

Supporting Information for

Estrogen Receptor Dependent Inhibitors of NF- κ B Transcriptional Activation-1: Synthesis and Biological Evaluation of Substituted 2-Cyanopropanoic Acid Derivatives: Pathway Selective Inhibitors of NF- κ B, a Potential Treatment for Rheumatoid Arthritis

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Synthesis and Characterization of Compounds (1-21)

All NMR's were run at 400MHz unless indicated otherwise.

Ethyl 2-cyano-3,3-di-1-naphthylpropanoate (1) was prepared according to the method of Latif et al(11).

mp 189 °C (lit 188)

MS (APCI) *m/z* 380 (M+H);

2-Cyano-3,3-di(1-naphthyl)propanoic acid (2)

Ethyl 2-cyano-3,3-di-1-naphthylpropanoate (1.5g, 4mmol) was dissolved in ethanol (100mL) and 1N NaOH (50mL) was added. The solution was stirred overnight. Isopropyl acetate (100mL) was added followed by 2N HCl (50mL). The organic layer was separated and the aqueous layer was extracted with isopropyl acetate. The pooled organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo to yield a yellow foam. Recrystallization from ethyl acetate hexanes provided 1.3g (3.7mmol) of the acid as a white solid. HPLC analysis showed the material to be 96.6% pure. mp 182-184 °C.

MS (ESI) *m/z* 350;

Anal. Calcd for C₂₄H₁₇NO₂: C, 82.03; H, 4.88; N, 3.99. Found: C, 79.79; H, 5.07; N, 3.68.

2-Cyano-3,3-di(1-naphthyl)propanamide (3)

Ethyl 2-cyano-3,3-di-1-naphthylpropanoate (250mg, 0.66mmol) is dissolved in THF (2mL) in a Carius tube. To this was added concentrated NH₄OH (5mL). The tube was stirred at room temperature for 24 hours and then was heated at 115° for 18 hours. The sample was taken up in CHCl₃ (20 mL) and was washed with saturated brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Chromatography yielded 38 mg of the amide as a white powder.

MS (APCI) *m/z* 368 (M+NH₄⁺);

Anal. Calcd for C₂₄H₁₈N₂O: C, 82.26; H, 5.18; N, 7.99. Found: C, 80.27; H, 5.69; N, 7.11.

Ethyl 2-cyano-2-methyl-3,3-di(1-naphthyl)propanoate (4)

A solution of 2-cyano-3,3-di-naphthalen-1-yl-propionic acid ethyl ester was dissolved in THF (3mL) and treated with sodium bis-trimethylsilyl amide (39 μ l, 1M in THF) at room temperature. After 5 minutes methyl iodide was added (9 μ l) and the reaction was stirred for 4 hours. The reaction was quenched with 1N HCl (3ml) and was diluted with isopropyl acetate (3mL). The organic layer was washed with bicarbonate then brine; dried over Na₂SO₄, filtered and evaporated to yield the title compound as a crystalline material. mp 186-188 °C;

¹H NMR (400 MHz, DMSO-D6) δ 0.81 (t, $J=7.08$ Hz, 3 H) 1.66 (s, 3 H) 4.01 (m, 2 H) 6.19 (s, 1 H) 7.32 (td, $J=7.69$, 1.22 Hz, 1 H) 7.43 (q, $J=7.57$ Hz, 2 H) 7.57 (d, $J=7.32$ Hz, 1 H) 7.62 (td, $J=7.69$, 3.90 Hz, 2 H) 7.77 (td, $J=7.69$, 0.98 Hz, 1 H) 7.89 (m, 4 H) 8.01 (d, $J=7.32$ Hz, 1 H) 8.10 (d, $J=7.08$ Hz, 1 H) 8.76 (d, $J=8.54$ Hz, 1 H)

MS (EI) m/z 393;

Anal. Calcd for C₂₇H₂₃NO₂: C, 82.42; H, 5.89; N, 3.56. Found: C, 82.20; H, 5.84; N, 3.52.

Anal. (C₂₇H₂₃NO₂) C, H, N.

Ethyl 2-cyano-3-(1-naphthyl)-3-(2-nitrophenyl)propanoate (5)

A solution of 2-cyano-3-(2-nitro-phenyl)-acrylic acid ethyl ester (492mg, 2mmol) in THF (20mL) was treated dropwise with 1-naphthyl magnesium bromide (9.6mL, 2.4mmol) at room temperature. The reaction was stirred for 3 hours, quenched with 1N HCl and diluted with ethyl acetate (40mL). The organic layer was separated and was washed sequentially with saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over Na₂SO₄, filtered and was concentrated in vacuo. Chromatography over silica gel (20% ethyl acetate/hexanes) yielded 221 mg of the title compound as a viscous oil.

MS (APCI) m/z 375;

Anal. Calcd for C₂₂H₁₈N₂O₄: C, 70.58; H, 4.85; N, 7.48. Found: C, 69.19; H, 4.87; N, 6.97.

Ethyl 2-cyano-3-(2-methoxyphenyl)-3-(1-naphthyl)propanoate (6)

The title compound was prepared according to the procedure for (5) using 2-cyano-3-naphthalen-1-yl-acrylic acid ethyl ester and 2-methoxyphenyl magnesium bromide as starting materials. This provided the title compound as a low melting solid which NMR shows to be a 50:50 mixture of diastereomers

¹H NMR (400 MHz, DMSO-D6) δ 0.88 (m, 3 H) 3.84 (s, 1.5 H) 3.94 (s, 1.5 H) 3.99 (m, 2 H) 5.15 (d, $J=8.30$ Hz, 0.5 H) 5.25 (d, $J=9.27$ Hz, 0.5 H) 5.84 (d, $J=8.30$ Hz, 0.5 H) 5.88 (d, $J=9.52$ Hz, 0.5 H) 6.78 (td, $J=7.44$, 0.98 Hz, 0.5 H) 6.88 (td, $J=7.38$, 0.85 Hz, 0.5 H) 6.95 (dd, $J=7.69$, 1.59 Hz, 0.5 H) 7.05 (t, $J=7.69$ Hz, 1 H) 7.23 (ddd, $J=15.68$, 7.99, 1.71 Hz, 1 H) 7.35 (dd, $J=7.81$, 1.71 Hz, 0.5 H) 7.52 (m, 3 H) 7.60 (d, $J=7.81$ Hz, 0.5 H) 7.65 (d, $J=7.08$ Hz, 0.5 H) 7.83 (d, $J=8.30$ Hz, 0.5 H) 7.90 (m, 3 H) 8.11 (d, $J=8.79$ Hz, 0.5 H)

MS (EI) m/z M+. (359);

Anal. (C₂₃H₂₁NO₃) C, H, N.

Ethyl-(RR,SS)- 2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoate (7)

A solution of 2-cyano-3-(2-methoxy-phenyl)-3-naphthalen-1-yl-propionic acid ethyl ester (205mg, 0.57mmol) in THF (10mL) is cooled in a dry ice ethanol bath. A solution of KHMDS (1.04ml, 0.68mmol, 0.66M toluene) is added dropwise. The bath is removed and the reaction is warmed to room temperature over an hour. To this is added methyl iodide (162mg, 1.14mmol) and the reaction is stirred at room temperature for 30 minutes. The reaction is quenched with 1NHCl and is diluted with ethyl acetate. The organic layer is isolated and is washed with saturated bicarbonate solution then brine. The organic layer is dried with Na₂SO₄, is filtered and evaporated to a solid. Chromatography over silica gel (20%ethyl acetate/hexane) yields the title compound as a solid. Recrystallization from MeOH yields the title compound (80mg) as white crystals. mp 134.5-135.5 °C;

¹H NMR (400 MHz, DMSO-D6) δ 0.75 (t, $J=7.08$ Hz, 3 H) 1.65 (s, 3 H) 3.98 (m, $J=17.79$, 10.65, 7.08, 3.78 Hz, 2 H) 4.05 (s, 3 H) 5.81 (s, 1 H) 6.83 (td, $J=7.50$, 1.10 Hz, 1 H) 7.16 (dt, $J=7.87$, 1.56 Hz, 1 H) 7.26 (td, $J=7.81$, 1.71 Hz, 1 H) 7.46 (m, 1 H) 7.58 (dd, $J=8.18$, 7.44 Hz, 1 H) 7.85 (d, $J=8.54$ Hz, 1 H) 7.89 (m, 1 H) 8.03 (d, $J=7.08$ Hz, 1 H)

MS (APCI) m/z [M+H]⁺ (374);

Anal. C₂₄H₂₃NO₃) C,H,N

Ethyl 2-cyano-3-(1-naphthyl)-3-(2-naphthyl)propanoate (8)

The title compound was prepared according to the procedure for (5), using 2-cyano-3-naphthalen-1-yl-acrylic acid ethyl ester and 2-naphthyl magnesium bromide. The sample is a viscous oil.

¹H NMR (400 MHz, DMSO-D6) δ 0.82 (t, $J=7.08$ Hz, 1.5 H) 0.89 (t, $J=7.08$ Hz, 1.5 H) 3.99 (m, 2 H) 5.46 (d, $J=9.76$ Hz, 0.5 H) 5.51 (d, $J=9.76$ Hz, 0.5 H) 5.70 (d, $J=9.76$ Hz, 0.5 H) 5.74 (d, $J=9.76$ Hz, 0.5 H) 7.51 (m, 5 H) 7.64 (m, 1 H) 7.83 (m, 4 H) 7.93 (m, 2 H) 8.02 (d, $J=7.08$ Hz, 0.5 H) 8.15 (d, $J=1.46$ Hz, 0.5 H) 8.25 (m, 0.5 H) 8.38 (d, $J=8.54$ Hz, 0.5 H)

MS (APCI) m/z 380 ([M+H]⁺);

Anal. C₂₆H₂₁NO₂) C, H, N

Ethyl 2-cyano-3-(3-methoxyphenyl)-3-(1-naphthyl)propanoate (9)

The title compound was prepared according to the procedure for (5), using 2-cyano-3-naphthalen-1-yl-acrylic acid ethyl ester and 3-methoxy-phenyl magnesium bromide. The sample is a viscous oil.

¹H NMR (400 MHz, DMSO-D6) δ 0.85 (t, $J=7.08$ Hz, 1.5 H) 0.90 (t, $J=7.20$ Hz, 1.5 H) 2.04 (s, 1 H) 3.66 (s, 1.5 H) 3.67 (s, 1.5 H) 3.97 (m, 2 H) 5.30 (d, $J=9.52$ Hz, 0.5 H) 5.38 (d, $J=10.01$ Hz, 0.5 H) 5.46 (d, $J=9.76$ Hz, 0.5 H) 5.50 (d, $J=9.76$ Hz, 0.5 H) 6.76 (m, 1 H) 6.89 (d, $J=8.30$ Hz, 0.5 H) 6.97 (t, $J=1.95$ Hz, 0.5 H) 7.10 (m, 1 H) 7.15 (t, $J=7.93$ Hz, 0.5 H) 7.20 (t, $J=7.93$ Hz, 0.5 H) 7.49 (m, 1.5 H) 7.57 (t, $J=7.69$ Hz, 0.5 H) 7.70 (d, $J=7.08$ Hz, 0.5 H) 7.81 (d, $J=8.05$ Hz, 0.5 H) 7.90 (m, 2 H) 8.16 (d, $J=9.52$ Hz, 0.5 H) 8.30 (d, $J=8.05$ Hz, 0.5 H)

MS (EI) m/z M⁺. (359);

Anal. calcd for C₂₃H₂₁NO₃: C:76.86 H:5.89 N:3.90 Found: C:75.45 H:5.83 N:3.58

Ethyl 2-cyano-3-(4-methylphenyl)-3-(1-naphthyl)propanoate (10)

The title compound was prepared according to the procedure for (5), using 2-cyano-3-naphthalen-1-yl-acrylic acid ethyl ester and 4-methylphenyl magnesium bromide. The sample is a viscous oil.

¹H NMR (400 MHz, DMSO-D6) δ 0.90 (dt, $J=12.45, 7.08$ Hz, 3 H) 2.06 (s, 3 H) 2.19 (s, 1.5 H) 2.22 (s, 1.5 H) 4.00 (ddd, $J=13.85, 7.02, 4.03$ Hz, 2 H) 5.28 (d, $J=9.52$ Hz, 0.5 H) 5.35 (d, $J=9.52$ Hz, 0.5 H) 5.46 (d, $J=9.76$ Hz, 0.5 H) 5.50 (d, $J=9.52$ Hz, 0.5 H) 7.09 (dd, $J=15.13, 7.81$ Hz, 2 H) 7.26 (d, $J=8.30$ Hz, 1 H) 7.41 (d, $J=8.30$ Hz, 1 H) 7.52 (m, 2.5 H) 7.70 (d, $J=6.59$ Hz, 0.5 H) 7.83 (d, $J=8.05$ Hz, 0.5 H) 7.91 (m, 1 H) 8.14 (dd, $J=5.13, 4.39$ Hz, 0.5 H) 8.26 (d, $J=8.54$ Hz, 0.5 H)

MS (EI) m/z M⁺. (343);

Anal. calcd for C₂₃H₂₁NO₂: C:80.44 H:6.16 N:4.08 Found: C:78.76 H:6.32 N:3.81.

Ethyl 2-cyano-3-(1-naphthyl)-3-phenylpropanoate (11)

A solution of 2-cyano-3-naphthalen-1-yl-acrylic acid ethyl ester (0.502mg, 2mmol) in THF (15mL) was treated with phenyl magnesium bromide (1.2mL, 2M in THF) dropwise with stirring under nitrogen. After one hour the reaction was quenched with 1N HCl. The solution was diluted with isopropyl acetate (15mL) and the organic layer was isolated. The organic layer was washed with bicarbonate solution and brine. Chromatography over silica gel (15% MTBE/hexane) provided the title compound as an oil from which solidified on standing. NMR suggests a 6:1 ratio of diastereomers.

¹H NMR (400 MHz, DMSO-D6) δ 0.89 (dt, $J=9.70, 7.11$ Hz, 3 H) 4.00 (ddd, $J=14.28, 7.08, 1.10$ Hz, 2 H) 5.33 (d, $J=9.76$ Hz, 0.8 H) 5.40 (d, $J=9.76$ Hz, 0.2 H) 5.51 (d, $J=9.76$ Hz, 0.8 H) 5.55 (d, $J=9.76$ Hz, 0.2 H) 7.25 (m, 3.2 H) 7.40 (d, $J=7.08$ Hz, 1.8 H) 7.52 (m, 2.6 H) 7.60 (t, $J=7.81$ Hz, 1 H) 7.72 (d, $J=7.08$ Hz, 0.2 H) 7.84 (d, $J=8.79$ Hz, 0.2 H) 7.90 (d, $J=8.05$ Hz, 1 H) 7.94 (m, 1.8 H) 8.18 (m, 0.8 H) 8.30 (d, $J=7.57$ Hz, 0.2 H)

MS (EI) m/z M⁺. (329);

Anal. (C₂₂H₁₉NO₂) C, H, N.

Ethyl 2-cyano-3-(2-fluorophenyl)-3-(1-naphthyl)propanoate (12)

The title compound was prepared according to the procedure for (5), using of 2-cyano (2-fluorophenyl)-acrylic acid ethyl ester and 1-naphthyl magnesium bromide. The sample is a viscous oil.

MS (APCI) m/z 348;

Ethyl 2-cyano-3-(1-naphthyl)-3-quinolin-4-ylpropanoate (13)

The title compound was prepared according to the procedure for **(5)**, using of 2-cyano-3-quinolin-4-yl-acrylic acid ethyl ester and 1-naphthyl magnesium bromide. The sample is a white foam.

MS (APCI) m/z 381;

Ethyl 2-cyano-3-(1-naphthyl)-3-[2-(trifluoromethyl)phenyl]propanoate (14)

2-(trifluoromethyl)phenyl magnesium bromide (550mg, 2 mmol) taken up in 10 mL dry THF with magnesium (59 mg, 2 mmol) overnight. To this was added ethyl (E)-2-cyano-3-(1-naphthyl)prop-2-enoate (502 mg, 2 mmol) in THF (10 mL). The reaction mixture allowed to stir overnight. The reaction was stirred 2 hrs., quenched with 1 N HCl, taken up in ethyl acetate, washed with NaHCO₃, brine, dried with MgSO₄, filtered, and evaporated. The crude reaction mixture was purified on silica gel (20% ethyl acetate/hexanes) to yield 692 mg of the title compound as a yellow oil.

¹H NMR (400 MHz, DMSO-D6) δ 0.76 (t, $J=7.08$ Hz, 1 H) 0.92 (t, $J=7.08$ Hz, 1 H) 3.87 (m, 1 H) 4.02 (q, $J=7.08$ Hz, 0.5 H) 4.07 (q, $J=7.08$ Hz, 0.5 H) 5.23 (d, $J=7.32$ Hz, 0.5 H) 5.36 (d, $J=8.30$ Hz, 0.5 H) 5.87 (d, $J=7.32$ Hz, 0.5 H) 5.94 (d, $J=8.30$ Hz, 0.5 H) 7.27 (d, $J=6.59$ Hz, 0.5 H) 7.59 (m, 5 H) 7.80 (m, 1.5 H) 7.94 (m, 3 H) 8.13 (d, $J=8.79$ Hz, 0.5 H) 8.18 (d, $J=7.81$ Hz, 0.5 H)

MS (APCI) m/z 398 ([M+H]⁺);

Anal. calcd for C₂₃H₁₈F₃NO₂: C:69.52 H:4.57 N:3.52 Found: C:68.50 H:4.09 N:3.22.

Ethyl 2-cyano-3-(2,4-dimethoxyphenyl)-3-(1-naphthyl)propanoate (15)

A solution of 2-cyano-3-(2,4-dimethoxy-phenyl)-acrylic acid ethyl ester (522mg, 2mmol) in THF (20mL) was treated dropwise with 1-naphthyl magnesium bromide (9.6mL, 2.4mmol) at room temperature. The reaction was stirred for 3 hours, quenched with 1N HCl and diluted with ethyl acetate (40mL). The organic layer was separated and was washed sequentially with saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over Na₂SO₄, filtered and was concentrated in vacuo. Chromatography over silica gel (20% ethyl acetate/hexanes) yielded 421 mg of the title compound as an off white solid.

¹H NMR (400 MHz, DMSO-D6) δ 0.90 (td, $J=7.08, 1.71$ Hz, 3 H) 3.68 (s, 1.5 H) 3.71 (s, 1.5 H) 3.84 (s, 1.5 H) 3.94 (s, 1.5 H) 4.00 (m, 2 H) 5.08 (d, $J=8.30$ Hz, 0.5 H) 5.20 (d, $J=9.27$ Hz, 0.5 H) 5.74 (d, $J=8.54$ Hz, 0.5 H) 5.78 (d, $J=9.27$ Hz, 0.5 H) 6.36 (dd, $J=8.54, 2.44$ Hz, 0.5 H) 6.45 (dd, $J=8.66, 2.32$ Hz, 0.5 H) 6.60 (dd, $J=8.18, 2.32$ Hz, 1 H) 6.80 (d, $J=8.54$ Hz, 0.5 H) 7.20 (d, $J=8.54$ Hz, 0.5 H) 7.51 (m, 3.5H) 7.64 (d, $J=6.83$ Hz, 0.5 H) 7.88 (m, 3.5 H) 8.06 (d, $J=8.54$ Hz, 0.5 H)

MS (APCI) m/z 390 ([M+H]⁺);

Anal. (C₂₄H₂₂NO₄) C, H, N.

Ethyl 2-cyano-3-[2-(methylthio)phenyl]-3-(1-naphthyl)propanoate (16)

The title compound was prepared according to the procedure for **(14)** using 2-(thiomethyl)phenyl magnesium bromide. The sample is a sticky white foam

¹H NMR (400 MHz, DMSO-D6) δ 0.91 (dt, $J=16.23, 7.14$ Hz, 3 H) 4.01 (m, 2 H) 5.36 (d, $J=9.52$ Hz, 0.5 H) 5.43 (d, $J=9.76$ Hz, 0.5 H) 5.56 (d, $J=9.52$ Hz, 0.5 H) 5.60 (d, $J=10.01$ Hz, 0.5 H) 7.39 (m, 3 H) 7.55 (m, 4 H) 7.72 (d, $J=6.83$ Hz, 0.5 H) 7.85 (d, $J=8.30$ Hz, 0.5 H) 7.92 (m, 2 H) 8.17 (m, 0.5 H) 8.29 (d, $J=8.54$ Hz, 0.5 H)

MS (APCI) m/z [M+H]⁺ (376);

Anal. (C₂₃H₂₁NO₂S) C, H, S, N.

Ethyl (RR, SS)-2-cyano-2-methyl-3-[2-(methylthio)phenyl]-3-(1-naphthyl)propanoate (17)

The title compound was prepared according to the procedure for **(7)** using ethyl 2-cyano-3-[2-(methylthio)phenyl]-3-(1-naphthyl)propanoate The title compound is obtained as white crystals from MeOH. mp 154-156 °C;

MS (APCI) *m/z* 390;

nal. (C₂₄H₂₃NO₂S) C, H, S, N.

tert-Butyl (RR,SS)-2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoate (18)

A solution of 2-cyano-3-(2-methoxy-phenyl)-3-naphthalen-1-yl-propionic acid tert-butyl ester in THF (25mL) was treated at room temperature with potassium bistrimethylsilyl amide (3.64mL, 2.4mmol, 0.66M in toluene). The reaction was stirred for two hours and then methyl iodide was added (0.5mL, 8mmol). The reaction was stirred at room temperature for one hour and was quenched with 1N HCl. The reaction was diluted with ethyl acetate and the organic layer was isolated. The organic layer was washed with saturated sodium bicarbonate solution and brine. The organic layer was dried over Na₂SO₄, filtered and was concentrated in vacuo. Trituration of the resulting solid with ethanol provided 700mg of the title compound as a white powder.

¹H NMR (400 MHz, DMSO-D₆) δ 1.02 (s, 9 H) 1.62 (s, 3 H) 4.04 (s, 3 H) 5.76 (s, 1 H) 6.83 (td, *J*=7.50, 1.10 Hz, 1 H) 7.21 (m, 3 H) 7.47 (m, 2 H) 7.60 (t, *J*=7.32 Hz, 1 H) 7.89 (m, 3 H) 8.06 (d, *J*=7.08 Hz, 1 H)

MS (APCI) *m/z* 402 ([M+H]⁺);

Anal. calcd for C₂₆H₂₇NO₃: C:77.78 H:6.78 N:3.49 Found: C:77.41 H:6.84 N:3.67.

Tert-Butyl (SS)-2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoate

tert-Butyl (RR)-2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoate

The ester was resolved into its enantiomers by preparative chiral chromatography on a Chiralcel OD column in 80/20 methanol/water. The first peak to elute is (+) tert-butyl (SS)-2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoate

Chemical purity= 99.9% with ee 100%.

[α]_D²⁵ = -283.8° (c =5.624mg/1.124mL, CHCl₃);

The second peak to elute is (-)tert-butyl (SS)-2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoate

Chemical purity = 98% with ee 96%

[α]_D²⁵ = +272.0° (c =5.399mg/1.080mL, CHCl₃);

(RR,SS)-3-(2-Methoxyphenyl)-2-methyl-3-(1-naphthyl)-2-(piperidin-1-ylcarbonyl)propanenitrile (19)

(RR,SS)-2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoic acid (1 g, 2.89 mmol) was dissolved in 50 mL THF. A catalytic amount of DMF was added to the reaction mixture. Oxalyl chloride (0.303 mL, 3.47 mmol) was added slowly. The reaction mixture was stirred until no more evolution of gas was observed. The reaction mixture was rapidly heated to reflux, then cooled and evaporated. 50 mL toluene was added and the reaction mixture was evaporated to dryness. The acid chloride was dissolved in 10 mL CH₂Cl₂ and placed under nitrogen. In a separate flask piperidine (0.49 mL, 4.91 mmol) was dissolved in 50 mL CH₂Cl₂ under nitrogen. To this stirred solution was added a catalytic amount of DMAP, and triethylamine (0.69 mL, 4.91 mmol). The acid chloride in CH₂Cl₂ was added rapidly to this stirred mixture and allowed to react for 2 hours after which water was added to the reaction mixture. The organic layer was separated and washed with brine, dried over MgSO₄, filtered, evaporated to dryness, and recrystallized from ethanol to yield 851 mg of the title compound as a crystalline solid.

mp 194-196 °C;

¹H NMR 400 MHz (DMSO-D₆): δ 7.94 (d, 1H, *J*=7.32 Hz), 7.85 (m, 2H), 7.78 (d, 1H, *J*=8.30 Hz), 7.52 (t, 1H, *J*=7.32 Hz), 7.40 (m, 2H), 7.21 (td, 1H, *J*=7.75 Hz, 1.71 Hz), 7.12 (dd, 1H *J*=8.30 Hz, 0.98 Hz), 7.06 (dd, 1H, *J*=7.81 Hz, 1.71 Hz), 6.77 (td, 1H, *J*=7.57 Hz, 0.98 Hz), 5.99 (s, 1H) 4.01 (s, 3H), 3.49 (bs, 4H), 1.58 (s, 1H), 1.41 (bs, 6H)

MS (APCI) *m/z* 413 ([M+H]⁺);

(2S)-3-[4-(3-Chloro-2-methylphenyl)piperazin-1-yl]-2-[(S)-(2-methoxyphenyl)(1-naphthyl)methyl]-2-methyl-3-oxopropanenitrile (20)

(S,S)-2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoic acid (12 g, 34.74 mmol) was dissolved in 500 mL THF. A catalytic amount of DMF was added to the reaction mixture. Oxalyl chloride (3.64 mL, 41.69 mmol) was added slowly. The reaction mixture was stirred until no more evolution of gas was observed. The reaction mixture was rapidly heated to reflux, then cooled and evaporated. 250 mL toluene was added and the reaction mixture was evaporated to dryness. The acid chloride was dissolved in 250 mL CH₂Cl₂ and placed under nitrogen. In a separate flask 1-(3-chloro-2-methylphenyl)piperazine hydrochloride (10.67 g, 41.69 mmol) was dissolved in 250 mL CH₂Cl₂ under nitrogen. To this stirred solution was added a catalytic amount of DMAP, and triethylamine (21.80 mL, 156.33 mmol). The acid chloride in CH₂Cl₂ was added rapidly to this stirred mixture and allowed to react overnight after which water was added to the reaction mixture. The organic layer was separated and washed with brine, dried over MgSO₄, filtered, evaporated to dryness, purified on silica gel (20% hexanes/CH₂Cl₂), the purified fractions were evaporated and recrystallized from ethyl acetate/hexanes to yield 12.58 g of the title compound as a crystalline solid.

mp 150-153 °C;

$[\alpha]_D^{25} = -167.9^\circ$ (1% , CHCl₃);

¹H NMR 500 MHz (DMSO-D6): • 8.00 (d, 1H, J=7.33 Hz), 7.88 (m, 2H), 7.86 (d(1H, J=8.25 Hz), 7.55 (t, 1H, J=7.64 Hz), 7.43 (m, 2H), 7.23 (td, 1H, J=7.79 Hz, 1.37 Hz), 7.14 (m, 3H), 6.86 (bs, 1H), 6.80 (t, 1H, J=7.48 Hz), 6.02 (s, 1H), 4.01 (s, 3H), 3.69 (bs, 4H), 2.70 (bs, 4H), 2.27 (s, 3H), 1.65 (s, 3H)

MS (ESI) m/z 538 ([M+H]⁺);

Anal. (C₃₃H₃₂ClN₃O₂) C, H, N.

(2S,3S)-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)-2-((4-[3-(trifluoromethyl)phenyl]piperidin-1-yl)carbonyl)propanenitrile (21)

The title compound was prepared in 75% yield according to the procedure for (20) using 4-(3-trifluoromethylphenyl)-piperidine. Recrystallization from ethyl acetate/hexane yielded white crystals
mp 123-127 °C;

$[\alpha]_D^{25} = -144.4^\circ$ (1%, CHCl₃);

¹H NMR 500MHz (DMSO-D6): • 8.02 (d,1H, J = 7.03Hz), 7.88 (m,2H), 7.82 (d,1H, J = 8.25Hz), 7.56 (t,1H, J = 7.79Hz),7.51 (brm,2H), 7.42 (d,1H, J = 7.48Hz), 7.42 (quin,1H, J = 3.51Hz), 7.23 (t,1H, J = 7.03Hz), 7.14 (m,2H), 6.80 (t,1H, J = 7.48Hz), 6.02 (s,1H),4.37 (brm, 2H), 4.01 (s, 3H), 2.88 (brm, 2H), 1.66 (s, 3H)

MS (ESI) m/z 557 ([M+H]⁺);

Anal. calcd for C₃₄H₃₁F₃N₂O₂: C:73.35 H:5.61 N:5.03 Found: C:73.99 H:6.00 N:4.72

(RR,SS)-2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoic acid

Ethyl-(RR,SS)- 2-cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoate (12.42g, 33.33 mmol) was dissolved in 100 mL THF to which was added 2.5 M NaOH (18 mL). Reaction mixture heated to reflux for 8 hrs, allowed to cool and stir overnight. The reaction mixture was acidified with 1 N HCl, taken up in ethyl acetate, washed with brine, dried with MgSO₄, filtered, evaporated, and recrystallized from ethanol to yield 11.44 g the title compound as a crystalline solid.

mp 229 °C (dec);

¹H NMR (400 MHz, DMSO-D6) • 1.62 (s, 2 H) 4.05 (s, 2 H) 5.77 (s, 1 H) 6.80 (td, J=7.50, 1.10 Hz, 1 H) 7.11 (dd, J=7.69, 1.59 Hz, 1 H) 7.15 (dd, J=8.30, 0.98 Hz, 1 H) 7.23 (td, J=7.81, 1.71 Hz, 1 H) 7.44 (m, 1 H) 7.59 (m, 1 H) 7.84 (d, J=8.30 Hz, 1 H) 7.89 (m, 1 H) 8.10 (d, J=7.32 Hz, 1 H)

MS (APCI) m/z 344 ([M-H]⁻);

Anal. (C₂₂H₁₉NO₃) C, H, N

Resolution of (-)-(2S, 3S)-2-Cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoic Acid

(2S, 3S)-2-Cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoic Acid Quinidine Salt

2-Cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl) propanoic acid (30 g, 87 mmoles) was dissolved in THF (250mL). This was added to a solution of quinidine (28.18g, 87 mmol) in CH₂Cl₂ (150 mL) and isopropyl acetate (200 mL). The solution was warmed to reflux to yield a clear solution, was cooled and evaporated to a solid in vacuo. The salt was refluxed in isopropyl acetate (1.4 L), filtered hot and cooled to room temperature. This provided 19.50 g of the diastereomeric salt with an ee of 98.5%. A second recrystallization from isopropyl acetate provided 17.5g of the salt with an ee 99.5%

mpt 171-172

$[\alpha]_D^{25} = -11.26^\circ$ (c = 1% SOLUTION, CHCl_3);

MS (ESI) m/z 344;

Anal. ($\text{C}_{42}\text{H}_{43}\text{N}_3\text{O}_5$) C, H, N.

(-)-(2S, 3S)-2-Cyano-3-(2-methoxyphenyl)-2-methyl-3-(1-naphthyl)propanoic Acid

The quinidine salt prepared in Part One was liberated to the acid by extraction with ethyl acetate / 1N hydrochloric acid. The organic phase was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated in vacuo to a foam which was taken up in hot ether and treated with an equal volume of hexane (100 mL) The sample were cooled in a refrigerator for 15 hours. Filtration afforded the title compound as a white crystalline solid. 5.46 g , 99.9 % ee, chemical purity:99.2 %)

mp 230-233 °C dec;

$[\alpha]_D^{25} = -270.0^\circ$ (c = 1% SOLUTION, CHCl_3);

MS (ESI) m/z 344;

Anal. ($\text{C}_{22}\text{H}_{19}\text{NO}_3$) C, H, N