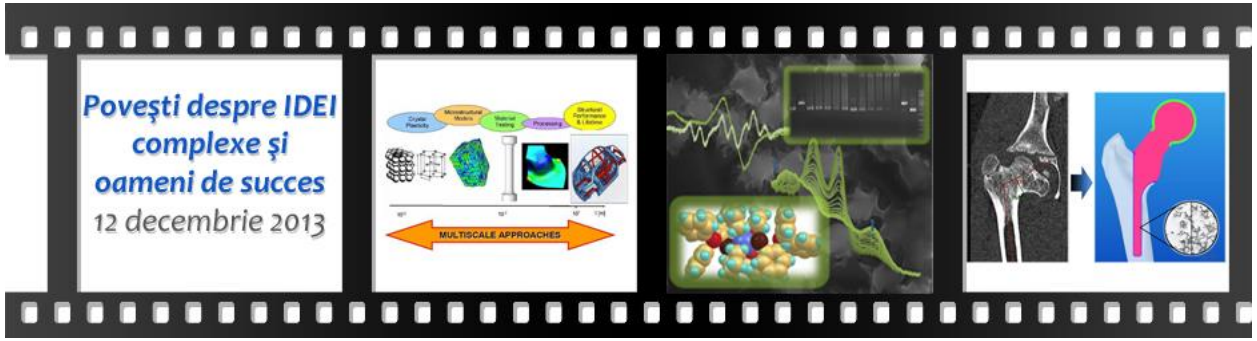

APLICATIILE BIO-MEDICALE ALE COMPUSILOR METALELOR – METALLOMICS

(BIOMEDICAL APPLICATIONS OF METALLIC DERIVATIVES – METALLOMICS)

PCCE 140/2008

Director de proiect,
Academician Ionel Haiduc

UNIVERSITAS NAPOCENSIS · ROMANIA · BABEŞ-BOLYAI

IOCN Împreună redăm speranţa! Membru al Organizaţiei Institutelor Europene de Cancer "OECI"

UMF UNIVERSITATEA DE MEDICINĂ ŞI FARMACIE IULIU HAŢIEGANU CLUJ-NAPOCA

UNIVERSITATEA TEHNICĂ DIN CLUJ-NAPOCA

PCCE 140/2008 APLICATIILE BIO-MEDICALE ALE COMPUSILOR METALELOR – METALLOMICS

Director proiect: Prof.univ.dr. Ionel HAIDUC, Membru al Academiei Romane

Instituţie coordonatoare proiect: UNIVERSITATEA BABES-BOLYAI CLUJ-NAPOCA, FACULTATEA DE CHIMIE SI INGINERIE CHIMICA
Responsabili echipe parteneri UBB:
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Conf.univ.dr. Radu Silaghi-Dumitrescu
Prof.univ.dr. Ionel Catalin Popescu
Prof.univ.dr. Luminita Silaghi-Dumitrescu,

Instituţii si responsabili echipe parteneri:
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Prof.univ.dr. Nagy Viorica, UNIVERSITATEA DE MEDICINA SI FARMACIE "I. HATIEGANU", CLUJ-NAPOCA, DEPARTAMENTUL ONCOLOGIE MEDICALĂ ȘI RADIOTERAPIE
Conf.dr. Nicoleta Gabriela Hadaruga, UNIVERSITATEA DE STIINTE AGRICOLE SI MEDICINA VETERINARA, BANAT, TIMISOARA, FACULTATEA DE TEHNOLOGIA PRODUSILOR ALIMENTARI, DEPARTAMENTUL DE BIOCHIMIE SI BIOLOGIE MOLECULARA,
Conf.dr.ing.Ovidiu Nemes, UNIVERSITATEA TEHNICA DIN CLUJ-NAPOCA, FACULTATEA DE STIINTA SI INGINERIA MATERIALELOR, LABORATORUL DE ANALIZA FORMELOR SI STRUCTURILOR TEHNOLOGICE

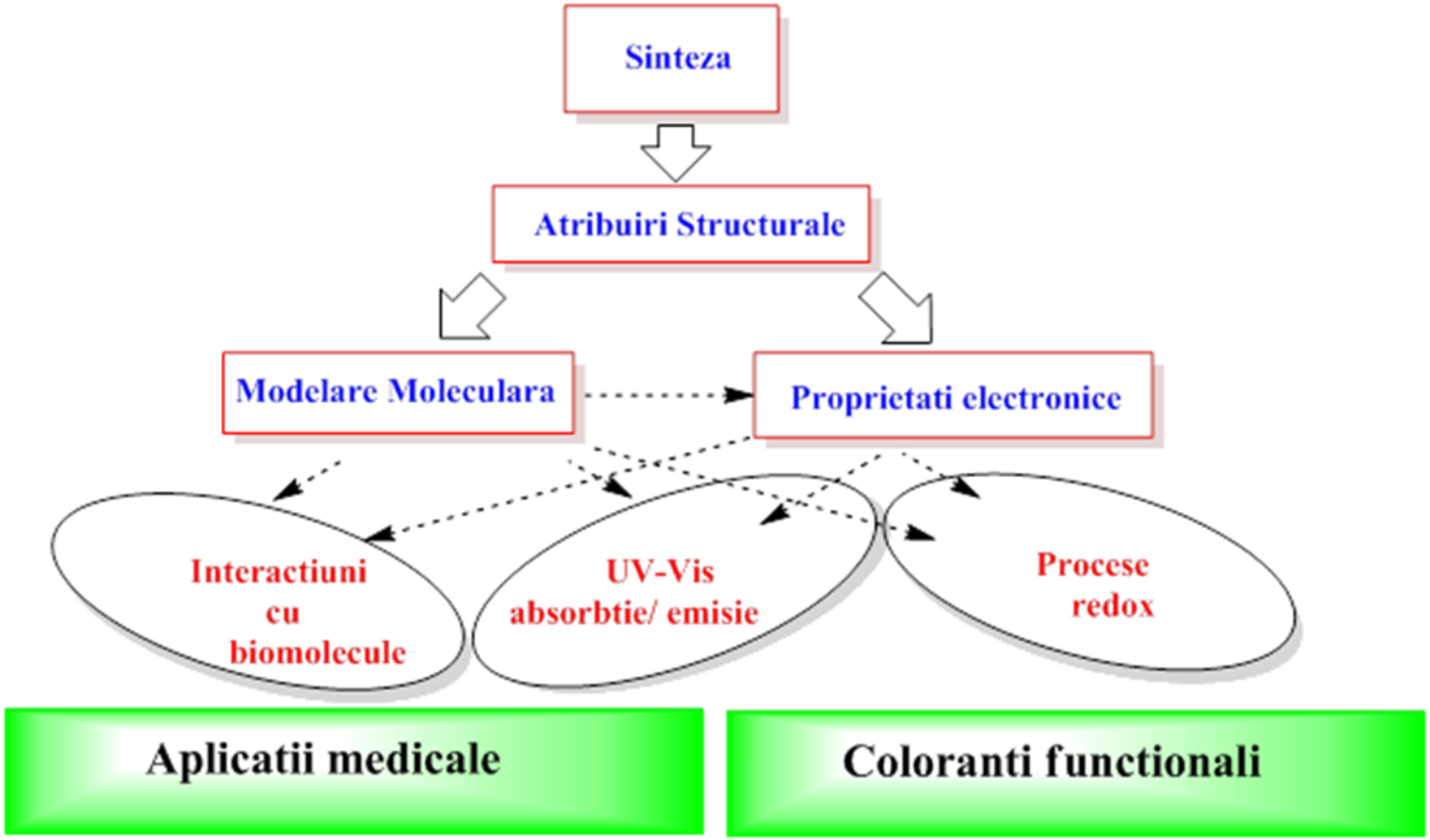
OBIECTIVELE PROIECTULUI

● Identificarea unor complecsi metalici si substante organometalice cu efect antimitotic, antiproliferativ cu indice terapeutic favorabil ca substante active pentru dezvoltarea de noi medicamente chimioterapeutice si substante radiosensibilizatoare in terapia cancerului. Studierea aspectelor biochimice, imunologice, moleculare, radiobiologice si de stres oxidativ al actiunii metalelor in celula vie eucariota.

● Intelegerea rolului monoxidului de azot si a peroxizilor in apoptoza si cancer, si identificarea de (metalo)proteine cheie in terapia cu metalocomplecsi si a mecanismelor prin care acestea functioneaza.

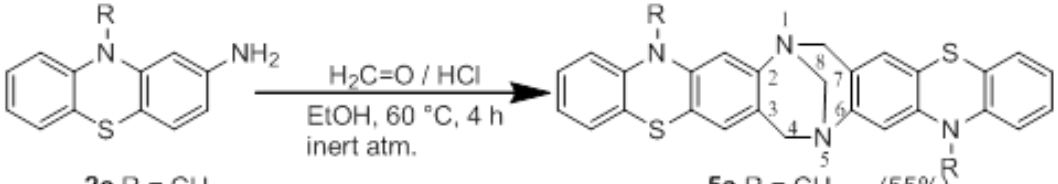
● Stabilirea relatiei structura-activitate biologica.

● Individualizarea si optimizarea tratamentului chimioterapeutic si neoadjuvant in radioterapie cu medicamente pe baza de compusi metalici; identificarea de markeri de chimiosensibilitate


Sinteza
Atribuiri Structurale
Modelare Moleculara
Proprietati electronice
Interactiuni cu biomolecule
UV-Vis absorbtie/ emisie
Procese redox
Aplicatii medicale
Coloranti functionali

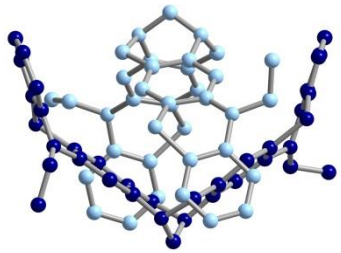
Phenothiazine analogues of Tröger's Base

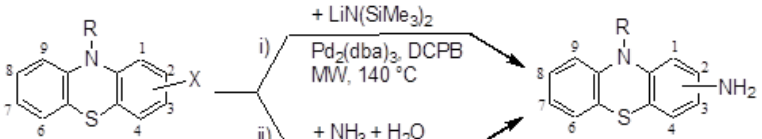
Synthesis, crystal and molecular structure



2c R = CH_3
4a R = C_2H_5
4b R = C_6H_{13}
4c R = C_8H_{17}

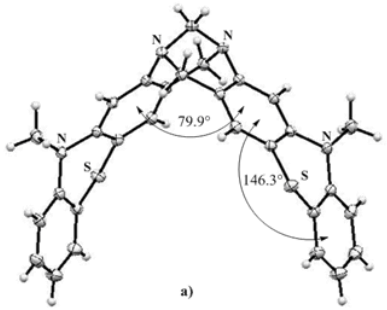
5a R = CH_3 (55%)
5b R = C_2H_5 (52%)
5c R = C_6H_{13} (47%)
5d R = C_8H_{17} (45%)

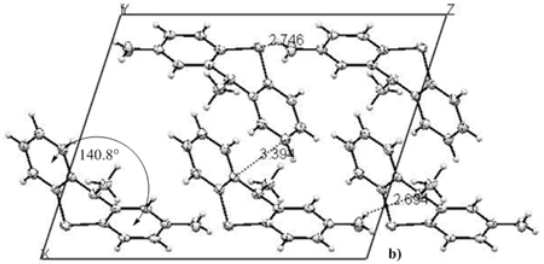




1a R = CH_3, X_1 = Br
1b R = H, X_2 = Cl
1c R = CH_3, X_2 = Cl
1d R = CH_3, X_3 = Br
1e R = CH_3, X_4 = Br
1f R = CH_3, $X_3 = X_7$ = Br

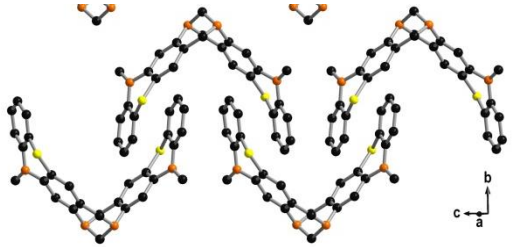
2a R = CH_3, 1-NH_2
2b R = H, 2-NH_2
2c R = CH_3, 2-NH_2
2d R = CH_3, 3-NH_2
2e R = CH_3, 4-NH_2
2f R = CH_3, 3,7-$(NH_2)_2$





Molecular modeling

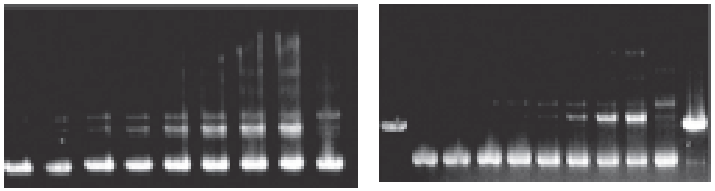
ΔE (kcal/mol) 0 11.61 (M06-2X) 5.19 (HF)



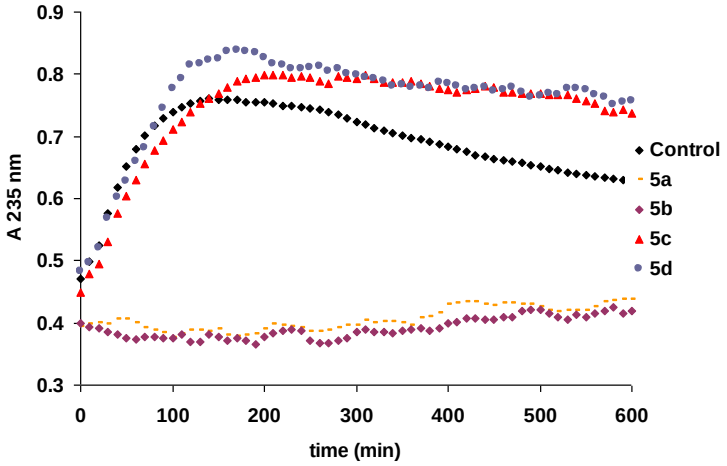
L Găină, L N. Mătărângă-Popa, E Gal, P Boar, P Lönnecke, E Hey-Hawkins, C Bischin, R Silaghi-Dumitrescu, I Lupan, C Cristea, L Silaghi-Dumitrescu, *Eur. J. Org. Chem.* **2013**, 5500–5508

Interaction with biomolecules

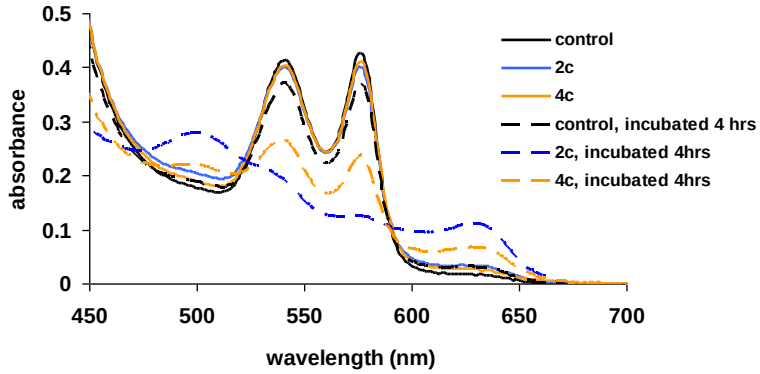
DNA intercalation



Lipid peroxidation induced by cytochrome c



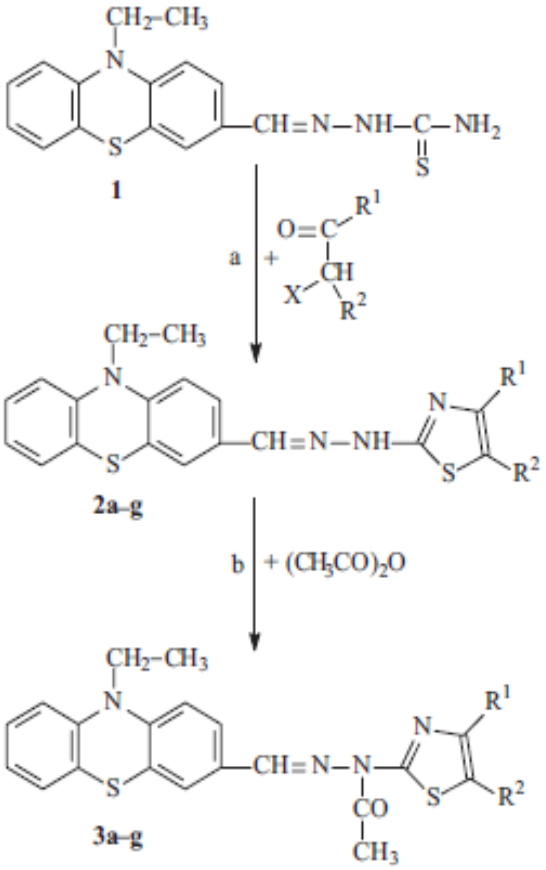
Autooxidation of hemoglobin



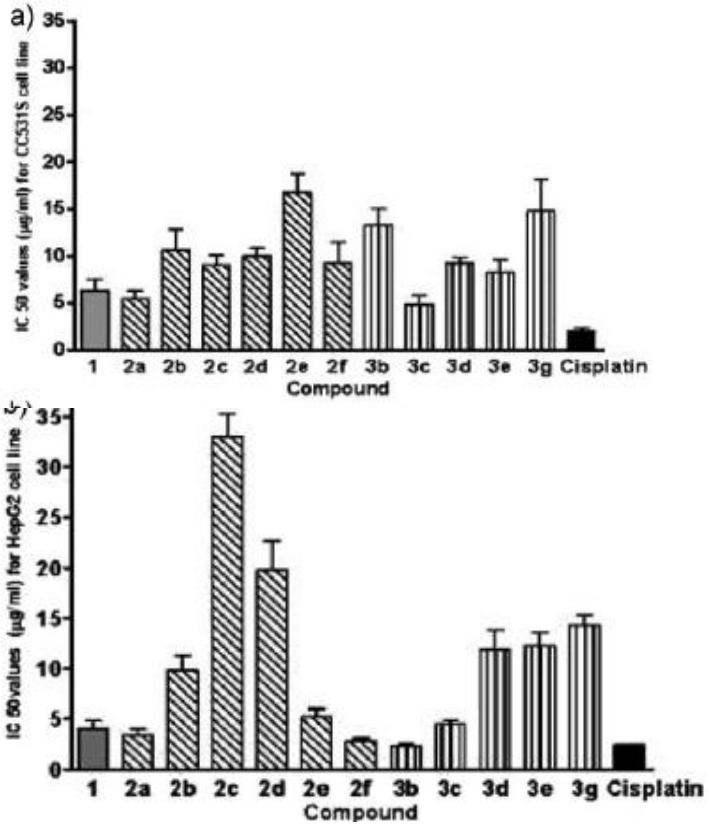
L Găină, L N. Mătărângă-Popa, E Gal, P Boar, P Lönnecke, E Hey-Hawkins, C Bischin, R Silaghi-Dumitrescu, I Lupan, C Cristea, L Silaghi-Dumitrescu, *Eur. J. Org. Chem.* **2013**, 5500–5508

Phenothiazinyl-Thiazolyl-Hidrazine

Chemical synthesis

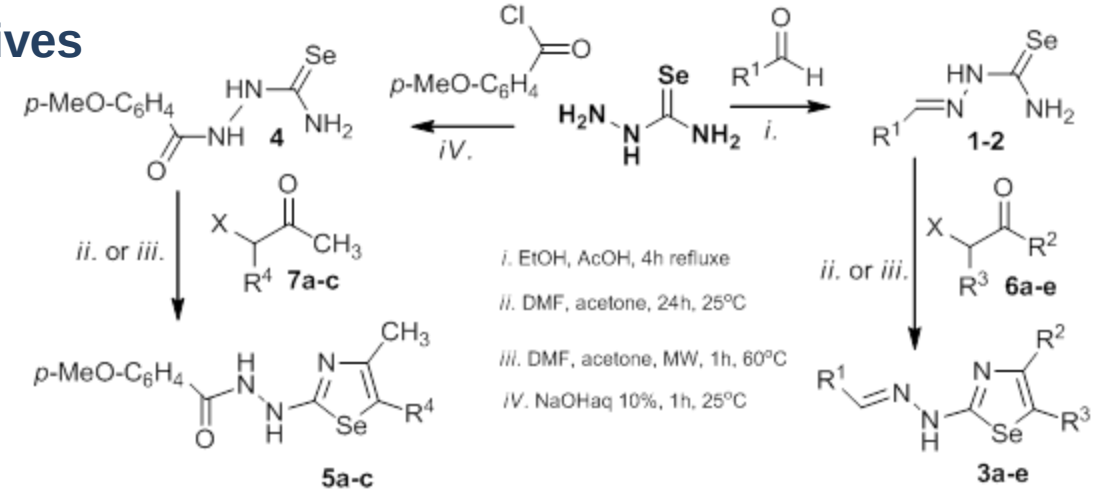


Antitumor activity



A Ignat, T Lovasz, M Vasilescu, E Fischer-Fodor, C B Tatomir, C Cristea, L Silaghi-Dumitrescu, V Zaharia,
Arch. Pharm. Chem. Life Sci. **2012**, 345, 574–583

Selenazole derivatives



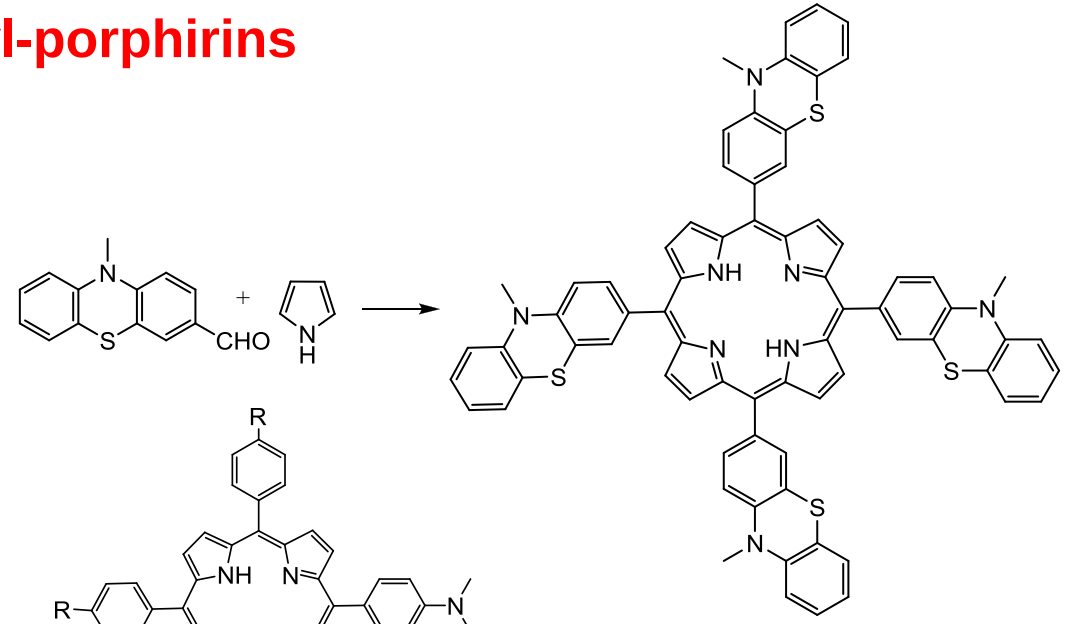
Compounds	Cell lines and IC_{50} values (μM)				
	CCRF-CEM	HL60	MDA-MB231	HCT116	U87MG
3a	6.36 ± 0.66	48.44 ± 11.14	>113.31	>113.31	>113.31
3b	8.87 ± 2.52	14.42 ± 234.31	72.60 ± 47.56	53.37 ± 8.67	66.53 ± 6.36
3c	5.11 ± 0.30	27.67 ± 8.45	85.24 ± 6.00	35.96 ± 4.17	65.41 ± 0.47
3d	9.97 ± 1.58	17.24 ± 1.66	42.68 ± 1.18	35.13 ± 3.77	30.32 ± 1.08
3e	8.40 ± 2.15	12.86 ± 1.99	65.72 ± 0.37	46.14 ± 0.97	59.12 ± 5.97
4	6.88 ± 1.53	10.62 ± 0.88	21.98 ± 0.63	23.51 ± 0.86	27.56 ± 10.02
5a	8.33 ± 2.03	29.88 ± 0.17	61.19 ± 4.86	24.99 ± 2.58	29.80 ± 1.68
5b	6.43 ± 0.96	13.23 ± 0.12	16.90 ± 4.55	22.25 ± 1.66	20.95 ± 1.62
5c	5.67 ± 3.87	11.94 ± 0.72	29.19 ± 1.92	34.66 ± 3.21	25.22 ± 7.23
Doxorubicin	0.20 ± 0.06	0.73 ± 0.20	1.10 ± 0.28	1.41 ± 0.29	1.06 ± 0.15

leukemia CCRF-CEM,
HL60,
breast MDA-MB231,
colon HCT116

glioblastoma U87MG

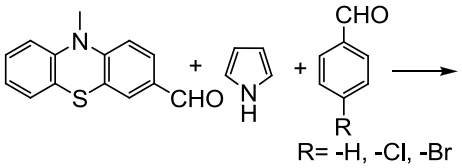
A Ignat, L Gaina , V Kuete, L Silaghi-Dumitrescu, T Efferth , V Zaharia, Microwave-Assisted Synthesis of New Selenazole Derivatives with Antiproliferative Activity, *Molecules* **2013,** *18*, 1-10

Phenothiazinyl-porphirins



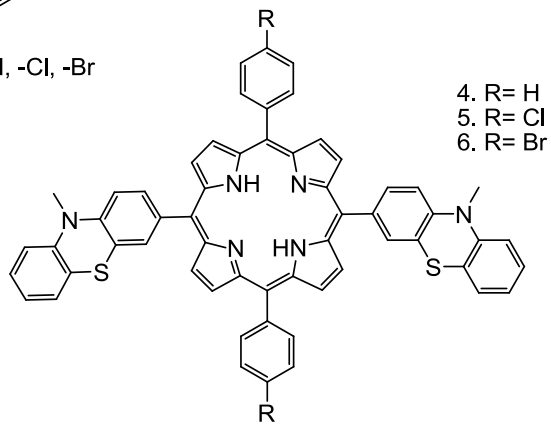
Reaction conditions
A) Method Lindsey
1) $CHCl_3$, N_2, BF_3-Et_2O
2) Chloranil
3) TEA

B) Method Adler Longo
Propanoic acid, Ac_2O, 135 ^oC

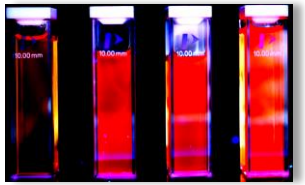


R= -H, -Cl, -Br

1. R= H
2. R= Cl
3. R= Br



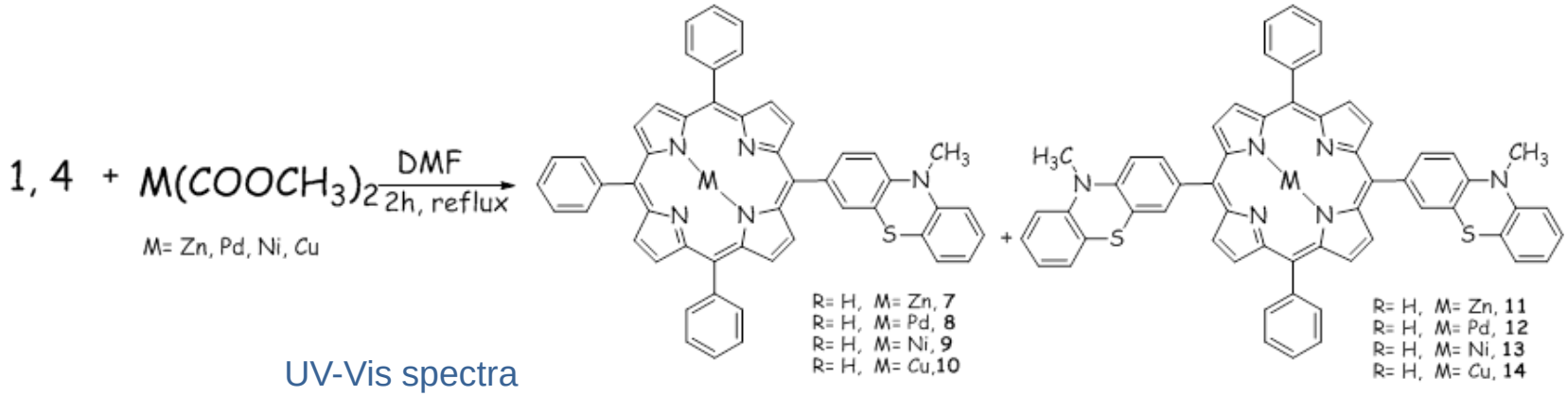
4. R= H
5. R= Cl
6. R= Br



in DCM upon irradiation UV 365 nm

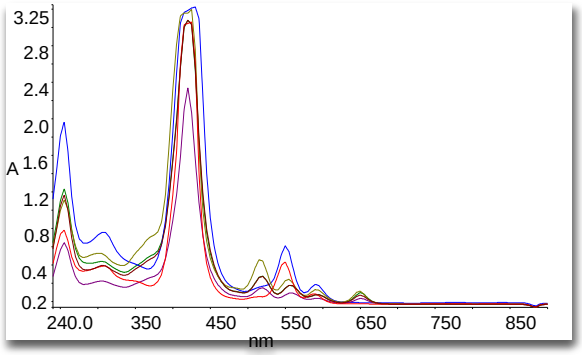
E. Gal, B. Brem, I. Pereţeanu, L. Găină, T. Lovasz, M. Perde-Schrepler, L. Silaghi-Dumitrescu, C. Cristea, L. Silaghi-Dumitrescu, *Dyes and Pigments,* **2013,** 99(1), 144-153.

Metal complexes

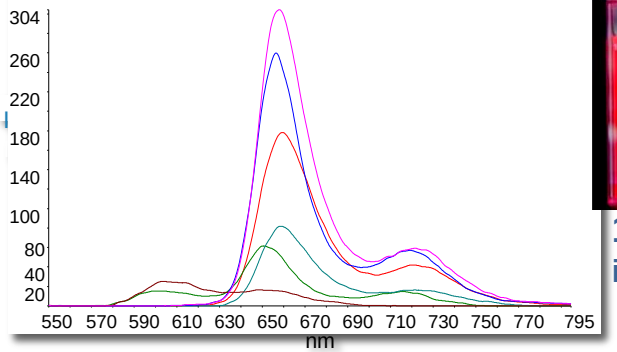


UV-Vis spectra

absorption

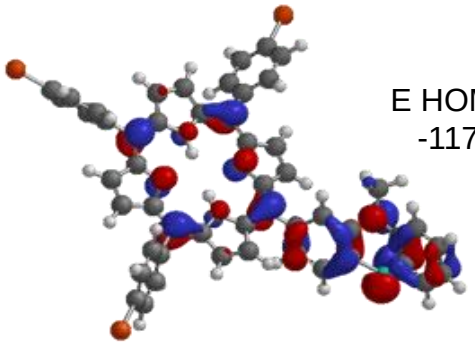


emission

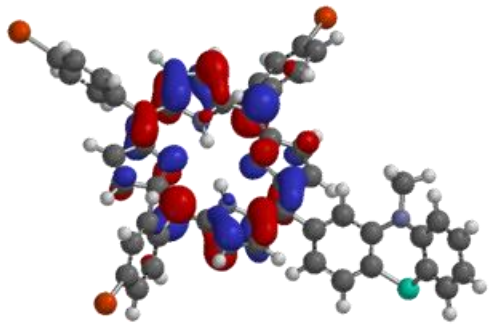


1 7 8 9 10

in DCM/irradiation UV 365 nm



E HOMO (kcal/mol)
-117.548160



E LUMO (kcal/mol)
-58.2664226

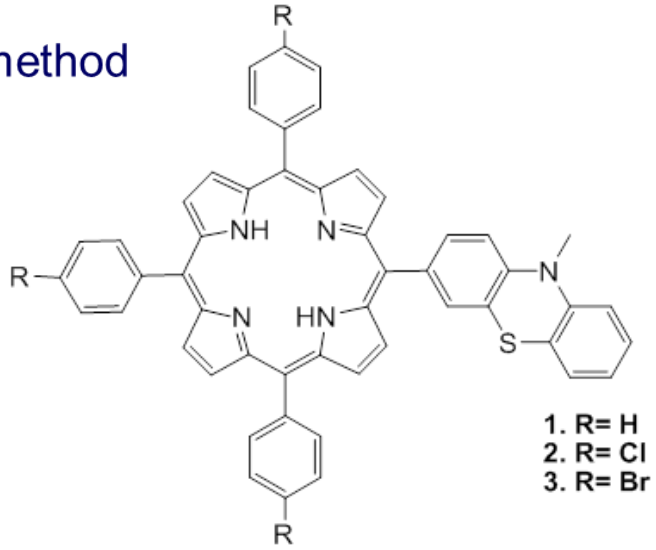
Photosenzitizers for Photodynamic Therapy

Human skin cell lines:

1) keratinocyte cell line HaCaT
2) epidermoid carcinoma cell line A431

The cytotoxic effect was assessed using MTT method

Photosenzitizers:



Light Source:

λ= 615-630 nm, 9 J/cm^2

λ= 400-505 nm, 4.25 J/cm^2

PDT experiment conclusions

-None was cytotoxic without irradiation

-2 has no photosensitizer properties

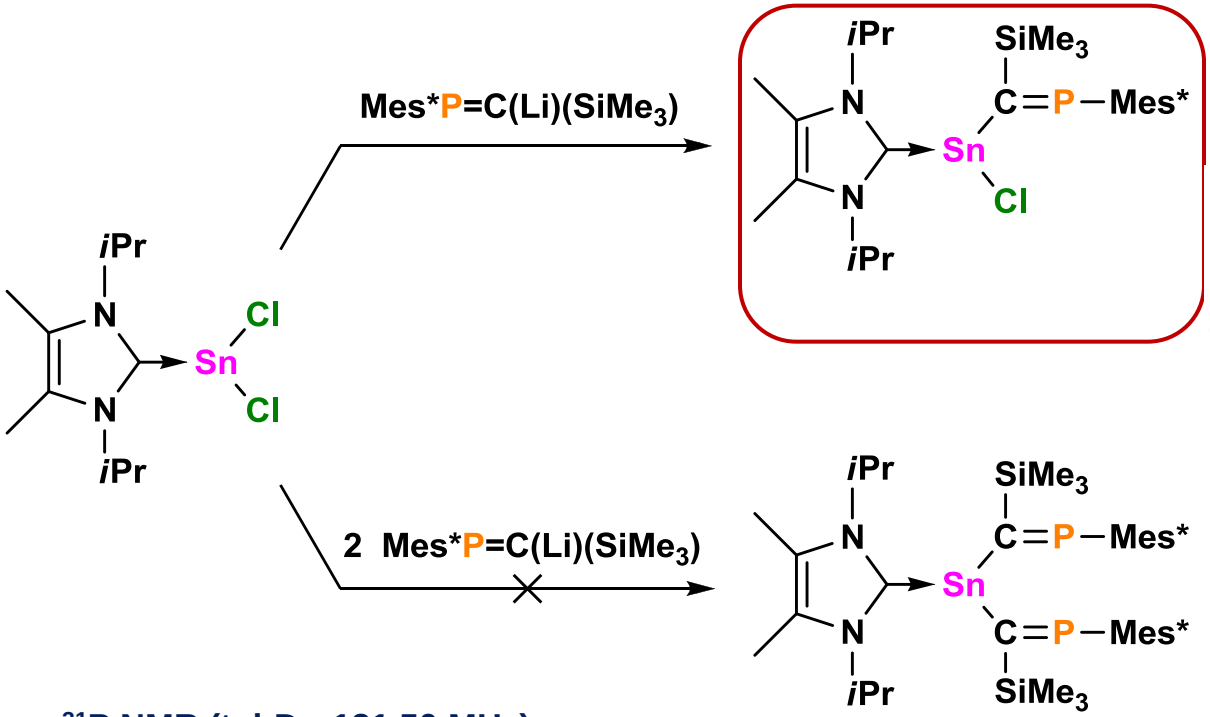
-3 had a significant photodynamic effect in A431 cells (tumor) when blue light was used

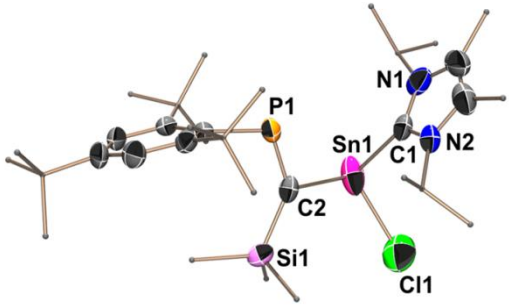
-1 photosensitizer both in red and blue light irradiation for both normal and tumor cell lines.

The first monosubstituted phosphaalkenyl-metallylenes

- synthesis of the mono- and di(phosphaalkenyl)germylene starting from the dibromophosphaalkene

- synthesis of the stannylene analogues



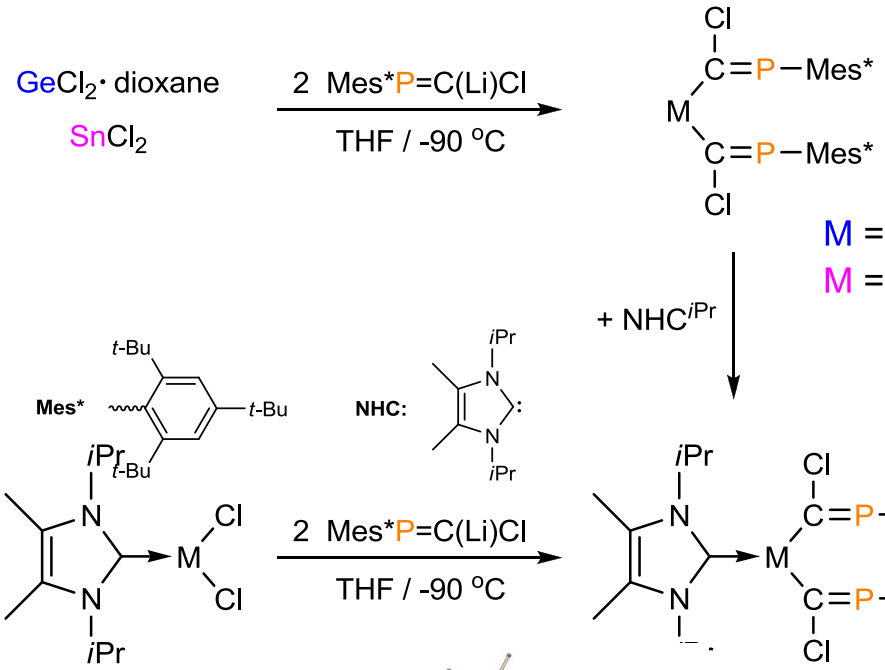


^{31}P NMR (tol-D$_8$, 121.50 MHz):
δ = 344.5 ppm ($^2J_{P\text{-}Sn}$ = 299.5 Hz)

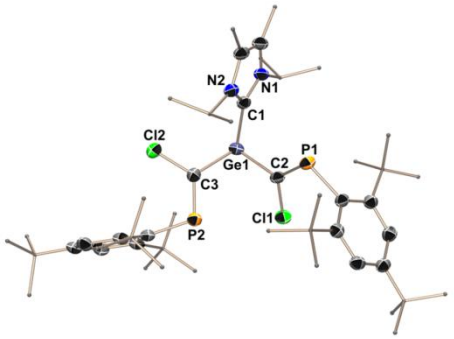
Matioszek, D.; Kocsor, T.-G.; Castel, A.; Nemeș, G.; Escudié, J.; Safforn, N.; *Chem. Commun*., **2012**, *48*, 3629-3631

Novel disubstituted phosphaalkenyl-metallylenes

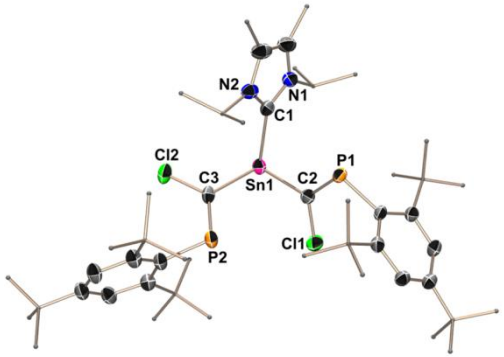
- transient formation of $Ge[C(Cl)=PMes^*]_2$ and $Sn[C(Cl)=PMes^*]_2$,
- stable phosphaalkenyl-metallylenes $NHC^{iPr}Ge[C(Cl)=PMes^*]_2$ and $NHC^{iPr}–Sn[C(Cl)=PMes^*]_2$.



M = Ge : ^{31}P NMR: 297 ppm (broad)
M = Sn : ^{31}P NMR: 264 ppm (broad)



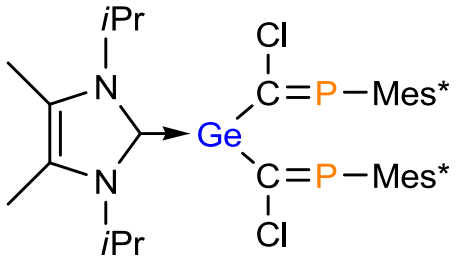
M = Ge
M = Sn



M = Ge : ^{31}P-NMR: 265.71 ppm
M = Sn : ^{31}P-NMR: 277.43 ppm

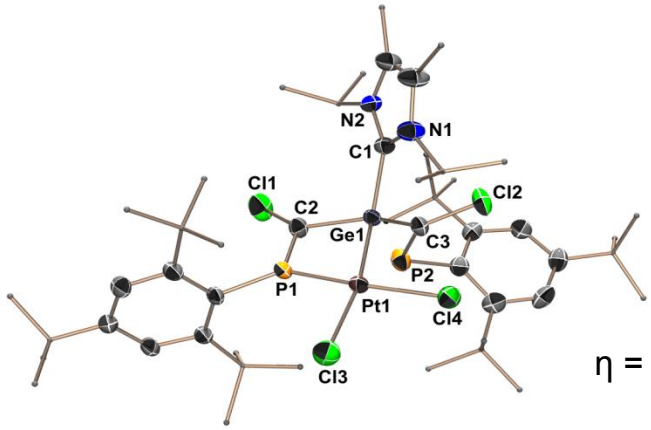
Matioszek, D.; Kocsor, T.-G.; Castel, A.; Nemeș, G.; Escudié, J.; Safforn, N.; *Chem. Commun.*, **2012**, *48*, 3629-3631

Synthesis of a platinum(diphosphaalkenyl)germylene

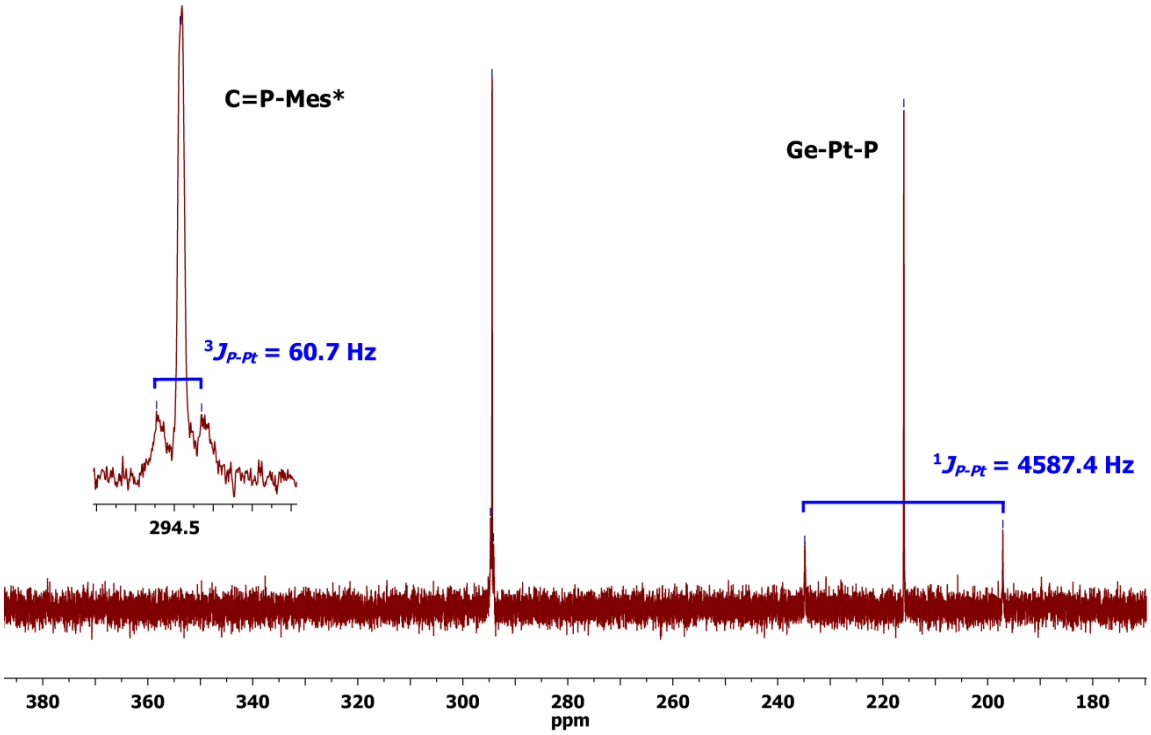


$PtCl_2(cod)$

THF



η = 93%



^{31}P NMR (CD_2Cl_2, 121.51 MHz)

Mp: 195-196 °C

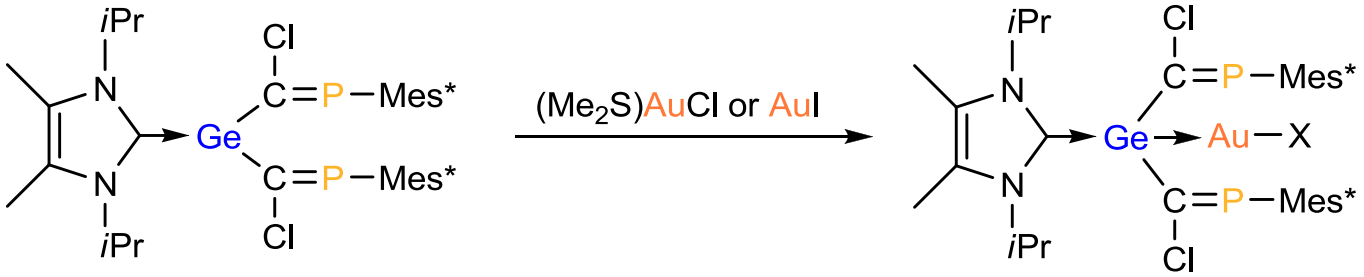
Bond distances [Å]:

Ge1–Pt1 2.3887(4)
Ge1–C1 2.018(4)
Ge1–C2 1.981(4)
Ge1–C3 1.949(4)
Pt1–P1 2.1777(10)

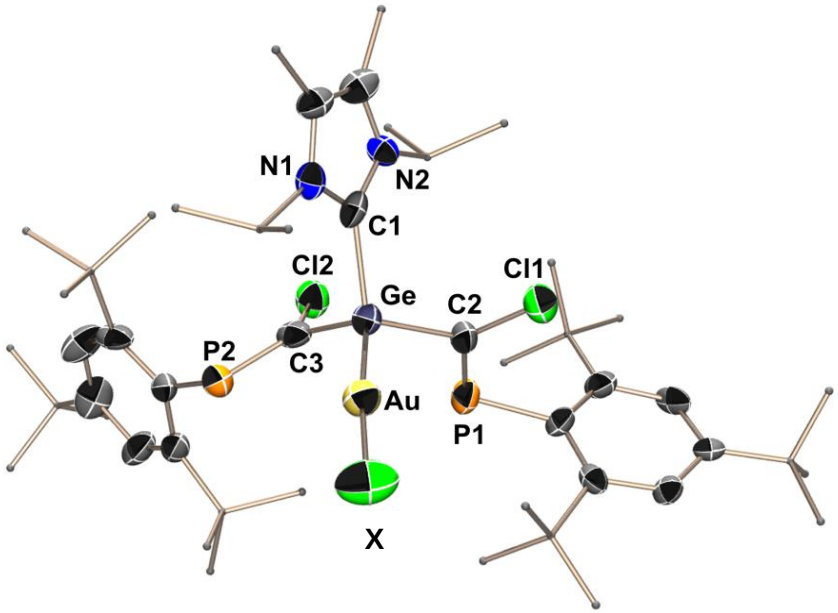
Bond angles [°]:

Ge1-C2-P1 94.62(17)
Ge1-C3-P2 119.3(2)
Pt1-Ge1-C1 120.56(10)
Pt1-Ge1-C2 88.32(11)
Pt1-Ge1-C3 121.08(11)

Synthesis of chloro- and iodo gold(diphosphaalkenyl)germylenes



X = Cl
X = I



^{31}P-NMR (C_6D_6):
δ = 293.0 ppm

X = Cl

Bond distances [Å]
Ge1–C1 2.031(3)
Ge1–Au1 2.3449(3)
Au1–Cl3 2.3128(9)
P1–C2 1.668(3)
P2–C3 1.665(3)

Bond angles [°]
Cl3-Au1-Ge1 177.07(3)
C2-Ge1-C3 106.66(12)
C1-Ge1-Au1 113.79(9)
C2-Ge1-Au1 116.06(9)
C3-Ge1-Au1 107.38(9)

^{31}P-NMR (C_6D_6):
δ = 292.6 ppm

X = I

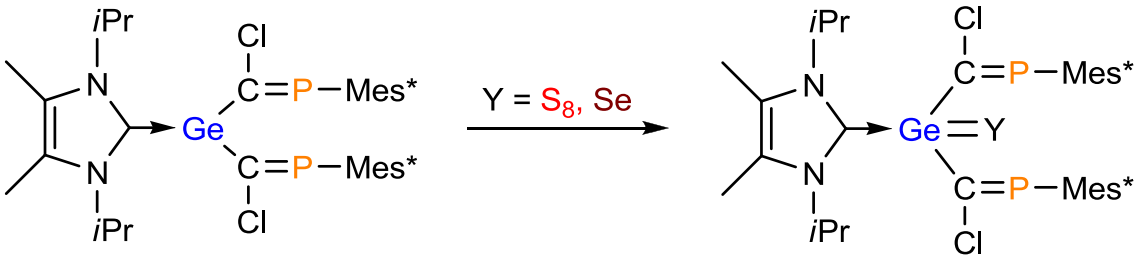
Bond distances [Å]
Ge1-C1 2.030(6)
Au1–Ge1 2.3641(6)
Au1–I1 2.5783(5)
P1–C2 1.671(5)
P2–C3 1.671(6)

Bond angles [°]
I1-Au1-Ge 176.75(2)
C2-Ge1-C3 107.1(2)
C1-Ge1-Au1 114.08(17)
C2-Ge1-Au1 111.01(15)
C3-Ge1-Au1 113.88(9)

Matioszek, D.; Kocsor, T.-G.; Castel, A.; Nemeș, G.; Escudié, J.; Safforn, N.; *Chem. Commun.*, **2012**, *48*, 3629-3631

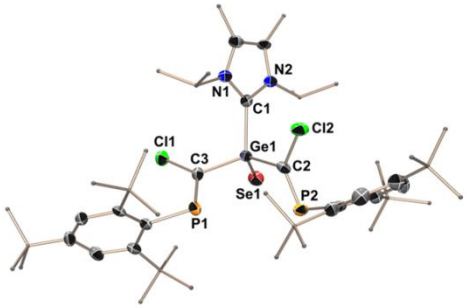
N-Heterocyclic carbene stabilized phosphaalkenyl Ge(II) and Sn(II) compounds: reactivity

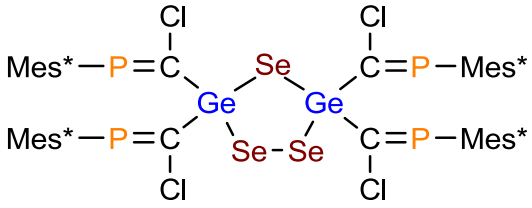
Oxidative addition reactions



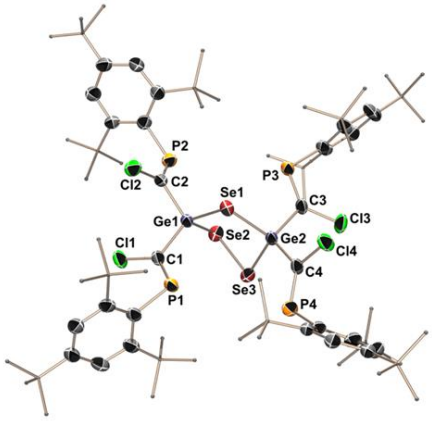
germathione: Y = S : ^{31}P-NMR = 289.95 ppm

germaselenone: Y = Se : ^{31}P-NMR = 291.28 ppm



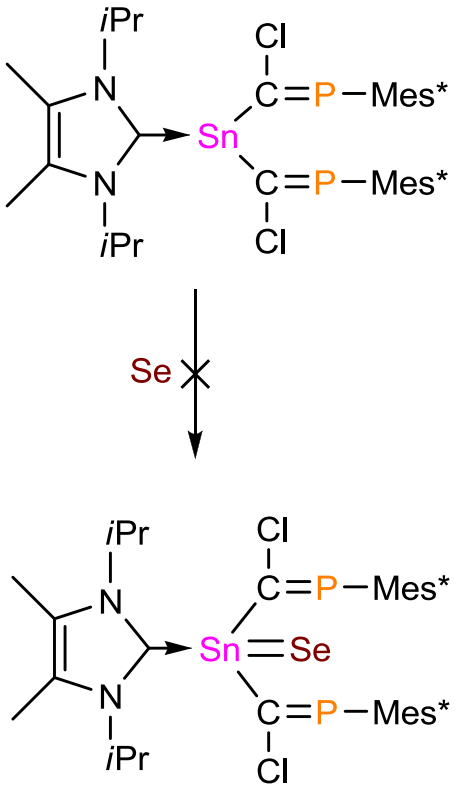


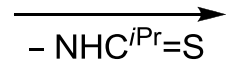
triselenadigermolane: ^{31}P-NMR = 295.80 ppm

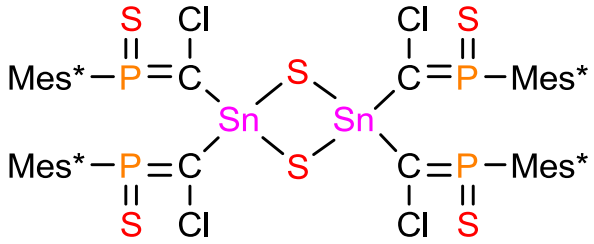


T.-G. Kocsor, D. Matioszek, G. Nemeș, A. Castel, J. Escudié, P. M. Petrar, N. Saffon-Merceron, I. Haiduc, *Inorg. Chem.*, **2012**, *51*, 7782-7787

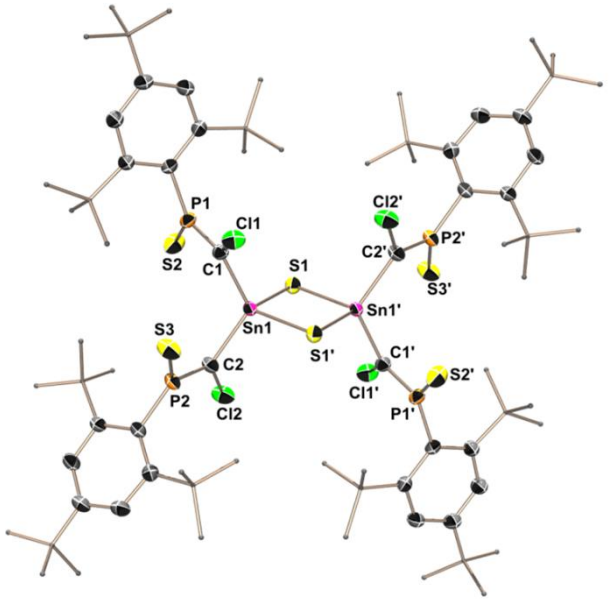
Oxidative reaction of bis(phosphaalkenyl)stannylene







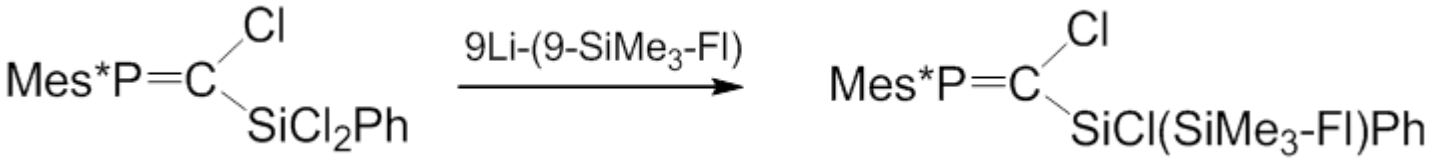
dithiadistannetanne: ^{31}P-NMR = 189.22 ppm



^{119}Sn-NMR (C_6D_6, 111.92 MHz, 298 K)

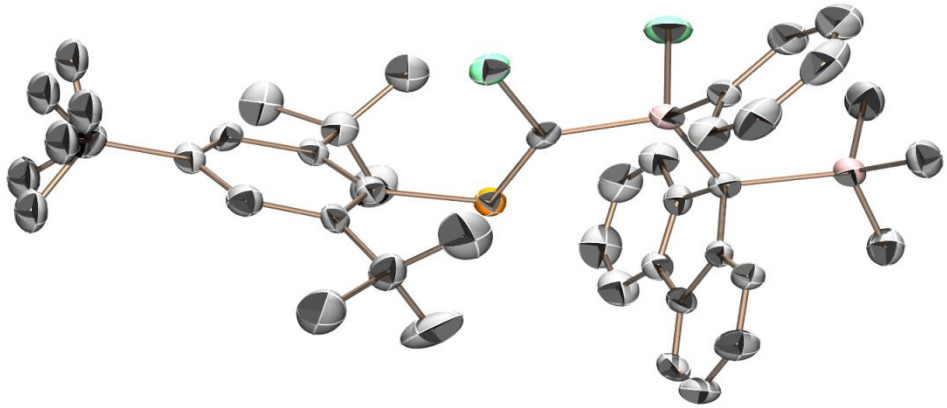
T.-G. Kocsor, D. Matioszek, G. Nemeș, A. Castel, J. Escudié, P. M. Petrar, N. Saffon-Merceron, I. Haiduc, *Inorg. Chem.*, **2012**, *51*, 7782-7787

Synthesis and characterization of new phosphasilapropenes



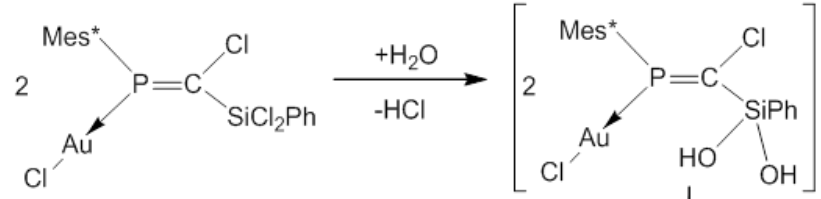
^{31}P RMN: δ = 321.58 ppm

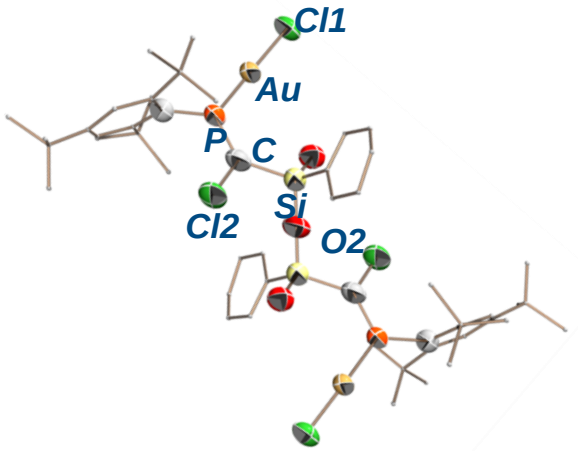
^{29}Si RMN: δ = 3.42 ppm ($^{2}J_{PSi}$ = 38.6 Hz)

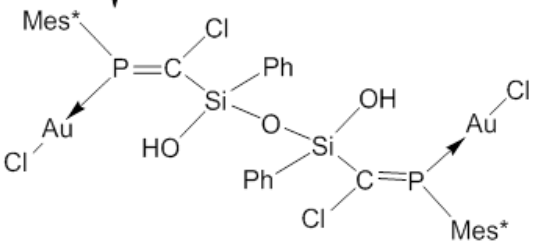


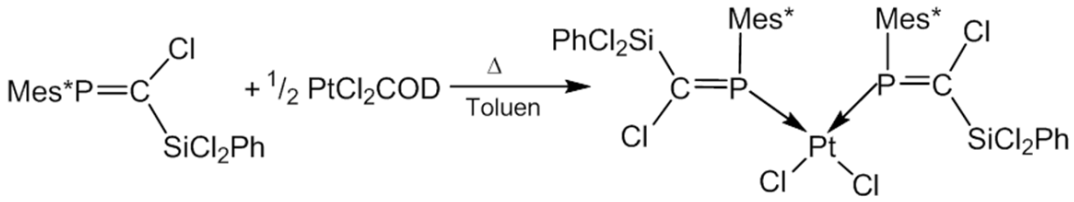
A. Bartok, R. Septelean, P. Petrar, G. Nemes, L. Silaghi-Dumitrescu, H. Ranaivonjatovo, S. Ladeira, N. Saffon, C. Hemmert, H. Gornitzka, *J. Organomet. Chem.*, **2012**, *DOI: 10.1016/j.jorganchem.2012.10.017*

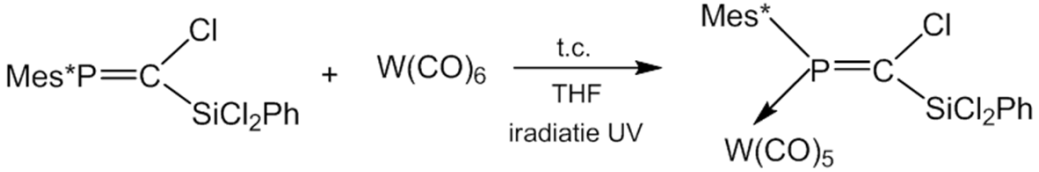
Metal complexes of phosphasilapropenes





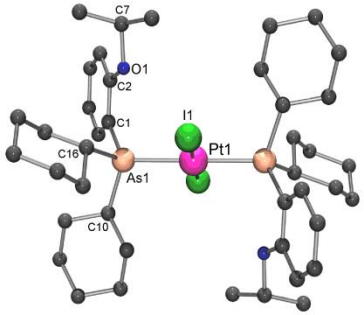




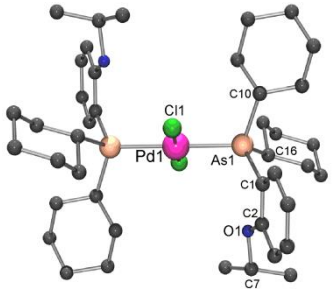


A. Bartok, R. Septelean, P. Petrar, G. Nemes, L. Silaghi-Dumitrescu, H. Ranaivonjatovo, S. Ladeira, N. Saffon, C. Hemmert, H. Gornitzka, *J. Organomet. Chem.*, **2012**, *DOI: 10.1016/j.jorganchem.2012.10.017*

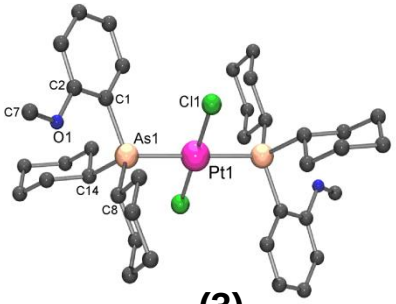
Platinum and palladium complexes of organoarsenic ligands



(1)



(2)



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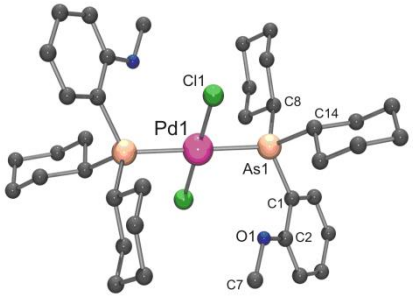
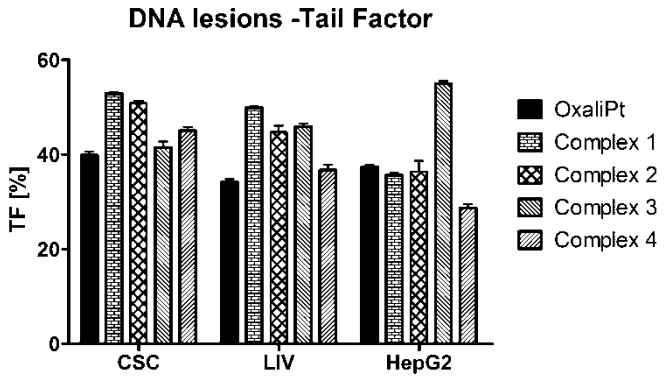
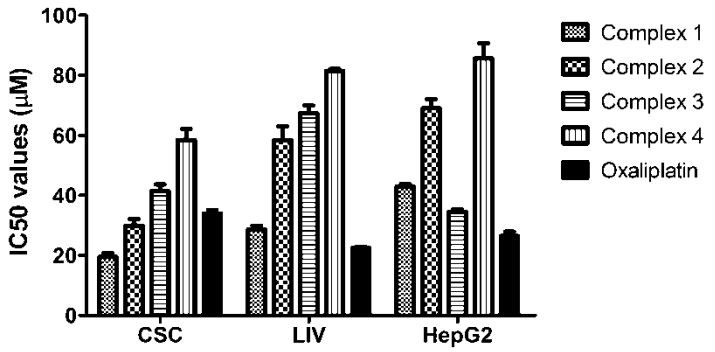


(4)

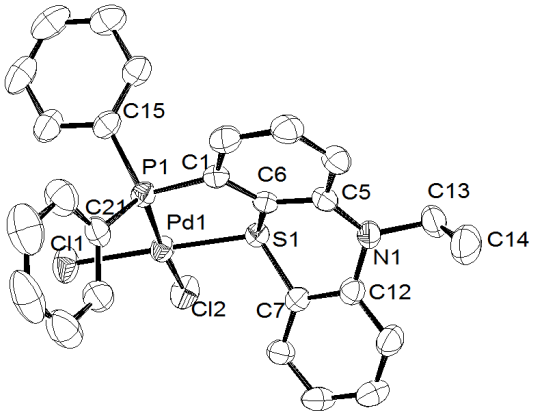
Molecular structure of
trans-[PtI_2{2-$Pr^iOC_6H_4As(C_6H_{11})_2$-κAs}$_2$] (**1**)
trans-[$PdCl_2${2-$Pr^iOC_6H_4As(C_6H_{11})_2$-κAs}$_2$] (**2**)
trans-[$PtCl_2${2-$MeOC_6H_4As(C_6H_{11})_2$-κAs}$_2$] (**3**)
trans-[$PdCl_2$(2-$MeOC_6H_4As(C_6H_{11})_2$-κAs}$_2$] (**4**)

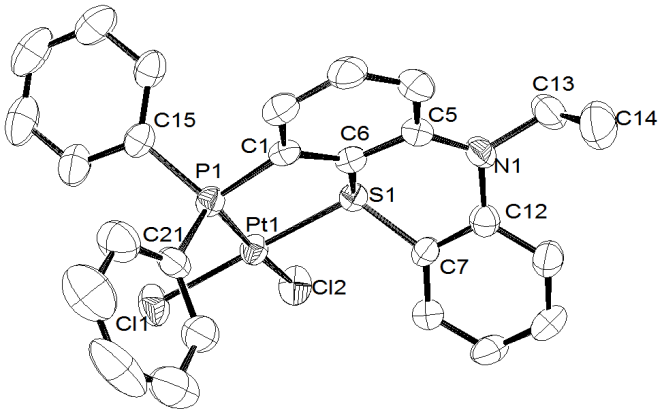




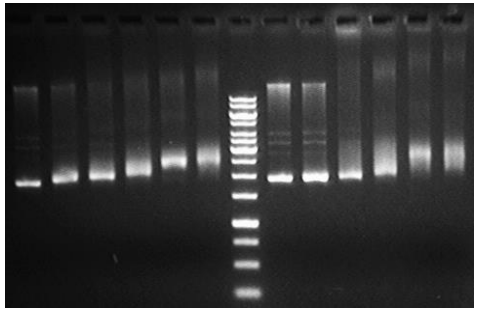
Antiproliferative effect and genotoxicity of novel synthesized palladium complexes with organoarsenic ligands, N. Miklasova, E. Fischer-Fodor, P. Loennecke, M. Schrepler, P. Virag, C. Tatomir, V.I. Cernea, E. Hey- Hawkins, L. Silaghi-Dumitrescu, *J. Inorg. Biochem.*, **2009**, *103*(12), 1739-1747

Phenothiazinyl-Phenyl-Phosphines





DNA intercalation



Antitumour activity

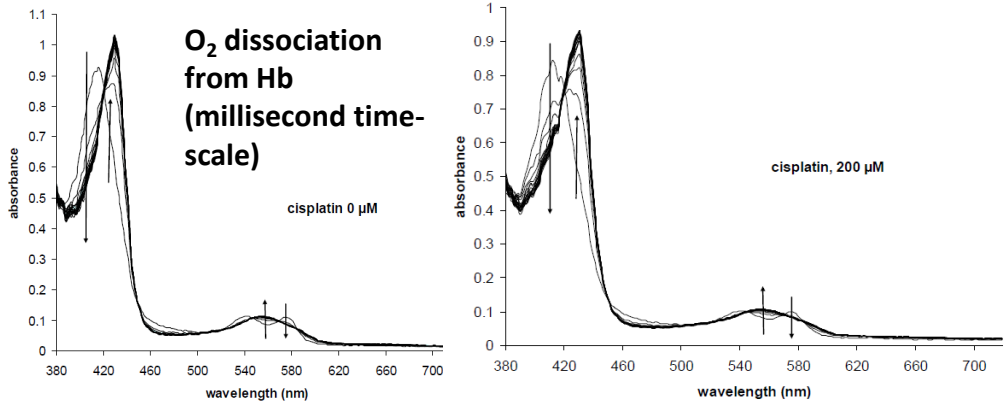
cytotoxic effect on:
MCF7 (human breast adenocarcinoma)
HepG2 (hepatocyte carcinoma)
DLD1 (colorectal adenocarcinoma)

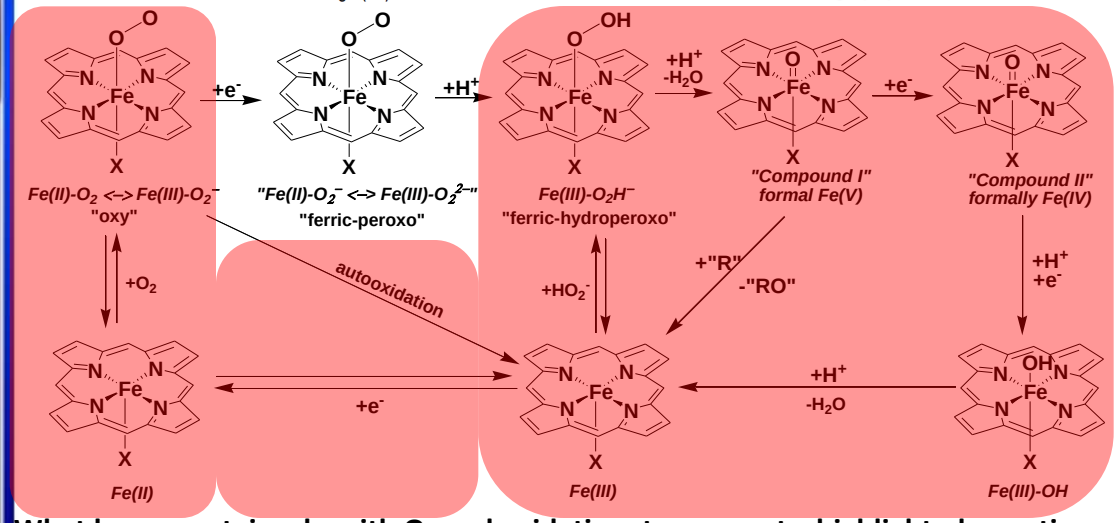
Molecular mechanisms of oxidative/nitrosative stress elicited by cisplatin & related compounds:

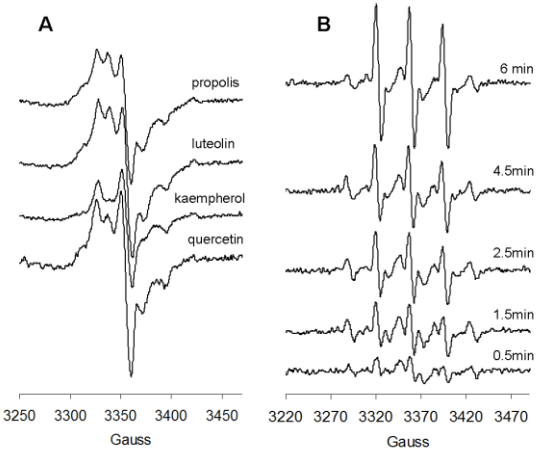
Hb affinity for O_2	P_{50} mmHg	n (cooperativity)
Hb	28 (±3)	1.9 (±0.1)
Hb, 400 μM Pt, inc 24 h (mM)	8 (±3)	1.4 (±0.1)
Hb, 400 μM Pt, inc 4 h (mM)	16 (±1)	1.2 (±0.1)
Hb, 400 μM Pt, non-inc	34 (±5)	1.6 (±0.1)

- Cisplatin and related drugs **bind reversibly as well as irreversibly** to **Hb as well as to many other proteins**
- This binding affects their **dynamics and functionality**. Examples: in Hb, affected are the **affinity for O_2**, direct **rate of O_2 binding**/leaving the heme in Hb (increased **rigidity**), **autooxidation** (generating superoxide as well as **prooxidant** ferric hemoglobin), the reaction of Hb with peroxides and ascorbate (a **free-radical** generating process)

New assays for prooxidant and antioxidant activity developed, based on metalloproteins; correlations identified with selective anticancer activity

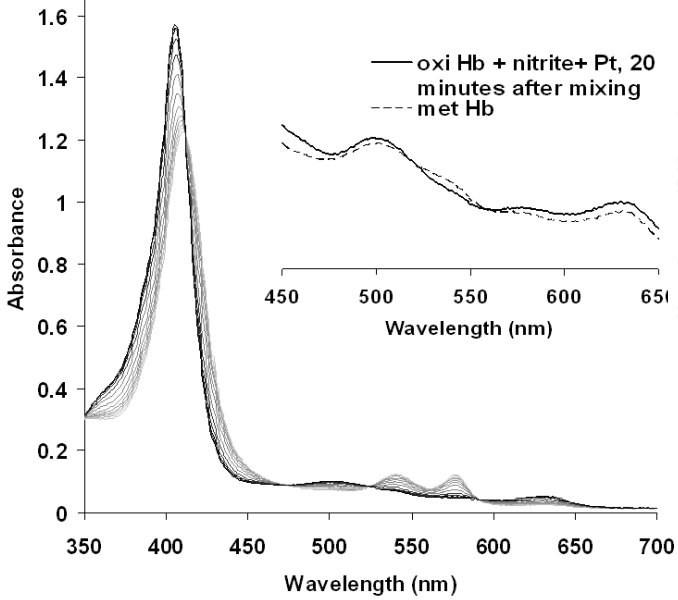


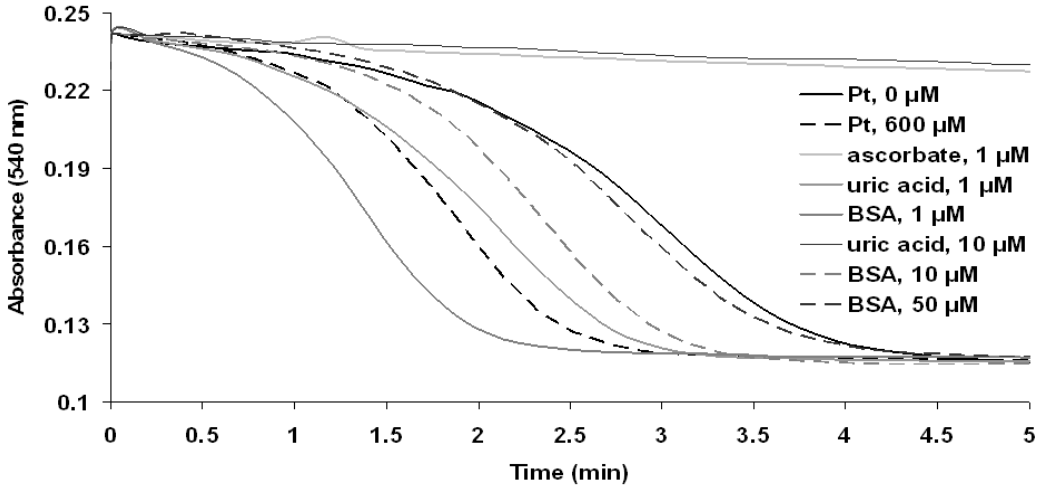


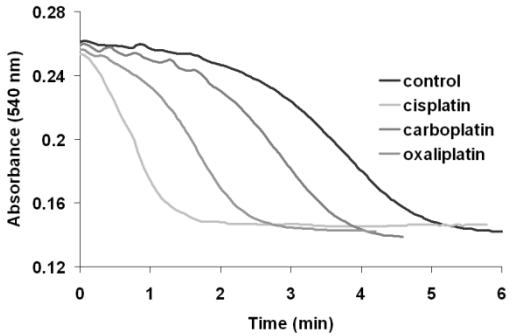


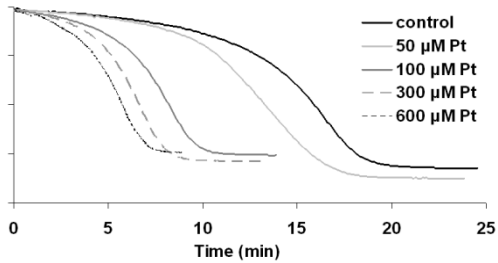
What heme proteins do with O_2 and oxidative stress agents; highlighted: reactions affected by cisplatin

Molecular mechanisms of oxidative/nitrosative stress elicited by cisplatin & related compounds:

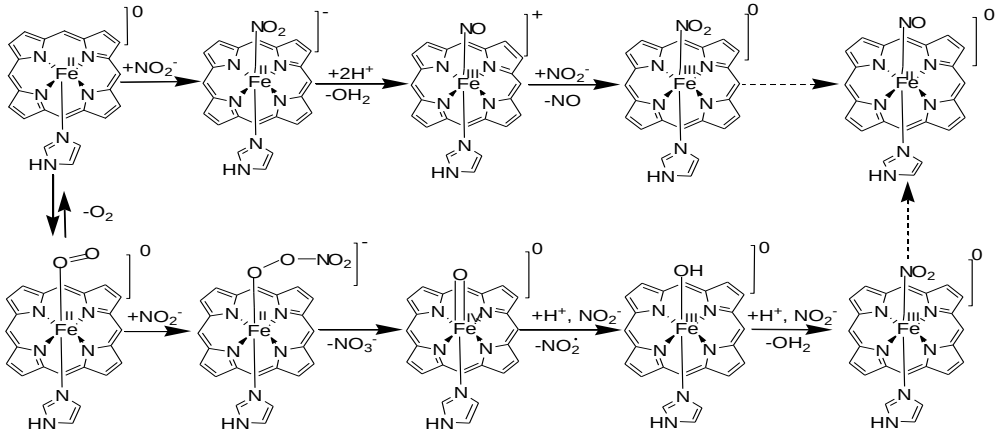


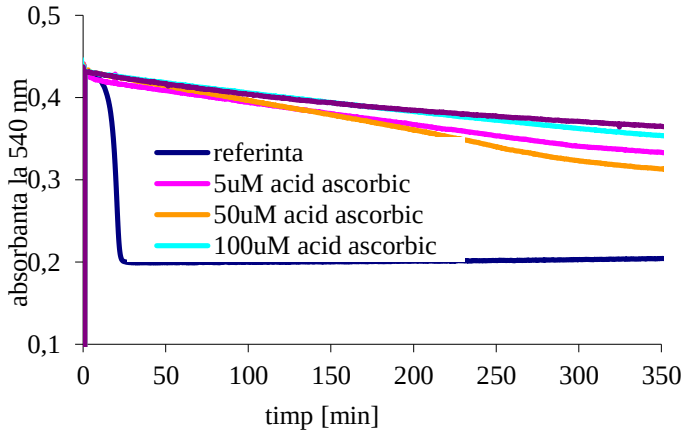




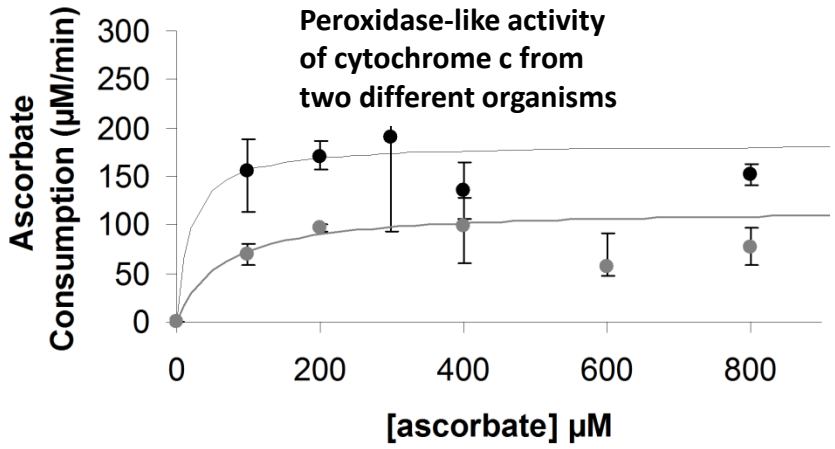


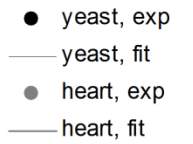
- Hemoglobin: **nitrite-induced autooxidation** affected by cisplatin
- Other Pt-containing drugs have similar but not identical effects
- Some **antioxidants** block, others accelerate the process – dictated by **concentration**

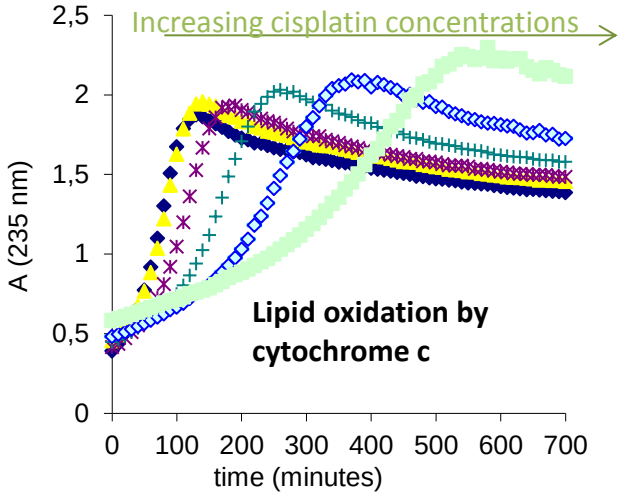


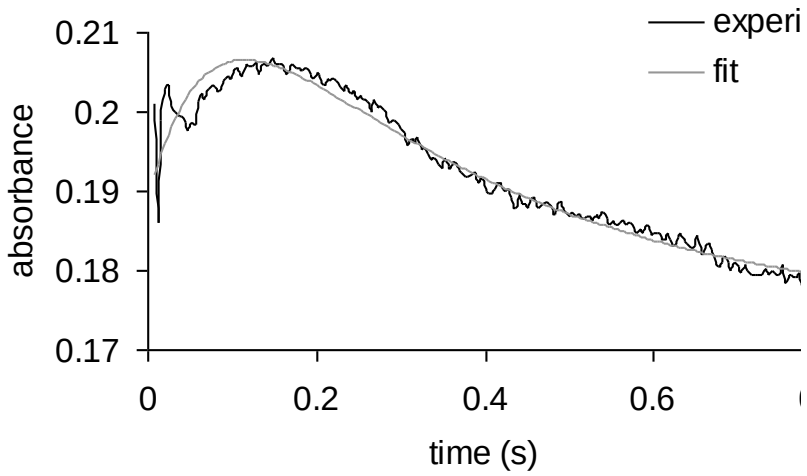


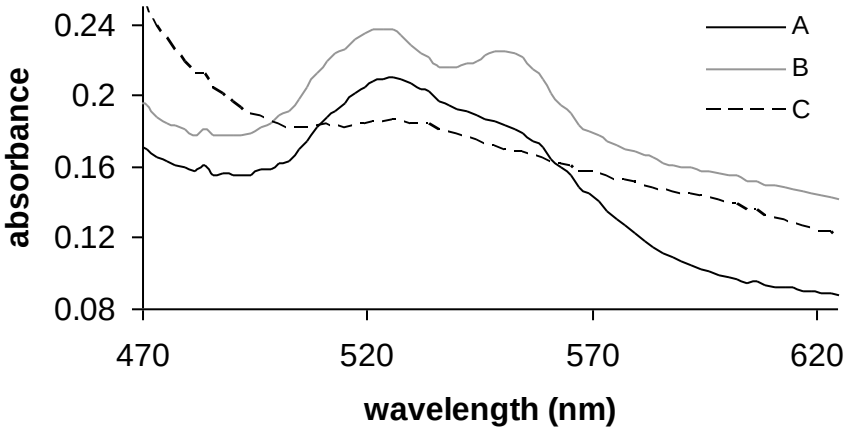
Molecular mechanisms of oxidative/nitrosative stress elicited by cisplatin & related compounds:



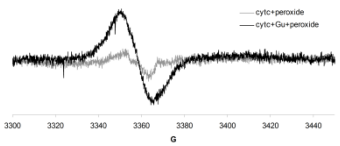




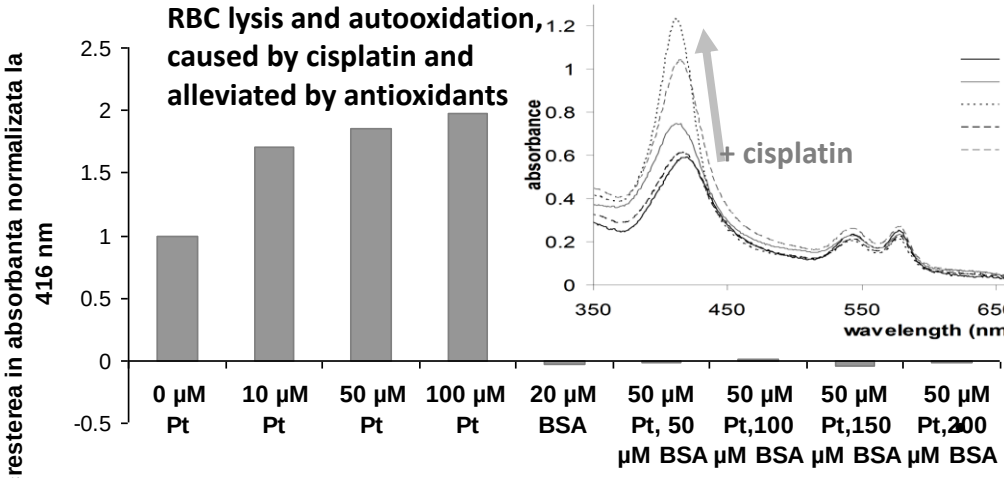


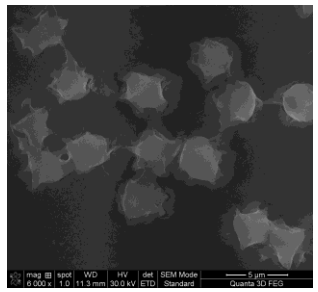


- Cytochrome *c* acts as peroxidase, including on lipid membranes (lipososmes)
- Mechanism demontsrated by detection of Fe(IV) cytochrome on millisecond-scale
- Prooxidant effect enhanced by cisplatin and controllled by antioxidants

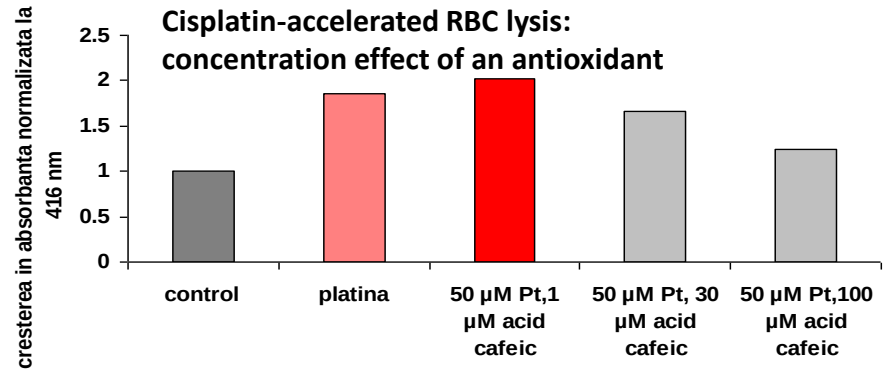


Molecular mechanisms of oxidative/nitrosative stress elicited by cisplatin & related compounds:





RBC+cisplatin: shape affected



Red blood cell lysis, accompanied by hemoglobin autooxidation, is enhanced by cisplatin. Certain antioxidants, depending on concentration, may alleviate or accelerate the process

- Shape of red blood cells affected by cisplatin
- **Free radical character proven. May explain side-effects, and partially other effects, of cisplatin and related compounds**
- **Battery of tests for prooxidant and pro-nitrosative effects of drugs, proposed**

Tamokou JD; Chouna JR; Fischer-Fodor E; Chereches G; Barbos O; Damian G; Benedec D; Duma M; Efouet APN; Wabo HK; Kuiate JR; Mot A; Silaghi-Dumitrescu R. *PloS ONE*, 2013, 8(2):e55880

Bischin C; Lupan A; Taciuc V; Silaghi-Dumitrescu R. *Mini-Rev Med Chem* 2011, 11, 214

Bischin C, Tusan C, Bartok A, Septelean R, Damian G, Silaghi-Dumitrescu R. *Phosphorus, Sulfur Sillicon Relat Elem*, 2014, in press

Mot A, Damian G, Coman C, Miron C, Sarbu C, Silaghi-Dumitrescu R., *Food Chem* 2014, 143, 214

Benedec D, Vlase L, Oniga I, Mot A, Damian G, Hanganu D, Duma M, Silaghi-Dumitrescu, R. *Molecules,* 2013, 18(8), 8725

Coman C, Mot A, Gal E, Parvu M, Silaghi-Dumitrescu R. *Fungal Biol*, 2013, 17(7-8), 528

Scurtu F, Zolog O, Iacob B, Silaghi-Dumitrescu, R. *Artif Cells Blood Subst Biotechnol* 2013, in press

Iacob B, Deac F, Cioloboc D, Damian G, Silaghi-Dumitrescu R. *Artif Cells Blood Subst Biotechnol* 2011, 39, 293-297

Fischer-Fodor E, Mot A, Deac F, Arkosi M, Silaghi-Dumitrescu R. *J Biosci* 2011, 36, 215-221

Bischin C, Deac F, Silaghi-Dumitrescu R, Worrall JAR, Rajagopal BS, Damian G, Cooper CE. *Free Rad Res* 2010, 45, 439

Stress mechanisms involving metals, as targets for modulating oxidative/nitrosative stress

As examined by density functional theory, post-Hartree-Fock (CASSCF, CASPT2, MP2, etc), dynamics (classical vs ab initio), spectrum simulations (UV-vis, NMR, EPR, vibrational), docking, semiempirical, molecular mechanics

- Nitrite reduction for NO liberation; NO reduction/oxidation
- Sulfide, sulfur oxides
- Superoxide/peroxide binding/reduction; free radical-forming reactions
- Cobalt vs iron as source of free radicals
- Binding to DNA; the case of iron vs cobalt vs metal-free bleomycin
- Globins, superoxide reductases/dismutases, perosidases, catalases, heme oxygenases, bleomycins, nitrate/nitrite reductases (xanthine oxidase-related), NO reductases, multiheme reductases, iron-sulfur proteins
- Fe, Co, Mn, Cu, Mo, Pt, Pd, Zn, Si, W

Attia A, Lupan A, Silaghi-Dumitrescu R. *RSC Advances*, 2013, 3 (48), 26194
Dereven'kov IA, Salnikov DS, Makarov SV, Surducan M, Silaghi-Dumitrescu R, Boss R. *J Inorg Biochem*, 2013, 125, 32
Attia A, Cioloboc D, Lupan A, Silaghi-Dumitrescu R. *J Biol Inorg Chem*, 2013, 18(1), 95
SurducanM, Lup D, Lupan A, Makarov SV, Silaghi-Dumitrescu R. *J Inorg Biochem* 2013, 118, 13
Silaghi-Dumitrescu R. *Structure & Bonding*, 2013, 150, 97
Silaghi-Dumitrescu R, Mich M, Matyas Cs, Cooper CE. *Nitric Oxide* 2012, 26(1), 27
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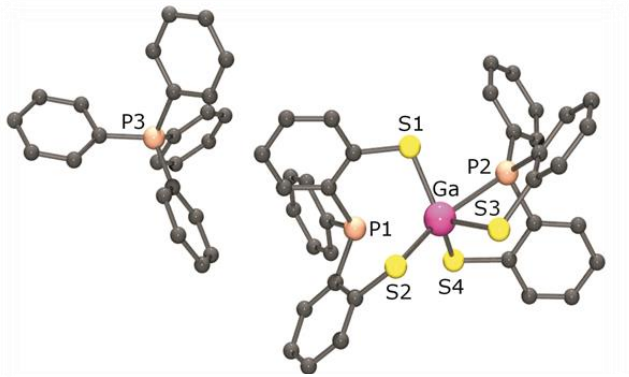
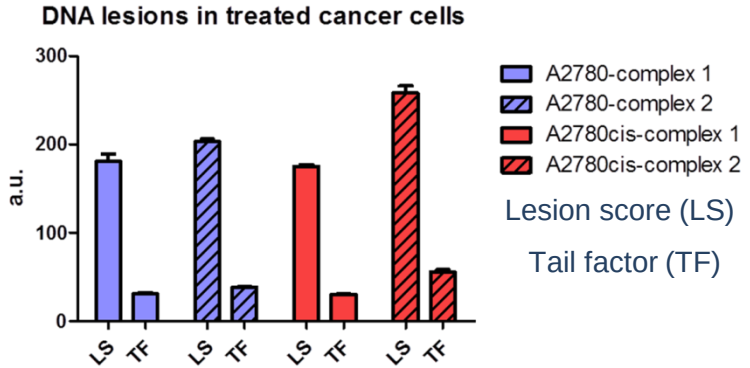
Silaghi-Dumitrescu R, Makarov SV, Uta MM, Dereven'kov IA, Stuzhin PA. *New J Chem*, 2011, 35(5), 1140

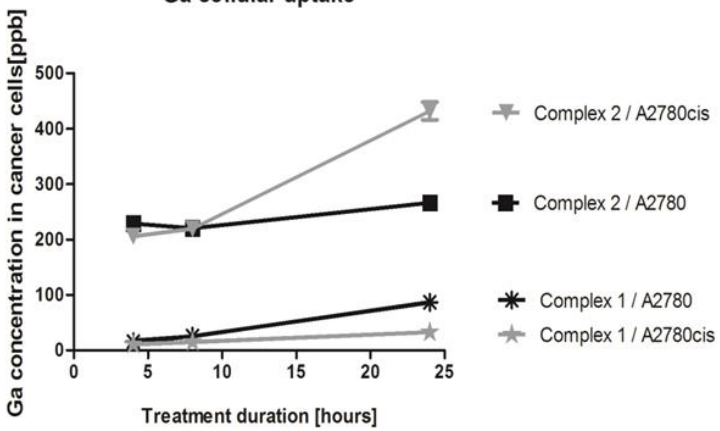
Gallium phosphinoarylbisthiolato complexes

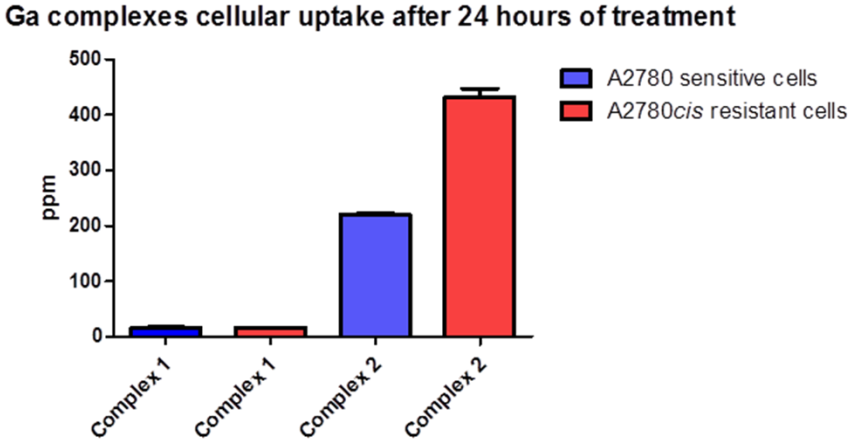
$[Ga\{[(SC_6H_4)_2\text{-}2\text{-}PPh]\text{-}\kappa^3S,S',P\}\{[(SC_6H_4)_2\text{-}2\text{-}PPh]\text{-}\kappa^2S,S'\}][HNEt_3]$ (1)

$[Ga\{[(SC_6H_4)_2\text{-}2\text{-}PPh]\text{-}\kappa^3S,S',P\}\{[(SC_6H_4)_2\text{-}2\text{-}PPh]\text{-}\kappa^2S,S'\}][PPh_4]$ (2)





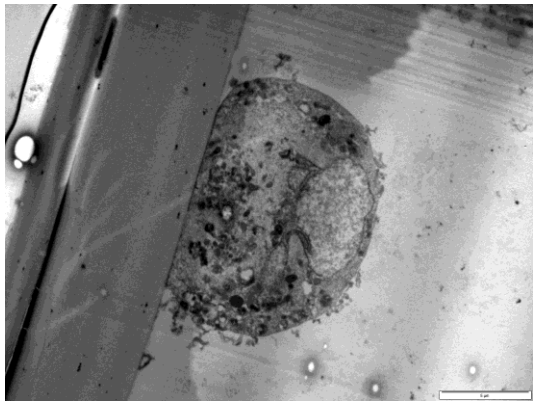


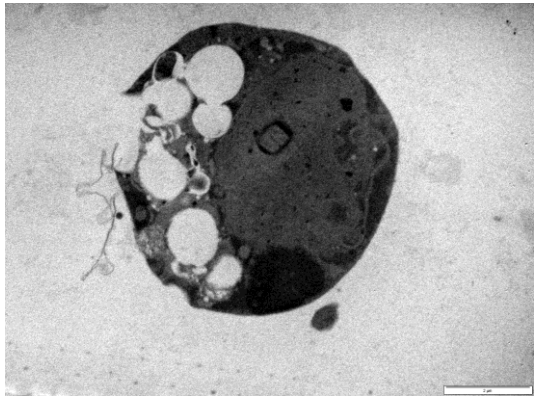


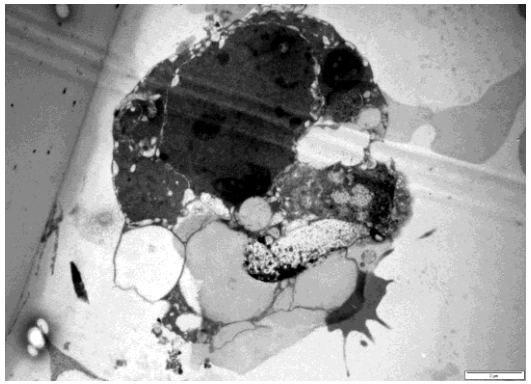
Eva Fischer-Fodor, Ana-Maria Vălean, Piroska Virag, Petru Ilea, CorinaTatomir, Florica Imre-Lucaci, Maria Perde Schrepler, Ludovic Tibor Krausz, Lucian Barbu Tudoran, Calin George Precup, Iulia Lupan, Evamarie Hey-Hawkins, Luminita Silaghi-Dumitrescu, *Metallomics*, accepted for publication, MT-ART-09-2013-000278.

Influence of Novel Gallium Complexes on the Homeostasis of Some Biochemical and Hematological Parameters in Rats, G. Gârban, R. Silaghi-Dumitrescu, H. Ioniţă, Z. Gârban, N. Hădărugă, G. D. Ghibu, C. Baltă, F-D. Simiz, C. Mitar, *Biol Trace Elem Res*., 2013, 155, 387–395

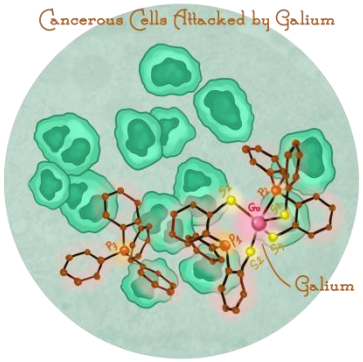
Ultrastructural studies

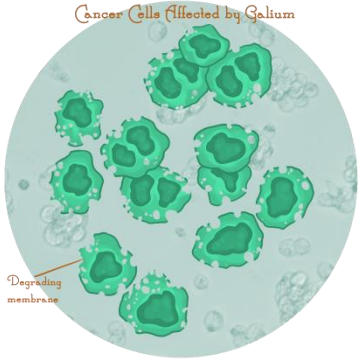


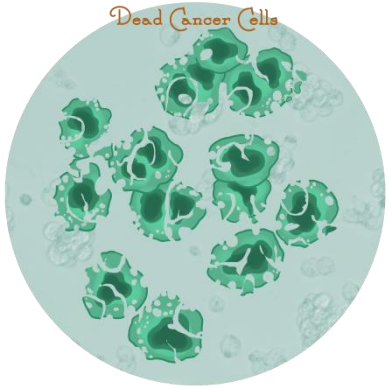




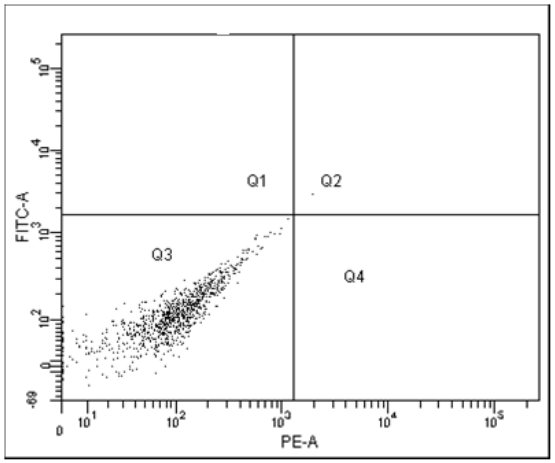
scale bar 2 µm



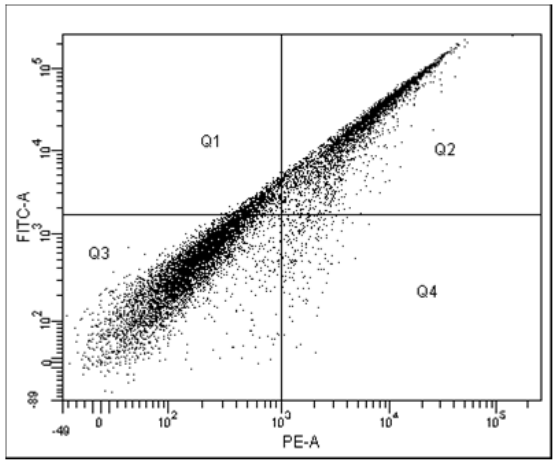




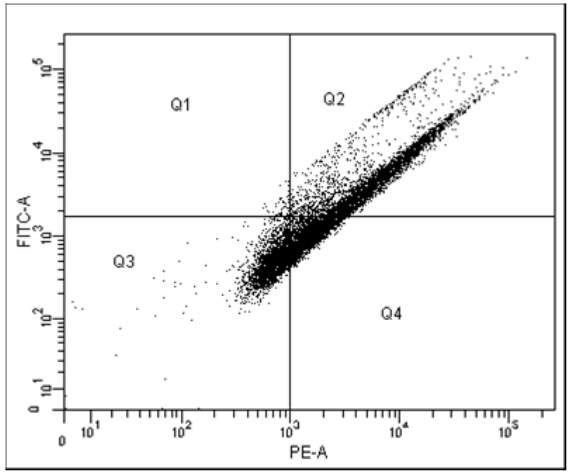
Apoptosis



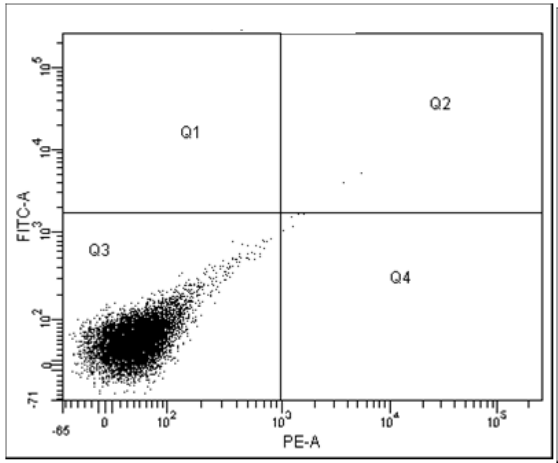
untreated chemosensitive cells



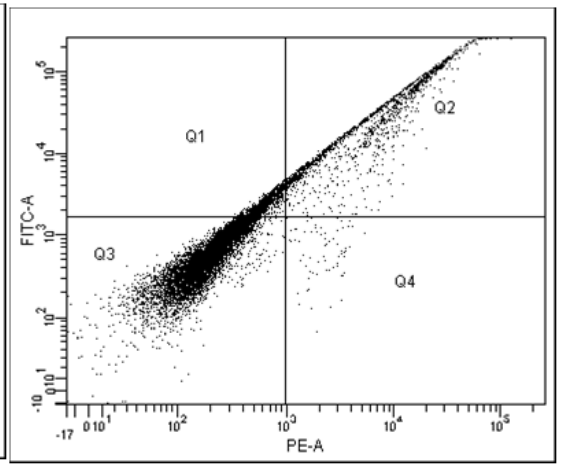
treatment with complex 1



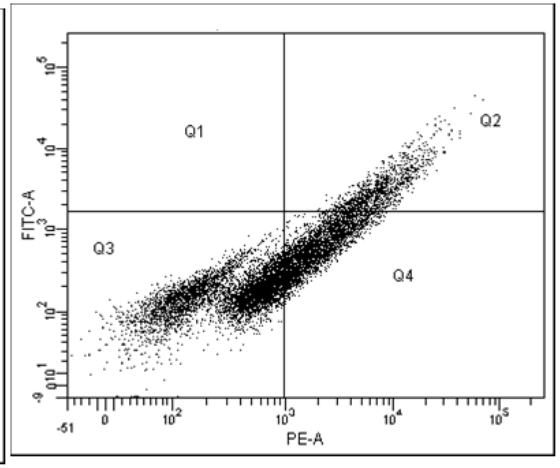
treatment with complex 2



untreated chemoresistant cells



treatment with complex 1



treatment with complex 2

Apoptosis assay was performed using the flow-cytometry technique ; Vybrant Apoptosis Assay Alexa Fluor apoptosis kit (Invitrogen).

In vitro effect on A2780 platinum sensitive and A2780*cis* platinum-resistant human ovary malignant cell lines:

- ✓ cell growth inhibitory effect (compound **2** is selective and more effective than platinum-based standard drugs).
- ✓ gallium incorporation into ovary carcinoma cells
- ✓ DNA damages occurrence
- ✓ early apoptosis
- ✓ ultrastructural cell changes
- ✓ interaction with the cell signaling pathways being able to modulate TGF-beta1, bcl-xL and FasL expression.
- ✓ complexes 1 and 2 are not substrates of Pgp-1 efflux pump, (overexpression of Pgp-1 does not occur in the treated cells pointing towards counteracting the multidrug resistance mechanisms in cancer cells which are defiant to standard metal drug action)

*In vivo studies…*hematological homeostasis. The only significant effect was the decrease of iron content in kidney tissue.

WHY GALLIUM ? THE ANSWER IS…

…novel facets of gallium action:

- The platinum-resistant carcinoma cells are responsive to the gallium phosphinoarylbisthiolates activity, therefore these complexes, in particular **2,** are good candidates to be used in combination with platinum or other standard antineoplastic drugs
- less side-effects during therapy

VALORIFICAREA REZULTATELOR

Cercetarea translationala (desfasurata in cadrul proiectului si corelata cu scopul final al acestuia) care vizeaza elucidarea unor tinte moleculare si mecanisme de actiune ale medicamentelor metalice consacrate in vederea optimizarii medicatiei antineoplastice, folosind o abordare metallomica.

- S-a elaborat o noua metoda de chimiosensibilitate a tumorilor la actiunea medicamentelor platinice standard, aflate in uzul clinic, cum ar fi: cisplatin, oxaliplatin, carboplatin.
- A fost evaluata actiunea in vitro a citostaticelor platinice si a fost comparata eficienta acestora fata de alte medicamente antineoplazice din protocoalele terapeutice cu o metoda noua de citometrie statica, in vederea stabilirii unor markeri de predictie ai eficientei tratamentului.
- S-a adaptat tehnica dispunerii celulelor pe suporturi "cellchip" pentru a facilita stabilirea unor parametrii de viabilitate a celulelor tumorale tratate.
- Metodele metalomice au fost aplicate si in urmarirea eficientei tratamentelor pe baza de platina. S-a efectuat un studiu clinic nerandomizat in care urmarirea pacientelor s-a facut concomitent cu determinarea platinei inglobate in fluidele biologice, si a parametrilor de angiogeneza legate de inhibitia cresterii tumorale. S-au pus astfel bazele unor scheme de terapie neoadjuvanta in cancerul de col uterin avansat locoregional. S-au comparat parametrii moleculari stabiliti cu evolutia clinica a bolii in cazul tratamentului concomitent radio-chimioterapeutic, respectiv in terapia neoadjuvanta, cu scopul determinarii unor markeri moleculari care pot fi corelati cu evolutia clinica. Ca urmare a acestor cercetari s-a elaborat o metodologie care poate fi aplicata in clinicile de oncologie.

DISEMINAREA REZULTATELOR

➢**64 lucrari in reviste cotate ISI** (40)

- *Eur.J.Org.Chem.,*
- *Eur.J.Inorg.Chem.,*
- *Eur.J.Bioinorg.Chem.,*
- *Eur.J.Med.Chem.,*
- *Chem.-Eur.J.*
- *Chem. Commun.,*
- *Dalton Trans.,*
- *Inorganic Chemistry,*
- *Structure and Bonding,*
- *Dyes and Pigments,*
- *New J.Chem.*
- *J.Organomet.Chem.*

➢Suma factorilor de impact: **>100** (60)

➢ **Participari la conferinte internationale cu lucrari in parteneriat**

Exemple:

- *International Symposium on Metallomics* (cele doua smpozioane organizate pe parcursul derularii proiectului , 2011, 2013),
- *Gordon Conferences: Metals in Medicine (2013)*
- *International Conference on BioInorganic Chemistry (2011, 2013).*

- Influence of Novel Gallium Complexes on the Homeostasis of Some Biochemical and Hematological Parameters in Rats, G. Gârban, R. Silaghi-Dumitrescu, H. Ioniţă, Z. Gârban, N. Hădărugă, G. D. Ghibu, C. Baltă, F-D. Simiz, C. Mitar, *Biol Trace Elem Res*., 2013, 155, 387–395
- Novel Meso-Phenothiazinyl-Porphyrin Dyes: Synthesis, Optical, Electrochemical Properties and PDT assay, E. Gal, B. Brem, I. Pereteanu, L. Gaina, T. Lovasz, M. Perde-Schrepler, L. Silaghi-Dumitrescu, C. Cristea, L. Silaghi-Dumitrescu*, Dyes and Pygments* 2013, 99, 144-153
- Microwave-Assisted Catalytic Amination of Phenothiazine; Reliable Access to Phenothiazine Analogues of Troger's Base, L. Gaina, L. Mataranga-Popa, E. Gal, P. Boar, P. Lonnecke, E. Hey-Hawkins, C. Bischin, R. Silaghi-Dumitrescu, I. Lupan, C. Cristea, L. Silaghi-Dumitrescu, *European Journal Of Organic Chemistry*, 2013, 24, 5500-5508
- Anticancer and antimicrobial activities of some antioxidant medicinal plants. J.D. Tamokou, J.R. Chouna, E. Fischer-Fodor,G. Chereches, O. Barbos, G. Damian, D. Benedec, M. Duma, A. P. Efouet, H. K. Wabo, J. R. Kuiate, A. Mot, R. Silaghi-Dumitrescu. *PloS ONE*, 2013, 8(2):e55880.
- Antiproliferative effect of novel platinum(II) and palladium(II) complexes on hepatic tumor stem cells in vitro, N. Miklasova, E. Fischer Fodor, P. Lonnecke, C.I. Tomuleasa, P.Virag, Schrepler, MP, R. Miklas, L. Silaghi Dumitrescu, E. Hey-Hawkins, *European Journal of Medicinal Chemistry*, 2012, 49, 41-47

•E. Fischer-Fodor, A. Mot, F. Deac, M. Arkosi, R. Silaghi-Dumitrescu, Towards hemerythrin-based blood substitutes: Comparative performance to hemoglobin on human leukocytes and umbilical vein endothelial cells *Journal Of Biosciences*, 2011, 36(2), 215-221,

• P. Virag, M. Perde-Schrepler, E. Fischer-Fodor, C. Tatomir, S.A. Dorneanu, V.I. Cernea, A. Irimie, Superior cytotoxicity and DNA cross-link induction by oxaliplatin versus cisplatin at lower cellular uptake in colorectal cancer cell lines, *Anticancer Drugs*, 2012, 23 (10), 1032-1038

• Cisplatin modulates stress-related reactivity in hemoglobin and in cytochrome c, Bischin Cristina, Garban Zeno, Garban Gabriela, Silaghi-Dumitrescu Radu, *Chemico-biological interactions,* 2013, in evaluare

•A New Polyethyleneglycol-Derivatized Hemoglobin Derivative with Decreased Oxygen Affinity and Limited Toxicity, Zolog O, Mot Augustin, Deac Florina, Roman A, Fischer-Fodor Eva, Silaghi-Dumitrescu Radu, *Protein Journal,* 2011, 30(1), 27-31,

RESURSA UMANA

- **78 de participanti**:
  - **48 % - cercetatori cu experienta**
  - **33 % - cercetatori postdoctoranzi**
  - **19 % - doctoranzi**

O parte dintre postdoctoranzi (11) au inceput sa lucreze in proiect ca si doctoranzi si au finalizat tezele de doctorat in perioada de derulare si cu sprijinul logistic al proiectului iar o parte dintre doctoranzi (6) au inceput sa lucreze in proiect ca si studenti masteranzi.

Proiecte depuse in parteneriat

•*Sistem de evaluare/diagnosticare diferentiata a bolilor din familia leucemiei*

•*Dezvoltarea unor teste inovatoare de diagnostic molecular si evaluare a chimiosensibilitatii pentru terapia tintita in cancerul colului uterin persistent, recidivat, metastazat*

• *Noi biomarkeri predictivi ai chimiorezistentei, ca posibile tinte terapeutice in carcinomul colorectal avansat si metastatic*

• *Dezvoltarea unei metode de detecţie şi izolare în timp real a celulelor tumorale circulante din fluxul sanguin al bolnavilor de cancer prin metode de procesare de imagine şi pattern recognition*,

•*Learning induced activation of p300 as a possible treatment for oxidative stress in neurons*.

Sunt in curs de derulare proiectele

•*Assessment of the platinum-based drugs effects in colorectal carcinoma with emphasize on tumor stem cells functional genomics and immunomodulation*

•*Activarea redox a moleculelor mici de catre centrii metalici cu relevanta biologica.*

Includerea in reteaua COST CM1201 *Biomimetic Radical Chemistry*

VA MULTUMESC PENTRU ATENTIE