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Synthesis and characterization of organotriethoxysilanes based on carbohydrates for functional mesoporous organosilica hybrids

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Aos meus pais e à minha irmã

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Abstract

Cancer is the second leading cause of death worldwide. Conventional therapies are characterized by clinical inefficiency and serious side effects, like high toxicity in healthy tissues. For these reasons, the investigation for more effective therapies increased in the recent years. With the progress in the area of medicinal chemistry, we read headlines almost every day about potential promising new drugs on the horizon for diseases like cancer, however, these drugs present poor stability, high toxicity, small half-lives, aggregation tendency and the transport is hindered by biobarriers such as the blood brain barrier or cell membranes. To solve these problems, researchers from different areas, such as biology, materials science, pharmacy, medicinal chemistry and chemistry, have oriented their work with the aim to develop more efficient drug delivery systems. In the past decades, the advances of nanotechnology have facilitated the development of several nanovehicles as drug delivery systems, as an advantage in the field of Medicinal Chemistry. Among the nanomaterials proposed, hybrid mesoporous organosilicas have aroused significant interest as candidates for nanomedical applications.

The aim of this work was to synthesize mono-organosilanes precursors based on carbohydrates derivatives. The use of carbohydrate as organic part is an innovative work with great potential to prepare anti-tumoral supports for drug delivery, once carbohydrates are involved in numerous important biological processes linked to cancer. In the first part of the present work, was synthesised the carbohydrates derivates, from D-glucose, D-ribose, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and methyl-α-D-glucopyranoside. In the second part of the work, was prepared the organotriethoxysilanes involving a cross-link between the carbohydrate derivatives and 3-(triethoxysilyl)propyl isocyanate. Then, these organotriethoxysilanes will be used to functionalized mesoporous hybrids organosilica, with the aim of achieve carrier systems for anti-tumoral drug delivery. The functionalities into the mesoporous materials will interact with potential new drugs or others already in the market, and release them to the specific target sites, giving new and better ways to hit the disease target.

Keywords

Carbohydrate derivative, organotriethoxysilanes, mesoporous hybrids organosilica, biomedical applications.

Resumo alargado

Atualmente, o cancro é segunda maior causa de morte no mundo, e a as terapias ditas convencionais, como por exemplo, a quimioterapia, trazem diversos efeitos adversos para o paciente, nomeadamente a elevada toxicidade nos tecidos saudáveis. Este tipo de terapias é ineficaz porque os métodos utilizados não são seletivos para o alvo pretendido. Posto isto, e devido à taxa limitada de sucesso e às consequências não desejadas das terapias convencionais, a procura de novas alternativas, é primordial, nomeadamente a procura de terapêuticas eficazes e seletivas, que promovam uma libertação controlada e uma entrega precisa no sítio-alvo biológico. Estes são os principais objetivos na área da química medicinal.

Os avanços na nanotecnologia têm facilitado o desenvolvimento de vários nano-veículos como sistemas de entrega de fármacos, o que se tornou numa vantagem na área da química medicinal. Os materiais híbridos mesoporosos de sílica têm atraído muita atenção devido as suas propriedades únicas, incluindo uma elevada área de superfície especifica, um grande volume de poro, tamanho do poro ajustável, natureza não tóxica, pouca reatividade para quelar grupos presentes no sistema, estabilidade química e a possibilidade de modificação da superfície do poro. A funcionalização destes materiais com precursores organotrietoxisilanos, permite a obtenção de materiais híbridos multifuncionais com características sem precedentes e combinações únicas, que permitiram a interação com fármacos e a sua libertação em locais específicos a uma velocidade controlada.

A utilização de hidratos de carbono como componente orgânica na síntese deste tipo de precursores é um trabalho inovador e pode ser uma vantagem na medida em que, são considerados os produtos naturais funcionalmente mais versáteis e podem originar glicoconjugados com grande importância em diversas áreas, particularmente na indústria farmacêutica, uma vez que vez que estão envolvidos em inúmeros processos biológicos, nomeadamente no reconhecimento da superfície celular. Consequentemente, a química medicinal dos hidratos de carbono tem sido incrivelmente desenvolvida ao longo dos anos assim como o seu uso como agentes terapêuticos. Além disso, a facilidade com que este tipo de moléculas tem em estabelecer ligações com outros compostos, faz deles ótimos candidatos para funcionalização de sistemas de entrega de fármacos, aumentando a sua eficácia, atividade e diminuindo possíveis efeitos adversos.

Deste modo, por forma a obter precursores organotrietoxisilanos baseados em derivados de hidratos de carbono, foram elaboradas uma série de reações: (1) proteção e desproteção seletiva de açúcares, por forma a melhorar a sua solubilidade no tipo de solventes utilizados nas reações consequentes; (2) reações de formação de precursores organotrietoxisilanos do tipo Z_3Si-R, entre os derivados glucídicos e o 3-(trietoxisilil)propil isocianato.

A síntese dos derivados de hidratos de carbono foi efetuada com base em três sequências reacionais. A primeira sequência reacional iniciou-se na metil-α-D-glucopiranose e na D-glucose e em cada um destes compostos foram realizadas reações de titilação, seguidas de uma acetilação e por ultimo uma destritilação, originando os compostos 2,3,4–O-triacetil–1–*O*–metil–ß–D-glucopiranose e 1,2,3,4-tetracetil-ß-D-glucopiranose respetivamente. A segunda sequência reacional iniciou-se com a D-ribose, a qual foi protegida com um grupo metil no hidroxilo do carbono 1 e protegida com o grupo isopropopilideno nas posições dos carbonos 2 e 3, num só passo, originando o metil-2,3-*O*-isopropilideno-ß-D-ribofuranose. A terceira e ultima sequência reacional iniciou-se com o 1,2:5,6-di-*O*-isopropilideno-α-glucofuranose que foi benzilado, e de seguida foi feita uma hidrólise, com o objetivo de remover os isopropilidenos das posições referentes aos carbonos 5 e 6. Posteriormente, foi feita uma clivagem oxidativa para a formação do aldeído na posição referente ao carbono 5. Numa fase seguinte, tentou sintetizar-se uma hidrazona através da redução do aldeído anteriormente sintetizado. Contudo, não foi possível obter-se o produto proposto, devido ao excesso de aldeído comparativamente à quantidade de hidrato de hidrazina utilizada na sua reação de síntese, ocorrendo uma dimerização, e formando-se a azina 5-(1',2'-dimetilenehidrazona)–*bis*-[3-*O*-Benzil-1,2:5,6-di-*O*-isopropylidene-α-D-glucopiranose].

1,2:5,6-di-*O*-isopropilideno-α-glucofuranose e 1,2-*O*-Isopropilideno-α-D-xilofuranose também foram utilizados como componente orgânica para a síntese de precursores.

Numa fase seguinte, foi realizada a síntese dos precursores organotrietoxisilanos, sendo a ligação entre o componente derivado de hidrato de carbono e o 3-(trietoxisilil)propil isocianato, efetuada por nós de reticulação de tipo ureia e uretano

Devido à impossibilidade de formação da hidrazona, optou-se por sintetizar o precursor 3,5,6-tri-*O*-metil(3-(trietoxisilil)propil)carbamato-1,2:5,6-di-*O*-isopropilideno-α–D-glucofuranose.

Os compostos propostos foram todos sintetizados com sucesso, com exceção dos compostos *Bis*(3,5-*O*-metil(3-(trietoxisilil)propil-carbamato-1,2-*O*-isopropilideno-a–D-glucofuranose) e 3,5,6-tri-*O*-metil(3-(trietoxisilil)-propil)carbamato-1,2:5,6-di-*O*-isopropilideno-α–D-glucofuranose, que por falta de tempo não foi possível uma nova tentativa de síntese, através de uma metodologia diferente.

Os precursores organotrietoxisilanos foram obtidos com rendimentos entre 65% e 90%.

As sínteses dos precursores organotrietoxisilanos baseados em hidratos de carbono, revelaram um tempo de reação bastante longo e um constante aperfeiçoamento, tanto da temperatura, como do tempo de reação, assim como do solvente a ser utilizado é necessário. O controlo dos parâmetros de reação é essencial, uma vez que neste tipo de compostos pode facilmente haver hidrólise dos grupos etóxidos e consequente perda do precursor.

Nesta dissertação são apresentados os resultados da síntese e a caracterização estrutural dos derivados de hidratos de carbono e dos respetivos precursores organotrietoxisilanos, sendo as

respetivas estruturas dos compostos obtidos, comprovadas por espetroscopia de ^{1}H-RMN, de ^{13}C-RMN e ainda por espetroscopia de infravermelho.

Palavras Chave

Derivados de hidratos de carbono, precursores organotrietoxisilanos, híbridos mesoporosos de organosilica, aplicações biomédicas.

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Å	Angstrom
λ	Lambda
σ	Tesla
2D	Two-dimensional
AcOH	Acetic acid
AC_2O	Acetic anhydrid
Acet/MeOH	Acetone/methanol
Ar	Aromatic
Ar-C	Carbon of aromatic
Ar-CH	Hydrogens of carbons of aromatic
ATR	Attenuated total reflectance
$CDCL_3$	Deuterated chloroform
C-dots	Cornell-dots
SDA	Structure directing agents
DCM	Dichloromethane
DDS	Drug delivery systems
DMAP	4-dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EA/H	Ethyl acetate/N-Hexane
EA	Ethyl acetate
EtOH	Ethanol
FA	Formic Acid
FDA	Food and Drug Administration
GRAS	Generally Recognized As Safe
ICPTES	3-(Triethoxysilyl)propyl isocyanate
IUPAC	International union of pure and applied chemistry
LCT	Liquid crystal template
MCM-41	Mobyl Composition of Matter No. 41
MCM-48	Mobyl Composition of Matter No. 48
MCM-50	Mobyl Composition of Matter No. 50
MSNs	Mesoporous Silica Nanoparticles
M41S	Mesoporous materials
M.W.	Molecular Weight
NPs	Nanoparticles
PMO	Periodic mesoporous organosilica

PMS	Periodic mesoporous silica
Py	Pyridine
qC	Quaternarium carbon
RF	Retention factor
r.t.	room temperature
SA	Sodium acetate
$Si(OR)_4$	Silicon alkoxides
SMILES	Simplified molecular input line entry specification
SN1	Nucleophilic substitution unimolecular
SP	Sodium periodate
TEOS	Tetraethyl orthosilicate
TMOS	Tetramethyl orthosilicate
THF	Tetrahydrofuran
TLC	Thin layer cromatography
TMS	Trimethylsilanol
Tol	Toluene

1. Introduction

Cancer is a complex disease characterized by growth and uncontrolled dissemination of abnormal cells.[1,2] There are over than 100 types of cancer and despite of all efforts in scientific research to their early diagnosis and treatment, this disease has high morbidity and mortality and your impact still rising.[1] It is estimated that in 2012 occurred 14 million of new cases, 8.2 million deaths per year in world population and is predicts an increase about 70% of new cases in the next twenty years. This is a present pathology but will be increasingly a condition of the future.[3]

Conventional therapies are the most utilized, however classical chemotherapy provides some undesirable effects to patient like the fact of anticancer agents in chemotherapy aren't very selective and consequently their toxicity in healthy tissues is very high.[4] Due to the limited rate of success and undesired effects of conventional therapies, search of new therapies instead of chemotherapy is crucial.[1]

Over the years, the search for new bioactive molecules to selectively target the tumour has been increasingly developed.[5] In addition, the increase of the progress in the field of medicinal chemistry, allowed the discover of large amounts of potentially promising new drugs. However, some therapeutic agents are usually restricted by poor stability, high toxicity, small half-lives, aggregation tendency and transport is hindered by biobarriers such as the blood brain barrier or cell membranes. In fact, until very recently, the most common ways to drug delivery in humans are injection and oral administration, but these methods are not efficient for some therapies and present some disadvantages, like serious side effects and low controllability levels.[6-8] Furthermore, the inability to deliver controlled therapeutic concentration of drugs to the desired location can also result in a decrease in the efficacy of drug.[8] For solve this problems, controlled release technologies started gaining increasing attention because presents numerous advantages comparing with conventional modality for cancer therapy.[9] Once drug carrier plays a critical role on loading and releasing of the drug, several research groups have present different nanovehicles as drug delivery systems.[10] Drugs controlled release principle involves the delivery of a predetermined quantity of drug in a specific period of time in a predictable behaviour and to be effective must be able to transport the desired drug molecules with little loss and release the guest molecules in a controlled manner before reaching the targeted destinations.[9] The researchers, supported by many fields of study, such as biology, materials science, pharmacy and chemistry, have been worked together to develop drug delivery systems.[11] Drug delivery systems has become one of the most important themes in the field of controlled release.[6,12] Formulations based on liposomes are already on the market and a variety of other delivery systems are still emerging.[13] With all your potential, nanotechnology-based drug delivery systems hold the promise of significantly improving quality of life through ''nanomedicine''.[14]

The advances of nanotechnology have facilitated the development of new drug carriers allowing to circumvent the previous problems. The field of present research involves creation and utilization of materials, devices or systems on the nanometer scale and is currently undergoing a huge development on many fronts, more recently in drug delivery. An example of this, involves the combination of nanotechnology-based target-specific drug therapy with methods for early diagnosis of pathologies that allow achieve functional drug delivery goals.[14] The advantages involving using nanomaterial-based drug delivery vehicles is increase the concentration of drugs to be delivered, which results in improved adsorption capacity and controlled release properties that consequently can enhance the efficacy of drugs.[8] In a perfect scenario, the delivery drug systems should be capable to respond to external stimulation, such as osmotic conditions, pH ranges, enzymes presence, magnetic field, ultrasounds, etc.[15] Drug delivery systems have gained more and more attention to get better, mainly chemotherapy and radiotherapy efficiency with the purpose of reduce the toxic side effects of anticancer drugs and selective reaching of target.[16] More recently, nanomaterials have also been used for genome editing.[17]

The ability of assemble and organize inorganic, organic, and even biological components in a single material can be an exciting direction for developing novel multifunctional materials presenting a wide range of novel properties and even change the material properties, giving more capable, intelligent and smaller systems.[18]

Among the nanovehicles proposed, ordered mesoporous silica or ordered mesoporous organosilica nanoparticles nave aroused significant interest as candidates for nanomedical applications.[19]

1.1. Ordered mesoporous materials

The first synthesis of an ordered mesoporous material was described in the patent literature in 1969. However due the lack of control[20] the remarkable features of this product were not recognized. A new class of sol-gel materials emerged in 1992 by Mobil's group, named ordered mesoporous molecular sieves M41S.[21], classed as Periodic Mesoporous Silicas (PMSs). The first member of this class, MCM-41 (Mobil Composition of Matter No. 41). MCM-41 materials are prepared by surfactant-mediated self-assembly synthesis of surfactant micelles and tetraethylorthosilicate (TEOS).[22] Due the need of larger pores, framework structure molding of these materials around surfactant micelles has been expanding microporous molecular sieves applications, beyond the 1-2 nm restrictions.[23] Surfactant micelles were removed by calcinations or solvent extraction, leaving behind well-ordered porous mesostructures silica (PMS) structures which pore diameters are between 2 and 5 nm and specific surface areas of about 900-1000 m^2/g.[24]The main characteristic of the previous

materials are their high pore volume (~1 cm^3/g) and a very narrow pore-size distribution (1.8 to 10 nm in novel type of silica diameter, depending on the surfactant used as template). [25,26] Numerous silica mesophases with different structures were obtained. The most well-known representatives of this class include:

- MCM-41 (Mobil Composition of Matter) (Figure 1), with a hexagonal arrangement of the mesopores. It is the first mesoporous solid synthesized that show a regular ordered pore arrangement and a very narrow pore size distribution[27];
- MCM-48 (Figure 1), with a cubic arrangement of the mesopores, more precisely, a bicontinous gyroid structure;[24,28]
- MCM-50, with a laminar structure (Figure 1).[24]

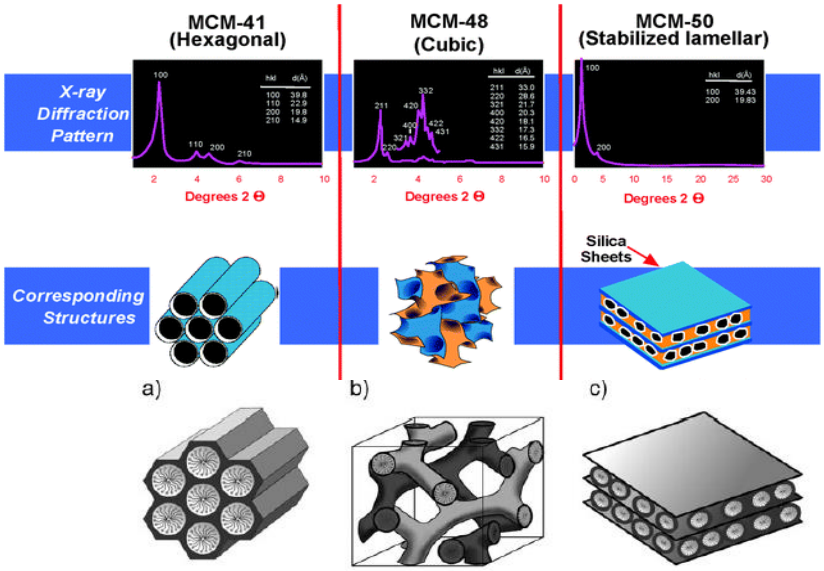


Figure 1- Structures of M41S family of mesoporous molecular sieves: a) MCM-41 (2D-haxagonal); b) MCM-48 (cubic structure) and c) MCM-50 (lamellar structure). [24,25]

An alternative, but less versatile approach to PMS materials was described by Kuroda et al.[21] The as-prepared materials were represented by the notation FSM-n (Folded Sheet Mesoporous Materials-n, where n is the number of carbon atoms in the surfactant alkyl chain). These PMS, are prepared under hydrothermal and basic conditions. Through the addition of aquaternary ammonium surfactant to a solutions of sol-gel precursors (e.g. metal alkoxides), were observed a formation of a highly two-dimensional ordered hexagonal array (honeycomb) of unidimensional pores with a very narrow pore size distribution.

Since the discovery of the MCM-41[29] and FSM-16[29], a large research effort has been invested in the synthesis and characterization of a variety of different, although related materials[21]. Ordered mesoporous materials, such as the families of Santa Barbara Amorphous (SBA), hexagonal mesoporous silica (HMS), Michigan State University (MSU), Mesoporous Silica

Template (KIT), Fundan University (FDU), Amnionic-surfactant-templeted Mesoporous Silica (AMS), Highly Ordered mesoporous silica (HOM), etc.,[30-44] characterized with highly controlled pore size, shape, and arrangement were proposed. Interesting chemical functionality were obtained, through innovative combinations of templates or texturing agents (ionic and non-ionic surfactants, amphiphilic block copolymers, biopolymers, ionic liquids, dendrimers, etc.), starting from mineral precursors (salts, alkoxides, organosilanes, nanobuilding blocks (clusters, nanoparticles, etc), and sol-gel reaction media (solvents, water content, pH, complexing agents, aging conditions, etc.) The chemical composition, molecular bonding and supramolecular architecture are responsible for the levels of organization of mesoporous structure. Macroscopic features such as grain size, texture and porosity are very important for determining mechanical strength and materials performance[23].

In the past decade has seen an explosive interest in PMS, as testified by the number of papers, mainly applied as drug carriers, in the field of controlled drug release. PMS present several advantages[15],such as good biocompability, non-toxic nature, etc.[24,45-47] In addition, they have been considered one of the most promising materials in biomedical applications[48], mainly in gene delivery[49,50], diagnostic imaging[51], photodynamic/photothermal therapy[52] and even tissue engineering[53]. However, the PMS frameworks have some limitations, like neutral natures and hydro-thermal stability. Although, both in aqueous medium it is possible functionalization the pores whit functional groups to expand your applications in different research areas.[54]

1.1.1. Mechanism of porous mesoporous silica

The formation process of the PMS is based on two different pathways, illustrated on scheme 1: (1) the Liquid Crystal Templating Mechanism (LCT)[25], where the concentration of the surfactant is so high, that a lyotropic liquid-crystalline phase is formed without requiring the presence of the precursor inorganic framework materials; and (2) Cooperative self-assembly process[21] (route 2) between the surfactant molecules (present at lower concentration) and the inorganic species.

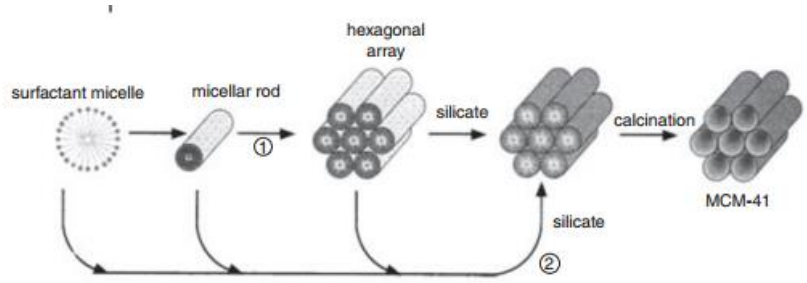
1.1.1.1. Liquid crystal template mechanism

Mobil's group, proposed the LCT mechanism for the formation of mesostructured materials.[55] The LCT mechanism opened a wide variety of approaches for developing new materials. The LCT is the most successful way to produce ordered mesoporous materials[56] (Scheme 1 (1)), and the successful preparation of new porous materials could be achieved by developing new synthesis pathways and by taking advantage of the liquid-crystal chemistry provided by the surfactant.[56,20] MCM-41 is synthesized using a micelle-based liquid crystal

templating method at a variety of pH values from a source of silica and a cationic trimethylammonium bromide surfactant at concentrations under which micelle formation of the organic phase is favorable.[57] New materials have been increasingly developed by many researchers and consequently the application of surfactants in synthesis in general. Thanks to this, comes up a huge variety of new materials based on templating mechanisms, phenomena and concepts.[25] The LCT involves the formation of a liquid-crystalline phase before condensation of the inorganic network occurs (route 1, scheme 1). The surfactants (SDAs) form first spherical micelles and then cylindrical micelles in the aqueous system. When the surfactant is concentrated enough, a liquid-crystal structure with regular hexagonal array will be produced. The inorganic precursors are deposited on the micelle rods of the liquid-crystalline phase through the attraction of the hydrophilic surfaces of the micelles. Then the inorganic monomer molecule or oligomer will polymerize, leading to the formation of the mesostructure organic/inorganic hybrid phase. This can be viewed as a hexagonal array of surfactant micellar rods embedded in the silica matrix. The removal of the surfactant through calcination or extraction produces an open mesoporous framework. Thus, the structure and pore dimensions of mesoporous materials are intimately linked to the properties of the surfactant (e.g., surfactant chain length and surfactant/inorganic precursor ratio) and of the solution chemistry (e.g., water concentration, processing humidity and evaporating temperature).[25,58]

1.1.1.2. Cooperative templating mechanism

This mechanism is the most popular mechanism for the formation of PMS proposed by Stucky and coworkers. (Scheme 1, route (2)) It is the cooperative interaction between organic and inorganic species at molecular scale that leads to assembly to 3D ordered arrangements. Silicate polyanions such as silicate oligomers interact with positively charged groups in cationic surfactants driven by Coulomb forces. The final mesophase is the ordered 3D arrangement with the lowest interface energy. Multiple mesostructures can be templated by one surfactant template, because the final mesostructure is determined on the matching charge density at the surfactant/ inorganic species interfaces. Different families of PMS have been proposed using this methodology.[55,59]



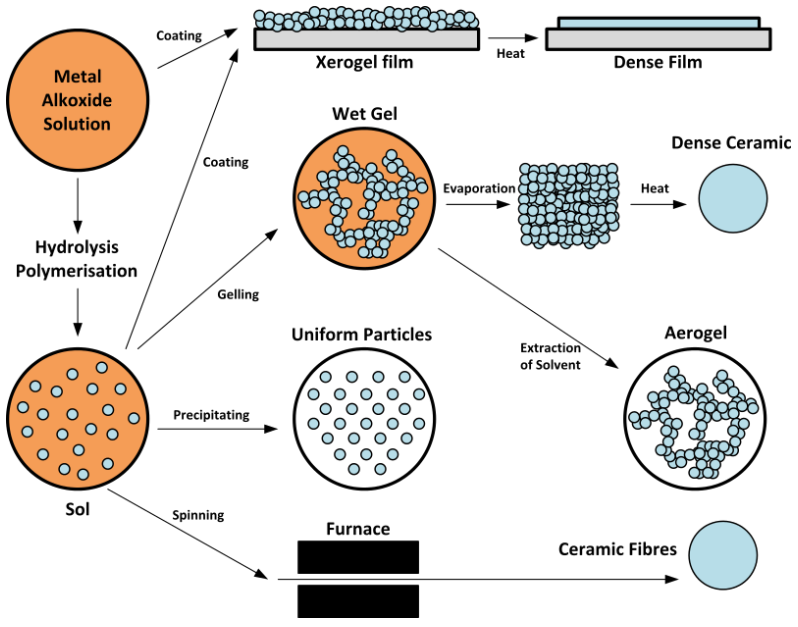
Scheme 1- Scheme for formation of mesoporous materials by structure-directing agents: (route 1) TLC mechanism, (route 2) cooperative self-assembling process.[55]

1.2. Sol-gel process

The combination of organic-inorganic building blocks within a single material is particularly attractive from the point of view of materials science because it is possible combine different organic functional variation with the advantages of a thermally stable and robust inorganic subtract. Synthesis of this type of materials requires soft conditions and sol-gel is usually the nanofabrication method in which occurs polymerisation of inorganic part through hydrolysis reactions to form reactive species that will condense.[60]

Sol-gel materials are metastable solids formed in kinetically controlled reactions from molecular precursors that are building blocks for the following materials. The sol-gel process is a versatile solution process for making advanced materials, including ceramics and organic-inorganic hybrids. In general, the sol-gel process involves the transition of a solution system from a liquid "sol" (mostly colloidal) into a solid "gel" phase. Utilizing the sol-gel process, it is possible to fabricate advanced materials in a wide variety of forms: ultrafine or spherical shaped powders, thin film coatings, fibers, porous or dense materials, and extremely porous aerogel materials. An overview of various sol-gel processes is illustrated in Figure 3.

Thus, the sol-gel process are constituted by two distinct phases[61] (Scheme 2): (1) Phase sol, who is a stable suspension of crystalline or amorphous nanoparticles in a liquid; (2) Phase gel, is a porous three-dimensionally continuous solid network.



Scheme 2- Schematic representation of the different stages and routes of the sol-gel technology.[62]

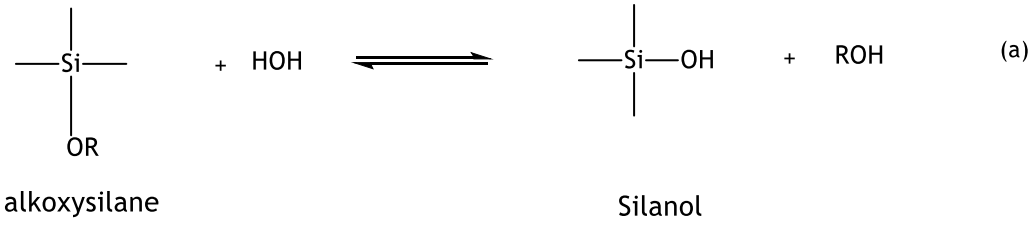
The control of the properties of the final material are achieved by controlling the chemical nature of the organic and inorganic phases, the size and morphology of these domains (nm to sub-pm scale) and the nature of the interphase interaction. The first step in the procedure is obviously to find some common suitable solvents and compatible reactants.[63]

The present silica-based materials taking the advantage of easy synthesis of organosilane precursors, good controllability in sol-gel condensation, flexibility for shaping and high chemical stability due the silica framework. The free energy of silica is very close to its most stable form crystalline quartz; Si-O bonds are so strong that the silica sol–gel process has highly irreversible character. Amorphous silica is stable over a very high temperature range and period of time. This means that the shape of silica can be formed at room temperature and then be retained practically infinitely. Once more, this distinguishes silica from other oxidic materials where crystallization frequently occurs.[27]

1.2.1. Polymerization

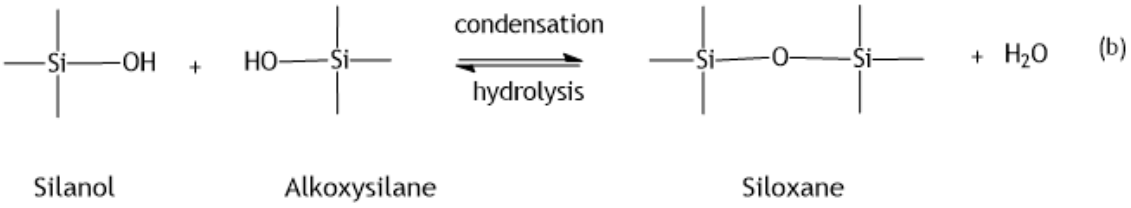
The chemical principle of silica-based materials is the transformation of Si-OR and Si-OH containing species in siloxane compounds by condensation reactions (Scheme 3). This occurs by connecting R-SiO_3 tetrahedra of hybrid materials by corner sharing. To obtain a stable sol-gel, the number of siloxane bounds, Si-O-Si, should be maximized, and consequently, the number of silanol (Si-OH) and alkoxy (Si-OR) groups should be minimized. In alkoxysilane-based systems, hydrolysis reaction must precede condensation to generate Si-OH groups. In the step of condensation, is observed the formation of Si-O-Si units, weither alcohol (Scheme 3 (C), or more frequently water (Scheme 3 (b).[64] Different factors can influence the velocities of hydrolysis and condensation of sol-gel process, like pH, temperature, reaction-time, concentration of reagents, nature and concentration of catalyst, solvent type, molar ratio H_2O/Si (R) and aging temperatures and drying.[65]

Step 1: Hydrolysis

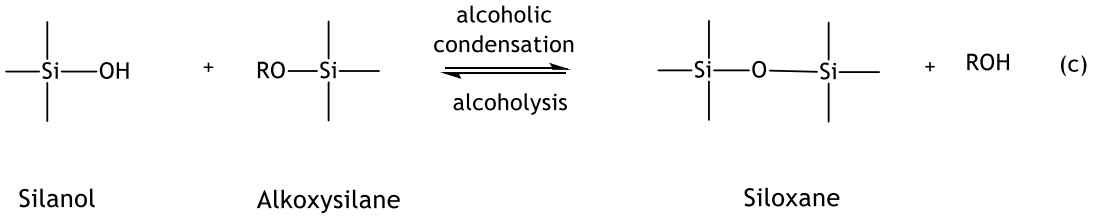


Step 2 - Condensation

a) water condensation



b) Alcohol Condensation



Scheme 3 - Chemical reactions of classical sol-gel process.[62]

More frequent precursors are aqueous solutions of silicates and silicon alkoxides $Si(OR)_4$, mainly tetramethoxysilane (TMOS) and TEOS. Molecular precursors R'-$Si(OR)_3$, (R'=alkyl, phenyl, H, *etc.*) are also used to produce hybrid materials.[64]

As, were refer previous, the gelation process is initiated in alkoxyde precursor system by water addiction, yielding the hydrolysis process to give Si-OH groups (Scheme 3 (a)). As the mixture of Si-$(OR)_4$ in water and alcohol react very slowly, sometimes it's necessary acid or basic catalyse to initiate the hydrolysis and condensation reactions of alkoxysilanes, that are employed either neat or dissolved in an organic solvent. Once, alkoxysilanes are immiscible

with water, alcohols are often used to homogenize the reaction mixture (same alcohol as liberated by the hydrolysis reaction to avoid alcohol exchange reactions). So-gel is the processing of alkoxysilanes from type R'-$Si(OR)_3$, R'=hydrolytically stable organic moiety, in silsesquioxanes, R'-$SiO_{3/2}$. Non-polar solvents, like tetrahydrofuran and dioxane are sometimes used for organotrialkoxysilanes, R'-$Si(OR)_3$ or incompletely hydrolysed alkoxide systems.[64]

1.3. Functionalized periodic mesoporous silica

The surface of PMS can be modified with various types of functional groups, introducing new catalytic adsorption functions inside the mesoporous wall.[66] This method allows the modification the physical and chemical properties of PMS, through the attachment of an organic group to the silicate wall. In addition, this Organic functionalization permits modifye the properties of the hybrids, such as hydrophobicity and hydrophilicity and allow the interaction with guest molecules.[67]

The functionalization evolves the reaction of organosilane, chlorosilanes or silazanes precursors [$(R'O)_3Si$-R, $ClSi$-R_3 or HN-$(SiR_3)_3$, respectively, where R`=CH_2 or CH_2CH_3, and R is an organic group with free silanol groups of the pore surface. Their introduction can be performed following two main strategies (Figure 2). Depending the way how this occurs we can have two situations[68]:

- (1) Grafting: If this occurs under synthetic procedure, silica phase can be retained, result consequently in a reduction of the porosity of the PMS; (Figure 2 (1))
- (2) Co-condensation: if the organosilane precursors react in the initial stages of the synthetic procedure, the diffusion of further molecules into the centre of the pores will be engaged, which result in nonhomogeneous distribution of the organic groups within the pores. (Figure 2 (2))

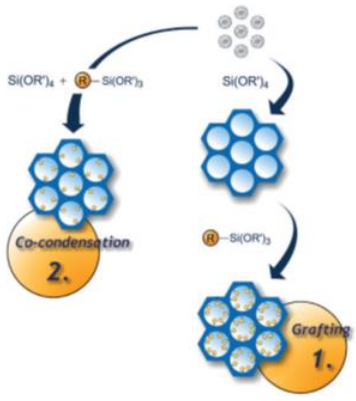


Figure 2- General modification methods to introduce organoalkoxysilanes as precursors. 1. Grafting and 2. Co-condensation.[24]

Organic functionalities that can be incorporated into the pore walls of the silica network are numerous, like alkyl, thiol, amino, cyano/isocyano vinyl/ allyl organophosphine alkoxy, aromatic groups and many others.[69] However, it is important refer that at high loading levels of functional groups, the control of the distribution of the precursors in the mesoporous channels is problematic and can damage the mesostructured arrangement and textural properties.[70]

1.3.1. Post-synthetic Grafting

Functionalization of PMS with organic moieties by post-synthetic grafting allows modifying the inner surfaces of PMSs with organic groups. The post-synthetic grafting (1) involves the reaction between organosilane, chlorosilanes or silazanes precursors under synthetic procedures with free silanol (Si-OH) groups of the PMS phase (Figure 2 (1) and Figure 3). In this case, the silica phase can be retained, who result in a reduction of the porosity of the PMS. Thus, in the present methodology it is possible the observation of pore blocking, especially in the case of small mesopores and large organic groups. [27,24]

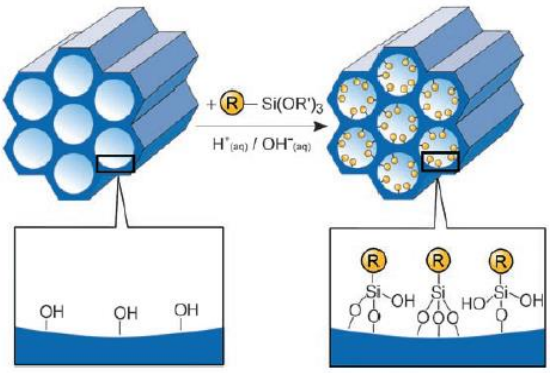


Figure 3- Grafting for organic modification of mesoporous pure silica phases with terminal organosilanes of the type $(R'O)_3Si$-R. R=organic functional group.[24]

1.3.2. Direct Co-condensation

Co-condensation (Figure 2 (2)) is an alternative method to synthesize organically functionalized PMS, where the hydrolysis and condensation of tetraalkoxysilanes (typically TEOS) and a non-bridged organosilane occurs in the initial stages of the synthetic procedure[58,71,72] (Figure 2 (2) and Figure 4). Instead of post-synthetic grafting, the direct co-condensation (one-pot synthesis) allow the introduction of large organic groups and high loadings of organics and ultra-large pore diameters. Moreover, the one-pot synthesis is

simple, efficient and less time-consuming than post-synthesis modification. A great number of organically modified silica phases have been synthesized by co-condensation.[24,27,73]

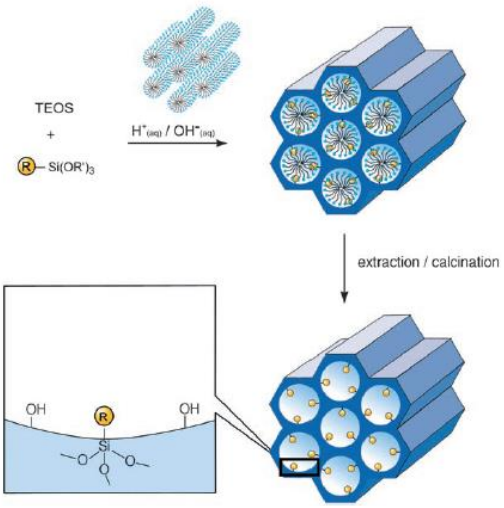


Figure 4- Co-condensation method (direct synthesis).[69]

1.4. Peridodic mesoporous organosilica

Limitations of PMS lead to discover periodic mesoporous organosilica (PMOs) in 1999 [23] With this discover, organosilicon chemistry proves to be very important for the design of new materials and consequently new mesoporous solid based on templating mechanisms have been increasingly developed[58].

PMO (Figure 5) are a class most representative of organic-inorganic hybrid materials in which bridged organosilica precursors $(RO)_3Si\text{-}R'\text{-}Si\text{-}(OR)_3$, where R' is an organic group and R= CH_2 and CH_2CH_3, are incorporated into three dimensional network structure of the silica matrix through two covalent bonds. PMO materials synthesis is originated by self-assembling of bridged organosilane precursors that are uniformly distributed in the porous wall which generally exhibit disordered pore systems with a relatively wide distribution of pore.[58,74,75] With the presence of the bridging organic groups inside the frameworks, PMOs may be more advantageous than purely PMS, due to the greater variability of pore surface properties that can be achieved. Presence of inorganic Si function in framework structure provides a robust framework and the organic functions make flexible frameworks that can be tailored in a number of important applications.[27] In addition, the PMO present advantages relatively to the PMS, such as excellent hydrothermal and mechanical stability, the hydrophobicity or hydrophilicity properties can be tuned by the choice of the organic component [24], and high concentration of organic functional group in the framework.

PMO has been largely used in catalysis, chromatography, hydrophobic drug carriers, enzyme immobilization, and low hemolytic materials.[76] One-dimensional nanostructures are the classes of materials more recently studied, such as nanowires, nanofibers, nanotubes, and nanorods in which, the last have been extensively studied for many applications especially as drug-delivery applications, more recently.[77]

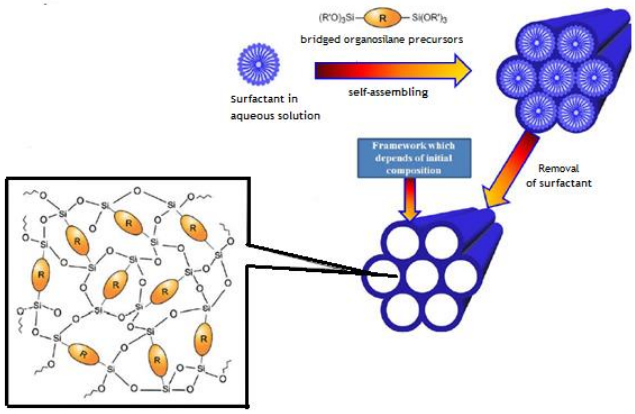


Figure 5- General self-assembling method to prepare PMO. R=organic bridge. Adapted[27,54]

1.5. Sylilated precursors

Since 1999, the appearance of new precursors increasingly (Figure 6). Due to the diversity of constitution formulae of organosilica precursors, the physical/ chemical property and corresponding functions of such PMOs can be facilely tuned by introducing adequate organic **R** parts homogeneously within the mesoporous framework.[75] Actually there is a huge variety of organic moieties (R) for structural control and functionalization of these materials. Although R group is limited to a relatively simple organic bridges such as ethylene, ethenylene, phenylene and thiophene.[78] More recently, new synthetic procedures were established to synthesize organosilane precursors, allowing the introduction of a great variety of organic groups, since hydrocarbons and heteroaromatics to metal complexes in frameworks and much more.[58,79,80]

The synthesis of promising hybrid materials depends critically on the nature of organosilane precursors, The number of organosilane precursors potentially available for the synthesis of PMO or PMS is extremely large, so the development of new material compositions will continue to be a fertile research area.[81,82]

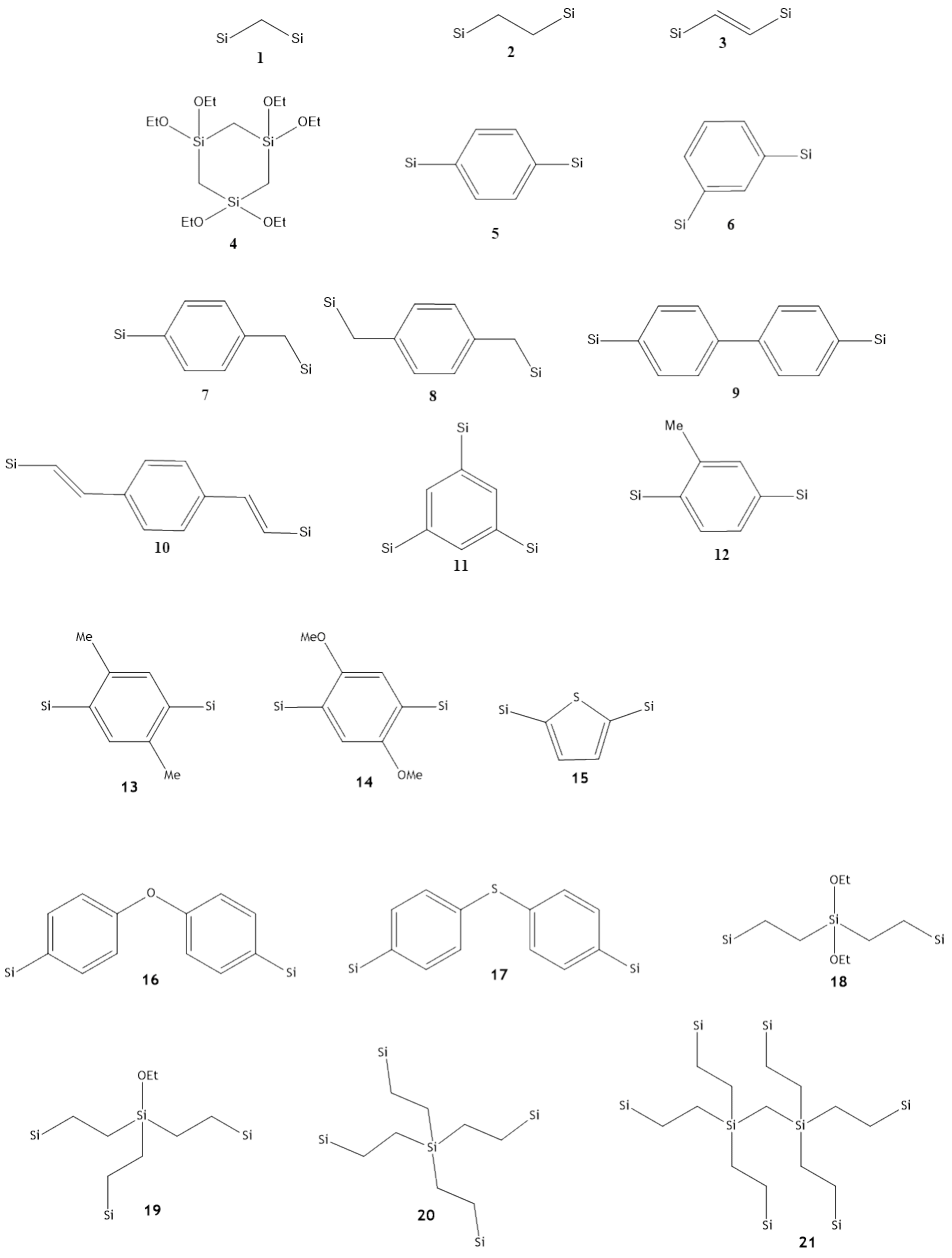


Figure 6- Examples of silylated organosilica precursors that have been converted into PMOs since 1999. Terminal Si atoms: $Si(OR)_3$ with R=CH_3, C_2H_5.[24]

1.6. Applications

Organic-inorganic nanocomposites are everywhere in nature, such as in crustacean carapaces, in mollusc shells and bone or teeth. Some companies already patented organic-inorganic materials and we can found them in paints, paper, coupling agents such as silanes, silicones

or another metal-organic molecules allowing modification of glass, ceramics or metallic surfaces.[24]

Hybrid materials represent an huge source of inspiration [68] and various potential applications have been suggested[13,45,47,50,53,83-92], such as optical materials and sensors[93], solid catalysts[93], bioencapsulation [94], and particularly promising is the work of drug delivery systems that react to an external stimulus by releasing an active compound (stimulus-response behaviour)[95].

Among the different types of inorganic nanomaterials, PMO and PMS nanoparticles have received growing attention by the scientific biomedical community and have emerged as promising multifunctional platforms for nanomedicine, due to some interesting features such as their biological stability and their drug-releasing properties.[96] Silica chemistry has been being one of the most active research subjects due to the existence of abundant silicate species, diverse chemical interactions and its contributions to material science, geology and pharmacy.[75] Silica is one of the most biocompatible materials manifested by the facts that it is an endogenous substance present mainly in bones and it has been used commercially as the excipient in oral-taken drugs.[97] Additionally, silica is "Generally Recognized As Safe (GRAS)" by the U. S. Food and Drug Administration (FDA).[98] Heart-stirringly dye-doped fluorescent silica nanoparticles, well-known as "Cornell-dots" (C-dots) [99] have been approved by FDA for human stage I molecular imaging of cancer, which gives the great confidence about future clinical translation potentials of silica-based NPs for cancer diagnosis and therapy.[100,101]

Pharmaceutical agents have been loaded into the PMS and PMO, with aim of to be them release in the body. This interaction between the PMS and the guest molecules would have a strong effect on the drug adsorption and release properties of the carrier matrices. Additionally, textural and structural properties have been observed to modulate the adsorption and release characteristics of these PMO and PMS. [90] The efficient internalization of MSN in a wide variety of cell lines has been demonstrated by several groups.[102]

Over the years numerous types of drug delivery systems based in PMOs and PMS, have been surged. Among them, the gold-capped mesoporous Silica nanospheres, in which different stimuli-responsive strategies, such as chemical, pH, electrostatic interaction, enzymatic, redox, and photoirradiation, have been applied as "triggers" for uncapping the pores and releasing the guest molecules from MSN.[103]

1.7. Carbohydrates

Carbohydrates, may also be called glucides or sugars and the last one is due their sweet taste. Those compounds are the most abundant biomolecules in world, and are truly important chemical compounds because are part of natural products group and have an important role in a great number of biological activities, being the major components of

human diet.[104,105] They are the most functionally versatile natural products and can be converted into important products to many field of research like food industry, textile, pharmaceutical and agrochemical. Over the years, carbohydrate chemistry has been an important link between organic chemistry, medicinal chemistry and biology.[106]

The nomination of carbohydrate was introduced in 19th century and it's due the sugars molecular form, $C_nH_{2n}O_n$. This formula was abandoned when was verified that compounds could also have in their structure, elements like sulphur, nitrogen and phosphorus. This compounds are water soluble due the presence of hydroxyl groups and there was always evidence for the carbonyl group of an aldehyde or ketone. In fact the condensation of aldehydes and ketones with alcohols and polyols is one of the first reactions of organic chemistry.[107] The three dimensional structures of carbohydrates are determinant by their chemical and physical properties. Despite some have the same empirical formula, can have configurational differences at successive stereogenic carbon centres, each has distinct chemical reactivity and chromatographic behavior.[108] Once carbohydrates have chiral centres in their structure, the number of possible stereoisomers is given by the formula 2^n (n= number of chiral centres). Carbohydrates include polyhydroxy aldehydes, ketones or acids constituting a diversified class of compounds due to their wide range of stereoisomers. These polyhydroxylated aldehydes or ketones were divided into two subclasses that are distinguished by the number of carbon atoms of each other, containing 3 to 9 carbons typically very functionalized. Glyceraldehyde is the simplest sugar with only 3 carbons. Aldoses, like glucose, which have linear carbon chains with an aldehyde (CHO) group at C-1, a varying number of secondary alcohols (-CHOH), (which offer a variable number of chiral centres) and a primary alcohol at the end of the chain, and ketoses, like fructose, which have a primary alcohol at both ends and a ketone in the chain, exists too, however are much less abundant than aldoses. Carbohydrates can be divided, in three distinct according to their number of structural units [108]:

- Monosaccharides;
- Oligosaccharides;
- Polysaccharides.

Monosaccharides are the simplest carbohydrates, so cannot be hydrolysable in simpler carbons, unlike oligosaccharides and polysaccharides that are achieved by glyosidic bonds between monosaccharides, making possible their hydrolysis.[107]

Once carbohydrates have both carbonyl and hydroxyl functions, they are able to form intramolecular hemiacetals. Furthermore, the equilibrium of this reaction is displaced to the formation of the cyclic hemiacetal[107], because the preferred chemical forms at most monosaccharides and the majority of their derivatives are based on cyclic tetrahydrofuran or tetrahydropyran structures, becoming the linear sugar form, non-existent, in both solution and solid form. In solutions of free sugars (aldoses, ketoses, some glycosylamines), the rings

were formed in chemical equilibrium with the acyclic aldehyde or keto form which is structurally identical to the fisher projection commonly used to present the stereochemical configurations of the monosaccharides.[108] The cyclic form is obtained by nucleophilic addition of the hydroxyl group on carbon-5 to the aldehyde group (carbon-1) in linear conformation. The cyclic structure formed have an extra stereogenic centre (carbon-1), so the product of cyclization may exist in two isomeric forms. This occurs at anomeric centres, where electronegative substituents in axial positions tend to be much more likely for sugars than they are for pure carbocyclic rings. An example is the methoxy group at C-1 of methylglucopyranoside that has higher occurrence in axial than in equatorial conformation. This phenomenon is called anomeric effect. Although, aqueous solutions of glucose in equilibrium contain 36 % of α-glucopyranose, with its axial O1H group, compared with 64% of the all-equatorial ß-form. In general, ß-form is more prevalent than α-form, thus the equatorial form is more stable than axial form. D-Aldopentoses and D-aldohexoses exist in aqueous solution primarily as a mixture of the α- and ß-pyranose forms and in this pyranoses forms, it is the chair convention that is almost always preferred, but in general cyclic carbohydrates are represented according to the Haworth convention. (Figure 7) Thus, the half-chair is a common conformation for some carbohydrate derivatives where chemical modification of the pyranose ring has occurred.[106,108]

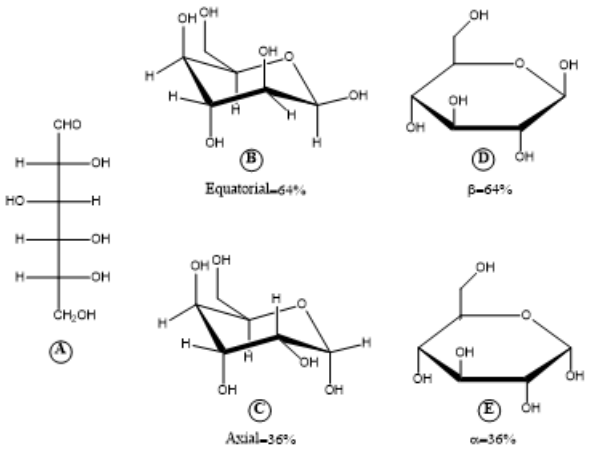


Figure 7- Structure of D-glucose in Fisher projection (A), half-chair equatorial disposed (B), and axial disposed (C) and Haworth projection in α-anomer (E) and ß-anomer (D).[108]

1.7.1. Protecting groups – hydroxyl protecting groups

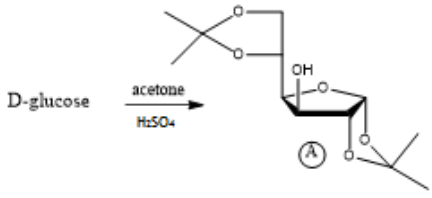
Protection strategies are important for all syntheses of organic molecules, mainly in carbohydrates chemistry because of the large number of functional groups. Traditional synthesis of saccharides requires tedious and time-consuming protection/deprotection steps. Hydroxyl groups are the functional groups more prevalent which necessitates regioselective protecting strategies, being the protection of these hydroxyl groups, the most important

protection reaction in carbohydrate chemistry, including the anomeric hemiacetal. Amino-protecting groups (for amino-deoxy sugars) and carboxyl protecting groups (for uronic and ulosonic acids) are also importants.[109] In this work it will be analysed some protecting groups that were used in experimental work.

The hydroxyl groups of carbohydrates have identical properties to simple alcohols and can be substituted to give ethers, esters or ketals. During oxidation, acylation, halogenation or dehydration reactions of these compounds, a hydroxyl group must be protected.[110] So, arise the dual needs of synthesis, the ability to carry out chemical reactions in carbohydrates, and protecting groups, introduced by chemical reaction that protect one part of molecule, yet allow access to another.[104] However, a selective protection is necessary when all functional groups of a molecule are from same type. Selective protection becomes an issue that has been addressed by the development of a number of new methods.[110] The hydroxyl groups protection reaction plays an important role in a sequence, so protecting groups has been developed over the years.[111] The most used hydroxyl protecting groups are acetates, benzoates, benzyl ethers, benzylidene and ispopropylidene acetals, that can be introduced to protect several hydroxyl groups simultaneously. Although several, other protecting groups can be used.[108]

1.7.1.1. Isopropilydene acetals

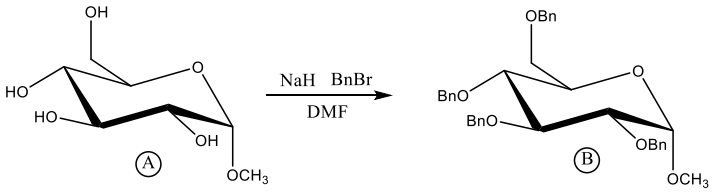
The introduction of isopropylidene acetals can be performed by the use of acetone and acid catalysis (scheme 4). When aldehydes or ketones react with open chain 1,2-diol or 1,3-diol produced cyclic acetals, like ispropylidenes. These protecting groups allow the protection of two hydroxyl groups in *cis*-position 1,2 or 1,3 simultaneously. If 1,2-diol is attached to a ring, like occurs in monosaccharides, formation of cyclic acetals happen only when the hydroxyl groups are in *cis*-position, one each other.[104,111]



Scheme 4- Introduction of isopropylidene acetals in D-glucose.[104]

1.7.1.2. Benzyl ethers

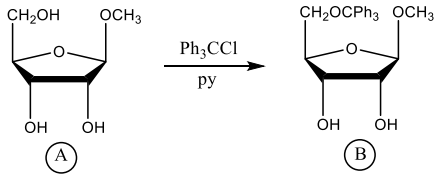
Benzylations are usually performed under strongly basic conditions. There are more alternatives but are usually less efficient and can be used for the introduction of only one or, at most, a few benzyl groups. These protecting groups promotes a type of protection non selective and offer a versatile means of protection for the hydroxyl groups.[104,109] (Scheme 5)



Scheme 5- Protection of α-D-methyl-glucopyranoside with benzyl ethers.[104]

1.7.1.3. Trityl ethers

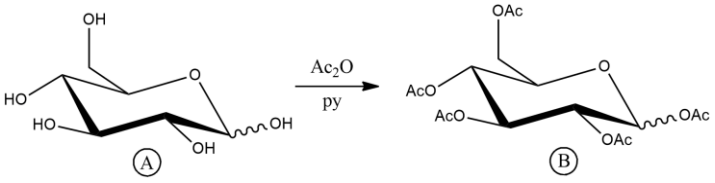
The trityl (Triphenylmethyl) ether is one group for the selective protection of a primary alcohol. Introduction of a trityl group is made by addition of trityl chloride and pirydine.[104] (Scheme 6)



Scheme 6- Selective protections of 1-O-methoxy-D-ribofuranose with triphenylmethyl ether.[104]

1.7.1.4. Acetates

Acetates are excellent protecting groups because they can be introduced and removed in high yields in large number under mild conditions. Standard conditions for esterification is acetic anhydride (especially for acetates) in pyridine. The reaction in pyridine is general and usually gives the same anomer of the penta-acetate as found in the parent free sugar. Sodium acetate can also be used, instead of pyridine, giving rapid anomerization of the free sugar and the more reactive anomer is then preferentially acetylated.[104,109](Scheme 7)



Scheme 7- Protection of D-glucose with acetates.[104]

1.7.2. Carbohydrates and glycoconjugates in drug development

The biological activity in carbohydrate chemistry have been increasingly and several biological roles for carbohydrates has emerged, ranging from functions like energy storage to complex processes that regulate transport, protein function, intercellular adhesion, signal

transduction, malignant transformation, and viral and bacterial cell-surface recognition.[109] In an ideal situation, both carbohydrate chemistry and glycobiology acting together.[112] The glycoconjugates are important compounds in biology, in which carbohydrates are covalently linked to non-sugar moieties like proteins, peptides or lipids. Both carbohydrates and glycoconjugates have important role in biological processes and naturally occurring in different biological processes. Scaffolds are an example of this. These kind of associations can be involved in the initiation steps of many diseases, such as stomach cancer, influenza and cholera, and biological processes like cancer metastasis.[113,114]

Carbohydrate-related drug discovery targets have been increasingly discovered and validated, carbohydrate with potential pharmaceutic activities has being exploited by the pharmaceutical industry.[115] A good drug is a target-specific drug and target specificity also means recognition, and this is where carbohydrates can be used.[112,113] Already exist numerous examples of applications of carbohydrate-based drugs (Figure 8), such as your use in diabetes type 1 and type 2[116], viral infection,[117] such as neuraminidase inhibitors that have been developed for treatment of *influenza* virus[118], HIV treatment[119] and inflammatory diseases[120], once carbohydrates molecules plays an important role in specific recognition events between cells that involves binding between oligosaccharide constituents of glycoproteins or other glycoconjugates and lectins on the surfaces of the binding components. For example, pathogenic bacteria and biological toxins are bound and ingested by macrophages and selectins on endothelial cell surfaces bind leukocytes of the blood and this results in the leukocytes migrating to neighbouring tissues to prevent inflammation. Other examples of potential applications of carbohydrate derivatives is in treatment of thrombosis,[121] bacterial infections[122] and anticancer vaccines.[123,124] Stereochemical diversity of carbohydrates makes them valuable tools for drug discovery. Carbohydrates can also inhibit carbohydrate-process enzymes, known as glycosidase inhibitors which are of considerable therapeutic value,[125] like inhibitors of intestinal α-glycosidase that are used to treat type 2 diabetes mellitus by blocking oligosaccharide hydrolysis and glucose uptake.[126] Some binding specificities of carbohydrate to proteins have already been identified, and others are been screened on glycoarrays[127] to determine their glycan-binding (glycopeptides and glycoproteins) epitopes which provide continuous supply of carbohydrate-related targets for the structure-based design of new chemical entities that mimic bioactive carbohydrates, giving a novel class of therapeutics.[128]

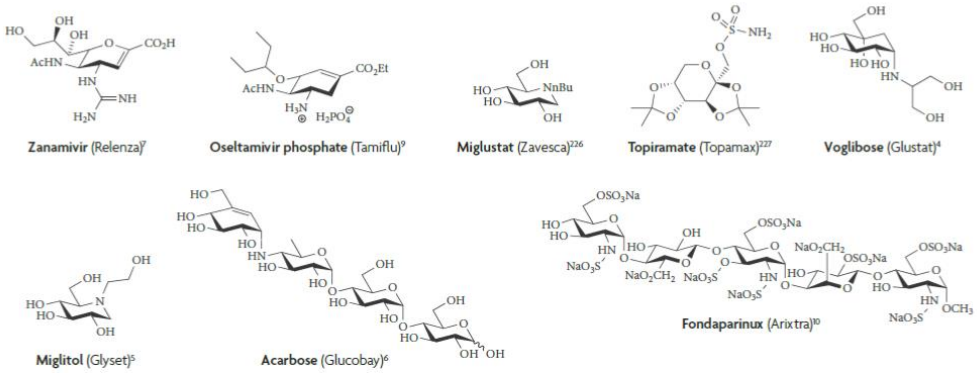


Figure 8- Examples of some carbohydrate and carbohydrate-derived drugs. These contained glycosidase inhibitors for the treatment of diabetes (voglibose, miglitol and acarbose), the prevention of influenza virus infections (zanamivir and oseltamivir), sulphated glycosaminoglycans for the treatment of thrombosis (fondaparinux). In addition, carbohydrate-derived drugs are used to treat Gaucher's disease (miglustat) and epilepsy (topiramate).[128]

1.7.3. Drug delivery systems based in glycoconjugates

Drug selectively targeting have several therapeutic advantages like low toxicity and lower dose levels to be efficient. This phenomenon involves exploiting either binding interaction of ligand to targeting receptor or binding interaction of receptor at the site for an introduced ligand, named glycotargeting.[129] Cell surface-bound receptors represent suitable entry sites for drug delivery into cells by receptor-mediated endocytosis and carbohydrates have the ability to bind proteins at the site of localization that make them candidates with great potential.[130] Although, your pharmacokinetic problems, in particular the fact that they are small molecules which makes them suffer from fast release.[131] Consequently, glycoconjugation with macromolecules allow longer circulation times and a more precisely delivery. Utilization of glycoconjugates to glycotargeting can be divided in two types[129]:

- Macromolecule is itself the drug or therapeutic agent;
- Macromolecule have an important role in aiding in delivery of drug or therapeutic agent.

Over the years have emerged numerous drug delivery systems based in glycoconjugates with aim to improve drug delivery, such as poly(amino acids), that are commonly used as macromolecules scaffolds, glycotargeted gene delivery systems that are conjugated with lipides[132], once liposomes give some insight into the behaviour of macromolecular construction, have been widely used.[130] Although, these are products of aggregation of glyconjugates with small MW and due your lipophilic nature, some drugs can be excluded.[129] Nanoparticles also have been widely used[133], such as the example of carbohydrate components conjugated to gold nanoparticles that have *in vitro* antibacterial activities against vancomycin-resistant *enterococci*[134]. Protein can be also itself the drug. The first example of a glycosylated protein drug was ß-glucocerebrosidase, used to treat Gaucher's syndrome. Although it is a commercial drug for several years, strong evidence has only

recently emerged that suggests the success of ß-glucocerebrosidase in part, due to the selective delivery to macrophages, which is mediated by glycan structures present in this protein.[135] The first example of targeting of glycoconjugates carriers was in 1999, a phase I clinical study in humans. Doxorubicin and galactosamine were linked to a polymer and, among other issues, the copolymer drug reduced in five times the cardiotoxicity compared to free doxorubicin.[129] Cyclodextrin are cyclic oligosaccharides and have mainly been used as pharmaceutical excipients for low molecular weight drugs to improve their solubility, stability, taste, bioavailability, etc,[136] but have recently been used as drug carrier combined with several functional materials such as ligands, polymers, nanosphere, microsphere, liposome, and micelle have recently been developed for low molecular weight drugs, proteins, or nucleic acids.[137] Glycoconjugates as drug delivery systems are one of the biomedical applications of carbohydrates that have been increasingly developed due to their great potential in this area.

1.7.4. Glycomimetics in drug discovery

Despite important biological role of carbohydrates, pharmacokinetic drawbacks are inherently linked to them, such as your high polarity that makes this type of compounds unable to cross passively through the enterocyte layer in the small intestine also due to their molecular mass and number of hydrogen bridged donors and acceptors. This makes oral availability almost impossible. Furthermore, as they are available for parenteral administration, their renal excretion it's higher. In addition to the lack of affinity, they suffer from low tissue permeability, short serum half-life and poor stability. This can be overcome by systematically eliminating polar groups and metabolic soft spots that aren't required to affinity by designing a prodrug, their oral availability become possible.[131] The challenges in field of medicinal chemistry are represented by increasingly drug discovery that can be achieved by the development of drug-like glycomimetics. Those compounds are design to overcome insufficient pharmacodynamic and pharmacokinetic properties.[138]

2. Aims

According to all information described above, the dissertation project aimed the synthesis and characterization of mono-organosilanes precursors, from type Z_3Si-R, in which Z is a hydrolysable group (usually ethoxy groups) and R is an organic group. These precursors assemble organic properties are carbohydrate-based derivatives. Finally, hybrid materials are prepared from previous precursors using the classical sol-gel process, as a start point for the development of several mesoporous hybrids nanoparticles as nanovehicles for drug delivery systems.

Carbohydrates are a type of biomolecules involved in numerous biological processes. Depending on their primary structures, they have a role of physical, chemical and biological properties, that can make them candidates with great potential to be part of monosylilated precursors. Your high number of hydrogen bridge donors and acceptors can be an advantage to establish hydrogen bonds with a drug or therapeutic agent. Cell-surface recognition also is very important property that allow to connect it with virus, bacteria even cancer cells. However, they have limited pharmacokinetic due the fact of they can have great water solubility (only in your unmodified form), because of your high polarity that makes them unable to cross passively through the enterocyte layer in small intestine that ally to the presence of charges (sulphates and carboxylates) makes oral availability impossible. Furthermore, they are molecules with small molar weight (MW) that promote your fast clearance. These drawbacks can be overcome by your association with silica-derived materials, that is an innovative work in drug delivery systems. This association will be able later to prepare organic-inorganic hybrid mesoporous materials. Once was proved that they have good biocompatibility and there is the possibility the inclusion of drugs into your pores by attachment with organosilane precursors. Thus, the synthesis of these carbohydrate-based silylated precursors may have a huge potential to prepare drug delivery systems for biomedical applications.

3. Discussion of results

In this chapter will be presented and discussed the experimental results of synthesis of starting materials sugar derivatives from monosaccharides like 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, methyl-α-D-glucopyranoside, D-glucose and D-ribose and the synthesis of organotriethoxysilanes precursors with a urethane cross-linked, even the failed synthesis of a type of precursors from organic\inorganic cross-linked obtained (table 6).

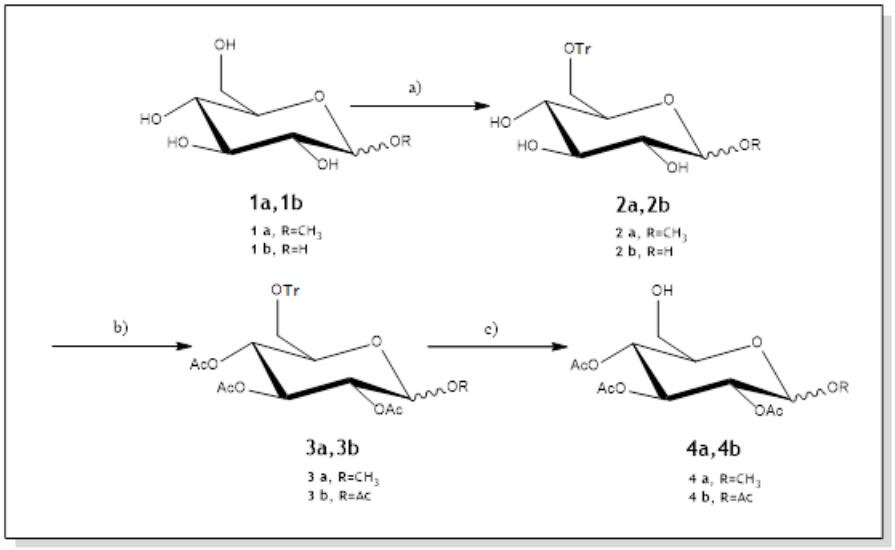
The results were discussed and presented by the chronological order in which they were synthesized, doing a brief reference about the relevance of the used type of synthesis.

3.1. Synthesis of carbohydrate derivatives

The aim is to synthesize carbohydrate-based compounds with a free hydroxyl group to be covalently bonded to the inorganic compound ICPTES (3-(triethoxysilyl)propyl isocyanate) **15**. (Table 1) Protection of hydroxyl groups is needed to improve solubility of the sugar derivatives in THF (tetrahydrofuran) that is the solvent used to synthetize the organotrioxysilane compounds. As THF is a polar aprotic solvent, unmodified carbohydrates are only soluble in polar solvents capable of hydrogen bonding interactions.[131] Therefore, were performed series of selective and non-selective, protections and deprotections, in order to get the minimum of free hydroxyl groups.

3.1.1. 2,3,4-*O*-tri-acetyl-1-*O*-methyl-ß-D-glucopyranose **(4a)** and 1,2,3,4-tetra-*O*-acetyl-ß-D-glucopyranose **(4b)**

2,3,4-tri-*O*-acetyl-1-*O*-methyl-ß-D-glucopyranose **4a** and 1,2,3,4-tetra-*O*-acetyl-ß-D-glucopyranose **4b,** are obtained from 1-*O*-methyl-α-D-glucopyranose **1a** and D-glucose **1b,** respectively, by a sequence reaction that is initiated with a tritylation[139], followed by an acetylation[140] and finally a detritylation[141], according to the described methods.(scheme 8).



Scheme 8- Synthetic strategy of final compounds 2,3,4-O-tri-*O*-acetyl-1-O-methoxy-ß-D-glucopyranose (4a) and 1,2,3,4-tetra-*O*-acetyl-ß-D-glucopyranose (4b). Conditions and yields: a) PhCCl, TEA, DMF, r.t., overnight, 2a=60%, 2b=44%; b) AC_2O, SA, reflux, 1h, 3a= 70%, 3b=78%; c) FA, ETOAc, r.t., 30 min, 4a=82%, 4b=75%.

3.1.1.1. Selective protection of primary alcohol

First, it was made a protection of the hydroxyl group of the carbon 6. Tritylation is a good option, once it is a regeoselective ether protection method for the primary alcohols.[142] 1-*O*-methyl-6-*O*-triphenylmethyl-ß-D-glucopyranose **2a** and 6-*O*-triphenylmethyl-D-glucopyranose **2b** are obtained by a selective reaction between -OH of C-6 and trityl chloride, under basic conditions provided by trimethylamine under nitrogen atmosphere. In the present procedure was used 4-dimethylaminopyridine (DMAP) used and as catalyst in order to get a better efficiency of the reaction. The yield in both **2a** and **2b,** 60% and 44%, respectively, was acceptable, once that technique provides better yields when the all hydroxyl groups are protected than in reducing monosaccharides[142], that explain the lower yield of compound **2b** than **2a.**

The structure of both compounds was proved comparing spectroscopic dates, ^{13}C and ^{1}H NMR (tables 1 and 2), to the literature.[139]

3.1.1.2. Protection with acetyl groups

The hydroxyl groups of the carbons 2, 3, 4 and 5 in the case of **2a** and 1, 2, 3, 4 and 5 in the case of compound **2b**, need also to be protected and for that was used the acetylation method. This reaction occurs with acetic anhydride under basic conditions. The method proposed is performed with sodium acetate[140] instead traditional method with pyridine[143], due to toxicity that is inherently linked to it.

The structure of both compounds was proved by comparing spectroscopic dates, ^{13}C NMR and ^{1}H NMR (tables 1 and 2), in the literature.[144]

Acetylation was proved by ^{1}H-RMN analyses of 6-*O*-triphenylmethyl-2,3,4-tri-*O*-acetyl-1-*O*-methyl-ß-D-glucopyranose **3a**, for the presence of 9 protons at δ 2.09, 1.99 and 1.73 ppm (3 CH_3) and in 6-*O*-triphenylmethyl-1,2,3,4-*O*-tetra-O-acetyl-ß-D-glucopyranose **3b** due to the presence of 12 protons at δ 1.99-2.214 ppm (4 CH_3). In ^{13}C-NMR is proved by the presence of 3 carbonyl groups at δ 171.20, 170.5 and 170.07 ppm for **3a** or 4 carbonyl groups at δ 170.24, 169.33, 169.05 and 168.95 ppm for **3b.**

After FTIR analysis we can prove the acetylation by the vibration of carbonyl group at 1733 cm^{-1}.

3.1.1.3. Selective deprotection of trityl group

Finally, a selective deprotection of trityl group was performed under acidic conditions, using formic acid. Procedures for its selective cleavage are scarce and most are aggressive methods that cannot be selective in the presence of other sensitive protecting groups. This method using an acid in ethyl acetate is more gently, and additionally is a very simple method for detritylation. Reactional conditions were optimized and were obtained acceptable yields with longer reaction times. The reactions were performed during 2h with 82% and 75% yield of compounds **4a** and **4b**, respectively.

Detritylation was verified the disappearance of trityl group at δ 7.18-7.57 ppm (m, 15 H) and appearance of a broad singlet at δ 2.66 and 2.35 ppm in ^{1}H-NMR of **4a** and **4b**, respectively. In ^{13}C-NMR spectrum data can observe also the presence of trityl group by the carbons at δ 143.6, 128.8, 127.9, 127.1 ppm (tables 1 and 2).

Table 1- Comparing compounds **2a** and **2b**, **3a** and **3b**, **4a** and **4b by** ^{1}H-NMR spectrum dates.

		Ph-H (Hz)	C-CH_3 (Hz)	O-CH_3 (Hz)	H-1 (Hz)	H-6a (Hz)	H-6b (Hz)
^{1}H-NMR	**2a**	7.50 – 7.16 (m, 15H)	a)	3.54 – 3.28 (m, 3H)	4.75 (d, 1H, J=3.8)	3.74 – 3.58 (m, 2H)	
	2b	7.36-7.14 (m, 15H)	a)	a)	4.92 (t, 1H, J=4.0 Hz)	3.65-3.51 (m, 2H)	
	3a	7.49 – 7.16 (m, 15H)	2.09, 1.99, 1.73 (3s, 9H)	3.46 (s, 3H)	5.01 (d, 1H, J=3.7)	3.19 (dd, 1H, J=10.4; 2.3)	3.12 (dd,1H, j=10.4; 5.3)
	3b	7.18-7.57 (m, 15H)	1.99-2.21 (3s, 12H)	a)	5.73 (d, J=3.6, 1H)	3.07 (dd, J=10.2; 2.5, 1H)	3.37 (dd, J=10.2; 5.1, 1H)
	4a	a)	2.08, 2.06, 2.02 (3s, 9H)	3.42 (s, 3H)	4.97(d, 1H, J=3.7)	3.80(dd,1H, J=2.7; 1.9)	3.60 (dd, 1H, J=4.6; 4.0)
	4b	a)	2.12, 2.07, 2.04, 2.03 (4s,12H)	a)	5.73 (d, 1H, J=8.2)	3.64 (dd, 2H, J=11.8; 10.0)	

a) Not applicable

Table 2- Comparing compounds **2a** and **2b**, **3a** and **3b**, **4a** and **4b** by ^{13}C-NMR spectrum dates.

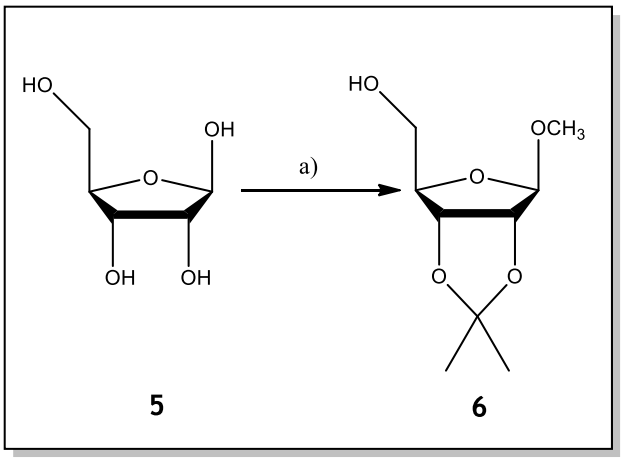
		Ph-C (Hz)	C-Ph_3 (Hz)	C=O (Hz)	O-CH_3 (Hz)	C-1 (Hz)	C-6 (Hz)
^{13}C-NMR	**2a**	143.75, 128.66, 127.90, 127.13	86.96	a)	55.21	99.10	74.62
	2b	148.20, 128.21, 128.00, 127.12	81.03	a)	a)	92.68	61.67
	3a	143.75, 128.66, 127.90, 127.13	82.94	171.20, 170.5, 170.07	56.42	72.6	60.91
	3b	143.6, 128.8, 127.9, 127.1	86.7	170.24, 169.33, 168.05, 168.95	a)	91.91	61.69
	4a	a)	a)	170.47, 170.19, 170.07	55.35	96.81	60.91
	4b	a)	a)	170.52, 170.15, 169.84	a)	92.03	60.94

a) Not applicable

3.1.2. 1-*O*-Methyl-2,3-*O*-isopropylidene-ß-D-ribofuranoside **(6)**

This procedure allows the protection with a methyl ether group in anomeric carbon (C-1) of D-ribose **5,** and simultaneously, the hydroxyls protection on carbons **2** and **3** with an isopropylidene group, in a one pot reaction. This method[145] was choosing because it is fast and simple, furthermore it allows good yields (89%). (Scheme 9)

The structure is proved by the presence of the quaternary carbon of the isopropylidene group at δ 112.2 ppm in ^{13}C-NMR spectrum and CH_3 of isopropylidene group at δ 1.28, 1.44 ppm in ^{1}H-NMR spectrum. (Table 3)



Scheme 9- Synthetic strategy of final compound **6**. Conditions and yield: a) Acetone, methanol, r.t., 48h, 89%.

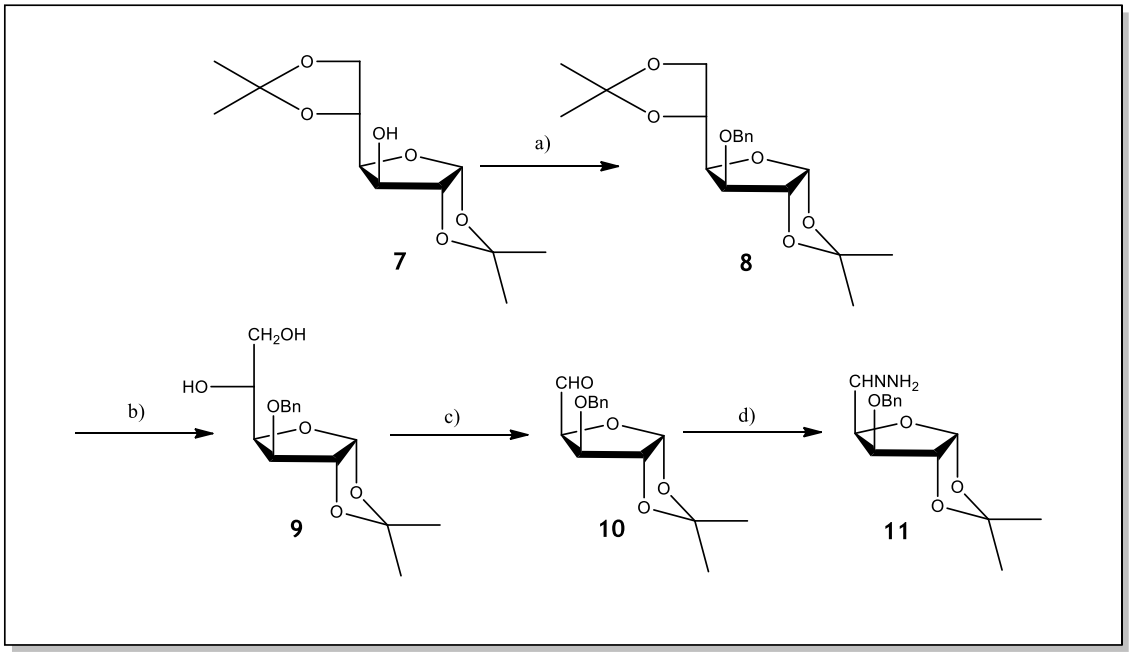
Table 3- ^{13}C-NMR and ^{1}H-NMR spectrum dates of compound 1-*O*-methyl-2,3-*O*-isopropylidene-ß-D-ribofuranoside **6** comparing to α-D-ribose.

		O-CH_3 (Hz)	**CH-1 (Hz)**	**CH-2 (Hz)**	**CH-3 (Hz)**	**CH_2-5 (Hz)**	**CH_3 (Hz)**	**C-CH_3 (Hz)**
^{13}C-NMR	6	55.6	110.1	81.6	85.9	64.1	24.8, 26.5	112.2
^{1}H-NMR		3.32 (s, 3H)	4.91 (s, 1H)	4.77 (dd, 1H, J=6.5, 5.3)	4.50 (dd, 1H, J=6.0, 2.3)	3.54-3.63 (m)	1.28, 1.44 (2s, 6H)	a)
^{13}C-NMR [146]	α-D-ribose	a)	97.8	72.4	71.50	62.9	a)	a)
^{1}H-NMR [147]		a)	5-6	2.1-3.1	4.81	3.8-4.3	a)	a)

a) Not applicable

3.1.3. 1,2-*O*-isopropylidene-3-*O*-benzyl-5-hydrazine-α-D-xylofuranose **(11)**

From a sequence reaction that is initiated by 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **7** was initiated by a benzylation[148] of hydroxyl on carbon 3, followed by a selective deprotection of isopropylidene[139] group between C5-C6, next an oxidative cleavage[139] to produce the aldehyde and finally formation of an hydrazone[139], according to the described methods, like is presented on following scheme (scheme 10).



Scheme 10- Synthetic strategy to obtain compound 11. Conditions and yield: a) BnBr, NaH/DMF, r.t., 20 min, 98%; b) AcOH 80%, 1h, 60ºC, 74%; c) 1.EtOH 2.SP/H_2O, 20 min, 95%; d) 1. $N_2H_4.H_2O$/EtOH 2. AcOH, 1h a 80ºC:

3.1.3.2. Benzylation

Primarily it was made a benzylation on hydroxyl group of C-3 in order to get all hydroxyl groups protected with aim to be able to the following reactions. This method[148] was choosing because allows good yields in an easy and fast method. Therefore, compound **7** as treated in N,N-dimethylformamide (DMF) with benzyl bromide (BnBr) and was used a Lewis base, sodium hydride (NaH), as catalyst to get 3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **8** with a yield of 98%.

The structure of this compound **8** was according to literature. [139]

3.1.3.3. Selective deprotection of 5, 6 hydroxyl groups

In order to synthesize the 3-*O*-benzil-1,2-*O*-isopropylidene-α-D-glucofuranose **9** was performed a selective deprotection of isopropylidene group in the position 5,6 of compound

8, by a reaction with acetic acid solution 80%, for 1h at 60°C. This method[139] is simple and fast, allowing a selective hydrolysis in a good yield of 74%.

The structure of this compound **9** was according to literature.[139]

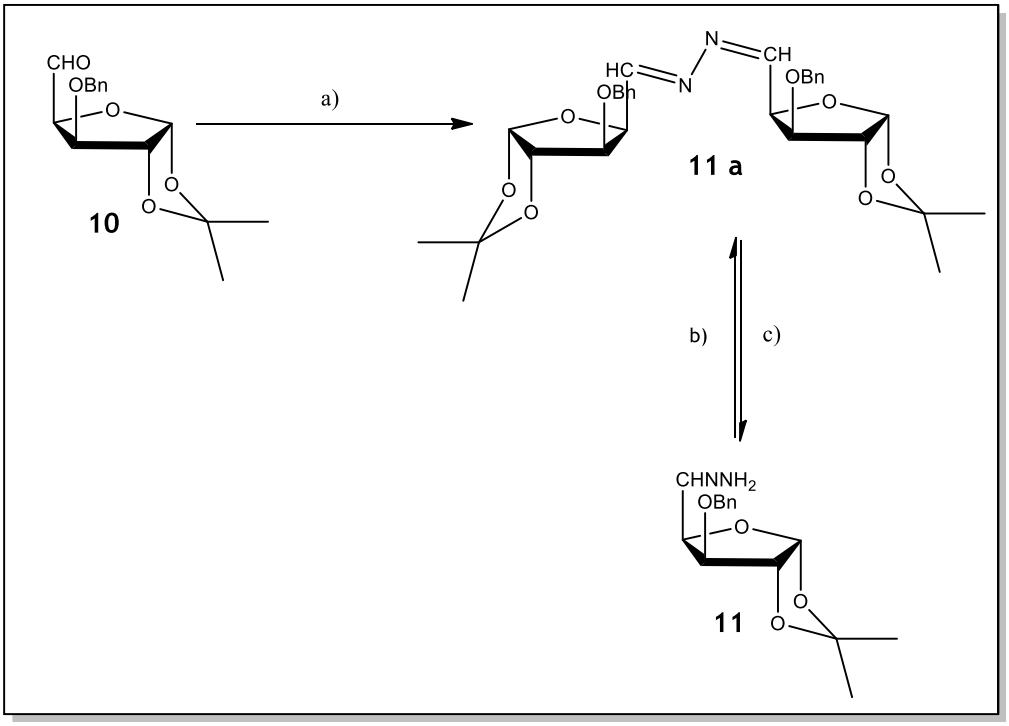
3.1.1.4. Oxidative cleavage

In this stage was performed an oxidative cleavage to the compound **9**, in order to cleave the C-C of vicinal diols and form an aldehyde (C-O). This synthetic method was realized [139] with sodium periodate in ethanol under light in high yields. The reaction was very fast because the vicinal diols are cis-diols and the obtained yield was 87%, according to the literature.[139]

The structure of 3-*O*-benzil-1,2-*O*-isopropilideno-α-D-*gluco*-pentodialdo-1,4-furanose **10** is proved by the presence of carbonyl group at δ 198.53 ppm in ^{13}C-NMR and the disappearance of H-5 in ^{1}H-NMR. (tables 4 and 5)

3.1.1.5. Aldehyde reduction

It was realized a wölf-kishner reduction in order to prepare an hydrazone **11** from aldehyde **10**. The reaction conditions were adapted and was performed with hydrazine hydrate 1 equivalent in ethanol and posteriorly addiction of acetic acid glacial over 1h at reflux. After 1h was observed that hydrazine hydrate had already reacted but there was still present aldehyde in the reaction. The workup was difficult but were isolated two fractions of chromatographic column. By ^{1}H-NMR and ^{13}C-NMR analysis (tables 4 and 5), it was observed that first fraction is very impure but are present 2 singlets at δ 8.25-7.85 ppm that are the two protons of amine group. By analysis of ^{1}H-NMR and ^{13}C-NMR of pure fraction it was observed that all signs are correct, including the sign of benzyl group at δ 7.55-7.05 ppm that integrate to 10 H, and the signals of sugar are duplicated, due the presence of chiral carbon which origins 2 isomers (α and ß). However, the signals of NH_2 aren't presents. By analysis of the literature [149] concludes that during the reaction one of the available amino groups of hydrazine reacts to form 1,2-*O*-isopropylidene-3-*O*-benzyl-5-hydrazine-α-D-xylofuranose **11**, or both amino groups react to form an azine, 5-(1',2'-dimetylenehydrazine)–*bis*-[3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose] **11a**, (scheme 11) depending on the stoichiometry and the experimental conditions. Aldehydes reacts readly with hydrazine in alcoholic solvents to give the corresponding azines. To solve this problem, a solution would be added a large excess of hydrazine hydrate and excluded the traces of acid[149].



Scheme 11- Proposal reaction mechanism to aldehyde reduction of compound **10**. Conditions and yield: a) 1.N_2H_4.H2O (< 1 equi.)/EtOH 2.AcOH reflux, 1h; b) $NH_2NH_2.H_2O$ (excess) EtOH, reflux; c) H^+, EtOH R'RCO; 25%.[149]

Table 4- Comparing compounds **10** and **11** by ^{1}H-NMR spectrum dates.

		Ar-CH (Hz)	**CH_3 (Hz)**	**CH_2-Ar (Hz)**	**H-5 (Hz)**	**CH_2-6a (Hz)**	**CH_2-6b (Hz)**	**NH_2**
^{1}H-NMR	**10**	7.36-7.31 (m)	1.60,1.36 (2s, 6H)	4.60-4.53 (m, 1H) 4.79-4.71 (m, 1H)	9.61 (s, 1H)	a)		a)
	11	7.55-7.05 (m)	1.49,1.31 (2s, 6H)	a)	4.64 (d, 1H, J=3.7)	a)		Not found

a) Not applicable

Table 5- Comparing compounds **10** and **11** by ^{13}C-NMR spectrum dates.

		Ar-C (Hz)	qC-Ar-C (Hz)	CHO (Hz)	CH-5 (Hz)	CH_2-Ar (Hz)	CH_2-6a (Hz)	CH_2-6b (Hz)	C=N (Hz)
^{13}C-NMR	**10**	128.50, 128.29, 128.04	113.44	198.53	a)	72.21	a)		a)
	11	129.75-127.29	137.04	a)	82.86	72.18	84.07		160.65

a) Not applicable

Table 6- Carbohydrate derivatives used as organic component to synthesize mono-organosilane precursors.

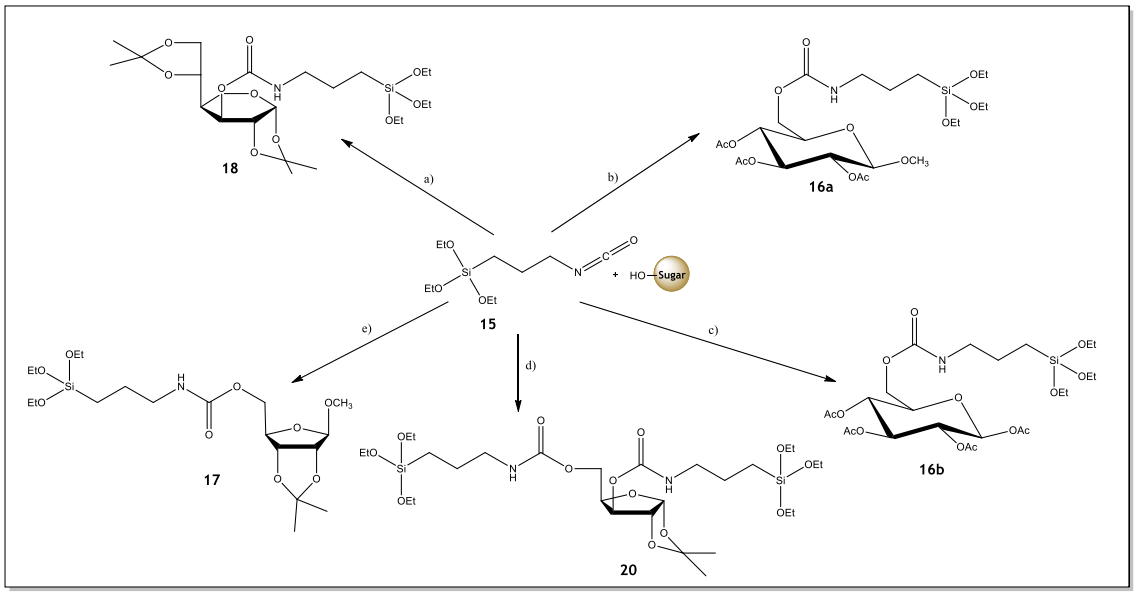
ORGANIC COMPOUND	YIELD (%)	ORGANIC/INORGANIC CROSS-LINK TYPE
4a	82%	Urethane
4b	75%	Urethane
6	89%	Urethane
7	a)	Urethane
19	a)	Urethane
21	b)	Urea

a) Not applicable

b) No obtained compound

3.2. Synthesis of nono-organosylilated precursors

In the present stage were prepared the silylated precursors[150] (Scheme 12) involving a urethane and urea cross-link between the carbohydrate derivatives and inorganic compound 3-(Triethoxysilyl)propyl isocyanate **15**. (table 15)

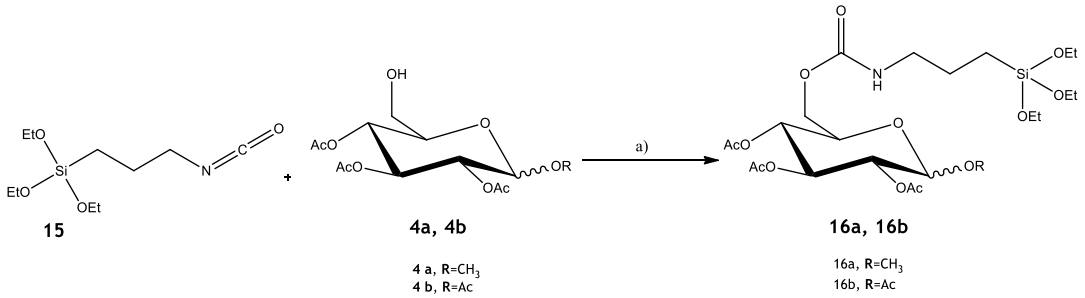


Scheme 12- Synthesis of organotriethoxysylilane based on carbohydrate. Conditions and yields: a) THF, 60°C, 10 days, 71%; b) THF, 50°C, 6 days, 90%; c) THF, 50°C, 6 days, 87% d) THF, 60°C, 10 days, 65%; e) THF, 60°C, 5 days, 80%.

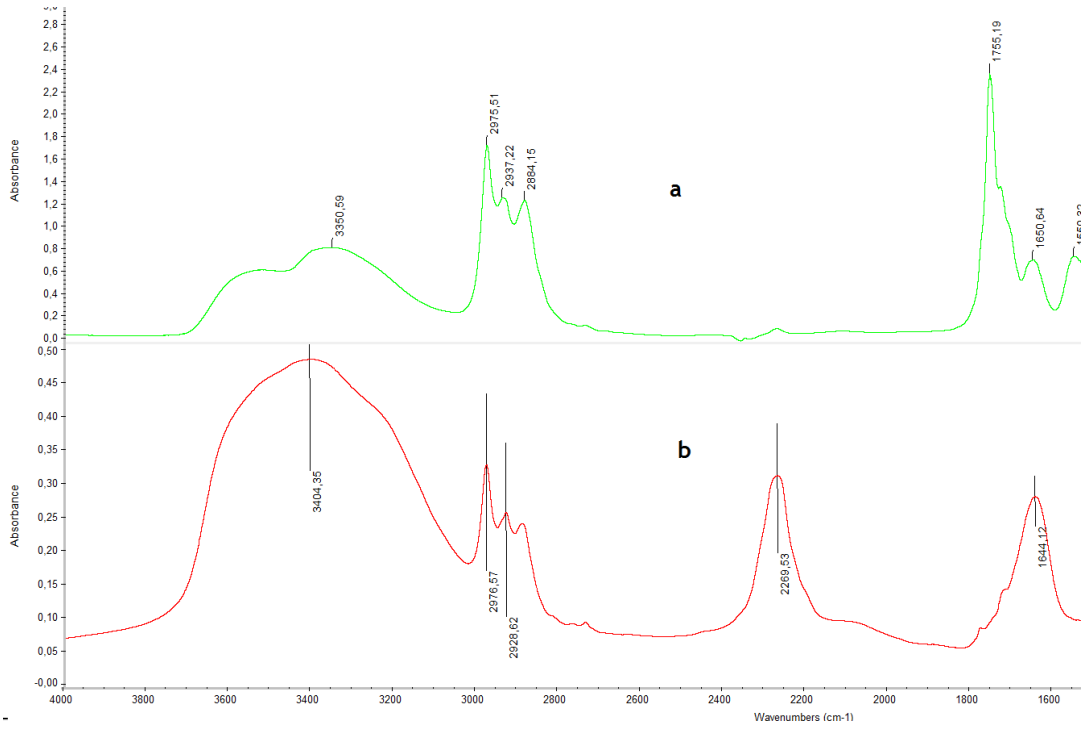
3.2.1. 6-*O*-methyl(3-(trietoxysilyl)propyl)carbamate-1-*O*-methyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranose **(16a)** and 6-*O*-methyl(3-(trietoxysilyl)propyl)carbamate-1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose **(16b)**

Synthesis of these precursors 6-*O*-methyl(3-(trietoxysilyl)propyl)carbamate-1-*O*-methyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranose **16a** and 6-*O*-methyl(3-(trietoxysilyl)propyl)carbamate-1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose **16b**, was obtained by urethane cross-link between the ICPTES **15** and compounds **4a** and **4b**. (Scheme 13) The synthetic method[150] is a simple technique but as is a SN1 reaction and the use of a polar aprotic solvent in the present procedure like THF promote slowing of the reaction. Reaction is initiated by nucleophilic attack of hydroxyl group of organic compound (**4a** and **4b**) to the carbonyl group of isocyanate group. In the first synthesis of the present precursor occurred formation of a film which means that might have occurred polymerization and decomposition, once silyl groups have high reactivity. This phenomenon could be related to the fact that the precursor was stored in a reaction flask without any solvent, so in the next reactions, all precursors were stored in solution. Control reaction of these two precursors, it's very important and was performed by

FTIR and we can easily both observe the existence of a linkage between the organic and inorganic compounds since during the formation of the urethane cross-link, a sharp absorption band in the region of 2273 cm^{-1}, assigned to the vibration of isocyanate group, decreased until disappear, at the end of reaction. (Graphic 1) At the same time, urethane group bands, become more intense and consequently appears a band at 1751 cm^{-1} assigned to the amide group. Furthermore, at 1756 cm^{-1} also appears a carbonyl group from acetate groups. According to the comparison between ^{1}H-NMR and ^{13}C-NMR of **4a** and **16a**, is observed a variation from the shifts of sugar **4a**, particularly an increase in shift of CH_2-6, relatively to **16a** (tables 7 and 8). Compound **16b** showed similar behaviour in relation to **16a**.



Scheme 13- Synthetic route[150] to prepare bridged organosilane precursors **16a** and **16b**. Conditions and yields: **16a**: THF 50°C, 6 days, 90%; **16b:** THF, 50°C, 6 days, 87%



Graphic 1- Comparison of ICPTES FTIR **(b)** to precursor **16a** FTIR **(a).** As it could be observed, isocyanate band at 2263 cm^{-1} **(b),** disappeared in precursor **(a)** after 6 days of reaction at 50°C/60°C. Appears a band at 1755 cm^{-1}**(a)** assigned to the amide group.

Table 7- ^{1}H-NMR spectrum signals of carbohydrate derivative **4a** comparing to signals of carbohydrate in the precursor **16a.**

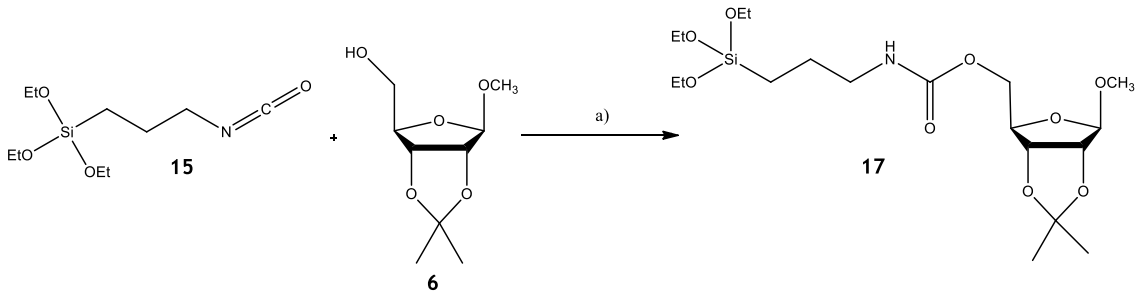
		H-1 (Hz)	H-2 (Hz)	H-3 (Hz)	H-4 (Hz)	H-5 (Hz)	CH_2-6a (Hz)	CH_2-6b (Hz)	C-CH_3
^{1}H-NMR	**4a**	4.97 (d,1H, J=3.7)	5.53 (t, 1H, J=9.8 Hz)	3.75-3.68 (m)	5.03 (t, 1H, J=9.8 Hz)	4.87 (dd, 1H, J= 10.2, 3.6)	3.80 (dd, 1H, J=2.7, 1.9)	3.60 (dd, 1H, J=4.6, 4.0)	2.08, 2.06, 2.02 (3s, 9H
	16a	4.93 (d, J=3.6, 1H)	5.45 (t, J=9.8,1H)	4.16 (d, J=4.3,1H)	5.01 (t, J=10,1H)	4.86 (dd, J=10.2, 3.6,1H)	4.11-3.91 (m, 2H)		2.06, 2.01, 1.98 (3s, 9H)

Table 8- ^{13}C-NMR spectrum signals of carbohydrate derivative **4a** comparing to signals of carbohydrate in the precursor **16a**.

		C-1 (Hz)	C-2 (Hz)	C-3 (Hz)	C-4 (Hz)	C-5 (Hz)	C-6 (Hz)	CH_3 (Hz)	C=O (Hz)
^{13}C-NMR	**4a**	96.81	70.96	68.85	69.84	69.28	60.91	20.67, 22.62, 22.65	170.47, 170.19, 170.07,
	16a	96.70	70.80	68.83	69.80	67.45	67.95	20.71. 20.67, 20.63	170.15, 170.07, 169.55

3.2.2. 5-*O*-ethyl(3-(trietoxysilyl)propyl)carbamate-1-O-methyl-2,3-O-isoropylidene-ß-D-glucofuranose **(17)**

Synthesis of this precursor 5-*O*-ethyl(3-(trietoxysilyl)propyl)carbamate-1-*O*-methyl-2,3-O-isoropylidene-ß-D-glucofuranose **17** [150] was also obtained by urethane cross-link, between the ICPTES **15** and compound **6** (scheme 14) Control reaction was realized by FTIR and is equally observed the existence of a linkage between the organic and inorganic compounds by disappearance of absorption band in the region of 2273 cm^{-1}. Reaction time was the same of the previous precursors (5 days). ^{1}H-NMR and ^{13}C-NMR are presented in table 9 and 10. According to the comparison between ^{1}H-NMR and ^{13}C-NMR of **6** and **17**, is observed a variation from the shifts of sugar **6**, particularly an increase in shift of CH_2-5, relatively to **17**. (Tables 9 and 10)



Scheme 14- Synthetic route[150] to prepare bridged organosilane precursor **17**. Conditions and yields: THF, 60°C, 5 days, 80%.

Table 9-^{1}H-NMR spectrum signals of carbohydrate derivative **6** comparing to signals of carbohydrate in the precursor **17.**

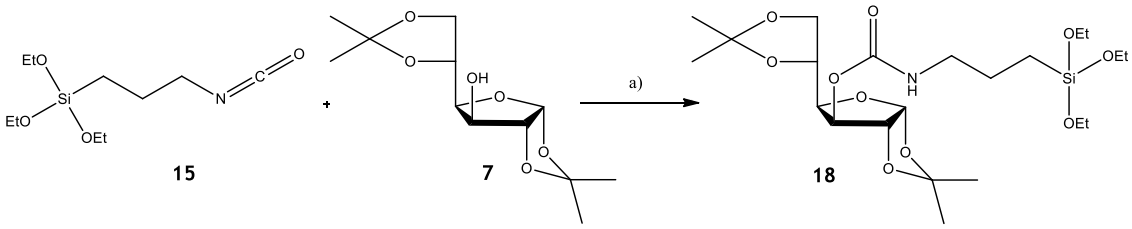
		H-1 (Hz)	H-2 (Hz)	H-3 (Hz)	H-4 (Hz)	CH_2-5 (Hz)	CH_3 (Hz)
^{1}H-NMR	**6**	4.93 (s, 1H)	4.79 (dd, J=6.5, 5.3, 1H)	4.55 (dd, J=6.0, 2.3, 1H)	4.37 (dd, J=7.2, 2.7, 1H)	3.54-3.63 (m, 2H)	1.28, 1.44 (2s, 6H)
	17	4.91 (s, 1H)	4.77 (dd, J=6.5, 5.3, 1H)	4.50 (dd, J=6.0, 2.3, 1H)	4.26 (dd, J=7.2, 2.7, 1H)	4.15-4.03 (m, 2H)	1.32, 1.51 (2s, 6H)

Table 10- ^{13}C-NMR spectrum signals of carbohydrate derivative **6** comparing to signals of carbohydrate in the precursor **17**.

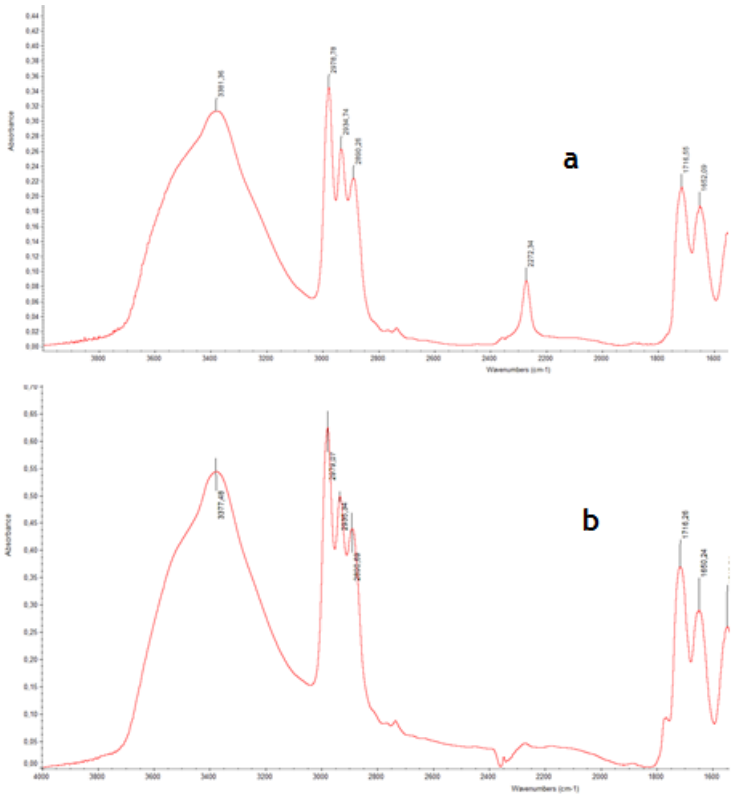
		C-1 (Hz)	C-2 (Hz)	C-3 (Hz)	C-4 (Hz)	C-5 (Hz)	CH_3 (Hz)	C-CH_3 (Hz)
^{13}C-NMR	**6**	110.10	81.60	85.90	88.40	64.10	24.80, 26.50	112.20
	17	109.94	81.35	81.46	67.94	68.92	24.96, 24.61	112.08

3.2.3. 3-*O*-ethyl(3-(trietoxysilyl)propyl)carbamate-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **(18)**

Synthesis of these precursor 3-*O*-ethyl(3-(trietoxysilyl)propyl)carbamate-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **18** was performed (scheme 15) [150]. Reaction time of this precursor is more slowly, once the hydroxyl group C-3 of commercial carbohydrate **7** is a nucleophile less reactive than the previous precursors. Reaction control was performed by FTIR and we can observe the existence of a linkage between the organic and inorganic compounds since during the formation of the urethane cross-link, a sharp absorption band in the region of 2273 cm^{-1}, assigned to the vibration of isocyanate group, decreased after 2 days of reaction until disappear, at the end of 10 days at 50-60ºC (Graphic 2) Urethane group bands, become more intense and consequently appears a band at 1714 cm^{-1} assigned to the amide group. This precursor precipitates in the reaction medium because it is poorly soluble. According to the comparison between ^{1}H-NMR and ^{13}C-NMR of **7** and **18**, is observed a variation from the shifts of sugar **7**, particularly an increase in shift of CH-3, relatively to **18**. (Tables 11 and 12)



Scheme 15- Synthetic route[150] to prepare bridged organosilane precursor **18**. Conditions and yields: THF, 60°C, 10 days, 71%.



Graphic 2- Comparison precursor **18** FTIR after 2 days of reaction (a) to precursor **18** FTIR after 10 days of reaction (b) at 50ºC/60ºC. As it could be observed, isocyanate band at 2263 cm^{-1} (a), disappeared completly in precursor (a) after 10 days of reaction at 50˚C/60˚C. Appears a band at 1716 cm^{-1} increasingly more intense (b) assigned to the amide group.

Table 11- ^{1}H-NMR spectrum signals of carbohydrate derivative **7** comparing to signals of carbohydrate in the precursor **18.**

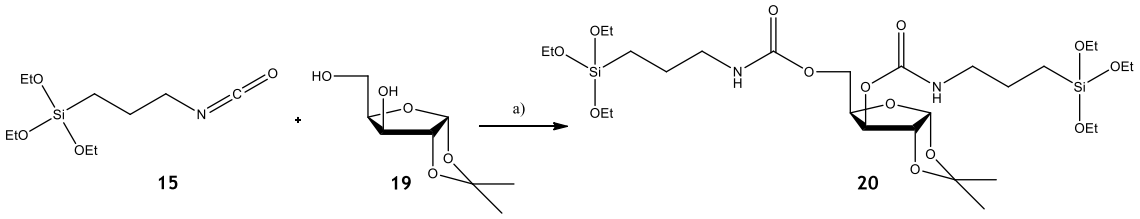
		H-1 (HZ)	H-2 (HZ)	H-3 (HZ)	H-4 (HZ)	H-5 (HZ)	CH_2-6a (HZ)	CH_2-b (HZ)	CH_3 (HZ)
^{1}H-NMR	**7** [151]	5.94 (d,1H, J=3.5)	4.53 (d, 1H, J=3.5)	4.33-4.22 (m, 1H)	4.05 (dd, 1H, J=6.1, 1.9	4.33-4.22 (m, 1H)	4.17 (dd, 1H, J=8.4, 6.3	4.01 (dd, J=8.4,6.1 , 1H)	1.45, 1.37, 1.50, 1.32 (4s, 12H)
	18	5.91 (d, J=3.6, 1H)	4.55 (d, J=3.6, 1H)	4.36-4.26 (m, 1H)	4.14 (dd, J=7.5, 6.2, 1H)	4.36-4.26 (m, 1H)	4.04 (dd, J=7.9, 2.8, 1H)	3.97 (dd, J=8.6, 5.3, 1H)	1.47, 1.42, 1.34, 1.29 (4s, 12H)

Table 12- ^{13}C-NMR spectrum signals of carbohydrate derivative **7** comparing to signals of carbohydrate in the precursor **18.**

		C-1 (HZ)	C-2 (Hz)	C-3 (Hz)	C-4 (Hz)	C-5 (Hz)	C-6 (Hz)	CH_3 (Hz)	C-CH_3 (Hz)
^{13}C-NMR	**7** [151]	105.3	85.10	74.90	81.20	73.20	67.6	26.8, 25.2, 26.8, 26.2	109.6, 11.8
	18	105.24	85.27	75.01	81.23	73.32	67.58	26.72 26.16 25.58 225.29	111.76

3.2.4. *Bis*(3,5-*O*-methyl(3-(trietoxysilyl)propyl)carbamate-1,2-*O*-isopropylidene-α-D-glucofuranose **(20)**

In contrast to other carbohydrate derivatives previously synthesized, these commercial compound, 1,2-*O*-Isopropylidene-α-D-xylofuranose **19** has two free hydroxyl groups, so the stoichiometry of the reaction changed from NCO/OH: 1/1 to NCO/OH: 2/1. (scheme 16) The used technique was adapted [150]. Reaction time of this precursor is equally slowly, because while hydroxyl group C-5 is a nucleophile more reactive, the hydroxyl group C-3 is less reactive. After 10 days of reaction the sharp absorption band in the region of 2273 cm^{-1}, assigned to the vibration of isocyanate group, completely disappear, (Graphic 3) Urethane group bands, become more intense and consequently appears a band at 1751 cm^{-1} assigned to the amide group. According to the comparison between ^{1}H-NMR and ^{13}C-NMR of **19**[152] and *Bis*-(3,5-O-Methyl(3-(trietoxysilyl)propyl)carbamate-1,2-*O*-isopropylidene-a-D-glucofuranose **20**, is observed a variation from the shifts of sugar **19**, particularly an increase at **δ** CH-3 and at **δ** CH_2-6 relatively to **20**, which proves the linkage of **15** in C-3 an C-6 of **19.** (Tables 13 and 14)



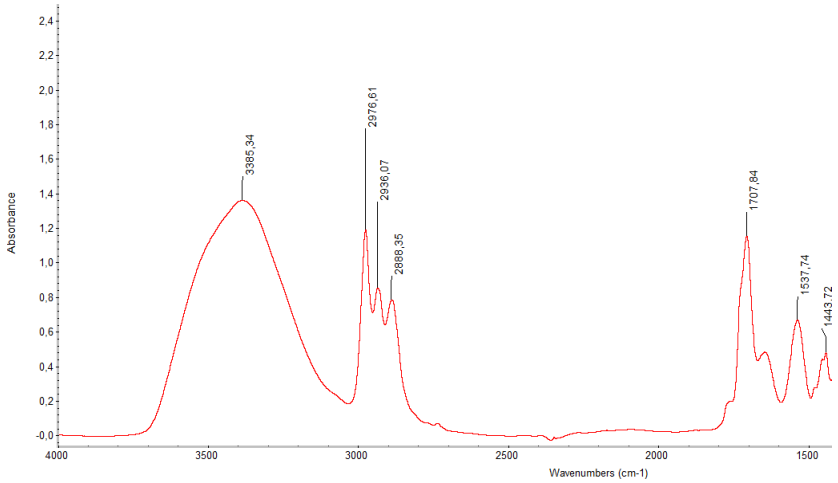
Scheme 16- Synthetic route[150] to prepare bridged organosilane precursor **20**. Conditions and yields: THF, 60°C, 10 days, NCO/OH: 2/1, 65%;

Table 13- ^{1}H-NMR spectrum signals of carbohydrate in the precursor **20**.

		H-1 (HZ)	H-2 (HZ)	H-3 (HZ)	H-4 (HZ)	C-CH_3 (HZ)	CH_2-5a (HZ)	CH_2-5b (HZ)
^{1}H-NMR	**20**	5.91 (d, J=3.6, 1H)	5.01 (d, J=3.6, 1H)	5.20-5.09 (m, 1H)	4.61-4.43 (m, 1H)	1.52, 1.31 (2s, 6H)	4.45 (dd, J=11.7, 4.8, 1H)	4.30 (dd, J=11.47, 4.8, 1H)

Table 14- ^{13}C-NMR spectrum signals of carbohydrate in the precursor **20.**

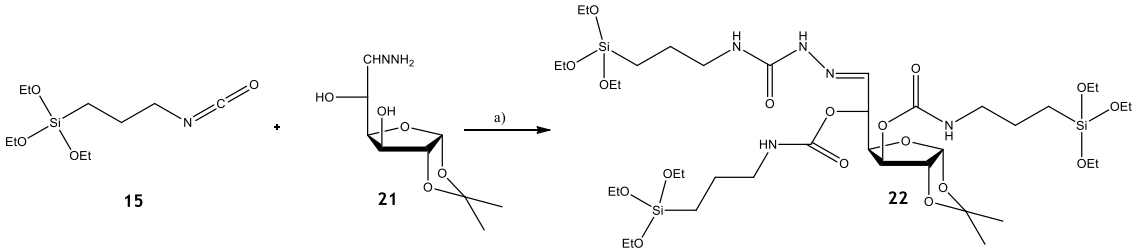
		C-1 (HZ)	C-2 (HZ)	C-3 (HZ)	C-4 (HZ)	C-5 (HZ)	C-CH_3 (HZ)	CH_3 (HZ)
^{13}C-NMR	**20**	104.55	79.93	84.96	76.66	69.7	112.20	26.70, 26.19



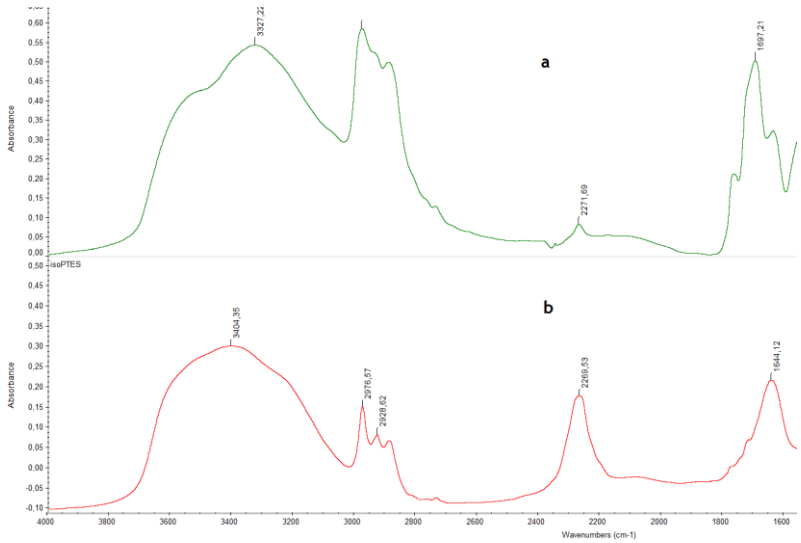
Graphic 3- FTIR of precursor **20** after 10 days at 50ºC/60ºC. As it could be observed, isocyanate band, disappeared completely. Appears a band at 1707 cm^{-1}, assigned to the amide group.

3.2.5. 3,5,6-tri-*O*-ethyl(3-(trietoxysilyl)propyl)carbamate-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **(22)**

Possible synthesis of these precursor[150] 3,5,6-tri-*O*-ethyl(3-(trietoxysilyl)propyl)carbamate-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **22** was obtained by urea and urethane cross-link between the ICPTES **15** and compound **21**[153]. (scheme 17) Reaction is initiated by nucleophilic attack of amine group of organic compound **21** to the carbonyl group of isocyanate group. This compound **21** has three free hydroxyl groups, so the stoichiometry of the reaction is NCO/(NH_2/OH): 3/1. Control reaction of these two precursors, was equally performed by FTIR and we can easily both observe the existence of a linkage between the organic and inorganic compounds since during the formation of the urea cross-link, a sharp absorption band in the region of 2273 cm^{-1}, assigned to the vibration of isocyanate group, decreased until disappear, at the end of reaction. At the same time, urea group bands, become more intense and consequently appears a band at 1697 cm^{-1} (Graphic 4). However, when was observed the ^{1}H and ^{13}C NMR, we can conclude that the precursor it was very impure, which means the precursor needs to be purified, but purification is a problem once silica-gel chromatography cannot be utilized for purification of conventional precursors unlike for general organic compounds. Recrystallization also they are not a good option because it's very difficult crystallize a carbohydrate due your properties.[131]



Scheme 17- Possible synthetic route[150] to prepare bridged organosilane precursor **22**. Conditions: THF, 60°C, 10 days.



Graphic 4- Comparison of ICPTES FTIR (b) to precursor 22 (a). As it could be observed, isocyanate band disappeared in precursor (a) after 8 days of reaction at 50°C/60°C. Appears a band at 1697 cm^{-1}(a) assigned to the urea group.

Table 15- Synthesis of organosilane bridged precursors: organic, inorganic, precursors and yields. Reaction conditions: ICPTES, organic compound/THF, 50-60°C.

Organic	Inorganic	Precursor	Yield (%)
4a	ICPTES	16a	90%
4b	ICPTES	16b	87%
6	ICPTES	17	80%
7	ICPTES	18	71%
19	ICPTES	20	65%
21	ICPTES	22	a)

a) No obtained compound

4. Conclusions and future work

The aim of this work was to synthesize monosilylated precursors with a carbohydrate derivative. In summary, was performed the synthesis and characterization of mono organosilylated precursors.

It was achieved with success, the synthesis of new types of mono-oranosylilated precursors **16a**, **16b**, **17**, **18**, **19** and **20** with carbohydrate derivatives **4a**, **4b** and **6** and with commercial carbohydrates **7** and **19**, in good yields.

The synthesis of compound **21** and **22** was not possible.

Synthesis of precursors is difficult and slow, furthermore, in the future, requires a great optimization namely in time and temperature.

As prospects for the future, these precursors were herein used to prepare mesoporous organosilica hybrid envisioning their future potential use as an anti-tumoral drug delivery platform with the aim of achieve new materials for biomedical applications, opening the opportunity to link it with potential new drugs or others already in the market, in particularly to have a controlled release of them, giving new and better ways to hit the disease target.

Loading a drug inside the pores walls, through the studies of interaction between the carbohydrate derivative and the therapeutic agent, we can study their delivery with pH changes and even, cytotoxic evaluation, should also be a prospect for the future.

5. Experimental section

5.1. General data

Reagents and solvents were bought from Fluka, Merck, Aldrich or Acros Organics and are analytically pure and, if necessary, were dried with molecular sieves 4 Å and purified by standardized methods.[154]

To the reactions that can be followed by thin layer chromatography, this technique was used to check the progress of reactions and during purification. Were used TLC plates (aluminium plates of 2 mm, coated with Silica-gel (Macherey-Nagel 60 G/UV_{254}) powered by UV light (λ= 254 nm) and immerse in a revealing solution and then heated at 200 ° C. The revealing solution was: Sulphuric acid (10%) in ethanol or Sulphuric acid (1.5 mL), vanillin (3 g) in ethanol (100 mL). Both eluent and volumetric proportion are referred for each case. The Rfs (retention factors) were calculated by the ratio between the distance moved by the product and the distance moved by the solvent.

The synthesized compounds were purified by chromatography columns using silica gel 60G (40-63 μm and 230-400 mesh) as stationary phase and chromatographic columns were performed with ambient pressure or medium pressure chromatography, using a pump.

The infrared by Fourier Transform (FTIR) spectra were obtained in attenuated total reflectance mode (ATR) in equipment Thermoscientific Nicolet IS10: smart iTR (Smart Omni Transmission Acessory; SmartrankBR) and Omnic 8.2 software. Precursors were analysed in solution form (tetrahydrofuran solvent). For FTIR data acquisition, on the face of a highly polished KBr plate, was applied the sample in solution which, after drying the solvent was placed the second plate. The two KBr plates were used as reference in absorbance calculations. All the sample spectra were collected at room temperature in the 4000-600 cm^{-1} range by averaging 32 scans at a spectral resolution of 4 cm^{-1}.

^{1}H Nuclear Magnetic Resonance (NMR) and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were performed on a Bruker spectrometers type Brüker Avance III (400,13 MHz and e 100,63 MHz, respectively) using Tetramethylsilane (TMS) as the internal standard, at Universidade da Beira Interior. Were processed in Topspin 3.1 software. DMSO-d_6 or $CDCl_3$, were used as solvents and also, as internal standard, (DMSO-d_6, δ= 2,50 ppm e 39,52 ppm or $CDCl_3$, δ= 7,26 ppm e 77,16 ppm in ^{1}H e ^{13}C NMR, respectively) 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 expressed in parts per million (ppm). The 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).

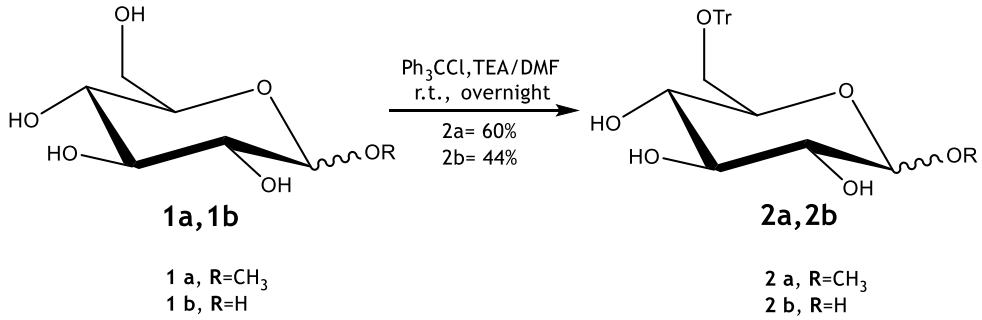
For each synthesized compound, both 2D structure and respective Simplified Molecular Input Line Entry Specification (SMILES) are represented. SMILES are important for in silico predictions and that was performed in Chembiodraw 13.0, ChembiodrawSoft® software.

5.2. Synthesis of carbohydrate derivatives - starting materials

For the synthesis of the organic component of the precursor were used as base carbohydrate, the 1-*O*-methyl-α-D-glucopyranose and D-Glucose, which were modified by a reaction sequence involving 3 steps, D-ribose which was methylated and protected with isopropylidene in only one step, and the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, which was modified by a reaction sequence involving 4 steps.

5.2.1. Reaction sequence from methyl-α-D-glucopyranoside **(1a)** and D-Glucose **(1b)**

5.2.1.1. 1-*O*-methyl-6-O-tripenhylmethyl-α-D-glucopiranoside (2a) and 6-*O*-thriphenylmethyl-α-D-glucopiranoside (2b)



Scheme 18- Preparation of **2a** and **2b** from **1a** and **1b**, respectively. Yield: **2a**=60%, **2b**=44%.

Chemical formula 2a/2b: $C_{26}H_{28}O_6$/ $C_{25}H_{26}O_6$

M.W. 2a/2b = 436.50/ 422.17 g/mol

It was prepared a solution of 1-*O*-methyl-α-D-glucopyranoside **1a** or D-glucose **1b** (1g, 5 mmol; 1g, 6 mmol), respectively, in DMF (2.67 mL; 3.20 mL). Then this solution, was placed under nitrogen atmosphere and was added trityl chloride (1.49 g, 5.3 mmol; 1.49 g, 6.36 mmol), thrietylamine (1.26 mL; 1.51 mL) and DMAP (49 mg; 58.8 mg). The reaction mixture was stirring at room temperature overnight. After addition of a mixture of ice and water (50 mL, 60 mL), an extraction was performed with dichloromethane (3x20 mL; 3x24 mL) and the organic phase was washed with a saturated solution of ammonium chloride (50 mL; 60 mL), distilled water (50 mL; 60 mL) and after drying with anhydrous sodium sulfate. Filtration and concentration under the pressure, gives a residue which was purified by column chromatography under moderate pressure using Ethyl Acetate/N-Hexane (EA/H) (2:1) as

eluent to afford the corresponding trityl derivative **2a or 2b**. (Scheme 18) **2a-** Yield: 60%. Rf: 0.21 (EA/H: 3/1). **2b-** Yield: 44%. Rf: 0.17 (EA/H: 3/1). [139]

2a:

FTIR (cm^{-1}): 3490 (OH), 1590 (C=C aromatic).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.16 (m, 15H, 3 Phenyl), 4.75 (d, *J* = 3.8 Hz, 1H, H-1), 3.74 – 3.58 (m, 2H, CH_2-6), 3.54 – 3.28 (m, 7H, H-2, H-3, H-4, H-5 and O-CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 143.75, 128.66, 127.90 and 127.13 (3 Phenyl + 1 qC aromatic) 99.10 (C-1), 86.96 (C-Ph_3), 74.62, 72.17, 71.67 and 70.01 (C-2, C-3, C-4 and C-5), 63.96 (C-6), 55.21 (O-$\underline{C}H_3$).

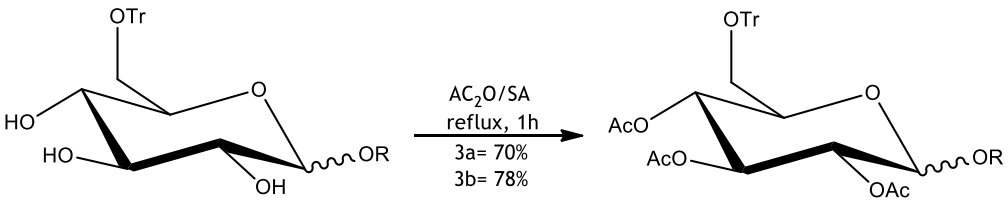
2b:

FTIR (cm^{-1}): 3490 (OH), 1590 (C=C aromatic).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 – 7.14 (m, 15H, 3 Ph-H), 4.92 (t, *J* = 4.0 Hz, 1H, H-1), 4.80 (d, *J* = 5.4 Hz, 1H, OH), 4.66 (d, *J* = 4.7 Hz, 1H, OH), 4.48 (d, *J* = 6.7 Hz, 1H, OH), 4.40 (bs, 1H, OH), 3.65 – 3.51 (m, 3H, CH_2-6, H-4 and H-5), 3.18 – 2.98 (m, 2H, H-2 and H-3).

^{13}C NMR (101 MHz, DMSO-d_6) δ 148.20, 128.21, 128.00 and 127.12 (3 Ph-C + 1 qC aromatic), 92.68 (C-1) 81.03 ($\underline{C}$-Ph_3), 73.54, 72.82, 72.41 and 71.03 (C-2, C-3, C-4 and C-5) 61.67 (C-6).

5.2.1.2. 6-*O*-triphenylmethyl-2,3,4-tri-*O*-acetyl-1-*O*-methyl-α-D-glucopyranose (3a) and 6-*O*-triphenylmethyl-1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranoside (3b)



2a,2b

2 a, **R**=CH_3
2 b, **R**=H

3a,3b

3 a, **R**=CH_3
3 b, **R**=Ac

Scheme 19- Preparation of **3a** and **3b** from **2a** and **2b**, respectively. Yield: **3a**=70%, **3b**=78%.

Chemical formula 3a/3b: $C_{32}H_{34}O_{9/}$ $C_{33}H_{34}O_{10}$

M.W. 3a/3b = 562.62/422.17 g/mol

Anhydrous sodium acetate (0.31 g) and acetic anhydride (5.7 mL, 60.3 mmol) was added into a reaction flask. This mixture was heated under reflux for 20 minutes. Then, compound **2a** (1 g, 2.29 mmol) or **2b** (1g, 2.37 mmol), was slowly added to previous solution at room temperature. The mixture was in reflux for 1 hour. After the end of reaction, the reaction mixture was drop in 10 mL of cold water to cause the precipitation of crystals. The mixture is put in an ice bath to continue the crystallization. In the end, the crystals are filtered under vacuum to give the acetylated compound **3a** or **3b**. (Scheme 19) The end of reaction is controlled by TLC. **3a**- Yield: 70%. Rf: 0.63 (EA/H: 1/3). **3b**- Yield: 78%. Rf: 0.60 (EA/H: 1/3). [140]

3a:

FTIR (cm^{-1}): 1733(C=O), 1590 (C=C aromatic).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.16 (m, 15H, 3 Ph-H), 5.43 (t, *J* = 10.2 Hz, 1H, H-2), 5.06 (t, *J* = 10.3 Hz, 1H, H-4), 5.01 (d, *J* = 3.7 Hz, 1H, H-1), 4.93 (dd, *J* = 10.2, 3.7 Hz, 1H, H-5), 3.95 – 3.88 (m, 1H, H-3), 3.46 (s, 3H, O-CH_3), 3.19 (dd, *J* = 10.4, 2.3 Hz, 1H, H-6a), 3.12 (dd, *J* = 10.4, 5.3 Hz, 1H, H-6b), 2.09 (s, 3H, C-CH_3), 1.99 (s, 3H, C-CH_3), 1.73 (s, 3H, C-CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.20 (C=O), 170.5 (C=O), 170.07(C=O), 143.75, 128.66, 127.90 and 127.13 (3 Ph-C + 1 qC aromatic), 82.94 (C-Ph_3), 75.20 (C-5), 72.6 (C-1), 71.8 (C-2), 70.95 (C-3), 68.7 (C-4), 60.91(C-6), 56.42 (O-CH_3), 20.67 (O=C-$\underline{C}H_3$), 22.65 (C-$\underline{C}H_3$), 22.62 (C-$\underline{C}H_3$).

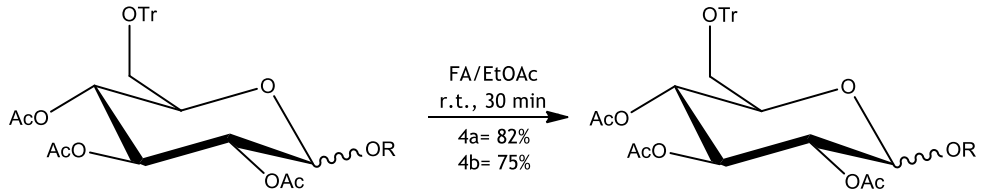
3b:

FTIR (cm^{-1}): 1733(C=O), 1590 (C=C aromatic).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18–7.57 (m, 15H, 3 Ph-H), 5.73 (1H, d, *J* = 3.6 Hz, H-1), 5.30 (1H, t, *J* = 10.0, Hz H-4), 5.11–5.47 (m, 3H, H-2, H-3 and H-5), 3.07 (1H, dd, *J* = 10.2, 2.5 Hz, H-6a), 3.37 (1H, dd, *J* = 10.2, 5.1 Hz, H6-b), 3.70 (1H, d, 3.4 Hz, H-5), 1.99–2.214 (3 s, 12H, C-CH_3);

^{13}C NMR (101 MHz, Chloroform-*d*) δ 20.6 (C-$\underline{C}H_3$), 170.24, 169.33, 169.05 and 168.95 (3 C=O), 143.6, 128.8, 127.9 and 127.1 (3 Ph-C + 1 qC aromatic), 91.91 (C-1), 86.7 (C–Ph3), 74.08 (C-5), 73.2 (C-3), 70.5 (C-2), 61.69 (C-6), 68.3 (C-4).

5.2.1.3. 6-*O*-triphenylmethyl-2,3,4-tri-*O*-acetyl-1-*O*-methyl-α-D-glucopyranoside (4a) and 1,2,3,4-tetra-*O*-acetyl-ß-D-glucopyranoside (4b)



3a,3b

3 a, R=CH_3
3 b, R=Ac

4a,4b

4 a, R=CH_3
4 b, R=Ac

Scheme 20- Preparation of **4a** and **4b** from **3a** and **3b**, respectively. Yield: **4a**=82%, **3b**=75%.

Chemical formula 4a/4b: $C_{15}H_{24}O_7$/ $C_{14}H_{20}O_{10}$

M.W. 4a/4b = 316.35/ 348.11 g/mol

The **3a** (1g, 1.77 mmol) or **3b** (1g, 2.37 mmol) compound was dissolved in a mixture of formic acid (FA) (4.2 mL; 7 mL) and EA (6.3 mL; 10.5 mL) at room temperature for 30 minutes. After the end of reaction, the solution was diluted with ethyl acetate, washed successively with brine and a saturated solution of sodium hydrogen carbonate until still neutral (3 series). Finally, the compound was dried with anhydrous sodium sulphate and concentration under the pressure. (Scheme 20) The residue was purified by column chromatography under moderate pressure using EA/H (2:1) as eluent. 4a- Yield: 82% Rf: 0.25 (EA/H: 1/3). 4b- Yield: 75%. Rf: 0.20 (EA/H: 1/3).[141]

4a:

FTIR (cm^{-1}): 3490 (OH), 1733(C=O).

^{1}H NMR (400 MHz, Chloroform-d) δ 5.53 (t, *J* = 9.8 Hz, 1H, H-2), 5.03 (t, *J* = 9.8 Hz, 1H, H-4), 4.97 (d, *J* = 3.7 Hz, 1H, H-1), 4.87 (dd, *J* = 10.2, 3.6 Hz, 1H, H-5), 3.80 (dd, *J* = 2.7, 1.9 Hz, 1H, H-6a), 3.75 – 3.68 (m, 1H, H-3), 3.60 (dd, *J* = 4.6, 4.0 Hz, 1H, H-6b), 3.42 (s, 3H, O-CH_3), 2.66 (bs, 1H, OH), 2.08 (s, 3H, C-CH_3), 2.06 (s, 3H, C-CH_3), 2.02 (s, 3H, C-CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.47 (C=O), 170.19 (C=O), 170.07 (C=O), 96.81 (C-1), 70.96 (C-2), 69.84 (C-4), 69.28 (C-5), 68.85 (C-3), 60.91 (C-6), 55.35 (O-CH_3), 20.67 (C-$\underline{C}H_3$), 22.65 (C-$\underline{C}H_3$), 22.62 (C-$\underline{C}H_3$).

4b:

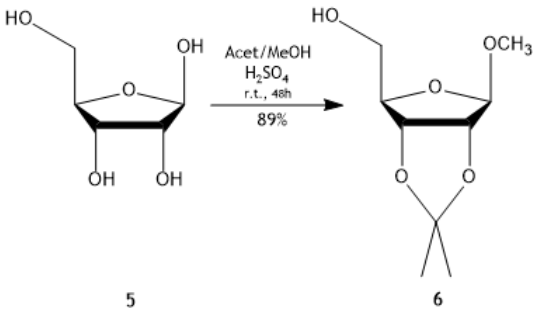
FTIR (cm^{-1}): 3325 (OH), 1733(C=O).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.73 (d, *J* = 8.2 Hz, 1H, H-1), 5.31 (t, *J* = 9.5 Hz, 1H, H-4), 5.15 – 5.05 (m, 2H, H-2 and H-3), 3.77 (d, *J* = 13.9 Hz, 1H, H-5), 3.64 (dd, *J* = 11.8, 10.0 Hz, 2H, CH_2-6), 2.35 (bs, 1H, OH), 2.12 (s, 3H, C-CH_3), 2.07 (s, 3H, C-CH_3), 2.04 (s, 3H, C-CH_3), 2.03 (s, 3H, C-CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.52 (C=O), 170.15 (C=O), 169.84 (C=O), 92.03 (C-1), 74.12 (C-4), 73.20 (C-2),70.55 (C-3), 68.36 (C-5), 60.94 (CH_2-6), 20.97, 20.95, 20.91, 20.90 (C-$\underline{C}H_3$).

5.2.2. Reaction sequence from D-Ribose **(5)**

5.2.2.1. 1-O-Methoxy-2,3-O-isopropylidene-ß-D-ribofuranose (6)



Scheme 21- Preparation of **6** from **5**. Yield: 89%.

Chemical formula: $C_9H_{16}O_5$

M.W. = 204.10 g/mol

D-ribose 5 (1 g, 6.66 mmol) was dissolved in 5 mL of dry acetone and 5 mL of dry methanol at room temperature. The sulphuric acid (0.5 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 MgSO4, filtered and evaporated in the evaporator. (Scheme 21) [145] Yield: (89%). Rf: 0.48 (EA/H: 1/1)

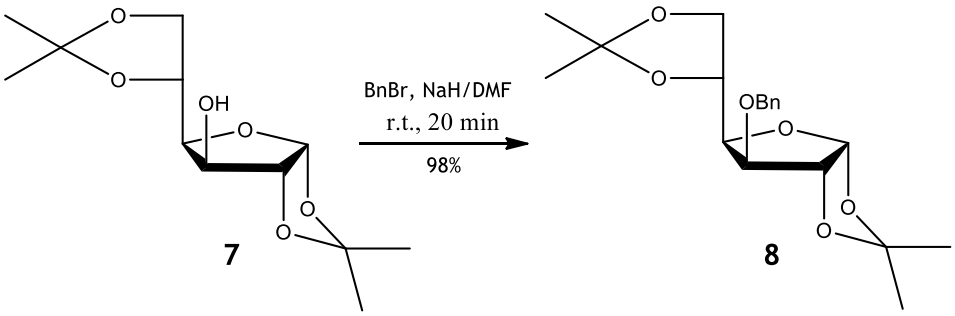
FTIR (cm^{-1}): 3570 (OH).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.28 (s, 3H, C-CH_3), 1.44 (s, 3H, C-CH_3), 3.23 (bs, 1H, OH), 3.39 (s, 3H, O-CH3), 3.54-3.63 (m, 2H, CH_2-5), 4.37 (dd, 1H, J=7.2, 2.7 Hz, H-4), 4.55 (dd, 1H, J= 6.0, 2.3 Hz, H- 3), 4.79 (dd, 1H, J=6.5, 5.3 Hz, H-2), 4.93 (s, 1H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 24.8 (C-$\underline{C}H_3$), 26.5 (C-$\underline{C}H_3$), 55.6 (O-CH_3), 64.10 (C-5), 81.60 (C-2), 85.90 (C-3) 88.40 (C-4), 110.10 (C-1), 112.2 ($\underline{C}$-CH3).

5.2.3. Reaction sequence from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (7)

5.2.3.1. 3-*O*-benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (8)



Scheme 22- Preparation of **8** from **7**. Yield: 98%.

Chemical formula: $C_{18}H_{24}O_6$

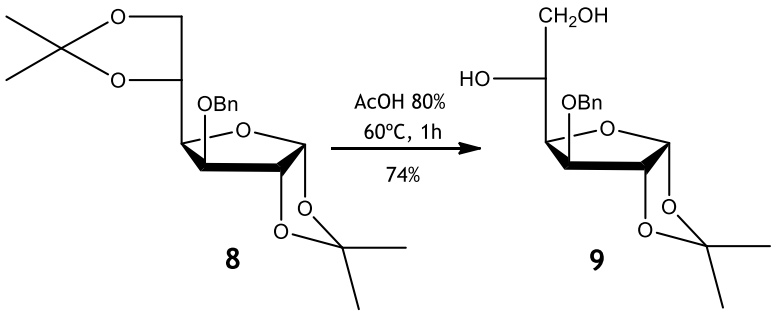
M.W.= 336.16 g/mol

D-glucose diacetonide **7** (2.5 g, 9.605 mmol) was dissolved in anhydrous DMF (4 mL). After that, the suspension was cooled in an ice bath and benzyl bromide (2.275 mL, 13.3 mmol) was added dropwise, followed by the addition slowly of sodium hydride (NaH) because the reaction is very exothermic. After the addition of compounds, the ice bath is removed after 10 min. Then, a tube with calcium chloride and cotton was introduce in the round bottom flask to retain the fumes released. The end of the reaction was controlled by TLC, and was completed after stirring at room temperature during 20 min, the end of reaction was controlled by TLC. To the reaction mixture was added slowly 2 mL of MeOH to react with the excess of the NaH. DMF was removed under reduced pressure, obtaining a residue that was dissolved in dichloromethane (DCM) (25 mL) and washed with water and brine, dried with magnesium sulphate ($MgSO_4$). In the last step the compound was filtered, and DCM was evaporated to give a yellow oil **14**.(Scheme 22)[155] Yield: 98%. Rf: 0.48 (Ethyl Acetate/Toluene (EA/Tol): 2/1)

FTIR (cm^{-1}): 1605 (C=C).

- ^{1}H-NMR and ^{13}C-NMR according to literature[139].

5.2.3.2. 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (9)



Scheme 23- Preparation of **9** from **8**. Yield: 74%.

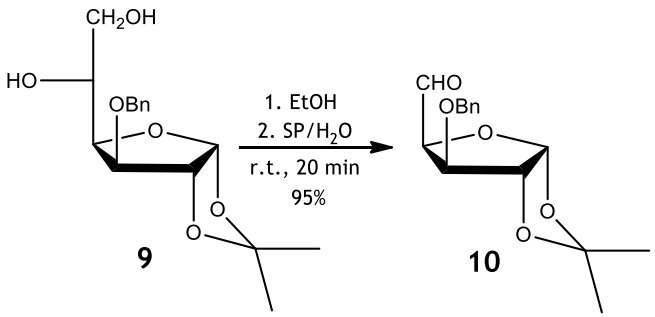
Chemical formula: $C_{15}H_{20}O_6$

M.W. = 296.13 g/mol

To the 3-*O*-Benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **8** (1g, 4.1 mmol) was added acetic acid 80% (28.6 mL), and heated at 60°C, over 1h. Followed the addition of toluene to the residue (21 mL) and after, was concentrated repeatedly for 3 times. The residue was purified by column chromatography under moderate pressure using EA/Tol: 1/5 as eluent. (Scheme 23) Yield: 74%, syrup. Rf: 0.39 (EA/H: 1/3).

- ^{1}H-NMR and ^{13}C-NMR according to literature[139].

5.2.3.3. 3-*O*-benzil-1,2-*O*-isopropylidene-α-D-gluco-pentodialdo-1,4-furanose (10)



Scheme 24- Preparation of **10** from **9**. Yield: 95%.

Chemical formula: $C_{14}H_{16}O_5$

M.W.= 264.10 g/mol

A solution of sodium periodate (SP) (1.67 g, 7.8 mmol) in water (33.4 mL), was poured over a solution of 3-O-Benzyl-1,2-O-isopropylidene-α-D-glucofuranose **9** (1,0 g, 3.22 mmol) in ethanol (EtOH) (6.7 mL). After 20 minutes with stirring at room temperature, under light, was added EtOH (330 mL). The suspension was filtrated and evaporated under the pressure (low

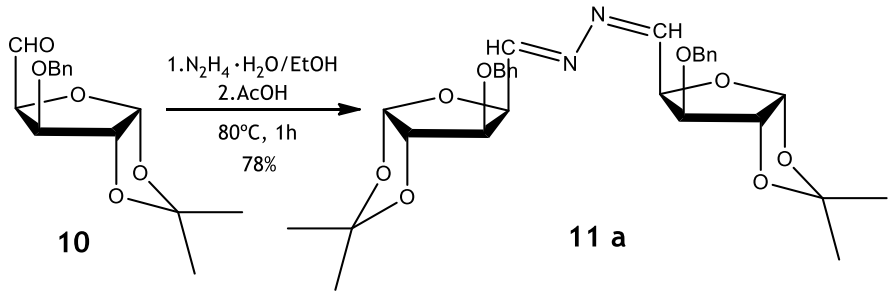
temperatures), and extracted with DCM (3x20 mL). All organic fractions were combined, dried with anhydrous sodium sulphate, filtrated and concentrated.[139] (Scheme 24) yield: 87%, syrup. Rf: 0.60 (EA/Tol: 2/1).

FTIR (cm^{-1}): 1730 (C=O), 1605 (C=C aromatic)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.61 (s, 1H, H-5), 7.36-7.31 (m, 5H, Ar-CH), 5.76 (d, *J*= 3.4, 1H, H-1,), 4.79-4.71 (m, 1H, CH_2-Ar), 4.60-4.53 (m, 1H, CH_2-Ar), 4.14 (d, *J*= 8.9, 1H, H-4), 3.93-3.84 (m, 1H, H-3), 1.60 (s, 3H, CH_3), 1.36 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.53 (C=O), 137.30 (qC-Ar-C), 128.50, 128.29, 128.04 (Ar-C), 113.44 (C-CH_3), 104.72 (C-1), 79.54 (C-4), 77.79 (C-2), 77.21(C-3), 72.21 ($\underline{C}H_2$-Ar), 26.93 (CH_3), 26.62 (CH_3).

5.2.3.4. 5-(1',2'-dimetylenehydrazone)-*bis*-[3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranoside] (11a)



Scheme 25- Preparation of **11a** from **10**. Yield: 25%.

Chemical formula: $C_{15}H_{20}N_2O_4$

M.W.= 292.33 g/mol

Mixture of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-gluco-pentodialdo-1,4-furanose **10** (0.733 g, 2.75 mmol) and hydrazine hydrate (0.2 mL, 3.02 mmol) was prepared and dissolved in ethanol (10 mL). After stirring at room temperature for 5 min, to a completely dissolution, was added glacial acetic acid dropwise (0.1 mL). Solution was heated at 80°C to 1h. The end of reaction was verified by TLC.[139] (Scheme 25) yield: 25 %, syrup. Rf: 0.60 (EA/Tol: 1/2).

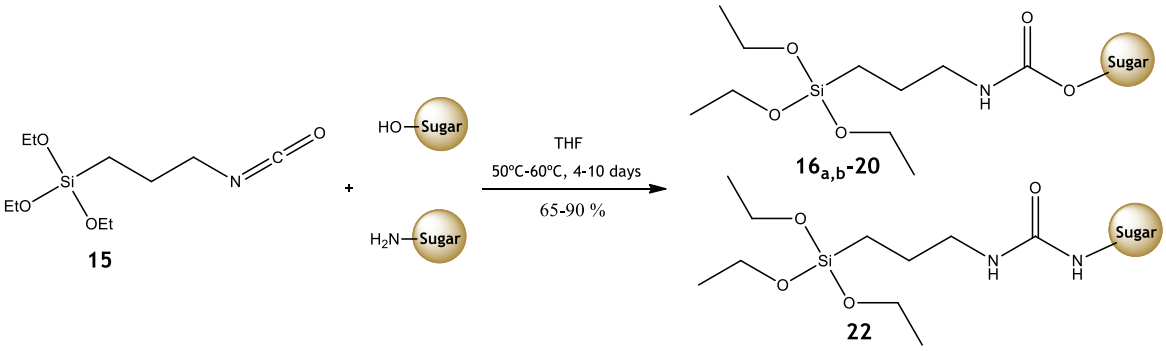
FTIR (cm^{-1}): 1570 (C=C aromatic). (C=N)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.05 (m, 10H, 2 Ar-CH), 6.05 and 6.00 (2 d, *J* = 3.7 Hz and *J* = 3.7 Hz, 1H, H-1), 4.88 and 4,76 (2 dd, *J* = 5.8, 3.4 Hz, and *J* = 6.3, 3.4 Hz, 1H, H-4), 4.64 (d, *J* = 3.7 Hz, 1H, H-5), 4.61 – 4.41 (m, 3H, CH_2-a, CH_2-b, H-3), 4.16 and 4.10 (2 d, *J* = 3.5 Hz and *J* = 3.5 Hz, 1H, H-2), 1.49 and 1.40 (2 s, 3H, CH_3), 1.32 and 1.28 (2 s, 3H, CH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.65 (C=N), 137.04, C-CH_3), 129.75-127.29 (Ar-C) 105.22 (C-1), 84.07 (C-2), 82.86 (C-5), 82.20 (C-3), 79.73 (C-4), 72.18 (CH_2-Ar), 26.92 and 26.38 (2 CH_3).

5.3. General procedure for synthesis of mono-organosilylated precursors

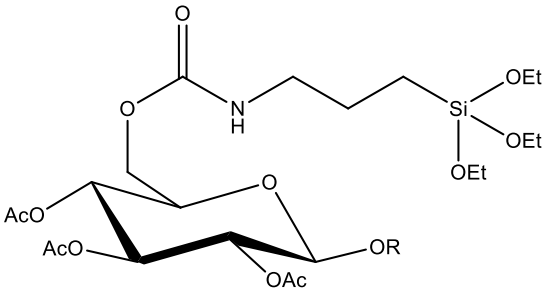
For the synthesis of the precursors were used as base carbohydrate, the starting materials, 6-*O*-triphenylmethyl-2,3,4-tri-*O*-acetyl-1-*O*-methyl-α-D-glucopyranoside **4a**, 1,2,34-tetra-*O*-acetyl-β-*O*-acetyl-β-D-glucopiranoside **4b** and 1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranose **6**. Furthermore, are also used as based carbohydrate, D-glucose diacetonide **7** and 1,2-*O*-Isopropylidene-α-D-xylofuranose **19.**



Scheme 26 - Preparation of **16a,b-20** from OH-sugar or NH_2-sugar **22** and ICPTES 15.

Sugar (1 eq, 4.04 mmol) was dissolved in THF (lowest possible) by stirring. A volume of 1 mL (1 eq, 4.04 mmol) of ICPTES 1**5** was added to this solution in a reaction flask. The flask was then sealed and the solution stirred for 4-10 days at moderate temperature (50-60ºC). Solvent was removed under the pression to give the correspondings monosilylated precursors **16a,b-20**. The reactions were controlled by FTIR and characterized with ^{13}C-NMR and ^{1}H-NMR.[150]

5.3.1. 6-*O*-ethyl(3-(triethoxysilil)propyl) carbamate-1-*O*-methyl-2,3,4-tri-*O*-acetyl-α-D-glucopyranose **(16a)** and 6-*O*-methyl (3-(triethoxysilyl)propyl) carbamate-1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranoside **(16b)**



16a, 16b

16a, **R**=CH_3
16b, **R**=Ac

Figure 9- Structure of **16a** and **16b**. Yield: 90%.

Chemical formula 16a/16b: $C_{24}H_{43}NO_{12}Si$ /$C_{25}H_{43}NO_{13}Si$

M.W. 16a/16b= 565.26/595.23g/mol

16a:

This compound (Figure 9) was prepared from sugar derivative **4a.**

Reaction time: 6 days**. Yield:** 90 (%). Oil;

FTIR (cm^{-1}): 3392 (NH), 1751 (urethane), 1706 (C=O), 1647 (urethane), 1227, 1038 (SiOEt), 956 (NCH_2) 774 (Si-O).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.45 (t, *J* = 9.8 Hz, 1H, H-2), 5.01 (t, *J* = 10.0 Hz, 1H, H-4), 4.93 (d, *J* = 3.6 Hz, 1H, H-1), 4.86 (dd, *J* = 10.2, 3.6 Hz, 1H, H-5), 4.16 (d, *J* = 4.3 Hz, 1H, H-3), 4.11 – 3.91 (m, 2H, CH_2), 3.80 (q, *J* = 7.0 Hz, 6H, CH_2-O), 3.39 (s, 3H, O-CH_3), 3.21 – 3.08 (m, 2H, N-CH_2), 2.06 (s, 3H, CH_3-isopropylidene), 2.01 (s, 3H, CH_3-isopropylidene), 1.98 (s, 3H, CH_3-isopropylidene), 1.67 – 1.52 (m, 2H, $\underline{CH_2}$-CH_2), 1.20 (t, *J* = 7.6 Hz, 9H, $\underline{CH_3}$-CH_2), 0.66 – 0.55 (m, 2H, CH_2-O).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.15, 170.07, 169.55 (C=O), 155.84 (O=C-NH), 96.70 (C-1), 70.80 (C-2), 69.80 (C-4), 68.83 (C-3), 67.95 (C-6), 67.45 (C-5), 58.43 ($\underline{C}H_2$-CH_3), 55.39 (O-CH_3), 43.52 ($\underline{C}H_2$-N), 23.18 ($\underline{C}H_2$-CH_2), 20.71, 20.67, 20.63 (CH_3-isopropylidene), 18.26 ($\underline{C}H_3$-CH_2),7.58 (CH_2-Si).

16b:

This compound was prepared from sugar derivative **4b.**

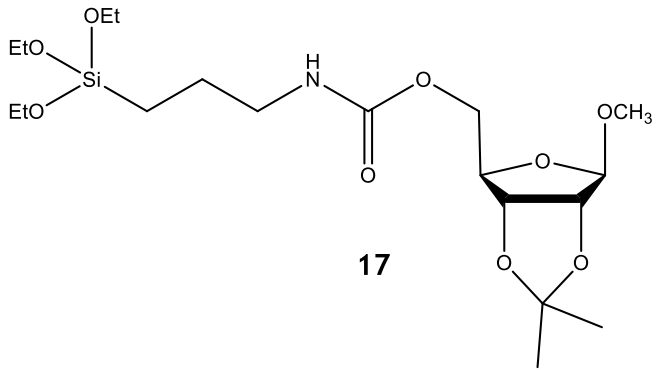
Reaction time: 6 days**. Yield:** 87 (%). Oil;

FTIR (cm^{-1}): 3392 (NH), 1751 (urethane), 1706 (C=O), 1647 (urethane), 1227, 1038 (SiOEt), 956 (NCH_2) 774 (Si-O).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.70 (t, *J* = 9.3 Hz, 1H, H-2), 5.33 – 5.17 (m, 1H, H-4), 5.11 (d, *J* = 9.5 Hz, 1H, H-1), 5.06 (dd, *J* = 11.9, 3.8 Hz, 1H, H-5), 4.52 (d, *J* = 4.3 Hz, 1H, H-3), 4.21 – 3.88 (m, 2H, CH_2-6), 3.80 (q, *J* = 7.1 Hz, 6H, $C\underline{H}_2$-CH_3), 3.19 – 3.07 (m, 2H, N-CH_2), 2.10 (s, 3H, CH_3-isopropylidene), 2.06 (s, 3H, CH_3-isopropylidene), 2.02 (s, 3H, CH_3-isopropylidene), 2.00 (s, 3H, CH_3-isopropylidene), 1.62-1.57 (m, 2H, $C\underline{H}_2$-CH_2) 1.21 (t, *J* = 6.9 Hz, 9H, $C\underline{H}_3$-CH_2), 0.65 – 0.57 (m, 2H, CH_2-Si).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.11, 169.09, 168.80, 168.06 (O=$\underline{C}$-CH_3) 156.92 (O=C-NH), 91.72 (C-1), 70.39 (C-2), 70.25 (C-4), 68.51 (C-3), 68.17 (C-5), 67.97 (C-6), 58.45 ($\underline{C}H_2$-CH_3), 43.27 (N-CH_2), 23.18 ($\underline{C}H_2$-CH_2), 20.71, 20.67, 20.63, 20.20 (CH_3-isopropylidene), 18.28 ($\underline{C}H_3$-CH_2), 7.59 (CH_2-Si).

5.3.2. 5-*O*-ethyl(3-(triethosysilyl) propyl) carbamate-1-*O*-methyl-2,3-*O*-isopropylidene-β-D-glucofuranose **(17)**



17

Figure 10- Structure of **17**. Yield: 80%.

Chemical formula: $C_{19}H_{37}NO_9Si$

M.W. = 451.22 g/mol

This compound (Figure 10) was prepared from sugar derivative **6.**

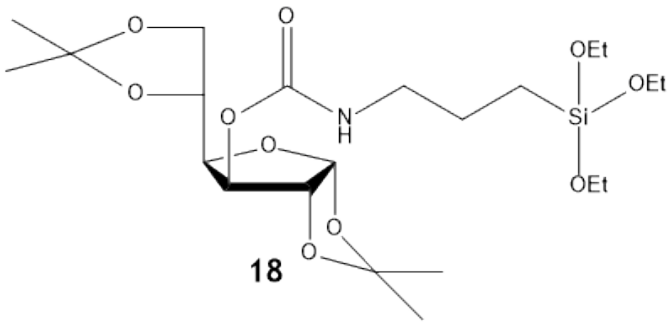
Reaction time: 5 days. Yield: 80 (%). Oil;

FTIR (cm^{-1}): 3392 (NH), 1751 (urethane), 1706 (C=O), 1647 (urethane), 1227, 1038 (SiOEt), 956 (NCH_2) 774 (Si-O**).**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.91 (s, 1H, H-1), 4.77 (dd, *J* = 6.5, 5.3 Hz, 1H, H-2), 4.50 (dd, *J* = 6.0, 2.3 Hz, 1H, H-3), 4.37 (dd, *J* = 7.2, 2.7 Hz, 1H, H-4), 4.15 – 4.03 (m, 2H, CH_2-5), 3.88 – 3.75 (m, 6H, $C\underline{H}_2$-CH_3), 3.32 (s, 3H, O-CH_3), 3.22 – 3.12 (m, 2H, N-$C\underline{H}_2$), 1.69 – 1.55 (m, 2H, $C\underline{H}_2$-CH_2), 1.48 (s, 3H, C-CH_3), 1.33 (s, *J* = 2.3 Hz, 3H, C-CH_3), 1.23 (t, *J* = 6.9 Hz, 9H, $C\underline{H}_3$-CH_2), 0.63 (m, *J* = 6.9 Hz, 2H, $C\underline{H}_2$-Si).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.94 (C=O), 112.08 (C-CH_3), 109.94 (C-1), 81.35 (C-2), 81.46 (C-3), 67.94 (C-4), 68.92 (C-5), 60.54 ($\underline{C}H_2$-CH_3), 55.48 (CH_3-O) 43.45 (CH_2-N), 24.68, 24.55 (CH_3-isopropylidene), 23.23 ($\underline{C}H_2$-CH_2), 18.25 (CH_2-$\underline{C}H_3$), 14.64, 7.60 (CH_2-Si)

5.3.3. 3-*O*-ethyl(3-(triethylsylil)propyl)carbamate-1,2:5.6-di-*O*-isopropylide-α-D-glucofuranose **(18)**



18

Figure 11- Structure of **18**. Yield: 71%.

Chemical formula: $C_{22}H_{41}NO_{10}Si$

M.W. = 507.25 g/mol

This compound (Figure 11) was prepared from commercial 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **7.**

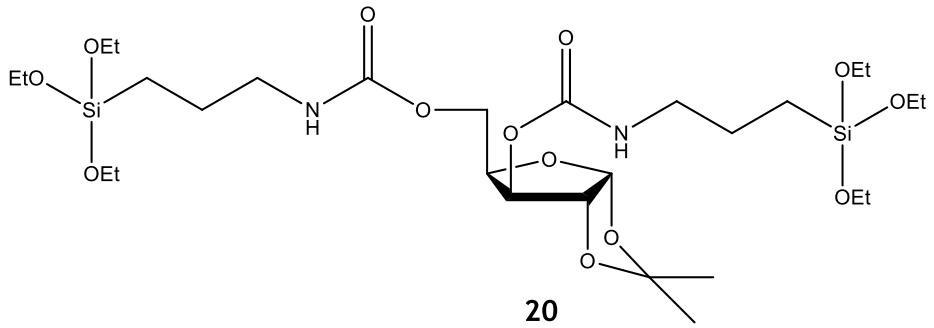
Reaction time: 10 days. Yield: 71(%). Oil;

FTIR (cm^{-1}): 3392 (NH), 1751 (urethane), 1706 (C=O), 1647 (urethane), 1227, 1038 (SiOEt), 956 (NCH_2) 774 (Si-O).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.91 (d, *J* = 3.6 Hz, 1H, H-1), 4.55 (d, *J* = 3.6 Hz, 1H, H-2), 4.36 – 4.26 (m, 2H, H-3, H-5), 4.14 (dd, *J* = 7.5, 6.2 Hz, 1H, H-4), 4.04 (dd, *J* = 7.9, 2.8 Hz, 1H, CH_2-6a), 3.97 (dd, *J* = 8.6, 5.3 Hz, 1H, CH_2-6b), 3.79 (q, *J* = 7.0 Hz, 6H, $C\underline{H}_2$-CH_3), 3.27 – 3.08 (m, 2H, N-CH_2), 1.66 – 1.53 (m, 2H, $C\underline{H}_2$-CH_2), 1.47 (s, 3H, CH_3-isopropylidene), 1.42 (s, 3H, CH_3-isopropylidene), 1.34 (s, 3H, CH_3-isopropylidene), 1.29 (s, 3H, CH_3-isopropylidene), 1.20 (t, *J* = 6.9 Hz, 9H, $C\underline{H}_3$-CH_2), 0.63 (m, *J* = 6.9 Hz, 2H, $C\underline{H}_2$-Si).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.87 (C=O), 111.76 (<u>C</u>-CH_3), 109.54, 109.2 (<u>C</u>-CH_3), 105.24 (C-1), 85.27 (C-2), 81.23 (C-4), 75.01 (C-3), 73.21 (C-5), 67.58 (C-6), 58.42 (<u>C</u>H_2-CH_3), 43.46 (CH_2-N), 26.72, 26.16, 25.58, 25.29 (CH_3-isopropylidene), 18.26 (CH_2-<u>C</u>H_3), 7.64 (CH_2-Si).

5.3.4. *Bis*(3,5-*O*-ethyl(3-(triethoxysilyl)propyl)carbamate-1,2-*O*-isopropylidene-α-D-glucofuranose (20)



20

Figure 12- Structure of **20**. Yield: 65%.

Chemical formula: $C_{27}H_{55}N_2O_{13}Si_2$

M.W. = 684.91 g/mol

This compound (Figure 12) was prepared from commercial 1,2-*O*-Isopropylidene-α-D-xylofuranose **19**. Contrary to other precursors, the stoichiometric ratio NCO/OH = 2/1.

Reaction time: 10 days. Yield: 65 (%). Oil;

FTIR (cm^{-1}): 3392 (NH), 1751 (urethane), 1706 (C=O), 1647 (urethane), 1227, 1038 (SiOEt), 956 (NCH_2) 774 (Si-O).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.91 (d, *J* = 3.6 Hz, 1H, H-1), 5.20 – 5.09 (m, 1H, H-3), 5.01 (d, *J*=3.6, 1H) 4.61 – 4.43 (m, 1H, H-4), 4.45 (dd, *J*=11.7, 4.8 Hz, 1H, CH_2-5a), 4.30 (dd, *J* = 11.7, 4.8 Hz, 1H, CH_2-5b), 3.82 (q, *J* = 7.2, 6.0 Hz, 12H, <u>C</u>H_2-CH_3), 3.25 – 3.10 (m, 4H, N-CH_2), 1.67 – 1.55 (m, 4H, CH_2-CH_2), 1.52 (s, 3H, C-CH_3), 1.31 (s, 3H, C-CH_3), 1.23 (t, *J* = 7.2 Hz, 18H, CH_3-CH_2), 0.63 (m, *J* = 6.9 Hz, 4H, <u>C</u>H_2-Si).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.80 (C=O), 112.20 (Cq), 104.55 (C1), 84.96 (C3), 79.93 (C2), 76.66 (C4), 69.71 (C-5) 58.45 (<u>C</u>H_2-CH_3), 43.20 (CH_2-N) 26.70 (CH_3), 26.25 (CH_2-CH_2), 26.19 (CH_3), 18.26 (<u>C</u>H_3-CH_2), 7.53 (CH_2-Si)

5.3.5. 3,5,6-tri-*O*-ethyl(3-(triethoxysilyl)propyl)carbamate-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (22)

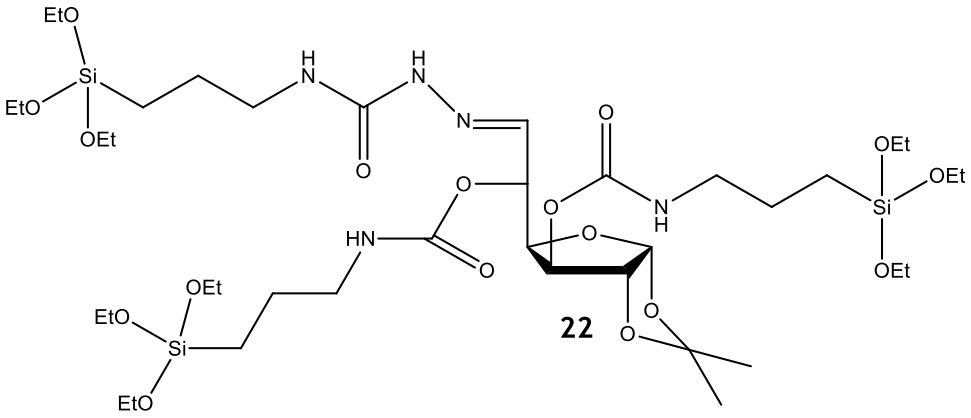


Figure 13- Possible structure of **22**.

FTIR (cm^{-1}): 3392 (NH), 2271.69 (isocyanate) 1697 (urea), 1700 (C=O), 1227, 1038 (SiOEt), 956 (NCH_2) 774 (Si-O).

This compound (Figure 13) was prepared from sugar derivative **21.** Reaction time: 10 days. Oil;

It was not possible purify.

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7. Attachments

Part of the present work was present in several scientific meetings:

- "Synthesis of mono-silylated carbohydrates-based precursors for the future preparation of hybrid mesoporous organosilica with potential biomedical applications"- A. Marta, S. C. Nunes, P. Almeida, S. Silvestre, M. Domingues, J. A. Figueiredo, M. I. Ismael, in: I Simpósio FinEnTech, at UBI, Covilhã, January 28-29 2016; Oral communication.

- "Synthesis of mono-sylilated carbohydrates-based precursors for preparation of hybrid mesoporous organosilica with potential biomedical application "– A.Marta, S.C.Nunes, P.Almeida, S.Silvestre, J.A.Figueiredo, M.I.Ismael, to present in XXII Encontro Luso-galego de Quimica, november 9-11 , Bragança, 2016; Poster communication.

- "Synthesis of hybrid mesoporous organosilica based on mono-silylated carbohydrates precursors with potential biomedical applications" in: Jornadas de Quimica e Bioquimica, at UBI, may 2016; Oral communication.