11th International Symposium on Applied Bioinorganic Chemistry

Barcelona, Spain

December 2nd – 5th, 2011

Welcome to ISABC11 !

Mercè Capdevila

Chair of ISABC11

On behalf of the Scientific and Organizing Committees of the 11th International Symposium on Applied Bioinorganic Chemistry,

I wish to send a warm welcome to Barcelona to all the ISABC11 participants.

During the next few days, we are going to explore the frontiers of Applied Bioinorganic Chemistry, and this is a big challenge! The symposium will cover all aspects of the broad discipline of metals in medicine, their environmental and toxicological aspects as well as biomaterials.

The meeting gathers about 300 participants from at least 31 countries. It is a great pleasure for me to thank all the participants for their attendance: young and “less young” researchers, “specialists” and non specialists. You are the main protagonists! We have just attempted to create the ideal conditions for providing a fruitful atmosphere during the meeting, and the best environment for scientific debate and discussion of ideas. Let me to stand out that I am in permanent debt to Professor Williams in particular for his acceptance to give the kick-off talk of the meeting.

We have intended the symposium to be a memorable event for all participants, not only because of its scientific program but also owing to its exceptional location. This meeting is an excellent opportunity of discovering the rich historical and cultural heritage of a unique city such as Barcelona. Please, enjoy it!

Finally, I feel urged to acknowledge the funding by all our sponsors that have helped us to provide you with all what we wanted to offer you and that otherwise would have not been possible.

Sincerely,

Mercè Capdevila

International Advisory Committee

David R. Williams (Chairman, Cardiff, UK)
Ettore Benedetti (Naples, IT)
Sue Berners-Price (Nathan, AU)
Mercè Capdevila (Barcelona, SP)
Maria Armenia Carrondo (Lisbon, PT)
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Liang-Nian Ji (Guangzou, CN)
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Tamas Kiss (Szeged, HU)
Bernhard Lippert (Dortmund, DE)
Guillermo Mendoza-Díaz (Guanajuato, ME)
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Franc Meyer (Goettingen, GE)
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Chris Orvig (Vancouver, CA)
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Enrico Rizzarelli (Catania, IT)
Peter Sadler (Warwick, UK)
Athanasios Salifoglou (Thessaloniki, GR)
Andrea Scozzafava (Florence, IT)
Helmut Sigel (Basel, CH)
Imre Sóvágó (Debrecen, HU)

Local Organizing Committee

Mercè Capdevila (Chair, UAB, Barcelona)
Olga Iranzo (Secretary, ITQB, Oeiras)

Sílvia Atrian (UB, Barcelona)
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Antonio Donaire (UM, Murcia)
Virtudes Moreno (UB, Barcelona)
Òscar Palacios (UAB, Barcelona)
Joan Suades (UAB, Barcelona)

SCIENTIFIC PROGRAM

Conference Schedule

	Friday 2nd	***Saturday 3rd***	***Sunday 4th***	***Monday 5th***
8:30-9:00			**PL-3 Fernandez**	**PL-5 Schibli**
9:00-9:30		**Opening Ceremony**		
9:30-10:00		**PL-1 Fontecave**	**KN-5 Luczkowski**	**OC-21** Pecoraro
				OC-22 Orvig
10:00-10:30			**OC-9** Hureau	**OC-23** Pessoa
			OC-10 Valensin	**OC-24** Rua
10:30-11:00		**KN-1 Ward**	**OC-11** Rodríguez	**KN-9 Blindauer**
			OC-12 Delangle	
11:00-11:30		***Coffee break***	***Coffee break***	***Coffee break***
11:30-12:00		**KN-2 Morrow**	**KN-6 Watt**	**KN-10 Amouroux**
12:00-12:30		**OC-1** Margiotta	**OC-13** Fuks	**OC-25** Freisinger
		OC-2 Mucha	**OC-14** Peacock	**OC-26** Sigel
12:30-13:00		**OC-3** Tshuva	**OC-15** Tircso	**OC-27** Pagani
		OC-4 Gambino	**OC-16** Saatchi	**OC-28** Dawson
13:00-14:30		***Lunch***	***Lunch***	***Lunch***
14:30-15:00		**PL-2 Romao**	**PL-4 Geraldes**	**KN-11 Marechal**
15:00-15:30				**OC-29** Sala
				OC-30 Grasso
15:30-16:00		**KN-3 Gibson**	**KN-7 Mareque**	**OC-31** Aono
				OC-32 Rovira
16:00-16:30	**Registration**	**OC-5** García-Ramos	**OC-17** Bardajee	***Coffee break***
		OC-6 Ronconi	**OC-18** Bayón	
16:30-17:00		***Coffee break***	***Coffee break***	**PL-6 O'Halloran**
17:00-17:30		**KN-4 Maiocchi**	**KN-8 Igartua**	
17:30-18:00		**OC-7** Griffith	**OC-19** Mawani	**12th ISABC 2013**
		OC-8 Chao	**OC-20** Policar	
18:00-18:30		**Poster Session (odd posters)**	**Poster Session (even posters)**	**Closing Ceremony**
18:30-19:00	**Opening Lecture Williams**			
19:00-19:30				
19:30-20:00	**Welcome Cocktail**			
20:15				**Buses departure**
21:00				**Gala Dinner**

Friday, December 2nd, 2011	
16:00-18:30	*Registration*
18:30-19:30	Chair: *Jan Reedijk* ***Opening Lecture (PL-0)**: David R. Williams (Cardiff, UK)* "Perception – Applied and Chemical! 50 years of ABC fun"
19:30-21:00	*Welcome Cocktail*

Saturday, December 3rd, 2011	
9:00-9:30	*Opening Ceremony*
9:30-11:00	Chair: *Bernt Kerbs* ***PL-1**: Marc Fontecave (Grenoble, France)* From Metalloenzymes to Bioinspired Catalysts: towards new Energy Conversion Systems ***KN-1**: Thomas R. Ward (Basel, Switzerland)* Artificial Metalloenzymes based on the Biotin-avidin Technology: Challenges and Recent Progress
11:00-11:30	*Coffee break*
11:30-13:00	Chair: *Mauro Ravera* ***KN-2**: Janet R. Morrow (Amherst, USA)* Iron(II) Complexes as PARACEST MRI Contrast Agents ***OC-1**: Nicola Margotta (Bari, Italy)* Bioactive Inorganic Matrices for the Local Delivery of Platinum-based Prodrugs in the Treatment of Bone Tumors ***OC-2**: Ariel Mucha (Birmingham, UK)* Molecular Recognition of DNA Tetrahedral Nanostructure by Metallosupramolecular Helicates ***OC-3**: Edit Y. Tshuva (Jerusalem, Israel)* Extraordinary Performance of Diamino Bis(Phenolato) Ti(IV) and V(V) Anti-Tumor Agents ***OC-4**: Dinorah Gambino (Montevideo, Uruguay)* Searching for novel Antitrypanosomal Agents: Bisphosphonate Transition Metal Complexes
13:00-14:30	*Lunch*
14:30-15:30	Chair: *Helmut Sigel* ***PL-2**: Carlos Romão (Oeiras, Portugal)* Metal Carbonyl in CO Therapy: Successes and Challenges

15:30-16:30	Chair: *Maria Helena García* ***KN-3**: Dan Gibson (Jerusalem, Israel)* On the Reduction of Antiproliferative Pt(IV) Complexes ***OC-5**: Juan Carlos García-Ramos (México DF, México)* Nuclease Activity of Antineoplastic Copper(II) Coordination Compounds: Casiopeínas ***OC-6**: Luca Ronconi (Padova, Italy)* Tailored Gold-based Anticancer Peptidomimetics for the Selective Delivery into the Tumor Cell
16:30-17:00	*Coffee break*
17:00-18:00	Chair: *Norah Barba-Behrens* ***KN-4**: Alessandro Maiocchi (Torino, Italy)* Gadolinium-based Nano-sized Systems for Magnetic Resonance Molecular Imaging Applications ***OC-7**: Darren Griffith (Dublin, Ireland)* Platinum Histone Deacetylase Inhibitor Conjugates as Potential Anti-cancer Agents ***OC-8**: Hui Chao (Guangzhou, China)* Ruthenium(II) Polypyridyl Complexes as DNA Topoisomerase Inhibitors
18:00-20:00	Chairs: *José M. Domínguez-Vera and Gotzone Barandika* ***Poster Session***: Odd posters

Sunday, December 4th, 2011	
8:30-11:00	Chairs: *Tamas Kiss and Giani Valensin* ***PL-3**: Claudio O. Fernández (Rosario, Argentina)* Interactions of Metal Ions and Metal-based Compounds with alpha-Synuclein: from basic Research to Therapy ***KN-5**: Marek Łuczkowski (Wroclaw, Poland)* Bioinorganic Chemistry of Amyloid-β Aggregation Inhibitors ***OC-9**: Christelle Hureau (Toulouse, France)* Copper Coordination to the Alzheimer Peptide and Impact on Redox Properties ***OC-10**: Daniela Valensin (Siena, Italy)* Variation of Astrocyte Metabolic Profile Induced by Amyloid **β** Treatment in Presence of Cu^{2+} and Zn^{2+} Metal Ions ***OC-11**: Cristina Rodríguez-Rodríguez (Vancouver, Canada)* *In silico* Approach for Drug Design in Alzheimer's Disease ***OC-12**: Pascale Delangle (Grenoble, France)* Design of Copper(I) Chelators to Fight Against Copper Overload

11:00-11:30	*Coffee break*
11:30-13:00	Chair: *Isabel Moura* ***KN-6**: Richard Watt (Provo, USA)* The Iron Storage Protein Ferritin is an Anti-Oxidant and a Pro-Oxidant: What Triggers the Change? ***OC-13**: Leon Fuks (Warsaw, Poland)* Technetium-99m Complexed with *n*-heterocyclic Aldehyde Thiosemicarbazones - Potential Precursors of the Radiopharmaceuticals ***OC-14**: Anna Peacock (Birmingham, UK)* MRI of Gadolinium Peptide Coiled Coils ***OC-15**: Gyula Tircsó (Debrecen, Hungary)* Lanthanide(III) Complexes of PCTA Tris(amide) Derivatives: Possible Candidates for Bimodal Imaging ***OC-16**: Katayoun Saatchi (Vancouver, Canada)* A Novel Unimolecular Nanoprobe for Blood Pool Imaging
13:00-14:30	*Lunch*
14:30-16:30	Chair: *Imre Sóvágó* ***PL-4**: Carlos F. G. C. Geraldes (Coimbra, Portugal)* Design and some Biomedical Applications of Metal-based targeted Molecular Imaging Agents ***KN-7**: Juan Carlos Mareque-Rivas (San Sebastián, Spain)* Biofunctionalised Inorganic Nanoscale Structures as Pathogen Mimics ***OC-17**: Ghasem Rezanejade Bardajee (Tehran, Iran)* A novel and smart Biomaterial based Hydrogel Silver Nanocomposite: Synthesis, Characterization and Antibacterial Effect ***OC-18**: Raquel Bayón (Eibar, Spain)* Novel Biocompatible TaN hard Coating for Improving Corrosion-wear behaviour of Biomedical Alloys in simulated Body Fluid
16:30-17:00	*Coffee break*
17:00-18:00	Chair: *Athanasios Salifoglou* ***KN-8**: Amaya Igartua (Eibar, Spain)* Biomaterials for Biomedical Implants ***OC-19**: Yasmin Mawani (Vancouver, Canada)* Lanthanide Complexes for the Treatment of Bone Density Disorders ***OC-20**: Clotilde Policar (Paris, France)* Photothermal IR-Spectromicroscopy for Subcellular Imaging: Cellular Mapping of a Metal-Carbonyl Exogenous Compound
18:00-20:00	Chairs: *Amparo Caubet and Joan Suades* ***Poster Session**:* Even posters

Monday, December 5th, 2011	
8:30-11:00	Chairs: *Dinorah Gambino and José Ruiz* ***PL-5**: Roger Schibli (Zürich, Switzerland)* Progress and Trends in Radiometal-Based Diagnostics and Therapeutics ***OC-21**: Vincent L. Pecoraro (Michigan, USA)* Designing Metallopeptides ***OC-22**: Chris Orvig (Vancouver, Canada)* Chloroquine and Mefloquine Ferrocenyl Conjugates for the Treatment of Malaria ***OC-23**: Joâo Costa Pessoa (Lisboa, Portugal)* Interaction of Vanadium Complexes with Serum Proteins ***OC-24**: Francesco Rua (Torino, Italy)* Bioinorganic Chemistry as a Mean to Reduce Animal Testing for new Drugs: Electrocatalysis of Monkey Cytochrome P450 2C20 ***KN-9**: Claudia A. Blindauer (Coventry, UK)* Discrimination between Essential Zinc and Toxic Cadmium by Soil-dwelling Organisms: Metallothioneins behaving in Unexpected Manners
11:00-11:30	*Coffee break*
11:30-13:00	Chair: *Etelka Farkas* ***KN-10**: David Amouroux (Pau, France)* The Biogeochemical Speciation of Mercury: linking Molecular and Isotopic Information in Metals Environmental Bio-interactions ***OC-25**: Eva Freisinger (Zürich, Switzerland)* Recruiting Sulfide Ligands to Increase the Detoxification Capacity of Metallothioneins ***OC-26**: Roland K. O. Sigel (Zürich, Switzerland)* The Application of NMR and Single Molecule FRET to Investigate the Toxic Effect of Ca^{2+} on Group II Intron Splicing ***OC-27**: M. Ayelen Pagani (Rosario, Argentina)* Soybean Metallothionein Family: A Role in Cadmium Accumulation? ***OC-28**: John H. Dawson (Columbia, USA)* *A. ornata* Dehaloperoxidase: the Mechanism of Oxidative Dehalogenation by Heme-Containing Peroxidases as Potential Bioremediation Catalysts
13:00-14:30	*Lunch*
14:30-16:00	Chair: *Ana Isabel Tomaz* ***KN-11**: Jean-Didier Maréchal (Barcelona, Spain)* Modeling Insights on Metal Mediated Environmental and Toxicological Responses ***OC-29**: Xavier Sala (Barcelona, Spain)* Molecular Catalysts for Artificial Photosynthesis

	***OC-30**: Giuseppe Grasso (Catania, Italy)* The Influence of Metallostasis on Insulin Degrading Enzyme Activity ***OC-31**: Shigetoshi Aono (Okazaki, Japan)* Structural basis for the Transcriptional Regulation of Heme Homeostasis in Lactic Acid Bacteria ***OC-32**: Carme Rovira (Barcelona, Spain)* The Molecular Mechanism of Catalase by QM/MM Metadynamics
16:00-16:30	*Coffee break*
16:30-17:30	Chair: *José Moura* ***PL-6**: Thomas V. O'Halloran (Evanston, USA)* Therapeutic Efficacy of Arsenic-bound Platinum Agents: Drug Synergy and Unexpected Inorganic Chemistry in Combination Chemotherapy for Triple Negative Breast Cancer
17:30-18:00	*Presentation of 12th ISABC 2013*
18:00-18:30	*Closing Ceremony*
20:15-21:00	*Buses departure*
21:00-24:00	*Gala Dinner*

Plenary Lectures

PL-0: "Perception – Applied and Chemical! 50 years of ABC fun"
D. R. Williams

PL-1: From Metalloenzymes to Bioinspired Catalysts: towards new Energy Conversion Systems
M. Fontecave

PL-2: Metal Carbonyl in CO Therapy: Successes and Challenges
C. Romão

PL-3: Interactions of Metal Ions and Metal-based Compounds with alpha-Synuclein: from basic Research to Therapy
A. Binolfi, G. R. Lamberto, M. L. Orcellet, A. A. Valiente-Gabioud, V. Torres-Monserrat, C. W. Bertoncini, L. Quintanar, M. Zweckstetter, C. Griesinger, C. O. Fernández

PL-4: Design and some Biomedical Applications of Metal-based targeted Molecular Imaging Agents
C. F. G. C. Geraldes

PL-5: Progress and Trends in Radiometal-Based Diagnostics and Therapeutics
R. Schibli

PL-6: Therapeutic Efficacy of Arsenic-bound Platinum Agents: Drug Synergy and Unexpected Inorganic Chemistry in Combination Chemotherapy for Triple Negative Breast Cancer
T. V. O'Halloran

Keynote Lectures

KN-1: Artificial Metalloenzymes based on the Biotin-avidin Technology: Challenges and Recent Progress
Th. R. Ward

KN-2: Iron(II) Complexes as PARACEST MRI Contrast Agents
J. R. Morrow, S. J. Dorazio, P. B. Tsitovich

KN-3: On the Reduction of Antiproliferative Pt(IV) Complexes
D. Gibson, A. Nemirovski, S. Salameh, J. Zhang, T. Hambley

KN-4: Gadolinium-based Nano-sized Systems for Magnetic Resonance Molecular Imaging Applications
C. Brioschi, C. Cabella, S. Ghiani, A. Maiocchi, L. Miragoli, M. Visigalli

KN-5: Bioinorganic Chemistry of Amyloid-β Aggregation Inhibitors
M. Łuczkowski, D. Valensin

KN-6: The Iron Storage Protein Ferritin is an Anti-Oxidant and a Pro-Oxidant: What Triggers the Change?
R. Watt, R. Hilton

KN-7: Biofunctionalised Inorganic Nanoscale Structures as Pathogen Mimics
J. C. Mareque-Rivas, M. Henriksen-Lacey, N. Gómez, B. M. Cobaleda, C. R. Maldonado, M. Krembuszewski, T. Barr, D. Gray

KN-8: Biomaterials for Biomedical Implants
A. Igartua, V. Sáenz de Viteri, E. Fuentes, R. Bayón

KN-9: Discrimination between Essential Zinc and Toxic Cadmium by Soil-dwelling Organisms: Metallothioneins behaving in Unexpected Manners
C. A. Blindauer, O. I. Leszczyszyn, S. Zeitoun-Ghandour, S. R. Stürzenbaum

KN-10: The Biogeochemical Speciation of Mercury: linking Molecular and Isotopic Information in Metals Environmental Bio-interactions
D. Amouroux

KN-11: Modeling Insights on Metal Mediated Environmental and Toxicological Responses
J.-D. Maréchal

Oral Communications

OC-1: Bioactive Inorganic Matrices for the Local Delivery of Platinum-based Prodrugs in the Treatment of Bone Tumors
N. Margotta, S. Piccinonna, M. Iafisco, N. Roveri, G. Natile

OC-2: Molecular Recognition of DNA Tetrahedral Nanostructure by Metallosupramolecular Helicates
A. Mucha, S. Phontongpasuk, M. J. Hannon

OC-3: Extraordinary Performance of Diamino Bis(Phenolato) Ti(IV) and V(V) Anti-Tumor Agents
E. Y. Tshuva

OC-4: Searching for novel Antitrypanosomal Agents: Bisphosphonate Transition Metal Complexes
B. Demoro, M. Galizzi, L. Malayil, R. Docampo, L. Otero, D. Gambino

OC-5: Nuclease Activity of Antineoplastic Copper(II) Coordination Compounds: Casiopeínas
J. C. García-Ramos, J. C. Carrero, J. P. Laclette, L. Ruiz-Azuara

OC-6: Tailored Gold-based Anticancer Peptidomimetics for the Selective Delivery into the Tumor Cell
L. Ronconi, D. Aldinucci, A. Trevisan, Q. P. Dou, F. Formaggio, D. Fregona

OC-7: Platinum Histone Deacetylase Inhibitor Conjugates as Potential Anti-cancer Agents
D. Griffith, C. J. Marmion

OC-8: Ruthenium(II) Polypyridyl Complexes as DNA Topoisomerase Inhibitors
H. Chao, L.-N. Ji

OC-9: Copper Coordination to the Alzheimer Peptide and Impact on Redox Properties
C. Hureau, V. Balland, Y. Coppel, P. Dorlet, J. M. Savéant, P. Faller

OC-10: Variation of Astrocyte Metabolic Profile Induced by Amyloid β Treatment in Presence of Cu^{2+} and Zn^{2+} Metal Ions
D. Valensin, C. Aldinucci, A. Rocchi, G. Giani, D. Pasqui, R. Barbucci, H. Kozlowski, E. Gaggelli

OC-11: *In silico* Approach for Drug Design in Alzheimer's Disease
C. Rodríguez-Rodríguez, M. Telpoukhovskaia, J. Cawthray, C. Orvig

OC-12: Design of Copper(I) Chelators to Fight Against Copper Overload
P. Delangle, A. M. Pujol, C. Lebrun, C. Gateau

OC-13: Technetium-99m Complexed with *n*-heterocyclic Aldehyde Thiosemicarbazones - Potential Precursors of the Radiopharmaceuticals
L. Fuks, E. Gniazdowska, P. Kozminski

OC-14: MRI of Gadolinium Peptide Coiled Coils
A. Peacock, M. Berwick, L. van Gemeren, J. Wilkie, M. Britton

OC-15: Lanthanide(III) Complexes of PCTA Tris(amide) Derivatives: Possible Candidates for Bimodal Imaging
Gy. Tircsó, E. Ádom, I. Tóth, Z. Kovács, A. D. Sherry, É. Jakab Tóth, I. Tóth

OC-16: A Novel Unimolecular Nanoprobe for Blood Pool Imaging
K. Saatchi, U. O. Häfeli, P. Gershkovich, K. M. Wasan, R. Kainthan, D. E. Brooks, N. Hundal, F. Bénard

OC-17: A novel and smart Biomaterial based Hydrogel Silver Nanocomposite: Synthesis, Characterization and Antibacterial Effect
G. R. Bardajee, Z. Hooshyar

OC-18: Novel Biocompatible TaN hard Coating for Improving Corrosion-wear behaviour of Biomedical Alloys in simulated Body Fluid
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OC-19: Lanthanide Complexes for the Treatment of Bone Density Disorders
Y. Mawani, K. Sachs-Barrable, J. Cawthray, K. M. Wasan, C. Orvig

OC-20: Photothermal IR-Spectromicroscopy for Subcellular Imaging: Cellular Mapping of a Metal-Carbonyl Exogenous Compound
C. Policar, S. Clède, F. Lambert, N. Delsuc, H. Bertrand, M.-A. Plamont, J. Waern, C. Mayet, A. Deniset, R. Prazeres, J.-M. Ortega, A. Vessières, A. Dazzi, C. Sandt, P. Dumas, Z. Gueroui

OC-21: Designing Metallopeptides
V. L. Pecoraro, M. Zastrow, V. Cangelosi, F. Yu, J. Plegaria

OC-22: Chloroquine and Mefloquine Ferrocenyl Conjugates for the Treatment of Malaria
C. Orvig, P. Salas, C. Herrmann, J. Cawthray, C. Nimphius, A. Kenkel, M. J. Adam

OC-23: Interaction of Vanadium Complexes with Serum Proteins
J. Costa Pessoa, E. Cobbinna, S. Mehtab, G. Gonçalves, G. Justino, I. Tomaz, I. Correia, T. Kiss, T. Jakusch, E. Enyedi, V. Moreno, E. Garriba

OC-24: Bioinorganic Chemistry as a Mean to Reduce Animal Testing for new Drugs: Electrocatalysis of Monkey Cytochrome P450 2C20
F. Rua, S. J. Sadeghi, S. Castrignanò, G. Di Nardo, G. Gilardi

OC-25: Recruiting Sulfide Ligands to Increase the Detoxification Capacity of Metallothioneins
X. Wan, T. Huber, E. Freisinger

OC-26: The Application of NMR and Single Molecule FRET to Investigate the Toxic Effect of Ca^{2+} on Group II Intron Splicing
R. K. O. Sigel

OC-27: Soybean Metallothionein Family: A Role in Cadmium Accumulation?
M. A. Pagani, J. Carrillo, M. Reggiardo, M. Tomas, C. S. Andreo, M. Capdevila, R. Bofill, S. Atrian

OC-28: *A. ornata* Dehaloperoxidase: the Mechanism of Oxidative Dehalogenation by Heme-Containing Peroxidases as Potential Bioremediation Catalysts
J. H. Dawson, S. Sun, C. Wang, J. Du, X. Huang, L. Lebioda

OC-29: Molecular Catalysts for Artificial Photosynthesis
X. Sala, L. Francàs, J. Aguió, L. Escriche, A. Llobet

OC-30: The Influence of Metallostasis on Insulin Degrading Enzyme Activity
G. Grasso, F. Bellia, C. Tosto, D. Milardi, E. Rizzarelli

OC-31: Structural basis for the Transcriptional Regulation of Heme Homeostasis in Lactic Acid Bacteria
H. Sawai, M. Yamanaka, H. Sugimoto, Y. Shiro, S. Aono

OC-32: The Molecular Mechanism of Catalase by QM/MM Metadynamics
M. Alfonso-Prieto, C. Rovira

Posters

P-1: Biological Activity of Iron Complexes with Bithiazole
A. Abedi, N. Safari, V. Amani, H. R. Khavasi, S. N. Ostad

P-2: Synthesis, Structure and Properties of Pt and Ru Complexes of 2,4-dithiohydantoins with Antitumor Activity
A. Ahmedova, K. Paradowska, G. Momekov, M. Marinov, M. Mitewa

P-3: Synthesis and Charaterization of new Coordination Compounds with Antihelmintic Activity in Monogeneos of Spotted Rose Snapper (*Lutjanus Guttatus*)
I. Alfaro-Fuentes, N. Barba-Behrens, E. J. Fajer-Ávila, M. Betancourt-Lozano

P-4: Synthesis and Characterization Complex of the $\{ReO\}^{3+}$ Core with Sn and N donor Ligands
N. Al-Hokbany, I. Al-Jammaz

P-5: Metal Ions Modulate Amyloid Formation
B. Alies, S. Sayen, E. Guillon, C. Bijani, C. Hureau, P. Faller

P-6: Development of Ru(II)/Os(II) Cage Type Ligand Complexes for Photocatalytic Reduction of NAD^+
T. Aoki, Y. Wasada-Tsutsui, T. Inomata, T. Ozawa, Y. Funahashi, H. Masuda

P-7: Crown Ether Azamacrocyclic Ligand Frameworks for Heteronuclear $Ca^{2+}/Mn^{2+/3+}$-complexes as Potential MRI Contrast Agents
I. Ivanović-Burmazović, J. Appelt

P-8: Complete Dinitrogen Activation by Vanadium Complexes
G. Aullón, B. Peigné

P-9: Biological, Spectroscopic and Structural Properties of Transition Metal Compounds with Imidazole Derivatives
N. Barba-Behrens, I. Alfaro-Fuentes, G. González-Gómez, H. López-Sandoval, S. Betanzos-Lara, I. Gracia, E. Fajer

P-10: New Insights in Tyrosinase Inhibition from a Bio-inorganic Strategy
C. Belle, C. Bochot, M. Orio, H. Jamet, G. Serratrice, R. Haudecoeur, A. Boumendjel, C. Dubois, R. Hardré, M. Réglier

P-11: Effects of Metal Binding to Carnosine Derivatives and Serum Carnosinase
F. Bellia, G. I. Grasso, V. Lanza, G. Vecchio, E. Rizzarelli

P-12: Antioxidant Activity and Tumor Cell Proliferation Inhibition of Mono-di-organo- and Bis-di-organo-tin(IV) Imines
H. I. Beltran, L. López, L. Arregui, E. Rivera-Becerril, J. Flores, F. González-Chávez, J. Guerrero

P-13: Study of Superoxide Dismutase Mimic Manganese Complexes
A.-S. Bernard, S. Iriart, M. D'Almeida, V. Grondin, G. Gazzah, J.-L. Boucher, N. Delsuc, M. Bachelet, J. Masliah, C. Policar

P-14: Potency of Antimetastatic (ImH)[trans-$RuCl_4$(dmso)(Im)] Complex as a NO Scavenger
M. Brindell, M. Gluszko, M. Oszajca

P-15: Synthesis of Di-magnesium Complexes as Artificial Ribonucleases
N. Byrne, A. Erxleben

P-16: The Mg(II)-dependent Folding of Group II Intron Ribozymes Characterised by Single Molecule FRET
L. Cardo, D. Kowerko, S. L. B. König, R. K. O. Sigel

P-17: Desulfovibrio alaskensis Orange Protein: Insights on the Protein Assisted Mo-Cu Cluster Synthesis
M. S. P. Carepo, R. Grazina, C. C. S. Carreira, A. Dolla, J. J. G. Moura, I. Moura

P-18: H-rich Ferritin as the Lactoferrin's Partner in the Iron Metabolism
F. Carmona, S. Zedat, D. Franzese, J. M. Domínguez-Vera

P-19: Targeting Aquaporin Function: Potent Inhibition of Aquaglyceroporin-3 by Metal Compounds
A. Casini, A. P. Martins, T. F. Mour, G. Soveral

P-20: Catalytic Oxidative Transformations
I. Prat, J. S. Mathieson, X. Ribas, M. Güell, J. M. Luis, L. Cronin, M. Costas

P-21: Characterization and Release Kinetics of Silver from Dressings used in Burns Care
M. Roman, C. Rigo, I. Munivrana, V. Vindigni, B. Azzena, C. Barbante, S. Crotti, W. R. L. Cairns

P-22: A New Approach to the Ferritin Iron Core Growth. Consequences on Iron Metabolism
R. Cuesta, J. D. López-Castro, J. J. Delgado, J. A. Perez-Omil, N. Gálvez, R. K. Watt, J. M. Domínguez-Vera

P-23: New Organometallic Compounds of Platinum(II) as Antitumor Agent against Breast Cancer
N. Cutillas, J. Ruiz, V. Rodríguez, M. Hannon

P-24: Mutant Colicin E7 Proteins Reveal the Conditions for Allosteric Control of the Enzymatic Action
A. Czene, E. Németh, I. G. Zóka, N. I. Simon, B. Gyurcsik, H. E. M. Christensen, K. Nagata

P-25: Intrinsic pK_a Values within a DNA Oligonucleotide: The Basis for Acid-Base Catalysis in DNAzymes and Ribozymes
A. Domínguez-Martín, S. Johannsen, R. K. O. Sigel

P-26: The Role of Ferritin in the Toxicity of Iron Oxide-based Nanodrugs
J. M. Domínguez-Vera, J. D. Lopez-Castro, J. J. Delgado, A. V. Maraloiu, N. Gálvez, M.-G. Blanchin

P-27: Exploring the Electronic Structure of Oxidized Blue Copper Proteins by means of ^{13}C NMR
A. Donaire, M. E. Zaballa, I. Díaz-Moreno, J. M. García-Heredia, M. A. de la Rosa, A. J. Vila

P-28: Phosphate Monoester Hydrolysis by Zirconium(IV) Complexes
A. Erxleben, F. Coleman

P-29: Bioinspired Investigation on Complexes of Desferrioxamine B, Desferricoprogen and their Model Ligands with Mn(II) and Mn(III)
E. Farkas, O. Szabó, Gy. Tircsó

P-30: Self-assembly of Metalloporphyrins: first TPP-bipy Coordination Polymer with Co^{II} (TPP = meso-tetraphenylporphyrin and bipy = 4,4´-bipyridine)
A. Fidalgo-Marijuan, G. Barandika, B. Bazán, M. K. Urtiaga, M. I. Arriortua

P-31: The Influence of Substitution at the Ligand on the Properties of Indoloquinoline-based Ruthenium- and Osmium-complexes
L. K. Filak, G. Mühlgassner, M. A. Jakupec, B. K. Keppler, V. B. Arion

P-32: Comparative Studies of Manganese SOD Mimetics: Interactions with Phosphate Can Be Crucial for their Physiological Application
F. Friedel, D. Lieb, I. Ivanović-Burmazović

P-33: Distorted Dicopper Complexes as a Biomimetic Model of Tyrosinase
Y. Funahashi, T. Shirota, T. Toyama, K. Yoshii, T. Nishikawa, Y. Wasada-Tsutsui, T. Inomata, T. Ozawa, H. Masuda

P-34: Copper-containing Carbosilane Dendrimers as Antiviral Agents
M. Galán, J. Sánchez, J. L. Jiménez, M. F. Ottaviani, M. A. Muñoz-Fernandez, R. Gómez, F. J. De la Mata

P-35: $[Cu(thp)_4][PF_6]$ as an Effective Therapeutic Agent for the Treatment of Solid Tumors, including Refractory Tumors
V. Gandin, F. Tisato, C. Santini, M. Pellei, M. Porchia, G. Papini, G. Gioia Lobbia, C. Marzano

P-36: Correlation between DNA Studies by Optic Spectra and AFM Images
M. H. Garcia, A. M. Santos, A. I. Tomaz, V. Moreno, C. Ciudad, V. Noe

P-37: Polyamine Anionic Metallodendrimers as dual Antiviral Agents
S. García-Gallego, J. Sánchez Rodríguez, J. L. Jiménez, M. Cangiotti, M. F. Ottaviani, M. A. Muñoz-Fernández, R. Gómez, F. J. De la Mata

P-38: Adenine-copper(II)-thiosemicarbazone System: Structural Studies and Biological Implications
R. Gil-García, M. Ugalde, G. Madariaga, B. Pérez-Picado, B. García, R. Ruiz, J. García-Tojal

P-39: New Strategies for Rational Design and Synthesis of Potential Metal-based Antitumour Agents
G. Gencheva

P-40: Heterologous Overexpression in *E.coli* of Recombinant Fuscoredoxin Proteins from *Desulfovibrio desulfuricans* (ATCC27774)
R. Grazina, J. J. G. Moura

P-41: Biological and Physico-chemical Evaluation of new Pyrazole Complexes with Cu(II)
M. Grażul, E. Budzisz, R. K. O. Sigel

P-42: Bioactive Nickel(II) and Cobalt(II) Complexes of Mannich Bases derived from 5-tert-butylpyrocatechin
A. Gres, N. Loginova, T. Kavalchuk, G. Polozov, N. Osipovich, I. Azarko, R. Zheldakova

P-43: Description of a Novel Ruthenium Antitumor Compound: [Ru(η-*p*-cymene) (1,10-phenanthroline-5,6-dione)][PF_6]
V. Moreno, D. Gambino, L. Otero, J. Lorenzo, H. Guiset

P-44: Hydroxamic Acids and Oximes for Bioinorganic Applications and Modelling
E. Gumienna-Kontecka, I. O. Fritsky

P-45: Design of a Novel Artificial Nuclease based on the HNH
B. Gyurcsik, A. Czene, N. I. Simon, E. Németh, I. G. Zóka, T. Körtvélyesi, H. E. M. Christensen, K. Nagata

P-46: Complexes of Macrocyclic Conjugates with Rigid Scaffolds for Cell Labeling
I. Řehoř, Z. Kotková, D. Jirák, V. Vilímová, P. Jendelová, V. Kubíček, J. Kotek, P. Hermann, I. Lukeš

P-47: Time-resolved Spectroscopic Analysis of Reaction Intermediate Species in a Non-heme Iron(II) Complex and Perbenzoic Acid System
Y. Inagaki, T. Inazumi, Y. Wasada-Tsutsui, T. Inomata, T. Ozawa, Y. Funahashi, H. Masuda

P-48: Modulation of DNA Binding by Reversible Metal-controlled Molecular Movements in Three Novel Scorpiand-like Ligands
M. Inclán, C. Serena, M. T. Albelda, J. Frías, A. García-España, E. García-España

P-49: Effect of Monensin on Cadmium-induced Hepatic Dysfunction
Ju. Ivanova, Y. Gluhcheva, K. Kamenova, S. Arpadjan, M. Mitewa

P-50: Redox Regulation of NO-signaling by Metal Complexes and H_2S
M. Filipović, I. Ivanović-Burmazović

P-51: N7 or S8 Coordination of 8-thio-theophyline Derivatives to $\{CpRuLL'\}^+$ Moieties (L = PTA, mTPA; L' = PTA, mPTA, PPh_3) (PTA = phosphaadamantane, mPTA = *N*-methyl-PTA)
V. Jara, L. Hajji, C. Saraiba, M Serrano-Ruiz, M. I. Montes Escudero, A. Romerosa

P-52: Inhibition of DNA Transcription by DNA-intercalative Polypyridyl Ruthenium(II) Complexes
F. Gao, X. Chen, L. P. Weng, L. N. Ji

P-53: Synthesis and Characterization of a new Lumazine-pyrano-lumazine fused Ligand
F. Hueso Ureña, N. A. Illán Cabeza, S. B. Jiménez Pulido, M. N. Moreno Carretero

P-54: Site Specific Metallation of a Metallothionein from Wheat
S. Johannsen, J. Loebus, E. Freisinger

P-55: Copper(II) Interaction with a Scrambled Human Prion Fragment. Coordination and Oxidation
C. Kallay, L. Nagy, I. Sovago, G. Pappalardo, E. Rizzarelli

P-56: Syntheses of Novel Au8 Clusters and their Optical Responses to Metal Ions
Y. Kamei, Y. Shichibu, K. Konishi

P-57: Organometallic Rhodium Compounds as Potential Anticancer Agents
W. Kandioller, M. Barasits, S. Aicher, B. K. Keppler, C. G. Hartinger

P-58: Mn(II) and Fe(II) Complexes of Sterically Hindered 1,2-Dihydroxybenzene Derivatives: Biological Evaluation and Reduction of Cytochrome *c*
T. Kavalchuk, N. Loginova, A. Gres, G. Polozov, Y. Faletrov, R. Zheldakova, N. Osipovich

P-59: Optical Resolutions of DL-Amino Acids via Cu(II) Ternary Complexes Containing Optically Active Amino Acids
M. Kimura, T. Yajima, T. Shiraiwa

P-60: Construction of Multicopper Oxidase Model Systems Using a Copper-clustering Core Capsulated in a Cage
W. Kinoshita, K. Nagata, K. Fukui, M. Fukui, Y. Wasada-Tsutsui, T. Inomata, T. Ozawa, Y. Funahashi, H. Masuda

P-61: Characterization of Anticancer Ru(II,III) Compounds in Aqueous Solution
T. Kiss, T. Jakusch, É. Sija, É. A. Enyedy, C. G. Hartinger, B. K. Keppler

P-62: DNA-binding and Topoisomerase IIα-inhibiting Ru(cymene) Complexes with Flavone-derived Ligands
A. Kurzwernhart, W. Kandioller, C. Bartel, S. Bächler, R. Trondl, G. Mühlgassner, M. A. Jakupec, V. B. Arion, D. Marko, B. K. Keppler, C. G. Hartinger

P-63: Interaction of Ni(II) with Non-steroidal Antiinflammatory Drug Diclofenac
M. Kyropoulou, C.P. Raptopoulou, V. Psycharis, G. Psomas

P-64: Copper(II) Interaction with Human Angiogenin Protein and Related Peptide Fragments
D. La Mendola, A. Magrì, F. Bellia, A. Travaglia, O. Hansson, F. Arnesano, G. Natile, L. De Gioia, R. P. Bonomo, E. Rizzarelli

P-65: Rhenium Carbonyl Compounds with Metallothionein for Radiopharmaceutical Applications
J. Lecina, O. Palacios, S. Atrian, M. Capdevila, J. Suades

P-66: Multifunctional Quantum-dot-based as Dual Platform for siRNA and Doxorubicin Delivery and Real-time Tracking of Delivery
J.-M. Li, Y.-Y. Wang, L.-N. Ji, Z.-W. Mao

P-67: Seven-Coordinated, Dinuclear Mn^{+} Complexes with Cyclic Polyamine Ligands as Potential Superoxide Dismutase Mimetics
D. Lieb, F. Friedel, A. Zahl, I. Ivanovic-Burmazovic

P-68: Stabilization of G-Quadruplex DNA and Inhibition of Telomerase Activity by Chiral Ruthenium(II) Complexes
D. Sun, J. Liu, L.-N. Ji

P-69: A Novel Therapeutic Role of Cisplatin: Potential Anti-tuberculosis Agent by Inhibition of Protein Splicing
Y. Zheng, Y. Liu

P-70: Solution Study of Metal Complexes with Macrocyclic Ligands having Carboxylate and Phosphonate Pendant Arms
P. Lubal, M. P. C Campello, R. Ševčík, J. Vaněk, R. Ševčíková, P. Hermann, I. Santos, M. Martínez

P-71: NMR Active MoS_4^{2-}-M (M = Cu, Cd and Gd) Clusters Use as a Structural Probe in Orange Protein
B. K. Maiti, T. Avilés, I. Moura, S. R. Pauleta, J. J. G. Moura

P-72: Application of Cyclodextrin in Bioinorganic Chemistry: from Metalloenzyme Models to Drug Carries
Z.-W. Mao

P-73: Receptor-Targeted Platinum and Ruthenium Complexes as Selective Antocancer Drugs
F. Barragán, D. Carrion, P. López-Senín, E. Escribano, A. González-Cantó, R. de Llorens, A. Massaguer, V. Moreno, V. Marchán

P-74: Design of Artificial Oxygenases for Drug Synthesis
C. Marchi-Delapierre, C. Esmieu, E. Girgenti, A. Jorge-Robin, S. Ménage, M. Cherrier, M. Iannello, J. Fontecilla-Camps, P. Amara, C. Cavazza

P-75: Metalloproteinase Inhibition: a new Metal-Binding Group in the Game
S. M. Marques, T. Tuccinardi, E. Nuti, S. Santamaria, A. Rossello, A. Martinelli, M. A. Santos

P-76: Synthesis, Characterization and Anti-tumor Activity
C. P. Matos, A. Valente, F. Marques, P. Adão, J. Costa Pessoa, M. H. Garcia, A. I. Tomaz

P-77: Interaction of Apotransferrin with Anticancer Ruthenium Complexes NAMI-A and its Reduced Form
O. Mazuryk, G. Stochel, M. Brindell

P-78: Fragmentation Methods on the Balance: Unambiguous Top-Down Mass Spectrometric Characterization of Oxaliplatin-Ubiquitin Binding Sites
S. M. Meier, Y. O. Tsybin, P. J. Dyson, B. K. Keppler, C. G. Hartinger

P-79: Antitumor 'Salan' Titanium(IV) Complexes: Steric and Electronic Effects on Hydrolysis and Cytotoxicity
S. Meker, E. Y. Tshuva

P-80: Combat Drug Resistance of Cisplatin by Gold Nanorods Based Drug Delivery System
Y. Min, D. Xu, Y. Liu

P-81: Protective Effect of Alanine on Neurite Growth in Rat Sympathetic Neuron-like Cells Exposed to Copper and Amyloid β-protein Fragment
T. Minami, M. Yoshida, Y. Takimiya, Y. Sakamoto, S. Ichida

P-82: Activity of Monensin Biometal(II) Complexes against Animal Tumor Cells
R. Alexandrova, T. Zhivkova, D. Ivanov, B. Andonova-Lilova, L. Dyakova, I. Pantcheva, M. Mitewa

P-83: *New Ruthenium(II) Cyclopentadienyl Compounds: Cytotoxicity and Proteins Binding*
T. S. Morais, M. H. Garcia, A. I. Tomaz, F. Marques, M. P. Robalo, P. J. A. Madeira

P-84: Synthesis of a Functional Model of Multinuclear Metal Complex for CO_2 Reduction
Y. Morimi, K. Nagata, M. Fukui, T. Inomata, T. Ozawa, Y. Funahashi, H. Masuda

P-85: Complexes of Cu(II) and Zn(II) with 7-amino-4-methylchromone: Spectroscopic, Electrochemical and Antioxidant Properties
B. Kupcewicz, K. Lux, P. Mucha, E. Budzisz

P-86: Computational Study and Refinement of an X-ray Catalytic Antibody Structure
V. Muñoz Robles, B. Golinelli-Pimpaneau, A. Lledós, R. Ricoux, J.-P. Mahy, J.-D. Maréchal

P-87: Oxidation of Alcohols Using a Cage Type Zn(II) Complex as a Functional Model of Alcohol Dehydrogenase
M. Murase, T. Aoki, Y. Morimi, T. Inomata, T. Ozawa, Y. Funahashi, H. Masuda

P-88: Interaction with DNA and Anticancer Studies of Pd(II) Complexes Containing Dithiocarbamato and 1,10-phenanthroline Derivatives
H. Furusawa, T. Sakai, M. Nakai, Y. Nakabayashi

P-89: Metalloprotein Mimics by Design: Strategies and Applications
F. Nastri, O. Maglio, R. Vitale, C. Andreozzi, L. Lista, P. Ringhieri, V. Pavone, A. Lombardi

P-90: Syntheses of α-Alkylserines by Forming Copper Complexes
H. Ogata, T. Yajima, T. Shiraiwa

P-91: Chemical Approaches for Epigenetic DNA Modification
A. Okamoto

P-92: Capacities of Computational Approaches to Predict Inert Inorganic Scaffolds Interacting with Proteins
E. Ortega-Carrasco, A. Lledós, J.-D. Maréchal

P-93: Mechanistic Studies on Chlorophyll Degradation Processes
Ł. Orzeł, D. Rutkowska-Żbik, B. Szmyd, T. Szumełda, L. Fiedor, G. Stochel

P-94: Mechanistic Insight into the Formation of Oxo-iron(IV) in the Reaction of Fe(III) Porphyrin with H_2O_2. The Influence of N-methylimidazole Ligation
M. Oszajca, A. Franke, M. Brindell, G. Stochel, R. van Eldik

P-95: The Interaction between Ferritin and Metallothioneins Promotes simultaneous Metal (Fe and Zn) Delivery
Ò. Palacios, R. Orihuela, B. Fernández, E. Valero, S. Atrian, R. K. Watt, J. M. Domínguez-Vera, M. Capdevila

P-96: Cyclotoxic Properties of Monensic Acid and its Biometal(II) Complexes against Human Tumor/Non-tumor Cell Lines
R. Alexandrova, T. Zhivkova, M. Alexandrov, G. Miloshev, M. Kirilova, I. Pantcheva, M. Mitewa

P-97: Superoxide Dismutase and Catalase Modeling using N_3 Ligands
J. S. Pap, B. Kripli, T. Váradi, M. Giorgi, J. Kaizer, G. Speier

P-98: Synthesis and Characterization of new Ruthenium(II)-arene Complexes with Chromon Derivatives
A. Pastuszko, A. Jóźwiak, E. Budzisz

P-99: A Step Forward to the Miniaturization of Biosensors incorporating Metallothioneins as Ionophores
S. Pérez-Rafael, Ò. Palacios, E. Fàbregas, S. Atrian, M. Capdevila

P-100: Metallothioneins as Detoxifying Agents for Pb(II)
C. Pérez-Zúñiga, Ò. Palacios, S. Atrian, M. Capdevila

P-101: New (Poly)metallic Architectures Suitables for Bioimaging
C. Deraeve, A. Boulay, N. Leygue, S. Laurent, C. Galaup, B. Mestre-Voegtlé, L. Vander Elst, E. Benoist, R. N. Muller, C. Picard

P-102: Gold Nanoparticles Modified by Thrombin Binding Aptamer
I. Pilarova, G. M. Castillo, L. Trnkova

P-103: A Peptidic Turn with High Affinity for Hg(II)
S. Pires, O. Iranzo

P-104: Hydridotris(azolyl)borato Phosphino-Cu(I) Complexes: Ligand Effect on their in vitro Cytotoxicity
M. Porchia, F. Refosco, F. Tisato, V. Gandin, C. Marzano, M. Pellei, C. Santini

P-105: Cobalt(II) Complexes with Non-steriodal Anti-inflammatory Drugs: Structure and Biological Evaluation
G. Psomas, S. Tsiliou, E. Pehlivanidou, F. Perdih, I. Turel, D. P. Kessissoglou

P-106: Imidazole Derivatives of Aminophosphonates as Efficient Chelators for Ni(II) and Cu(II) Ions
M. Pyrkosz, E. Gumienna-Kontecka, W. Goldeman

P-107: Experimental Determination and Modeling of the Lipophilicity in Platinum Complexes
M. Ravera, E. Gabano, G. Ermondi, G. Caron, J. A. Platts, D. Osella

P-108: Synthesis and Characterization of Novel Asymmetrical M(III) (M = Re, ^{99g}Tc) Complexes as Models for the Development of Potential Tracers for SPECT Imaging and Radiotherapy
F. Refosco, N. Salvarese, N. Morellato, D. Carta, A. Galenda, A. Venzo, A. Dolmella, C. Bolzati

P-109: Platinum(II) Complexes derived from Carbazoles. A new Step for the Design of Luminescent Antitumoral Agents
M. Reig, D. Velasco, C. López

P-110: Au(I)-mediated Base Pairs
T. Richters, J. Müller

P-111: New Ruthenium Antitumor Complexes: Synthesis, Anti-proliferative Activity and Interaction with Human Albumin
O. L. Rojas, F. C. Santos, M. J. Brito, F. Marques, M. P. Robalo, R. F. M. de Almeida, M. H. Garcia, A. I. Tomaz

P-112: Cellular Uptake Studies of *N,N*-chelated Organometallic Ruthenium(II) Anticancer Complexes
I. Romero, A. M. Pizarro, A. Habtemariam, P. J. Sadler

P-113: A Comparative Study of the Anticancer Activity of the Hetero-metallic Complexes $\{[(PTA)_2CpRuDMSO]\text{-}\mu\text{-}AgCl_2\}_n$ and $[(PTA)_2CpRuDMSO][AgCl_2]$
M. Serrano-Ruiz, A. Romerosa, L. G. León, J. M. Padrón

P-114: Novel Ruthenium(II), Rhodium(III) and Iridium(III) Antitumor Complexes with a Levonorgestrel Pendant
J. Ruiz, N. Cutillas, V. Rodríguez, M. Hannon

P-115: Metal-Linked Neurodegenerative Processes in Alzheimer's Disease. Pathogenetic and Neuroprotective Insights
A. Salifoglou

P-116: Pt-based Anticancer Drugs: Studying their Interaction with Proteins and Oligonucleotides
K. G. Samper, E. Ortega-Carrasco, V. Rodríguez, C. Vicente, S. Atrian, J. D. Marechal, N. Cutillas, J. Ruiz, M. Capdevila, O. Palacios

P-117: Biocomjugate Metalloporphyrins/Ferritin Nanoparticles
P. Sánchez, D. Pinto, V. Landaeta, E. Valero, J. M. Domínguez-Vera, N. Gálvez

P-118: DNA as a Potential Biological Target for new Ruthenium(II) Polypyridyl Anti-tumor Complexes
F. C. Santos, O. L. Rojas, F. Santos, R. F. M. de Almeida, M. H. Garcia, A. I. Tomaz

P-119: Carbonic Anhydrase IX Inhibitor Coated Nanoparticles: new Diagnostic and Therapeutic Approaches for Cancer Treatment
A. Scozzafava

P-120: Chimeric GNA/DNA Metal-mediated Base Pairs
K. Seubert, C. Fonseca Guerra, F. M. Bickelhaupt, J. Müller

P-121: Concentration–dependent Pd(II)–C Bond Formation in Complexes with a 2N-donor Ligand Containing an Indole Moiety
S. Iwatsuki, Y. Shimazaki

P-122: Using Peptide-based Models for Understanding of Binding and Mechanism of Copper(I) Metallochaperone Proteins
M. S. Shoshan, D. E. Shalev, E. Y. Tshuva

P-123: Xanthosine 5'-Monophosphate. A Nucleotide with Unusual Acid-base and Metal Ions-binding Properties
H. Sigel, A. Sigel

P-124: Mechanism of 1-aminocyclopropane-1-carboxylic Acid Oxidase: Contribution of Model Complexes and Kinetic Studies
N. El Bakkali-Tahéri, L. Brisson, W. Ghattas, E.-H. Ajandouz, T. Tron, M. Réglier, A. J. Simaan

P-125: Solution Structure and Metal Ion-binding Properties of the 5' Splice Site in Group II Intron Retrohoming
M. Skilandat, R. K. O. Sigel

P-126: Transmetallation Reaction between Zn(II) and Tc-99m as a Tool to Prepare new Radiopharmaceuticals
J. Lecina, A. Carrer, L. Melendez-Alafort, U. Mazzi, J. Suades

P-127: Synthetic Approach to Oxygen Evolving Complex by Construction of Multinuclear Manganese Core Structure
A. Suzuki, W. Kinoshita, T. Aoki, Y. Morimi, M. Imai, H. Naganuma, T. Inomata, T. Ozawa, Y. Funahashi, H. Masuda

P-128: Investigating Oxidoreductase Enzymes Mimicking Properties of Manganese Complex
I. Cs. Szigyártó, L. Szabó, L. I. Simándi

P-129: Expression of Metallothionein mRNA on Fetus Brain after the Injection of Thimerosal to Pregnancy Mouse
Y. Takimiya, M. Yoshida, Y. Sakamoto, S. Ichida, T. Minami

P-130: Luminescent Cyclometalated Iridium(III) Polypyridine β-carboline Complexes: Synthesis, Cytotoxicity, Cellular Uptake and Apoptosis-inducing Properties
C.-P. Tan, Y.-Z. Zhao, Z.-W. Mao, L.-N. Ji

P-131: Synthesis, Characterization and Biological Activity of Copper(II) and Zinc(II) Complexes with N(4)-alkyl Substituted Thiosemicarbazone
K. W. Tan, H. L. Seng, C. H. Ng, S. C. Cheah, M. R. Mustafa, S. W. Ng, M. J. Maah

P-132: Zinc(II) Complexes with Antimicrobial Drug Flumequine: Structure, DNA- and Albumin-Binding
A. Tarushi, A. A. Pantazaki, J. Kljun, I. Turel, G. Psomas, D. P. Kessissoglou

P-133: DNA Binding and Biological Activity of Transition Metal Complexes
A. Terenzi, G. Barone

P-134: Studies of the Interactions between Amyloid-β peptides (Aβ16/Aβ28) and the Heme *b*: Implications in Alzheimer's Disease
G. Thiabaud, D. Ciregna, E. Monzani, L. Casella

P-135: Copper(II) Complexes as Models of the Active Centre of the Cu,Zn-SOD Enzyme
S. Timári, K. Várnagy

P-136: Insights into the Failure of the Potential, Neutral Myocardial Imaging Agent TcN-NOET: Physico-chemical Identification of By-products and Degradation Species
F. Tisato, F. Refosco, C. Bolzati, M. Porchia, R. Seraglia, D. Carta, R. Pasqualini

P-137: Preparation of some Zinc Complexes of *meso*-Mixedly substituted Porphyrins (ZnMMSPs) and the Equilibria of Pyridine Ligation to them
A. Tohara

P-138: Sepiolite and Clinoptilolite Nanoclays. A Comparative Study in vitro and in vivo
Y. Toledano, L. Flores, G. Montes de Oca, A. González, J. C. Carrero

P-139: Interaction of Cu(II) with Non-steroidal Antiinflammatory Drug Flufenamic Acid
Ch. Tolia, C. P. Raptopoulou, V. Psycharis, G. Psomas

P-140: Heavy-metal Detoxification Capacity of Different Soybean Metallothioneins
M. Tomàs, J. Carrillo, C. S. Andreo, M. Capdevila, A. Pagani, S. Atrian, R. Bofill

P-141: Ruthenium(II) Binuclear Thiosemicarbazone Compounds as Potential Anti-tumor Agents: Activity and Serum Protein Binding
B. Demoro, R. F. M. de Almeida, F. Marques, C. P. Matos, C. Sarniguet, L. Otero, J. Costa Pessoa, D. Gambino, A. I. Tomaz

P-142: Photoinduced Multi-Electron Transfer to a Multicopper Oxidase Resulting in Dioxygen Reduction into Water
A. J. Simaan, Y. Mekmouche, C. Herrero, P. Moreno, A. Aukauloo, J. A. Delaire, M. Réglier, T. Tron

P-143: Mechanistic Investigations on the Reaction of Heme Model Complexes with Carbon Monoxide and Superoxide
O. Tröppner, K. Dürr, R. Lippert, N. Jux, I. Ivanović-Burmazović

P-144: Synthesis and Cytotoxicity of new Transition Metal Hematoporphyrin IX Complexes
D. Tsekova, V. Skumryev, G. Momekov, G. Gochev, G. Gencheva

P-145: Manganese(II) Complexes with Non-steroidal Antiinflammatory Drug Niflumic Acid: Synthesis, Characterization, DNA- and Albumin-Binding
P. Tsiliki, G. Psomas

P-146: Copper(II) and Nickel(II) Complexes of Model Peptides Related to the Metal Binding Site of Prion Protein
I. Turi, I. Sóvágó

P-147: Coordination and Redox Properties of Copper(II) and Iron(II/III) Complexes of Bis(imidazol-2-yl) Ligands
K. Várnagy, S. Timári, G. Csire, N. Lihi

P-148: Modulation of Metal-Induced Aβ Aggregation by Bifunctional Macrocyclic Chelators
X.-Y. Wang, X.-H. Wang, T.-T. Chen, Z. Guo

P-149: *E. coli*'s SlyD Protein Binds Nickel in an Unusual Way
D. Witkowska, M. Rowińska-Żyrek, D. Valensin, W. Kamysz, H. Kozłowski

P-150: Preparations of Optically Active Amino Acids via Complexation with Cu(II) Ion and L-Histidine Derivatives
T. Yajima, H. Matsumoto, S. Kosaka, A. Uno, T. Shiraiwa

P-151: Thimerosal Induces Necroptosis to Mouse Cerebellar Microglia Cell Line, C8-B4 Cells
M. Yoshida, Y. Sakamoto, S. Ichida, T. Minami

P-152: Structure, DNA- and Albumin Binding of Manganese(II) Complexes with Non-steroidal Antiinflammatory Drug Diclofenac
M. Zampakou, C. P. Raptopoulou, V. Psycharis, G. Psomas

P-153: Modified Vitamin B12 Derivatives with Tunable Coordination and Redox Properties
F. Zelder, K. Zhou

P-154: Bis-β-cyclodextrin Confined Dinuclear Phosphate Esterase Mimics
M. Zhao, Z.-W. Mao, L.-N. Ji

P-155: Pt(II) Squares an Effective G-quadruple Binders and Potential Cancer Therapeutics
X.-H. Zheng, H.-Y. Chen, L.-L. Mao, L.-N. Ji, Z.-W. Mao

PLENARY LECTURES

"Perception – Applied and Chemical! 50 years of ABC fun"

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"Applied Bioinorganic Chemistry" - easier to research than to define - embraces such topics as geological events (heavy-metal pollution) - *e.g.* rad-waste and E-waste disposal, health, medicine, diagnosis, and nutrition. Regardless of the topic, scientists and their knowledge of the chemistries prevailing have a pivotal role to play in terms of finding solutions to problems. Although the well-motivated medic, or perhaps epidemiologist, may reveal the need, it invariably falls to the chemist to find a solution *and to communicate it* to fellow researchers, to students, to public, and to the media.

The public's perception of an acceptable definition of the term *"safe"* demands clarity and consistency of communication from all-concerned in new plans and flawless track-records of the scientists involved.[1,2]

The sociologists and psychologists in our midst have already tackled, to their benefits, the gap which exists between scientist and the lay public. Many research papers have been published on our inability to communicate, and upon different groups in society having different views. Meanwhile, scientists, government officials, and funding agencies, all have to balance decisions without really knowing the difference between *price* and *cost* of breakthroughs.

Symptoms of our not convincingly winning-over their trust - a most delicate flower - may be seen in examples such as: (i) nuclear fission discovery to first commercial reactor took a mere 17 years; understanding speciation of rad-waste dispersal - still floundering 70 years later! (ii) beneficial powers of drugs like thalidomide - lost; new biodegradable 'EDTAs' - opposed! (iii) 'metals in diagnosis, therapy, and neurosciences, their environmental and toxicological aspects and related metabolic diseases, biomaterials, and mimetics of metalloproteins' - will these be publically discussed outside ISABC?

C. P. Snow warned that the two cultures of science and of politics 'must talk' or our destinies will be decided by what occurs in the vacuum formed. **F**ocus **U**pon **N**ew science, its communication *ab initio*, and win others over support for our labours![3]

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From Metalloenzymes to Bioinspired Catalysts: towards new Energy Conversion Systems

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One of the grand challenges of twenty-first century chemistry is to convert abundant energy-poor molecules to energy-rich molecules using sunlight as the energy source. Hydrogen from water is such a solar fuel. However its production and use currently depend on noble metals such as Platinum which is expensive and not abundant enough. Viable renewable energy systems such as (photo)electrolyzers and fuel cells, will require new catalysts made from earth-abundant materials, cheap and robust. We will describe our bioinspired strategy, aiming at chemically reproducing the unique active sites of hydrogenase enzymes, which use nickel and iron atoms to efficiently catalyze the water-hydrogen interconversion. This strategy has led to remarkable nickel- and iron-based as well as cobalt-based (photo)catalysts for hydrogen production and oxidation.

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Metal Carbonyl in CO Therapy: Successes and Challenges

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Carbon monoxide (CO) is an endogenous mediator that plays important roles in mammalian physiology.[1] Inhalation of CO doses well below toxic levels has been shown to prevent inflammation, thrombosis, oxidative stress and apoptosis, and to have therapeutic effects on a wide variety of diseases like rheumatoid arthritis, multiple sclerosis, cerebral malaria and many others.[2]

Since CO gas is of limited therapeutic use because it is strongly scavenged by hemoglobin after inhalation, several efforts have been undertaken in recent years to generate molecules, which deliver CO to diseased tissues in a more specific way. Transition metal carbonyls emerge as the most versatile source of CO-Releasing Molecules (CO-RMs) and various of them have been shown to reproduce and/or improve on the therapeutic effects of CO seen in inflammatory and other diseases. However, most metal carbonyl CO-RMs used in these studies still lack drug-like properties and their interactions with components in the physiologic media (e.g. proteins) are still not well understood.[3] Indeed, a number of hurdles have to be transposed in order to obtain metal carbonyl CO-RMs with acceptable pharmacological properties.

This presentation reviews the state-of-the-art in this field and discusses some recent advances that may be bringing the first transition metal CO-RMs close to clinical application.

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Interactions of Metal Ions and Metal-based Compounds with alpha-Synuclein: from Basic Research to Therapy

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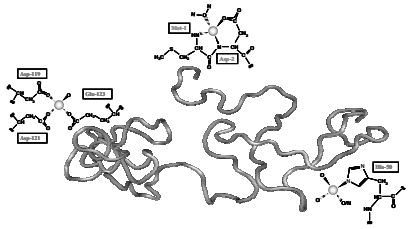
The aggregation of alpha-synuclein (AS) is a critical step in the etiology of Parkinson's disease (PD). Protein-metal interactions play an important role in AS aggregation and might represent the link between the pathological processes of protein aggregation, oxidative damage and neuronal cell loss. Our studies revealed a hierarchal effect of metal interactions on AS aggregation kinetics, dictated by structural factors corresponding to different protein domains.[1-3] These results constituted the basis to investigate the impact of metal ion occupancy on the binding and inhibitory capacity of anti-amyloidogenic small molecules.[4,5] The elucidation of molecular and structural determinants of these interactions serves as scaffold for on going structure-based drug discovery efforts targeting AS amyloid formation.



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Design and some Biomedical Applications of Metal-based targeted Molecular Imaging Agents

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High relaxivity and specificity of targeted MRI contrast agents (CAs) are currently the most important objectives in the development of such diagnostic imaging tools. The design and relaxivity optimization procedures of Gd^{3+}- chelates as CAs will be discussed,[1] as well as their extension to bimodal (MRI/Optical Imaging) applications. Examples of the use of nanosized platforms to enhance the efficacy of such agents will also be given.[2,3]

The combined use of NMR and molecular modeling techniques to optimize the binding specificity of CAs to their molecular targets will be illustrated through the study the interaction of small Gd^{3+}-based chelates with target proteins. Several examples will be described, including the interaction of Gd^{3+} glycoconjugates with the lectin *Ricinus Communis* agglutinin (RCA_{120}) as a model for the hepatocyte asialoglycoprotein receptor (ASGPR),[4] angiographic MRI agents interacting with human serum albumin (HSA) and the chiral recognition of two enantiomers of a Gd^{3+} chelate by HSA.[5]

Acknowledgements

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Progress and Trends in Radiometal-Based Diagnostics and Therapeutics

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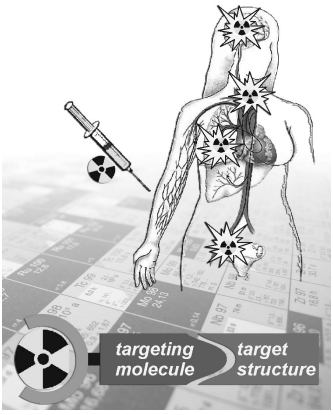
Studies of the EU-commission revealed that at the time patients are first diagnosed with cancer, already 40 % have developed metastatic lesions, which results often in poor prognosis. Thus, early diagnosis and effective therapy of (disseminated) tumors are of paramount interest. Application of tumor-seeking molecules labeled with diagnostic radionuclides (γ-emitters for SPECT; β^+-emitters for PET) is currently one of the most sensitive methodologies for the non-invasive detection of cancer in vivo. Systemic delivery of molecules radiolabeled with particle emitting radionuclides such as α-, β^-- and Auger-emitters allow destruction of disseminated tumors. It is important to recognize that with a few examples like most radionuclides currently used in nuclear medicine or in development are metals (e.g. $^{64/67}$Cu, $^{67/68}$Ga, ^{89}Zr, ^{99m}Tc, ^{111}In, ^{177}Lu etc.). The production of such radionuclides and moreover their stable and rapid incorporation into tumor targeting molecules represent a challenging tasks for inorganic and bioinorganic chemistry. This lecture will include the presentation of strategies for the preparation of new bifunctional metal chelating systems e.g. via “click-chemistry” and novel technologies for the bio-orthogonal and enzymatic functionalization of vitamins, peptides and antibodies. Selected preclinical and clinical examples of the development of novel vitamin B9[1] and B12[2] radiotracers and peptides labeled with different radiometal for diagnosis and potential therapy of prostate cancer will be presented.



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Therapeutic Efficacy of Arsenic-bound Platinum Agents: Drug Synergy and Unexpected Inorganic Chemistry in Combination Chemotherapy for Triple Negative Breast Cancer

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We are studying a variety of ways to use recent breakthroughs in the understanding of metal trafficking and homeostasis pathways in the discovery and development of inorganic agents for the treatment cancers. Basal-like breast cancers are highly aggressive tumors that frequently metastasize to distant sites and are not cured by traditional cytotoxic chemotherapy. One approach uses tetrathiomolybdate to target copper-dependent pathways that are important for the promotion of neovascularization by metastatic microtumors. In other studies we have developed a novel drug delivery vehicle, [NB(Pt,As)], that encapsulates high-density forms of cisplatin and arsenic trioxide (ATO) inside a lipid vesicle to treat basal-like breast cancer. These nanobins have a well-controlled size (100 nm) and are passivated with polyethylene glycol, which increases the serum lifetime and allows increased accumulation of both drugs in tumors. The drug payload of these nanobins is stabilized as a nanocrystalline material, and drug release is negligible until triggered by intra-cellular thiols. Further analysis indicates that NB(Pt,As) particles are stabilized by an unprecedented system of Pt-As bonds. Cytotoxicity studies of untargeted as well as folate-targeted NB(Pt,As) reveal the agents to be stable and of modest activity until the intact nanoparticles are taken into the cell. The therapeutic efficacy of NB(Pt,As) was examined in an orthotopic model of basal-like breast cancer that spontaneously metastasizes to the lung using MDA-MB-435-lvbr cells labeled with mCherry. The NB(Pt,As) both inhibited tumor growth and reduced the number of lung metastases. Progress toward the next generation of receptor-targeted nanobins will be discussed. Targeted systems include the tumor-associated urokinase plasminogen activator receptor (uPAR) pathways. Furthermore, these agents exhibit significant preclinical activity against triple negative breast cancer. Refinement of the nanobin platform to ameliorate the systemic toxicity and also enhance the activity of combinations of potent inorganic agents provides a promising strategy to treat this intractable disease.

KEYNOTE LECTURES

Artificial Metalloenzymes based on the Biotin-avidin Technology: Challenges and Recent Progress

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Artificial metalloenzymes are created by incorporating an organometallic catalyst within a host protein. The resulting hybrid can thus provide access to the best features of two distinct, and often complementary, systems: homogeneous and enzymatic catalysts.

Owing to the remarkable affinity of biotin for either avidin or streptavidin, covalent linking of a biotin anchor to a catalyst precursor ensures that, upon stoichiometric addition of (strept)avidin, the metal moiety is quantitatively incorporated within the host protein. In this presentation, we review our progress in preparing and optimizing these artificial metalloenzymes, beginning with catalytic hydrogenation as a model and expanding from there.

These artificial metalloenzymes can be optimized by both chemical (variation of the biotin-spacer-ligand moiety) and genetic (mutation of avidin or streptavidin) means. Such chemogenetic optimization schemes were applied to various enantioselective transformations. The reactions implemented thus far include the following: (i) The rhodium–diphosphine catalyzed hydrogenation of *N*-protected dehydroaminoacids. (ii) The palladium-diphosphine catalyzed allylic alkylation of 1,3-diphenylallylacetate. (iii) The ruthenium pianostool-catalyzed transfer hydrogenation of prochiral ketones and imines. (iv) The vanadyl-catalyzed oxidation of prochiral sulfides. (v) The osmium-catalyzed dihydroxylation of olefins.

A number of noteworthy features are reminiscent of homogeneous catalysis, including straightforward access to both enantiomers of the product, the broad substrate scope, organic solvent tolerance, and an accessible range of reactions that are typical of homogeneous catalysts. Enzyme-like features include access to genetic optimization, an aqueous medium as the preferred solvent, Michaelis–Menten behaviour, and single-substrate derivatization. The X-ray characterization of artificial metalloenzymes provides fascinating insight into possible enantioselection mechanisms involving a well-defined second coordination sphere environment. Thus, such artificial metalloenzymes combine attractive features of both homogeneous and enzymatic kingdoms.

Iron(II) Complexes as PARACEST MRI Contrast Agents

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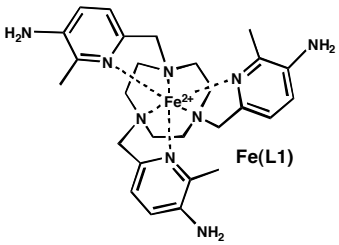
A new research direction in our group is the development of contrast agents that utilize endogenous metal ions as an alternative to Ln(III) contrast agents. We have developed Fe(II) complexes that function as on/off MRI contrast agents through paramagnetic chemical exchange saturation transfer (PARACEST). The coordination chemistry of Fe(II) as a transition metal ion is distinct from that of Ln(III) ions in that a wider variety of donor groups can be used, enabling the development of new ligands for PARACEST agents.



The first examples of Fe(II) PARACEST agents developed in our group contain macrocyclic ligands that stabilize the Fe(II) oxidation state and saturate the Fe(II) coordination sphere with six ligand donor groups.[1] Both amide and amine protons (**Fe(L1)**) are used to enable magnetic resonance imaging through chemical exchange saturation transfer (CEST). In the CEST experiment, the exchangeable protons of the macrocyclic Fe(II) complex are irradiated with a radiofrequency presaturation pulse at their resonant frequency. Exchange of these partially saturated NH protons with the protons of water gives rise to a decrease in the water signal. The paramagnetic Fe(II) center induces a shift in the amine and amide proton resonances to give a CEST response that is distinct from the bulk water resonance. The most highly shifted CEST signal (69 ppm) is observed for an amide complex. Such a large difference in the chemical shift of the proton resonances of the exchangeable ligand proton and the bulk water protons ($\Delta\omega$) is advantageous for imaging in tissue to avoid interference from magnetization transfer effects. In addition, these Fe(II) complexes are being developed as temperature and pH responsive chemical shift agents.[2] Work is underway to prepare complexes with different heterocyclic amine donor groups that contain exchangeable protons and different macrocyclic frameworks with the goal of increasing $\Delta\omega$, and the rate constant for ligand proton exchange with bulk water.

In conclusion, Fe(II) is readily incorporated into macrocyclic ligands to form air stable complexes for applications as PARACEST MRI contrast agents. Opportunities abound for the further development of transition metal complexes as contrast agents that are responsive to pH and temperature.

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On the Reduction of Antiproliferative Pt(IV) Complexes

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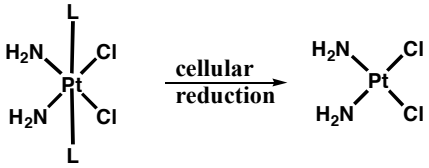
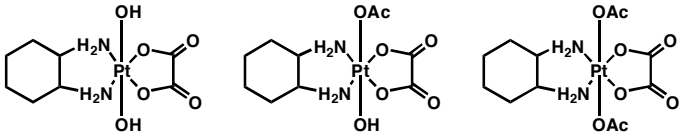
Cisplatin, carboplatin and oxaliplatin are square planar Pt(II) complexes that are administered intravenously resulting in discomfort to patients and costly hospitalization. Octahedral Pt(IV) complexes are inert prodrugs which are activated by reduction in the cancer cell to the cytotoxic Pt(II) complexes by loss of the two axial ligands.



The ease of reduction of Pt(IV) complexes depends primarily on the nature of the axial ligands. When the axial ligands are chlorido the reduction is fast, medium with carboxylato axial ligands and slow with hydroxido axial ligands. Clinically, the most successful Pt(IV) prodrugs (Satraplatin, LA-12) have two axial carboxylato ligands.

We studied the reduction of Pt(IV) prodrugs in cancer cell extracts, by labeling them with ^{15}N or ^{13}C isotopes and monitoring reduction by 2D NMR, and showed that the rate of reduction depends also on the nature of the cancer cell and that contrary to the notion that reduction occurs primarily by ascorbate or GSH, reduction is more facile in the high MW fraction of the cell extracts.[1] We found that reduction of the Pt(IV) analogs of carboplatin and oxaliplatin with axial carboxylato ligands is extremely slow while reduction of their dihydroxido analogs is much faster. Similar behaviour occured with Pt(IV) complexes with N4 equatorial coordination spheres.



FASTEST **FAST** **SLOW**

We also found that reduction of Pt(IV) complexes with axial diacetato ligands can yield more than one product.[2]

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Gadolinium-based Nano-sized Systems for Magnetic Resonance Molecular Imaging Applications

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Magnetic Resonance Imaging (MRI) is one of the most important non-invasive imaging modalities in clinical diagnostics and preclinical research. The success of MRI is due to the ability to image tissues with high resolution in three dimensions, routinely down to 1 mm at clinical field strengths.

These attributes make MRI highly suited to molecular imaging applications, namely the imaging of events at the cellular and subcellular level.[1] However, the detection of events at this level often requires nanomolar sensitivity, thus precluding the use of conventional gadolinium chelates as molecular MR imaging agents, as they display only micromolar sensitivity. In order to overcome this limitation several research groups designed new gadolinium-based nano-sized systems endowed with both enhanced and efficient routes of accumulation of the imaging probes at the sites of interest.[2] The most common procedure adopted to increase the sensitivity of MRI molecular imaging protocols was a huge payload of image contrasting units for each nanoparticle. Several nanoparticle platforms were proposed differing in their main constituents which were both organic or inorganic in nature.[3,4] The routes of accumulation of this nano-sized contrast agents in the target tissues were modulated modifying their size and also decorating their surface with suitable ligands with high affinity for specific epitopes or receptors. There are many successful examples of gadolinium-based nano-sized systems in the literature with applications mainly in the cardiovascular and cancer imaging.

However the preferential accumulation of these nanoparticles in the mononuclear phagocyte system after an intravenous administration, strongly reduces the chance of their translation to the clinical practice. In this survey we will critically discuss the limitations on the practical use of these systems together with several suitable strategies to reduce the risk of adverse events in future patients.

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Bioinorganic Chemistry of Amyloid-β Aggregation Inhibitors

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The studies on the metal ions involvement in neurodegenerative diseases has focused on their interactions with the signature proteins that play a major role in the progress of these neurological syndromes. The question of the metal ion involvement in the inhibition of the aggregation processes of amyloidβ, the hallmark of Alzheimer's disease, has gained minor interest. The largest number of studies has been carried out with amyloidβ, the hallmark of Alzheimer's disease. The peptide and its precursor protein are known to interact with number of protein partners located within or in close proximity to cellular membrane.

BRI2 is type 2 transmembrane protein of unknown function, that consists of a 266 amino acid residues. It is expressed at high levels in the brain and cleaved by furin or furin-like proteases at its C-terminus to produce a 23 amino acid peptide (Bri2–23).[1] This product of proteolytic cleavage of BRI2 demonstrates an inhibitory effect on amyloid-β deposition *in vivo* and aggregation *in vitro*, thus indicating that BRI2 is a novel factor that modulates amyloid-β aggregation and deposition.[2] Since BRI2-23 incorporates the amino acid residues that are considered good metal binding sites (thiolates and imidazoles), our studies focused on examination of the peptide binding properties towards metal ions essential in biology of amyloid-β, with the special interest in Cu(I). Due to the fact that studies on Cu(I) are tremendously challenging, we used Hg(II) as molecular probe. That allow us comprehensive characterization of the system with the application of methods inaccessible to Cu(I) ions, like PAC spectroscopy. Some preliminary studies on the Aβ aggregation inhibitory properties of BRI23 and its Hg(II) complexes have been performed.

To address the question of Cu(II) involvement in Aβ aggregation we have studied aggregation inhibitory properties of synthetic peptide (OR2) and its metal complexes. OR2 contain the sequence segment that is believed to be responsible for self-association of the amyloid-β peptide. Our preliminary results indicate that the effective interaction requires full-length Aβ.

Acknowledgements

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The Iron Storage Protein Ferritin is an Anti-Oxidant and a Pro-Oxidant: What Triggers the Change?

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Alzheimer's, Parkinson's, diabetes and chronic kidney disease all have oxidative damage as a biomarker of the disease. Iron is a known catalyst for oxidative damage and free iron or elevated iron levels are biomarkers of these diseases. Ferritin and transferrin are the two major proteins present in cells and serum to bind iron and protect the organism from the dangerous effects of free iron. In fact, ferritin is up regulated by inflammatory cytokines in these diseases, presumably to sequester free iron. However, free iron in these diseases suggests the presence of inhibitory molecules that prevent ferritin and transferrin from binding and sequestering iron. We have identified and studied metabolites present at elevated levels in these diseases and propose three potential mechanisms that result in free iron. The metabolic intermediates: 1) inhibit iron loading into ferritin, 2) complex the iron and prevent it from binding to ferritin, or 3) release iron from ferritin resulting in free iron.[1] We discuss two metabolites, phosphate and homocysteine, that inhibit iron loading or release iron from ferritin and transferrin. Phosphate competes with ferritin and transferrin for iron by forming soluble Fe-phosphate complexes. Once formed, the Fe-phosphate complexes are not substrates for ferritin or transferrin but may contribute to the free iron pool. Electron microscopy showed that the iron-phosphate complex was spherical nanoparticles with diameters of 10-20 nm. The ferroxidase center of H ferritin competes with phosphate for the binding and oxidizing Fe^{2+}. Homocysteine acts as a reducing and complexing agent to remove iron from ferritin resulting in free iron. Thus, Homocysteine is a catalyst for liberating iron as a catalyst for reactive oxygen species. Homocysteine also produces magnetite inside ferritin, which is a biomarker of Alzheimer's disease. **Conclusions**. These *in vitro* data support the hypothesis that elevated metabolites disrupt the ability of ferritin and transferrin to bind iron.

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Biofunctionalised Inorganic Nanoscale Structures as Pathogen Mimics

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The use of synthetic inorganic nanoparticles (iNPs) for molecular imaging applications has attracted considerable interest in the last few years. Semiconductor nanocrystals (quantum dots, QDs) and superparamagnetic iron oxide nanoparticles (SPIONs) in particular have become important alternatives to traditional organic and genetically-encoded fluorophores and gadolinium-based MRI contrast agents.[1,2] However, suitably functionalised QDs and SPIONs could potentially become more than passive bio-probes.

Because the immune system has the essential task of controlling host defenses against infections and can be used to recognize and kill cancer cells, we have asked whether we can gain insights into pathogen-host interactions and initiate and modulate inmune responses using these iNPs. One notable finding is that QDs biofunctionalised with specific pathogen-associated molecular patterns (PAMPs – conserved molecular motifs which are present in a bacteria and/or a virus and are absent in mammalian cells) provide strong stimulation of the mammalian immune system via activation of Toll-like receptors (TLRs) in both *in vitro* and *in vivo* experiments.[3] Recently, we have functionalised QDs and SPIONs with a model protein antigen (hen egg lysozyme) and a model TLR ligand (Kdo_2 Lipid A), and we have found that the magnitude and quality of the immune response was significantly improved when both molecules are attached to the same iNP. These preliminary results suggest that these traceable nanoscopic materials can, as new pathogen-mimetic materials, make important contributions in fundamental and applied research concerned with development of safer and more effective vaccines.

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Biomaterials for Biomedical Implants

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A description of the characteristics and limitations of different biomaterials (ceramics, polymers, metals and coatings) and properties of synovial fluid for biomedical implants are described.

Firstly, the mechanical properties of different ceramic scaffolds candidates is screened in comparison with bone properties using advanced characterization techniques like impact, compression resistance, elastic modulus, speed of sound and porosity. The cortical veal bone is the most compressive resistant material, withstanding a maximum load of 144 MPa. However, the sample hydroxyapatite with collagen offers the highest compression resistance of all the scaffolds tested, and their value is close to that of the natural bone. The thermal treatment reduces the compression resistance but improve the impact resistance.[1] Secondly, the characteristics of different polymers used for biomedical implants are described, and the effect of the texturing avoiding friction, wear and stick slip effects is described. Thirdly, the synovial fluid properties characterization is described making emphasis on the reduction of the viscosity in presence of a disease, normally caused by dilution of the synovial fluid. The effect of the reduction of viscosity in tribological properties is described when using high molecular weight Polyethylene (HMWPE) prosthesis in combination with metal and ceramic prosthesis. The lower friction, wear and increase of temperature is found for ceramic/HMWPE with low viscosity fluids.

Finally, metal and coatings, limitations and opportunities for biomedical implants are described. The development of DLC coatings for Titanium Knee prosthesis, CrCoMo and AISI 306 Steel hip prosthesis are described.The Ti-DLC coatings seems a promising alternative to improve the corrosion, wear and tribocorrosion performance of the substrates and seems to be a good alternative to improve the lifetime of the medical prosthesis.[2]

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Discrimination between Essential Zinc and Toxic Cadmium by Soil-dwelling Organisms: Metallothioneins behaving in Unexpected Manners

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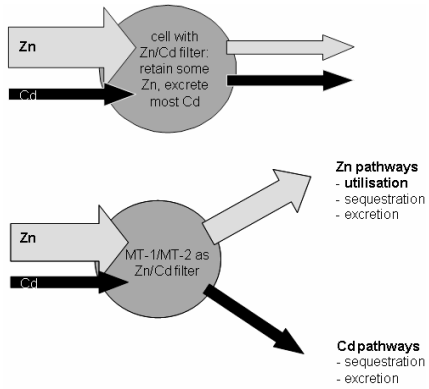
Organisms taking up nutrients from soil have a requirement to discriminate between toxic cadmium and essential zinc. We are interested in the role that metallothioneins (MTs) play in this discrimination process, in particular, those MTs for which functional studies suggest a role in zinc homeostasis. Two case studies will be discussed, highlighting two concepts of how proteins that have a proven overall thermodynamic preference for Cd(II) still can be exploited for "preferential" binding of zinc: (i) the embryo-specific E_C from wheat, a plant type 4 MT,[1] is well folded in the Zn-bound form, but unable to fold properly in the presence of Cd(II), and (ii) the two MTs from the nematode *C. elegans* work in tandem to partition Zn and Cd,[2,3] illustrating the importance of relative affinities. In both cases, histidine residues play a pivotal role to modulate the metal-binding properties of the MTs. Coordination chemistry is only the first step for understanding metal specificity *in vivo* - it is equally important to take higher levels of organisation into consideration, including protein structure, whole cells, and whole organisms.



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The Biogeochemical Speciation of Mercury: linking Molecular and Isotopic Information in Metals Environmental Bio-interactions

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It is now accepted that the presence of metals and metalloids, such as mercury, in different ecosystems is a key factor in their ecological balance, either by their stimulating effect on biological processes, or by their inhibitory action when their concentration exceeds the toxicity threshold of living organisms. Biological organisms are able to accumulate within cells (bioaccumulation), transform chemically (biotransformation) or neutralize by specific ligands (biocomplexes) forms more or less toxic metals and metalloids. The biogeochemical cycles and contamination processes of metals and metalloids are mainly related to the knowledge of the physico-chemical forms in which the element is engaged and their interaction with the environment. The transfer and the impact of metals and metalloids in ecosystems and biological organisms are often related to the formation of metastable species which exhibit higher biological activity and toxicity. The speciation of inorganic and organometallic compounds in the environment requires the combination of hyphenated and sensitive analytical techniques, such as gas or liquid chromatography coupled to elemental or molecular mass spectrometry. Recently, Multicollector ICPMS has introduced a new dimension enabling the investigation of isotopic fractionation during physico-chemical pathways in non-traditionnal trace metals, including mercury.

In this keynote, specific results obtained on the molecular and isotopic speciation of mercury in environmental samples will be presented. Both field investigation and lab experiments have allowed exhibiting both chemical transformation and isotopic fractionation of Hg at the molecular scale. The presentation will be highlighted by original results obtained during mercury methylation experiments by anaerobic bacteria, and after speciation analysis in aquatic mammals' organs involving both Hg metabolism and detoxification. Overall, combining both molecular characterisation and isotopic signature of a specific element, such as mercury, opens now a novel research field to better constrain its physico-chemical fate and toxicological impact.

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Modeling Insights on Metal Mediated Environmental and Toxicological Responses

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Metal mediated biological interactions play a major role in many toxicological and environmental responses of the organism. A description at the atomic scale is often crucial to decode, understand and ultimately predict their physiological mechanism. It also helps in the design of novel, safer or more effective drugs and therapeutic treatments. Despite the massive amount of molecular information that experimental tools afford, computational approaches have now reached a place of choice in providing atomic descriptions on these bioinorganic events.

The aim of the present talk is double. On one side, I will try to cover as extensively as possible the applicability of computational approaches in metal mediated protein ligand interactions and reactivity. Focus on advantages, limitations and future perspectives will be given. On the other, I will show how applications of nowadays molecular modeling approaches can be relevant for the present topic. Past and recent studies on cytochromes P450 will be discussed and results on our latest advances in metal related side effects and diseases like Alzheimer presented.

ORAL COMMUNICATIONS

Bioactive Inorganic Matrices for the Local Delivery of Platinum-based Prodrugs in the Treatment of Bone Tumors

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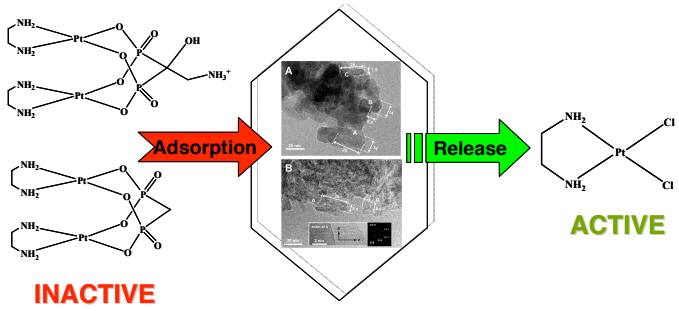
Calcium-containing matrices based on silica xerogels[1] and synthetic hydroxyapatite (HA) nanocrystals[2] have been used to load platinum(II)-bisphosphonate complexes specifically designed to act as prodrugs in the local treatment of bone tumors. The matrix promotes the activation of the Pt-complexes into their active forms. The inorganic composite materials can be potentially used as bone fillers to be implanted locally, at the site of an osteosarcoma after surgery, and act both as bone substitutes and as platinum drug releasing agents. The final goal is that of inhibiting locally the tumour re-growth and reducing the systemic toxicity typical of cisplatin and other platinum-based antitumor drugs.[3]

We have extended the investigation to nanocrystalline apatites which can be administered by injection. The role of the Ca/P ratio in influencing the adsorption as well as the release of the active platinum complexes from the nanocrystals has also been investigated.



The cytotoxicity of the Pt complexes released from the apatite were tested against human cervical, colon, and lung cancer cells as well as against osteosarcoma cells. In agreement with our previous finding, the Pt complexes released from the nanocrystals were found to be more cytotoxic than those used for loading the nanocrystalline apatites.

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Molecular Recognition of DNA Tetrahedral Nanostructure by Metallosupramolecular Helicates

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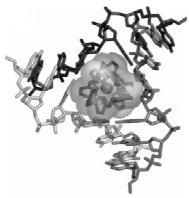
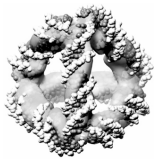
Nanoscale supramolecular structures are emerging as a new and exciting class of DNA recognition agents that recognise and stabilise unusual DNA motifs.[1,2] Foremost at this new chemistry/biology interface have been the metallosupramolecular cylinders: dinuclear, triple helical complexes. These cylinders recognise and bind at the very heart of DNA three-way junction,[2,3] exciting biological targets as DNA fork structures play a key role in processing DNA information. The helicates enter cancer cells, bind to the nuclear DNA, inducing cytostasis and subsequently apoptosis[3,4] without mutagenic or genotoxic side-effects.[3]



DNA is already the target for widely used anticancer molecules, but at the same time it is an ideal building structure of various DNA nanostructures,[5] that have a wide range of potential applications including DNA cages for drug delivery[6] and medical diagnosis.[7] We now demonstrate that the supramolecular cylinder can interact with and modify DNA tetrahedral nanostructure. Gel electrophoresis results show that the cylinder accelerates the mobility of the DNA tetrahedra. This suggests that DNA tetraheda have changed into a more compact structure. By contrast, the mobility of the DNA tetrahedra is retarded by ethidium bromide. The binding has also been studied by AFM and fluorescence spectroscopy.



Acknowledgements

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Extraordinary Performance of Diamino Bis(Phenolato) Ti(IV) and V(V) Anti-Tumor Agents

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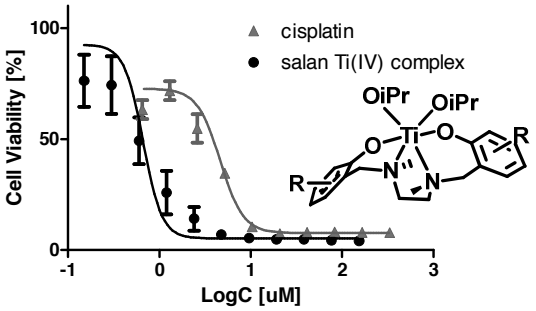
The success of cisplatin as a chemotherapeutic agent is limited by its relatively narrow activity range, development of resistance, and the severe side effects accompanying its therapeutic activity. Therefore, other transition metal complexes are widely studied with the aim to produce safe cytotoxic agents that may offer alternative treatments.

We have recently introduced a new class of highly cytotoxic Ti(IV) complexes of "salan" type diamino bis(phenolato) ligands.[1-3] Complexes of this class demonstrate cytotoxic activity towards a number of cell lines that is substantially higher than that of cisplatin. In addition, exceptionally high hydrolytic stability and defined hydrolysis process are observed. Structure-activity relationship investigations will be discussed, revealing the influences of ligand substitutions[2-3], complex geometry[4], stereochemistry[5] and metal center[6] on the hydrolytic behavior and cytotoxicity of the complexes, with a particular focus on their mechanistic implications.



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Searching for novel Antitrypanosomal Agents: Bisphosphonate Transition Metal Complexes

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American Trypanosomiasis (Chagas disease), caused by the protist parasite *Trypanosoma cruzi* (*T. cruzi*), is a major health concern in Latin America. Furthermore, globalization and immigration of unknowingly infected people from Latin America has also led to the appearance of several infection cases in developed countries mainly due to lack of controls and screening in blood and organ banks. Current chemotherapy mostly relies on drugs that are more than 50 years old and that suffer from poor efficacy, high toxicity and increasing resistance development. No effective method of immune prophylaxis is available.[1,2]

The development of bioactive metal complexes is a promising new approach in the search for a treatment of the disease. During the last years we have been successfully working in this area through a strategy based on the complexation of ligands bearing antiparasitic activity with suitable metal ions.[1] On the other hand, according to a current pharmaceutical development practice, well established drugs, clinically used for the treatment of different pathologies, are being evaluated in the search of new therapeutic uses. In this sense, several bisphosphonates prescribed for the treatment of bone diseases showed to be active against *T. cruzi.* Their main parasitic target is the enzyme farnesyl diphosphate synthase (TcFPPS) which is involved in the biosynthesis of polyisoprenoids and sterols.

In this work a comparative study of Cu, Mn, Ni and Co complexes of the bioactive bisphosphonates risedronate, pamidronate and alendronate will be presented, including synthesis, characterization, anti *T. cruzi* activity, toxicity on mammalian cells and inhibitory studies on TcFPPS and human FPPS (HuFPPS). The complexes showed higher activity on intracellular *T. cruzi* amastigotes than the free ligands. Significant toxic effects on mammalian cells (Vero cells) were not observed. Antitrypanosomal activity could be correlated with selective TcFPPS inhibition, suggesting this enzyme as potential target. HuFPPS inhibition was not observed at doses up to 100 times higher than the corresponding IC_{50} for the inhibition of TcFPPS. Results point out some of these complexes as interesting candidates for further *in vivo* studies.

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Nuclease Activity of Antineoplastic Copper(II) Coordination Compounds: Casiopeínas

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Metal complexes have gained a growing interest as pharmaceuticals for their use as diagnostic agents or as chemotherapeutic drugs.[1] Many efforts have been done in the development of anticancer agents employing essential metals. An interesting example is the family of copper (II) compounds known as Casiopeínas®. Mentioned compounds have a general formula $[Cu(N\text{-}N)(X\text{-}Y)(H_2O)]NO_3$ where N-N is a diimine (phen or bipy) and X-Y is a bidentate ligand (acac, salal, aminoacidate or peptide). These compounds have shown cytostatic, cytotoxic and antineoplastic activity *in vitro* and *in vivo*.[2]

The action mechanism still not completely elucidated. However, experimental evidence suggests the interaction of coordination compounds with DNA (nuclear or mitochondrial) and their components and the generation of reactive oxygen species (ROS) as the main action pathways. With these in mind, the present work presents the nuclease activity studies of 4 Casiopeínas® employing plasmidic DNA (pRSET-B) in several reaction conditions.

Comparison of the results shown that compounds with phenanthroline in the copper (II) coordination sphere have an extraordinary DNA cleavage capacity only with the oxygen present in the reaction vial (the system was not saturated with O2) after 2 hours of incubation at 37 ºC, when ascorbic acid was added to the mixture a complete degradation of the plasmidic DNA was reached after 5 minutes of incubation. Meanwhile, bipyridine compounds did not shown cleavage activity only with oxygen until 24 hours of incubation was reached, even with ascorbic acid the cleavage was observed after 2 hours. For bypiridine compounds, the DNA cleavage in short times was observed only when H_2O_2 was added to the reaction mixture. These results suggest an important contribution of the diimine structure to the cleavage process, and an intercalation process as the first step for the DNA damage.

Acknowledgements

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Tailored Gold-based Anticancer Peptidomimetics for the Selective Delivery into the Tumor Cell

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Peptide transporters are integral plasma membrane proteins that mediate the cellular uptake of di- and tripeptides and peptide-like drugs (*i.e.* peptidomimetics). They are present predominantly in epithelial cells of the small intestine, bile duct, mammary glands, lung, choroid plexus and kidney, and, intriguingly, seem to be overexpressed in some types of tumor, thus representing excellent targets for the delivery of pharmacologically active compounds.[1]

In order to develop an innovative metal-based target chemotherapy, we have been designing some gold(III)-peptidedithiocarbamato peptidomimetics of the type $[Au^{III}X_2(pdtc)]$ (X = Cl, Br; pdtc = di-/tripeptidedithiocarbamate) which can be able to combine the well-known antitumor properties of the gold(III) metal center and the potential chemoprotective function of dithiocarbamates,[2] with an enhanced bioavailability and tumor selectivity through the di-/tripeptide-mediated cellular internalization. The object compounds showed outstanding *in vitro* antitumor properties toward several human tumor cell lines and no cross-resistance with the reference anticancer drug cisplatin, accounting for a different mechanism of action likely involving the proteasome as a major biological target. Moreover, they were proved to hold back the "normal" development of tumors *in vivo* by inducing up to 90% and 65% reduction of breast and prostate cancer, respectively, together with negligible (or even no) organ and acute toxicity (LD_{50} *ca.* 30 mg kg^{-1}).

These results allowed us to file an international patent for their use in cancer chemotherapy (just extended in several countries worldwide),[3] and they are due to enter Phase I clinical trials early next year.

Acknowledgements
Financial support from the EU (MERG-CT-2007-204828) and the Fondazione ABO is acknowledged.

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Platinum Histone Deacetylase Inhibitor Conjugates as Potential Anti-cancer Agents

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Metal complexes are attractive for drug design and over the past 30 years platinum (Pt) compounds have played a vital role in treating cancer.[1] The application and efficacy of Pt drugs is limited by drawbacks though such as limited activity against certain cancers, resistance and toxicity.[1] There is therefore an urgent need to develop novel and innovative therapeutic strategies for combating cancer.

Chromatin is a complex structure that plays a key role as an epigenetic regulator of gene expression in eukaryotic cells. The fundamental repeating unit of chromatin is the nucleosome consisting of core histones around which DNA coils.[2] Histone deacetylases (HDAC's) are enzymes that deacetylate core histone lysine residues which leads to a condensed chromatin structure and transcriptional repression. Inhibition of HDAC's can therefore dramatically affect chromatin structure and thus function. Consequently HDAC inhibitors (HDACI) have emerged as novel anti-cancer agents.[2]

We have designed and developed novel Pt-HDACI conjugates. The rationale behind their development and their synthesis will be described. A summary of the pharmacological results obtained to date, in which conjugates have been shown to be highly cytotoxic towards cancer cells as well as having enhanced selectivity for cancer cells over normal cells, will also be provided.

Acknowledgements

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Ruthenium(II) Polypyridyl Complexes as DNA Topoisomerase Inhibitors

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DNA topoisomerases are essential enzymes that control and modify the topological states of DNA. In accordance, topoisomerase activities are activated in cancer cell growths, and thus are important cellular targets for antineoplastic drugs. Ru(II) complexes with polypyridyl ligands, due to a combination of easily constructed rigid chiral structures spanning all three spatial dimensions and a rich photophysical repertoire, have prominent DNA binding properties. Here a series of DNA-intercalating ruthenium(II) polypyridyl complexes have been synthesized and characterized. Topoisomerase inhibition and DNA strand passage assay confirmed that complexes are efficient inhibitors of topoisomerases I and II by interference with the DNA religation. In MTT cytotoxicity studies, Ru(II) complexes exhibited antitumor activity against HeLa, MCF-7, HepG2 and BEL-7402 tumor cell lines. Flow cytometry analysis, AO/EB staining assay and the alkaline single-cell gel electrophoresis (comet assay) demonstrated that Ru(II) complexes act as inhibitors of topoisomerases I and II and cause DNA damage that can lead to cell cycle arrest and/or cell death by apoptosis.

Acknowledgements

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Copper Coordination to the Alzheimer Peptide and Impact on Redox Properties

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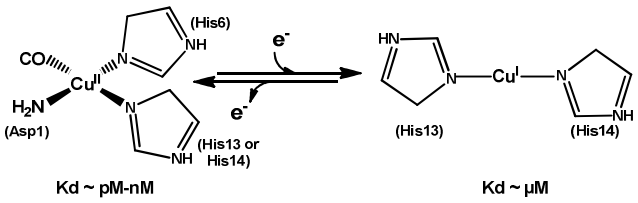
There is a growing interest in metal ions in neurodegenerative diseases, such as Alzheimer's disease (AD). Several evidences indicate that redox active ions are involved in the neurodegenerative process via production of reactive oxygen species (ROS).[1] However, little is known on the ROS production mechanism by the Cu(Aβ) complex at a molecular level, where Aβ is the amyloïd-β peptide involved in AD. As the redox cycling between Cu^{II}(Aβ)/Cu^{I}(Aβ) is the underlying process of ROS production, understanding this reaction is of high interest.

Coordination of Cu^{II} and Cu^{I} to the Aβ peptide has been assessed using a combination of techniques (NMR, pulsed-EPR spectroscopy on isotopically labelled peptide, XANES and EXAFS). In the Cu^{II}(Aβ) species predominant at physiological pH, the Cu^{II} ion is equatorially bound by the -NH_2 terminal amine, two histidine residues and a carbonyl function from the backbone.[2,3] Regarding the coordination of the Cu^{I} state, a bis-linear geometry is observed in which two His residues are bound to the metal center.[4,5] A direct consequence of these two significantly different coordination modes is that the redox process does not proceed by a classical outersphere electron transfer mechanism.[6]



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Variation of Astrocyte Metabolic Profile Induced by Amyloid β Treatment in Presence of Cu^{2+} and Zn^{2+} Metal Ions

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Alzheimer's disease (AD) is a highly debilitating condition that results in progressive degeneration and/or death of neuronal cells. Although the etiopathogenesis of AD is still far from being understood it is widely accepted that amyloid-β (Aβ) plaques and neurofibrillary tangles are the main pathological signs of neurodegeneration in AD.[1] The accumulation and aggregation of Aβ peptides leads to alterations of synaptic function, activation of microglia and astrocytes, and oxidative injury.[2] Transition metal ions like Cu^{2+}, Zn^{2+}, Fe^{3+} and well as Al^{3+} are believed to be directly involved in the etiopathogenesis of AD and they are found abundant in Aβ plaques of AD patients.[3]

In this work, the changes on U-373 MG astrocytes cultures induced by $A\beta_{42}$ and $A\beta_{28}$, have been investigated by cellular assay and by ^{1}H NMR spectroscopy. Astrocyte cultures were incubated with $A\beta_{42}$ in presence and in absence of Cu^{2+} and/or Zn^{2+}. The effects of $A\beta_{42}$ on astrocytes, were investigated by cellular assay and the culture supernatants were analyzed by ^{1}H NMR spectroscopy. NMR analysis has revealed selective changes on signal belonging to important metabolites (glucose, lactate, glutamate and acetate), strictly dependent on Cu^{2+} or Zn^{2+} Aβ interactions. The obtaining finding are discussed in respect to different metal binding modes and to different peptide aggregation state.[4] Finally medium culture NMR studies were confirmed as useful tool to analyze metabolism *in-vitro*.

Acknowledgements
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In silico Approach for Drug Design in Alzheimer's Disease

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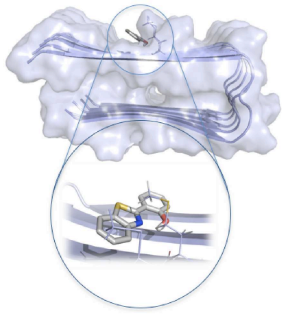
Alzheimer's disease (AD) is characterized by cerebral deposits of extracellular amyloid plaques and intracellular tangles. The amyloid plaques comprise mixtures of aggregated amyloid-β peptides (Aβ) with lengths of 39–42 amino acids. From among these Aβ peptides, Aβ(1–40) and Aβ(1–42) are the more common, the latter being the most toxic with the highest tendency to aggregate. In addition to this, there is evidence that metal ions such Zn(II), Cu(II) and Fe(III) are implicated in Aβ aggregation and deposition of these plaques.[1]

Metal chelation could offer the possibility of reducing the effects of excess metal ions in the brain. Recently, it has been shown that linking a metal chelator to an amyloid-targeting motif may be a successful strategy for developing the next generation of agents for AD.[2] To get an insight into the interaction between some of these small potential molecules and the two peptides Aβ(1-40) and Aβ(1-42) (the latter shown in the Figure), here we present an *in silico* approach using molecular dynamic simulations, molecular docking and Density Functional Theory (DFT) calculations. Comparison between theoretical results and biological assays will be discussed.



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Design of Copper(I) Chelators to Fight Against Copper Overload

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Metal overload plays an important role in several diseases or intoxications, like in Wilson's disease, a major genetic disorder of copper metabolism in humans. As free Cu can promote Fenton-like reactions its intracellular concentration needs to be rigorously controlled.[1] In Wilson's disease, impairment of the copper transport in hepatocytes, results in cytosolic Cu accumulation with associated cellular injury. Since the pool of intracellular copper is in the +I oxidation state, we figured that a chelator that would enter the hepatic cells and be specific for Cu^{I} could represent an efficient strategy to treat metal overload.

Proteins involved in copper homeostasis are outstanding sources of inspiration for the design of efficient Cu^{I} chelators. In metallochaperones, Cu^{I} is mainly bound by thiolates of cysteines ; this led us to design peptides including two cysteines, which show an affinity for Cu^{I} similar to that of the metallochaperones (K_d~10^{-16}) and a high selectivity over Zn(II), another essential metal ion found in cells. Even more efficient Cu^{I} chelators were obtained by favoring a CuS_3 coordination, as found in metallothioneins (MT): tripodal ligands extended by three cysteines (L^1 Fig.1), demonstrate an affinity for Cu^{I} as high as MT (K_d~10^{-19}).[2]

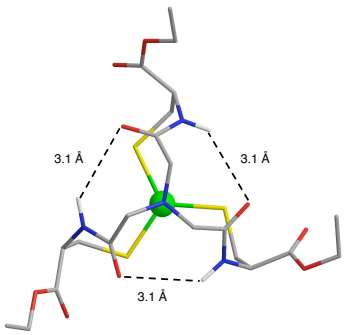

Figure 1. C_3-symmetrical structure of the mononuclear complex CuL^1 showing the hydrogen-bonds in the "upper cavity"

Finally, two chelators were functionalized by specific ligands of receptors located at the liver's surface to obtain glycojugates, which have been demonstrated to chelate intracellular copper in hepatocytes.[3] Therefore, these glycoconjugates are promising candidates to fight against copper overload in the liver in Wilson's disease patients.

Acknowledgements

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Technetium-99m Complexed with *n*-heterocyclic Aldehyde Thiosemicarbazones - Potential Precursors of the Radiopharmaceuticals

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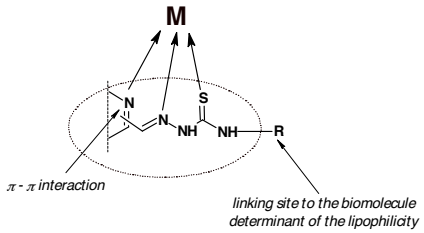

N-heterocyclic aldehyde thiosemicarbazone ligands (TSCs) are chosen because of their well-known pharmacological properties. It has been found that TSCs alone, as well as numerous of their transition metal complexes, bear the antimicrobial, antiviral, antineoplasm, antimalarial and/or anti-cancer properties.[e.g. 1-4] In spite of the fact that numerous transition metal complexes have been tested as potential diagnostic/therapeutic agents, data for the technetium/rhenium compounds are more than poor. Modification of the existing TSC molecules may lead to better binding different biomolecules, followed by proper targeting human organs of interest.

Technetium and rhenium, similarly to their congener - manganium, form cations/anions in one from a group of eight valence states. It is of interest to compare the physico-chemical and biological properties of the mono-, tri- and pentavalent technetium containing complexes (the most popular technetium/rhenium cations in the radiopharmaceutical since) with the same ligand.

This work presents our studies of the selected TSC labeled with the technetium/rhenium radionuclides. Biologically important physico-chemical properties of the mono-, tri- and pentavalent technetium/rhenium complexes are presented.

Acknowledgements

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MRI of Gadolinium Peptide Coiled Coils

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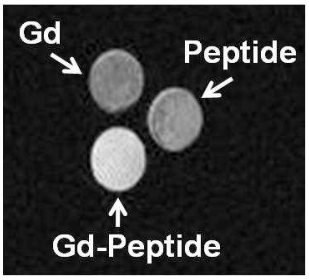
Our goal is to generate and evaluate novel gadolinium molecular resonance imaging (MRI) contrast agents, by combining peptide design, computational modelling and MR imaging studies.



Incorporation of lanthanides into designed peptides offers the opportunity to generate novel fluorescent probes or MRI agents. One example of a designed peptide is TRI, Ac-G(LKALEEK)$_4$G-NH$_2$, which assembles in aqueous solution to form a three-stranded coiled coil.[1] This scaffold provides a stable framework in the interior of which one can design challenging metal binding sites by incorporating amino acids capable of binding to metal ions. Our efforts have been directed towards designing a gadolinium binding site in the interior of one of these coiled coils, and performing T_1 and T_2 relaxation experiments with the resulting gadolinium complex. Dramatically enhanced T_2 values were obtained for the gadolinium complex compared to free gadolinium (see T_2 weighted Figure), most likely as a result of reduced tumbling. These studies were complimented by molecular dynamics simulations on model gadolinium coiled coils, which confirmed both water access to the gadolinium site, and the exchange of coordinated water molecules with the bulk solvent. Efforts are now directed towards peptide redesign. By correlating peptide design and computational modelling with MR data, we aim to understand the mechanism by which we produce contrast.

Acknowledgements

Generous financial support from the University of Birmingham, PSIBS Doctoral Training Centre, Advantage West Midlands and the Royal Society is acknowledged.

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Lanthanide(III) Complexes of PCTA Tris(amide) Derivatives: Possible Candidates for Bimodal Imaging

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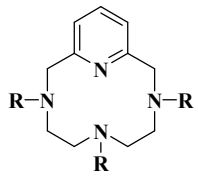
In the last two decades various metal complexes of ligands derived from 1,4,7,10-tetraazacyclododecane, in particular, DOTA and its derivatives, have become important in medical diagnosis and therapy. The closely related tetraaza-macrocycle that incorporates a pyridine chromophore within the macrocyclic framework has received much less attention. The ligand PCTA was found to form complexes with Ln^{3+} ions much faster than DOTA while the resulting complexes retain satisfactory kinetic inertness and acceptable thermodynamic stability.[1] Our recent research focused on Ln^{3+}-complexes of PCTA-tris(amide)s has shown that these complexes are promising MRI and optical contrast agents.[2] Three new tris(amide) derivatives of PCTA were prepared and the stabilities of the complexes formed with some biogenic and Ln^{3+} ions were determined. The stabilities of the Ln^{3+}-complexes were found to be relatively low (12 – 13 log K units). However, their surprisingly high kinetic inertness and fast water exchange rate (measured for Gd^{3+} complexes) combined with acceptable photophysical properties of Eu and Tb complexes renders them potentially useful for *in vivo* use as T_1 contrast and/or optical imaging agents.



Pyclen (R=H)
PCTA (R=CH_2-COOH)
PCTA3Am (R=CH_2-$CONH_2$)
PCTA3PipAm (R=CH_2-$CONC_5H_{10}$)
PCTA3Gly (R=CH_2-CONH-CH_2-COOH)

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A Novel Unimolecular Nanoprobe for Blood Pool Imaging

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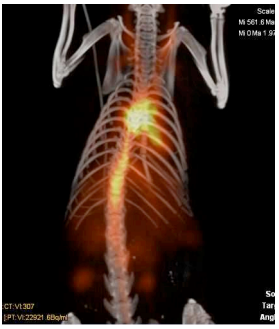
High molecular weight hyperbranched polyglycerols (HPG) were initially synthesized and investigated for their application as a human serum substitute.[1] Over the past few years there has been growing interest in these macromolecules for many applications. Examples include drug delivery agents for the treatment of bladder cancer[2] and coatings for the protection of cell surfaces.



Our interest lies in the modification of these nanosized macromolecules with applications in nuclear medicine. Herein we report the development of a ^{68}Ga modified HPG as a diagnostic probe for blood pool imaging to substitute the currently used ^{99m}Tc-labeled red blood cells (RBC). NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid) modified HPG was radiolabelled at room temperature within 2 min at >98% radiolabelling efficiency. No adverse effects were observed in various blood and cell toxicity assays. Complete pharmacokinetic studies determined a biological half life of 50.7 h for ^{67}Ga-HPG. Dynamic PET imaging proved a biodistribution consistent with an intravascular blood pool agent, with <3% urinary excretion of ^{68}Ga. In gated PET imaging studies, the wall motion and cardiac contractility was assessed and the ejection fractions calculated. Furthermore, dosimetric analyses showed a 3.4-fold reduction in patient dose compared to ^{99m}Tc-RBC in cardiac blood pool imaging.

Radiolabelled HPG is thus an excellent cardiac blood pool imaging agent with many advantages over the current techniques used in clinic including easy kit preparation, good availability of generator produced ^{68}Ga and no need for blood handling with this radiopharmaceutical.

Acknowledgements

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A novel and smart Biomaterial based Hydrogel Silver Nanocomposite: Synthesis, Characterization and Antibacterial Effect

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Hydrogels are water-swollen polymeric materials that maintain a distinct three-dimensional structure. They were the first biomaterials designed for use in the human body.[1] Due to their biocompatible and often stimuli-responsive nature, hydrogels are used extensively in biomedical research.[2] To successfully prepare hydrogels with the desired biological and physical properties, several factors such as a biocompatibility, biodegradability, sterilizability, mechanical strength, drug loading capacity, water content (degree of swelling), and the components of the hydrogels etc., must be carefully considered.[3] Because of high drug loading capacity and high water content, highly swelling hydrogels could be very important in biomedical research. The silver nanoparticles (nano-Ag) have proved to be most effective as they exhibit potent antimicrobial efficacy against bacteria, viruses and eukaryotic micro-organisms. The hydrogel networks around nanoparticles effectively inhibit their aggregation for longer periods and can be extracted into water whenever they are required. In the present study, we report a facile and eco-friendly method for the preparation of a novel silver nanocomposite hydrogel based on poly(acrylic acid) grafted onto salep biopolymer as a backbone for the first time. This method excludes restrictions such as using chemical reducing agents which cause toxicity or biological hazards. The presence of silver nanoparticles (Nano-Ag) in the hydrogel base biopolymer was confirmed by Fourier transform infrared (FT-IR) spectroscopy and thermo-gravimetric (TG) analysis. The scanning electron microscopic (SEM) images illustrated the presence of embedded nano-Ag throughout the hydrogel. In addition, the formed nano-Ag had an average particle size of 5-10 nm as observed by transmission electron microscopy (TEM). The antibacterial activity of the entitled biomaterial based hydrogel nanocomposite demonstrated significant effects against *Escherichia Coli* and *Bacillus Liconiformis*. Lastly, potential of obtained hydrogels for Tetracycline hydrochloride (TH) release in colon was also examined.

Acknowledgements
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Novel Biocompatible TaN hard Coating for Improving Corrosion-wear behaviour of Biomedical Alloys in simulated Body Fluid

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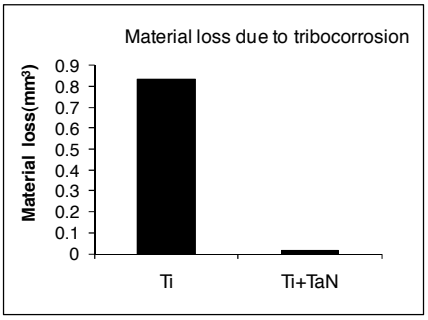
Thin films of transition metal nitrides are widely used as protective coatings due to their high hardness and mechanical strength, corrosion and wear resistance, and chemical inertness. Within them, very little work has been reported on tantalum nitride (TaN). Nevertheless, it shows superior properties on biomedical[1] and tribological[2, 3] applications where properties mentioned above are required.

TaN coatings deposited by DC magnetron sputtering PVD technique, have revealed outstanding wear and corrosion behaviour.[4-6]



In the present work, a tantalum nitride coating has been deposited on metallic biomedical alloys named Ti cp and AISI 316. Corrosion and tribocorrosion behaviour of the coated systems was studied in a simulated body fluid composed by phosphate buffered solution. Coatings show an excellent corrosion resistance of the order of 10^6 Ohm and electrochemical stability with time. Under mechanical-electrochemical conditions, TaN film reduces the substrates volume loss by reducing their surface mechanical damage, and their electrochemical dissolution under tribological conditions. The good corrosion and tribocorrosion response of these TaN coatings make them a promising alternative for improving biomedical materials performance.

Acknowledgements

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Lanthanide Complexes for the Treatment of Bone Density Disorders

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Osteoporosis, the most prevalent bone density disorder, is a skeletal disease that is characterized by low bone mineral mass and a deterioration of bone tissue. Often known as a "silent" disease because it is asymptomatic until fracture occurs, it affects 200 million women worldwide, putting escalating pressure on health care systems. Current medications, while effective, suffer from low bioavailability, a multitude of side effects, including bone mineralization and strict guidelines for patients, which all lead to extremely low patient compliance. The need to develop a drug with reduced side effects has led us to investigate lanthanides (Ln(III)) as a treatment for osteoporosis. Lanthanides are of interest because they are found to preferentially accumulate in bone (*in vivo*), stimulate osteoblast proliferation and inhibit osteoclast activity (*in vitro*). This knowledge, along with previous work performed in the Orvig group has indicated that 3-hydroxy-4-pyridinone complexes of lanthanides may be an effective agent for delivering lanthanides to bone, treating bone density disorders. Initial screening helped identify a lead compound, having 10-fold greater cell uptake in Caco-2 cells, *in vitro*, than other tested compounds.[1] Building upon this success, we have synthesized a family of 3-hydroxy-4-pyridinones with carefully selected targeting moieties in order to increase the selectivity of the complexes *in vivo,* thus increasing their potency. The synthesized Ln(III) complexes exhibit low toxicity profiles for both Caco-2 cells and osteoblast-like cells (MG-63), which are responsible for bone formation. Hydroxyapatite (HAP) binding studies furthermore indicate that these lanthanides bind >98% to HAP, the main mineral component of bone. Ligand-HAP binding studies demonstrate that with appropriate ligand functionalization the complexes can be directed towards bone. Described are the synthesis, characterization and *in vitro* studies of a series of LnL_3 compounds with hydroxyl, carboxyl, phosphate and bisphosphonate functional groups appended to them.

Acknowledgements
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Photothermal IR-Spectromicroscopy for Subcellular Imaging: Cellular Mapping of a Metal-Carbonyl Exogenous Compound

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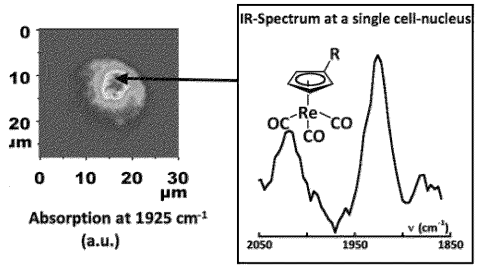
The IR-energy range is particularly attractive for chemical-imaging[1] as vibrational excitations in the IR induce no photo-bleaching. However, in classical optical microscopy, sub-cellular or sub-micrometric resolutions are not attainable in the IR-range, as the diffraction criteria imposes a resolution higher than the μm. The near-field technique AFM-IR couples an AFM and a tunable infrared laser to record spatially resolved IR-absorption measurements and enables subcellular mapping.[2]

We have recently shown[3] that P89, an hydroxy-tamoxifene hormone conjugated with a Re-tris-carbonyl displays, after cellular incubation (1h, 10 μM, MDA-MB231 cells, non-hormono-dependent breast-cancer), an intense signal in classical FTIR and allows an efficient mapping inside cells using AMF-IR. In this communication, we will present both the results of the quantification of the cellular content by FTIR, the chemical imaging of P89 inside MDA-MB231 cells and spectra inside the nucleus recorded using the AFM-IR technique.[3] Recent results obtained using other imaging techniques and other probes will also be presented.



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Designing Metallopeptides

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Metalloprotein design represents a potentially powerful approach for the development of new catalysts capable of desired chemical transformations in aqueous solution. The first development of such catalysts is for the preparation of biomimetics of hydrolytic or redox active enzymes. Eventually, one can hope to catalyze reactions not presently found in the biosphere, opening up an entirely new method of achieving chemical catalysis.

This presentation will document our progress on preparing new catalytic systems utilizing first row transition elements in a tris histidine coordination environment. It will be shown that this strategy allows for unprecedented rate enhancements that begin to rival those found in naturally evolved enzymes.

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Chloroquine and Mefloquine Ferrocenyl Conjugates for the Treatment of Malaria

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Malaria is one of the main causes of mortality and morbidity in the world, endangering billions and affecting millions of people each year, leading to approximately one million fatalities annually.[1] Resistance to common antimalarial drugs has proven to be a challenging problem in malaria control.[2] In an attempt to develop an effective and affordable treatment for malaria based on the previous successes of organometallic derivatives of classical pharmacophores,[3] and ferrocenoyl carbohydrates,[4] a series of ferrocenyl conjugates, incorporating a common antimalarial drug and/or a monosaccharide molecule, has been developed.

Diverse synthetic pathways have yielded different compounds that include 1,1´-heteroannular- and 1,2-homoannular-substituted ferrocenyl conjugates of chloroquine- or mefloquine-derivatives in combination with a carbohydrate (glucose or galactose derivatives). In addition, a series of chloroquine and mefloquine ferrocenyl conjugates with unusual ferrocene-bridging binding modes was synthesized and characterized.

The antimalarial activity of these compounds, evaluated *in vitro* against chloroquine-sensitive (D10) and chloroquine-resistant (Dd2, K1) malaria parasite (*Plasmodium falciparum*) strains as well as the cytotoxicity profiles and anti-proliferative activity evaluated in various human cell lines will be presented. A combination of structural interaction studies based on physicochemical properties and preliminary molecular modeling will also be discussed, to give some insight in explaining the antimalarial activity observed.

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Interaction of Vanadium Complexes with Serum Proteins

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For therapeutic use of V compounds understanding its transport and delivery to cells is a crucial issue. It was shown that $V^{IV}O^{2+}$ is able to bind human serum albumin (HSA), immunoglobulin G (IgG) and transferrin (hTf), the binding to hTf being much stronger than to HSA or IgG, V is thus mostly transported by hTf.[1]

Here we report the study of the interaction of V^{III}, V^{IV}, V^{V} and of a few $V^{IV}O(carrier)_2$ complexes with hTf and HSA. Studies using ^{51}V NMR, EPR, CD, AFM and MM calculations are presented. These confirm the binding of V^{III} or $V^{IV}O^{2+}$ mainly to hTf. It was shown by EPR that a dinuclear complex $(VO)_2{}^{d}HSA$ is formed in equimolar conditions. Using a molar excess of $V^{IV}O^{2+}$, $(VO)_x{}^{m}HSA$ is the prevalent species, x indicating the number of V^{IV} ions bound to HSA.[2] The interaction of $V^{IV}O^{2+}$ with HSA, bovine serum albumin (BSA) and porcine serum albumin (PSA) are studied using EPR and CD. It is confirmed that $V^{IV}O^{2+}$ occupies two types of binding sites on HSA, which we designate by VBS1 $\{(VO)_2{}^{d}HSA\}$ and VBS2 $\{(VO)_x{}^{m}HSA\}$.

VBS1 binds 1 equivalent of $V^{IV}O^{2+}$, this corresponding to very weak visible CD and EPR signals, but $V^{IV}O^{2+}$ bound at VBS2 yields strong CD and EPR signals. The A_z for VBS2 on HSA and BSA are $\sim 168\times10^{-4}$ cm^{-1}, and $\sim 166\times10^{-4} cm^{-1}$ on PSA,. Competition studies were done with Cu^{II} and Zn^{II}. These indicate that VBS1 is located close to the Cu^{II} primary site. VBS2 is a collection of sites including the 'multiple binding site': MBS, and Zn^{II} is able to displace $V^{IV}O^{2+}$ from the MBS. Comparatively, $V^{IV}O^{2+}$ binds the MBS as strongly as Cu^{II}.

Acknowledgements

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Bioinorganic Chemistry as a Mean to Reduce Animal Testing for new Drugs: Electrocatalysis of Monkey Cytochrome P450 2C20

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Cytochrome P450 2C20 from *Macaca Fascicularis* is the homologue of human hepatic cytochrome P450 2C8 which is known to turnover more than 8% of drugs cleared by P450 Phase I drug metabolism.

In this work, the gene coding for CYP2C20 was cloned in the expression vector pCW and successfully expressed in a soluble form in *E.coli* with a yield of 11 mg of pure protein per litre of culture. The solubilised protein was subsequently immobilised on glassy carbon and gold electrode surfaces using different approaches; non-orientated entrapment within a cationic polymer PDDA (poly(diallyldimethylammonium chloride)) on the former surface and oriented immobilisation on a self-assembled monolayer of sulfhydryl-reactive DTME (dithio-bismaleimidoethane) on the latter surface taking advantage of covalent linkage between the DTME and surface accessible cysteine residues of this enzyme. Cyclic voltammograms of the P450 2C20 immobilised on the glassy carbon electrode showed the presence of a redox couple attributed to the haem FeIII/FeII with a midpoint potential of -247 ± 4 mV (vs Ag/AgCl) which is comparable to data published by our group for other cytochrome P450 enzymes.[1-3]

In order to test the capability of the immobilised enzyme to turnover specific substrates (i.e. drugs) of its human homologue P450 2C8, chromoamperometry experiments were carried out where a bias of -650mV (vs Ag/AgCl) was applied for a duration of 30 minutes. The products of the electrochemical turnover of the selected drugs, Paclitaxel (anti-cancer) and Amodiaquine (anti-malarial) were separated using high pressure liquid chromatography. By immobilizing 15 μM of P450 2C20 enzyme on glassy carbon and gold electrodes 0.04 and 0.11 nmol of 6-beta-hydroxy Paclitaxel and, 1.8 and 4.1 nmol N-desethylamodiqauine were produced, respectively.

These preliminary results on the 2C20 immobilized either in a mono- or multi-layer form on electrode surfaces represent the first step towards the development of an alternative *in vitro* method that can be useful for preclinical testing of new chemical entities in the drug discovery process.

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Recruiting Sulfide Ligands to Increase the Detoxification Capacity of Metallothioneins

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In analogy to their mammalian counterparts, plant metallothioneins (MTs) are small cysteine-rich proteins with a preference for metal ions with the electron configuration d^{10}. Studies have shown that MTs from very different families are able to incorporate sulfide ions *in vitro*, which usually increases the binding capacity of the respective MT for metal ions.[1] Next to the phytochelatins, small peptides that are enzymatically synthesized in response to heavy metal ion stress, MTs are the main detoxification machinery in plants. Plant MTs display high sequence diversity and are currently subgrouped into four subfamilies. Members of each subgroup differ in the number of their cysteine residues and hence the amount of metal ions they can bind.[2] We focused our investigation on the MT2 form from *Cicer arietinum* (chickpea), cicMT2. cicMT2 consists of 79 amino acids and contains 14 cysteine residues, which are clustered in the N- and C-terminal part of the protein separated by a 41 amino acids long cysteine-free linker. We could previously show that cicMT2 is able to coordinate five Zn^{II} or Cd^{II} ions in a single metal-thiolate cluster formed by the combined N- and C-terminal Cys-rich regions.[3] When incubated with sulfide ions in presence of excess Cd^{II}, the binding capacity of the protein for Cd^{II} is significantly increased recruiting sulfide ions as additional ligands. Here we present our analytical study showing the dependence of the metal ion binding capacity on the amount of sulfide ions provided and revealing insights into the mechanism of metal-sulfide cluster formation.[4] Comparative experiments performed with mammalian MTs show distinct differences in the metal ion incorporation process and hence corroborate a possible role not only of sulfide ions but also of the long Cys-free linker regions so typical for plant MTs in metal accumulation and detoxification in plants.

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The Application of NMR and Single Molecule FRET to Investigate the Toxic Effect of Ca^{2+} on Group II Intron Splicing

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Group II intron ribozymes are among the largest catalytic RNAs known today. These large RNAs of up to 2500 nucleotides in length catalyze their own excision from precursor RNA, a process called self-splicing. In addition, they can also reinsert into DNA, i.e. retrohoming, making them mobile genetic elements.[1] Based on this peculiar abilities, they have already been applied in gene therapy.

The folding pathway, structure, and catalysis of group II introns is strictly dependent on Mg^{2+}, which is considered to be the natural cofactor. We have recently shown that splicing of the mitochondrial Sc.ai5γ ribozyme from yeast is severely hampered by small amounts of Ca^{2+}, which is freely available in these cell organelles.[2] In order to investigate this stunning effect of metal ion specificity and toxicity, we applied NMR spectroscopy and single molecule Fluorescence Resonance Energy Transfer (smFRET).[3,4]

We have solved the NMR solution structures of the crucial recognition complex between the exon and the intron, resembling both the self-splicing and the retrohoming situation, and investigated their metal ion binding properties. The backbone adopts an unusual strong kink, which is stabilized by a M^{2+} cation being close to the 5'-splice site.[5]

smFRET studies not only reveal a new folding paradigm for large RNAs, but also show that the active state is only transiently reached in the presence of Mg^{2+}, and that the addition of Ca^{2+} leads to two distinct subpopulations.[3,4] We could show now that the differential influence of Mg^{2+} and Ca^{2+} is also exhibited on the splice site formation on the single molecule level. This exemplifies the power of smFRET spectroscopy for the application in bioinorganic chemistry.

Acknowledgements

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Soybean Metallothionein Family: A Role in Cadmium Accumulation?

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Cadmium (Cd) is a highly toxic heavy metal for both plants and animals. The presence of Cd in agricultural soils is of great concern regarding its entry into the food chain.[1] Compounds of Cd are soluble, so they are readily taken up by plants, and accumulated in edible parts. Soybean, for instance, shows high levels of Cd concentration in grains. In this context, the study of its molecular determinants of Cd accumulation -such as metallothioneins (MT)– is of great importance.

Four MT genes/proteins, belonging to the 4 plant MTs types,[2] are currently under studies. All of them are expressed at high levels in soybean tissues: MT1, 2 and 3 in root, shoot and seeds, and MT4 only in seeds. Heterologous expression in MT-null *S. cerevisiae* strains restores Cd tolerance but only marginally enhances Zn tolerance; also it improves resistance to different oxidative stress agents. Soybean MTs, obtained through recombinant synthesis in *E. coli* cells cultured in metal supplemented media, render better folded polypeptides with Cd than with Zn. These results point towards a role in metal sequestration, with preference of Cd over its physiological chemical equivalent –zinc-, and/or palliation of the oxidative stress induced by heavy metals in excess, for all soybean MTs studied.

Acknowledgements

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A. ornata Dehaloperoxidase: the Mechanism of Oxidative Dehalogenation by Heme-Containing Peroxidases as Potential Bioremediation Catalysts

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Dehaloperoxidase (DHP), from the terebellid polychaete *Amphitrite ornata*, is the first heme-containing globin possessing peroxidase enzymatic activity. DHP catalyzes the H_2O_2-dependent dehalogenation of halophenols with concommitant O-atom addition to generate the corresponding quinones. It has been proposed that DHP evolved from a dioxygen carrier protein and therefore possesses dual physiological roles of O_2 carrier and dehaloperoxidase. In this study, designed "Mb-like" DHP mutants and "peroxidase-like" sperm whale myoglobin (Mb) mutants have been prepared and studied to probe hypotheses about the mechanistic role of specific amino acids near the heme center of DHP. In parallel, the oxygen binding affinities of these Mb and DHP mutants have been investigated. In addition, although DHP is isolated in the oxyferrous state, the ferric state is catalytically active. We find that in the presence of TCP, H_2O_2 is able to convert oxyferrous DHP to the enzymatically active ferric state. Factors influencing this switch in DHP oxidation state, including parallel studies with Mb, have been further explored. These observations provide a link between the O_2 carrier role of ferrous DHP and the peroxidase activity of the ferric enzyme in this bifunctional protein. A more complete understanding of the mechanism of oxidative dehalogenation of halophenols by DHP and other peroxidases capable of catalyzing this reaction is necessary for the development of a peroxidase-based bioremediation protocol.

Acknowledgements

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Molecular Catalysts for Artificial Photosynthesis

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Nature has been using water and sunlight as a source of energy in green plants and algae photosynthetic processes for thousands of millions of years. The overall photosynthetic process can be written as,

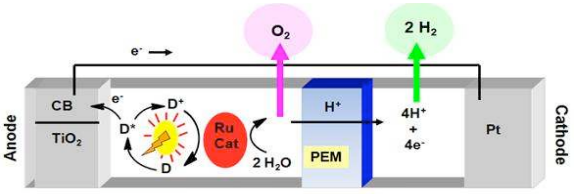
$$H_2O + CO_2 \rightarrow 1/n\ (CH_2O)_n + O_2 \qquad (1)$$

This reaction involves the reduction of CO_2 to carbohydrates and the oxidation of water by a $4H^+/4e^-$ pathway (equation (2)).

$$2\ H_2O \rightarrow O_2 + 4\ H^+ + 4\ e^- \qquad (2)$$

The latter is the terminal reaction that occurs at photosystem II (PSII) in green plants and takes place at a polynuclear Ca-Mn_4 complexcomplex. However, while the degree of knowledge of the structure of the oxygen-evolving complex is getting more precise, the mechanism through which oxygen is produced is controversial.

The purely biological interest in understanding the water oxidation mechanism at the OEC-PSII is nowadays merged by the urgent need our present society has of clean and renewable energy. The discovery of a sufficiently rugged and efficient water oxidation catalyst will represent a significant advancement towards building a complex device for clean energy harvesting as the one shown in the figure.



We tackle this challenging topic by designing low molecular weight PSII models and studying their electrochemical and spectroscopic properties,[1] analyzing their reaction mechanisms[2] and constructing modified conducting electrodes ready to be integrated into a larger device for the photo-production of H_2.[3]

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The Influence of Metallostasis on Insulin Degrading Enzyme Activity

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The aetiology of Alzheimer Disease (AD) and diabetes mellitus type 2 (DM) remains unknown and genetic factors can explain only a small percentage of cases. However, metal ions such as copper and zinc are known to play an important role in many biomolecular processes and their dyshomeostasis has been considered a critical factor in the development of AD and DM. Furthermore, accumulating evidence correlates insulin dysmetabolism with dementia-linked brain plaques and IDE (insulin-degrading enzyme) has been observed to degrade both Aβ peptides and insulin. For this reason, an altered activity of IDE has been proposed as a possible factor bridging AD and DM pathogenesis. Therefore, the therapeutic potentials offered by the ability to regulate the activity of IDE are thought to be highly promising.

In an attempt to unveil some of the molecular determinants lying at the root of AD and DM and inspired by all these issues, we have focused on the effects that metal ions may have on the activity of IDE.[1,2] In particular, we have investigated the activity of IDE in different experimental conditions towards various substrates, including ubiquitin and polyubiquitin chains. Our results allowed us to gain insights in the role played by copper and zinc in modulating IDE activity and, in turn, in the regulation of the cross-talk between different cellular proteolytic pathways.

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Structural basis for the Transcriptional Regulation of Heme Homeostasis in Lactic Acid Bacteria

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Though a lactic acid bacterium *Lactococcus lactis* lacks heme biosynthesis genes, it can uptake and use heme molecules provided externally to grow by oxygen respiration. As free heme molecules are toxic for cells, cellular concentrations of heme should control strictly. *L. lactis* controls cellular heme concentrations by operating a heme efflux system. The expression of the heme efflux system is regulated by a heme-sensing transcriptional regulator HesR (heme efflux system regulator). In this work, we have determined X-ray crystal structures of HesR in heme-binding (holo-) and heme-free (apo-) forms to elucidate the structure and functions relationships of HesR.

HesR is a homo-dimer in the both of apo- and holo-forms as shown in Figure. HesR monomer consists of the N-terminal DNA-binding domain and the C-terminal heme binding domain that binds one heme molecule. Global fold of HesR is similar to that of TetR family transcriptional regulators. HesR is the first example of heme-sensing TetR family transcriptional regulator. A change in the relative orientation of the DNA-binding domain is induced upon heme-binding, which results in the regulation of DNA-binding activity of HesR.

We have found that apo-HesR can bind the target DNA, but holo-HesR can not. DNA-binding affinity of apo-HesR is determined to be Kd = 0.7 nM by fluorescence anisotropy measurements. These results indicate that heme molecule acts as a physiological effector of HesR to regulate its DNA-binding activity.

HesR shows a very high affinity for heme binding. When apo-HesR is mixed with holo-myoglobin, it can extract heme from myoglobin. The estimated heme binding affinity of HesR is comparable to that of myoglobin.

We will discuss detail mechanisms of heme-responsive functional regulation of HesR based on the crystal structures.

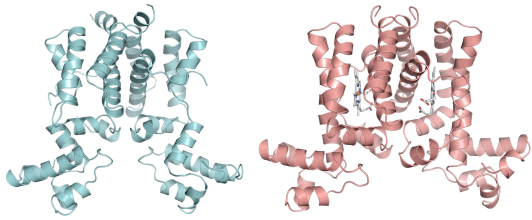

Figure. X-ray crystal structures of apo-HesR (left) and holo-HesR (right)

The Molecular Mechanism of Catalase by QM/MM Metadynamics

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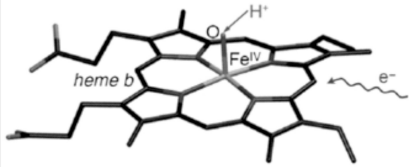
Catalases are ubiquitous enzymes that prevent cell oxidative damage by degrading hydrogen peroxide to water and oxygen ($2H_2O_2 \rightarrow 2\ H_2O + O_2$) with high efficiency.[1] The enzyme is first oxidized to a high-valent iron intermediate, known as Compound I (Cpd I) which, at difference from other hydroperoxidases, is reduced back to the resting state by further reacting with H_2O_2. The normal catalase activity is reduced if Cpd I is consumed in a competing side reaction, forming a one-electron reduced species named Cpd I*. By means of hybrid QM/MM metadynamics simulations,[2] we unravel the mechanism of the reduction of Compound I by H_2O_2 in catalase.[3,4] We found that the Cpd I:H_2O_2 complex evolves to a Cpd II-like species through the transfer of a hydrogen atom from the peroxide to the oxoferryl unit. To complete the reaction, two mechanisms may be operative: an *His-mediated* (Fita-Rossmann) mechanism,[2] which involves the distal His as an acid-base catalyst mediating the transfer of a proton (associated with an electron transfer), and a *direct mechanism*, in which a hydrogen atom transfer occurs. Independently of the mechanism, the reaction proceeds by two one-electron transfers rather than one two-electron transfer, as has long been the lore. The calculations provide a detailed view of the atomic and electronic reorganizations during the reaction, and highlight the key role of the distal residues to assist the reaction.[3,4] Calculations of the one-electron reduction potential and proton transfer free energy suggest that the energetics of the oxoferryl protonation is the key factor regulating the propensity to form Cpd I* in catalases and possibly also in other hydroperoxidases.[5]



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POSTERS

Biological Activity of Iron Complexes with Bithiazole

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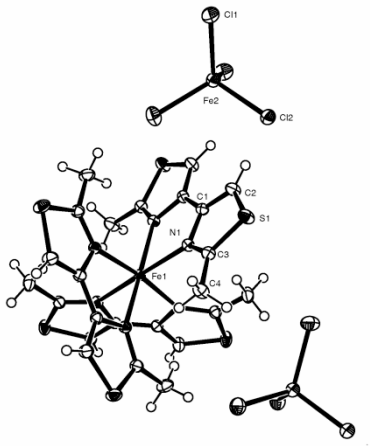
There has been considerable interest in the synthesis and characterizes and properties of iron complexes with aromatic nitrogen heterocycles. These studies are performed to understand biomimetic processes, spin transition phenomena, mixed valent complexes and magnetic properties.[1]

In following the studies on bithiazoles as bio-active ligands and the investigation of biological properties of metal-bithiazole complexes, we considered 2,2'-dimethyl-4,4'-bithiazole (dm4bt) as ligands and treated them with FeX_3 salts (X= Cl and Br).



To our surprise, octahedral Fe(II) complexes were prepared by interaction of the ligands with Fe(III) salts where the oxidation number of Fe center is reduced to +2 in main tris(N-N) complex but remained +3 in counterion, as we received to $[Fe(dm4bt)_3][FeCl_4]_2$ (1) and $[Fe(dm4bt)_3][FeBr_4]_2$ (2). The complexes were thoroughly characterized.[2]

We expected the cation parts of the compounds can show DNA-bonding properties, like similar tris ruthenium complexes, i.e. $Ru(bipy)_3^{+2}$ and $Ru(phen)_3^{+2}$. Therefore the *In Vitro* evaluation of the complexes were performed in three cancer cell lines (Caco-2, HT-29 and T47D) and also a nonmalignant fibroblast cell (NIH-3T3) by MTT assay and the results were compared with cis-platin, a currently used metal-based drug that demanded in spite of complex **2**, complex **1** shows more cytotoxicity than cis-platin.

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Synthesis, Structure and Properties of Pt and Ru Complexes of 2,4-dithiohydantoins with Antitumor Activity

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Hydantoin derivatives are known as antiepileptic drugs. Additionally, it was found that some hydantoin compounds show antiproliferative activity and aldosoreductase inhibition. Thioanalogues of hydantoins are also subject of increasing interest regarding their structure and biological activities. Recently, we undertook a systematic study on the synthesis, structure and complexation properties of various dithiohydantoins (imidazolidine-2,4-dithiones) with copper, nickel and platinum.[1]

The current contribution is focused on platinum and ruthenium complexes of 9'-fluorene-5-spiro-2,4-dithiohydantoin (L1) and benzocyclohexane-5-spiro-2,4-dithiohydantoin (L2). The crystal structure of benzocyclohexane-5-spiro-2,4-dithiohydantoin was resolved from single-crystal X-ray diffraction data. The complexes were synthesized from cis-$(NH_3)_2PtCl_2$ and $RuCl_3$. The structure of the Pt(II) complexes were studied by means of spectroscopic (IR and ^{13}C CPMAS NMR) and theoretical methods (DFT). Different model structures for the complexes were optimized in order to suggest the most probable one, basing on comparison between the calculated and the experimental spectroscopic properties. Ruthenium complexes were initially studied by EPR spectroscopy of powder samples at room temperature. All compounds were tested fot antitumor activity against four types of human tumor cell lines using the MTT test.

In conclusion, the structure of the newly synthesised complexes is predicted by combined spectroscopic ad quantum-chemical approach, suggesting dimeric structures for both Pt and Ru complexes. Preliminary results for antitumor activity for the complexes show concentration dependent cytotoxic effect in HL-60 leukemic cells.

Acknowledgements
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Synthesis and Charaterization of new Coordination Compounds with Antihelmintic Activity in Monogeneos of Spotted Rose Snapper (*Lutjanus Guttatus*)

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Imidazole and benzimidazole derivatives have shown antimicrobial, antihelmintic, antispasmodic, antifungal and antiviral activity. [1] Coordination compounds with these ligands have presented antibacterial and antitumor activity.[2] In this context we are studying the behaviour of 1-(2-ethylsulfonylethyl)-2-methyl-5-nitro-imidazole (tnz) towards transition metal ions and their biological activity.

Coordination compounds with tnz were synthesized from ethanol. The obtained compounds, $[M(tnz)_2(X)_2]$, (CoX_2, CuX_2 and $ZnCl_2$; X = Cl and Br) were characterized X-ray diffraction (Figure 1). The metal ions are in a tetrahedral geometry, coordinated by two ligands through the imidazolic nitrogen atom and two halogen atoms complete the coordination sphere. These compounds were evaluated with monogeneans parasites, which cause anaemia in spotted rose snapper (*Lutjanus guttatus*). The *in vitro* activity study showed that the $[Cu(tnz)_2Cl_2]$, $[Cu(tnz)_2Br_2]$, $[Zn(tnz)_2Cl_2]$ and $[Zn(tnz)_2Br_2$ compounds were the most active. From their LC_{50}, it was observed that between 2-4 hours, the zinc(II) compounds had better activity than de copper(II) compounds.

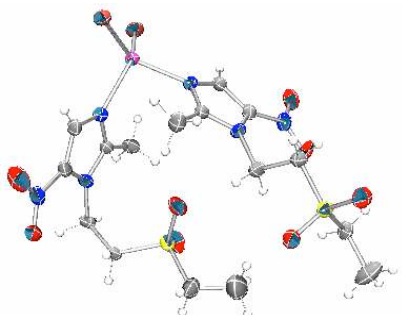

Fig. 1. ORTEP diagram for $[Zn(tnz)_2Br_2]$

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Synthesis and Characterization Complex of the $\{ReO\}^{3+}$ Core with Sn and N donor Ligands

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A novel mixed ligand ^{99m}Tc complex with mercaptobenzothiazole as ligand and Aminothiazole as coligand was prepared and evaluated as potential brain radiopharmaceutical. Preparation at tracer level was accomplished by substitution, using ^{99m}Tc-gluconate as precursor and a coligand/ ligand ratio of 5. Under these conditions the labeling yield was over 87% and a major product with radiochemical purity >87% was isolated by HPLC methods and used for biological evaluation. The reaction of $[ReO(Citrate)_2]^-$ with mercaptobenzothiazole and Aminothiazole in hot MeOH yields $[ReO(mer)(amino)OH(H_2O)_2]$. The structure and DFT study demonstrated that the complex consists of distorted octahedral ReO(V). The coordination geometry at the rhenium is defined by a terminal oxo-group, the nitrogen and sulfur donors of the chelating mercaptobenzothiazole, the nitrogen of Aminothazole ligand, is present as a deprotonated amido nitrogen. Biodistribution in mice demonstrated early brain uptake, fast blood clearance and excretion through hepatobiliary system. Although brain/blood ratio increased significantly with time, this novel ^{99m}Tc complex did not exhibit ideal properties as brain perfusion radiopharmaceutical since brain uptake was too low.

Acknowledgements

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Metal Ions Modulate Amyloid Formation

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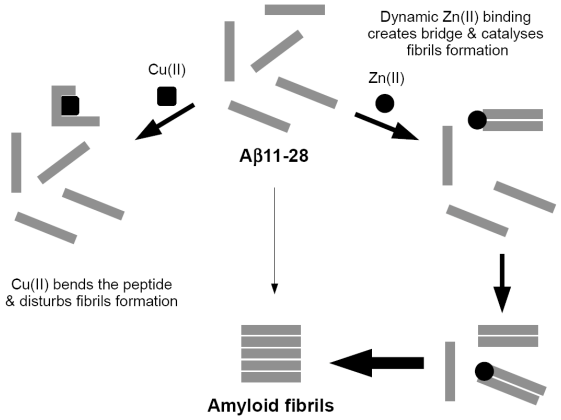
Supramolecular assembly of peptides and proteins leading to amyloid fibrils is a central event in neurodegenerative disease such as Alzheimer's Disease (AD). Moreover, in case of AD, interaction between the amyloid-β (Aβ) peptide and metal ions has been proposed to be linked to the aetiology of the disease. [1] Understanding the role of metal ions in the amyloid formation is thus of paramount importance.

Our studies focus on the amyloidogenic Aβ11-28 as a model peptide and on its interaction with Cu(II) and Zn(II) ions. Here, we will show how the presence of ions modulates the fibrillization process from structural and kinetic aspects.[2, 3, 4] Zn(II) is able to enhance fibrils formation while Cu(II) precludes it. Spectroscopic studies (EPR, NMR and XAS) have demonstrated that whilst the Cu(II) and Zn(II) binding sites are both located in the N-terminal region, their coordination spheres are different, inducing different aggregation processes. More precisely, Zn(II) is responsible for the formation of dimers that promote fibrillization whereas Cu(II) induces bending of the peptide that disturbs fibrils formation. Moreover, Zn(II) is labile and hence even substoichiometric amounts are necessary to propagate fibrillization.



These results establish first insights into the impact of metal ions in amyloid formation.

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Development of Ru(II)/Os(II) Cage Type Ligand Complexes for Photocatalytic Reduction of NAD^+

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Owing to the globally growing concerns on sustainable energy, it is getting more important to convert solar energy into chemical energy in the form of a reductant, such as dihydronicotinamide adenine dinucleotide (NADH). NADH is used as a cofactor in various biological reactions by oxidoreductases. NADH-evolving photocatalysts have been studied, because the cofactor is commercially expensive. Some Ru(II)-polypyridine ligands complexes, such as Ru(tpy)(bpy)(py)]$(PF_6)_2$,[1] have been employed as a photosensitizer for catalytic reduction of NAD^+ to NADH, driven by light energy (Fig. 1).

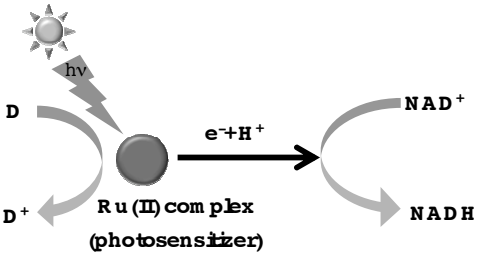

Figure 1. Photocatalytic reduction of NAD^+.

In this work, we are developing new Ru(II)/Os(II) photocatalysts reproducing NADH for its reuse. We synthesized a new mononuclear Ru(II) complex, $[Ru^{II}(L)(tpy)](ClO_4)_2$ (Fig. 2) (tpy = 2,2′:6′,2″-terpyridine) by refluxing a mixture of L,[2] $Ru^{III}(tpy)Cl_3$, and triethylamine in ethanol. X-ray studies of the isolated crystal of 1 from methanol, clearly showed that the ruthenium(II) center has 6-coordinate octahedral geometry occupied with three nitrogen atoms of tpy and three nitrogen atoms in one of the three bis(aminomethyl)pyridyl spacers of L.

We succeeded in synthesizing mononuclear Ru^{II}/Os^{II}-tpy complex inside the cage-type ligand. The studies of photocatalytic reduction of NAD^+ to NADH are in progress.

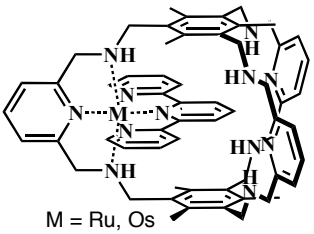

Figure 2. Structure of $[M^{II}(L)(tpy)](ClO_4)_2$.

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Crown Ether Azamacrocyclic Ligand Frameworks for Heteronuclear $Ca^{2+}/Mn^{2+/3+}$-complexes as Potential MRI Contrast Agents

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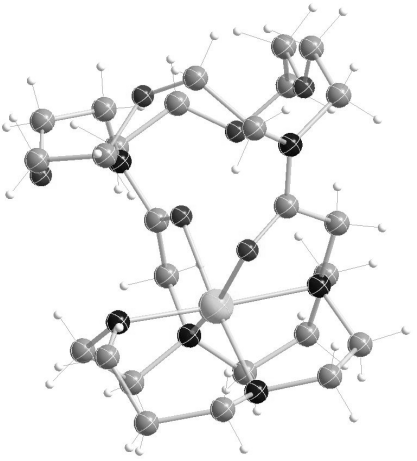
Macrocyclic frameworks, such as crown ether polyaza-conjugates, are able to form heteronuclear complexes with various alkaline earth and transition metals. Herein we present a type of framework which is designed to complex Ca^{2+} and $Mn^{2+/3+}$ at the same time. Due to the low toxicity of manganese, its complexes, in particular polynuclear, are currently highly attractive as new diagnostic tools, replacing gadolinium MRI contrast agents.



Multi-step synthesis of the ligands is presented and formation of their metal complexes is supported by ultra high resolution ESI mass spectrometry.

In order to clarify bio-relevant mechanistic behaviour, kinetic and electrochemical methods will be applied. Finally, their potential as contrast agents in MRI will be investigated.

Complete Dinitrogen Activation by Vanadium Complexes

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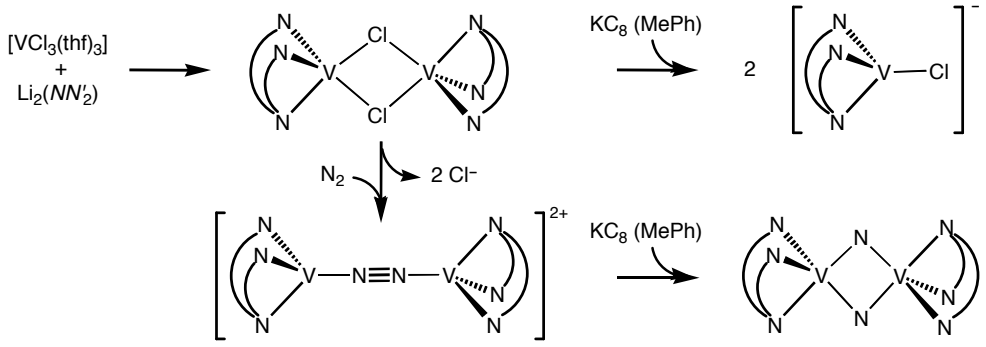
Ammonia is a molecule that has changed our world in the past centuries.[1] Industrial production generated through the Haber-Bosch process from constituent elements has however a high energy cost. In contrast, the nitrogenase enzyme can transform dinitrogen into ammonia under mild conditions such as room temperature and atmospheric pressure.[2] In order to incorporate this process into homogeneous catalysis, we have investigated the coordination of dinitrogen to several transition metals and the influence of complexation to its activation. This can be considered as the initial step for the fixation of dinitrogen.

Complexes containing vanadium can produce a complete scission of dinitrogen bond.[3] The accepted pathway includes the generation of a V_2N_2 species, which then undergoes a reorganization. A theoretical analysis of the chemical properties for the V_2N_2 unit provides useful information of this rearrangement. Information retrieved from the *Cambridge Structural Database* confirms the following mechanism for the activation of the dinitrogen molecule:



Acknowledgements

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Biological, Spectroscopic and Structural Properties of Transition Metal Compounds with Imidazole Derivatives

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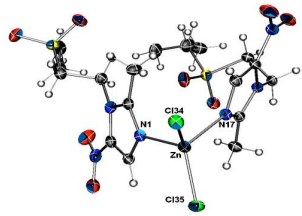
We have been interested to study the coordination ability of biological active molecules towards transition metal ions and the structural properties of these coordination compounds. On the other hand, we have been investigating their antineoplasic and antimicrobial activity.[1,2]

In this work we present the synthesis, structural, spectroscopic and biological characterisation of a series of cobalt(II) copper(II) and zinc(II) coordination compounds with a series of imidazole and nitroimidazole derivatives. According to the spectroscopic characterization and X-ray diffraction analyses, the metal ion in the coordination compounds may present different geometries depending on the anion present in the coordination sphere. The cobalt(II) and zinc(II) halide compounds $[ML_2X_2]$, present tetrahedral structures. Dinuclear compounds with copper(II) acetate were obtained, while octahedral structures for the nitrate compounds were stabilised.



The compounds were evaluated for their in vitro antineoplasic activity towards *HeLa (cervic uterine), HCT15(colon), SKLU-1*(*lung), MCF7*(*breast), PC3(prostate) and U373* (*glioblastoma).* The antiparasitary activity of tinidazole compounds were tested on the monogenean (dactylogyrus) of red snapper (lutjanos guttatus), as their toxicity was investigated.

Acknowledgements

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New Insights in Tyrosinase Inhibition from a Bio-inorganic Strategy

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Tyrosinases (Ty) are copper-containing metalloenzymes which catalyze the oxidation of phenolic compounds into catechols and catechol into *o*-quinone successively.[1] In mammals, Ty is involved in the two-step oxidation of L-tyrosine into dopaquinone, which is the key product for melanin pigment biosynthesis. Melanin-related disorders are known to cause serious lesions and Ty inhibition is a well-known approach against increased production and accumulation of melanins.

In relation with Ty inhibition mechanism, the molecules targeting binuclear copper sites represent a relevant strategy to achieve Ty inhibition specificity. In this regard, the detailed studies of small molecules binding on model complexes in relation with the inhibition behaviour are fundamental to established binding properties/inhibition activity relationship. Recently, we first demonstrated that some substituted pyridine-*N*-oxide are new and efficient Ty inhibitors. We studied the interaction of these inhibitors with Ty functional models in order to elucidate their binding mode (chelating or bridging) on a dicopper(II) center.[2,3] Combining spectroscopic studies and quantum chemical modelling, the obtained results led us to propose new scaffolds, which better target the Ty metal active site for more selective and potent inhibitor development.[4]

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Financial support from the French Agence Nationale pour la Recherche (Program ANR-09-BLAN-0028-01/02/03) is acknowledged.

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Effects of Metal Binding to Carnosine Derivatives and Serum Carnosinase

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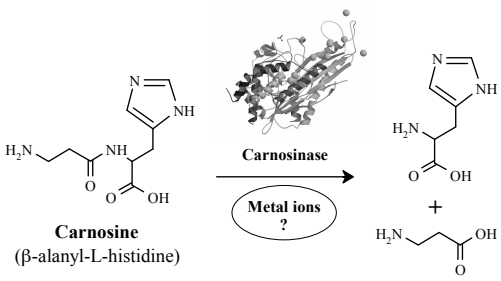
Carnosine (β-alanyl-L-histidine) is an endogenous dipeptide widely and abundantly distributed in muscle and nervous tissues of several animal species.[1] Many functions have been proposed for this compound, such as antioxidant and metal ion-chelator in vivo.[2] However, the main limitation on its potential therapeutic use is associated with hydrolysis by the specific dipeptidase carnosinase.[3] A promising approach to overcome this limitation consists in the functionalization of the natural dipeptide with several sugar. Coherently with our previously reported results,[4] the glyco-conjugation protects the dipeptide moiety from the carnosinase hydrolysis, thus potentially improving the availability of carnosine. The characterization of the copper(II) complexes has brought to light similarities and differences among all the glycoside conjugates and the dipeptide.



Serum carnosinase (CN1), predominantly expressed in the liver and brain, is involved in the homeostasis of carnosine. The cerebral levels of CN1 increase with age and are differently distributed in the cerebral regions.[5] Since the same trend has been reported for several metal ions, such as copper and zinc, it has been tested how the binding of metal ions to CN1 and to the substrate influences the enzyme activity.

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Antioxidant Activity and Tumor Cell Proliferation Inhibition of Mono-di-organo- and Bis-di-organo-tin(IV) Imines

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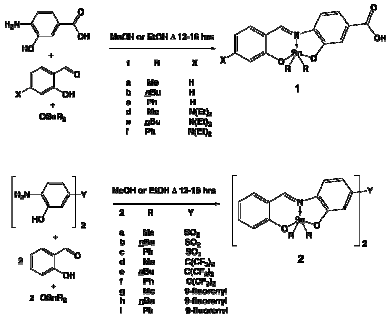
Herein were synthesized and characterized (FT-IR, NMR and MS) six mono- (**1a-f**) and nine bis- (**2a-i**) di-organotin(IV) compounds. The double condensation reactions carried in order to obtain **1a-f** and **2a-i** where three component one pot azeotropic strategies giving pure products with good yields (58-94 %). According to the spectroscopic analysis, compounds of type **1** and **2** were identified as monomeric species and present distorted trigonalbypyramidal shapes around the tin atoms (in non coordinating solvents such as $CDCl_3$). The **1** series was designed to bear only one di-organotin moiety, and free carboxylate or diethylamino fragments. This latter functionalization was performed in order to mimic zwitterionic behaviour such as that present in aminoacids and proteins important in molecular recognition trying to enhance the biological activities found in analogous systems.[1,2] The **2** series was designed to bear two di-organotin moieties and different bridging fragments. The presence of one or two di-organotin moieties in the same molecular entity is going to be correlated with the biological effect to find a linear or a synergistic effect. This has been performed since it is well known the potential of di-organotin derivatives as prototype antitumours or antioxidants.[2] Hence, DPPH scavenging and tumour cell proliferation inhibition experiments were carried out. Indeed, both types of di-organotin derivatives **1** and **2** exhibited varying degrees of activity depending on substitution and nuclearity related to the number of tin centres present. The rationale of these findings is by now under way through experimental-theoretical QSAR analysis as we have been already performed analogously.[2]



Acknowledgements
We thank support from CONACyT and UAM.

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Study of Superoxide Dismutase Mimic Manganese Complexes

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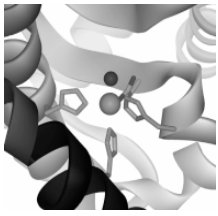
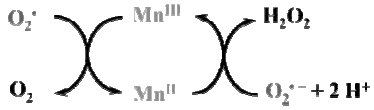
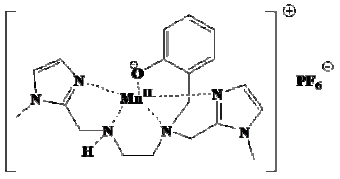
In aerobic organisms, dioxygen is used for cellular respiration through oxidoreduction pathways. They generate production of reactive oxygen species (ROS) including toxic superoxide ion $O_2^{\bullet -}$, mainly produced in the mitochondrion. Therefore, organisms have developed natural enzymatic defenses among which superoxide dismutase (SOD).[1] These metalloproteins act as the first line of defense by catalyzing superoxide dismutation into dioxygen and hydrogen peroxide. In some pathological situations, antioxidant defenses can be overwhelmed by the flow of ROS. In the literature, SOD mimic Mn complexes have been shown to display efficient cellular anti-oxidative stress activity.[2,3] We designed biomimetic Mn complexes, whose coordination sphere is inspired from the MnSOD active site and that show *in vitro* antioxidant activity.[4] A cellular model of oxidative stress has been developed in order to study its *in cellulo* activity, cellular penetration and localization. Results will be presented for $[Mn(enPI_2)]PF_6$ and for a series of complexes designed to improve its physicochemical properties, by functionalizing the parent ligand $enPI_2$ with sugar, carbon chain or peptide.



MnSOD active site



superoxide dismutation



$[Mn(enPI_2)]PF_6$ complexe

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Potency of Antimetastatic (ImH)[*trans*-$RuCl_4$(dmso)(Im)] Complex as a NO Scavenger

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The anti-tumour activity of ruthenium complexes as an alternative to platinum complexes has recently received much attention from researchers. Up to now two Ru(III) complexes have entered clinical trials: (ImH)[*trans*-$RuCl_4$(dmso)(Im)] and (IndH)[*trans*-$RuCl_4(Ind)_2$] (where Im is imidazole, Ind is indazole).[1,2] The first of them, so called NAMI-A, is of particular interest due to its antimetastatic activity. One of the hypothesis explaining activity of NAMI-A against spreading of tumors is based on interfering nitric oxide(II) (NO) metabolism *in vivo*. It has been shown that NO can promote tumour progression and metastasis by maintaining the angiogenesis.[3] NO can mediate angiogenesis directly through the sGC-cGMP (soluble Guanylyl Cyclases-cyclic GMP) pathway as well as S-nitrosylation effecting DNA synthesis, cell proliferation and migration of endothelial cells or indirectly by influencing many angiogenic factors function. The potential role of NAMI-A as NO scavenger was checked under physiological conditions (pH 7.4, 0.1-0.15 M NaCl, 37^{o}C). NAMI-A complex is not stable under such conditions, it undergoes relatively fast hydrolysis leading to stepwise dissociation of two Cl^- and one dmso ligands.[4] Moreover, taking into account the redox environment in blood serum (ascorbic acid) or in cells (gluthation) the reduction of Ru(III) to Ru(II) is expected.[4] The chemical behaviour of NAMI-A after injection into blood can strongly influence the NO scavenging properties of this complex. The formation of the ruthenium nitrosyl complexes from various derivatives of NAMI-A complex will be reported.

Acknowledgements

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Synthesis of Di-magnesium Complexes as Artificial Ribonucleases

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Ribonucleases are a class of enzymes that catalyse the hydrolysis of ribonucleic acid (RNA). RNase H is an example that has two metal ions in its active site. [1] The development of metal complexes that mimic the function and structure of artificial ribonucleases is of interest for several reasons. Due to their size, robustness and availability they are useful for studying the mechanism of ribonucleases. Also the possibility to attach them to recognition agents can make them sequence specific. Therefore they have been proposed as potential drugs. [2]

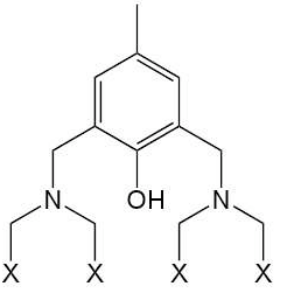

Figure 1

Several dinucleating ligands were synthesised (see figure for general structure, X = carboxylic acid or pyridine). Using those, di-metallic complexes of Magnesium were prepared and were characterised spectroscopically. The stability of the complexes was measured in the pH range 3-10. Their ability to catalyse the hydrolysis of RNA is currently being investigated.

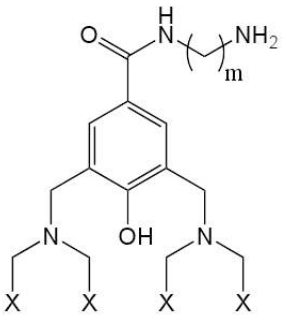

Figure 2

Derivatives of the ligands were synthesised. These were linked to di-amino chains of varying length (see fig 2 for structure m=4, 6). The amino functional group can allow it to be coupled to a recognition agent such as an oligonucleotide chain via a modified nucleobase.

Acknowledgements

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The Mg(II)-dependent Folding of Group II Intron Ribozymes Characterised by Single Molecule FRET

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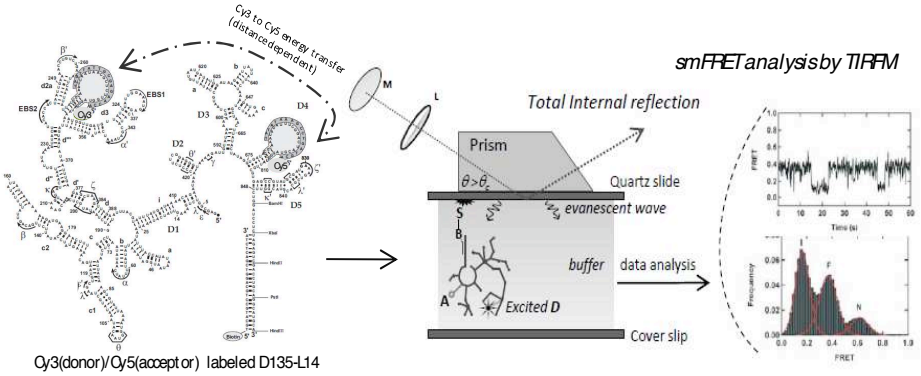
S. Cerevisiae (Sc.) ai5 is a multi-domain RNA (~900 nts) belonging to the class of group II intron ribozymes, whose folding and splicing activity are influenced by the coordination of divalent metal ions to the nucleobases [1]. We designed a derivative of this large ribozyme, named D135-L14, which is labeled with the Cy3-Cy5 fluorophore pair and preserves the dynamics and the catalytic activity of the parent ribozyme [2]. The folding of the labeled D135-L14 has been characterised by single molecule (sm) FRET using Total Internal Reflection Microscopy (TIRFM). smFRET time trajectories revealed a new paradigm folding for this construct, characterised by three FRET states whose distribution depends on the type and concentration of metal ions (i.e. Mg(II) and Ca(II)) in the system [2,3]. We now designed different derivatives of D135-L14 containing point mutations and/or domain deletions in those positions of the intron that are responsible for inter-domain dockings. Herein, we present the smFRET analysis of these derivatives where we aim to assign each FRET state and the corresponding dwell times to specific intermediates of the Mg(II)-dependent folding process.



Acknowledgements

Financial support by the European Research Council (ERC Starting grant to RKOS) and the University of Zurich is gratefully acknowledged.

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Desulfovibrio alaskensis Orange Protein: Insights on the Protein Assisted Mo-Cu Cluster Synthesis

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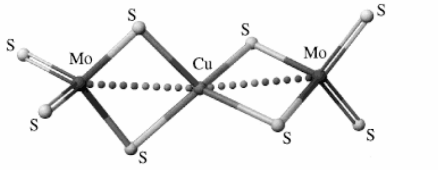
Tetrathiomolybdates (TTMs) are highly reactive and have the ability to form a wide range of heterometallic complexes between molybdenum and other metals such as iron or copper. The antagonism between TTM and copper has been exploited for the treatment of Wilson's disease and breast cancer by dietary supplement on tetrathiomolybdate.



An intense orange color protein (ORP) containing both Cu and Mo in the same cluster, was purified from *Desulfovibrio gigas.* EXAFS studies revealed the presence of quite unique mixed metal sulfur cluster $[S_2MoS_2CuS_2MoS_2]^{3-}$.[1] This protein is small monomeric protein of 11.9 kDa. The Uv-visible spectra contains two characteristic absorption maxima at 340 and 480 nm, identified as ligand to metal charge-transfer bands involving Mo, and a shoulder at 433 nm.[2].

In this work we present an ORP isolated from *D. alaskensis.* This is a low molecular mass protein of 12.8 kDa, containing a 2Mo:1Cu cluster. This ORP was heterologously expressed in *E. coli* and purified as apo-protein. The holo-protein was obtained *in vitro* using TTM and copper chloride. UV-visible titrations of (ORP+TTM) with Cu^{2+} and (ORP+ Cu^{2+}) with TTM will be presented. The influence of pH in the cluster formation is also investigated. Titrations of the two metals in the absence of ORP were performed in order to investigate the role of ORP in the cluster formation.

Acknowledgements
Financial support from Fundação para a Ciência e a Tecnolgia (PTDC/QUI-BIQ/098071/2008) is acknowledged.

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H-rich Ferritin as the Lactoferrin's Partner in the Iron Metabolism

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The structure of mammalian ferritin consists of a hollow protein shell that surrounds an aqueous cavity, capable of accommodating up to 4500 iron atoms. The shell is assembled from 24 polypeptide chains of two types: heavy H (21 kDa) and light L subunits (19 kDa). It is assumed that H subunit plays a key role in rapid detoxification of iron because it contains a catalytical ferroxidase center for rapid iron(II) oxidation, whereas L subunit is associated with iron nucleation and storage. The H/L ratio in a ferritin shell varies widely in different tissues. L-subunit-rich ferritin predominates in iron storage organs, such as the liver and spleen whereas H-subunit-rich ferritin predominates in organs of low iron content, such as the heart, brain or human milk.

Lactoferrin, a protein of the transferrin family, is a glycoprotein (80 kDa) that is widely represented in various secretory fluids, especially in human milk. Lactoferrin is one of the components of the immune system, due in part to its high iron(III) affinity, thus depriving pathological microorganisms from iron, an essential metal for its growth.

We have studied the ability for oxidizing iron(II) to iron(III) of ferritins having different H/L ratio by a simple protocol based on the iron(II) and iron(III) monitorization with ferrozine and lactoferrin, respectively. The ferroxidase activity increases with the ferritin H/L ratio. Moreover, the as formed iron(III) is more available as higher the H/L ratio is. The results are extremely clear when we compare the data obtained with the recombinant H- and L-pure apoferritins.

Therefore, following this easy and elegant protocol, we unequivocally demonstrate that H-rich ferritin has a strong ferroxidase but not iron storing activity unlike L-rich ferritin, which stores high levels of iron in making it unavailable for other processes. Conclusion: A mixture of H-rich ferritin and lactoferrin is the best way to avoid any form of free and toxic iron.

Acknowledgements

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Targeting Aquaporin Function: Potent Inhibition of Aquaglyceroporin-3 by Metal Compounds

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Aquaporins (AQPs) belong to a highly conserved group of membrane proteins present in all type of organisms and involved in the transport of water and small solutes such as glycerol, nitrate and urea.[1] The 13 human AQP isoforms (AQP0-12) are differentially expressed in many types of cells and tissues in the body and can be divided into two major groups: those strictly selective for water (called orthodox aquaporins) and those that besides water are also permeable to small solutes including glycerol (called “aquaglyceroporins”). Both groups of channels serve in many physiological functions.[2]

There is considerable potential for transferring knowledge of AQP structure, function and physiology to the clinic, and certainly there is great translational potential in aquaporin-based therapeutics. AQP-based modulator drugs are predicted to be of broad potential utility in the treatment of several diseases such as kidney diseases, cancer, obesity, glaucoma, brain edema and epilepsy. However, there are at present very few reported AQP inhibitors that are suitable candidates for clinical trials.

Here we report on the AQP inhibitory effect of a series of metal complexes based on different transition metals, comprising Ru, Pt, Ag and Au evaluated by a stopped-flow technique on cells. Among the various compounds tested, the potent (nM range) and selective inhibition of the glycerol permeability through the aquaglyceroporin AQP3 in human red blood cells by gold(III) complexes was observed.[3] Additional results, also supported by docking studies, shed light on the mechanism of inhibition of AQP3 by gold compounds. The peculiar AQP inhibition properties exerted by gold complexes might open the way to the development of new metal-based drugs as innovative scaffolds for targeted therapies or as molecular biological tools to detect protein activities in cells.

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High Valent Iron-oxo Species in Enzyme-like Catalytic Oxidative Transformations

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Iron-based enzymes, such as cytochrome P450 and Rieske dioxygenases, use O_2 to catalyse highly selective C–H and C=C oxidation reactions, key steps in the metabolic synthesis of metabolites, xenobiotic degradation and other crucial functions. At the heart of these transformations, it is proposed that the catalytic iron centre forms a highly oxidizing oxo-iron species. In P450 the active species, formally Fe(V)=O, is best described as an oxo-Fe(IV)-porphyrin radical cation,[1] but in the case of the Rieske dioxygenases family of enzymes, which lack the redox non-innocent porphyrin ligand, one postulation is that an oxo-iron(V) species is the reactive species.[2] In this work, cryospray technology allowed the temperature-controlled trapping and characterization of a Fe(V)=O species in a model system that acted as a functional model of Rieske dioxygenases. Isotopic labelling studies were used to provide accurate chemical descriptions of these species and demonstrated atom transfer, via the Fe complex, from the reagent to the product, that is the cis-dihydroxylation of an olefin. The data presented in this work allowed us to elucidate the nature of the iron-based species responsible for performing alkane hydroxylation and olefin cis-dihydroxylation in a synthetic biomimetic system.

Acknowledgements
We thank the Engineering and Physical Sciences Research Council and WestCHEM for funding, and Bruker Daltonics for collaboration. L.C. thanks the Royal Society and Wolfson Research for a merit award. M.C. and X.R. thank the Ministerio de Ciencia e Innovación (MICINN) for Project CTQ2009-08464, and Generalitat de Catalunya for Institució Catalana de Recerca i Estudis Avançats Academia Awards. M.C. thanks the European Research Foundation for Project ERC-2009-StG-239910. I.P. thanks MICINN for a PhD grant. L.C. and M.C. thank COST Action D40.

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Characterization and Release Kinetics of Silver from Dressings used in Burns Care

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Since mediaeval times, silver has been used for the treatment of chronic wounds, ulcers, burns and infections. Today several different silver dressings -composed of a polymeric scaffold impregnated with silver salts or nanoparticles- have been commercialized and are widely used in burns centres. The interest in using silver to heal wounds has increased recently as an alternative to antibiotics due to the rise of resistant bacteria. Despite this interest in their application, no systematic study of the chemical composition, release kinetics and biochemical action of these products is available.

In this work we have characterized four commercial silver dressings by scanning electron microscopy (SEM) to determine the morphology of silver distribution. In order to determine the total silver concentration by inductively coupled plasma-mass spectrometry (ICP-MS), different methods to completely mineralize the dressings where developed. Quantitative data on silver content has been obtained using both external calibration and isotope dilution analysis (IDA) and results confirm the declared concentrations ranging from 2.2 to 159 mg/g. Once the dressings were characterized, the kinetics of silver release were investigated in three different matrices of increasing complexity: (a) ultra pure water, (b) normal saline solution (0.9% m/v NaCl) and (c) human serum substitute. Ultra pure water was chosen as the simplest matrix for studying release, whereas a saline solution was chosen to chemically simulates the physiological salts presence in the wound environment. Finally, serum substitute -containing the most abundant proteins of human serum- was used to investigate how these proteins could affect silver release. After the silver release experiments, the same dressings were re-characterized using the SEM to spot any morphological modifications.

A New Approach to the Ferritin Iron Core Growth. Consequences on Iron Metabolism

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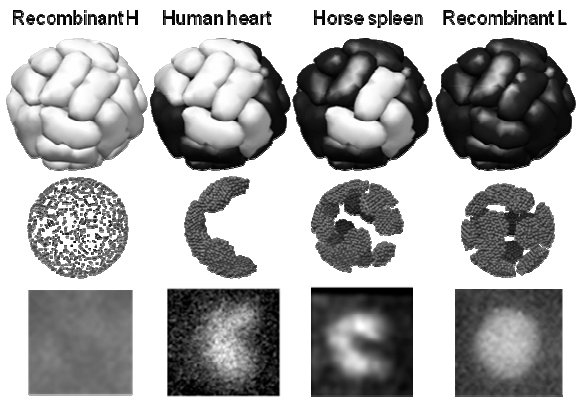
An Electron Microscopy study, in combination with modeling and image simulation, of reconstituted horse spleen ferritins (L subunit-rich) with increasing iron loading suggests a new mechanism of iron core formation. Our model is based on the fact that every L subunit contains a nucleation center and the iron core forms in the apoferritin cavity by the formula 24-n centers (where n is the number of H subunits).



This model explains i) why all ferritin particles, even the heavily loaded iron cores, are hollow, ii) why horse spleen ferritin, with 90% L chain subunits forms cores with morphologies that have slight imperfections compared to the idealized model of ferritin with 24 nucleation sites, iii) why human heart ferritin, with 67% H chain subunits forms cores with complex morphologies, far from the cubic symmetry and iv) why homopolymers of recombinant human H ferritin do not form organized cores because they lack nucleation sites, but, homopolymers of L ferritin form well-defined, electron-dense cores. The ferritin core morphology is therefore a fingerprint of the protein composition.

Acknowledgements

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New Organometallic Compounds of Platinum(II) as Antitumor Agent against Breast Cancer

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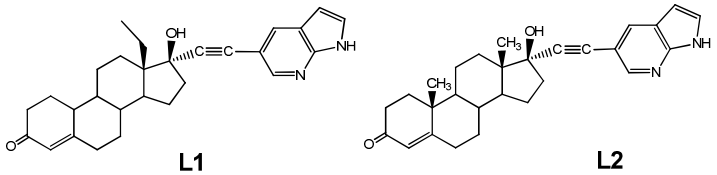
Platinum-based drugs such as cisplatin, carboplatin, and oxalilplatin are widely used against various solid tumors. However, only a tiny fraction of the platinum complex administered reaches the DNA of the cancer cell. Most of the drug binds to non-DNA biological nucleophiles resulting toxic effects.[1] Recently, new strategies have been developed to try to decrease these side effects or to increase the activity spectrum through more effective delivery of the drug.[2] Bio-molecules as sex hormones (estrogens and androgens) are of particular interest as delivery vectors because of their importance in reproductive system cancers. Natural and synthetic estrogens have been attached to a range of different organometallic and coordination units with the aim of targeting the estrogen receptors (ER).[3,4]

In this communication, we report the synthesis and caracterization of the novel levonorgestrel and testosterone modified ligands L1 and L2, through the corresponding Sonogashira coupling reactions, and some C,N-cycloplatinated bioconjugates:



$(C,N)Pt(\mu\text{-}Cl)_2Pt(C,N) + 2\,L \longrightarrow 2\,(C,N)Pt(Cl)L$

(C,N) = dmba, ppy L = L1, L2

The cytotoxic activity of the new platinum(II) derivatives has been evaluated against resistant human breast cancer cell line T47D (ER+ and AR+, being cisplatin resistant).

Acknowledgements

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Mutant Colicin E7 Proteins Reveal the Conditions for Allosteric Control of the Enzymatic Action

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Colicin E7 (ColE7) is a nuclease toxin of *E. coli*. To exert cell killing activity the domain with nuclease activity (NColE7) enters the inner part of the target cell. ColE7 belongs to the HNH superfamily of nucleases[1] possessing a 30-40 amino acids long ββα-type metal ion binding motif in their active centre. The H and N amino acids are highly conserved within the sequence $HHX_{14}NX_8HX_3H$ in the C-terminal region of bacterial colicins and pyocins. The first His acts as a general base in the DNA hydrolysis. The Asn residue plays structural role by constraining the loop by hydrogen-bonding interactions. The third conserved residue is a metal-binding His (HNH). The Zn^{2+}-ion is not required for DNA-binding, but it is essential for DNA-hydrolysis. The HNH-motif of ColE7 binds to the 3' site of the scissile phosphate in the minor groove of the DNA while the other parts of the nuclease domain provide strong, nonspecific binding within the major groove.

It was demonstrated that the R447 residue at the N terminus of NColE7 is essential for the cell killing activity.[2] The necessity of the N-terminal amino acids for the function of the C-terminal catalytic centre poses a possibility of a positive allosteric control within the enzyme. The N-terminal end of NColE7 forms a loop leaning near the active centre, and the interactions between them might be decisive for the control of the function. In this work N-terminal deletion mutants of NColE7 were expressed and the cell killing, DNA and Zn^{2+}-binding activities were investigated to better understand the role of the N-terminal loop in the catalyzed reaction and its structural effects. Gel-shift assay, synchrotoron-radiation circular dichroism fluorescence spectroscopic and mass spectrometric experiments were carried out.

Acknowledgements

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Intrinsic pK_a Values within a DNA Oligonucleotide: The Basis for Acid-Base Catalysis in DNAzymes and Ribozymes

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The mechanism of catalytic DNAs and RNAs is often believed to follow a general acid-base mechanism: The experimentally determined rates of these catalytic reactions are pH dependent and sometimes following in parallel the hydrolysis constant of the added divalent metal ion. However, neither the pK_a of a hydrated Mg^{2+} ion, nor the pK_a values of any nucleobase are close to the physiological pH range. It is unknown how complex nucleic acids achieve a perturbation of their pH active groups by two log units or more in order to perform acid-base catalyzed reactions at physiological pH. The pK_a values of the building blocks as well as the influence of metal ions or base modification on their acid base properties is well established,[1] but data on intrinsic pK_a values of nucleobases within a DNA or RNA strand longer than two nucleotides is scarce.[2-4]

Here we determine the intrinsic pK_a values of the nucleobases within the hexamer 5'-d(AGGCCT)[5] and compare our results with those of the corresponding free nucleobases. NMR spectroscopy allows us to measure intrinsic acidities and thus to quantify the effect of a given nucleobase on its neighbour. At the same time the assignment of NOEs allows us to draw conclusions on the structure of the single strand in solution.

Our results provide a first insight into how complex DNA and RNA structures influence and adjust the pK_a values of their building blocks to carry out catalytic reactions at physiological pH.

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The Role of Ferritin in the Toxicity of Iron Oxide-based Nanodrugs

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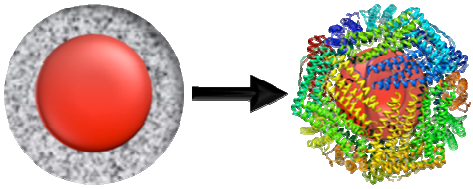
Superparamagnetic Iron Oxide Nanoparticles (SPIO) are considered the most promising nanostructures for biomedical applications, including MR imaging, image guided drug delivery and hyperthermia. However, some questions are being raised over these particles due to their long-term toxicity related to the production of toxic free iron during their biodegradation. Free iron (non-protein bound) is highly toxic due to its capacity to participate in the formation of reactive oxygen species superoxide, peroxide and hydroxyl radicals that cause damage to cell.

Here we show by Electron Microscopy (STEM-HAADF) how USPIO P904 (Guerbet, Paris), which are under clinical investigation for imaging aortic atherosclerosis, are degraded after they are taken up by macrophages at the liver and spleen, so that iron from the USPIO core is progressively incorporated into the iron-storing protein ferritin, a nontoxic form of iron, thus avoiding long-term toxicity related to free iron.



Acknowledgements
GUERBET Laboratories (Paris, France) are gratefully acknowledged for providing P904 nanoparticles. We are grateful to the MICINN (project CTQ2009-9344), Junta de Andalucía (FQM2007-2525), ANR (project INFLAM, Contract TECSAN-009-5) and EU I3 Project ESTEEM (Contract n° 026019 RII3) for financial support.

Exploring the Electronic Structure of Oxidized Blue Copper Proteins by means of ^{13}C NMR

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Blue Copper Proteins (BCPs) participate as electron transporters in numerous processes in living organisms. Copper in BCPs is equatorially coordinated to two imidazol nitrogens from histidines, and to one thiolate sulphur from a cysteine. The coordination sphere is typically completed by a methionine in axial position. The knowledge of the electronic structure of Cu(II) is a crucial issue about the stabilization of this redox state in these systems and, hence, on both the thermodynamics and the kinetics in BCPs.

Nuclear Magnetic Resonance is one of the most powerful techniques for the study of the paramagnetic state of soluble proteins in solution. The hyperfine shift provides information on how the unpaired electrons are delocalized onto the ligands. Some of us have been successful in applying exchange spectroscopy with ^{13}C in the CuA center of Cytochrome c oxidase.[1] In this last system, magnetic coupling between the two existing copper ions (formally with a redox state +1.5 each) allows copper ions relax faster, providing relatively narrow ^{13}C signals that facilitate the assignment. One further step is the assignment of ^{13}C signals in mononuclear Cu(II) systems (with a net unpaired electron), such as occurs in the BCPs family. We have concretely studied rusticyanin, azurin and plastocyanin. For some BCPs, we assigned the ^{1}H NMR signals corresponding to the ligands of the Cu(II) ion in the past.[2] Now, we have extended the assignment to ^{13}C nuclei. The complete heteronuclei assignment has allowed us to improve the knowledge of the unpaired spin delocalization onto the ligands and, hence, of how Cu(II) interacts with them. We present here some singular and interesting conclusions about this.

Acknowledgements

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Phosphate Monoester Hydrolysis by Zirconium(IV) Complexes

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Phosphate monoester hydrolysis is one of the most fundamental reactions in biology. With the half-time for attack by water on alkyl phosphate dianions being in the order of 10^{12} y, phosphatases that are involved in cell signalling and regulation are among the most efficient enzymes known.[1] Metal-catalyzed phosphate ester hydrolysis has attracted significant interest over the last decades and much effort has been devoted to designing metal complexes that mimic the catalytic function of metallophosphatases.[2] However, work has largely focused on phosphate diester hydrolysis and relatively few examples of metal complexes that hydrolyze phosphomonoesters have been reported. Since hydrolysis reactions of phosphomono- and diesters often take place by different mechanisms, there is a great need to study catalysts for monoester hydrolysis. Zr^{4+} ions are among the most efficient catalysts for phosphodiester hydrolysis.[3] However, the aqueous chemistry of Zr^{4+} is dominated by the formation of polyhydroxo species and precipitation at physiological pH hampers catalytic activity of Zr salts. Here we report mono- and dinuclear Zr complexes that bring about rapid hydrolysis of the phosphate monoester p-nitrophenyl phosphate, NPP, at pH 7. (Table 1). Enzyme-like Michaelis-Menten behaviour is observed. Remarkably, Zr complexes of L^1 and L^2 are approximately two orders of magnitude more reactive towards NPP than towards the phosphate diester bis(p-nitrophenyl)phosphate.

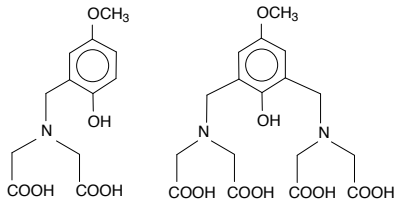

Table 1. Kinetic and thermodynamic data of Zr(IV)-mediated hydrolysis of NPP

	k (M^{-1} s^{-1})	k_{cat} (s^{-1})	$1/K_M$ (M^{-1})	$\Delta S^{\ddagger}$ (J K^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	E_a (kJ mol^{-1})
$[ZrL^1]^+$	0.042	2.27 x 10^{-5}	806	-92.0	67.3	69.9
$[Zr_2L^2]^{3+}$	0.17	1.10 x 10^{-4}	556	-75.6	71.4	73.9

pH 7.0; 50 mM HEPES; 25 °C, I = 0.1 M (NaCl)

Acknowledgements

Financial support from Science Foundation Ireland is gratefully acknowledged.

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Bioinspired Investigation on Complexes of Desferrioxamine B, Desferricoprogen and their Model Ligands with Mn(II) and Mn(III)

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Manganese is involved in numerous biological processes.[1,2] Nowadays, the interaction between manganese and hydroxamates came also to light: (i) Hydroxamate based compounds inhibit metalloenzymes including manganese containing ones. (ii) Given its five unpaired d-electrons, long electronic relaxation time, fast water exchange and its lower toxicity compared to Gd(III), Mn(II)-hydroxamate complexes are candidates for MRI contrast agents. (iii) Competition between Mn^{3+} and Fe^{3+} in the siderophore-mediated iron uptake is assumed.[3]

Only a few equilibrium data are known for Mn(II)/(III) – hydroxamate complexes. That is the reason, why investigation of manganese complexes formed with selected mono-, di- and two trihydroxamate-based siderophores, desferrioxamine-B and desferricoporogen, was perfomed under anaerobic and aerobic conditions by pH-metry, UV-visible spectrophotometry, relaxometry, ESI-MS and CV.

Maximum three hydroxamates were found to coordinate to the Mn(II) ion, but the presence of water molecules in the inner-sphere was suggested even in the tris-chelated complexes. Moreover, prototropic exchange processes were found to increase the relaxivity of the Mn(II)-siderophore complexes at physiological pH.

Air oxygen became an oxidizing agent of Mn(II) under basic condition (pH>7.5) in all studied complexes, but the oxidation became stoichiometric only if the ligand is a siderophore. The formed Mn(III)-complexes did not show any degradation for weeks, but a peculiar difference was found between both the stability and redox behaviour of the complexes with DFC and DFB. The former was more stable and only its reduction to the corresponding Mn(II) species was reversible.

Acknowledgements

OTKA-NKTH CK77586 and TÁMOP 4.2.1./B-09/1/KONV-2010-0007 supports are acknowledged.

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Self-assembly of Metalloporphyrins: first TPP-bipy Coordination Polymer with Co^{II} (TPP = meso-tetraphenylporphyrin and bipy = 4,4´-bipyridine)

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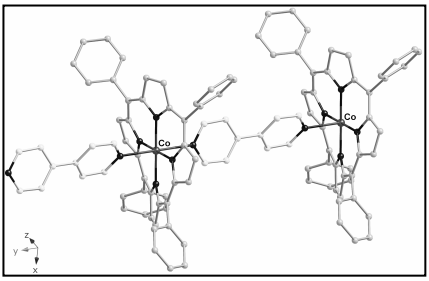
Supramolecular entities based on self-assembly of metalloporphyrins are paradigmatic examples of the great efficiency of the nanodevices used by natural systems in photosynthesis, oxygen transport, electron transfer and catalysis.[1]



Obtaining supramolecular entities may be approached by different strategies of synthetic design. One of them consists on the use of external dipyridyl ligands to assemble the metallated porphyrin units, so the range of compounds that can be used is endless. In this context, our research group is working with different combinations of organic ligands and metalloporphyrins,[2] and the work herein presented corresponds to the compound $[CoTPP(bipy)]\cdot[CoTPP]_{0.22}\cdot TPP_{0.78}$ (TPP = meso-tetraphenylporphyrin and bipy = 4,4´-bipyridine), obtained by solvothermal synthesis.

Its crystal structure consists of chains of alternating [CoTPP(bipy)]·octahedra where bipy molecules are on the axial positions. Within the voids between the parallel chains, isolated [CoTPP]·monomers and TPP units are located.

So far, very few compounds with TPP and bipy have been described, just one of them[3] being a real 1D coordination polymer. It is also remarkable that, as far as we know, this is the first structure with these ligands based on Co.

Acknowledgements

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The Influence of Substitution at the Ligand on the Properties of Indoloquinoline-based Ruthenium- and Osmium-complexes

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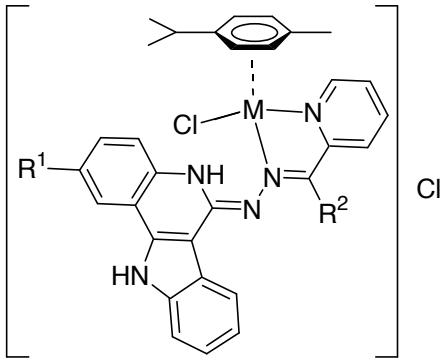
Several indoloquinolines have been shown to exhibit a quite promising activity against human cancer cells. By complexation of indoloquinolines with an ethylene-diamine chelating unit to ruthenium and osmium arene moieties, the properties of this heteroaromatic system could be strongly altered. However, the resulting complexes were relatively unstable in biological media.[1] By replacing the sp^3-hybridised N-donor atoms of the chelating ethylene-diamine unit by sp^2-hybridised ones of the pyridine enamine unit stability towards hydrolysis could be improved significantly, preventing the ligand dissociation from the metal-arene moiety.[2]



R^1 = H, F, Cl, Br, CH_3, NO_2
R^2 = H, CH_3
M = Ru(II), Os(II)

Herein, we report on the synthesis and thorough characterisation of 16 ruthenium- and osmium-arene complexes where the indolo-[3,2-*c*]quinoline ligand is substituted in position 2. The complexes were studied by X-ray diffraction, spectroscopy (IR, NMR) as well as ESI-MS and TG/DTA. Stability towards hydrolysis was monitored by UV–vis spectroscopy. The biological activity was tested on three different human cancer cell lines (A549, non-small cell lung cancer; SW480, colon adenocarcinoma; CH1, ovarian carcinoma) and yielded IC_{50} values between 0.19 and 10 μM.[2]

Structure-antiproliferative activity relationships are discussed.

Acknowledgements
Financial support from the FWF (Austrian Science Fund, Project Number P22339) is kindly acknowledged.

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Comparative Studies of Manganese SOD Mimetics: Interactions with Phosphate Can Be Crucial for their Physiological Application

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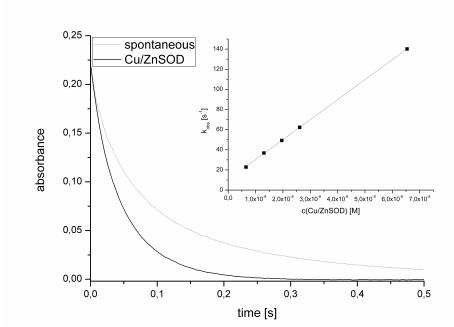
Many mechanistic studies on manganese superoxide dismutase mimics (SODm) have been performed and reviewed in the literature.[1,2] Different direct methods (pulse radiolysis and stopped-flow analysis) and indirect methods (e.g. cytochrome-c assay or NBT assay) are used to determine the catalytic rate constant of SODm, however, all these methods contain various flaws. Additionally, different combinations of buffers (e.g. Hepes or phosphate), conditions and pH values are used so that results are difficult to be compared directly.

Therefore, we have developed a new diode array stopped-flow method and applied it for the comparative study of catalytic activity of putative manganese SOD mimetics known in the literature and free manganese ions under physiological conditions.[3]



These results demonstrate that phosphate anions play an important role in the actual activity of manganese SOD mimetics. Due to the fact that Mn(II) cations possess SOD activity that is comparable with those of other mimetics in the presence of phosphate, in the future design of the SOD mimetics for potential therapeutic application needs to include investigations of their possible interactions with $H_2PO_4^-/HPO_4^{2-}$ anions. Furthermore, based on these results one can envisage the concept where even SOD inactive manganese complexes could turn into, *in vivo,* an effective catalyst upon its de-complexation in the phosphate containing physiological environment. In this scenario the ligand design should be directed to ensure delivery of the manganese ions to the desired site for maximum physiological benefit.

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[3] *Submitted*

Distorted Dicopper Complexes as a Biomimetic Model of Tyrosinase

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Tyrosinase (Tyr) contains a Type III dicopper site, catalyzing *o*-hydroxylation of a residual phenol ring of L-tyrosine in biological systems. In the deoxy-form, the reduced dicopper (I) site reacts with dioxygen to form a μ-η^2:η^2-peroxo-dicopper(II) species in the similar mode to that of oxyhemocyanin. The μ-peroxo dicopper(II) complexes, mimicking Type III copper sites, have been studied, giving important findings for understanding the biological systems.[1] In our studies of dicopper-O_2 complex systems using (–)-Sparteine and α-isosparteine (*Sp* and α*Sp*),[2] a organic solvent solutions of the precursor Cu(I) complex, [Cu^{I}(α*Sp*/*Sp*)$(CH_3CN)_x$]SbF_6, (**1a**/**1b**) was bubbled with O_2 to generate $Cu_2(\mu\text{-}O)_2$ species at -80 °C. To this brown colored solution of **1a**, salts of benzoate (Bz)/ 2,3,5,6-tetramethyl-4-trifluoromethyl-phenolate (TFTP) were added, and the solution color changed to dark green, showing two characteristic absorption bands centered at λ_{max} = 372, 745 nm and λ_{max} = 379, 607 nm for μ-peroxo species, [Cu^{II}_2(α*Sp*)$_2$(μ-η^2:η^2-O_2)(Bz)]$^+$ (**3**) (Fig. 1) and **4**, respectively. These μ-peroxo species, **3** and **4**, are also directly formed from **1a** in the presence of Bz/TFTP, and these formation rates were accelerated with the exogeneous ligands. Addition of active *o*-/*m*-methyl substituted phenols to **1b** gave corresponding catechols in the high yields, and **1b**-carvacrol system also exhibited an enantioselective hydroxylation.[3] These detailed studies will give mechanistic insights for competitive inhibition and phenolase activity in Tyr.

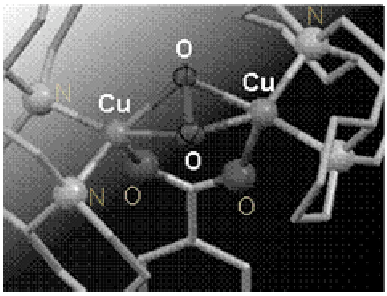

Figure 1. Structure of the *bridged-butterfly*-type μ-peroxo dicopper(II) complex, **3**.

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Copper-containing Carbosilane Dendrimers as Antiviral Agents

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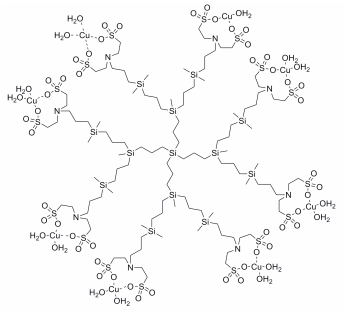
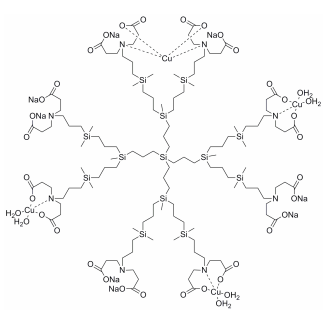
Copper (II) complexes of polyanionic-terminated carbosilane (CBS) dendrimers have been recently synthesized in our research group as new antiviral agents against HIV. Polyanionic compounds can inhibit HIV by interfering in the first steps of the virus replicative cycle. These steps are also excellent points of attack for some transition metal complexes.[1] Therefore, by combination of both strategies, these compounds have been designed where antiviral properties are synergic.[2]

Previously synthesized CBS dendrimers with carboxylate and sulfonate groups in their periphery were used as precursors for the synthesis of metal complexes, in different metal:dendrimer ratios. First and second generation dendrimers, as well as the ones based in triethylsilane named as generation zero, were complexed with copper(II) cations to provide water soluble copper(II)-containing dendrimers. Only when using high metal/dendrimer ratios for carboxylate dendrimers charge compensation occurs and the complexes were insoluble. The resulting water-soluble complexes were characterized by UV-Vis and EPR techniques, and evaluated their biocompatibility and their antiviral properties against HIV.





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This work has been supported by FPU-MEC Grant

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$[Cu(thp)_4][PF_6]$ as an Effective Therapeutic Agent for the Treatment of Solid Tumors, including Refractory Tumors

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Among the variety of copper-based compounds synthetized so far for application in pharmaceutical studies, phosphine copper(I) compounds of 'CuP_4' stoichiometry represent a class of promising candidates as antitumor agents.[1] The monocationic copper(I) complex $[Cu(thp)_4][PF_6]$ (CP), highly soluble and stable in water solution, has been designed and investigated with the aim of discovering an alternative metallodrug to cisplatin (CDDP) showing advantage either in terms of overcoming of the drug resistance phenomenon and in terms of lower toxicity.[2]

The in vitro antitumor activity evaluation on a wide panel of human cancer cell lines (including the vast majority of human cancers of the NCI screening panel) revealed an impressive efficacy of CP, being up to 50-fold more cytotoxic than CDDP. Tested against a panel of colon carcinoma cell lines corresponding to different stages of disease progression and endowed with different degree of sensitivity to CDDP or oxaliplatin (OXP), CP elicited IC_{50} values up to 15 and 35-fold lower than OXP and CDDP, respectively. Interestingly, evaluating the cytotoxic activity of CP on human non-tumor cell lines, selectivity index (SI) values about 20- and 3-fold higher than those obtained with CDDP and OXP have been recorded. The characterization of CP-induced effects in cancer cells revealed the triggering of a non-apoptotic programmed cell death (PCD) defined as paraptosis (type III B cell death) likely due to the inhibition of proteolytic activities of 26S proteasome.

By in vivo animal tests the toxicity profile of CP has been explored after acute and repeated dose administrations. Studies on the antitumor efficacy of CP in a model of solid tumor, the syngeneic murine Lewis lung carcinoma (LLC), showed that CP was safe at a therapeutically effective dose, it showed a favorable pharmacokinetic profile and it was therapeutically effective against the murine solid tumor model. The examination of CP biodistribution characteristics in tumor-bearing mice demonstrated that the copper drug achieved significant and selective accumulation in the solid tumor mass.

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Correlation between DNA Studies by Optic Spectra and AFM Images

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Developments on the field of inorganic and organometallic compounds for anticancer applications as lead to several cases of success.[1] Promising results have been reported in the literature regarding numerous metal-based compounds, and in recent years organometallic complexes have conquered a relevant position as potential effective antitumor agents.

Particularly, our group has been interested in half-sandwich ruthenium compounds which had already revealed very promising cytotoxic results in the micro- and nanomolar range against several cancer cell lines.[2] These good results lead us to extent our synthesis to the preparation of new half-sandwich iron compounds for their evaluation as anti-cancer drugs. Several new [FeCp(dppe)L] complexes (Cp = Cyclopentadienyl; dppe = 1,2-Bis(diphenylphosphino)ethane) with L as N-hetero-aromatic ligands functionalized with one or two nitrile groups were already synthesized and revealed promising anti-proliferative activity against leukemia (HL-60 cells).[3] Interaction studies with DNA were also performed by AFM and optic spectroscopy. The present communication reports our attempts of correlation between these two techniques having in mind the results of the anti-proliferative assays as well. The finding of preliminary tests such as for example studies by optic spectroscopy are of prime importance to screen the potential of drugs in this field, regarding the very high costs and the time consuming techniques associated with more sophisticated studies.

Acknowledgements

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Polyamine Anionic Metallodendrimers as dual Antiviral Agents

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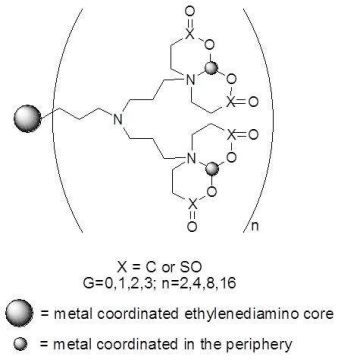
Dendrimers are highly branched monodisperse nanostructures, used in the biomedical field as drug carriers or therapeutic agents. Polyanionic dendrimers have been presented as antiviral agents, especially against HIV.[1] The antiviral action can be improved by including transition metal ions in their structure, as some metal complexes can interfere in the initial events of the replicative cycle,[2] or in latter steps.

Water soluble nickel, cobalt, copper and zinc metallodendrimers were prepared from polyamine dendrimers containing an ethylenediamino core and a polyanionic periphery. Their characterization was carried out by different techniques, such as nuclear magnetic resonance, electronic paramagnetic resonance, elemental analysis, and UV-Vis spectrophotometry. At concentrations lower than 5 μM, zero generation metal complexes were biocompatible in PBL cells, and the inhibition assays for the HIV replication showed that the metal complexes have a therapeutic-preventive behavior, as they inhibit the replication in previously infected cells and also in cells treated after the infection.[3] For higher generations, preliminary studies point to a most effective action.



In conclusion, well characterized polyamine anionic metallodendrimers are presented as effective antiviral agents, with a dual preventive – therapeutic action.

Acknowledgements

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Adenine-copper(II)-thiosemicarbazone System: Structural Studies and Biological Implications

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DNA macromolecules are among the numerous biological targets of thiosemicarbazone metal complexes.[1,2] Recent studies on copper(II) derivatives of pyridine-2-carbaldehyde thiosemicarbazone (HL) have revealed their behaviour as groove binders and a preference for the linkage to adenine-thymine fragments. [3] Taking into account that no thymine compounds are obtained at physiological pH values, [4] one can conclude that binding to adenine (Hade) is essential to understand the interaction between DNA and such thiosemicarbazonecopper(II) complexes. Thus, we describe here the reaction between copper(II) perchlorate, Hade and HL together with the molecular structures of $[\{CuL(ClO_4)\}_2]$ (Figure 1), $[Cu_2(ade)(Hade)_3(H_2O)_2](ClO_4)_3{\cdot}8H_2O$ (Figure 2) and $[\{CuL(Hade)\}_2](ClO_4)_2{\cdot}2H_2O$ (Figure 3). As a conclusion, the N(3) atom of adenine could play a key role in the binding of these complexes to DNA.

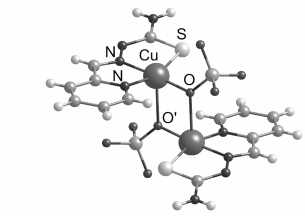

Figure 1

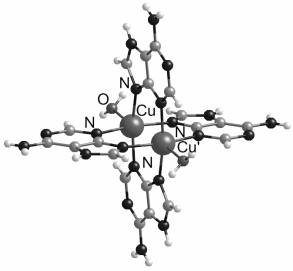

Figure 2

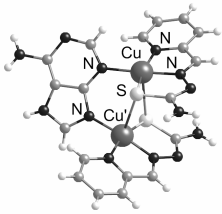

Figure 3

Acknowledgements
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New Strategies for Rational Design and Synthesis of Potential Metal-based Antitumour Agents

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The metal coordination compounds with so-called "slow" kinetics of the ligand exchange-reactions, comparable with the rate of the cell division processes, often are effective in killing of cancer cell lines.[1] This is particularly characteristic for the complexes of platinum and ruthenium. The interest to this class of heavy-metal compounds has its origin in the 1960s, with the landmark discovery (Rosenberg) of the antitumour properties of cisplatin. Today, cisplatin and structurally related platinum-based drugs represent a unique and important class of antitumour agents. Among them, the most potent antitumour agent, cisplatin has limited clinical use due to its side-toxic effects and manifestation of drug resistance. The incapacity of cisplatin-like drugs to overcome the disadvantages of the prototype has spurred the investigations in the field of synthesis of new metal-based anticancer agents with different mechanisms of action.

This study aims to analyze several new approaches towards the design and synthesis of non-classical platinum analogues. They are developed on basis of knowledge for the molecular structure, kinetic behavior and thermodynamic stability of the platinum coordination compounds. In the structural design, different strategies were applied: 1) using of ligands, which ensure preferably accumulation in the neoplastic tissue or compounds with structures resembling biomolecules (such as hematoporphyrin IX, 3-amino-2-chloropyridine, 2,2'-dipyridylketone, etc); 2) synthesis of high oxidation octahedral platinum complexes with variables axial ligands; 3) substitution of platinum with metals such as ruthenium, palladium, gold, etc in isoelectronic complexes; 4) applying of stable complexes of metals in unusual oxidation states, such as Pt^{III}, Ru^{IV}, Pd^{III}, Au^{II}, etc in. Thus, series of novel complexes with antineoplastic properties have been synthesized. They proved to exert concentration-dependent antiproliferative effects against a spectrum of cell lines representative for some important types of neoplastic disease in humans.[2]

Acknowledgements

Financial support from the National Scientific Fund (Project – DDVU-02/66-2011), Bulgarian Ministry of Education, Youth and Education is acknowledged.

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Heterologous Overexpression in *E.coli* of Recombinant Fuscoredoxin Proteins from *Desulfovibrio desulfuricans* (ATCC27774)

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Fuscoredoxin is a unique iron containing *protein* of yet unknown function originally discovered in the sulfate reducers of the *Desulfovibrio* genus. This protein contains two type of [Fe-S] centres: a cubane [4Fe-4S] cluster and a mixed oxo- and sulfide-bridged 4Fe cluster unique in nature.[1,2]

In this work were overexpressed in large scale, in *E.coli*, two recombinant Fuscoredoxin proteins from *Desulfovibrio desulfuricans* (ATCC 27774). One of the proteins, is constituted by the complete amino acids chain (FR1), while the other lacks the *N*-terminal region (FR2). This way, the FR2 protein only contains the mixed rare centre since the cubane is linked to the *N*-terminal region. This strategy makes possible to study and characterize individually this unique centre. Both proteins, were overexpressed fusioned with the GST-*tag* protein and purified by affinity chromatography. These proteins, were characterized by standard biochemical techniques and by UV/Vis spectroscopy. The iron content in the protein samples was also determined by ICP-AES spectroscopy. Both proteins showed to incorporate the metal ion however is still necessary to optimize the growth conditions to improve the amount of holoprotein produced.

Acknowledgments

We would like to acknowledge to FCT-MCTES for financial support.

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Biological and Physico-chemical Evaluation of new Pyrazole Complexes with Cu(II)

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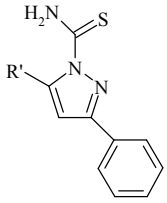
The physico-chemical and biological characterisation of three novel complexes of Cu(II) with pyrazole ligands have been performed. UV-spectra show that all complexes are stable in aqueous solution for more than 24h. The lipophilicity of the complexes and the ligands alone was measured by the shake flask method in *a n*-octanol/water system and expressed as partition coefficient log P.[1,2] The log P_{oct} value was the highest for $L1CuCl_2$ complex. In addition we performed toxicity tests that show that the $L1_2CuCl_2$ complex possesses a higher cytotoxic activity against squamous cell carcinoma (HNSCC) UMB-SCC-**745** and UMB-SCC-969, HeLa as well as human breast adenocarcinoma MCF7 adherent cell lines compared to other related complexes. The cytotoxicity against HeLa and MCF7 cells was better than the cytotoxicity of cisplatin. Annexin V/propidium iodide/Hoechst staining of the various cell lines indicate that the $L1CuCl_2$ complex is able to induce apoptosis in HeLa cells. To understand the effect of our complexes on DNA we tested their cleavage ability by agarose gel electrophoresis. The $L2CuCl_2$ complex nicks the DNA Form I into Forms II and III meaning that probably this complex is able to cut the dsDNA strand at two positions. CD spectroscopy indicate that all our tested complexes possess only moderate influence on the geometry of dsDNA.



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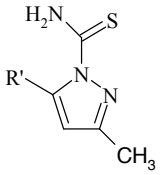

L2

Acknowledgements

Financial support from the Scientific Exchange Programme between Switzerland and the New Member States of the EU (Sciex-NMSch by the CRUS) and the University of Zurich is gratefully acknowledged.

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Bioactive Nickel(II) and Cobalt(II) Complexes of Mannich Bases derived from 5-*tert*-butylpyrocatechin

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The health problem demands searching and synthesizing a new class of antimicrobial compounds effective against pathogenic microorganisms that developed resistance to the antibiotics used in the current regimen. Functional modifying certain biologically active substances and some of the known pharmaceuticals by binding them up into metal complexes in order to increase their pharmacological effect appears to be a worthwhile idea. Mannich bases have been reported as potential biological agents. Various phenolic derivatives have been reported to possess antioxidant, antifungal, antiviral, neurotropic, and nootropic properties. Prompted by these observations, the complexation of Mannich bases derived from 5-*tert*-butylpyrocatechin with bioactive metal ions, such as Co(II) and Ni(II), was studied by potentiometric titration method, and the overall stability constants of the metal complexes, varying in the range $2.1 \cdot 10^{10} \div 1.1\ 10^{13}$, were calculated. Co(II) and Ni(II) complexes with 5-*tert*-butyl-3-(pyrrolidine-1-ilmethyl)-1,2-dihydroxybenzene (**I**), 5-*tert*-butyl-3-(piperidine-1-ilmethyl)-1,2-dihydroxybenzene (**II**), 5-*tert*-butyl-3-(azenone-1-ilmethyl)-1,2-dihydroxybenzene (**III**), 5-*tert*-butyl-3-(morpholine-1-ilmethyl)-1,2-dihydroxybenzene (**IV**), and 5-*tert*-butyl-3-(methylpiperazine-1-ilmethyl)-1,2-dihydroxybenzene (**V**) have been synthesized and characterized by means of elemental analysis, TG/DTA, FT-IR, ESR, UV-Vis spectroscopy and conductivity measurements. According to the data obtained the synthesized complexes have the composition described by the general formula ML_2. The low values of the molar conductivity in acetonitrile for all the complexes (Λ_{mol}=7.7÷19.8 $\Omega^{-1}cm^2mol^{-1}$) indicate their being essentially non-electrolytes in this solvent. The compounds **I-V** coordinate in their singly deprotonated forms in an *O,N*-bidentate fashion. The Co(II) and Ni(II) complexes are characterized by square planar geometry of their coordination cores MO_2N_2. These compounds were found to have a moderate inhibition activity against Gram-negative bacteria, while Gram-positive ones are more sensitive to Mannich bases and their metal complexes. A high level of activity of all the complexes under study against *Staphylococcus aureus*, *Sarcina lutea* and *Mycobacterium smegmatis* should be noted. These observations show that the majority of the metal complexes investigated are more active than the respective Mannich bases.

Description of a Novel Ruthenium Antitumor Compound: [Ru(η^6-*p*-cymene)(1,10-phenanthroline-5,6-dione)][PF_6]

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The interest in metal antitumor compounds has rocketed in the last decades, with platinum giving way to other metals. Among these, ruthenium presents some attractive advantages, having the ability to mimic iron, and therefore being less toxic to the organism. Its oxidation states (Ru^{II}, Ru^{III}) available under physiological conditions further modulate its mechanism of action.[1] To the present day, only two ruthenium compounds, NAMI-A and KP1019, have entered clinical trials. Recently, organometallic ruthenium (II)-arene compounds have been researched,[2] showing considerable antiproliferative effect *in vitro* and *in vivo*. It is also noteworthy that some ruthenium compounds could have antimetastatic action. Finally, the biological targets are still being discussed, and could include not only DNA but several proteins.

The compound described here is an organometallic ruthenium(II) complex with "piano stool" structure. The metal is coordinated to an arene ligand (p-cymene), one chloride ligand and a bidentate nitrogenated ligand (1,10-phenanthroline-5,6-dione). It has been chemically characterized by spectroscopic techniques and elemental analysis. Its interaction with DNA has been studied by means of atomic absorption (yielding the amount of metal bound to DNA), agarose gel electrophoresis, circular dichroism, atomic force microscopy and viscosity measures. Its interaction with the protein ubiquitin has also been assessed. Finally, *in vitro* cytotoxicity in human acute promyelocytic leukemia cell line HL-60 has been evaluated. The reported complex has been found to interact with DNA, with intercalation of the nitrogenated ligand. Some tests also suggest the presence of hydrogen bonding, and electrostatic interaction should not be ruled out, giving the cationic nature of the metal moiety. The compound also binds to ubiquitin, without changing the protein conformation. The IC_{50} values are similar to the ones found for cisplatin and other previously described ruthenium compounds in HL-60 cells.

Acknowledgements

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Hydroxamic Acids and Oximes for Bioinorganic Applications and Modelling

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Hydroxamic acids and oximes are multi donor ligands which biological activity stems from complexing capacity towards various metal ions. Diversity of coordination modes of these functions with metals makes them very promising ligands in coordination and bioinorganic chemistry.

Main directions in hydroxamic acids/oximes research undertaken by us in recent years include [1-3]:

- development of novel highly efficient and selective chelating agents with mixed donor functions;
- study of hydroxamic acids as metaloenzymes inhibitors aimed in development of novel pharmaceuticals;
- investigation of oximes as new models of polymetallic active sites of redox enzymes;
- use of hydroxamate ligands for preparation of high nuclearity discrete coordination compounds and coordination polymers as promising objects for molecular magnetism, supramolecular chemistry and metal complex catalysis.

Because recently there is a growing interest in the molecular design and coordination chemistry of structurally modified ligands containing various coordination sites, we have designed and studied the coordination ability of ligands based on mixed functional groups, possessing apart hydroxamic/oximic group other functions like amide or pyridine. The predictive information obtained in our studies will guide the strategy of synthesis of new metal chelators for biological purposes.

Acknowledgements

E.G.-K. thanks the Polish Ministry for Science and Higher Education for the support.

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Design of a Novel Artificial Nuclease based on the HNH

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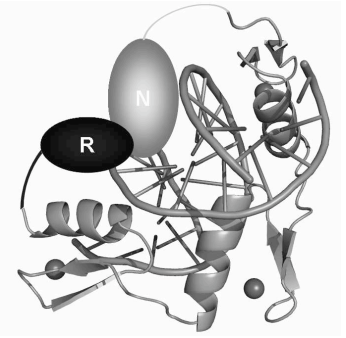
DNA targeting within the cell - induced by specifically positioned double-strand cleavage in DNA near the mutated sequence - can be applied for gene therapy of monogenic diseases. For this purpose highly specific artificial nucleases are needed. Zinc-finger nucleases are the most prominent examples of such enzymes. However, their minor cytotoxicity must be avoided in therapeutic applications.[1]

The HNH motif is a conserved $\beta\beta\alpha$-metal-binding structure found in more than 3000 proteins.[2] It functions together with positively charged amino acid side-chains, which are distant in the amino acid sequence, but close in space to the active centre. As such, it may serve as a replacement for the FokI nuclease domain in the novel artificial nucleases.



Our project is divided into three parallel parts: (1) To design a specific nuclease, the target DNA sequence shall be determined. For gene therapy applications this target sequence has to be identified within a DNA as large as a human chromosome. A method is being elaborated for a general diagnosis of most of the mutations causing the Duchenne Muscular Dystrophy. (2) We contributed to the design of specific DNA binding zinc finger proteins. (3) The function of the catalytic zinc(II)-containing HNH motif at the C-terminus of Colicin E7 poses the possibility of a positive allosteric control and the conditions for this are being studied in a novel artificial metallonuclease.

Acknowledgements
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Complexes of Macrocyclic Conjugates with Rigid Scaffolds for Cell Labeling

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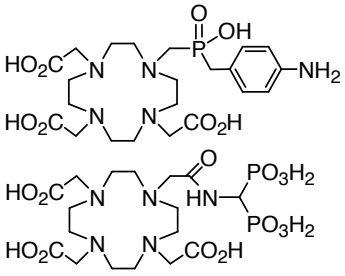
There is rising interest to track a fate of transplanted cells in the body by non-invasive techniques. The method of choice is magnetic resonance imaging (MRI) do its high spatial resolution. But this method suffers from a rather low sensitivity. Thus, the contrast agents (CA) must be used and they have to have a high efficiency. CA's producing signal enhancement (positive CA's) are generally preferred. These CA's are mostly based on Gd^{3+} complexes.



DOTA derivatives with one phosphinic acid pendant arm were bound to rigid cyclodextrin core to produce CA's endowed with a very high relaxivity. The conjugate was also modified with fluorescein leading to the MRI-fluorescence bimodal probe used for labeling of Langerhans islets or stem cells.[1] Complexes of DOTA derivatives with phosphonic or bis(phosphonic) acid groups in the side chain were used for modification of nanocrystalline TiO_2. It was proved that bis(phosphonate) group gave very stable surface modification with no leaching of the anchored molecules.[2] The MRI-fluorescence bimodal probe (with a rhodamine dye) was also prepared and used for successful labeling of the same cells.[3]

Acknowledgements

Financial support from the Ministry of Education of the Czech Republic (Grants MSM0021620857 and SVV 261206/2010) and the Grant Agency of the Czech Republic (grant no. 203/09/1056) is acknowledged. This work was carried out in the framework of COST D38 Action (MŠMT OC179).

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Time-resolved Spectroscopic Analysis of Reaction Intermediate Species in a Non-heme Iron(II) Complex and Perbenzoic Acid System

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Non-heme iron oxygenases would form high-valent iron(IV)-oxo intermeditate species in the catalytic reaction, such as “compound J“ in α-ketoacid-dependent Taurine/α-ketoglutarate dioxygenase (TauD).[1] Generally, the coordination structures of mononuclear non-heme iron centers are not stable on the basis of Crystal Field Theory, but also distorted and unsaturated, and the less covalent coordination bonds are elongated.[1] In this study, we performed UV-vis and IR spectral measurement of a reaction between a distorted iron(II) complex and *m*-choroperbenzoic acid (*m*CPBA), using rapid-mixing and rapid scanning method

The crystal structure of $[Fe^{II}(Sp)(m\text{-Cl-OBz})_2]$ (Sp = (–)-Sparteine) had a twisted and unsaturated coordination geometry due to binding of Sp. The reaction of $[Fe^{II}(Sp)(m\text{-Cl-OBz})_2]$ with *m*CPBA gave an unstable intermediate species, exhibiting characteristic absorption bands at 420 nm and 870 nm, rapidly decayed in the short life time (k_{obs} = 0.43 s^{-1}, $t_{1/2}$ = 1.6 s, 233 K). These bands appear to be similar to thoses of $[Fe^{IV}(O)(TMG_3tern)]$ (TMG_3tern = 1,1,1-tris{2-[N2-(1,1,3,3-tetramethylguanidino)]ethyl}amine) in the high-spin state.[2] IR spectral changes in this reaction were also measured and a peak at ν = 830 cm^{-1} was observed in the lower energy region, which would be attributed to Fe=O stretching vibration. This value is similar to those of Fe^{IV}=O intermediate species, J (821 cm^{-1})[1] and $[Fe^{IV}(O)(TMG_3tern)]$ (843 cm^{-1}).[2] In this study, we succeeded in monitoring a short lived intermediate species of a distorted iron(II) complex and *m*CPBA system, using the time-resolved spectroscopic methods.

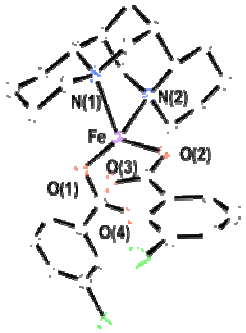

Figure 1. Crystal structure of $[Fe^{II}(Sp)(m\text{-Cl-OBz})_2]$

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Modulation of DNA Binding by Reversible Metal-controlled Molecular Movements in Three Novel Scorpiand-like Ligands

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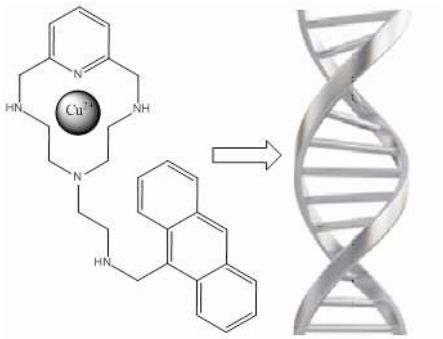
Scorpiand polyamines are compounds consisting of a "fixed" aza-macrocyclic core appended with an arm containing additional amine donor groups. They were prepared by Lotz and Kaden for the first time[1] and the main feature is that the pendant arm is flexible enough to fold and bind the metal ion encircled by the macrocycle, producing a change in the conformation of the ligand.

Compounds capable of interacting with DNA are of great interest in medicinal chemistry because of the fact that they can exhibit a wide spectrum of antibacterial, antiprotozoal, antiviral, and antitumor activity.[2] For this reason, our ligands have been further functionalized with DNA intercalating units (anthracene or pyrene).



A wide variety of experiments have been performed to understand the conformational changes induced by metal cations, the DNA binding properties of the free and complexed ligands, and the antiproliferative effect on different cancer cell lines.

Our results show how the molecular motion, induced by the presence/absence of Cu^{2+}, is able to modulate the interaction between the ligand and DNA, by reducing the accessibility of the intercalating moiety.

Acknowledgements

Financial support from the Ministerio de Ciencia e Innovación (CSD2010-00065) is acknowledged.

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Effect of Monensin on Cadmium-induced Hepatic Dysfunction

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In the last years many papers about the correlation between chronic cadmium intoxication and diseases such as cancer, osteoporosis, infertility, anemia, renal and hepatic dysfunctions have been published. Our studies on ICR mice model have shown that the polyether ionophorous antibiotic monensin positively affects cadmium-induced pathology in some hematology parameters and leads to excretion of toxic metal ions from heart, spleen, lung, testes, liver and kidney of Cd-treated mice.[1,2] Furthermore our data have demonstrated that monensin significantly improves cadmium-induced iron deficiency.[2] In this study we present experimental evidences that monensin positively affects cadmium-induced hepatic dysfunction. Exposure of ICR male mice to Cd(II) acetate treatment resulted in elevation of cadmium concentration and significant depletion of endogenous iron level in the liver of the animals compared to the control. 40 % increase of activity of aspartate aminotransferase and alanine aminotransferase in the plasma of Cd-treated mice was observed. Treatment of Cd-intoxicated animals with monensin restored towards control values activity of both enzymes in the plasma. Data from the histopathological analysis of the liver of cadmium-treated animals revealed that cadmium induced inflammation and distortion of the hepatic structure. Monensin ameliorated Cd-induced inflammation in the liver and recovered the hepatic architecture. Taken together all these results illustrated that monensin significantly improved cadmium-induced hepatic dysfunction.

Acknowledgment
The presentation of this work is supported by Sofia University Fund for Science Research (grant 029/2011) and Bulgarian National Foundation for Scientific Research (Grant N: DO-02-84/2008)

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Redox Regulation of NO-signaling by Metal Complexes and H_2S

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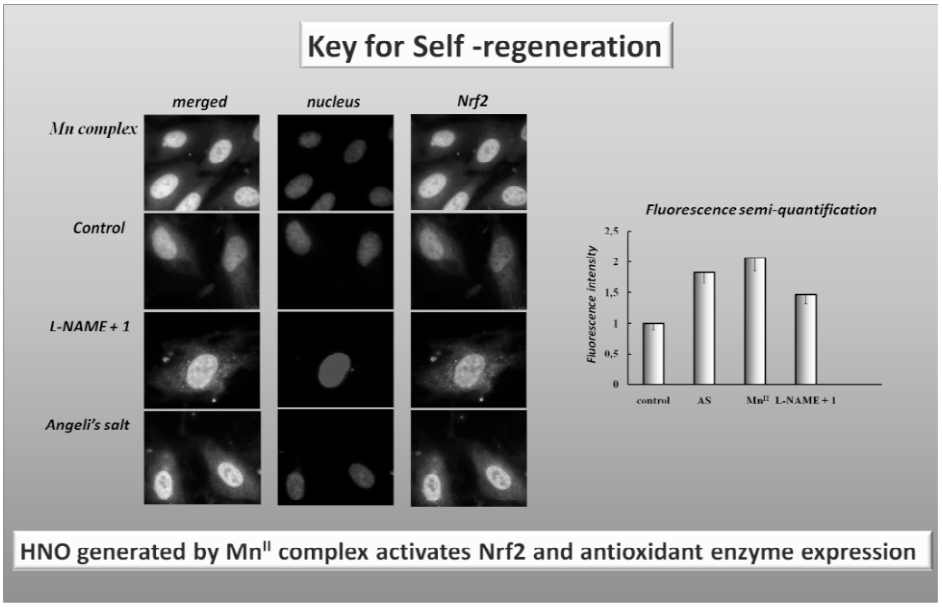
Nitric oxide (NO) is important signaling molecule that regulates numerous physiological functions. However, only a part of effects that have been attributed to nitric oxide truly originate from NO as such. The other part is modulated by NO congeners, nitroxyl (NO^-/HNO) and nitrosonium (NO^+). Biological sources and mechanisms for their generation are, however, unknown.

In series of chemical, biochemical and physiological studies we showed that manganese-based complexes that possess superoxide dismutase activity (SOD) could cause NO dismutation as well, leading to different cellular signaling. In a similar way, hydrogen sulfide, recently recognized as important gasotransmitter, also reacts with NO and modulates NO signaling leading to change of intracellular redox status.



This redox-modulation of NO signaling proved to be a new route for self-regeneration of tissues and potential treatment of diabetes.

N7 or S8 Coordination of 8-thio-theophyline Derivatives to $\{CpRuLL'\}^+$ Moieties (L = PTA, mTPA; L' = PTA, mPTA, PPh_3) (PTA = phosphaadamantane, mPTA = *N*-methyl-PTA)

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Water-soluble complexes are excellent candidates to be a new family of active drugs against diseases such as cancer, malaria, etc. Recently, we have shown that organometallic water soluble ruthenium complexes with the moiety $\{CpRuLL'\}^+$ display valuable anti-cancer activity.[1] Interestingly interaction of the starting water soluble complex [RuClCpLL'] (L = PTA, mTPA; L' = PTA, mPTA, PPh_3) with 8-Me-S-theophyllinate leads to anticancer active complexes in which the thiopurine is coordinated to the metal by the S atom instead of the N7 imidazolic atom as found until now for thio-purines and lineal-thio-ethers.[2] To clarify the reasons for this "new and anomalous coordination mode of the thiopurines derivatives" an extensive DFT theoretical study was performed in gas phase and aqueous and ethanol solution. As observed in the table, the Ru-S complexes, which display the highest dipolar moment, are the most stable in gas phase but particularly in solution.

	G^0_{gas} kcal/mol	$G^0_{solv,water}$ kcal/mol	$G^0_{solv,ethanol}$ kcal/mol	ΔG^0_{gas} kcal/mol	ΔG^0_{water} kcal/mol	$\Delta G^0_{ethanol}$ kcal/mol	μ Debyes
[RuCl(8-MTT-κ*S*)$(PTA)_2$]	363,51	-35,89	-34,39	-1,68	-18,0	-17,23	15,73
[RuCl(8-MTT-κ*N7*)$(PTA)_2$]	365,19	-19,57	-18,84				7,06
[RuCl(8-MTT-κ*S*)(PTA)(mPTA)]	434,08	-52,17	-50,44	-1,55	-4,21	-4,14	14,1
[RuCl(8-MTT-κ*N7*)(PTA)(mPTA)]	435,63	-49,51	-47,85				12,36
[RuCl(8-MTT-κ*S*)$(mPTA)_2$]	487,11	-148,84	-144,07	-0,01	-7,12	-6,81	27,8
[RuCl(8-MTT-κ*N7*)$(mPTA)_2$]	487,12	-141,73	-137,27				19,76

Acknowledgements

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Inhibition of DNA Transcription by DNA-intercalative Polypyridyl Ruthenium(II) Complexes

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Transcription from DNA to RNA is the central dogma of cellular genetic processes. Many antitumor drugs and antiviral agents act as inhibitors of transcription, by inhibiting the transcription process through their interaction with the template DNA, binding to the active site of RNA polymerase, blocking the DNA/RNA channel, or targeting transcription factors.[1] Stabilization of the DNA duplex structure is one of the most important means of inhibiting transcription.[2,3] We will present a series of polypyridyl ruthenium(II) complexes with high DNA-binding ability. The complexes molecules bound to DNA were found to prevent the separation of DNA double strands, which is essential to the DNA transcription, and to block the interaction between RNA polymerase and the template DNA. As a result, these complexes can inhibit the transcription reaction of pGEM template DNA by T7 RNA polymerase and the growth of four kinds of tumor cells. We have further explored the relationship between inhibitory activity and structures of these polypyridyl ruthenium(II) complexes experimentally and theoretically, by modulating the intercalative or ancillary ligand. It has been found that improving the DNA binding ability of Ru(II) polypyridyl complexes has a profound effect on their DNA transcription inhibition activity.

Acknowledgements

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Synthesis and Characterization of a new Lumazine-pyrano-lumazine fused Ligand

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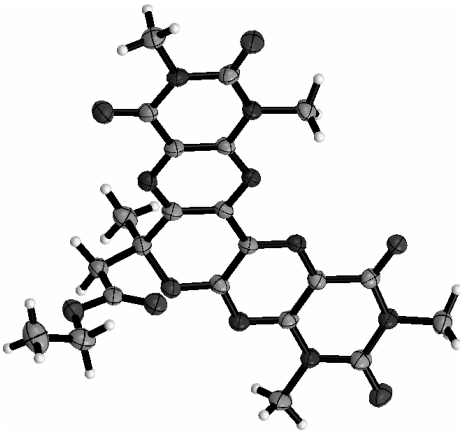
Pteridine-metal complexes have been studied to mimic both the metal environment and reactivity of the metal site of enzymes, being characterized by X-ray crystallography some of them.[1-3]



In our previous studies, the solubility in organic solvents or water enabled us to isolate crystals of a number of metal-lumazine (pteridine-2,4(1*H*,3*H*)-dione) complexes, which allowed to establish the N5-O4 coordination arrangement. Now, we report the synthesis and structural caracterization of a new ligand derived from lumazine with five condensed rings (see left) and new potential coordination behaviours. Also, the ligand exhibits strong luminescence properties.

The ligand has been synthetized by refluxing during several days 6-amino-1,3-dimethyl-5-nitroso-uracyl and ethylacetoacetate; the resulting solution allowed to isolate yellow single crystals suitable for X-ray diffraction.The ligand has been also characterized by analytical techniques (elemental analysis and TG), spectral methods (IR, ^{13}C, ^{15}N and ^{1}H-NMR) and luminiscence studies.

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Site Specific Metallation of a Metallothionein from Wheat

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The ability of cells to distinguish between essential Zn^{II} ions and toxic Cd^{II} ions on a molecular level has puzzled researchers from many fields.[1] A class of proteins, believed to be involved in this process are metallothioneins (MTs) that can be found basically in all living organisms. These small (2-10 kDa), cysteine rich (up to 33%) metalloproteins coordinate preferentially d^{10} metals ions thereby forming metal–thiolate clusters. The plant MT E_c-1 from *Triticum aestivum*, common bread wheat, is one of the most important Zn^{II} associated proteins in the wheat grain. Upon binding of up to six Zn^{II} ions it folds into two independent metal-thiolate clusters, the β_E-domain and the γ-domain. NMR solutions structures expose that the β_E-domain exhibits two separate metal centers, a mononuclear binding site of the form $Zn^{II}Cys_2His_2$ unprecedented for MTs so far and a $Zn^{II}{}_3Cys_9$ cluster. The γ-domain reveals a $Zn^{II}{}_2Cys_6$ cluster, presenting a novel stoichiometry for MTs as well.[2,3]

In the study presented here we investigated the metal-thiolate cluster structure of the smaller γ-domain by various [^{113}Cd]-NMR experiments. Thereby the Cys-Cd-connectivities were established by careful evaluation of 2D-^{1}H-^{113}Cd-HSQC and ^{113}Cd-HSQC-TOCSY spectra. The date provides evidence for two tetrahedrally coordinated metal centers and surprisingly reveals two putative metal cluster connectivities.[3] Even more interestingly, upon exposure of Cd^{II} to fully metallated Zn_2-γ-E_c-1, we observed a metal specificity for the two metal binding sites (Fig. 1).

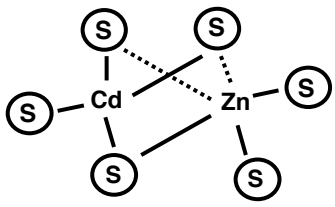

Fig. 1. Schematic display of the $ZnCdCys_6$ metal cluster. The number in the circles represents the number of the coordinating cystein.

Acknowledgements

Financial support from the Swiss National Science Foundation is gratefully acknowledged (Marie-Heim Vögtlin Fellowship to SJ and SNSF-Professorship PP002-119106/1 to EF).

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Copper(II) Interaction with a Scrambled Human Prion Fragment. Coordination and Oxidation

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The prion protein is a high-affinity copper binding protein that plays a role in neurodegenerative diseases. Transition metal ions, particularly copper, are central to oxidative processes, participating in metal catalyzed oxidation reactions.

Copper(II) complexes and copper(II) ion induced oxidation of the scrambled HuPrP106-126 fragment (Ac-NGAKALMGGHGATKVMVGAAA-NH_2) was studied. Potentiometric and spectroscopic techniques (UV-Vis, CD and EPR) were used to study the speciation, affinity, folding and bonding details of copper(II) complexes, the oxidation of the peptide in the presence of copper(II) ions were studied by HPLC-ESI-MS.

Only 1:1 complexes are formed at any copper(II) ion to ligand ratios. The histidine residue is the anchoring binding site and the successive deprotonation and coordination of amide functions takes place toward the N-termini.

The metal-catalyzed oxidation of the studied fragment is a site-specific process in which certain amino acids at the metal binding site are preferentially oxidized. Cu(II)/hydrogen peroxide as the oxidizing agent were applied at pH 7.4 where $[CuL]^{2+}$ and $[CuLH_{-1}]^{+}$ (2N and 3N) complexes are formed.

Oxidation products containing 1, 2 and 3 additional oxygen atoms were detected. The oxidation of the histidine residue to 2-oxo-histidine and methionine residue at position 112 to methionine sulfoxide and sulfone is suggested.

Acknowledgements
Financial support from the CNR-MTA bilateral agreement, the projects MIUR-FIRB RBPR05JH2P (Italy), OTKA-NKTH 77586, GVOP-3.2.1-2004-04-0152/3.0 and TAMOP 4.2.1/B-09/1/KONV-2010-0007 (Hungary) is acknowledged.

Syntheses of Novel Au8 Clusters and their Optical Responses to Metal Ions

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Ligand-coordinated gold clusters with defined metal numbers and geometrical structures have attracted continuing interest due to their unique properties, which have potential for the development of novel nanomaterials. Recently, we have disclosed the utility of post-synthetic methods utilizing growth/etching processes for the facile generation of novel cluster species.[1] In this presentaion, we show the syntheses and unique optical properites of two novel Au8 cluster cations $[Au_8(L)_4Cl_2]^{2+}$ (**2**) and $[Au_8(L)_4]^{2+}$(**4**) (L = dppp; $Ph_2P(CH_2)_3PPh_2$). containing edge-shared gold tetrahedron motifs We also highlight the selective optical response of **2** towards mercury ions.[2]

The growth of $[Au_6L_4]^{2+}$ (**1**) took place readily through a reaction with $Au(PPh_3)Cl$ in MeOH to give $[Au_8L_4Cl_2]^{2+}$ (**2**) quantitatively. X-ray crystallographic studies revealed the di-edge-bridged bi-tetrahedral geometry of the cluster core. Another type of Au8 cluster ($[Au_8L_4]^{2+}$) with an isomeric edge-shared tri-tetrahedral geometry was generated by the etching reaction of $[Au_9(PPh_3)_8]^{3+}$ (**3**) with L. Spectrophotometric studies revealed that these two Au8 clusters (**2** and **4**) show characteristic visible absorption/photoluminescence properties that are strictly dependent on the core geometries associated with the oxidation states of the cluster cores. By using these clusters, we investigated the optical response to chloride or nitrate salts of several metal ions (Mn^{II}, Zn^{II}, Cr^{III}, Fe^{III}, Cd^{II}, Co^{II}, Ni^{II}, Cu^{II}, Pb^{II}, Hg^{II}, Ag^{I}, Pd^{II}, Ru^{III}). For **2**, negligible changes were observed upon the addition of most of the above metal ions. The only exception was mercury (Fig. 1); the addition of Hg^{II} to **2** in MeCN caused quenching of photoluminescence and an instant color change from pink to brown. On the other hand, such selective responses were not observed for **4**.

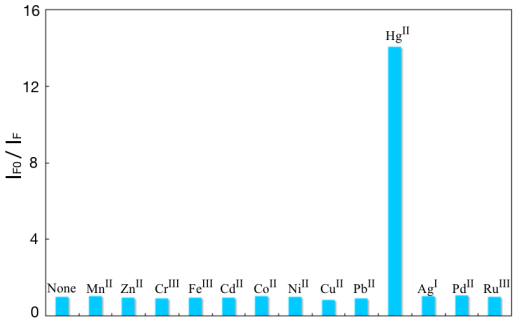

Fig. 1. PL responses of **2** upon the addition of various metal ions (2 molar equiv. in MeCN).

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Organometallic Rhodium Compounds as Potential Anticancer Agents

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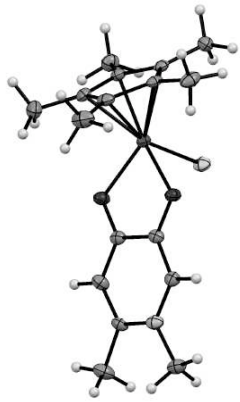
Pyrone scaffolds are often present in natural products and many derivatives exhibit therefore favorable biocompatibility and toxicity profiles. Hydroxypyrones are obtained by isolation from natural sources, are commercially available or can be synthesized by different well established approaches and can easily be converted into the analogous hydroxypyridones. These features make them well suited for drug development and other biological applications. Our working group has investigated organometallic Ru(II) and Os(II) hydroxypyr(id)onato complexes as potential anticancer agents.[1] Organometallic Ru–arene compounds containing a maltol ligand were shown to be nearly inactive *in vitro*, due to decomposition of the complexes in the presence of amino acids.[2,3] With the aim to prepare stable complexes bearing the pyr(id)one motif with anticancer activity, we have synthesized complexes of the general formula [Rh(η^5-C_5Me_5)(pyr(id)one)X] (X = halide, tosylate). The synthesis, characterization, and studies on their stability and behavior in aqueous solution of such organometallic rhodium compounds will be discussed.



Acknowledgements

We thank the University of Vienna, the Austrian Science Fund (FWF), the Johanna Mahlke geb. Obermann Foundation, and COST D39 for financial support.

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Mn(II) and Fe(II) Complexes of Sterically Hindered 1,2-Dihydroxybenzene Derivatives: Biological Evaluation and Reduction of Cytochrome c

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Previously we have synthesized Cu(II), Co(II) and Ni(II) complexes with sterically hindered 1,2-dihydroxybenzene and *o*-aminophenol derivatives.[1] Using the method of cyclic voltammetry, we have shown these compounds to be also of a pronounced reducing ability correlating with antimicrobial activity in a limited series of these compounds. This allowed us to suggest that redox processes could play an important part in realizing the mechanism of biological activity of the said compounds. Thus, one of the possible types of their biological macromolecular targets may be comprised by oxidoreductases which are components of mammalian electron transport chains, namely: cytochrome *c* (Cyt *c*), NADPH: cytochrome P450-reductase (P450R). In the present work the reduction of bovine heart Cyt *c* with some of sterically hindered 1,2-dihydroxybenzene derivatives as well as with their redox-active Mn(II) and Fe(II) complexes, and the effect of electron transfer proteins of mammalian P450-dependent monooxygenase systems on this process were investigated spectrophotometrically.

Synthetic procedures for the complexes of sterically hindered 1,2-dihydroxybenzene derivatives with ferrous and manganous ions have been worked out, and composition, geometry as well as physico-chemical characteristics of the complexes have been determined. Pharmacological screening revealed ligands and Fe(II) and Mn(II) metal complexes that may be considered as potential chemotherapeutic agents with activities comparable to those of some standard antibiotics (streptomycin, ampicillin, nystatin, terbinafin). The direct correlation that we have discovered between antimicrobial properties of the most active compounds, evaluated by pharmacological screening, and their reducing ability determined electrochemically deserves a particular attention. Based on these results, an assumption can be made that biological redox processes and the enzymes catalyzing them (oxidoreductases) would be closely related to pharmacological properties of the compounds studied. The results obtained bring out clearly that redox interaction with oxidoreductases as macromolecular targets can be essential for realizing their antimicrobial and antioxidant activity.

Optical Resolutions of DL-Amino Acids *via* Cu(II) Ternary Complexes Containing Optically Active Amino Acids

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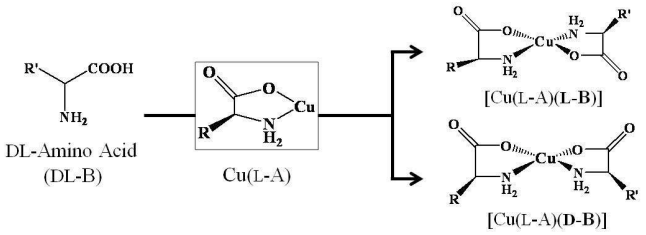
D-Amino acids, the enantiomer of L-amino acids, are useful as materials of drugs, medicines, and antibiotics because of less decomposition of compounds containg them in *vivo*. Therefore, it is required to get pure D-amino acids to product effective drugs. We have been studied to obtain unnatural D-amino acids by optical resolution using various crystallization methods, preferential crystallization, replacing crystallization, and separation of diastereoisomeric salts, because asymmetric syntheses or column chromatographic methods are difficult to use to obtain optically active compounds in large quantities.



Scheme 1. Optical resolution of DL-amino acids *via* formation of ternary Cu(II) complexes

Metal ions can be bound with ligands, such as DL-amino acids, which we want to resolve optically, and optically active amino acids, using as resolving reagents. In this study, we tried to resolve DL-amino acids by formation of ternary copper(II) complexes with optically active amino acids (Scheme 1). When [Cu(L-A)(D-B)] is less soluble than [Cu(L-A)(D-B)], [Cu(L-A)(D-B)] will be crystallized selectively from an aqueous solution containing L-A, DL-B, and Cu ion. D-B can be obtained from precipitated [Cu(L-A)(D-B)] after removing L-A and Cu ion.

On the basis of this prospect, it was attemped to resolve DL-Tryptophan (DL-Trp) optically using Cu ion and D-alloisoleucine (D-alle), since [Cu(D-alle)(D-Trp)] is less soluble in water than [Cu(D-alle)(L-Trp)]. After DL-Trp was added to a solution of [Cu(D-alle)$_2$], the mixture was kept at 5 ºC over night. Precipitated Cu(II) complex was collected and treated with 8-quinolinol to obtain D-Trp (24 %*ee*). To improve optical purity of D-Trp, the hydrochloride of the obtained D-Trp was recrystallized from 2-propanol to give 95 %*ee* of D-Trp·HCl. Now we are trying optical resolution of various DL-amino acids using Cu complexes of some optically active amino acids.

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Construction of Multicopper Oxidase Model Systems Using a Copper-clustering Core Capsulated in a Cage

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Multicopper Oxidase (MCO) catalyzes substrate oxidation simultaneously to reduce dioxygen to water. In MCO, three types of copper sites, Type I, II, and III, are arranged to work, cooperatively,[1] and the electrons are transferred from the Type I copper site to a tricopper core composed of those Type II and III copper sites, reducing dioxygen in stages.[2] This four-electron reduction of O_2 is of not only great biological interest but also technological significance, such as in fuel cells.

In our study, we newly synthesized biomimetic tricopper complexes by using a 'cage' type ligand, $\mathbf{L_{NH}}$ (Fig. 1). This ligand has host space capturing a substrate molecule, and it facilely forms multinuclear metal center inside the cage structure. In this cage, the core structure could be strongly supported by the ligand framework, preventing the reaction intermediate species from rapid decomposition.

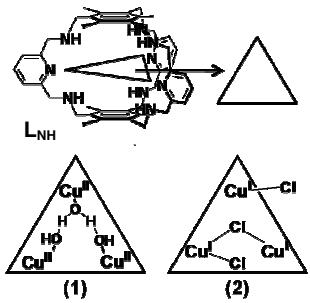

Figure 1. Tricopper complexes, **1** and **2**, of $\mathbf{L_{NH}}$.

In this work, we prepared tricopper complexes, $[Cu^{II}_3(\mathbf{L_{NH}})(OH)_2(H_2O)](ClO_4)_4$ (**1**) and $[Cu^{I}_3(\mathbf{L_{NH}})Cl_3]$ (**2**) of $\mathbf{L_{NH}}$, as a precursor of adducts with hydrogen peroxide, dioxygen, and superoxide (Fig. 1). These reaction were investigated by spectroscopic methods. We report and discuss about new dioxygen adducts of multinuclear copper complexes using a cage-type ligand, $\mathbf{L_{NH}}$ in detail.

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Characterization of Anticancer Ru(II,III) Compounds in Aqueous Solution

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Ruthenium compounds are highly potent antitumor agents and especially efficient in the treatment of metastases. Many of them are currently undergoing preclinical and clinical studies. NAMI-A and KP1019 are the two most promising Ru(III) compounds being in clinical Phase (II) trials. The *in vivo* reduction of Ru(III) is assumed to be a important step in the activation mechanism and thus development of new organometallic Ru(II) compounds with potential antitumor activity also attracts attention.[1] Among the preclinical and clinical studies less attention were paid for their solution properties, which can be one of the key information for understanding their possible biotransfromation ways.

In contrast with other Ru(III) compounds the EDTA complex of Ru(III) is kinetically labile[2] in acidic pH and the chloride ligand can be replaced by other monodentate ligand. However, applying bidentate ligands one of the carboxylates of the EDTA, besides the chloride, can also be replaced under fast kinetic conditions. Accordingly, this system gives us the chance to *compare* the binding ability of the different bidentate ligands to Ru(III) in the Ru(III)-EDTA-B ternary systems. The pH dependent speciation of $[Ru(II)(\eta^6\text{-}p\text{-cymene})(H_2O)_3]^{2+}$ with some *O*,*O*-ligands had already been reported.[3] As an extension of the work interactions with *O*,*N*- and *O*,*S*-ligands have been studied in our laboratory by pH-potentiometry, UV-Vis spectrophotometry, and ^{1}H-NMR spectrometry. The main finding is, that ruthenium in both oxidation states has much higher affinity to *O*,*S*-ligands than to *O*,*O*- or *O*,*N*-, which may mean that the importance of the Ru-thiolate interaction during biotransformation reactions of the drug candidate compounds most probable are more important than believed earlier.

Acknowledgements.
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DNA-binding and Topoisomerase IIα-inhibiting Ru(cymene) Complexes with Flavone-derived Ligands

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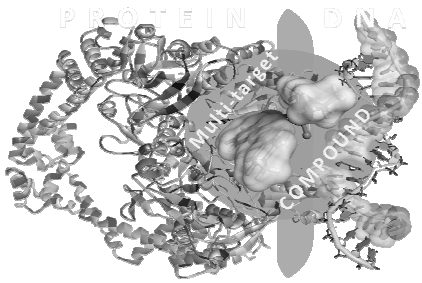
The concept of multi-targeted anticancer agents (see Figure), *i.e.*, components of a molecule impact individual targets, offers several advantages over "classic" chemotherapeutics, such as altered pharmacological properties and tunable antitumor activity.[1] Such biologically active molecules with multi-targeted properties can be prepared by linking metal fragments to biologically active ligand systems.[2,3] Flavonoids as secondary metabolites of plants are known to exhibit various biological properties such as antiradical and antioxidant, anti-inflammatory, antimicrobial and also anticancer activity[4] and are known to inhibit enzymes such as topoisomerase.



On the other hand, ruthenium compounds are currently considered the most promising drug candidates in clinical and preclinical trials and they are known to be capable of covalently interacting with DNA.[5] By linking flavonols to Ru^{II}(arene) moieties, we prepared a series of novel multi-targeted compounds with high *in vitro* antitumor activity, which are able to inhibit human topoisomerase IIα, whereas the metal fragment can form a covalent bond to DNA.

Acknowledgements

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Interaction of Ni(II) with Non-steroidal Antiinflammatory Drug Diclofenac

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Nickel is an element of expanding biological interest; not only it is present in the active centre of some enzymes such as urease and superoxide dismutase but also diverse nickel complexes of biological activity have been reported.[1] Regarding the interaction of Ni(II) complexes with DNA, it has been mainly dependent on the structure of the ligand exhibiting intercalative behaviour[2] and/or DNA cleavage ability.[3]

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medical drugs as analgesic, anti-inflammatory and antipyretic agents.[4] The chemical classes of NSAIDs comprise salicylate derivatives, phenylalkanoic acids, oxicams, anthranilic acids, sulfonamides and furanones. Diclofenac sodium is a potent non-steroidal anti-inflammatory drug (NSAID), used in inflammatory and painful diseases of rheumatic and non-rheumatic origin. This drug inhibits cyclooxygenase enzyme (COX) activity *in vitro* with no significant effect on phospholipase A_2 or on lipoxygenase enzymes.[5]

In this context, we report the synthesis, characterization, electrochemical and biological properties of Ni(II) complexes with the drug diclofenac in the absence or presence of nitrogen-donor heterocyclic ligand such as bipy, phen, Hpko or pyridine. The binding properties of the complexes with calf-thymus DNA have been investigated by UV spectroscopy, cyclic voltammetry and viscosity measurements. Competitive binding studies with ethidium bromide have been performed in order to investigate the existence of a potential intercalation of the complexes to DNA. The affinity of the complexes for bovine and human serum albumin has been investigated by fluorescence spectroscopy.

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Copper(II) Interaction with Human Angiogenin Protein and Related Peptide Fragments

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Human angiogenin (hAng) is a single-chain blood plasma protein present in physiological conditions, but over-expressed in patients affected by different types of cancers.[1] Interestingly, the binding affinity between Ang and endothelial cells is largely increased in the presence of copper ions. It is well known that copper(II) is a strong angiogenic signal *in vivo*, but the specific molecular mechanism by which it works and the targets of its activity remain unclear. In this context, the characterization of copper(II) complex species with protein is a valuable aid in a better understanding of potential mutual biological influences. It is important to note that in almost all published papers on angiogenin, the experimental data have been obtained by using the recombinant protein (rAng) which encompasses a methionine as first amino acid. The wild type protein has a glutamic acid as first residue which spontaneously make a pyroglutamic cycle (<Glu(1)Ang) so that there is not a free N-amino terminal group. We report the coordination properties of rAng protein and wild type protein by means of NMR, EPR, UV-vis and CD spectroscopic techniques as well as MD computational analysis. Moreover, in order to better understand the coordination features of potential metal elective binding sites within the whole protein, different Ang peptide fragments were synthesized and their copper(II) complexes characterized.[2] The results obtained show that the angiogenin is a potential copper(II) binding protein.

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Rhenium Carbonyl Compounds with Metallothionein for Radiopharmaceutical Applications

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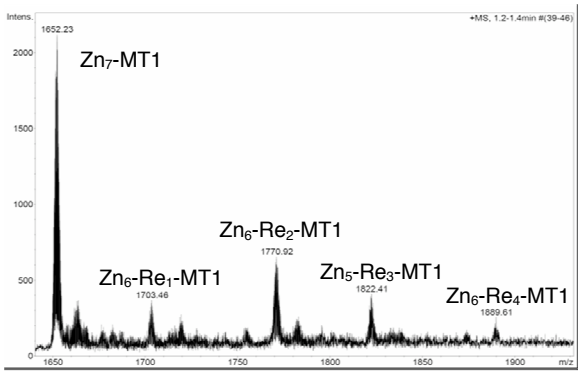
Nuclear Medicine progressively demands more target-specific compounds. The ^{99m}Tc-based drugs are commonly used in SPECT for diagnosis but very few examples of second generation radiopharmaceuticals are employed or are under study in clinical trials. These compounds contain a biologically active molecule covalently linked to an appropriate technetium fragment. In this context, metallothioneins (MT) are proteins that can bind a wide range of heavy metal ions and that have been poorly studied as a tool to prepare new radiopharmaceuticals.[1] With the aim of exploring this topic, we studied the reaction between the $[Re(H_2O)_3(CO)_3]^+$ cation, as a model compound of $[^{99m}Tc(H_2O)_3(CO)_3]^+$, and the four mammalian MT isoforms by spectroscopic (CD, UV-Vis) and spectrometric (ESI-MS) techniques. Preliminary experiments showed that the reactivity against the rhenium tricarbonyl core was clearly dependent on the Zn- or Cu-thionein character[2] of the assayed proteins. Therefore, MT1 (Zn-thionein) showed certain reluctance to exchange Zn^{2+} by rhenium, rendering heterometallic Zn,Re-complexes coexisting with the initial Zn_7-MT1 species (ESI-MS spectrum above). In contrast, those isoforms with a higher Cu-thionein character[2] exchanged Zn^{2+} much more easily yielding major heterometallic Zn,Re-compounds and also homometallic species.



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Multifunctional Quantum-dot-based as Dual Platform for siRNA and Doxorubicin Delivery and Real-time Tracking of Delivery

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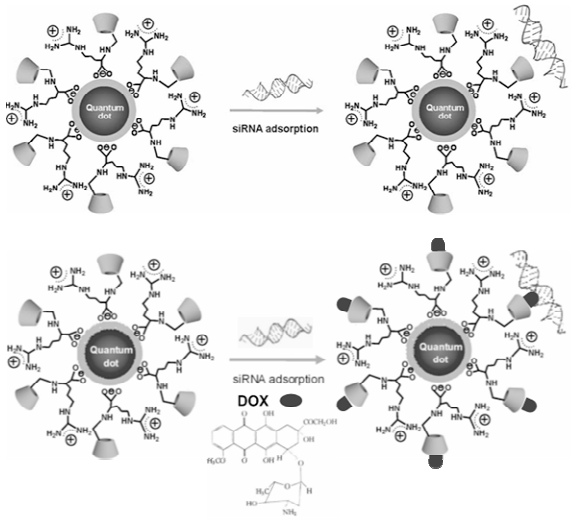
The modified QDs (β-CD-L-Arg-QDs) were used as carriers to deliver siRNA which targeted HPV 18 E6 with HeLa cells and have the potential to act as dual delivery platform for targeted MDR1 siRNA and doxorubicin (Dox) in order to surmount obstacle in combining gene silencing technology with chemotherapy to reverse multidrug resistance and elevate the drug sensitivity of cancer cells. The QDs could also be used as nanocrystal probing agents, allowing real-time tracking and localization of QDs during delivery and transfection.



The properties and capabilities of the QDs showed that amino acid-CD-modified QDs could be used as useful siRNA and DOX carriers to effectively silence a target gene and inhibit cancer cells growth as well as fluorescence probes to analyze intracellular imaging *in vivo*.

Acknowledgements

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Seven-Coordinated, Dinuclear Mn^{2+} Complexes with Cyclic Polyamine Ligands as Potential Superoxide Dismutase Mimetics

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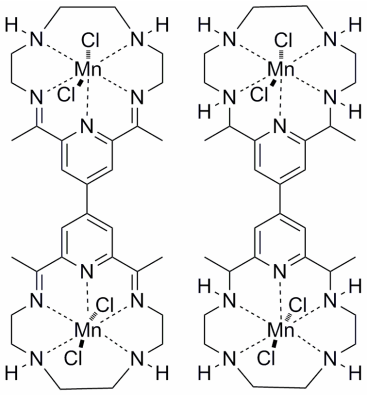
Catalytic dismutation of superoxide by metal centers proceeds in two reaction steps, where a metal center cycles between its oxidized and reduced forms. Therefore, an interesting concept is to design a dinuclear metal complex with two redox active centers potentially capable of simultaneous oxidation and reduction of superoxide.

With this goal in mind, two novel dinuclear Mn^{2+} complexes $[Mn_2(\mathbf{L1})Cl_4]$ and $[Mn_2(\mathbf{L2})Cl_4]$ were synthesized and fully characterized. Stability constants of the complexes and pK_a values of the ligands were determined by potentiometric titration. Temperature dependent magnetic susceptibility measurements for both complexes revealed that there is no electronic communication between the two high-spin d^5 Mn^{2+} centers. Redox potentials for both metal-complexes were determined in aqueous (PIPES/CAPS buffer) and non-aqueous (DMSO) solutions. The water exchange process on the Mn^{2+} centers was studied in details, by temperature and pressure dependent ^{17}O-NMR techniques, as this is an important elementary reaction step within the overall catalytic cycle, required for the efficient electron transfer according to the inner-sphere mechanism. At the same time, tuning of water exchange is crucial for development of paramagnetic metal complexes as MRI contrast agents. Due to the low toxicity of manganese, its complexes, in particular polynuclear, are currently highly attractive as new diagnostic tools, replacing gadolinium(III) contrast agents. Finally, the superoxide dismutase (SOD) activity of new complexes was determined using highly accurate rapid scan stopped-flow measurements and increased SOD activity was observed in comparison to mononuclear analogues.



$[Mn_2(\mathbf{L1})Cl_4]$ $[Mn_2(\mathbf{L2})Cl_4]$

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Stabilization of G-Quadruplex DNA and Inhibition of Telomerase Activity by Chiral Ruthenium(II) Complexes

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Telomerase has an elevated activity in 85-90% of human cancer cells in comparison to normal somatic cells.[1] Thus, telomerase inhibition has been identified as an attractive target for cancer chemotherapy with the potential for selective toxicity for cancer cells over normal ones.[2]

Here two chiral ruthenium(II) complexes Λ-$[Ru(phen)_2(p\text{-MOPIP})]^{2+}$ and Δ-$[Ru(phen)_2(p\text{-MOPIP})]^{2+}$, where phen is 1, 10 phenanthroline and *p*–MOPIP is 2-(4-methoxyphenyl)-imidazo[4,5f][1,10]phenanthroline, have been synthesized and characterized. The complex's chiral selectivity and its ability to discriminate quadruplex DNA have been studied by UV-vis, fluorescence spectroscopy, circular dichroism (CD) spectroscopy, fluorescence resonance energy transfer (FRET) melting assay, polymerase chain reaction (PCR) stop assay and telomerase repeat amplification protocol (TRAP). In summary, we report an example that one enantiomer of a chiral metal complex is capable of inducing the formation of human telomeric G-quadruplex and discriminating between different quadruplex sequences under salt-deficient conditions. Complex Λ-$[Ru(phen)_2(p\text{-MOPIP})]^{2+}$ can be a potential drug candidate targeting towards G-quadruplex DNA and our findings should prompt rational design and screening of chiral anticancer agents targeting towards G-quadruplex DNA.

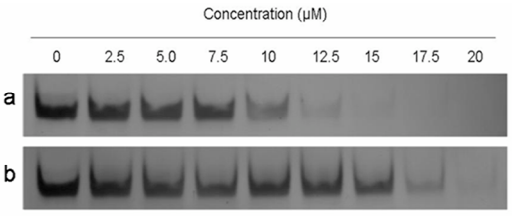

Figure. Dose-dependent inhibition of HTG21 PCR amplification by Λ-$[Ru(phen)_2(p\text{-MOPIP})]^{2+}$ (a), Δ-$[Ru(phen)_2(p\text{-MOPIP})]^{2+}$ (b).

Acknowledgements

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A Novel Therapeutic Role of Cisplatin: Potential Anti-*tuberculosis* Agent by Inhibition of Protein Splicing

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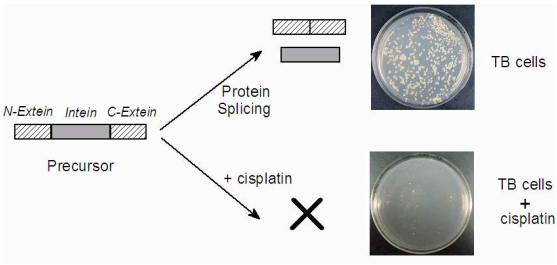
Protein splicing is a unique post translational process in which the intervening protein (intein) is cleaved from the precursor proteins, while the two flanking proteins (extein) are seamlessly ligated to generate target proteins. Three enzymes (RecA, DnaB and SufB) in *Mycobacterium tuberculosis* are synthesized in an inactive form with an intein insertion.[1] These proteins have to undergo protein splicing before the functionalization. Inhibition of protein splicing could prevent the maturity of these proteins, and inhibit the proliferation of *M. tuberculosis*.

The *in vitro* screening was performed on a fusion protein of green fluorescence protein (GFP) with intein insertion adjacent to the residue 129 of GFP.[2] The fluorescence recovery quantitatively indicates the protein splicing efficiency. Over 40 complexes from seven metals (Cu, Co, Ni, Zn, Au, Pt, and Ru) with different ligands have been tested. Results showed that the coordination geometry and ligand types could influence the inhibition of intein activity. Cisplatin showed the best *in vitro* inhibition efficiency (IC_{50} =2.5 μM). The *in vivo* assay was preformed on a TS report system on *E. coli* as a model system.[3] Results showed that our inhibitors can be effective to intein in bacterial cells. Finally, the inhibition of *M. tuberculosis* cell growing was analyzed. Results demonstrated that the cell growing was completely inhibited by cisplatin at 40 μM. This minimal inhibitory concentrations (MIC) value is in the similar range of antimycobacterial agents, ethambutol and rifampicin, which are currently in clinical use for the treatment of TB. We also performed the complementary assay to confirm that cisplatin really targeted intein. By transforming intein plasmid, TB cells acquired drug resistance to cisplatin. This result suggests that the intein inhibitors can be potentially used for TB treatment. This funding provides a novel approach for the anti-TB drug development.



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Solution Study of Metal Complexes with Macrocyclic Ligands having Carboxylate and Phosphonate Pendant Arms

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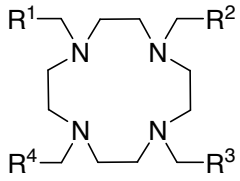
Ln(III) and Cu(II) complexes are utilized in medicine and preclinical research as magnetic resonance, optical or nuclear probes for diagnostics and/or for cancer treatment. For biomedical applications, such complexes should exhibit a high thermodynamic stability as well as kinetic inertness under physiological conditions. Thus, knowledge of their thermodynamic/kinetic properties (e.g. dissociation rate constants for an estimation of kinetic inertness) is important to evaluate their use in these applications. Here, thermodynamic and kinetic properties of Cu(II), Ce(III) and Eu(III) complexes with macrocyclic cyclen-based ligands where acetate pendant arms were substituted by phosphonates (H_4dota, H_5do3ap, *trans*-H_6do2a2p, H_7doa3p, H_8dotp) are presented.[1,2] The substitution of acetate functional group(s) by phosphonate(s) has a definite impact on the kinetic inertness of the mentioned metal complexes and, therefore, this fact should be taken for possible *in vivo* application as BFC's.



R^1, R^2, R^3, R^4 = COOH	**H_4dota**
R^1, R^2, R^3 = COOH; R^4 = $P(O)(OH)_2$	**H_5do3ap**
R^1, R^4 = CO_2H; R^2, R^3 = $P(O)(OH)_2$	**H_6do2a2p**
R^1 = COOH; R^2, R^3, R^4 = $P(O)(OH)_2$	**H_7doa3p**
R^1, R^2, R^3, R^4 = $P(O)(OH)_2$	**H_8dotp**

Acknowledgements

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NMR Active MoS_4^{2-}- M (M = Cu, Cd and Gd) Clusters Use as a Structural Probe in Orange Protein

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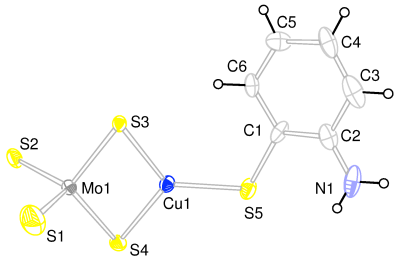
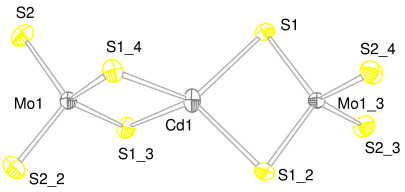
A unique type of mixed metal sulfide cluster containing molybdenum and copper was found in the Orange Protein (ORP) isolated from *Desulfovibrio gigas*.[1] Recently, the NMR assignment of the apo-form of ORP was made.[2] So far, the exact location of the cofactor in the protein is unclear between apo- and holo- ORP, since the cluster is diamagnetic, and does not contain easily NMR observable atoms (i.e., H, C, N, P). To overcome this problem, synthesis of several hetero-metal clusters of tetrathiomolybdate with transition metals were reported.[3] We have envisaged two different ways where NMR or EPR active synthetic structural model compounds could be used for probing the cluster-binding site. The first is based on the substitution reaction where either aromatic or aliphatic thiols reacts with $[PPh_4]_2[MoS_4CuCl]$ in the presence of strong base, resulting into the formation of $[Et_4N]_2[S_2MoS_2Cu(L)]$ (L=Thiol). Another one is the incorporation of ^{113}Cd into tetrathiomolybdate to give $[PPh_4]_2[(MoS_4)_2Cd]$, which can be used in NMR experiments. All clusters were characterized by X-ray diffraction, UV-visible, CV, EPR and NMR spectroscopies. Two new structures are shown in the figure.



$[S_2MoS_2CuSPh(NH_2)]^{2-}$



$[S_2MoS_2CdS_2MoS_2]^{2-}$

Acknowledgements

The authors acknowledge the financial support from FCT-Portugal (SFRH/BPD/63066/2009, PTDC/QUI-BIQ/098071/2008 and PTDC/QUI-QUI/099873/2008).

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Application of Cyclodextrin in Bioinorganic Chemistry: from Metalloenzyme Models to Drug Carries

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Supramolecular assembly and recognition of host cyclodextrins (CDs) and guest molecules have attracted more and more attentions in recent years because of their potential to serve as platforms for the construction of molecular machines, drug carriers, reaction mediation and the recognition of ionic species. Recently, we focused our interest on design of metalloenzyme models and drug carriers with CDs. We synthesized various cyclodextrin monomer/dimers linked by mono- or binuclear metal complexes or inclusion systems of cyclodextrin derivatives with metal complexes as metallohydrolase or Cu,Zn-SOD mimics, and found that the weak interactions produced by cyclodextrin with functional pendants play important roles for enhancing catalytic activities of the mimics. We also synthesized quantum dots (QDs) nanoparticles coated with CD coupled to amino acids with different surface charges (positive, negative and neutral) through direct ligand-exchange reactions and used them to deliver siRNA. Our study not only provides new insights into the mechanisms of amino acid-mediated delivery but also greatly facilities the monitoring of gene silencing studies.

Acknowledgements

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Receptor-Targeted Platinum and Ruthenium Complexes as Selective Antocancer Drugs

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In spite of the clinical success of cisplatin and its second-generation derivatives in the treatment of some types of cancer, the severe toxic side-effects together with the development of resistance in cells have stimulated researchers to design innovative metal-based anticancer drugs. The main challenge concerns the improvement of the targeting strategies either by using ligands to improve cellular uptake and tumour selectivity ("tumor targeting device") or by designing non-toxic pro-drugs whose activity might be triggered within the cancer cell.[1]

The overexpression of the receptors for many regulatory peptides in human tumor cells in comparison to their expression in normal cells, has prompted research on their use in tumor targeting both for diagnostic and therapeutic purposes.[2] Folate receptor is also overexpressed by a variety of humans tumors, making folic acid a promising ligand for specific targeting of cancer cells.[3] Hence, from a therapeutical point of view, a promising approach for the treatment of cancer consists on the attachment of a metal based anticancer drug to a peptide moiety or to folic acid with the aim of improving its activity and bioavailability. This targeted anticancer strategy will result on therapeutic agents with increased tumor selectivity and decreased toxicity in normal tissues.

Herein we report on the synthesis, characterization and biological activity of several conjugates in which platinum(II and IV) and organometallic ruthenium(II) complexes are covalently bound to receptor-binding peptides (octreotide analogues and RGD constructs) as well as to folic acid.[4,5]

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Design of Artificial Oxygenases for Drug Synthesis

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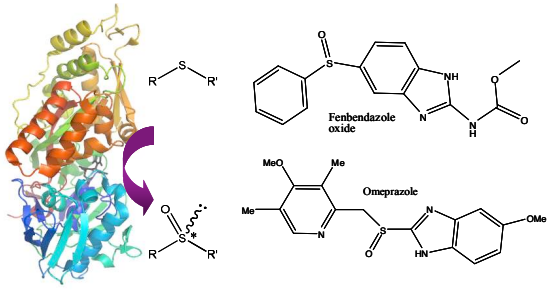
Exploring new reactions and designing efficient catalysts considering environmental and economic aspects remains a big challenge. Enzymes are indeed powerful biocatalysts which can provide enantiopure products under mild conditions; however they are very substrate-specific which limits their application. In this context, artificial metalloenzymes have appeared as a promising avenue to a new generation of "green" efficient enantioselective biocatalysts.[1] The combination of non pollutant inorganic iron complexes with protein scaffolds leads to systems which could display both enzymatic and homogeneous inorganic catalysis advantages. In this context, the laboratory has focused on the design of artificial monooxygenases. Our strategy consists of the development of modular biocatalytic systems in which the folding of the protein will modulate the selectivity of the oxygen transfer reaction whereas the inorganic complexes will conduct the reactivity. We decided to exploit the NikA technology[2] in the synthesis of drugs based on a sulfoxide backbone as the anti-secretory gastric Omeprazole® or the anthelmitic Fenbendazole®.



Based on docking experiments, we choose a new sulfide family which showed a good recognition with the catalytic pocket. Some new model sulfides have been synthesized and their oxidation pathway with NaOCl and a series of hybrids has been studied. The first catalysis results will be discussed.

Acknowledgements

Financial support from the ANR is acknowledged.

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Metalloproteinase Inhibition: a new Metal-Binding Group in the Game

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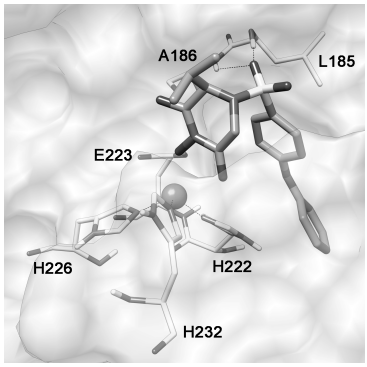
Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases, which, when over-expressed, may be involved in several diseases, namely arthritis, neuroinflammatory diseases, angiogenesis, and cancer. Up to now, most of the MMP inhibitors reported include a hydroxamic acid (HA) as a zinc-binding group (ZBG), but they have failed in clinical trials due to severe side effects or ineffectiveness.[1] Seeking for non-hydroxamic ZBGs, we have identified new potent MMP inhibitors containing the 1-hydroxypiperazine-2,6-dione (HPD) moiety (IC_{50} values in the nanomolar range).[2] The binding mode of these compounds was investigated by a computational method involving docking and hybrid quantum mechanical and molecular mechanical (QM/MM) dynamic simulations. These studies suggested that the HPD moiety binds bidentately to the catalytic zinc, revealing itself as a new potential substitute for the HA group. The present leading compounds open the way to a new generation of MMP inhibitors with improved bioavailability, and enable further straightforward structure optimization towards activity and selectivity enhancements.



Acknowledgements

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New Polidentate Ruthenium Complexes: Synthesis, Characterization and Anti-tumor Activity

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Ruthenium complexes have attracted great interest for their potential use as metallodrugs for cancer treatment, and represent the class of most widely studied non-platinum compounds in this field.[1,2]

We have been engaged in the development of "$Ru^{II}Cp$" compounds (Cp = η^5-cyclopentadienyl) for several different applications,[3,4] and have recently reported a family of organometallic "$Ru^{II}Cp$" complexes with N-heteroaromatic co-ligands which were shown to exhibit anti-proliferative activity in the nanomolar range against human colon adenocarcinoma, pancreatic cancer and leukemia, reinforcing the great potential of Ru^{II} compounds as antitumor agents.[5,6]

We present herein the synthesis and characterization of a new family of ruthenium complexes with polidentate ligands with N-donors. The new compounds were fully characterized by common techniques: IR, NMR spectroscopy (^1H, ^{13}C), ESI-MS and UV-Visible Absorption. The cytotoxic activity of both complexes and ligands against different human cancer cell lines was investigated to evaluate their anti-tumor potential.

Acknowledgements

The authors thank financial support from the Portuguese Foundation for Science and Technology, FCT (*PTDC/QuiQui/101187/2008, PEst-OE/QUI/UI0100/2011, PEst-OE/QUI/UI0612/2011, PEst-OE/QUI/UI0536/201, Ciência2007 and Ciência2008 Initiatives*).

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Interaction of Apotransferrin with Anticancer Ruthenium Complexes NAMI-A and its Reduced Form

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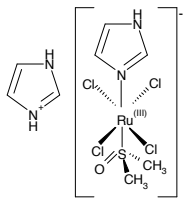
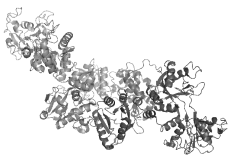
NAMI-A is a novel ruthenium(III) complex with promising antimetastatic activity, which has been classified for II phase of clinical trials.[1] This complex is almost inactive towards primary tumours, but remarkable activity against secondary tumours with low general toxicity make NAMI-A incredibly interesting and worth further research.



NAMI-A

After intravenous administration NAMI-A undergoes rapid hydrolysis and reduction in the present of an ascorbic acid.[2] The main form in which this complex occurs in blood is ruthenium adducts with serum blood proteins, mostly with albumin and transferrin (more than 95 %). It is been postulate that protein-bound forms of this complex are responsible for its activity. Transferrin can act as a selective drug transporter while albumin might be used as a depot of Ru ions for the transferrin cycle's needs.[3]



Apotransferrin
(pdb id. 2HAU)

The main aim of this study is to investigate the binding between apotransferrin (protein unloaded with Fe ions) and NAMI-A under physiological conditions. Due to redox environment in the blood it is important to examine not only hydrolytic derivatives of NAMI-A complex (Ru(III)) but also their reduced forms. With the use of UV-Vis and fluorescence spectroscopy the association constants for Ru-apotransferrin adducts were determent.

Acknowledgements

Financial support from the National Science Center (grant № N N204 247340) is acknowledged.

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Fragmentation Methods on the Balance: Unambiguous Top-Down Mass Spectrometric Characterization of Oxaliplatin-Ubiquitin Binding Sites

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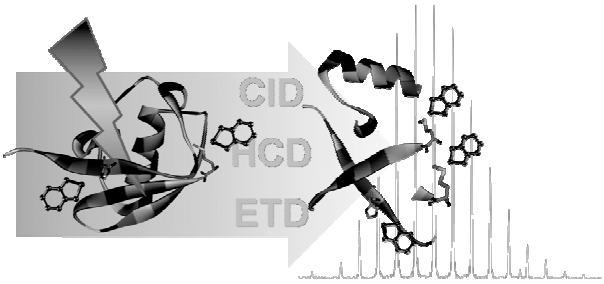
The interaction between oxaliplatin and the model protein ubiquitin (Ub) was investigated in a top-down approach by means of high resolution electrospray ionization mass spectrometry (ESI-MS) using tandem mass spectrometric (MS/MS) techniques, including collision-induced dissociation (CID), higher energy C-trap dissociation (HCD) and electron transfer dissociation (ETD).

Interestingly, ETD-based MS/MS outperformed both CID and HCD in terms of number of identified metallated peptide fragments and the localization of the binding sites. For example, only ETD allowed the simultaneous and exact determination of Met1 and His68 residues as binding partners for oxaliplatin. In addition, CID-based MS/MS experiments were carried out on orbitrap and ICR FT mass spectrometers and both instruments yielded similar results with respect to the number of metallated fragments and the localization of the binding sites.



Furthermore, a comparison of the solution-phase protein secondary structure with the protein fragment ion abundance distributions generated by CID and HCD of the [Ub + Pt(chxn)] adduct [chxn = (*1R,2R*)-cyclohexanediamine] revealed a strong correlation with cleavages in solution random coil areas, indicating that the *N*-terminal β-hairpin and α-helix structures of the metallated Ub may be retained in the gas phase.

Acknowledgements
The authors are indebted to the Austrian Science Fund (FWF; I496-B11), the Hochschuljubiläumsstiftung Vienna, COST D39 and CM0902 for financial support.

Antitumor 'Salan' Titanium(IV) Complexes: Steric and Electronic Effects on Hydrolysis and Cytotoxicity

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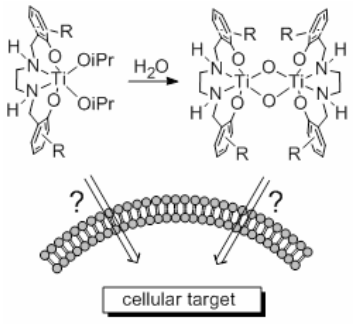
Two titanium(IV) antitumor agents that have been studied extensively are titanocene dichloride and budotitane. Despite their high activity, these complexes failed clinical trials mainly due to their poor water stability and formation of unidentified aggregates in water solutions. Our research group focuses on the synthesis and characterization of new families of antitumor Ti(IV) complexes lacking Cp or diketonato ligands. We recently reported the synthesis, characterization, and cytotoxicity of "salan" type Ti(IV) complexes.[1,2] The well defined hydrolytic behavior, high stability, and high cytotoxicity of these compounds are strongly correlated to ligand structure. This allows fine tuning of complex activity by ligand modifications.

Herein we focus on the steric and electronic effects induced by substitutions on the phenolato rings and on the amines on the cytotoxicity and hydrolytic stability of the complexes. The correlation between the three complex properties: structure, hydrolytic stability and cytotoxicity revealed interesting insights on the biological mechanism of the cytotoxicity of "salan" Ti(IV) complexes and the parameters affecting it.



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Combat Drug Resistance of Cisplatin by Gold Nanorods Based Drug Delivery System

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Cisplatin is one of the most widely used antitumor agents against a variety of solid tumors, such as testicular, ovarian, and bladder carcinomas. It is generally accepted that DNA is the ultimate target of platinum antitumor drugs.[1] However, many extracellular and intracellular proteins can interact with platinum drugs and could be involved in the drug side-effects and tumor resistance, which determine the limitation of clinical application of platinum drugs.[2]

Recently, the inorganic nanosystem has emerged as a highly effective means for platinum drug delivery. In this work, we have used PEGylated GNRs (PEG-GNRs) as a carrier for platinum drug delivery. The prodrug Pt(IV) complex *c,c,t*-$[Pt(NH_3)_2Cl_2(O_2CCH_2CH_2CO_2H)_2]$ was conjugated to PEG-GNRs. On entering cells, the Pt(IV) prodrug can be reduced by cellular reductants to the active divalent platinum; meanwhile cisplatin is released from the carrier. It has been proven that PEG-GNRs are highly stable, relatively noncytotoxic in vivo. Our results showed that the cell uptake of platinum drug was enhanced by the PEG-GNRs conjugates, and the cytotoxicity of this delivery system is significantly enhanced compared with cisplatin.

While the drug carrier can significantly enhance the drug efficacy of cisplatin, this drug delivery conjugate can also overcome the drug resistance. It has been demonstrated that the resistant factor of A549R cell, which show resistance to cisplatin, has largely decrease by PEG-GNRs. Two factors results in the circumvention of the resistance. PEG-GNRs loaded with Pt(IV) can overcome the resistance induced by metallothionein (MT). Our result shows that Pt(IV) reacts with MT more slowly compared with cisplatin. On the other hand, PEG-GNRs can enhance the cellular uptake of platinum drug. hCTR1 plays an important role in cisplatin influx and it is low expressed in resistant cell A549R. PEG-GNRs can avoid this defect and deliver platinum drug into resistant cancerous cell.

In conclusion, the constructed PEG-GNRs can be used as a carrier for platinum drug delivery. This conjugate can significantly enhance the drug efficacy of cisplatin and reduce the resistance induced by high expression of MT or low expression of hCTR1.

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Protective Effect of Alanine on Neurite Growth in Rat Sympathetic Neuron-like Cells Exposed to Copper and Amyloid β-protein Fragment

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β-Amyloid-mediated neurotoxicity is hastened by redox active metal ion including copper. The purpose of the present study is to observe whether alanine can reduce the toxic effect of copper (II) ion on neurite growth using rat sympathetic neuron-like cells. Rat pheochromocytoma cells, PC12, were plated in poly-L-lyisine-coated 96-well plates and maintained in D-MEM containing 10 % horse serum and 5 % fetal bovine serum. Twenty-four hours after incubation, the cells were treated with NGF (50 ng/ml) and incubated for 48 hours. Then, the effects of copper, amyloid β-protein fragment (25-35) (AP), and alanine on sympathetic neuron-like cells were compared. Cell survival ratio significantly decreased in more than 10 μM of copper (II) ion. And when cell were treated with more than 1 μM AP with 10 μM copper ion, the cell survival ratio significantly decreased in comparison with copper alone group. The survival ratio of AP alone group did not differ from the control group. In addition, the ratio decreased by the addition of copper and AP recovered by the addition of L-alanine. Then, we observed the effect of alanine on the neurite growth. When copper and AP were added to the sympathetic neuron-like cells, the number of cells bearing neurite, the number of neurite per cell, and the length of neurite decreased as compared to the control group. When alanine was added to the medium containing copper and AP, both number and length of neurite recovered. From these results, it is concluded that copper ion induces not only cell death but also the reduction of cell function, and the addition of AP promotes neurotoxicity to occur with copper. Furthermore, it is thought that alanine is combined with copper and reduces neurotoxicity induced by copper ion.

Activity of Monensin Biometal(II) Complexes against Animal Tumor Cells

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Monensin is a polyether ionophore produced by *Streptomyces cinnamonensis*, applied in veterinary medicine as coccidiostatic and antibacterial agent. Recently the interest to biological activity of this carboxylic Na^+/H^+ ionophore has been increased by the data concerning its antitumor properties against cell lines established from various malignancies.

The potential antineoplastic activity of Monensin and its metal(II) compounds already reported[1,2] provokes our interest to expand the variety of cell lines to be examined in order to make deeper insights into the properties of these new substances. In the present study we discuss the results on ability of Monensic acid and its complexes $[M(Mon)_2(H_2O)_2]$ (M = Mg, Ca, Mn, Co) to inhibit viability and proliferation of cultured cells isolated from virus- and chemically-induced transplantable tumors in chicken (hepatoma LSCC-SF-Mc29) and rat (sarcoma LSR-SF-SR and tumor of Zajdela). The LSCC-SF-Mc29 and LSR-SF-SR cell lines express the oncogenes *v-myc* and *v-src*, respectively, which human analogues are involved in pathogenesis of a wide variety of malignancies. The studies were carried out by thiazolyl blue tetrazolium bromide (MTT) test, neutral red (NR) uptake cytotoxicity assay and trypan blue (TB) dye exclusion method.

The results obtained have shown that the compounds tested decrease significantly the viability and proliferation of the treated cells in a time- and concentration-dependent manner, with metal(II) complexes being more effective than the non-coordinated Monensic acid.

Acknowledgements
Financial support from the Bulgarian Scientific Research Fund (DO-02-84/2008) is acknowledged.

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New Ruthenium(II) Cyclopentadienyl Compounds: Cytotoxicity and Proteins Binding

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The search in the field of ruthenium based anticancer drugs both in coordination and organometallic chemistry has been certainly stimulated by the successful results obtained with some ruthenium coordination compounds to target metastasis tumours.[1] We have recently reported the excellent anti-proliferative activity of organometallic compounds derived from the "RuCp" moiety, which exhibited significant toxicity against human adenocarcinoma of the colon, pancreatic cancer and leukemia.[2,3]

The present communication reports our most recent results involving new organometallic "RuCp" compounds. The activity of the synthesized complexes towards a panel of human tumor cell lines of typically low, medium and high resistance to metallodrugs was investigated. We carried out extensive characterization of the reactivity of this metal compounds with various proteins via different approaches, including a combination of techniques like UV-vis optical spectra, circular dichroism, fluorescence emission and mass spectrometry.

Acknowledgements

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Synthesis of a Functional Model of Multinuclear Metal Complex for CO_2 Reduction

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Recently, the amount of carbon dioxide in the atmosphere have been increased to affect ambient temperature by the global warming effect. Moreover, carbon dioxide is also expected as a resource material of sun-light energy conversion, when fossil fuel will dry up in near future. Then, effective CO_2-reductoin catalysts are required for production of renewable fuels by using solar energy, converting CO_2 to CO, formic acid, and methanol.

In biological system, CO dehydrogenases (CODHs) are known for catalyzing the direct conversion from CO_2 to CO, and the active site structure has attracted much attention. These enzymes contain either a Mo-Cu-S or a Ni-Fe-S active site, catalyzing the reversible reaction $CO + H_2O = CO_2 + 2\ H^+ + 2\ e^-$ as a primary process in the global carbon cycle. The latter Ni-containing CODH[1] utilizes "C-cluster" at their catalytic site for CO/CO_2 interconversion. In the catalytic core, one Ni and one Fe centers of the cluster cooperatively work as CO_2 binding and Lewis acid sites, respectively. In this case, two metal centers in the clustering structure are essentially used for C-O bond cleavage upon CO_2 reduction.

In this study, we are synthesizing a stable multinuclear metal core in a cage-type ligand, having multi-coordination sites inside the molecule. We have ever synthesized multi-metal complexes with several types of cryptands having three bridging spacers as coordination sites.[2] In this report, we synthesized a tricobalt complex with a new mesityl-capped cryptand having bis(imino)pyrrolyl spacers, H_3L (Fig. 1). We synthesized a new pyrrole ring-containing cryptand complex with a multinuclear cobalt core. Further studies are ongoing to investigate the reduction activity of CO_2.

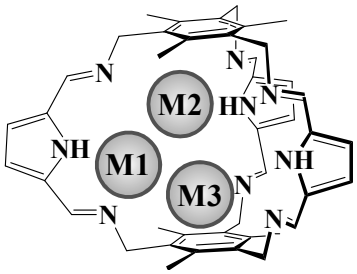

Figure 1. Multinuclear metal core in a cage type ligand.

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Complexes of Cu(II) and Zn(II) with 7-amino-4-methylchromone: Spectroscopic, Electrochemical and Antioxidant Properties

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Molecules containing the chromone (4*H*-benzopyran-4-one) structure are of great interest because of their biological activities include cytotoxic (anticancer), neuroprotective, HIV-inhibitory, antimicrobial, antifungal and antioxidant.[1-2]

In the present study we report synthesis and X-ray structure of 7-amino-4-methylchromone complexes with Cu(II) (Fig. 1) and Zn(II) (Fig. 2) ions. The zinc ion is coordinated with two ligand molecules by *O*-atom of carbonyl group, whereas the copper ion is surprisingly coordinated by carbonyl group of one ligand molecule and by *N*-atom of amine group of second ligand molecule.

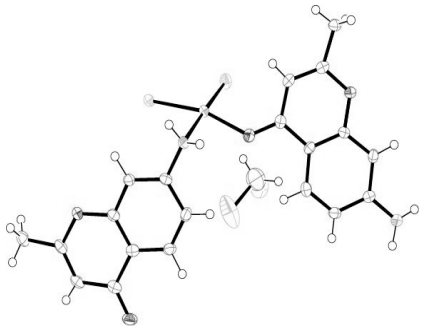

Figure 1

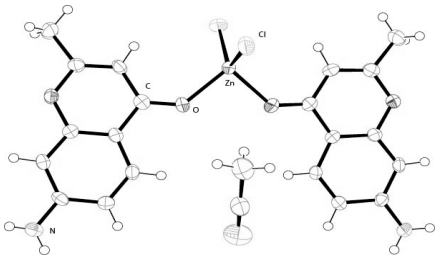

Figure 2

Also the electrochemical properties of compounds have been studied by cyclic voltammetry in DMSO solutions over the potential range from -1.5 to 1.5 V. The ligand and complexes have been characterized by UV/Vis and fluorescence spectroscopy. Moreover total antioxidant status (TAS) of all compounds was measured.

Acknowledgements

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Computational Study and Refinement of an X-ray Catalytic Antibody Structure

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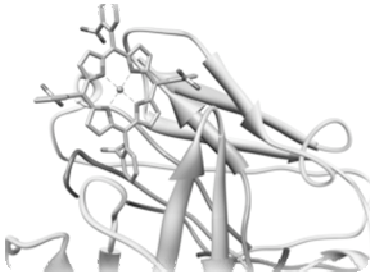
Several catalytic antibodies (abzymes) have been generated by designing specific antibodies against inorganic catalysts. These artificial metalloenzymes have interesting catalytic properties, such as substrate specificity and enantioselectivity. Little structural information, though, is available on this kind of biocatalysts and structure activity relationships are therefore particularly difficult to profile. This represents a key missing element for the rational design of novel, more efficient species. Efforts from both wet and dry sides are needed to provide with the relevant amount of molecular knowledge in this field.



Here we present a combination of X-ray crystallography and molecular modeling study to investigate the structural and energetic features of a family of abzymes developed by Mahy and coworkers.[1] Starting from a crystallographic structure with uncertainties on the exact binding mode of the cofactor but complete definition of the binding site, protein-ligand docking are carried out on the Fe(ToCPP) derivatives. The computational study started with the position occupied by the cofactor in the soaked crystal. The study is pursued on the entire family of porphyrinic derivatives which activity has been tested in solution. This work allows understanding better the complementarities between both inorganic and biological partners, particularly the impact of the substituents of the cofactor in its interaction with the binding site of the apo abzyme.

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Oxidation of Alcohols Using a Cage Type Zn(II) Complex as a Functional Model of Alcohol Dehydrogenase

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In the few decades, various biomimetic metal complexes had been synthesized as functional metal of the active sites of metalloenzymes, and a lot of findings were obtained for understanding the reaction mechanisms. However, it is generally very difficult to mimic the active metal centers with a cooperatively working coenzyme.

We try to construct a functional model of alcohol dehydrogenase (ADH),[1] having nicotinamide adenine dinucleotide (NAD^+) as a coenzyme. In this protein, NAD^+ is linked with the Zn(II) center through one of the ligating water molecules. In the proposed reaction mechanism of NAD^+,[2] ethanol binds to the Zn(II) center, causing deprotonation of the substrate. At this moment, the electron deficient nicotinamide moiety of NAD^+ could be reduced by hydride-transferring from the ligating ethoxide, to generate NADH and acetaldehyde as products.

In this model study using a cage type ligand, $\mathbf{L_{NH}}$, a Zn(II) ion binding to one of the three coordination sites inside of $\mathbf{L_{NH}}$, having a host space for a guest molecule.[3] The structure of Zn(II)-$\mathbf{L_{NH}}$ with ancillary ligands, such as acetate ions, was determined by ^{1}H-NMR and X-ray single crystal structure analysis. To this system, 1-benzylnicotinamide (ND_{BZ}^+) was added as a NAD^+ analogue. When this Zn(II) complex was mixed with various alcohols in the presence of ND_{BZ}^+, we observed increasing optical absorption near 350 nm, which is attributed to formation of 1-benzyl-1,4-dihydronicotinamide ($ND_{BZ}H$). These results strongly indicate two-electron reduction of ND_{BZ}^+ by variouis alcohol derivatives. Futher study on this system are in progress.

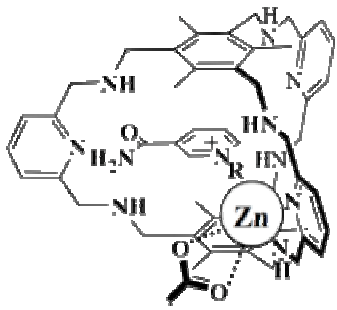

Figure1. Assembly of an active Zn(II) ion and a coenzyme model, ND^+, inside a cage type ligand, $\mathbf{L_{NH}}$.

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Interaction with DNA and Anticancer Studies of Pd(II) Complexes Containing Dithiocarbamato and 1,10-phenanthroline Derivatives

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In order to modulate activity and toxicity of platinum-based anticancer drugs, new strategies are under study on the metal complexes containing N and S donors. Pd(II) complexes are good models *in vivo* because of their more labile nature than Pt(II) complexes. Recently, Pt(II) and Pd(II) mixed complexes containing diimine and dithiocarbamato ligands were synthesized and evaluated for *in vitro* cytotoxicity against human tumor cell line K562.[1] In this study, we examined interaction with DNA and anticancer activity of Pd(II) complexes containing dithiocarbamato and 1,10-phenanthroline derivatives (Fig. 1). The interaction was investigated using competitive ethidium bromide (EtBr) studies and circular dichroic (CD) spectroscopy. The fluorescence intensities of EtBr-CT-DNA decreased with increasing Pd(II) complex concentrations. From the plots of these intensities against complex concentrations the apparent DNA binding constants were calculated. The DNA-binding abilities of the Pd(II) complexes follow the order: $[\mathbf{1}]^+ > [\mathbf{2}]^+ > [\mathbf{3}]^+ > [\mathbf{4}]^+$. Upon adding $[\mathbf{2}]^+$, $[\mathbf{3}]^+$, or $[\mathbf{4}]^+$, the CD spectrum of DNA underwent slight changes in both the positive and negative bands, and slight shifts in band position were also observed. In contrast, upon adding $[\mathbf{1}]^+$, the CD spectrum of DNA was drastically changed, suggesting that $[\mathbf{1}]^+$ may allow to change DNA structure.

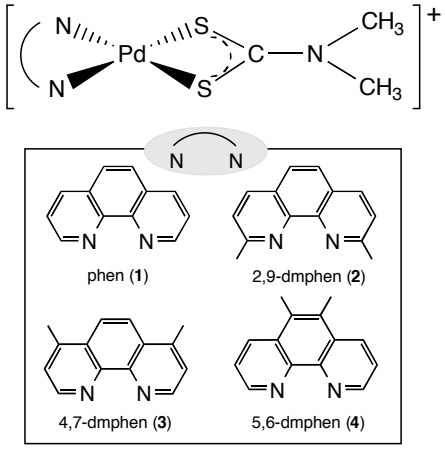

Fig. 1. Pd(II) complexes used in this study.

The strong interactions of the Pd(II) complexes with CT-DNA and a correlation was found between the *in vitro* cytotoxicity and DNA interaction studies of the Pd(II) complexes. The antitumor screening of $[\mathbf{1}]^+$ proved to be highly active against cisplatin resistant L1210.

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Metalloprotein Mimics by Design: Strategies and Applications

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Metalloproteins take part in a variety of life-sustaining processes and catalyze difficult reactions with efficiency and selectivity that few other natural or artificial molecules can achieve.[1] For this reason, structural and functional studies on metalloproteins have been the focus of many years of research. These studies require a simultaneous and accurate analysis of both the polypeptide chain and the metal cofactor herein embedded. In fact, the plethora of interactions that occur between the metal cofactor and the protein environment mutually affects the properties of each other, thus enhancing, diversifying or tuning their individual functions.[2] Over the years, a large number of low molecular weight chemical catalysts has been developed as metalloenzyme mimics.[1,2] They have been basic in elucidating structure and function of metalloproteins and metalloenzymes; however they often fail in reproducing several features of biocatalysts, such as high turn-over number under mild conditions and high selectivity. Combining the advantages of chemical and biological catalysts would represent a daunting goal for chemists. Tailoring synthetic models requires the development of sophisticated molecular architectures that distil the quintessential elements responsible for activities. Thus, peptide-based models seem valuable candidates to mimic both the structural features and reactivity of the natural systems.

Using a structure-based strategy we have reproduced by design metalloprotein active sites. We centered our attention on iron-containing proteins, and we developed models for heme[3] and diiron-oxo[4] proteins. The structural and functional characterization demonstrates their usefulness in biomedical and environmental applications, as well in biosensor construction.

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Syntheses of α-Alkylserines by Forming Copper Complexes

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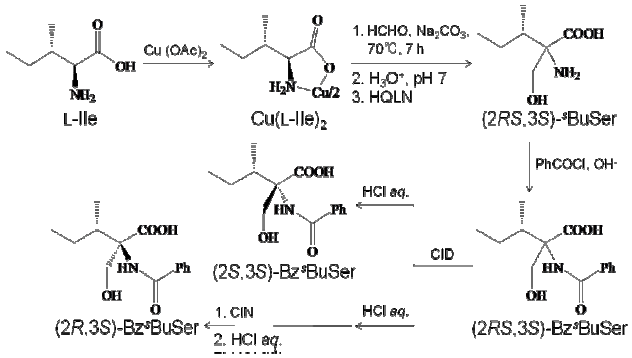
Optical active α-alkylserines, which have amphiphilic properties, are known as efficient materials improving pharmaceutical effects of peptides. For example, water solubility of cyclolinopeptide A (CLA), which isolated from linseed oil and has a strong immunosuppressive activity in water, was improved by substitution of an α-alkyl amino acid in CLA to an α-alkylserine.[1]

Syntheses of α-alkylserines from alkyl amino acids have been required tedious prosesses, protection and deprotection of the amino group,[2] so we tried a method for synthesis of α-alkylserine from formaldehyde and an copper complex of an alkyl amino acid under basic conditions. Cu ion has a potential to make α-proton of a coordinated amino acid more reactive than an uncoordinated amino acid and to protect functional groups like -COOH and -NH_2 of the coordinated amino acid.

$Cu(L\text{-Ile})_2$, Na_2CO_3 and formaldehyde was dissolved in water, and resulting solution stirred at 70 ºC for 7 h. The reaction solution was added 8-quinolinol (HQLN) in acetone, and the formed $Cu(QLN)_2$ was removed by filtration to give (2*RS*,3*S*)-^{s}BuSer from filtrate in 24.1% of yield.



After purification and isolation of (2*RS*,3*S*)-^{s}BuSer, we tried separation of diastereoisomeric *N*-benzoyl derivatives of (2*RS*,3*S*)-^{s}BuSer to obtain optically pure ^{s}BuSer using cinchonidine (CID) and cinchonine (CIN) as separating agents.

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Chemical Approaches for Epigenetic DNA Modification

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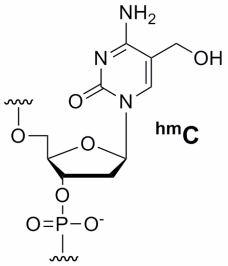
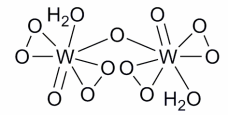
5-Hydroxymethylcytosine (^{hm}C) is a natural nucleobase that is abundant in neurons and embryonic stem cells [1-3]. Given the critical role of 5-methylcytosine (^{m}C) in epigenetic regulation, ^{hm}C may play an important biological role in vivo, such as an intermediary role in the pathway of active DNA demethylation. An effective method to detect the presence and abundance of ^{hm}C in DNA is required to elucidate the relationship between the generation of ^{hm}C and the mechanism of demethylation.



A fluorescein-labeled model sequence containing CG, ^{m}CG, or ^{hm}CG dinucleotides, DNA1(X) 5′-fluorescein-AAAAAAGXGAA-AAAA-3′ (X = C, ^{m}C, or ^{hm}C), was prepared, and several metal oxidants have been tested as oxidation agents of DNA1(X), considering their reactivity against nucleobases, reagent availability, and solubility in water [4]. The metal oxidant (5 mM) was added to a solution of DNA1(X) (5 μM) in a 50 mM sodium phosphate (pH 7.0). The mixture was incubated at 50 °C for 5 h, and then it was desalted through a filter. The sample was treated with hot piperidine and analyzed using PAGE to find the oxidized nucleotides in DNA through DNA cleavage. The dinuclear peroxotungstate, $K_2[\{W(=O)(O_2)_2(H_2O)\}_2(\mu\text{-}O)]\cdot 2H_2O$ was the most effective ^{hm}C-selective oxidant among metal oxidants tested in this experiment. PAGE analysis of the strand cleavage product after the reaction of DNA1(X) with peroxotungstate and the subsequent hot piperidine treatment showed a band at the ^{hm}C site of DNA1(^{hm}C). The cleavage bands observed at the ^{m}C and C sites in DNA1(^{m}C) and DNA1(C), respectively, were negligible.



We will also report a facile preparation protocol for ^{hm}C-containing oligodeoxynucleotides and an ^{hm}C-positive reaction that is effective for the discrimination of ^{hm}C from C and ^{m}C in a single-stranded DNA of interest.

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Capacities of Computational Approaches to Predict Inert Inorganic Scaffolds Interacting with Proteins

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Protein-Ligand docking is a well-known methodology to predict the binding of ligands to proteins and is nowadays a key element in numerous chemical and biological fields.[1] The effectiveness of this approach has been tested in a large number of biochemical systems whether for descriptive or predictive applications. In the special case of protein-ligand dockings where the ligand is a metallic complex (i.e. metalodrugs or artificial cofactors), qualities and pitfalls have been rarely investigated.

In function of the coordination features of the metal, two different kinds of interactions between the inorganic complex and the protein can be found. If the first coordination sphere of the metal is not altered in the binding process, the inorganic moiety results as an inert scaffold where the metal does not participate through coordination bound in the recognition process. If ligand exchange is possible between protein and inorganic moieties, the metal takes an active part in the binding and can chelate a residue of the protein.[2]

In this work, we aim to benchmark standard computational approaches for inert scaffolds interacting with proteins. To do so, protein-ligand docking calculations have been performed using different scoring functions. The need of parameter optimization is discussed and the application of the methodology for high throughput virtual screening and rational design is analysed.

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Mechanistic Studies on Chlorophyll Degradation Processes

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Growing interest in metal interactions with tetrapyrroles arises from both the well known roles played by metalloporphyrins in biological systems as well as from their new possible applications (such as photodynamic therapy, PDT). Mechanistic studies conducted on metal insertion (metalation) and metal exchange (transmetalation) processes showed high sensitivity to the reaction conditions, especially redox-activity of metal ion, solvent and counter ion properties.[1] Thus slight change in the composition of the reaction medium results in the substantial change of reaction pathway. Two different mechanisms of chlorophylls oxidation were distinguished on the basis of spectroscopic investigations of the reactions of pheophytin *a* (Pheo *a*) and chlorophyll *a* (Chl *a*) with various copper(II) salts in organic solvents. One of them, typical for the free base species of photosynthetic dye (Pheo *a*), leads to gradual degradation of the tetrapyrrolic system, which results in the ring opening and formation of the chain species. The other, typical for reactions involving Chl *a*, is a reversible one-electron oxidation of the macrocycle which terminates at the bimetallic (Mg-Chl *a*-Cu) complex. Obtained kinetic data, as well as the results of spectroscopic and electrochemical investigations, provided not only with the premises for detailed mechanisms of these reactions but also with the explanation of role played by acetic ion, which was found to activate Chl *a* and secure non-redox reaction pathway.[2]

Acknowledgements
Financial support from the National Science Centre (grant No. NN204439640) is acknowledged.

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Mechanistic Insight into the Formation of Oxo-iron(IV) in the Reaction of Fe(III) Porphyrin with H_2O_2. The Influence of *N*-methylimidazole Ligation

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For decades biomimetic studies on the "peroxo-shunt" oxidation reactions by applying synthetic iron(III) porphyrin complexes and various terminal oxidants have provided valuable information on the mechanism of reactive intermediate formation in oxygenation reactions. These substantially advanced the understanding of the chemistry of *in vivo* oxygenation processes. The reaction of hydrogen peroxide with iron(III)-porphyrins is of particular interest since several different kinds of heme enzymes catalyze the oxidation of a variety of compounds by H_2O_2, e.g. peroxidases. Therefore, our recent research focuses on the studies of the kinetics and mechanism of the reaction of hydrogen peroxide with synthetic iron(III)-porphyrins as biomimetic models for oxygenases.

In this context, we present the results of a detailed mechanistic study of the reaction of hydrogen peroxide with water-soluble iron(III) porphyrin, [*meso*-tetrakis(2,4,6-trimethyl-3-sulfonatophenyl)porphinato]iron(III), Fe^{III}(TMPS), in alkaline (pH =10) aqueous solution. The formation of oxoferryl porphyrin was studied in the absence and presence of various excess of N-methylimidazole in order to gain more mechanistic information on the role of axial ligands on the formation and reactivity of the Fe(IV)=O species in the studied system. With the application of a rapid-scan technique we were able to follow complete UV/Vis spectral changes related to the formation of (TMPS)(X)Fe^{IV}=O and decay in the presence of various substrates. The kinetic studies involving the determination of the rate of oxo-iron(IV) porphyrin formation under conditions of different oxidant concentration, temperature and pressure were performed using stopped-flow UV/Vis spectroscopy techniques. The obtained results allowed us to extract the second order rate constants and activation parameters for the studied reactions. These data enabled us to develop a detailed understanding of the underlying reaction mechanisms. Moreover, the application of a sequential mixing stopped-flow technique enabled the determination of rate constant for oxygenation of organic compounds.

The Interaction between Ferritin and Metallothioneins Promotes simultaneous Metal (Fe and Zn) Delivery

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Iron, an essential metal for living organisms, plays a crucial role in many biological processes. However, excess iron is toxic and Fe^{II} reacts with oxygen to produce reactive oxygen species (ROS). ROS are extremely powerful oxidizing agents capable of causing cell damage. The iron storage protein, ferritin (Ft), plays a crucial role in protecting the cell from iron catalyzed ROS formation and is often observed at elevated levels in some radical-mediated diseases presumably devoted to sequester free iron. The physiological functions of metallothioneins (MTs) are still unknown, although they have been related to the homeostasis of copper and zinc, metal detoxification, as well as to radical scavenging. Surprisingly, the possible interaction between MTs and Fts has never been considered, despite the known affinity of thiolate ligands for iron-binding and the lack of a defined receptor for the iron released from ferritin.

Our recent studies demonstrate, in contrast with the data already published, that the interaction between Ft and MT gives rise to a Zn^{2+} and Fe^{2+} delivery process. Therefore, the Zn-forms of mammalian metallothionein isoforms (MT1, MT2 & MT3) release iron from ferritin by electron tunneling (MTs are too big to penetrate the ferritin channels) and Fe^{3+} is reduced and mobilized from the ferritin cavity. In this reaction the MT Cys residues become oxidized to disulfide with the concomitant release of Zn^{2+}, which probably induces the synthesis of further Zn-MT. These results point out a so far unrecognized process by which proteins that independently bind metal ions to protect the cell against metal toxicity can cause damage if interacting when coming together. Our *in vitro* results claim for further *in vivo* studies to determine which mechanisms could operate to prevent this Ft-MT interaction and/or the deleterious consequences of the generated radicals in case it effectively takes place.

Acknowledgements

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Cyclotoxic Properties of Monensic Acid and its Biometal(II) Complexes against Human Tumor/Non-tumor Cell Lines

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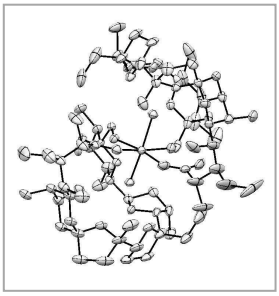
The anticancer activity of Monensic acid (MonH) and its biometal(II) complexes $[M(Mon)_2(H_2O)_2]$ (M = Mg, Ca, Mn, Co, Ni, Zn)[1-3] was evaluated for the first time against cultured human permanent cell lines established from glioblastoma multiforme (8MGBA) and cancers of the lung (A549), breast (MCF-7), uterine cervix (HeLa) and liver (HepG2). The non-tumor human cell line Lep3 was also tested for comparative purposes. The investigations were carried out using thiazolyl blue tetrazolium bromide test, neutral red uptake cytotoxicity assay, crystal violet staining, colony forming method and double staining with acridin orange and propidium iodide. The results obtained reveal that the compounds applied at concentrations of 0.5-25 μg/mL for 24-72 h decrease the viability and proliferation of the treated cells in a time- and concentration-dependent manner. The investigated metal(II) complexes (especially those of Co(II), Ni(II) and Zn(II)) has been found to express higher cytotoxic and cytostatic activities as compared to the non-coordinated Monensic acid.



The data obtained merit further investigations to clarify better the cellular targets, mechanism(s) of action and biological safety of these compounds. The knowledge concerning the relationship between the chemical structure of such compounds and their biological activities will facilitate the design of drugs with improved anticancer properties.

Acknowledgements
Financial support from the Bulgarian Scientific Research Fund (DO-02-84/2008) is acknowledged.

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Superoxide Dismutase and Catalase Modeling using N_3 Ligands

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Superoxide dismutases (SODs) and catalases are key regulators of reactive oxygen species (ROS) that are responsible for oxidative stress. SODs utilize Fe, Cu/Zn, Mn or Ni as cofactors while catalases contain Fe or Mn. Understanding the connection between the oxidative damage (induced by high levels of ROS) and various deseases has lead to studies on selective, non-toxic enzyme mimics for medical purposes. Activity of well characterized complexes has also been tested, supporting the design of potential pharmaceuticals. We present a comprehensive study on Mn(II), Fe(II), Ni(II) and Cu(II) complexes[1-5] with systematically modified isoindoline-based ligands (Fig. 1). Key features to control the activities are usually the redox behavior and the coordination environment, *e.g.* identity of co-ligands by isoindolines. In case of our SOD mimics, systematic modifications in the ligand environment control the redox properties for the metals. Comparison of the metal/ligand combinations highlights differences between the metals in analogous ligand environment: activity of Fe is dominated by its redox potential, while that of the Mn mainly influenced by the peripheral ligand functions. Cu complexes exhibit activity that is dependent on a combination of multiple factors. Mn complexes also served as catalase models with increasing activity by the addition of strong π-donor co-ligands.

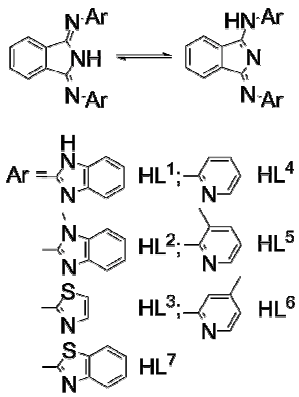

Figure 1

Acknowledgements

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Synthesis and Characterization of new Ruthenium(II)-arene Complexes with Chromon Derivatives

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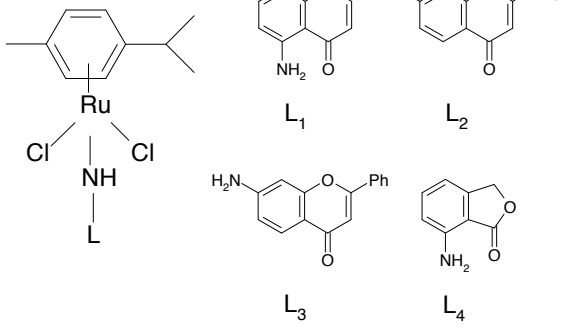
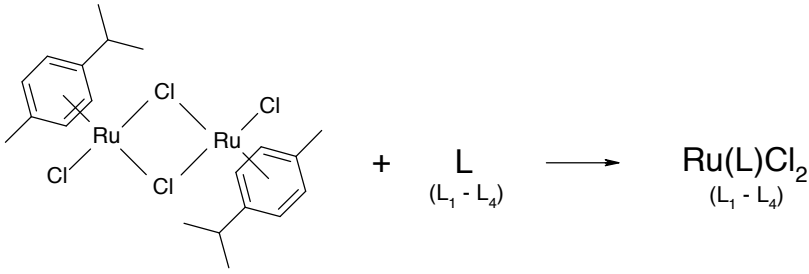
Ruthenium-based compounds are one of the most promising candidates for anticancer drugs. For the last four decades many strategies and numerous compounds have emerged in order to develop potent chemotherapeutics. Recently, much attention is paid to half-sandwich arene ruthenium complexes. Their nature allows an insertion of biologically active groups and make them ideal for preparing multifunctional drugs.[1]



Four novel Ru(II)-arene complexes with chromon derivatives have been prepared. In this paper we raport on the synthesis and characterization of newly formed compounds. Preliminary study of cytotoxic effect was also investigated.



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A Step Forward to the Miniaturization of Biosensors incorporating Metallothioneins as Ionophores

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Many ion-selective electrodes (ISE) have been reported for metal ions. The construction of potentiometric biosensors has mainly been achieved by a biomembrane superposition on the ISE. The use of a matrix of polysulfone (PS), a porous polymer, makes possible to embed enzymes, antibodies or, as in our case, metallothioneins (MTs). Construction of PS-based biosensors required small amounts of biomaterial and provides many advantages in terms of manipulation and storing.

Recent works have reported the use of MTs as ionophores for the quantification both of metal ions[1] as well as of certain mammalian MTs.[2] However, these were of considerable size and their use required considerable amounts of calibrating solutions. This impares their application to real biological samples, from which normally only small volumes are available.

The work here presented aims to the miniaturization of the PS-based potentiometric biosensors embedding MTs as ionophores for the quantification of metals ions and of MTs in very small amounts of real samples.

The first results show similar quantification limits in the Ag^+-ISEs than in those previously reported but the sizes of sample required for the measurements are about 20 times lower, just one drop, than the previous ones.

Acknowledgements

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Metallothioneins as Detoxifying Agents for Pb(II)

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Lead is one of the major hazards in human health due to its wide distribution in the environment. Pb(II) preferentially interacts with proteins containing Zn(II) (ALAD, CadC, GATA, Zn-fingers) and Ca(II) (CaM, PKC, syt) causing not only interferences in some metabolic processes, mainly the biosynthesis of hemoglobin, but also the inhibition of several enzymes and damages to the central nervous system (CNS). Against these deleterious effects, living organisms have developed defense and Pb(II)-detoxification mechanisms among which we can find metallothioneins (MTs).

Metallothioneins (MTs) are the most versatile metal-binding proteins present in all organisms because their unusually high Cys content confers them a high capacity to chelate heavy metal ions, both *in vivo* and *in vitro*, allowing them to act as detoxifying agents.

This work is focused in the determination of the capability of the four mammalian MT isoforms -MT1 and MT2 (both ubiquitous), MT3 (in CNS) and MT4 (in stratified epithelium)- to detoxify Pb(II) under physiological conditions (pH 7 and 37ºC), by means of spectroscopic (CD and UV-vis) and spectrometric (ESI-MS) techniques.

The results obtained confirm that the Zn-loaded mammalian MTs isoforms show a quite differentiated behavior when binding Pb(II). Strikingly, Zn-MT4 is unable to bind Pb(II) while Zn-MT1, Zn-MT2 and Zn-MT3 can bind up to 10 Pb(II) equivalents quite readily. In spite of this capacity of MT1, MT2 and MT3 for forming Pb(II)-complexes, ESI-MS monitorization of the distinct Zn-MTx + Pb(II) reactions have shown that the distinct Zn- *vs*. Cu-thionein character of each isoform[1] clearly determine its capacity of retaining the initially bound Pb(II). Interestingly, among all mammalian MT isoforms, MT3 exhibited the best abilities to detoxify Pb(II). This final finding is especially relevant if taken into account that this isoform is only present in CNS and the damages that lead can precisely exert to its crucial structures.

Acknowledgements

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New (Poly)metallic Architectures Suitables for Bioimaging

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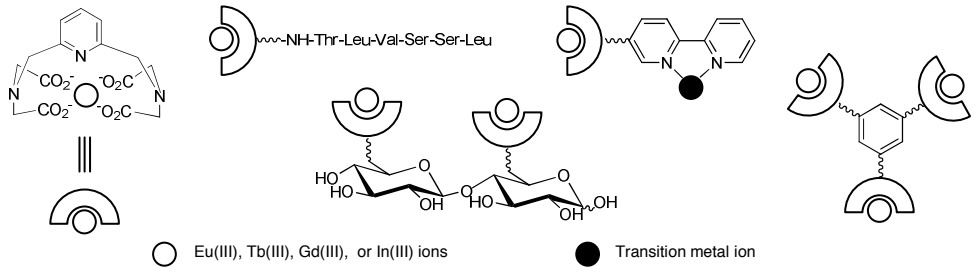
Recently, we have demonstrated that Ln(III) complexes derived from 2,6-pyridinediylbis(methylene nitrilo)tetraacetic acid (PMN-tetraacetic acid) ligand show interesting properties either for optical (fluorescence) imaging and for magnetic resonance imaging (MRI).[1] In the Gd(III) complex, the presence of two metal-bound water molecules ensures an efficient MRI efficacy with a larger proton relaxivity than that found in Gd(III)-based contrast agents used in clinical practice. For Eu(III) ones, this hydration sphere does not impair the luminescence efficacy which remains competitive with that of Eu(III)-based commercial luminescent probes.

Currently, we will show that this ligand can be easily derived on the pyridine ring for imaging biotargeting purposes or designing new di- or tri- metallic architectures potentially suitable for bimodal imaging.



The synthesis and physicochemical properties of these various metallic architectures will be discussed. According to these studies, these new complexes might be potential new candidates for molecular imaging or bimodal imaging (MRI/Optical, SPECT/Optical).

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Gold Nanoparticles Modified by Thrombin Binding Aptamer

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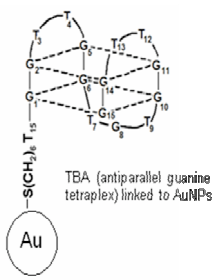
In the last few decades nanotechnology has been bringing new possibilities for the construction of biosensors and development of new bioassays.[1] The greatest attention has been paid to gold nanoparticles (AuNPs) which, due to their good biocompatibility, conductivity and unique structural, electronic, magnetic, optical and catalytic properties, are very attractive materials for the construction of chemical sensors and biosensors.[2,3] For the study of proteins the construction of biosensors consists in modified AuNPs anchored on the surface of electrodes, aptamer bonding to the protein studied.[4] The most intensively studied aptamer is a DNA 15-mer known as thrombin binding aptamer (TBA), which binds thrombin and inhibits its activity in the formation of a blood clot.[5] This contribution is focused on the preparation of a thrombin biosensor which is constructed by self–assembling a thiol-modified thrombin binding aptamer with a sequence of GGT TGG TGT GGT TGG (TBA) onto the gold nanoparticle surface. On this created self-assembled monolayer (SAM) the thrombin is attached. The aptasensor system was characterized by UV-Vis spectroscopy and transmission electron microscopy (TEM). The aim of our work is a comparative study of the GNPs-TBA conjugates, depending on the size of nanoparticles (5 - 20 nm) and on ionic strength (from 0.1 to 0.8 M).

The analysis of our study led to (a) an improvement of the understanding of the aptamer-thrombin recognition at the molecular level and (b) to a knowledge of the effect of NPs size and the composition of solutions on the stability of the aptasensor system.



TBA (antiparallel guanine tetraplex) linked to AuNPs

Acknowledgments

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A Peptidic Turn with High Affinity for Hg(II)

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Environmental contamination by heavy metals is increasing due to human activity and this is leading to a high concentration of these metals in water. Mercury is considered to be one of the most dangerous heavy metals because all its forms (inorganic and organic mercury) have been related with several human health problems representing thus, a serious threat to public health.[1] Different strategies have been developed to remediate mercury contamination from aqueous environments and are still being developed since more effective and economical strategies are needed.[2]

Our goal is to design new chelating ligands for the removal of Hg(II) from water using small peptidic turns containing Cys. In this work, we will present the general design strategy of the ligand and the evaluation of the Hg(II) coordination properties. Different spectroscopic studies, among them UV-Vis, CD and NMR, as well as ESI mass spectrometry showed a high affinity of the ligand for Hg(II) at a wide pH range. The stability of the ligand and the Hg(II) complex under different experimental conditions were also analyzed and will be presented.

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Hydridotris(azolyl)borato Phosphino-Cu(I) Complexes: Ligand Effect on their *in vitro* Cytotoxicity

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In the last three decades the research of new antitumor agents has spread over complexes of metals other than platinum. Among the considered metals, copper has gained a growing interest and many classes of copper(I/II) complexes have demonstrated anticancer activity and the ability of overcoming inherited or acquired resistance to cisplatin.[1] In the last years we have focused our attention on copper(I) derivatives and due to the "soft" nature of Cu(I) the choice of ligands having soft donor atoms such phosphorous in tertiary phosphines or aromatic sp^2 hybridized nitrogen of pyrazolyl derivatives, allowed us to obtain stable active derivatives. In particular, we have reported the synthesis of homoleptic phosphine copper(I) complexes and of heteroleptic copper(I) compounds comprising both phosphine and scorpionate ligands.[2,3] Trying to find a structure-activity relationship for copper(I) compounds containing a tridentate scorpionate or tris(azolyl)borate ligand (L) and an auxiliary monodentate phosphine (P), we have prepared and screened a series of '3+1' $[CuLP]^{0/+}$ compounds. All reported complexes showed in vitro antitumor activity comparable to that of cisplatin, the reference metallodrug. Among them, the complex $[Cu(HB(pz)_3)(PCN)]$ ($HB(pz)_3$ = tris(pyrazolyl) borate, PCN = tris-cyanoethylphoshine), showed IC_{50} values up to 15-fold lower than those recorded with the reference compound, demostrating a particular efficacy against human 2008 ovarian adenocarcinoma and A431 cervix carcinoma cells. The correlation between cytotoxicity, liphophilicity and steric hindrance of the ligands as well as final charge of the complexes is discussed.

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Cobalt(II) Complexes with Non-steriodal Anti-inflammatory Drugs: Structure and Biological Evaluation

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The biological role of cobalt is mainly focused on its presence in the active center of vitamin B12, which regulates indirectly the synthesis of DNA. Additionally, Co is involved in the co-enzyme of vitamin B12 used as a supplement of the vitamin and in other cobalt-dependent proteins.[1] Diverse structurally characterized cobalt complexes showing antitumor-antiproliferative, antimicrobial, antifungal, antiviral and antioxidant activity have been reported.[2]

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medicinal drugs and are used as analgesic, anti-inflammatory and antipyretic agents. They have also exhibited chemopreventive and anti-tumorigenic activity and a synergistic role on the activity of certain antitumor drugs. The interaction of NSAIDs directly at the DNA level is of great interest in order to explain the tentative anticancer as well as the anti-inflammatory activity.[3] Indomethacin belongs to the NSAID group of phenylalkanoic acids exhibiting favourable anti-inflammatory, analgesic and antipyretic properties while tolfenamic acid is a NSAID derivative of anthranilic acid and resembles chemically to flufenamic and mefenamic acids and other fenamates in clinical use.[4-6] In this context, we have initiated the interaction of cobalt with diverse NSAIDs[2] and we present herein the synthesis, structural characterization, electrochemical and biological properties of the Co(II) complexes with the NSAIDs indomethacin and tolfenamic acids in the absence or presence of the N-donor ligands bipy or bipyam. The crystal structures of $[Co(tolf)_2(bipyam)]$ and $[Co_2(indo)_4(bipy)_2(H_2O)]$ have been determined by X-ray crystallography.

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Imidazole Derivatives of Aminophosphonates as Efficient Chelators for Ni(II) and Cu(II) Ions

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Aminophosphonates are analogues of aminocarboxylates in which a carboxylic moiety is replaced by a phosphonic, $PO(OH)_2$ groups. Many of these compounds act as antagonists of amino acids, inhibit (metallo)enzymes involved in the peptide and amino acid metabolisms and thus affect the physiological activity of cells.[1] The inhibitory action is performed through the phosphonate group coordination to metal center of the enzyme.[2] Taking into account all the possible applications lots of analogs have been synthesized and studied towards metal ions binding. Our studies fit well in this subject.[3,4] In this work, we present solution studies of Cu(II) and Ni(II) with 2-imidazole derivatives of aminophosphonates. The presence of the 2-imidazol ring makes studied phosphonates very efficient ligands, with Ni(II) ions chelation much more effective than by the previously designed 4-imidazol analogues. Introduction of *ortho*-pyridine as additional donor in the side chain further increases the binding ability. The effectiveness of this compound is due to chelation of metal ions through imidazol, imino and pyridine nitrogen donors.

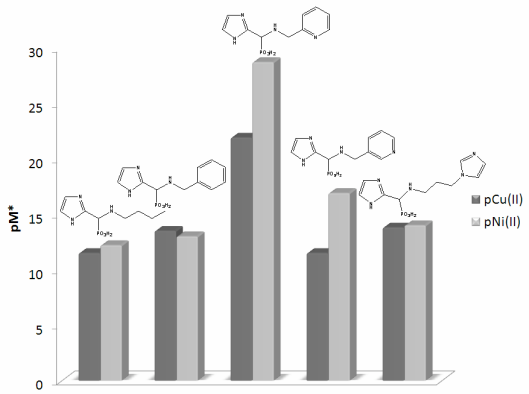

Figure 1. pM values for Cu(II) and Ni(II) complexes of studied ligands $pM^{*}=-[\log M(II)]_{free}$ calculated at pH 7.4 $C_{M(II)}=1\cdot10^{-6}$ $C_L=1\cdot10^{-5}$ M

Acknowledgements

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Experimental Determination and Modeling of the Lipophilicity in Platinum Complexes

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The ADME (Absorption, Distribution, Metabolism and Excretion) profile is of paramount importance in the drug design process in order to enable chemists to design out negative properties (e.g. chemically reactive moieties, readily metabolized sites) and incorporate positive attributes (e.g. optimal water solubility, good membrane permeability). The lipophilicity, expressed as the log of the octanol/water partition coefficient (log $P_{o/w}$), is a crucial factor governing passive membrane diffusion and, hence, the cellular uptake of a drug. For antitumor Pt(II)-complexes, log $P_{o/w}$ has been reported to be exponentially related to Pt uptake.

The experimental determination of lipophilicity is not a trivial matter. On the other hand, mathematical predictions based on the weighting of functional groups within a molecule have been performed with impressive accuracy. Unfortunately, Pt(II) complexes represent a dataset of not easy integration in larger databases of organic compounds, and thus, of difficult comparison with standard pharmaceutical products. This occurs mainly because their peculiar chemical properties often require particular experimental conditions to obtain lipophilicity data.

The experimental and *in silico* tools that may be used to determine and predict log $P_{o/w}$ values of antitumor Pt(II) drug candidates will be discussed. In particular, the calculation of molecular descriptors of potential application in ADME virtual screening suggests a strategy to identify good Pt(II) complexes prior to their synthesis. At the same time, this approach allow to eliminate as soon as possible drug candidates with unfavorable pharmacokinetic profile.

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Synthesis and Characterization of Novel Asymmetrical M(III) (M = Re, ^{99g}Tc) Complexes as Models for the Development of Potential Tracers for SPECT Imaging and Radiotherapy

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Development of new ^{99m}Tc and $^{186/188}$Re radiopharmaceuticals still remain an interesting research topic thanks to their ideal nuclear properties. ^{99m}Tc is the radioisotope of election for SPECT-imaging (E_γ=140 keV, $t_{1/2}$=6.02 h), and $^{186/188}$Re are important radionuclides with therapeutic potential (^{186}Re: E_β=1.07 MeV, E_γ=137 keV, $t_{1/2}$=90.6 h; ^{188}Re: E_β=2.12 MeV, E_γ=155 keV, $t_{1/2}$=17 h). Despite the rich and diverse coordination chemistry of these two congeners, very few M(III)-complexes are reported in literature and none have clinical applications.

Within we report the synthesis and the characterization of a new series of neutral, asymmetrical, hexacoordinated Re/^{99g}Tc-complexes of the type [$M^{III}(PS)_2(L)$] where PS is the strong π-acceptor 2-(diphenyphosphino)ethanethiolate (PS2) or the completely alkylic non-π-acceptor 2-(diisopropyl)ethanetiolate (PSiso) P,S-bidentate ligands, while L is a dithiocarbamate (DTCn) or pyridine-2-thiolate (MPy) ligands.

Stable [$M^{III}(PS)_2(L)$] complexes were synthesized, in moderate to good yield, starting from precursors where the metal is in different oxidation states, involving ligand exchange reactions and/or reduction-ligand exchange reactions. All the compounds were characterized by elemental analysis, multinuclear NMR, ESI(+)-MS, and cyclic voltammetry. X-ray diffraction analysis was performed on crystallized [$^{99g}Tc^{III}$/$Re^{III}(PS2)_2(DTC1)$], [$Re^{III}(PS2)_2(DTC2)$], (DTC1 = pyrrolidine-1-carbodithioate; DTC2 = 4-(ethoxycarbonyl)piperidine-1-carbodithioate), and [$Re^{III}(PS2)_2(MPy)$]. For [$M^{III}(PS)_2(DTCn)$] X-ray analysis revealed a distorted octahedral geometry, where the four Sulfur atoms occupy the equatorial plane and the two Phosphorus atoms span the trans apical positions. [$^{99g}Tc^{III}(PS2)_2(DTC1)$] is isostructural and isomorphic with [$Re(PS2)_2(DTC1)$]. X-rays diffraction data of [$Re^{III}(PS2)_2(MPy)$] show the presence of the pyridine-2-thiolate. The collected results indicate the possibility to consider this new class of complexes suitable for the development of novel ^{99m}Tc/$^{186/188}$Re-agents useful in theragnostic applications. Studies are currently in progress in order to transfer this technology at tracer level.

Platinum(II) Complexes derived from Carbazoles. A new Step for the Design of Luminescent Antitumoral Agents

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The design and preparation of new luminescent materials able to exhibit this property in biological media is one of the common challenges of Chemistry, Biochemistry, Pharmacy and Biomedicine nowadays, because they may be useful as diagnosis agents, sensors or even to trace the effect produced by a therapeutic agent and also to accurate the doses required to an improved treatment.[1]

Despite the relevance of *cis*-$[PtCl_2(NH_3)_2]$ (*cisplatin*) in the treatment of cancer, the development of more effective antitumoral drugs with lower toxicity and side effects than cisplatin is one of the most attractive areas of Inorganic Chemistry. One of the strategies used to achieve this aim consists on the search of novel *N*-donor ligands for the synthesis of optimized platinum(II) complexes.[2] Polycyclic organic compounds (derived from thiazoles or azoles) are typical arrays of a wide variety of bioluminescent materials (such as luciferin or coelentetrazine).[3] However, platinum(II) complexes with ligands derived from carbazole still remain unknown.

In this contribution we present the synthesis, characterization and the study of the luminescent properties of two new 3-substituted carbazole derivatives (**1**). Thiophene and thiazole heterocycles bonded in position 3 to the carbazole unit have been considered and a comparative study of their reactivity in front of Pt(II) has been undertaken. This has allowed us to isolate and characterize different sorts of platinum(II) complexes, including *cis*- and *trans*-isomers of $[PtCl_2(\mathbf{1})L]$ (L = neutral ligand) in which the environment of platinum(II) is similar to those of other antitumoral platinum(II) based drugs.

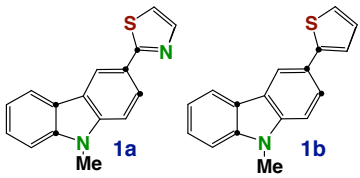

Figure 1. Carbazole derivatives under study.

Acknowledgements

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Au(I)-mediated Base Pairs

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Due to their polyanionic nature, the natural nucleic acids DNA and RNA always occur in combination with cations.[1] In an effort to expand the metal-ion binding capability of nucleic acids and to allow also predictable site-specific functionalization with metal-ions, metal-mediated base pairs have been developed.[2] These base pairs typically consist of artificial nucleosides with an increased affinity towards metal ions. However, also natural nucleosides can be used.

Inspired by the successful incorporation of Ag(I) into an oligonucleotide double helix containing imidazole as artificial nucleobase,[3] different oligonucleotides were studied via UV and CD spectroscopy with regard to the incorporation of Au(I). The use of Au(I) is of particular interest due to possible aurophilic interactions between neighbouring metal-mediated base pairs.[4] Initial spectroscopic results will be presented.

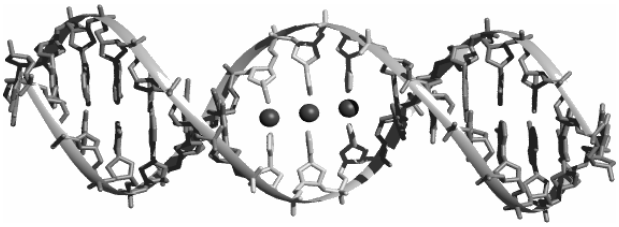

Figure. Oligonucleotide duplex with neighbouring Ag(I)-mediated base pairs.[3]

Acknowledgements
Financial support from the Deutsche Forschungsgemeinschaft DFG (IRTG1444) is acknowledged.

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New Ruthenium Antitumor Complexes: Synthesis, Anti-proliferative Activity and Interaction with Human Albumin

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Cancer is the second largest cause of death in developed countries and the number of global cancer death is projected to increase 50% until 2030.[1] Cisplatin and platinum-based drugs are the most widely used in cancer therapy. Nevertheless ruthenium compounds have conquered a prominent position in metallodrug development for cancer therapy. Some complexes are selective antitumor agents with anti-metastatic properties and low toxicity,[2] and high anti-proliferative activity.[3] Ru^{II} polypyridyl systems exhibit unique chemical and physical properties, and have been reported to interact with DNA and to bind proteins, which makes them attractive compounds for antitumor drug developen.[4]

We present herein the synthesis and characterization of a new family of complexes with the 'Ru^{II}(NN)' moiety (NN = 2,2'-bipyridine, 1,10-phenantroline). These new compounds were fully characterized by spectroscopic techniques (IR, ^{1}H, ^{13}C NMR, UV-Vis absorption and fluorescence spectroscopy) and cyclic voltammetry. The anti-proliferative activity of the complexes against ovarian, breast and colon adenocarcinoma human tumors was assessed using the MTT cell viability test. Our continuous work on this field led us to explore the possibility that these new Ru^{II} complexes may be effectively distributed by blood plasma. Our first results on the interaction of these compounds with human serum albumin are presented (MTT = 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide).

Acknowledgements

Authors thank financial support from the Portuguese Foundation for Science and Technology (FCT): PTDC/QUI/66148/2006, PTDC/Qui-Qui/101187/2008, PEst-OE/QUI/UI0536/2011, PEst-OE/QUI/UI0612/2011 and *Ciência2007/Ciência2008* Initiatives). Oscar L. Rojas acknowledges *Xunta de Galicia*, the Spanish Ministry of Education for his fellowship and *Universidade da Coruña*.

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Cellular Uptake Studies of *N,N*-chelated Organometallic Ruthenium(II) Anticancer Complexes

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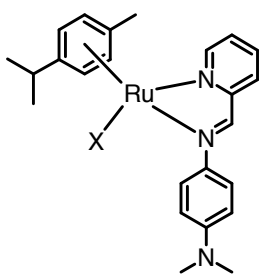
Most of the metal drugs in clinical use are platinum-based. However, our group has been working on ruthenium(II) arene complexes as anticancer agents,[1] with the aim of reducing common toxic side effects of platinum drugs and overcoming inherent and acquired resistance.[2] Ruthenium(II) piano-stool complexes with a general formula $[Ru(\eta^6\text{-}p\text{-cymene})X(YZ)]PF_6$, where X is a monodentate substituent and YZ is a *N,N*-bidentate ligand, exhibit promising cytotoxic activity. These complexes can be tuned by changes in the three main building blocks around the metal centre[3] to improve their activity and pharmacological properties. In the present work changes to the monodentate ligand X are used to influence cellular uptake and accumulation.

Complexes $[Ru(\eta^6\text{-}p\text{-cymene})(X)(N,N\text{-dimethyl-}N'\text{-}[(E)\text{-pyridine-2-ylmethylidene}]$ benzene-1,4-diamine)$]PF_6$ have been fully characterized by nuclear magnetic resonance, electrospray mass spectrometry and elemental analysis. Their cytotoxic activity (IC_{50} values) in four human carcinoma cell lines (A2780, A549, HCT116 and MCF7, ovarian, lung, colon and breast cancer cells, respectively) was determined using the sulforhodamine B colourimetric assay. The time-, concentration- and temperature-dependence of the cellular accumulation of Ru in A2780 human cancer cells has also been studied and compared to the corresponding data for cisplatin. Furthermore, the time dependence of cellular efflux has been explored.



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A Comparative Study of the Anticancer Activity of the Hetero-metallic Complexes $\{[(PTA)_2CpRuDMSO]$-μ-$AgCl_2\}_n$ and $[(PTA)_2CpRuDMSO][AgCl_2]$

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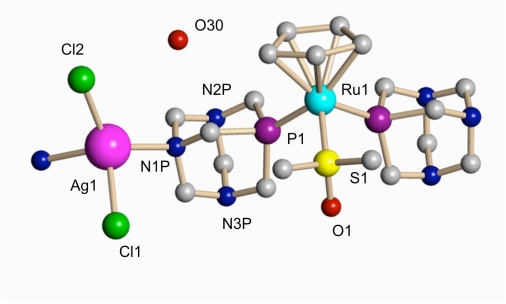
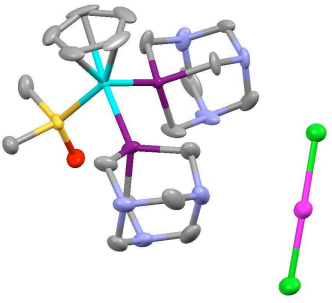
The anticancer activity of ruthenium complexes is even more investigated as they shown activity when others compounds are inactive. Most of the ruthenium complexes are not water-soluble what limits their use in water or systems with large concentration of water, like biological systems. Here we present the anticancer activity of the first example of the air stable water-soluble hetero-organometallic polymer $\{[(PTA)_2CpRuDMSO]$-μ-$AgCl_2\}_n$ (Figure-left)[1] and the bimetallic $[(PTA)_2CpRuDMSO][AgCl_2]$, in which the Ag is not coordinate to the N-PTA atom (Figure-right) (PTA = 1,3,5-triaza-7-phosphaadamantane). The hetero-metallic-polymer complex is significantly anticancer active (GI_{50} = 27 nM en células HeLa) larger that the bimetallic (GI_{50} = 3.0 μM in HeLa cells), being this complex the first example of this kind active against cancer cells.





Acknowledgements

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Novel Ruthenium(II), Rhodium(III) and Iridium(III) Antitumor Complexes with a Levonorgestrel Pendant

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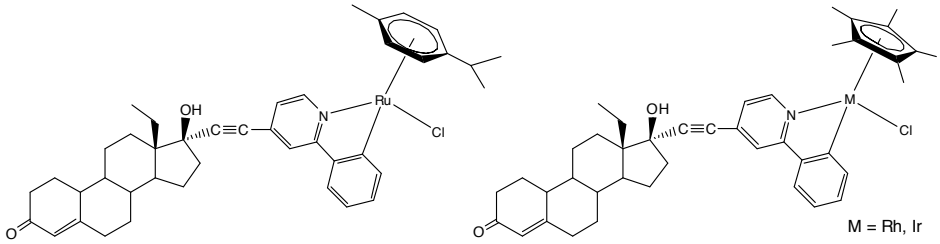
One of the main goals in the field of inorganic (or organometallic) antitumor drugs is to overcome the two major limitations of cisplatin, namely, poor selectivity and high incidence of drug resistance. Where cisplatin is of limited used, ruthenium has emerged as an attractive alternative to platinum because of its excellent activity in tumors and low general toxicity. In this context, one of the most investigated class of organometallic compounds is based on the Ru(II)-arene unit, which have antitumor or antimetastatic properties both *in vitro and in vivo*.[1,2]

In this work, we report the synthesis and characterization of the novel 17α-(2-phenylpyridin-4-yl)levonorgestrel molecule (LNG-Phpy) and some new steroid-C,N-chelate Ru(II), Rh(III) or Ir(III) conjugates of the type [M(LNG-Pphy)Cl(ring)] (ring = *p*-cymene or Cp*).



We studied the *in vitro* antiproliferative activity of these new complexes in the cisplatin resistant human breast cancer cell line T47D (oestrogen receptor positive ER+ and androgen receptor AR+, T47D being cisplatin resistant).

Acknowledgements

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Metal-Linked Neurodegenerative Processes in Alzheimer's Disease. Pathogenetic and Neuroprotective Insights

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Alzheimer's disease reflects neurodegenerative processes that inflict damage to key brain loci, outstanding of which is the hippocampus. The pathologoanatomical features of the disease include senile plaques and neurofibrillary tangles, with both of them being attested to in post mortem studies. Metallotoxins are among the key contributors to oxidative stress known to initiate, promote and/or exacerbate oxidative stress, ultimately leading to neuronal degeneration in Alzheimer's dementia. Both inherent and environmental metals turn into toxins and bring about lesions that accumulate and degrade the neuronal structure and function of the human brain. Poised to investigate the effects of such metallotoxins, attention was focused on iron, copper and aluminium, with the last one having been at the forefront of scientific conjecture over the years. In the case of Al(III), structural speciation studies have shown the involvement of discrete species arising from binary and ternary interactions with low and high molecular mass physiological ligands. The role of such discrete and potentially bioavailable species has been probed through in vitro cytotoxic studies, inquiring into their chemical reactivity toward whole neuronal cells, specific cellular structures linked to oxidative stress-induced neurodegeneration, and neuronal (and glial) death. Interestingly enough, physiological substrates of hydroxycarboxylate nature appear to play a significant role not only as bioavailable Al(III) solubilizers but also as neuroprotection agents[1,2] at the level of interactions perused.

The collective results delineate the role of Al(III) in the specific neurodegenerative processes and emphasize the salient structural features of the substrates that either enhance its bioavailability[3] or/and assist in the process of neuroprotection against the onset of molecular symptomatic events, intimately linked with the progress of the disease.

Acknowledgements

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Pt-based Anticancer Drugs: Studying their Interaction with Proteins and Oligonucleotides

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Platinum complexes, such as cisplatin, are widely known as anticancer drugs since some time ago.[1] Indeed, following their clinical success in the treatment of various cancer forms, second generation of Pt-based anticancer drugs were designed and tested, trying to avoid the problems derived from the use of cisplatin. DNA is generally accepted to be the target for platinum-based drugs,[2] which induce structural modifications on the helix, thus promoting apoptosis.[1] Potential responses leading to drug resistance include, among others, increased production of intracellular thiol-containing molecules. Due to the strong reactivity exhibited by Pt compounds towards S-donor ligands and the formation of very stable Pt^{II}-S bonds, intracellular thiols confer resistance to antitumor Pt drugs through their competition with DNA. On the other hand, the interactions of platinum drugs with proteins may play crucial roles in their uptake and biodistribution processes as well as in determining their toxicity profile.

In this work we have studied the *in vitro* reactivity of two related Pt complexes: $[Pt(dmba)(9AA\text{-}N1)(PPh_3)]^+$ (dmba = *N*,*N*-dimethylbenzylamine-κN,κC; 9AA = 9-aminoacridine)[3] and [Pt(dmba)(aza-N1)(DMSO)] (aza = azaindolate),[4] which showed sub-micromolar activity in several human tumor cell lines. The analysis of the interaction of both complexes with several proteins and a designed DNA fragment (oligonucleotides) by several techniques has revealed specific and unexpected reactivities of the complexes when interacting with both, proteins and oligonucleotides. This has made necessary the use of theoretical calculations in order to better understand the differential reactivity of these Pt compounds.

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Biocomjugate Metalloporphyrins/Ferritin Nanoparticles

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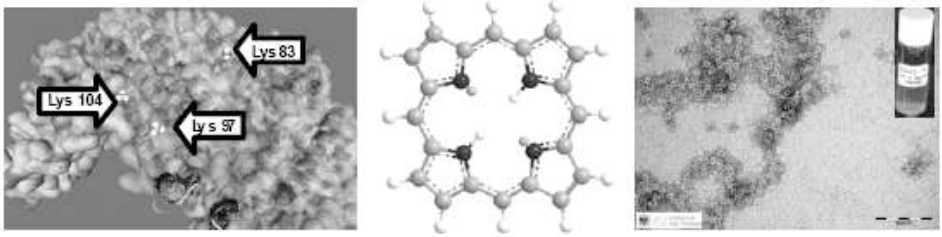
Ferritins are a family of proteins that are widely distributed in nature and they are generally characterized by a 24 subunit polypeptide shell within which an iron core of variable content and composition is deposited.[1] The protein shell provides a platform for chemical functionalization by lysine or cysteine groups.

On the other hand, porphyrins are representative of photofunctional biomolecules, and they show remarkable photo-, electro- and biochemical properties.[2] Some porphyrin derivatives are known to selectively accumulate in the tumor tissue.[3]



We have synthesized a library of bifunctional porphyrin apoferritin nanoparticles in order to be used as bifunctional nano-objets in medical applications. The fluorescence of these multimodal nanoparticles, the water solubility and its reduced size (*ca.* 12 nm) represent important advantages that make these compounds an appealing candidate to be tested in biological systems. The particles have been characterized by TEM, UV-Vis, EDX, IR, electrophoresis gel and TG/DSC.

Acknowledgements
We are grateful to the MICINN (project CTQ2009-9344) and Junta de Andalucia (FQM2007-2525) for financial support.

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DNA as a Potential Biological Target for new Ruthenium(II) Polypyridyl Anti-tumor Complexes

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The development of Cisplatin as a cytotoxic agent in the late 60's was a breakthrough in cancer chemotherapy. Given their remarkable efficiency, cisplatin, oxaliplatin and carboplatin are the most widely used against cancer even today[1] regardless their lack of selectivity, the severe dose limiting side-effects reported and the development of resistance to treatment often observed. These drawbacks provided an urge to seek different approaches, and ruthenium compounds are now a proven effective alternative in cancer treatment.[2,3]

We have recently reported a family of organometallic "$Ru^{II}Cp$" compounds (Cp = η^5-cyclopentadienyl) which were shown to exhibit anti-proliferative activity in the nanomolar range against human colon adenocarcinoma, pancreatic cancer and leukemia, highlighting the great potential of Ru^{II} compounds as antitumor agents.[3,4] We have now synthesized and fully characterized a new family of fluorescent ruthenium complexes with the '$Ru^{II}(bpy)_2$' moiety (bpy = 2,2'-bipyridine), and investigated their anti-proliferative activity against ovarian, breast and colon adenocarcinoma human tumors.[5] Our continuous work on this field led us to explore DNA as a potential biological target for these new Ru^{II} complexes.

We present herein our first results on the interaction of these compounds with DNA obtained by a combination of different techniques, namely UV-Vis absorption and fluorescence spectroscopies and viscometry.

Acknowledgements

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Carbonic Anhydrase IX Inhibitor Coated Nanoparticles: new Diagnostic and Therapeutic Approaches for Cancer Treatment

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The carbonic anhydrases (CAs) are ubiquitous metalloenzymes which catalyze the reversible hydration of carbon dioxide. Recently emerged that CAs could have also potential as novel antiobesity, anticancer, and anti-infective drugs. A critical problem in the design of CAs inhibitors (CAIs) is related to the high number of isoforms in mammals their diffuse localization in many tissues/organs, and the lack of isozyme selectivity of the presently available inhibitors.

Human CA IX (hCA IX) is an extracellular, transmembrane isoform which was recently shown to constitute a novel and interesting target for the anticancer therapy due to its overexpression in many cancer tissues and not in their normal counterparts.[1]

Nanoparticles (NPs) on their side are receiving now great attention for their biomedical applications as site-specific delivery of drugs, laser thermal activation or contrast agent in imaging NMR techniques.

We report here the synthesis of CAIs coated Au NPs which show excellent CA IX inhibitory properties and selectivity for the inhibition of the tumor-associated isoform.[2] We also developed CAIs coated Iron Oxide NPs which could be used for NMR Imaging.

In vitro and in vivo data show promising results of these systems for imaging of perianoxic region of tumor mass, for the decrease of primary tumor volume as well as the control of metastasis.

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Chimeric GNA/DNA Metal-mediated Base Pairs

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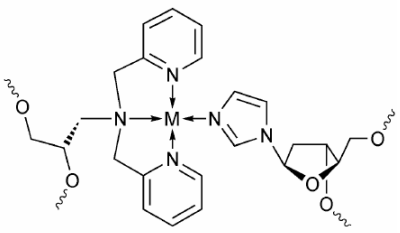
The introduction of transition metals into ether DNA or GNA *via* metal-ion-mediated base pairs is a promising strategy towards a functionalization of these supramolecules (GNA = glycol nucleic acid).[1,2] The possibility to combine different nucleic acid backbones within one metal-mediated base pair expands the applicability of metal-functionalized nucleic acids.

We report the introduction of chimeric GNA/DNA metal-mediated base pairs in DNA double helices. The base pairs are built from tridentate GNA dipicolylamine nucleoside and complementary monodentate DNA azole nucleosides (imidazole, 1,2,4-triazole and tetrazole). In this way, a planar complexation can be obtained (Scheme to the left with monodentate imidazole as example).



UV and CD spectroscopic data indicate a Ag(I)- and Au(III)-ion mediated stabilization of all three base pairs. Other transition metal ions do not lead to significant thermal stabilization. To verify the formation of a silver(I)-mediated base pair, theoretical calculations based on dispersion-corrected density functional theory were performed. The calculations support an incorporation of Ag(I) into oligonucleotides.[3]

Acknowledgements

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Concentration–dependent Pd(II)–C Bond Formation in Complexes with a 2N-donor Ligand Containing an Indole Moiety

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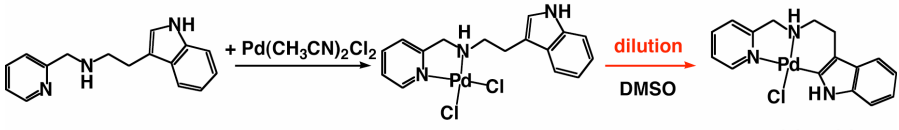
The indole ring of the tryptophyl residue with the highest hydrophobicity among α-amino acids is known to form a hydrophobic environment for specific binding of molecules and to be involved in electron transfer pathways. Further, formation of the indolyl radical from a tryptophyl residue in proteins has been established for the intermediate, compound I, formed in the catalytic reaction of the cytochrome *c* peroxidase (C*c*P). Tryptophan (Trp) coordinates to metal ions through the amino and carboxylate groups, whereas only a few metal ion-indole ring interactions have been characterized for biological systems. On the other hand, various Pd complexes have been reported to play important roles in various catalysts, such as C-C bond formations, C-X bond activations, and the most of these reactions have been considered via Pd-C intermediates. In these points in mind, we have synthesized a novel indole-binding Pd(II) complex and characterized its reactivity.

Reaction of 3-(N-2-pyridyilmethylamino)ethylindole (L) with $PdCl_2$ in CH_3CN at room temperature gave Pd(II) complex of $Pd(L)Cl_2$ (**1**) as pale yellow powder. ^{1}H-NMR spectrum of complex **1** displayed that the shift of the indole protons signals were rather small in comparison of other indole-binding Pd complexes, therefore, we assigned the structure of **1** to a square planar geometry with two nitrogen atoms and two chloride anions coordination. However, addition of triethylamine to the DMF/CH_3CN (1:1 v/v) solution of complex **1** showed gradually color change to dark yellow to give complex **2** as yellow crystals. Absorption spectrum of **2** showed an intense absorption peak at 304nm, indicating a formation of Pd-C bond. X-ray crystal structure analysis of **2** revealed to have the in2 carbon atom of the indole ring bound to Pd(II) ion. Dilution of the DMSO solution of Pd(II) complex **1** leads to the C–H bond activation of the pendent indole moiety and formation of Pd(II)-indole binding complex **2**. The initial step of the conversion was assigned to the replacement of a coordinated Cl^- ion with DMSO, which was promoted at low concentrations of **1**. Further details will be discussed in this conference.



L [Pd(L)Cl$_2$] (1) [Pd(L)Cl] (2)

Using Peptide-based Models for Understanding of Binding and Mechanism of Copper(I) Metallochaperone Proteins

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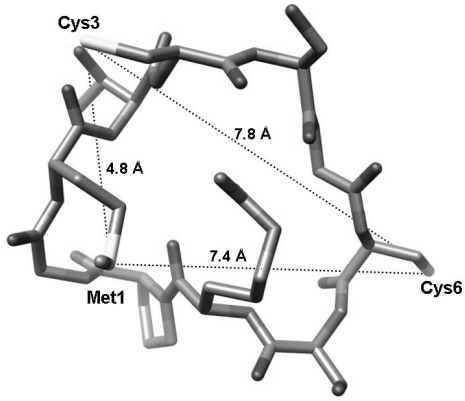
Copper serves as an important catalytic cofactor in proteins that perform fundamental biological functions. The ability of copper to readily switch between +1 and +2 oxidation states enables catalytic functionality in redox chemistry, but may also cause high toxicity by producing reactive oxygen species such as those that occur in a number of neurodegenerative diseases.

Copper metallochaperones are intracellular proteins that specifically bind Cu(I) ions, inhibit their oxidation and deliver them to the target proteins via protein-protein interactions, thus protecting the cellular environment from harmful copper-mediated reactions.[1] The active sites of these proteins contain a conserved sequence: *MH/TCXXC.* NMR and crystallography have shown tight binding to Cu(I) ions through two soft thiolato ligands of the side chains of the two cysteine residues in a low coordination number of 2. It is generally accepted that the methionine residue does not participate in copper binding.

Herein, a Cu(I) complex of a model peptide was studied in three solutions that model acidic, neutral and basic pH conditions. The NMR-derived structures showed an unexpected coordination mode under acidic conditions with interesting effect of pH, revealing a coordination of methionine and cysteine instead of the native mode, an observation that suggesting a possible role of Met in metal transport.[2]



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Xanthosine 5'-Monophosphate. A Nucleotide with Unusual Acid-base and Metal Ions-binding Properties

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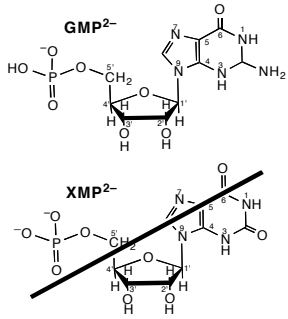
Xanthosine and its nucleotides are important metabolic intermediates participating [1] in diverse enzymic reactions, e.g., in xanthine oxidase, purine phosphoribosyl-transferases, purine nucleoside phosphorylases, nucleoside hydrolases, etc., and they occur in all kingdoms of life, including bacteria, plants as well as humans, and are consequently widely studied. In the literature, including textbooks, the structure of xanthosine 5'-monophosphate (XMP) is commonly shown in analogy to that of guanosine 5'-monophosphate (GMP^{2-}). Unfortunately this structure is not correct and thus, in many instances revisions regarding mechanistic considerations, etc., will be needed. (i) XMP^{2-} is a minority tautomer that occurs only to about 10%; the dominating one (90%) is $(X - H{\cdot}MP{\cdot}H)^{2-}$[2] which carries a proton at the phosphate group, but has lost one from the (N1)H/(N3)H sites, giving thus rise to further ambiguities. (ii) Most importantly, in the physiological pH range of about 7.5 XMP is present as the 3-fold negatively charged $(X - H{\cdot}MP)^{3-}$ species. –Both properties are reflected in the structure of the complexes: In $(M{\cdot}X - H{\cdot}MP{\cdot}H)^{\pm}$ complexes the metal ion is mainly at N7 of the deprotonated xanthine residue[2] and the proton is at the phosphate group. Outersphere macrochelation involving the $P(O)_2(OH)^-$ group occurs for nine metal ions studied with a formation degree of about 65%, i.e., independent of the M^{2+} involved. This is different[2] for the $(X - H{\cdot}MP{\cdot}M)^-$ complexes, in which the PO_3^{2-} group is the main binding site; here the extent of macro-chelate formation involving N7 varies widely, i.e., from about zero (Mg^{2+}, Ca^{2+}) to 90% (Zn^{2+}, Cd^{2+}) or more (Ni^{2+}, Cu^{2+}). Of course, further isomeric equilibria are possible[2,3] including aromatic-ring stacking[4,5] of the deprotonated xanthine residue. No doubt, XMP is a truly chameleon-like nucleotide.



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Mechanism of 1-aminocyclopropane-1-carboxylic Acid Oxidase: Contribution of Model Complexes and Kinetic Studies

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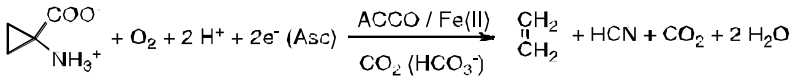
The use of metal cofactors in enzymes is a widespread strategy to achieve dioxygen activation in oxidation processes. In particular, mononuclear non-heme iron(II) centres, with their great catalytic versatility, have attracted attention. The largest subgroup of non-heme iron(II) oxidizing enzymes utilizes 2-oxoglutarate (2-OG) as a cosubstrate and shares a conserved fold (double stranded β-helix fold, DSBH) that forms the core for the active site. Another key structural motif is their 2-His-1-Asp facial triad constituting the Fe(II) coordination pattern. ACC Oxidase (ACCO) is an atypical member of this family since it does not require 2-OG, but ascorbate, for activity. It catalyzes the last step of ethylene biosynthesis, a key hormone in plant development and defense (Figure 1). The crystal structure of ACCO from *Petunia hybrida* was obtained in 2004 but no data is available on the binding of the substrates/cofactors.[1] The role of carbon dioxide/bicarbonate that is required for activity is also unknown.



Scheme 1. Reaction catalyzed by ACCO

Thanks to an interdisciplinary approach we aim at getting more information on ACCO. We have prepared and characterized several Cu-ACC and Fe-ACC complexes.[2] Recent kinetic and theoretical studies using substrate analogs providing a model of possible interactions of ACC, HCO_3^- and ascorbate at the active site, will also be discussed.

Acknowledgements
Financial support from the Agence Nationale de la Recherche (ANR -09-JCJC-0080) is acknowledged.

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Solution Structure and Metal Ion-binding Properties of the 5' Splice Site in Group II Intron Retrohoming

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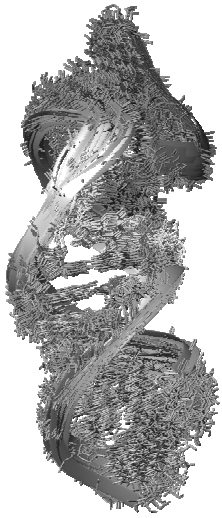
Group II introns are large catalytic RNAs located in different organellar precursor transcripts of a great variety of species. During so-called self-splicing, the intron catalyzes its own excision from the RNA transcript and the ligation of the flanking exons.



As mobile genetic elements, group II introns can reinsert into RNA or DNA by catalyzing a reverse splicing reaction with the aid of intron-encoded proteins.[1,2] This process is referred to as retrohoming if the recipient molecule is DNA. Group II intron catalysis depends on the presence of magnesium(II) ions.

Both splicing and retrohoming events are initiated by recognition and binding of the three exon binding sites (EBS) of the intron to their corresponding intron binding sites (IBS) on the target strand.

To investigate the contact formation and metal ion binding during this first step of retrohoming, we have solved the solution structure of the isolated EBS1-dIBS1 interaction, where dIBS1 is the DNA sequence directly upstream of the 5' splice site, and conducted binding studies with Mg(II), Mn(II) and cobalt(III)hexamine ions by NMR.

Our results suggest a magnesium(II) binding site near the 5' end of EBS1 where the RNA backbone displays an unusual kink. We suspect this structural motive might be important to coordinate a catalytically relevant Magnesium(II) ion[3] in close proximity to this splice site.

Acknowledgements

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Transmetallation Reaction between Zn(II) and Tc-99m as a Tool to Prepare new Radiopharmaceuticals

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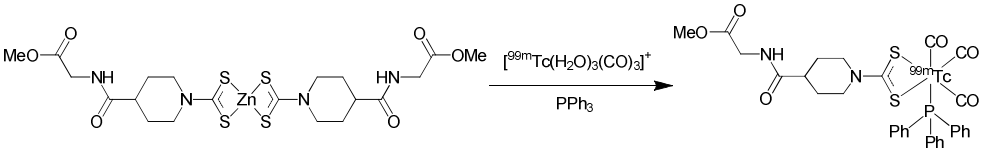
We are developing an innovative method to prepare new rhenium and technetium compounds for radiopharmaceutical applications by means of a transmetallation reaction with Zn(II) compounds.[1] We previously reported that this transmetallation reaction works very well between zinc and rhenium with Zn(II) dithiocarbamates. The studied zinc compounds were prepared from the succinimidyl ester of the Zn(II) dithiocarbamate of isonipecotic acid because we proved that it is an excellent synton for bioconjugating zinc to biomolecules.[1,2]

In the present communication, the study of the transmetallation reaction has been extended to the radionuclide Tc-99m with the methyl esters of glycine and β-alanine that were chosen as a model compounds of bioconjugated Zn(II) dithiocarbamates. Thus, the results have shown that the reaction between the $[^{99m}Tc(H_2O)_3(CO)_3]^+$ cation and a suspension of the solid dithiocarbamate lead to the expected Tc-99m dithiocarbamate with a radiochemical yield of 97-98 % as it is shown in the following scheme for the glycine derivative:



Tc-99m products were characterised by HPLC analysis showing a retention time of 13.0 min, similar to the homologous rhenium complexes previously characterised (12.6 min).[1,2]

It should be emphasised that this reaction is so favourable that takes place in water although the solubility of the Zn(II) dithiocarbamates are extremely low. Consequently, the low concentration of the unlabeled biomolecule in the reaction medium, using this approach, allow to obtain Tc-99m products with high specific activity and make them a good option for radiopharmaceuticals preparation.

Acknowledgements

Financial support from projects CTQ2007-63913 and BIO2009-12513-C02-02 is acknowledged.

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Synthetic Approach to Oxygen Evolving Complex by Construction of Multinuclear Manganese Core Structure

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Photoinduced water splitting reaction has attracted much attention due to its potential application toward artificial solar energy and conversion and storage. This reaction is catalyzed by the oxygen-evolving complex (OEC) of PhotosystemII (PSII) in the thylakoid membranes of green plants, cyanobacteria, and algae.[1] Recentry, the detailed crystal structure analysis revealed the Mn_4CaO_5 core in OEC.[2] Despite effective manganese cluster complexes oxidixing water to dioxygen for solar energy conversion, are not yet attained.[3]

In this study, we used a cage type ligand, L, for construction of manganese clustering model compounds of OEC. The cage type ligand could stablize the cluster structure due to its linked framework, We synthesized a new cage type ligand, $\mathbf{L_{OAc}}$, which is a poly-acetic acid substituted analogue of **L** (Fig. 1) and characterized it by spectroscopic and physicochemical methods. In this work, we have already prepared manganese complexes, $[Mn_2(\mu\text{–}O)_2(bpy)_4](ClO_4)_3{\cdot}CH_3CN)_3$ (**1**)[4] and $[Mn_3(\mu_3\text{–}O)(pyr)_3(OAc)_6](ClO_4)$ (**2**),[5] as starting materials. We challenged to stnthesize new multinuclear manganese complxes using these reported manganese complexes with the new cage type ligand, $\mathbf{L_{OAc}}$ (Fig. 2).

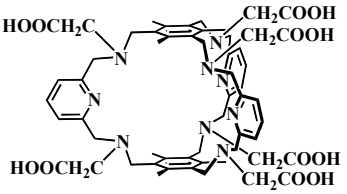

Figure 1. Structutre of $\mathbf{L_{OAc}}$.

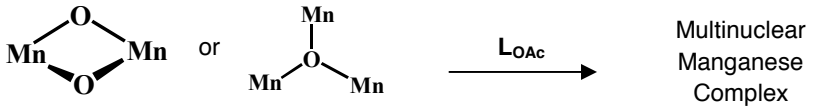

Figure 2. Shematic view of synthesiging manganese clustering complex

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Investigating Oxidoreductase Enzymes Mimicking Properties of Manganese Complex

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Manganese-containing redox enzymes are ubiquitous in nature and perform a number of vital functions. Some of their representatives are manganese superoxide dismutase, manganese catalases, peroxidase and manganese catechol oxidase.

We have previously investigated the functional catechol oxidase and phenoxazinone synthase models using cobalt-, iron-, and manganese(II) complexes in methanol solution.[1,2] We have extended our work in carbonate-bicarbonate buffer using a catecholamine derivative, adrenaline as a model substrate. Dioximatomanganese complex accelerates the autoxidation of substrate to adrenochrome. The observed kinetic behavior is consistent with a mechanism involving the formation of a ternary catalyst-dioxygen-substrate complex as active intermediate, which decomposes in rate-determining step to adrenochrome product.[3]

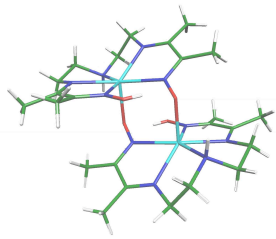

Figure. Structure of dioximatomanganese(II) dimer complex

Superoxide and hydroxyl radical anions are formed in living systems during enzyme-catalyzed processes. Superoxide dismutase catalyzes the dismutation of superoxide anion radical to oxygen and hydrogen peroxide. Catalases are enzymes that accelerate the disproportion of hydrogen peroxide into dioxygen and water. Preliminary results suggest that manganese complex increase the disproportion rate of hydrogen peroxide in potassium phosphate buffer at pH 7.0. In the kinetic experiment the disproportion was followed by measuring the decrease in absorbance of hydrogen peroxide at λ = 240 nm. The initial rates of disproportion were determined as a function of catalyst and substrate concentration.

Acknowledgements

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Expression of Metallothionein mRNA on Fetus Brain after the Injection of Thimerosal to Pregnancy Mouse

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Thimerosal, an ethyl mercury compound, is recommended as preservative vaccines and toxoids, because it is cheap with supposedly stable preservative action without side effects. However, it was suspected that thimerosal induced autism as thimerosal produces ethyl mercury in the body. This suspicion was rejected by large-scale epidemiological surveys, but it is reported that ethyl mercury has an adverse effect on the central nervous system even at clinical doses of thimerosal. In contast, we previously observed that mercury contents did not increase in mouse cerebrum when clinical dose of thimerosal was injected. Therefore, it is still unclear whether thimerosal affects the brain, especially fetus brain. Metallothionein(MT)-1 and MT-2 are acute-phase proteins, and both MT-1 and MT-2 are induced simultaneously in the brain when either mercury vapor or methyl mercury affects the brain. It is thought that MTs are used as a biomaker. In the present study, thimerosal was subcutaneously injected into pregnancy mice (gestation day 16). Twenty-four hours after the injection, both cerebrum and cerebellum of fetus mice were removed and stocked into the RNA*later* solution. The expression of MT mRNAs and RPS-18 mRNA, housekeeping gene, in cerebrum and cerebellum were measured by using a two-step multiplex quantitative RT-PCR methhod. The expression of MT-1 mRNA did not change in both cerebrum and cerebellum of fetus 24 hours after the injection of thimerosal (25 μg/kg or 50μg/kg). However, MT-2 mRNA in fetus cerebellum was significant higher 25μg/kg or 50μg/kg of thimerosal-injected group than the control group, although the expression of MT-2 mRNA in cerebrum did not have a difference in each group. From these results, the expression of MT mRNAs is useful as a biomaker and thimerosal may affect the fetus brain, especially cerebellum, when thimerosal is injected into the pregnancy mouse.

Luminescent Cyclometalated Iridium(III) Polypyridine β-carboline Complexes: Synthesis, Cytotoxicity, Cellular Uptake and Apoptosis-inducing Properties

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Recently, cyclometalated iridium(III) polypyridine complexes have attracted much attention as biomolecular and cellular probes and organic light-emitting devices (OLEDs) due to their relatively short excited state lifetime, high photoluminescence efficiencies, and excellent color tenability.[1] In the present study, a series of luminescent cyclometalated iridium(III) polypyridine β-carboline complexes, $[Ir(N\text{-}C)_2(N\text{-}N)](PF_6)$ (HN-C = 2-phenylpyridine or 1-phenylisoquinoline; N-N = β-carboline alkaloids), have been synthesized, characterized, and their photophysical and lipophilicity have been investigated. The Iridium(III) complexes have been evaluated for in vitro cytotoxic potency against a panel of human cancer cell lines, and the IC_{50} values of the complexes are significantly smaller than those of cisplatin obtained under the same experimental conditions. The cellular uptake of the complexes has been investigated by flow cytometry and laser-scanning confocal microscopy. The microscopy images indicated that these complexes are localized within certain cellular regions, such as cytoplasm and the dense region of RNA in the nucleus. Further studies show that the Ir(III) complexes can induce apoptosis in cancer cells. Our study shows that the combination of Iridium and β-carboline alkanoids, which are the active ingredients of a traditional Chinese medicine *Peganum harmala*, may provide a novel strategy for developing anticancer drugs.

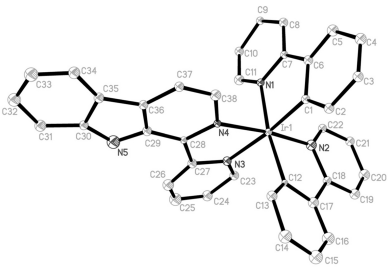

Figure 1. Molecular structures of $[Ir(Ppy)_2(1\text{-}Py\text{-}\beta C)][PF_6]$ determined by X-ray diffraction.

Acknowledgements

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Synthesis, Characterization and Biological Activity of Copper(II) and Zinc(II) Complexes with *N*(4)-alkyl Substituted Thiosemicarbazone

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Four ternary complexes of formulation [Cu(phen)(L1)] (**1**), [Cu(phen)(L2)] (**2**), [Zn(phen)(L1)] (**3**) and [Zn(phen)(L2)] (**4**) (phen = 1,10'-phenanthroline; L1 = 2,4-dihydroxybenzaldehyde-*N*(4)-methyl thiosemicarbazone; L2 = 2,4-dihydroxybenzaldehyde-*N*(4)-ethyl thiosemicarbazone have been synthesized, characterized and their DNA binding, DNA cleavage, cytotoxicity and Topoisomerase I inhibition activity studied. X-ray diffraction study indicates that complex **1** is five coordinate and the coordination geometry around copper(II) is square pyramidal. The doubly deprotonated thiosemicarbazone acts as a tridentate *O,N,S*-donor ligand while 2,2-bipyridne as the *N,N*-donor ligand displaying axial-equatorial coordination. [Zn(phen)(L2)] shows highest selectivity for the ds(AT)6 sequence for the *N*(4) alkyl substituted thiosemicarbazones. Both copper complexes can cleave DNA in the absence of exogenous agents. Radical scavenging experiments show that the cleavage mechanism involves a combination of reactive oxygen species such as singlet oxygen, superoxide anion and hydroxyl radical. Complex **2**, **3** and **4** can also inhibit human Topoisomerase 1.

The zinc complexes are less cytotoxic compared with the copper complexes towards HepG2 human hepatocellular carcinoma cells but interestingly, all the zinc complexes are non-cytotoxic towards WRL-68 normal hepatic cells.

Acknowledgements

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Zinc(II) Complexes with Antimicrobial Drug Flumequine: Structure, DNA- and Albumin-Binding

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Quinolones are antibacterial drugs and are commonly used as treatment for many infections since their main targets are both gyrases (type II topoisomerases) and topoisomerases IV and, as a result, they inhibit the DNA replication.[1] Flumequine is a synthetic first-generation quinolone mainly used in veterinary medicine for the treatment of animal diseases caused by a wide-range of Gram-negative bacteria for the last three decades. Nevertheless, only three Ni(II) complexes of flumequine have been structurally characterized.[2]

The biological importance of zinc may be summarized in its presence in the active centre of enzymes and its significance for numerous cell processes and in the metabolism of cells.[3] Additionally, diverse zinc complexes with drugs used for the treatment of Alzheimer disease or others exhibiting antibacterial, antidiabetic, anti-inflammatory, antimicrobial, antiproliferative and/or antitumor activity have been reported in the literature.[4] Taking into consideration the reported biological role and activity of Zn(II) and its complexes and the significance of the quinolones in medicine, we present herein the synthesis, structural characterization and study of biological properties (interaction with DNA, competitive studies with ethidium bromide and bovine and human serum albumin binding) of Zn(II) complexes with flumequine in the absence or presence of the *N*-donor heterocyclic ligands 2,2'-bipyridine or 1,10-phenanthroline. The crystal structures of the complexes have been determined by X-ray crystallography.

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DNA Binding and Biological Activity of Transition Metal Complexes

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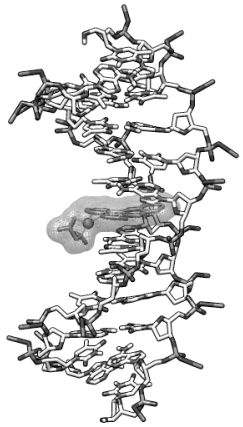
The principal aim of our work is mostly focused on the synthesis of novel transition metal complexes able to non-covalently recognize DNA, using Schiff base, oxadiazole and dipyrydil derivatives as ligands. The coordination geometries of the molecules obtained range from tetracoordinate mononuclear complexes to binuclear metallo-supramolecular assemblies.



For instance, the DNA binding of Ni^{II}, Cu^{II} and Zn^{II} complexes of Salphen[1,2] and oxadiazole[3,4] ligands mainly occurs by intercalation and groove-binding for the former and the latter, respectively. Moreover, Cu^{II} and Zn^{II} heteroleptic complexes of dipyrido[3,2-a:2',3'-c]phenazine (dppz) and amino acids are strong DNA-intercalators. Finally, a 2,7-diazapyrenium binuclear Pt^{II} rectangular box-shaped metallacycle[5] is a major-groove binder that induces DNA coiling.

Interestingly, the DNA binding properties of the complexes find a positive feedback in their *in vitro* biological activity. For example, Cu^{II} complexes of both 1,2,4- and 1,3,4-oxadiazole ligands as well as the Pt^{II} metallacycle reduce the vitality of different human cancer cell lines in a dose- and time-dependent manner.

Acknowledgements

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Studies of the Interactions between Amyloid-β peptides (Aβ16/Aβ28) and the Heme *b*: Implications in Alzheimer's Disease

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The Alzheimer disease[1] is characterized by a neurodegerative process in which toxic protagonists and steps that lead to the cellular death are not well identified. The beta-amyloid precursor protein (APP, type-1 membrane protein) is at the root of the pathway leading to amyloidosis. APP can be proteolytically processed by three proteases, namely α, β and γ-secretases. The concerted action of α and γ–secretases gives rise to a group of amyloid beta peptides which differ in length (40 AA > 42 > 38, 39…) because of the alternative cleavage from the γ-secretase. These fragments, by forming toxic aggregates, provoke cell dysfunction and later cell death observed in the brain of patients. Moreover, some metal ions (Zn^{II}, Cu^{II} and Fe^{III}) seem to intervene in the process of aggregation and more generally in the toxicity of the aggregates. In fact they could be structural agents,[2] and because of their electronic properties, they could also generate reactive species (ROS) which would induce important chemical modifications on the amyloid beta peptides themselves[3] and/or on the components of the cell.[4]

In this poster are presented some results from the studies of the interactions between two different peptides, namely Abeta16 and Abeta28, and the heme b which contains a Fe^{III} ion. Firstly is described the characterization of the complexes Abeta16-Fe^{III}(heme)/Abeta28-Fe^{III}(heme). The second part of the poster illustrates the reactive properties of these complexes, on themselves and against various exogenous substrates, in the presence of several reagents like the superoxide anion, hydrogen peroxide (oxidative modifications) and nitrite/H_2O_2 (nitration modifications). Finally we search to know what kind of effect (toxic and/or protective) could these compound have on their biological environment, and their contribution in the disease.

Acknowledgements

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Copper(II) Complexes as Models of the Active Centre of the Cu,Zn-SOD Enzyme

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Histidine imidazole nitrogens are frequent side chain donor groups in proteins and play important roles in the binding of transition metal ions. Such metal ion / protein interaction can be found for example in the Cu,Zn superoxide-dismutase enzyme. To mimic the active site of Cu,Zn superoxide-dismutase enzyme several histidine containing peptides were synthesized and their coordination ability was investigated. These peptides containing varying numbers of histidine in different positions in the peptide chain were studied by pH potentiometry,[1] cyclic voltammetry and spectrophotometry.

The equilibrium studies of the copper(II) complexes of these peptides showed that the presence of several histidyl residues in the molecules provides a high possibility for the formation of macrochelates (ML) *via* the binding of imidazole-N donor atoms. The increase in the number of histidyl residues results in enhanced stability of the complexes and these species are present predominantly under slightly acidic or neutral pH conditions (pH 5-7).[1] These complexes can be seen as structural models of the copper(II) binding site of the Cu,Zn-SOD enzyme.

To support this view we studied the redox properties and the SOD activity of those complexes in which the metal ion is bound through imidazole-N atoms. The redox potential values were studied by cyclic voltammetry and the SOD activity by spectrophotometry.[2]

The redox potential values of those complexes in which the copper(II) ion is bound exclusively through imidazole-N atoms fall into the redox potential range that characterizes the SOD enzyme. The SOD activity of these complexes is similar to the previously published SOD models. Thus the cyclic voltammetric measurements and the SOD activity assay in agreement with the equilibrium studies showed that those complexes can be capable of decomposing the superoxide radical anion in which the metal ion is coordinated through imidazole nitrogen atoms

Acknowledgements

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Insights into the Failure of the Potential, Neutral Myocardial Imaging Agent TcN-NOET: Physico-chemical Identification of By-products and Degradation Species

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The neutral complex [^{99m}Tc(N)(NOEt)$_2$], often referred to as TcN-NOET, (NOEt = N-ethoxy,N-ethyldithiocarbamate(1-)) was proposed several years ago as a myocardial imaging agent. Despite some favourable clinical properties evidenced during phase I and phase II studies, the overall results of the European and American phase III clinical studies have been judged insufficient for a successful approval process by the regulatory Agencies.

Non-carrier added (nca) and carrier added (ca) experiments using short-lived ^{99m}Tc and long-lived ^{99g}Tc have been utilised to prepare a series of bis-substituted [Tc(N)(DTC)$_2$] complexes (DTC = dithiocarbamate(1-)). They have been purified by means of chromatographic techniques (HPLC and TLC) and identified via double detection (UV-vis and radiometric) by comparison with authenticated samples of ^{99g}Tc compounds prepared by conventional bench chemistry.

The molecular structure of the lipophilic, neutral complex *cis*-[Tc(N)(NOEt)$_2$] has been assigned by comparison with similar nitrido-Tc(V) complexes already reported in the literature.[1] Novel bis-substituted nitrido-Tc complexes containing hydrolysed portions of coordinated NOEt, namely N-ethyldithiocarbamate (NHEt(1-)) and N-hydroxy, N-ethyldithiocarbamate (NOHEt(1-)) have been prepared and characterised by means of multinuclear NMR spectroscopy and mass spectrometry.

Despite of the identification of these 'hydrolysed' species, it is still unclear whether the failure to reach the clinical goal of the perfusion tracer [^{99m}Tc(N)(NOEt)$_2$] is related to the degradation processes evidenced in this study or is the result of the mediocre imaging properties of the tracer. If the failure is connected with the chemical degradation, it appears to be necessary to replace succinic dihydrazide (SDH) with alternative sources of the nitride group that, while keeping unaltered their N^{3-} donor ability, exhibit less reactivity toward the dithiocarbamate moiety.

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Preparation of some Zinc Complexes of *meso*-Mixedly substituted Porphyrins (ZnMMSPs) and the Equilibria of Pyridine Ligation to them

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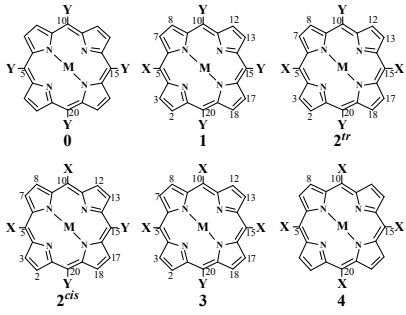
In recent years, the synthesis of porphyrins and metalloporphyrins has been widely investigated in order to provide a synthetic basis for a variety of materials applications in fields of engineering and also in medicine because of their extreme versatility. In the biological sciences, synthetic porphyrins are being extensively applied in models of biological systems. In such studies, it is essential to design ligation spaces that mimic the binding sites involved in enzymatic reactions.

With the aim of obtaining a series of porphyrins, each with a systematically different ligation space, we prepared some *meso*-mixedly substituted porphyrins (MMSPs) with two types of functionalized phenyl X and Y at four *meso* positions.

A specific combination of X and Y results in a certain "family", $H_2X_mY_{4-m}P$, which comprises 6 members: H_2Y_4P (m = 0), H_2XY_3P (m = 1), *trans*-$H_2X_2Y_2P$ ($m = 2^{tr}$), *cis*-$H_2X_2Y_2P$ ($m = 2^{cis}$), H_2X_3YP (m = 3) and H_2X_4P (m = 4).

In this work, we report the preparation of $H_2X_mY_{4-m}P$ and pyridine ligation equilibria to Zn(4-methoxyphenyl)$_m$(9-anthryl)$_{4-m}$P.



X = [2,6-dimethoxyphenyl], [3,5-dimethoxyphenyl] or [4-methoxyphenyl]
Y = [2,6-dichlorophenyl] or [9-anthryl], M = 2H or Zn

Fig. Structures of 6 members (**0**, **1**, **2**^{tr}, **2**^{cis}, **3** and **4** of the family).

Five MMSP families derived from five combinations of X and Y as substituents, being symmetric along the porphyrin plane at the *meso* positions, were successfully prepared: X = 2,6-dimethoxyphenyl and Y = 9-anthryl (**a**), X=3,5-dimethoxyphenyl and Y = 9-anthryl (**b**), X=4-methoxyphenyl, and Y = 9-anthryl (**c**), X=2,6-dimethoxyphenyl and Y = 2,6-dichlorophenyl (**d**), and X = 3,5-dimethoxyphenyl and Y = 2,6-dichlorophenyl (**e**). Isolation of six members of the individual families was also successful by an open column chromatography. Thermodynamic parameters of pyridine ligation to **c**(Zn) were determined as follows: equilibrium constant ln K at 303K is 7.7, 8.3, 8.7, 8.8, 9.3 and 9.5 for **4**, **3**, **2**^{cis}, **2**^{tr}, **1** and **0** respectively. It is interesting that ln K for **0** is largest in spite of bulkiness of anthryl moieties, and furthermore, main contribution to the $\Delta\ln K(\mathbf{0}) = \ln K(\mathbf{0}) - \ln K(\mathbf{4})$ is entropy factor $\Delta\Delta S(\mathbf{0})/R = \Delta S(\mathbf{0})/R - \Delta S(\mathbf{4})/R$.

Sepiolite and Clinoptilolite Nanoclays. A Comparative Study in vitro and in vivo

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Nanocomposites are not new materials; we can found it in nature, for example in the structure of the abalone shell and bone. They differ from conventional composite materials due to the high surface to volume ratio of the reinforcing phase and its high aspect ratio.[1] A relatively small amount of nanoscale reinforcement can have an observable effect on the macroscale properties of the composite. For example, adding nanoparticulates may result in enhanced optical, dielectric, heat resistance or mechanical properties. Industry is using nanoclays as flame retardants,[2] enzyme stabilizers,[3] additive in other materials,[4] etc.

The properties of nanocomposites are increasing their applications, but are necessary to know if they can present a toxic effect in people, animals and in environment. This work aims to develop a model for testing in vitro toxicity of nanocomposites utilizing phagocytic organisms and cells like Entamoeba histolytica and macrophages from human peripheral blood, for in vivo tests CD1 mice are normally used.

In vitro tests showed a dose and time dependence with a decrease of maximum 18%, for in vivo model the application of a suspension of nanoclays intramuscularly, intravenous, oral, cutaneous and subcutaneous at different times of exposure (24, 48, 72 hours, 1 week and 1 month) showed the formation of a capsule without inflammatory response. Serological exams indicated that liver and kidney function are normal. There was no evidence of toxicity in these materials.

Acknowledgements

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Interaction of Cu(II) with Non-steroidal Antiinflammatory Drug Flufenamic Acid

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Copper is one of the most interesting biometals due to its biological role and its potential synergetic activity with drugs.[1,2] Copper(II) complexes with diverse drugs have been the subject of a large number of research studies, since they exhibit potential synergetic activity with drugs and numerous biological activities such as antitumor, antibacterial and antifungal.[3]

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medical drugs as analgesic, anti-inflammatory and antipyretic agents.[2] The chemical classes of NSAIDs comprise salicylate derivatives, phenylalkanoic acids, oxicams, anthranilic acids, sulfonamides and furanones.[4,5] Flufenamic acid (= Hfluf) belongs to the derivatives of anthranilic acid NSAIDs and resembles chemically to tolfenamic and mefenamic acids and other fenamates in clinical use.[3,6]

In this context, we have initiated the study of Cu(II) complexes with NSAIDs as ligands. Here we present the synthesis, characterization, electrochemical and biological properties (interaction with DNA, competitive studies with ethidium bromide and bovine and human serum albumin binding studied by spectroscopic techniques) of Cu(II) complexes with flufenamic acid in the absence or presence of nitrogen-donor heterocyclic ligand such as 2,2'-bipyridine (= bipy), 1,10-phenanthroline (= phen) or 2,2'-bipyridylamine (= bipyam). The crystal structure of [Cu(fluf)(bipyam)Cl] has been determined by X-ray crystallography.

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Heavy-metal Detoxification Capacity of Different Soybean Metallothioneins

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Soybean (*Glycine max*) represents the legume crop with the highest agroeconomical importance in Argentina. Therefore, the analysis of the molecular determinants of its heavy metal resistance capacity becomes of utmost interest. Among those, metallothioneins (MTs) -low molecular weight, Cys-rich proteins with high heavy metal binding capacity- become of special interest. Here, we perform a comparative analysis of the metal binding abilities of four *G. max* MT isoforms –each of them belonging to one of the four plant MT types[1]– obtained through recombinant synthesis in Zn(II)-, Cd(II)- or Cu(II)-supplemented cultures of *E. coli*. Metal-MT stoichiometries for the M(II)-GmMT1, M(II)-GmMT2 and M(II)-GmMT3 complexes (M = Zn or Cd) match well with those described in the literature for MTs from other vegetal species of the same type,[2] and GmMT4 generates a mixture of Zn_5- and Zn_6-GmMT4. When comparing these results with those from the wheat E_c-1 protein,[3] the best known type 4 plant MT that generates unique Zn_6-E_c-1 complexes, it is clear that GmMT4 possesses a lower Zn(II) binding capacity, probably because of the absence of one His residue in relation to E_c-1. On the other hand, preliminary results with the Cu(I)-GmMT complexes show a higher Cu(I) preference for isoforms 1 and 3 with respect to isoforms 2 and 4.

Acknowledgements
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Ruthenium(II) Binuclear Thiosemicarbazone Compounds as Potential Anti-tumor Agents: Activity and Serum Protein Binding

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Ruthenium complexes have been among the most widely studied non-platinum metallodrug candidates, and hold great potential as alternatives in cancer treatment. We present herein results on the anti-tumor potential of two organometallic Ru^{II} compounds, $[Ru_2(p\text{-cym})_2L_2]Cl_2$ (*p*-cym = *para*-cymene; L = thiosemicarbazone ligand derived from 5-nitrofuraldehyde). Both complexes and all thiosemicarbazone ligands were screened for their cytotoxicity against different human cancer cell lines. While the $[Ru_2(p\text{-cym})_2Cl_4]$ precursor complex was inactive, the $[Ru_2(p\text{-cym})_2L_2]Cl_2$ complex (L being the thiosemicarbazone phenyl derivative) was found to exhibit an IC_{50} value close to that of cisplatin in A2780 (ovarian, cisplatin sensitive) while also being active against MCF7 (breast) and more resistant PC3 (prostate with metastatic potential) human cancer cells.

As an approach to the pharmacokinetics of these complexes their interaction with human serum albumin (HSA) at 37ºC was assessed by spectroscopic techniques (Circular Dichroism (CD), UV-visible absorption and Fluorescence, both steady-state and time-resolved) in simulated blood plasma conditions. The effect of serum proteins on the cytotoxic activity of the Ru phenyl derivative in the human ovarian cancer cell line (A2780) is also addressed. Binding of the phenyl derivative to HSA occurs with a quite intense induced CD signal, observed after an incubation time as short as 1 h, although higher contact times (24 h) are needed to reach equilibrium. Fluorescence emission from the HSA Trp214 is strongly affected both in spectral intensity and fluorescence lifetime by Ru-complex binding. Fluorescence data imply that the Ru-complex and Trp214 are in close proximity, indicating the formation of a Ru-complex↔protein adduct. Our results thus suggest that these potential anti-tumor Ru-complexes can be transported in the blood stream by albumin.

Acknowledgements
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Photoinduced Multi-Electron Transfer to a Multicopper Oxidase Resulting in Dioxygen Reduction into Water

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Laccases are very well known biocatalysts with great potentials in various industrial processes in particular because of their robustness, high oxidation power and substrate versatility (among other properties). Laccases belong to the Blue Copper Binding Domain (BCBD) family of proteins in which the archetypal member is the electron plant or bacterial electron transfer protein cupredoxin (CUP). In this family, function is modulated by the number of CUP domains, the number and type copper atoms and the fusion to non metalled domains. Taking natural plasticity within the BCBD family as a source of inspiration for the engineering of laccases, we aim at shaping new catalysts using the enzyme as a platform functionalized with "plug-ins".

One of our targets is to develop robust systems where light absorption triggers electron transfer events that subsequently lead to the activation of a catalytic centre. The efficient accumulation of multi charges at the catalytic unit is a challenging issue. We report here on the light driven four-electron reduction of a laccase that ultimately converts dioxygen into water using ruthenium(II) polypyridine-type chromophores and EDTA as sacrificial electron donor. Reduction of copper centres was demonstrated by UV/VIS and ESR spectroscopies. The fully reduced enzyme was able to reduce dioxygen into water.[1]

Acknowledgements
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Mechanistic Investigations on the Reaction of Heme Model Complexes with Carbon Monoxide and Superoxide

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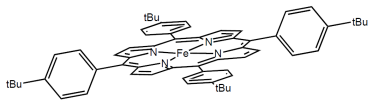
The aim of this research is to investigate and compare the reactivity of three different heme model systems, [Fe(II)(Porph)Cl] (**1**), [Fe(II)(TBuTPP)Cl] (**2**) and [Fe(II)(PorphBR)Cl] (**3**), towards small molecules such as carbon monoxide and the superoxide radical.[1,2] The influence of the different steric surroundings, temperature, pressure and the presence or absence of alkaline and earth alkaline metals, such as K^+ and Ca^+, on the reaction mechanism and behaviour are still being determined. In order to clarify the mechanism of these reactions such methods as ultra high resolution ESI mass spectrometry, temperature- and pressure dependent stopped-flow, paramagnetic high pressure NMR spectroscopy and temperature dependent NMR spectroscopy were employed.



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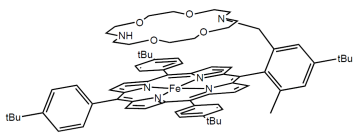

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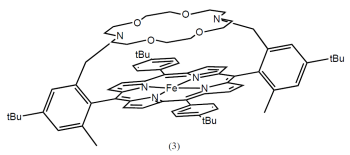

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Synthesis and Cytotoxicity of new Transition Metal Hematoporphyrin IX Complexes

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Metal complexes have shown intriguing results as antitumour drugs and among them, cisplatin and several analogues such as carboplatin and oxaliplatin have wide application in current cancer chemotherapy. In spite of the great efficacy of cisplatin, the drug reveals dose-limiting adverse effects and manifests primary and acquired resistance. The great success of cisplatin together with the limitations in its clinical utility initiated efforts to develop new "non-classic" platinum and based on other transition heavy metals complexes with improved therapeutic properties. To design structurally new chemotherapeutics, different strategies have been applied. The application of proper caring ligand systems is one approach to achieve better selectivity of the drug. Porphyrins are among the ligands, which ensure selective accumulation within malignant tissue and could participate in augmentation of the cytotoxicity upon light irradiation. Here we present the synthesis, structure and cytotoxic properties of series of platinum (Figure 1), palladium, gold copper and iron complexes with hematoporphyrin IX (Hp, 7,12-bis(1-hydroxyethyl)-3,8,13,17-tetramethyl-21H-23H-porphyn-2,18-dipropionic acid). A remarkable feature of hematoporphyrin IX is to stabilize metal ions in intermediate oxidation states such as Pt^{III}, Pd^{III} and Au^{II}. The metal ions in all complexes have an octahedral coordination with N,O-hematoporphyrin donor atoms and additional ligands such as NH_3, H_2O, Cl^-. Most of the complexes studied showed a promising cytotoxicity comparable and in any cases even higher than that of cisplatin in *in vitro* test against a panel of human leukaemic and lymphoma-derived cell lines. The design and synthesis of these complexes represent a new approach for a development of the cytotoxic agents with improved properties.

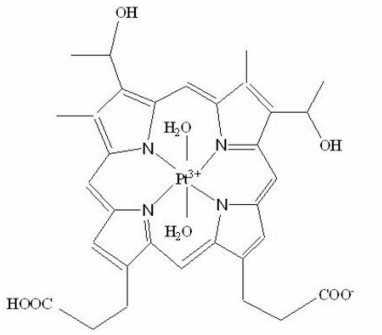

Fig. 1. Pt^{III}-Hematoporphyrin IX Complex

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Financial support from the National Scientific Fund (Project – DDVU-02/66-2011) Bulgarian Ministry of Education, Youth and Education is acknowledged.

Manganese(II) Complexes with Non-steroidal Antiinflammatory Drug Niflumic Acid: Synthesis, Characterization, DNA- and Albumin-Binding

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Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medical drugs as analgesic, anti-inflammatory and antipyretic agents.[1] The chemical classes of NSAIDs comprise salicylate derivatives, phenylalkanoic acids, oxicams, anthranilic acids, sulfonamides and furanones.[2,3] Niflumic acid (= Hnifl) belongs to the derivatives of anthranilic acid NSAIDs and resembles chemically to tolfenamic, flufenamic and mefenamic acids and other fenamates in clinical use.[4,5]

Given the importance and role of manganese[6] in the biological systems, we have initiated the study of Mn(II) complexes with diverse NSAIDs. Additionally, the interaction of NSAIDs directly at the DNA level is of great interest in order to explain the tentative anticancer as well as the anti-inflammatory activity.[4] In this context, we present the synthesis, structural characterization, electrochemical and biological properties (interaction with DNA, competitive studies with ethidium bromide and bovine and human serum albumin binding) of the Mn(II) complexes with the NSAID niflumic acid in the absence or presence of the *N*-donor heterocyclic ligand such as 1,10-phenanthroline (= phen).

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Copper(II) and Nickel(II) Complexes of Model Peptides Related to the Metal Binding Site of Prion Protein

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A great number of literature studies support that histidine containing peptide fragments of prion protein (PrP) and their mutants can effectively bind both copper(II) and nickel(II) ions. It was found that the peptide fragments can bind as many copper(II) ions as the number of independent histidyl residues. The nickel(II) binding capacity of the same peptides is less than that of copper(II) and the histidines outside the octarepeat domain were considered as nickel(II) binding sites. In the case of copper(II), the species bonded at His111 were found to be the most abundant coordination isomers, while His96 was the most common binding site for nickel(II).[1] These results support that the non-coordinating side chain residues around the specific sites (His96 and His111) may also contribute to metal binding. To understand the role of the specific sequences of the peptides a series of tetra- and octa-peptides has been synthesized both with free amino termini and in the N-protected forms. The ligands include: NH_2-GTHS-NH_2, NH_2-MKHM-NH_2, Ac-GTHS-NH_2, Ac-MKHM-NH_2, NH_2-GTHSMKHM-NH_2, NH_2-MKHMGTHS-NH_2 Ac-GTHSMKHM-NH_2 and Ac-MKHMGTHS-NH_2. These peptides can be considered as the simplest models of the fragments PrP(94-97) and PrP(109-112).

Copper(II) and nickel(II) complexes have been studied by the combined application of potentiometric, UV-Vis and CD spectroscopic measurements. It was found that the peptides with free amino termini had especially high metal binding affinity towards these metal ions, because their sequence corresponds to that of the ATCUN motif. The same selectivity for copper(II) and nickel(II) binding was, however, observed for these complexes, too. It was also evident that the octepeptides can form dinuclear complexes, in which the histidyl residues are the primary metal binding sites. As a consequence, the mixed metal complexes of the octapeptides have also been studied and the preference for the formation of various coordination isomers evaluated.

Acknowledgements

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Coordination and Redox Properties of Copper(II) and Iron(II/III) Complexes of Bis(imidazol-2-yl) Ligands

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In biological systems the N donor atom of the imidazole ring is a main binding site for copper ion, but it plays a role in the coordination of iron(II) or iron(III) too. Copper and iron as essential elements usually take part in the catalysis of redox processes (Cu,Zn superoxide dismutase (CuZnSOD) enzyme, cytochrome c oxidase, cytochromes etc.)

To understand the role of the imidazole rings in the metal binding of the ligands and in the redox processes of these complexes various compounds containing bis(imidazol-2-yl) residue were synthesised and their copper(II)[1,2] and iron(II), iron(III) complexes characterized. The stoichiometry and stability of complexes were determined by means of pH-potentiometry and UV-Vis spectroscopy. These measurements have demonstrated that two imidazole nitrogens are the primary binding site for all studied metal ions in the acidic range, their stabilities, however, are significantly different. This coordination mode is the most favourable for copper(II) ion, while the hydrolysis of iron(III) could not be hindered by the complex formation processes in the slightly acidic pH range.

To characterize the redox properties of the imidazole coordinated species a series of cyclic voltammetric measurements of copper(II) and iron(III) complexes were performed. It is clear from the characteristic formal potential values of the species that the formation of bis(imidazol-2-yl) coordinated complexes stabilizes the higher oxidation state of metal ion in both cases.

For copper(II) complexes the data were completed with superoxide dismutase (SOD) activity measurements as well. The results of both cyclic voltammetric and SOD activity measurements reveal that the copper(II) complex of histidine derivatives of bis(imidazol-2-yl) residue is the most promising model of the CuZnSOD enzyme.

Acknowledgements
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Modulation of Metal-Induced Aβ Aggregation by Bifunctional Macrocyclic Chelators

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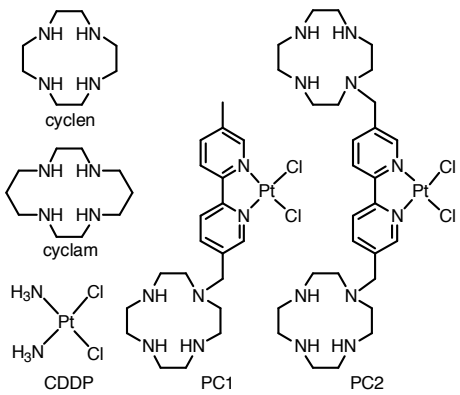
Deviant homeostasis of cerebral metal ions such as Zn^{2+} and Cu^{2+} may induce amyloid β-peptide (Aβ) to aggregate in the brain and bring about neurotoxic reactive oxygen species, which play crucial roles in the aetiology of Alzheimer's disease (AD).[1,2] Metal chelators are potential therapeutic agents of AD because they can regulate the metal-induced Aβ aggregation and neurotoxicity through removing the metal ions from Aβ plaques.[3] We thus developed a series of bifunctional macrocyclic chelators from cyclen and investigated their impacts on the Zn^{2+}- or Cu^{2+}-induced Aβ aggregation using various methods. Simple chelators cyclen and cyclam markedly inhibit the metal-induced Aβ aggregation and Cu-Aβ-mediated H_2O_2 generation.[4] The Pt(II) center with planar aromatic group in bifunctional chelators PC1 and PC2 can target the metal binding site of Aβ (His-14) to modify its behavior via π-π stacking interaction and coordination. Assisted by the chelating effect of cyclen, PC1 and PC2 can more effectively inhibit the metal-induced Aβ aggregation and suppress the H_2O_2 generation. Further, they can diminish the neurotoxicity of Aβ aggregates in cortical neuronal cells of mice in vitro, and attenuate the Aβ aggregation in transgenic mice brain homogenates. By contrast, the related anticancer drug cisplatin (CDDP) exhibits no inhibition on the Aβ aggregation. These chelators may represent a new type of anti-AD agents.



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E. coli's SlyD Protein Binds Nickel in an Unusual Way

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Nickel is an important transition metal for many microorganisms.[1] *Escherichia coli* contains three putative membrane-associated H_2-using hydrogenase enzymes. Optimal maturation of the active sites of all of the three hydrogenases in *E.coli* requires the SlyD (sensitive to lysis D) protein.[2] This protein is rich in histidine residues, which are known to be excellent anchoring sites for transition metal ions.[3,4]

We studied the binding mode and thermodynamic stability of the complexes of divalent nickel and copper ions with two fragments: Ac-AHGHVHGAHDHHHD-NH_2 (SlyD7) and Ac-GHGHDHGHEH-NH_2 (SlyD5) of the C-terminal domain of *E.coli's* SlyD. We showed by MS, NMR and potentiometric methods, that binuclear complexes of both metals with the SlyD7 peptide are formed at physiological pH, also when the 2:1 peptide/metal ratio is used.

The calculations based on the pH-metric titrations of SlyD5–Cu^{2+} and SlyD5–Ni^{2+} solutions suggest the formation of only mononuclear species. The MS spectra confirm this stoichiometry. Both peptides are very efficient in biding Cu^{2+} and Ni^{2+} ions through the histidine residues and at higer pH through amide nitrogens.

Acknowledgements
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Preparations of Optically Active Amino Acids *via* Complexation with Cu(II) Ion and L-Histidine Derivatives

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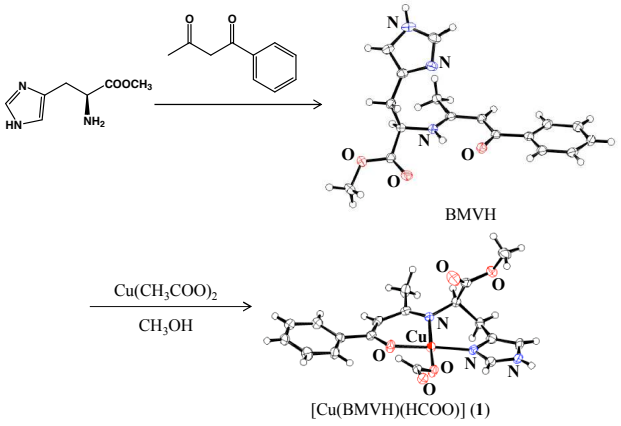
A lot of bioactive substances have chiralities, which decide physiological activities of them. Optically active amino acids, especially D-amino acids, are important materials of these bioactive substances, such as medicines, drugs, and agrochemicals. However, D-amino acids are difficult to obtain from natural products. Optically-active unnatural amino acids have been obtained from synthesized racemic amino acids by optical resolutions, asymmetric hydrolyses with enzymes, chiral chromatographic methods, and so on. We have been studied optical resolutions of DL-amino acids using copper(II) ternary complexes containing L-histidine derivatives as chiral sources to develop a new method of optical resolution.

DL-Phenylalanine (DL-Phe) can form two diastereoisomeric ternary copper(II) complexes with methyl L-histidinate (L-HisMe). The CD spectra of these ternary complexes showed that inter-ligand interactions between HisMe and Phe are different in each distereoisomeric complex by influence of the methoxycarbonyl group of HisMe. The fact implied that copper complexes of derivatives of histidine esters may have abilities as optically resolving agents for optical resolution of DL- amino acids.

Methyl *N*-(1-methyl-3-oxo-3-phenyl-1-propen-1-yl)-L-histidinate (BMVH) was obtained from benzoylacetone and methyl L-histidinate, followed by formation of a copper(II) complex, [Cu(BMVH)(HCOO)] (**1**), by reacted with copper acetate in methanol. Structures of BMVH and complex **1** were determined by X-ray crystal structure analyses (Scheme 1). DL-Tryptophan (DL-Trp) was attempted to be resolved optically using **1** to give 11 %ee of D-Trp.



Scheme 1. Synthesis of Cu-BMVH complex

Thimerosal Induces Necroptosis to Mouse Cerebellar Microglia Cell Line, C8-B4 Cells

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Thimerosal, an organomercury chemical composed of ethyl mercury and thiosalicylic acid, has been widely used as a preservative in vaccines. About ten years ago, thimerosal was discussed about the relation with autism. Large-scale epidemiological surveys have revealed contradictory evidence of a link between autism and thimerosal exposure. And thimerosal is still recommended as a cheap and stable vaccine preservative. However, the effect of thimerosal on central nervous system is still unclear. In the present study, we observed the effect of thimerosal on mouse cerebellum using cerebellar microglia cell line, C8-B4 cells. C8-B4 cells ($1x10^4$ cells/well) was incubated for 48 hours. Thimerosal or relative chemicals was added to the well and cell viability was measured. Thimerosal and ethyl mercury decreased the ratio of cell survival and the 50 % cell survival rate was 7 μM both. On the contrary, thiosalicylic acid increased cell survival rate in comparison with the control. From the results of flow cytometry, necrosis occurred C8-B4 cells by both thimerosal and ethyl mercury. When necrostatin-1, an inhibitor of receptor-interacting serine/threonine kinase 1 (RIPK1) required for necroptosis, was mixed with thimerosal and added into the cells, cell survival ratio recovered in a dose-dependent manner. From these results, it is concluded that thimerosal-induced cell damage is caused by ethyl mercury and necroptosis may occur.

Structure, DNA- and Albumin Binding of Manganese(II) Complexes with Non-steroidal Antiinflammatory Drug Diclofenac

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Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medicinal drugs used as analgesic, anti-inflammatory and antipyretic agents. They have also exhibited chemopreventive and anti-tumorigenic activity and a synergistic role on the activity of certain antitumor drugs. Their main known mode of action is through inhibition of the cyclooxygenase (COX)-mediated production of prostaglandins.[1] The interaction of NSAIDs directly at the DNA level is of great interest in order to explain the tentative anticancer as well as the anti-inflammatory activity.[2]

Metal complexes of NSAIDs have also exhibited synergistic activity. Sodium diclofenac (Nadicl), belongs to the NSAID group of phenylalkanoic acids, exhibits favourable anti-inflammatory, analgesic and antipyretic properties and is used in painful and inflammation conditions like rheumatoid arthritis, spondilytis, and osteoarthritis.[3]

Given the importance and role of manganese[4] in the biological systems, we have initiated the interaction of manganese with diverse NSAIDs. In this context, we present the synthesis, structural characterization, electrochemical and biological properties (interaction with DNA, competitive studies with ethidium bromide and bovine and human serum albumin binding) of the Mn(II) complexes with the NSAID diclofenac in the absence or presence of the N-donor heterocyclic ligand 1,10-phenanthroline (= phen). The crystal structure of $[Mn_3(dicl)_6(phen)_2(MeOH)]$ has been determined by X-ray crystallography.

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Modified Vitamin B12 Derivatives with Tunable Coordination and Redox Properties

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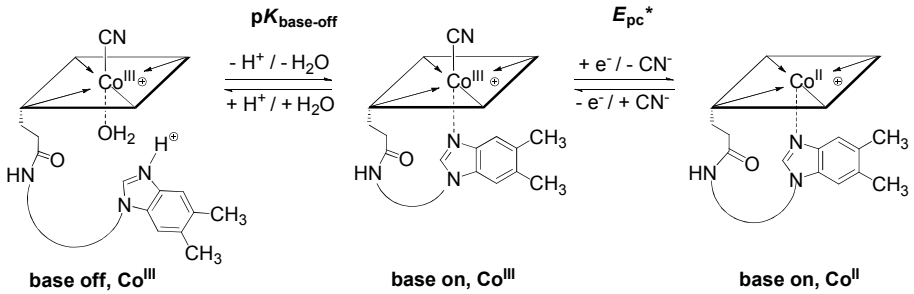
Cobalamins (Cbls) are essential for the metabolism of humans.[1] Axially bound ligands modulate the electrochemical properties at the cobalt center, which is important for the transport, the conversion and the reactivity of Cbls in biological systems.[2] Little is known about the influence of structural modifications at the ("lower") α-site on the redox and coordination properties at the cobalt center.



We are interested in the development of modified vitamin B_{12} derivatives with tunable coordination and redox properties for physico-chemical studies and biological applications. For this purpose, we replaced the α-ribofuranotide moiety at the f-side chain of B_{12} with different peptide structures.[3] A linear relationship between the base-on stability ($pK_{base\text{-}off}$, Scheme left) and the cathodic reduction potential from cobalt(III) to Co(II) (E_{pc}, Scheme right) has been observed. This behavior influences also the reactivity in B_{12} dependant reactions.[4]

We also demonstrated that backbone modified B_{12} derivatives were useful for the identification of related natural products.[5]

Acknowledgements

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Bis-β-cyclodextrin Confined Dinuclear Phosphate Esterase Mimics

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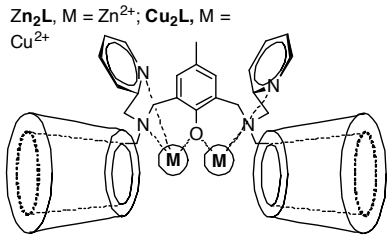
Phosphoryl-transfer is ubiquitous in numerous biological processes, such as DNA degradation and protein modification. The processes are mediated by various phosphate esterases, in which two adjacent divalent metals are frequently encountered at the active core.[1] To better understand the function-structure relationships and further contribute to applications, we prepared two dinuclear phosphodiesterase mimics, Zn_2L[2] and Cu_2L,[3] where the metal sites are confined by bis-β-cyclodextrin outer sphere (see inserted figure).



Zn_2L gives two tandem sets of active species, $Zn_2L(OH)$ (pK_a = 7.5) and $Zn_2L(OH)_2$ (pK_a = 9.9) toward Bis(4-nitrophenyl) phosphate (BNPP), and the latter ranks one the most active Zn-OH nucleophile. Substrate specificity is observed by comparing BNPP with 2-hydroxypropyl-4-phosphate (HPNP) due to the molecular recognition for BNPP over HPNP, which is drawn from inhibition studies. As for Cu_2L, the most striking observation is the low pK_a = 4.3 of $Cu_2L(OH)$, the lowest one for a divalent transitional metal bound water ever, which results in the observable phosphodiesterase activity even at pH 4. The results may provide valuable insights for developing bio-inspired Metallohydrolase and the ones that are able to function in acid solution, especially when considering the biological significance of lysosomal acid phosphatases, dysfunction of which was related to the lysosomal storage disease.

Acknowledgements

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Pt(II) Squares an Effective G-quadruple Binders and Potential Cancer Therapeutics

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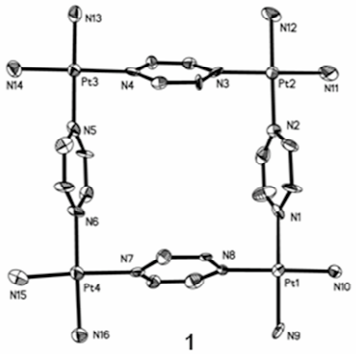
Human telomeric DNA G-quadruplexes are promising anticancer targets.[1] A new approach for anticancer drug design is to develop small molecules that can effectively stabilize G-quadruplex.[2,3] To achieve this, two self-assembled platinum molecular squares $[Pt(NH_3)_2(pyrazine)]_4$ (**1**) and $[Pt(en)(pyrazine)]_4$ (**2**) have been synthesized, and **1** was characterized structurally (see inserted figure).



1

PCR-stop and CD results show that the two Pt(II) squares are capable of inducing the formation of intramolecular parallel G-quadruplex, while **1** is more efficient than **2**. FRET melting measurements prove that the two Pt(II) squares strongly binds G-quadruplex. A systematic molecular docking studies indicate that the two Pt(II) squares bind to G-quadruplex by a parallel end-stacked mode. The binding affinity and the binding modes and stoichiometries of the two Pt(II) squares to G-quadruplex structure are consistent with that from the thermodynamic studies using ITC. Interestingly, we find that the binding constants K_b of **1** with the more hydrophilic NH_3 is 10^2-fold higher than **2**. The antiproliferative activities of Pt(II) squares are evaluated against HeLa (human cervical cancer), HepG2 (human hepatocellular liver carcinoma), MCF-7 (human breast adenocarcinoma), A549 (cisplatin sensitive) and A549/cisR (cisplatin resistant) human lung adenocarcinoma epithelial cell lines. For **1** and **2**, the cytotoxic potencies are in accordance with their G4-DNA binding affinities. Moreover, The cytotoxic potency of the two Pt(II) squares is comparable to that of cisplatin, may being as a potential cancer therapeutics.

Acknowledgements

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AUTHOR INDEX

A

Abedi, A. **P-1**
Adam, M.J. OC-22
Adão, P. P-76
Ádom, E. OC-15
Aguió, J. OC-29
Ahmedova, A. **P-2**
Aicher, S. P-57
Ajandouz, E.-H. P-124
Albelda, M.T. P-48
Aldinucci, C. OC-10
Aldinucci, D. OC-6
Alexandrov, M. P-96
Alexandrova, R. P-82, P-96
Alfaro-Fuentes, I. **P-3**, P-9
Alfonso-Prieto, M. OC-32
Al-Hokbany, N. **P-4**
Alies, B. **P-5**
Al-Jammaz, I. P-4
Amani, V. P-1
Amara, P. P-74
Amouroux, D. **KN-10**
Andonova-Lilova, B. P-82
Andreo, C.S. OC-27, P-140
Andreozzi, C. P-89
Aoki, T. **P-6**, P-87, P-127
Aono, S. **OC-31**
Appelt, J. **P-7**
Arion, V.B. P-31, P-62
Arnesano, F. P-64
Arpadjan, S. P-49
Arregui, L. P-12
Arriortua, M.I. P-30
Atrian, S. OC-27, P-65, P-95, P-99, P-100, P-116, P-140
Aukauloo, A. P-142
Aullón, G. **P-8**
Avilés, T. P-71
Azarko, I. P-42
Azzena, B. P-21

B

Bachelet, M. P-13
Bächler, S. P-62
Balland, V. OC-9
Barandika, G. P-30
Barasits, M. P-57
Barba-Behrens, N. P-3, **P-9**
Barbante, C. P-21
Barbucci, R. OC-10
Bardajee, G.R. **OC-17**
Barone, G. P-133
Barr, T. KN-7
Barragán, F. P-73
Bartel, C. P-62
Bayón, R. KN-8, **OC-18**
Bazán, B. P-30
Belle, C. **P-10**
Bellia, F. OC-30, **P-11**, P-64
Beltran, H.I. **P-12**
Bénard, F. OC-16
Benoist, E. P-101
Bernard, A.-S. **P-13**
Bertoncini, C.W. PL-3
Bertrand, H. OC-20
Berwick, M. OC-14
Betancourt-Lozano, M. P-3
Betanzos-Lara, S. P-9
Bickelhaupt, F.M. P-120
Bijani, C. P-5
Binolfi, A. PL-3
Blanchin, M.-G. P-26
Blindauer, C.A. **KN-9**
Bochot, C. P-10
Bofill, R. OC-27, P-140
Bolzati, C. P-108, P-136
Bonomo, R.P. P-64
Boucher, J.-L. P-13
Boulay, A. P-101
Boumendjel, A. P-10
Brindell, M. **P-14**, P-77, P-94
Brioschi, C. KN-4
Brisson, L. P-124
Brito, M.J. P-111
Britton, M. OC-14
Brooks, D.E. OC-16
Budzisz, E. P-41, P-85, P-98
Byrne, N. **P-15**

C

Cabella, C. KN-4
Cairns, W.R.L. P-21
Campello, M.P.C P-70
Cangelosi, V. OC-21
Cangiotti, M. P-37
Capdevila, M. OC-27, P-65, P-95, P-99, P-100, P-116, P-140
Cardo, L. **P-16**
Carepo, M.S.P. **P-17**
Carmona, F. **P-18**
Caron, G. P-107
Carreira, C.C.S. P-17
Carrer, A. P-126
Carrero, J.C. OC-5, P-138
Carrillo, J. OC-27, P-140
Carrion, D. P-73
Carta, D. P-108, P-136
Casella, L. P-134
Casini, A. **P-19**
Castillo, G.M. P-102
Castrignanò, S. OC-24
Cavazza, C. P-74
Cawthray, J. OC-11, OC-19, OC-22
Chao, H. **OC-8**
Cheah, S.C. P-131
Chen, H.-Y. P-155
Chen, T. P-148
Chen, X. P-52
Cherrier, M. P-74
Christensen, H.E.M. P-24, P-45
Ciregna, D. P-134
Ciudad, C. P-36
Clède, S. OC-20
Cobaleda, B.M. KN-7
Cobbinna, E. OC-23
Coleman, F. P-28
Coppel, Y. OC-9
Correia, I. OC-23
Costa Pessoa, J. **OC-23**, P-76, P-141
Costas, M. **P-20**
Cronin, L. P-20
Crotti, S. **P-21**
Csire, G. P-147
Cuesta, R. **P-22**
Cutillas, N. **P-23**, P-114, P-116
Czene, A. **P-24**, P-45

D

D'Almeida, M. P-13
Dawson, J.H. **OC-28**
Dazzi, A. OC-20
De Almeida, R.F.M. P-111, P-118, P-141
De Gioia, L. P-64
De la Mata, F.J. P-34, P-37
De la Rosa, M.A. P-27
De Llorens, R. P-73
Delaire, J.A. P-142
Delangle, P. **OC-12**
Delgado, J.J. P-22, P-26
Delsuc, N. P-13, OC-20
Demoro, B. OC-4, P-141
Deniset, A. OC-20
Deraeve, C. P-101
Di Nardo, G. OC-24
Díaz-Moreno, I. P-27
Docampo, R. OC-4
Dolla, A. P-17
Dolmella, A. P-108
Domínguez-Martín, A. **P-25**
Domínguez-Vera, J.M. P-18, P-22, **P-26**, P-95, P-117
Donaire, A. **P-27**
Dorazio, S.J. KN-2
Dorlet, P. OC-9
Dou, Q.P. OC-6
Du, J. OC-28
Dubois, C. P-10
Dumas, P. OC-20
Dürr, K. P-143
Dyakova, L. P-82
Dyson, P.J. P-78

E

El Bakkali-Tahéri, N. P-124
Enyedy, É.A. OC-23, P-61
Ermondi, G. P-107
Erxleben, A. P-15, **P-28**
Escribano, E. P-73
Escriche, L. OC-29
Esmieu, C. P-74

F

Fàbregas, E. P-99
Fajer-Ávila, E.J. P-3, P-9
Faletrov, Y. P-58
Faller, P. OC-9, P-5
Farkas, E. **P-29**
Fernández, B. P-95
Fernández, C.O. **PL-3**
Fidalgo-Marijuan, A. **P-30**
Fiedor, L. P-93
Filak, L.K. **P-31**
Filipović, M. P-50
Flores, J. **P-12**
Flores, L. P-138
Fonseca Guerra, C. P-120
Fontecave, M. **PL-1**
Fontecilla-Camps, J. P-74
Formaggio, F. OC-6
Francàs, L. OC-29
Franke, A. P-94
Franzese, D. P-18
Fregona, D. OC-6
Freisinger, E. **OC-25**, P-54
Frías, J. P-48
Friedel, F. **P-32**, P-67
Fritsky, I.O. P-44
Fuentes, E. KN-8
Fuks, L. **OC-13**
Fukui, K. P-60
Fukui, M. P-60, P-84
Funahashi, Y. P-6, **P-33**, P-47, P-60, P-84, P-87, P-127
Furusawa, H. P-88

G

Gabano, E. P-107
Gaggelli, E. OC-10
Galán, M. **P-34**
Galaup, C. P-101
Galenda, A. P-108
Galizzi, M. OC-4
Gálvez, N. P-22, P-26, P-117
Gambino, D. **OC-4**, P-43, P-141
Gandin, V. **P-35**, P-104
Gao, F. P-52
Garcia, M.H. **P-36**, P-76, P-83, P-111, P-118
García, B. P-38
García-España, A. P-48
García-España, E. P-48
García-Gallego, S. **P-37**
García-Heredia, J.M. P-27
García-Ramos, J.C. **OC-5**
García-Tojal, J. **P-38**
Garriba, E. OC-23
Gateau, C. OC-12
Gazzah, G. P-13
Gencheva, G. **P-39**, P-144
Geraldes, C.F.G.C. **PL-4**
Gershkovich, P. OC-16
Ghattas, W. P-124
Ghiani, S. KN-4
Giani, G. OC-10
Gibson, D. **KN-3**
Gilardi, G. OC-24
Gil-García, R. P-38
Gioia Lobbia, G. P-35
Giorgi, M. P-97
Girgenti, E. P-74
Gluhcheva, Y. P-49
Gluszko, M. P-14
Gniazdowska, E. OC-13
Gochev, G. P-144
Goldeman, W. P-106
Golinelli-Pimpaneau, B. P-86
Gómez, N. KN-7
Gómez, R. P-34, P-37
Gonçalves, G. OC-23
González, A. P-138
González-Cantó, A. P-73
González-Chávez, F. P-12
González-Gómez, G. P-9
Gracia, I. P-9
Grasso, G.I. **OC-30**, P-11
Gray, D. KN-7
Grazina, R. P-17, **P-40**
Grażul, M. **P-41**
Gres, A. **P-42**, P-58
Griesinger, C. PL-3
Griffith, D. **OC-7**
Grondin, V. P-13
Güell, M. P-20
Gueroui, Z. OC-20

Guerrero, J. P-12
Guillon, E. P-5
Guiset, H. **P-43**
Gumienna-Kontecka, E. **P-44**, P-106
Guo, Z. P-148
Gyurcsik, B. P-24, **P-45**

H

Habtemariam, A. P-112
Häfeli, U.O. OC-16
Hajji, L. P-51
Hambley, T. KN-3
Hannon, M.J. OC-2, P-23, P-114
Hansson, O. P-64
Hardré, R. P-10
Hartinger, C.G. P-57, P-61, P-62, P-78
Haudecoeur, R. P-10
Henriksen-Lacey, M. KN-7
Hermann, P. **P-46**, P-70
Herrero, C. P-142
Herrmann, C. OC-22
Hilton, R. KN-6
Hooshyar, Z. OC-17
Huang, X. OC-28
Huber, T. OC-25
Hueso Ureña, F. P-53
Hundal, N. OC-16
Hureau, C. **OC-9**, P-5

I

Iafisco, M. OC-1
Iannello, M. P-74
Ichida, S. P-81, P-129, P-151
Igartua, A. **KN-8**, OC-18
Illán Cabeza, N.A. P-53
Imai, M. P-127
Inagaki, Y. **P-47**
Inazumi, T. P-47
Inclán, M. **P-48**
Inomata, T. P-6, P-33, P-47, P-60, P-84, P-87, P-127
Iranzo, O. P-103
Iriart, S. P-13
Ivanov, D. P-82
Ivanova, Ju. **P-49**
Ivanović-Burmazović, I. P-7, P-32, **P-50**, P-67, P-143
Iwatsuki, S. P-121

J

Jakab Tóth, É. OC-15
Jakupec, M.A. P-31, P-62
Jakusch, T. OC-23, P-61
Jamet, H. P-10
Jara, V. **P-51**
Jendelová, P. P-46
Ji, L.-N. OC-8, **P-52**, P-66, P-68, P-130, P-154, P-155
Jiménez, J.L. P-34, P-37
Jiménez Pulido, S.B. **P-53**
Jirák, D. P-46
Johannsen, S. P-25, **P-54**
Jorge-Robin, A. P-74
Jóźwiak, A. P-98
Justino, G. OC-23
Jux, N. P-143

K

Kainthan, R. OC-16
Kaizer, J. P-97
Kallay, C. **P-55**
Kamei, Y. **P-56**
Kamenova, K. P-49
Kamysz, W. P-149
Kandioller, W. **P-57**, P-62
Kavalchuk, T. P-42, **P-58**
Kenkel, A. OC-22
Keppler, B.K. P-31, P-57, P-61, P-62, P-78
Kessissoglou, D.P. P-105, P-132
Khavasi, H.R. P-1
Kimura, M. **P-59**
Kinoshita, W. **P-60**, P-127
Kirilova, M. P-96
Kiss, T. OC-23, **P-61**
Kljun, J. P-132
König, S.L.B. P-16
Konishi, K. P-56
Körtvélyesi, T. P-45

Kosaka, S. P-150
Kotek, J. P-46
Kotková, Z. P-46
Kovács, Z. OC-15
Kowerko, D. P-16
Kozłowski, H. OC-10, P-149
Kozminski, P. OC-13
Krembuszewski, M. KN-7
Kripli, B. P-97
Kubíček, V. P-46
Kupcewicz, B. P-85
Kurzwernhart, A. **P-62**
Kyropoulou, M. **P-63**

L

La Mendola, D. **P-64**
Laclette, J.P. OC-5
Lambert, F. OC-20
Lamberto, G.R. PL-3
Landaeta, V. P-117
Lanza, V. P-11
Laurent, S. P-101
Lebioda, L. OC-28
Lebrun, C. OC-12
Lecina, J. **P-65**, P-126
León, L.G. P-113
Leszczyszyn, O.I. KN-9
Leygue, N. P-101
Li, J.-M. **P-66**
Lieb, D. P-32, **P-67**
Lihi, N. P-147
Lippert, R. P-143
Lista, L. P-89
Liu, J. **P-68**
Liu, Y. **P-69**, P-80
Lledós, A. P-86, P-92
Llobet, A. OC-29
Loebus, J. P-54
Loginova, N. P-42, P-58
Lombardi, A. P-89
López, C. P-109
López, L. P-12
López-Castro, J.D. P-22, P-26
López-Sandoval, H. P-9
López-Senín, P. P-73
Lorenzo, J. P-43
Lubal, P. **P-70**
Łuczkowski, M. **KN-5**
Luis, J.M. P-20
Luis, J.M. P-20
Lukeš, I. P-46
Lux, K. P-85

M

Maah, M.J. P-131
Madariaga, G. P-38
Madeira, P.J.A. P-83
Maglio, O. P-89
Magrì, A. P-64
Mahy, J.-P. P-86
Maiocchi, A. **KN-4**
Maiti, B.K. **P-71**
Malayil, L. OC-4
Maldonado, C.R. KN-7
Mao, L.-L. P-155
Mao, Z.-W. P-66, **P-72**, P-130, P-154, P-155
Maraloiu, A.V. P-26
Marchán, V. **P-73**
Marchi-Delapierre, C. **P-74**
Maréchal, J.-D. **KN-11**, P-86, P-92, P-116
Mareque-Rivas, J.C. **KN-7**
Margiotta, N. **OC-1**
Marinov, M. P-2
Marko, D. P-62
Marmion, C.J. OC-7
Marques, F. P-76, P-83, P-111, P-141
Marques, S.M. **P-75**
Martinelli, A. P-75
Martínez, M. P-70
Martins, A.P. P-19
Marzano, C. P-35, P-104
Masliah, J. P-13
Massaguer, A. P-73
Masuda, H. P-6, P-33, P-47, P-60, P-84, P-87, P-127
Mathieson, J.S. P-20
Matos, C.P. **P-76**, P-141
Matsumoto, H. **P-150**
Mawani, Y. **OC-19**
Mayet, C. OC-20
Mazuryk, O. **P-77**
Mazzi, U. P-126

Mehtab, S. OC-23
Meier, S.M. **P-78**
Meker, S. **P-79**
Mekmouche, Y. P-142
Melendez-Alafort, L. P-126
Ménage, S. P-74
Mendizabal, L. OC-18
Mestre-Voegtlé, B. P-101
Milardi, D. OC-30
Miloshev, G. P-96
Min, Y. **P-80**
Minami, T. **P-81**, P-129, P-151
Miragoli, L. KN-4
Mitewa, M. P-2, P-49, **P-82**, P-96
Momekov, G. P-2, P-144
Montes de Oca, G. P-138
Montes Escudero, M.I. P-51
Monzani, E. P-134
Morais, T.S. **P-83**
Morellato, N. P-108
Moreno, P. P-142
Moreno, V. OC-23, P-36, P-43, P-73
Moreno Carretero, M.N. P-53
Morimi, Y. **P-84**, P-87, P-127
Morrow, J.R. **KN-2**
Mour, T.F. P-19
Moura, I. P-17, P-71
Moura, J.J.G. P-17, P-40, P-71
Mucha, A. **OC-2**
Mucha, P. **P-85**
Mühlgassner, G. P-31, P-62
Muller, R.N. P-101
Müller, J. P-110, P-120
Munivrana, I. P-21
Muñoz Robles, V. **P-86**
Muñoz-Fernández, M.A. P-34, P-37
Murase, M. **P-87**
Mustafa, M.R. P-131

N

Naganuma, H. P-127
Nagata, K. P-24, P-45, P-60, P-84
Nagy, L. P-55
Nakabayashi, Y. **P-88**
Nakai, M. P-88
Nastri, F. **P-89**
Natile, G. OC-1, P-64
Németh, E. P-24, P-45
Nemirovski, A. KN-3
Ng, C.H. P-131
Ng, S.W. P-131
Nimphius, C. OC-22
Nishikawa, T. P-33
Noe, V. P-36
Nuti, E. P-75

O

O'Halloran, T.V. **PL-6**
Ogata, H. **P-90**
Okamoto, A. **P-91**
Orcellet, M.L. PL-3
Orihuela, R. P-95
Orio, M. P-10
Ortega, J.-M. OC-20
Ortega-Carrasco, E. **P-92**, P-116
Orvig, C. OC-11, OC-19, **OC-22**
Orzeł, Ł. **P-93**
Osella, D. P-107
Osipovich, N. P-42, P-58
Ostad, S.N. P-1
Oszajca, M. P-14, **P-94**
Otero, L. OC-4, P-43, P-141
Ottaviani, M.F. P-34, P-37
Ozawa, T. P-6, P-33, P-47, P-60, P-84, P-87, P-127

P

Padrón, J.M. P-113
Pagani, A. P-140
Pagani, M.A. **OC-27**
Palacios, O. P-65, **P-95**, P-99, P-100, P-116
Pantazaki, A.A. P-132
Pantcheva, I. P-82, **P-96**
Pap, J.S. **P-97**
Papini, G. P-35
Pappalardo, G. P-55

Paradowska, K.	P-2
Pasqualini, R.	P-136
Pasqui, D.	OC-10
Pastuszko, A.	**P-98**
Pauleta, S.R.	P-71
Pavone, V.	P-89
Peacock, A.	**OC-14**
Pecoraro, V.L.	**OC-21**
Pehlivanidou, E.	P-105
Peigné, B.	P-8
Pellei, M.	P-35, P-104
Perdih, F.	P-105
Perez-Omil, J.A.	P-22
Pérez-Picado, B.	P-38
Pérez-Rafael, S.	**P-99**
Pérez-Zúñiga, C.	**P-100**
Phontongpasuk, S.	OC-2
Picard, C.	**P-101**
Piccinonna, S.	OC-1
Pilarova, I.	**P-102**
Pinto, D.	P-117
Pires, S.	**P-103**
Pizarro, A.M.	P-112
Plamont, M.-A.	OC-20
Platts, J.A.	P-107
Plegaria, J.	OC-21
Policar, C.	**OC-20**, P-13
Polozov, G.	P-42, P-58
Porchia, M.	P-35, **P-104**, P-136
Prat, I.	P-20
Prazeres, R.	OC-20
Psomas, G.	P-63, **P-105**, P-132, P-139, P-145, P-152
Psycharis, V.	P-63, P-139, P-152
Pujol, A.M.	OC-12
Pyrkosz, M.	**P-106**

Q

Quintanar, L.	PL-3

R

Raptopoulou, C.P.	P-63, P-139, P-152
Ravera, M.	**P-107**
Refosco, F.	P-104, **P-108**, P-136
Reggiardo, M.	OC-27
Réglier, M.	P-10, P-124, P-142
Řehoř, I.	P-46
Reig, M.	**P-109**
Ribas, X.	P-20
Richters, T.	**P-110**
Ricoux, R.	P-86
Rigo, C.	P-21
Ringhieri, P.	P-89
Rivera-Becerril, E.	P-12
Rizzarelli, E.	OC-30, P-11, P-55, P-64
Robalo, M.P.	P-83, P-111
Rocchi, A.	OC-10
Rodríguez, V.	P-23, P-114, P-116
Rodríguez, C.	**OC-11**
Rojas, O.L.	**P-111**, P-118
Roman, M.	P-21
Romão, C.	**PL-2**
Romero, I.	**P-112**
Romerosa, A.	P-51, **P-113**
Ronconi, L.	**OC-6**
Rossello, A.	P-75
Roveri, N.	OC-1
Rovira, C.	**OC-32**
Rowińska-Żyrek, M.	P-149
Rua, F.	**OC-24**
Ruiz, J.	P-23, **P-114**, P-116
Ruiz, R.	P-38
Ruiz de Gopegui, U.	OC-18
Ruiz-Azuara, L.	OC-5
Rutkowska-Żbik, D.	P-93

S

Saatchi, K.	**OC-16**
Sachs-Barrable, K.	OC-19
Sadeghi, S.J.	OC-24
Sadler, P.J.	P-112
Sáenz de Viteri, V.	KN-8
Safari, N.	P-1
Sakai, T.	P-88
Sakamoto, Y.	P-81, P-129, P-151
Sala, X.	**OC-29**
Salameh, S.	KN-3
Salas, P.	OC-22

Salifoglou, A. **P-115**
Salvarese, N. P-108
Samper, K.G. **P-116**
Sánchez, J. P-34
Sánchez, P. **P-117**
Sánchez Rodríguez, J. P-37
Sandt, C. OC-20
Santamaria, S. P-75
Santini, C. P-35, P-104
Santos, A.M. P-36
Santos, F. P-118
Santos, F.C. P-111, **P-118**
Santos, I. P-70
Santos, M.A. P-75
Saraiba, C. P-51
Sarniguet, C. P-141
Savéant, J.M. OC-9
Sawai, H. OC-31
Sayen, S. P-5
Schibli, R. **PL-5**
Scozzafava, A. **P-119**
Seng, H.L. P-131
Seraglia, R. P-136
Serena, C. P-48
Serrano-Ruiz, M. P-51, P-113
Serratrice, G. P-10
Seubert, K. **P-120**
Ševčík, R. P-70
Ševčíková, R. P-70
Shalev, D.E. P-122
Sherry, A.D. OC-15
Shichibu, Y. P-56
Shimazaki, Y. **P-121**
Shiraiwa, T. P-59, P-90, P-150
Shiro, Y. OC-31
Shirota, T. P-33
Shoshan, M.S. **P-122**
Sigel, A. P-123
Sigel, H. **P-123**
Sigel, R.K.O. **OC-26**, P-16, P-25, P-41, P-125
Sija, É. P-61
Simaan, A.J. **P-124**, P-142
Simándi, L.I. P-128
Simon, N.I. P-24, P-45
Skilandat, M. **P-125**
Skumryev, V. P-144
Sóvágó, I. P-55, P-146
Soveral, G. P-19
Speier, G. P-97
Stochel, G. P-77, P-93, P-94
Stürzenbaum, S.R. KN-9
Suades, J. P-65, **P-126**
Sugimoto, H. OC-31
Sun, D. P-68
Sun, S. OC-28
Suzuki, A. **P-127**
Szabó, L. P-128
Szabó, O. P-29
Szigyártó, I.Cs. **P-128**
Szmyd, B. P-93
Szumełda, T. P-93

T

Takimiya, Y. P-81, **P-129**
Tan, C.-P. **P-130**
Tan, K.W. **P-131**
Tarushi, A. **P-132**
Telpoukhovskaia, M. OC-11
Terenzi, A. **P-133**
Thiabaud, G. **P-134**
Timári, S. **P-135**, P-147
Tircsó, Gy. **OC-15**, P-29
Tisato, F. P-35, P-104, **P-136**
Tohara, A. **P-137**
Toledano, Y. **P-138**
Tolia, Ch. **P-139**
Tomàs, M. OC-27, **P-140**
Tomaz, A.I. OC-23, P-36, P-76, P-83, P-111, P-118, **P-141**
Torres-Monserrat, V. PL-3
Tosto, C. OC-30
Tóth, Id. OC-15
Tóth, Im. OC-15
Toyama, T. P-33
Travaglia, A. P-64
Trevisan, A. OC-6
Trnkova, L. P-102
Tron, T. P-124, **P-142**
Trondl, R. P-62
Tröppner, O. **P-143**
Tsekova, D. **P-144**

Tshuva, E.Y.	**OC-3**, P-79, P-122
Tsiliki, P.	**P-145**
Tsiliou, S.	P-105
Tsitovich, P.B.	KN-2
Tsybin, Y.O.	P-78
Tuccinardi, T.	P-75
Turel, I.	P-105, P-132
Turi, I.	**P-146**

U

Ugalde, M.	P-38
Uno, A.	P-150
Urtiaga, M.K.	P-30

V

Valensin, D.	KN-5, **OC-10**, P-149,
Valente, A.	P-76
Valero, E.	P-95, P-117
Valiente-Gabioud, A.A.	PL-4
van Eldik, R.	P-94
van Gemeren, L.	OC-14
Vander Elst, L.	P-101
Vaněk, J.	P-70
Váradi, T.	P-97
Várnagy, K.	P-135, **P-147**
Vecchio, G.	P-11
Velasco, D.	P-109
Venzo, A.	P-108
Vessières, A.	OC-20
Vicente, C.	P-116
Vila, A.J.	P-27
Vilímová, V.	P-46
Vindigni, V.	P-21
Visigalli, M.	KN-4
Vitale, R.	P-89

W

Waern, J.	OC-20
Wan, X.	OC-25
Wang, C.	OC-28
Wang, X.-H.	P-148
Wang, X.-Y.	**P-148**
Wang, Y.-Y.	P-66
Ward, Th.R.	**KN-1**
Wasada-Tsutsui, Y.	P-6, P-33, P-47, P-60
Wasan, K.M.	OC-16, OC-19
Watt, R.K.	**KN-6**, P-22, P-95
Weng, L.P.	P-52
Wilkie, J.	OC-14
Williams, D.R.	**PL-0**
Witkowska, D.	**P-149**

X

Xu, D.	P-80

Y

Yajima, T.	P-59, P-90, **P-150**
Yamanaka, M.	OC-31
Yoshida, M.	P-81, P-129, **P-151**
Yoshii, K.	P-33
Yu, F.	OC-21

Z

Zaballa, M.E.	P-27
Zahl, A.	P-67
Zampakou, M.	**P-152**
Zastrow, M.	OC-21
Zedat, S.	P-18
Zeitoun-Ghandour, S.	KN-9
Zelder, F.	**P-153**
Zhang, J.	KN-3
Zhao, M.	**P-154**
Zhao, Y.-Z.	P-130
Zheldakova, R.	P-42, P-58
Zheng, X.-H.	**P-155**
Zheng, Y.	P-69
Zhivkova, T.	P-82, P-96
Zhou, K.	P-153
Zóka, I.G.	P-24, P-45
Zweckstetter, M.	PL-3