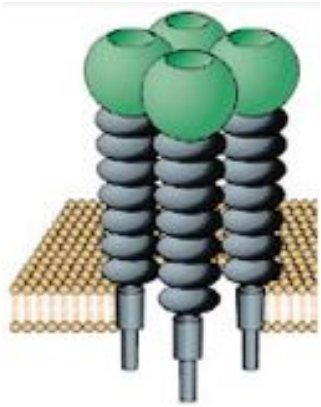
Biological Results

TRANSFECTION IN HUMAN CELL STUDIES: Inhibition of Ebola virus infection



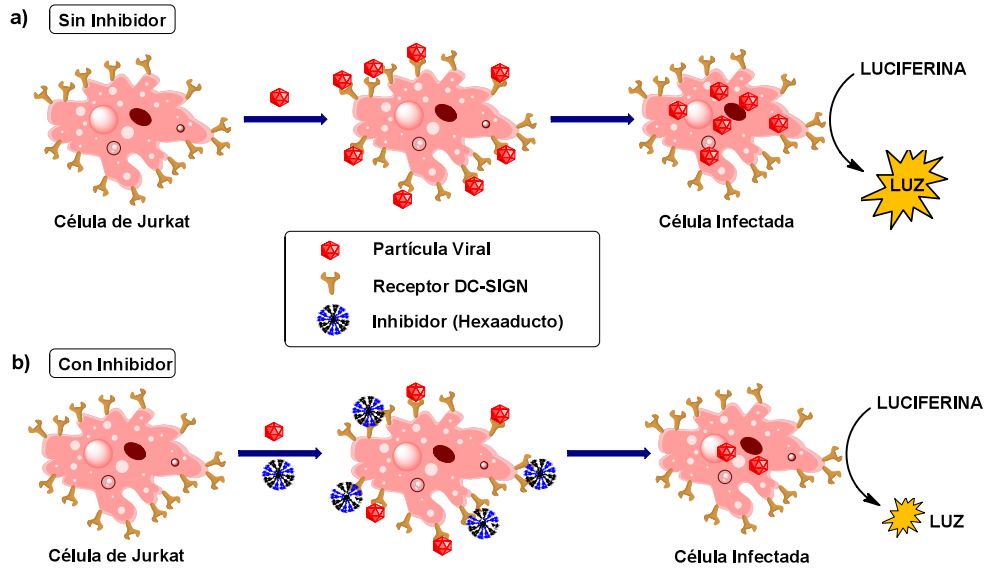
DC-SIGN Receptor

- Lectine expressed in dendritic cells
- It is considered a universal receptor of patogens
- Viruses like HIV and Ébola take advantage of the DC-SIGN interaction for starting the infection process
- It recognises glycoproteins with a high content in mannoses

In collaboration with Dr. Rafael Delgado from Hospital 12 de Octubre

Biological Results

TRANSFECTION IN HUMAN CELL STUDIES: Inhibition of Ebola virus infection



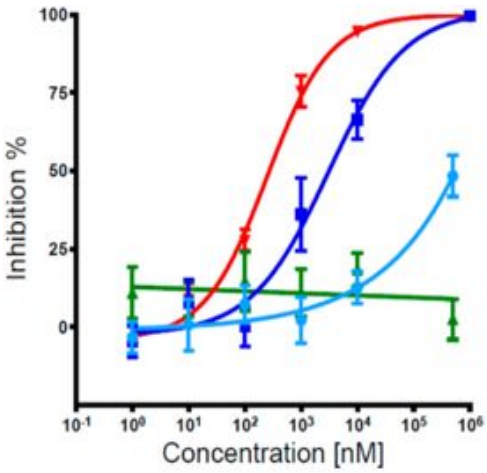
In collaboration with Dr. Rafael Delgado from Hospital 12 de Octubre

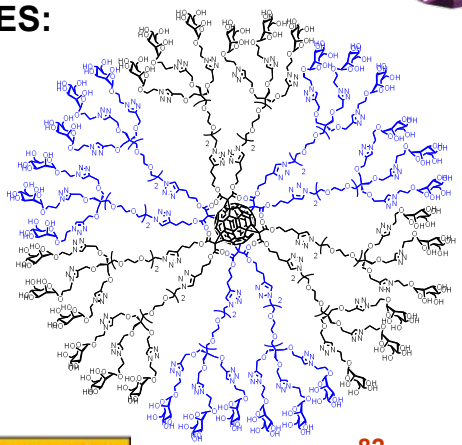
Science **1998**, *279*, 1034.

Biological Results

TRANSFECTION IN HUMAN CELL STUDIES: Inhibition of Ebola virus infection

- Hexaadduct with 12 galactoses as a negative control





82

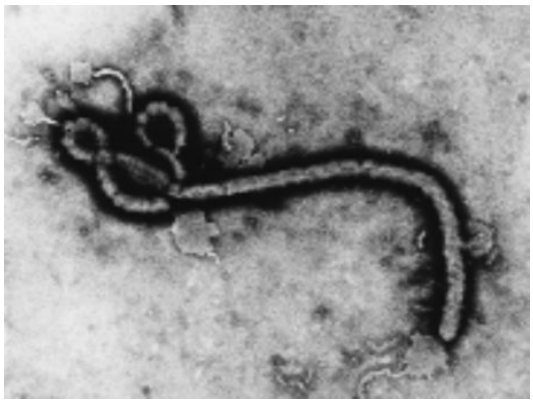
Compuesto	IC_{50} (μM)
76 (12- Man)	2
81 (36-Man, n=1)	68
82 (36-Man, n=2)	0.3

Biomacromolecules **2013**, *14* , 431

Biological Results

Ebola virus features:

- Highly lethal pathogens (60-80%)
- Biological security Labs P4
- Citotoxicity?
- Natural reservoir?
- Celular receptor?
- Lack of medicaments



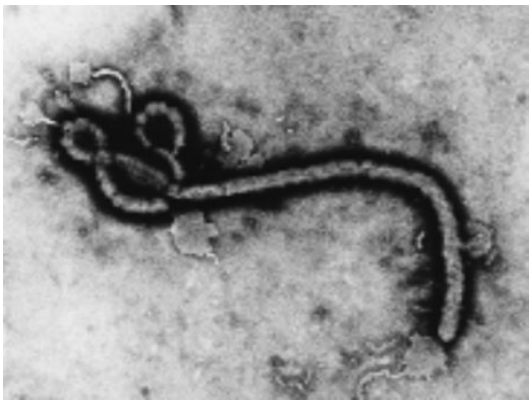
Ebola virus was first recognized during two major disease outbreaks, which occurred almost simultaneously in Zaire and Sudan in 1976.

Biological Results

Ebola virus features:

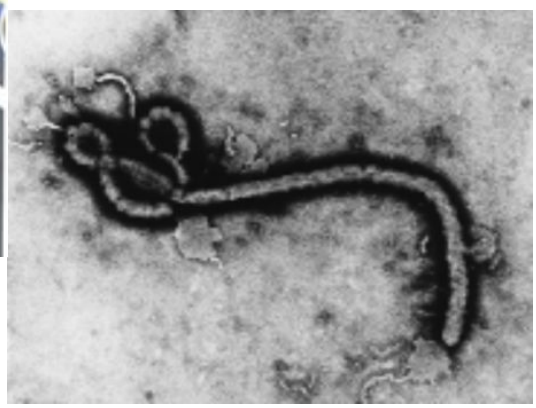
La enfermedad por el virus del Ebola (EVE), antes llamada **fiebre hemorrágica del Ebola**, es un enfermedad grave, a menudo mortal en el ser humano. El **virus es transmitido** al ser humano por animales salvajes y se propaga en las poblaciones humanas por transmisión de persona a persona. Los brotes de enfermedad por el virus del Ebola (EVE) tienen una **tasa de letalidad** que es de aproximadamente 50%. En brotes anteriores, las tasas fueron de 25% a 90%. Los primeros brotes de EVE se produjeron principalmente en aldeas remotas de África central y occidental, cerca de la selva tropical. Pero el más reciente brote en el oeste de África ha afectado a grandes centros urbanos, así como las zonas rurales La participación de la comunidad es fundamental para el éxito del **control de los brotes**. Un buen control de los brotes depende de la aplicación de diferentes intervenciones, como la atención a los casos, la vigilancia y el rastreo de los casos, los entierros en condiciones de seguridad o la movilización social. El **tratamiento** de apoyo precoz con rehidratación y el tratamiento sintomático mejoran la supervivencia. Todavía no hay ningún tratamiento aprobado que neutralice el virus de forma demostrada, pero están en fase de desarrollo diversas formas de hemoterapia, inmunoterapia y farmacoterapia. Tampoco hay todavía **vacunas** aprobadas para el Ebola, pero se están evaluando dos posibles vacunas candidatas.

Organización Mundial de la Salud



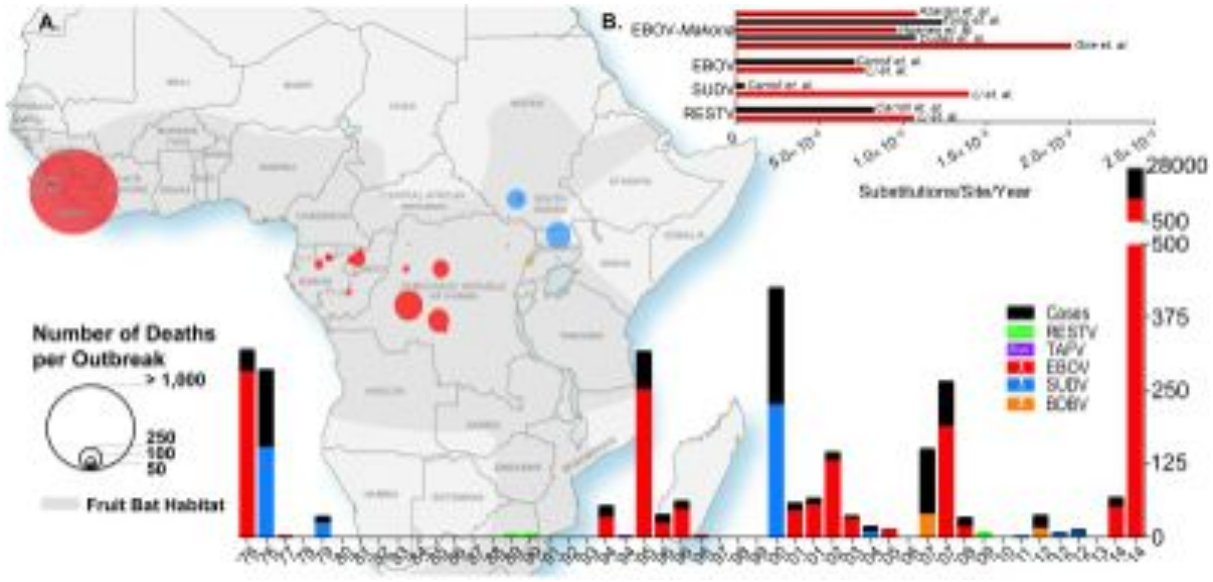
Biological Results

Ebola virus features: BSL4 Laboratory



Ebola virus was first recognized during two major disease outbreaks, which occurred almost simultaneously in Zaire and Sudan in 1976.

Ebola virus outbreaks past and present



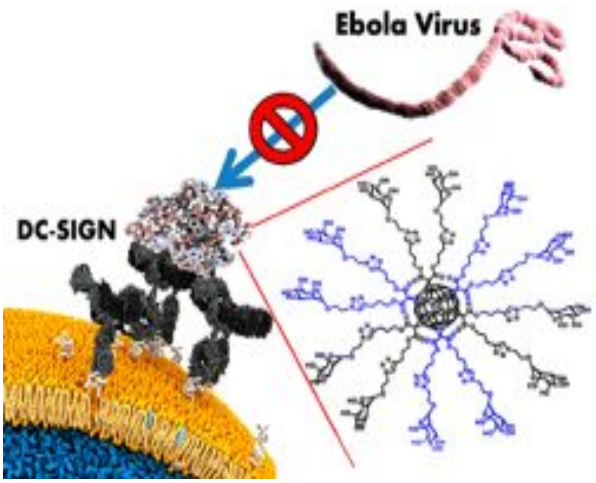
Ebolavirus outbreaks past and present.
(A) The geographic map of Africa and the bottom histogram illustrate the number of cases, deaths, and the geographic distribution of several Ebola viruses including Reston (RESTV), Tai Forest (TAFV), Ebola (EBOV, formerly Zaire), Sudan (SUDV), and Bundibugyo (BDBV). The histogram in the top right (B) is a review of the calculated evolutionary rates available for EBOV, EBOV-*Makona*, SUDV, and RESTV from various publications.

Biological Results

TRANSFECTION IN HUMAN CELL STUDIES: Inhibition of Ebola virus infection

Biological Results

TRANSFECTION IN HUMAN CELL STUDIES: Inhibition of Ebola virus infection



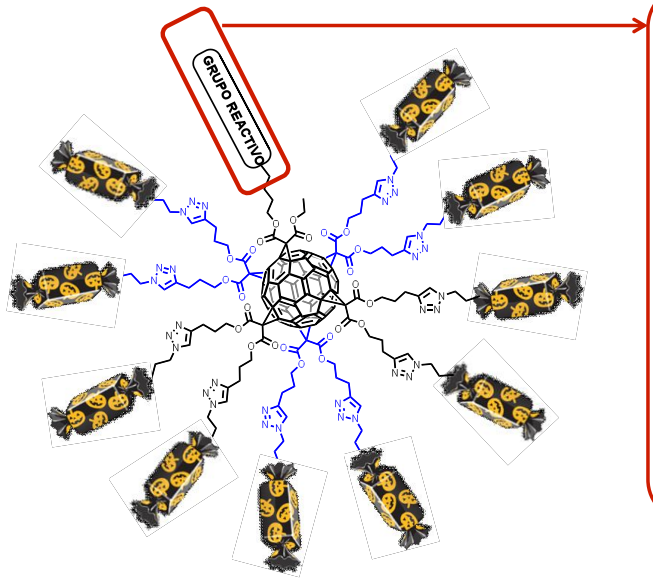
CONCLUSIONS

- **Hexaaducts are not toxic and are a suitable scaffold for the multivalent presentation of carbohydrates**
- **They Inhibit the Ebola virus infection by blocking the DC-SIGN lectine in the nanomolar range**
- **The number of multivalent ligands is as important as the size and morphology of the scaffold where they are presented**

Biomacromolecules **2013**, *14* , 431.

New Designs

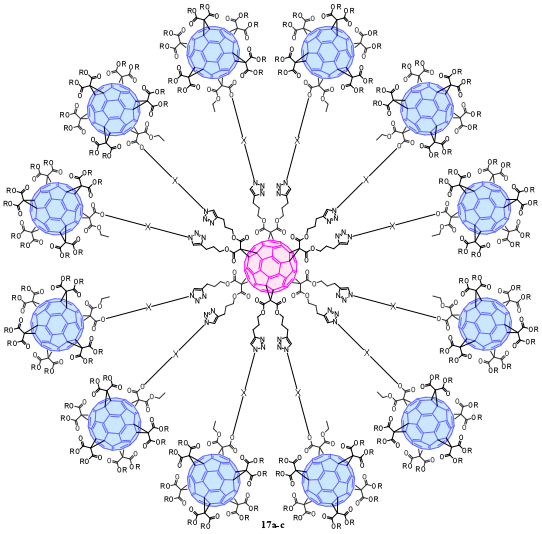
SYNTHESIS OF ASSYMMETRIC HEXAADUCTS



- **A new reactive group able to undergo further functionalization**
- **New building blocks**
- **“Fullerene sugar balls” with two functional groups**
- **Glycosilated fluorescent tracers**
- **Functional groups able to conjugate with biomolecules**
- **Linkage to an epitope or antigenic determinant (precursor of synthetic vaccines)**

New Designs: Tridecafullerenes

DESIGN OF NEW MORPHOLOGIES OF GLYCOMIMMETICS



- **12 “Click” reactions on the [60]fullerene core**
- **Molecule decorated with 120 carbohydrates on its periphery**
- **Globular symmetry**
- **The fastest dendrimeric growing up, without using protecting groups**

Nature Chem., **2016,** *8*, 50- 57 DOI: 10.1038/NCHEM.2387

New Designs: Tridecafullerenes

DESIGN OF NEW MORPHOLOGIES OF GLYCOMIMMETICS

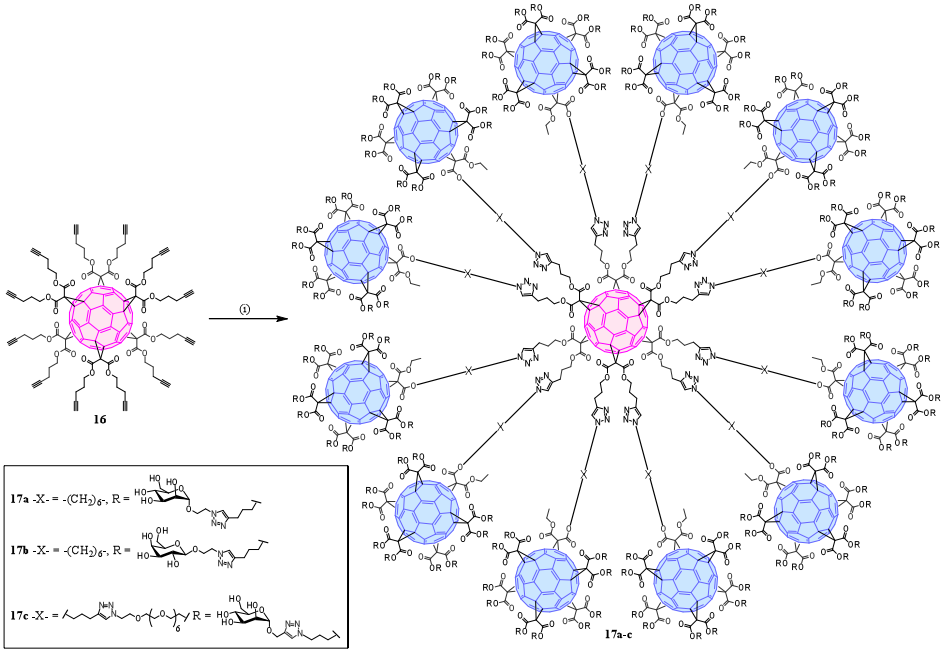
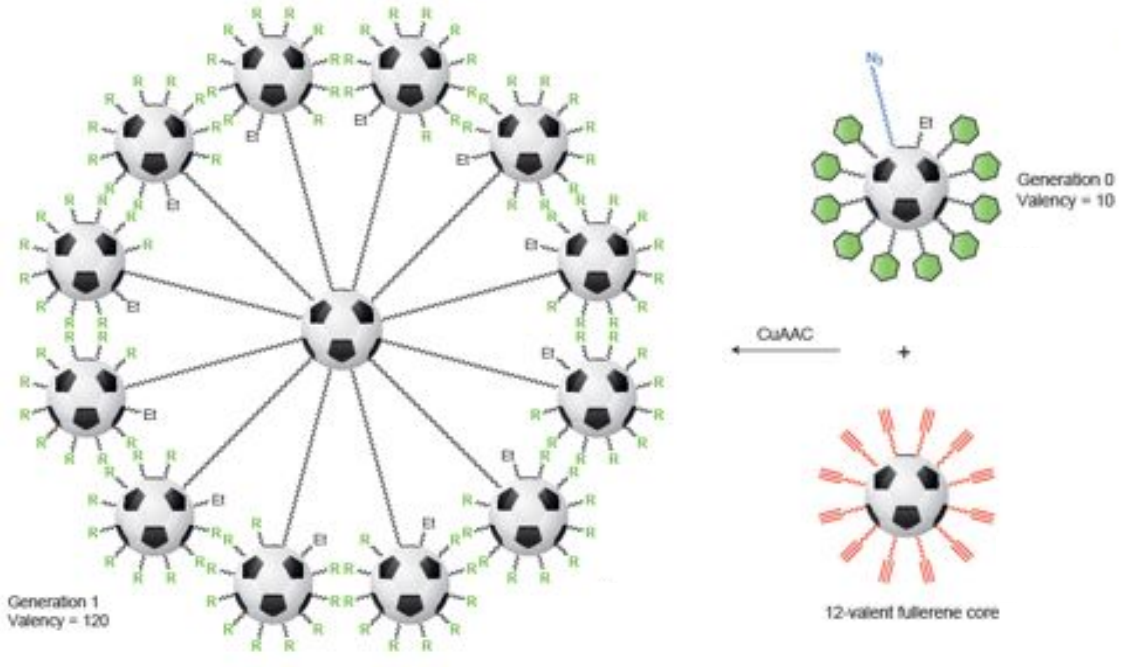


Figure. Synthetic scheme for tridecafullerenes 17a-c. *Reagents and conditions*. For compounds **17a-b**: (i) **15a-b**, CuBr·S(CH_3)$_2$, sodium ascorbate, Cu^0, DMSO, 25°C, 48 h [**17a** (from **15a**): 73%; **17b** (from **15b**): 79%]. For compound **17c**: (i) **9**, $CuSO_4$.5H_2O, sodium ascorbate, THF/H_2O, 80°C (MW), 2 h (76%).

Nature Chem., **2016,** *8*, 50- 57 DOI: 10.1038/NCHEM.2387

New Designs: Tridecafullerenes

news & views



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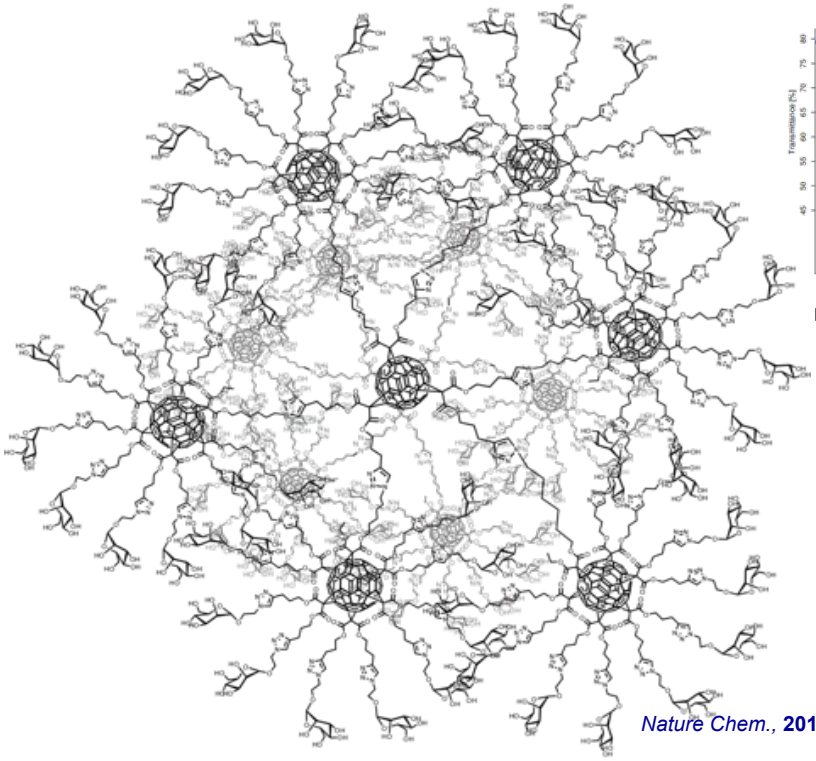

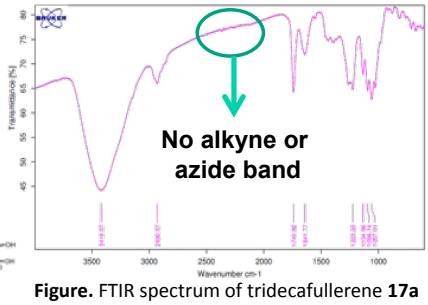

Figure. FTIR spectrum of tridecafullerene **17a**

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New Designs: Tridecafullerenes

DESIGN OF NEW MORPHOLOGIES OF GLYCOMIMMETICS

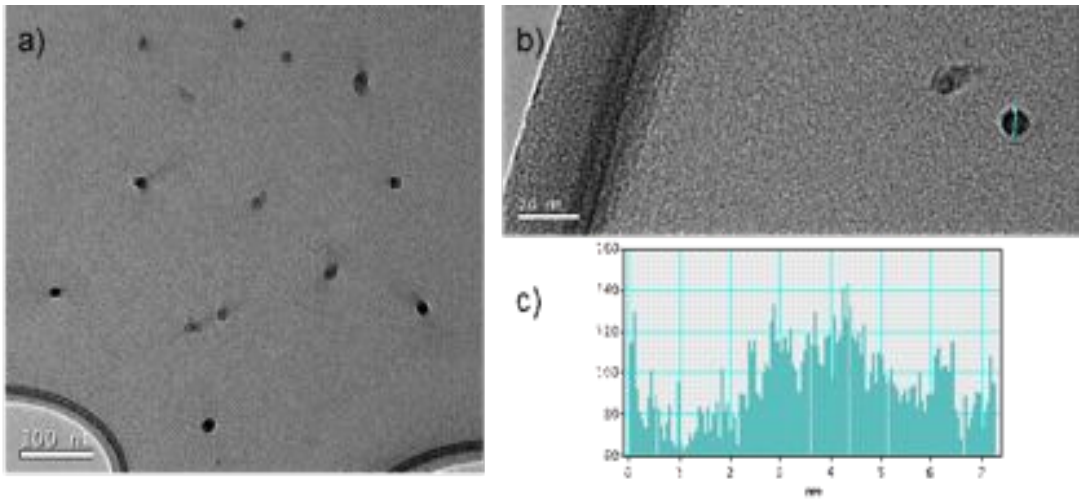

Figure. TEM images of tridecafullerene 17a. a) TEM images of compound **17a** upon deposition of a 0.01 mg/mL solution in H_2O. b) Detail of a particle corresponding apparently to one molecule. c) Width profile of the particle shown in b).

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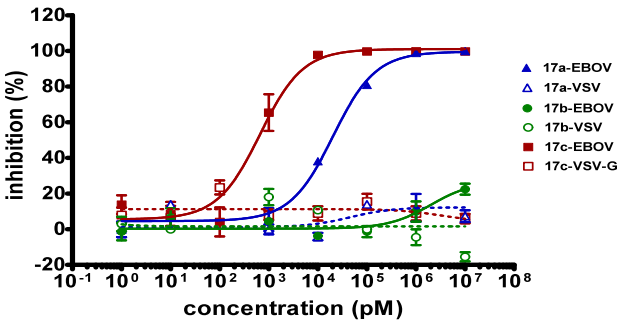
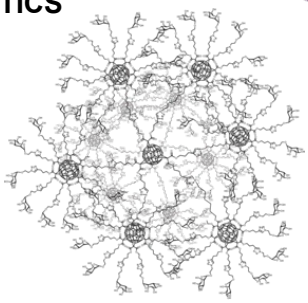
New Designs: Tridecafullerenes

DESIGN OF NEW MORPHOLOGIES OF GLYCOMIMMETICS





Second generation "Fullerene sugar balls" inhibit Ébola virus infection at IC_{50}= 0.66 nM

Figure. Biological study of tridecafullerenes (17a-c). Inhibition of infection with EBOV or VSV GP-pseudotyped lentiviral particles of Jurkat DC-SIGN$^+$ cells using **17a** (blue), **17b** (green) and **17c** (red). In the cis-infection experiments 2.5x10^{5}Jurkat DC-SIGN$^+$ were challenged with 5000 TCID of recombinant lentiviral particles. Results represent the mean of 6 independent experiments +/- SEM.

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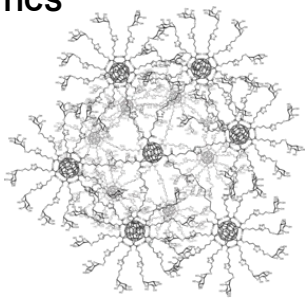
New Designs: Tridecafullerenes

DESIGN OF NEW MORPHOLOGIES OF GLYCOMIMMETICS

Table 1 | Comparison of IC_{50} and RIP values of different mannosylated multivalent compounds.

Compound	IC_{50} (nM)	Mannoses (No.)	RIP*	Reference
17c (120 mannoses)	0.667	120	1.58×10^4	This work
VLP† (1,620 mannose)	0.91	1,620	8.6×10^2	33
17a (120 mannoses)	20.375	120	5.2×10^2	This work
VLP† (540 mannoses)	9.62	540	2.44×10^2	33
C60LL (36 mannoses)‡	300	36	1.17×10^2	20
C60 (36 mannoses)‡	68,000	36	0.5	20
C60 (12 mannoses)‡	2,000	12	53	20
α-methyl-D-mannopyranoside	1.27×10^6	1	1	34

Data obtained from inhibition studies using pseudotyped EBOV particles for the new compounds **17a** and **17c** in comparison with other carbohydrate multivalent systems previously reported by us; *RIP, calculated as $(IC_{50})_{mono}/IC_{50}$*valency. †Virus like particles (see main text). ‡See Supplementary Fig. 5 for the chemical structure.



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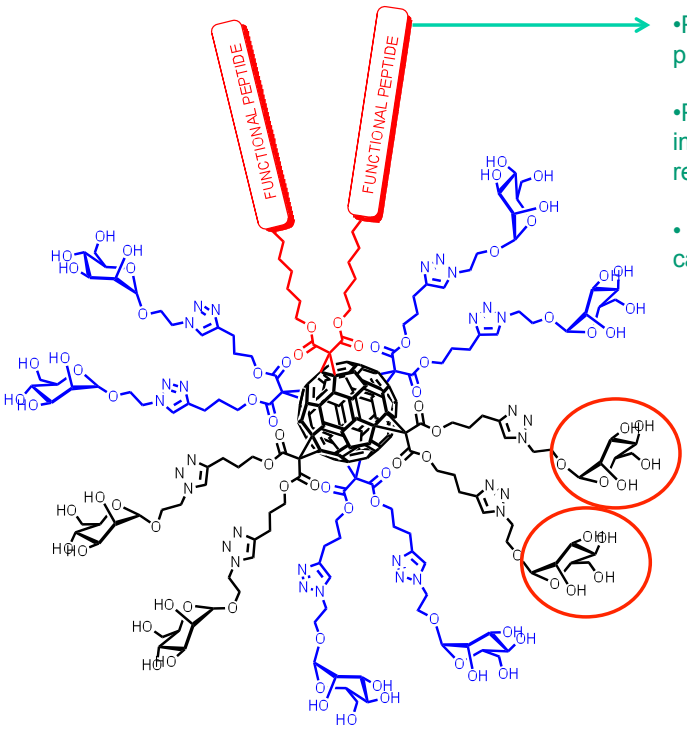
Future perspectives:

Fullerenes with Dual-Biofuntional with multivalent effects: TOWARS SYNTHETIC VACCINES…



- •Peptides and proteins with many biological properties.
- •Peptide fragments recognized by the immune system that trigger an immune response. New vaccines???
- • This study can be also extended to other carbon nanoforms…

- •Specific Interaction with Glycocalix.
- •Different Selectivity changing the carbohydrate.
- •Signaling on the cell surface.

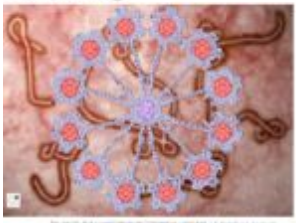
Social impact…


SUGAR BALL BLOCKS EBOLA


C&EN
CHEMICAL & ENGINEERING NEWS
SCIENCE & TECHNOLOGY CONCENTRATES

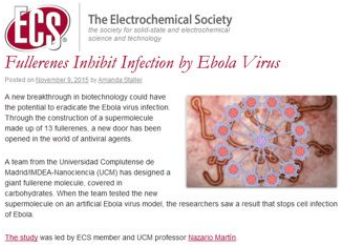
EL PAÍS

Anular un virus mortal con 13 balones de fútbol microscópicos



EL MUNDO

Una 'superbola' de azúcar contra el ébola


The Electrochemical Society
the society for solid-state and electrochemical science and technology

Fullerenes Inhibit Infection by Ebola Virus

Posted on November 9, 2015 by Amanda Stalter

A new breakthrough in biotechnology could have the potential to eradicate the Ebola virus infection. Through the construction of a supermolecule made up of 13 fullerenes, a new door has been opened in the world of antiviral agents.

A team from the Universidad Complutense de Madrid/IMDEA-Nanociencia (UCM) has designed a giant fullerene molecule, covered in carbohydrates. When the team tested the new supermolecule on an artificial Ebola virus model, the researchers saw a result that stops cell infection of Ebola.

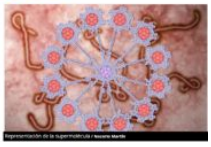
The study was led by ECS member and UCM professor Nazario Martín

LA VANGUARDIA

Crean una macromolécula de azúcar capaz de bloquear en las células el ébola

laverdad.es

Crean una gran molécula artificial que impide la infección del ébola



NANOMATERIALES

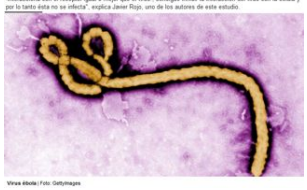
Investigadores españoles diseñan una pelota cubierta de azúcares que, en concentraciones mínimas, ha logrado inmunizar células in vitro frente al virus

Este desarrollo abre la puerta a la elaboración de un nuevo tipo de fármacos basados en nanomateriales que se aprovechan de la flexibilidad del carbono

antena3.com

Una 'superbola de azúcar', capaz de impedir la infección por el Ébola

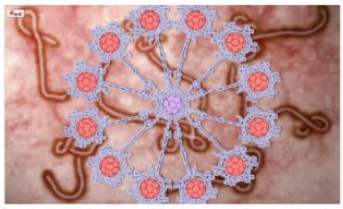
Esta macromolécula recubierta de azúcar es capaz de frenar el acceso del ébola precisamente bloqueando la molécula receptora, que actúa como una puerta de entrada del virus. "Si la macromolécula es eficiente -interacciona con el receptor igual o mejor que el virus-, consigue inhibir la interacción del virus con la célula y por lo tanto évita no se infecta", explica Javier Rojo, uno de los autores de este estudio.



Virus ébola | Foto: GettyImages

PHYS.ORG

Giant fullerene system inhibits infection by artificial Ebola virus



The actors…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Dr. B. Illescas

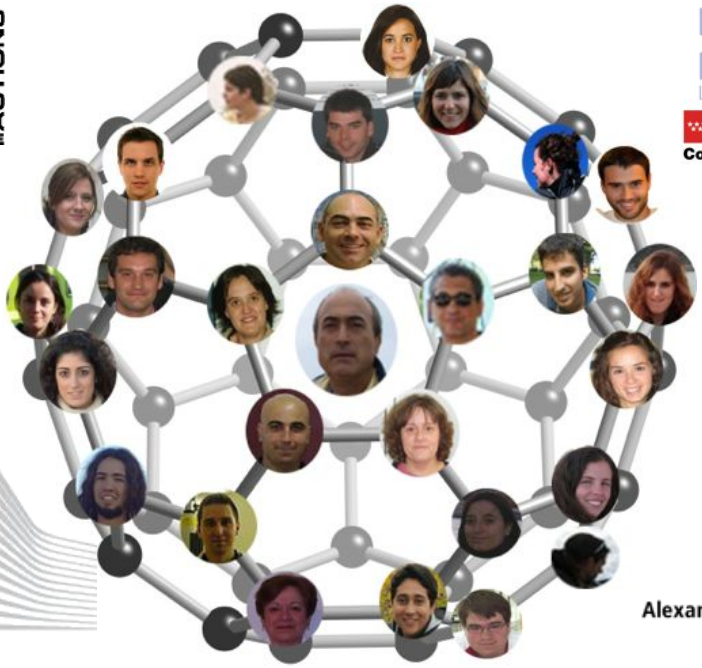

Dr. M. Sánchez-Navarro


Dr. L. Rodriguez


Prof. Javier Rojo


Prof. Rafael Delgado

ORGANIC MOLECULAR MATERIALS GROUP



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European Commission (EUROMAP)
Proyecto Singular Estratégico (MICINN)
Marie Curie (MOLESCO)
CONSOLIDER "Nanociencia molecular"
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