Supporting Information for :

Water soluble PDCA derivatives for selective Ln(III)/An(III) and Am(III)/Cm(III) separation

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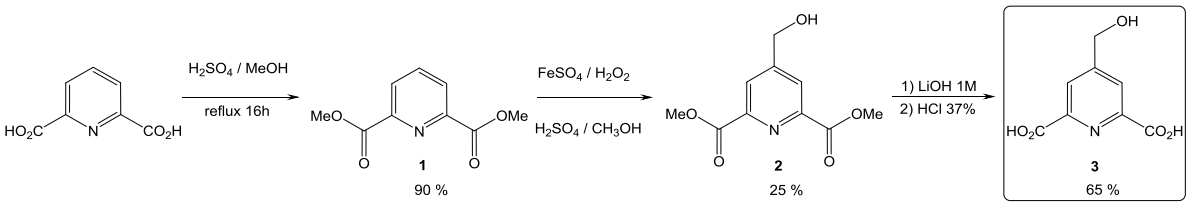
- **Chemicals and Identification Techniques**

Chemicals (analytically Pure) were purchased from Sigma-Aldrich or Acros and were used without further purification. Reactions were monitored by Thin layer chromatography (Merck TLC Silica Gel 60 F_{254}) using different revelatory system, Si 60 silica gel 40-63µm (Merck) was used for column chromatograph.

NMR analyses were performed on DRX-300 spectrometer (^{1}H : 300 MHz ; ^{13}C : 75 MHz). Displacements are reported in ppm using internal reference of the solvent ($CDCl_3$: 7.26 ppm ^{1}H, D_2O: 4.79 ppm ^{1}H, $DMSO_{d6}$: 2.50 ppm ^{1}H; $CDCl_3$: 77.16 ppm ^{13}C).

- **Synthetic Procedures & Characterizations**



Dimethyl pyridine-2,6-dicarboxylate (1):

Dimethyl 2,6-pyridinedicarboxylate was synthesized using an adapted literature protocol.[1] Concentrate sulphuric acid (97%, 900 µL) was added dropwise to a suspension of 5.2 g (31 mmol) of pyridine-2,6-dicarboxylic acid in anhydrous methanol (20 mL). The reaction mixture was stirred under reflux for 16 h. After return to room temperature the solvent was evaporated leading a white solid. Saturated $NaHCO_3$ solution was added until neutralization occurred, the solution was extracted with dichloromethane (CH_2Cl_2 2 x 150 mL) and the organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the desired product (dimethyl 2,6-pyridinedicarboxylate, **1**) as a white solid (5.3 g, 90%).

^{1}H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 8.25 (d, J = 7.3 Hz, $2H_{ar}$) ; 7.97 (t, J = 7.3 Hz, 1H) ; 3.96 (s, 6H, C*H*$_3$)

Dimethyl 4-(Hydroxymethyl)pyridine-2,6-dicarboxylate (2):

Dimethyl 4-(Hydroxymethyl)pyridine-2,6-dicarboxylate was synthesized using an adapted literature protocol.[2,3]

A solution of H_2SO_4 (30% aqueous solution, 70 mL) and methanol (30 mL) was added to 5.1 g (26 mmol) of **1**.

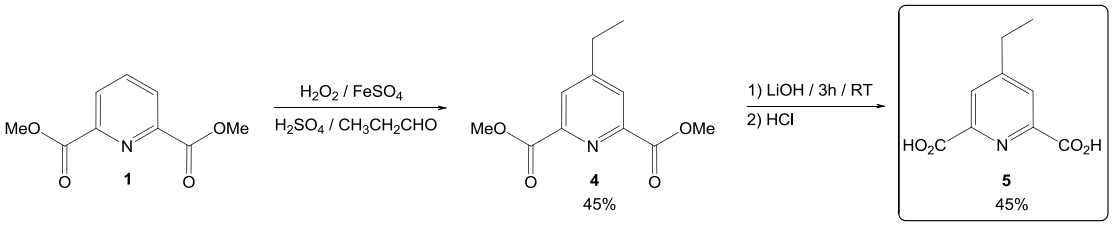
The resulting suspension was cooled (-10°C) using an ice bath, 50 mL of an aqueous solution containing 7.23 g of $FeSO_4 \cdot 7H_2O$ (26 mmol) and H_2O_2 (30% aqueous solution, 40 mL, 350 mmol) were added dropwise simultaneously to the mixture over a period of one hour. After the addition was complete, the solution was stirred for an additional 15 min at room temperature. Saturated aq. K_2CO_3 (50 mL) was added until the solution reached to pH 2. The mixture was extracted with ethyl acetate (2 x 100 mL), the combined extracts were dried over sodium sulphate, filtered and evaporated under vacuum to yield a beige solid. This residue was purified by flash chromatography (CH_2Cl_2 / MeOH: 96 / 4) to yield the desired compound **2** as a white solid (0.6 g, 20%).

^{1}H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 8.34 (s, 2H, H_{ar}); 4.93 (s, 2H, C*H*$_2$OH) ; 4,04 (s, 6H, C*H*$_3$)

4-(Hydroxymethyl)pyridine-2,6-carboxylic acid (3):

A LiOH solution (1 M, 10 mL) was added to the diester **2** (633 mg, 2.8 mmol), the resulting solution was stirred at room temperature for 3 h. HCl (37% aqueous solution) was added until the solution reached to pH 2 whereupon the resulting suspension was filtered and washed with water (2 x 3 mL). The white solid **3** was dried under *vacuum* at 40°C for 6h (436 mg, 65%).

^{1}H (DMSO$_{d6}$, 300 MHz, 298K), δ (ppm) : 8.10 (s, 2H$_{ar}$) ; 4.68 (s, 2H, C*H*$_2$OH).



Dimethyl 4-(ethyl)pyridine-2,6-dicarboxylate (4):

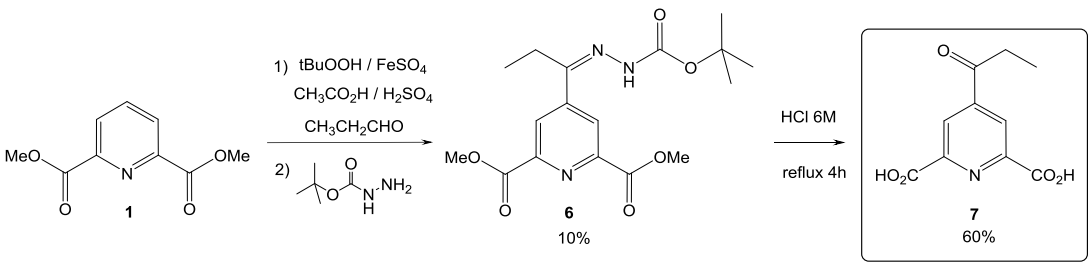
Propanal (1.12 mL, 15.3 mmol) was added dropwise to a suspension of **1** (1 g, 5.12 mmol) in H_2SO_4 (30% aqueous solution, 31 mL). The resulting solution was cooled (0°C) using an ice bath, H_2O_2 (30% aqueous solution, 1 mL, 10 mmol) and 2 mL of an aqueous solution containing 570 mg of $FeSO_4 \cdot 7H_2O$ (2 mmol) were added dropwise simultaneously to the mixture over a period of 15 min. After the addition was complete, the solution was maintained at 0°C and stirred for an additional 15 min. at room temperature. Saturated aq. K_2CO_3 (20 mL) was added until the solution reached to pH 2. The mixture was extracted with ethyl acetate (2 x 50 mL), the combined extracts were dried over sodium sulphate, filtered and evaporated under *vacuum* to yield orange oil which crystallise after few minutes. This residue was purified by flash chromatography (Cyclohexane / AcOEt: 1 / 1) to yield the desired compound **4** as a yellow solid (550 mg, 45%).

^{1}H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 8.17 (s, 2H, H$_{ar}$) ; 4.03(s, 6H, CO_2CH_3) ; 2.84 (q, J = 7.7 Hz, 2H, CH_2CH_3); 1.34 (t, J = 7.7 Hz, 3H, CH_2CH_3)

4-(ethyl)pyridine-2,6-carboxylic acid (5):

A LiOH solution (1 M, 10 mL) was added to the diester **4** (817 mg, 3.7 mmol), the resulting solution was stirred at room temperature for 4 h. HCl (37% aqueous solution) was added until the solution reached to pH 2 whereupon the resulting suspension was filtered and washed with water (2 x 3 mL). The white solid **5** was dried under *vacuum* at 40°C for 3h (320 mg, 45%).

^{1}H ($DMSO_{d6}$, 300 MHz, 298K), δ (ppm) : 8.11 (s, 2H, H_{ar}) ; 2.81 (q, J = 7.53 Hz, 2H, CH_2CH_3) ; 1.23 (t, J = 7.53 Hz, 3H, CH_2CH_3)



Dimethyl 4-(tert-Butoxycarbonyl-hydrazono)-propyl)pyridine-2,6-dicarboxylate (6):

A mixture of **1** (4 g, 20 mmol), $FeSO_4.7H_2O$ (5.56 g, 20 mmol), water (3.2 mL), H_2SO_4 (97%, 3.2 mL) and propanal (2.9 mL, 40 mmol) were suspended in acetic acid (4.8 mL). The resulting mixture was cooled (0°C) using an ice bath and a solution of tBuOOH (70%, 5.48 mL, 40 mmol) in acetic acid (2.4 mL) was added dropwise to the mixture over a period of 5 min. After the addition was complete, the solution was stirred for an additional 15 min. at room temperature and water (40 mL) was then added. The mixture was extracted with diethyl ether (2 x 50 mL), the combined extracts were dried over sodium sulphate, filtered and evaporated under *vacuum* to yield yellow oil which crystallise after few minutes.

This redidue was dissolved in THF (6 mL) and added dropwise to a solution of *tert*-butyl carbazate (3.3 g, 25 mmol) in THF (3.5 mL). A white precipitate was obtained after 2h, the

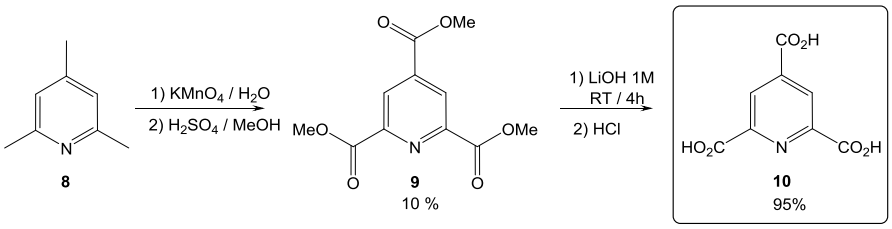
mixture was left without stirring overnight. The precipitate was filtered and the solid recrystallized in ethanol (25 mL) to give the desired compound **6** (730 mg, 10%).

^{1}H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 8.64 (s, 2H, H_{ar}) ; 8.12 (s, 1H, N*H*) ; 4.04 (s, 6H, CO_2CH_3) ; 2.73 (q, J = 7.72 Hz, 2H, CH_2CH_3); 1.59 (s, 9H, $OC(CH_3)_3$) ; 1.24 (t, J = 7.7 Hz, 3H, CH_2CH_3)

4-(propionyl)pyridine-2,6-carboxylic acid (7):

Compound **6** (300 mg, 0.82 mmol) was refluxed in HCl (6M, 3 mL) for 3h. After the return to room temperature the precipitate formed was filtered and washed with water. The solid **7** was dried under *vacuum* at 40°C for 4h (150 mg, 60%).

^{1}H ($DMSO_{d6}$, 300 MHz, 298K), δ (ppm) : 8.53 (s, 2H, H_{ar}) ; 3.21 (q, J = 6.96 Hz, 2H, CH_2CH_3) ; 1.11 (t, J = 6.96 Hz, 3H, CH_2CH_3)



Trimethyl pyridine-2,4,6-tricarboxylate (9):

2,4,6-Pyridinetricarboxylic acid was synthesized by oxidization of 2,4,6-trimethylpyridine with potassium permanganate using an adapted literature protocol.[4]

In a typical experiment, to a mixture of 2,4,6-trimethylpyridine (2 mL, 15 mmol) and 30 ml water, solid $KMnO_4$ (19 g, 120 mmol) was added in 3 equal portions in 30 min under stirring at 50°C. After the addition was complete, the mixture was allowed to stir for an additional 18h at 50°C. The resulting suspension was filtered and washed twice with hot water; the

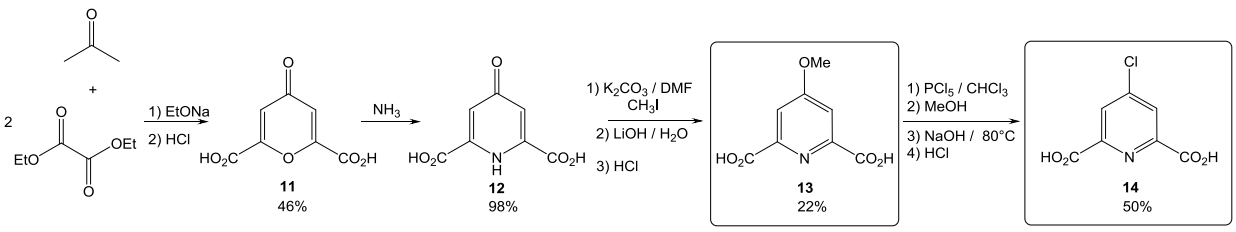
filtrate was acidified with conc. HCl to pH 2 and concentrated under *vacuum* to give a white solid. The white solid was dried under *vacuum* at 40°C for 6h, and then this crude product was suspended in a solution of H_2SO_4 (97%, 500 µL) in methanol (15 mL), the mixture was refluxed for 18h. After evaporation of the solvent a white solid was obtained and saturated aq. $NaHCO_3$ was added until the solution reached to pH 7. The mixture was extracted with dichloromethane, the combined extracts were washed with brine then dried over sodium sulphate, filtered and evaporated under *vacuum* to a white solid. The solid was recrystallized in toluene to give the desired compound **9** (350 mg, 10%).

^1H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 8.83 (s, 2H, H_{ar}) ; 4.07 (s, 6H, N=C(CO_2CH_3)$_2$); 4.04 (s, 3H, CO_2CH_3)

Pyridine-2,4,6-tricarboxylic acid (10):

A LiOH solution (1 M, 10 mL) was added to the triester **9** (625mg, 2.5 mmol), the resulting solution was stirred at room temperature for 4 h. HCl (37% aqueous solution) was added until the solution reached to pH 2. The mixture was cooled to 0°C; the resulting solid was filtered and dried under *vacuum* at 40°C for 5h to give the desired compound **10** as a white solid (500 mg, 95%).

^1H ($DMSO_{d6}$, 300 MHz, 298K), δ (ppm) : 8.49 (s, 2H, H_{ar})



Chelidonic acid (4-oxo-4H-pyran-2,6-dicarboxylic acid) (11):

Chelidonic acid was synthesized using an adapted literature protocol.[5]

In a typical experiment, EtONa (69.4 g, 1.02 mol) was suspended in ethanol (300 mL). After 45 min at 60°C, a solution of dry acetone (29 g, 38 ml, 0.5 mol) and diethyl oxalate (155 g, 144 ml, 1.06 mol) was added over a period of 1h. After the addition was complete, the solution was maintained at 60°C and stirred for an additional 14 h. Then 230 mL of HCl (37% aqueous solution) and 100 ml of water were added and the mixture was stirred for one day. After 24h, about half of aqueous ethanol was removed under reduced pressure then 300 mL of water and 60 mL of HCl (37% aqueous solution) were added to this mixture and stirring was continued for 20h at 50°C. The resulting solid was filtered off, washed first with water then with acetone before recrystallization from boiling water using charcoal. The filtrate was left at room temperature until formation of crystals. The white crystals were collected and dried under *vacuum* to give the desired compound 11 (42.3 g, 46%).

^{1}H ($DMSO_{d6}$, 300 MHz, 298K), δ (ppm) : 6.98 (s, 2H, H_{ar})

Chelidamic acid (1,4-dihidro-4-oxo-2,6-pyridinedicarboxylic acid) (12):

Chelidamic acid was synthesized using an adapted literature protocol.[5]

In a typical experiment, 425 mL of NH_3 (30% aqueous solution) was added dropwise at 0°C to **11** (41.8 g, 0.21 mol) over a period of 1h.. After the addition was complete, the resulting suspension was stirred at room temperature for 48h. The excess of aqueous ammonia solution was removed under reduced pressure and the residue was refluxed for 15 min with 50 ml of water using charcoal. After filtration, the hot filtrate was collected and after return to room temperature acidified with HCl (37% aqueous solution) until the solution reached to pH 1. The resulting white solid was filtered off, washed several times with cold water and dried under *vacuum* for 16h. The desired compound 12 was obtained as a white solid (42 g, 98%).

^{1}H (D_2O, NaOD, 300 MHz, 298K), δ (ppm) : 6.97 (s, 2H, H_{ar}).

^{13}C (D_2O, NaOD, 300 MHz, 298K), δ (ppm) :176,1 (*C*=O) ; 174,9 (*C*O_2H) ; 154,5 (C- *C*O_2H) ; 116,8 (*C*-C=O).

4-methoxy-pyridine-2,6-dicarboxylic acid (13):

Chelidamic acid **12** (2.62 g,14.3.mmol) was suspended in dry DMF (105 mL) under nitrogen atmosphere. Solid K_2CO_3 (13.04 g, 94.5.mmol) and CH_3I (5.88 mL, 94.5.mmol) were added to the mixture and heated at 35°C. After 24 h, the mixture was filtered over celite and washed with CH_2Cl_2. The filtrate was concentrated and CH_2Cl_2 (150 mL) and water (200 mL) were added to the residue. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL), the combined extracts were washed with HCl (1 M), brine and then dried over sodium sulphate, filtered and evaporated under *vacuum* to yield a yellow powder. The solid was suspended in a solution of LiOH (1g) in water (20 mL) and the mixture was stirred at room temperature for 3h30.The mixture was filtered and the filtrate was acidified with HCl (37% aqueous solution) until the solution reached to pH 1. The resulting white solid was filtered off, and dried under *vacuum* for 4h. The desired compound **13** was obtained as a white solid (623 mg, 22%).

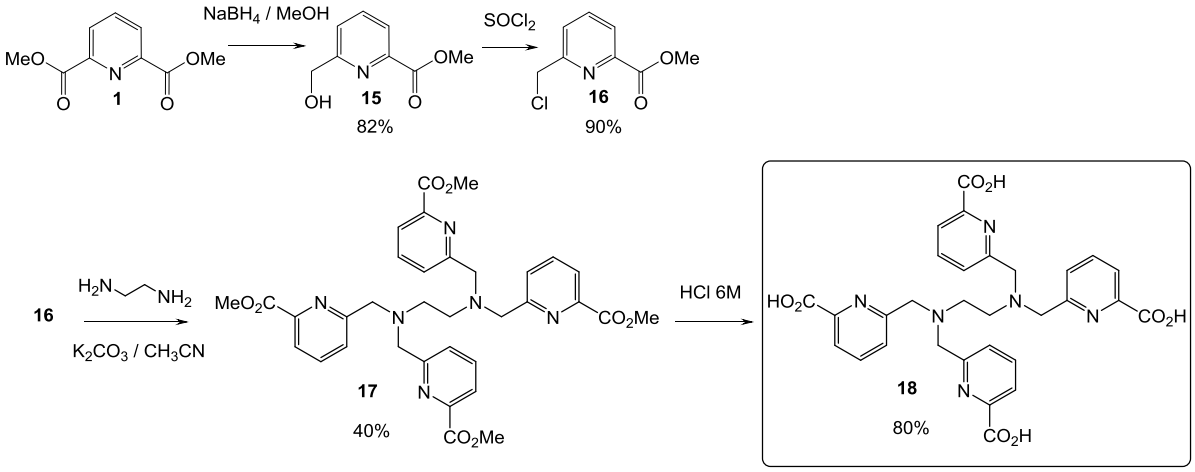
^{1}H ($DMSO_{d6}$, 300 MHz, 298K), δ (ppm) : 7,72 (s, 2H, H_{ar}) ; 3,97 (s, 3H, OC*H*$_3$)

4-chloro-pyridine-2,6-dicarboxylic acid (14):

Compound **13** (2.5 g, 12.4.mmol) was suspended in $CHCl_3$. (30 mL), then PCl_5 (10.6 g, 51 mmol) was added to the mixture. The mixture was refluxed for 3 days, after cooling to 0°C, methanol (20 mL) was slowly added until the end of the gas evolution. The solution was stirred for 2h at room temperature and then concentrated. Saturated aq. $NaHCO_3$ was added until the solution reached to pH 7. The mixture was filtered, the solid residue was kept and the filtrate was extracted with AcOEt (200 mL). The organic phase was dried over sodium

sulphate, filtered and evaporated under *vacuum*. The previous solid residue was added to the concentrated organic phase and dissolved with AcOEt. The solution was evaporated under *vacuum* to yield a white powder. The solid was suspended in a solution of NaOH (0.1 M, 20 mL) and heated at 80°C for 3h. The mixture was cooled at 0°C and then acidified with HCl (2 M) until the solution reached to pH 2. The resulting white solid was filtered off, washed several times with water and dried under *vacuum* at 40°C for 5h. The desired compound **14** was obtained as a white solid (1.21 g, 50%).

^{1}H (DMSO$_{d6}$, 300 MHz, 298K), δ (ppm) : 8.18 (s, 2H, H$_{ar}$)



Methyl (6-hydroxymethyl)-pyridine-2-carboxylate (15):

Methyl (6-hydroxymethyl)-pyridine-2-carboxylate was synthesized using an adapted literature protocol.[6]

$NaBH_4$ (590 mg, 15.6 mmol) was added in 3 equal portions over a period of 30 min to a stirred solution of dimethylpyridine-2,6-dicarboxylate **1** (2 g, 10 mmol) in MeOH (90 mL) at 0 °C. The mixture was stirred at room temperature for 24 h. The mixture was then acidified with HCl (37% aqueous solution) until the solution reached to pH 3 and then concentrated.

The resulting solid was suspended in water (100 mL) and saturated aq. $NaHCO_3$ was added until the solution reached to pH 7.The resulting aqueous solution was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over sodium sulphate, filtered and evaporated under *vacuum* to give **15** as a white solid (1.41 g, 82%).

^1H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 8.04 (dt, J = 7.7 Hz, J = 0.6 Hz, 1H, H_{ar}) ; 7,86 (t, J = 7.7 Hz, 1H, H_{ar}) ; 7.57 (dt, J = 7.7 Hz, J = 0.6 Hz, 1H, H_{ar}) ; 4.88 (s, 2H, C*H*$_2$OH) ; 3.99 (s, 6H, C*H*$_3$)

^{13}C, DEPT 135, ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 138.1 (C_{ar}) ; 124.5 (C_{ar}) ; 124.2 (C_{ar}) ; 65.1 (*C*H_2OH) ; 53.3 (*C*H_3)

Methyl (6-chloromethyl)-pyridine-2-carboxylate (16):

Methyl (6-chloromethyl)-pyridine-2-carboxylate was synthesized using an adapted literature protocol.[6]

$SOCl_2$ (4.5 mL) was added over **15** (2.25 g, 12.8 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h, and the excess of $SOCl_2$ was removed under reduced pressure, then MeOH was added until the end of the gas evolution. After evaporation, the residue was dissolved in toluene (100 mL), and this organic solution was washed with a cold solution of $NaHCO_3$ (10% aqueous solution, 2 x 50 mL). The aqueous phase was extracted with toluene (100 mL), the combined extracts were washed with water, brine and then dried over sodium sulphate, filtered and evaporated under *vacuum* to yield **16** as yellow oil which crystallise after few minutes (2.32 g, 90%).

^1H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 8.10 (d, J = 7.71 Hz, 1H, H_{ar}) ; 7.92 (t, J = 7.71 Hz, 1H, Ha_r) ; 7,75 (d, J = 7.71 Hz, 1H, H_{ar}) ; 4.79 (s, 2H, C*H*$_2$Cl) ; 4.03 (s, 6H, C*H*$_3$)

^{13}C, DEPT 135, ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 138.6 (C_{ar}) ; 126.6 (C_{ar}) ; 124.9 (C_{ar}) ; 53.5 (*C*H_3) ; 40.7 (*C*H_2Cl)

N,N,N'N'-tetrakis[(6-carboxymethyl pyridin-2-yl)methyl]-ethylenediamine (17):

N,N,N'N'-tetrakis[(6-carboxymethyl pyridin-2-yl)methyl]-ethylenediamine was synthesized using an adapted literature protocol.[7]

Compound **16** (2 g, 10.8 mmol) was dissolved in anhydrous acetonitrile (36 mL) under argon atmosphere, then freshly distilled ethylenediamine (175 µL, 2.6 mmol) and anhydrous K_2CO_3 (1.49 g, 10.8 mmol) were successively added to the solution under argon atmosphere. The mixture was refluxed for 14 hours. After filtration and evaporation of the solvent a yellow oil was obtained which crystallised after few minutes. The residue was dissolved in dichloromethane (100mL). This organic solution was washed with water (2 x 40 mL) and then dried over sodium sulphate, filtered and evaporated under *vacuum* to yield orange solid. The solid was recrystallized in isopropanol to give the desired compound **17** as a beige solid (700 mg, 40%).

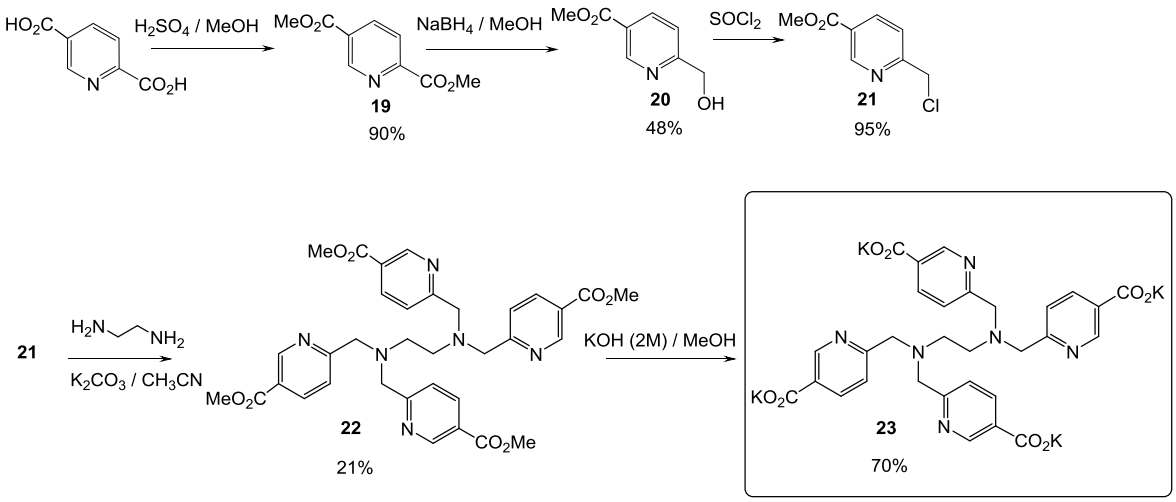
^{1}H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 7.97 (dd, J = 6.96 Hz, J = 1.68 Hz, 1H, H_{ar}) ; 7.71 (m, 2H, H_{ar}) ; 3.98 (s, 12H, C*H*$_3$) ; 3.89 (s, 8H, PyC*H*$_2$N) ; 2.78 (s, 4H, NC*H*$_2$C*H*$_2$N)

^{13}C, DEPT 135, ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 137.8 (C_{ar}) ; 126.3 (C_{ar}) ; 124.0 (C_{ar}) ; 60.9 (N*C*H$_2$Py) ; 53.3 (*C*H$_3$) ; 52.9 (NCH$_2$*C*H$_2$)

N,N,N'N'-tetrakis[(6-carboxyl pyridin-2-yl)methyl]-ethylenediamine "h4tpaen" (18):

Compound **17** (825 mg, 1.26 mmol) was suspended in an aqueous solution of HCl (6M, 4.5 mL). The mixture was refluxed for 14h, the solid was filtered, washed with water (2 x 2 mL) and dried under *vacuum* at room temperature for 14h to give **18** as a beige solid (690 mg, 80%).

^{1}H ($DMSO_{d6}$, 300 MHz, 298K), δ (ppm) : 7.91 (m, 2H, H_{ar}) ; 7.67 (m, 1H, H_{ar}) ; 4.51 (s, 8H, PyC*H*$_2$N) ; 3.70 (s, 4H, NC*H*$_2$C*H*$_2$N)



Dimethyl pyridine-2,5-dicarboxylate (19):

Dimethyl 2,5-pyridinedicarboxylate was synthesized using the same procedure used for **1**.

The desired compound **19** was obtained as a white solid (5.3 g, 90%).

^{1}H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 9.24 (d, J = 1.89 Hz, $1H_{ar}$) ; 8.38 (dd, J=8.2 Hz, 1H, H_{ar}) ;8.15 (d, J = 8.2 Hz, $1H_{ar}$) ; 3.97 (s, 3H, C*H*$_3$) ; 3.92 (s, 3H, C*H*$_3$)

Methyl 5-(hydroxymethyl)pyridine-2-carboxylate (20):

Methyl (5-hydroxymethyl)-pyridine-2-carboxylate was synthesized using an adapted literature protocol.[8]

A mixture of **19** (5.12 g, 26.3 mmol), in 1:2 THF:EtOH (165 mL), and calcium chloride (11.67 g, 0.105 mol) was cooled at 0 °C. Then $NaBH_4$ (2.48 g, 65.6 mmol) was added slowly and the reaction was maintained at 0 °C for 8 h. The mixture was then acidified with HCl (37% aqueous solution) until the solution reached to pH 3 and then concentrated. The residue was suspended in water (50 mL) and saturated aq. $NaHCO_3$ was added until the solution reached to pH 7.The resulting aqueous solution was extracted with CH_2Cl_2 (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2x 50 mL), the combined organic extracts were

dried over sodium sulphate, filtered and evaporated under *vacuum* to give **15** as a yellow solid. (2.12 g, 48%)

^{1}H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 9.10 (d, J = 1.89 Hz, 1H, H_{ar}) ; 8.26 (dd, J = 8.28 Hz, J = 1.89 Hz, 1H, H_{ar}) ; 7.40 (d, J = 8.28 Hz, 1H, H_{ar}); 4.81 (s, 2H, C*H*$_2$OH) ; 4.34 (s, 1H, OH) ; 3.93 (s, 3H, C*H*$_3$)

^{13}C ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 166.0 (*C*=O) ; 164.5 (CH_2*C*N) ; 150.3 (C*C*N) ; 138.2 (C*H*CC(O)) ; 125.2 (*C*C(O)) ; 120.5 (CH_2C*C*H) ; 64.8 (*C*H_2OH) ; 52.8 (O*C*H_3)

Methyl 5-(chloromethyl)pyridine-2-carboxylate (21):

Methyl 5-(chloromethyl)pyridine-2-carboxylate was synthesized using the same procedure used for **16**.The desired compound **21** was obtained as yellow oil which crystallise after few minutes (2.13 g, 95%).

^{1}H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 9.18 (d, J = 2.25 Hz, 1H, H_{ar}) ; 8.35 (dd, J = 8.10 Hz, J = 2.25 Hz, 1H, H_{ar}) ; 7.60 (d, J = 8.10 Hz, 1H, H_{ar}); 4.73 (s, 2H, C*H*$_2$Cl) ; 3.98 (s, 3H, C*H*$_3$)

^{13}C, DEPT 135, ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 166.4 (*C*=O) ; 164.7 (CH_2*C*N) ; 150.9 (C*C*N) ; 138.6 (C*H*CC(O)) ; 122.7 (CH_2C*C*H) ; 52.9 (O*C*H_3) ; 46.5 (*C*H_2Cl)

N,N,N'N'-tetrakis[(5-carboxymethyl pyridin-2-yl)methyl]-ethylenediamine (22):

N,N,N'N'-tetrakis[(5-carboxymethyl pyridin-2-yl)methyl]-ethylenediamine was synthesized in the same way as **17** with anhydrous DMF instead of anhydrous acetonitrile. The desired compound **22** was obtained as an orange-brown solid (650 mg, 21%).

^{1}H ($CDCl_3$, 300 MHz, 298K), δ (ppm) : 9.10(s, 1H, H_{ar}) ; 8.20 (d, J = 8.10 Hz, 1H, H_{ar}) ; 7.51 (d, J = 8.10 Hz, 1H, H_{ar}); 3.97 (s, 12H, C*H*$_3$) ; 3.86 (s, 8H, PyC*H*$_2$N) ; 2,80 (s, 4H, NC*H*$_2$C*H*$_2$)

N,N,N'N'-tetrakis[(5-carboxyl pyridin-2-yl)methyl]-ethylenediamine "h5tpaen" (23):

Compound **22** (150 mg, 1.26 mmol) was suspended in a methanolic solution of KOH (2M, 2.5 mL). The mixture was refluxed for 14h, the resulting homogeneous solution was cooled to room temperature and a precipitated was formed. The solid was filtered, washed with methanol and dried under *vacuum* at room temperature for 4h to give **23** in potassium salt form a a yellow solid (98 mg, 70%).

^{1}H (D_2O, 300 MHz, 298K), δ (ppm) : 8.66 (d, J = 2.28 Hz, 1H, H_{ar}) ; 7.98 (dd, J = 8.10 Hz, J = 2.28 Hz, 1H, H_{ar}) ; 7.31 (d, J = 8.10 Hz, 1H, H_{ar}) ; 3.67 (s, 8H, PyCH_2N) ; 2.63 (s, 4H, NCH_2CH_2)

REFERENCES

1. Schmuck, C.; Machon, U., Amino Acid Binding by 2-(Guanidiniocarbonyl)pyridines in Aqueous Solvents: A Comparative Binding Study Correlating Complex Stability with Stereoelectronic Factors. *Chemistry – A European Journal* **2005,** *11* (4), 1109-1118; Chrystal, E. J. T.; Couper, L.; Robins, D. J., Synthesis of a key intermediate in the diaminopimelate pathway to L-Lysine: 2,3,4,5-tetrahydrodipicolinic acid. *Tetrahedron* **1995,** *51* (37), 10241-10252.

2. Shelkov, R.; Melman, A., Free-Radical Approach to 4-Substituted Dipicolinates. *European Journal of Organic Chemistry* **2005,** *2005* (7), 1397-1401.

3. Rui-ren, T.; Qiang, Z.; Zi-er, Y.; Yi-ming, L., Synthesis of Novel Derivatives of Pyridine-2,6-dicarboxylic Acid. *Synthetic Communications* **2006,** *36* (14), 2027-2034.

4. Syper, L.; Kloc, K.; Mz.xl; lochowski, J., Synthesis of ubiquinone and menaquinone analogues by oxidative demethylation of alkenylhydroquinone ethers with argentic oxide or ceric ammonium nitrat. *Tetrahedron* **1980,** *36* (1), 123-129.

5. Howáth, G.; Rusa, C.; Köntös, Z.; Gerencsér, J.; Huszthy, P., A new Efficient Method for the Preparation of 2,6-Pyridinedihiethyl Ditosylates from Dimethyl 2,60-Pyridinedicarboxylates. *Synthetic Communications* **1999,** *29* (21), 3719-3731.

6. Fornasier, R.; Milani, D.; Scrimin, P.; Tonellato, U., Functional micellar catalysis. Part 8. Catalysis of the hydrolysis of p-nitrophenyl picolinate by metal-chelating micelles containing copper(II) or zinc(II). *Journal of the Chemical Society, Perkin Transactions 2* **1986,** (2), 233-237; Mato-Iglesias, M.; Roca-Sabio, A. n.; Pálinkás, Z. n.; Esteban-Gómez, D.; Platas-Iglesias, C.; Tóth, E. v.; de Blas, A. s.; Rodríguez-Blas, T., Lanthanide Complexes Based on a 1,7-Diaza-12-crown-4 Platform Containing Picolinate Pendants: A New Structural Entry for the Design of Magnetic Resonance Imaging Contrast Agents. *Inorganic Chemistry* **2008,** *47* (17), 7840-7851.

7. Chatterton, N.; Bretonniere, Y.; Pecaut, J.; Mazzanti, M., An efficient design for the rigid assembly of four bidentate chromophores in water-stable highly luminescent lanthanide complexes. *Angewandte Chemie-International Edition* **2005,** *44* (46), 7595-7598.

8. Jabre, N. D.; Respondek, T.; Ulku, S. A.; Korostelova, N.; Kodanko, J. J., A Divergent Strategy for Attaching Polypyridyl Ligands to Peptides. *The Journal of Organic Chemistry* **2010,** *75* (3), 650-659.