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Synthesis of carbohydrate derivatives with biological activities

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Tese para obtenção do Grau de Doutor em

Química

(3º ciclo de estudos)

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To my grandparents, parents, sister and boyfriend

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Abstract

In this work the objective was to synthesize new molecules with potential biological activity. Among the synthesized compounds, *C*-nucleosides, azidosugars, iminosugars and triazoles stand out.

C-nucleosides were synthesized through a precursor derived from glucosamine HCl. Glucosamine HCl was transformed in two different aldehydes, which by Biginelli reaction originated a new heterocyclic ring connected to a carbohydrate through a carbon-carbon bond. Through this method was possible to obtain oxopyrimidines and thioxopyrimidines attached to carbohydrate.

Simple azidosugars derived from commercial carbohydrates where synthesized. The synthesis of these azido-sugars may be found in literature. The obtained yields were similar to the ones found in literature. The scope of this synthesis was the application of azido-sugars as triazol precursors, i.e., its application in Click Chemistry reaction.

Azido-sugars were also fused with the 1,3-oxazolidine-2-thione, 1,3-oxazolidin-2-one and 2-benzylsulfanil-1,3-oxazoline ring. This way a new methodology was developed for synthesis of these innovative structures.

Iminosugars fused with an 1,3-oxazolidin-2-one ring were synthesized. A new methodology using azidosugars precursors fused with 1,3-oxazolidin-2-ones was developed. Alkynyl-lactams were prepared starting from azidolactams already described in literature. Applying “Click Chemistry” triazoles where synthesized, using as precursors the azides and alkynyl lactams previously synthesized.

The biological activity of some compounds was tested. The ability to inhibit the growth of *Rhipicephalus (Boophilus) microplus* and consequently the oviposition (laying eggs). The ability of some molecules was tested for inhibiting glycosidases. Cell viability was determined for some molecules. Some compounds showed promising activities.

Keywords

Oxopyrimidines, Thioxopyrimidines, Azido-sugars, 1,3-Oxazolidine-2-thiones, 2-Benzylsulfanyl-1,3-oxazolines, 1,3-Oxazolidin-2-ones, Iminosugars, Alkynyl-lactam, Click Chemistry

Resumo

Os *C*-nucleósidos são um grupo de compostos que possuem na sua estrutura um anel de açúcar liagdo a um anel heterocíclico através do carbono anomérico (C-1) por uma ligação carbono-carbono, enquanto nos nucleósidos a ligação entre os dos anéis heterocíclicos é realizada por uma ligação carbono-azoto.

Os *C*-nucleósidos apresentam atividade biológica, nomeadamente como fármacos, pesticidas e herbicidas. Dadas estas aplicações são considerados compostos de grande interesse para os investigadores, motivando assim a sua síntese e isolamento, quer por novas vias de síntese quer por otimização das vias já existentes.

Com base nas propriedades apresentadas pelos anéis pirimidínicos, dentro das quais se destaca a sua ação como bloqueadores dos canais de cálcio, anti-hipertensivos, anti-inflamatórios, antibacterianos, antioxidantes e antivirais, realizou-se a síntese de derivados de oxopirimidinas e de tioxopirimidinas.

As oxopirimidinas e tioxopirimidinas, também denominados compostos de Biginelli, possuem uma relação direta entre as suas propriedades farmacológicas e a quiralidade existente no carbono C-4 do anel pirimidínico e o tipo de substituintes nas outras posições do anel. Os compostos deste tipo denominados: sináptico, cerebrocrast, monastrol e nifepidina são quatro fármacos derivados de anéis pirimidínicos que estão disponíveis no mercado farmacêutico (Figura i).

O sináptico é um fármaco desenvolvido pela Merk e é utilizado no tratamento de tumores benignos da próstata. O cerebrocrast é um fármaco muito utilizado no tratamento de diabetes e também é um neuroprotetor. O monastrol faz parte de uma família de novos compostos considerados antitumorais, que atuam ao nível da divisão celular (mitose). Nitractin é.um antiviral utilizado no tratamento de tracoma vírus, compostos da mesma família actuam também como antibacterianos.

2 Sináptico

3 Cerebrocrast

4 Monastrol

5 Nitractin

Figura i- Fármacos derivados de anéis pirimidínicos.

O núcleo pirimidina pode ser obtido através de reações multicomponentes. Nestas reações o material de partida é composto por pelo menos três componentes, que reagem entre si originando um produto. Os compostos obtidos dependem das condições reacionais aplicadas bem como dos materiais de partida.

As reações multicomponentes têm tido uma importância crescente na síntese química pois permitem a formação de bibliotecas de compostos com atividade biológica e permitem a sua utilização como fármacos.

Nas sínteses que vamos realizar a reação multicomponente consiste na reação em um só passo, de dois compostos e uma espécie eletrófila. Os compostos precisam de possuir um esqueleto do tipo N-C-N (por exemplo ureia ou tioureia) e um esqueleto do tipo C-C-C (por exemplo acetoacetato de etilo), a espécie eletrófila pode ser um derivado de hidrato de carbono.

Aplicando estes requesitos, decidimos usar como espécie eletrófila dois aldeídos diferentes derivados do hidrocloreto de glucosamina. Assim fazendo reagir estes aldeídos, separadamente, com ureia/tioureia e acetoacetato de etilo, em etanol sob aquecimento vamos obter novos *C*-nucleósidos (Esquema i).

+ $CH_3COCH_2CO_2Et$ — ureia/tioureia, EtOH, △ →

13 R=H
25 R=Ac

21 R= H, X= O
22 R=H, X=S
26 R= Ac, X= O
27 R=Ac, X= S

Esquema i - Reação multicomponente para obtenção de C-nucleósidos.

Desta forma foi possível obter 4 novos *C*-nucleósidos (Figura ii) derivados de oxopirimidinas e tioxopirimidinas. Após a análise dos espetros dos *C*-nucleósidos concluímos que apesar de formar um novo centro quiral em C-4 do anel pirimidínico apenas é possível obter um dos diastereoisómeros esperados, demostrando assim que a reação é bastante estereosseletiva.

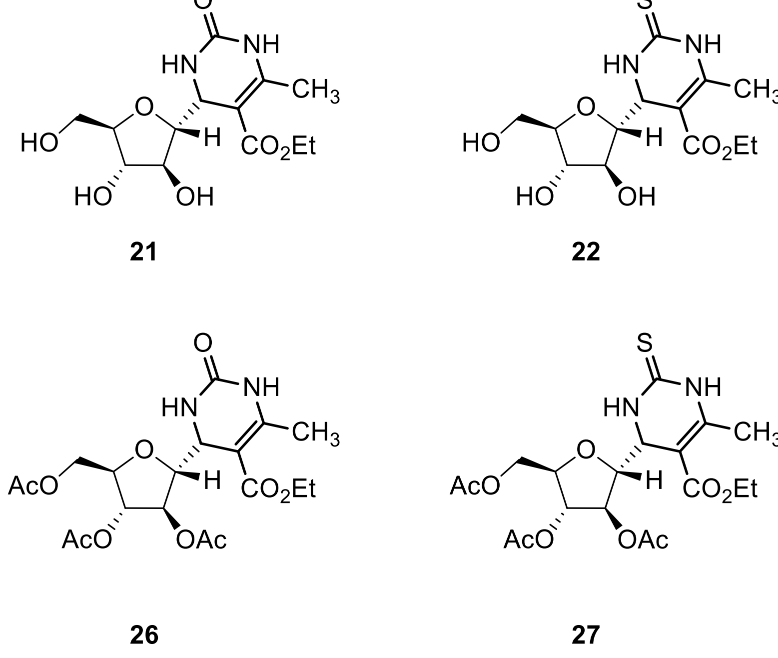

Figura ii – C-nucleósidos sintetizados.

A reação de Biginelli permite a obtenção de 4 novos *C*-nucleósidos com potencial atividade biológica, em que a principal diferença verificada entre os espetros é o valor do desvio químico apresentado por C=O (aproximadamente 170 ppm) e por C=S (aproximadamente 185 ppm) nos espetros de ^{13}C (parâmetro que confere a definição de oxopirimidina ou tioxopirimidina, respetivamente).

Os azido-açúcares são açúcares que possuem na sua constituição um grupo azida (N_3). As azidas orgânicas têm demostrado grande interesse por parte dos químicos pois são compostos intermediários em numerosas reações de síntese orgânica de várias espécies químicas, nomeadamente na 'Click Chemistry' como percursores de triazóis.

As azidas são compostos fáceis de obter. Partindo de açúcares comerciais, protegendo seletivamente os grupos hidroxilo é possível substituir um álcool primário por um halogénio através de uma técnica desenvolvida por Garegg e Samuelsson. A obtenção de azido-açúcares é possível após substituição nucleofílica de um halogénio pelo azoto. Assim esta sequência permite a obtenção de azidas simples partindo de hidratos de carbono comerciais.

Partindo da D-ribose, D-glucose e D-galactose é possível obter diferentes azidas através de reações comumente usadas em química orgânica. O iodo mostrou ser um bom grupo abandonante na substituição nucleofílica do iodo pela azida pois foi eficaz e obtiveram-se bons rendimentos. Estes azido-açúcares (Figura iii) foram sintetizados com o objetivo de serem utilizados posteriormente na 'click chemistry', estando a sua síntese e caraterização bem descrita na literatura.

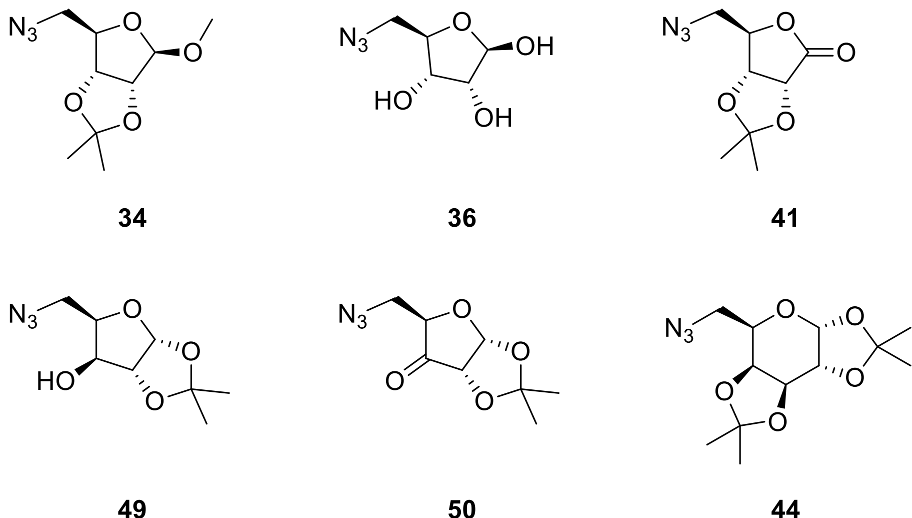

Figura iii – Azodo-açúcares derivados de hidratos de carbono comercias.

A combinação do heterocíclo 1,3-oxazolidinine-2-tiona com hidratos de carbono pode originar estruturas inovadoras dando oportunidade de desonvlover novas metodologias para a síntese de azido-1,3-oxazolidin-2-onas derivadas de hidratos de carbono.

De entre as várias aplicações, os OZT fundidos com hidratos de carbono são usados como auxiliares quirais, inibidores de glicosidases ou percursores de nucleósidos. Vários autores referenciam a síntese de tiocarbamatos fundidos com hidratos de carbono (Zemplen, Bromund, Wickstrom/Wold e Girniene). Com base em resultados obtidos por Girniene e Silva foram utilizadas as mesmas condições reacionais, obtendo-se assim tiocarbamatos (1,3-oxazolidine-2-tionas) em diferentes templates (D-ribose, D-xilose, D-arabinose e L-sorbose). Posteriormente estes tiocarbamatos foram alquilados seletivamente através de S-benzilação, originando 2-alquilsulfanil-1,3-oxazolinas. As 2-alquilsulfanil-1,3-oxazolinas foram oxidadas seletivamente na ligação C-SBn com *m*-CPBA originando 1,3-oxazolidin-2-onas (Esquema ii).

HO, OH, HO, OH — KSCN, HCl / H_2O → NH, S

63 **78**

78 — BnBr, Et_3N, DCM → **79** (SBn)

79 — $NaHCO_3$, *m*-CPBA, DCM → **80**

Esquema ii – Esquema geral para obtenção de 1,3-oxazolidin-2-onas.

Foi possível obter as 1,3-oxazolidine-2-tionas, 2-alquilsulfanil-1,3-oxazolinas e as 1,3-oxazolidin-2-onas nos templates D-ribose, D-xilose, D-arabinose e L-sorbose. Os rendimentos obtidos variam de template para template. A oxidação da ligação C-SBn é mais eficiente quando é feita em derivados de hidratos de carbono totalmente protegidos.

Desde a descoberta da Nojirimicina, um inibidor da glicosidade, que as piperidinas poli-hidroxiladas, também conhecidas como iminoaçúcares têm merecido bastante atenção por parte da comunidade científica e têm sido alvo de numerosas estratégias sintéticas nos últimos anos. O desenvolvimento de sínteses eficientes de iminoaçúcares naturais e seus análogos apresenta uma importância considerável devido ao seu potencial como inibidores das glicosidases.

Os iminoaçúcares (Figura iv) são utilizados como fármacos. Em 1996 foi introduzido no mercado o Glyset, pimeiro iminoaçúcar usado como farmaco no tratamento de diabetes tipo I. Em 2003, o Zavesca começa a ser comercializado, para o tratamento da doença de Gaucher.

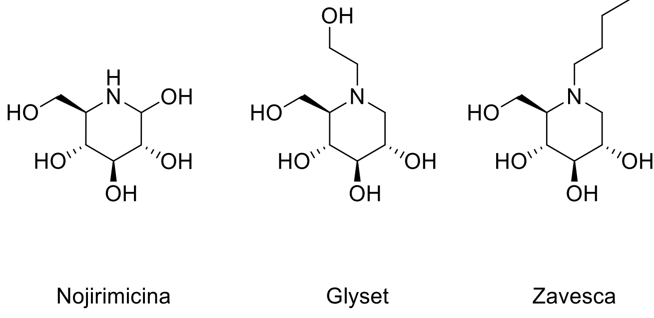

Figura iv – Exemplo de iminoaçúcares.

A reatividade das 1,3-oxazolidene-2-tionas, 2-benzilsulfanil-1,3-oxazolinas e 1,3-oxazolidin-2-onas foi estudada. O substituinte na posição 2 destes aneis heterocíclicos vai influenciar a reatividade e consequentemente a formação dos iminoaçúcares.

A redução de Staudinger foi aplicada nos diferentes derivados de tiocarbamatos. Desta forma concluímos que quando aplicadas estas condições às 1,3-oxazolidine-2-tionas apenas efetuamos a redução do azido-açúcar a amino-açúcar ($N_3 \rightarrow NH_2$). Verificamos os mesmos resultados com as 2-alquilsulfanil-1,3-oxazolinas, apenas ocorre redução. Já com as 1,3-oxazolidin-2-ones verifica-se a redução seguida de ciclização no átomo de azoto, originando a formação de iminoaçúcares inovadores. Desta forma foi possível obter 6 novos iminoaçúcares (Figura v) derivados de 1,3-oxazolidin-2-onas. Este método é inovador e não se encontra descrito na literatura, permitindo assim o acesso a uma nova classe de compostos, iminoaçúcares fundidos com o anel 1,3-oxazolidin-2-ona.

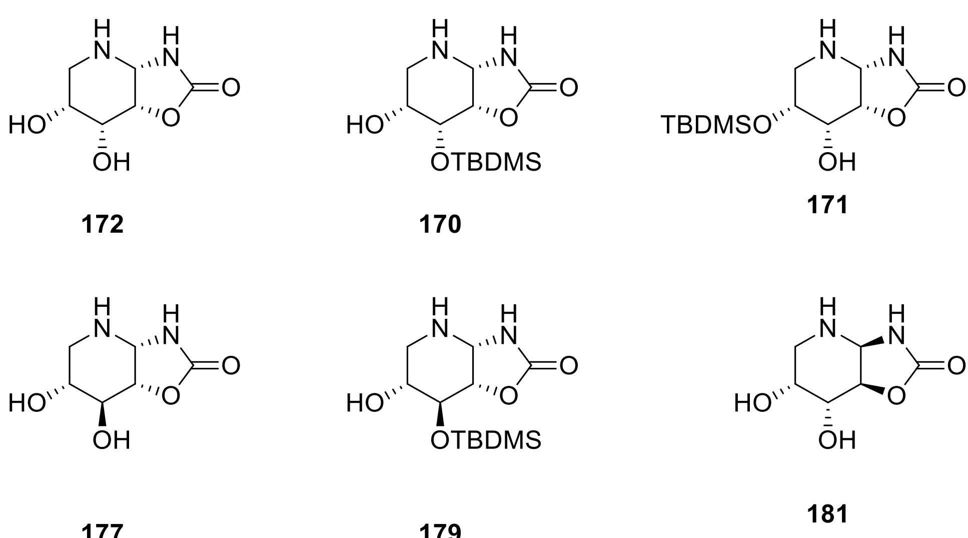

Figura v – Iminoaçúcares fundidos com 1,3-oxazolidin-2-onas sintetizados.

Aplicando o mesmo princípio, a redução de um derivado de lactona conduz à formação de um iminoaçúcar que posteriormente é usado na 'Click chemistry'. A lactama resultante desta redução, através de proteção seletiva e/ou reação com brometo de propargilo, vai originar dois novos derivados com cadeias carbonadas que possuem ligações insaturadas (Figura vi).

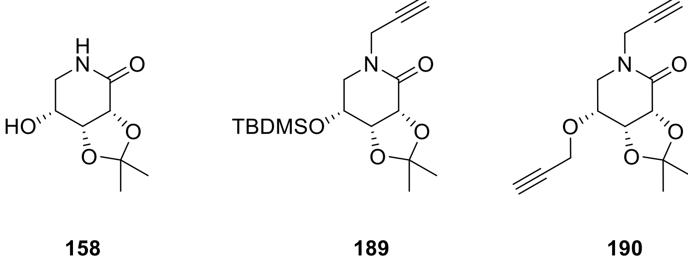

Figura vi – Lactama e seus alcinil derivados.

A ‘Click chemistry’ é um conceito introduzido por Barry Sharpless em 2001, descreveu as reações químicas que originam substâncias de forma rápida e simples, ligando duas unidades diferentes. Entre estas reações a mais popular é a cicloadição de Huisgen que é uma cicloadição 1,3-dipolar entre uma função azida e uma função alcino que conduz à formação de um anel triazol.

Os triazois constituem uma família de compostos importantes dentro da química dos heterocíclos azotados. Possuem um vasto campo de aplicações, que vão desde usos como explosivos, até como agroquímicos e fármacos.

Neste trabalho estuda-se a cicloadição azida-alcino catalisada por cobre (I) (CuAAC) por forma a obter novos triazois disubstituídos. Devido à utilização de cobre (I) como catalisador vamos ober exclusivamente compostos do tipo 1,4-triazolicos.

A cicloadição azida-alcino é efetuada através da condensação de azidas previamente sintetizadas e de um derivado de lactama com um terminal alcino, usando cobre (I) como catalisador, originado 4 novos triazois 1,4-disubstituidos (Figura vii).

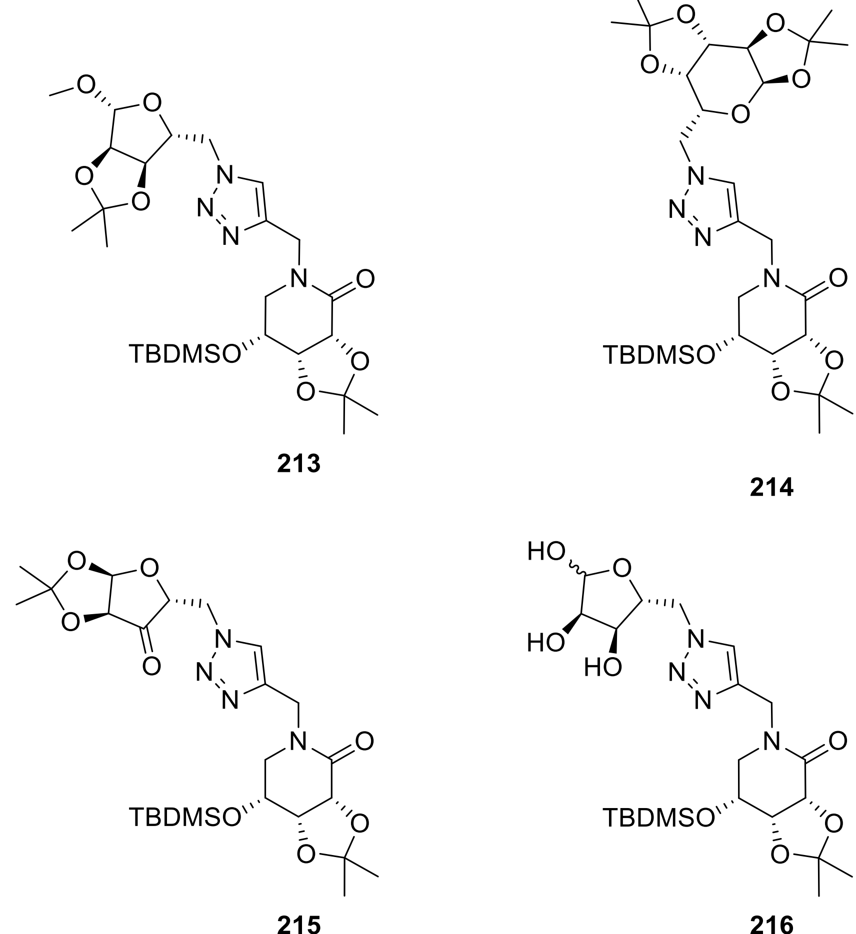

Figura vii – 1,4-Triazois disubstuidos.

A cicloadição azida-alcino é efetuada através da condensação de azidas previamente sintetizadas e de um derivado de lactama com dois terminais alcino, usando cobre (I) como catalisador, originado 6 novos bis-triazois 1,4-disubstituidos (Figura viii).

218 219

220 221

222 223

Figura viii - 1,4-Bistriazois disubstituidos.

A cicloadição azida-alcino efetuada através da condensação de azida de sódio e de um derivado da lactama (com um terminal alcino ou com dois terminais alcino) leva à degradação total do produto esperado.

Tendo em conta a resistência criada por *Rhipicephalus (Boophilus) microplus* aos acaricidas presentes no mercado tornou-se necessário a pesquisa der novas moléculas que inibam o seu crescimento e reprodução. Foi testada a capacidade de alguns grupos de moléculas (oxopirmidinas, tioxopirimidinas, iminoaçúcares e alguns intermediários) para inibir o crescimento e reprodução (postura de ovos) de Rhipicephalus (Boophilus) microplus. De entre os compostos testados, a glucosamina tetra-acetilada **24** inibiu em 80% o número de fêmeas vias e consequentemente a postura de ovos. A inibição por parte do acetil-aminoaçúcar **193** também se aproxima destes valores. As oxopirimidinas **21** e **26** também apresentaram uma inibição promissora. O iodo-açúcar **101** e a azido-oxazolidinona **108** inibiram em mais de 50% o crescimento de fêmeas. No geral os compostos apresentaram uma atividade satisfatória e em alguns casos muito boa.

As glicosidases são enzimas essenciais ao metabolismo dos hidratos de carbono, catalizam a hidrólise das ligações glicosídicas. Devido à sua importância são alvos terapêuticos para o desenvolvimento de fármacos antidiabéticos. Como exemplo de fármacos antidiabéticos temos o Glyset, que é prescrito no tratamento de diabetes tipo I. Foi testada a capacidade de inibição das glicosidases por parte de vários iminoaçúcares sintetizados. O iminoaçúcar **181** (configuração D-arabino) mostrou inibir a ß-D-glucosidase de amendôa. O iminoaçúcar **232** (configuração L-arabino) mostrou inibir a α-D-galactosidase de grãos verdes de café. Os iminoaçúcares**181** e **232** mostraram inibições moderadas da ß-D-glucosidase e da α-D-galactosidase, respetivamente.

As células neoplásicas são caracterizadas por uma proliferação descontrolada, indiferenciação e perda da função bem como pelo seu poder invasor e capacidade de gerar metástases. Os agentes antineoplásicos atualmente utilizados, em particular os que são citotóxicos, afetam na maioria apenas uma das características das células cancerígenas, o processo de divisão celular, sendo, portanto, apenas agentes anti-proliferativos. Considerando a necessidade de novas abordagens para o tratamento do cancro, estudos bioquímicos dos mecanismos de transdução de sinal celular possibilitam uma melhor compreensão da biologia da célula neoplásica. Desta forma novos mecanismos de ação são explorados no desenvolvimento de novos fármacos citotóxicos. A citotoxicidade e proliferação celular são dois conceitos que se relacionam entre si e permitem determinar a viabilidade celular. A viabilidade celular foi determinada perante a exposição de linhas celulares específicas a determinadas concentrações de alguns compostos sintetizados.

Palavras Chave

Oxopirimidinas, Tioxopirimidinas, Azido-açúcares, 1,3-Oxazolidina-2-tionas, 2-Benzillsulfanil-1,3-oxazolinas, 1,3-Oxazolidin-2-onas, Iminoaçúcares, Alcinil-lactama, Click chemistry.

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List of acronyms

λ	wavelength
^{13}C	NMR carbon spectrum
^{1}H	NMR proton spectrum
Ac	acetyl
Ac_2O	acetic anhydride
Bn	benzyl
BnBr	benzyl bromide
Bz	benzoyl
BzCl	benzoyl chloride
Cbz	carboxybenzyl
COSY	NMR correlation ^{1}H-^{1}H
Cq	quaternary carbon atom
d	doublet
DCM	dichloromethane
dd	doublet doublet
ddd	doublet doublet doublet
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
$(CD_3)_2S{=}O$	dimethylsulfoxide
dt	doublet triplet
EA	ethyl acetate
eq.	equivalent(s)
Et	ethyl

Et_3N	triethylamine
Hex	Hexane
h	Hour(s)
Hz	Hertz
IR	Infrared
J	coupling constant
m	mulpiplet
m/z	Mass-to-charge-ratio
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
min	minute(s)
MS	mass spectroscopy
M.W	molecular weight
NMR	Nuclear Magnetic Ressonance
OXT	1,3-oxazoline-2-thione
OZO	1,3-oxazolidin-2-one
OZT	1,3-oxazolidine-2-thione
PDC	pyridinium dichromate
PE	petroleum ether
Ph_3P	triphenylphosphine
q	quartet
r.t.	room temperature
Rf	retention factor
s	singulet

t	triplet
TBDMSCl	*tert*-butyldimethylsilyl chloride
t-Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TsCl	4-toluenesulfonyl chloride
TsOH	toluenesulfonic acid
UV	Ultraviolet
δ	chemical shift in ppm
Δ	reflux

Chapter 1 - Synthesis of oxo/thioxo-pyrimidines linked to carbohydrate template

1.1 - General introduction

This chapter is an introduction to the main characteristics of carbohydrates. This introduction is important to get a better understanding about the reactivity and the efficency of carbohydrates as substrate for the synthesis of new compounds with potential biological activity. It is intended to synthesize innovative and functional structures, namely the *C*-nucleosides. These structures can have multiple biological activities, emphasizing their applicability as DNA markers and as antibiotics, featuring also antibacterial, antiviral and antitumoral activity.

In this chapter the Biginelli condensation was explored in the formation of oxo- and thioxopyrimidine heterocyclic rings. The synthesis of these heterocyclic rings connected to carbohydrate derivatives, lead to the formation of *C*-nucleosides. Due to the polyhydroxylated nature of the carbohydrates, it was necessary to perform the selective protection of the hydroxyl groups in order to obtain carbohydrate template much easier to study.

1.1.1 - Carbohydrates: a compound class with biological activity

Carbohydrates are the most abundant biomolecules belonging to class of organic compounds found in living organisms on earth. Each year, more than 100 billion metric tons of carbon dioxide and water are converted into cellulose and other plant products due to photosynthesis. Living matter is largely made of biomolecules consisting of water and complex polymers of amino acids, lipids, nucleotides and carbohydrates. Carbohydrates are most special of them in that they remain associated with the three other polymers mentioned. Carbohydrates are linked with amino acid polymers (proteins) forming glycoproteins and with lipids as glycolipids. Carbohydrates are present in DNA and RNA, which are essentially polymers of D-ribose-phosphate and 2-deoxy-D-ribose phosphate to which purines and pyrimidines bases are attached at the C-1 position. Carbohydrates are a widely diverse group of compounds that are ubiquitous in nature. More than 75% of the dry weight of the plant world is carbohydrate in nature - particularly cellulose, hemicellulose and lignin.

Carbohydrates comprise a comprehensive group of naturally occurring substances, which include innumerable sugars and sugar derivatives, as well as high-molecular weight carbohydrates (polysaccharides) like starch and cellulose in plants and glycogen in animals. A polysaccharide molecule is composed of a large number of sugar or sugar-like units. Carbohydrates are of great importance in biology. The unique reaction, which makes life possible on Earth, namely the assimilation of the green plants, produces sugar, from which originate, not only all carbohydrates but, indirectly, also all other components of living organisms.

The important role of carbohydrates, generally, in the metabolism of living organisms, is well known. The biological breakdown of carbohydrates (often spoken of as "combustion") supplies the principal part of the energy that every organism needs for various vital processes. It is not surprising; therefore, that the carbohydrates and their metabolism have been the subject of comprehensive and in many respects successful biochemical and medical research for a long time.

Carbohydrates are polyhydroxylated aldehydes or ketones and their derivatives. The word "carbohydrate" includes polymers and other compounds synthesized from polyhydroxylated aldehydes and ketones. They can be synthesized in the laboratory or in living cells. Simple carbohydrates or the entire carbohydrate family may also be called saccharides. In general carbohydrates have the empirical formula $(CH_2O)_n$. The term generated from carbon and hydrate; though some also contain nitrogen, phosphorus, or sulfur. Chemically, carbohydrates are molecules that are composed of carbon, along with hydrogen and oxygen - usually in the same ratio as that found in water (H_2O).They exist primarily in their hemiketal or ketal forms.

Carbohydrates are divided in accordance to their molecule size: monosaccharides, oligosaccharides and polysaccharides. Monosaccharides feature stereogenic centers (chirals) in their structure, except for formaldehyde, being the number of stereoisomers given by the expression 2^n, where **n** is the number of chiral centers. Oligosaccharides are carbohydrates consisting in 2 to 10 monosaccharide units. Polysaccharides are carbohydrates consisting in more than 10 monosaccharide units.[1]

Monosaccharides possess either an aldehyde or a ketone function in their structure. Due to the presence of this carbonyl group in the structure, an internal cyclization reaction occurs between the electrophilic group and a hydroxyl function in positions 4 or 5. From this reaction two main outcomes may be presented, a variation of the ring size (a 5-atom cyclic hemiketal (furanoside form) or a 6-atom cyclic hemiketal (pyranoside form)) and the formation of a new chiral center, the carbon anomer (leading to two anomeric bonds in α or β position).

1.1.1.1- Use of protecting groups in carbohydrate synthesis

Protecting groups are functional groups introduced selectively to block the reactivity of certain sites in a molecule while desired transformations are carried out on different positions. After the desired transformations are accomplished, the protecting groups are removed. Reactions involving carbohydrates often require the use of protecting groups due to the multiple sites of reactivity present in carbohydrates. Common protecting groups for the alcohol functional groups in carbohydrates include ethers, esters, acetals or ketals which will be seen through out the thesis.

1.1.1.2 - Hydroxyl groups protection

Due to the multifunctional nature of sugars, it becomes necessary to introduce protecting groups from hydroxyl functions when trying to perform a chemical reaction in a certain position of the molecule, thus preventing the remaining hydroxyl groups present in the molecule to react under the applied reaction conditions.

Protection of hydroxyl groups has an important impact in the chemistry of sugars. The protecting group should present the following characteristics: ease of introduction, stability under the required reaction conditions and ease of removal.

It must be also taken into account other considerations such as cost and toxicity of reagents used in the reaction, choosing always the most appropriate for the situation. It is also necessary to ensure that the released protecting groups are stable under the reaction conditions used in the following steps.

The sugars can be protected by conversion of hydroxyl groups in acetals, ketals, esters or ether as there is a wide variety of protecting groups, with different selectivity, allowing the formation of unwanted compounds.

The protecting groups used in this work are the isopropylidene group, the *tert*-butyldimethylsilyl group, the acetyl group, the benzyl group, the benzoyl group and the carboxybenzyl group.

1.1.2 - *C*-Nucleosides

C-Nucleosides (Figure 1.1) are a group of compounds that have in their structure a sugar ring (carbohydrate derivative) connected at the anomeric carbon to a heterocyclic ring (C-1) by a carbon-carbon bond.

HO O HO OH H N O NH O

1

Figure 1.1 - Pseudouridine, first natural *C*-Nucleoside to be discovered.

Over recent years, synthetic base-modified nucleosides and *C*-nucleosides have proven their important impact in various therapeutical fields. Their biological properties have found application as antiviral tools against hepatitis virus, herpes virus and human immunodeficiency virus.[2,3] Their biological properties have application as pharmaceuticals, pesticides and herbicides.

C-Nucleosides can be divided in two classes: *C*-nucleosides isolated from natural products and *C*-nucleosides synthesized in laboratory. Due these applications *C*-nucleosides are taken as big challenger for researchers, leading interest in their synthesis and isolation, either by new methods of synthesis or by optimization of the already existing methods.

1.1.2.1 - Preparation of heterocyclic rings using two different heteroatoms

For obtention of new C-nucleosides we have synthesized compounds with 2-oxopyrimidine and 2-thioxopyrimidine units, anchored on a sugar template.

Pyrimidine ring is present in a large number of biologically important compounds such as alkaloids, drugs, agrochemicals or antimicrobial agents and, since the early years of twenty century, numerous studies on the synthesis and structure-activity relationships of pyrimidine derivatives have been reported.[4,5,6] Oxopyrimidines and their derivatives, also known as Biginelli compounds, take an important place in pharmacology and organic synthesis due to their remarkable properties as calcium channel blockers,[7,8] antihypertensive,[9,10] anti-inflammatory,[11,12] antibacterial,[13,14] antioxidative,[15] anticancer[16,17] and antiviral compounds.[18]

Synaptic is a pharmaco developed by Merk,[19] represents a strong candidate in treatment of benign prostatic tumors. Cerebrocrast is a new drug that is widely used in diabetes treatment and represents also a neuroprotector.[20] Monastrol is part of a family of compounds known for having antitumoral activities, which operate at the cell division level (mitosis).[21] Nitractin as an agent against the trachoma group of viruses, compounds of the same group also exhibit antibacterial activity.[22] It is well known that this compound (Figure 1.2) have a direct relationship with its pharmaceutical properties and existing chirality of the C-4 carbon dihydropyridin ring and the type of substituents in other ring positions[23] (dihydropyrimidines are flexible molecules, in which the C-4 moiety and de C-3/C-5 substituents can rotate, and the conformation of the 1,4-dihydropyridine can change).[24]

2 Synaptic; 3 Cerebrocrast; 4 Monastrol; 5 Nitractin

Figure 1.2 - Structure of four DHP used as pharmaceuticals.

The pyrimidine core can be obtained by use of multicomponent reactions. Multicomponent reactions are convergent reactions, in which three or more starting materials react to form a product, where essentially all or most of the atoms contribute to the newly formed product. The result is clearly dependent of reaction conditions: solvent, temperature, catalyst,

concentration, starting materials and functional groups. In the synthesis of a multicomponent reaction consists in a one-pot reaction of two compounds and an electrophilic species. The compounds must possess an N-C-N skeleton type (for example urea or thiourea) and a C-C-C skeleton type (for example acetoacetate), the electrophile species may be a carbohydrate derivative. The multicomponent reactions have been considered of great importance in the field of chemical synthesis as they allow the formation of libraries with biological active compounds and its employment as pharmaceuticals.

1.1.2.2 - General methods for *C*-nucleoside preparation

The first synthesis of dihydropyrimidinones was reported by Biginelli[25] in 1893, however, the synthetic potential of this heterocyclic synthesis remained unexplored for quite some time. In the 1970's interest gradually increased, and the scope of the original cyclocondensation reaction (Scheme 1.1) was gradually extended by variation of all the building blochs, allowing access to a large number of multifuncionalized dihydropyrimidines. Since the late 1980's, a tremendous increase in activity has again occurred, as evident by the growing number of publications and patents on the subject. This is mainly due to the fact that the multifunctionalized dihydropyrimidine scaffold ("Biginelli compounds") represents a heterocyclic system of remarkable pharmacological efficiency. Since then several reviews on synthesis and chemical properties of pyrimidinones have been published. The search for new and efficient methods for the synthesis of pure compounds has been active area of research in organic synthesis. From a modern point of view, Biginelli protocol is obviously very attractive for combinatorial chemistry and has been rarely used for parallel synthesis, a new avenue could be connected with an elaboration of catalytic procedures.[26]

The Biginelli reaction has been described for the first time for more than two centuries ago, but it keeps, however with some changes, the main method for synthesis of di-hidropyrimidinon or 2-oxopyrimidine cores. Biginelli reaction is an acid-catalyzed three-component condensation reaction between an aldehyde, a ß-ketoester and urea (or thiourea) according to Scheme 1.1. It constitutes a rapid and facile synthesis of dihydropyrimidines, which are interesting compounds with a potential for pharmaceutical application.

Scheme 1.1 - Biginelli condensation.

The condensation of aldehydes, ß-carbonyl compounds and (thio) urea in ethanol, leads to dihydropyrimidinones when in a strong acidic medium, however in low yields. Sometimes when a reagent is added in excess this mistake hardens the possibility to isolate the product.[27] Due to the importance of these compounds, new synthetic methods have been implemented in order to improve yields. A number of improved variants employing new reagents, catalyst, methodologies and techniques have emerged. Several synthetic methods have been used to catalyze the Biginelli reaction, some of them include the use of Lewis acid catalysts such as $BF_3.OEt$,[28] $CoCl_2.6H_2O$,[29] $FeCl_3.6H_2ONiCl_2.6H_2O$,[30,31] In (III) halides,[32,33,34] $SnCl_2.2H_2O$,[35] $LaCl_3.7H_2O$,[36] $CeCl_3.7H_2O$,[37] $ZrCl_4$,[38] metal triflates such as $Zn(OTf)_2$,[39] $Cu(OTf)_2$,[40] $Bi(OTf)_2$,[41] $Yb(OTf)_2$ [42] and $La(OTf)_2$,[43,44] ionic liquids,[45] TMSI,[46] solid phase,[47] polymer support,[48] Lithium salts,[49,50] heterogeneous catalysis by SiO_2,[51,52] and the use of alternative eating sources like ultrasound,[53] and microwave.[54,55,56,57]

Ramalingam and co-workers[58] report the synthesis of Biginelli derivative **11** according to Scheme 1.2.

Scheme 1.2 - Procedure applied by Ramalingam and co-workers.

1.1.2.2 - Mechanism of the Biginelli reaction

The first step in the mechanism is believed to be the condensation between the aldehyde and (thio) urea, with some similarities to the Mannich condensation. The iminium intermediate generated acts as an electrophile for the nucleophilic addition of the ketoester enol, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea NH_2 to give the cyclized product (Figure 1.3).[59]

Figure 1.3 – Proposed mechanism for the formation of the dihydropyrimidine ring.

1.1.2.3 - Preparation of aldehyde precursors

The use of carbohydrate derivatives such as compounds of Biginelli cyclocondensation allows the synthesis of *C*-nucleosides obtained.

In order to synthesize new *C*-nucleosides as dihydropyrimidinones, Biginelli compounds, it was decide to use glucosamine HCl as starting sugar. To obtain the aldehyde from this sugar, a reaction was performed (Scheme 1.3) which is already described in literature by Jung and co-workers.[60] Other reactional conditions can also be used.[61,62,63] Most of *C*-nucleosides synthesized use D-ribose as starting material. In this work glucosamine HCl was chosen as starting material, as it is a less studied sugar.

Scheme 1.3 - Synthesis of aldehyde precursor of *C*-nucleosides.

1.1.2.4 - Reactions of primary aliphatic amines with nitrous acid

Nitrous acid (HONO) is a weak and unstable acid. It is always prepared *in situ*, usually by treating $NaNO_2$ with an aqueous solution of a strong acid.

$$HCl\ (aq) + NaNO_2\ (aq) \rightarrow HONO\ (aq) + NaCl\ (aq)$$

$$H_2SO_4\ (aq) + NaNO_2\ (aq) \rightarrow 2\ HONO\ (aq) + Na_2SO4\ (aq)$$

Primary aliphatic amines react with nitrous acid through a reaction called diazotization to yield highly unstable aliphatic diazonium salts. Even at low temperatures, aliphatic diazonium salts decompose spontaneously by losing nitrogen to form carbocations.[64] The carbocations go on to produce mixtures of alkenes, alcohols and alkyl halides by removal of a proton, reaction with H_2O, and reaction with X^- (Figure 1.4).

General reaction:

$$R—NH_2 + NaNO_2 + 2\ HX \xrightarrow[H_2O]{HONO} [R—N^+\equiv N{:}\ X^-] + NaX + 2\ H_2O$$

Aliphatic diazonium salt
(highly unstable)

$$\downarrow -N_2$$

$$\text{Alkenes, alcohols, alkyl halides} \leftarrow R^+ + X^-$$

Figure 1.4 - Diazotization of aliphatic amines.

Diazotization of primary aliphatic amines are of little synthetic importance mainly because they yield complex mixtures of products. Diazotizations of primary aliphatic amines are used in some analytical procedures because the evolution of nitrogen is quantitative. They can also be used to generate and thus study behavior of carbocations in water, acetic acid, and other solvents.

1.2 - Presentation and discussion of results

In the last decade, Biginelli reaction, a three-component reaction, has become the center of increasing attention since it permits a rapid access to combinatorial libraries of dihydropyrimidones as well as their sulfur analogues. Pyrimidinones or dihydropyrimidones are well known for their wide range of bioactivities and their applications in the field of drug research have stimulated the development of a wide range of synthetic methods for their preparation and chemical transformations.

Attractive aspects of these Biginelli compounds lie in an expected increase in bioavailability and water solubility and in the generation of new families of *C*-nucleosides.

Several anomeric sugar aldehydes can be used. The anomeric position (C1) is already a well referenced topic. As example (Scheme 1.4), there are various articles of Dondoni and co-workers[27,65,66] but also other related publications of synthesis of pseudo-C-nucleosides.[67]

Scheme 1.4 – Aplication of an anomeric aldehyde.

1.2.1 - Synthesis of *C*-nucleosides containing 2-oxopyrimidine and 2-thioxopyrimidine heterocyclic rings

A reaction scheme used to prepare 2-oxopyrimidines, and 2-thiooxopyrimidines was based on an experimental procedure described in literature[67] which allowed the synthesis of an heterocyclic ring at the anomeric position of the furanoside ring. However, recent literature advise the use of catalysts to increase the yields.

The synthesis of the pyrimidine ring can be carried out using sulfuric acid catalysis, however substrate degradation is described under these conditions. Sugar derivatives are known to be very sensitive to strong acids. As our working group has already carried out the synthesis of pseudo-*C*-nucleoside we decided to apply the same conditions.[67] Using the advantage as a catalyst, we obtain the products in satisfactory yields (based on literature results) to yield a single compound, however, a stereogenic center is formed in position 4 of the heterocyclic ring.

The description of the synthesis of the compound with a single sugar derivative attached to the heterocyclic ring can be found in the literature. The aldehydes are 2,3-*O*-isopropylidene-D-glyceraldehyde, 2,4-*O*-ethylidene-D-threose, D-erythrose and 2,5-anhydro-D-xylose aldehyde.

In this work, we performed the synthesis of two single aldehydes, 2,5-anhydro-D-mannose and 2,5-anhydro-3,4,6-tri-*O*-acetyl-D-mannitol. The synthesis of the dihydropyrimidine ring was performed by reaction with the aldehyde, ethyl acetoacetate and urea/thiourea in ethanol during 5h at 75ºC (Scheme 1.5).

R−CHO **18** + $CH_3COCH_2CO_2Et$ **6** —(ureia/thioureia, EtOH)→ **19** X= O, **20** X= S; R= sugar derivative

Scheme 1.5 - General method for the synthesis of 2-oxo/2-thioxopyrimidines.

Not only 2-oxopyrimidines have pharmaceutical applications, the 2-thioxopyrimidine are also biologically active. For the importance of these compounds, it was performed the synthesis of compounds that have in their structure the 2-thioxopyrimidine ring. The technique used in the synthesis of these compounds is similar to the technique used in the obtention of oxopyrimidines, but instead of using urea, it was used thiourea, in the same equivalents number.

For adopted numbering of oxopyrimidines and thioxopyrimidines heterocyclic rings (Figure 1.5) is the following:

19 X= O
20 X= S
R= sugar derivative

Figure 1.5 – Heterocyclic rings numbering convention.

1.2.1.1 - Synthesis of 2,5-anhydromannose 13 (aldehyde precursor)

Using as starting material glucosamine HCl **12**, it was performed the synthesis of the aldehyde **13** by reaction with sodium nitrite, acetic acid and water, applying the conditions found in literature (Scheme 1.6).[59]

Scheme 1.6 - Synthesis of aldehyde percursor of C-nucleosides.

Studying NMR spectrum of the compound is evident that this was obtained (Table 1.1). It can be observed that the compound has 6 carbons, at 202.8 ppm there is the carbon for the aldehyde, which confirms the transformation of the pyranosidic ring into a furanosidic ring, and the aldehyde group in the structure.

Table 1.1 - ^{1}H NMR/^{13}C NMR shift of the aldehyde **13**.

σ (ppm) / Compound	CHO ^{1}H	OH ^{1}H	CHO ^{13}C	CH_2 ^{13}C
	9.57 (s, 1H)	3.58 (ls, 3H)	202.8	61.5

1.2.1.2 - Synthesis of 2-oxopyrimidine 21 and 2-thio-oxopyrimidine 22

Using the 2,5-anhydromannose **13**, ethyl acetoacetate, urea/thiourea, in ethanol, under reflux for 5 hours lead to the synthesis of two heterocyclic rings **21** and **22** (Scheme 1.7).

Scheme 1.7 - Synthesis of oxopyrimidine **21** and thiooxopyrimidine **22**.

The formation of oxopyrimidine **21** and thiooxopyrimidine **22** was confirmed by the NMR spectrum (Table 1.2 and Table 1.3).

Table 1.2 – ^{1}H NMR shift of the oxo/thioxo-pyrimidines **21** and **22**.

σ (ppm) / **Compound**	**NH** ^{1}H	**CH-4** ^{1}H	**$CH_2\underline{CH_3}$** ^{1}H	**$\underline{CH_2}CH_3$** ^{1}H	**CH_3** ^{1}H
	7.28 (s, 2H)	4.26 (s, 1H)	1.26-1.31 (m, 3H)	3.99-4.08 (m, 2H)	2.05 (s, 3H)
	6.83 (s, 2H)	4.56 (s, 1H)	1.25-1.28 (m, 3H)	3.68-3.83 (m, 2H)	1.98 (s, 3H)

Table 1.3 – ^{13}C NMR shift of the oxo/thioxo-pyrimidines **21** and **22.**

σ (ppm) / **Compound**	**C=O** ^{13}C	**C=s** ^{13}C	**Cq (C-5, C-6 and $\underline{C}O_2Et$)** ^{13}C	**CH_2 ethyl and CH_2 sugar** ^{13}C	**CH_3 ethyl and CH_3** ^{13}C	**C-4** ^{13}C
	170.4	-	127.9 157.5 172.1	36.1 61.6	14.1 21.0	49.1
	-	185.5	128.0 158.1 172.2	36.9 62.9	14.5 23.3	49.6

The formation of two new *C*-nucleosides derivatives from glucosamine HCl **12** was confirmed. Both 2-oxopyrimidine **21** as well as 2-thioxopyrimidine **22** were not easy to be isolated as the

free hydroxy groups in both compounds difficult their purification. The ^{13}C NMR data spectrum of oxopyrimidine **21** and from thioxopyrimidine **22** are similar, except for the heterocyclic ring quaternary carbon signal which gives the justification of oxopyrimidine or thioxopyrimidine ring's which are at 170.4 ppm and 185.5 ppm, respectively. It is also noted the yields are similar for the synthesis of this two new *C*-nucleosides.

Due to this fact it was decided to synthesize *C*-nucleosides with protected hydroxyl groups starting from glucosamine HCl **12**.

1.2.1.3. - Synthesis of 2,5-anhydro-3,4,6-tri-O-acetyl-D-mannitol 25 (aldehyde precursor)

A new synthetetic scheme was designed starting from glucosamine HCl **12**. In order to achieve less polar synthesis of oxopyrimidines and thio-pyrimidines, a new way to protect selectively the hydroxyl groups. The acetyl group was the protect hydroxyl group used. This way it was necessary to previously protect the amine group in order to avoid acetylation of this group with *p*-anisaldehyde.

The synthesis of compound **24** can be found in literature[68,69, 70,71, 72, 73, 74, 75,76] described by Bergmann and co-workers.[68] The synthesis of aldehyde **25**, has been described[77] but with different reactional conditions (Scheme 1.8).

12 → 1) NaOH 1M, p-anisaldehyde, 86%; 2) AC_2O, DMAP, pyridine 74% → 23 → HCl, acetone 94% → 24 → $NaNO_2$, AcOH, H_2O 96% → 25

Scheme 1.8 – Synthesis of aldehyde **25**.

The structures of these compounds have been confirmed by NMR (Table 1.4 and Table 1.5).

Table 1.4 – ^{1}H NMR shift of the aldehyde **25**.

σ (ppm) / **Compound**	**Ac** ^{1}**H**	**OCH_3** ^{1}**H**	**C_6H_4** ^{1}**H**	**N=CH** ^{1}**H**	**NH_2** ^{1}**H**	**CHO** ^{1}**H**
	0.88 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.10 (s, 3H)	3.84 (s, 3H)	6.90 (d, 2H), 7.66 (d, 2H)	8.16 (s, 1H)	-	-
	1.97 (s, 3H), 1,99 (s, 3H), 2.02 (s, 3H), 2.16 (s, 3H)	-	-	-	8.75 (ls, 2H)	-
	2.10 (s, 9H)	-	-	-	-	9.72 (s, 1H)

Table 1.5 – ^{13}C NMR shift of the aldehyde **25**.

σ (ppm) / **Compound**	**Ac** ^{13}**C**	**OCH_3** ^{13}**C**	**C_6H_4** ^{13}**C**	**N=CH** ^{13}**C**	**CHO** ^{13}**C**
	20.5, 20.7, 20.8, 20.8 , and Cq at 168.8, 169.5, 169.9, 170.7	55.4	114.1, 130.3, and Cq at 128.3, 162.3	164.3	-
	20.4, 20.5, 20.9, 21.0, and Cq at 168.8, 169.4, 169.9, 170.0	-	-	-	-

AcO, O, CHO, AcO, OAc	20.7, 20.8, 20.9, and Cq at 169.5, 169.6, 170.6	-	-	-	9.72 198.1

The aldehyde **25** was made by diazotization of primary amines to synthesize the completely protected furanosidic aldehyde. The conversion of the pyranosidic ring into a furanosidic ring is confirmed. In literature may be found a description of the synthesis of aldehyde **25** using different synthesis method than the method used by us.[77]

1.2.1.4 - Synthesis of 2-oxopyrimidine 26 and 2-thioxopyrimidine 27

The synthesis of two pyrimidine rings of molecules **26** and **27** was performed using aldehyde 3,4,6-tri-0-acetyl-2,5-anhydro-D-mannose **25** by applying the conditions already described in literature (Scheme 1.9).

25 + $CH_3COCH_2CO_2Et$ **6** → (ureia/thioureia, EtOH)

26 X= O, 30%
27 X= S, 42%

Scheme 1.9 - Synthesis of oxopyrimidine **26** and thiooxopyrimidine **27**.

The synthesis of both compounds may be confirmed by NMR (Table 1.6 and Table 1.7).

Table 1.6 – ^{1}H NMR shift of the oxo/thioxo-pyrimidine **26** and **27**.

σ (ppm) / Compound	NH ^{1}H	CH-4 ^{1}H	$CH_2\underline{CH_3}$ ^{1}H	$\underline{CH_2}CH_3$ ^{1}H	CH_3 ^{1}H	Ac ^{1}H
	6.88 (ls, 2H)	4.68 (s, 1H)	1.31-1.34 (m, 3H)	3.40-3.45 (m, 2H)	2.01 (s, 3H)	1.40 (s, 9H)

	6.42 (s, 2H)	4.56 (s, 1H)	1.31-1.34 (m, 3H)	3.40-3.45 (m, 2H)	2.01 (s, 3H)	1.40 (s, 9H)

Table 1.7 - ^{13}C NMR shift of the oxo/thioxo-pyrimidine **26** and **27**.

σ (ppm) / **Compound**	**C=O** ^{13}C	**C=s** ^{13}C	**Cq (C-5, C-6 and <u>C</u>O₂Et)** ^{13}C	**CH_2 ethyl and CH_2 sugar** ^{13}C	**CH_3 ethyl and CH_3** ^{13}C	**C-4** ^{13}C	**Ac** ^{13}C
	169.7	-	128.3 155.4 171.5	36.6 61.6	14.1 23.1	48.4	20.7, 20.8, 20.9 and Cq at 169.9, 170.0, 170.6
	-	185.5	128.0 158.1 172.2	36.9 62.9	14.5 23.3	49.6	20.7, 20.8, 20.9 and Cq at 169.9, 170.0, 170.6

Thus, the formation of two new *C*-nucleoside derivatives of glucosamine HCl **12** has been confirmed. The ^{13}C NMR spectra of 2-oxopyrimidine **26** and 2-thioxopyrimidine **27** are very similar, except the quaternary carbon of the heterocyclic ring signal which gives a definition of oxopyrimidine or thioxopyrimidine found in 169.7 ppm and 185.5 ppm, respectively.

Yields are lower than those obtained in the synthesis of oxo/thioxopyrimidines unprotected (**21** and **22**, respectively). It should verify precisely the opposite, these Biginelli derivatives should be easier to isolate because they are more apolar that derivatives **21** and **22**.

1.3 - Conclusions

✓ The synthesis of carbohydrate derivatives **21** and **26** containing 2-oxopyrimidine heterocyclic rings was performed starting from aldehyde **13** derived from D-glucosamine.

✓ The synthesis of carbohydrate derivatives **22** and **27** containing 2-thioxopyrimidine heterocyclic rings was performed starting from aldehyde **25** derived from D-glucosamine.

✓ After analysis of C-nucleosides ^{13}C NMR spectrum of compounds **21**, **22**, **26** and **27**, it was observed a single chemical shift of tertiary carbon of the six-membered ring (C-4). Even though the formation of a stereogenic center (C4) in Biginelli adduct, was only detected the formation of one diastereoisomer. This Biginelli reaction were quite stereoselective. The chemical shifts for tthis tertiary carbon atom at position 4 of the six-membered heterocycle roughly 49 ppm in *C*-nucleosides **21**, **22**, **26** and **27**.

✓ The chemical shifts for the quaternary carbon atom at position 2 of the six-membered heterocycle varied from roughly 170 ppm (−N−C=O) in oxopyrimidines (**21** and **26**) and 186 ppm (−N-C=S) in thioxopyrimidines (**22** and **27**).

✓ Yields are more favorable when the Biginelli adducts was unprotected (**21** and **22**) (Table 1.8). *C*-nucleoside with a better overall yield was thioxopyrimidine **22**. Compounds **26** and **27** are less polar, which should facilitate putificação and improve yield, there are just the opposite. The overall yield reduction is justified by the increase number of steps.

Table 1.8 – Yields obtained for *C*-nucleosides.

***C*-nucleosides**	**Yield (cyclocondensation)**	**Global yield**
21	56%	76%
22	60%	78%
26	30%	59%
27	42%	65%

Chapter 2 - Synthesis of simple azidocarbohydrates

2.1 - General introduction

Azido-carbohydrates have in their composition an azido group (N_3), usually this group is introduced in one of the end of carbon chain or by substitution of a free hydroxyl group. In the literature can be found some synthesis of azido-sugars as they can be precursors of triazoles. Azido-sugars are normally used in click chemistry reactions and to obtain amino compounds (reduction of azido group).

Preparation of these substrates (azido-carbohydrates) is performed based on literature,[78] following preparation of carbohydrate acetonides, a better leaving group at terminal carbon, the target of the subsequent reactions, was obtained by iodination. Then the azidocarbohydrates were prepared by a nucleophilic substitution reaction with sodium azide according to Scheme 2.1.

HO–O–OPG (**28**) → [Ph_3P, imidazole, I_2, toluene; 5h, reflux] → I–O–OPG (**29**) → [NaN_3, DMF; 100ºC, 3h] → N_3–O–OPG (**30**)

Scheme 2.1 - General synthesis of azido-sugars.

Based on this scheme and starting from different commercial sugars, the insertion of an azide in one of the extremities of the molecule was performed. This way different azidocarbohydrates were obtained, which will be used as substrate for “Click Chemistry”.

2.1.1 – Condensation of carbohydrates with acetone

The condensation of acetone with aldoses, leading to the formation of O-isopropylidene derivatives has been widely used in synthesis, structural and conformational studies and its importance to the carbohydrate chemist has become inestimable.[79]

Several methods to synthesize O-isopropylidene derivatives have been reported in the literature. The conventional method consists of the condensation of a diol with acetone in the presence of a catalyst under anhydrous conditions. As catalyst several agents have been used such as mineral acid,[80,81] anhydrous zinc chloride together with phosphoric acid,[82] ion exchange resins,[83,84] anhydrous copper (II) sulfate,[85,86] iodine,[87] anhydrous ferric chloride,[88] boron trifluoride etherate and anhydrous aluminum chloride.[89] The major products formed in these reactions are reported to be the thermodynamically more stable, except when anhydrous copper (II) sulfate is used. In this case it appears that some kinetic control is necessary.[90,91] Other reagents than acetone used for condensation are known, namely 2-methoxypropene, in

dimethylformamide and in the presence of *p*-toluenesulfonic acid. This reaction occurs exclusively under kinetic control.[92]

The method employed consists in the reaction of the monosaccharide with acetone in presence of a catalyst, or 2-dimethoxypropane in acetone and in the presence of *p*-toluenesulfonic acid.[93,94] The substrates used were D-ribose, D-glucose and D-galactose.

2.1.2 - Ionic deoxygenation of sugars

Iodination is a classical reaction commonly used in organic synthesis. The replacement of a hydroxyl group by iodine has been widely used in carbohydrate chemistry and it has aroused many interest in the last decades.[95,96,97,98]

Deoxyhalogeno sugars especially deoxyiodo are very useful intermediates in many syntheses[99,100] of azido-, amino and thio-deoxy derivatives by substitution,[99] or deoxy sugars by reduction, which allows the preparation of natural compounds of biological importance such as antibiotic substances, cardiac glycosides, and bacterial antigens.[101] Their capacity to create radicals allows its applications in the synthesis of some natural compounds.

The deoxy-halogen-sugars are susceptible to nucleophilic attacks. The easiness of removability of a halide decreases in the order I> Br> Cl> F, in this work we will use the iodine.[102]

The method applied by Garegg and Samuelsson consists essentially in a reaction between a free hydroxyl group and the triphenylphosphine/iodine/imidazole system using toluene as a solvent.[103,104] The inversion of configuration occurs when there is replacement of the hydroxyl group by iodide ion. The same mechanism was proposed by the same researchers in 1980[102] which is presented (Figure 2.1).

$$Ph_3P + I_2 + 2\ HN(imidazole) \longrightarrow Ph_3\overset{+}{P}N(imidazole)\ I^- + HN(imidazole)\ HI$$

$$Ph_3\overset{+}{P}N(imidazole)\ I^- + R\text{-}OH \longrightarrow Ph_3P{+}\ ORI^- + HN(imidazole)$$

$$Ph_3P + ORI^- \longrightarrow Ph_3P{=}O + RI$$

Figure 2.1 - Garegg Samuelsson proposed mechanism.

2.1.3 - Azidation

Azides are versatile intermediates in organic synthesis, since they can be used for the preparation of a variety of amines or amino compounds that show interesting biological activities. Azides have recently been drawing much attention in synthetic organic chemistry.[105]

Azido reagents can be used to perform addition, condensation, rearrangement and substitution reactions, and the reduction of azides leads to amines products. Although considered a good nucleophile, azides often react very slowly with many halides and other alkylating agents. Such reactions cannot usually be heated since the product azides frequently decompose or have the hazardous nature in general.[106] The deoxy-halogen-sugars are susceptible to nucleophilic attacks. To do this fact azides are a good nucleophile reagent, and react with halide-sugars to give azido-sugars.

2.1.4 - Reduction of hydroxyl group

While the acid-base reactions can be characterized as proton transfer processes, reactions known as oxidation-reduction, or redox, are considered electron transfer reactions. A reaction involving the gain of electrons is called the reaction of reduction. The reduction is a chemical change that occurs where there is a decrease of oxidation number of a specific chemical species. When an element is oxidized, it acts as a reducing agent, since it donates electrons to another substance, causing its reduction. When, however, one element is reduced, it acts as an oxidizing agent because it accepts electrons, causing its oxidation.

Aldoses (and ketoses) can be reduced with $NaBH_4$ to compounds called alditols. The $NaBH_4$ reduces aldehydes to primary alcohols according to Figure 2.2.

Figure 2.2 - Reduction of aldehydes to primary alcohols.

2.1.5 - Chain-clevage reactions: oxidative cleavage of α-diols

A number of oxidizing agents are used to identify functional groups of carbohydrates, in elucidation of their structures, and for synthresis of new compounds. The most important are Benedict's or Tollens' reagents, bromine water, nitric acid, and periodic acid. Each of these reagents produces a different and usually specific effect when it is allowed to react with a monosaccharide.

Compounds that have hydroxyl groups on adjacent atoms undergo oxidative cleavage when it is treated with aqueous periodic acid (HIO_4). The reaction breaks carbon-carbon bonds and produces carbonyl compounds (aldehydes, ketones, or acids).

Reaction of α-diols with periodic acid H_5IO_6 or its salts (in this case with $NaIO_4$) gives rise to cyclic ester intermediates which cleave in a two-electron oxidation process to give two carbonyl products and iodate. This method was used to reduce the size of the carbon chain. The sodium

periodate is often used in derivatives of carbohydrates. The proposed mechanism for oxidative cleavage is represented in Figure 2.3.

Figure 2.3 - Mechanism of oxidative cleavage.

2.2 - Presentation and discussion of results

2.2.1 - Azido-sugars in D-ribose template

We focused on the preparation of an azidoribose derivative for which the hydroxyl groups at positions two and tree were protected with isopropylidene group. Thus, the commercially available D-ribose was asubmitted to protection of the anomeric hydroxyl group and the hydroxyl of positions two and tree of furanosidic ring.[107] Hydroxyl group at C-5 was substitued by iodine by reaction of triphenylphosphine/iodine/imidazole.[108,109] Azidation[110] were perfomed with sodium azide, and the removal of isopropylidene and methoxyl groups was made in a strong acid medium according to Scheme 2.2.

Scheme 2.2 - Synthesis of azido-sugars **34** and **36**.

The structure of compound **34** can be confirmed by NMR (Table 2.1 and Table 2.2). Then to obtain the desired unprotected azio-sugar, the removal of the isopropylidene group together with the methoxy group was needed. Using the method a) the major product obtained is acetylated derivative **35**. It is necessary to use stronger acidic conditions to remove the metoxy group and to prevent the formation of the acetylated product **35**. Apply the conditions of method b), can prevent the formation of the acetylated product and obtain the desired product (azido-sugar **36**) in good yield. Compound **37** is a byproduct resulting from the removal of the isopropylidene group. It is observed that methoxy group is more difficult to remove than the isopropylidene group.

Table 2.1 – ^{1}H NMR shift of the azido-sugars **34** and **36**.

σ (ppm) / Compound	**CH_2-5 (^{1}H)**	**$C(CH_3)_2$ (^{1}H)**	**OCH_3 (^{1}H)**
	3.11 (t, 1H). 3.25 (dd, 1H')	1.28 (s, 3H), 1.43 (s, 3H)	3.32 (s, 3H)
	3.27 (dd, 2H),	1.32 (s, 3H), 1.49 (s, 3H)	3.38 (s, 3H)
	3.31-3.36 (m, 1H), 3.47-3.51 (m, 1H')	-	-

Table 2.2 - ^{13}C NMR shift of the azido-sugars **34** and **36**.

σ (ppm) / Compound	**CH_2-5 (^{13}C)**	**$C(CH_3)_2$ (^{13}C)**	**OCH_3 (^{13}C)**
	6.9	25.1, 26.5	55.3
	53.8	24.9, 26.4	55.2
	53.1 for α isomer, 54.6 for β isomer	-	-

Starting form D-ribose and through selective oxidation of the anomeric hydroxyl group, lactone derivated compounds can be obtained by reactions in Scheme 2.3.[111] This oxidation in C-1 allows the ribose functionalization aiming the synthesization of simple but functional azides.

Scheme 2.3 – Synthesis of azido-lactone **41**.

The compound structure can be confirmed by NMR (Table 2.3 and Table 2.4).

Table 2.3 – ^{1}H NMR shift of the azido-lactone **41**.

σ (ppm) / **Compound**	**CH_2-5 (^1H)**	**$C(CH_3)_2$ (^1H)**
	3.58-3.68 (m, 2H)	1.32 (s, 3H), 1.36 (s, 3H)
	3.39-3.47 (m, 2H)	1.40 (s, 3H), 1.48 (s, 3H)
	3.68 (dd, 1H), 3.80 (dd, 1H’)	1.39 (s, 3H), 1.47 (s, 3H)

Table 2.4 - ^{13}C NMR shift of the azido-lactone **41**.

σ (ppm) / Compound	CH_2-5 (^{13}C)	$C(CH_3)_2$ (^{13}C)	=O (^{13}C)
HO	60.9	25.6, 27.0	174.8
I	5.7	25.5, 26.5	173.0
N_3	52.5	25.5, 26.6	173.4

2.2.2 - Azido-sugars in D-galactose template

Starting from commercial 1,2:3, 4-di-O-isopropylidene-D-galactopyranose the acquisition of azido-sugar is possible in two steps (Scheme 2.4).

Ph_3P, Imidazole, I_2, Toluene; reflux, 5h, 98%

NaN_3, DMF; reflux, 3h, 88%

42 **43** **44**

Scheme 2.4 - Synthesis of azido-sugar **44**.

The compound structure can be confirmed by NMR (Table 2.5).

Table 2.5- ^{1}H NMR/^{13}C NMR shift of the azido-sugar **34**.

σ (ppm) / Compound	CH_2-6 (^{1}H)	$C(CH_3)_2$ (^{1}H)	CH_2-6 (^{13}C)	$C(CH_3)_2$ (^{13}C)
	3.17-3.55 (m, 2H)	1.33 (s, 3H), 1.35 (s, 3H), 1.44 (s, 3H), 1.54 (s, 3H)	2.5	24.6, 25.0, 26.1, 26.2
	3.20-3.33 (m, 2H)	1.19 (s, 3H), 1.20 (s, 3H), 1.26 (s, 3H), 1.36 (s, 3H)	50.7	23.7, 24.2, 25.4, 25.4

2.2.3 – Azido-sugars in D-xylose template

Starting from D-glucose and after 5 stages azido-sugar derivative **49** was obtained (Scheme 2.5) in the D-xylose template. This was possible by a sequence multiple reaction, like removal of protective groups, oxidative cleavage and oxidation of aldehydes to alcohols.

45 → AcOH (80%), 60ºC, 1h, 96% → 46 → 1) $NaIO_4$, H_2O, EtOH, r.t., 30 min; 2) $NaBH_4$, EtOH, 0ºC, 1h, 43% → 47

→ Ph_3P, Imidazole, I_2, Toluene, reflux, 5h, 71% → 48 → NaN_3, DMF, reflux, 3h, 83% → 49 → PCC, molecular sieves, DCM, r.t., 16h, 83% → 50

Scheme 2.5 - Synthesis of azido-sugar **49** and **50**.

The compound structure can be confirmed by NMR (Table 2.6).

Table 2.6 – ^{1}H NMR/^{13}C NMR shift of the azido-sugar **49**.

σ (ppm) / **Compound**	**CH_2-5 (^{1}H)**	**$C(CH_3)_2$ (^{1}H)**	**CH_2-5 (^{13}C)**	**$C(CH_3)_2$ (^{13}C)**
	4.00 (dd, 1H), 4.11 (dd, 1H’)	1.32 (s, 3H), 1.48 (s, 3H)	66.1	26.2, 26.8
	3.23-3.33 (m, 2H)	1.32 (s, 3H), 1.51 (s, 3H)	0.0	27.5, 28.0
	3.52 (d, 2H)	1.34 (s, 3H), 1.49 (s, 3H)	50.8	26.4, 27.1

2.3 - Conclusions

✓ This azidocarbohydrates were synthesized with the aim at using them in cycloaddition namely "click chemistry" (Chapter 5).

✓ The synthesized azidocarbohydrates were obtained using known sequences commonly used in organic chemistry. Functionalization of C-5 and C-6 in furanose and pyranose series, respectively, was explored via Garegg's methodologies. Iodine is a good leaving group. The nucleophilic substitution of the iodine by the azide was effective and good global yields were obtained in the synthesis of azidocarbohydrates (Table 2.7).

Table 2.7 – Global yields of synthesis of azidocarbohydrates

Azidocarbohydrate		Global yield
D-ribose template	**34**	87%
	36	84%
	41	89%
D-galactose ptemplate	**44**	93%
D-xylose template	**49**	73%
	50	78%

✓ The ^{13}C NMR chemical shifts for the primary carbon atom at C5 position of the five-membered ring varied from roughly 5 ppm shift in iodinecarbohydrates to approximately 50 ppm in azidocarbohydrates (compounds **34**, **36**, **41**, **49** and **50**).

✓ The ^{13}C NMR chemical shifts for the primary carbon atom at C6 position of the six-membered ring varied from roughly 2 ppm for the iodinated derivatives to approximately 50 ppm for the azidocarbohydrates (compound **44**).

Chapter 3 - Synthesis of azidocarbohydrates fused with1,3-oxazolidine-2-thione and 1,3-oxazolidin-2-one rings

3.1 – General introduction

3.1.1 - General methods for the synthesis of 1,3-oxazolidine-2-thiones fused on carbohydrate templates

The synthesis of 1,3-oxazolidine-2-thione (OZT) heterocyclic ring linked to carbohydrates can generate new structures, by several methods, originated oxazolidin-2-ones fused on azido carbohydrate templates.

The junction of an OZT with a carbohydrate has been described by Girniene[112,113,114,115] and co-workers. These synthesis are related to carbohydrate-based 1,3-oxazolidine-2-thiones, since those heterocycles are structurally related.

In the fact, such structural arrangements have given birth to analogues of natural compounds such as pseudo *C*-nucleosides, pseudo-*N*-nucleosides,[116,117,118] spironucleosides[119,120] and spiro-*C*- glycosides.[121]

The present chapter is dedicated to the methodologies developed to prepare fused bicycles containing an oxazolidinone moiety.

Among the different applications, the fused OZT sugar derivatives can potentially be exploited as chiral auxiliaries,[122] glycosidase inhibitors[123] or precursors of nucleosides.[124,125,126,127,128,129,130]

3.1.1.1 - Condensation of aldoses and ketoses with thiocyanic acid

For the synthesis of fused thiocarbamates, a more simple approach consists of using an α-hydroxyaldehyde or ketone possessing an extra γ- or δ-hydroxyl group, able to promote intramolecular cyclization during the condensation process with thiocyanic acid, and thus leading to fused furano-structures.

The first preparation of bicyclic structures on carbohydrates structures (Figure 3.1) was described by Zemplen and co-workers,[131] the thiocyanic acid was generated *in situ* with unprotected sugars. In the D-gluco[131] and the D-fructo[132] series, the products were described as oxazolidine-2-thiones fused to pyrano skeletons of D-glucose and D-fructose.

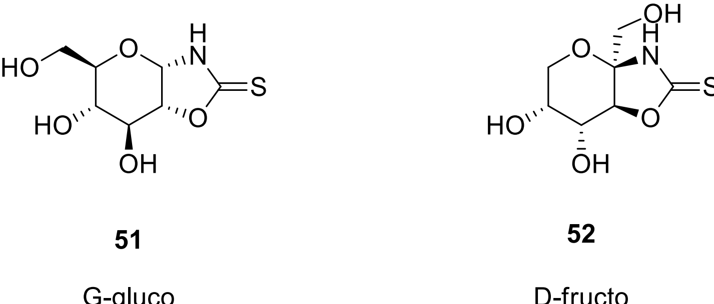


Figure 3.1 - Bicyclic strictures synthetised by Zemplen.

Bromund and co-workers,[133] have explored the same reaction in diverse aldose series (D-galacto, D-xylo, L-arabino). Similar bicyclic fused structures (OZT-pyrano backbone) were proposed (Figure 3.2).

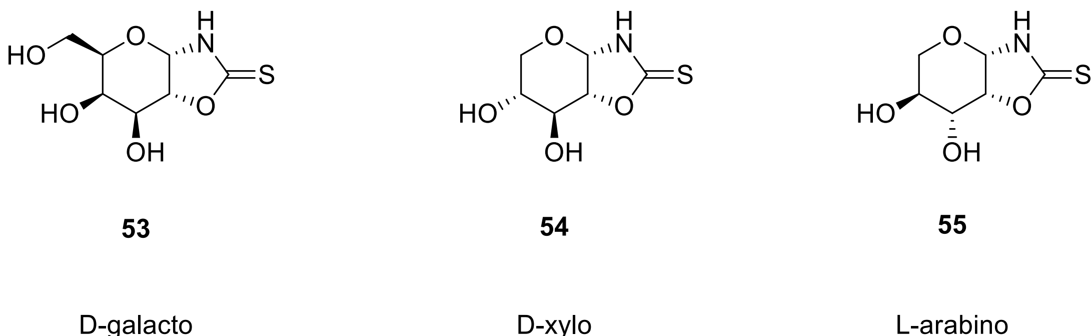


Figure 3.2 – Bicyclic strictures synthetised by Bromund.

The structural determination of those bicyclic compounds remained under discussion for some time, until Wickstrom and Wold[134] confirmed the formation of the fused bicyclic OZT-sugars and, demonstrated the furano form for aldoses and the pyrano forms for ketoses (Figure 3.3). The previously described results were confirmed by Jochims and co-workers,[135] who performed the first NMR analysis on OZTs.

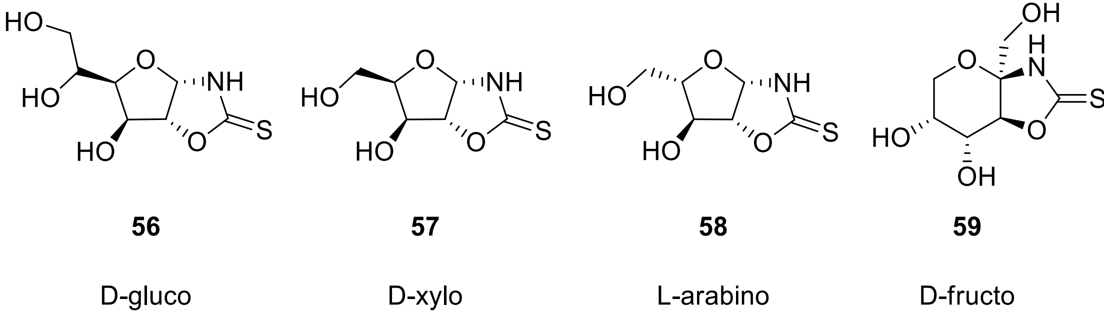


Figure 3.3 - Bicyclic strictures synthetised by Wickstrom and Wold.

In 1975, Ranganathan[124] used OZT derived from D-arabinofuranose as a starter to purine nucleosides. The fusion between OZT and D-xylofuranose was later described in 1986 by Gosselin[127] for the same purpose, and for the synthesis of α-and β- D-xylofuranosyl nucleosides.

The potential for condensation of aldoses with thiocyanic acid (generated in situ from potassium thiocyanate and hydrochloric acid) and the production in good yields of bicyclic furano compounds were shown. Almost nothing has been proposed about the mechanism. The reaction is the result of equilibrium between hemiacetal and aldehyde free form of the carbohydrate, which undergoes a nucleophilic addition of HSCN, followed by intramolecular addition of a hydroxyl function to a transient isothiocyanate to generate the OZT ring thermodynamically stable (Figure 3.4).

Figure 3.4 - Mechanism of OZT formation.

Ketoses should react following a similar pathway. Applying the same protocol to ketohexoses leads to more complex mixtures of open chain, cyclic and dehydrated products. Indeed, an important aspect of ketoses lies in the lack of chemical selectivity due to (1) the complexity of the tautomeric equilibrium, and (2) their susceptibility to form tertiary oxocarbenium ions under acidic conditions.[120] Variations on the OZT structures obtained from D-fructose, were published by Zemplen, Wickstrom and Wold and more recently by Grouiller. The first authors considered the fusion of OZT on a pyrano form of fructose, while Grouiller suggested the formation of a mixture of fused OZTs with β-pyrano and β-furano forms (Scheme 3.1).[128]

KSCN, HCl

4ºC, 8 weeks

60

61

62

D-frutose

Scheme 3.1- Grouiller suggestion of formation of OZTs.

In order to learn how aldoses and ketohexoses react with thiocyanic acid, the synthesis and reactivity of these bicyclic OZT-sugar systems has been studied. Girniene/Leconte and co-workers[130, 136] selected this method the only one leading directly to fused OZTs from deprotected carbohydrates.

Bicyclic OZT-sugar systems prepared by Girniene conditions[130] demonstrated that the geometries of the sugar ring were completely defined. A furano form was obtained, and the

anomeric configuration was controlled by the presence of the hydroxyl group in position C-2. Girniene's[130] results are presented in Scheme 3.2.

64	L-arabino	97%
65	D-arabino	90%
66	D-xylo	80%
67	D-ribo	70%

Scheme 3.2 – Girniene conditions and results.

In the case of ketohexoses, condensations are not so simple. So reacting those with HSCN, one can expect the formation of up to ten different thionocarbamates: fused and spiro bicycles on pyranose or furanose skeletons, as well as acyclic OXTs.[137]

The reaction of D-fructose and L-sorbose with thiocyanic acid in aqueous solution was studied by Girniene/Tatibouët and co-workers [113,138]. As expected, a complex mixture was obtained leading to difficult separations by column chromatography. According to Grouiller, the crude material was per-O-silylated (TBDMS), in order to facilitate isolation of the fused bicyclic thionocarbamates. For both ketose series, the same type of fused-furano thionocarbamate was isolated. Acid-catalyzed deprotection gave the deprotected OZTs in good yield (Scheme 3.3).

Scheme 3.3 - Girniene and co-workers studies.

Enhancing the regioselectivity in the OZT formation, i.e. reducing the number of isomers, Girmene and co-workers[113] have performed selective hydroxyl protections. As an example, the free ketoses were first protected with isopropylidene acetals and then the primary alcohol protected by benzylation or allylation. Acid-catalyzed hydrolysis of the isopropylidene groups, followed by condensation with HSCN produced efficiently the fused bicyclic OZTs. In all cases, a unique OZT isomer was isolated (Scheme 3.4).

60 D-frutose → 1) H_2SO_4/ acetone 2) R-Br, NaH, DMF → 72 → TFA/H_20 → 73 → KSCN, HCl 50ºC → 74

69 L-sorbose → 1) H_2SO_4/ acetone 2) R-Br, NaH, DMF → 75 → TFA/H_2O → 76 → KSCN, HCl 50ºC → 77

Scheme 3.4 - Girmene results of selective protection.

3.1.1.2 - Condensation of aldoses and ketoses with potassium cyanate

Similar structures have been obtained with 1,3-oxazolidin-2-ones instead of OZT by Lichtenthaler and co-workers[139] who demonstrated that reacting D-fructose with potassium cyanate gave four OZOs (one fused furano-structure and three spiro-structures).

Studies developed by Kovács[140,141] and co-workers report the reaction of free aldoses with potassium cyanate in water in the presence of weakly acidic buffers (NH_4Cl, NaH_2PO_4) yields OZOs. These transformations are made in D-allose, L-gulose, D-idose and D-altrose, for D-allose and D-idose no identifiable by-products were observed but for D-altrose, under the same conditions, a mixture of three isomeric cyclic carbamates besides unreacted D-altrose, separated by column chromatography, were obtained. For the L-gulose, under the same conditions, a complex mixture of four cyclic carbamates partially separated by column chromatography was obtained.

3.1.1.3 - Reactivty of thionocarbamates

Thionocarbamates display different functionality, offering diverse reactivities.[142,115] The different properties coud be explained by Pearson's hard– soft acid–base (HSAB) theory,[143] where the nitrogen atom reacts as a hard basic center while the sulfur atom shows a soft base character. This reactivity has been extensively investigated by Tatibouët[144,145,146,147,148]. and co-workers reagents of R-X.

3.1.1.4 - Selective S-benzylation

In order to understand more about the reactivity of the N and S-center, the alkylation reaction was also attempted on OZT.

Chemoselective S-alkylations were reported on some simple OZTs,[148] taking advantage of the smooth electrophilic character of various haloalkanes. Preferential alkylation at the sulfur atom

was achieved in good yields to form enantiopure S-alkylthiooxazolines. Davidson[149] and Meszaros[150] reported that reaction of chloromethane or *p*-chlorobenzyl chloride with saccharidic OZTs also lead to the corresponding 2-alkylsulfanyloxazolines.

Girniene[130] and co-workers applied the standard alkylation conditions – NaH then benzyl bromide in DMF - to the non-protected saccharidic OZT, obtaining a per-alkylated derivative. They hypothesized that under oxidizing conditions the benzylsulfanyl substituent might be converted into better leaving groups, thus facilitating further hydrolysis to the OZO.

The thio selective reaction with halides on OZTs was afforded, in basic medium, in order to produce 2-benzylsulfanyl-1,3-oxazoline derivatives (Scheme 3.5).

RO NH S O O **78** → BnBr, Et_3N, DCM, -5ºC, r.t., 12h → RO N SBn O O **79**

R=H, OTBDMS

Scheme 3.5 - Selective S-alkylation.

3.1.1.5 - Oxidation of the C-SBn bond

Considering the importance of oxazolidinones (OZOs) described in the literature, it appeared essential to explore the oxidative desulfurization of some OZTs synthesized in this chapter. Among various organic and inorganic reagents, *m*-CPBA demonstrated to be a good candidate to smoothly convert OZTs into OZOs.[151, 138]

Oxidative desulfurization is a type of transformation that can be achieved by direct or indirect procedures using a wide range of reagents and conditions. In the literature we can find directly desulfuration of thiocarbamate with hidrogen peroxide.[131, 152] Another method is used by Girniene and co-workers[113] by reacting 1-O-alkyl ketoses with potassium cyanate, which would procedure the desired products, but the yields observed were rather low and not reproducible. In the same publication they report the use of *m*-CPBA as oxidizing agent.

Another method of oxidative desulfurization has also been performed after preliminary S-alkylation, Girniene and co-workers[113] try the oxidation of S-benzylated forms with an excess of *m*-CPBA, the sulfur function would be oxidized to an unstable sulfone derivative. This intermediate should be sensitive to a nucleophilic attack of the remaining water in the medium, leading to formation of an OZO through expulsion of a sulfanyl moiety.

The oxidizing agent (*m*-CPBA) was chosen based on previous results obtained in our laboratory. The benzylsulfanyloxazolines were submitted to oxidation in DCM and the corresponding 1,3-oxazolidin-2-ones were obtained (Scheme 3.6).

RO SBn $NaHCO_3$, *m*-CPBA DCM, 0ºC, r.t., 12h RO NH O

79 **80**

R=H, OTBDMS

Scheme 3.6 - Oxidation of the C-SBn bond.

3.2 - Presentation and discussion of results

3.2.1 - OZTs fused on carbohydrate templates in pentose series

3.2.1.1 - Assays with D-ribo pentofuranose

With the objective of synthesizing new innovative and functional azide-carbohydrate derivatives, the synthesis of azides coupled to OZT and OZO carbohydrate derivatives was performed. Different approaches were realized either from a 5-azido-D-ribose **36** then introducing the OZT heterocycle or by inversing the approach incorporating the OZT to obtained derivative **67** then functionalized the 5th position through the iodo derivative **81** followed by the nucleophilic substitution to obtain tha azido compound **82** (Scheme 3.7). In both cases, the final yield was not very efficient.

Scheme 3.7 – Global scheme to obtain OZT D-ribose derivative **82**.

The formation of different compounds is confirmed by NMR. The results are presented in Table 3.1.

Table 3.1 - ^{1}H NMR/^{13}C NMR shift of the OZT derivative **82**.

σ (ppm) / Compound	CH_2-5 (^{1}H)	CH_2-5 (^{13}C)	C=S (^{13}C)
	3.36-3.46 (m, 2H)	60.2	190.0
	3.26-3.33 (m, 1H) 3.53-3-57 (m, 1H')	6.5	189.5
	3.46 (dd, 1H)	51.6	192.2

After this series of reactions being held, it could be verified the existence of degradation of compound **82**. Due to bad yields obtained in the azidation, it was decided to protect the hydroxyl group in C-3, because it is foreseen that this hydroxyl group might participate in the degradation observed during the synthesis compound **82**. Thus, a new sequence was developed, Scheme 3.8, through protecting the hydroxyl function in C-3.

TBDMSCl, imidazole, DCM

r.t., 12h, 59%

81 → **83**

NaN_3, DMF, 70ºC, 3h, 54%

84a + **84b**

Scheme 3.8 – Global scheme to obtain OXT D-ribose derivative **84a** and **84b**.

The confirmation of obtained results can be found in Table 3.2.

Table 3.2 - ^{1}H NMR/^{13}C shift of the OXT derivative **84a** and **84b**.

σ (ppm) / Compound	CH_2-5 (^{1}H)	TBDMS (1H)	CH_2-5 (^{13}C)	C=S (^{13}C)	TBDMS (^{13}C)
	3.26-3.33 (m, 1H), 3.53-3-57 (m, 1H')	-	6.5	189.5	-
	3.30-3.40 (m, 1H), 3.56-3.52 (m, 1H')	0.25 (s, 6H) 1.00 (s, 9H)	5.2	192.1	-4.6, -4.4 and Cq at 18.9

+	3.34 (d, 1H), 3.51 (dd, 1H’)	0.02 (s, 6H), 0.11 (s, 6H), 0.85 (s, 9H), 0.87 (s, 9H)	52.6 53.3	C=N at 163.3 C=S at 178.9	-5.0, -4.6, -4.4, Cq at 18.0 and 18.1

With this procedure it could be observed that the compound obtained was not the one expected. The conditions allowed the ring opening and the formation of a 1,3-oxazoline-2-thione in 54% yields. As the objective was to obtain an azide connected to a 1,3-oxazolidine-2-thione fused to the carbohydrate template, the protection of the sulfur group has been introduced in order to prevent the opening of the furanose ring (Scheme 3.9).

Scheme 3.9 - Global scheme to obtain OZO D-ribose derivative **88**.

We have compared two sequences to access the compound **86**. Obviously it is necessary to protect the alcohol function and the oxazolidinethione function. The best approach was to perform the alkylation of the sulfur then the silylation of the free hydroxyl, leading to a global yield of 80%. The alternative sequence, where the hydroxyl group was first protected and then the sulfur, the global yield was reduced to 58%. In the future, benzylation will be done before silylation in order to improve the global yield of the synthesis procedure. The formation of compounds was confirmed by NMR (Table 3.3 and Table 3.4).

Table 3.3 - ^{1}H NMR shift of the OZO derivative **88**.

σ (ppm) / **Compound**	**CH_2-5 (^{1}H)**	**OTBDMS (^{1}H)**	**Bn (^{1}H)**
	3.30-3.40 (m, 1H), 3.56-3.62 (m, 1H')	0.25 (s, 6H), 1.00 (s, 9H)	-
	3.31-3.38 (m, 1H), 3.59 (dd, 1H')	-	4.36 (q, 2H) and 7.42-7.46 (m, 5H)
	3.30-3.36 (m, 1H), 3.56 (dd, 1H')	0.22 (s, 6H), 0.97 (s, 9H)	4.32 (s, 2H) and 7.31-7.38 (m, 3H), 7.42-7.46 (m, 2H)
	3.31-3.38 (m, 1H), 3.64 (dd, 1H')	0.20 (s, 6H), 0.97 (s, 9H)	4.33 (s, 2H) and 7.29-7.38 (m, 3H), 7.42-7.46 (m, 2H)
	3.32-3.39 (m, 1H), 3.69 (dd, 1H')	0.20 (s, 6H), 0.97 (s, 9H)	-

Table 3.4 - ^{13}C NMR shift of the OZO derivative **88**.

σ (ppm) / **Compound**	**CH_2-5 (^{13}C)**	**OTBDMS (^{13}C)**	**Bn (^{13}C)**	**C=S (^{13}C)**	**C=N (^{13}C)**	**C=O (^{13}C)**
	5.2	-4.4, -4.4, Cq at 18.9, 26.2	-	192.1	-	-

	4.9	-	36.8, 128.7, 129.7, 130.0 and Cq at 138.0	-	173.2	-
	5.6	-4.5, -4.3, Cq at 18.8, 26.3	36.7, 128.7, 129.7, 129.9 and Cq at 137.9	-	172.9	-
	51.2	-4.9, -4.5, Cq at 18.9, 26.2	36.7, 128.8, 129.7, 130.0 and Cq at 137.9	-	173.1	-
	51.2	-5.0, -4.6, Cq at 18.9, 26.2	-	-	-	160.9

Looking to the best sequence to obtain the oxazolidinone **90**, two approaches has been studied. Scheme 3.10). The TBDMS removal of compound **88** showed some reluctance thus, an alternative pathway was designed from the benzylsulfanyloxazolidine **85**. Both sequence showed similar results on the last steps of deprotection with low yields of 22 and 28% yields.

85 → (NaN_3, DMF, 80ºC, 3h, 92%) → **89** → ($NaHCO_3$, *m*-CPBA, DCM, 0ºC, r.t., 12h, 22%) → **90**

88 → (TBAF, THF, 0ºC, r.t., 12h, 28%) → **90**

Scheme 3.10 - Global scheme to obtain OZO D-ribose derivative **90**.

Thus we have verified that no degradation occurred when the nucleophilic replacement took place with the alkylsulfanyloxazolidine. The OZO **90** was obtained by oxydation of the connection C-SBn or by removal of the protecting group TBDMS of the previously synthesized

OZO **88**. The yields were low, this could be explained by the difficult purification of the product.The analysis of compounds could be found in Table 3.5 and Table 3.6.

Table 3.5 - ^{1}H NMR shift of the OZO derivative **90**.

σ (ppm) / Compound	CH_2-5 (^{1}H)	Bn (^{1}H)
	3.37(dd, 1H) 3.66(dd,1H')	4.30 (q, 2H) 7.24-7.39 (m, 5H)
	3.38 (dd, 1H) 3.65 (dd, 1H')	-

Table 3.6 ^{1}C NMR shift of the OZO derivative **90**.

σ (ppm) / Compound	CH_2-5 (^{13}C)	Bn (^{13}C)	C=N (^{13}C)	C=O (^{13}C)
	50.2	36.5, 127.8, 128.7, 128,9, Cq at 136.1	170.8	-
	51.7	-	-	160.6

3.2.1.2 - Assays with D-xylo pentofuranose

After developing the synthesis of 1,3-oxazolidine-2-thiones, 2-alkylsulfanyl-1,3-oxazolidines and 1,3-oxazolidin-2-one on a D-ribose template, we have applied the same sequence of reaction to other pentoses, such as D-xylose. We have taken into account the developed knowledge while performing the synthesis of these compounds on the D-ribose template. We

have performed the synthesis applying the more advantageous conditions in order to obtain a better global yield (Scheme 3.11).

Scheme 3.11 - Global scheme to obtain OZO D-xylose derivative **95**.

The obtained structures were confirmed by NMR (Table 3.7 and Table 3.8).

Table 3.7 - ^{1}H NMR shift of the OZO derivative **95**.

σ (ppm) / Compound	CH_2-5 (^{1}H)	Bn (^{1}H)
	2.66-2.77 (m, 2H)	-
	3.22-3.32 (m, 2H)	-
	3.23-3.35 (m, 2H)	4.29 (q, 2H), 7.28-7.40 (m, 5H)

	3.58-3.66 (m, 2H)	4.24-4.32 (m, 2H), 7.28-7.38 (m, 5H)
	3.49-3.58 (m, 2H)	-

Table 3.8 - ^{1}H NMR shift of the OZO derivative **95**.

σ (ppm) / **Compound**	**CH_2-5 (^{13}C)**	**Bn (^{13}C)**	**C=S (^{13}C)**	**C=N (^{13}C)**	**C=O (^{13}C)**
	58.5	-	188.5	-	
	0.0	-	188.4	-	
	-2.1	36.6, 128.0, 128.9, 129.1 and Cq at 136.1	-	170.4	-
	48.9	36.5, 128.0, 128.8, 129.1 and Cq at 136.1		170.5	-
	50.4	-		-	160.1

Further, using unprotected pentose entity in C-3, the D-xylose derived OZO **95** was obtained with a global yield of 72%, which is quite satisfactory, taking into account that the hydroxyl

group in C-3 difficult the isolation of the product.In order to study the reactivity, later, we are going to synthesize the OZO derivative **100** with the hydroxyl group in C-3 protected with TBDMS group (Scheme 3.12).

Scheme 3.12 - Global scheme to obtain OZO D-xylose derivative **98** and **100**.

The obtention of the compounds was confirmed by NMR (Table 3.9 and Table 3.10).

Table 3.9 – ^{1}H NMR shift of the OZO derivatives **98** and **100**.

σ (ppm) / Compound	CH_2-5 (^{1}H)	OTBDMS (^{1}H)	Bn (^{1}H)
	3.04-3.10 (m, 2H)	0.02 (s, 6H), 0.74 (s, 9H)	4.08-4.16 (m, 2H), 7.08-7.21 (m, 5H)
	3.27 (dd, 1H), 3.44-3.48 (m, 1H')	0.01 (s, 6H), 0.76 (s, 9H)	4.15 (q, 2H), 7.11-7.24 (m, 5H)
	3.28 (dd), 3.47 (dd)	0.01 (s, 6H), 0.78 (s, 9H)	-

	3.02-3.09 (m, 2H)	0.002 (s, 6H), 0.73 (s, 9H)	-

Table 3.10 – ^{13}C NMR shift of the OZO derivatives **98** and **100**.

σ (ppm) / Compound	**CH$_2$-5 (^{13}C)**	**OTBDMS (^{13}C)**	**Bn (^{13}C)**	**C=N (^{13}C)**	**C=O (^{13}C)**
	-1.7	-4.5, -4.4, Cq at 18.2, 25.9	36.7, 127.9, 128.8, 129.4, Cq at 136.2	170.0	-
	49.0	-5.1, -4.7, Cq at 18.2, 25.8	36.7, 127.9, 128.8, 129.1, Cq at 136.2	169.8	-
	49.3	-5.2, -4.8, Cq at 18.1, 25.7	-	-	157.7
	-1.8	-4.6, -4.5, Cq at 18.1	-	-	157.7

Attempting the preservation of the 1,3-oxazolidine-2-thione function, the hydroxyl in C-3 and the NH with the benzoyl group were protected. This way the insertion of the azide in C-5 might have been possible. The nucleophilic substitution of the iodo derivative **101** was not successful; we have observed the total degradation of the desired compound. However it can be confirmed the protection with 2 benzoyl groups by observation on the NMR spectrum, but the azidation attempts to total degradation of the product (Scheme 3.13).

Scheme 3.13 – Synthesis D-xylose derivative **101**.

3.2.1.3 - Assays with D-arabino pentofuranose

After the good results obtained with the D-xylose, we moved to an other pentose. Similar sequences were apply on D-arabinose (Scheme 3.14).

Scheme 3.14 – Global scheme to obtain OZO D-arabinose derivative **108**.

Insertion of the azido function was efficient following the sequence of iodination, selective S-benzylation followed by nucleophilic substitution, the last step being the oxidation to obtain the 1,3-oxazolidin-2-one **108**. The sequence starting with the D-arabinose lead to the OZO **108** in 5 steps and 80% overall yield. The structure of the different compounds was confirmed by NMR (Table 3.11 and Table 3.12).

Table 3.11 - ^{1}H NMR shift of the OZO derivative **108**.

σ (ppm) / Compound	CH_2-5 (^{1}H)	Bn (^{1}H)
	3.16-3.29 (m, 2H)	-
	3.12-3.22 (m, 2H)	-
	2.88 (dd, 1H), 3.09 (dd, 1H')	4.27 (q, 2H), 7.25-7.39 (m, 5H)
	3.14 (dd, 1H), 3.25 (dd, 1H')	4.28 (s, 2H), 7.26-7.39 (m, 5H)
	3.33-3.41 (m, 2H)	-

Table 3.12 - ^{13}C NMR shift of the OZO derivative **108**.

σ (ppm) / Compound	CH_2-5 (^{13}C)	Bn (^{13}C)	C=S (^{13}C)	C=N (^{13}C)	C=O (^{13}C)
	60.9	-	188.2	-	-
	6.2	-	188.1	-	-

	5.1	36.5, 128.0, 128.8, 129.2, Cq at 136.2	-	170.3	-
	51.9	36.5, 128.0, 128.8, 129.2, Cq at 136.2	-	170.3	-
	53.4	-	-	-	159.8

Attempts to introduce the azido function onto the iodo-OZT **92** did not succeed. Even in the previously explored conditions, the opening of the ring and formation of the oxazolinethione of **105** into **108**, did not occur (Scheme 3.15).

TBDMSCl, imidazole, DMF; r.t., 12h, 44% — NaN_3, DMF; 70ºC, 2h, 0%

104 **105** **108**

Scheme 3.15 - Synthesis D-arabinose derivative **108**.

3.2.1.4 - Assays with L-sorbose derivative

Starting with an existing compound **109** in the laboratory, derived from L-sorbofuranose, we have applied a similar synthesis to obtain the OZO derivative **111** in a global yield of 78% (Scheme 3.16).

BnBr, Et_3N, DCM; -5ºC, r.t., 2h, 67% — $NaHCO_3$, *m*-CPBA, DCM; 0ºC, r.t., 12h, 88%

109 **110** **111**

Scheme 3.16 - Global scheme to obtain OZO L-sorbose derivative **111**.

The structure of the compounds was confirmed by NMR (Table 3.13).

Table 3.13 – 1H NMR/^{13}C NMR shift of the OZO derivative **111**.

σ (ppm) / **Compound**	**SBn** (^{1}**H**)	**N=S** (^{13}**C**)	**C=O** (^{13}**C**)
	4.27 (s, 2H)	170.5	-
	-	-	159.7

To push forward the study on the azido-OZO derivative **111**, it was necessary to prepare again the molecule. Starting from the 1-*O*-benzyl-L-sorbose **112** (Scheme 3.17),[113] we have applied the same approaches to obtain the azido OZO **119**.

Scheme 3.17 - Global scheme to obtain OZO L-sorbose derivative **119**.

The obtention of the compounds was confirmed by NMR (Table 3.14 and Table 3.15). Silylation of the iodinated derivatives **114** and **116** appeared very difficult to realise, only poor yields were observed respectively of 6 and 4%. Indeed, it is difficult to give a reason for these poor yields considering the good yields obtained with the azido derivative **110** which gave the sillylated molecule **118** in 76%.

Table 3.14 – ^{1}H NMR shift of the OZO derivative **119**.

Compound / **σ (ppm)**	**CH_2-6** (**[1]H**)	**SBn** (**[1]H**)	**OTBDMS** (**[1]H**)
	3.33-3.48 (m, 2H)	-	-
	3.50 (d, 1H) 3.63 (d, 1H)	-	-
	3.23-3.30 (m, 2H)	-	-
	3.24-3.31 (m, 2H)	4.25 (s, 2H), 7.21-7.44 (m, 5H)	-
	3.32 (dd, 1H), 3.49 (dd, 1H’)	4.44-4.55 (m, 2H), 7.15- 7.29 (m, 5 H).	0.04 (s, 6H), 0.77 (s, 9H)
	3.49-3.54 (m, 2H)	4.24 (s, 2H), 7.22-7.37 (m, 5H)	-
	3.32 (dd, 1H), 3.49 (dd, 1H)	4.41-4.59 (m, 2H), 7.15-7.29 (m, 5H)	0.02 (s, 6H) 0.77 (s, 9H)

	3.28 (dd, 1H), 3.45 (dd, 1H’)	-	0.00 (s, 6H), 0.76 (s, 9H)

Table 3.15 - ^{13}C NMR shift of the OZO derivative **119**.

σ (ppm) / **Compound**	**CH_2-6 (^{13}C)**	**CH_2 of SBn (^{13}C)**	**OTBDMS (^{13}C)**	**C=S (^{13}C)**	**C=N (^{13}C**	**C=O (^{13}C)**
	66.2	-	-	-	-	-
	58.8	-	-	188.4	-	-
	-2.7	-	-	190.0	-	-
	-2.0	36.6	-	-	170.7	-
	-1.2	36.7	-5.2, -4.6, Cq at 18.1, 25.7	-	169.0	-
	48.9	36.5	-	-	170.4	-

OBn, O, N, SBn, O, N_3, TBDMSO	49.1	36.7	-5.2, -4.6, Cq at 18.1, 25.7	-	169.0	-
OBn, H, N, O, O, O, N_3, TBDMSO	49.2	-	-5.2, -4.7, Cq at 18.0, 25.7	-	-	157.0

3.3 - Conclusion

✓ Some variability in S-benzylation and silylation yields can be observed and no apparent motif justifies this difference of reactivity in D-ribo, D-xylo, D-arabino and L-sorbo templates.

✓ It can be observed that it is more efficient performing silylation after benzylation in D-ribose template. There isn't any apparent reason for this result as the yield should have been similar, regardless the first protection chosen (Bn or TBDMS).

✓ It can be observed that it is more efficient performing benzylation after silylation in D-xylose template.

✓ It can be observed that it is necessary to perform the silylation after benzylation in L-sorbose template. Silylation made before benzylation leads silylated compound in low yield.

✓ It can be concluded that selective protection of sulfur is very important as it prevents degradation/opening of the carbohydrate ring when we perform nucleophilic substitution of iodine by the azide.

✓ The chemical shifts for the quaternary sp^2 carbon atom at position 2 of the five-membered heterocycle varied from roughly 190 ppm (N−C=S in 1,3-oxazolidine-2-thione) to approximately 170 ppm (N=C−SBn in 2-benzylsulfanyl-1,3-oxazoline) and to approximately 160 ppm (N-C=O in 1,3-oxazolidin-2-one).

✓ The oxidation of C-SBn group with *m*-CPBA is more efficient when performed exclusively with protected molecules in D-ribose and D-xylose templates. The free hydroxyl in C-3 of the synthesized 2-benzylsulfanyl-1,3-oxazolinein this templates lowers the yield of the reaction, as it makes the treatment of the reaction more difficult, which leads to product loss in the treatment and isolation process. Due to chemical nature of *m*-CPBA it is necessary to use neutralizations, which leads to loss of product to the aqueous phase when the product has a free hydroxyl in C-3.

✓ Mainly, the insertion of an azido group onto the bicyclic system could be perform efficiently on the 1,3-oxazolidin-2-one or on the benzylsulfanyloxazoline while with the oxazolidinethione, the yields were rather poor or lead to the opening of the furanose ring. Nonetheless we have been able to set up a method to introduce an azido function on a bicyclic heterocyclic system incorporating the OZO and OZT rings and thus ready to explore the chemistry of the azido function.

✓ L-sorbose is the template with better overall yields (Table 3.16). The most problematic step is the oxidation of C-SBN bond of unprotected OZO in D-ribose template.

Table 3.16 – Global yields from OZOs.

Template	1,3-oxazolidine-2-thione (OZT)	2-alkylsulfanyl-1,3-oxazoline	1,3-oxazolidin-2-one (OZO)	Global yield
D-ribose	84%	73%	22% unprotected in C3	60%
			80% protected in C3	79%
D-xylose	74%	71%	60% unprotected in C3	68%
			83% protected in C3	76%
D-arabinose	92%	89%	58% unprotected in C3	80%
1-O-benzyl-L-sorbose	92%	89%	88% unprotected in C4	90%
			58% protected in C4	80%

Chapter 4 – Synthesis of iminosugar derivatives

4.1 - General introduction

Since the discovery of Nojirimicin, a glucosidase inhibitor, the polyhydroxy piperidines, also known as iminougars (the oxygen atom of the heterocyclic ring of a carbohydrate is replaced by a nitrogen atom) have received considerable attention from the scientific community and have been targeted with inumerous synthesis strategies over the last years. The development of efficient synthesis of natural iminosugars and its analogues present a considerable importance due to its potential as glucosidase inhibitors. Given the broad range of biological and pathological processes in which glycosidases are involved, from the catabolism of sugars to the biosynthesis of the complex oligosaccharide chains in glycoproteins and glycolipids, specific inhibitors of these enzymes bear strong potential for the development of new pharmaceuticals. Examples include the treatment of viral infections,[153,154] such as human immunodeficiency virus (HIV), human hepatitis C (HCV) or dengue virus, cancer,[155,156,157] diabetes,[158,159,160] tuberculosis,[161,162] and lysosomal storage diseases (LSDs),[163,164,165,166,167,168] which has strongly stimulated research in this area of glycobiology.[169,170] There are many available iminosugars but the problem is the lack of specificity. [171]

Two first iminosugar based drugs have been released on the market. In 1996, Glyset™ for handling with type II diabetes complications and in 2003 Zavesca™ for the treatment of Gaucher's disease, a lysosomal storage disorder.[172]

4.1.1 - Synthesis of imosugars fused with an OZO ring

The piperidine-type iminosugar, nojirimycin **120** and its 1-deoxy analogue **121**, which have the same hydroxylation pattern as D-glucose, are potent inhibitors of α- and ß-glucosidases.[173] The related bicyclic indolizidine-type iminosugar (+)-castanospermine **122** displays higher enzyme specificity when compared to iminosugars **120** or **121**, and this has been ascribed to the conformational restriction imposed by the rigidity of the system, particularly at the bond equivalent to C(5)–C(6) in hexopyranosides (Figure 4.1). Nevertheless, the anomeric specificity remains poor, which is not surprising when considering the absence of a pseudoanomeric substituent with a precise configuration at the glycosidic site.

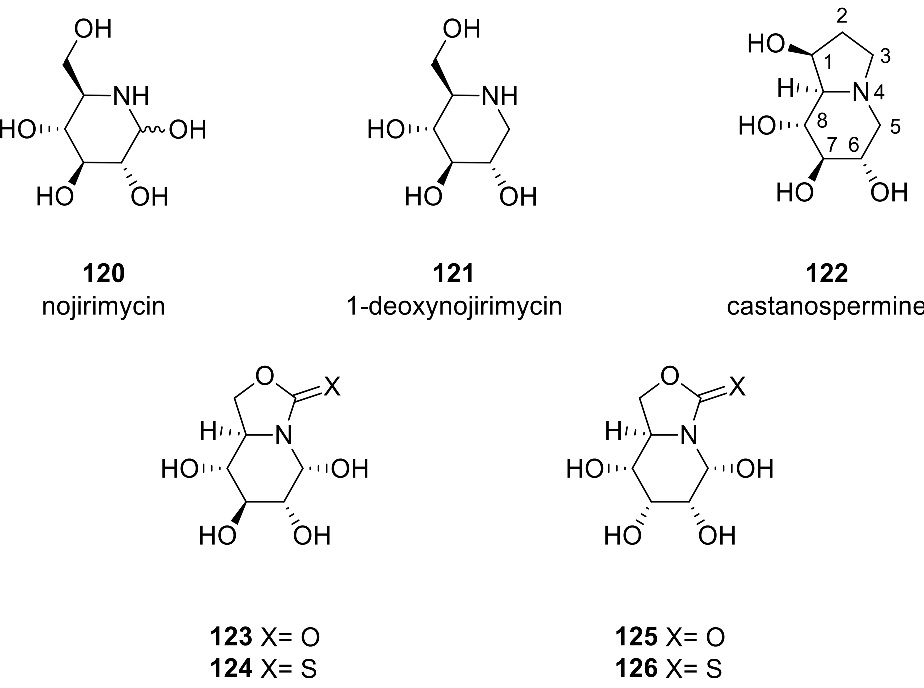


Figure 4.1 – Piperidine-type iminosugars

Normally, placing an oxygen substituent with a clearly defined orientation at the pseudoanomeric position in glycomimetic structures should increase the anomeric selectivity towards glycosidases by matching the stereocomplementarity of the cleavable aglyconic oxygen atom in the natural substrate with the crucial bilateral carboxylic groups in the active site of the enzyme.[174,175,176,177] The instability of the hemiaminal functional group prevents implementation of this strategy in classical iminosugars. Replacing the sp^3 nitrogen atom with a pseudoamide-type nitrogen (with substantial sp^2 character) has been shown to dramatically enhance the stability at N-C-O segments by virtue of the generalized anomeric effect, simultaneously promoting the axial orientation of pseudoanomeric groups even in the case of reducing hemiaminal-type derivatives.[171] For instance, the bicyclic carbamate and thiocarbamate nojirimycin derivatives **122** and **123** were found exclusively in the α-configuration in water solution.[178] Interestingly, they behaved as very selective inhibitors of α-glucosidases. Structure-activity studies indicated that the endocyclic oxygen of the thiocarbamate ring was critical for inhibitory activity.[179] Modifications at the hydroxyl groups equivalent to OH-2 and OH-4 in D-glucopyranose also abolished enzyme binding.[179] The α-glucosidase inhibition activity was significantly decreased after modification at OH-3, e.g., epimerization to the d-allo-configured bicyclic (thio) carbamates **125** and **126**, but a higher enzyme selectivity was also observed. Further results have shown that modifications at the sp^2-iminosugar framework[180,181,182,183,184,185] and the incorporation of substituents at selected positions[186,187] offers unprecedented opportunities to control the affinity and selectivity towards glycosidases, leading to the identification of compounds with great potential for anticancer [188] and pharmacological chaperone therapies.[189,190,191,192]

Modifications at the hydroxyl groups equivalent to OH-2 and OH-4 in D-glucopyranose also abolished enzyme binding.[179] The α-glucosidase inhibition activity was significantly decreased after modification at OH-3, e.g., epimerization to the D-allo-configured bicyclic (thio)carbamates **125** and **126**, but a higher enzyme selectivity was also observed. Further results have shown that modifications at the sp^2- iminosugar framework[193,194,195,196,197,198] and the incorporation of substituents at selected positions[199,200] offers unprecedented opportunities to control the affinity and selectivity.

Structural studies on sp^2-iminosugar: glycosidase complexes have shown that the piperidine ring of the bicyclic core is significantly distorted from its initial chair conformation after binding at the active site.[201,202] Flexibility at this region seems to be an important aspect.[203]

Silva and co-workers[204] describe a retro-synthesis of bicyclic iminosugars. Due to the experience of Silva in oxazole-2(3H)-thione (OXT) motif synthesization,[144] they have performed the synthesis of a new class of castanospermine analogues in which the five-membered ring is replaced by an OXT. A retrosynthetic analysis based on previous work by Victor Pérez[178] and co-workers presupposes that the bicyclic framework of iminosugars of type **127** and **128** can be built up through intramolecular nucleophilic addition of the nitrogen atom of five-membered ring (thio)carbamates with pseudo-*C*-nucleoside structure **131** and **132**, to the masked carbonyl in aldose precursors (Scheme 4.1).

127 R= H
128 R= Bn

129 R= H
130 R= Bn

131 R= H
132 R= Bn

Scheme 4.1 - Retrosynthetic analysis for the target OXT-piperidine bicyclic.

The method consisted in the formation of a diol at one extremity of a D-gluco- or D-allofuranose derivatives (which were obtained starting with diisopropylidene glucose following classical carbohydrate protocols). The pseudo-*C*-nucleoside **135** and **136** were obtained from the oxidation of the hydroxyl in C-5 using *N*-bromosuccinimide and later OXT formation from standard conditions (KSCN, EtOH, HCl). The feasibility of the intramolecular nucleophilic addition of the nitrogen atom of these pseudo-*C*-nucleoside was then investigated by Silva[204] and co-workers. Acid-catalysed hydrolysis of the anomeric acetal protecting group led the bicyclic structures (Scheme 4.2). The reaction was performed in D-ribo and D-xylo template derivatives.

Scheme 4.2 – Synthesis of OXT-piperidine bicyclic.

A similar compound was prepared earlier by C. Ortiz-Mellet using 5-amino-5-deoxy-1,2-*O*-isopropylidene-3-0-benxyl-α-D-glucofuranose **139**, by thiocarbonylation they have introduced an OZT heterocycle. Subsequent removal of the anomeric isopropyliden by acid hydrolysis yields the potent glycosidase inhibitor **141** (Scheme 4.3).

Scheme 4.3 - Scheme for the synthesis of OZT-piperidine bicyclic.

Belfita[184] and co-workers describes the synthesis of sulfamide-type indolizidines, a bicyclic iminosugar composed of a sulphate unit. The general synthetic strategy implemented to build the 2-aza-3,3-dioxo-3-thiaindolizidine skeleton relies on the ability of the carbonyl group of a monosaccharide in its open-chain aldehyde (Scheme 4.4) form to act as an electrophile against a pseudoamide nitrogen atom located at 1,5-relative position. The hydroxylation profile in the final compounds **144** and **145** matches the targeted D-gluco- and D-manno- configurations.

Scheme 4.4 - Scheme for the preparation of sulfamide-type castanospermine analogues.

The approach developed by the authors followed a multistep procedure were the reduction of an azido derivative by Staudinger conditions afford a 5-amino-5-deoxy derivative, wich was transformed into Boc-protected cyclic sulfamide by treatment with a Burgess-type reagent. Removeral of the protecting groups, followed by piperidine rearrangement afforded the desired bicyclic sulfamide indolizidines (Scheme 4.5).

Scheme 4.5 – Scheme for synthesis of sulfamide-type indolizidine.

4.1.1.1 - Staudinger reduction

Azides may be converted to amines by hydrogenation, but another possibility is the Staudinger reaction, which is a very mild azide reduction. As there are a variety of methods for preparing azides readily, the Staudinger reaction makes it possible to use -N_3 as an -NH_2 synthon (Figure 4.2).[205]

Figure 4.2 - Staudinger reaction.

Mechanism of the Staudinger reaction:

Triphenylphosphine reacts with the azide to generate a phosphazide, which loses N_2 to form an iminophosphorane. Aqueous work up leads to the amine and the very stable phosphine oxide (Figure 4.3).[206,207]

Figure 4.3 - Mechanism of the Staudinger reaction.

Based on literature a retro-synthesis scheme (Scheme 4.6) may be prepared where the reduction of an azido sugar to amino sugar by Staudinger reaction and subsequent heterocyclic ring opening, leads, after rearrangement, to cyclization of the compound originating a piperidine.

150 X= S
151 X= O

152 X= S
153 X= O

154 X= S
155 X= O

156 X= S
157 X= O

Scheme 4.6 - Retrosynthesis of piperidines.

In this chapter we describe the preparation of iminosugars fused with an oxazolidinone ring. The development of a new methodology for synthesis of innovative iminosugars, allows the access to a new class of iminosugars: OZO fused iminosugars. These new compounds are highly promissing as they are potential glucusidases inhibitors.

4.1.2 – Synthesis of lactams

Ever since the discovery of iminosugars as potent glycosidase inhibitors, they have attracted considerable interest for their impact in medicinal chemistry, glycobiology and organic synthesis. On the organic synthesis point of view, functionalization of iminosugars became an important technique as it allows obtaining iminosugar derivatives with potential biological activity.

Several hundred of them have been synthesized to date by a broad variety of approaches based mainly on ring-closing reactions, such as intramolecular reductive amination,[208,209,210,211] amination of C=C bonds,[212,213] or intramolecular nucleophilic amination.[214]

As an example, Dötz and co-workers[215] report the synthesis of a lactam, by convertion of D-ribono-1,4-lactone in acetal compound **39**. This acetal was converted quantitatively to the

tosylate compound and then treated with sodium azide in DMF to give the azido lactone. Hydrogenation in the presence of 6 mol% palladium on charcoal give the desired lactam **158** (Scheme 4.7).

Scheme 4.7 – Global synthesis of lactam **158**.

4.1.2.1 - Alkynyl lactams

The synthesis of iminosugars may be found in literature. These iminosugars have in their structure an N-Azide terminal or an N-alkynyl terminal. The insertion of these groups allows its functionalization and later application on click chemistry either as 1,3-dipole or either as dipolarophile, respectively.

Diot and co-workers[216] report the synthesis of a series of mono-, di-, and trivalent iminosugars based in alkynyl-armed oligo (ethylene glycol) scaffolds and N-substituted deoxynojirimycin (DNJ) epitopes/azide-functionalized 1-DNJ derivatives by click chemistry.

Senthilkumar and co-workers[217] reporte the synthesis of N-alkylated iminosugars. Stereoselective arylation of the *in situ* generated iminium ions, derived from tosylate D-ribose derivative using various amines, with resorcinol resulted in the isolation of the corresponding iminosugar-β-C-glycosides in very good yields, including an alkynyl-iminosugar.

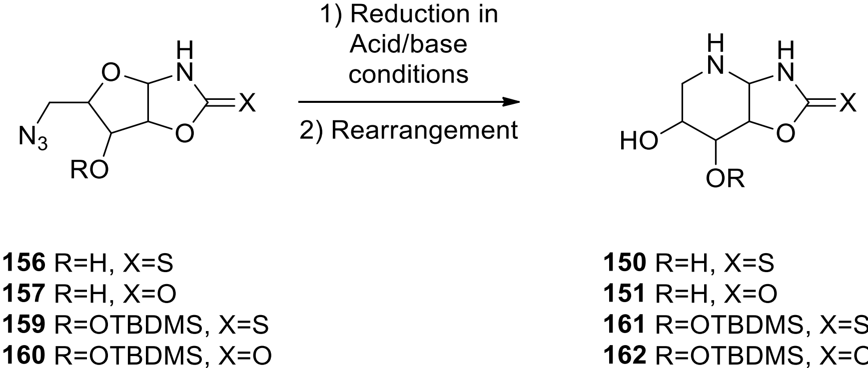
The insertion of the alkyne group by using propargyl bromide allows the introduction of a side chain on the molecule incorporating a triple bond, this approach will be described in the following chapter.

4.2 - Presentation and discussion of results

4.2.1 - Iminosugars fused with an OZO ring

With the previously synthesized OZTs and OZOs, we are going to synthesize a new class of iminosugars. We are also going to explore the reactivity of oxazolidinethiones, alkylsulfanyloxazolidines and oxazolidinones.

In this chapter will be performed the synthesis of iminosugars starting from oxazolidinethione, alkylsulfanyloxazolines and oxazolidinones synthesized in the previous chapter. This way, it is possible to study the reactivity of sulfur and oxygen, both present in position 2 of the heterocyclic ring, and check its behavior when faced with the same conditions (Scheme 4.8). It was considered performing the synthesis of the iminosugars by two distinct processes, reduction using acid conditions that promove the sugar heterocyclic ring opening and subsequent cyclization in the nitrogen atom or by performing reduction using basic conditions in order to promove the sugar heterocyclic ring opening and subsequent cyclization in the nitrogen atom.



Scheme 4.8 - Methode applyed for the synthesis of iminosugars

4.2.1.1 - With D-ribose template

With the sinthesized azides from D-Ribose frame we are going to test the best method to perform the reduction followed by opening and rearrangement in order to cyclize the nitrogen atom, this way it is possible to obtain iminosugars connected to a heterocyclic ring with two different heteroatoms.

Conditions presented in Scheme 4.9 and Table 4.1 were applied to sinthesize the iminosugars.

87 → (Ph_3P, THF/H_2O, r.t., 12h, 86%) → 163 → (Benzyl chloroformate, Et_3N, DMAP, DCM, 0ºC, r.t., 1h, 98%) → 164 –X→ 165

Scheme 4.9 - Aproach for the synthesis of iminosugars fused with benzylsulfanyloxazoline ring.

Table 4.1 – Experimental conditions used for synthesis of iminosugars fused with benzylsulfanyloxazoline ring..

Entry	Reagent.	Drying Agent	Solvente	Time	Temperature	Results
1	BF_3Et_2O 0.1 eq	M.S 4 Å	DCM	2h	-20ºC to r.t.	No reaction
2	BF_3Et_2O 1 eq	M.S 4 Å	DCM	2h	-20ºC to r.t.	No reaction
3	TMSOTf 1 eq.	M.S 4 Å	DCM	3h	-20 to r.t.	No reaction

By applying these 3 different conditions it wasn't possible to obtain the expected iminosugar. The ring opening attempt using Lewis acids did not work. The application of this conditions wasn't effective, other experimental conditions are going to be tested in order to obtain the iminosugars. Based on this result was tested the ring opening through reduction following the usage of a base.

Triphenilphosfine was chosen to act as reductor agent, the reactivity of different compounds was tested, in order to understand the mechanism involved in this reaction (Scheme 4.10).

Scheme 4.10 – Reactivity of OZT and alkylsulfanyloxazoline D-ribose derivatives.

Triphenylphosphine was used as reducing agent, allowing the reduction of the azide. It was verified the obtainance of aminosugars from azido-sugars. It was also tested the reduction with triphenylphosphine in OZTs and in alkylsulfanyloxazolines, next step is to test the same reduction method in OZOs (Scheme 4.11).

Scheme 4.11 - Reactivity of OZO D-ribose derivative **88**.

After being analyzed by NMR, the 3 different spots obtained are in fact 3 different compounds. These compounds are very difficult to separate through column chromatography. This is due to the similarity of the obtained compounds, through the NMR spectrums we can conclude that we have 2 iminosugars and one aminosugar (product of reduction). The main difference is in the C-1 chemical schift variations determine by COSY and HSQC experimetns. These C-1 values are close to 90 ppm for the azido-sugars and aminosugars and changed to approximatly 70 ppm when the iminosugar is formed. This way the formation of 2 iminosugars can be observed, this result may be explained due to a migration of the silyl group present in the molecule. So, we can say that when we perform the reduction of the OZO **88** the formation of 3 distinctive compounds takes place, which are products of the reduction and two iminosugars.

Using other reactional conditions (Pd/C and HCO_2NH_4) the obtained results are similar (Scheme 4.12) which leads to the belief that there is a balance between the reduced form and the iminosugar.

Pd/C, HCO_2NH_4, EtOH
44ºC, 12h

88	169	170	171
	25%	14%	30%

Scheme 4.12 - Reactivity of OZO D-ribose derivative **88**.

For both methods it is possible to obtain 3 different products, a migration of the silyl group in between the iminosugars is observable. The difference of yields between these two methods is not significant. It was decided to acetylate the reactional mixture of both iminosugars and the aminosugar in order to ease the purification of these 3 compounds (there is always a non-separable mixture of the compounds 2 by 2). The obtained result wasn't quite satisfactory as it was verified that the molecules are able to acetylate at several sites, which leads to an increased number of compounds to be separated, verifying this waythat we obtained an inseparable mixture of acetylated iminosugars and acetylated aminosugars in different positions.

It was decided to remove the TBDMS group from both iminosugars **170** and **171** in a tentative to eliminate the problem of the migration of the silyl group (Scheme 4.13), or from the corresponding oxazolidinone with the free hydroxyl group in C-3. The obtained yields are similar, very poor but it is possible to identify and characterize the product.

170 + **171**: TFA, THF/H2O (3/1), 0ºC, r.t., 12h, **16%**

90: polymer-bond Ph_3P, THF/H_2O (5/1), r.t., 12h, **15%**

→ **172**

Scheme 4.13 – Synthesis of iminosugar **172**.

In an attempt to facilitate separation of compounds **169** and **171**, where as after column always obtain a fraction which is a mixture of the two compounds, we tried to acetylate this fraction (mixture of 2 compounds, iminosugar and aminosugar) (Scheme 4.14). After purification we observed the formation of three compounds, with different positions acetylated. We conclude that acetylation difficult purification due to the formation of by-products (very close spots in TLC).

169 + **171**

Ac_2O, pyridine, 0°C, r.t., 2h

173 + **174** + **175**

Scheme 4.14 – Acetylation of the reaction mixture obtained after column.

4.2.1.2 - With D-xylose template

By testing the same conditions on the D-xylose derivated OZO, it is intended to understand the reactivity of OZO applying the same conditions applied on OZTs, alkylsulfanyloxazolidines, and D-ribose derivated OZO (Scheme 4.15).

95 → (Ph_3P, THF/H_2O, r.t, 12h) → **176** + **177**

176: 5%

177: 41%

Scheme 4.15 – Reactivity of OZO D-xylose derivative **95**.

With the D-xylose derived OZO it was verified that the iminosugar was obtained with good yield, it is also verifiable that the resulting compound of the reduction is also present but in minimal amounts. This way we are going to test the reactivity of the silylated OZO in order to verify if there is any migration from the silyl group (Scheme 4.16).

Ph_3P, THF/H_2O, r.t., 12h

100 → 178 (0%) + 179 (56%)

Scheme 4.16 – Reactivity of OZO D-xylose derivative **100**.

The obtained results were surprising verifying the formation of the iminosugar. It was also verified that there is no migration of the silyl group. This result allows us to draw conclusions regarding the influence of stereochemistry in formation of iminosugars.

4.2.1.3 - With D-arabinose template

With the D-arabinose derived OZO we are going to test the reactivity of the oxazolidinone. This way we are going to apply the conditions applied before in the other OZOs (Scheme 4.17).

Ph_3P, THF/H_2O, r.t., 12h

108 → 180 (0%) + 181 (67%)

Scheme 4.17 – Reactivity of OZO D-arabinose derivative **108**.

After purification by column chromatrography of reactional mixture, it was obtained only the iminosugar **181** with a good yield. Again is proved the importance of the stereochemistry which interferes in the balance between the aminosugar **180** and the iminosugar **181**, in this case the reaction is complete and allows an easy isolation of the iminosugar **181**.

With these results it can be assured by comparing the D-ribose/xylose/arabinose derived iminosugars, that C-2 and C-3 are influenced by stereochemistry of the molecule, verifying that is necessary that C-2 and C-3 are on opposite sides of the plan for the reaction to be almost complete.

4.2.1.4. - With L-sorbose template

With compound **109**, a derivative of L-sorbose previously synthesized in the laboratory, we tested the reactivity of OZT. We verified that when a carbohydrate fused with an oxazolidine-2-thione ring, and applying the reaction conditions $Ph_3P/H_2O/THF$ only occurs reduction of azido-compound **109** (Scheme 4.18).

Scheme 4.18 - Reactivity of OZT L-sorbose derivative 109.

With the L-sorbose derived OZO **110** we are going to test the same reactional conditions applied on the other OZOs (Scheme 4.19).

Scheme 4.19 - Reactivity of OZO L-sorbose derivative **110**.

Surprisingly, and without apparent reason the obtained product is the result of the cyclization between the free hydroxyl group in C-3 and the amino group result in reduction. It was expected the formation of the L-sorbose derived iminosugar but that wasn't verified. It will be necessary to repeat the synthesis and protect the free hydroxyl group in C-3 in order to prevent the formation of carbamate, and allow the synthesis of the correspondent L-sorbose derived iminosugar (Scheme 4.20).

Ph_3P, THF/H_2O

r.t., 12h

119 → **186** + **187**

186: 0%

187: 0%

Scheme 4.20 - Reactivity of OZO L-sorbose derivative **119**.

The identification and characterization of the D-xylose derived iminosugar allows the identification of a particular characteristic presented by this iminosugar. So, using COSY (Figure 4.4) and HSQC (Figure 4.5) it is possible to state that there was a major change of the chemical deviation value of C-1. This fact is due to cyclization of the heterocyclic ring in the nitrogen atom.

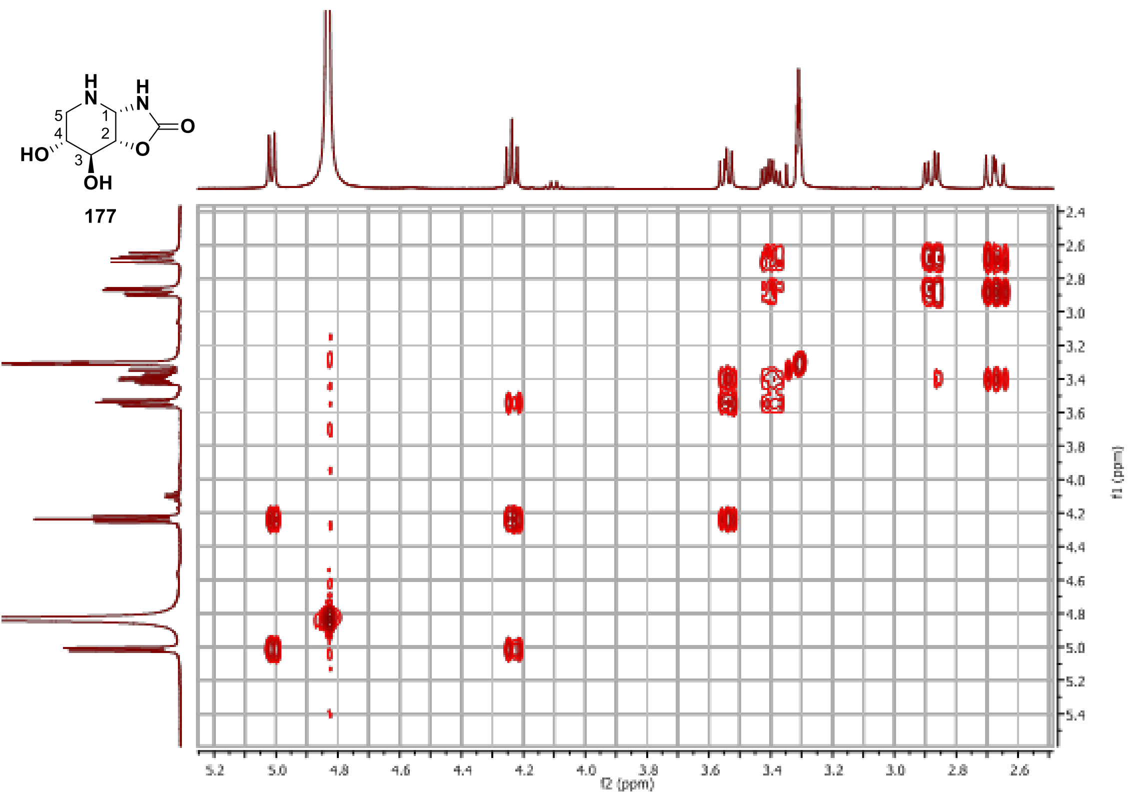


Figure 4.4 - COSY iminosugar **177**.

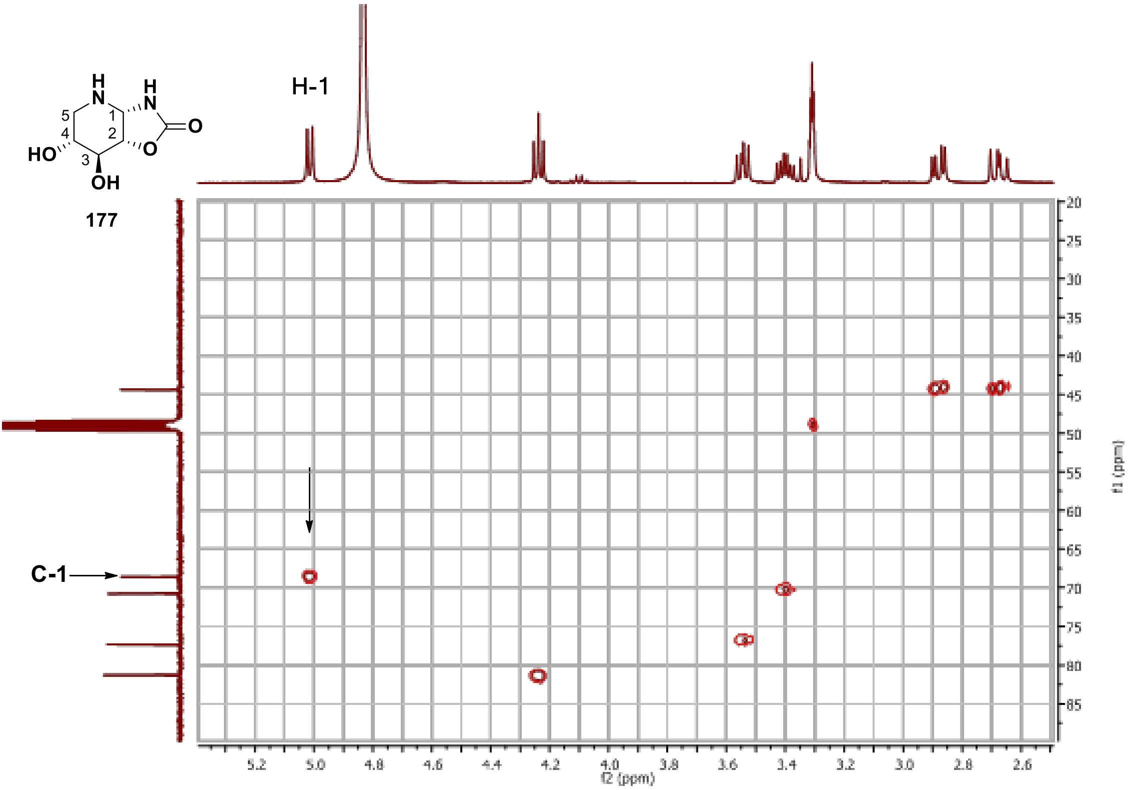


Figure 4.5 - HSQC iminosugar **177**.

The obtention of diferent iminosugars was confirmed by NMR (Figure 4.6).

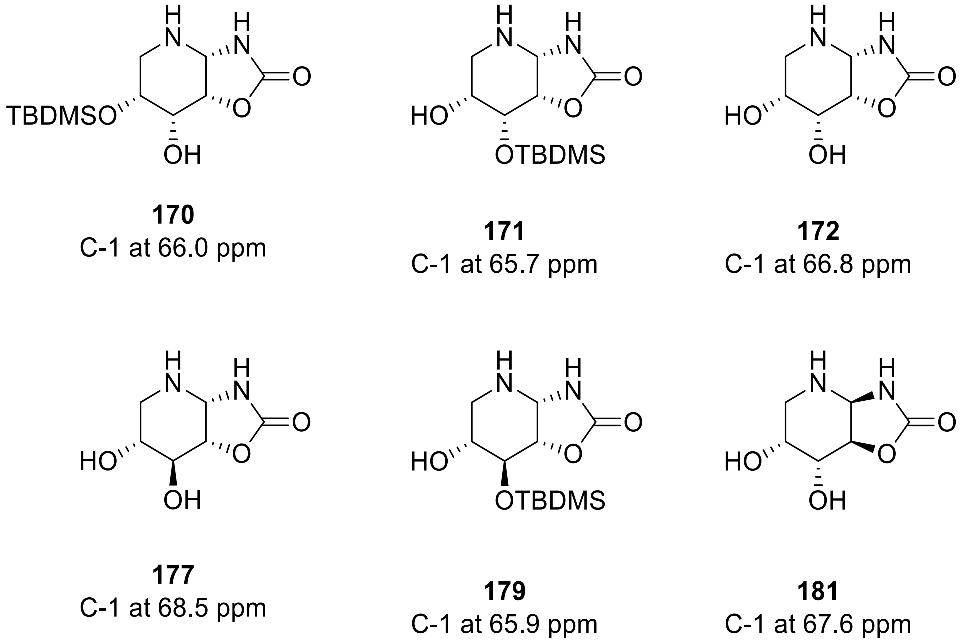


Figure 4.6 – Obtained iminosugars fused with 1,3-oxazolidin-2-one ring.

It is verifiable that the main difference between the reduced oxazolidinone and the iminosugar lies on the C-1 value. As the molecular mass value is the same (on the reduced oxazolidinone

and on the iminosugar), it is by NMR (COSY, HSQC and ^{13}C) that we confirm the obtention of the diferent iminosugars.

4.2.2 - Lactams

Synthesis of the lactam **158** is performed using methods described in literature, starting from D-ribose. Functionalization of the lactam by inserting triple bonds allows the formation of a precursor used in the "Click chemistry" (Scheme 4.21).

41 → 158: Pd/C, HCO_2NH_4, Ethyl acetate, reflux, 2h, 75%

158 → 190: $CHCCH_2Br$, NaH, DMF, 0°C, 30 min., r.t., 2h, 86%

158 → 188: TBDMSCl, Imidazole Pyridine, r.t., 12h, 60%

188 → 189: $CHCCH_2Br$, NaH, DMF, 0°C, 30 min., r.t., 2h, 72%

Scheme 4.21 - Reactivity of azido-lactone **41**.

It is verified that compound **41** undergoes reduction followed by ring-opening and subsequent cyclization at the nitrogen atom in order to originate the lactam **158**.

The obtention of diferent alkynyl-iminosugars was confirmed by NMR (Table 4.2 and Table 4.3).

Table 4.2 - ^1H NMR shift of the alkynyl-lactams **189** and **190**.

σ (ppm) / Compound	CH_2-5 ^1H	TBDMS ^1H	CH_2CCH ^1H
	2.98-3.03 (m, 1H) 3.25 (t, 1H')	-	-

	3.13-3.17 (m, 1H) 3.52-3.57 (m, 1H')	0.01 (s, 6H) 0.78 (s, 9H)	2.11 (d, 2H) 2.11 (s, 1H)
	3.50-3.54 (m, 1H) 3.69-3.74 (m, 1H')	-	2.30 (d, 2H, CH_2O) 2.55 (d, 2H, CH_2N) 2.88 (s, 1H, CH of O) 2.97 (s, 1H, CH of N)

Table 4.3 - ^{13}C NMR shift of the alkynyl-lactams **189** and **190**.

σ (ppm) / Compound	CH_2-5 ^{13}C	TBDMS ^{13}C	CH_2CCH ^{13}C	C=O ^{13}C
	41.8	-	-	168.4
	47.0	-4.7, -4.7, Cq at 18.3, 25.7	35.9 (CH_2) 72.5 (CH) 77.7 (Cq)	167.0
	44.0	-	36.1(CH2N), 57.0 (CH2O), 72.8 (CH of N), 75.8 (CH of O), 77.3 (Cq of N), 78.7 (Cq of O)	166.7

To study the reactivity of another derivative of D-ribose, azido-sugar **34**, we will apply the reaction conditions previously applied to the azido-lactone **41** (Scheme 4.22).

Scheme 4.22 - Reactivity of azido-sugar **34**.

Due to the difficulty in identifying the product, that is, difficulty in verifying the product formed would be the aminosugar or iminosugar was necessary to oxidize the obtained product. It was found that the obtained product was the aminosugar **191** because when the oxidation verified the acetylation of the product. Compound **191** has no hydroxyl groups, it is impossible to perform an oxidation of this compound. Due to the experimental conditions used verified the acetylation of the compound **191**. Obtention of the compound is confirmed by the appearance of a quaternary carbon at 170.3 ppm in 1^{3}C spectra (C=O) and also by the appearance of a CH_3 at 23.3 ppm corresponding to the CH_3 of acetyl group.

4.3 - Conclusion

- ✓ The attempt of synthesis of iminosugars starting from 2-benzylsulfanyl-1,3-oxazolidine **87** using Lewis acids wasn't effective.

- ✓ Using 2-benzylsulfanyl-1,3-oxazolidine **87** and 1,3-oxazolidine-2-thione **82** it is only possible to reduce the azido group, not being possible to obtain the corresponding iminosugars by Staudinger reduction.

- ✓ The synthesized 1,3-oxazolidin-2-ones **88**, **90**, **95**, **100** and **108** originated, unexpectedly, the corresponding iminosugars by applying Staudinger reduction.

- ✓ The chemical shifts in D-ribose, D-xylose, D-arabinose and L-sorbose templates for the tertiary carbon atom at position 1 of the five-membered heterocycle varied from roughly 90 ppm (carbohydrate five-membered ring) to approximately 65 ppm (iminosugar six-membered ring).

- ✓ The stereochemistry explains the obtained results, it was concluded that the spatial disposition of the substituents in C-2 and C-3 of iminosugars **170**, **171**, **172**, **177**, **179** and **181** is very important in the formation of the iminosugars fused with 1,3-oxazolidin-2-one ring. The substituents in C2 and C-3 must be in opposite positions in the plan, this way the formation of the desired product (iminosugar) is easier. Best yields obtained when the C2-C3 substituents are in opposite position of the plan (Figure 4.7) (iminosugars **177**, **179** and **181**). This fact is explained due to stability problems such as steric interaction/electronic repulsion on position 2-3 of the ring. The position of the C-4 substituents in the plan does not influences the formation of iminosugars.

170	**171**	**172**
15%	36%	16%

177	**179**	**181**
41%	56%	67%

Figure 4.7 – Yields of synthesized iminosugars.

✓ Due to the value of the $J_{1,2}$ (~6Hz) coupling constants , and as described in literature[218], the obtained iminosugars by Staudinger reduction are of type (Figure 4.8, Figure 4.9, Figure 4.10 and Figure 4.11):

194 R= H, TBDMS

Figure 4.8 – Iminosugars in D-ribose template.

195 R= H, TBDMS

Figure 4.9 - Iminosugars in D-xylose template.

180

Figure 4.10- Iminosugar in D-arabinose template.

186 R= TBDMS

Figure 4.11 – Iminosugar in L-sorbose template.

✓ The most likely mechanism that explains the reduction of oxazolidinones and formation of iminosugars fused with ozaxolidinone ring is the one found on Figure 4.12. The reaction is a combination of a Staudinger reaction followed by a retro-Michael and Michael type addition. This mechanism it is applied to oxazolidinones **88**, **90**, **95**, **100** and **108**.

R= H, TBDMS

Figure 4.12 - Reactivity of 1,3-oxazolidin-2-one.

The most likely mechanism that explains the reduction of oxazolidinethione **82** and benzylsulfanyloxazoline **87** to aminosugars could be explained in the Figure 4.13 and Figure 4.14, respectively.

R= H, TBDMS

Figure 4.13 - Reactivity of 1,3-oxazolidine-2-thione.

The stabilization of the charge on the sulfur atom might block the retro-Michael reaction.

Staudinger reductiom

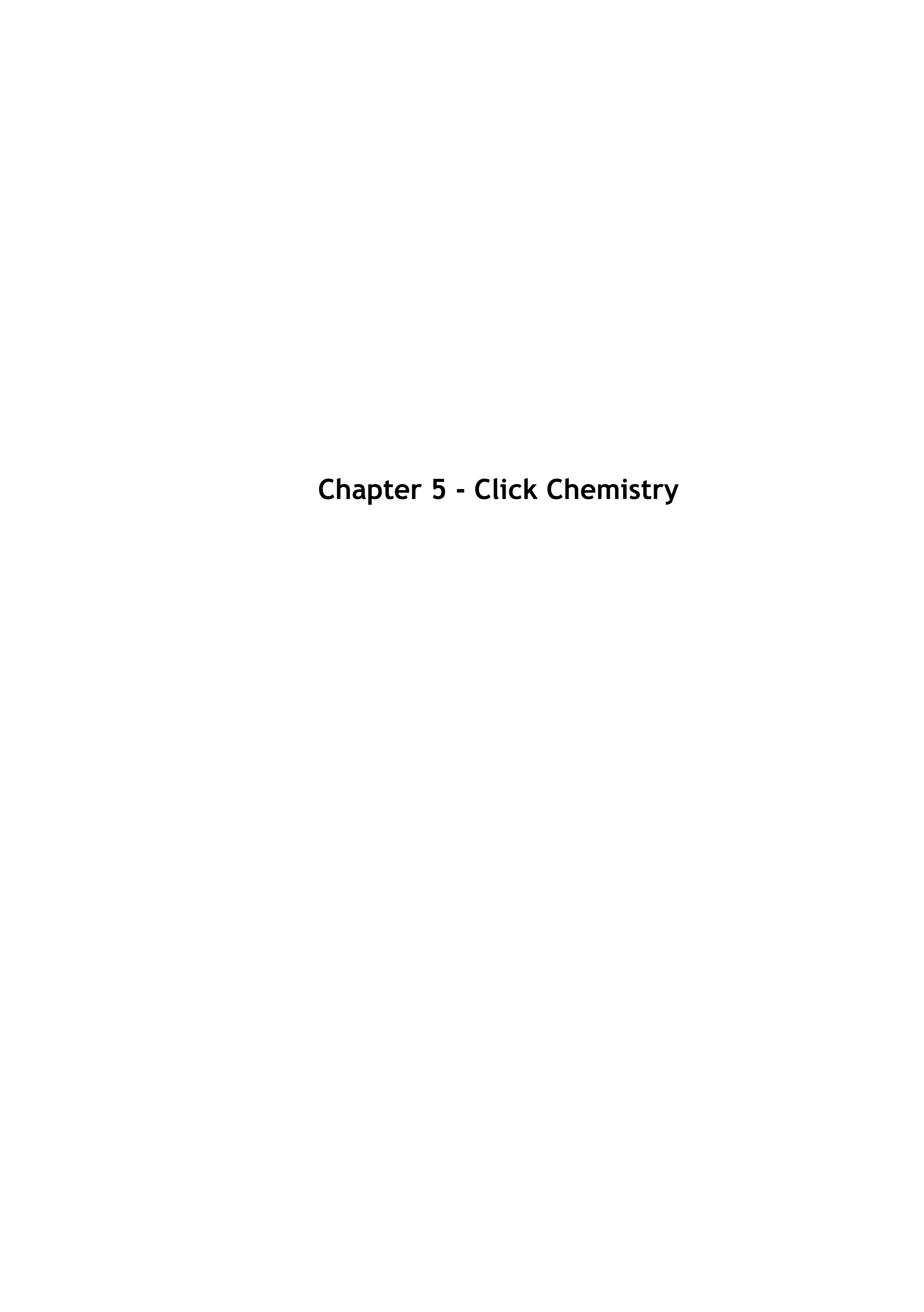
N_3 RO SBn → H_2N RO SBn

R= H, TBDMS

Figure 4.14 - Reactivity of alkylsulfanyloxazolines.

With the benzylsulfanyl derivative, no cyclisation could be observed due to the absence of any labile proton on the oxazoline ring. Only Staudinger reduction could occur.

- ✓ Reduction of lactone **41** yielded lactam **158**. The chemical shifts for the quaternary carbon atom varied from roughly 173 ppm in lactone **41** (O-C=O) to approximately 168 ppm in lactam **158** (N-C=O).
- ✓ The protection of the hrydroxyl group in C-3 of the lactam **158** leads to formation of alkynyl-lactam **189** with a lactam extremity.
- ✓ The direct reaction of the lactam **158** with propargyl bromide leads to the formation of alkynyl-lactam **190** with two extremities alkynyl.
- ✓ The chemical shifts for the secondary, tertiary and quaternary carbon atoms at carbon chain elongation (extremity alkynyl) varied from roughly 36.1 ppm (CH_2N)/ 57.0 ppm (CH_2O), 73 ppm and 78 ppm, respectively in lactams **189** and **190**.
- ✓ Global yields from lactam **189** are 69% and 81% to lactam **190**. The lactam function is maintained when unsaturated carbon chains are added.
- ✓ Reduction of azidocarbohydrate **34** allowed the obtention of aminocarbohydrate **191**.



Chapter 5 - Click Chemistry

5.1 - General introduction

Click chemistry is a concept introduced by Barry Sharpless in 2001, describing chemical reactions that generate substances in a simple and quick way by connecting two different units. Between these reactions the most popular one is the Huisgens cycloaddition, which consists in a 1,3-dipolar cycloaddition between an azide function and a alkyne function that leads to the formation of a triazol ring. This cycloaddition is a [4+2] cycloaddition that performs similarly as the Diels-Alder reaction. The catalysis of this reaction with copper allows obtaining exclusively the 1,4 regioisomer. This reaction presents several vantages, like the use of non-dangerous solvents, with this reaction there is the formation of pure products while reaction conditions are simple and there is no formation of secondary products presenting good yields and making it applicable to a vaste number of substrates.

In this chapter a bibliographic review about click chemistry is presented. This technique allows the obtention of new compound libraries connected by a triazol ring. Triazols constitute an important family compound inbetween the chemistry nitrogen heterocycles. In this chapter we are going to study the azida-alkyne cycleaddition catalyzed by copper (I) (CuAAC) in order to obtain new disubstituted triazoles.

5.1.1 - Click Chemistry – Azide-Alkyne Cycloaddition

The research of multifunctional and efficient chemical reactions has been a priority of the scientific community."Click Chemistry" is a term that was introduced by Sharpless in 2001 to describe reactions that are high yielding, wide in scope, create only byproducts that can be removed without chromatography, are stereospecific, simple to perform, and can be conducted in easily removable or benign solvents.[219]

This concept was developed in parallel with the interest within the pharmaceutical, materials, and other industries in capabilities for generating large libraries of compounds for screening in discovery research. Several types of reaction have been identified that fulfill these criteria, thermodynamically-favored reactions that lead specifically to one product, such as nucleophilic ring opening reactions of epoxides and aziridines, non-aldol type carbonyl reactions, such as formation of hydrazones and heterocycles, additions to carbon-carbon multiple bonds, such as oxidative formation of epoxides and Michael Additions, and cycloaddition reactions.[220]

For example, an examination of the azide-alkyne cycloaddition shows that it fulfills many of the prerequisites. Many of the starting monosubstituted alkynes and organic azides are available commercially, many others can easily be synthesized with a wide range of functional groups, and their cycloaddition reaction selectively gives 1,2,3-triazoles.

The thermal Huisgen 1,3-dipolar cycloaddition of alkynes to azides requires elevated temperatures and often produces mixtures[221] of the two regioisomers when using asymmetric alkynes (Figure 5.1).

Figure 5.1 – Huisgen cycloaddition.

In this respect, the classic 1,3-dipolar cycloaddition fails as a true click reaction. A copper-catalyzed variant that follows a different mechanism can be conducted under aqueous conditions, even at room temperature. Additionally, whereas the classic Huisgen 1,3-dipolar cycloaddition often gives mixtures of regioisomers, the copper-catalyzed reaction allows the synthesis of the 1,4-disubstituted regioisomers specifically (Figure 5.2).

Figure 5.2 - Copper-catalyzed reaction.

By contrast, a later developed ruthenium-catalyzed reaction gives the opposite regioselectivity with the formation of 1,5-disubstituted triazoles (Figure 5.3).

Figure 5.3 - Ruthenium-catalyzed reaction.

Thus, these catalyzed reactions comply fully with the definition of click chemistry and have put a focus on azide-alkyne cycloaddition as a prototype click reaction.

In this work copper was used as catalyst to obtain 1,4-disubstituted triazoles.

5.1.2 - Catalytic system

In literature multiple methods for obtention of Cu(I) ions in the reactional mixture may be found, in this work we are going to use only copper salts (II).

Reduction in situ of copper salts (II):

The reduction in situ of copper salts(II), provided in the form of pentahydrate copper sulfate ($CuSO_4.5H_2O$) or of copper acetate ($[Cu(OAc)_2]$), is the most frequently found method. It is

necessary an excessively addition of a reduction agente, generally sodium ascorbate (Figure 5.4).[222]

$$R{-}N_3 + \equiv{-}R' \xrightarrow[H_2O\ /\ tBuOH\ (1:1),\ r.t.,\ 6-12h]{0.24-2\ mol\text{-}\%\ CuSO_4.5H_2O,\ 5-10\ mol\text{-}\%\ sodium\ ascorbate}$$

R: alkyl, CH_2OBn
R': Ph, CO_2H

Figure 5.4 – Method found in the literatire for Huisgen 1,3-dipolar cycloaddition.

5.1.3 - The influence of the solvent

Depending on the origin of the Cu salts(I) and the nature of the used azides and alkynes, click chemistry may work with a great variety of solventes, polars or apolars. The mixture of tert-butanol/water is the most commonly found in the literature, but it is also frequent to find other solvents (alone or mixtured with water) like toluene, tetrahydrofuran, N, N-dimethylformamide, dimethylsulfoxide, acetone, chloroform, acetonitrile or solely water.

Multiple studies show that water as a main role in the performance of the reaction. Click reactions may work in water even when various reagents or products are insoluble in this reaction medium.[223]

The Table 5.1 summarizes the principal systems [catalyst-solvent] cited in most “click chemistry” publications. Merdal and co-workers have established an exhaustive list of sources of Cu (I) used between 2001 and 2008 as well as the associated experimental conditions.

Table 5.1 – Experimental conditions employed.

Initial oxidation state	**Catalyst (0.25-2 mol %)**	**Reducing or oxidizing agent**	**Additional bases**	**Solvents**
Cu(II)	Cu(II) $CuSO_4.5H_2O$	Sodium ascorbate	None	1:1 H_2O: *t*-BuOH 1:1 H_2O: EtOH
Cu(I)	CuI CuBr $[Cu(PPh_3)_3Br]$	None	Triethylamine 2,6-lutidine DIPEA PMDETA	DMF THF Toluene MeCN
Cu(0)	Copper metal powders / nanoparticles	Amonium salt	None	2:1 H2O: *t*-BuOH

5.1.4 - Mechanism of the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC)

As one of the best click reactions to date, the copper-catalyzed azide-alkyne cycloaddition features an enormous rate acceleration of 107 to 108 compared to the uncatalyzed 1,3-dipolar cycloaddition. It succeeds over a broad temperature range, is insensitive to aqueous conditions and a pH range over 4 to 12, and tolerates a broad range of functional groups. Pure products can be isolated by simple filtration or extraction without the need for chromatography or recrystallization.

The reaction of an azide and an alkyne leads to the formation of disubstituted triazoles. This reaction is relatively slow, needs higher temperatures and leads, generally, to the formation of a mixture of triazole isomers 1,4 and 1,5 disubstituted in 1:1 proportions (Figure 5.5).

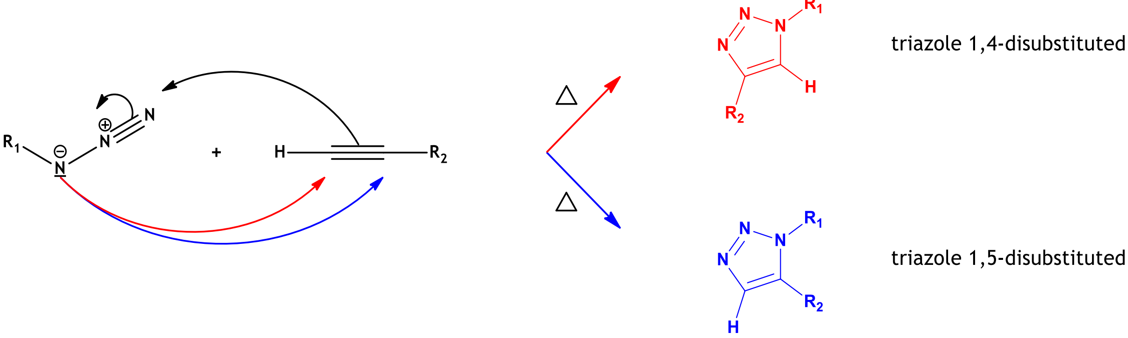


Figure 5.5 - Classical cycloaddition reaction, thermally.

After several efforts to control this regioselectivity in favor of 1,4-disubstituted isomer, Kolband co-workers[215] proposed the usage of copper(I) as catalyst of the cycloaddition between an azide and an alkyne. The usage of this catalyst lead to the formation of a 1,4-disubstituted triazole, also allowing the usage of heating in the reaction. Figure 5.6 describes the mechanism proposed by Himo and co-workers[214] for cycloaddition catalyzed by Cu(I).

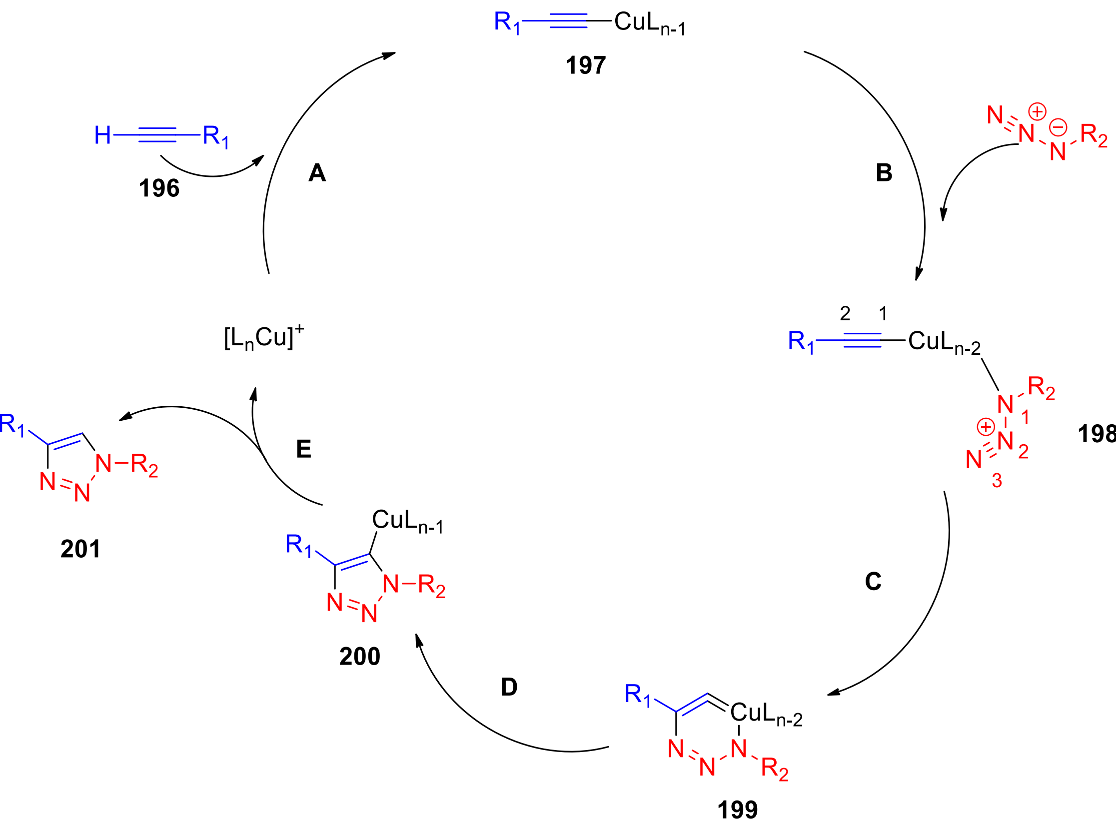


Figure 5.6 – Cu (I) catalized 1,3-cycloaddition mechanism.

The mechanism is comprised on 5 stages:

Stage A: the alkyne **196** forms a complex with the copper named “Cu-acetylide” **197** as follows (Figure 5.7):

Figure 5.7- Formation of complex “Cu-acetylide”.

This stage needs labile ligands around the copper atom in order to allow the competition with the azide fixation.

Stage B: the copper atom activates the azida function, which substitutes a link to form the intermediate **198**.

Stage C: both reactive parts may arise face to face, allowing the posibility of the attack of the acetylide carbon-2 over the azide nitrogen-3 to form the 6-membered metallacycle **(199)**, with copper in oxydation state III.

Stage D: concentration of metallacycle **199** leads to the copper-triazole derivate **200**.

Stage E: at last, protonation of the copper-triazole derivate allows the isolation of the desired 1,4-disubstituted triazole compound **201** and regeneration of the copper catalyst.

5.1.5 – Copper acetate disruptive mechanisms

As proved until now CuAAC is a reliable and efficient reaction. However, there are two colateral reactions that might narrow the yield and lead to formation of sub-products. The first consists in homo-coupling of two terminals alkyne functions, also catalysed using copper which may disturb some CuAAC reactions (Figure 5.8). The use of bases with a great steric volume could slow the reaction.[224]

Figure 5.8 – Supposed copper catalysed homo-coupling mechanism.

The second reaction has its origin from the Cu catalyst (I) saturation in the presence of polyacetylenes. Therefore, it looks like the proximity of the alkynes may saturate the Cu (I) atom by chelating action. The complexation of copper with different alkyne functions blocks the reaction with the azide[217]. In a general way, these two reactions are rarely mentioned in literature, which should be insignificante or not observed in the majority of cases.

5.1.6 - The azidophobic effect

The low interest in the azida-alkyne cycloaddition before the 2000 year may be explained in part by the azidophobic phenomena, from the flammable or explosive character of some azide derivates. In fact, following the example of the hydrogen azide, numerous azide compounds decompose in releasing nitrogen due to a small external stimulus (pression, impact, heat). The

inorganic azides constituents of heavy metals are, sometimes, used as detonators. The sodium azide is equaly used in airbag technology.

Finnaly, some small organic azides may decompose in an explosive way. In the category of synthesized azides, from the most potentially explosive we have hexakis (azidomethyl) benzene **201**, triazidotrinitrobenzene **202**, azidotetrazole **203**, diazidomethane **204**, azidomethane **205** (Figure 5.9).[225] However, it is possible that other azide derivates with low molecular weight may likewise decompose in an unpredictable way.

202 **203** **204** **205** **206**

Figure 5.9 - Potentially explosive azides

Generally, in order to obtain non-explosive compounds, it is necessary that the number of nitrogen atoms doesn't exceed the number of carbon atoms, and that the following equation be met: $(N_C + N_O)/N_N \geq 3$.[218, 226] It looks like the azide groups that are directly connected to aromatic compounds, carbonyl compounds or olefins are more dangerous rather than the aliphatic azides.[212]

An important point consists on the photosensitivity of the azido derivatives. Photodegradation of azido compounds into nitrenes was known for long time (Figure 5.10). Furthermore, several studies have been recently conducted aiming to understand the decomposition mechanisms of the organic azides under the effect of light radiation.[227,228] In particular, Abbenante and co-workers have observed that alkyl azides decompose rapidly (1%/day) under fluorescent light at ambiente temperature. [229] The storage of azides in absence of light is necessary in order to avoid loss of total functionality or degradation of product.

$$R-N_3 \xrightarrow{h\nu} R-\overline{N}: + N_2$$

Figure 5.10 - Photodegradation of organic azides.

5.1.7 - Triazol derivatives

We have just seen that the click chemistry reaction, the Huisgen 1,3-dipolar cicloaddition, leads to formation of 1,2,3-triazol, and sometimes to tetrazole, depending on selected monomer. We are interested in the different properties of this compound and its applications.

1,2,3- or 1,2,4-triazoles (Figure 5.11) have a pseudo-aromatic structure, which results notable from the interactions between π bonds ("π-sacking"), of a great dipolar moment and from a great capacity of forming hydrogen bridges.[222, 230] These compounds are very stable when compared with other chemical oxydation and reduction reagents.

207 1,2,3-triazole

208 1,2,4-triazole

Figure 5.11 - Chemical structure of 1,2,3- and 1,2,4-triazoles.

From a biological point of view, compounds that have a triazolic group in their structure have been capturing attention from chemists as they present a wide range of biological activity.[231,232,233,234,235] Kolb and Co-workers[215] shown that these compounds behave with units with rigid bonds, this way, triazols replicate the electronic properties of the amide connections, but without the same susceptibility to hydrolytic cleavage (Figure 5.12).

209 R1-R2 = 3.9 Å

210 R1-R2 = 5 Å

Figure 5.12 – Topological and electronic similarity between amide units and 1,2,3-triazole.

The 1,2,3-triazole rings, which have, an higher dipolar moment than the amida bonds, which gives electrophilic and nucleophilic properties, are similar to peptide bonds. In fact, triazol nitrogen atoms are hydrogen bond acceptors, while the triazol proton, highly polarized, may play as donor of an hydrogen bond, as well as the proton of an amide function.[236] By coincidence, the 1,2,3-triazol units are frequently used instead of a peptidic bond. This way, Meldal and co-workers have sinthesized peptide-mimetic molecules by CuAAC.[237] Similarly, Horne and co-workers modified physical properties of the peptidic structures through insertion of triazol units. [238, 239] Triazole units are also used in some cases to substitute inter-peptidic bonds, maintaining its initial biological activity. They are notably used as aminoacid analogues.[240]

5.1.8 - Click chemistry reaction applications

Click chemistry has widespread applications. Some of them are: two-dimensional gel electrophoresis separation;[241] preparative organic synthesis of 1,4-substituted triazoles; modification of peptide function with triazoles; modification of natural products and pharmaceuticals; natural product discovery;[242] drug discovery; macrocyclizations using Cu(I) catalyzed triazole couplings; modification of DNA and nucleotides by triazole ligation; supramolecular chemistry: calixarenes, rotaxanes, and catenanes; dendrimer design; carbohydrate clusters and carbohydrate conjugation by Cu(I) catalyzed triazole ligation reactions; polymers and biopolymers;[243] surfaces;[244] material science; nanotechnology,[245] and bioconjugation, for example, azidocoumarin; biomaterials.[246] Click chemistry has also been used for selectively labeling biomolecules within biological systems.

5.2 - Presentation and discussion of results

The copper-catalyzed click reaction between azides and terminal alkynes is ideal for many applications. Amides have a significant resonance struture wherein the lone par of electrons on the nitrogen atom is deslocalized between the nitrogen and carbonyl. The balance of satability and reactivity give the opportunity to develop new iminosugars with a linking moiety.

With the previously synthesized azidocarbohydrates from Chapter 2 and with the alkynil-lactams synthesized in chapter 4, there were perform 1,3-dipolar cycloaddition. The junction of these compounds using click chemistry allows connection between these compounds through a heterocyclic triazol.

This way, taking into account Scheme 5.1, through 1,3-dipolar cycloaddition between a 1,3 dipole (azido-sugar) and a dipolarophile (alkynil-lactam), we can obtain triazole di-substituted compounds. The choosen catalyst was $CuSO_4.5H_2O$ because it is an economic, non-toxic and easy access reagent.

SUGAR-N_3 + TBDMSO ... (189) → $CuSO_4.5(H_2O)$, Sodium ascorbate, *tert*-But/H_2O (1/1), reflux, 3h → SUGAR–N (triazole) ... TBDMSO (212)

211 189 212

Scheme 5.1 - General scheme to obtain triazoles di-substituted.

Varying the azido-sugars and maintaining the alkyne we may obtain the compounds presented on Figure 5.13. The obtained yields are satisfatory. Depending on the number of free hydroxyles the easiness of obtaining the product varies.

213

96%

214

89%

215

51%

216

40%

Figure 5.13 – Compounds obtained by click chemistry.

In Table 5.2 we can confirme the obtention of different triazoles by formation of the triazole ring.

Table 5.2 – ^{1}H NMR/^{13}C NMR shift of the triazole compounds **213-216**.

σ (ppm) / Compound	C<u>H</u> (^{1}H) Triazol Ring	<u>C</u>H (^{13}C) Triazol Ring	Cq (^{13}C) Triazol Ring
213	7.69 (s, 1H)	123.6	143.3
214	7.67 (s, 1H)	124.5	142.6
215	7.60 (s, 1H)	124.6	143.4
216	7.76 (s, 1H)	123.6	143.3

If in lactam are introduced terminal alkynes, this gives access to formation of a bis-triazole compound. This way, using conditions from Scheme 5.2 it is possible to perform the 1,3-dipolar

cycloaddition between the diferent azides and alkyne-lactam to originate disubstituted bis-triazole compounds.

SUGAR-N_3 + **211** **190** → ($CuSO_4.5(H_2O)$, Sodium ascorbate, *tert*-But/H_2O (1/1), reflux, 3h) **217**

Scheme 5.2 – General scheme to obtain bis-triazoles di-substituted.

Through this technique and varying only the used azido-sugar it is possible to obtain the compounds presented on Figure 5.14. It was verified that the yields are lower than ones obtained for the disubstituted triazole compounds, however the yields are still satisfatory.

218

95%

219

58%

220

46%

221

40%

222

37%

223

32%

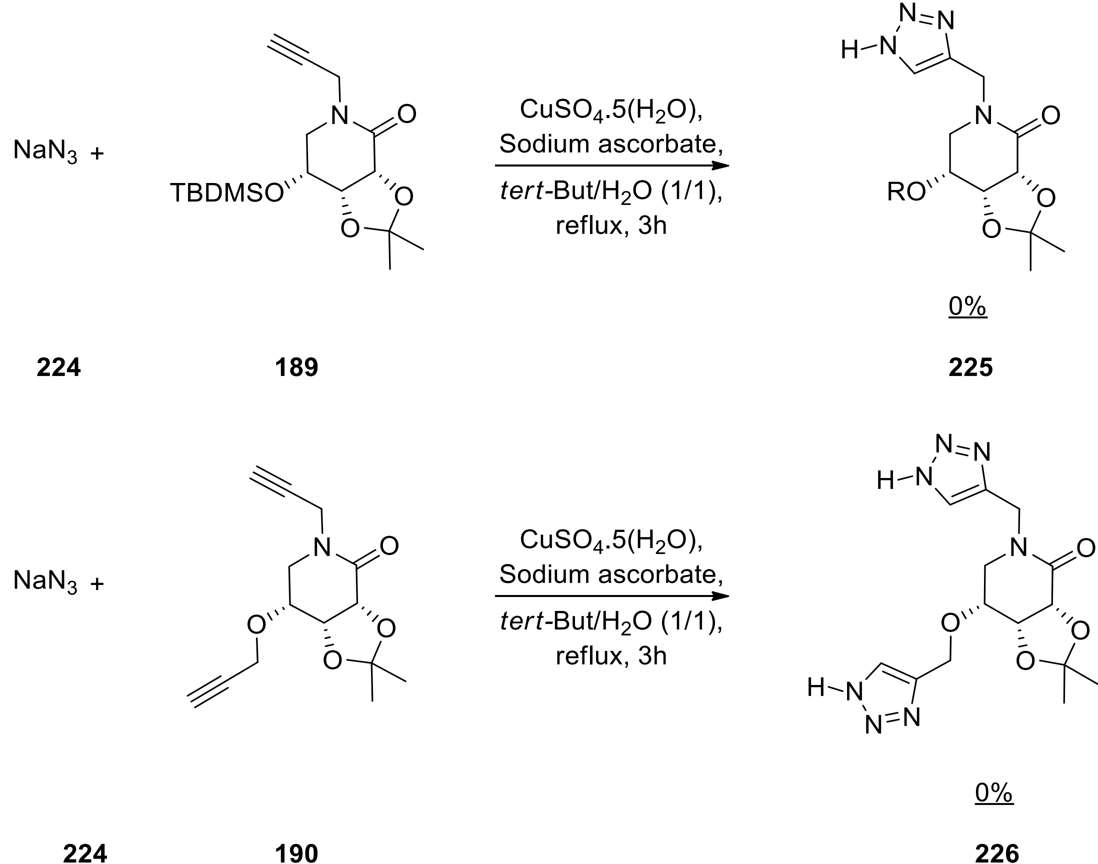
Figure 5.14 – Compounds obtained by click chemistry.

In Table 5.3 we can confirme the obtention of different triazoles by formation of the triazole ring.

Table 5.3 - ^{1}H NMR/^{13}C NMR shift of the triazole compounds **218-223**.

σ (ppm) / Compound	CH (H underlined) Triazol Ring	CH (C underlined) Triazol Ring	Cq Triazol Ring
218	7.74 (s, 2H)	124.3 and 124.2	142.5 and 143.9
219	7.71 (s, 2H)	123.5 and 123.6	143.1 and 144.6
220	7.71 (s, 1H) and 7.69 (s, 1H)	125.0 and 125.1	143.4 and 144.0
221	7.91 (s, 1H) and 8.03 (s, 1H)	124.4 and 125.2	142.8 and 143.8
222	7.76 (s, 1H) and 7.80 (s, 1H)	124.4 and 124.6	142.6 and 144.4
223	7.68 (s, 1H) and 7.79 (s, 1H)	121.5 and 124.6	143.3 and 145.0

Reacting comercial azides with aklynil-lactams it should be possible to obtain triazol derivatives (Scheme 5.3), this fact wasn't verified. Applying reactional conditions from Huisgen 1,3-dipolar cycloaddition it was verified the complete degradation of starting products.



Scheme 5.3 – Huisgen 1,3-dipolar cycloadiction.

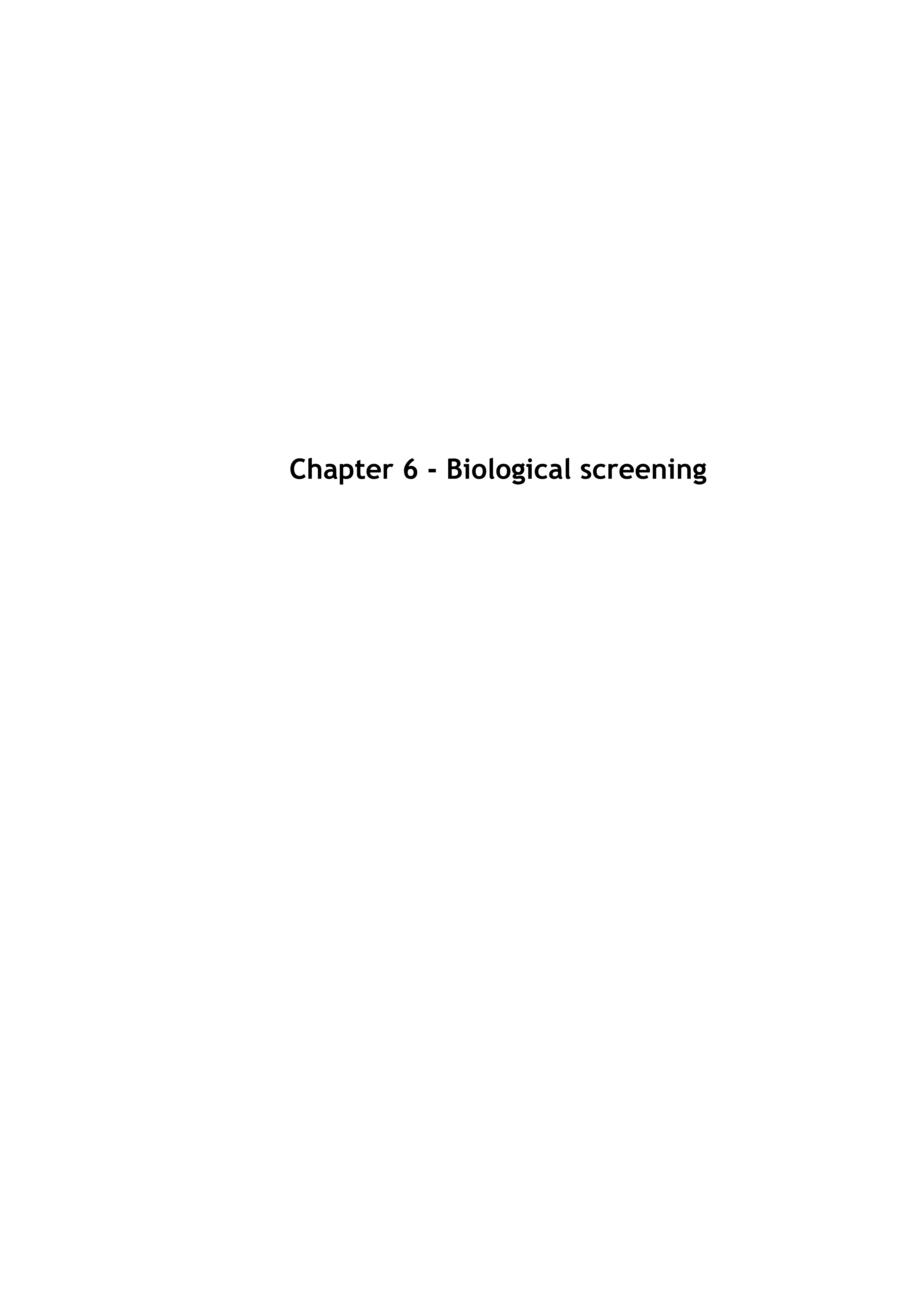
5.3 – Conclusion

✓ Click chemistry consists in 1,3-dipolar cyclicaddition between an azidocatbohydrate and analkynyl-lactam originating a disubstituted triazole. Copper (I) was used as catalyst, allowing the obtention of 1,4-disubstituted triazoles.

✓ With lactam **189**, 4 new disubstituted triazoles **213-216** were obtained. This confirms the formation of the triazole ring by the appearance of a CH around 124 ppm and a Cq around 144 ppm, corresponding at two carbons of the triazolic ring.

✓ With lactam **190**, 6 new disubstituted bis-triazoles **218-223** were obtained. This confirms the formation of the triazole ring by the appearance of two CH around 124 ppm and two Cq around 144 ppm, corresponding at two carbons of two triazolic rings.

✓ Yields are higher when compounds connected by a single triazole ring (disubstituted triazoles) are obtained. Yield from 'Click' reactions increases with polarity decrease. Using sodium azide (commercial azide) total degradation of starting compounds occours when performing 'Click' reaction.



Chapter 6 - Biological screening

6.1 - *Rhipicephalus (Boophilus) microplus* inhibitors

The synthesis of new 2-oxopyrimidinones, 2-thiooxopyrimidinones, azido-sugars, iminosugars and theirs intermediates opening a way to the formation of various classes of new compounds, new methodologies and unexpected results.

Part of our interest was also dedicated to explore the biological potential of those new molecules. We were convinced that inside those oxo/thioxopyrimidine and azide families and your intermediates possess a significant biological profile. Despite of the fact that, to the best of our knowledge, the literature is scarce on sintetic anti-parasitic drugs.

Rhipicephalus microplus (Figure 6.1) is considered to be the most important tick parasite of livestock in the world. *R. microplus* is a hard tick that can be found on many hosts including cattle, buffalo, horses, donkeys, goats, sheep, deer, pigs, dogs and some wild animals. Heavy tick burdens on animals can decrease production and damage hides.[247]

Figure 6.1 - Rhipicephalus (Boophilus) microplus.

The infestation of cattle with internal and external parasites is considered to be a major problem in livestock production systems. Inside the ectoparasites group, family Ixodidae ticks have received great attention because it is estimated that 80% of the world cattle are affected by these species. Its presence is associated with blood loss, reducing the weight gain rates and decreased milk production and quality of furs. Globally, economic losses associated with ticks were estimated at US $ 7 billion; in Latin America. These losses amount to one billion and, in the case of Uruguay to 32.5 million dollars per year. Also, ticks are associated with the transmission of diseases caused by causative agents such as Babesia bovis, Babesia bigémina and Anaplasmosis.

R. microplus can transmit babesiosis (caused by the protozoal parasites babesia bigemina and babesia bovis) and anaplasmosis (caused by anaplasma marginale).[248]

Life cycle:

R. microplus is a one-host tick; all stages are spent on one animal. The eggs hatch in the environment and the larvae crawl up grass or other plants to find a host. They may also be blown by the wind. In the summer, *R. microplus* can survive for as long as 3 to 4 months without feeding. In cooler temperatures, they may live without food for up to six months. Ticks that do not find a host eventually die of starvation. Newly attached seed ticks (larvae) are usually found on the softer skin inside the thigh, flanks, and forelegs. They may also be seen on the abdomen and brisket. After feeding, the larvae molt twice, to become nymphs and then adults. Each developmental stage (larva, nymph and adult) feeds only once, but the feeding takes places over several days. Adult male ticks become sexually mature after feeding, and mate with feeding females. An adult female tick that has fed and mated detaches from the host and deposits a single batch of many eggs in the environment. Typically, these eggs are placed in crevices or debris, or under stones. The female tick dies after ovipositing. Ticks in the subgenus *Boophilus* have a life cycle that can be completed in 3 to 4 weeks; this characteristic can result in a heavy tick burden on animals (Figure 6.2).[248]

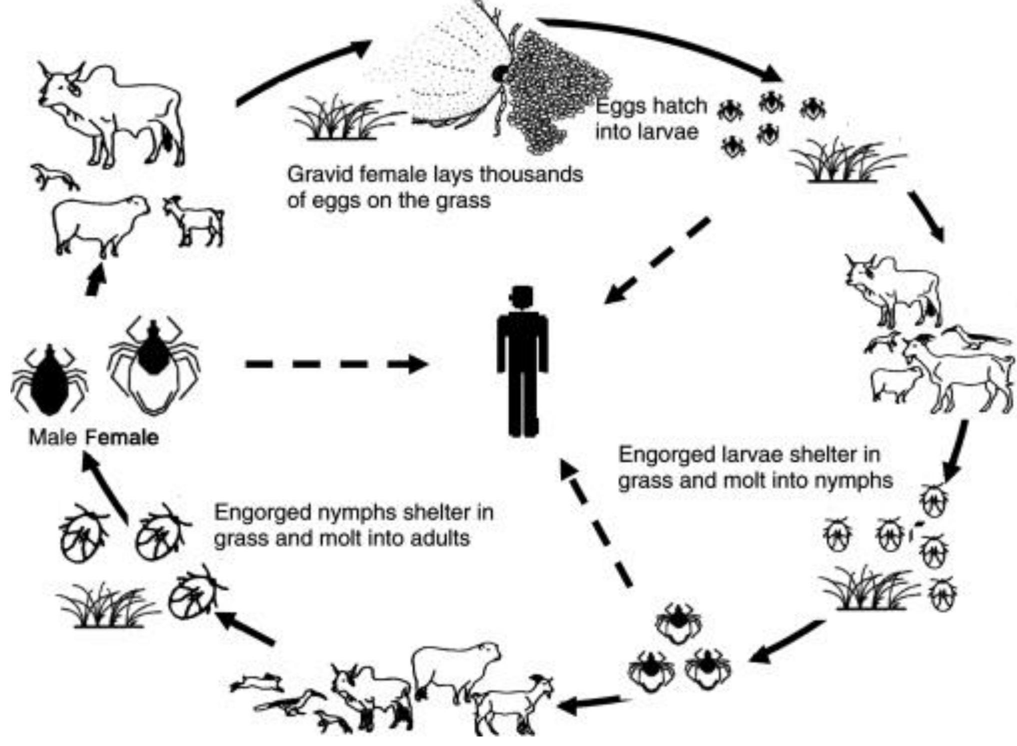


Figure 6.2 – Life cycle of *R. microplus*

6.1.1 - Chemical Control of *Rhipicephalus (B.) microplus*

The high potential acaricide exhibited by some synthetic molecules led to livestock producers indiscriminate and often erroneous acaricide, a situation which resulted in the emergence of resistance *Rhipicephalus (B) microplus* and a range of new active compounds.

Many drug classes have been used as acaricides to treat ticks from cattle, this include arsenicals, organochlorides, organophosphates, carbamates, amidines, phenylpyrazoles, insect growth regulators and synthetic pyrethroids.[249] It is worth mentioning that prior to placing on the market of commercial formulations with organochlorine compounds had been reported cross-resistance to organochlorine and experimental synthetic pyrethroids.

Available chemicals used in the treatment of ectoparasites of veterinary importance act either systemically, following uptake of the compound from host tissues, or by direct contact with the target parasites following external application. Virtually all ectoparasiticides are neurotoxins, exerting their effect on the ectoparasite nervous system.[250]

6.1.1.1 - Resistance of *Rhipicephalus (B.) microplus* to Acaricides:

In Mexico, *R. microplus* has developed resistance to all main classes of acaricides in past decades due to intensive use of chemical acaricides.

According to the current challenges in livestock production the need to reduce the negative impact of production systems over the past two decades has shown the growing interest of researchers around the world. Resistance arises through genetic changes in a cattle tick population that causes modifications to the target site, increased metabolism or sequestration of the acaricide, or reduced ability of the acaricide to penetrate through the outer protective layers of the tick's body. Thus that problema i tis necessary to develop new antiparasitic drugs.[251]

Previously, were referenced some functional classes of compounds that have been used as antiparasitic drugs. Due to the need to develop new antiparasitic drugs we decided to test, randomly, some compounds synthesized by us.

Different compounds synthesized during this work were tested. Thus followed to analyze several families of compounds to be tested for their ability to inhibit the growth of *R. microplus*, due to the toxicity exerted by the tested compounds and subsequent inhibition of reproduction (inhibition of posture).

6.1.2 - Methodology for inhibition assays *in vitro*

The following compounds were tested in the inhibition to the growth of *R. microplus* and simultaneously in the inhibition oviposition by these parasites.

Assay *in vitro*:

The different compounds tested are shown in Figure 6.3.

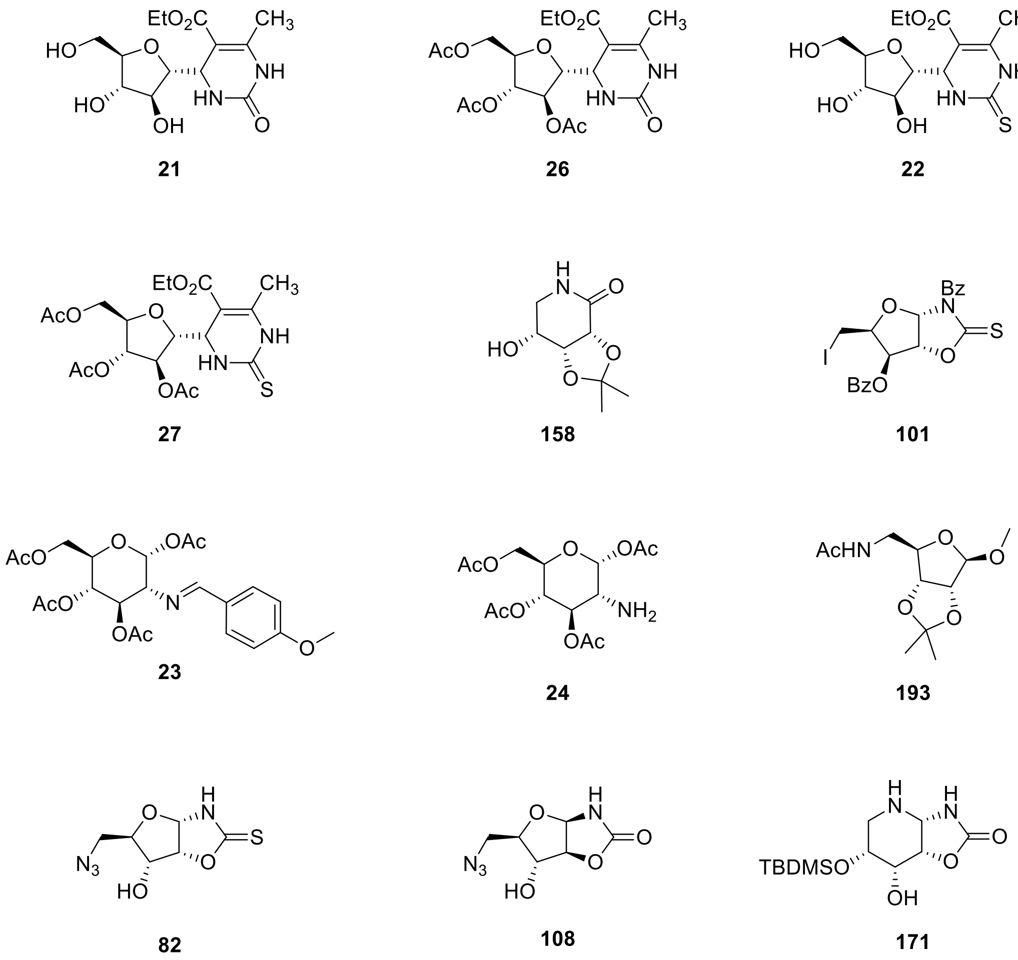


Figure 6.3 – Potentital Rhipicephalus (B.) microplus inhibitors.

6.1.2.1 - Adult Immersion Test:

- ✓ The engorged adult females were collected to establish the tests. These were obtained from host animals. The females then are transported to the laboratory as soon as possible, in conditions that ensure their survival.
- ✓ Once in the laboratory, females are collected and washed with tap water and dried with absorbent towels.
- ✓ Select females. Discard those that show discoloration, which show damage on its surface; who have made oviposition or those who do not move under light stimuli.
- ✓ The fully engorged and larger females should be selected, this shall ensure proportionality between the weight and the number of eggs laid.
- ✓ The selected females are arranged in teleogines of 10 units. Weigh the females, and submits them to the corresponding immersion treatment (solution at 0.1%(m/v) of tested compounds in water) for 30 minutes.
- ✓ Subsequently, the ticks are dried on paper towels, and arranged radially or longitudinally in a double-sided adhesive tape, in a petri dish such that each female oviposition be displayed separately.

✓ Incubate the Petri dishes at 27 or 28 ° C, assuring a relative humidity of 80% for one week (7 days). In all tests, a negative control (water immersion) should be included.
✓ The number of living female corresponds to the number of females that laid eggs. Record the weight of the eggs.

The values obtained are shown in Table 6.1 and in Graphic 6.1.

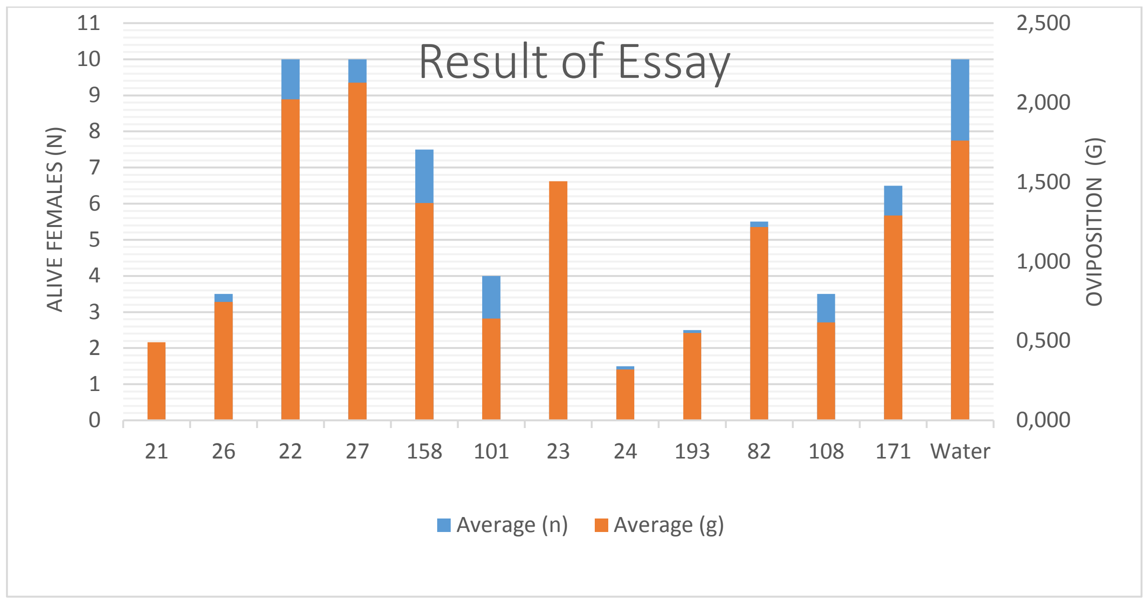
Table 6.1 – Results of essay 1 and essay 2.

		Essay 1		Essay 2		Average	
Drug	**[] (%)**	**Alive Females (n)**	**Oviposition (g)**	**Alive Females (n)**	**Oviposition(g)**	**(n)**	**(g)**
21	0.1	2	0,414	2	0,5698	2	0,492
26	0.1	4	0,932	3	0,5577	3,5	0,745
22	0.1	10	2,04	10	2	10	2,020
27	0.1	10	2,23	10	2,02	10	2,125
158	0.1	8	1,6302	7	1,105	7,5	1,368
101	* < 0.1	4	0,8022	4	0,4794	4	0,641
23	* < 0.1	6	1,5236	5	1,485	5,5	1,504
24	0.1	2	0,3856	1	0,2563	1,5	0,321
193	0.1	2	0,57	3	0,5292	2,5	0,550
82	* < 0.1	6	1,441	5	0,9944	5,5	1,218
108	0.1	4	0,8134	3	0,4212	3,5	0,617
171	0.1	6	1,441	7	1,1375	6,5	1,289
Water	100%	10	2,59	10	0,932	10	1,761

[(n) stand for number of units, (g) for grams]

* The compound is not completely soluble in water

According to the results obtained we can verify that compound **24** is the most promising compound, inhibits more than 50% growth females alive and consequently reduces the egg-laying (oviposition) by these females. Next comes the compound **21** and **193**, are good candidates at anti-parasitic drug. Compounds **26**, **101** and **108** also provide good inhibition. These compounds exhibit significant inhibition relative to the control (water). The results are expressed in Graphic 6.1, which lists the oviposition rather than the number of alive females.



Graphic 6.1 – Alive females/oviposition. [(n) stand for number of units, (g) for grams.]

6.2 - Glycosidases inhibitors

In this PhD project were made the synthesis of iminosugars fused with 1,3-oxazolidin-2-ones is way to the formation of various classes of new compounds, new methodologies and unexpected results.

Part of our interest was also dedicated to explore the biological potential of those new molecules. We were convinced that inside those OZOs families, many compounds also possess a significant biological profile. Despite of the fact that, to the best of our knowledge, the literature is scarce on the bio-activity of OZOs, our conviction was based on what can be found about OXTs, OZTs and some related compounds in terms of biological properties. We are focused in a potential glycosidases inhibition by those new molecules (iminoaugars fused with 1,3-oxazolidin-2-one).

6.2.1 - Glycosidases

Glycosidases are very important enzymes for their implication in numerous key-biological processes.[274] Compounds that can modify or inhibit such enzymes, the glycosidase inhibitors, bear strong biological potential in different therapies. Carbohydrates mimics with nitrogen replacing the endocyclic oxygen have attracted an impressive amount of interest as inhibitors of glycosidases.[275,276,277,278]

As reported in chapter IV, Pérez[179] and co-workers have developed a new family of highly selective glycosidase inhibitors, analogues to castanospermine **122**, in which the sp^3 amine-type nitrogen typical of iminosugars is replaced by a thiocarbamic and carbamic type nitrogen atom, with a substantial sp^2-character.[115,123] Two compounds of this family, the

castanospermine analogues **123** and **124**, exhibited total anomeric selectivity, behaving as potente competitive inhibitors of yeast α-glucosidase. The derivative **125**, with D-allo configuration, showed very weak inhibition of α-glucosidase. Compounds **227** and **228**, having D-galacto configuration, showed moderate inibition of α-galactosidase (Figure 6.4).

Rollin[196] and co-workers developed a new family of compounds - N-thiocarbonyl iminosugars (Castanospermine analogues bearing oxazole-2(3H)-thione moieties). Introduction of double bond in **229**, sharing D-xylo configuration, significantly reduced the inhibition of yeast α-glucosidase, when compared to castanospermine analogues **124**, weak inhibition of β-glucosidase was also noticed. The C-7 epimer **230**, sharing D-ribo configuration, was a more potent and selective inhibitor of isomaltase; although it also exhibited some affinity towards maltase and trehalase. This behaviour is drastically different from that observed for the 7-O-benzyl drerivative of **124 (231)**, sharing D-allo configuration, which did not inhibit any of the assayed α-glucosidases (Figure 6.4).

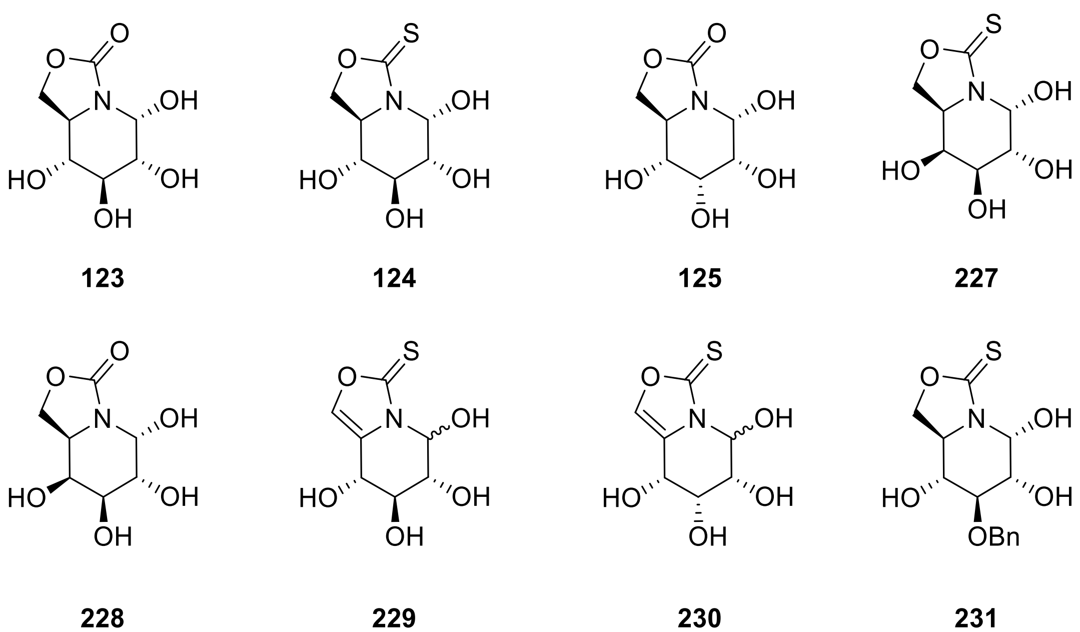


Figure 6.4 – Potential inhibitors of glycosidases found in literature

We have considered compounds **123**, **125** and **228** as a reference, as its structure is closely related to the structures of the OZOs iminosugars synthesized in this work. Therefore, in collaboration with Dr Pierre Lafite and Prof Richard Daniellou, we were able to test iminosugars **170, 171**, **172**, **177**, **181** and **231** as glycosidase inhibitors and compare the results with derivatives **123**, **125** and **232** (Figure 6.5).

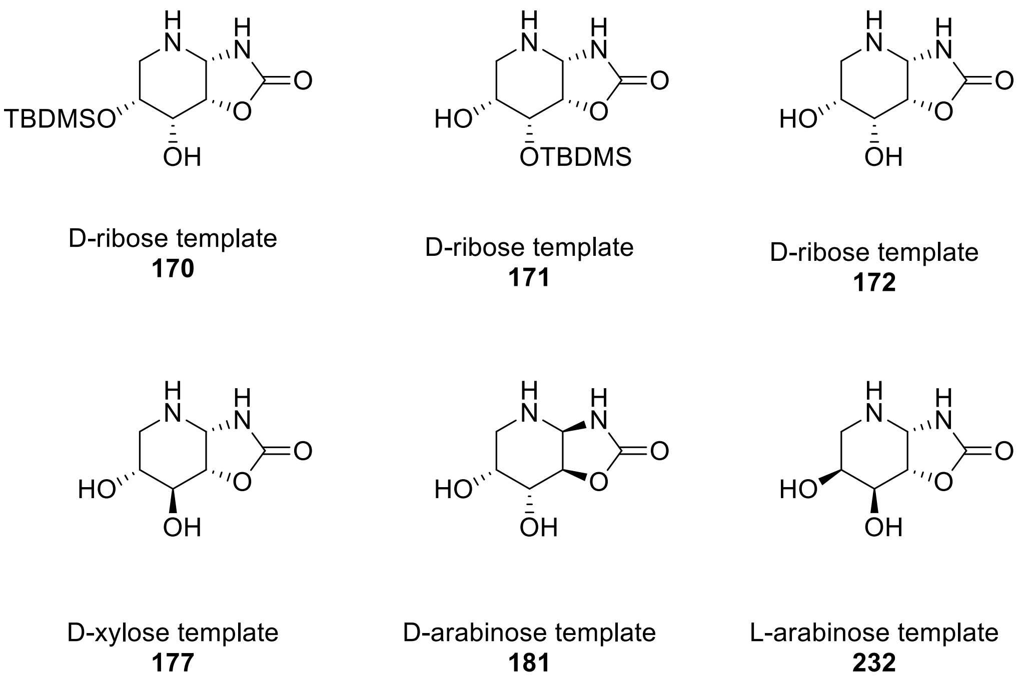


Figure 6.5 – Potential glycosidase inhibitors.

6.2.2 - Methodology for inhibition assays

6.2.2.1 - Enzymatic assays

A-D-glucosidase (from *S. cerevisiae*), β-D-glucosidase (from almonds), α-D-galactosidase (from green coffee beans), β-D-galactosidase (from *E. coli*), α-D-mannosidase (from jack beans), β-D-glucuronidase (from bovine liver) were purchased from Sigma (St Louis, USA). β-D-mannosidase (from *D. thermophilum*) was cloned, expressed in-house (Guillotin *et al.*, unpublished data). 4-nitrophenylglycosides substrates were purchased from Carbosynth (UK).

Glycosidases activities were assayed for 30 minutes at 37 °C in 200 µL reaction mixture containing 4-nitrophenyl-glycoside substrate, inhibitor (1 mM) in Tris buffer (50 mM, pH 7.0) or 2-(N-morpholino)ethanesulfonic (MES) buffer (50 mM, pH 5.0). Individual conditions (e.g. origin and concentration of enzymes, substrate concentration) are reported in Table 5.2.

After incubation, 100 µL of 1M sodium carbonate was added, and the amount of para-nitrophenol produced was quantified by absorbance measurement at 405 nm (ε_{405}= 19,500 $M^{-1}.cm^{-1}$). Product formation rates were extracted and remaining activies were determined using DMSO instead of inhibitor as control. Means and standard deviations were calculated from 3 independent data.

Table 6.2 - Individuals conditions.

Enzyme	Activity[a] (units)	Substrate	[Substrate] (μM)	pH
α-Glucosidase	10	pNP-α-D-Glucoside[b]	2500	7
β-Glucosidase	0.3	pNP-β-D-Glucoside	2500	7
α-Galactosidase	0.03	pNP-α-D-Galactoside	2500	5
β-Galactosidase	172	pNP-β-D-Galactoside	80	5
α-Mannosidase	0.5	pNP-α-D-Mannoside	1000	5
β-Mannosidase	-	pNP-β-D-Mannoside	100	7
β-Glucuronidase	5000	pNP-β-D-Glucuronide	450	5

[a] : enzymatic activity added per 200μl reaction

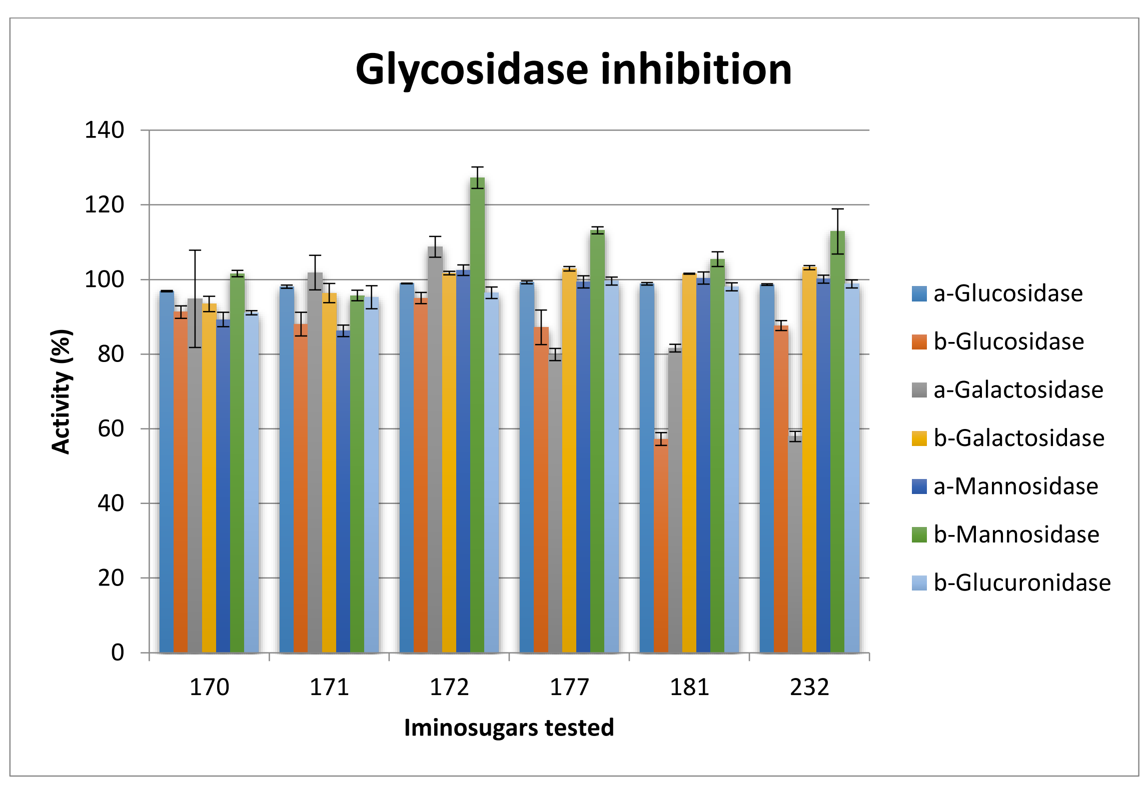
[b] : pNP : *para*-nitrophenyl

6.3.2.1 - Results of enzymatic assays

The experimental results of enzymatic assays are Table 6.3, Graphic 6.2 and Figure 6.6.

Table 6.3 – Inhibition essay of glycosidases.

Enzyme		DMSO	170	171	172	177	181	232
α-Glucosidase	Moy.		96,8581747	98,0712604	98,8974547	99,2500405	98,8383728	98,602045
	SD		*0,15375061*	*0,443557*	*0,08036917*	*0,37976684*	*0,31672282*	*0,20194795*
β-Glucosidase	Moy.		91,2751678	88,0399243	95,0094648	87,1966959	57,2190673	87,6441232
	SD		*1,65311443*	*3,20420122*	*1,50642855*	*4,60516355*	*1,71363129*	*1,34371518*
α-Galactosidase	Moy.		94,8219993	101,844371	108,751332	79,8739347	81,6028942	57,9434482
	SD		*13,029488*	*4,60261344*	*2,82605996*	*1,60699894*	*1,01345332*	*1,41033551*
β-Galactosidase	Moy.		93,4435658	96,3479511	101,710999	102,890007	101,538462	103,191948
	SD		*2,04821713*	*2,59791242*	*0,46122257*	*0,57566474*	*0,15148316*	*0,55369862*
α-Mannosidase	Moy.		89,2831337	86,2560917	102,515104	99,3435516	100,381263	100,116839
	SD		*1,89267443*	*1,52277827*	*1,42128062*	*1,6258135*	*1,6390133*	*1,07870159*
β-Mannosidase	Moy.		101,579587	95,6865128	127,27825	113,183475	105,467801	112,879708
	SD		*0,87619715*	*1,41569626*	*2,85734533*	*0,9644294*	*1,98915013*	*6,03602104*
β-Glucuronidase	Moy.		91,0743456	95,2460733	96,4314136	99,5895288	98,0565445	98,8356021
	SD		*0,57705361*	*3,10204507*	*1,52123786*	*1,06028169*	*1,06927762*	*1,0664437*



Graphic 6.2 - Activity of glycosidases. [a-stand for *alpha*, b- for *beta*].

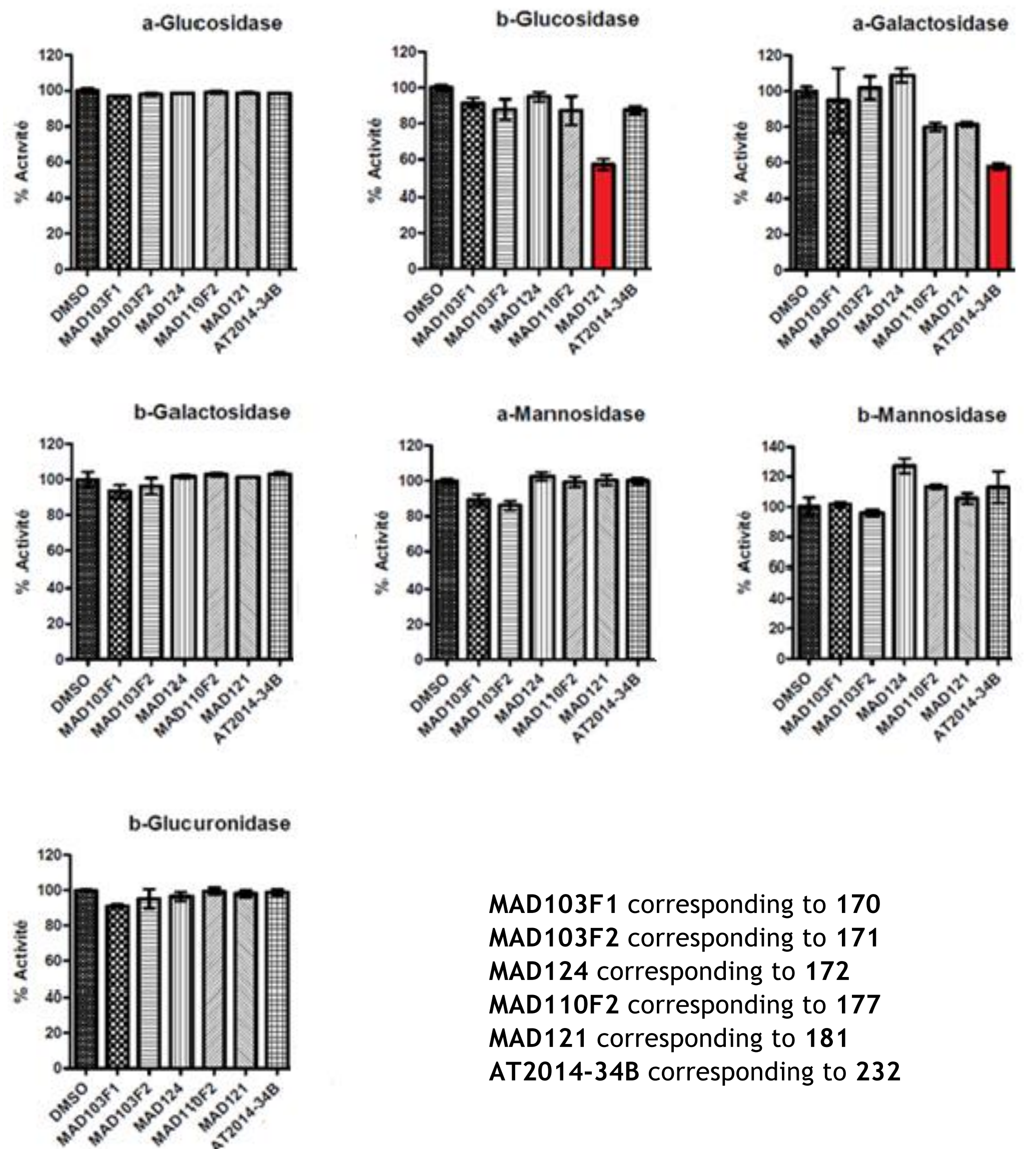


Figure 6.6 - % Activity for tested compounds for each glycosidases.[a-stand for alpha, b- for beta, % Activité- % Activity]

Based on the results we can say that the compound **181** and **232** showed to have some inhibitory activity. The compound **181** was showed inhibit the β-D-glucosidase from almonds. The compound **232** showed inhibit α-D-galactosidase from green coffee beans. The remaining iminosugars fused to the oxazolidin-2-one ring have not showed any inhibition. The inhibition showed by iminosugars **181** and **232** was moderate. The remaining iminosugars showed poor inhibition.

6.3 - Cytotoxicity and cell proliferation

Neoplastic cells are characterized by their uncontrolled proliferation, indifferentiation and loss of function as well as its invasive power and ability to generate metastases. The antineoplastic agents used today, in particular those which are cytotoxic, affect mostly only one of the characteristics of cancer cells, the cell division process, and are, therefore, only anti-proliferative agents. Considering the need for new approaches to cancer treatment, biochemical studies of cellular signal transduction mechanisms enable a better understanding of the neoplastic cell biology. Thus new mechanisms of action are explored in the development of new cytotoxic drugs. Cytotoxicity is simply the cell-killing property of a chemical compound (such as a food, cosmetic, or pharmaceutical) or a mediator cell (such as a cytotoxic T cell), independent from the mechanisms of death. Cell proliferation is the measurement of the number of cells that are dividing in a culture. The cytotoxicity and cellular proliferation are two concepts that relate to each other and determining cell viability. Cell viability was determined after exposure to cell lines specific for certain concentrations of some synthesized compounds (Figure 6.7).

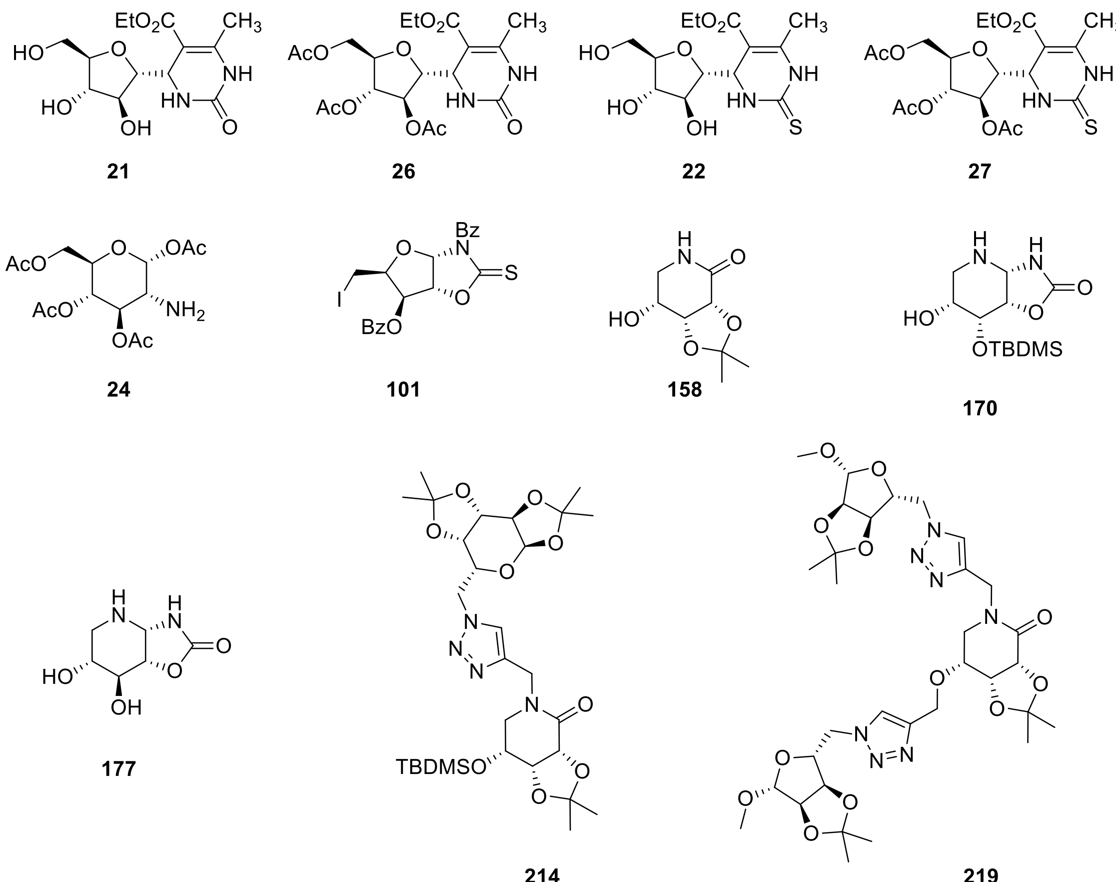


Figure 6.7 – Compounds tested to determine cell viability

6.3.1 - In vitro cell viability studies using MCF-7, T47D, and NHDF cells

The cells used in this study were human breast (MCF-7 and T47D) cancer cells as well as normal human dermal fibroblasts (NHDF) (all acquired to ATCC—American Type Culture Collection). Unless otherwise stated, chemicals (analytical grade), assay reagents, culture media, and supplements are all from Sigma-Aldrich. The studied compounds were dissolved in dimethylsulfoxide (DMSO) and the maximum final solvent concentration in the MTT experiment was 0.5%. This concentration of DMSO has no significant effects on cell viability (data not shown).

6.3.1.1 - Culture of cells

Cells were routinely maintained in 75 or 150 cm2 T-flasks at 37 °C in a humidified atmosphere containing 5% CO2. Human dermal fibroblasts were cultured in RPMI medium supplemented with 10% fetal bovine serum (FBS), HEPES (0.01 M), L-glutamine (0.02 M), and sodium pyruvate (0.001 M) and 1% antibiotic/antimycotic (10,000 units/ml penicillin, 10 mg/ml streptomycin and 25 µg/ml amphotericin B). Dubelco's Modified Eagle's Medium high glucose supplemented with 10% fetal bovine serum and 1% antibiotic/antimycotic was used to culture MCF-7 cells. T47D cells were cultured in RPMI medium supplemented with 10% FBS and 1% antibiotic (10,000 units/ml penicillin and 10 mg/ml streptomycin). The cells used in the experiments were in passages 8-9 (NHDF), 37-38 (MCF-7), and 16-17 (T47D).

6.3.1.2 - MTT assay

Cell viability was evaluated by quantifying the extent of the reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) according to a previously described procedure.[252, 253] Briefly, cells were seeded in 96-well plates (2×104 cells/mL; 100µL/well) in the culture medium and after 48 h they were treated with the different compounds at 30 µM for 72 h, with untreated cells serving as negative control and 5-fluouracil (5-FU) as positive control. For the dose-response studies, the concentrations evaluated were 0.01, 0.1, 1, 10, 25, and 50 µM. At the end of incubation the media in wells were removed and replaced with fresh media and MTT solution (5 mg/ml in phosphate buffer saline) and incubated at 37 °C for 4 h. Next, media-containing MTT were removed and formazan crystals were dissolved with DMSO and absorbance was recorded in a Bio-Rad X-Mark Microplate Spectrophotometer, at 570 nm. The extent of cell death was expressed as the percentage of cell viability in comparison with negative control cells.

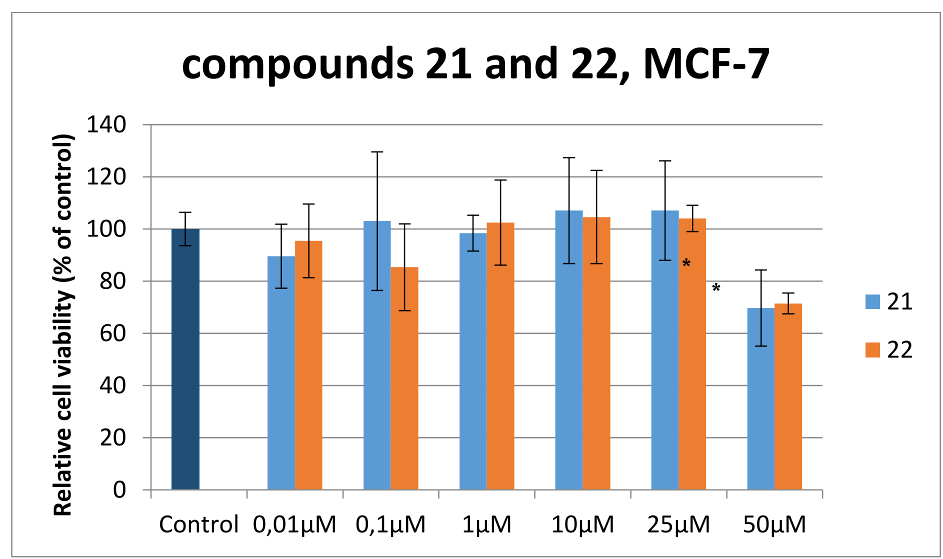
6.3.1.3 - Statistics

The experiments were performed in quadruplicate and repeated at least two times and the results of the cell proliferation were expressed as average ± standard deviation (SD). These

calculations were performed using the program Microsoft Excel 2010. The comparison between groups was analyzed using Student's t-test and the differences were considered statistically significant at $p < 0.05$.

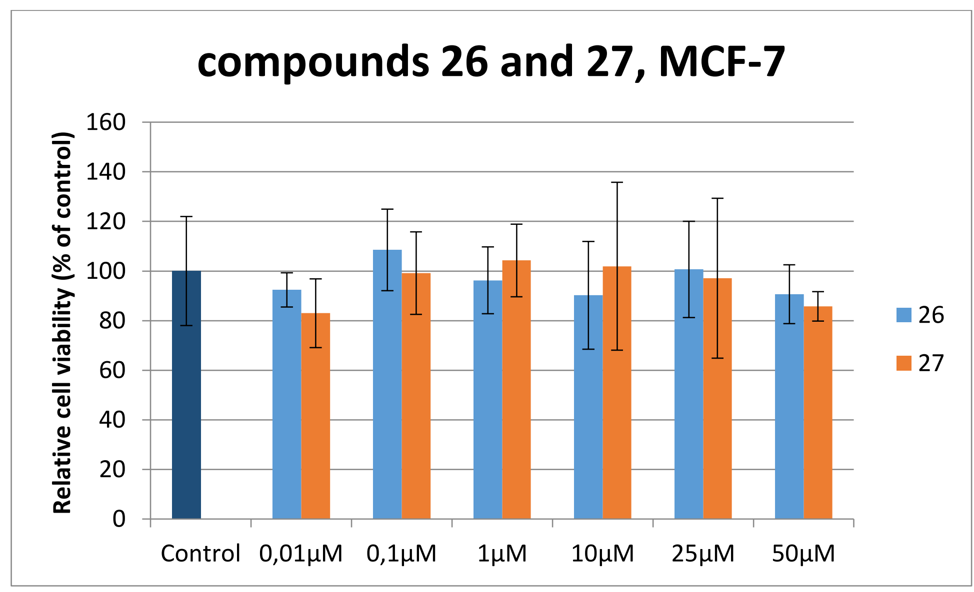
6.3.2 - C-Nucleosides

Due to the structural similarity between these Biginelli adducts and the natural nucleosides[254] it was decided to perform an *in vitro* evaluation of the cell proliferation effects of compounds **21**, **22**, **26** and **27**, in human cancer (MCF-7 and T47D) and normal (NHDF) cell lines. For this, cells were exposed to different concentrations of the compounds (0.01, 0.1, 1, 10, 25 and 50µM) during 72h, and then a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was effected. A positive control, 5-fluouracil (5-FU), which is in clinical use as antitumor agent, was also included in this study. Another reason for the concomitant evaluation of 5-FU is the fact that this prodrug is transformed in a nucleotide within cells.[255]
Considering the data on Graphic 6.4, Graphic 6.6, Graphic 6.7, Graphic 6.9 and Graphic 6.10, it is clear that compounds **21**, **22**, **26** and **27** have low to moderate effects on the proliferation of these cells under study in these experimental conditions. In fact, it can be observed that compounds **21** and **22** (at 50µM) in MCF-7 and NHDF cells and compounds **22** (at 10, 25 and 50µM) and **26** (at 50µM) in T47D cells led to a significant decrease on cell proliferation. Thus, the most antiproliferative of these four Biginelli adducts is clearly compound **22**. On the other hand, a small but significant increase in cell proliferation was also observed for compounds **21** (at 0.01 and 1µM) and 27 (at 0.01µM) in the tumoral T47D cells and for compounds **21** (at 10µM) and **26** and **27** (at 1 and 10µM) in normal cells. In spite of the fact that this is only a preliminary study, overall it can be considered that these four Biginelli adducts have low cytotoxicity in these experimental conditions. In addition and as expected, in a similar range of concentrations, 5-FU exhibited a strong antiproliferative effect in all these cells (Graphic 6.5, Graphic 6.8 and Graphic 6.11).



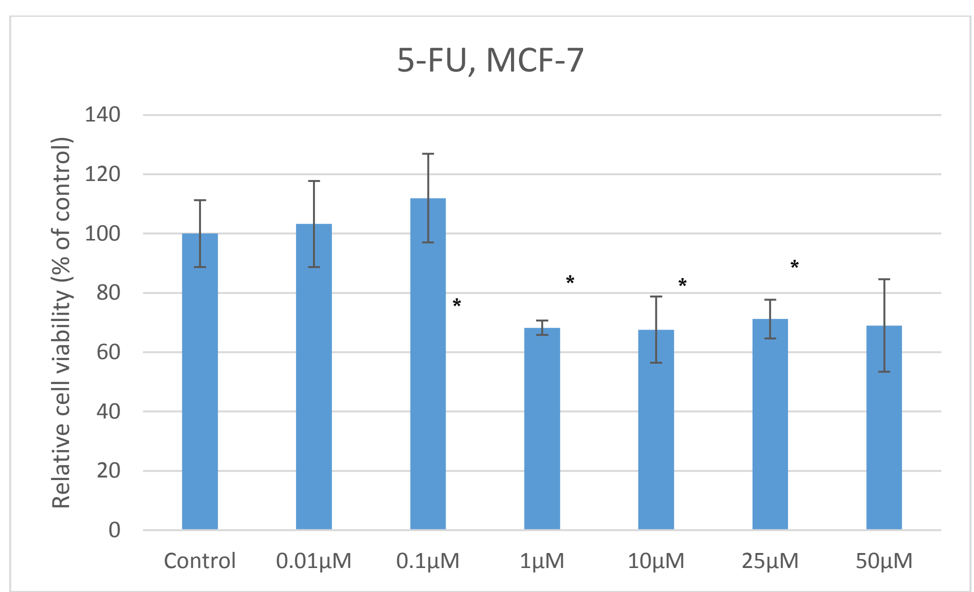
Graphic 6.3 - Relative cell viability of MCF-7 cells when exposed for 72 h to compounds **21** and **22**, in concentrations ranging from 0.01 to 50µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *p<0.05 versus the control (Student's t-test, n = 4).



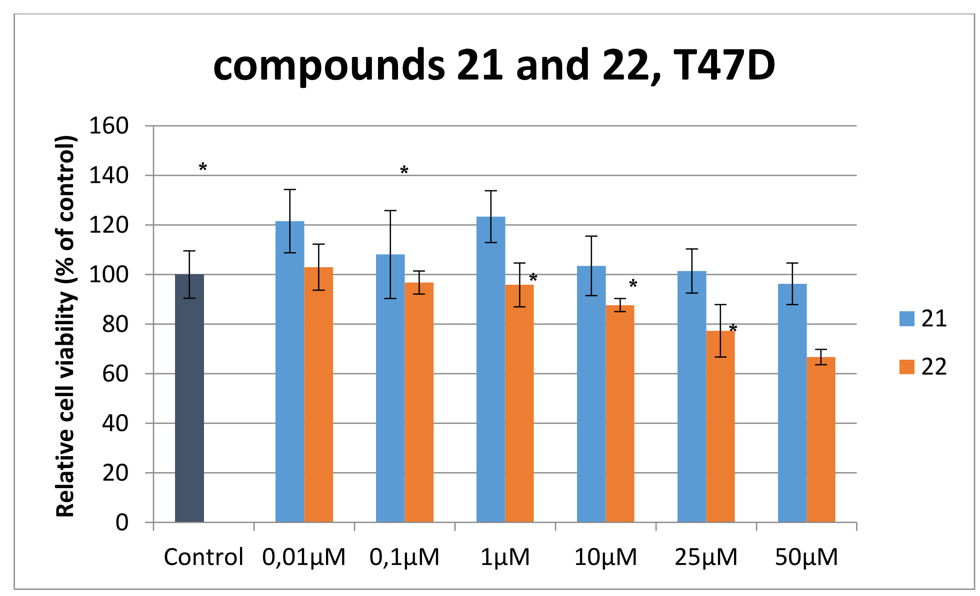
Graphic 6.4 - Relative cell viability of MCF-7 cells when exposed for 72 h to compounds **26** and **27** in concentrations ranging from 0.01 to 50µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD (n = 4).



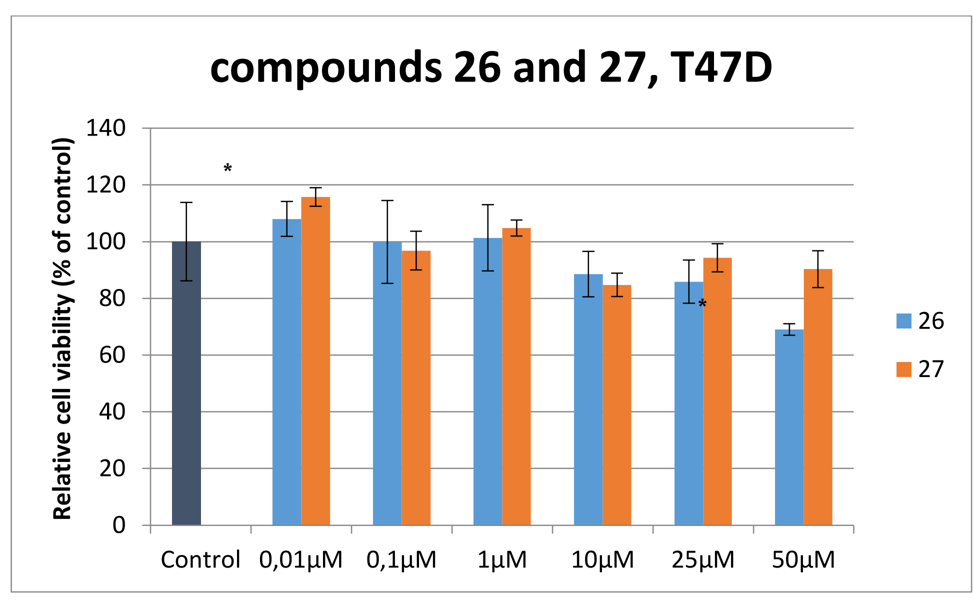
Graphic 6.5 - Relative cell viability of MCF-7 cells when exposed for 72 h to 5-FU, in concentrations ranging from 0.01 to 50µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *p<0.05 versus the control (Student's t-test, n = 4).



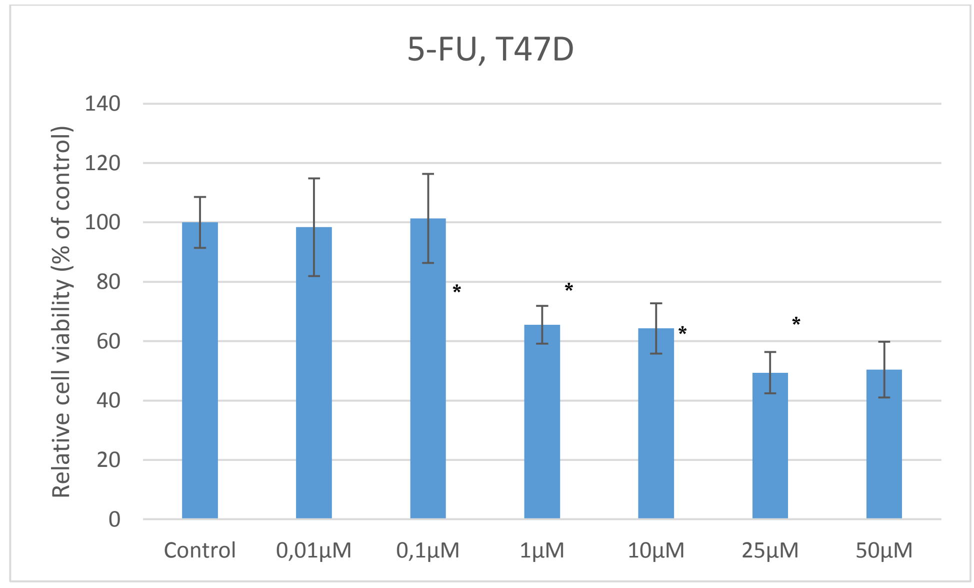
Graphic 6.6 - Relative cell viability of T47D cells when exposed for 72 h to compounds **21** and **22**, in concentrations ranging from 0.01 to 50µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *p<0.05 versus the control (Student's t-test, n = 4).



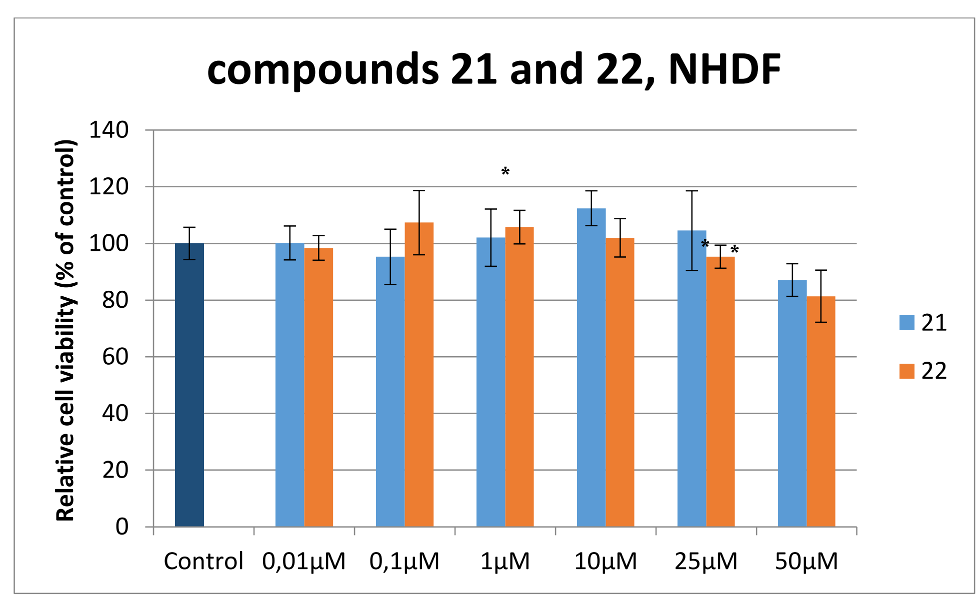
Graphic 6.7 - Relative cell viability of T47D cells when exposed for 72 h to compounds **26** and **27**, in concentrations ranging from 0.01 to 50µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *p<0.05 versus the control (Student's t-test, n = 4).



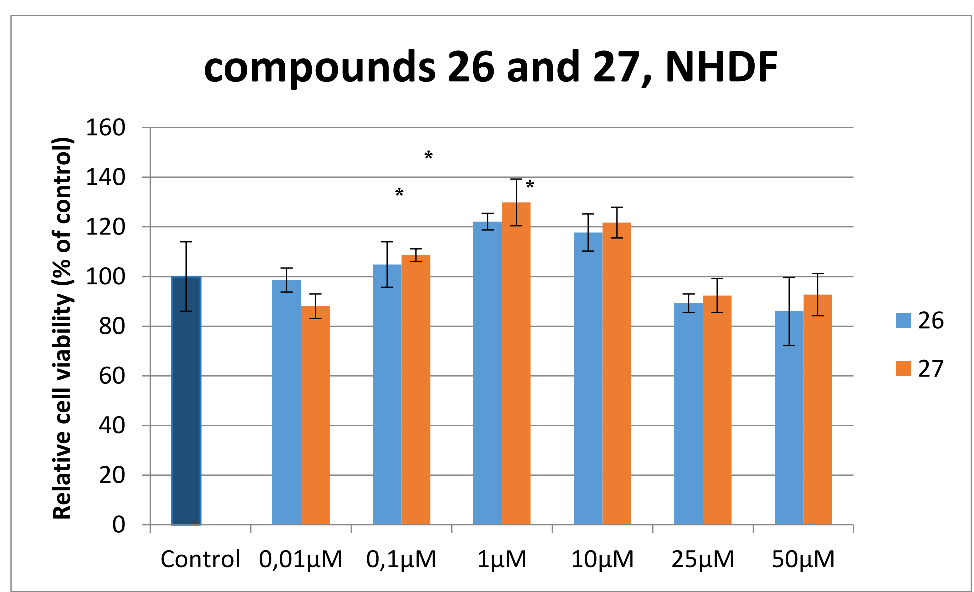
Graphic 6.8 - Relative cell viability of T47D cells when exposed for 72 h to 5-FU, in concentrations ranging from 0.01 to 50µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *p<0.05 versus the control (Student's t-test, n = 4).



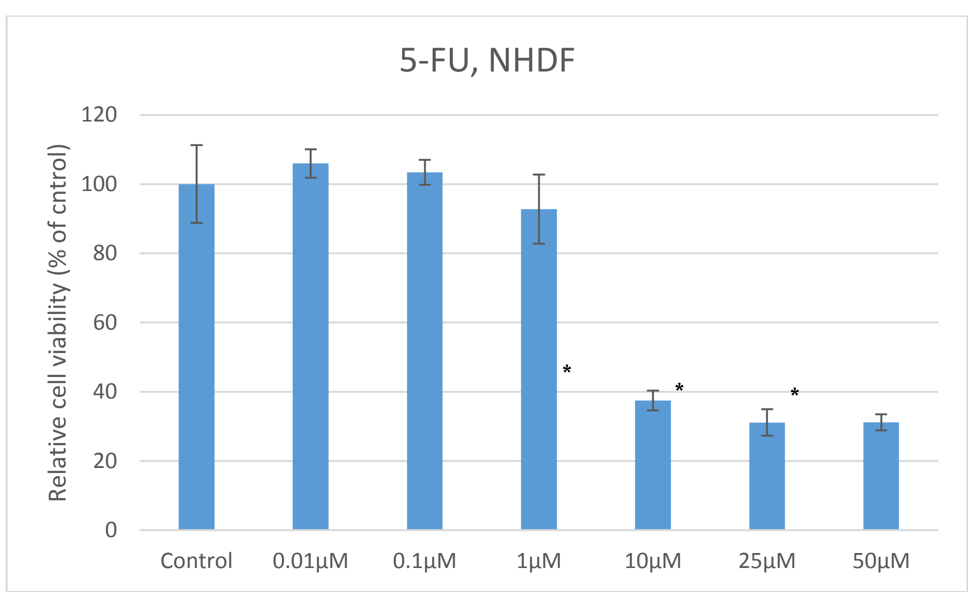
Graphic 6.9 – Relative cell viability of NHDF cells when exposed for 72 h to compounds **21** and **22**, in concentrations ranging from 0.01 to 50µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *p<0.05 versus the control (Student's t-test, n = 4).



Graphic 6.10 – Relative cell viability of NHDF cells when exposed for 72 h to compounds **26** and **27**, in concentrations ranging from 0.01 to 50µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *p<0.05 versus the control (Student's t-test, n = 4).



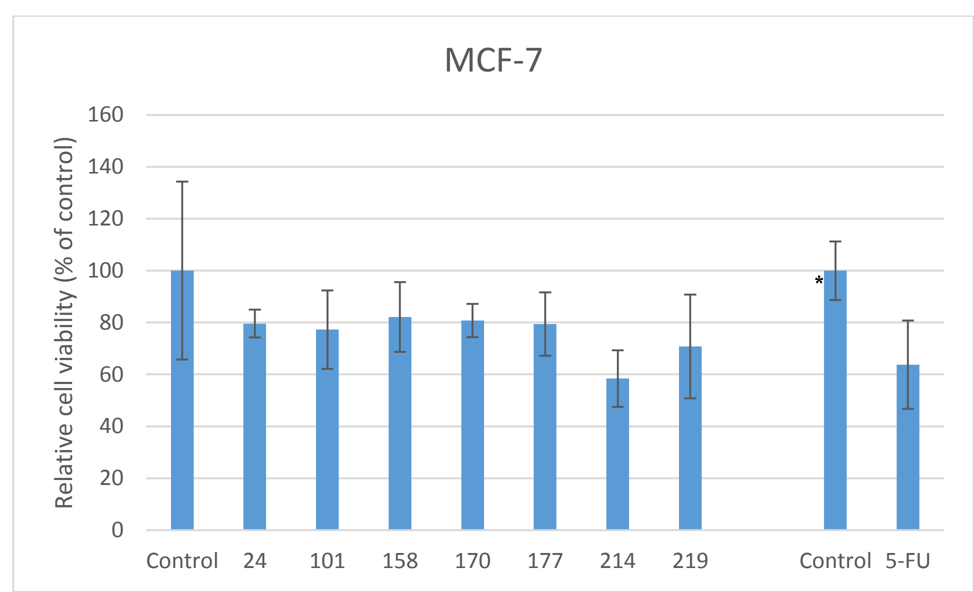
Graphic 6.11 – Relative cell viability of NHDF cells when exposed for 72 h to 5-FU, in concentrations ranging from 0.01 to 50µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *p<0.05 versus the control (Student's t-test, n = 4).

6.3.3 - Carbohydrate derivatives

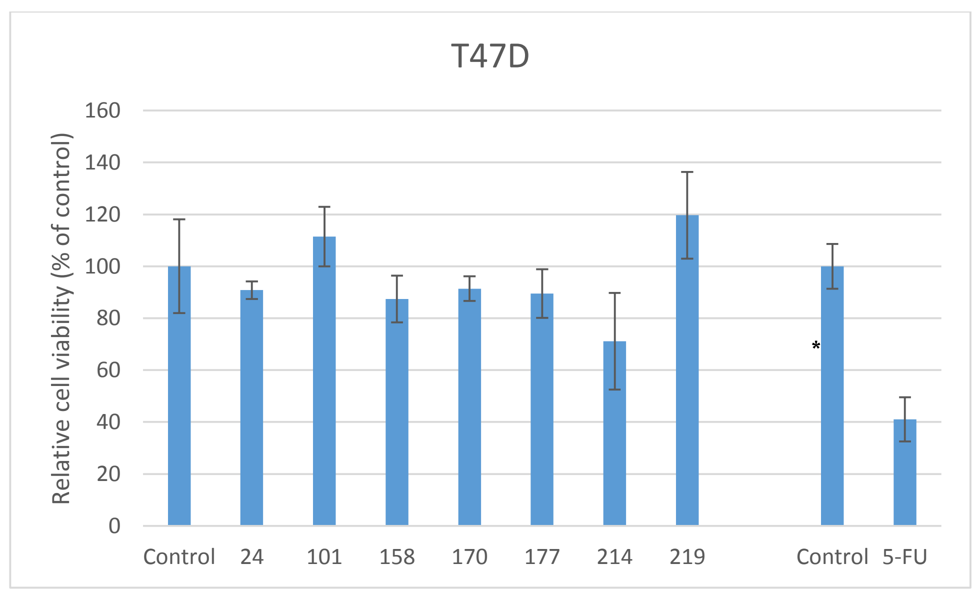
Due to the known pharmacological significance of carbohydrates and their derivatives as well as the triazole scaffold[256] it was also decided to perform an *in vitro* basic evaluation of the cell proliferation effects of some selected compounds (**24**, **101**, **158**, **170**, **177**, **214** and **219**). This study was performed using human cancer (MCF-7 and T47D) and normal (NHDF) cell lines, which were exposed to a 30µM concentration of the compounds during 72h, followed by the previously mentioned MTT assay. Again, 5-FU was also included as a positive control[257] and was evaluated in similar conditions.

Considering the data on Graphic 6.12, Graphic 6.13 and Graphic 6.14, it can clearly be concluded that these compounds have not significant effects on the proliferation of these cells in these experimental conditions. Within this group of compounds, only the structure **214** seem to led to some decrease in cell proliferation although not significant in comparison with the corresponding negative control.



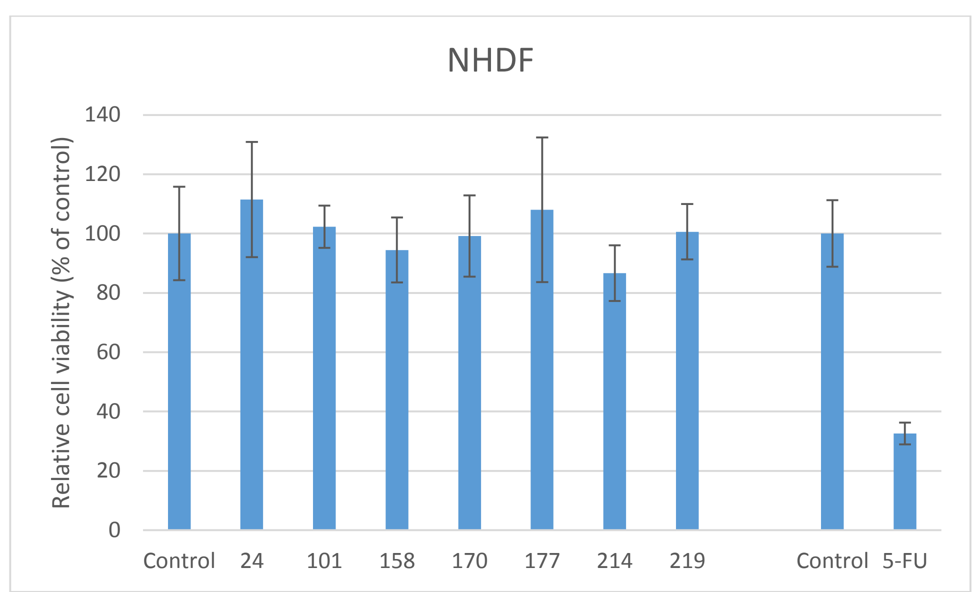
Graphic 6.12 - Relative cell viability of MCF-7 cells when exposed for 72 h to compounds **24**, **101**, **158**, **170**, **177**, **214**, **219** and 5-FU, in a concentration of 30µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *$p<0.05$ versus the control (Student's t-test, n = 4).



Graphic 6.13 – Relative cell viability of T47D cells when exposed for 72 h to compounds **24**, **101**, **158**, **170**, **177**, **214**, **219** and 5-FU, in a concentration of 30µM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *$p<0.05$ versus the control (Student's t-test, n = 4).

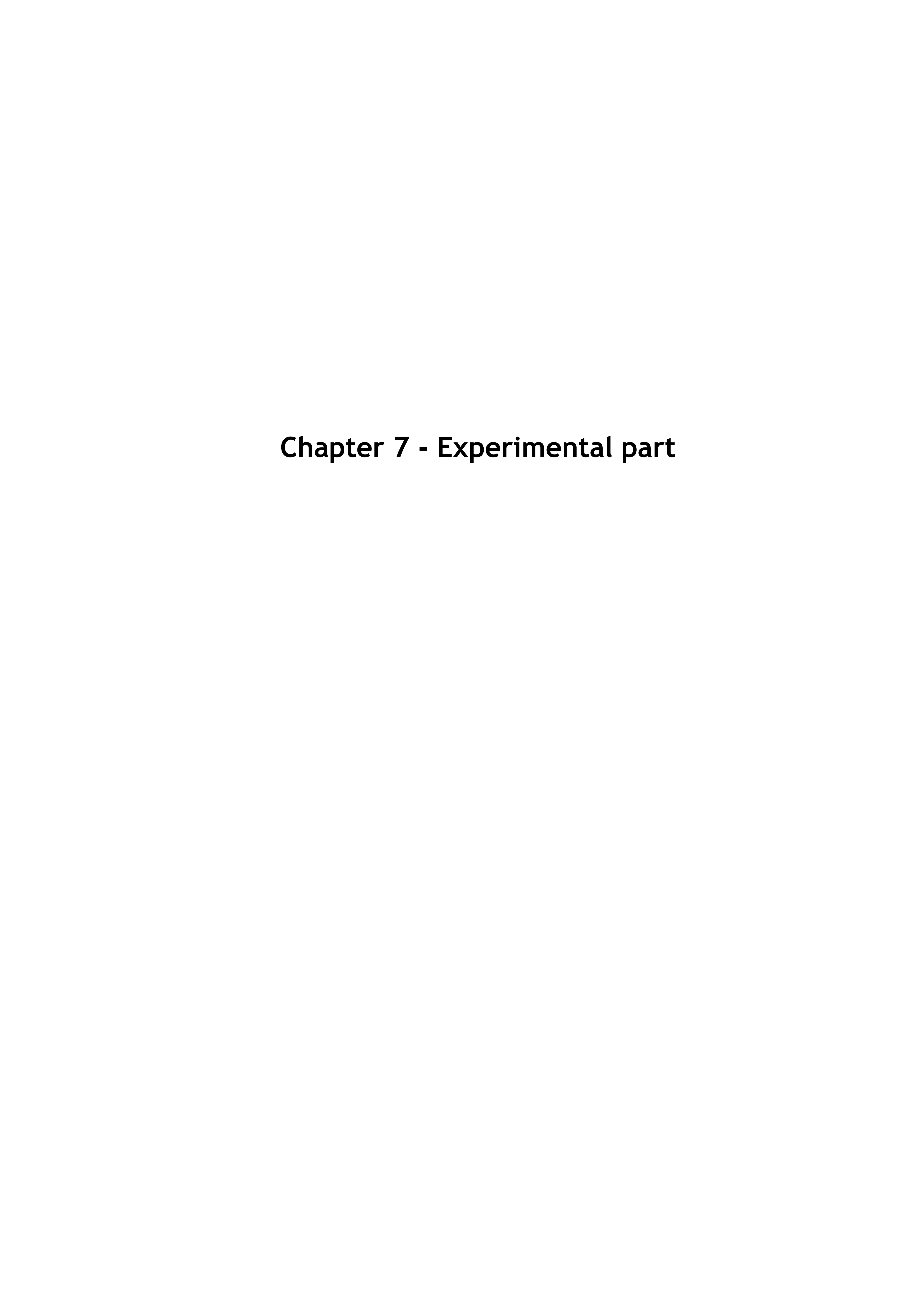


Graphic 6.14 – Relative cell viability of MCF-7 cells when exposed for 72 h to compounds **24**, **101**, **158**, **170**, **177**, **214**, **219** and 5-FU, in a concentration of 30μM (MTT assay).

Data are expressed as a relative % of cell viability in comparison with the control; the bars represent the mean and the lines represent the associated SD; *p<0.05 versus the control (Student's t-test, n = 4).

6.4 – Conclusion

- ✓ The tetra-acetylated glucosamine **24** was showed better results, they inhibit 85% the growth females, and consequently inhibition in 82% of oviposition by them.
- ✓ Oxopyrimidines **21** and **26** also inhibit drastically the growth and oviposition.
- ✓ The acetylated aminosugar **193**, the azido-1,3-oxazolidin-2-one **108** and anisald-tetrahydro-acetylated glucosamine **23** are also inhibit the growth and oviposition.
- ✓ .All these compounds (**24**, **21**, **23**, **26**, **108**, **193**) have shown to be promising in inhibiting the growth of females and subsequently oviposition, they are good candidates for anti-parasitic drugs.
- ✓ The iminosugars **181**(D-arabinose template) and **232** (L arabinose template), proved to be inhibitors of ß-glucosidase and α-galactosidase, respectively.
- ✓ Compounds **21**, **22**, **24**, **26**, **27**, **101**, **158**, **170**, **177**, **214** and **219** are not cytotoxic, these results are promising if these compounds inhibit acetylcholinesterase.



Chapter 7 - Experimental part

7.1 - General methods

Thin layer chromatography is used to check the progress of reactions and during purification. TLC plates (aluminum plates coated with silica gel Silica) proved / powered by UV light (λ= 254 nm) and immerse in a revealing solution and then heated at 150 ° C. The revealing solution were: - Sulfuric acid (10%) in ethanol; - Phosphomolybdic acid (5%) in ethanol; - Sulfuric acid (1.5 mL), vaniline (3 g) in ethanol (100 mL).

Solvents and reagents were bought from Fluka, Merck, Aldrich or Acros Organics, and use without further purification.

The Rf, ie, the ratio between the height of elution of the product and that of the eluent were calculared.

The synthesized compounds were purified by column chromatography on silica gel. To do this, we use silica gel SI 60 (40-63 µm) and chromatographic columns were eluted with the help of compressed air or pumps.

The obtained products were analyzed using different techniques:

✓ Proton NMR spectra were recorded in $(CD_3)_2S{=}O$, CD_3OD and $CDCl_3$ with Bruker spectrometers type AV 250 (250 MHz) and Bruker AV 400 (400 MHz) using TMS as the internal standard, at ICOA and UBI. Correlations homonuclear 2-dimensional COSY type (*Correlated Spectrometry*) were performed to allow completion of the assignment of certain signals. Chemical shifts (δ) of the various signals are reported in parts per million (ppm), coupling constants (J) are given in Hertz (Hz) and the multiplicity of signals is indicated on the spectra, using the abbreviations: bs (broad singlet), s (singlet), d (doublet), dd (double doublet), q (quartet), dt (double triplet), td (triple doublet), ddd (double double doublet), m (multiplet) and t (triplet).

✓ Carbon NMR spectra were recorded at 100 MHz and 62.5 MHz in the same spectrometers that ^{1}H NMR spectra, with the same deuterated solvents. For the interpretation of certain signals, we also performed two-dimensional heteronuclear correlation between the proton and carbon 13 of HSQC (^{1}H detection mode *Hetero Single-Quantum Correlation*)

The results of mass specter were expressed as a percentage of the most intense peak as a function of mass/charge ratio (m / z).

The optical rotations (α) were determinated at 20° C, using a polarimeter, a sodium lamp at 589 nm and the length of the used cell was 1 dm.

7.2 - Compound description

2,5-anhydro-D-mannose **(13)**

$C_6H_{10}O_5$

M.W=162,14 g/mol

D-glucosamine (1 g, 2.319 mmol) was dissolved in 3.5 mL of water to give a colorless solution at room temperature. The reaction was cooled to -2ºC, the sodium nitrite (0.399 g, 5.797 mmol, 2.5 eq.) was added. The reaction was cooled to -5ºC, the dilute acetic acid (0.33 mL, 5.797 mmol, 2.5 eq.) in water (0.7 mL) was added with a separatory funnel over one hour without going above 2ºC. The reaction was left for one hour at -2ºC and then one hour at room temperature and then bubbled with nitrogen for 2 hours. The solution was evaporated to dryness then solubilized in methanol. The salts were removed by filtration over celite and de filtrate collected and evaporated in a evaporator rotary to dryness. The crude solid is used directly in next reaction.

CAS [495-75-0]; Yield: 96%; Rf= 0.66 (EA/MeOH: 50/50).

^{1}H NMR (400 MHz, $(CD_3)_2S=O$) δ = 3.23-3.24 (m, 1H,CH-4), 3.58 (ls, 3H, OH), 3.88-3.90 (m, 2H, CH_2-5), 4.02-4.14 (m, 1H, CH-3), 4.16-4.17 (m, 1H, CH-2), 5.03 (d, 1H, J= 5.5 Hz, CH-1,), 9.57 (s, 1H, CHO).

^{13}C NMR (100 MHz, $(CD_3)_2S=O$) δ = 61.5 (CH_2-5), 76.3 (CH-2), 79.2 (CH-3), 87.3 (CH-4), 89.7 (CH-1), 202.8 (CHO).

5-Pyrimidinecarboxylic acid, 4-α-D-arabinofuranosyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-, ethyl ester **(21)**

$C_{13}H_{20}N_2O_7$
M.W= 316,31 g/mol

2,5-anhydro-D-mannose **13** (0.726 g, 4.478 mmol) was dissolved in 28 mL of anhydrous ethanol at room temperature. Urea (1.227 g, 9.852 mmol, 2.2 eq.) and ethyl acetoacetate (3.8 mL, 14.330 mmol, 3.2 eq.) were added and allowed to react for 3 hours at 80ºC, in reflux. After cooling to room temperature the solvent was evaporated in the evaporator.[67] The residue was purified by silica gel column chromatography using EA as eluent.

Yield: 56%; **Rf=** 0.38 (EA/MeOH: 95/5); $[\alpha]_D^{20}$(0.667, MeOH)= 15

IR (cm^{-1}): 1652 (C=C), 1724 (C=O), 3372 (OH + NH).

^1H NMR (400 MHz, $CDCl_3$) δ= 1.26-1.31 (m, 3H, CH_3 of ethyl), 2.05 (s, 3H, CH_3 of C6), 3.45-3.47 (m, 1H, CH-4'), 3.76-3.82 (m, CH_2-5'), 3.99-4.08 (m, 2H, CH_2 of ethyl), 4.11-4.14 (m, 1H, CH-3'), 4.17-4.20 (m, 1H, CH-2'), 4.26 (s, 1H, CH-4), 5.98 (d, 1H, J= 4 Hz, CH-1'), 7.28 (s, 2H, NH-1 and NH-3).

^{13}C NMR (100 MHz,$CDCl_3$) δ = 14.1 ($CH_2\underline{C}H_3$), 21.0 (CH_3 of C6), 36.1 (($\underline{C}H_2CH_3$), 49.1(CH of C4), 61.6 (CH_{2}-5'), 77.0 (CH-2'), 80.0 (CH-3'), 83.9 (CH-4'), 127.9 (Cq of C5), 128.0 (CH-1'), 157.5 (Cq of C6), 170.4 (Cq of NC=ON), 172.1 (Cq of C$\underline{C}O_2$Et).

5-Pyrimidinecarboxylic acid, 4-α-D-arabinofuranosyl-1,2,3,4-tetrahydro-6-methyl-2-thiono-, ethyl ester **(22)**

$C_{13}H_{20}N_2O_6S$

M.W= 332.10 g/mol

2,5-anhydro-D-mannose **13** (2.256 g, 13.913 mmol) was dissolved in 41,6 mL of anhydrous ethanol at room temperature. Thiourea (2.33 g, 30.609 mmol, 2.2 eq.) and ethyl acetoacetate (5.7 mL, 44.522 mmol, 3.2 eq.) were added and allowed to react for 5 hours at 80ºC, in reflux. After cooling to room temperature the solvent was evaporated in in the evaporator. The residue was purified by silica gel column chromatography us ing EA as eluent.

Yield: 60%; **Rf=** 0.27 (EA); $[\alpha]_D^{20}$(0.837, MeOH)= 10.75

IR (cm^{-1}): 1646 (C=C), 1716 (C=S), 3328 (OH + NH).

^{1}H NMR (400 MHz, $(CD_3)_2S$=O) δ= 1.25-1.28 (m, 3H, CH_3 of ethyl), 1.98 (s, 3H, CH_3 of C6), 3.53-3.54 (m, 1H, CH-4'), 3.62-3.66 (m, CH_2-5'), 3.68-3.83 (m, 2H, CH_2 of ethyl), 4.06-4.08 (m, 1H, CH-3'), 4.14-4.22 (m, 1H, CH-2'), 4.56 (s, 1H, CH-4), 5.93 (d,1H, J= 8 Hz, CH-1'), 6.83 (ls, 2H, NH-1 and NH-3).

^{13}C NMR (100 MHz,$(CD_3)_2S$=O) δ = 14.5 ($CH_2\underline{C}H_3$), 23.3 (CH_3 of C6), 36.9 ($\underline{C}H_2CH_3$), 49.6 (CH of C4), 62.9 (CH_2-5'), 78.5 (CH-2'), 80.7(CH-3'), 84.1 (CH-4'), 128.0 (Cq of C5), 128.6 (CH-1'), 158.1 (Cq of C6), 172.2 (Cq of $C\underline{C}O_2Et$), 185.5 (Cq of NC=SN).

2-(4-methoxybenzylidene)imino-2-deoxy-1,3,4,6-tetra-O-acetyl-ß-D-glucopyranose **(23)**

$C_{22}H_{27}NO_{10}$

M.W= 465,45 g/mol

Procedure 1:

D-Glucosamine (1.000 g, 4.638 mmol) was dissolved in 2.2 mL of sodium hydroxide 1M at room temperature. The *p*-anisaldehyde (0.631 g, 4.638 mmol, 1 eq.) was added and stirred violently until a white precipitate appeared and put in the cold room for overnight crystallization. The precipitate was washed with water, filtered and the crude solid was dried with diethyl ether to obtain anisald-D-glucosamine. Anisald-D-Glucosamine (1.000 g, 3.366 mmol) was dissolved in 6 mL of dry pyridine at room temperature. The acetic anhydride (3.7 mL, 33.656 mmol, 10 eq.) was added and allowed to react for 40 hours at room temperature. The mixture was evaporated in the evaporator and co-evaporated three times with toluene. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (35:75) as eluent. **Yield**: 46%

Procedure 2:

D-Glucosamine (0.500 g, 2.319 mmol) was dissolved in 2.08 mL of sodium hydroxide 1M at room temperature. The p-anisaldehyde (0.287 g, 2,319 mmol, 1 eq.) was added and stirred violently until a white precipitate appeared and put in the cold room for overnight crystallization. The precipitate was washed with water, filtered and the crude solid was dried with diethyl ether to obtain anisald-D-glucosamine. Anisald-D-Glucosamine (0.789 g, 2.655 mmol) was dissolved in 4.7 mL of dry pyridine at room temperature. The reaction mixture was placed in an ice bath. The acetic anhydride (2.5 mL, 26.555 mmol, 10 eq.) and DMAP (0.260 g, 2.124 mmol, 0.8 eq.) were added and allowed to react for 1 hour at room temperature. The mixture was evaporated in the evaporator and co-evaporated three times with toluene. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (25:75) as eluent. **Yield**: 80%

CAS [7597-81-1]; **Rf=** 0.22 (EA/Hex: 50/50).

^{1}H NMR (400 MHz, $CDCl_3$) δ= 1.88 (s,3H, Ac), 2.02 (s, 3H, Ac),2.04 (s, 3H, Ac), 2.10 (s, 3H, Ac), 3.43-3.47 (m, 2H, CH_2-6), 3.84 (s, 3H, OCH_3), 4.12-4.15 (m, 1H, CH-5), 4.35-4.40 (m, 1H, CH-

4), 5.14 (t, 1H, J= 9.8 Hz, CH-2), 4.43 (t, 1H, J= 9.8 Hz, CH-3), 5.94 (d, 1H, CH-1,), 6.90 (d, 2H, J= 2.76 Hz, CH benzyl), 7.66 (d, 2H, CH benzyl), 8.16 (s, 1H, N=CH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 20.5 ($CO\underline{C}H_3$), 20.7 ($CO\underline{C}H_3$), 20.8 ($CO\underline{C}H_3$), 20.8 ($CO\underline{C}H_3$), 55.4 (OCH_3), 61.9 (CH_2-6), 68.1 (CH-4), 72.8 (CH-3), 72.9 (CH-5), 73.3 (CH-2), 93.2 (CH-1), 114.1 (CH benzyl), 128.3 (Cq benzyl (CCH=N)),130.3 (CH benzyl), 162.3 (Cq benzyl ($COCH_3$)), 164.3 (N=CH), 168.8 ($\underline{C}OCH_3$), 169.5 ($\underline{C}OCH_3$), 169.9 ($\underline{C}OCH_3$), 170.7 ($\underline{C}OCH_3$).

1,3,4,6-tetra-*O*-acetyl-ß-D-glucosamine HCl **(24)**

$C_{14}H_{22}ClNO_9$
M.W= 383.10 g/mol

Compound **23** (0.700 g, 1.827 mmol) was dissolved in 13.4 mL of acetone at room temperature. The HCl (0.12 mL, 3.884 mmol, 2.1 eq.) was added at room temperature. A precipitate began to form in a few minutes. The solution was stirred for one hour and half and then filtrated. The compound was washed with acetone.

CAS [10034-20-5]; **Yield:** 94%; **Rf=** 0.06 (AE/Hex: 85/15).

^{1}H NMR (400 MHz, $(CD_3)_2S=O$) δ= 1.97 (s, 3H, Ac), 1,99 (s, 3H, Ac), 2.02 (s, 3H, Ac), 2.16 (s, 3H, Ac), 3.55-3.58 (m, 1H, CH-2), 3.97-4.03 (m, 1H, CH_2-6), 4,04-4.06 (m, 1H, CH-5), 4.18 (dd, 1H, J= 4.3 Hz, CH_2-6), 4.92 (t, 1H, J= 9.52 Hz, CH-4), 5.35 (t, 1H, J= 9.52 Hz, CH-3), 5.89 (d, 1H, J= 8.64 Hz, CH-1), 8.75 (ls, 2H, NH_2).

^{13}C NMR (100 MHz, $(CD_3)_2S=O$) δ= 20.4 (CH_3 of Ac), 20.5 (CH_3 of Ac), 20.9 (CH_3 of Ac), 21.0 (CH_3 of Ac), 52.2 (CH-2), 61.3 (CH_2-6), 67.8 (CH-4), 70.4 (CH-3), 71.7 (CH-5), 90.2 (CH-1), 168.8 (Cq of Ac), 169.4 (Cq of Ac), 169.9 (Cq of Ac), 170.0 (Cq of Ac).

3,4,6-tri-0-acetyl-2,5-anhydro-D-mannose **(25)**

AcO O CHO AcO OAc

$C_{12}H_{16}O_8$

M.W= 288,12 g/mol

Compound **24** (0.221 g; 0.576 mmol) was dissolved in double distilled water (8.8 mL) and chilled in an ice-salt bath. A solution of sodium nitrite (0.119g, 1.728 mmol, 3 eq.) in water (0.44 mL) was added. Glacial acetic acid (0.11 mL, 1.901 mmol, 3.3 eq) was then added in several portions to the mixture which start bubbling. The solution was kept stirring for two hours, then bubbled for half an hour with nitrogen. The solution was evaporated to dryness.

CAS [50710-97-9]; Yield: 96%; **Rf=** 0.1(EA/Hex: 50/50).

^{1}H NMR (400 MHz,$CDCl_3$) δ= 2.10 (s, 9H, CH_3 of Ac), 4.22-4.28 (m, 1H, CH_2-5), 4.30-4.34 (m, 1H, CH_2-5'), 4.36-4.37 (m, 1H, CH-3), 4.54 (m, 1H, CH-4), 5.13-5.14 (m, 1H, CH-2), 5.37-5.38 (m, 1H, CH-1), 9.72 (ls, 1H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.7 ($\underline{C}H_3$ of Ac), 20.8 ($\underline{C}H_3$ of Ac), 20.9 ($\underline{C}H_3$ of Ac), 63.0 (CH_2-5), 77.2 (CH-2), 77.4 (CH-3), 82.7 (CH-4), 87.4 (CH-1), 169.5 (Cq of Ac), 169.6 (Cq of Ac), 170.6 (Cq of Ac), 198.1 (C=O).

5-Pyrimidinecarboxylic acid, 4-α-D-2',3',5'-tri-*O*-acetylarabinofuranosyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-, ethyl ester **(26)**

EtO_2C CH_3 AcO O NH HN AcO OAc O

$C_{19}H_{26}N_2O_{10}$

M.W= 442,42 g/mol

3,4,6-tri-0-acetyl-2,5-anhydro-D-mannose **25** (0.650 g, 2.411 mmol) was dissolved in 7.2 mL of anhydrous ethanol at room temperature. The urea (0.319 g, 5.304 mmol, 2.2 eq.) and ethyl acetoacetate (0.78 mL, 7.715 mmol, 3.2 eq.) were added and allowed to react for 5 hours at 80ºC, in reflux. After cooling to room temperature the solvent was evaporated in the evaporator. The residue was dissolved in ethyl acetate, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (50:50) as eluent.

Yield: 30%; **Rf=** 0.06 (EA); $[\alpha]_D^{20}$(3.187, MeOH)= 4.71

IR(cm^{-1}): 1369 ($COCH_3$), 1670 (C=C), 17 33 (C=O), 3335 (NH).

^{1}H NMR (400 MHz,$CDCl_3$) δ= 1.31-1.34 (m, 3H, $CH_2\underline{CH_3}$),1.40 (s, 9H, CH_3 of Ac), 2.01 (s, 3H, CH_3 of C6), 3.40-3.45 (m, 2H, CH_2 of ethyl), 3.58-3.60 (m, 1H, CH-4'), 3.80-3.90 (m, 2H, CH_2-5'), 4.16-4.18 (m, 1H, CH-3'), 4.25-4.27 (m, 1H, CH-2'), 4.68 (s, 1H, CH-4), 6.01 (d, 1H, J= 4 Hz, CH-1'), 6.88 (ls, 2H, NH-1 and NH-3).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1 ($CH_2\underline{C}H_3$), 20.7 (CH_3 of Ac), 20.8 (CH_3 of Ac), 20.9 (CH_3 of Ac), 23.1 (CH_3 of C6), 36.6 (CH_2 of ethyl), 48.4 (CH of C4), 62.9 (CH_2-5'),70.1 (CH-2'), 79.2 (CH-3'), 84.4 (CH-4'), 128.3 (Cq of C5), 128.4 (CH-1'), 155.4 (Cq of C6), 169.7 (Cq of NC=ON), 169.9 (Cq of Ac), 170.0 (Cq of Ac), 170.6 (Cq of Ac), 171.5 (Cq of $C\underline{C}O_2Et$).

5-Pyrimidinecarboxylic acid, 4-α-D-2',3',5'-tri-*O*-acetylarabinofuranosyl-1,2,3,4-tetrahydro-6-methyl-2-thiono-, ethyl ester **(27)**

$C_{19}H_{26}N_2O_9S$

M.W =458,48 g/mol

3,4,6-tri-0-acetyl-2,5-anhydro-D-mannose **25** (1.284 g, 4.454 mmol) was dissolved in 13 mL of anhydrous ethanol at room temperature. The thiourea (0.847 g, 11.136 mmol, 2.5 eq.) and ethyl acetoacetate (1.99 mL, 15.591 mmol, 3.5 eq.) were added and allowed to react for 5 hours at 80ºC, in reflux. After cooling to room temperature the solvent was evaporated in the evaporator. The residue was dissolved in ethyl acetate, filtered and evaporated in the

evaporator evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (50:50) as eluent.

Yield: 42%; **Rf=** 0.41 (EA); $[\alpha]_D^{20}$(0.560, MeOH)= -13316.07 and 2803.57

IR(cm^{-1}): 1369 ($COCH_3$), 1678 (C=C), 1724 (C=S), 3323 (NH).

^1H NMR (400 MHz,$CDCl_3$) δ= 1.20-1.28 (m, 3H, $CH_2\underline{CH_3}$), 2.05 (s, 3H, CH_3 of C6), 2.12 (s, 9H, CH_3 of Ac), 3.68-3.71 (m, 2H, CH_2 of ethyl), 4.10-4.15 (m, 1H,CH-4'), 4.18-4.24 (m, 2H, CH_2-5'), 4.35-4.37 (m, 1H, CH-3'), 4.40-4.45 (m, 1H, CH-2'), 4.56 (s, 1H, CH-4), 5.31-5.32 (m, 1H, CH-1'), 6.42 (ls, 2H, NH-1 and NH-3).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.5 ($CH_2\underline{C}H_3$), 20.7 (CH_3 of Ac), 20.8 (CH_3 of Ac), 20.9 (CH_3 of Ac), 23.3 (CH_3 of C6), 36.9 (CH_2 of ethyl), 49.6 (CH of C4), 62.9 (CH_2-5'), 78.5 (CH-2'), 80.7 (CH-3'), 84.1 (CH-4'), 128.0 (Cq of C5), 128.6 (CH-1'), 158.1 (Cq of C6), 169.9 (Cq of Ac), 170.0 (Cq of Ac), 170.6 (Cq of Ac), 172.2 (Cq of $C\underline{C}O_2Et$), 185.5 (Cq of NC=SN).

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methyl-2,3-O-isopropylidene-β-D-ribofuranoside **(32)**

$C_9H_{16}O_5$
M.W=204.22 g/mol

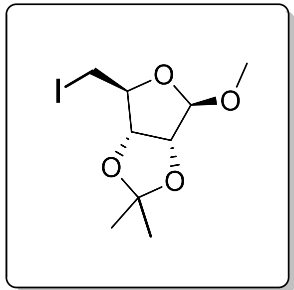
D-ribose **31** (10 g, 66.6 mmol) were dissolved in 50 mL of dry acetone and 50 mL of dry methanol at room temperature. The sulfuric acid (5 mL) was slowly added. The stirred mixture was kept for 48h at room temperature, and the reaction was quenched with $NaHCO_3$ to neutralize the solution. The mixture was filtered and concentrated to a reduced volume. The resulting residue was dissolved with water, extracted three times with ethyl acetate, dried with $MgSO_4$, filtered and evaporated in the evaporator.

CAS [4099-85-8]; **Yield**: 85%; **Rf**= 0.79 (EA/PE: 90/10).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.28 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$), 3.23 (dd, 1H, OH), 3.39 (s, 3H, OCH_3), 3.54-3.63 (m, 2H, CH_2-5), 4.37 (ls, 1H, CH-4), 4.55 (d, 1H, J= 4.0 Hz, CH-3), 4.79 (d, 1H, J= 4.0 Hz, CH-2), 4.93 (s, 1H, CH-1).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 24.8 (C(<u>C</u>H_3)$_2$), 26.5 (C(<u>C</u>H_3)$_2$), 55.6 (OCH_3), 64.1 (CH_2-5), 81.6 (CH-2), 85.9 (CH-3) 88.4 (CH-4), 110.1 (CH-1), 112.2 (<u>C</u>(CH_3).

Methyl-5-iodo-5-deoxy-2,3-*O*-isopropylidene-β-D-ribofuranoside **(33)**



$C_9H_{15}IO_4$
M.W=314.12 g/mol

Ribofuranoside **32** (1 g, 4.897 mmol) was dissolved in 16.3 mL of toluene at room temperature. The Ph_3P (2.565 g, 9.79 mmol, 2 eq.), imidazole (0.664 g, 9.79 mmol, 2 eq.) and iodine (1.741 g, 6.856 mmol, 1.4 eq) were added and allowed to react for 5 hours at 80ºC, in reflux. After cooling to room temperature the solvent was evaporated. The solution was diluted with ethyl acetate. The organic phase was washed twice with a saturated $Na_2S_2O_3$ solution and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/PE (5:95) as eluent.

CAS [38838-06-1]; **Yield**: 88%; **Rf**= 0.77 (PE/EA: 95/5).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.28 (s, 3H, $C(CH_3)_2$), 1.43 (s, 3H, $C(CH_3)_2$), 3.11 (t, 1H, J= 9.99 Hz, CH_2-5), 3.25 (dd, 1H, J= 9.99 Hz, J= 6.07 Hz, CH_2-5'), 3.32 (s, 3H, OCH_3), 4.39 (dd, 1H, J= 12.56 Hz, CH-4), 4.59 (d, 1H, J= 5.91 Hz, CH-3), 4.72 (d, 1H, J= 5.91 Hz CH-2), 5.0 (s, 1H, CH-1).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 6.9 (CH_2-5), 25.1 (C(<u>C</u>H_3)$_2$), 26.5 (C(<u>C</u>H_3)$_2$), 55.3 (OCH_3), 83.1 (CH-2), 85.4 (CH-3), 87.5 (CH-4), 109.7 (CH-1), 112.7 (<u>C</u>(CH_3)$_2$).

Methyl-5-azido-5-deoxy-2,3-*O*-isopropylidene-ß-D-ribofuranoside **(34)**

$C_9H_{15}N_3O_4$
M.W=229.23 g/mol

Iodoriboside **32** (2 g, 6.367 mmol) was dissolved in 24.5 mL of DMF at room temperature. The NaN_3 (1.242 g, 19.101 mmol, 3 eq.) was added and was allowed to react for 3 hours at 100ºC, in reflux. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of AE/Hex (20:80) as eluent.

CAS [62819-24-3]; **Yield:** 93%; **Rf=** 0.65 (Hex/AE: 70/30).

^{1}H NMR (400 MHz, $CDCl_3$) δ =1.32 (s, 3H, $C(CH_3)_2$), 1.49 (s, 3H, $C(CH_3)_2$), 3.27 (dd, 2H, J= 6.76 Hz, J= 12.52 Hz , CH_2-5), 3.38 (s, 3H, OCH_3), 3.45 (dd, 1H, J= 12.56 Hz, J= 7.4 Hz, CH-4), 4.29 (t, 1H, J= 7.4 Hz, CH-3), 4.60 (s, 1H, CH-2), 5.00 (s, 1H, CH-1).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.9 ($C(\underline{C}H_3)_2$), 26.4 ($C(\underline{C}H_3)_2$), 53.8 (CH_2-5), 55.2 (OCH_3), 82.1 (CH-2), 85.2 (CH-3), 85.4 (CH-4), 109.8 (CH-1), 112.7 ($\underline{C}(CH_3)_2$).

5-azido-5-deoxy-2,3-O-acetyl-ß-D-ribofuranoside **(35)**

$C_9H_{13}N_3O_6$
M.W=259.22 g/mol

Azido-sugar **34** (0.1 g, 0.436 mmol) was dissolved in 5.3 mL of acetic acid. A solution of H_2SO_4 4M (0.65 mL, 12.194 mmol, 28 eq.) was added and was allowed to react for 12 hours at room temperature. The reaction was quenched with a satured solution of $NaHCO_3$ to neutralize de

solution. The reaction mixture was evaporated in the evaporator. The residue was diluted with methanol, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of AE/Hex (50:50) as eluent.

CAS [1005768-65-9]; **Yield**: 34%; **Rf=** 0.65 (AE/Hex: 80/20).

Selected signs of the α and β isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.00 (s, 6H, CH_3 of Ac), 2.06 (s, 3H, CH_3 of Ac), 2.08 (s, 3H, CH_3 of Ac), 3.37-3.42 (m, 2H, CH_2-5), 3.43-3.56 (m, 2H, CH_2-5'), 4.16-4.18 (m, 1H, CH-4), 4.28 (m, 1H, CH-4'), 5.02-5.05 (m, 1H, CH-3), 5.12-5.14 (m, 1H, CH-3'), 5.15-5.17 (m, 1H, CH-2), 5.29-5.32 (m, 1H, CH-2'), 5.51-5.52 (m, 2H, CH-1 and CH-1').

Selected signs of the α and β isomers: ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.4 ($\underline{C}H_3$ of Ac), 20.5 ($\underline{C}H_3$ of Ac), 20.6($\underline{C}H_3$ of Ac),20.7 ($\underline{C}H_3$ of Ac), 52.1 (CH_2-5), 53.0 (CH_2-5'), 71.1 (CH-2), 71.2 (CH-2'), 75.4 (CH-3), 75.5(CH-3'), 79.8 (CH-4), 80.6 (CH-4'), 95.6(CH-1), 100.2 (CH-1'), 169.5 (Cq of Ac), 169.6 (Cq of Ac), 169.7 (Cq of Ac), 169.8 (Cq of Ac).

5-azido-5-deoxy-β-D-ribofuranoside **(36)**

N_3 O OH HO OH

$C_5H_9N_3O_4$
M.W=175,14 g/mol

Procedure 1:

Azido-sugar **34** (0.1 g, 0.436 mmol) was dissolved in 5.3 mL of acetic acid. A solution of H_2SO_4 4M (0.65 mL, 12.194 mmol, 28 eq.) was added and was allowed to react for 12 hours at room temperature. The reaction was quenched with a satured solution of $NaHCO_3$ to neutralize de solution. The reaction mixture was evaporated in the evaporator. The residue was diluted with methanol, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of AE/Hex (50:50) as eluent. **Yield**: 12%

Procedure 2:

Azido-sugar **34** (0.613 g, 2.675 mmol) was dissolved in 17 mL of HCl 3M. The H_2SO_4 4M (2.7 mL, 50.653 mmol, 18.9 eq.) was slowly added and was allowed to react for 12 hours at room temperature. The reaction was quenched with NaOH 4M to neutralize de solution. The reaction mixture was evaporated in the evaporator. The residue was diluted with methanol, filtered and

evaporated in rotary. The resulting crude was purified by silica gel column chromatography using a mixture of AE/Hex (50:50) as eluent. **Yield**: 70%

CAS [182575-45-7]; **Rf=** 0.28 (AE/Hex: 80/20).

Selected signs of the α and β isomers: ^{1}H NMR (400 MHz, C_3D_6O) δ = 3.16 (ls, 3H, OH), 3.31-3.36 (m , 1H, CH_2-5), 3.47-3.51 (m, 1H,CH_2-5'), 3.89-3.92 (m, 1H, CH-4), 3.93-3.95 (m, 1H, CH-4'), 3.97-4.02 (m, 2H, CH-3 and CH-3'), 4.04-4.06 (m, 2H, CH-2 and CH-2'), 5.18-5.20 (m, 2H, CH-1 and CH-1').

Selected signs of the α isomer: ^{13}C NMR (100 MHz, C_3D_6O) δ = 53.1 (CH_2-5), 71.9 (CH-2), 72.5 (CH-3), 82.0 (CH-4), 97.7 (CH-1).

Selected signs of the β isomer: ^{13}C NMR (100 MHz, C_3D_6O) δ = 54.6 (CH_2-5), 73.0 (CH-2), 76.8 (CH-3), 82.3 (CH-4), 103.2 (CH-1).

Methyl-5-azido-5-deoxy-β-D-ribofuranoside **(37)**

$C_6H_{11}N_3O_4$

M.W=189,17 g/mol

Procedure 1:

Azido-sugar **34** (0.1 g, 0.436 mmol) was dissolved in 5.3 mL of acetic acid. A solution of H_2SO_4 4M (0.65 mL, 12.194 mmol, 28 eq.) was added and was allowed to react for 12 hours at room temperature. The reaction was quenched with a satured solution of $NaHCO_3$ to neutralize de solution. The reaction mixture was evaporated in the evaporator. The residue was diluted with methanol, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of AE/Hex (50:50) as eluent. **Yield**: 12%

Procedure 2:

Azido-sugar **34** (0.613 g, 2.675 mmol) was dissolved in 17 mL of HCl 3M at room temperature. A solution of H_2SO_4 4M (2.7 mL, 50.653 mmol, 18.9 eq.) was slowly added and was allowed to react for 12 hours at room temperature. The reaction was quenched with NaOH 4M to neutralize de solution. The mixture was evaporated in the evaporator. The residue was diluted with

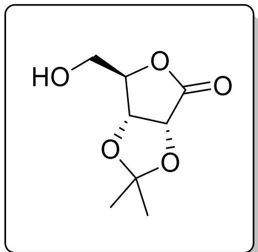
methanol, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of AE/Hex (50:50) as eluent. **Yield**: 3%

CAS [35509-22-9]; **Yield**: 10%; **Rf=** 0.49 (AE/Hex:80/20).

^{1}H NMR (400 MHz, C_3D_6O) δ = 3.34 (s, 3H, OCH_3), 3.30-3.31 (m, 1H, CH_2-5), 3.49 (dd, 1H, J= 4 Hz, J= 12 Hz, CH_2-5'), 3.91 (t, 1H, CH-4), 4.03-4.05 (m, 1H, CH-3), 4.08-4.11 (m, 1H, CH-3), 4.22 (d, 1H, CH-2), 4.34 (d, 1H, CH-2), 4.78 (d, 1H, J= 4 Hz, CH-1).

^{13}C NMR (100 MHz, C_3D_6O) δ = 54.6 (CH_2-5), 55.3 (OCH_3), 73.0 (CH-2), 75.8 (CH-3), 82.8 (CH-4), 109.8 (CH-1).

2,3-*O*-Isopropylidene-D-ribono-1,4-lactone **(39)**



$C_8H_{12}O_5$
M.W= 188,18 g/mol

D-(+)-Ribonic γ-lactone (0.500 g, 3.376 mmol) was dissolved in 10.5 mL of dry acetone at room temperature. The 2,2-dimethoxypropane (2.5 mL, 20.026 mmol, 6 eq.) and TsOH (0.032 g, 0.169 mmol, 0.04 eq.) was added and allowed to react for 2 hours at room temperature. The reaction was quenched with sodium bicarbonate to neutralize de solution. The residue was filtered on celite and evaporated in the evaporator.

CAS [30725-00-9]; **Yield**: 96%; **Rf=** 0.55 (AE/MeOH: 50/50)

^{1}H NMR (400 MHz, $(CD_3)_2S$=O) δ = 1.32 (s, 3H,$C(CH_3)_2$), 1.36 (s, 3H,$C(CH_3)_2$), 3.58-3.68 (m, 2H, CH_2-5), 4.61-4.62 (m, 1H, CH-4), 4.78 (d, 2H, J= 5.56 Hz, CH-2 and CH-3), 4.31(t, 1H, J= 5 Hz, OH).

^{13}C NMR (100 MHz, (CD3)2S=O) δ = 25.6 ($C(\underline{C}H_3)_2$), 27.0 ($C(\underline{C}H_3)_2$), 60.9 (CH_2-5), 75.5 (CH-3), 78.6 (CH-2), 82.7 (CH-4), 112.1 ($\underline{C}(CH_3)_2$), 174.8 (C=O).

2,3-O-isopropylidene-5-deoxy-5-iodo-D-ribonono-1,4-lactone **(40)**

$C_8H_{11}IO_4$
M.W= 298,08 g/mol

Lactone **39** (0.200 g, 1.063 mmol) was dissolved in 10 mL of toluene at room temperature. The Ph_3P (0.560 g, 2.126 mmol, 2 eq.), imidazole (0.145 g, 2.126 mmol, 2 eq.) and iodine (0.378 g, 1.488 mmol, 1.4 eq) were added and allowed to react for 3 hours at 80ºC, in reflux . After cooling to room temperature the solvent was evaporated. The solution was diluted with ethyl acetate. The organic phase was washed twice with a saturated $Na_2S_2O_3$ solution and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (1:99) as eluent.

CAS [96239-82-6]; Yield: 82%; **Rf**= 0.37 (EA/Hex: 20/80).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.40 (s, 3H,$C(CH_3)_2$), 1.48 (s, 3H,$C(CH_3)_2$), 3.39-3.47 (m, 2H, CH_2-5), 4.62-4.66 (m, 2H, CH-3 and CH-4), 4.99 (d, 1H, J= 5.88 Hz, CH-2).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 5.7 (CH_2-5), 25.5 ($C(\underline{C}H_3)_2$), 26.5 ($C(\underline{C}H_3)_2$), 75.3 (CH-3), 80.4 (CH-2), 80.9 (CH-4), 114.0 ($\underline{C}(CH_3)_2$), 173.0 (C=O).

5-azido-5-deoxy-2,3-O-isopropylidene-D-ribonic-γ-lactone **(41)**

$C_8H_{11}N_3O_4$
M.W= 213,19 g/mol

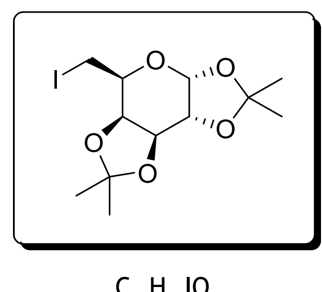
Iodine-lactone **40** (0.900 g, 3.019 mmol) was dissolved in 15 mL of DMF at room temperature. The NaN_3 (0.589 g, 9.058 mmol, 3 eq.) was added and was allowed to react for 3 hours at 100ºC, in reflux. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of AE/Hex (25:75) as eluent.

CAS [23709-18-4]; Yield: 90%; **Rf**= 0.74 (EA/Hex: 60/40).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.39 (s, 3H,$C(CH_3)_2$), 1.47 (s, 3H,$C(CH_3)_2$), 3.68 (dd, 1H, J= 2.44 Hz, J= 13.28 Hz, CH_2-5), 3.80 (dd, 1H, CH_2-5'), 4.64-4.68 (m, 2H, CH-3 and CH-4), 4.86 (d, 1H, J= 5.68 Hz, CH-2).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.5 ($C(\underline{C}H_3)_2$), 26.6 ($C(\underline{C}H_3)_2$), 52.5 (CH_2-5), 75.1 (CH-3), 77.4 (CH-2), 80.1 (CH-4), 113.6 ($\underline{C}(CH_3)_2$), 173.4 (C=O).

6-deoxy-6-iodo-1,2,3,4-di-O-isopropylidene-α-D-galactopyranose **(43)**



$C_{12}H_{19}IO_5$
M.W= 370,03 g/mol

1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.400 g, 1.537 mmol) was dissolved in 30 mL of toluene at room temperature. The Ph_3P (0.806 g, 3.074 mmol, 2 eq.), iodine (0.547 g, 2.152 mmol, 1.4 eq) and imidazole (0.209 g, 3.074 mmol, 2 eq.) was added and was allowed to react for 3 hours at 80ºC, in reflux . After cooling to room temperature the solvent was evaporated. The solution was diluted with ethyl acetate. The organic phase was washed twice with a saturated $Na_2S_2O_3$ solution and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (1:99) as eluent.

CAS [4026-28-2], **Yield**: 98%, **Rf**= 0.67 (EA/Hex: 20/80).

^{1}H NMR (250 MHz, $CDCl_3$) δ = 1.33 (s, 1H, $C(\underline{C}H_3)_2$), 1.35 (s, 1H, $C(\underline{C}H_3)_2$), 1.44 (s, 1H, $C(\underline{C}H_3)_2$), 1.54 (s, 1H, $C(\underline{C}H_3)_2$), 3.17-3.55 (m, 2H, CH_2-6), 3.91-3.96 (m, 1H, CH-5), 4.28-4.31 (m, 1H, CH-

2), 4.40 (dd, 1H, J= 2.5 Hz, J= 5 Hz, CH-4), 4.61 (dd, 1H, J= 2.5 Hz, J= 7.5 Hz CH-3), 5.53 (d, 1H, J= 5 Hz, CH-1).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ = 2.5 (CH_2-6), 24.6 ((C($\underline{C}H_3)_2$)), 25.0 ((C($\underline{C}H_3)_2$)), 26.1 ((C($\underline{C}H_3)_2$)), 26.2 ((C($\underline{C}H_3)_2$)), 69.1 (CH-5), 70.7 (CH-2), 71.3 (CH-3), 71.7 (CH-4), 96.8 (CH-1), 109.0 ($\underline{C}(CH_3)_2$), 109.7 ($\underline{C}(CH_3)_2$).

6-deoxy-6-azido-1,2,3,4-di-O-isopropylidene-α-D-galactopyranose **(44)**

$C_{12}H_{19}N_3O_5$

M.W= 285,13 g/mol

Iodine-pyranose **43** (0.540 g, 1.460 mmol) was dissolved in 10 mL of DMF at room temperature. The NaN_3 (0.285 g, 4.380 mmol, 3 eq.) was added and was allowed to react for 3 hours at 100ºC, in reflux. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of AE/Hex (25:75) as eluent.

CAS [4711-00-6]; Yield: 88%; **Rf**= 0.8 (EA/Hex: 40/60).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.19 (s, 3H, C($\underline{C}H_3)_2$), 1.20 (s, 3H, C($\underline{C}H_3)_2$), 1.26 (s, 3H, C($\underline{C}H_3)_2$), 1.36 (C($\underline{C}H_3)_2$), 3.20-3.33 (m, 2H, CH_2-6), 3.83-3.87 (m, 1H, CH-5), 4.13 (dd, 1H, J= 1.96 Hz, J= 7.88 Hz, CH-2), 4.24-4.26 (m, 1H, CH-4), 4.53 (dd, 1H, J= 2.48 Hz, J= 7.88 Hz, CH-3), 5.38 (d, 1H, J= 5.04 Hz, CH-1).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.7 (C($\underline{C}H_3)_2$), 24.2 (C($\underline{C}H_3)_2$), 25.39 (C($\underline{C}H_3)_2$), 25.4 (C($\underline{C}H_3)_2$), 50.7 (CH_2-6), 67.2 (CH-5), 70.4 (CH-2), 70.9 (CH-3), 71.3 (CH-4), 96.3 (CH-1), 108.3 ($\underline{C}(CH_3)_2$), 109.0 ($\underline{C}(CH_3)_2$).

1,2-O-Isopropylidene-α-D-glucofuranose **(46)**

$C_9H_{16}O_6$

M.W= 220,09 g/mol

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (6.000 g, 23.052 mmol) was dissolved in 160 mL of acetic acid 80% at room temperature. The reaction misture was allowed to react for 1 hour at 60ºC, in reflux. After to cooling at room temperature the residue was evaporated in the evaporator. Co-evaporated the residue with toluene in the evaporator.

CAS [18549-40-1]; Yield: 96%; **Rf**= 0.28 (EA).

^{1}H NMR (400 MHz, CD_3OD) δ = 1.18 (s, 3H, C(C̲H_3)$_2$), 1.33 (s, 3H, C(C̲H_3)$_2$), 3.45 (dd, 1H, J=5.9 Hz, CH-6), 3.62-3.65 (m, 1H, CH-5), 3.90 (dd, 1H, J= 2.6, CH_2-6'), 4.09 (d, 1H, J= 2.6 Hz, CH-3), 4.09 (d, 1H, CH-4), 4.36 (d, 1H, J= 3.6 Hz, CH-2), 5.75 (d, 1H, CH-1);

^{13}C NMR (100 MHz, CD_3OD) δ = 26.2 ((C(C̲H_3)$_2$), 26.8 ((C(C̲H_3)$_2$), 66.1 (CH_2-6), 69.5 (CH-3), 75.7 (CH-5), 79.3 (CH-4), 85.2 (CH-2), 105.0 (CH-1), 111.9 (C̲(CH_3)$_2$).

1,2-O-Isopropylidene-α-D-xylofuranose **(47)**

$C_8H_{14}O_5$

M.W= 190,08 g/mol

Compound **46** (5.071 g, 23.052 mmol) was dissolved in 120 mL of ethanol in the absence of light at room temperature. The $NaIO_4$ (11.975 g, 55.903 mmol, 2.4 eq.) was dissolved in 185 mL of water and was added and allowed to react for 20 minutes in absence of light at room temperature. Extract the residue with 120 mL of ethanol. The residue was filtered and evaporated in the evaporator.

The crude solid (4.333 g, 23.052 mmol) was dissolved in 50 mL of annydrous ethanol at 0º C. The $NaBH_4$ (1.308 g, 34.578 mmol, 1.5 eq.) was slow added and allowed to react for 1 hour at 0º C. The residue was evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (50:50) as eluent.

CAS [20031-21-4]; Yield: 43%; **Rf**= 0.33 (EA).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.32 (s,3H, $C(CH_3)_2$), 1.48 (s, 3H, $C(CH_3)_2$), 4.00 (dd, 1H, J= 12.3 Hz, J= 2.7 Hz, CH_2-5), 4.11 (dd,1H, J= 4.5 Hz, CH_2-5'), 4.15-4.19 (m, 1H, CH-4), 4.34 (d,1H, J= 2.7 Hz,C H-3), 4.53 (d,1H, J= 3.6 Hz, CH-2), 5.97 (d, 1H,CH-1);

^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.2 (($C(\underline{C}H_3)_2$), 26.8 (($C(\underline{C}H_3)_2$), 50.8 (CH_2-5), 75.7 (CH-3), 79.3 (CH-4), 85.2 (CH-2), 105.0 (CH-1), 111.9 ($\underline{C}(CH_3)_2$).

5-Deoxy-5-iodo-1,2-O-isopropylidene-α-D-xylofuranose **(48)**

$C_8H_{13}IO_4$
M.W= 299,99 g/mol

Xylofuranose **47** (0.950 g, 5.000mmol) was dissolved in 70 mL of toluene at room temperature. Ph_3P (2.620 g, 10.000 mmol, 2 eq.), iodine (1.178 g, 7.000 mmol, 1.4 eq) then imidazole (0.681 g, 10.000 mmol, 2 eq.) were added and allowed to react for 3 hours at 80ºC, in reflux. After cooling to room temperature the solvent was evaporated. The solution was diluted with ethyl acetate. The organic phase was washed twice with a saturated $Na_2S_2O_3$ solution and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (10:90) as eluent.

CAS [50600-39-0]; Yield: 71%; **Rf**= 0.56 (EA/Hex: 40/60)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.32 (s, 3H, $C(CH_3)_2$), 1.51 (s, 3H, $C(CH_3)_2$), 2.17 (d, 1H, OH), 3.23-333 (m, 2H, CH_2-5), 4.38-4.45 (m, 2H, CH-4 and CH-3), 4.57 (d, 1H, J= 4 Hz, CH-2), 5.98 (d, 1H, CH-1).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 0.0 (CH_2-5), 27.5 (C($\underline{C}H_3)_2$), 28.0 (C($\underline{C}H_3)_2$), 76.1 (CH-3), 82.0 (CH-4), 86.2 (CH-2), 106.7 (CH-1), 113.3 ($\underline{C}(CH_3)_2$).

5-Deoxy-5-azido-1,2-*O*-isopropylidene-α-D-xylofuranose **(49)**

$C_8H_{13}N_3O_4$

M.W= 215,09 g/mol

Iodine-xylofuranose **48** (0.544 g, 1.814 mmol) was dissolved in DMF at room temperature. NaN_3 (0.354 g, 5.442 mmol, 3 eq.) was added and allowed to react for 3 hours at 100ºC. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (10:90) as eluent.

CAS [84711-03-9]; **Yield**: 83%; **Rf**= 0.76 (EA/Hex: 50/50).

^1H NMR (250 MHz, $CDCl_3$) δ = 1.34 (s, 3H, $C(CH_3)_2$), 1.49 (s, 3H, $C(CH_3)_2$), 3.33-3.36 (m, 1H, OH), 3.52 (d, 2H, J= 7.5 Hz, CH_2-5), 4.12 (d, 1H, CH-3), 4.22-4.28 (m, 1H, CH-4), 4.52 (d, 1H, J= 2.5 Hz, CH-2), 5.93 (d, 1H, CH-1).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ= 26.4 (C($\underline{C}H_3)_2$), 27.1 (C($\underline{C}H_3)_2$), 50.8 (CH_2-5), 75.6 (CH-3), 80.8 (CH-4), 86.8 (CH-2), 106.3 (CH-1), 112.8 ($\underline{C}(CH_3)_2$).

(1,2-dideoxy-ß-D-arabinofuranoso)[1,2-d]-1,3-oxazolidine-2-thione **(65)**

$C_6H_9NO_4S$

M.W= 191,03 g/mol

D-arabinose (3.000 g, 19.983 mmol) was dissolved in 41,6 mL of water at room temperature. HCl (12N, 9,9 mL) and KSCN (4.466g, 45.960 mmol, 2.3 eq.) were added and allowed to react for 24 hours at 56°C. The solution was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (70:30) as eluent.

Yield: 92%; **Rf**= 0.4 (EA/PE: 95/5); **M.p=** 135-138°C; $[\alpha]_D^{20}$(0.50, MeOH)= -25.64

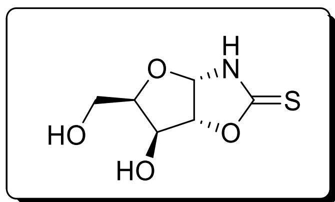
M.S (IS): m/z= 192.0 $[M + H]^+$, 209.0 $[M + NH_4]^+$, 383.5 $[2M + H]^+$, 400.0 $[2M + NH_4]^+$, 405.0 $[2M + Na]^+$.

IR (cm^{-1}): 1032 (CN), 1151 (C=S), 3299 (NH + OH).

^{1}H NMR (250 MHz, $(CD_3)_2S=O$) δ = 3.16-3.29 (m, 3H, 2H of CH_2-5 and 1H of OH of C3), 3.85-3.91 (dtd, 1H, J= 1.9 Hz, J= 6.1 Hz, J= 7.9 Hz, CH-4), 4.25 (s, 1H,CH-3), 5.05 (d, 1H, J= 5.7 Hz, CH-2), 5.70 (s, 1H, OH of C5), 5.80 (dd, 1H, J= 1.3 Hz, J= 5.8 Hz CH-1), 10.82 (s, 1H, NH).

^{13}C NMR (62.5 MHz, $(CD_3)_2S=O$) δ= 60.9 (CH_2-5), 74.3 (CH-3), 87.1 (CH-4), 89.3 (CH-1), 91.5 (CH-2), 188.2 (C=S).

(1,2-dideoxy-α-D-xylofuranoso)[1,2-d]-1,3-oxazolidine-2-thione **(66)**



$C_6H_9NO_4S$
M.W= 191,03 g/mol

D-xylose (3.000 g, 19.983 mmol) was dissolved in 41.6 mL of water at room temperature. HCL (12N, 9,9 mL) and KSCN (4.466g, 45.960 mmol, 2.3 eq.) were added and allowed to react for 24 hours at 56°C. The residue was evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (60:40) as eluent.

Yield: 74%; **Rf**= 0.33 (EA/PE: 95/5); **M.p=** 130-132°C; $[\alpha]_D^{20}$(0.39, MeOH)= 20.67

M.S (IS): m/z= 192.0 $[M + H]^+$,209.0 $[M + NH_4]^+$, 231.0 $[M + K]^+$, 383.0 $[2M + H]^+$, 400.0 $[2M + NH_4]^+$, 405.0 $[2M + Na]^+$.

IR (cm^{-1}): 1126 (C=S), 3366 (NH + OH).

^{1}H NMR (250 MHz, $(CD_3)_2S=O$) δ = 2.66-2.77 (m, 3H, 2 H of CH_2-5 and 1H of CH-4), 3.22 (s, 1H,CH-3), 3.83 (t, 1H, J= 5.3 Hz, OH of C3), 4.08 (d, 1H, J= 5.4 Hz, CH-2), 4.61 (d, 1H, J= 4.5 Hz, OH of C5), 4.89 (d, 1H, J= 5.4 Hz, CH-1), 9.80 (ls, 1H, NH).

^{13}C NMR (62.5 MHz, $(CD_3)_2S=O$) δ= 58.5 (CH_2-5), 72.5 (CH-3), 80.7 (CH-4), 88.5 (CH-1), 90.0 (CH-2), 188.5 (C=S).

(1,2-dideoxy-α-D-ribofuranoso)[1,2-d]-1,3-oxazolidine-2-thione **(67)**

$C_6H_9NO_4S$

M.W =191,21g/mol

D-ribose **31** (3.000 g, 19.983 mmol) was dissolved in 41,6 mL of water at room temperature. The HCl (12N, 9,9 mL) and the KSCN (4.466g, 45.960 mmol, 2.3 eq.) were added and allowed to react for 48h at 56°C. The residue was evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/PE (70:30) as eluent.

Yield: 84%; **Rf=** 0.25 (EA/PE: 95/5); **M.p.=** 165-167°C; $[\alpha]_D^{20}$(0.42, MeOH)= 68.56

M.S (IS): m/z= 192.0 $[M + H]^+$, 209.0 $[M + NH_4]^+$, 383.0 $[2M + H]^+$, 405.0 $[2M + Na]^+$.

IR(cm^{-1}): 1086 (C=S), 1521(NH), 3436 (OH + NH).

^{1}H NMR (250 MHz, (CD3)2S=O) δ = 3.36-3.46 (m, 2H, CH_2-5), 3.64-3.71 (m, 1H, CH-4), 3.83-3.89 (m, 1H, CH-3), 4.77 (dd, 1H, J= 3.5 Hz, J= 7.8 Hz, OH of C5), 5.07 (t, 1H, J= 5.3 Hz, CH-2), 5.59 (d, 1H, J= 6.2 Hz, OH of C3), 5.58 (d, 1H,J= 5.3 Hz, CH-1), 10.68 (ls, 1H, NH).

^{13}C NMR (62.5 MHz, (CD3)2S=O) δ= 60.2 (CH_2-5), 71.1 (CH-3), 79.9 (CH-4), 85.1 (CH-2), 88.1 (CH-1), 190.0 (C=S).

(1,2,5-trideoxy-5-iodo-ß-D-ribofuranoso)[1,2-d]-1,3-oxazoldiine-2-thione **(81)**

$C_6H_8INO_3S$

M.W=301,10 g/mol

Oxazolidinethione **67** (0.710 g, 3.717 mmol) was dissolved in 12 mL of THF at room temperature. Ph_3P (1.948 g, 7.435 mmol, 2 eq.) and imidazole (0.506 g, 7.435 mmol, 2 eq.) were added, the stirred mixture was kept for 15 minutes at 0°C. Iodine (1.889 g, 7.435 mmol, 2 eq) was slowly added and was allowed to react for 1h 30 minutes at room temperature. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (40:60) as eluent.

Yield: 90%; **Rf**= 0.71 (EA/PE: 90/10)**; M.p.**= 171-174°C; $[\alpha]_D^{20}$(0.33, MeOH)= 24.24

M.S (IS): m/z= 302.0 $[M + H]^+$, 319.0 $[M + NH_4]^+$, 603.0 $[2M + H]^+$, 620.0 $[2M + NH_4]^+$, 625.0 $[2M + Na]^+$.

IR(cm^{-1}): 601(IC), 1073 (C=S), 1518(NH), 3279 (OH + NH).

^{1}H NMR (250 MHz, $(CD_3)_2S=O$) δ = 3.26-3.33 (m, 2H, CH_2-5 and CH-4), 3.53-3.57 (m, 1H, CH_2-5'), 3.72-3.77 (m, 1H, CH-3), 5.16 (t, 1H, J= 5.3 Hz, CH-2), 5.73 (d,1H, J= 6.4 Hz, CH-1), 5.88 (d, 1H, J= 6.2 Hz, OH), 10.79 (s, 1H, NH).

^{13}C NMR (62.5 MHz, $(CD_3)_2S=O$) δ= 6.5 (CH_2-5), 74.9 (CH-3), 77.0 (CH-4), 84.9 (CH-2), 87.5 (CH-1), 189.5 (C=S).

(5-azido-1,2,5-trideoxy-ß-D-ribofuranoso)[1,2-d]-1,3-oxazolidine-2-thione **(82)**

$C_6H_8N_4O_3S$

M.W= 216,03 g/mol

Procedure 1:

Iodine-oxazolidinethione **81** (1.116 g, 3.708 mmol) was dissolved in 40 mL of DMF at room temperature. NaN_3 (1.205 g, 18.540 mmol, 5 eq.) was added and allowed to react for 1 hour at 70ºC. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/EP (20:80) as eluent. **Yield:** 11%

Procedure 2:

Azido-sugar **36** (0.878 g, 5.017 mmol) was dissolve in 10.5 mL of water at room temperature. Then HCl (12N, 2.5 mL) and KSCN (1.121 g, 11.539 mmol, 2.3 eq.) were added and allowed to react for 24 hours at 56°C. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (20:80) as eluent. **Yield**: 30%

Rf= 0.68 (EA/PE: 80/20); **M.p.=** 138-140°C; $[\alpha]_D^{20}$(0.423, $CHCl_3$)= -3879.43 and 17451.54

M.S (IS): m/z= 217.0 $[M + H]^+$, 234.0 $[M + NH_4]^+$, 239.0 $[M + Na]^+$, 433.0 $[2M + H]^+$, 450.0 $[M + NH_4]^+$, 455.0 $[2M + Na]^+$, 471.0 $[2M + K]^+$.

IR(cm^{-1}): 1111 (C=S), 1517(NH), 2101 (N_3), 3274 (OH + NH).

^{1}H NMR (250 MHz, CD_3OD) δ = 3.35 (dt, 1H, J= 1.7 Hz, J= 3.3 Hz, OH), 3.42 (dd, 1H, J= 5.3 Hz, J= 13.6 Hz,CH_2-5), 3.70 (dd, 1H, J= 2.6 Hz, J= 13.6 Hz, CH_2-5'), 3.75-3.82 (m, 1H, CH-4), 4.12 (dd, 1H, J= 5.3 Hz, J= 9.4 Hz, CH-3), 4.19 (t, 1H, J= 5.3 Hz, CH-2), 5.82 (d, 1H,J= 5.3 Hz, CH-1).

^{13}C NMR (62.5 MHz, CD_3OD) δ= 51.6 (CH_2-5), 73.5 (CH-3), 79.0 (CH-4), 86.2 (CH-2), 89.5 (CH-1), 192.2 (C=S).

(3-*tert*butyldimethylsilyl-1,2,5-trideoxy-5-iodo-α-D-ribofuranoso)[1,2-d]-1,3-oxazolidine-2-thione **(83)**

$C_{12}H_{22}INO_3SSi$

M.W= 415,01 g/mol

Iodine-oxazolidinethione **82** (2.777 g, 9.226 mmol) was dissolved in 65 mL of DCM at room temperature. The TBDMSCl (3.476 g, 23.065 mmol, 2.5 eq.) and imidazole (2.512 g, 36.904 mmol, 4 eq.) were added and allowed to react for 12 hours at room temperature. The solution was diluted with ethyl acetate. The organic phase was washed once with water and once with a solution of HCl 1M, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (5:95) as eluent.

Yield: 59%; **Rf**= 0.79 (EA/PE: 90/10); **M.p.=** 138-140°C; $[\alpha]_D^{20}$(0.49, $CHCl_3$)= 63.27

M.S (IS): m/z= 416.0 $[M + H]^+$, 438.0 $[M + Na]^+$, 831.0 $[2M + H]^+$, 848.0 $[2M + NH_4]^+$, 853.0 [2M + Na]$^+$.

IR(cm^{-1}): 632(IC), 1146 (C=S), 1247 ($SiCH_3$), 1484(NH), 3180 (NH).

^{1}H NMR (250 MHz, CD_3DO) δ = 0.25 (s, 6H, $Si(CH_3)_2$)), 1.00 (s, 9H, $SiC(CH_3)_3$), 3.30-3.40 (m, 2H, 1 H of CH_2-5 and 1H of CH-4), 3.56-3.62 (m, 1H, CH_2-5'), 4.07 (dd, 1H, J= 5.2 Hz, J= 8.4 Hz, CH-3), 5.20 (t, 1H, J= 5.3 Hz, CH-2), 5.79 (d, 1H,J= 5.4 Hz, CH-1).

^{13}C NMR (62.5 MHz, CD_3OD) δ= -4.6 ($Si(CH_3)_2$), -4.4 ($Si(CH_3)_2$), 5.2 (CH_2-5), 18.9 ($Si\underline{C}(CH_3)_3$), 26.2 ($SiC(\underline{C}H_3)_3$), 77.9 (CH-3), 78.1 (CH-4), 85.9 (CH-2), 89.4 (CH-1), 192.1 (C=S).

3-azido-1-*tert*butyldimethylsilyloxy-2-hydroxypropyl-1,3-oxazoline-2-thione **(84)**

N3 OH NH TBDMSO O S

$C_{12}H_{22}N_4O_3SSi$

M.W= 330,12 g/mol

Iodo-oxazolidinethione **83** (1.000 g, 2.469 mmol) was dissolved in 39 mL of DMF at room temperature. NaN_3 (0.803 g, 12.346 mmol, 5 eq.) was added and allowed to react for 3 hour at 70 ºC. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (6:94) as eluent.

Yield: 54%; **Rf**= 0.5 (EA/PE: 50/50); $[\alpha]_D^{20}$(0.31, $CHCl_3$)= +32.3

M.S (IS): m/z= 331.0 $[M + H]^+$, 348.0 $[M + NH_4]^+$, 353.0 $[M + Na]^+$, 661.5 $[2M + H]^+$, 678.0 $[M + NH_4]^+$, 683.5 $[2M + Na]^+$.

IR (cm^{-1}): 1077 (C=S), 1252 ($SiCH_3$), 1471 (C=N), 1651 (C=C), 2101 (N_3), 3126 (OH + NH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $Si(CH_3)_2$), 0.11 (s, 6H, $Si(CH_3)_2$), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.87 (s, 9H, $SiC(CH_3)_3$), 3.43 (d, 2H, J= 4.2 Hz, CH_2-5), 3.47-3.55 (m, 2H, CH_2-5), 4.02-4.06 (m, 1H, CH-4), 4.08-4.12 (m, 1H, CH-4), 4.58 (d, 1H, J= 6.7 Hz, CH-3), 4.65 (d, 1H, J= 6.3 Hz, CH-3), 6.84 (s, 2H, CH-1), 11.49 (ls, 2H, NH and SH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -5.0 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$), -4.4 ($Si(CH_3)_2$), 18.0 ($Si\underline{C}(CH_3)_3$), 18.1 ($Si\underline{C}(CH_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 52.9 (CH_2-5), 53.3 (CH_2-5), 67.4 (CH-3), 67.9 (CH-3), 72.3 (CH-4), 72.5 (CH-4), 113.8 (CH-1), 114.1 (CH-1), 149.0 (Cq of C-2), 149.3 (Cq of C-2), 163.3 (CS), 178.9 (C=S).

2-Benzylsulfanyl-4,5-dihydro-(1,2,5-trideoxy-5-iodo-α-D-ribofuranoso)[1,2-d]-1,3-oxazole **(85)**

O N SBn I O HO

$C_{13}H_{14}INO_3S$

M.W= 390,97g/mol

Iodine-oxazolidinethione **81** (1.126 g, 3.740 mmol) was dissolved in 38 mL of anhydrous THF at room temperature. The reaction mixture was placed in an ice-salt bath. Et_3N (2.09 mL, 14.963 mmol, 4 eq.) and BnBr (0.89 mL, 7.482 mmol, 2 eq.) were added and allowed to react for 12 hours at room temperature. The reaction mixture was evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using a mixture of EA/PE (10:90) as eluent.

Yield: 73%; **Rf**= 0.85 (EA/PE: 50/50); **M.p.=** 86-88°C; $[\alpha]_D^{20}$(0.39, $CHCl_3$)= +35.9

M.S (IS): m/z= 392.0 $[M + H]^+$, 414.0 $[M + Na]^+$, 783.0 $[2M + H]^+$, 805.0 $[2M + Na]^+$.

IR (cm^{-1}): 606 (IC), 1566 (N=C), 3184 (OH).

^{1}H NMR (250 MHz, CD_3OD) δ = 3.17 (dtd, 1H, J= 2.8 Hz, J= 5.9 Hz, J= 8.8 Hz, CH-4), 3.31-3.38 (m, 1H, CH_2-5), 3.59 (dd, 1H, J= 2.8 Hz, J= 11.1 Hz, CH_2-5'), 3.91 (dd, 1H, J= 5.5 Hz, J= 8.9 Hz,

CH-3), 4.36 (q, 2H,J= 13.3 Hz, J= 18.8 Hz, CH_2 of benzyl), 4.99 (t, 1H, J= 5.4 Hz, CH-2), 5.96 (d, 1H, J= 5.3 Hz, CH-1), 7.29-7.39 (m, 3H, CH of benzyl), 7.42-7.46 (m, 1H, CH of benzyl).

^{13}C NMR (62.5 MHz, CD_3DO) δ= 4.87 (CH_2-5), 36.8 (CH_2 of benzyl), 77.1 (CH-3), 78.0 (CH-4), 85.0 (CH-2), 99.7 (CH-1), 128.7 (CH of benzyl), 129.7 (CH of benzyl), 130.0 (CH of benzyl), 138.0 (Cq benzyl), 173.2 (N=C).

2-Benzylsulfanyl-4,5-dihydro-(3-*tert*butyldimethylsilyl-1,2,5-trideoxy-5-iodo-α-D-ribofuranoso)[1,2-d]-1,3-oxazole **(86)**

$C_{19}H_{28}INO_3SSi$

M.W = 505,06 g/mol

<u>Pocedure 1:</u>

Iodine-oxazolidinethione **83** (0.462 g, 1.113 mmol) was dissolved in 11.3 mL of anhydrous THF at room temperature. The reaction mixture was placed in an ice-salt bath. Et_3N (0.62 mL,4.452 mmol, 4 eq.) and BnBr (0.265 mL, 2.226 mmol, 2 eq.) were successively added and allowed to react for 2 hours at room temperature. The reaction mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (10:90) as eluent. **Yield**: 56%

<u>Procedure 2:</u>

Iodinated benzylsulfanyloxazolidine **85** (0.613 g, 0.1560 mmol) was dissolved in 11 mL of DMF at room temperature. TBDMSCl (0.591 g, 3.920 mmol, 2.5 eq.) and imidazole (0.0.464 g, 6.816 mmol, 4 eq.) were added and allowed to react for 12 hours at room temperature. The solution was diluted with ethyl acetate. The organic phase was washed once with water and once with a solution of HCl 1M, then dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (20:80) as eluent. **Yield**: 87%

Rf= 0.95 (EA/PE: 50/50); $[\alpha]_D^{20}$(0.49, $CHCl_3$)= +67.35

M.S (IS): m/z= 506.0 $[M + H]^+$, 528.0 $[M + Na]^+$, 1011.0 $[2M + H]^+$, 1033.0 $[2M + Na]^+$, 1049.0 $[2M + K]^+$.

IR (cm^{-1}): 672 (IC), 1251 ($SiCH_3$), 1591 (N=C).

^1H NMR (250 MHz, CD_3OD) δ = 0.22 (s, 6H, $Si(CH_3)_2$)), 0.97 (s, 9H, $SiC(CH_3)_3$), 3.03-3.10 (m, 1H, CH-4), 3.30-3.36 (m, 1H, CH_2-5), 3.56 (dd, 1H,J= 3.1 Hz, J= 11.2 Hz, CH_2-5'), 4.02 (dd, 1H, J= 5.5 Hz, J= 8.5 Hz, CH-3), 4.32 (s, 2H, CH_2 of benzyl), 4.94 (t, 1H, J= 5.5 Hz, CH-2), 5.98 (d, 1H, J= 5.4 Hz, CH-1), 7.31-7.38 (m, 3H, CH of benzyl), 7.42-7.46 (m, 2H, CH of benzyl).

^{13}C NMR (62.5 MHz, CD_3OD) δ= -4.5 ($Si(CH_3)_2$), -4.3 ($Si(CH_3)_2$), 5.6 (CH_2-5), 18.8 ($Si\underline{C}(CH_3)_3$), 26.3 ($SiC(\underline{C}H_3)_3$), 36.7 (CH_2 of benzyl), 77.6 (CH-4), 78.0 (CH-3), 84.1 (CH-2), 100.0 (CH-1), 128.7 (CH of benzyl), 129.7(CH of benzyl), 129.9 (CH of benzyl), 137.9 (Cq benzyl), 172.9 (N=C).

2-Benzylsulfanyl-4,5-dihydro-(5-azido-3-*tert*butyldimethylsilyl-1,2,5-trideoxy-α-D-arabinofuranoso)[1,2-d]-1,3-oxazole **(87)**

$C_{19}H_{28}N_4O_3SSi$

M.W= 420,17 g/mol

Benzylsulfanyloxazolidine **86** (0.373 g, 0.739 mmol) was dissolved in 12 mL of DMF at room temperature. NaN_3 (0.240 g, 3.693 mmol, 5 eq.) was added and allowed to react for 3 hour at 80°C. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (20:80) as eluent.

Yield: 74%; **Rf**= 0.84 (EA/PE: 20/80); $[\alpha]_D^{20}$(0.22, $CHCl_3$)= +77.27

M.S (IS): m/z= 421.5 $[M + H]^+$, 443.5 $[M + Na]^+$, 841.5 $[2M + H]^+$, 863.0 $[2M + Na]^+$.

IR (cm^{-1}): 1251 ($SiCH_3$), 1592 (N=C), 2097 (N_3).

^1H NMR (250 MHz, CD_3OD) δ = 0.20 (s, 6H, $Si(CH_3)_2$)), 0.97 (s, 9H, $SiC(CH_3)_3$), 3.31-3.38 (m, 1H, CH_2-5), 3.46-3.53 (m, 1H, CH-4), 3.64 (dd, 1H, J_3= 2.6 Hz, J= 13.5 Hz, CH_2-5'), 4.21 (q, 1H, J= 5.5 Hz, J_3= 8.8 Hz, CH-3), 4.33 (s, 2H, CH_2 of benzyl), 4.93 (t, 1H, J= 5 .4Hz, CH-2), 6.00 (d, 1H, J= 5.3 Hz, CH-1), 7.29-7.38 (m, 3H, CH of benzyl), 7.42-7.46 (m, 2H, CH of benzyl).

^{13}C NMR (62.5 MHz, CD_3OD) δ= -4.9 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), 18.9 ($Si\underline{C}(CH_3)_3$), 26.2 ($SiC(\underline{C}H_3)_3$), 36.7 (CH_2 of benzyl), 51.2 (CH_2-5), 74.3 (CH-3), 78.7 (CH-4), 83.9 (CH-2), 100.4 (CH-1), 128.8 (CH of benzyl), 129.7(CH of benzyl), 130.0 (CH of benzyl), 137.9 (Cq of benzyl), 173.1 (N=C).

(5-azido-3-*tert*butyldimethylsilyl-1,2,3-trideoxy-α-D-ribofuranoso)[1,2-d]-1,3-oxazolidin-2-one **(88)**

$C_{12}H_{22}N_4O_4Si$

M.W= 314,14 g/mol

The azido-sugar **87** (0.215 g, 0.512 mmol) was dissolved in 5 mL of DCM at room temperature. $NaHCO_3$ (0.129 g, 1.536 mmol, 3 eq.) was added. The reaction mixture was placed in an ice bath and then *m*-CPBA (0.344 g, 1.536 mmol, 3 eq.) was added and allowed to react for 20 minutes at 0 °C. The reaction mixture was placed at room temperature and allowed to react for 12 hours at room temperature. The solution was then diluted with DCM. The organic phase was washed once with water, once with a saturated Na2S2O5 solution, once with a NaOH 1M solution and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (15:85) as eluent.

Yield: 80%; **Rf**= 0.26 (EA/PE: 20/80); **M.p.**= 86-89 °C, $[\alpha]_D^{20}$(0.43, $CHCl_3$)= +80.83

M.S (IS): m/z= 332.5 $[M + NH_4]^+$, 629.5 $[2M + H]^+$, 646.0 $[M + NH_4]^+$, 651.5 $[2M + Na]^+$, 667.5 $[2M + K]^+$.

IR (cm^{-1}): 1251 ($SiCH_3$), 1753 (C=O), 2104 (N_3), 3325 (NH).

^1H NMR (250 MHz, CD_3OD) δ = 0.20 (s, 6H, $Si(CH_3)_2$)), 0.97 (s, 9H, $SiC(CH_3)_3$), 3.32-3.39 (m, 1H, CH_2-5), 3.69 (dd, 1H, J= 2.6 Hz, J= 13.7 Hz, CH_2-5'), 3.82-3.88 (m, 1H, CH-4), 4.20 (dd, 1H, J= 5.3 Hz, J= 8.9 Hz, CH-3), 4.96 (t, 1H, J= 5.3 Hz, CH-2), 5.71 (d, 1H, J= 5.3 Hz, CH-1).

^{13}C NMR (62.5 MHz, CD_3OD) δ= -5.0 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$), 18.9 ($Si\underline{C}(CH_3)_3$), 26.2 ($SiC(\underline{C}H_3)_3$), 51.2 (CH_2-5), 73.7 (CH-3), 78.8 (CH-4), 80.4 (CH-2), 86.6 (CH-1), 160.9 (C=O)

2-Benzylsulfanyl-4,5-dihydro-(5-azido-1,2,5-trideoxy-α-D-arabinofuranoso)[1,2-d]-1,3-oxazole **(89)**

$C_{13}H_{14}N_4O_3S$
M.W= 306,08 g/mol

The benzylsulfanyloxazoline **85** (1.895 g, 4.847 mmol) was dissolved in 91 mL of anhydrous DMF at room temperature. NaN_3 (1.575 g, 24.233 mmol, 5 eq.) was added and allowed to react for 3 hours at 80ºC. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of AE/PE (10:90) as eluent.

Yield: 92%; **Rf**= 0.81 (EA/PE: 80/20); $[\alpha]_D^{20}$(0.22, MeOH)= +23.04

M.S (IS): m/z= 307.0 $[M + H]^+$, 329.0 $[M + Na]^+$, 613.5 $[2M + H]^+$, 635.0 $[2M + Na]^+$.

IR (cm^{-1}): 1581 (C=N), 2096 (N_3), 3241 (OH).

^1H NMR (400 MHz, $CDCl_3$) δ = 3.02-3.09 (m, 1H, OH), 3.37 (dd, 1H, J= 4.6 Hz, J= 13.3 Hz, CH_2-5), 3.42-3.46 (m, 1H, CH-4), 3.66 (dd, 1H, J= 2.8 Hz, J= 13.3 Hz, CH_2-5'), 4.05 (dd, 1H, J= 5.7 Hz, J= 9.1 Hz, CH-3), 4.30 (q, 2H, J= 13.3 Hz, J= 21.2 Hz, CH_2 of benzyl), 4.85 (t, 1H, J= 5.5 Hz, CH-2), 5.99 (d, 1H,J= 5.2 Hz, CH-1), 7.24-7.39 (m, 5H, CH of benzyl), 7.96 (s, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 36.5 (CH_2 of benzyl), 50.2 (CH_2-5), 72.5 (CH-3), 76.8 (CH-4), 82.4 (CH-2), 98.9 (CH-1), 127.8 (CH of benzyl), 128.7 (CH of benzyl), 128.9 (CH of benzyl), 136.1 (Cq of benzyl), 170.8 (C=N).

4,5-dihydro-(1,2,3-trideoxy-5-azido-α-D-ribofuranosid)[1,2-d]-1,3-oxazolin-2-one **(90)**

$C_6H_8N_4O_4$
M.W= 200,05 g/mol

Procedure 1:

Azido-sugar **88** (0.500 g, 1.592 mmol) was dissolved in 12.5 mL of dry THF at room temperature. The mixture was placed in an ice bath; then TBAF (3.82 mL, 3.822 mmol, 2.4 eq) was added dropwise. The resulting mixture was stirred for 12 hours at room temperature. The solution was diluted with ethyl acetate. The organic phase was washed twice with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of AE/PE (10:90) as eluent. **Yield**: 28%

Procedure 2:

Azido-sugar **89** (1.300 g, 4.248 mmol) was dissolved in 39 mL of DCM at room temperature. $NaHCO_3$ (1.071 g, 12.745 mmol, 3 eq.) was added. The reaction mixture was placed in an ice bath and *m*-CPBA (2.856 g, 12.745 mmol, 3 eq.) was added and allowed to react for 20 minutes at 0 °C. The reaction mixture was placed at room temperature and allowed to react for 12 hours at room temperature. The solution was neutralized with $Na_2S_2O_5$ and evaporated under reduced pressure. The residue was dissolved in methanol, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/PE (50:50) as eluent. **Yield**: 22%

Rf= 0. (EA/PE: 80/20); **M.p=** 116-121 °C; $[\alpha]_D^{20}$(1.3, MeOH)= +36.6

M.S (IS): m/z= 201.0 $[M + H]^+$, 401.0 $[2M + H]^+$, 423.0 $[2M + Na]^+$, 440.5 $[2M + K]^+$.

IR (cm^{-1}): 1716 (C=O), 2099 (N_3), 3300 (NH).

^{1}H NMR (400 MHz, CD_3OD) δ = 3.38 (dd, 1H, J= 5.4 Hz, J= 13.6 Hz, CH_2-5), 3.65 (dd, 1H, J= 2.6 Hz, J= 13.6 Hz, CH_2-5'), 3.82-3.85 (m, 1H, CH-4), 4.02 (dd, 1H, J= 5.4 Hz, J= 9.3 Hz, CH-3), 4.96 (t, 1H, J = 5.3 Hz, CH-2), 5.68 (d, 1H, J= 5.3 Hz, CH-1).

^{13}C NMR (100 MHz, CD_3OD) δ= 51.7 (CH_2-5), 73.0 (CH-3), 78.3 (CH-4), 80.6 (CH-2), 86.5 (CH-1), 160.6 (C=O).

(1,2,5-trideoxy-5-iodo-α-D-xylofuranoso)[1,2-d]-1,3-oxazolidine-2-thione **(92)**

$C_6H_8INO_3S$

M.W= 300,93 g/mol

The oxazolidinethione **66** (1.700 g, 8.901 mmol) was dissolved in 51 mL of THF at room temperature. Ph_3P (4.664 g, 17.801 mmol, 2 eq.) and imidazole (1.212 g, 17.801 mmol, 2 eq.) were added, the stirred mixture was kept for 15 minutes at 0°C. Then iodine (1.889 g, 7.435 mmol, 2 eq.) was slowly added and allowed to react for 1h30 minutes at room temperature. After completion, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (50:50) as eluent.

Yield: 75%; **Rf**= 0.3 (EA/PE: 50/50); **M.p=** 168-170°C; $[\alpha]_D^{20}$(0.33, MeOH)= +24.0

M.S (IS): m/z= 620.5 $[2M + NH_4]^+$, 642.0 $[2M + K]^+$.

IR (cm^{-1}): 628 (IC), 1155 (C=S), 3314 (NH +OH).

^{1}H NMR (250 MHz, ($CDCl_3$) δ = 3.22-3.32 (m, 2H, CH_2-5), 3.86-3.90 (ddd, 1H, J= 2.6 Hz, J= 6.9 Hz, CH-4), 3.23 (dd, 1H, J= 2.7 Hz, J= 5.3 Hz, CH-3), 5.12 (d, 1H, J= 5.4 Hz, CH-2), 5.81 (d, 1H, J= 5.3 Hz, OH), 5.88 (d, 1H,J= 5.4 Hz, CH-1), 10.82 (s, 1H, NH).

^{13}C NMR (62.5 MHz, ($CDCl_3$) δ= 0.0 (CH_2-5), 72.6 (CH-3), 80.4 (CH-4), 88.7 (CH-1), 90.0 (CH-2), 188.4 (C=S).

2-Benzylsulfanyl-4,5-dihydro-(5-iodo-1,2,5-trideoxy-α-D-xylofuranoso)[1,2-d]-1,3-oxazole **(93)**

$C_{13}H_{14}INO_3S$

M.W= 390,97 g/mol

Iodine-oxazolidinethione **92** (0.926 g, 3.076) was dissolved in anhydrous THF at room temperature. The reaction mixture was placed in an ice-salt bath. Et_3N (1.716 mL, 12.304 mmol, 4 eq.) then BnBr (0.549 mL, 4.615 mmol, 1.5 eq.) were added and allowed to react for 12 hours at room temperature. The reaction mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (20:80) as eluent.

Yield: 71%; **Rf**= 0.67 (EA/PE: 50/50); **M.p=** 144-146 °C; $[\alpha]_D^{20}$(0.48, $CHCl_3$)= +46.1

M.S (IS): m/z= 392.0 $[M + H]^+$, 414.0 $[M + Na]^+$, 783.0 $[2M + H]^+$.

IR (cm^{-1}): 616 (IC), 1589 (C=N), 3473 (OH).

^{1}H NMR (250 MHz, $CDCl_3$) δ = 3.23-3.35 (m, 2H, CH_2-5), 3.86 (dtd, 1H, J= 2.7 Hz, J= 5.9 Hz, J= 8.8 Hz, CH-4), 4.29 (q, 2H, J= 13.2 Hz, J= 15.4 Hz, CH_2 of benzyl), 4.40-4.43 (m, 1H, CH-3), 4.88 (d, 1H, J= 5.4 Hz, CH-2), 6.19 (d, 1H, J= 5.5 Hz, CH-1), 7.28-7.40 (m, 5H, CH of benzyl).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ= -2.1 (CH_2-5), 36.6 (CH_2 of benzyl), 74.5 (CH-3), 79.4 (CH-4), 88.2 (CH-2), 100.4 (CH-1), 128.0 (CH of benzyl), 128.9 (CH of benzyl), 129.1 (CH of benzyl), 136.1 (Cq of benzyl), 170.4 (C=N).

2-Benzylsulfanyl-4,5-dihydro-(5-azido-1,2,5-trideoxy-α-D-xylofuranoso)[1,2-d]-1,3-oxazole
(94)

$C_{13}H_{14}N_4O_3S$
M.W= 306,08 g/mol

The iodo-benzylsulfanyloxazolidine **93** (0.250 g, 0.639 mmol) was dissolved in 12 mL of anhydrous DMF at room temperature. NaN_3 (0.208 g, 3.197 mmol, 5 eq.) was added and allowed to react for 3 hour at 80ºC. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (10:90) as eluent.

Yield: 82%; **Rf**= 0.74 (EA/PE: 30/70); **M.p=** 117-120ºC; $[\alpha]_D^{20}$(0.48, $CHCl_3$)= +18.6

M.S (IS): m/z= 307.0 $[M + H]^+$, 329.0 $[M + Na]^+$, 613.5 $[2M + H]^+$, 635.0 $[2M + Na]^+$.

IR (cm^{-1}): 1584 (C=N), 2088 (N_3), 3139 (OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.11 (s, 1H, OH), 3.58-3.66 (m, 2H, CH_2-5), 3.7 (td, 1H,J= 2.8 Hz, J= 5.9 Hz, CH-4), 4.24-4.32 (m, 3H, 2H of CH_2 of benzyl and 1H of CH-3), 4.83 (d, 1H, J= 5.4 Hz, CH-2), 6.15 (d, 1H, J= 5.4 Hz, CH-1), 7.28-7.38 (m, 5H, CH of benzyl).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 36.5 (CH_2 of benzyl), 48.9 (CH_2-5), 74.7 (CH-3), 77.0 (CH-4), 88.4 (CH-2), 99.7 (CH-1), 128.0 (CH of benzyl), 128.8 (CH of benzyl), 129.1 (CH of benzyl), 136.1 (Cq of benzyl), 170.5 (C=N).

(5-azido-1,2,3-trideoxy-α-D-xylofuranoso)[1,2-d]-1,3-oxazolidin-2-one **(95)**

$C_6H_8N_4O_4$
M.W= 200,05 g/mol

The azido-benzylsulfanyloxazolidine **94** (1.260 g, 4.118 mmol) was dissolved in 38 mL of dichloromethane at room temperature. $NaHCO_3$ (1.037 g, 12.353 mmol, 3 eq.) was added. The reaction mixture was placed in an ice bath and then *m*-CPBA (2.769 g, 12.353 mmol, 3 eq.) was added and allowed to react for 20 minutes at 0 °C. The reaction mixture was placed at room temperature and allowed to react for 12 hours at room temperature. The solution was neutralized with $Na_2S_2O_5$ and evaporated under reduced pressure. The residue was dissolved in methanol, filtered and evaporated again. The residue was then purified by silica gel column chromatography using a mixture of EA/ PE (50:50) as eluent.

Yield: 60%; **Rf=** 0.43 (EA/PE: 80/20); $[\alpha]_D^{20}$(0.96, MeOH)= -18.69

M.S (IS): m/z= 218.0 $[M + NH_4]^+$, 401.0 $[2M + H]^+$, 418.5 $[2M + NH_4]^+$, 423.0 $[2M + Na]^+$.

IR (cm^{-1}): 1082 (CN), 1694 (C=O), 2088 (N_3), 3241 (NH + OH).

^{1}H NMR (400 MHz, CD_3OD) δ =3.49-3.58 (m, 2H, CH_2-5), 4.05 (dtd, 1H, J= 2.9 Hz, J= 5.3 Hz, J= 7.1 Hz, CH-4), 4.24 (d, 1H, J= 2.8 Hz, CH-3), 4.87 (d, 1H, J= 5.4 Hz, CH-2), 5.78 (d, 1H,J= 5.4 Hz, CH-1).

^{13}C NMR (100 MHz, CD_3OD) δ= 50.4 (CH_2-5), 74.8 (CH-3), 79.4 (CH-4), 86.7 (CH-2), 87.4 (CH-1), 160.1 (C=O).

4,5-dihydro-(1,2,5-trideoxy-5-iodo-3-tertbutyldimethylsilyl-α-D-xylofuranoso) [1,2-d]-1,3-oxazoline-2-thione **(96)**

$C_{12}H_{22}INO_3SSi$
M.W= 415.01 g/mol

The iodo-oxazolidinethione **92** (1.822 g, 6.053 mmol) was dissolved in 28 mL of DMF at room temperature. The TBDMSCl (1.095 g, 7.264 mmol, 1.2 eq.) and imidazole (1.030 g, 15.133 mmol, 2.5 eq.) were added and allowed to react for 12 hours at room temperature. The residue was diluted with ethyl acetate. The organic phase was washed three times with water, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/H (10:90) as eluent.

Yield: 86%; **Rf=** 0.84 (EA/H: 40/60); $[\alpha]_D^{20}$(0.41, $CHCl_3$)= +19.5

IR (cm^{-1}): 612 (IC), 1131 (C=S), 1257 ($SiCH_3$), 3207 (NH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $Si(CH_3)_2$), 0.71 (s, 9H, $SiC(CH_3)_3$), 2.98-3.05 (m, 2H, CH_2-5), 4.01-4.04 (m, 1H, CH-4), 4.31 (d, 1H, J= 2.4 Hz, CH-3), 4.84 (d, 1H, J= 5.4 Hz, CH-2), 5.71 (d, 1H, J= 5.4 Hz, CH-1), 7.77 (s, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -4.6 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), -2.7 (CH_2-5), 18.0 (Cq of Si<u>C</u>$(CH_3)_3$), 25.7 (SiC(<u>C</u>$H_3)_3$), 74.2 (CH-3), 81.5 (CH-4), 88.8 (CH-2), 90.6 (CH-1), 189.1 (C=S).

2-Benzylsulfanyl-4,5-dihydro-(3-*tert*butyldimethylsilyl-1,2,5-trideoxy-5-iodo-α-D-xylofuranoso)[1,2-d]-1,3-oxazole **(97)**

$C_{19}H_{28}INO_3SSi$

M.W= 505.06 g/mol

<u>Procedure 1:</u>

Iodine-benzylsulanyloxazolidine **93** (1.363 g, 3.486 mmol) was dissolved in 19 mL of DMF at room temperature. The TBDMSCl (0.630 g, 4.183 mmol, 1.2 eq.) and imidazole (0.593 g, 8.716 mmol, 2.5 eq.) was added and allowed to react for 12 hours at room temperature. The residue was diluted with ethyl acetate. The organic phase was washed three times with water, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/H (10:90) as eluent. **Yield:** 60%

<u>Procedure 2:</u>

Iodine-oxazolidinethione **96** (2.913 g, 7.013 mmol) was dissolved in 71.7 mL of anhydrous THF at room temperature. The reaction mixture was placed in an ice-salt bath. The Et_3N (3.913 mL, 28.053 mmol, 4 eq.) and BnBr (1.668 mL, 14.026 mmol, 2 eq.) were added and allowed to react

for 12 hours at room temperature. The reaction mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/H (10:90) as eluent. **Yield:** 57%

Rf= 0.74 (EA/H: 20/80); $[\alpha]_D^{20}$(0.19, $CHCl_3$)= +10.5

IR (cm^{-1}): 614 (IC), 1254 ($SiCH_3$), 1594 (N=C).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $Si(CH_3)_2$), 0.74 (s, 9H, $SiC(CH_3)_3$), 3.04-3.10 (m, 2H, CH_2-5), 3.68 (dtd, 1H, J= 2.6 Hz, J= 5.4 Hz, J= 8.3 Hz, CH-4), 4.08-4.16 (m, 3H, 2H of CH_2 of Bn and 1H of CH-3), 4.54 (d, 1H, J= 5.4 Hz, CH-2), 5.97 (d, 1H, J= 5.4 Hz, CH-1), 7.08-7.21 (m, 5H, CH of benzyl).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -4.5 ($Si(CH_3)_2$), -4.4 ($Si(CH_3)_2$), -1.7 (CH_2-5), 18.2 (Cq of Si<u>C</u>$(CH_3)_3$), 25.9 (SiC(<u>C</u>$H_3)_3$), 36.7 (CH_2 of Bn), 74.9 (CH-3), 80.5 (CH-4), 88.4 (CH-2), 100.2 (CH-1), 127.9 (CH of Bn), 128.8 (CH of Bn), 129.2 (CH of Bn), 136.2 (Cq of Bn), 170.0 (C=N).

(3-*tert*butyldimethylsilyl-1,2,3-trideoxy-5-iodo-α-D-xylofuranoso)[1,2-d]-1,3-oxazolidin-2-one **(98)**

$C_{12}H_{22}INO_4Si$
M.W= 399.04 g/mol

Benzylsulfanyloxazolidine **97** (1.060 g, 2.099 mmol) was dissolved in 19.2 mL of DCM at room temperature. $NaHCO_3$ (0.529 g, 6.296 mmol, 3 eq.) was added. The reaction mixture was placed in an ice bath and then *m*-CPBA (1.411 g, 6.296 mmol, 3 eq.) was added and allowed to react for 20 minutes at 0 °C. The reaction mixture was placed at room temperature and allowed to react for 12 hours at room temperature. The solution was diluted with DCM. The organic phase was washed once with water, once with a saturated $Na_2S_2O_5$ solution, once with NaOH 1M solution and further with a saturated NaCl solution. The resulting organic phase was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/ H (5:95) as eluent.

Yield: 65%; **Rf=** 0.31 (EA/H: 20/80); $[\alpha]_D^{20}$(0.2, $CHCl_3$)= +5.0

IR (cm^{-1}): 619 (IC), 1264 ($SiCH_3$), 1768 (C=O), 3306 (NH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $Si(CH_3)_2$), 0.73 (s, 9H, $SiC(CH_3)_3$), 3.02-3.09 (m, 2H, CH_2-5), 4.10 (dtd, 1H, J= 2.5 Hz, J= 6.2 Hz, J= 8.4 Hz, CH-4), 4.24 (d, 1H, J= 2.4 Hz, CH-3), 4.62 (d, 1H, J= 5.3 Hz, CH-2), 5.61 (d, 1H, J= 5.3 Hz, CH-1), 6.58 (s, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -4.6 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), -1.8 (CH_2-5), 18.1 (Cq of $Si\underline{C}(CH_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 74.5 (CH-3), 80.9 (CH-4), 85.3 (CH-2), 86.1 (CH-1), 157.7 (C=O).

2-Benzylsulfanyl-4,5-dihydro-(1,2,5-trideoxy-5-azido-3-tertbutyldimethylsilyl-α-D-xylofuranoso)[1,2-d]-1,3-oxazole **(99)**

$C_{19}H_{28}N_4O_3SSi$
M.W= 420.17 g/mol

Benzylsulfanyloxazolidine **97** (0.930 g, 1.841 mmol) was dissolved in 34 mL of anhydrous DMF at room temperature. Sodium azide (0.599 g, 9.207 mmol, 3 eq.) was added and allowed to react for 3 hours at 80°C. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/H (20:80) as eluent.

Yield: 86%; **Rf=** 0.94 (EA/H: 50/50); $[\alpha]_D^{20}$(0.18, $CHCl_3$)= +16.4

IR (cm^{-1}): 1253 ($SiCH_3$), 1595 (C=N), 2099 (N_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.01 (s, 6H, $Si(CH_3)_2$), 0.76 (s, 9H, $SiC(CH_3)_3$), 3.27 (dd, 1H, J= 6.3 Hz, J= 12.2 Hz, CH_2-5), 3.44-3.48 (m, 1H, CH_2-5'), 3.54 (ddd, J= 2.9 Hz, J= 6.3 Hz, CH-4), 4.04 (d, 1H, J= 2.9 Hz, CH-3), 4.15 (q, 2H, J= 12.0 Hz, J= 16.0 Hz, CH_2 of Bn), 4.53 (d, 1H, J= 5.4 Hz, CH-2), 5.97 (d, 1H, J= 5.4 Hz, CH-1), 7.11-7.24 (m, 5H, CH of Bn).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -5.1 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$), 18.2 (Cq of $Si\underline{C}(CH_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 36.7 (CH_2 of Bn),49.0 (CH_2-5), 75.3 (CH-3), 77.8 (CH-4), 88.6 (CH-2), 99.9 (CH-1), 127.9 (CH of Bn), 128.8 (CH of Bn), 129.1 (CH of Bn), 136.2 (Cq of Bn), 169.8 (C=N).

4,5-dihydro-(1,2,3-trideoxy-5-azido-3-tertbutyldimethylsilyl-α-D-xylofuranosid)[1,2-d]-1,3-oxazolin-2-one **(100)**

$C_{12}H_{22}N_4O_4Si$
M.W= 314.14 g/mol

The azido-benzyllsulfanyloxazolidine **98** (0.623 g, 1.483 mmol) was dissolved in 13.5 mL of DCM at room temperature. $NaHCO_3$ (0.374 g, 4.448 mmol, 3 eq.) was added. The reaction mixture was placed in an ice bath and the m-CPBA (0.997 g, 4.448 mmol, 3 eq.) was added and allowed to react for 20 minutes at 0 °C. The reaction mixture was placed at room temperature and allowed to react for 12 hours at room temperature. The solution was diluted with DCM. The organic phase was washed once with water, once with a saturated $Na_2S_2O_5$ solution, once with a NaOH 1M solution and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/ H (5:95) as eluent.

Yield: 83%; **Rf=** 0.7 (EA/H: 50/50); $[\alpha]_D^{20}$(0.75, $CHCl_3$)= -9.4

IR (cm^{-1}): 1255 ($SiCH_3$), 1746 (C=O), 2095 (N_3), 3296 (NH).

^1H NMR (400 MHz, $CDCl_3$) δ = 0.01 (s, 6H, $Si(CH_3)_2$), 0.78 (s, 9H, $SiC(CH_3)_3$), 3.28 (dd, 1H, J= 5.3 Hz, J= 12.6 Hz, CH_2-5), 3.47 (dd, 1H, J= 7.2 Hz, J= 12.6 Hz, CH_2-5'), 4.98-4.01 (m, 1H, CH-4), 4.18 (d, 1H, J= 2.7 Hz, CH-3), 4.62 (d, 1H, J= 5.3 Hz, CH-2), 5.65 (d, 1H, J= 5.3 Hz, CH-1).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -5.2 ($Si(CH_3)_2$), -4.8 ($Si(CH_3)_2$), 18.1 (Cq of Si$\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 49.3 (CH_2-5), 74.9 (CH-3), 78.4 (CH-4), 85.4 (CH-2), 85.9 (CH-1), 157.7 (C=O).

1-N-benzoyl-4,5-dihydro-(1,2,5-trideoxy-3-benzoyl -5-iodo-α-D-xylofuranoso) [1,2-d]-1,3-oxazoline-2-thione **(101)**

$C_{20}H_{16}INO_5S$
M.W= 508,98 g/mol

Iodo-oxazolidinethione **92** (0.500 g, 1.661 mmol) was dissolved in 25 mL of DCM/Pyr (2/1) at rooom temperature. The reaction mixture was placed in an ice-salt bath. The BzCl (0.58 mL, 4.983 mmol, 3 eq.) and DMAP (0.041 g, 0.332 mmol, 0.2 eq.) were added and allowed to react for 2 hours at room temperature. The solution was diluted with DCM. The organic phase was washed once with HCl 1M, once with satured $NaHCO_3$, once with water and once with satured NaCl solution, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (2:98) as eluent.

Yield: 98%; **Rf**= 0.92 (EA/PE: 50/50); **M.p=** 173-176°C; $[\alpha]_D^{20}$(0.5, $CHCl_3$)= +58.0

M.S (IS): m/z= 532.0 $[M + Na]^+$.

IR (cm^{-1}): 605 (IC), 1056 (CN), 1092 (C=S), 1726 (C=O).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.35-3.44 (m, 2H, CH_2-5), 4.69 (dtd, 1H, J = 2.9 Hz, J = 6.3 Hz, J= 8.2 Hz, CH-4), 5.31(d, 1H, J = 5.3 Hz, CH-2), 5.90 (d, 1H, J = 2.9 Hz, CH-3), 6.66 (d, 1H, J= 5.4 Hz, CH-1), 7.45-7.53 (m, 4H, CH of Bz), 7.58-7.67 (m, 2H, CH of Bz), 7.72-7.75 (m, 4H, CH of Bz), 8.03-8.07(m, 4H, CH of Bz).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -4.3 (CH_2-5), 75.1 (CH-3), 80.6 (CH-4), 85.2 (CH-2), 91.3 (CH-1), 128.5 (CH of Bz), 128.6 (CH of Bz), 129.0 (CH of Bz), 129.7 (CH of Bz), 130.0 (CH of Bz), 132.7 (CH of Bz), 133.5(CH of Bz), 134.3 (CH of Bz), 164.9 (Cq of Bz), 169.78 (Cq of Bz), 184.2 (C=S).

4,5-dihydro-(1,2,5-trideoxy-5-iodo-β-D-arabinofuranoso) [1,2-d]-1,3- oxazoline-2-thione **(104)**

$C_6H_8INO_3S$
M.W= 300,93 g/mol

Iodine-oxazolidinethione **65** (0.697 g, 3.649 mmol) was dissolved in 20 mL of THF at room temperature. Ph_3P (1.912 g, 7.298 mmol, 2 eq.) and imidazole (0.497 g, 7.298 mmol, 2 eq.) were added, the stirred mixture was kept for 15 minutes at 0°C The iodine (1.854 g, 7.298 mmol, 2 eq.) was slowly added and allowed to react for 2 hours at room temperature. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (30:70) as eluent.
Yield: 85%; **Rf**= 0.45 (EA/PE: 50/50); **M.p=** 169-173°C; $[\alpha]_D^{20}$(0.407 g/100 mL, MeOH)= -24.57

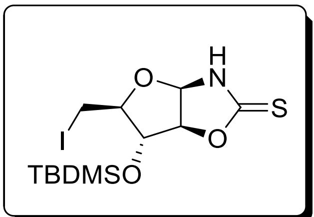
M.S (IS): m/z= 302.0 $[M + H]^+$, 620.0 $[2M + NH_4]^+$, 625.0 $[2M + Na]^+$.

IR (cm^{-1}): 607 (IC), 1035 (CN), 1151 (C=S), 3296 (NH + OH).

^{1}H NMR (400 MHz, $(CD_3)_2S=O$) δ = 3.17 (qd, 2H,J= 7.2 Hz, J= 10.5 Hz, CH_2-5), 4.05 (td, 1H, J= 2.2 Hz, J= 7.2 Hz, CH-4), 4.24-4.27 (m, 1H, CH-3), 5.12 (dd, 1H, J= 1.1 Hz, J= 5.6 Hz, CH-2), 5.89 (d, 1H, J= 5.7 Hz, CH-1), 5.96 (d, 1H, J= 4.4 Hz,OH), 10.99 (s, 1H, NH).

^{13}C NMR (100 MHz, $(CD_3)_2S=O$) δ= 6.2 (CH_2-5), 76.4 (CH-3), 85.5 (CH-4), 89.6 (CH-1), 91.3 (CH-2), 188.1 (C=S).

(1,2,5-trideoxy-5-iodo-3-tert-butyldimethylsilyl-ß-D-arabinofuranoso)[1,2-d]-1,3-oxazolidine-2-thione **(105)**



$C_{12}H_{22}INO_3SSi$
M.W= 415,01 g/mol

The oxazolidinethione **104** (2.081 g, 6.914 mmol) was dissolved in 62 mL of DMF at room temperature. The TBDMSCl (1.250 g, 8.296 mmol, 1.2 eq.) and imidazole (1.177 g, 17.284 mmol, 2.5 eq.) was added and allowed to react for 12 hours at room temperature. The solution was diluted with ethyl acetate. The organic phase was washed three times with water, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (10:90) as eluent.

Yield: 44%; **Rf**= 0.89 (EA/PE: 50/50); **M.p=** 112-114 °C; $[\alpha]_D^{20}$(1.0, $CHCl_3$)= -66.9

M.S (IS): m/z= 416.0 $[M + H]^+$, 438.0 $[M + Na]^+$, 831.0 $[2M + H]^+$, 853.0 $[2M + Na]^+$.

IR (cm^{-1}): 610 (IC), 1032 (CN), 1153 (C=S), 1270 ($SiCH_3$), 3299 (NH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.18 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 3.10 (t, 1H,J= 10.1 Hz, CH_2-5), 3.22 (dd, 1H,J= 5.6 Hz,J= 10.4 Hz, CH_2-5'), 4.23-4.28 (m, 1H, CH-4), 4.59 (dd, 1H, J= 0.9 Hz, J= 1.6 Hz, CH-3), 5.04 (dd, 1H, J= 0.9 Hz,J= 5.6 Hz, CH-2), 5.93 (dd, 1H, J= 1.1 Hz, J= 5.6 Hz, CH-1), 7.75 (s, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -4.5 ($Si(CH_3)_2$), -4.4 ($Si(CH_3)_2$), 4.0 (CH_2-5), 18.0 (Si<u>C</u>$(CH_3)_3$), 25.8 (SiC(<u>C</u>$H_3)_3$), 77.7 (CH-3), 87.7 (CH-4), 89.8 (CH-2), 92.7 (CH-1), 188.7 (C=S).

2-Benzylsulfanyl-4,5-dihydro-(1,2,5-trideoxy-5-iodo-ß-D-arabinofuranoso)[1,2-d]-1,3-oxazole **(106)**

$C_{13}H_{14}INO_3S$
M.W= 390,97 g/mol

The iodo-oxazolidinethione **104** (0.500 g, 1.661 mmol) was dissolved in 17 mL of anhydrous THF at room temperature. The reaction mixture was placed in an ice-salt bath. Then Et_3N (1.85 mL, 13.288 mmol, 8 eq.) and BnBr (0.79 mL, 6.645 mmol, 4 eq.) were successively added and allowed to react for 3 hours at room temperature. The reaction mixture was removed under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (30:70) as eluent.

Yield: 89%; **Rf**= 0.53 (EA/PE: 50/50); $[\alpha]_D^{20}$(0.9, $CHCl_3$) = -44.0

M.S (IS): m/z= 392.0 $[M + H]^+$, 783.0 $[2M + H]^+$.

IR (cm^{-1}): 606 (IC), 1579 (C=N), 3241 (OH).

^1H NMR (400 MHz, $CDCl_3$) δ = 2.88 (dd, 1H, J = 9.5 Hz, J = 10.3 Hz, CH_2-5), 3.09 (dd, 1H, J = 5.3 Hz, J = 10.3 Hz, CH_2-5'), 4.16-4.20 (m, 1H, CH-4), 4.27 (q, 2H, J= 13.4 Hz, J= 15.3 Hz,CH_2 of benzyl), 4.42-4.43 (m, 1H, CH-3), 4.91 (dd, 1H,J= 1.2 Hz, J= 5.9 Hz, CH-2), 6.14 (d, 1H, J = 5.9 Hz, CH-1), 7.25-7.39 (m, 5H, CH of benzyl).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 5.1 (CH_2-5), 36.5 (CH_2 of benzyl), 78.6 (CH-3), 85.9(CH-4), 90.2 (CH-2), 101.1 (CH-1), 128.0 (CH of benzyl), 128.8 (CH of benzyl), 129.2 (CH of benzyl), 13621 (Cq of benzyl), 170.3 (C=N).

2-Benzylsulfanyl-4,5-dihydro-(1,2,5-trideoxy-5-azido-ß-D-arabinofuranoso)[1,2-d]-1,3-oxazole **(107)**

$C_{13}H_{14}N_4O_3S$
M.W= 306,08 g/mol

The benzylsulfanyloxazolidine **106** (0.371 g, 0.949 mmol) was dissolved in 18 mL of anhydrous DMF at room temperature. NaN_3 (0.308 g, 4.744 mmol, 5 eq.) was added and allowed to react for 3 hour at 76°C. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (10:90) as eluent.

Yield: 76%; **Rf**= 0.67 (EA/PE: 60/40); **M.p=** 95-98°C; $[\alpha]_D^{20}$(0.6, $CHCl_3$)= +1.7

M.S (IS): m/z= 307.0 $[M + H]^+$, 613.0 $[2M + H]^+$, 635.0 $[2M + Na]^+$.

IR (cm^{-1}): 1584 (C=N), 2101 (N_3), 3172 (OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.14 (dd, 1H, J = 6.0 Hz , J =12.8 Hz, CH_2-5), 3.25 (dd, 1H, J = 6.4 Hz, J = 12.8 Hz, CH_2-5'), 4.04 (td, 1H, J = 3.6 Hz, J = 6.4 Hz, CH-4), 4.26(dd, 1H, J = 1.6 Hz, J = 3.6 Hz, CH-3), 4.28 (s, 2H, CH_2 of benzyl) 4.88 (dd, 1H, J = 1.6 Hz, J = 6 Hz, CH-2), 6.07 (d, 1H, J = 6 Hz, CH-1), 7.26-7.39 (m, 5H, CH of benzyl).

^{13}C NMR (100 MHz, $CDCl_3$) δ= 36.5 (CH_2 of benzyl), 51.9 (CH_2-5), 77.6 (CH-3), 83.6 (CH-4), 90.1 (CH-2), 100.7 (CH-1), 128.0 (CH of benzyl), 128.8 (CH of benzyl), 129.2 (CH of benzyl), 136.2 (Cq of benzyl), 170.3 (C=N).

(5-azido-1,2,5-trideoxy-ß-D-arabinofuranoso)[1,2-d]-1,3-oxazolidin-2-one **(108)**

$C_6H_8N_4O_4$
M.W= 200,05 g/mol

Azido-oxazolidinone **107** (1.346 g, 4.399 mmol) was dissolved in 41 mL of DCM at room temperature. The $NaHCO_3$ (1.109 g, 13.196 mmol, 3 eq.) was added. The heterogeneous solution was cooled in an ice bath, then *m*-CPBA (2.957 g, 13.196 mmol, 3 eq.) was added and allowed to react for 20 minutes at 0 °C. The reaction mixture was placed at room temperature and allowed to react for 12 hours at room temperature. The solution was neutralized with $Na_2S_2O_5$ and evaporated in the evaporator. The residue was dissolved in methanol, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (50:50) as eluent.

Yield: 58%; **Rf**= 0.24 (EA/PE: 50/50); **M.p=** 133-137°C; $[\alpha]_D^{20}$(0.34, MeOH)= +32.0

M.S (IS): m/z= 218.0 $[M + NH_4]^+$, 223.0 $[M + Na]^+$, 401.0 $[2M + H]^+$, 418.5 $[2M + NH_4]^+$, 423.0 $[2M + Na]^+$.

IR (cm^{-1}): 1093 (CN), 1731 (C=O), 2100 (N_3), 3296 (NH + OH).

^{1}H NMR (400 MHz, CD_3OD) δ = 3.33-3.41 (m, 2H, CH_2-5), 4.01-4.05 (m, 1H, CH-4), 4.21 (dd, 1H, J = 1.4 Hz, J = 3.6 Hz, CH-3), 4.86 (dd, 1H, J = 1.4 Hz, J = 5.6 Hz, CH-2), 5.72 (d, 1H, J = 5.6 Hz, CH-1).

^{13}C NMR (100 MHz, CD_3OD) δ= 53.4 (CH_2-5), 77.4 (CH-3), 85.6 (CH-4), 88.1 (CH-2), 88.2 (CH-1), 159.8 (C=O).

2-Benzylsulfanyl-4,5-dihydro-(2,3,6-trideoxy-6-azido-1-*O*-benzyl-α-L-sorbofuranoso)[2,3-d]-1,3-oxazole **(110)**

$C_{21}H_{22}N_4O_4S$

M.W= 426,14 g/mol

<u>Procedure 1:</u>

Azido-oxazolidinethione **109** (0.120 g, 0.357 mmol) was dissolved in 3,6 mL of anhydrous THF at room temperature. The reaction mixture was placed in an ice-salt bath. Et_3N (0.204 mL, 1.427 mmol, 4 eq.) and BnBr (0.085 mL, 0.714 mmol, 2 eq.) were added and allowed to react for 2 hours at room temperature. The reaction mixture was evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/PE (20:80) as eluent.**Yield**: 67%.

Procedure 2:

Benzylsulfanyloxazolidine **116** (0.300 g, 0.587 mmol) was dissolved in 9 mL of anhydrous DMF at room temperature. NaN_3 (0.191 g, 2.933 mmol, 5 eq.) was added and allowed to react for 4 hours at 80°C. After cooling to room temperature the solution was diluted with ethyl acetate. The organic phase was washed twice with water, dried with $MgSO_4$, filtered and removed under vacuum. The residue was purified by silica gel column chromatography using a mixture of EA/H (10:90) as eluent. **Yield:** 84%.

Rf= 0.69 (EA/PE: 30/70); $[\alpha]_D^{20}$(1.69, MeOH)= -4.14

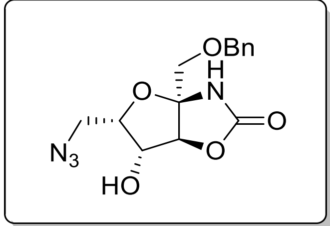
M.S (IS): m/z= 427.2 $[M + H]^+$, 853.2 $[2M + H]^+$.

IR (cm^{-1}): 1583 (C=N), 2097 (N_3), 3260 (OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.34 (d, 1H, J= 11.7 Hz, OH), 3.56-3.59 (m, 2H, CH_2-6), 3.62 (s, 1H, CH_2-1), 3.79 (td, 1H, J = 2.3 Hz, J = 6.5 Hz, CH-5), 4.01 (d, 1H, J= 10.0 Hz, CH_2-1'), 4.16 (dd, 1H, J= 2.4 Hz, J= 11.8 Hz, CH-4), 4.27 (s, 2H, CH_2 of benzyl), 4.59 (d, 1H, J= 11.8 Hz, CH_2 of benzyl), 4.69 (s, 1H, CH_2 of benzyl), 4.71 (s, 1H, CH-3), 7.28-7.41 (m, 10H, CH of 2×benzyl)

^{13}C NMR (100 MHz, $CDCl_3$) δ= 36.6 (CH_2 of benzyl), 49.0 (CH_2-6),71.2 (CH-1), 73.7 (CH-4), 74.1 (CH_2 of benzyl), 79.1 (CH-5), 89.1 (CH-3), 108 9 (Cq-2), 127.9 (CH of benzyl), 128.0 (CH of benzyl), 128.4 (CH of benzyl), 128.7 (CH of benzyl), 128.8 (CH of benzyl) 129.1 (CH of benzyl), 136.0 (Cq of benzyl), 136.8 (Cq of benzyl), 170.5 (C=N).

4,5-dihydro-(1,2,5-trideoxy-6-azido-1-benzyl-L-sorbofuranosid)[2,3-d]-1,3-oxazolin-2-one **(111)**



$C_{14}H_{16}N_4O_5$
M.W= 320,11 g/mol

Azido-benzylsulfanyloxazoline **110** (0.102 g, 0.258 mmol) was dissolved in 3 mL of DCM at room temperature. The $NaHCO_3$ (0.065 g, 0.774 mmol, 3 eq.) was added. The reaction mixture was placed in an ice bath and the *m*-CPBA (0.173 g, 0.774 mmol, 3 eq.) was added and allowed to react for 20 minutes at 0 °C. The reaction mixture was placed at room temperature and allowed to react for 12 hours at room temperature. The solution was neutralized with $Na_2S_2O_5$ and

evaporated under reduced pressure. The residue was dissolved in methanol, filtered. The resulting filtrate was removed under vacuum. The crude was purified by silica gel column chromatography using a mixture of EA/ PE (50:50) as eluent.

Yield: 88%; **Rf**= 0.78 (EA/PE: 70/30); **M.p=** 107-110°C; $[\alpha]_D^{20}$(1.3, MeOH)= +1.5

M.S (IS): m/z= 321.0 $[M + H]^+$, 641.1 $[2M + H]^+$, 658.2 $[2M + NH_4]^+$.

IR (cm^{-1}): 1073 (CN), 1742 (C=O), 2104 (N_3), 3240 (NH + OH).

^1H NMR (400 MHz, CD_3OD) δ = 3.47-3.57 (m, 2H, CH_2-6), 3.70 (q, 2H, J = 10.3 Hz, J = 31.6 Hz, CH_2-1), 4.10-4.14 (m, 1H, CH-5), 4.21 (d, 1H, J= 2.9 H, CH-4), 4.60 (q, 2H, J= 11.9 Hz, J= 15.0 Hz, CH_2 of benzyl), 4.70 (s, 1H, CH-3), 7.26-7.39 (m, 5H, CH of benzyl).

^{13}C NMR (100 MHz, CD_3OD) δ= 50.4 (CH_2-6), 71.2 (CH-1), 74.6 (CH_2 of benzyl), 75.0 (CH-4), 80.4 (CH-5), 87.7 (CH-3), 97.5 (Cq-2), 128.9 (CH of benzyl), 128.9 (CH of benzyl), 129.5 (CH of benzyl), 139.0 (Cq of benzyl), 159.7 (C=O).

1-*O*-benzyl-L-sorbose **(112)**

$C_{13}H_{18}O_6$
M.W= 270,11 g/mol

1-*O*-benzyl-2,3;4,6-di-*O*-isopropylidene-α-L-sorbofuranose (1.000 g, 3.224 mmol) was dissolved in 10 mL of dioxane at room temperature. The HCl 3M (5 mL, 15.000 mmol, 4.7 eq.) was added and allowed to react for 3 hours at 66°C. The residue was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using EA/MeOH (98/2) as eluent.

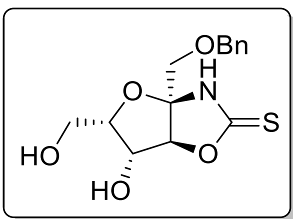
Yield: 91%; **Rf**= 0.18 (EA/PE: 95/5); **M.p=** 116 °C-120 °C; $[\alpha]_D^{20}$(0.4, MeOH)= -5.0

IR (cm^{-1}): 3346 (OH).

^1H NMR (400 MHz, $(CD_3)_2S=O$) δ = 3.18-3.24 (m, 2H, 1H of CH-4 and 1H of CH-5), 3.33-3.48 (m, 5H, 1H of CH-3, 2H of CH_2-6 and 2H of CH_2-1), 4.47 (dd, 2H, J= 6.6 Hz, J= 12.6 Hz, CH_2 of Bn), 4.63 (d, 1H, J= 4.8 Hz, OH), 4.78 (d, 1H, J= 5.0 Hz, OH), 5.46 (s, 1H, OH), 7.22-7.30 (m, 5H, CH of Bn).

^{13}C NMR (100 MHz, $(CD_3)_2S{=}O$) δ= 62.2 (CH_2-6), 70.2 (CH-4), 70.8 (CH-5), 72.1 (CH_2-1), 72.5 (CH_2 of Bn), 74.2 (CH-3), 97.6 (Cq of C-2), 127.3 (CH of Bn), 127.4 (CH of Bn), 128.2 (CH of Bn), 138 (Cq of Bn).

(1-O-benzyl-α-L-sorbofuranoso)[2,3-d]-1,3-oxazolidine-2-thione **(113)**



$C_{14}H_{17}NO_5S$

M.W= 311,08 g/mol

Procedure 1:

L-sorbose **112** (1.870 g, 6.923 mmol) was dissolved in 14.4 mL of H_2O ar room temperature. HCl (12N, 3.4 mL) and KSCN (1.547 g, 15.923 mmol, 2.3 eq.) were added and allowed to react for 24 hours at 56°C. The residue was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/H (60:40) as eluent. **Yield:** 92%

Procedure 2:

(1-O-benzyl-4,6-isopropylidene-α-L-sorbofuranoso)[2,3-d]-1,3-oxazolidine-2-thione (4.467 g, 12,723 mmol) was dissolved in 37 mL of dioxane at room temperature. The HCl 3M (17 mL, 50.890 mmol, 4 eq.) was added and wallowed to react for 3 hours at 66ºC. The residue was evaporated in the evaporator. The residue was purified by silica gel column chromatography using EA/H (50/50) as eluent. **Yield:** 58%

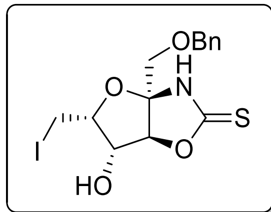
Rf= 0.60 (EA/PE: 90/10); $[\alpha]_D^{20}$(0.383, MeOH)= 2.61

IR (cm^{-1}): 1100 (C=S), 3332 (NH+OH).

^{1}H NMR (400 MHz, $(CD_3)_2S{=}O$) δ = 3.50 (d, 1H, J= 10.9 Hz, CH_2-6), 3.54 (d, 1H, J= 8.3 Hz, CH_2-1), 3.63 (d, 1H, J= 2.1 Hz, CH_2-6'), 3.67 (d, 1H, J= 10.3 Hz, CH_2-1'), 3.72-3.76 (m, 1H, CH-5), 4.16 (s, 1H, CH-4), 4.56 (q, 2H, J= 12.0 Hz, J= 15.8 Hz, CH_2 of Bn), 4.73 (ls, 1H, OH), 4.79 (s, 1H, CH-3), 5.50 (ls, 1H, OH), 7.26-7.37 (m, 5H, CH of Bn),10.83 (ls, 1H, NH).

^{13}C NMR (100 MHz, $(CD_3)_2S{=}O$) δ= 58.8 (CH_2-6), 69.5 (CH_2-1), 73.0 (CH-4), 73.2 (CH_2 of Bn), 82.0 (CH-5), 90.6 (CH-3), 99.4 (Cq of C-2), 128.1 (CH of Bn), 128.8 (CH of Bn), 138.2 (Cq of Bn), 188.4 (C=S).

(2,3,6-trideoxy-6-iodo-α-L-sorbofuranoso)[2,3-d]-1,3-oxazolidine-2-thione **(114)**



$C_{14}H_{16}INO_4S$

M.W= 420,98 g/mol

Oxazolidinethione **113** (2.030 g, 6.526 mmol) was dissolved in 36 mL of THF at room temperature. The PH_3P (3.419 g, 13.051 mmol, 2 eq.) and imidazole (0.889 g, 13.051 mmol, 2 eq.) were added, the stirred mixture was kept for 15 minutes at 0°C The iodine (3.315 g, 13.051 mmol, 2 eq.) was slowly added and allowed to react for 12 hours at room temperature. The solvent was evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/H (30:70) as eluent.

Yield: 46%; **Rf=** 0.77 (EA/H: 60/40); $[\alpha]_D^{20}$(0.58, MeOH)= -13.9

IR (cm^{-1}): 606 (IC), 1091 (C=S), 3229 (NH+OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.23-3.30 (m, 2H, CH_2-6), 3.64-3.79 (m, 2H, CH_2-1), 4.08-4.14 (m, 1H, CH-5), 4.26-4.30 (m, 1H, , CH-4), 4.46 (d, 1H, J= 9.0 Hz, OH), 4.56-4.66 (m, 2H, CH_2 of Bn), 5.00 (s, 1H, CH-3), 7.29- 7.40 (m, 5H, CH of Bn), 8.35 (d, 1H, J= 5.7 Hz, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -2.7 (CH_2-6), 69.3 (CH_2-1), 73.5 (CH_2 of Bn), 74.2 (CH-4), 82.1 (CH-5), 91.6 (CH-3), 99.2 (Cq of C-2), 128.1 (CH of Bn), 128.7 (CH of Bn), 128.9 (CH of Bn), 136.2 (Cq of Bn), 190.0 (C=S).

(4-*O*-*tert*butyldimethylsilyl-2,3,6-trideoxy-6-iodo-α-L-sorbofuranoso)[2,3-d]-1,3-oxazolidine-2-thione **(115)**

$C_{21}H_{22}INO_4S$

M.W= 511,03 g/mol

Iodine-oxazolidinethione **114** (0.783 g, 1.864 mmol)) was dissolved in 10 mL of DMF at room temperature. The TBDMSCl (0.337 g, 2.237 mmol, 1.2 eq.) and imidazole (0.317 g, 4.660 mmol, 2.5 eq.) was added and allowed to react for 12 hours at room temperature. The residue was diluted with ethyl acetate. The organic phase was washed three times with water, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/H (5:95) as eluent.

Yield: 4%; **Rf**= 0.66 (EA/H: 20/80); $[\alpha]_D^{20}$(0.3, MeOH)= -3.3

IR (cm^{-1}): 604 (IC), 1064 (C=S), 1254 ($SiCH_3$), 3258 (NH).

^1H NMR (400 MHz, $CDCl_3$) δ = -0.03 (s, 6H, $Si(CH_3)_2$), 0.68 (s, 9H, $SiC(CH_3)_3$), 2.95-3.05 (m, 2H, CH_2-6), 3.45 (q, 2H, J= 10.4 Hz, J= 47.0 Hz, CH_2-1), 4.09 (dtd, 1H, J= 2.5 Hz, J= 5.5 Hz, J= 8.2 Hz, CH-5), 4.29 (d, 1H, J= 2.3 Hz, CH-4), 4.39 (q, 2H, J= 12.1 Hz, J= 32.4 Hz, CH_2 of Bn), 4.65 (s, 1H, CH-3), 7.06– 7.20 (m, 5 H, CH of Bn), 7.93 (ls, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -4.7 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), -2.7 (CH_2-6), 18.0 (Cq of $Si\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 69.4 (CH_2-1), 73.6 (CH_2 of Bn), 74.2 (CH-4), 82.2 (CH-5), 90.9 (CH-3), 99.6 (Cq of C-2), 128.1 (CH of Bn), 128.3 (CH of Bn) , 128.7 (CH of Bn), 136.8 (Cq of Bn), 188.8 (C=S).

2-Benzylsulfanyl-3,4-dihydro-(1-*O*-benzyl-2,3,6-trideoxy-6-iodo-α-L-sorbofuranoso)[2,3-d]-1,3-oxazole **(116)**

$C_{21}H_{22}INO_4S$
M.W= 511,03 g/mol

Iodinated oxazolidinethione **114** (0.712 g, 1.691 mmol) was dissolved in 17.3 mL of anhydrous THF at room temperature. The reaction mixture was placed in an ice-salt bath. Et_3N (0.944 mL, 6.765 mmol, 4 eq.) and BnBr (0.402 mL, 3.383 mmol, 2 eq.) were added and allowed to react for 12 hours at room temperature. The reaction mixture was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/H (10:90) as eluent.

Yield: 43%; **Rf**= 0.73 (EA/H: 50/50); $[\alpha]_D^{20}$(0.31, $CHCl_3$)=+9.7

IR (cm^{-1}): 610 (IC), 1582 (N=C), 3386 (OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.24-3.31 (m, 3H, 2H of CH_2-6 and 1H of OH), 3. 54 (d, 1H, J= 10.0 Hz, CH_2-1), 3.90-3.94 (m, 1H, CH-5), 3.96 (d, 1H, J= 10.0 Hz, CH_2-1'), 4.25 (s, 2H, CH_2 of Bn), 3.65 (dd, 1H, J= 1.9 Hz, J= 11.8 Hz, CH-4), 4.62 (q, 2H, J = 11.7 Hz, J= 51.1 Hz, CH_2 of Bn), 4.72 (s, 1H, CH-3), 7.21– 7.44 (m, 10 H, CH of 2×Bn).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -2.0 (CH_2-6), 36.6 (CH_2 of Bn), 71.4 (CH_2-1), 73.7 (CH-4), 74.1 (CH_2 of Bn), 81.2 (CH-5), 89.2 (CH-3), 109.5 (Cq of C-2), 128.0 (CH of Bn), 128.1 (CH of Bn), 128.4 (CH of Bn), 128.8 (CH of Bn), 129.1 (CH of Bn) , 136.0 (Cq of Bn), 136.7 (Cq of Bn), 170.7 (C=N).

2-Benzylsulfanyl-3,4-dihydro-(1-*O*-benzyl-4-*O*-*tert*butyldimethylsilyl-2,3,6-trideoxy-6-iodo-α-L-sorbofuranoso)[2,3-d]-1,3-oxazole **(117)**

$C_{27}H_{36}INO_4SSi$
M.W= 625,12 g/mol

The iodined benzylesulfanyloxazole **116** (0.354 g, 0.693 mmol) was dissolved in 8 mL of DMF at room temperature. Thne TBDMSCl (0.125 g, 0.831 mmol, 1.2 eq.) and imidazole (0.118 g, 1.732 mmol, 2.5 eq.) were added and allowed to react for 12 hours at room temperature. The reaction was diluted with ethyl acetate. Then the organic phase was washed three times with water, dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by silica gel column chromatography using a mixture of EA/H (20:80) as eluent.

Yield: 6%; **Rf**= 0.76 (EA/H: 50/50); $[\alpha]_D^{20}$(0.34, MeOH)= -11.9

IR (cm^{-1}): 605 (IC), 1253 ($SiCH_3$), 1596 (N=C).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.77 (s, 9H, $SiC(CH_3)_3$), 3.32 (dd, 1H, J= 6.5 Hz, J= 12.3 Hz, CH_2-6), 3.49 (dd, J = 6.5 Hz, J= 12.2 Hz, CH_2-6'), 3.59 (d, 1H, J= 10.4 Hz, CH_2-1), 3.65 (td, 1H, J= 2.9 Hz, J= 6.5 Hz, CH-5), 3.73 (d, 1H, J= 10.4 Hz, CH_2-1'), 4.06 (d, 1H, J= 2.8 Hz, CH-4), 4.14-4.27 (m, 2H, J = 13.2 Hz, J= 28.8 Hz, CH_2 of Bn), 4.44-4.55 (m, 3H, 1H of CH-3 and 2H of CH_2 of Bn), 7.15– 7.29 (m, 10 H, CH of 2×Bn).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -5.2 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$), 1.2 (CH_2-6), 18.1 (Cq of $Si\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 36.7 (CH_2 of Bn), 71.5 (CH_2-1), 73.8 (CH_2 of Bn), 75.3 (CH-4), 78.6 (CH-5), 88.8 (CH-3), 109.3 (Cq of C-2), 127.8 (CH of Bn),127.8 (CH of Bn), 127.9 (CH of Bn), 128.5 (CH of Bn), 128.8 (CH of Bn), 129.2 (CH of Bn), 136.4 (Cq of Bn), 138.1 (Cq of Bn), 169.0 (N=C).

2-Benzylsulfanyl-3,4-dihydro-(6-azido-1-*O*-benzyl-4-*O*-*tert*butyldimethylsilyl-2,3,6-trideoxy-α-L-sorbofuranoso)[2,3-d]-1,3-oxazole **(118)**

$C_{27}H_{36}N_4O_4SSi$

M.W= 540,22 g/mol

The azido-benzylsulfanyloxazole **110** (0.188 g, 0.441 mmol) was dissolved in 8 mL of DMF at room temperature. TBDMSCl (0.166 g, 1.103 mmol, 2.5 eq.) and imidazole (0.188 g, 2.757 mmol, 5 eq.) were added and allowed to react for 12 hours at room temperature. The reaction was diluted with ethyl acetate. The organic phase was washed three times with water, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/H (40:60) as eluent.

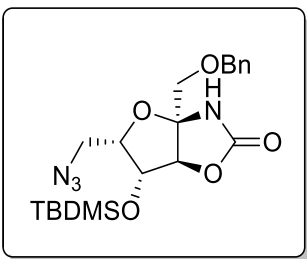
Yield: 76%; **Rf=** 0.85 (EA/H: 40/60); $[\alpha]_D^{20}$(0.9, MeOH)= -7.8

IR (cm^{-1}): 1253 ($SiCH_3$), 1595 (N=C), 2099 (N_3).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $Si(CH_3)_2$), 0.77 (s, 9H, $SiC(CH_3)_3$), 3.32 (dd, 1H, J= 6.5 Hz, J= 12.3 Hz, CH_2-6), 3.49 (dd, J = 6.5 Hz, J= 12.2 Hz, CH_2-6'), 3.59 (d, 1H, J= 10.4 Hz, CH_2-1), 3.65 (dd, 1H, J= 3.2 Hz, J= 6.5 Hz, CH-5), 3.73 (d, 1H, J= 10.4 Hz, CH_2-1'), 4.06 (d, 1H, J= 2.8 Hz, CH-4), 4.21 (q, 2H, J = 13.2 Hz, J= 28.8 Hz, CH_2 of Bn), 4.41–4.59 (m, 3H, 1H of CH-3 and 2H of CH_2 of Bn), 7.15– 7.29 (m, 10 H, CH of 2×Bn).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -5.2 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$), 18.1 (Cq of $Si\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 36.7 (CH_2 of Bn), 49.1 (CH_2-6), 71.5 (CH_2-1), 73.8 (CH_2 of Bn), 75.3 (CH-4), 78.6 (CH-5), 88.8 (CH-3), 109.3 (Cq of C-2), 127.8 (CH of Bn), 127.8 (CH of Bn), 127.9 (CH of Bn), 128.5 (CH of Bn), 128.8(CH of Bn) , 129.2 (CH of Bn), 136.4 (Cq of Bn), 138.1(Cq of Bn), 169.0 (C=N).

(6-azido-1-*O*-benzyl-2,3,6-trideoxy-3-*O*-*tert*butyldimethylsilyl-α-L-sorbofuranoso)[2,3-d]-1,3-oxazolidin-2-one **(119)**



$C_{20}H_{30}N_4O_5Si$

M.W= 434,20 g/mol

Azido-benzylsulfanyloxazolidinone **118** (0.343 g, 0.635 mmol) was dissolved in 15 mL of DCM at room temperature. $NaHCO_3$ (0.160 g, 1.905 mmol, 3 eq.) was added. The reaction mixture was cooled in an ice bath and *m*-CPBA (0.427 g, 1.905 mmol, 3 eq.) was added and allowed to react for 20 minutes at 0 °C. The reaction mixture was placed at room temperature and allowed to react for 12 hours at room temperature. The solution was neutralized with $Na_2S_2O_5$ and evaporated under reduced pressure. The residue was dissolved in methanol, filtered and the solvent removed under vacuum. The residue was purified by silica gel column chromatography using a mixture of EA/ H (20:80) as eluent.

Yield: 70%; **Rf=** 0.68 (EA/H: 50/50); $[\alpha]_D^{20}$(0.26, MeOH)= -3.9

IR (cm^{-1}): 1252 ($SiCH_3$), 1755 (C=O), 2096 (N_3), 3234 (NH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.00 (s, 6H, $Si(CH_3)_2$), 0.76 (s, 9H, $SiC(CH_3)_3$), 3.28 (dd, 1H, J= 5.6 Hz, J= 12.5 Hz, CH_2-6), 3.45 (dd, J = 4.8 Hz, J= 7.9 Hz, CH_2-6'), 3.48 (d, 1H, J= 5.3 Hz, CH_2-1), 3.59 (d, 1H, J= 10.3 Hz, CH_2-1'), 4.05 (ddd, 1H, J= 2.7 Hz, J= 5.6 Hz, J= 7.1 Hz, CH-5), 4.15 (d, 1H, J= 2.7 Hz, CH-4), 4.40–4.55 (m, 3H, 1H of CH-3 and 2H of CH_2 of Bn), 6.27 (s, 1H, NH), 7.15– 7.27 (m, 5 H, CH of Bn).

^{13}C NMR (100 MHz, $CDCl_3$) δ=-5.2 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$), 18.0 (Cq of Si$\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 49.2 (CH_2-6), 70.1 (CH_2-1), 73.7 (CH_2 of Bn), 74.8 (CH-4), 79.3 (CH-5), 86.2 (CH-3), 96.0 (Cq of C-2), 128.0 (CH of Bn), 128.2 (CH of Bn) , 128.7 (CH of Bn), 137.2 (Cq of Bn), 157.0 (C=O).

5-Amino-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam **(158)**

$C_8H_{13}NO_4$

M.W= 187,19 g/mol

Azido-lactone **41** (0.350 g, 1.643 mmol) was dissolved in 28 mL of dry ethyl acetate at room temperature. Pd/C (0.436 g, 4.107 mmol, 2 eq.) and HCO_2NH_4 (0.311 g, 4.928 mmol, 3 eq.) were slowly added and allowed to react for 2 hours under reflux. After cooling to room temperature the residue was filtered on celite and evaporated to dryness. The residue was purified by silica gel column chromatography using a mixture of EA/H (90:10) as eluent.

CAS [18908-34-4]; Yield: 62%; **Rf**= 0.57 ($CHCl_3$/MeOH: 80/20); **M.p=** 136-140°C.

M.S (IS): m/z= 188.0 $[M + H]^+$, 205.0 $[M + NH_4]^+$, 210.0 $[M + Na]^+$, 375.0 $[2M + H]^+$, 392.5 $[2M + NH_4]^+$, 397.0 $[2M + Na]^+$, 413.5 $[2M + K]^+$.

^{1}H NMR (400 MHz, $(CD_3)_2S=O$) δ = 1.37 (s, 3H,$C(CH_3)_2$), 1.40 (s, 3H,$C(CH_3)_2$), 2.98-3.03 (m, 1H, CH_2-5), 3.25 (t, 1H, J= 10.84 Hz, CH_2-5'), 3.93-3.96 (m, 1H, CH-4), 4.34 (d, 1H, J= 6.4Hz, CH-2), 4.43-4.45 (m, 1H, CH-3), 5.25 (d, 1H, J= 5.12 Hz, OH), 7.69 (s, 1H, NH).

^{13}C NMR (100 MHz, $(CD_3)_2S=O$) δ = 25.7 ($C(\underline{C}H_3)_2$), 27.1 ($C(\underline{C}H_3)_2$), 41.8 (CH_2-5), 65.0 (CH-4), 74.1 (CH-2), 76.2 (CH-3), 109.6 ($\underline{C}(CH_3)_2$), 168.4 (C=O).

2-Benzylsulfanyl-4,5-dihydro-(5-amino-1,2,5-trideoxy-α-D-arabinofuranoso)[1,2-d]-1,3-oxazole **(163)**

$C_{19}H_{30}N_2O_3SSi$

M.W= 394,17 g/mol

Azido-sugar **87** (0.204 g, 0.486 mmol) was dissolved in 6 mL of THF/H_2O (5/1) at room temperature. Ph_3P (0.127 g, 0.486 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was evaporated under reduce pressure. The residue was purified by silica gel column chromatography using a mixture of EA/PE (50:50) as eluent.

Yield: 86%; **Rf**= 0.27 (EA/PE: 90/10); $[\alpha]_D^{20}$(0.75, $CHCl_3$)= +61.1

M.S (IS): m/z= 395.0 $[M + H]^+$, 789.5 $[2M + H]^+$.

IR (cm^{-1}): 1250 ($SiCH_3$), 1591 (N=C), 3386 (NH).

^1H NMR (250 MHz, CD_3OD) δ **=** 0.22 (s, 6H, $Si(CH_3)_2$), 0.99 (s, 9H, $SiC(CH_3)_3$), 2.78 (dd, 1H, J= 7.1 Hz, J= 13.4 Hz, CH_2-5), 3.02 (dd, 1H, J= 3.0 Hz, J= 13.5 Hz, CH_2-5'), 3.41-3.49 (m, 1H, CH-4), 4.06 (dd, 1H, J= 5.5 Hz, J= 9.0 Hz, CH-3), 4.35 (s, 2H, CH_2 of benzyl), 4.94 (t, 1H, J= 5.4 Hz, CH-2), 6.00 (d, 1H, J= 5.4 Hz, CH-1), 7.32-7.41 (m, 3H, CH of benzyl), 7.44-7.48 (m, 2H, CH of benzyl).

^{13}C NMR (62.5 MHz, DC_3DO) δ= -4.9 ($Si(CH_3)_2$), -4.4 ($Si(CH_3)_2$), 18.9 ($Si\underline{C}(CH_3)_3$), 26.2 ($SiC(\underline{C}H_3)_3$), 36.7 (CH_2 of benzyl), 43.3 (CH_2-5), 75.4 (CH-3), 80.2 (CH-4), 84.3 (CH-2), 100.3 (CH-1), 128.8 (CH of benzyl), 129.7(CH of benzyl), 130.0 (CH of benzyl), 137.9 (Cq of benzyl), 172.8 (N=C).

2-Benzylsulfanyl-4,5-dihydro-(5-benzyloxycarbamido-1,2,5-trideoxy-α-D-arabinofuranoso)[1,2-d]-1,3-oxazole **(164)**

$C_{27}H_{36}N_2O_5SSi$

M.W= 528,21 g/mol

Amino-sugar **163** (0.435 g, 1.104 mmol) was dissolved in 20 mL of DCM at room temperature. The Et_3N (0.616 mL, 4.416 mmol, 4 eq.) was added. The reaction mixture was placed in an ice bath. Then benzyl chloroformate (0.332 mL, 2.207 mmol, 2 eq.) and DMAP (0.067 g, 0.502 mmol, 0.5 eq.) were added and allowed to react for 1 hours at room temperature. The solution was diluted with dichloromethane. The organic phase was washed twice with NaOH 1M and once with a saturated NaCl solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/PE (90:10) as eluent.

Yield: 98%; **Rf**= 0.87 (EA/PE: 90/10); $[\alpha]_D^{20}$(0.767, $CHCl_3$)= 50.85

M.S (IS): m/z= 529.5 $[M + H]^+$, 551.0 $[M + Na]^+$, 1057.0 $[2M + H]^+$.

IR (cm^{-1}): 1253 ($SiCH_3$), 1589 (C=N), 1720 (C=O), 3366 (NH).

^1H NMR (250 MHz, CD_3OD) δ = 0.17 (s, 6H, $Si(CH_3)_2$), 0.96 (s, 9H, $SiC(CH_3)_3$), 3.34 (dt, 1H, 1H, J= 1.6 Hz, J= 3.3 Hz, CH_2-5), 3.38-3.54 (m, 2H, 1H of CH_2-5' and 1H of CH-4), 4.02 (dd, 1H, J= 5.5 Hz, J= 8.0 Hz, CH-3), 4.31 (s, 2H, CH_2 of benzyl), 4.91 (d, 1H, J= 5.5 Hz, CH-2), 5.10 (q, 2H, J= 12.6 Hz, J= 15.9 Hz, CH_2 of Cbz), 5.95 (d, 1H, J= 5.4 Hz, CH-1), 7.27-7.44 (m, 10H, 5H of benzyl of Bn and 5H of benzyl of Cbz).

^{13}C NMR (62.5 MHz, CD_3OD) δ= -4.9 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), 18.9 ($Si\underline{C}(CH_3)_3$), 26.2 ($SiC(\underline{C}H_3)_3$), 36.7 (CH_2 of Bn), 42.1 (CH_2-5), 67.5 (CH_2 of Cbz), 74.9 (CH-3), 78.6 (CH-4), 84.2 (CH-2), 100.3 (CH-1), 128.8 (CH of benzyl), 128.9 (CH of benzyl), 129.0(CH of benzyl), 129.5(CH of benzyl), 129.7 (CH of benzyl), 130.0 (CH of benzyl), 137.9 (Cq of benzyl), 138.3 (Cq of benzyl), 158.8 (C=O of Cbz), 172.8 (N=C)..

(5-amino-1,2,5-trideoxy-α-D-ribofuranoso)[1,2-d]-1,3-oxazolidine-2-thione **(166)**

$C_6H_{10}N_2O_3S$

M.W= 190,04 g/mol

The azido-sugar **82** (0.150 g, 0.694 mmol) was dissolved in 8 mL of THF/H_2O (3/1) at room temperature. Ph_3P (0.182 g, 0.694 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/PE (50:50) as eluent.

Yield: 7%; **Rf**= (EA/PE: 80/20); $[\alpha]_D^{20}$(0.13, MeOH)= +30.8

M.S (IS): m/z= .191.0 $[M + H]^+$, 213.0 $[M + Na]^+$.

IR (cm^{-1}): 1118 (C=S), 3371 (NH + OH).

^1H NMR (250 MHz, CD_3OD) δ = 2.83 (dd, 1H, J = 6.7 H, J= 13.6 Hz, CH_2-5), 3.02 (dd, 1H, J= 3.2 Hz, J= 13.6 Hz , CH_2-5'), 3.66 (dtd, 1H, J = 3.2 Hz,J= 6.7 Hz, J= 9.7 Hz, CH-4), 3.96 (dd, 1H, J= 5.3 Hz, J= 9.5 Hz, CH-3), 5.15 (t, 1H, J= 5.3 Hz, CH-2), 5.76 (d, 1H, J= 5.3 Hz, CH-1).

^{13}C NMR (62.5 MHz, CD_3OD) δ= 42.9 (CH_2-5), 74.3 (CH-3), 79.6 (CH-4), 86.5 (CH-2), 89.5 (CH-1), 192.1(C=S)

(5-amino-3-*O-tert*butyldimethylsilyl-1,2,5-trideoxy-α-D-ribofuranoso)[1,2-d]-1,3-oxazolidine-2-one **(169)**

$C_{12}H_{24}N_2O_4Si$

M.W= 288,15 g/mol

Procedure 1:

The azido sugar **88** (0.3 g, 0.955 mmol) was dissolved in 12 mL of THF/H_2O (5/1) at room temperature. Ph_3P (0.250 g, 0.955 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography using a mixture of PE/AE (50:50) as eluent. **Yield**: 32%

Procedure 2:

The azido sugar **88** (0.270 g, 0.860 mmol) was dissolved in 10 mL of EtOH at room temperature. Pd/C (0.183 g, 1.720 mmol, 2 eq.) and the HCO_2NH_4 (0.163 g, 2.580 mmol, 3 eq.) were added and allowed to react for 12 hours at 44°C. The residue was filtered sob celite and evaporated under reduce pressure. The residue was purified by silica gel column chromatography using AE as eluent. **Yield**: 25%

Rf= 0.11 (EA/MeOH: 85/15); **M.p=** 96-99 °C; $[\alpha]_D^{20}$(0.6, MeOH)= +27.7

M.S (IS): m/z= 289.0 $[M + H]^+$, 577.5 $[2M + H]^+$.

IR (cm^{-1}): 1086 (CN), 1251 ($SiCH_3$), 1748 (C=O), 3275 (NH).

^{1}H NMR (250 MHz, $CDCl_3$) δ = 0.09 (s, 6H, $Si(CH_3)_2$), 0.80 (s, 9H, $SiC(CH_3)_3$), 2.81 (dd, 1H, J= 5.2 Hz, J= 9.3 Hz, CH_2-5), 3.03-3.09 (m, 1H, J CH_2-5'), 3.74-3.80 (m, 1H, CH-4), 3.89-3.92 (m, 1H, CH-3), 4.73 (t, 1H, J= 5.2Hz, CH-2), 5.59 (d, 1H, J= 5.3 Hz, CH-1).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ= -4.9 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$), 18.1 ($Si\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 44.1 (CH_2-5), 73.1 (CH-3), 79.0 (CH-4), 79.1 (CH-2), 85.1 (CH-1), 158.9 (C=O).

(5-Amino-3-*O*-tertbutyldimethylsily-5-deoxy-α-D-ribopyranoso)[1,2-d]-1,3-oxazolidine-2-one **(170)**

$C_{12}H_{24}N_2O_4Si$
M.W= 288,15 g/mol

Procedure 1:

The azido-sugar **47** (0.3 g, 0.955 mmol) was dissolved in 12 mL of THF/H_2O (5/1) at room temperature. Ph_3P (0.250 g, 0.955 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of PE/AE (50:50) as eluent. **Yield**: 36%

Procedure 2:

Azido-sugar **47** (0.270 g, 0.860 mmol) was dissolved in 10 mL of EtOH at room temperature. The Pd/C (0.183 g, 1.720 mmol, 2 eq.) and the HCO_2NH_4 (0.163 g, 2.580 mmol, 3 eq.) were added and allowed to react for 12 hours at 44°C. The residue was filtered sob celite and evoparated in the evaporator. The residue was purified by silica gel column chromatography using AE as eluent. **Yield**: 30%

Rf= 0.17 (EA/MeOH: 85/15); **M.p=** 98-102 °C; $[\alpha]_D^{20}$(0.36, MeOH)= +30.6

HRMS (ESI+) calculated for $C_{12}H_{24}N_2O_4Si$ $[M+H]^+$: 289.1578 Found: 289.1580

IR (cm^{-1}): 1244 ($SiCH_3$), 1749 (C=O), 3272 (NH + OH).

^1H NMR (250 MHz, $CDCl_3$) δ = 0.12 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 2.83 (dd, 1H,J= 4.3 Hz, J= 14.0 Hz, CH_2-5), 3.07 (dd, 1H, J= 4.8 Hz, J= 14.0 Hz,CH_2-5'), 3.83 (dtd, 1H, J= 1.1 Hz, J= 4.3 Hz, J= 5.1 Hz, CH-4), 3.87-3.89 (t, 1H,J= 4.2 Hz, CH-3), 4.42-4.44 (m, 1H, CH-2), 4.70 (d, 1H, J= 5.9 Hz, CH-1).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ= -4.7 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$), 18.3 ($Si\underline{C}(CH_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 44.2 (CH_2-5), 66.0 (CH-1), 66.6 (CH-4), 68.9 (CH-3), 76.4 (CH-2), 159.3 (C=O).

(5-Amino-4-*O*-tertbutyldimethylsily-5-deoxy-α-D-ribopyranoso)[1,2-d]-1,3-oxazolidine-2-one **(171)**

$C_{12}H_{24}N_2O_4Si$

M.W= 288,15 g/mol

Procedure 1:

Azido-sugar **88** (0.300 g, 0.955 mmol) was dissolved in 12 mL of THF/H_2O (5/1) at room temperature. The Ph_3P (0.250 g, 0.955 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was evoparated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/PE (50:50) as eluent. **Yield**: 15%

Procedure 2:

Azido-sugar **88** (0.270 g, 0.860 mmol) was dissolved in 10 mL of EtOH at room temperature. The Pd/C (0.183 g, 1.720 mmol, 2 eq.) and the HCO_2NH_4 (0.163 g, 2.580 mmol, 3 eq.) were added and allowed to react for 12 hours at 44\°C. The residue was filtered sob celite and evoparated in the evaporator. The residue was purified by silica gel column chromatography using AE as eluent. **Yield**: 14%

Rf= 0.31 (EA/MeOH: 85/15); **M.p=** 134-137; $[\alpha]_D^{20}$(0.36, MeOH)= +33.1

HRMS (ESI+) calculated for $C_{12}H_{24}N_2O_4Si$ $[M+H]^+$: 289.1578 Found: 289.1580

IR (cm^{-1}): 1248 ($SiCH_3$), 1723 (C=O), 3290 (NH + OH).

^1H NMR (250 MHz, $CDCl_3$) δ = 0.09 (s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $SiC(CH_3)_3$), 2.83 (dd, 1H, J= 5.1 Hz, J= 13.7 Hz, CH_2-5), 3.05-3.09 (m, 1H, J= 5.5 Hz, J= 13.7 Hz, CH_2-5’), 3.79-3.84 (m, 1H, CH-3), 3.87-3.89 (q, 1H, J= 4.9 Hz, J= 9.7 Hz, CH-4), 4.42-4.44 (m, 1H, CH-2), 4.70 (d, 1H, J= 6.6 Hz, CH-1), 6.55 (ls, 1H, NH or OH).

^{13}C NMR (250 MHz, $CDCl_3$) δ= δ= -4.8 ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), 18.1 ($Si\underline{C}(CH_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 44.7 (CH_2-5), 65.7 (CH-1), 67.0 (CH-4), 67.3 (CH-3), 76.1 (CH-2), 158.9 (C=O).

N-acetyl (5-acetamido-3-*O*-tertbutyldimethylsilyl-1,2,5-trideoxy-α-D-ribofuranoso)[1,2-d]-1,3-oxazolidine-2-one **(172)**

$C_{16}H_{28}N_2O_6Si$
M.W= 372,17 g/mol

A crude mixture of **169** and **171** (0.115 g, 0.399 mmol) was dissolved in 6 mL of pyridine at room temperature. The reaction mixture was placed in an ice bath. The Ac_2O (0.380 mL, 3.993 mmol, 10 eq.) was added and allowed to react for 2 hours at room temperature. The solution was diluted with water. Extracted three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and evaporated under vacuum. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (50:50) as eluent.

Yield: 3%; **Rf**= 0.6 (EA/MeOH: 90/10); $[\alpha]_D^{20}$(0.13, $CHCl_3$)= +30.1

M.S (IS): m/z= 390.5 $[M + NH_4]^+$, 395.0 $[M + Na]^+$.

IR (cm^{-1}): 1097 (CN), 1252 ($SiCH_3$), 1755 (C=O), 3292 (NH).

^{1}H NMR (250MHz, $CDCl_3$) δ = 0.15 (s, 6H, $Si(CH_3)_2$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.98 (s, 3H, Ac), 2.56 (s, 3H, Ac), 3.55-3.59 (m, 2H, CH_2-5), 3.79-3.86 (m, 1H, CH-4), 4.93 (dd, 1H, J= 5.1 Hz, J= 7.1 Hz, CH-3), 4.73 (t, 1H, J= 5.4 Hz, CH-2), 5.73 (ls, 1H, NH), 6.16 (d, 1H, J= 5.4 Hz, CH-1).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ= -4.9 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$), 18.2 ($Si\underline{C}(CH_3)_3$), 23.4 (CH_3 of Ac), 23.9 (CH_3 of Ac), 25.7 ($SiC(\underline{C}H_3)_3$), 38.8 (CH_2-5), 73.0 (CH-3), 76.1 (CH-2), 78.3 (CH-4), 84.9 (CH-1), 152.7 (C=O), 170.2 (Cq of Ac), 170.3 (Cq of Ac).

(5-acetamido-3-*O*-tertbutyldimethylsilyl-1,2,5-trideoxy-α-D-ribofuranoso)[1,2-d]-1,3-oxazolidine-2-one **(173)**

$C_{14}H_{26}N_2O_5Si$
M.W= 330,16 g/mol

The mixture of **169** and **171** (0.115 g, 0.399 mmol) was dissolved in 6 mL of pyridine at room temperature. The reaction mixture was placed in an ice bath. The Ac_2O (0.380 mL, 3.993 mmol, 10 eq.) was added and allowed to react for 2 hours at room temperature. The solution was diluted with water. Extracted three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of EA/ PE (50:50) as eluent.

Yield: 17%; **Rf**= 0.54 (EA/MeOH: 90/10); **M.p=** 90-94 °C; $[\alpha]_D^{20}$(0.397, $CHCl_3$)= 50.4

M.S (IS): m/z= 331.5 $[M + H]^+$,348.0 $[M + NH_4]^+$, 661.5 $[2M + H]^+$, 683.0$[2M + Na]^+$.

IR (cm^{-1}): 1252 ($SiCH_3$), 1754 (C=O), 3290 (NH).

^1H NMR (250MHz, $CDCl_3$) δ = 0.13 (s, 6H, $Si(CH_3)_2$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.99 (s, 3H, Ac), 3.51-3.55 (m, 2H, CH_2-5), 3.83-3.85 (m, 2H, CH-3 and CH-4), 4.77-4.81 (m, 1H, CH-2), 5.63 (dd, 1H, J= 1.3 Hz, J= 5.4 Hz, CH-1), 6.05 (t, 1H, J= 5.4 Hz, NH of OZO), 6.74 (s, 1H, NH of sugar).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ= -4.9 ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$), 18.2 ($Si\underline{C}(CH_3)_3$), 23.7 (CH_3 of Ac), 25.8 ($SiC(\underline{C}H_3)_3$), 39.9 (CH_2-5), 73.9 (CH-3), 77.0 (CH-4), 79.0 (CH-2), 85.0 (CH-1), 158.4 (C=O), 170.5 (Cq of Ac).

N-acetyl (5-Acetamido-4-*O*-tertbutyldimethylsily-5-deoxy-α-D-ribopyranoso)[1,2-d]-1,3-oxazolidine-2-one **(174)**

$C_{16}H_{28}N_2O_6Si$
M.W= 372,17 g/mol

A mixture of **169** and **171** (0.115 g, 0.399 mmol) was dissolved in 6 mL of pyridine at room temperature. The reaction mixture was placed in an ice bath. The Ac_2O (0.380 mL, 3.993 mmol, 10 eq.) was added and allowed to react for 2 hours at room temperature. The solution was diluted with water. Extracted three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of PE/AE (50:50) as eluent.

Yield: 36%; **Rf**= 0.58 (EA/MeOH: 90/10); **M.p=** 199-206 °C; $[\alpha]_D^{20}$(0.58, $CHCl_3$)= -8.6

IR (cm^{-1}): 1071 (CN), 1237 ($SiCH_3$), 1746 (C=O), 3163 (NH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.08 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 2.09 (s, 3H, Ac), 2.14 (s, 3H, Ac), 3.59-3.68 (m, 2H, CH_2-5), 4.19 (q, 1H, J= 6.0 Hz, J= 12.1 Hz, CH-3), 4.62 (dd, 1H, J= 4.12 Hz, J= 8.2 Hz , CH-2), 4.77-4.82 (m, 1H, CH-4), 5.96-6.00 (m, 1H, CH-1), 6.91 (ls, 1H, NH).

^{13}C NMR (400 MHz, $CDCl_3$) δ= -5.0 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$), 18.2 ($Si\underline{C}(CH_3)_3$), 21.0 (CH_3 of Ac), 22.3 (CH_3 of Ac), 25.7 ($SiC(\underline{C}H_3)_3$), 40.1 (CH_2-5), 60.9 (CH-1), 66.8 (CH-3), 67.9 (CH-2), 76.3(CH-4), 157.5 (Cq of C=O), 170.2 (Cq of Ac), 172.7 (Cq of Ac).

(5-Amino-4-*O*-tertbutyldimethylsily-5-deoxy-α-D-ribopyranoso)[1,2-d]-1,3-oxazolidine-2-one **(175)**

$C_6H_{10}N_2O_4$

M.W= 174,06 g/mol

Procedure 1:

The azido-oxazolidinone **90** (0.188 g, 0.940 mmol) was dissolved in 12 mL of THF/H_2O (5/1) at room temperature. The polymer-bound Ph_3P (0.294 g, 0.940 mmol, 1 eq.) was added and allowed to react 12 hours at room temperature. The mixture was filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of AE/MeOH (98:2) as the eluent**. Yield**: 15%.

Procedure 2:

The iminosugars **170** and **171** (0.431 g, 1.497 mmol) were dissolved in 14 mL of THF/H_2O (6/1) at room temperature. The mixture was placed in an ice bath and then TFA (6 mL, 78.355 mmol, 52.3 eq.) was added and allowed to react for 12 hours at room temperature. The mixture was dissolved with water and evaporated in the evaporator. The crude residue was purified by silica gel column chromatography using a mixture of AE/MeOH (90:10) as eluent. **Yield**: 16%

Rf= 0.23 (EA/MeOH: 80/20); **M.p=** 90-93 ºC; $[\alpha]_D^{20}$(1.293 g/100 mL, MeOH)= 23.20

HRMS (ESI+) calculated for $C_6H_{10}N_2O_4$ [M+H]$^+$: 175.0713 Found: 175.0714

IR (cm^{-1}): 1082 (CN), 1716 (C=O), 3242 (NH + OH).

^{1}H NMR (250 MHz, CD_3OD) δ = 2.85 (dd, 1H, J= 5.0 Hz, J= 13.6 Hz, CH_2-5), 2.95 (dd, 1H, J= 6.2 Hz, J= 13.6 Hz, CH_2-5'), 3.81-3.85 (m, 1H,CH-4), 3.91 (t, 1H, J= 4.1 Hz, CH-3), 4.57 (dd, 1H, J= 4.3 Hz, J= 6.4 Hz, CH-2), 4.78 (d, 1H, J= 6.4 Hz, CH-1).

^{13}C NMR (62.5 MHz, CD_3OD) δ= 44.4 (CH_2-5), 66.8 (CH-1), 67.2 (CH-4), 68.6 (CH-3), 77.8 (CH-2), 161.6 (C=O).

(5-amino-1,2,5-trideoxy-α-D-xylofuranoso)[1,2-d]-1,3-oxazolidine-2-one **(176)**

$C_6H_{10}N_2O_4$
M.W= 174,06 g/mol

The azido-oxazolidinone **95** (0.406 g, 2.03 mmol) was dissolved in 24 mL of of THF/H_2O (5/1) at room temperature. Ph_3P (0.532 g, 2.03 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was evaporated in the evaporator. The residue was purified by silica gel column chromatography using AE as eluent.

Yield: 5%; **Rf=** 0.28 (EA/MeOH: 80/20); $[\alpha]_D^{20}$(0.007, $CHCl_3$)= 298.51

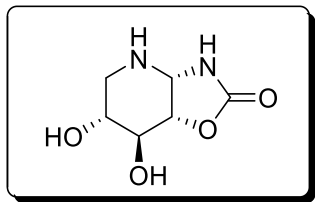
M.S (IS): m/z= 175.0 [M + H]$^+$, 349.0 [2M + H]$^+$.

IR (cm^{-1}): 1082 (CN), 1703 (C=O), 3241 (NH + OH).

^{1}H NMR (400 MHz, CD_3OD) δ = 3.27-3.33 (m, 1H, CH_2-5), 3.51 (dd, 1H,J= 6.9 Hz, J= 14.2 Hz, CH_2-5), 3.93 (td, 1H, J= 2.6 Hz, J= 6.6 Hz, CH-4), 4.18 (d, 1H,J= 2.6 Hz, CH-3), 4.87 (d, 1H, J= 5.4 Hz, CH-2), 5.75 (d, 1H, J= 5.4 Hz, CH-1).

^{13}C NMR (100 MHz, CD_3OD) δ= 39.0 (CH_2-5), 74.6 (CH-3), 79.9 (CH-4), 86.5 (CH-2), 87.3 (CH-1), 160.3 (C=O).

(5-amino-1,2,5-trideoxy-α-D-xylopyranoso)[1,2-d]-1,3-oxazolidine-2-one **(177)**



$C_6H_{10}N_2O_4$
M.W= 174,06 g/mol

The oxazolidinone **95** (0.406 g, 2.03 mmol) was dissolved in 24 mL of of THF/H_2O (5/1) at room temperature. The Ph_3P (0.532 g, 2.03 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography using AE as eluent.

Yield: 41%; **Rf**= 0.21 (EA/MeOH: 80/20); **M.p=** 153-156°C; $[\alpha]_D^{20}$(0.27, MeOH)= +44.0

HRMS (ESI+) calculated for $C_6H_{10}N_2O_4$ $[M+H]^+$: 175.0713 Found: 175.0718

IR (cm^{-1}): 1082 (CN), 1696 (C=O), 3241 (NH + OH).

^{1}H NMR (400 MHz, CD_3OD) δ = 2.68 (dd, 1H, J= 9.6 Hz, J= 12.7 Hz, CH_2-5), 2.88 (dd, 1H, J= 4.6 Hz, J= 12.7 Hz, CH_2-5’),3.40 (ddd, 1H, J= 6.5 Hz, J= 8.7 Hz, J= 9.7 Hz,CH-4), 3.55 (dd, 1H, J= 6.5 Hz, J= 8.8 Hz, CH-3), 4.24 (t, 1H, J= 6.8 Hz, CH-2), 5.01 (d, 1H, J= 7.0 Hz, CH-1)

^{13}C NMR (100 MHz, CD_3OD) δ= 44.3 (CH_2-5), 68.5 (CH-1), 70.8 (CH-4), 77.3 (CH-3), 81.3 (CH-2), 161.2 (C=O).

(5-amino-3-*O-tert*butyldimethylsilyl-1,2,5-trideoxy-α-D-xylopyranoso)[1,2-d]-1,3-oxazolidine-2-one **(179)**

$C_{12}H_{24}N_2O_4Si$
M.W = 288,15 g/mol

The azido-oxazolidinone **100** (0.333 g, 1.061 mmol) was dissolved in 13.3 mL of of THF/H_2O (5/1) at room temperature. Ph_3P (0.278 g, 1.061 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using EA/H (80/20) as eluent.

Yield: 56%; **Rf=** 0.23 (EA/H: 95/5); $[\alpha]_D^{20}$(0.457, MeOH)= 19.69

IR (cm^{-1}): 1251 ($SiCH_3$), 1742 (C=O), 3272 (NH+ OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $Si(CH_3)_2$), 0.77 (s, 9H, $SiC(CH_3)_3$), 2.65 (dd, 1H, J= 7.1 Hz, J= 13.1 Hz, CH_2-5), 2.65 (dd, 1H, J= 3.7 Hz, J= 13.1 Hz, CH_2-5'), 3.38-3.43 (m, 1H, CH-4), 3.77 (t, 1H, J= 4.8 Hz, CH-3), 4.08 (t, 1H, J= 4.8 Hz, CH-2), 4.75 (d, 1H, J= 6.0 Hz, CH-1).

^{13}C NMR (100 MHz, $CDCl_3$) δ= -4.8 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$), 18.1 (Cq of Si$\underline{C}(CH_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 42.5 (CH_2-5), 65.9 (CH-1), 69.0 (CH-4), 73.3 (CH-3), 78.6 (CH-2), , 159.4 (C=O).

(5-amino-1,2,5-trideoxy-β-D-arabinopyranoso)[1,2-d]-1,3-oxazolidine-2-one **(181)**

$C_6H_{10}N_2O_4$
M.W= 174,06 g/mol

Azido-oxazolidinone **108** (0.247 g, 1.235 mmol) was dissolved in 16 mL of THF/H_2O (5/1) at room temperature. Ph_3P (0.324 g, 1.235 mmol, 1 eq.) was added and allowed to react for 12

hours at room temperature. The solvent was removed under vacuum. The residue was purified by silica gel column chromatography using AE as eluent.

Yield: 67%; **Rf**= 0.31 (EA/MeOH: 90/10); $[\alpha]_D^{20}$(0.25, MeOH)= -52

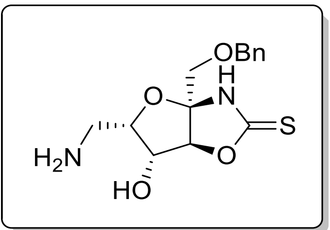
HRMS (ESI+) calculated for $C_6H_{10}N_2O_4$ $[M+H]^+$: 175.0713 Found: 175.0716

IR (cm^{-1}): 1076 (CN), 1718 (C=O), 3276 (NH + OH).

^{1}H NMR (400 MHz, CD_3OD) δ = 2.83 (dd, 1H, J = 4.3 Hz , J =13.9 Hz, CH_2-5), 2.96 (dd, 1H, J = 2.7 Hz, J = 13.9 Hz, CH_2-5'), 3.78 (dd, 1H, J = 3.0 Hz, J = 6.6 Hz, CH-3), 3.83 (td, 1H, J = 2.9 Hz, J = 4.4 Hz, CH-4), 4.42 (t, 1H, J = 6.7 Hz, CH-2), 5.00 (d, 1H, J = 6.8 Hz, CH-1).

^{13}C NMR (100 MHz, CD_3OD) δ= 44.5 (CH_2-5), 67.6 (CH-1), 68.6 (CH-4), 72.3 (CH-3), 80.2 (CH-2), 161.1 (C=O).

(6-amino-2,3,6-trideoxy-α-L-sorbofuranoso)[2,3-d]-1,3-oxazolidine-2-thione **(182)**



$C_{14}H_{18}N_2O_4S$
M.W= 310,10 g/mol

The azido-oxazolidinethione **109** (0.170 g, 0.505 mmol) was dissolved in 6.5 mL of of THF/H_2O (5/1) at room temperature. Ph_3P (0.132 g, 0.505 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was removed under vacuum. The residue was purified by silica gel column chromatography using AE as eluent.

Yield: 50%; **Rf**= 0.15 (EA/MeOH: 80/20); **M.p=** 87-91°C; $[\alpha]_D^{20}$(0.193, MeOH)= -10.4

M.S (IS): m/z= 311.4 $[M + H]^+$, 327.2 $[M + NH_4]^+$, 621.0 $[2M + H]^+$.

IR (cm^{-1}): 997 (CN), 1093 (C=S), 3160 (NH + OH).

^{1}H NMR (400 MHz, CD_3OD) δ = 2.98 (dd, 2H, J = 1.5 Hz , J =5.8 Hz, CH_2-6), 3.69 (d, 1H, J = 10.4 Hz , CH_2-1), 3.77 (d, 1H, J = 10.4 Hz, CH_2-1'), 3.93 (td, 1H, J = 2.9 Hz, J = 5.7 Hz, CH-5), 4.30 (d, 1H, J = 2.9 Hz, CH-4), 4.59-4.66 (m, 2H, CH_2 of benzyl), 4.89 (s, 1H, CH-3), 7.26-7.36 (m, 5H, CH of benzyl).

^{13}C NMR (100 MHz, CD_3OD) δ= 40.6 (CH_2-6), 70.6 (CH_2-1), 74.7 (CH_2 of benzyl), 75.4 (CH-4), 82.3 (CH-5), 92.6 (CH-3), 100.8 (Cq-2), 128.9 (CH of benzyl), 129.0 (CH of benzyl), 129.0 (CH of benzyl), 129.5 (CH of benzyl), 139.0 (Cq of benzyl), 190.8 (C=S).

(4,6-*O,N*-carbamido-2,3,6-trideoxy-α-L-sorbofuranoso)[2,3-d]-1,3-oxazolidine-2-one **(184)**

$C_{15}H_{16}N_2O_6$
M.W= 320,10 g/mol

The azido-oxazolidinone **110** (0.067 g, 0.209 mmol) was dissolved in 6 mL of of THF/H_2O (5/1) at room temperature. The Ph_3P (0.055 g, 0.209 mmol, 1 eq.) was added and allowed to react for 12 hours at room temperature. The solvent was evaporated in the evaporator. The residue was purified by silica gel column chromatography using EA/PE(90/10) as eluent.

Yield: 55%; **Rf**= 0.30 (EA/PE: 98/2); **M.p=** 241-244°C; $[\alpha]_D^{20}$(0.243, DMSO)= -29090.5 and 8102.9

HRMS (ESI+) calculated for $C_{15}H_{17}N_2O_6$ $[M+H]^+$: 321.1081 Found: 321.1084

IR (cm^{-1}): 1066 (CN), 1689 (C=O), 1766 (C=O), 3318 (NH + OH).

^1H NMR (400 MHz, $(CD_3)_2S{=}O$) δ = 3.25-3.30 (m, 1H, CH_2-6), 3.45-3.51 (m, 1H, CH_2-1), 3.55 (d, 1H, J= 3.2 Hz, CH_2-6’), 3.67 (d, 1H, J = 10.4 Hz, CH_2-1’), 4.37(dd, 1H, J = 1.3 Hz, J = 2.6 Hz, CH-5), 4.58 (s, 2H, CH_2 of benzyl), 4.78 (s, 1H, CH-3), 4.90 (d, 1H, J = 2.5 Hz, CH-4), 7.27-7.40 (m, 5H, CH of benzyl), 8.97 (ls, 1H, NH),.

^{13}C NMR (100 MHz, $(CD_3)_2S{=}O$) δ= 39.4 (CH_2-6), 68.6 (CH-5), 69.7 (CH_2-1), 72.7 (CH_2 of benzyl), 79.4 (CH-3), 83.4 (CH-4), 95.9 (Cq-2), 127.6 (CH of benzyl), 127.6 (CH of benzyl), 128.3 (CH of benzyl), 137.7 (Cq of benzyl), 150.3 (C=O), 156.2 (C=O).

5-Amino-4-*O-tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam **(188)**

$C_{14}H_{27}NO_4Si$
M.W= 301,45 g/mol

Lactam **158** (0.130 g, 0.695 mmol) was dissolved in 5 mL of pyridine at room temperature. The tert-butyldimethylsilyl chloride (0.261 g, 1.737 mmol, 2.5 eq.) and imidazole (0.189 g, 2.780 mmol, 4 eq.) were added and allowed to react for 12 hours at room temperature. The solution was diluted with ethyl acetate. The organic phase was washed once with water and once with a HCl 1M solution, dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (10:90) as eluent.

CAS [127181-02-6]; Yield: 60%; **Rf**= 0.7 ($CHCl_3$/MeOH: 80/20); **M.p=** 114-116°C.

M.S (IS): m/z= 302.5 $[M + H]^+$, 319.0 $[M + NH_4]^+$, 324.0 $[M + Na]^+$, 603.5 $[2M + H]^+$, 625.5 $[2M + Na]^+$.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.00(s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$), 0.80 (s, 9H, $SiC(CH_3)_3$), 1.30 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, $C(CH_3)_2$), 3.01-3.06 (m, 1H, CH_2-5), 3.39-3.44 (m, 1H, CH_2-5'), 3.97-4.00 (m, 1H, CH-4), 4.27-4.31 (m, 2H, CH-2 and CH-3), 7.49 (ls, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.7 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$), 18.2 ($Si\underline{C}(CH_3)_3$), 25.3 ($C(\underline{C}H_3)_2$), 25.8 ($SiC\underline{(CH_3)_3}$), 26.9 ($C(\underline{C}H_3)_2$), 42.6 (CH_2-5), 66.4 (CH-4), 73.7 (CH-2), 76.2 (CH-3), 111.0 ($\underline{C}(CH_3)_2$), 170.5 (C=O).

4-*O*-*tert*butyldimethylsilyl-5-deoxy-2,3-*O*-isopropylidene-5-*N*-Propargylamino-D-ribonono-1,5-lactam **(189)**

$C_{17}H_{29}NO_4Si$

M.W= 339,19 g/mol

Lactam **188** (0.108 g, 0.358 mmol) was dissolved in 8 mL of dry DMF at 0ºC. Then NaH (0.100 g, 2.506 mmol, 7 eq.) and propargyl bromide (0.37 mL, 3.222 mmol, 9 eq.) were slowly added and allowed to react for 30 minutes at 0ºC. Warming at room temperature, the mixture was stirred for 2 hours at room temperature. The residue was diluted with water. Extract three times with ethyl acetate. The organic layers were dried with $MgSO_4$, filtered and evaporated in the evaporator evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (25:75) as eluent.

Yield: 72%; **Rf**= 0.82 (EA/Hex: 50/50); $[\alpha]_D^{20}$(0.440 g/100 mL, MeOH)= 15.91

M.S (IS): m/z= 340.5 $[M + H]^+$, 357.0 $[M + NH_4]^+$, 362.0 $[M + Na]^+$, 679.5 $[2M + H]^+$, 696.5 $[M + NH_4]^+$.

IR(cm^{-1}): 1253 ($SiCH_3$), 1647 (C=O), 2126 ($\underline{CC}H$), 3270 ($C\underline{CH}$).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.01 (s, 6H, $Si(CH_3)_2$), 0.78 (s, 9H, $SiC(CH_3)_3$), 1.27 (s, 3H, $C(CH_3)_2$), 1.32 (s, 3H, $C(CH_3)_2$), 2.11 (d, 2H, J= 4.0 Hz, $CH\underline{CH_2}N$), 2.11 (s, 1H, $\underline{CH}CCH_2N$), 3.13-3.17 (m, 1H, CH_2-5), 3.52-3.57 (m, 1H,CH_2-5'), 3.96-3.98 (m, 1H, CH-4), 4.22 (d, 1H, J= 4 Hz, CH-2), 4.25-4.33 (m, 1H, CH-3).

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.7 ($Si(CH_3)_2$), -4.7 ($Si(CH_3)_2$), 18.3 ($Si\underline{C}(CH_3)_3$), 25.3 ($C(\underline{C}H_3)_2$), 25.7 ($SiC\underline{(CH_3)_3}$), 26.9 ($C(\underline{C}H_3)_2$), 35.9 ($CHC\underline{C}H_2N$),.47.0 (CH_2-5), 66.2 (CH-4), 72.5 ($\underline{C}HCCH_2$), 74.4 (CH-2), 76.3 (CH-3), 77.7 ($CH\underline{C}CH_2$), 111.1 ($\underline{C}(CH_3)_2$), 167.0 (C=O).

4-*O*-propargyl-5-deoxy-2,3-*O*-isopropylidene-5-*N*-Propargylamino-D-ribonono-1,5-lactam **(190)**

$C_{14}H_{17}NO_4$
M.W= 263,29 g/mol

Lactam **158** (0.200 g, 1.069 mmol) was dissolved in 24 mL of dry DMF at 0ºC. The NaH (0.299 g, 7.440 mmol, 7 eq.) and propargyl bromide (1.142 mL, 9.560 mmol, 9 eq.) were slowly added and allowed to react for 30 minutes at 0ºC. After cooling at room temperature, the mixture was stirred for 2 hours at room temperature. The residue was diluted with water. Extract three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (20:80) as eluent.

Yield: 96%; **Rf**= 0.39 (EA/Hex: 60/40); $[\alpha]_D^{20}$(0.857, MeOH)= 12.8

M.S (IS): m/z= 164.0 $[M + H]^+$, 281.5 $[M + NH_4]^+$, 286.0 $[M + Na]^+$, 527.5 $[2M + H]^+$, 544.4 $[M + NH_4]^+$,549.5 $[2M + Na]^+$.

IR(cm^{-1}): 1652 (C=O), 2116 (C̲C̲H), 3260 (CC̲H̲).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.43 (s, 3H,$C(CH_3)_2$), 1.46 (s, 3H,$C(CH_3)_2$), 2.30 (d, 2H, J= 4 Hz, CH_2O), 2.55 (d, 2H, J= 4.8 Hz, CH_2N), 2.88 (s, 1H,CH triple bond of $CHCCH_2O$), 2.97 (s, 1H, CH triple bond of $CHCCH_2N$), 3.50-3.54 (m, 1H, CH_2-5), 3.69-3.74 (m, 1H, CH_2-5'), 4.10-4.14 (m, 1H, CH-4), 4.53 (d, 1H, J= 6.2 Hz, CH-2), 4.67-4.68 (m, 1H, CH-3).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.3 ($C(\underline{C}H_3)_2$), 26.7 ($C(\underline{C}H_3)_2$), 36.1 ($CHC\underline{C}H_2N$), 44.0 (CH_2 lactam), 57.0 ($CHC\underline{C}H_2O$), 70.7 (CH-4 lactam), 72.8 ($\underline{C}HCCH_2N$), 73.8 (CH-2 lactam), 74.3 (CH-3 lactam), 75.8 ($\underline{C}HCCH_2O$), 77.3 ($CH\underline{C}CH_2N$), 78.7 ($CH\underline{C}CH_2O$), 111.3 ($\underline{C}(CH_3)_2$), 166.7 (C=O).

Methyl 2,3-*O*-isopropylidene-5-amino-5-deoxy-β-D-ribofuranoside **(191)**

$C_9H_{17}NO_4$

M.W= 203,24 g/mol

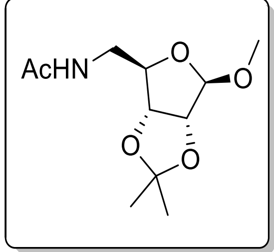
Azido-sugar **34** (1.084g, 4.729 mmol) was dissolved in 78 mL of dry ethyl acetate at room temperature. The Pd/C (1.003g, 9.458 mmol, 2 eq.) and HCO_2NH_4 (0.895g, 14.187mmol, 3 eq.) were slowly added and allowed to react for 3 hours at 70ºC, in reflux. After cooling to room temperature the residue was filtered on celite and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (65:35) as eluent.

CAS [14131-74-9]; **Yield**: 55%; **Rf=** 0.55 ($CHCl_3$/MeOH: 80/20).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.29 (s, 3H,$C(CH_3)_2$), 1.44 (s, 3H,$C(CH_3)_2$), 2.74 (d, 2H, J= 4 Hz, CH_2-5), 3.34 (s, 3H, OCH_3), 4.15 (t, 1H, J= 8 Hz, CH-4), 4.59 (d, 1H, J= 4 Hz, CH-3), 4.67 (d, 1H, J= 4 Hz, CH-2), 4.92 (s, 1H, CH-1).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.9 ($C(\underline{C}H_3)_2$), 26.5 ($C(\underline{C}H_3)_2$), 45.4 (CH_2-5), 55.1 (OCH_3), 82.1 (CH-4), 85.4 (CH-2), 88.7 (CH-3), 109.6 (CH-1), 112.3 ($\underline{C}(CH_3)_2$).

Methyl 2,3-*O*-isopropylidene-5-acetamido-5-deoxy-β-D-ribofuranoside **(193)**



$C_{11}H_{19}NO_5$

M.W= 245,13 g/mol

Amino-sugar **191** (0.200 g, 0,990 mmol) was dissolved in 4 mL of dry DCM at room temperature. The PDC (0.261 g, 0.659 mmol, 0.67 eq.) and Ac_2O (0.28 mL, 2.968 mmol, 3 eq.) were added and allowed to react for 2 hours at 40ºC, in reflux. After cooling to room temperature the

residue was diluted with diethyl ether. Extract the residue with diethyl ether overnight at room temperature. The residue was filtered on florisil and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (50:50) as eluent.

CAS [83122-79-6]; **Yield**: 80%; **Rf=** 0.61 (AE).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.31 (s, 3H,$C(CH_3)_2$), 1.47 (s, 3H,$C(CH_3)_2$), 2.00 (s, 3H, CH_3 of Ac), 3.40 (s, 3H, OCH_3), 3.44-3.49 (m, 2H, CH_2-5), 4.34 (t, 1H, CH-4), 4.58 (m, 2H, CH-2 and CH-3), 4.98 (s, 1H, CH-1), 6.28 (ls, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.3 (CH_3 of Ac), 24.9 ($C(\underline{C}H_3)_2$), 26.4 ($C(\underline{C}H_3)_2$), 42.3 (CH_2-5), 55.4 (OCH_3), 82.1 (CH-4), 85.5 (CH-2), 86.0 (CH-3), 110.0 (CH-1), 112.5 ($\underline{C}(CH_3)_2$), 170.3 (C=0 of Ac).

1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-1-O-methyl-2,3-O-isopropylidene-ß-D-ribofuranoside)-4-[5-amino-4-O-tertbutyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam]

(213)

$C_{26}H_{44}N_4O_8Si$

M.W= 568,29 g/mol

Alkynyl-lactam **189** (0.026 g, 0.114 mmol) and azido-sugar **34** (0.058 g, 0.171 mmol) were dissolved in 5 mL of *tert*-butanol/water(1/1) at room temperature. Sodium ascorbate (0.013 g, 0.065 mmol, 0.6 eq.) and $CuSO_4.5H_2O$ (0.011 g, 0.44 mmol, 0.4 eq.) were added and allowed to react for 3 hours at 40ºC. After cooling to room temperature the residue was evaporated in the evaporator evaporator. The residue was diluted with water. Extract three times with ethyl acetate. The organic layers were dried with $MgSO_4$, filtered and removed under vacuum. The residue was purified by silica gel column chromatography using a mixture of EA/ H (75:25) as eluent.

Yield: 96%; **Rf**= 0.61 (EA); $[\alpha]_D^{20}$(0.76, $CHCl_3$)= -10.5

IR (cm-1): 837 (C=C),1211 ($SiCH_3$), 1657 (C=O).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.06 (s, 6H, $Si(CH_3)_2$), 0.84 (s, 9H, $SiC(CH_3)_3$), 1.27 (s, 3H, $C(CH_3)_2$), 1.31 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$), 1.42 (s, 3H, $C(CH_3)_2$), 3.31-3.32 (m, 1H, CH_2 of lactam), 3.35 (s, 3H, CH_3 metoxi), 3.65-3.70 (m, 1H, CH_2' of lactam), 4.01-4.05 (m, 1H, CH-4 of lactam), 4.34-4.41 (m, 3H, 1H CH_2 of sugar, 1H CH-2 of lactam and 1H CH-3 of lactam), 4.47-4.56 (m, 2H, 1H CH_2' of sugar and 1H CH-4 of sugar), 4.61-4.63 (m, 3H, 1H CH-3 of sugar and 2H of CH_2N), 4.71 (d, 1H, J= 5.6 Hz, CH-2 of sugar), 4.97 (s, 1H, CH-1 sugar), 7.69 (s, 1H, CH triazol).

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.8 ($Si(CH_3)2$), 4.8 ($Si(CH_3)2$), 18.2 ($Si\underline{C}(CH_3)_3$), 25.0 ($C(\underline{C}H_3)_2$), 25.2 ($C(\underline{C}H_3)_2$), 25.7 ($SiC(\underline{C}H_3)_3$), 26.2 ($C(\underline{C}H_3)_2$), 26.9 ($C(\underline{C}H_3)_2$), 42.6 (CH_2N), 48.5 (CH_2-5 lactam), 53.2 (CH_2-5 sugar), 55.6 (CH_3 metoxi), 66.1 (CH-4 lactam), 74.3 (CH-2 lactam), 76.3 (CH-3 lactam), 81.8 (CH-2 sugar), 85.0 (CH-3 sugar), 85.2 (CH-4 sugar), 110.0 (CH-1 sugar), 110.9 ($\underline{C}(CH_3)_2$ lactam), 112.9 ($\underline{C}(CH_3)_2$ sugar), 123.6 (CH triazol), 143.3 (Cq triazol), 167.4 (C=O).

1H-1,2,3-triazol-4-yl-1-methyl-(6-deoxi-1,2;3,4-di-O-isopropylidene-α-D-galactopyranoside)-4-[5-amino-4-*O*-*tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam]

(214)

$C_{29}H_{48}N_4O_9Si$

M.W= 624,32 g/mol

Alkynyl-lactam **189** (0.044 g, 0.130 mmol) and azido-sugar **44** (0.037 g, 0.130 mmol) were dissolved in 5 mL of *tert*-butanol/water(1/1) at room temperature. Sodium ascorbate (0.015 g, 0.078 mmol, 0.6 eq.) and $CuSO_4.5H_2O$ (0.013 g, 0.051 mmol, 0.4 eq.) were added and allowed to react for 3 hours at 40ºC. After cooling to room temperature the solvent was evaporated

under reduce pressure. The residue was diluted with water. Extract three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and removed under vacuum. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (50:50) as eluent.

Yield: 89%; **Rf**= 0.56 (EA); $[\alpha]_D^{20}$(0.27, $CHCl_3$)= -22.2

IR (cm-1): 836 (C=C), 1210 ($SiCH_3$), 1659 (C=O).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.02 (s, 6H, $Si(CH_3)_2$), 0.79 ($SiC(CH_3)_3$), 1.21 ($C(CH_3)_2$), 1.25 ($C(CH_3)_2$), 1.28 ($C(CH_3)_2$), 1.30 ($C(CH_3)_2$), 1.33 ($C(CH_3)_2$), 1.41 ($C(CH_3)_2$), 3.22-3.26 (m, 1H, CH_2-5 of lactm), 3.57-3.62 (m, 1H, CH_2-5' of lactam), 4.07-4.09 (m, 1H, CH-5 of sugar), 4.25 (d, 1H, J= 2.0 Hz, CH-4 of sugar), 4.29-4.31 (m, 1H, CH-4 of lactam), 4.35-4.37 (m, 1H, CH-2 of sugar), 4.47-4.49 (m, 3H, 1H CH_2-6 of sugar, 1H CH-3 of lactam and 1H CH-2 of lactam), 4.49-4.54 (m, 2H, 1H of CH_2N and 1H CH_2-6' of sugar), 4.61 (s, 1H, CH-3 of sugar), 4.64 (s, 1H, CH_2N'), 5.41 (d, 1H, J= 4.96 Hz, CH-1 sugar), 7.67 (s, 1H, CH of triazol).

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.8($Si(CH_3)$2), -4.8 ($Si(CH_3)$2), 18.1 ($Si\underline{C}(CH_3)_3$), 24.5 ($C(\underline{C}H_3)_2$), 24.8 ($C(\underline{C}H_3)_2$), 25.2 ($C(\underline{C}H_3)_2$), 25.7 ($SiC(\underline{C}H_3)_3$), 25.9 ($C(\underline{C}H_3)_2$), 26.0 ($C(\underline{C}H_3)_2$), 26.7 ($C(\underline{C}H_3)_2$), 42.4 (CH_2N), 48.3 (CH_2-5 lactam), 50.3 (CH_2-6 sugar), 66.0 (CH-5 sugar), 67.0 (CH-4 lactam), 70.3 (CH-2 sugar), 70.7 (CH-3 sugar), 71.0 (CH-4 sugar), 74.3 (CH-2 lactam), 76.2 (CH-3 lactam), 96.2 (CH-1 sugar), 109.0 ($\underline{C}(CH_3)_2$ sugar), 109.9 ($\underline{C}(CH_3)_2$ sugar), 110.8 ($\underline{C}(CH_3)_2$ lactam), 124.5 (CH triazol), 142.6 (Cq triazol), 167.2 (C=O).

1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-1,2-O-isopropylidene-ß-D-ribofuranoside-3-ulose)-4-[5-Amino-4-*O-tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam]

(215)

$C_{25}H_{40}N_4O_8Si$

M.W= 552,26 g/mol

Alkynyl-lactam **189** (0.040 g, 0.118 mmol) and azido-sugar **50** (0.038 g, 0.177 mmol) was dissolved in 5 mL of *tert*-butanol/water(1/1) at room temperature. Sodium ascorbate (0.014 g, 0.071 mmol, 0.6 eq.) and copper sulfate (0.012 g, 0.047 mmol, 0.4 eq.) was added and allowed to react for 3 hours at 40ºC. After cooling to room temperature the solvent was evaporated under reduce pressure. The residue was diluted with water. Extract three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and removed under vacuum. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (45:55) as eluent.

Yield: 51%; **Rf**= 0.24 (EA); $[\alpha]_D^{20}$(0.373 g/100 mL, $CHCl_3$)= 2.68

IR (cm-1): 837 (C=C), 1216 ($SiCH_3$), 1657 (C=O lactame), 1726 (C=O ketone).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.10 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.25 (s, 6H,$C(\underline{C}H_3)_2$), 1.33 (s, 6H, $C(\underline{C}H_3)_2$), 3.31-3.35 (m, 1H, CH_2-5 lactam), 3.68-3.73 (m, 1H, CH_2-5' lactam),4.03-4.07 (m, 1H, CH-4 lactam), 4.38-4.43 (m, 2H, 1H CH-4 of sugar and 1H CH-2 of lactam), 4.51-4.57 (m, 3H, 1H CH-3 of lactam, 1H CH_2N and 1H CH_2-5 of sugar), 4.59-6.65 (m, 2H, 1H CH_2N' and 1H CH_2-5' of sugar),.68-4.73 (m, 1H, CH-2 sugar), 5.80 (d, 1H, J= 4.28 Hz, CH-1 sugar), 7.60 (s, 1H, CH triazol).

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.7(Si(CH_3)2), 18.2 ($Si\underline{C}(CH_3)_3$), 25.2 ($C(\underline{C}H_3)_2$), 25.6 ($C(\underline{C}H_3)_2$), 25.8 ($C(\underline{C}H_3)_2$), 26.5 ($SiC(\underline{C}H_3)_3$), 26.8 ($C(\underline{C}H_3)_2$), 27.0 ($C(\underline{C}H_3)_2$), 27.3 ($C(\underline{C}H_3)_2$), 42.7 (CH_2N), 48.7 (CH_2-5 lactam), 50.1 (CH_2-5 sugar), 66.1 (CH-4 lactam), 74.3 (CH-2 lactam), 76.2 (CH-3 lactam), 78.3 (CH-4 sugar), 79.5 (CH-2 sugar), 103.4 (CH-1 sugar), 111.0 ($\underline{C}(CH_3)_2$), 114.6 ($\underline{C}(CH_3)_2$), 124.6 (CH triazol), 143.4 (Cq triazol), 167.5 (C=O), 206.2 (C=O of C-3).

1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-ß-D-ribofuranoside)-4-[5-Amino-4-*O*-*tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam] **(216)**

$C_{22}H_{38}N_4O_8Si$

M.W= 514,25 g/mol

Alkynyl-lactam **189** (0.042 g, 0.124 mmol) and azido-sugar **36** (0.022 g, 0.124 mmol) was dissolved in 5 mL of *tert*-butanol/water(1/1) at room temperature. Sodium ascorbate (0.015 g, 0.074 mmol, 0.6 eq.) and $CuSO_4.5(H_2O)$ (0.013 g, 0.050 mmol, 0.4 eq.) was added and allowed to react for 3 hours at 40ºC. After cooling to room temperature the solvent was evaporated under reduce pressure. The residue was diluted with water. Extract three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and removed under vacuum. The residue was purified by silica gel column chromatography using a mixture of EA/ Hex (60:40) as eluent.

Yield: 56%; **Rf**= 0.18 (EA).

IR (cm-1): 836 (C=C), 1254 ($SiCH_3$), 1639 (C=O), 3338 (OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.00 (s, 6H, $Si(CH_3)_2$), 0.77 (s, 9H, $SiC(CH_3)_3$), 1.24 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, $C(CH_3)_2$), 3.23-3.34 (m, 1H, CH_2-5 lactam), 3.56-3.64 (m, 1H, CH_2-5' lactam), 4.02-4.08 (m, 4H, 1H of CH-4 lactam,1H of CH-2 sugar and 2H of CH2-5 sugar), 4.32-4.40 (m, 5H, 1H of CH-2 lactam, 2H of CH_2N, 1H of CH-3 lactam and 1H of CH-3 sugar), 4.50 (s, 1H, CH-4 sugar), 4.16 (s, 1H, CH-1 sugar), 7.76 (s, 1H, CH triazol).

^{13}C NMR (100 MHz, $CDCl_3$) δ = -4.7(Si(CH$_3$)2), 4.7 (Si(CH$_3$)2), 18.2 ($Si\underline{C}(CH_3)_3$), 25.3 ($C(\underline{C}H_3)_2$), 25.8 ($SiC(\underline{C}H_3)_3$), 26.8 ($C(\underline{C}H_3)_2$), 42.9 ($\underline{C}H_2N$), 48.9(CH_2-5 lactam), 60.4 (CH_2-5 sugar), 65.6 (CH-4 lactam), 70.6 (CH-2 sugar), 71.3 (CH-2 lactam), 74.2 (CH-3 lactam), 76.2 (CH-3 sugar), 80.2 (CH-4 sugar), 96.6 (CH-1 sugar), 111.0 ($\underline{C}(CH_3)_2$ lactam), 123.6 (CH triazol), 143.3 (Cq triazol), 168.4(C=O).

1H-1,2,3-triazol-4-yl-1-methyl-(6-deoxi-1,2;3,4-di-O-isopropylidene-α-D-galactopyranoside**)-** 4-[5-Amino-4-*O-tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam]-4-methyl-(1H-1,2,3-triazol-4-yl-1-methyl)-(6-deoxi-1,2;3,4-di-O-isopropylidene-α-D-galactopyranoside] **(218)**

$C_{38}H_{55}N_7O_{14}$

M.W= 833,38 g/mol

Alkynyl-lactam **190** (0.036 g, 0.137 mmol) and azido-sugar **44** (0.078 g, 0.274 mmol) was dissolved in 8 mL of *tert*-butanol/water(1/1) at room temperature. Sodium ascorbate (0.016 g, 0.082 mmol, 0.6 eq.) and $CuSO_4.5(H_2O)$ (0.014 g, 0.55 mmol, 0.4 eq.) was added and allowed to react for 3 hours at 40ºC, in reflux. After cooling to room temperature the solvent was evaporated under reduce pressure. The residue was diluted with water. Extract three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and removed under vacuum.The residue was purified by silica gel column chromatography using a mixture of EA/ Hex (50:50) as eluent.

Yield: 95%; **Rf**= 0.17 (EA); $[\alpha]_D^{20}$(0.463, $CHCl_3$)= -34.6

IR (cm-1): 794 (C=C), 1658 (C=O).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (s, 3H,$C(CH_3)_2$), 1.27 (s, 3H,C(CH3)$_2$), 1.29 (s, 3H,$C(CH_3)_2$), 1.32 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 1.37 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.40 (s, 3H, $C(CH_3)_2$), 1.49 (s, 3H, $C(CH_3)_2$), 1.50 (s, 3H, $C(CH_3)_2$), 3.40-3.45 (m, 1H, CH_2-5 of lactam), 3.65-3.70 (m, 1H, CH_2-5' of lactam), 3.86-3.90 (m, 1H, CH-4 lactam), 4.11-23 (m, 4H, 2 x CH-5 of sugar, 2 x CH-3 of sugar), 4.31.4.34 (m, 2H, CH-4 of sugar), 4.42-4.45 (m, 2H, 1H CH_2-6

of sugar and 1H 2 CH-3 of lactam), 4.51-4.55 (m, 2H, 1H CH-2 of lactam and 1H of CH_2N), 4.61-4.66 (m, 3H, 1H CH_2-6' of sugar and 1H 2x CH-2 of sugar), 4.71-4.76 (m, 3H, 1H of CH_2N' and 2H of CH_2O), 5.50 (d, 1H, J= 5.88 Hz, CH-1 sugar), 5.49 (t, 2H, J= 5.56 Hz, 2 x CH-1 of sugar), 7.74 (s, 2H, 2 x CH of triazol).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.4 ($C(\underline{C}H_3)_2$), 24.5 ($C(\underline{C}H_3)_2$), 24.7 ($C(\underline{C}H_3)_2$), 24.9 ($C(\underline{C}H_3)_2$), 25.3 ($C(\underline{C}H_3)_2$), 25.5 ($C(\underline{C}H_3)_2$), 25.9 ($C(\underline{C}H_3)_2$), 26.0 ($C(\underline{C}H_3)_2$), 26.4 ($C(\underline{C}H_3)_2$), 26.7 ($C(\underline{C}H_3)_2$), 42.4 (CH_2N), 45.0 (CH_2-5 of lactam), 50.4 (CH_2-6 of sugar), 50.6 (CH_2-6 of sugar), 62.7 (CH_2O), 67.1 (CH-5 sugar), 67. 2 (CH-5 sugar), 70.3 (CH-4 lactam), 70.8 (CH-2 sugar), 70.9 (CH-2 sugar), 71.0 (CH-3 sugar), 71.0 (CH-3 sugar), 71.1 (CH-4 sugar), 71.1 (CH-4 sugar), 74.2 (CH-2 lactam), 74.5 (CH-3 lactam), 96.2 (CH-1 sugar), 96.2 (CH-1 sugar), 1109.0 ($\underline{C}(CH_3)_2$ sugar), 109.0 ($\underline{C}(CH_3)_2$ sugar), 109.9 ($\underline{C}(CH_3)_2$ lactam), 110.9 ($\underline{C}(CH_3)_2$ sugar), 111.0 ($\underline{C}(CH_3)_2$ sugar), 124.3 (CH triazol), 124.4 (CH triazol), 142.5 (Cq triazol), 143.9 (Cq triazol), 167.0 (C=O).

1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-1-O-methyl-2,3-O-isopropylidene-ß-D-ribofuranoside)-4-[5-amino-4-*O-tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam]-4-methyl-[(1H-1,2,3-triazol-4-yl-1-methyl)-(5-deoxi-1-O-methyl-2,3-O-isopropylidene-ß-D-ribofuranoside)] **(219)**

$C_{32}H_{47}N_7O_{12}$
M.W= 721,76 g/mol

Alkynyl-lactam **190** (0.043 g, 0.163 mmol) and azido-sugar **34** (0.049 g, 0.217 mmol) were dissolved in 5 mL of *tert*-butanol/water(1/1) at room temperature. Sodium ascorbate (0.013 g, 0.065 mmol, 0.6 eq.) and $CuSO_4.5(H_2O)$ (0.011 g, 0.044 mmol, 0.4 eq.) were added and allowed to react for 3 hours at 40ºC. After cooling to room temperature the solvent was evaporated under reduce pressure. The residue was diluted with water. Extract three times with ethyl

acetate. The organic phase was dried with $MgSO_4$, filtered and removed under vacuum.The residue was purified by silica gel column chromatography using a mixture of EA/ Hex (75:25) as eluent.

Yield: 56%; **Rf**= 0.33 (EA); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$(0.75, $CHCl_3$)= -16.0

IR (cm-1): 825 (C=C), 1652 (C=O).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.30 (s, 3H, $C(\underline{C}H_3)_2$), 1.31(s, 3H, $C(\underline{C}H_3)_2$), 1.34 (s, 3H, $C(\underline{C}H_3)_2$), 1.37 (s, 3H, $C(\underline{C}H_3)_2$), 1.45 (s, 3H, $C(\underline{C}H_3)_2$), 1.46 (s, 3H, $C(\underline{C}H_3)_2$), 3.37 (s, 3H, CH_3 metoxi), 3.40 (s, 3H, CH_3 metoxi), 3.49-3.53 (m, 1H, CH_2-5 of lactam),3.71 (t, 1H, J= 10.8 Hz, CH_2-5' of lactam),3.91-3.94 (m, 1H, CH-4 of lactam), 4.45-4.51 (m, 9H, 2x2H CH_2 of sugar, 1H of CH_2N, 1H of CH-2 of lactam, 1H of CH-3 of lactam and 2x1H of CH-3 of sugar), 4.60-4.70 (m, 2H, 2x1H CH-4 of sugar), 4.72-4.77 (m, 5H, 1H of CH_2N, 2H of CH_2O and 2x1H CH-2 of sugar), 5.01 (d, 2H, J= 13.6 Hz, 2x1H CH-1 of sugar), 7.71 (s, 2H, 2x1H CH of triazol).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.9 ($C(\underline{C}H_3)_2$), 25.0 ($C(\underline{C}H_3)_2$), 25.1 ($C(\underline{C}H_3)_2$), 25.2 ($C(\underline{C}H_3)_2$), 26.4 ($C(\underline{C}H_3)_2$), 26.6 ($C(\underline{C}H_3)_2$), 42.5 (CH_2N), 45.4 (CH_2-5 of lactam), 55.6 (OCH_3), 55.6 (OCH_3), 62.9 (CH_2O), 71.2 (CH-4 lactam), 74.2 (CH-2 lactam), 74.4 (CH-3 lactam), 81.8 (CH-2 sugar), 81.8 (CH-2 sugar), 85.0 (CH-3 sugar), 85.0 (CH-3 sugar), 85.1 (CH-4 sugar), 85.2 (CH-4 sugar), 110.0 (CH-1 sugar), 110.1 (CH-1 sugar), 111.0 ($\underline{C}(CH_3)_2$ lactam), 112.9 ($\underline{C}(CH_3)_2$ sugar), 113.0 ($\underline{C}(CH_3)_2$ sugar), 123.5 (CH triazol), 123.6 (CH triazol), 143.1 (Cq triazol), 144.6 (Cq triazol), 167.1 (C=O).

1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-1,2-O-isopropylidene-ß-D-ribofuranoside-1-ulose)-4-[5-Amino-4-*O-tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam]-4-methyl-[1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-1-O-methyl-2,3-O-isopropylidene-ß-D-ribofuranoside-1-ulose] **(220)**

$C_{30}H_{39}N_7O_{12}$

M.W= 689,27 g/mol

Alkynyl-lactam **190** (0.050 g, 0.190 mmol) and azido-sugar **41** (0.053 g, 0.253 mmol) were dissolved in 5 mL of *tert*-butanol/water(1/1) at room temperature. Sodium ascorbate (0.015 g, 0.076 mmol, 0.6 eq.) and $CuSO_4.5(H_2O)$ (0.013 g, 0.051 mmol, 0.4 eq.) were added and allowed to react for 3 hours at 40ºC After cooling to room temperature the solvent was evaporated under reduce pressure. The residue was diluted with water. Extract three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and removed under vacuum.The residue was purified by silica gel column chromatography using a mixture of EA/Hex (90:10) as eluent.

Yield: 46 %; **Rf**= 0.15 (EA); $[\alpha]_D^{20}$(0.23, $CHCl_3$)= -21.5

IR (cm-1): 794 (C=C), 1651 (C=O lactame), 1786 (lactone).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.35 ($C(\underline{C}H_3)_2$), 1.36 ($C(\underline{C}H_3)_2$), 1.40 ($C(\underline{C}H_3)_2$), 1.43 ($C(\underline{C}H_3)_2$), 2.45 ($C(\underline{C}H_3)_2$), 1.46 ($C(\underline{C}H_3)_2$), 3.54-3.57 (m, 1H, CH_2-5 lactam), 3.69-3.75 (m, 1H, CH_2-5' lactam), 3.92-4.01 (m, 2H, 1H of CH-4 lactam and 1H of CH-2 lactam), 4.17(d, 2H, 2x 1H of CH-3 sugar), 3.30-4.31 (m, 2H, CH_2O), 4.50-4.53 (m, 2H, 2x 1H of CH-2 sugar), 4.63-4.74 (m, 7H, 1H of CH-3 lactam, 2H of CH_2N and 2x 2H of CH_2-5 sugar), 4.77-4.78 (m, 1H, CH-4 lactam), 4.94-4.96 (m, 2H, 2x 1H of CH-4 sugar), 7.69 (s, 1H, CH triazol), 7.71.(s, 1H, CH triazol).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.3 ($C(\underline{C}H_3)_2$), 25.4 ($C(\underline{C}H_3)_2$), 25.4 ($C(\underline{C}H_3)_2$), 26.5 ($C(\underline{C}H_3)_2$), 26.6 ($C(\underline{C}H_3)_2$), 26.8 ($C(\underline{C}H_3)_2$), 42.6 (CH_2N), 45.7 (CH_2-5 lactam), 51.3 (CH_2-5 of sugar), 51.4 (CH_2-5 of sugar), 57.2 (CH_2O), 70.9 (CH-4 lactam), 71.4 (CH-2 lactam), 72.8 (CH-3 sugar), 74.0 (CH-3 sugar), 74.1 (CH-3 lactam), 74.3 (CH-2 sugar), 74.3 (CH-2 sugar), 78.9 (CH-4 sugar), 79.9 (CH-4 sugar), 111.3 ($\underline{C}(CH_3)_2$ lactam), 114.2 ($\underline{C}(CH_3)_2$ sugar), 114.2 ($\underline{C}(CH_3)_2$ sugar), 125.0 (CH triazol), 125.1 (CH triazol), 143.4 (Cq triazol), 144.0 (Cq triazol) 166.8 (C=O sugar), 167.1 (C=O sugar), 172.6 (C=O lactam).

1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-ß-D-ribofuranoside)-4-[5-Amino-4-*O*-*tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam]-4-methyl-[1H-1,2,3-triazol-4-yl)methyl-(5-deoxi-ß-D-ribofuranoside)] **(221)**

$C_{24}H_{35}N_7O_{12}$

M.W= 613,23 g/mol

Alkynyl-lactam **190** (0.050 g, 0.190 mmol) and azido-sugar **36** (0.022 g, 0.126 mmol) were dissolved in 5 mL of *tert*-butanol/water (1/1) at room temperature. Sodium ascorbate (0.015 g, 0.076 mmol, 0.6 eq.) and $CuSO_4.5(H_2O)$ (0.012 g, 0.050 mmol, 0.4 eq.) were added and allowed to react for 3 hours at 40ºC, in reflux. After to cooling at room temperature the residue was evaporated in the evaporator. The residue was diluted with water. Extract three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (80:20) as eluent.

Yield: 40 %; **Rf**= 0.05 (EA); $[\alpha]_D^{20}$(1.0, DMSO)= +5.8

IR (cm-1): 823 (C=C), 1652 (C=O), 3265 (OH).

^{1}H NMR (400 MHz, $(CD_3)_2S{=}O$) δ = 1. 23 (s, 3H, $C(CH_3)_2$), 1.30 (s, 3H, $C(CH_3)_2$), 3.38-3.40 (m, 2H, CH_2-5 of lactam), 3.65 (s, 1H, CH-3 of sugar), 3.95-3.99 (m, 7H, 1H CH-4 of lactam, 1H 2x CH-2 of sugar, 2x 1H CH-4 of sugar and 2H of CH_2O), 4.40-4.44 (m, 4H, 1H of CH_2N, 1H 2x CH_2-5 of sugar and 1H CH-2 of lactam), 4.57-4.63 (m, 5H, 1H of CH_2N', 1H 2x CH_2-5' of sugar, 1H CH-3 of lactam and 2x 1H CH-3 of sugar), 4.96 (s, 2H, CH-1 sugar), 4.97 (s, 1H, CH-1'), 7.91 (s, 1H, CH of triazol), 8.03 (s, 1H, CH' of triazol).

^{13}C NMR (100 MHz, $(CD_3)_2S{=}O$) δ = 25.8 ($C(\underline{C}H_3)_2$), 27.0 ($C(\underline{C}H_3)_2$), 40.6 (CH_2N), 45.2 (CH_2-5 of lactam), 53.7 (CH_2-5 of sugar), 53.9 (CH_2-5 of sugar), 62.4 (CH_2O), 70.8 (CH-4 lactam), 71.3 (CH-2 sugar), 72.3 (CH-2 sugar), 72.4 (CH-3 sugar), 74.1 (CH-3 sugar), 74.2 (CH-2 lactam), 74.5

(CH-3 lactam), 75.6 (CH-4 sugar), 80.3 (CH-4 sugar), 97.0 (CH-1 sugar), 102.5 (CH-1 sugar), 110.1 (C(CH_3)$_2$ lactam), 124.4 (CH triazol), 125.2 (CH triazol), 142.8 (Cq triazol), 143.8 (Cq triazol), 166.7 (C=O lactam).

1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-1,2-O-isopropylidene-ß-D-ribofuranoside)-4-[5-Amino-4-*O-tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam]-4-methyl-[1H-1,2,3-triazol-4-yl)methyl-(5-deoxi-1,2-O-isopropylidene-ß-D-ribofuranoside)] **(222)**

$C_{30}H_{43}N_7O_{12}$

M.W= 693,30 g/mol

Alkynyl-lactam **190** (0.050 g, 0.190 mmol) and azido-sugar **49** (0.082 g, 0.380 mmol) was dissolved in 8 mL of *tert*-butanol/water(1/1) at room temperature. Sodium ascorbate (0.023 g, 0.114 mmol, 0.6 eq.) and $CuSO_4.5(H_2O)$ (0.019 g, 0.076 mmol, 0.4 eq.) was added and allowed to react for 3 hours at 40ºC, in reflux. After to cooling at room temperature. The residue was evaporated in the evaporator. The residue was diluted with water. Extract three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and evaporated in the evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (50:50) as eluent.

Yield: 37%; **Rf**= 0.13 (EA); $[\alpha]_D^{20}$(1.0, $CHCl_3$)= -7.2

IR (cm-1): 827 (C=C), 1644 (C=O), 3308 (OH).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.29 (s, 3H, C(CH_3)$_2$), 1.31 (s, 3H, C(CH_3)$_2$), 1.36 (s, 3H, C(CH_3)$_2$), 1.38 (s, 3H, C(CH_3)$_2$), 1.44 (s, 3H, C(CH_3)$_2$), 1.45 (s, 3H, C(CH_3)$_2$), 3.38-3.43 (m, 1H, CH_2-5 of lactam), 3.65-3.70 (m, 1H, CH_2-5' of lactam), 3.89-3.91 (m, 1H, CH-4 of lactam), 4.19-4.26 (m, 2H, CH-2 of lactam and CH-3 of lactam), 4.49-4.50 (m, 2H, 1H 2x CH-4 of sugar), 4.57-4.60 (m,

7H, 1H of CH_2N, 1H 2x CH_2-5 of sugar, 1H 2x CH-3 of sugar and 1H 2x CH-2 of sugar), 4.61-4.77 (m, 5H, 1H of CH_2N', 1H 2x CH_2-5' of sugar and 2H of CH_2O, 5.96 (d, 1H, J= 3.36 Hz, CH-1), 6.00 (d, 1H, J= 3.36 Hz, CH-1'), 7.76 (s, 1H, CH of triazol), 7.80 (s, 1H, CH' of triazol).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.1 ($C(\underline{C}H_3)_2$), 25. 4 ($C(\underline{C}H_3)_2$), 25.7 ($C(\underline{C}H_3)_2$), 26.2 ($C(\underline{C}H_3)_2$), 26.5 ($C(\underline{C}H_3)_2$), 26.8 ($C(\underline{C}H_3)_2$), 42.2 (CH_2N), 45.6 (CH_2-5 of lactam), 48.5 (CH_2-5 of sugar), 48.7 (CH_2-5 of sugar), 63.1 (CH_2O), 71.2 (CH-4 lactam), 74.2 (CH-3 sugar), 74.3 (CH-3 sugar), 74.5 (CH-2 lactam), 76.2 (CH-3 lactam), 77.9 (CH-4 sugar), 78.8 (CH-4 sugar), 85.4 (CH-2 sugar), 85.4 (CH-2 sugar), 105.1 (CH-1 sugar), 105.2 (CH-1 sugar), 111.2 ($\underline{C}(CH_3)_2$ lactam), 112.0 ($\underline{C}(CH_3)_2$ sugar), 112.0 ($\underline{C}(CH_3)_2$ sugar), 124.4 (CH triazol), 124.6 (CH triazol), 142.6 (Cq triazol), 144.4 (Cq triazol), 167.5 (C=O).

1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-1,2-O-isopropylidene-ß-D-ribofuranoside-3-ulose)-4-[5-Amino-4-*O-tert*butyldimethylsilyl-5-deoxy-2,3-O-isopropylidene-D-ribonono-1,5-lactam]-4-methyl-[1H-1,2,3-triazol-4-yl-1-methyl-(5-deoxi-1-O-methyl-1,2-O-isopropylidene-ß-D-ribofuranoside-1-ulose] **(223)**

$C_{30}H_{39}N_7O_{12}$

M.W= 689,27 g/mol55

Alkynyl-lactam **25** (0.050 g, 0.190 mmol) and azido-sugar (0.081 g, 0.380 mmol) was dissolved in 8 mL of *tert*-butanol/water(1/1) at room temperature. Sodium ascorbate (0.023 g, 0.114 mmol, 0.6 eq.) and $CuSO_4.5(H_2O)$ (0.019 g, 0.076 mmol, 0.4 eq.) was added and allowed to react for 3 hours at 40ºC, in reflux. After to cooling at room temperature the residue was evaporated in the evaporator. The residue was diluted with water. Extract three times with ethyl acetate. The organic phase was dried with $MgSO_4$, filtered and evaporated in the

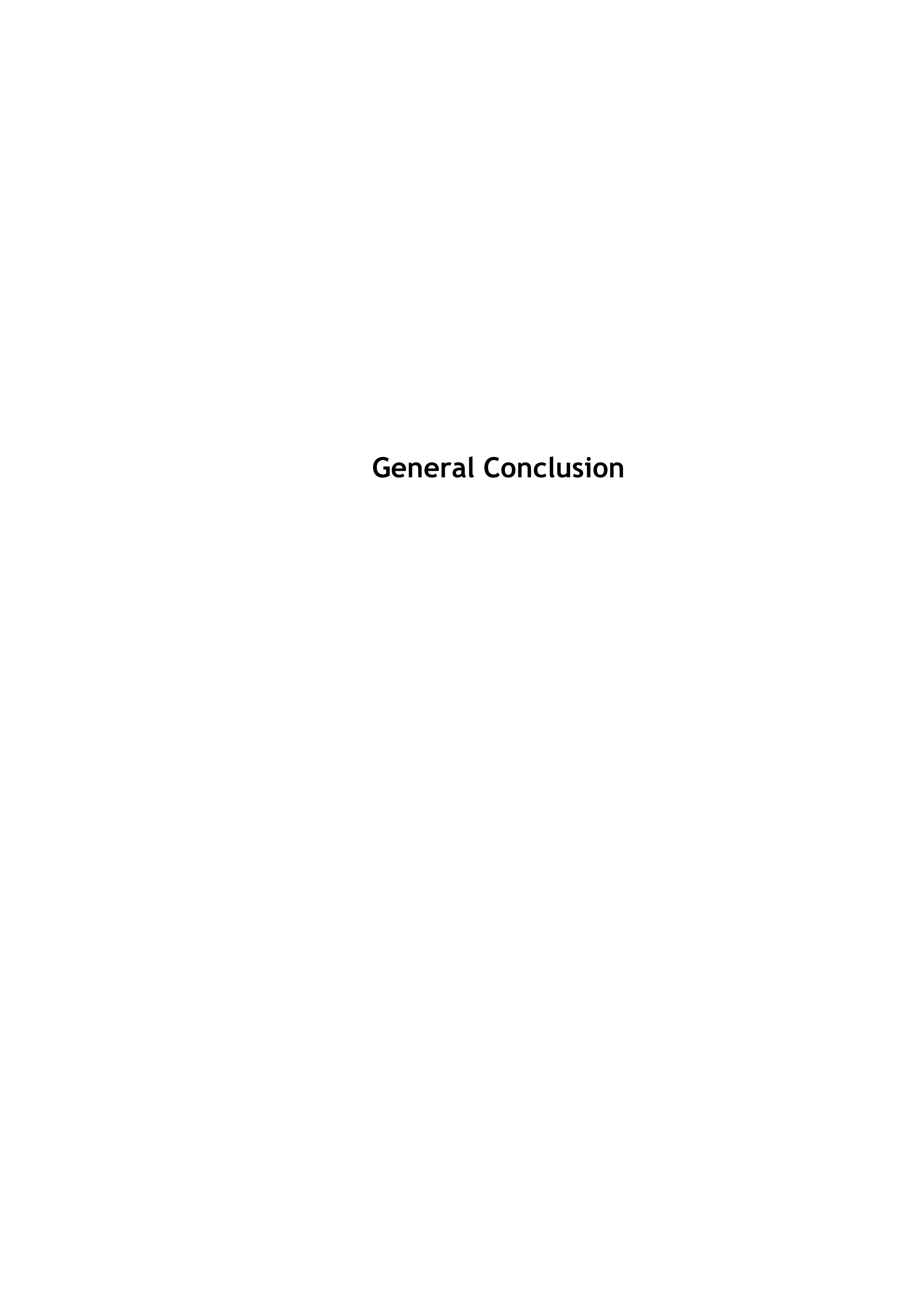
evaporator. The residue was purified by silica gel column chromatography using a mixture of EA/Hex (40:60) as eluent.

Yield: 32%; **Rf**= 0.19 (EA); $[\alpha]_D^{20}$(0.25, $CHCl_3$)= -4.1

IR (cm-1): 790 (C=C), 1645 (C=O lactame), 1730 (C=O ketone).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.24 (s, 3H, $C(CH_3)_2$), 1.36 (s, 3H, $C(CH_3)_2$), 1.39 (s, 3H, $C(CH_3)_2$), 1.45 (s, 3H, $C(CH_3)_2$), 1.49 (s, 3H, $C(CH_3)_2$), 1.51 (s, 3H, $C(CH_3)_2$), 3.54-3.56 (m, 1H, CH_2-5 of lactam), 3.71-3.72 (m, 1H, CH_2-5' of lactam), 3.99-4.01 (m, 1H, CH-4 of lactam), 4.50-4.53 (m, 4H, 1H of CH_2N, 1H CH-3 of lactam and 1H 2x CH-4 of sugar), 4.68-4.72 (m, 4H, 1H of CH_2N', 1H 2x CH_2-5 of sugar and1H CH-2 of lactam), 5.07-5.10 (m, 4H, 2H of CH_2O and 1H 2x CH-2 of sugar), 5.88 (d, 1H, J= 3.96 Hz, CH-1), 5.92 (d, 1H, J= 3.76 Hz, CH-1'), 7.68 (s, 1H, CH of triazol), 7.79 (s, 1H, CH' of triazol).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.1 ($C(\underline{C}H_3)_2$), 25.3 ($C(\underline{C}H_3)_2$), 26.6 ($C(\underline{C}H_3)_2$), 26.7 ($C(\underline{C}H_3)_2$), 27.0 ($C(\underline{C}H_3)_2$), 27.3 ($C(\underline{C}H_3)_2$), 42.6 (CH_2N), 44.2 (CH_2-5 of lactam), 45.5 (CH_2-5 of sugar), 46.8 (CH_2-5 of sugar), 62.9 (CH_2O), 71.6 (CH-4 lactam), 75.7 (CH-2 lactam), 76.7 (CH-3 lactam), 77.4 (CH-4 sugar), 78.7 (CH-4 sugar), 85.0 (CH-2 sugar), 85.2 (CH-2 sugar), 103.5 (CH-1 sugar), 103.6 (CH-1 sugar), 111.3 ($\underline{C}(CH_3)_2$ lactam), 114.0 ($\underline{C}(CH_3)_2$ sugar), 114.6 ($\underline{C}(CH_3)_2$ sugar), 121.5 (CH triazol), 124.6 (CH triazol), 143.3 (Cq triazol), 145.0 (Cq triazol), 166.8 (C=O), 206.2 (C=O sugar), 206.3 (C=O sugar).



General Conclusion

✓ *C*-Nucleosides have proven their important impact in various therapeutical fields. Biginelli cyclocondensation gives access to the synthesis of these molecules. D-Glucosamine is the precursor of the aldehydes required for the cyclocondensation. This methodology allows the synthesis of oxopyrimidines **21**and **26**, and thioxopyrimidines **22** and **27**. The chemical shifts for the quaternary carbon atom at position 2 of the six-membered heterocycle varied from roughly 170 ppm (N−C=O) in oxopyrimidines and 186 ppm (N-C=S) in thioxopyrimidines.
Yields are more favorable when the Biginelli adducts was unprotected (oxo/thioxopyrimidine **21** and **22**). Global yields of unprotected adducts is approximatedly 75% for compounds **21** and **22**, and 60% for protected adducts **26** and **27**. Biginelli adducts **21** and **26** showed to be potential candidate as antiparasitic drugs (inhibiting more than 50% of the alive females and its oviposition). Quite intriguingly, Glucosamine tetra-acetylated **24** showed also good inhibition.

✓ The azide function had already shown its versatility in organic synthesis. It is an important functional group for carbohydrate modifications. Simple azidocarbohydrates in D-ribose, D-xylose and D-galactose templates were synthesized having as precursors commercial carbohydrates. Selective Iodination using a modified Garegg methodology was used to incorporate the azido group by nucleophilic substitution. This simple change in the structure gave a strong modification for the chemical shifts of the primary carbon atom at C5 position from roughly 5 ppm for the iodocarbohydrates to approximately 50 ppm with the azidocarbohydrates. The chemical shifts for the secondary carbon atom at C6 position of the six-membered ring varied from roughly 2 ppm in iodinecarbohydrates to approximately 50 ppm in azidocarbohydrates. Overall yields are very close to each other, around 78% to D-ribose template, 75% D-xylose template and 93% to D-galactose template.

In order to provide the functionalization of carbohydrates, we have performed the condensation of carbohydrates with thiocyanic acid. The obtained carbohydrates fused with 1,3-oxazolidine-2-thione gave the opportunity to introduce an azido group. The reactivity of these innovative structures was studied.
On the D-ribose template we have determined the necessity of protecting the thionocarbamate to prevent ring opening and or carbohydrate degradation when we performed the nucleophilic substitution reaction. Masking the sulfur with a benzyl group yielded carbohydrates fused with 2-benzylsulfanyl-1,3-oxazoline ring. Furthermore, oxidation of C-SBn in carbohydrates fused with 2-benzylsulfanyl-1,3-oxazolidine leads the carbohydrate fused with 1,3-oxazolidin-2-one ring. Mainly, the insertion of an azido group onto the bicyclic system could be perform efficiently on the 1,3-oxazolidin-2-one or on the benzylsulfanyloxazoline while with the oxazolidinethione, the yields were rather poor or lead to the opening of the furanose ring. Nonetheless we have been able to set up a method to introduce an azido function on a bicyclic heterocyclic system incorporating the OZO and OZT rings and thus ready to explore the chemistry of the azido function.

The chemical shifts for the quaternary sp^2 carbon atom at position 2 of the five-membered heterocycle varied from roughly 190 ppm (N–C=S in 1,3-oxazolidine-2-thione) to approximately 170 ppm (N=C–SBn in 2-benzylsulfanyl-1,3-oxazoline) and to 160 ppm (N-C=O in 1,3-oxazolidin-2-one). Yields on different carbohydrate structures (Table 8.1) are good with some minor variations, which are justified by the protection order in the molecule. □In D-ribose template is more efficient performing silylation after benzylation, in D-xylose template is precisely the opposite and in L-sorbose template is necessary to perform the silylation after benzylation and nucleophilic substitution. Silylation made before benzylation/nucleophilic substitution leads silylated compound in low yield. The oxidation of C-SBn group with m-CPBA in D-ribose template is more efficient when performed exclusively with protected molecules.

Table 8.1 – Yields of different templates.

Template	1,3-oxazolidine-2-thione (OZT)	2-alkylsulfanyl-1,3-oxazoline	1,3-oxazolidin-2-one (OZO)	Global yield
D-ribose	84%	73%	22% unprotected in C3	60%
			80% protected in C3	79%
D-xylose	74%	71%	60% unprotected in C3	68%
			83% protected in C3	76%
D-arabinose	92%	89%	58% unprotected in C3	80%
1-O-benzyl-L-sorbose	92%	89%	88% unprotected in C4	90%
			58% protected in C4	80%

✓ The development of an efficient synthesis of iminosugars analogues represent a considerable importance due to its potential as glucosidase inhibitors. The search for new approachs for synthesis of iminosugars give us new opportunities to explore the chemistry properties of azidocarbohydrates to originate these innovative structures.

Attempt to synthesize these innovative structures, the use of Lewis acids did not allow the synthesis of iminosugars from azidocarbohydrates fused with 2-benzylsulfanyl-1,3-oxazolidine ring.

Applying the Staudinger reduction onto azidocarbohydrates fused with 1,3-oxazolidin-2-thione or benzylsulfanyl-1,3-oxazolidine ring only lead to the reduction of the azido group to the amine function. The same reaction on carbohydrate bearing the 1,3-oxazolidin-2-one ring, also lead to the reduction but with a further retro-Mickael then aza-Michael reaction. This, three steps in a row gave access to a new class of molecules allowing the synthesis of innovative iminosugars fused with 1,3-oxazolidin-2-one ring in D-ribo, D-xylo, D-arabino and L-sorbo templates (Figure 8.1).

170 15% | **171** 36% | **172** 16%

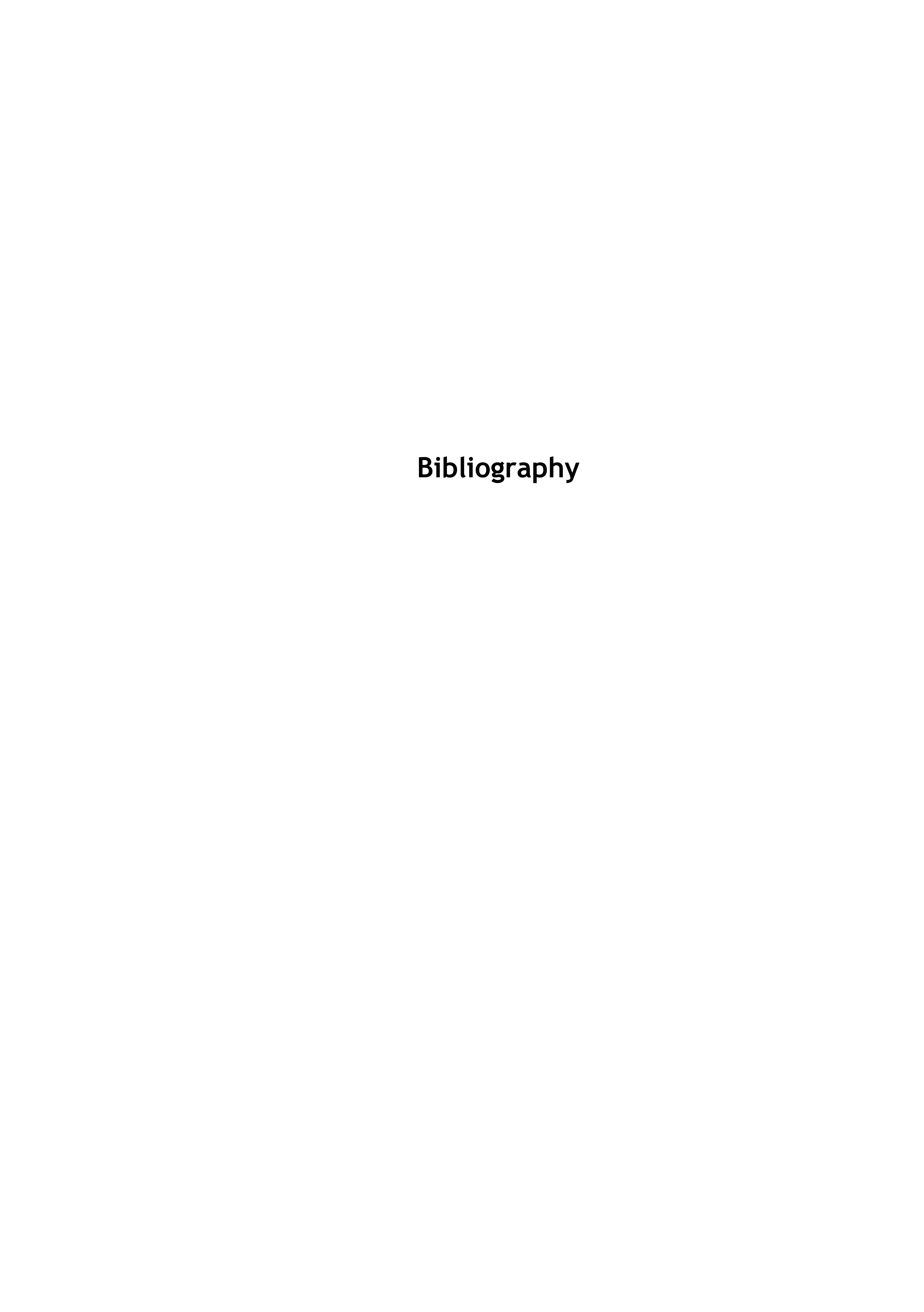
177 41% | **179** 56% | **181** 67%

Figure 8.1- Inovative iminosugars synthesized.

The stereochemistry might explained the yields, it was concluded that the spatial disposition of the substituents in C-2 and C-3 of iminosugars **170**, **171**, **172**, **177**, **179** and **181** is very important in the formation of the iminosugars fused with 1,3-oxazolidin-2-one ring. The best yields were obtained when the C2-C3 substituents are in trans position (iminosugars **177**, **179** and **181**). This fact could explained with electronic repulsion or steric interaction on position 2-3 of the ring. Cyclization at nitrogen atom was more efficient in D-xylose and D-arabinose templates.

Amides have a significant resonance struture wherein the lone par of electrons on the nitrogen atom is deslocalized between the nitrogen and carbonyl. The balance of stability and reactivity give the opportunity to develop new iminosugars with a linking moiety. Reduction of azidolactone **41** yieldeds the lactam **158**. By selective protections and elongation of carbon chain two iminosugars whit alkynyl terminals were synthesized (iminosugars **189** and **190**). The same procedure was apllyed at azidocarbohydrate analogue **34**, but only occurs reduction.

✓ Iminosugars with a linking moiety are advantageous for their use in alternative synthetic approaches to make cyclocondensations. Alkylnyl sid chains incorporated in the lactam skeleton gave access to “Click Chemistry” funtionalisation. This 1,3-dipolar cyclocondensation has been used to connect different molecules with azide and alkyne extremities.
Copper-catalyzed azide-alkyne cycloaddition (CuAAC) between azidocarbohydrates synthesized in Chapter 2 and alkynyl iminosugars synthesized in Chapter 4. “Click Chemistry” reaction allowed the obtention of 4 new 1,4-disubstituted triazoles (molecules **213**-**216**) and 6 new 1,4-disubstituted bis-triazoles (molecules **218**-**223**). Yields from ‘Click’ reactions increases when polarity decrease.Yields in “Click chemistry” are higher when compounds are connected by a single triazole ring (disubstituted triazoles).



Bibliography

[1] R.W.Binkley, “Carbohydrate Chemistry”, Editorial Board, New York, **1988**, 1st edition.

[2] Rando, R.; Nguyen-Ba, N.; *Drug Discov. Today*, **2000**, 5, 465-476.

[3] McGuigan, C.; Yarnold, C.; Jones, G.; Velazquez, S.; Barucki,H.; Brancale, A., Andrei, G.; Snoeck, R., Clercq, E.; Balzarini, J.; *J. Med. Chem.*, **1999**, 42, 4479-4484.

[4] Ostrowski, S.; Swat, J.; Makosza, M.; *Arkivoc*, **2000**, vi, 905-908.

[5] Hu, E.; Sidler, D.; Dolling, U.; *J. Org. Chem.*, **1998**, 63, 3454-3457.

[6] Stiasni, N.; Kappe, C.; *Arkivoc*, **2002**, viii, 71-79.

[7] Jauk, B.; Pernat, T.; Kappe, C.; Luo, G.; *Molecules*, **2000**, 5, 227-239.

[8] Yu, Y.; Liu, D.; Liu, C.; Luo, G.; *Bioorg. Med. Chem. Lett.*, **2007**, 17, 3508-3510.

[9] Kappe, C.; *Eur. J. Med. Chem*, **2000**, 35, 1043-1052.

[10] Bahekar, S.; Shinde, B.; *Acta Pharm.*, **2003**, 53, 223-229.

[11] Grover, G.; Dzwonczyk, S.; McMullen, D.; Normadin, D.; Parham, C.; Sleph, P.; Moreland, S.; *J. Cardiovas. Pharmacol*, **1995**, 26, 289-294.

[12] Bahekar, S.; Shinde, D.; *Bioorg. Med. Chem. Lett.*, **2004**, 14, 1733-1736.

[13] Brands, M.; Endermann, R.; Gahlmann, R.; Kruger, J.; Raddatz, S.; *Bioorg. Med. Chem. Lett.*, **2003**, 13, 241-245.

[14] Tozkoparan, B.; Ertan, M.; Kelicen, P.; Demirdamar, R.; *Il Farmaco*, **1999**, 54, 588-593.

[15] Stefani, H; Oliveira, C.; Almeida, R.; Pereira, C.; Braga, R.; Cella, R.; Borges, V.; Savegnago, L.; Nogueira, C.; *Eur. J. Med. Chem.*, **2006**, 41, 513-518.

[16] Haggarty, S.; Mayer, T.; Miyamoto, D.; Fathi, R.; King, R.; Mitchison, T.; Schreiber, S.; *Chem. Biol.*, **2000**, 7, 275-286.

[17] Holla, B.; Rao, B.; Sarojini, B.; Akberali, P.; *Eur. J. Med. Chem.*, **2004**, 39, 777-783.

[18] Kumar, D.; Mishra, B.; Roa, V.; *Ind. J. Chem.*, **2006**, 45B, 2325-2329.

[19] Jauk, B.; Belaj, F.; Kappe, C.; *J. Chem. Soc. Perkin Trans. 1*, **1999**, 307-314.

[20] Fernandes, M.; Santos, M.; Vicente, J.; Moreno, A.; Velena, A.; Duburs, G.; Oliveira, C.; *Mitochondrion*, **2003**, 3, 47–59.

[21] Maliga, Z.; Kapoor, T., Mitchison, T.; *Chemistry & Biology*, **2002**, 9, 989–996.

[22] Hurst, E.; Hull, R.; *Med. Pharm. Chem. Gem.*,1961, 3, 215-229.

[23] Dondoni, A.; Massi, A.; *Molecular Diversity*, **2003**, 6, 261-270.

[24] Goldman, S.; Stoltefuss, J.; *Angew. Chem., Int. Ed. Engl.*, **1991**, 30, 1559.

[25] Biginellli, P.; *Chim. Ital.*, **1893**, 23, 360-413.

[26] Phucho, I.; Nongpiur, A.; Tumtin, S.; Nongrum, R.; Nongkhlaw, R.; *Rasayan J. Chem.*, **2009**, 2, 662-676.

[27] Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V.; *J. Org. Chem.*, **2002**, 67, 6979-6994.

[28] Hu, E..; Sidler, D.; Dolling, U.; *J. Org. Chem.*, **1998**, 63, 3454-3457.

[29] Lu, J.; Bai, Y.-J.; Guo, Y.-H.; Wang, Z.-J.; Ma, H.-R.; *Chinese J. Chem.*, **2002**, 20, 681-687.

[30] Lu, J.; Ma, H.; *Synlett*, **2000**, 1, 63-64.

[31] Lu, J.; Bai, Y.; *Synthesis*, **2002**, 12, 466-470.

[32] Ranu, B.; Hajra, A.; Jana, U.; *J. Org. Chem.*, **2000**, 65, 6270-6272.

[33] Fu, N.-Y.; Yuan, Y.-F.; Cao, Z.; Wang, S.; Wang, J.-T.; Peppe, C.; *Tetrahedron*, **2002**, 58, 4801-4807.

[34] Fu, N.-Y.; Yuan, Y.-F.; Pang, M.-L.; Wang, J.-T.; Peppe, C.; *J. Oragnomet. Chem.*, **2003**, 672, 52-570.

[35]Russowsky, D.; Lopes, F.; Silva, V.; Canto, K.; D'Oca, M.; Godoi, M.; *J. Braz. Chem. Soc.*, **2004**, 15, 165-169.

[36] Lu, J.; Bay, Y.; Wang, Z.; Yang, B.; Ma, H.; *Tetrahedron Lett.*, **2000**, 41, 9075-9078.

[37] Bose, D.; Fatima, L.; Mereyala, H.; *J. Org. Chem.*, **2003**, 68, 587-590.

[38] Reddy, Ch.-V.; Mahesh, M.; Raju, P.; Babu, T.; Reddy, V.; *Tetrahedron Lett.*, **2002**, 43, 2657-2659.

[39] Xu, H.; Wang, Y.-G.; *Chinese J. Chem.*, **2003**, 21, 327-331.

[40] Paraskar, A.; Dewkar, G.; Sudalai, A.; *Tetrahedron Lett.*, **2003**, 44, 3305-3308.

[41] Varala, R.; Alam, M..; Adapa, S.; *Synlett*, **2003**, 67-70.

[42] Dondoni, A.; Massi, A.; *Tetrahedron Lett.*, **2001**, 42, 7975-7978.

[43] Ma, Y.; Qian, C.; Wang, L.; Yuang, M.; *J. Org. Chem.*, **2000**, 65, 3864-3868.

[44] Chen, R.-F.; Qian, C.-T.; *Chinese J. Chem.*, **2002**, 20, 427-430.

[45] Peng, J.; Deng, Y.; *Tetrahedron Lett.*, **2001**, 42, 5917–5919.

[46] Sabitha, G.; Reddy, G.; Reddy, C.; Yadav, J.; *Synlett*, **2003**, 858-860.

[47] Kappe, C.; *Biorg. Med Chem. Lett.*, **2000**, 10, 49-51.

[48] Xia, M.; Wang, Y.-G.; *Tetrahedron Lett.*, **2002**, 43, 7703-7705.

[49] Maiti, G.; Kundu, P.; Guin, C.; *Tetrahedron Lett.*, **2003**, 44, 2757-2758.

[50] Yadav, J.; Reddy, B.; Srinivas, R.; Venugopal, C.; Ramalingam, T.; *Synthesis*, **2001**, 1341-1345.

[51] Martínez, S.; Meseguer, M.; Casas, L.; Rodríguez, E.; Molins, E.; Moreno-Manas, M.; Roig, A.; Sabastián, R.; Vallribera, A.; *Tetrahedron*, **2003**, 59, 1553-1556;

[52] Salchi, P.; Dabiri, M.; Zolfigol, M.; Fard, M.; *Tetrahedron Lett.*, **2003**, 44, 2889-2891.

[53] Li, J.-T.; Han, J.-F.; Yang, J.-H.; Li, T.-S.; *Ultrason. Sonochem.*, **2003**, 10, 119-122.

[54] Eynde, J.; Mayenee, A.; *Molecules*, **2003**, 8, 381-391.

[55] Stadler, A.; Yousefi, B.; Dallinger, D.; Walla, P.; Vander , E.; Kaval, N.; Kappe, C.; *Org. Process Res. Dev.*, **2003**, 7, 707-716.

[56] Stadler, A.; Kappe, C.; *J. Comb. Chem.*, **2001**, 3, 624-630.

[57] Kappe, C.; Kumar, D.; Varma, R.; *Synthesis*, **1999**, 12, 1799-1803.

[58] Ramalingam, S.; Kumar, P.; *Synthetic Communications*, **2009**, 39, 1299–1309.

[59] Kappe, C.; *J. Org. Chem.*, **1997**, 62, 7201-7204.

[60] Jung, M.;Trifunovich, I.; Gardiner, J.; Clevenger, G.; *J. Chem. Soc., Chem. Commun.*, **1990**, 84-85.

[61] Nowicki, M.; Tulloch, L.; Worralll, L.; McNae, I.; Hannaert, V.; Michels, P.; Fothergill-Gilmore, L.; Walkinshawb, M.; Turnera, M.; *Bioorg. Med. Chem.*, **2008**, 16, 5050-5061.

[62] Manna, C.; Samanta, S.; Ghosh, S.; Pathak, T.; *Tetrahedron Letters*, **2013**, 54, 3971-3973.

[63] Lei, Z.; Zhang, L.; Zhang, L.; Chen, J.; Min, J.; Zhang, L.; *Nucleic Acids Research*, **2001**, 29, 1470-1475.

[64] Salomons, T.; Fryhle, C.; *Organic Chemeistry*, **2011**, John Wiley & Sons, Asia, pag. 955, **2011**.

[65] Dondoni, A.; Massi, A.; Sabbatini, S.; *Tetrahedron Letters*, **2001**, 42, 4495-4497.

[66] Ducatti, D.; Massi, A.; Noseda, M.; Duarteb, M.; Dondoni, A.; *Org. Biomol. Chem.*, **2009**,7, 1980-1986.

[67] Figueiredo, A.; Ismael, M.; Pinheiro, J.; Silva, A.; Justino, J.; Silva, F.; Goulart, M.; Mira, D.; Araújo, M.; Campoy, R.; Rauter, A.; *Carbohydrate Research*, **2012**, 347, 47–54.

[68] Bergmann, M.; Zervas, L.; *Chem. Ber.*, **1931**, 64B, 975.

[69] Silva, D.; Wang, H.; Allanson, N.; Jain, R.; Sofia, M.; *J. Org. Chem.*, **1999**, 64, 5926-5929.

[70] Myszka, H.; Bednarczyk, D.; Najder, M.; Kaca, W.; *Carbohydrate Research*, **2003**, 338, 133-141

[71] Chauvière, G.; Bouteille, B.; Enanga, B.; Albuquerque, C.; Croft, S.; Dumas, M.; Périé, J.; *J. Med. Chem.*, **2003**, 46, 427-440.

[72] Becker, C.; Hoben, C.; Kunza, H.; *Adv. Synth. Catal.*, **2007**, 349, 417-424.

[73] Ran, C.; Pantazopoulos, P.; Medarova, Z., Moore, A.; *Angew. Chem. Int. Ed.*, **2007**, 46, 8998 –9001.

[74] Mensah, E.; Nguyen, H.; *J. AM. CHEM. SOC.*, **2009**, 131, 87.78-8780.

[75] Krishnamurthy, V.; Dougherty, A.; Kamat, M.; Song, X.; Cummings, R.; Chaikof, E.; *Carbohydrate Research*, **2010**, 345, 1541-1547.

[76] Bedekar, A.; Naik, A.; Pise, A.; *Asian Journal of Chemistry*, **2009**, 21, 6661-6666.

[77] Sastre, J.; Molina, J.; Olea, D.; Romero-Avila, C.; *CAN. J. CHEM.*, **1988**, 66, 2975-2980.

[78] Ferreira, S.; Sodero, A.; Cardoso, M.; Lima, E.; Kaiser, C.; Silva, F.; Ferreira, V.; *J. Med. Chem.*, **2010**, 53, 2364-2375.

[79] Rauter, A.; Ramôa-Ribeiro, F.; Fernandes, A.; Figueiredo, A.; *Tetrahedron*, **1995**, 51, 6529-6540.

[80] Stevens, J.; *Chem. Commun.*, **1969**, 1140-1141.

[81] Hughes, N.; Speakman, P., *Carbohydr. Res.*, **1965**, 1, 171-175.

[82] Schmidt, O.; *Methods in Carbohydr. Chem.*, **1963**, 2, 318-320.

[83] Nair, P.; Shah, P.; Sreenivasan, B.; *Sturch*, **1981**, 33,384-387.

[84] Nikiforov, V.; Zarutsski, V.; Chapanov, I.; Vasil'eva, I.; Dolgushina, N.; *Khim.-Farm Zh.*, **1982**, 16, 1102-1103.

[85] Morgenlie, S.; *Actu Chem. Stand.*, **1973**, 27, 3609-3610.

[86] Morgenlie, S.; *Acta Chem. Scund.Ser. B*, **1975**, 29, 367-372.

[87] Kartha, K.; *Tetrahedron Lett.*, **1986**, 27, 3415-3416.

[88] Singh, P.; Gharia, M.; Dasgupta, F.; Stivastava, H.; *Tetrahedron Lett.*, **1977**, 439-440.

[89] Lal, B.; Gidwani, R.; Rupp, R.; *Synthesis*, **1989**, 711-713.

[90] Fanton, E., Gelas, J., Horton, D.; *J. Chem. Soc. Chem. Commun.*, **1980**, 21-22.

[91] Fanton, E.; Gelas, J.; Horton, D.; *J. Org. Chem.*, **1981**, 46, 4057-4060.

[92] Cornier, J.; Nothias, T.; *Biofutur*, **1989**, 51-56.

[93] Brock, E.; Davies, S.; Lee, J.; Roberts, P.; Thomson, J.; *Org. Lett.*, **2011**, 13, 1594–1597.

[94] Palmer, A.; Jäger, V.; *Eur. J. Org. Chem.*, **2001**, 1293-1308.

[95] Barnett, E.; *Adv. Carbohydr. Chem.*, **1967**, 22, 177.

[96] Szarek, W.; *Adv. Carbohydr. Chem.*, **1973**, 28, 225.

[97] Tipson, R.; Cohen, A.; *Carbohydr. Res.*, **1965**, 1, 338.

[98] Liu, Z.; Classon, B.; *J. Org. Chem.*, **1990**, 55, 4273.

[99] Rondot, B.; Durand, T.; Rossi, J-C.; Rollin, P.; *Carbohydr. Res.*, **1994**, 261, 149.

[100] Izquierdo, I.; Plaza, M.; Yañez, V.; *Tetrahedron*, **2007**, 63, 1440–1447.

[101] Garegg, P.; Samuelsson, B.; *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2866-2869.

[102] Collins, P.; Ferrier, R.; *"Monosaccharides: their chemistry and their roles in natural products"*; John Wiley & Sons; 1st edition; **1995**.

[103] Garegg, P.; Samuelsson, B.; *J. Chem. Soc., Chem. Commun.*, **1979**, 978-980.

[104] Garegg, P.; Samuelsson, B.; *Synthesis*, **1979**, 469, 813.

[105] Park, S.; *Bull. Korean Chem. Soc.*, **2003**, 24, 253-255.

[106] Sheradsky, T.; "Chemistry of the Azido Group", 1971, Patai, S., Ed.; Inter Science, New York, p 331.

[107] Schleiss, J.; Rollin, P.; Tatibouet, A.; *Angew. Chem.*, **2010**, 122, 587–590.

[108] Garegg, P.; Samuelsson, B.; *J. Chem. Soc., Chem. Commun.*, **1979**, 978-980.

[109] Garegg, P.; Samuelsson, B.; *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2866-2869.

[110] Ferreira, S.; Sodero, A.; Cardoso, M.;Lima, E.; Kaiser, C. ; Silva, F.; Ferreira, V.; *J. Med. Chem.*, **2010**, 53, 2364-2375.

[111]Dötz, K.; Klumpe, M.; Nieger, M.; *Chem. Eur. J.*, **1999**, 5, 691-699.

[112] Girniene, J.; Gueyrard, D.; Tatibouët, A.; Sackus, A.; Rollin, P.; *Tetrahedron Letters*, **2001**, 42, 2977–2980.

[113] Girniene, J.; Tatibouët, A.; Sackus, A.; Yang, J.; Holman, G.; Rollin, P; *Carbohydrate Research*, **2003**, 338, 711–719.

[114] Girniene, J.; Apremont, G.; Tatibouët, A.; Sackus, A.; Rollin, P.; *Tetrahedron*, **2004**, 60, 2609–2619.

[115] Silva, S.; Sylla, B.; Suzenet, F.; Tatibouët, A.; Rauter, A.;Rollin, P.; *Org. Lett.*, **2008**, 10, 853-856.

[116] Fernández, J.; Ortiz, C.; Fuentes, J.; *J. Org. Chem.*, **1993**, 58, 5192-5199.

[117] Bolaños, J.; Zafra, E.; Lopez, O.; Robina, I.; Fuentes, J.; *Tetrahedron: Asymm.*, **1999**, 10, 3011-3023.

[118] Gasch, C.; Pradera, A.; Salameh, B.; Molina, J.; Fuentes, J.; *Tetrahedron: Asymm.*, **2000**, 11, 435-452

[119] Bolaños, J.; López, A.; Mota, J.; *Carbohydr. Res.*, **1990**, 199, 239-242.

[120] Mota, J.; Blanco, J.; Ortiz, C.; Fernández, J.; *Carbohydr. Res.*, **1994**, 257, 127-135.

[121] Gasch, C.; Pradera, A.; Salameh, B.; Molina, J.; Fuentes, J.; *Tetrahedron: Asymm.*, **2001**, 12, 1267-1277.

[122] Leoni, O.; Bernardi, R.; Gueyrard, D.; Rollin, P.; Palmieri, S.; *Tetrahedron: Asymm.*, **1999**, 10, 4775-4780.

[123] Blanco, J.; Pérez, V.; Mellet, C.; Fuentes, J.; Fernandez, J.; Arribas, J.; Canada, F.; *J. Chem. Soc.*, *Chem. Commun.*, **1997**, 1960-1970.

[124] Ranganathan, R.; *Tetrahedron Lett.*, **1975**, 13, 1185-1188.

[125] Ranganathan, R.; *Tetrahedron Lett.*, **1977**, 15, 1291-1294.

[126] Rayner, B.; Tapiero, C., Imbach J.; *Heterocycl. Chem.*, **1982**, 19, 593-596.

[127] Gosselin, G.; Bergogne, M.; Rudder, J.; Clerq, E.; Imbach, J.; *Med. Chem.*, **1986**, 29, 203-213.

[128] Grouiller, A.; Mackenzie, G.; Najib, B.; Shaw, G.; Ewig, D.; J. *Chem. Soc., Chem. Commun.*, **1988**, 671-672.

[129] Buchanan, J.; McGaig, A.; Wightman, R.; *J. Chem. Soc. Perkin Trans. 1*, **1990**, 955-963.

[130] Girniene, J.; Gueyrard, D.; Tatibouët, A.; Sackus, A.; Rollin, P.; *Tetrahedron Lett.*, **2001**, 42, 2977-2980.

[131] Zemplen, G.; Gerecs, A.; Rados, M.; *Ber.*, **1936**, 39, 748-754.

[132] Zemplen, G.; Gerecs, A.; Illés, E.; *Ber.*, **1938**, 71, 590-596.

[133] Bromund, W.; Herbst, R., *J. Org. Chem.*, **1945**, 10, 267-276.

[134] Wickstrom, A.; Wold, J.; *Acta Chem. Scand.*, **1959**, 13, 1129-1136.

[135] Jochims, J.; Seeliger, A.; Taigel, G.; **Chem. Ber.**, **1967**, 100, 845-854.

[136] Leconte, N.; Silva, S.; Tatibouët, A.; Rauter, A.; Rollin, P.; *Synlett*, **2006**, 301-305.

[137] Jochims, J.; Seeliger, A.; Taigel, G.; *Chem. Ber.*, **1967**, 100, 845-854.

[138] Tatibouët, A.; Lawrence, S.; Rollin, P.; Holmanb, H.; *Synlett*, **2004**, 11, 1945-1948.

[139] Lichtenthaler, F.; Klotz, J.; Flath, F.; *Liebigs Ann.*, **1995**, 2069-2080.

[140] Kovács, J.; Pintér, I.; Albeln, D., Kopf, J.; Köll, P.; *Carbohyrate Res.*, **1994**, 257, 97-106.

[141] Kovács, J.; Pintér, I.; Köll, P.; *Carbohyrate Research*, **1995**, 272, 255-262.

[142] Simão, A.; Rousseau, J.; Silva, S.; Rauter, A.; Tatibouët, A.; Rollin, P.; "*Carbohydrate Chemistry. Chemical and Biological Approaches*", RSC Publishing: Dorchester, U.K., pp 127–172, **2009**, 35 edition.

[143] Ho, T.; *Chem. Rev.*, **1975**, 75, 1–20.

[144] Silva, S.; Simão, A.; Tatibouët, A.; Rollin, P.; Rauter, A.; *Tetrahedron Lett.*, **2008**, 49, 682–686.

[145] Tardy, S.; Tatibouët, A.; Rollin, P.; Dujardin, G.; *Synlett*, **2006**, 108, 1425–1427.

[146] Girniene, J.; Tardy, S.; Tatibouët, A.; Sackus, A.; Rollin, P.; *Tetrahedron Lett.*, **2004**, 45, 6443–6446.

[147] Gueyrard, D.; Leoni, O.; Palmieri, S.; Rollin, P.; *Tetrahedron: Asymmetry*, **2001**, 12, 337–340.

[148] Gueyrard, D.; Grumel, V.; Leoni, O.; Palmieri, S.; Rollin, P.; *Heterocycles*, **2000**, 52, 827–843.

[149] Davidson, R., Byrd, G.; White, E.; Margolis, S.; Coxon, B; *Magn. Res. Chem.*, **1986**, 24, 929-937.

[150] Meszaros, P.; Pinter, I.; Kovacs, J.; Toth, G.; *Carbohydr. Res.*, **1994**, 258, 287-291.
[151] Gueyrard, D.; Grumel, V.; Leoni, O.; Palmieri, S.; Rollin, P.; *Heterocycles*, **2000**, 52, 827-843
[152] Kovács, J.; Pintér, I.; *Carbohydrate Res.*, **1991**, 210, 155-166.
[153] Durantel, D.; Alotte, C.; Zoulim, F.; *Curr. Opin. Invest. Drugs*, **2007**, 8, 125–129.
[154] Greimel, P.; Spreitz, J.; Stütz, A.; Wrodnigg, T.; *Curr. Top. Med. Chem.*, **2003**, 3, 513–523.
[155] Wrodnigg, T.; Steiner, A.; Ueberbacher, B.; *Anti-Cancer Agents Med. Chem.*, **2008**, 8, 77–85.
[156] Sun, J.; Zhu, M..; Wang, S.; Miao, S.; Xie, Y.; Wang, J.; *Phytomedicine*, **2007**, 14, 353–359.
[157] Paulsen, H.; Brockhausen, I.; *Glycoconjugate J.*, **2001**, 18, 867–870.
[158] Anzeveno, P.; Creemer, L.; Daniel, J.; King, C.; Liu, P.; *J. Org. Chem.*,**1989**, 54, 2539–2542.
[159] Balfour, J.; Tavish, D.; *Drugs*, **1993**, 46, 1025–1054.
[160] Tsujino, D; Nishimura, R; Taki, K.; Morimoto, A.; Tajima, N.; Utsunomiya, K.; *Diabetes Technol. Ther.*, **2011**, 13, 303–308.
[161] Cren, S.; Gurcha, S.; Blake, A.; Besra, G.; Thomas, N.; *Org. Biomol. Chem.*, **2004**, 2, 2418–2420.
[162] Wrodnigg, T.; Sprenger, F.; Mini-Rev. Med. Chem. 2004, 4, 437–459.
[163] Benito, J.; García Fernández, J.; Ortiz, C., *Expert Opin. Ther. Pat.*, **2011**, 21, 885–903.
[164] Parenti, G.; *EMBO Mol. Med.*, **2009**, 1, 268–279.
[165] Wennekes, T.; Berg, R.; Boot, R.; Marel, G.; Overkleeft, H.; Aerts, J.; *Angew. Chem., Int. Ed.*, **2009**, 8848–8869.
[166] Fan, J.*; Biol. Chem.*, **2007**, 389, 1–11.
[167] Futerman, A.; Meer, G.; *Nat. Rev. Mol. Cell Biol.*, **2004**, 5, 554–565.
[168] Meikle, P.; Fietz, M.; Hopwood, J.; *Expert. Rev. Mol. Diagn.*, **2004**, 4, 677–691.
[169] Alonzi, D.; Butters, T.; *Chimia*, **2011**, 65, 35–39.
[170] Butters, T.; Dwek, R.; Platt, F.,
Chem. Rev. 2000, 100, 4683–4696.
[171] Blanco, J.;Pérez, V.; Mellet, C.; Fuentes, J.; García Fernández, J.;Arribas, J.; Cañada, F.; Chem. Commun., 1997, 1969-1970.
[172] Compain, P.; Martin, O.; "*Iminosugars: from synthesis to therapeutical applications*", Wiley, 2007.
[173] Asano, N.; *Glycobiology*, **2003**, 13, 93R-104R.
[174] Lillelund, V.; Jensen, H.; Liang, X.; Bols, M.; *Chem. Rev.*, **2002**, 102, 515-553.
[175] Heightman, T.; Vasella, A.; *Angew. Chem.*, **1999**, 111, 794.
[176] Heightman, T.; Vasella, A.; *Angew. Chem. Int. Ed.*, **1999**, 38, 750-770.
[177] Ermert, P., Vasella, A., Weber, M., Rupitz, K.; Withers, S.; *Carbohydr. Res.*, **1993**, 250, 113-128.
[178] Pérez, V.; García Moreno, M.; Mellet, C.; Fuentes,J.; Arribas, J., Cañada, F.; Fernández, J.; *J. Org. Chem.*, **2000**, 65, 136-143.

[179] Pérez, P.; García-Moreno, M.; Mellet, C.; Fernández, J.; *Eur. J. Org. Chem.*, **2005**, 2903-2913.

[180] Aguilar, M.; Pérez, P.; García-Moreno, M.; Mellet, C.; Fernández, J.; *J. Org. Chem.*, **2008**, 73, 1995–1998;

[181] García-Moreno, M.; Lucena, D.; Mellet, C.; Fernández, J.; *J. Org. Chem.*, **2004**, 69, 3578-3581.

[182] García-Moreno, M.; Benito, J.; Mellet, C.; Fernández, J.; *J. Org. Chem.*, **2001**, 66, 7604-7614.

[183] García-Moreno, M.; Mellet, C.; Fernández, J.; *Tetrahedron: Asymmetry*, **1999**, 10, 4271-4275.

[184] Belfita, M.; García-Moreno, M.; Mellet, C.; Fernández, J.; Wadouachi, A.; *Bioorg. Med. Chem. Lett.*, **2008**, 18, 2805–2808.

[185] Aguilar-Moncayo, M.; Mellet, C.; Fernández, J.; García-Moreno, M.; *J. Org. Chem.*, **2009**, 74, 3595–3598.

[186] Sánchez-Fernández, E.; Rízquez-Cuadro, R.; Mellet, C.; Fernández, J.; Nieto, P.; Angulo, J.; *Chem. Eur. J.*, **2012**, 18, 8527–8539

[187] Sánchez-Fernández, E.; Rísquez-Cuadro, R.; Aguilar-Moncayo, M.; García-Moreno, M.; Mellet, C.; Fernández, J.; *Org. Lett.*, **2009**, 11, 3306–3309

[188] Sánchez-Fernández, E.; Rísquez-Cuadro, R.; Chasseraud, M.; Ahidouch, A.; Mellet, C., Ouadid-Ahidouch, H.; Fernandez, J.; Chem. Commun., 2010, 46, 5328–5330.

[189] Luan, Z.; Higaki, K., Aguilar-Moncayo, M.; Ninomiya, H., Ohno, K., García-Moreno, M., Mellet, C., Fernández, J.; Suzuki, Y.; *ChemBioChem*, **2009**, 10, 2780–2792.

[190] Luan, Z.; Higaki, K.; Aguilar-Moncayo, M.; Li, L.; Ninomiya, H.; Nanba, E.; Ohno, K.; García-Moreno, M.; Mellet, C.; Fernández, J.; Suzuki, Y.; *ChemBioChem*, **2010**, 11, 2453–2464.

[191] Aguilar-Moncayo, M.; Takai, T.; Higaki, K.; Mena-Barragán, T.; Hirano, Y., Yura, K., Li, L.; Yu, Y.; Ninomiya, H., Garcıía-Moreno, M.; Ishii, S.; Sakakibara, Y.; Ohno, K., Nanba, E.; Mellet, C.; Fernández, J.; Suzuki, Y.; *Chem. Commun.*, **2012**, 48, 6514–6516.

[192] Tiscornia, G.; Vivas, E.; Matalonga, L.; Berniakovich, I.; Monasterio, M.; Argaiz, C.; Gort, L.; González, F.; Mellet, C.; Fernández, J.; Ribes, A.; Veiga, A.; Belmonte, J.; *Human Molecular Genetics*, **2013**, 22, 633–645.

[193] Aguilar, M.; Pérez, P.; García-Moreno, M.; Mellet, C.; Fernández, J.; *J. Org. Chem.*, **2008**, 73, 1995–1998;

[194] García-Moreno, M.; Lucena, D.; Mellet, C.; Fernández, J.; *J. Org. Chem.*, **2004**, 69, 3578-3581.

[195] García-Moreno, M.; Benito, J.; Mellet, C.; Fernández, J.; *J. Org. Chem.*, **2001**, 66, 7604-7614.

[196] García-Moreno, M.; Mellet, C.; Fernández, J.; *Tetrahedron: Asymmetry*, **1999**, 10, 4271-4275.

[197] Belfita, M.; García-Moreno, M.; Mellet, C.; Fernández, J.; Wadouachi, A.; *Bioorg. Med. Chem. Lett.*, **2008**, 18, 2805–2808.

[198] Aguilar-Moncayo, M.; Mellet, C.; Fernández, J.; García-Moreno, M.; *J. Org. Chem.*, **2009**, 74, 3595–3598.

[199] Sánchez-Fernández, E.; Rízquez-Cuadro, R.; Mellet, C.; Fernández, J.; Nieto, P.; Angulo, J.; *Chem. Eur. J.*, **2012**, 18, 8527–8539

[200] Sánchez-Fernández, E.; Rísquez-Cuadro, R.; Aguilar-Moncayo, M.; García-Moreno, M.; Mellet, C.; Fernández, J.; *Org. Lett.*, **2009**, 11, 3306–3309

[201] Brumshtein, B.; Moncayo, M.; García-Moreno, M.; Mellet, C.; Fernández, J.; Silman, I.; Shaaltiel, Y.; Aviezer, D.; Sussman, J.; Futerman, A.; *ChemBioChem*, **2009**, 10, 1480–1485.

[202]Moncayo, M.; Gloster, T.; Turkenburg, J.; García-Moreno, M.; Mellet, C.; Davies, G.; Fernández, J.; *Org. Biomol. Chem.*, **2009**, 7, 2738–2747.

[203] Aguilar, M.; Gloster, T.; García-Moreno, M.; Mellet, C.; Davies, G.; Llebaria, A.; Casas, J.; Egido-Gabás, M.; Fernández, J.; *ChemBioChem*, **2008**, 9, 2612–2618.

[204] Silva, S.; Sánchez-Fernández, E.; Mellet, C.; Tatibouët, A.; Rauter, A.; Rollin, P.; *Eur. J. Org. Chem.*, **2013**, 7941–7951.

[205] Lin, F.; Hoyt, H.; Halbeek, H.; Bergman, R.; Bertozzi, C.; *J. Am. Chem. Soc*, **2005**, 127, 2686-2695.

[206] Tian, W.; Wang, Y.; *J. Org. Chem.*, **2004**, 69, 4299.

[207] Lin, F.; Hoyt, H.; Halbeek, H.; Bergman, R.; Bertozzi, C.; *J. Am. Chem. Soc.*, **2005**, 127, 2686.

[208] Bashyal, B.; Chow, H.; Fleet, G.; *Tetrahedron Lett.*, **1986**, 27, 3205-3208.

[209] Bashyal, B.; Chow, H.; Fellows, F., Fleet, G.; *Tetrahedron*, **1987**, 43, 415-422.

[210] Fleet, G.; Fellows, F.; Smith, P.; *Tetrahedron*, **1987**, 43, 979-990.

[211] Fleet, G.; Ramsden, N.; Witty, D.; *Tetrahedron*, **1989**, 45, 327-336.

[212] Bernotas, R.; Ganem, B.; *Tetrahedron Lett.*, **1985**, 26, 4981-4982

[213] Tong, M.; Blumenthal, E.; Ganem, B.; *Tetrahedron Lett.*, **1990**, 31, 1683-1684.

[214] Park, K.; Yoon, Y.; Lee, S.; *J. Chem. Soc. Perkin Trans.1*, **1994**, 2621-2623.

[215] Dötz, K.; Klumpe, M.; Nieger, M.; *Chem. Eur. J.*, **1999**, 5,691-699.

[216] Diot, J.; Moreno, I.; Gouin, S.; Mellet, C.; Hauptc, K.; Kovensky, J.; *Org. Biomol. Chem.*, **2009**, 7, 357–363.

[217] Senthilkumar, S.; Prasad, S.; Kumar, P.; Baskaran, S.; *Chem. Commun.*, **2014**, 50, 1549-1551.

[218] Kovács, J.; Pintér, I.; Messmer, A.; *Carbohydrate Research*, **1987**, 166, 101-111.

[219] Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, K.; *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596-2599.

[220] Kolb, H.; Finn, M.; Sharpless, K.; *Ang. Chem .Int. Ed.*, **2001**, 40, 2004-2021.

[221] Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, K.*; Angew. Chem. Int. Ed.*, ***2002***, 41, 2596-2599

[222] Himo, F., Lovell, T., Hilgraf, R.; Rostovtsev, V., Noodleman, L., Sharpless, K., Fokin, V.; *J. Am. Chem. Soc.*, **2005**, 127, 210-216.

[223] Kolb, H.; Sharpless, K.; *Drug Discovry Today*, **2003**, 8, 1128-1137.

[224] Bock, V.; Hiemstra, H.; Maarseveen, J.; *Eur. J. Org. Chem.*, **2006**, 51-68.

[225] Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V.; *Ang. Chem. Int. Ed.*, **2005**, 44, 5188-5240.

[226] Smith, P.; “*Open chain nitrogen compounds*”, New YorK, Vol. 11, **1966**.

[227] Sahu, S.; Panda, S.; Sadafule, D.; Kumbhar, C.; Kulkarni, S.; Thakur, J.; *Polymer-Degradation and Stability*, **1998**, 62, 495-500.

[228] Abbenante, G.; Le, G.; Fairlie, D.; *Chem. Commun.*, **2007**, 4501-4503.

[229] Li, C.; Finn, M.; *Polym. Sci Part A: Polym. Chem.*, **2006**, 44, 5513-5518.

[230] Abboud, J.; Foces-Foces, C.; Natorio, R.; Trifonov, R.; Volovodenko, A.; Ostrovskii, V.; Alkorta, I.; Elguero, J.; *Eur .J. Org. Chem.*, **2001**, 3013-3024.

[231] Isloor, M.; Kalluraya, B.; Shetty, P., *Eur. J. Med. Chem.*, **2009**, 44, 3784-3787.

[232] Kumar, R.; Nair, R.; Dhiman, S.; Sharma, J.; Prakash, O.; *Eur. J. Med. Chem.*, **2009**, 44, 2260-2264.

[233] Chabchoub, F.; Messaâd, M.; Mansour, H.; Ghdira, L.; Salem, M., *Eur. J. Med. Chem.*, **2007**, 42, 715-718.

[234] Savini, L.; Chiasserini, L.; Pellerano, C.; Filippelli, W.; Falcone, G.; *Il Farmaco*, **2001**, 56, 939-945.

[235] Johnson, T.; Martin, T.; Mann, R.; Pobanz, M.; *Bioorg. Med. Chem.*, **2009**, 17, 4230-4240.

[236] Bock, V.; Hiemstra, H.; Maarseveen, J.; *Eur. J. Org. Chem.*, **2006**, 51-68.

[237] Link, A.; Tirrell, D.; *J. Am. Chem. Soc.*, **2003**, 125, 11164-11165.

[238] Horne, W.; Stout, C.; Ghadiri, M.; *J. Am. Chem. Soc.*, **2003**, 125, 9372-9376.

[239] Horne, W.; Yadav, M.; Stout, C.; Ghadiri, M.; *J. Am. Chem. Soc.*, **2004**, 126, 15366-15367.

[240] Demko, Z.; Sharpless, K.; *Org. Lett.*, **2002**, 4, 2525-2527.

[241] Osterman, I.; Ustinov, A.; Evdokimov, D.; Korshun, V.; Sergiev, P.; Serebryakova, M.; Demina, I.; Galyamina, M.; Govorun, V.; Dontsova, O.; *Proteomics*, **2013**, 13, 17-21.

[242] Cox, C.; Tietz, J.; Sokolowski, K.; Melby, J.; Doroghazi, J.; Mitchell, D.; *ACS Chemical Biology*, **2014**.

[243] Floros, M.; Leão, A.; Narine, S.; *BioMed Research International*, **2014**, 1-14.

[244] London, G.; Chen, K.; Carroll, G.; Feringa, B.; *Chemistry – A European Journol*, **2013**, 19, 10690-10697.

[245] Moses, J.; Moorhouse, A.; *Chem. Soc. Rev.*, 2007, 36, 1249–1262.

[246] Lutz, J-F; Zarafshani, Z.; *Advanced Drug Delivery Reviews*, **2008**, 60, 958–970.

[247]Echeverri, F., Rossini, C.; “Productos naturales contra parasitos externos del gando bobino y ovino, tales como mosca de los cuernos y garrapatas”, pag 70-87, Ediciones de la Universidad de Magallanes.

[248]Santos, C.; Voge, F.; *Revista Portuguesa de Ciências Veterinárias*, **2012**, 111, 121-124.

[249] Beugnet, F.; Franc, M.; *Trends in Parasitology*, **2012**, 28, 267-279.

[250] Vivas, R.; Cogollo, L.; Aguilar, J.; Chi, M.; Martinez, I.; Miller, R.; Li, A.; León, A.; Guerrero, F.; Klafke, G; *Braz. J. Vet. Parasitol.*, **2014**, 23, 113-122.

[251] Guerrero, F.; Lovis, L.; Martins, J.; *Rev. Bras. Parasitol. Vet.*, **2012**, 21, 1-6.

[252] Cruz, C.; Cairrão, E.; Silvestre, S.; Breitenfeld, L.; Almeida, P.; Queiroz, J.A.; *PLoS One*, **2011**, 6, e27078
[253] Freshney, R.; "Cytotoxicity In Culture of Animal Cells: A Manual of Basic Technique"; John Wiley & Sons: Hoboken, NJ, **2005**; Chapter 22, pp 359-373.
[254] Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P.; *Chem. Rev.*, **2010**, 110, 3337–3370.
[255] Pan, X.; Wang, C.; Wang, F.; Li, P.; Hu, Z.; Shan, Y.; Zhang, J.; *Curr. Med. Chem.*, **2011**, 18, 4538-4556.
[256] Stallforth, P.; Lepenies, B.; Adibekian, A.; Seeberger, P.; *J. Med. Chem.*, **2009**, 52, 5561-5577.
[257] Kharb, R.; Sharma, P.; Yar, M.; *J. Enzyme Inhib. Med. Chem.*, **2011**, 26, 1-21.

Publications

Posters

Oxopyrimidines and thioxopyrimidines as potentialacetylcholinesterase inhibitors and antitumoral molecules; M. Domingues, M. I. Ismael, J. A. Figueiredo, M. Gomes, M. Lucas, M. Schuler, A. Tatibouët, S. Silvestre, A. P. Duarte; 19th European Symposium on Organic Chemistry (12 – 16 July 2015); University of Lisboa, Lisboa, Portugal.

Iminosugars fused with 1,3-oxazolidin-2-ones as glycosidase inhibitors; M. Domingues, M. I. Ismael, J. A. Figueiredo, M. Gomes, M. Lucas, M. Schuler, A. Tatibouët, S. Silvestre, A. P. Duarte; 19th European Symposium on Organic Chemistry (12 – 16 July 2015); University of Lisboa, Lisboa, Portugal.

Click Chemistry: new approach for the synthesis of Iminosugars derivatives; M. Domingues, M. I. Ismael, J. A. Figueiredo, Marie Schuler, Arnaud Tatibouët; IX Symposium do CICS-UBI (30 - 01 July 2014); University of Beira Interior, Covilhã, Portugal.

Application of Click Chemistry Reaction in Iminosugars Derivatives; M. Domingues, M. I. Ismael, J. A. Figueiredo, Marie Schuler, Arnaud Tatibouët; 10º Encontro Nacional de Química Orgânica (04 – 06 September 2013); Pharmacy Faculty of the University of Lisbon, Lisbon, Portugal.

Synthesis of sugar derivatives by click chemistry; M. Domingues, M. I. Ismael, J. A. Figueiredo; 23rd National Meeting of the Portuguese Chemistry Society (12 - 14 June 2013); University of Aveiro, Aveiro, Portugal.

Synthesis of iminosugars; M. Domingues, M. I. Ismael, J. A.Figueiredo, A. Tatibouët, M. Schuler; ESOC 2013 (07 – 12 July 2013); Marseille, France.

Synthesis of Biginelli sugar derivatives; M. Domingues, M. I. Ismael, J. A. Figueiredo, M. Schuler, A. Tatibouët; 6th Spanish-Portuguese-Japanese Organic Chemistry Symposium (18 – 20 July 2012); Faculty of Sciences, University of Lisbon, Lisbon, Portugal.

Synthesis of Dihydropyrimidinones from sugar derivatives; M. Domingues, M. I. Ismael, J. A. Figueiredo, A. Tatibouët, M. Schuler; 26th International Carbohydrate Symposium (ICS 2012 – 22 – 27 July 2012); Madrid, Spain.

Oral Communications

Iminosugars fused with 1,3-oxazolidin-2-one ring as potential glycosidase and acetylcholinesterase inhibitors; M. Domingues, M. I. Ismael, J. A. Figueiredo, S. Silvestre, M. Schuler, A. Tatibouet; 11th International Meeting of the Portuguese Carbohydrate Group - 6th Iberian Carbohydrate Meeting (06 – 10 September 2015), Polytechnic Institute of Viseu, Viseu, Portugal.

Application de la chimie "click" aux iminosucres; M. Domingues, M. I. Ismael, J. A. Figueiredo, Marie Schuler, Arnaud Tatibouët; Journées Scientifiques de la Section Régionale Centre- Ouest de la Société Chimique de France à Limoges (29 - 31 January 2014); Technopôle ESTER de Limoges, Limoges, France.

Synthesis and characterization of iminosugars; M. Domingues, M. I. Ismael, J. A. Figueiredo, A. Tatibouët, M. Schuler; 4th Symposium of Materials and Sustainable Processes, 07 December 2012, University of Beira Interior, Covilhã, Portugal.