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Synthesis, characterization, photoluminescence and electrochemical properties of Pt(II) and Ag (I) complexes of tetradentate aminomethylphosphine ligands and antiproliferative activities on HT-29 human colon cancer

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Novel N^1,N^1,N^4,N^4-tetrakis((diphenylphosphino)methyl)benzene-1,4-diamine (L1), N^1,N^1,N^5,N^5-tetrakis((diphenylphosphino) methyl)naphthalene-1,5-diamine (L2) and 4,4′-methylenebis(*N*,*N*-bis((diphenylphosphino)methyl)aniline) (L3) ligands and their Pt(II) and Ag(I) complexes have been synthesized under nitrogen atmosphere using the Schlenk technique. The ligands and the complexes were characterized using ^{1}H NMR, ^{31}P NMR and Fourier transform infrared spectroscopies, thermogravimetric/differential thermal analysis, elemental analysis (C, H, N), inductively coupled plasma optical emission spectrometry (metal content), cyclic voltammetry and photoluminescence. All the complexes were investigated as anticancer agents on HT-29 human colon cancer cell line. HT-29 cells were treated with various concentrations (10, 25, 50, 100, 250 μM) of Pt(II) and Ag(I) tetrakisditertiaryaminomethylphosphine complexes. Cisplatin was tested at the same concentrations in order to compare the antiproliferative activities of the synthesized Pt(II) and Ag(I) complexes. Pt(II) complexes of L1 and L3 and Ag(I) complexes of L1, L2 and L3 showed a similar inhibition effect of cancer cell proliferation when compared to cisplatin up to 50 μM; at 100 μM and higher concentrations, L1–Pt(II) and L3–Ag(I) complexes showed a much greater effect than cisplatin. Copyright © 2016 John Wiley & Sons, Ltd.

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Keywords: phosphine; anticancer; HT-29; cyclic voltammetry; photoluminescence

Introduction

Pt(II) complexes have been used as used in tumour chemotherapy for about three decades. However, they have severe side effects on human cells and the applicability of them is limited because of increasing drug resistance. These problems have not been resolved yet. Studies of antimicrobial and antitumoral activities of Ag(I) and Au(I) complexes using phosphines have reported them to show a wide spectrum of antimicrobial activities.[1,2] Some AgN, AgP, NAgP and AgC types of silver(I) complexes were synthesized and cytotoxic activity was found against some Gram-positive and Gram-negative bacteria.[1–3]

It has also been reported that Au(I) bis(diphosphine) complexes such as $[Au(dppe)_2]^+$ (where dppe is 1,2-bis(diphenylphosphino) ethane) and optically active phosphine–Au(I) complexes are active against some types of cancer.[4]

Functionalized chelating ditertiary aminomethylphosphines of the type $(R_2PCH_2)_2NR'$ can be obtained by treating phosphonium salts $[R_2P(CH_2OH)_2]Cl$ with primary amines $R'NH_2$.[5–10] Even though there has been much research on the chemistry and catalytic activities of metal–aminophosphine complexes, there have not been enough studies up to now on the biological activities of aminomethylphosphines having P–C–N linkages. Thus, we have focused on the synthesis of novel aminomethylphosphine–metal complexes of Au(I), Ag(I), Cu(I) and Co(II) and have explored some of the biological properties of these complexes.[6,11–16] Ditertiary aminomethylphosphine ligands having soft $NCPPh_2$ donor atoms coordinated to metal centres have a significant *trans* effect. Chloro

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ligands located at the *trans* position of $NCPPh_2$ groups can easily leave the metal centres and *trans*-labilization is increased for DNA coordination to the metal centres. If comparing the *trans* effect of the phosphorus donor atom of $NCPPh_2$ groups with either nitrogen or oxygen, several phosphine-based complexes inhibit tumour growth.[1,17,18]

Our synthesized Pt(II) complexes of L1 and L3 and Ag(I) complexes of L1, L2 and L3 showed a similar inhibition effect on cancer cell proliferation compared to cisplatin up to a concentration of 50 μM; at 100 μM and higher concentrations, L1–Pt(II) and L3–Ag(I) complexes showed a much greater effect than cisplatin.

Experimental

General

^1H NMR and ^{31}P NMR spectra were recorded at 25°C in $CDCl_3$ using an Avance III HD Ascend 600 ULH NMR spectrometer. Fourier transform infrared (FT-IR) spectra were recorded with a PerkinElmer Spectrum 400 FT-IR system. Elemental analyses were performed using a LECO CHNS 932 instrument. Mass spectra of the ligands were recorded with a Zivak Tandem Gold LC-MSMS spectrometer (ESI). The positive and negative ion modes were used simultaneously in MS analyses. The complexes were digested with HNO_3 + H_2O_2 solution using a Berghof MWS 3+ microwave oven and metal contents were determined with a PerkinElmer Optima 2100 DV inductively coupled plasma optical emission spectrometer. Calibration standards of Pt(II) and Ag(I) ions were prepared from Inorganic Ventures (USA) calibration stocks (about 1000 mg l^{-1}). Ultrapure water obtained from a Milli-Q purifier system (Millipore Corp., Bedford, MA) was used for the calibration standards. The thermal properties of the ligands were investigated with a SII thermal system under nitrogen atmosphere at a heating rate of 10°C min^{-1} in the range 30–1000°C.

Dimethylformamide (DMF) stock solutions (1×10^{-4} M) of the phosphine ligands and their metal complexes were used for electrochemical studies. Cyclic voltammograms were recorded using an Iviumstat electrochemical workstation equipped with a low current module (BAS PA-1) recorder. The electrochemical cell was equipped with a BAS glassy carbon working electrode (area of 4.5 mm^2), a platinum coil auxiliary electrode and an Ag^+/AgCl reference electrode filled with tetrabutylammonium tetrafloroborate (0.1 M) in DMF solution and adjusted to 0.00 V versus SCE. Cyclic voltammetric measurements were performed at room temperature in an undivided cell (BAS model C-3 cell stand) with a platinum counter electrode and an Ag^+/AgCl reference electrode (BAS). All potentials are reported with respect to Ag^+/AgCl. The solutions were deoxygenated by passing dry nitrogen through them for 15 min prior to the experiments, and during the experiments the flow was maintained over the solution. Digital simulations were performed using DigiSim 2.0 for windows (BAS Inc.). Experimental cyclic voltammograms used for the fitting process had the background subtracted and were corrected electronically for ohmic drop. A Hanna pH meter was used for the pH measurements using a combined electrode (glass reference electrode) with an accuracy of ±0.01.

UV–visible spectra in the range 200–1000 nm were obtained with samples in DMF solvent using a PerkinElmer Lambda 45 spectrophotometer. Photoluminescence properties were investigated with a PerkinElmer LS55 instrument.

All chemicals and reagents were purchased from Merck, Fluka, Sigma or Aldrich and all solvents were dried using established procedures and immediately distilled under nitrogen atmosphere prior to use.

Synthesis of Tetrakis(aminomethylphosphine) Ligands (L1, L2, L3)

$[PPh_2(CH_2OH)_2]Cl$ salt was obtained according to the literature.[6,7,9,13] The novel tetrakis(aminomethylphosphine) ligands were synthesized using the reaction of 1,4-phenylenediamine, 4,4′-diaminodiphenylmethane, 1,5-naphthalenediamine and $[PPh_2(CH_2OH)_2]Cl$ with NEt_3 using the Schlenk technique under nitrogen atmosphere.[5–9,12–16] An amount of 0.1 g (0.3537 mmol) of $[Ph_2P(CH_2OH)_2]Cl$ was dissolved in EtOH–water (1:1) and 1.0 ml of triethylamine (99%) and 0.088 mmol of aryldiamine were added to this solution respectively. After refluxing this mixture for 1 h, the synthesized tetrakis (aminomethylphosphine) ligands were extracted with 10 ml of dichloromethane. The dichloromethane phase were washed three times with appropriate amount of water and dried with anhydrous Na_2SO_4. An oily product was obtained when the dichloromethane phase was evaporated.

N^1,N^1,N^4,N^4-Tetrakis((diphenylphosphino)methyl)benzene-1,4-diamine (L1)

Yield 0.06537 g (81%). Molecular formula $C_{58}H_{52}N_2P_4$. Anal. Calcd (%): C, 77.32; H, 5.82; N, 3.11. Found (%): C, 77.34; H, 5.84; N, 3.08. FT-IR (KBr, ν, cm^{-1}): 3054 (aromatic C C for PPh_2 and disubstituted benzene), 2918 (aliphatic C H), 1607, 1510 (aromatic C C for PPh_2 and disubstituted benzene), 1432 (P Ph), 1094 (*tert*-amine C N). ^1H NMR ($CDCl_3$, δ, ppm): 7.20–7.44 (m, 40H, P Ph_2), 6.72 (br, 4H, N Ar N), 3.90 (s, 8H, N CH_2 PPh_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 154.72 (PhC N), 149.21, 142.14, 137.85 (PPh_2 carbons), 130.07 (central ArC), 57.64 (N CH_2 P). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): −27.12 (s, PPh_2). MS-ESI: *m/z* 900 ($[M-1]^+$, 25%), 901 ($[M]^+$, 54%), 902 ($[M+1]^+$, 50%).

N^1,N^1,N^5,N^5-Tetrakis((diphenylphosphino)methyl)naphthalene-1,5-diamine (L2)

Yield 0.0724 g (86%). Molecular formula $C_{62}H_{54}N_2P_4$. Anal. Calcd (%): C, 78.30; H, 5.72; N, 2.96. Found (%): C, 78.24; H, 5.74; N, 3.01. FT-IR (KBr, ν, cm^{-1}): 3052 (aromatic C H), 2915 (aliphatic C H), 1602, 1525 (aromatic C C for PPh_2 and disubstituted naphthalene), 1432 (P Ph), 1114 (*tert*-amine C N). ^1H NMR ($CDCl_3$, δ, ppm): 7.82–7.33 (m, 40H, P Ph_2), 7.28 (br, 2H, α-H of naphthalene), 6.95 (d, J = 7.8 Hz, 2H, β-H of naphthalene), 6.75 (d, J = 7.8 Hz, 2H, γ-H of naphthalene), 4,20 (s, 8H, N CH_2 PPh_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 155.62, (naphthalene C N), 150.96, 143.01, 139.18 (PPh_2 carbons), 152.84, 137.88, 133.24, 130.13 (other naphthalene carbons), 58.45 (N CH_2 P). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): −26.06 (s PPh_2). MS-ESI: *m/z* 950 ($[M-1]^+$, 32%), 951 ($[M]^+$, 54%), 952 ($[M+1]^+$, 60%), 953 ($[M+2]^+$, 35%).

4,4′-Methylenebis(N,N-bis((diphenylphosphino)methyl)aniline) (L3)

Yield 0.0746 g (85%). Molecular formula $C_{65}H_{58}N_2P_4$. Anal. Calcd (%): C, 78.77; H, 5.90; N, 2.83. Found (%): C, 78.74; H, 5.84; N, 2.84. FT-IR (KBr, ν, cm^{-1}): 3051 (aromatic C H), 2910 (aliphatic C H), 1610, 1512 (aromatic C C for PPh_2 and disubstituted benzene), 1433 (P Ph), 1119 (*tert*-amine C N). ^1H NMR ($CDCl_3$, δ, ppm): 7.85–7.12 (m, 40 H, P Ph_2), 6.98 (d, J = 8.6 Hz, 4H, *ortho*-H of N Ar N), 6.72 (d, J = 8.6 Hz, 4H, *meta*-H of N Ar N), 4.80 (s, 2H, Ph CH_2 Ph), 3.92 (s, 8H, N CH_2 PPh_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 151.91 (ArC N), 150.20, 145.15, 138.01 (PPh_2 carbons), 148.01, 141.22, 139.24 (central-Ph carbons), 57.66 (N CH_2 P), 42.19 (Ph CH_2 Ph). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): −27.57 (s, PPh_2). MS-ESI: *m/z* 990 ($[M-1]^+$, 32%), 991 ($[M]^+$, 44%), 992 ($[M+1]^+$, 20%), 993 ($[M+2]^+$, 12%).

Synthesis of Metal Complexes

Pt(II) complexes

Tetrakis(aminomethylphosphine) ligand L1, L2 or L3 (0.088 mmol) was dissolved in dichloromethane and a solution of 0.156 mmol of $[Pt(COD)Cl_2]$ in EtOH–water (1:1) was added to the solution. The mixture was stirred under refluxed for 6 h under nitrogen atmosphere. Addition of diethyl ether, the complexes precipitated which was then filtered off and dried at 60°C.

$[Pt_2(L1)Cl_4]\cdot(NEt_3)(H_2O)$ (**1**). Yield 0.1113 g (81%). Molecular formula $C_{64}H_{69}Cl_4N_3OP_4Pt_2$. Anal. Calcd (%): C, 49.52; H, 4.48; N, 2.71; Pt, 25.14. Found: C, 49.48; H, 4.41; N, 2.74; Pt, 25.18. FT-IR (KBr, ν, cm^{-1}): 3332 (OH), 3050 (aromatic C H), 2962 (aliphatic C H), 1611, 1512 (aromatic C C for PPh_2 and disubstituted benzene), 1434 (P Ph), 1099 (*tert*-amine C N). ^1H NMR ($CDCl_3$, δ, ppm): 6.8–7.9 (m, 44H, Ar-H), 4.37 (s, 8H, N CH_2 PPh_2), 3.08 (q, J = 7.7 Hz, 6H, N CH_2 CH_3), 1.3 (t, J = 7.7 Hz, 9H, N CH_2 CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 154.21 (PhC N), 149.10, 142.24, 136.98 (PPh_2 carbons), 130.92 (central ArC), 57.25 (N CH_2 P). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 53.01 (J_{PPt} = 10.9 Hz, *P*Ph_2 Pt *P*Ph_2).

>$[Pt_2(L2)Cl_4]\cdot(NEt_3)(H_2O)$ (**2**). Yield 0.1107 g (78%). Molecular formula $C_{68}H_{71}Cl_4N_3OP_4Pt_2$. Anal. Calcd (%): C, 50.98; H, 4.47; N, 2.62; Pt, 24.35. Found (%): C, 50.93; H, 4.43; N, 2.64; Pt, 24.30. FT-IR (KBr, ν, cm^{-1}): 3387 (OH), 3063 (aromatic C H), 2987 (aliphatic C H), 1613, 1526 (aromatic C C for PPh_2 and disubstituted naphthalene), 1434 (P Ph), 1101 (*tert*-amine C N). ^1H NMR ($CDCl_3$, δ, ppm): 8.1–6.9 (m, 46H, Ar-H), 4.47 (s, 8H, N CH_2 PPh_2), 1.38 (t, J = 7.3 Hz, 9H, N CH_2 CH_3), 3.1 (q, J = 7.3 Hz, 6H, N CH_2 CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 155.01 (Naphthalene C N), 148.97, 150.77, 150.83 (PPh_2 carbons), 155.22, 141.46, 140.90, 138.25 (other naphthalene carbons), 58.22 (N CH_2 P). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 53.04 (J_{PPt} = 10.6 Hz, *P*Ph_2 Pt *P*Ph_2).

$[Pt_2(L3)Cl_4]\cdot(NEt_3)(H_2O)$ (**3**). Yield 0.1193 g (82%). Molecular formula $C_{71}H_{75}Cl_4N_3OP_4Pt_2$. Anal. Calcd (%): C, 51.93; H, 4.60; N, 2.56; Pt, 23.76. Found (%): C, 51.92; H, 4.63; N, 2.54; Pt, 23.71. FT-IR (KBr, ν, cm^{-1}): 3338 (OH), 3053 (aromatic C H), 2901 (aliphatic C H), 1612, 1514 (aromatic C C for PPh_2 and disubstituted benzene), 1435 (P Ph), 1101 (*tert*-amine C N). ^1H NMR ($CDCl_3$, δ, ppm): 6.9–8.0 (m, 48H, Ar-H), 4.9 (s, 2H, Ph CH_2 Ph), 4.27 (s, 8H, N CH_2 PPh_2), 3.12 (q, J = 7.3 Hz, 6H, N CH_2 CH_3), 1.42 (t, J = 7.3 Hz, 9H, N CH_2 CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 152.23 (ArC N), 150.75, 145.34, 137.12 (PPh_2 carbons), 148.54, 142.13, 138.59 (PPh_2 carbons), 57.89 (N CH_2 P), 42.11 (Ph CH_2 Ph). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 53.06 (J_{PPt} = 10.6 Hz, *P*Ph_2 Pt *P*Ph_2).

Ag(I) complexes

Tetrakis(aminomethylphosphine) ligand L1, L2 or L3 (0.088 mmol) was dissolved in dichloromethane and a solution of 0.156 mmol of $AgNO_3$ in EtOH–water (1:1) was added into the ligand solution. The mixture was stirred under refluxed for 6 h under nitrogen atmosphere in the dark. Addition of diethyl ether, the complexes precipitated which was then filtered off and dried at 60°C.

$[Ag_2(L1)(NO_3)_2(NEt_3)_2]\cdot H_2O$ (**4**). Yield 0.1023 g (79%). Molecular formula $C_{70}H_{84}Ag_2N_6O_7P_4$. Anal. Calcd (%): C, 57.54; H, 5.80; N, 5.75; Ag, 14.77. Found (%): C, 57.59; H, 5.78; N, 5.81; Ag, 14.71. FT-IR (KBr, ν, cm^{-1}): 3296 (OH), 3040 (aromatic C H), 2987 (aliphatic C H), 1309 (N O), 1610, 1514 (aromatic C C for PPh_2 and disubstituted benzene), 1434 (P Ph), 1098 (*tert*-amine C N). ^1H NMR ($CDCl_3$, δ, ppm): 7.8–6.8 (m, 44H, Ar-H), 4.29 (s, 8H, N CH_2 PPh_2), 3.12 (q, J = 7.5 Hz, 6H, N CH_2 CH_3), 1.38 (t, J = 7.5 Hz, 9H, N CH_2 CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 153.98 (PhC N), 150.11, 143.01, 137.14 (PPh_2 carbons), 129.34 (central ArC), 57.42 (N CH_2 P). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 30.76 (s-br, *P*Ph_2 Ag *P*Ph_2).

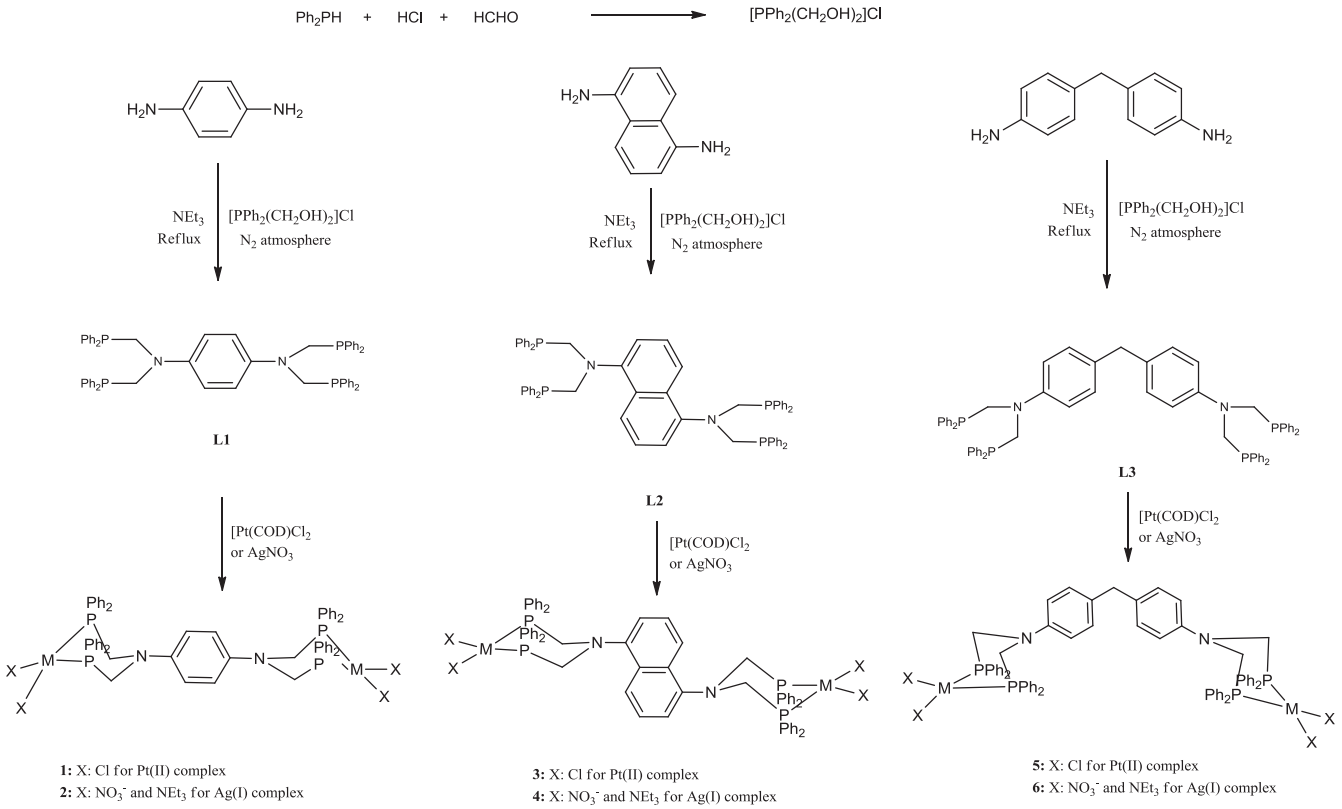

Figure 1. Synthesis of the ligands and their Pt(II) and Ag(I) complexes. $[PPh_2(CH_2OH)_2]Cl$ salt was synthesized according to the literature.[6,7,9,13]

$[Ag_2(L2)(NO_3)_2(NEt_3)_2]\cdot H_2O$ (**5**). Yield 0.1094 g (78%). Molecular formula $C_{74}H_{94}Ag_2N_6O_{11}P_4$. Anal. Calcd (%): C, 58.52; H, 5.74; N, 5.56; Ag, 14.28. Found (%): C, 58.48; H, 5.79; N, 5.52; Ag, 14.24. FT-IR (KBr, ν, cm^{-1}): 3306 (OH), 3071 (aromatic C H), 2987 (aliphatic C H), 1325 (N O), 1604, 1532 (aromatic C C for PPh_2 and disubstituted benzene), 1433 (P Ph), 1098 (*tert*-amine C-N). ^{1}H NMR ($CDCl_3$, δ, ppm): 6.8–7.8 (m, 46H, Ar-H), 4.38 (s, 8H, N CH_2 PPh_2), 3.18 (q, J = 7.3 Hz, 12H, N CH_2 CH_3), 1.41 (t, J = 7.3 Hz, 9H, N CH_2 CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 155.56 (naphthalene C N), 150.89, 142.76, 139.55 (PPh_2 carbons), 123.22, 137.38, 133.22, 130.37 (PPh_2 carbons), 58.32 (N CH_2 P). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 30,06 (J_{PAg} = 54.7 Hz, PPh_2 Ag PPh_2).

$[Ag_2(L3)(NO_3)_2(NEt_3)_2]\cdot H_2O$ (**6**). Yield 0.1107 g (77%). Molecular formula $C_{77}H_{98}Ag_2N_6O_{11}P_4$. Anal. Calcd (%): C, 59.62; H, 5.85; N, 5.42; Ag, 13.91. Found (%): C, 56.99; H, 5.92; N, 5.23; Ag, 13.88. FT-IR (KBr, ν, cm^{-1}): 3321 (OH), 3062 (aromatic C H), 2987 (aliphatic C H), 1307 (N O), 1611, 1514 (aromatic C C for PPh_2 and disubstituted benzene), 1434 (P Ph), 1098 (*tert*-amine C N). ^{1}H NMR ($CDCl_3$, δ, ppm): 7.1–8.2 (m, 48H, Ar-H), 4.9 (s, 2H, Ph CH_2 Ph), 4.1 (s, 8H, N CH_2 PPh_2), 3.20 (q, J = 7.3 Hz, 12H, N CH_2 CH_3), 1.39 (t, J = 7.3 Hz, 9H, N CH_2 CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 152.15 (ArC N), 150.02, 145.23, 138.25 (PPh_2 carbons), 148.17, 140.95, 139.61 (PhC R), 57.75 (N CH_2 P), 42.21 (Ph CH_2 Ph). $^{31}P\{^1H\}$ NMR ($CDCl_3$, δ, ppm): 31.55 (br, PPh_2 Ag PPh_2).

Antiproferative Activity on HT-29 Human Colon Cancer

Human colon cancer cell culture

The culturing of cancer cells was performed at the Laboratory of Tissue Culture and Stem Cells (Department of Pharmacology, School of Medicine, Kahramanmaras Sütçü İmam University, Kahramanmaras, Turkey). Human colon cancer cell line (HT-29) was obtained from the American Type Cell Collection (Manassas, VA, USA). Cells were cultured in McCoy's 5a Medium (Gibco Life Technologies, Carlsbad, CA, USA) supplemented with 10% foetal bovine serum (Gibco Life Technologies) and 100 U ml^{-1} penicillin (Sigma-Aldrich, St Louis, MO, USA) at 37°C in a humidified atmosphere of 5% CO_2. For three days prior to the experiment, HT-29 cells were cultured with phenol red free medium (Gibco Life Technologies). The negative control condition for all assays was untreated medium containing vehicle (0.1% dimethylsulfoxide (DMSO)). Cisplatin and DMSO were purchased from Sigma-Aldrich.

MTT assay

HT-29 cells were treated with various concentrations (10, 25, 50, 100, 250 μM) of Pt(II) and Ag(I) complexes of L1, L2 and L3. Cisplatin was used at the same concentrations in order to compare with the synthesized Pt(II) and Ag(I). Cells were placed in 96-well plates and incubated for 48 h. Following incubation, MTT solution (Sigma-Aldrich) was added controlled to each well at a concentration of 0.5 mg ml^{-1}, and incubated for 4 h at 37°C. At the end of this period, 100 μl of DMSO solvent was added to each well. The absorbance values (optical density) at 570 nm for the solution in each well were read using a spectrophotometer (ELx800 Absorbance Reader; BioTek Instruments Inc., Winooski, VT, USA).

Table 1. ^{31}P NMR data for the complexes

Ligand δ_P (ppm)		Complex	δ_P (ppm)	J_{PMP}	$\Delta\delta$ (ppm)[a]
L1	−27.12	$[Pt_2(L1)Cl_4]\cdot N(Et)_3(H_2O)$	53.01	10.86	80.13
		$[Ag_2(L1)(NO_3)_2(N(Et)_3)_2]\cdot H_2O$	30.76	—	57.88
L2	−27.68	$[Pt_2(L2)Cl_4]\cdot N(Et)_3(H_2O)$	53.03	10.66	80.71
		$[Ag_2(L2)(NO_3)_2(N(Et)_3)_2]\cdot H_2O$	30.05	—	57.73
L3	−27.57	$[Pt_2(L3)Cl_4]\cdot N(Et)_3(H_2O)$	53.06	10.63	80.63
		$[Ag_2(L3)(NO_3)_2(N(Et)_3)_2]\cdot H_2O$	31.55	—	59.12

[a]Coordination shift values of the complexes: $\Delta\delta = \delta$(complex) − δ(free ligand).[13]

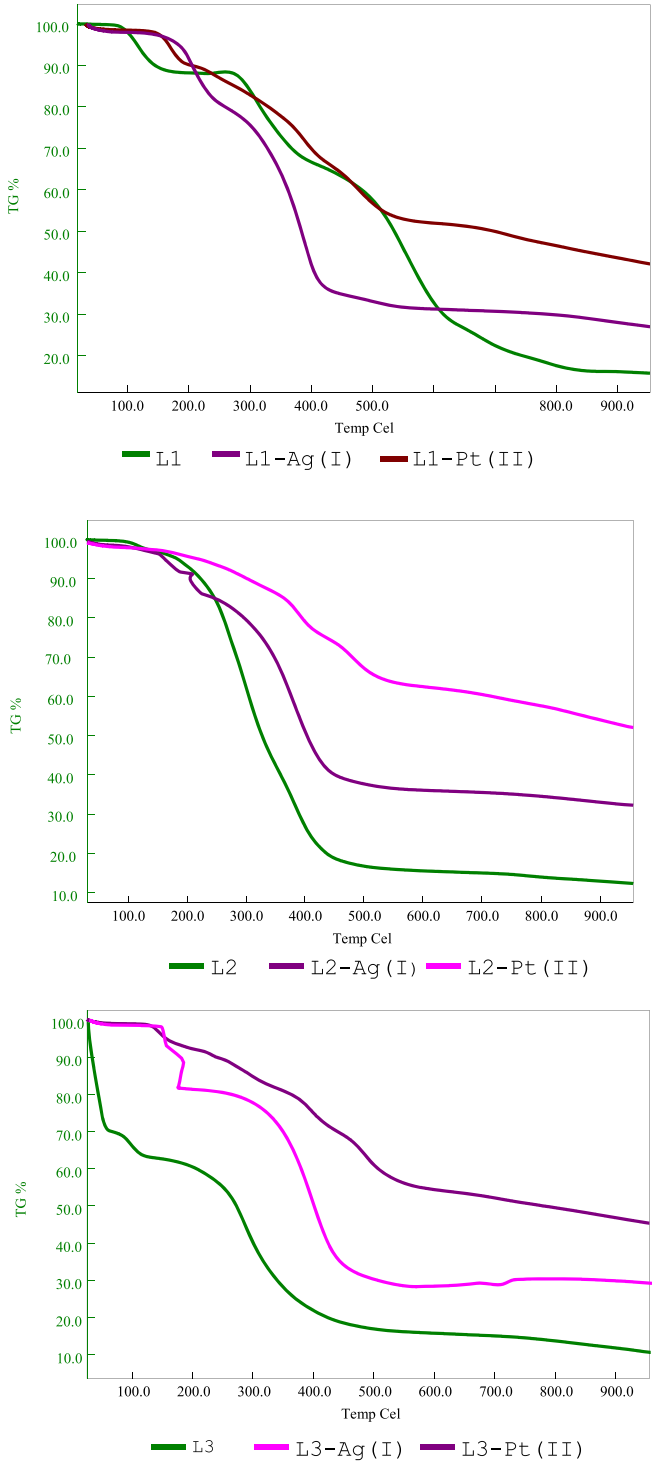

Figure 2. TG analysis curves.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 3.0 (GraphPad, San Diego, CA, USA). For all data, statistical analysis was performed using repeated measurements of ANOVA followed by *post hoc* analysis with the Bonferroni test to detect differences between the groups. Results are expressed as mean standard errors of the mean. A *P* value of less than 0.05 was considered significant.

Results and Discussion

Synthesis and Characterization

The novel ligands L1, L2 and L3 have been synthesized using the reaction of 1,4-phenylenediamine, 4,4′-diaminodiphenylmethane and 1,5-naphthalenediamine, respectively, with $[PPh_2(CH_2OH)_2]Cl$ salt under nitrogen atmosphere using the Schlenk technique according to a modified method in the literature (Fig. 1).[5–9,11–17] $[PPh_2(CH_2OH)_2]Cl$ phosphonium salt was obtained according to the literature.[6,7,9,13] Pt(II) and Ag(I) complexes of these tetradentate ditertiary aminomethylphosphine ligands have been obtained from the reactions of the synthesized ligands and $[Pt(COD)Cl_2]$ and $AgNO_3$ complexes by refluxing for 6 h under nitrogen atmosphere (Fig. 1).

The ligands and their Pt(II) and Ag(I) complexes were characterized using NMR (^{31}P and ^{1}H) and FT-IR spectroscopies, elemental analysis (C, H, N and metal content), thermogravimetric/differential thermal analysis (TG/DTA), cyclic voltammetry (CV) and photoluminescence. In FT-IR spectra of the ligands, aromatic C H stretches of P aryl and aromatic backbone were assigned to the band at about 3050 cm^{-1} as a medium peak. Aliphatic C H stretches of P CH_2 N groups appeared at about 2940 cm^{-1}. Aromatic C C bending for PPh_2 and disubstituted aromatic backbone was observed at about 1510–1610 cm^{-1}. C N stretches of tertiary amine were seen at about 1100 cm^{-1}. Sharp peaks at about 1430 cm^{-1} were assigned to P Ph stretches according to the literature. There are no significant differences between the ligands and Pt(II) and Ag(I) complexes in FT-IR spectra.[1,6–26]

All the tetrakis ditertiary aminomethylphosphine ligands have symmetric structures and have similar proton resonances in ^{1}H NMR spectra. The ^{1}H NMR signals of the aromatic protons were observed at two different areas for L1 and three different areas for L2 and L3. The backbone protons resonances of L1 were recorded at 6.72 ppm as a broad signal. Two phenyl rings bound to one phosphorus have multiple proton signals at about 7.20–7.44 ppm. A singlet peak at 3.90 ppm was from N CH_2 P proton resonance. Symmetric aminophosphine ligand L1 has a single ^{31}P NMR peak at −27.12 ppm in the ^{31}P NMR spectrum (supporting information).

Table 2. Electrochemical data for the metal complexes in DMF[a]

Compoud	Scan rate (mV s^{-1})	E_{pa} (V)	E_{pc} (V)	E_{pa}/E_{pc}	$E_{1/2}$ (V)	ΔE_p (V)
L1–Ag(I)	100	−0.71, 0.31	1.00, 0.15, −0.50	1.42	—	−0.21
	250	−0.72, 0.32	1.01, 0.16, −0.52	1.38	—	−0.20
	500	−0.73, 0.33	1.02, 0.17, −0.54	1.33	—	−0.19
	750	−0.74, 0.34	1.03, 0.18, −0,56	1.32	—	−0.18
	1000	−0.75, 0.35	1.04, 0.19, −0.58	1.29	—	−0.17
L2–Ag(I)	100	−0.60, 0.20	0.21, 0.61	0.95	0.20	−0.01
	250	−0.61, 0.21	0.22, 0.62	0.95	0.21	−0.01
	500	−0.62, 0.22	0.23, 0.63	0.95	0.22	−0.01
	750	−0.63, 0.23	0.24, 0.64	0.95	0.23	−0.01
	1000	−0.64, 0.24	0.25, 0.65	0.96	0.24	−0.01
L3–Ag(I)	100	−0.40, 1.10	0.59, 0.08, −0.41	0.97	0.41	0.01
	250	−0.41, 1.09	0.60, 0.09, −0.42	0.97	0.42	0.01
	500	−0.42, 1.08	0.61, 0.10, −0.43	0.97	0.43	0.01
	750	−0.43, 1.07	0.62, 0.11, −0.44	0.97	0.44	0.01
	1000	−0.44, 1.06	0.64, 0.12, −0.45	0.97	0.45	0.01
L1–Pt(II)	100	−0.69, 0.90	0.25, −0.35	1.97	—	−0.34
	250	−0.70, 0.91	0.26, −0.36	1.94	—	−0.34
	500	−0.71, 0.92	0.27, −0.37	1.91	—	−0.34
	750	−0.72, 0.93	0.28, −0.38	1.89	—	−0.34
	1000	−0.73, 0.94	0.29, −0.39	1.87	—	−0.34
L2–Pt(II)	100	−0.40, 0.30	0.10, −0.80	0.50	0.60	−0.40
	250	−0.41, 0.31	0.10, −0.81	0.50	0.61	−0.40
	500	−0.42, 0.32	0.11, −0.82	0.51	0.62	−0.40
	750	−0.43, 0.34	0.12, −0.82	0.52	0.63	−0.39
	1000	−0.44, 0.35	0.13, −0.83	0.53	0.64	−0.39
L3–Pt(II)	100	−0.31	0.09	3.44	—	−0.40
	250	−0.32	0.10	3.20	—	−0.42
	500	−0.33	0.11	3.00	—	−0.44
	750	−0.34	0.12	2.83	—	−0.46
	1000	−0.35	0.13	2.69	—	−0.48

[a]Supporting electrolyte: tetrabutylammonium tetrafluoroborate (Bu_4NBF_4) (0.1 M); concentration of compound: 1×10^{-3} M. All potentials referenced to Ag^+/AgCl (0.03 M $AgNO_3$). E_{pa} and E_{pc} are anodic and cathodic potentials, respectively. $E_{1/2} = 0.5 \times (E_{pa} + E_{pc})$. $\Delta E_p = E_{pa} - E_{pc}$.

Naphthalene protons had signals as three different doublet peaks in ^{1}H NMR spectra. Phosphorus-bound phenyl ring proton signals were at 7.33–7.82 ppm as a multiplet peak for L2. α-H of naphthalene was observed at 7.28 ppm as a broad signal. Doublet proton resonances of β-H and γ-H of naphthalene were seen at 6.95 ppm (J = 7.8 Hz) and 6.75 ppm (J = 7.8 Hz), respectively. N CH_2 P protons were detected as a singlet peak at 4.20 ppm. Phosphorus resonance was assigned at −26.06 ppm as a singlet peak in the ^{31}P NMR spectrum (supporting information).

Aromatic proton resonances of L3 were observed at three different regions in the ^{1}H NMR spectrum. Mono-substituted phenyl protons bound to phosphorus showed signals at 7.12–7.85 ppm

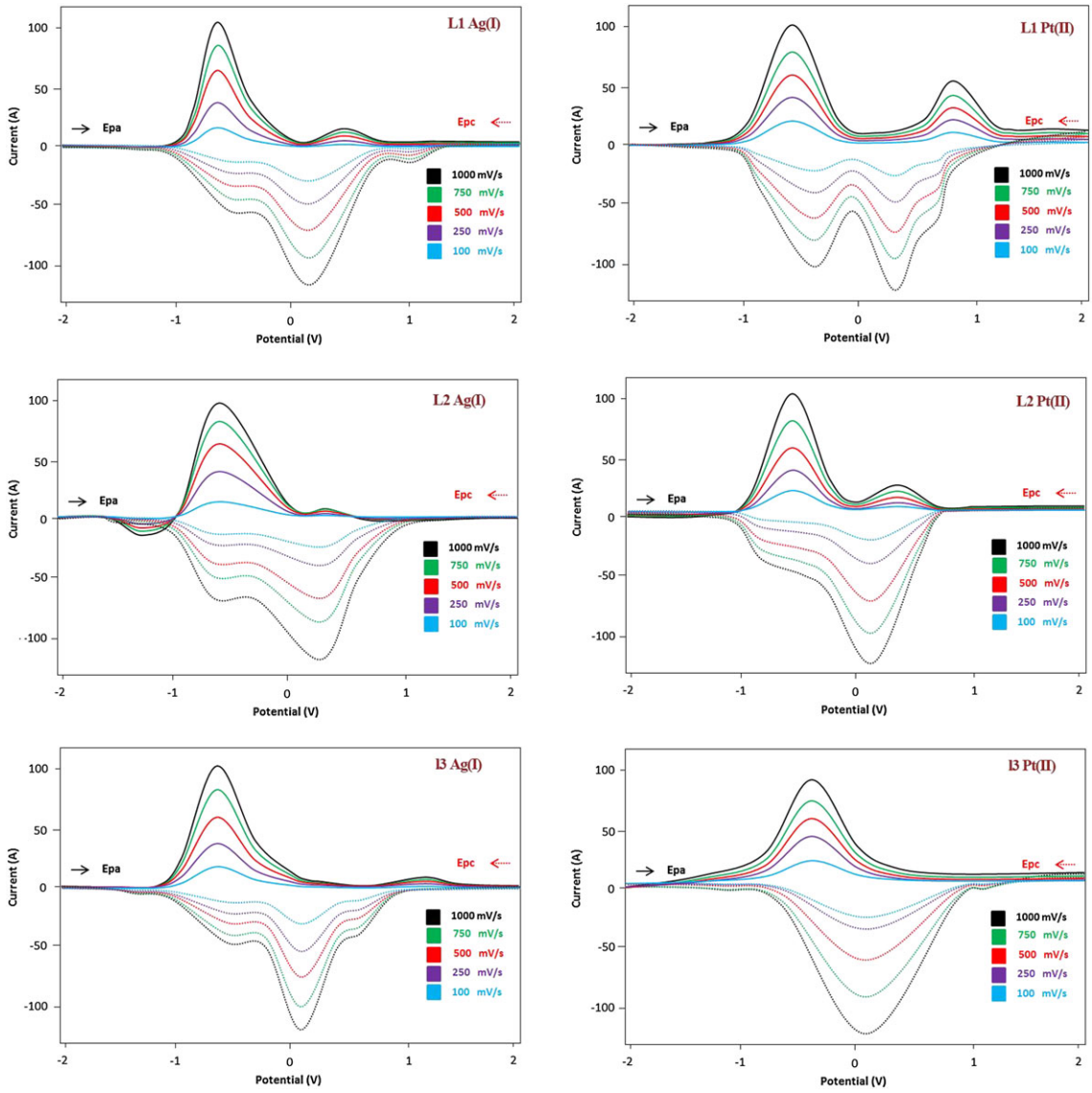

Figure 3. Cyclic voltammograms of the metal complexes in the presence of 0.1 M NBu_4BF_4–DMF solution at various scan rates.

Table 3. UV–visible absorption, emission and excitation spectral data of metal complexes

	λ_{max}				λ (ε)
	Excitation (nm)	Intensity	Emission (nm)	Intensity	
L1–Ag(I)	587	920	729	955	335 (0.64×10^4), 436 (0.18×10^4)
L2–Ag(I)	544	980	718	1000	340 (0.95×10^4), 440 (0.39×10^4)
L3–Ag(I)	543	935	720	995	342 (0.56×10^4), 444 (0.14×104)
L1–Pt(II)	544	975	716	990	355 (0.76×10^4), 450 (0.24×10^4)
L2–Pt(II)	390	945	547	1000	360 (0.53×10^4), 460 (0.18×10^4)
L3–Pt(II)	546	930	717	980	365 (0.53×10^4), 470 (0.36×10^4)

as a multiplet. *Ortho* and *meta* proton signals of di-substituted benzene of symmetric L3 ligand were observed at 6.98 ppm (J = 8.6 Hz) and 6.72 ppm (J = 8.6 Hz), respectively. Other singlet peaks of L3 appeared at 4.80 and 3.92 ppm assigned to Ph CH_2 Ph and N CH_2 P protons, respectively. As the other ligands, L3 showed a singlet ^{31}P resonance at −27.27 ppm in the ^{31}P NMR spectrum (supporting information).

Additionally to ^{1}H NMR spectra, symmetric structures were observed in proton decoupled ^{13}C NMR spectra for all the compounds. Ligands L1 and L2 showed three types of resonances in the ^{13}C NMR spectra. These were backbone aromatic structure, PPh_2 and N CH_2 P resonances. L3 showed a fourth ^{13}C resonance because of methylene groups of Ph CH_2 Ph structure. All the ligands and complexes showed similar ^{13}C peaks in ^{13}C NMR spectra. While PPh_2 carbons showed signals at about 137–150 ppm as three peaks, N CH_2 P showed one peak at about 58 ppm. N CH_2 P carbon signal shifted to low field due to N and P binding. PPh_2 carbon signals also shifted to low-field region because of the magnetic anisotropic effect of aromatic structures and the phosphorus binding effect.

Although ^{1}H NMR and ^{13}C NMR spectra of the Pt(II) and Ag(I) complexes of the ligands are similar to those of the ligands, ^{31}P resonance peaks of the complexes were shifted from −27 ppm to about 53 ppm for Pt(II) complexes and to about 31 ppm for Ag(I) complexes in ^{31}P NMR spectra. These shifts of ^{31}P resonances were due to the metal–phosphorus binding.[6–16] Additionally, M–P spin–spin coupling effects were observed because of the NMR-active Pt (II) and Ag(I) nuclei. Especially, Pt(II) complexes showed doublet ^{31}P peaks at about 53 ppm. Accordingly, these shifts of ^{31}P resonances and phosphorus–metal spin–spin couplings were proof of the synthesized complexes (Table 1).

All ^{1}H NMR and ^{31}P NMR signals prove that the novel ligands and their Pt(II) and Ag(I) complexes have been synthesized successfully.[5–26]

All the ligands have one degradation band between 100 and 1000°C. Pt(II) and Ag(I) complexes have four endothermic peaks in

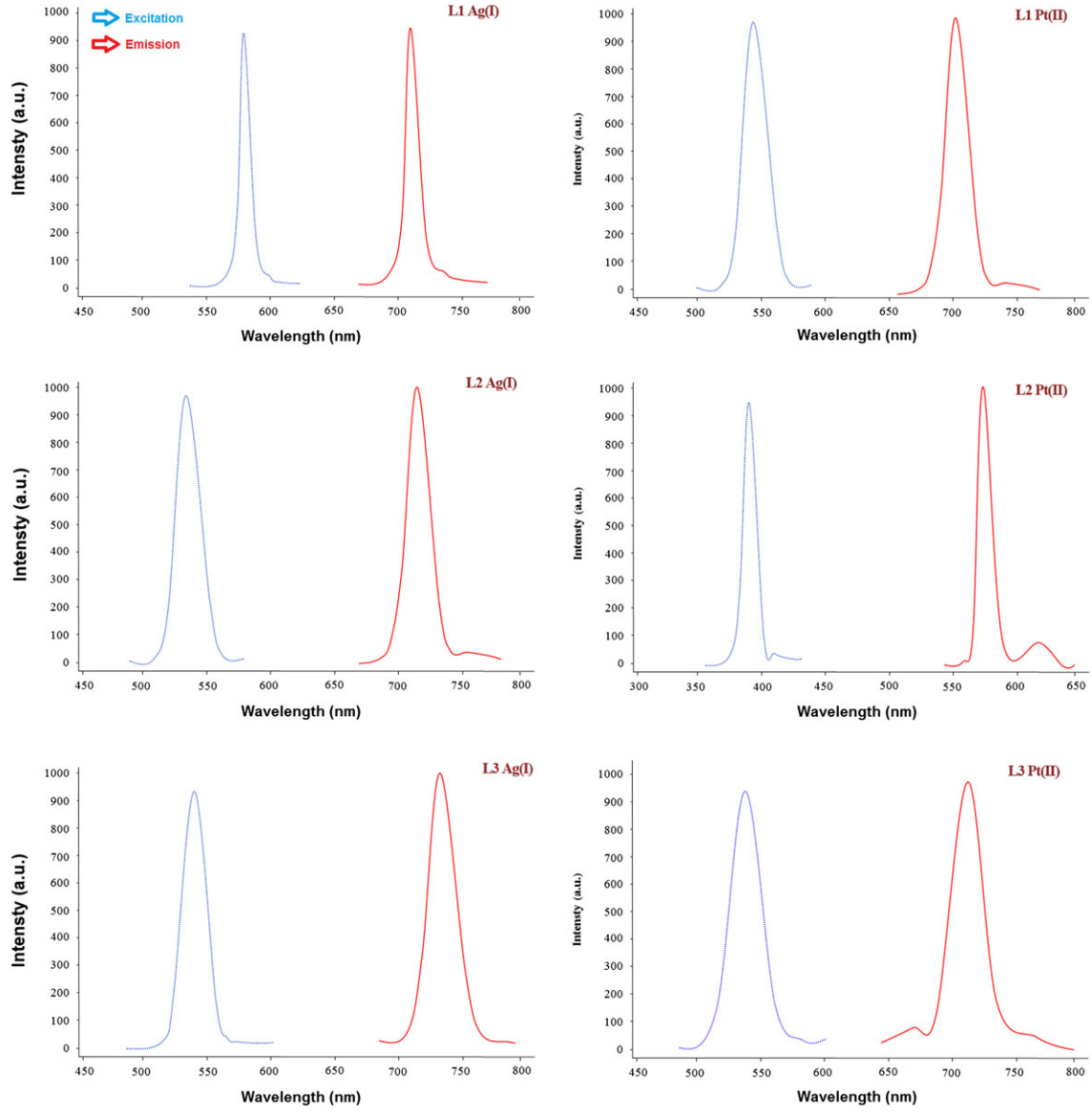

Figure 4. Photoluminescence of the metal complexes at the solid state.

TG analyses. Hydrated water decomposed between 40 and 100°C for all Pt(II) complexes. The second peak at about 100–205°C was attributed to chloro ligand and trimethylamine degradation and the largest band between 205 and 510°C was because of the degradation of aminophosphine ligands. After 600°C, metal oxide formation was observed for Pt(II) complexes. Hydrated water decomposition was observed at about 40–100°C for all Ag(I) complexes as well as Pt(II) complexes. Trimethylamine degradation followed the hydrated water loss. Aminophosphine ligands decomposed between 200 and 550°C and metal oxide formation began after 550°C (Fig. 2).

Electrochemical properties of the phosphine ligands and their metal complexes were investigated in DMF–3 M Bu_4NBF_4 as supporting electrolyte at 293 K. All potentials quoted refer to measurements run at scan rates of 100, 250, 500, 750 and 1000 mV s^{-1} range and against an internal ferrocene–ferrocenium standard. The electrochemical studies were conducted in 1×10^{-4} M DMF solutions and the obtained data are summarized in Table 2. The potentials for reduction or oxidation of phosphine containing strongly electron-withdrawing groups at the phosphine positions of the macrocycle will depend upon the electronic properties of the diamine. In addition, the shift in redox potentials between neutral and positively or negatively charged ligands (L1–L3) depends on the conjugation between the positively or negatively charged group at the phosphine and the π-ring system. The phosphine ligands are planar and show conjugation by π-electrons. The ligands contain strongly electron-withdrawing groups such as P C N linkage. Metallophosphines containing electro-inactive Pt(II) and Ag(I) metal ions undergo only reactions involving the π-ring system (see Table 2). In the CV curves of ligands L1 and L2 (Fig. 3), all redox processes at scan rates of 100-1000 mV s^{-1} in 1×10^{-3} M solutions are reversible. But ligand L3 shows a quasi-reversible redox process at all scan rates. The L2–Ag(I) and L3–Ag(I) complexes show reversible redox couples at all scan rates. The L2–Pt(II) complex shows quasi-reversible couples at 0.50/0.53 V at all scan rates. The L1–Ag(I), L1–Pt(II) and L3–Pt(II) complexes show irreversible redox processes (Fig. 3).

The single-photon fluorescence spectra of the phosphine ligands and their metal complexes were collected with a PerkinElmer LS55 luminescence spectrometer. Photoluminescence properties of the ligands and their metal complexes were investigated in the solid state and obtained data are summarized in Table 3. The photoluminescence spectra of the metal complexes are shown in Fig. 4. The excitation bands of L1–Ag(I), L2–Ag(I) and L3–Ag(I) were in the range 543–587 nm in the excitation spectra. The group (NO_3^-) bound to the metal did not affect the excitation bands for Ag(I) complexes. The excitation bands of the L1–Pt(II), L2–Pt(II) and L3–Pt(II) complexes were in the range 390–546 nm in the excitation spectra. Highest red shift was seen in the spectrum of L3–Pt(II). The emission bands of the L1–Ag(I), L2–Ag(I) and L3–Ag(I) metal complexes were observed in the range 718–729 nm as one band in the emission spectra. Additionally, in the spectra of the L1–Pt(II), L2–Pt(II) and L3–Pt(II) complexes, the emission bands were in the range 647–664 nm. The emission and excitation bands were shifted to lower wavelengths than those of L1–Ag(I), L2–Ag(I) and L3–Ag(I). Depending on the reduction of the concentration, the band intensities of the compounds decreased. As a result, a concentration change has a slight effect on the emission and excitation bands.

Antiproferative Activity on HT-29 Human Colon Cancer

All the complexes were used as anticancer agents on the HT-29 human colon cancer cell line. HT-29 cells were treated with various concentrations (10, 25, 50, 100, 250 μM) of the Pt(II) and Ag(I) complexes in 96-well plates and incubated for 48 h. Cisplatin was used at the same concentrations in order to compare with the synthesized Pt(II) and Ag(I) complexes. When comparing cisplatin with the synthesized Pt(II) and Ag(I) complexes, the Pt(II) complexes of L1 and L3 and Ag(I) complexes of L1, L2 and L3 significantly decreased cell proliferation at a concentration of 100 μM, whereas L2–Pt(II) and control did not significantly differ (Figs 5 and 6). While the Pt(II) complexes of L1 and L3 and Ag(I) complexes of L1, L2 and L3 showed similar inhibition effect of cancer cell proliferation compared to cisplatin up to 50 μM concentration, at 100 μM and higher concentrations, L1–Pt(II) and L3–Ag(I) complexes showed a much greater effect than cisplatin (Figs 5-7). It is possible that the sterically hindered ligands labilize the *trans* leaving of *cis*-positioned chloro ligands in these complexes and the ligands prevent the axial binding of any ligands to the metal which would inhibit the formation of five-coordinated metal complex intermediates that would lead to a ligand substitution.[1] L2–Pt(II) and L2–Ag(I) complexes did not show anticancer activities because of the too bulky structure of naphthalene tetrakis ditertiary aminomethylphosphine ligands coordinating to metal centres. This structure does not labilize *cis*-chloro leaving from metal centres and this steric hindrance would not permit high selectivity to DNA binding.[1,27–30] Because phosphine compounds are strong-field ligands, Pt(II) complexes have dsp^2 and Ag(I) complexes have sp^3 hybridization. Thus, Pt(II) complexes have square planar structure with *cis*-chloro ligands

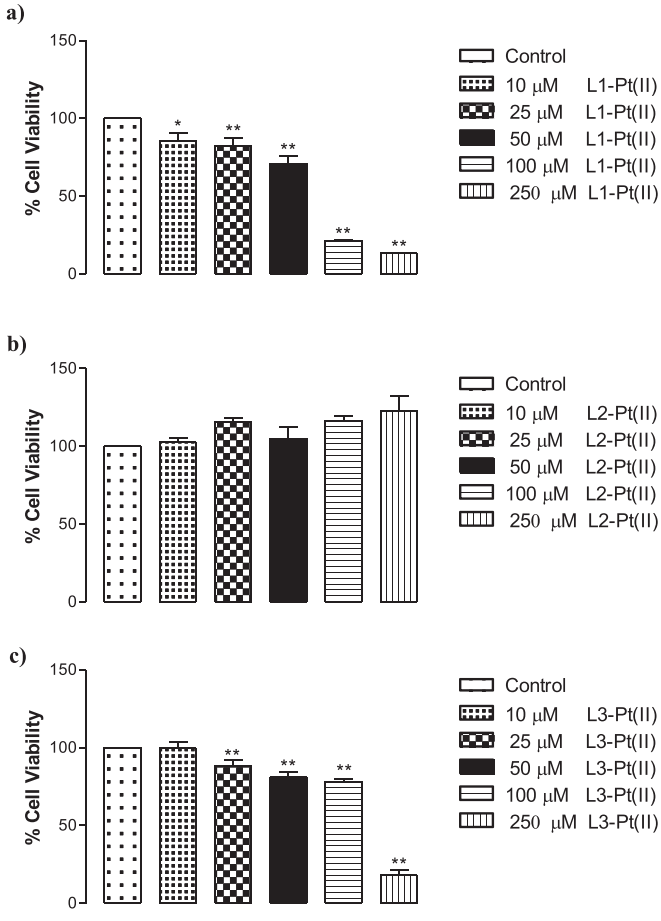

Figure 5. HT-29 human colon cancer cells treated with Pt(II) complexes (10, 25, 50, 100, 250 μM, $n = 8$), assessed by MTT assay (*$p < 0.05$, **$p < 0.01$ versus vehicles).

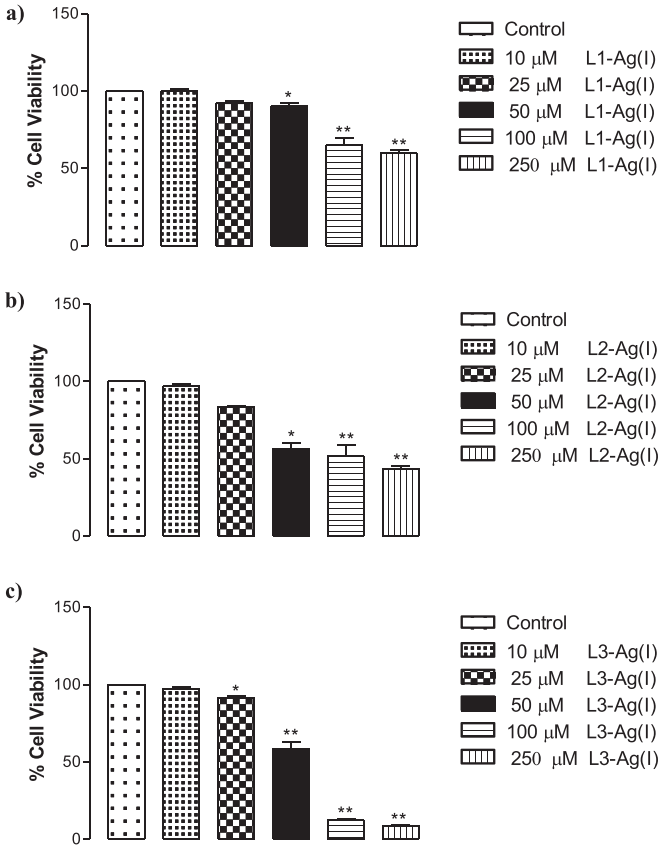

Figure 6. HT-29 human colon cancer cells treated with Ag(I) complexes (10, 25, 50, 100, 250 μM, $n = 8$), assessed by MTT assay (*$p < 0.05$, **$p < 0.01$ versus vehicles).

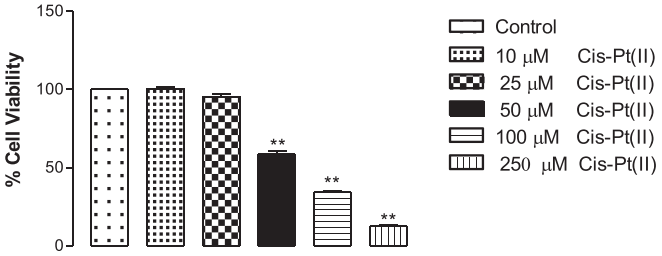

Figure 7. HT-29 human colon cancer cells treated with Cis-Pt(II) complexes (10, 25, 50, 100, 250 μM, $n = 8$), assessed by MTT assay (**$p < 0.01$ versus vehicles).

trans to chelated ditertiary aminomethylphosphine ligands, and Ag (I) complexes have tetrahedral structure with *cis*-chloro ligands *trans* to chelated ditertiary aminomethylphosphine ligands. The cytotoxicity mechanism of the synthesized complexes is probably similar to the proposed mechanism of action of cisplatin because of the *cis*-positioned chloro ligands in the complexes. As for the cisplatin mechanism, square planar Pt(II) complexes bind to DNA by intercalation. Possibly the Ag(I) metal centre is smaller than Pt(II) showing a similar effect.[1,31–33]

Consequently, L1–Pt(II) and L3–Ag(I) complexes showed a much greater effect than cisplatin at 100 μM and higher concentrations, and they can be said to be potential anti-tumour agents. Further biological investigations should be conducted to elucidate the intercalation modes and study the structure–activity relationships of the complexes.

Conclusions

Pt(II) and Ag(I) complexes of tetradentate ditertiary aminomethylphosphine complexes have been synthesized using Schlenk techniques. All the ligands and their metal complexes were characterized using ^{1}H NMR, ^{31}P NMR and FT-IR spectroscopies, TG/DTA, elemental analysis, CV and photoluminescence techniques. All the complexes were used as anticancer agents on the HT-29 human colon cancer cell line. Cisplatin was used at the same concentrations in order to compare with the synthesized Pt(II) and Ag(I) complexes. When comparing cisplatin with the synthesized Pt (II) and Ag(I) complexes, Pt(II) complexes of L1 and L3 and Ag(I) complexes of L1, L2 and L3 significantly decreased cell proliferation at a concentration of 100 μM, whereas L2–Pt(II) and control did not significantly differ. L1–Pt(II) and L3–Ag(I) complexes showed a much greater effect than cisplatin at 100 μM and higher concentrations. These efficient results on the antiproliferative activity on human colon cancer cells indicate that the novel synthesized L1–Pt(II) and L3–Ag(I) complexes are worth focusing on in pharmacological studies in order to verify their ability to reach cancer tissues.

Acknowledgements

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Supporting information

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