Short Communication

The synthesis of new platinum(II) complexes linked to non-steroidal estrogens

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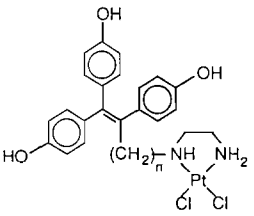
Abstract

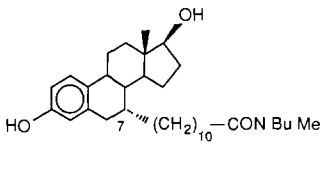
New platinum(II) complexes linked to triphenylethylene are efficiently synthesised in seven steps from desoxyanisoin with an overall yield exceeding 30%. The methodology described gives access to interesting non-steroidal cytotoxic estrogens designed for the treatment of breast cancer.

Breast cancer is the most common form of cancer among women in North America [1]. Much progress has been accomplished for the treatment and detection of this disease. The successful treatment of this malady is limited by the fact that essentially all breast cancers become resistant to chemotherapy [2a] and endocrine therapy [2b]. New and more selective chemotherapeutic agents must be designed to rapidly eradicate the disease before any signs of resistance occur.

The concept of linking and anti-cancer agent to a ligand with affinity for a tumor cell has some encouraging experimental precedent. As early as the 1960s, researchers investigated the possibility of linking nitrogen mustard groups to a steroidal skeleton in order to induce cytotoxic effects on hormone-dependent tumor cells [3]. Since that time, several compounds (steroids and others) have been linked to various alkylating agents, including nitrogen mustard [4], nitrosoureas [5] and platinum complexes [6].



1 a-c



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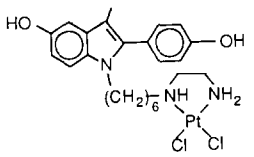

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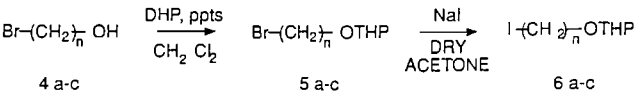
We now report the synthesis of novel triphenylethylene–platinum(II) complexes **1** designed for the treatment of breast cancer. The choice of the length of the starting bromoalcohol **4** with six, eight and ten carbon atoms is important in order to imitate closely the antiestrogen ICI 164384 (**2**). Moreover, it has been observed that at least six carbon atoms are needed to give platinum derivatives such as dihydroxy-2-phenylindole (**3**) sufficient ERBA (estrogen receptor binding affinity) allowing the estrogen receptor to direct the cytotoxic agent towards the target cell [6b]. As illustrated below, the alcohols **4a–c** were protected as a tetrahydropyranyl ether (THP) [7] to give compounds **5a–c**, which upon treatment with sodium iodide in dry acetone, gave the corresponding iodotetrahydropyranyl ethers **6a–c** (95% average yield for the two steps).



4 a-c 5 a-c 6 a-c

n = 6(a), 8(b), 10(c)

Alkylation of the commercially available desoxyanisoin (**7**) with the iodotetrahydropyranyl ethers **6a–c** was achieved using sodium hydride in tetrahydrofuran to give compounds **8a–c** with an average yield of 65% (98% taking into account the alkyliodide recovered, Scheme 1). Addition of an excess of *p*-methoxyphenylmagnesium bromide to ketones **8a–c** and subsequent treatment of the crude tertiary alcohols with pyridinium *p*-toluenesulfonate (PPTS) in ethanol at reflux afforded directly the triphenylethylene alcohols **9a–c** in an average yield of 90% as the result of dehydration of the tertiary alcohol intermediates and simultaneous de-

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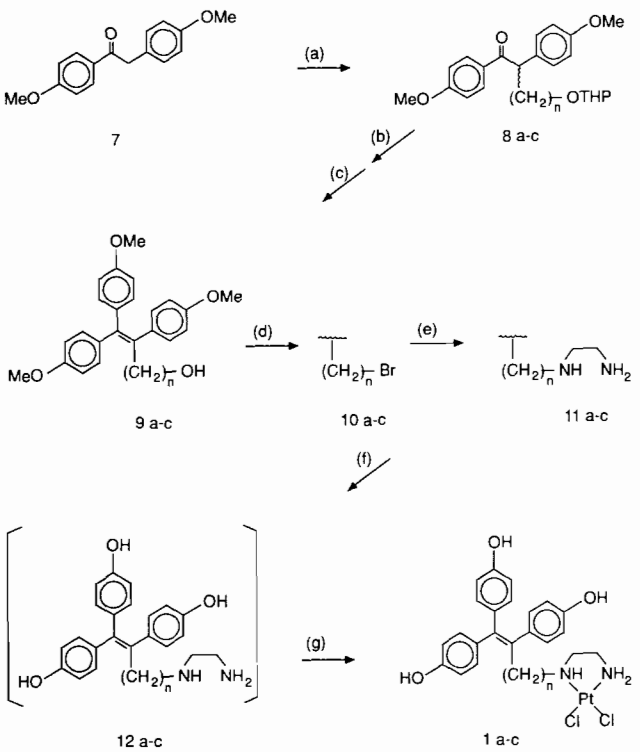

Scheme 1. $n=6$(a), 8(b), 10(c). Reagents: (a) NaH, I–$(CH_2)_n$–OTHP, THF, 25 °C, 17 h, 65% (98%); (b) Me-OC_6H_4MgBr, ether, 25 °C, 17 h; (c) crude tertiary alcohol, ethanol, PPTS, reflux, 5 h, 90% from **8**; (d) CBr_4, Ph_3P, ether, 25 °C, 24 h, 85%; (e) $H_2NCH_2CH_2NH_2$, methanol, reflux, 24 h, 95% crude; (f) BBr_3, CH_2Cl_2, −60 to 25 °C (15 h) to reflux (2 h), (g) K_2PtCl_4, DMF: H_2O, 2 days, 60% from **11**.

protection of the tetrahydropyranyl ethers [7]. With the desired triphenylethylenes in hand the following sequence of reactions is simple functional group transformations. Initially, alcohols **9a–c** were transformed to the bromides **10a–c** (85% average yield) with carbon tetrabromide and triphenylphosphine in dry diethyl ether [8]. The amines **11a–c** were obtained in an average yield of 95% by refluxing bromides **10a–c** with an excess of ethylenediamine in dry methanol [6b]. Finally, demethylation with boron tribromide gave the intermediate tris-phenols **12a–c**, which upon treatment with potassium tetrachloroplatinate(II) in a mixture of DMF and water, led to the desired platinum(II) complexes **1a–c** (60% average yield for the two steps) [6b]. All spectra (300 MHz, ^1H and ^{13}C NMR and MS) are in agreement with the assigned structures.

The following data are given in order to illustrate our results.

*1-[cis-[(2-Aminoethyl)amino]dichloroplatinum(II)]-7,8,8-tris(4-hydroxyphenyl)-7-octene (**1a**)*
($C_{28}H_{34}Cl_2N_2O_3Pt$)

Melting point: > 148 °C decomp. IR (KBr): 3640–3050 (N–H, O–H), 1605 (C=C), 1223 (C–O) cm^{-1}. ^1H NMR (acetone-d_6, δ ppm): 8.6–8.2 (3H, massive, 3×–OH), 7.02, 6.83 and 6.94, 6.64 and 6.69, 6.48 (12H, 3×two d, $J=8.57$, 8.59 and 8.59 Hz, 3×*para*-substituted phenol), 5.64, 5.08 and 4.97 (3H, 3×massive, –N*H*$CH_2CH_2NH_2$), 3.15 (6H, large s, –CH_2NHCH_2-CH_2NH_2), 3.03 (2H, massive, –CH_2CH_2NH–), 2.80–2.55 (2H, massive, $CH_2CH_2CH_2$NH–), 2.39 (2H, m, –C=CCH_2–), 1.80–1.10 (4H, m, –C=CCH_2–(CH_2)$_2$–). ^{13}C NMR (acetone-d_6, δ ppm): 156.70, 156.20, 155.88, 139.39, 138.78, 136.16, 135.93, 134.64, 132.55(2), 131.43(2), 131.26(2), 115.61(2), 115.44(2), 114.84(2), 56.11, 53.43, 47.67, 36.21, 27.58, 26.81. (N.B. Two carbons are hidden by acetone.) *Anal.* Calc. for $C_{28}H_{34}Cl_2N_2O_3Pt$: C 47.26, H 4.78, N 3.94. Found: C 47.52, H 4.50, N 3.61%.

*1-[cis-[(2-Aminoethyl)amino]dichloroplatinum(II)]-9,10,10-tris(4-hydroxyphenyl)-9-decene (**1b**)*
($C_{30}H_{38}Cl_2N_2O_3Pt$)

Melting point: > 155 °C decomp. IR (KBr): 3700–3000 (N–H, O–H), 1605 (C=C), 1223 (C–O) cm^{-1}. ^1H NMR (acetone-d_6, δ ppm): 8.53, 8.39 and 8.32 (3H, 3×massive, 3×–OH), 7.02, 6.83 and 6.94, 6.64 and 6.69, 6.48 (12H, 3×two d, $J=8.50$, 8.60 and 8.64 Hz, 3×*para*-substituted phenol), 5.75, 5.19 and 5.05 (3H, 3×massive, –N*H*$CH_2CH_2NH_2$), 3.24 (6H, large s, –CH_2NHCH_2-CH_2NH_2), 3.08 (2H, massive, –CH_2CH_2NH–), 2.73 (2H, massive, –$CH_2CH_2CH_2$NH–), 2.39 (2H, m, –C=CCH_2–), 1.80–1.10 (8H, m, –C=CCH_2–(CH_2)$_4$–). ^{13}C NMR (acetone-d_6, δ ppm): 156.01, 155.62, 155.20, 138.87, 138.10, 135.54, 135.25, 134.03, 131.88(2), 130.71(2), 130.58(2), 114.91(2), 114.76(2), 114.19(2), 55.43, 52.90, 46.99, 35.69, 27.12, 26.54. (N.B. Four carbons are hidden by acetone.) *Anal.* Calc. for $C_{30}H_{38}Cl_2N_2O_3Pt$: C 48.71, H 5.14, N 3.79. Found: C 49.46, H 5.14, N 3.68%.

*1-[cis-[(2-Aminoethyl)amino]dichloroplatinum(II)]-11,12,12-tris(4-hydroxyphenyl)-11-dodecene (**1c**)*
($C_{32}H_{42}Cl_2N_2O_3Pt$)

Melting point: > 150 °C decomp. IR (KBr): 3775–3050 (N–H, O–H), 1605 (C=C), 1223 (C–O) cm^{-1}. ^1H NMR (δ ppm): 8.53, 8.39 and 8.32 (3H, 3×s, 3×–OH), 7.02, 6.81 and 6.93, 6.63 and 6.69, 6.48 (12H, 3×two d, $J=8.51$, 8.62 and 8.65 Hz, 3×*para*-substituted phenol), 5.72, 5.11 and 4.98 (3H, 3×massive, –N*H*$CH_2CH_2NH_2$), 3.14 (6H, large s, –CH_2NHC$H_2CH_2NH_2$), 3.05 (2H, massive, –CH_2CH_2NH–), 2.72 (2H, massive, –CH_2-CH_2CH_2NH–), 2.39 (2H, m, –C=CCH_2–), 1.80–1.10 (12H, m, –C=CCH_2–(CH_2)$_6$–). ^{13}C NMR (acetone-d_6, δ ppm): 156.72, 156.23, 155.88, 139.59, 138.70, 136.23, 135.63, 134.70, 132.58(2), 131.39(2), 131.27(2), 115.52(2), 115.40(2), 114.89, 114.84, 56.13, 53.51, 47.82, 36.43, 27.82, 27.26. (N.B. Six carbons are hidden by acetone.) *Anal.* Calc. for $C_{32}H_{42}Cl_2N_2O_3Pt$: C 50.20, H 5.49, N 3.66. Found: C 50.53, H 5.83, N 4.10%.

In conclusion, we are reporting the synthesis of three new cytotoxic non-steroidal estrogens. The methodology described above gives access to compound **9a–c** which could easily be linked to other types of DNA alkylating agents such as nitrogen mustards and nitrosoureas. The biological activity of these derivatives will be reported elsewhere.

Supplementary material

Experimental procedures, yields and spectral data (IR, ^{1}H and ^{13}C NMR and MS) of compounds **5a–c**, **6a–c**, **8a–c**, **9a–c**, **10a–c**, **11a–c** (11 pages) are available from the authors on request.

Acknowledgements

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