

## Supporting Information

### **Synthesis of 5-Nitro-2-furancarbohydrazides and their *cis*-Diamminedichloroplatinum Complexes as Bitopic and Irreversible Inhibitors of Large Thioredoxin Reductases**

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#### **Contents:**

S2: General synthetic notes and procedures.

S2 – S10: Synthesis and characterization of compounds **1** to **20**.

S10: Elemental analyses of the four complexes **13<sub>a-c</sub>** and **20**.

**Chemistry.** Melting points were determined on a Büchi 530 capillary melting point apparatus and are uncorrected. Analytical TLC was performed on silica gel 60 (Alugram® Sil G/UV<sub>254</sub>, Macherey-Nagel) with fluorescent indicator UV<sub>254</sub>. The spots were located by uv (254 nm); R<sub>f</sub> values are given for guidance. Silica gel (Merck, 60 PF<sub>254</sub>) was used in preparative thick-layer chromatography. Column chromatographies were undertaken using silica gel 60 (230-400 mesh ASTM) from Macherey-Nagel. Analytical high pressure liquid chromatography (HPLC) was performed on a Shimadzu system equipped with C<sub>18</sub> VYDAC column (C18V, 4 x 300 mm, 5 μm, 100 Å) or a C<sub>18</sub> NUCLEOSIL (C18N, 4 x 300 mm, 5 μm, 100 Å) and a UV detector set at 215 and 254 nm. Compounds were dissolved in EtOH and injected through a 20 μL loop. Elution was performed with the following two systems: solution A (0.05 % trifluoroacetic acid (TFA) in H<sub>2</sub>O) and solution B (0.05 % TFA, 20 % H<sub>2</sub>O, 80 % CH<sub>3</sub>CN). HPLC retention times (HPLC *t<sub>R</sub>*) were obtained, at flow rates of 1 mL/min, using two different conditions: condition A, a gradient run from 100% eluent A to 100% eluent B over the next 30 min; condition B, a gradient run from 100% eluent A during 5 min and then to 100% eluent B over the next 25 min. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker 300 MHz spectrometer using tetramethylsilane as an internal standard. <sup>195</sup>Pt NMR spectra were recorded at 298 K using K<sub>2</sub>PtCl<sub>4</sub> as an internal standard (δ -1623.7.8 ppm in DMF-*d*<sub>7</sub>) on a Bruker 300 MHz spectrometer at the facilities of the Chemistry Department, Heidelberg University. Chemical shifts δ were expressed in ppm and the splitting patterns were designated as follows: s singlet, bs broad singlet, t triplet, d doublet, dd doublet of doublets, m multiplet, bm broad multiplet. Mass spectra were recorded on a time of flight plasma desorption mass spectrometer (TOF-PDMS) using a Californium source or on a JEOL MS 700 mass spectrometer for the diamminoplatinum complexes in the FAB mode from nitrobenzyl alcohol matrix. All complexes displayed molecular ions corresponding to M + 1, with an isotopic cluster pattern characteristic for the PtCl<sub>2</sub> unit. For the determination of platinum content, high resolution inductively coupled plasma mass spectra (ICP-MS) were recorded with a PlasmaQuad PQ II+ ICP mass spectrometer (Institut Pasteur de Lille, Dr. P. Thomas). The FTIR spectra were determined as potassium bromide discs with a Bruker Vector 22 spectrophotometer; absorbances are reported in ν (cm<sup>-1</sup>). Elemental analyses for C, H, N, were performed by the « Service de microanalyse » (Université Pierre et Marie Curie, France), and are consistent with the empirical formulas.

***N*-tert-Butoxycarbonylethylene Diamine (1).** Di-*tert*-butyl dicarbonate (10.9 g, 50.0 mmol, 1 eq) dissolved in 350 mL of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise to a solution of ethylene diamine (30.1 g, 0.50 mol, 10 eq) in 350 mL of CH<sub>2</sub>Cl<sub>2</sub> during 3h in an ice bath. The reaction mixture was stirred for 16 h at room temperature and was then washed with 4 x 250 mL of water. The CH<sub>2</sub>Cl<sub>2</sub> solution was dried over MgSO<sub>4</sub>, removed under reduced pressure to give **1** as a colorless oil (5.20 g). Yield 65%. TLC R<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.15-0.30. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.12 (bs, 1H, NH), 3.10 (q, 2H, *J* = 7.0 Hz, NCH<sub>2</sub>), 2.72 (t, 2H, *J* = 6.4 Hz, NCH<sub>2</sub>), 1.78 (s, 2H, NH<sub>2</sub>), 1.37 (s, 9H, Boc). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 150.2, 79.0, 43.4, 41.9, 28.6. MS (TOF) *m/z* 160 (M<sup>+</sup>).

***N*<sup>α</sup>-Benzyl-*N*<sup>ω</sup>-*tert*-butoxycarbonylethylene Diamine (2).** Benzaldehyde (4.66 g, 44 mmol, 1.1 eq) and molecular sieve 3 Å were added to a solution of **1** (6.40 g, 40 mmol, 1 eq) in 60 mL of MeOH. The reaction was stirred at room temperature for 4 h and then was cooled to -5 °C. NaBH<sub>4</sub> (9.07 g, 0.24 mol, 6 eq) was added in small portions during 30 min and the reaction mixture was stirred for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic solution was extracted with a solution of 0.5 N HCl (3 x 100 mL). The aqueous solution was cooled to 0 °C and was neutralized with NH<sub>4</sub>OH (25%). The product was extracted with chloroform (3 x 100 mL), dried over MgSO<sub>4</sub>, and evaporated to give **2** as a colorless oil (6.10 g). Yield 61%. TLC R<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.65. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.48-7.24 (m, 5H, H<sub>Ar</sub>), 5.00 (bs, 1H, NH), 3.78 (s, 2H, CH<sub>2</sub>-Ph), 3.26 (q, 2H, *J* = 6.0 Hz, NCH<sub>2</sub>), 2.74 (t, 2H, *J* = 6.0 Hz, NCH<sub>2</sub>), 1.49 (bs, 10H, Boc + NH). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 156.1, 140.3, 128.6, 128.2, 127.2, 79.0, 53.7, 48.7, 40.4, 28.6.

HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  14.43 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  100%,  $t_R$  18.72 min. MS (TOF)  $m/z$  250 ( $M^+$ ).

**Benzyl 2-(benzyl{2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)acetate (3).** 2-Benzyl bromoacetate (1.90 mL, 12.0 mmol, 1eq) in 10 mL of DMF was added to a solution of **2** (3.0 g, 12.0 mmol, 1 eq) with DIEA (3.13 mL, 18.0 mmol, 1.5 eq) in 15 mL of DMF in an ice bath, and stirred for 1 h at 0 °C. The solution was allowed to warm to room temperature and then stirred for 16 h. The solvent was removed under reduced pressure and the reaction was partitioned between EtOAc and H<sub>2</sub>O. The organic layer was washed with citric acid (5%), dried over MgSO<sub>4</sub> and concentrated to give **3** as a colorless oil (4.30 g). Yield 90%. TLC  $R_f$  (EtOAc) = 0.8. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.32-7.16 (m, 10H, H<sub>Ar</sub>), 5.08 (s, 2H, OCH<sub>2</sub>-Ph), 3.71 (s, 2H, NCH<sub>2</sub>-Ph), 3.29 (bs, 2H, C <sup>$\alpha$</sup> H<sub>2</sub> (Gly)), 3.16 (q, 2H,  $J$  = 6.1 Hz, NCH<sub>2</sub>), 2.72 (t, 2H,  $J$  = 6.2 Hz, NCH<sub>2</sub>), 1.56 (bs, 1H, NH (Boc)), 1.37 (s, 9H, Boc). <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  170.3, 155.9, 137.4, 134.9, 127.9, 127.6, 127.4, 127.35, 127.3, 126.6, 79.0, 65.5, 57.2, 52.3, 37.2, 27.5. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  21.03 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  100%,  $t_R$  24.95 min. MS (TOF)  $m/z$  398 ( $M^+$ ).

**2-({2-[(*tert*-Butoxycarbonyl)amino]ethyl}amino)acetic Acid (4).** Ammonium formate (1.58 g, 25.1 mmol, 10 eq) and Pd/C (10%, 200 mg) were added to a solution of **3** (1.00 g, 2.51 mmol, 1 eq) in 40 mL of MeOH. The solution was heated at reflux and stirred for 16 h. The solution was allowed to warm to room temperature and then, Pd/C was filtered. The filtrate was removed under reduced pressure. The oil thus obtained was crystallized from ether/MeOH (19:1) to give **4** as a white powder (383 mg). Yield 70%. TLC  $R_f$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 6:4) = 0.8. Mp: 200-202 °C. <sup>1</sup>H NMR (D<sub>2</sub>O)  $\delta$  7.00-6.82 (m, 1H, NH), 5.88 (bs, 1H, NH (Boc)), 3.75-3.00 (m, 4H, NCH<sub>2</sub> + C <sup>$\alpha$</sup> H<sub>2</sub>(Gly)), 2.75-2.50 (m, 2H, NCH<sub>2</sub>), 1.37 (s, 9H, Boc). <sup>13</sup>C NMR (D<sub>2</sub>O)  $\delta$  172.6, 153.6, 80.0, 58.0, 51.0, 41.2, 28.5. MS (TOF)  $m/z$  218 ( $M^+$ ).

**2-((*tert*-Butoxycarbonyl){2-[(*tert*-butoxycarbonyl)amino]ethyl}amino)acetic Acid (5).** Sodium hydroxide (1N, 12.3 mL, 12.3 mmol, 2 eq) and di-*tert*-butyl dicarbonate (2.68 g, 12.3 mmol, 2 eq) were added to a solution of **4** (1.34 g, 6.14 mmol, 1eq) in 50 mL of dioxane/H<sub>2</sub>O (4:1). The reaction was stirred for 16 h, and then removed under reduced pressure. The residue was partitioned with CH<sub>2</sub>Cl<sub>2</sub> and NaOH. The aqueous phase was neutralized with HCl (1N), extracted with EtOAc (2 x 75 mL), dried over MgSO<sub>4</sub>, and evaporated to give **5** as a white solid (1.48 g). Yield 76%. Mp: 74-75 °C. TLC  $R_f$  (EtOAc) = 0.75. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  12.75 (s, 1H, COOH), 6.77 (bs, 1H, NH (Boc)), 3.89 (d, 2H,  $J$  = 15.7 Hz, C <sup>$\alpha$</sup> H<sub>2</sub>(Gly)), 3.25 (t, 2H, NCH<sub>2</sub>,  $J$  = 6.5 Hz), 3.14-3.02 (m, 2H, NCH<sub>2</sub>), 1.48 (bs, 18H, 2 x Boc). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$  172.4, 156.3, 156.0, 79.8, 78.4, 50.0, 47.8, 39.1, 29.0, 28.7. MS (TOF)  $m/z$  318 ( $M^+$ ).

***N'*-(*tert*-Butoxycarbonyl)-5-nitro-2-furancarbohydrazide (6).** 5-Nitro-2-furoic acid (5.00 g, 31.8 mmol, 1 eq), PyBOP (18.2 g, 35.0 mmol, 1.1 eq) and DIEA (16.6 mL, 95.5 mmol, 3 eq) were added to a solution of *tert*-butylcarbazate (4.20 g, 31.8 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) (ice bath). The solution was stirred for 16 h at room temperature, and then the solvent was evaporated. The residue obtained was dissolved in EtOAc and washed successively with saturated NaHCO<sub>3</sub> solution, HCl (0.25N) and H<sub>2</sub>O. The organic phase was dried over MgSO<sub>4</sub>, filtered and evaporated. The oil thus obtained was subjected to chromatography on a 5-x 40-cm flash column using cyclohexane/EtOAc (6:4) as the eluting solvent to give **6** as a yellow powder (6.12 g). Yield 71%. TLC  $R_f$  (cyclohexane/EtOAc 1:1) = 0.6. Mp: 59-61 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  10.80 (bs, 1H, NH (hydrazine)), 9.12 (s, 1H, NH (hydrazine)), 7.76 (d, 1H,  $J$  = 3.9 Hz, H<sub>furyl</sub>), 7.47 (d, 1H,  $J$  = 4.1 Hz, H<sub>furyl</sub>), 1.38 (s, 9H, Boc). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>)  $\delta$  156.9, 155.9, 152.8, 147.5, 117.2, 114.0, 80.5, 28.9. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  17.64 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  100%,  $t_R$  19.37 min. MS (TOF)  $m/z$  294 ( $M + Na$ )<sup>+</sup>.

**5-Nitro-2-furancarbohydrazide hydrochloride (7).** Compound **6** (3.00 g, 11.1 mmol, 1 eq) was dissolved in MeOH (30 mL), and a concentrated HCl solution (12 N, 5 mL) was added. The reaction

was stirred for 16 h. The solvent was removed under reduced pressure, and the residue **7** that was obtained was filtered, and washed with ether to give a yellow powder (2.19 g). Yield 95%. TLC  $R_f$  (EtOAc) = 0.25. Mp: 182-184 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  10.98 (s, 1H, NH (hydrazine)), 10.28 (s, 1H, NH (hydrazine)), 7.75 (d, 1H,  $J = 3.7$  Hz,  $\text{H}_{\text{furyl}}$ ), 7.53 (d, 1H,  $J = 3.7$  Hz,  $\text{H}_{\text{furyl}}$ ), 6.91 (d, 1H,  $J = 6.3$  Hz, NH), 6.26 (d, 1H,  $J = 6.3$  Hz, NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  155.9, 152.8, 147.3, 145.8, 128.4. MS (TOF)  $m/z$  194 ( $\text{M} + \text{Na}$ ) $^+$ .

***N'*-(2-naphthylmethyl)-5-nitro-2-furancarbohydrazide (8)**. 2-Naphthylacetic acid (1.00 g, 5.37 mmol, 1 eq), PyBOP (3.07 g, 5.91 mmol, 1.1 eq) and DIEA (2.81 mL, 16.1 mmol, 3 eq) were added to **7** (1.23 g, 5.37 mmol, 1 eq) in  $\text{CH}_2\text{Cl}_2$  (50 mL) (ice bath). The solution was stirred for 16 h at room temperature, and then the solvent was evaporated. The residue obtained was dissolved in EtOAc and washed successively with saturated  $\text{NaHCO}_3$  solution, HCl (0.25N) and  $\text{H}_2\text{O}$ . The organic phase was dried over  $\text{MgSO}_4$ , filtered and evaporated. The oil thus obtained was chromatographed on a 5-x 40-cm flash column using cyclohexane/EtOAc (6:4) as the eluting solvent to give **8** as a yellow powder (1.19 g). Yield 65%. TLC  $R_f$  (cyclohexane/EtOAc 1:1) = 0.3. Mp: 171-172 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  10.91 (d, 1H,  $J = 1.8$  Hz, NH (hydrazine)), 10.28 (d, 1H,  $J = 1.8$  Hz, NH (hydrazine)), 7.87-7.76 (m, 4H,  $\text{H}_{\text{Ar}}$ ), 7.74 (d, 1H,  $J = 3.9$  Hz,  $\text{H}_{\text{furyl}}$ ), 7.58-7.40 (m, 4H,  $3\text{H}_{\text{Ar}} + \text{H}_{\text{furyl}}$ ), 3.78 (s, 2H,  $\text{CH}_2$ ).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  170.2, 156.3, 152.7, 147.3, 134.0, 133.8, 132.7, 128.6, 128.4, 128.3, 127.0, 126.5, 117.4, 114.1, 41.6. HPLC (C18V, condition A)  $\text{P}_{\text{HPLC}}$  99.5%,  $t_R$  18.43 min; HPLC (C18N, condition B)  $\text{P}_{\text{HPLC}}$  100%,  $t_R$  22.98 min. MS (TOF)  $m/z$  339 ( $\text{M}^+$ ).

**General Procedure for Preparation of *N'*-(*N*-tert-Butoxycarbonyl-DL-AA)-5-nitro-2-furancarbohydrazide (9a-c)**. 5-Nitro-2-furancarbohydrazide hydrochloride **7** (1.00 g, 4.82 mmol, 1 eq), PyBOP (3.77 g, 7.25 mmol, 1.5 eq) and DIEA (2.52 mL, 14.5 mmol, 3 eq) were added to a solution of appropriate *N*-Boc-amino acid (4.82 mmol, 1 eq) in 50 mL of  $\text{CH}_2\text{Cl}_2$  (ice bath). The reaction mixture was stirred for 24 h at room temperature, and then the solvent was removed *in vacuum*. The residue obtained was dissolved in EtOAc and washed successively with saturated  $\text{NaHCO}_3$  solution, citric acid (5%) and  $\text{H}_2\text{O}$ . The organic phase was dried over  $\text{MgSO}_4$ , filtered and evaporated to yield an oil which was purified by thick-layer chromatography ( $\text{SiO}_2$ , cyclohexane/EtOAc 5:5).

***N'*-(*N*-tert-Butoxycarbonyl-DL-phenylglycinyl)-5-nitro-2-furancarbohydrazide (9a)**. Yellow powder (1.36 g). Yield 70%. TLC  $R_f$  (EtOAc/cyclohexane 1:1) = 0.35. Mp: 140-141 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  10.90 (bs, 1H, NH (hydrazine)), 10.50 (bs, 1H, NH (hydrazine)), 7.74 (d, 1H,  $J = 3.9$  Hz,  $\text{H}_{\text{furyl}}$ ), 7.60-7.20 (m, 6H,  $5\text{H}_{\text{Ar}} + \text{H}_{\text{furyl}}$ ), 5.34 (d, 1H,  $J = 8.8$  Hz,  $\text{C}^\alpha\text{H}$  (Phg)), 1.38 (s, 9H, Boc).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  169.6, 156.1, 155.8, 152.7, 146.9, 139.1, 129.1, 128.5, 128.3, 117.0, 114.1, 79.3, 57.1, 27.2. HPLC (C18V, condition A)  $\text{P}_{\text{HPLC}}$  100%,  $t_R$  18.76 min; HPLC (C18N, condition B)  $\text{P}_{\text{HPLC}}$  100%,  $t_R$  23.03 min.

***N'*-(*N*-tert-Butoxycarbonyl-DL-2-(naphthyl)alaninyl)-5-nitro-2-furancarbohydrazide (9b)**. Yellow powder (1.15 g). Yield 51%. TLC  $R_f$  (EtOAc/cyclohexane 1:1) = 0.35. Mp: 87-89 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  10.98 (bs, 1H, NH (hydrazine)), 10.40 (bs, 1H, NH (hydrazine)), 7.88-7.77 (m, 5H,  $4\text{H}_{\text{Ar}} + \text{H}_{\text{furyl}}$ ), 7.60-7.40 (m, 4H,  $3\text{H}_{\text{Ar}} + \text{H}_{\text{furyl}}$ ), 7.16 (d, 1H,  $J = 8.6$  Hz, NH (Boc)), 4.46-4.32 (m, 1H,  $\text{C}^\alpha\text{H}$  (Nal)), 3.25-2.94 (m, 2H,  $\text{C}^\beta\text{H}$  (Nal)), 1.27 (s, 9H, Boc).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  172.2, 156.2, 154.8, 153.8, 147.3, 136.6, 133.8, 132.7, 128.6, 128.4, 128.3, 128.2, 128.1, 126.8, 126.3, 117.3, 114.1, 78.9, 55.3, 38.4, 27.2. HPLC (C18V, condition A)  $\text{P}_{\text{HPLC}}$  100%,  $t_R$  22.80 min; HPLC (C18N, condition B)  $\text{P}_{\text{HPLC}}$  100%,  $t_R$  25.98 min.

***N'*-(*N*-tert-Butoxycarbonyl-DL-1-(naphthyl)alaninyl)-5-nitro-2-furancarbohydrazide (9c)**. Yellow powder (1.87 g). Yield 83%. TLC  $R_f$  (EtOAc/cyclohexane 1:1) = 0.3. Mp: 117-119 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  10.90 (bs, 1H, NH (hydrazine)), 10.40 (bs, 1H, NH (hydrazine)), 8.23 (d, 1H,  $J = 8.2$  Hz,  $\text{H}_{\text{Ar}}$ ), 7.94-7.75 (m, 3H,  $2\text{H}_{\text{Ar}} + \text{H}_{\text{furyl}}$ ), 7.60-7.39 (m, 5H,  $4\text{H}_{\text{Ar}} + \text{H}_{\text{furyl}}$ ), 7.23 (d, 1H,  $J = 8.6$  Hz, NH (Boc)), 4.46-4.35 (m, 1H,  $\text{C}^\alpha\text{H}$  (Nal)), 3.63-3.58 (m, 1H,  $\text{C}^\beta\text{H}$  (Nal)), 3.25-3.17 (m, 1H,  $\text{C}^\beta\text{H}$  (Nal)),

1.25 (s, 9H, Boc). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 171.4, 156.2, 156.1, 152.6, 134.5, 134.2, 132.4, 129.5, 128.4, 127.9, 126.9, 126.4, 126.2, 124.5, 116.7, 114.3, 78.9, 54.6, 35.6, 27.2. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 22.11 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 25.90 min.

**General Procedure for Preparation of *N'*-(DL-AA)-5-nitro-2-furancarbohydrazide Hydrochloride (10a-c).** 5-Nitro-2-furancarbohydrazide (**9a-c**) (2.08 mmol) was dissolved in MeOH (30 mL) and a concentrated HCl solution (12 N, 5 mL) was added. The reaction was stirred for 16 h. The solvent was evaporated under reduced pressure, and the residue **9a-c** that was obtained was filtered and washed with petroleum ether.

***N'*-(DL-Phenylglycyl)-5-nitro-2-furancarbohydrazide Hydrochloride (10a).** Yellow powder (673 mg). Yield 95%. TLC *R*<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.7. Mp: 195-199 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.18 (bs, 1H, NH (hydrazine)), 11.06 (bs, 1H, NH (hydrazine)), 8.97 (bs, 3H, NH<sub>3</sub><sup>+</sup>), 7.75 (d, 1H, *J* = 3.9, H<sub>furyl</sub>), 7.68-7.55 (m, 3H, H<sub>Ar</sub>), 7.49-7.39 (m, 3H, 2H<sub>Ar</sub> + H<sub>furyl</sub>), 5.15 (bs, 1H, C<sup>α</sup>H (Phg)). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 167.45, 155.9, 152.8, 146.9, 134.5, 130.1, 129.6, 129.0, 117.7, 114.1, 55.0. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 9.90 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 13.96 min. MS (TOF) *m/z* 304 (M<sup>+</sup>).

***N'*-(DL-2-(Naphthyl)alaninyl)-5-nitro-2-furancarbohydrazide hydrochloride (10b).** Yellow powder (631 mg). Yield 75%. TLC *R*<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.4. Mp: > 250 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.31 (s, 1H, NH (hydrazine)), 11.16 (s, 1H, NH (hydrazine)), 8.50 (bs, 3H, NH<sub>3</sub><sup>+</sup>), 8.00-7.85 (m, 4H, H<sub>Ar</sub>), 7.80 (d, 1H, *J* = 3.8 Hz, H<sub>furyl</sub>), 7.69 (d, 1H, *J* = 3.8 Hz, H<sub>furyl</sub>), 7.65 (dd, 1H, *J* = 8.41 Hz, *J'* = 1.2 Hz, H<sub>Ar</sub>), 7.56-7.47 (m, 2H, H<sub>Ar</sub>), 4.32 (bs, 1H, C<sup>α</sup>H (Nal)), 3.65-3.50 (m, 2H, C<sup>β</sup>H (Nal)). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 168.25, 156.1, 152.8, 147.0, 133.9, 133.2, 133.1, 129.5, 128.9, 128.8, 128.5, 128.4, 126.9, 126.7, 117.8, 114.1, 53.1, 37.9. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 15.13 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 19.37 min. MS (TOF) *m/z* 368 (M<sup>+</sup>).

***N'*-(DL-1-(Naphthyl)alaninyl)-5-nitro-2-furancarbohydrazide Hydrochloride (10c).** Yellow powder (631 mg). Yield 75%. TLC *R*<sub>f</sub> (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.6. Mp: > 250 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.28 (bs, 1H, NH (hydrazine)), 11.00 (bs, 1H, NH (hydrazine)), 8.59 (bs, 3H, NH<sub>3</sub><sup>+</sup>), 8.39 (d, 1H, *J* = 7.9 Hz, H<sub>Ar</sub>), 7.95 (d, 1H, *J* = 7.6 Hz, H<sub>Ar</sub>), 7.91 (d, 1H, *J* = 6.2 Hz, H<sub>Ar</sub>), 7.77 (d, 1H, *J* = 3.9 Hz, H<sub>furyl</sub>), 7.66-7.40 (m, 5H, 4H<sub>Ar</sub> + H<sub>furyl</sub>), 4.22 (bs, 1H, C<sup>α</sup>H (Nal)), 3.67-3.49 (m, 2H, C<sup>β</sup>H (Nal)). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 168.2, 155.8, 152.9, 147.1, 134.6, 132.6, 131.4, 129.7, 129.1, 127.4, 126.8, 126.7, 125.0, 124.6, 117.9, 114.2, 52.4, 35.4. HPLC (C18V, condition A) P<sub>HPLC</sub> 99.3%, *t*<sub>R</sub> 14.60 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 18.91 min. MS (TOF) *m/z* 368 (M<sup>+</sup>).

**General Procedure for Preparation of *N'*-(*N*-(*tert*-butoxycarbonyl)-*N*-(2-[(*tert*-butoxycarbonyl)amino]ethyl)-Gly-DL-AA)-5-nitro-2-furancarbohydrazide (11a-c).** Carboxylic acid **5** (200 mg, 0.63 mmol, 1 eq), PyBOP (489 mg, 0.94 mmol, 1.5 eq) and DIEA (0.32 mL, 1.88 mmol, 3 eq) were added to a solution of appropriate 5-nitro-2-furancarbohydrazide (**10a-c**) (0.63 mmol, 1 eq) in 50 mL of CH<sub>2</sub>Cl<sub>2</sub> (ice bath). The reaction mixture was stirred for 24 h at room temperature, and then the solvent was removed under reduced pressure. The residue obtained was dissolved in EtOAc and washed successively with saturated NaHCO<sub>3</sub> solution, citric acid (5%) and H<sub>2</sub>O. The organic phase was dried over MgSO<sub>4</sub>, filtered and evaporated to yield an oil which was purified by thick-layer chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 7:3).

***N'*-(*N*-(*tert*-Butoxycarbonyl)-*N*-(2-[(*tert*-butoxycarbonyl)amino]ethyl)-Gly-DL-phenylglycyl)-5-nitro-2-furancarbohydrazide (11a).** Orange powder (293 mg). Yield 77%. TLC *R*<sub>f</sub> (EtOAc) = 0.5. Mp: 108-109 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.5-10.5 (bs, 2H, NH (hydrazine)), 8.76 (d, 1H, *J* = 8.2 Hz, NH (Phg)), 7.74 (d, 1H, *J* = 3.9 Hz, H<sub>furyl</sub>), 7.52-7.25 (m, 6H, 5H<sub>Ar</sub> + H<sub>furyl</sub>), 6.73 (t, 1H, *J* = 4.9 Hz, NH (Boc)), 5.72-5.64 (m, 1H, C<sup>α</sup>H (Phg)), 4.00-3.90 (m, 2H, C<sup>α</sup>H<sub>2</sub> (Gly)), 3.19-3.16 (m, 2H, NCH<sub>2</sub>), 3.05-3.00 (m, 2H, NCH<sub>2</sub>), 1.38 (s, 18H, 2 x Boc). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 170.1, 169.2, 156.1, 155.8, 152.2, 147.3, 146.7, 139.5, 129.1, 128.5, 128.0, 116.2, 114.2, 79.6, 78.4, 55.3, 51.0, 39.2, 39.0, 29.0,

27.2. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  20.88 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  100%,  $t_R$  25.16 min. MS (TOF)  $m/z$  604 ( $M^+$ ).

***N'*-(*N*-(*tert*-Butoxycarbonyl)-*N*-(2-[(*tert*-butoxycarbonyl)amino]ethyl)-Gly-DL-2-(naphthyl)alaninyl)-5-nitro-2-furancarbohydrazide (11b).** Orange powder (181 mg). Yield 43%. TLC  $R_f$  (EtOAc) = 0.7. Mp: 122-123 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  11.0 (bs, 1H, NH (hydrazine)), 10.50 (bs, 1H, NH (hydrazine)), 8.41-8.33 (m, 1H, NH (Nal)), 7.85-7.70 (m, 5H, 4H<sub>Ar</sub> + H<sub>furyl</sub>), 7.50-7.41 (m, 4H, 3H<sub>Ar</sub> + H<sub>furyl</sub>), 6.77-6.60 (m, 1H, NH (Boc)), 5.00-4.75 (m, 1H, C $^\alpha$ H (Nal)), 4.00-3.90 (m, 2H, C $^\alpha$ H<sub>2</sub> (Gly)), 3.37 (bs, 2H, C $^\beta$ H<sub>2</sub> (Nal)), 3.04 (m, 2H, NCH<sub>2</sub>), 2.88 (bs, 2H, NCH<sub>2</sub>), 1.38 (bs, 18H, 2 x Boc).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ) 169.9, 168.1, 156.1, 155.8, 152.6, 148.0, 147.0, 136.1, 133.8, 132.8, 128.4, 128.3, 128.2, 126.8, 126.4, 126.35, 126.3, 116.9, 114.2, 80.0, 78.3, 53.5, 50.7, 49.8, 49.5, 38.7, 28.7, 28.5. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  24.31 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  100%,  $t_R$  27.31 min. MS (TOF)  $m/z$  668 ( $M^+$ ).

***N'*-(*N*-(*tert*-Butoxycarbonyl)-*N*-(2-[(*tert*-butoxycarbonyl)amino]ethyl)-Gly-DL-1-(naphthyl)alaninyl)-5-nitro-2-furancarbohydrazide (11c).** Orange powder (202 mg). Yield 48%. TLC  $R_f$  (EtOAc) = 0.7. Mp: 98-100 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  11.0 (bs, 1H, NH (hydrazine)), 10.5 (bs, 1H, NH (hydrazine)), 8.55-8.45 (m, 1H, NH (Nal)), 8.26 (t, 1H,  $J$  = 8.7 Hz, H<sub>Ar</sub>), 7.92 (d, 1H,  $J$  = 8.7 Hz, H<sub>Ar</sub>), 7.78 (d, 1H,  $J$  = 8.7 Hz, H<sub>Ar</sub>), 7.76 (d, 1H,  $J$  = 3.9 Hz, H<sub>furyl</sub>), 7.57-7.40 (m, 5H, 4H<sub>Ar</sub> + H<sub>furyl</sub>), 6.70 (m, 1H, NH (Boc)), 4.85-4.75 (m, 1H, C $^\alpha$ H (Nal)), 4.00-3.60 (m, 2H, C $^\alpha$ H<sub>2</sub> (Gly)), 3.32-3.20 (m, 2H, C $^\beta$ H<sub>2</sub> (Nal)), 3.10-3.00 (m, 2H, NCH<sub>2</sub>), 2.90-2.80 (m, 2H, NCH<sub>2</sub>), 1.39 (s, 9H, Boc), 1.36 (s, 9H, Boc).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  169.8, 169.7, 156.4, 156.1, 152.6, 149.5, 145.0, 134.2, 134.0, 132.4, 129.5, 128.4, 128.0, 127.0, 126.4, 126.2, 124.5, 116.9, 114.2, 79.5, 78.4, 52.8, 47.9, 43.7, 39.8, 36.5, 28.7. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  24.21 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  100%,  $t_R$  27.27 min. MS (TOF)  $m/z$  668 ( $M^+$ ).

**General Procedure for Preparation of *N'*-(2-(Amino)ethyl-Gly-DL-AA)-5-nitro-2-furancarbohydrazide Dihydrochloride (12a-c).** Appropriate 5-nitro-2-furancarbohydrazide (**11a-c**) (0.25 mmol) was dissolved in MeOH (30 mL) and a concentrated HCl solution (12 N, 5 mL) was added. The reaction was monitored by HPLC and stirred until complete hydrolysis of **11a-c** (16 h). The solvent was removed under reduced pressure, and the residue **11a-c** was filtered and washed with ether.

***N'*-(2-(amino)ethyl-Gly-DL-phenylglycine)-5-nitro-2-furancarbohydrazide Dihydrochloride (12a).** Yellow powder (113 mg). Yield 95%. TLC  $R_f$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.5. Mp: 82-83 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  11.09 (s, 1H, NH (hydrazine)), 10.87 (bs, 1H, NH (hydrazine)), 9.56 (bs, 2H, NH<sub>2</sub><sup>+</sup>), 9.45 (d, 1H,  $J$  = 8.2 Hz, NH (Phg)), 8.48 (bs, 3H, NH<sub>3</sub><sup>+</sup>), 7.78 (d, 1H,  $J$  = 3.9 Hz, H<sub>furyl</sub>), 7.70-7.25 (m, 6H, 5H<sub>Ar</sub> + H<sub>furyl</sub>), 5.73 (d, 1H,  $J$  = 8.2 Hz, C $^\alpha$ H (Phg)), 3.89 (bs, 2H, C $^\alpha$ H<sub>2</sub>(Gly)), 3.25 (bs, 2H, NCH<sub>2</sub>), 3.16 (bs, 2H, NCH<sub>2</sub>).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  169.3, 165.5, 156.2, 152.8, 147.1, 138.4, 129.3, 128.8, 128.1, 117.5, 114.1, 55.5, 48.5, 45.0, 35.9. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  97.9%,  $t_R$  10.22 min; HPLC (B)  $P_{\text{HPLC}}$  100%,  $t_R$  13.73 min. MS (TOF)  $m/z$  404 ( $M^+$ ).

***N'*-(2-(amino)ethyl-Gly-DL-2-(naphthyl)alaninyl)-5-nitro-2-furancarbohydrazide Dihydrochloride (12b).** Yellow powder (128 mg). Yield 95%. TLC  $R_f$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.1-0.25. Mp: > 100 °C (hygroscopic).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  11.06 (s, 1H, NH (hydrazine)), 10.63 (s, 1H, NH (hydrazine)), 9.40 (bs, 2H, NH<sub>2</sub><sup>+</sup>), 9.05 (d, 1H,  $J$  = 8.5 Hz, NH (Nal)), 8.40 (bs, 3H, NH<sub>3</sub><sup>+</sup>), 8.26-7.46 (m, 9H, 7H<sub>Ar</sub> + 2H<sub>furyl</sub>), 4.85 (m, 1H, C $^\alpha$ H (Nal)), 3.80-3.00 (m, 8H, C $^\alpha$ H<sub>2</sub>(Gly) + 2 x NCH<sub>2</sub> + C $^\beta$ H (Nal)).  $^{13}\text{C}$  NMR (DMSO- $d_6$ ) 170.7, 165.6, 156.2, 152.8, 147.2, 135.7, 133.8, 132.8, 128.7, 128.6, 128.4, 128.3, 126.9, 126.4, 117.5, 114.1, 53.7, 48.4, 44.8, 39.0, 35.9. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  14.52 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  100%,  $t_R$  18.28 min. MS (TOF)  $m/z$  468 ( $M^+$ ).

***N'*-(2-(amino)ethyl-Gly-DL-1-(naphthyl)alaninyl)-5-nitro-2-furancarbohydrazide Dihydrochloride (12c).** Yellow powder (102 mg). Yield 75%. TLC  $R_f$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.1-0.25. Mp: > 100 °C (hygroscopic).  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  11.06 (s, 1H, NH (hydrazine)), 11.00-10.50 (bs,

1H, NH (hydrazine)), 9.00 (bs, 2H, NH<sub>2</sub><sup>+</sup>), 8.80 (bs, 3H, NH<sub>3</sub><sup>+</sup>), 8.28 (d, 1H, *J* = 8.0 Hz, NH (Nal)), 8.00-7.30 (m, 9H, 7H<sub>Ar</sub> + 2H<sub>furyl</sub>), 4.89 (m, 1H, C<sup>α</sup>H (Nal)), 3.80-3.00 (m, 8H, C<sup>α</sup>H<sub>2</sub>(Gly) + 2 x NCH<sub>2</sub> + C<sup>β</sup>H (Nal)). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 171.7, 156.8, 153.4, 147.9, 134.9, 134.5, 133.0, 130.1, 129.3, 128.8, 127.7, 127.15, 126.9, 125.2, 118.2, 114.8, 53.5, 50.2, 46.2, 38.5, 36.7. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 14.31 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 17.93 min. MS (TOF) *m/z* 468 (M<sup>+</sup>).

**Platination. General Procedure for Preparation of (N'-[2-(Amino)ethyl-Gly-DL-AA]-5-nitro-2-furancarbohydrazide) Dichloroplatinum (II) (13a-c).** Appropriate 5-nitro-2-furancarbohydrazide hydrochloride (**12a-c**) (0.27 mmol, 1 eq) and K<sub>2</sub>PtCl<sub>4</sub> (112 mg, 0.27 mmol, 1 eq) were dissolved in DMF/H<sub>2</sub>O (1:3). The reaction was monitored by HPLC and stirred until complete chelation of **12a-c** (about 10 days). The solvent was removed under reduced pressure and the residue obtained was filtered, washed with H<sub>2</sub>O and rinsed with MeOH and Et<sub>2</sub>O to give **13a-c**.

**(N'-[2-(Amino)ethyl-Gly-DL-phenylglyciny]-5-nitro-2-furancarbohydrazide) Dichloroplatinum (II) (13a).** Brown powder (162 mg). Yield 90%. Mp: 216-219 °C. IR (KBr, cm<sup>-1</sup>) 3261.8 (NH), 2924.0, 1672.7 (CO), 1581.0, 1538.6, 1386.5, 1350.9, 1249.8, 1018.5, 966.7, 811.9, 747.8, 668.7, 477.8 (Pt-N). <sup>1</sup>H NMR (DMF-*d*<sub>7</sub>) δ 11.26 (bs, 1H, NH), 10.86 (s, 0.5H, NH), 10.81 (s, 0.5H, NH), 9.15 (d, 1H, *J* = 7.4 Hz, NH (Phg)), 7.94-7.91 (m, 1H, H<sub>Furyl</sub>), 7.70-7.25 (m, 6H, 5H<sub>Ar</sub> + H<sub>Furyl</sub>), 6.10 (bs, 1H, NH), 6.00-5.75 (m, 1H, C<sup>α</sup>H (Phg)), 5.61 (bs, 2H, NH<sub>2</sub>), 4.50-3.90 (m, 2H, C<sup>α</sup>H<sub>2</sub>(Gly)), 3.30-3.10 (m, 2H, NCH<sub>2</sub>), 2.75-2.55 (m, 2H, NCH<sub>2</sub>). <sup>195</sup>Pt NMR (DMF-*d*<sub>7</sub>) δ -2343.3. HPLC (C18V, condition A) *t*<sub>R</sub> 12.25 min (50%), 12.69 min (50%); HPLC (C18V, condition B) *t*<sub>R</sub> 15.33 min (50%), 15.77 min (50%), 2 isomers. MS (FAB) *m/z* 671 (MH)<sup>+</sup>. Anal. (C<sub>17</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>6</sub>Pt · 2H<sub>2</sub>O) C, H, N.

**(N'-[2-(Amino)ethyl-Gly-2-DL-(naphthyl)alaniny]-5-nitro-2-furancarbohydrazide) Dichloroplatinum (II) (13b).** Brown powder (188 mg). Yield 95%. Mp: 205-208 °C. IR (KBr, cm<sup>-1</sup>) 3221.3 (NH), 2923.6, 1674.2 (CO), 1597.0, 1539.2, 1386.7, 1351.3, 1250.9, 1018.3, 966.6, 812.3, 748.0, 668.1, 477.8 (Pt-N). <sup>1</sup>H NMR (DMF-*d*<sub>7</sub>) δ 11.12 (s, 0.5H, NH (hydrazine)), 11.09 (s, 0.5H, NH (hydrazine)), 10.55 (s, 0.5H, NH (hydrazine)), 10.49 (s, 0.5H, NH (hydrazine)), 8.85-8.80 (m, 1H, NH (Nal)), 8.06-7.52 (m, 9H, H<sub>Ar</sub>), 6.10 (bs, 0.5H, NH), 5.80 (bs, 0.5H, NH), 5.40-5.25 (bs, 2H, NH<sub>2</sub>), 5.10-4.90 (m, 1H, C<sup>α</sup>H (Nal)), 4.10-3.05 (m, 4H, C<sup>α</sup>H<sub>2</sub>(Gly) + C<sup>β</sup>H<sub>2</sub> (Nal)), 2.95-2.85 (m, 2H, NCH<sub>2</sub>), 2.80-2.70 (m, 2H, NCH<sub>2</sub>). <sup>195</sup>Pt NMR (DMF-*d*<sub>7</sub>) δ -2346.8. HPLC (C18V, condition A) *t*<sub>R</sub> 16.17 min (50%), 17.02 min (50%); HPLC (C18V, condition B) *t*<sub>R</sub> 19.16 min (50%), 19.89 min (50%), 2 isomers. MS (FAB) *m/z* 735 (MH)<sup>+</sup>. Anal. (C<sub>22</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>6</sub>Pt · 8H<sub>2</sub>O) C, N, H: calcd, 4.59%; found, 3.01%.

**(N'-[2-(Amino)ethyl-Gly-1-DL-(naphthyl)alaniny]-5-nitro-2-furancarbohydrazide) Dichloroplatinum (II) (13c).** Brown powder (190 mg). Yield 95%. Mp: 200-204 °C. IR (KBr, cm<sup>-1</sup>) 3210.2 (NH), 2923.6, 1669.8 (CO), 1596.5, 1539.3, 1386.6, 1350.6, 1253.5, 1018.4, 967.1, 811.32, 778.9, 738.5, 668.8, 579.4, 477.9 (Pt-N). <sup>1</sup>H NMR (DMF-*d*<sub>7</sub>) δ 11.11 (s, 0.5H, NH (hydrazine)), 11.09 (s, 0.5H, NH (hydrazine)), 10.60 (s, 0.5H, NH (hydrazine)), 10.50 (s, 0.5H, NH (hydrazine)), 8.86-8.77 (m, 1H, NH (Nal)), 8.33-7.43 (m, 9H, H<sub>Ar</sub>), 6.05 (bs, 0.5H, NH), 5.87 (bs, 0.5H, NH), 5.40 (bs, 2H, NH<sub>2</sub>), 5.25-4.75 (m, 1H, C<sup>α</sup>H (Nal)), 4.20-3.30 (m, 4H, C<sup>α</sup>H<sub>2</sub>(Gly) + C<sup>β</sup>H<sub>2</sub> (Nal)), 2.90-2.50 (m, 4H, 2 x NCH<sub>2</sub>). <sup>195</sup>Pt NMR (DMF-*d*<sub>7</sub>) δ -2346.4. HPLC (C18V, condition A) *t*<sub>R</sub> 16.18 min (50%), 16.92 min (50%), HPLC (C18V, condition B) *t*<sub>R</sub> 19.06 min (50%), 19.67 min (50%) 2 isomers. MS (FAB) *m/z* 735 (MH)<sup>+</sup>. Anal. (C<sub>22</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>6</sub>Pt · 3½H<sub>2</sub>O) H, N, C: calcd, 33.13%; found, 32.45%.

**General Procedure for Preparation of 5-Nitro-2-furancarbohydrazide Derivatives (14a-c).** Appropriate acid (1.80 mmol, 1.5 eq), PyBOP (1.25 g, 2.40 mmol, 2.0 eq) and DIEA (0.63 mL, 3.60 mmol, 3 eq) were added to a solution of appropriate 5-nitro-2-furancarbohydrazide hydrochloride (**7**) (249 mg, 1.20 mmol, 1 eq) in 50 mL of CH<sub>2</sub>Cl<sub>2</sub> (ice bath). The reaction mixture was stirred for 24 h at room temperature, and then the solvent was removed under reduced pressure. The residue obtained was dissolved in EtOAc and washed successively with saturated NaHCO<sub>3</sub> solution, citric acid (5%) and

H<sub>2</sub>O. The organic phase was dried over MgSO<sub>4</sub>, filtered and evaporated to yield an oil which was purified by thick-layer chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 7:3).

**N'-(Benzyl)-5-nitro-2-furancarbohydrazide (14a).** Yellow powder (264 mg). Yield 76%. TLC *R<sub>f</sub>* (EtOAc/CH<sub>2</sub>Cl<sub>2</sub> 7:3) = 0.50. Mp: 133-134 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.76 (bs, 1H, NH (hydrazine)), 10.41 (bs, 1H, NH (hydrazine)), 7.76 (d, 2H, *J* = 3.9 Hz, H<sub>fur</sub>yl), 7.50 (d, 2H, *J* = 3.9 Hz, H<sub>fur</sub>yl), 7.30-7.20 (m, 5H, H<sub>Ar</sub>), 3.55 (s, 2H, CH<sub>2</sub>). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 170.2, 156.3, 147.4, 136.4, 129.9, 129.1, 127.4, 117.3, 114.1, 40.2. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 13.86 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 19.38 min.

**N'-(2-Naphthyl)-5-nitro-2-furancarbohydrazide (14b).** Yellow powder (98 mg). Yield 25%. TLC *R<sub>f</sub>* (EtOAc/CH<sub>2</sub>Cl<sub>2</sub> 7:3) = 0.6. Mp: 170-171 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.15-10.50 (m, 2H, NH (hydrazine)), 8.52 (s, 1H, H<sub>Ar</sub>), 8.10-7.85 (m, 4H, H<sub>Ar</sub>), 7.80 (d, 1H, *J* = 3.8 Hz, H<sub>fur</sub>yl), 7.68-7.58 (m, 2H, H<sub>Ar</sub>), 7.56 (d, 1H, *J* = 3.9 Hz, H<sub>fur</sub>yl). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 166.3, 156.6, 152.8, 148.0, 135.3, 132.9, 130.5, 129.8, 129.1, 128.9, 128.8, 128.6, 127.8, 124.8, 117.1, 114.2. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 19.59 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 22.30 min.

**N'-(1-Naphthyl)-5-nitro-2-furancarbohydrazide (14c).** Yellow powder (109 mg). Yield 28%. TLC *R<sub>f</sub>* (EtOAc/CH<sub>2</sub>Cl<sub>2</sub> 5:5) = 0.4. Mp: 122-123 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.15-10.60 (m, 2H, NH (hydrazine)), 8.36 (d, 1H, *J* = 7.0 Hz, H<sub>Ar</sub>), 8.07 (d, 1H, *J* = 8.0 Hz, H<sub>Ar</sub>), 8.00 (dd, 1H, *J* = 5.8 Hz, *J*' = 2.9 Hz, H<sub>Ar</sub>), 7.81 (d, 1H, H<sub>fur</sub>yl, *J* = 3.9 Hz), 7.70 (d, 1H, *J* = 6.6 Hz, H<sub>Ar</sub>), 7.65-7.51 (m, 4H 3H<sub>Ar</sub> + H<sub>fur</sub>yl). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 168.6, 156.7, 152.8, 147.6, 134.0, 133.1, 131.4, 130.7, 129.1, 127.9, 127.3, 126.5, 126.1, 125.9, 117.4, 114.2. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 17.0 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 21.72 min.

**6-[(*tert*-Butoxycarbonyl)amino]-2-naphthoic Acid (15).** Di-*tert*butyl dicarbonate (3.50 g, 16.0 mmol, 1.5 eq) and NaOH (1N, 21.4 mL, 21.4 mmol, 2.0 eq) were added to a solution of 6-[(*tert*-butoxycarbonyl)amino]-2-naphthoic acid (2.00 g, 10.7 mmol, 1 eq) in 50 mL of dioxane/H<sub>2</sub>O (4/1). The reaction was stirred for 16 h and then the solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The aqueous phase was adjusted to pH = 4 with a solution of HCl (0.25 N) and extracted with EtOAc. The organic phase was dried over MgSO<sub>4</sub>, and evaporated to give **15** as a brown solid (2.33 g). Yield 76%. TLC *R<sub>f</sub>* (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) = 0.8. Mp: 195-196 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 12.50 (s, 1H, COOH), 9.66 (s, 1H, NH (Boc)), 8.39 (s, 1H, H<sub>Ar</sub>), 8.10 (s, 1H, H<sub>Ar</sub>), 7.92 (d, 1H, *J* = 9.0 Hz, H<sub>Ar</sub>), 7.81 (d, 1H, *J* = 8.6 Hz, H<sub>Ar</sub>), 7.75 (d, 1H, *J* = 8.7 Hz, H<sub>Ar</sub>), 7.49 (dd, 1H, *J* = 8.9 Hz, *J*' = 2.1 Hz, H<sub>Ar</sub>), 1.43 (s, 9H, Boc). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 168.4, 153.6, 140.3, 136.7, 131.1, 130.8, 128.9, 128.15, 126.9, 126.5, 121.0, 113.7, 80.4, 28.9. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 23.94 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 25.80 min. MS (TOF) *m/z* 287 (M<sup>+</sup>).

**N'-[(6-(*tert*-Butoxycarbonyl)amino-2-naphthyl)carbonyl]-5-nitro-2-furancarbohydrazide (16).** 5-Nitro-2-furancarbohydrazide hydrochloride **7** (792 mg, 3.82 mmol, 1 eq), PyBOP (2.98 g, 5.74 mmol, 1.5 eq) and DIEA (2.0 mL, 11.5 mmol, 3 eq) were added to a solution of 6-[(*tert*-butoxycarbonyl)amino]-2-naphthoic acid (**15**) (1.10 g, 3.82 mmol, 1 eq) in 50 mL of CH<sub>2</sub>Cl<sub>2</sub> (ice bath). The reaction mixture was stirred for 16 h, and then the solvent was evaporated under reduced pressure. The residue obtained was washed with MeOH and filtered to give **16** as a yellow solid. (1.01 g). Yield 61%. TLC *R<sub>f</sub>* (EtOAc) = 0.85. Mp: 222-223 °C. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 11.05 (s, 1H, NH (hydrazine)), 10.70 (bs, 1H, NH (hydrazine)), 9.73 (s, 1H, NH (Boc)), 8.42 (s, 1H, H<sub>Ar</sub>), 8.18 (s, 1H, H<sub>Ar</sub>), 7.96-7.87 (m, 3H, H<sub>Ar</sub>), 7.78 (d, 1H, H<sub>fur</sub>yl, *J* = 3.9 Hz), 7.60-7.54 (m, 2H, H<sub>Ar</sub> + H<sub>fur</sub>yl), 1.49 (s, 9H, Boc). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>) δ 166.5, 156.7, 152.8, 147.4, 136.0, 131.7, 129.1, 128.1, 125.7, 122.3, 117.5, 114.1. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 21.04 min; HPLC (C18N, condition B) P<sub>HPLC</sub> 100%, *t<sub>R</sub>* 24.87 min. MS (TOF) *m/z* 440 (M<sup>+</sup>).

**N'-[(6-Amino-2-naphthyl)carbonyl]-5-nitro-2-furancarbohydrazide Trifluoroacetate (17).** Compound **16** (1.00 g, 2.27 mmol, 1 eq) was added to a solution of CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and trifluoroacetic



acid (30 mL) in an ice bath. The reaction mixture was stirred for 4 h, then, the solution was removed under reduced pressure to give **17** as a green solid (855 mg). Yield 100%. TLC  $R_f$  (EtOAc) = 0.55. Mp: 180-181 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  11.08 (s, 1H, NH (hydrazine)), 10.80 (bs, 1H, NH (hydrazine)), 8.51 (s, 1H,  $H_{Ar}$ ), 8.08-7.85 (m, 4H,  $H_{Ar}$ ), 7.82 (d, 1H,  $H_{furyl}$ ,  $J$  = 3.9 Hz), 7.60 (d, 1H,  $H_{furyl}$ ,  $J$  = 3.9 Hz), 7.43 (d, 1H,  $J$  = 8.35 Hz).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  116.7, 156.7, 152.8, 147.5, 144.3, 137.0, 131.3, 129.2, 127.6, 126.9, 126.8, 125.3, 121.0, 117.4, 114.1, 111.0. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  11.70 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  100%,  $t_R$  15.91 min. MS (TOF)  $m/z$  340 ( $M^+$ ).

***N*-[6-(2-[(5-Nitro-2-furyl)carbonyl]hydrazinocarbonyl)-2-naphthyl]-2-[(2-*N*-(*tert*-butoxycarbonylamino)-*N*-(2-[(*tert*-butoxycarbonyl)amino]ethyl)acetamide (**18**)**

PyBROP (1.36 g, 2.92 mmol, 2 eq) and DIEA (1.2 mL, 5.84 mmol, 4 eq) were added to a solution of carboxylic acid **5** (929 mg, 2.92 mmol, 2 eq) in 25 mL of DMF. The reaction mixture was stirred for 1 h at room temperature, then the 5-nitro-2-furancarbohydrazide trifluoroacetate **17** (663 mg, 1.46 mmol, 1 eq) was added to the solution. After 16 h, the solvent was removed under reduced pressure. The residue obtained was dissolved in EtOAc and washed successively with saturated  $\text{NaHCO}_3$  solution, citric acid (5%) and  $\text{H}_2\text{O}$ . The organic phase was dried over  $\text{MgSO}_4$ , filtered and evaporated. The oil thus obtained was chromatographed on a 3-x 40-cm flash column using cyclohexane/EtOAc (1:9) as the eluting solvent to give **18** as a yellow solid (236 mg). Yield 25%. TLC  $R_f$  (EtOAc/cyclohexane 9:1) = 0.30. Mp: 204-205 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  10.99 (bs, 1H, NH (hydrazine)), 10.74 (s, 1H, NH (hydrazine)), 10.34 (d, 1H,  $J$  = 7.8 Hz, NH (Amide)), 8.44 (s, 1H,  $H_{Ar}$ ), 8.37 (d, 1H,  $J$  = 3.3 Hz,  $H_{Ar}$ ), 8.00 (d, 1H,  $J$  = 9.0 Hz,  $H_{Ar}$ ), 7.92 (s, 2H,  $H_{Ar}$ ), 7.79 (d, 1H,  $H_{furyl}$ ,  $J$  = 3.9 Hz), 7.66 (t, 1H,  $J$  = 8.8 Hz,  $H_{Ar}$ ), 7.56 (d, 1H,  $H_{furyl}$ ,  $J$  = 3.9 Hz), 6.78-6.65 (m, 1H, NH (Boc)), 4.03-3.92 (m, 2H,  $\text{C}^\alpha\text{H}_2$  (Gly)), 3.22-2.98 (m, 4H, 2 x  $\text{NCH}_2$ ), 1.40-1.29 (m, 18H, 2 x Boc).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  171.9, 166.5, 156.7, 152.8, 151.2, 147.4, 139.3, 136.1, 130.7, 128.8, 128.6, 128.5, 125.3, 122.3, 121.6, 117.5, 115.5, 114.1, 78.5, 78.4, 52.8, 49.4, 45.0, 39.8, 36.5, 29.1, 28.8. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  21.87 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  100%,  $t_R$  25.57 min. MS (TOF)  $m/z$  640 ( $M^+$ ).

***N*-[6-(2-[(5-Nitro-2-furyl)carbonyl]hydrazinocarbonyl)-2-naphthyl]-2-[(2-aminoethyl)amino]acetamide Dihydrochloride (**19**)**

Acetamide **18** (200 mg, 0.31 mmol, 1 eq) was dissolved in MeOH (30 mL) and a concentrated HCl solution (12 N, 5 mL) was added. The reaction was monitored by HPLC and stirred for 72 h at room temperature. The solvent was evaporated under reduced pressure, and the residue **19** that was obtained was filtered and washed with petroleum ether as a yellow solid. Yield 95%. Mp: > 250 °C.  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  11.33 (s, 1H, NH), 11.14 (s, 1H, NH), 10.83 (s, 1H, NH), 9.76 (s, 2H,  $\text{NH}_2^+$ ), 8.52 (s, 1H,  $H_{Ar}$ ), 8.47 (bs, 3H,  $\text{NH}_3^+$ ), 8.41 (s, 1H,  $H_{Ar}$ ), 8.08 (d, 1H,  $J$  = 9.0 Hz,  $H_{Ar}$ ), 7.97 (s, 2H,  $H_{Ar}$ ), 7.82 (d, 1H,  $H_{furyl}$ ,  $J$  = 3.9 Hz), 7.78 (d, 1H,  $J$  = 9.0 Hz,  $H_{Ar}$ ), 7.65 (d, 1H,  $H_{furyl}$ ,  $J$  = 3.9 Hz), 4.15 (bs, 2H,  $\text{C}^\alpha\text{H}_2$  (Gly)), 3.40-3.30 (m, 2H,  $\text{NCH}_2$ ), 3.24 (bs, 2H,  $\text{NCH}_2$ ).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  166.5, 165.1, 156.7, 152.8, 149.0, 147.4, 138.5, 135.9, 131.0, 129.8, 129.2, 128.9, 128.6, 125.5, 121.4, 117.5, 116.0, 114.1, 49.4, 45.0, 44.9. HPLC (C18V, condition A)  $P_{\text{HPLC}}$  100%,  $t_R$  11.41 min; HPLC (C18N, condition B)  $P_{\text{HPLC}}$  99.2%,  $t_R$  15.10 min. MS (TOF)  $m/z$  440 ( $M^+$ ).

***N*-[6-(2-[(5-Nitro-2-furyl)carbonyl]hydrazinocarbonyl)-2-naphthyl]-2-[(2-aminoethyl)amino]acetamide Dichloroplatinum (II) (**20**)**

Diamine dihydrochloride (**19**) (130 mg, 0.25 mmol, 1eq) and  $\text{K}_2\text{PtCl}_4$  (105 mg, 0.25 mmol, 1 eq) were dissolved in DMF/ $\text{H}_2\text{O}$  (1:3). The reaction mixture was heating at 60°C, monitored by HPLC and stirred until complete chelation of **19** (7 days). The solvent was removed under reduced pressure and the residue obtained was filtered, washed with  $\text{H}_2\text{O}$  and rinsed with MeOH and  $\text{Et}_2\text{O}$  to give **20** as a brown powder (168 mg). Yield 95%. Mp: > 250 °C. IR (KBr,  $\text{cm}^{-1}$ ) 3212.0 (NH), 2924.9, 1647.4.2 (CO), 1632.4 (CO), 1583.0, 1541.1, 1496.8, 1388.5, 1350.8, 1274.4, 1241.9, 1020.9, 967.3, 882.5, 811.9, 738.8, 669.0, 653.8, 580.9, 474.4 (Pt-N).  $^1\text{H}$  NMR (DMF- $d_7$ )  $\delta$  11.30 (s, 1H, NH amide), 10.97 (s, 1H, NH (hydrazine)), 10.83 (s, 1H, NH (hydrazine)), 8.71 (s, 1H,  $H_{Ar}$ ), 8.65 (s, 1H,  $H_{Ar}$ ), 8.20-8.10 (m, 4H,  $H_{Ar}$ ), 7.98 (d, 1H,  $J$  = 3.9 Hz,

H<sub>furyl</sub>), 7.93 (d, 1H, *J* = 8.9 Hz, H<sub>Ar</sub>), 6.53 (bs, 1H, NH), 5.97 (s, 2H, NH<sub>2</sub>), 4.75-4.60 (d, 1H, *J* = 15.5 Hz, C<sup>α</sup>H<sub>2</sub> (Gly)), 4.20-4.00 (m, 1H, C<sup>α</sup>H<sub>2</sub> (Gly)), 3.40-3.30 (m, 2H, NCH<sub>2</sub>), 3.24 (bs, 2H, NCH<sub>2</sub>). <sup>13</sup>C NMR (DMF-*d*<sub>7</sub>) δ 166.7, 156.7, 147.4, 139.0, 136.2, 130.6, 129.9, 128.6, 128.4, 125.4, 121.3, 117.3, 115.8, 113.6, 58.4, 56.1, 47.8. <sup>195</sup>Pt NMR (DMF-*d*<sub>7</sub>) δ -2348.8. HPLC (C18V, condition A) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 13.78 min; HPLC (C18V, condition B) P<sub>HPLC</sub> 100%, *t*<sub>R</sub> 18.63 min. MS (FAB) *m/z* 707 (MH)<sup>+</sup>. Anal. calcd (C<sub>20</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>6</sub>O<sub>6</sub>Pt · 3H<sub>2</sub>O) C, H, N.

**Elemental analyses of the four complexes 13<sub>a-c</sub> and 20:**

Compound	Anal. (%)	calc. C	calc. H	calc. N	found C	found H	found N
<b>13a</b> C <sub>17</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>6</sub> O <sub>6</sub> Pt · 2 H <sub>2</sub> O		28.91	3.42	11.90	28.50	3.19	11.49
<b>13b</b> C <sub>22</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>6</sub> O <sub>6</sub> Pt · 8 H <sub>2</sub> O		30.08	4.59	9.57	29.58	3.01	9.04
<b>13c</b> C <sub>22</sub> H <sub>24</sub> Cl <sub>2</sub> N <sub>6</sub> O <sub>6</sub> Pt · 3.5 H <sub>2</sub> O		33.13	3.92	10.54	32.45	3.42	10.37
<b>20</b> C <sub>20</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>6</sub> O <sub>6</sub> Pt · 3 H <sub>2</sub> O		31.59	3.45	11.05	31.40	3.13	10.94