Urbino
11th - 14th June
ISMEC 2023
International Symposium
on Metal Complexes

Acta of the

International Symposia on Metal Complexes

ISMEC 2023

International Symposium on Metal Complexes

Urbino, June 11th-14th, 2023

1506
UNIVERSITÀ
DEGLI STUDI
DI URBINO
CARLO BO

I S Me C
International Group for the Thermodynamics of Complexes

Acta of the

International Symposia on Metal Complexes

Edited by:

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1506 UNIVERSITÀ DEGLI STUDI DI URBINO CARLO BO
DISPEA
DIPARTIMENTO DI SCIENZE PURE E APPLICATE

1506 UNIVERSITÀ DEGLI STUDI DI URBINO CARLO BO

ISMeC
International Group for the Thermodynamics of Complexes

Foreword:

ISMEC 2023 is the 51th edition of a series of meetings that begun in Parma in 1973 as the annual congress of the Italian group of "Thermodynamics of Metal Complexes" followed by a meeting in Florence in 1974. In 1989 in Modena it became an Italian-Spanish (or Spanish-Italian) congress with annual meetings starting in Peñíscola (Spain) in 1990 and from then on alternating between Italy and Spain. From the 2010 meeting held in Bilbao, the participation was widened at an international level and took the name of International Symposium on Metal Complexes.

The scientific program is organised in lectures, oral communications and poster sessions, focused on recent scientific advances in the thermodynamics and the kinetics of complexes in the fields of Analytical, Biological, Environmental, Inorganic Medicinal and Physical Chemistry. Main topics include, but are not limited to:

- Complexation thermodynamics and kinetics
- Solution equilibria and coordination chemistry
- Complexation processes in supramolecular chemistry
- Metal-based reactivity and catalysis
- Metal-complex interactions with biomolecules
- Metals in diseases: transport, homeostasis and toxicity
- Metal-based drugs: diagnosis and therapy
- Metal complexes of environmental and biological interests
- Nanostructured metal complexes
- Analytical methods and sensors based on complexation equilibria
- Computer methods for equilibrium analysis

The Symposium aims to provide a valuable discussion forum on the above areas, fostering new collaborations among researchers from diverse backgrounds with complementary skills and goals. In addition to lectures, covering a wide range of topics, a poster session provides multiple opportunities for informal discussions in a friendly atmosphere. The presentation of oral communications by young researchers is promoted.

The Symposium is located in the historical center of Urbino, cradle of the Renaissance and birthplace of Raffaello Sanzio.

Vieri Fusi
Chair of the Organizing Committee ISMEC 2023
University of Urbino, Italy

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ISMEC Acta webpage: www.ismecgroup.org/ismec-acta/

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PROGRAM


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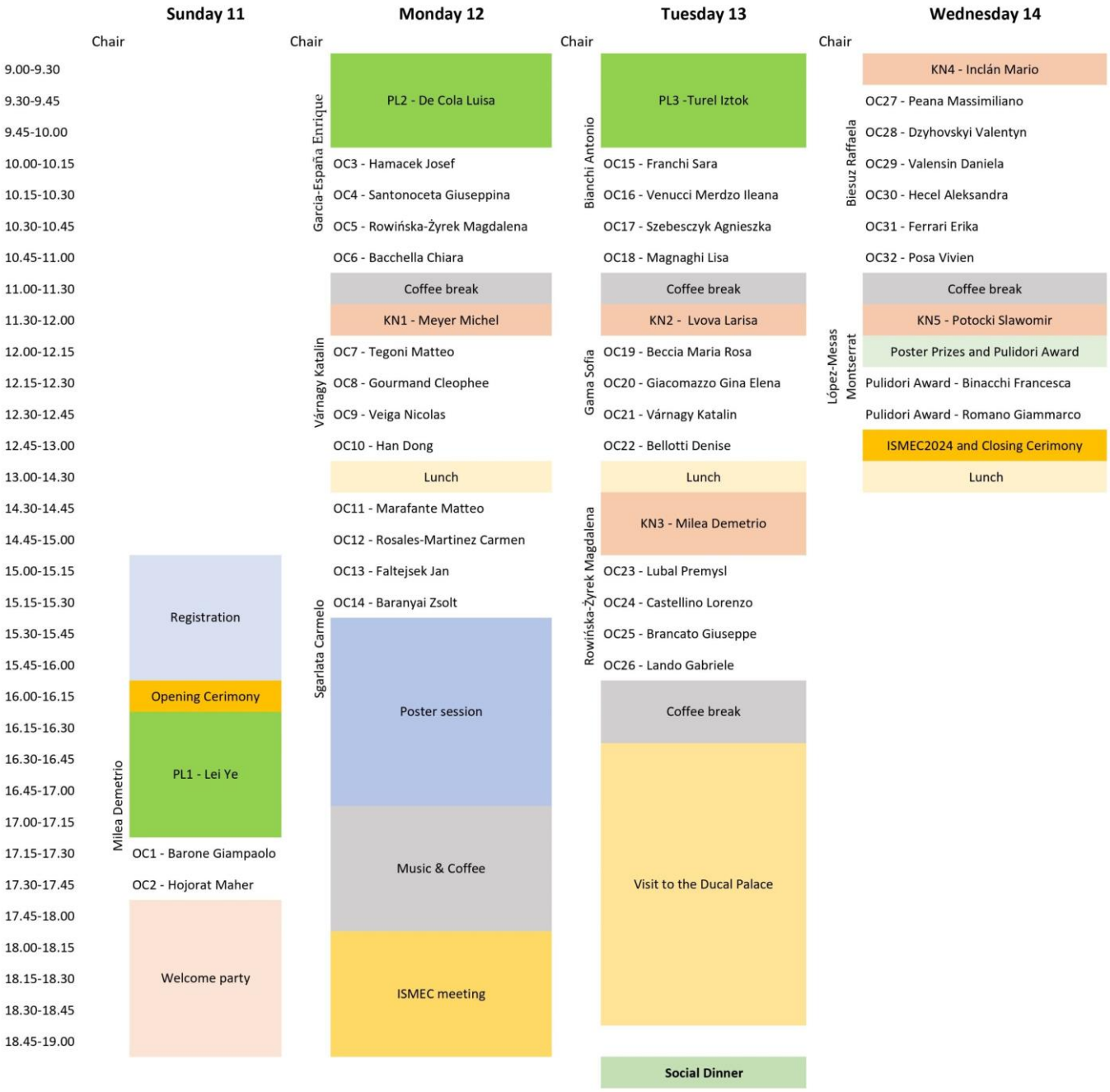
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Tuesday 13
Wednesday 14
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10.30-10.45
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18.45-19.00
Milea Demetrio
Registration
Opening Cerimony
PL1 - Lei Ye
OC1 - Barone Giampaolo
OC2 - Hojorat Maher
Welcome party
Garcia-España Enrique
PL2 - De Cola Luisa
OC3 - Hamacek Josef
OC4 - Santonoceta Giuseppina
OC5 - Rowińska-Żyrek Magdalena
OC6 - Bacchella Chiara
Coffee break
KN1 - Meyer Michel
Várnagy Katalin
OC7 - Tegoni Matteo
OC8 - Gourmand Cleophee
OC9 - Veiga Nicolas
OC10 - Han Dong
Lunch
OC11 - Marafante Matteo
OC12 - Rosales-Martinez Carmen
OC13 - Faltejsek Jan
OC14 - Baranyai Zsolt
Sgarlata Carmelo
Poster session
Music & Coffee
ISMEC meeting
Bianchi Antonio
PL3 -Turel Iztok
OC15 - Franchi Sara
OC16 - Venucci Merdzo Ileana
OC17 - Szebesczyk Agnieszka
OC18 - Magnaghi Lisa
Coffee break
KN2 - Lvova Larisa
Gama Sofia
OC19 - Beccia Maria Rosa
OC20 - Giacomazzo Gina Elena
OC21 - Várnagy Katalin
OC22 - Bellotti Denise
Lunch
KN3 - Milea Demetrio
Rowińska-Żyrek Magdalena
OC23 - Lubal Premysl
OC24 - Castellino Lorenzo
OC25 - Brancato Giuseppe
OC26 - Lando Gabriele
Coffee break
Visit to the Ducal Palace
Social Dinner
Biesuz Raffaela
KN4 - Inclán Mario
OC27 - Peana Massimiliano
OC28 - Dzyhovskyi Valentyn
OC29 - Valensin Daniela
OC30 - Hecel Aleksandra
OC31 - Ferrari Erika
OC32 - Posa Vivien
Coffee break
López-Mesas Montserrat
KN5 - Potocki Slawomir
Poster Prizes and Pulidori Award
Pulidori Award - Binacchi Francesca
Pulidori Award - Romano Giammarco
ISMEC2024 and Closing Cerimony
Lunch

Scientific Program

Sunday 11th

15:00 - 16:00 **Registration**

16:00 - 16:15 **Opening Ceremony**

Chairman: Milea Demetrio

16:15 - 17:15 PL1 - **Lei Ye**

"Metal complexes for polymer engineering, catalysis and sensing"

17:15 - 17:30 OC1 - **Barone Giampaolo**

"Guanine oxidation catalysed by Cu^{2+} aquo and Schiff base complexes: Effects on the DNA G-quadruplex structure"

17:30 - 17:45 OC2 - **Hojorat Maher**

"Cyclam as Relevant Platform to Design ^{99m}Tc, ^{64}Cu, or ^{109}Pd Radiopharmaceuticals in Nuclear Medicine"

17:45 - 19:00 **Welcome party**

Monday 12th

Chairman: García-España Enrique

09:00 - 10:00 PL2 - **De Cola Luisa**

"Self-assembly of luminescent molecules in solution and in living systems"

10:00 - 10:15 OC3 - **Hamacek Josef**

"Tetrahedral Cages with Lanthanides: Insight into Thermodynamics and Self-Assembly Mechanism"

10:15 - 10:30 OC4 - **Santonoceta Giuseppina D. G.**

"pH-responsive metal-coordinated assemblies containing methotrexate: from multiple solution equilibria to in vitro anticancer applications"

10:30 - 10:45 OC5 - **Rowińska-Żyrek Magdalena**

"Zn(II) and Cu(II) complexes with modified antimicrobial peptides – exciting bioinorganic chemistry explains their biological potential"

10:45 - 11:00 OC6 - **Bacchella Chiara**

"Investigating how membrane models interact with copper ions bound to neuronal protein fragments"

11:00 - 11:30 **Coffee break**

Monday 12th

Chairwoman: Várnagy Katalin

11:30 - 12:00 KN1 - **Meyer Michel**

"Chelation of f-elements by hydroxamic siderochelates: from the bench to the field"

12:00 - 12:15 OC7 - **Tegoni Matteo**

"Artificial catalytic copper proteins based on the Spy technology"

12:15 - 12:30 OC8 - **Gourmand Cléophée**

"Thermodynamics of M(II) adsorption on functionalised mesoporous silica: isothermal titration calorimetry (ITC) applied to solid-liquid systems"

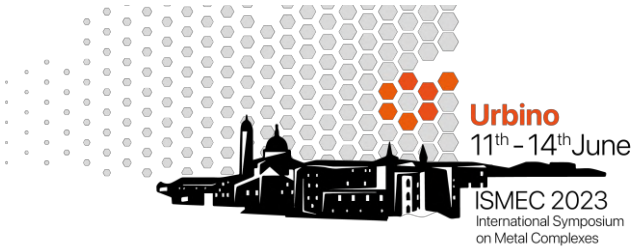
12:30 - 12:45 OC9 - **Veiga Nicolás**

"Imprinted polymers as promising materials for the decontamination of dye pollutants"

12:45 - 13:00 OC10 - **Han Dong**

"Adsorption of Trace Cisplatin and Carboplatin onto Thiol-functionalized Sponges: Synchrotron XAS and Surface Complexation"

13:00 - 14:30 **Lunch**



Monday 12th

Chairman: Sgarlata Carmelo

14:30 - 14:45 OC11 - **Marafante Matteo**

"Multi-techniques characterization and speciation of oxovanadium(IV)/8-hydroxyquinoline-2-carboxylic acid aqueous system"

14:45 - 15:00 OC12 - **Rosales-Martínez Carmen**

"Unprecedented link between the Irving-Williams series and the stoichiometry in crystals of first-row transition metal(II) complexes with M = Co-Zn, oxydiacetate chelator (oda) and adenine (Hade)"

15:00 - 15:15 OC13 - **Faltejsek Jan**

"Ln(III)–18-py$_2$N$_4$Ac$_4$ Complexes: Formation Kinetics, Mechanism of Complexation and Implications for the f-Block Metal Radiochemistry"

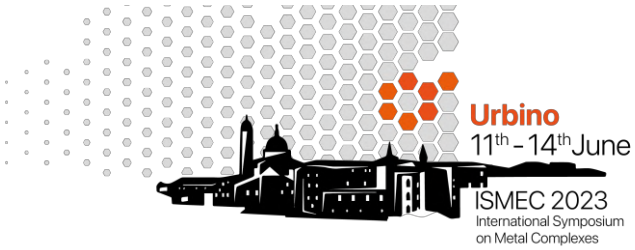
15:15 - 15:30 OC14 - **Baranyai Zsolt**

"Boosting Bi^{III}-complexation for targeted α-therapy (TAT) applications with the mesocyclic chelating agent AAZTA"

15:30 - 17:00 **Poster session**

17:00 - 18:00 **Music & Coffee**

18:00 - 19:00 **ISMEC meeting**



Tuesday 13th

Chairman: Bianchi Antonio

09:00 - 10:00 PL3 - **Turel Iztok**

"Metal complexes with some approved drugs and selected biologically active ligands"

10:00 - 10:15 OC15 - **Franchi Sara**

"Exploring the Coordination Preferences of Ra^{2+} and Ba^{2+} for the Rational Design of Ra-223 and Ba-131/135m Chelators for Theranostic Radiopharmaceuticals"

10:15 - 10:30 OC16 - **Venucci Merdzo Ileana**

"TRASUTA: a new hexadentate spirocyclic chelator for 68Ga based PET imaging"

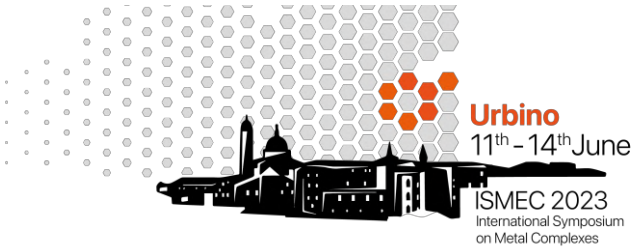
10:30 - 10:45 OC17 - **Szebesczyk Agnieska**

"Expect (un)expected – peptide fragments of HSPB1 and their binding to metal ions"

10:45 – 11:00 OC18 - **Magnaghi Lisa Rita**

"Is there still anything to discover about "old-fashioned" albumin interaction with bromocresol green and similar dyes?"

11:00 - 11:30 **Coffee break**



Tuesday 13th

Chairwoman: Gama Sofia

11:30 - 12:00 KN2 - **Lvova Larisa**

"Porphyrinoids metal complexes-based sensors for environmental and biological applications"

12:00 - 12:15 OC19 - **Beccia Maria Rosa**

"A close look at uranium complex formation in marine algae after bioaccumulation"

12:15 - 12:30 OC20 - **Giacomazzo Gina Elena**

"Ruthenium(II) polypyridyl complexes as versatile tools in the

design of photoresponsive therapeutic agents"

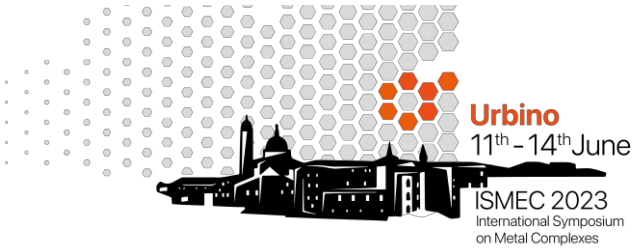
12:30 - 12:45 OC21 - **Várnagy Katalin**

"The effect of serine and threonine on the complex formation and hydrolytic stability of model peptides of tau and tubuline proteins"

12:45 - 13:00 OC22 - **Bellotti Denise**

"A glance at the metal binding ability of fungal ZIP transporters: Zn(II) and Cu(II) interaction with the Zrt2 protein"

13:00 - 14:30 **Lunch**



Tuesday 13th

Chairwoman: Rowińska-Żyrek Magdalena

14:30 - 15:00 KN3 - **Milea Demetrio**

"Medium and ionic strength dependence of formation constants. The "pure water" model."

15:00 - 15:15 OC23 - **Lubal Přemyls**

"Thermodynamics of chelate effect of Pd(II)-oxalate system"

15:15 - 15:30 OC24 - **Castellino Lorenzo**

"Notes and advancements in the development of PyES, an open-source software for the simulation of thermodynamic equilibria in soluble and precipitable systems"

15:30 - 15:45 OC25 - **Brancato Giuseppe**

"Simulating the chemical equilibria of metal complexes: Insights into the ligand exchange mechanism"

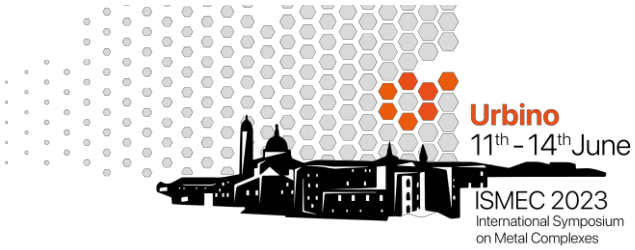
15:45 - 16:00 OC26 - **Lando Gabriele**

"Intercalibration network for potentiometric measurements: the case study of EDTA"

16:00 - 16:30 **Coffee break**

16:30 - 18:45 **Visit to the Ducal Palace**

Social Dinner



Wednesday 14th

Chairwoman: Biesuz Raffaela

09:00 - 09:30 KN4 - **Inclán Mario**

"The potential of polyamines in the fight against antimicrobial resistance"

09:30 - 09:45 OC27 - **Peana Massimiliano Francesco**

"Zn(II) and Cu(II) interaction with peptide models of the recognition interface of ACE2 receptor for SARS-CoV-2 spike protein"

09:45 - 10:00 OC28 - **Dzyhovskyi Valentyn**

"Divalent metal ion binding to Staphylococcus aureus transporters"

10:00 - 10:15 OC29 - **Valensin Daniela**

"New insights on structure and antioxidant activity of copper(II) complexes with Hydroxycinnamic acids"

10:15 - 10:30 OC30 - **Hecel Aleksandra**

"Peptidic metallophores as a key to understanding the diverse transport of metal ions in bacteria"

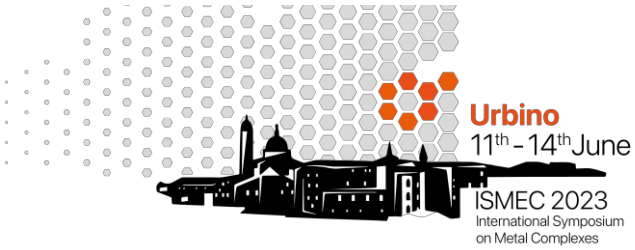
10:30 - 10:45 OC31 - **Ferrari Erika**

"On the road to new Oxaliplatin derivatives for colorectal cancer treatment"

10:45 - 11:00 OC32 - **Pósa Vivien**

"A comparative study on complexation and biological activity of the anticancer iron chelator VLX600 and its derivatives with essential metal ions"

11:00 - 11:30 **Coffee break**



Wednesday 14th

Chairwoman: López-Mesas Montserrat

11:30 - 12:00 KN5 - **Potocki Sławomir**

"Coordination properties of metal-binding sites of bacterial and fungal virulence proteins"

12:00 - 12:15 **Poster Prizes and Pulidori Award**

12:15 - 12:30 Pulidori Award-**Binacchi Francesca**

"A biophysical study of the interactions of palladium(II), platinum(II) and gold(III) complexes of aminopyridyl-2,2'-bipyridine ligands with RNAs and other nucleic acid structures"

12:30 - 12:45 Pulidori Award-**Romano Giammarco Maria**

"Polyamine receptors containing anthracene as fluorescent probes for ketoprofen in H_2O/EtOH solution"

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13:00 - 14:30 **Lunch**

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PL2 **Luisa DE COLA - University of Milano (Italy).** *Self-assembly of luminescent molecules in solution and in living systems.*

PL3 **Iztok TUREL - University of Ljubljana (Slovenia).** *Metal complexes with some approved drugs and selected biologically active ligands.*

KEYNOTE PRESENTATIONS

KN1 **Michel MEYER - University of Bourgogne (France)**. *Chelation of f-elements by hydroxamic siderochelates: from the bench to the field.*

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The "pure water" model.

KN4 **Mario INCLÁN - University of Valencia (Spain)**. *The potential of polyamines in the fight against antimicrobial resistance.*

KN5 **Sławomir POTOCKI - University of Wroclaw (Poland)**. *Coordination properties of metal-binding sites of bacterial virulence proteins*

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OC15 **Sara FRANCHI - University of Padova (Italy).** *Exploring the Coordination Preferences of Ra^{2+} and Ba^{2+} for the Rational Design of Ra-223 and Ba-131/135m Chelators for Theranostic Radiopharmaceuticals.*

OC16 **Ileana Venucci MERDZO - Bracco Imaging spa (Italy), University of Trieste (Italy).** *TRASUTA: a new hexadentate spirocyclic chelator for ^{68}Ga based PET imaging.*

OC17 **Agnieszka SZEBESCZYK - University of Opole (Poland).** *Expect (un)expected – peptide fragments of HSPB1 and their binding to metal ions.*

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OC28 **Valentyn DZYHOVSKYI - University of Wroclaw (Poland).** *Divalent metal ion binding to Staphylococcus aureus transporters.*

OC29 **Daniela VALENSIN - University of Siena (Italy).** *New insights on structure and antioxidant activity of copper(II) complexes with Hydroxycinnamic acids.*

OC30 **Aleksandra HECEL - University of Wroclaw (Poland).** *Peptidic metallophores as a key to understanding the diverse transport of metal ions in bacteria.*

OC31 **Erika FERRARI - Università of Modena and Reggio Emilia (Italy).** *On the road to new Oxaliplatin derivatives for colorectal cancer treatment.*

OC32 **Vivien PÓSA - University of Szeged (Hungary).** *A comparative study on complexation and biological activity of the anticancer iron chelator VLX600 and its derivatives with essential metal ions.*

PULIDORI AWARDS

Francesca BINACCHI - University of Pisa (Italy). *A biophysical study of the interactions of palladium(II), platinum(II) and gold(III) complexes of aminopyridyl-2,2'-bipyridine ligands with RNAs and other nucleic acid structures.*
Giammarco Maria ROMANO - University of Firenze (Italy). *Polyamine receptors containing anthracene as fluorescent probes for ketoprofen in H_2O/EtOH solution.*

POSTERS

P1 **Sabriye AYDINOĞLU - University of Çukurova (Turkey).** *Thermodynamic Studies on Nickel(II) - Favipiravir Antiviral Drug Complex Formation*.

P2 **Anna BARYŁKA - University of Białystok (Poland).** *The protonation equilibria of 8- hydroxyquinoline-2-carboxylic acid (8-HQA) and its precursors: an ITC thermodynamic characterization.*

P3 **Silvia BERTO - University of Torino (Italy).** *Chemical characterization and speciation of the soluble fraction of Artic PM10.*

P4 **Raffaela BIESUZ - University of Pavia (Italy).** *Dyes in food chemistry: empirical use versus descriptor-based design.*

P5 **Francesca BINACCHI - University of Pisa (Italy).** *Ethyl versus butyl: a story about the different solution equilibria and biological properties of two Ag(I) anthracenyl bis-NHC silver complexes.*

P6 **Tarita BIVER - University of Pisa (Italy).** *Anticancer potential of diruthenium bis-cyclopentadienyl carbonyl complexes.*

P7 **Valentina BORGHESANI - University of Parma (Italy)**. *Redesign of Spy construct to obtain artificial metalloproteins: metal binding, molecular modelling and catalysis.*

P8 **Jérémy BRANDEL - University of Strasbourg (France).** *Investigation of the competition effects in M(II) adsorption on functionalised mesoporous silica by Isothermal Titration Calorimetry (ITC).*

P9 **Clemente BRETTI - University of Messina (Italy).** *Complexation of environmentally and biologically relevant metals with 3-hydroxy-1,2-dimethyl-4(1H)-pyridone (Deferiprone).*

P10 **Rosita CAPPAI - University of Sassari (Italy).** *Kojic acid derivatives for oxovanadium(IV) complexation.*

P11 **Orsolya DÖMÖTÖR - University of Wien (Austria), University of Szeged (Hungary).** *A comprehensive study on the biospeciation of two half-sandwich organoruthenium complexes.*

P12 **Lukáš HANZL - University of Pardubice (Czech Republic).** *Ionic liquids containing vanadium.*

P13 **Jan HONZÍČEK - University of Pardubice (Czech Republic).** *Investigation of the effect of metal-containing ionic liquids on curing of epoxy/anhydride systems by Near-IR spectroscopy.*

P14 **Arian KOLA - University of Siena (Italy).** *Implications of copper(II) and Lycorine on structural and redox behaviour of the Amyloid β peptide.*

P15 **Hilda KOVÁCS - University of Szeged (Hungary).** *Study of Complex formation of ML324, a histone demethylase KDM4 inhibitor, with essential metal ions.*

P16 **Andrea LÁZARO-GÓMEZ - University of Valencia (Spain).** *Synthesis and evaluation of the stabilising effect and binding mode of extended tri-biphenylamine-based ligands towards non-canonical nucleic acid structures by biophysical and computational methods.*

P17 **Silvia LEVERARO - University of Ferrara (Italy).** *The effect of Ala-to-Ser substitution on calcitermin derivatives.*

P18 **Daniele LOPEZ - University of Urbino (Italy)**. *A joint chemical and biological study on fluorescent molecules for sustainable environmental investigations.*

P19 **Pablo NAVARRO-MADRAMANY - University of Valencia (Spain).** *Modulating antioxidant activity of superoxide dismutase and catalase/peroxidase mimetics through tunning of pyridine electron-density.*

P20 **Juan NICLÓS-GUTIÉRREZ - University of Granada (Spain).** *Molecular recognition aspects from the structure of 'inner' and 'out' sphere copper(II) complexes with 2,6-pyridinedicarboxilatechelator (pdc) and creatinine (crea) or creatininium (Hcrea+) counterparts.*

P21 **Mario PACHECO - University of República (Uruguay).** *Magnetostructural characterization of tetrabromonitrosylrhenate(II) complexes through Hirsfheld Surfaces Analysis.*

P22 **Erika PALAZZETTI - University of Urbino (Italy).** *HBO-based ligand: a Fluorescent Sensor for Rare Earth Metal Ions.*

P23 **Delfina QUIÑONE - University of República (Uruguay).** *Anion-imprinted polymers for the selective sensing of fluoride in dmso and water*.

P24 **Giammarco Maria ROMANO - University of Firenze (Italy).** *Metal complexes with fluorescent deferoxamine derivatives as PET/fluorescence dual imaging probes.*

P25 **M. Amélia SANTOS - Instituto Superior Técnico University of Lisboa (Portugal).** *Rivastigmine-Indole hybrids as a new family of multitarget metal-modulating anti-Alzheimer´s Disease agents: Cu(II) and Fe(III) chelation studies.*

P26 **Matteo SAVASTANO - University of Firenze (Italy), University of San Raffaele Roma (Italy).** *Ligand Denticity and Oxygen Reduction Reaction Activity of Pd(II) Macrocyclic Complexes: κ3 vs κ4.*

P27 **Carmelo SGARLATA - University of Catania (Italy).** *Development of hyaluronic acid – carnosine complexes as potential non-covalent drug delivery systems.*

P28 **Yschtar Tecla SIMONINI STEINER - University of Florence (Italy).** *Cyanine based receptors for the recognition of antibiotics in aqueous media.*

P29 **Marilena TOLAZZI - University of Udine (Italy).** *Cobalt/nickel separation by solvent extraction with a phosphonium based ionic liquid.*

P30 **Marcia VILTRES PORTALES - Autonomous University of Barcelona (Spain).** *Direct selenium speciation in biofortified microgreens by synchrotron-based X-Ray Absorption Spectroscopy.*

P31 **Emel YILDIZ - University of Çukurova (Turkey).** *Hydrothermal Synthesis of New Generation Perovskite Structures including Lanthanides.*

PLENARY LECTURES

Metal complexes for polymer engineering, catalysis and sensing

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Metal complexes play indispensable roles in metalloproteins and structured nucleic acids to enable molecular recognition and catalysis. Embedding metal complexes in polymers provides an opportunity to create biomimetics of metalloproteins for technical applications. In molecular imprinting, target-selective binding sites are created by crosslinking polymerization using designed molecular templates. Metal complexation can be utilized to stabilize template-monomer interaction, thereby improving the molecular recognition performance of the obtained polymers, notably in aqueous solutions.

To understand the molecular imprinting process in more detail, we combined solution NMR, dynamic light scattering and fluorescence spectroscopy to monitor the molecular status of reaction components during the whole imprinting reactions. Research in this line has helped to gain a better insight into molecular imprinting process and led to several optical sensors for organic pollutants and metal ions.[1,2]

For bio-separation of proteins, immobilized polymer brushes are very suitable carriers to present affinity ligands for efficient target binding. Nanoparticle-supported polymer brushes have been synthesized using surface-initiated atom transfer radical polymerization (ATRP).[3,4] By replacing small metal complexes with a metalloprotein (myoglobin) to catalyse the ATRP reaction, the polymer product is obtained from a "greener" approach and more suitable for separation of therapeutic proteins.[5]

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Self-assembly of luminescent molecules in solution and in living systems

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Keywords: luminescence, in vivo self-assembly, bioimaging, aggregation induced emission.

Luminescent molecules that can undergo self-assembly are of great interest for the development of new materials, sensors, biolabels. In some cases the assembly can lead to an enhancement of the emission, a change in the luminescence energy and even to unexpected biological phenomena.

The talk will illustrate some of the recent results on the self-assembly of platinum complexes and their evolution in solution.[1] The different species that evolve from the initial assembly can be visualize thanks to their different photophysical properties and the control of the solvents determines the kinetics of their evolutions. The stabilization of transient species, formed in the assembly process can be achieved using cage type structures can lead to their stabilization or even existence in solution, in a condition out of equilibrium. We recently demonstrated[2] that it is possible to entrap intermediate states of luminescent assemblies and prevent their thermodynamic evolution towards the equilibrium state. Furthermore the use of nanocages able to break on demand allows the transport and release in cells of such species and therefore their dynamics can be observed in living cells.

Finally some water soluble compounds where studied to follow the self-assembly in vivo and the resulting reactivity/toxicity of such species. We employed transparent polyps, Hydra vulgaris to study the self-assembly in living animals that can be monitored by the appearance of an intense green/yellow emission. Interestingly, differences in the fluorescence emissions were observed in tentacle and body regions. Also morphological or behavioural alterations where followed to understand dose dependent toxicity when the Hydra were treated with different doses of Pt(II) complex.

An extraordinary phenomenon was detected with one of the complex that showed a clear effect on pluripotent stem cell proliferation, especially at low doses. This effect was further demonstrated by the increased number of differentiated cells, i.e. neurons and gland cells and it is still under study.

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Metal complexes with some approved drugs and selected biologically active ligands

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An important area of bioinorganic chemistry are the interactions of metal ions with biologically important compounds. The American chemist Barnett Rosenberg discovered the cytotoxic properties of cisplatin[1] and this was undoubtedly one of the main triggers for the strong development of this popular field of chemistry.

Nowadays it is known that many clinically used drugs require the presence of certain metal ions for their action. On the other hand, many metal ions can also react with drugs and reduce their effectiveness. Reasons for the latter effect may be the formation of sparingly soluble compounds, blocking of functional groups of the molecule that are crucial for its activity, etc. In addition, it also became clear that many metal complexes of clinically used drugs may exhibit increased or altered biological activity. Often, a synergistic activity can occur after the binding of metal ions to drugs.[2]

It is well known nowadays that the development of a new drug is a lengthy, extremely expensive, and unpredictable process.[3] Therefore, the repurposing of old drugs is an attractive topic taken up by several research groups[4] and the approach of using old drug to discover a new one is thus very appealing.[5]

A common research strategy in my group is to bind selected clinically used drugs to different metal ions and study the physicochemical properties in such complex equilibria. Prepared compounds are tested for various biological activities in collaboration with partner groups. In my talk, I will present selected examples of such studies in which drugs were used as versatile ligands. In metal complexes, quinolone antibacterial agents act most frequently as O,O- ligands.[6] Antibacterial activity is lost or reduced after coordination, but other types of activity have been observed. Bidentate binding of oxygen atoms to the metal centre is also typical for some ligands from the nonsteroidal anti-inflammatory drugs (NSAID) family and curcumin analogues.[7,8] Promising results have also been obtained with substituted pyridine- N-oxides (e.g., pyrithione), which are normally bidentately coordinated via O,S- atoms. Ruthenium complexes with such ligands have high anticancer potential and are inhibitors of many enzymes overexpressed in some diseases.[9,11] Interestingly, we have also found that zinc pyrithione complexes are potent inhibitors

of PL^{Pro} and cathepsin-L enzymes with *ex vivo* inhibition of SARS-CoV-2 entry and replication.[12] In addition, we have also studied interactions with compounds containing nitrogen atoms that can

coordinate to the metal ion. Typical examples include the antiviral drug acyclovir (N- or N,O- binding), which is a modified nucleobase,[13] the antibacterial agent clioquinol and its derivatives (N,O- binding),[14,15] antifungal azoles (N- binding)[16] and substituted bypyridines (N,N- binding).[17,18]

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KEYNOTES LECTURES

Chelation of f-elements by hydroxamic siderochelates: from the bench to the field

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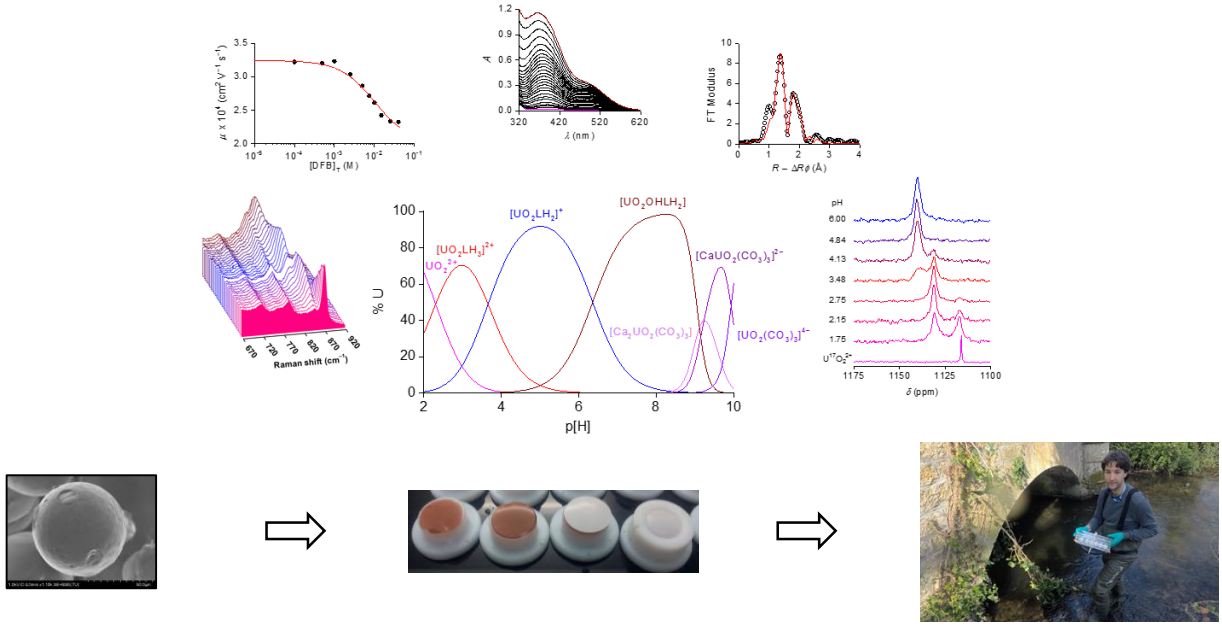
Uranium mining, nuclear fuel production and reprocessing, massive use of phosphate fertilizers, and coal combustion are the main sources of environmental releases of uranium. The monitoring of contaminated sites requires new breakthroughs in analytical chemistry in order to finely evaluate the impact of anthropogenic releases, the contribution of natural sources, transfers between the various biosphere compartments, and the risks of contamination of food chains. Diffusive gradients in thin-films (DGT) devices are particularly attractive and versatile on-field sampling tools.[1] They are used to passively pre-concentrate *in natura* the potentially bioavailable labile fraction of trace contaminants, before their quantification in the laboratory. However, most of the commercially available DGT samplers recommended for uranium[2] or those described in the literature[3,4] incorporate either a non-selective ion exchange resin (*e.g.* Chelex-100®) or adsorbing material (*e.g.* TiO_2). Hence, major interfering ions present in fresh- or seawaters, such as calcium, magnesium, or hydrogenocarbonate, often limit their performances and their range of applications.

To overcome these limitations, new chelating resins were prepared by covalent grafting of hydroxamic siderophores on hydrophilic polymer beads bearing carboxylate groups.

Our molecular strategy relied on the selection of high affinity chelators for the UO_2^{2+} ion, the coordination properties of which were carefully determined beforehand.[5,6] The lecture will cover both aspects, namely the structural and speciation studies of the free uranyl chelates in homogeneous solution, as well as the characterization of the extracting materials[7] and DGT's made thereof. Finally, the first field validation studies will be presented.



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Porphyrinoids metal complexes-based sensors for environmental and biological applications

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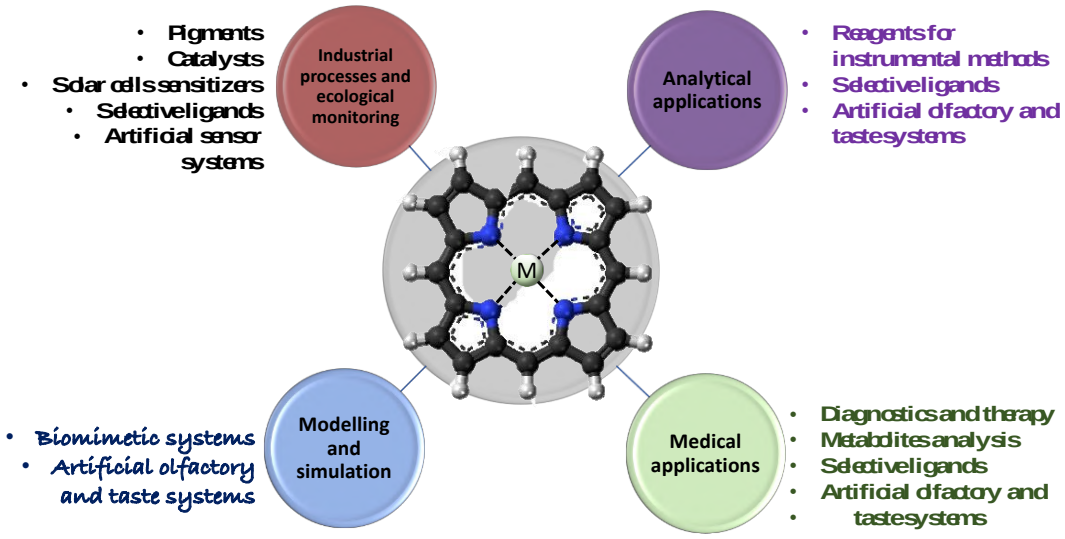
Porphyrinoids are heteroatomic macrocycles, that, thanks to their rich optical and electrocatalytic properties have previously obtained a lot of attention in different fields, as well as sensing materials for chemical sensors development,[1] Scheme 1.



Scheme 1. Porphyrinoids application fields.

The developed synthetic chemistry of porphyrinoids allows the rational functionalization of such macrocycles, with the aim to modulate their sensitive properties, to perform the deposition of the sensing layers by various techniques, and to use different transduction principles. In this work our recent achievements in the employment of porphyrinoids metallic complexes for various sensing materials development from classical ionophores[2,4] and chromophores,[5,8] to molecular wires,[9] antennas,[10] mass-sensitive coatings[11,12] and photosensitive nanocomposite materials[13] will be presented.

KN 2

The characterization of obtained porphyrin-based sensing materials by means of different instrumental methods (such as SEM, AFM, etc), and electrochemical techniques in order to select the sensing materials with the best characteristics will be illustrated.[12,14] Moreover, the principles of multisensory and multi-transduction analyses with selected applications of porphyrin-based sensor arrays will be introduced.[15,18]
The particular attention will be given to the use of porphyrinoids metal complexes-based sensors and multisensor systems for environmental monitoring, foodstuff analysis and biological purposes.[15,17]

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Medium and ionic strength dependence of formation constants. The "pure water" model

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Speciation models based on chemical equilibrium data use stability constants to account for the formation of different species. The accuracy of those models depends, other than the nature of species considered, also on the value of the constants used to express the stability of those species: wrong values lead to wrong speciation models. Constants reported in main collections and databases, as well as single papers, are mainly stoichiometric constants, i.e., they are expressed in terms of concentrations instead of activities. As such, stoichiometric constants, like activity coefficients, are dependent on the chemico-physical conditions of the system under study (i.e., medium composition, ionic strength, temperature, pressure). Several models exist to take into account the dependence of activity coefficients (and, in turn, of stability constants) on system conditions, with particular reference to ionic strength and temperature (since most reactions occur at ambient pressure, dependence on the latter assumes relevance in just particular cases like, e.g., in geochemical studies). However, the most common theories and approaches (e.g., Davies, Bromley, Pitzer, Specific ion Interaction Theory – SIT) can be considered as evolutions of the (Extended) Debye-Hückel equation. All of them have pros and cons, so that none can be considered better than others. For example, simplest equations (e.g. Davies) often lack of sufficient accuracy, while most complete models show quite complex mathematical formulation (e.g. Pitzer), especially for calculations in multicomponent systems, like many natural waters and biological fluids.[1]

Between the '80s and '90s, the group of Prof. Silvio Sammartano from the University of Messina proposed, with the precious support of colleagues from the Italian Universities of Torino, Catania and Palermo, a model[2] (with the relative equation), for the ionic strength (and temperature) dependence of formation constants, based on three simple assumptions:

[H1]: It is possible to express the dependence on ionic strength of formation constants by a simple equation, independently of the type of reactants and products, and dependent on the type of reaction only.

[H2]: All the deviations from the predicted behaviour are ascribed to weak complex formation between components and/or species under study and the background ions (e.g., the ionic medium). This implies that "pure water" is considered as reference state, and some ions as non-interacting with the reactants and/or products involved in the studied equilibrium.

[H3]: Perchlorate does not interact with cationic species, tetraethylammonium cations (and higher tetraalkylammonium analogues) do not with O-donor ligands, and Na^+ and K^+ do not with N-donor ligands.

Evidences collected during more than half a century in those universities demonstrated the validity of this "pure water model", and showed the potential of this approach to model the speciation of several multicomponent complex systems in a very simple way.

This contribution describes the main features of the pure water model through some examples, highlighting the theoretical and practical aspects of this approach in the speciation modelling of systems of different complexity, including real systems.

Acknowledgements:

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The potential of polyamines in the fight against antimicrobial resistance

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Antimicrobial resistance (AMR) has become a major global health problem. The estimates made in 2016 painted a grim feature in which AMR would become the leading cause of death, with a prediction of 10 million deaths per year by 2050.[1,2] Polyamines, both biogenic and synthetic, as well as their derivatives, have shown a wide array of interesting biomedical applications.[3] Here, we present the latest results concerning the antimicrobial activity (antiparasitic, antibacterial and antifungal) of a series of polyamines and their metal complexes, with particular attention to the scorpiand-type polyamine derivatives. The results have been obtained by an array of techniques, from *in silico* to *in vivo* studies and show the interesting potential of these family of compounds for the development of new orally administered antimicrobials.

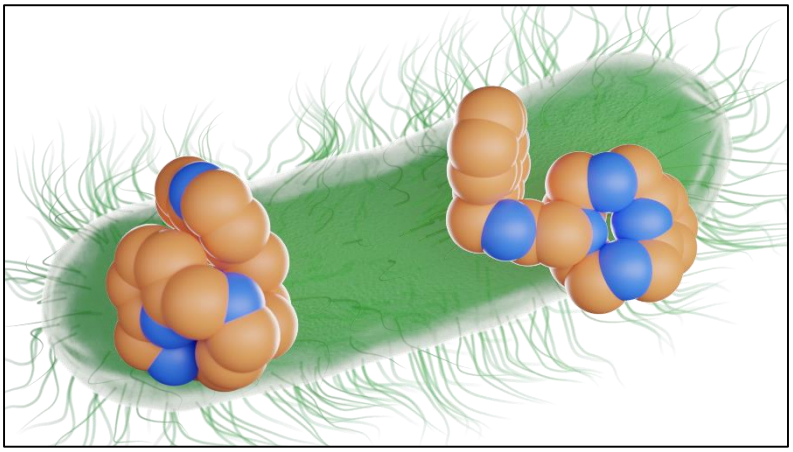

Figure: Space-fill models of the minimum energy conformers of a scorpiand-type polyamine in two different protonation degrees, as obtained by molecular dynamics calculations.

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KN 4

Coordination properties of metal-binding sites of bacterial virulence proteins

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The increasing number of antibiotic-resistant pathogens has become one of the major health problems of modern times, including infections caused by bacteria and fungi. One of the most lethal and multidrug-resistant bacteria is Mycobacterium tuberculosis (Mtb), which causes tuberculosis (TB). Whether they are bacterial or fungal infections, new therapeutic protein targets are constantly being sought.[1,2]

Here, we present the results on metal complexes of important metal-dependent virulence factors binding sites and influence of point mutations on their thermodynamic properties. We studied SmtB/BigR4 transcription regulators (*Mycobacterium tuberculosis/Mycobacterium smegmatis*)[1,3] and M10 metallopeptidase (*Streptococcus pneumonia*).[4] The thermodynamic properties of M(II) complexes (including Zn, Ni and Cu) were examined by potentiometry, NMR, MS, UV-Vis, CD, EPR and also DFT methods. The applied approach of introducing mutations enabled the identification of the most important side chains from the point of view of the ability to bind biologically relevant metals. With our research, we try to determine possible critical changes in the protein sequence, which may be of great importance in the process of designing drugs aimed at these molecular targets, but also simply and above all, provide better understanding of the interaction of metals with key virulence factors important in pathogen homeostasis.

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ORAL COMUNICATIONS

Guanine oxidation catalysed by Cu^{2+} aquo and Schiff base complexes: Effects on the DNA G-quadruplex structure

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Transition metal complexes of chiral Salen derivatives are well known catalysts for the asymmetric oxidation of olefins[1-3]. In this context, we have recently found that a Cu^{2+} Salphen-like complex, Fig. 1a, shows surprising catalytic activity for the selective epoxidation of styrene (Fig.1b). Since analogous transition metal complexes are also effective and selective G-quadruplex (G4) DNA binders[4], we are currently investigating the possible catalytic oxidation of guanine (G) DNA bases into 8-oxoguanine (OG), and how this may affect the DNA structure and stability. Fleming and Burrows[5] pointed out recently that G oxidation strongly affects the G4 structural stability (Fig. 1c). To restore the oxidated structure, OG move to a loop position and is replaced by a close G of the same sequence. However, our computational studies suggest the hypothesis that G oxidation does not induce unfolding of the G4 conformation[6]. Such studies are supported by circular dichroism and mass spectrometry results, in which G4 oxidation is promoted by H_2O_2, in presence of catalytic amounts of Cu^{2+} complexes.

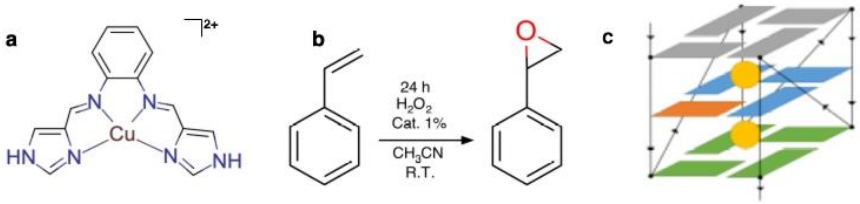

Figure 1: a) Structure of a metal complex with promising catalytic oxidative activity; b) styrene epoxidation; c) schematic drawing of three guanine tetrads present in a G-quadruplex DNA.

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OC 1

Cyclam as Relevant Platform to Design ^{99m}Tc, ^{64}Cu, or ^{109}Pd Radiopharmaceuticals in Nuclear Medicine

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Although several imaging tools have been developed over time, radiopharmaceuticals have emerged providing high-resolution anatomical imaging and effective therapy in nuclear medicine. We will present the first results of our work on the synthesis of new bifunctional chelators that form complexes with radiometal ions for high-resolution bioimaging. These bifunctional chelators are synthesized from the same intermediate, with a modification in the synthetic route, to reach cyclam-based chelators (oxocyclam or TE1PA) (Fig. 1) capable of forming stable and inert complexes when coordinated to d-block metals on the macrocyclic site of the molecule. The *C*-functionalization of these macrocyclic chelators allows their conjugation to different biomolecules (protein, peptide, antibody), facilitating targeting them through the body. The modification of the coordinated radiometal will allow us to investigate the use of these complexes for imaging of venous thrombosis by several imaging techniques such as SPECT and PET with ^{99m}Tc and ^{64}Cu as radionuclides respectively,[1,2] in addition to their application for cancer treatment with ^{109}Pd as therapeutic radionuclide.[3]

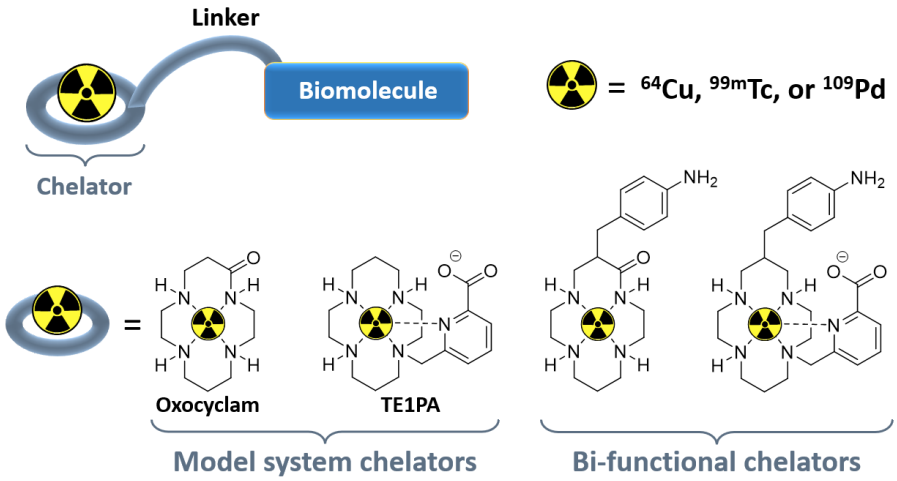

Fig. 1:Cyclam-based (oxocyclam and TE1PA) chelators for d-block radionuclides.

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Tetrahedral Cages with Lanthanides: Insight into Thermodynamics and Self-Assembly Mechanism

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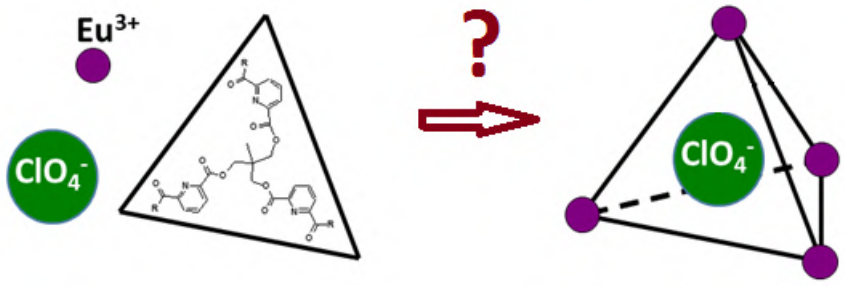
The preparation of complex supramolecular assemblies containing several lanthanide cations requires a good control of self-assembly process, since Ln(III) are kinetically labile and have high coordination numbers. A good stereochemical match between cations and ligands as well as secondary interactions contribute to a thermodynamic stabilisation of resulting edifices. These fundamental aspects are rarely investigated in details; more effort is dedicated to the study of catalytical, photophysical and magnetic properties.

In this contribution, we are interested in exploring tetrahedral cages with lanthanides. The self-assembly of tripodal ligands with Ln(III) results in the formation of tetranuclear complex, which hosts a perchlorate anion within the edifice[1]. In addition to structural characteristics, we present here the speciation of Ln(III) complexes formed at different metal to ligand ratios along the Ln(III) series. Moreover, the exchange of anions inside the cage was followed with NMR and we could determine the role of perchlorate during the assembly process[2]. Kinetics of complex formation was also studied with NMR and stopped-flow spectrophotometry. All these experiments provide a complete insight into the self assembly mechanism, which will be discussed during the conference.



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pH-responsive metal-coordinated assemblies containing methotrexate: from multiple solution equilibria to *in vitro* anticancer applications

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Methotrexate (MTX) is a methylated derivative of folic acid characterized by a pteridine ring and a dimethyl-p-aminobenzoic acid residue linked with glutamic acid. MTX is a key drug widely employed in a broad spectrum of diseases, mostly for the treatment of several human malignancies[1]. However, the drug ability to inhibit key cellular functions causes a lack of selectivity toward neoplastic cells, resulting in severe side effects. This inconvenience, along with poor solubility, short half-life in the bloodstream and drug resistance by targeted cells, strongly affects the drug efficacy. Consequently, many studies have focused on the development of delivery systems able to enhance drug bioavailability and efficacy by improving tumour-targeted delivery[2]. Among these, polymer-based systems have increasingly gained attention as polymers exhibit flexibility and diversity in their composition and properties and can be easily functionalized to respond to specific stimuli[3].

Taking advantage of the pH differences between cancerous and healthy cells, in this study we propose a couple of pH-responsive metal-coordinated assemblies containing MTX, biologically relevant metal ions (Cu^{2+} or Zn^{2+}) and polyacrylic acid (PAA, a polymer containing functionalities that respond to pH changes) (*Figure 1*) to overcome most of the drawbacks affecting the chemotherapy drug and enhance its bioavailability and efficacy in the controlled/targeted delivery.

These systems have been designed and developed by taking advantage of the binding features and the energetics of the multiple interactions occurring among the components of the assembly. Both MTX and PAA are negatively charged at physiological pH and may efficiently interact through the coordination of suitable metal ions.

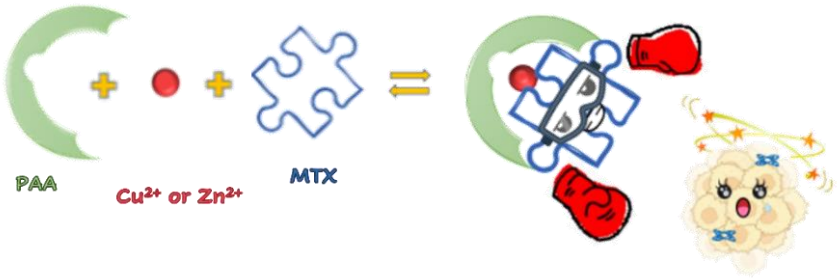

Figure 1. Schematic representation of the metal-coordinated assembly

The quantitative analysis of the species, binding affinity and thermodynamic signature of the formation equilibria was investigated in aqueous solution at 25 °C and physiological pH by isothermal titration calorimetry. The binding ability of MTX toward the polymer-metal complexes was also examined at the solid-liquid interface by quartz-crystal microbalance with dissipation monitoring. These results provided evidence for the adsorption of MTX onto the polymer-metal layer confirming their ability to interact as well as to release the drug under different pH values[4,5].

Furthermore, dynamic light scattering, zeta-potential and scanning electron microscopy measurements provided a thorough physicochemical and morphological characterization of the MTX-based assemblies. The *in vitro* cytotoxicity of the assemblies was assessed in the U87 glioblastoma cell line through the Alamar Blue assay; the results highlighted the more efficient anticancer activity of the three-component complexes compared to the free chemotherapy drug. The internalization of the assemblies in glioblastoma cancer cells was observed by confocal microscopy. Finally, flow cytometry analysis of samples treated with the metal-based assemblies allowed us to assess the role of reactive oxygen species generation in the mechanism of cell death.

Overall, the analysis of multiple solution equilibria involving different components permitted the rational design of MTX-based metal complexes able to simultaneously enhance the loading and the controlled release of drugs. Moreover, the biological *in vitro* studies suggest that these assemblies are promising and effective systems to deliver MTX to target cancer cells.

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Zn(II) and Cu(II) complexes with modified antimicrobial peptides – exciting bioinorganic chemistry explains their biological potential

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With a broad spectrum of activity and negligible antimicrobial resistance, antimicrobial peptides (AMPs) are potential treasure troves for finding novel, efficient antibacterial classes of dugs. We have recently shown that the coordination of Zn(II) to AMPs enhances their therapeutic potential via altering the peptide charge and/or structure.

We discuss the cases of semenogelins (AMPs from the human semen; the charge of the complex is important for its biological activity), clavanins (AMPs from the marine organism *Styela clava*; pre-organisation of the metal binding site plays a crucial role)[1], pramlintide (an analogue of antidiabetic amylin; Zn(II) coordination induces its fibril formation)[2] and an antimicrobial peptide from shrimp (where Zn(II) binding changes the structure of the peptide).

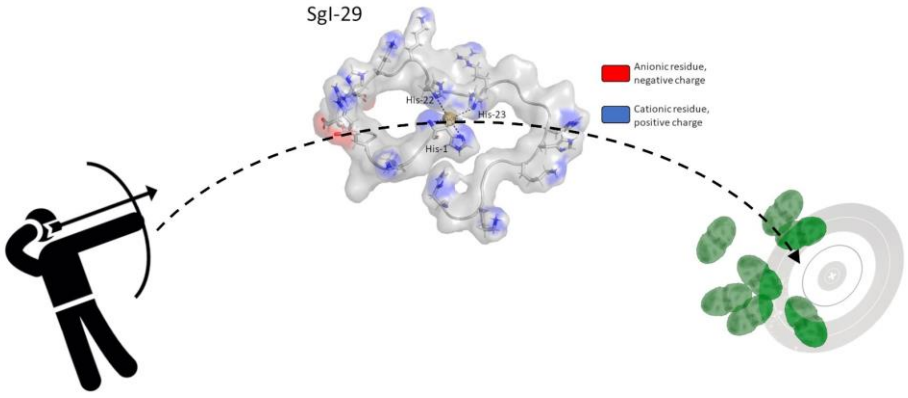

Figure 1. Potential mode of action of semenogelin SgI-29.

OC 5

We focus on the complexes' bioiniorganic chemistry, showing how their antimicrobial potential can be exploited and discussing their biggest drawback – the fact that their use is limited by rapid proteolysis. Ideas to overcome this obstacle are underway and include the use of the retro-inverso strategy.

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Investigating how membrane models interact with copper ions bound to neuronal protein fragments

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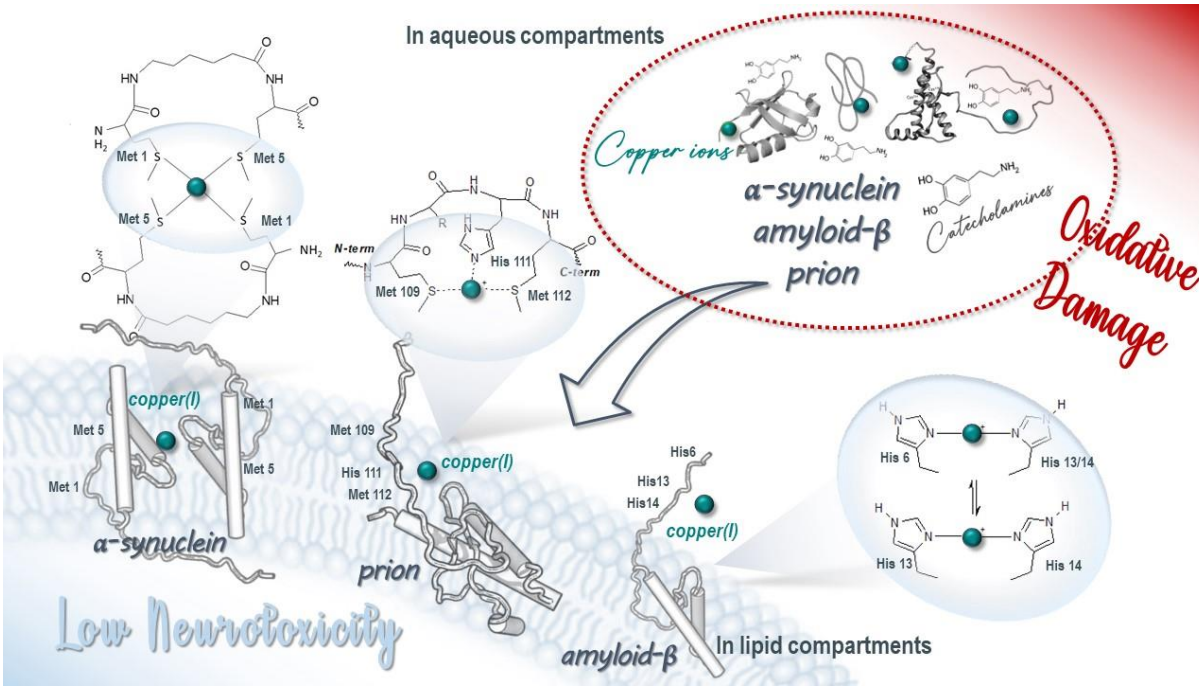

Figure 1: Schematic representation of the interaction of prion, α-synuclein and amyloid-β with lipids showing the localization of copper binding site inside (for the first two complexes) and outside (for the latest one).

The imbalance in metal homeostasis and the presence of misfolded protein deposits contribute to the pathogenesis of various neurodegenerative diseases, including Alzheimer's, Parkinson's and prion disorders. Excessive transition metal ions, such as copper and iron, play a critical role in protein aggregation and in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). In our lab, detailed characterization of redox activity

of copper promoted by catecholamines, i.e. dopamine, in the presence of several neuronal amyloidogenic peptides, including β-amyloid (Aβ),[1-3] α-synuclein (αSyn)[4] and prion (PrP) fragments,[5] was performed.[6] However, radical species and metal ions are not only factors contributing to the structural changes of neuroproteins but also their interaction with phospholipids may have an important role.

We have studied the conformation properties and the redox reactivity of copper-complexes with different Aβ/PrP/αSyn sequences in a membrane-mimetic environment (provided by SDS micelles and large unilamellar vesicles), choosing the amino acid regions mainly implicated in metal binding. Indeed, copper coordination sphere is strongly influenced by protein/peptide backbone structure, which can be affected by membrane-like environment.

We have assayed that prions and Aβ peptides exhibit very different behaviours when added to model membrane systems: the redox reactivity of Cu-prion complexes in micelle is significantly quenched,[7] and similar results have been obtained in the presence of αSyn protein.

In particular, we have determined that the reactivity shutdown is due to the trapping of Cu(I)-species in membrane-like structures: indeed, both prion and α-synuclein sequences contain a couple of methionine residues separated by 2-3 amino acids that are able to strongly coordinate copper(I) ions, thus generating an almost totally unreactive complex in micelle/LUV. On the other hand, whereas in the copper(I)-prion system the metal binding occurs intramolecularly due to the presence of an additional ligand provided by one histidine, in the copper(I)-αSyn complex, the metal ion is coordinated by four Met residues to give a Cu: protein complex 1:2.[8]

Conversely, copper-Aβ complexes are not internalized in micelles and their interaction with micelles only partly reduces the oxidative ability of the metal ion in both redox states.[7] Moreover, copper binding and its redox cycling are involved in the release of toxic reactive species able to modify endogenous biomolecules as DNA, RNA, lipids and proteins. Therefore, we have investigated how the presence of copper and catecholamines can induce the oxidative modification of these neuronal proteins and peptides and how their interaction with phospholipids can influence the modification patterns.[7,8]

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Artificial catalytic copper proteins based on the Spy technology

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Metalloproteins promote several of the most complex biomolecular processes in nature. The design of new metalloproteins is therefore of interest in the field of the development of new efficient biocatalysts which can carry out reactions that are not relevant for biological systems but are important for applications in bio- and nanotechnology.[1]

In the redesign of metalloproteins one of the major challenges is the introduction of metal binding sites in specific position of the construct. Here we present two new copper proteins designed using the SpyCatcher/SpyTag construct[2] The SpyCatcher construct is a β-barrel protein (Figure 1, blue) which binds covalently an oligopeptide called SpyTag (Figure 1, green) through the formation of an isopeptide bond between an Asp and a Lys residues. We have studied two Spy proteins obtained using two different SpyTag peptides, one bearing an ATCUN fragment at the N-terminus, and one bearing a His-His site, to specifically direct copper binding to these sites.

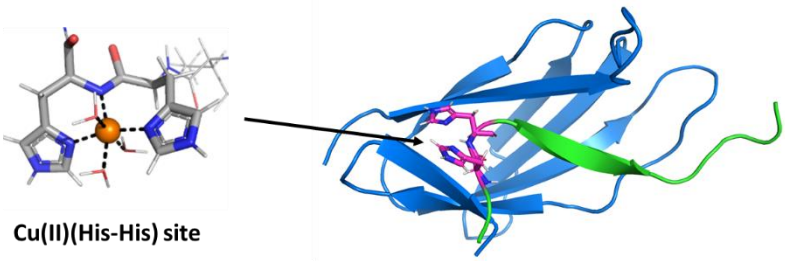

Figure 1: Representation of the SpyCatcher/SpyTag adduct. SpyCatcher is represented in blue, SpyTag is represented in green. The His-His copper binding site is represented in magenta.

The binding of copper(I) and copper(II) to the two proteins was studied using spectroscopic methods, together with the catalytic properties in hydrolysis of phosphoesters and oxidation of catechols. The aspects related to the design of the protein construct and of the catalytic site will be discussed.

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Thermodynamics of M(II) adsorption on functionalised mesoporous silica: isothermal titration calorimetry (ITC) applied to solid-liquid systems

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The rapid growth of industry and human activity led to the generation of large amounts of wastewater contaminated with hazardous metals, such as Cd or Pb, which are a great threat to the environment and may have serious consequences for all living organisms[1]. In this work, a material (SBA-GSH) based on mesoporous silica SBA-15 and glutathione (GSH), a biologically relevant ligand, has been developed (Fig. 1)[2]. GSH is the main source of non-protein thiols in cells, known for its ability to bind metal ions[3]. Therefore, the developed material showed good adsorption capacities for several metal ions such as Cd(II) (1,03 $mmol_{Cd}.g^{-1}$) or Pb(II) (0,70 $mmol_{Pb}.g^{-1}$), lower affinities for Cu(II) and a selectivity for Pb(II).

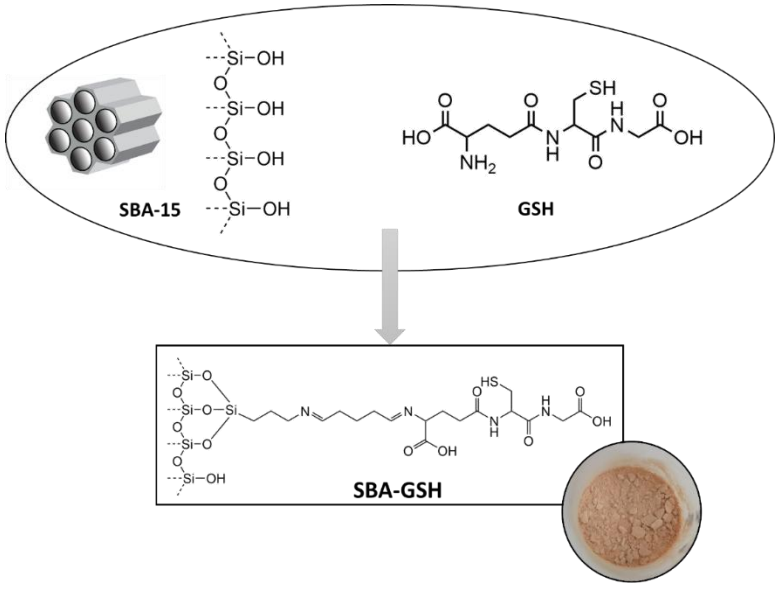

Figure 1 Structure of SBA-GSH material

In order to use these adsorbents in metal ions removal from complex industrial effluents, a better understanding of (i) the interactions operating between the adsorbed species and the solid surface and (ii) of the competitive effects between different metal ions is required.

In this work, we used isothermal titration calorimetry (ITC) to determine the thermodynamics of adsorption of three metal ions: Cd(II), Cu(II) and Pb(II) on SBA-GSH. Isothermal titration calorimetry (ITC) appeared as a good technique to get information on both the adsorption thermodynamics and competition effects in this system.[4,5]

Results showed an affinity for Pb(II) > Cu(II) > Cd(II) in single-metal systems and allowed to better understand the nature of the interactions involved in the adsorption mechanism. In particular, it was found that Cd(II) adsorption relied mainly on physical contributions while Cu(II) and Pb(II) adsorption was shown to be chemically driven.

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Imprinted polymers as promising materials for the decontamination of dye pollutants

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Nowadays, the flourishing of the textile industries has led to a sharp increase in the contamination of ecosystems, mostly due to the discharge of effluents containing dye pollutants [1]. In the quest for new inexpensive and efficient methodologies of effluent treatment, our group has been devoting its efforts to design two types of polymeric materials: i) solid phases with high absorption capacity towards dye pollutants, and ii) Fenton-like heterogeneous catalysts for the green oxidative degradation of dyes. As a way to enhance the absorption or catalytic activity, we employed the molecular imprinting technique. Regarding the first type of polymers (i), and as a way to extend the range of dyes that can be efficiently captured, we prepared composites starting from a polymeric matrix as a supporting phase compatible with the packing into wastewater treatment procedures, imprinting absorptive cavities using nanoparticles of zeolitic imidazolate framework (ZIF-8), which exhibit high capacity at dye absorption [2]. In the case of the polymeric catalysts (ii), we imprinted the matrices using iron(III) complexes with proved ability at the oxidative degradation of the dyes upon H_2O_2 addition. The types of dye pollutants included in this work are shown in Figure 1.

Concerning the polymeric absorbents (i), a non-imprinted polymer (NIP) was synthesized in a 1.5:2 methanol:ethanol mixture using methacrylamide as functional monomer, N,N-methylenebisacrylamide as crosslinker and AIBN as radical initiator. The solid phase was tested as dye absorbent in water at pH = 6 and 9. The results show a very low dye capture capacity (mg dye/g NIP): 0.2 – 3.4 (azure A), 3.6 (methylene blue), 0.0 – 0.6 (methyl orange), 0.0 (methyl red) and 0.9 – 2.1 (methyl violet). To enhance the absorption performance, ZIF-8 nanoparticles were employed as templates to imprint catalytic cavities into a molecularly imprinted polymer (MIP), using the above-mentioned polymerization protocol (Figure 1). The MIP showed capture profiles that were highly dependent on the pollutant dye (mg dye/g MIP): 6.3 – 7.4 (azure A), 7.1 – 7.3 (methylene

blue), 0.0 (methyl orange), 0.0 (methyl red), 7.3 – 9.7 (methyl violet). Remarkably, the ZIF-8-based molecular imprinting led to a sharp improvement in the absorption capacity of thiazine- and triphenylmethane-based pollutants, with increments of 281%, 100% and 467% for azure A, methylene blue and methyl violet, respectively. Conversely, both MIP and NIP have no capture ability towards azo dyes. We are now focusing our work on testing other MOFs to enhance the absorption performance.

In the case of the catalytic polymers (ii), we first carried out a screening of Fe(III) complexes with H_2O_2-mediated dye degradation ability [3]. Fe(III)-BMPA and Fe(III)-NTP resulted the best candidates (Figure 1), displaying above 70% of methyl orange degradation in 3 hours. The degradation percentage is enhanced to more than 95% when those complexes are used as templates to imprint cavities into water-compatible polymers, employing the polymerization protocol described above but using $K_2S_2O_8$ as initiator in water (Figure 1). We have extended the range of dye pollutants, as well as tested new iron complexes, bearing ligands with different topologies, coordination numbers, geometries, and donor atoms (Figure 1). Among them, those bearing IDA or ODA ligands show a 50% decrease in the time needed for a complete dye degradation in solution (1.5 hours). We are now encapsulating the best-performance complexes into MIPs. Preliminary results show that the Fe(III)-BMPA-imprinted polymer can decompose methyl orange, methylene blue and malachite green with degradation percentages of 96%, 91% and 38% in 3 hours, respectively.

Both types of imprinted polymers constitute examples of highly promising materials in the search for efficient and low-cost wastewater treatment systems in textile industries.

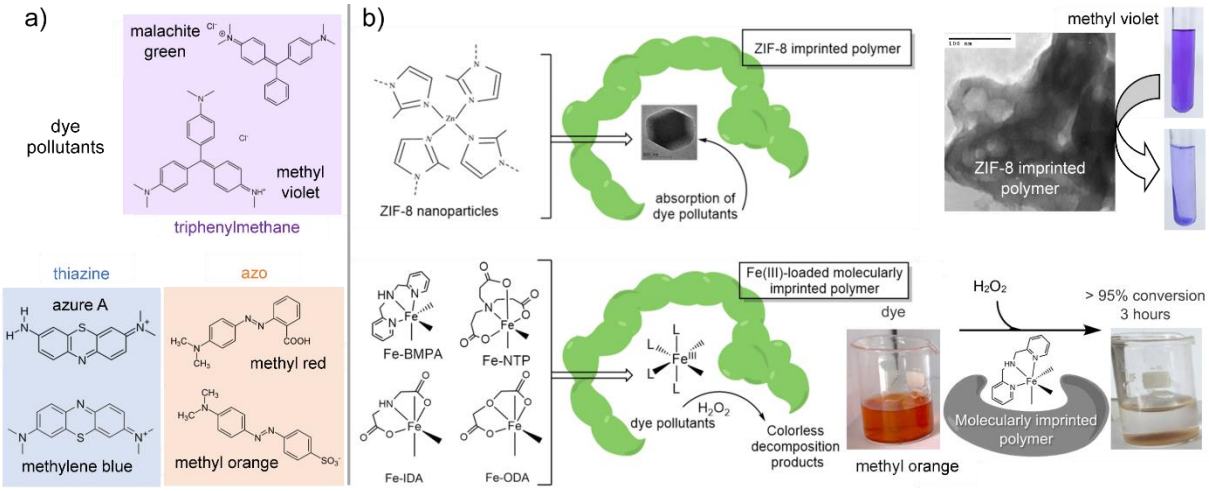

Figure 1. a) Pollutant dyes tested in this work. b) Absorbent and catalytic MIPs prepared and their application. The Fe(III)-loaded MIP catalyses the degradation of methyl orange in water using H_2O_2. Also, a SEM picture of the ZIF-8-imprinted polymer is shown, along with the change in the dye solution before and after the treatment with the composite.

Acknowledgements:

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Adsorption of Trace Cisplatin and Carboplatin onto Thiol-functionalized Sponges: Synchrotron XAS and Surface Complexation

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The presence of Platinum-based cytostatic drugs (Pt-CDs) in hospital wastewater matrices has been observed at concentrations of up to one hundred μg L^{-1}, thereby raising significant environmental concerns.[1,2]

This study investigated the efficient adsorption of trace cisplatin and carboplatin from aqueous solutions using an open-celled cellulose Metalzorb®sponge (Sponge) functionalized with 3-mercaptopropionic acid (MPA) and L-Cysteine (Cys), while examining the influence of pH, time, initial concentration, and temperature on the process. The synthesized MPA@Sponge and Cys@Sponge exhibited significantly higher removal efficiency compared to the original Sponge, with MPA@Sponge achieving a maximum removal of 88.9 ± 0.5% for cisplatin and 85.2 ± 0.4% for carboplatin, and Cys@Sponge achieving a maximum removal of 75 ± 2% and 59 ± 1%. This improvement suggests that thiol functional groups serve as favorable binding sites for Pt-CDs complexation in chelation-dominant chemisorption. The coordination environment of low-loaded Pt on thiol-functionalized sponges was determined through synchrotron EXAFS analysis. It indicates square-planar Pt (II) molecules were complexed on thiol-functionalized sponges via Pt-S bonds (≈2.3 Å). The pseudo-second-order kinetic model effectively characterized the rapid adsorption processes involving diffusion and chemisorption, while the Langmuir model was consistent with the observed monolayer adsorption. The adsorption was significantly enhanced when temperature was increased, and the chelation of cisplatin and carboplatin with thiol groups was an endothermic reaction. The methodology was validated by testing diluted urine samples spiked with Pt-CDs to simulate hospital wastewater, where MPA@Sponge showed high removal efficiency, although matrix effects were observed.

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Multi-techniques characterization and speciation of oxovanadium(IV)/8-hydroxyquinoline-2-carboxylic acid aqueous system

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8-Hydroxyquinolines (8-HQs) belong to an interesting class of heterocyclic compounds showing moderate metal-binding abilities. In the last decades, 8-hydroxyquinolines and their derivatives attracted attention since they seem to be useful structures for the design of new drug candidates. 8-HQ derivatives are widely diffused in nature. In particular, 8-HQ carboxylic acids can be found in bacteria, plants and various animals[1]. 8-Hydroxyquinoline-2-carboxylic acid (8-HQA) shows interesting features such as biological activity and pronounced coordination abilities. 8-HQA is a non-competitive inhibitor of class II fructose 1,6-biphosphate aldolase (II FBA). Considering that II FBA is a zinc metalloenzyme, the interaction between the 8-HQA and the metal ion seems to be crucial in biological systems[2]. The study of the interaction between 8-HQA and biologically relevant metal ions could be interesting to understand its role in the body. In recent years the 8-HQA has been studied in combination with different metal ions, in particular Fe^{2+} and Fe^{3+}[3], and MoO_4^{2-}[4]. Nevertheless, the interaction between the 8-HQA and the oxovanadium(IV) is still unexplored. The study of the speciation of this system in aqueous solution could expand the knowledge about the complexing abilities of the 8-HQA ligand and the chemistry of oxovanadium metal complexes. Vanadium is a trace metal involved in several processes in the human body and essential for some living organisms[5]. Since vanadium ions can play a role in the biological environment, a huge research activity was aimed to explore their chemistry, biochemistry and their possible application in medicinal chemistry.

In the case of the VO^{2+}/8-HQA system, a multi-technique approach was adopted to fully characterize the interactions and the thermodynamic equilibria taking place in the solution. Potentiometric and UV/Vis spectrophotometric titrations were performed, in $KCl_{(aq)}$ 0.2 mol·L^{-1} and T = 298.15 K. Voltammetric experiments and EPR spectroscopy were exploited, to expand the characterization of the system. The metal to ligand ratios studied were 1:1, 1:2, 1:3, with maximum concentration of the ligand $1.2 \cdot 10^{-3}$ mol·L^{-1}. Since the system showed instability due to the possible oxidation of the VO^{2+} ion at alkaline pH, free-O_2 experiments were conducted to explore the system in the unstable region. Combining the information obtained from all the different techniques, it was possible to achieve a good grade of knowledge about the VO^{2+}/8-HQA system. The main species formed in the solution at various pH were identified. The stoichiometries and coordination mode were hypothesized. Lastly, the stability constants of the complexes were estimated, and the pH stability range established. The results suggest the formation of mainly two metal complexes, [VO(8-HQA)] and $[VO(8\text{-HQA})_2]^{2-}$, in the considered pH range (2 – 7) (Figure 1– left). Both complexes contain the fully deprotonated form of 8-HQA, in which the carboxylic group and the phenolic oxygen have released the proton (Figure 1 – right). The complexes are stable only until pH 7 in aerobic conditions. As reported, to extend the stability of the system O_2 must be excluded.

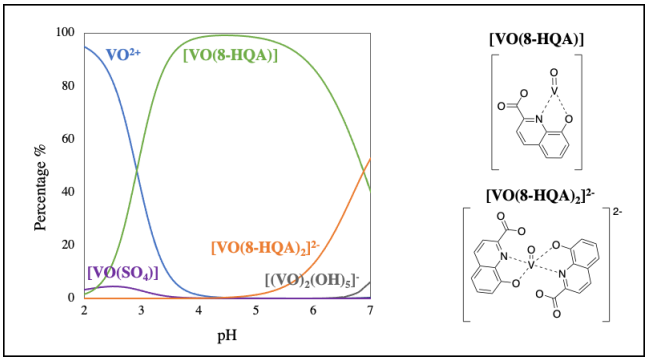

Figure 1. (Left) Speciation diagram of a solution with M:L ratio 1:3 and (Right) hypothesized coordination modes of the formed complexes.

Furthermore, some experiments were conducted by adding an equivalent of Kojic acid (KA) to the solution. The addition is an attempt of increasing the stability of the system forming a mixed complex. Despite the fact that this does not lead to a strong stabilization of the system at pH > 7, the formation of a mixed complex with stoichiometry VO/8-HQA/KA 1:1:1 is observed.

Acknowledgements:

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Unprecedented link between the Irving-Williams series and the stoichiometry in crystals of first-row transition metal(II) complexes with M = Co-Zn, oxydiacetate chelator (oda) and adenine (Hade).

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After some initial trends[1] the renowned by H.M.N.H. Irving and R.J.P. Williams series or natural order (hereafter I-W series) based on increasing empirical/experimental data of stability constants for metal complexes, focuses huge attention.[2,3] Recently its validity has been considered in natural and also in model systems within biological chemistry, both in solution and in solid state.[4-6] Moreover, some anti-Irving-Williams behaviour is also claimed.[7] In fact, isotype metal complexes (M^{II} = Mn-Zn) in crystalline phases are well documented for two, three or four of these metal ions.

In a previous work we reported the crystal structure of $\{(H_2O)_2$**Cu**$_2(ade)_4[$**Cu**$(oda)(H_2O)]_4\}\cdot 6H_2O$, having a hexanuclear complex molecule built on a controlled expansion of a dinuclear core of four bridging μ_3-N3,N9-adeninate(1-) ligands holding together two **Cu**(II) centres. Finally, that results in the mentioned hexanuclear molecule (with anionic adeninate and a windmill-shaped topology).[8]

Now we refer to an unprecedented link between the I-W series in solution to the stoichiometry of ternary metal complexes of M^{II} = Co, Ni, Cu[8] or Zn, with oxydiacetate (oda) and adenine (Hade) as coligands. To extend our results[8] to other M^{II} ions (M = **Co**, **Ni** and **Zn**), we have designed synthesis for M = Co, Ni or Zn and various molar ratios, M:oda:Hade = 1:1:1, 1:1:2, 1:1:3 or 1:1:4. Being the M:oda:Hade ratio = 1:1:2, both Co(II) and Zn(II) give the isotype compounds **1** and **2** respectively, with general formula *trans*-$[M(oda)(Hade)(H_2O)_2]\cdot Hade\cdot 3H_2O$ (monoclinic system, space group $P2_1/c$, figure 1). In clear contrast, the solution with molar ratio Ni:oda:Hade = 1:1:2 initially yields the compound *trans*-[**Ni**$(oda)(Hade)(H_2O)_2]\cdot 2H_2O$ without

Hade solvate (**3**, monoclinic system, space group C2, figure 2-left). That raises the Hade in excess up to a Ni:oda:Hade ratio ~1:1:3! And it leads to the crystallization of *trans*-[Ni(oda)(Hade)$(H_2O)_2$]·Hade·$3H_2O$ (**4,** monoclinic system, space group $P2_1/c$, figure 2-right). Note that his latter compound **4** is isotype with **1** and **2**! Indeed, **4** is mainly obtained from a solution with Ni:oda:Hade ratio = 1:1:3, and better enough with Ni:oda:Hade ratio = 1:1:4 (what finally also gives white crystals of Hade).

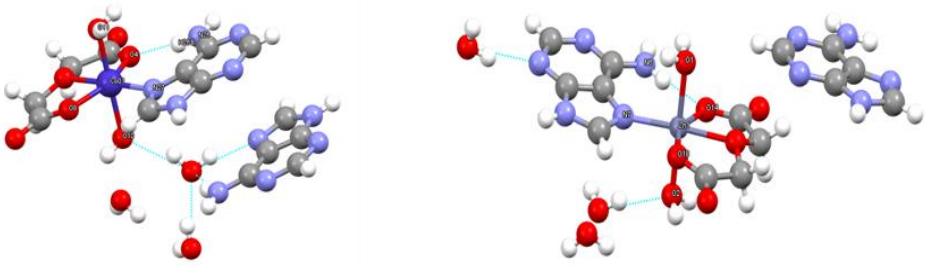

Figure 1. Isotype structures of *trans*-[M(oda)(Hade)$(H_2O)_2$]·Hade·$3H_2O$ (left M = Co, **1**) and (right M = Zn, **2**).

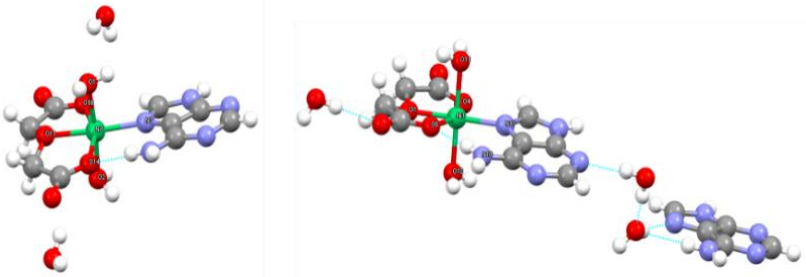

Figure 2. *trans*-[Ni(oda)(Hade)$(H_2O)_2$]·$2H_2O$ (left, **3**) and *trans*-[Ni(oda)(Hade)$(H_2O)_2$]·Hade·$3H_2O$ (right, **4**), the latter being isotype with **1** and **2**, shown in Fig. 1.

Being the basicity order of adenine N9>N1>N7>N3>N6[9], all here reported compounds have its most stable tautomer H(N9)ade. Furthermore, the molecular recognition (metal chelate)-Hade consists of the cooperation of the M-N7(Hade) bond with an interligand interaction (Hade)N6-H···O(oda donor atom), irrespectively of the presence (1, 2 and 4) or absence (3) of Hade-solvate. We conclude that in M-oda-Hade systems (M = Co-Zn) there is an unprecedented link between the assumed I-W series in solution and the stoichiometry in the crystals, being Co ~ Zn < Ni << Cu.

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Ln(III)–18-py$_2$N$_4$Ac$_4$ Complexes: Formation Kinetics, Mechanism of Complexation and Implications for the f-Block Metal Radiochemistry

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Polyazamacrocyclic ligands have been used in radiomedicine for a long time and their complexes are used as diagnostic and therapeutic agents. For potential use of the ligands for radionuclide complexation, it is important to optimize/accelerate formation of their complexes. Since half-lives of most of the metal radionuclides are short, it is of the utmost importance that complexation of these radionuclides has to be rapid. To overcome generally slow complex formation with macrocyclic ligands, a common procedure is radiolabelling at high temperature in a buffered solution and with the ligand in a high excess. However, the high radiolabelling temperature is not compatible with sensitive biologically active substrates for targeted radionuclide therapy and/or for PET/SPECT imaging.

This work deals with formation kinetics and investigation of reaction mechanism of lanthanide(III) complexes 18-membered hexaazamacrocyclic ligand, 18-py$_2$N$_4$Ac$_4$ (in the older literature referred to as H$_4$pyta, (Figure 1). Although this ligand has been known for a long time, its studies are limited.[1,2] It is only known that the light Ln(III) ions are deca-coordinated and one acetate pendant is released with heavy Ln(III) ions giving nona-coordinated species. However, no kinetic/mechanistic data have been published.

Potentiometric studies showed that the trivalent lanthanide complexes of H$_4$pyta ligand are thermodynamically stable enough (logK_{LnL} 22–25) for the aforementioned applications. Combination of kinetic, NMR, UV-Vis and structural solid-state data showed that mechanism of the Ln(III) complex formation is more complicated than for "gold" standards, Ln(III)–H$_4$dota complexes[3] and well-distinguished processes involving two *in-cage* species are present. The complexation follows the common complexation pathway of macrocyclic ligands with a fast formation of weak *out-of-cage* intermediate. It quantitatively re-arranges in a pH-dependent (the common hydroxide catalysis)[3] process to a kinetic *in-cage* intermediate, isomer ***I***. The species slowly coverts into the final thermodynamic *in-cage* complex, isomer ***II***. The second reaction is also slightly pH dependent with an optimal solution pH 3.5–4.5. Kinetics of both processes was quantitatively assessed. From X-ray and NMR data, it was confirmed isomer ***I*** is deca-coordinated for large Ln(III) ions and all the acetate pendants are located on the same side of the approximate N$_6$-plane (Figure 1).

The final complex has two and two pendant arms located on the opposite sides of the N_6-plane (Figure 1). Thus, the second process must involve two ring amine inversions and another intermediate with only one "inversed" acetate arm was also structurally characterised (Figure 1). Rates of overall complexation reactions of Ln(III) ions with H_4pyta and H_4dota are similar.

The deca-coordinated complexes with large early Ln(III) ions are formed relatively quickly at room temperature and, thus, H_4pyta is a suitable parent ligand for radioisotopes of La(III) and Ce(III) where H_4dota is not the most suitable ligand. The data confirmed suitability of 18-membered hexaazamacrocyles for large metal ions.

After a thorough study of the formation kinetics of the H_4pyta ligand it was determined to that the complexation consists of two reaction steps. First, isomer ***I*** is formed quantitatively. After that this isomer slowly isomerizes to more thermodynamically stable isomer ***II***. This final isomer is interesting from the application point of view as it is very kinetically inert.

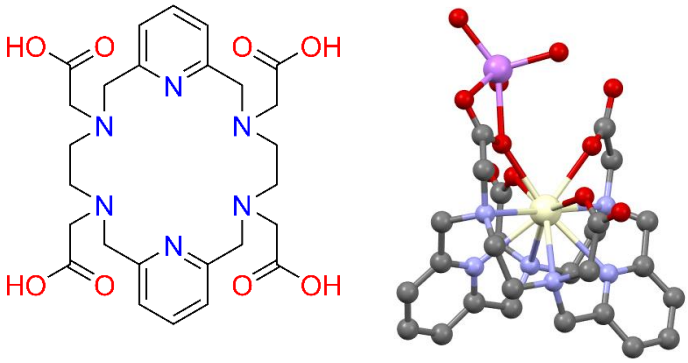

Figure 1: Ligand H_4pyta (left) and crystallographic structures of the intermediate complex with Ce(III) (isomer ***I***, middle) and the kinetically inert final complex with Ce(III) (isomer ***II***, right)

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Boosting Bi^{III}-complexation for targeted α-therapy (TAT) applications with the mesocyclic chelating agent AAZTA

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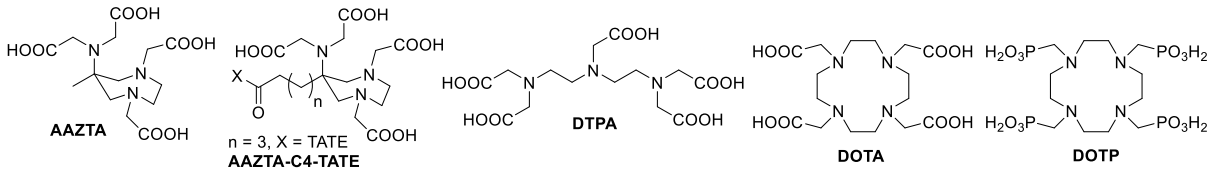
Targeted α therapy (TAT) is a promising tool in the therapy of cancer. Radionuclides $^{212/213}Bi^{III}$ show favorable physical properties for this application, but the fast and stable chelation of this metal ion remains challenging.[1] Different chelating agents (CAs) have been scrutinised for an efficient complexation of Bi^{III} (isotopes) (Figure 1). Acyclic CAs as DTPA form Bi^{III}-complexes with modest inertness, generally not suitable for a safe in vivo use. Rigidification of the acyclic DTPA backbone (i.e. CHX-DTPA) significantly improves the stability of the corresponding chelate, allowing preclinical studies.[2] Macrocyclic CAs bind Bi^{III} with unrivalled stability and for this reason most of the investigated Bi^{III}-radiopharmaceuticals were developed starting from the "gold standard" DOTA.[3] $^{213}Bi^{III}$- and $^{225}Ac^{III}$-complexes of DOTA-peptides conjugates are currently in clinical trials as TAT-agents for the treatment of neuroendocrine tumours.[3] However the formation of Bi^{III}-complexes with DOTA and similar macrocyclic polyaminocarboxylates is extremely slow and requires high temperatures and long times to complete, conditions hardly compatible with the preparation of labile bioconjugates of short-lived isotopes.[4,5]

In this work we demonstrate that the mesocyclic chelator AAZTA quickly coordinates Bi^{III} at room temperature leading to a robust complex. A comprehensive study of the structural, thermodynamic and kinetic properties of $[Bi(AAZTA)]^-$ is reported, along with the targeted agent

[Bi(AAZTA-C4-TATE)]$^-$, embodying the SSR agonist Tyr^3-octreotate.

The equilibrium properties of the Bi^{III}-complexes with AAZTA and AAZTA-C4-TATE have been investigated by following the competition reaction between $[Bi(NTA)]^{3-}$ and AAZTA by pH-potentiometry, spectrophotometry and Capillary Zone Electrophoresis (0.15 M $NaClO_4$, 25°C). The kinetic inertness of the Bi^{III}-complexes with AAZTA and AAZTA-C4-TATE have been determined by monitoring the ligand exchange reactions with DTPA and DOTP as exchanging ligands with spectrophotometry in the pH range 8 – 11. In order to acquire deeper insight into the solution and solid state structure, variable temperature (VT) multinuclear 1D and 2D NMR studies of $[Bi(AAZTA)]^-$ and X-ray diffraction studies of single crystals of $[Bi(HAAZTA)(H_2O)]\cdot 3H_2O$ and $\{[C(NH_2)_3][Bi(AAZTA)]\}\cdot 3.5H_2O$ have been performed.



Scheme 1: Structure of the chelatig agents AAZTA, AAZTA-C4-TATE, DTPA, DOTA and DOTP

Results of the equilibrium and transchelation studies reveal the unexpected increase in the stability and kinetic inertness of the peptide conjugate $[Bi(AAZTA\text{-}C4\text{-}TATE)]^-$ in a respect to the parent $[Bi(AAZTA)]^-$ complex ($\log K_{Bi(AAZTA)}^{cond}$=23.5 and $\log K_{Bi(AAZTA\text{-}C4\text{-}TATE)}^{cond}$=24.3 at pH=7.4, 25°C; $t_{1/2}^{Bi(AAZTA)}$=4.8 and $t_{1/2}^{Bi(AAZTA\text{-}C4\text{-}ATE)}$=43.4 h at pH=9.0, 25°C). The ^{13}C NMR spectra showed eight resonances corresponding to 2:2:2 equally intense methylene and carboxylate carbon atoms of pendant arms and the ring, and 1:1 methyl and quaternary C, indicating that $[Bi(AAZTA)]^-$ has C_2 symmetry in the entire temperature range due to the fast arm rotation and ring-wagging motions. X-ray diffraction studies demonstrate that the coordination polyhedrons around the Bi^{III} ion can be described by an irregular dodecahedron defined by a 1:4:3 stack with the apical H_2O or bridging carboxylate-O^- in $[Bi(HAAZTA)(H_2O)]$ and $[Bi(AAZTA)]^-$ complexes, respectively. Cyclotron produced $^{205/206}Bi$ mixture was used as a model of ^{213}Bi in labelling-, stability- and biodistribution experiments allowing to estimate the efficiency for $[^{213}Bi(AAZTA\text{-}C4\text{-}TATE)]^-$. High accumulation in AR42J tumour and a reduced kidney uptake was observed with respect to the macrocyclic chelate $[^{213}Bi(DOTA\text{-}TATE)]^-$ in AR42J tumour-bearing mice. Based on the detailed physico-chemical, *in vitro* and *ex vivo* studies $[^{213}Bi(AAZTA\text{-}C4\text{-}TATE)]^-$ is a promising alternative to $[^{213}Bi(DOTA\text{-}TATE)]^-$ in the TAT of neuroendocrine tumours.[6]

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Exploring the Coordination Preferences of Ra^{2+} and Ba^{2+} for the Rational Design of Ra-223 and Ba-131/135m Chelators for Theranostic Radiopharmaceuticals

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Introduction

Radium-223 (^{223}Ra, $t_{1/2}$ = 11.43 d) is an α and γ emitter suitable for the treatment of small metastatic tumours. It is currently used in the form of [^{223}Ra]$RaCl_2$ (Xofigo®) for the palliative treatment of bone metastases in patients with castration-resistant prostate cancer. The low fraction of γ emission (< 2%) enables a rather low-quality imaging by Single Photon Emission Computed Tomography (SPECT).[1] Barium-131 (^{131}Ba, $t_{1/2}$ = 11.50 d) and barium-135m (^{135m}Ba, $t_{1/2}$ = 28.7 h) decay by electron capture and isomeric transition, respectively, and might be suitable ^{223}Ra-analogues for improved SPECT imaging, allowing the so-called theranostic approach in cancer management.[2] To enlarge the plethora of potential treatable tumours and prevent the accumulation of these calcimimetic alkaline earth metals in the bones, they should be stably complexed by a chelator, in turn conjugated to a biologically active moiety to direct the emitted radiation solely to the tumour site.[3] However, the shortage of chelating agents capable to firmly coordinate these radioisotopes *in vivo* has hindered their use in targeted cancer therapy to date. The fundamental coordination chemistry of Ba^{2+} and especially Ra^{2+} has not been explored to a large extent so far, hampering the rational design of proper chelators.[4] Therefore, the aim of this work is to explore the coordination preferences of Ba^{2+} and Ra^{2+} in terms of affinity to different donor atoms or groups, thus setting the bases for the subsequent design and development of suitable chelators to be employed in cutting-edge ^{223}Ra- and $^{131/135m}$Ba-based radiopharmaceuticals.

Methods

The following monodentate or bidentate ligands were investigated: acetonitrile (ACN), dimethylsulfoxide (DMSO), benzoic acid (Benz), acetic acid (Ac), phenylphosphonic acid (PhPO), ethyl or methylphosphonic acid (EtPO, MePO), thiophenol (PhS), phenol (PhO), anthranilic acid (Ant), picolinic acid (pa), malonic acid (Mal), 2-hydroxypyridine 1-oxide (1,2-HOPO), glycine (Gly), 3-hydroxy-2-pyridone (2,3-HOPO), salicylic acid (Sal), catechol (Cat).

To compare the behaviour of Ba^{2+} and Ra^{2+}, the electronic binding energies (ΔE) for the reaction $M^{2+} + L^{n-} \rightarrow [ML]^{(2-n)+}$ in water (where M^{2+} is Ba^{2+} or Ra^{2+}, L is the ligand and n its charge in the fully deprotonated form) were calculated by Density Functional Theory (DFT) at the COSMO-ZORA-PBE-D3/TZ2P level of theory.[5] The thermodynamic stabilities (logβ) of the $[BaL]^{(2-n)+}$ complexes were determined by ^{1}H-NMR titrations in H_2O + 10% D_2O by adding increasing amounts of $Ba(ClO_4)_2$ to a fixed amount of L at 25°C and constant pH. Conditional stability constants (logβ') at pH 7.4 were derived from the logβ to consider both the metal-ligand affinity and the protonation state of the ligand under physiologically relevant conditions.

Results and discussion

DFT calculations highlighted that Ba^{2+} and Ra^{2+} behave very similarly since their electronic binding energies are almost identical with all the investigated ligands (*Figure 1A*). The trend of the experimentally determined stability constants (logβ) of the Ba^{2+} complexes is quite in agreement with that of the computed ΔE (*Figure 1A,B*). As expected due to the different number of donor atoms, bidentate ligands usually give more stable $[ML]^{(2-n)+}$ complexes than monodentate ones. Both methods indicate that Ba^{2+} and Ra^{2+} generally prefer more negatively charged ligands - *e.g.* 2− phosphonates (PhPO and EtPO) > 1− carboxylates (Benz and Ac) > DMSO - and oxygen rather than nitrogen or sulphur donors - *e.g.* compare O with S in PhO *vs* PhS, and the pair N,O with O,O in Ant *vs* Sal.

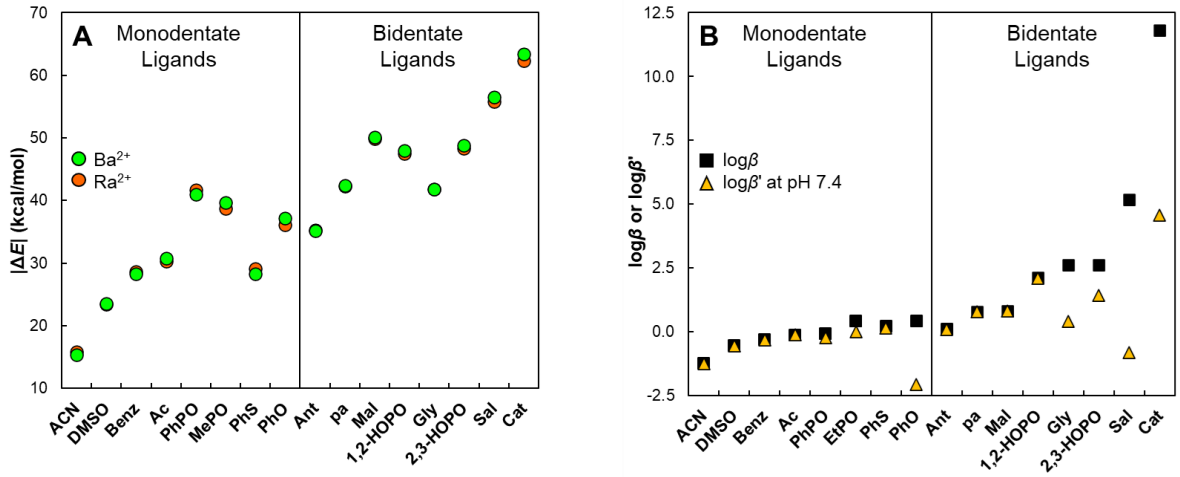

Figure 2. A) Electronic binding energies for $M^{2+} + L^{n-} \rightarrow [ML]^{(2-n)+}$ in water. *B)* Thermodynamic and conditional stability constants at pH 7.4 of $[BaL]^{(2-n)+}$ complexes.

Conclusions and perspectives

This work allowed to select a series of ligands which are more prone to coordinate Ba^{2+} and Ra^{2+} thanks to their chemical structure or donor atoms properties. These include picolinic and malonic acid, 1,2-HOPO and 2,3-HOPO, catechol, and phosphonates. Polydentate chelators based on these pivotal structures are now being developed and studied by our group to open the way towards ^{223}Ra and $^{131/135m}$Ba-labelled targeted radiopharmaceuticals.

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TRASUTA: a new hexadentate spirocyclic chelator for ^{68}Ga based PET imaging

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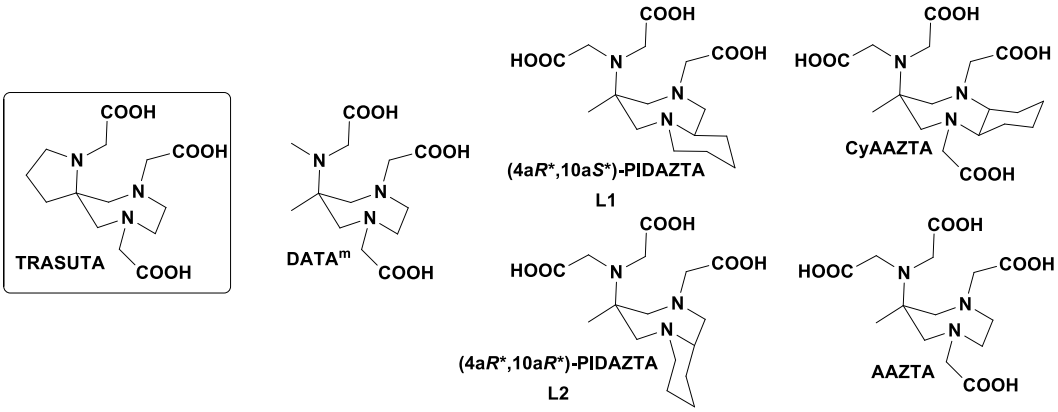
PET is one of the most sensitive imaging techniques used in medical diagnosis, capable of visualizing a variety of disorders and metabolic processes. To obtain the PET image, β^+-emitter isotopes are required and must be placed selectively in the diagnostically relevant region of the living system. Among the positron-emitting radionuclides ^{18}F has very good radiochemical properties: i) short half-life ($t_{1/2}$ = 109.8 min), ii) relatively low β^+ energy ($E_{\beta+}$ = 633.5 keV), iii) easy preparation with small and middle size cyclotrons (^{18}O(p,n)^{18}F), which justifies its wide application in PET. One the most frequently used ^{18}F-based PET radiopharmaceuticals is Fluorodeoxyglucose (^{18}F-FDG). However, the production of ^{18}F-FDG requires a very long and hard synthetic procedure that causes a loss of activity and a risk of radiation to the operating staff due to the decay of the ^{18}F isotope during the labelling process.[1] In this scenario a new interest has been recently devoted to the study of radiometals, in particular those that are available through a generator thus avoiding the dependence from a cyclotron. The ^{68}Ga^{3+} isotope is one of the most promising candidates for PET application because of its wide availability from the benchtop ^{68}Ge/^{68}Ga generator and the easy labelling procedure, which involves a short time complexation with a suitable bifunctional chelating agent.[2]

In this work, the synthesis of the new hexadentate rigid AAZTA ligand TRASUTA* (Scheme 1) and the physico-chemical properties of the corresponding Ga(III), Ca(II), Zn(II), Mn(II) and Cu(II) complexes are summarized. The solution equilibria, the kinetic inertness and the structural properties of the [Ga(TRASUTA)] complex were studied by pH-potentiometry, spectrophotometry and multinuclear NMR spectroscopy.

Equilibrium studies revealed that the formation of the anionic $[Ga(TRASUTA)OH]^-$ species predominates in physiological conditions. The cumulative stability constant $\log\beta_{Ga(L)OH}$ of $[Ga(TRASUTA)OH]^-$ was found to be 11.15, which is the lowest among the Ga(III)-complexes formed with the other AAZTA derivatives ($[Ga(L1)OH]^-$: $\log\beta_{Ga(L)OH}$=14.74[3], $[Ga(L2)OH]^-$: $\log\beta_{Ga(L)OH}$=17.94[3], $[Ga(DATA^m)OH]^-$: $\log\beta_{Ga(L)OH}$=15.29[4], $[Ga(CyAAZTA)OH]^{2-}$: $\log\beta_{Ga(L)OH}$=14.08[5], $[Ga(AAZTA)OH]^{2-}$: $\log\beta_{Ga(L)OH}$=16.57[6], 0.15 M NaCl, 25°C).



Scheme 1: Structure of the AAZTA derivatives

The kinetic inertness of Ga(TRASUTA) complex was determined by following the transmetallation reaction between $[Ga(TRASUTA)OH]^-$ and Cu^{2+} ions in the presence of citrate as an auxiliary ligand. The transmetallation reactions take place by the spontaneous (k_0) and the OH^- assisted (k_{OH}) dissociation of $[Ga(TRASUTA)OH]^-$, followed by the fast reaction between the released TRASUTA ligand and the free Cu^{2+} ions. The comparison of the half-life ($t_{½}$) calculated for physiological conditions (pH=7.4, 25°C) indicates that the half-life of $[Ga(TRASUTA)OH]^-$ is 0.18 hours, which is the shortest among the Ga(AAZTA) derivatives ($[Ga(L1)OH]^-$: $t_{½}$=0.27 h[3], $[Ga(L2)OH]^-$: $t_{½}$=295 h[3], $[Ga(DATA^m)]$: $t_{½}$=11.2 h[4], $[Ga(CyAAZTA)]^-$: $t_{½}$=8.25 h[5], $[Ga(AAZTA)]^-$: $t_{½}$=21 h[6], pH = 7.4, 25°C). Variable pH and temperature ^1H, ^{71}Ga and ^{13}C NMR studies were performed to gain insight on the structural properties of [Ga(TRASUTA)] and $[Ga(TRASUTA)OH]^-$ complexes. In the ^1H NMR spectrum of [Ga(TRASUTA)], there are several sharp multiplets, which are broadened by the formation of $[Ga(TRASUTA)OH]^-$ species. This phenomenon was attributed to the faster fluctional motion, i.e. intramolecular rearrangement of the $[Ga(TRASUTA)OH]^-$ species, which might be responsible for the faster spontaneous and OH^- assisted dissociation of the Ga(III)-complex.

* TRASUTA = 1,7,10-triazaspiro[4.6]undecane-1,7,10-triacetic acid

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Expect (un)expected – peptide fragments of HSPB1 and their binding to metal ions

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Heat shock protein B1 (HSPB1, also known as Hsp27) is an ATP-independent chaperone that belongs to the small heat shock protein (sHsp) family. Its expression is increased upon heat shock, oxidative stress, or stimulation by cytokines[1]. HSPB1 is responsible for maintaining denatured proteins in a folding-competent state. It is also responsible for the phosphorylation and axonal transport of neurofilament protein[2,3]. It plays a role in stress resistance and actin organization.

In general, sHsps are able to form large homo- and hetero-oligomers and possess a so-called holdase activity - they are able to bind misfolded proteins, preventing their aggregation.[4,5] Ten sHsps are known to be expressed in the human organism. They differ in their molecular weight, stress susceptibility, oligomeric structure, and tissue distribution.[5,6]
Some Hsps are able to bind metal ions - for proper function, to improve the stability of the polymers they form, or they are formed in response to the presence of selected metal ions or free radicals generated in reactions stimulated by some metal ions[7,8]. sHsps present in the crystalline lens are called crystallins, and bridges between the subunits formed by zinc ions have been found to increase the stability of α-crystallin oligomers[9]. Some of the sHsps are also able to bind copper ions (II) with picomolar affinity.[10] The α-crystallin sequence is conserved in the sHsps structures - they all contain the "α-crystallin domain". Within this domain, a fragment containing His and Glu residues - a potential binding motif in HSPB1 - was studied by our group. A series of analogs of peptides containing this motif were designed to test whether they could bind metal ions: Copper and Zinc.

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        10         20         30         40         50
MTERRVPFSL LRGPSWDPFR DWYPHSRLFD QAFGLPRLPE EWSQWLGGSS
        60         70         80         90        100
WPGYVRPLPP AAIESPAVAA PAYSRALSRQ LSSGVSEIRH TADRWRVSLD
       110        120        130        140        150
VNHFAPDELT VKTKDGVVEI TGKHEERQDE HGYISRCFTR KYTLPPGVDP
       160        170        180        190        200
TQVSSSLSPE GTLTVEAPMP KLATQSNEIT IPVTFESRAQ LGGPEAAKSD

ETAAK
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Fig. 1. Amino acid sequence of HSPB1 with marked possible binding motif.

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Is there still anything to discover about "old-fashioned" albumin interaction with bromocresol green and similar dyes?

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The interaction between albumins, both bovine (BSA) and human (HSA), and bromocresol green (BCG) at a certain specific pH value was firstly reported by Doumas and co-workers in 1971 and rapidly further investigated by several research groups worldwide in the following years.[1,2] These pioneer works have attracted a considerable interest thanks to the opportunity to quantify, by simple and robust spectrophotometric or colorimetric techniques, such an abundant and important protein exploiting low-cost and commercially available dyes; as a consequence, several slightly different versions have been proposed, changing working pH, adding different surfactants or electrolytes and testing also bromocresol purple (BCP) as reactive dye.[2] More than fifty years later, we can undoubtedly affirm that these methods definitely deserved such interest being still employed both in laboratory routine procedures and in commercial assays.[3]

Going back to our initial question, one might think that the research on albumin interaction with BCG or similar molecules is concluded and this topic has no surprises in store, but this would be a serious pitfall. In fact, despite a quite significant number of publications on this topic, up to our knowledge a systematic investigation and characterisation of albumin-sulfonephthalein dyes interaction has never been carried out but only random tests using different dyes, buffers, pH and medium compositions have been proposed.[2,3] Only on this basis, the knowledge of interaction is fully understood and the most convenient conditions for a practical application can be hunted.

To pursue the scope, we explored by UV-Vis spectroscopy the possible interaction with BSA of five different halogen-containing sulfonephthalein dyes with different protonation constants:[4] bromophenol blue (BPB, $\log K_a$=3.75), bromocresol green (BCG, $\log K_a$=4.42), chlorophenol red (CFR, $\log K_a$=5.74), bromocresol purple (BCP, $\log K_a$=6.03) and bromothymol blue (BTB, $\log K_a$=6.72). Taking into account some preliminary results and BSA behaviour vs. pH as found in

literature,[5-7] UV-Vis spectra of the five dyes (dye concentration 10 µM) at increasing BSA concentrations, ranging from 0 to 1500 mg L^{-1}, were acquired in buffered solutions (buffer concentration 0.01 M) at 4 different pH values (3.5, 6.0, 7.5 and 9.0) at native ionic strength and after the addition of NaCl 0.5 M.

This experimental plan, developed according to a Design of Experiments approach, allow to systematically investigate the system and, opposite to what was expected according to previous literature, to identify in almost all the cases a sort of interaction between albumin and dyes, with different impact on the UV-Vis spectra, as shown in Figure 1. These findings were further confirmed by circular dichroism, fluorescence and ^{1}H-NMR spectra.

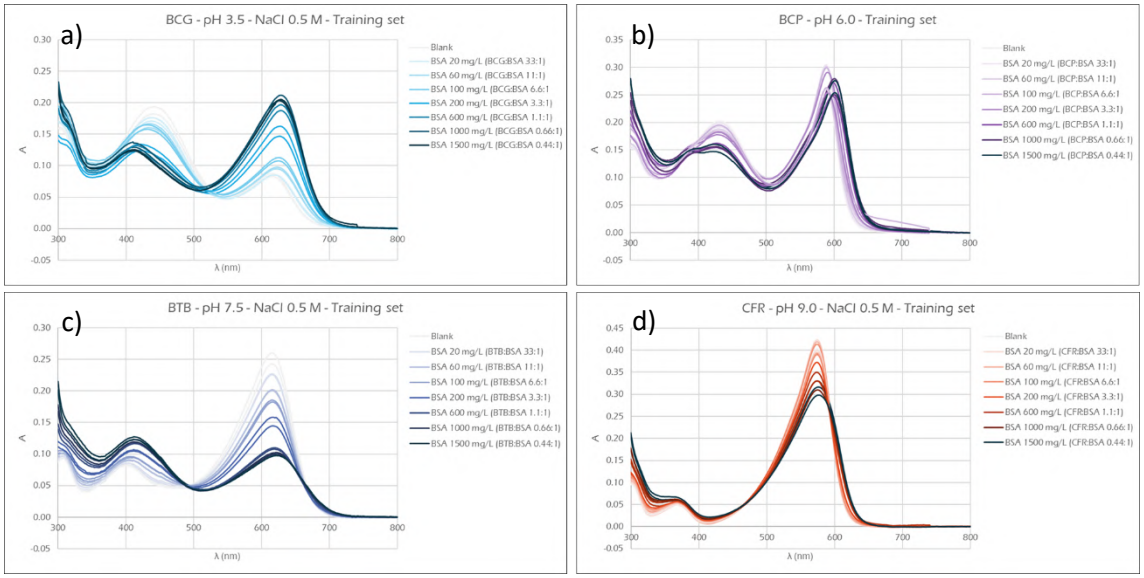

Figure 1: UV-Vis spectra of the dyes (10 µM) at increasing BSA concentrations, ranging from 0 to 1500 mg L^{-1}; in details BCG in citrate buffer 0.01 M + NaCl 0.5 M at pH=3.5 (a), BCP in citrate buffer 0.01 M at pH=6.0 (b), BTB in phosphate buffer 0.01 M + NaCl 0.5 M at pH=7.5 (c) and CFR in carbonate buffer 0.01 M + NaCl 0.5 M at pH=9.5 (d).

Besides, the acquired dataset was then used as benchmark for various multivariate data treatment: Principal Component Analysis (PCA) was exploited to identify the experimental conditions leading to the larger modification on UV-Vis spectra, thus promising even for naked-eye detection or application in sensing devices. In parallel, Partial Least Square regression (PLS) was applied to develop multivariate calibration models for all the tested experimental conditions whose predictive performances were finally compared to optimise the method.

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A close look at uranium complex formation in marine algae after bioaccumulation

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Seawater is one of the top priority environmental compartments for radioactive metal (RM) contamination, being the final and largest receptacle for contaminated waters, which may expose marine organisms to these toxic elements. Current studies aim at providing inventories of RMs in the environment, but the complexity of marine ecosystems is such that a holistic multiscale approach, beyond inventories, is crucial to describe RM reactivity and transfer.[1]

We present here the investigation of uranium uptake by the brown alga *Ascophyllum nodosum* at multiple scales, from tissue to molecular level. To this end we used a laboratory-assembled model ecosystem, doped with uranium (^{nat}U) solutions.[2] Kinetics of ^{nat}U uptake were evaluated by performing contamination experiments in well-controlled conditions. Uranium distribution in the algal tissues was mapped by combining electronic microscopy imaging (SEM), X-ray absorption spectroscopy (XAS) and X-ray fluorescence (μ-XRF). We identified an active bioaccumulation mechanism leading to a specific compartmentalization of ^{nat}U in the organism. SEM highlighted a superficial absorption in thallus and branches and several hotspots in the gametes. XAS analysis identified the formation of uranyl-phosphate complexes (pseudo-autunite phase) in the gametes. Since alginate is the main component of cell walls, the uranyl-alginate complex formation was also investigated *in vitro*.

This type of multiscale strategy and use of complementary spectroscopies can be useful for predicting the risk associated with contamination of living organisms, not only in the case of radioactive elements, but can also be extended to other toxic metals and related complexes.

Figure 1. Picture of *Ascophyllum nodosum* brown algae in seawater

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Ruthenium(II) polypyridyl complexes as versatile tools in the design of photoresponsive therapeutic agents

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The well-known side effects related to the use of commonly employed antitumoral drugs, along with the rising multidrug resistance of bacterial pathogens, make it urgent to develop new and effective antitumoral and antimicrobial agents, which should be based on a new class of compounds rather than analogues of known scaffolds.

In this scenario, ruthenium(II) polypyridyl complexes (RPCs) are an appealing family of compounds due to their unique chemical-physical repertoires, which include light-triggered singlet oxygen sensitizing properties, a good ability to interact with key biological targets, and structural diversity, which enables access to various therapeutic modes of action through a careful selection of the ancillary ligands. The key benefit in each case is having the capacity to spatially and temporally regulate the drug's activation using a light source, thereby improving the ability to distinguish between malignant and healthy tissues.[1]

The efforts in this work were focused on the precise design of novel RPCs to enable their adaptability to various therapeutic circumstances. In this regard, we present a series of bis-heteroleptic RPCs with the general formula $[Ru(dppn)_2L]^{n+}$, containing the popular π-expansive benzo[i]dipyrido[3,2-a:2',3'-c]phenazine (dppn) ligand. Their promising effectiveness as photosensitizers was evaluated in the photodynamic therapy of non-melanoma skin cancer. Additionally, their encapsulation in cubosomes, soft nanoparticles with a lyotropic liquid crystalline core, was explored to enhance their biopharmaceutical properties.[2]

Secondly, the need for drugs that are active even in hypoxic (<1% O_2) conditions prompted us to design a new series of light-responsive RPCs capable of releasing biologically active compounds via an O_2-independent mechanism for the treatment of anaerobic bacterial diseases. For this purpose, Nitroimidazole-based antibiotics were incorporated on a ruthenium scaffold capable of releasing them upon light activation, providing novel photoresponsive tools effective in "*photorelease antimicrobial therapy*" (PAT) [3].

The aim of this communication is to highlight the versatility of RPCs in the development of effective therapeutic agents with widespread application.

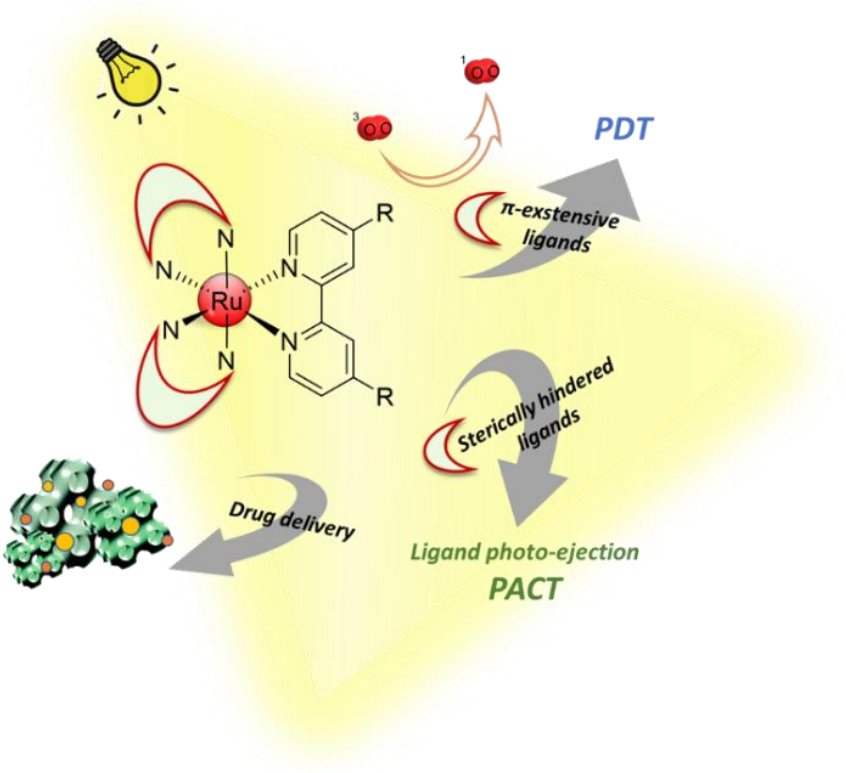

Figure 1: Alternative mechanisms of activation of the RPCs herein reported.

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The effect of serine and threonine on the complex formation and hydrolytic stability of model peptides of tau and tubuline proteins

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Ni(II)-induced selective hydrolysis of peptide bonds has been studied in detail for oligopeptides with different systematically designed amino acid sequences and subsequently for natural protein fragments. These studies have shown that Ni(II)-dependent hydrolysis of the peptide bond occurs in the amino acid sequences –YaaSerXaaHisZaa– or –YaaThrXaaHisZaa– (where Yaa and Zaa represent any amino acid residue and Xaa represents any amino acid residue except Pro). The hydrolysed bond is located between the Yaa and Ser/Thr residues. Ni(II) binding occurs by a planar 4 N coordination through a histidine imidazole-N and 3 preceding peptide N atoms. This causes a bending of the peptide chain and the nucleophilic Ser/Thr hydroxyl group is becomes sterically close to the preceding peptide bond. This results in the formation of an intermediate ester product, which then undergoes spontaneous hydrolysis in aqueous solution. At the beginning the studies of hydrolysis were performed at 45-50 °C, pH range 8.2-8.5.[1-3]

The –SXH– or –TXH– sequence, which is susceptible to Ni(II)-dependent hydrolysis, is present in many proteins (histone, annexin, zinc-finger protein, etc.) but only some of them are capable of undergoing Ni(II)-induced hydrolysis under physiological conditions. It has been shown that the type of amino acid residue near the potential hydrolysis site has a significant influence on the reaction rate.

Numerous natural proteins contain the -(S/T)XH- motif, highlighted two interesting ones, the tubuline and tau proteins. Both proteins related to the neurodegenerative disorders. Alzheimer's disease is characterized by the formation of neurofibrillary tangles composed of hyperphosphorylated Tau and accumulation of extra-cellular amyloid plaques.[4-6] Physiologically, tau regulates microtubule stability by binding to microtubules. Phosphorylation of tau at specific sites, such as Ser262 and Thr231 regulates its binding ability to microtubules. In AD patients, hyperphoshorylated tau proteins have low tubulin-binding activity, and form paired helical filements, which are hypothesized to lead to microtubule destabilization and cytoskeletal abnormailities.[7-9]

Potential metal ion binding sites for both tau and tubulin fragments have –SXH– or –TXH– sequences and these fragments may be sensitive to hydrolysis induced by nickel(II) ions. In our work, we studied the structural change of the formed complexes and the possibility of hydrolysis

under the conditions of solution equilibrium and spectroscopic measurements in case of -SXH-/-TXH- model peptides and the natural tubuline and tau fragments. The role of serine/threonine can be the facilitation of hydrolytic processes by the formation of a defined complex geometry; however, this preliminary step is not enough in each case for the final cleavage of the peptide. Our preliminary HPLC and MS studies show that nickel(II)-induced hydrolysis occurs for Tau(26-33) and Tub(189-195) protein fragments. The hydrolysis products could be detected within one hour at 25 °C.[10]

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A glance at the metal binding ability of fungal ZIP transporters: Zn(II) and Cu(II) interaction with the Zrt2 protein

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Zrt2 is a zinc transporter of the ZIP family, located in the cell membrane and proved to be the major zinc importer in *Candida albicans* under acidic conditions.[1] Since many transition metal ions, and in particular zinc, are crucial for the survival and proliferation of *C. albicans* cells in the human organism, understanding the mechanisms of metal acquisition and regulation is necessary to design new effective antifungal drugs.[2] The predicted three-dimensional structure of Zrt2 protein showed the presence of an extra-membrane, disordered loop containing at least three possible metal binding sequences which have not been characterized before: GPHTHSHFGD, PSHFAHAQEHQDP and DDEEEDLE. Therefore, the corresponding model peptides protected at their termini have been thermodynamically and spectroscopically investigated to elucidate their Zn(II) and Cu(II) coordination properties and to identify the most effective metal binding site. Potentiometric titrations, mass spectrometry and different spectroscopic techniques (UV-Vis absorption, circular dichroism, electron paramagnetic resonance) have been employed to thoroughly study the metal interaction with the selected protein fragments.

To better understand the biological role of the Zrt2 protein, we compared its ability to bind metal ions with that of potential competitor systems, including the zinc-transporter Zrt1 and the human zinc-binding peptide calcitermin, which proved to be active against *C. albicans*.[3]

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Thermodynamics of chelate effect of Pd(II)-oxalate system

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Palladium(II) chemistry in aqueous solution is of interest as a model for analogous platinum(II) systems, due to higher reactivity, well-defined oxidation state and ease of preparation of the aqua ion. Thermodynamic and kinetic data for palladium(II) oxalato complexes are relevant *per se*, but also for example for the understanding of the *in vivo* reactivity of platinum(II) oxalato compounds used as cancerostatic drugs, *e. g.* oxaliplatin.[1]

Oxalic acid (H_2ox) and other carboxylic acids are found in soil solutions in comparatively high concentrations (10^{-4}-10^{-3} mol.dm^{-3}) therefore they are typically present in surface waters in low concentration.[1] Since palladium as the isotope ^{107}Pd is abundant among the long-lived fission products in spent nuclear fuel,[1] modelling of its chemical transformations and migration in natural waters requires reliable thermodynamic and kinetic sequestering data, including data for oxalate complex formation.

Complex formation between $[Pd(H_2O)_4]^{2+}$ and oxalate (ox = $C_2O_4^{2-}$) has been studied by molecular absorption spectroscopy in aqueous solution. Thermodynamic parameters ($\log_{10} K_{1,H}$ = 3.38(8), ΔH^0 = -33(3) kJ.mol^{-1}, ΔS^0 = -48(11) J.K^{-1}.mol^{-1}, T = 298.2 K, I = 1.00 mol.dm^{-3} $HClO_4$ [1]) have been determined for the reaction:

$$[Pd(H_2O)_4]^{2+} + H_2ox \rightleftharpoons [Pd(H_2O)_2(ox)] + 2\,H_3O^+$$

Stability constants for $[Pd(H_2O)_2(ox)]$ and $[Pd(ox)_2]^{2-}$ species ($\log_{10} \beta_1^0$ = 9.04(6), $\log_{10} \beta_2^0$ = 13.1(3), T = 298.2 K, I = 0 mol.dm^{-3})[1] have been calculated by means of SIT.

Formation of $[Pd(H_2O)_2(ox)]$ from $[Pd(H_2O)_4]^{2+}$ is a two-step process, monitored by variable-temperature stopped-flow spectrophotometry. Rate-determining formation of a monodentate $[Pd(H_2O)_3(ox)]$ complex is followed by ring closure to the thermodynamically stable

$[Pd(H_2O)_2(ox)]$ complex. Thermodynamic parameters calculated for both steps show that increased stability of the [Pd(ox)] species for the first step (formation of monodentate complex) is caused by increased higher entropic contribution, while the enthalpic contribution is important for the second step (chelate-ring closure). These results are compared with the ones obtained for Pd(II)-chloroacetate complex.[2] Structural and energetic data obtained by means of DFT (B3LYP-D3 functional with the def2-TZVPP basis set) calculations were carried out for the reaction between $[Pd(H_2O)_4]^{2+}$ and Hox^- with solvent effects introduced by the PCM approach and also with one additional water molecule. The calculated energy barriers for the formation of the bi-dentate complex are slightly higher for the ring closure step.

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Notes and advancements in the development of PyES, an open-source software for the simulation of thermodynamic equilibria in soluble and precipitable systems

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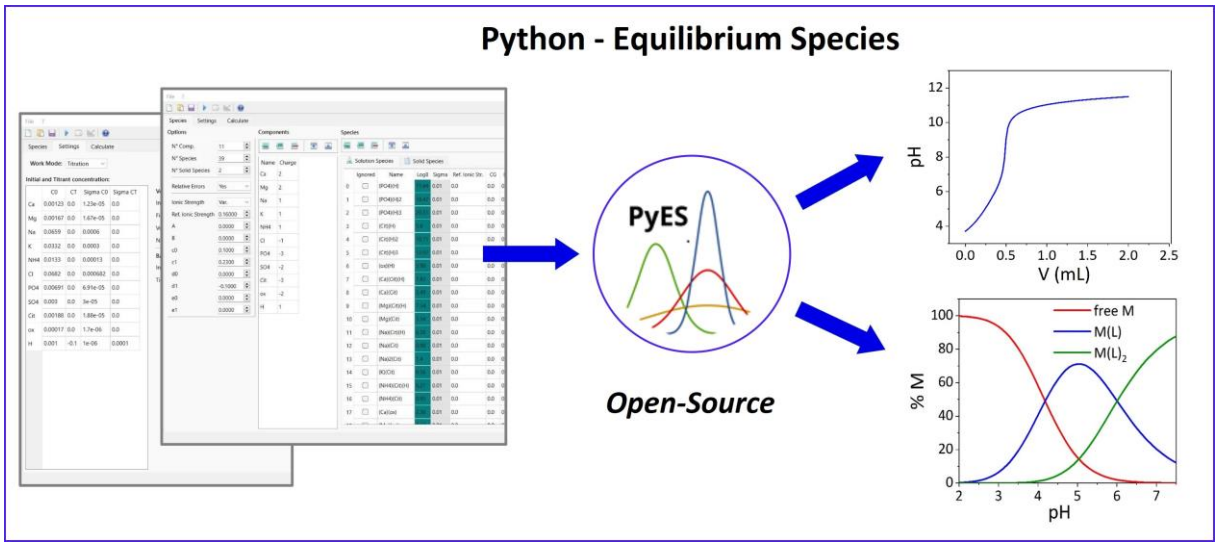

ES4 (Equilibrium Species 4) was a computer program written by Prof. Silvio Sammartano from the Università degli Studi di Messina and his co-workers in the last century leveraging the BASIC programming language [1-5]. It was created to solve chemical equilibria in solutions, and it proved its usefulness in aiding chemists interested in the study of thermodynamic equilibria by calculating species distribution and simulating potentiometric titration curves.

Its development stopped in the ‘90s, with the last versions being terminal based and requiring the input of data through text files.

From a survey conducted among the participants of the Network for Equilibria and Chemical Thermodynamics Advanced Research (COST ACTION – NECTAR CA18202 [6]) it surfaced the need for new and improved computer tools for the study of thermodynamic equilibria. For this reason, we decided to write PyES: a new, open-source, practical, modern and multi-platform Python application, based on the principles of ES4.

As its predecessor, the software has two work modes: potentiometric titration simulation and species distribution at different concentration of one of the components present. Direct improvements from ES4 are the ability to manage solid species and to perform calculations at variable ionic strength, taking into account the dependence of the stability constants on it by an expanded Debye-Hückel equation, both quite desirable features. Moreover, it can boast a new and improved graphical interface, allowing an easier access to the system definition and results export.

PyES has reached the end of its first development cycle with the release of v1.0.0. New improvements in this last version include: computation of uncertainties for the calculated concentrations, improved precipitate calculation, new quick interface commands and general bug fixes. An article in open-access form is currently under-review and the pre-publishing manuscript is already *available for consultation [7]. The software can be downloaded for all major platforms at the link: https://github.com/Kastakin/PyES.*

Acknowledgments:

This contribution is based upon work from COST Action CA18202, NECTAR − Network for Equilibria and Chemical Thermodynamics Advanced Research, supported by COST (European Cooperation in Science and Technology).

Dedication:

PyES and this work are in memory of Prof. Silvio Sammartano, for his invaluable contribution to the development of computer programs for solution equilibria.

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Simulating the chemical equilibria of metal complexes: Insights into the ligand exchange mechanism

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Despite the rich history of experimental studies focusing on the thermochemistry and kinetics associated with metal-ligand complex formation and ligand exchange mechanism,[1] molecular-level computational studies on the complete chemical equilibrium and rate constants of these systems are scarce. In this presentation, we illustrate an integrated computational strategy aiming at effectively describing the structural, thermodynamic, and dynamic properties of various metal ion-amine complexes. Our innovative computational protocol is rooted into molecular dynamics simulations, enhanced sampling techniques, and a stochastic model of ligand exchange kinetics,[2] in addition to recently optimized interaction force fields.[3] Results demonstrate that an accurate description of complex chemical equilibria is computationally feasible and provide some valuable insights into the complex formation and ligand exchange mechanisms.

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Intercalibration network for potentiometric measurements: the case study of EDTA

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Within the purposes of COST Action CA18202 – NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research, the development of new analytical protocols for the design of potentiometric measurements aimed at the determination of equilibrium constants is one of the main issues. In this contribution, the experimental plan and the preliminary results of an intercalibration network are presented for a case study represented by ethylenediaminetetraacetic acid (EDTA), which was selected on the basis of previous knowledge, availability of pure compounds, and presence of equilibrium constants in a wide pH range ($\log K_1^H \sim 10$, $\log K_6^H \sim 2$). Such a ligand carries a tetranionic charge in alkaline conditions (pH > 10), whereas it is dicationic in very acidic conditions (pH < 2).

This feature of EDTA, as well as other highly charged molecules, lead to a variation of ionic strength during a potentiometric titration that, for obvious reasons, has to be considered while designing a potentiometric experiment aimed at the determination of the equilibrium constants. Moreover, all experimental procedures, namely the reactant concentration, the solution volume and the glassware used for the delivery into the vessel should be well planned because they will influence the result of the experiment.

All this considered, a series of laboratories located in different European countries, namely Italy (Messina and Florence), Spain (Valencia), Czech Republic (Praha) have undertaken this intercalibration network under the auspices of NECTAR, agreeing about the instrumental parameters to be adopted for the measurements in terms of conditions (i.e., signal drift = 0.2 mV min^{-1}) and times required to consider the thermodynamic equilibrium to be reached (minimum and maximum are set to 30 and 60 s, respectively).

Then, four concentration levels were selected to measure EDTA protonation constants, namely 0.5 mM, 1 mM, 2 mM, and 3 mM. Ionic strength was set as 0.1 M, KCl was chosen as background electrolyte and the counter ions of all reactants were K^+ or Cl^-. In this sense, the source of EDTA was its dipotassium salt ($K_2H_2EDTA \cdot 2\ H_2O$), whereas KOH and HCl were used as strong base and acid, respectively.

An excel spreadsheet was used to optimize the procedure for the EDTA standardization (with Zn^0 as standard, ammonia buffer and Eriochrome T Black as the indicator) computing the error propagation of a 5-digit analytical balance, burettes and volumetric flasks after each step of the standardization: i) EDTA solution preparation; ii) weighing of Zn^0 and K_2H_2EDTA, iii) reaching of the equivalent volume, and also taking into account the volume of EDTA to be delivered for the potentiometric measurement into a 25 mL vessel. Among several options, the best result was reached (with a percentage error of 0.59 % on the EDTA concentration) preparing 250 mL of a 0.0075 M EDTA solution and using a 50 mL burette for the standardization.

Then, PyES software was used to simulate potentiometric titrations to choose the values for titrant and vessel concentration yielding the smallest ionic strength variation during measurements. It turned out that the best option is to use a ~ 0.1 M KOH as titrant when dealing with 2 and 3 mM EDTA solutions and ~ 0.2 M for 0.5, and 1 mM ones.

Once all experimental plan was established, three sets of measurements were performed in the Messina lab. All sets were identical, but all solutions were freshly prepared before the beginning of a set. Measurements were performed at least in triplicate, and were preceded by a calibration in similar condition of total acid concentration to refine parameters such as standard electrode potential (E^0), acidic junction potential coefficient (j_a), total acid concentration ($c_H{}^0$), ionic product of water ($\log K_w$). Therefore, twelve titrations and twelve calibrations were performed in a set. Other variables were kept constants (operator, instrumental setup, titration parameters, glassware, analytical balance). Potentiometric titrations of EDTA were analyzed with BSTAC4 software in different ways, namely each titration alone, as a group of three replicate and as a set. ANOVA, goodness of fit, principal component analysis and t-tests were used to compare results and to check for repeatability and reproducibility.

Acknowledgements:

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Zn(II) and Cu(II) interaction with peptide models of the recognition interface of ACE2 receptor for SARS-CoV-2 spike protein

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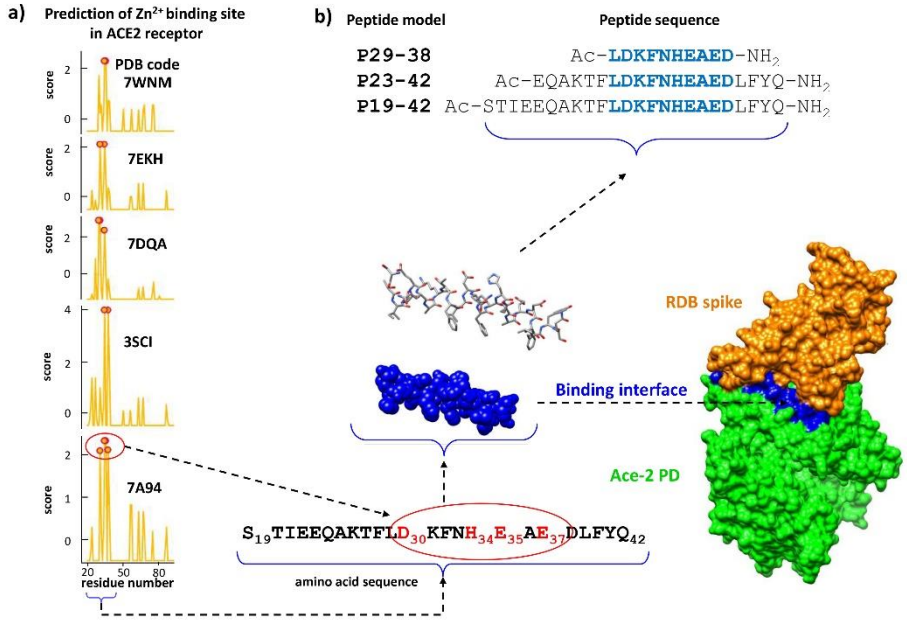
The coordination ability of Zn(II) and Cu(II) ions with selected peptide fragments from the C-terminus region of ACE-2 receptor, that play a crucial role in the binding with spike (S) protein of SARS-CoV-2, has been investigated by a combination of potentiometry, UV-Vis, CD, and NMR spectroscopic techniques. In this region there are specific amino acids involved in the interaction between S protein and ACE2 receptor. This specificity is critical for the virus to establish a systemic infection and cause COVID-19 disease. This fragment is abundant in coordination residues such as aspartates, glutamates and histidine that could be targeted by metal ions. Zn^{2+} ion binds to the ACE2 receptor in its catalytic site and modulates its activity, but it could also contribute to the structural stability of the entire protein. The ability of the human ACE2 receptor to coordinate metal ions, such Zn^{2+}, in the same region where it binds to the S protein could have a crucial impact in the mechanism of recognition and interaction of ACE2-S with consequences on their binding affinity that deserve to be investigated. This study confirmed the bioinformatic previsions obtained by MIB2, which evidenced a specific region (D30-Glu37) in the recognition interface of ACE2 for S protein for Zn(II) and Cu(II) binding (Figure 1) [1].

Figure 1. a) MIB2 prediction of Zn ion-binding sites from a selection of ACE2 X-ray structures. The residues recurrent in all predictions are located in the binding interface between ACE2 and the S protein, localized in the fragment 30-37 aa; b) selected peptide fragments of the binding interface of ACE2 analysed in this study.



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Divalent metal ion binding to *Staphylococcus aureus* transporters

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Staphylococcus aureus belongs to commensal flora; however, it may turn to an opportunistic pathogen. It can harmlessly colonize the anterior nares and is associated with skin colonization [1]. This bacterium can cause a wide variety of diseases, such as wound infections, sepsis, endocarditis, and others. *S. aureus* uses metal ions as cofactors in numerous biochemical processes involving the rearrangement of organic molecules, electron transfer in respiratory processes, structural components of biomolecules, *etc.* [2]. To ensure an adequate level of essential metal ions, the bacterium uses appropriate transporters, for example, FeoB (ferrous iron transporter), MntH (the Nramp-type manganese(II) transporter), CopA (copper ATPase), ZnuB (zinc(II) transporter) and others [3]. These different transporters can be divided into two major types: ATP-binding cassette (ABC) and natural resistance-associated macrophage protein (Nramp) transporters. ABC transporters have been extensively studied and identified as transporters for nearly every biologically important transition metal ion, whereas Nramps have only been identified as transporters for iron and manganese [4]. Herein, combined potentiometric, spectroscopic and mass spectrometry studies were carried out to determine Cu^{2+}, Fe^{2+}, and Zn^{2+} binding by ligands containing fragments of FeoB and MntH from *S. aureus*. The fragments of interest are as follows: Ac-IDYHKLMK-NH_2, Ac-ETSHDKY-NH_2, Ac-SFLHMVGS-NH_2 from FeoB [5], and MNNKRHSINE-NH_2, Ac-KDHRSS-NH_2, Ac-IMPHNLYLHSSI-NH_2, and Ac-YSRHNEE-NH_2 from MntH. The calculated overall stability constants of all complex species allowed us to compare the binding strength of metal ions among ligands and the affinity of individual ligands to different metal ions.

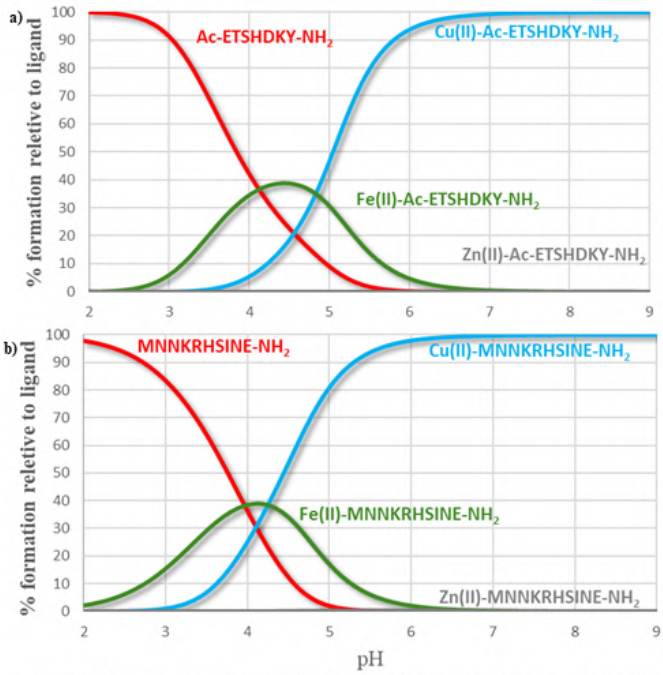

Figure 1. Competition plots for solutions containing equimolar concentrations of M(II) and ligands ([L] = 1 mM) among all studied metal ions towards a) Ac-ETSHDKY-NH_2 and b) MNNKRHSINE-NH_2

For this purpose, previously calculated stability constants were applied to a situation where equimolar amounts of metal ions and each ligand are present in the solution. As can be seen in Figure 1, cupric ions are the most effectively chelated by the Ac-ETSHDKY-NH_2 and MNNKRHSINE-NH_2 fragments. Noteworthy, iron(II) ions compete with copper(II) ions in the acidic pH range. It is important since the physiological pH of human skin is slightly acidic, where anaerobes, like *S. aureus*, are the predominant components of the normal flora and are a common cause of infections with endogenous origin [6].

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New insights on structure and antioxidant activity of copper(II) complexes with Hydroxycinnamic acids

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Natural compounds, present as bioactive constituents in traditional medicinal plants, have been used since the ancient times, and nowadays, they are being introduced as therapeutic agents in several diseases. Among them, natural neuroprotective alkaloids, polyphenols, polysaccharides and terpenoids have been deeply investigated for the treatments of Alzheimer Disease (AD) [1-5]. AD consists of pathological neurostructural degeneration proceeding in a slow and progressive way until the death of the patient [6]. This phenomenon is correlated to the increased life expectancy leading to a major exposure to oxidative factors altering the regular balance of neuronal structures.

Copper is a vital trace element of microorganisms, plants, animals and humans. Its concentration in the human brain is the second highest after the liver (ca. 2.9-10.7 µg) indicating its major role in the central nervous system (CNS). Maintaining copper homeostasis in brain is extremely important in the context of neurodegenerative diseases. Concentration of copper is increased within amyloid plaques, but at the same time other regions of the brain are copper deficient [7, 8]. Copper can bind directly to Amyloid β (Aβ) peptide, inducing formation of oligomeric Aβ species, which are believed to be even more toxic than the fibrillar forms.

Cu^{2+}-Aβ complex formation triggers oxidative stress by producing cytotoxic excess of ROS by Fenton and Haber-Weiss reactions [9]. In AD, mitochondrial dysfunction is also associated with increased oxidative stress levels leading to severe cellular damage. Oxidative stress, mitochondrial dysfunction and protein misfolding are strongly interdependent (Figure 1) and although playing a key role in AD etiology, their implications as a cause or consequence has not been clarified yet.

In this study copper(II) interactions with selected hydroxycinnamic acids and their derivatives were investigated by combining several spectroscopic techniques, like UV-Vis, CD, EPR and NMR providing the structural features of the metal complexes. At the same time, the ability of the investigated compounds to interact with monomeric Aβ peptide was evaluated by means of NMR spectroscopy. Finally, neuroprotective, anti-aggregating and antioxidant properties were evaluated in order to better understand the role played by these compounds in neurodegeneration [4,5].

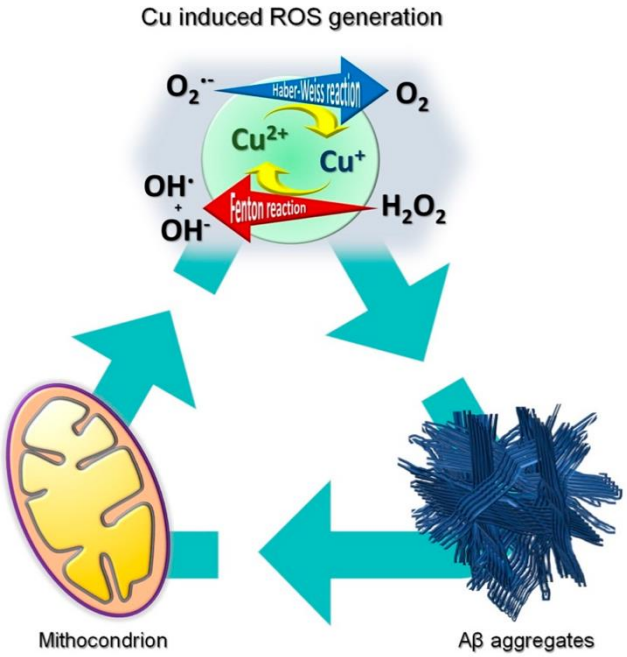

Figure 1: Schematic representation of the interplay between mitochondria activity, copper induced ROS generation and Aβ aggregates.

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Peptidic metallophores as a key to understanding the diverse transport of metal ions in bacteria

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Transition metal ions are essential elements for many pathogens. These nutrients are required in significant structural and catalytic roles in many biological processes. Effective acquisition of metal ions is crucial for the survival and virulence of many pathogens, thus maintaining metal homeostasis is a critical process that must be precisely coordinated by them. To achieve this, bacteria need to use numerous of diverse metal uptake and efflux systems controlled by metalloregulatory proteins. Understanding a novel *metal-acquisition mechanisms* in microbes will make a significant contribution to the development and design of new therapeutics against resistant pathogens, which could be a good alternative for commonly used drugs [1].

The task of zinc uptake in bacteria is far from being trivial. The human host organism does not make zinc uptake easier. In fact, the infected vertebrates seem to realize the importance of this nutrient for bacteria: to hamper pathogen growth, mammals reduce the levels of free zinc. Host restriction of microbial access to certain key nutrients is a process termed 'nutritional immunity. Bacterial cells regulate the uptake, distribution and excretion of zinc through several systems, including the Zn(II)-specific uptake system (ZnuABCD). The crystal structure of ZnZnuA transporter from *E. coli* reveals two metal binding sites: (i) the primary binding site, His143, located close the His-rich loop and (ii) the secondary binding site, involving His224. The interactions of Zn(II) with two model sequences from *E. coli* ZnZnuA were studied [2]. For both Zn(II) binding sites, histidine residues constitute the main anchoring donors forming loop structures when bound to Zn(II). The His-rich loop has a role in the capture of zinc(II), which is then further delivered into other regions of the protein. ZnuD is outer membrane zinc transporter finding in *Neisseria maningitidis*. Cluster 2 from ZnuD is a flexible loop that captures Zn(II) ions, acting as a 'fishing net'. While the binding of native Zn(II) has no significant impact on the structure of its transporter, **Cu(II) binding induces a conformational change of cluster 2 to a polyproline II-like helix.** To the best of our knowledge, **this is the first evidence of a copper(II)-induced formation of a polyproline II-like structure in a sequence that does not contain proline residues [3].**

Nickel is especially challenging for pathogens to obtain from the host, since Ni(II) ions are toxic for humans, and they are present in the serum at very low concentrations (ca. 3 nM).

Thus, Ni(II) must be actively transported into the cell of the pathogen, to reach an appropriate concentration (e.g. ca. 60 nM in *H. pylori*). In contrast to copper or zinc, the host does not use nickel to intoxicate pathogenic cells in macrophages. Two main types of nickel transport systems have been described in bacteria: ATP-binding cassette (ABC)-type transporters, and single permeases.

HypB is one of the chaperones required for proper nickel insertion into [NiFe]-hydrogenase. *E. coli* HypB has two potential Ni(II) and Zn(II) binding sites - the N-terminal one and the so-called GTPase one. We showed that the N-terminal region binds metal ions with higher affinity than the G-domain. Moreover, the N-terminal HypB region is also more effective in Ni(II) binding than the previously studied SlyD metal binding regions. Considering that the nickel chaperone SlyD activates the release of nickel and blocks the release of zinc from the N-terminal high-affinity metal site of HypB, we may speculate that such pH-dependent metal affinity might modulate HypB interactions with SlyD [4].

Acknowledgments:

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On the road to new Oxaliplatin derivatives for colorectal cancer treatment.

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Colorectal cancer (CRC) is the third cancer type for the estimated new cases and deaths in both males and females in the USA [1] and developed countries. Despite recent developments in molecular targeted therapy, chemotherapy still remains the bedrock of CRC treatment, both in the first-line single-agent therapy and in combined regimens such as FOLFOX that associates 5-fluorouracil (5-FU) and oxaliplatin (OX) [2]. OX is a well-known and widely used third-generation platinum-based pharmaceutical, targeting DNA and blocking its replication.

In the search for new, possibly less toxic and more active OX analogues, we have explored the combination of the Pt-binding groups with the stable amino-pyrimidine curcumin moiety. Firstly, several amino-pyrimidine derivatives were synthesized and fully characterized in solution by $^{1}H/^{13}C$ NMR, UV-Vis spectroscopy and mass spectrometry. Then, acid-base equilibria were investigated and preliminary results on biological activity were collected by cell viability assays on different cancer cell lines (HCT-116, HT-29).

The lead compound MPY was linked through an oxopropyl spacer to *N,N* bidentate ligands DAP (1,3-diaminopropane) and DACH (*trans*-1,2-Diaminocyclohexane) and then complexed with Pt(II) (**Figure 1**).

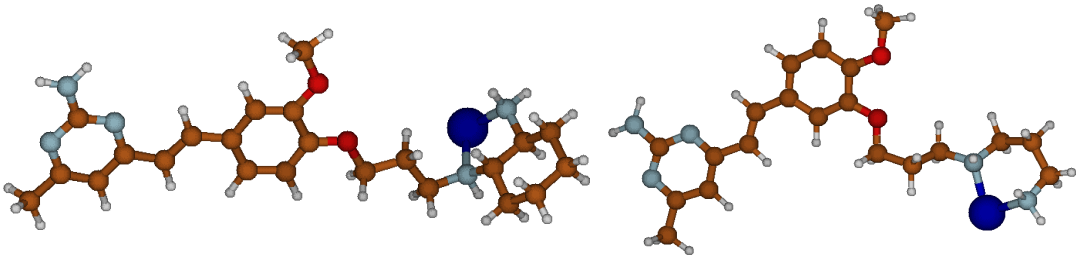

Figure 1: Selected configurations for complexes PtMPY1 and PtMPY2. Solvent is not shown. (Pt= blue, C=brown, H=light grey, N=light blue, O=red).

The investigated Pt(II) complexes underwent solution study (NMR, UV-Vis) and DFT calculations. Computations using Gaussian09 with SCRF implicit solvation. The geometry of Pt(II) complexes was optimized at different levels of theory and the shielding constants were computed in order to predict NMR resonances.

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A comparative study on complexation and biological activity of the anticancer iron chelator VLX600 and its derivatives with essential metal ions

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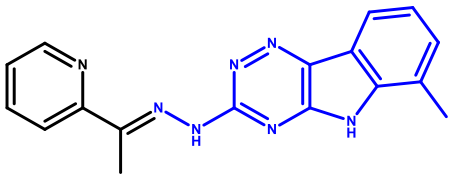
Transition metal ions (iron, copper, zinc) are vital micronutrients, and dysregulation of their homeostasis contributes to the pathogenesis of different types of cancer. [1] These metal ions play a crucial role in the growth and proliferation of rapidly dividing cancer cells, so they have a greater need and preference for iron than healthy cells. [1,2] A novel iron chelator, 6-methyl-3-{(2E)-2-[1-(2-pyridinyl)ethylidene]hydrazino}-5H-[1,2,4]triazino[5,6-b]indole, VLX600 [3] (Scheme 1) was designed to interfere with intracellular iron metabolism, leading to inhibition of mitochondrial respiration. VLX600 displayed antitumor activity with a high therapeutic index both *in vitro* and *in vivo* and was investigated in a phase I clinical trial. [3]

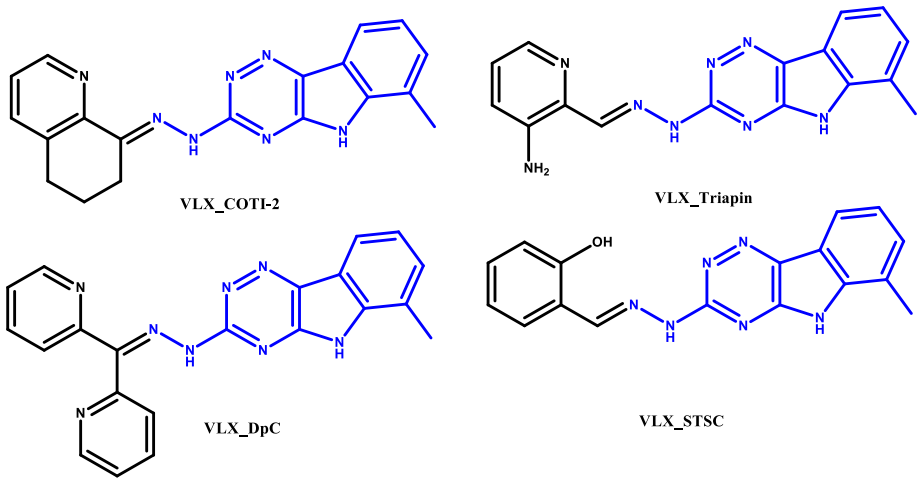
Scheme 1: Chemical formula of VLX600.



In this work we synthesized VLX600 and four different derivatives (Scheme 2), which contain analogous groups to prominent thiosemicarbazones, some of them already in clinical trials (COTI-2, Triapine, DpC, STSC).

First, to better understand their behaviour in solution we determined the proton dissociation processes, thermodynamic aqueous solubility of VLX600 and its derivatives.

Scheme 2: Chemical formula of VLX600 derivatives.



The complex formation of VLX600 with essential metal ions was investigated using UV-visible (Fe^{II}, Cu^{II}, Zn^{II}), electron paramagnetic resonance (EPR) (Cu^{II}) and ^{1}H NMR (Zn^{II}) spectroscopic methods. Based on our findings, we were able to compare the metal binding properties of VLX600 towards the various metal ions. Cyclic voltammetry and spectro-electrochemical measurements were performed to characterize redox properties of the iron complexes of all five ligands. *In vitro* cytotoxic activity of the ligands was determined in different human cancer cell lines (A549, CH1/PA-1, SW480) and was also assayed in the presence of the metal ions. The ability of VLX600 to induce reactive oxygen species (ROS) was investigated by the DCFH-DA assay in CH1/PA-1 and SW480 cells. Although the compounds did not show any notable ROS production, even in the presence of the metal ions, they were highly cytotoxic (IC_{50} values ranging from 0.039 μM to 0.51 μM) and qualify for further preclinical evaluation.

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Acknowledgements:

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POSTERS


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on Metal Complexes

Thermodynamic Studies on Nickel(II) - Favipiravir Antiviral Drug Complex Formation

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Favipiravir (FVP), 6-Fluoro-3-hydroxypyrazine-2-carboxamide (Figure 1), is an antiviral drug that has a great efficiency on various RNA viruses [1-3].

Figure 1. Chemical Structure of FVP

Previous studies pointed out that metal complexes of different active drugs which may act as ligands have increased pharmacological and therapeutic activity [4,5]. In this frame, the present study is aimed at a detailed evaluation of the thermodynamic parameters of the complexation reaction between Ni2+ and FVP. These have been evaluated by spectrophotometric measurements performed at constant temperature for different pH values at constant ionic strength (0.1 M NaCl). Different temperatures in the 20 – 40°C range have been considered.

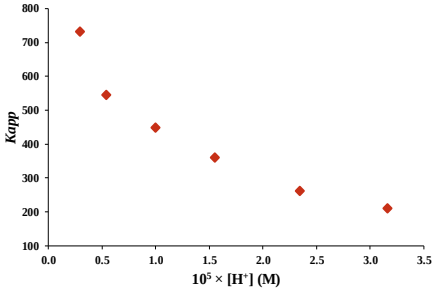

Figure 2. Dependence of *Kapp* on H^+ concentration for the Ni(II)-FVP system., [FVP] = 5.32×10^{-5} M, [Ni^{2+}] = 0-6.0×10^{-3} M, [NaCl] = 0.1 M, I = 0.11 M, T = 25°C.

This contribution will show and discuss the obtained results.

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The protonation equilibria of 8- hydroxyquinoline-2-carboxylic acid (8-HQA) and its precursors: an ITC thermodynamic characterization

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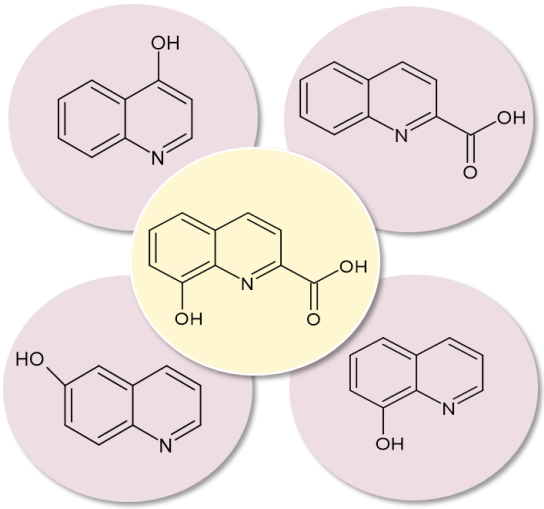
The interest in quinolines, and specifically in 8-hydroxyquinoline (8-HQ) derivatives, has been grown exponentially in the last decades. Many examples of their anticancer, anti-microbial, antioxidant and anti-neurodegenerative activity can be found in the literature [1,2]. It is not surprising that, due to the rich and diverse aforementioned properties, 8-HQ is considered a privileged scaffold in medicinal chemistry. Interestingly, quinolinic carboxylic acid derivatives are widely distributed in nature, from plants to insects and bacteria. For example, 8-hydroxy-4-methoxyquinoline-2-carboxylic acid is a siderophore used for the efficient uptake of iron in *Pseudomonas fluorescens* [3] and 8-hydroxyquinoline-2-carboxylic acid was recently reported as regulator on bacterial abundance and diversity in the midgut of *S. littoralis larvae*, mainly due to its iron chelation properties [4,5]. For a better interpretation of the biological activity of 8-HQA, the knowledge of its chemical speciation is fundamental. During the last years, we dedicated our work to the chemical speciation of different 8-HQA based systems, in particular Fe^{2+} and Fe^{3+}/8-HQA [5] and MoO_4^{2+}/8-HQA [6]. For that purpose, we started by the study of 8-HQA protonation processes.

Nevertheless, all these studies were performed at 298.15 K and, frequently, real systems are at different temperatures. Consequently, we used isothermal titration calorimetry (ITC) for a complete thermodynamic characterization of the protonation equilibria of the mentioned ligand. Through the direct measurement of the heat absorbed/released during a reaction, the ITC technique enables to split the Gibbs free energy values in their enthalpic and entropic contributions, thus providing the driving forces of the protonation equilibria.



ITC experiments were carried out at 298.15 K in $KCl_{(aq)}$ at I = 0.2 mol dm^{-3}. To maximize the formation of each species according to the distribution diagrams, different pH windows were examined allowing an accurate determination of the ΔH^0 values for each protonated species formed in solution.

From the obtained results we could observe that, as long as the acidity of the function group increases (OH > N > COOH), the heat involved in the protonation process decreases meaning that the reaction becomes less exothermic. The first protonation step is enthalpy driven along with a favorable entropic contribution likely due to desolvation, whilst different forces drive the protonation of nitrogen and carboxylate moieties. These results are also compared with the values obtained through the application of van't Hoff equation to the data previously determined by ISE-H^+ (glass electrode) potentiometric titrations at different temperatures ($288.15 \leq T / K \leq 318.15$). For a more extensive understanding on the thermodynamic contribution of each functional group and its position in the hydroxyquinoline structure, several 8-HQA precursors/derivatives were also studied at the same conditions, such as quinaldic acid and a series of hydroxyquinolines, being the relative position of the hydroxyl group discussed.

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Chemical characterization and speciation of the soluble fraction of Artic PM10

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The soluble fraction of atmospheric particulate matter can affect the chemistry of the atmospheric aqueous phase. Compounds such as transition metal ions are known for their (photo-)catalytic behaviour and their tendency to form complexes in solution [1]. The chemical form of metal ions depends on the soluble fraction composition and can affect the fate and the (photo-)catalytic properties of metals. This study was focused on the definition of the components concentration and of the species distribution in the soluble fraction of Arctic PM10 samples collected at Ny-Ålesund (Svalbard Islands) in 2012. The concentration of Na^+, K^+, NH_4^+, Ca^{2+}, Mg^{2+}, Mn^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+}, Al^{3+}, Cl^-, NO_2^-, NO_3^-, SO_4^{2-}, PO_4^{3-}, formate, acetate, malonate, and oxalate in water were determined by ICP-OES, SF-ICP-MS, and ion chromatography. Principal component analysis was used to describe the similitudes and seasonal differences between samples by the variability in the concentrations of the components. Speciation models were applied to define the major species that were formed in solution as a function of pH using the software PyES [2]. As first approximation, the formation of mixed species was neglected. The formation constants of the species potentially involved in the chemical system were derived from the literature data [3, 4, 5]. When it was possible, it was chosen those estimated at quite low ionic strength, because of the low concentration of the ionic components in the samples. The extended Debye-Hückel equation [6] was applied to take into account the variation of the ionic strength of the chemical system as a function of the concentration of the charged species and the species concentration was then estimated at the actual ionic strength value. The model highlighted: *i*) the presence of the main cations such as Na^+, K^+, Mg^{2+}, and Ca^{2+} in the form of aquoions through all of the investigated pH range (2-10); (*ii*) Cu^{2+}, Zn^{2+}, and in particular Fe^{3+} and Al^{3+} are mostly present in their hydrolytic forms; *iii*) Al^{3+}, Fe^{3+}, and Cu^{2+} have solid hydrolytic species that precipitate at pH slightly higher than neutrality; *iv*) Al^{3+}, Fe^{3+}, and Cu^{2+} these metals show interesting interactions with oxalate and sulphate ions. The speciation models were also calculated considering the seasonal variability of the concentration of the components and at higher concentration level to better simulate the real environmental conditions. In fact, the water associated to the particulate at low temperatures is very scarce. The results highlighted the main role of oxalate as ligand in solution. These must be considered as preliminary results useful for defining the main species that could be formed in solution. In fact, the thermodynamic constants used here for the speciation models were defined at 25 °C, a temperature far away from the temperature found at the Svalbard. Future studies will be therefore necessary to estimate the formation constants of these species, together with the related protonation constants of the ligands, at low temperatures and at different ionic strengths, to improve the modelling capacity.

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Dyes in food chemistry: empirical use versus descriptor-based design

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In the last decades a plethora of old molecules able to change their colour with the pH, like sulfonphtalein dyes do, has arisen a new success. Some of them are reported in Figure 1. While synthetized mostly around the middle of the past century, and mainly employed as acid-base indicators, sulfonphtaleins have been intensively used almost in each branch of chemistry, directly in solutions or immobilized on sensors.

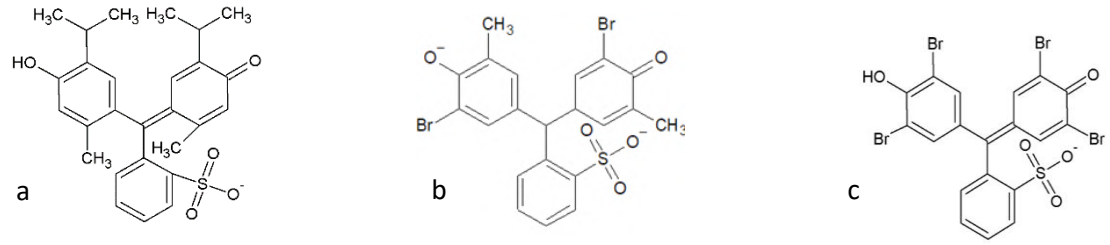

Figure 1-The chemical structure of a) thymol blue b) bromocresol purple and c) bromophenol red.

For example, in marine chemistry, the use of molecules such as thymol blue (Fig. 1a), but also *o*-cresol red and *m*-cresol violet, had started since the early 1980s, for accurate measurements of the pH of marine waters, where the potentiometric ones manifested all their limitations [1]. The not-trivial question of the effect of dyes' impurities on the colour change has also been discussed [2]. In this specific context, the proposed solutions always refer to the peculiar conditions such as high salinity and low temperatures of ocean waters. In biochemistry and medicine, surprisingly, indicators still play a crucial role in the detection of cellular abnormalities. Bromocresol purple (Fig. 1b) was originally proposed as reagent for colorimetric of albumin detection [3], and it has been recently included into a commercial assay [4] demonstrating the

endless interest towards these old reagents. In food science and technology, sulfonphtaleins have intensively exploited for their capability to sense the different acidity of molecules developed in the headspace over a packed proteinaceous food allowing to establish the spoilage level.

Despite of this wide interest, the choice of these dyes, especially in implemented devices, is often totally empirical.

It means that the behaviour of some, sometimes many, of them is experimentally tested, and the effect on the specific phenomenon registered. The choice of the selected dye is valid only under the selected conditions, and there are scarce attempts to understand the reason of the choice.

Food science gives exemplary cases: authors claim to employ a pH indicator to detect biogenic amines when the choice of the dyes reflects the rather limited presence of basic molecules in volatilome [5]. Conversely, the selection is made in lab condition and the possible change of log$K$ caused by modified conditions (embedding of dyes into a sensor that causes a different hydrophobicity [6] or change as function of T) is almost never taken into account.

A systematic study of the effect of temperature on log$K$ obtained by potentiometric measurements of the most common sulfonphtaleins is presented. The reactions are all exothermic, i.e. the protonation constants decrease increasing T. On this basis it is possible to rationalize some previous findings, and once again the equilibrium constants prove to be above all a practical and universal tool for designing and predicting the behaviour of the receptor according to its application.

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Ethyl versus butyl: a story about the different solution equilibria and biological properties of two Ag(I) anthracenyl bis-NHC silver complexes

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Silver compounds have been tested for many years as antimicrobial, starting from the spread use of silver nitrate in ancient times [1, 2]. Among them, Ag(I) complexes of N-heterocyclic carbenes (NHCs) have been extensively used for their diverse applications, like intermediate for transmetallation reactions [3], catalysts [4], and the interest not only as antibacterial agents but also for their application as anticancer drugs increased [5].

Here we propose two Ag(I)-bisNHC (Figure 1) that only differ in the length of the carbon chain attached to the N atom of the imidazole. A study on the thermodynamics of the binding with CT-DNA, DNA G-quadruplex (Tel-23), synthetic RNA and bovine serum albumin has been performed. Spectrophotometric and spectrofluorimetric titrations have been used to evaluate the binding constants at different temperatures, and HR-MS experiments enabled us to highlight the different binding modes with the protein.

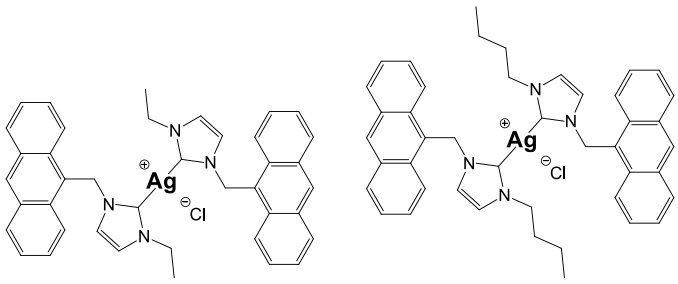

Figure 1. Molecular structure of the studied Ag(I)-bisNHC complexes.

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Anticancer potential of diruthenium bis-cyclopentadienyl carbonyl complexes

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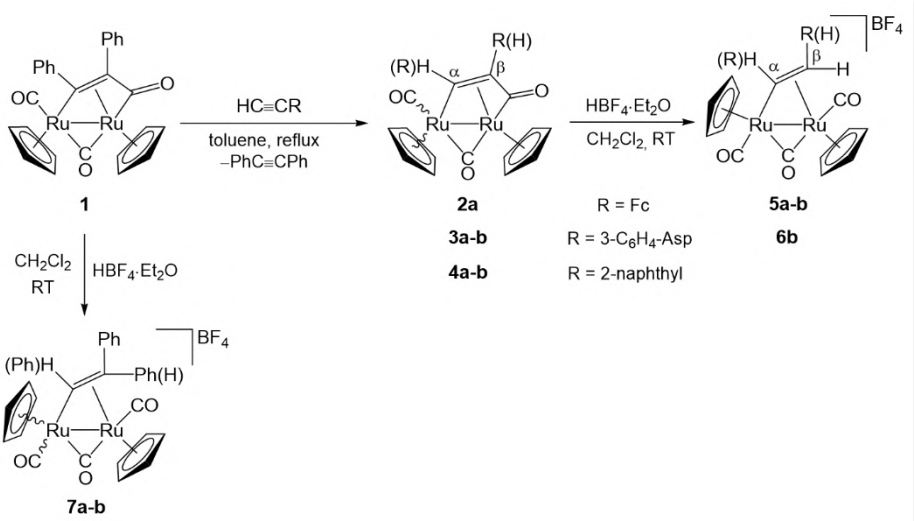
Within the wide efforts devoted to the search for new anticancer drugs based on metal complexes, ruthenium plays a major role [1]. Also, the presence of a bimetallic scaffold was found to produce some advantages over platinum-based drugs [2] but the detailed mechanistic reasons for this reactivity are still poorly investigated. Therefore, we thought that it can be of interest to synthesise a series of diruthenium complexes, obtained thanks to the incorporation of an alkyne and also bearing residues of known cellular properties (ferrocene, naphthalene, aspirin) (Scheme 1).



Scheme 1. Synthesis of diruthenacyclopentenone (**2**-**4**) and μ-alkenyl complexes (**5**-**7**). **2a**-**7a** refer to the geometric isomer with H on α carbon, while **2b**-**7b** refer to the alternative geometric isomer with substituents given in parentheses (R on β carbon).

Indeed, complexes **5**-**7** were found to be cytotoxic with activity comparable to that of cisplatin, and **2**, **5**, **6** and **7** overcome cisplatin resistance in A2780cis cells. Complexes **2**, **5** and **7** (but not **6**) induced an increase in intracellular ROS levels.

To get further insights on these properties, we have carried out an analysis of solution equilibria connected to the binding of **5**-**7** to different biosubstrates such as calf thymus (CT-DNA), synthetic RNA (poly(rA)poly(rU)) and the serum albumin protein. The results of these studies show that the diruthenium metal complexes **5**-**7** have very different affinities for the different substrates considered: this aspect will be discussed.

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Redesign of Spy construct to obtain artificial metalloproteins: metal binding, molecular modelling and catalysis.

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Metalloproteins promote several of the most complex biomolecular processes in nature. Metalloprotein design is a powerful tool for development of tailored proteins, allow us not only mimic biologically relevant metal sites and protein functions [1] but also develop new systems able to response to the increasing demand for synthetic catalysts with enzyme-like performances. Recent efforts focused on development of artificial metalloenzymes.[1-3] In this context, the "Trojan-horse" strategy is an efficient method to afford one of the major challenge in the redesign of metalloprotein; the introduction of metal binding sites in specific position of the construct. Adding a protein, bearing a metal site, the interaction between the protein and its substrate allows the metal site to be anchored to the protein.

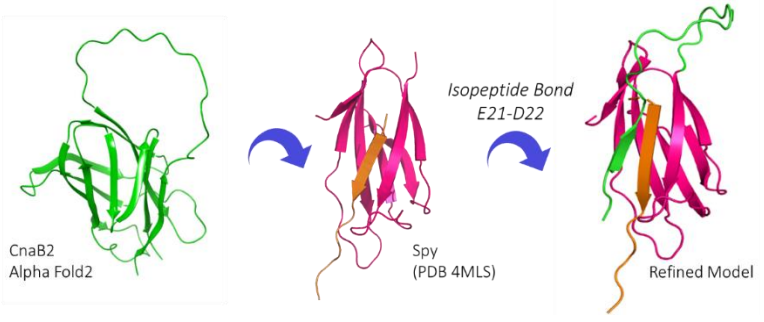

Figure 1: Representation of the molecular modeling approach used to refine the SpyCatcher/SpyTag complex. A refined models of CnaB2 (PDB: 2X5P) with the predicted N-terminus β-strand loop was used for Spy complex (PDB: 4MLS) refinement and isopeptide bond parametrization. The resulting SpyCatcher/SpyTag refined model shows in green the predicted N-terminal β-strand (SpyCatcher. Magenta; SpyTag. Orange).

Here we present a molecular modeling study of the SpyCatcher/SpyTag complex. The SpyCatcher construct is a β-barrel protein (rational optimized by Howarth and co-workers[4-5] starting from the domain CnaB2).
SpyCatcher (Figure 1, magenta) binds covalently an oligopeptide called SpyTag (Figure 1, orange) through an almost instantaneous formation of an isopeptide bond between an Asp and a Lys residues.

However, since the crystallography structure of CnaB2 it is not completely resolved also the Spy complex is not completely resolved in the N-terminal region. By a complementary approach between homology modeling and artificial intelligence modeling we confirmed that Spy's predicted structure could complete with a N-terminus β-strand loop (Figure 1, green). That allows us to hypothesize to consider the modelled structure as a new starting point for future for the metal enzyme design development.

At the same time, SpyTag ad SpyCatcher were independently fully characterized by absorption, CD and fluorescence. Also the construct SpyCatcher/SpyTag was investigated,

Spectroscopic data showing that the Spy complex binds two equivalents of Cu(II); where the first Cu(II) binds at the metal ion site of SpyTag and the second equivalent of Cu(II) binds at the N-terminus of SpyCatcher The data obtained proves the binding of metal ions, occurs sequentially in the Spy complex; in agreement with the affinities determined for the two individual components.

Finally, the catalytic properties in hydrolysis of phosphoesters and oxidation of catechols will be present.

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Investigation of the competition effects in M(II) adsorption on functionalised mesoporous silica by Isothermal Titration Calorimetry (ITC)

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The expansion of industrial activity such as chemical, textile, electronics, pharmaceutical, metallurgical industries and nuclear power plants drastically increased the quantity and diversity of pollutants releases in water, air and soil. Among these pollutants are found hazardous metals, which are a great threat to the environment and may have serious consequences for all living organisms [1]. A variety of techniques have been developed to remove selectively and efficiently these metallic pollutants from wastewater at low concentrations, among which adsorption appears as a simple, low cost, and efficient technology [2]. Due to the co-occurrence of multiple metal ions in aqueous effluents, one of the main challenges is to study the competition and selectivity effects between different metal ions on a given adsorption system.

In this work, isothermal titration calorimetry (ITC) was used in biphasic solid/liquid systems to determine the competition effects between Cd(II) and Pb(II) and between Cu(II) and Pb(II) in their adsorption on a glutathione-functionalised SBA-15 silica [3]. In the case of the Cu(II) + Pb(II) system, no competition has been identified, while in the Cd(II) + Pb(II) system, both ions are competing for the same adsorption sites. This combined adsorption/ITC study thus highlighted the presence of different mechanisms for each metal ion and could be used as a tool to investigate its applicability for industrial effluents treatment.

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Complexation of environmentally and biologically relevant metals with 3-hydroxy-1,2-dimethyl-4(1H)-pyridone (Deferiprone).

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3-hydroxy-1,2-dimethyl-4(1H)-pyridone (Deferiprone, DFP) is an approved orally active chelating drug for the treatment of iron overload patients [1]. DFP can cross the brain-blood barrier and consequently it can be useful for other medical applications, i.e., as anticancer agent in the form of metallodrugs [2]. As expected, most of published data in literature are focused on the biological and therapeutic activity of DFP, while relatively few data [3] are reported on its solution chemistry, despite the thorough knowledge of its acid-base and coordination behaviour are of fundamental importance for the understanding of its properties in aqueous solution, as biological fluids are. Moreover, the relatively few thermodynamic data available (necessary to assess the speciation of this ligand in the system under study) are reported in single, specific conditions, while it is well known that the most of biological fluids (and natural waters) are, from a chemico-physical perspective, multielectrolyte aqueous solutions of very variable composition, ionic strength, and temperature. Therefore, in this contribution we report the results obtained, by potentiometric and spectrophotometric measurements, on the binding ability of DFP towards Mg^{2+}, Ca^{2+}, Cd^{2+} and Pb^{2+} in KCl_{aq} at T = 298.15 K and different ionic strengths ($0 < I$ / mol $dm^{-3} \leq 1.0$). Despite the importance of these cations, since they are involved in many mechanisms both biological and environmental, to our knowledge almost no data are present in literature on these interactions. For all the metals under study, from preliminary results the main species were the ML and ML_2 and MLOH species only for Cd^{2+} and Pb^{2+}. The sequestering ability of DFP towards M^{2+} was evaluated by determining $pL_{0.5}$ (the ligand total concentration required to bind the 50% of the metal cation). The whole set of the data collected may be crucial for the development of DFP-based materials for natural fluids selective decontamination from heavy metals. The dependence on medium, ionic strength of the complex formation constants obtained has been modelled by classical approaches, such as the Extended Debye-Hückel (EDH) and Specific ion Interaction Theory (SIT).

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Kojic acid derivatives for oxovanadium(IV) complexation

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Vanadium compounds display pharmacological human activities, such as antiviral, antibacterial, anticancer and antidiabetic ones. Among them several salts have been used for their insulin mimetic activity and, recently, metal complexes have been recognized for their ability to be absorbed by the gastro-intestinal tract and transported in the blood. Promising compounds in this regard are those formed by 3-hydroxy-2-methyl-4*H*-pyran-4-one (maltol) and 3-hydroxy-1,2-dimethylpyridin-4(1*H*)-one (deferiprone, DFP) [1,2].

In the frame of this work we present oxovanadium(IV) complexes of tetradentate ligands (L1 and L8) containing two hydroxypyrone moieties due to the presence of kojic acid and standing out for methyl group of the linker. The characterization of the complex formation equilibria have been done by potentiometry, UV and EPR spectroscopy supported by DFT calculations.

The complexation starts at very low pH values with the formation of 1:1 complex ($(V^{IV}O)LH$) reaching the formation of binuclear species ($(V^{IV}O)_2L_2$) since pH 4. The arrangement of the two donor groups around V(IV) is (equatorial-equatorial); (equatorial-axial), as for kojato ligand. The distances V–O_{keto} are 2.068–2.096 Å, while those V–O^-_{phen} are 1.963–1.964 Å in the equatorial plane and 2.119–2.127 Å in the axial position; the V–OH_2 lengths are 2.119–2.104 Å. The distance V···V is 7.201 Å. Moreover, two symmetrical intramolecular hydrogen bonds take place, between the hydroxymethyl groups and the coordinating water ligands. Finally, the interaction with proteins, such as lysozyme have been investigated by docking studies.

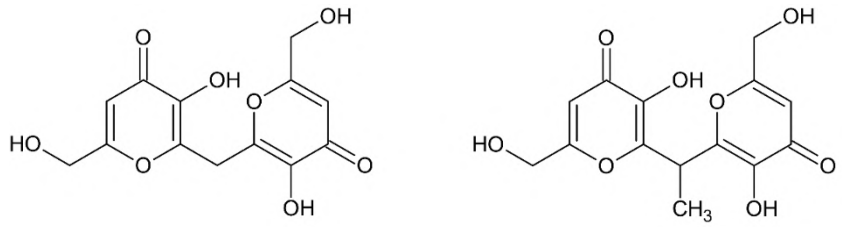

Figure 1: Chemical structures of ligands with acronyms: L1 (6-5-hydroxy-2-hydroxymethyl-pyran-4-one]-5-hydroxy-2- hydroxymethyl-pyran-4-one; L8 (2-2′-Ethanediylbis(3-hydroxy-6-(hydroxymethyl)-4H-pyran-4-one)).

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A comprehensive study on the biospeciation of two half-sandwich organoruthenium complexes

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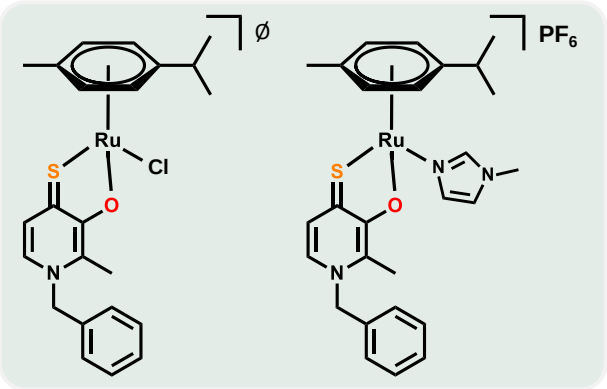
In the research field of anticancer metal complexes ruthenium compounds NAMI-A, KP1019, NKP1339 (BOLD-100) and recently the Ru(II)-containing TLD-1433 have entered into clinical trials [1-3]. Half-sandwich Ru(II)-η^6-arene complexes are extensively investigated, since the reduced forms of clinically relevant Ru(III) drug candidates were proposed to exert the anticancer effect.



Complexes of Ru(II)(η^6-*p*-cymene) bearing a bidentate ligand (see figure) are widely studied, and recently numerous organometallic compounds were synthesized and tested against human cancer cells. Initially, DNA was suggested as primary target of half-sandwich complexes as well, however, attention directed soon to intra- and extracellular protein targets [4,5]. Proteins have a crucial role in the transport and mode of action of metal-based drugs pointing out the importance of studying metal complex – protein interactions in order to understand their pharmacokinetic and pharmacodynamic behavior.

Binding towards transport proteins *e.g.* to human serum albumin (HSA) may have an important effect on the distribution, metabolism and excretion of a metal complex. Advantage of HSA binding shows up by the enhanced permeability and retention effect of solid tumor tissues resulting in the accumulation of protein bound drugs close to the cancer cells.

The complexes studied in this work possess a bidentate thiopyridone ligand, they differ in the monodentate ligand, which is chloride ion or an acid sensitive leaving group N-methyl-imidazole (see figure). These complexes were proven to be active against A549 and SW480 cancer cells *in vitro* [6].

Herein we report the aqueous stability of the two Ru(II)(η^6-*p*-cymene) complexes along with their binding to HSA and blood serum components. Binding to HSA and protein constituents of whole serum was investigated via equilibrium dialysis, UV-vsisble spectrophotometry and spectrofluorometry.

Acknowledgement:

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Ionic liquids containing vanadium.

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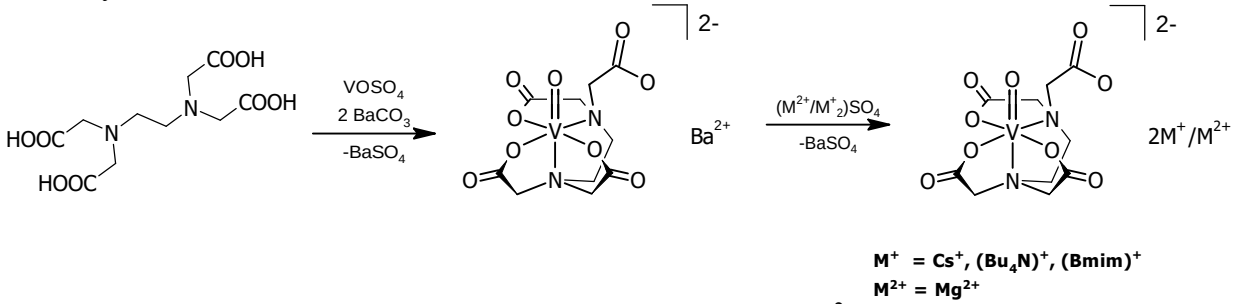
Ionic liquids (ILs) are salts with relatively low melting points (<100 °C). They offer several advantages compared to conventional organic solvents such as non-volatility and non-flammability. Their physical-chemical properties are tunable through the modification of either the cation or the anion [1]. ILs commonly exhibit catalytic activity, being used as a combination solvent/catalyst. For instance, a tricomponent system has been studied as a more sustainable option compared to the commonly used amine/epoxide system. Vanillin-based epoxide resins in combination with succinic acid and imidazolium-based IL have been cured without need for a co-solvent, co-catalyst or conventional polymerization initiator [2].

ILs containing transition metals are also comprehensively studied. For example, 1-butyl-3-methylimidazolium heptachloridodiferrate, (Bmim)[Fe_2Cl_7], shows promising catalytic activity towards the copolymerization of limonene oxide with cyclic anhydrides [3]. Vanadium-based ILs were only sparsely studied. An IL containing vanadium in the form of a metavanadate anion and was studied as liquids for electrochromic cells fulfilling the role of both the electrochrome and the electrolyte [4].



Scheme 1: Synthesis of the complexes ($2M^+/M^{2+}$)[VO(EDTA)]

In this study, oxidovanadium(IV) bearing a polydentate ethylenediaminetetraacetate (EDTA) ligand was chosen as a complex anion. The reaction of aqueous solution of oxidovanadium(IV) sulfate with H_4EDTA in presence of barium carbonate affords $Ba[VO(EDTA)]\cdot 5H_2O$ in high yield. Such compound serves as suitable precursor for alkali metal and alkali-earth metal salts. The barium cation is easily exchanged by the action with the appropriate sulfate as exemplified in the reactions with cesium and magnesium sulfate (Scheme 1).

Both products, $Cs_2[VO(EDTA)]\cdot 2H_2O$ and $Mg[VO(EDTA)]\cdot 0.5(dioxane)\cdot 8H_2O$ were characterized by EPR spectroscopy, elemental analysis, and mass spectrometry. Solid state structure of the magnesium salt was determined by X-ray crystallography (Fig. 1). The vanadium atom has a distorted octahedral coordination sphere with nitrogen and two neighboring carboxylates occupying one octahedron face.

The opposed octahedron face contains the second EDTA nitrogen atom, one carboxylate and the vanadyl oxygen. One carboxylate of the EDTA stays out of the vanadium coordination sphere. It is connected with four water molecules by hydrogen bonds. The magnesium(II) cation is surrounded by six water molecules. It is noteworthy that the unit cell contains two water molecules out of magnesium coordination sphere and half a dioxane molecule per each cation-anion pair.

Vanadium-containing ILs are accessible by similar pathway as alkali metal and alkali earth metal salts. Two representatives were prepared by a reaction of $Ba[VO(EDTA)]\ 5H_2O$ with tetrabutylammonium sulfate and 1-butyl-3-methylimidazolium sulfate. In both cases, the presence of the organic cations and complex anions was confirmed by mass spectrometry. The retention of $[VO(EDTA)]^{2-}$ anion was further confirmed using EPR spectroscopy. Tests of the catalytic activity of these ILs on the ring-opening polymerization epoxide/anhydride systems are currently ongoing.

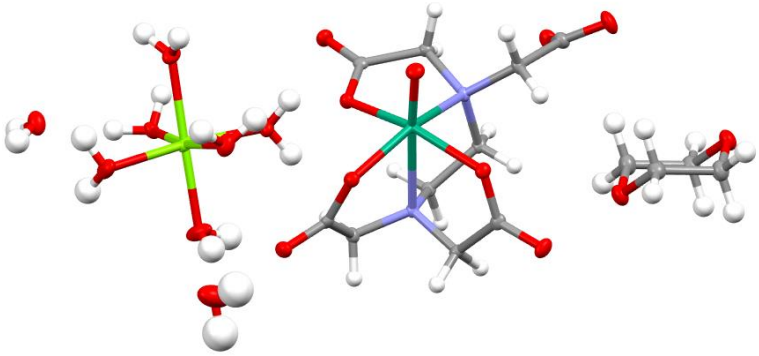


Figure 1: Crystal structure of $Mg[VO(EDTA)]\cdot 0.5(dioxane)\cdot 8H_2O$

Acknowledgement:

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Investigation of the effect of metal-containing ionic liquids on curing of epoxy/anhydride systems by Near-IR spectroscopy.

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Cyclic anhydrides of dicarboxylic acids are commonly used curing agents for epoxy resins for many years [1]. Over more pronounced amine hardeners, they give several advantaged such as longer pot life and much low exothermic heats of the reaction. Due to lower heat generation and little shrinkage, the epoxy/anhydride systems are suitable for production of larger and thicker objects. Cured material usually exhibits better thermal, mechanical, and electrical properties than similar epoxy/amine systems. The curing of epoxy/anhydride systems proceeds at elevated temperature. Catalysis by tertiary amines enables to lower curing temperature bellow 200°C [2]. Recently, metal-containing imidazolium-based ionic liquids (ILs) have been suggested as promising catalysts for epoxy/anhydride systems exhibiting high activity due to cooperative activity of imidazolium ring and metal complex anion [3].
This study is focused on description of chemical processes proceeding in epoxy/anhydride system. The curing process was followed by Near-IR spectroscopy at elevated temperature. Figure 1 shows developments of the spectra in time together with assignment of characteristic bands. The effect of ILs containing Zn, Co and Fe was investigated on commercially used mixtures of epoxy resin with anhydride hardener. Obtained results are compared formulation treated with base catalyst (1-methylimidazole) and with common IL without metal. Catalytic activity at low temperature was observed for iron-containing IL. Effect of metal concentration on the low temperature process is currently ongoing.

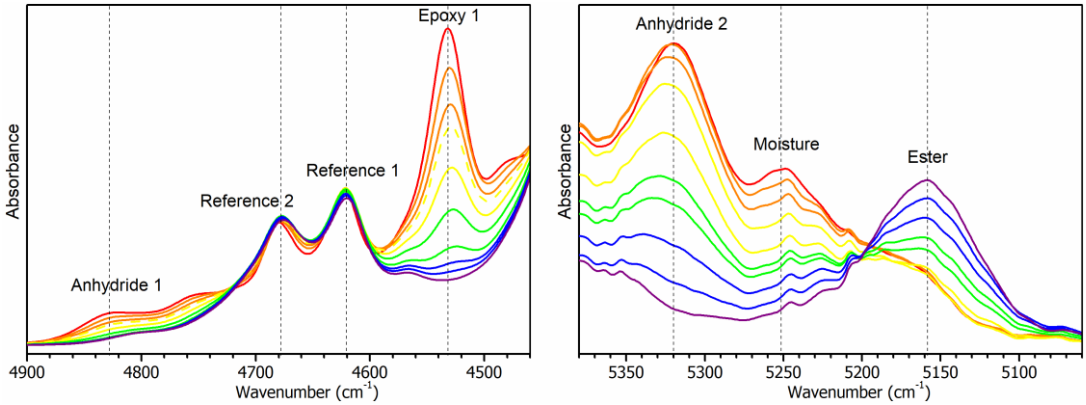

Figure 1: Development of characteristic bands in Near-IR spectra of epoxy/anhydride system.

Acknowledgement:

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Implications of copper(II) and Lycorine on structural and redox behaviour of the Amyloid β peptide

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Lycorine (LYC) is a very interesting molecule exhibiting a broad spectrum of biological functions [1], including antibacterial [2], anti-inflammatory [3], antitumor [4], and AChE inhibitory activity [5]. Furthermore, a recent study conducted by Zhang et al. corroborates LYC ability to suppress stress-induced premature cellular senescence by stabilizing the genome of human cells, potentially delaying the onset of age-associated diseases like Alzheimer Disease (AD) [6]. Recently we have demonstrated that LYC weakly interact with the monomeric Aβ peptide as proved by the analysis of tr-NOEs [7]. Our findings indicate that the alkaloid regions exhibiting the largest effects upon Aβ addition is the pyrrole portion pointing out that the Aβ40-alkaloid association is mediated by the tertiary amino group, positively charged at the applied experimental conditions. Similarly to copper(II), LYC interact with the N-terminal region of Aβ. In addition, our data point out LYC performance in reducing ascorbate oxidation, supporting its ability to effectively prevent ROS production induced by copper(II) [7].

In this study, we focused on the N-terminal region of Aβ (Aβ16) to clarify the residues involved in LYC binding and to evaluate the effect of LYC in Cu^{2+}- Aβ16 interaction. NMR and UV-Vis spectroscopies were used to gain insights on the structural features of copper(II) complexes in presence and in absence of LYC.

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Study of Complex formation of ML324, a histone demethylase KDM4 inhibitor, with essential metal ions

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8-hydroxyquinoline (8HQ) and its derivatives have potential medicinal application, due to their antimicrobial, antifungal and anticancer activities. Based on the literature data, there is relationship between the biological activity of 8HQs and their metal chelating ability [1,2]. N-(3-(dimethyamino)propyl-4-(8-hydroxyquinolin-6-yl)benzamide (ML324) is a selective 8-hydroxyquinoline-based KDM4 (histone lysine demethylase 4) inhibitor. Histone demethylases demonstrated the importance in a variety of important biological processes and diseases (*e.g.* cancer). Thus, they emerged as medical targets for cancer treatment. ML324 is the first potent and cell permeable KDM4 inhibitor with desirable *in vitro* ADME properties.

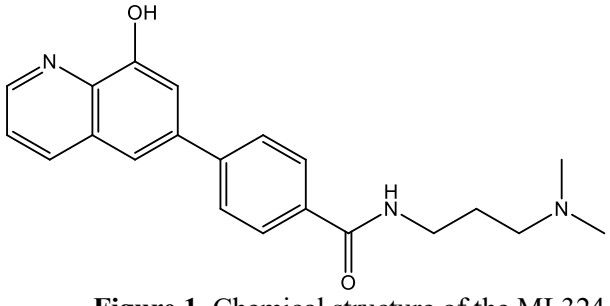

Figure 1. Chemical structure of the ML324.

P 15

The mechanism of action of KDM4 is linked to its interaction with the target enzyme bearing Fe(II) ions in the active center [3]; however, there is limited information about the Fe(II)-binding ability of ML324 and its interaction with other endogenous metal ions. Therefore, herein we aimed to explore the solution chemical properties of ML324 including its complexation with various metal ions. We have characterized the lipophilicity of ML324 by *n*-octanol/H_2O partitioning, and its proton dissociation processes using UV-visible and ^1H NMR spectroscopic titrations. The stoichiometry and formation constants of the complexes formed with essential metal ions, namely Cu(II), Fe(III), Fe(II), and Zn(II), were determined via UV-visible spectrophotometric titrations, and in the case of Cu(II) EPR spectroscopy was also applied. For the iron and copper complexes, cyclic voltammetric and spectroelectrochemical measurements were performed to monitor the redox properties. For comparison, the measurements were also performed with a more water-soluble, well-known 8HQ derivative, 8-hydroxyquinoline 5-sulfonate (HQS). The cytotoxic activity of the ML324 was assayed in chemosensitive and multidrug resistant cell pairs along with the coincubation with Zn(II), Cu(II) and Fe(III) ions.

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Synthesis and evaluation of the stabilising effect and binding mode of extended tri-biphenylamine-based ligands towards non-canonical nucleic acid structures by biophysical and computational methods

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Among various alternative DNA structures, G-Quadruplex (G4) DNAs have attracted considerable interest over the last two decades (**Figure 1**). These non-canonical secondary DNA structures are formed under physiological conditions by the self-assembly of guanine-rich nucleic acid sequences and predominantly exist in biologically important regions such as gene promoters or telomeres, which are involved in crucial biological processes, including DNA replication, gene transcription and genome maintenance. Evidence suggests their pivotal role in neurological diseases, ageing processes and cancer [1]. However, the exact nature of their biological significance is still poorly understood. Consequently, these G4 structures have been proposed as potential targets for therapeutic intervention and in order to unravel the biological processes in which G4s are involved, several strategies have emerged such as antibodies and small optical probes [2-3].

In this line, our team has launched a project of G4 probes based on the triphenylamine scaffold and found two ligands with strong interaction and selectivity for G4 structures [4-5]. Herein, we present our synthetic efforts to develop a second generation of extended triphenylamine-based molecules with an extended aromatic core in order to enhance the photophysical features for bioimaging while maintaining excellent binding abilities for G4s. In addition to the already reported NBTE [6] (a molecule formed by a triphenylamine core with three ethylenic chains in para position), we have prepared its methylated version with the amine in para (TPPA-4pyrM) and meta (TPPA-3pyrM) position.

A range of biophysical assays (FRET melting, fluorescence spectroscopy and molecular modelling) has been used to characterize the binding mode of action. Overall, our results point out the importance of the organic core, the extended aromatic scaffold and the aliphatic conjugation to obtain strong G4 binders with fluorescent emission properties to be applied as optical probes for detecting G4 structures.

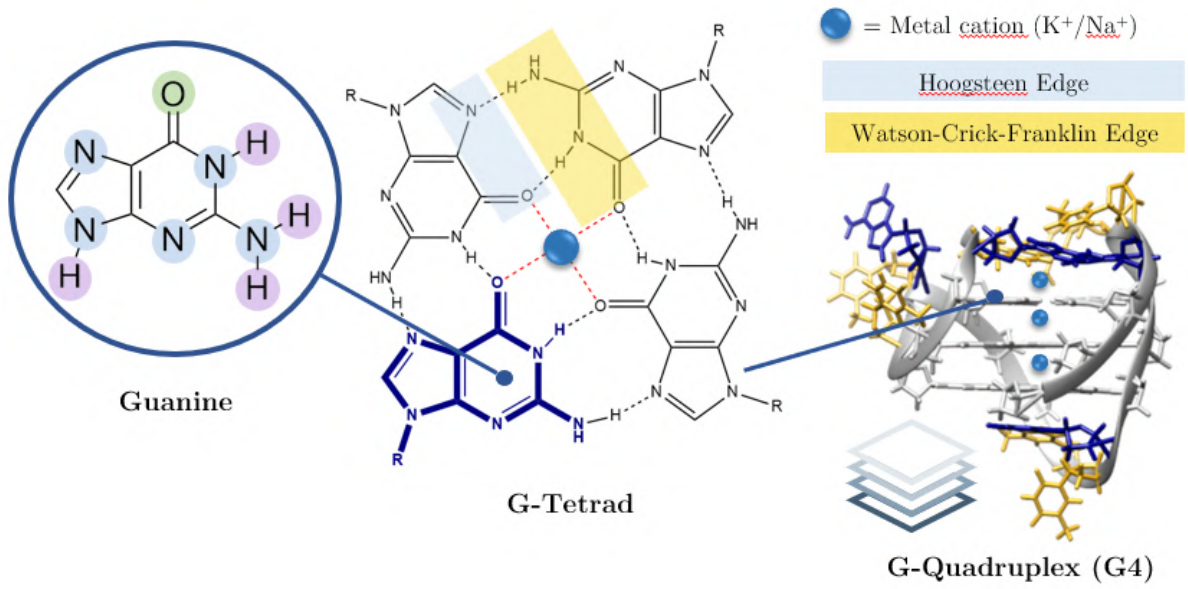

Figure 1 Representation of a G-Quadruplex (PDB: 2JSM) with its structural features.

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The effect of Ala-to-Ser substitution on calcitermin derivatives

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Nowadays the phenomenon of antimicrobial resistance (AMR) is one of the most urgent threats to public health, causing serious problems in the prevention and successful treatment of many diseases. AMR occurs when microorganisms including bacteria, viruses, fungi and parasites become able to adapt and grow in the presence of previously effective medications. Despite different actions taken in recent decades to tackle this problem, the trend of global AMR demonstrates no improvements. Misusing and overusing antibacterial agents are considered the major reasons behind the drug-resistance emergence, together with spontaneous evolution and mutation of pathogenic microorganisms. In order to overcome the global AMR crisis, the use of antimicrobial peptides (AMPs) represent a promising strategy for the design of new drugs. AMPs are phylogenetically ancient biomolecules with a broad spectrum of activity and scarce attitude to induce antimicrobial resistance. They are known to be effective against a wide variety of pathogens, like Gram-positive and Gram-negative bacteria, fungi, viruses and even cancer cells, and are present in all living organisms. Their activity can be expressed in different ways, including the interaction with cell membranes and through the innate immune response termed “nutritional immunity”. Thanks to this mechanism, AMPs sequestrate essential metal micronutrients such as Zn(II), Cu(II), Mn(II), Fe(II) or Ca(II), which are fundamental for pathogen subsistence.

Among several AMPs, we are interested in calcitermin [1, 2], a human 15 amino-acid antimicrobial peptide (VAIALKAAHYHTHKE) corresponding to the C-terminal domain of calgranulin C, a pro-inflammatory protein of the S100 family. Calcitermin presents an effective metal-binding domain with three alternated histidine residues (His 9, His11 and His13) and the free terminal amino and carboxyl groups. It exhibits an increased microbicide activity when Zn(II) or Cu(II) ions are present in the culture medium. In order to improve the metal binding ability and the biologic activity of calcitermin, we synthesized and studied the analogues VAIALKSAHYHTHKE (A7S), VAIALKASHYHTHKE (A8S) and VAIALKSSHYHTHKE

(A7S/A8S), in which the alanine residues in position 7 and/or 8 have been replaced with a serine. In fact, several studies carried out on metal chelating peptides have previously shown that the presence of one or more serine residues in the proximity of coordinated histidines stabilized the Cu^{2+} complexes when the metal ion begins to interact with the amides of the peptide chain [3].

We also studied the complexes with zinc ion, which is the most important endogenous metal ion capable to interact with calcitermin. The characterization of the complexes has been achieved by means of mass spectrometry, potentiometry, UV-Vis spectrophotometry, circular dichroism, electron paramagnetic resonance. The results show that all the investigated peptides are efficient ligands for the considered metal ions and can form stable mono-nuclear complexes. The proteolytic stability of these three peptides has been tested in human plasma by means of HPLC, evaluating the degradation content after different times of incubation at 37 °C. The results show that they are slightly more stable than native calcitermin. Finally, the antimicrobial activity of calcitermin derivatives and their metal complexes with Zn(II) and Cu(II), has been studied *in vitro* against human pathogenic strains.

Financial support of the Polish National Science Centre (UMO-2020/37/N/ST4/03165), of the University of Ferrara (FAR 2021) and of the COST Action CA18202-Nectar is gratefully acknowledge.

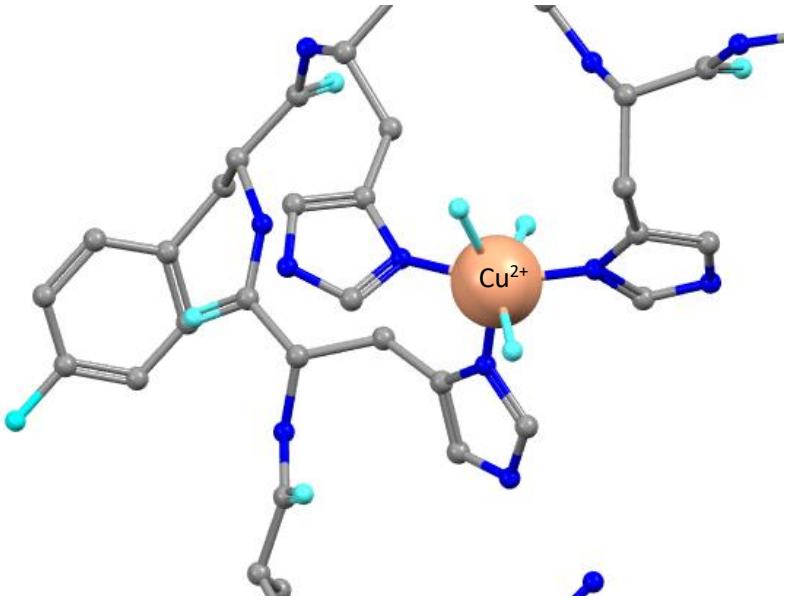

Figure 1. Proposed binding mode for the Cu(II) -VAIALKASHYHTHKE complex at acidic pH.

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A joint chemical and biological study on fluorescent molecules for sustainable environmental investigations

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The number of pollutants affecting water and soil poses relevant potential risks to animal and environmental health and is constantly increasing. In both aquatic and terrestrial environment, heavy metal ions have attracted special interest among various types of pollutants [1-4] due to their central role in human health. Recently, the research and industrial worlds have cooperated in finding new rapid solutions to trace pollutants [5,6], particularly heavy metals, in different biologic matrices and bioindicator organisms.

The present study is aimed to exploit fluorescent molecules for assessing pollution in specific bio-indicators in both soil and water. Certain species/biocenosis can indeed provide crucial information for environmental analysis. Terrestrial isopods represent interesting constituents of biodiversity in a variety of natural and agricultural ecosystems [7] and are utilised as valuable bio-indicators for the surveillance of environmental quality. Among them, *Armadillidium vulgare* and *Mytilus galloprovincialis* have been selected for the present study. A series of ligands containing different fluorophore and polyamine moieties (**L1**-**L4**, Figure 1) was evaluated to develop optical chemosensors able to detect selected metal ions in solution and biological environment.

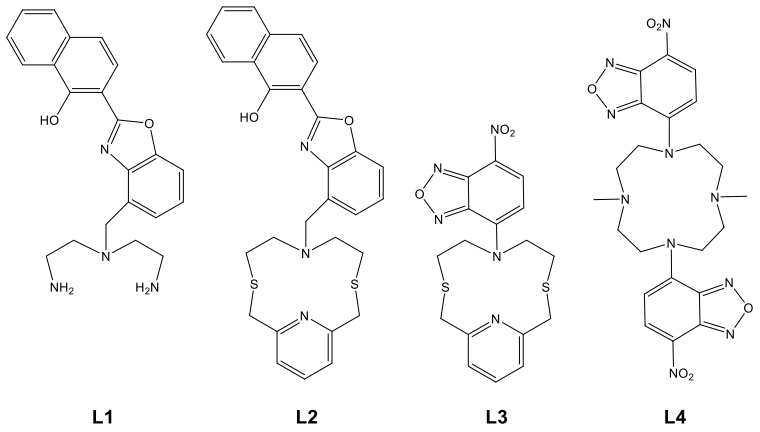

Figure 1. Ligands used in this study

L1, containing the 2-(2-hydroxy-3-naphthyl)-4-benzoxazolylmethyl fragment (HNBO) coupled to *N*,*N*-bis(2-aminoethyl)amine, showed the highest fluorescence response to Mg(II) both in DMSO and ACN upon formation of a 1:1 ligand to metal complex [8]. The ability to signal the presence of Mg(II) is maintained also in other aprotic solvents (THF, dioxane) while the selectivity moved to Zn(II) and Cd(II) in protic solvents (water, MeOH, EtOH). Subsequently, analyses were conducted to evaluate the use of **L1** as a chemosensor for metal ions in *in vitro* systems. Unfortunately, although interesting results were obtained, selectivity is focused on Mg(II) and outcomes were found not to be reproducible over time.

The open chain amine fragment in **L1** was replaced by the 2,8-dithia-5-aza-2,6-pyridinophane moiety in **L2**, trying to move the fluorescence selectivity towards heavy metal ions [9]. To this purpose, **L2** was evaluated in an *in vitro* Cd pollution model on epithelial tumour cell line (HT-29 cells), returning a preliminary positive response. In **L3** the macrocyclic portion was maintained, while the HNBO fluorophore was replaced with the 7-nitrobenzo[1,2,5]oxadiazol-4-yl group (NBD) [10]. The same test on the *in vitro* Cd pollution model was performed, but no fluorescence response was observed.

L4, containing two NBD moieties linked to a 1,7-dimethyl-1,4,7,10-tetraazacyclododecane [11], was tested to trace the endo/lysosome organelles alteration upon pollution: in hepatopancreatic cells of *Armadillidium vulgare* from polluted sites, a reduction of **L4** fluorescence was found, suggesting a decrease of acidic vacuoles with Cd(II), in agreement with Zhao Y. *et al.* [12]. Evaluations were performed in cell line *in vitro* model and *in vivo* samples of *Armadillidium vulgare*. All the analyses were carried out by means of flow cytometry and confocal microscopy, to ensure a quantitative and qualitative evaluation of the “dye-cells system”.

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Modulating antioxidant activity of superoxide dismutase and catalase/peroxidase mimetics through tunning of pyridine electron-density

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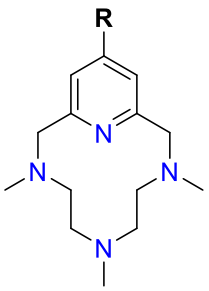
The malfunction of the nervous system associated with several neurodegenerative disorders has been linked to the misregulation of free metal ions and oxidative stress. For example, in Alzheimer's disease, the accumulation of Fe and Cu in beta-amyloid plaques is thought to be responsible for increased oxidative damage in certain areas of the brain. These transition metals promote the aggregation of protein fibrils into peptide aggregates and mediate the production of reactive oxygen species (ROS) through Fenton reactions, with superoxide radicals playing a major role. Ultimately, the imbalance between the generation and removal of ROS results in oxidative stress. Ongoing research is focused on the chelation of these redox active transition metals to avoid their participation in the formation of the peptide aggregates, as well as on the reversion of their activity from ROS generation to antioxidant activity. [1]

A family of tetraaza-pyridinophane macrocycles capable of chelating Fe(II) and Cu(II) has been synthesized and characterized. Potentiometric and UV-Vis titrations, along with superoxide dismutase and H_2O_2 removal activity assays, indicate that the synthesized macrocycle can coordinate quantitatively Cu(II) and Fe(II) at physiological pH, resulting in the formation of complexes with remarkable SOD activity and a significant capacity to scavenge H_2O_2 from solution. [2] Both antioxidant activities have been modulated through the electron-density of the pyridine ring, by introducing in *para*- position to the nitrogen of the pyridine different substituents ranging from COOMe to OH (see Figure 1).



R = H, OMe, OH, Cl, COOMe

Figure 2. Family of chelating ligands synthesized and studied.

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Molecular recognition aspects from the structure of 'inner' and 'out' sphere copper(II) complexes with 2,6-pyridinedicarboxilatechelator (pdc) and creatinine (crea) or creatininium ($Hcrea^+$) counterparts.

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Creatinine (hereafter crea) is a metabolite that becomes considered an interesting bio-ligand, presenting two main tautomers. Its coordinating properties were first reviewed by M. Mitewa [1]. Until now, eight Cu(II)-crea complexes are structurally reported in the CSD database (version 5.43).

This work deals on the synthesis and crystal structures of two copper(II)-crea compounds also having the rigid-planar 2,6-pyridinedicarboxylic acid (H_2pdc) or its anionic forms ($Hpdc^-$ or pdc^{2-}). To these purposes $Cu_2CO_3(OH)_2$ (malachite) and H_2pdc were reacted in water, following the addition of crea in stoichiometric amounts as to obtain a molecular inner-complex 'Cu(pdc)(crea)' as well as two potential out-sphere complexes, of the types '$(H_3O)(Hcrea)[Cu(pdc)_2]$' and '$(Hcrea)_2[Cu(pdc)_2]$', these last two so-called 'semi-out' and 'out-sphere' creatininium(1+) compounds, respectively.

A synthesis in water with equimolar ratio Cu:pdc:crea (1:1:1) yields the compound *trans*-$[Cu(pdc)(crea)(H_2O)_2]\cdot H_2O$ (**1**) (Figure 1) with the following insights: (a) Cu(II) centre exhibits an elongated O_h coordination, type ~4+2. (b) The N-crea (1.996 Å), N-pdc (2.031 Å) and both O-aqua donors (2.012, 2.019 Å) occupy the four closest proximal Cu(II) coordination sites, whereas both O-(carboxylate) pdc atoms act as distal donors (2.389, 2.431 Å). (c) The Cu-N(crea) distance in **1** falls in the range of related crea compounds with distorted O_h or square-base pyramidal compounds (1.955 [2] - 2.014 [3] Å, averaging 1.992 Å), but longest than the Cu-N(crea) bond in the T_d molecule $[Cu(crea)_2Cl_2]$ (1.928 Å [4]). (d) The molecular recognition crea-Cu(pdc) chelate consists of the

cooperation between the short Cu-N(crea) bond and the (crea)N-H···O(carboxylate donor, pdc) interligand interaction (2.731 Å, 152.70°). Therefore, the dihedral angle between the mean planes crea/pdc is only of 21.0°.

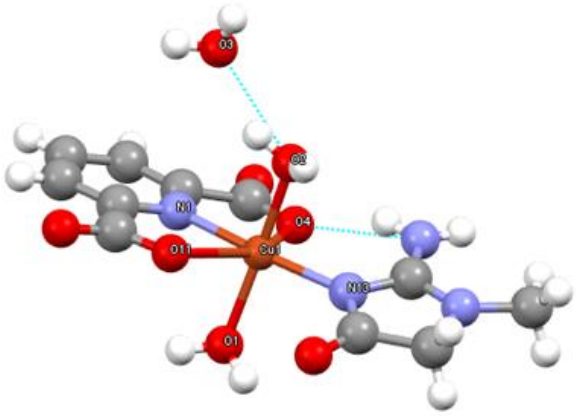

Figure 1. Asymmetric unit of *trans*-[Cu(pdc)(crea)(H_2O)$_2$]·H_2O (**1**), showing the molecular recognition between the Cu(pdc) chelate and the bio-ligand crea.

The slow evaporation of an aqueous solution with molar ratio Cu:H_2pdc:pdc:crea 1:1:1:1 do not yield a desired ´semi-out' sphere compound. In contrast, it firstly yields nice blue crystals of the bis-oxonium salt (H_3O)$_2$[Cu(pdc)$_2$]·H_2O, reported in CSD database as FAYPUR [5], to give later the 'out-sphere´' complex (Hcrea)$_2$[Cu(pdc)$_2$] (**2**). In the crystal framework of **2** each $[Cu(pdc)_2]^{2-}$ anion results H-bonded to two symmetry-related pairs of $Hcrea^+$ cations (Figure 2). As we can anticipate, the octahedral coordination of the $[Cu(pdc)_2]^{2-}$ anion and the protonation of the available N-donor atom of crea in the $Hcrea^+$ cation precludes the formation between them of an 'inner'-sphere metal complex formation.

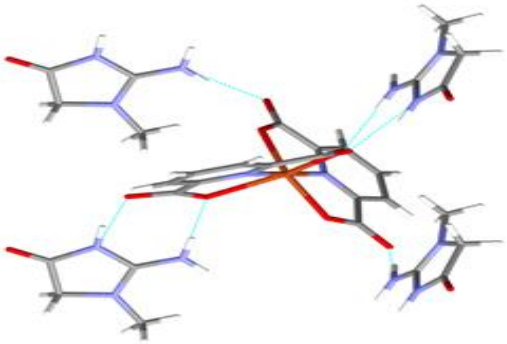

Figure 2. Distinct H-bonding patterns between the $[Cu(pdc)_2]^{2-}$ bis-chelate anion with two pairs of symmetry related $Hcrea^+$ cations in the crystal of compound **2**.

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Magnetostructural characterization of tetrabromonitrosylrhenate(II) complexes through Hirsfheld Surfaces Analysis

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Our research group has made incursions into the least-known chemistry of rhenium(II). Literature shows that Re(II) mononuclear complexes are attractive in molecular magnetism due to high magnetic anisotropy due to a significant spin-orbit coupling, turning them a potential source for discovering new molecular magnets [1]. In this work, we present the characterization and crystal structure analysis of four novel Re(II) mononuclear complexes of general formula $NBu_4[Re(NO)Br_4(L)]$ [L = pyrazole, imidazole, 1,2,4-triazole, and 1H-tetrazole]. The crystal structure of these complexes contains NBu_4^+ cations and mononuclear $[Re(NO)Br_4(L)]^-$ units. These new complexes could act as building blocks for high nuclearity clusters with interesting magnetic properties. This work is in progress in our lab.

Moreover, we examined the magnetic properties of the compounds over the temperature range of 2-300K. Cryomagnetic measurements show that these complexes behave as quasi-magnetically isolated spin doublets with weak antiferromagnetic interactions at low temperatures. The magnetic behavior of Re(II) was modeled by the influence of the ligand field, tetragonal distortion, spin-orbit coupling, and covalence effects. In addition, the antiferromagnetic exchange coupling was correlated to the nature of the intermolecular interactions.[2] Also, the inter-anionic contacts were thoroughly analyzed using Hirshfeld surface analyses (plots over the d_{norm}, shape index, and 2D fingerprints).

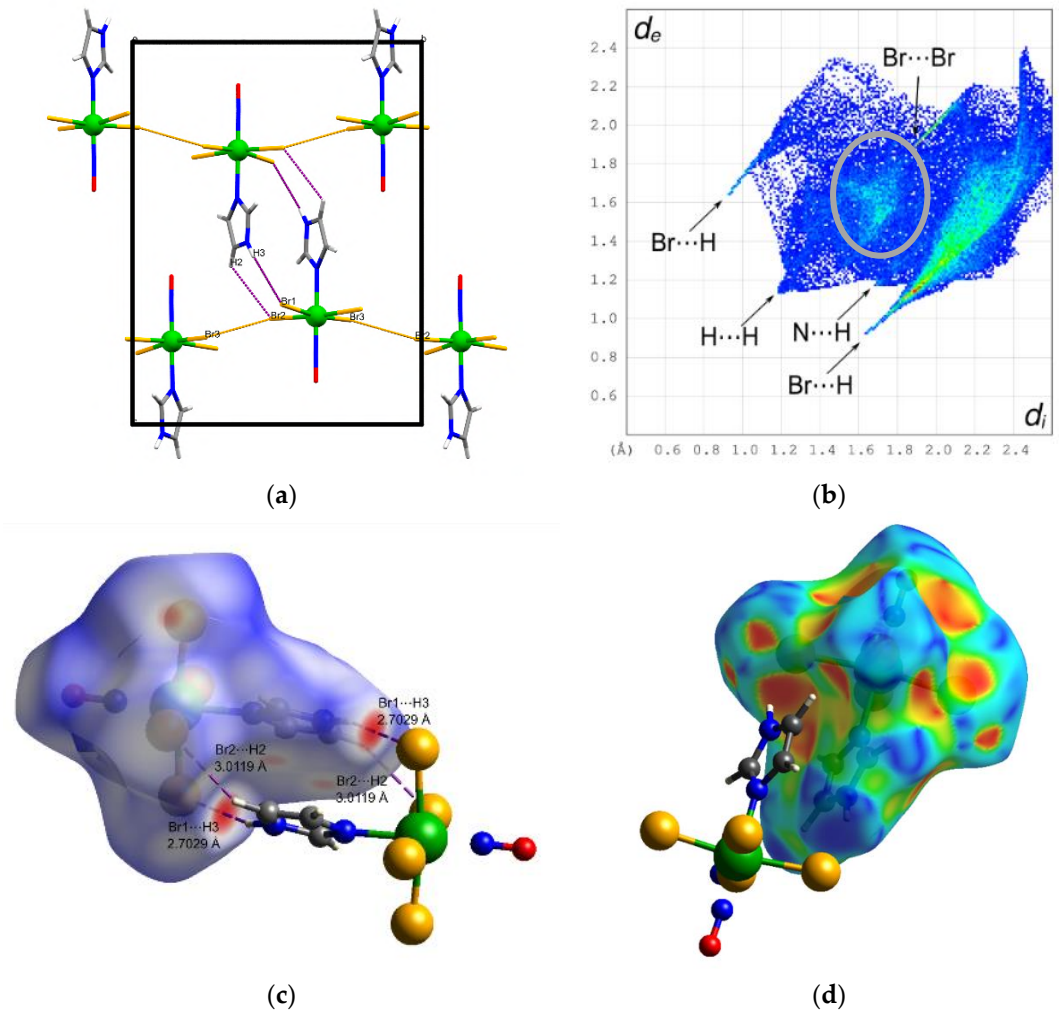

Figure 1: (**a**) Packing diagram down the crystallographic *a* axis, (**b**) fingerprint plot, (**c**) d_{norm} surface, and (**d**) shape index surface of the $[Re(NO)Br_4(HIm)]^-$ anionic units. Short Br···Br (yellow), Br···H (purple) contacts and π-π stacking interactions (grey ovals) are shown.

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HBO-based ligand: a Fluorescent Sensor for Rare Earth Metal Ions

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Rare earth ions (RE) have been widely applied in many fields, for example, as probes and labels in chemical and biological applications.[1] Due to their ubiquity in several aspects of our everyday life, there is as well growing interest on the environmental, medicinal and biological effects of RE. The development of simple and fast systems of lanthanides' detection in different matrices is therefore highly desirable, and fluorescent chemosensors represent a suitable approach to this task due to their simplicity, reliability, rapidity and low cost. Most lanthanide ions are luminescent itself but are characterized by weak absorption coefficients and emission quantum yields, to overcome this problem fluorescent ligands able to bind and signal lanthanide (III) are needed. Here we describe a new fluorescent chemosensor suitable for RE(III) analysis containing two HBO (2-(benzo[d]oxazol-2-yl)-6-methylphenol) fuorophore[2,3] linked to a dimethylethylenediamine scaffold. The coordination and optic properties towards RE(III) ions have been studied in different conditions founding that the ligand shows a good selectivity for RE(III) ions acetonitrile/water solvent mixtures.

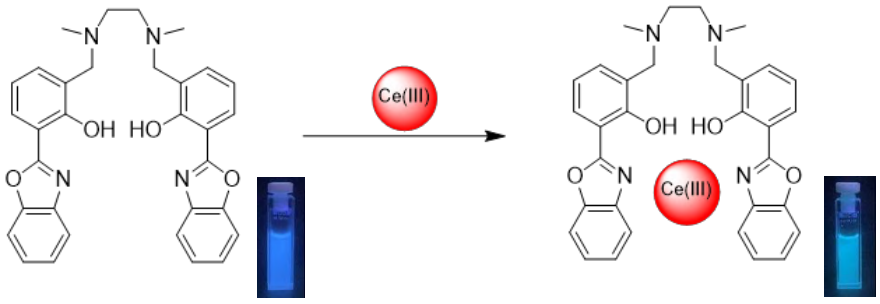

Figure 1 Increased fluorescence intensity of **L** in the presence of 0.5 eq of Ce(III)

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Anion-imprinted polymers for the selective sensing of fluoride in dmso and water.

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Fluoride anion has aroused special interest in the scientific community, although it is known to be beneficial for dental health and the treatment of osteoporosis, the increase in its concentration due to industrial and medical activities can cause pollution of soils and water sources [1]. Even though the World Health Organization has set the upper limit for fluoride in drinking water at 1.5 mg/L. However, for several countries the desired level is often exceeded [1]. In this context, the detection and quantification of fluoride through convenient and low-cost methods, like by *discrete* optical chemosensors, has become a topic of high impact. Among the explored optical sensors, those containing a urea-like anion binding site (receptor) attached to a signaling unit (*e.g.* fluorophore) have received much attention, as they exhibit high sensitivity, very low detection limits and use simple and affordable equipment [1]. Nevertheless, they suffer from two main drawbacks: i) they tend to display low selectivity levels, being also sensitive to other anionic interferences, and ii) its use in aqueous media has been hampered by the low solubility of the sensors, making fluoride recognition by urea groups in water one of the biggest challenges in Anion Chemistry [2].

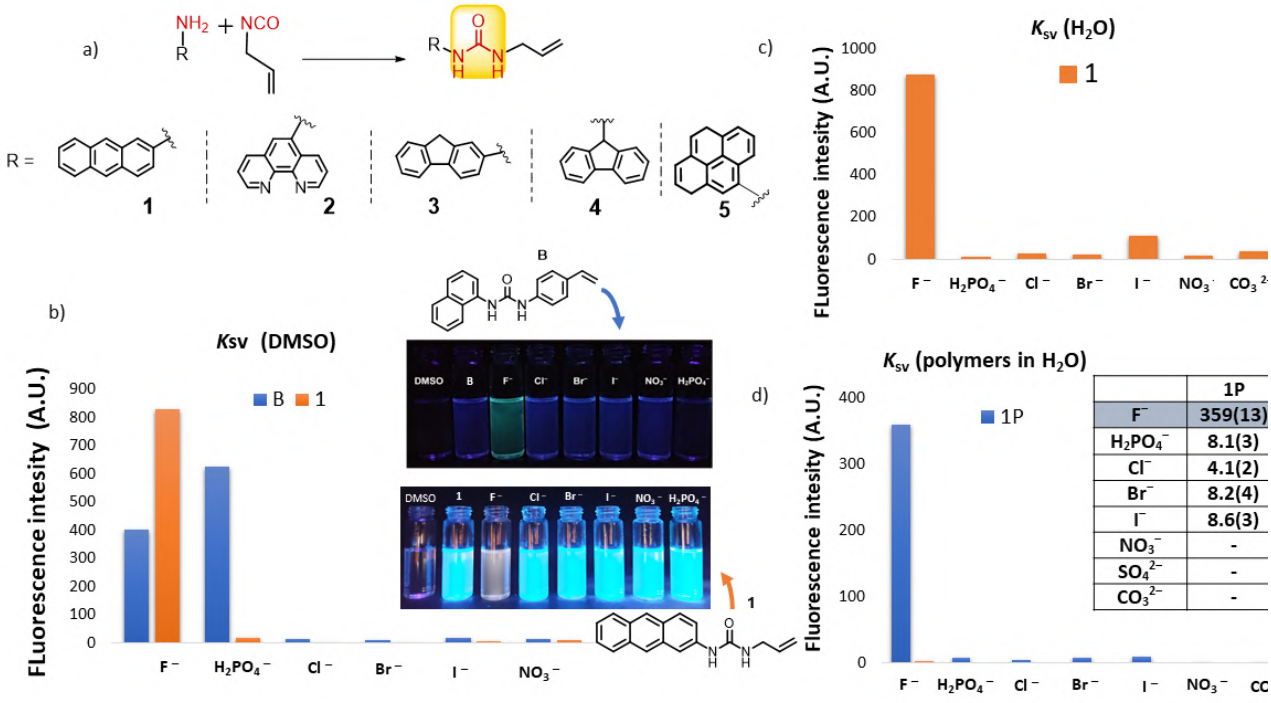
In order to overcome those issues, our group has been working on the design of novel *discrete* and *polymeric* fluorescent chemosensors, for the selective detection and quantification of the fluoride anion. We started by preparing a family of *discrete* fluoride sensors (**1-5**, Figure 1a), bearing a urea-like binding site, a terminal polymerizable C=C group, and different signaling units (fluorophores). All molecules resulted fluorescent in DMSO and compound **1** displayed the highest sensitivity towards F^- (Stern-Volmer constant, $K_{SV}(F^-)$ = 830(28) M^{-1}; LOD =8.8 µM; linear range =0.2-1.0 mM). When tested against other anions in DMSO, **1** showed significant levels of selectivity, being responsive only for fluoride (Figure 1b). In comparison with sensor **B** already reported by our group [3], compound **1** achieved twice the sensitivity and more than a 6400% improvement in the selectivity towards $H_2PO_4^-$.

In order to extend the applicability of the sensors, we tested them in aqueous media. Discrete sensors previously reported by us (including **B**) resulted insoluble [3], making impossible to assay them as water-compatible sensors.

Remarkably, compound **1** is not only soluble in water, but also highly fluorescent in water, showing high sensitivity towards fluoride (Figure 1c, $K_{SV}(F^-) = 871(50)\ M^{-1}$; LOD=8.4 µM; linear range=0-0.25 mM) and being selective in the presence of other interferences such as Cl^-, CO_3^{2-}, SO_4^{2-}, $H_2PO_4^-$ and NO_3^- at pH = 6.5.

In the light of these results, and with the aim of enhancing the optical performance while obtaining reusable and robust solid-state sensors, we set out to prepare the molecularly imprinted polymeric sensor (MIP) starting from **1** and employing F^- as template. The resulting MIP (**1P**) was tested in water, displaying satisfactory fluorescent response (Figure 1d). It showed high sensitivity towards fluoride ($K_{SV}(F^-) = 359(13)\ M^{-1}$; LOD=16 µM; linear range=0.9-6.3 mM), being 160 times higher than that for the MIP of **B** (**BP**). Interestingly, **1P** showed very high anion specificity, being almost non-responsive in the presence of the anionic interferences. The imprinting strategy allowed to design a more robust phase for heterogenous sensing with a 6% increase in the optical selectivity against $H_2PO_4^-$. These results point **1P** as the first polymeric chemosensor for the selective optical detection and quantification of fluoride.

Figure 1: a) Discrete anion receptors synthesized in this work. b) Optical performance of **1** and **B**[3] in the



	1P
F^-	359(13)
$H_2PO_4^-$	8.1(3)
Cl^-	4.1(2)
Br^-	8.2(4)
I^-	8.6(3)
NO_3^-	-
SO_4^{2-}	-
CO_3^{2-}	-

presence of the anions in DMSO. c) Optical behavior of **1** towards the anions in water. d) Sensitivity of the fluoride-imprinted polymeric optical sensors **1P** and **BP**[3] towards the anions in water.

Acknowledgements:

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Metal complexes with fluorescent deferoxamine derivatives as PET/fluorescence dual imaging probes

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In the last few years, the development of novel metal complexes for application in positron emission tomography (PET) imaging has received increasing attention. In fact, to obtain high quality tissue/organ images, current research is primarily focused on the synthesis of novel chelating agents capable of forming very stable, thermodynamically, metabolically, and kinetically inert metal complexes with radionuclides with long half-lives. Among these, $^{89}Zr^{4+}$ represents one of the most appealing radionuclides to be employed in PET, thanks to its physical properties [1]. $^{64}Cu^{2+}$ complexes are also under study for PET imaging, although they appear less promising than $^{89}Zr^{4+}$, due to ^{64}Cu short lifetime. Deferoxamine (DFO), a well known natural siderophore used in medicinal chemistry as Fe(III) chelator and able to form stable complexes with 'hard' transition metal cations, is currently an absolute benchmark in $^{89}Zr^{4+}$ chelation [2,3].

Here, we present two new fluorescent chelating agents whose metal complexes can be exploited as multimodal probes, coupling both positron and fluorescence emission. To this purpose, we have synthesized two new fluorescent ligands, DFOC and DFO-KC (Figure 1a), featuring a deferoxamine unit, as metal chelator, coupled with a coumarin-343 and a coumarin-466 fluorophore, respectively. While in DFOC, the free terminal amine group of DFO has been employed to directly attach the fluorophore, ligand DFO-KC, thanks to the presence of a lysine (Lys) molecule as linker between DFO and coumarin-466, is characterized by the presence of a free

amine group (ε-amine group of Lys), which can be exploited to introduce appropriate targeting vectors in the ligand scaffold [4], such as biotin, in order to better visualize cancer tissues/cells with over-expressed receptors for the chosen vector.

In this study, the protonation properties of the ligands and their coordination properties towards metals, whose radionuclides are used in PET imaging, specifically Cu^{2+} and Zr^{4+}, have been investigated by coupling potentiometric, UV-vis absorption, and fluorescence emission measurements. We have determined the species formed in aqueous solution and the formation constants of the complexes, which result sufficiently stable to be used in biological environment as PET imaging probes.

Generally speaking, the paramagnetic Cu^{2+} and the heavy Zr^{4+} could suppress the emission of fluorescent ligands. In the case of DFOC and DFO-KC, metal complexation has not significant effects on the fluorescence features of the ligands, which remain strongly emissive. The retention of fluorescence emission outlines the concrete possibility to use these DFO-based metal complexes also for optical (fluorescent) imaging, thus unlocking bimodal PET/fluorescence imaging by exploiting the complexes with $^{64}Cu^{2+}$ or $^{89}Zr^{4+}$.

Biological test performed on NIH-3T3 fibroblasts and MDA-MB 231 mammary cancer cell lines showed that, at typical radiodiagnostic doses, the Zr^{4+} complex with DFOC had no cytotoxicity nor metabolic impairment. The results of a clonogenic colony-forming experiment on X-irradiated MDA-MB 231 cells revealed that the Zr^{4+} complex had no effect on radiosensitivity. Similar cells were used in morphological biodistribution (confocal fluorescence, TEM) experiments, which revealed that the complex was internalised in cells through endocytosis [5].

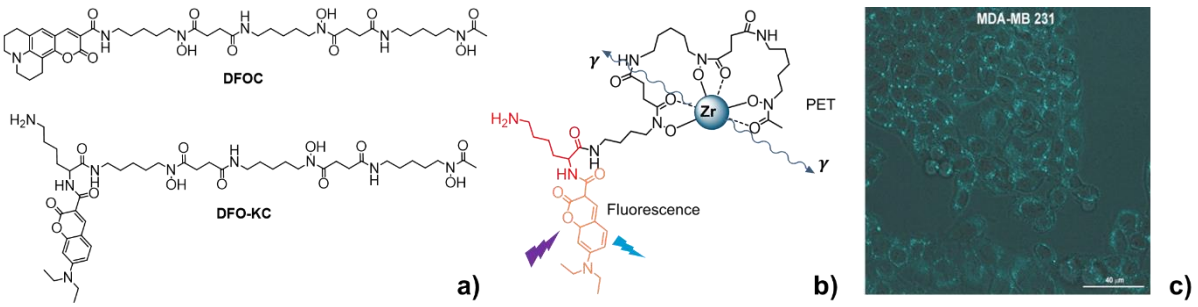

Figure 1. a) Drawing of the ligands; b) schematic representation of the dual imaging Zr(IV)-DFO-KC probe; c) merged enhanced-contrast (DIC) and fluorescent (λ_{em}=540 nm) images of MDA-MB 231 human breast adenocarcinoma cells exposed to 0.08 μM ZrDFOC for 10 min.

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Rivastigmine-Indole hybrids as a new family of multitarget metal-modulating anti-Alzheimer´s Disease agents: Cu(II) and Fe(III) chelation studies

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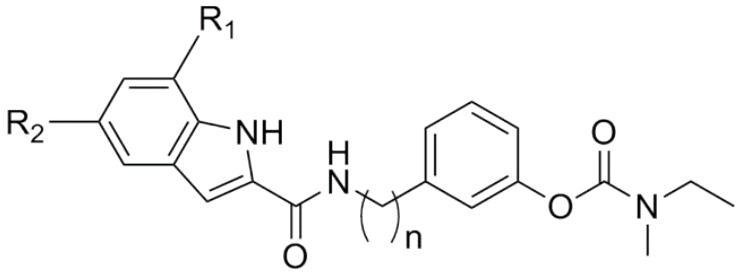
Alzheimer´s disease (AD) is the most common and severe cause of dementia, representing ca 70% of the neurodegenerative diseases, affecting nowadays ca 50 million people worldwide. Despite numerous research efforts to find effective drugs for AD, its etiology and pathogenesis remains elusive, although several pathological hallmarks of AD have already been identified, such as protein misfolding (amyloid aggregates and senile plaque formation), the loss of cholinergic neurotransmitters, metal ion dysregulation and oxidative damage. Currently the main class of approved anti-AD drugs are of cholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine), which can only lead to some symptomatic relief but not halt the neurodegeneration [1].

The numerous and complex pathological features of this disease are surely the main reason for the, so far, absence of disease-modifying drugs. Therefore, to combat this multifactorial disease, the development of multitarget therapeutic agents has been recognized as a promising strategy [2]. Persuading this strategy in combination with a drug-repositioning approach, we have developed a new library of rivastigmine-indole (RIV-IND) hybrids, conjugating the drug rivastigmine (cholinesterase inhibitor) with derivatives of indole (IND), a privileged scaffold that can exhibit diverse biological activities [3]. In particular, hydroxyl-substituted indole moieties are able to endow the hybrids with several capacities, namely anti-oxidation, inhibition of β-amyloid (Aβ) aggregation and chelation of specific biometal ions (e.g. Cu, Fe) known to be involved in Aβ aggregation and in oxidative stress [4]. Herein, solution equilibrium studies are presented and demonstrate the chelating ability of one representative hybrid compound (**4a3**) towards copper(II)

and iron(III), involving coordination through the phenolic oxygen and the nitrogen atoms of IND moiety.

The effect of these hybrids on the inhibition of self-mediated and Cu-induced Aβ_{42} aggregation, are also discussed in terms of structure-activity relationship, providing indications of the most promising compounds to be further modified in the search for multitarget anti-AD drugs.



RIV-IND hybrids

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Ligand Denticity and Oxygen Reduction Reaction Activity of Pd(II) Macrocyclic Complexes: κ^3 vs κ^4.

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In the last years, some of us developed a number of ligands of the binding site-spacer-anchoring group type designed for the supramolecular, π-π stacking, decoration of graphitic materials (activated carbon [1,2], carbon nanotubes [3], graphene [4], graphene nanoplatelets [5]) with Pd(II) complexes, thus obtaining hybrid materials intended as heterogeneous catalysts.

First generation catalysts were intended for alkyne/halide Pd-catalysed Sonogashira cross-coupling, which, as all couplings of this kind, features a transition state where both organic reagents are simultaneously present in the metal cation first coordination sphere. To facilitate the formation of such an intermediate, tridentate κ^3 ligands (linear, tripodal, macrocyclic [6]) were used, which left an open position in the Pd(II) coordination sphere normally occupied by an easily displaceable Cl^- ancillary ligand. This strategy led indeed to highly efficient catalysts.

Similar systems were then transposed as cathode catalysts for fuel cells, addressing the oxygen reduction reaction (ORR), again with success [7]. However, it is worth noticing that, differently from cross coupling, in principle ORR does not feature two reagents and thus a bimolecular transition state. The point was first computationally addressed, showing how ORR on such complexes does not involve detachment of the chloride ligand, yet it rather takes effect through transient coordination of O_2 molecule to the Pd(II) centre in a fifth axial position [8]. If such is the case, then much simpler κ^4 ligands, also affording generally more robust and redox-stable Pd(II) complexes, could be used as ORR electrocatalysts.

To corroborate theoretical results a simple N4 macrocycle, H_2L, a derivative of trans-dimethylated-cyclen, was prepared. The ligand bears two anchoring groups for firm chemisorption onto graphitic surfaces.

The ligand was characterized concerning its solution (acid/base) behaviour, it was shown to form stable Cu(II), Zn(II), and Pd(II) complexes, as expected and displayed in obtained crystal structures, although exact evaluation of the complexes stability was prevented by kinetic inertness.

Stable and inert Pd(II) complexes were then grafted on carbon nanotubes and they ORR activity was evaluated. Indeed, noticeable ORR activity was demonstrated.

Overall, the obtained results show that straightforward κ^4 ligands, completely fulfilling Pd(II) stereoelectronic requirements, can be directly employed as ORR catalysts: this extends the range of possible candidate ligands and simplifies the synthetic requirements for active complexes, which do not seem to benefit from the presence of an easily displaceable chloride ligand.

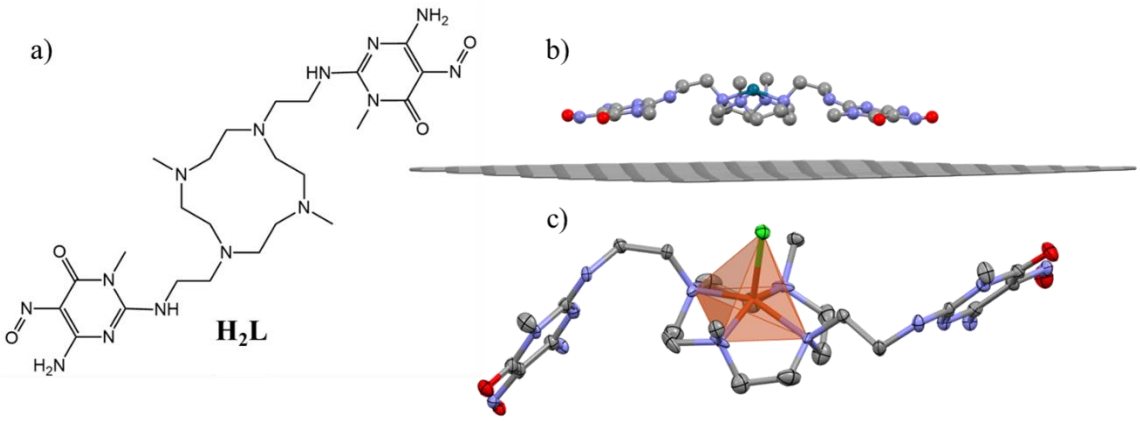

Figure 1. a) H_2L ligand drawing; b) MD minimization of $[H_2L(Pd)]^{2+}$ interaction with a graphene surface; c) Crystal structure of the $[Cu(H_2L)Cl]ClO_4$ complex.

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Development of hyaluronic acid – carnosine complexes as potential non-covalent drug delivery systems

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The increasing interest in drug delivery as a strategy for administering pharmaceutical compounds and achieving therapeutic effects in human diseases lies in the prospect to overcome most of the drawbacks encountered when a drug is supplied to the patient, such as degradation, interaction with other cells, inability to penetrate tissues, unwanted side effects. Macroscopically, conventional drug administration relies on pills, eye drops, ointments or intravenous solutions; at the molecular level, novel drug delivery approaches include drug entrapment within suitable nano-containers, often made of polymeric materials, that may reach the desired bodily compartments [1,2].

Hyaluronic acid (HA) is a linear polymer consisting of repeating disaccharide units of glucuronic acid and glycosaminoglycan. HA is the major physiological constituent of the extracellular matrix and its chemical-physical properties are closely related to its molecular weight [3,4]. Carnosine (Car) is a dipeptide composed by alanine and histidine and it is known to have antioxidant and metal ion-chelating properties, for example, towards Cu^{2+} ion [5]. Recently, a covalent conjugate HA-Car has been patented and showed unprecedented healing properties toward osteoarticular diseases [6,7].

For its versatility, physiological activity and healing properties, HA has potential applications in drug delivery as "host" system. Nonetheless, simply mixing HA with the desired "guest" drug cannot ensure the formation of a properly functioning drug delivery system (DDS). In this work, we developed non-covalent assemblies based on HA and Car or its Cu^{2+} complex as potential DDSs for the cure of osteoarticular and/or ophthalmological diseases. The interactions of both high and low molecular weight HA with the dipeptide or its metal complex were investigated in neutral (buffered) aqueous solution through isothermal titration calorimetry, which provided the stability of the resulting adducts as well as the relevant thermodynamic parameters [8,9]. The various complexes and species obtained as well as the driving forces for their formation in solution are discussed with regards to the peculiar properties of the starting building blocks.

The binding of the polymer with Car or Car/Cu^{2+} was further investigated at the solid-liquid interface by quartz crystal microbalance experiments, which revealed interesting insights on the absorption and viscoelastic properties of the resulting assemblies at the interface.

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Cyanine based receptors for the recognition of antibiotics in aqueous media

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Antibiotics represent one of the main class of pharmaceuticals referred as emerging pollutants. Emerging pollutants are identified as synthetic or naturally occurring chemicals not included in routine monitoring programs but extremely persistent in the environment causing known or suspected adverse ecological and human effects.[1] Particularly, antibiotics have been detected globally due to their extensive use and the ease at which they are able to reach the natural environment especially through water bodies. The fate and behavior of these substances is not often clarified so the development of new sensing tools able to detect these compounds even at very low concentration is a current challenge of environmental chemistry. Most of antibiotic classes, such as fluoroquinolones, penicillins, cefalosphorins, contain easily ionizable functions and are often in anionic form at neutral pH. Accordingly to the receptor-spacer-fluorophore modular approach,[2] we planned to detect the targeted analytes taking advantage from the assembly of polyamine units, linked to hydrophobic fluorescent moieties, able to signal substrate binding *via* change in their emission properties.[3] As concerns the polyamine units, a further advantage of polyamines is related to their ability to give stable metal complexes, in particular with transition metals. The coordinated metal can be used as anchoring point for the anionic head of the analytes, which can lead to highly stable complexes. Among transition metals, we planned to use Zn(II). This cation, in fact, generally forms emissive metal complexes with fluorescent ligands. At the same time, Zn(II) can easily change/expand its coordination sphere, favoring the binding with the anionic groups of antibiotics.

Cyanine-based chemosensors have been designed to take advantage of their property of absorbing and emitting in the region of 700-900 nm (NIR region), to avoid the interference with the absorption and emission of pollutants substrates (i.e. fluoroquinolones and tetracyclines), which occurs at lower wavelengths, thus increasing the recognition ability of the chemosensors.[4] In this communication, we present the first results about the ability of receptor **L** *(Figure 1)* to bind and optical sense fluoroquinolones and tetracycline antibiotics in aqueous solution.

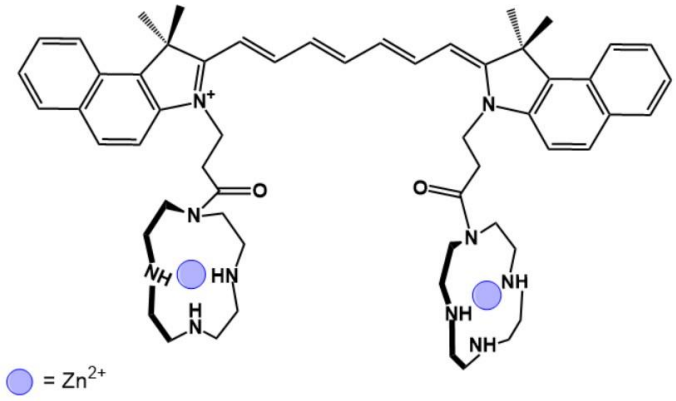

Figure 3:Receptor L

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Cobalt/nickel separation by solvent extraction with a phosphonium based ionic liquid

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Cobalt, one of the main components of cathode used in Li ion battery (LIB) is reported on the 2020 list of critical raw materials [1]. In 2030, the demand for Co will increase five times compared to the current supply of this element. The demand is highly driven by the transition to electrical mobility approach that intends to take over the current internal combustion engine vehicles with the more environmentally friendly electric vehicles [2]. Recycling and reusing end – of – life materials is another approach for sustainable development of new batteries. LIBs recycling boost energy consumption and CO_2 emissions reduction, saves natural resources avoiding raw materials mining and importing. [3]. Current hydrometallurgical processes for the recovery of the Co(II) ions from aqueous solutions have some interesting advantages (low energy consumption, process flexibility, higher purity), but require the use of significant amounts of toxic volatile organic compounds (VOCs) in the solvent extraction stages and of multiple extracting ligands to separate the different metals present in the leachates [4]. Ionic liquids (ILs) have many potential applications. They are powerful solvents with many advantages such as negligible vapor pressure, non-toxicity, reusability and high thermal stability [5]. Most commonly used hydrophobic ILs are Aliquat (nitrogen-based IL) and Cyphos® (phosphonium based IL) [6]. In comparison to the nitrogen-based ILs, phosphonium-ones possess higher thermal stability and are more stable in strong basic media due to the absence of acidic proton. Most leaching processes, at least for nickel (Ni) laterites and sulfides, extract both Co, Ni and result in a mixed solution that needs to be separated [7].

A more environmentally friendly IL with decanoate anion was compared with two ILs with halogen contra-anion (chloride and bromide) whose efficiency is already proven [6]. Acid concentration in water media and timing for extraction was tested. After extraction, the water phase was measured by ICP-OES to quantitatively determine metal concentrations. Pure water was utilized for stripping of pure Co from IL phase. UV-Vis spectroscopy was used for spectral observation of IL phase. Lastly, thermodynamic parameters of extraction in decanoate IL were determined by Isothermal Titration Calorimetry (ITC).

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Direct selenium speciation in biofortified microgreens by synchrotron-based X-Ray Absorption Spectroscopy

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Selenium (Se) is a unique trace element considered essential for humans but toxic in high concentrations. The role of Se in the organism's physiology is mainly related to selenoproteins with a key role in maintaining a healthy immune system and scavenging free radicals [1]. Biofortification of crops with this nutrient has been addressed as a solution to selenium deficiency. In the plant-based food market, microgreens have increased their popularity as food ingredients in recent years because of their high nutritional value and their distinctive flavours and textures [2]. In this work, three different species of Se-biofortified microgreens (*kale, red cabbage and wheat*) have been produced. The enrichment was evaluated in terms of biomass production, total Se concentration, and Se speciation. Also, Se speciation was realized using X-Ray absorption spectroscopy (XAS) at ALBA synchrotron (Barcelona, Spain) to understand the Se transformation into organic species through the microgreens metabolization pathways. This approach allowed the analysis of five main selenium species: selenomethionine, methylselenocysteine, selenocystine, selenite and selenate. The results obtained have shown good yields and a significant concentration of total Se in the biofortified microgreens of kale (133 µg $Se \cdot DW^{-1}$), red cabbage (127 µg $Se \cdot DW^{-1}$) and wheat (28 µg $Se \cdot DW^{-1}$). Speciation results confirmed the presence of organic species (mainly as C-Se-C and C-Se-Se-C forms) in the three plants. The high proportion of organic Se compounds (approximately 80%) is the result of the ability of the plants' metabolism to completely transform inorganic selenium into non-toxic and bioavailable organic forms. These Se-enriched microgreens may contribute to the recommended intake of this micronutrient in the human diet to overcome Se-deficiency.

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Hydrothermal Synthesis of New Generation Perovskite Structures including Lanthanides

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Solar cells are among the prominent alternatives for renewable energy sources. Different materials have been researched to reduce the production costs of solar cells and to develop technologies compatible with new applications. With this study, it will have the potential to be used in solar cell applications, Perovskite structures that can increase the current yield were synthesized by hydrothermal method. In this study, two single perovskites, in different temperature and time combinations of TiO_2 and lanthanides Lanthanum La(III), Cerium Ce(III), $LaTiO_3$, $CeTiO_3$ structures were synthesized. In addition, tin oxide (SnO_2) is seen as promising for perovskite solar cells due to its high electron mobility and superior photocatalytic stability. The single perovskite structures obtained for this purpose were converted into double perovskites with SnO_2. The naostructures were characterized by FT-IR, SEM, XRD, AFM devices.

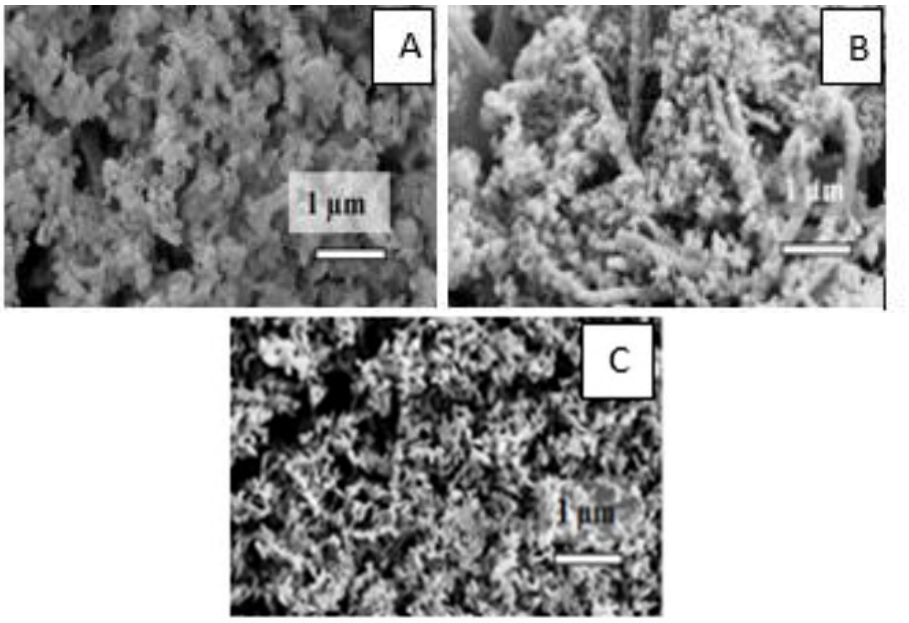

Figure 1. SEM images of a) TiO_2, b) $LaTiO_3$, c) $CeTiO_3$

The doping was successful, and in the morphological results, the peak intensities and partic sizes were consistent with the literature, and superficially homogeneous structures were formed. Thes results are promising in photovoltaic applications for the synthesized nanostructures.

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