

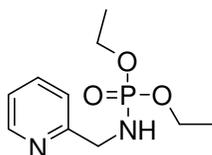
Supporting Information for:

Synthesis and Structure-Activity Relationships of Azamacrocyclic C-X-C Chemokine Receptor 4 Antagonists: Analogs Containing a Single Azamacrocyclic Ring are Potent Inhibitors of T-tropic (X4) HIV-1 Replication.

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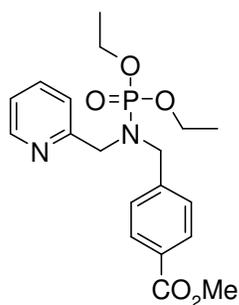
Supporting information contains experimental procedures and characterization data for the synthesis of (4-chloromethyl-benzyl)-pyridin-2-ylmethyl-phosphoramidic acid diethyl ester (**34b**) and compounds **30** through **58b**. Characterization data is available for compounds **3a-i**.

EXPERIMENTAL



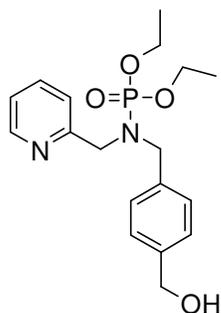
Pyridin-2-ylmethyl-phosphoramidic acid diethyl ester.

To a stirred room temperature solution of aminomethylpyridine (5.0 g, 46 mmol) and triethylamine (10 mL, 70 mmol) in dichloromethane (200 mL, anhydrous) was added diethyl chlorophosphate (8.8 g, 51 mmol). Stirring was continued under a nitrogen environment for 16 h. The reaction mixture was washed with water (4 x 100 mL), dried over MgSO₄, and concentrated to give pyridin-2-ylmethyl-phosphoramidic acid diethyl ester as an orange oil (9.6 g, 85%). ¹H NMR (CDCl₃) δ 1.27 (t, 6H, *J* = 7.5Hz), 3.83 (s br, 1H), 4.04 (q, 4H, *J* = 7.5Hz), 4.21 (dd, 2H, *J* = 7.5, 6.0Hz), 7.16 (dd, 1H, *J* = 6.0, 3.0 Hz), 7.29 (d, 1H, *J* = 7.5 Hz), 7.64 (t, 1H, *J* = 7.5 Hz), 8.52 (d, 1H, *J* = 3.0 Hz).



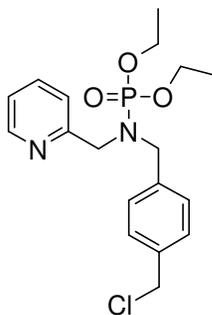
4-[[diethoxyphosphoryl]pyridin-2-ylmethyl-amino]-methylbenzoic acid methyl ester.

To a stirred room temperature solution of pyridin-2-ylmethyl-phosphoramidic acid diethyl ester (9.6 g, 39 mmol) in DMF (200 mL) was added sodium hydride (1.4 g, 60 mmol) in three portions followed by methyl-4-bromomethyl-benzoate (8.2 g, 36 mmol). The mixture was stirred under a nitrogen atmosphere for 16 h and concentrated under reduced pressure. The resultant residue was partitioned between saturated sodium bicarbonate solution (400 mL) and ethyl acetate (500 mL). The layers were separated and the organic layer was washed with brine (3 x 300 mL), dried over MgSO_4 , and concentrated. Purification of the crude material on a silica gel column (1:2, EtOAc:hexanes) provided pure 4-[[diethoxyphosphoryl]pyridin-2-ylmethyl-amino]-methylbenzoic acid methyl ester as an orange oil (10.2 g, 72%). $^1\text{H NMR}$ (CDCl_3) δ 1.28 (t, 6H, $J = 7.5$ Hz), 3.88 (s, 3H), 3.99-4.12 (m, 4H), 4.23 (t, 4H, $J = 10.5$ Hz), 7.15 (dd, 1H, $J = 6.0, 3.0$ Hz), 7.36 (d, 3H, $J = 7.5$ Hz), 7.62 (t, 1H, $J = 7.5$ Hz), 7.95 (d, 2H, $J = 7.5$ Hz), 8.51 (d, 1H, $J = 3.0$ Hz).



(4-Hydroxymethylbenzyl)pyridin-2-ylmethyl-phosphoramidic acid diethyl ester.

To a stirred -78°C solution of 4-[[diethoxy-phosphoryl]-pyridin-2-ylmethyl-amino]-methyl]-benzoic acid methyl ester (10.2 g, 26 mmol) in anhydrous dichloromethane (150 mL) was added a 1.0 M solution of DIBAL-H in dichloromethane (83 mL, 83 mmol) and stirring was continued for 1.5 h under a nitrogen atmosphere. The solution was allowed to warm to room temperature. The mixture was quenched with potassium sodium tartrate (500 mL) and vigorous stirring was continued for 2 h. The layers were separated and the aqueous layer was extracted with DCM (250 mL). The combined organic portions were dried over MgSO_4 and concentrated to afford (4-hydroxymethyl-benzyl)-pyridin-2-ylmethyl-phosphoramidic acid diethyl ester as an orange oil (8.7 g, 92%). $^1\text{H NMR}$ (CDCl_3) δ 1.28 (t, 6H, $J = 7.5$ Hz), 3.98-4.11 (m, 4H), 4.17 (t, 4H, $J = 10.5$ Hz), 4.62 (s, 2H), 7.15 (dd, 1H, $J = 6.0, 3.0$ Hz), 7.22-7.29 (m, 4H), 7.38 (d, 1H, $J = 7.5$ Hz), 7.64 (t, 1H, $J = 7.5$ Hz), 8.49 (d, 1H, $J = 3.0$ Hz).



(4-Chloromethyl-benzyl)-pyridin-2-ylmethyl-phosphoramidic acid diethyl ester (34b).

To a stirred room temperature solution of (4-Hydroxymethyl-benzyl)-pyridin-2-ylmethyl-phosphoramidic acid diethyl ester (1.45 g, 3.98 mmol) and NEt_3 (3.5 ml, 11.95 mmol) in dichloromethane (40 mL) was added methyl sulfonylchloride (0.92 ml, 11.95 mmol). The resulting mixture was warmed up to 50°C and stirring was continued for 18 hours then cooled down to room temperature. The reaction mixture was diluted with ethyl acetate (200 mL) and washed with sat. NH_4Cl then brine. The organic layer was dried over MgSO_4 and concentrated to afford (4-chloromethyl-benzyl)-pyridin-2-ylmethyl-phosphoramidic acid diethyl ester as colorless oil (553 mg, 37%). $^1\text{H NMR}$ (CDCl_3) δ 1.28 (t, 6H, $J = 7.5$ Hz), 3.91-4.12 (m, 4H), 4.14-4.25 (m, 4H), 4.57 (s, 2H), 7.17 (dd, 1H, $J = 6.0, 3.0$ Hz), 7.28-7.30 (m, 4H), 7.40 (d, 1H, $J = 7.5$ Hz), 7.62 (t, 1H, $J = 7.5$ Hz), 8.54 (d, 1H, $J = 3.0$ Hz).

***N*-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-benzylamine pentahydrobromide (3a)**. Off-white solid: mp 245-250°C (dec); ¹H NMR (D₂O) δ 1.9-2.1 (m, 4H), 3.2-3.6 (m, 16H), 4.12 (s, 2H), 4.15 (s, 2H), 4.36 (s, 2H), 7.30 (s, 5H), 7.41 (d, 2H, *J* = 8.3 Hz) 7.46 (d, 2H, *J* = 8.3 Hz); ¹³C NMR (D₂O) δ 18.43, 19.06, 37.29, 37.46, 37.63, 41.09, 41.32, 41.68, 44.46, 47.74, 50.18, 51.00, 58.79, 129.53, 129.97, 130.18, 130.35, 130.68, 131.18, 131.92, 133.14; FAB MS *m/z* 492 (M+H⁸¹Br, 13), 490 (M+H⁷⁹Br, 13), 410 (M+H, 100), 201 (36). Anal. (C₂₅H₃₉N₅·5HBr) C, H, N, Br.

***N*-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-amino-benzylamine pentahydrobromide (3b)**. White solid: mp 203-206°C (dec); ¹H NMR (D₂O) δ 1.85-2.13 (m, 4H), 3.02-3.58 (m, 16H), 4.23 (s, 2H), 4.31 (s, 4H), 7.23-7.54 (m, 8H); ¹³C NMR (D₂O) δ 18.03, 19.29, 37.78 (3C), 41.37 (2C), 42.00, 44.82, 46.25, 47.96, 51.16, 58.68, 124.04, 124.40, 129.40, 130.75, 131.21 (2C), 131.88, 131.96, 132.46, 132.83; FAB MS *m/z* 507 (M+H⁸¹Br, 15), 505 (M+H⁷⁹Br, 18), 425 (M+H, 100), 320 (30), 201 (51). Anal. (C₂₅H₄₀N₆·5.75HBr·0.5H₂O) C, H, N, Br

***N*-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-amino-benzylamine hexahydrobromide (3c)**. Yellow solid: mp 120-125°C (dec); ¹H NMR (D₂O) δ 1.8-2.0 (m, 4H), 2.9-3.4 (m, 16H), 4.1 (s, 2H), 4.18 (s, 4H), 7.2-7.5 (m, 8H); ¹³C NMR (D₂O) δ 18.86, 19.57, 38.14, 41.76, 43.74, 45.14, 48.24, 50.14, 50.42, 51.49, 58.38, 124.13, 131.13, 131.30, 131.83, 131.92, 131.96, 132.67; FAB MS *m/z* 507 (M+H⁸¹Br, 5), 505 (M+H⁷⁹Br, 5), 425 (M+H, 45), 201 (47), 155 (75), 106 (100). Anal. (C₂₅H₄₀N₆·6HBr·HOAc) C, H, N, Br.

***N*-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-3-(amino-methyl)pyridine hexahydrobromide (3e)**. White solid: mp 198-202°C (dec); ¹H NMR (D₂O) δ 1.83-2.07 (m, 4H), 2.96-3.47 (m, 16H), 4.11 (s, 2H), 4.32 (s, 2H), 4.49 (s, 2H), 7.38-7.56 (m, 4H), 8.04 (t, 1H, *J* = 6.4 Hz), 8.63 (d, 1H, *J* = 8.3 Hz), 8.76 (d, 1H, *J* = 5.6 Hz), 8.86 (s, 1H); ¹³C NMR (D₂O) δ 18.23, 18.87, 36.92, 37.29 (2C), 40.88, 41.05, 41.43, 44.17, 47.22, 47.60, 51.18, 59.04, 128.29, 130.01, 131.49, 132.14, 132.66 (2C), 142.55, 142.76, 148.98; FAB MS *m/z* 493 (M+H⁸¹Br, 7), 491 (M+H⁷⁹Br, 6), 411 (M+H, 100), 320 (33), 247 (24). Anal. (C₂₄H₃₈N₆·6HBr) C, H, N, Br.

***N*-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-)amino-methyl)pyridine hexahydrobromide (3f)**. White solid: mp 201-204°C (dec); ¹H NMR

(D₂O) δ 1.91-2.12 (m, 4H), 3.00-3.49 (m, 16H), 4.13 (s, 2H), 4.34 (s, 2H), 4.53 (s, 2H), 7.39-7.57 (m, 4H), 8.02 (d, 2H, $J = 6.3$ Hz), 8.74 (d, 2H, $J = 6.3$ Hz); ¹³C NMR (D₂O) δ 18.26, 18.88, 36.94, 37.29, 37.36, 40.89, 41.06, 41.44, 44.21, 47.61, 49.17, 51.43, 59.02, 127.84, 130.21, 131.64, 132.15, 132.45, 142.19, 151.67; FAB MS m/z 493 (M+H⁸¹Br, 8), 491 (M+H⁷⁹Br, 10), 411 (M+H, 83), 320 (37), 247 (58), 201 (100). Anal. (C₂₄H₃₈N₆·6HBr) C, H, N, Br.

***N*-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-*N*-methyl-2-(aminomethyl)pyridine hexahydrobromide hydrate (3g).** White solid: mp 220-225°C (dec); ¹H NMR (D₂O) δ 2.06 (m, 4H), 2.76 (s, 3H), 3.20-3.65 (m, 16H), 4.47 (bs, 4H), 4.65 (s, 2H), 7.54 (bs, 4H), 7.80 (t, 1H), 7.87 (d, 1H), 8.28 (t, 1H), 8.68 (d, 1H); ¹³C NMR (D₂O) δ 18.14, 18.75, 18.89, 36.74, 37.04, 37.15, 37.62, 40.38, 40.72, 40.91, 41.28, 44.05, 47.50, 56.98, 58.88, 60.28, 127.60, 128.86, 130.78, 130.96, 132.16, 132.64, 144.91, 145.04, 146.12; FAB MS m/z 507 (M+H⁸¹Br, 27), 507 (M+H⁷⁹Br, 22), 425 (M+H, 100). Anal. (C₂₅H₄₀N₆·6HBr ·1.5H₂O) C, H, N, Br.

***N*-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(aminoethyl)pyridine hexahydrobromide (3h).** White solid: mp 195-198°C (dec); ¹H NMR (D₂O) δ 1.98-2.17 (m, 4H), 3.20-3.38 (m, 8H), 3.38-3.63 (m, 12H), 4.27 (s, 2H), 4.39 (s, 2H), 7.50 (s, 4H), 7.80-7.89 (m, 2H), 8.42 (m, 1H), 8.58 (d, 1H, $J = 5.8$ Hz); ¹³C NMR (D₂O) δ 18.51, 19.14, 29.85, 37.56 (3C), 41.21, 41.41, 41.82, 44.57, 45.27, 47.83, 51.10, 58.74, 126.35, 127.93, 130.66, 131.27, 131.99, 132.69, 141.89, 147.79, 150.91; FAB MS m/z 507 (M+H⁸¹Br, 40), 505 (M+H⁷⁹Br, 34), 425 (M+H, 100). Anal. (C₂₅H₄₀N₆·6HBr) C, H, N, Br.

***N*-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-(2-amino-methyl-5-methyl)pyrazine pentahydrobromide (3i).** White solid: mp 194-197°C (dec); ¹H NMR (D₂O) δ 1.93-2.12 (m, 4H), 2.42 (s, 3H), 3.25 (s, 8H), 3.48 (s, 8H), 4.28 (s, 2H), 4.30 (s, 2H), 4.33 (s, 2H), 7.44 (s, 4H), 8.33 (s, 1H), 8.46 (s, 1H); ¹³C NMR (D₂O) δ 18.01, 18.72, 19.80, 36.66, 37.05, 37.13, 40.70, 40.89, 41.27, 43.99, 47.47, 48.14, 50.61, 59.06, 129.97, 131.43, 132.04, 132.99, 140.93, 144.98, 146.49, 153.51; FAB MS m/z 509 (M+H⁸¹Br, 17), 507 (M+H⁷⁹Br, 15), 426 (M+H, 100), 320 (21), 247 (20). Anal. (C₂₄H₃₉N₇·5.5HBr) C, H, N, Br.

4-Bromomethylbenzyl alcohol (30). To a solution of methyl 4-bromomethylbenzoate (**29**) (5.73 g, 25 mmol) in dry CH₂Cl₂ (150 mL) cooled to -78 °C with stirring under nitrogen was added dropwise a solution of DIBAL-H (82.5 mL, 1.0 M solution in THF). Stirring was continued for 1.5 h at -78 °C, and the reaction mixture was then allowed to warm to 0 °C and quenched with H₂O. The organic layer was separated and the aqueous was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were dried (MgSO₄) and evaporated to give the desired alcohol (**30**) (5.0 g, 100%) as a white solid: ¹H NMR (CDCl₃) δ 1.84 (br, 1H), 4.49 (s, 2H), 4.67 (s, 2H), 7.33 (d, 2H, *J* = 8.2 Hz), 7.38 (d, 2H, *J* = 8.2 Hz).

***N*-(2-Nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (32).** A solution of 2-nitrobenzenesulfonylchloride (16.62 g, 0.075 mol) in dry CH₂Cl₂ (120 mL) was added dropwise via cannula to a stirred solution of 2-(aminomethyl)pyridine (**31**) (5.41 g, 0.05 mol) and Et₃N (13.9 mL, 0.10 mol) in dry CH₂Cl₂ (150 mL) under nitrogen. The reaction mixture was stirred for 3 h at room temperature, and then quenched with water (20 mL). The aqueous layer was separated and extracted with EtOAc (5 x 80 mL). The combined organic extracts were dried (MgSO₄) and evaporated to small volume to give a white precipitate which was collected by filtration and washed with cold CH₂Cl₂ to give the desired product (**32**) (11.37 g, 78%) as a white solid: ¹H NMR (Acetone-d₆) δ 4.46 (s, 2H), 7.19 (dd, 1H, *J* = 7.4, 4.5 Hz), 7.25-7.35 (br s, 1H), 7.39 (d, 1H, *J* = 7.7 Hz), 7.68 (ddd, 1H, *J* = 7.7, 7.5, 1.8 Hz), 7.76-7.88 (m, 2H), 7.94 (dd, 1H, *J* = 7.7, 1.5 Hz), 8.04 (dd, 1H, *J* = 7.5, 1.8 Hz), 8.38 (d, 1H, *J* = 4.5 Hz).

***N*-[1-Methylene-4-(hydroxymethylene)phenylene]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (33).** A mixture of **32** (5.87 g, 20 mmol), **30** (4.02 g, 20 mmol) and K₂CO₃ (5.53 g, 40 mmol) in dry CH₃CN (150 mL) were heated at 60 °C for 4 h with stirring under nitrogen. The mixture was then allowed to cool to room temperature, the solvent evaporated and the residue was partitioned between water and CH₂Cl₂. The separated aqueous phase was extracted with CH₂Cl₂, and the combined organic extracts were dried (MgSO₄) and evaporated. The residue was suspended in EtOAc/hexane (1:1) and collected by filtration to give the desired product **33** (6.87 g, 83%) as a white solid: ¹H NMR (CDCl₃) δ 1.78 (t, 1H, *J* = 5.8 Hz), 4.58 (s, 2H), 4.60 (s, 2H), 4.64 (d, 2H, *J* =

5.8 Hz), 7.13-7.26 (m, 6H), 7.54-7.59 (m, 2H), 7.66-7.68 (m, 2H), 7.98 (d, 1H, $J = 7.4$ Hz), 8.40 (d, 1H, $J = 3.8$ Hz).

***N*-[1-Methylene-4-(chloromethylene)phenylene]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (34a).** To a stirred solution of **33** (1.91 g, 4.62 mmol) and Et₃N (2.0 mL, 14 mmol) in CH₂Cl₂ (20 mL) cooled in an ice bath under nitrogen, was added methanesulfonyl chloride (0.73 mL, 9.4 mmol) and the reaction mixture was then heated to reflux for a further 6 h. The solution was diluted with CH₂Cl₂ (60 mL) and washed with 10% aqueous HCl (2 × 20 mL), 5% aqueous NaHCO₃ (20 mL), and H₂O (25 mL) then dried (MgSO₄) and concentrated *in vacuo* to give **34a** (1.95 g, 98%) as an orange oil: ¹H NMR (CDCl₃) δ 4.52 (s, 2H), 4.60 (s, 4H), 7.12-7.26 (m, 6H), 7.55 (m, 2H), 7.67 (d, 2H, $J = 4.0$ Hz), 7.94 (d, 1H, $J = 8.0$ Hz), 8.41 (d, 1H, $J = 4.8$ Hz). This was used without further purification.

2,6-Bis[*N*-(2-nitrobenzenesulfonyl)-2-aminoethyl]pyridine (15a). To a stirred solution of 2,6-bis(2-aminoethyl)pyridine (**13a**²⁸) (2.7 g, 16 mmol) and Et₃N (5.7 mL, 41 mmol) in CH₂Cl₂ (35 mL) was added 2-nitrobenzenesulfonyl chloride (8.01 g, 36.1 mmol) in CH₂Cl₂ (20 mL) and the mixture was stirred at room temperature under nitrogen for 42 h. The mixture was washed with brine (25 mL) and the organic phase was dried (MgSO₄) and concentrated *in vacuo*. The brown residue was purified by column chromatography on silica gel (50% then 60% THF/hexane) to give **15a** (5.2 g, 59%) as a pale yellow solid: ¹H NMR (CDCl₃) δ 3.01 (m, 4H), 3.52 (m, 4H), 6.38 (m, 2H), 6.94 (d, 2H, $J = 7.7$ Hz), 7.47 (t, 1H, $J = 7.7$ Hz), 7.72 (m, 4H), 7.82 (m, 2H), 8.13 (m, 2H).

7-Diethoxyphosphoryl-4,10-bis(2-nitrobenzenesulfonyl)-4,7,10,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (19a). Using General Procedure A: Reaction of **15a** (5.2 g, 9.7 mmol) and *N*-(diethoxyphosphoryl)-*O,O'*-bis(2-methylsulfonyl)di-ethanolamine (**17**²⁸) (4.25 g, 10.7 mmol) followed by silica gel column purification (60% then 90% THF/hexane) of the reaction products gave **19a** (1.48 g, 21%) as a yellow amorphous solid: ¹H NMR (CDCl₃) δ 1.23 (t, 6H, $J = 7.1$ Hz), 2.60 (m, 4H), 2.98-3.08 (m, 8H), 3.84-3.94 (m, 8H), 7.11 (d, 2H, $J = 7.6$ Hz), 7.56-7.74 (m, 7H), 8.07 (m, 2H).

4,10-Bis(2-nitrobenzenesulfonyl)-4,7,10,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (22a). Using General Procedure B: Reaction of **19a** (1.04 g, 1.4

mmol) gave **22a** (744 mg, 88%) as a yellow amorphous solid: $^1\text{H NMR}$ (CDCl_3) δ 2.81 (m, 4H), 3.08 (m, 4H), 3.33 (m, 4H), 3.88 (m, 4H), 7.07 (d, 2H, $J = 7.7$ Hz), 7.54-7.71 (m, 7H), 8.02 (m, 2H).

***N*-[7-[4,10-Bis(2-nitrobenzenesulfonyl)-4,7,10,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-N-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35a)**. Using General Procedure C: Reaction of **22a** and **34a** (610 mg, 1.4 mmol) followed by silica gel column purification (50% then 80% THF/hexane) of the reaction products gave **35a** (648 mg, 54%) as a yellow amorphous solid: $^1\text{H NMR}$ (CDCl_3) δ 2.26 (m, 4H), 3.03 (m, 8H), 3.37 (s, 2H), 3.94 (m, 4H), 4.56 (s, 2H), 4.57 (s, 2H), 6.95-7.17 (m, 8H), 7.52-7.72 (m, 11H), 7.85 (m, 2H), 7.98 (d, 1H, $J = 7.7$ Hz), 8.39 (d, 1H, $J = 4.8$ Hz).

***N*-[7-(4,7,10,17-Tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Hexahydrobromide Trihydrate (36)**. Using General Procedure D: Reaction of **35a** (640 mg, 0.64 mmol) with thiophenol (0.24 mL, 2.3 mmol) followed by purification of the crude product by column chromatography on alumina (CH_2Cl_2 followed by 10% MeOH/ CH_2Cl_2) gave the free base of the title compound (83 mg, 29%) as a yellow oil: $^1\text{H NMR}$ (CDCl_3) δ 2.57 (m, 8H), 3.01 (s, 8H), 3.36 (s, 2H), 3.78 (s, 2H), 3.92 (s, 2H), 6.64 (d, 2H, $J = 8.0$ Hz), 7.07 (m, 4H), 7.18 (m, 1H), 7.33 (d, 1H, $J = 7.7$ Hz), 7.67 (m, 2H), 8.58 (d, 1H, $J = 4.8$ Hz).

Using General Procedure E: The free base (74 mg, 0.17 mmol) was converted to the hydrobromide salt to give **36** (153 mg, 93%) as a white solid: $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 2.81 (br s, 4H), 3.28 (m, 8H), 3.61 (br s, 4H), 3.85 (s, 2H), 4.27 (s, 2H), 4.36 (s, 2H), 7.29 (d, 2H, $J = 7.7$ Hz), 7.36 (d, 2H, $J = 7.7$ Hz), 7.53 (m, 3H), 7.63 (d, 1H, $J = 7.7$ Hz), 7.80 (t, 1H, $J = 7.7$ Hz), 7.99 (m, 1H), 8.69 (d, 1H, $J = 5.3$ Hz); FAB-MS m/z 527 (MH + H^{81}Br), 525 (MH + H^{79}Br), 445 (M + H). Anal. ($\text{C}_{27}\text{H}_{36}\text{N}_6 \cdot 6\text{HBr} \cdot 3\text{H}_2\text{O}$) C, H, N, Br.

1,3-Phenylenebis(ethylene)diamine (13b). To a solution of 1,3-phenylenediacetonitrile (9.37 g, 60 mmol) in CH_3OH (saturated with NH_3 , 150 mL) was added Raney-Ni (*ca.* 20 g, previously washed with CH_3OH several times) and the mixture was hydrogenated at 45 psi on a Parr apparatus for 48 h. The reaction mixture was filtered through Celite and the filtrate evaporated to give the crude product **13b** (9.45 g, 96%) as a light green oil: ^1H

NMR (CDCl₃) δ 0.80-1.50 (br s, 4H), 2.70-2.76 (m, 4H), 2.94-2.99 (m, 4H), 7.01-7.07 (m, 3H), 7.18-7.26 (m, 1H). This was used in the next step without further purification.

***N,N'*-Bis(2-nitrobenzenesulfonyl)-1,3-phenylenebis(ethylene)diamine (15b)**. A solution of 2-nitrobenzenesulfonylchloride (19.94 g, 0.090 mol) in dry CH₂Cl₂ (70 mL) was added dropwise via cannula to a stirred solution of 1,3-phenylenebis(ethylene)diamine (4.92 g, 0.030 mol) and Et₃N (16.7 mL, 0.12 mol) in dry CH₂Cl₂ (80 mL) under nitrogen. The reaction mixture was stirred overnight at room temperature, and then quenched with water (20 mL). The precipitate was collected by filtration and washed with H₂O, CH₃OH, and Et₂O to give **15b** (9.22 g, 58%) as a white solid: ¹H NMR (DMSO-d₆) δ 2.66 (t, 4H, *J* = 7.7 Hz), 3.08-3.18 (br s, 4H), 6.94 (d, 2H, *J* = 6.4 Hz), 6.98 (s, 1H), 7.12 (dd, 1H, *J* = 6.4, 6.4 Hz), 7.78-7.84 (br m, 4H), 7.90-7.64 (br m, 4H), 8.16 (br s, 2H).

7-Diethoxyphosphoryl-4,10-bis(2-nitrobenzenesulfonyl)-4,7,10-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (19b). Using General Procedure A: Reaction of **15b** (8.74 g, 16.4 mmol) with **17** (6.50 g, 16.4 mmol) followed by silica gel column purification of the reaction products (1:15:35 CH₃OH/Et₂O/CH₂Cl₂) gave **19b** (4.03 g, 33%) as a yellow foam: ¹H NMR (CDCl₃) δ 1.21 (t, 6H, *J* = 6.4 Hz), 2.39-2.46 (br m, 4H), 2.83-2.97 (br m, 8H), 3.68-3.72 (m, 4H), 3.80-3.92 (m, 4H), 7.16 (d, 2H, *J* = 6.5 Hz), 7.18 (s, 1H), 7.24 (dd, 1H, *J* = 6.5, 6.5 Hz), 7.60-7.74 (m, 6H), 8.04-8.08 (m, 2H).

4,10-Bis(2-nitrobenzenesulfonyl)-4,7,10-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (22b). Using General Procedure B: Reaction of **19b** (1.27 g, 1.72 mmol) followed by silica gel column purification of the reaction products (1:15:25 CH₃OH/EtOAc/CH₂Cl₂ then 20% CH₃OH in CH₂Cl₂) gave **22b** (574 mg, 57%) as a light yellow foam: ¹H NMR (CDCl₃) δ 1.42-1.50 (br, 1H), 2.01 (t, 4H, *J* = 5.4 Hz), 2.90-3.10 (br m, 4H), 3.08 (t, 4H, *J* = 5.4 Hz), 3.56-3.60 (br m, 4H), 7.16 (d, 2H, *J* = 6.8 Hz), 7.31 (dd, 1H, *J* = 6.8, 6.8 Hz), 7.36 (s, 1H), 7.61-7.63 (m, 2H), 7.70-7.73 (m, 4H), 8.01-8.04 (m, 2H).

***N*-[7-[4,10-Bis(2-nitrobenzenesulfonyl)-4,7,10-triazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35b)**. Using General Procedure C: Reaction of **22b** (420 mg,

0.7 mmol) with **34a** (302 mg, 0.7 mmol) followed by silica gel column purification of the reaction products (1:3 Et₂O/CH₂Cl₂) gave **35b** (491 mg, 70%) as a pale yellow solid: ¹H NMR (CDCl₃) δ 1.97-2.02 (br m, 4H), 2.73-2.78 (br m, 4H), 2.90-2.94 (br m, 4H), 3.32 (s, 2H), 3.64-3.67 (br m, 4H), 4.55 (s, 2H), 4.58 (s, 2H), 6.93 (d, 2H, *J* = 8.0 Hz), 7.04 (d, 2H, *J* = 8.0 Hz), 7.09-7.16 (br m, 4H), 7.23 (s, 1H), 7.29 (dd, 1H, *J* = 7.9, 7.9 Hz), 7.51-7.72 (m, 10H), 7.80-7.83 (m, 2H), 7.98 (d, 1H, *J* = 7.8 Hz), 8.39 (m, 1H).

***N*-[7-(4,7,10-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Pentahydrobromide Dihydrate (37)**. Using General Procedure D: Reaction of **35b** (380 mg, 0.38 mmol) with thiophenol followed by basic alumina column purification of the reaction products (1:20 CH₃OH/CH₂Cl₂) gave the free base of the title compound.

Using General Procedure E: Conversion of the free base to the hydrobromide salt gave **37** (110 mg, 34% overall) as a white solid: ¹H NMR (DMSO-*d*₆) δ 2.80-2.88 (br s, 4H), 3.02-3.06 (br s, 4H), 3.10-3.16 (br s, 4H), 3.38-3.44 (br s, 4H), 3.80-3.86 (br s, 2H), 4.25-4.30 (br s, 2H), 4.33-4.37 (br s, 2H), 7.27-7.32 (br m, 4H), 7.42-7.63 (br m, 6H), 7.96 (dd, 1H, *J* = 7.7, 7.7 Hz), 8.10-8.30 (br s, 3H), 8.69 (d, 1H, *J* = 4.9 Hz), 9.45-9.62 (br s, 2H); FAB-MS *m/z* 526 (MH + H⁸¹Br), 524 (MH + H⁷⁹Br), 444 (M + H, 100). Anal. (C₂₈H₃₇N₅·5HBr·2H₂O) C, H, N, Br.

***N*-[7-(4,7,10,15-Tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Dihydrate (38)**. Using General Procedures A-C: 3,5-Bis[*N*-(2-nitrobenzenesulfonyl)-2-aminoethyl]pyridine (**15c**) gave *N*-[7-[(4,10-bis(2-nitrobenzenesulfonyl)-4,7,10,15-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (**35c**).

Using General Procedure D: **35c** (134 mg, 0.13 mmol) was reacted with thiophenol and the crude product was purified by column chromatography on silica gel (94:3:3 CH₂Cl₂/MeOH/NH₄OH) to give **38** (40 mg, 67%) as a yellow oil: ¹H NMR (CDCl₃) δ 1.30 (brs 2H), 2.44 (brs, 4H), 2.52-2.53 (m, 4H), 2.72-2.73 (m, 4H), 2.80-2.83 (m, 4H), 3.22 (s, 2H), 3.76 (s, 2H), 3.88 (s, 2H), 6.38 (d, 2H, *J* = 7.8 Hz), 7.11 (m, 3H), 7.32 (d, 1H, *J* = 7.8 Hz), 7.54 (s, 1H), 7.61 (t, 1H, *J* = 7.7 Hz), 8.39 (s, 2H), 8.39 (d, 1H, *J* = 1.8 Hz); ¹³C NMR (CDCl₃) δ 32.99 (2C), 47.82 (2C), 49.57 (2C), 53.52, 54.89, 56.12

(2C), 59.24, 122.26, 122.64, 128.31 (2C), 128.84 (2C), 134.74 (2C), 136.78, 137.20, 138.42, 139.30, 149.15 (2C), 149.66, 160.29; ES-MS m/z 445 (M+H). Anal. ($C_{27}H_{36}N_6 \cdot 1.9H_2O$) C, H, N.

***N,N'*-Bis(2-nitrobenzenesulfonyl)-1,7-heptanediamine (16a)**. To a stirred solution of 1,7-heptanediamine (**14a**) (5.01 g, 38.5 mmol) and Et_3N (13.5 mL, 96.9 mmol) in CH_2Cl_2 (70 mL) was added a solution of 2-nitrobenzenesulfonyl chloride (18.80 g, 84.83 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at room temperature under nitrogen for 72 h and then concentrated *in vacuo*. The residue was stirred in diethyl ether (100 mL), and the precipitate was collected by filtration and washed with H_2O (300 mL) followed by diethyl ether (300 mL) to give **16a** (18.5 g, 96%) as a gray solid: 1H NMR ($DMF-d_7$) δ 1.21 (m, 6H), 1.49 (m, 4H), 3.04 (m, 4H), 7.87 (m, 2H), 7.95 (m, 4H), 8.04 (m, 2H), 8.15 (m, 2H).

4-Diethoxyphosphoryl-1,7-bis(2-nitrobenzenesulfonyl)-1,4,7-triazacyclotetradecane (20a). Using General Procedure A: Reaction of **16a** (9.00 g, 18.0 mmol) and **17** (7.95 g, 20.0 mmol) followed by purification of the crude product by column chromatography on silica gel (EtOAc) gave **20a** (2.52 g, 20%) as a yellow amorphous solid: 1H NMR ($CDCl_3$) δ 1.32 (t, 6H, $J = 7.1$ Hz), 1.51 (m, 6H), 1.61 (m, 4H), 3.33 (m, 12H), 4.03 (m, 4H), 7.61 (m, 2H), 7.71 (m, 4H), 8.03 (m, 2H).

1,7-Bis(2-nitrobenzenesulfonyl)-1,4,7-triazacyclotetradecane (23a). Using General Procedure B: Reaction of **20a** (1.88 g, 2.66 mmol) gave **23a** (1.23 g, 81%) as a yellow amorphous solid: 1H NMR ($CDCl_3$) δ 1.46-1.67 (m, 10H), 2.90 (m, 4H), 3.34 (m, 8H), 7.61 (m, 2H), 7.70 (m, 4H), 7.97 (m, 2H).

***N*-[4-[1,7-Bis(2-nitrobenzenesulfonyl)-1,4,7-triazacyclotetradecanyl]-1,4-phenylenebis(methylene)]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35d)**. Using General Procedure C: Reaction of **23a** (1.1 g, 1.9 mmol) with **34a** (0.98 g, 2.3 mmol) followed by purification of the crude product by column chromatography on silica gel (3% MeOH/ CH_2Cl_2) and a second column purification on silica gel (EtOAc) gave **35d** (940 mg, 49%) as a pale yellow amorphous solid: 1H NMR ($CDCl_3$) δ 1.44 (br s, 6H), 1.60 (br s, 4H), 2.75 (m, 4H), 3.23-3.33 (m, 8H), 3.59 (s, 2H), 4.58 (s, 2H), 4.59 (s, 2H), 7.08-7.20 (m, 6H), 7.55-7.70 (m, 10H), 7.82 (dd, 2H, $J = 7.6, 1.6$ Hz), 7.99 (d, 1H, $J = 7.8$ Hz), 8.40 (d, 1H, $J = 4.7$ Hz).

***N*-[4-(1,4,7-Triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Pentahydrobromide Dihydrate (39)**. Using General Procedure D: **35d** (870 mg, 0.90 mmol) was reacted with thiophenol (0.33 mL, 3.2 mmol) and the crude product was purified by column chromatography on basic alumina (CH₂Cl₂, 1% MeOH/CH₂Cl₂, and 10% MeOH/CH₂Cl₂) to give the free base (134 mg, 36%) as a yellow oil: ¹H NMR (CDCl₃) δ 1.48 (br s, 6H), 1.60 (br s, 4H), 2.61 (m, 12H), 3.56 (s, 2H), 3.83 (s, 2H), 3.92 (s, 2H), 7.16 (m, 1H), 7.24 (m, 2H), 7.32 (m, 3H), 7.79 (m, 1H), 8.56 (d, 1H, *J* = 4.7 Hz).

Using General Procedure E: The free base (134 mg, 0.33 mmol) was converted to the corresponding hydrobromide salt to give **39** (178 mg, 63%) as a white solid: ¹H NMR (DMSO-*d*₆) δ 1.44 (br s, 6H), 1.75 (br s, 4H), 3.04 (br s, 8H), 3.37 (m, 4H), 4.06 (br s, 2H), 4.31 (s, 2H), 4.38 (s, 2H), 7.52-7.68 (m, 6H), 8.01 (m, 1H), 8.70 (d, 1H, *J* = 5.0 Hz); FAB-MS *m/z* 492 (MH+H⁸¹Br), 490 (MH+H⁷⁹Br), 410 (M+H). Anal. (C₂₅H₃₉N₅·5HBr·0.1Et₂O·2.3H₂O) C, H, N, Br.

***N,N*-[Bis(2-nitrobenzenesulfonyl)]-bis(3-aminopropyl)ether (16b)**. To a stirred solution of bis(3-aminopropyl)ether (**14b**) (513 mg, 3.88 mmol) and triethylamine (1.7 mL, 11.78 mmol) in CH₂Cl₂ (15 mL) was added a solution of 2-nitrobenzenesulfonylchloride (1.95 g, 8.53 mmol) in CH₂Cl₂ (5 mL) and the reaction mixture was allowed to stir overnight at room temperature. Water was added to the reaction and the organic layer was separated, washed with sat. aqueous NaHCO₃, then brine, dried (MgSO₄) and evaporated. Purification of the crude product by column chromatography on silica gel (10:90 EtOAc/CH₂Cl₂) gave **16b** (1.80 g, 92%) as a dark yellow oil: ¹H NMR (CDCl₃) δ 1.79-1.87 (tt, 4H, *J* = 6.0, 6.0 Hz), 3.20-3.26 (dt, 4H, *J* = 6.0, 6.0 Hz), 3.49-3.53 (t, 4H, *J* = 6.0 Hz), 5.75-5.79 (t, 2H, *J* = 6.0 Hz), 7.29-7.76 (m, 4H), 7.86-7.88 (m, 2H), 8.13-8.16 (m, 2H).

8-Diethoxyphosphoryl-5,11-bis(2-nitrobenzenesulfonyl)-1-oxa-5,8,11-triazacyclotetradecane (20b). Using General Procedure A: Reaction of **16b** (1.8 g, 3.59 mmol) with **17** (1.9 g, 4.78 mmol) followed by purification of the crude product by column chromatography on silica gel (30:70 EtOAc/CH₂Cl₂) gave **20b** (1.25 g, 55%) as a yellow foam: ¹H NMR (CDCl₃) δ 1.25-1.35 (m, 6H), 1.87-1.91 (m, 4H), 3.05-3.14 (m, 4H), 3.41-3.48 (m, 12H), 3.96-4.07 (m, 4H), 7.61-7.63 (m, 2H), 7.68-7.71 (m, 4H), 8.05-

8.09 (m, 2H); ^{13}C NMR (CDCl_3) δ 16.51, 16.60, 30.63, 44.68, 44.74, 44.92, 47.24, 63.07, 63.14, 67.69, 124.52, 131.34, 132.26, 133.58, 134.11, 148.32; exact mass m/z calcd. for $\text{C}_{26}\text{H}_{38}\text{N}_5\text{O}_{12}\text{PS}_2$ 707.17, found $[M+H]^+$ 708.5.

5,11-Bis(2-nitrobenzenesulfonyl)-1-oxa-5,8,11-triazacyclotetradecane (23b). Using General Procedure B: Reaction of **20b** (1.25 g, 1.77 mmol) followed by purification of the crude product by column chromatography on silica gel (3:3:94 MeOH/ NH_4OH / CH_2Cl_2) gave **23b** (736 mg, 74%) as a yellow oil: ^1H NMR (CDCl_3) δ 1.87-1.91 (b, 4H), 2.85-2.88 (b, 4H), 3.39-3.91 (t, 4H, $J = 6.0$ Hz), 3.49-3.56 (m, 8H), 7.59-7.70 (m, 6H), 7.98-8.01 (m, 2H); ^{13}C NMR (CDCl_3) δ 29.61, 47.90, 48.71, 68.36, 124.37, 131.07, 132.17, 133.45, 133.77, 148.65; exact mass m/z calcd. for $\text{C}_{22}\text{H}_{29}\text{N}_5\text{O}_9\text{S}_2$ 571.14, found $[M + H]^+$ 572.20.

***N*-[8-(5,11-Bis(2-nitrobenzenesulfonyl)-1-oxa-5,8,11-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35e).** Using General Procedure C: Reaction of **23b** (736 mg, 1.29 mmol) with **34a** (980 mg, 2.27 mmol) followed by purification of the crude product by column chromatography on silica gel (10:90 EtOAc/ CH_2Cl_2) gave **35e** (799 mg, 64%) as a light yellow foam: ^1H NMR (CDCl_3) δ 1.80-1.84 (b, 4H), 2.58-2.62 (t, 4H, $J = 7.1$ Hz), 3.38-3.42 (m, 8H), 3.50-3.55 (m, 6H), 4.59 (b, 4H), 7.06 (b, 4H), 7.11-7.15 (m, 1H), 7.18-7.21 (d, 1H, $J = 7.8$ Hz), 7.54-7.70 (m, 10H), 7.87-7.89 (d, 2H, $J = 7.8$ Hz), 7.99-8.01 (d, 1H, $J = 7.8$ Hz), 8.41 (d, 1H); ^{13}C NMR (CDCl_3) δ 29.93, 44.77, 46.17, 51.28, 52.00, 52.30, 59.46, 67.21, 122.57, 124.11, 128.46, 128.82, 130.48, 131.06, 131.71, 133.38, 133.53, 133.61, 134.07, 136.67, 138.20, 147.93, 149.26, 155.62; exact mass m/z calcd. for $\text{C}_{42}\text{H}_{46}\text{N}_8\text{O}_{13}\text{S}_3$ 966.23, found $[M+H]^+$ 967.20.

***N*-[8-(1-Oxa-5,8,11-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Tetrahydrobromide Tetrahydrate (40).** Using General Procedure D: Reaction of **35e** (780 mg, 0.81 mmol) with thiophenol (644 mg, 5.84 mmol) followed by purification of the crude product on silica gel (3:3:94 CH_3OH / NH_4OH / CH_2Cl_2) using a Chromatron gave the free base of the title compound (170 mg, 51%) as a yellow oil.

Using General Procedure E: The free base was converted to the corresponding hydrobromide salt to give **40** (140 mg, 46%) as a white solid: ^1H NMR (D_2O) δ 1.99-2.03

(br m, 4H), 2.85-2.88 (br m, 4H), 3.25-3.29 (br m, 8H), 3.73-3.76 (t, 4H, $J = 5.3$ Hz), 3.82 (s, 2H), 4.41 (s, 2H), 4.55 (s, 2H), 7.39-7.41 (d, 2H, $J = 8.1$ Hz), 7.52-7.55 (d, 2H, $J = 8.1$ Hz), 7.76-7.79 (m, 2H), 8.22-8.24 (m, 1H), 8.68-8.70 (m, 1H); ^{13}C NMR (D_2O) δ 25.58, 44.74, 46.92, 49.16, 49.98, 51.33, 55.08, 70.39, 126.57, 130.48, 130.95, 131.41, 137.27, 143.11, 147.01, 147.92; exact mass m/z calcd. for $\text{C}_{24}\text{H}_{37}\text{N}_5\text{O}$ 411.30, found $[M+H]^+$ 412.30. Anal. ($\text{C}_{24}\text{H}_{37}\text{N}_5\text{O}\cdot 4.1\text{HBr}\cdot 4.1\text{H}_2\text{O}$) C, H, N, Br.

Bis(3-aminopropyl)thioether (14c). To a stirred solution of 3,3'-thiodipropionitrile (1.81 g, 12.91 mmol) in THF (10 mL) was added $\text{BH}_3\cdot\text{Me}_2\text{S}$ (Aldrich 10 M solution, 4.5 mL, 45 mmol) and the mixture was heated to reflux overnight. The reaction was allowed to cool and quenched with 6 N HCl (30 mL) followed by 10 N NaOH (18 mL). Evaporation of the solvent gave **14c** (1.4 g, 73%). ^1H NMR (CDCl_3) δ 1.18-1.26 (br m, 4H), 1.68-1.79 (m, 4H), 2.55-2.60 (t, 4H, $J = 7.5$ Hz), 2.77-2.81 (t, 4H, $J = 6.0$ Hz). This material was used without further purification in the next step.

***N,N*-[Bis(2-nitrobenzenesulfonyl)]-bis(3-aminopropyl)thioether (16c).** Using an identical procedure to that described for the synthesis of **16b** above, the diamine (**14c**) (1.41 g, 9.51 mmol) was reacted with 2-nitrobenzenesulfonylchloride (4.7 g, 20.57 mmol) in CH_2Cl_2 (40 mL) containing triethylamine (4.2 mL, 29.01 mmol). Purification of the crude product by column chromatography on silica gel (10:90 EtOAc/ CH_2Cl_2) gave **16c** (4.5 g, 91%) as a dark yellow oil: ^1H NMR (CDCl_3) δ 1.78-1.87 (tt, 4H, $J = 6.8, 6.8$ Hz), 2.52-2.57 (t, 4H, $J = 7.5$ Hz), 3.18-3.25 (dt, 4H, $J = 6.0, 6.0$ Hz), 5.45-5.49 (t, 2H, $J = 6.0$ Hz), 7.75-7.78 (m, 4H), 7.78-7.86 (m, 2H), 8.13-8.16 (m, 2H).

8-Diethoxyphosphoryl-5,11-bis(2-nitrobenzenesulfonyl)-1-thia-5,8,11-triazacyclotetradecane (20c). Using General Procedure A: Reaction of **16c** (2.6 g, 5.01 mmol) with **17** (2.4 g, 6.04 mmol) followed by purification of the crude product by column chromatography on silica gel (30:70 EtOAc/hexanes) gave **20c** (810 mg, 23%) as a light yellow foam: ^1H NMR (CDCl_3) δ 1.11-1.33 (m, 6H), 1.92-1.97 (m, 4H), 2.61-2.65 (t, 4H, $J = 6.0$ Hz), 3.20-3.25 (m, 4H), 3.40-3.50 (m, 8H), 3.97-4.05 (m, 4H), 7.63-7.73 (m, 6H), 8.05-8.09 (m, 2H).

5,11-Bis(2-nitrobenzenesulfonyl)-1-thia-5,8,11-triazacyclotetradecane (23c). Using General Procedure B: Reaction of **20c** (810 mg, 1.12 mmol) gave **23c** (596 mg, 91%): ^1H NMR (CDCl_3) δ 1.96-2.05 (m, 4H), 2.60-2.65 (t, 4H, $J = 7.5$ Hz), 2.89-2.93 (t, 4H, $J =$

6.0 Hz), 3.35-3.38 (t, 4H, $J = 4.5$ Hz), 3.42-3.46 (t, 4H, $J = 6.0$ Hz), 7.63-7.73 (m, 6H), 7.96-7.99 (m, 2H). This was used without further purification in the next step.

***N*-[8-(5,11-Bis(2-nitrobenzenesulfonyl)-1-thia-5,8,11-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35f)**. Using General Procedure C: Reaction of **23c** (596 mg, 1.01 mmol) with **34a** (770 mg, 1.78 mmol) followed by purification of the crude product by column chromatography on silica gel (10:90 EtOAc/CH₂Cl₂) gave **35f** (400 mg, 40%) as a light yellow oil: ¹H NMR (CDCl₃) δ 1.94-2.05 (m, 4H), 2.58-2.62 (t, 4H, $J = 6.0$ Hz), 2.68-2.73 (t, 4H, $J = 7.5$ Hz), 3.31-3.36 (t, 4H, $J = 7.5$ Hz), 3.43-3.48 (t, 4H, $J = 7.5$ Hz), 3.56 (s, 2H), 4.60 (s, 2H), 4.75 (s, 2H), 7.10-7.20 (m, 7H), 7.58-7.71 (m, 9H), 7.82 (d, 2H), 8.0 (d, 1H), 8.45 (d, 1H).

***N*-[8-(1-Thia-5,8,11-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Tetrahydrobromide Trihydrate (41a)**. Using General Procedure D: Reaction of **35f** (400 mg, 0.41 mmol) with thiophenol (322 mg, 2.92 mmol) followed by purification of the crude product by chromatography on silica gel (3:3:94 CH₃OH/NH₄OH/CH₂Cl₂) using a Chromatron gave the free base of the title compound (107 mg, 61%) as a light yellow oil.

Using General Procedure E: The free base was converted to the corresponding hydrobromide salt to give **41a** (196 mg, 89%) as a white solid: ¹H NMR (D₂O) δ 2.03-2.07 (b, 4H), 2.88 (b, 8H), 3.29-3.32 (b, 4H), 3.35-3.39 (t, 4H, $J = 6.2$ Hz), 3.80 (s, 2H), 4.43 (s, 2H), 4.61-4.62 (d, 2H, $J = 3.0$ Hz), 7.45-7.48 (d, 2H, $J = 7.8$ Hz), 7.52-7.55 (d, 2H, $J = 7.8$ Hz), 7.84-7.95 (m, 2H), 8.34-8.42 (m, 1H), 8.75 (b, 1H); ¹³C NMR (D₂O) δ 24.30, 30.12, 45.09, 47.92, 48.41, 50.27, 51.55, 55.48, 127.27, 127.42, 130.33, 130.99, 131.60, 137.59, 145.10, 145.76, 146.96; exact mass m/z calcd. for C₂₄H₃₇N₅S: 427.28, found $[M+H]^+$ 428.30. Anal. (C₂₄H₃₇N₅S·4.3HBr·2.6H₂O) C, H, N, Br.

***N*-[8-(1-Sulfoxo-5,8,11-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (41b)**. A solution of Oxone® (504 mg, 0.82 mmol) in water (15 mL) was added dropwise to a cooled (-10 °C) stirred solution of **41a** (350 mg, 0.82 mmol) in methanol (15 mL). The mixture was stirred at -10 °C for 10 min then poured into saturated NaHCO₃ solution (40 mL) and extracted with CHCl₃ (4 x 50 mL). The separated organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of

the crude product by chromatography on silica gel (3% MeOH/CH₂Cl₂) gave **41b** (75 mg, 21%): ¹H NMR (CDCl₃) δ 1.90-2.01 (m, 2H), 2.06-2.17 (m, 2H), 2.59-2.85 (m, 14H), 3.07-3.18 (m, 2H), 3.57 (s, 2H), 3.83 (s, 2H), 3.92 (s, 2H), 7.17 (dd, 2H, *J* = 7.5, 4.7 Hz), 7.23 (d, 2H, *J* = 7.7 Hz), 7.32 (d, 2H, *J* = 7.7 Hz), 7.65 (td, 1H, *J* = 7.5, 1.7 Hz), 8.56 (d, 1H, *J* = 4.9 Hz); ¹³C NMR (CDCl₃) δ 24.36 (2), 47.52 (2), 48.30 (2), 52.38 (2), 52.81 (2), 53.55, 54.87, 59.11, 122.35, 122.73, 128.67 (2), 129.23 (2), 136.85, 138.00, 139.43, 149.68, 160.07; exact mass calcd. for C₂₄H₃₇N₅OS: 443, found: *m/z* 444 [M+H]⁺. Anal. (C₂₄H₃₇N₅OS·0.6 Et₂O·0.4H₂O) C, H, N.

N-[8-(1-Sulfonyl-5,8,11-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Tetrahydrobromide Trihydrate (41c). Di-*tert*-butyldicarbonate (278 mg, 1.3 mmol) was added to a solution of **41a** (136 mg, 0.32 mmol) in THF (3.5 mL) and H₂O (0.1 mL), and the mixture was stirred at room temperature overnight, under a nitrogen atmosphere. The mixture was concentrated and the residue was partitioned between CH₂Cl₂ (20 mL) and H₂O (10 mL). The separated organic layer was washed with H₂O (3 x 10 mL) and saturated NaCl solution (10 mL), dried (MgSO₄), and concentrated *in vacuo*. Flash chromatography on silica gel (3% MeOH/CH₂Cl₂) provided the desired Boc-protected intermediate (240 mg, 100%) as a clear oil: ¹H NMR (CDCl₃) δ 1.31-1.58 (m, 27H), 1.82-1.91 (m, 4H), 2.58-2.80 (m, 8H), 3.29-3.44 (m, 8H), 3.62 (s, 2H), 4.43 (s, 2H), 4.51 (d, 2H, *J* = 7.4 Hz), 7.12-7.23 (m, 6H), 7.65 (t, 1H, *J* = 7.5 Hz), 8.54 (d, 1H, *J* = 4.0 Hz).

A solution of Oxone® (197 mg, 0.32 mmol) in water (2 mL) was added dropwise to a cooled (-10 °C) stirred solution of the Boc-protected intermediate from above (232 mg, 0.32 mmol) in methanol (2 mL). The mixture was stirred at -10 °C for 10 mins then poured into saturated aqueous NaHCO₃ solution (5 mL) and extracted with CHCl₃ (4 x 10 mL). The separated organic layers were dried (MgSO₄) and concentrated *in vacuo* to give a clear, viscous oil. The crude material was purified by column chromatography on a silica gel column (3% MeOH/CH₂Cl₂) to give the desired sulfone (73.3 mg, 30%): ¹H NMR (CDCl₃) δ 1.39-1.50 (m, 27H), 2.06-2.14 (m, 4H), 2.60-2.68 (m, 4H), 3.10 (t, 4H, *J* = 7.2 Hz), 3.29-3.44 (m, 8H), 3.62 (s, 2H), 4.43 (s, 2H), 4.52 (d, 2H, *J* = 4.8 Hz), 7.15-7.21 (m, 6H), 7.65 (t, 1H, *J* = 7.5), 8.54 (d, 1H, *J* = 4.4 Hz); exact mass calcd for C₃₉H₆₁N₅O₈S: 759, found: *m/z* 760 [M+H]⁺.

The sulfone (73 mg, 0.96 mmol) was dissolved in a minimum amount of acetic acid and treated with a saturated solution of HBr in acetic acid (5 mL). The mixture was stirred under nitrogen for 63 h at room temperature and diethyl ether (100 mL) was added. A precipitate formed and was allowed to settle to the bottom of the flask and the supernatant solution was decanted. The white solid was washed with diethyl ether (5 x 100 mL) and the remaining traces of solvent were removed by blowing nitrogen through the flask followed by drying under vacuum overnight at 55 °C to give **41c** (70 mg, 84%) as a white solid: $^1\text{H NMR}$ (CDCl_3) δ 2.36-2.44 (m, 4H), 2.84-2.87 (m, 4H), 3.21-3.23 (m, 4H), 3.38 (t, 4H, $J = 5.4$ Hz), 3.67-3.70 (m, 4H), 3.73 (s, 2H), 4.34 (s, 2H), 4.39 (s, 2H), 7.44-7.51 (m, 6H), 7.93 (td, 1H, $J = 7.8, 1.7$ Hz), 8.58 (d, 1H, $J = 6.1$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ 18.76 (2), 45.41 (2), 47.04 (2), 47.79, 50.57 (2), 51.83, 51.88 (2), 56.71, 127.90, 128.23, 130.07, 131.03 (2), 131.29 (2), 138.44, 144.62, 145.95, 146.77; exact mass calcd. for $\text{C}_{24}\text{H}_{37}\text{N}_5\text{OS}$: 459, found: m/z 460 $[\text{M}+\text{H}]^+$. Anal. ($\text{C}_{24}\text{H}_{37}\text{N}_5\text{O}_2\text{S}\cdot 4\text{HBr}\cdot 3\text{H}_2\text{O}$) C, H, N, Br.

4,4-Difluoroheptanedioic acid diethyl ester (5). To a neat solution of (diethylamino)-sulfur trifluoride (2.02 g, 12.55 mmol) in a plastic bottle was added, 4-oxo-heptanedioic acid diethyl ester (**4**) (2.56 g, 11.13 mmol) at room temperature. The resulting mixture was allowed to stir for 12 days and then diluted with EtOAc (500 mL). The organic solution was washed with sat. NaHCO_3 , brine and dried over Na_2SO_4 . Evaporation of the solvent and purification of the residue by column chromatography on silica gel (20% EtOAc/hexanes) gave **5** (1.2 g, 43%) as a colorless oil: $^1\text{H NMR}$ (CDCl_3) δ 1.26 (t, 6H, $J = 8.0$ Hz), 2.11-2.28 (m, 4H), 2.52 (t, 4H, $J = 7.8$ Hz), 4.16 (q, 4H, $J = 4\text{H}$); $^{13}\text{C NMR}$ (CDCl_3) δ 14.16, 27.09, 27.16, 27.22, 31.52, 31.85, 32.19, 60.80, 120.18, 123.38, 126.58, 172.26; $^{19}\text{F NMR}$ (CDCl_3) δ -25.78–25.42(m); ES-MS m/z 275.1 (M+Na).

4,4-Difluoroheptane-1,7-diol (6). To a solution of **5** (1.3 g, 5.65 mmol) in diethyl ether (35 mL) at 0 °C under N_2 was slowly added solid LAH (638 mg, 11.80 mmol). The resulting mixture was allowed to stir for 30 mins at room temperature and then heated to reflux for 2 h. Upon cooling, water (0.5 mL) was added, followed by 15% NaOH (0.5 mL) and water (1.5 mL). The resulting mixture was stirred for another 2 h at room temperature and then diluted with EtOAc (500 mL). The organic solution was dried over Na_2SO_4 without aqueous work-up. Evaporation of the solvent gave **6** (0.646 g, 68%) as a

colorless oil. ^1H NMR (CDCl_3) δ 1.71-1.80 (m, 4H), 1.87-2.03 (m, 4H), 3.69 (t, 4H, $J = 6.0$ Hz); ^{13}C NMR (CDCl_3) δ 25.81, 25.87, 25.92, 32.99, 33.33, 33.67, 122.38, 125.56, 128.74; ^{19}F NMR (CDCl_3) δ -22.64-22.28(m).

1,7-Bis(toluene-4-sulfonic acid)-4,4-difluoroheptyl ester (7). To a pre-cooled (ice bath) solution of **6** (450 mg, 2.67 mmol) and triethylamine (1.2 mL, 8.31 mmol) in CH_2Cl_2 (5 mL) was added a solution of *p*-toluensulfonyl chloride (1.13 g, 5.94 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was allowed to stir for 18 h at room temperature and then diluted with EtOAc (200 mL). The organic solution was washed with sat. NaHCO_3 , then brine and dried over Na_2SO_4 . Evaporation of the solvent and purification of the residue by column chromatography on silica gel (20% EtOAc/hexanes) gave **7** (1.1 g, 83%) as a colorless oil: ^1H NMR (CDCl_3) δ 1.75-1.90 (m, 8H), 2.44 (s, 6H), 4.01-4.05 (m, 4H), 7.33 (d, 4H, $J = 8.1$ Hz), 7.75 (d, 4H, $J = 8.1$ Hz); ^{13}C NMR (CDCl_3) δ 22.06, 22.22, 22.28, 22.34, 32.80, 33.14, 33.48, 33.71, 69.96, 70.07, 121.06, 124.26, 127.46, 128.27, 130.36, 133.18, 145.42; ^{19}F NMR (CDCl_3) δ -24.27 (t); ES-MS m/z 477.1 (M+H).

4-Diethoxyphosphoryl-1,7-bis(2-nitro-benzenesulfonyl)-11,11-difluoro-1,4,7-triazacyclotetradecane (21a). Using General Procedure A: Reaction of bis-[2-(2-nitrobenzenesulfonylamino)-ethyl]-phosphoramidic acid diethyl ester (**18**²⁸) (1.5 g, 2.46 mmol) and **7** (1.07 mg, 2.25 mmol) followed by purification of the crude product by column chromatography on silica gel (50% EtOAc/ CH_2Cl_2) gave **21a** (311 mg, 19%) as a light yellow solid: ^1H NMR (CDCl_3) δ 1.32 (t, 6H, $J = 7.1$ Hz), 1.72-1.79 (m, 4H), 1.95-2.05 (m, 4H), 3.30 (s, 4H), 3.32 (s, 4H), 3.40 (t, 4H, $J = 6.15$ Hz), 3.96-4.08 (m, 4H), 7.60-7.66 (m, 2H), 7.69-7.76 (m, 4H), 7.99-8.05 (m, 2H); ^{13}C NMR (CDCl_3) δ 16.54, 16.63, 22.52, 32.07, 32.42, 32.77, 47.16, 47.89, 47.95, 50.17, 63.19, 63.27, 122.42, 124.65, 124.87, 125.67, 128.87, 131.55, 131.60, 132.16, 134.44, 148.72; ^{19}F NMR (CDCl_3) δ -14.87-14.61 (m); ES-MS m/z 742.2 (M+H).

1,7-Bis(2-nitrobenzenesulfonyl)-11,11-difluoro-1,4,7-triazacyclotetradecane (24a). Using General Procedure B: Reaction of **21a** (311 mg, 0.41 mmol) gave **24a** (239 mg, 94%) as white foam: ^1H NMR (CDCl_3) δ 1.82-1.91 (m, 4H), 1.99-2.15 (m, 4H), 2.91 (t, 4H, $J = 5.1$ Hz), 3.30-3.38 (m, 8H), 7.60-7.63 (m, 2H), 7.69-7.75 (m, 4H), 7.90-7.94 (m, 2H); ^{13}C NMR (CDCl_3) δ 23.25, 32.22, 32.57, 32.90, 50.22, 50.86, 50.96, 123.50,

124.60, 126.71, 129.89, 130.73, 132.02, 132.22, 134.27, 148.94; ^{19}F NMR (CDCl_3) δ -14.12 (t); ES-MS m/z 606.3 (M+H). This was used without further purification in the next step.

***N*-[4-(1,7-Bis(2-nitrobenzenesulfonyl)-11,11-difluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35g)**. Using General Procedure C: Reaction of **24a** (239 mg, 0.39 mmol) with **34a** (512 mg, 1.18 mmol) followed by purification of the crude product by column chromatography on silica gel (50% EtOAc/ CH_2Cl_2) gave **35g** (289 mg, 73%) as white foam: ^1H NMR (CDCl_3) δ 1.73-1.77 (m, 4H), 1.89-1.99 (m, 4H), 2.75 (t, 4H, $J = 6.8$ Hz), 3.24 (t, 4H, $J = 7.5$ Hz), 3.34 (t, 4H, $J = 6.3$ Hz), 3.58 (s, 2H), 4.56 (s, 2H), 4.59 (s, 2H), 7.08-7.18 (m, 6H), 7.52-7.75 (m, 10H), 7.83 (dd, 2H, $J = 1.5, 7.8$ Hz), 7.99 (d, 1H, $J = 7.8$ Hz), 8.40 (d, 1H); ^{13}C NMR (CDCl_3) δ 22.43, 32.32, 46.84, 48.99, 51.71, 52.36, 54.65, 59.30, 122.90, 122.96, 124.57, 124.61, 128.93, 129.76, 130.35, 131.12, 131.49, 132.12, 132.24, 133.83, 134.14, 134.29, 134.45, 134.84, 137.06, 138.30, 148.33, 148.63, 149.68, 155.96; ^{19}F NMR (CDCl_3) δ -14.52 (t); ES-MS m/z 1001.3 (M+H).

***N*-[4-(11,11-Difluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (42)**. Using General Procedure D: Reaction of **35g** (289 mg, 0.29 mmol) with thiophenol (222 mg, 2.02 mmol) followed by purification of the crude product by chromatography on silica gel (1:1:98 MeOH/ $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$) using a Chromatron gave **42** (80 mg, 62%) as a light yellow oil: ^1H NMR (CDCl_3) δ 1.63-1.72 (m, 4H), 2.00-2.15 (m, 4H), 2.60-2.65 (m, 12H), 3.57 (s, 2H), 3.83 (s, 2H), 3.93 (s, 2H), 7.14-7.18 (m, 1H), 7.20-7.34 (m, 5H), 7.60-7.67 (m, 1H), 8.55 (d, 1H, $J = 4.8$ Hz); ^{13}C NMR (CDCl_3) δ 23.47, 32.64, 32.98, 33.32, 47.69, 48.66, 53.61, 54.21, 54.94, 59.67, 122.32, 122.71, 127.03, 128.59, 129.28, 136.81, 138.49, 139.36, 149.71, 160.16; ^{19}F NMR (CDCl_3) δ -15.50 (q, $J = 12.65$ Hz); ES-MS m/z 446.4 (M+H). Anal. ($\text{C}_{25}\text{H}_{37}\text{F}_2\text{N}_5$) C, H, N.

Acetic acid, 7-acetoxy-4-hydroxyheptyl ester (9). To a solution of heptane-1,4,7-triol (**8**) (162 mg, 1.09 mmol) in pyridine (4 mL) was added acetic anhydride (216 mg, 2.28 mmol) at 0 °C. The resulting mixture was allowed to stir for 4 h at 0 °C and then diluted with EtOAc (100 mL). The organic solution was washed with sat. NaHCO_3 , brine and dried over Na_2SO_4 . Evaporation of the solvent and purification of the residue by column

chromatography on silica gel (30% EtOAc/hexanes) gave **9** (120 mg, 50%) as a colorless oil: ^1H NMR (CDCl_3) δ 1.41-1.86 (m, 8H), 2.05 (s, 6H), 3.62-3.70 (m, 1H), 4.11 (t, 4H, $J = 6.6$ Hz); ^{13}C NMR (CDCl_3) δ 21.01, 24.92, 33.82, 64.41, 71.06, 171.20.

Acetic acid, 7-acetoxy-4-fluoroheptyl ester (10). To a solution of (diethylamino)-sulfur trifluoride (571 mg, 3.54 mmol) in CH_2Cl_2 was added a solution of **9** (403 mg, 1.74 mmol) in CH_2Cl_2 (10 mL) at -78 °C. The resulting mixture was allowed to stir for 15 mins at -78 °C, 30 mins at room temperature and then diluted with EtOAc (300 mL). The organic solution was washed with sat. NaHCO_3 , brine and dried over Na_2SO_4 . Evaporation of the solvent and purification of the residue by column chromatography on silica gel (15% EtOAc/hexanes) gave **10** (386 mg, 94%) as a colorless oil: ^1H NMR (CDCl_3) δ 1.55-1.83 (m, 8H), 2.05 (s, 6H), 4.05-4.15 (m, 4H), 4.39-4.63 (m, 1H); ^{13}C NMR (CDCl_3) δ 20.97, 24.42, 24.48, 31.51, 31.79, 64.03, 92.22, 94.45, 171.12; ^{19}F NMR (CDCl_3) δ -106.44-105.27(m); ES-MS m/z 257.3 (M+Na).

4-Fluoroheptane-1,7-diol (11). MeOH (15 mL) saturated with anhydrous NH_3 gas was added to **10** (500 mg, 2.13 mmol) contained in round-bottomed flask closed by a glass stopper. The mixture was allowed to stir for over 28 h at room temperature and then concentrated. Purification of the residue by column chromatography on silica gel (5% MeOH/ CH_2Cl_2) gave **11** (320 mg, 100%) as a colorless oil: ^1H NMR (CDCl_3) δ 1.59-1.83 (m, 8H), 3.67 (t, 4H, $J = 5.7$ Hz), 4.47-4.67 (m, 1H); ^{13}C NMR (CDCl_3) δ 28.73, 28.75, 31.78, 32.06, 62.88, 93.56, 95.98; ES-MS m/z 173.2 (M+Na).

1,7-Bis(toluene-4-sulfonic acid)-4-fluoroheptyl ester (12). To a pre-cooled (ice bath) solution of **11** (320 mg, 2.13 mmol) and triethylamine (1.0 mL, 6.90 mmol) in CH_2Cl_2 (10 mL) was added a solution of *p*-toluensulfonyl chloride (812 mg, 4.27 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred for 18 h at room temperature and then diluted with EtOAc (200 mL). The organic solution was washed with sat. NaHCO_3 , brine and dried over Na_2SO_4 . Evaporation of the solvent and purification of the residue by column chromatography on silica gel (20% EtOAc/hexanes) gave **12** (627 mg, 100%) as a colorless oil: ^1H NMR (CDCl_3) δ 1.52-1.86 (m, 8H), 2.45 (s, 6H), 4.00-4.08 (m, 4H), 4.28-4.44 (m, 1H), 7.37 (d, 4H, $J = 8.4$ Hz), 7.77 (d, 4H, $J = 8.4$ Hz); ^{13}C NMR (CDCl_3)

δ 22.06, 25.09, 25.15, 31.32, 31.60, 70.34, 91.97, 94.21, 128.29, 130.30, 133.36, 145.28; ^{19}F NMR (CDCl_3) δ -107.54-107.02 (m); ES-MS m/z 481.3 (M+Na).

4-Diethoxyphosphoryl-1,7-bis(2-nitrobenzenesulfonyl)-11-fluoro-1,4,7-triazacyclotetradecane (21b). Using General Procedure A: Reaction of **18** (1.07 g, 1.75 mmol) and **12** (687 mg, 1.49 mmol) followed by purification of the crude product by column chromatography on silica gel (50% EtOAc/ CH_2Cl_2) gave **21b** (560 mg, 55%) as a light yellow solid: ^1H NMR (CDCl_3) δ 1.31 (ddd, 6H, $J = 0.6, 7.2, 7.2$ Hz), 1.65-1.89 (m, 8H), 3.22-3.46 (m, 12H), 3.93-4.14 (m, 4H), 4.67-4.83 (m, 1H), 7.60-7.65 (m, 2H), 7.68-7.75 (m, 4H), 7.99-8.05 (m, 2H); ^{13}C NMR (CDCl_3) δ 16.54, 16.64, 22.65, 22.74, 29.66, 29.95, 47.04, 47.37, 47.43, 50.22, 63.17, 63.25, 91.38, 93.62, 124.59, 131.67, 131.96, 132.06, 134.22, 148.69; ^{19}F NMR (CDCl_3) δ -99.84-99.41 (m); ES-MS m/z 724.6 (M+H).

1,7-Bis(2-nitrobenzenesulfonyl)-11-fluoro-1,4,7-triazacyclotetradecane (24b).

Using General Procedure B: Reaction of **21b** (560 mg, 0.77 mmol) gave **24b** (454 mg, 100%) as white foam. ^1H NMR (CDCl_3) δ 1.75-1.99 (m, 8H), 2.90 (t, 4H, $J = 5.0$ Hz), 3.26-3.39 (m, 8H), 4.61-4.77 (m, 1H), 7.60-7.65 (m, 2H), 7.68-7.72 (m, 4H), 7.94-7.97 (m, 2H); ES-MS m/z 588.3 (M+H). This was used without further purification in the next step.

N-[4-(1,7-Bis(2-nitrobenzenesulfonyl)-11-fluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-N-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35h).

Using General Procedure C: Reaction of **24b** (454 mg, 0.77 mmol) with **34a** (743 mg, 1.72 mmol) followed by purification of the crude product by column chromatography on silica gel (50% EtOAc/ CH_2Cl_2) gave **35h** (445 mg, 59%) as white foam: ^1H NMR (CDCl_3) δ 1.67-1.83 (m, 8H), 2.69-2.76 (m, 4H), 3.19 (td, 4H, $J = 8.1, 8.1$ Hz), 3.34 (t, 4H, $J = 6.2$ Hz), 3.75 (s, 2H), 4.50 (s, 2H), 4.60 (s, 2H), 4.59-4.80 (m, 1H), 7.08-7.20 (m, 7H), 7.51-7.73 (m, 9H), 7.81 (dd, 2H, $J = 1.8, 7.5$ Hz), 8.01 (d, 1H, $J = 7.8$ Hz), 8.38 (d, 1H); ^{19}F NMR (CDCl_3) δ -99.61-98.50 (m); ES-MS m/z 983.3 (M+H).

N-[4-(11-Fluoro-1,4,7-triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (43).

Using General Procedure D: Reaction of **35h** (445 mg, 0.45 mmol) with thiophenol (348 mg, 3.17 mmol) followed by purification of the crude product by chromatography on silica gel (1:1:98 MeOH/ $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$) gave **43** (80 mg, 62%): ^1H NMR (CDCl_3) δ 1.52-1.85 (m, 8H), 2.53-2.63 (m, 12H), 3.57 (s, 2H), 3.83

(s, 2H), 3.93 (s, 2H), 5.07-5.30 (m, 1H), 7.14-7.33 (m, 6H), 7.64 (ddd, 1H, $J = 1.8, 7.8, 7.8$ Hz), 8.55-8.57 (m, 1H); ^{13}C NMR (CDCl_3) δ 24.43, 32.13, 32.41, 47.32, 48.47, 52.44, 53.21, 54.52, 58.92, 121.94, 122.32, 128.26, 128.87, 136.42, 137.80, 139.04, 149.33, 159.75; ^{19}F NMR (CDCl_3) δ -102.30-103.00 (m); ES-MS m/z 428.3 (M+H). Anal. ($\text{C}_{25}\text{H}_{38}\text{FN}_5$) C, H, N.

4-Diethoxyphosphoryl-7-(2-nitrobenzenesulfonyl)-1,4,7-triazacyclotetradecane (25).

Using a Modified General Procedure D: To a stirred solution **20a** (1.32 g, 1.87 mmol) and K_2CO_3 (654 mg, 4.73 mmol) in DMF (11 mL) under nitrogen was added dropwise a solution of thiophenol (0.15 mL, 1.46 mmol, 0.8 equiv.) in DMF (8 mL) over 1 h. The mixture was stirred for an additional 3 h and then concentrated *in vacuo*. The residue was partitioned between CHCl_3 (50 mL) and H_2O (25 mL). The aqueous phase was separated and extracted with CHCl_3 (3 \times 20 mL) and the combined organic extracts were dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by column chromatography on basic alumina (CHCl_3 then 3% MeOH/ CHCl_3) to give **25** (178 mg, 23%) as a yellow oil: ^1H NMR (CDCl_3) δ 1.31 (t, 6H, $J = 7.0$ Hz), 1.40-1.67 (m, 10H), 2.65 (m, 2H), 2.78 (m, 2H), 3.12 (m, 2H), 3.26-3.37 (m, 4H), 3.48 (m, 2H), 3.97-4.09 (m, 4H), 7.61 (m, 1H), 7.68 (m, 2H), 8.06 (m, 1H).

***N*-[1-[4-Diethoxyphosphoryl-7-(2-nitrobenzenesulfonyl)-1,4,7-triazacyclotetradecanyl]-1,4-phenylenebis(methylene)]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35i).** Using General Procedure C: Reaction of **25** (236 mg, 0.453 mmol) and **34a** (238 mg, 0.551 mmol) followed by purification of the crude product by column chromatography on silica gel (50% then 80% THF/hexane) gave **35i** (305 mg, 73%) as a yellow amorphous solid: ^1H NMR (CDCl_3) δ 1.27 (t, 6H, $J = 7.1$ Hz), 1.43 (br s, 8H), 1.63 (br s, 2H), 2.32 (br s, 2H), 2.55 (m, 2H), 3.13-3.41 (m, 8H), 3.49 (s, 2H), 3.85-4.02 (m, 4H), 4.57 (s, 2H), 4.58 (s, 2H), 7.07-7.22 (m, 6H), 7.51-7.71 (m, 7H), 7.98 (d, 1H, $J = 7.4$ Hz), 8.04 (m, 1H), 8.41 (d, 1H, $J = 4.0$ Hz).

***N*-[1-(1,4,7-Triazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Pentahydrobromide Dihydrate (44).** Compound **44** was prepared by stepwise de-protection of the Dep- and Ns- groups as follows:

Using General Procedure B: Reaction of **35i** (300 mg, 0.328 mmol) gave *N*-[1-[7-(2-nitrobenzenesulfonyl)-1,4,7-triazacyclotetra-decanyl]-1,4-phenylenebis(methylene)]-

N-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (214 mg, 84%) as a yellow amorphous solid: $^1\text{H NMR}$ (CDCl_3) δ 1.34-1.44 (m, 8H), 1.69 (br s, 2H), 2.34 (m, 2H), 2.52 (m, 2H), 2.62 (m, 2H), 2.82 (m, 2H), 3.42 (m, 6H), 4.58 (s, 2H), 4.59 (s, 2H), 7.08-7.24 (m, 6H), 7.52-7.71 (m, 7H), 8.01 (m, 2H), 8.42 (d, 1H, $J = 4.1$ Hz).

A mixture of the intermediate from above (209 mg, 0.268 mmol), K_2CO_3 (298 mg, 2.16 mmol), and thiophenol (0.17 mL, 1.7 mmol) in acetonitrile (3 mL) were heated to 50°C for 16.5 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine (10 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried (MgSO_4) and evaporated. The residue was purified by column chromatography on basic alumina (CHCl_3 then 10% MeOH/ CHCl_3) to give the free base of title compound (92 mg, 84%) as a yellow oil: $^1\text{H NMR}$ (CDCl_3) δ 1.21-1.62 (m, 10H), 2.40-2.49 (m, 4H), 2.60 (m, 6H), 2.79 (m, 2H), 3.49 (s, 2H), 3.80 (s, 2H), 3.91 (s, 2H), 7.14 (m, 1H), 7.28 (m, 5H), 7.62 (m, 1H), 8.54 (d, 1H, $J = 4.4$ Hz).

Using General Procedure E: The free base (86 mg, 0.21 mmol) was converted to the corresponding hydrobromide salt to give **44** (128 mg, 70%) as a white solid: $^1\text{H NMR}$ (D_2O) δ 1.48 (br s, 6H), 1.82 (m, 4H), 3.22-3.36 (m, 10H), 3.50 (br s, 2H), 4.48 (s, 4H), 4.64 (s, 2H), 7.62 (s, 4H), 7.88 (m, 1H), 7.94 (d, 1H, $J = 8.0$ Hz), 8.38 (m, 1H), 8.77 (d, 1H, $J = 5.2$ Hz); FAB-MS m/z 492 ($\text{MH}+\text{H}^{81}\text{Br}$), 490 ($\text{M}+\text{H}^{79}\text{Br}$), 410 ($\text{M}+\text{H}$). Anal. ($\text{C}_{25}\text{H}_{39}\text{N}_5\cdot 5\text{HBr}\cdot 2.5\text{H}_2\text{O}\cdot 0.1\text{Et}_2\text{O}$) C, H, N, Br.

7-Diethoxyphosphoryl-10-(2-nitrobenzenesulfonyl)-4,7,10,17-tetraazabicyclo

[11.3.1]heptadeca-1(17),13,15-triene (26a). Using a modification to General Procedure D: To a solution of **19a** (1.48 g, 2.00 mmol) was added thiophenol (0.8 equiv.), dropwise over 1 h and the DMF solution was heated at 50°C for 1.5 h. Purification of the crude reaction product by column chromatography on silica gel (8% MeOH/ CHCl_3) gave **26a** (423 mg, 52%) as a light yellow oil: $^1\text{H NMR}$ (CDCl_3) δ 1.23 (t, 6H, $J = 7.0$ Hz), 2.50 (br s, 2H), 2.79 (br s, 2H), 3.02-3.15 (m, 10H), 3.82-3.98 (m, 6H), 7.06 (d, 2H, $J = 7.6$ Hz), 7.54-7.63 (m, 2H), 7.70 (m, 2H), 8.01 (br s, 1H).

N-[4-[7-Diethoxyphosphoryl-10-(2-nitrobenzenesulfonyl)-4,7,10,17-tetraazabicyclo

[11.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-N-(2-

nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35j). Using General Procedure C:

Reaction of **26a** (410 mg, 0.738 mmol) and **34a** (397 mg, 0.919 mmol) followed by

purification of the crude reaction product by column chromatography on silica gel (50%, 80%, and 90% THF/hexane) gave **35j** (441 mg, 63%) as a white amorphous solid: ^1H NMR (CDCl_3) δ 1.15 (t, 6H, $J = 7.0$ Hz), 2.42 (m, 4H), 2.77 (m, 2H), 2.92-3.02 (m, 6H), 3.10 (m, 2H), 3.59 (s, 2H), 3.66-3.91 (m, 6H), 4.58 (s, 2H), 4.59 (s, 2H), 6.94 (d, 1H, $J = 7.6$ Hz), 7.07-7.14 (m, 6H), 7.22 (d, 1H, $J = 7.8$ Hz), 7.51-7.72 (m, 8H), 8.00 (d, 1H, $J = 7.8$ Hz), 8.04 (m, 1H), 8.42 (d, 1H, $J = 4.0$ Hz).

***N*-[4-[4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Hexahydrobromide Hydrate (45)**. Compound **45** was prepared by a stepwise deprotection of the Ns and Dep groups as follows:

A mixture of **35j** (434 mg, 0.456 mmol), K_2CO_3 (508 mg, 3.68 mmol), and thiophenol (0.28 mL, 2.7 mmol) were heated to 50 °C in CH_3CN (3.5 mL) under nitrogen for 15 h. Upon cooling, the reaction mixture was partitioned between CHCl_3 (15 mL) and brine (15 mL) and the aqueous layer was separated and extracted with CHCl_3 (3 \times 5 mL). The combined organic extracts were dried (MgSO_4) and concentrated *in vacuo* and the residue was purified by column chromatography on basic alumina (CHCl_3 then 10% MeOH/ CHCl_3) to give *N*-[4-[7-diethoxyphosphoryl-4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-*N*-2-(aminomethyl)pyridine (218 mg, 82%) as a yellow oil: ^1H NMR (CDCl_3) δ 1.16 (t, 6H, $J = 7.1$ Hz), 2.35 (m, 2H), 2.55 (m, 2H), 2.75 (m, 2H), 2.82 (m, 2H), 2.96-3.08 (m, 6H), 3.16 (m, 2H), 3.68 (s, 2H), 3.69-3.88 (m, 4H), 3.82 (s, 2H), 3.93 (s, 2H), 6.95 (d, 1H, $J = 7.6$ Hz), 7.00 (d, 1H, $J = 7.5$ Hz), 7.15-7.34 (m, 6H), 7.50 (m, 1H), 7.65 (m, 1H), 8.56 (d, 1H, $J = 4.7$ Hz).

To a stirred solution of the intermediate from above (211 mg, 0.36 mmol) in acetic acid (0.6 mL) was added a freshly prepared solution of saturated HBr(g) in acetic acid (6 mL) and the reaction mixture was allowed to stir at room temperature for 4 h. Addition of diethyl ether (10 mL) gave a white precipitate that was allowed to settle to the bottom of the flask and the supernatant solution was decanted. The solid was washed by decantation with MeOH (4 \times 5 mL) and ether (6 \times 5 mL) and the remaining traces of ether were removed by evaporation under reduced pressure. The product was dried *in vacuo* at 40 °C for 17 h, to give **45** (223 mg, 63%) as a pale yellow solid: ^1H NMR (D_2O)

δ 3.14-3.36 (m, 10H), 3.55 (m, 4H), 3.75 (m, 2H), 4.45 (s, 2H), 4.50 (s, 2H), 4.64 (s, 2H), 7.22 (m, 2H), 7.53 (s, 4H), 7.70 (m, 1H), 7.95 (m, 1H), 8.00 (d, 1H, $J = 7.9$ Hz), 8.46 (m, 1H), 8.79 (d, 1H, $J = 3.9$ Hz); FAB-MS m/z 527 (MH+H⁸¹Br), 525 (MH+H⁷⁹Br), 445 (M+H). Anal. (C₂₇H₃₆N₆·6HBr·1.5H₂O·0.2Et₂O) C, H, N, Br.

7-Diethoxyphosphoryl-10-(2-nitrobenzenesulfonyl)-4,7,10-triazabicyclo[11.3.1]

heptadeca-1(17),13,15-triene (26b). Reaction of **19b** (1.11 g, 1.5 mmol) with thiophenol (0.8 equiv.) added dropwise over 1 h, followed by silica gel column purification of the reaction products (2:5:20 CH₃OH/Et₂O/CH₂Cl₂ then 1:5 CH₃OH/CH₂Cl₂) gave **26b** (300 mg, 54%) as a pale yellow oil: ¹H NMR (CDCl₃) δ 1.21 (t, 6H, $J = 7.1$ Hz), 1.78-1.92 (br s, 1H), 2.31-2.38 (br m, 2H), 2.56-2.60 (br m, 2H), 2.81-2.98 (br m, 10H), 3.60-3.64 (br m, 2H), 3.75-3.91 (m, 4H), 7.05-7.12 (m, 2H), 7.24-7.29 (m, 2H), 7.60-7.63 (m, 1H), 7.68-7.71 (m, 2H), 8.02-8.06 (m, 1H).

N-[4-[7-Diethoxyphosphoryl-10-(2-nitrobenzenesulfonyl)-4,7,10-triazabicyclo

[11.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-N-(2-

nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35k). Using General Procedure C: Reaction of **26b** (290 mg, 0.52 mmol) with **34a** (271 mg, 0.63 mmol) followed by silica gel column purification of the reaction products (1:12:12 CH₃OH/Et₂O/CH₂Cl₂) gave **35k** (298 mg, 60%) as a pale yellow solid: ¹H NMR (CDCl₃) δ 1.17 (t, 6H, $J = 7.0$ Hz), 2.29-2.45 (br m, 4H), 2.55-2.65 (br m, 2H), 2.71-2.75 (br s, 4H), 2.85-2.91 (br m, 2H), 2.96-2.98 (br m, 2H), 3.57 (s, 2H), 3.67-3.84 (br m, 6H), 4.57-4.61 (br s, 4H), 7.07-7.28 (br m, 10H), 7.55-7.71 (br m, 7H), 7.99-8.02 (m, 2H), 8.42-8.46 (m, 1H).

N-[4-[4,7,10-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl]-1,4-

phenylenebis(methylene)]-2-(aminomethyl)pyridine Pentahydrobromide Dihydrate (46). Compound **46** was prepared by stepwise deprotection of the Dep and Ns groups as follows:

Using General Procedure B: Reaction of **35k** (290 mg, 0.31 mmol) gave *N*-[4-[10-(2-nitrobenzenesulfonyl)-4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (240 mg, 95%) as a white solid: ¹H NMR (CDCl₃) δ 1.65-1.79 (br s, 1H), 2.15-2.19 (br m, 4H), 2.44-2.48 (br m, 2H), 2.61-2.65 (br m, 2H), 2.67-2.71 (br m, 2H), 3.00-3.04 (br m, 2H), 3.10-3.14 (br m, 2H), 3.56-3.60 (br s, 4H), 4.55 (s, 2H), 4.61 (s, 2H), 6.96 (d, 1H, J

= 7.8 Hz), 7.02-7.10 (br m, 6H), 7.22-7.28 (br m, 3H), 7.52-7.72 (br m, 7H), 7.96-7.99 (m, 2H), 8.42-8.46 (m, 1H). This was used without further purification in the next step.

Using General Procedure D: Reaction of the intermediate from above (236 mg, 0.29 mmol) with thiophenol followed by alumina column purification of the reaction products (1:99 CH₃OH/CH₂Cl₂ then 1:10 CH₃OH/CH₂Cl₂) gave the free base of the title compound (111 mg, 86%) as a pale yellow oil: ¹H NMR (CDCl₃) δ 2.24-2.28 (br s, 3H), 2.43-2.50 (br m, 4H), 2.58-2.62 (br m, 2H), 2.73-2.79 (br m, 8H), 2.95-2.98 (br m, 2H), 3.50 (s, 2H), 3.77 (s, 2H), 3.90 (s, 2H), 6.83-6.87 (br m, 3H), 7.05-7.33 (br m, 7H), 7.63-7.67 (m, 1H), 8.54-8.56 (m, 1H).

Using General Procedure E: The free base (104 mg, 0.23 mmol) was converted to the corresponding hydrobromide salt to give **46** (101 mg, 52%) as a white solid: ¹H NMR (D₂O) δ 2.90-2.94 (br m, 2H), 2.97-3.01 (br m, 2H), 3.12-3.16 (br m, 2H), 3.17-3.21 (br m, 2H), 3.24-3.28 (br m, 4H), 3.47-3.51 (br m, 2H), 3.57-3.61 (br m, 2H), 4.38-4.42 (m, 6H), 7.34-7.40 (m, 2H), 7.46-7.60 (m, 8H), 7.90-7.94 (m, 1H), 8.58-8.62 (m, 1H); FAB-MS *m/z* 526 (MH+H⁸¹Br), 524 (MH+H⁷⁹Br), 444 (M+H, 100). Anal. (C₂₈H₃₇N₅·5HBr·2.5H₂O) C, H, N, Br.

***N*-[3-(6-Diethoxyphosphoryl-3,6,17-triazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)-*N*-(diethoxyphosphoryl)-2-**

(aminomethyl)pyridine (35I). Using General Procedure C: Reaction of 6-diethoxyphosphoryl-3,6,17-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (**27a**⁵⁰) (76 mg, 0.21 mmol) with *N*-[1-methylene-4-(chloromethylene)phenylene]-*N*-(diethoxyphosphoryl)-2-(aminomethyl)pyridine (**34b**, See supplementary material) (134 mg, 0.35 mmol) followed by purification of the crude product by chromatography on silica gel (30:70 EtOAc/CH₂Cl₂) using a Chromatron gave **35I** (91 mg, 62%) as a light yellow solid: ¹H NMR (CDCl₃) δ 1.11-1.21 (m, 2H), 1.22-1.32 (m, 14H), 1.51 (b, 2H), 1.92-1.94 (m, 2H), 2.47-2.57 (m, 2H), 2.61-2.66 (m, 2H), 2.77-2.80 (m, 2H), 3.10-3.18 (m, 2H), 3.64 (s, 2H), 3.81 (s, 2H), 3.83-4.17 (m, 8H), 4.19 (dd, 4H, *J* = 10.2, 15.9 Hz), 6.97 (d, 1H, *J* = 7.2 Hz), 7.06 (d, 1H, *J* = 7.8 Hz), 7.12 (dd, 1H, *J* = 5.4, 6.6 Hz), 7.27-7.41 (m, 5H), 7.50 (t, 1H, *J* = 7.7 Hz), 7.60 (dt, 1H, *J* = 1.5, 7.5 Hz), 8.52 (d, 1H); ¹³C NMR (CDCl₃) δ 16.52, 24.87, 25.02, 26.13, 26.45, 37.40, 42.45, 45.37, 45.38, 49.74, 50.21, 51.04, 59.48, 59.92, 62.11, 62.86, 121.94, 122.42, 122.70, 122.84, 129.19, 129.36,

136.75, 136.75, 138.78, 149.55, 158.82, 158.83, 159.30, 161.12; exact mass m/z calcd. for $C_{36}H_{55}N_5O_6P_2$: 715.36, found $[M+H]^+$ 716.42.

***N*-[3-(3,6,17-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Tetrahydrobromide Tetrahydrate (47)**. A saturated solution of HBr(g) in acetic acid (5 mL) was added to **35l** (91 mg, 0.13 mmol) contained in round bottomed flask closed by a glass stopper and the resulting solution was allowed to stir overnight at room temperature. Diethyl ether (50 mL) was added to give a white precipitate, which was allowed to settle to the bottom of the flask and the supernatant solution was decanted. The solid was washed by decantation with diethyl ether (5 x) then dried *in vacuo* overnight at 50 °C to give **47** (99 mg, 92%) as a white solid: 1H NMR (D_2O) δ 1.09-1.19 (m, 2H), 1.43-1.47 (m, 2H), 1.70-1.74 (m, 2H), 1.89 (b, 2H), 2.60 (t, 2H, $J = 7.2$ Hz), 2.76 (t, 2H, $J = 5.6$ Hz), 3.14 (t, 2H, $J = 6.0$ Hz), 3.35 (t, 2H, $J = 5.4$ Hz), 4.04 (s, 2H), 4.12 (s, 2H), 4.37 (s, 2H), 4.42-4.43 (m, 2H), 7.45-7.60 (m, 7H), 7.78 (d, 1H, $J = 7.8$ Hz), 7.97-8.00 (m, 1H), 8.27 (t, 1H, $J = 8.0$ Hz), 8.62 (b, 1H); ^{13}C NMR (D_2O) δ 22.87, 23.20, 23.50, 26.16, 32.39, 43.37, 44.64, 45.82, 49.54, 51.23, 56.22, 56.86, 126.14, 126.17, 126.24, 127.91, 130.77, 130.82, 131.84, 135.29, 142.34, 146.84, 147.66, 148.59, 152.16, 159.39; exact mass m/z calcd. for $C_{28}H_{37}N_5$ 443.30, found $[M+H]^+$ 444.22. Anal. ($C_{28}H_{37}N_5 \cdot 4.3HBr \cdot 3.8H_2O$) C, H, N, Br.

***N*-[4-(7-Diethoxyphosphoryl-4,7,17-triaza-bicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-*N*-(diethoxyphosphoryl)-2-(aminomethyl)pyridine (35m)**. Using General Procedure C: Reaction of 7-diethoxyphosphoryl-4, 7, 17-triaza-bicyclo[11.3.1]heptadeca-1(17), 13, 15-triene (**27b**⁵⁰) (23 mg, 0.062 mmol) with *N*-[1-methylene-4-(chloromethylene)phenylene]-*N*-(diethoxyphosphoryl)-2-(aminomethyl)pyridine (**34b**) (41 mg, 0.10 mmol) followed by purification of the crude product by chromatography on silica gel (97:3 $CH_2Cl_2/MeOH$) using a Chromatron gave **35m** (35 mg, 80%) as a light yellow solid: 1H NMR ($CDCl_3$) δ 1.13 (t, 6H, $J = 7.1$ Hz), 1.20-1.26 (m, 2H), 1.29 (t, 6H, $J = 7.1$ Hz), 1.41 (t, 2H, $J = 6.6$ Hz), 1.92 (b, 2H), 2.34-2.49 (m, 4H), 2.76-2.87 (m, 6H), 3.03-3.06 (m, 2H), 3.65 (s, 2H), 3.72-3.86 (m, 4H), 4.07-4.26 (m, 8H), 6.89 (d, 1H, $J = 7.5$ Hz), 6.96 (d, 1H, $J = 7.5$ Hz), 7.15-7.23 (m, 5H), 7.39 (d, 1H, $J = 7.5$ Hz), 7.47 (dd, 1H, $J = 7.7, 7.7$ Hz), 7.62 (td, 1H, $J = 7.5, 1.5$ Hz), 8.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 16.42, 16.60, 24.40, 27.55, 28.61, 37.34, 37.65, 46.17, 46.24,

49.61, 50.79, 50.85, 54.70, 54.88, 59.27, 61.96, 62.82, 121.28, 121.97, 122.43, 122.71, 129.07, 129.20, 136.42, 136.76, 139.49, 149.57, 158.77, 161.01, 161.66; exact mass m/z calcd. for $C_{36}H_{55}N_5O_6P_2$: 715.36, found $[M+H]^+$ 716.41.

***N*-[4-(4,7,17-Triaza-bicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Pentahydrobromide Dihydrate (48)**. A saturated solution of HBr(g) in dioxane (1.5 mL) was added to **35m** (29 mg, 0.041 mmol) contained in round bottomed flask closed by a glass stopper. The resulting solution was allowed to stir overnight at room temperature and then diethyl ether (50 mL) was added. The white precipitate that formed was allowed to settle to the bottom of the flask and the supernatant solution was decanted. The solid was washed by decantation with diethyl ether (5 x) and then dried *in vacuo* overnight at 50 °C to give **48** (29 mg, 85%) as a white solid: 1H NMR (D_2O) δ 1.27-1.31 (m, 2H), 1.52 (b, 2H), 1.93 (b, 2H), 2.79 (b, 2H), 2.94 (b, 2H), 3.06 (b, 6H), 3.19-3.21 (m, 2H), 3.75, (m, 2H), 4.33 (s, 2H), 4.37 (s, 2H), 7.16 (d, 2H, $J = 7.8$ Hz), 7.38-7.49 (m, 4H), 7.58-7.61 (m, 1H), 7.86 (dd, 2H, $J = 8.0, 8.0$ Hz), 8.05-8.09 (m, 1H), 8.57-8.59 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.84, 26.36, 29.44, 33.51, 35.02, 46.33, 48.39, 51.90, 52.28, 53.80, 55.60, 58.14, 128.80, 128.88, 133.09, 133.33, 133.91, 139.61, 145.23, 149.63, 149.89, 150.85, 158.18, 160.81; exact mass m/z calcd. for $C_{28}H_{37}N_5$ 443.30, found $[M+H]^+$ 444.26. Anal. ($C_{28}H_{37}N_5 \cdot 5.1HBr \cdot 2.3H_2O \cdot 2.3C_4H_8O_2$) C, H, N, Br.

***N*-[4-(4,7,17-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-trien-6-one-yl)-1,4-phenylenebis(methylene)]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (35n)**. Using General Procedure C: Reaction of 4,7,17-triaza-bicyclo[11.3.1]heptadeca-1(17),13,15-trien-6-one (**28⁵⁰**) (30 mg, 0.12 mmol) with **34a** (55 mg, 0.13 mmol) followed by purification of the crude product by chromatography on silica gel (3:97 MeOH- CH_2Cl_2) using a Chromatron gave **35n** (61 mg, 79%) as a light yellow solid: 1H NMR ($CDCl_3$) δ 1.31-1.36 (m, 2H), 1.56-1.59 (m, 2H), 1.88-1.92 (m, 2H), 2.89-2.95 (m, 6H), 3.00 (s, 2H), 3.27-3.29 (m, 2H), 3.50 (s, 2H), 4.55 (s, 2H), 4.57 (s, 2H), 6.73 (d, 2H, $J = 9.0$ Hz), 6.83 (d, 1H, $J = 6.0$ Hz), 6.97 (d, 2H, $J = 9.0$ Hz), 7.05-7.07 (m, 3H), 7.18 (d, 1H), 7.47-7.52 (m, 3H), 7.65 (d, 2H, $J = 3.0$ Hz), 7.94 (d, 1H), 8.42 (d, 1H).

***N*-[4-(4, 7, 17-triazabicyclo[11.3.1]heptadeca-1(17), 13, 15-trien-6-one-yl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Tetrahydrobromide Hydrate (49)**.

Using General Procedure D: Reaction of **35n** (61 mg, 0.09 mmol) with thiophenol (54 mg, 0.48 mmol) followed by purification of the crude product by chromatography on silica gel (3:3:94 CH₃OH/NH₄OH/CH₂Cl₂) using a Chromatron gave the free base of the title compound (20 mg, 49%) as a light yellow oil.

The free base was re-dissolved in a saturated solution of HBr(g) in dioxane (1 mL) and the resulting solution was allowed to stir for 30 min. at room temperature. Diethyl ether (50 mL) was added and the white precipitate that formed was allowed to settle to the bottom of the flask and the supernatant solution was decanted. The solid was washed by decantation with diethyl ether (5 x) and dried *in vacuo* at 50 °C overnight to give **49** (31 mg, 88%) as a white solid: ¹H NMR (D₂O) δ 1.06-1.14 (m, 2H), 1.47-1.50 (m, 2H), 1.83-1.87, (m, 2H), 3.06-3.10 (m, 4H), 3.37-3.39 (m, 2H), 3.44 (s, 2H), 3.52-3.53 (m, 2H), 4.14 (s, 2H), 4.38 (s, 2H), 4.40 (s, 2H), 7.37 (d, 2H, *J* = 8.1 Hz), 7.49 (d, 4H, *J* = 8.4 Hz), 7.71 (d, 1H, *J* = 7.8 Hz), 7.78 (d, 1H, *J* = 7.8 Hz), 7.90 (td, 1H, *J* = 7.8, 1.8 Hz), 8.31 (dd, 1H, *J* = 8.0, 8.0 Hz), 8.59 (m, 1H); ¹³C NMR (D₂O) δ 25.13, 28.77, 29.09, 33.44, 34.63, 40.29, 53.19, 53.31, 57.33, 58.88, 62.62, 127.19, 127.60, 127.76, 129.03, 133.51, 133.92, 134.26, 137.63, 141.88, 149.30, 152.11, 152.76, 156.73, 161.06, 172.25; exact mass *m/z* calcd. for C₂₈H₃₅N₅O 457.62, found [*M+H*]⁺ 458.2. Anal. (C₂₈H₃₅N₅O·3.9HBr·H₂O) C, H, N, Br.

2-(4-Cyano-benzyl)-malonic acid dimethyl ester (51). Dimethyl malonate (**50**) (10.00 g, 75.7 mmol) was added to a stirred suspension of NaH (60% in oil, 3.33 g, 83.3 mmol) in THF (100 mL) over 20 minutes at room temperature. The mixture was heated at 80 °C for 15 minutes, and then a solution of α-bromotolunitrile (14.84 g, 75.69 mmol) in THF (100 mL) was added. Heating was continued at 80 °C for 1 h, then at 50 °C for 64 h. Upon cooling, the reaction was quenched with water (30 mL), and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (MgSO₄) and concentrated. Purification of the crude product by column chromatography on silica gel (25% EtOAc/hexanes) gave **51** (8.49 g, 45%) as colorless crystals: ¹H NMR (CDCl₃) □ 3.27 (d, 2H, *J* = 9.0 Hz), 3.67 (t, 1H, *J* = 9.0 Hz), 3.70 (s, 6H), 7.32 (d, 2H, *J* = 9.0 Hz), 7.58 (d, 2H, *J* = 9.0 Hz).

***N*-[4-(3-Hydroxy-2-hydroxymethyl-propyl)-benzyl]-2-nitro-*N*-pyridin-2-ylmethyl-benzenesulfonamide (52)**. To a stirred solution of 2-(4-cyano-benzyl)-malonic acid dimethyl ester (**51**) (8.47 g, 34.3 mmol) in THF (30 mL) cooled to 0 °C was added LiAlH₄ (1.0 M in THF, 206 mL, 206 mmol), and the mixture was heated to reflux for 19.5 h. The mixture was cooled to 0 °C, and H₂O (8 mL) was added dropwise followed by 15% NaOH(aq) (8 mL) and H₂O (24 mL). The mixture was stirred at room temperature for 45 minutes, then dried (MgSO₄) and filtered. The filtrate was concentrated to give the crude diol (5.16 g) as a yellow oil: ¹H NMR (MeOD) δ 1.90 (m, 1H), 2.63 (d, 2H, *J* = 7.2 Hz), 3.53 (d, 4H, *J* = 5.7 Hz), 3.73 (s, 2H), 7.18 (d, 2H, *J* = 8.1 Hz), 7.25 (d, 2H, *J* = 8.1 Hz). This was used without further purification in the next step.

To a stirred solution of the crude diol from above (5.13 g) in CH₂Cl₂ (105 mL) cooled to 0 °C was added Et₃N (4.00 mL, 28.7 mmol), followed by 2-nitrobenzenesulfonyl chloride (5.90 g, 26.6 mmol). The solution was stirred at room temperature for 17 h and then washed with brine (70 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL) and the combined organic phases were dried (MgSO₄) and concentrated. Purification of the crude product by chromatography on silica gel (80% THF/hexanes) gave the protected diol (3.06 g) as a yellow solid: ¹H NMR (CDCl₃) δ 1.99 (m, 1H), 2.14 (br, 2H), 2.57 (d, 2H, *J* = 9.0 Hz), 3.63 (m, 2H), 3.76 (m, 2H), 4.29 (d, 2H, *J* = 6.0 Hz), 5.71 (br, 1H), 7.06 (d, 2H, *J* = 7.5 Hz), 7.15 (d, 2H, *J* = 7.5 Hz), 7.69 (m, 2H), 7.82 (d, 1H, *J* = 7.5 Hz), 8.03 (d, 1H, *J* = 7.5 Hz).

The protected diol from above (2.87 g), 2-picolyl chloride hydrochloride (3.69 g, 22.5 mmol), Et₃N (5.2 mL, 37.5 mmol), K₂CO₃ (3.10 g, 22.5 mmol), and KBr (270 mg, 2.28 mmol) were heated to reflux in acetonitrile (80 mL) for 17.5 h. Water (60 mL) was added, and the mixture was extracted with EtOAc (150 mL). The organic extract was washed with brine (60 mL), and the aqueous phase was extracted with EtOAc (3 × 60 mL). The combined organic extracts were dried (MgSO₄) and concentrated. Purification of the crude product by chromatography on silica gel (97:3 CH₂Cl₂-MeOH) gave **52** (3.02 g, 19% over 3 steps) as a yellow oil: ¹H NMR (CDCl₃) δ 2.00 (m, 1H), 2.56 (d, 2H, *J* = 7.5 Hz), 3.64 (m, 2H), 3.78 (m, 2H), 4.57 (s, 2H), 4.60 (s, 2H), 7.02-7.14 (m, 5H), 7.23 (d, 1H, *J* = 7.8 Hz), 7.56 (m, 2H), 7.67 (d, 2H, *J* = 3.9 Hz), 7.97 (d, 1H, *J* = 7.8 Hz), 8.41 (d, 1H, *J* = 4.8 Hz).

***N*-[4-(3-Cyano-2-cyanomethyl-propyl)-benzyl]-2-nitro-*N*-pyridin-2-ylmethyl-benzenesulfonamide (53).** To a stirred solution of (52) (1.80 g, 3.82 mmol) and Et₃N (1.30 mL, 9.33 mmol) in CH₂Cl₂ (30 mL) at 0 °C was added methanesulfonyl chloride (0.65 mL, 8.4 mmol). The solution was stirred at room temperature for 30 minutes, and then concentrated. EtOAc (50 mL) was added, and the organic phase was washed with H₂O (20 mL), saturated NaHCO₃ (aq) (2 × 15 mL), and brine (15 mL) then dried (MgSO₄) and concentrated to give the crude mesylate (2.36 g) as a yellow oil: ¹H NMR (CDCl₃) δ 2.41 (m, 1H), 2.69 (d, 2H, *J* = 7.5 Hz), 3.04 (s, 6H), 4.13 (m, 2H), 4.26 (m, 2H), 4.59 (d, 2H, *J* = 3.0 Hz), 7.05 (d, 2H, *J* = 7.5 Hz), 7.13 (d, 2H, *J* = 7.5 Hz), 7.22 (d, 1H, *J* = 7.5 Hz), 7.25 (d, 1H, *J* = 7.8 Hz), 7.56 (m, 2H), 7.68 (d, 2H, *J* = 3.9 Hz), 8.00 (d, 1H, *J* = 7.8 Hz), 8.40 (d, 1H, *J* = 4.8 Hz). This was used without further purification.

A mixture of the crude mesylate (2.36 g), cetyltrimethylammonium bromide (137 mg, 0.376 mmol), and NaCN (1.3 g, 27 mmol) in a mixture of benzene (20 mL) and H₂O (10 mL) were heated at reflux for 18 h. The mixture was diluted with EtOAc (100 mL) and washed with H₂O (20 mL), saturated NaHCO₃ (aq) (2 × 20 mL), and brine (10 mL) then dried (MgSO₄) and concentrated. Purification of the crude product by chromatography on silica gel (80% EtOAc/hexanes) gave 53 (824 mg, 44% over 2 steps) as a yellow oil: ¹H NMR (CDCl₃) δ 2.31-2.55 (m, 5H), 2.79 (d, 2H, *J* = 6.0 Hz), 4.59 (s, 2H), 4.60 (s, 2H), 7.04-7.25 (m, 6H), 7.51-7.64 (m, 2H), 7.69 (m, 2H), 8.03 (d, 1H, *J* = 7.8 Hz), 8.41 (d, 1H, *J* = 4.8 Hz).

Methanesulfonic acid, 5-methanesulfonyloxy-3-(4-[(2-nitro-benzenesulfonyl)-pyridin-2-ylmethyl-amino]-methyl)-benzyl)-pentyl ester (54). A stirred solution of (53) (2.36 g, 4.82 mmol) in a mixture of 4:1 concentrated HCl(aq)/AcOH (25 mL) was heated to reflux for 17 h. Upon cooling, water (80 mL) was added, and the mixture was extracted with EtOAc (5 × 25 mL). The organic phase was extracted with saturated NaHCO₃(aq) (5 × 20 mL) and H₂O (2 × 20 mL). The combined aqueous extracts were acidified (pH 1-2) with concentrated HCl(aq) and extracted with further portions of EtOAc (5 × 25 mL). The combined organic extracts were then dried (MgSO₄) and concentrated to give the crude diacid (1.25 g): ¹H NMR (CDCl₃) δ 2.34 (d, 4H, *J* = 6.0 Hz), 2.64 (d, 2H, *J* = 6.0 Hz), 2.69 (m, 1H), 4.49 (s, 2H), 4.64 (s, 2H), 6.87 (d, 2H), 7.03

(d, 2H), 7.18-7.30 (m, 2H), 7.43 (d, 1H, $J = 7.2$ Hz), 7.62-7.75 (m, 3H), 8.01 (d, 1H, $J = 7.8$ Hz), 8.41 (d, 1H, $J = 4.8$ Hz). This was used without further purification.

To a solution of the crude diacid (1.25 g) in THF (20 mL) was added $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (10 M in BH_3 , 2.9 mL, 29 mmol). The mixture was heated to reflux for 30 minutes, then MeOH (30 mL) was added, and the solution was concentrated. The residue was dissolved in MeOH (30 mL) and the solution was concentrated once again to give the corresponding diol as a yellow foam (1.04 g).

To a stirred solution of the crude diol from above (1.00 g) and Et_3N (1.4 mL, 10 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C was added methanesulfonyl chloride (0.70 mL, 9.0 mmol). The mixture was stirred at room temperature for 20 mins, and then concentrated. The residue was partitioned between EtOAc (30 mL) and saturated NaHCO_3 (aq) (15 mL) and the organic phase was washed with saturated NaHCO_3 (aq) (15 mL) and brine (5 mL), then dried (MgSO_4) and concentrated. Purification of the crude product by chromatography on silica gel (10:10:1 $\text{CH}_2\text{Cl}_2/\text{EtOAc}/\text{MeOH}$) gave **54** (450 mg, 15% over 3 steps) as a yellow oil: ^1H NMR (CDCl_3) δ 1.75 (m, 4H), 2.01 (m, 1H), 2.59 (d, 2H, $J = 7.2$ Hz), 3.00 (s, 6H), 4.23 (m, 4H), 4.58 (s, 2H), 4.59 (s, 2H), 7.02 (d, 2H, $J = 8.1$ Hz), 7.11 (m, 3H), 7.25 (d, 1H, $J = 8.4$ Hz), 7.53-7.61 (m, 2H), 7.69 (m, 2H), 8.00 (m, 1H), 8.42 (m, 1H).

***N*-[7-[4,10-Bis(2-nitrobenzenesulfonyl)-(4,10,17-triazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine (55)**. Using General Procedure A: Reaction of **54** (560 mg, 0.854 mmol) and **15a** (380 mg, 0.710 mmol) followed by purification of the crude product by column chromatography on silica gel (40:40:1 $\text{CH}_2\text{Cl}_2/\text{EtOAc}/\text{MeOH}$) followed by basic alumina (CHCl_3) gave **55** (174 mg) as a yellow foam.

***N*-[7-(4,10,17-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Pentahydrobromide Dihydrate (56)**. To a stirred solution of the intermediate from above (**55**) (115 mg, 0.115 mmol) and K_2CO_3 (191 mg, 1.38 mmol) in acetonitrile (2.3 mL) was added thiophenol (0.11 mL, 1.1 mmol) and the mixture was heated to 40 °C for 16 h. Upon cooling, brine (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 \times 10 mL). The combined organic extracts were dried (MgSO_4) and concentrated. Purification of the crude product by column

chromatography on neutral alumina (CH₂Cl₂ and 10% MeOH/CH₂Cl₂) gave the free base of the title compound (39 mg, 19% over 2 steps) as a yellow oil.

Using General Procedure E: The free base (39 mg, 0.088 mmol) was converted to the corresponding hydrobromide salt to give **56** (65 mg, 84%) as a colorless solid: ¹H NMR (D₂O) δ 1.75 (m, 4H), 1.92 (m, 1H), 2.68 (d, 2H, *J* = 6.9 Hz), 3.09 (m, 2H), 3.24 (m, 6H), 3.41-3.60 (m, 4H), 4.38 (s, 2H), 4.58 (s, 2H), 7.28-7.43 (m, 6H), 7.86 (m, 3H), 8.35 (m, 1H), 8.74 (d, 1H, *J* = 5.4 Hz); ¹³C NMR (D₂O) δ 27.62, 31.42, 34.55, 39.65, 43.12, 45.62, 48.48, 51.57, 123.65, 127.05, 127.16, 128.63, 130.62, 130.72, 140.16, 141.64, 144.62, 146.02, 147.24, 157.50; ES-MS *m/z* 444 (M+H). Anal. (C₂₈H₃₇N₅·4.8 HBr·2.5 H₂O) C, H, N, Br.

***N*-[8-[(5,11-Bis(2-nitrobenzenesulfonyl)-1-oxa-5,11-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]]-*N*-(2-nitrobenzenesulfonyl)-2-(aminomethyl)pyridine**

(57a). Using General Procedure A: Reaction of **16b** (190 mg, 0.38 mmol) and **54** (250 mg, 0.38 mmol) followed by purification of the crude product by column chromatography on silica gel (EtOAc/CH₂Cl₂) gave **57a** (203 mg, 51%): ¹H NMR (CDCl₃) δ 1.47-1.71 (m, 9H), 2.42 (d, 2H, *J* = 6.1 Hz), 3.15-3.32 (m, 12H), 4.53 (s, 2H), 4.55 (s, 2H), 6.94 (d, 2H, *J* = 6.4 Hz), 7.03 (d, 2H, *J* = 6.4 Hz), 7.05 (d, 1H, *J* = 5.8 Hz), 7.52 (m, 4H), 7.64 (m, 6H), 7.91 (m, 5H), 8.44 (d, 1H, *J* = 5.4 Hz).

***N*-[8-(1-Oxa-5,11-diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-**

(aminomethyl)pyridine Tetrahydrobromide Trihydrate (58a). To a stirred solution of **57a** (203 mg, 0.203 mmol) and K₂CO₃ (450 mg, 3.05 mmol) in acetonitrile (8 mL) was added thiophenol (0.25 mL, 2.44 mmol) and the mixture was stirred overnight at room temperature. Standard work-up, followed by purification of the crude product by column chromatography on silica gel (85:12:3 CH₂Cl₂/MeOH/NH₄OH) gave the free base of the title compound (47 mg, 57%) as a white foam: ¹H NMR (CDCl₃) δ 1.44-1.89 (m, 8H), 1.93 (m, 3H), 2.51 (m, 4H), 2.68 (m, 2H), 2.72 (m, 2H), 3.10 (br s, 2H (NH)), 3.54 (m, 4H), 3.81 (s, 2H), 3.91 (s, 2H), 7.09 (d, 2H, *J* = 6.1 Hz), 7.13 (m, 1H), 7.29 (d, 2H, *J* = 6.1 Hz), 7.32 (m, 1H), 7.64 (t, 1H, *J* = 5.8 Hz), 8.54 (d, 1H, *J* = 5.4 Hz).

Using General Procedure E: The free base was converted to the corresponding hydrobromide salt to give **58a** (42 mg): ¹H NMR (D₂O) δ 1.73 (m, 4H), 2.00 (m, 5H), 2.65 (d, 2H, *J* = 7.2 Hz); 3.04-3.19 (m, 8H), 3.51 (br s, 4H), 4.38 (s, 2H), 4.58 (s, 2H),

7.32 (d, 2H, $J = 7.5$ Hz), 7.43 (d, 2H, $J = 7.5$ Hz), 7.85 (t, 1H, $J = 6.9$ Hz), 7.89 (d, 1H, $J = 8.4$ Hz), 8.34 (d, 1H, $J = 7.5$ Hz), 8.74 (d, 1H, $J = 5.1$ Hz); ^{13}C NMR (CDCl_3) δ 24.01, 26.30, 34.51, 39.35, 41.88, 44.74, 47.47, 51.58, 69.66, 127.05, 127.16, 128.44, 130.47 (2C), 130.72 (2C), 141.74, 144.62, 146.00, 147.25; ES-MS m/z 411 (M+H). Anal. ($\text{C}_{25}\text{H}_{38}\text{N}_4\text{O}\cdot 4.0\text{HBr}\cdot 3.5\text{H}_2\text{O}$) C, H, N, Br.

***N*-[4-(1,7-Diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine Tetrahydrobromide Trihydrate (58b)**. Using similar procedures to those described above, the title compound was obtained as a white solid: ^1H NMR (CD_3OD) δ 1.55 (b, 6H), 1.77-1.86 (m, 8H), 2.23-2.28 (m, 1H), 3.74-2.77 (d, 2H, $J = 7.5$), 3.09-3.20 (m, 8H), 4.38 (s, 2H), 4.53 (s, 2H), 7.41-7.44 (d, 2H, $J = 7.8$ Hz), 7.53-7.56 (d, 2H, $J = 7.8$ Hz), 7.66-7.71 (dd, 1H, $J = 5.5, 6.8$ Hz), 7.79-7.81 (d, 1H, $J = 7.8$ Hz), 8.14-8.20 (ddd, 1H, $J = 1.5, 7.8, 7.8$ Hz), 8.78 (d, 1H); ^{13}C NMR (CD_3OD) δ 21.74, 22.78, 25.48, 26.54, 35.13, 40.34, 41.20, 44.43, 51.41, 125.46, 125.72, 129.54, 130.62, 131.00, 141.39, 142.19, 147.93, 150.06; exact mass m/z calcd. for $\text{C}_{26}\text{H}_{40}\text{N}_4$: 408.33, found $[M+H]^+$ 409.4. Anal. ($\text{C}_{26}\text{H}_{40}\text{N}_4\cdot 3.6\text{HBr}\cdot 3.1\text{H}_2\text{O}$) C, H, N, Br.

Table 4: Microanalysis data

| Compound No. | Formula | Calc. | | | | Found | | | |
|--------------|--|-------|------|-------|-------|-------|------|-------|-------|
| | | C | H | N | Br | C | H | N | Br |
| 3a | C ₂₅ H ₃₉ N ₅ 5HBr | 36.88 | 5.45 | 8.60 | 49.07 | 36.79 | 5.56 | 8.48 | 48.79 |
| 3b | C ₂₅ H ₄₀ N ₆ ·5.75HBr·0.5H ₂ O | 33.42 | 5.19 | 9.35 | 51.14 | 33.69 | 5.35 | 9.00 | 51.13 |
| 3c | C ₂₅ H ₄₀ N ₆ ·6HBr·HOAc | 33.43 | 5.19 | 8.66 | 49.42 | 33.42 | 5.49 | 8.62 | 49.23 |
| 3d | C ₂₄ H ₃₈ N ₆ ·6HBr | 32.36 | 4.98 | 9.44 | 53.21 | 32.20 | 5.00 | 9.30 | 53.10 |
| 3e | C ₂₄ H ₃₈ N ₆ ·6HBr | 32.17 | 4.95 | 9.34 | 53.50 | 32.08 | 5.02 | 9.25 | 53.28 |
| 3f | C ₂₄ H ₃₈ N ₆ ·6HBr | 32.17 | 4.95 | 9.34 | 53.50 | 32.16 | 5.03 | 9.41 | 53.28 |
| 3g | C ₂₅ H ₄₀ N ₆ ·6HBr·1.5H ₂ O | 32.04 | 5.27 | 8.97 | 51.15 | 31.88 | 5.30 | 8.93 | 51.00 |
| 3h | C ₂₅ H ₄₀ N ₆ ·6HBr | 32.99 | 5.09 | 9.23 | 52.67 | 32.79 | 5.34 | 9.11 | 52.45 |
| 3i | C ₂₄ H ₃₉ N ₇ ·5.5HBr | 33.10 | 5.15 | 11.26 | 50.47 | 32.80 | 5.41 | 11.00 | 50.58 |
| 36 | C ₂₇ H ₃₆ N ₆ ·6HBr·3H ₂ O | 32.95 | 4.92 | 8.54 | 48.72 | 32.75 | 4.89 | 8.39 | 48.61 |
| 37 | C ₂₈ H ₃₇ N ₅ ·5HBr·2H ₂ O | 38.03 | 5.24 | 7.92 | 45.18 | 38.37 | 5.28 | 7.76 | 45.36 |
| 38 | C ₂₇ H ₃₆ N ₆ ·1.9H ₂ O | 67.72 | 8.38 | 17.55 | | 67.64 | 7.99 | 17.29 | |
| 39 | C ₂₅ H ₃₉ N ₅ ·5HBr·0.1Et ₂ O·2.3H ₂ O | 35.35 | 5.79 | 8.11 | 46.29 | 35.55 | 5.70 | 8.18 | 46.17 |
| 40 | C ₂₄ H ₃₇ N ₅ O·4.1HBr·4.1H ₂ O | 35.28 | 6.08 | 8.57 | 40.09 | 35.42 | 6.07 | 8.50 | 39.92 |
| 41a | C ₂₄ H ₃₇ N ₅ S·4.3HBr·2.6H ₂ O | 35.05 | 5.70 | 8.52 | 41.78 | 35.18 | 5.52 | 8.48 | 41.53 |
| 41b | C ₂₄ H ₃₇ N ₅ OS·0.6Et ₂ O·0.4H ₂ O | 64.02 | 8.91 | 14.14 | | 64.06 | 8.72 | 13.98 | |
| 41c | C ₂₄ H ₃₇ N ₅ O ₂ S·4HBr·3H ₂ O | 33.14 | 5.49 | 8.05 | 40.42 | 33.36 | 5.39 | 7.70 | 40.25 |
| 42 | C ₂₅ H ₃₇ F ₂ N ₅ | 67.39 | 8.37 | 15.72 | | 67.52 | 8.49 | 15.43 | |
| 43 | C ₂₅ H ₃₈ FN ₅ | 70.22 | 8.96 | 16.38 | | 69.99 | 8.96 | 16.42 | |
| 44 | C ₂₅ H ₃₉ N ₅ ·5HBr·2.5H ₂ O·0.1Et ₂ O | 35.20 | 5.82 | 8.08 | 46.10 | 35.48 | 5.66 | 8.10 | 46.05 |
| 45 | C ₂₇ H ₃₆ N ₆ ·6HBr·1.5H ₂ O·0.2Et ₂ O | 34.35 | 4.87 | 8.65 | 49.33 | 34.57 | 5.04 | 8.68 | 49.09 |
| 46 | C ₂₈ H ₃₇ N ₅ ·5HBr·2.5H ₂ O | 37.65 | 5.30 | 7.84 | 44.73 | 37.53 | 5.26 | 7.79 | 44.75 |
| 47 | C ₂₈ H ₃₇ N ₅ ·4.3HBr·3.8H ₂ O | 39.11 | 5.73 | 8.14 | 39.95 | 39.24 | 5.62 | 7.96 | 39.82 |
| 48 | C ₂₈ H ₃₇ N ₅ ·5.1HBr·2.3H ₂ O·2.3C ₄ H ₈ O ₂ | 40.61 | 5.96 | 6.36 | 37.03 | 40.45 | 5.59 | 6.37 | 36.67 |
| 49 | C ₂₈ H ₃₅ N ₅ O·3.9HBr·1H ₂ O | 42.51 | 5.21 | 8.85 | 39.39 | 42.67 | 5.43 | 8.61 | 39.12 |
| 56 | C ₂₈ H ₃₇ N ₅ | 38.35 | 5.38 | 7.99 | 43.73 | 38.47 | 5.03 | 7.66 | 43.56 |
| 58a | C ₂₅ H ₃₈ N ₄ O·4.0HBr·3.5H ₂ O | 37.66 | 6.19 | 7.03 | 40.09 | 37.67 | 6.06 | 6.92 | 40.24 |
| 58b | C ₂₆ H ₄₀ N ₄ ·3.6HBr·3.1H ₂ O | 41.32 | 6.64 | 7.41 | 38.06 | 41.40 | 6.48 | 7.27 | 37.93 |