



HAL
open science

Synthesis and structural characterization of benzyl-functionalized N-heterocyclic carbene platinum complexes: Dramatic substituent effect on anti-cancer activity

Georges Dahm, Mathilde Bouché, Corinne Bailly, Lydia Karmazin, Stéphane
Bellemine-Lapponnaz

► To cite this version:

Georges Dahm, Mathilde Bouché, Corinne Bailly, Lydia Karmazin, Stéphane Bellemine-Lapponnaz. Synthesis and structural characterization of benzyl-functionalized N-heterocyclic carbene platinum complexes: Dramatic substituent effect on anti-cancer activity. *Journal of Organometallic Chemistry*, 2019, 899, pp.120908. 10.1016/j.jorganchem.2019.120908 . hal-02330381

HAL Id: hal-02330381

<https://hal.science/hal-02330381>

Submitted on 23 Oct 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Synthesis and structural characterization of benzyl-functionalized N-heterocyclic carbene platinum complexes: dramatic substituent effect on anti-cancer activity.

by

Georges Dahm,^a Mathilde Bouché,^a Corinne Bailly,^b Lydia Karmazin,^b Stéphane Bellemin-Laponnaz*^a

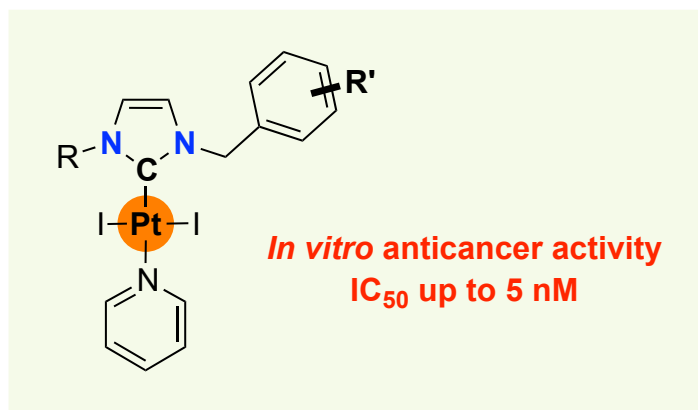
^a Institut de Physique et Chimie des Matériaux de Strasbourg, Université de Strasbourg-CNRS UMR 7504, 23 rue du Loess, BP 43, 67034 Strasbourg cedex 2, France. Fax: +33 (0)388107246; Tel: +33 (0)388107166; E-mail: bellemin@unistra.fr

^b Service de Radiocristallographie, Fédération de Chimie « Le Bel » FR2010, 1, rue Blaise Pascal, 67008 Strasbourg, France.

Abstract

A series of platinum(II) complexes bearing N-heterocyclic carbene NHC ligands functionalized by various benzyl moieties were synthesized and characterized. The molecular structure of two complexes has been confirmed by X-ray diffraction studies on single crystals. Investigation of *in vitro* cytotoxic activities against various cancer cell lines revealed a strong substituent effect: IC_{50} as low as 0.005 μ M were obtained depending on the substituent on the benzyl moiety.

Graphical abstract



1. Introduction

N-Heterocyclic carbenes (NHCs) are neutral ligands defined as singlet carbenes, in which the divalent carbenic center, possessing 6 valence electrons, is connected directly to at least one nitrogen atom within the heterocycle.^[1] The ease of synthesis and versatility of NHCs have contributed to their recognition as ubiquitous ligands in organometallic chemistry as evidenced by their wide use ranging from homogeneous catalysis to material sciences.^[2] More recently, several groups pointed out the importance of N-heterocyclic carbene ligands as new structures for the development of metallodrugs.^[3,4] Indeed, the high stability of the corresponding complexes and the ease of derivatization of the NHC-ligands make them suitable candidates for drug development.^[5] In addition to their antimicrobial properties, NHC complexes have been highlighted as promising agents for anticancer applications. For this purpose, several metals have been studied, especially gold, silver, copper, palladium and platinum, displaying antitumor activities through various mechanisms that differ from the cisplatin used in clinics.^[6]

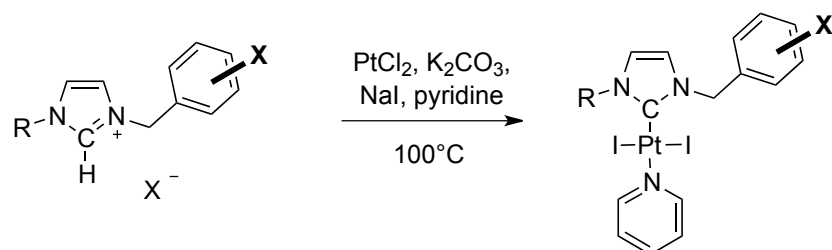
In 2010, Marinetti and coworkers demonstrated the efficiency of *trans*-configured platinum complexes of general formula (NHC)PtX₂(L) (with L = amine) against cancer cell lines.^[3b] Cytotoxicity was investigated on leukemia cells and lung cancer cells and showed that most complexes exhibit similar or higher activities than cisplatin⁷ against both cell lines. Further investigations on cisplatin resistant cells from human ovarian cancers showed better activities than cisplatin and oxaliplatin. Altogether, these results demonstrate the potency of *trans*-Pt(II)-NHC complexes as anticancer agents. Indeed, despite the fact that *trans*-platinum complexes have for long time been overlooked due to the low activity observed with transplatin,^[8] recent work in the area showed the ability of *trans*-Pt-NHC complexes to induce cytotoxic activities (even on cisplatin resistant cells), which may indicate a different mechanism of action than cisplatin.

Soon after, Marinetti^[3b] and others^[9,10,11] investigated the effect on cell activity of several N-heterocyclic carbene platinum complexes. These studies established that both the nature of the NHC backbone and the amine that is *trans*-coordinated to the carbene might influence the cytotoxic activity of the corresponding Pt complex. In the search for more potent species, we investigated the effect of the nature of the N-benzyl substituent onto the carbene, while keeping all substituents identical (*i.e.* iodide and pyridine ligands). Indeed, Tacke and collaborators already pointed out in early 2010 that benzyl-substitution on Ag, Au, Cu or Ru NHC complexes could positively influence their biological activities.^[12] We report here that little change on the benzyl moiety (*i.e.* introducing *p*-NO₂ or *p*-Br for example) can significantly enhance the cytotoxicity of the complexes.

2. Result and discussion

All imidazolium salts were prepared using standard and well-established synthetic procedures.¹³ All platinum complexes were then prepared by reaction of the imidazolium salt in the presence of platinum dichloride, excess NaI and K₂CO₃ in dry pyridine at 100°C overnight, under nitrogen atmosphere (Scheme 1). The (NHC)PtI₂(pyridine) complexes were purified by flash chromatography on silica with pentane/dichloromethane as eluent. Figure 1 displays the molecular structures of all complexes. The 4-position of the benzyl moiety was functionalized with either bromo, nitro or formyl substituents, leading to complexes **2**, **3** and **4**, respectively. The platinum complex **5** contains polyethylene glycol chains that may increase the solubility of the system in aqueous media. Complexes **6** and **7** were substituted with 9-methylanthracenyl or 1-methylpyrenyl moieties. Compound **8** is a trinuclear platinum complex whereas complexes **9** and **10** have identical substituents on both nitrogen atoms (*i.e.* 4-nitrobenzyl and 9-methylanthracenyl, respectively). Isolated yields are ranging from ca. 85-90 % (complexes **2**, **3**) to ca. 20 % (complexes **4**, **5** and **8**). The yield for Pt complex **4** is

found surprisingly low (19 %). This result may be due to the presence of the benzaldehyde moiety that may react with the free carbene (benzoin-type reactivity). Starting from $\text{PtCl}_2(\text{COD})$ as precursor, compound **4** was obtained in 80 % yield. The greater solubility of this platinum source may allow the quick trapping of the *in situ* formed carbene, thus preventing side reactions due to the presence of the aldehyde moiety.



Scheme 1. General synthesis of the platinum pyridine NHC complexes.

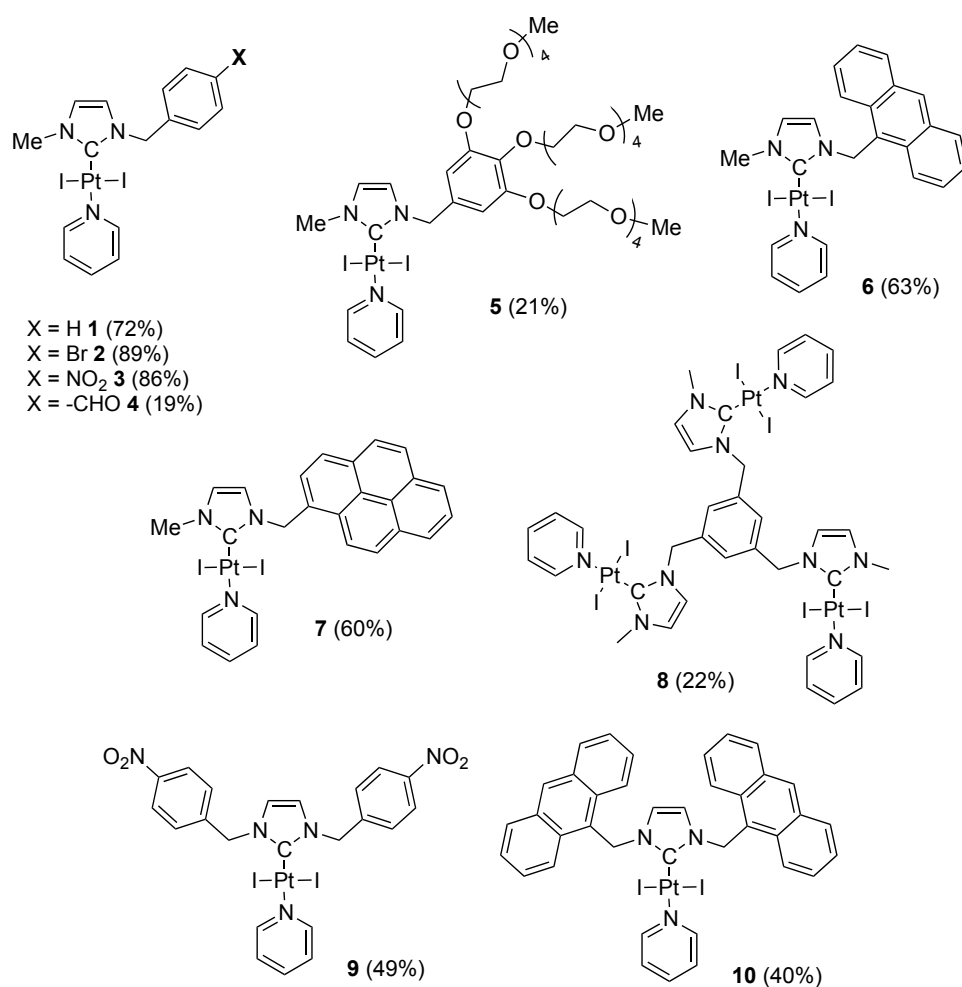


Figure 1. Molecular structure of the platinum pyridine NHC complexes and complexation yield.

The formation of the (NHC)Pt-pyridine complexes was confirmed by the typical appearance of a signal at δ 135-143 ppm in the ^{13}C NMR spectrum, which was assigned to the carbenic carbon, and also by the absence of the resonance peak from the *2H*-imidazolium proton in the ^1H NMR spectrum. The molecular structures of compounds **3** and **7** were determined by X-ray diffraction studies (Figures 2 and 3). The platinum center displays a classical square planar geometry where the pyridine is located *trans* to the carbene. The NHC-platinum bond lengths are 1.974(3) Å and 1.969(6) Å, whereas the metal-pyridine bond lengths are 2.089 Å in both cases.^{3b,14}

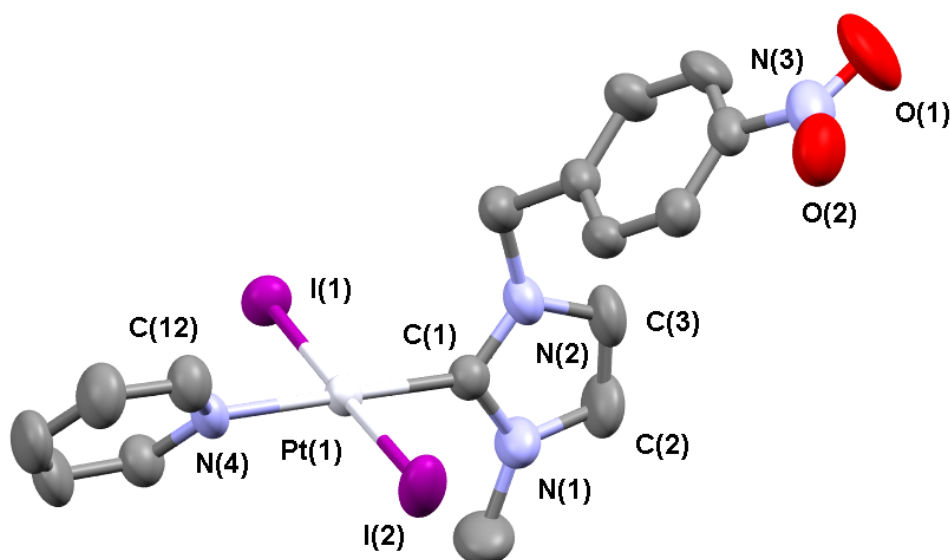


Figure 2. Molecular structure of complex **3**. Selected bond distances (Å) and angles (deg): C(1)-Pt(1), 1.974(3); Pt(1)-N(4), 2.089(3); Pt(1)-I(1), 2.5887(3); Pt(1)-I(2), 2.5979(3); N(2)-C(1)-N(1), 105.2(3); N(4)-Pt(1)-I(1), 89.70(7); N(4)-Pt(1)-I(2), 90.69(7); I(1)-Pt(1)-I(2), 178.436(9); C(1)-Pt(1)-N(4), 178.85(12); C(12)-N(4)-C(1)-N(2), -43.0(3); I(1)-I(2)-C(1)-N(4), -1.9(4).

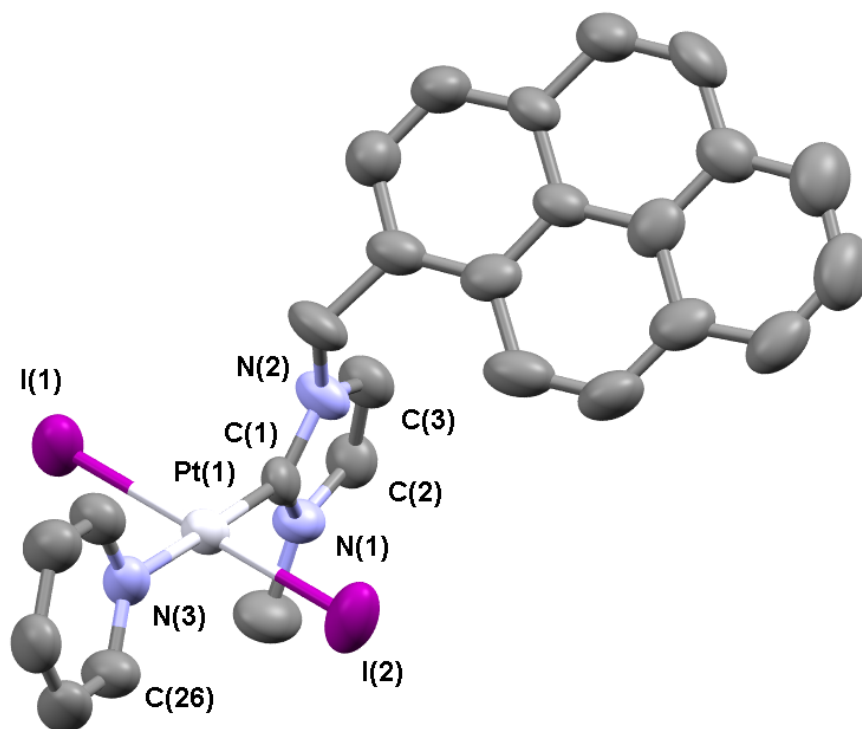


Figure 3. Molecular structure of the Pt complex **7**. Selected bond distances (Å) and angles (deg): C(1)-Pt(1), 1.969(6); Pt(1)-N(3), 2.089(5); Pt(1)-I(1), 2.5936(6); Pt(1)-I(2), 2.5863(6); N(1)-C(1)-N(2), 104.5(5); N(3)-Pt(1)-C(1), 177.8(3); I(1)-Pt(1)-I(2), 179.46(2); C(26)-N(3)-C(1)-N(1), 24.30(10); I(1)-I(2)-C(1)-N(3), 1.15(11).

The platinum complexes were evaluated for their IC₅₀ values on a panel of different cancer cell lines (MCF7, HCT116, PC3, OV3 and MRC5) and non-cancer cell line (EPC) and the results are enlisted in Table 1. Cisplatin was used as reference, and displayed significantly lower activity compared to all complexes, except for **5** and **10**.¹⁵ The introduction of a bromo or formyl group in 4-position of the benzyl is not found to affect the overall activities of the compounds (compare compound **1** with **2** and **4**). Surprisingly, the nitrobenzyl-containing complex **3** presented excellent cytotoxicity with IC₅₀ value below 5 nM toward both HCT116 and MRC5 cancer cells. The presence of an anthracenyl or pyrenyl moiety also lead to promising results with IC₅₀ ranging from 0.165 μM to 0.01 μM, whereas introduction of PEG chains onto the compound (complex **5**) induced a significant drop of the activity. Trinuclear platinum complex **8** also displayed a moderate activity compared to mononuclear species.¹⁶

Finally, the bis-nitrobenzyl complex **9** was found less active than the mono-nitrobenzyl complex **3** and bis-anthracenyl derivative **10** was inactive, which may be due to its low solubility. The enhanced activities may be related to a synergistic effect since the most active complexes are combining NHC Pt complexes with a benzylic moiety that is able to intercalate into DNA base pairs.^[17]

Compound	MCF7	HCT116	PC3	OV3	MRC5	EPC
Cisplatin	19.8±0.6	6.4±0.2	10.0±1.0	18±2	12.5±0.1	76±10
1	0.21±0.02	0.22±0.01	0.35±0.03	-	-	-
2	0.36±0.01	0.30±0.02	-	-	-	0.81±0.02
3	0.035±0.005	0.005±0.005	0.9±0.2	0.075±0.005	0.005±0.005	0.075±0.005
4	0.49±0.07	4.6±3.3	0.93±0.03	1.5±0.4	0.60±0.02	1.8±0.2
5	64.9±0.7	42±2	74±8	67±2	56±2	32±6
6	0.085±0.005	0.01±0.01	0.035±0.005	0.02±0.01	0.02±0.01	0.085±0.005
7	0.145±0.005	0.010±0.005	0.16±0.02	0.165±0.005	0.03±0.01	0.11±0.01
8	8.0±2.0	4.5±0.2	-	-	-	5.0±2.0
9	0.36±0.05	0.25±0.01	-	-	-	0.54±0.08
10	89±7	40±6	76±1	84±1	47±11	>100

^[a] MCF7, breast carcinoma; HCT116, colon cancer cells; PC3, prostate adenocarcinoma; SK-OV3, human ovarian cancer cells; MRC5, human fetus lung cells; EPC, endothelial progenitor cells.

Table 1. Half inhibitory concentrations IC₅₀ (in μM) of the compounds against human cancer and non-cancer cell lines (after 72h of incubation).^[a]

3. Conclusion

In summary, a series of platinum complexes bearing N-heterocyclic carbene ligands functionalized by various benzyl moieties has been synthesized and characterized. The complexes show a high stability both in solid state and in solution. The compounds have demonstrated variable *in vitro* activities, which was found to be dependent on the substituents

on the benzyl moiety. Nonetheless, they usually show cytotoxic activities significantly higher than that of cisplatin on 6 different cell lines. Low IC₅₀ values up to 0.005 μM were obtained when a nitrobenzyl was introduced onto the NHC ligand. Further studies will focus on mechanistic investigations to gain more insights into the therapeutic potential of these compounds.

Acknowledgments

The authors gratefully acknowledge the Ministère de l'Enseignement Supérieur et de la Recherche for Ph.D. grants to G. D. and M. B. This work was also supported by La Ligue contre le Cancer – Région Grand Est and University of Strasbourg/CNRS—Program IDEX Interdisciplinaire. Biological evaluations of cell proliferation inhibition have been performed at the Ciblothèque Cellulaire ICSN (Gif sur Yvette, France).

References

- [1] (a) A.J. Arduengo III, *Acc. Chem. Res.* 32 (1999) 913. (b) D. Bourissou, O. Guerret, F. Gabbai, G. Bertrand, *Chem. Rev.* 100 (2000) 39. (c) C.M. Crudden, D.P. Allen, *Coord. Chem. Rev.* 248 (2004) 2247. (d) S.D. Díez-González, S.P. Nolan, *Coord. Chem. Rev.* 251 (2007) 874. (e) F. Glorius, *Top. Organomet. Chem.* 21 (2007) 1.
- [2] (a) W.A. Herrmann, *Angew. Chem. Int. Ed.* 41 (2002) 1290. (b) M.C. Perry, K. Burgess, *Tetrahedron: Asymmetry* 14 (2003) 951. (c) V. César, S. Bellemin-Laponnaz, L.H. Gade, *Chem. Soc. Rev.* 33 (2004) 619. (d) L.H. Gade, S. Bellemin-Laponnaz, *Top. Organomet. Chem.* 21 (2007) 117. (e) L. Mercks, M. Albrecht, *Chem. Soc. Rev.* 39 (2010) 1903; (f) *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*, Ed. S. Díez-González, RSC Catalysis Series, Royal Society of Chemistry, Cambridge, UK (2010).
- [3] (a) S. Ray, R. Mohan, J.K. Singh, M.K. Samantaray, M.M. Shaikh, D. Panda, P. Ghosh, *J. Am. Chem. Soc.* 129 (2007) 15042; (b) M. Skander, P. Retailleau, B. Bourri, L. Schio, P. Mailliet, A. Marinetti, *J. Med. Chem.* 53 (2010) 2146.
- [4] For general review on metallodrugs, see: (a) K. Kowalski, *ChemPlusChem* 84 (2019) 403; (b) G. Jaouen, A. Vessières, S. Top, *Chem. Soc. Rev.* 44 (2015) 8802; (c) Y. C. Ong, S. Roy, P. C. Andrews, G. Gasser, *Chem. Rev.* 119 (2019) 730; (d) K. Kowalski, *Coord. Chem. Rev.* 366 (2018) 91.
- [5] (a) E. Chardon, G.-L. Puleo, G. Dahm, G. Guichard, S. Bellemin-Laponnaz, *Chem. Commun.* 47 (2011) 5864. (b) E. Chardon, G. Dahm, G. Guichard, S. Bellemin-Laponnaz, *Chem Asian J* 8 (2013) 1232. (c) A. Hospital, C. Gibard, C. Gaulier, L. Nauton, V. Théry, M. El-Ghozzi, D. Avignant, F. Cisnetti, A. Gautier, *Dalton Trans.* 41 (2012) 6803.
- [6] For reviews on the medicinal properties of metal-NHC complexes, see: (a) K. M. Hindi, M.J. Panzner, C.A. Tessier, C.L. Cannon, W.J. Youngs, *Chem. Rev.* 109 (2009) 3859; (b) M.-L. Teyssot, A.-S. Jarrousse, M. Manin, A. Chevry, S. Roche, F. Norre, C. Beaudoin, L. Morel, D. Boyer, R. Mahioue, A. Gautier, *Dalton Trans.* (2009) 6894. (c) A. Gautier, F. Cisnetti, *Metallomics* 4 (2012) 23.
- [7] B. Rosenberg, L. Van Camp, J.E. Trosko, V.H. Mansour, *Nature* 222 (1969) 385.
- [8] S.M. Aris, N.P. Farrell, *Eur. J. Inorg. Chem.* 10 (2009) 1293.
- [9] G. Gasser, I. Ott, N. Metzler-Nolte, *J. Med. Chem.* 54 (2011) 3.

-
- [10] P. Z. Zhang, P. J. Sadler, *J. Organomet. Chem.* 839 (2017) 5.
- [11] S.H. Hussaini, R.A. Haque, M.R. Razali, *J. Organomet. Chem.* 882 (2019) 96.
- [12] (a) M. Tacke, *J. Organomet. Chem.* 782 (2015) 17; (b) F. Hackenberg, M. Tacke, *Dalton Trans.* 43 (2014) 8144; (c) K. Strohfeldt, M. Tacke, *Chem. Soc. Rev.* 37 (2008) 1174.
- [13] L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-Lapponnaz, V. César, *Chem. Rev.* 111 (2011) 2705.
- [14] G. Dahm, C. Bailly, L. Karmazin, S. Bellemin-Lapponnaz, *J. Organomet. Chem.* 794 (2015) 115.
- [15] Cisplatin was used as reference for the studies; however due to the instability of cisplatin in DMSO, the latter was used as stock solution in water.
- [16] M. Chtchigrovsky, L. Eloy, H. Jullien, L. Saker, E. Ségal-Bendirdjian, J. Poupon, S. Bombard, T. Cresteil, P. Retailleau, A. Marinetti, *J. Med. Chem.* 56 (2013) 2074.
- [17] (a) A. Sischka, K. Toensing, R. Eckel, S.D. Wilking, N. Sewald, R. Ros, D. Anselmetti. 88 (2005) *Biophysical Journal* 404. (b) F.A. Tanious, T.C. Jenkins, S. Neidle, W.D. Wilson, 31 (1992) *Biochemistry* 11632.