Inorganica Chimica Acta 415 (2014) 88–94

Contents lists available at ScienceDirect

Inorganica Chimica Acta

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

Synthesis, characterization and anticancer properties of (salicylaldiminato)platinum(II) complexes

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ARTICLE INFO

Article history:
Received 13 November 2013
Received in revised form 9 February 2014
Accepted 16 February 2014
Available online 5 March 2014

Keywords:
Cancer
Glioma
Platinum
Salicylaldimine
Schiff base

ABSTRACT

Twelve new (salicylaldiminato)platinum(II) complexes have been prepared, characterized and examined for their *in vitro* cytotoxic properties against three human glioma cell lines LN18, LN405 and Hs683. Initial biotesting was done on platinum complexes **1**–**6**, which display a wide range of physicochemical properties. Whereas introduction of aromatic rings in the complexes did not seem to have a significant impact on bioactivities, the length of the aliphatic group positively correlated with cytotoxicity in all cell lines. Complexes **2** and **3** were found to be particularly potent against LN18 cells as demonstrated by stronger cell growth inhibition when compared to cisplatin. These initial findings led us to develop an additional series of mono (salicylaldiminato)platinum(II) complexes **7**–**12**, which were subjected to additional cytotoxicity studies but were less cytotoxic compared to the bis Schiff base complexes. These organometallic compounds could serve as interesting starting points for the development of novel therapeutic strategies to treat brain tumors.

1. Introduction

Cisplatin (Fig. 1a) is a remarkably small molecule that has made a huge impact in medicinal chemistry. Indeed, this simple coordination complex has achieved considerable success in the treatment of ovarian, testicular, head and neck, bladder, cervical and small cell lung cancer [1]. Unfortunately, cisplatin has several serious side effects, such as oto-, neuro-, and nephrotoxicity, which decrease its overall effectiveness in cancer therapy [2]. Since its discovery, a plethora of second generation platinum complexes based on the structure of cisplatin, such as [$PtCl_2$(*cis*-1,4-DACH)] (Fig. 1b) and carboplatin (Fig. 1c), have been developed and examined for their potential anticancer properties. The mechanism of action of these platinum drugs is believed to arise by initial ligand substitution with the anionic ligands (chlorides or carboxylates) by molecules of water to give a charged platinum molecule. Coordination of the metal to nitrogenous bases of DNA, most likely through the N7 of guanine, interferes with cell replication and ultimately causes them to undergo apoptosis, or programmed cell death. Although modest improvements have been made over the past fifty years, most of this work has involved varying either the inert amine ligands or the labile chloride ligands in an effort to enhance delivery of the platinum metal to the cancerous cells [3].

An interesting recent development has been in the combined use of radiotherapy and platinum chemotherapy for the treatment of glioblastomas [4–9]. The synergy between cancer treatments enables the reduction of platinum dose and thereby diminishes side effects. Gliomas are classified into four clinical grades and glioblastoma multiforme (GBM) is the most aggressive, whereby the median survival period for patients diagnosed with a GBM is only twelve months. Unfortunately, tumors infiltrate into regions of the brain that render complete surgical extraction difficult. Although some improvements in the prognosis of GBM patients have been observed using chemotherapeutic agents, such as cisplatin and its derivatives, the search for novel agents to treat GBM is of utmost importance in an effort to improve this combined form of therapy.

While the coordination chemistry of most transition metals (i.e. Co, Cu, Pd, Ni, etc.) containing simple salicylaldimines has been extensively studied [10], it is somewhat surprising that relatively little is known about the corresponding platinum complexes

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http://dx.doi.org/10.1016/j.ica.2014.02.028
0020-1693/

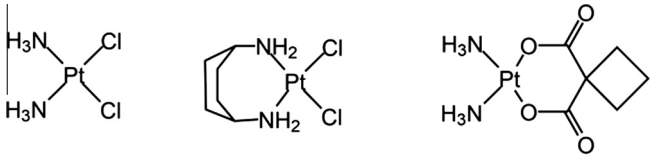


Fig. 1. Common platinum anticancer agents.

Table 1
Crystallographic data-collection parameters.

Complex	**3**	**4**
Formula	$C_{30}H_{44}N_2O_2Pt$	$C_{26}H_{20}N_2O_2Pt$
Molecular weight	659.76	587.53
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$C2/m$
a (Å)	14.739(2)	11.867(3)
b (Å)	5.6317(8)	10.079(3)
c (Å)	17.185(2)	9.657(3)
α (°)	90	90
β (°)	97.515	113.208(5)
γ (°)	90	90
V (Å^3)	1414.2(3)	1061.5(5)
Z	2	2
ρ_{calc} (Mg m^{-3})	1.549	1.838
Crystal size (mm^3)	0.57 × 0.10 × 0.10	0.15 × 0.15 × 0.03
T (K)	198(1)	188(1)
Radiation	Mo K_α (λ = 0.71073 Å)	Mo K_α (λ = 0.71073 Å)
μ (mm^{-1})	4.989	6.635
Total reflections	9105	3519
Total unique reflections	3126	1244
Number of variables	183	140
θ Range (°)	2.39–27.49	2.29–27.50
Largest difference peak and hole (e Å^3)	1.027 and −1.163	3.304 and −1.174
S (Goodness of fit (GOF)) on F^2	1.130	1.182
R_1[a] ($I > 2\sigma$ (I))	0.0348	0.0261
wR_2[b] (all data)	0.0971	0.0633

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.
[b] $wR_2 = (\Sigma[w(F_o^2F_c^2)^2]/\Sigma[wF_o^4])^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (0.0313{\cdot}P)^2 + (1.9366{\cdot}P)]$ (**3**) and $1/[\sigma^2(F_o^2) + (0.0439{\cdot}P)^2]$ (**4**), where $P = (\max(F_o^2, 0) + 2{\cdot}F_c^2)/3$.

[11–16]. In one study, tetradentate salen-type platinum complexes have been reported and examined primarily for their potential to be used as electroluminescent devices [15]. More relevant to this study is a recent report that has shown that complexes of this type can also be used to inhibit the growth of MCF-7 and MDA-MB 231 cancer cells [16]. These results, along with our interest in designing new families of biologically-active platinum complexes [17], led us to develop a series of easily prepared Schiff base platinum complexes derived from salicylaldehyde and a variety of primary amines with different physicochemical properties.

2. Experimental

2.1. General methods

Reagents and solvents used were obtained from Aldrich Chemicals. $[PtCl_2(\eta^2\text{-coe})]_2$ (coe = *cis*-cyclooctene) [18] and the Schiff bases [19] were synthesized according to literature procedures. NMR spectra were recorded on a JEOL JNM-GSX400 FT NMR spectrometer. ^{1}H NMR chemical shifts are reported in ppm and are referenced to residual protons in deuterated solvent at 400 MHz. ^{13}C NMR chemical shifts are referenced to solvent carbon resonances as internal standards at 100 MHz. ^{19}F NMR chemical shifts are referenced to CF_3CO_2H as an external standard at 376 MHz. Multiplicities are reported as singlet (s), doublet (d), triplet (t), multiplet (m), broad (br), and overlapping (ov) with coupling constants (J) reported in hertz. FT-IR spectra were obtained with a Thermo Fisher Scientific Nicolet iS5 FT-IR spectrometer in ATR mode and are reported in cm^{-1}. Melting and decomposition points were measured uncorrected with a Mel-Temp apparatus. Elemental analyses for C, H, and N were carried out at Guelph Chemical Laboratories (Guelph, ON) and Laboratoire d'Analyse Élémentaire de l'Université de Montréal (Montréal, QC).

2.2. General procedure for the synthesis of complexes **1**–**6**

Under an atmosphere of dinitrogen, a hexane solution of *n*-BuLi (0.5 M equivalent) was added to a toluene solution of the appropriate Schiff base. Upon stirring the reaction mixture for 8 h, a toluene (5 mL) solution of $[PtCl_2(\eta^2\text{-coe})]_2$ (0.25 M equivalents, coe = *cis*-cyclooctene) was added and the mixture was heated at reflux for 18 h. Upon cooling to RT, the reaction was transferred to ambient conditions and passed through a plug of silica. Removal of solvent under vacuum afforded crude products as orange-red solids. Complexes **1** and **4**–**6** were isolated upon recrystallization from a minimum amount of hot toluene, filtered and then stored at 5 °C whereas compounds **2** and **3** were similarly isolated from hexane.

2.2.1. Di-(2-((isopentylimino)methyl)phenolato-κ^2-N,O)platinum(II) (**1**)

A toluene solution of the Schiff base (612 mg, 3.20 mmol) was deprotonated with *n*-BuLi (2.0 mL of a 1.6 M solution in hexanes, 3.20 mmol) and added to a toluene solution of $[PtCl_2(\eta^2\text{-coe})]_2$ (600 mg, 0.80 mmol). Yellow-orange solid; yield: 710 mg (77%); mp: 279–281 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.91 (s, J_{H-Pt} = 59.8 Hz, 2H, C*H*=N), 7.35–7.22 (ov m, 4H, Ar), 6.88 (d, J_{H-H} = 8.7 Hz, 2H, Ar), 6.57 (t, J_{H-H} = 7.7 Hz, 2H, Ar), 3.86 (br t, J_{H-H} = 6.2 Hz, 4H, NC*H*$_2$), 1.73–1.69 (ov m, 6H, C*H*$_2$ and C*H*(CH$_3$)$_2$), 0.96 (d, J_{H-H} = 5.4 - Hz, 12H, CH(C*H*$_3$)$_2$). ^{13}C{^{1}H} NMR ($CDCl_3$) δ (ppm): 163.5 (*C*–O), 158.8 (*C*=N), 133.7, 133.4, 120.9, 120.3, 115.7, 57.2 (N–CH$_2$), 41.7 (NCH$_2$CH$_2$), 26.5 (*C*H(CH$_3$)$_2$), 22.9 (*C*H$_3$). IR (Nujol) (cm^{-1}): 2945 (s), 2901 (s), 2859 (s), 1616 (s, $\nu_{C=N}$), 1597 (m), 1537 (m), 1465 (s), 1450 (s), 1405 (m), 1377 (m), 1354 (w), 1320 (m), 1200 (w), 1147 (w), 1126 (w), 910 (w), 752 (s), 735 (w). *Anal.* Calc. for $C_{24}H_{32}N_2O_2Pt$ (575.66): C, 50.07; H, 5.61; N, 4.87. Found: C, 50.25; H, 5.80; N, 4.61%.

2.2.2. Di-(2-((hexylimino)methyl)phenolato-κ^2-N,O)platinum(II) (**2**)

A toluene solution of the Schiff base (656 mg, 3.20 mmol) was deprotonated with *n*-BuLi (2.0 mL of a 1.6 M solution in hexanes, 3.20 mmol) and added to a toluene solution of $[PtCl_2(\eta^2\text{-coe})]_2$ (600 mg, 0.80 mmol). Yellow-orange solid; yield: 821 mg (85%); mp: 186–187 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.90 (s, J_{H-Pt} = 59.9 Hz, 2H, C*H*=N), 7.32 (ddd, J_{H-H} = 8.4, 6.9, 1.7 Hz, 2H, Ar), 7.25 (dd, J_{H-H} = 7.7, 1.7 Hz, 2H, Ar), 6.87 (d, J_{H-H} = 8.4 Hz, 2H, Ar), 6.57 (ddd, J_{H-H} = 7.7, 6.9, 1.0 Hz, 2H, Ar), 3.83 (t, J_{H-H} = 6.9 Hz, 4H, NC*H*$_2$), 1.81 (quint, J_{H-H} = 6.9 Hz, 4H, NCH$_2$C*H*$_2$), 1.41–1.23 (ov m, 12H, (C*H*$_2$)$_3$), 0.87 (t, J_{H-H} = 6.9 Hz, 6H, C*H*$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$) δ (ppm): 163.5 (*C*–O), 158.7 (*C*=N), 133.7, 133.5, 120.8, 120.4, 115.7, 59.0 (N–*C*H$_2$), 32.5, 31.7, 26.7, 22.7, 14.2 (*C*H$_3$). IR (Nujol) (cm^{-1}): 2919 (s), 2854 (s), 1616 (s, $\nu_{C=N}$), 1538 (s), 1467 (s), 1431 (s), 1405 (w), 1321 (s), 1203 (m), 1148 (m), 750 (s), 735 (m). *Anal.* Calc. for $C_{26}H_{36}N_2O_2Pt$ (603.72): C, 51.72; H, 6.02; N, 4.64. Found: C, 51.96; H, 5.99; N, 4.34%.

2.2.3. Di-(2-((octylimino)methyl)phenolato-κ^2-N,O)platinum(II) (**3**)

A toluene solution of the Schiff base (747 mg, 3.20 mmol) was deprotonated with *n*-BuLi (2.0 mL of a 1.6 M solution in hexanes, 3.20 mmol) and added to a toluene solution of $[PtCl_2(\eta^2\text{-coe})]_2$ (600 mg, 0.80 mmol). Yellow-orange solid; yield: 897 mg (85%);

mp: 158–159 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.90 (s, J_{H-Pt} = 53.9 Hz, 2H, C*H*═N), 7.32 (ddd, J_{H-H} = 8.4, 6.7, 1.7 Hz, 2H, Ar), 7.24 (dd, J_{H-H} = 7.9, 1.7 Hz, 2H, Ar), 6.87 (d, J_{H-H} = 8.4 Hz, 2H, Ar), 6.57 (ddd, J_{H-H} = 7.9, 6.7, 1.0 Hz, 2H, Ar), 3.83 (t, J_{H-H} = 6.9 Hz, 4H, NCH_2), 1.81 (quint, J_{H-H} = 6.9 Hz, 4H, NCH$_2$CH_2), 1.44–1.18 (ov m, 20H, (CH_2)$_5$), 0.85 (t, J_{H-H} = 6.9 Hz, 6H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$) δ (ppm): 163.5 (*C*–O), 158.7 (*C*═N), 133.7, 133.5, 120.8, 120.4, 115.6, 59.0 (N–CH_2), 32.5, 31.9, 29.5, 29.4, 27.0, 22.7, 14.2 (CH_3). IR (Nujol) (cm^{-1}): 2927 (s), 2854 (s), 1616 (s, $\nu_{C=N}$), 1538 (m), 1466 (s), 1451 (s), 1405 (w), 1377 (w), 1354 (w), 1322 (s), 1198 (w), 1148 (w), 914 (w), 751 (m), 736 (w). *Anal.* Calc. for $C_{30}H_{44}N_2O_2Pt$ (659.84): C, 54.60; H, 6.73; N, 4.25. Found: C, 54.76; H, 7.01; N, 4.05%.

2.2.4. Di-(2-((phenylimino)methyl)phenolato-κ^2-N,O)platinum(II) (**4**)

A toluene solution of the Schiff base (631 mg, 3.20 mmol) was deprotonated with *n*-BuLi (2.0 mL of a 1.6 M solution in hexanes, 3.20 mmol) and added to a toluene solution of [$PtCl_2$(η^2-coe)]$_2$ (600 mg, 0.80 mmol). Orange solid; yield: 771 mg (82%); decomposition point: 288–294 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.01 (s, J_{H-Pt} = 64.6 Hz, 2H, C*H*═N), 7.46–7.34 (ov m, 10H, Ar), 7.24–7.17 (ov m, 4H, Ar), 6.51 (ddd, J_{H-H} = 7.9, 6.7, 1.0 Hz, 2H, Ar), 6.12 (d, J_{H-H} = 8.8 Hz, 2H, Ar). ^{13}C{^{1}H} NMR ($CDCl_3$) δ (ppm): 163.8 (*C*–O), 159.6 (*C*═N), 149.9, 134.4, 133.8, 128.2, 126.7, 124.8, 121.0, 120.7, 116.1. IR (Nujol) (cm^{-1}): 2963 (m), 2868 (m), 1602 (s, $\nu_{C=N}$), 1524 (s), 1461 (s), 1440 (s), 1316 (s), 1178 (s), 1143 (m), 758 (s), 691 (s). *Anal.* Calc. for $C_{26}H_{20}N_2O_2Pt$ (587.56): C, 53.15; H, 3.44; N, 4.77. Found: C, 52.94; H, 3.41; N, 4.60%.

2.2.5. Di-(2-((4-methoxyphenylimino)methyl)phenolato-κ^2-N,O)platinum(II) (**5**)

A toluene solution of the Schiff base (727 mg, 3.20 mmol) was deprotonated with *n*-BuLi (2.0 mL of a 1.6 M solution in hexanes, 3.20 mmol) and added to a toluene solution of [$PtCl_2$(η^2-coe)]$_2$ (600 mg, 0.80 mmol). Burgundy solid; yield: 901 mg (87%); decomposition point: 223–228 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.99 (s, J_{H-Pt} = 60.4 Hz, 2H, C*H*═N), 7.31–7.18 (ov m, 8H, Ar), 6.93 (d, J_{H-H} = 8.9 Hz, 4H, Ar), 6.50 (ddd, J_{H-H} = 7.9, 7.0, 1.0 Hz, 2H, Ar), 6.22 (d, J_{H-H} = 8.9 Hz, 2H, Ar), 3.88 (s, 6H, OCH_3). ^{13}C{^{1}H} NMR ($CDCl_3$) δ (ppm): 163.8 (*C*–O), 159.6 (*C*═N), 158.3 (*C*–OCH$_3$), 143.2, 134.3, 133.7, 125.7, 120.9, 120.8, 116.0, 113.2, 55.7 (OCH$_3$). IR (Nujol) (cm^{-1}): 2971 (s), 2881 (s), 2838 (s), 1600 (s, $\nu_{C=N}$), 1539 (w), 1506 (s), 1464 (s), 1442 (s), 1377 (m), 1304 (s), 1250 (m), 1181 (m), 1149 (w), 1125 (w), 839 (s), 750 (s). *Anal.* Calc. for $C_{28}H_{24}N_2O_4Pt$ (647.62): C, 51.93; H, 3.74; N, 4.33. Found: C, 52.21; H, 3.50; N, 4.16%.

2.2.6. Di-(2-((4-fluorophenylimino)methyl)phenolato-κ^2-N,O)platinum(II) (**6**)

A toluene solution of the Schiff base (689 mg, 3.20 mmol) was deprotonated with *n*-BuLi (2.0 mL of a 1.6 M solution in hexanes, 3.20 mmol) and added to a toluene solution of [$PtCl_2$(η^2-coe)]$_2$ (600 mg, 0.80 mmol). Bright orange solid; yield: 838 mg (84%); decomposition point: 245–247 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.00 (s, J_{H-Pt} = 62.4 Hz, 2H, C*H*═N), 7.34–7.22 (ov m, 8H, Ar), 7.15–7.07 (ov m, 4H, Ar), 6.53 (ddd, J_{H-H} = 7.9, 6.9, 1.0 Hz, 2H, Ar), 6.19 (d, J_{H-H} = 8.9 Hz, 2H, Ar). ^{13}C{^{1}H} NMR ($CDCl_3$, 50 °C) δ (ppm): 164.0 (*C*–O), 161.4 (d, J_{CF} = 246 Hz, *C*–F), 159.8 (*C*═N), 145.9 (d, J_{CF} = 3 Hz), 134.6, 133.7, 126.3 (d, J_{CF} = 8 Hz), 120.9, 120.6, 116.2, 114.8 (d, J_{CF} = 23 Hz). ^{19}F{^{1}H} NMR ($CDCl_3$) δ (ppm): −116.2. IR (Nujol) (cm^{-1}): 2943 (m), 2855 (m), 1604 (s, $\nu_{C=N}$), 1589 (s), 1531 (m), 1499 (s), 1465 (s), 1441 (s), 1379 (m), 1353 (w), 1308 (m), 1226 (m), 1178 (s), 1146 (s), 1125 (m), 1093 (w), 837 (s), 762 (m). *Anal.* Calc. for $C_{26}H_{18}N_2F_2O_2Pt$ (623.54): C, 50.08; H, 2.92; N, 4.49. Found: C, 49.91; H, 2.77; N, 4.72%.

2.3. General procedure for the synthesis of complexes **7**–**12**

Under an atmosphere of dinitrogen, a hexane solution of *n*-BuLi (1 M equivalent) was added to a toluene (5 mL) solution of the appropriate Schiff base. Upon stirring the reaction mixture for 3 h at RT, a toluene (20 mL) suspension of [$PtCl_2$(η^2-coe)]$_2$ (0.5 M equivalents) was added and the mixture was stirred at RT for 18 h. After removal of the reaction from the inert atmosphere, the suspension was passed through a plug of alumina to remove the lithium salts and the solvent was removed under vacuum to afford the desired platinum complexes.

2.3.1. (Chlorido)(η^2-cis-cyclooctene)(2-((2-ethyl-1-hexylimino)-methyl)phenolato-κ^2-N,O)platinum(II) (**7**)

A toluene solution of the Schiff base (373 mg, 1.60 mmol) was deprotonated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes, 1.60 mmol) and added to a toluene solution of [$PtCl_2$(η^2-coe)]$_2$ (600 mg, 0.80 mmol). Orange oil. Yield: 743 mg (81%). ^{1}H NMR ($CDCl_3$): δ = 7.76 (s, J_{HPt} = 67.6 Hz, 1H, C(*H*)═N), 7.33 (ddd, J_{HH} = 8.4, 6.8, 1.8 Hz, 1H, Ar), 7.25 (dd, J_{HH} = 8.0, 1.8 Hz, 1H, Ar), 6.85 (d, J_{HH} = 8.4 Hz, 1H, Ar), 6.65 (ddd, J_{HH} = 8.0, 6.8, 0.8 Hz, 1H, Ar), 5.45 (br m, J_{HPt} = 57.2 Hz, 2H, *HC*═C*H*), 4.08 (dd, J_{HH} = 7.0, 7.0 Hz, 2H, NCH_2), 2.44 (m, 2H, CH_2 (coe)), 2.30 (m, 2H, CH_2 (coe)), 2.10 (m, 1H, C*H*), 1.81 (m, 2H, CH_2 (coe)), 1.59–1.50 (ov m, 6H, CH_2 (coe)), 1.33–1.23 (ov m, 8H, CH_2 (2-ethyl-1-hexyl)), 0.94–0.86 (ov m, 6H, CH_3) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 163.6 (*C*–O), 161.4 (*C*═N), 135.7, 134.4, 120.1, 119.8, 116.9, 94.3 (s, J_{CPt} = 163.2 Hz, *C*═*C*), 67.1 (N–CH_2), 40.4, 29.8, 28.9, 28.4, 26.6, 25.8 (br), 23.3, 23.2, 14.3, 10.6. IR (Nujol) (cm^{-1}): 2956 (m), 2923 (m), 1608 (s, $\nu_{C=N}$), 1540 (m), 1468 (m), 1447 (m), 1403 (w), 1380 (w), 1357 (w), 1318 (m), 1172 (w), 1150 (m), 1130 (w), 1039 (w), 1024 (w), 975 (w), 908 (w), 849 (w), 816 (w), 752 (s), 734 (s), 667 (w), 612 (w). *Anal.* Calc. for $C_{23}H_{36}NClOPt$ (573.07): C, 48.20; H, 6.33; N, 2.44. Found: C, 47.95; H, 6.34; N, 2.40%.

2.3.2. (Chlorido)(η^2-cis-cyclooctene)(2-((decylimino)methyl)-phenolato-κ^2-N,O)platinum(II) (**8**)

A toluene solution of the Schiff base (418 mg, 1.60 mmol) was deprotonated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes, 1.60 mmol) and added to a toluene solution of [$PtCl_2$(η^2-coe)]$_2$ (600 mg, 0.80 mmol). Orange oil. Yield: 788 mg (82%). ^{1}H NMR ($CDCl_3$): δ = 7.89 (s, J_{HPt} = 66.6 Hz, 1H, C(*H*)═N), 7.34 (ddd, J_{HH} = 8.4, 6.8, 1.8 Hz, 1H, Ar), 7.26 (dd, J_{HH} = 8.0, 1.8 Hz, 1H, Ar), 6.87 (d, J_{HH} = 8.4 Hz, 1H, Ar), 6.65 (ddd, J_{HH} = 8.0, 6.8, 1.0 Hz, 1H, Ar), 5.49 (br m, J_{HPt} = 56.4 Hz, 2H, *HC*═C*H*), 4.17 (t, J_{HH} = 7.4 Hz, 2H, NCH_2), 2.47 (m, 2H, CH_2 (coe)), 2.31 (m, 2H, CH_2 (coe)), 1.90–1.82 (br m, 4H, CH_2 (decyl and coe)), 1.59–1.51 (ov m, 6H, CH_2 (coe)), 1.33–1.27 (ov m, 14H, CH_2 (decyl)), 0.89 (t, J_{HH} = 6.0 Hz, 3H, CH_3) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 163.3 (*C*–O), 161.0 (*C*═N), 135.7, 134.4, 120.0, 119.5, 116.8, 94.4 (s, J_{CPt} = 158.8 Hz, *C*═*C*), 63.2 (N–CH_2), 32.9, 32.1, 29.9, 29.8, 29.6 (2C), 28.9, 26.8, 26.6, 25.8 (br), 22.9, 14.4 (CH_3). IR (Nujol) (cm^{-1}): 2925 (s), 2855 (s), 1613 (s, $\nu_{C=N}$), 1460 (m), 1377 (m), 722 (w). *Anal.* Calc. for $C_{25}H_{40}NClOPt$ (601.12): C, 49.95; H, 6.71; N, 2.33. Found: C, 49.93; H, 6.90; N, 2.25%.

2.3.3. (Chlorido)(η^2-cis-cyclooctene)(2-((hexadecylimino)methyl)-phenolato-κ^2-N,O)platinum(II) (**9**)

A toluene solution of the Schiff base (553 mg, 1.60 mmol) was deprotonated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes, 1.60 mmol) and added to a toluene solution of [$PtCl_2$(η^2-coe)]$_2$ (600 mg, 0.80 mmol). Further purified by passing a Et_2O solution of the complex through a plug of alumina. Orange oil. Yield: 866 mg (79%). ^{1}H NMR ($CDCl_3$): δ = 7.88 (s, J_{HPt} = 66.2 Hz, 1H, C(*H*)═N), 7.32 (ddd, J_{HH} = 8.6, 6.8, 1.6 Hz, 1H, Ar), 7.26 (dd, J_{HH} = 7.8, 1.6 Hz, 1H, Ar), 6.85 (d, J_{HH} = 8.6 Hz, 1H, Ar), 6.63 (ddd,

J_{HH} = 7.8, 6.8, 1.0 Hz, 1H, Ar), 5.47 (br m, J_{HPt} = 56.0 Hz, 2H, *HC*=C*H*), 4.15 (t, J_{HH} = 7.6 Hz, 2H, NCH_2), 2.46 (m, 2H, CH_2 (coe)), 2.29 (m, 2H, CH_2 (coe)), 1.90–1.74 (br m, 4H, CH_2 (hexadecyl and coe)), 1.58–1.51 (ov m, 6H, CH_2 (coe)), 1.31–1.25 (ov m, 26H, CH_2 (hexadecyl)), 0.88 (t, J_{HH} = 6.0 Hz, 3H, CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 163.2 (*C*–O), 161.0 (*C*=N), 135.6, 134.4, 120.0, 119.5, 116.8, 94.2 (s, J_{CPt} = 160.2 Hz, *C*=*C*), 63.1 (N–*C*H_2), 32.9, 32.2, 30.0 (4C), 29.9 (3C), 29.8, 29.6, 29.5, 28.9, 26.7, 26.6, 25.8 (br), 22.9, 14.4 (*C*H_3). IR (Nujol) (cm^{-1}): 2918 (s), 2850 (m), 1610 (s, $\nu_{C=N}$), 1540 (m), 1469 (m), 1448 (m), 1402 (w), 1358 (w), 1327 (m), 1203 (w), 1150 (w), 1130 (w), 1025 (w), 959 (w), 912 (w), 847 (w), 751 (s), 735 (m), 594 (w). *Anal.* Calc. for $C_{31}H_{52}NClOPt{\cdot}Et_2O$ (759.40): C, 55.36; H, 8.23; N, 1.84. Found: C, 55.28; H, 7.96; N, 2.04%.

2.3.4. (Chlorido)(η^2-cis-cyclooctene)(2-(octadecylimino)methyl)-phenolato-κ^2-N,O)platinum(II) (**10**)

A toluene solution of the Schiff base (598 mg, 1.60 mmol) was deprotonated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes, 1.60 mmol) and added to a toluene solution of [$PtCl_2(\eta^2$-coe)]$_2$ (600 mg, 0.80 mmol). Further purified by passing a Et_2O solution of the complex through a plug of alumina. Orange oil. Yield: 959 mg (84%). ^1H NMR ($CDCl_3$): δ = 7.89 (s, J_{HPt} = 65.8 Hz, 1H, C(*H*)=N), 7.33 (ddd, J_{HH} = 8.4, 6.8, 1.8 Hz, 1H, Ar), 7.25 (dd, J_{HH} = 8.0, 1.8 Hz, 1H, Ar), 6.86 (d, J_{HH} = 8.4 Hz, 1H, Ar), 6.64 (ddd, J_{HH} = 8.0, 6.8, 1.0 Hz, 1H, Ar), 5.48 (br m, J_{HPt} = 57.2 Hz, 2H, *HC*=C*H*), 4.16 (t, J_{HH} = 7.6 Hz, 2H, NCH_2), 2.46 (m, 2H, CH_2 (coe)), 2.25 (m, 2H, CH_2 (coe)), 1.90–1.74 (br m, 4H, CH_2 (octadecyl and coe)), 1.57–1.50 (ov m, 6H, CH_2 (coe)), 1.31–1.25 (ov m, 30H, CH_2 (octadecyl)), 0.88 (t, J_{HH} = 6.0 Hz, 3H, CH_3) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 163.3 (*C*–O), 161.0 (*C*=N), 135.7, 134.4, 120.0, 119.5, 116.8, 94.3 (s, J_{CPt} = 158.8 Hz, *C*=*C*), 63.2 (N–*C*H_2), 32.9, 32.2, 30.0 (6C), 29.8 (4C), 29.6, 29.5, 28.9, 26.8, 26.6, 25.8 (br), 23.0, 14.4 (*C*H_3). IR (Nujol) (cm^{-1}): 2920 (s), 2850 (s), 1610 (s, $\nu_{C=N}$), 1540 (m), 1469 (s), 1448 (s), 1358 (w), 1328 (m), 1202 (w), 1150 (w), 1130 (w), 1025 (w), 959 (w), 912 (w), 847 (w), 817 (w), 751 (m), 729 (m), 594 (w). *Anal.* Calc. for $C_{33}H_{56}NClOPt{\cdot}Et_2O$ (787.46): C, 56.43; H, 8.45; N, 1.78. Found: C, 56.36; H, 8.33; N, 1.92%.

2.3.5. (Chlorido)(η^2-cis-cyclooctene)(2-((2-(1-cyclohexenyl)-ethylimino)methyl)phenolato-κ^2-N,O)platinum(II) (**11**)

A toluene solution of the Schiff base (367 mg, 1.60 mmol) was deprotonated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes, 1.60 mmol) and added to a toluene solution of [$PtCl_2(\eta^2$-coe)]$_2$ (600 mg, 0.80 mmol). Orange oil. Yield: 710 mg (78%). ^1H NMR ($CDCl_3$): δ = 7.74 (s, J_{HPt} = 60.5 Hz, 1H, C(*H*)=N), 7.32 (ddd, J_{HH} = 8.4, 6.8, 1.8 Hz, 1H, Ar), 7.21 (dd, J_{HH} = 7.8, 1.8 Hz, 1H, Ar), 6.85 (d, J_{HH} = 8.4 Hz, 1H, Ar), 6.62 (ddd, J_{HH} = 7.8, 6.8, 1.0 Hz, 1H, Ar), 5.46 (s, 1H, C=C*H*), 5.27 (br m, J_{HPt} = 71.5 Hz, 2H, *HC*=C*H*), 4.23 (t, J_{HH} = 7.3 Hz, 2H, NCH_2), 2.47 (m, 2H, CH_2 (coe)), 2.41 (t, J = 7.3 Hz, 2H, NCH_2CH_2), 2.26 (m, 2H, CH_2 (coe)), 1.98 (m, 2H, CH_2 (cyclohexenyl)), 1.90 (m, 2H, CH_2 (cyclohexenyl)), 1.81 (m, 2H, CH_2 (coe)), 1.62–1.43 (ov m, 10H, CH_2 (coe + cyclohexenyl)) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 163.2 (*C*–O), 161.3 (*C*=N), 135.6, 134.3, 134.0, 125.1, 120.0, 119.4, 116.8, 94.4 (s, J_{CPt} = 162.2 Hz, *C*=*C*), 61.3 (N–*C*H_2), 40.9, 29.0, 28.9, 26.6, 25.8 (br), 25.6, 23.2, 22.6. IR (Nujol) (cm^{-1}): 2920 (m), 2851 (m), 1611 (s, $\nu_{C=N}$), 1541 (m), 1471 (m), 1446 (m), 1401 (w), 1358 (w), 1327 (m), 1174 (w), 1148 (w), 1129 (w), 1009 (w), 915 (m), 842 (w), 746 (s), 734 (m), 619 (w). *Anal.* Calc. for $C_{23}H_{32}NClOPt$ (569.04): C, 48.55; H, 5.67; N, 2.46. Found: C, 49.16; H, 5.77; N, 2.31%.

2.3.6. (Chlorido)(η^2-cis-cyclooctene)(2-((cyclooctylimino)methyl)-phenolato-κ^2-N,O)platinum(II) (**12**)

A toluene solution of the Schiff base (370 mg, 1.60 mmol) was deprotonated with *n*-BuLi (1.0 mL of a 1.6 M solution in hexanes, 1.60 mmol) and added to a toluene solution of [$PtCl_2(\eta^2$-coe)]$_2$ (600 mg, 0.80 mmol). Recrystallization from a CH_2Cl_2/hexane (5 mL:2 mL) solution afforded **12** as a yellow solid. Yield: 731 mg (80%); decomposition point: 75–78 °C. ^1H NMR ($CDCl_3$): δ = 7.83 (s, J_{HPt} = 69.6 Hz, 1H, C(*H*)=N), 7.24 (ddd, J_{HH} = 8.4, 7.0, 1.8 Hz, 1H, Ar), 7.17 (dd, J_{HH} = 7.8, 1.8 Hz, 1H, Ar), 6.77 (d, J_{HH} = 8.4 Hz, 1H, Ar), 6.57 (ddd, J_{HH} = 7.8, 7.0, 1.0 Hz, 1H, Ar), 5.41 (br m, J_{HPt} = 57.2 Hz, 2H, *HC*=C*H*), 5.10 (m, 1H, NC*H*), 2.40 (m, 2H, CH_2 (coe)), 2.22 (m, 2H, CH_2 (coe)), 2.01 (m, 2H, CH_2 (coe)), 1.75–1.43 (ov m, 20H, CH_2 (cyclooctyl + coe)) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 162.7 (*C*–O), 159.2 (*C*=N), 135.5, 134.2, 120.7, 119.8, 116.8, 93.7 (s, J_{CPt} = 158.7 Hz, *C*=*C*), 66.1 (N–*C*H), 36.0, 28.9, 26.6, 26.5, 26.3, 25.7 (br), 25.1. IR (Nujol) (cm^{-1}): 2918 (m), 2848 (m), 1610 (s, $\nu_{C=N}$), 1539 (m), 1469 (m), 1449 (m), 1412 (w), 1337 (m), 1199 (w), 1150 (w), 1028 (w), 913 (w), 752 (s), 600 (w). *Anal.* Calc. for $C_{23}H_{34}NClOPt$ (571.05): C, 48.37; H, 6.00; N, 2.45. Found: C, 48.53; H, 6.10; N, 2.37%.

2.4. Stability testing of platinum complexes in DMSO-d_6

Compounds **2**, **4**, and **11** were dissolved in DMSO-d_6 and analyzed by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. The degree of decomposition over time was determined by comparing the NMR spectra collected after 1, 24, and 96 h.

2.5. X-ray diffraction studies

Crystals of **3** and **4** were grown from a saturated toluene solution stored at 5 °C. Single crystals were coated with Paratone-N oil, mounted using a polyimide MicroMount, and frozen in the cold stream of the goniometer. A hemisphere of data was collected on a Bruker AXS P4/SMART 1000 diffractometer using ω and ϕ scans with a scan width of 0.3° and 10 s (**3**) and 30 s (**4**) exposure times. The detector distance was 5 cm. For **3**, the data were reduced (SAINT) [20] and corrected for absorption (SADABS) [21]. The structure was solved by direct methods and refined by full-matrix least squares on F^2 (SHELXTL) [22]. The octyl group was disordered and the site occupancies determined using an isotropic model as 0.6 (C(8)–C(15)) and 0.4 (C(8′)–C(15′)) and fixed in subsequent refinement cycles. For **4**, the crystal was a multiple twin and the orientation matrix for the major component was determined (CELL_NOW) [23]. Solving the structure in a lower symmetry space group or larger cell setting did not alleviate the disorder. The data were reduced (SAINT) [20] and corrected for absorption (TWINABS) [24]. The structure was solved by direct methods and refined by full-matrix least squares on F^2 (SHELXTL) [22]. The ligand was disordered over two sites, generated by symmetry operators of the space group. All non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogen atoms were included in calculated positions and refined using a riding model. Bond distances and thermal parameters within the side chain of **3** were restrained.

2.6. Cell cultures

Human glioma cells LN18, LN405 and Hs683 were maintained in an incubator at 37 °C and 5% CO_2 in DMEM supplemented with 10% FBS (foetal bovine serum) and antibiotics (Invitrogen) and have been described elsewhere [25]. All cell lines were kind gifts of Adrian Merlo (Laboratory of Molecular Neuro-oncology, University of Basel, Basel, Switzerland).

2.7. MTT assays

10 000 cells were seeded in triplicates in 96-wells plates in 200 μL of cell medium and incubated for 24 h at 37 °C and 5% CO_2. Medium was replaced with medium containing 0.5 μM of complexes dissolved in DMSO (or DMF) and further incubated for

48 h. Complexes were substituted for DMSO (or DMF) in control wells. Following incubation, 20 μL of a 5 mg/mL solution of MTT in PBS was added to each well. Cells and MTT were incubated for 3 h and removed afterwards. Stained cells were re-suspended in 100 μL of a 1:24 1 M HCl/95% EtOH and read at 560 nm on a Varioskan (Scanlab). All data presented are mean ± standard error of the mean (SEM).

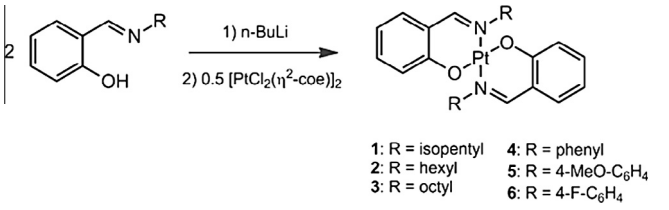
3. Results and discussion

3.1. Chemistry

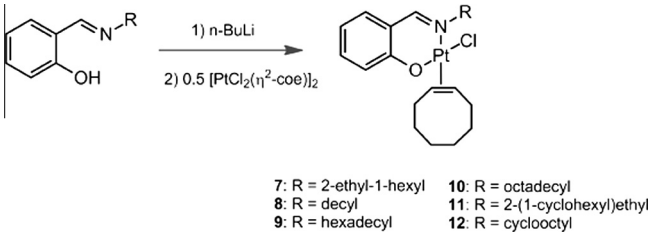
Addition of *n*-BuLi to the readily prepared salicylaldimine ligands followed by addition of $[PtCl_2(\eta^2\text{-coe})]_2$ (coe = *cis*-cyclooctene) afforded the corresponding bis(salicylaldiminato)platinum(II) complexes **1**–**6** in good yields (Scheme 1). Compounds **1**–**3** contain aliphatic chains of various lengths to increase the lipophilicity of the platinum complexes to overcome some of the drawbacks associated with cisplatin therapy. Indeed, considerable effort has been directed towards improving the lipophilicity of the metal complex by encapsulating the drug in liposomes [26]. On the other hand, compounds **4**–**6** contain aromatic rings with electron donating (**5**) and electron withdrawing (**6**) groups in the para position in order to assess the role electronic effects may play on bioactivities. Compounds **1**–**6** were only sparing soluble in polar organic solvents (i.e. DMSO, DMF, etc.) and completely insoluble in water.

All new complexes have been characterized by multinuclear NMR and FT-IR spectroscopy, as well as elemental analyses. A significant upfield shift in the ^{1}H NMR spectra from δ 9 ppm to 8 ppm is observed for the imine proton upon coordination of the ligand to the d^8 metal center. Likewise, the imine carbon (N=C) in the $^{13}C\{^1H\}$ NMR spectra has shifted only marginally from δ 160 ppm to 163 ppm upon complexation. No peaks are observed for the cyclooctene group suggesting that two equivalents of the salicylaldiminato ligands are bound to platinum. The diagnostic C=N stretch in the FT-IR spectra has also shifted (Schiff base is at ν 1620 cm^{-1}) to a slightly lower wavenumber (approximately ν 1605–1615 cm^{-1} for metal complexes) and elemental analyses are consistent with a bis Schiff base formulation. Also of note, is the absence of the broad OH peak in the FT-IR spectra when the ligands are coordinated to platinum. Complexes **3** and **4** have been characterized by single crystal X-ray diffractions studies, the molecular structures of both square planar complexes are shown in Fig. 2 (Table 1). Bond distances and angles are similar to those found in the related bis salicylaldoximato *trans*-(*N*,*N*)-[Pt(o-OC_6H_4-$CH{=}NOH)_2$], where the Pt–N distance is 1.974(6) Å and the Pt–O bond is 1.978(5) Å [27]. The C=N bonds are N1–C1 1.282(7) Å (**3**) and 1.302(11) Å (**4**), respectively, suggesting a significant double bond character. In comparison the related C–N singles bonds from the amine group are N1–C8 1.480(7) Å (**3**) and 1.449(10) Å (**4**). As with related species, only one isomer is observed where the imine nitrogens are *trans* to one another. Complexes **1**–**6** were stable in DMSO for days, but eventually decomposed to give a number of unidentified platinum complexes, including platinum metal, resulting from disassociation of the Schiff base ligand. The poor solubilities associated with **1**–**6** precludes their potential use as therapeutics, where one the major difficulties, and hence side effects, associated with cisplatin is its limited solubility in both aqueous and organic media. As such, a novel family of complexes was prepared containing only one Schiff base ligand and an organic soluble cyclooctene (coe) ligand. Introduction of a cyclooctene group to platinum is known to vastly enhance the solubilities of the corresponding complexes in simple organic solvents [18].

A series of mono Schiff base organometallic complexes **7**–**12** was prepared from organic soluble long chain alkyl amines and salicylaldehyde (Scheme 2) and characterized by multinuclear NMR and FT-IR spectroscopy and elemental analyses. Although complexes **7**–**12** showed no appreciable solubility in water, these organometallic derivatives are now soluble in common organic solvents such as dichloromethane and THF. Multinuclear NMR spectroscopic data confirmed the presence of a bound cyclooctene



Scheme 1. Synthesis of complexes **1**–**6**.



Scheme 2. Synthesis of complexes **7**–**12**.

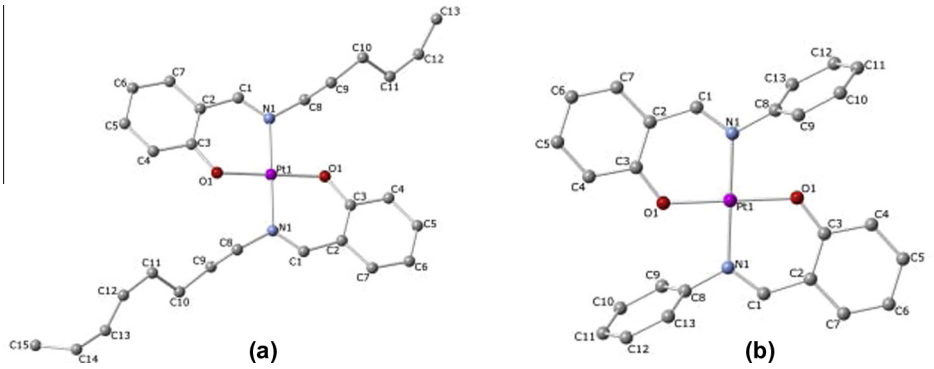


Fig. 2. Ball and stick diagrams of the molecular structures of complexes **3** (a) and **4** (b) with hydrogen atoms omitted for clarity. Selected bond distances: Pt–N(1) 2.018(4), Pt–O(1) 1.985(4) Å (**3**); Pt–N(1) 1.995(8), Pt–O(1) 1.977(5) Å (**4**).

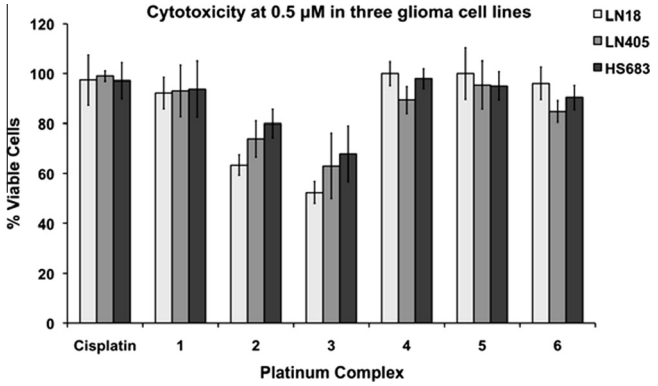


Fig. 3. Cytotoxic effects of platinum complexes in three glioma cell lines. % Viability ± standard error is expressed as an average of triplicates.

group, as the ^{1}H NMR data showed a broad peak at around δ 5.5 ppm attributed to the olefinic C–H bonds with platinum coupling (J_{H-Pt} = 57 Hz), suggesting that the cyclooctene unit is still coordinated to the metal center, and showing the expected platinum satellites. Similarly, the coordinated alkene shows up at about δ 94 ppm in the ^{13}C NMR spectra, consistent with a platinum bound alkene. Like the bis Schiff base complexes, the diagnostic C=N stretch in the FT-IR spectra also shifted to a lower wavenumber (approximately ν 1610 cm^{-1} for metal complexes) and elemental analyses are consistent with a mono Schiff base cyclooctene formulation. The absence of a broad OH peak in the FR-IR spectra was also noted when the ligands were coordinated to platinum. Unfortunately, all attempts to isolate single crystals for an X-ray diffraction study to confirm the structure of these complexes proved unsuccessful. A previous study in our laboratory, however, showed that the nitrogen atom is *trans* to the alkene group of the cyclooctene group [28]. Once again, complexes **7**–**12** were stable in DMSO or DMF for days at room temperature, but upon heating to 60 °C small amounts of decomposition products were observed. Interestingly, it appears that the Schiff base ligand becomes uncoordinated and decomposes back to the starting aldehyde and amine. No evidence was observed by multinuclear NMR spectroscopy, however, for free cyclooctene, suggesting that this ligand remains bound to the platinum center.

3.2. In vitro tests

Initial tests were conducted on the first class of platinum complexes **1**–**6**, using cisplatin as a standard, for their cytotoxic properties against three glioma cell lines using the MTT method. LN405 and LN18 are two GBM cell lines with distinct PTEN, p14/ARF and p16 tumor suppressors expression status [25]. Hs683 cells are derived from a human oligodendroglioma, a glioma less aggressive than its GBM counterpart, and have been characterized elsewhere [29]. Unfortunately, the poor solubilities of **1**–**6** allowed a maximum concentration of only 0.5 μM. The length of the aliphatic R group in complexes **1**–**3** was associated with an increase in cytotoxicity in all three cell lines tested when compared to cisplatin (Fig. 3), a compound with a long history of therapeutic use in high-grade gliomas [30,31]. Complex **3**, the one possessing the longest aliphatic and most lipophilic chain, was particularly cytotoxic to all three glioma cell models. Introduction of aromatic rings in the platinum complexes **4**–**6**, however, did not lead to any significant cytotoxic effects on glioma cells.

Owing to the increased solubilities, the cytotoxic activities of the six new organometallic complexes were examined in greater detail, using cisplatin as a control, against the same three glioma cell lines performed at final concentrations of 100, 10 and 1 μM. Overall, the results (Fig. 4) showed that four complexes **7**, **8**, **11**, and **12** all exhibited greater cytotoxic activity than cisplatin against all three cell lines. In contrast, the platinum complexes with the longest saturated lipophilic chains, hexadecyl (**9**) and octadecyl (**10**), had the least potent cytotoxic effect. Of significance is the observation that complex **11** displayed greater cytotoxicity against LN18 at 10 μM than cisplatin at 100 μM. The cytotoxicities of all platinum complexes against the less aggressive oligodendrocytoma cell line (Hs683) were similar to that observed against the other GBM models. Further studies are needed, however, to determine the structure–activity relationship of these complexes and the role of the alkene group, the results of which will be published in due course.

4. Conclusions

In summary, two novel families of platinum complexes were prepared and evaluated for their *in vitro* cytotoxic potential in three brain tumor cell lines LN18, LN405 and Hs683. Complexes possessing moderately long aliphatic chains, while being able to maintain solubility in physiological media, were particularly cytotoxic to all three glioma cell models. The ability to readily alter the salicylaldiminato ligands will allow us to generate a wide range of potentially useful platinum chemotherapeutic agents with various physical and chemical properties, which will be the subject of further studies, along with studies to understand the mechanism of action in these new complexes.

Acknowledgements

We thank NSERC, MAU, and U de M for the financial support. AEP thanks the Beatrice Hunter Cancer Research Foundation for a summer grant. Dan De Lion Durant is thanked for his expert technical assistance and anonymous reviewers for the very helpful suggestions.

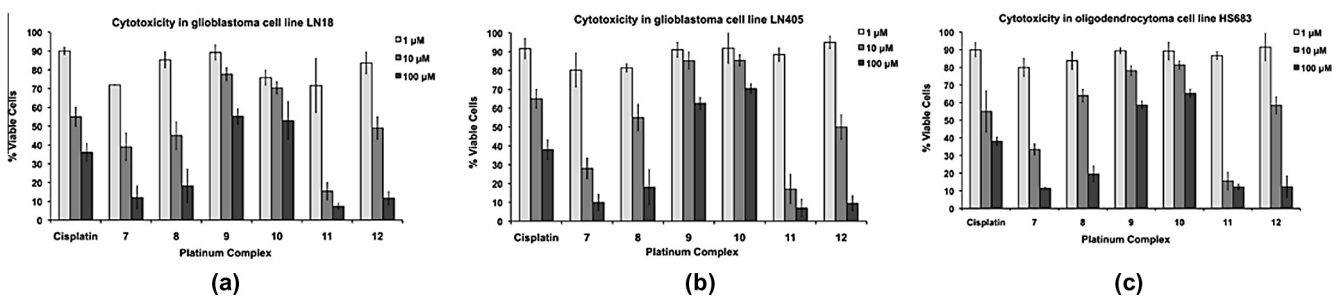


Fig. 4. Cytotoxicity of cisplatin and novel platinum complexes **7**–**12** against glioblastoma cell line (a) LN18 (b) LN405, and (c) Hs683 at 100, 10 and 1 μM. % Viability ± standard error is expressed as an average of triplicates.

Appendix A. Supplementary material

CCDC 970375 and 970378 contain the supplementary crystallographic data for **3** and **4**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2014.02.028.

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