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UNIVERSITÀ DEGLI STUDI DI SASSARI

Società Chimica Italiana

Università di Cagliari

MEDINLAB s.r.l.

La parola ai giovani 2016

Venerdi 28 Ottobre 2016, Dipartimento di Chimica e Farmacia Complesso Didattico, Aula Consiliare, Via Vienna 2, Sassari

Il comitato organizzatore:

Prof.ssa Lidia De Luca
Prof. Giuseppe Baldovino Suffritti
Dr.ssa Silvia Gaspa
Prof. Gianpiero Boatto
Dott. Massimo Carraro
Dott.ssa Gloria Modugno
Dott. Massimiliano Peana
Dott.ssa Laura Maiore

La XIV edizione del convegno “La Parola ai Giovani”, organizzato quest’anno dall’Università degli Studi di Sassari con il patrocinio della SCI, Società Chimica Italiana (Sezione Sardegna), dà la possibilità, come dice il titolo stesso del convegno, ai giovani ricercatori di esporre i risultati delle loro ricerche sia come presentazione orale sia sotto forma di poster.

Società Chimica Italiana

Sezione Sardegna

Si ringraziano la MedinLab srl e il Laboratorio Leonardi per il supporto finanziario e il Dipartimento di Chimica e Farmacia per il sostegno alle attività di organizzazione del Convegno.

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Il comitato organizzatore

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Dott. Massimiliano Peana

Dott.ssa Laura Maiore

Programma

h 09:00 – 09:30	**Registrazione partecipanti**
h 09:30 – 09:45	**Apertura dei lavori**
h 09:45 – 10:45	**Prof. Elzbieta Lodyga-Chruscinska** - *Physicochemical and biological properties of a hesperetin hydrazone*
h 10:45 – 11:00	**Coffee break**
h 11:00 – 11:20	**Giovanni Pireddu** - *Self-diffusion in microporous materials: a reductionistic representation*
h 11:20 – 11:40	**Monica Demurtas** - *Design, synthesis and pharmacological investigation of new DNA methyltransferase inhibitors*
h 11:40 – 12:00	**Sara Pischedda** - *Synthesis and characterization of Pt^{II} and Pd^{II} complexes*
h 12:00 – 12:20	**Mondina Sedda** - *Recent advances in Pt(II) rollover chemistry*
h 12:20 – 12:40	**Giancarlo Simula** - *Mn-peptides complexes involved in γ-radiation resistance in Deinococcus radiodurans*
h 12:40 – 14:30	**Pausa pranzo**
h 14:30 – 15:30	**Sessione poster**
h 15:30 – 15:50	**Davide Moi** - *Ureidoarylsulfamates acting as carbonic anhydrase inhibitors*
h 15:50 – 16:10	**Alessio Pelucelli** - *The coordination properties of a small peptide fragment from Human TLR4 sequence are relevant in Nickel Allergy mechanism*
h 16:10 – 16:30	**Luca Nuvoli** - *Double Responsive Copolymer Hydrogels Prepared by Frontal Polymerization*
h 16:30 – 17:00	**Chiusura dei lavori**

O1

Self-diffusion in microporous materials: a reductionistic representation

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Zeolites and other microporous materials are currently employed in several fields and for different purposes, such as separation of gas from mixtures and heterogeneous catalysis.
Sufficiently small molecules are capable of being adsorbed and diffuse through material's pores [1]. In this context, computational and theoretical chemistry can provide mathematical models and numerical simulations in order to describe, represent and simulate phenomena of interest in this kind of molecular systems [2].
Given the absence of macroscopic gradients, self-diffusion is a measure of molecular motion's efficiency. In order to develop more efficient *in silico* simulations and to investigate larger space-time scales, a reductionistic representation of diffusion under tight confinement is of great interest.
In this work we present a method to represent self-diffusion in microporous materials, without considering single species identities, without requiring any microscopic dynamics to be defined, which transfers all the relevant matter exchange properties of the whole system into the properties of one single cavity of the host material and yet maintaining a description of correlations between guest molecules.

References

[1] J. Karger and D. M. Ruthven, *"Diffusion in Zeolites and Other Microporous Materials"*, 1st ed., Wiley, New York, **1992**

[2] F. Pazzona, G. B. Suffritti and P. Demontis, *J. Chem. Phys.* 12, 194709, **2007**

O2

DESIGN, SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF NEW DNA METHYLTRANSFERASE INHIBITORS

Monica Demurtas(1), Gianfranco Balboni(1), Alessandro Deplano(1), Paola B. Arimondo(2), Veronique Masson(2), Valentina Onnis(1)

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2)USR 3388 Pharmacochimie de la régulation epigénétique du cancer, CNRS-Pierre Fabre, BP 13562 - 3 avenue Hubert Curien 31 035 Toulouse Cedex 01, France

Epigenetic modifications regulate gene expression in response to environmental factors without modifying the DNA sequence. Epigenetic regulation is essential in physiological processes and is also involved in many diseases, including cancer[1]. In humans, DNA methylation is the most stable epigenetic mark and it is catalyzed by C5-DNA methyltransferases (DNMTs) and their expression is increased in various tumors, making therefore DNMTs attractive therapeutic targets[2-3]. Several DNMT inhibitors with nucleoside or non-nucleoside structure (DNMTi) have been proposed to treat cancers. Despite their high efficiency, the nucleoside analogs use is limited by the poor bioavailability and by undesired side effects[4]. Thus non-nucleoside DNMTis might be safer and more drugable. We have recently reported identified N-phthaloyl-L-tryptophan **(RG108)** as lead compound[5]. The findings led us to design a new series of DNMT inhibitors (Figure 1) by replacement of the indole with a benzimidazole ring, by modification of carboxylate and phthalimide moieties, and by preparation of homologues and simplified analogs.

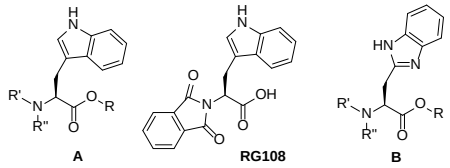

Figure 1. The lead compound RG108 and its analogs A and B.

References:

1. Portela, A. et al, Nat. Biotechnol. **2010**, 28, 1057−1068.
2. Jurkowska, R. Z.; et al, ChemBioChem. **2011**, 12, 206−222.
3. Fahy J. et al, Expert Opin. Ther. Pat. **2012**, 22, 1427−1442.
4. Issa J. P. et al, Clin. Cancer Res. **2009**, 15, 3938−3946
5. Brueckner, B.; Arimondo, P.B. et al, J. Med. Chem. **2014**, 57, 421−434

O3

Synthesis and characterization of Pt^{II} and Pd^{II} complexes

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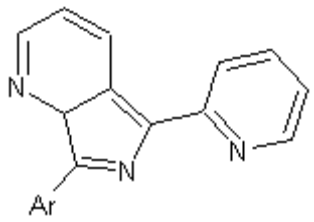
The cyclometalation reactions of 6-substituted-2,2'-bipyridine with transition metal ions in d^8 configuration, platinum(II), palladium(II) and gold(III), are well known. In this work, we report the attempts to obtain ciclometallate species with a series of N-heterocyclic ligands of pyridyl-imidazole type with formula:



Ar = Ph, o-tolyl, mesityl and benzyl.

Up to now, unlike the 6-substituted-2,2'-bipyridine only adducts have been obtained, despite the considerable efforts on the ligand to promote the cyclometalation (modification of the substituents on the ring, insertion of spacers). Among these adducts, the structure of the one with the Pd centre has been resolved by X-Ray Diffraction method.
Different experimental conditions are under investigation to obtain some new derivatives with Pd^{II} and Pt^{II}. In addition, the survey will be extended to the ion Au^{III}.

O4

Recent advances in Pt(II) rollover chemistry

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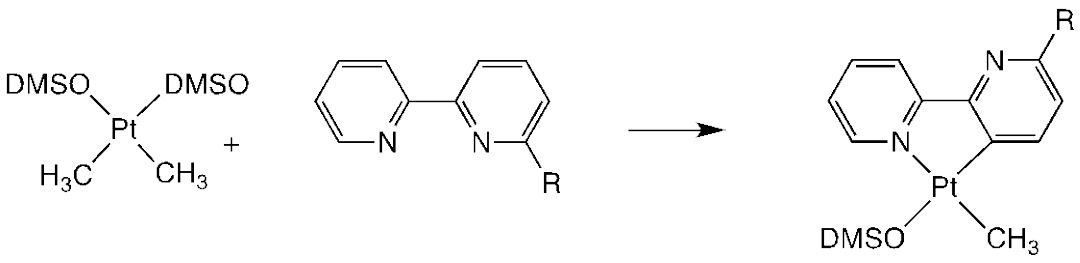
Rollover cyclometalation is a special case of intramolecular C-H bond activation shown by only a few bidentate heterocyclic ligands.[1] Following our long-standing interest in this field we recently started to investigate the influence of steric and electronic factors in both the activation process and the properties of the corresponding cyclometalated complexes.[2]

Herein we present our most recent results regarding a series of 6-substituted-2,2'-bipyridines (bpy^R R=Me, Et, OMe, CF_3, etc) where the substituents furnish different electronic and steric properties. In the case of 6-MeO-2,2'-bipyridine the substituent has a double nature, electron-releasing (positive mesomeric effect, +M) and electron-withdrawing (negative inductive effect, -I).

By reaction of electron-rich Platinum(II) precursors several rollover platinum(II) species were synthetized and characterized. The reactivity and properties of the new complexes were studied and compared.



R = Me, Et, OMe

References

[1] (a) B. Butschke, H. Schwarz; *Chem. Sci.*, **2012**, *3*, 308. (b) A. Zucca, G. L. Petretto, S. Stoccoro, M. A. Cinellu, M. Manassero, C. Manassero, and G. Minghetti, *Organometallics*, **2009**, *28*(7), 2150.

[2] L. Maidich, G. Dettori, S. Stoccoro. M.A. Cinellu, J.P. Rourke and A. Zucca, *Organometallics*, **2015**, *34*, 817−828.

O5

Mn-peptides complexes involved in γ-radiation resistance in *Deinococcus radiodurans*

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Deinococcus Radiodurans (Dr) is a bacterium which has drawn a lot of attention on its extraordinary radioprotective properties since its discovery in 1956. Different authors have reported that Mn-peptide complexes, isolated from Dr cell-free extract, could act as scavenging agents by neutralizing ROS molecules induced through radiation exposure [1]. In this study we have investigated the interaction between Mn(II) and two different peptides, DP1(DEHGTAVMLK) and DP2 (THMVLAKGED), as a model of the antioxidative mechanism in Dr. The amino acid composition of these peptides was chosen randomly on the basis of their natural abundance in the Dr protein-free cell extract (ultrafiltrate). We have focused our attention on the coordination of Mn(II) with DP1 and DP2 peptides by using NMR, EPR and ESI-MS techniques. Additionally, competition experiments have been done to study the equilibrium between Mn-peptides and Mn-phosphate complexes, which, according to recent findings, could be a key point to explain the radiation resistance of Dr [2].

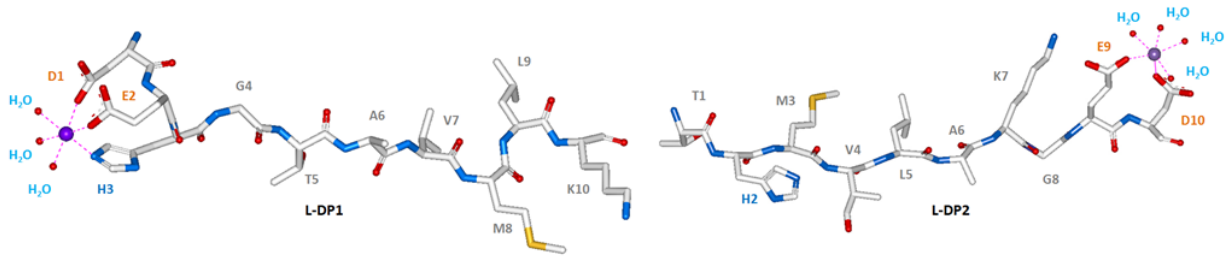

Figure 1: models of the Mn(II)-DP1 and DP2 complexes [2].

References:

[1] P. Gupta, M. Gayen, J.T. Smith, E.K. Gaidamakova, V.Y. Matrosova, O. Grichenko, B. Knollmann-Ritschel, M.J. Daly, J.G. Kiang, R.K. Maheshwari, *PLoS One*, **2016,** *11* e0160575.
[2] M. Peana, S. Medici, H.A. Pangburn, T.J. Lamkin, M. Ostrowska, E. Gumienna-Kontecka, M.A. Zoroddu, *J Inorg Biochem*, **2016,** doi 10.1016/j.jinorgbio.2016.08.012

O6

UREIDOARYLSULFAMATES ACTING AS CARBONIC ANHYDRASE INHIBITORS

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Carbonic anhydrases (CA) are a superfamily of widespread metallo-enzyme which catalyze the conversion of carbon dioxide (CO_2) into bicarbonate (HCO_3^-) and protons (H^+)[1]. These enzymes are involved in many physiopathologic processes, for this reason a lot of CA inhibitors have been reported for their antiglaucoma, antiepilepsy, anticancer activity. In growing cancer cells, the CA9 and CA12 isoforms are overexpressed due to their involvement in pH control and tumor survival[2]. Recently SLC-0111, a selective CA9 and CA12 inhibitor, entered in Phase I clinical trials[3]. Based on these results we designed new analogs of SLC-011. In this comunication the synthesis and biological evalutation of a new class of ureidoarylsulfamates (Figure 1) will be described.

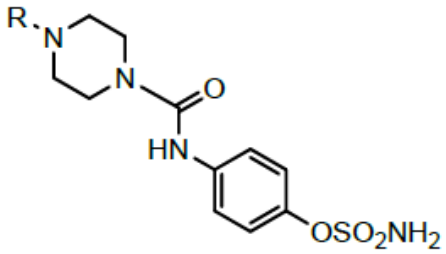

Figure 1: General structure of new ureidoarylsulfamates

References:

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[2] Alterio V., Hilvo M., Di Fiore A., Supuran C. T., Pan P., Parkkila S., Scaloni A., Pastorek J., Pastorekova S., Pedone C., Scozzafava A., Monti S. M., De Simone G. PNAS 106 (2009):16233-16238.
[3] Congiu C., Onnis V., Deplano A., Balboni G., Ceruso M., Supuran C.T. Bioorg. & Med. Chem. 23 (2015): 5619-5625.

07

The coordination properties of a small peptide fragment from Human TLR4 sequence are relevant in Nickel Allergy mechanism.

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Nickel Allergy (NA) is a contact allergy which could occur in sensitised persons exposed for long periods of time to objects containing Nickel. In recent years, the human TLR4 (hTLR4) has been recognized as a key target in the Nickel-induced inflammation that eventually lead to allergy symptoms [1]. A peptide of 32 amino acids from 429-460 sequence of hTLR4 receptor has been selected as a simplified model to study the molecular mechanism of NA. The fragment contains three histidines, the non-conserved H_{431}, and the conserved H_{456} and H_{458} in human (Fig. 1) which could be important for Ni(II) activation hTLR4 and to trigger an inflammatory response. The aim of our study was to confirm the coordination ability of a peptide fragment toward the H_{456} and H_{458} histidines potentially involved in hTLR4 activation. Spectroscopic (NMR, UV-Vis, CD, MS) and potentiometric techniques confirm the important role of the histidine-rich 429-460 hTLR4 fragment in Ni(II) coordination and its relevance in NA mechanism [2].

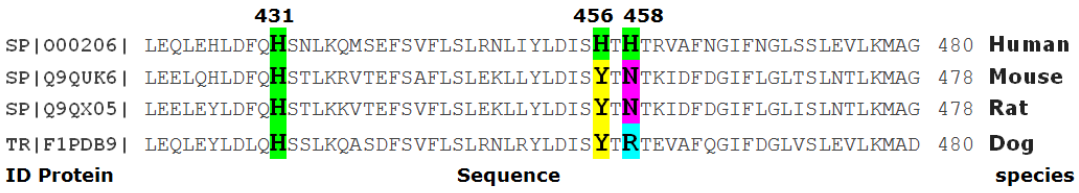

Figure 1: Species-specific hTLR4 activation requires distinct sequence motifs present in humans and other primates but not in mouse or dog, a species not sensitive to nickel-induced allergies.

References:

[1] M. Schmidt, B. Raghavan, V. Müller, T. Vogl, G. Fejer., S. Tchaptchet, S. Keck, C. Kalis, P. J. Nielsen, C. Galanos, J. Roth, A. Skerra, S. F. Martin, M. A. Freudenberg, M. Goebeler, *Nat. Immunol.*, **2010**, 11(9), pp. 813-820.
[2] M. A. Zoroddu, M. Peana, S. Medici, S. Potocki and H. Kozlowski, *Dalton Trans.*, **2014**, 43, pp.2764-2771.

O8

Double Responsive Copolymer Hydrogels Prepared by Frontal Polymerization

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Frontal polymerization [1] was successfully used to synthesize copolymer hydrogels [2] of poly(N-vinylcaprolactam-co-itaconic acid). All materials were characterized by response to stimuli (pH and/or temperature), depending on the itaconic acid content. Namely, relatively low amounts of this latter were found to be crucial for determining the degree of swelling. In particular, hydrogels behave differently if swollen at pH values that are higher or lower of 7–8 (Figure 2), and exhibit temperature response as well (lower critical solution temperature at ca. 30 °C, figure 1), which makes these materials potentially interesting for biomedical applications.

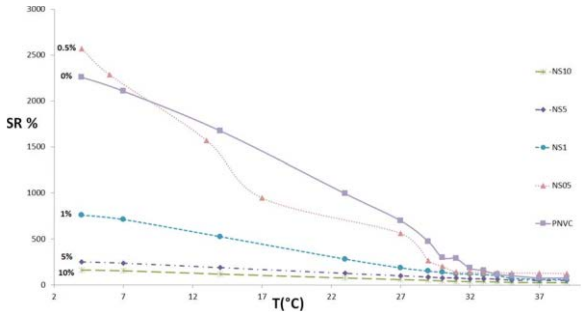

Figure 1: SR% as a function of temperature for samples containing various IA amounts (reported on the left of any corresponding curve)

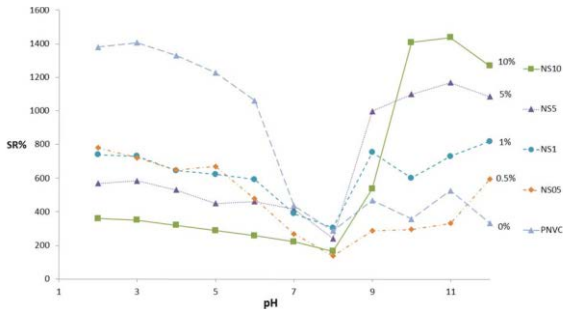

Figure 2: SR% as a function of pH for samples containing different IA amounts (reported on the right of any corresponding curve)

References:

[1] R. Sanna, D. Sanna, V. Alzari, D. Nuvoli, S. Scognamillo, M. Piccinini, M. Lazzari, E. Gioffredi, G. Malucelli, A. Mariani, J. Polym. Sci. Part A: Polym. Chem., 2012, 50, 4110–4118
[2] D. Nuvoli, V. Alzari, L. Nuvoli, M. Rassu, D. Sanna, A. Mariani, Carbohydrate Polymers, 2016, 150, 166–171

P1

Natural collagenic skeleton of marine sponges in pharmaceutics: innovative biomaterial for topical drug delivery

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Sponges are the most ancient multicellular animals alive on the planet today [1]. The value of the proteic skeleton of sponges is linked to their soft and elastic texture and they were also appointed to promote wound healing. Some sulfur amino acids, such as cysteine, play a vital role in re-establishing wound inflammation. The present work focuses on the use and valorization of natural skeleton of marine sponges as bio-based dressing for the topical delivery of L-cysteine hydrochloride (CysHCl). Characterization studies of the sponges were performed, i.e morphology studies and the assessment of the technological features (swelling behavior, fluid uptake ability). The selected sponge skeleton (*S. lamella*) was ground and the powder obtained was evaluated for particle size and microbiological quality [2]. CysHCl was loaded into *S. lamella* powder by testing various drug concentrations and different drying parameters. A biocompatible film incorporating the loaded powder was also prepared. Two leader formulations were selected. Drug content, SEM analyses and *in vitro* permeation studies were performed to test their suitability. To this respect, drying time and temperature are key parameters for the interesting drug crystallization observed within the sponge fibers. This behavior seems to influence drug loading and permeation profiles of formulations. Cysteine, indeed, is released more slowly than the pure drug within 1h. The obtained results suggest that such bio-based systems might be proposed as innovative topical dressings for wound treatment.

References:

[1]J.N.A Hooper; R.W.M. Van Soest, *Kluwer Academic/Plenum Publishers*, **2002,** New York.
[2]European Pharmacopoeia (8th edition), Council of Europe, Strasbourg (2014).

P2

Speciation and biorelevant reactions of the potential anti-tumor agent vanadocene dichloride

Valeria Ugone, [a] Daniele Sanna,[b] Maria Serra,[b] Tiziana Pivetta,[c] Elisa Valletta,[c] Laura Manca,[d] Monica Pirastru,[d] Péter Buglyó,[e] Linda Bíró,[e] Giovanni Micera,[a] and Eugenio Garribba[a]

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Vanadium compounds exhibit a wide variety of pharmacological properties, like anti-diabetic and anti-tumor [1]. Among the vanadium compounds with anti-tumor activity, vanadocene dichloride ($[Cp_2VCl_2]$ or VDC) has been proposed since 1983 in the treatment of Ehrlich ascites tumor [2]. Despite all VDC derivatives studied subsequently showed high activity in human cancer cells, their mechanism of action is not fully known. In this work, the interaction of VDC with several components of the blood serum and its uptake by red blood cells were studied through the combined application of spectroscopic (EPR, ESI-MS and UV-vis spectroscopy) and computational (DFT) methods [3]. Moreover the interaction of VDC with some relevant cellular bioligands, the DNA cleavage activity and the capability to generate $^{\bullet}OH$ radicals were studied [4].This transformation in the blood and in the cellular environment could be related to the mechanism of action of VDC.

References:

[1] J. Costa Pessoa, S. Etcheverry and D. Gambino, *Coord. Chem. Rev*. **2015**, *301-302*,24.
[2] P. Köpf-Maier and D. Krahl, *Chem. Biol. Interact*. **1983**, *44*,317.
[3] D. Sanna, V. Ugone, G. Micera, T. Pivetta, E. Valletta and E. Garribba, *Inorg. Chem.* **2015**, *54*, 8237.
[4] D. Sanna, M. Serra, V. Ugone, L. Manca, M. Pirastru, P. Buglyó, L. Bíró, G. Micera and E. Garribba, *Metallomics* **2016**, *8*, 532.

P3

A Novel Model of the Osmotic Behaviour of Human Mesenchymal Stem Cells

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The ability to readily expand in culture while maintaining a self-renewing phenotype and the non-invasive and painless collection has made human Mesenchymal Stem Cells (hMSCs) from Umbilical Cord Blood (UCB) a promising candidate for many cell-based therapies. Storing this cell lineage represents a crucial step in regenerative medicine applications. The most common preservation method to make cells available on demand consists of cooling them to a cryogenic temperature. Unfortunately, cryopreservation could damage the cells leading to up to 50 % loss in viability. This loss is unacceptable for the hMSCs from UCB whose collection and isolation is known to be difficult. For this reason, optimization of the cryopreservation protocol is mandatory. Due to the high number of trials required for experimental optimization, mathematical optimization could be a practical solution. In order to develop a model describing the process of cryopreservation, the osmotic behaviour due to the addition of permeant and non-permeant cryoprotectants to the cells needs to be investigated first. In this work, for the first time the osmotic behaviour of hMSC for UCB has been investigated and a novel model has been proposed to describe cell osmotic response. An understanding of the osmotic behaviour will enable the osmosis-driven change in the volume of intracellular water to be optimised in order to control the formation of intracellular ice and its amount.

P4

Synthesis and Characterization of New Polydiolcitrates with Tunable Properties

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In this work, a new type of polydiolcitrates made of citric acid (CA) and ethylene glycol (EG) and/or poly(ethylene glycol) (PEG) is investigated. By varying both the EG/PEG and the CA/diol molar ratios, materials exhibiting very different swelling behavior, mechanical and thermal properties are obtained [1]. In particular, the substitution of EG segments with longer and flexible PEG ones results in an increase in crosslinking density, with remarkable effects on swelling capacity, glass transition temperature (T_g) and Young modulus. Moreover, polyesters with CA/diol molar ratio equal to 1:1 exhibit shape memory properties (Fig. 1), with full capacity of keep- ing the temporary shape and high capacity of recovering the original shape. This work demonstrates that the appropriate choice of polyester composition allows modulating the sample properties, that permits to these materials to cover a wide range of possible applications [2].

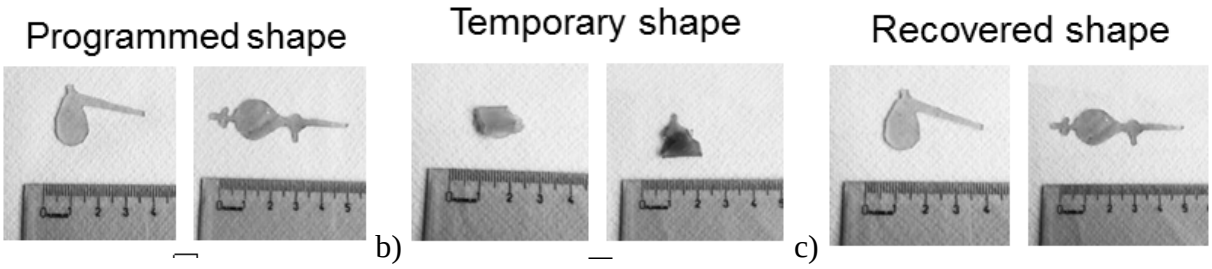

Figure 1: a) samples are at ambient temperature in the programmed shape $T<T_g$; b) after heating above the T_g, samples underwent an external deformation in order to obtain the desired temporary shape, which was subsequently fixed by reducing the temperature ($T< T_g$); c) the original shape was recovered by heating the samples again over the transition temperature ($T > T_g$).

References:

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[2] Q. Liu, L. Jiang, R. Shi, L. Zhang, *Prog. Polym. Sci.* **2012**, *37*, 715–765.

P5

Design, synthesis and in vitro biological evaluation of new Benzotriazole derivatives as potent and selective Respiratory Syncytial virus inhibitors

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Abstract

In this study we present the design and synthesis of the chloro-phenyl-benzotriazole derivatives obtained starting from aminophenyl-dichlorobenzotriazoles with the aim .to obtain effective anti-RSV agents.

Respiratory syncytial virus (RSV) is the most frequent cause of bronchiolitis and pneumonia in infants and children younger than 1 year of age in United States. It is also the second most common viral cause of pneumonia in adults and it results particularly frightening for elderly, representing a significant cause of respiratory illness in older people.

Clinical studies have shown that early treatments of RSV patients with aerosolized ribavirin improve prognosis; however ribavirine use has been limited because it is very costly, toxic, teratogenic and induce myelosuppression.

Therefore, there is the need for urgent development of specific antiviral drugs. In the search for new RNA virus inhibitors, we evaluated, in cell-based assays, a series of variously substituted benzotriazole derivatives against RSV. Several of them resulted fairly potent (at □M concentrations) and selective inhibitors of RSV in plaque and focus reduction assays, respectively. Hereby we report the chemical route followed and the biological results from in vitro evaluation, data obtained using Ribavirin and 6-Azauridine as reference compounds.

P6

Synthesis, pharmacological evaluation, adme prediction and molecular docking of novel pyridazinone-based cannabinoid receptor type-2 ligands

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In the last few years, cannabinoid type-2 receptor2 (CB_2R) selective ligands have shown a great potential as novel therapeutic drugs in several diseases. With the aim of discovering new selective cannabinoid ligands, a series of pyridazinone-4-carboxamides were designed, synthesized, and tested for their affinity toward the *h*CB_1R and *h*CB_2R. Compound**16** displayed the high CB_2-affinity (K_i-CB_2 = 2.0 ± 0.81 nM) and a notable selectivity (K_i-CB_1/K_i-CB_2 > 2000). In addition, **16** and other active new synthesized derivatives have demonstrated to behave as CB_2R inverse agonists in [^{35}S]-GTPγS binding assay. ADME predictions of the newly synthesized CB_2R ligandssuggest a favorabledruggability profile for these new compounds. Docking studies disclosed the specific pattern of interactionsof these derivatives. Our results support that pyridazinone-4-carboxamides represent a new promising scaffold for the development of potent and selective CB_2R ligands.

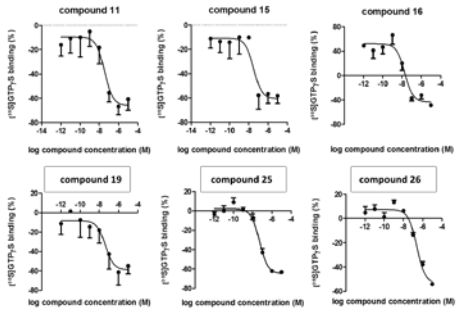

Figure 1. Representative curves for compounds **11, 15, 16, 19, 25** and **26** in the GTPγS binding bioassay