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Luminescent Cyclometallated Platinum(II) Complexes: Highly Potential EGFR/DNA Probes and Dual-Targeting Anticancer Agents

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Electronic Supplementary Information

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Experimental Section

1. Synthesis and characterization

1.1 Synthesis and characterization of 4-anilinoquinazoline derivatives. The 4-anilinoquinazoline derivatives **1** and **2** were synthesized following the method described in our previous publication [1] with slight modification.

6-(2-(1H-imidazol-1-yl)ethoxy)-4-(3'-chloro-4'-fluoro-anilino)-7-methoxyquinazoline (1). 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (6.0 g, 18.8 mmol) and potassium carbonate (12.0 g, 86.8 mmol) were mixed in DMF (250 mL). Then 1,2- dibromoethane (6 mL, 69.3 mmol) was added and the resulting mixture was heated at 80 ºC for 8 h. After cooling to room temperature, the mixture was filtered in vacuum and the filtrate was collected. Then the solvent was evaporated in vacuum and the residue was recrystallized from ethanol and further purified by flash chromatography on Silica gel using ethyl acetate/ petroleum (5: 2) as eluent to give 4-(3'-chloro-4'-fluoroanilino)-6-(2-bromoethoxy)-7-methoxyquinazoline (**1'**) as white powder (3.6 g, 45%). Then imidazole (266 mg, 3.9 mmol), tetrabutyl ammonium bromide (TBAB) (31 mg, 0.1 mmol) and NaOH (468 mg, 11.7 mmol) were mixed in acetonitrile (50 mL). The reaction mixture was heated to 90 °C and refluxed for 1 h, then the intermediate **1'** (1.0 g, 2.34 mmol) was added and the mixture was further refluxed for 5 h. After cooling to room temperature, the mixture was filtered in vacuum and the filtrate was collected and evaporated to give yellow oil. Then water (40 mL) and ethyl acetate (40 mL) was added. A light yellow solid was appeared between water and ethyl acetate after ultrasonic vibration 5 min and standing for 1 h, the mixture was filtered in vacuum and washed with water and ethyl acetate to give **1** as light yellow powder (0.6 g, 62%). m.p. 259 – 261 °C (from water and ethyl acetate). ESI-MS: *m/z* (the most abundant isotopomer) 414.2 ($[M + H]^+$, $C_{20}H_{18}ClFN_5O_2$ requires 414.1). ^{1}H NMR (400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 9.53 (s, 1H), 8.47 (s, 1H), 8.06 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.77 (s, 1H), 7.74 – 7.71 (m, 2H),7.41 (t, J = 9.2 Hz, 1H), 7.29 (s, 1H), 7.19(s, 1H), 6.91 (s, 1H), 4.48 (t, J = 5.2 Hz, 2H), 4.38 (dd, J_1 = 4.8 Hz, J_2 = 5.6 Hz, 2H), 3.93 (s, 3H). Elemental analysis: calculated for

$C_{20}H_{17}ClFN_5O_2$: C, 58.05; H, 4.14; N, 16.9; Found: C, 58.04; H, 4.20 ; N, 16.32.

6-(3-(1H-imidazol-1-yl)propoxy)-4-(3'-chloro-4'-fluoro-anilino)-7-methoxy-quinazoline (2). 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (6.0 g, 18.8 mmol) and potassium carbonate (12.0 g, 86.8 mmol) were mixed in acetone (300 mL). The reaction mixture was further refluxed for 0.5 h. Then 1, 3-dibromopropane (7.6 mL, 74.6 mmol) was added and the resulting mixture was refluxed for 10 h. After cooling to room temperature, the mixture was filtered in vacuum and the filtrate was collected. Then the solvent was evaporated in vacuum and the residue was recrystallized from ethanol .The yellow crude residue was further purified by flash chromatography on Silica gel using ethyl acetate/ petroleum (5: 2) as eluent to give 4-(3'-chloro-4'-fluoroanilino)-6-(3-bromopropoxy)-7-methoxyquinazoline (**2'**) as white powder (3.0 g, 36%). Imidazole (258 mg, 3.8 mmol), tetrabutyl ammonium bromide (TBAB) (30 mg, 0.1 mmol) and NaOH (454 mg, 11.3 mmol) were mixed in acetonitrile (50 mL) .The reaction mixture was heated to 90 °C and refluxed for 1 h, then the intermediate **2'** (1.0 g, 2.27 mmol) was added and the mixture was refluxed for 5 h. After cooling to room temperature, the mixture was filtered in vacuum and the filtrate was collected and evaporated to give yellow oil. Then water (40 mL) and ethyl acetate (40 mL) was added. A light yellow solid was appeared between water and ethyl acetate after ultrasonic vibration 5 min and standing for 1h, the mixture was filtered in vacuum and washed with water and ethyl acetate to give **2** as light yellow powder (0.7 g, 72%). m.p. 201 – 203 °C (from water and ethyl acetate). ESI-MS: *m/z* (the most abundant isotopomer) 428.2 ($[M + H]^+$, $C_{21}H_{20}ClFN_5O_2$ requires 428.1). ^{1}H NMR (400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 9.51 (s, 1H), 8.50 (s, 1H), 8.10 (dd, J_1 = 2.4 Hz, J_2 = 2.8 Hz, 1H), 7.79 – 7.75 (m, 2H),7.64 (s, 1H), 7.43 (t, J = 9.2 Hz, 1H), 7.22 (s, 2H), 6.91 (s, 1H), 4.20 (t, J = 6.8 Hz, 2H), 4.08 (t, J = 6.0 Hz, 2H), 3.97 (s, 3H), 2.33 – 2.27 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d^6, Me_4Si) δ_C (ppm): 156.5, 155.0, 153.2, 148.5, 147.6, 137.8, 129.1, 123.9, 122.7, 119.8, 119.3, 119.2, 117.0, 116.8, 109.2, 107.9, 103.5, 66.2, 56.4, 43.4, 30.6. Elemental analysis: calculated for $C_{21}H_{19}ClFN_5O_2 \cdot H_2O$: C, 56.57; H, 4.75; N, 15.71; Found: C, 56.51; H,4.61 ; N,15.46.

1.2 Synthesis and characterization of (C^N^N) ligands. 4,6-diphenyl-2,2'-bipyridine (dpbp).[2] 4,6-diphenyl-2,2'-bipyridine was synthesized according to the literature method of 4′-phenyl-2,2′:6′,2"-terpyridine with slight modification. Acetophenone (3 mL, 25.5 mmol), benzaldehyde (2.6 mL, 25.5 mmol) and NaOH (1.2 g, 30 mmol) were stirred in water (50 mL) at ambient temperature for 12 h. Then 2-acetylpyridine (3mL, 26.7 mmol), NaOH (9.0 g, 225 mmol) were added. The reaction mixture was further stirred at 80 °C for 12 h. After cooling, the flask was kept at -20 ºC overnight. Then the layer yellow oil was poured out, ethanol (200 mL) and ammonium acetate (18.0 g, 233.5 mmol) were added to the residues and stirred at 80 ºC for 8 h, resulting in clear red-orange solution. The ethanol was removed in vacuum and the crude product was purified by column chromatography (silica gel, ethyl acetate / petroleum ether = 1: 30 as eluent) to give 4,6-diphenyl-2,2'-bipyridine (dpbp) as white solid. Yield: 2.8 g (36%). m.p. 160 – 164 ºC. ESI-MS: *m/z* (the most abundant isotopomer) 309.2 ($[M + H]^+$, $C_{22}H_{17}N_2$ requires 309.1).^{1}H NMR (400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 8.75 (d, *J* = 4.4 Hz, 1H), 8.63 (d, *J* = 8.0 Hz, 2H), 8.37 (d, *J* = 7.2 Hz, 2H), 8.30 (d, *J* = 1.2 Hz, 1H), 8.05 – 7.98 (m, 3H), 7.61 – 7.49 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d^6, Me_4Si) δ_C (ppm): 157.0, 156.2, 155.7, 150.0, 149.8, 139.0, 138.1, 137.8, 130.0, 129.8, 129.7, 129.6, 129.3, 129.2, 127.7, 127.6, 127.5, 127.4, 124.9, 121.3, 118.5, 117.0. Elemental analysis: calculated for $C_{22}H_{16}N_2$: C, 85.69; H, 5.23; N, 9.08; Found: C, 85.69; H, 5.20; N, 8.88 .

6-(2-naphthalenyl)-2,2'-bipyridine (nabp).[3] (2-Pyridacyl) pyridium Iodide[4]: Iodine (8.4 g, 33.1 mmol) dissolved in warm pyridine (50 mL) was added under argon to a solution of 2-acetylpyridine (12.6 mL). The reaction mixture was stirred at 80 °C for 4h. After cooling, the precipitated solid was collected by filtration and washed with cold pyridine (15 mL), recrystallized from ethanol to give (2-pyridacyl) pyridium iodide as yellow-green solid. Yield (7.0 g, 65%). ESI-MS: *m/z* (the most abundant isotopomer) 199.0 (M^+, $[C_{12}H_{11}N_2O]^+$, requires 199.1).

3-dimethylamino-1-(naphthalen-2-yl)-1-propanone hydrochloride [5]: A suspension of 2-acetonaphthone (6.0 g, 35.3 mmol), dimethyl amine hydrochloride

(3.0 g, 36.8 mmol) and paraformaldehyde (1.0 g, 11.1 mmol) in a mixture of 30 mL of ethanol and 1 mL of conc. HCl was refluxed for 5h. Then ethanol was removed in vacuo and the crude product was purified by column chromatography (silica gel, CH_2Cl_2 / MeOH = 50: 1 as eluent) as white solid. Yield: 8.1 g (87%). ESI-MS: *m/z* (the most abundant isotopomer) 228.1 (M^+, $[C_{15}H_{18}NO]^+$ requires 228.1).

A mixture of (2-pyridacyl)pyridium Iodide (1.8 g, 5.5 mmol), 3-dimethylamino-1-(naphthalene-2-yl)-1-propanone hydrochloride salt (1.4 g, 5.3 mmol) and excess ammonium acetate (10.2 g, 132.3 mmol) was heated in methanol (150 mL) for 12h to give compound L2. The crude product was filtered from the solution mixture, washed with water and cold methanol, and purified by column chromatography (silica gel, ethyl acetate/ petroleum ether =1: 20 as eluent) as white solid. Yield: 0.4 g (28%). mp 115 – 119 ºC (from ethyl acetate and petroleum ether). ESI-MS: *m/z* (the most abundant isotopomer) 283.2 ($[M + H]^+$, $C_{20}H_{15}N_2$ requires 283.1). ^{1}H NMR (400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 8.80 (s, 1H), 8.74 (d, J = 4.0 Hz, 1H), 8.68 (d, J = 8.0 Hz, 1H), 8.44 (t, $J_1 = J_2$ = 1.6 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 7.6 Hz, 1H), 8.11 – 7.98 (m, 2H), 7.52 – 7.49 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d^6, Me_4Si) δ_C (ppm): 155.8, 155.8, 155.6, 149.8, 138.9, 137.8, 136.3, 133.8, 133.6, 129.2, 128.8, 128.1, 127.3, 127.0, 126.5, 124.9, 124.8, 121.3, 121.2, 119.7. Elemental analysis: calculated for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92; Found: C, 85.19 ; H, 5.14; N, 9.75 .

1.3 Synthesis and characterization of [(C^N^N)PtCl] complexes. The complexes [(C^N^N-L)PtCl] (L = L1 (**3**) or L2 (**4**) were prepared adapting the method reported in the literature.[6, 7]

Complex 3. The mixture of 4,6-diphenyl-2,2'-bipyridine (dpbp) (75 mg, 0.24 mmol) and K_2PtCl_4 (100 mg, 0.24 mmol) was refluxed in a mixture of acetonitrile and water (15 ml, 1: 1) for 24 h. The precipitate was filtered and rinsed with a mixture of acetonitrile and water and recrystallized from CH_2Cl_2 to afford **3** (81 mg, 62 % yield) as orange crystal (Scheme S3). m.p. 356 – 360 °C (from CH_2Cl_2). ESI-MS: *m/z* (the most abundant isotopomer) 502.2 ($[M – Cl]^+$, $C_{22}H_{15}N_2Pt$ requires 502.1). ^{1}H NMR

(400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 8.87 (d, J = 4.4 Hz, 1H), 8.71 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 0.4 Hz, 1H), 8.34 (m, 1H), 8.29 (s, 1H), 8.11 – 8.09 (m, 2H), 7.88 (dd, J_1 = 6.0 Hz, J_2 = 6.8 Hz, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.60 – 7.59 (m, 3H), 7.47 (d, J = 7.2 Hz, 1H), 7.14 – 7.05 (m, 2H). Elemental analysis: calculated for $C_{22}H_{15}ClN_2Pt \cdot H_2O$: C, 47.53; H, 3.08; N, 5.04; Found: C, 47.66; H, 2.80; N, 5.33.

Complex 4.[3] A mixture of K_2PtCl_4 (100 mg, 0.24 mmol) and 6-(2-naphthalenyl)-2,2'-bipyridine (L2) (68 mg, 0.24 mmol) in glacial acetic acid (35 mL) was refluxed for 24 h to give yellow suspension. The yellow solid was isolated by filtration in vacumm, washed with water and acetone, and recrystallized from CH_2Cl_2 to afford 4 (89 mg, 72% yield) as yellow crystalline solid (Scheme S3). m.p. 358 – 362 °C (from CH_2Cl_2). ESI-MS: *m/z* (the most abundant isotopomer) 476.2 ([M – Cl]$^+$, $C_{20}H_{13}N_2Pt$ requires 476.1). ^{1}H NMR (400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 8.96 (d, J = 4.0 Hz, 1H), 8.51 (d, J = 8.0 Hz,1H), 8.33 (m, 1H), 8.23 – 8.15 (m, 4H), 7.91 (t, J = 6.4 Hz, 1H), 7.81 (dd, J_1 = 7.2 Hz, J_2 = 8.4 Hz, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.44 (dd, J_1 = 6.8 Hz, J_2 = 7.2 Hz, 1H), 7.37 (dd, J_1 = 7.6 Hz, J_2 = 6.8 Hz, 1H). Elemental analysis: calculated for $C_{20}H_{13}ClN_2Pt$: C, 46.93; H, 2.56; N, 5.47; Found: C, 46.68 ; H, 2.52; N, 5.45.

1.4. Synthesis and characterization of [(C^N^N)Pt(L)]PF_6 (5 – 8), general procedure: The four compounds [(C^N^N)Pt(L)]PF_6 (**5** – **8**) (L= **1** or **2**) were prepared adapting the methods described in the literature.[8] The 4-anilinoquinazoline derivatives **1** or **2** (0.11 mmol) and corresponding [(C^N^N)PtCl] (0.1 mmol) were dissolved in methanol (60 mL), the mixture was refluxed until the solution to be clear. After cooling to room temperature, the solution was filtered and ammonium hexafluorophosphate (0.4 mmol) was added to this mixture and further stirred for 30 min at 298 K to precipitate the product. The solid was collected by filtration, washed with methanol, recrystallized from CH_3CN to give the products.

Complex 5. Yellow solid. Yield: 94 mg (89%). m.p. 192 – 196 ºC (from CH_3CN). ESI-MS: *m/z* (the most abundant isotopomer) 916.2 (M^+, $C_{42}H_{32}ClFN_7O_2Pt$ requires 916.2). ^{1}H NMR (400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 9.46 (s, 1H), 8.77 (s, 2H),

8.54 (s, 1H), 8.47 (s, 1H) 8.35 (t, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 2H), 8.07 (d, *J* = 4.0 Hz,1H), 7.88 (d, *J* = 8.0 Hz, 2 H), 7.78 – 7.76 (m, 2H), 7.61 (m, 4H), 7.47 (s, 1H), 7.33 (dd, J_1 = 12.0 Hz, J_2 = 8.0 Hz, 1H), 7.21 (s, 1H), 7.10 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H), 6.96 (dd, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 4.77 (s, 2H), 4.64 (s, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d^6, Me_4Si) δ_C (ppm): 165.7, 162.8, 157.0, 156.4, 155.3, 154.9, 153.4, 152.8, 152.3, 148.9, 147.9, 147.7, 141.4, 141.1, 141.0, 137.2, 137.2, 136.2, 133.0, 131.2, 131.0, 129.6, 128.8, 128.2, 126.4, 125.2, 123.4, 123.2, 122.3, 122.2, 119.3, 119.1, 117.7, 117.2, 117.0, 116.8, 109.1, 108.2, 104.1, 68.2, 56.5, 48.0. Elemental analysis: calculated for $C_{42}H_{32}ClF_7N_7O_2PPt$•H2O: C, 46.74; H, 3.18; N, 9.08; Found: C, 46.45; H, 3.54; N, 8.83.

Complex 6. Red-orange solid. Yield: 56 mg (52%). m.p. 186 – 189 ºC (from CH_3CN). ESI-MS: m/z (the most abundant isotopomer) 929.2 (M+, $C_{43}H_{34}ClFN_7O_2Pt$ requires 929.2). 1H NMR (400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 9.46 (s, 1H), 8.72 (d, *J* = 4.0 Hz, 1H), 8.69 (s, 1H), 8.53 (s, 1H), 8.48 (s, 1H), 8.30 – 8.27 (m, 2H), 8.09 – 8.05 (m, 4H), 7.84 (d, *J* = 4.0 Hz, 3H), 7.61 (s, 1 H), 7.51 (s, 1H), 7.40 – 7.36 (t, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 7.01 (d, *J* = 4.0 Hz, 1H), 6.94 (d, *J* = 4.0 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 4.47 (s, 2H), 4.19 (s, 2H), 3.91 (s, 3H), 2.52 – 2.49 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d^6, Me_4Si) δ_C (ppm): 165.7, 162.8, 156.8, 156.4, 155.2, 155.0, 153.2, 152.6, 148.4, 147.8, 147.6, 141.2, 141.1, 140.7, 137.2, 137.1, 136.1, 133.0, 131.2, 131.0, 130.0, 129.5, 128.8, 128.1, 126.3, 125.1, 125.0, 123.6, 122.5, 122.4, 119.3, 119.1, 117.6, 117.1, 117.0, 116.8, 109.2, 108.0, 104.1, 66.7, 56.4, 45.6, 29.7. Elemental analysis: calculated for $C_{43}H_{34}ClF_7N_7O_2PPt$•H2O: C, 47.24; H, 3.32; N, 8.83; Found: C, 46.99; H, 3.33; N, 8.58.

Complex 7. Yellow solid. Yield: 82 mg (79%). m.p. 190 – 194 ºC (from CH_3CN). ESI-MS: m/z (the most abundant isotopomer) 889.3 (M+, $C_{40}H_{30}ClFN_7O_2Pt$ requires 889.2). ^{1}H NMR (400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 9.50 (s, 1H), 8.83(s, 1H), 8.52 (d, J = 8.0 Hz, 1H), 8.47 (s, 1H), 8.37 – 8.32 (m, 1H), 8.28 (s, 1H), 8.24 – 8.21 (dd, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 2H), 8.07 (d, *J* = 4.0 Hz ,1H), 7.99 (d, *J* = 8.0 Hz, 1H),

7.92 (s, 1H), 7.86(s, 1H), 7.76 (d, $_J$ = 8.0 Hz, 2H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.37 – 7.30 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 2H), 7.16 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.83 (s, 2H), 4.68 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d^6, Me_4Si) δ_C (ppm): 164.3, 162.8, 156.6, 156.4, 154.9, 254.4, 253.4, 148.7, 148.0, 147.7, 146.8, 141.1, 137.1, 137.1, 135.0, 134.7, 131.4, 129.6, 129.2, 128.8, 127.8, 127.0, 126.0, 125.5, 124.8, 123.4, 123.3, 122.3, 122.2, 121.0, 119.3, 119.1, 117.0, 116.8, 109.1, 108.2, 104.0, 68.4, 56.4, 48.0. Elemental analysis: calculated for $C_{40}H_{30}ClF_7N_7O_2PPt$: C, 46.41; H, 2.92; N, 9.47; Found: C, 46.44; H, 3.32; N, 9.58.

Complex 8. Yellow solid. Yield: 79 mg (72%). m.p. 184 – 187 ºC (from CH_3CN). ESI-MS: m/z (the most abundant isotopomer) 904.2 (M+, $C_{41}H_{32}ClFN_7O_2Pt$ requires 904.2). ^{1}H NMR (400 MHz, DMSO-d^6, Me_4Si) δ_H (ppm): 9.41 (s, 1H), 8.79 (s, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.46 (s, 1H), 8.27 – 8.25 (m, 3H), 8.22 – 8.20 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 4.0 Hz , 1H), 8.02 (t, *J* = 4.0 Hz, 1H), 7.89 (d, *J* = 12.0 Hz, 2H), 7.75 – 7.72 (m, 2H), 7.67 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H), 7.60 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.18 – 7.13 (m, 2H), 6.80 (s, 1H), 4.53 (t, *J* = 4.0 Hz, 2H), 4.23 (t, *J* = 4.0 Hz, 2H), 3.88 (s, 3H), 2.56 – 2.53 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d^6, Me_4Si) δ_C (ppm): 164.3, 162.8, 156.5, 156.3, 155.0, 154.3, 153.2, 148.8, 148.4, 147.6, 146.7, 141.0, 140.8, 137.1, 137.1, 135.1, 134.7, 131.4, 130.0, 129.2, 128.6, 127.8, 127.0, 125.4, 124.7, 123.5, 122.6, 122.4, 122.3, 121.0, 119.3, 119.1, 117.0, 116.7, 109.2, 108.0, 104.1, 66.7, 56.3, 45.6, 29.7. Elemental analysis: calculated for $C_{41}H_{32}ClF_7N_7O_2PPt$: C, 46.93; H, 3.07; N, 9.34; Found: C, 46.78; H, 3.30; N, 9.53.

2. X-ray crystallography

Single-crystal X-ray diffraction analysis for compound **1**, **4** was carried out on a Rigaku Saturn 724 diffractometer (Rigaku Corporation, Japan) using graphite monochromated MoKα radiation (λ = 0.71073 Å) on a Rigaku Saturn 724 CCD area detector. All data were collected at 173 K, and structure solution and refinement were performed using the SHELXL-97. The crystallographic data are listed in Table S1, S3,

the selected bond lengths and angles in Table S2, S4. Standard data relating to the X-ray crystal structure of compounds **1** and **4** have been also deposited in the Cambridge Crystallographic Data Centre with the code number of CCDC 1418031-1418032.

3. Fluorescent quantum yield study

Complex **5** was dissolved in DMSO and diluted using deionized water to give a 10 μM solution containing 1% DMSO. The reference compound fluorescein was dissolved in 0.1 M NaOH to afford a 10 μM solution. The UV-Visible absorption spectroscopy was performed on a SHIMADZU UV-2550 spectrophotometer (Japan), and fluorescence emission spectroscopy was carried out on a HITACHI F-4600 Fluorescence spectrophotometer (Japan). Measurement parameter: EX Slit: 5.0 nm; EM Slit: 5.0 nm; PMT Voltage: 700 V. The excited wavelengths of complex 5 and fluorescein were set at 330 nm and 410 nm, respectively, and the emission spectra were recorded from 400 to 750 nm. The fluorescent quantum yield (φ) was calculated based on the equation as following: $\varphi = \varphi_{ref} \times (F \times A_{ref}) / (F_{ref} \times A)$, where F is the fluorescence intensity, A is the optical density at excited wavelength.

4. High performance liquid chromatography (HPLC)

An Agilent 1200 series quaternary pump and a Rheodyne sample injector with a 20 μL loop, an Agilent 1200 series UV-Vis DAD detector and Chemstation data processing system were used. The mobile phases were water containing 0.1% TFA (solvent A) and acetonitrile containing 0.1% TFA (solvent B). The detection of the platinum compounds was carried out on an Agilent Eclipse XDB-C18 reversed-phase column (4.6× 150 mm, 5 μm, Agilent Technologies). The gradient (B) was: or 10% to 80% from 0 to 25 min, keeping at 80% to 27 min, and finally resetting to 10% at 30 min.

5. Electrospray ionization mass spectroscopy (ESI-MS)

The positive-ion ESI mass spectra for the platinum compounds were obtained with a Micromass Q-TOF (Waters) equipped with a Masslynx (ver. 4.0) data processing system for analysis and post processing. For the online LC-ESI-MS assays, an Agilent 1200 system was interfaced with the mass spectrometer, using the same column and gradients as described above for the HPLC assays with a flow rate of 1 mL / min and a splitting ratio of 1 / 10 into mass spectrometer. The spray voltage and the cone voltage were 2.8 ~ 3.8 kV and 55 ~ 70 V, respectively. The desolvation temperature was 393 K and the source temperature 373 K. Nitrogen was used as both cone gas and desolvation gas with a flow rate of 50 L h^{-1} and 500 L h^{-1}, respectively. The collision energy was set up to 10 V. The spectra were acquired in the range of 200 ~ 2500 *m/z*. The mass accuracy of all measurements was within 0.001 *m/z* unit, and all *m/z* values are the mass-to-charge ratios of the most abundant isotopomer for observed ions.

6. Elemental analysis and NMR spectroscopy

Elemental analysis was performed on a Flash EA 1112 element analysis instrument (ThermoQuest). The 1D NMR spectra and 2D [^{1}H, ^{15}N] HMBC NMR spectra were obtained on Bruker Avance III HD 400 and 500 spectrometers (Germany), respectively.

7. Enzyme-linked immunosorbent assay (ELISA)

The receptor tyrosine kinase solution in 50% glycerol, containing 50 mM HEPES (pH 7.6), 150 mM NaCl, 0.1% Triton and 1 mM dithiothreitol (DTT) was purchased from Sigma Chemical Company; Signal Transduction Protein (Tyr66) biotinylated peptide, Phospho-Tyrosine Mouse mAb (P-Tyr-100), HTScan® Tyrosine Kinase Buffer (4×), Adenosine- triphosphate (ATP), DL-Dithiothreitol (DTT) were purchased from Cell Signaling Company (USA); HRP-labeled Goat Anti-Mouse lgG (H + L) was purchased from Zhongshan Golden bridge Biotechnology Co. Ltd (China), Bovine Serum Albumin (BSA), 3, 3', 5, 5'- Tetra methy benzidine (TMB)

from Xinjingke Biotechnology Co. Ltd (China), and Streptavidin from Tianjin Biotechnology Co. Ltd (China); 96-well plates were purchased from Beijing BioDee BioTech Co. Ltd. The epidermal growth factor (EGF) was purchased from Sigma.

The ELISA screening was performed following the instruction provided by the supplier of the assay kits (No. 7909, Cell Signalling Technology, Inc). Each well of a microtitre plate was coated with 100 μL of 10 μg mL^{-1} streptavidin in carbonate-bicarbonate buffer and incubated overnight at 277 K, and then blocked with 1.5% bovine serum albumin (BSA) in PBS/T (PBS solution contain 0.05% Tween-20) at 310 K for 2 h, followed by three times of washing with PBS/T prior to use. Each test compound was dissolved in dimethylsulfoxide (DMSO) to give a 4 mM solution which was diluted with deionised water to give a 40 μM solution. The ATP/peptide mixture was prepared by addition of 0.36 μL of 10 mM ATP to 4.5 μL of 6 μM substrate peptide, and then diluted with D_2O to 9 μL, stored temporarily at 4 °C. An aliquot (0.12 μL) of the enzyme solution was added to 4.38 μL DTT kinase buffer which is consist of 51.25 M DTT and 4× HTScan® Tyrosine Kinase Buffer (240 mM HEPES (pH 7.5), 20 mM $MgCl_2$, 20 mM $MnCl_2$, 12 μM Na_3VO_4).

An aliquot (4.5 μL) of the solution of a tested compound was mixed with as-prepared EGFR solution (4.5 μL) and incubated at 298 K for 5 minutes, followed by addition of 9 μL of ATP/substrate mixture, and then the resulting mixture was incubated at 310 K for 1 h. The phosphorylation reaction was terminated by the addition of 18 μL/well stop buffer (50 mM EDTA, pH 8). Each well of a microtitre plate was coated with 100 μL of 10 μg mL^{-1} streptavidin in carbonate-bicarbonate buffer and incubated overnight at 277 K, and then blocked with 1.5% bovine serum albumin (BSA) in PBS/T (PBS solution contain 0.05% Tween-20) at 310 K for 2 h, followed by three times of washing with PBS/T prior to use. Then, 25 μL/well of each enzymatic reaction mixture and 75 μL/well of D_2O were added to the plate (in triplicate) for incubation at 310 K for 1 h. Following three times of washing with PBS/T, 100 μL of primary antibody (Phospho-Tyrosine Mouse mAb, 1: 1000 in PBS/T with 1.5% BSA) was added to each well and the plate was incubated at 310 K

for another 1 h. The plate was again washed three times with PBS / T, and then 100 μL of secondary antibody (HRP-labelled Goat Anti-Mouse lgG, 1: 1000 in PBS / T with 1.5% BSA) was added to each well for 1 h of incubation at 310 K, followed by three times of washing with PBS/T. Finally, 100 μL of TMB substrate [TMB (1 mg/mL): Citric Acid-Dibasic Sodium Phosphate buffer (pH 5.0): 30% H_2O_2=100: 900: 1) was added to each well and the plate was incubated at 310 K for 15 min, and then the reaction was stopped by addition of 100 μL of 2 M H_2SO_4 to each well, and the plate was read on the ELISA plate reader (SpectraMax M5 Molecular Devices Corporation) at 450 nm to determine the OD values.

All reported IC_{50} values were averages of three independent experiments and expressed as mean ± SD (standard deviation).

For determination of EGFR expressed in different cancer lines, we firstly extracted the membrane protein from lysates of cells using the Bestbio Membrane Protein Extraction Kit (Beijing Tiangen Bio-Technology Co., China). Then the content of the total membrane protein in the extracts was determined by using BCA protein assay kit (Shanghai, Beibo Technology Co., China). Finally, the human EGFR (full length) ELISA Kit (Invitrogen, USA) was applied to determine the content of EGFR in each protein extracts.

8. ICP-MS

Complexes **3** and **5** were dissolved in DMSO to yield a 5 mM stock solution. HeLa cells were seeded in a corning cellular culture dish containing 8 mL of growth medium, when coverage up to 90%, the HeLa cells were treated with 25 μM (0.5% DMSO) of the complexes **3** and **5** at 310K for 24 h. Then the media were removed, the cells were washed with PBS solution three times. PBS containing 0.04% EDTA (3 mL) was used to detach the cells. The combined cells were centrifuged for 3 min at 4 °C, 500 g, and the cells were washed three times with 1 mL of ice–cold PBS. The suspension was divided into two parts. One part was used to analyze the metal content

in the membrane protein and the other was used for nucleus analysis. The Bestbio-Membrane Protein Extraction kit and TIANamp Genomic DNA Kit, RNase A (TIANGEN Biotech (Beijing) Co., Ltd.) were used to extract the membrane protein and nuclear fractions, respectively. Protein concentration was determined using BCA Protein Assay Kit (TIANGEN Biotech (Beijing) Co., Ltd.).[9] The DNA concentration was determined by UV-Visible spectroscopy. The protein and DNA extracts were mineralized with 50% HNO_3 and deionized water, then completely dried at 200 °C. The solid extracts were re-dissolved in 1% HNO_3 and platinum was quantified by ICP-MS (Agilent 7700, USA). Cellular metal levels were expressed as pg Pt per mg of membrane protein or DNA. Results are presented as the mean of three independent determinations and expressed as mean ± SD.

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Table S1. Crystallographic data of 4-anilinoquinazoline derivative **1**.

Formula	$C_{20}H_{17}ClFN_5O_2 \bullet 2H_2O$
Molecular weight	449.87
T (K)	173.1500
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
a (Å)	7.369(2)
b (Å)	10.914(3)
c (Å)	14.365(5)
α (°)	69.058(11)
β (°)	83.580(15)
γ (°)	72.354(11)
V(Å^3)	1028.3(6)
Z	2
D_x (g / cm^3)	1.453
μ (mm^{-1})	0.234
F (000)	468
Crystal size (mm)	0.55 × 0.05 × 0.04
Crystal description	Rod
Crystal colour	Colorless
Index ranges	-8 <= h <= 9, -14 <= k <= 14, -14 <= l <= 18
Reflections collected	8802
Independent reflections	4645
θ_{max}(°)	27.480
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.5909
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	4645 / 0 / 293
Data collection mode	ω scans
R_{int}	0.0406
Final R and R_w	0.0614, 0.1484
No. of parameters	293
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e.Å^{-3})	0.305, −0.328

Table S2. Selected bond lengths (Å), angles and torsion (°) of 4-anilinoquinazoline derivative **1**

N1-C2	1.371(3)	N1-C3	1.322(3)
N2-C1	1.374(3)	N2-C3	1.343(3)
N2-C4	1.464(3)	C1-C2	1.352(4)
C4-C5	1.508(3)	O1-C5	1.423(2)
C6-O1-C5	117.02(15)	O1-C5-C4	107.08(16)
N2-C4-C5	112.08(17)	C3-N2-C4	126.61(18)
C1-N2-C4	126.8(2)	C3-N2-C1	106.55(19)
N2-C1-C2-N1	-0.2(3)	N2-C4-C5-O1	62.9(2)
C1-N2-C3-N1	0.4(3)	C1-N2-C4-C5	-100.2(3)
C2-N1-C3-N2	-0.5(3)	C3-N1-C2-C1	0.4(3)
C3-N2-C1-C2	-0.1(3)	C3-N2-C4-C5	76.0(3)
C4-N2-C1-C2	176.7(2)	C4-N2-C3-N1	-176.48(19)

Table S3. Crystallographic data of platinum complex **4**.

Formula	$(C_{20}H_{13}ClN_2Pt)_2 \bullet CH_2Cl_2$
Molecular weight	1108.65
T (K)	173(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	*C2/c*
a (Å)	19.794(5)
b (Å)	7.7967(18)
c (Å)	23.287(6)
α (°)	90
β (°)	106.577(4)
γ (°)	90
V(Å^3)	3444.5(14)
Z	4
D_x (g / cm^3)	2.138
μ (mm^{-1})	8.463
F (000)	2104
Crystal size (mm)	0.05 × 0.05 × 0.03
Crystal description	plate
Crystal colour	yellow
Index ranges	-25 <= h <= 25, -6 <= k <= 10, -27 <= l <= 29
Reflections collected	13531
Independent reflections	3894 [R(int) = 0.0696]
θ_{max}(°)	0.989
Absorption correction	Numerical
Max. and min. transmission	0.7853 and 0.6770
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3894 / 0 / 231
Data collection mode	ω scans
R_{int}	0.0696
Final R and R_w	0.0554, 0.1161
No. of parameters	231
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e.Å^{-3})	1.973, −1.544

Table S4. Selected bond lengths (Å), angles and torsion (°) of platinum complex **4**.

Pt(1)-N(1)	1.953(8)	Pt(1)-N(2)	2.110(7)
Pt(1)-Cl(1)	2.303(2)	Pt(1)-C(9)	1.995(8)
C(9)-C(10)	1.430(11)	C(10)-C(11)	1.448(12)
N(1)-C(11)	1.362(12)	N(1)-C(15)	1.349(11)
C(15)-C(16)	1.483(13)	N(2)-C(16)	1.354(12)
N(1)-Pt(1)-Cl(1)	177.7(2)	N(2)-Pt(1)-Cl(1)	98.5(2)
C(9)-Pt(1)-Cl(1)	99.5(3)	N(1)-Pt(1)-N(2)	79.6(3)
C(9)-Pt(1)-N(2)	161.9(3)	N(1)-Pt(1)-C(9)	82.4(3)
C(9)-Pt(1)-N(1)-C(15)	-179.2(7)	N(2)-Pt(1)-N(1)-C(15)	-0.2(6)
Cl(1)-Pt(1)-N(1)-C(15)	35(6)	C(9)-Pt(1)-N(1)-C(11)	2.5(6)
N(2)-Pt(1)-N(1)-C(11)	-178.6(6)	Cl(1)-Pt(1)-N(1)-C(11)	-144(5)
N(1)-Pt(1)-N(2)-C(16)	0.1(6)	C(9)-Pt(1)-N(2)-C(16)	3.4(12)
Cl(1)-Pt(1)-N(2)-C(16)	-178.6(6)	N(1)-Pt(1)-N(2)-C(20)	-177.9(8)
C(9)-Pt(1)-N(2)-C(20)	-174.6(9)	Cl(1)-Pt(1)-N(2)-C(20)	3.5(7)

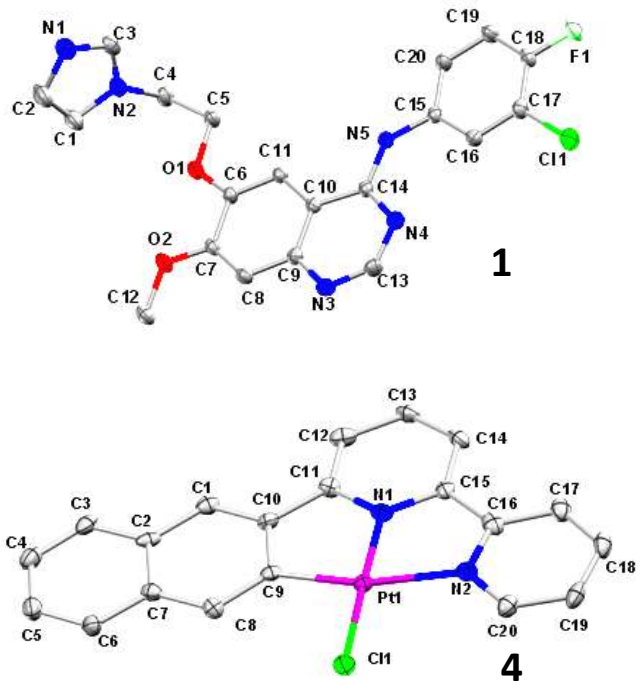

Figure S1. X-ray crystal structures of compounds **1** and **4**. The hydrogen atoms are omitted for clarity, and the crystallographic data have been deposited to the Cambridge Crystallographic Data Centre with a reference number of CCDC 1418031-1418032.

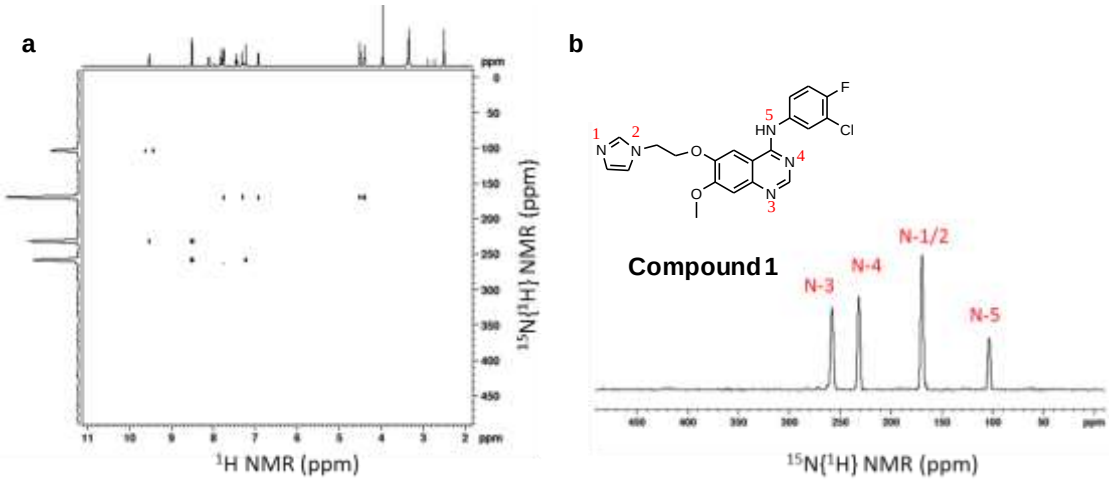

Figure S2. (a) [^{1}H,^{15}N] HMBC and (b) ^{15}N{^{1}H } NMR spectra of compound **1** in DMSO-d^{6} at 298K.

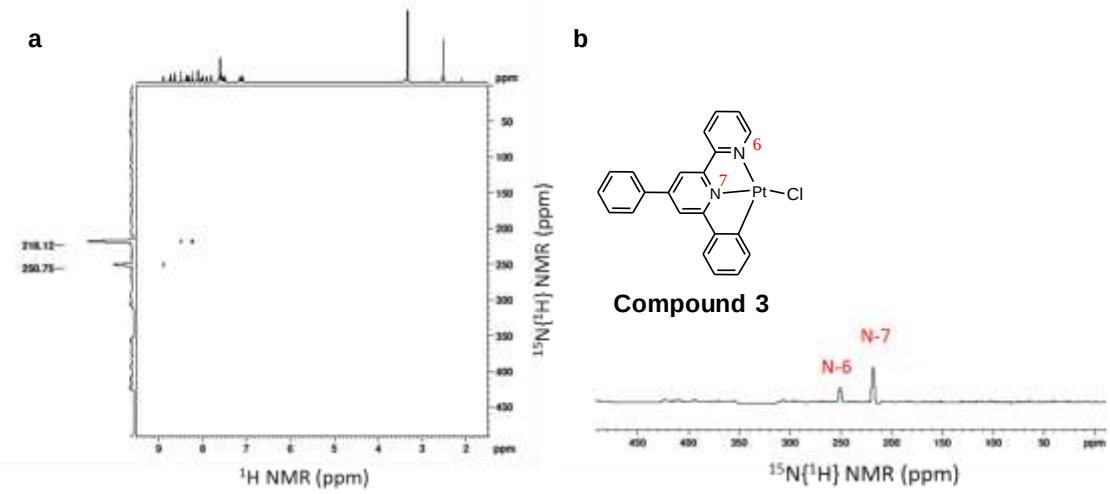

Figure S3. (a) [^{1}H,^{15}N] HMBC and (b) ^{15}N{^{1}H } NMR spectra of compound **3** in DMSO-d^{6} at 298K.

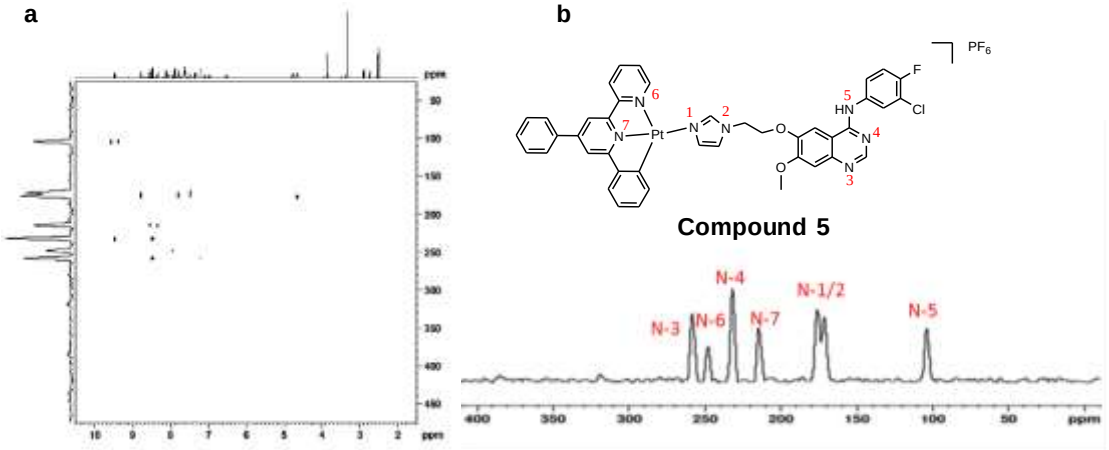

Figure S4. (a) [^{1}H,^{15}N] HMBC and (b) ^{15}N{^{1}H } NMR spectra of compound **5** in DMSO-d^{6} at 298K.

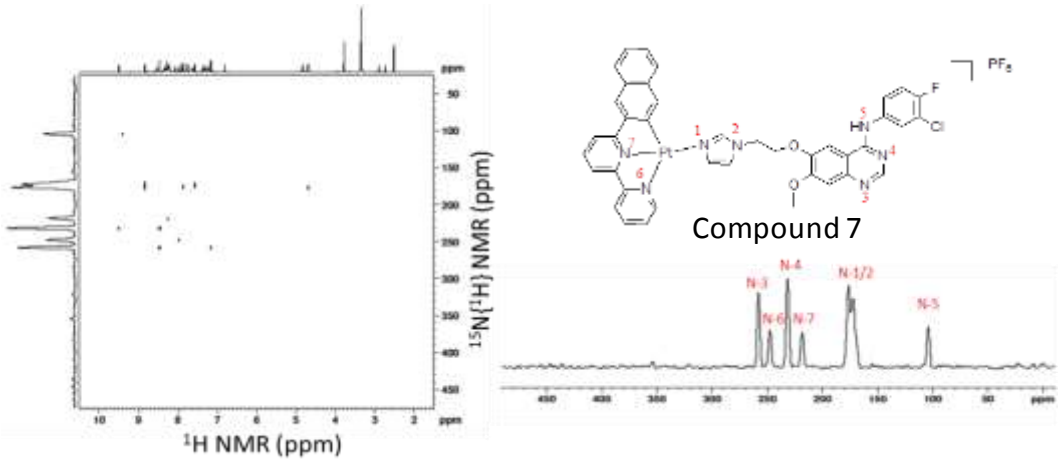

Figure S5. (a) [^{1}H,^{15}N] HMBC and (b) ^{15}N{^{1}H } NMR spectra of compound **7** in DMSO-d^{6} at 298K.

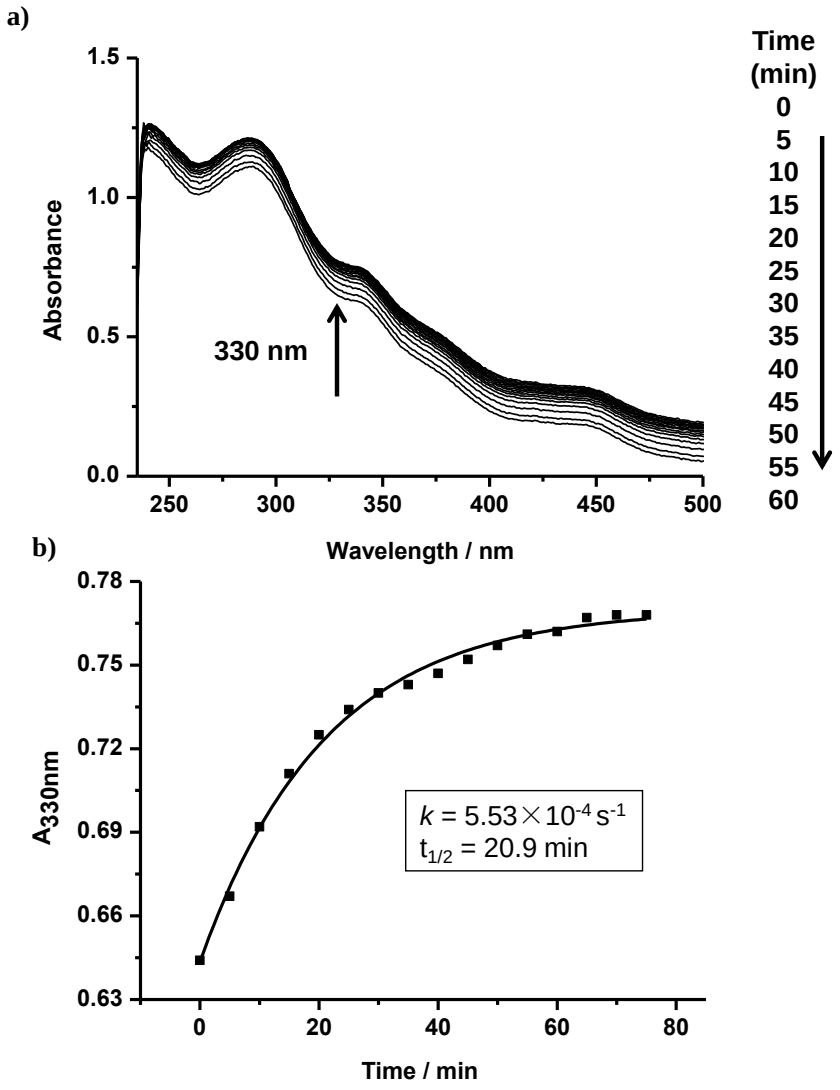

Figure S6. (a) Time evolution of UV-Vis absorption spectra for the hydrolysis of **3** (0.04 mM) at 310 K. (b) Time-dependence of the absorbance at selected wavelength (330 nm) for the hydrolysis of **3** (0.04 mM) at 310K. The full lines represent computer fits giving the first order rate constants (k) and half-lives ($t_{1/2}$) shown in the insets.

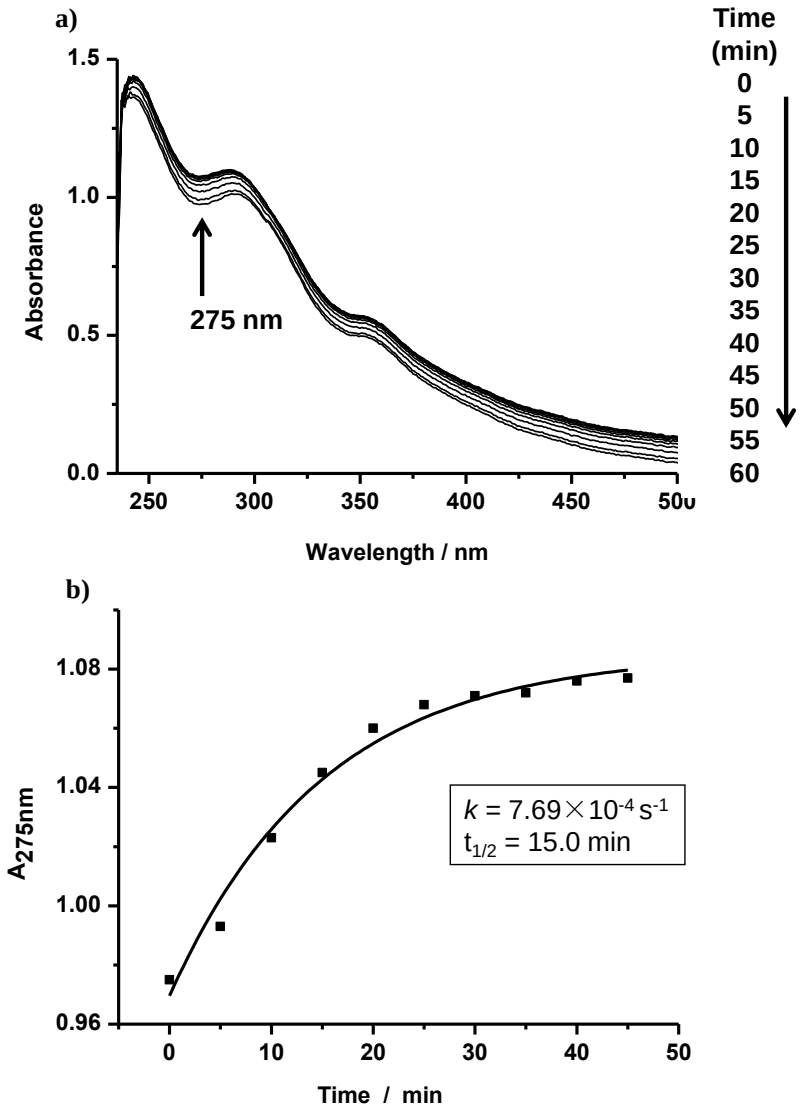

Figure S7. (a) Time evolution of UV-Vis absorption spectra for the hydrolysis of **4** (0.04 mM) at 310 K. (b) Time-dependence of the absorbance at selected wavelength (330 nm) for the hydrolysis of **4** (0.04 mM) at 310K. The full lines represent computer fits giving the first order rate constants (k) and half-lives ($t_{1/2}$) shown in the insets.

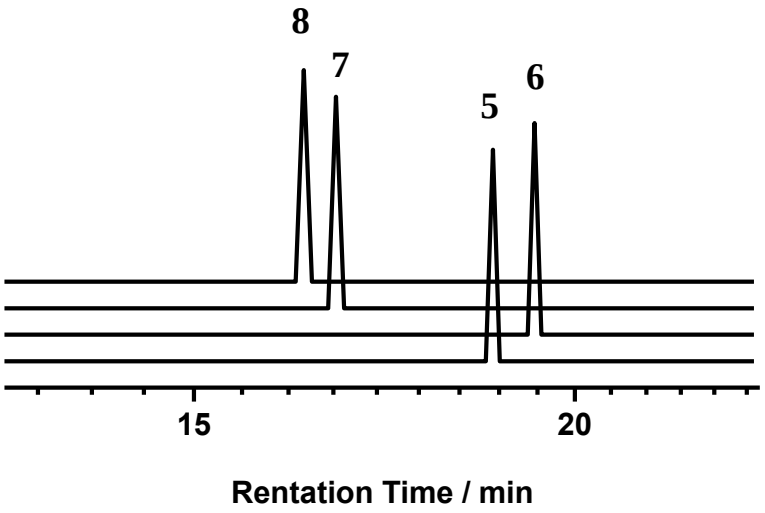

Figure S8. HPLC Chromatograms with UV detection at 360 nm of complexes **5 – 8** (25 μM) in Tris buffer solution.

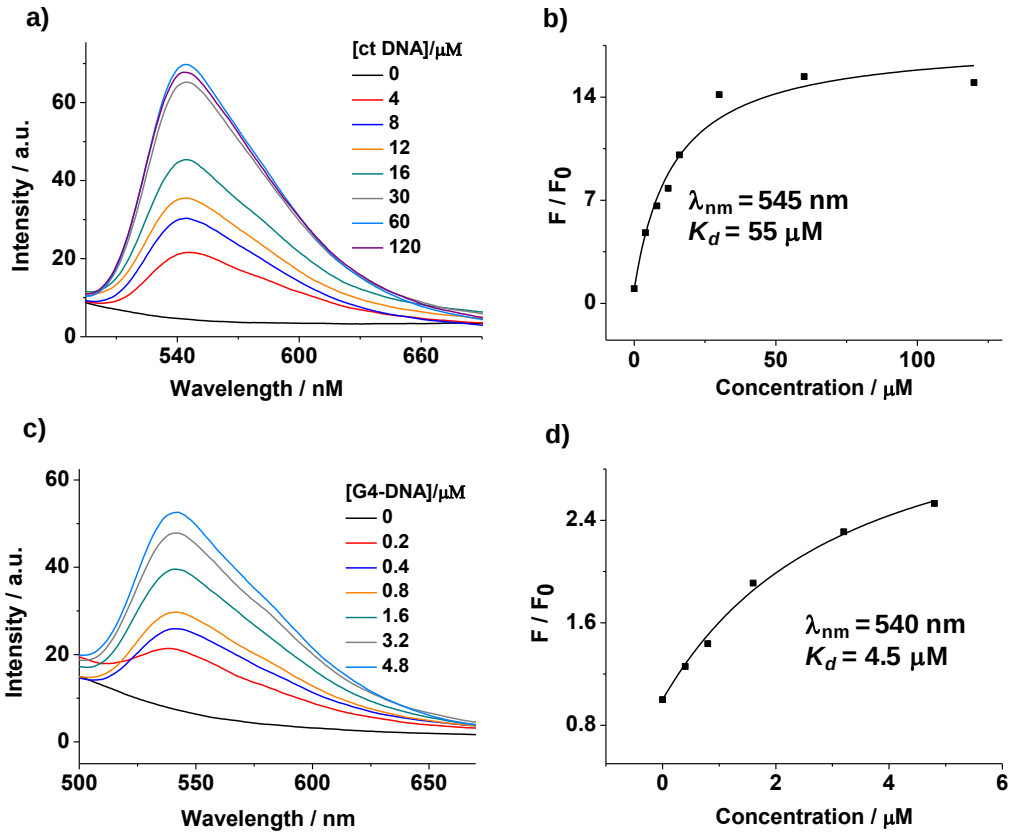

Figure S9. (a, c) Fluorescence emission spectra of complex **3** in Tris buffer solution in the presence of increasing concentration of ctDNA (a) and G4-DNA (c), respectively. Concentration of **3**: (a) 2 μM and (c) 0.8 μM; λ_{ex}: 405 nm. (b, d) Plots of the relative fluorescence emission intensity of **3** vs. concentrations of ctDNA (b) and G4-DNA (d), of which the computer-fitting following the 2-site binding equations of ligand-to-receptor gives the binding constants of **3** to ctDNA and to G4-DNA to be 55 and 4.5 μM, respectively.

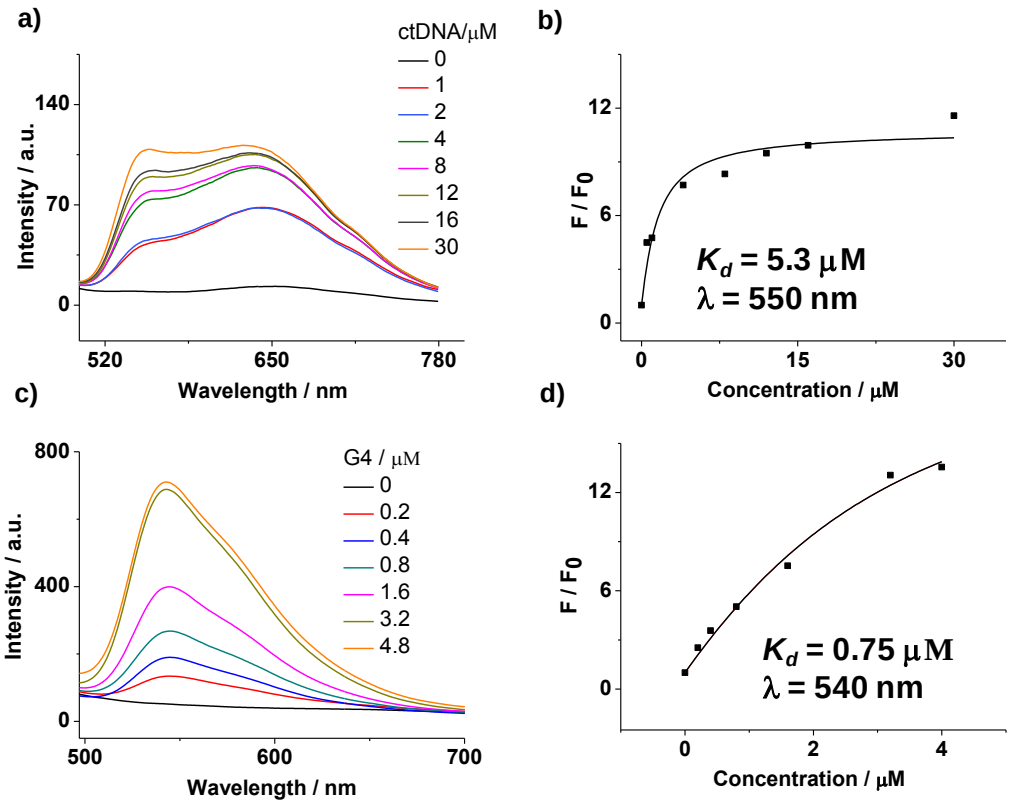

Figure S10. (a, c) Fluorescence emission spectra of complex **6** in Tris buffer solution in the presence of increasing concentration of ctDNA (a) and G4-DNA (c), respectively. Concentration of **6**: (a) 2 μM and (c) 0.8 μM; λ_{ex}: 405 nm. (b, d) Plots of the relative fluorescence emission intensity of **6** vs. concentrations of ctDNA (b) and G4-DNA (d), of which the computer-fitting following the 2-site binding equations of ligand-to-receptor gives the binding association constants of **6** to ctDNA and to G4-DNA to be 5.3 and 0.75 μM, respectively.

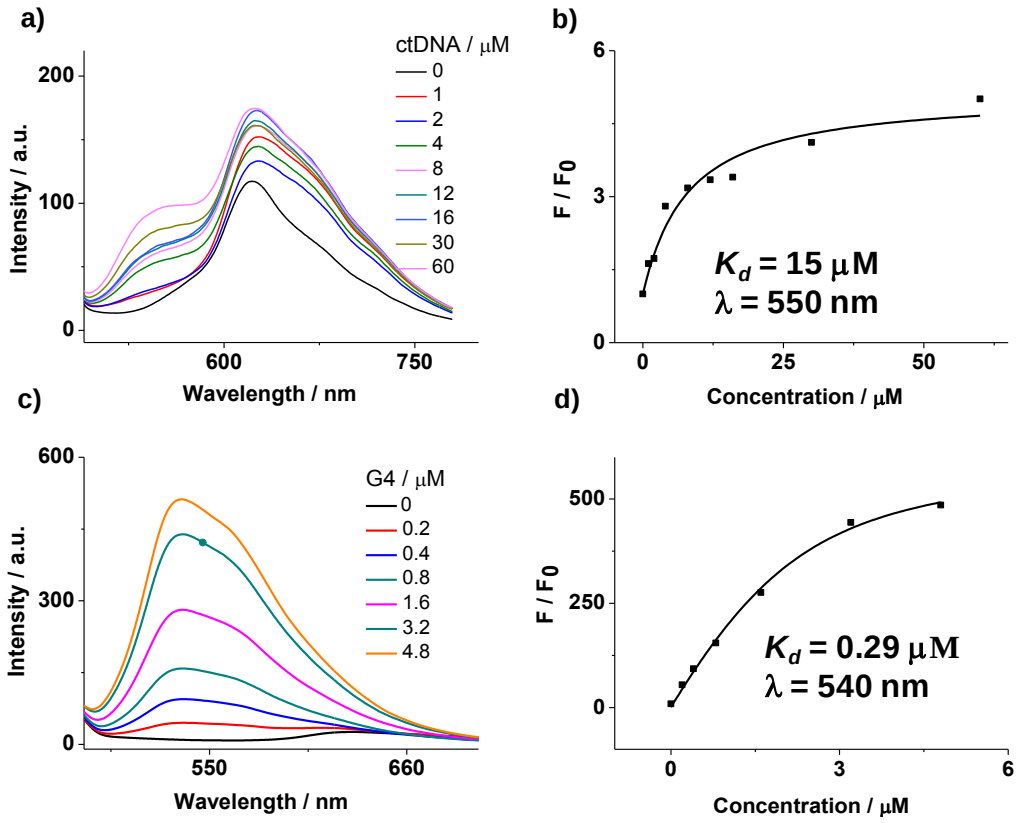

Figure S11. (a, c) Fluorescence emission spectra of complex **7** in Tris buffer solution in the presence of increasing concentration of ctDNA (a) and G4-DNA (c), respectively. Concentration of **7**: (a) 2 μM and (c) 0.8 μM; λ_{ex}: 405 nm. (b, d) Plots of the relative fluorescence emission intensity of **7** vs. concentrations of ctDNA (b) and G4-DNA (d), of which the computer-fitting following the 2-site binding equations of ligand-to-receptor gives the binding association constants of **7** to ctDNA and to G4-DNA to be 15 and 0.29 μM, respectively.

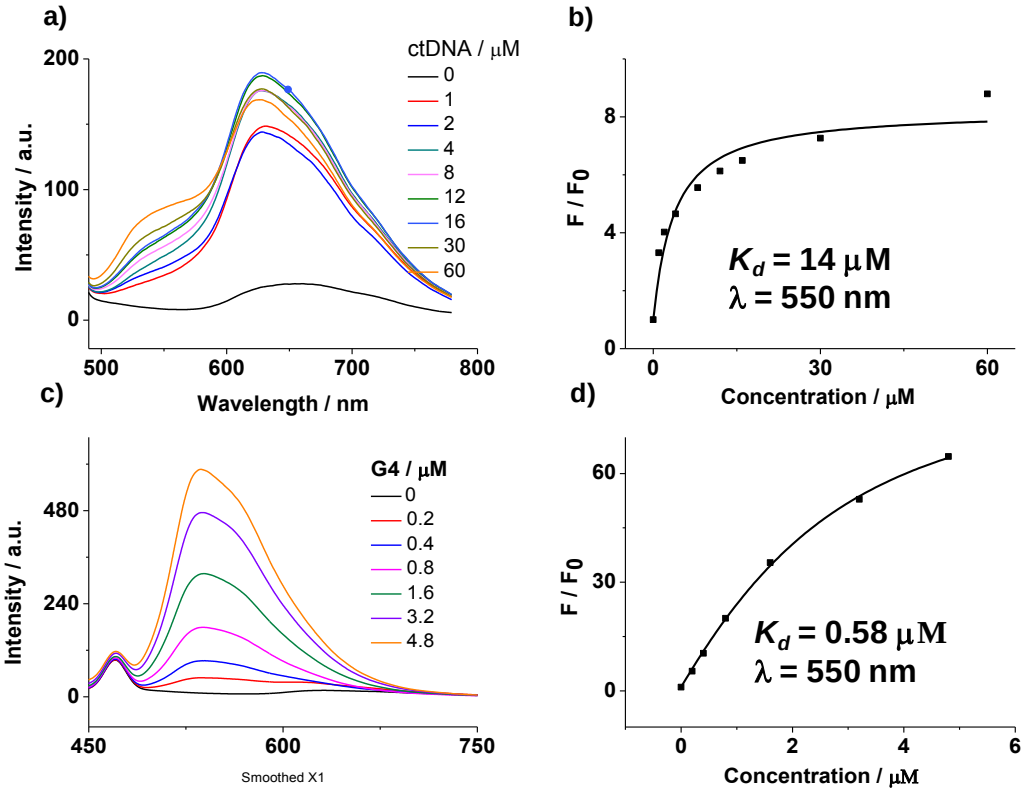

Figure S12. (a, c) Fluorescence emission spectra of complex **8** in Tris buffer solution in the presence of increasing concentration of ctDNA (a) and G4-DNA (c), respectively. Concentration of **8**: (a) 2 μM and (c) 0.8 μM; λ_{ex}: 405 nm. (b, d) Plots of the relative fluorescence emission intensity of **8** vs. concentrations of ctDNA (b) and G4-DNA (d), of which the computer-fitting following the 2-site binding equations of ligand-to-receptor gives the binding association constants of **8** to ctDNA and to G4-DNA to be 14 and 0.58 μM, respectively.

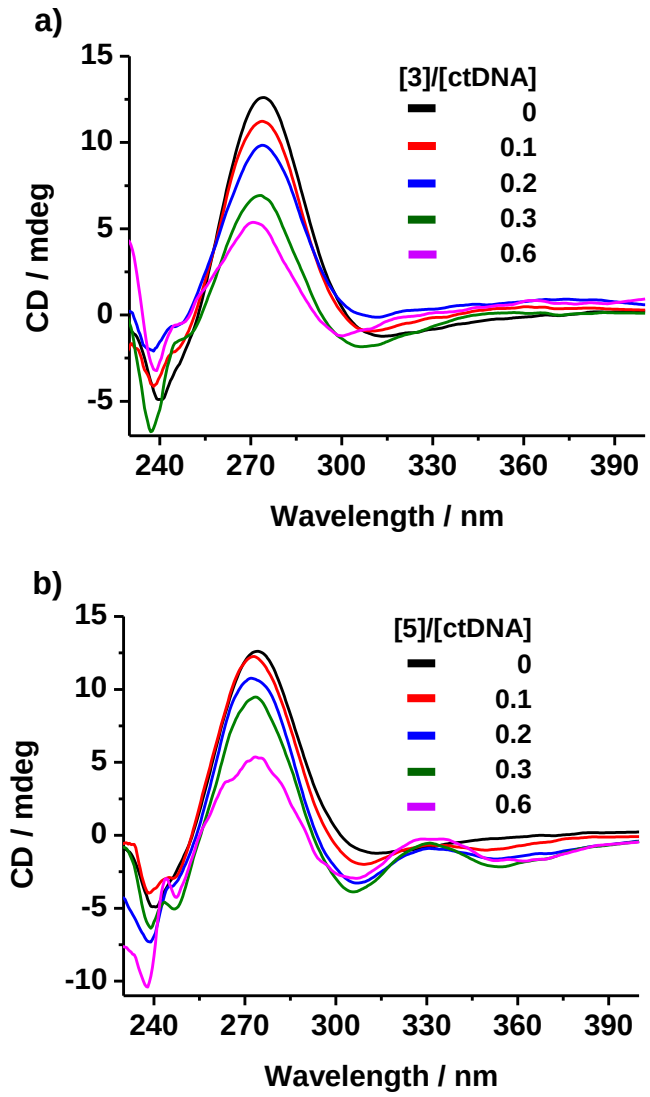

Figure S13. CD spectra of ctDNA (100 μM) treated with different concentrations of platinum complexes (a) **3** and (b) **5**.

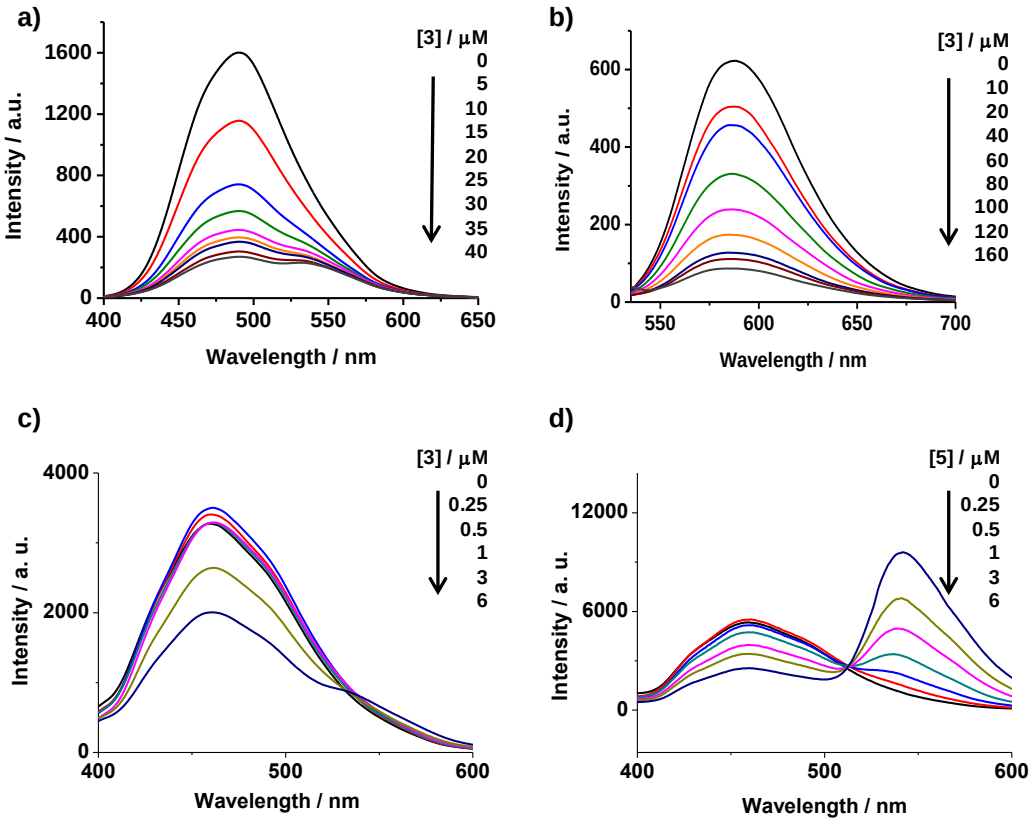

Figure S14. (a, b) Fluorescence titration of Hoechst-ctDNA complex (a) and EB-ctDNA complex (b) with complex **3**. The Hoechst-ctDNA complex (Hoechst : ctDNA = 20 : 200 μM) and the EB-ctDNA complex (EB : ctDNA = 20 : 200 μM) were excited at 370 nm and 525 nm, respectively. (c, d) Fluorescence titration of BPBC-G4 complex with complex **3** (c) and complex **5** (d). The BPBC-G4 complex (Hoechst : ctDNA = 1 : 0.8 μM) was excited at 320.

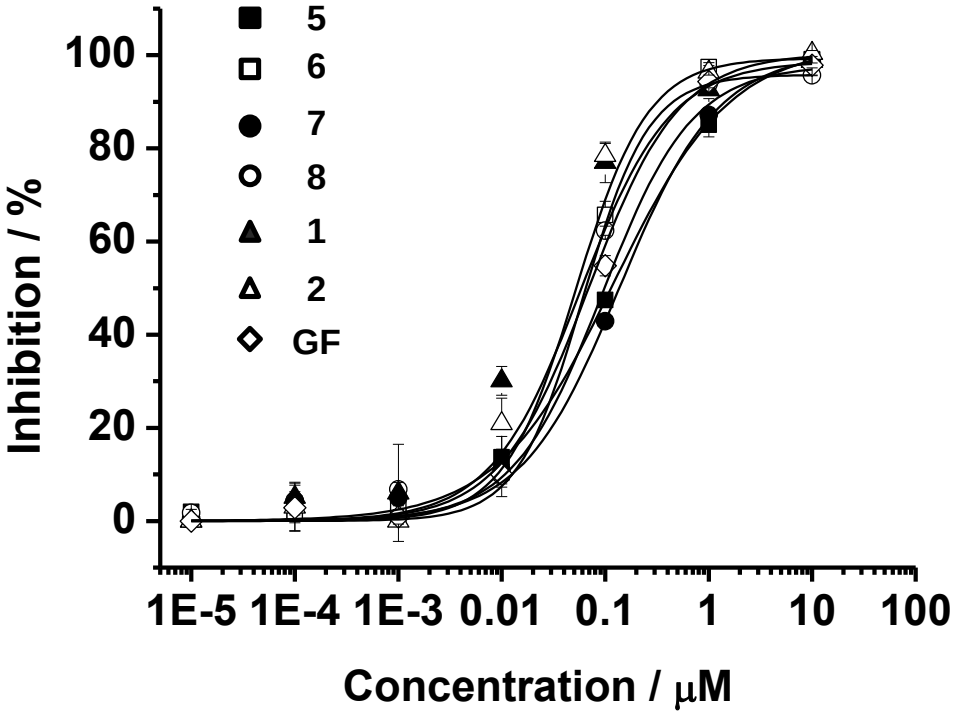

Figure S15. Dose-dependent inhibition curves of the [(C^N^N)Pt(L)]PF_6 compounds **5** – **8** and 4-anilinoquinazoline derivative **1**, **2** and Gefitinib against EGFR. Points: mean ± SD of triplicate determinations. Lines: computer-fitted curves which give the IC_{50} values to be 103.3, 86.2, 101.8, 85.4, 57.4, 69.6 and 94.0 nM for compounds **5**, **6**, **7**, **8**, **1**, **2** and Gefitinib, respectively**.**

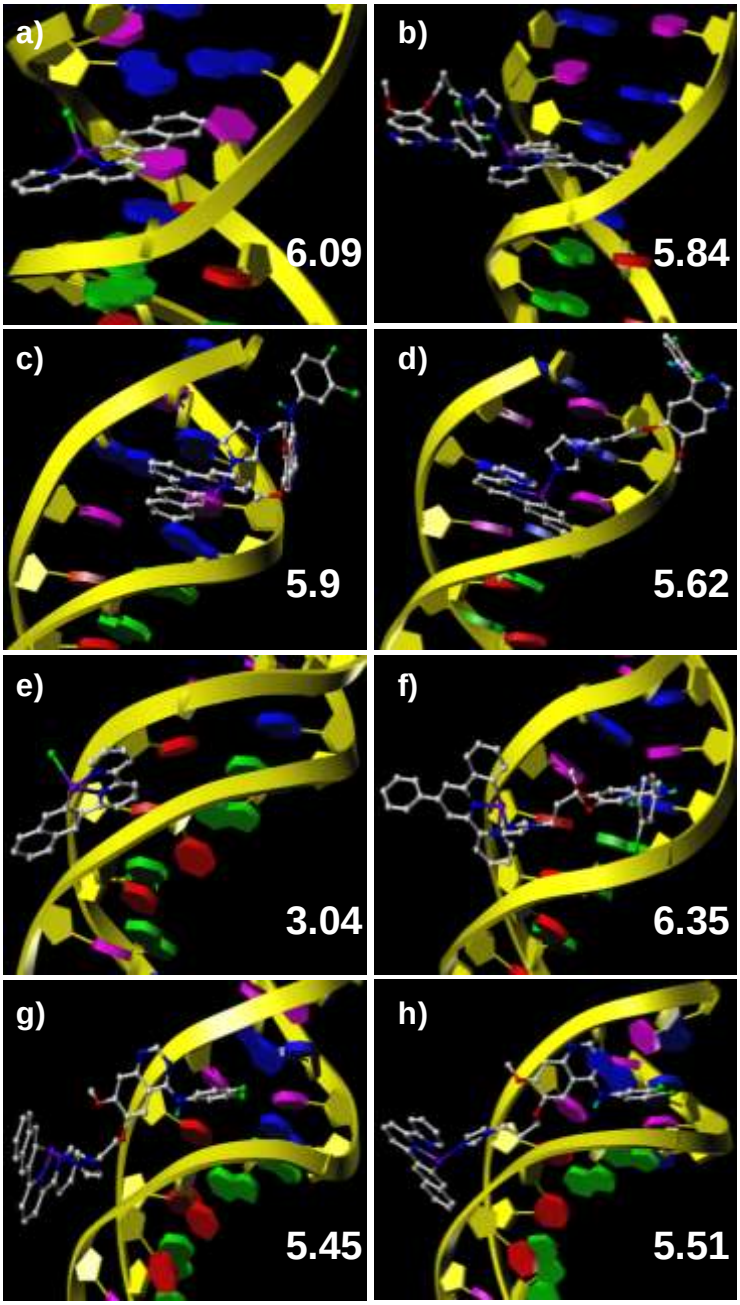

Figure S16. The molecular models constructed by using the Surflex-Dock module of Sybyl X 1.1 program illustrate the interactions of cyclometallated platinum complexes **4** (a, e), **6** (b, f), **7** (c, g) and **8** (d, h) with the duplex DNA 5′-d(CGCGAATTCGCG)·d(CGCGAATTCGCG)-3′ (**I**). (a - d) **4** and **6 - 8** as DNA intercalators, (e –f h) **4** and **6 - 8** as minor groove binders. The number shown in each graphics is the docking scores for corresponding binding.

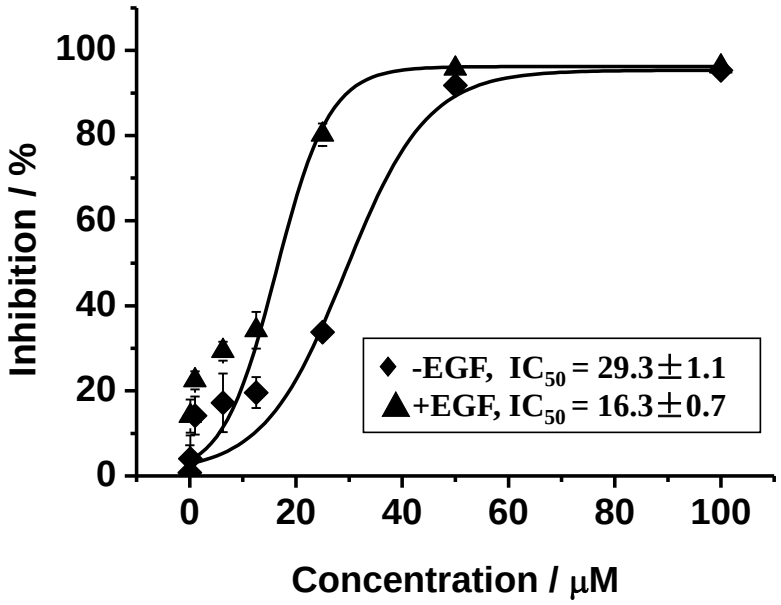

Figure S17. Dose-dependent inhibition curves of the equal molar mixture of cisplatin and gefitinib on the growth of MCF-7 cell line in the absence or in the presence of EGF (100 ng/mL). Points: mean ± SD of triplicate determinations. Lines: computer-fitted curves which give IC_{50} values as shown in the inset.

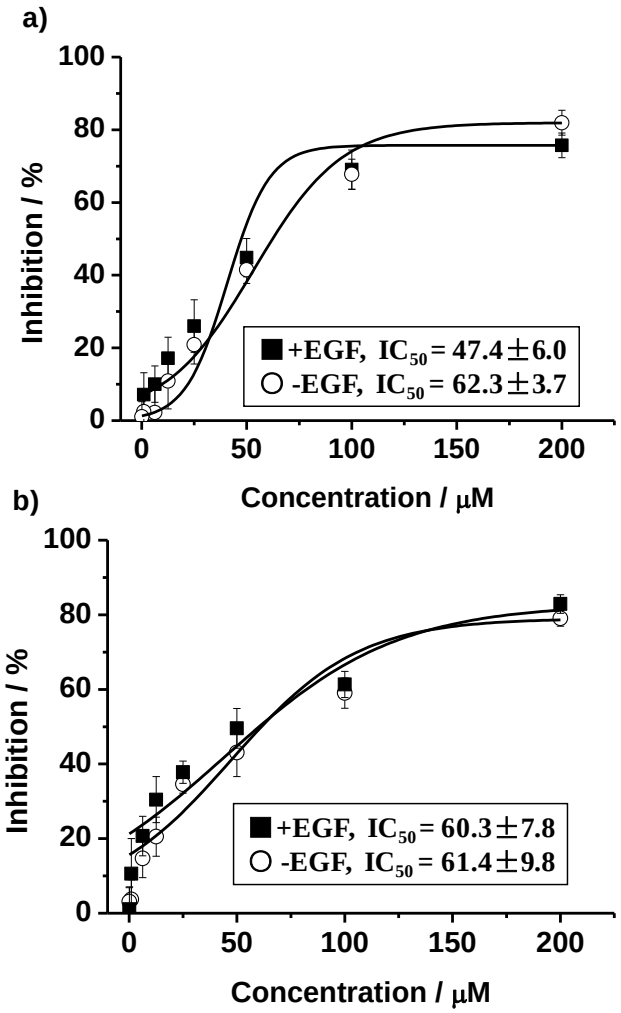

Figure S18. Dose-dependent inhibition curves of compounds (a) **5** and (b) **6** on the growth of the normal human embryonic kidney (HEK293) cell line in the absence or in the presence of EGF (100 ng/mL). Points: mean ± SD of triplicate determinations. Lines: computer-fitted curves which give IC_{50} values as shown in the inset.