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Inorganica Chimica Acta 358 (2005) 3369–3376
Inorganica Chimica Acta
www.elsevier.com/locate/ica

cis-Dichloroplatinum (II) complexes with aminomethylnicotinate and -isonicotinate ligands

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Received 17 February 2005; received in revised form 26 April 2005; accepted 11 May 2005
Available online 16 June 2005

Abstract

6-Aminomethylnicotinic acid (**1a**) and 2-aminomethylisonicotinic acid (**1b**) were each reacted with K_2PtCl_4 in aqueous 1 M HCl to give the corresponding *N*,*N*-chelated *cis*-dichloroplatinum(II) complexes **2**. These were converted into amides **3** via their mixed anhydrides by treating them first with ethyl chloroformate and then with the respective 1° or 2° amine. The analogous 6-aminomethylnicotinic acid ester complexes **7** were obtained by reaction of the preformed ligands with K_2PtCl_4.

Keywords: Platinum complexes; Nicotinic acid; Amidation; Yamaguchi esterification; GMP interactions

1. Introduction

Cisplatin and its three marketed congeners carboplatin, oxaliplatin and nedaplatin are still widely used in the treatment of solid tumours although resistance poses an increasingly severe problem for the clinician [1–3]. Attempts to circumvent it by employing new platinum complexes with modified structures and modes of action are as numerous as are the various pathways of tumour resistance themselves [4,5]. More recent examples include *trans*-Pt(II) and Pt(IV) compounds [6] or *cis*-Pt(II) complexes with planar [6] or with non-NH ligands [7–9]. Particularly attractive appear conjugates of platinum complexes with other drugs that are either cytostatic [1,5,10], or which can act as shuttle systems, homing devices, or scavengers for deactivating molecules in the cell [11]. These conjugates are customarily prepared by complexation of a preformed ligand–ancillary drug combination onto a suitable inorganic platinum source such as K_2PtCl_4 [12]. In this way we obtained new *cis*-dichloroplatinum complexes with various alcohols linked to a 6-aminomethylnicotinoyl chelate ligand. We also report a conceptually reverse method that links ancillary amines to preformed carboxy functionalized *cis*-dichloroplatinum (II) complexes via amide bond formation under mild conditions and in good yields. These complementary approaches should also be applicable to hydroxy- or amino-terminated co-drugs with further delicate functionalities.

2. Experimental

2.1. Synthesis of 6-aminomethylnicotinic acid (*1a*) and 2-aminomethylisonicotinic acid (*1b*)

6-Cyanonicotinic acid or 2-cyanoisonicotinic acid (1.48 g, 10.0 mmol), as obtained [13] from nicotinic acid *N*-oxide or isonicotinic acid *N*-oxide (4.67 g, 33.6 mmol) and a mixture of NaCN (4.92 g, 100 mmol), TMSCl (25.6 mL, 200 mmol) and NEt_3 (24.7 mL, 180 mmol) in dry DMF, was added to a suspension of Pd (10%)

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0020-1693/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ica.2005.05.015

on charcoal (100 mg) in methanol (50 mL) and pressurised with 1 bar of hydrogen gas for 4 h. The formed precipitate was redissolved by addition of water and the resulting mixture was filtered over a plug of celite. The filtrate was evaporated to dryness and the residue thus obtained was recrystallized from hot water/ethanol to leave off-white powdery solids.

Compound ***1a***: 1.21 g (80%); m.p. 280 °C [14]; ν_{max} (KBr)/cm^{-1}: 3038, 2839, 1596, 1580, 1527, 1380; ^{1}H NMR (300 MHz, D_2O): δ 4.37 (2H, s, CH_2), 7.49 (1H, d, ^3J 8.06 Hz, 5-H), 8.19 (1H, d, ^3J 8.06 Hz, 4-H), 8.91 (1H, s, 2-H); ^{13}C NMR (75.5 MHz, D_2O/1 M HCl): δ 42.5 (CH_2), 123.4 (C-5), 126.8 (C-3), 140.5 (C-4), 149.3 (C-2), 155.0 (C-6), 167.7 (CO); *m/z* (EI) 153 (37), 152 (47), 125 (43), 124 (72), 78 (67), 51 (100).

Compound ***1b***: 1.06 g (70%); m.p. 230 °C (dec.). $C_7H_8N_2O_2$ requires: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.22; H, 5.32; N, 18.29%. ν_{max} (KBr)/cm^{-1}: 3198, 2839, 1596, 1549, 1505, 1375; ^{1}H NMR (300 MHz, D_2O): δ 4.38 (2H, s, CH_2), 7.70 (1H, d, ^3J 5.12 Hz, 5-H), 7.74 (1H, s, 3-H), 8.63 (1H, d, ^3J 5.12 Hz, 6-H); ^{13}C NMR (75.5 MHz, D_2O): δ 43.3 (CH_2), 121.7 (C-5), 122.8 (C-3), 146.1 (C-4), 149.4 (C-6), 152.2 (C-2), 172.6 (CO); *m/z* (EI) 152 (99), 124 (100), 106 (10), 78 (35), 51 (63).

2.2. Synthesis of cis-dichloro(6-aminomethylnicotinic acid)platinum (II) (*2a*) and cis-dichloro(2-aminomethylisonicotinic acid)platinum (II) (*2b*)

A solution of **1** (185 mg, 1.22 mmol) and K_2PtCl_4 (505 mg, 1.22 mmol) in aqueous 1 M HCl (20 mL) was gently stirred at 50 °C for 3 days under exclusion of air and sun light. The eventually formed yellow precipitate was collected on a Büchner funnel, thoroughly washed with water (100 mL), acetone (50 mL) and diethyl ether (50 mL) and finally dried on an oil pump.

Complex ***2a***: 433 mg (85%); yellow solid, m.p. > 250 °C. $C_7H_8Cl_2N_2O_2Pt$ requires: C, 20.11; H, 1.93; N, 6.70. Found: C, 20.21; H, 2.02; N, 6.52%. ν_{max} (KBr)/cm^{-1}: 3435, 3264, 3206, 1724, 1571, 1384, 1232; ν_{max} (polyethylene)/cm^{-1}: 335, 327; ^{1}H NMR (300 MHz, DMF-d_7): δ 4.48 (2H, t, ^3J 5.92 Hz, CH_2), 6.3–6.4 (2H, m, NH_2), 7.88 (1H, d, ^3J 8.20 Hz, 5-H), 8.64 (1H, d, ^3J 8.20 Hz, 4-H), 9.86 (1H, s,$^3J_{PtH}$ 37 Hz, 2-H); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 53.7 (CH_2), 122.4 (C-5), 128.0 (C-3), 139.1 (C-4), 148.7 (C-2), 164.8 (C-6), 170.4 (CO); ^{195}Pt NMR (64.4 MHz, DMF-d_7): δ 2439.

Complex ***2b***: 356 mg (70%); yellow solid, m.p. > 250 °C. $C_7H_8Cl_2N_2O_2Pt$ requires: C, 20.11; H, 1.93; N, 6.70. Found: C, 20.32; H, 1.99; N, 6.71%. ν_{max} (KBr)/cm^{-1}: 3231, 3189, 1738, 1567, 1376, 1260; ν_{max} (polyethylene)/cm^{-1}: 342, 325, 318; ^{1}H NMR (300 MHz, DMF-d_7): δ 4.47 (2H, t, ^3J 5.98 Hz, CH_2), 6.3–6.4 (2H, m, NH_2), 7.97 (1H, d, ^3J 6.09 Hz, 5-H), 8.15 (1H, s, 3-H), 9.45 (1H, d, ^3J 6.09, $^3J_{PtH}$ 31 Hz, 6-H); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 53.6 (CH_2), 121.8 (C-5), 124.0 (C-3), 140.2 (C-4), 148.7 (C-6), 165.6 (C-2), 167.8 (CO); ^{195}Pt NMR (64.4 MHz, DMF-d_7): δ 2466.

2.3. Synthesis of amides (*3*)

Under exclusion of air and moisture a solution of **2** (100 mg, 0.24 mmol) in dry DMF (15 mL) was chilled to 0 °C and treated with NEt_3 (34 μL, 0.24 mmol) and ethyl chloroformate (26 μL, 0.26 mmol). After stirring for 30 min at 0 °C the respective amine (0.24 mmol) was added and stirring was continued for another 12 h at room temperature. For workup, a mixture of methanol and CH_2Cl_2 (1:20, v/v; 50 mL) was added, the resulting crude was extracted with water (20 mL) and the aqueous phase was re-extracted with the above solvent mixture (5 × 20 mL). The combined organic phases were finally concentrated in vacuo and the yellow residue thus obtained was purified by column chromatography (silica gel 60; CH_2Cl_2/acetone 1:1, v/v).

Complex ***3a***: 45 mg (40%) from pyrrolidine (20 μL); yellow solid, m.p. > 250 °C; R_f = 0.14 (CH_2Cl_2/acetone 1:1, v/v). $C_{11}H_{15}Cl_2N_3OPt$ requires: C, 28.04; H, 3.20; N, 8.92. Found: C, 27.96; H, 3.16; N, 8.88%. ν_{max} (KBr)/cm^{-1}: 3158, 1607, 1438; ν_{max} (polyethylene)/cm^{-1}: 358, 351, 330, 324; ^{1}H NMR (300 MHz, DMF-d_7): δ 1.9–2.0 (4H, m, CCH_2C), 3.5–3.6 (4H, m, NCH_2CH_2), 4.42 (2H, t, ^3J 5.92 Hz, H_2NCH_2), 6.3–6.4 (2H, m, NH_2), 7.81 (1H, d, ^3J 8.13 Hz, 5-H), 8.39 (1H, d, ^3J 8.13 Hz, 4-H), 9.47 (1H, s, $^3J_{PtH}$ 36 Hz, 2-H); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 24.3, 26.5, 46.6, 49.4, 53.6 (NCH_2), 121.9 (C-5), 133.7 (C-3), 137.3 (C-4), 146.6 (C-2), 164.3 (CO), 167.6 (C-6); ^{195}Pt NMR (64.4 MHz, DMF-d_7): δ 2439; *m/z* (EI) 205 (26) [$M^+ - PtCl_2$], 177 (14), 135 (48), 36 (100) [Cl^+]; *m/z* (ESI) 494.08 (100) [M^+ + Na].

Complex ***3b***: 87 mg (75%) from piperidine (24 μL); yellow solid, m.p. > 250 °C; R_f = 0.19 (CH_2Cl_2/acetone 1:1, v/v). $C_{12}H_{17}Cl_2N_3OPt$ requires: C, 29.70; H, 3.53; N, 8.66. Found: C, 29.80; H, 3.56; N, 8.45%. ν_{max} (KBr)/cm^{-1}: 3157, 1612, 1470; ν_{max} (polyethylene)/cm^{-1}: 355, 335, 329, 319; ^{1}H NMR (300 MHz, DMF-d_7): δ 1.6–1.7 (6H, m, CCH_2C), 3.4–3.7 (4H, m, NCH_2CH_2), 4.43 (2H, t, ^3J 5.84 Hz, H_2NCH_2), 6.2–6.4 (2H, m, NH_2), 7.82 (1H, d, ^3J 8.10 Hz, 5-H), 8.26 (1H, d, ^3J 8.10 Hz, 4-H), 9.32 (1H, d, $^3J_{PtH}$ 32 Hz, 2-H); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 24.4, 25.7, 26.5, 43.1, 53.6 (NCH_2), 122.2 (C-5), 133.1 (C-3), 137.2 (C-4), 145.9 (C-2), 165.0 (CO), 167.5 (C-6); *m/z* (EI) 219 (11) [$M^+ - PtCl_2$], 218 (16), 189 (9), 135 (24), 84 (19), 36 (100) [Cl^+]; *m/z* (ESI) 508.07 (100) [M^+ + Na].

Complex ***3c***: 42 mg (36%) from piperidine (24 μL); yellow solid, m.p. > 250 °C; R_f = 0.40 (CH_2Cl_2/acetone 1:1, v/v). $C_{12}H_{17}Cl_2N_3OPt$ requires: C, 29.70; H, 3.53; N, 8.66. Found: C, 29.77; H, 3.44; N, 8.60%. ν_{max}

(KBr)/cm^{-1}: 3266, 1627, 1572, 1451; ν_{max} (polyethylene)/cm^{-1}: 367, 343, 330; ^{1}H NMR (300 MHz, DMF-d_7): δ 1.5–1.7 (6H, m, CCH_2C), 3.3–3.4 (2H, m, NCH_2CH_2), 3.6–3.7 (2H, m, NCH_2CH_2), 4.41 (2H, t, ^3J 5.96 Hz, H_2NCH_2), 6.2–6.4 (2H, m, NH_2), 7.55 (1H, d, ^3J 6.04 Hz, 5-H), 7.73 (1H, s, 3-H), 9.30 (1H, d, ^3J 6.04, $^3J_{PtH}$ 34 Hz, 6-H); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 24.4, 25.6, 26.4, 42.7, 48.3, 53.7 (NCH_2), 122.1 (C-3, C-5), 146.5 (C-4), 148.3 (C-6), 166.1 (C-2), 167.4 (CO); *m/z* (EI) 219 (19) [$M^+ - PtCl_2$], 190 (13), 136 (15), 108 (19), 36 (100) [Cl^+].

Complex ***3d***: 71 mg (60%) from aniline (33 μL); yellow solid, m.p. > 250 °C; R_f = 0.39 (CH_2Cl_2/acetone 1:1, v/v). $C_{13}H_{13}Cl_2N_3OPt$ requires: C, 31.65; H, 2.65; N, 8.52. Found: C, 31.45; H, 2.48; N, 8.41%. ν_{max} (KBr)/cm^{-1}: 3197, 1644, 1602, 1533, 1443; ^{1}H NMR (300 MHz, DMF-d_7): δ 4.46 (2H, t, ^3J 5.90 Hz, CH_2), 6.3–6.4 (2H, m, NH_2), 7.1–7.2 (1H, m, Ph-H), 7.3–7.4 (2H, m, Ph-H), 7.8–7.9 (3H, m, Ph-H, 5-H), 8.75 (1H, d, ^3J 8.24 Hz, 4-H), 9.76 (1H, s, 2-H), 10.83 (1H, s, NH); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 54.4 (CH_2), 121.4 (Ph-C_m), 122.7 (C-5), 125.3 (Ph-C_p), 129.8 (Ph-C_o), 132.9 (C-3), 138.2 (C-4), 140.2 (Ph-C_{ipso}), 148.3 (C-2), 169.7 (C-6); ^{195}Pt NMR (64.4 MHz, DMF-d_7): δ 2437; *m/z* (EI) 494 (8) [$M^+ + 1$], 225 (52), 199 (49), 78 (11), 36 (100) [Cl^+].

Complex ***3e***: 47 mg (40%) from aniline (33 μL); yellow solid, m.p. > 250 °C; R_f = 0.66 (CH_2Cl_2/acetone 1:1, v/v). $C_{13}H_{13}Cl_2N_3OPt$ requires: C, 31.65; H, 2.65; N, 8.52. Found: C, 31.56; H, 2.55; N, 8.50%. ν_{max} (KBr)/cm^{-1}: 3137, 1668, 1528, 1439;^{1}H NMR (300 MHz, DMF-d_7): δ 4.47 (2H, t, ^3J 5.97 Hz, H_2NCH_2), 6.3–6.4 (2H, m, NH_2), 7.1–7.3 (1H, m, Ph-H), 7.4–7.5 (2H, m, Ph-H), 7.8–7.9 (2H, m, Ph-H), 8.18 (1H, s, 3-H), 9.41 (1H, d, ^3J 6.17 Hz, 6-H), 10.77 (1H, s, NH); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 54.4 (CH_2), 121.3 (Ph-C_p), 121.4 (Ph-C_o), 123.3 (C-5), 125.5 (C-3), 129.9 (Ph-C_m), 139.9 (Ph-C_{ipso}), 144.7 (C-4), 148.9 (C-6), 164.0 (C-2), 168.1 (CO); ^{195}Pt NMR (64.4 MHz, DMF-d_7): δ 2459; *m/z* (EI) 232 (8), 205 (7), 110 (12), 36 (100) [Cl^+].

Complex ***3f***: 32 mg (26%) from 1-naphthylamine (34 mg); yellow solid, m.p. > 250 °C; R_f = 0.42 (CH_2Cl_2/acetone 2:1, v/v). $C_{17}H_{15}Cl_2N_3OPt$ requires: C, 37.58; H, 2.78; N, 7.73. Found: C, 37.66; H, 2.70; N, 7.64%. ν_{max} (KBr)/cm^{-1}: 3196, 1652, 1532, 1504; ^{1}H NMR (300 MHz, DMF-d_7): δ 4.51 (2H, t, ^3J 5.89 Hz, H_2NCH_2), 6.40 (2H, m, NH_2), 7.5–7.7 (3H, m, Ph-H), 7.82 (1H, d, ^3J 7.31 Hz, Ph-H), 7.94 (1H, d, ^3J 8.21 Hz, Ph-H), 8.1–8.3 (2H, m, Ph-H), 8.32 (1H, s, 3′-H), 9.47 (1H, d, ^3J 6.12 Hz, 6′-H), 10.90 (1H, s, NH); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 54.5 (CH_2), 121.6 (C-8a), 123.6 (C-5′), 124.2 (C-2), 124.3 (C-4), 126.6 (C-7), 127.2 (C-3), 127.3 (C-8), 127.8 (C-5), 129.3 (C-6), 129.9 (C-4a), 134.4 (C-1), 135.4 (C-3′), 144.6 (C-4′), 149.0 (C-6′), 165.0 (C-2′), 168.2 (CO); ^{195}Pt NMR (64.4 MHz, DMF-d_7): δ 2459; *m/z* (EI) 247 (4) [$M^+ - PtCl_2 - CH_2NH_2$], 198 (31), 154 (30), 127 (39) [$C_{10}H_9^+$], 115 (22), 43 (100), 36 (97) [Cl^+].

2.4. Synthesis of ester functionalized complexes (*7*)

2.4.1. Synthesis of 6-(*N*-*t*-butoxycarbonylaminomethyl) nicotinic acid (*4*)

Compound **4** (330 mg, 91%) was prepared according to a known procedure [15,16] from **1a** (200 mg, 1.32 mmol) and di-*t*-butyl dicarbonate (530 mg, 2.43 mmol) in water/*t*-butanol (20 mL, 1:1, v/v) at pH 9–10 and 0 °C → r.t. ν_{max} (KBr)/cm^{-1}: 3314, 2977, 1686, 1529, 1288; ^{1}H NMR (300 MHz, MeOD): δ 1.47 (9H, s, CH_3), 4.41 (2H, s, CH_2), 7.47 (1H, d, ^3J 8.14 Hz, 5-H), 8.35 (1H, d, ^3J 8.14 Hz, 4-H), 9.04 (1H, s, 2-H); ^{13}C NMR (75.5 MHz, MeOD): δ 28.9 (CH_3), 46.7 (CH_2), 80.8 (CMe_3), 122.0 (C-5), 127.0 (C-3), 139.8 (C-4), 151.2 (C-2), 158.7 (OCON), 164.8 (C-6), 168.0 (CO_2); *m/z* (EI) 252 (1) [M^+], 197 (30), 179 (15), 151 (15), 136 (10), 78 (5), 57 (100).

2.4.2. Synthesis of esters (*5*)

Compound **4** (200 mg, 0.79 mmol) was dissolved in dry DMF (2 mL) and treated with triethylamine (110 μL, 0.79 mmol). 2,4,6-Trichlorobenzoyl chloride (127 μL, 0.79 mmol) was added and the suspension was stirred under argon at room temperature for 20 min. Benzyl alcohol (163 μl, 1.58 mmol), 2-methyl-2,4-pentanediol (202 mL, 1.58 mmol), (–)-menthol (247 mg, 1.58 mmol) or cholesterol (611 mg, 1.58 mmol), respectively, and DMAP (192 mg, 1.58 mmol) in dry toluene (20 mL) were added and the resulting mixture was stirred under argon at room temperature for a further 16 h. After dilution with diethyl ether (100 mL) and washing with water (100 mL) the organic phase was dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography (silica gel 60; solvent as indicated).

Compound ***5a***: 244 mg (90%); colourless oil; R_f = 0.37 (ethyl acetate/*n*-hexane 1:2, v/v);ν_{max} (KBr)/cm^{-1}: 3358, 2977, 1711, 1589, 1498, 1365, 1271, 1164, 1108; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (9H, s, CH_3), 4.45 (2H, d, ^3J 5.63 Hz, CH_2), 5.34 (2H, s, OCH_2), 5.7–5.8 (1H, m, NH), 7.2–7.5 (6H, m, Ph-H, 5-H), 8.23 (1H, d, ^3J 8.16 Hz, 4-H), 9.12 (1H, s, 2-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 28.3 (CH_3), 45.7 (CH_2), 66.9 (OCH_2), 79.6 (CMe_3), 121.0 (C-5), 124.5 (C-3), 128.1 (Ph-C_o), 128.4 (Ph-C_p), 128.6 (Ph-C_m), 135.4 (Ph-C_{ipso}), 137.7 (C-4), 150.4 (C-2), 155.9 (OCON), 162.2 (C-6), 164.9 (CO_2); *m/z* (EI) 342 (5) [M^+], 287 (100), 269 (31), 243 (30), 241 (24), 214 (16), 179 (15), 161 (8), 135 (29), 106 (8), 91 (98).

Compound ***5b***: 222 mg (80%); colourless oil; R_f = 0.20 (ethyl acetate/*n*-hexane 1:1, v/v); ν_{max} (KBr)/cm^{-1}: 3364, 2975, 1694, 1599, 1517, 1365, 1281, 1164, 1115; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08 (3H, s, 1′-H),

1.12 (3H, s, 2′-CH_3), 1.30 (3H, d, ^3J 6.29 Hz, 5′-H), 1.40 (9H, s, Boc-CH_3), 1.66 (1H, dd, ^2J14.56 Hz, ^3J 3.28 Hz, 3′-H^a), 1.92 (1H, dd, ^2J14.56 Hz, ^3J 8.15 Hz, 3′-H^b), 4.28 (2H, d, ^3J 6.12 Hz, CH_2N), 4.34 (1H, s, 2′-OH), 5.2–5.4 (1H, m, 4′-H), 7.40 (1H, d, ^3J 8.20 Hz, 5-H), 7.52 (1H, t, ^3J 6.12 Hz, NHBoc), 8.27 (1H, d, ^3J 8.20 Hz, 4-H), 8.99 (1H, s, 2-H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 21.6 (C-5′), 28.2 (CMe_3), 28.8 (C-1′), 30.8 (2′-CH_3), 45.5 (CH_2N), 48.6 (C-3′), 68.0 (C-2′), 69.3 (C-4′), 78.1 (CMe_3), 120.3 (C-5), 124.5 (C-3), 137.4 (C-4), 149.4 (C-2), 155.9 (OCON), 164.1 (C-6), 164.2 (CO_2); *m/z* (EI) 352 (6) [M^+], 297 (100), 279 (31), 197 (55), 179 (62), 152 (45), 135 (20), 57 (99).

Compound ***5c***: 240 mg (78%); colourless oil; R_f = 0.35 (ethyl acetate/*n*-hexane 1:3, v/v);ν_{max} (KBr)/cm^{-1}: 3363, 2956, 2929, 1713, 1599, 1503, 1366, 1288, 1275, 1167, 1115, 1023, 731; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73 (3H, d, ^3J 6.95 Hz, 9′-H), 0.8–1.0 (7H, m, 8′-H, 10′-H, 4′-H^{ax}), 1.0–1.2 (2H, m, 3′-H^{ax}, 6′-H^{ax}), 1.41 (9H, s, Boc-CH_3), 1.5–1.6 (2H, m, 2′-H, 5′-H), 1.6–1.7 (2H, m, 3′-H^{eq}, 4′-H^{eq}), 1.8–2.0 (1H, m, 7′-H), 2.0–2.1 (1H, m, 6′-H^{eq}), 4.44 (2H, d, ^3J 5.61 Hz, CH_2N), 4.89 (1H, dt, ^3J 10.86 Hz, 4.40 Hz, 1′-H), 5.6–5.8 (1H, m, NHBoc), 7.31 (1H, d, ^3J 8.15 Hz, 5-H), 8.20 (1H, d, ^3J 8.15 Hz, 4-H), 9.08 (1H, s, 2-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.5 (C-9′), 20.6 (C-8′), 21.9 (C-9′), 23.6 (C-3′), 26.5 (C-7′), 28.3 (CMe_3), 31.4 (C-5′), 34.2 (C-4′), 40.8 (C-6′), 45.8 (CH_2N), 47.1 (C-2′), 75.4 (C-1′), 79.6 (*C* Me_3), 121.0 (C-5), 125.2 (C-3), 137.7 (C-4), 150.4 (C-2), 155.9 (OCON), 161.9 (C-6), 164.6 (CO_2); *m/z* (EI) 390 (17) [M^+], 335 (26), 197 (17), 179 (21), 153 (30), 135 (18), 95 (28), 81 (20), 57 (100), 41 (54).

Compound ***5d***: 350 mg (80%); white solid; m.p. 159 °C; R_f = 0.22 (ethyl acetate/*n*-hexane 1:3, v/v); ν_{max} (KBr)/cm^{-1}: 3244, 2932, 1711, 1702, 1598, 1365, 1290, 1120; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (3H, s, 18′-H), 0.84 (6H, d, ^3J 6.60 Hz, 26′-H, 27′-H), 0.90 (3H, d, ^3J 6.51 Hz, 21′-H), 0.9–2.0 (38H, sterol-H, Boc-CH_3), 2.44 (2H, d, ^3J 7.54 Hz, 4′-H), 4.47 (2H, d, ^3J 5.45 Hz, CH_2N), 4.8–4.9 (1H, m, 3′-H), 5.3–5.4 (1H, m, 6′-H), 5.5–5.6 (1H, m, NH), 7.32 (1H, d, ^3J 8.24 Hz, 5-H), 8.23 (1H, d, ^3J 8.24 Hz, 4-H), 9.10 (1H, s, 2-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.9 (C-18′), 18.7 (C-21′), 19.4 (C-19′), 21.1 (C-11′), 22.6 (C-26′), 22.8 (C-27′), 23.8 (C-23′), 24.3 (C-15′), 27.8 (CMe_3), 28.0 (C-25′), 28.2 (C-16′), 31.9 (C-7′), 31.9 (C-8′), 35.8 (C-20′), 36.2 (C-22′), 36.6 (C-10′), 37.0 (C-1′), 38.1 (C-2′), 39.5 (C-24′), 39.7 (C-12′), 42.3 (C-4′), 42.3 (C-13′), 45.8 (CH_2N), 50.0 (C-9′), 56.1 (C-17′), 56.7 (C-14′), 75.2 (C-3′), 79.7 (*C* Me_3), 121.0 (C-6′), 123.0 (C-5), 125.3 (C-3), 137.7 (C-4), 139.4 (C-5′), 150.4 (C-2), 156.0 (OCON), 161.8 (C-6), 164.6 (CO_2); *m/z* (EI) 622 (1) [M^+ + 1], 368 (23), 247 (5), 178 (9), 145 (12), 121 (12), 105 (18), 91 (21), 81 (37), 57 (36), 55 (49), 43 (100).

*2.4.3. Synthesis of 6-aminomethylnicotinates (**6**)*

Compound ***6a***: Benzyl 6-(*t*-butoxycarbonylaminomethyl)nicotinate **5a** (238 mg, 0.69 mmol) was treated with 4 M HCl/dioxane (10 ml) and stirred for 30 min. The colourless precipitate of benzyl 6-aminomethylnicotinate hydrochloride was collected, washed with diethyl ether and dried. Yield: 154 mg (71%), m.p. 155–156 °C; ν_{max} (KBr)/cm^{-1}: 2962, 2858, 1731, 1614, 1496, 1453, 1387, 1295; ^{1}H NMR (300 MHz, D_2O): δ 4.44 (2H, s, CH_2N), 5.34 (2H, s, OCH_2), 7.4–7.6 (5H, m, Ph-H), 7.61 (1H, d, ^3J 8.22 Hz, 5-H), 8.44 (1H, d, ^3J 8.22 Hz, 4-H), 9.15 (1H, s, 2-H); ^{13}C NMR (75.5 MHz, D_2O): δ 42.8 (CH_2), 67.8 ($PhCH_2$), 122.8 (C-5), 125.9 (C-3), 128.4 (Ph-C_o), 128.8 (Ph-C_p), 128.9 (Ph-C_m), 135.3 (Ph-C_{ipso}), 139.2 (C-4), 149.9 (C-2), 156.0 (C-6), 166.3 (CO); *m/z* (EI) 242 (100) [M^+], 214 (86), 197 (6), 151 (9), 135 (97), 107 (11), 91 (100).

Compound ***6b***: Compound **5b** (275 mg, 0.78 mmol) was treated with 4 M HCl/dioxane (20 mL) and stirred for 45 min. Diethyl ether was added and the colourless precipitate of 4-hydroxy-4-methylpent-2′-yl 6-aminomethylnicotinate hydrochloride was collected, washed with THF and diethyl ether and dried. Yield: 164 mg (65%), m.p. 105 °C; ν_{max} (KBr)/cm^{-1}: 3384, 3049, 2970, 1725, 1644, 1478, 1461, 1357, 1293; ^{1}H NMR (300 MHz, D_2O): δ 1.21 (3H, s, 5′-H), 1.23 (3H, s, 4′-CH_3), 1.37 (3H, d, ^3J 6.28 Hz, 1′-H), 1.82 (1H, dd, ^2J 15.16 Hz, ^3J 2.76 Hz, 3′-H^a), 2.13 (1H, dd, ^2J 15.16 Hz, ^3J 8.72 Hz, 3′-H^b), 4.44 (2H, s, CH_2N), 5.3–5.5 (1H, m, 2′-H), 7.63 (1H, d, ^3J 8.22 Hz, 5-H), 8.47 (1H, d, ^3J 8.22 Hz, 4-H), 9.15 (1H, s, 2-H); ^{13}C NMR (75.5 MHz, D_2O): 20.7 (C-1′), 27.9 (C-5′), 28.1 (4′-CH_3), 42.7 (CH_2N), 47.7 (C-3′), 70.5 (C-4′), 71.1 (C-2′), 123.0 (C-5), 126.6 (C-3), 139.6 (C-4), 149.6 (C-2), 155.5 (C-6), 165.8 (CO); *m/z* (EI) 252 (7) [M^+ − 2HCl], 152 (41), 135 (52), 124 (69), 107 (18), 79 (38), 59 (100).

Compound ***6c***: Compound **5c** (200 mg, 0.51 mmol) was treated with 4 M HCl/dioxane (15 mL) and stirred for 1 h. The formed colourless precipitate was collected, washed with diethyl ether and dried. Yield: 152 mg (82%), m.p. 194 °C; ν_{max} (KBr)/cm^{-1}: 3043, 2940, 1723, 1644, 1358, 1292, 1120, 1084, 959, 891, 755; ^{1}H NMR (300 MHz, D_2O): δ 0.70 (3H, d, ^3J 6.91 Hz, 9′-H), 0.8–1.0 (7H, m, 8′-H, 10′-H, 4′-H^{ax}), 1.0–1.2 (2H, m, 3′-H^{ax}, 6′-H^{ax}), 1.3–1.7 (4H, m, 2′-H, 3′-H^{eq}, 4′-H^{eq}, 5′-H), 1.8–1.9 (1H, m, 7′-H), 2.0–2.1 (1H, m, 6′-H^{eq}), 4.43 (2H, s, CH_2N), 4.87 (1H, dt, ^3J 10.80 Hz, 4.39 Hz, 1′-H), 7.62 (1H, d, ^3J 8.18 Hz, 5-H), 8.33 (1H, d, ^3J 8.18 Hz, 4-H), 9.06 (1H, s, 2-H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 17.6 (C-9′), 21.3 (C-8′), 22.8 (C-10′), 24.4 (C-3′), 27.5 (C-7′), 32.0 (C-5′), 34.6 (C-4′), 41.4 (C-6′), 43.5 (CH_2N), 47.6 (C-2′), 76.8 (C-1′), 123.6 (C-5), 126.6 (C-3), 139.2 (C-4), 150.7 (C-2), 157.9 (C-6), 165.8 (CO); *m/z* (EI) 290 (12) [M^+ − 2HCl], 262 (5), 152 (100), 135 (46), 124 (60), 95 (28), 81 (21), 55 (31), 41 (41).

2.4.4. Synthesis of 6-aminomethylnicotinate complexes (7)

Complex 7a: Compound **6a** (120 mg, 0.38 mmol) was dissolved in water (10 mL), the pH value was adjusted to ca. 6 with aqueous NaOH, and K_2PtCl_4 (158 mg, 0.38 mmol) in water (10 mL) was added. The resulting mixture was stirred for 24 h at room temperature while the pH was kept at 5–6. The yellow solid precipitate was collected, washed with water, acetone and diethyl ether and dried. Yield: 152 mg (80%), m.p. > 250 °C. $C_{14}H_{14}Cl_2N_2O_2Pt$ requires: C, 33.08; H, 2.78; N, 5.51. Found: C, 33.34; H, 2.92; N, 5.55%. ν_{max} (KBr)/cm^{-1}: 3253, 3195, 3049, 1721, 1622, 1573, 1375, 1290, 1148; ^{1}H NMR (300 MHz, DMF-d_7): δ 4.48 (2H, t, ^3J 5.94 Hz, CH_2N), 5.48 (2H, s, $PhCH_2$), 6.3–6.4 (2H, m, NH_2), 7.3–7.6 (5H, m, Ph-H), 7.91 (1H, d, ^3J 8.25 Hz, 5-H), 8.69 (1H, d, ^3J 8.25 Hz, 4-H), 9.91 (1H, s, $^3J_{PtH}$ 33 Hz, 2-H); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 53.7 (CH_2), 67.5 ($PhCH_2$), 122.6 (C-5), 127.0 (C-3), 128.5 (Ph-C$_o$), 128.7 (Ph-C$_p$), 128.9 (Ph-C$_m$), 136.2 (Ph-C$_{ipso}$), 139.0 (C-4), 148.5 (C-2), 163.4 (C-6), 170.9 (CO); ^{195}Pt NMR (64.4 MHz, DMF-d_7): δ 2441; *m/z* (EI) 509 (1) [M$^+$], 507 (1) [M$^+$], 419 (5), 330 (23), 302 (7), 242 (29), 214 (25), 135 (31), 91 (100).

Complex 7b: 97 mg (60%) from **6b** (100 mg, 0.31 mmol) and K_2PtCl_4 (129 mg, 0.31 mmol); yellow solid of m.p. > 250 °C. $C_{13}H_{20}Cl_2N_2O_3Pt$ requires: C, 30.13; H, 3.98; N, 5.40. Found: C, 29.58; H, 4.06; N, 5.39%. ν_{max} (KBr)/cm^{-1}: 3425, 3198, 2972, 1719, 1622, 1366, 1296, 1147; ^{1}H NMR (300 MHz, DMF-d_7): δ 1.20 (3H, s, 5′-H), 1.22 (3H, s, 4′-CH_3), 1.38 (3H, d, ^3J 6.28, 1′-H), 1.77 (1H, dd, ^2J14.62 Hz, ^3J 3.50 Hz, 3′-H^a), 2.00 (1H, dd, ^2J 14.62 Hz, ^3J 7.94 Hz, 3′-H^b), 4.42 (1H, s, OH), 4.47 (2H, t, ^3J 5.95 Hz, CH_2N), 5.4–5.5 (1H, m, 2′-H), 6.3–6.4 (2H, m, NH_2), 7.90 (1H, d, ^3J 8.24 Hz, 5-H), 8.67 (1H, d, ^3J 8.24 Hz, 4-H), 9.87 (1H, s, $^3J_{PtH}$ 30 Hz, 2-H); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 21.5 (C-1′), 29.1 (C-5′), 30.9 (4′-CH_3), 49.2 (C-3′), 53.7 (CH_2N), 68.5 (C-4′), 71.0 (C-2′), 122.5 (C-5), 127.6 (C-3), 138.9 (C-4), 148.5 (C-2), 163.0 (C-6), 170.7 (CO); ^{195}Pt NMR (64.4 MHz, DMF-d_7): δ 2438; *m/z* (EI) 252 (5) [M$^+$ − $PtCl_2$], 152 (38), 135 (33), 124 (28), 67 (49), 59 (46), 36 (100).

Complex 7c: 147 mg (78%) from **6c** (124 mg, 0.34 mmol) and K_2PtCl_4 (140 mg, 0.34 mmol); yellow solid of m.p. > 250 °C. $C_{17}H_{26}Cl_2N_2O_2Pt$ requires: C, 36.70; H, 4.71; N, 5.04. Found: C, 37.17; H, 4.85; N, 5.04%. ν_{max} (KBr)/cm^{-1}: 3215, 2954, 1727, 1618, 1406, 1289, 1124, 954, 753; ^{1}H NMR (300 MHz, DMF-d_7): δ 0.80 (3H, d, ^3J 6.95 Hz, 9′-H), 0.8–1.0 (7H, m, 8′-H, 10′-H, 4′-H^{ax}), 1.1–1.3 (2H, m, 3′-H^{ax}, 6′-H^{ax}), 1.5–1.6 (2H, m, 2′-H, 5′H), 1.7–1.8 (2H, m, 3′-H^{eq}, 4′-H^{eq}), 1.9–2.0 (1H, m, 7′-H), 2.0–2.2 (1H, m, 6′-H^{eq}), 4.48 (2H, t, ^3J 5.92 Hz, CH_2N), 4.95 (1H, dt, ^3J 10.86 Hz, 4.41 Hz, 1′-H), 6.3–6.4 (2H, m, NH_2), 7.91 (1H, d, ^3J 8.24 Hz, 5-H), 8.68 (1H, d, ^3J 8.24 Hz, 4-H), 9.89 (1H, s, $^3J_{PtH}$ 32 Hz, 2-H); ^{13}C NMR (75.5 MHz, DMF-d_7): δ 16.4 (C-9′), 20.5 (C-8′), 21.8 (C-10′), 23.7 (C-3′), 26.8 (C-7′), 31.5 (C-5′), 34.2 (C-4′), 40.9 (C-6′), 47.4 (C-2′), 53.7 (CH_2N), 76.2 (C-1′), 122.6 (C-5), 127.3 (C-3), 138.9 (C-4), 148.5 (C-2), 163.1 (C-6), 170.8 (CO); ^{195}Pt NMR (64.4 MHz, DMF-d_7): δ 2439; *m/z* (EI) 290 (7) [M$^+$ − $PtCl_2$], 152 (42), 124 (30), 95 (50), 36 (100).

Complex 7d: Compound **5d** (166 mg, 0.27 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (10 mL) was added [12]. The mixture was stirred for 1 h at room temperature. After evaporation of the solvent the residue was dissolved in THF (10 mL) and treated with a solution of K_2PtCl_4 in water (5 mL); the pH was adjusted to 5–6 with aqueous $NaHCO_3$. After stirring for 24 h at room temperature the formed precipitate was collected, washed with water, acetone and diethyl ether and dried. Yield: 84 mg (40%), yellow solid of m.p. 240 °C (dec.). $C_{34}H_{52}Cl_2N_2O_2Pt$ requires: C, 51.90; H, 6.66; N, 3.58. Found: C, 52.70; H, 6.73; N, 3.53. ν_{max} (KBr)/cm^{-1}: 3234, 2934, 1725, 1622, 1466, 1293, 1276, 1131, 751; ^{1}H NMR (300 MHz, DMF-d_7): δ 0.73 (3H, s, 18′-H), 0.88 (6H, d, ^3J 6.61 Hz, 26′-H, 27′-H), 0.9–2.1 (32H, sterol-H), 2.4–2.6 (2H, m, 4′-H), 4.48 (2H, t, ^3J 5.93 Hz, CH_2N), 4.7–4.9 (1H, m, 3′-H), 5.4–5.5 (1H, m, 6′-H), 6.3–6.4 (2H, m, NH_2), 7.91 (1H, d, ^3J 8.21 Hz, 5-H), 8.68 (1H, d, ^3J 8.21 Hz, 4-H), 9.87 (1H, s, 2-H); *m/z* (EI) 368 (44), 353 (11), 255 (13), 213 (10), 147 (27), 105 (38), 81 (45), 55 (51), 41 (88), 36 (100).

*2.5. Reaction of the complexes (**2a**), (**2b**), (**3b**) and (**7b**) with disodium 5′-GMP*

The reactions were carried out in Eppendorf vials in D_2O/10% DMF-d_7. Two equivalents of disodium guanosine 5′-monophosphate (5′-GMP; Sigma-Aldrich) were dissolved and added to the respective complex to yield a concentration of 8 mM in a total volume of 1 mL. The resulting mixture was shaken at 37 °C for 48 h while monitor ^{1}H NMR spectra were taken at intervals of 1 h for 12 h and in addition at the times indicated in Fig. 1 and after 24 and 48 h (DMF signal at 8.03 ppm taken as an internal shift standard).

3. Results and discussion

3.1. Synthesis

Planar monodentate as well as chelating arylamines such as pyridine, quinoline, dipyridyl [1] or 2-aminomethylpyridine [11a] were found to confer enhanced antitumour activity to both *cis*- and *trans*-Pt(II) complexes. We chose 6-aminomethylnicotinic acid (**1a**) and 2-aminomethylisonicotinic acid (**1b**) as chelate ligands that provide a carboxylic group as an anchor for the attachment of ancillary amino or hydroxy moieties.

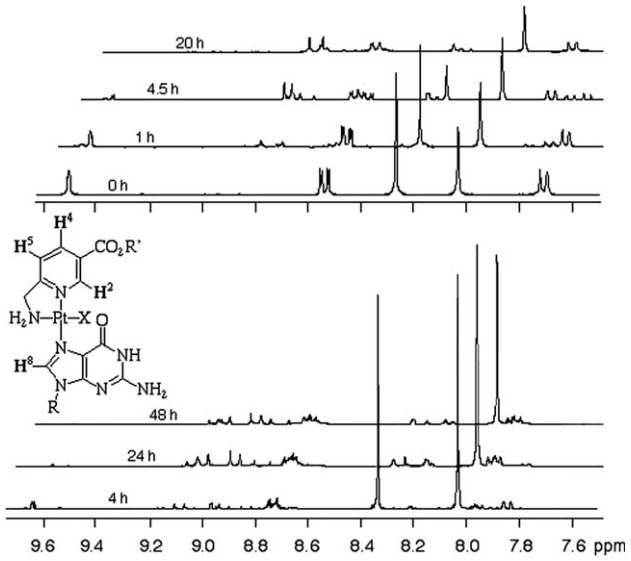


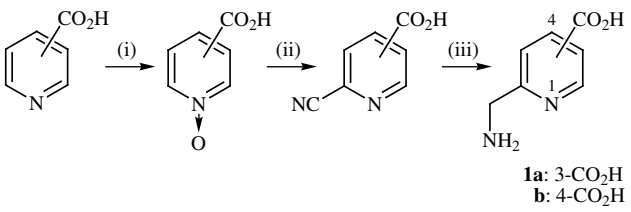
Fig. 1. ^{1}H NMR monitoring of reactions of **2a** (top) and **7b** (bottom) with 5′-GMP in 10% DMF-d_7/D_2O at 37 °C to give complexes as shown in the middle (X = Cl or GMP).

Compounds **1** were readily obtained from nicotinic and isonicotinic acid, respectively, by modified literature procedures [13,14] via the corresponding *N*-oxides and α-cyano derivatives (Scheme 1).

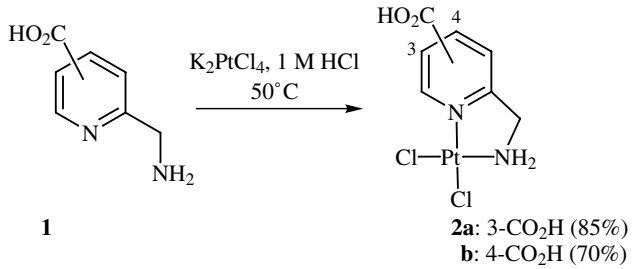
Brunner [11a] obtained *cis*-2-aminomethylpyridine(dichloro)platinum (II) from reaction of 2-aminomethylpyridine with K_2PtCl_4 under slightly acidic conditions. While the analogous reaction of 3,4-diaminobenzoic acid in our hands only led to the formation of a dark-green compound which we think is a salt of the Magnus-type $[Pt(diamine)]^{2+}$ $[PtCl_4]^{2-}$ [17], the reaction of **1** with K_2PtCl_4, carried out in 1 M HCl at 50 °C, gave the complexes **2** as yellow crystalline precipitates (Scheme 2).

3.2. Spectroscopy

^{1}H NMR spectra of complexes **2** were recorded of solutions in DMF-d_7 and found to be quite well resolved and sharp. All protons exhibited a downfield shift when compared with the signals of the free ligands, most significantly so the protons H-2 in **2a** ($\Delta\delta = -0.95$; $^3J_{PtH} = 37$ Hz) and H-6 in **2b** ($\Delta\delta = -0.82$ ppm; $^3J_{PtH} = 31$ Hz). The ^{195}Pt NMR spectra also showed distinct signals [**2a**: $\delta = 2439$ ppm; **2b**: $\delta = 2466$ ppm, relative to $\Xi(^{195}Pt) = 21.4$ MHz] with line widths of 250–300 Hz which is typical of *N*-ligated platinum. The far IR spectra, recorded of samples embedded in polyethylene disks, were diagnostic of the *cis*-$PtCl_2$ moiety [**2a**: $\nu = 335, 327$ cm^{-1}; **2b**: $\nu = 342, 325, 318$ cm^{-1}].



Scheme 1. Reagents and conditions: (i) H_2O_2 (30%), AcOH, 90 °C, 85%; (ii) NEt_3, TMSCl, NaCN, DMF, 105 °C, 55%; (iii) H_2, Pd/C (10%), MeOH, r.t., (**1a:** 80%; **1b:** 70%).



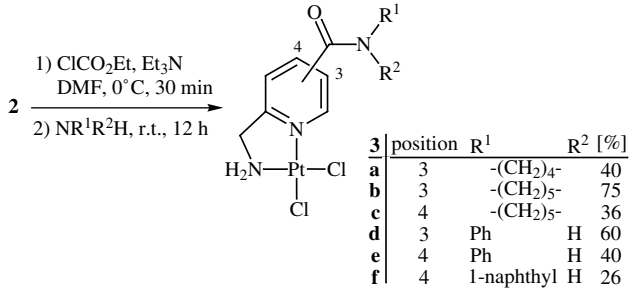
Scheme 2. Synthesis of *cis*-diamine(dichloro)platinum(II) complexes **2**.

3.3. Amide bond formation

Attachment of amines to the carboxylic acid group of complexes **2** was accomplished by amide formation via the mixed anhydrides generated by treatment with ethyl chloroformate and triethylamine at room temperature or below. Subsequent addition of primary amines (aniline, 1-naphthylamine) or secondary amines (pyrrolidine, piperidine) to these highly reactive anhydrides yielded the corresponding amides in 25–75% (Scheme 3). Other amidation methods employing condensation reagents such as DCC/DMAP (Steglich conditions) failed to give pure products in reasonable yields.

3.4. Ester bond formation

Contrary to the amidation described above, the attachment of alcohols to the preformed complexes **2** failed when attempted under the usual conditions, including the mixed anhydride method. Hence the nicotinate complexes **7** were best prepared following the opposite strategy: synthesis of the required 6-aminomethylnicotinates **6** (not shown) by Yamaguchi esterification



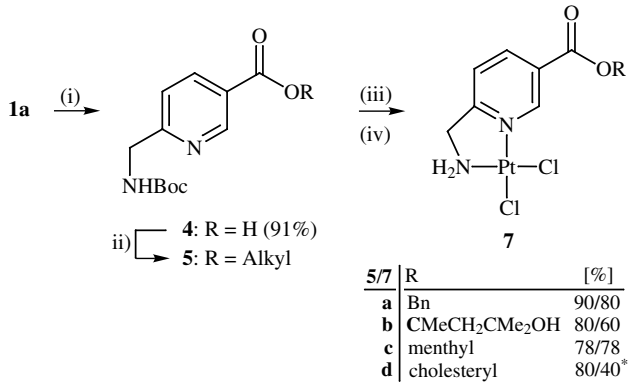
3	position	R^1	R^2	[%]
a	3	-$(CH_2)_4$-		40
b	3	-$(CH_2)_5$-		75
c	4	-$(CH_2)_5$-		36
d	3	Ph	H	60
e	4	Ph	H	40
f	4	1-naphthyl	H	26

Scheme 3. Amidation of complexes **2** to give **3**.

of the Boc-protected [15] acids **4** and subsequent deprotection, and finally ligation of **6** by treatment with K_2PtCl_4 in H_2O at pH 5–6 (Scheme 4). The Yamaguchi protocol [18] is quite effective under mild conditions and allows to discriminate between primary/secondary and between secondary/tertiary hydroxy groups which might be advantageous for the conjugation of more complex hydroxy substituted co-drugs.

*3.5. Interaction of complexes **2**, **3** and **7** with guanosine 5′-monophosphate disodium salt*

Antineoplastic platinum (II) complexes target the DNA by binding irreversibly to N-7 of accessible guanine residues. Hence prospective drug candidates of this type, apart from other requirements such as sufficient accumulation by the cell and robustness against deactivation and damage–repair mechanisms, should readily react with free guanosine 5′-monophosphate (5′-GMP). This process is easily monitored by ^{1}H NMR spectroscopy [12,19]. We shook Eppendorf vials containing solutions of complexes **2a**, **2b**, **3b** or **7b**, respectively, and two equivalents of disodium 5′-GMP in 10% DMF-d_7/D_2O at 37 °C and recorded ^{1}H NMR spectra at regular intervals of 1 h for up to 48 h. In the case of **2a**,**b** half of the GMP became coordinated to platinum within 2 to 3 h and formation of the respective bis–GMP adducts was found complete after ca. 20 h. Longer half times of GMP in the presence of **3b** and **7b** were probably due not to a lower reactivity but to their lower solubilities. While the reaction progressed the intensity of the 8-H^G signal of unbound 5′-GMP at 8.26 decreased and new signals cropped up between 8.7 and 9.1 originating from the 8-H^G protons in the platinum (N-7)GMP adducts. Fig. 1 shows the representative ^{1}H NMR spectra for the reactions of 5′-GMP with **2a** (top) and **7b** (bottom). The multiplying of the 8-H^G signals in the GMP adducts of **7b** when compared to those of **2a** reflects the presence of a stereogenic centre in the (racemic) ester side chain leading to diastereoisomers. However, in principle, multiple signals can also arise from rotamers. Interestingly, the protons 4-H^N and 5-H^N of the aminomethylnicotinic acid ligand also shifted downfield, e.g., in the case of **2a** from 8.53 and 7.71 ppm in the starting complex to 8.58 and 7.85 ppm, respectively, in the platinum bis–GMP adduct. An intermediate signal at 7.77 ppm, observable between 1 and 4.5 h after reaction start can be assigned to a relatively long-lived platinum mono–GMP adduct. Also worthy of note is that 2-H^N, peaking at 9.48 ppm for the dichloro complex **2a**, is no longer visible in the respective bis–GMP adduct, presumably due to hydrogen bond formation with nearby groups on the GMP ligand *cis* to the pyridine N atom, while a small signal at 9.51 ppm is likely to stem from the 2-H^N of the *trans*-mono–GMP adduct.



5/7	R	[%]
a	Bn	90/80
b	CMeCH$_2$CMe$_2$OH	80/60
c	menthyl	78/78
d	cholesteryl	80/40*

Scheme 4. Reagents and conditions: (i) Boc_2O, H_2O/*t*-BuOH, r.t., 24 h; (ii) Et_3N, $C_6H_2Cl_3COCl$, DMAP, ROH, DMF/toluene (1:10), r.t.; (iii) 4M HCl/dioxane, r.t. (for **5a-c**), TFA/CH_2Cl_2, r.t. (for **5d**); (iv) K_2PtCl_4, H_2O, pH 5-6, r.t. *Yield with respect to **5d**; **6d** not isolated.

In summation we found that *cis*-dichloro[methylamino(iso-)nicotinate]platinum (II) complexes of types **2**, **3** and **7** readily interact with guanosine. The syntheses of the amide and ester conjugate complexes **3** and **7** are straightforward. Amines can be attached in one step to the carboxylic acid group of *cis*-dichloro[aminomethyl(iso-)nicotinic acid]platinum (II) **2** to give **3**, while the ester complexes **7** are best prepared from the preformed ligands and K_2PtCl_4. We are currently applying both methods to the synthesis of conjugates of complexes **2** with various natural and synthetic NH_2- and OH-functionalized electrophiles and intercalators of proven bioactivity.

Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft for financial support (Grant Scho 402/8) and to Bayer, BASF and Degussa for donations of chemicals.

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