# New Findings in Metal Complexes with Antiproliferative Activity Containing 1,3,5-triaza-7-phosphaadamantane (PTA) and Derivative Ligands.

Franco Scalambra,[a] Pablo Lorenzo-Luis,[b] Isaac de los Ríos[c] and Antonio Romerosa*[a]

**Abstract:** This microreview summarizes some of the most significant findings published in the last years on metal complexes containing PTA and PTA derivatives ligands such as dmoPTA, with antiproliferative activity (PTA = 1,3,5-triaza-7-phosphaadamantane; dmoPTA = 3,7-dimethyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (dmoPTA). If significance, comments on other biological properties of the complexes are also indicated.

## 1. Introduction

The phosphane ligands 1,3,5-triaza-7-phosphaadamantane (PTA)[1] and its derivatives, such as the monometil derivative N-methyl-1,3,5-triaza-7-phosphaadamantane (mPTA) and the 3,7-dimethyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (dmoPTA), are versatile ligands able to coordinate mainly to metals by both its phosphorous and nitrogen atoms (Figure1). The metal complexes containing these phosphanes usually display interesting properties various fields such as catalysis,[2] materials design,[3] and particularly they display significant antiproliferative activity towards different cancer cell lines, including platinum resistant cancer cells. [4–6]

Coordination compounds with metals other than platinum, particularly ruthenium(II)-based complexes, are emerging as promising antiproliferative and antimetastatic agents with potential uses. Since FDA approval in 1978, cisplatin,[7–10] has been used in medical cancer treatment, which is notable as it was the first transition metal complex found to have anticancer activity. It is also worth to stress that cisplatin is effective against cancers such as sarcomas, carcinomas (small cell lung and ovarian cancer), lymphomas, and germ cell tumours. Nevertheless, this platinum complex displays two important issues: the emergence of resistance and toxicity to normal tissues.[11–16] Additionally, cisplatin shows other problems such as: its administration has to be intravenous, its negative side effects and its high price due the low abundance of Pt. These problems have pushed the worldwide researchers to find new active anticancer metal complexes based on cheaper and less

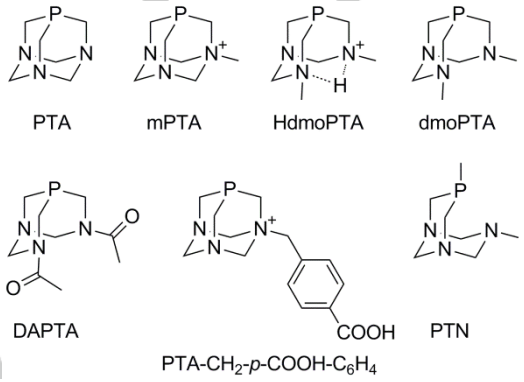



**Figure 1.** Structures of PTA and derivatives named in this paper.

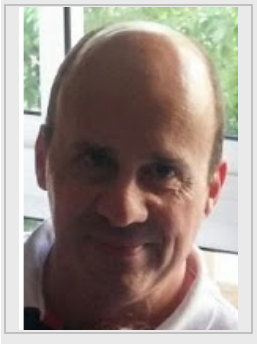
Antonio Romerosa graduated in Chemistry in 1987 (U. of Granada) and received his PhD (U. Autonoma de Barcelona) in January 1992. The same year he undertook a postdoctoral research at the ISSECC CNR (Florence, Italy), now ICCOM CNR, before becoming Lecture Professor (1997) and finally Full Professor (2009) at the University of Almeria (Spain). He has authored of more than 150 papers, 4 books, 9 Spanish and international patents, more than 210 presentations at national and international meetings and supervisor of more than 17 PhD. His research interests range over homogeneous catalysis and organometallic chemistry in water, phosphorus chemistry, photo-inorganic-chemistry, bioinorganic chemistry and natural stones.

Franco Scalambra received the degree in Pharmaceutical chemistry in 2010 (Universitá di Ferrara) and obtained his Ph.D. in 2016 working in the group of Prof. Antonio Romerosa, at the University of Almería, in the field of coordination and organometallic chemistry. He is currently working in the Chemistry and Physics Department of the University of Almería. His main research interests concern the fields of materials, catalysis and bioinorganic chemistry.

[a] Dr. F. Scalambra, Prof. Dr. A. Romerosa, Área de Química Inorgánica-CIESOL. Universidad de Almería, Carretera Sacramento s/n, Almería, Spain. E-mail: fs649@inlumine.ual.es; romerosa@ual.es.

[b] Prof. Dr. P. Lorenzo, Inorganic Chemistry Section, Chemistry Department, Universidad de La Laguna. C/Astrofísico Francisco Sánchez 2, 38206 La Laguna, Spain. E-mail: plorenzo@ull.es

[c] Prof. Dr. Isaac de los Rios Departamento de Ciencia de los Materiales e Ingeniería Metalúrgica y Química Inorgánica, Facultad de Ciencias, Universidad de Cádiz, 11510 Puerto Real (Cádiz), Spain. E-mail: isaac.delosrios@uca.es



Isaac de los Ríos, born in Jerez de la Frontera (Spain) in 1970, studied chemistry at the University of Cadiz and received his Ph.D. in 1997 working under the supervision of Prof. M.C. Puerta and Prof. Pedro Valerga. He then joined the group of Dr. M. Peruzzini at ISSECCC-CNR (Florence, Italy) for a four-years postdoctoral stay. Thereafter, he returned to the University of Cádiz where he is currently "Profesor Titular de Universidad". His research interests cover the activation of alkynes and alkynols by transition metal complexes as well as the coordination chemistryof wáter soluble phosphane and homogeneous catalysis.

Pablo Lorenzo-Luis completes his B.Sc. Degree at La Laguna-University-ULL and he received his Ph.D. from the same University (July 1998) under the supervision of Full Professor P. Gili. Soon after, he moved to ISSECC-CNR-Florence, Italy with Dr. S. Midollini where he worked in the Metal Phosphonate Chemistry. He spent two months (2001) in the same place (now ICCOM-CNR) with Dr. M. Peruzzini conducting basic research on Organometallic Chemistry and Catalysis. He is currently as Lecturer at that University (ULL- Inorganic Chemistry Section from 2004-) and coauthor of more than a sixty scientific papers in peerreviewed journals and he has been supervisor of several Ph.D. students on ruthenium complexes with "Doctor Europaeus Mention".

toxic metals.

The fact that not all of the Pt complexes displayed anticancer activity suggested from the beginning that the selection of adequate ligands is very important to obtain an anticancer active metal complex. Ligands could stabilize a particular metal coordination geometry and oxidation state, and are also very important to determine the complex solubility. Particularly, the hydrophilic/hydrophobic balance is central for the *in vivo* behaviour and efficiency of a metal complex under physiological conditions: it should be soluble enough in water, which is the main component of physiological fluids, but also in organic media to pass through the cellular membrane into the cell.[4–6,17] The ligands PTA and dmoPTA have showed to be excellent to stabilize low valence metal oxidation states and provide an adequate hydrophilic/hydrophobic balance. These ligands are usually stable, easy to be prepared and soluble in water and organic solvents.

There are recent reviews that present comprehensively complexes with PTA and some PTA derivatives.[18-20] Due to their novelty monometallic and heterometallic complexes containing the ligand dmoPTA have not been reviewed until now. This minireview wants to fill this gap by summarizing the published complexes containing dmoPTA and, for the sake of comparison, the most significant metal complexes displaying antiproliferative activity containing PTA and its derivatives.

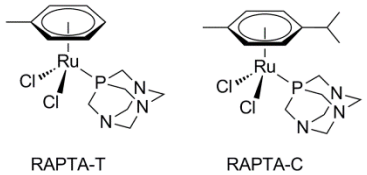
## 2. Complexes with PTA and Derivatives different to dmoPTA

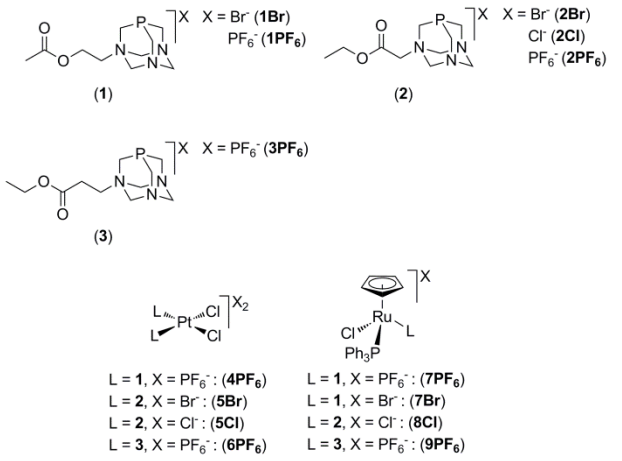
In 2011 Dyson *et al.* showed that is possible to prepare a family of organometallic ruthenium complexes containing PTA with substantial anticancer activity, particularly effective against platinum resistant cancer cells.[4] These complexes, generically named RAPTA (Figure 2), have been exstensively studied, inducing the broad use of the ligand PTA and its derivatives as constituent of antiproliferative and antimicrobial active metal complexes. Nice and recent reviews have been targeted to describe the antiproliferative properties of the complexes containing PTA and its derivatives,[18–20] some of them being mainly focused on RAPTA complexes.[4,21–25]

There are valuable and very interesting examples of very active antiproliferative transition metal complexes containing ligands of the PTA family, being platinum and ruthenium among the most represented metals.[26] Lately new Ru complexes with significant antiproliferative activity including also PTA derivatives, but different to the RAPTA family, have been published. It is worth mention the Pt(II) and Ru(II) complexes *cis*-$[PtCl_2(L)_2]X_2$ (**4-6**) and $[RuCpCl(PPh_3)(L)]X$ (**7-9**) (L = 1, 2, 3, X = Br, Cl, $PF_6$), which contain the PTA derivatives ($PTAC_2H_4OCOMe)X$ (**1**) (X = $Br^-$ (**1Br**), $PF_6^-$ (**1PF$_6$**)), ($PTACH_2COOEt)X$ (**2**) (X = Br; (**2Br**) X = Cl (**2Cl**), X = $PF_6$ (**2PF$_6$**)) and ($PTACH_2CH_2COOEt)X$ (**3**) (X = $PF_6$, **3PF$_6$**). These complexes show comparable antiproliferative activity to cisplatin and salts **1PF$_6$**, **2Cl**, and **3PF$_6$** were also found to interfere with the cholinergic cascade involved in Alzheimer disease. These complexes could also act as carriers for metal ions through the blood−brain barrier, allowing them to act as metallotherapeutics in the central nervous system.[27]

Other attractive complexes are the neutral $[Ru(N–N)(PTA)_2Cl_2]$ (N–N = bpy (**10**), N–N = phen (**11**)), monocationic $[Ru(N–N)(PTA)_3Cl]Cl$ (N–N = bpy (**12**), N–N = phen(**13**)) and, dicationic $[Ru(N–N)(mPTA)Cl_2](BF_4)_2$ (N–N = bpy (**14**), N–N = phen (**15**)) (bpy = 2,2'-bipyridyl; phen = 1,10-phenanthroline; mPTA = N-methyl-1,3,5-triaza-7-phosphaadamantane) (Scheme 1). Complex **11** was found to be the most effective in blocking cell cycle, inducing also necrotic cell death in Multiple Myeloma

**Figure 2.** Structure of RAPTA-T and RAPTA-C.






**Scheme 1.** Structure of Pt and Ru complexes of PTA **7**-**9**. Adapted from ref [27].

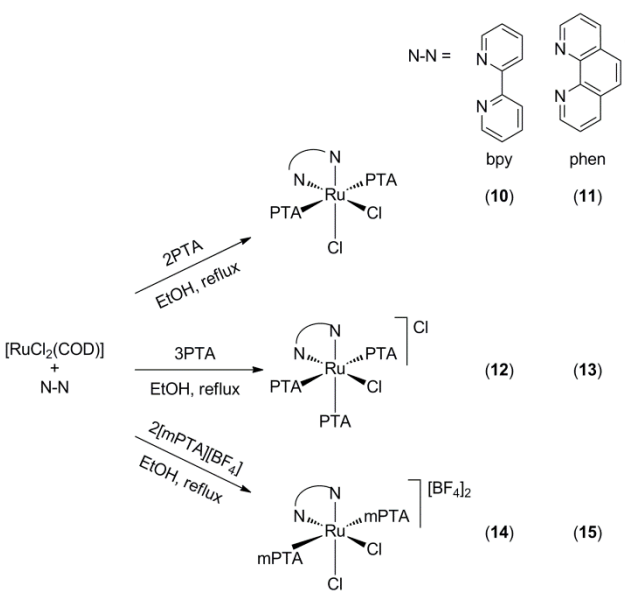
(MM) cell lines.[28] Homeostasis of organisms depends on an intricate balance between cell death and renewal, which could be disrupted by diseases and external agents.

Recently new Pt-PTA complexes (**16**, **17**, Scheme 2) with improved antiproliferative properties have been published.[29–31] It was showed that the co-ligands bonded to the {Pt(2,2-bpy)}$^{+}$ moiety have a large influence on the reaction kinetics of the complexes with biomolecules such as amino acids, proteins, and DNA.[30] The ligand PTA decreases the reactivity of the its metal complexes with biomolecules but increases antineoplastic activity. The final conclusion is that it is possible to fine-tune Pt(II) compounds, targeting different cancer pathways overcoming the side effects associated with cisplatin. In contrast, PTA containing Pt(II) complexes [PtCl(hq)(pta)] (**18**-**25**) (hq = 5-chloro-7-iodo-8-quinolinol (**18**), 8-hydroxy-5-nitroquinoline (**19**), 5,7-dichloro-8-quinolinol (**20**), 5,7-diiodo-8-quinolinol (**21**), 5,7-dibromo-8-quinolinol (**22**), 5,7-dichloro-8-hydroxy-2-methyl-quinoline (**23**), 8-hydroxyquinoline (**24**) and 8-quinolinethiol (**25**)) (Scheme 3) showed good selectivity towards cancer cells with a possible mode-of-action involving the increase of reactive oxygen species (ROS) generation and good embryo toxic profile. Complex [PtCl(5,7-dibromo-8-hydroxyquinolinato)(PTA)] (**22**) was showed to be the most promising complex for therapeutically applications.[31]

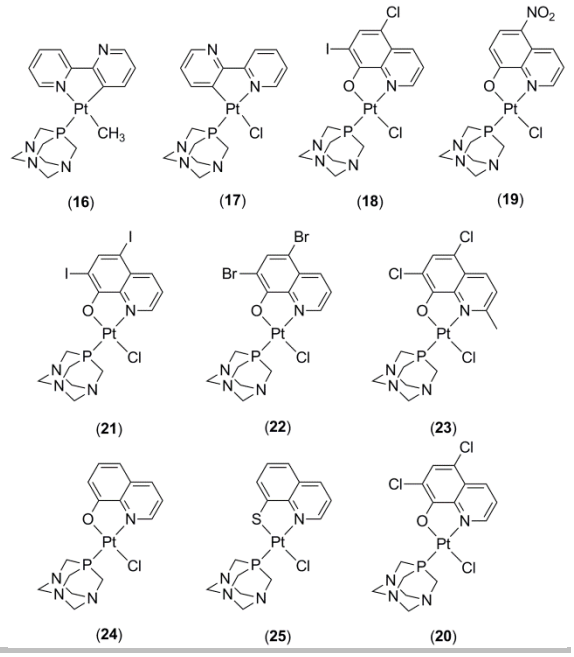
Even if Ru and Pt complexes are the most popular among the antiproliferative metal compounds, the Re-PTA, Re-DAPTA and RE-THP complexes $[Re(CO)_3(NN)(L)]^+$ (**26**-**35**) (NN = diimine ligand; DAPTA = 1,4-diacetyl-1,3,7-triaza-5-phosphabicylco[3.3.1]nonane; THP = tris(hydroxymethyl)phosphine) have been showed to be highly cytotoxic (Scheme 4). It is important to point out that THP-Re and DAPTA-Re compounds display triplet-based luminescence in air-equilibrated aqueous solutions (Φ = from 3.4 to 11.5%), photo substitute one CO ligand (365 nm light; Φ = from 1.1 to 5.5%) and sensitize the formation of $^1O_2$ (Φ = up 70 %). In contrast and interestingly, complexes with PTA are non-emissive and do not undergo photo substitution. Assessment under light of the activity of the complexes against human cervical HeLa, ovarian A2780, cisplatin-resistant ovarian A2780 and CP70 cancer cell lines, showed that THP and DAPTA complexes exhibit a cytotoxic response upon irradiation with minimal toxicity in the absence of light. The complex with DAPTA and 1,10-phenanthroline displayed an $IC_{50}$ value of 6 μM in HeLa cells, which was the highest until that moment.[32]

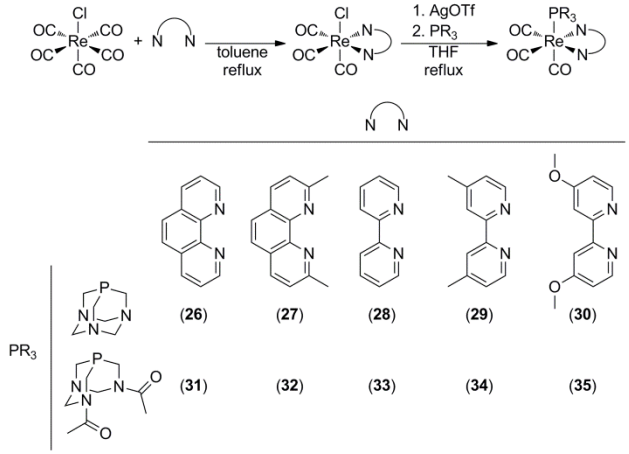
Other interesting antimetastatic compounds are the $[Rh(Cp^*)Cl(X,Y)]^{n+}$ (X, Y = Cl, PTA, n = 0 (**36**); X, Y = en, n = 1; X, Y = acac, n = 0; X, Y = cur, n = 0, where Cp* =

**Scheme 2.** Synthesis and structure of complexes **10**-**15**. Adapted from ref [28]




**Scheme 3**. Structures of complexes 1**6**-**25**. Adapted from ref [31]



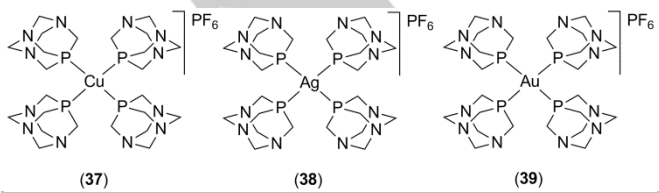



**Scheme 4**. Structure and synthesis of complexes **26**-**35**. Adapted from ref [32].

pentamethylcyclopentadienyl; cur = curcumin; en = 1,2-ethanediamine; acac = 2,4-pentanedionato).[33] These complexes are not more active than cisplatin but they suffered easily ligand-exchange substitution reactions with biomolecules. Unfortunately, complex **36**, which is the only one containing PTA, is not cytotoxic.

It is important to point out that PTA-Cu(I) and PTA-Ag(I) complexes $[M(PTA)_4]^+$ (M = $Cu^+$ (**37**), $Ag^+$ (**38**), Au (**39**)) (Scheme 5) display potential clinical use as antiproliferative agents. The combination of DFT calculations and thermodynamic experimental data was used to estimate the stability constants of the complexes supporting that ligand PTA prefers Cu(I) to the Ag(I). Complexes **37** and **38** dissociate into stoichiometrically-lower species when diluted to the micromolar concentration range, such as it is typical in vitro testing. Complexes $[Cu(PTA)_2]^+$, $[Cu(PTA)_3]^+$ and $[Ag(PTA)_2]^+$ are predicted to be the species involved in the cytotoxic mechanism of these compounds.[34] Complexes **37**, **39** display a high antiproliferative activity for a wide range of solid tumours, also platinum-drug resistant.[35] Complex **39** is neurotoxic, and produces the inhibition of proteasome activity in DRG neurons even at lower concentrations than the $IC_{50}$, while copper complex **37** does not induce neurotoxicity. Experiments In vitro and in vivo showed that copper complex **37** is more active as antiproliferative agent and also show reduced peripheral neurotoxicity profile. Preliminary results obtained from studies made in vivo with mice showed that copper compounds are markedly better tolerated with respect to the reference platinum drugs.[36] Furthermore, the complex $[Cu(THP)_4]PF_6$ displays efficacy in the treatment of Lewis pulmonary tumour in mice in both early and advanced stage treatment schedule.[37]

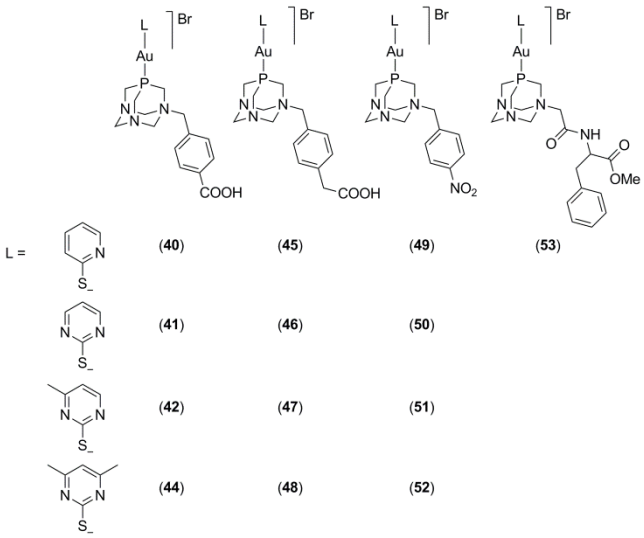
**Scheme 5.** Structure of complexes **37, 38** and **39.** Adapted from ref [34]



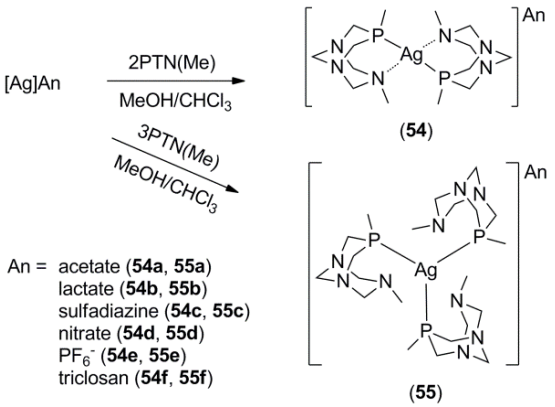

New PTA-thiolate-gold(I) complexes **40**-**53** have showed optimal hydro/lipophilicity properties (Scheme 6).[38] Their activity against Caco-2 cells was found to be very high and similar to that found for auranofin. Interesting, these complexes displayed a very low cytotoxic against enterocyte-like differentiated cells. The stability under physiological conditions was permitted by the thiolate ligands, which confer to the complexes also a larger cytotoxic activity. It is also interesting to point out that the presence of a substituent as $-NO_2$, which is a typical electron-withdrawer, in the benzene-*para* position of these PTA derivatives led to a better stability and lipophilicity but does not improve significantly the antiproliferative activity. The mechanistic studies showed that these complexes induce cell death by arrest of the cell cycle and apoptosis, facilitating the reduction of 5-fluorouracil dose, but also by increasing the intracellular ROS levels. The reason for this last finding was proposed to be the interaction of the complexes with the enzyme TrxR, which produce the modification of the cell the redox balance.

Very attractive antiproliferative water soluble silver complexes were obtained with the PTA derivative 3,7-dimethyl-1,3,5-triaza-7-phosphabicyclo[3.3.1]nonane (PTN) (**54(a-f)**-**55(a-f**)) (Scheme 7).[39] The ligand PTN was found to be P,N bidentate when only two ligands are coordinated to the metal, while only P-mono-coordination to the metal center was observed for complexes with three ligands. The silver complexes, in which the ligand is bis-coordinated, decompose under air but also under visible light irradiation also in inert atmosphere. Nevertheless, parent tris-ligated complexes display greater stability both under air and particularly to photodecomposition. Single crystal X-ray structure of **54** and **55** showed that, as expected, there is a strong bond between silver and the phosphorus atom but a very weak bond with the terminal nitrogen atom, particularly in the bis-ligated complexes **54b** and **54e**. The crystal structure of **55d** is

**Scheme 6.** Structure of complexes **40**-**53**. Adapted from ref [38]



constituted by a silver bonded by a pseudo $\kappa^2$-P,N binding mode. Density functional theory (DFT) studies revealed that the bi-substituted PTN-Ag(I) species are characterized by a total enthalpy for the tetrahedral C2-symmetric structure, marginally lower by −0.6 kcal mol$^{-1}$ than that for the planar C2h structure. This results were analogous to that found for the parente $\{Au(PTN)_2\}^+$ complex ($\Delta H$ = −0.5 kcal mol$^{-1}$).




**Scheme 7.** Synthesis and structure of **54** and **55**. Adapted from ref [39].

The antimicrobial and antifungal activity of these complexes were evaluated using the agar well diffusion test. The activity was found to be correlated with the counterion nature, being silver complexes with the deprotonated triclosan as the counterion the most active. Complexes containing triclosan showed the best activity but complexes **54f** and **55f** showed to have similar or higher activity than triclosan, depending on the microorganism tested. The study shows how the metal nature is important for obtaining an adequate antibacterial activity but also the presence of the triclosan anion is an important factor for obtaining a high anti-microbial activity.

In addition to the monometallic complexes containing PTA, also polymetallic complexes with antiproliferative and antimicrobial activity were described,[40–42] but they were included and discussed in the previously indicated reviews. Nevertheless, it is worth to mention that studies targeted to evaluate their stability in physiological conditions have not been performed yet and therefore there is scarce knowledge on the real antiproliferative active species.

## 3. Complexes with dmoPTA

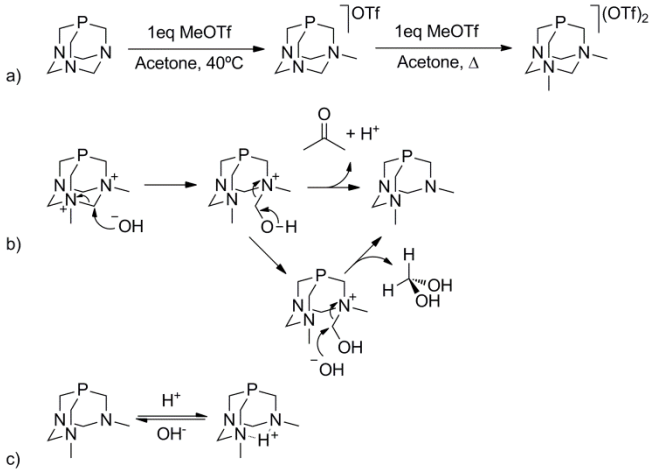
### 2.2. Heterometallic Complexes

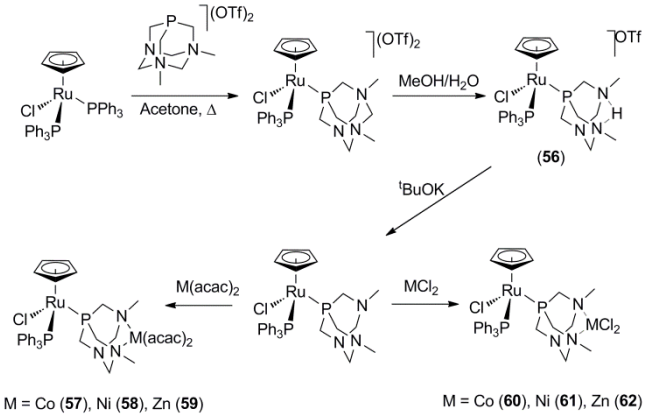
As indicated in the introduction, researchers are looking for new PTA derivatives with similar but specifically tuned properties.[18,20,43] A huge number of new ligands derived from PTA have been synthesized and some representative metal complexes obtained. Nevertheless, there are few examples of bi-functionalization of the PTA at the two N,. In particular, mono-methylation of PTA on one N is a trivial reaction but multi-methylation, usually yields a mixture of compounds.[12–15,44] Finally, the bi-N-methylated PTA, N,N'-dimethyl-1,3,5-triaza-7-phosphaadamantane (dmPTA), and its derivative 3,7-H-3,7-dimethyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (HdmoPTA) weres obtained by reaction of PTA with 2 equiv of $Me(CF_3SO_3)$ in refluxing acetone (Scheme 8).[45,46] The ligand dmPTA is soluble in water and organic solvents such as $CDCl_3$, acetone, etc., and it is stable enough in non protic solvents. Nevertheless, in presence of protic solvents such as EtOH, MeOH or $H_2O$, the ligand dmPTA suffers the elimination of the $CH_2$ group between the $N_{CH3}$ atoms giving rise to the new HdmoPTA, which can be isolated as tetrafluoroborate salt by reaction with $HBF_4$. This ligand can be easily deprotonated and the resulting neutral phosphane-amine 3,7-dimethyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (dmoPTA) is able to coordinate metals by the soft P but also through the two hard $N_{CH3}$ atoms, behaving in the latter case as a chelate (Scheme 8).[44] The ligand dmoPTA is somewhat soluble in water but displays good solubility in organic solvents such as $CHCl_3$, acetone, toluene, etc.

The reaction of dmPTA$(CF_3SO_3)_2$ with $[RuClCp(PPh_3)_2]$ in refluxing acetone/MeOH/water, gives the yellow complex $[RuClCp(1\kappa P\text{-HdmoPTA})(PPh_3)](OSO_2CF_3)$ (**56**), which was the first component of the the so-called 1$^{st}$ generation of complexes containing the ligand dmoPTA (Scheme 9).[46]

The proton between both $N_{CH3}$ atoms in **56** can be removed easily using a 0.01 M KOH water solution or $^t$BuOK in MeOH at room temperature, which gives the option to the ligand to coordinate a second metal through the $N_{CH3}$ atoms. In fact, The distance between the methylated nitrogens (2.702(12) Å) is adequate to chelate a metal without inferring significant distortion to the dmoPTA cage. Therefore the ligand could be coordinated through the P and $N_{CH3}$ atoms. The reaction of **56** with $^t$BuOK and $M(acac)_2$ in methanol leads to the bimetallic complex $[RuClCp(PPh_3)\text{-}\mu\text{-dmoPTA-}1\kappa P{:}2\kappa^2 N,N'\text{-}M(acac\text{-}\kappa^2 O,O')_2]$ (M = Co (**57**), Ni (**58**), Zn (**59**)) in which the dmoPTA is bonded to the Ru by the P and by the $N_{CH3}$ to the metal M (Figure 3, Scheme 9).[47,48]

**Scheme 8.** a) Synthesis of dmPTA; b) Formation of dmoPTA from dmPTA; c) acid/base equilibrium dmoPTA/HdmoPTA.






**Scheme 9.** Synthesis of **56-62**.

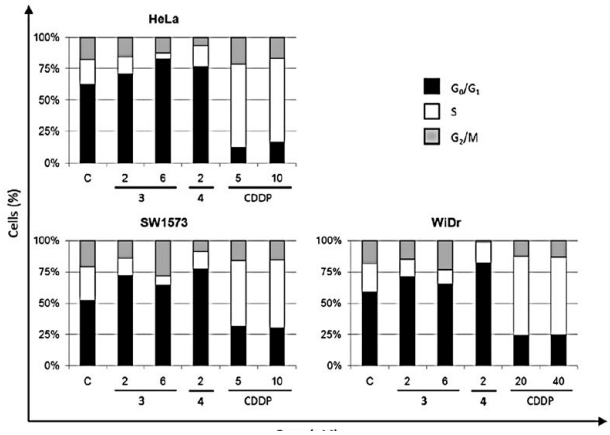


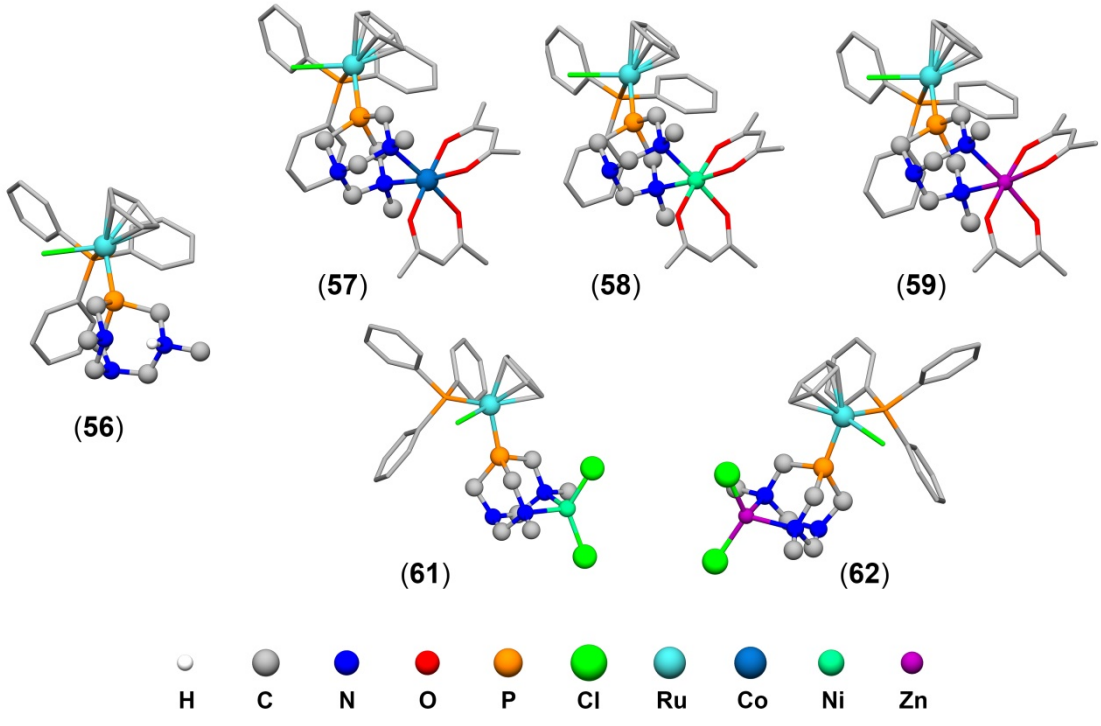

**Figure 4.** Cell cycle phase distribution of untreated cells (C) and cells treated with Ru(II) complexes **55–58** and cisplatin (CDDP) for 24 h. Adapted from ref [16]

Interestingly, complex Ru-redox properties depend on the metal bonded to the atoms $N_{CH3}$, which could be a consequence of steric but mainly due to electronic effects. Therefore, the unit {dmoPTA-$\kappa^2$N,N'-M}$^{m+}$ can be considered as a new ligand derived from PTA, whose properties can be tuned by the appropriate selection of the metal, its oxidation state and its ancillary ligands.

Monomeric Ru complex **56** and bimetallic Ru-M complexes **57**-**58** inhibit cell proliferation of human solid tumour cell lines with a better activity profile (Table1) than the standard anticancer drugs cisplatin, NAMI-A, KP1019 and RAPTA complexes (Scheme 1). Additionally, cell cycle analysis points out that the new Ru(II) complexes act by a different action mechanism than cisplatin as cell cycle arrest in G1 and there is an absence of interaction with DNA (Figure 4).[16] Nevertheless, the exact biological target has not been identified yet.

To have more information on how the metal bonded to the dmoPTA-$N_{CH3}$ atoms modulate the chemical properties of the {RuCpCl(dmoPTA)($PPh_3$)}-moiety, the new bimetallic complexes

**Figure 3.** Representation of the crystal structures of complexes 55-61. Adapted from ref [45-49].



[RuClCp($PPh_3$)-μ-dmoPTA-1κP:2κ$^2$N,N′-$MCl_2$] (M = Co (**60**), Ni (**61**) and Zn (**62**)) were synthesized (Scheme 9), which contain the simple and more reactive {$MCl_2$} unit, by a procedure similar to that used for synthesizing the bimetallic complexes **57**-**59**.[49] These complexes showed similar properties than those with acac,[45] particularly the ruthenium atom of the {RuCpCl(dmoPTA)($PPh_3$)}-moiety was found to have a clear sensitiveness to the metal bonded to $N_{CH3}$ but also to the ligands bonded to this metal. Therefore the unit {dmoPTA-κ$^2$N,N'-$MX_2$} can be considered such as a family of ligands with properties related but different than those for dmoPTA. This finding open the door to obtain new ligands with very precise tuned properties by a clever selection of metals (M) and its ancillary ligands (X).

The antiproliferative activities of compounds **60-62** were studied in the panel of human solid tumour cells HBL-100, HeLa, SW1573, and WiDr (Table 1). Compounds containing {$CoCl_2$} (**59**) and {$NiCl_2$} (**60**) units showed somewhat more potent activity than the Ru-$ZnCl_2$ (**61**). Nevertheless, all complexes induce growth inhibition in all cell lines with $GI_{50}$ values in the range 0.8–6.5 μM, which are clearly better than those for cisplatin. It is important to stress that the activity is particularly high against the breast T-47D and the colon WiDr cells that are less sensitive to cisplatin. The results point out that the three compounds are active in both drug-sensitive (HBL-100) and drug-resistant (T-47D and WiDr) cell lines.

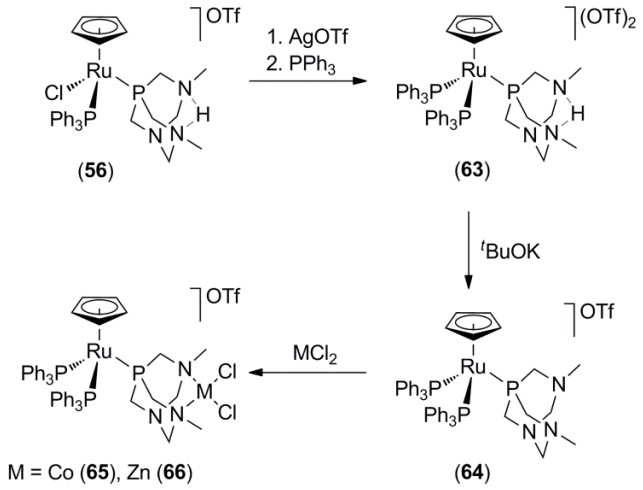
It was determined that Ru-$CoCl_2$ (**60**) and Ru-$NiCl_2$ (**61**) complexes are transformed quickly in a DMSO–water mixture into [RuClCp(dmoPTA)($PPh_3$)]$^+$ by releasing the {$MCl_2$} unit. These experimental facts suggested that antiproliferative activities of **60** and **61** are probably due to the released [RuClCp(dmoPTA)($PPh_3$)]$^+$ cationic complex. In contrast, the complex Ru-$ZnCl_2$ (**62**) was found to be stable enough over the antiproliferative experiment time, being the amount released of the cationic complex [RuClCp(dmoPTA)($PPh_3$)]$^+$ non-significant. These results suggest that the observed activity should be associated exclusively to the action of the bi-metallic complex. This suspicion was confirmed by the fact that the antiproliferative activity of **63** is similar but somewhat larger than those for starting complex [RuClCp(HdmoPTA)($PPh_3$)]($OSO_2CF_3$) and former bimetallic complexes containing acac (**57**-**59**), which are stable enough in a DMSO–water mixture.

To elucidate whether the exchange of the chlorine bonded to the ruthenium is implicated in the antiproliferative activity of this family of complexes and therefore has some importance in the action mechanism as observed for platinum complexes, this ligand was substituted. The phosphane $PPh_3$ was selected as substituted of the Cl as it is a stable ligand that usually is strongly bonded to the Ru and could provide extra lipophilic solubility to the final complex, as well as it can be easily studied by $^{31}$P NMR.

Abstraction of the chloride in [RuClCp(HdmoPTA)($PPh_3$)]($OSO_2CF_3$) by $AgCF_3SO_3$ and further reaction with one mole of $PPh_3$ leads to the complex [RuCp($PPh_3$)$_2$(HdmoPTA-1κP)]($CF_3SO_3$)$_2$ (**63**), which as

| Complex | A549 (lung) | HBL-100 (breast) | T-47D (breast) | SW1573 (lung) | HeLa (cervix) | WiDr (colon) | $E_{½}$ Ru(II)/Ru(III) (mV) | $^{31}$P{$^1$H} NMR (dmoPTA) δ(ppm) | Solvent |
|---|---|---|---|---|---|---|---|---|---|
| **56** | | | 1.9 (±0.5) | 1.5 (±0.1) | 2.6 (±0.2) | 1.7 (±0.4) | 710(5) | -2.93 | $CD_3OD$ |
| **57** | | | 1.9 (±0.1) | 1.4 (±0.2) | 2.3 (±0.6) | 1.5 (±0.4) | 915(5) | 51.56 | $CD_3OD$ |
| **58** | | | 2.0 (±0.3) | 1.4 (±0.1) | 2.5 (±0.1) | 1.6 (±0.2) | 812(5) | 62.6 | $CDCl_3$ |
| **59** | | | 2.3 (±0.6) | 1.4 (±0.4) | 2.6 (±0.3) | 2.6 (±0.3) | 900(5) | -0.93 | $CDCl_3$ |
| **60** | | | 1.4 (±0.2) | 1.1 (±0.1) | 1.3 (±0.1) | 1.5 (±0.3) | 840(5) | 277 | $CDCl_3$ |
| **61** | | | 1.2 (±0.2) | 1.0 (±0.1) | 1.4 (±1.1) | 1.1 (±0.2) | 770(5) | 152 | $CDCl_3$ |
| **62** | | | 6.5 (±3.0) | 4.6 (±0.1) | 4.0 (±0.1) | 5.7 (±1.4) | 798(5) | 2.56 | $CDCl_3$ |
| **63** | 0.29 (0.09) | 0.21 (0.04) | 0.25 (±0.04) | 0.20 (±0.02) | 0.17 (±0.04) | 0.20 (± 0.03) | | 38.40 | $CDCl_3$ |
| **64** | 0.062 (0.019) | 0.088 (0.008) | 0.33 (±0.01) | 0.19 (±0.05) | 0.19 (±0.05) | 0.27 (0.03) | | -7.42 | $CDCl_3$ |
| **65** | 0.036 (0.019) | 0.072 (0.008) | 0.21 (±0.05) | 0.054 (±0.013) | 0.084 (±0.022) | 0.065 (±0.010) | | 211.35 | $CDCl_3$ |
| **66** | 0.14 (0.02) | 0.32 (0.03) | 0.083 (±0.05) | 0.030 (±0.013) | 0.051 (±0.022) | 0.054 (±0.010) | | –15.10 | $CDCl_3$ |
| **cisplatin** | | | 1.5 (±2.3) | 3.0 (±0.4) | 2.0 (±0.3) | 2.6 (±5.3) | | | |

**Table 1.** $GI_{50}$ of complexes **56-66** compared to cisplatin. Adapted from ref [45-50,52,53].



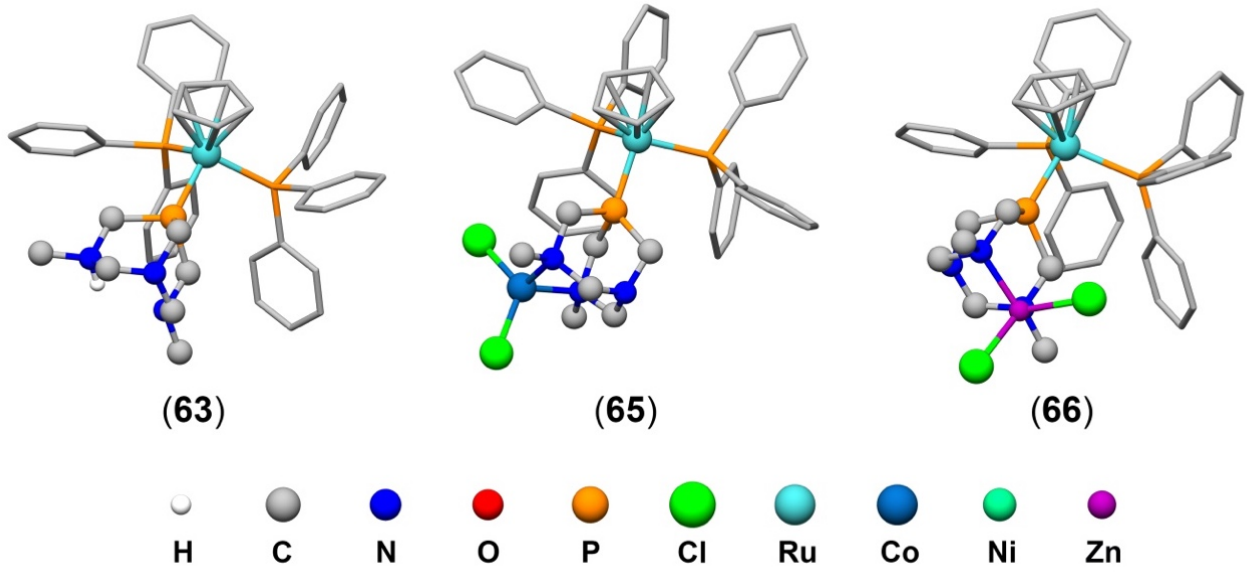

**Scheme 10.** Synthesis of complexes **63-66**.

expected is more soluble than **56** in organic solvents (Scheme 10). Nevertheless, in contrast with the first expectations, this complex showed a substantial enhancement of the antiproliferative activity with respect to the starting complex **56**, constituting the first component of the so-called 2nd generation of this family of complexes containing dmoPTA.[50] The obtained $GI_{50}$ values, for the same panel of tumour cancer cells, which are given in Table 1, show that this compound displays a bigger antiproliferative activity than those for cisplatin and RAPTA complexes (in the range 0.17−0.29 μM). Noteworthy differences between the antiproliferative activity of **63** and cisplatin were observed for T-47D (*ca*. 70:1) and WiDr (>100:1) cells, which are the more cisplatin-resistant cellular lines. The cell cycle phase distribution of this complexes studied by flow cytometry[51] showed to be clearly different to that for cisplatin (Figure 4). Cell cycle experiments discarded DNA as the main biological target of these complexes. The charge density calculation of the complex **63** with density functional theory (DFT) showed that the electronic distributions in the monometallic Ru complexes of the first and second complex generations are similar and could not justify the large antiproliferative activity differences found between them. The calculation results suggest that there are not probable interactions between the complexes and the negatively charged cell membrane.

The experimental results indicate that the antiproliferative activity of **56** is not dependent on the substitution of the Cl by another ligand, such as a DNA or other bio-molecules. This conclusion opens the door to obtain a large library of complexes probably with larger and tuned antiproliferative activity by substitution of the Cl in **55** by other ligands with different electronic and steric properties and solubility. It is evident that the next step to be accomplished was the synthesis of the biheterometallic complexes by coordination of a metal unit to dmoPTA-$NCH_3$, expecting that these bimetallic complexes showed higher antirproliferative activity than the starting monometallic Ru complex **63**. All the presuntions were confirmed by the synthesis of the new bimetallic Ru-Co complex $[RuCp(PPh_3)_2$-μ-dmoPTA-1κP:2κ$^2$N,N'-$CoCl_2](OTf)\cdot 0.25H_2O$ (**65**) that was obtained by reaction of **63** with potassium terbutoxide (T-butOK), providing the deprotonate complex **64**, and further reaction with $CoCl_2\cdot 6H_2O$ in MeOH (Scheme 10).[52] The antiproliferative activity of this complex was found to be much better than that for starting complex. Similarly to that observed for starting complex **63**, the Ru-Co complex **65** produces the accumulation of cells in the G1 phase of the cell cycle (Table 1), which indicates that both complexes show a comparable mechanism of action against the studied cell lines.

The Ru-Co complex **65** in DMSO-$d_6$ at room temperature releases in short time (10 min) the $\{CoCl_2\}$ unit and the deprotonated complex $\{RuCp(PPh_3)_2(dmoPTA)\}^+$. Quick addition of water (or cell culture) avoids the fast release of the $\{CoCl_2\}$ unit. In this mixture of solvents, the complete release of this moiety is obtained in 2 hours at 40 °C. The elimination of $PPh_3$ was also observed, but after more than one day only a 5% of the

**Figure 5.** Representation of the crystal structures of **62**, **64** and **65**. Adapted from ref [50, 52,53]



phosphine was eliminated. Interestingly, it was also reported that, in a lipophilic environment as the solvent $CDCl_3$, the complex releases $PPh_3$ for first and then the $\{CoCl_2\}$ moiety.

The obtained experimental results suggested that inside the cell the $\{CoCl_2\}$ moiety, which is inactive outside, act as an antiproliferative agent and/or synergize the activity of the other released product such as the $\{RuCp(PPh_3)_2(dmoPTA)\}^+$ complex and the ligand $PPh_3$. The authors propose that the complex could work as a "Trojan horse" to introduce all these compounds into the cell. As a conclusion, it is evident that the combination of the metal units containing Ru and Co in the complex leads to a significant enhancement of the antiproliferative activity of both metal units. When Cl is in the medium, cationic complex $\{RuCpCl(PPh_3)(dmoPTA\text{-}1\kappa P)\}^+$ was also observed. Protonation/deprotonation of this complex showed to have a non-significant influence on its antiproliferative activity, as it was similar than that for deprotonated complex **64** (Table 1).

The last published example of this second generation of bimetallic compounds containing dmoPTA is the Ru-Zn complex $RuCp(PPh_3)_2$-μ-dmoPTA-1κ*P*:2$\kappa^2$*N,N'*-$ZnCl_2](CF_3SO_3)$ (**66**).[56] This compound was initially synthetized by a procedure similar to that used for previously described bimetallic complexes, but it was revelled to be not good enough as is very sensitive to reaction conditions.[53] A new synthetic procedure was designed from the complex $[RuCp(PPh_3)_2(1\kappa P\text{-dmoPTA-})](CF_3SO_3)$ (**64**), which was synthetized by reaction of starting complex **63** with 1.1 equivalent of t-ButOK in THF (Scheme 10). The deprotonated complex is stable in solid state for months and soluble in organic solvents such as $CHCl_3$. Reaction of this complex with $ZnCl_2$ in EtOH provide the Ru-Zn complex **66** by a robust method (Scheme 10).

The new Ru-Zn complex (**66**) displays a better activity (1.2-2.5 times) than the sibling Ru-Co and much better (26-426 times) than cisplatin. Remarkably, complex **66** is alo 3-8 times more active against the tumour cell lines than against the tested non-tumour cell line (non-tumour human cell line BJ-hTert) while starting monometallic deprotonate complex **64** shows similar toxicity against tumour and non-tumour cells. Complex **66** is significantly more stable than **65** complex. Therefore, stability studies suggest that the observed higher antiproliferative activity of **66** should be consequence of its bimetallic nature and the adequate combination of metals.

The structure of the published complexes containing the ligand dmoPTA are similar (Figure 3 and 5). The ligands are disposed around the Ru with a piano-stool disposition constituted by a $\eta^5$-Cp, a Cl (or $PPh_3$), a $PPh_3$ and a dmoPTA bonded by the P atom. The bimetallic complexes substituted the H bonded to the dmoPTA-$N_{CH3}$ atoms by a metal unit. Selected bond lengths and angles for these complexes are included in Table 2. The $^{31}P$ NMR chemical shift for the dmoPTA ligand is also includes in Table 2. The chemical shift shows if the complexes are monometallic or bimetallic and the magnetic nature of the metal bonded to the dmoPTA-$N_{CH3}$ atoms.

Complexes containing dmoPTA have showed a very high antiproliferative activity, being the Ru-Zn complex **66** the most active of the family synthesized until now. This complex is also one of the most antiproliferative complexes among those published, and also displays a significant selectivity between tumour and non-tumour cells. Considering that the number of complexes containing the ligand dmoPTA is still scarce and there are a large amount of possible combinations of metal and ancillary ligands, new compounds with improve properties are expected to be obtained in short future.

## Conclusions

Despite the large time from the discovery of cisplatin and the intense research devoted to find new compounds with improved antiproliferative properties, and the large number of interesting complexes synthesized and studied; there are not any valuable

| | **55** | **56** | **57** | **58** | **60** | **61** | **62** | **64** | **65** |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | **Bond Lengths (Å)** | | | | |
| Ru-Cp | 2.221(9)[b] | 2.183(12)[b] | 1.839(1) | 1.855(1) | 1.853(2) | 1.845(5) | 2.239(5)[b] | 1.893 | 1.894 |
| Ru-P($PPh_3$) | 2.291(3) | 2.316(3) | 2.312(2) | 2.321(2) | 2.297(7) | 2.295(1) | 2.3895(11)<br>2.3660(11) | 2.370(9)<br>2.378(4) | 2.3527(11)<br>2.3998(11) |
| Ru-P(dmoPTA) | 2.277(3) | 2.436(3) | 2.288(2) | 2.2943(19) | 2.279(7) | 2.276(2) | 2.3207(11) | 2.319(7) | 2.3148(10) |
| Ru-Cl | 2.447(2) | 2.436(3) | 2.4410(19) | 2.448(2) | 2.445(7) | 2.447(2) | | | |
| | | | | | **Angles (º)** | | | | |
| N-M-N | | 81.8(3) | 83.2(2) | 80.9(2) | 91.40(9) | 91.10(18) | | 91.92(11) | 90.16(15) |

**Table 2.** Selected bond distances and angles for complexes **56**-**66**. Adapted from ref [45-50,52,53].

alternative with metals different to platinum that finally can be used as medicine drugs for the treatment of cancer. New metal complexes useful in medicine have to be still synthesized, which have to display also selective and improve antiproliferative properties, with lower side effects, with an easier and less intrusive administration. Additionally, these new complexes have to be easily available to all population and therefore they should be obtained by easy and cheap procedures. Complexes containing PTA and its derivatives, particularly the dmoPTA, are among the most promising new compounds that could give answers to these requirements.

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**Keywords:** PTA, dmoPTA, metal complexes, antiproliferative activity, cancer.

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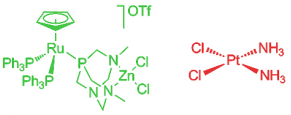
Layout 1:

## MINIREVIEW

Recent significant findings on antiproliferative active PTA, PTA derivatives and dmoPTA-metal complexes are summarized (PTA = 1,3,5-triaza-7-phosphaadamantane; dmoPTA = 3,7-dimethyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (dmoPTA).




| | $GI_{50}$ (μM) | |
|---|---|---|
| T-47D | 0.083 (±0.05) | 1.5 (±2.3) |
| SW1573 | 0.030 (±0.013) | 3.0 (±0.4) |
| HeLa | 0.051 (±0.022) | 2.0 (±0.3) |
| WiDr | 0.054 (±0.010) | 2.6 (±5.3) |

**PTA, dmoPTA, PTA derivatives, metal complexes, antiproliferative activity, cancer.**

*Franco Scalambra, Pablo Lorenzo-Luis, Isaac de los Rios, Antonio Romerosa**

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**Antiproliferative PTA Complexes.**