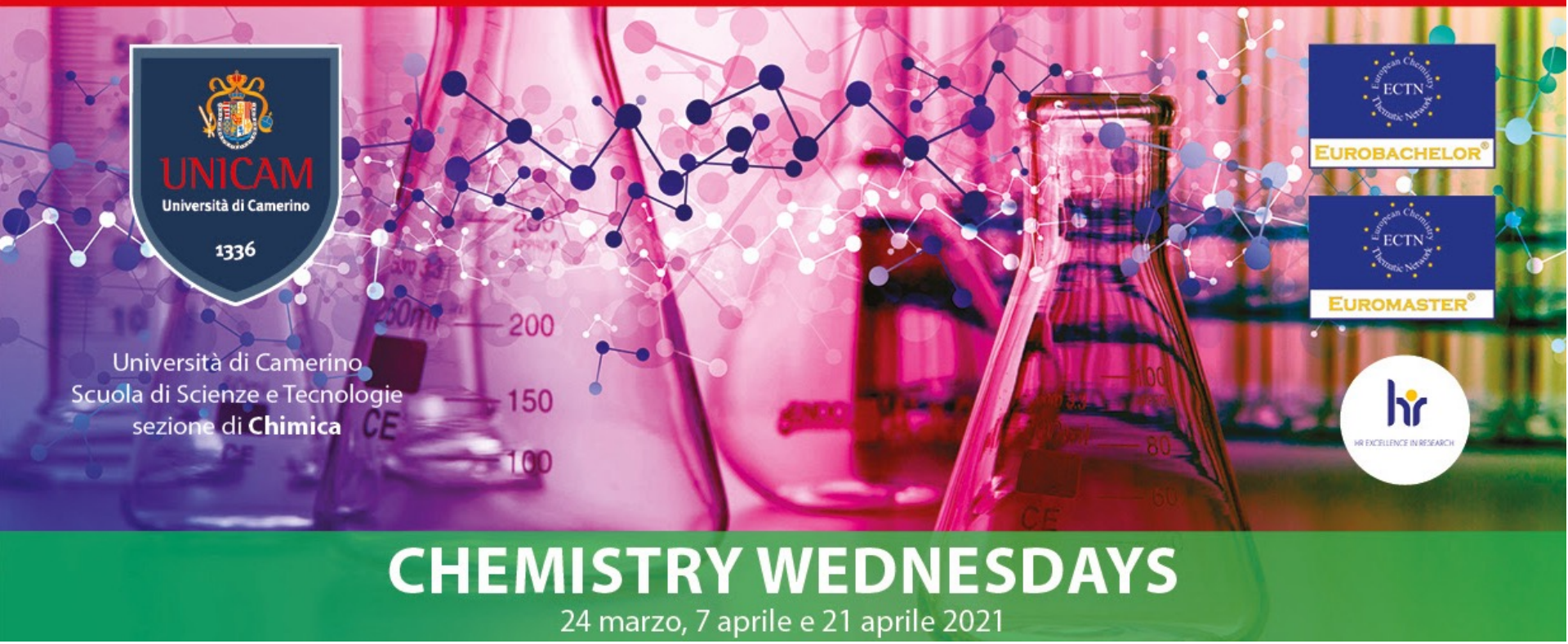


# Multidisciplinary strategies involving metal complexes: from biological to catalytic and technological applications

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PhD students

**Luca Bagnarelli** and **Riccardo Vallesi**

# Research Topics

## Metal-based drugs

Copper-, Silver- and Gold-based anticancer drugs
Targeted cancer therapy
Combined Chemotherapy with Synchrotron Radiation
Radiometal-based anticancer agents: $^{64}Cu$ and $^{67}Cu$

## Coinage metals N-Heterocyclic carbene complexes

Anticancer drugs
Conjugation with Au-NPs
Drug delivery

## Antivirals or antimalarials coinage metal complexes

## Study of new inorganic/organic hybrid materials for the polymer industry

Study of the chemical-physical properties of innovative polymeric materials
Eco-friendly flame retardant fillers

## Copper catalysts

C-N and C-C coupling reactions (Sonogashira reactions)
Allylic oxidation (Kharasch-Sosnovsky reactions)

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 Gruppo dell'azoto | 16 Chalcogens | 17 Alogeni | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 H Idrogeno 1,008 | | | | | | | | | | | | | | | | | 2 He Elio 4,0026 |
| 2 | 3 Li Litio 6,94 | 4 Be Berillio 9,0122 | | | | | | | | | | | 5 B Boro 10,81 | 6 C Carbonio 12,011 | 7 N Azoto 14,007 | 8 O Ossigeno 15,999 | 9 F Fluoro 18,998 | 10 Ne Neon 20,180 |
| 3 | 11 Na Sodio 22,990 | 12 Mg Magnesio 24,305 | | | | | | | | | | | 13 Al Alluminio 26,982 | 14 Si Silicio 28,085 | 15 P Fosforo 30,974 | 16 S Zolfo 32,06 | 17 Cl Cloro 35,45 | 18 Ar Argon 39,948 |
| 4 | 19 K Potassio 39,098 | 20 Ca Calcio 40,078 | 21 Sc Scandio 44,956 | 22 Ti Titanio 47,867 | 23 V Vanadio 50,942 | 24 Cr Cromo 51,996 | 25 Mn Manganese 54,938 | 26 Fe Ferro 55,845 | 27 Co Cobalto 58,933 | 28 Ni Nichel 58,693 | 29 Cu Rame 63,546 | 30 Zn Zinco 65,38 | 31 Ga Gallio 69,723 | 32 Ge Germanio 72,630 | 33 As Arsenico 74,922 | 34 Se Selenio 78,971 | 35 Br Bromo 79,904 | 36 Kr Kripton 83,798 |
| 5 | 37 Rb Rubidio 85,468 | 38 Sr Stronzio 87,62 | 39 Y Ittrio 88,906 | 40 Zr Zirconio 91,224 | 41 Nb Niobio 92,906 | 42 Mo Molibdeno 95,95 | 43 Tc Tecnezio (98) | 44 Ru Rutenio 101,07 | 45 Rh Rodio 102,91 | 46 Pd Palladio 106,42 | 47 Ag Argento 107,87 | 48 Cd Cadmio 112,41 | 49 In Indio 114,82 | 50 Sn Stagno 118,71 | 51 Sb Antimonio 121,76 | 52 Te Tellurio 127,60 | 53 I Iodio 126,90 | 54 Xe Xeno 131,29 |
| 6 | 55 Cs Cesio 132,91 | 56 Ba Bario 137,33 | 57–71 | 72 Hf Afnio 178,49 | 73 Ta Tantalio 180,95 | 74 W Tungsteno 183,84 | 75 Re Renio 186,21 | 76 Os Osmio 190,23 | 77 Ir Iridio 192,22 | 78 Pt Platino 195,08 | 79 Au Oro 196,97 | 80 Hg Mercurio 200,59 | 81 Tl Tallio 204,38 | 82 Pb Piombo 207,2 | 83 Bi Bismuto 208,98 | 84 Po Polonio (209) | 85 At Astato (210) | 86 Rn Radon (222) |
| 7 | 87 Fr Francio (223) | 88 Ra Radio (226) | 89–103 | 104 Rf Rutherfordio (267) | 105 Db Dubnio (268) | 106 Sg Seaborgio (269) | 107 Bh Bohrio (270) | 108 Hs Hassio (277) | 109 Mt Meitnerio (278) | 110 Ds Darmstadtio (281) | 111 Rg Roentgenio (282) | 112 Cn Copernicio (285) | 113 Nh Nihonio (286) | 114 Fl Flerovio (289) | 115 Mc Moscovio (290) | 116 Lv Livermorio (293) | 117 Ts Tennesso (294) | 118 Og Oganesson (294) |
| | | | 6 | 57 La Lantanio 138,91 | 58 Ce Cerio 140,12 | 59 Pr Praseodimio 140,91 | 60 Nd Neodimio 144,24 | 61 Pm Promezio (145) | 62 Sm Samario 150,36 | 63 Eu Europio 151,96 | 64 Gd Gadolinio 157,25 | 65 Tb Terbio 158,93 | 66 Dy Disprosio 162,50 | 67 Ho Olmio 164,93 | 68 Er Erbio 167,26 | 69 Tm Tulio 168,93 | 70 Yb Itterbio 173,05 | 71 Lu Lutezio 174,97 |
| | | | 7 | 89 Ac Attinio (227) | 90 Th Torio 232,04 | 91 Pa Protoattinio 231,04 | 92 U Uranio 238,03 | 93 Np Nettunio (237) | 94 Pu Plutonio (244) | 95 Am Americio (243) | 96 Cm Curio (247) | 97 Bk Berkelio (247) | 98 Cf Californio (251) | 99 Es Einsteinio (252) | 100 Fm Fermio (257) | 101 Md Mendelevio (258) | 102 No Nobelio (259) | 103 Lr Laurenzio (266) |

Atomic
Simbolo
Nome
Weight

C Solidi

Hg Liquidi

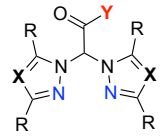
H Gas

Rf Sconosciuto

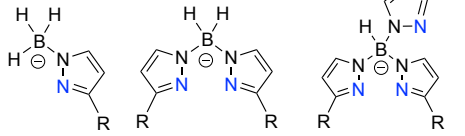
Metallo
- Metalli alcalini
- Metalli alcalino terrosi
- Lantanoidi
- Attinoidi
- Elementi di transizione
- Metalli di post-transizione

Semimetallo

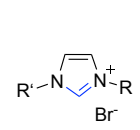
Non metallo
- Nonmetalli
- Gas nobili



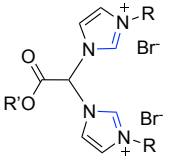

R = H, Me
**X** = CH or N
Y = OH, OR, $NR_2$, SH



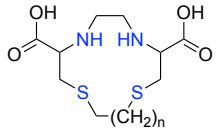

R = $CF_3$, $NO_2$



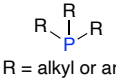

R = $^t$Bu, Mes, Me
R' = alkyl/aryl-$SO_3^-$




R = $^t$Bu, Mes, Cy, Me

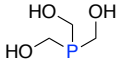



n = 1, 2 or 3




R = alkyl or aryl

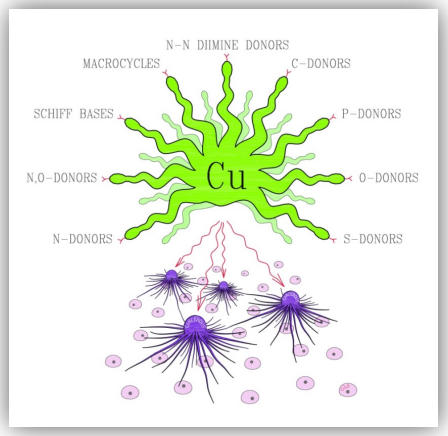
$PR_3$




thp

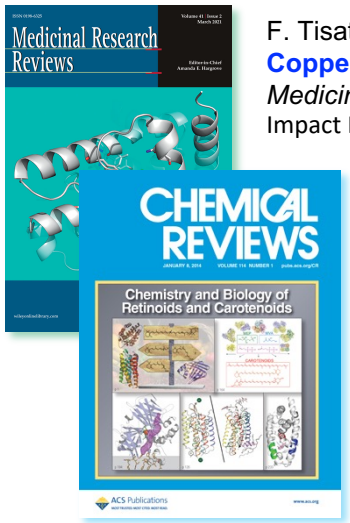

PTA

# Metal-based anticancer strategies




**Copper-based anticancer drugs**

- ✓ **Specificity**
- ✓ **Reduced toxicity**
- ✓ **Maximum therapeutic efficacy**




F. Tisato, C. Marzano, M. Porchia, M. Pellei and C. Santini
**Copper in Diseases and Treatments, and Copper-based Anticancer Strategies**
*Medicinal Research Reviews,* 4 (2010) 708-749
Impact Factor = 9,300

C. Santini, M. Pellei, V. Gandin, M. Porchia, F. Tisato and C. Marzano.
**Advances in Copper Complexes as Anticancer Agents**
*Chem. Rev.,* 114 (2014) 815-862.
Impact Factor = 52,758

**To achieve this goal it is necessary to develop new drugs directed towards specific targets expressed or at least over-expressed in cancer and metastatic cells**

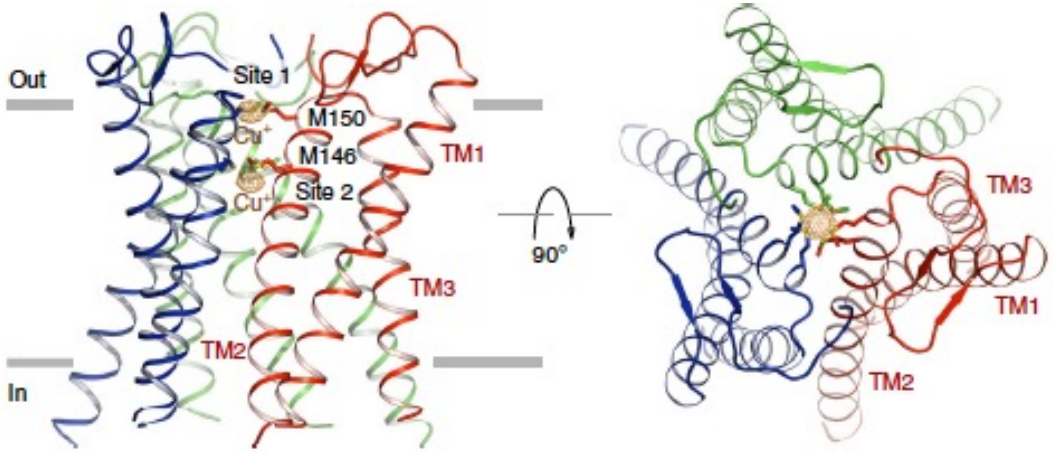
# Metal-based anticancer agents

## ➢ Why copper?

- Copper is a **micro-element essential** for several functions in mammalian physiology. Our physiology is able to manage copper through complex homeostatic mechanisms;
- copper is a crucial co-factor in **angiogenesis**;
- ex-vivo studies have demostrated that several cancer cells show an **abnormal content of copper**, largely exceeding its content in non-tumor cells.

## ➢ Why Cu(I)?

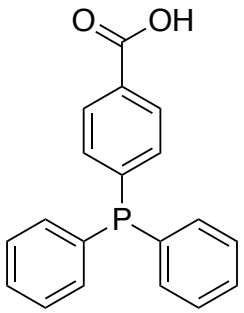
- Biochemists have reached a general consensus that physiological copper is primarily internalised in cells ***via* active transport mechanisms** as Cu(I) rather than Cu(II);
- human copper transporter 1 (**hCtr1**) is recognized as the trans-membrane protein that internalises copper(I).



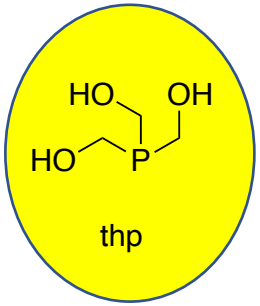

**hCtr1** $Cu^+$ selectivity filter (F. Ren et al. *Nature Communications* 10 (2019) 1386)

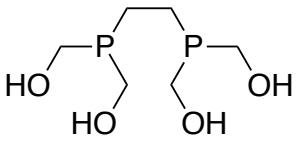
# Why $Cu^{(I)}$-phosphanes complexes?

- Phosphanes ($PR_3$) are able to **stabilize** copper in its reduced Cu(I) state avoiding disproportionation to Cu and $Cu^{(II)}$
- **hydrophilic** $[Cu^{(I)}(P)_4]^+$ complexes are easy to handle in biological tests
- $[Cu^{(I)}(P)_4]^+$ complexes are **labile**, somehow mimicking *cis*-Pt

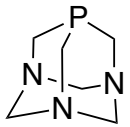



$PPh_2(p\text{-}C_6H_4COOH)$

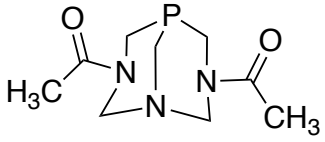


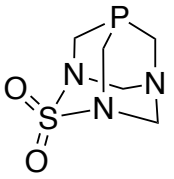

bhpe




PTA



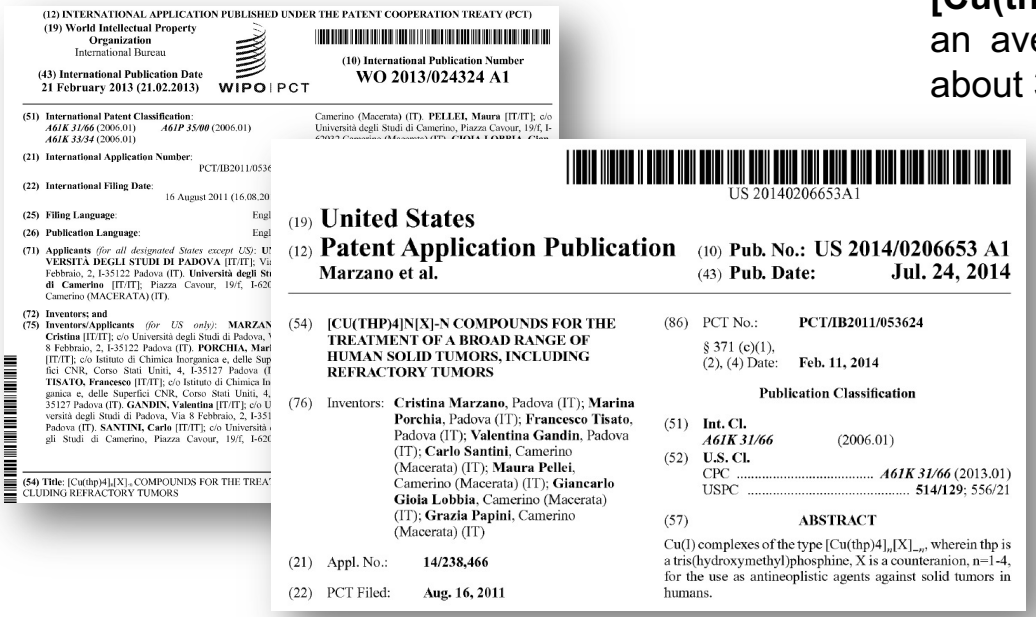

DAPTA




PTA-$SO_2$

- ✓ **High *in vitro* cytotoxicity** (generally higher than *cis*-Pt)
- ✓ **Overcoming of *cis*-Pt resistance** (… different mechanism of action)
- ✓ **Selectivity** toward tumor cells *vs* non-tumor cells
- ✓ **Specificity** toward cancer cells derived from solid tumors (colon cancer cells)
- ✓ **Cellular internalization** by active transport *via* transmembrane protein hCtr1
- ✓ **In *vivo* antitumor efficacy** (Lewis lung carcinoma (LLC) murine model).

# Patents



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(19) World Intellectual Property Organization
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(21) International Application Number:
PCT/IB2011/053

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(54) Title: [Cu(thp)4]n[X]n COMPOUNDS FOR THE TREA
CLUDING REFRACTORY TUMORS

Camerino (Macerata) (IT). **PELLEI, Maura** [IT/IT]; c/o Università degli Studi di Camerino, Piazza Cavour, 19/f, I-

US 20140206653A1

(19) **United States**
(12) **Patent Application Publication**
**Marzano et al.**

(10) **Pub. No.: US 2014/0206653 A1**
(43) **Pub. Date: Jul. 24, 2014**

(54) **[CU(THP)4]N[X]-N COMPOUNDS FOR THE TREATMENT OF A BROAD RANGE OF HUMAN SOLID TUMORS, INCLUDING REFRACTORY TUMORS**

(76) Inventors: **Cristina Marzano**, Padova (IT); **Marina Porchia**, Padova (IT); **Francesco Tisato**, Padova (IT); **Valentina Gandin**, Padova (IT); **Carlo Santini**, Camerino (Macerata) (IT); **Maura Pellei**, Camerino (Macerata) (IT); **Giancarlo Gioia Lobbia**, Camerino (Macerata) (IT); **Grazia Papini**, Camerino (Macerata) (IT)

(21) Appl. No.: **14/238,466**

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§ 371 (c)(1),
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**Publication Classification**

(51) **Int. Cl.**
***A61K 31/66*** (2006.01)

(52) **U.S. Cl.**
CPC ..... ***A61K 31/66*** (2013.01)
USPC ..... **514/129**; 556/21

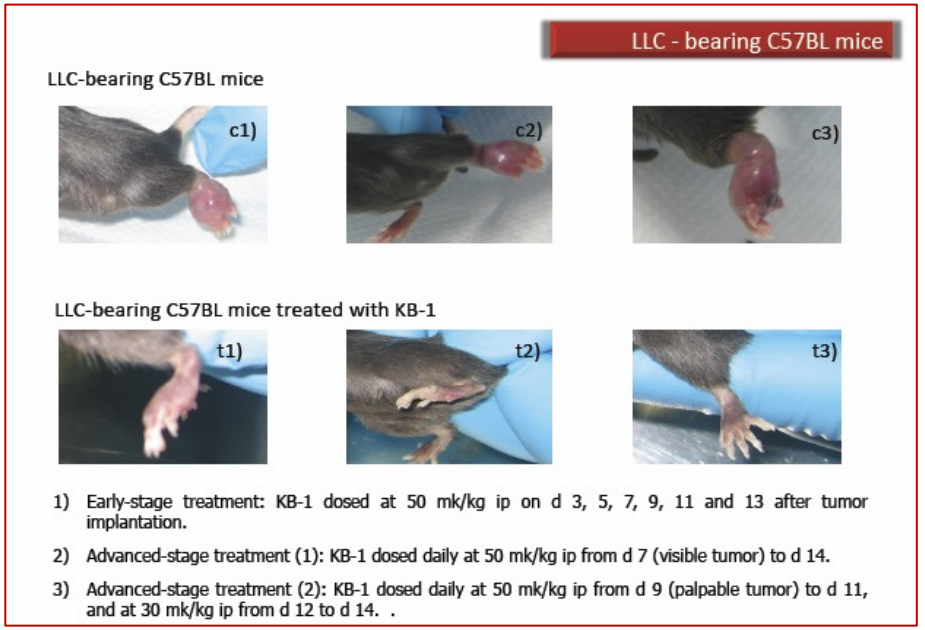
(57) **ABSTRACT**

Cu(I) complexes of the type $[Cu(thp)4]_n[X]_{-n}$, wherein thp is a tris(hydroxymethyl)phosphine, X is a counteranion, n=1-4, for the use as antineoplistic agents against solid tumors in humans.

**[Cu(thp)$_4$]X** showed great antitumor efficacy with an average $IC_{50}$ over nine cell types that was about 30 times lower than that of cisplatin

**A549 = lung cancer**
**CaCo2, HCT-15 = colon cancer**
**Hela = cervix cancer**
**MCF-7 = breast cancer**
**HL60 = leukemia**
**Daudi = lymphoma**
**HepG2 = epatoma**
**A375 = melanoma**

*In vivo* tests on LLC murine cancer model




- ✓ **Soluble and stable** in $H_2O$
- ✓ 30 **times more active than cisplatin**
- ✓ **Not cross-resistance**
- ✓ **Up to 90% regression of the tumor mass** (*in vivo, 15 days* C5C57BL mice treated)
- ✓ **Non-systemic toxicity**

Patent purchased in 2018 by the **SAPIR PHARMACEUTICALS** (New York, USA)

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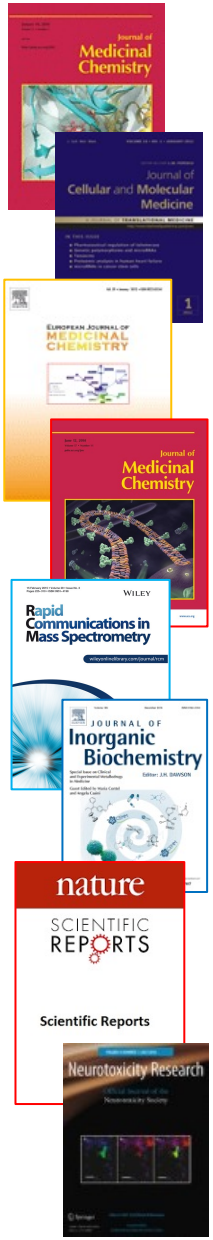



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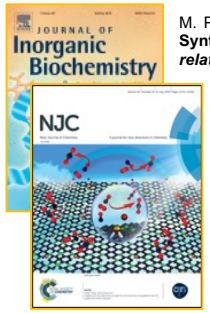
*Neurotoxicity Research*, 34 (2018) 93–108

# Targeted Cancer Therapy

## Rational design and biological evaluation of novel conjugated heteroscorpionate ligands and related copper(I/II) complexes

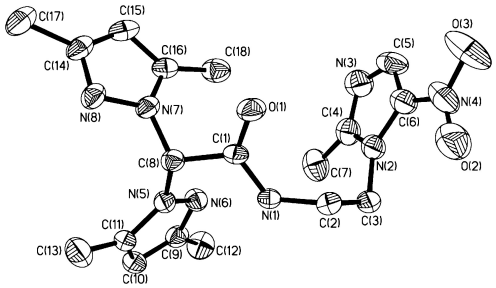

M. Pellei, G. Papini, A. Trasatti, M. Giorgetti, D. Tonelli, M. Minicucci, C. Marzano, V. Gandin, A. Dolmella, G. Aquilanti and C. Santini. **Nitroimidazole and glucosamine conjugated heteroscorpionate ligands and related copper(II) complexes. Syntheses, biological activity and XAS studies.** *Dalton Transactions* 40 (2011) 9877-9888

Front Cover



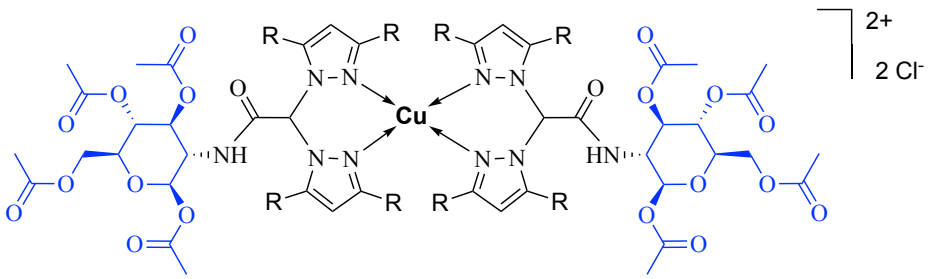

M. Pellei, V. Gandin, C. Cimarelli, W. Quaglia, N. Mosca, L. Bagnarelli, C. Marzano and C. Santini. **Syntheses and biological studies of nitroimidazole conjugated heteroscorpionate ligands *and related Cu (I) and Cu (II) complexes.*** *Journal of Inorganic Biochemistry* 187 (2018) 33-40.

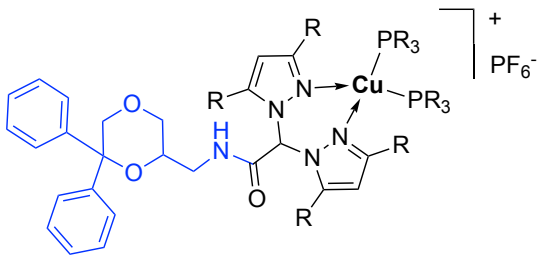
M. B. Morelli, C. Amantini, G. Santoni, M. Pellei, C. Santini, C. Cimarelli, E. Marcantoni, M. Petrini, F. Del Bello, G. Giorgioni, A. Piergentili and W. Quaglia. **Novel antitumor copper(II) complexes designed to act through synergistic mechanisms of action, due to the presence of an NMDA receptor ligand and copper in the same chemical entity.** *New Journal of Chemistry* 42 (2018) 11878-11887.

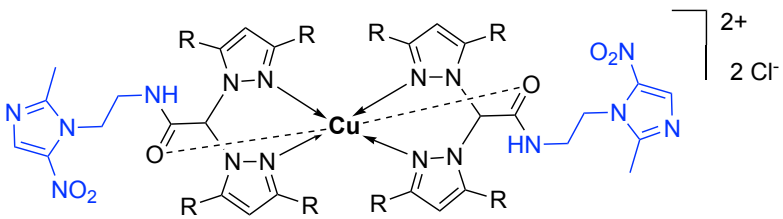



Crystal structure of $L^{MN}$ ligand

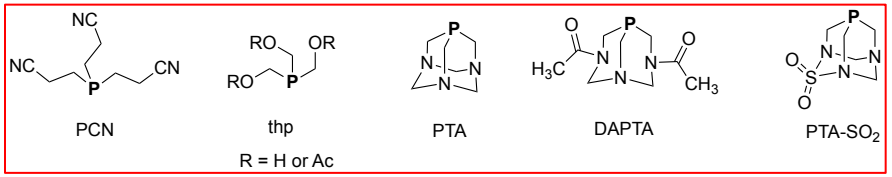
## Synthesis of novel copper(I) and copper(II) derivatives evaluated for their cytotoxic activity




$PR_3$



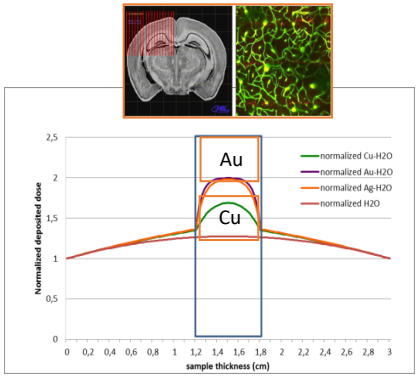
# Combined Chemotherapy (CTX) with Synchrotron Radiation (SR)


*Current Medicinal Chemistry*, 2014, *20*, 1-29 

**The Combined Therapeutical Effect of Metal-based Drugs and Radiation Therapy: The Present Status of Research**

C. Ceresa[1,*], A. Bravin[2], G. Cavaletti[1], M. Pellei[3] and C. Santini[3,*]

*[1]Department of Surgery and Translational Medicine, University of Milano - Bicocca, Monza, Italy; [2]Biomedical Beamline (ID17), European Synchrotron Radiation Facility (ESRF), Grenoble, France; [3]School of Science and Technology - Chemistry Division, University of Camerino, Camerino, Italy*




## ➢ Principle

- Tumor loaded with a **high Z element** (Pt, Cu, Au, Ag), with high probability for adsorbing radiation

## ➢ Effect

- Induction of **photoelectric effect** by irradiation with **monochromatic X-rays** beams (keV scale) tuneable to the adsorption edges of the high Z element

## ➢ Advantage

- To reduce toxic effects on the surrounding healthy tissues
- To increase tumor control

ESRF
The European Synchrotron

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

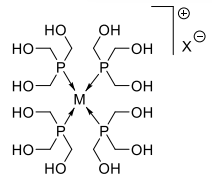
**SYRA3 COST Action TD1205:** ***Innovative Methods in Radiotherapy and Radiosurgery Using Synchrotron Radiation***

*Director: A. Bravin (ESRF, Grenoble, France)*

**Unicam expertise**: CMST (Chemistry and Molecular Sciences and Technologies) - Inorganic Chemistry, Coordination Chemistry, Metal-based drugs.

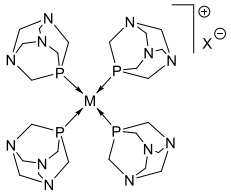
**13 Countries**
**30 Research Group**
- 26 UE
- 1 Canada
- 1 United States
- 2 Australia

Its aim is to setup and coordinate a multidisciplinary network to develop synchrotron radiotherapy and radiosurgery techniques to treat **brain tumours** and other diseases of the central nervous system.



**1**, M = Cu, X = $PF_6$
**2**, M = Ag, X = $PF_6$
**3**, M = Au, X = Cl

$[M(thp)_4]X$



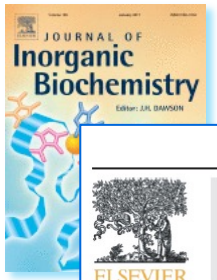
**4**, M = Cu, X = $PF_6$
**5**, M = Ag, X = $PF_6$
**6**, M = Au, X = Cl

$[M(PTA)_4]X$

## *Radiation-enhanced metal-based chemotherapy in the treatment of solid tumors*

Scientific partners: Prof. Guido Cavaletti, P.I. (Università degli Studi di Milano - Bicocca); Dr. Alberto Bravin (ESRF Grenoble, France)

# Antimalarial coinage metal complexes




Journal of Inorganic Biochemistry 166 (2017) 1–4

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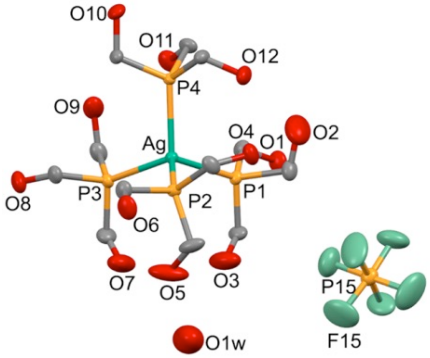
journal homepage: www.elsevier.com/locate/jinorgbio

Short communication

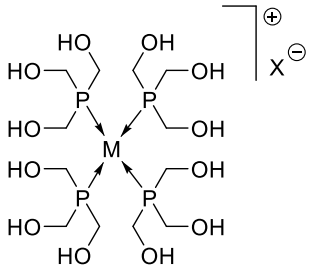
## Novel metalloantimalarials: Transmission blocking effects of water soluble Cu(I), Ag(I) and Au(I) phosphane complexes on the murine malaria parasite *Plasmodium berghei*

Sofia Tapanelli [a], Annette Habluetzel [a,*], Maura Pellei [b,*], Luciano Marchiò [c], Alessia Tombesi [b], Ambra Capparè [b], Carlo Santini [b]

[a] School of Pharmacy, University of Camerino, Piazza dei Costanti, Camerino, MC, Italy
[b] School of Science and Technology – Chemistry Division, University of Camerino, via S. Agostino 1, Camerino, MC, Italy
[c] Department of Chemistry, University of Parma, Parco Area delle Scienze 17A, Parma, Italy




*In vitro* testing on malaria parasite stages developing in the mosquito midgut

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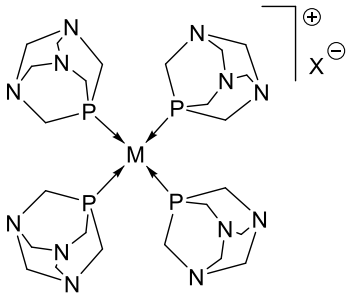
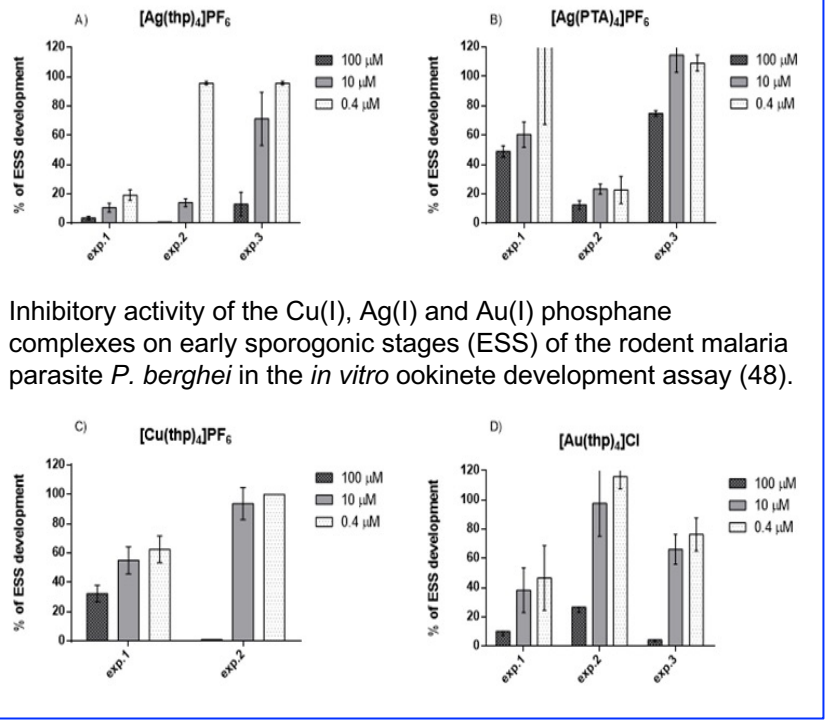
**2**, M = Ag, X = $PF_6$
**3**, M = Au, X = Cl

**$[M(thp)_4]X$**



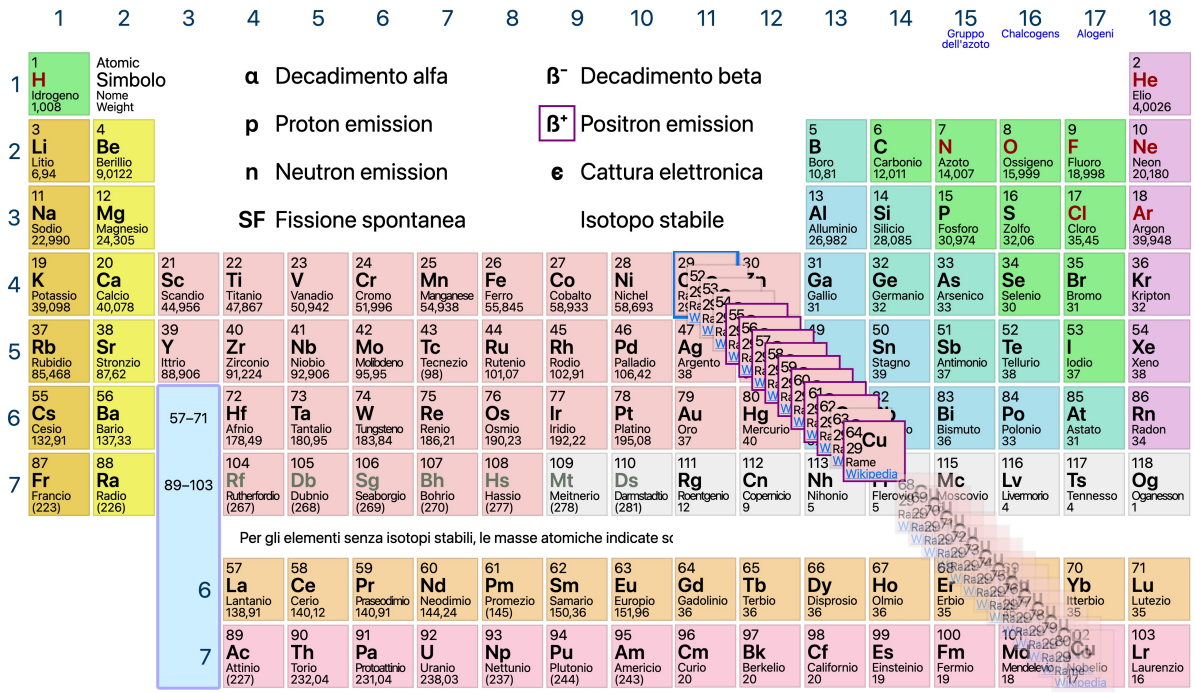

**4**, M = Cu, X = $PF_6$
**5**, M = Ag, X = $PF_6$
**6**, M = Au, X = Cl

**$[M(PTA)_4]X$**




Inhibitory activity of the Cu(I), Ag(I) and Au(I) phosphane complexes on early sporogonic stages (ESS) of the rodent malaria parasite *P. berghei* in the *in vitro* ookinete development assay (48).

# Copper radioisotopes

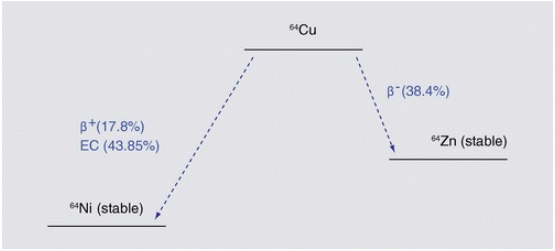



**Main isotopes of copper**

($_{29}$Cu)

| Isotope | abundance | half-life ($t_{1/2}$) | Decay mode | Decay product |
|---|---|---|---|---|
| $^{63}$Cu | 69.17% | stable | | |
| $^{64}$Cu | syn | 12.70 h | ε | $^{64}$Ni |
| | | | β⁻ | $^{64}$Zn |
| $^{65}$Cu | 30.83% | stable | | |
| $^{67}$Cu | syn | 61.83 h | β⁻ | $^{67}$Zn |

**Standard atomic weight** $A_{r,\,standard}$(Cu) = 63.546(3)[1]




- ✓ $^{64}$Cu was produced in large quantities and with in high specific activity in **biomedical cyclotrons** by the nuclear reaction $^{64}$Ni(p,n)$^{64}$Cu
- ✓ $^{64}$Cu is a **positron emitter** making it a viable **PET imaging** radionuclide which can give real time images of the physiological processes in the system.
- ✓ Radiotherapeutic efficacy of $^{64/67}$Cu depends highly upon the radioligand delivery to the target cells, so the development of bifunctional chelates is central to development of $^{64/67}$Cu's potential as a radiopharmaceutical.

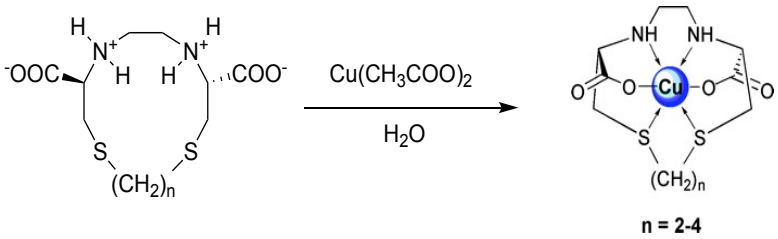
# Radiometal-based anticancer agents: $^{64}$Cu and $^{67}$Cu

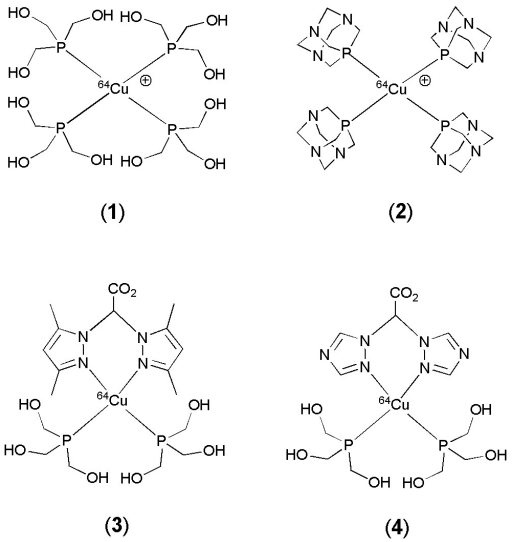
Washington University in St. Louis
School of Medicine
Mallinckrodt Institute of Radiology

Memorial Sloan Kettering Cancer Center
Department of Radiology,
Radiochemistry and Imaging Sciences Service

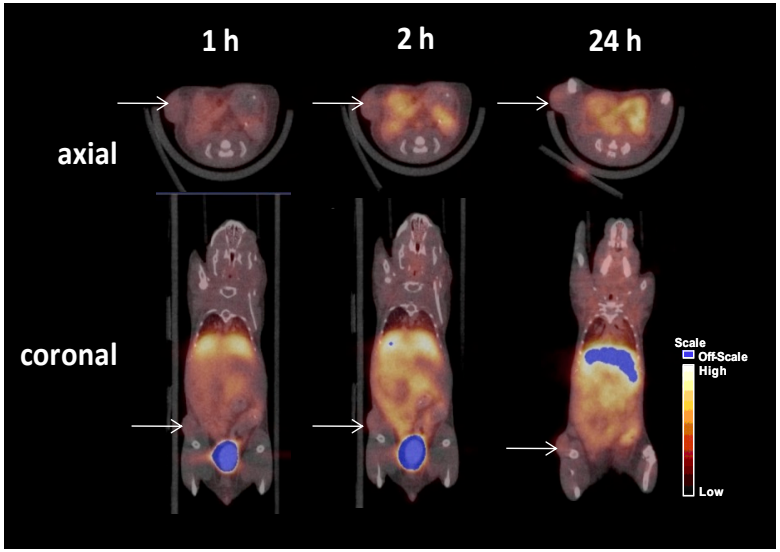
ACOM Srl
Advanced Center Oncology Macerata

- ✓ A novel class of $^{64}$Cu(II) labeled complexes with new **macrocyclic ligands**
- ✓ *in vitro* and *in vivo* characterization of $^{64}$Cu(I) complexes derived from hydrophilic **phosphane ligands**

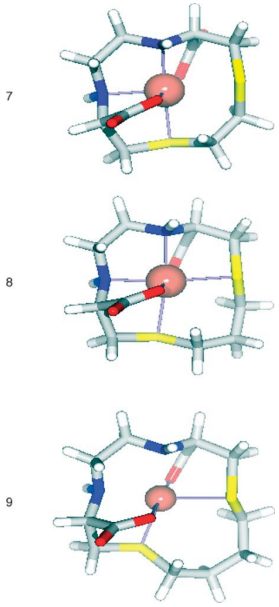



Structures of the $^{64}$Cu(I) complexes




PET imaging with complex **1** in a mouse




The DFT (B3LYP/LACVP*) optimized structures

# New theranostic copper complexes and their bioconjugates for a multi-modal anticancer strategy

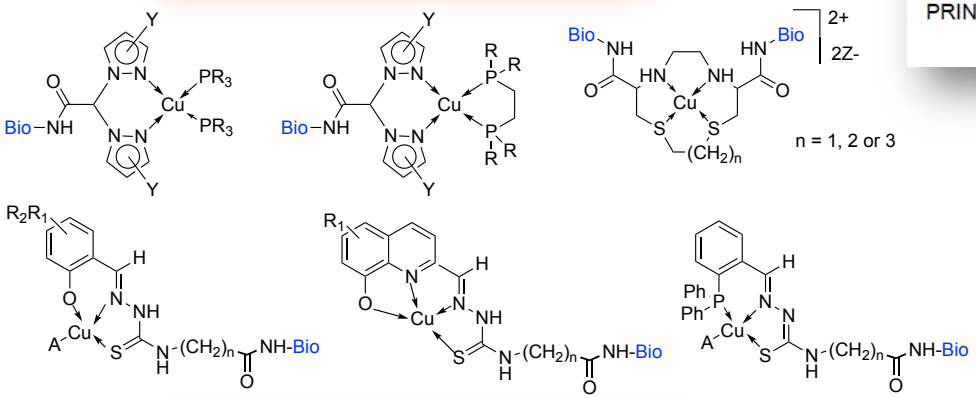

m_pi.AOODGRIC.REGISTRO_PRIN2020.0001185.25-01-2021

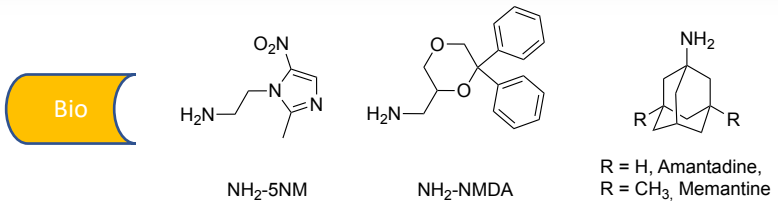
*Ministero dell'Università e della Ricerca*

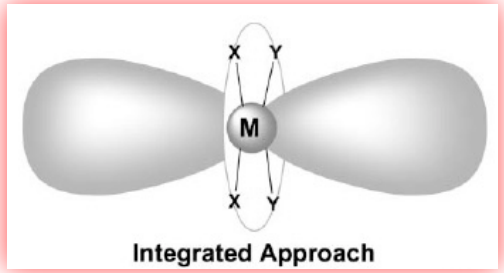
Segretariato Generale

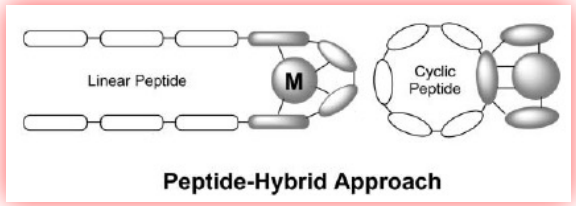
Direzione Generale per il coordinamento e la valorizzazione della ricerca e dei suoi risultati

PRIN: PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE – Bando 2020
Prot. 20208M5FWM



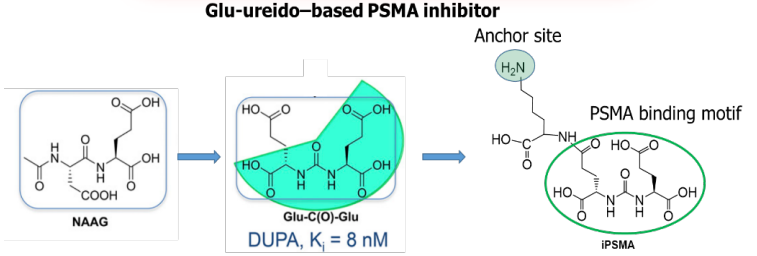




**Figure 3**. Glu-ureido–based PSMA inhibitor (iPSMA) exemplifying rational design of urea-based glutamate carboxypeptidase II inhibitors. NAAG 5 N-acetyl-L-aspartyl-L-glutamate; DUPA 5,2-[3-(1,3-dicarboxypropyl)ureido]pentanedioic acid.

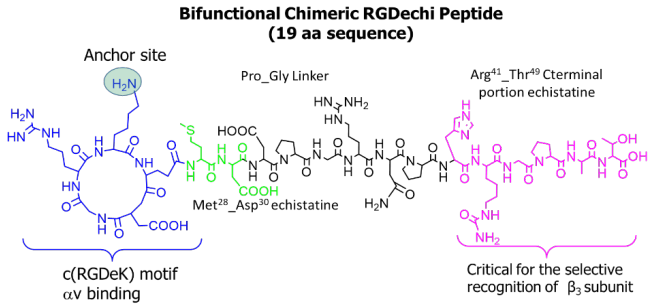
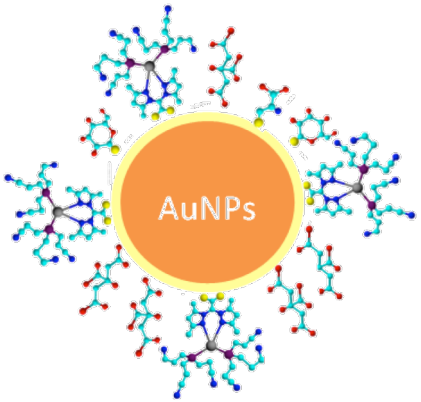
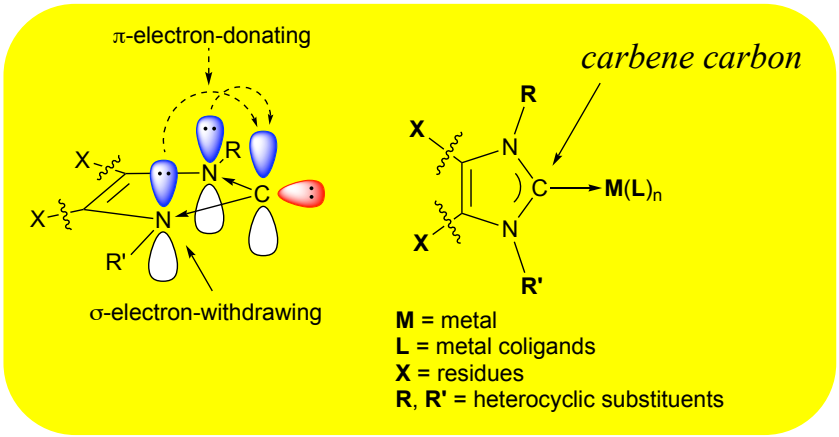


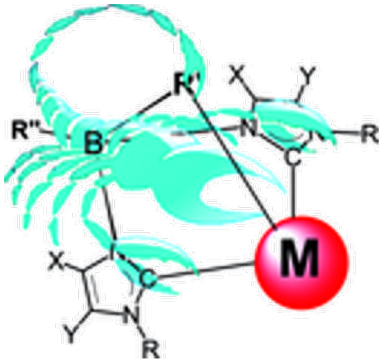

**Figure 4**. RGDechi structure: the selectivity of the peptide derives from its chimeric nature; in particular, from residues located at the C-terminal portion of the echistatin moiety, in the region encompassing HCit[15]-Thr[19]. Indeed, the main role is played by the ε-carbamoyl group of HCit[15] that, in combination with the Gly[16], is found to establish specific interaction only with the $\beta_3$ subunit.

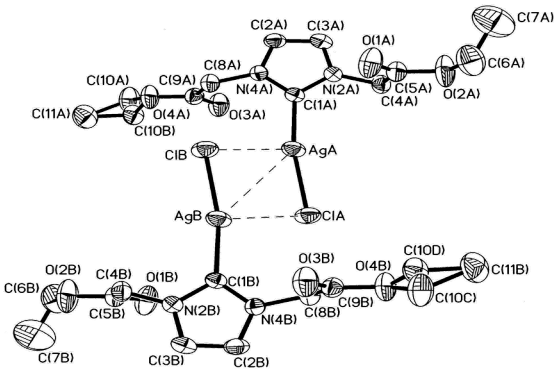
# Why metal carbenes complexes?

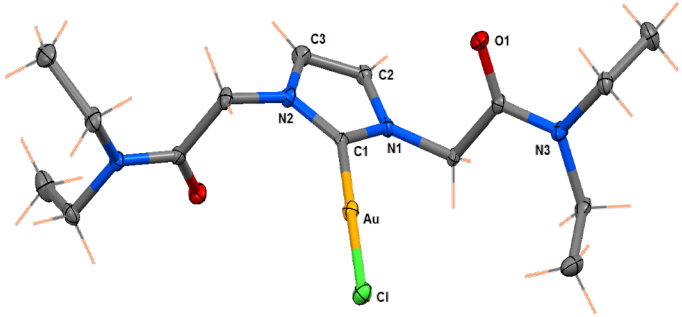
- Versatile class of soft ligands able to stabilize metals in their reduced state;
- wide range of applications in metal-based catalysis and organocatalysis;
- carbenes precursors are useful as ionic liquids;
- anchors for surface modifications, stabilization and functionalization of metal nanoparticles;
- M-NHCs complexes are labile, somehow mimicking *cis*-Pt.

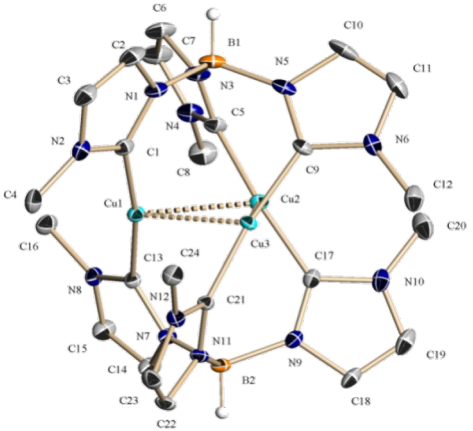


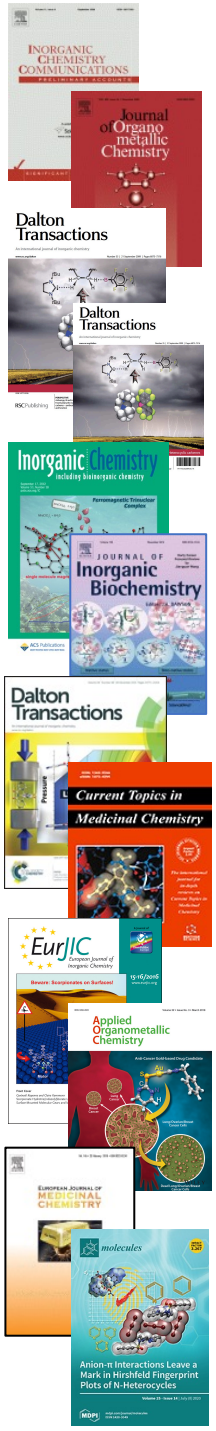







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**New homoleptic carbene transfer ligands and related coinage metal complexes**
*Inorganic Chemistry Communications*, 11 (2008) 1103-1106.

Andrea Biffis, Giancarlo Gioia Lobbia, Grazia Papini, Maura Pellei, Carlo Santini, Elena Scattolin, Cristina Tubaro
**Novel scorpionate-type triscarbene ligands and their silver and gold complexes**"
*Journal of Organometallic Chemistry,* 693 (2008) 3760–3766

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*Dalton Transactions*, 2009, 7223-7229.

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**Sulfonate- or carboxylate-functionalized N-heterocyclic bis-carbene ligands and related water soluble silver complexes**
*Dalton Transactions*, 2009, 6985-6990

M. Pellei, V. Gandin, M. Marinelli, Cristina Marzano, M. Yousufuddin, H. V. Rasika Dias, and C. Santini
**Synthesis and biological activity of ester- and amide-functionalized imidazolium salts and related water-soluble coinage metal-NHC complexes**
*Inorganic Chemistry*, 51 (2012) 9873-9882

V. Gandin, M. Pellei, M. Marinelli, C. Marzano, A. Dolmella, M. Giorgetti, C. Santini.
***Synthesis and in vitro antitumor activity of water-soluble sulfonate- and ester-functionalized silver(I) N-heterocyclic carbene complexes.***
*J. Inorg. Biochem.* 129 (2013) 135-144.

M. Pellei, V. Gandin, M. Marinelli, A. Orsetti, F. Del Bello, C. Santini and C. Marzano
**Novel triazolium based 11th group NHCs: synthesis, characterization and cellular response mechanisms**
*Dalton Trans.*, 2015, 44, 21041–21052

Marika Marinelli, Carlo Santini and Maura Pellei
**Recent Advances in Medicinal Applications of Coinage-Metal (Cu and Ag) N-Heterocyclic Carbene Complexes**
*Current Topics in Medicinal Chemistry*, 16, 26 (2016) 2995-3017

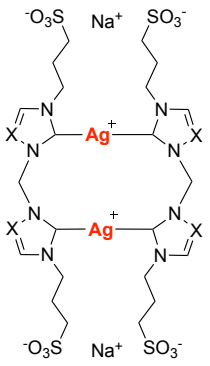
Carlo Santini, Marika Marinelli and Maura Pellei
**Boron-Centered Scorpionate-Type NHC-Based Ligands and Their Metal Complexes**
*European Journal of Inorganic Chemistry, 1*5-16 (2016) 2312-2331

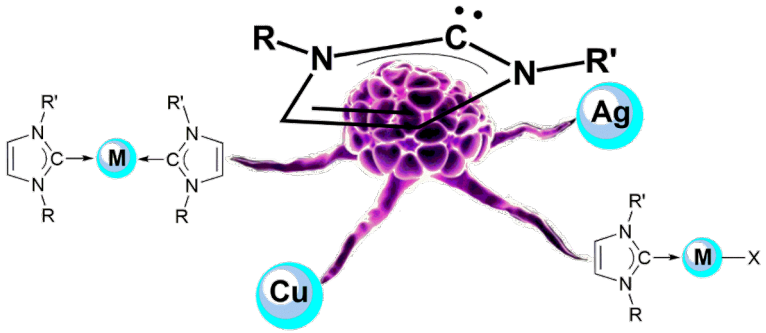
Maura Pellei, Valentina Gandin, Cristina Marzano, Marika Marinelli, Fabio Del Bello and Carlo Santini
**The first water soluble copper(I) complexes bearing sulfonated imidazole- and benzimidazole-derived NHCs: synthesis and anticancer studies**
*Applied Organometallic Chemistry*, 32 (2018) e4185

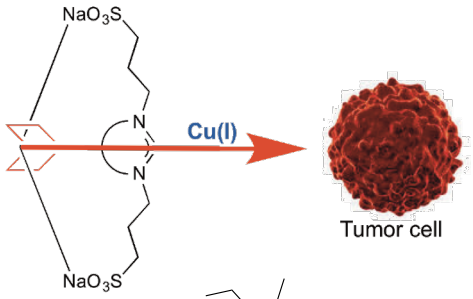
Marina Porchia, Maura Pellei, Marika Marinelli, Francesco Tisato, Fabio Del Bello and Carlo Santini
**New insights in Au-NHCs complexes as anticancer agents**
*European Journal of Medicinal Chemistry* 146 (2018) 709-746

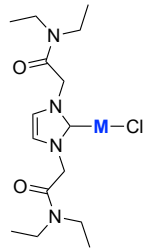
Maura Pellei, Riccardo Vallesi, Luca Bagnarelli, H. V. Rasika Dias and Carlo Santini
**Syntheses and Reactivity of New Zwitterionic Imidazolium Trihydridoborate and Triphenylborate Species**
*Molecules* 2020, 25, 3184

# Coinage metals N-Heterocyclic carbene complexes

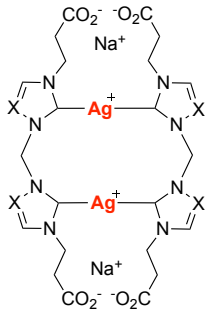



**M** = Cu, Ag or Au

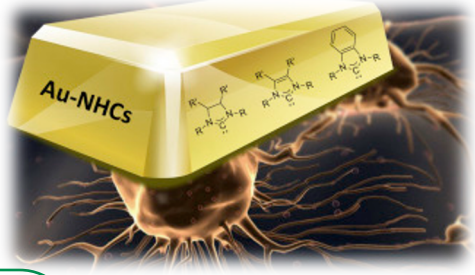


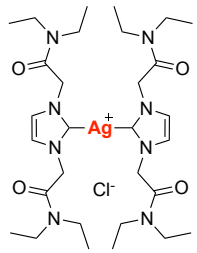


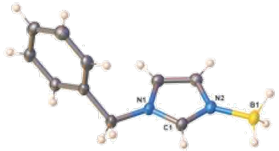
R, R' = alkyl or aryl

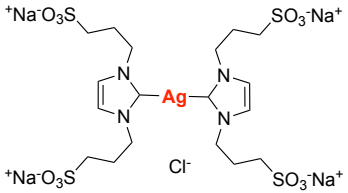
R = alkyl or aryl
X = main-group element

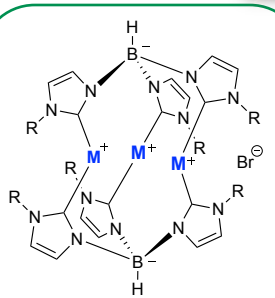
**NHC-$BR_3^-$**
R = alkyl or aryl



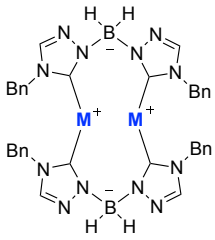



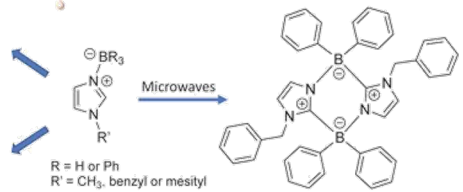


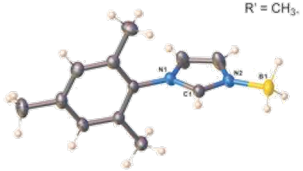




**M** = Ag or Au




**M** = Ag or Au



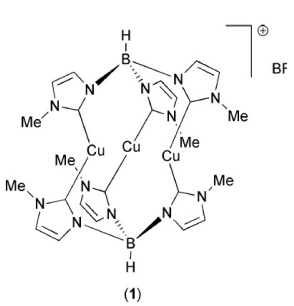
# Copper catalysts

✓ C-N and C-C coupling reactions (Sonogashira reactions)

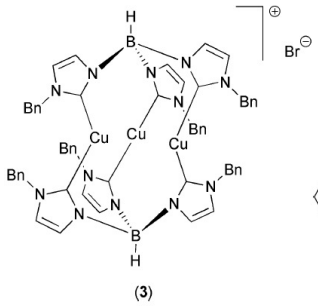

PAPER www.rsc.org/dalton | Dalton Transactions

**Trinuclear copper(I) complexes with triscarbene ligands: catalysis of C–N and C–C coupling reactions†**

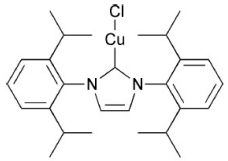
Andrea Biffis,*[a] Cristina Tubaro,[a] Elena Scattolin,[a] Marino Basato,[a] Grazia Papini,[b] Carlo Santini,*[b] Eleuterio Alvarez[c] and Salvador Conejero[c]



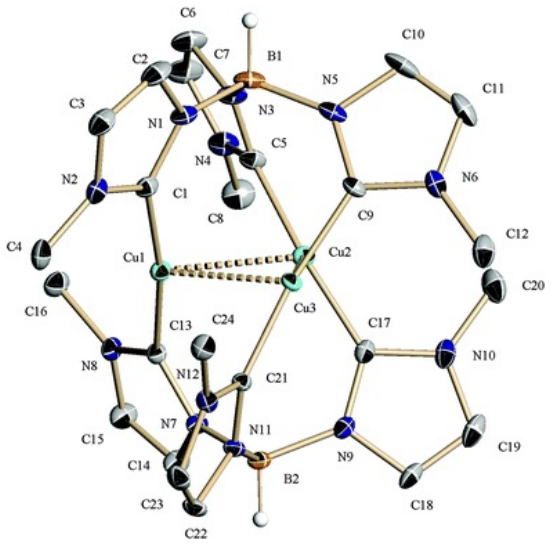

(1)

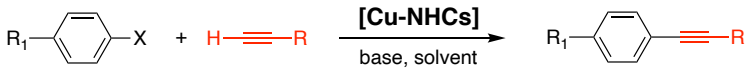



(3)




(4)



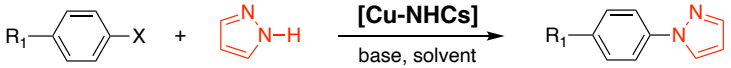
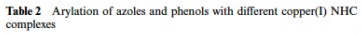




**Table 2** Arylation of azoles and phenols with different copper(I) NHC complexes



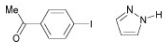
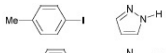
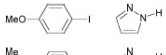
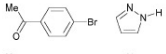
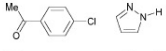
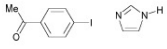
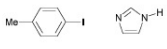
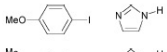
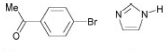
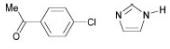
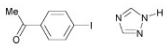
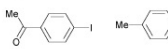
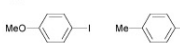
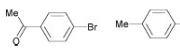
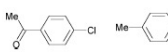
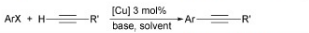
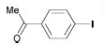

| Entry | Aryl halide | Azole | Yield (%)[a] 1[b,c] | 3[c] | 4[d] |
|---|---|---|---|---|---|
| 1 |  |  | 93 | nd | 90 |
| 2 |  |  | 21 | nd | 54 |
| 3 |  |  | 50 | nd | 23 |
| 4 |  |  | 73 | nd | 60 |
| 5 |  |  | 44 | nd | 50 |
| 6 |  |  | >99 | 85 | 86 |
| 7 |  |  | 20 | 93 | nd |
| 8 |  |  | 50 | 33 | 67 |
| 9 |  |  | 70 | 54 | 86 |
| 10 |  |  | 50 | 24 | 57 |
| 11 |  |  | >99 | >99 | nd |
| 12 |  |  | >99 | >99 | 85 |
| 13 |  |  | 15 | nd | 9 |
| 14 |  |  | 70 | nd | 86 |
| 15 |  |  | 50 | nd | 71 |

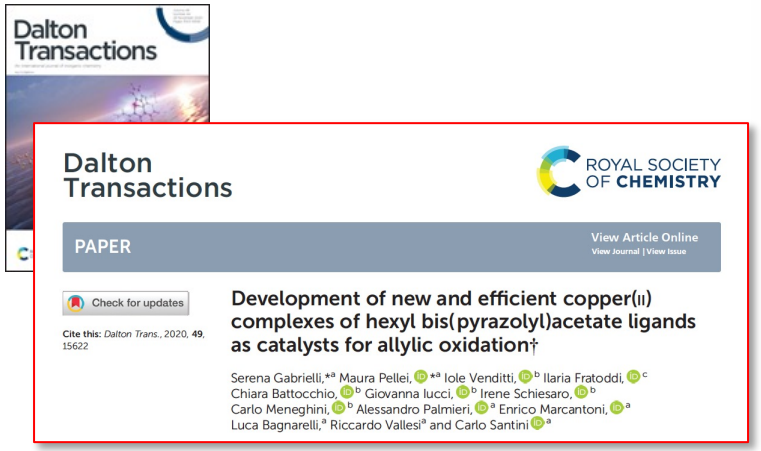
**Table 3** Sonogashira reactions with different copper(I) NHC complexes

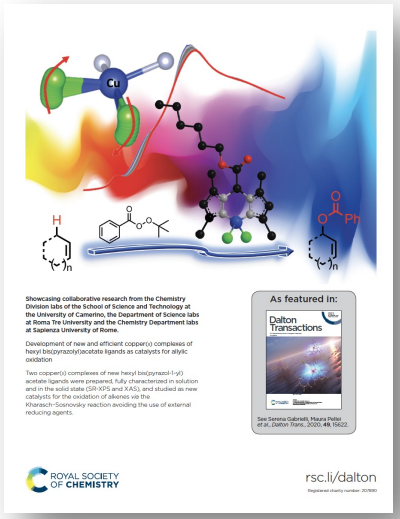



| Entry | Aryl halide | Alkyne | Base Solvent | Yield (%)[a] 1 | 3 |
|---|---|---|---|---|---|
| 1 |  |  | TBAA DMF | 95 | nd |
| 2 |  |  | $Cs_2CO_3$ DMF | >99 | 42 |
| 3 |  |  | $Cs_2CO_3$ DMSO | 90 (5) | 97 (1) |
| 4 |  |  | $Cs_2CO_3$ DMF | >99 | 9 |
| 5 |  |  | $Cs_2CO_3$ DMSO | nd | 0 |
| 6 |  |  | $Cs_2CO_3$ DMF | 54 | 8 |
| 7 |  |  | $Cs_2CO_3$ DMSO | 93 | 4 |
| 8 |  |  | $Cs_2CO_3$ DMF | 10 | nd |
| 9 |  |  | $Cs_2CO_3$ DMF | 0 | nd |
| 10 |  |  | $Cs_2CO_3$ DMF | 41 | nd |
| 11 |  |  | $Cs_2CO_3$ DMF | 37 | nd |

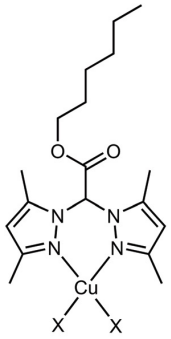
# Copper catalysts

✓ Allylic oxidation (Kharasch-Sosnovsky reactions)

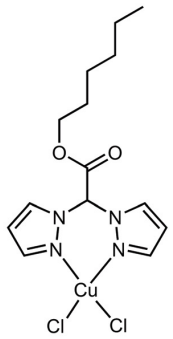


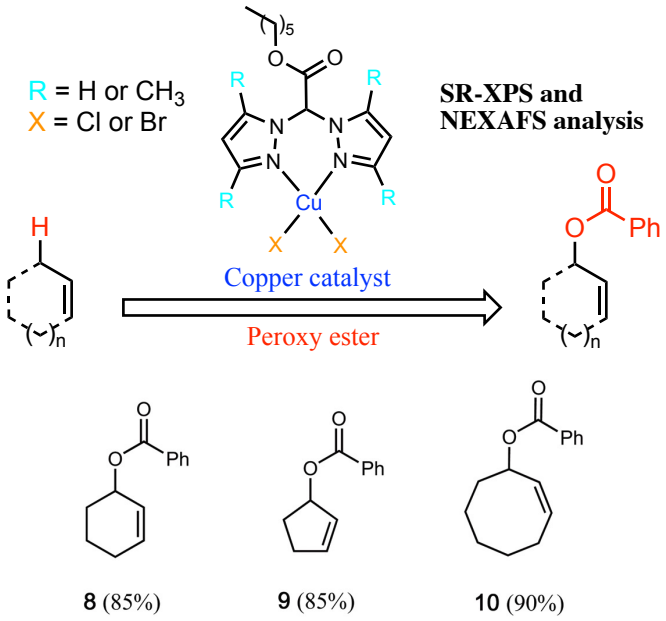

Back Cover, *Dalton Trans.*, 2020, Issue **49**



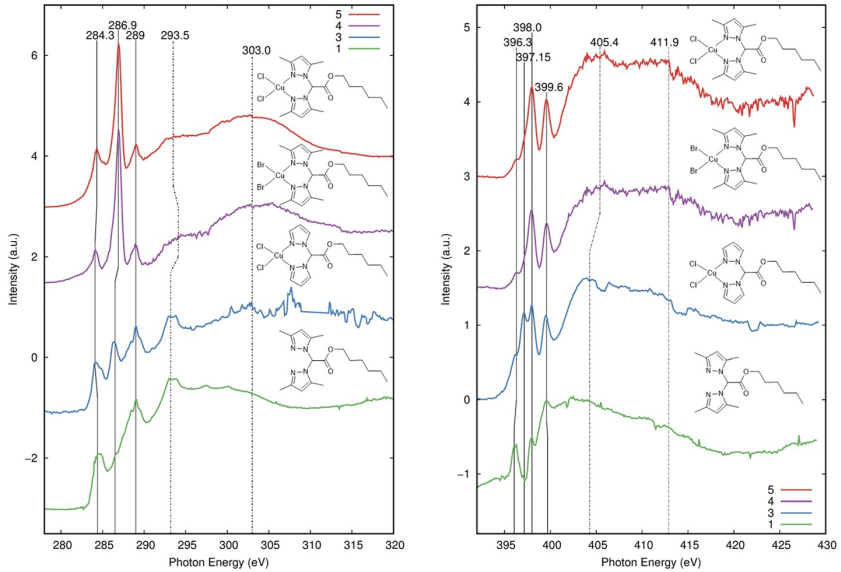

**3**: X = Cl
**4**: X = Br




**5**



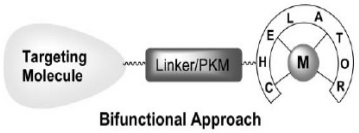

Synthesis of oxygenate allylic compounds via the Kharasch-Sosnovsky reaction using 5 mol% of complex 4.

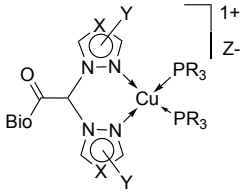


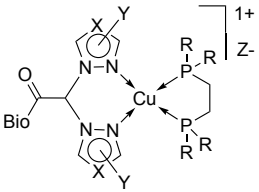

NEXAFS spectra of samples 3, 4, 5 and 1

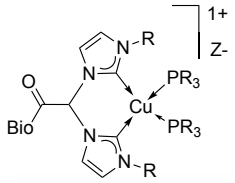
# Antiviral coinage metal complexes

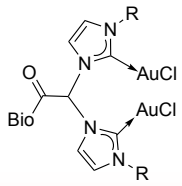
From molecular design and synthesis to antiviral evaluation of new copper/gold entities against the SARS-CoV-2 infection

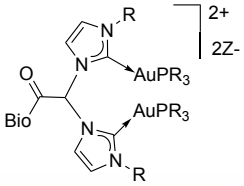


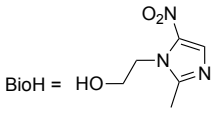



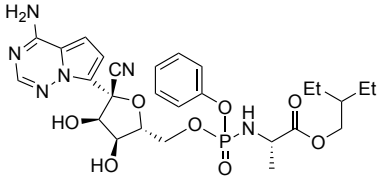



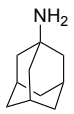



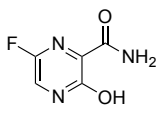

**Metronidazole**




**Remdesivir**



**Amantadine**




**Favipiravir**

m_pi.AOODGRIC.REGISTRO_PRIN2020.0002132.25-01-2021

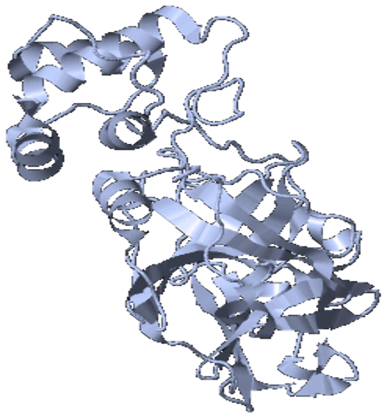
*Ministero dell'Università e della Ricerca*

Segretariato Generale

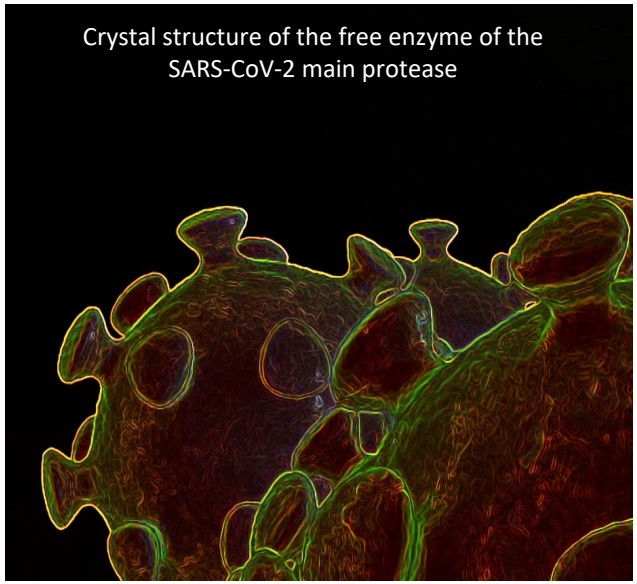
Direzione Generale per il coordinamento e la valorizzazione della ricerca e dei suoi risultati

PRIN: PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE – Bando 2020
Prot. 2020K77SB3

## Are Cu(I) and Au(I) complexes candidates for SARS-CoV-2 inhibition?



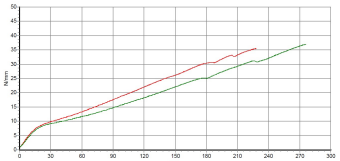
In a stable docked structures copper could readily bond to the CYS 145 thiolate



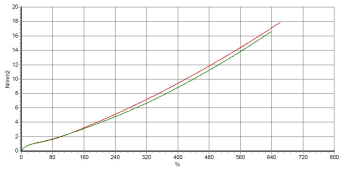
# Study of new inorganic and organic/inorganic hybrid materials for the polymer industry

EVA 18 : 82
(18% acetate)

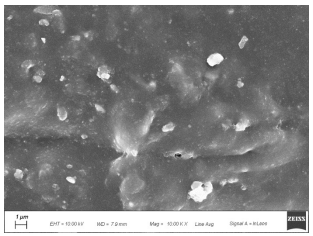
Physical tests
(ISO regulations)



Tear resistance (ISO 34)



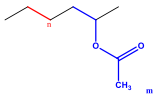
Tear strength and breaking elongation (ISO 37)



Scanning Electron Microscopy (SEM)

Delta Spa
since 1972

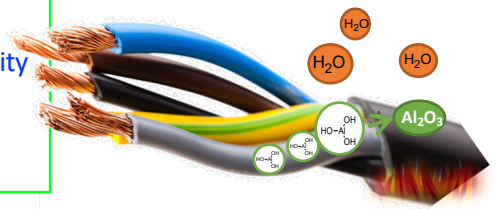
EVA soles

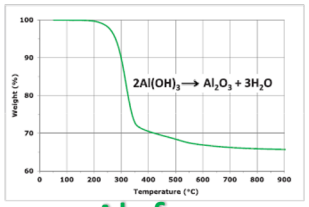


Ethylene Vinyl Acetate (EVA)

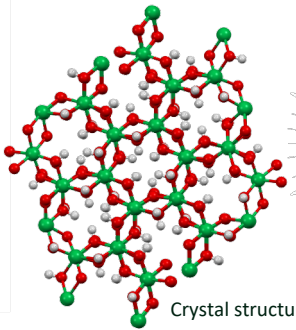
## MINERAL FILLERS

- ✓ environmentally friendly
- ✓ halogen-free
- ✓ non-toxic
- ✓ non-corrosive
- ✓ reduced smoke density
- ✓ non volatile
- ✓ inert
- ✓ economical

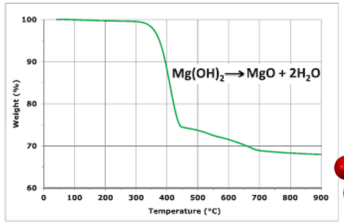


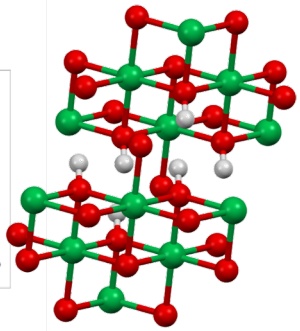

Alufy
Aluminum hydroxide



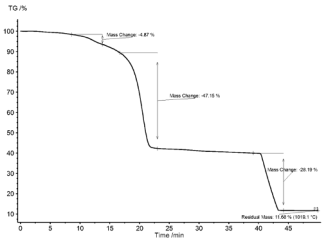
Crystal structure of gibbsite



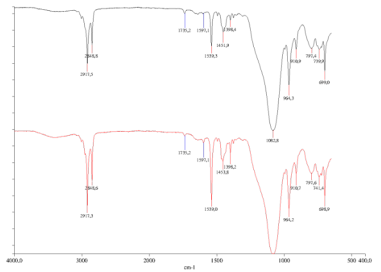

Hydrofy
Magnesium hydroxide



Crystal structure of brucite




ThermoGravimetric Analysis (TGA)

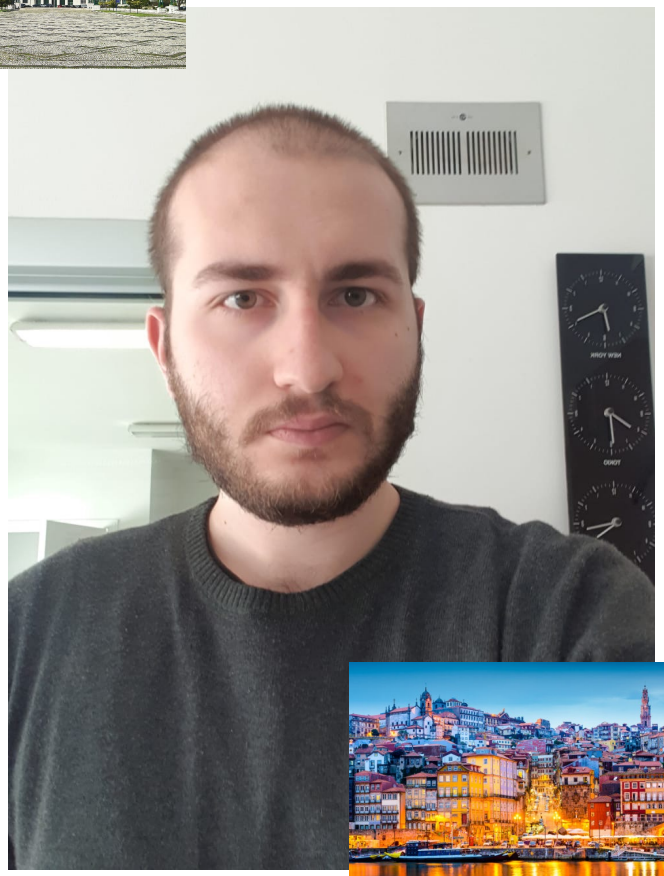


FT-IR spectra

Chemical tests

NUOVA IMA Srl

# *Riccardo Vallesi*





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  (Instituto Superior Técnico, Lisbona, Portogallo)
  (September 2016 – February 2017)
- **Master degree in Chemistry: IST Lisboa**
  (December 2017)
- **Fellowship UNICAM/Delta Spa**
  (February 2018 – November 2018)
- **PhD: UNICAM/Delta Spa**
  (November 2018 – November 2021)

**Study of the chemical-physical and morphological properties of innovative polymeric materials: evaluation of parameters and problems in outsoles industries**

***Riccardo Vallesi***

# Study of the chemical-physical and morphological properties of innovative polymeric materials: evaluation of parameters and problems in outsoles industries

POLYURETHANE (PU)

Polyester-PU

Polyether-PU

PU paints

RUBBER

EVA

Rubber/Polyurethane

TPU/Polyurethane

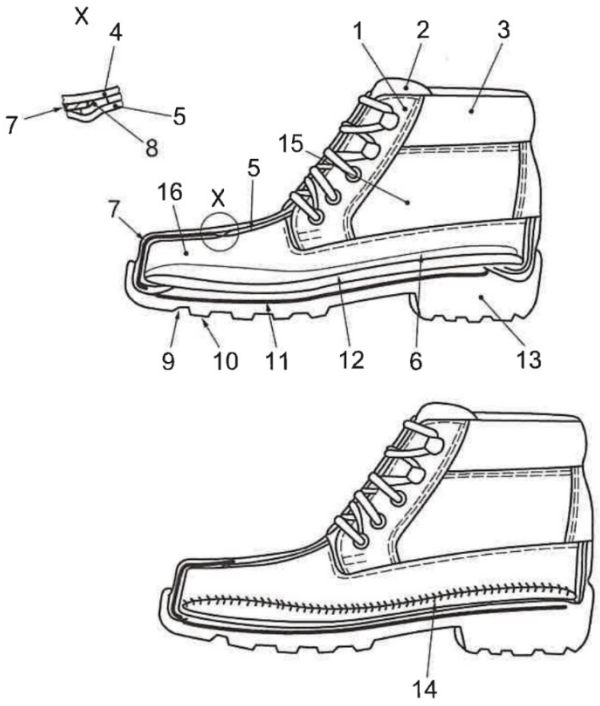
Delta Spa since 1972

UNICAM Università di Camerino 1336


- **R. Vallesi**, **C. Santini**, F. M. Iaccarino, M. Biagioli, **M. Pellei**, S. Fonti "Chlorination studies in rubber articles for footwear applications" *EPF 9th Summer School - Dynamic and Reversible Polymer Networks* (Bertinoro (FC), 20-24 maggio 2019) Book of Abstracts, P39.
- **Vallesi, R.**; Frattali, A.; **Pellei, M.**; Biagioli, M.; Iaccarino, F. M.; **Santini, C.**, "PE based polyurethane/leather yellowing in footwear industry: a case study", *MIPOL (MIlan POlymer days) web edition*, Milano, 15-17 July 2020

*Riccardo Vallesi*

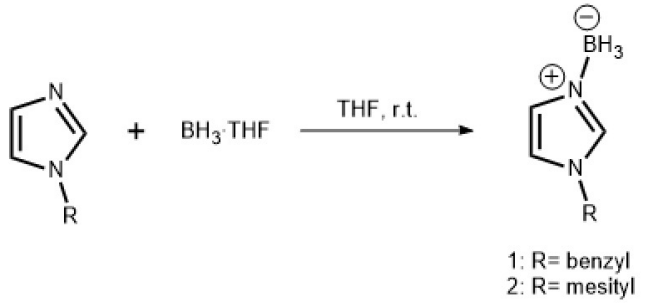
# Study of the chemical-physical and morphological properties of innovative polymeric materials: evaluation of parameters and problems in outsoles industries

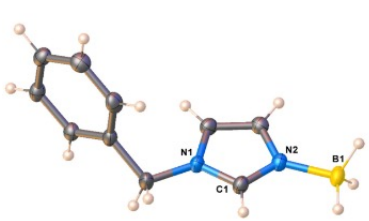



Fonte: UNI EN 20345

# *Riccardo Vallesi*

# Study of the chemical-physical and morphological properties of innovative polymeric materials: evaluation of parameters and problems in outsoles industries

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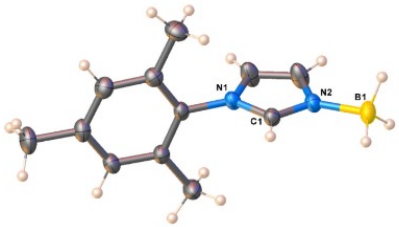


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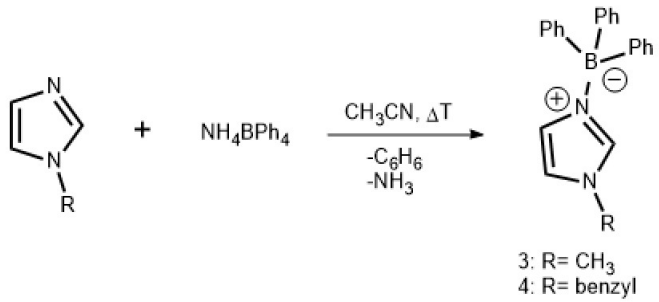
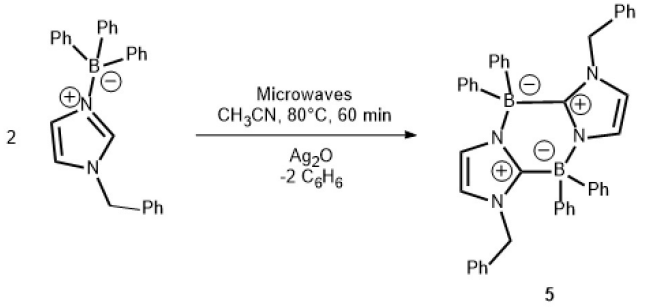


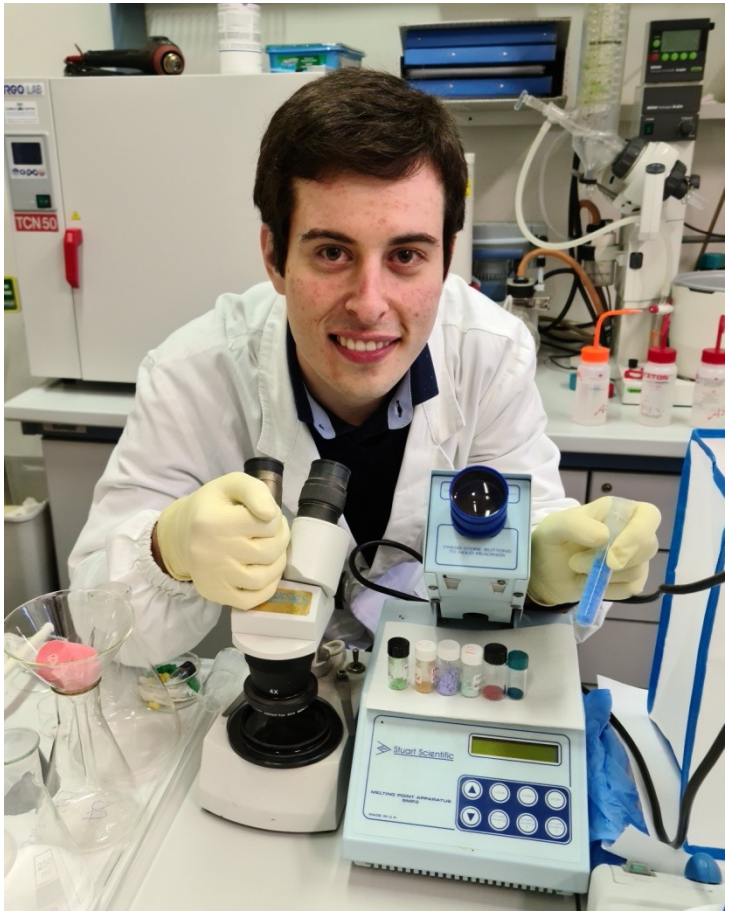

- **1-4** + $^{n}$BuLi = decomposition species
- **1-4** + $Ag_2O$ (or $Ag(CH_3COO)_2$)= unsuccessful reactions

Delta Spa since 1972

UNICAM Università di Camerino 1336

**Pellei, M.; Vallesi, R.; Bagnarelli, L.;** Dias, H.V.R.; **Santini, C.,** *Molecules*, **2020**, 25, 318

# *Luca Bagnarelli*

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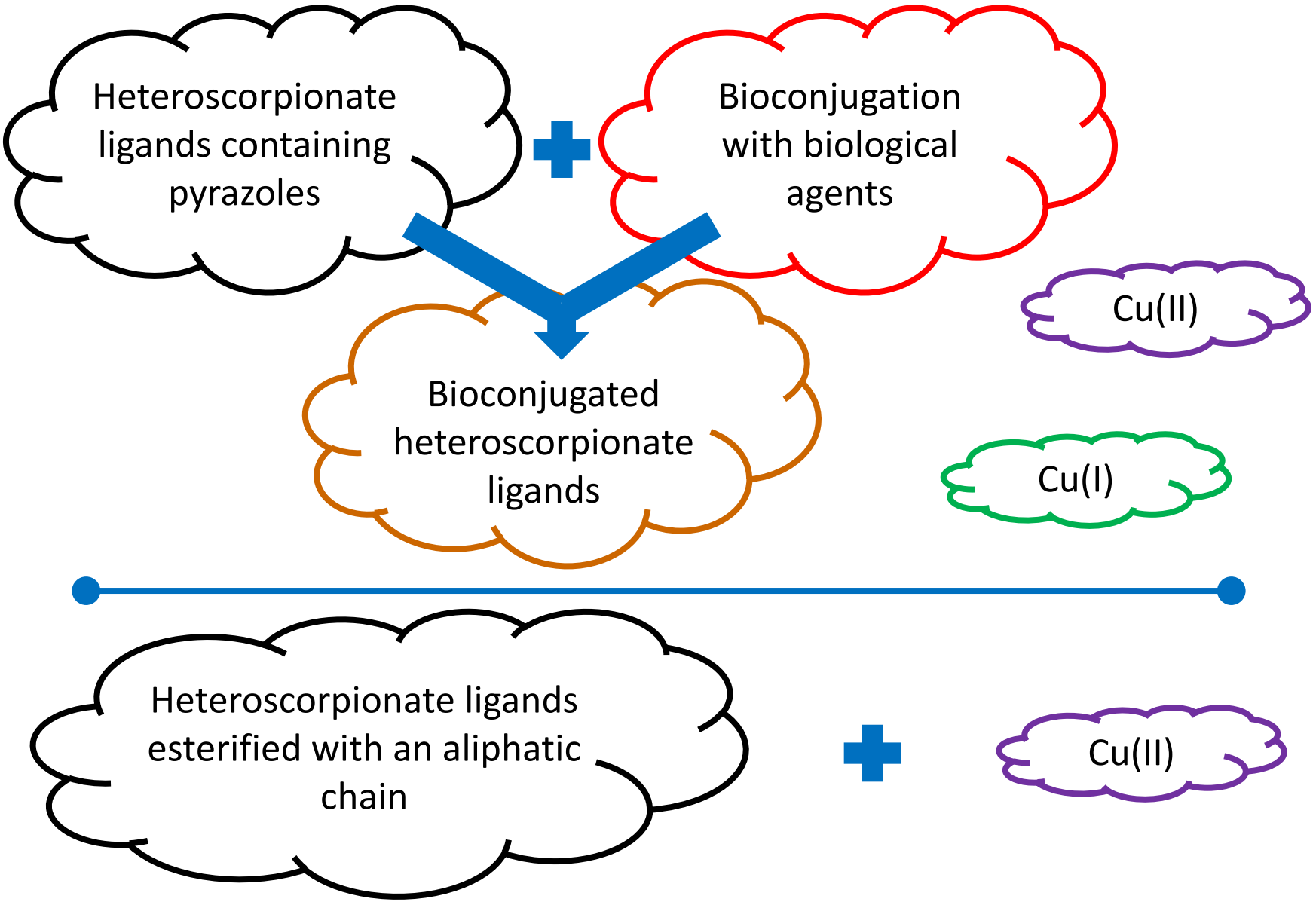
  (September 2016 – February 2017)
- **Laureato frequentatore/**
  **Fellowship "Tutor PLS": UNICAM**
  (April 2018 – October 2018)
- **Doctoral course: UNICAM**
  (November 2018 – November 2021)

**Design, synthesis and characterization of metal complexes as versatile agents with biological and catalytic activity**


JUVENTUS

# *Luca Bagnarelli*

**Design, synthesis and characterization of metal complexes as versatile agents with biological and catalytic activity**



# *Luca Bagnarelli*

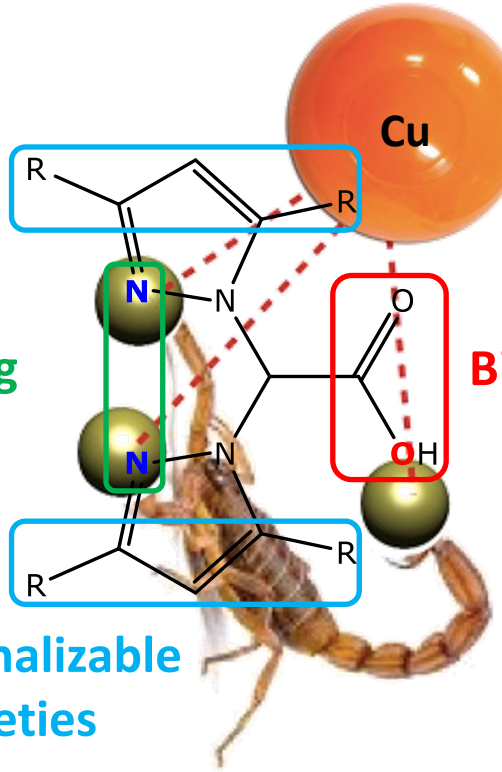
**Design, synthesis and characterization of metal complexes as versatile agents with biological and catalytic activity**

**Biological studies**

**Catalytic studies**

# *Luca Bagnarelli*

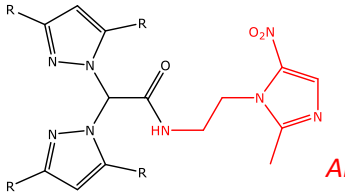
**Design, synthesis and characterization of metal complexes as versatile agents with biological and catalytic activity**



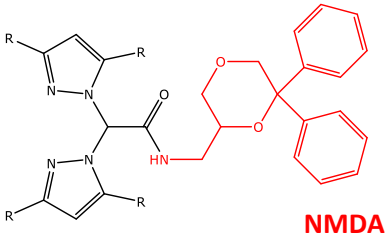

**Coordinating moiety**

**Bioconjugable moiety**

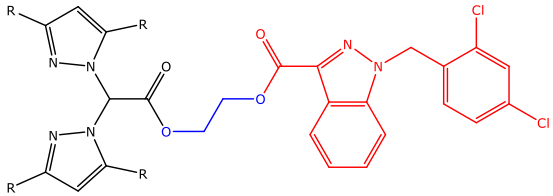
**Functionalizable moieties**



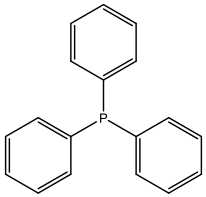
**Metronidazole**
*Antibiotic and antiprotozoal agent*



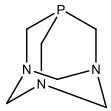
**NMDA receptor antagonist**
*Antagonist for the N-methyl-D-aspartate receptor*



**Lonidamine**
***a**ntineoplastic agent*



triphenylphosphine
$PPh_3$



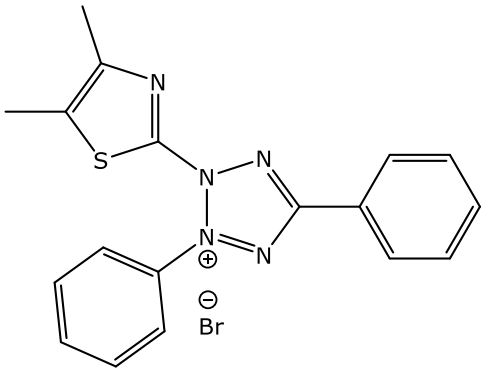
1,3,5-triaza-7-phosphaadamantane
PTA


- Morelli M. B., Amantini C., Santoni G., **Pellei M.**, **Santini C.**, Cimarelli C., Marcantoni E., Petrini M., Del Bello F., Giorgioni G., Piergentili A., Quaglia W.; *New Journal of Chemistry*; 42, 11878-11887, **2018**.
- **Pellei M.**, **Bagnarelli L.**, Luciani L., Del Bello F., Giorgioni G., Piergentili A., Quaglia W., De Franco M., Gandin V., Marzano C., **Santini C.**; *International Journal of Molecular Sciences*; 21, 2616, **2020**.
- **Pellei M.**, Gandin V., Cimarelli C., Quaglia W., Mosca N., **Bagnarelli L.**, Marzano C., **Santini C.**; *Journal of Inorganic Biochemistry*; 187, 33-40, **2018**.

# *Luca Bagnarelli*

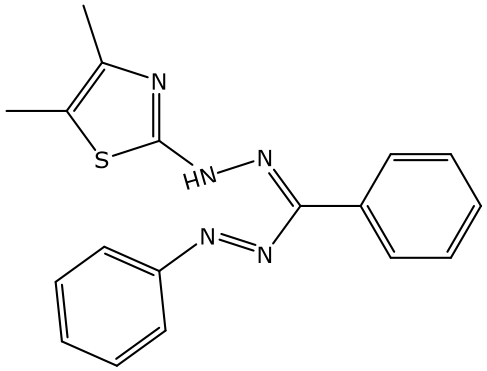
# Design, synthesis and characterization of metal complexes as versatile agents with biological and catalytic activity

MTT



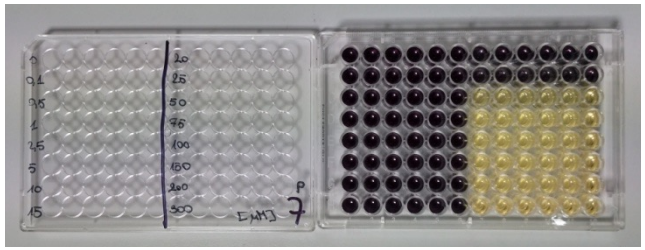

2-(4,5-dimethylthiazol-2-yl)-3,5-diphenyl-2*H*-tetrazol-3-ium bromide

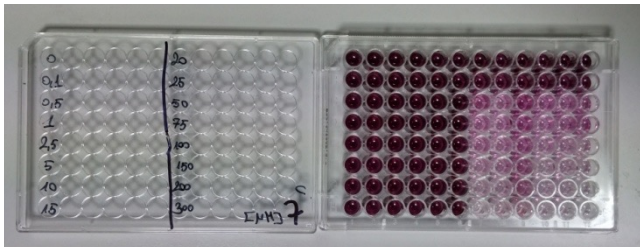
Mitochondrial reductase



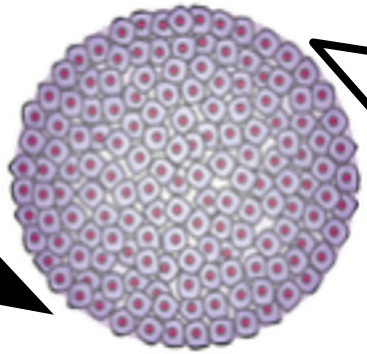

(*E*,*Z*)-5-(4,5-dimethylthiazol-2-yl)-1,3-diphenylformazan

FORMAZAN





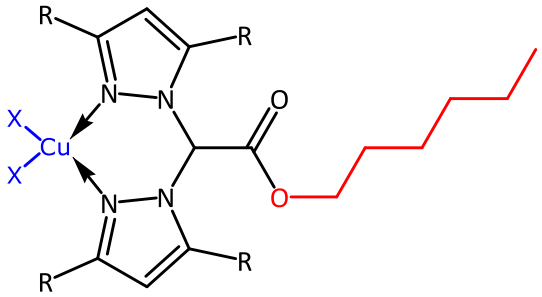
**Spheroids (3D cancer cell cultures)**



**Recent and predictive test for *in vivo* results**

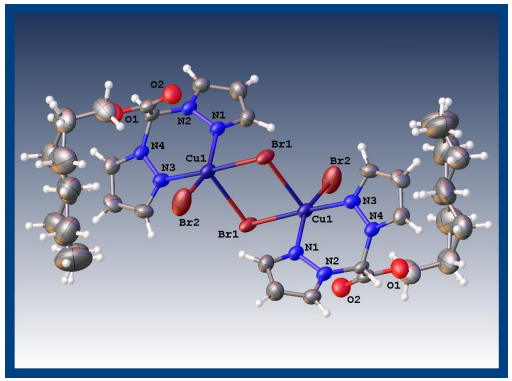
# *Luca Bagnarelli*

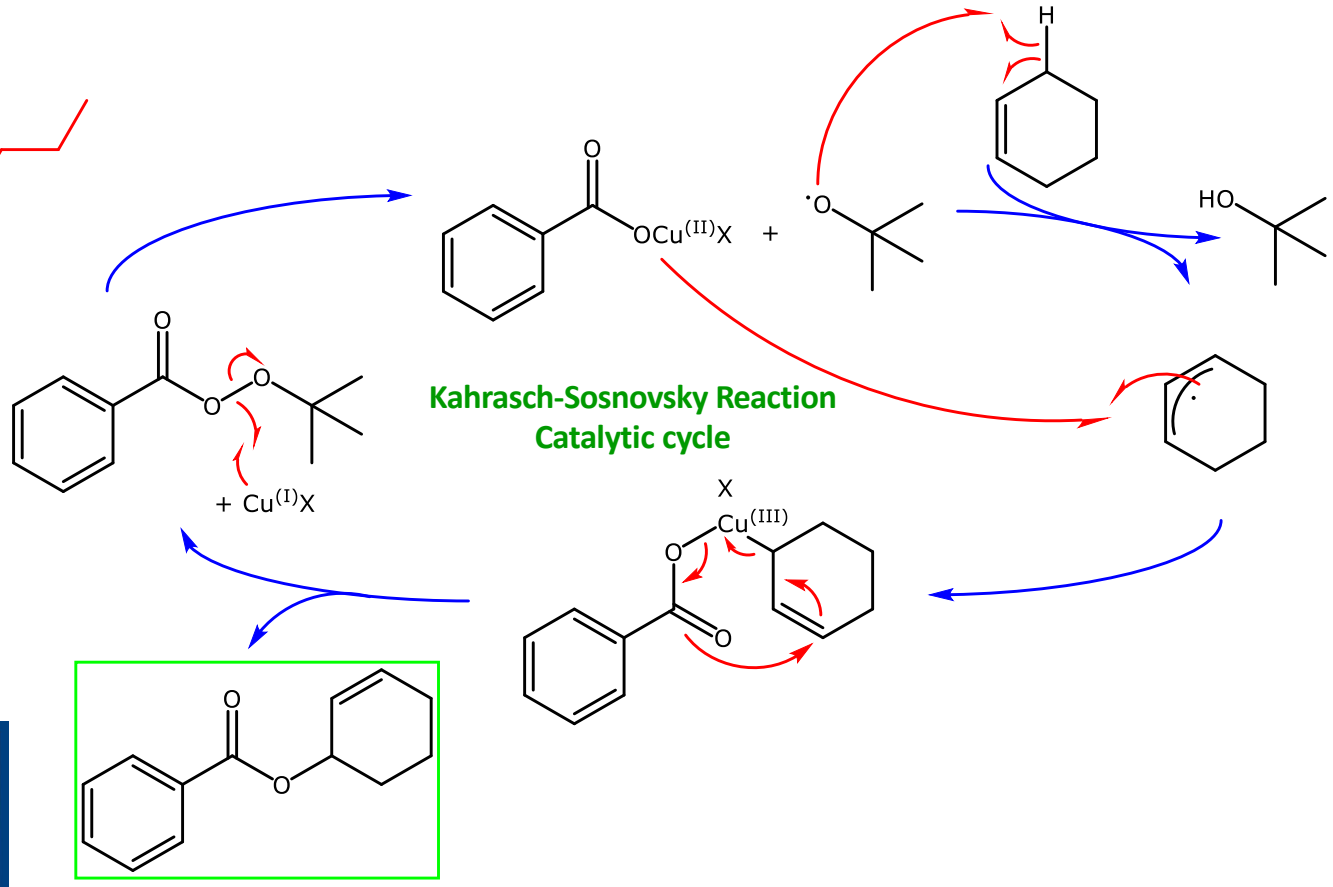
## Design, synthesis and characterization of metal complexes as versatile agents with biological and catalytic activity




**Hexyl ester**

*Increased lipophilicity*




Gabrielli S., **Pellei M.**, Venditti I., Fratoddi I., Battocchio C., Iucci G., Schiesaro I., Meneghini C., Palmieri A., Marcantoni E., **Bagnarelli L.**, **Vallesi R.**, **Santini C.**; *Dalton Transactions*; 49, 15622-15632, **2020**.

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Department of Pharmaceutical and Pharmacological Science;
Department of Biomedical Sciences
(University of Padova)

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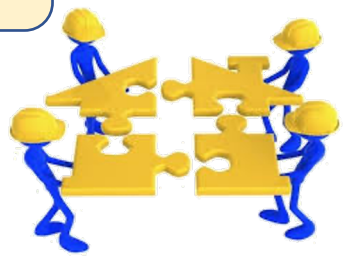
Nanoscience Section
(Roma Tre University)



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(ICMATE-CNR Padova)

Istituto di Struttura della Materia-CNR (ISM-CNR),
Division of Ultrafast Processes in Materials (FLASHit – Roma)

*The scientist does not study nature because it is useful; he studies it because he delights in it, and he delights in it because it is beautiful. If nature were not beautiful, it would not be worth knowing, and if nature were not worth knowing, life would not be worth living.*

*Henry Poincaré*

Legnaro National laboratories
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Arlington USA

Italian National Institute Of Health
(Istituto Superiore di Sanità, ISS)
Department of Infectious Diseases
National Center for Drug Research and Evaluation

Departments of Radiology and the Molecular Pharmacology, Memorial Sloan Kettering Cancer Center, New York, USA

European Synchrotron Radiation Facility
Medical Beamline
(ESRF, Grenoble, France)