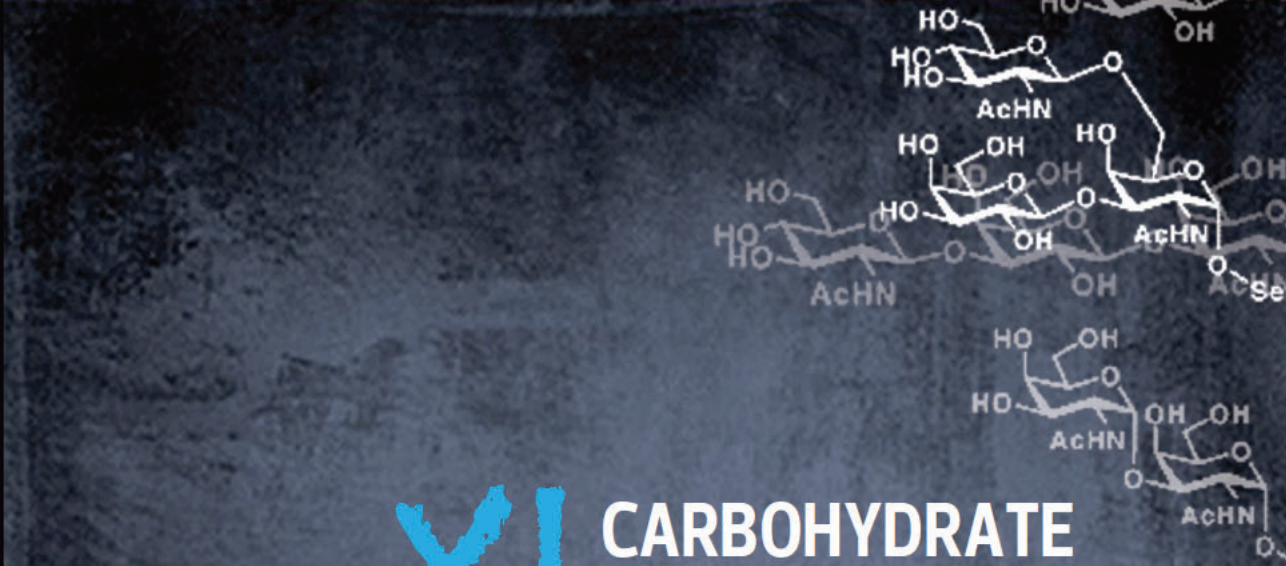


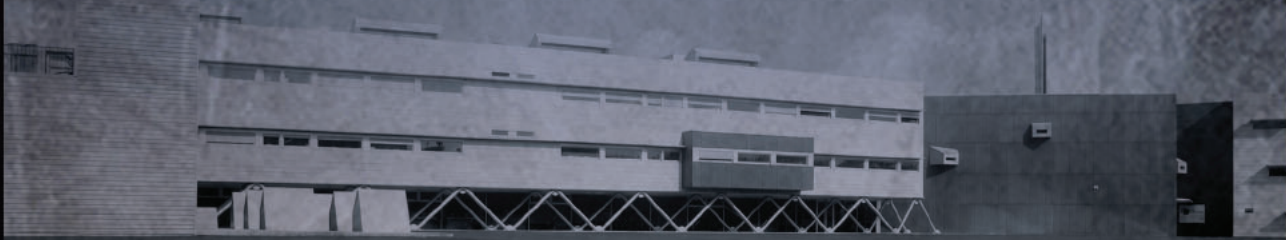
XI CARBOHYDRATE SYMPOSIUM

JORNADAS DE CARBOHIDRATOS

Real Sociedad Española de Química
Grupo Especializado de Hidratos de Carbono

May 28–30, 2014
Logroño, La Rioja, Spain

In honour of Prof. Manuel Martín-Lomas



UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM
XI JORNADAS DE CARBOHIDRATOS

Jesús Manuel Peregrina García, Jesús Héctor Busto Sancirián
Alberto Avenoza Aznar, Francisco Corzana López
María del Mar Zurbano Asensio (Editores)

XI CARBOHYDRATE SYMPOSIUM
XI JORNADAS DE CARBOHIDRATOS

UNIVERSIDAD DE LA RIOJA
Logroño
2014

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Sumario

Welcome

On behalf of the organizing committee, we are honoured to announce the **XI Jornadas de Carbohidratos** (XI Carbohydrate Symposium) in Logroño, Spain, from May 28th to 30th, 2014.

The **Jornadas de Carbohidratos** symposium is the most important national event in Carbohydrate Chemistry, biennially organized under the auspices of the *Grupo Especializado de Hidratos de Carbono* (Specialized Group of Carbohydrates) **–HIC–** of the *Real Sociedad Española de Química* (Spanish Royal Society of Chemistry) **–RSEQ–**, since the first meeting held in 1989 (Granada, Spain).

The symposium will cover all the branches of modern glycosciences, from basic to applied research. The symposium will take place in Logroño (Departamento de Química, Universidad de La Rioja).

This event will comprise plenary lectures, invited lectures, oral communications, flash communications and poster sessions.

We would like to thank all the public and private institutions that kindly contribute economical to this scientific event.

We are pleased to announce that the congress is dedicated to the scientific career of Prof. Manuel Martín-Lomas.

Jesús Manuel Peregrina
President of the Organizing Committee

Contact

Congress Secretariat:

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Universidad de La Rioja
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Previous Carbohydrate Symposia

26 International Carbohydrate Symposium
Madrid, July 22th to 27th, 2012

X Jornadas de Carbohidratos
Granada, September 16th to 18th, 2010

IX Jornadas de Carbohidratos and **IV Encuentro Ibérico de Carbohidratos**
Santiago de Compostela, September 10th to 12th, 2008

VIII Jornadas de Carbohidratos
Alcalá de Henares, September 13th to 15th, 2006

VII Jornadas de Carbohidratos
Tarragona, September 16th to 18th, 2004

VI Jornadas de Carbohidratos and **II Encuentro Ibérico de Carbohidratos**
Ronda, September 25th to 28th, 2002

V Jornadas de Carbohidratos
Badajoz, September 28th to 30th, 2000

IV Jornadas de Carbohidratos
Aguadulce, June 25th to 27th, 1997

III Jornadas de Carbohidratos
La Rábida, June 16th to 18th, 1993

II Jornadas de Carbohidratos
Medina del Campo, June 12th to 14th, 1991

I Jornadas de Carbohidratos
Granada, November 6th to 8th, 1989

Scientific and Social Program

	Wednesday 28th	Thursday 29th	Friday 30th
9:00 – 9:15		**PL2: J. Paulson** Chairman: F. Santoyo	**IL8**: C. González-Bello Chairman: S. Castillón
9:15 – 9:30			
9.30 – 9:45			**IL9**: O. Boutureira Chairman: S. Castillón
9:45 – 10:00		**IL3**: C. Ortíz Mellet Chairman: F. Santoyo	
10:00 – 10:15			**OC9**: L. Masgrau Chairman: S. Castillón
10:15 – 10:30		**OC3**: J. J. Reina Chairman: F. Santoyo	**OC10**: J. Echevarría Chairman: S. Castillón
10:30 – 10:45		**OC4**: L. Gallego Chairman: F. Santoyo	**OC11**: J. R. López Benito Chairman: S. Castillón
10:45 – 11:30		Coffee break (Poster Session)	
11:30 – 11:45		**IL4**: E. Cocinero Chairman: J. M. García Fernández	**IL10**: N. Reichardt Chairman: J. Cañada
11:45 – 12:00			
12:00 – 12:15		**IL5**: C. Rovira Chairman: J. M. García Fernández	**OC12**: A. Fernández Chairman: J. Cañada
12:15 – 12:30			**Ceremony in honour of M. Martín-Lomas** **(PL4)** Chairman: J. Jiménez-Barbero
12:30 – 12:45	Registration	**OC5**: F. Plou Chairman: J. M. García Fernández	
12:45 – 13:00		**OC6**: J. M. Benito Chairman: J. M. García Fernández	
13:00 – 13:15		**FC (1-5)**	RSEQ –CG Meeting & Closing Remarks
13:15 – 13:30			
13:30 – 15:00		Lunch	
15:00 – 15:30	Opening		
15:30 – 16:15	**PL1: G.-J. Boons** Chairman: F. Corzana	**PL3: A. Davis** Chairman: S. Penadés	
16:15 – 16:45	**IL1**: S. Martín-Santamaría Chairman: F. Corzana	**IL6**: J. L. de Paz Chairman: S. Penadés	
16:45 – 17:30	Coffee break (Poster Session)		
17:30 – 18:00	**IL2**: J. L. Asensio Chairman: J. Rojo	**IL7**: R. Hurtado Chairman: R. Estévez	
18:00 – 18:15	**OC1**: A. Canales Chairman: J. Rojo	**OC7**: R. Balo Chairman: R. Estévez	
18:15 – 18:30	**OC2**: J. Angulo Chairman: J. Rojo	**OC8**: M. Guerín Chairman: R. Estévez	
	Social Program	Dinner & Awards	

PL = Plenary Lecture **IL** = Invited Lecture **OC** = Oral Communication **FC** = Flash Communication

Plenary Lectures *(in alphabetical order)*

Geert-Jan Boons

Whistler Award in Carbohydrate Chemistry for 2014
Distinguished Professor in Biochemical Sciences

Complex Carbohydrate Research Center
The University of Georgia
315 Riverbend Rd.
Athens, Georgia 30602, USA

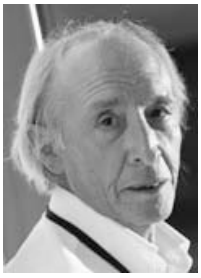
Functional glycomics through chemical synthesis

Anthony P. Davis

Professor of Supramolecular Chemistry

School of Chemistry
University of Bristol
Cantock's Close
Bristol BS8 1TS, UK

Synthetic lectins: Progress in biomimetic carbohydrate recognition



Manuel Martín-Lomas

Founding Scientific Director
Principal Investigator of Biofunctional Nanomaterials

Research Unit CIC biomaGUNE
Centro de Investigación Cooperativa en Biomateriales
Paseo Miramón 182
20009 Donostia/San Sebastián. SPAIN

The activation of fibroblast growth factors by glycosaminoglycans

James C. Paulson

Chair, Department of Cell and Molecular Biology

The Scripps Research Institute
MEM-L71 10550 N. Torrey Pines Road
La Jolla, CA 92037, USA

Sialic acids as determinants of self

Invited Lectures *(in alphabetical order)*

Juan Luis Asensio
Instituto de Química Orgánica. CSIC. Madrid.
Studies on the molecular recognition of aminoglycoside antibiotics by RNA and resistance enzymes

Omar Boutureira
Departament de Química Analítica i Química Orgànica. Universitat Rovira i Virgili. Tarragona.
Fluorinated carbohydrate probes for chemical biology

Emilio J. Cocinero
Dpto. Química Física. Facultad de Ciencia y Tecnología. Universidad del País Vasco. Leioa.
Elucidating the structure of sugars in the gas phase

José Luis de Paz
Instituto de Investigaciones Químicas (IIQ) cicCartuja. CSIC. Sevilla.
New approaches to the synthesis of hyaluronic acid and chondroitin sulfate oligosaccharides

Concepción González-Bello
Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS). Universidad de Santiago de Compostela.
Development of new antibiotics by targeting essential enzymes in bacteria: structure-based design and simulation studies

Ramón Hurtado-Guerrero
Instituto de Biocomputación y Física de Sistemas Complejos (BIFI). Universidad de Zaragoza.
Combined structural snapshots and metadynamics reveal a substrate-guided SNi-type reaction for polypeptide GalNAc-transferase T2

Sonsoles Martín-Santamaría
Facultad de Farmacia. Universidad CEU San Pablo. Madrid.
TLR4/MD2 and galectins recognition by modulators. Molecular modelling approaches

Carmen Ortiz Mellet
Departamento de Química Orgánica. Universidad de Sevilla.
Glycosidase inhibitors and effectors as therapeutic tools

Niels-Christian Reichardt
Biofunctional Nanomaterials Department. CICbiomaGUNE. Parque Tecnológico de San Sebastián.
Studying the chemical biology of N-glycans with microarrays

Carme Rovira
Departament de Química Orgànica. Facultad de Química. Universitat de Barcelona.
Molecular mechanism of retaining glycosyltransferases investigated by QM/MM metadynamics

Meeting Program

Wednesday 28th May

12:30 – 15:00 **Registration**

15:00 – 15:30 **Opening**

15:30 – 16:15 *Chairman: Francisco Corzana*

PL1 Geert-Jan Boons

Functional glycomics through chemical synthesis

Sponsored by Gobierno de La Rioja

16:15 – 16:45 **IL1 Sonsoles Martín-Santamaría**

TLR4/MD2 and galectins recognition by modulators. Molecular modelling approaches

16:45 – 17:30 Coffee Break and Poster Session

17:30 – 18:00 *Chairman: Javier Rojo*

IL2 Juan Luis Asensio

Studies on the molecular recognition of aminoglycoside antibiotics by RNA and resistance enzymes

18:00 – 18:30 **Oral Communications** (Session I)

OC1 Ángeles Canales

Breaking pseudo-symmetry in multiantennary complex N-glycans using lanthanide-binding tags and NMR pseudo-contact shifts

OC2 Jesús Angulo

NMR conformational analysis of glycosylated iminosugars inhibitors of barley β-amylase

Thursday 29th May

09:00 – 09:45 *Chairman: Francisco Santoyo*

PL2 James C. Paulson

Sialic acids as determinants of self

Sponsored by Real Sociedad Española de Química

09:45 – 10:15 **IL3 Carmen Ortíz Mellet**

Glycosidase inhibitors and effectors as therapeutic tools

10:15 – 10:45 **Oral Communications** (Session II)

OC3 José J. Reina

Development of BODIPY-labeled sulphated carbosilane and mannose dendrons as topical microbicides to prevent HIV-1 sexual transmission

OC4 Laura Gallego-Yerga

Glycotargeted self-assembled nanocarriers from calixarene-cyclodextrin heterodimers for site-specific delivery of docetaxel

10:45 – 11:30 Coffee Break and Poster Session

11:30 – 12:00 *Chairman: José Manuel García Fernández*

IL4 Emilio Cocinero

Elucidating the structure of sugars in the gas phase

12:00 – 12:30 **IL5 Carme Rovira**

Molecular mechanism of retaining glycosyltransferases investigated by QM/MM metadynamics

12:30 – 13:00 **Oral Communications** (Session III)

OC5 Francisco Plou

Galactooligosaccharides formation during enzymatic hydrolysis of lactose: Towards prebiotic-enriched milk

OC6 Juan M. Benito

Tailoring self-assembling and targeting capabilities of CD-based nanoparticles for gene delivery

13:00 – 13:30 **Flash Communications**

FC1 Alessandra Lacetera
FC2 Luca Unione
FC3 Lucía Pérez-Regidor
FC4 Pilar Elías-Rodríguez
FC5 David Madariaga

13:30 – 15:30 Lunch

15:30 – 16:15 *Chairman: Soledad Penadés*

PL3 Anthony P. Davis

Synthetic lectins: Progress in biomimetic carbohydrate recognition
Sponsored by Grupo Especializado de Hidratos de Carbono

16:15 – 16:45 **IL6 José L. de Paz**

New approaches to the synthesis of hyaluronic acid and chondroitin sulfate oligosaccharides

16:45 – 17:30 Coffee Break and Poster Session

17:30 – 18:00 *Chairman: Ramón Estévez*

IL7 Ramón Hurtado-Guerrero

Combined structural snapshots and metadynamics reveal a substrate-guided SNi-type reaction for polypeptide GalNAc-transferase T2

18:00 – 18:30 **Oral Communications** (Session IV)

OC7 Rosalino Balo

Shikimic acid: A promising scaffold for new materials, drugs and catalysts

OC8 Marcelo E. Guerín

Conformational transitions as key features of PimA-mediated glycosyl transfer

Friday 30th May

09:00 – 09:30 *Chairman: Sergio Castillón*

IL8 Concepción González-Bello

Development of new antibiotics by targeting essential enzymes in bacteria: Structure-based design and simulation studies

09:30 – 10:00 **IL9 Omar Boutureira**

Fluorinated carbohydrate probes for chemical biology

10:00 – 10:45 **Oral Communications** (Session V)

OC9 Laura Masgrau

Molecular insights into the synthesis of the heparin/ HS linker by retaining glycosyltransferase EXTL2. A QM/MM study

OC10 Juan Echevarría

Rapid and quantitative glyco-analysis by MALDI using isotopically labelled glycans

OC11 Jorge R. López-Benito

Augmented reality applied to molecular modeling

10:45 – 11:30 Coffee Break and Poster Session

11:30 – 12:00 *Chairman: Javier Cañada*

IL10 Niels C. Reichardt

Studying the chemical biology of N-glycans with microarrays

12:00 – 12:15 **Oral Communications** (Session VI)

OC12 Alberto Fernández-Tejada

Development of QS-21–inspired minimal synthetic saponins as novel vaccine adjuvants: Improving on nature

12:15 – 12:30 **Ceremony in honour of Prof. Manuel Martín-Lomas**

12:30 – 13:15 *Chairman: Jesús Jiménez-Barbero*

PL4 Manuel Martín-Lomas

The activation of fibroblast growth factors by glycosaminoglycans
Sponsored by Universidad de La Rioja

13:15– 13:30 **RSEQ Carbohydrate Group Meeting & Closing Remarks**

13:30 – 15:30 Lunch

UNIVERSIDAD DE LA RIOJA

Plenary Lectures

May 28-30, 2014

Plenary Lectures

Functional glycomics through chemical synthesis

Geert-Jan Boons

Complex Carbohydrate Research Center. University of Georgia. 315 Riverbend Road, Athens, GA 30602, USA

Most cell surface and secreted proteins are modified by covalently-linked glycans which are essential mediators of biological processes such as protein folding, cell signaling, fertilization, embryogenesis, and the proliferation of cells and their organization into specific tissues. Overwhelming data support the relevance of glycosylation in pathogen recognition, inflammation, innate immune responses, and the development of autoimmune diseases and cancer, Although the functional importance of glycoconjugates are well-established, molecular mechanisms by which these compounds exert their functions have been difficult to define. We have addressed these difficulties by the development of methods for complex oligosaccharide and glycoconjugate synthesis, application of the new methods for the preparation of biologically important targets such as tumor-associated antigens, capsular polysaccharides, lipopolysaccharides, and heparan sulfates, and use of the resulting compounds in biological and biomedical studies. Several examples of such programs will be described.

Sialic acids as determinants of self

James C. Paulson, Robert DeVries, Wenjie Peng, Ryan McBride, Corwin M. Nycholat, Britni M. Arlian, and Matthew S. Macauley

Departments of Cell and Molecular Biology, Physiological Chemistry, and Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA 92037

Sialic acids are found as terminal sugars on glycans of glycoproteins and glycolipids of all mammalian cells. The 'sialoglycome' represents a highly diverse set of structures that varies from cell to cell, presenting a prominent molecular signature to the extracellular environment, mediating recognition by pathogens and neighboring cells. Influenza virus is an exemplary pathogen that recognizes sialosides as receptors for initial binding to and infection of airway epithelium. It is now clear that avian and human viruses recognize different sialoside receptors, representing a species barrier for transmission of avian viruses in human hosts. Avian viruses that acquire specificity for human type receptors are considered to have increased pandemic risk. We seek to identify the glycans that comprise the molecular signature recognized by human influenza virus, to better understand the nature of the barrier for new pandemic viruses from animal populations. The mammalian immune system has also evolved a family of receptors called siglecs that aid immune cells in distinguishing between self and non-self. Our work on the B cell siglec, CD22 (Siglec-2) has shown that it helps prevent activation of B cells to membrane self-antigens. Ligands on antigen expressing cells recruit CD22, preventing upregulation of B cells that recognize the antigen, resulting in suppression of B cell activation, and eventually apoptosis of the cell, eliminating it from the B cell repertoire. This function of CD22 can be exploited to induce antigen specific tolerance in an animal administering liposomal nanoparticles displaying both the desired antigen and a high affinity ligand of CD22, resulting in selective deletion of B cells that recognize the antigen. (Supported by NIH grants: AI51043, AI099141, AI099274, HL107151)

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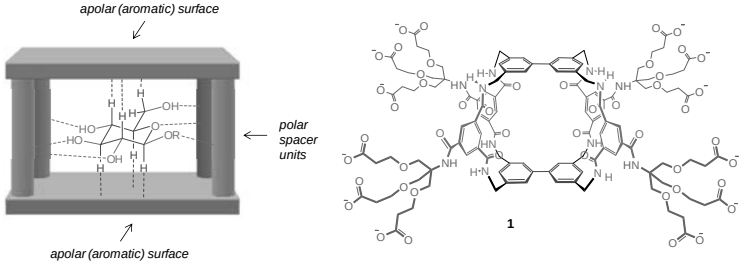
XI CARBOHYDRATE SYMPOSIUM

Synthetic lectins: Progress in biomimetic carbohydrate recognition

Anthony P. Davis

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS

Carbohydrate recognition is a difficult task, even for natural receptors such as lectins. The problems are two-fold. Firstly, saccharides are coated with hydroxyl groups and are therefore hydromimetic, being difficult to distinguish from a background of water molecules. Secondly they are structurally complex, and often differ only subtly from each other. It is not surprising, therefore, that lectins show notoriously weak affinities and often quite modest selectivities. If proteins perform moderately, one might expect that synthetic receptors would fail completely. However surprisingly good results have been achieved for one family of carbohydrate substrates, those with all-equatorial arrays of functionality (β-glucosyl, β-GlcNAc etc.). The key to success is the provision of cavities which complement both apolar and polar moieties. For all-equatorial saccharides, this implies parallel apolar surfaces separated by polar spacers, as illustrated in the cartoon below and exemplified by prototype **1**.[1] This lecture will discuss the chemistry and binding properties of **1** and, especially, more recent systems based on similar principles.[2] At their best, these "synthetic lectins" come close to matching the affinities of some lectin-carbohydrate interactions, while showing selectivities which are arguably superior. Given such performance, the prospects for applications may soon be realistic. For example, further development could lead to tools for studying the *O*-GlcNAc protein modification, and to molecular components for glucose sensors.



[1] E. Klein, M. P. Crump and A. P. Davis, *Angew. Chem., Int. Ed.*, 2005, **44**, 298-302. Y. Ferrand, E. Klein, N. P. Barwell, M. P. Crump, J. Jimenez-Barbero, C. Vicent, G. J. Boons, S. Ingale and A. P. Davis, *Angew. Chem., Int. Ed.*, 2009, **48**, 1775-1779. F. Corzana, A. Fernandez-Tejada, J. H. Busto, G. Joshi, A. P. Davis, J. Jimenez-Barbero, A. Avenoza and J. M. Peregrina, *ChemBioChem*, 2011, **12**, 110-117. A. P. Davis, *Org. Biomol. Chem.*, 2009, **7**, 3629-3638.

[2] For example: Y. Ferrand, M. P. Crump and A. P. Davis, *Science*, 2007, **318**, 619-622. N. P. Barwell, M. P. Crump and A. P. Davis, *Angew. Chem., Int. Ed.*, 2009, **48**, 7673-7676. B. Sookcharoenpinyo, E. Klein, Y. Ferrand, D. B. Walker, P. R. Brotherhood, C. F. Ke, M. P. Crump and A. P. Davis, *Angew. Chem., Int. Ed.*, 2012, **51**, 4586-4590. C. Ke, H. Destecroix, M. P. Crump and A. P. Davis, *Nature Chem.*, 2012, **4**, 718-723.

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XI JORNADAS DE CARBOHIDRATOS

The activation of fibroblast growth factors by glycosaminoglycans

Manuel Martín-Lomas

CIC biomaGUNE, Paseo Miramón 182, 20009 San Sebastián, Guipúzcoa, Spain;
e-mail: mmartinlomas@cicbiomagune.es

Fibroblast growth factors (FGFs) constitute a family of signalling polypeptides which are involved in key biological events including cell proliferation, differentiation and angiogenesis. The FGFs exert their biological functions by interacting with specific receptors at the cell surface (FGFRs). In humans twenty two *fgf* genes encode the ligands (FGFs) and five *fgfr* genes encode the cognate membrane receptors (FGFRs). FGFRs consist of two or three extracellular immunoglobulin domains linked to a cytoplasmic domain which contains a tyrosine kinase. The latter becomes phosphorylated, leading to downstream signalling events, following binding of an FGF to an FGFR together with the obligatory co-receptor heparan sulphate (HS). HS is the carbohydrate moiety of cell surface HS proteoglycans (HSPGs). The stimulation of cell proliferation requires, therefore, the formation of a ternary complex of the FGF, the FGFR and the HS co-receptor.

This lecture intends to give an overview of work performed in Madrid (Centro de Investigaciones Biológicas), Seville (Instituto de Investigaciones Químicas) and San Sebastián (CIC biomaGUNE) aimed at elucidating the molecular basis of this complex biological process from a carbohydrate chemistry perspective. The presentation will include: a) the development of strategies for the synthesis of HS-like oligosaccharides, both in solution and in solid phase; b) the investigation of the three dimensional structure of these oligosaccharides in solution; c) a study of the influence of oligosaccharide size and charge distribution on the binding to and on the stimulation of the mitogenic activity of FGF 1; d) the determination of the three dimensional structure of a FGF1-hexasaccharide binary complex and of a FGF1-octasaccharide-FGFR2 ternary complex in solution.

The obtained results which, in conjunction with other biophysical evidences, shed some new light on the specificity of FGF-HS-FGFR interaction, the geometry of the biologically active FGF-HS-FGFR ternary complex and the molecular mechanism of the process will be discussed.

UNIVERSIDAD DE LA RIOJA

Invited Lectures

May 28-30, 2014

XI JORNADAS DE CARBOHIDRATOS

Invited Lectures

Logroño, La Rioja, Spain

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

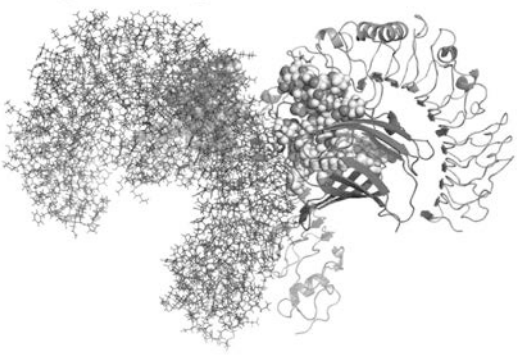
TLR4/MD-2 and galectins recognition by modulators. Molecular modelling approaches

Sonsoles Martín-Santamaría

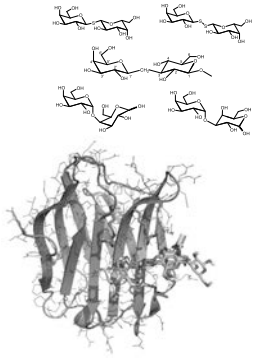
Department of Chemistry and Biochemistry, Faculty of Pharmacy, Universidad CEU San Pablo. Urbanización Montepríncipe, 28668-Boadilla del Monte, Madrid, Spain; e-mail: smsantamaria@ceu.es

Toll-like receptors (TLRs) recognize specific molecular patterns that are present in microbial components (as lipopolysaccharides, LPS). Several new compounds modulating TLRs are now undergoing preclinical and clinical evaluation, for the treatment of sepsis and inflammatory diseases, cancer, and rheumatoid arthritis.[1] TLR4, along with its accessory protein myeloid differentiation factor 2 (MD2), forms a heterodimeric complex (Figure, A), which specifically recognizes LPS, and confers an intracellular signaling cascade that results in the inflammatory and immune response. Our group has applied molecular modelling techniques to the study of TLR4 interactions with novel and reported agonists and antagonists such as taxanes, opioids, natural LPSs, and synthetic small molecules.[2] Our studies can be very valuable for the understanding of the interaction mechanism of these compounds, with high potential to design new molecules able to modulate TLR4 immune response.

On the other hand, we focused on human galectins, biomedically relevant lectins which can act as a proinflammatory and protumoral effectors. In this context, the elucidation of the mechanisms that govern how oligosaccharides are bound can afford a perspective for galectin modulation and rational drug design (Figure, B).[3] Binding studies of several glycomimetics to galectins 1 and 3, by means of molecular modeling techniques, will be presented.[4]



A)



B)

[1] Hennessy, E. J.; Parker, A. E.; O'Neill, A. J. *Nat. Rev. Drug Discov.*, **2010**, *9*, 293.
[2] Cighetti, R.; Ciaramelli, C.; Sestito, S. E.; Zanoni, I.; Kubik, Ł.; Ardá-Freire, A.; Calabrese, V.; Granucci, F.; Jerala, R.; Martín-Santamaría, S.; Jiménez-Barbero, J.; Peri, F. *ChemBioChem*. **2014**, *15*, 250.
[3] Martín-Santamaría, S.; Gabius, H.-J.; Jiménez-Barbero, J. *Pure Appl. Chem.* **2012**, *84*, 49.
[4] Vidal, P.; Roldós, V.; Fernández-Alonso, M. C.; Vauzeilles, B.; Bleriot, Y.; Cañada, F. J.; André, S.; Gabius, H-.J.; Jiménez-Barbero, J.; Espinosa, J. F.; Martín-Santamaría, S. *Chem. Eur. J.* **2013**, *19*, 14581.

UNIVERSIDAD DE LA RIOJA

XI JORNADAS DE CARBOHIDRATOS

Studies on the molecular recognition of aminoglycoside antibiotics by RNA and resistance enzymes

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Aminoglycosides are highly potent, broad-spectrum antibiotics widely used in clinics. These drugs bind specifically to the bacterial decoding site, in the 16S ribosomal RNA (A-site), and thereby interfere with the accuracy of protein synthesis, leading to bacterial cell death. Additional targets such as the DIS kissing-loop complex, the Tat-responsive element and the Rev-responsive element, have been identified within the HIV genomic RNA and are also located in different functionally relevant RNA fragments, including self-splicing ribozymes and tRNAs. In addition, to specifically interact with RNA receptors, aminoglycosides are also recognized by the enzymes involved in antibiotic inactivation that play a central role in bacterial resistance processes. These proteins represent primary pharmacological targets. The emergence of high-resolution structural data for aminoglycoside/protein and /RNA complexes, during last decade, has greatly stimulated the structural based design of new bioactive derivatives with improved properties. More specifically, research has been focused on the preparation of tighter and more specific RNA binders, enzymatic inhibitors and new drugs non susceptible to enzymatic inactivation. Unfortunately, design efforts have frequently met a limited success, which, in our opinion, partially reflects our incomplete understanding of the molecular forces that stabilize the aminoglycoside complexes at a fundamental level.

Herein, we analyze several key aspects of the aminoglycoside recognition by RNA and proteins employing a pluridisciplinar approach that includes molecular modeling, organic synthesis, combinatorial chemistry and different biophysical techniques. The implications of our results for the design of improved amionglycoside-based ligands will be discussed.

[1] Jiménez-Moreno, E; Gómez-Pinto, I.; Corzana, F.; Santana, A. G.; Revuelta, J.; Bastida, A.; Jiménez-Barbero, J.; González, C.; Asensio, J. L. *Angew. Chem. Int. Edit.* **2013**, *52*, 3148.

[2] Santana, A. G.; Jiménez-Moreno, E; Gómez, A. M.; Corzana, F.; González, C.; Jímenez-Oses, G.; Jiménez-Barbero, J.; Asensio, J. L. *J. Am. Chem. Soc.* **2013**, *135*, 3347.

[3] Vacas, T.; Corzana, F.; Jiménez-Oses, G.; González, C.; Gómez, A.M.; Bastida, A.; Revuelta, J.; Asensio, J. L. *J. Am. Chem. Soc.* **2010**, *132*, 12074.

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XI CARBOHYDRATE SYMPOSIUM

Glycosidase inhibitors and effectors as therapeutic tools

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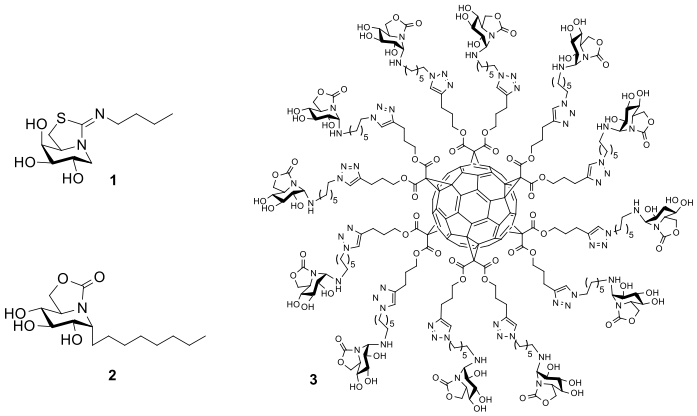
Glycosyl hydrolases play important roles in biological proccesses that result in the maintenance of life, including the degradation of polysaccharides, the lysosomal catabolism of glycoconjugates and the biosytnthesis of the oligosaccharide units in glycoproteins and glycolipids. Consequently, compounds that interfer with their function bear many prospects in medicine and biotechnology. Selectivity is a key issue for those channels. sp^2-Iminosugars, a family of glycomimetics characterized by the presence of an endocyclic pseudoamide-type nitrogen atom have shown much promise in this respect. Notably, several representatives exhibited potent glycosidase inhibitory activity and higher enzyme selectivity as compared with the parent iminosugars. At subinhibitory concentrations, some of these compounds acted as effectors of misfolded mutant enzymes involved in lysosomal storage disorders, showing high promise as pharmacological chaperones. In vitro and in vivo data support their potential for the treatment of Gaucher, GM_1 gangliosidosis (e.g. **1**)[1] and Fabry diseases. Moreover, sp^2-iminosugars pseudoglycosides (e.g. **2**) have been shown to interfere with glycoprotein biosynthesis in cancer cells, selectively promoting cell cycle arrest and apoptosis.[2] The possibility to modulate the biological activity of these compounds by multivalent presentation (e.g. **3**) will be also discussed.[3]



[1] Takai, K.; Higaki, K.; Aguilar-Moncayo, M.; Mena-Barragán, T.; Hirano, Y.; Yura, K.; Yu, L.; Ninomiya, H.; García-Moreno, M. I.; Sakakibara, Y.; Ohno, K.; Nanba, E.; Ortiz Mellet, C.; García Fernández, J.M.; Suzuki, Y. *Mol. Ther.* **2013**, *21*, 526.

[2] Allan, G.; Ouadid-Ahidouch, H.; Sánchez-Fernández, E.; Rízquez-Cuadro, R.; García Fernández, J. M.; Ortiz Mellet, C.; Ahidouch. A. *PLOS ONE*. **2013**, *8* e76411.

[3] Rízquez-Cuadro, R.; García Fernández, J. M.; Nierengarten, J.-F.; Ortiz Mellet, C. *Chem. Eur. J.* **2013**, *19*, 16791.

UNIVERSIDAD DE LA RIOJA

XI JORNADAS DE CARBOHIDRATOS

Elucidating the structure of sugars in the gas phase

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Carbohydrates are one of the most versatile biochemical building blocks, widely acting in energetic, structural or recognition processes. We present several structural studies on carbohydrates exploiting an experimental strategy which combines microwave (MW) and laser spectroscopies in high-resolution. MW and laser spectroscopies exhibit complementary functionalities. Laser spectroscopy offers high sensitivity coupled to mass and conformer selectivity, making it ideal for medium or large biochemical systems. On the other hand, microwave spectroscopy provides much higher resolution and direct access to molecular structure through the moments of inertia. This combined approach provides not only accurate chemical insight on conformation, structure and molecular properties, but also benchmarking standards guiding the development of theoretical calculations.

In order to illustrate the possibilities of a combined MW-laser approach we present results on the conformational landscape and structural properties of several monosaccharide,[1,2] disaccharides,[3] a pentasaccharide[4] including microsolvation processes of carbohydrates[3] and molecular recognition processes using a peptide which can sense *anomeric* and *conformational* differences.[5]

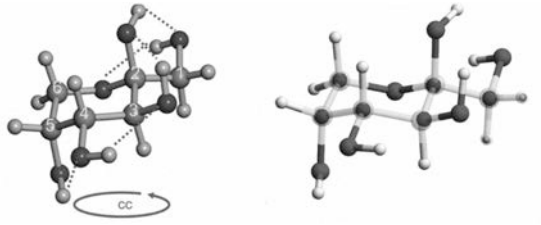

Figure: Structure of fructose: Comparison experiment versus theory

[1] Cocinero, E. J.; Lesarri, A.; Écija, P.; Cimas, Á.; Davis, B. G.; Basterretxea, F. J.; Fernández, J. A. and Castaño, F. *J. Am. Chem. Soc.*, **2013**, *135*, 2845-1852.

[2] Peña, I.; Cocinero, E. J.; Cabezas, C.; Lesarri, A.; Mata, S.; Écija, P.; Daly, A. M.; Cimas, Á.; Bermúdez, C.; Basterretxea, F. J., Blanco, S., Fernández, J. A., López, J. C.; Castaño F. and Alonso**,** J. L. *Angew. Chem. Int. Ed.***, 2013**, *125*, 12056-12061.

[3] Cocinero, E. J., Gamblin, D. P., Davis, B. G. and Simons, J. P. *J. Am. Chem. Soc.*, **2009**, *131*, 11117-11123.

[4] Barry, C. S.; Cocinero, E. J.; Çarçabal, P.; Gamblin, D. P.; Stanca-Kaposta, E. C.; Remmert, S. M. Fernández-Alonso, M. C.; Rudić, S.; Simons, J. P. and Davis, B. G. *J. Am. Chem. Soc.*, **2013**, *135*, 16895-16903.

[5] Cocinero, E. J.; Çarcabal, P.; Vaden, T. D.; Simons J. P. and Davis, B. G. *Nature*, **2011**, *469*, 76-80.

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Molecular mechanisms of retaining glycosyltransferases investigated by QM/MM metadynamics

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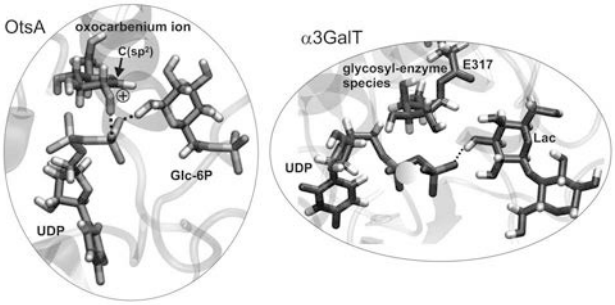
The catalytic mechanism of nucleotide-sugar dependent glycosyltransferases (GTs), especially those that act with retention of anomeric configuration, remains one an intriguing unanswered questions in glycobiology. In contrast to the well-characterized mechanistic strategies used by glycoside hydrolases (GHs) to catalyze the cleavage of glycosidic bonds, the mechanisms of retaining GTs remain unclear. Double displacement mechanisms have been proposed (but not fully proved) by analogy to retaining GHs. In addition, many GTs do not have a putative nucleophile protein residue. This prompted some authors to suggest an unusual mechanism, in which the reaction proceeds via a front side single displacement. This mechanism, usually named as S_Ni-like in the literature, has been surrounded by a strong controversy, since in principle it implies that two covalent bonds are forming and breaking, respectively, in the same region of space.



By means of QM/MM metadynamics simulations, based on Density Functional Theory (DFT), we demonstrate that the "front-face" mechanism is feasible in a GT lacking a putative nucleophile residue (trehalose-6-phosphate synthase, OtsA), thanks to the formation of a short-lived oxocarbenium-ion-like species (Figure).[1] In contrast, a GT with a putative nucleophile residue, such as α3-galactosyltransferase (α3GalT, right panel), operates via a double-displacement mechanism, with the formation of a glycosyl-enzyme covalent intermediate.[2] A detailed picture of the atomic rearrangement during the complete reaction pathway will be provided and differences between both mechanisms will be analyzed.

[1] Ardèvol, A.; Rovira, C. *Angew. Chem. Int. Ed.* **2011**, 50, 10897-10901.
[2] Rojas-Cervellera, V.; Ardèvol, A.; Boero, M.; Planas, A.; Rovira, C. *Chem. Eur. J.* **2013**, 42, 14018–14023.

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XI JORNADAS DE CARBOHIDRATOS

New approaches to the synthesis of hyaluronic acid and chondroitin sulfate oligosaccharides

José L. de Paz, Giuseppe Macchione, Susana Maza, M. Mar Kayser, Javier López-Prados, Jesús Angulo, and Pedro M. Nieto

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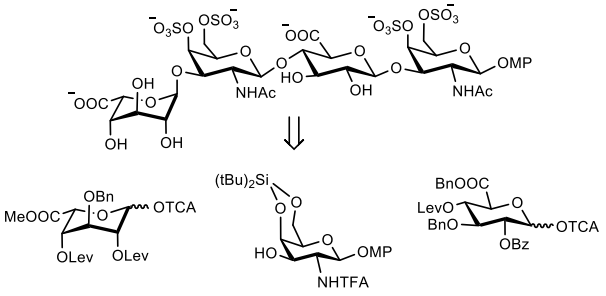
Glycosaminoglycans (GAGs), such as hyaluronic acid, chondroitin sulfate and heparin, modulate important biological processes by their interactions with different protein receptors. Synthetic oligosaccharides are crucial for the study of GAG-protein interactions and the establishment of structure-activity relationships, improving our understanding of the role that these complex polisaccharides play in nature. Despite the recent advances in GAG oligosaccharide synthesis, the preparation of these compounds is still challenging. For example, glycosylation of poorly reactive uronic acids often leads to moderate yields. Final deprotection/sulfation steps are also associated with experimental problems such as long reaction times and low isolated yields.

In this lecture, we present our contributions to the synthesis of hyaluronic acid and chondroitin sulfate oligosaccharides. We have explored the use of perfluorated tags to facilitate the purification of the protected intermediates in a hyaluronic acid synthetic sequence. We have also developed a novel strategy for the preparation of chondroitin/dermatan sulfate oligosaccharides that is based on the use of *N*-trifluoroacetyl-protected galactosamine building blocks.[1] Glycosylation reactions proceeded in high yields using our protecting group design. Following this approach, several tetrasaccharides, bearing different uronic acid compositions and sulfation patterns, were successfully synthesized. On the other hand, we have employed a fluorescence polarization assay to evaluate the interactions between the synthesized oligosaccharides and FGF-2, a model GAG-binding protein. Our results show that this method is an excellent platform for the rapid analysis of GAG-protein interactions in solution.



[1] Maza, S.; Kayser, M. M.; Macchione, G.; López-Prados, J.; Angulo, J.; de Paz, J. L.; Nieto, P. M.; *Org. Biomol. Chem.* **2013**, *11*, 3510.

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Combined structural snapshots and metadynamics reveal a substrate-guided SNi-type reaction for polypeptide GalNAc-transferase T2

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Glycosyltransferases (GTs) are an ubiquitous group of enzymes that catalyze the transfer of sugar moieties from activated donors, mostly nucleotide sugars, into a diverse number of acceptor substrates.[1] They are responsible for protein glycosylation, the most recurrent post-translational modification occurring in nature for cell recognition and signaling. GT alterations cause several diseases, such as infection, inflammation, and either normal or abnormal cellular developments. Given their importance in both normal development and pathological conditions, GTs are targets for inhibition and thus their molecular mechanisms of action are the focus of intense study.

In this context, the catalytic mechanism of GTs, specially the retaining ones, have been a controversial subject in recent times. Here using the retaining protein GalNAc-T2, a member of a large family of human glycosyltransferases and responsible for a very abundant post-translational modification, and substrates, we describe different structural snapshots along the catalytic cycle to uncover the reaction coordinates. Furthermore, we combine the experimental atomic information with QM/MM metadynamics to unravel the catalytic mechanism of this retaining enzyme at atomic-electronic detail. Our study reveals key features of substrate recognition, the specificity of acceptor Thr versus Ser residues and a front-face S_Ni-type reaction with substrate-assisted catalysis for the glycosyl transfer.[2]

[1] Lairson, L. L.; Henrissat, B.; Davies, G. J.; Withers, S. G. Glycosyltransferases: structures, functions, and mechanisms. *Annual Review of Biochemistry* **2008**, *77*, 521-555.

[2] Lira-Navarrete, E.; Iglesias-Fernández, J.; Zandberg, W. F.; Compañón, I.; Kong, Y.; Corzana, F.; Clausen, H.; Vocadlo, D.; Peregrina, J. M.; Rovira, C.; Hurtado-Guerrero, R. *Angew Chem. Int. Ed.* **2014**, in press (DOI: 10.1002/anie.201402781 and 10.1002/ange.201402781).

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XI JORNADAS DE CARBOHIDRATOS

Development of new antibiotics by targeting essential enzymes in bacteria: Structure-based design and simulation studies

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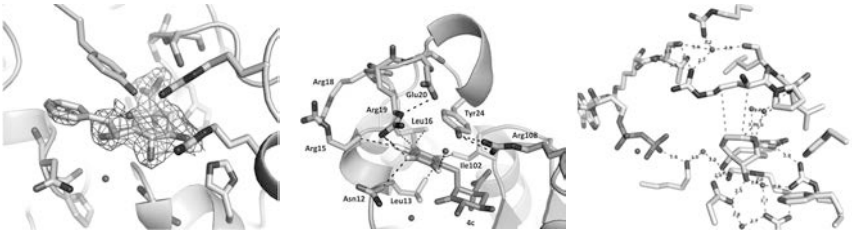
Infectious diseases are the second cuase of death worldwide. To its prevalence has undoubledly contributed the increasing development and spread of resistance to current antibiotics. To change this trend, the discovery of novel drugs and therapies to treat antibiotic-resistant infections and, particularly of drugs with new mechanisms of action is needed. In our research group we are studing the possible development of new antibiotics whose mode of action is based on the selective and effective inhibition of an essential route in bacteria that does not have any counterpart in human cells, the shikimic acid pathway. In particular, we have focused in the inhibition of the third and the fifth enzyme of this pathway, type II dehydroquinase and shikimate kinase. Both enzymes are essential in important pathogenic microorganisms, such as *Mycobacterium tuberculosis* and *Helicobacter pylori*, which are responsible for tuberculosis and stomach cancer, respectively. The key interactions of the substrate and product binding and the enzyme movements that are essential for catalytic turnover of both enzymes have been investigated by structural and computational studies. Based on the mode of action of the enzyme, molecular modeling, dynamic simulations and structural studies and by creating favorable interactions with key residues in the enzymatic mechanism several potent inhibitors were designed and identified.[1-3] Some of them are analogues of the natural substrate, and the others are mimics of the enzyme reaction intermediate. The crystal structures of enzyme/inhibitors complexes reveal an important change in the conformation and flexibility of the loop that closes over substrate binding. Our recent progress in the project will be presented.



[1] Coderch, C.; Lence, E.; Peón, A.; Lamb, H.; Hawkins, A. R.; Gago, F.; González-Bello, C. *Biochem. J.* **2014**, doi:10.1042/BJ20131103, *in press*.

[2] Blanco, B.; Prado, V.; Lence, E.; Otero, J. M.; Garcia-Doval, C.; van Raaij, M. J.; Llamas-Saiz, A. L.; Lamb, H.; Hawkins, A. R.; González-Bello, C. *J. Am. Chem. Soc.* **2013**, *135*, 12366.

[3] Lence, E.; Tizón, L.; Otero, J. M.; Peón, A.; Prazeres, V. F. V.; Llamas-Saiz, A. L.; Fox, G. C.; van Raaij, M. J.; Lamb, H.; Hawkins, A. R.; González-Bello, C. *ACS Chem. Biol.* **2013**, *8*, 568.

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XI CARBOHYDRATE SYMPOSIUM

Fluorinated carbohydrate probes for chemical biology

Omar Boutureira

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Chemical Glycobiology has experienced an impressive growth in the last decade as a result of the discovery of the role of carbohydrates in relevant recognition processes, yet the use of fluorinated glycoconjugates to study such events is still in its infancy. Selective incorporation of fluorine into biomolecules allows simultaneous modulation of their electronic, lipophilic and steric parameters, all of which can influence their biological function. Moreover, this element has been widely employed as structural, functional and mechanistic probe for the study of biological processes by several cutting-edge non-invasive molecular imaging techniques such as ^{19}F-MRI and ^{18}F-PET.

In this abstract we present a survey of synthetic methods developed to access novel fluorinated carbohydrates probes and their application as (a) selective, carbohydrate reporters for disease diagnosis[1] and (b) reagents in complementary chemical site-selective protein modification protocols that provide a unique opportunity to introduce a fluorine atom at a single designated amino acid residue and allow the preparation of well-defined synthetic fluorinated glycoproteins and importantly [^{18}F]-radiolabelled glycoproteins.[2,3]

[1] Backus, K. M.; Boshoff, H. I.; Barry, C. S.; Boutureira, O.; Patel, M. K.; D'Hooge, F.; Lee, S. S.; Via, L. E.; Tahlan, K.; Barry III, C. E.; Davis, B. G. *Nat. Chem. Biol.* **2011**, *7*, 228.

[2] Boutureira, O.; D'Hooge, F.; Fernández-González, M.; Bernardes, G. J. L.; Sánchez-Navarro, M.; Koeppe, J. R.; Davis, B. G. *Chem. Commun.* **2010**, *46*, 8142.

[3] Boutureira, O.; Bernardes, G. J. L.; Fernández-González, M.; Anthony, D. C.; Davis, B. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 1432.

Studying the chemical biology of *N*-glycans with microarrays

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In the last years our laboratory has developed convergent routes for the chemo-enzymatic synthesis of *N*-glycans with full control of number of antennae, type of terminal sugars and core modifications. Currently over 100 structures with a particular focus on antigenic invertebrate and plant glycans are available for the preparation of glycan arrays on glass and ITO coated slides for high-throughput interaction studies. In this talk strategies for the synthesis of this class of natural glycodendrimers will be discussed and applications for the **1)** array-assisted trapping and assignment of lectins from complex mixtures, **2)** the screening of binding specificities of C-type lectins involved in antigen recognition **3)** the screening of antibodies from *S. mansoni* infected patient sera and **4)** their use in the quantitative glycan profiling by SALDI-MS presented.

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Oral Communications

May 28-30, 2014

XI JORNADAS DE CARBOHIDRATOS

Oral Communications

Logroño, La Rioja, Spain

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XI CARBOHYDRATE SYMPOSIUM

Breaking pseudo-symmetry in multiantennary complex N-glycans using lanthanide-binding tags and NMR pseudo-contact shifts

Angeles Canales,[a] Alvaro Mallagaray,[b] Javier Pérez-Castells,[c] Irene Boos,[d] Carlo Unverzagt,[d] Sadine André,[e] Hans-Joachim Gabius,[e] Francisco Javier Cañada,[b] and Jesús Jiménez-Barbero[b]

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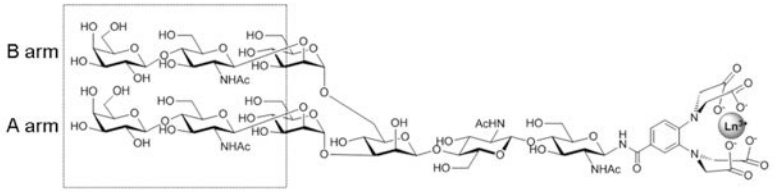
Molecular recognition is of vital significance for life. In terms of biological coding and translating signals into cellular effects, glycans have gained a particula status, owing to their unsurpassed coding capacity and widespread presence of receptors (lectins) to read the encoded information.[1] In this context, we herein present a novel NMR approach to individually monitor the behavior of each arm, A and B, of N-glycans (Scheme 1) and thereby provide a global perspective of their conformational and interaction features in solution.



Scheme 1. Nonasaccharide derivative studied in this work. The 1–3 and 1–6 arms attached to the β-mannose unit are labeled as A and B, respectively.

The use of the lanthanide tag has permitted to break the inherent pseudo-symmetry of the NMR spectra of the identical branches, revealing that the T-shaped *gg* rotamer at the Manα1-6Man junction is the major one in solution, with minor contributions of other backfolded geometries.[2]

In addition, the recognition of this nonasaccharide by human galectin-3 has been studied. In this line, the novel methodology employed has permitted the characterization of the binding epitopes of the symmetrical N-glycan, showing that both arms are involved in the recognition of human galectin-3.[2]

[1] Gabius, H.-J.; André, S.; Jiménez-Barbero, J.; Romero, A.; Solís, L. *Trends Biochem. Sci*, **2011**, *36*, 298-313.

[2] Canales, A.; Mallagaray, A.; Pérez-Castells, J. Boos, I; Unverzagt, C.; André, S.; Gabius, H.-J.; Cañada F.J.; Jiménez-Barbero, J. . *Angew Chem. Int. Ed.* **2013**, 52, 1-6.

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XI JORNADAS DE CARBOHIDRATOS

NMR conformational analysis of glycosylated iminosugars inhibitors of barley β-amylase

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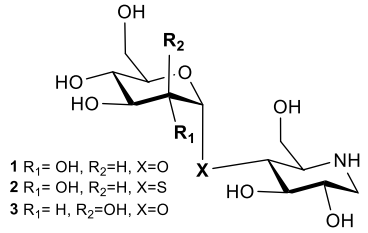
Starch, a polymer of glucose, has an enormous societal and commercial importance, reflected by the huge scale of cereal production per year.[1] On the other hand, the expected increase in world population in next decades is pushing its demand up to levels that will need substantial improvements in crop yields. In the context of a reverse chemical genetic approach, aimed to deepen the understanding of metabolic pathways in barley seeds, three glycosylated iminosugars were prepared as inhibitors of one of the ezymes involved in starch metabolism, the barley β-amylase.[2]



Interestingly, observed differences in inhibition potencies could not be fully rationalized on the grounds of their 3D structures of the complexes obtained from X-ray crystallography. In the present work the conformational properties of the three compounds in the free state have been studied by NMR spectroscopy and molecular modelling. Interglycosidic proton-proton distances have been obtained from NOE experiments, and compared with theoretical models obtained from Monte Carlo Stochastic Dynamics (MC/SD) simulations. The data revealed a significant increase in the flexibility of the S-substituted glycosydic linkage, which allowed to rationalize the unexpected reduction in inhibitory activity of **2**.

[1] Tester, R.F.; Karkalas, J. *Polysaccharides II*; Vandamme, E.J., De Baets, S., Steinbuchel, A. Eds.; Biopolymers; Wiley-VCH: Weinhem, 2002.

[2] Rejzek, M.; Stevenson, C. E.; Southard, A. M.; Stanley, D.; Denyer, K.; Smith, A. M.; Naldrett, M. J.; Lawson, D. M.; Field, R. A. *Molecular BioSystems* **2011**, 7, 718.

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XI CARBOHYDRATE SYMPOSIUM

Development of BODIPY-labeled sulphated carbosilane and mannose dendrons as topical microbicides to prevent HIV-1 sexual transmission

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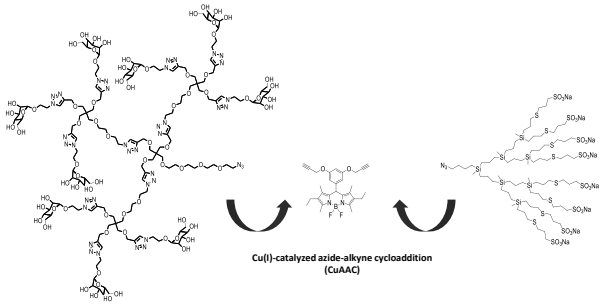
The concept of a 'microbicide' product has been born out due to the unavailability of a vaccine against HIV-1 and the problems of women in negotiating the use of preventive prophylaxis by their partners, especially in developing countries. Different strategies has been followed for the development of HIV-1 microbicides. Two important examples are: the non-specific polyanionic polymers that interact with positive areas of HIV surface and the multivalent systems based on carbohydrates that block dendritic cell receptors like DC-SIGN, mediating HIV infection through recognition of viral envelope glycoprotein gp120.



We have developed two sulphated carbosilane dendrons and two mannose dendrons with different valency labeled with a BODIPY fluorescent tag using "click chemistry" to evaluate their ability to block HIV infection. Additionally, we have developed a compound that combine a sulphate carbosilane dendron and a mannose dendron in a single entity with the objective of producing a synergetic effect, blocking simultaneously some important mechanism used by HIV-1 to achieve its target cells, the T-Cells. This strategy could produce a new combinatorial therapy with two efficient microbicides that prevent HIV infection and dissemination in the early stages of the infection process.

[1] De la Mata, F.J.; Muñoz-Fernández, M.A.; Vacas-Cordoba, E.; Relloso, M.; Sanchéz-Torres, C.; García, F.; Pérez-Ávarez, L.; Pion, M.; Gomez-Ramirez, R.; Arnaiz-Garrido, E. *AIDS* **2013**, *27*, 1219.

[2] Berzi, A.; Reina, J.J.; Ottria, R.; Sutkeviciute, I.; Antonazzo, P.; Sanchez-Navarro, M.; Chabrol, E.; Biasin, M.; Trabattoni, D.; Cetin, I.; Rojo, J.; Fieschi, F.; Bernardi, A.; Clerici, M. *AIDS* **2012**, *26*, 127.

[3] Ribeiro-Viana, R.; Garcia-Vallejo, J.J.; Collado, D.; Perez-Inestrosa, E.; Bloem, K.; van Kooyk, Y.; Rojo, J. *Biomacromolecules*, **2012**, *13*, 3209

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XI JORNADAS DE CARBOHIDRATOS

Glycotargeted self-assembled nanocarriers from calixarene-cyclodextrin heterodimers for site-specific delivery of docetaxel

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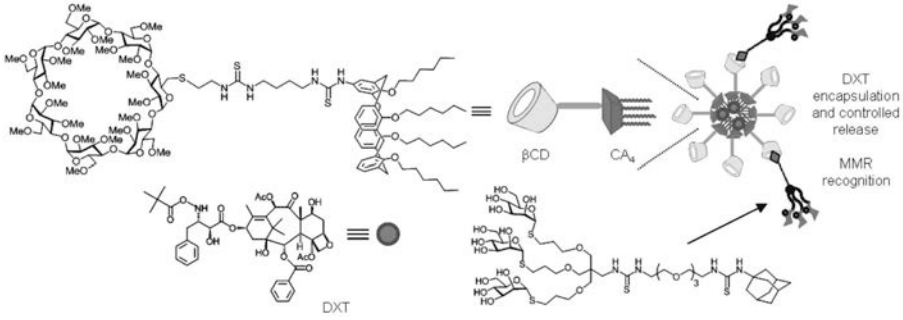
The development of well-ordered functional nanostructures filled with the capacity to assemble under dilute conditions in water or buffer media continues to be one of the more fascinating challenges facing modern chemistry, with relevance in areas like imaging, diagnostics, tissue engineering or drug deliver, among others. Many of those channels require the supramolecular system to be capable of encapsulating a cargo, targeting specific cell surface receptors and allowing the gradual release of the payload. Monodisperse building blocks of the calixarene (CA)[1] and cyclodextrin (CD)[2,3] families are privileged platforms towards this end because of their capacity to form host-guest superstructures and the possibility to be tailored to achieve a predictable and controlled non-covalent organization. In this work we report the successful construction of nanospheres entangling an inner core formed by hydrophobic calix[4]arene (CA_4) units and an external hydrophilic shell exposing β-cyclodextrin (βCD) motifs by the self-assembly in water of amphiphilic CA_4—βCD heterodimers (see Figure). The CA_4 scaffold is very well suited to promote tight packing of fatty chains installed at the narrower ring in its cone conformation, providing a lipid matrix where hydrophobic drugs can be entrapped, whereas the presence of βCD at the nanosphere surface allows host-guest directed decoration. The potential of the new systems in nanomedicine is illustrated by their capacity to encapsulate and provide sustained release of the anticancer drug docetaxel and undergo supramolecular surface post-modification with adamantane-armed glycoligands targeting the macrophage mannose receptor.



[1] Sansone, F.; Casnati, A. *Chem. Soc. Rev*. **2013**, *42*, 4623.
[2] Martínez, A.; Ortiz Mellet, C.; García Fernández, J. M. *Chem. Soc. Rev*. **2013**, *42*, 4746.
[3] Ortiz Mellet, C.; García Fernández, J. M.; Benito, J. M. *Chem. Soc. Rev*. **2011**, *40*, 1586.

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XI CARBOHYDRATE SYMPOSIUM

Galactooligosaccharides formation during enzymatic hydrolysis of lactose: Towards prebiotic-enriched milk

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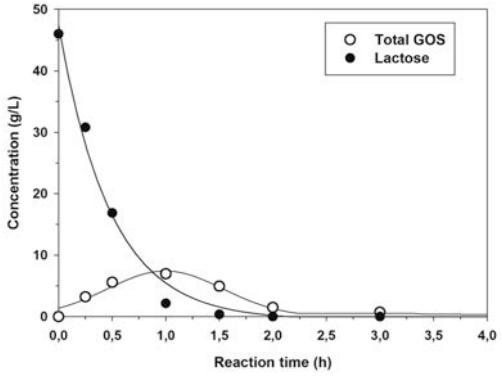
Human milk oligosaccharides (HMOs) constitute a family of more than a hundred structurally diverse carbohydrates. To mimic the multiple benefits of HMOs over breast-fed infants, several related carbohydrates, in particular galactooligosaccharides (GOS) and fructooligosaccharides (FOS) are added to infant formulas.[1] The incorporation of GOS and FOS into baby foods favours the microbiota composition in the infant's feces (prebiotic effect) and reduce allergenic manifestations (e.g. atopic dermatitis) and infections during the first years of life. Apart from lactose hydrolysis, β-galactosidases (EC 3.2.1.23) catalyze a transgalactosylation reaction in which lactose or other carbohydrates serve as galactosyl acceptors, yielding GOS with different polymerization degree and type of linkages. The formation of GOS in milk during the treatment with several β-galactosidases (*Bacillus circulans*, *Kluyveromyces lactis* and *Aspergillus oryzae*) was analyzed in this work. The maximum GOS concentration was obtained at a lactose conversion of approx. 40-50% with *B. circulans* and *A. oryzae* β-galactosidases, and at 95% with *K. lactis* β-galactosidase. Using an enzyme dosage of 0.1% (v/v), the maximum GOS yield with *K. lactis* enzyme was achieved in 1 h and 5 h at 40°C and 4°C, respectively. Milk containing 7.0 g/L GOS −HMOs concentration is between 5-15 g/L−, and with a low content of residual lactose (2.1 g/L, compared with 44-46 g/L in the initial milk sample) was obtained with *K. lactis* β-galactosidase. The major GOS synthesized were 6-galactobiose [Gal-β(1→6)-Gal], allolactose [Gal-β(1→6)-Glc] and 6´-O-β-galactosyl-lactose [Gal-β(1→6)-Gal-β(1→4)-Glc].



[1] Angus, F.; Smart, S.; Shortt, C. *Probiotic Dairy Products* **2007**, 120-137.
[2] Rodriguez-Colinas, B.; Fernandez-Arrojo, L.; Ballesteros, A.O.; Plou, F.J. *Food Chemistry* **2014**, 145, 388-394.

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XI JORNADAS DE CARBOHIDRATOS

Tailoring self-assembling and targeting capabilities of CD-based nanoparticles for gene delivery

Juan M. Benito,[a] Iris Pflueger,[a] David Rodriguez-Lucena,[a] Carmen Ortiz Mellet,[b] and José M. García Fernández[a]

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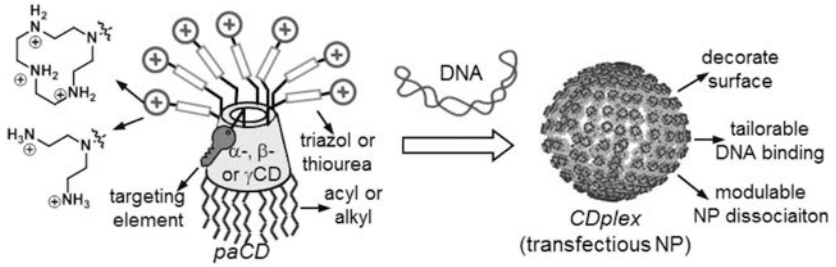
Nucleic acid-based drugs hold an unparalleled therapeutic potential due to their predictable and tailorable mode of action. Unfortunately, their bioavailability is poor and clinical application critically depends on the development of suitable delivery systems. Despite their innate capabilities for such task, the use of viral carriers is plagged of risks (e.g. immunogenicity or scaled-up production). Among artificial alternatives, cationic polymers and lipids hold a prominent position.[1] Aimed at merging the virtues of both, we conceived a new family of artificial gene vectors based on molecularly well-defined cyclodextrins (CDs) feturing segregated cationic and lipophilic domains (polycationic amphiphilic cyclodextrins, *paCDs*).[2] paCDs self-assemble in the presence of DNA to render tiny nanoparticles (*CDplexes*) exhibiting gene transfer capabilities that are intimately dependent on paCD molecular structure, eventually surpassing those of commercial standards (e.g. PEI).[3] Moreover, in contrast to most investigational artificial gene vectors, the flexibility of the synthetic scheme permits the modification of virtually any element on the CD scaffold with relative ease. Herein we wish to illustrate how this strategy can be implemented to (i) pinpoint the role of the hydrophilic/hydrophobic balance on paCD-DNA complex formation and dissociation, (ii) assess the influence of paCD cationic motifs on DNA binding, and (iii) decorate CDplex surface with specific binding epitopes (see figure). In the frame of a more ambitious project, aimed at devising targeted non-viral gene carriers, structural modifications will be correlated to gene transfer efficiency capabilities towards model cell lines.



[1] Mintzer, M.A.; Simanek, E.E. *Chem. Rev.* **2009**, *109*, 259.
[2] Ortiz Mellet, C.; Benito, J.M.; García Fernández, J. M. *Pure Appl. Chem.* **2013**, *85*, 1825 and references therein.
[3] Martínez, A.; Bienvenu, C.; Jiménez Blanco, J. L.; Vierling, P.; Ortiz Mellet, C.; García Fernández, J. M.; Di Giorgio, C. *J. Org. Chem.* **2013**, *78*, 8143 and references therein.

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XI CARBOHYDRATE SYMPOSIUM

Shikimic acid: a promising scaffold for new materials, drugs and catalysts

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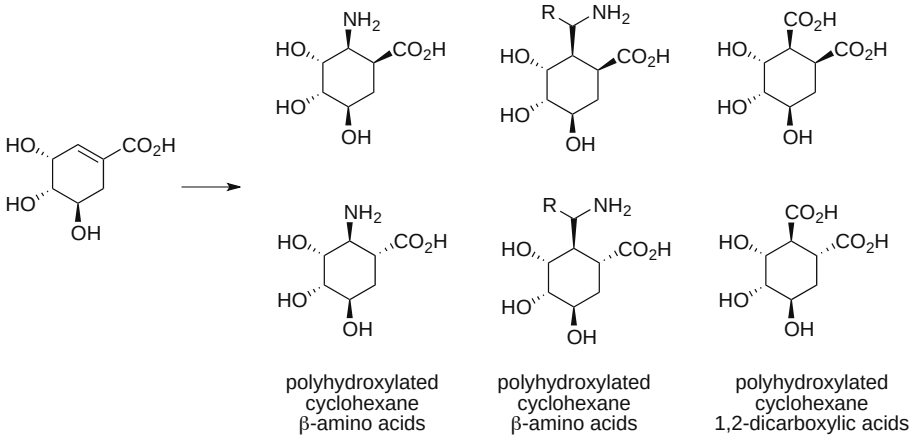
(-)-Shikimic acid is a natural compound that acts as a key intermediate in the biosynthesis of amino acids. Consequently, this derivative is widely present in many plants and has interesting biological properties. But besides the pharmacological relevance of shikimic acid itself, it is also an intermediate in the synthesis of many drugs, being the most relevant the antiviral agent oseltamivir (Tamiflu™).[1]

Shikimic acid includes several relevant structural subunits: a cyclohexane ring, an α,β-unsaturated ester moiety and three hydroxy groups attached in a defined spatial orientation. Accordingly, it offers an atractive alternative to sugars for the preparation of highly functionalized molecules.[2]

Our research group is involved on a project aimed at the exploration of new synthetic possibilities offered by this promising and attractive starting material. We will present our studies on polyhydroxylated cyclohexane β– and γ–amino acids, and polyhydroxylated cyclohexane 1,2-dicarboxylic acids.



[1] Amalia M. Estévez and Ramón J. Estévez. *Mini-Reviews in Medicinal Chemistry*, **2012**, *12*, 1443.
[2] Montserrat Carballido, Luis Castedo, and Concepción González-Bello. *Eur. J. Org. Chem.* **2004**, 3663.

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XI JORNADAS DE CARBOHIDRATOS

Conformational transitions as key features of PimA-mediated glycosyl transfer

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Remarkable progress has been made in recent years in our understanding of the catalytic mechanism and structural basis of glycosyl transfer. However, the study of the conformational changes and dynamics that govern substrate recognition and catalysis remains a major challenge in the field of glycosyltransferases (GTs).[2] Here we focus in PimA, an essential enzyme involved in the biosynthesis of phosphatidyl-*myo*-inositol mannosides (PIMs), which are key glycolipids of the mycobacterial cell envelope1. PimA is a paradigm of this family of GTs, which the molecular mechanism of substrate/membrane recognition and catalysis is still unknown. We have solved the crystal structure of PimA from *M. smegmatis* in complex with its donor substrate GDP-Man. The notion of a membrane-associated protein via electrostatic interactions is consistent with the finding of an amphipathic α-helix in the N-terminal domain of PimA. Based on structural, biophysics and biochemical studies, we proposed a model of interfacial catalysis in which PimA recognizes the fully acylated acceptor substrate, phosphatidyl-myo-inositol (PI), with its polar head within the catalytic cleft and the fatty acid moieties only partially sequestered from the bulk solvent. In addition, we provided strong evidence showing that PimA undergoes significant conformational changes upon substrate binding.[3] Single-molecule force spectroscopy revealed that the mannosyltransferase PimA exhibits weak mechanical stability albeit displaying -sheet topology expected to unfold at much higher forces. Notably, PimA unfolds following heterogeneous multiple step mechanical unfolding pathways at low force akin to molten globule states.[1] Interestingly, the ab initio low resolution envelopes obtained from small angle x-ray scattering of the unliganded PimA and the PimA-GDP complexed forms clearly demonstrate that not only the "open" and "closed" conformations of the GT-B enzyme are largely present in solution, but in addition, PimA experiences remarkable flexibility that undoubtedly corresponds to the N-terminal "Rossmann fold" domain, which has been proved to participate in protein-membrane interactions. Altogether, our experimental data support a model wherein the flexibility and conformational transitions confer adaptability of PimA to the substrates/membrane, which seems to be of importance during catalysis. The proposed mechanism has fundamental implications for the comprehension of membrane-associated GTs at the molecular level and the development of GT inhibitors.

[1] Giganti et al., *J. Biol. Chem.* 288, 29797-29808 (2013).
[2] Guerin et al., *J. Biol. Chem.* 285, 33577-33583 (2010).
[3] Guerin et al., *J. Biol. Chem.* 284, 21613-21625 (2009).

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XI CARBOHYDRATE SYMPOSIUM

Molecular insights into the synthesis of the heparin/ HS linker by retaining glycosyltransferase EXTL2. A QM/MM study

Laura Masgrau,[a] Maria Fernanda Mendoza,[a,b] Hansel Gómez,[b] and José M. Lluch

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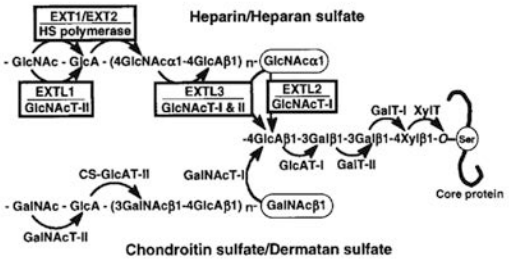
Heparin/heparan sulphate (HS) are glycoconjugates with important biological roles that go from the regulation of blood coagulation to that of tumor metastasis. After addition of a common linker to the core protein by the action of several glycosyltransferases, the heparin/HS biosynthesis diferentiates with the addition of an αGlcNAc to the glucoronic acid (GlacA) end of that linker. The formation of this new glycosidic bond, with an α1,4 specificity, is catalyzed by the retaining glycosyltransferase EXTL2.



Our recent computational studies on the molecular details of the reaction catalyzed by EXTL2, and also its substrate specificity, will be presented. Finally, the mechanistic results will be discussed in the context of the reaction mechanism of retaining GTs, area in which we have performed several studies in the last years and for which the scientific debate seems to remain still open.[1-3]

[1] Gómez, H.; Polyak, I.; Thiel, W.; Lluch, J.M; Masgrau, L. *J. Am. Chem. Soc.* **2012**, *134*, 4743.
[2] Gómez, H.; Lluch, J.M; Masgrau, L. *J. Am. Chem. Soc.* **2013**, *135*, 7053.
[3] Gómez, H.; Rojas, R; Tabak, L.; Lluch, J. M; Masgrau, L. "Initiation of mucin-type O-glycosylation by polypeptide GalNAc transferase T2. A combined computational and experimental study", *Submitted*.

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XI JORNADAS DE CARBOHIDRATOS

Rapid and quantitative glyco-analysis by MALDI using isotopically labelled glycans

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Numerous diseases are known to involve changes in glycosylation. Altered glycosylation is a universal feature of cancer cells and some glycan structures are well-known markers for tumours and tumour progression.[1] Also, the biopharmaceutical industry is particularly interested in the glycosylation of monoclonal antibodies and other therapeutical proteins as glycans can be important determinants of their biological activity and therapeutic efficacy as well as in the immunogenicity of the protein. As a result, methods for the comprehensive analysis of protein glycosylation and glycan composition are of interest to the scientific community.

Owing to its high sensitivity at low concentrations, mass spectrometry is often used in the analysis of the resulting complex mixtures.[2] However, the signal intensity of particular analytes is dependent, amongst many other factors, on the physical properties of the analyte, making any relative quantification very difficult. Identification of glycans common to two samples and their relative quantification may be facilitated by use of derivatisation of the glycan mixtures to incorporate isotopic tags.[3] However, the introduction of additional steps (labeling and washing procedures) make these methods time-consuming and less accurate, providing only semi-quantitative results and difficulting the high-throughput. There exists an unmet need for improved methods for rapidly and easily analysing the content of released glycan mixtures.

We present here the use of stable isotopologues of individual N-glycans as standards in matrix assisted mass spectrometry for the quantitative analysis of protein glycosylation. Following a chemo-enzymatic approach, a library of ^{13}C-labeled N-glycans has been prepared. The glycoprotein of interest can be spiked with a mixture of these standards and directly analysed by MALDI, after the corresponding glycan release, in a quantitative way using the isotope dilution analysis principle. This method of analysis may have utility both in the identification of glycan markers associated with particular disorders and diseases and for the monitoring and control of glycosylation in biopharmaceutical manufacturing, as it provides a rapid and easily automated method for the determination of the absolute content of glycans in a sample.

[1] Hart, G. W.; Copeland, R. J. *Cell.* **2010**, *143*, 672.
[2] Morelle, W.; Michalski, J. C. *Nat. Protoc.* **2007**, *2*, 1585.
[3] Ruhaak, L. R.; Zauner, G.; Huhn, C.; Bruggink, Am. M.; Deelder, A. M.; Wuhrer, M. *Anal. Bioanal. Chem.* **2010**, *397*, 3457.

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XI CARBOHYDRATE SYMPOSIUM

Augmented reality applied to molecular modeling

Jorge R. López Benito, and Enara Artetxe González

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Augmented Reality (AR) consists on the superposition of virtual elements into the real world. It is an innovative technology which is starting to be introduced in many fields, including research and education, as a complementary system for improving understanding and visualization of complex concepts.

This communication presents a mobile application automatized to display Protein Data Bank (PDB) files in Augmented Reality, with configurable displaying options and environments. The standard format of the PDBs and the extensive existing data bank in the network allows this application to be universalized and introduced in a wide range of fields.

The innovation that offers the fact of transforming a plain text file into a three dimensional model displayed in the real world and which can be easily manipulated presents special interest for:

- Researching scenarios, as a complementary tool for visualization and collaborative works.
- Education and Conferences as a support during explanations enhancing the interactivity between lecturer and audience.

The creation of self-explanatory posters and books where pictures can come alive and add dinamyc content to the static descriptions.

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XI JORNADAS DE CARBOHIDRATOS

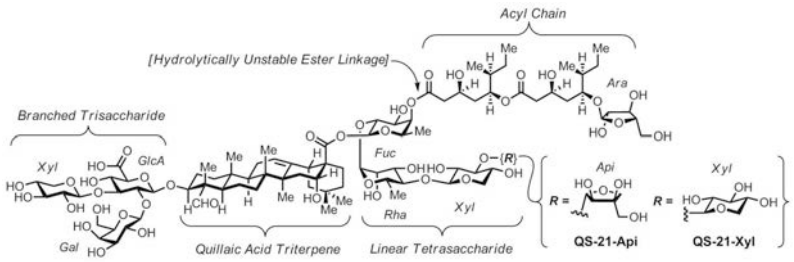
Development of QS-21−inspired minimal synthetic saponins as novel vaccine adjuvants: Improving on nature

Alberto Fernández-Tejada,[a] Eric K. Chea,[a] Constantine George,[b] Kishore Pillarsetty,[c] Govind Ragupathi,[b] Samuel J. Danishefsky,[a] and David Y. Gin[a]

a) Department of Molecular Pharmacology and Chemistry; b) Melanoma & Sarcoma Service, Department of Medicine; c) Radiochemistry & Imaging Science Service, Department of Radiology; Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065; e-mail: fernanA2@mskcc.org

The immune response to vaccines is often enhanced by the presence of adjuvants – compounds that are themselves not necessarily immunogenic but augment significantly the immunogenicity of a coadministered antigen. Few adjuvants have both sufficient potency and acceptable toxicity for clinical use. QS-21, a saponin natural product, has shown promise in numerous vaccine clinical trials; however, its utility remains constrained by several factors, including scarcity, dose-limiting toxicity and chemical instability.[1] Further, its molecular mechanism of action is still largely unknown.

To address these challenges, we have rationally designed and synthesized novel simplified saponin variants with improved stability and high adjuvant potency.[2] Extensive structure-function exploration of the QS-21 molecule has provided important new insights into the key structural features that are critical for activity. This has led to the development of potent minimal saponin adjuvants that are synthetically accessible, non-toxic, and successfully decouple adjuvant activity from toxicity.[3] These efforts have enabled the development of QS-21−derived molecular probes with more favorable therapeutic profiles as a powerful platform for mechanistic studies of these saponins.



Acknowledgement: A.F.-T thanks EC-REA (Marie Curie Postdoctoral Fellowship, MC-IOF) for funding.

[1] Ragupathi, G., Gardner, J. R.; Livingston, P. O.; Gin, D. Y. *Expert Rev. Vaccines* **2011**, *10*, 463.

[2] Chea, E. K.; Fernández-Tejada, A.; Damani, P.; Adams, M. M.; Gardner, J. R.; Livingston, P. O.; Ragupathi, G.; Gin, D. Y. *J. Am. Chem. Soc.* **2012**, *134*, 13448.

[3] Fernández-Tejada, A.; Chea, E. K.; George, C.; Pillarsetty, K.; Gardner, J. R.; Livingston, P. O.; Ragupathi, G.; Lewis, J. S.; Tan, D. S.; Gin, D. Y. *Nature Chem.* **2014**, *6*, accepted.

UNIVERSIDAD DE LA RIOJA

Flash Communications

May 28-30, 2014

XI JORNADAS DE CARBOHIDRATOS

Flash Communications

Logroño, La Rioja, Spain

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Molecular recognition of galectins by different glycans: *in silico* comparative studies

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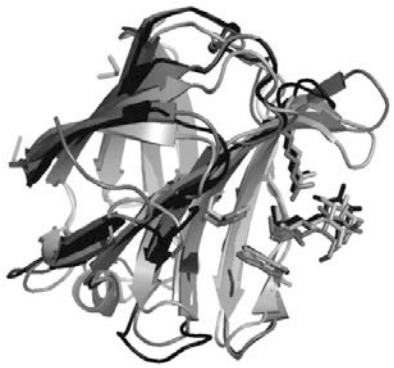
Carbohydrates are involved in a variety of physiological processes, acting as signals for cellular recognition.[1] Among these processes, immune and inflammatory responses, organogenesis, metastasis, and diverse infectious processes should be mentioned.[2] In this context, the elucidation of the mechanisms that govern how oligosaccharides are accommodated in the binding sites of lectins (such as galectins), antibodies, and enzymes is currently a topic of major interest because of its long-range potential for clinical applications.



In particular human galectins 1, 3, and 7 (in figure complexed with lactose), present specific and selective recognition for different types of glycans, also exhibiting differencies in the recognition patterns. Taking advantage of experimental data, computational studies were performed [3]. By means of docking and MD simulations, it is possible to deepen into the specific recognition of different glycans, and into the key carbohydrate/protein interactions at atomic detail. These studies can assist in the design of novel ligands with potential therapeutic applications.

[1] Gabius, H.J.; André, S.; Jiménez-Barbero, J.; Romero, A.; Solis, D. *Trends Biochem. Sci.* **2011**, *36*, 298.
[2] Gabius, H.J. *The Sugar Code. Fundamentals of glycosciences;* Wiley-VCH: Weinheim, **2009**.
[3] Martin-Santamaria, S.; Gabius, H.J.; Jiménez-Barbero, J. *Pure Appl. Chem.* **2012**, *84*, 49.

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XI JORNADAS DE CARBOHIDRATOS

gem-Difluoro-carbasugars: the recovery of the exo-anomeric effect restrains the conformational space

L. Unione[a], D. Díaz[a], S. Martín-Santamaría[b], F. J. Cañada[a], B. Xu[c], Y. Zhang[c], M. Sollogoub[c], and J. Jiménez-Barbero[a]

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Molecular recognition of carbohydrates is at the heart of different events of paramount biomedical interest. In this context, the employment of sugar mimics as enzyme inhibitors or molecular probes has been widely developed in the last years [1]. Among them, we herein present our advances in the use of fluorine-containing carbasugars. The replacement of the ring-oxygen by a CHF or CF_2 group could somehow restore the typical stereo-electronic effects occurring in natural sugar as the anomeric effect [2].

The origin of the anomeric effects remains a topic of discussion [3]. Herein, the stereoelectonic properties of a novel type of sugar mimics whose endocyclic oxygen atom has been replaced by CF_2 (gem-difluorocarbasugars) have been explored by NMR spectroscopy and computational methods. Strikingly, these difluorinated pseudosugars retain the structural features of the exo-anomeric effect, a key factor for modulating the conformational preferences of these relevant biomolecules. The presence of the exo-anomeric effect is demonstrated both experimentally and theoretically.

[1] Deleuze, A., Menozzi, C., Sollogoub, M., & Sinay, P. *Angew. Chem.* 2004, **48**, 6848-6851
[2] Jiménez-Barbero, J., Sollogoub, M., et al. *Chem. Asian J.* 2008, **3**, 51-58
[3] Cocinero, E. J., Çarçabal, P., Vaden, T. D., Simons, J. P., and Davis, B. G. *Nature Letters, 2011, **469**, 76-80.*

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XI CARBOHYDRATE SYMPOSIUM

Understanding of Toll-Like Receptor 4 recognition: searching for novel modulators and probes

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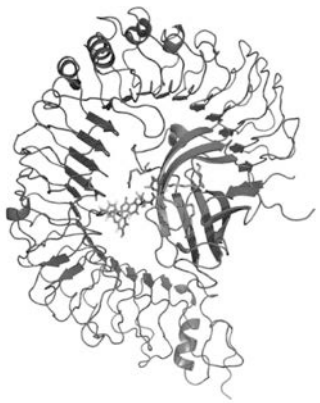
The family of Toll-like receptors (TLRs) are potential regulators and controllers of the immune response through their ability to recognize pathogen-associated molecular patterns. TLRs are involved in the modulation of the immune system, including the processes of inflammation and defence against cancer. In particular, TLR4 is located in the plasma membrane, where binds to lipopolysaccharides (LPSs), a membrane constituent of gram-negative bacteria, and together with MD-2, forms a heterodimeric complex which leads to the activation of the innate immune system response.[1] LPS interaction with MD-2/TLR4 involves at least two other proteins: the lipopolysaccharide binding protein, and CD14. The major role for CD14 is to enhance the sensitivity of the TLR4/MD-2 signaling complex, dropping the binding affinity for LPS to picomolar concentrations.



TLR4 activation has also been associated with certain autoimmune diseases, noninfectious inflammatory disorders, and neuropathic pain, suggesting a wide range of possible clinical settings for application of TLR4 antagonists.[2] However, agonists of TLR4 can also be useful as adjuvants in vaccine development and in cancer immunotherapy.

Since the direct interactions of these proteins with different ligands remain un-clarified, we have undertaken computational studies in order to characterize, at atomic level, the involved molecular recognition processes, and to understand the key features of agonism/antagonism behaviour to propose new chemical scaffolds for the development of new TLR4 modulators and probes.[3]

[1] Park, B.S.; Song, D.H.; Kim, H.M.; Choi, B.S.; Lee, H.; Lee, J.O. *Nature*. **2009**, *458*(7242), 1191-5.
[2] Peri, F. Piazza, M. *Biotechnol. Adv.* **2012**, *30(1)*, 251.
[3] R. Cighetti, C. Ciaramelli, S. Enza Sestito, I. Zanoni, L. Kubik, A. Ardá-Freire, V. Calabrese, F. Granucci, R. Jerala, S. Martín-Santamaría, J. Jiménez-Barbero, F. Peri. *ChemBioChem*, **2014**, *15*, 250.

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XI JORNADAS DE CARBOHIDRATOS

Rapid discovery of potent α-L-fucosidase inhibitors by *in situ* screening of (pyrrolidin-2-yl)triazoles

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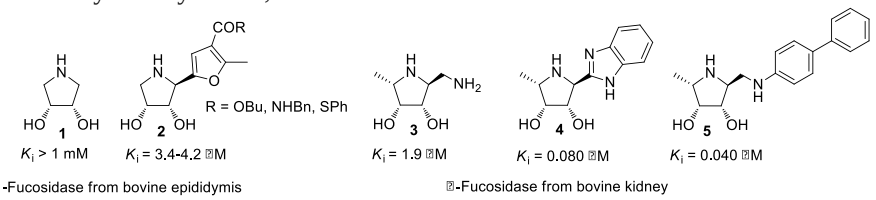
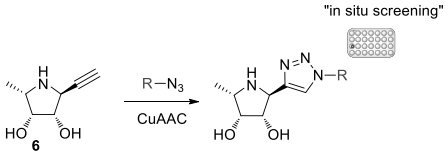
Over recent years we have been actively working on the development of new iminocyclitols with inhibitory activity towards α-L-fucosidases.[1-3] We have shown that the presence of an additional heteroaromatic (furyl, imidazolyl) or aromatic (phenyl, biphenyl) moiety, close to a five membered iminocyclitol framework, increases notably their inhibitory activity: **1** *vs* **2**, or **3** *vs* **4** and **5**.



In order to look into chemical diversity on the above 5-membered iminocyclitols by the systematic variation of the aromatic group in a quick and easy way, we have applied the *in situ* screening towards α-L-fucosidases by means of copper catalyzed click chemistry, CuACC.[4] Click reaction between unprotected alkynyl iminocyclitol **6** with synthetic or commercial azides afforded a small library of (pyrrolidin-2-yl)triazoles. This aproximation has allowed the discovery of an α-L-fucosidase inhibitor in the low nanomolar range.



The synthesis of lead compound **6** as well as the biological results of the library will be reported.

[1] Moreno-Vargas, A. J.; Robina, I.; Demange, R.; Vogel, P. *Helv. Chim. Acta*, **2003**, *86*, 1894.
[2] Moreno-Vargas, A. J.; Carmona, A. T.; Mora, F.; Vogel, P.; Robina, I. *Chem. Commun.* **2005**, 4949.
[3] Moreno-Clavijo, E.; Carmona, A. T.; Vera-Ayoso,Y.; Moreno-Vargas, A. J.; Bello, C.; Vogel, P.; Robina, I. *Org. Biomol. Chem.* **2009**, *7*, 1192.
[4] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Serine *versus* threonine glycosylation with α-*O*-GalNAc: Implications for the molecular recognition

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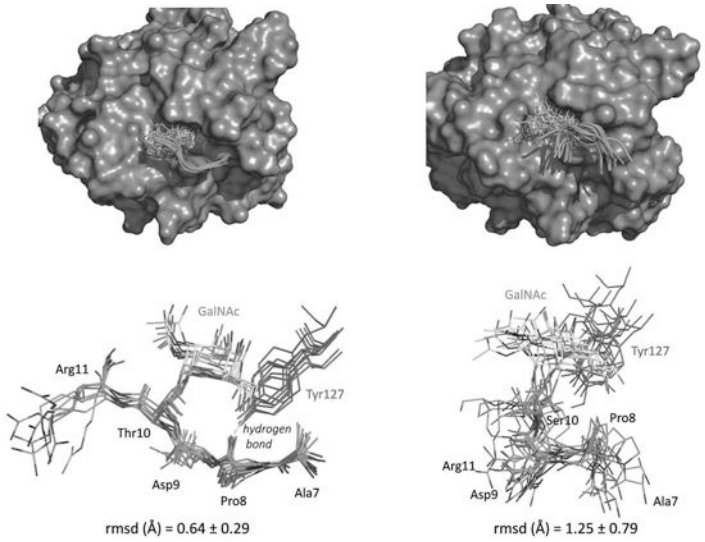
Tn antigen is one of the most specific human tumor-associated structures.[1] Although its structure is referred as α-*O*-GalNAc-Ser/Thr, not discriminating the amino acid to which GalNAc is linked, this work yields unexpected results for molecular recognition of this antigen by three lectins (*Soybean agglutinin* –SBA–, *Vicia Villosa agglutinin* –VVA– and *Helix Poamatia agglutinin* –HPA–). The study reveals that the aglyconic part of Tn (serine or threonine) plays a subtle but interesting role in the protein recognition. This feature has been tested using different glycopeptides that include Tn antigen (α-*O*-GalNAc-Ser or α-*O*-GalNAc-Thr). For SBA and VVA lectins, Tn antigen bearing threonine exhibits higher affinity than its serine homologue. In contrast, HPA lectin shows a clear preference for the serine-Tn antigen. The origin of the selectivity of the proteins studied here for Tn antigen is explained by the different presentation of the sugar moiety in the bound state.[2]



[1] Ju, T., Otto, V. I., Cummings, R. D. (). *Angew. Chem. Int. Ed.* **2011**, *50*, 1770.
[2] Corzana, F., Busto, J. H., Jiménez-Osés, G., García de Luis, M., Asensio, J. L., Jiménez-Barbero, J., Peregrina, J. M., Avenoza, A. *J. Am. Chem. Soc.* **2007**, *129*, 9458.

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XI JORNADAS DE CARBOHIDRATOS

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XI CARBOHYDRATE SYMPOSIUM

Glycan epitope presentation to lectins by NMR and molecular modeling

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Lectins are carbohydrate binding proteins that through the specific recognition of endogeneous glycans play important roles in a wide diversity of key biological events.[1] Lectins are usually classified according to their specificity toward mono or disaccharide epitopes.[2] However these glycan epitopes are differentially presented to their receptors as part of larger oligosaccharides.

Herein we have studied the recognition at a molecular level of biologically relevant glycan structures by different lectins. By using a combinaton of different NMR experiments, both from the ligand and from the protein points of view, and molecular modeling approaches we have been able to propose the corresponding binding modes, in which not only the presence of a specific epitope is important, but also its presentation is determinant.[3]

[1] Gabius, H. C. *The Sugar Code: Fundamentals of Glycosciences*; Wiley-Blackwell, 2009.
[2] Nilsson, C. L. *Lectins. Analytical Technologies*, Elsevier, Amsterdam, 2007.
[3] Ardá, A.; Blasco, P.; Varón Silva, D.; Schubert, V.; André, S.; Bruix, M.; Cañada, F. J.; Gabius, H. J.; Unverzagt, C.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **2013**, *135*, 2667-75.

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XI JORNADAS DE CARBOHIDRATOS

Lanthanide-chelating carbohydrate conjugates as tools for structural studies of sugars and their recognition by receptors

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a) Dept. Biología Físico-Química, Centro de Inv. Biológicas, CSIC, Madrid, Spain; b) Dpto. Quimica Orgánica I, Fac. C.C. Químicas, Universidad Complutense de Madrid, Spain; c) Facultad de Farmacia, Dpto. Química, Universidad San Pablo CEU, Madrid, Spain; d) Faculty of Veterinary Medicine, Ludwig-Maximilians University, Munich, Germany; e-mail: maberbis@cib.csic.es

Paramagnetism offers a rich source of long-range structural restraints through the induction of residual dipolar couplings, paramagnetic relaxation enhancement (PRE) and pseudocontact shifts (PCS), which have been thoroughly employed for structural characterization of biological molecules.[1,2] Previously, we reported the synthesis of the first lanthanide-chelating linker attached to a sugar molecule,[3] which allowed us successfully measuring PCSs in the carbohydrate moiety. The use of paramagnetic restraints emerges as a very convenient approach for the structural elucidation of carbohydrate molecules, as there are often problems to obtain structural information on these systems by NOEs, due to signal overlapping, strong coupling, and/or the scarcity of key NOE information.

Importantly, we show that the so-produced paramagnetic sugars can also be used as tools for the study of structural aspects of their recognition by macromolecular receptors. In particular, we studied the recognition of paramagnetic mono- and disaccharides by a prototype lectin, i.e. the CRD of human galectin-3 (gal-3), demonstrating that paramagnetic effects can be transferred through the space to the protein from the non-covalently bound ligand, as shown in ^{1}H-^{15}N HSQC spectra.

Also, for those instances where recombinant production or isotopic labeling are not possible (e.g., proteins isolated from natural sources), we conceived a strategy suitable to detect binding events, involving the tagging of the protein by a fluorine-containing probe and the monitoring of paramagnetic perturbations, exerted by ligands, of the protein fluorine signals in 1D ^{19}F-NMR spectra.

Finally, we present additional studies on the molecular recognition of systems involving non-protein receptors, such as cyclodextrins. We show that paramagnetic tagging of hydrophobic guests of β-cyclodextrin increases the sensitivity of the characterization of their binding by NMR methods, and permits the extraction of topological information.

[1] Su X.C, Otting G., J Biomol NMR, **2010**, *46*, 101.
[2] Yamamoto S. et al., Chemistry Eur J., **2011**, *17*, 9280.
[3] Mallagaray A. et al., ChemComm (Camb)., **2011**, *47*, 7179.

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XI CARBOHYDRATE SYMPOSIUM

Methyl orthoesters as glycosyl donors. Acid-washed molecular sieves (AW-MS) mediated glycosylations

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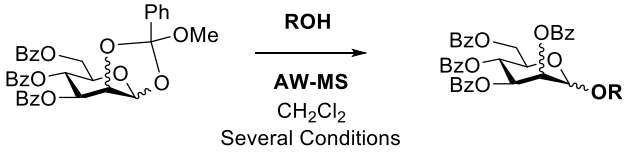
We have recently introduced the use of methyl orthoesters (MeOEs), e.g. **1**, as a donor in glycosylation protocols.[1] We have also found that this process is highly dependent on the choice of the acid promoter. Thus, when BF_3OEt_2 is used as the promoter the glycosylation takes place in moderate to good yields, whereas the use of different Lewis Acids ($Yb(OTf)_3$, TMSOTf, TsOH) led to poorer yields of the desired disaccharides.

In this context, we have been interested in the development of an, operationally simple, experimental procedure for glycosylation that could allow the easy glycosyl coupling of natural products. On the other hand, commercially available 4A acid-washed molecular sieves (AW-MS) has been used to facilitate the rearrangement of orthoester by-products to their corresponding glycosides,[2] and more recently, Castillon and co-workers have reported on the use of AW-MS in the rearrangement of orthoester by-products leading to β-glycosphingolipids.[3]

We have evaluated the use of AW-MS as a heterogenous promotor in the glycosylation of different alcohols and polyols with methyl *manno-* and *gluco-*orthobenzoates. The glycosylation takes place to give good yields of saccharides, and good regioselectivity is observed when diols, or polyols are used as acceptors.



ROH : monosaccharides, natural products

Acknowledgements: The authors are grateful to the *Ministerio de Economía y Competitividad* and *Comunidad de Madrid* for grants CTQ2009-10343, CTQ2012-32114, and grant S2009/PPQ-1752, respectively.

[1] Uriel, C.; Ventura, J.; Gómez, A.M.; López, J.C. and Fraser-Reid, B. *Eur. J. Org. Chem.* **2012**, 3122.
[2] Wilstermann, M. and Magnusson, G. *Carbohydr. Res*. **1995**, 272, 1.
[3] Morales-Serna, J.A.; Díaz, Y.; Matheu, M.I. and Castillón, S. *Eur. J. Org. Chem.* **2009**, 3849.

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XI JORNADAS DE CARBOHIDRATOS

Synthesis of enaminone sugar/ferrocene derivatives

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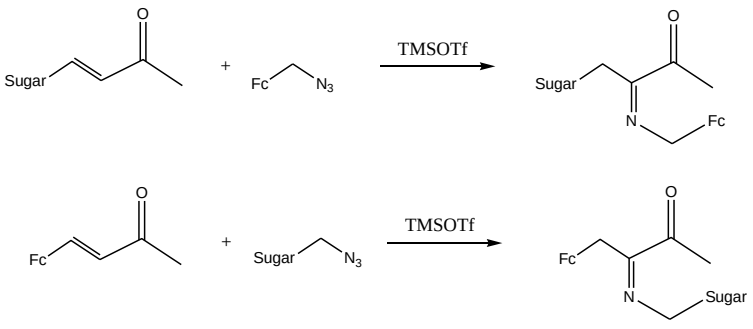
Water-soluble ferrocenes are particularly of interest as their reversible and tunable redox properties could have biological applications, for example, in the development of biosensors.[1]

The ferrocene attached carbohydrates are used as hematinic and anticancer agents in clinical therapy. This renders the ferrocene tethered C-glycosyl heterocycles more attractive in both chemistry and biological chemistry.[2] Enaminones, enamines of β-dicarbonyl compounds are compounds that demonstrated a potential as multipurpose synthetic intermediates in organic synthesis, in pharmaceutical development, and in heterocyclic synthesis.[3]

In this work we present the reaction of sugar derivatives with α,β-unsaturated ketone group, with ferrocenyl azides and the reaction of ferrocenyl derivatives with α,β-unsaturated ketone group with sugar azides (scheme 1).



Sugar = monosaccharide residue
Fc = ferrocenyl

Scheme 1

[1] Casas-Solvas, J.M.; Vargas-Berenguel, A.; Capitán-Vallvey, L.F.; Santoyo-González, F. *Org. Lett.*, **2004**, *6*, 3687.
[2] Prasanna, R.; Purushothaman, S.; Suresh, M.; Raghunathan, R. *Tetrahedron Lett.*, **2011**, *52*, 792.
[3] Edafiogho, I.O.; Scott, K.R., et al, *J. Pharmaceutical Sci*, **2007**, *96*, 2509.

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XI CARBOHYDRATE SYMPOSIUM

Synthesis of fluorinated analogues of KRN7000

David Collado, M. Isabel Matheu, and Omar Boutureira

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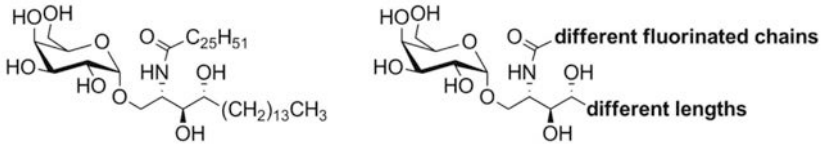
Glycosphingolipids are important biomolecules commonly found in eukaryotic cell membranes. They play a critical role in cell communication, growth, differentiation and programmed cell death and have also shown promising activities against diverse pathologies.[1] For example, the complex formed by the association of α-glycosphingolipid KRN7000 and CD1d proteins interacts with a component of the immune system, the Natural Killer T (NKT) cells, and upon its activation, NKT cells release cytokines, which are signaling molecules involved in cellular communication and immune response.[2] Several KRN7000 analogues have been synthesized featuring modifications in both the sugar and the lipid moieties, all of which with the aim of developing new structures for clarifying and exploring their biological role and therapeutic potential. Particularly relevant examples are those incorporating fluorine moieties in their structure, which are known to confer some interesting properties such as higher metabolic stability, binding and lipophilicity and membrane permeability.[3] Although several fluorinated KRN7000 analogues at the carbohydrate moiety have been synthesized as well as those with partial fluorination of the lipid portion, the preparation of derivatives with fully or partially perfluorinated acyl chains able to modulate the lipid-receptor interaction is unprecedented. Here we describe our progress on the development of a diversity-oriented synthesis approach to perfluorinated analogues of KRN7000 at the ceramide moiety to gain insight into the underlying mechanisms of glycolipid-protein interactions.



α-GalCer (KRN 7000)

[1] Banchet-Cadeddu, A.; Hénon, E.; Dauchez, M.; Renault, J.-H.; Monneaux, F.; Haudrechy, A. *Org. Biomol. Chem.* **2011**, *9*, 3080.
[2] Yu, K. O. A.; Porcelli, S. A. *Immunology Letters* **2005**, *100*, 42.
[3] Ojima, I. *J. Org. Chem.* **2013**, *78*, 6358.

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XI JORNADAS DE CARBOHIDRATOS

Chemical interrogation of drug/RNA complexes: from chemical reactivity to drug design[1]

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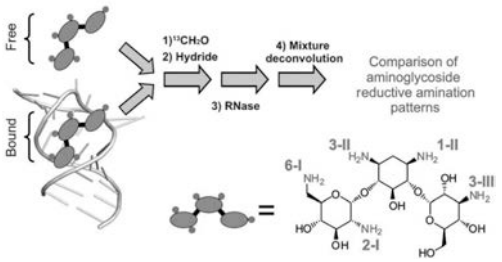
Medicinal chemistry efforts oriented to the optimization of bioactive compounds have traditionally relied on the synthesis and evaluation of a large number of structurally related chemical derivatives. This procedure, in most cases expensive and time consuming, represents a major challenge for complex molecular architectures containing numerous equivalent reactive positions. Unfortunately, such feature is non unusual among natural ligands as carbohydrates or polyamine RNA binders, as aminoglycosides (a family of antibiotic RNA-binding oligosaccharides).



Inspired by the principles of dynamic combinatorial chemistry,[2] we hypothesized that the chemical reactivity exhibited by the aminoglycosides in complexes with their target RNAs could provide valuable guidelines for accessing to a reduced number of binders. Thus, the synthesis and evaluation process of the potential drug derivatives would be highly facilitated. As a proof of principle, we have analyzed kanamycin-B methylation (a chemical modification of general importance for the molecular recognition of nucleic acids[3]) in the context of three different RNA fragments, whose structures in complex with this or closely related aminoglycosides have already been described. The proposed methodology is based on the detailed comparison of the drug *N*-methylation patterns obtained from reductive amination reactions performed with the free and RNA-bound drug. Our concept may be exploited and adapted to a variety of examples within the molecular recognition and drug design fields.

[1] Jiménez-Moreno, E., Gómez-Pinto, I., Corzana, F., Santana, A. G., Revuelta, J., Bastida, A., Jiménez-Barbero, J., González, C. and Asensio, J. L *Angew. Chem. Int. Ed*., **2013**, *52*, 3148
[2] Santana A. G., Jiménez-Moreno E., Gómez A. M., Corzana F., González G., Jiménez-Oses G., Jiménez-Barbero J., Asensio J. L. *J. Am. Chem. Soc*., **2013**, *135 (9)*, 3347
[3] Vacas T., Corzana F., Jiménez-Oses G., González C., Gómez A. M., Bastida A., Revuelta J., Asensio J. L., *J. Am. Chem. Soc*. **2010**, *132*, 12074.

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XI CARBOHYDRATE SYMPOSIUM

Engineered glycated amino dendritic polymers as non-viral gene delivery vectors targeting the receptor for advanced glycation end products

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The receptor for advanced glycation end products (RAGE) is expressed in cells involved in pathological processes, as diabetes or angiogenesis in tumors.[1,2] Under pathological conditions, RAGE is overexpressed and stimulate signaling pathways that promote cell proliferation. The objective of the present work is to engineer the amino dendritic polymers PEI 25 kDa and alkylated derivatives of PAMAM-G2 by exploiting the non-enzymatic Maillard glycation reaction for the preparation of novel AGE-containing non-viral gene delivery vectors targeting the RAGE.[3] The glycated versions of those dendritic polymers were easily prepared and retained the capability to bind and protect DNA from endonucleases. Furthermore, while glycation decreased the transfection efficiency of the dendriplexes in the CHO-k1 cell line that does not express RAGE, glycated dendriplexes acted as efficient transfection reagents in CHO-k1 cells that stably express recombinant RAGE. In addition, pre-incubation with BSA-AGEs, a natural ligand of the RAGE or dansyl cadaverine, an inhibitor of the RAGE internalization, blocked transfection for the dendriplexes of the glycated vectors confirming their specificity for the RAGE. The transfection efficiency and specificity of the glycated dendriplexes was confirmed in NRK and RAW264.7 cell lines that naturally express the RAGE. The glycated compounds retain its transfection capability towards cells expressing RAGE in the presence of serum and are able to promote *in vivo* transfection in a mouse model. Together these findings suggest that the RAGE is a suitable molecular target from which the development of site-directed engineered glycated non-viral gene vectors is feasible.

[1] Bierhaus, A.; Humpert, P. M.; Morcos, M.; Wendt, T.; Chavakis, T.; Arnold, B.; Stern, D. M.; Nawroth, P. P. *J. Mol. Med. (Heidelberg, Ger.)* **2005**, *83*, 876.
[2] Vlassara, H.; Uribarri, J. *Curr. Diabetes Rep.* **2014**, *14*, 1.
[3] Tessier, F. J. *Pathologie Biologie* **2010**, *58*, 214.

Nanostructured weathering steel for matrix-free desorption ionisation mass spectrometry and imaging of metabolites, drugs and complex glycans

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Weathering steel has been employed for the first time to prepare sample plates for matrix-free laser desorption ionisation mass spectrometry (LDI-MS) of small molecules up to a mass range of around 1500 Da. The effective UV absorption, heat conductivity and porosity of the nanostructured inner rust layer formed during passivation determines the excellent performance in LDI-MS for a broad range of different analyte classes. The inexpensive material was evaluated in a series of relevant analytical applications ranging from the matrix-free detection of serum metabolites, lactose quantification, lipid analysis in milk to the glycoprofiling of antibodies and imaging mass spectrometry of brain tissue samples.

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XI CARBOHYDRATE SYMPOSIUM

Design of cationic amphiphilic carbohydrates as modulators of innate immunity

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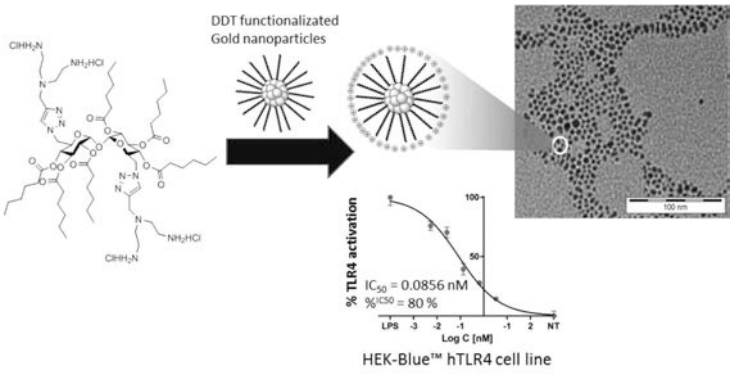
The identification of the bacterial endotoxin receptors for innate immunity, most notably TLR4 (Toll-like receptor 4),[1] has sparked great interest in the therapeutic manipulation of the innate immune system. Among microbial components, LPS and LOS (lipopoly- and lipoligosaccharides, respectively) and their bioactive portion, the lipodisaccharide lipid A, constitute the bacterial endotoxin and are potent stimulants of immune responses. An inherent charateristic of the endotoxin is its multi-tail amhiphilic character. Recently, several research groups have developed synthetic amphiphilic molecules capable of modulating the TLR4-mediated LPS signalling in animal and human cells.[2] Taking advantage of our previous experience in the design of carbohydrate-scaffolded polycationic facial amphiphiles,[3] we have synthesized a novel collection of derivatives based on methyl α-D-glucoside and α,α'-trehalose differing in the structure of the cationic heads and the number of lipophilic tails.[3] Self-assembly capabilities of these compounds have been evaluated by micellar critical concentration measurements and difusion light scattering techniques. Some of the compounds exhibited remarkable inhibitory activity of TLR4-mediated inmune response in the presence of lipid A when tested on HekBlue (human embrionic kidney) cells transfected with all the receptors involved in the TLR-4 route. Data for derivatives immobilized in gold nanoparticles will be also presented in this poster.



[1] Beutler, B.; Jiang, Z.; Georgel, P.; Crozat, K.; Croker, B.; Rutschmann, S.; Du, X.; Hoebe, K. *Annu. Rev. Immunol.* **2006**, *24*, 353.
[2] Piazza, M.; Rossini, C.; Della Fiorentina, S.; Pozzi, C.; Comelli, F.; Bettoni, I.; Fusi, P.; Costa, B.; Peri, F. *J. Med. Chem.* **2009**, *52*, 1209-1213.
[3] Ortiz Mellet, C.; Benito, J. M.; García Fernández, J. M. *Chem. Eur. J.* **2010**, *78*, 6728-6742.

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XI JORNADAS DE CARBOHIDRATOS

Exploring the structural basis for glycosidase inhibition by multivalent glycomimetics: the *inhibitory multivalent effect*

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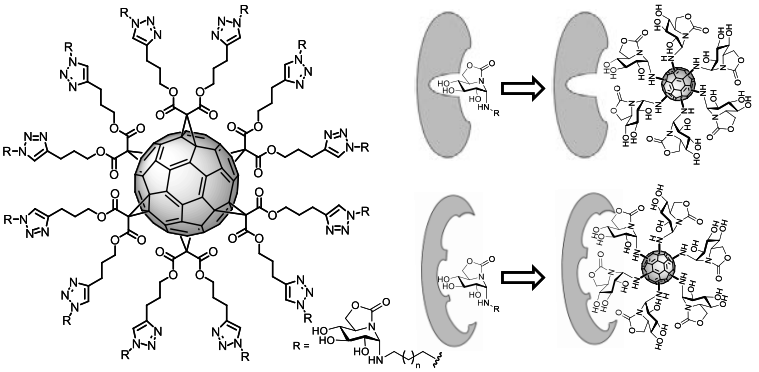
It was commonly assumed that the mechanisms by which lectins and glycosidases recognize their cognate sugar partners are intrinsically different: multivalency is a characteristic feature of carbohydrate-lectin interactions, whereas glycosidases bind to their substrates or substrate-analogue inhibitors in monovalent form. Recent observations on the glycosidase inhibitory potential of multivalent iminosugars displayed onto different platforms, including fullerene, cyclodextrin, porphyrines or self-assembled nanoparticles,[1,2] have questioned this paradigm and led to postulate an *inhibitory multivalent effect*. We have explored the structural basis for such effect by developing an sp^2-iminosugar glycomimetic acting as lectin ligand and glycosidase inhibitor and conducting lectin-glycosidase competitive binding experiments after displaying it onto a fullerene scaffold.[3] The ensemble of results point to a shift in the binding mode towards glycosidases on going from monovalent to multivalent systems: in the first case a typical "key-lock" model involving, essentially, the high-affinity active site can be assumed, whereas in the second a lectin-like behavior implying low-affinity non-glycone sites probably operates (see Figure). The differences in responsiveness to multivalency can then be rationalized in terms of the structure and accessibility of the corresponding carbohydrate binding regions.



[1] Brissonnet, Y.; Ortiz Mellet, C.; Morandat, S.; Garcia-Moreno, M. I.; Deniaud, D.; Matthews, S.; Vidal, S.; Sestak, S.; El Kirat, K.; Gouin, S. *J. Am. Chem. Soc.* **2013**, *135*, 18427-18435.

[2] Bonduelle, C.; Huang, J.; Mena-Barragán, T.; Ortiz Mellet, C. Decroocq, E. Etamé, A. Heise, A.; Compain, P.; Lecommandoux, S. *Chem.Commun.* **2014**, 50, 3350-3352.

[3] Rísquez-Cuadro, R.; J. M.; García Fernández, J. M.; Nierengarten, J.-F.; Ortiz Mellet, C. *Chem. Eur. J.* **2013**, *19*, 16791-16803.

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XI CARBOHYDRATE SYMPOSIUM

Relationship between foaming properties and polysaccharide composition of sparkling wines

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Sparkling wines elaborated following the champenoise method undergo a second fermentation in closed bottles of base wines, followed by aging of wines with lees for at least 9 months. The foam of sparkling wines is a key parameter of their quality but the compounds that are directly involved in foam quality are not yet completely established. Some authors have attempted to correlate the amount of mannoproteins in sparkling wines with the quality of their foam properties but there are few studies regarding other grape or yeast polysaccharides. Therefore, the aim of this work was to correlate the foaming properties with the polysaccharide composition in different white and rosé sparkling wines elaborated during three consecutive vintages. Foam instrumental parameters were analyzed by the Mosalux method.[1] Wine polysaccharides were recovered by precipitation after ethanolic dehydration and their carbohydrate composition was determined by GC-MS of their trimethylsilyl-ester O-methyl glycolsyl-residues.[2]

Table 1. Correlation coefficients (*r*) and significance levels (*p*) between parameters that determine foam instrumental properties (HM, HS, TS) and wine polysaccharides

	HM		HS		**TS**	
	r	*p*	*r*	*p*	*r*	*p*
Total polysaccharides	0.071	0.679	0.189	0.270	**0.641**	**0.000**
Polysaccharides from yeast	-0.081	0.637	0.054	0.753	**0.533**	**0.001**
Polysaccharides from grapes	0.184	0.283	0.280	0.098	**0.684**	**0.000**
Mannoproteins	0.150	0.383	0.157	0.360	**0.465**	**0.004**
Glucans	-0.225	0.187	-0.041	0.811	**0.396**	**0.017**
Polysaccharides rich in arabinose and galactose	0.042	0.806	0.285	0.092	**0.723**	**0.000**
Homogalacturonans	0.290	0.087	0.209	0.221	**0.577**	**0.000**
Rhamnogalacturonans type II	0.602	0.589	0.240	0.846	0.204	0.869

None of the wine polysaccharides was correlated with the foam maximum height (HM) or the foam stability height (HS), indicating that they would not affect the foamability of sparkling wines. On the contrary, positive correlations were found between foam stability time (TS) and all wine polysaccharides with the exception of rhamnogalacturonans type II. Polysaccharides rich in arabinose and galactose showed the highest correlations.

[1] Maujean, A.; Poinsaut, P.; Dantan, H.; Brissonnet, F.; Cossiez, E. *Bull OIV*. **1990**, *63*, 405.
[2] Guadalupe, Z.; Martinez-Pinilla, O.; Garrido, A.; Carrillo, J. D.; Ayestarán, B. *Food Chemistry* **2012**, *131*, 367.

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XI JORNADAS DE CARBOHIDRATOS

Design and synthesis of a modular drug delivery system based on monovinyl sulfone β-cyclodextrin

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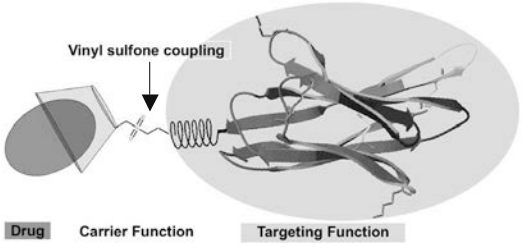
Among the different strategies to deliver drugs to specific physiological sites where pharmacological action is required, active targeting is an appealing approach that relies on the use of specific interactions with the target to direct and concentrate the drug at the site of action. The coupling of the therapeutic agent to the targeting agent and the stability of the linkage are important issues that have been approached by rigid designs that link a particular drug to a specific carrier, constraining the generalization of this approach.[1,2]

We have hypothesized that a modular design that decouples the carrier function from the targeting function leads to a flexible system that allows the targeting of different organs with different drugs. As a proof of concept we have synthesized monovinyl sulfone β-cyclodextrin (VSCD) as a key element that combines the good reactivity of the vinyl sulfone group toward biomolecules (targeting function) with the ability of β-cyclodextrin to form inclusion complexes with a wide range of drugs.



Our hypothesis was put to test by targeting different drugs to Trypanosoma sp [3]. VSC was directed linked to the targeting element (a nanobody raised against Trypanosoma sp) or via protein A (i.e. a protein with high affinity for IgG) and loaded with nitrofurazone, 5-chloro-2-mercaptobenzimidazol or camptothecin. The effect on cultures of parasites was evaluated.

[1] Yin, J.J.; Zhou, Z.W.; Zhou, S.F. *Drug Deliv. And Transl. Res.* **2013**, 3, 364..
[2] Kralova, J.; Kejik, Z.; Briza, T.; Pouckova, P.; Kral, A.; Martasek, P.; Kral, V. *J. Med. Chem*. **2010**, 53 128.
[3] del Castillo, T.; Morales-Sanfrutos, J.; Santoyo-Gozález, F.; Magez S., Lopez-Jaramillo, F.J.; Garcia-Salcedo J.A. *ChemMedChem* **2014**, 9, 383.

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XI CARBOHYDRATE SYMPOSIUM

Unraveling the chiroptical response of sugar-protected gold nanoparticles through their Gold(I) sugar-thiolate precursors

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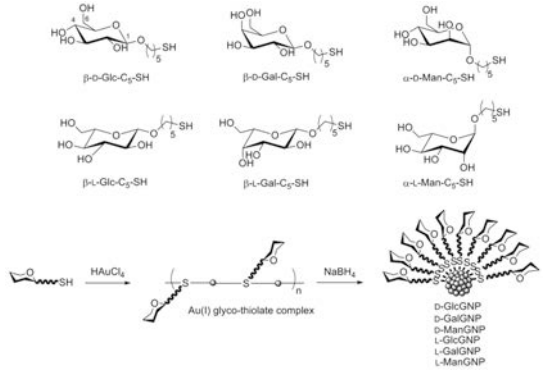
The concept of chirality has intrigued the scientific community since the 1870's but in the last years the optical activity of nanostructures has attracted a great deal of attention and discussion[1]. As a consequence of their particular properties and potential applications, thiolate-protected gold nanoparticles and nanoclusters have become a focus of increased interest[2]. Particularly, understanding the origin of the chirality in these nanostructures has demanded detailed studies on the structure-property relationship. Nevertheless, the dependence of the structure and chirality on the cluster-size remains not being completely understood[3]. Herein, the evidence of a strong chiroptical response by Circular Dichroism (CD) in the byproduct isolated from the preparation of 1.6 nm sugar-thiolated gold glyconanoparticles (GNPs) is presented. This byproduct was also characterized by UV-Vis, ^{1}H-NMR, Size-Exclusion Chromatography (SEC), X-ray Photoelectron Spectroscopy (XPS) and X-ray Diffraction (XRD) proving that its structure and properties are similar to those of a Au(I)-thiolate polymer obtained by the direct reaction of Au(III) salts with glycoconjugate-thiol species in water. Both byproduct and polymer were studied by mass spectrometry showing a major peak corresponding to a cyclic tetrameric unit $[Au(I)SC_5R]_4$. Thus, it is concluded that Au(I)-thiolate species are the origin of the ellipticity observed for the first time in gold glyconanoparticles. The results were also reproducible throughout the series of gold nanoparticles protected by enantiomeric pure thiol-conjugates of the natural monosaccharides D-glucose (Glc), D-galactose (Gal) and D-mannose (Man) and their corresponding non-natural L-enantiomers.



[1] Wang, Y.; Xu, J.; Wang, Y.; Chen, H. *Chem. Soc. Rev.* **2013**, *42*, 2930.
[2] Boisselier, E.; Astruc, D. *Chem. Soc. Rev* **2009**, *38*, 1759.
[3] Häkkinen, H. *Nature Chemistry* **2012**, *4*, 443.

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XI JORNADAS DE CARBOHIDRATOS

A mannan polysaccharide enhances the allergenic vaccines effect stimulating the immunity response

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Immunotherapy anti-allergic treatments are based on the administration of therapeutic vaccines which contained allergen-antigens. These allergens are proteins from pollens, dust mites, epithelia, etc. It is widely accepted that the clinical efficiency of these vaccines are associated to the dose of allergen administered, for which the OPS and the consensus guides of the numerous companies scientific recommend that the vaccines should be prepared by a sufficient concentration of allergens. It is required to reduce the risk of adverse effects in the allergic patients. In order to achieve this goal, there is an increase use of vaccines based on modified allergens (allergoids) with minor capacity of reaction with the antibodies IgE (decrease inflammatory response).[1,2]

The dendritic cells are specialized to stimulate T-lymphocytes by means of endocytosis, using receptors. There are a great variety of receptors implicated in endocytosis, such as mannose receptors (CD206, CD209), stimulating immunity response.

Herein, we have developed an inmunogenic complex (allergoid) that contains a mixture of the antigen and the mannan polisaccharide that forms a polimeric matrix. The polisaccharide was obtained from *S. cerevisae* yeast. The mannan core is formed by manα(1-6)-man repeating units with manα(1-2)branches. This polysaccharide is attached to the proteins through an O-glycosidic bond. The antigen-mannan complex presented in this work will stimulate the T-lymphocites inmune response and decrease inflamatory response. Therefore, this inmunogenic complex will be used to generate allergenic vaccines, against: plants (gramineas: phelum pratense, lolium perenne...), dust mites (Dermatophagoides pteronyssinus, Dermotophagoides farinae...), etc.

[1] Subiza, J.; Feliu, A.; Subiza, J. L.; Uhlig, J.; Fernandez-Caldas, E. *Clin Exp Allergy* **2008**, *38*, 987.
[2] Heydenreich, B.; Bellinghausen, I.; Lorenz, S.; Henmar, H.; Strand, D.; Wurtzen, P. A.; Saloga, J. *Immunology* **2012**, *136*, 208.

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XI CARBOHYDRATE SYMPOSIUM

Synthesis of 1-phospha-sugars by ARF-Arbuzov-cyclization reactions

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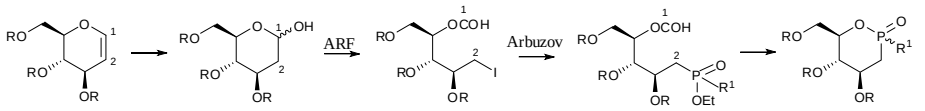
1-Phospha-sugars are analogs in which the anomeric carbon atom is replaced by a phosphorus atom. Cyclic phosphonate analogs also know as phostones[1] have received continued attention in the literature mainly due to they are potential inhibitors of glycosidases. Phosphinosugars (phostines) are considered as mimes of glycosides and have shown anticancer activities. Of special interest are 2-deoxy-1-phospha-sugars that possess a certain structural relation with ß-KDO and the sialic acids in general.

Herein we report on a new general methodology for the synthesis of phostones and phostines that has been developed in only four steps starting from glycals. The alkoxyl radical fragmentation (ARF) reaction of carbohydrate anomeric alcohols with hypervalent iodine reagents in the presence of iodine has been investigated by this laboratory[2] and used as key step. Following the literature glycals **1** can be converted to 2,3-dideoxy-hexopyranoses **2**. The anomeric ARF of these compounds gave iodo compounds **3** in high yields. Organophosphorus **4** were obtained by Arbuzov[3] reaction that followed by saponification of the formyl ester and subsequent cyclization produce 1-phospha-sugars **5** in good yields.



1 Glycals **2** **3** **4** **5** Phospha Sugars

R = Protecting Group

R^1 = OEt, Ph

These organophosphorus compounds may be powerful building blocks for the preparation of complex systems and scaffolds in biological chemistry.

[1] Thiem, J.; Günther, M.; Paulsen, H.; Kopf, J. *Chem. Ber.* **1977**, *110*, 3190.

[2] Suárez, E.; Rodríguez, M. S. *β-Fragmentation of Alkoxyl Radicals: Synthetic Applications;* Renaud, P.; Sibi, M. P., Eds.; Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001.

[3] Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.

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XI JORNADAS DE CARBOHIDRATOS

Exploring gold glyconanoparticles (GNPs) as carriers to prepare fully synthetic vaccines against HIV

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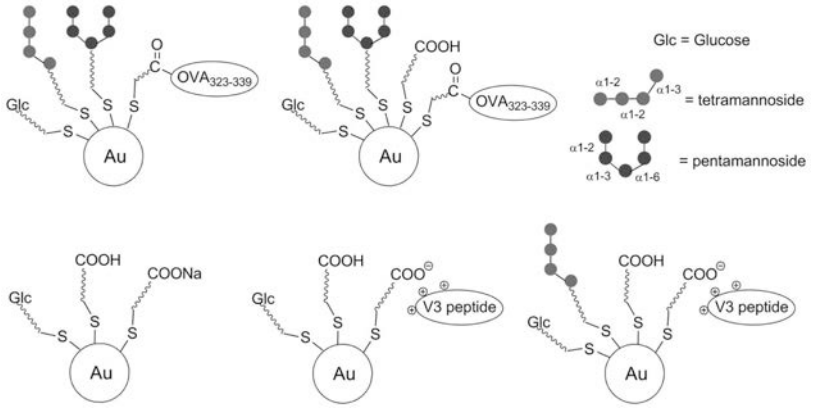
The infection by the human immunodeficiency virus (HIV) is the cause of AIDS and is one of the greatest infectious diseases ever seen. HIV infects cells of the human immune system such as T-helper cells (specifically CD4+ T cells), macrophages, and dendritic cells. After almost 30 years of reasearch, an effective vaccine against HIV is still a challenge.[1]

We have already demonstrated by surface plasmon resonance (SPR) and STD-NMR that gold glyconanoparticles (GNPs) coated with oligomannosides of HIV-1 glycoprotein gp120 are able to mimic the carbohydrate epitope of 2G12 antibody.[2]

Recently, we have also demonstrated that ~2nm GNPs are a suitable platform to construct a potential carbohydrate-based vaccine against *S. pneumoniae* type 14. The co-presence of the T cell-stimulating $OVA_{323–339}$ peptide and the tetrasaccharide antigen β-D-Gal*p*-(1–4)-β-D-Glc*p*-(1–6)-[β-D-Gal*p*-(1–4)-]β-D-Glc*p*NAc-(1–), which corresponds to a single epitope of the capsular polysaccharide allowed the induction of specific and functional IgG antibodies against this bacterium.[3]

We now explore the use of GNPs as a platform to prepare a fully synthetic vaccine against HIV. In these work we have synthesized two series of GNPs, one bearing oligomannosides and $OVA_{323–339}$ peptide and one with oligomannosides and the highly immunogenic gp120 V3 peptide (see figure).



Rabbit immunization experiments with oligomannosides/$OVA_{323–339}$ GNPs and oligomannosides/ V3 GNPs were performed and the results will be presented.

[1] Barouch, D. H. et al., *Nature*, **2008**, *455*, 613.
[2] Marradi, M. et al., *J. Mol. Biol.* **2011**, *410*, 798.
[3] Safari, D. et al., *Nanomedicine* **2012**, *7*, 651.

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Synthesis of fused tetrazolo iminosugars from azido monosaccharide derivatives

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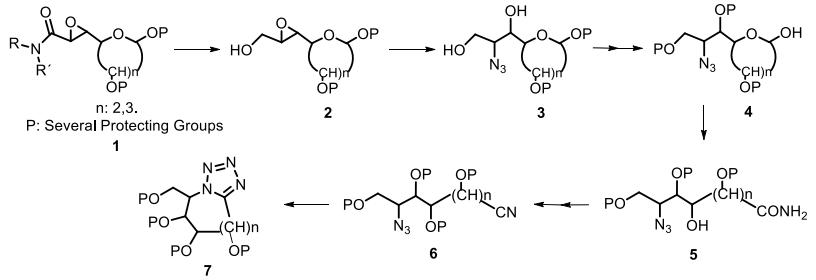
Iminosugars, by virtue of their structural resemblance to monosaccharides, are among the most potent inhibitors of glycosidases, mimicking the transition states of the sugars involved in processes of inhibition. Due to this fact, a variety of monocyclic and bicyclic iminosugars have been synthesized or isolated from natural sources over the years. As part of our ongoing work on the preparation of glycosidase inhibitors, we developed stereoselective methods for synthesizing iminosugars from 2,3-epoxyamides **1** obtained from monosaccharides.[1] Now our attention is focused on the syntheses of novel bicyclic tetrazoles **7**, by intramolecular cycloaddition, due to the possibility of combining azido and ciano groups in the same molecule. The tetrazole system is widely found in bioactive products but only a few examples of syntheses of fused pyrrolidines and piperidines with tetrazoles[2,3] have been reported to be evaluated as inhibitors.

Whit the aim of obtaining new and more potent analogues, we studied the formation of tetrazolic systems fused to different heterocycles formed from monosaccharide derivatives. Epoxyamides **1** were sequentially transformed into epoxyalcohols **2** and azido alcohols **3**. Deprotection of the anomeric hydroxyl group after convenient functionalization gave **4**. Conversion to azidoamides **5** and further transformation into azidonitriles **6** gave tetrazolobicycles **7** by cycloaddition.



[1] Oña N.; Romero A.; Assiego, C.; Bello, C.; Vogel, P.; Pino-González, M. S., *Tetrahedron: Asymmetry* **2010**, *21*, 2092 and references therein.

[2] Davis, B.; Btandstetter, T. W.; Smith, C.; Hackett, L.; Winchester, B. G.; Fleet, G. W. J., *Tetrahedron Lett.* **1995**, *36*, 7507.

[3] Davis, B.; Btandstetter, T. W.; Hackett, L.; Winchester, B. G.; Nash, R. H.; Watson, A.; Griffiths, R. C.; Smith, C.; Fleet, G. W. J., *Tetrahedron* **1999**, *55*, 4489.

UNIVERSIDAD DE LA RIOJA

XI JORNADAS DE CARBOHIDRATOS

A nitro sugar based route to branched-chain poly-hydroxylated octahydro-1*H*-indole-4,5,6-triols, as new potential glycosidase inhibitors

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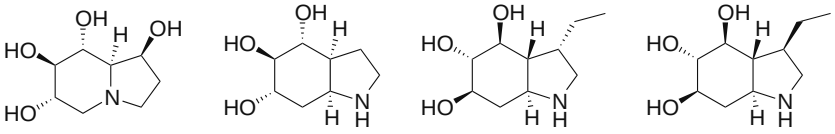
Glycosidases became an important class of targets for pharmaceutical research due to the roles they play on the control of the cellular oligosaccharide processing involved in digestion, biosynthesis of proteins and catabolism of glyconconjugates.[1] This is the reason why glycosidase inhibitors have been extensively studied over the last years, as potential terapeutic agents.[2] Specifically, castanospermine (**1**) is an indolizidine alkaloid first isolated from the seeds of *Castanospermum australe*, which shows to be a potent inhibitor of some glucosidase enzymes and has antiviral activity.[3]

Some castanospermine analogs, have been reported, including the poly-hydroxylated octahydro-1*H*-indole-4,5,6-triol **2**, which, as a rigidified mimic of disaccharides, is expected to exhibit significant antidiabetic properties.[4]

In connection with an ongoing project aimed at the development of new synthetic applications of nitro sugars, a synthesis of the branched-chain poly-hydroxylated octahydro-1*H*-indole-4,5,6-triols **3** and **4** has recently been developed.



1 **2** **3** **4**

Castanospermine — Castanospermine analogs

Studies on the glycosidase inhibition properties for these novel compounds **3** and **4** have also been carried out.

[1] Sinnott, M. L. *Chem. Rev.* **1990**, *90*, 1171.
[2] Asano, N. *Glicobiology* **2003**, *13*, 93R.
[3] Moorthy, N. S. H. N.; Ramos, M. J.; Fernandes, P. A. *Mini-Rev. Med. Chem.* **2012**, *12*, 713.
[4] Gravier-Pelletier, C.; Malton, W.; Le Merrer, Y. *Synlett* **2003**, 333.

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XI CARBOHYDRATE SYMPOSIUM

Glycosylation and lectin-binding properties of thiolated polymers

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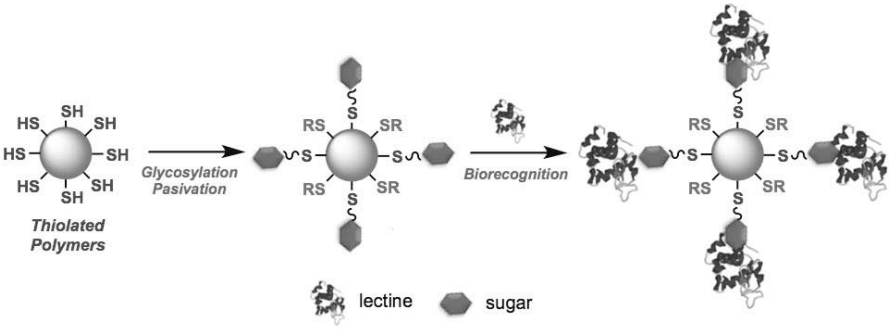
The importance of the glycosylation in Biology has led to the coining of terms such as *glycomics* and *sugar code* to express the perspective of a new function and *lectinomics* to forecast trends in lectin-biorecognition technology.[1,2] In this context, the search for new materials is a key element for the development of lectin related diagnostics and thiolated polymer are good candidates.

Immobilization of saccharides to the thiolated polymers was easily performed by a variety of efficient glycosylation techniques including both direct and indirect strategies. In the direct approach, halo and vinyl sulfone anomeric saccharide derivatives were used for the branching by means of the nucleophilic substitution or the Michael-type addition reaction, respectively. By contrast, in the indirect approach the thiolated polymers were first transformed in their corresponding azido and alkyne counterparts by exploiting the sulfur chemistry of these compounds and later conjugation with suitable clickable complementarily functionalized saccharides derivatives.

The resulting glycomaterials were assayed against commercial lectins and some of them were put to test with biological challenge: detection of lectins that are produced by plant as defense proteins against phytophagous insects.[3]



[1] Gabius, H.J.; André, S.; Kaltner, H.; Siebert, H.C. *Biochim Biophys. Acta* **2002**, 1752, 165.
[2] Gemeiner, P; Mislovicova, D.; Tkac, J.; Svitel, J.; Paotprsty, V.; Hrabarova, E.; Kogan, G.; Kozar, T. *Biotechnol. Adv.* **2009**, *27*, 1.
[3] Vandenborre, G.; Smagghe, G.; Van Damme, E.J.M. *Phytochemistry* **2011**, 72, 1538.

UNIVERSIDAD DE LA RIOJA

XI JORNADAS DE CARBOHIDRATOS

Enantioselective synthesis of nectrisine

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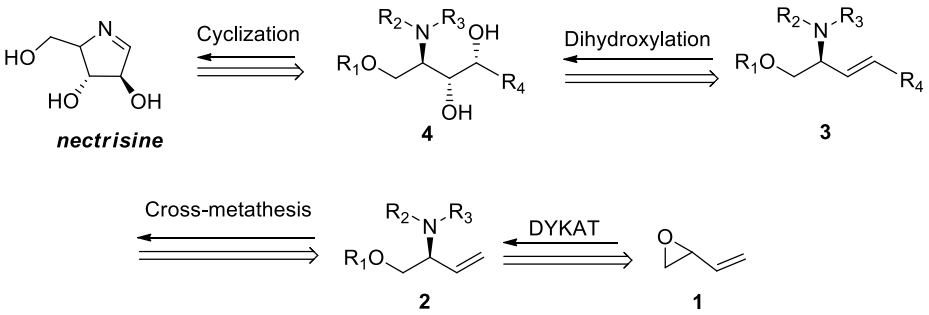
Nectrisine is an azasugar isolated from a strain of the fungus *Nectricine lucida* as immunomodulator FR-900483 and found to exhibit inhibitory activity on α–glycosidases.[1] Moreover, nectrisine is involved in the prevention of different diseases such as Newcastle disease virus. Due to this important biological activity many organic chemists are focused on the development of new methods to synthesize nectrisine.

We recently described that Trost's DYKAT process based on Pd-catalyzed asymmetric allylic amination in combination with cross-metathesis and dihydroxylation reactions is an efficient strategy for accessing important natural products such as Jaspine.[3] Here we explore an enantioselective synthesis of nectrisine based on Pd-catalyzed asymmetric allylic amination, cross-metathesis and dihydroxylation as key steps. The scheme below shows the retrosyntheis proposed, where the key synthon is the allylamine **2** which is obtained in high enantiomeric purity by a deracemization process using Pd/DACH as a catalytic system.



[1] Ganem B., *Acc. Chem. Res*. **1996**, *29*, 340–347.
[2] Tsujii, E.; Muroi, M.; Shiragami, N.; Takatsuki, A. *Biochem. Biophys. Res. Commun.* **1996**, *220*, 459–466.
[3] Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillón, S. *Eur. J. Org. Chem.* **2011**, 1514–1519.

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Influence of polysaccharide commercial product addition on volatile composition of white sparkling wines

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Natural sparkling wines are obtained after a second fermentation in closed bottles, and they remain in contact with the yeast lees for at least 9 months. During sparkling wine aging, different compounds such as polysaccharides can be released due to yeast autolysis that can cause important changes in wine composition, affecting the quality of sparkling wines. Yeast autolysis is a slow natural process that takes long time. Therefore, the aim of this work was to study the effect of the addition of several commercial products rich in polysaccharides and/or mannoproteins on the volatile composition of white sparkling wines elaborated from two white grape varieties (*Godello* and *Verdejo*), and aged for 9 months. The volatile compounds were analyzed by gas chromatography coupled to a mass detector, after a previous liquid-liquid extraction.[1] The polysaccharide and monosaccharide composition of the commercial preparations was determined by GC-MS of their trimethylsilyl-ester O-methyl glycosyl residues obtained after acidic methanolysis and derivatization.[2]

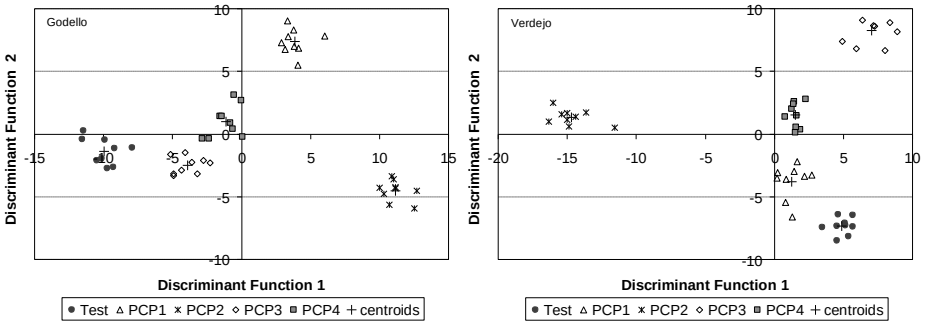

Figure 1. Distribution of wines in the plane defined by the first two discriminant functions. Test: control wines; PCP: wines treated with polysaccharide commercial products

The discriminant analysis indicated that the wines treated with PCP2 showed the highest differences in the volatile composition of both sparkling wines studied, being the ethyl esters, alcohol acetates and terpenes the compounds that were affected in a greater extent. PCP2 was the product with the highest percentage of mannoproteins.

[1] Rodríguez-Bencomo, J.J.; Ortega-Heras, M.; Pérez-Magariño, S. *European Food Research and Technology* **2010**, *230*, 485.

[2] Guadalupe, Z.; Martínez-Pinilla, O.; Garrido, A.; Carrillo, J. D.; Ayestarán, B. *Food Chemistry* **2012**, *131*, 367.

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UNIVERSIDAD DE LA RIOJA

XI JORNADAS DE CARBOHIDRATOS

Applications of ^{1}H and ^{19}F NMR spectroscopy in combination with computational methods for the screening of fluorine-tagged oligosaccharides versus lectin receptors

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Lectins are ubiquitous proteins from non-immune origin that specifically bind saccharide epitopes showed by the cell surface and thus promote a wide array of physiological processes. In particular, plant lectins are known because of their series of potent biological activities, such as agglutination, toxicity, or anti-proliferation of cancer cells, as well as having anti-fungal and anti-bacterial action.[1] From this perspective, it can be ackwnoledged that the study of the rational behind lectin-carbohydrates interaction events represents a key step to design new molecular probes, which could lead to novel sugar-based therapeutic agents. Indeed, different experimental studies have allowed to get a deeper understanding of the molecular basis of this phenomenon.[2]

NMR spectroscopy has become an established tool to provide high-resolution molecular structures in solution and valuable informations on ligand binding. In particular, ^{19}F nuclei can act as reporter atoms for carbohydrate recognition by lectins. Thus, herein we present a combination of NMR-based protocols assisted by molecular modelling methods for unraveling the key features of the interaction between different glycomimetics with fluorine atoms and several lectins of biomedical interest.

[1] Syed, Rashel K.*; Md.Mahamodun, N.; Ariful, H.; Rokon Uz, Z.; Zahid Hayat, M.; Md.Abu, R. Pea lectin inhibits growth of Ehrlich ascites carcinoma cells by inducing apoptosis and G_2/M cell cycle arrest *in vivo* in mice *Phytomedicine* **2013**, *20*, 1288.

[2] Roldós, V.; Cañada, F.J.; Jiménez-Barbero, J.* Carbohydrate-Protein interactions: A 3D View by NMR *ChemBioChem* **2011**, *12*, 990.

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XI CARBOHYDRATE SYMPOSIUM

Carbohydrate-responsive gated silica mesoporous supports as controlled delivery systems

Isabel García,[a,b] Ravishankar Bhat,[c] Elena Aznar,[b,c] Ramón Martínez-Máñez,[c,b] and Soledad Penadés[a,b]

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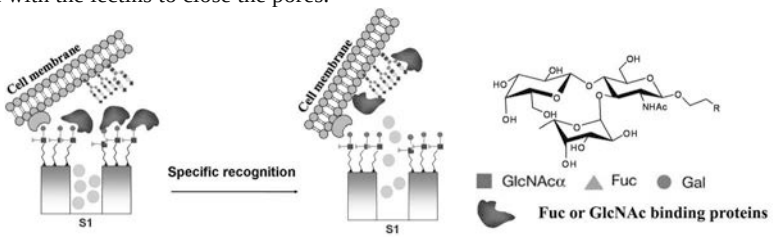
Colon cancer is one of the most prevalent cancers worldwide. Although early detection, increased awareness, and developments in treatment have increased complete cure rates especially in some advanced countries, distant metastasis is still a critical event that makes colon cancer a lethal disease. Drug delivery systems are being developed as novel therapeutic approaches to inhibit metastasis. Here we present mesoporous silica supports (SMPS) functionalized with Sialyl Lewis x (sLex) and sialyl Lewis a (sLea) antigens. sLex and sLea glycans are expressed on highly metastatic colon cancer cells.[1] They promote extravasation of cancer cells and tumor angiogenesis via interacting with E-selectin on endothelial cells.[2] High sLex/a expression levels in colon cancer patients are correlated with poor prognosis. Therefore, these glycans are frequently evaluated as tumor markers. Whereas the diagnostic utility of sLex/a has been well established, effective approaches targeting these glycans are not well developed for treatment the disease.

Gated silica mesoporous supports (SMPS) functionalized with molecules that act as "molecular gates" have demonstrated to have high potential in delivery applications.[3] In these hybrid systems, specific interactions trigger the opening of the "gate" allowing the delivery of the cargo in the desired cells/tissues. We have elaborated a new bio-gated support for controlled delivery of drugs against cancer colon cells. The gated SMPS is functionalized with the Lewis x antigen able to interact with fucose or glucosamine binding proteins that act as a cap for the gate of the SMPS. The isocyanate-functionalized solid was first loaded with ATO- 430LS dye, and then functionalized with ethylamino glycosidated Lewis x by a urea bond and finally was capped with the lectins to close the pores.



As a proof of concept and before cell studies, an opening protocol was performed. This was carried out by a displacement of the lectin by addition of specific carbohydrate ligands. Delivery of the dye has been studied in the presence of fucose in phosphate-buffered saline (PBS; pH 7.5, 1 mM $CaCl_2$, 2 mM $MgCl_2$). An increase in the fluorescence was observed in the solution.

[1] Hittelet, A.; Camby, I.; Nagy, N.; Legendre, H.; Bronckart, Yves.; Decaestecker, C.; Kaltner, H.;. Nifant'ev, N.; Bovin, N. V.; Pector, J-C.; Salmon, I.; Gabius, H-J.; Kiss, R.; Yeaton, P. *Lab. Inves.***2003**, *83*, 777.
[2] Kannagi, R.; Izawa, M.; Koike, T.; Miyazaki, K.; Kimura, N.; *Cancer Sci*, **2004**, *95*, 377.
[3] Coll, C.; Bernardos, A.; Martínez-Máñez, R.; Sancenón, F.; *Acc. Chem. Res.* **2013**, *46*, 339.

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XI JORNADAS DE CARBOHIDRATOS

Synthesis and biological evaluation of furyl galactosides and non-carbohydrate multivalent ligands with affinity towards enterotoxins

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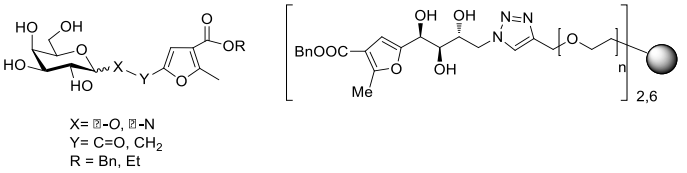
Vibrio cholerae (CT) toxin and the closely related heat-labile toxin of *Escherichia coli* (LT) are proteins that present heterophilic binding with their receptors.[1] They belong to the bacterial AB_5 holotoxin family where the B subunits are responsible for binding to ganglioside GM1.

Several glycomimetics have been reported presenting affinity towards CT and LT.[2,3] We have recently described the synthesis of a new type of non-hydrolyzable bidentate ligands featuring D-thiogalactose and polyhydroxyalkylfuroic esters as pharmacophoric residues. They constitute novel mimetics of GM1 ganglioside. STD-NMR experiments, have allowed the identification of the binding epitopes of the ligands interacting with the protein. The non-carbohydrate moiety based on polyhydroxyalkylfuroic ester structure showed the highest affinity.[4]

In this communication we present the synthesis of new *N*- and *O*-galactosides bearing substituted furoates as aglycones and the assembly of polyhydroxyalkyl furoates into multivalent structures.



Biological evaluation of some of the conjugates will be presented.

[1] Watt; S. M.; Teixeira, A. M.; Zhou, G.-Q.; Doyonnas, R.; Zhang, Y.; Grunert, F.; Blumberg, R. S.; Kuroki, M.; Skubitz, K. M.; Bates, P. A. *Blood*. **2001**, *98*, 1469-1479.

[2] Bernardi, A.; Podlipnik, C.; Jiménez-Barbero, J. *Protein-Carbohydrate Interactions in Infectious Diseases*, **2006**, 73-91.

[3] Podlipnik, C.; Bergström, M.; Bernardi, A. *Chem. Eur. J.* **2010**, *16*, 1951-1967.

[4] Ramos-Soriano, J.; Niss, U.; Angulo, J.; Angulo, M.; Moreno-Vargas, A. J.; Carmona, A. T.; Ohlson, S. Robina, I. *Chem. Eur. J.* **2013**, *19*, 17989-18003.

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XI CARBOHYDRATE SYMPOSIUM

Divalent ligand targeting MMP12 and Gal3: studying interactions by NMR

Javier Sastre-Martínez,[a] Ana Ardá,[a] Cristina Nativi,[b] Marco Fragai,[b] H.-J. Gabius,[c] F. Javier Cañada,[a] and Jesús Jiménez Barbero[a]

a) Chemical and Physical Biology, CIB-CSIC, Madrid, Spain;.b) Chemistry Department, Universitá degli Studi di Firenze, Firenze, Italy; c) Veterinary Pharmacy, Ludwig Maximillian Univ., München. Germany; e-mail: jsastre@cib.csic.es

Matrix metalloproteinases (MMP) family is implicated in various pathologic states such as tumor invasion, diseases of central nervous system (CNS) and disorders of the immune system. MMPs are zinc dependent metalloproteins responsible of degradation of most extracellular matrix macromolecules in cell growth.[1] In particular, MMP12 plays important role in cancer growth and metastasis where is found to be overexpressed. In fact, MMP12s has been chosen as a versatile pharmaceutical target to design potent MMP inhibitors (MMPIs).

On the other hand, Galectin 3(Gal3) has been observed indeed related with MMPs in tumor progression. Gal3 is present in tumoral cells and regulates cell proliferation.[2] Particularly, cytoplasmic Gal3 has anti-apoptotic activity maintaining mitochondrial integrity being upregulated in tumoral events.

Exhaustive study of both proteins, MMP12 and Gal3, has allowed the design of potent inhibitors and potential drugs. Thus, compound **1** (fig.1) provides hydroxamic acid epitope for binding with MMP12 and lactose residue for the case of Gal3. To investigate the ability of compound 1 to bind MMP12 and Gal3, NMR techniques have been used.

STD-NMR has been used to study interactions with Gal3 from ligand point of view providing information of epitope mapping. In the case of binding with MMP12, protein point of view techniques have been chosen such as HSQC titration with compound 1. HSQC requires labelled ^{15}N MMP12 and it is very sensitive to chemical environment change. During binding, signals of the aminoacids of binding site suffer a change on chemical environment resulting in a change of their chemical shifts. Moreover, ternary system was also studied by diffusion NMR (DOSY).

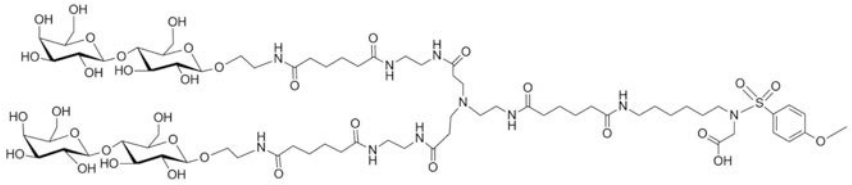

Figure 1. Compound 1.

[1] Fingleton, B. *Sem. Cell Dev. Biol.* **2008**, *19*, 61.
[2] Radosavljevic, G.; Volarevic, V.; Jovanovic, I.; Milovanovic, M.; Pejnovic, N.; Arsenijevic, N.; Hsu, D.; Lukic, M. *Immunol Res* **2012**, *52*, 100.

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XI JORNADAS DE CARBOHIDRATOS

Intramolecular 1,8-hydrogen atom transfer processes in cyclodextrin systems

Ángeles Martín, Dimitri Álvarez-Dorta, Elisa I. León, Inés Pérez-Martín, and Ernesto Suárez

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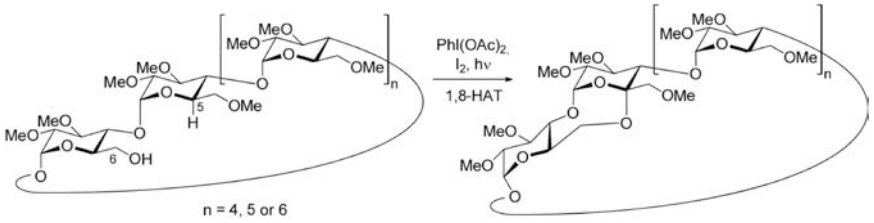
During the last decades cyclodextrins (CDs) and their derivatives have been widely investigated for their important applications such as catalysis, molecular receptors towards a great variety of guest molecules and building blocks in supramolecular chemistry.[1] Thus, an important amount of work has been made in an attempt to improve their functions. However, selective modifications in these structures are not easy to control because of steric factors derived from the torus shape and the large number of hydroxy groups.[2]

According to our previous studies based on intramolecular 1,8-hydrogen atom transfer (1,8-HAT) reaction between the two pyranose units of (1→4)-*O*-disaccharides promoted by 6-*O*-yl radical,[3] herein we show our lastest results by extension of this methodology of remote functionalization to more complex carbohydrates such as CDs. The glucose units in these systems present a proper spatial disposition giving abstraction exclusively at C-5 position of the vicinal unit in a regioselective manner and without modifying the rest of the polysaccharide.



Acknowledgements. We thank the Ministerio de Economía y Competitividad (CTQ2010-18244) and the Gobierno de Canarias (SolSubC200801000192) for financial support.

[1] Dodziuk, H. *Cyclodextrins and Their Complexes. Chemistry, Analytical Methods, Applications*; Wiley-VCH: Weinheim, 2006.

[2] Zaborova, E.; Guitet, M.; Prencipe, G.; Blériot, Y.; Ménand, M.; Sollogoub, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 639−644.

[3] Francisco, C. G.; Herrera, A. J.; Kennedy, A. R.; Martín, A.; Melián, D.; Pérez-Martín, I.; Quintanal, L. M.; Suárez, E. *Chem. Eur. J.* **2008**, *14*, 10369−10381.

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Trifluoromethylation of 2-iodoglycals with fluoroform derived $CuCF_3$

Jordi Mestre,[a] Omar Boutureira,[a] Sergio Castillón,[a] Anton Lischynskyi,[b] and Vladimir Grushin[b]

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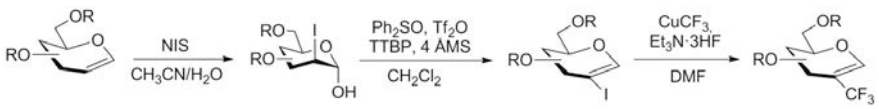
Fluorinated carbohydrates are used in many medical applications since they play important roles as enzyme inhibitors, non-invasive diagnostic agents, antiviral and antitumoral agents.[1] More recently they have been identified as ligands in proteincarbohydrate interactions and molecular recognition processes.

Despite recent efforts for the preparation of advanced fluoro sugars probes the incorporation of important CF_3 units is still scarce. Only few examples of trifluoromethylated carbohydrates are known and were prepared either starting from trifluoromethylated synthons (building block approach) or by the nucleophilic trifluoromethylation of oxosugars with the Ruppert's reagent.[2]

Here we describe a short and simple late-stage cross-coupling methodology for the synthesis of 2-trifluoromethyl-glycals with the $CuCF_3$ reagent derived from fluoroform developed by Grushin *et al*.[3] The method operates under mild conditions and has proven regioselective and tolerant to a wide range of protecting groups.



[1] Akiyama, Y.; Hiramatsu, C.; Fukuhara, T.; Hara, S. *Journal of Fluorine Chemistry*. **2006**, *7*, 920.
[2] Plantier-Royon, R.; Portella, C. *Carbohydr. Res.* **2000**, *327*, 119.
[3] Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901.

UNIVERSIDAD DE LA RIOJA

XI JORNADAS DE CARBOHIDRATOS

Hyperbranched glycolipids as multivalent inhibitors of carbohydrate-lectin interactions

Míriam Salvadó, Isidro Cobo, José Antonio Morales-Serna, M. Isabel Matheu, Yolanda Díaz, Sergio Castillón, and Omar Boutureira

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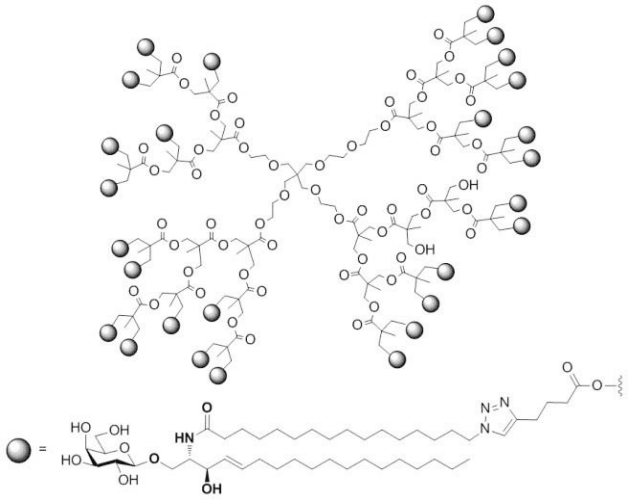
The synthesis of multivalent neoglycoconjugates is currently promoted by the extensive findings of multiple ligand-receptor interactions that occur in Nature and by the phenomenon generally referred to as the glycoside cluster effect. In this context, inhibition of pathogen binding by targeting surface protein receptors is a particularly attractive approach with therapeutic potential for the treatment of several diseases that utilize surface glycolipid receptors.[1]

In the present work, we present the synthesis and characterization of a series of water soluble glycoclusters consisting in Boltorn H30 hyperbranched polymers functionalized with β-neoglycolipids ligands[2] that could potentially mimic those natural glycolipidenriched domains. These functionalized dendritic polymers were evaluated against Cholera toxin (CTB5) and other lectins using Surface Plasmon Resonance (SPR).



[1] Bernardi, A. *et. al. Chem. Soc. Rev.* **2013**, *42*, 4709.
[2] Morales-Serna, J. A.; Boutureira, O.; Serra, A.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Eur. J. Org. Chem.* **2010**, 2657.

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Application of microarrays containing parasitic N-glycans

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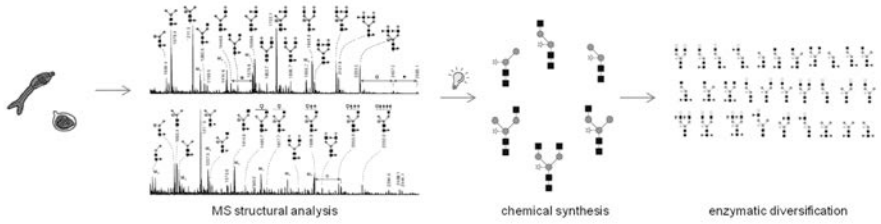
Helminth infections such as *S.mansoni* (snail fever, bilharzia) are the second after malaria major health problem caused by parasites. Even though 200 million people are affected worldwide, a diagnostic test or vaccine candidate is still missing on the market.[1]

Knowing that important immunogenic responses in mammalians infected with helminth are directed towards glycans and based on glycomics analysis of most infectious stages of *S.mansoni* lifecycle,[2] we had chosen and synthesised six xylosylated structures of N- glycans[3] which after further diversification with glycosyltransferases gave us library of compounds decorated with core fucose, Lewis X, LDN and LDNF epitopes.



Newly synthesized xylosylated, parasitic structures were combined with compounds available in our laboratory for the preparation of glycan microarray. We have found core xylosylation, next to other core modifications to have significant impact on the antibodies responses developed in human populations living in schistosomiasis endemic areas, as well as on the interactions with certain C-type lectins receptors.

[1] Nyame, A.K., Kawar, Z.S. & Cummings, R.D., *Antigenic glycans in parasitic infections: implications for vaccines and diagnostics. Arch. Biochem. Biophys.* ***2004****, 426(2),* pp.182–200.

[2] Hokke, C.H. et al., *Glycomics-driven discoveries in schistosome research. Exp Parasitol.* ***2007****, 117(3),* pp.275–283.

[3] Serna, S. et al., *Synthesis of a core trisaccharide building block for the assembly of N-glycan neoconjugates. Tetrahedron: Asymmetry.* **2009**, *20(6-8),* pp.851–856.

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XI JORNADAS DE CARBOHIDRATOS

Synthesis, conformational analysis and biological evaluation of an antitumor vaccine derived from a non-natural MUC1 fragment

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A Tn antigen (αGalNAc-Thr) mimic, based on the replacement of Thr by the non-natural quaternary amino acid α-methylserine (MeSer),[1] has been incorporated in the tandem repeat sequence (AHGVTSAPDT^{10}RPAPGSTAPPA) of MUC1 mucin glycoprotein at 10-position. In addition, a conformational analysis, combining NMR data with molecular dynamics, has been carried out on the small glycopeptidic sequence Pro-Asp-MeSer(αGalNAc)-Arg in water solution indicating that the main backbone conformation obtained matches a X-ray structure corresponding to a small peptide bound to a monoclonal anti-MUC1 antibody (SM3). Once demonstrated by ELISA tests that this monoclonal antibody recognized the above-cited 21-mer fragment, a tripartite vaccine[2] containing this Tn antigen mimic at the most immunogenic domain PDTR has been synthesized and tested on mice. This novel vaccine elicits immune response, recognizing both glycosylated and unglycosylated tumor-associated MUC1 derivatives.[3]

[1] Lakshminarayanan, V.; Thompson, P.; Wolfert, M. A.; Buskas, T.; Bradley, J. M.; Pathangey, L. B.; Madsen, C. S.; Cohen, P. A.; Gendler, S. J.; Boons, G. J. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 261.

[2] Corzana, F.; Busto, J. H.; Marcelo, F.; García De Luis, M.; Asensio, J. L.; Martín-Santamaría, S.; Sáenz, Y.; Torres, C.; Jiménez-Barbero, J.; Avenoza, A.; Peregrina, J. M. *Chem. Commun.* **2011**, *47*, 5319.

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Designing non-natural cancer vaccines by replacing the methyl group of Thr-10 in MUC1 derivatives

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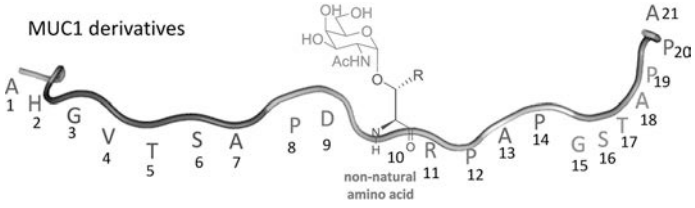
MUC1 mucin is an *O*-glycoprotein which is being widely studied as a potential cancer vaccine.[1] Its importance lies in the fact that in tumor cells these proteins are overexpressed and their carbohydrates are pretty simple due to incomplete glycosylation. As a consequence, different tumor-associated carbohydrate antigens (TACAs), such as the Tn determinant (α-*O*-GalNAc-Ser/Thr), are exposed to the immune system. Unfortunatelly, most TACAs are self-antigens, hence tolerated by the immune system. Our research group has a great deal of experience in organic synthesis of amino acids. Particularly, we are focused on the synthesis of the non-natural ones,[2] which presumably can overcome the aforementioned issue.



In this regard, we are currently developing non-natural mucins based on the replacement of the methyl group of Thr by different substituents. The sudy involves the synthesis, using conventional and SPPS methodology, conformational analysis, supported by molecular dynamics simulations, and biological evaluation to different anti-MUC1 antibodies with ELISA tests. As a future prospective, the best candidates will be selected to be assembled to a TLR2 antagonist and a T_{helper} fragment to give a three-component vaccine, which has been proved to elicit strong immune response.[3] The novel vaccines will be tested *in vivo* studies.

[1] Gaidzik, N.; Westerlind, U.; Kunz, H. *Chem. Soc. Rev.* **2013**, *42*, 4421.
[2] Doctoral Thesis of Martínez-Sáez, N. *Diseño racional de derivados de mucina como candidatos a vacunas contra el cáncer*, Logroño, 2013.
[3] Lakshminarayanan, V.; Thompson, P.; Wolfert, M. A.; Buskas, T.; Bradley, J. M.; Pathangey, L. B.; Madsen, C. S.; Cohen, P. A.; Gendler, S. J.; Boons, G.-J. *Proc. Natl. Acad. Sci.* **2012**, *109*, 261

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XI JORNADAS DE CARBOHIDRATOS

S-Glycosylated mixed α,β-peptides stabilized by CH/π interactions

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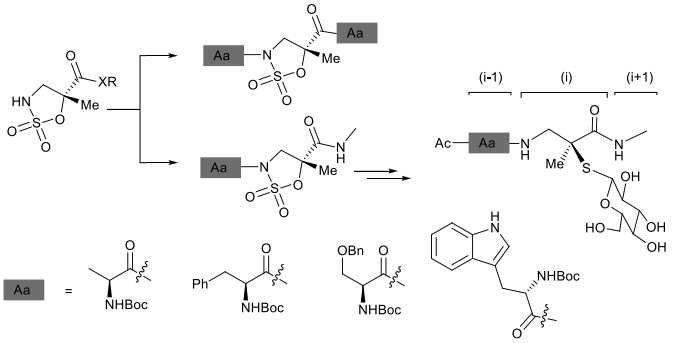
It is well-known that the incorporation of β-amino acids into peptides provides a high degree of stability.[1] In this context, the combination of proteinogenic α-amino acid residues and β-amino acids opens the door to a larger pool of accessible structures with potential applications. A lot of studies exists in this field, but there are few analyzed cases on $\beta^{2,2}$-amino acids incorporated in peptide chains.[2] Our research group has developed an efficient strategy to the synthesis of $\beta^{2,2}$-amino acids through the ring opening of cyclic sulfamidates.[3]

Additionally, it is clear that a variety of weak hydrogen bonds play crucial roles in the behavior of molecules and molecular assemblies. In this context, the CH/π interactions[4] make an important contribution to understanding the crystal packing, structures of biological molecules and molecular recognition processes.

In this work, we present the synthesis of several mixed peptides by the incorporation of $\beta^{2,2}$-amino acids in different peptides through ring opening of cyclic sulfamidates with thioglucose. Conformational studies of these compounds were obtained by combination of NMR experiments and molecular dynamics calculations. Remarkably, in the cases of Phe and Trp, a CH/π interaction between the aromatic ring of these (i-1) α-amino acids and the α-methyl group of $\beta^{2,2}$-amino acid (i) contributes to stabilize the backbone conformation.



[1] Mohle, K.; Gunther, R.; Thormann, M.; Sewald, N.; Hofmann, H. J. *Biopolymers* **1999**, *50*, 167.
[2] Hook, D. F.; Gessier, F.; Noti, C.; Kast, P.; Seebach, D. *ChemBioChem* **2004**, *5*, 691.
[3] Mata, L.; Avenoza, A.; Busto, Corzana, F.; J. H.; Peregrina, J. M. *Chem. Eur. J.* **2012**, *18*, 15822.
[4] Asensio, J. L.; Ardá, A.; Cañada, F. J.; Jiménez-Barbero, J. *Acc. Chem. Res.* **2013**, *46*, 946.

UNIVERSIDAD DE LA RIOJA

XI CARBOHYDRATE SYMPOSIUM

Glycopeptides incorporating sulfur-based Tn antigen mimics

Carlos Aydillo, Victor Rojas, Ismael Compañón, Marta I. Gutiérrez-Jiménez, Miguel Ayala, Francisco Corzana, María del Mar Zurbano, Jesús H. Busto, Alberto Avenoza, and Jesús M. Peregrina

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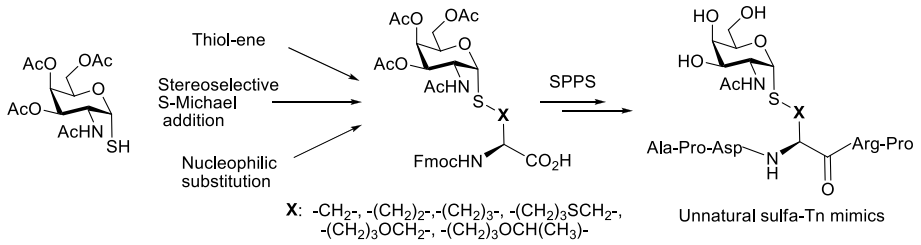
Tn antigen (α-*O*-GalNAc-Ser/Thr) is involved in the recognition processes of cancerous cells. This simple structure is found in a great number of recognition epitopes of glycoproteins, i.e., MUC1 mucin.[1] For this reason, the synthesis of new Tn mimics has been atracting the interest of carbohydrate chemists. In this sense, we have been carrying out the synthesis of different sulfur-based Tn antigen mimics. Changing oxygen by sulfur can provide different affinities of the Tn antigen when including in epitope glycopeptides. The synthesis of different sulfa-Tn building blocks were achieved through three strategies starting from tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-α-D-galactose: radical thiol-ene reaction over alkenes, nucleophilic substitution over bromo-compounds and stereoselective *S*-Michael additions to chiral dehydroalanines.[2]



Various sulfa-Tn building blocks were incoporated in the Ala-Pro-Asp-Xaa*-Arg-Pro sequence. Competitive enzyme-linked lectin assays (ELLA) were carried out to evaluate the affinities with *Soybean agglutinin* (SBA) lectin. We demonstrated that non-natural sulfa-Tn antigen mimics show comparable affinity to α-*O*-GalNAc-Ser for this lectin.[2]

[1] Varki, A. *Glycobiology* **1993**, *3*, 97.
[2] Aydillo, C.; Compañón, I.; Avenoza, A.; Busto, J. H.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M., *J. Am. Chem. Soc.* **2014**, *136*, 789.

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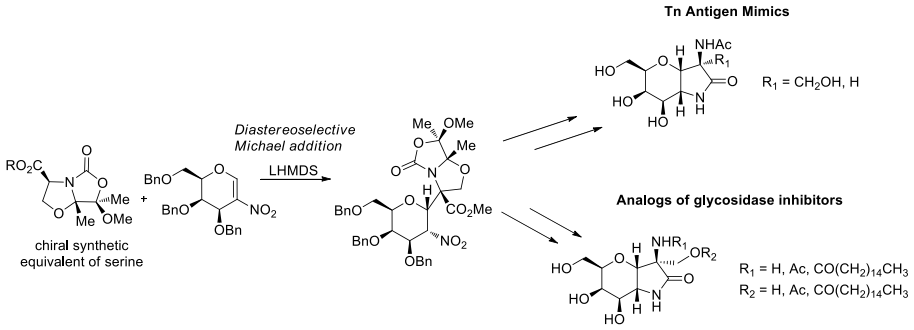
XI JORNADAS DE CARBOHIDRATOS

A double diastereoselective Michael-type addition as an entry to Tn antigen mimics and analogs of Thiamet-G

Claudio D. Navo,[a] Carlos Aydillo,[a] Alberto Avenoza,[a] Jesús H. Busto,[a] Francisco Corzana,[a] María M. Zurbano,[a] Carmen Ortiz Mellet,[c] José M. García Fernández,[b] and Jesús M. Peregrina[a]

a) Departamento de Química, Universidad de La Rioja, Centro de Investigación en Síntesis Química, C/Madre de Dios, 51, 26006 Logroño, La Rioja, Spain; b) Department of Organic Chemistry, Faculty of Chemistry, University of Seville, 41012 Seville; c) Instituto de Investigaciones Químicas (IIQ), CSIC – Universidad de Sevilla, 41092 Sevilla; e-mail: claudio-daniel.navon@unirioja.es.

Our research group has recently reported a double diastereoselective Michael-type addition between chiral synthetic equivalents of serine, bicyclic *N*,*O*-acetals in this case, and a chiral Michael acceptor, such as tri-*O*-benzyl-2-nitro-D-galactal, affording a unique diastereoisomer of the eight possible ones.[1]



Using this adduct as starting point, we have been able to synthesize neoglycoamino acids, analogs of Tn antigen (α-*O*-GalNAc-Ser/Thr), which is recently attracting a deal of interest for the development of vaccines for cancer treatment.[2] We have carried out the conformational analysis in aqueous solution of these compounds, as well as *enzyme-linked lectin assays* (ELLA) to determine their behavior as Tn antigen mimics.

Following this synthetic strategy, a battery of different compounds structurally analogs of Thiamet-G is also presented here. Thiamet-G has been described as a potent inhibitor of 2-acetamido-2-desoxy-β-D-glucopyranosidase and it is being investigated as therapeutic potential for the treatment of Alzheimer.[3] Some of these compounds have shown interesting results as inhibitors.

[1] Aydillo, C.; Navo, C. D.; Busto, J. H.; Corzana, F.; Zurbano, M. M.; Avenoza, A.; Peregrina, J. M. *J. Org. Chem.* **2013**, *78*, 10968.
[2] Heimburg-Molinaroa, J.; Lumb, M.; Vijayc, G.; Jain, M.; Almogrene, A.; Rittenhouse-Olson, K. *Vaccine* **2011**, *29*, 8802.
[3] Yuzwa S. A.; Shan X. Y.; Macauley M. S.; Clark T.; Skorobogatko, Y.; Vosseller, K.; Vocadlo D. J. *Nat. Chem. Biol.* **2012**, *8*, 393.

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XI CARBOHYDRATE SYMPOSIUM

A study of CH/π interactions and their role in the stabilization of carbohydrate-receptor complexes by using model systems

Dolores Díaz, M. Carmen Fernández-Alonso, Luca Unione, Ana Manzano, and Jesús Jiménez-Barbero

Department of Chemical and Physical Biology, Centro de Investigaciones Biológicas (C.S.I.C.), C/Ramiro de Maeztu 9, 28040 Madrid, Spain

Carbohydrates play an important role in numerous biological routes.[1,2,3] Besides being considered a natural storage of energy in Nature, it is known that the specific interaction between sugars and their natural receptors (i.e. lectins) triggers many crucial biological processes. Thus, knowledge of both the chemical and structural factors that are decisive for an effective interaction is of great interest for the development of novel sugar-based drugs. Hence, biophysical techniques such as X-Ray crystallography or NMR spectroscopy, among others, usually assisted by molecular modeling, have been extensively used in this field to confirm conformational requirements that favour the formation of sugar-protein complexes.

Among the stabilizing factors that may contribute for an effective ligand-protein interaction into the receptor active site, we are particularly interested in the so-called "CH/π interaction" between carbohydrates and aromatic amino acid side chains[4,5,6] In this context, herein we present our investigations on the interaction of simple carbohydrates or analogous with aromatic moieties by NMR spectroscopy and molecular modeling. We have analyzed the variations in the chemical shifts of several sugar-like ligands upon addition of aromatic entities which have been correlated with specific interaction geometries.

[1] Gabius, H.-J.; Siebert, H.-C.; Andre, S.; Jiménez-Barbero J.; Rudiger H. *ChemBioChem* **2004**, *5*, 740.
[2] Solís, D.; Kogelberg, H.; Jiménez-Barbero, J. *Curr. Opin. Struct. Biol*. **2003**, *13*, 646.
[3] G. Colombo, G.; Meli, M.; Cañada, J.; Asensio, J.L.; Jiménez-Barbero, J. *Carbohydr. Res.* **2004**, *339*, 985.
[4] Nishio, N.; Hirota, M.; Umezawa, Y. *The CH-Pi Interaction: Evidence, Nature, and Consequences.* Wiley-VCH**, 1998**, Wiley-VCH: New York
[5] Fernández-Alonso, M.C.; Cañada, F.J.; Jiménez-Barbero, J.; Cuevas, G. *J. Am. Chem. Soc.* **2005**, *127*, 7379.
[6] S. Vandenbussche, S.; Diaz, D.; Fernández-Alonso, M.C.; Pan, W.; Vincent, S.P.; Cuevas, G.; Cañada, F.J.; Jiménez-Barbero, J.; Bartik, S. *Chem. Eur. J.* **2008**, 14, 7570.

UNIVERSIDAD DE LA RIOJA

XI JORNADAS DE CARBOHIDRATOS

Targeting galectins. Virtual screening of fragment libraries for design of novel glycans

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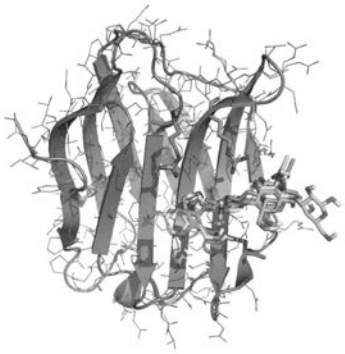
Carbohydrates are involved in a variety of physiological processes, acting as signals for cellular recognition.[1] Among these processes, immune and inflammatory responses, organogenesis, metastasis, and diverse infectious processes should be mentioned.[2] In this context, the search of novel ligands able to mimic oligosaccharides in the binding sites of lectins (such as galectins), antibodies, and enzymes is currently a topic of major interest because of its long-range potential for clinical applications.[3] In particular, we are interested in the identification of novel scaffolds able to lead to second generation of LacNAc derivatives with putative modulating activity on human galectins 1, 3, and 7. We have undertaken docking and virtual screening studies to identify moieties which can be accommodated in the secondary pockets close to the carbohydrate recognition domains of galectins. These studies can assist in the design of synthetic glycans with potential therapeutic applications.[4,5]



[1] Gabius, H.J.; André, S.; Jiménez-Barbero, J.; Romero, A.; Solis, D. From lectin structure to functional glycomics: principles of the sugar code. *Trends Biochem. Sci.* **2011**, *36*, 298.
[2] Gabius, H.J. *The Sugar Code. Fundamentals of glycosciences;* Wiley-VCH: Weinheim, **2009**.
[3] Gabius, H.-J. (2006) Cell surface glycans: the why and how of their functionality as biochemical signals in lectin-mediated information transfer. *Crit. Rev. Immunol.* 26, 43-80.
[4] Martin-Santamaria, S.; Gabius, H.J.; Jiménez-Barbero, J. Structural studies on the interaction of saccharides and glycomimetics with galectin-1: A 3D perspective using a combined molecular modeling and NMR approach. *Pure Appl. Chem.* **2012**, *84*, 49
[5] Sörme, P.; Arnoux, P.; Kahl-Knutsson, B.; Leffler, H.; Rini, J. M.; Nilsson, U. J. *J. Am. Chem. Soc.* **2005**, *127*, 1737.

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XI JORNADAS DE CARBOHIDRATOS

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Logroño, La Rioja, Spain

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May 28-30, 2014

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