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The synthesis and characterization of new triphenylethylene platinum(II) complexes

Gervais Bérubé *, Yuehua He, Serge Groleau, Alexandre Séné, Hélène-Marie Thérien, Madeleine Caron

Département de Chimie-biologie, Université du Québec à Trois-Rivières, C.P. 500, Trois-Rivières, Que., G9A 5H7, Canada

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Abstract

In our search for a chemotherapeutic agent with a better therapeutic index and selectivity for the treatment of breast cancer, we have synthesized a series of cytotoxic analogs of tamoxifen. The new triphenylethylene platinum(II) derivatives were designed to possess binding affinity for the estrogen receptor. The synthesis of this type of compound is straightforward and efficient. The new complexes were fully characterized by their IR, ^{1}H NMR and ^{13}C NMR spectra as well as their elemental analysis. The estrogen receptor binding affinity (RBA) of some of these triphenylethylenes was also evaluated and was found to be comparable to the affinity of the reference drug, i.e. tamoxifen, RBA = 1.3%.

Keywords: Platinum complexes; Triphenylethylene complexes; Cytotoxic complexes

1. Introduction

Several platinum coordination complexes such as *cis*-diamminedichloroplatinum(II) (cisplatin, **6**) and carboplatin (**7**) are currently used in the chemotherapy of neoplastic diseases (Scheme 1) [1]. These complexes of a non-essential heavy metal exhibit a remarkable antitumor effectiveness and a broad spectrum of activity. It is widely believed that the antitumor activity of platinum drugs is a consequence of their interaction with DNA [2,3]. Cisplatin binds readily to guanine residues of DNA molecules [3]. Cisplatin has proved very successful in the treatment of a variety of human solid tumors such as genitourinary and gynecologic tumors as well as head, neck and lung tumors [1]. Unfortunately, the development of cellular resistance to cisplatin in mammalian cells is common [4–6] and is believed to occur via four main mechanisms: (a) increased efficiency of repair of platinum–DNA lesions [7–10]; (b) increased inactivation of the drug by elevated levels of cellular low-molecular weight thiols, particularly glutathione [11–13]; (c) metallothionein [14–16]; (d) decreased cellular uptake of the drug [17–21]. The clinical utility of the drug is also limited by its toxic effects, particularly kidney toxicity [2].

In order to improve the low activity of platinum(II) complexes against breast cancer [22], we investigated the covalent attachment of dichloroplatinum to diamino analogs of triphenylethylene. The choice of the triphenylethylene moiety of structure **1** (see Scheme 1) was based on both the structure of tamoxifen (**3**) and the triphenylacrylonitrile derivatives (**2**). It was previously demonstrated that triphenylacrylonitriles bearing two or three hydroxy groups, located as presented on structure **2**, possess high affinity for the estrogen receptor (ER) (receptor binding affinity (RBA) = 270%) [23–25]. We were hoping that such an arrangement of hydroxy groups would confer to our new cytotoxic triphenylethylenes high RBAs. These derivatives could also be considered cytotoxic analogs of tamoxifen (**3**), the latter being an efficient drug for the treatment [26] and potential prevention [27,28] of breast cancer. The new compounds **1** were also synthesized on the structural basis of the steroidal anti-estrogens ICI 164 384 (**4**) and ICI 182 780 (**5**), the side chain being in the middle part of the molecule [29,30]. Therefore, considering the fact that hormonal therapy will be ultimately followed by chemotherapy or a combination of both therapies at the onset of treatment, we synthesized a number of non-steroidal cytotoxic estrogens hoping to obtain products with dual activity, i.e. anti-estrogenic and cytotoxic. Moreover, these compounds might also be multidrug resistance (MDR) modulators (chemosensitizers) as per their

* Corresponding author. Tel.: (819) 376-5170, ext: 3353; fax: (819) 376-5084; e-mail: Gervais_Berube@uqtr.uquebec.ca

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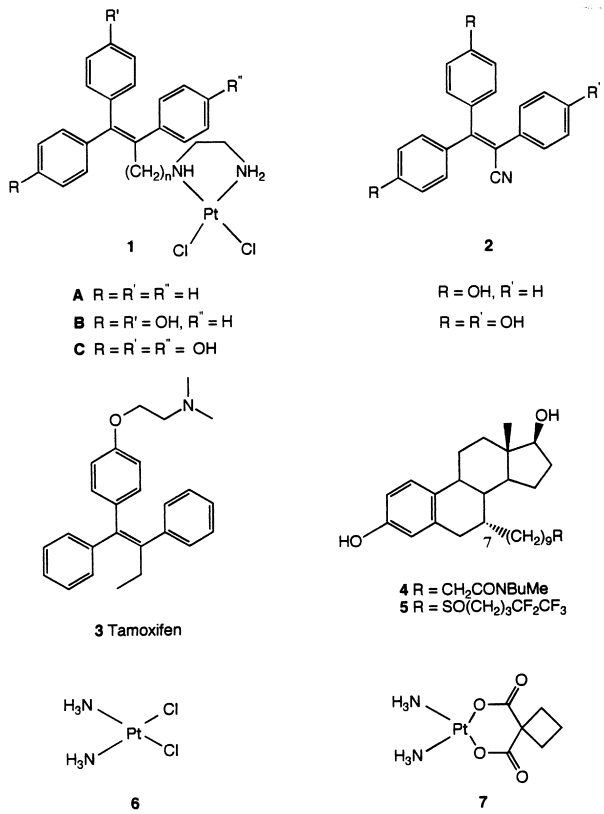


Scheme 1.

lipophilic character [31,32]. The present paper describes in detail the synthesis of eleven members of this new family of cytotoxic triphenylethylenes [33] and the RBA of several of these derivatives.

2. Experimental

2.1. Synthesis of Pt(II) complexes

2.1.1. Materials

Anhydrous reactions were performed under an inert atmosphere, the set-up assembled and cooled under dry nitrogen. Unless otherwise noted, starting material, reactant and solvents were obtained commercially and were used as such or purified and dried by standard means [34]. Organic solutions were dried over magnesium sulfate ($MgSO_4$), and evaporated on a rotatory evaporator and under reduced pressure. All reactions were monitored by thin-layer chromatography (TLC). The plates were visualized by UV fluorescence, or by staining with iodine or spraying with an aqueous solution of phosphomolybdic acid followed by heating the plate at ~135°C. Commercial TLC plates were Sigma T 6145 (polyester silica gel 60 Å, 0.25 mm). Preparative TLC was performed on 1 mm silica gel 60 Å, 20×20 plates (Whatman, 4861 840). Flash chromatography was performed according to the method of Still et al. on Merck grade 60 silica gel, 230–400 mesh [35]. All solvents used in chromatography had been distilled. Melting points (m.p.) were recorded on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were taken on a Nicolet model 205 FT-IR, or on a Perkin-Elmer model 2000 FT-IR spectrophotometer. Mass spectral assays (MS, m/e) were obtained using a VG Micromass 7070 HS instrument using an ionization energy of 70 eV. Elemental analyses were conducted by Microanalysis Laboratories Limited, Markham, Ontario. Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ solution, unless otherwise noted, on a General Electric GE 300-NB (300 MHz) or a Bruker AMX-2 (500 MHz) instrument: chemical shifts were measured relative to internal standards: tetramethylsilane (TMS, δ 0.0 ppm) for ^1H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR. Multiplicities are described by the following abbreviations: s (singlet), d (doublet), q (quartet), p (pentet), m (multiplet), dd (double doublet), tq (triple quartet), and so on. The NMR assignments were assisted by ^{13}C–^1H correlation (HET-CORR) 2-D spectra.

2.2. General procedure for the conversion of bromoalcohols to iodotetrahydropyranyl ethers

2.2.1. 1-Tetrahydropyranyloxy-n-bromoalkane (9)

A solution of bromoalcohol **8** (27.6 mmol), dihydropyran (2.57 g, 30.6 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 10 mg, 0.04 mmol) in dichloromethane (CH_2Cl_2, 50 ml) was stirred for 5 h under nitrogen. Afterwards, sodium bicarbonate ($NaHCO_3$, 500 mg) and $MgSO_4$ (5.0 g) were added to the reaction mixture and stirred for 15 min before being filtered on a short pad of Celite/silica gel (1 cm/4 cm) using CH_2Cl_2 as eluent. The filtrate was evaporated to a viscous oil **9** (98% yield), which was used without further purification in the next step.

The spectroscopic data for derivatives **9a–c** were reported earlier [36].

2.2.2. 1-Tetrahydropyranyloxy-11-bromoundecane (9d)

IR, ν_{max} (thin film): 1170–1000 (C–O) cm^{-1}. ^1H NMR (δ ppm): 4.58 (1H, t, J = 3.5 Hz, –OCHO–), 3.87, 3.73, 3.50 and 3.38 (4H, 4xm, –C*H*$_2$OCHOC*H*$_2$–), 3.41 (2H, t, J = 6.8 Hz, –CH_2Br), 1.2–2.0 (24H, m, –CH_2–). MS (m/e): 335 ($M^+ + 1$), 233 ($M^+ - $OTHP).

2.2.3. 1-Tetrahydropyranyloxy-n-iodoalkane (10)

Sodium iodide (6.07 g, 40.5 mmol) was added to a solution of the crude bromide **9** (27 mmol) in dried acetone. The reaction mixture was stirred at 22°C for 5 h. Then, most of the solvent was evaporated and the residue was transferred to an extraction flask with ether (150 ml) and water (100 ml). The organic phase was washed with water (6×50 ml), dried, filtrated and concentrated to a viscous liquid. The crude iodide **10** (98% yield) was used as such at the alkylation step.

The spectroscopic data for derivatives **10a–c** were reported earlier [36].

*2.2.4. 1-Tetrahydropyranyloxy-11-iodoundecane (**10d**)*

IR, ν_{max} (thin film): 1170–1000 (C–O) cm^{-1}. ^1H NMR (δ ppm): 4.58 (1H, t, $J=3.5$ Hz, –OCHO–), 3.87, 3.73, 3.50 and 3.38 (4H, 4×m, –CH_2OCHOCH_2–), 3.19 (2H, t, $J=7.0$ Hz, –CH_2I), 1.2–2.0 (24H, m, –CH_2–). MS (m/e): 381 (M^+-H), 281 (M^+-OTHP).

*2.3. General procedure for the conversion of benzyl-4-hydroxyphenyl ketone to bihydroxy and bimethoxy triphenylethylene platinum(II) complexes **1Ba–e** and **17***

*2.3.1. Synthesis of benzyl-4-methoxyphenyl ketone (**11B**)*

Benzyl-4-hydroxyphenyl ketone (2.12 g, 10 mmol) and sodium hydroxide (0.60 g, 15 mmol) were dissolved in 250 ml ethanol by heating. Dimethyl sulfate (1.51 g, 12 mmol) was added dropwise to the initial solution. The reaction mixture was refluxed for 4 h. After evaporation, the residue was diluted with ether (200 ml) and washed with water (5×50 ml). The ethereal phase was dried and evaporated to give a white powder which was purified by flash column chromatography (hexane:acetone, 9:1). The yield was 80% (98% taking in consideration the hydroxy-ketone recovered). M.p. 76.2–77.0°C. IR, ν_{max} (KBr): 1680 (C=O), 1600 (C=C), 1254 (C–O) cm^{-1}. ^1H NMR (δ ppm): 7.98, 6.90 (4H, 2×d apparent, $J=8.87$ Hz, H in *para*-substituted anisyl group), 7.30–7.21 (5H, m, Ar–H), 4.20 (2H, s, –CH_2–), 3.80 (3H, s, –OCH_3). ^{13}C NMR (δ ppm): 196.06, 163.37, 134.83, 130.79(2), 129.44, 129.25(2), 128.48(2), 126.63, 113.65(2), 55.32, 45.11. MS (m/e): 226 (M^+), 135 ($M^+-CH_2C_6H_5$).

*2.3.2. Synthesis of 1-(4′-methoxyphenyl)-2-phenyl-n-tetrahydropyranyl-oxy-alkanone (**12B**)*

To a stirred suspension of sodium hydride (448 mg, 11.2 mmol, 60% dispension in mineral oil) in dry tetrahydrofuran (THF, 150 ml) was added rapidly ketone **11B** (2.30 g, 10.2 mmol). The reaction mixture was heated (50°C) in a water bath for 1 h under a nitrogen atmosphere. After cooling, 1-tetrahydropyranyloxy-n-iodoalkane (**10**) (11.2 mmol) was added dropwise and the resulting mixture stirred overnight (18 h) at room temperature (22°C). Most of the solvent was then evaporated and the residue was diluted with ether (200 ml) and treated with water (50 ml). The ethereal phase was washed thoroughly with water (6×50 ml), dried and evaporated to give an oil that was purifed by flash column chromatography (hexane:acetone, 95:5). A viscous oil was obtained. The average yield was 75% (98% taking into account the alkyl iodide **10** recovered).

*2.3.3. 1-(4′-Methoxyphenyl)-2-phenyl-8-tetrahydropyranyl-oxy-octanone (**12Ba**)*

IR, ν_{max} (thin film): 1680 (C=O), 1600 (C=C), 1254 (C–O) cm^{-1}. ^1H NMR (δ ppm): 7.95, 6.85 (4H, 2×d apparent, $J=8.93$ Hz, H in *para*-substituted anisyl group), 7.32–7.14 (5H, m, Ar–H), 4.55 (1H, t, $J=3.51$ Hz, –OCHO–), 4.49 (1H, t, $J=7.25$ Hz, –CH–), 3.84, 3.69, 3.48, 3.34 (4H, 4×m, –CH_2OCHOCH_2–), 3.79 (3H, s, –OCH_3), 2.23–1.18 (16H, m, –CH_2–). ^{13}C NMR (δ ppm): 198.44, 163.12, 140.17, 130.82(2), 129.84, 128.69(2), 128.03(2), 126.73, 113.56(2), 98.73, 67.48, 62.24, 55.30, 53.17, 33.97, 30.70, 29.59, 29.40, 27.62, 25.99, 25.42, 19.60. MS (m/e): no M^+, 326 (M^+-DHP), 239 ($M^+-C_5H_{10}$OTHP).

*2.3.4. Synthesis of x-phenyl-y,y-bis(4′-methoxyphenyl)-x-alken-1-ol (**13B**)*

A Grignard reagent, *p*-methoxyphenyl magnesium bromide was prepared from magnesium (432 mg, 18.0 mmol) and 4-methoxyphenylbromide (2.81 g, 15.0 mmol) in the presence of a crystal of iodine in 100 ml of dry ether. The Grignard reagent was usually ready after stirring at room temperature (22°C) overnight (18 h), but sometimes required heating at reflux to initiate the reaction. A solution of the ketone **12B** (3.0 mmol) in dry ether was treated with excess of the Grignard reagent for 6 h under nitrogen at room temperature (22°C) and was then hydrolyzed with 50 ml of 10% aqueous ammonium chloride. The ether phase was washed with water (5×50 ml), dried and evaporated to give the crude tertiary alcohol intermediate. The oily residue was dehydrated and deprotected in 100 ml 95% ethanol in the presence of PPTS (100 mg, 0.40 mmol) at reflux for 3 h. After evaporation of the solvent, the residue was taken with ether and extracted with water (5×50 ml). The ethereal phase was dried and evaporated to an oil. Flash column chromatography (hexane:acetone, 7:1) gave pure **13B** in 85% average yield as a viscous oil.

*2.3.5. 7-Phenyl-8,8-bis(4′-methoxyphenyl)-7-octen-1-ol (**13Ba**)*

IR, ν_{max} (thin film): 3640–3150 (OH), 1600 (C=C), 1240 (C–O) cm^{-1}. ^1H NMR (δ ppm): 7.18–7.05 (7H, m, Ar–H), 6.87 (2H, d apparent, $J=8.72$ Hz, H in *para*-substituted anisyl group), 6.77, 6.53 (4H, 2×d apparent, $J=8.82$ Hz, H in *para*-substituted anisyl group), 3.82, 3.66 (6H, 2×s, 2×–OCH_3), 3.55 (2H, t, $J=6.60$ Hz, –CH_2OH), 2.43 (2H, m, –C=C–CH_2–), 1.65 (1H, br s, –OH), 1.50 (2H, p, $J=7.30$ Hz, –CH_2CH_2OH), 1.30–1.10 (6H, m, –$(CH_2)_3$–). ^{13}C NMR (δ ppm): 158.16, 157.37, 142.87, 139.73, 138.06, 136.25, 135.73, 131.84(2), 130.56(2), 129.54(2), 127.80(2), 125.85, 113.39(2), 112.66(2), 62.91, 55.18, 54.95, 35.85, 32.60, 29.42, 28.82, 25.32. MS (m/e): 416 (M^+), 329 ($M^+-C_5H_{10}$OH).

*2.3.6. Synthesis of 1-bromo-x-phenyl-y,y-bis(4′-methoxyphenyl)-x-alkene (**14B**)*

A solution of the alcohol **13B** (2.25 mmol), carbon tetrabromide (2.98 g, 9.00 mmol) and triphenylphosphine (2.36 g, 9.00 mmol) in dry ether (100 ml) was stirred at room temperature (22°C) for 24 h under a nitrogen atmosphere. The triphenylphosphine oxide precipitate was filtrated and the resulting solution was washed thoroughly with water (5×25 ml), dried and evaporated to an oil. The crude material was purified by flash column chromatography

(hexane:acetone, 95:5) to give the bromide **14B** in 85% yield.

*2.3.7. 1-Bromo-7-phenyl-8,8-bis(4′-methoxyphenyl)-7-octene (**14Ba**)*

IR, ν_{max} (thin film): 1600 (C=C), 1240 (C–O) cm^{-1}. ^1H NMR (δ ppm): 7.18–7.05 (7H, m, Ar–H), 6.88 (2H, d apparent, $J=8.73$ Hz, H in *para*-substituted anisyl group), 6.77, 6.53 (4H, 2×d apparent, $J=8.81$ Hz, H in *para*-substituted anisyl group), 3.82, 3.66 (6H, 2×s, 2×–OCH_3), 3.32 (2H, t, $J=6.86$ Hz, –CH_2Br), 2.43 (2H, m, –C=C–CH_2–), 1.74 (2H, p, $J=7.30$ Hz, –CH_2CH_2Br), 1.40–1.18 (6H, m, –$(CH_2)_3$–). ^{13}C NMR (δ ppm): 158.23, 157.40, 142.81, 139.59, 138.20, 136.20, 135.69, 131.84(2), 130.54(2), 129.54(2), 127.84(2), 125.89, 113.43(2), 112.67(2), 55.20, 54.96, 35.77, 33.91, 32.62, 28.75, 28.65, 27.80. MS (m/e): 478 (M^+), 480 ($M^+ + 2$), 329 ($M^+ - C_5H_{10}Br$).

*2.3.8. Synthesis of 1-[(2′-aminoethyl)amino]-x-phenyl-y,y-bis(4′-methoxyphenyl)-x-alkene (**15B**)*

Under a nitrogen atmosphere, ethylenediamine (900 mg, 15.0 mmol) was added to a solution of the bromide **14B** (1.50 mmol) in 80 ml of dry methanol. After boiling for 2 days under reflux (sometimes a longer reaction period was required), the solvent was evaporated. The resulting residue was dissolved in ether (150 ml) and washed with a solution of $NaHCO_3$ (30 ml, 5% aqueous) and with water (5×30 ml). The ethereal phase was dried and evaporated to a viscous oil **15B**. The yield was 90%.

*2.3.9. 1-[(2′-Aminoethyl)amino]-7-phenyl-8,8-bis-(4′-methoxyphenyl)-7-octene (**15Ba**)*

IR, ν_{max} (thin film): 3560–3130 (N–H), 1600 (C=C), 1240 (C–O) cm^{-1}. ^1H NMR (δ ppm): 7.18–7.05 (7H, m, Ar–H), 6.87 (2H, d apparent, $J=8.65$ Hz, H in *para*-substituted anisyl group), 6.77, 6.53 (4H, 2×d apparent, $J=8.75$ Hz, H in *para*-substituted anisyl group), 3.82, 3.67 (6H, 2×s, 2×–OCH_3), 2.79, 2.64 (4H, 2×t, $J=5.92$ Hz, –NHCH_2C$H_2$$NH_2$), 2.54 (2H, t, $J=7.25$ Hz, –CH_2NH–), 2.43 (2H, m, –C=C–CH_2–) 1.78 (3H, br s, –NH– and –NH_2), 1.43–1.18 (8H, m, –$(CH_2)_4$–). ^{13}C NMR (δ ppm): 158.14, 157.33, 142.86, 139.76, 137.99, 136.23, 135.73, 131.84(2), 130.55(2), 129.53(2), 127.78(2), 125.81, 113.37(2), 112.63(2), 55.16, 54.93, 52.42, 49.74, 41.58, 35.88, 29.90, 29.60, 28.86, 26.99. MS (m/e): 458 (M^+), 428 ($M^+ - CH_2NH_2$), 415 ($M^+ - CH_2CH_2NH$), 329 ($M^+ - C_5H_{10}NHCH_2CH_2NH_2$).

*2.3.10. Synthesis of 1-{cis-[(2′-aminoethyl)amino]-dichloroplatinum(II)}-x-phenyl-y,y-bis(4′-hydroxyphenyl)-x-alkene (**1B**)*

A solution of **15B** (0.665 mmol) in dry CH_2Cl_2 (30 ml) was treated with a solution of boron tribromide (1 M in CH_2Cl_2, 1.60 ml, 1.60 mmol) at −60°C, under nitrogen atmosphere. After the addition, the reaction mixture was allowed to warm to room temperature (22°C) and was stirred for 18 h. The mixture was refluxed for 2 h. The reaction was cooled down with an ice bath before adding 10 ml methanol. The resulting solution was concentrated to 2–3 ml, treated with saturated $NaHCO_3$ solution (30 ml), and extracted with ethyl acetate (5×30 ml). The crude yield is around 60–80%. The diol-diamine was used without further purification in the next step.

A solution of potassium tetrachloroplatinate(II) (219 mg, 0.528 mmol) in 7.5 ml of a mixture of DMF and water (2:1) was added to a warm (35°C) solution of the crude diol-diamine (0.528 mmol) in 5 ml of DMF. The resulting mixture (pH = 9–10) was stirred in the dark for 2–3 days until the pH value reached 4–5. Then, 1 drop of *N,N*-dimethyl sulfoxide was added and the stirring was continued for 2 h. The solvent was evaporated and the residue was suspended in saturated potassium chloride solution (30 ml). A vigorous stirring was essential in order to pulverize the lumps of precipitated platinum(II) complex **1B**. The resulting suspension was filtered, washed with water (100–250 ml) and dried in a desiccator. The product was further purified either by flash column chromatography or by preparative TLC (CH_2Cl_2:CH_3OH, 95:5). The crude yield was around 80%.

*2.3.11. 1-{Cis-[(2′-aminoethyl)amino]dichloroplatinum(II)}-7-phenyl-8,8-bis(4′-hydroxyphenyl)-7-octene (**1Ba**)*

M.p. > 138°C (dec.). IR, ν_{max} (KBr): 3400–3100 (O–H, N–H), 1600 (C=C), 1225 (C–O) cm^{-1}. ^1H NMR (acetone-d_6, δ ppm): 8.32, 8.09 (2H, 2×br s, 2×Ar–OH), 7.20–7.10 (5H, m, Ar–H), 7.07, 6.86 (4H, 2×d apparent, $J=8.52$ Hz, H in *para*-substituted phenol), 6.71, 6.48 (4H, 2×d apparent, $J=8.62$ Hz, H in *para*-substituted phenol), 5.68, 5.11, 4.98 (3H, 3×br s, –NH– and –NH_2), 3.21, 3.06, 2.77, 2.67 (6H, 4×br s, –CH_2NHCH_2C$H_2$$NH_2$), 2.46 (2H, m, –C=C–$CH_2$–), 1.78, 1.56 (2H, 2×br s, –C$H_2$$CH_2$NH–), 1.40–1.10 (6H, m, –$(CH_2)_3$–). ^{13}C NMR (acetone-d_6, δ ppm): 156.88, 156.07, 143.94, 139.72(2), 135.93, 135.62, 132.62(2), 131.30(2), 130.41(2), 128.07(2), 126.55, 115.73(2), 114.93(2), 56.12, 53.42, 47.78, 36.33, 27.64, 26.82 (N.B. 2 carbons are hidden by acetone). *Anal.* Calc. for $C_{28}H_{34}Cl_2N_2O_2Pt \cdot 2H_2O$: C, 45.68; H, 5.26; N, 3.80. Found: C, 45.72; H, 5.28; N, 3.70%.

*2.3.12. Synthesis of 1-{cis-[(2′-aminoethyl)amino]-dichloroplatinum(II)}-12-phenyl-13,13-bis(4′-methoxyphenyl)-12-tridecene (**17**)*

The platinum(II) complex **17** was obtained following the same procedure as for compound **1B** taking **16** as the starting material (see Scheme 4). The crude yield was around 80%. The product can be further purified either by flash column chromatography or by preparative TLC (CH_2Cl_2:CH_3OH, 98:2). M.p. > 173°C (dec.). IR, ν_{max} (KBr): 3560–3140 (N–H), 1600 (C=C), 1240 (C–O) cm^{-1}. ^1H NMR (δ ppm): 7.16–7.08 (7H, m, Ar–H), 6.86 (2H, d apparent, $J=8.62$ Hz, H in *para*-substituted anisyl group), 6.76, 6.53

(4H, 2 × d apparent, $J = 8.73$ Hz, H in *para*-substituted anisyl group), 5.65, 5.05, 4.92 (3H, 3 × br s, –NH– and $–NH_2$), 3.80, 3.66 (6H, 2 × s, 2 × $–OCH_3$), 4.05, 3.18, 2.95, 2.75 (6H, 4 × br s, $–CH_2NHCH_2CH_2NH_2$), 2.43 (2H, m, –C=C–CH_2–), 1.75, 1.52 (2H, 2 × br s, $–CH_2CH_2NH$–), 1.40–1.06 (16H, m, $–(CH_2)_8$–). ^{13}C NMR (δ ppm): 158.15, 157.34, 142.93, 139.90, 137.93, 136.28, 135.81, 131.88(2), 130.61(2), 129.58(2), 127.80(2), 125.83, 113.40(2), 112.67(2), 55.45, 55.22, 54.98, 53.47, 46.93, 35.98, 29.78, 29.55(2), 29.45, 29.34, 29.24, 28.97, 27.41, 26.56. *Anal.* Calc. for $C_{35}H_{48}Cl_2N_2O_2Pt$: C, 52.89; H, 6.09; N, 3.52. Found: C, 52.83; H, 6.06; N, 3.51%.

The conversion of desoxybenzoin and desoxyanisoin to triphenylethylene platinum(II) complexes **1Aa–c** and **1Cd,e** was done in a similar fashion as for the synthesis of platinum(II) complexes **1Ba–e** described above.

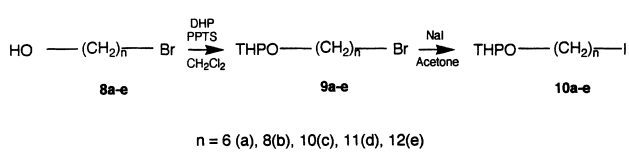
3. Results and discussion

*3.1. Synthesis of triphenylethylene platinum(II) complexes **1Aa–c**, **1Ba—e**, **17** and **1Cd,e***

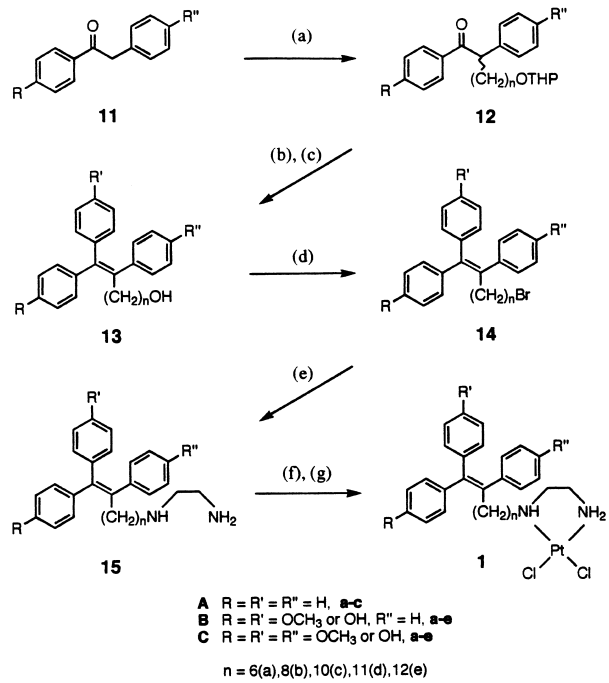
The appropriate iodotetrahydropyranyl ethers **10a–e** were prepared in high yield as described previously (Scheme 2) [36]. As shown in Scheme 3, five new platinum(II) complexes **1Ba–e** (R = R′ = OH; R″ = H) were obtained with a 30% overall yield from commercially available benzyl-4-hydroxyphenyl ketone, after eight steps. Benzyl-4-hydroxyphenyl ketone was initially protected as a methyl ether **11** (R = OCH_3; R″ = H) by using dimethylsulfate and sodium hydroxide [37]. The yield for this reaction was 80%.

Alkylation of **11** with the iodotetrahydropyranyl ethers **10a–e** was achieved using sodium hydride in tetrahydrofuran to give compounds **12Ba–e** with an average yield of 75% (98% based on recovered alkyliodide **10**). Addition of an excess of *p*-methoxyphenylmagnesium bromide to the ketones **12Ba–e** and subsequent treatment of the crude tertiary alcohol intermediates with pyridinium-*p*-toluenesulfonate (PPTS) in ethanol at reflux afforded the triphenylethylene alcohols **13Ba–e** as the result of dehydration of the tertiary alcohols and simultaneous deprotection of the tetrahydropyranyl ethers (85% average yield for the two steps).

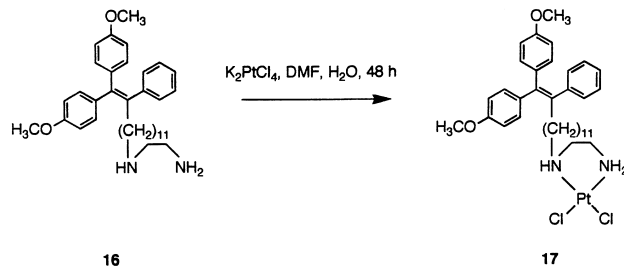
With the desired triphenylethylenes **13Ba–e** in hand, simple functional group transformations were carried out in the following sequence of reactions. Initially, alcohols **13Ba–e** were transformed to the bromides **14Ba–e** with carbon tetrabromide and triphenylphosphine in dry diethyl ether (85% average yield). The amines **15Ba–e** were obtained with an



Scheme 2.



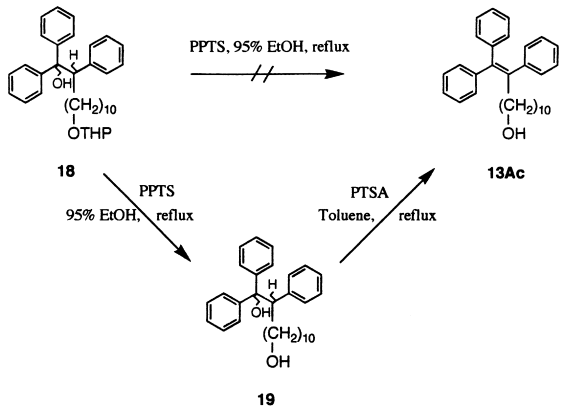
Scheme 3. Reagents: (a) NaH, I–$(CH_2)_n$-OTHP, THF:DMSO, 25°C, 17 h, 75%; (b) R′C_6H_4MgBr, Et_2O, 25°C, 17 h; (c) crude tertiary alcohol, PPTS or pTSA, EtOH, reflux, 5 h, 85% from **12**; (d) CBr_4, Ph_3P, Et_2O, 25°C, 24 h, 85%; (e) $H_2NCH_2CH_2NH_2$, CH_3OH, reflux, 24 h, 95%; (f) BBr_3, CH_2Cl_2, −60 to 25°C, 15 h to reflux 2 h; (g) K_2PtCl_4, DMF:H_2O, 48 h, 60% from **15**.



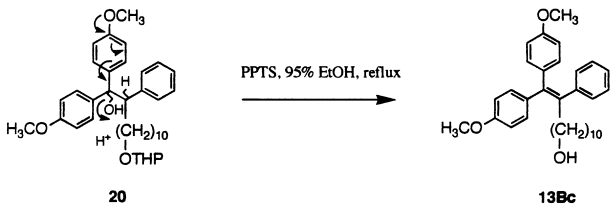
Scheme 4.

average yield of 90% by refluxing the bromides **14Ba–e** in the presence of an excess of ethylenediamine in dry methanol. Finally, demethylation with boron tribromide gave the intermediate bis-phenols, which, upon treatment with potassium tetrachloroplatinate(II) in a mixture of dimethylformamide (DMF) and water, led to the desired platinum(II) complexes **1Ba–e** (R = R′ = OH; R″ = H) (60% average yield for the two steps) [36]. As presented in Scheme 4, the platinum(II) complex **17** was easily obtained by reacting the amine **16** with potassium tetrachloroplatinate(II) in a mixture of DMF and water for 48 h (80% yield).

The triphenylethylene platinum(II) complexes **1Aa–c** (R = R′ = R″ = H) were synthesized from commercially available starting material deoxybenzoin **11** (R = R″ = H), in a similar sequence of reactions as used earlier for compounds **1Ba–e**. However, *p*-toluenesulfonic acid (PTSA) was used instead of PPTS for the dehydration step. The total yield



Scheme 5.



Scheme 6.

exceeded 40%. These are the reference derivatives which should not show affinity for the estrogen receptor (ER). Also, two new derivatives **1Cd,e** were made from desoxyanisoin as described previously for compounds **1Ca–c** in order to complete the series [36].

It is noteworthy that all our platinum(II) complexes were purified using flash column chromatography instead of recrystallization. Chromatography was possible due to the substantial organic portion of the molecules. This methodology yielded very pure platinum(II) complexes, homogeneous on thin-layer chromatography. All new compounds obtained were characterized by their IR, ^{1}H NMR, ^{13}C NMR and mass spectra. The final products **1Aa–c**, **1Ba–e**, **17** and **1Cd,e** have good elemental analysis with respect to calculated values (Table 1).

One reaction which we would like to emphasize here is the dehydration and deprotection of the tertiary alcohol **18** as presented in Scheme 5. Initially, we followed the same procedure as for the dehydration and deprotection of the tertiary alcohol intermediate **20** (Scheme 6). The tertiary alcohol **18** was allowed to react in the presence of PPTS in 95% ethanol at reflux for 8 h (Scheme 5). We expected simultaneous dehydration of tertiary alcohol and deprotection of THP ether to form the alkylalcohol **13Ac**. Unfortunately, it was not the case. Instead, we obtained the diol **19** which was confirmed by its IR, ^{1}H NMR ^{13}C NMR and mass spectra. Further treatment of **19** with a stronger acidic catalyst, i.e. PTSA, in toluene at reflux produced the desired compound **13Ac**, the structure of which was also confirmed by spectroscopy. This interesting result can be explained easily, if we compare the structure of the substances **18** and **20**. An electron-donating group is present on compound **20**, i.e. a methoxy group which can assist the dehydration reaction to give derivative **13Bc** (Scheme 6). Therefore, compound **18** without an electron-donating group on its aromatic rings needs a stronger acidic catalyst PTSA and higher reaction temperature to achieve the same reaction.

This result emphasizes that a very subtle change in reaction conditions and the chemical structure of the substrate may drastically change the outcome of a chemical reaction. Moreover, the availability of a derivative such as **19** (present as a mixture of four isomers) could lead to the development of interesting new platinum(II) complexes in the future.

3.2. Estrogen receptor binding affinity

The RBAs of derivatives **1Aa–c**, **1Ba–c** and **1Ca–c** for the ER were determined by a competitive cytosolic binding assay [38]. The binding affinity for estradiol (E_2) was set to 100%. As expected, compounds **1Aa–c** do not bind to the ER (RBA = 0%). Derivatives containing two or three hydroxy groups possess the following RBA values: **1Ba** = 1.1%, **1Bb** = 1.4%, **1Bc** = 0.8%, **1Ca** = 0.2%, **1Cb** = 0.8%, **1Cc** =

Table 1
Elemental analysis data of platinum complexes and melting point

Complex	$C_{aa}H_{bb}Cl_cN_dO_ePt$	Found (Calc.) (%)			M.p. (°C)
		C	H	N	
1Aa	$C_{28}H_{34}Cl_2N_2Pt$	50.63 (50.60)	5.20 (5.17)	4.19 (4.22)	>210 dec.
1Ab	$C_{30}H_{38}Cl_2N_2Pt$	52.05 (52.01)	5.51 (5.54)	4.02 (4.05)	>210 dec.
1Ac	$C_{32}H_{42}Cl_2N_2Pt$	53.28 (53.32)	5.90 (5.89)	3.92 (3.89)	>210 dec.
1Ba	$C_{28}H_{34}Cl_2N_2O_2Pt\cdot 2H_2O$	45.72 (45.68)	5.28 (5.26)	3.70 (3.80)	>138 dec.
1Bb	$C_{30}H_{38}Cl_2N_2O_2Pt\cdot 2H_2O$	47.40 (47.37)	5.62 (5.57)	3.73 (3.68)	>138 dec.
1Bc	$C_{32}H_{42}Cl_2N_2O_2Pt\cdot 2H_2O$	48.65 (48.73)	5.78 (5.88)	3.61 (3.55)	>138 dec.
1Bd	$C_{33}H_{44}Cl_2N_2O_2Pt\cdot 2H_2O$	49.32 (49.38)	6.08 (6.03)	3.52 (3.49)	>138 dec.
1Be	$C_{34}H_{46}Cl_2N_2O_2Pt\cdot 2H_2O$	49.93 (49.98)	6.21 (6.17)	3.41 (3.43)	>138 dec.
1Cd	$C_{33}H_{44}Cl_2N_2O_3Pt\cdot 2H_2O$	48.36 (48.39)	5.94 (5.91)	3.44 (3.42)	>162 dec.
1Ce	$C_{34}H_{46}Cl_2N_2O_3Pt$	51.25 (51.23)	5.79 (5.82)	3.49 (3.52)	>170 dec.
17	$C_{35}H_{48}Cl_2N_2O_2Pt$	52.83 (52.89)	6.06 (6.09)	3.51 (3.52)	>173 dec.

dec. = decomposition.

1.0%, tamoxifen = 1.3%. The level of affinity for the ER of our compounds was not as high as expected, but is similar to that of tamoxifen. This could be due to the poor solubility of these complexes.

The present report describes the synthesis of eleven members of this new family of cytotoxic triphenylethylenes. The synthesis is straightforward and efficient and could be done on a larger scale as well as in industry. Derivatives with two or three hydroxy groups possess affinity for the ER comparable to that of tamoxifen. Unfortunately, the level of affinity for the ER was not as high as expected initially with the kind of estrogenic portion we used. A high RBA of the drug is essential for specificity of these cytotoxic agents [39]. However, it is estimated on the basis of the number of receptors per cell (1000–10 000) and the possible drug concentration that an RBA value of at least 1% of the E_2 RBA is sufficient for selectivity [39]. Consequently, some of the new triphenylethylene platinum(II) complexes might show specificity on ER positive breast cancer cells in vivo. These derivatives will be further studied in our laboratory.

4. Supplementary material

Experimental procedures, yields and spectral data (IR, ^{1}H and ^{13}C NMR and MS) of derivatives **9e, 10e, 12Bb–e, 13Bb–e, 14Bb–e, 15Bb–e, 1Bb–e, 12Aa–c, 19Aa,c, 13Aa–c, 14Aa–c, 15Aa–c, 1Aa–c, 12Cd,e, 13Cd,e, 14Cd,e, 15Cd,e, 1Ce** are available from the authors on request.

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