 2.7Hz, 1H, H-4) 3.31 (s, 1H, H-13'), 3.28 - 3.18 (m, 1H), 3.12 - 3.06 (m, 2H), 3.00 (dd, *J* = 3.2, 9.2Hz, 1H), 2.95 - 2.75 (m,4H), 2.64 (t, *J* = 8.3Hz, 2H, H-2'), 2.51 (t, *J* = 7.5Hz, 2H, H-1'), 1.87 - 1.75 (m, 2H, cyclopentyl-CH_2),1.64 - 1.53 (m, 2H, cyclopentyl-CH_2), 1.49 - 1.41(m, 2H, cyclopentyl-CH_2), 1.36 - 1.25 (m, 2H, cyclopentyl-CH_2); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.25, 143.82, 123.46, 88.00, 80.69, 76.23, 71.19, 70.48, 63.35, 62.66, 57.09, 55.50, 53.22, 34.25, 30.21, 25.00, 24.89; **MS (ESI)** calcd for $C_{19}H_{32}N_4O_{10}S_2$ + $[H]^+$: 525.16, found 525.20.

Compound 3.68



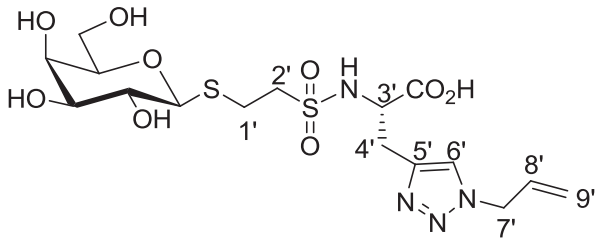
To a solution of compound **3.63** (0.035 g, 49 μmol) in 3 mL of dry methanol, 1M NaOMe solution was added until reaction mixture pH was 9-10, after 4 hrs of reaction time following the general procedure described above (**8.2.4**). The deprotected β-D-thiogalactopyranoside **3.68** (16 mg, 29 μmol) was obtained. $\mathbf{R}_f$ 0.3 (CH_2Cl_2/MeOH 9.0:1.0); $[\alpha]_D^{22}$ - 11.92 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (CD_3OD, 300 MHz): δ 7.42 (s, 1H, H-6'), 6.99 - 6.89 (m, 5H, H_{Arom}), 5.18 (s, 2H, H-7'), 3.97 (t, *J* = 8.4Hz, 1H, H-3'), 3.48 (d, *J* = 2.4Hz, 1H, H-4), 3.38 - 3.24 (m, 1H), 3.30 (s, 1H, H-11'), 3.19 - 3.13 (m, 2H), 3.07 (dd, *J*=3.3, 9.2Hz, 1H), 3.01 - 2.79 (m, 4H), 2.68 (dd, *J* = 8.6, 14.8Hz, 2H, H-2'), 2.56 (t, *J* = 7.41Hz, 2H, H-1'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 173.26, 144.37, 136.79, 130.01, 129.49, 129.03, 124.99, 87.99, 80.68, 76.21, 71.18, 70.48, 62.66, 57.10, 55.39, 54.92, 53.17, 30.14, 24.89; **MS (ESI)** calcd for $C_{21}H_{30}N_4O_9S_2 + [H]^+$: 547.14 found 547.3.

Compound 3.69



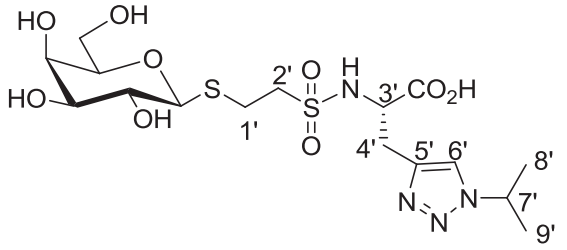
To a solution of compound **3.64** (15 mg, 30 μmol) in mixed solvent of THF : MeOH : H_2O (3:2:1) was added a 1M soln. of LiOH (1.5 mg, 36 μmol) followed by general saponification procedure (**8.2.5**) to obtain β-D-thiogalactopyranoside **3.69** as product (13 mg, 27 μmol); $\mathbf{R}_f$ 0.22 (CH_3CN/H_2O 8:2); $[\alpha]_D^{21}$ - 2.30 (*c* 1.0, MeOH); **^{1}H NMR** (D_2O, 300 MHz): δ 8.14 (s, 1H, H-6'), 4.43 - 4.52 (m, 2H, H-7'), 3.87 - 4.04 (m, H-3'), 3.60 - 3.71 (m, 3H, sugar H), 3.40 - 3.57 (m, 5H, sugar-H, H-1'), 3.18 - 3.27 (m, 3H, sugar H, H-2'), 1.99 - 1.86 (m, 2H, H-8'), 0.84 - 0.86 (m, 3H, H-9'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 215.85, 174.07, 142.22, 126.47, 86.992, 79.52, 74.47, 73.99, 70.05, 69.31, 61.62, 56.10, 54.17, 53.57, 28.56, 24.39, 23.48, 10.65; **MS (ESI)** calcd for $C_{16}H_{28}N_4O_9S_2$ + $[H]^+$: 485.12, found 485.13.

Compound 3.70



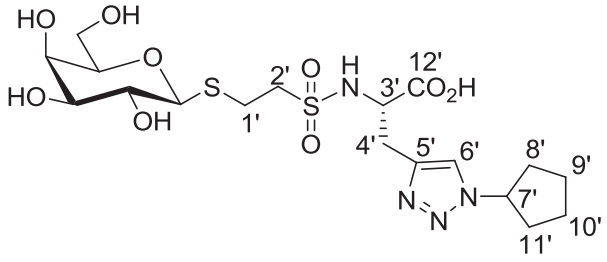
To a solution of compound **3.65** (10 mg, 20μmol) in mixed solvent of THF:MeOH: H_2O (3:2:1) was added a 1M soln. of LiOH (1 mg, 24 μmol) followed by general saponification procedure (**8.2.5**) to obtain β-D-thiogalactopyranoside **3.70** as product (8 mg, 16 %). $\mathbf{R}_f$ 0.2 (CH_3CN/H_2O 8:2); $[\alpha]_D^{21}$ + 4.3 (*c* 1.0, MeOH); **^{1}H NMR** (D_2O, 300 MHz): δ 8.08 (s, 1H, H-6'), 6.14 - 5.97 (1H, m, H-8') 5.28 (d, *J* = 5.1Hz, 2H, H-9'9') 5.06 (d, *J* = 5.1Hz, 1H, H7') 4.48 (d, *J* = 9.8Hz, 1H, H-1) 4.37 - 4.41(m, 1H, H-3') 3.96 (d, *J* = 3.4Hz, 1H, H-4) 3.74 - 3.61 (m, 2H,sugar H) 3.52 (t, *J* = 9.5Hz, 2H, H-1') 3.31 - 3.47 (m, 3H, sugar H) 3.12 - 3.20 (m, 2H, H-2') 2.88 - 3.01 (m, 2H, H-4'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 215.86, 174.40, 143.17, 131.68, 125.91, 120.27, 86.99, 79.52, 74.46, 70.04, 61.60, 53.45, 28.87, 24.38; **MS (ESI)** calcd for $C_{16}H_{26}N_4O_9S_2$ + $[H]^+$: 483.11, found 482.12.

Compound 3.71



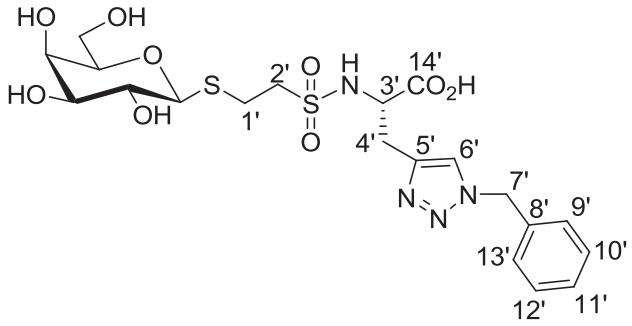
To a solution of compound **3.66** (32 mg, 64 μmol) in mixed solvent of THF:MeOH: H_2O (3:2:1) was added a 1M soln of LiOH (3.2 mg, 77 μmol) followed by general saponification procedure (**8.2.5**) to obtain β-D-thiogalactopyranoside **3.71** (26 mg, 54 μmol) as product. $\mathbf{R}_f$ 0.22 (CH_3CN/H_2O 8:2); $[\alpha]_D^{21}$ - 4.04 (*c* 1.0, MeOH); **^{1}H NMR** (D_2O, 300 MHz): δ 8.03 (s, 1H, H-6'), 4.48 (d, *J* = 9.6Hz, 1H, H-1), 4.34 - 4.38 (m, 1H, H-7'), 4.20 (dd, *J* = 4.7Hz, *J* = 8.3Hz, 1H, sugar-H), 3.95 (d, *J* = 3.0Hz, 1H, H-4), 3.60 - 3.74 (m, 2H, sugar-H), 3.45 - 3.55 (m, 2H sugar-H), 3.35 (ddd, *J* = 4.5Hz, *J* = 10.5Hz, *J* = 14.5Hz, 2H, H-1'), 3.13 (dd, *J* = 7.2Hz, *J* = 15.3Hz, 2H, H-2'), 2.96 (dd, *J* = 5.8Hz, *J* = 9.9Hz, 2H, H-4'), 1.54 (d, *J* = 6.7Hz, 1H, H-8',9'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 215.89, 174.48, 142.53, 135.32, 128.30, 123.69, 87.09, 79.56, 74.52, 70.08, 69.33, 61.62, 56.28, 54.87, 54.22, 28.97, 24.42, 22.58; **MS (ESI)** calcd for $C_{16}H_{28}N_4O_9S_2$ + $[H]^+$: 485.12, found 485.13.

Compound 3.72



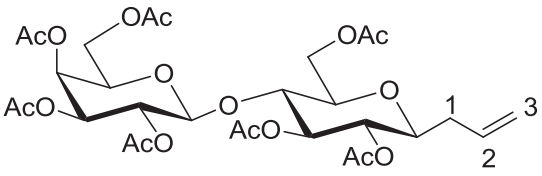
To a solution of compound **3.67** (10 mg, 19 μmol) in mixed solvent of THF: MeOH: H_2O (3:2:1) was added a 1M soln. of LiOH (1 mg, 22μmol) followed by general saponification procedure (**8.2.5**) to obtain β-D-thiogalactopyranoside **3.72** as product (9 mg, 16 μmol); $\mathbf{R}_f$ 0.25 (CH_3CN/H_2O 8:2); $[\alpha]_D^{21}$ + 4.6 (*c* 1.0, MeOH); **^{1}H NMR** (D_2O, 300 MHz): δ 7.99 (1H, s, H-6'), 4.89 - 4.85 (1H, m, H-7'), 4.39 (d, *J* = 9.6Hz, 1H, H-1), 4.25 - 4.20 (1H, m, H-3'), 3.80 (d, *J* = 2.7Hz, 1H, H-4), 3.45 - 3.65 (3H, m, sugar-H), 3.32 - 3.42 (2H, m, sugar-H), 3.2 - 3.3 (2H, m, H-1'), 2.95 - 3.1 (2H, m, H-2'), 2.7 - 2.9 (2H, m, H-4'), 2.05 - 2.20 (2H, m, cyclopentyl-CH_2), 1.80 - 1.95 (2H, m,cyclopentyl-CH_2), 1.54 - 1.63 (2H, m, cyclopentyl-CH_2); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 174.25, 142.22, 124.91, 86.83, 79.56, 74.54, 70.14, 69.42, 63.99, 61.69, 56.205, 54.32, 33.36, 33.33, 28.65, 24.18, 24.12; **HRMS (ESI)** calcd for $C_{18}H_{30}N_4O_9S_2$ + $[H]^+$: 511.14542, found 511.15270.

Compound 3.73



To a solution of compound **3.68** (30 mg, 54 μmol) in mixed solvent of THF: MeOH : H_2O (3:2:1) was added a 1M soln. of LiOH (2.7 mg, 64 μmol) followed by general saponification procedure (**8.2.5**) to obtain β-D-thiogalactopyranoside **3.73** as product (22 mg, 41 μmol); $\mathbf{R}_f$ 0.3 (CH_3CN/H_2O 8:2); $[\alpha]_D^{21}$ + 6.28 (*c* 1.0, MeOH); **^{1}H NMR** (D_2O, 300 MHz): δ 7.90 (s, 1H, H-6'), 7.42 (d, *J* = 6.1Hz, 1H, H_{Arom}), 7.33 (d, *J* = 7.6Hz, 1H, H_{Arom}), 5.59 (s, 2H, H-7'), 4.47 (d, *J* = 9.6Hz, 1H, H-1), 4.17 (dd, *J* = 4.8Hz, *J* = 9.6Hz, 2H, sugar-H), 3.97 (d, *J* = 2.8Hz, 1H, H-4), 3.62 - 3.74 (m, 2H, sugar-H), 3.45 - 3.57 (m, 1H, sugar-H), 3.24 - 3.33 (m, 2H, H-1'), 3.04 (dd, *J* = 9.2Hz, *J* = 15.0Hz, 2H, H-2'), 2.84 - 2.96 (m, 2H, H-4'); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 176.30, 144.30, 135.64, 129.77, 129.33, 128.58, 125.43, 97.09, 87.13, 79.58, 74.50, 70.12, 69.38, 61.67, 57.79, 54.49, 54.00, 30.89, 29.54, 24.51; **MS (ESI)** calcd for $C_{20}H_{28}N_4O_9S_2$ + $[H]^+$: 533.12, found 532.13.

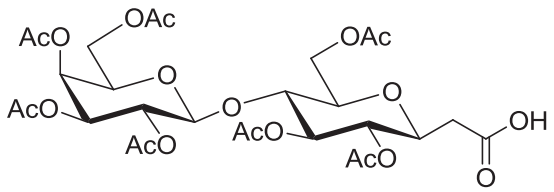
Compound 3.77



Allyl magnesium bromide (125 mL of a 1 M soln in THF) was added to solution of α-bromo-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl(1→4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (8.8 g, 12.6 mmol) in THF (15 ml) at -78^{o}C. The mixture was warmed up to 23^{o} C within 0.5 h after adding allyl magnesium bromide and then poured in to H_2O (400 mL). Glacial acetic acid (40 mL) was added to dissolve the magnesium salts and the mixture was shaken with Et_2O until two separate layers were observed. Then the aqueous layer was evaporated to dryness and the residue was stirred overnight with Ac_2O (200 mL), pyridine (200 mL) and catalytic amount of DMAP. After removal of the solvent , the remaining oil was diluted in EtOAc, washed with 1 M HCl soln, water, brine and dried over $MgSO_4$, The concentrated crude product was purified by silica gel column chromatography (hexane:EtOAc 3:1) to afford the compound **3.77** (4.5 g, 6.8 mmol). $\mathbf{R}_f$ 0.38 (DCM/MeOH 9.7:0.3); $[\alpha]_D^{22}$ + 1 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.79 (td, *J* = 17.2, 6.7 Hz, 1H, H-2), 5.35 (d, *J* = 3.3Hz, 1H, H-4^{II}), 5.17 (t, *J* = 9.3 Hz, 1H, H-3^{II}), 5.12 (t, *J* = 9.1 Hz, 1H, H-3^{I}), 5.08 - 5.02 (m, 2H, H-3), 4.96 (dd, *J* = 10.4, 2.1 Hz, 1H, H-2^{II}), 4.83 (t, *J* = 9.6 Hz, 1H, H-2^{I}), 4.47 (dd, *J* = 21.1, 9.9 Hz, 2H, H-1^{II}, H-6^{II}), 4.14 - 4.04 (m, 4H, H-6^{II}, H-6,6^{I}, H-4^{I}), 3.87 (t, *J* = 6.8 Hz, 2H, H-5^{I}), 3.75 (t, *J* = 9.4 Hz, 2H, H-1^{I}, H-4^{I}), 3.58 - 3.51 (m, 1H, H-1^{I}), 3.47 - 3.41 (m, 1H, H-5^{I}), 2.25 - 2.18 (m,

2H. H-1), 2.16, 2.11, 2.07, 2.05, 2.04, 2.03, 1.97 (7S, 3H each,-C (O) CH3); **^{13}C-NMR** (150MHz) δ 170.33, 170.24, 170.07, 169.97, 169.87, 169.77, 132.83, 117.53, 100.97, 76.78, 76.58, 76.36, 74.28, 71.84, 70.90, 70.52, 69.03, 66.53, 62.27, 60.72, 35.68, 29.63, 20.80, 20.72, 20.60, 20.46; **MS (ESI)** calcd for $C_{28}H_{38}O_9$ + $[Na]^+$: 683.22, found 683.10.

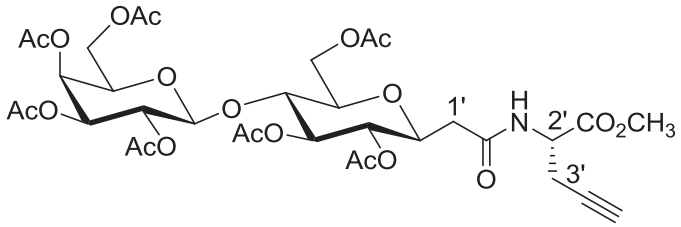
Compound 3.78



To the solution of *C*-allyl lactose **3.77** (0.1 g 151 μMol) in 2 mL ACN:Water(1:1) was added $NaIO_4$ 4.2 eq (0.130 g, 605 μMol) and $RuCl_3$ (catalytic) and stirred at RT for about 1 hr. DCM was added and the reaction mixture was filtered, separated into two layers and the organic layer washed with NH_4Cl, 1 N HCl and Brine solution. The organic layer was dried over $MgSO_4$, evaporated and the crude product was purified by flash column chromatography using 1-5% MeOH in DCM to obtain compound **3.78** (51 mg, 75 μmol); $\mathbf{R}_f$ 0.2 (DCM/MeOH 9.7:0.3); $[\alpha]_D^{25}$ + 18.99 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz) δ 5.35 (d, *J* = 3.3Hz, 1H, H-4^{II}), 5.19 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.11 (dd, *J* = 8.0Hz, *J* = 10.2Hz, 1H, H-3^{I}), 4.95 (dd, *J* = 3.4Hz, *J* = 10.4Hz, 1H, H-2^{II}), 4.85 (t, *J* = 9.6Hz, 1H, H-2^{I}), 4.45 (dd, *J* = 9.9Hz, *J* = 24.4Hz, 2H, H-1^{II}, H-6 ^{II}), 4.15 - 4.05 (m, 3H, H-6 ^{II}, H-6,6 ^{I}), 3.92 - 3.85 (m, 2H, H-1^{I},4^{I}), 3.78 (t, *J* = 9.5Hz, 1H, H-5^{I}), 3.63 (dd, *J* = 3.6Hz, *J* = 9.8Hz, 1H, H-5^{II}), 2.53 - 2.46 (m, 2H, H-1), 2.16, 2.10, 2.07, 2.05, 2.04, 2.04, 1.97 (7S,3H each,-C(O)CH_3); **^{13}C-NMR** (151MHz) δ174.43, 170.38, 170.36, 170.15, 170.07, 169.92,

169.83, 169.06, 100.96, 76.69, 76.27, 73.92, 73.87, 71.66, 70.96, 70.66, 69.06, 66.60, 62.09, 60.82, 36.75, 20.77, 20.76, 20.61, 20.60, 20.60, 20.48. **HRMS (ESI)** calcd for $C_{28}H_{38}O_9 + [Na]^+$: 701.1905, found 701.1905.

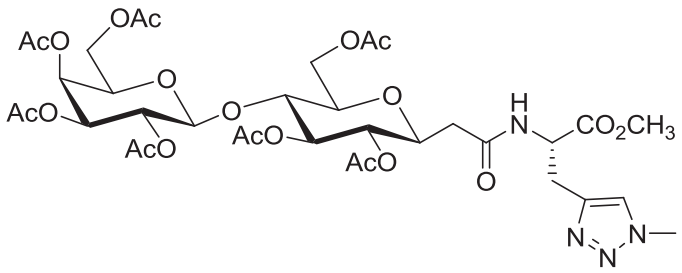
Compound 3.79



To a solution of lactose acid **3.78** (0.338 g, 49 μMol), L-propargyl glycine methyl ester HCl (0.121 g, 74 mmol) and BOP reagent (0.330 g, 74 μMol) in Dry THF under nitrogen atmosphere was added DIPEA (0.303 mL, 1.7 mmol) drop wise and the reaction mixture left to stir overnight. The reaction mixture was concentrated and the residue dissolved in CH_2Cl_2 and washed with 1M $KHSO_4$, $NaHCO_3$ and brine solution. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography using 0.5-1% MeOH in DCM to obtain **3.79** (0.215 g, 107 μmol); $\mathbf{R_f}$ 0.66 (DCM/MeOH 9.5:0.5); $[\alpha]_D^{25}$ +17.532 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz) δ 6.89 (d, *J* = 7.8Hz, 1H, NH), 5.35 (dd, *J* = 0.7Hz, *J* = 3.3Hz, 1H, H-4''), 5.20 (t, *J* = 9.2Hz, 1H, H-3''), 5.11 (dd, *J* = 7.9Hz, *J* = 10.4Hz, 1H, H-3'), 4.96 (dd, *J* = 3.5Hz, *J* = 10.4Hz, 1H, H-2''), 4.85 (t, *J* = 9.7Hz, 1H, H-2'), 4.73 (dt, *J* = 9.5, 4.9 Hz, H-2) 4.56 (dd, *J* = 1.8Hz, *J* = 12.1Hz, 1H, H-1''), 4.49 (dd, *J* = 7.9Hz, *J* = 13.7Hz, 1H, H-6''), 4.14 (dd, *J* = 6.2Hz, *J* = 11.1Hz, 1H, H-6''), 4.11 - 4.05 (m, 2H, H-6,6'), 4.14 (dd, J = 6.2Hz, *J* = 11.1Hz, 1H, H-4), 3.81 (d, J = 3.3 Hz, 1H, H-5'), 3.80 (s, 3H, C(O)**CH3**), 3.78 - 3.64 (m,

1H, H-5''), 2.82 - 2.74 (m, 2H, H-3), 2.49 (dd, *J* = 2.5Hz, *J* = 15.2Hz, 2H, H-1), 2.12 (t masked under singlet 1H, alkyne-H), 2.16, 2.13, 2.07, 2.05(6H), 2.04, 1.97(6S,3H each,-C(O)CH_3); **^{13}C-NMR** (150 MHz) δ 170.554, 170.413, 170.229, 170.093, 170.024, 169.933, 169.711, 168.975, 168.811, 100.944, 78.587, 76.691, 75.974, 74.501, 73.803, 71.407, 71.384, 70.915, 70.591, 69.026, 66.0520, 62.041, 60.728, 52.740, 50.634, 38.601, 29.193, 22.196, 20.857, 20.754, 20.628, 20.582, 20.559, 20.448; **HRMS** (**ESI)**calcd for $C_{34}H_{45}NO_{20}$ + $[H]^+$: 788.2613 found: 788.2605.

Compound 3.80

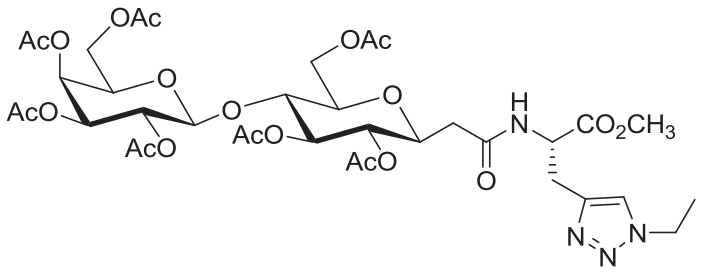


a) To a solution of compound **3.79** (0.05 g, 63 μmol) in 2 mL THF:H_2O (1:1), MeI (2eq) NaN_3 (3 eq), $CuSO_4.5H_2O$ (3 mg 20%) and sodium ascorbate (5 mg, 40%) were added and after 16 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-lactopyranoside **3.80** (27 mg, 24 μmol) was obtained.

b) Methyl azide was distilled at 90^{o}C while preparing it in another RBF (MeI (1 eq) + NaN_3 (2eq) + DMF + Water (1:1)), then added to another RBF containing a solution of compound **3.79** (0.05 g, 63 μmol) in 2 mL THF:H_2O (1:1), $CuSO_4.5H_2O$ (3 mg 20%) and sodium ascorbate (5 mg, 40%) for 16h of reaction time following the general procedure (**7.2.1**) described above to obtain β-D-lactopyranoside **3.80** (33 mg, 39 μmol) as product.

R_f 0.25 (DCM:MeOH 9.7:0.3); $[\alpha]_D^{25}$ + 9.44 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz) δ ^{1}H-NMR (600 MHz) 7.34 (s, 1H, H-4), 7.18 (d, *J* = 7.7Hz, 1H, NH), 5.28 (d, *J* = 3.4Hz, 1H, H-4^{II}), 5.10 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.05 (dd, *J* = 7.9Hz, *J* = 10.4Hz, 1H, H-3^{I}), 4.90 (dd, *J* = 3.5Hz, *J* = 10.4Hz, 1H, H-2^{II}), 4.82 - 4.81 (m, 1H, H-2), 4.74 (t, *J* = 9.6Hz, 1H, H-2^{I}), 4.50 (d, *J* = 11.8Hz, 1H, H-1^{II}), 4.45 (d, *J* = 7.9Hz, 1H, H-6^{II}), 4.08 (dd, *J* = 6.1Hz, *J* = 11.1Hz, 1H, H-6^{II}), 4.03 - 4.00 (m, 2H, H-6^{I},6'), 4.01 (s, 1H, H-5), 3.82 (t, *J* = 6.8Hz, 1H, H-1^{I}), 3.78 (t, *J* = 9.7Hz, 1H, H-4^{I}), 3.74 - 3.72 (m, 1H, H-5^{II}), 3.66 (s, 1H, C(O)**CH3**), 3.60 (dd, *J* = 1.9Hz, *J* = 9.5Hz, 1H, H-5^{I}), 3.2 - 3.16 (m, 2H, H-3), 2.37 - 2.29 (m, 2H, H-1), 2.09, 2.03, 2.00, 1.99, 1.97, 1.96, 1.90 (7S,3H each,-C(O)CH_3); **^{13}C-NMR** (150MHz) δ 171.27, 170.415, 170.33, 170.16, 170.08, 169.88, 169.81, 169.01, 142.90, 123.35, 100.91, 75.80, 74.28, 73.89, 71.36, 70.94, 70.56, 68.99, 66.55, 61.77, 60.72, 53.71, 52.50, 51.65, 38.42, 36.58, 29.20, 27.52, 20.89, 20.78, 20.64, 20.61, 20.48. **HRMS** (**ESI)** calcd for $C_{35}H_{48}N_4O_{20}$ + $[H]^+$: 845.2940 found: 845.2927.

Compound 3.81

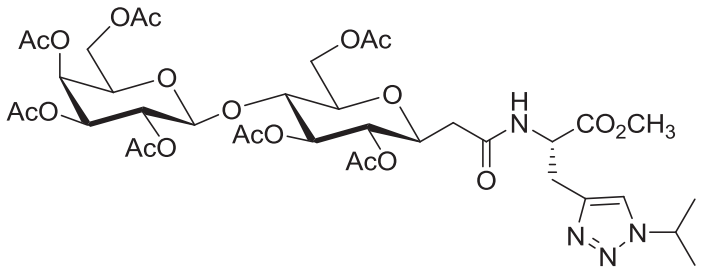


A. To a solution of compound **3.79** (0.05 g, 63 μmol) in 2 mL THF:H_2O (1:1), EtBr (2eq) NaN_3 (3 eq), $CuSO_4.5H_2O$ (3 mg 20%) and sodium ascorbate (5 mg, 40%) were

added and after 12h of reaction time at 40°C following the general procedure described above, β-D-lactopyranoside **3.81** (28 mg, 32 μmol) was obtained.

B. Ethyl azide was distilled at 90°C while preparing it in another RBF (EtBr (1eq) + NaN3(2eq) + DMF + Water (1:1)) then added to another RBF containing the solution of compound **3.79** (0.05 g, 63 μmol) in 2 mL THF:H_2O (1:1), $CuSO_4.5H_2O$ (3 mg 20%) and sodium ascorbate (5 mg, 40%) for 16 hrs of reaction time, following the general procedure (7.2.1) described above to obtain β-D-lactopyranoside **3.81** (35mg, 40 μmol); $\mathbf{R}_f$ 0.28 (DCM/MeOH 9.7:0.3); $[\alpha]_D^{25}$ + 3.61 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz) δ 7.39 (s, 1H, H-4), 7.24 (d, *J* = 7.4Hz, 1H, NH), 5.35 (d, *J* = 3.4Hz, 1H, H-4”), 5.17 (t, *J* = 9.2Hz, 1H, H-3”), 5.12 (dd, *J* = 8.0Hz, *J* = 10.3Hz, 1H, H-3’), 4.96 (dd, *J* = 3.4Hz, *J* = 10.4Hz, 1H, H-2”), 4.90 - 4.89 (m, 1H, H-2), 4.81 (t, *J* = 9.6Hz, 1H, H-2’), 4.58 (d, *J* = 12.1Hz, 1H, H-1”), 4.51 (d, *J* = 7.9Hz, 1H, H-6”), 4.38 (dd, *J* = 7.4Hz, *J* = 14.7Hz, 2H, H-5), 4.15 (dd, *J* = 6.1Hz, *J* = 11.1Hz, 1H, H-6”), 4.11 - 4.06 (m, 2H, H-6’,6’), 3.88 (t, *J* = 6.8Hz, 1H, H-1’), 3.84 (t, *J* = 9.5Hz, 1H, H-4’), 3.80 - 3.79 (m, 1H, H-5”), 3.72 (s, 3H, C(O)**CH3**) 3.67 (dd, *J* = 1.7Hz, *J* = 9.9Hz, 1H, H-5”), 3.35 - 3.19 (m, 2H, H-3), 2.47 - 2.34 (m, 2H, H-1), 2.16, 2.10, 2.07, 2.06, 2.04, 2.02, 1.97 (7S,3H each,-C(O)CH_3), 1.55 (t, 1H, *J* = 7.3Hz, H-6); **^{13}C-NMR** (150MHz) δ 171.24, 170.42, 170.32, 170.14, 170.07, 169.87, 169.79, 169.08, 169.01, 142.83, 121.70, 100.96, 76.63, 75.85, 74.30, 73.96, 71.44, 71.00, 70.63, 69.06, 66.81, 52.51, 51.87, 45.47, 38.47, 29.66, 27.53, 20.92, 20.80, 20.67, 20.62, 20.61, 20.49. **HRMS (ESI)** calcd for $C_{36}H_{50}N_4O_{20}$ + $[H]^+$: 859.3097 found: 859.3085.

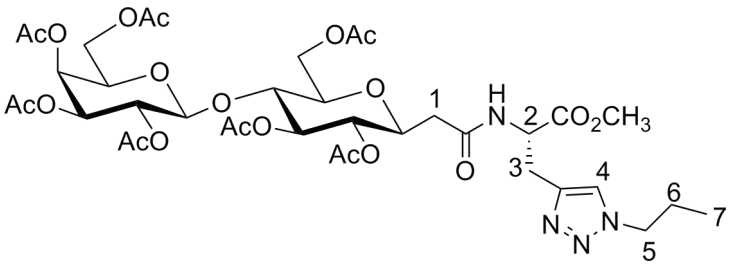
Compound 3.82



To a solution of compound **3.79** (0.1 g, 126 µmol) in 2 mL THF:H_2O (1:1), n-propyl azide (15 mg, 190 µmol) $CuSO_4.5H_2O$ (6 mg 20%) and sodium ascorbate (10 mg, 40%) were added and after 16 hrs of reaction time following the general procedure (**8.2.1**) described above, β-D-lactopyranoside **3.82** (73 mg, 83 µmol) was obtained; $\mathbf{R}_f$ 0.25 (DCM/MeOH 9.7:0.3); $[\alpha]_D^{25}$ + 9.61 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz) δ 7.38 (s, 1H, H-4), 7.29 (d, *J* = 8.0Hz, 1H, NH), 5.34 (d, *J* = 3.4Hz, 1H,H-4"), 5.15 (t, *J* = 9.3Hz, 1H, H-3"), 5.10 (dd, *J* = 8.0Hz, *J* = 10.4Hz, 1H, H-3'), 4.94 (dd, *J* = 3.4Hz, *J* = 10.4Hz, 1H, H-2"), 4.87 (dd, *J* = 5.6Hz, *J* = 13.1 Hz, 1H, H-2), 4.80 (t, *J* = 9.7Hz, 1H, H-2'), 4.76 (dd, *J* = 6.7Hz, *J* = 13.4Hz, 1H, H-5), 4.56 (d, *J* = 11.1Hz, 1H, H-1"), 4.49 (d, *J* = 7.9Hz, 1H, H-6"), 4.13 (dd, *J* = 6.3Hz, *J* = 11.1 Hz, 1H, H-6"), 4.06 - 4.09 (m, 2H, H-6',6') 3.87 (t, *J* = 6.9 Hz, 1H, H-1'), 3.83 (t, *J* = 9.5 Hz, 1H, H-4'), 3.77 - 3.73 (m, 1H, H-5"), 3.69 (s, 1H, C(O)**CH3**), 3.67 - 3.66 (m, 1H, H-5'), 3.24 (ddd, *J* = 5.4Hz, *J* = 15.0Hz, *J* = 19.6Hz, 2H, H-3), 2.39 - 2.37 (m, 2H, H-1), 2.14, 2.09, 2.06, 2.04, 2.02, 2.01, 1.95 (7S,3H each,-C(O)CH_3), 1.55 (dd, *J* = 3.8Hz, *J* = 6.7Hz, 1H, H-6,7); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.25, 170.33, 170.28, 170.11, 170.04, 169.84, 169.76, 169.05, 168.98, 142.54, 119.57, 100.94, 76.57, 75.85, 74.28, 73.95, 71.46, 70.98, 70.59, 69.03, 66.59, 61.84, 60.75, 53.00,

52.42, 51.71, 38.44, 29.63, 27.63, 22.93, 20.88, 20.76, 20.59, 20.46. **HRMS (ESI)** calcd for $C_{37}H_{52}N_4O_{20}$ + $[H]^+$: 873.3253; found: 873.3246.

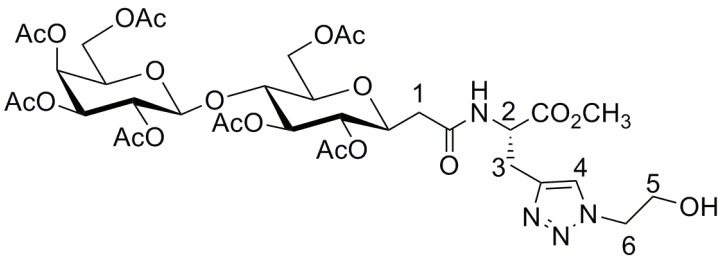
Compound 3.83



To a solution of compound **3.79** (0.1 g, 126 μmol) in 2 mL THF:H_2O (1:1), n-propyl azide (15 mg, 190 μmol) $CuSO_4.5H_2O$ (6 mg 20%) and sodium ascorbate (10 mg, 40%) were added and after 16 hrs of reaction time following the general procedure (7.2.1) described above, β-D-lactopyranoside **3.83** (70 mg, 80 μmol) was obtained; $\mathbf{R}_f$ 0.3 (DCM/MeOH 9.7:0.3); $[\alpha]_D^{25}$ + 14.90 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz) δ 7.34 (s, 1H, H-4''), 7.23 (d, 1H, *J* = 8.0Hz, NH), 5.34 (d, 1H, *J* = 3.3Hz, H-4''), 5.16 (t, 1H, *J* = 9.2Hz, H-3''), 5.10 (dd, 1H, *J* = 8.1Hz, *J* = 10.3Hz, H-3'), 4.95 (dd, 1H, *J* = 3.4Hz, *J* = 10.4Hz, H-2''), 4.88 (dd, 1H, *J* = 5.6Hz, *J* = 12.8Hz, H-2), 4.80 (t, 1H, *J* = 9.6Hz, H-2'), 4.56 (d, 1H, *J* = 12.0Hz, H-1''), 4.50 (d, 1H, *J* = 7.9Hz, H-6''), 4.27 (t, 2H, *J* = 7.0Hz, H-6,6'), 4.13 (dd, 1H, *J* = 6.2Hz, *J* = 11.2Hz, H-6''), 4.10 - 4.05 (m, 2H, H-5), 3.87 (t, 1H, *J* = 6.8Hz, H-1'), 3.83 (t, 1H, *J* = 9.5Hz, H-4'), 3.80 - 3.74 (m, 1H, H-5'), 3.70 (s, 3H, C(O)**CH3**), 3.67 (d, *J* = 6.2 Hz, H-5''), 3.66-3.64 (m, 2H, H-3), 3.24 (ddd, 1H, *J* = 5.3Hz, *J* = 15.0Hz, *J* = 19.6Hz, H-1), 2.38, 2.14, 2.09, 2.06, 2.05, 2.02, 2.01 (7S,3H each,-C(O)CH_3); 1.92 - 1.87 (m, 1H, H-6), 0.93 (t, 1H, *J* = 7.3Hz); **^{13}C-NMR** (151MHz)

171.17, 170.39, 170.31, 170.13, 170.14, 170.06, 169.86, 169.79, 169.09, 169.00, 142.59, 122.23, 100.93, 76.59, 75.82, 74.26, 73.94, 71.41, 70.97, 70.597, 69.02, 66.59, 61.80, 60.74, 52.48, 51.68, 38.42, 27.47, 23.58, 20.89, 20.775, 20.64, 20.60, 20.47, 10.94; **HRMS (ESI).** calcd for $C_{37}H_{52}N_4O_{20}$ + $[H]^+$: 873.3253 found: 873.3237.

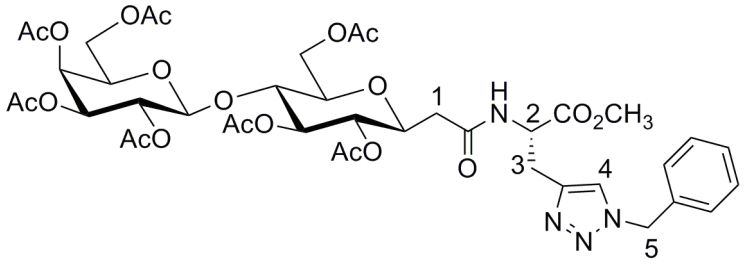
Compound 3.84



To a solution of compound **3.79** (0.065 g, 82 μmol) in 2 mL THF:H_2O (1:1), 2-azidoethanol (10 mg, 123 μmol), $CuSO_4.5H_2O$ (4 mg 20%) and sodium ascorbate (6 mg, 40%) were added and after 16 hrs of reaction time following the general procedure (7.2.1) described above, β-D-lactopyranoside **3.84** (46 mg, 53 μmol) was obtained; $\mathbf{R_f}$ 0.28 (DCM/MeOH 9.7:0.3); $[\alpha]_D^{25}$ + 6.388 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz) δ 7.59 (s, 1H, H-4), 7.31 (d, 1H, *J* = 6.3Hz, NH), 5.34 (d, 1H, *J* = 2.8Hz, H-4”), 5.16 (t, 1H, *J* = 9.3Hz, H-3”), 5.09 (dd, 1H, *J* = 8.1Hz, *J* = 10.3Hz, H-2”), 4.96 (dd, 1H, *J* = 3.4Hz, *J* = 10.4Hz, H-2”), 4.89 (dd, 1H, *J* = 5.5Hz, *J* = 13.0Hz, H-2), 4.78 (t, 1H, *J* = 9.6Hz, H-2’), 4.54 (d, 1H, *J* = 12.1Hz, H-1”), 4.50 (d, 1H, *J* = 8.0Hz, H-6”), 4.48 - 4.41 (m, 2H, H-6), 4.14 (dd, 1H, *J* = 6.1Hz, *J* = 11.1Hz, H-6”), 4.08 - 4.03 (m, 2H, H-6,6’), 4.00 (t, 2H, *J* = 4.4Hz, H-5), 3.88 (t, 1H, *J* = 6.9Hz, H-1’), 3.81 (t, 1H, *J* = 9.5Hz, H-4’), 3.75 (s, 3H, C(O)**CH3**), 3.74 - 3.71 (m, 1H, H-5’), 3.62 (dd, 1H, *J* = 1.8Hz, *J* = 9.9Hz, H-5”), 3.29 (d,

2H, *J* = 4.4Hz, H-3), 2.37 - 2.36 (m, 2H, H-1), 2.15, 2.10, 2.07, 2.05, 2.02, 2.02, 1.96 (7S,3H each,-C(O)CH_3); **^{13}C-NMR** (151MHz) δ 171.12, 170.85, 170.35, 170.12, 170.03, 169.90, 169.33, 169.24, 142.18, 124.12, 100.83, 76.47, 75.78, 74.29, 73.85, 71.36, 70.86, 70.58, 69.09, 66.58, 61.84, 60.83, 60.73, 53.11, 52.64, 51.61, 38.37, 27.55, 20.93, 20.77, 20.64, 20.59, 20.46; **HRMS (ESI)** calcd for $C_{36}H_{50}N_4O_{21}$ + $[H]^+$: 875.3046; found: 875.3028.

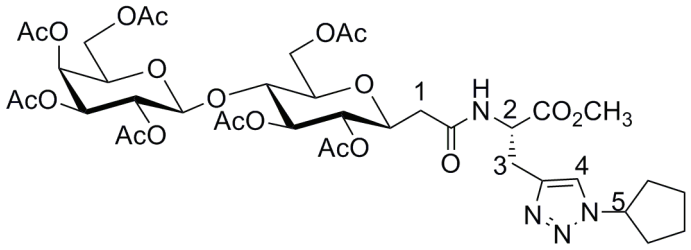
Compound 3.85



To a solution of compound **3.79** (0.1 g, 126 μmol) in 2 mL THF:H_2O (1:1), benzyl azide (25 mg, 190 μmol) $CuSO_4.5H_2O$ (6 mg, 20%) and sodium ascorbate (10 mg, 40%) were added and after 16 hrs of reaction time following the general procedure (7.2.1) described above, β-D-lactopyranoside **3.85** (81 mg, 88 μmol) was obtained; $\mathbf{R}_f$ 0.3 (DCM/MeOH 9.7:0.3); $[\alpha]_D^{22}$ + 8.26 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz) δ 7.43 - 7.35 (m, 3H, H_{Arom}), 7.30 (s, 1H, H-4) 7.26 - 7.21 (m, 1H, H_{Arom}), 7.18 (d, 1H, *J* = 8.1Hz, NH), 5.48 (s, 1H, H-5), 5.35 (d, 1H, *J* = 3.2Hz, H-4''), 5.16 - 5.09 (m, 1H, H-3''), 4.96 (dd, 1H, *J* = 3.5Hz, *J* = 10.4Hz, H-3'), 4.88 (td, 1H, *J* = 5.6Hz, *J* = 7.7Hz, H-2), 4.78 (t, 1H, *J* = 9.7Hz, H-2'), 4.59 (dd, 1H, *J* = 1.4Hz, *J* = 12.1Hz, H-1''), 4.49 (d, 1H, *J* = 8.0Hz, H-6''), 4.14 (dd, 1H, *J* = 6.2Hz, *J* = 11.2Hz, H-6'), 4.09 (dd, 1H, *J* = 7.5Hz, *J* = 11.1Hz, H-6'), 4.04 (dd, 1H, *J*

= 3.9Hz, *J* = 12.3Hz, H-6''), 3.88 (t, 1H, *J* = 6.9Hz, H-1'), 3.81 (t, 1H, *J* = 9.6Hz, H-4'), 3.66 (s, 1H, C(O)**CH3**), 3.64 (dd, 1H, *J* = 4.9Hz, *J* = 8.0Hz, H-5'), 3.52 (ddd, 1H, *J* = 1.9Hz, *J* = 3.6Hz, *J* = 10.1Hz, H-5''), 3.23 (dq, 2H, *J* = 5.5Hz, *J* = 15.1Hz, H-3), 2.36 (m, 2H, H-1), 2.16, 2.08, 2.07, 2.05, 2.04, 2.03,1.97 (7S,3H each,-C(O)CH_3); **^{13}C-NMR** (150MHz) δ 171.111, 170.287, 170.214, 170.050, 169.959, 169.745, 169.703, 168.940, 168.891, 134.520, 129.091, 128.996, 128.981, 128.778, 127.817, 121.900, 100.852, 76.450, 75.687, 74.102, 73.757, 71.311, 70.834, 70.472, 68.885, 66.489, 61.548, 60.659, 53.941, 52.319, 51.492, 38.349, 27.590, 20.791, 20.681, 20.547, 20.517, 20.494, 20.379; **HRMS (ESI)** calcd for $C_{41}H_{52}N_4O_{20}$ + $[H]^+$: 921.3253, found: 921.3230.

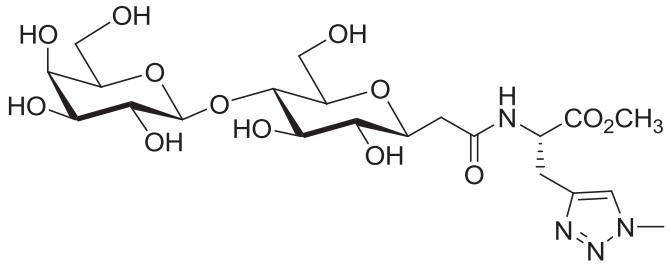
Compound 3.86



To a solution of compound **3.79** (0.1 g, 126 μmol) in THF:H_2O (1:1) 2 mL, cyclopentyl azide (21 mg, 190 μmol) $CuSO_4.5H_2O$ (6 mg, 20%) and sodium ascorbate (10 mg, 40%) were added and after 16 hrs of reaction time following the general procedure (**7.2.1**) described above, β-D-lactopyranoside **3.86** (68 mg, 76 μmol) was obtained; $\mathbf{R}_f$ 0.25 (DCM/MeOH 9.7:0.3); $[\alpha]_D^{25}$ + 9.03 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.34 (s, 1H, H-4), 7.24 (d, *J* = 8.0Hz, 1H, NH), 5.33 (d, *J* = 3.1Hz, 1H, H-4''), 5.14 (t, *J* = 9.2Hz, 1H, H-3''), 5.09 (dd, *J* = 8.0Hz, *J* = 10.4Hz, 1H, H-3'), 4.94 (dd, *J* = 3.4Hz, *J* =

10.4Hz, 1H, H-2''), 4.85 (td, *J* = 7.4Hz, *J* = 10.0Hz, 2H, H-2, 5), 4.79 (t, *J* = 9.6Hz, 1H, H-2'), 4.55 (dd, *J* = 1.6Hz, *J* = 12.2Hz, 1H, H-1''), 4.49 (d, *J* = 7.9Hz, 1H, H-6''), 4.12 (dd, *J* = 6.3Hz, *J* = 11.1Hz, 1H, H-6"), 4.06 (dd, *J* = 5.5Hz, *J* = 16.1Hz, 2H, H-6, 6'), 3.86 (t, *J* = 6.9Hz, 1H, H-1'), 3.81 (t, *J* = 9.6Hz, 1H, H-4'), 3.76 - 3.72 (m, 1H, H-5'), 3.68 (s, 3H, C(O)**CH_3**), 3.64 (ddd, *J* = 1.8Hz, *J* = 3.9Hz, *J* = 10.0Hz, 1H, H-5"), 3.21 (ddd, *J* = 5.5Hz, *J* = 15.1Hz, *J* = 19.7Hz, 2H, H-3), 2.40 - 2.33 (m, 2H, H-1), 2.23 - 2.20 (m, 2H, cyclopentyl **CH_2**) 2.13, 2.07, 2.04, 2.03, 2.01s, 2.00, 1.94 (7S, 3H each,-C(O)CH_3), 1.90 - 1.81 (m, 2H, cyclopentyl **CH_2**), 1.78 - 1.72 (m, 2H, cyclopentyl **CH_2**); **^{13}C-NMR** (150MHz, $CDCl_3$) δ 171.23, 170.30, 170.24, 170.07, 169.98, 169.79, 169.71, 168.99, 168.94, 142.52, 120.53, 100.90, 76.55, 75.82, 74.26, 73.93, 71.43, 70.94, 70.57, 69.00, 66.58, 61.80, 60.72, 53.36, 51.66, 38.43, 33.28, 33.23, 27.57, 23.92, 20.82, 20.72, 20.59, 20.54, 20.41; **HRMS (ESI)** calcd for $C_{39}H_{54}N_4O_{20}$ + [H] $^+$: 899.3410, found: 899.3397.

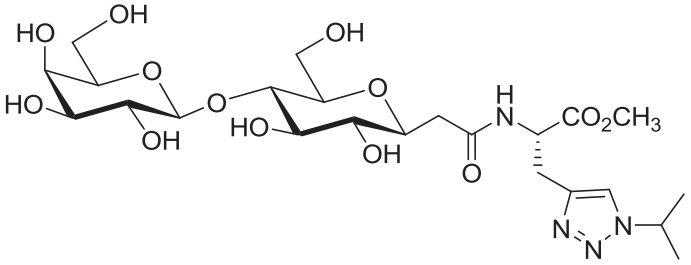
Compound 3.87



To a solution of compound **3.80** (0.020 g, 23 μmol) in 2 mL of dry methanol, 0.1 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**7.2.4**) described above to obtain the deprotected β-D-*C*-

lactopyranoside **3.87** (12 mg, 22 μmol); $\mathbf{R}_f$ 0.20 (CH_2Cl_2/MeOH 4:1); $[\alpha]_D^{24}$ + 7.89 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.80 (s, 1H), 4.83 - 4.80 (m, 1H), 4.45 (d, *J* = 7.6 Hz, 1H), 4.07 (s, 3H), 3.94 (d, *J* = 19.7 Hz, 2H), 3.86 - 3.78 (m, 2H), 3.76 (s, 3H), 3.71 (d, *J* = 22.4 Hz, 2H), 3.68 - 3.58 (m, 4H), 3.54 (t, *J* = 8.8 Hz, 1H), 3.44 (s, 1H), 3.33 – 3.15 (m, 3H), 2.78 (t, *J* = 12.6 Hz, 1H), 2.42 (dd, *J* = 14.7, 9.4 Hz, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 173.99, 173.27, 143.21, 125.90, 103.37, 89.92, 88.83, 79.25, 76.54, 76.31, 75.89, 73.34, 73.28, 72.01, 69.18, 61.69, 60.60, 53.66, 53.03, 38.89, 37.07, 27.49. **HRMS (ESI)** calcd for $C_{20}H_{34}N_4O_{14}$ + $[H]^+$: 551.2201; found: 551.2197

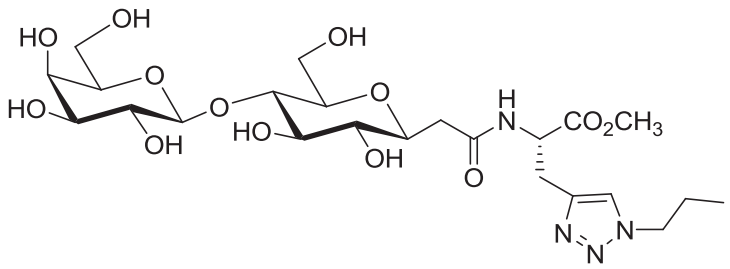
Compound 3.88



To a solution of compound **3.82** (0.015 g, 17 μmol) in 2 mL of dry methanol, 0.1 ml of NaOMe /MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**7.2.4**) described above to obtain the deprotected β-D-*C*-lactopyranoside **3.88** (9 mg, 16 μmol); $\mathbf{R}_f$ 0.18 (CH_2Cl_2/MeOH 4:1); **^{1}H NMR** (600 MHz, D_2O) δ 7.95 (s, 1H), 4.90 - 4.80 (m, 1H), 4.55 (dt, *J* = 19.7, 5.6 Hz, 1H), 4.47 - 4.38 (m, 2H), 3.99 - 3.88 (m, 2H), 3.79 (s, 3H), 3.77 - 3.73 (m, 2H), 3.71 (dt, *J* = 15.0, 7.2 Hz, 1H), 3.68 - 3.57 (m, 4H), 3.53 (dd, *J* = 9.7, 8.1 Hz, 1H), 3.46 - 3.27 (m, 4H), 3.11 (dd, *J* = 14.1, 10.0 Hz, 1H), 3.07 - 2.98 (m, 1H), 2.96 - 2.88 (m, 1H), 2.79 (dt, *J* = 14.5,

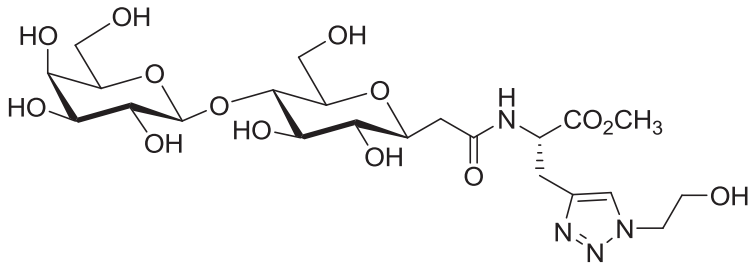
7.1 Hz, 1H), 1.53 (dd, *J* = 6.7, 1.4 Hz, 6H); **^{13}C NMR** (150 MHz, D_2O) δ 173.47, 142.62, 122.70, 103.51, 78.92, 78.82, 76.59, 76.36, 76.01, 73.31, 73.18, 71.61, 69.23, 61.70, 60.76, 54.41, 53.67, 53.24, 38.68, 30.89, 27.60, 22.66; **HRMS (ESI)** calcd for $C_{23}H_{38}N_4O_{13}$+ $[H]^+$: 579.2514, found: 579.2506.

Compound 3.89



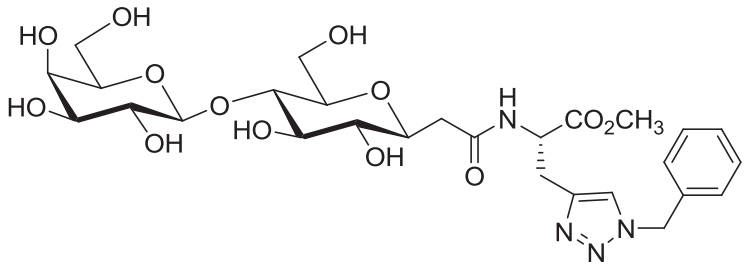
To a solution of compound **3.83** (0.040 g, 45 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**7.2.4**) described above to obtain the deprotected β-D-*C*-lactopyranoside **3.89** (23 mg, 41 μmol); $\mathbf{R}_f$ 0.18 (CH_2Cl_2:MeOH 4:1); $[\alpha]_D^{24}$ + 8.02 (*c* 1 in MeOH); ^{1}H NMR (600 MHz, D_2O) δ 7.95 (s, 1H), 4.78 - 4.71 (m, 1H), 4.44 (d, *J* = 7.6 Hz, 1H), 4.35 (t, *J* = 6.7 Hz, 2H), 3.92 (d, *J* = 2.8 Hz, 1H), 3.87 - 3.75 (m, 4H), 3.74 (s, 3H), 3.72 (d, *J* = 8.8 Hz, 2H), 3.68 - 3.58 (m, 4H), 3.54 (dd, *J* = 17.6, 8.6 Hz, 1H), 3.44 (d, *J* = 8.5 Hz, 1H), 3.33 – 3.15 (m, 3H), 2.85 - 2.62 (m, 1H), 2.50 - 2.33 (m, 1H), 1.93 - 1.77 (m, 2H), 0.89 - 0.75 (m, 3H); ^{13}C NMR (151 MHz, D_2O) δ 173.78, 173.38, 143.27, 124.88, 103.49, 78.87, 76.55, 76.33, 75.97, 73.29, 73.15, 71.58, 69.18, 61.66, 60.64, 53.63, 53.20, 52.63, 38.68, 30.89, 27.49, 23.68, 10.68; **HRMS (ESI)** calcd for $C_{23}H_{38}N_4O_{13}$+ $[H]^+$: 579.2514, found: 579.2508.

Compound 3.90



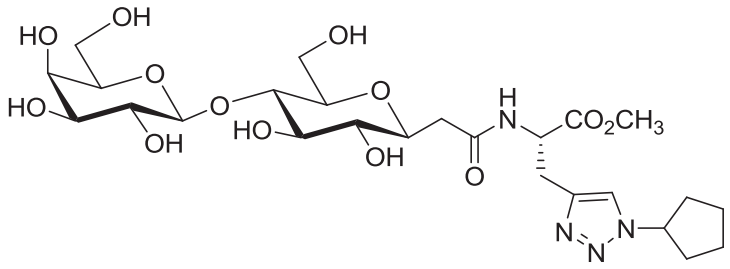
To a solution of compound **3.84** (0.043 g, 49 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (7.2.4) described above to obtain the deprotected β-D-*C*-lactopyranoside **3.90** (26 mg, 45 μmol); $\mathbf{R}_f$ 0.12 (CH_2Cl_2/MeOH 4:1); $[\alpha]_D^{24}$ + 11 (*c* 1 in MeOH); ^{1}H NMR (600 MHz, D_2O) δ 7.87 (s, 1H), 4.81 (dd, *J* = 12.2, 6.0 Hz, 1H), 4.52 (dd, *J* = 11.8, 6.8 Hz, 2H), 4.44 (d, *J* = 7.8 Hz, 1H), 3.97 (t, *J* = 5.1 Hz, 3H), 3.92 (d, *J* = 3.3 Hz, 1H), 3.87 - 3.77 (m, 3H), 3.75 (s, 3H), 3.72 (tt, *J* = 12.8, 6.6 Hz, 2H), 3.62 (tdd, *J* = 15.8, 9.3, 3.5 Hz, 4H), 3.57 - 3.52 (m, 1H), 3.45 (dd, *J* = 4.6, 2.2 Hz, 1H), 3.33 - 3.19 (m, 3H), 2.77 (tt, *J* = 16.4, 8.2 Hz, 1H), 2.42 (ddd, *J* = 22.9, 11.2, 6.6 Hz, 1H); **^{13}C NMR** (151 MHz, D_2O) δ 173.34, 172.87, 142.70, 124.80, 102.95, 78.31, 78.32, 76.00, 75.79, 75.43, 72.76, 72.61, 71.04, 68.65, 61.13, 60.19, 60.10, 53.14, 52.70, 52.54, 38.23, 38.14, 26.91; **HRMS (ESI)** calcd for $C_{22}H_{36}N_4O_{14}$+ $[H]^+$: 581.2306, found 581.2300.

Compound 3.91



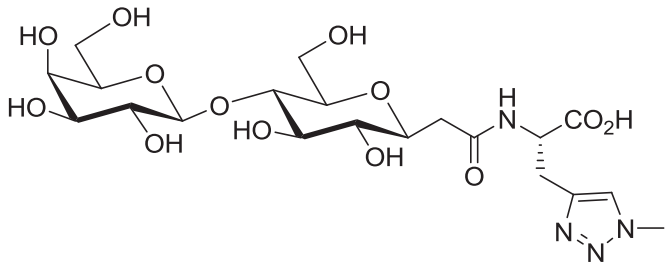
To a solution of compound **3.85** (0.070 g, 76 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above to obtain the deprotected β-D-*C*-lactopyranoside **3.91** (42 mg, 68 μmol); $\mathbf{R}_f$ 0.25 (CH_2Cl_2/MeOH 4:1); $[\alpha]_D^{24}$ + 7.87 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.81 (s, 1H), 5.53 (s, 2H), 4.78 - 4.64 (m, 2H), 4.41 (d, *J* = 7.7 Hz, 1H), 3.92 (d, *J* = 3.2 Hz, 1H), 3.77 (ddd, *J* = 15.7, 11.9, 6.3 Hz, 3H), 3.72 – 3.68 (m, 3H), 3.67 (s, 3H), 3.66 – 3.61 (m, 2H), 3.54 (dddd, *J* = 19.1, 12.1, 9.3, 3.5 Hz, 4H), 3.30 - 3.19 (m, 2H), 3.18 - 3.08 (m, 1H), 2.78 - 2.62 (m, 1H), 2.43 - 2.26 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 165.87, 165.42, 142.22, 135.85, 127.75, 121.98, 121.59, 120.71, 117.04, 95.67, 71.01, 70.92, 68.65, 68.44, 68.15, 65.49, 65.36, 63.75, 61.36, 53.84, 52.75, 46.59, 45.77, 45.21, 30.89, 23.04, 19.73; **HRMS (ESI)** calcd for $C_{27}H_{38}N_4O_{13}$+ $[H]^+$: 627.2514, found: 627.2510.

Compound 3.92



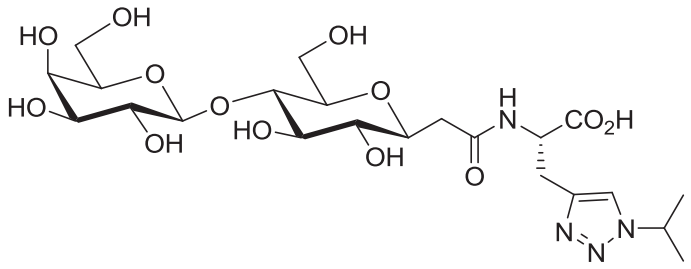
To a solution of compound **3.86** (0.040 g, 44 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above to obtain the deprotected β-D-*C*-lactopyranoside **3.92** (25 mg, 41 μmol); $\mathbf{R}_f$ 0.16 (CH_2Cl_2/MeOH 4:1); $[\alpha]_D^{24}$ + 8.82 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.86 (s, 1H), 5.00 - 4.93 (m, 1H), 4.78 - 4.69 (m, 1H), 4.44 (dd, *J* = 7.8, 1.0 Hz, 1H), 3.92 (t, *J* = 6.1 Hz, 1H), 3.86 - 3.75 (m, 4H), 3.74 (s, 3H), 3.74 - 3.69 (m, 2H), 3.66 (dt, *J* = 6.6, 4.5 Hz, 2H), 3.64 - 3.58 (m, 2H), 3.54 (dd, *J* = 17.4, 9.0 Hz, 2H), 3.46 - 3.38 (m, 1H), 3.31 - 3.14 (m, 4H), 2.83 - 2.70 (m, 1H), 2.43 (qd, *J* = 14.9, 9.3 Hz, 1H), 2.30 - 2.18 (m, 2H), 2.00 - 1.90 (m, 2H), 1.86 - 1.69 (m, 4H); **^{13}C NMR** (150 MHz, D_2O) δ 174.26, 173.46, 143.19, 123.44, 103.49, 78.88, 76.57, 76.34, 75.99, 73.37, 73.29, 73.17, 71.59, 69.20, 62.98, 61.67, 60.64, 53.65, 53.32, 53.16, 38.68, 33.48, 33.44, 27.56, 24.21; **HRMS (ESI)** calcd for $C_{25}H_{40}N_4O_{13}$+ $[H]^+$: 605.2670; found: 605.2663.

Compound 3.93



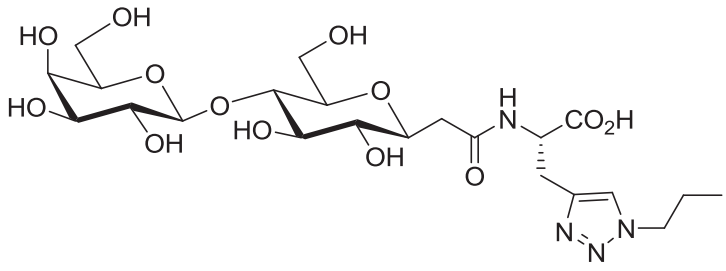
To a solution of compound **3.87** (10 mg, 1.8 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added LiOH.H_2O 1M soln. (0.018mL, 1eq) and stirred for 2 hrs, according to general saponification procedure (**8.2.5**) to obtain **3.93** (9 mg, 95%); $\mathbf{R}_f$ 0.20 (ACN/ H_2O 8:2); $[\alpha]_D^{22}$ + 8.01 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.83 (s, 1H), 4.43 (dd, *J* = 7.8, 3.6 Hz, 2H), 4.07 (d, *J* = 8.4 Hz, 3H), 3.92 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.85 - 3.74 (m, 3H), 3.74 – 3.68 (m, 3H), 3.63 (tdd, *J* = 12.3, 9.8, 5.6 Hz, 5H), 3.54 (dt, *J* = 13.7, 7.9 Hz, 2H), 3.42 (t, *J* = 13.7 Hz, 1H), 3.35 - 3.28 (m, 1H), 3.27 - 3.17 (m, 2H), 2.76 (ddd, *J* = 32.3, 19.7, 12.3 Hz, 1H), 2.47 - 2.37 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 103.51, 90.11, 80.46, 78.86, 76.68, 76.39, 76.31, 75.99, 73.37, 73.18, 72.55, 71.61, 69.22, 61.70, 60.85, 30.88, 21.77.

Compound 3.94



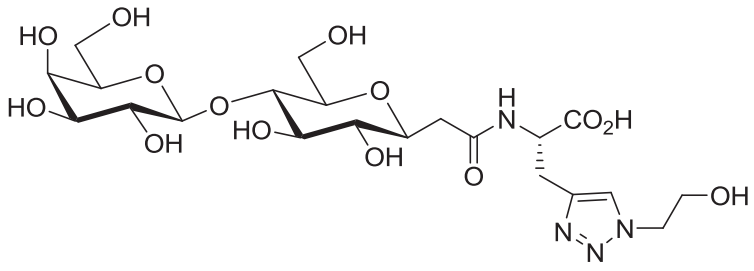
To a solution of compound **3.88** (9 mg, 1.8 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added LiOH.H_2O 1M soln. (0.018mL, 1eq) and stirred for 2 hrs, according to general saponification procedure (**8.2.5**) to obtain **3.94** (8mg, 90%); $\mathbf{R}_f$ 0.22 (ACN/H_2O 8:2); **^{1}H NMR** (600 MHz, D_2O) δ 7.91 (s, 1H), 4.78 - 4.72 (m, 2H), 4.49 - 4.42 (m, 1H), 3.95 (t, *J* = 10.4 Hz, 2H), 3.88 - 3.77 (m, 3H), 3.74 (ddd, *J* = 19.9, 11.9, 7.9 Hz, 2H), 3.68 (dd, *J* = 10.3, 3.8 Hz, 2H), 3.64 - 3.59 (m, 3H), 3.59 - 3.52 (m, 1H), 3.50 - 3.40 (m, 1H), 3.37 - 3.15 (m, 3H), 2.83 - 2.75 (m, 1H), 2.50 - 2.41 (m, 1H), 1.57 - 1.51 (m, 6H); **^{13}C NMR** (150 MHz, D_2O) δ 175.20, 173.66, 143.39, 122.92, 103.78, 78.91, 76.59, 76.31, 76.07, 73.44, 73.38, 71.90, 69.34, 63.11, 61.81, 60.79, 57.94, 54.58, 53.26, 38.79, 27.90, 22.49.

Compound 3.95



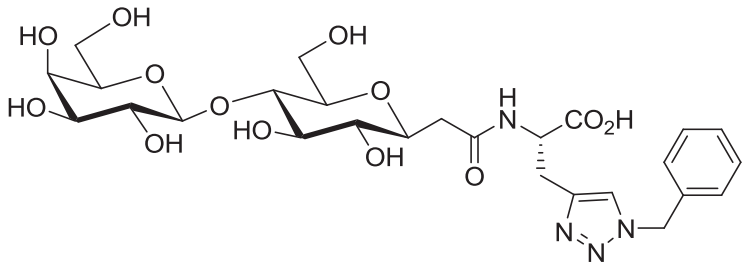
To a solution of compound **3.89** (15 mg, 3.5 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added LiOH.H_2O 1M soln. (0.025mL, 1eq) and stirred for 2 hrs, according to general saponification procedure (7.2.5) to obtain **3.95** (13 mg, 95%); $\mathbf{R}_f$ 0.22 (ACN /H_2O 8:2); $[\alpha]_D^{22}$ + 12.13 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.86 (s, 1H), 4.74 (ddd, *J* = 18.1, 8.0, 5.3 Hz, 1H), 4.46 – 4.42 (m, 1H), 4.35 (t, *J* = 6.8 Hz, 2H), 3.91 (d, *J* = 3.3 Hz, 1H), 3.80 - 3.74 (m, 3H), 3.74 - 3.69 (m, 2H), 3.62 (dddd, *J* = 16.2, 13.1, 9.3, 3.6 Hz, 2H), 3.57 - 3.50 (m, 3H), 3.46 - 3.38 (m, 1H), 3.37 - 3.14 (m, 3H), 2.81 - 2.70 (m, 1H), 2.41 (dt, *J* = 15.2, 8.9 Hz, 1H), 1.92 - 1.80 (m, 2H), 0.87 - 0.79 (m, 3H); **^{13}C NMR** (150 MHz, D_2O) δ 174.72, 173.81, 143.28, 125.02, 103.51, 78.90, 76.57, 76.35, 76.00, 73.31, 73.18, 71.61, 69.22, 61.70, 60.64, 53.18, 52.76, 38.72, 27.54, 23.70, 23.69, 10.71; **HRMS (ESI)** calcd for $C_{20}H_{31}NO_{13}$+ $[H]^+$: 565.2357, found: 565.2349.

Compound 3.96



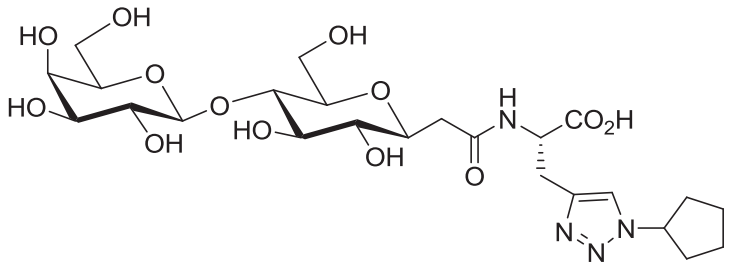
To a solution of compound **3.90** (15 mg, 3.5 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added LiOH.H_2O 1M soln. (0.025 mL, 1eq) and stirred for 2 hrs, according to general saponification procedure (7.2.5) to obtain **3.96** (12 mg, 90%); $\mathbf{R_f}$ 0.19 (ACN/H_2O 8:2); $[\alpha]_D^{22}$ + 16.12 (*c* 1.0, H_2O); ^{1}H NMR (600 MHz, D_2O) δ 7.87 (s, 1H), 4.76 - 4.66 (m, 1H), 4.54 - 4.49 (m, 2H), 4.44 (dd, *J* = 7.8, 2.5 Hz, 1H), 3.99 - 3.95 (m, 2H), 3.92 (d, *J* = 3.4 Hz, 1H), 3.87 - 3.74 (m, 4H), 3.74 - 3.68 (m, 1H), 3.68 - 3.57 (m, 4H), 3.57 - 3.51 (m, 1H), 3.47 - 3.41 (m, 1H), 3.35 - 3.16 (m, 3H), 2.77 (ddd, *J* = 14.9, 7.9, 2.8 Hz, 1H), 2.42 (ddd, *J* = 14.6, 9.3, 5.2 Hz, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 174.98, 173.76, 125.31, 103.51, 78.90, 76.58, 76.35, 75.99, 73.39, 73.33, 73.17, 71.61, 69.22, 61.69, 60.76, 60.65, 53.45, 53.12, 38.74, 27.70; **HRMS (ESI)** calcd for $C_{21}H_{34}N_4O_{14}$+ $[H]^+$: 567.2150, found: 567.2144.

Compound 3.97



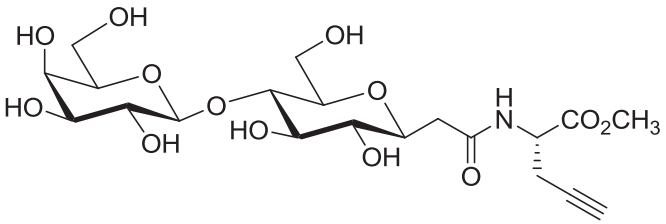
To a solution of compound **3.91** (30 mg, 4.7 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added LiOH.H_2O 1M soln. (0.047 mL, 1eq) and stirred for 2 hrs, according to general saponification procedure (**7.2.5**) to obtain **3.97** (26 mg, 90%); $\mathbf{R}_f$ 0.24 (ACN : H_2O 8:2); $[\alpha]_D^{22}$ + 8.22 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.82 (s, 1H), 7.45 - 7.34 (m, 3H), 7.32 - 7.19 (m, 2H), 5.53 (s, 2H), 4.75 - 4.68 (m, 1H), 4.42 - 4.36 (m, 1H), 3.89 (t, J = 10.4 Hz, 1H), 3.81 – 3.73 (m, 2H), 3.73 – 3.66 (m, 2H), 3.66 – 3.57 (m, 3H), 3.57 - 3.51 (m, 3H), 3.51 - 3.42 (m, 1H), 3.30 - 3.07 (m, 4H), 2.68 (dt, J = 6.1, 2.9 Hz, 1H), 2.38 - 2.20 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 166.96, 165.81, 136.05, 127.75, 121.95, 121.58, 120.70, 117.12, 95.65, 70.97, 70.90, 68.66, 68.42, 68.14, 65.49, 65.36, 63.76, 61.36, 53.84, 52.70, 46.60, 45.24, 23.03, 19.84; **HRMS (ESI)** calcd for $C_{26}H_{36}N_4O_{13}$+ $[H]^+$: 613.2357, found: 613.2350.

Compound 3.98



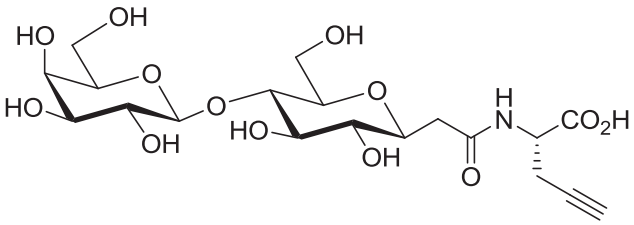
To a solution of compound **3.92** (15 mg, 2.4 μmol) in mixed solvent of THF:MeOH: H_2O (3:2:1) was added LiOH.H_2O 1M soln. (0.024mL, 1eq) and stirred for 2 hrs, according to general saponification procedure (**7.2.5**) to obtain **3.98** (13 mg, 90%); $\mathbf{R}_f$ 0.20 (ACN/H_2O 8:2); $[\alpha]_D^{22}$ + 10.35 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.87 (dd, *J* = 13.4, 5.9 Hz, 1H), 5.02 - 4.92 (m, 1H), 4.69 (dd, *J* = 17.7, 12.2 Hz, 1H), 4.43 (d, *J* = 7.8 Hz, 1H), 3.92 (d, *J* = 3.3 Hz, 1H), 3.86 - 3.69 (m, 5H), 3.68 - 3.48 (m, 5H), 3.46 - 3.36 (m, 1H), 3.36 - 3.23 (m, 2H), 3.21 - 3.10 (m, 1H), 2.75 (dd, *J* = 9.3, 2.3 Hz, 1H), 2.41 (dt, *J* = 15.0, 9.7 Hz, 1H), 2.29 - 2.16 (m, 2H), 2.00 - 1.89 (m, 2H), 1.80 (dd, *J* = 14.1, 8.1 Hz, 2H), 1.75 (dd, *J* = 14.4, 7.1 Hz, 2H); **^{13}C NMR** (151 MHz, D_2O) δ 172.62, 171.08, 120.87, 100.88, 76.29, 76.11, 73.99, 73.74, 73.38, 70.70, 70.57, 69.00, 66.61, 60.43, 59.08, 58.01, 50.84, 36.20, 36.11, 28.28, 25.19, 21.63; **HRMS (ESI)** calcd for $C_{24}H_{38}N_4O_{13}$+ $[H]^+$: 591.2514, found: 591.2503.

Compound 3.99



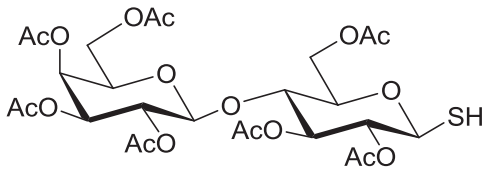
To a solution of compound **3.79** (0.025 g, 31 μmol) in 2 mL of dry methanol, 0.1 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time according to general procedure (**7.2.4**) described above to obtain deprotected β-D-*C*-lactopyranoside **3.99** (15 mg, 90%); $\mathbf{R}_f$ 0.22 (CH_2Cl_2/MeOH 4:1); $[\alpha]_D^{24}$ + 6.54 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 4.67 (td, *J* = 5.9, 2.7 Hz, 1H), 4.50 - 4.42 (m, 1H), 3.93 (t, *J* = 4.0 Hz, 2H), 3.81 (d, *J* = 3.5 Hz, 1H), 3.79 (s, 3H), 3.78 - 3.75 (m, 2H), 3.75 - 3.68 (m, 3H), 3.65 (dt, *J* = 19.3, 6.0 Hz, 3H), 3.58 - 3.49 (m, 2H), 3.33 (q, J = 9.2 Hz, 1H), 2.90 - 2.72 (m, 3H), 2.55 - 2.41 (m, 2H); **^{13}C NMR** (150 MHz, D_2O) δ 174.14, 172.80, 103.31, 78.73, 76.54, 76.25, 75.97, 73.35, 73.20, 72.61, 71.24, 68.96, 61.70, 60.36, 53.67, 51.70, 38.61, 21.28; **HRMS (ESI)** calcd for $C_{20}H_{31}NO_{13}$+ $[H]^+$: 516.1693, found: 516.1687.

Compound 3.100



To a solution of compound **3.99** (10 mg, 20 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added LiOH.H_2O 1M soln. (0.02mL, 1eq) and stirred for 2 hrs, following the general saponification procedure (**7.2.5**) to obtain **3.100** (9 mg, 92%); $\mathbf{R}_f$ 0.19 (ACN /H_2O 8:2); $[\alpha]_D^{22}$ + 7.58 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 4.58 (t, *J* = 5.8 Hz, 1H), 4.47 (t, *J* = 7.2 Hz, 1H), 3.97 - 3.91 (m, 2H), 3.80 (ddd, *J* = 21.2, 11.8, 6.2 Hz, 3H), 3.76 - 3.70 (m, 3H), 3.71 - 3.62 (m, 3H), 3.59 - 3.49 (m, 2H), 3.34 (dd, *J* = 17.3, 8.5 Hz, 1H), 2.88 (dd, *J* = 20.2, 7.7 Hz, 1H), 2.81 - 2.76 (m, 2H), 2.52 (dd, *J* = 15.0, 9.3 Hz, 1H), 2.45 (d, *J* = 1.6 Hz, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 103.51, 90.11, 80.46, 78.86, 76.68, 76.39, 76.31, 75.99, 73.37, 73.18, 72.55, 71.61, 69.22, 61.70, 60.85, 52.55, 30.88, 21.77; **HRMS (ESI)** calcd for $C_{19}H_{29}NO_{13}$+ $[H]^+$: 502.1537, found 502.1529.

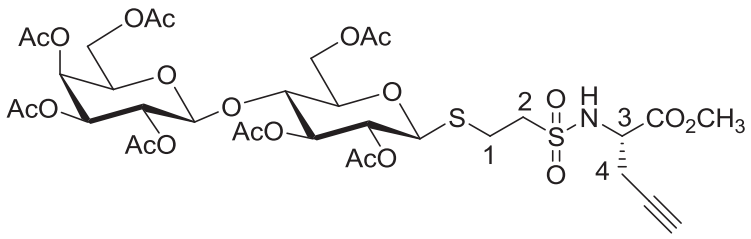
Compound 3.101



To a solution of α-bromo lactose **3.76** (2.2 g, 3.1 mmol) in 25 ml of acetone was added thiourea (0.359g, 4.7 mmol) and the reaction mixture refluxed overnight. The reaction mixture was concentrated to get the thiouronium salt. The thiouronium salt dissolved in 9 ml of water and 12 ml of dichloromethane and 0.84 g 1.5 eq of $K_2S_2O_5$ added then refluxed for 20 minutes. The reaction mixture was allowed to cool to room temperature. The organic and aq. layers were separated. The organic layer washed with satd. brine solution then dried over $MgSO_4$ and concentrated to obtain 1.65 g of crude thiol galactose. The crude product was purified by flash column chromatography using dichloromethane alone to obtain 0.560 g of pure β- lactose thiol **3.101** (60 %); $\mathbf{R}_f$ 0.25 (EtOAc/Hexane 60:40); $[\alpha]_D^{21}$ -10.5 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (300 MHz), 5.34 (d, *J* = 2.7Hz, 1H, H-4^{II}), 5.18 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.10 (dd, *J* = 7.8Hz, *J* = 10.4Hz, 1H, H-3^{I}), 4.96 (d, *J* = 3.4Hz, 1H, H-2^{II}), 4.86 (d, *J* = 9.5Hz, 1H, H-2^{I}), 4.54 (d, *J* = 9.7Hz, 1H, H-1^{II}), 4.44 - 4.40 (m, 1H, H-1^{I}), 4.23 - 3.98 (m, 3H, H-6,6^{II}, H-6^{I}), 3.95 - 3.72 (m, 2H, H-6^{I}, H-5^{I}), 3.63 (ddd, *J* = 1.8Hz, J = 5.2Hz, *J* = 10.0Hz, 1H, H-5^{II}), 2.25 (d, *J* = 9.7Hz, 1H, SH), 2.15, 2.13, 2.07, 2.06, 2.04, 1.96 (7S,21H,-C(O)CH_3); **^{13}C-NMR** (75MHz) δ 170.294, 170.081, 169.998, 169.838, 169.569, 169.038, 101.048, 78.404, 77.110, 76.006,

73.824, 73.418, 70.925, 70.671, 69.009, 66.543, 62.168, 60.757, 20.830, 20.708, 20.591, 20.568, 20.450; **HRMS (ESI)** calcd for $C_{26}H_{36}O_{17}S$ + $[Na]^+$: 675.1571, found 675.1568.

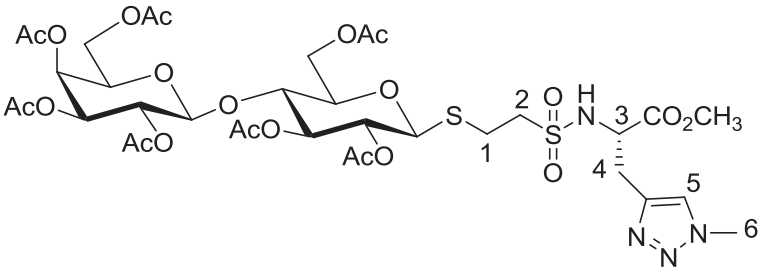
Compound 3.102



To a solution of **6.15** (0.1 g, 153 μmol) and β-D-lactose thiol **3.101** (0.033 g, 153 μmol) in CH_2Cl_2 5mL was added 4 drops of TEA and stirred at RT overnight. The reaction mixture was concentrated on a rotovap and the crude purified by flash column chromatography using 1-2% MeOH in CH_2Cl_2 to obtain β-D-thiolactoyranoside **3.102** (93 mg, 70%); $\mathbf{R}_f$ 0.4 (CH_2Cl_2/MeOH 9.7:0.3); $[\alpha]_D^{21}$ -8.44 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 5.40 (d, *J* = 8.8Hz, 1H, NH), 5.34 (d, *J* = 3.3Hz, 1H, H-4^{II}), 5.20 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.09 (dd, *J* = 8.0Hz, *J* = 10.3Hz, 1H, H-3^{I}), 4.96 (dd, *J* = 3.5Hz, *J* = 10.6Hz, 1H, H-2^{II}), 4.92 (d, *J* = 9.9Hz, 1H, H-2^{I}), 4.55 (dd, *J* = 6.4Hz, *J* = 11.0Hz, 1H, H-1^{II}), 4.49 (d, *J* = 7.9Hz, 1H, H-1^{I}), 4.32 (td, *J* = 5.0Hz, *J* = 9.7Hz, 1H, H-3), 4.12 - 4.04 (m, 4H, H-6^{I},6^{I}, 6^{II}, 6^{II}), 3.88 (t, *J* = 6.8Hz, 1H, H-4^{I}), 3.80 (s, 3H, C(O)**CH$_3$**), 3.77 (t, *J* = 9.5Hz, 1H, H-5^{II}), 3.46 - 3.33 (m, 2H, H-1), 3.44 (ddd, *J* = 5.1Hz, *J* = 11.4Hz, *J* = 16.1Hz, 1H, H-2), 2.78 (ddq, *J* = 2.6Hz, *J* = 5.0Hz, *J* = 17.1Hz, 1H, H-4), 2.14, 2.13, 2.05, 2.03, 2.03, 1.95 (6S,21H,-C(O)CH_3); **^{13}C-NMR** (150MHz, $CDCl_3$) δ 170.596, 170.544, 170.280, 170.053, 169.986, 169.590, 169.531, 101.027, 83.745, 77.768, 76.866,

75.989, 73.423, 72.565, 70.850, 70.635, 69.791, 69.008, 66.540, 61.788, 60.729,54.941, 54.258, 53.132, 24.117, 24.015, 20.786, 20.696, 20.628, 20.592, 20.576, 20.548, 20.444; **HRMS (ESI)** calcd for $C_{34}H_{47}NO_{21}S_2$ + $[Na]^+$: 892.1980, found: 892.1960.

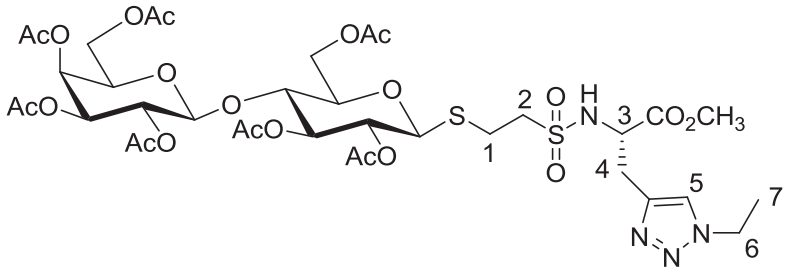
Compound 3.103



To a solution of compound **3.102** (0.065 g, 74 μmol) in 2 mL THF (dry), methyl azide (7 mg, 112 μmol) CuI (1 mg 20%) and DIPEA (1 drop) were added and after 12 hrs of reaction time following the general procedure (**8.2.3**) described above, β-D-*S* lactopyranoside **3.103** (41 mg, 60%) was obatianed; $\mathbf{R}_f$ 0.26 (CH_2Cl_2/MeOH 9.7:0.3); $[\alpha]_D^{24}$ +1.16 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.47 (s, 1H, H-5), 5.92 (d, *J* = 8.5Hz, 1H, H-NH), 5.32 (d, *J* = 1.2Hz, 1H, H-4^{II}), 5.18 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.06 (t, *J* = 9.1Hz, 1H, H-3^{I}), 4.95 (dd, *J* = 2.9Hz, *J* = 10.4Hz, 1H, H-2^{II}), 4.89 (t, *J* = 9.7Hz, 1H, H-2^{I}), 4.56 (d, *J* =10.1Hz, 1H, H-1^{II}), 4.50 - 4.46 (m, 3H, H-1^{II}, 3, 6^{II}, 6), 4.10 - 4.02 (m, 3H, H-6,6^{I}, 6^{II}), 4.06 (s, 3H, H-6), 3.88 (t, *J* = 6.6Hz, 1H, H-4^{I}), 3.77 - 3.74 (m, 1H, H-5^{I}), 3.74 (s, 3H, C(O)O**CH_3**), 3.64 (dd, *J* = 5.7Hz, *J* = 7.6Hz, 1H, H-5^{II}), 3.39 - 3.34 (m, 2H, H-1), 3.31 - 3.25 (m, 2H, H-4), 2.98 - 2.95 (m, 2H, H-2), 2.12, 2.09, 2.03, 2.01, 1.93 (5S, 21H, C(O)CH_3); **^{13}C-NMR** (150MHz, $CDCl_3$) δ 171.44, 170.53, 170.23, 170.017, 169.92, 169.55, 169.52, 168.97, 142.16, 123.51, 100.98, 83.74, 76.69, 76.03,

73.46, 70.85, 70.57, 69.83, 69.02, 66.56, 61.90, 60.69, 60.26, 55.17, 54.65, 52.88, 36.77, 28.92, 24.23, 20.70, 20.65, 20.59, 20.52, 20.49, 20.38, 14.07; **HRMS (ESI)** calcd for $C_{35}H_{50}N_4O_{21}S_2 + [H]^+$: 927.2487; found: 927.2476.

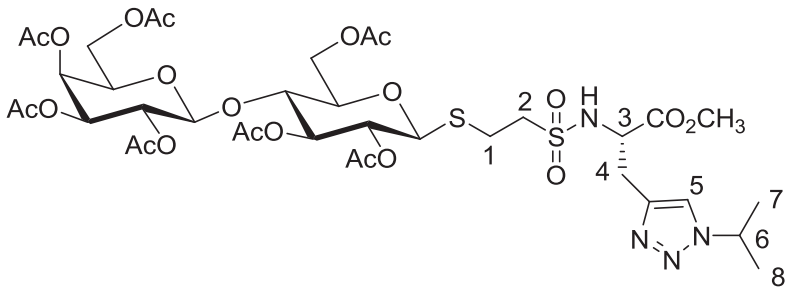
Compound 3.104



To the solution of compound **3.102** (0.065 g, 74 μmol) in 2 mL THF (dry), ethyl azide (8 mg, 112 μmol) CuI (1 mg 20%) and DIPEA (1 drop) were added and after 12 hrs of reaction time following the general procedure (**8.2.3**) described above, β-D-*S* lactopyranoside **3.104** (45 mg, 65%) was obtained; $\mathbf{R}_f$ 0.21 (CH_2Cl_2/MeOH 9.7:0.3); $[\alpha]_D^{24}$ + 0.74 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.52 (s, 1H, H-5), 5.93 (d, *J* = 8.5Hz, 1H, NH), 5.34 (d, *J* = 3.2Hz, 1H, H-4^{II}), 5.20 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.09 (dd, *J* = 7.9Hz, *J* = 10.3Hz, 1H, H-3^{I}), 4.96 (dd, *J* = 3.5Hz, *J* = 10.4Hz, 1H, H-2^{II}), 4.91 (t, *J* = 9.7Hz, 1H, H-2'), 4.58 (d, *J* = 10.1Hz, 1H, H-1^{II}), 4.52 - 4.46 (m, H-1^{I},H-6^{II}, 3H, H-3), 4.41 (q, *J* = 7.3Hz, 1H, H-6), 4.11 - 4.03 (m, 3H, H-6^{II}, H-6^{I},6^{I}), 3.89 (t, *J* = 6.9Hz, 1H, H-4'), 3.79 (d, *J* = 9.6Hz, 1H, H-5' Partially masked under C(O)O**CH$_3$**), 3.76 (s, 3H, C(O)O**CH3**), 3.66 (ddd, *J* = 1.7Hz, *J* = 5.7Hz, *J* = 9.9Hz, 1H, H-5^{II}), 3.41 - 3.3.26 (m, 4H, H-4, H-1), 3.00 – 2.98 (m, 1H, H-2), 2.14, 2.11, 2.05, 2.03, 2.03, 1.95 (6S, 21H, C(O)**CH$_3$**) 1.55 (t, 1H, J = 7.4Hz, H-7) ; **^{13}C-NMR** (150MHz, $CDCl_3$) δ 171.384,

170.552, 170.248, 170.032, 169.943, 169.565, 169.536, 168.984, 141.792, 122.210, 101.000, 83.768, 76.706, 76.051, 73.485, 70.869, 70.590, 69.857, 69.025, 66.561, 61.899, 60.692, 55.231, 55.153,54.678, 52.916, 45.673, 28.831, 24.254, 20.729, 20.672, 20.605, 20.541, 20.527, 20.509, 20.403, 15.217; **HRMS (ESI)** calcd for $C_{36}H_{52}N_4O_{21}S_2$ + $[H]^+$: 941.2644, found: 941.2627.

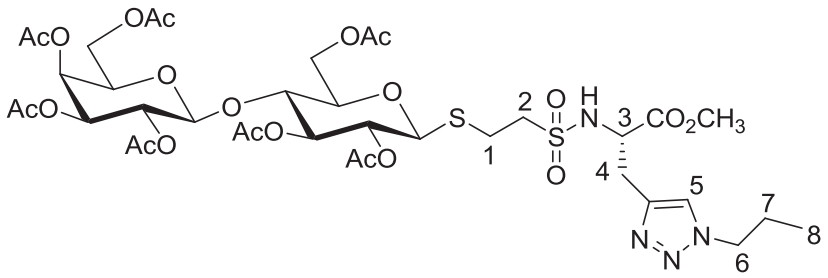
Compound 3.105



To the solution of compound **3.102** (0.1 g, 114 μmol) in 2 mL THF (dry), isopropyl azide (14.6 mg, 172 μmol) CuI (1 mg 20%) and DIPEA (1 drop) were added and after 12 hrs of reaction time following the general procedure (**8.2.3**) described above, β-D-*S* lactopyranoside **3.105** (71 mg, 65%) was obtained; $\mathbf{R}_f$ 0.24 (CH_2Cl_2/MeOH 9.7:0.3); $[\alpha]_D^{23}$ - 2.47 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.52 (s, 1H, H-5), 5.90 (d, *J* = 8.6Hz, 1H, NH), 5.35 (d, *J* = 2.8Hz, 1H, H-4^{II}), 5.22 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.10 (dd, *J* = 8.0Hz, *J* = 10.3Hz, 1H, H-3^{I}), 4.97 (dd, *J* = 3.4Hz, *J* = 10.4Hz, 1H, H-2^{II}), 4.93 (t, *J* = 9.7Hz, 1H, H-2^{I}), 4.86 - 4.79 (m, 1H, H-6), 4.59 (d, *J* = 10.1Hz, 1H, H-1^{II}), 4.55 (d, *J* = 12.0Hz, 1H, H-1^{I}), 4.50 (dd, *J* = 9.9Hz, *J* = 16.0Hz, 2H, H-3, 6^{II}), 4.13 - 4.05 (m, 3H, H-6,6^{I}, 6^{II}), 3.90 (t, *J* = 6.8Hz, 1H, H-4^{I}), 3.80 - 3.75 (m, 1H, H-5^{I} part of the peak masked under C(O)O**CH$_3$**), 3.77(s, 3H, C(O)O**CH$_3$**), 3.67 (dd, *J* = 5.3Hz, *J* = 9.3Hz, 1H, H-5^{II}),

3.37 (dddd, *J* = 5.1Hz, *J* = 13.5Hz, *J* = 19.6Hz, *J* = 25.2Hz, 4H, H-1,4), 3.01 – 2.98 (m, 2H, H-2), 2.15, 2.13, 2.06, 2.05, 2.04, 1.97 (7S,3H each,-C(O)CH_3), 1.59 (d, *J* = 6.7Hz, 1H, H-7,8); **^{13}C-NMR** (150MHz, $CDCl_3$) δ 171.363, 170.637, 170.322, 170.110, 170.025, 169.639, 169.600, 169.030, 141.491, 120.461, 101.113, 83.878, 76.143, 73.549, 70.940, 70.671, 69.906, 69.071, 66.583, 61.906, 60.724, 55.160, 54.795, 53.662, 53.018, 28.948, 24.332, 22.888, 22.845, 20.824, 20.757, 20.683, 20.629, 20.619, 20.594, 20.484. **HRMS (ESI)** calcd for $C_{37}H_{54}N_4O_{21}S_2$ + $[H]^+$: 955.2800, found: 955.2785.

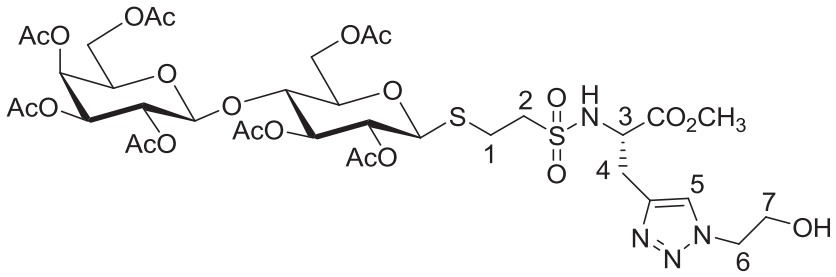
Compound 3.106



To the solution of compound **3.102** (0.05 g, 57 μmol) in 2 mL THF (dry), n-propyl azide (7 mg, 86 μmol), CuI (1 mg 20%) and DIPEA (1 drop) were added and after 12 hrs of reaction time following the general procedure described above (**8.2.3**), β-D-*S* lactopyranoside **3.106** (33 mg, 60%) was obtained; $\mathbf{R}_f$ 0.22 (CH_2Cl_2/MeOH 9.7:0.3); $[\alpha]_D^{23}$ -0.528 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.39 (s, 1H, H-5), 5.76 (d, *J* = 8.7Hz, 1H, NH), 5.31 (d, *J* = 2.7Hz, 1H, H-4^{II}), 5.18 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.07 (dd, *J* = 7.9Hz, *J* = 10.4Hz, 1H, H-3^{I}), 4.93 (dd, *J* = 3.5Hz, *J* = 10.4Hz, 1H, H-2^{II}), 4.89 (t, *J* = 9.7Hz, 1H, H-2 ^{I}), 4.55 (d, *J* = 10.1Hz, 1H, H-1^{II}), 4.51 - 4.44 (m, 4H, H-1^{I}, H-6^{II}, H-3), 4.26 (t, *J* = 7.1Hz, 2H, H-6), 4.07 (dd, *J* = 5.7Hz, *J* = 11.6Hz, 1H, H-6,6^{I}), 4.02 (dd, *J* =

5.8Hz, *J* = 12.2Hz, 1H, H-6^{II}), 3.86 (t, *J* = 6.8Hz, 1H, H-4^{I}), 3.75 (d, *J* = 9.6Hz, 1H, H-5^{I}), 3.72 (s, 3H, C(O)O**CH$_3$**), 3.63 (ddd, *J* = 1.9Hz, *J* = 5.7Hz, *J* = 9.8Hz, 2H, H-5^{II}), 3.38 (ddd, *J* = 6.3Hz, *J* = 10.1Hz, *J* = 14.3Hz, 2H, H-1), 3.31 - 3.22 (m, 2H, H-4), 3.02 - 2.94 (m, 2H, H-2), 2.11 2.09 2.02 2.01 2.00 1.89 (7S, 3H each, -C(O)CH$_3$), 1.88 (q, *J* = 7.3Hz, *J* = 14.5Hz, 1H, H-7), 0.91 (t, *J* = 7.4Hz, 3H, H-8); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 171.501, 170.571, 170.271, 170.058, 169.976, 169.583, 169.552, 168.990, 142.013, 122.110, 101.089, 83.875, 76.732, 76.149, 73.524, 70.905, 70.637, 69.886, 69.045, 66.562, 61.919, 60.713, 55.263, 54.774, 52.882, 51.905, 29.626, 24.385, 23.590, 20.764, 20.725, 20.652, 20.593, 20.557, 20.455, 10.967; **HRMS (ESI)** calcd for $C_{37}H_{54}N_4O_{21}S_2$ + $[H]^+$: 955.2800, found: 955.2785.

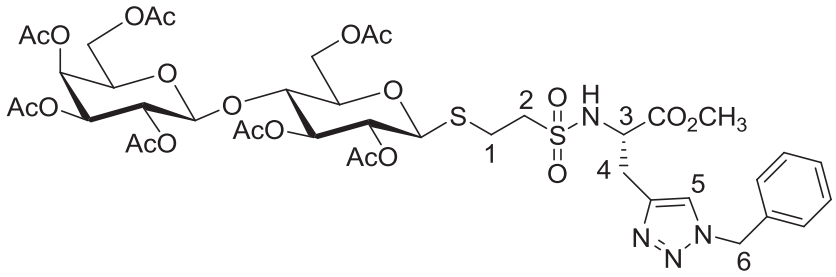
Compound 3.107



To the solution of compound **3.102** (0.065 g, 74 μmol) in 2 mL THF (dry), 2-azido ethanol (10 mg, 112 μmol), CuI (1 mg 20%) and DIPEA (1 drop) were added and after hrs of reaction time following the general procedure (**8.2.3**) described above, β-D-*S* lactopyranoside **3.107** (50 mg, 70%) was obtained; **R$_f$** 0.14 (CH_2Cl_2/MeOH 9.7:0.3); $[\alpha]_D^{24}$ -3.5 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.69 (s, 1H, H-5), 6.02 (d, *J* = 8.7Hz, 1H, NH), 5.35 (d, *J* = 3.2Hz, 1H, H-4^{II}), 5.22 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.10 (dd, *J*

= 8.0Hz, *J* = 10.3Hz, 1H, H-3^{I}), 4.98 (dd, *J* = 3.4Hz, *J* = 10.4Hz, 1H, H-2^{II}), 4.92 (t, *J* = 9.7Hz, 1H, H-2^{I}), 4.60 (d, *J* = 10.1Hz, 1H, H-1^{II}), 4.54 - 4.46 (m, 5H, H-1^{II}, H-3, H-6^{II}, H-6^{II}), 4.14 - 4.05 (m, 3H, H-6,6^{I}, 6^{II}), 4.03 - 4.01 (m, 2H, H-7), 3.90 (t, *J* = 6.8Hz, 1H, H-5^{I} Partially masked under C(O)O**CH$_3$**), 3.79 (s, 3H, C(O)O**CH$_3$),** 3.68 - 3.65 (m, 1H, H-5^{II}), 3.40 - 3.27 (m, 4H, H-1,4), 3.05 - 2.93 (m, 2H, H-2), 2.15, 2.13, 2.06, 2.05, 2.04, 1.97 (6S, 3H each and 1s 6H-C(O)CH$_3$); **^{13}C-NMR** (150MHz, $CDCl_3$) δ 171.466, 170.783, 170.363, 170.104, 170.239, 169.726, 169.680, 169.131, 141.742, 124.258, 101.062, 83.737, 76.076, 73.471, 70.907, 70.632, 69.877, 69.088, 66.588, 61.957, 60.942, 60.720, 55.368, 54.727, 53.037, 52.980, 29.002, 24.164, 20.833, 20.757, 20.692, 20.623, 20.597, 20.482; **HRMS (ESI)** calcd for $C_{36}H_{52}N_4O_{22}S_2$ + [H] $^{+}$: 957.2593, found: 957.2568.

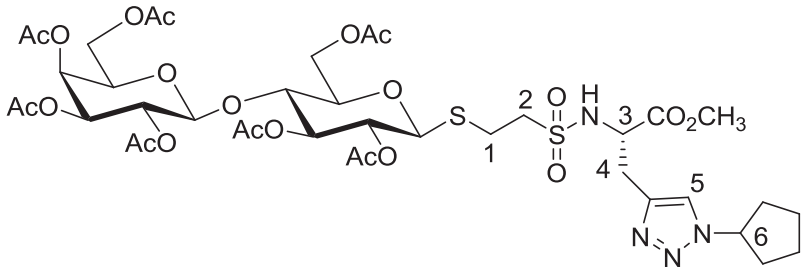
Compound 3.108



To the solution of compound **3.102** (0.1 g, 114 μmol) in 2 mL THF (dry), benzyl azide (22 mg, 172 μmol), CuI (1 mg 20%) and DIPEA (1 drop) were added and after 12 hrs of reaction time following the general procedure (**8.2.3**) described above, β-D-*S* lactopyranoside **3.108** (80mg, 70%) was obtained; **R$_f$** 0.2 (CH_2Cl_2/MeOH 9.7:0.3); $[\alpha]_D^{24}$ +6.376 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.37 - 7.34 (m, 4H, H-5, H_{Arom}),

7.24 - 7.23 (m, 2H, H_{Arom}) 5.87 (d, *J* = 8.7Hz, 1H, NH), 5.50 (s, 2H. H-6), 5.33 (d, *J* = 3.1Hz, 1H, H-4^{II}), 5.20 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.09 (dd, *J* = 8.0Hz, *J* = 10.3Hz, 1H, H-3^{I}), 4.96 (dd, *J* = 3.4Hz, *J* = 10.4Hz, 1H, H-2^{II}), 4.92 (t, *J* = 9.7Hz, 1H, H-2^{I}), 4.58 (d, *J* = 10.1Hz, 1H, H-1^{II}), 4.52 - 4.44 (m, 3H, H-1^{I},3,6^{II}), 4.11 - 4.03 (m, 3H, H-6^{II},6^{II},6'), 3.89 (t, *J* = 6.8Hz, 1H, H-4^{I}), 3.78 (t, *J* = 9.5Hz, 1H, H-5^{I}), 3.69 (s, 3H, C(O)O**CH_3**), 3.65 (ddd, *J* = 1.8Hz, *J* = 5.7Hz, *J* = 9.8Hz, 1H, H-5^{II}), 3.41 - 3.24 (m, 2H, H-2), 3.23 - 3.17 (m, 2H, H-4), 2.98 - 2.89 (m, 2H, H-1), 2.13, 2.09, 2.04, 2.03, 2.02, 2.02, 1.95 (7S,3H each,-C(O)CH_3); **^{13}C-NMR** (150MHz, $CDCl_3$) δ 171.4, 170.5, 170.2, 170.0, 169.9, 169.5, 169.5, 168.9, 142.4, 134.3, 129.0, 128.7, 127.9, 122.4, 101.0, 83.8, 76.6, 76.0, 73.4, 70.8, 70.5, 69.8, 69.0, 66.5, 61.9, 60.6, 55.1, 54.6, 54.1, 52.824, 29.0, 24.3, 20.7, 20.6, 20.6, 20.5, 20.5, 20.4; **HRMS (ESI)** calcd for $C_{41}H_{54}N_4O_{21}S_2$ + $[H]^+$: 1003.2800, found: 1003.2781.

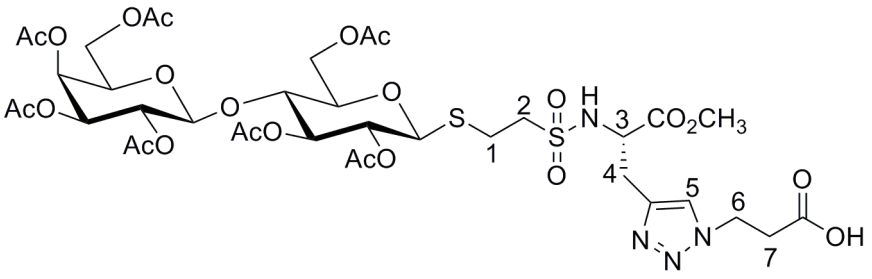
Compound 3.109



To the solution of compound **3.102** (0.065 g, 74 μmol) in 2 mL THF (dry), cyclopentyl azide (12 mg, 112 μmol), CuI (1 mg 20%) and DIPEA (1 drop) were added and after 12 hrs of reaction time following the general procedure (**8.2.3**) described above β-D-*S* lactopyranoside **3.109** (46 mg, 63%) was obtained; $\mathbf{R}_f$ 0.25 (CH_2Cl_2/MeOH 9.7:0.3);

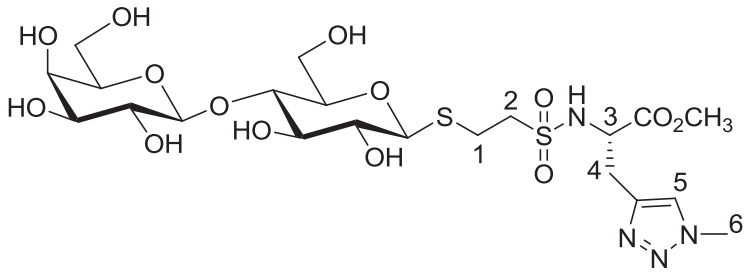
$[\alpha]_D^{23}$ -3.87 (*c* 1.0, CH_2Cl_2); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.54 (s, 1H, H-5), 5.99 (d, *J* = 8.6Hz, 1H,NH), 5.35 (d, *J* = 3.3Hz, 1H, H-4^{II}), 5.21 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.10 (dd, *J* = 7.9Hz, *J* = 10.3Hz, 1H, H-3^{I}), 4.97 (dd, *J* = 3.5Hz, *J* = 10.4Hz, 1H, H-2^{II}), 4.93 (t, *J* = 9.6Hz, 1H, H-2^{I}), 4.58 (d, *J* = 10.1Hz, 1H, H-1^{II}, 4.55 - 4.47 (m, 3H, H-1^{I},H-6^{II},H-3), 4.06 - 3.98 (m, 3H, H-6^{II}, H-6^{I}, H-6^{I}), 3.90 (t, *J* = 6.9Hz, 1H, H-4^{I}), 3.80 (d, *J* = 9.6Hz, 1H, H-5^{I} Partially masked under C(O)O**CH_3**), 3.78 (s, 3H, C(O)O**$C\underline{H_3}$**), 3.61 - 3.58 (m, 1H, H-5^{II}), 3.39 - 3.22 (m, 4H, H-4, H-1), 2.99-2.92 (m, 2H, H-2), 2.22 - 2.17 (m, 2H, Cyclopentyl **$C\underline{H_2}$**), 2.10 - 2.04 (m, 2H, Cyclopentyl **$C\underline{H_2}$**), 2.15, 2.13, 2.06, 2.05, 2.04, 1.96(6S, 21H, C(O)**$C\underline{H_3}$**), 1.93 - 1.86 (m, 2H, Cyclopentyl **$C\underline{H_2}$**), 1.80 - 1.74 (m, 2H, Cyclopentyl **$C\underline{H_2}$**); **^{13}C-NMR** (150MHz, $CDCl_3$) δ 171.214, 170.619, 170.297, 170.077, 169.992, 169.617, 169.575, 169.022, 141.256, 122.039, 101.048, 83.798, 32476.078, 73.543, 70.920, 70.644, 69.908, 69.076, 66.591, 62.810, 61.904, 60.715, 55.076, 54.747, 53.030, 33.257, 28.566, 24.234, 23.926, 20.789, 20.715, 20.641, 20.570, 20.439; **HRMS (ESI)** calcd for $C_{39}H_{56}N_4O_{21}S_2 + [H]^+$: 981.2957; found: 981.2934.

Compound 3.110



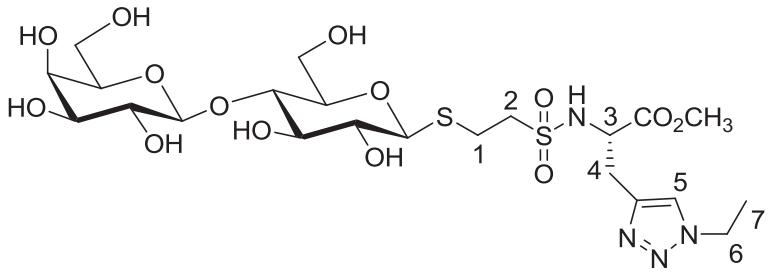
To the solution of compound **3.102** (0.065 g, 74 μmol) in 2 mL THF (dry), 3-azidopropionic acid (20 mg, 172 μmol), CuI (1 mg 20%) and DIPEA (1 drop) were added and after 12 hrs of reaction time following the general procedure (**8.2.3**) described above β-D-*S* lactopyranoside **3.110** (79 mg, 70%) was obtained; **^{1}H-NMR** (600 MHz, $CDCl_3$) 7.65 (s, 1H, H-5), 6.00 (d, *J* = 8.8Hz, 1H, NH), 5.34 (d, *J* = 3.1Hz, 1H, H-4^{II}), 5.21 (t, *J* = 9.2Hz, 1H, H-3^{II}), 5.08 (dd, *J* = 8.1Hz, J = 10.2Hz, 1H, H-3^{I}), 4.98 (dd, *J* = 3.4Hz, J = 10.4Hz, 1H, H-2^{II}), 4.91 (t, *J* = 9.7Hz, 1H, H-2'), 4.64 (t, *J* = 5.9Hz, 2H, H-6), 4.58 (d, *J* = 10.1Hz, 1H, H-1^{II}), 4.54 - 4.49 (m, 1H, H-1^{I}, H-6^{II}), 4.49 - 4.40 (m, 1H, H-3), 4.12 (dd, *J* = 6.3Hz, J=11.1Hz, 1H, H-6^{II}), 4.07 (td, *J* = 7.0Hz, *J* = 12.2Hz, 2H, H-6^{I}, 6^{I}), 3.90 (t, *J* = 6.8Hz, 1H, H-4^{I}), 3.79 (t, *J* = 9.6Hz, 1H, H-5^{II}), 3.76 (s, 1H, C(O)O**C$\underline{\mathbf{H}}_3$**), 3.67 (dt, *J* = 20.2, 10.0 Hz, 1H, H-5^{I}), 3.38 - 3.30 (m, 1H, H-4), 3.29 - 3.20 (m, 3H, H-4, H-1), 3.00 (t, *J* = 5.8Hz, 1H, H-7), 2.93 (t, *J* = 8.1Hz, 1H, H-2), 2.14 2.11 2.05 2.04 2.03 1.96 (5S, 3Heach, 1S, 6H, C(O)**C$\underline{\mathbf{H}}_3$**); **^{13}C-NMR** (150MHz, $CDCl_3$) δ 173.00, 171.696, 170.86, 170.44, 170.12, 170.06, 169.81, 169.77, 169.22, 141.88, 123.89, 100.97, 83.70, 76.68, 76.00, 73.50, 70.88, 70.56, 69.91, 69.11, 66.61, 62.02, 60.74, 55.42, 54.59, 52.94, 45.69, 34.16, 28.89, 24.17, 20.771, 20.72, 20.65, 20.59, 20.56, 20.55, 20.44.

Compound 3.111



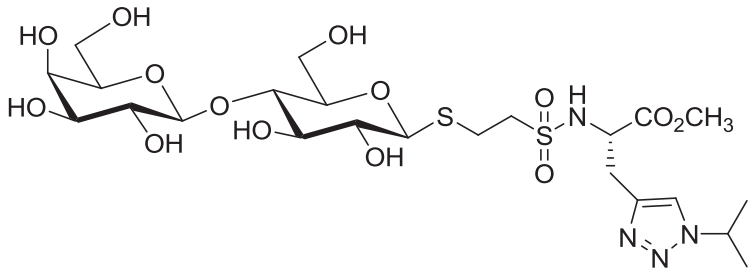
To a solution of compound **3.103** (0.078 g, 84 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above, to obtain the deprotected β-D-S-lactopyranoside **3.111** (40 mg, 75%); $\mathbf{R}_f$ 0.1 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{23}$ - 10.14 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.84 (s, 1H), 4.56 (t, *J* = 9.7 Hz, 1H), 4.44 (d, *J* = 7.8 Hz, 2H), 4.08 (s, 3H), 3.99 - 3.92 (m, 1H), 3.91 (d, *J* = 3.0 Hz, 1H), 3.80 (s, 3H), 3.75 (dd, *J* = 11.4, 7.7 Hz, 2H), 3.71 (dt, *J* = 13.6, 6.6 Hz, 2H), 3.68 - 3.62 (m, 2H), 3.56 - 3.50 (m, 2H), 3.41 - 3.27 (m, 3H), 3.12 (dd, *J* = 14.9, 9.1 Hz, 2H), 3.02 (dt, *J* = 21.5, 11.1 Hz, 1H), 2.98 – 2.86 (m, 1H), 2.86 - 2.76 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 173.66, 143.27, 126.27, 103.52, 86.28, 86.01, 79.34, 78.67, 76.36, 76.00, 73.17, 72.50, 71.59, 69.20, 61.68, 60.78, 56.48, 54.27, 54.14, 53.94, 37.27, 28.93, 24.12, 23.89.

Compound 3.112



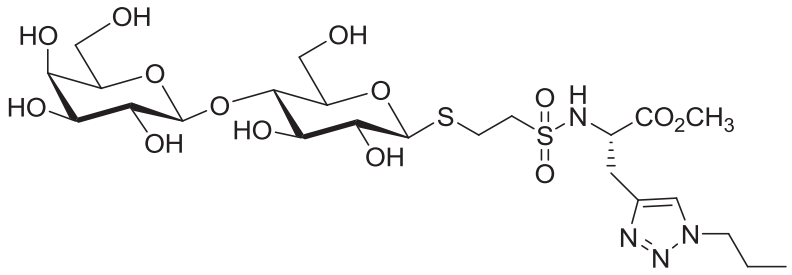
To a solution of compound **3.104** (0.068 g, 63 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above, to obtain the deprotected β-D-S-lactopyranoside **3.112** (30 mg, 72%); $\mathbf{R}_f$ 0.25 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{24}$ - 9.70 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.90 (s, 1H), 4.56 (t, *J* = 9.6 Hz, 1H), 4.48 - 4.35 (m, 4H), 4.00 - 3.93 (m, 1H), 3.91 (t, *J* = 7.6 Hz, 1H), 3.80 (s, 3H), 3.79 - 3.69 (m, 2H), 3.68 - 3.57 (m, 2H), 3.54 (t, J = 8.8 Hz, 2H), 3.54 (t, *J* = 8.8 Hz, 2H), 3.34 (ddd, *J* = 19.8, 16.1, 6.6 Hz, 5H), 3.12 (ddd, *J* = 14.9, 9.1, 2.1 Hz, 2H), 3.06 - 2.98 (m, 1H), 2.99 - 2.86 (m, 1H), 2.84 - 2.74 (m, 1H), 1.49 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (150 MHz, D_2O) δ 173.67, 143.24, 124.78, 103.52, 86.27, 79.35, 78.68, 76.36, 76.00, 73.17, 72.51, 71.59, 69.20, 61.68, 60.78, 56.54, 54.28, 53.94, 46.35, 28.98, 28.96, 24.12, 15.37. **HRMS (ESI)** calcd for $C_{22}H_{38}N_4O_{14}S_2 + [H]^+$: 647.1904, found: 647.1895.

Compound 3.113



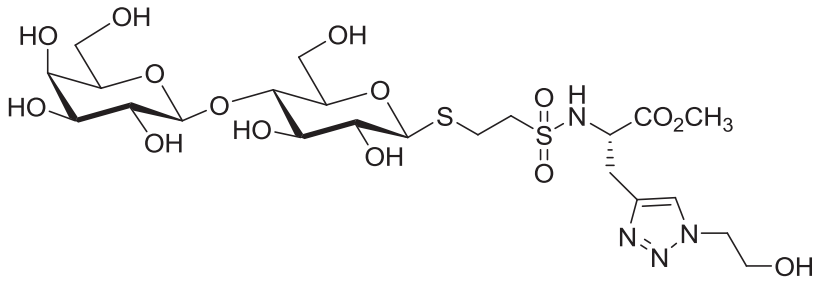
To a solution of compound **3.105** (0.057 g, 59 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above, to obtain the deprotected β-D-S-lactopyranoside **3.113** (31 mg, 79%); $\mathbf{R}_f$ 0.17 (CH_2Cl_2/MeOH 4:1); $[\alpha]_D^{23}$ - 10.84 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.95 (d, J = 8.3 Hz, 1H), 4.87 - 4.80 (m, 1H), 4.55 (dt, J = 19.7, 5.6 Hz, 1H), 4.47 - 4.37 (m, 2H), 3.95 (ddd, J = 13.8, 7.8, 5.6 Hz, 1H), 3.90 (t, J = 8.9 Hz, 1H), 3.79 (s, 3H), 3.78 - 3.69 (m, 2H), 3.68 - 3.59 (m, 2H), 3.57 - 3.50 (m, 2H), 3.44 - 3.27 (m, 5H), 3.11 (dd, J = 14.1, 10.0 Hz, 1H), 3.06 - 2.97 (m, 1H), 2.98 - 2.87 (m, 1H), 2.79 (dt, J = 14.5, 7.1 Hz, 1H), 1.53 (dd, J = 6.7, 1.4 Hz, 6H); **^{13}C NMR** (150 MHz, D_2O) δ 173.61, 143.00, 123.25, 103.51, 86.26, 79.35, 78.66, 76.36, 73.16, 72.51, 71.58, 69.20, 61.67, 60.78, 56.54, 54.52, 54.16, 53.93, 28.98, 24.10, 23.90, 22.68. **HRMS (ESI)** calcd for $C_{23}H_{40}N_4O_{14}S_2 + [H]^+$: 661.2061, found: 661.2064.

Compound 3.114



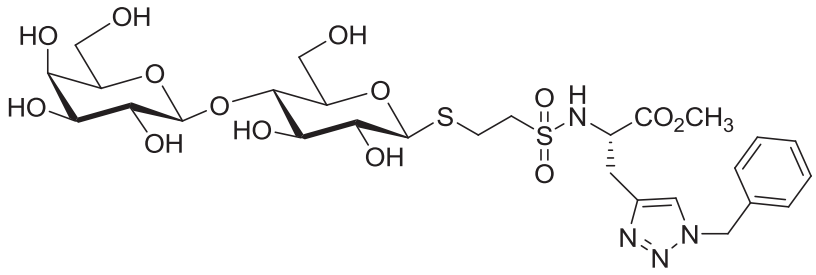
To a solution of compound **3.106** (0.068 g, 72 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above, to obtain the deprotected β-D-S-lactopyranoside **3.114** (36 mg, 75%); $\mathbf{R}_f$ 0.17 (CH_2Cl_2/MeOH 4:1); $[\alpha]_D^{24}$ - 13.15 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.90 (s, 1H), 4.60 - 4.55 (m, 1H), 4.45 (dd, J = 7.7, 6.5 Hz, 1H), 4.37 (q, J = 6.8 Hz, 2H), 4.03 - 3.94 (m, 1H), 3.92 (t, J = 8.4 Hz, 1H), 3.83 - 3.80 (m, 1H), 3.78 (s, 3H), 3.69 - 3.62 (m, 4H), 3.60 - 3.50 (m, 2H), 3.48 - 3.28 (m, 5H), 3.13 (ddd, J = 15.0, 9.3, 2.2 Hz, 1H), 3.09 - 3.01 (m, 1H), 3.00 - 2.91 (m, 1H), 2.84 (dt, J = 14.8, 7.6 Hz, 1H), 1.93 – 1.86 (m, 2H), 0.85 (dd, J = 7.9, 7.4 Hz, 3H); **^{13}C NMR** (150 MHz, D_2O) δ 173.65, 143.26, 126.27, 103.52, 86.27, 79.34, 78.67, 76.36, 76.00, 73.17, 72.50, 71.59, 69.20, 61.67, 60.78, 56.47, 54.26, 53.94, 37.27, 28.93, 24.11, 23.89. **HRMS (ESI)** calcd for $C_{23}H_{40}N_4O_{14}S_2 + [H]^+$: 661.2061, found: 661.2052.

Compound 3.115



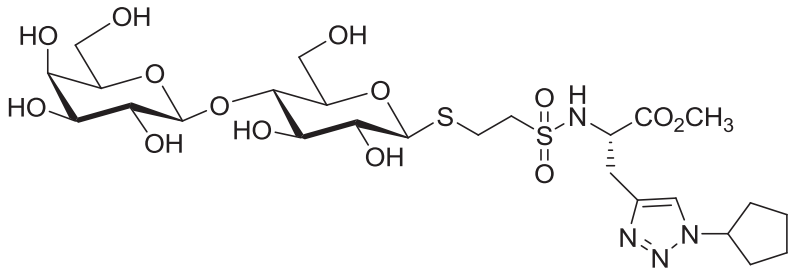
To a solution of compound **3.107** (0.062 g, 64 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above, to obtain the deprotected β-D-S-lactopyranoside **3.115** (30 mg, 70%); $\mathbf{R}_f$ 0.1 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{24}$ - 8.40 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.95 (d, *J* = 11.9 Hz, 1H), 4.61 - 4.52 (m, 3H), 4.51 - 4.41 (m, 3H), 4.04 - 3.93 (m, 4H), 3.91 (t, *J* = 7.1 Hz, 1H), 3.80 (s, 3H), 3.79 - 3.74 (m, 2H), 3.71 (ddd, *J* = 11.5, 7.7, 3.1 Hz, 2H), 3.68 - 3.57 (m, 1H), 3.54 (t, *J* = 8.9 Hz, 1H), 3.49 - 3.27 (m, 5H), 3.23 - 3.12 (m, 1H), 3.10 - 3.00 (m, 1H), 2.94 (ddd, *J* = 20.3, 11.7, 5.9 Hz, 1H), 2.88 – 2.79 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 173.67, 143.26, 126.27, 103.51, 86.03, 79.33, 78.65, 76.36, 76.00, 73.16, 72.49, 72.45, 71.59, 69.20, 61.68, 60.76, 56.44, 54.15, 53.95, 28.98, 24.12; **HRMS (ESI)** calcd for $C_{22}H_{38}N_4O_{15}S_2$ + [H] $^+$: 663.1853, found: 663.1845.

Compound 3.116



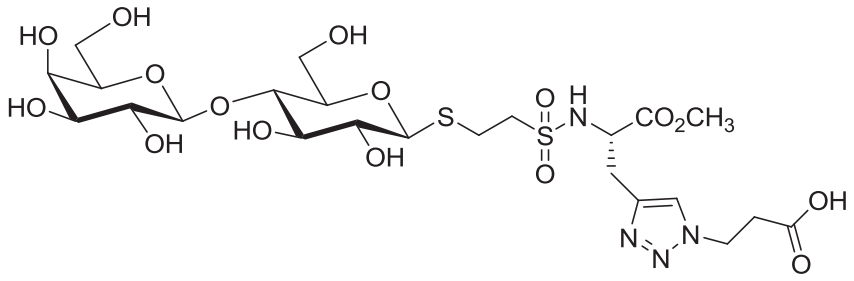
To a solution of compound **3.108** (0.050 g, 49 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above, to obtain the deprotected β-D-S-lactopyranoside **3.116** (28 mg, 80%); $\mathbf{R}_f$ 0.3 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{23}$ - 9.28 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.89 (s, 1H), 7.47 - 7.35 (m, 3H), 7.29 (d, *J* = 7.1 Hz, 2H), 5.54 (s, 2H), 4.53 (dd, *J* = 9.9, 4.9 Hz, 1H), 4.43 (dd, *J* = 7.7, 3.1 Hz, 2H), 3.87 (s, 3H), 3.83 - 3.74 (m, 2H), 3.73 (s, 4H), 3.72 - 3.68 (m, 2H), 3.68 - 3.60 (m, 2H), 3.56 (dt, *J* = 17.7, 7.1 Hz, 4H), 3.41 - 3.20 (m, 6H), 3.06 (s, 1H), 3.01 - 2.94 (m, 1H), 2.88 (pd, *J* = 14.1, 5.7 Hz, 1H), 2.83 - 2.71 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 173.57, 135.58, 129.77, 129.41, 128.63, 103.55, 86.08, 79.34, 78.69, 76.39, 76.03, 73.20, 72.49, 71.61, 69.22, 61.69, 60.81, 56.51, 54.55, 54.20, 53.90, 29.02, 24.11, 23.94. **HRMS** (**ESI)** calcd for $C_{27}H_{40}N_4O_{14}S_2 + [H]^+$: 709.2061, found: 709.2052.

Compound 3.117



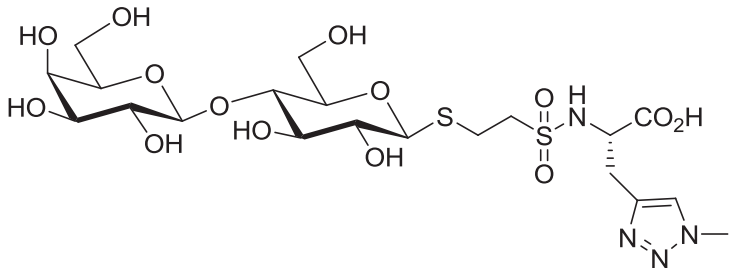
To a solution of compound **3.109** (0.050 g, 51 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above, to obtain the deprotected β-D-S-lactopyranoside **3.117** (28 mg, 80%); $\mathbf{R}_f$ 0.34 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{23}$ - 7.39 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.92 (s, 1H), 5.03 - 4.92 (m, 1H), 4.61 - 4.52 (m, 1H), 4.49 - 4.38 (m, 2H), 3.95 (d, *J* = 10.5 Hz, 1H), 3.90 (t, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 3.78 - 3.68 (m, 2H), 3.68 - 3.58 (m, 2H), 3.52 (dd, *J* = 23.0, 13.4 Hz, 2H), 3.41 - 3.26 (m, 5H), 3.16 - 3.05 (m, 1H), 3.04 - 2.97 (m, 1H), 2.95 - 2.85 (m, 1H), 2.78 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.31 - 2.16 (m, 2H), 1.96 (dd, *J* = 12.3, 6.2 Hz, 2H), 1.81 (dd, *J* = 14.3, 7.7 Hz, 2H), 1.77 - 1.70 (m, 2H); **^{13}C NMR** (150 MHz, D_2O) δ 173.67, 143.24, 124.78, 103.52, 86.27, 79.35, 78.68, 76.36, 73.17, 72.51, 71.59, 69.20, 61.68, 60.78, 56.54, 54.28, 53.94, 46.35, 28.98, 24.12, 23.90, 15.37; **HRMS (ESI)** calcd for $C_{25}H_{42}N_4O_{14}S_2$ + $[H]^+$: 687.2217, found: 687.2209.

Compound 3.118



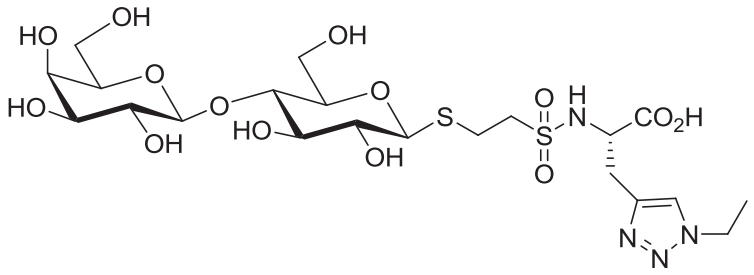
To a solution of compound **3.110** (0.070 g, 71 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs of reaction time following the general procedure (**8.2.4**) described above, to obtain the deprotected β-D-S-lactopyranoside **3.118** (36 mg, 74%); $\mathbf{R}_f$ 0.05 (CH_2Cl_2/MeOH 5:1); $[\alpha]_D^{23}$ - 14.78 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 7.92 (s, 1H, 1H), 5.30 - 5.16 (m, 1H), 5.00 - 4.86 (m, 2H), 4.73 - 4.62 (m, 2H), 4.64 - 4.51 (m, 1H), 4.48 - 4.33 (m, 2H), 4.06 - 3.82 (m, 3H), 3.83 - 3.74 (m, 3H), 3.72 (dt, *J* = 20.8, 8.8 Hz, 2H), 3.69 - 3.48 (m, 3H), 3.47 - 3.26 (m, 5H), 3.12 (dd, *J* = 14.9, 9.1 Hz, 1H), 3.07 - 2.98 (m, 2H), 2.99 - 2.83 (m, 1H), 2.18 - 2.04 (m, 2H); **^{13}C NMR** (150 MHz, D_2O) δ 173.61, 143.07, 125.53, 103.74, 86.63, 83.27, 79.69, 78.68, 75.53, 75.50, 72.97, 72.47, 71.43, 69.09, 62.07, 60.81, 56.88, 54.33, 46.28, 35.17, 28.96, 24.27, 21.20; **HRMS (ESI)** calcd for $C_{23}H_{38}N_4O_{16}S_2$ + $[H]^+$: 691.1802, found: 691.1794.

Compound 3.119



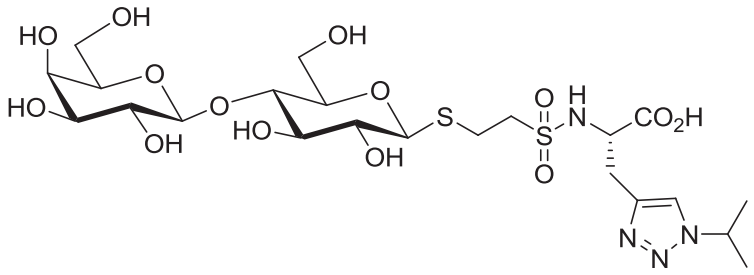
To a solution of compound **3.111** (19 mg, 3 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln (0.03 mL, 1eq) and stirred for 2 hrs, following the general saponification (**8.2.5**) procedure to obtain **3.119** (14 mg, 78%); $\mathbf{R_f}$ 0.18 (ACN/H_2O 8:2); $[\alpha]_D^{21}$ - 4.9 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.82 (s, 1H), 4.55 (t, *J* = 9.7 Hz, 1H), 4.43 (d, *J* = 7.8 Hz, 2H), 4.09 (s, 3H), 3.97 - 3.91 (m, 1H), 3.90 (d, *J* = 3.0 Hz, 1H), 3.73 (dd, *J* = 11.4, 7.7 Hz, 2H), 3.70 (dt, *J* = 13.6, 6.6 Hz, 2H), 3.67 - 3.61 (m, 2H), 3.55 - 3.49 (m, 2H), 3.37 - 3.24 (m, 3H), 3.09 (dd, *J* = 14.9, 9.1 Hz, 2H), 3.02 (dt, *J* = 21.5, 11.1 Hz, 1H), 2.98 - 2.86 (m, 1H), 2.86 - 2.76 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 173.65, 143.28, 126.25, 103.55, 86.26, 86.03, 79.37, 78.65, 76.33, 75.98, 73.15, 72.48, 71.54, 69.20, 61.68, 60.78, 56.50, 54.27, 54.14, 37.26, 28.9, 24.12, 23.89. **ESI-HRMS** calcd for $C_{20}H_{34}N_4O_{14}S_2 + [H]^+$: 633.1748, found 633.1738.

Compound 3.120



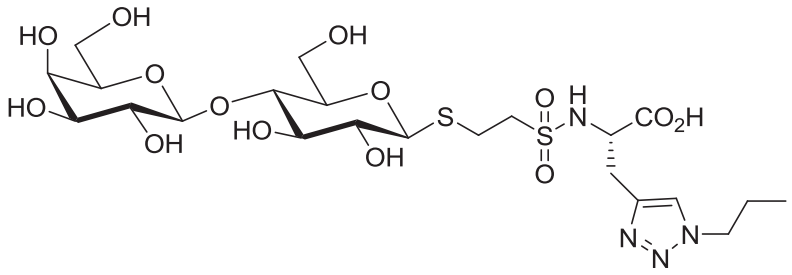
To a solution of compound **3.112** (22 mg, 3 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln. (0.03mL, 1eq) and stirred for 2 hrs, following the general saponification procedure (**8.2.5**) to obtain **3.120** (16 mg, 75%); $\mathbf{R_f}$ 0.18 (ACN/H_2O 8:2); $[\alpha]_D^{21}$ - 6.62 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.89 (s, 1H), 4.55 (t, *J* = 9.6 Hz, 1H), 4.46 - 4.33 (m, 4H), 4.00 - 3.94 (m, 1H), 3.89 (t, *J* = 7.6 Hz, 1H), 3.78 - 3.68 (m, 2H), 3.68 - 3.57 (m, 2H), 3.54 (t, J = 8.8 Hz, 2H), 3.53 (t, *J* = 8.8 Hz, 2H), 3.31 (ddd, *J* = 19.8, 16.1, 6.6 Hz, 5H), 3.11 (ddd, *J* = 14.9, 9.1, 2.1 Hz, 2H), 3.05 - 2.96 (m, 1H), 2.97 - 2.85 (m, 1H), 2.84 - 2.74 (m, 1H), 1.49 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (150 MHz, D_2O) δ 173.66, 143.14, 124.48, 103.51, 86.24, 79.25, 78.66, 76.35, 76.00, 73.15, 72.49, 71.58, 69.19, 61.67, 60.75, 56.53, 54.27, 46.34, 28.97, 28.95, 24.11, 15.36. **HRMS (ESI)** calcd for $C_{21}H_{36}N_4O_{14}S_2 + [H]^+$: 619.1591, found 633.1591.

Compound 3.121



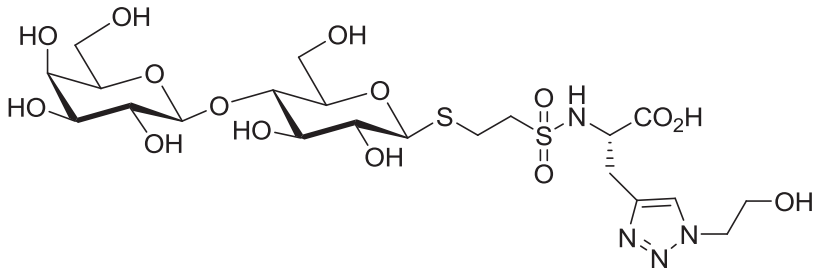
To a solution of compound **3.113** (22 mg, 3 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln. (0.03mL, 1eq) and stirred for 2 hrs, following the general saponification procedure (**8.2.5**) to obtain **3.121** (14 mg, 73%); $\mathbf{R_f}$ 0.19 (ACN/H_2O 8:2); $[\alpha]_D^{21}$ - 8.23 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.92 (s, 1H), 4.85 - 4.78 (m, 1H), 4.54 (dt, J = 19.7, 5.6 Hz, 1H), 4.46 - 4.35 (m, 2H), 3.89 (ddd, J = 13.8, 7.8, 5.6 Hz, 1H), 3.88 (t, J = 8.9 Hz, 1H), 3.76 - 3.67 (m, 2H), 3.65 - 3.59 (m, 2H), 3.56 - 3.49 (m, 2H), 3.41 - 3.26 (m, 5H), 3.10 (dd, J = 14.1, 10.0 Hz, 1H), 3.05 - 2.96 (m, 1H), 2.96 - 2.85 (m, 1H), 2.77 (dt, J = 14.5, 7.1 Hz, 1H), 1.52 (dd, J = 6.7, 1.4 Hz, 6H); **^{13}C NMR** (150 MHz, D_2O) δ 173.60, 143.01, 123.24, 103.50, 86.27, 79.31, 78.61, 76.34, 73.16, 72.52, 71.58, 69.19, 61.66, 60.75, 56.53, 54.51, 54.15, 28.96, 24.09, 23.89, 22.66. **HRMS (ESI)** calcd for $C_{22}H_{38}N_4O_{14}S_2$ + $[H]^+$: 647.1904, found 647.1897.

Compound 3.122



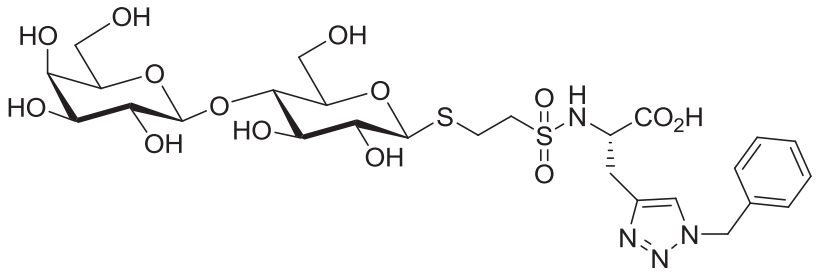
To a solution of compound **3.114** (16 mg, 2.4 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln. (0.03 mL, 1 eq) and stirred for 2 hrs, following the general saponification procedure (**8.2.5**) to obtain **3.122** (13 mg, 80%); $\mathbf{R}_f$ 0.19 (ACN/H_2O 8:2); $[\alpha]_D^{21}$ - 8.52 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.90 (s, 1H), 4.59 - 4.54 (m, 1H), 4.39 (dd, J = 7.7, 6.5 Hz, 1H), 4.35 (q, J = 6.8 Hz, 2H), 3.99 - 3.95 (m, 1H), 3.89 (t, J = 8.4 Hz, 1H), 3.81 - 3.79 (m, 1H), 3.66 - 3.58 (m, 4H), 3.59 - 3.50 (m, 2H), 3.47 - 3.26 (m, 5H), 3.10 (ddd, J = 15.0, 9.3, 2.2 Hz, 1H), 3.09 - 2.99 (m, 1H), 2.98 - 2.89 (m, 1H), 2.84 (dt, J = 14.8, 7.6 Hz, 1H), 1.91 - 1.84 (m, 2H), 0.85 (dd, J = 7.9, 7.4 Hz, 3H); **^{13}C NMR** (150 MHz, D_2O) δ 173.64, 143.25, 126.24, 103.49, 86.25, 79.33, 78.64, 76.35, 75.99, 73.16, 72.49, 71.57, 69.19, 61.66, 60.79, 56.44, 54.24, 37.26, 28.91, 24.10, 23.88. **HRMS (ESI)** calcd for $C_{22}H_{38}N_4O_{14}S_2$ + $[H]^+$: 647.1904; found, 647.1897.

Compound 3.123



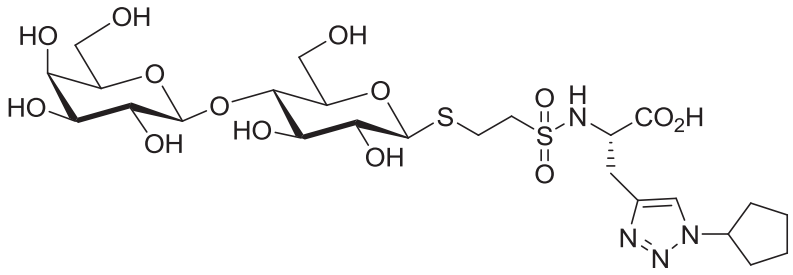
To a solution of compound **3.115** (28 mg, 4.2 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln. (0.05 mL, 1 eq) and stirred for 2 hrs, following the general saponification procedure (**8.2.5**) to obtain **3.123** (19 mg, 70%); $\mathbf{R}_f$ 0.15 (ACN/H_2O 8:2); $[\alpha]_D^{22}$ - 10.98 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.93 (d, *J* = 11.9 Hz, 1H), 4.59 - 4.49 (m, 3H), 4.47 - 4.37 (m, 3H), 4.06 - 3.89 (m, 4H), 3.88 (t, *J* = 7.1 Hz, 1H), 3.77 - 3.72 (m, 2H), 3.70 (ddd, *J* = 11.5, 7.7, 3.1 Hz, 2H), 3.66 - 3.56 (m, 1H), 3.53 (t, *J* = 8.9 Hz, 1H), 3.47 - 3.25 (m, 5H), 3.21 - 3.11 (m, 1H), 3.10 - 3.00 (m, 1H), 2.92 (ddd, *J* = 20.3, 11.7, 5.9 Hz, 1H), 2.86 - 2.77 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 173.67, 143.22, 126.25, 103.50, 86.02, 79.31, 78.62, 76.34, 76.01, 73.15, 72.46, 72.44, 71.55, 69.17, 61.65, 60.74, 56.44, 54.15, 28.98, 24.10. **HRMS (ESI)** calcd for $C_{21}H_{36}N_4O_{15}S_2 + [H]^+$: 649.1697, found: 649.1690.

Compound 3.124



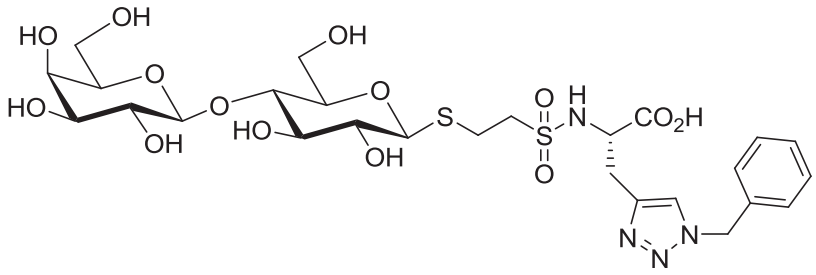
To a solution of compound **3.116** (16 mg, 2.4 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln. (0.03mL, 1 eq) and stirred for 2 hrs, following the general saponification procedure (**8.2.5**) to obtain **3.124** (12 mg, 77%); $\mathbf{R}_f$ 0.25 (ACN/H_2O 8:2); $[\alpha]_D^{22}$ - 2.79 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.75 (s, 1H), 7.47 - 7.35 (m, 3H), 7.29 (d, *J* = 7.1 Hz, 2H), 5.43 (s, 2H), 4.60 (dd, *J* = 9.9, 4.9 Hz, 1H), 4.36 (dd, *J* = 7.7, 3.1 Hz, 2H), 3.40 - 3.49 (m, 2H), 3.73 (s, 4H), 3.70 - 3.66 (m, 2H), 3.68 - 3.60 (m, 2H), 3.56 (dt, *J* = 17.7, 7.1 Hz, 4H), 3.35 - 3.20 (m, 6H), 3.06 (s, 1H), 3.01 - 2.94 (m, 1H), 2.88 (pd, *J* = 14.1, 5.7 Hz, 1H), 2.83 - 2.71 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 173.56, 135.54, 129.75, 129.43, 128.65, 103.51, 86.10, 79.24, 78.69, 76.39, 76.03, 73.20, 72.50, 71.61, 69.22, 61.70, 60.88, 56.51, 54.55, 54.20, 29.02, 24.11, 23.94. **HRMS (ESI)** calcd for $C_{26}H_{38}N_4O_{14}S_2 + [H]^+$: 695.1904, found: 695.1900.

Compound 3.125



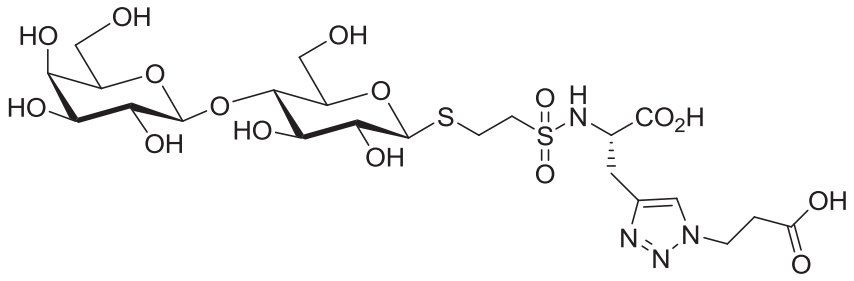
To a solution of compound **3.117** (16 mg, 2.4 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln. (0.03mL, 1eq) and stirred for 2 hrs, following the general saponification procedure (**8.2.5**) to obtain **3.125** (11 mg, 70%); $\mathbf{R}_f$ 0.22 (ACN/H_2O 8:2); $[\alpha]_D^{22}$ - 5.57 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.90 (s, 1H), 5.02 - 4.91 (m, 1H), 4.59 - 4.50 (m, 1H), 4.48 - 4.37 (m, 2H), 3.93 (d, *J* = 10.5 Hz, 1H), 3.89 (t, *J* = 9.2 Hz, 1H), 3.77 - 3.68 (m, 2H), 3.66 - 3.57 (m, 2H), 3.50 (dd, *J* = 23.0, 13.4 Hz, 2H), 3.39 - 3.19 (m, 5H), 3.14 - 3.06 (m, 1H), 3.03 - 2.96 (m, 1H), 2.93 - 2.86 (m, 1H), 2.68 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.29 - 2.09 (m, 2H), 1.89 (dd, *J* = 12.3, 6.2 Hz, 2H), 1.79 (dd, *J* = 14.3, 7.7 Hz, 2H), 1.75 - 1.69 (m, 2H); **^{13}C NMR** (150 MHz, D_2O) δ 173.66, 143.19, 124.69, 103.49, 86.19, 79.33, 78.71, 76.35, 73.16, 72.52, 71.61, 69.21, 61.68, 60.77, 56.54, 54.28, 46.35, 28.99, 24.12, 23.91, 15.37; **HRMS (ESI)** calcd for $C_{24}H_{40}N_4O_{14}S_2 + [H]^+$: 673.2061, found: 673.2052.

Compound 3.124



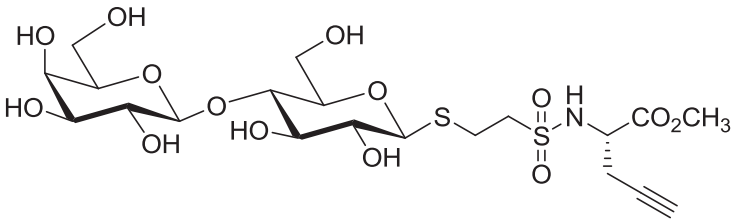
To a solution of compound **3.116** (16 mg, 2.4 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln. (0.03 mL, 1 eq) and stirred for 2 hrs, following the general saponification procedure (**8.2.5**) to obtain **3.124** (12 mg, 77%); $\mathbf{R}_f$ 0.25 (ACN/H_2O 8:2); $[\alpha]_D^{22}$ - 2.79 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.75 (s, 1H), 7.47 – 7.35 (m, 3H), 7.29 (d, *J* = 7.1 Hz, 2H), 5.43 (s, 2H), 4.60 (dd, *J* = 9.9, 4.9 Hz, 1H), 4.36 (dd, *J* = 7.7, 3.1 Hz, 2H), 3.40 - 3.49 (m, 2H), 3.73 (s, 4H), 3.70 - 3.66 (m, 2H), 3.68 - 3.60 (m, 2H), 3.56 (dt, *J* = 17.7, 7.1 Hz, 4H), 3.35 - 3.20 (m, 6H), 3.06 (s, 1H), 3.01 - 2.94 (m, 1H), 2.88 (pd, *J* = 14.1, 5.7 Hz, 1H), 2.83 - 2.71 (m, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 173.56, 135.54, 129.75, 129.43, 128.65, 103.51, 86.10, 79.24, 78.69, 76.39, 76.03, 73.20, 72.50, 71.61, 69.22, 61.70, 60.88, 56.51, 54.55, 54.20, 29.02, 24.11, 23.94. **ESI-HRMS** calcd for $C_{26}H_{38}N_4O_{14}S_2$ + $[H]^+$: 695.1904, found: 695.1900.

Compound 3.126



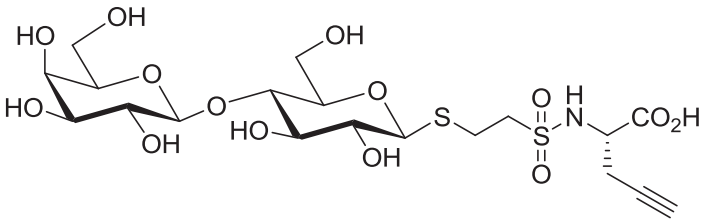
To a solution of compound **3.118** (40 mg, 6 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln. (0.03 mL, 1 eq) and stirred for 2 hrs, following the general saponification procedure (**8.2.5**) to obtain **3.126** (28 mg, 72%); $\mathbf{R_f}$ 0.09 streak (ACN : H_2O 8:2); $[\alpha]_D^{22}$ - 7.36 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.90 (s, 1H, 1H), 5.29 - 5.15 (m, 1H), 5.01 - 4.84 (m, 2H), 4.74 - 4.59 (m, 2H), 4.66 - 4.49 (m, 1H), 4.50 - 4.31 (m, 2H), 4.004 - 3.84 (m, 3H), 3.79 - 3.76 (m, 2H), 3.71 (dt, *J* = 20.8, 8.8 Hz, 2H), 3.66 - 3.44 (m, 3H), 3.45 - 3.25 (m, 5H), 3.14 (dd, *J* = 14.9, 9.1 Hz, 1H), 3.07 - 2.98 (m, 2H), 2.99 - 2.85 (m, 1H), 2.20 - 2.03 (m, 2H); **^{13}C NMR** (150 MHz, D_2O) δ 173.41, 142.86, 125.30, 103.64, 86.53, 83.16, 79.58, 78.48, 75.45, 75.33, 72.73, 72.26, 71.33, 68.88, 61.91, 60.66, 56.77, 46.14, 35.07, 28.72, 24.17, 21.20; **HRMS (ESI)** calcd for $C_{21}H_{36}N_4O_{15}S_2 + [H]^+$: 677.1646, found 677.1641.

Compound 3.127



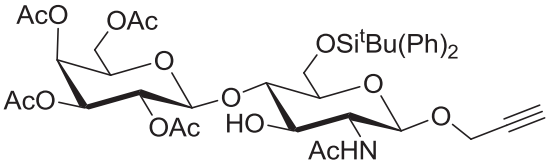
To a solution of compound **3.102** (0.1 g, 127 μmol) in 2 mL of dry methanol, 0.2 ml of NaOMe/MeOH solution (pH = 10) was added and stirred at RT for 4 hrs following the general procedure (**8.2.4**) described above, to obain the deprotected β-D-S-lactopyranoside **3.127** (58 mg, 80%); $[\alpha]_D^{24}$ - 9.54 (*c* 1 in MeOH); **^{1}H NMR** (600 MHz, D_2O) δ 4.65 (t, *J* = 8.4 Hz, 1H), 4.49 - 4.39 (m, 2H), 3.98 (t, *J* = 13.5 Hz, 1H), 3.92 (d, *J* = 19.7 Hz, 1H), 3.83 (s, 3H), 3.79 (dt, *J* = 18.6, 4.9 Hz, 2H), 3.73 (dd, *J* = 11.6, 8.1 Hz, 2H), 3.67 (dt, *J* = 10.4, 8.8 Hz, 4H), 3.65 - 3.58 (m, 4H), 3.58 - 3.50 (m, 1H), 3.42 (dd, *J* = 13.3, 5.2 Hz, 1H), 3.30 - 3.06 (m, 2H), 2.82 (d, *J* = 5.8 Hz, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 172.60, 102.95, 85.64, 78.82, 78.13, 75.79, 75.44, 72.60, 71.91, 71.02, 68.63, 61.11, 60.23, 54.66, 53.89, 53.48, 23.66, 22.86; **HRMS (ESI)** calcd for $C_{20}H_{33}NO_{14}S_2$ + $[Na]^+$: 598.1240, found: 598.1236.

Compound 3.128



To a solution of compound **3.127** (40 mg, 69 μmol) in mixed solvent of THF:MeOH:H_2O (3:2:1) was added a 1M LiOH.H_2O soln. (0.06mL) and stirred for 2 hrs, following the general saponification procedure (**8.2.5**) to obtain **3.128** (14 mg, 78%); $\mathbf{R}_f$ 0.20 (ACN/H_2O 8:2); $[\alpha]_D^{22}$ - 4.76 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 4.61 (d, *J* = 9.9 Hz, 1H), 4.44 (dd, *J* = 7.8, 1.1 Hz, 2H), 4.26 (dt, *J* = 8.6, 4.3 Hz, 1H), 3.96 (dt, *J* = 17.3, 8.7 Hz, 2H), 3.90 (dd, *J* = 14.1, 3.5 Hz, 2H), 3.82 - 3.73 (m, 4H), 3.73 - 3.68 (m, 3H), 3.68 - 3.63 (m, 4H), 3.59 (ddd, *J* = 24.0, 15.9, 7.8 Hz, 5H), 3.53 (dd, *J* = 9.7, 8.0 Hz, 2H), 3.38 (td, *J* = 9.9, 2.5 Hz, 1H), 3.16 (t, *J* = 7.9 Hz, 1H), 2.79 - 2.75 (m, 3H), 2.48 (q, *J* = 2.5 Hz, 1H); **^{13}C NMR** (150 MHz, D_2O) δ 174.96, 103.49, 86.35, 86.09, 80.27, 79.33, 78.65, 76.33, 75.98, 73.15, 72.96, 72.47, 71.59, 69.19, 61.67, 60.78, 55.75, 54.26, 24.40, 24.12, 23.76; **HRMS (ESI)** calcd for $C_{19}H_{31}NO_{14}S_2$ + $[H]^+$: 584.1084, found: 584.1076.

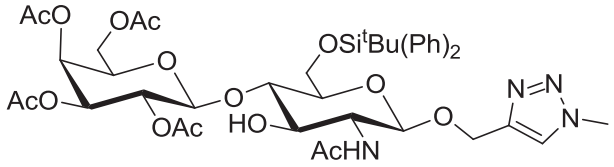
Compound 3.137



To a solution of acceptor **3.136** (200 mg, 0.41 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate **3.133** (297 mg, 0.62 mmol) in 10mL of dry

dichloromethane under nitrogen was added powdered molecular sieves (4 A, 0.5 g). The mixture was stirred for 2 h at room temperature, and then cooled to - 45°C. $BF_3{\cdot}Et_2O$ (50 µL, 0.41mmol) was added drop wise. After 1 h the mixture was neutralized with triethylamine, diluted with dichloromethane (10 mL), filtered through celite, and washed with dichloromethane. The combined filtrate and washings were dried over $MgSO_4$, filtered and concentrated. The syrupy residue was purified by silica gel chromatography to give **3.137** (272 mg, 82%); R_f = 0.31 (DCM : MeOH, 9.8 : 0.2, v/v); **^{1}H NMR (600 MHz, $CDCl_3$):** δ = 7.79 – 7.65 (m, 4H, H_{arom}), 7.52 - 7.30 (m, 6H, H_{arom}), 5.57 (d, $^3J_{NH\text{-}H2}$ = 8.0 Hz, 1H, AcN*H*), 5.37 (d, $^3J_{3,4}$ = $^3J_{4,5}$ = 3.4 Hz, 1H, *H*-4^{II}), 5.20 (dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 10.4 Hz, 1H, *H*-2^{II}), 4.97 (dd, $^3J_{3,4}$ = 3.4 et $^3J_{2,3}$ = 10.4 Hz, 1H, *H*-3^{II}), 4.87 (d, $^3J_{1,2}$ = 8.2 Hz, 1H, *H*-1^{I}), 4.72 (d, $^3J_{1,2}$ = 8.0 Hz, 1H, *H*-1^{II}), 4.35 (dd, *J* = 59.0, 15.6 Hz, 2H, *H*-6^{II}), 4.15 (d, $^4J_{H\text{-}H}$ = 6.5 Hz, 2H, OC*H*$_2$), 4.05 - 3.75 (m, 6H, *H*-3^{I}, *H*-4^{I}, *H*-5^{I}, *H*-5^{II}, *H*-6^{I}), 3.59 (dd, *J* = 17.5, 8.6 Hz, 1H, *H*-2^{I}), 3.43 (d, $^3J_{3,OH}$ = 9.1 Hz, 1H, O*H*-3^{I}), 2.44 (t, $^4J_{H,CH2}$ = 2.4 Hz, 1H, C≡C*H*), 2.16, 2.07, 2.04, 1.99 (4 x s, 9H, COC*H*$_3$), 1.72 (s, 3H, NHCOC*H*$_3$), 1.08 ppm (s, 9H, SiCMe$_3$) ; **^{13}C NMR (150 MHz, $CDCl_3$):** δ = 170.6, 170.4, 170.1, 169.9, 169.1 (*C*O), 135.9, 135.5, 133.4, 132.5, 129.9, 129.9, 127.9, 127.7 (*C*$_{arom}$), 100.9 (*C*-1^{II}), 97.6 (*C*-1^{I}), 79.8 (*C*≡CH), 78.7 (C≡*C*H), 75.0 (*C*-4^{I}), 74.6 (*C*-5^{I}), 71.6 (*C*-3^{I}), 71.2 (*C*-5^{II}), 70.8 (*C*-3^{II}), 68.8 (*C*-2^{II}), 66.9 (*C*-4^{II}), 61.7 (*C*-6^{I}), 61.2 (*C*-6^{II}), 56.5 (O*C*H$_2$), 55.2 (*C*-2^{I}), 26.8 (SiC*Me*$_3$), 23.7 (NHCO*C*H$_3$), 20.6, 20.6, 20.5, 20.3 (CO*C*H$_3$), 19.3 ppm (Si*C*Me$_3$). **HRMS (ESI)** calculated for $C_{41}H_{54}NO_{15}Si$ $[M + H]^+$: 828.32572, found 828.32504.

Compound 3.138

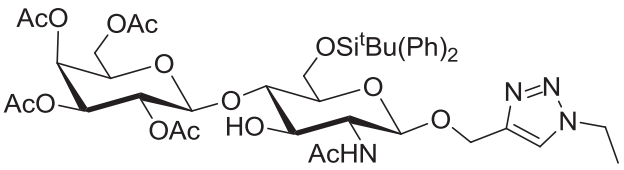


a) To a solution of compound **3.137** (0.083 g, 100 μmol) in THF:H_2O (1:1) 2 mL, MeI (2eq) NaN_3 (3 eq), $CuSO_4.5\ H_2O$ (5 mg 20%) and sodium ascorbate (8 mg, 40%) were added and after 12h of reaction time at 40°C following the general procedure (**7.2.1**) described above, the LacNAc triazole derivative **3.138** (44 mg, 50 %) was obtained;

b) Methyl azide was distilled at 90°C while preparing it in another RBF (MeI (1 eq) + NaN_3 (2eq) + DMF + Water (1:1)) then added to a RBF containing the solution of compound **3.137** (0.083 g, 100 μmol) in THF:H_2O (1:1) 2 mL, $CuSO_4.5H_2O$ (5 mg 20%) and sodium ascorbate (8 mg, 40%). After 12 h of reaction time at 40°C following the general procedure (**7.2.1**) described above, the LacNAc triazole derivative **3.138** (79 mg, 90 %) was obtained; $\mathbf{R}_f$ = 0.23 (DCM/MeOH, 9.8:0.2, v/v); $[\alpha]_D^{21}$ - 2.23 (*c* 1.0, $CHCl_3$); **^{1}H-NMR** (600 MHz) δ = 7.73 (td, *J* = 5.6, 3.0 Hz, 4H, H_{arom}), 7.49 (s, 1H, click-H), 7.47 - 7.32 (m, 6H, H_{arom}), 6.02 (d, $^3J_{NH-H2}$ = 8.0 Hz, 1H, AcN*H*), 5.36 (d, $^3J_{3,4}$ = $^3J_{4,5}$ = 3.4 Hz, 1H, *H*-4^{II}), 5.19 (dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 10.4 Hz, 1H, *H*-2^{II}), 4.97 (dd, $^3J_{3,4}$ = 3.4 and $^3J_{2,3}$ = 10.4 Hz, 2H, *H*-3^{II,} *H*-1^{I}), 4.73 (dd, *J* = 5.6Hz, *J* = 7.8Hz, 3H, H-6a6b^{II}, H-1^{II}), 4.14 (d, $^4J_{H-H}$ = 6.5 Hz, 2H, OC*H*$_2$), 4.05 (s, 3H, N-$\underline{CH_3}$), 3.88 (ddd, *J* = 14.6, 11.4, 4.7 Hz, 4H, H-3^{I}, H-4^{I}, H-6a, 6b^{I}), 3.71 (dd, *J* = 8.3Hz, *J* = 17.5Hz, 1H, H-2^{I}), 3.43 (d, $^3J_{3,OH}$ = 5.8 Hz, 1H, O*H*-3^{I}), 2.15, 2.06, 1.99, 1.92, (4 x s, 9H, COC*H*$_3$), 1.73 (s, 3H,

NHCOCH_3), 1.08 (s, 9H, SiCMe$_3$); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 170.8, 170.3, 170.0, 169.8, 169.1 (*C*O), 144.87 (triazole-*C*) 135.8, 135.4, 133.4, 132.4, 129.9, 127.8, 127.6 (C_{arom}), 123.4 (triazole-*C*) 100.8 (*C*-1^{II}), 99.6 (*C*-1^{I}), 79.5 (*C*-4^{I}), 74.6 (*C*-5^{I}), 72.1 (*C*-3^{I}), 71.1 (*C*-5^{II}), 70.7 (*C*-3^{II}), 68.8 (*C*-2^{II}), 66.8 (*C*-4^{II}), 61.9 (*C*-6^{I}), 61.8 (*C*-6^{II}), 61.1 (O*C*H$_2$), 56.3 (*C*-2^{I}), 36.6 (*N*-CH$_3$), 26.8 (SiC*Me*$_3$), 23.4 (NHCO*C*H$_3$), 20.57, 20.53, 20.48, 20.32 (CO*C*H$_3$), 19.32 ppm (Si*C*Me$_3$). **HRMS (ESI)** calculated for $C_{42}H_{57}N_4O_{15}Si$ $[M + H]^+$: 885.35842, found 885.35736.

Compound 3.139

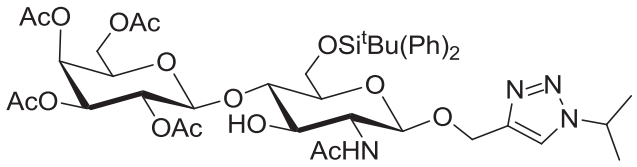


a) To a solution of compound **3.137** (0.083 g, 100 μmol) in THF:H_2O (1:1) 2 mL, EtBr (2eq) NaN_3 (3 eq), $CuSO_4$.5 H_2O (5 mg 20%) and sodium ascorbate (8 mg, 40%) were added and after 12h of reaction time at 40^{o}C following the general procedure (**7.2.1**) described above, the LacNAc triazole derivative **3.139** (50 mg, 55 %) was obtained.

b) Ethyl azide was distilled at 90^{o}C while preparing it in another RBF (EtBr (1eq) + NaN3 (2eq) + DMF + Water (1:1)) then added to a RBF containing the solution of compound **3.137** (0.083 g, 100 μmol) in THF: H_2O (1:1) 2mL, $CuSO_4$. 5H_2O (5 mg 20%) and sodium ascorbate (8 mg, 40%). After 12h of reaction time at 40^{o}C following the general procedure ((**7.2.1**) described above the LacNAc triazole derivative **3.139** (82 mg, 91 %) was obtained; $\mathbf{R}_f$ 0.27 (DCM/MeOH, 9.7 : 0.3, v/v) ; $[\alpha]_D^{22}$ - 1.23 (*c* 1.0, $CHCl_3$);

^{1}H-NMR (600 MHz) δ = 7.72 (dd, *J* = 9.2, 4.1 Hz, 4H, H_{arom}), 7.52 (s, 1H, click-H), 7.48 - 7.30 (m, 4H, H_{arom}), 6.15 (d, $^{3}J_{NH-H2}$ = 7.8 Hz, 1H, AcN*H*), 5.36 (d, d, 1H, $^{3}J_{3,4}$ = $^{3}J_{4,5}$ = 3.4 Hz, 1H, *H*-4^{II}), 5.18 (dd, $^{3}J_{1,2}$ = 8.1 Hz, $^{3}J_{2,3}$ = 10.3 Hz, 1H, *H*-2^{II}), 4.96 (dd, $^{3}J_{3,4}$ = 3.0 and $^{3}J_{2,3}$ = 10.3 Hz, 2H, *H*-3^{II,} *H*-1^{I}), 4.72 (dd, *J* = 9.7Hz, *J* = 16.2Hz, 3H, H-6a6b^{II}, H-1^{II}), 4.36 (q, J=7.4Hz, 2H, N-$\underline{CH_2}CH_3$), 4.14 (d, $^{4}J_{H-H}$ = 6.5 Hz, 2H, OCH_2), 3.92 (ddd, *J* = 25.1, 19.5, 11.3 Hz, 4H, H-3^{I}, H-4^{I}, H-6a,6b^{I}), 3.72 (dd, *J* = 8.1Hz, *J* = 14.8Hz, 1H, H-2^{I}), 3.42 (d, $^{3}J_{3,OH}$ = 8.4 Hz, 1H, O*H*-3^{I}), 2.14, 2.05, 1.98, 1.97 (4 x s, 9H, COCH_3), 1.72, (s, 3H, NHCOCH_3), 1.52 (t, *J* = 7.4Hz, 3H, N-CH$_2\underline{CH_3}$) 1.07 (s, 9H, SiCMe$_3$); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 170.8, 170.3, 170.0, 169.8, 169.1 (*C*O), 144.87 (triazole-*C*) 135.8, 135.4, 133.4, 132.4, 129.9, 127.8, 127.6 (C_{arom}), 121.8 (triazole-*C*) 100.7 (*C*-1^{II}), 99.6 (*C*-1^{I}), 79.5 (*C*-4^{I}), 74.6 (*C*-5^{I}), 72.1 (*C*-3^{I}), 71.1 (*C*-5^{II}), 70.7 (*C*-3^{II}), 68.7 (*C*-2^{II}), 66.8 (*C*-4^{II}), 61.9 (*C*-6^{I}), 61.7 (*C*-6^{II}), 61.1 (OCH_2), 56.3 (*C*-2^{I}), 45.23 (*N*-$\underline{C}H_2CH_3$), 26.7 (SiC*Me*$_3$), 23.4 (NHCO*C*H$_3$), 20.53, 20.49, 20.45, 20.28 (CO*C*H$_3$), 19.28 (Si*C*Me$_3$), 15.38 ppm (*N*-CH$_2\underline{C}H_3$). **HRMS (ESI)** calculated for $C_{43}H_{59}N_4O_{15}Si$ $[M + H]^+$: 899.37407, found 899.37341.

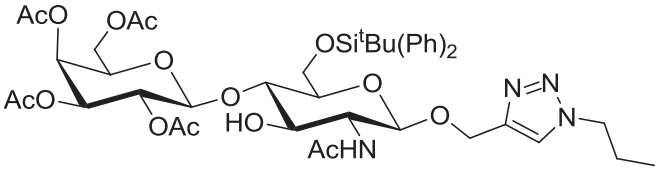
Compound 3.140



To a solution of compound **3.137** (0.083 g, 100 μmol) in THF:H_2O (1:1) 2 mL, isopropyl azide (13 mg, 150 μmol) $CuSO_4.5H_2O$ (5 mg 20%) and sodium ascorbate (8 mg, 40%) were added and after 12 hrs of reaction time following the general procedure ((**7.2.1**)

described above, the LacNAc triazole derivative **3.140** (87 mg, 95 %) was obtained; $\mathbf{R}_f$ 0.23 (DCM:MeOH, 9.5:0.5, v/v); ; $[\alpha]_D^{22}$ - 20.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.88 - 7.65 (m, 4H, H_{arom}), 7.49 (s, 1H, click-H), 7.46 - 7.29 (m, 6H, H_{arom}), 6.10 (d, $^3J_{NH-H2}$ = 7.7 Hz, 1H, AcN*H*), 5.36 (d, $^3J_{3,4} = {}^3J_{4,5}$ = 3.4 Hz, 1H, *H*-4^{II}), 5.19 (dd, $^3J_{1,2}$ = 8.1 Hz, $^3J_{2,3}$ = 10.4 Hz, 1H, *H*-2^{II}), 4.97 (dd, $^3J_{3,4}$ = 3.0 and $^3J_{2,3}$ = 10.3 Hz, 2H, *H*-3^{II,} *H*-1^{I}), 4.77 (qd, *J* = 6.6Hz, *J* = 14.9Hz, 4H, H-6a6b^{II}, H-1^{II}, N-C<u>H</u>$(CH_3)_2$), 4.13 (d, $^4J_{H-H}$ = 6.7 Hz, 2H, OC*H*$_2$), 4.09 - 3.79 (m, 6H, H-3^{I}, H-4^{I}, H-6a, 6b^{I}, H-5^{I}, H-5^{II}), 3.70 (d, *J* = 9.5 Hz, 1H, H-2^{I}), 3.44 (d, $^3J_{3,OH}$ = 8.4 Hz, 1H, O*H*-3^{I}), 2.16, 2.06, 1.99, 1.98, (4 x s, 9H, COC*H*$_3$), 1.73 (s, 3H, NHCOC*H*$_3$) 1.56 (dd, *J* = 6.7, 1.4 Hz, 2H, N-CH(C<u>H</u>$_3)_2$), 1.08 (s, 9H, $SiCMe_3$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 170.80, 170.34, 170.06, 169.84, 169.09 (*C*O), 144.29 (triazole-*C*), 135.85, 135.43, 133.44, 132.44, 129.84, 127.82, 127.63 (C_{arom}), 119.92 (triazole-*C*), 100.79 (*C*-1^{II}), 99.59 (*C*-1^{I}), 79.59 (*C*-4^{I}), 74.66(*C*-5^{I}), 72.17 (*C*-3^{I}), 71.14(*C*-5^{II}), 70.76(*C*-3^{II}), 68.79 (*C*-2^{II}), 66.83 (*C*-4^{II}), 62.06 (*C*-6^{I}), 61.78 (*C*-6^{II}), 61.11 (O*C*H$_2$), 56.44 (*C*-2^{I}), 52.96 (N-<u>C</u>H$(CH_3)_2$), 26.78 (SiC*Me*$_3$), 23.46 (NHCO*C*H$_3$), 22.95, 22.92 (N-CH(<u>C</u>H$_3)_2$), 20.56, 20.52, 20.47, 20.29 (CO*C*H$_3$), 19.30 (Si*C*Me$_3$); **HRMS (ESI)** calculated for $C_{44}H_{61}N_4O_{15}Si$ $[M + H]^+$: 913.38972, found 913.38883.

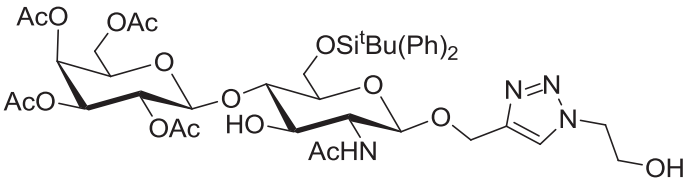
Compound 3.141



To a solution of compound **3.137** (0.083 g, 100 μmol) in THF:H_2O (1:1) 2 mL, n-propyl azide (13 mg, 150 μmol) $CuSO_4.5H_2O$ (5 mg 20%) and sodium ascorbate (8 mg, 40%) were added and after 12h of reaction time following the general procedure ((**7.2.1**) described above, the LacNAc triazole derivative **3.141** (86 mg, 94%) was obtained; $\mathbf{R}_f$ 0.22 (DCM/MeOH, 9.8 : 0.3, v/v); $[\alpha]_D^{21}$ - 7.23 (*c* 1.0, $CHCl_3$); **^{1}H-NMR** (600 MHz) δ = 7.79 - 7.69 (m, 4H, H_{arom}), 7.50 (s, 1H, click-H), 7.48 - 7.32 (m, 6H, H_{arom}), 6.06 (d, $^3J_{NH-H2}$ = 7.7 Hz, 1H, AcN*H*), 5.37 (d, d, 1H, $^3J_{3,4}$ = $^3J_{4,5}$ = 3.4 Hz, 1H, *H*-4^{II}), 5.20 (dd, $^3J_{1,2}$ = 8.1 Hz, $^3J_{2,3}$ = 10.4 Hz, 1H, *H*-2^{II}), 4.97 (dd, $^3J_{3,4}$ = 3.0 and $^3J_{2,3}$ = 10.3 Hz, 2H, *H*-3^{II,} *H*-1^{I}), 4.75 (dd, *J* = 6.6Hz, *J* = 14.9Hz, 3H, H-6a6b^{II}, H-1^{II}), 4.29 (t, *J* = 7.2Hz, 1H, N-$\underline{CH_2}CH_2CH_3$), 4.15 (d, $^4J_{H-H}$ = 6.7 Hz, 2H, O*C*H_2), 3.90 (ddd, *J* = 15.6, 13.5, 9.0 Hz, 6H, H-3^{I}, H-4^{I}, H-6a,6b^{I}, H-5^{I}, H-5^{II}), 3.75 - 3.73 (m, 1H, H-2^{I}), 3.45 (d, $^3J_{3,OH}$ = 8.4 Hz, 1H, O*H*-3^{I}), 2.16, 2.06, 1.99, 1.98, (4 x s, 9H, COCH_3), 1.92 - 1.89 (m, 2H, N-$CH_2\underline{CH_2}CH_3$), 1.73 (s, 3H, NHCOCH_3), 1.08 (s, 9H, $SiCMe_3$), 0.96 (t, *J* = 7.4Hz, 3H, N-$CH_2CH_2\underline{CH_3}$); **^{13}C NMR** (150 MHz, $CDCl_3$): δ=170.8, 170.4, 170.1, 169.9, 169.1 (*C*O), 144.87 (triazole-*C*) 135.9, 135.4, 133.5, 132.5, 129.9, 127.8, 127.6 (C_{arom}), 122.39 (triazole-*C*) 100.8 (*C*-1^{II}), 99.7 (*C*-1^{I}), 79.7 (*C*-4^{I}), 74.7 (*C*-5^{I}), 72.2 (*C*-3^{I}), 71.2 (*C*-5^{II}), 70.8 (*C*-3^{II}), 68.8 (*C*-2^{II}), 66.8 (*C*-4^{II}), 61.9 (*C*-6^{I}), 61.8 (*C*-6^{II}), 61.1 (O*C*H_2), 56.4 (*C*-2^{I}), 52.06 (*N*-

$\underline{C}H_2$-CH_2-CH_3), 26.8 (SiC*Me*$_3$), 23.4 (NHCO*C*H_3), 23.51 (*N*-CH_2-$\underline{C}H_2$-CH_3), 20.60, 20.55, 20.51, 20.33 (CO*C*H_3), 19.35 (Si*C*Me_3), 11.02 ppm (*N*-$CH_2\underline{C}H_3$). **HRMS (ESI)** calculated for $C_{44}H_{61}N_4O_{15}Si$ $[M + H]^+$: 913.38972, found 913.38885.

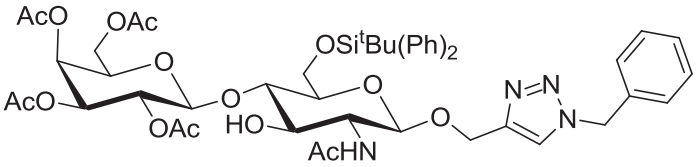
Compound 3.142



To a solution of compound **3.137** (0.083 g, 100 μmol) in THF:H_2O (1:1) 2 mL, 2-azido ethanol (13 mg, 150 μmol) $CuSO_4.5H_2O$ (5 mg 20%) and sodium ascorbate (8 mg, 40%) were added and after 12h of reaction time following the general procedure ((**7.2.1**) described above, the LacNAc triazole derivative **3.142** (83 mg, 91%) was obtained; $\mathbf{R}_f$ 0.20 (DCM/MeOH, 9.5:0.5, v/v); $[\alpha]_D^{22}$ - 24.10 (*c* 1.0, $CHCl_3$); **^{1}H-NMR** (600 MHz) δ = 7.75 (ddd, *J* = 7.6, 6.2, 2.1 Hz, 4H, H_{arom}), 7.60 (s, 1H, click-H), 7.51 - 7.33 (m, 6H, H_{arom}), 6.32 (d, $^3J_{NH\text{-}H2}$ = 7.2 Hz, 1H, AcN*H*), 5.36 (d, $^3J_{3,4}$ = $^3J_{4,5}$ = 3.2 Hz, 1H, *H*-4^{II}), 5.18 (dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 10.4 Hz, 1H, *H*-2^{II}), 5.03 - 4.93 (m, 3H, H-3^{II,} H-6a,6b^{II}), 4.78 - 4.65 (m, 2H, N-$\underline{CH2}$-CH_2-OH), 4.58 - 4.33 (m, 2H, N-CH2-$\underline{CH_2}$-OH), 4.13 (d, $^4J_{H\text{-}H}$ = 6.6 Hz, 2H, OCH_2), 3.83 - 3.71 (m, 6H, H-3^I, H-4^I, H-6a,6b^I, H-5^I, H-5^{II}), 3.44 (d, $^3J_{3,OH}$ = 7.9 Hz, 1H, O*H*-3^I), 3.13 (dd, *J* = 17.4, 8.1 Hz, 1H, H-2^I), 2.15, 2.04, 1.98, 1.85 (4 x s, 9H, COCH_3), 1.73(s, 3H, NHCOCH_3), 1.08(s, 9H, $SiCMe_3$) **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 171.4, 170.2, 170.1, 169.9, 169.06 (*C*O), 143.24 (triazole-*C*) 135.9, 135.4, 133.4, 132.4, 129.88, 127.84, 127.6 (C_{arom}), 124.6 (triazole-*C*) 100.8 (*C*-1^{II}), 96.1 (*C*-1^I),

80.18 (*C*-4^{I}), 74.5 (*C*-5^{I}), 71.1 (*C*-3^{I}), 70.68 (*C*-5^{II}), 70.3 (*C*-3^{II}), 68.7 (*C*-2^{II}), 66.8 (*C*-4^{II}), 66.7 (*C*-6^{I}), 61.7 (*C*-6^{II}), 61.1 (*N*-$CH_2\underline{C}H_2$-OH) 60.72 (O*C*H_2), 58.0 (O*C*H_2), 56.4 (*C*-2^{I}), 53.40 (*N*-$\underline{C}H_2$-CH_2-OH), 26.6 (SiC*Me*$_3$), 23.4 (NHCO*C*H_3), 23.28 (*N*-CH_2-$\underline{C}H_2$-CH_3), 20.56, 20.51, 20.48, 20.3 (CO*C*H_3), 19.31 (Si*C*Me$_3$). **HRMS (ESI)** calcd for $C_{43}H_{59}N_4O_{16}Si$ $[M + H]^+$: 915.36898, found 915.36782.

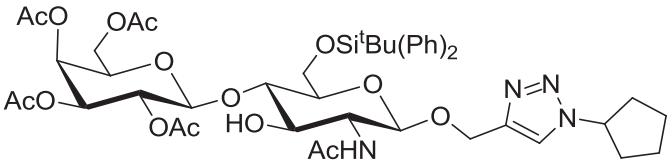
Compound 3.143



To a solution of compound **3.137** (0.083 g, 100 μmol) in THF:H_2O (1:1) 2 mL, benzyl azide (20 mg, 150 μmol) $CuSO_4$.5 H_2O (5 mg 20%) and sodium ascorbate (8 mg, 40%) were added and after 12h of reaction time following the general procedure ((**7.2.1**) described above, the LacNAc triazole derivative **3.143** (91 mg, 95 %) was obtained; $\mathbf{R_f}$ 0.35 (DCM/MeOH, 9.8:0.2, v/v); $[\alpha]_D^{21}$ - 2.30 (*c* 1.0, $CHCl_3$); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.82 - 7.62 (m, 4H), 7.47 - 7.31 (m, 10H), 7.29 - 7.21 (m, 2H), 6.07 (d, *J* = 7.8 Hz, 1H), 5.48 (s, 2H), 5.36 (d, *J* = 3.3 Hz, 1H), 5.19 (dd, *J* = 10.4, 8.0 Hz, 1H), 5.05 - 4.87 (m, 2H), 4.72 (dd, *J* = 13.7, 5.9 Hz, 3H), 4.14 (d, *J* = 6.5 Hz, 2H), 4.01 - 3.77 (m, 6H), 3.70 (d, *J* = 8.0 Hz, 1H), 3.41 (s, 1H), 2.15, 2.04, 1.98, 1.85 (4 x s, 9H, CO*C*H_3), 1.73(s, 3H, NHCO*C*H_3); **^{13}C NMR** (150 MHz, $CDCl_3$): δ=170.7, 170.3, 170.0, 169.8, 169.0 (*C*O), 144.87 (triazole-*C*) 135.8, 135.4, 134.4, 133.4, 132.4, 129.8, 129.0, 128.7, 128.0, 127.7, 127.6 (C_{arom}), 122.40 (triazole-*C*) 100.7 (*C*-1^{II}), 99.5 (*C*-1^{I}), 79.5 (*C*-4^{I}),

74.5 (*C*-5^{I}), 72.1 (*C*-3^{I}), 71.1 (*C*-5^{II}), 70.7 (*C*-3^{II}), 68.7 (*C*-2^{II}), 66.8 (*C*-4^{II}), 61.8 (*C*-6^{I}), 61.7 (*C*-6^{II}), 61.0 (O*C*H$_2$), 56.2 (*C*-2^{I}), 54.07 (*N*-C$\underline{H}_2$-Ph), 26.7 (SiC*Me*$_3$), 23.3 (NHCO*C*H$_3$), 20.5, 20.48, 20.43, 20.26 (CO*C*H$_3$), 19.25 (Si*C*Me$_3$) ppm. **HRMS (ESI)** calculated for $C_{48}H_{61}N_4O_{15}Si$ $[M + H]^+$: 961.38972, found 961.38948.

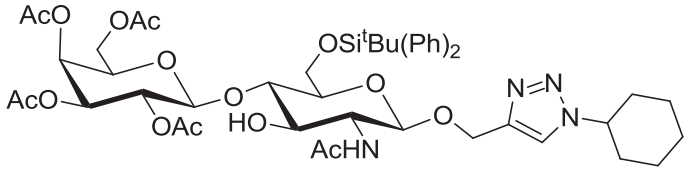
Compound 3.144



To a solution of compound **3.137** (0.083 g, 100 μmol) in THF:H$_2$O (1:1) 2 mL, cyclopentyl azide (17 mg, 150 μmol) $CuSO_4.5H_2O$ (5 mg 20%) and sodium ascorbate (8 mg, 40%) were added and after 12h of reaction time following the general procedure ((**7.2.1**) described above, the LacNAc triazole derivative **3.144** (87 mg, 93 %) was obtained; **R**$_f$ 0.3 (DCM/MeOH, 9.8:0.2, v/v) ; $[\alpha]_D^{22}$ - 15.17 (*c* 1.0, $CHCl_3$); **^{1}H-NMR** (600 MHz) δ = 7.73 (dd, *J* = 9.5, 4.1 Hz, 4H, H$_{arom}$) 7.50 (s, 1H,click-H) 7.48 - 7.29 (m, 6H, H$_{arom}$), 6.24 (d, $^3J_{NH-H2}$ = 11.6 Hz, 1H, AcN*H*) 5.35 (d, d, 1H, $^3J_{3,4}$ = $^3J_{4,5}$ = 3.2 Hz, 1H, *H*-4^{II}) 5.18 (dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 10.4 Hz, 1H, *H*-2^{II}) 5.03 - 4.92 (m, 3H, H-3^{II,} H-6a,6b^{II}) 4.81 - 4.69 (m, 3H, H-1^{I}, H-6a,6b^{II}) 4.39 (ddd, *J* = 2.8Hz, *J* = 7.2Hz, *J* = 11.8Hz, 1H, N-CH $_{cyclopentyl}$) 4.13 (d, $^4J_{H-H}$ = 6.6 Hz, 2H, OC*H*$_2$) 3.92 (ddd, *J* = 25.1, 21.3, 11.3 Hz, 6H, H-3^{I}, H-4^{I}, H-6a,6b^{I}, H-5^{I}, H-5^{II}), 3.70 (d, *J* = 9.2 Hz, 1H, H-2^{I}) 3.42 (d, $^3J_{3,OH}$ = 7.9 Hz, 1H, O*H*-3^{I}), 2.40 – 2.19 (m, 2H, C$\underline{H}_{2cyclopentyl}$), 2.14, 2.04, 1.97, 1.95 (4 x s, 9H, COC*H*$_3$), 1.87 (d, *J* = 6.5 Hz, m, 2H, C$\underline{H}_{2cyclopentyl}$), 1.81 – 1.66 (m, 2H,

C<u>H</u>$_{2cyclopentyl}$), 1.71 (s, 3H, NHCOCH_3), 1.07 (s, 9H, SiCMe$_3$) 1.01 - 0.78 (m, 2H, C<u>H</u>$_{2cyclopentyl}$); **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 170.8, 170.3, 170.0, 169.8, 169.0 (*C*O), 143.99 (triazole-*C*) 135.8, 135.3, 133.3, 132.4, 129.8, 127.7, 127.5 (C_{arom}), 120.3 (triazole-*C*) 100.7 (*C*-1^{II}), 99.6 (*C*-1^{I}), 79.5 (*C*-4^{I}), 74.6 (*C*-5^{I}), 72.2 (*C*-3^{I}), 71.0 (*C*-5^{II}), 70.7 (*C*-3^{II}), 68.7 (*C*-2^{II}), 66.8 (*C*-4^{II}), 62.0 (*C*-6^{I}), 61.7 (*C*-6^{II}), 61.0 (O*C*H$_2$), 60.03 (N-C$_{cyclopentyl}$) 56.4 (*C*-2^{I}), 33.4, 33.3 (N-C$_{cyclopentyl}$) 26.7 (SiC*Me*$_3$), 25.0, 24.9 (N-C$_{cyclopentyl}$) 23.3 (NHCO*C*H$_3$), 20.5 (N-C$_{cyclopentyl}$), 20.60, 20.55, 20.51, 20.33 (CO*C*H$_3$), 19.35 (Si*C*Me$_3$); **HRMS (ESI)** calculated for $C_{46}H_{63}N_4O_{15}Si$ $[M + H]^+$: 939.40592, found 939.40537.

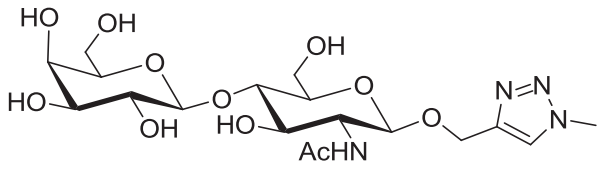
Compound 3.145



To a solution of compound **3.137** (0.083 g, 100 μmol) in THF:H_2O (1:1) 2 mL, cyclohexyl azide (13 mg, 150 μmol) $CuSO_4.5H_2O$ (5 mg 20%) and sodium ascorbate (8 mg, 40%) were added and after 12h of reaction time following the general procedure ((**7.2.1**) described above, the LacNAc triazole derivative **3.145** (90 mg, 94 %) was obtained; R_f 0.15 (DCM/MeOH, 9.8:0.2, v/v) ; $[\alpha]_D^{21}$ - 8.23 (*c* 1.0, $CHCl_3$); **^{1}H-NMR** (600 MHz) δ = 7.75 - 7.71 (m, 4H, H$_{arom}$), 7.50 (s, 1H,click-H), 7.47 - 7.23 (m, 6H, H$_{arom}$), 6.24 (,$^3J_{NH-H2}$ = 11.6 Hz, 1H,AcN*H*), 5.35 (d, d, 1H, $^3J_{3,4}$ = $^3J_{4,5}$ = 3.2 Hz, 1H, *H*-4^{II}), 5.18 (dd, $^3J_{1,2}$ = 8.0 Hz, $^3J_{2,3}$ = 10.4 Hz, 1H, *H*-2^{II}), 4.96 (m, 3H, H-3^{II,} H-6a,6b^{II}),

4.81 – 4.69 (m, 3H, H-1^{I}, H-6a,6b^{II}), 4.39 (ddd, J = 2.8Hz, J = 7.2Hz, J = 11.8Hz, 1H, N-CH $_{cyclohexyl}$), 4.13 (d, $^{4}J_{H\text{-}H}$ = 6.6 Hz, 2H, OCH_2), 4.04 - 3.83 (m, 6H, H-3^{I}, H-4^{I}, H-6a,6b^{I}, H-5^{I}, H-5^{II}), 3.71 - 3.69 (m, 1H, H-2^{I}), 3.42 (d, $^{3}J_{3,OH}$ = 7.9 Hz, 1H,OH-3^{I}), 2.29 - 2.20 (m, 2H, C$\underline{H_2}$ $_{cyclohexyl}$), 2.15, 2.05, 1.98, 1.97 (4 x s, 9H, COCH_3), 1.71 (s, 3H, NHCOCH_3), 1.88 - 1.85 (m, 2H, C$\underline{H_2}$$_{cyclohexyl}$), 1.07 (s, 9H, SiCMe$_3$), 1.0 - 0.95 (m, 2H, C$\underline{H_2}$ $_{cyclohexyl}$), some multiplets belonging to C$\underline{H_2}$ $_{cyclohexyl}$ masked under singlets at 2.4-1.5 ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 170.8, 170.3, 170.0, 169.8, 169.0 (*C*O), 143.99 (triazole-*C*) 135.8, 135.3, 133.3, 132.4, 129.8, 127.7, 127.5 (C_{arom}), 120.3 (triazole-*C*) 100.7 (*C*-1^{II}), 99.6 (*C*-1^{I}), 79.5 (*C*-4^{I}), 74.6 (*C*-5^{I}), 72.2 (*C*-3^{I}), 71.0 (*C*-5^{II}), 70.7 (*C*-3^{II}), 68.7 (*C*-2^{II}), 66.8 (*C*-4^{II}), 62.0 (*C*-6^{I}), 61.7 (*C*-6^{II}), 61.0 (O*C*H$_2$), 60.03 (N-C$_{cyclohexyl}$) 56.4 (*C*-2^{I}), 33.4, 33.3 (N-C$_{cyclohexyl}$) 26.7 (SiC*Me*$_3$), 25.0, 24.9 (N-C$_{cyclohexyl}$) 23.3 (NHCO*C*H$_3$), 20.5 (N-C$_{cyclohexyl}$), 20.60, 20.55, 20.51, 20.33 (CO*C*H$_3$), 19.35 (Si*C*Me$_3$); **HRMS (ESI)** calculated for $C_{47}H_{65}N_4O_{15}Si$ $[M + H]^+$: 953.42157, found : 953.42160.

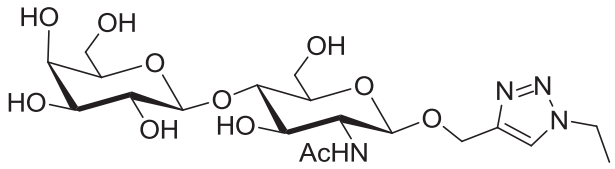
Compound 3.146



To a solution of compound **3.138** (0.025 g, 28 μmol) in 1.5 mL THF (Dry) was added a 1M TBAF/THF soln (0.056 ml, 2eq) and the reaction mixture stirred overnight under nitrogen atmosphere, then the reaction mixture was evaporated under reduced pressure. Dry methanol 2 mL and 1 ml of NaOMe/MeOH (pH 10) were added then stirred for 4 hrs. Acid resin was then added to neutralize the reaction mixture and evaporated. The

reaction mixture was washed with acid base mix resin in water to remove the traces of TBAF, and lyophilized to obtain white foam like compound **3.146** (13 mg, 95%); $\mathbf{R}_f$ 0.11 (ACN/H_2O 5.8:1.5, v/v); $[\alpha]_D^{24}$ + 8.6 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 7.87 (d, *J* = 96.5 Hz, 1H), 4.91 (d, *J* = 12.9 Hz, 1H), 4.80 (d, *J* = 8.5 Hz, 1H), 4.60 (d, *J* = 8.1 Hz, 1H), 4.46 (d, *J* = 7.8 Hz, 1H), 4.11 (d, *J* = 5.0 Hz, 3H), 4.01 - 3.97 (m, 1H), 3.92 (t, *J* = 3.5 Hz, 1H), 3.84 (dd, *J* = 12.3, 5.2 Hz, 1H), 3.80 - 3.62 (m, 8H), 3.59 (ddd, *J* = 9.3, 5.2, 2.2 Hz, 1H), 3.57 - 3.50 (m, 1H), 1.91 (s, 3H); **^{13}C NMR** (150 MHz, D_2O) δ 175.03, 144.12, 126.75, 103.53, 100.64, 79.01, 76.00, 75.49, 73.16, 72.89, 72.71, 71.62, 69.20, 63.13, 62.57, 61.67, 60.70, 55.67, 37.19, 22.66; **HRMS** (**ESI**) m/z calculated for $C_{18}H_{30}N_4O_{11}$ $[M+H]^+$ 479.1989; found 479.1984.

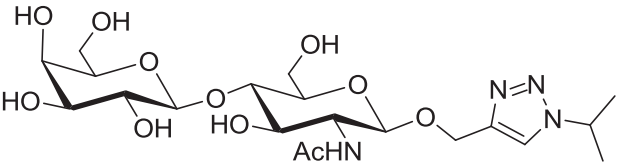
Compound 3.147



To a solution of compound **3.139** (0.038 g, 42 μmol) in 1.5 mL THF (Dry) was added a 1 M TBAF/THF soln. (0.084 ml 2eq) and the reaction mixture stirred overnight under nitrogen atmosphere, Then the reaction mixture was evaporated under reduced pressure. Then dry methanol 2 mL and 1 ml of NaOMe/MeOH (pH 10) were added, then stirred for 4 hrs. Acid resin was then added to neutralize the reaction mixture and evaporated. The reaction mixture was washed with acid base mix resin in water to remove the traces of TBAF, and lyophilized to obtain white foam like compound **3.147** (19 mg, 90%); $\mathbf{R}_f$

0.15 (ACN/H_2O, 5.8:1.5, v/v); $[\alpha]_D^{24}$ - 22.30 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 8.01 (s, 1H), 4.91(d, *J* = 12.9 Hz, 1H), 4.83 (d, *J* = 8.5 Hz, 1H), 4.60 (d, *J* = 7.8 Hz, 1H), 4.49 - 4.42 (m, 3H), 3.98 (dd, *J* = 12.2, 2.0 Hz, 1H), 3.94 - 3.90 (m, 2H), 3.83 (dt, *J* = 13.8, 7.0 Hz, 1H), 3.79 - 3.64 (m, 8H), 3.59 (dd, *J* = 12.4, 10.3 Hz, 1H), 3.53 (dd, *J* = 10.0, 7.8 Hz, 1H), 1.90 (s, 3H), 1.51 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (150 MHz, D_2O) δ 175.00, 144.07, 125.29, 103.53, 100.71, 79.01, 76.00, 75.47, 73.17, 72.87, 71.62, 69.20, 62.62, 61.67, 60.70, 55.68, 46.34, 22.68, 15.28; **HRMS (ESI)** calculated for $C_{19}H_{32}N_4O_{11}$ $[M+H]^+$ 493.2146, found 493.2146.

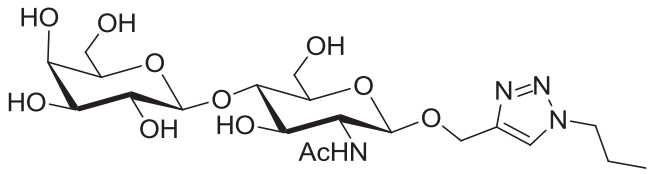
Compound 3.148



To a solution of compound **3.140** (0.067 g, 73 μmol) in 1.5 mL THF (Dry) was added 1 M TBAF/THF soln (0.146 ml, 2eq) and the reaction mixture stirred overnight under nitrogen atmosphere. Then, the reaction mixture was evaporated under reduced pressure and dry methanol 2 mL and 1 ml of NaOMe/MeOH (pH 10) were added, then stirred for 4 hrs. Acid resin was then added to neutralize the reaction mixture and evaporated. The reaction mixture was washed with acid base mix resin in water to remove the traces of TBAF, and lyophilized to obtain white foam like compound **3.148** (35 mg, 92%); $\mathbf{R}_f$ 0.15 (ACN/H_2O, 5.8:1.5, v/v); $[\alpha]_D^{24}$ - 10.74 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 8.08 (d, *J* = 5.1 Hz, 1H), 4.92 (t, *J* = 8.9 Hz, 1H), 4.83 (d, *J* = 9.9 Hz, 1H), 4.62 (d, *J* = 6.8 Hz,

1H), 4.49 (d, *J* = 7.8 Hz, 1H), 4.00 (d, *J* = 10.8 Hz, 1H), 3.96 - 3.91 (m, 1H), 3.86 (dd, *J* = 12.2, 5.1 Hz, 1H), 3.81 - 3.66 (m, 8H), 3.65 - 3.59 (m, 1H), 3.57 (dd, *J* = 17.6, 9.5 Hz, 1H), 1.93 (s, 3H), 1.58 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (150 MHz, D_2O) δ 174.95, 123.65, 103.47, 100.70, 78.96, 75.94, 75.39, 73.11, 72.79, 71.57, 69.15, 62.63, 61.61, 60.65, 55.65, 54.43, 31.04, 22.66, 22.60; **HRMS (ESI)** calculated for $C_{20}H_{34}N_4O_{11}$ $[M + H]^+$ 507.2302, found 507.2295.

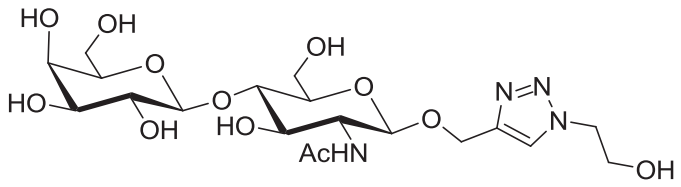
Compound 3.149



To a solution of compound **3.141** (0.080 g, 87 μmol) in 1.5 mL THF (Dry) was added 1 M TBAF/THF soln (0.174 ml, 2eq) and the reaction mixture stirred overnight under nitrogen atmosphere. Then, the reaction mixture was evaporated under reduced pressure and dry methanol 2 mL and 1 ml of NaOMe/MeOH (pH 10) were added, then stirred for 4 hrs. Acid resin was then added to neutralize the reaction mixture and evaporated. The reaction mixture was washed with acid base mix resin in water to remove the traces of TBAF, and lyophilized to obtain white foam like compound **3.149** (40 mg, 92%); R_f 0.15 (ACN/H_2O, 5.8:1.5, v/v); $[\alpha]_D^{24}$ - 16.92 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 8.03 (d, *J* = 5.1 Hz, 1H), 4.93 (d, *J* = 12.9 Hz, 1H), 4.83 (d, *J* = 12.4 Hz, 1H), 4.66 - 4.60 (m, 1H), 4.49 (d, *J* = 7.8 Hz, 1H), 4.41 (t, *J* = 6.9 Hz, 3H), 4.03 - 3.98 (m, 1H), 3.94 (t, *J* = 6.1 Hz, 1H), 3.86 (dt, *J* = 10.8, 5.5 Hz, 1H), 3.81 - 3.67 (m, 8H), 3.65 - 3.59 (m, 1H),

3.56 (dd, *J* = 9.9, 7.9 Hz, 1H), 1.96 - 1.89 (m, 5H), 0.88 (t, *J* = 7.4 Hz, 4H); **^{13}C NMR** (150 MHz, D_2O) δ 174.95, 144.04, 125.77, 103.47, 100.72, 78.96, 75.94, 75.40, 73.11, 72.80, 71.56, 69.15, 62.57, 61.61, 60.65, 55.64, 52.65, 23.65, 22.63, 10.71; **HRMS (ESI)** calculated for $C_{20}H_{34}N_4O_{11}$ $[M + H]^+$ 507.2302, found 507.2294.

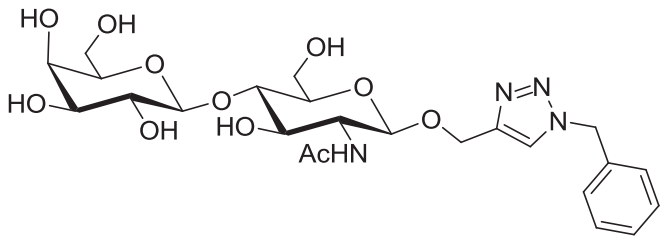
Compound 3.150



To a solution of compound **3.142** (0.022 g, 24 μmol) in 1.5 mL THF (Dry) was added 1 M TBAF/THF soln (0.047 ml, 2eq) and the reaction mixture stirred overnight under nitrogen atmosphere. Then, the reaction mixture was evaporated under reduced pressure and dry methanol 2 mL and 1 ml of NaOMe/MeOH (pH 10) were added, then stirred for 4 hrs. Acid resin was then added to neutralize the reaction mixture and evaporated. The reaction mixture was washed with acid base mix resin in water to remove the traces of TBAF, and lyophilized to obtain white foam like compound **3.150** (11 mg, 90%); $\mathbf{R}_f$ 0.10 (ACN/H_2O, 5.8:1.5, v/v); $[\alpha]_D^{24}$ - 5.48 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 8.05 (d, *J* = 23.8 Hz, 1H), 4.95 (d, *J* = 13.0 Hz, 1H), 4.87 (d, *J* = 8.5 Hz, 1H), 4.64 (t, *J* = 8.9 Hz, 2H), 4.61 - 4.57 (m, 1H), 4.49 (d, *J* = 7.8 Hz, 1H), 4.05 - 4.00 (m, 3H), 3.95 (t, *J* = 3.4 Hz, 1H), 3.90 - 3.83 (m, 1H), 3.80 - 3.67 (m, 8H), 3.63 (dd, *J* = 7.3, 5.3 Hz, 1H), 3.56 (dd, *J* = 9.8, 8.0 Hz, 1H), 1.93 (s, 3H); **^{13}C NMR** (150MHz, D_2O) δ 174.94, 144.08, 126.25, 103.47, 100.53, 78.96, 75.94, 75.42, 73.10, 72.84, 71.56, 69.14, 62.48, 61.60,

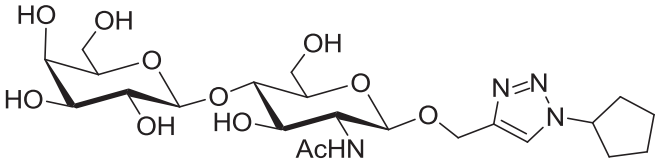
60.67, 55.60, 53.11, 22.63; **HRMS (ESI)** calculated for $C_{19}H_{32}N_4O_{12}$ $[M + H]^+$ 509.2095, found 509.2088.

Compound 3.151



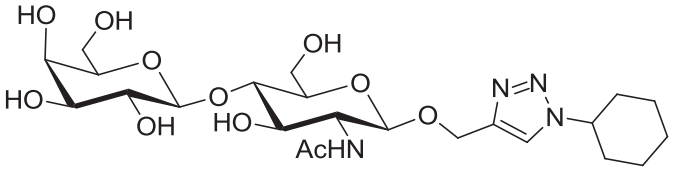
To a solution of compound **3.143** (0.050 g, 52 μmol) in 1.5 mL THF (Dry) was added 1 M TBAF/THF soln (0.103 ml, 2eq) and the reaction mixture stirred overnight under nitrogen atmosphere. Then, the reaction mixture was evaporated under reduced pressure and dry methanol 2 mL and 1 ml of NaOMe/MeOH (pH 10) were added, then stirred for 4 hrs. Acid resin was then added to neutralize the reaction mixture and evaporated. The reaction mixture was washed with acid base mix resin in water to remove the traces of TBAF, and lyophilized to obtain white foam like compound **3.151** (27 mg, 94%); $\mathbf{R}_f$ 0.19 (DCM/ MeOH 8:2); $[\alpha]_D^{24}$ - 19.35 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 8.01 (s, 1H), 7.50 – 7.41 (m, 3H), 7.38 (d, *J* = 6.7 Hz, 2H), 5.65 - 5.57 (s, 2H), 4.88 (t, *J* = 13.0 Hz, 1H), 4.80 - 4.75 (m, 1H), 4.63 - 4.53 (m, 1H), 4.49 (dd, *J* = 16.0, 6.0 Hz, 1H), 3.97 - 3.90 (m, 2H), 3.87 - 3.63 (m, 8H), 3.60 - 3.52 (m, 2H), 1.81 (s,3H); **^{13}C NMR** (150 MHz, D_2O) δ 174.96, 144.53, 135.35, 129.82, 129.49, 128.82, 125.79, 103.49, 100.82, 78.92, 75.97, 75.39, 73.14, 72.81, 71.59, 69.17, 62.63, 61.64, 60.63, 55.61, 54.56, 22.58; **HRMS (ESI)** calculated for $C_{24}H_{34}N_4O_{11}$ $[M + H]^+$ 555.2302, found 555.2300.

Compound 3.152



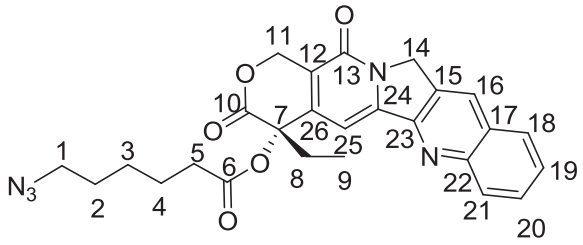
To a solution of compound **3.144** (0.061 g, 64 μmol) in 1.5 mL THF (Dry) was added 1 M TBAF/THF soln (0.12 ml, 2eq) and the reaction mixture stirred overnight under nitrogen atmosphere. Then, the reaction mixture was evaporated under reduced pressure and dry methanol 2 mL and 1 ml of NaOMe/MeOH (pH 10) were added, then stirred for 4 hrs. Acid resin was then added to neutralize the reaction mixture and evaporated. The reaction mixture was washed with acid base mix resin in water to remove the traces of TBAF, and lyophilized to obtain white foam like compound **3.152** (49 mg, 88%) $\mathbf{R}_f$ 0.1 (DCM/ MeOH 8:2). $[\alpha]_D^{24}$ - 8.74 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 8.06 (d, *J* = 5.1 Hz, 1H), 5.08 - 5.00 (m, 1H), 4.92 (d, *J* = 13.0 Hz, 1H), 4.82 (d, *J* = 9.4 Hz, 1H), 4.65 - 4.59 (m, 1H), 4.49 (d, *J* = 7.8 Hz, 1H), 4.00 (dd, *J* = 12.2, 1.8 Hz, 1H), 3.96 - 3.92 (m, 1H), 3.86 (dt, *J* = 11.9, 6.0 Hz, 1H), 3.82 - 3.66 (m, 9H), 3.62 (dd, *J* = 7.2, 4.6 Hz, 1H), 3.56 (dd, *J* = 9.8, 8.0 Hz, 1H), 2.30 (td, *J* = 13.4, 7.4 Hz, 2H), 2.30 (td, *J* = 13.4, 7.4 Hz, 2H), 2.00 (td, *J* = 13.4, 6.4 Hz, 2H), 1.92 (s, 3H), 1.91 - 1.83 (m, 2H), 1.83 - 1.73 (m, 2H); **^{13}C NMR** (150 MHz, D_2O) δ 124.37, 103.51, 100.75, 79.04, 75.96, 75.42, 73.15, 72.82, 71.58, 69.16, 62.97, 62.65, 61.61, 60.69, 55.66, 33.46, 24.19, 22.67; **HRMS (ESI)** calculated for $C_{22}H_{36}N_4O_{11}$ $[M + H]^+$ 532.2381, found 532.2450.

Compound 3.153



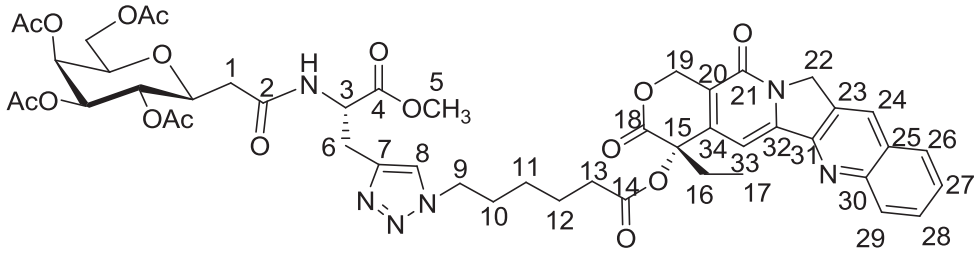
To a solution of compound **3.145** (0.068 g, 71 μmol) in 1.5 mL THF (Dry) was added 1 M TBAF/THF soln (0.146 ml, 2eq) and the reaction mixture stirred overnight under nitrogen atmosphere. Then, the reaction mixture was evaporated under reduced pressure and dry methanol 2 mL and 1 ml of NaOMe/MeOH (pH 10) were added, then stirred for 4 hrs. Acid resin was then added to neutralize the reaction mixture and evaporated. The reaction mixture was washed with acid base mix resin in water to remove the traces of TBAF, and lyophilized to obtain white foam like compound **3.153** (36mg, 93%); $\mathbf{R}_f$ 0.1 (DCM/MeOH 8:2); $[\alpha]_D^{24}$ - 9.68 (*c* 1.0, H_2O); **^{1}H NMR** (600 MHz, D_2O) δ 8.07 (s, 1H), 4.93 (d, *J* = 13.0 Hz, 1H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.67 - 4.60 (m, 1H), 4.55 (tt, *J* = 11.8, 3.7 Hz, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 4.01 (d, *J* = 10.7 Hz, 1H), 3.95 (t, *J* = 5.2 Hz, 1H), 3.87 (dd, *J* = 12.3, 5.1 Hz,1H), 3.83 - 3.66 (m, 9H), 3.62 (m, 1H), 3.59 - 3.54 (m, 1H), 2.18 (d, *J* = 11.0 Hz, 2H), 1.93 (s, 3H), 1.79 (ddd, *J* = 35.7, 17.9, 8.4 Hz, 2H), 1.50 (q, *J* = 12.9 Hz, 2H), 1.38 – 1.27 (m, 2H); **^{13}C NMR** (150 MHz, D_2O) δ 174.89, 143.73, 123.85, 103.56, 100.81, 79.09, 76.01, 75.95, 75.46, 75.40, 73.19, 72.86, 71.63, 69.21, 62.70, 61.66, 61.27, 60.73, 55.70, 33.57, 25.25, 22.73; **HRMS (ESI)** calculated for $C_{23}H_{38}N_4O_{11}$ $[M + H]^+$ 547.2615, found 547.2613.

Camptothecin Azide (4.3)



To a solution of camptothecin in dry DCM 5ml, was added 6-azidohexanoic acid (**4.2**), $Sc(OTf)_3$ and DMAP. This was stirred at RT for 30 min, then diisopropylcabodiimide (DIPC) was added and stirred at reflux for about 16 hrs, then the reaction mixture was concentrated and purified by flash column chromatography with just dichloromethane to flush the urea byproduct of DIPC. Once all the urea was eluted, the solvent was changed to 20-30% ethyl acetate in hexane to elute the product **4.3** (0.056 g, 85%). $\mathbf{R}_f$ 0.33 (EtOAc:Hexane 8.5:1.5) **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.42 (s, 1H, H-16), 8.23 (d, *J* = 8.6Hz, 1H, H-18), 7.97 (d, *J* = 8.4Hz, 1H, H-21), 7.86 (t, *J* = 7.0Hz, 1H, H-19), 7.69 (t, *J* = 7.5Hz, 1H, H-20), 7.22 (s, 1H, H-25), 5.64 (d, *J* = 17.2 Hz, 1H, H-11), 5.37 (d, *J* = 17.2 Hz, 1H, H-11), 5.31 (s, 2H, H-14), 3.24 (t, *J* = 6.8Hz, 2H, H-5), 2.53 (dt, *J* = 4.6Hz, *J* = 7.3Hz, 2H, H-1), 2.29 - 2.08 (m, 2H, H-8), 1.68 - 1.52 (m, 4H, H-2,H-3), 1.47 (dd, *J* = 6.0Hz, *J* = 9.2Hz, 2H, H-4), 0.99 (t, *J* = 7.5Hz, 3H, H-9); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 172.41, 167.54, 157.35, 152.36, 148.86, 146.22, 145.87, 131.26, 130.72, 129.54, 128.46, 128.23, 128.18, 128.06, 120.31, 118.43, 95.90, 75.78, 67.11, 51.12, 49.90, 33.56, 31.84, 29.68, 28.49, 26.03, 24.167.55. **MS (ESI)** calcd for $C_{26}H_{25}N_5O_5 + [H]^+$: 488.19, found: 488.1.

Compound 4.4

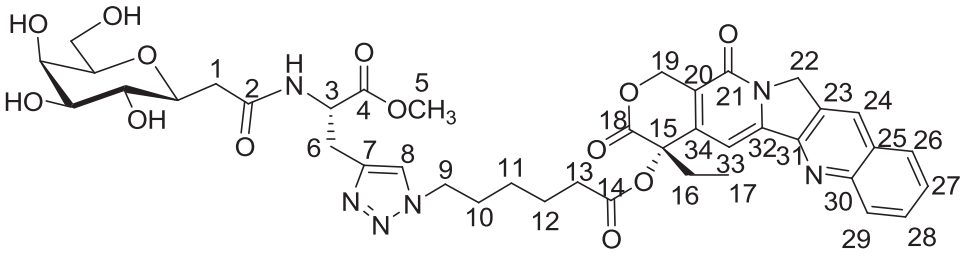


To a solution of compound **4.3** (0.02 g, 40 μmol) in THF:H_2O (3:1) 2 mL, camptothecin azide **4. 3** (0.020 g, 41 μmol), $CuSO_4.5H_2O$ (2 mg 20%) and sodium ascorbate (3 mg, 40%) were added. After 12h of reaction time following the general procedure (**8.2.1**) described above, the β-D-galactopyranoside conjugate **4.4** (0.030g, 78%) was obtained.

R_f 0.30 (EtOAc:Hexane 8.5:1.5); $[\alpha]_D^{22}$ + 5.43 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.41 (s, 1H, H-24), 8.19 (d, *J* = 8.4Hz, 1H, H-26), 7.95 (d, *J* = 7.8Hz, 1H, H-29) 7.83 (t, *J* = 7.3Hz, 1H, H-27), 7.67 (t, *J* = 7.1Hz, 1H, H-28), 7.32 (s, 1H, H-8), 7.22 (d, *J* = 8.0Hz, 1H, NH), 7.19 (s, 1H, H-33), 5.68 (d, *J* = 17.3 Hz, 1H, H-19), 5.40 (d, *J* = 14.0 Hz, 1H, H-19), 5.43 (s, 1H), 5.29 (d, *J*=0.8Hz, 1H, H-4sugar), 5.14 - 5.01 (m, 2H, H-2, H-3sugar), 4.88 (dd, *J* = 4.7Hz, *J* = 12.3Hz, 1H, H-3), 4.36-4.21 (m, 1H, H-6), 4.10-4.04 (m, 3H, H-5, 6, 6' sugar), 3.96 - 3.88 (m, 1H, H-1 sugar), 3.69 (s, 1H, H-5), 3.30 - 3.13 (m, 2H, H-9), 2.54 - 2.45 (m, 1H, H-13), 2.27 (dd, *J* = 7.5Hz, *J* = 14.0Hz, 1H, H-10), 2.13, 2.03, 1.97, 1.97 (4S,3H each,-C(O)CH_3), 1.93 - 1.83 (m, 2H, H-12), 1.73 - 1.64 (m, 2H, H-11), 1.45-1.35 (m, H-16), 0.97 (t, *J* = 7.4Hz, 1H, H-17); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 172.31, 171.22, 170.32, 170.24, 170.07, 169.86, 169.23, 167.58, 157.34, 148.80, 146.23, 145.86, 142.60, 131.27, 130.75, 129.47, 128.50, 128.25, 128.07, 122.02, 120.22,

118.47, 95.91, 75.85, 75.03, 74.10, 71.89, 68.57, 67.54, 67.10, 61.18, 52.47, 51.78, 49.95, 38.68, 33.36, 31.81, 30.65, 29.78, 29.34, 27.61, 25.64, 23.90, 20.73, 20.63, 20.57, 7.54. **HRMS (ESI)** calcd for $C_{48}H_{54}N_6O_{17}$ + $[H]^+$: 987.3624, found 987.3608.

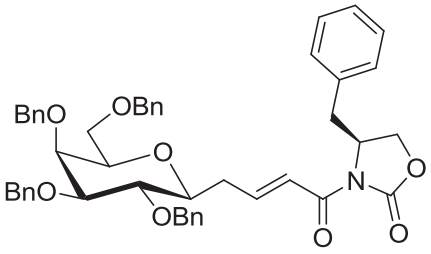
Compound 4.5



To a solution of **4.4** in 2 ml of dry methanol was added 2 ml of NaOMe/MeOH (pH = 8 - 9) and stirred at RT overnight. The reaction mixture was concentrated under vacuum to obtain the crude product, which was purified by flash column chromatography using 5-10% water in ACN to get final product **4.5** (19 mg, 84%) $\mathbf{R}_f$ 0.28 (H_2O/ACN 1:9); **^{1}H NMR** (300 MHz, CD_3OD) δ 8.64 (s, 1H), 8.22 - 8.12 (m, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.96 - 7.80 (m, 1H), 7.77 - 7.64 (m, 1H), 7.36 (s, 1H), 5.68 - 5.57 (m, 1H), 5.67 - 5.39 (m, 1H), 4.79 - 4.55 (m, 2H), 4.34 (dd, *J* = 11.2, 9.4, 4.7 Hz, 2H), 3.86 (d, *J* = 6.8 Hz, 3H), 3.70 (dd, *J* = 8.2, 4.3 Hz, 2H), 3.67 - 3.58 (m, 4H), 3.51 - 3.37 (m, 3H), 3.35 - 3.33 (m, 2H), 3.13 (ddd, *J* = 15.4, 11.3, 6.4 Hz, 2H), 2.72 (dd, *J* = 10.4, 4.9 Hz, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 2.48 - 2.29 (m, 2H), 2.28 - 2.07 (m, 2H), 1.90 (dt, *J* = 7.3, 6.3 Hz, 2H), 1.79 - 1.64 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.84, 172.75, 149.72, 148.09, 133.10, 131.46, 129.76, 129.20, 124.17, 97.83, 80.35, 78.46, 77.31, 75.88, 72.02, 70.97, 67.90, 62.88, 53.69, 52.86, 51.67, 50.98, 39.31, 34.42, 34.29, 32.27,

32.11, 30.93, 30.76, 30.70, 28.47, 26.88, 26.85, 25.30, 25.12, 7.98; **HRMS (ESI)** calcd for $C_{40}H_{46}N_6O_{13}$ + $[H]^+$: 819.31956, found 819.31778.

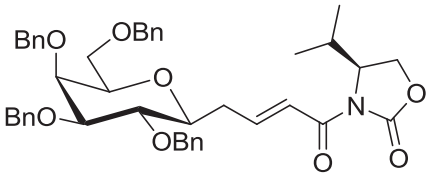
Compound 5.8



To a solution of 3-(tetra-*O*-benzyl-β-D-galactopyranosyl)1-propene **5.6** (100 mg, 177 μmol) and *N*-acryloyl-(S)-4-benzyl-2-oxazolidinone **5.15** (196 mg, 531 μmol) in 5 mL dry dichloromethane was added Grubbs 2nd generation catalyst (15 mg, 0.1%). The reaction was refluxed under nitrogen environment for 12 hrs. The reaction mixture was concentrated on rotovap and the crude product was purified by flash column chromatography to obtain **5.8** (80 mg, 60%) using 10% ethyl acetate in hexane; $\mathbf{R}_f$ 0.38 (EtOAc/Hexane 4:6); $[\alpha]_D^{22}$ + 37.06 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 - 7.24 (m, 25H), 7.19 (d, *J* = 6.9 Hz, 1H), 5.07 - 4.90 (m, 2H), 4.83 - 4.57 (m, 5H), 4.55 - 4.38 (m, 2H), 4.11 (d, *J* = 5.4 Hz, 2H), 4.03 (d, *J* = 2.4 Hz, 1H), 3.77 (t, *J* = 9.2 Hz, 1H), 3.67-3.56 (m, 4H), 3.52 - 3.38 (m, 1H), 3.27 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.91 - 2.64 (m, 2H), 2.64 - 2.46 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.60, 153.08, 147.78, 138.58, 138.14, 138.09, 137.88, 135.28, 129.26, 128.74, 128.27, 128.23, 128.21, 128.06, 127.89, 127.81, 127.75, 127.54, 127.49, 127.39, 127.35, 127.08, 121.74, 84.55, 78.37, 78.19,

76.93, 75.06, 74.34, 73.53, 73.36, 71.99, 68.65, 65.84, 55.03, 37.66, 35.12; **HRMS (ESI)** calculated for $C_{48}H_{49}NO_8$ $[H]^+$: 768.3536, found 768.3537.

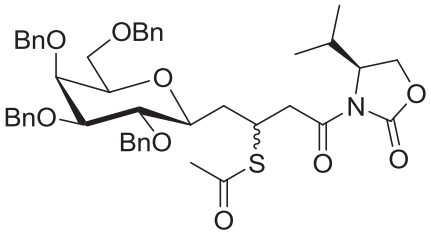
Compound 5.9



To a solution of 3-(tetra-*O*-benzyl-β-D-galactopyranosyl)-1-propene **5.6** (200 mg, 354 μmol) and *N*-acryloyl-(S)-4-isopropyl-2-oxazolidinone **5.12** (196 mg, 0.1 mmol) in 5 mL dry dichloromethane was added Grubbs 2nd generation catalyst (30 mg, 0.1%). The reaction was refluxed under nitrogen environment for 12 hrs. The reaction mixture was concentrated on rotovap and the crude product purified by flash column chromatography using 10% EtOAc in hexane to obtain pure **5.9** (161 mg, 62%); $\mathbf{R}_f$ 0.15 (EtOAc:Hexane 3:7); $[\alpha]_D^{22}$ + 3.64 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 - 7.21 (m, 25H), 7.16 (dd, *J* = 15.5, 6.7 Hz, 1H), 4.93 (dd, *J* = 11.3, 8.7 Hz, 2H), 4.65 (ddd, *J* = 17.3, 11.7, 7.6 Hz, 4H), 4.51 - 4.32 (m, 3H), 4.23 - 4.09 (m, 3H), 3.98 (d, *J* = 2.6 Hz, 2H), 3.70 (t, *J* = 9.2 Hz, 1H), 3.63 - 3.48 (m, 1H), 3.38 (td, *J* = 8.7, 3.6 Hz, 4H), 2.81-2.71 (m, 1H), 2.56 - 2.40 (m, 1H), 2.39-2.26 (m, 1H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 180.37, 164.67, 153.78, 147.57, 138.61, 138.14, 138.12, 137.88, 128.31, 128.27, 128.25, 128.09, 127.95, 127.84, 127.81, 127.59, 127.53, 127.43, 127.39, 121.68, 84.57, 78.51, 78.28, 76.93, 75.09, 74.37, 73.50, 73.39,

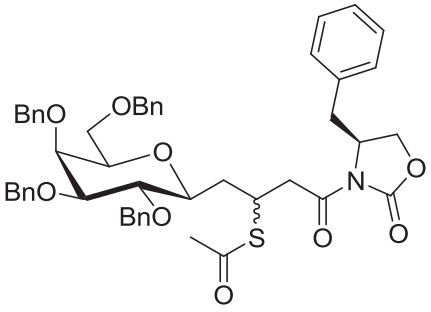
72.02, 68.62, 63.08, 58.32, 35.21, 28.28, 17.89, 14.53; **HRMS (ESI)** calculated for $C_{44}H_{50}NO_8$ $[M + H]^+$: 720.35364, found 720.35359.

Compound 5.16



To a solution of **5.9** (20 mg, 27 μmol) in dichloromethane (5 mL) was added thioacetic acid (2 mg, 26 μmol) and one drop of triethylamine. The reaction mixture was stirred at room temperature for 12 hrs, then concentrated to obtain 1,4-addition product **5.16** (16 mg, 77%) with a ds ratio of 60:40 based on the ^{1}H NMR quantification of the thioacetate singlet proton. The diastereomers were inseparable by flash chromatography for NMR characterization. $\mathbf{R}_f$ 0.32 (EtOAc:Hexane 3:7).

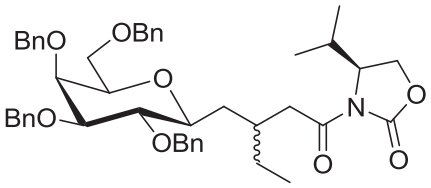
Compound 5.17



To a solution of **5.8** (20 mg, 26 μmol) in dichloromethane (5 mL) was added thioacetic acid (2 mg, 26 μmol) and one drop of triethylamine. Then reaction mixture was stirred at room temperature for 12 hrs, then concentrated to obtain 1,4-addition product **5.17** (19

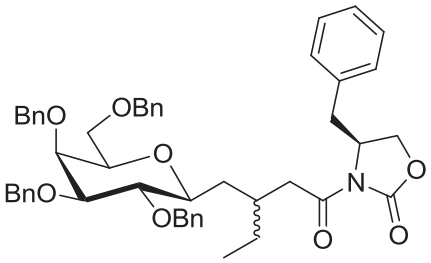
mg, 85%) with a ds ratio of 60:40 based on the ^{1}H NMR quantification of the thioacetate singlet proton. The diastereomers were inseparable by flash chromatography for NMR characterization. $\mathbf{R}_f$ 0.32 (EtOAc:Hexane 3:7).

Compound 5.18



CuBr.DMS (26 mg, 126 μmol) and a stir bar were added to oven dried 5 mL RBF, which was then sealed with rubber septum and purged with nitrogen. Dry THF (1 mL) was added via a syrange in to the flask under nitrogen atmosphere. The solution was cooled to -78^{o}C and EtMgBr (1M solution in diethyl ether) was added drop wise while controlling the temperature at -78^{o}C. The reaction mixture was allowed to stir at -78^{o}C for 30 minutes. Solution of **5.9** (20 mg, 26 μmol) in dry THF (0.5 mL) was prepared under nitrogen atmosphere and added drop wise to the round bottom flask containing EtMgBr while maintaining the temperature at -78^{o}C. After 30 minutes of reaction time the mixture was quenched using saturated NH_4Cl and concentrated. The crude was taken up with dichloromethane, washed with brine solution and dried over $MgSO_4$ and concentrated to get crude 1, 4 - addition product **5.18** with a ratio of ds 60:40 (18 mg, 87%). Diastereoselectivity was quantified unambiguously using HPLC. The diastereomers were inseparable via flash column for NMR characterization. $\mathbf{R}_f$ 0.44 (EtOAc : Hexane 3 : 7); **HRMS (ESI)** calculated for $C_{46}H_{58}NO_8 + [H]^+$: 750.4005, found: 750.3999.

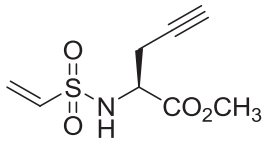
Compound 5.19



CuBr.DMS (26 mg, 126 μmol) and a stir bar were added to oven dried 5 mL RBF, which was then sealed with rubber septum and purged with nitrogen. Dry THF (1 mL) was added via a syrange in to the flask under nitrogen atmosphere. The solution was cooled to -78^{o}C and EtMgBr (1M solution in diethyl ether) was added drop wise while controlling the temperature at -78^{o}C. The reaction mixture was allowed to stir at -78^{o}C for 30 minutes. Solution of **5.9** (20 mg, 26 μmol) in dry THF (0.5 mL) was prepared under nitrogen atmosphere and added drop wise to the round bottom flask containing EtMgBr while maintaining the temperature at -78^{o}C. After 30 minutes of reaction time the mixture was quenched using saturated NH_4Cl and concentrated. The crude was taken up with dichloromethane, washed with brine solution and dried over $MgSO_4$ and concentrated to get crude 1, 4 - addition product **5.19** with a ratio of ds 97:3 (18 mg, 87%). Diastereoselectivity was quantified unambiguously using HPLC. The crude product was used to quantify the diasreoselectivity to avoid any kind of separation of diastereomers by flash column chromatography, although this was was more challenging compared to previous procedures; $\mathbf{R}_f$ 0.22 (EtOAc : Hexane 2 : 8); $[\alpha]_D^{22}$ + 29.75 (*c* 1.0, CH_2Cl_2); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 - 7.09 (m, 25H), 4.95 (dd, *J* = 11.3, 5.0 Hz, 2H), 4.80 -

4.60 (m, 4H), 4.60 - 4.52 (m, 1H), 4.45 (q, *J* = 11.7 Hz, 2H), 4.14 - 3.96 (m, 3H), 3.72 - 3.47 (m, 5H), 3.40 - 3.22 (m, 2H), 3.05 (dd, *J* = 5.9, 5.9 Hz, 1H), 2.85 (dd, *J* = 7.5, 7.4 Hz, 1H), 2.69 (dd, *J* = 13.2, 9.8 Hz, 1H), 2.23 (m, 1H), 1.92 - 1.75 (m, 1H), 1.69 - 1.54 (m, 3H), 1.44 (dd, *J* = 11.2, 7.3 Hz, 2H), 1.26 (s, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.94, 153.31, 138.82, 138.48, 138.39, 138.12, 135.47, 129.40, 128.87, 128.37, 128.34, 128.29, 128.19, 128.16, 128.03, 127.84, 127.62, 127.55, 127.54, 127.49, 127.22, 85.00, 79.06, 77.67, 76.85, 75.34, 74.49, 73.79, 73.42, 72.23, 68.91, 65.90, 55.26, 38.74, 37.87, 34.84, 32.65, 27.05, 11.09; **HRMS (ESI)** calculated for $C_{50}H_{56}NO_8 + [H]^+$: 798.40059, found 798.3988.

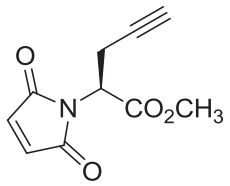
Compound 6.15



To a suspension of L-propargylglycine methyl ester HCl **6.7** (0.672 g, 4.1 mmol) in dichloromethane (26 mL) was added DIPEA (0.16 mL) and allowed to stir in order to dissolve **6.7** completely. The reaction mixture was cooled to 0^{o}C. 2-bromoethanesulfonylchloride (1.02 g, 4.9 mmol) was dissolved in DCM (52 mL) and added drop wise to the reaction mixture keeping the temperature at 0^{o}C. The reaction mixture was allowed warm up to RT and stirred overnight. Then the reaction mixture was diluted with DCM, washed with 5% citric acid, 5% $NaHCO_3$ and brine then dried over $MgSO_4$ and rotovapped to obtain crude product. The product was purified by flash column chromatography using 0.5% MeOH in DCM to obtain pure vinyl sulfonamide

6.15 (500 mg, 56%); $\mathbf{R_f}$ 0.11 (CH_2Cl_2:MeOH 9.7:0.3); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.57 (ddd, *J* = 16.5, 9.8, 0.6 Hz, 1H), 6.27 (d, *J* = 16.5 Hz, 1H), 5.94 (d, *J* = 9.8 Hz, 1H), 5.29 (d, *J* = 8.9 Hz, 1H), 4.17 (dt, *J* = 9.4, 4.8 Hz, 1H), 3.81 (s, 3H), 2.90 - 2.65 (m, 2H), 2.10 (dd, *J* = 2.9, 2.4 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.33, 136.25, 126.73, 72.48, 53.99, 53.07, 24.10; **MS (ESI)** calcd for $C_8H_{11}NO_4S + [H]^+$: 218.04; found: 218.1.

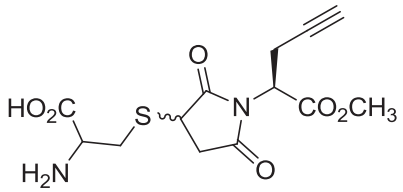
Compound 6.17



To a suspension of L-propargylglycine methyl ester HCl **6.7** (0.140 g, 0.85 mmol) in dry THF (18 mL) was added maleic anhydride (83 mg, 0.85 mmol) and DIPEA (0.45 mL, 0.25 mmol). The reaction mixture was stirred overnight then *N*-OH succinamide (98 mg, 0.85 mmol) and DCC (206 mg, 0.11 mmol) were added and stirring continued another 12 hrs. The reaction was concentrated and crude dissolved in DCM and purified by gravity silica gel chromatography using DCM as eluent. The product elutes with dicyclohexyl urea (DCU) side product which is separated by dissolving the evaporated fractions containing the product in EtOAc and leaving them in the freezer at -20^{o}C overnight. The DCU precipitates and can be filtered to obtain **6.17** (106 mg, 60%) as product; $\mathbf{R_f}$ 0.88 (CH_2Cl_2:MeOH 9.5:0.5); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.78 (s, 2H), 4.89 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.75 (s, 2H), 3.23 - 2.93 (m, 2H), 1.95 (t, *J* = 2.7 Hz, 1H); **^{13}C NMR** (75

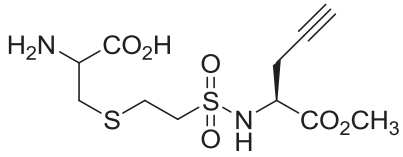
MHz, $CDCl_3$) δ 169.53, 168.06, 134.23, 78.83, 70.87, 53.02, 50.45, 19.39; **MS (ESI)** calcd for $C_{10}H_9NO_4$ + $[H]^+$: 208.0, found 208.2.

Compound 6.18



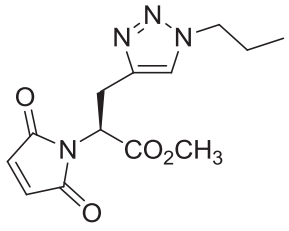
To a solution of L-propargyl maleimide **6.17** (5 mg, 2μmol) in 2 ml phosphate buffer (pH 7.4) was added cysteine (excess) and allowed to stirr at room temperature. The reaction was monitored by TLC and was observed to be completed in 10 min.

Compound 6.19



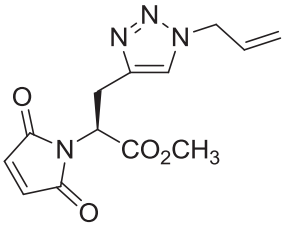
To a solution of vinyl sulfonamide **6.15** (5 mg, 2μmol) in 2 ml phosphate buffer (pH 7.4) was added cysteine (excess) and allowed to stirr at room temperature. The reaction was monitored by TLC and was observed to be completed in 45 min.

Compound 6.21



To a solution of compound **6.17** (0.120 g, 5 μmol) in toluene (5 mL) was added *n*-propyl azide (0.059 g, 5.8 μmol) CuI (5 mg, 2%) and DIPEA (0.08 mL, 2%). After 12 hrs of reaction time following the general procedure described above (**8.2.3**), maleimido triazole **6.21** (101 mg, 60 %) was obtained; $\mathbf{R}_f$ 0.44 (CH_2Cl_2 : MeOH 9.5 : 0.5); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.68 (s, 2H), 5.11 - 4.90 (m, 1H), 4.25 (t, *J* = 7.0 Hz, 2H), 3.77 (s, 3H), 3.59 (d, *J* = 7.8 Hz, 10.2 Hz, 2H), 1.88 (dd, *J* = 14.3, 7.1 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.61, 168.86, 142.95, 134.14, 122.16, 52.83, 51.72, 51.53, 25.12, 23.52, 10.82; **MS (ESI)** calcd for $C_{13}H_{14}N_4O_4$ + $[H]^+$: 293.12, found 293.1.

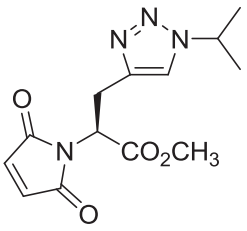
Compound 6.22



To a solution of compound **6.17** (0.100 g, 4.8 μmol) in toluene (5 mL) was added allyl azide (0.060 g, 5.8 μmol) CuI (5 mg, 2%) and DIPEA (0.08 mL, 2%). After 12 hrs of reaction time following the general procedure described above (**8.2.3**), maleimide triazole **6.22** (80 mg, 57%) was obtained; $\mathbf{R}_f$ 0.46 (CH_2Cl_2 : MeOH 9.5 : 0.5); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.66 (s, 2H), 6.01-5.85 (m, 1H), 5.37 - 5.22 (m, 1H), 5.16 (d, *J* = 17.5 Hz, 1H), 4.95 (dt, *J* = 14.5, 7.2 Hz, 1H), 4.87 (d, *J* = 5.9 Hz, 2H), 3.72 (s, 3H), 3.64 - 3.40 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.63, 168.84, 143.12, 134.16,

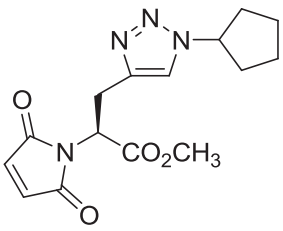
131.21, 121.75, 119.67, 52.84, 52.41, 51.53, 29.57, 25.13; **MS (ESI)**calcd for $C_{13}H_{14}N_4O_4 + [H]^+$: 291.10, found 291.1.

Compound 6.23



To a solution of compound **6.17** (0.100 g, 4.8 μmol) in toluene (5 mL) was added isopropyl azide (0.049 g, 5 μmol) CuI (5 mg, 2%) and DIPEA (0.08 mL, 2%). After 12 hrs of reaction time following the general procedure described above (**8.2.3**), maleimide triazole **6.23** (84 mg, 60 %) was obtained; $\mathbf{R}_f$ 0.43 (CH_2Cl_2 : MeOH 9.5 : 0.5); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.67 (s, 1H), 4.98 (dd, *J* = 9.4, 5.9 Hz, 1H), 4.72 (dd, *J* = 13.3, 6.7 Hz, 1H), 3.76 (s, 3H), 3.55 – 3.41 (m, 2H), 1.51 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR** (75MHz, $CDCl_3$) δ 169.56, 168.82, 142.46, 134.09, 119.34, 52.75, 52.69, 51.45, 25.06, 22.76; **MS (ESI)** calcd for $C_{13}H_{14}N_4O_4 + [H]^+$: 293.12, found 293.1.

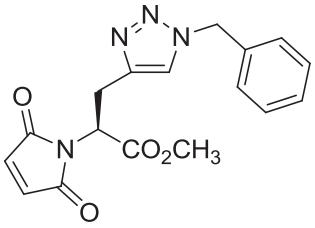
Compound 6.24



To a solution of compound **6.17** (0.90 g, 4.3 μmol) in toluene (5 mL) was added cyclopentyl azide (0.057 g, 5.2 μmol) CuI (3.5 mg, 2%) and DIPEA (0.08 mL, 2%). After

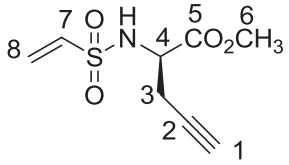
12 hrs of reaction time following the general procedure described above (**8.2.3**) maleimide triazole **6.24** (85 mg, 75%) was obtained; $\mathbf{R}_f$ 0.41 (CH_2Cl_2 : MeOH 9.5 : 0.5); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.68 (s, 2H), 4.98 (dd, *J* = 9.7, 5.7 Hz, 1H), 4.93 – 4.70 (m, 1H), 3.76 (s, 3H), 3.70 - 3.40 (m, 3H), 2.30 - 2.08 (m, 2H), 2.04 - 1.89 (m, 2H), 1.89 - 1.78 (m, 2H), 1.73 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.67, 168.95, 142.68, 134.17, 120.27, 76.58, 61.62, 52.86, 51.61, 33.25, 29.62, 25.19, 23.93; **MS (ESI)** calcd for $C_{15}H_{18}N_4O_4 + [H]^+$: 318.13, found 318.1.

Compound 6.25



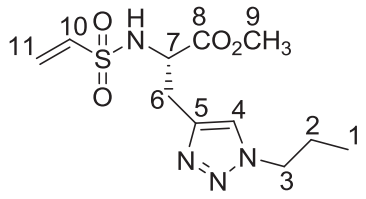
To a solution of compound **6.17** (0.100 g, 5 μmol) in toluene (5 mL) was added benzyl azide (0.059 g, 2.8 μmol) CuI (5 mg, 2%) and DIPEA (0.08 mL, 2%). After 12 hrs of reaction time following the general procedure described above (**8.2.3**) maleimide triazole **6.25** (123 mg, 75%) was obtained; $\mathbf{R}_f$ 0.48 (CH_2Cl_2 : MeOH 9.5 : 0.5); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 - 7.30 (m, 3H), 7.27 (s, 1H), 7.18 (dd, *J* = 6.5, 3.0 Hz, 2H), 6.64 (s, 2H), 5.60 - 5.38 (m, 2H), 5.30 (s, 2H), 5.10 - 4.84 (m, 1H), 3.75 (s, 3H), 3.51 (d, *J* = 11.4 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.61, 168.86, 142.95, 134.14, 129.17, 128.90, 128.17, 122.16, 55.83, 51.72, 51.53, 25.12, 23.52, 10.82.

Compound 6.15



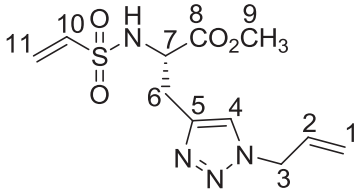
To a solution of L-propargyl glycine methyl ester HCl (0.67 g, 4.1mmol) and DIPEA (1.59 g, 12.3 mmol) in dry CH_2Cl_2, cooled to 0^oC in an ice bath was added 2-bromo ethane sulfonyl chloride drop wise (1.02g, 4.9 mmol). The reaction mixture was allowed to come up to RT and stirred overnight. The reaction mixture was washed with 5% citric acid, 5% $NaHCO_3$ solution, and brine, then dried over $MgSO_4$. The crude compound purified by flash column chromatography using CH_2Cl_2 alone to obtain compound **6.15** (0.499 g, 2.3 mmol); $\mathbf{R}_f$ 0.75 (CH_2Cl_2 : MeOH 9.7 : 0.3); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 6.57 (ddd, *J* = 16.5, 9.8, 0.6 Hz, 1H, H-7), 6.27 (d, *J* = 16.5 Hz, 1H, H-8a), 5.94 (d, *J* = 9.8 Hz, 1H, H-8b), 5.29 (d, *J* = 8.9 Hz, 1H, NH), 4.16 (dt, *J* = 9.4, 4.8 Hz, 1H, H-4), 3.81 (s, 3H, H-6), 2.88 - 2.69 (m, 2H, H-3), 2.09 (dd, *J* = 2.9, 2.4 Hz, 1H, H-1); **^{13}C NMR** (CDCl3, 75 MHz): δ170.56 (C-5), 136.48 (C-7), 126.96 (C-8), 72.71(C-2), 54.21 (C-1), 53.30 (C-6), 24.31 (C-3); **MS (ESI)** calcd for $C_8H_{11}NO_4S + [H]^+$: 218.04, found 218.1.

Compound 6.26



To a solution of compound **6.15** (0.080 g, 368 μmol) in THF:H_2O (3:1.5) 2.5 mL was added, n-propyl azide (0.062 g, 736 μmol) $CuSO_4.5H_2O$ (14 mg, 20%) and sodium ascorbate (30 mg, 40%). After 12 hrs of reaction time following the general procedure described above (**8.2.1**), vinyl sulfonamide **6.26** (102 mg, 339 μmol) was obtained; $\mathbf{R}_f$ 0.22 (CH_2Cl_2:MeOH 9.5:0.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.47 (s, 1H, H-4), 6. 39 (6.45 (ddd, *J* = 16.5, 9.8, 1.9 Hz, 1H, H-10), 6.15 (dd, *J* = 16.6, 2.4 Hz, 1H, H-11a), 5.85 (d, 1H, *J* = 8.79 Hz, NH), 5.78 (dd, 1H, *J* = 9.8, 2.22 Hz, H-11b), 4.24 (dd, *J* = 9.9, 4.3 Hz,2H, H-3), 4.18 - 4.09 (m, 1H, H-7), 3.65 (s, 3H, H-9), 3.22 (d, *J* = 5.5 Hz, 2H, H-6), 2.04 - 1.73 (m, 2H, H-2), 0.89 (dt, *J* = 7.4, 1.9 Hz, 3H, H-1); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ171.28 (C-8),141.80 (C-5), 136.05 (C-4), 126.31 (C-10), 122.45 (C-11), 55.09 (C-7), 52.66 (C-9), 52.73 (C-3), 29.17 (C-6), 23.48 (C-2), 10.82 (C-1); **MS** (**ESI)** calcd for $C_{11}H_{18}N_4O_4S + [H]^+$: 303.10, found: 303.20.

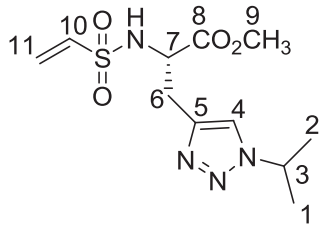
Compound 6.27



To a solution of compound **6.15** (0.080 g, 368 μmol) in THF:H_2O (3:1.5) 2.5 mL was added, allyl azide (0.061 g, 737 μmol) $CuSO_4.5H_2O$ (14 mg, 20%) and sodium ascorbate (30 mg, 40%). After 12h of reaction time following the general procedure described above **(8.2.1)**, vinyl sulfonamide **6.27** (94 mg, 313 μmol) was obtained; $\mathbf{R}_f$ 0.22 (CH_2Cl_2:MeOH 9.5:0.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.43 (s, 1H, H-4), 6. 41 (dd, 1H,

J = 9.88Hz, H-10), 6.13 (d, 1H, *J* = 14 Hz, H-11a), 5.98 (dddd, *J* = 15.3, 10.3, 6.9, 5.3 Hz, 1H, H-2), 5.81 (d, 1H, *J* = 7.69 Hz, H-11b), 5.74 (d, 1H, *J* = 7.69 Hz, NH), 5.25 (2d, 2H, *J* = 10.16, 17.03 Hz, H-1a,b), 4.87 (d, 2H, *J* = 4.94 Hz, H-3), 4.35 - 4.21 (m, 1H, H-7), 3.67 (s, 3H, H-9), 3.20 (d, 2H, J = 5.49 Hz, H-6); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.53 (C-8), 142.378 (C-5), 136.33 (C-4), 131.40 (C-10), 126.75 (C-11), 122.072(C-2), 120.25(C-1), 55.33 (C-3), 53.05 (C-7) 52.82 (C-9) 29.58 (C-6); **MS** (**ESI)** calcd for $C_{11}H_{16}N_4O_4S + [H]^+$: 301.08, found 301.2.

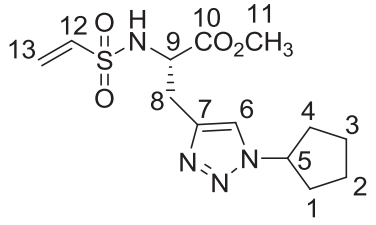
Compound 6.28



To a solution of compound **6.15** (0.030 g, 138 μmol) in THF:H_2O (3:1.5) 1.5 mL, was added isopropyl azide (0.0235 g, 276 μmol) $CuSO_4.5H_2O$ (5 mg, 20%) and sodium ascorbate (11 mg, 40%). After 12h of reaction time following the general procedure described above **(8.2.1)**, vinyl sulfonamide **6.28** (31 mg, 103 μmol) was obtained; $\mathbf{R}_f$ 0.21 (CH_2Cl_2:MeOH 9.5:0.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.43 (s, 1H, H-4), 6. 43 (dd, 1H, *J* = 9.88, 9.61 Hz, H-10), 6.14 (d, 1H, *J* = 16.48 Hz, H-11a), 5.81 (d, 1H, *J* = 9.88 Hz, H-11b), 5.68 (d, 1H, *J* = 8.24 Hz, NH), 4.77 (hept, *J* = 6.7 Hz, 1H, H-3), 4.28-4.18 (m, 1H, H-7), 3.69 (s, 3H, H-9), 3.20 (d, 2H, *J* = 5.49 Hz, H-6), 1.50 (d, 6H, *J* = 6.59Hz, H-1,2); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 171.32 (C-8),141.84 (C-5), 136.11 (C-4),

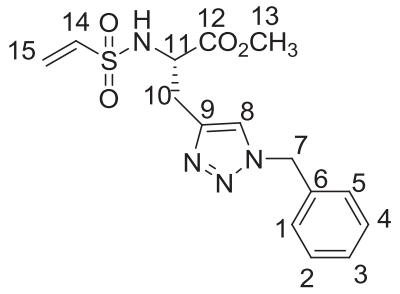
126.45 (C-10), 120.01 (C-11), 55.09 (C-7), 52.93 (C-9), 52.78 (C-2), 29.40 (C-6), 22.89, 22.87(2C, C-1,2); **MS (ESI)** calcd for $C_{11}H_{18}N_4O_4S + [H]^+$: 303.10, found 303.2.

Compound 6.29



To a solution of compound **6.15** (0.080 g, 368 μmol) in THF:H_2O (3:1.5) 2.5 mL, was added cyclopentyl azide (0.081 g, 736 μmol) $CuSO_4.5H_2O$ (14 mg, 20%) and sodium ascorbate (30 mg, 40%). After 12h of reaction time following the general procedure described above **(8.2.1)**, vinyl sulfonamide **6.29** (112 mg, 342 μmol) was obtained; $\mathbf{R_f}$ 0.24 (CH_2Cl_2 : MeOH 9.5 : 0.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.43 (s, 1H, H-6), 6. 41 (dd, 1H, *J* = 9.61, 9.88 Hz, H-12), 6.12 (d, 1H, *J* = 16.48 Hz, H-13a), 5.79 (d, 1H, *J* = 9.88 Hz, H-13b), 4.94 – 4.78 (m, 1H, H-5), 4.22 – 4.20 (m, 1H, H-9), 3.67 (s, 3H, H-11), 3.18 (d, 2H, *J* = 5.27 Hz, H-8), 2.34 - 2.12 (m, 2H, $CH_{2Cyclopentyl}$), 2.11 - 1.90 (m, 2H, $CH_{2Cyclopentyl}$), 1.89 - 1.79 (m, 2H, $CH_{2Cyclopentyl}$), 1.79 - 1.65 (m, 2H, $CH_{2Cyclopentyl}$); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ171.61 (C-10), 136.40 (C-6), 126.57 (C-12), 62.04 (C-5), 55.37 (C-9), 53.00 (C-11), 33.50 (2c, C-1 and 4)) 29.55 (C-8), 24.19 (2C, C-2 and 3); **MS (ESI)** calcd for $C_{13}H_{20}N_4O_4S + [H]^+$: 329.12, found 329.2.

Compound 6.30



To a solution of compound **6.15** (0.080 g, 368 μmol) in THF : H_2O (3:1.5) 2.5 mL, was added benzyl azide (0.098 g, 737 μmol) $CuSO_4.5H_2O$ (14 mg, 20%) and sodium ascorbate (30 mg, 40%). After 12h of reaction time following the general procedure described above **(8.2.1)**, vinyl sulfonamide **6.30** (103 mg, 294 μmol) was obtained; $\mathbf{R_f}$ 0.31 (CH_2Cl_2:MeOH 9.5:0.5); **^{1}H NMR** ($CDCl_3$, 300 MHz): δ7.37 (s, 1H, H-8), 7.36 – 7.25 (m, 3H, $H_{Aromatic}$), 7.20 (td, *J* = 6.3, 1.3 Hz, 2H, $H_{Aromatic}$), 6. 36 (dd, 1H, *J* = 9.88, 9.89 Hz, H-14), 6.10 (d, 1H, *J* = 16.75 Hz, H-15a), 5.74 (d, 1H, *J* = 9.88 Hz, H-15b), 5.428 (d, *J* = 2.9 Hz, 2H, H-7), 4.30 – 4.15 (m, 1H, H-11), 3.64 (s, 3H, H-13), 3.17 (d, 2H, *J* = 5.49 Hz, H-10); **^{13}C NMR** ($CDCl_3$, 75 MHz): δ δ171.57 (C-12), 141.84 (C-9), 136.32 (C-8), 134.92 (C-6), 129.28-128.18(5C, C1-5), 126.70 (C-15) 122.86 (C-14), 55.40 (C-7), 54.26 (C-11), 53.00 (C-13), 29.56 (C-10); **MS (ESI)** calcd for $C_{15}H_{18}N_4O_4S$ + $[H]^+$: 351.10, found 351.20.

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