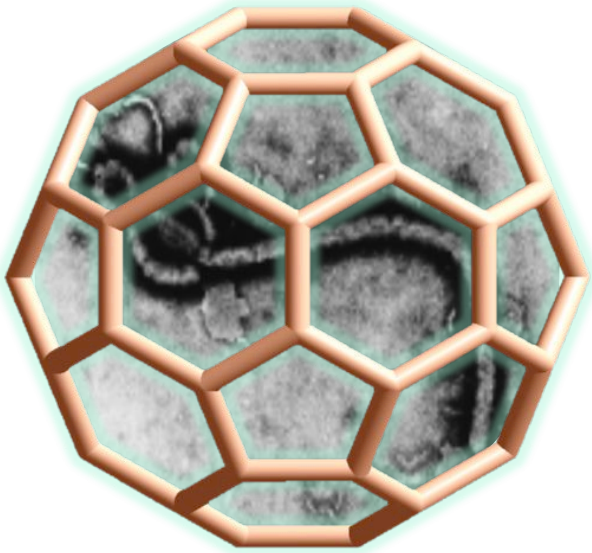
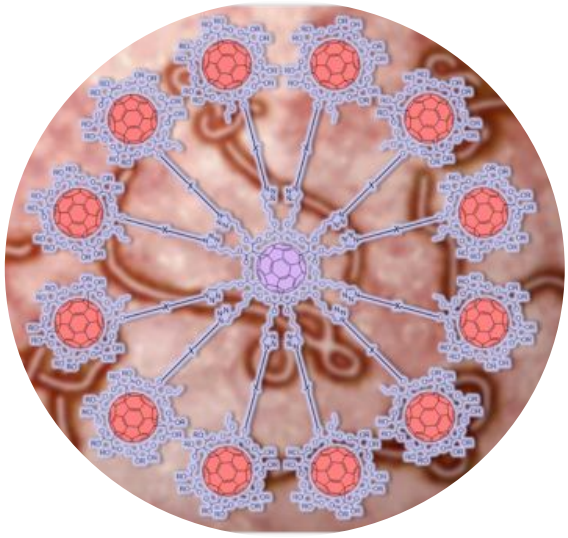
Fullerenos para aplicaciones biológicas

V Curso de Divulgación: Los Avances de la Química y su Impacto en la Sociedad

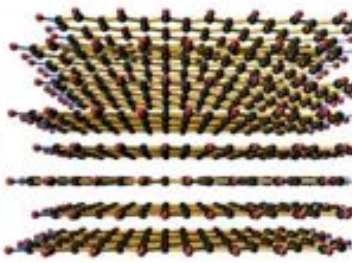




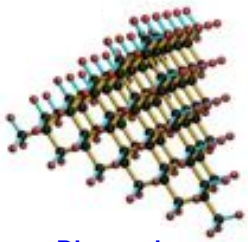
Nazario Martín

Departamento de Química Orgánica. Facultad de Ciencias Químicas
Universidad Complutense de Madrid/IMDEA-Nanociencia

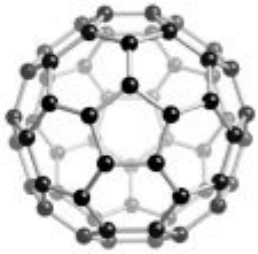
The fascinating forms of carbon…



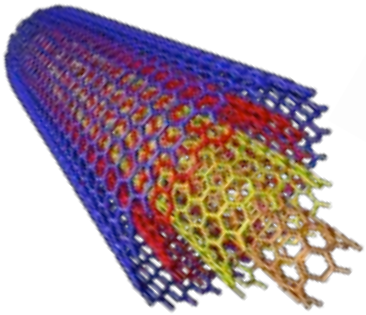
Graphite



Diamond

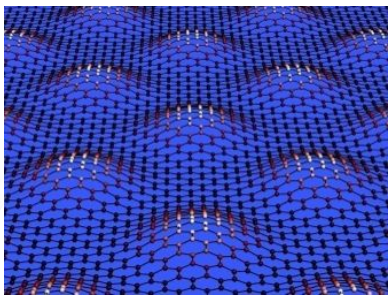


Fullerenes (1985)
Kroto, Smalley, Curl, 1996



Multiwall carbon nanotubes (1991)

Singlewall carbon nanotubes (1993)

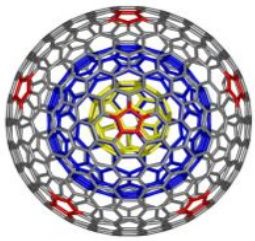


Graphene (2004)
Geim, Novoselov, 2010

J. Mater. Chem. **2008**, *18*, 1415-1592
Special issue on Carbon Nanostructures

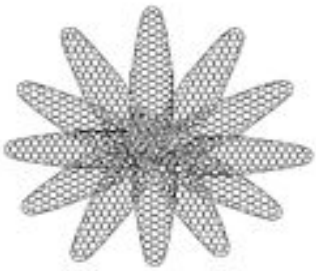
The fascinating forms of carbon…

Carbon nanoonions

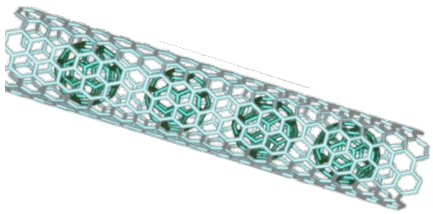


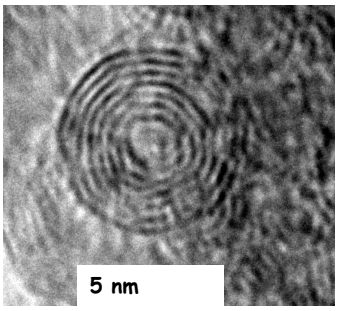
$C_{60}@C_{240}@C_{540}$

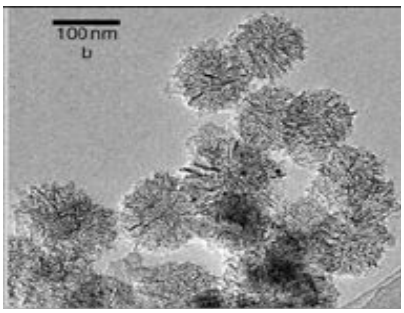
Nanohorns

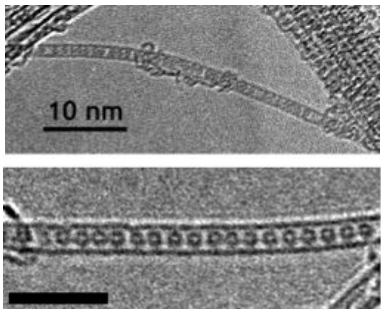


Peapods









J. Mater. Chem. **2008**, *18*, 1415-1592
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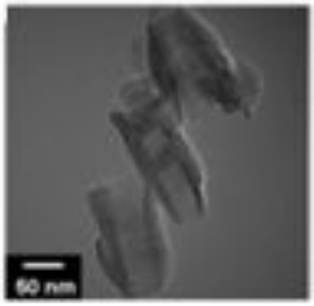
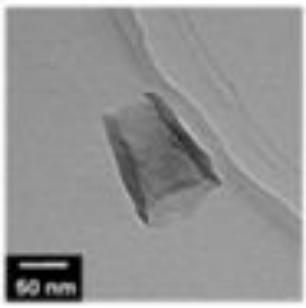
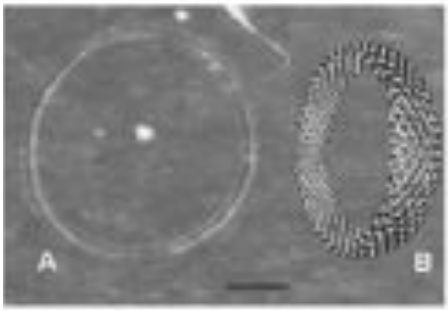
The fascinating forms of carbon…

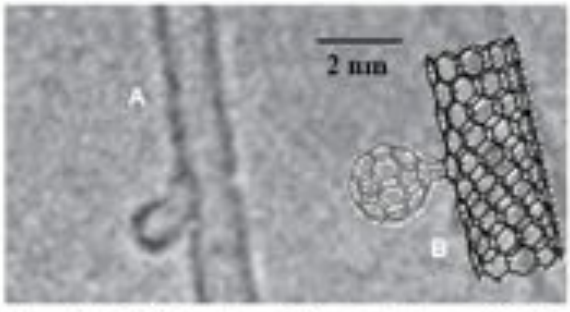




Nanocups



Nanotorus



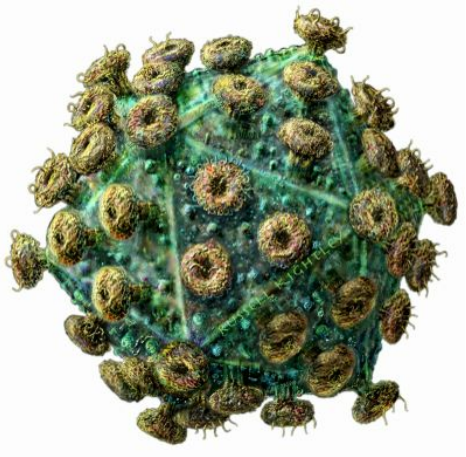
Nanobuds

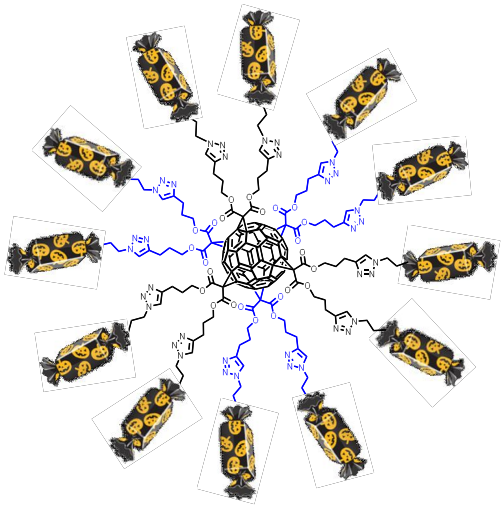
J. Mater. Chem. **2008**, *18*, 1415-1592
Special issue on Carbon Nanostructures

Fullerenos para aplicaciones biológicas

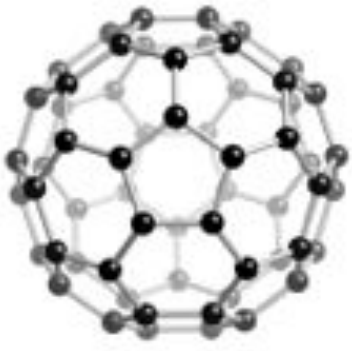
Content:

- **Introduction (short) to the use of Fullerenes for biological applications**
- **Carbohydrate-protein interactions**
- **Synthesis of [60]Fullerene derivatives as "multivalent" Scaffold**
- **Glycofullerenes as new and potent inhibitors of viral Infection**
- **Other carbon nanoforms (SWCNT and SWCNH) as "multivalent" scaffolds**





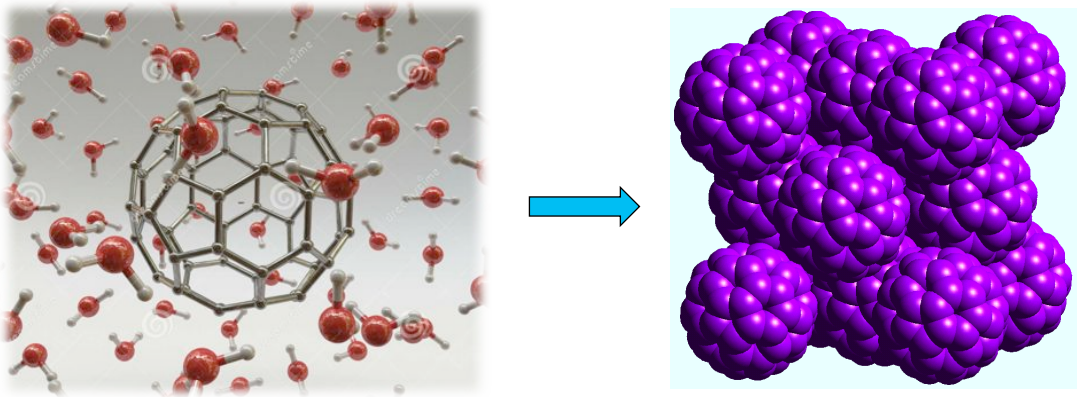
Biological Applications of Fullerenes?



C_{60} in toluene

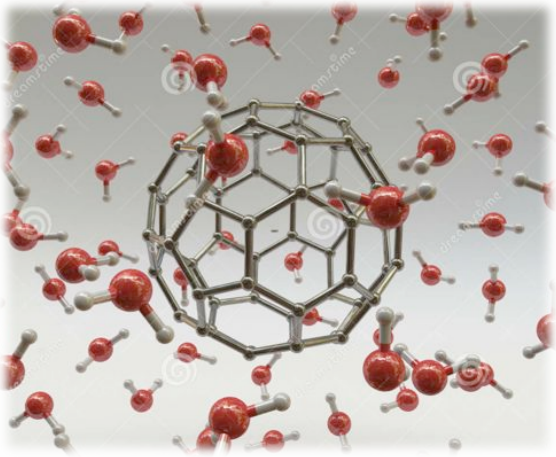
- Fullerene C_{60} is a **toxic molecule** which is insoluble in water!!!

Biological Applications of Fullerenes?



- Fullerenes in contact with water form toxic colloidal aggregates (nC_{60}).
- Clusters of C_{60} can cause oxidative damage to lipids in the brains of fish.
- C_{60} is highly hydrophobic and redox active, therefore, it can potentially cause oxidative damage. Water dispersed C_{60} provokes oxidative stress in the brain of largemouth bass and depletion of glutathione in the gills of fish.
- This *in vivo* study, showing the adverse effect of C_{60} in aquatic species, may predict potential effects in humans.

Biological Applications of Fullerenes?

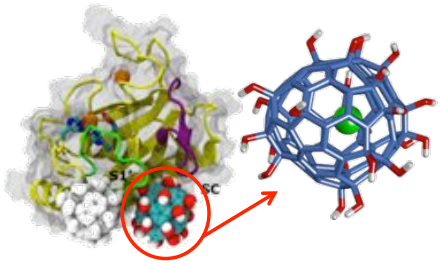


- Fullerene C_{60} is a **toxic molecule** which is insoluble in water!!!

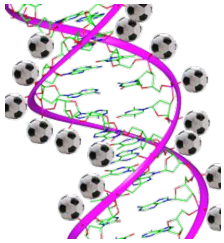
- Therefore, different strategies have been explored to **render fullerenes biocompatible**.
- **Solubilization** and **chemical functionalization** are the starting point to integrate this material into living systems (aminoacids, sugars, cyclodextrins, etc)

Biological Applications of Fullerenes?

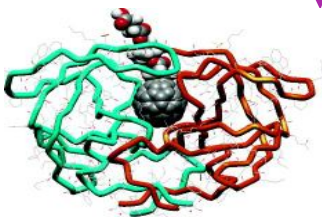
Suitably functionalized, fullerenes show interesting biological properties

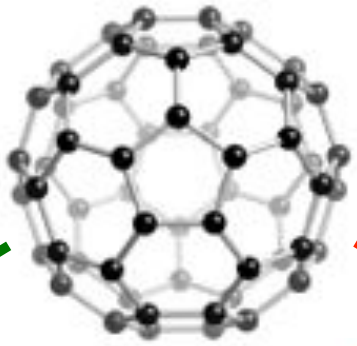


Anticancer and
Inmunological properties

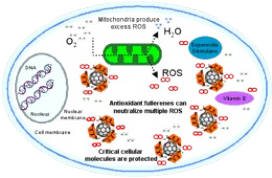


Fullerenes as antiviruses

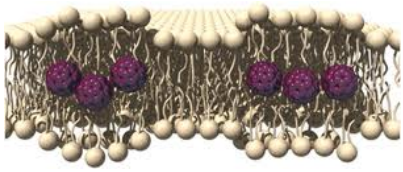




Photodynamic Therapy

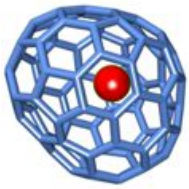


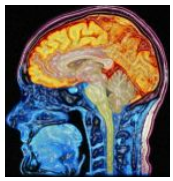
Fullerenes for drug delivery



Neuroprotection and antioxidants

Fullerenes for MRI





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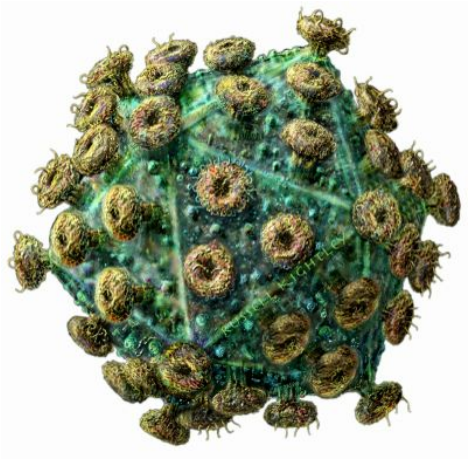
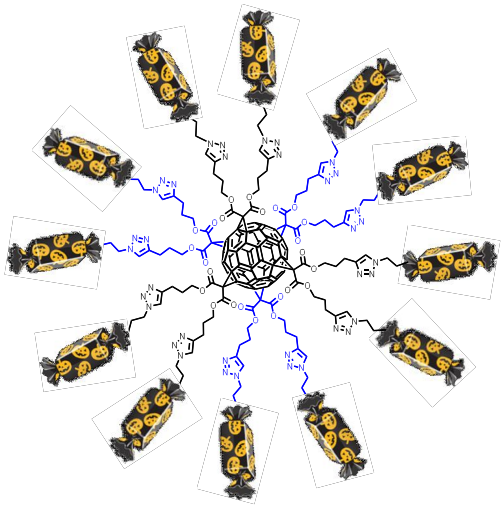
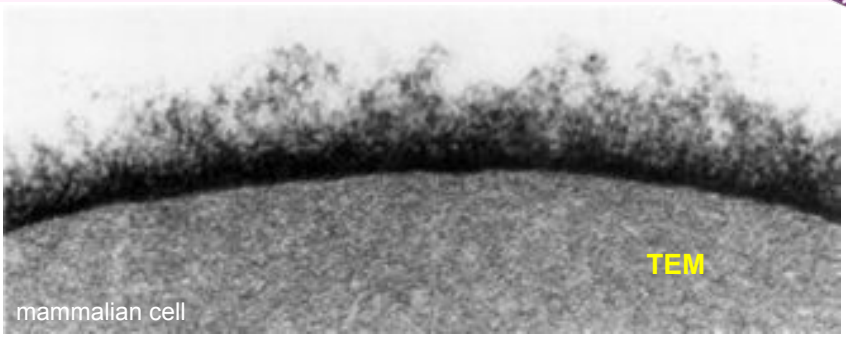




Carbohydrate Interactions

Glycocalyx

- Protection
- Social Behaviour



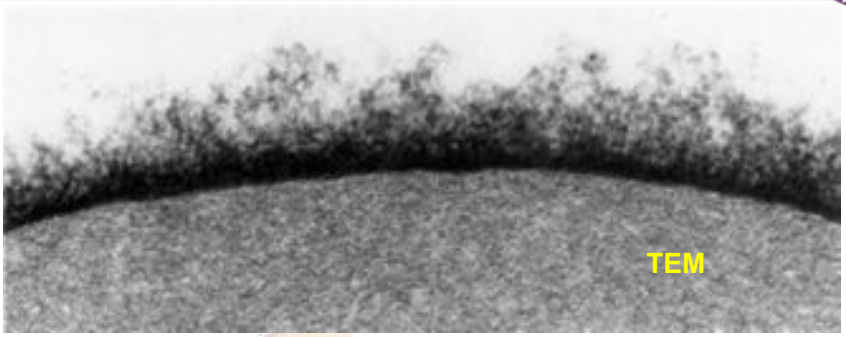
Funtions of glycocalyx:

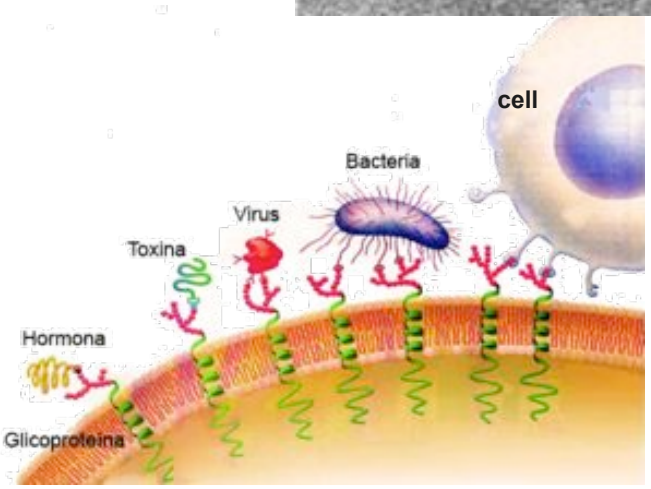
• **Protection**: Cushions the plasma membrane and protects it from chemical injury.
• **Immunity to infection**: Enables the immune system to recognize and selectively attack foreign organisms.
• **Defense against cancer**: Changes in the glycocalyx of cancerous cells enable the immune system to recognize and destroy them.
• **Transplant compatibility**: Forms the basis for compatibility of blood transfusions, and organ transplants.
• **Adhesion**: Binds cells together so that tissues do not fall apart
• **Inflammation regulation**: Glycocalyx coating on endothelial walls in blood vessels revents leukocytes from rolling/binding in healthy states
• **Fertilization**: Enables sperm to recognize and bind to eggs
• **Embryonic development**: Guides embryonic cells to their destinations in the body.

Carbohydrate Interactions

Glycocalyx

- Protection
- Social Behaviour



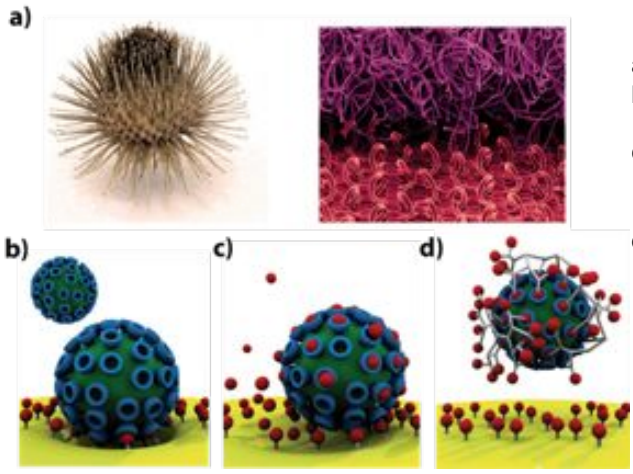


Carbohydrate-protein Interactions

- **Highly selective**
- **Calcium dependent**
- **Low affinity**
- **Multivalent interaction**

Multivalence

MULTIVALENT SYSTEMS AND INTERACTION WITH THE GLYCOME

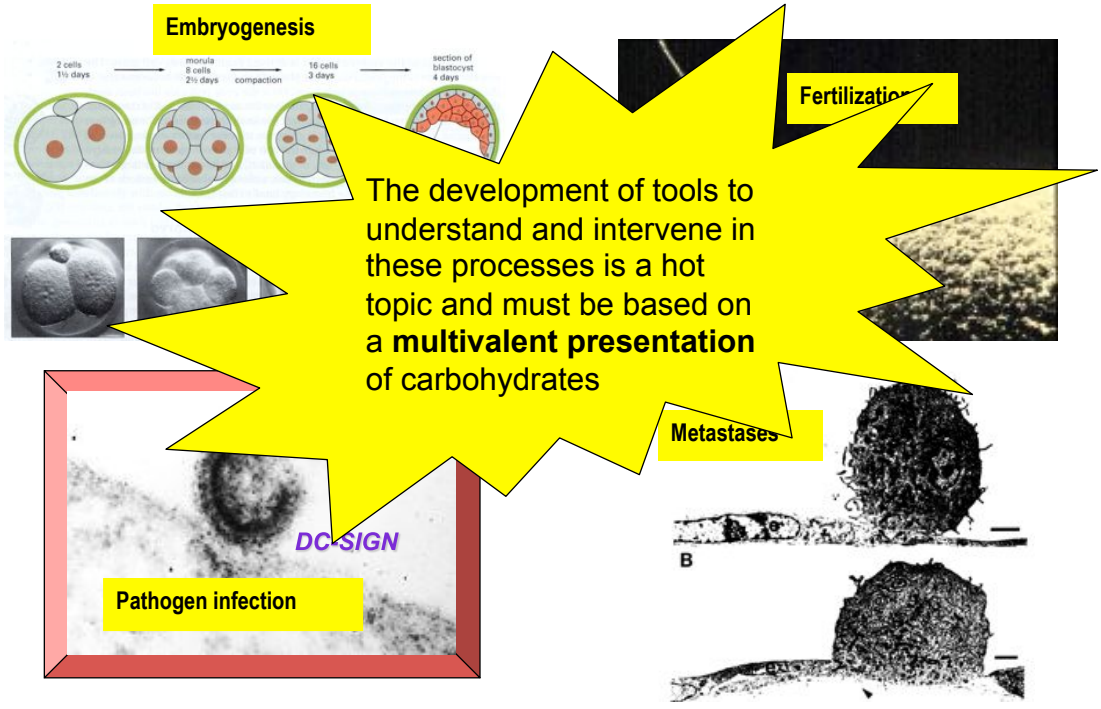


a) Bardane fruits and Velcro™
b) A virus connecting to many celular receptors
c) Linkage in the presence of a monovalent inhibitor (farmacological classical approach)
d) Inhibiting the linkage and infection by using a multivalent inhibitor

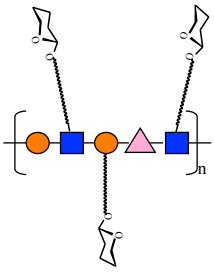
R. Haag *et al. Angew. Chem. Int. Ed*. **2012**, *51*, 10472.

Biological examples

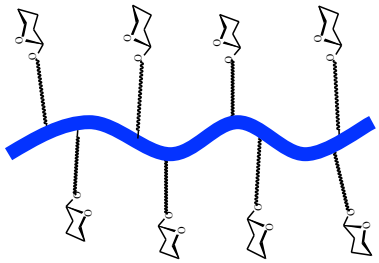
(natural and pathogenic processes)



Carbohydrate Multivalent Architectures
(synthetic scaffolds)



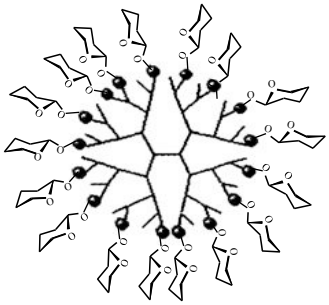
Glycopetides and Glycoproteins



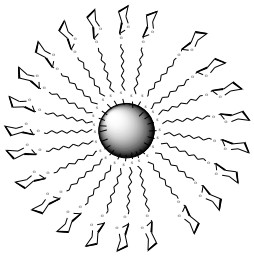
Glycopolymers

Glycocyclodextrines and glycocalixarenes

Glycoliposomes



Glycodendrimers

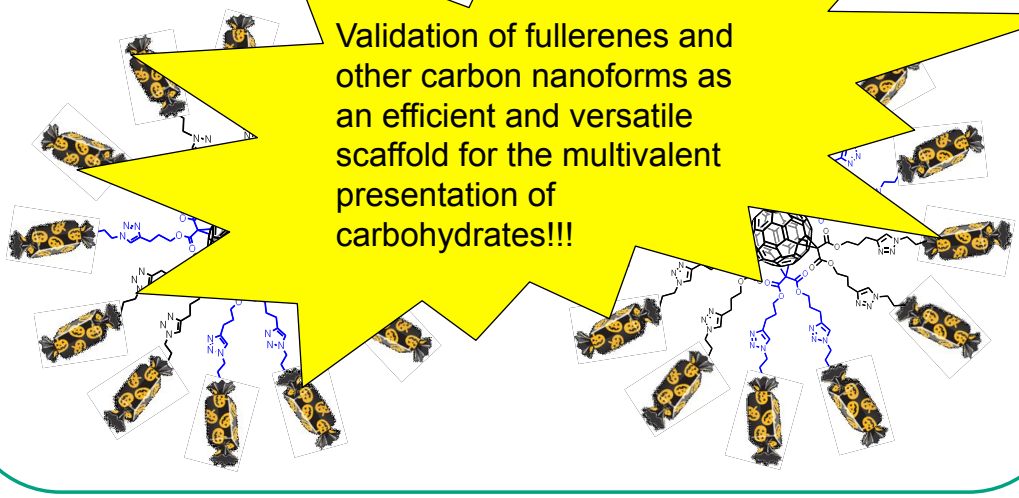


Glyconanoparticles

Goals

SYNTHESIS OF NEW WATER SOLUBLE C_{60} DERIVATIVES
(biocompativility and toxicity effects. Globular shape and size control)

Hexaaducts of [60]fullerene fu...lized...ohydrates



Synthetic approach based on Bingel reaction and further 1,3-dipolar cycloadditions between alkynes and azides catalyzed by Cu(I) (CuAAC).

Synthesis

CHEMICAL MODIFICATION OF FULLERENES:
Toward water soluble fullerenes

Optimizing the CuAAC reaction

N_3

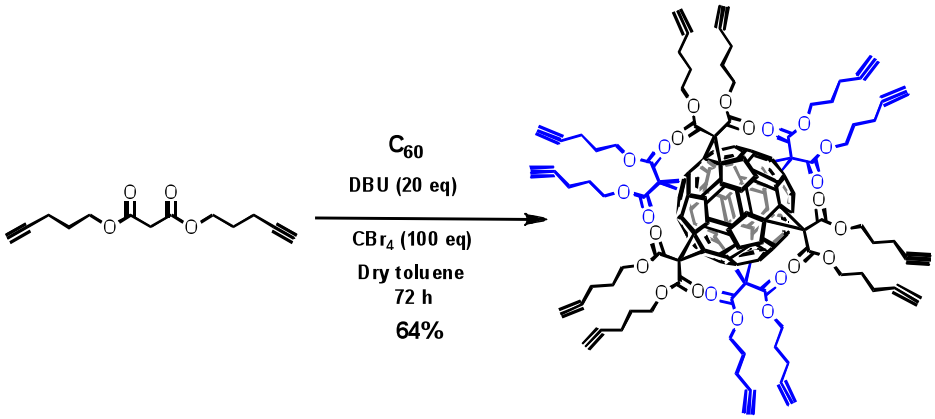
Click Chemistry

Reaction conditions:

Catalyst: $CuBr{\cdot}S(CH_3)_2$/ Cu^0
Solvent: DMSO
Reductant: Sodium ascorbate

Synthesis

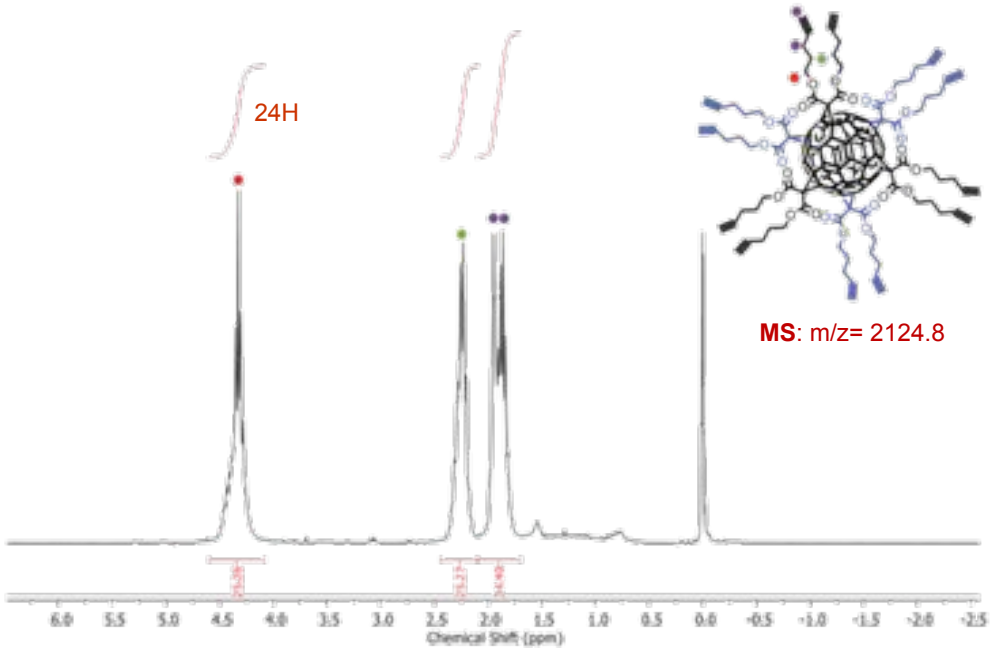
SYNTHESIS AND CHARACTERIZATION OF C_{60} HEXAADUCTS



Chem. Eur. J. **2011**, *17*, 766.

Synthesis

SYNTHESIS AND CHARACTERIZATION OF C_{60} HEXAADUCTS

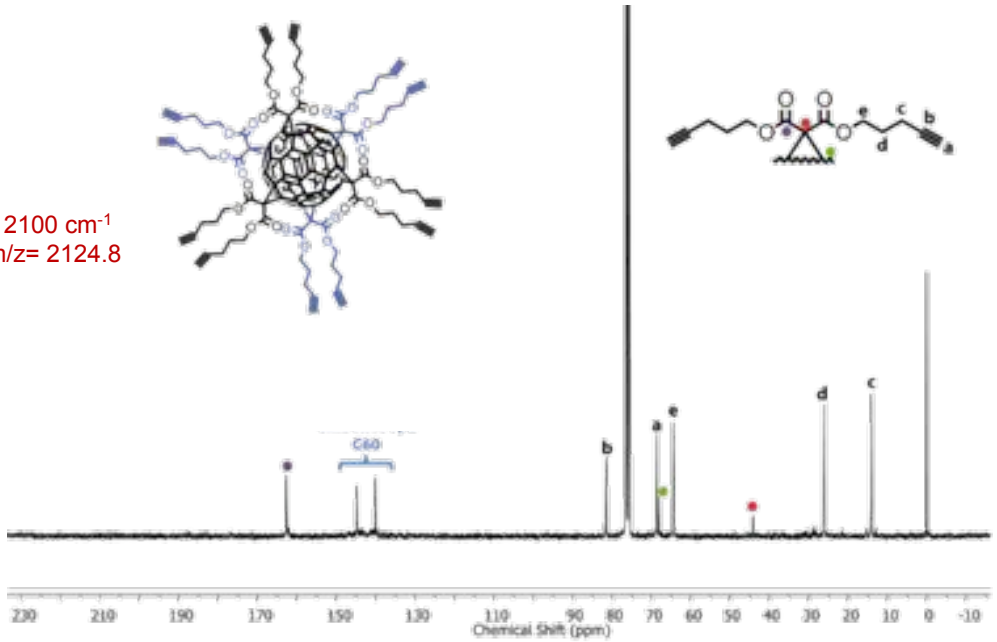


^{1}H-NMR (700 MHz, $CDCl_3$, 298 K) of alkyne-substituted hexaadduct showing its 84 protons

Synthesis

SYNTHESIS AND CHARACTERIZATION OF C_{60} HEXAADUCTS

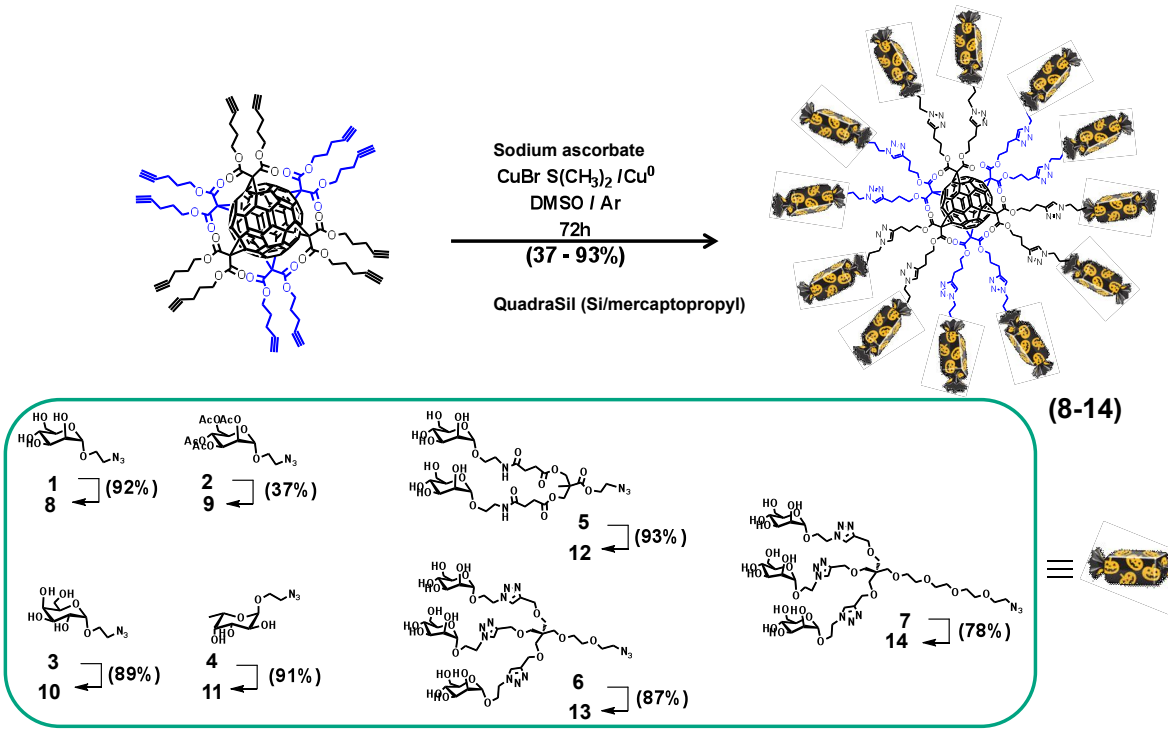
FTIR: 2100 cm^{-1}
MS: m/z= 2124.8



^{13}C-NMR (175 MHz, $CDCl_3$, 298 K) of alkyne substituted hexaadduct (**only 2 sp^2 carbons of fullerene!!!**)

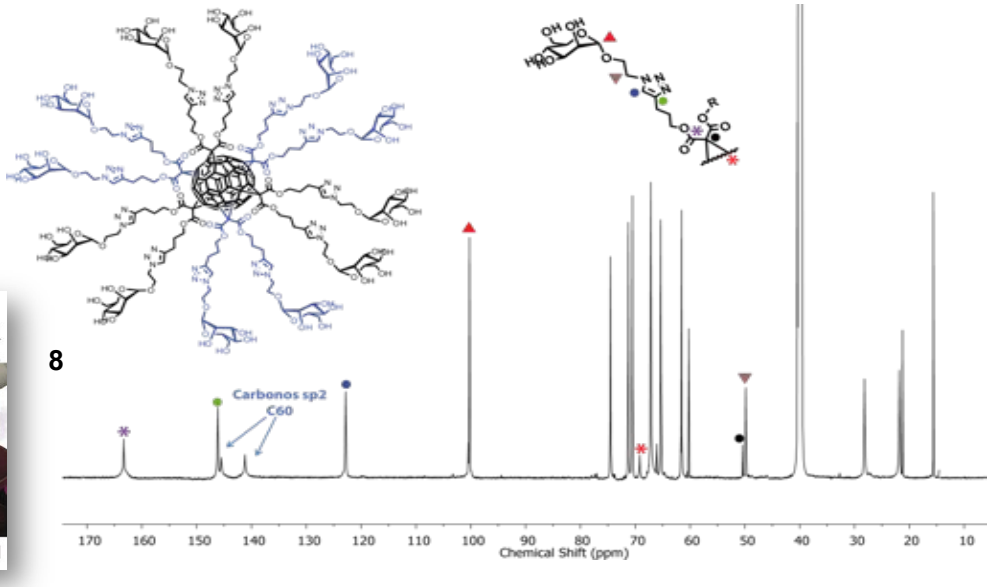
Synthesis

SYNTHESIS AND CHARACTERIZATION OF C_{60} HEXAADUCTS



Synthesis

SYNTHESIS AND CHARACTERIZATION OF C_{60} HEXAADUCTS

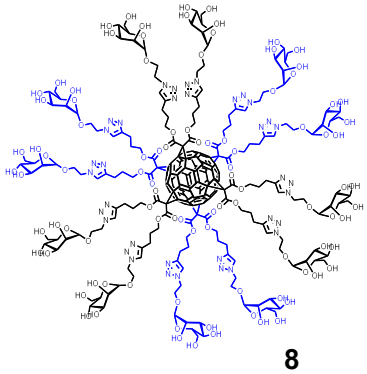


^{13}C-NMR spectrum (175 MHz, DMSO-d_6, 298 K) of compound **8**

Chem. Commun. **2010**, *46*, 3860.

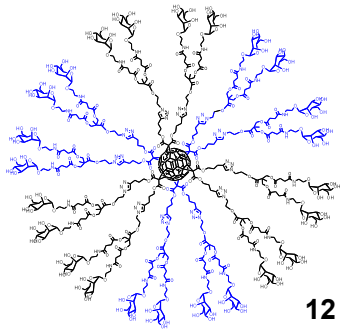
Properties

Interaction between lectines and glycofullerenes



8

- Excellent multivalent ligand
- Validation of fullerenes as efficient plataform for the multivalent presentation of carbohydrates

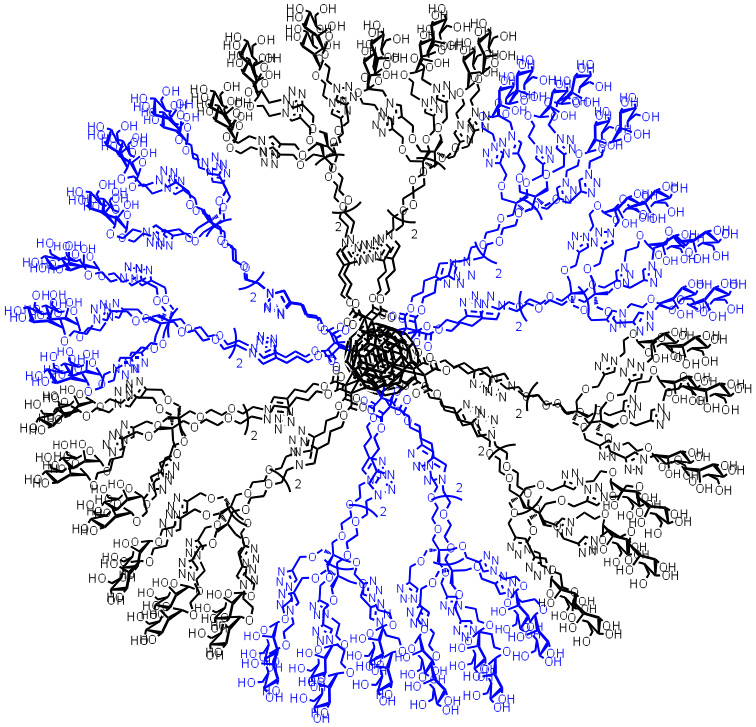


12

- Increased valence in carbohydrates, but poorer interaction with Con A
- Possible steric congestion and self-association phenomena

Chem. Eur. J. **2011**, *17*, 766.

Diferent Molecular Sructures



¡¡36 CARBOHYDRATES PER MOLECULE!!

We increase the number of carbohydrates per molecule as well as the spacer length…

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