MINISTRY OF EDUCATION, LIFELONG LEARNING AND RELIGIOUS AFFAIRS
GENERAL SECRETARIAT FOR RESEARCH & TECHNOLOGY
NATIONAL CENTER FOR SCIENTIFIC RESEARCH "DEMOKRITOS"

INSTITUTE OF PHYSICAL CHEMISTRY
Molecular & Supramolecular Chemistry and Chemical Biology
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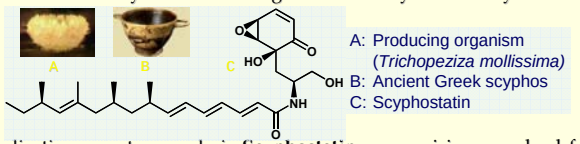
Natural Products Synthesis

Natural products (secondary metabolites; naturally occurring small organic molecules), with their diverse and often complex structures and important biological activity: i) play a pivotal role in modern *drug discovery*, ii) they are valuable tools for *Chemical Biology* (i.e. the exploration of biological systems using chemistry techniques) and, iii) historically, they define the *state of the art of organic chemistry*. The synthesis of natural products or designed analogues is pursued by the "Natural Products Synthesis & Bioorganic Chemistry" laboratory.



A: Producing organism (*Trichopeziza mollissima*)
B: Ancient Greek scyphos
C: Scyphostatin

An indicative recent example is **Scyphostatin**, a promising new lead for the development of novel therapeutics for the treatment of inflammation, immunological and neurological disorders: A *concise synthetic strategy* for the preparation of the pharmacophoric core has been developed.[1] It has lead to the discovery of an *equipotent simplified analogue*[2] that was used as a *molecular probe* to study malignant pleural effusion[3] and has paved the way for the *total synthesis* of the natural product, in collaboration with the group of Prof. E.-I. Negishi (Nobel Prize in Chemistry, 2010).[4]

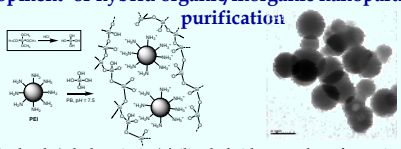
References: 1. *Org. Lett.* **2005**, *7*, 2245–2248; *Greek Patent*: 1005093 issued January 13, **2006**. 2. *ChemMedChem* **2006**, *1*, 718–721. 3. *Cancer Research* **2007**, *67*, 9825–9834. 4. *Chem. Commun.* **2010**, *46*, 2200–2202.

Nanomaterials for water purification

Dendritic Polymers on ceramic supports for the Production of Ultrapure Water

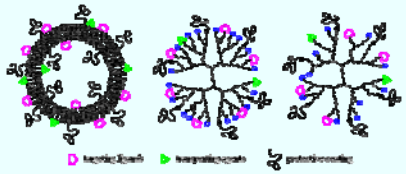
SEM micrograph of the interior of Al_2O_3 filters impregnated with alkylated poly(ethylene imine) hyperbranched polymer (left) and the developed filter module (right) for water purification.

Development of hybrid organic/inorganic nanoparticles for water purification



Hyperbranched poly(ethylene imine)/silica hybrid nanosphere formation process (left) and TEM micrograph of the resulting hybrid organic/silica nanoparticles (right)

Nanomaterials as Drug Delivery Systems



Multifunctional liposomes, Dendrimers and Hyperbranched Polymers as Drug and gene Delivery Systems

ANTIBIOTICS OF THE FUTURE

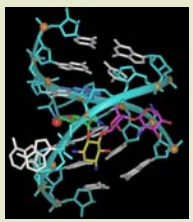
CHEMICAL BIOLOGY LABORATORY
(http://vourloumis_group.chem.demokritos.gr/)

THE DISCOVERY PROCESS

THE PROBLEM: The discovery of antibiotics, small molecules of natural and synthetic origin that specifically interfere with biological processes in bacteria, has been one of the major breakthroughs of medicine in the 20th century, allowing the treatment of life-threatening infectious diseases and, thus, saving millions of lives. Early after their discovery, emergence of resistance mechanisms has been observed in bacteria, which counter their action. The challenge of antibiotic resistance is particularly severe as most antibacterial drug classes used today have been in the clinic for more than 30 years.

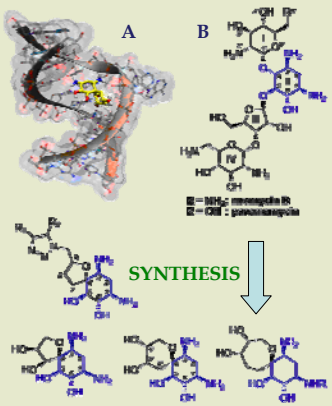
THE TARGET: The **Nobel Prize in Chemistry for 2009** was awarded for studies of one of life's core processes: **the ribosome's translation of DNA-information into life**. As ribosomes (Figure 1) are crucial to life, they are also a **major target for new antibiotics** (*Acc. Chem. Res.* **2001**, *34*, 836-843).

Figure 1. Molecular representation of the Bacterial Ribosome with all ribosomal RNAs and proteins.



TARGETING: **Aminoglycoside antibiotics** are currently the only well-characterized class of small natural products that selectively bind RNA at the decoding site (**A-site**) of the bacterial ribosome (Figure 2) (*Nature* **1994**, *370*, 659-662).

Figure 2. Molecular representation of neomycin bound to the A-site (co-crystallization data).



Computational Chemistry revealed the **spiro-skeleton** shown in figure 3A capable of **mimicking the desired interactions** within the biological target, with similar structural characteristics as neomycin (*ChemBioChem* **2011**, *12*, 1188-1192; *ChemBioChem* **2011**, *12*, 71-87; *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7488-7492; *ChemBioChem* **2009**, *10*, 1969-1972).

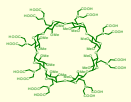
The designed analogues (Figure 3B) have been synthesized and are currently under **biological evaluation** against **bacterial infections, Hepatitis C** and **HIV**.

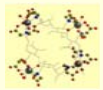
Figure 3. A) Surface representation of RNA / A-site complex with the spiro-compound shown in yellow. **B)** Evolution of neomycin B to the new antibiotics **through synthesis**.

Novel Antibiotics of the future

New cyclodextrin materials for improved contrast in MAGNETIC TOMOGRAPHY (MRI)

PATEND: Greek Patent No 1006924, priority date Sept. 2009

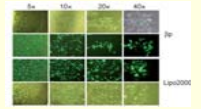




Derivatives of cyclodextrins synthesised from inexpensive parent compounds bind gadolinium (III) ions and give **new**, **non toxic MRI contrasting agents** with significantly **improved characteristics compared to existing contrast agents** (*Org. Biomol. Chem.* 2010 *8, 1910)*

Cell penetrating cyclodextrins (CPCDs) for Drug and gene delivery

PATENTS
Greek Patent: 1004952, priority date 10 Sept. 2004
US Patent: US7,834,174 B2, No. 11/662,450, Nov. 16, 2010
European patent: EP05731803.2, Jan. 19, 2011-03-04



CPCDs perform gene transfection

Fluorescence of CPCDs inside cells (*Chem. Eur. J.* **2008**, *14*, 4188)

CPCDs block pore-forming toxins (*Antimicrob.AgentsChemother.* **2011**, 55, 3594)

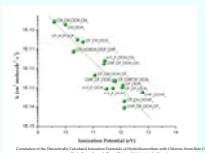
Next generation of cyclodextrin-based drug carriers

NCSRD coordinates *CYCLON* a EU PEOPLE-ITN 4-year project involving 8 academic groups and 1 private company from Europe.

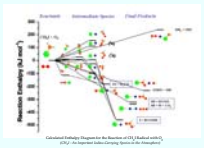
'Smart materials' to boost new drug research

N.C.S.R. "Demokritos", Imperial College London and U of Surrey scientists have developed a new method to induce protein crystallisations using **'smart materials'** (Molecularly imprinted polymers, MIPs) that remember the protein shape (*Proc. Natl. Acad. Sci. U.S.A.* 2011, *108*, 11081-11086)

Quantum-Mechanical Calculations of Molecular Structure and Material Properties



Reactivity Prediction for Potential Substitutes of CFC (Freons)
Environmental Impact Assessment of New CFC Substitutes
Cost-Effective Design of Industrial Molecular Materials



Degradation Mechanism of Natural and Anthropogenic Compounds
Determination of Atmospheric Degradation Products
Assessment of the Impact of Substances on Atmospheric Quality