Supporting Information

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New Peptide Labels Containing Covalently Bonded Platinum(II) Centers as Diagnostic Biomarkers and Biosensors

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Experimental

General. Syntheses involving organolithium compounds were carried out under nitrogen atmosphere using standard Schlenk techniques. THF, benzene and Et_2O were dried from Na/benzophenone and destilled prior to use. CH_2Cl_2 was destilled from CaH_2, DMF and NEt_3 were flash-distilled from CaH_2 and stored on molecular sieves. The organoplatinum complexes **7** and **8**,[1] the platinum salt $[Pt(tol\text{-}4)_2(SEt_2)]_2$,[2] and the ligand precursor [NC(Br)N-I-4] **1**[3] were prepared according to published procedures. All other reagents were obtained commercially and used without further purification. The ^1H and ^{13}C $\{^1H\}$ NMR spectra were recorded at 300 and 75 MHz, respectively, at 25 ˚C and were referenced to external $SiMe_4$ ($\delta = 0.00$, J in Hz), ^{195}Pt NMR spectra (64.5 MHz) were referenced to external K_2PtCl_4 ($\delta = -1630$). Elemental analyses were performed by Kolbe, Mikroanalytisches Laboratorium (Mülheim, Germany).

[NC(Br)N-CHO-4] 2. To a solution of **1** (2.19 g, 5.52 mmol) in dry Et_2O (30 mL) was added dropwise at –100 °C *t*-BuLi (6.2 mL, 1.7 M in hexane, 10.5 mmol). The solution was stirred for 10 min. and subsequently treated with DMF (15 ml, large excess). After stirring for 16 h at ambient temperature, water (20 mL) was added and stirring was continued for 1 h. The mixture was diluted with NaOH (2M, 40 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine and dried over $MgSO_4$ to afford the crude product. Column chromatography (Al_2O_3 (4% NH_4OH), pentane/ethylacetate, 3:1) yielded **2** as a yellowish oil (1.43 g, 87%). ^1H NMR ($CDCl_3$): $\delta = 2.33$ (s, 12H, NMe_2), 3.60 (s, 4H, CH_2), 7.86 (s, 2H, Ar*H*), 10.02 (s, 1H, CHO); ^{13}C $\{^1H\}$ NMR ($CDCl_3$): $\delta = 45.7$ (NMe_2), 63.7 (CH_2), 129.8 (C_{aryl}), 133.6 (C_{aryl}), 134.8 (C_{aryl}), 140.2 (C_{aryl}), 191.8 (CHO); elemental analyses calcd (%) for $C_{13}H_{19}BrN_2O$ (298.07): C 52.18, H 6.40, N 9.37; found C 52.22, H 7.07, N 9.37.

[NC(Br)N-(CH_2-L-Val-OMe)-4] 3. A mixture of **2** (1.75 g, 5.85 mmol), L-valine methylester hydrochloride (1.96 g, 12 mmol), triethylamine (1.63 mL, 12 mmol) and an excess of $MgSO_4$ (8 g) were stirred in CH_2Cl_2 (25 mL) at ambient temperature for 16 h. All solids were filtered off, and the volatiles were removed under reduced pressure to yield a yellow oil, which was redissolved in MeOH (20 mL) and HOAc (0.33 mL, 5.85 mmol). This solution was cooled below 10 °C and $NaBH_3CN$ (0.73 g, 12 mmol) was added in portions. The reaction

mixture was allowed to warm to ambient temperature and stirred for additional 2 h. All volatiles were removed in vacuo and the resulting residue was diluted with NaOH (2M, 50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The volatiles were removed and the resulting oil was purified by column chromatography (Al_2O_3, 6% H_2O, hexane/EtOAc, 4:1) to yield **3** as a colorless oil (2.04 g, 87%). ^{1}H NMR ($CDCl_3$): δ = 0.91 (d, $^3J_{HH}$ = 5.6, 3H, CMe_2) 0.94 (d, $^3J_{HH}$ = 5.2, 3H, CMe_2), 1.88 (m, 1H, C*H*$(Me)_2$), 2.24 (s, 1H, NH), 2.31 (s, 12H, NMe_2), 2.96 (d, $^3J_{HH}$ = 6.2, 1H, NH-C*H*-CO), 3.52 (highfield part of AB signal, 1H, Ar-CH_2-NH), 3.53 (s, 4H, CH_2NMe_2), 3.71 (s, 3H, OMe), 3.81 (lowfield part of AB signal, 1H, Ar-CH_2-NH), 7.29 (s, 2H, Ar*H*); ^{13}C {^{1}H} NMR ($CDCl_3$): δ = 18.63 (*C*H_3CH), 19.3 (*C*H_3CH), 31.7 (*C*H$(Me)_2$), 45.6 (NMe_2), 51.3 (OMe), 51.7 (*C*H_2NH), 64.0 (*C*H_2NMe_2), 66.4 (N*C*H-COO), 125.3 (C_{ipso}), 129.3 (C_{meta}), 138.5 (C_{ortho}), 138.6 (C_{para}), 175.6 (*C*OOMe); elemental analyses calcd (%) for $C_{19}H_{32}BrN_3O_2$ (413.17): C 55.07, H 7.78, N 10.14; found C 55.21, H 7.85, N 9.96.

[PtBr(NCN-{CH_2-L-Val-OMe}-4)] 4. *Method A:* A mixture of **3** (172 mg, 0.43 mmol) and $[Pt(tol\text{-}4)_2(SEt_2)]_2$ (200 mg, 0.22 mmol) in dry benzene (30 mL) was refluxed for 3 h. All volatiles were removed at reduced pressure and the resulting oil was washed with pentane (2 × 30 mL). The formed precipitate was removed by centrifugation and decanting of the clear supernatant. This supernatant was concentrated and purified by gradient chromatography (SiO_2, hexane/CH_2Cl_2/acetone). The platinum-containing fractions were collected and evaporated to dryness, yielding **4** as a yellow solid (150 mg, 59%).

Method B: A mixture of **5** (110 mg, 0.23 mmol), L-valine methylester hydrochloride (75 mg, 0.45 mmol), triethylamine (0.06 ml, 0.45 mmol) and $MgSO_4$ (1 g) were stirred in CH_2Cl_2 (10 mL) at ambient temperature for 2 d. All solids were filtered off, the volatiles were removed under reduced pressure and the residue was redissolved in MeOH (10 mL) and HOAc (0.02 mL, 0.23 mmol). This solution was kept below 10 °C while adding portions of $NaBH_3CN$ (27.9 mg, 0.44 mmol). The reaction mixture was then warmed to ambient temperature and stirred for 2 h. All volatiles were removed in vacuo and the residue was extracted with NaOH (2M, 20 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The $MgSO_4$ was filtered off and the volatiles from the filtrate were removed

in vacuo. The resulting oil was purified as described in method A. Yield of **4**: 85 mg (64%). ^{1}H NMR ($CDCl_3$): δ = 0.88 (d, $^{3}J_{HH}$ = 3.4, 3H, CMe_2) 0.92 (d, $^{3}J_{HH}$ = 3.8, 3H, CMe_2), 1.90 (m, 1H, C*H*$(Me)_2$), 2.28 (s, 1H, NH), 3.07 (s, $^{3}J_{PtH}$ = 37.8, 12H, NMe_2), 3.05 (d, $^{3}J_{HH}$ = 17.2, 1H, NH-C*H*-CO), 3.39 (highfield part of AB signal, 2H, Ar-CH_2-NH), 3.61 (lowfield part of AB signal, 2H, Ar-CH_2-NH), 3.69 (s, 3H, OMe), 3.97 (s, $^{3}J_{PtH}$ = 46.0, 4H, CH_2NMe_2), 6.77 (s, 2H, Ar*H*); ^{13}C {^{1}H} NMR ($CDCl_3$): δ = 18.7 (*C*H_3CH), 19.1 (*C*H_3CH), 31.6 (*C*HMe_2), 51.4 (OMe), 53.3 (CH_2NH), 55.0 (NMe_2), 66.6 (N*C*H-COO), 77.4 ($^{3}J_{PtC}$ = 53.6, *C*H_2NMe_2), 119.6 (C_{meta}), 135.0 (C_{para}), 143.3 ($^{2}J_{PtC}$ = 78.4, C_{ortho}), 145.0 (C_{ipso}), 175.4 (*C*OOMe); MS ES (m/z): 610.4 (calcd for M+H^+: 610.5); elemental analyses calcd (%) for $C_{19}H_{32}BrN_3O_2Pt$ (609.48): C 37.44, H 5.29, N 6.89; found C 37.30, H 5.22, N 6.78.

[PtBr(NCN-CHO-4)] 5. A mixture of **2** (200 mg, 0.67 mmol) and $[Pt(tol\text{-}4)_2(SEt_2)]_2$ (312 mg, 0.67 mmol) in dry benzene (20 mL) was stirred for 3 h at 80 ˚C. All volatiles were removed under reduced pressure and the residue crystallized from CH_2Cl_2/pentane to afford **5** as needle-shaped crystals (0.25 g, 76%). ^{1}H NMR ($CDCl_3$): δ = 3.14 (s, $^{3}J_{PtH}$ = 38.7, 12H, NMe_2), 4.08 (s, $^{3}J_{PtH}$ = 46.2, 4H, CH_2), 7.34 (s, 2H, Ar*H*), 9.85 (s, 1H, CHO); ^{13}C {^{1}H} NMR ($CDCl_3$): δ = 55.0 (NMe_2), 76.8 (CH_2), 121.3 ($^{3}J_{PtC}$ = 36, C_{meta}), 133.1 (C_{para}), 144.1 ($^{2}J_{PtC}$ = 77.3, C_{ortho}), 157.5 (C_{ipso}), 191.8 (CHO); elemental analyses calcd (%) for $C_{13}H_{19}BrN_2OPt$ (493.03): C 31.59, H 3.87, N 5.67; found C 31.80, H 3.95, N 5.59.

References

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