Supplementary Material (ESI) for Chemical Communications


# Triarylpyridines: A Versatile Small Molecule Scaffold for G-Quadruplex Recognition

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SUPPORTING INFORMATION for Chemical Communications

**Contents**

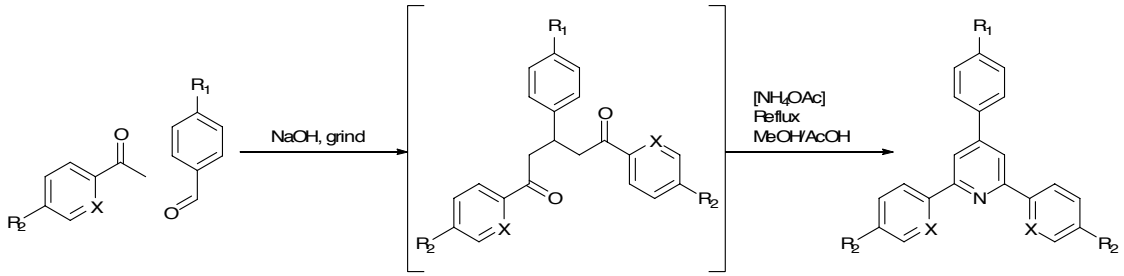
## 1.0 General Experimental

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Armarego, W. L. F., Purification of Laboratory Chemicals, 3rd edition, Pergamon Press, Oxford, 1988 or used as supplied from commercial sources, as appropriate. NMR spectra were acquired on Bruker DRX-400, Bruker DPX-400 and DRX-500 instruments using deuterated solvents as detailed and at ambient probe temperature (300 K) unless otherwise stated. Notation for the $^1$H-NMR spectral splitting patterns includes: singlet (*s*), doublet (*d*), triplet (*t*), broad (*br*) and multiplet/overlapping peaks (m). Signals are quoted as δ values in ppm, coupling constants (*J*), are quoted in Hertz. IR spectra were recorded on an ATI Matteson Genesis Fourier Transform spectrometer. Notation for the IR intensity data includes: strong (*s*), medium (*m*), weak (*w*), very strong (*vs*), very weak (*vw*), broad (*br*); bands are quoted in $cm^{-1}$. Mass spectra were recorded on Micromass Q-Tof (ESI) spectrometer. TLC were performed on Merck Kieselgel 60 F254 plates, and spots were visualised under UV light. Flash chromatography (FC) were performed using Merck Kieselgel 60 at RT under a positive pressure of nitrogen using previously distilled solvents.

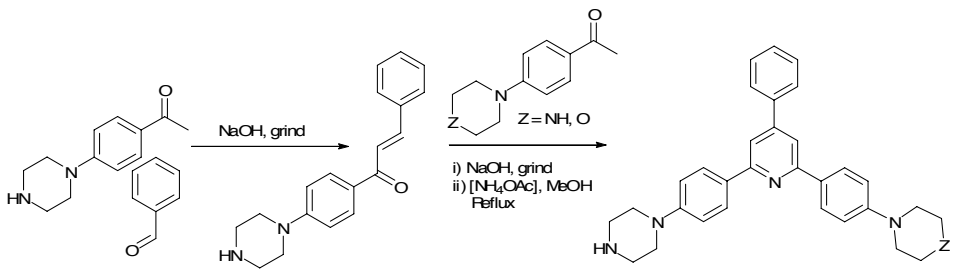
All compounds tested were HPLC purified using a Varian Pursuit C18, 5 μ column (250 × 21.2 mm) and a gradient elution with 0.1% TFA/$H_2O$ (solvent A) and 0.1% TFA/MeCN (solvent B) at a flow rate of 12.0 mL/min.

## 2.0 Synthesis

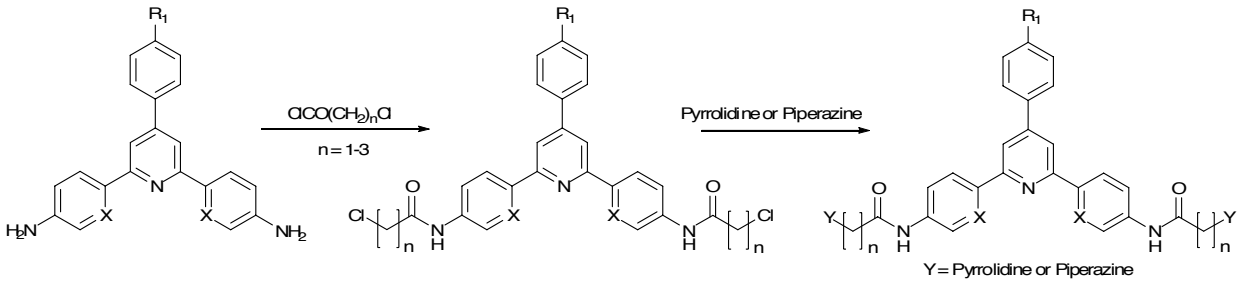
## 2.1 Reaction Schemes



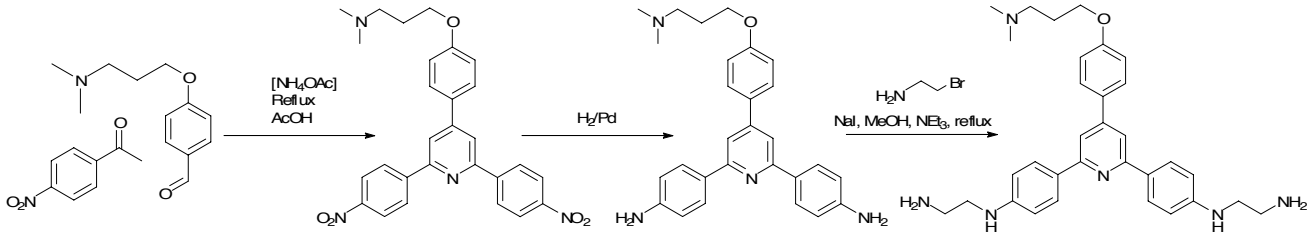

*Scheme S1: Synthesis via Route 1*




*Scheme S2: Modified synthesis via Route 1 for **2a, 2** and **3***




*Scheme S3: Synthesis via Route 2 and Route 3*




*Scheme S4: Synthesis of **13**, **14a** and **14***

## 2.2 General Routes

### Route 1

Substituted acetophenone/acetylpyridine (2 eq) and sodium hydroxide (1 eq) were ground thoroughly in a pestle and mortar with the appropriate substituted benzaldehyde (1 eq). The mixture was heated in a microwave oven (700 W) until melted (6×5 seconds) and ground thoroughly to a powdery solid. The solid was dissolved in AcOH or MeOH and refluxed with ammonium acetate (excess) for 2 h. The cooled solution was basified with $K_2CO_3$ and/or NaOH. The resulting precipitate was filtered, dissolved in methanol and filtered again to remove excess salts then the solvent removed *in vacuo*.

### Route 2

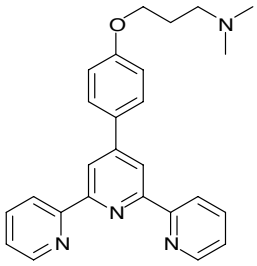
Substituted amino-TAP (1 eq) and the appropriate acyl chloride (>10 excess, solvent and reagent) were stirred overnight. Ice-cold ether was added and the resulting precipitate was filtered, dissolved in methanol and filtered again to remove excess salts then the solvent removed *in vacuo*.

**Route 3**

Substituted amide-TAP (1 eq) and either pyrrolidine (>10 excess, solvent and reagent) or piperazine HCl (>10 excess dissolved in THF and triethylamine) were stirred overnight. Ice-cold saturated sodium bicarbonate solution was added and a precipitate formed. The solid was centrifuged and the supernatant removed. The solid was washed with further portions of aqueous saturated sodium bicarbonate solution then dissolved in MeOH, filtered and dried *in vacuo*.

## 2.3 Synthesis of TAP molecules

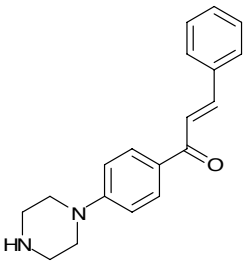
**Dimethyl-[3-(4-[2,2';6',2'']terpyridin-4'-yl-phenoxy)-propyl]-amine (1)**



According to **route 1** with 2-acetylpyridine (0.54 mL, 4.83 mmol), sodium hydroxide (97 mg, 2.42 mmol) and 4-[3(dimethylamino)propoxyl] benzaldehyde (0.48 mL, 2.42 mmol), refluxed in AcOH and ammonium acetate (1.9 g, 24 mmol). Recrystallisation from MeOH/$H_2O$ yielded the product as taupe leaflets (0.33 g, 13%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 80% MeCN over 22 min, $R_t$=17.6 min). **$^1$H-NMR (400 MHz, $CDCl_3$):** 8.72 (*d*, 2H, *J*=5.5 Hz); 8.70 (*s*, 2H ); 8.65 (*d*, 2H, *J*=8.0 Hz); 7.41-7.26 (*m*, 4H); 7.41-7.26 (*m*, 2H); 7.02 (*d*, 2H, *J*=8.0 Hz); 4.07 (*t*, 2H, *J*=7.1 Hz); 2.49 (*t*, 2H, *J*=7.1 Hz); 2.27 (*s*, 6H,); 2.02-1.96 (*m*, 2H). **$^{13}$C-NMR (100 MHz, $CDCl_3$):** 160.4,

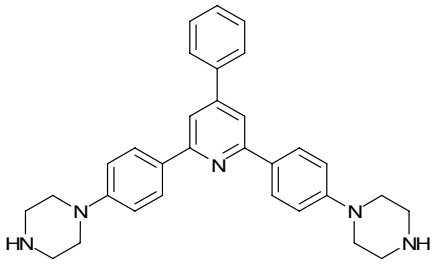
156.8, 156.2, 150.2, 149.5, 137.2, 131.0, 128.9, 124.1, 121.7, 118.6, 115.3, 66.8, 56.8, 46.0, 28.0. **IR (Neat):** 3051*w*, 2955*w*, 1607*s*, 1583*m*, 1515*m*, 1468*m*, 1391*m*, 1252*m*, 1230*m*, 1185*m*, 1036*m*, 842*m*, 791*vs*, 740*m*. **HRMS (ESI):** Calculated for $C_{26}H_{27}N_4O$ ($[M+H]^+$): 411.2179. Found: 411.2175.

**3-Phenyl-1-(4-(piperazin-1-yl)phenyl)prop-2-en-1-one (2a)**



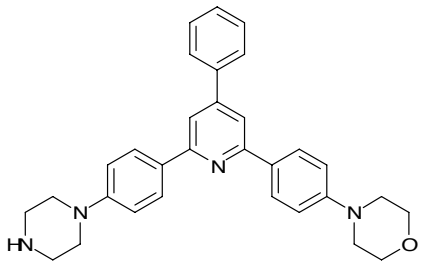

Benzaldehyde (0.50 mL, 0.51 g, 4.90 mmol), sodium hydroxide (0.10 g, 2.50 mmol) and 4-Piperazinoacetophenone (0.50 g, 2.45 mmol) were ground thoroughly in a pestle and mortar. The mixture was heated in a microwave oven (700 W) until melted (6×5 seconds) and ground thoroughly to a yellow powder. FC ($CHCl_3$/MeOH, 20:1) afforded **2a** (0.61 g, 85%) as a canary yellow powder. **$^1$H-NMR (400 MHz, MeOD):** 8.00 (*d*, 2H, *J*=9.0 Hz); 7.78 (*d*, 1H, *J*=15.5 Hz); 7.64-7.62 (*m*, 2H); 7.54 (*d*, 1H, *J*=15.5 Hz); 7.42-7.37 (*m*, 3H); 6.90 (*d*, 2H, *J*=9.0 Hz); 3.34 (*t*, 4H, *J*=5.0 Hz); 3.03 (*t*, 4H, *J*=5.0 Hz). **$^{13}$C-NMR (100 MHz, $CDCl_3$):** 188.4, 154.8, 143.4, 137.3, 135.7, 131.0, 130.4, 129.2, 128.6, 122.4, 113.8, 48.7, 46.1. **IR (Neat):** 2845*w*, 1647*m*, 1587*s,* 1447*m*, 1386*m*, 1336*m*, 1230*s*, 1194*s*, 984*m*, 936*m*, 819*s*, 767*vs*, 734*m*, 694*m*, 673*m*. **HRMS (ESI):** Calculated for $C_{19}H_{21}N_2O$ ($[M+H]^+$): 293.1648. Found: 293.1649.

**1,1'-(4,4'-(4-Phenylpyridine-2,6-diyl)bis(4,1-phenylene))dipiperazine (2)**



According to **route 1** with **2a** (200 mg, 0.68 mmol), 4-piperazinoacetophenone (140 mg, 0.68 mmol) and sodium hydroxide (0.10 g, 2.50 mmol), refluxed in MeOH and and ammonium acetate (1.9 g, 24 mmol) **2** was recovered as a green-yellow oil (249 mg, 78%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 80% MeCN over 22 min, $R_t$=17.8 min). **$^1$H-NMR (400 MHz, MeOD):** 8.19 (*s*, 2H); 8.05-7.99 (*m*, 6H); 7.66-7.60 (*m*, 3H); 7.24 (*d*, 4H, *J*=9.2 Hz); 3.64 (*t*, 8H, *J*=5.2 Hz); 3.40 (*t*, 8H, *J*=5.2 Hz). **$^{13}$C-NMR (100 MHz, MeOD):** 154.4, 153.5, 151.3, 150.4, 136.4, 129.6, 128.6, 128.4, 127.4, 116.9, 115.2, 44.7, 42.6. **IR (Neat):** 2986*w*, 2839*w*, 2752*w,* 1667*s*, 1602*s*, 1542*w*, 1520*m*, 1452*w*, 1427*w*, 1386*w*, 1243*m*, 1179*s*, 1041*m*, 926*m*, 830*m*, 797*s*, 766*m*, 720*s*, 699*m*. **HRMS (ESI):** Calculated for $C_{31}H_{34}N_5$ ($[M+H]^+$): 476.2809. Found: 476.2808.

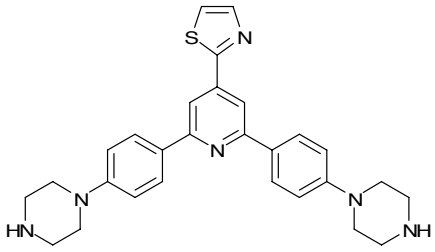
**4-(4-(4-Phenyl-6-(4-(piperazin-1-yl)phenyl)pyridin-2-yl)phenyl)morpholine (3)**



According to **route 1** with **2a** (200 mg, 0.68 mmol), 4-morpholinoacetophenone (140 mg, 0.68 mmol) and sodium hydroxide (100 mg, 2.50 mmol), refluxed in MeOH and

ammonium acetate (1.9 g, 24 mmol). **3** was recovered as a yellow oil (299 mg, 92%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 80% MeCN over 22 min, $R_t$=21.0 min). **$^1$H-NMR (400 MHz, $CDCl_3$)**: 7.75-7.71 (*m*, 6H); 7.70-7.62 (*m*, 2H); 7.54-7.51 (*m*, 3H); 6.94-6.91 (*m*, 4H); 6.25 (*br s*, 1H); 3.79 (*t*, 4H, *J*=4.4 Hz); 3.72 (*br t*, 4H); 3.47 (*t*, 4H, *J*=4.4 Hz); 3.17 (*br t*, 4H). **$^{13}$C-NMR (125 MHz, $CDCl_3$):** 156.5, 154.2, 153.8, 153.5, 152.1, 135.6, 131.5, 130.2, 130.0, 129.7, 127.6, 122.6, 119.0, 115.5, 114.6, 66.4, 47.5, 44.9, 42.9. **IR (Neat):** 2975*w*, 2848*w,* 1673*s*, 1602*s*, 1521*m*, 1449*m*, 1385*w*, 1235*w*, 1200*s*, 1179*s*, 1123*vs*, 1045*w*, 927*m*, 839*m*, 800*s*, 766*m*, 723*s*, 700*m*. **HRMS (ESI):** Calculated for $C_{31}H_{33}N_4O$ ($[M+H]^+$): 477.2649. Found: 477.2642.

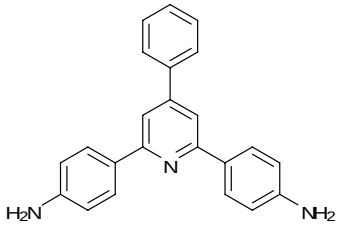
**2-(2,6-Bis(4-(piperazin-1-yl)phenyl)pyridin-4-yl)thiazole (4)**




According to **route 1** with 4-piperazinoacetophenone (1.0 g, 4.90 mmol), sodium hydroxide (0.1 g, 2.45 mmol) and 2-thiazolecarboxaldehyde (0.28 g, 0.21 mL, 2.45 mmol), refluxed in MeOH and ammonium acetate (1.9 g, 24 mmol). **4** was recovered as a dark red-orange solid (0.98 g, 83%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 50% MeCN over 22 min, $R_t$=18.5 min). **$^1$H-NMR (400 MHz, MeOD)**: 8.20 (*s*, 2H); 8.13 (*d*, 4H, *J*=8.8 Hz); 8.05 (*d*, 1H, *J*=3.2 Hz); 7.84 (*d*, 1H, *J*=3.2 Hz); 7.18 (*d*, 4H, *J*=8.8 Hz); 3.52 (*t*, 8H, *J*=5.2 Hz); 3.4 (*t*, 8H, *J*=5.2 Hz). **$^{13}$C-NMR (125 MHz, MeOD):** 167.2, 158.3, 152.8, 145.5, 144.2, 131.0, 129.6, 123.4, 117.4, 115.7, 47.0, 44.7. **IR (Neat):** 3397*w*, 2996*w*, 2924*w,* 2850*w*, 1672*s*, 1604*s*, 1520*m*, 1429*m*, 1240*m*, 1201*s*,

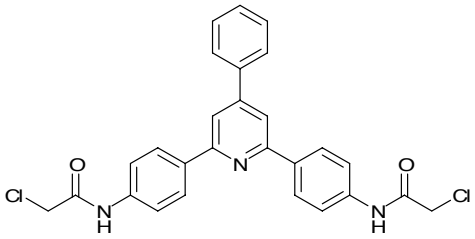
1133*s*, 1044*w*, 928*m*, 836*m*, 800*m*, 723*m*. **HRMS (ESI):** Calculated for $C_{28}H_{31}N_6S$ ($[M+H]^+$): 482.2269. Found: 482.2247.

**4-Phenyl-2,6-bis(4-aminophenyl) pyridine (5a)**




**5a** was prepared as previously described.[1]

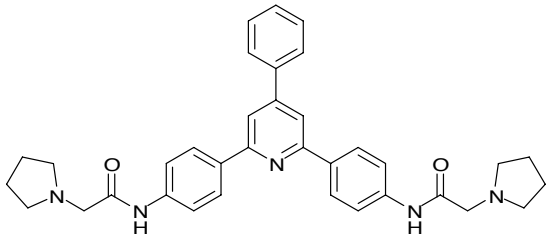
***N,N'*-(4,4'-(4-phenylpyridine-2,6-diyl)bis(4,1-phenylene))bis(2-chloroacetamide) (5b)**




According to **route 2** with **5a** (150 mg, 0.45 mmol) and chloroacetylchloride (1 mL, 12.5 mmol, excess reagent and solvent). The cream coloured solid was recrytallized from acetone/water to give **5b** as a cream white solid (138 mg, 63%). **$^1$H-NMR (500 MHz, DMSO-$d_6$):** 8.32 (*d*, 4H, *J*=8.8 Hz); 8.12 (*s*, 2H); 8.01 (*d*, 2H, *J*=7.2 Hz); 7.76 (*d*, 4H, *J*=8.8); 7.61-7.45 (*m*, 3H); 4.30 (*s*, 4H). **$^{13}$C-NMR (125 MHz, DMSO-$d_6$):** 164.9, 155.9, 149.5, 139.6, 137.9, 134.2, 129.3, 129.1, 127.6, 127.4, 119.4, 115.7, 43.7. **IR (Neat):** 3261*m*, 3040*vw*, 1664*s*, 1592*m*, 1531*s*, 1498m, 1390*m*, 1249*m*, 840*s*, 761*vs*, 686*s*. **HRMS (ESI):** Calculated for $C_{27}H_{22}Cl_2N_3O_2$ ($[M+H]^+$): 490.1095. Found: 490.1089.

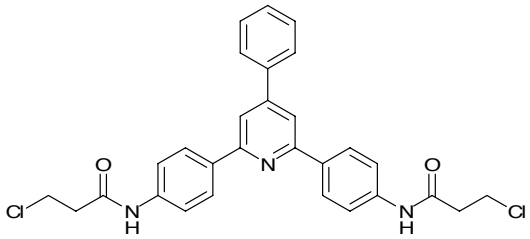
[1] B. Tamami and H. Yeganeh, *Polymer,* 2001, **42**, 415

***N,N'*-(4,4'-(4-phenylpyridine-2,6-diyl)bis(4,1-phenylene))bis(2-(pyrrolidin-1-yl)acetamide) (5)**



According to **route 3** with **5b** (50 mg, 0.1 mmol) and pyrrolidine (1 mL, 12 mmol, solvent and reagent, excess) to afford **5** as a yellow oil (51 mg, 89%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 60% MeCN over 22 min, $R_t$=19.5 min). **$^1$H-NMR (400 MHz, DMSO-$d_6$, 373 K)**: 8.20 (*d*, 4H, *J*=8.5 Hz); 7.97 (*s*, 2H); 7.87 (*d*, 2H, *J*=5.5 Hz); 7.67 (*d*, 4H, *J*=8.5 Hz); 7.57-7.45 (*m*, 3H); 4.16 (*s*, 4H); 3.12 (*br s*, 8H); 1.95 (*m*, 8H). **$^{13}$C-NMR (125 MHz, MeOD):** 173.3, 165.3, 159.0, 148.5, 147.3, 143.9, 138.8, 138.6, 137.2, 136.8, 128.9, 125.3, 65.5, 63.8, 32.3. **IR (Neat):** 3261*w*, 2963*w*, 1667*m*, 1620*m*, 1594*m*, 1517*m*, 1379*m*, 1258*m*, 1184*m*, 1088*m*, 1015*s*, 766*s*, 695*m*. **HRMS (ESI):** Calculated for $C_{35}H_{38}N_5O_2$ ($[M+H]^+$): 560.3025. Found: 560.3020.

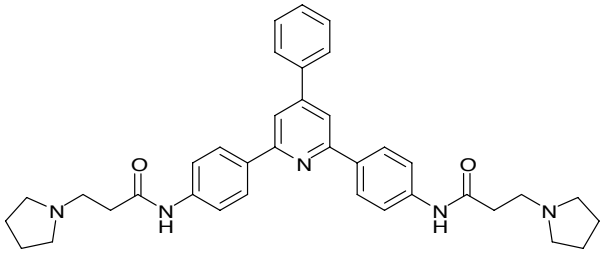
***N,N'*-(4,4'-(4-phenylpyridine-2,6-diyl)bis(4,1-phenylene))bis(3-chloropropanamide) (6a)**



According to **route 2** with **5a** (0.15 g, 0.45 mmol) and 2-chloropropionyl chloride (1 mL, 5.9 mmol, excess reagent and solvent). The cream coloured solid was recrytallized from

acetone/water to give **6a** as a cream white solid (0.25 g, >99%). **$^1$H-NMR (500 MHz, DMSO-$d_6$):** 10.25 (*s*, 2H); 8.30 (*d*, 4H, *J*=8.8 Hz); 8.10 (*s*, 2H); 8.00 (*d*, 2H, *J*=7.2 Hz); 7.76 (*d*, 4H, *J*=8.8 Hz); 7.57-7.44 (*m*, 3H); 3.89 (*t*, 4H, *J*=6.6 Hz); 2.85 (*t*, 4H, *J*=6.6 Hz). **$^{13}$C-NMR (125 MHz, DMSO-$d_6$):** 170.0, 157.8, 151.2, 141.9, 139,7, 135.5, 131.1, 130.9, 129.3, 129.2, 120.8, 117.3, 42.6, 40.9. **IR (Neat):** 3036*w*, 1666*m*, 1646*m*, 1598*s*, 1530*s*, 1513*s*, 1427*m*, 1417*m*, 1294*m*, 992*m*, 833*vs*, 757*vs*, 679*s*. **HRMS (ESI):** Calculated for $C_{29}H_{26}Cl_2N_3O_2$ ($[M+H]^+$): 518.1402. Found: 518.1402.

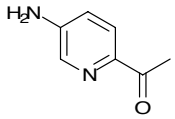
***N*,*N*'-(4,4'-(4-phenylpyridine-2,6-diyl)bis(4,1-phenylene))bis(3-(pyrrolidin-1-yl)propanamide) (6)**



According to **route 3** with **6a** (50 mg, 0.09 mmol) and pyrrolidine (1 mL, 12 mmol, solvent and reagent, excess) to afford **6** as a yellow oil (41 mg, 72%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 70% MeCN over 22 min, $R_t$=20.5 min). **$^1$H-NMR (500 MHz, MeOD):** 8.18 (*d*, 4H, *J*=8.0 Hz); 8.02 (*d*, 2H); 7.88 (*d*, 4H, *J*=7.5 Hz); 7.78 (*d*, 2H, *J*=8.0 Hz); 7.57-7.50 (*m*, 3H); 3.72 (*br m*, 4H); 3.58 (*br m*, 4H); 3.16 (*br m*, 4H); 2.95 (*br m*, 4H); 2.18 (*br m*, 4H); 2.06 (*br m*, 4H). **$^{13}$C-NMR (100 MHz, MeOD):** 179.0, 170.5, 156.5, 147.9, 143.3, 141.6, 130.4, 130.4, 129.5, 128.6, 121.0, 118.5, 55.5, 52.2, 32.9, 24.0. **IR (Neat):** 3080*w*, 2962*w*, 1696*m*, 1661*s*, 1607*m*, 1596*m*, 1537*w*, 1520*m*, 1453*m*, 1416*m*, 1382*w*, 1308*w*, 1186*vs*, 1137*s*, 853*m*, 838*m*, 799*m*,

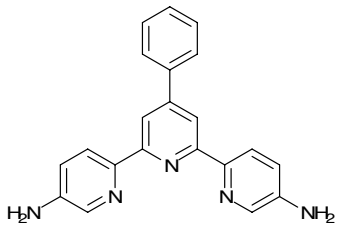
734*m*, 764*m*, 721*m*, 688*w*. **HRMS (ESI):** Calculated for $C_{37}H_{42}N_5O_2$ ($[M+H]^+$): 588.3333. Found: 588.3347.

**1-(5-Aminopyridin-2-yl)ethanone (7a)**



A solution of 5'-amino-2-cyanopyridine (5.0 g, 42 mmol) in anhydrous THF was cooled to 0 ºC. Methyl magnesium bromide (3 M in $Et_2O$, 42 mL, 126 mmol, 3 eq) was added drop-wise so the temperature in the flask did not exceed 5 ºC. After the addition was complete, the solution was stirred for a further 2 h at 0 ºC then the contents poured into icy water. The product was extracted into THF:EtOAc (50:50). The organic phases were combined and the solvent removed *in vacuo* to afford **7a** (5.4 g, 95%) as a brown solid. Our data concurred with that in the literature.[2]

**4-Phenyl-5''-(3-amino)-[2,2';6',2'']terpyridin-5-yl]-3-amine (7b)**

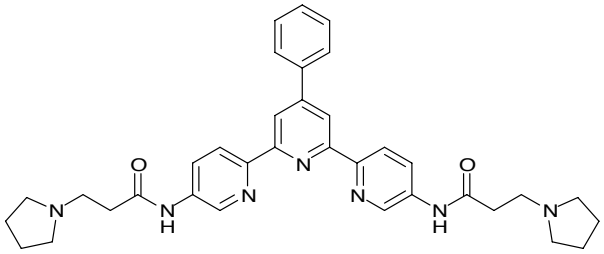


According to **route 1** with **7a** (500 mg, 3.68 mmol), sodium hydroxide (74 mg, 1.84 mmol) and benzaldehyde (195 mg, 0.19 mL, 1.84 mmol), refluxed in AcOH and ammonium acetate (1.9 g, 24 mmol). On cooling the product precipitated and was filtered and washed with MeOH. **7b** was recovered as a chocolate brown solid (0.27 g, 66%).

[2] J. T. Edward and L. Y. S. Mo, *J. Hetrocyclic. Chem.,* 1973, **10**, 1047

**$^{1}$H-NMR (400 MHz, DMSO-d$_6$, 413K):** 8.26 (*s*, 2H); 8.20 (*d*, 2H, *J*=8.5 Hz); 8.04 (*d*, 2H, *J*=3.0 Hz); 7.72 (*d*, 2H, *J*=7.5 Hz); 7.48-7.38 (*m*, 3H); 7.05 (*dd*, 2H, *J*=8.5, 3.0 Hz). **$^{13}$C-NMR (125 MHz, DMSO-d$_6$, 413K):** 155.9, 148.1, 144.5, 144.1, 138.3, 135.4, 128.3, 128.0, 126.0, 120.6, 120.0, 114.3. **IR (Neat):** 3447*w*, 3313*w*, 3194*w*, 1668*w*, 1621*s*, 1593*s*, 1562*s*, 1540*vs*, 1488*s*, 1445*m*, 1436*w*, 1389*s*, 1362*w*, 1311*s*, 1291*m*, 1274*m*, 1235*m*, 1136*m*, 1077*m*, 1018*m*, 879*w*, 837*s*, 812*m*, 770*s*, 756*s*, 733*m*, 689*s*. **HRMS (ESI):** Calculated for $C_{21}H_{18}N_5$ ($[M+H]^+$): 340.1557. Found: 340.1554.

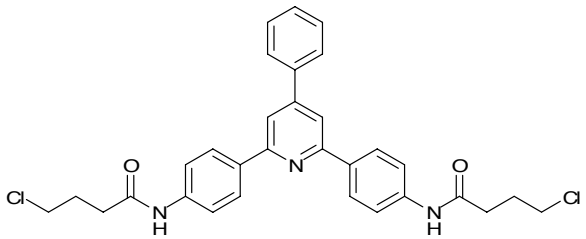
**4-Phenyl-5''-(3-pyrrolidin-1-yl-propionylamino)-[2,2';6',2'']terpyridin-5-yl]-3-pyrrolidin-1-yl-propionamide (7)**



According to **route 2** with **7b** (30 mg, 0.088 mmol) and 3-chloropropionylchloride (1 mL, 5.9 mmol, excess reagent and solvent) to give a cream coloured solid. The intermediate (42.7 mg, 93%) was used as crude according to **Route 3** with pyrrolidine (1 mL, 12 mmol, solvent and reagent, excess) to afford **7** as a yellow oil (40 mg, 84%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 80% MeCN over 22 min, $R_t$=16.0 min). **$^{1}$H-NMR (400 MHz, MeOD):** 9.11 (*d*, 2H, *J*=2.4 Hz); 8.71 (*d*, 2H, *J*=8.8 Hz); 8.67 (*s*, 2H); 8.40 (*dd*, 2H, *J*=8.8, 2.4 Hz); 7.97 (*d*, 2H, *J*=6.8 Hz); 7.62-7.53 (*m*, 3H); 3.73 (*m*, 4H); 3.60 (*t*, 4H, *J*=6.8 Hz); 3.18 (*m*, 4H); 3.02 (*t*, 4H, *J*=6.8 Hz); 2.18 (*m*, 4H); 2.08 (*m*, 4H). **$^{13}$C-NMR (125 MHz, MeOD):** 170.7, 139.2, 139.0, 138.1, 131.5,

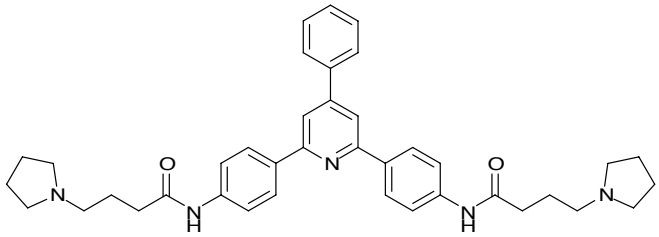
131.3, 130.6, 128.5, 124.6, 121.0, 120.6, 118.7, 116.4, 55.6, 51.8, 33.0, 24.0. **IR (Neat):** 3375*w*, 3048*w*, 1666*vs*, 1541*w*, 1490*w*, 1453*w*, 1412*w*, 1192*s*, 1134*s*, 843*w*, 800*m*, 723*m*. **HRMS (ESI):** Calculated for $C_{35}H_{40}N_7O_2$ ($[M+H]^+$): 590.3238. Found: 590.3233.

***N,N'*-(4,4'-(4-phenylpyridine-2,6-diyl)bis(4,1-phenylene))bis(4-chlorobutanamide) (8a)**



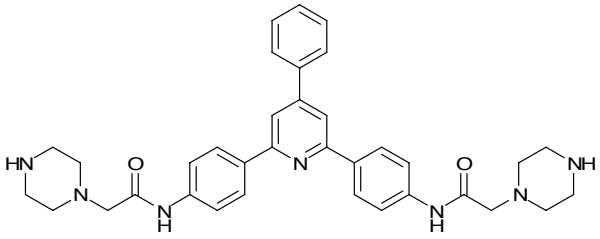

According to **route 2** with **5a** (150 mg, 0.45 mmol) and 4-chlorobutyryl chloride (1 mL, 8.9 mmol, excess reagent and solvent). The cream coloured solid was recrystallized from acetone/water to give **8a** as a cream white solid (205 mg, 84%). **$^1$H-NMR (500 MHz, DMSO-$d_6$):** 10.17 (*s*, 2H); 8.28 (*d*, 4H, *J*=8.8 Hz); 8.09 (*s*, 2H); 8.01 (*d*, 2H, *J*=9.0 Hz); 7.76 (*d*, 4H, *J*=8.8 Hz); 7.57-7.49 (*m*, 3H); 3.72 (*t*, 4H, *J*=6.5 Hz); 2.53 (*t*, 4H, *J*=6.5 Hz); 2.08-2.03 (*m*, 4H). **$^{13}$C-NMR (125 MHz, DMSO-$d_6$):** 170.5, 156.0, 149.5, 140.3, 137.9, 129.3, 129.1, 127.5, 127.4, 119.0, 115.5, 45.1, 33.5, 27.9. **IR (Neat):** 3232*w*, 3111*w*, 3049*w*, 2958*w*, 1651*s*, 1599*s*, 1543*s*, 1513*vs*, 1497*s*, 1450*m*, 1433*m*, 1416*m*, 1391*m*, 1365*m*, 1305*m*, 1258*m*, 1178*m*, 832*s*, 758*vs*, 724*m*, 697*s*. **HRMS (ESI):** Calculated for $C_{31}H_{30}Cl_2N_3O_2$ ($[M+H]^+$): 546.1742. Found: 546.1715.

***N,N'*-(4,4'-(4-phenylpyridine-2,6-diyl)bis(4,1-phenylene))bis(4-(pyrrolidin-1-yl)butanamide) (8)**



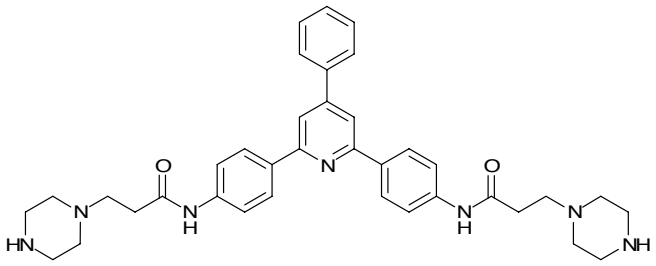
According to **route 3** with **8a** (50 mg, 0.09 mmol) and pyrrolidine (1 mL, 12 mmol, solvent and reagent, excess) to afford **8** as a yellow oil (51 mg, 95%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 70% MeCN over 22 min, $R_t$=18.5 min). **$^1$H-NMR (400 MHz, MeOD):** 8.09 (*s*, 2H); 8.04 (*d*, 4H, *J*=8.8 Hz); 7.93 (*d*, 2H, *J*=8.0 Hz); 7.80 (*d*, 4H, *J*=8.8 Hz); 7.58-7.54 (*m*, 3H); 3.75-3.65 (*br m*, 4H); 3.25-3.30 (*m*, 4H); 3.05-3.15 (*br m*, 4H); 2.11-2.06 (*m*, 4H); 2.02-1.95 (*m*, 12H). **$^{13}$C-NMR (125 MHz, MeOD):** 171.3, 155.3, 155.3, 140.6, 137.1, 131.5, 129.9, 129.0, 128.1, 127.3, 119.6, 117.8, 54.3, 53.8, 32.8, 22.6, 21.2. **IR (Neat):** 3032*w*, 1667*s*, 1597*s*, 1532*s*, 1517*s*, 1498*m*, 1449*w*, 1419*m*, 1393*m*, 1316*m*, 1251*m*, 1177*s*, 1125*vs*, 1016*w*, 961*w*, 836*s*, 799*s*, 765*s*, 720*s*, 697*m*. **HRMS (ESI):** Calculated for $C_{39}H_{46}N_5O_2$ ($[M+H]^+$): 616.3652. Found: 616.3637.

***N,N'*-(4,4'-(4-phenylpyridine-2,6-diyl)bis(4,1-phenylene))bis(2-(piperazin-1-yl)acetamide) (9)**



According to **route 3** with **5b** (40 mg, 0.10 mmol) and piperazine•HCl (180 mg, 2.04 mmol) in THF (2 mL) and triethylamine (2 mL). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 60% MeCN over 22 min, $R_t$=17.4 min) afforded **9** as a pale yellow oil (58 mg, 98%). **$^1$H-NMR (400 MHz, MeOD):** 8.10 (*s*, 2H); 8.20 (*d*, 4H, *J*=8.8 Hz); 7.94-7.91 (*m*, 2H); 7.84 (*d*, 4H, *J*=8.8 Hz); 7.59-7.53 (*m*, 3H); 3.71 (*s*, 4H); 3.47-3.45 (*m*, 8H); 3.24-3.21 (*m*, 8H). **$^{13}$C-NMR (100 MHz, MeOD):** 170.2, 158.1, 157.9, 143.8, 139.8, 133.9, 133.7, 132.6, 132.1, 130.9, 123.5, 122.2, 63.0, 52.8, 45.7. **IR (Neat):** 3465*w*, 2967*w*, 1665*s*, 1600*s*, 1518*s*, 1419*m*, 1393*m*, 1316*m*, 1252*m*, 1122*vs*, 1016*m*, 960*m*, 839*s*, 797*s*, 765*s*, 720*s*, 696*m*. **HRMS (ESI):** Calculated for $C_{35}H_{40}N_7O_2$ ($[M+H]^+$): 590.3231. Found: 590.3238.

***N,N'*-(4,4'-(4-phenylpyridine-2,6-diyl)bis(4,1-phenylene))bis(3-(piperazin-1-yl)propanamide) (10)**



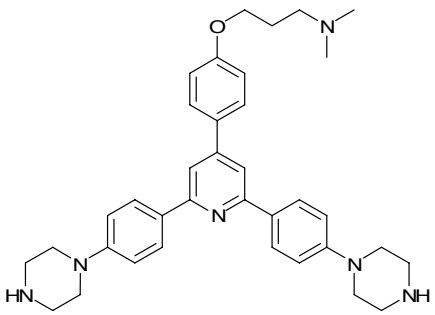

According to **route 3** with **6a** (50 mg, 0.09 mmol) and piperazine•HCl (0.18 g, 2.04 mmol) in THF (2 mL) and triethylamine (2 mL). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 80% MeCN over 22 min, $R_t$=15.7 min) afforded **10** as a pale yellow oil (32 mg, 54%). **$^1$H-NMR (400 MHz, MeOD):** 8.18 (*s*, 2H); 8.08 (*d*, 4H, *J*=8.8 Hz); 7.99-7.96 (*m*, 2H); 7.84 (*d*, 4H, *J*=8.8 Hz); 7.62-7.56 (*m*, 3H); 3.58-3.47 (*m*, 24H). **$^{13}$C-NMR (100 MHz, MeOD):** 172.6, 158.4, 157.6, 144.1, 140.1, 134.1, 133.6, 132.5,

131.8, 130.7, 123.0(CH) 121.8, 56.2, 52.2, 44.7, 34.5. **IR (Neat):** 3025*w*, 2854*w*, 1664*s*, 1621*m*, 1598*s*, 1536*m*, 1519*m*, 1420*w*, 1395*w*, 1319*w*, 1252*s*, 1180*s*, 1125*vs*, 1048*w*, 1017*w*, 975*w*, 837*s*, 798*s*, 766*w*, 722*s*, 698*w*. **HRMS (ESI):** Calculated for $C_{37}H_{44}N_7O_2$ ($[M+H]^+$): 618.3556. Found: 618.3569.

**11 and 12**

According to **route 1** with 4-piperazinoacetophenone (985 mg, 4.83 mmol), sodium hydroxide (97 mg, 2.42 mmol) and 4-[3(dimethylamino)propoxyl] benzaldehyde (0.48 mL, 2.42 mmol), refluxed in AcOH and ammonium acetate (1.9 g, 24 mmol). After refluxing in AcOH the solid recovered was a mixture of **11**, **12** and bis-acylated product. A sample (100 mg) was purified by HPLC (gradient: starting from Solvent A:Solvent B 95:5 to 70% MeCN over 22 min, $R_t$=12.0 min) afforded the product **11** as a bright yellow solid (10 mg, 9%) and **12** $R_t$=13.6 min (13 mg, 13%). Refluxing in MeOH yielded **11** as a single product (1.11 g, 80%).

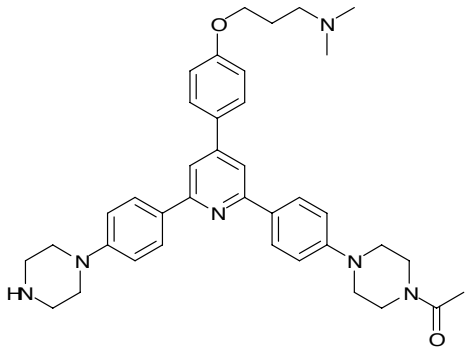
**(3-{4-[2,6-Bis-(4-piperazin-1-yl-phenyl)-pyridin-4-yl]-phenoxy}-propyl)-dimethyl-amine (11)**




**$^1$H-NMR (400 MHz, MeOD):** 8.15 (*s*, 2H); 8.03 (*d*, 2H, *J*=8.9 Hz); 8.01 (*d*, 4H, *J*=9.0 Hz); 7.27 (*d*, 4H, *J*=9.0 Hz); 7.21 (*d*, 2H, *J*=8.9 Hz); 4.26 (*t*, 2H, *J*=5.7 Hz); 3.66 (*t*, 8H,

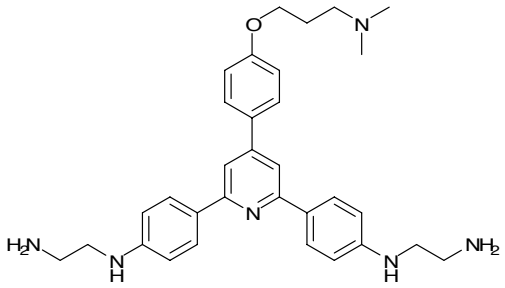
*J*=4.7 Hz); 3.42 (*t*, 8H, *J*=4.7 Hz); 2.99 (*t*, 2H); 2.99 (*s*, 6H); 2.34-2.27 (*m*, 2H). **$^{13}$C-NMR (125 MHz, MeOD):** 156.5, 155.2, 153.7, 130.9, 130.8, 129.9, 126.0, 119.0, 117.1, 116.8, 116.6, 66.3, 56.6, 46.7, 44.5, 43.6, 25.7. **IR (Neat):** 3400*w* 3008*w* 2810w, 1669*s*, 1599*s*, 1517*m* 1431*m*, 1390*m*, 1239*m*, 1178*s*, 1123*s*, 1042*m*, 928*s*, 824*m*, 798*m*, 791*m*, 720*s*. **HRMS (ESI):** Calculated for $C_{36}H_{45}N_6O$ ($[M+H]^+$): 577.3649. Found: 577.3650.

**1-(4-{4-[4-[4-(3-Dimethylamino-propoxy)-phenyl]-6-(4-piperazin-1-yl-phenyl)-pyridin-2-yl]-phenyl}-piperazin-1-yl)-ethanone (12)**



**$^{1}$H-NMR (400 MHz, MeOD):** 8.21 (*s*, 2H); 8.10 (*d*, 2H, *J*=8.9 Hz); 8.02-7.97 (*m*, 4H); 7.29 (*d*, 2H, *J*=8.8 Hz); 7.22 (*d*, 4H, *J*=8.9 Hz); 4.25 (*t*, 2H, *J*=5.7 Hz); 3.78-3.69 (*m*, 4H); 3.56-3.55 (*m*, 2H); 3.51-3.40 (*m*, 10H); 2.99 (*s*, 6H); 2.31 (*m*, 2H); 2.19 (*s*, 3H). **$^{13}$C-NMR (100 MHz, MeOD):** 172.3, 163.4, 158.0, 131.6, 131.5, 129.8, 124.9, 123.3, 119.8, 119.6, 117.4, 117.1, 116.6, 116.2, 66.7, 57.0, 47.3, 46.6, 44.9, 44.0, 42.7, 26.1, 21.5($CH_3$). **IR (Neat):** 3387*w*, 3041*w*, 2854*vw*, 1671*s*, 1600*s*, 1512*m*, 1431*m*, 1393*m*, 1291*w*, 1234*m*, 1199*vs*, 1181*vs*, 1129*s*, 1047*m*, 1008*w*, 983*w*, 952*w*, 928*w*, 830*m*, 800*m*, 721*m*. **HRMS (ESI):** Calculated for $C_{38}H_{47}N_6O_2$ ($[M+H]^+$): 619.3743. Found: 619.3760.

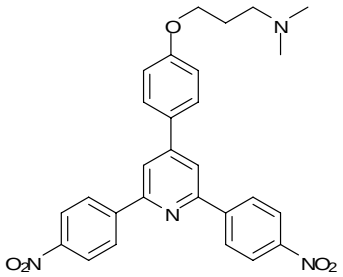
***N1,N1'*-(4,4'-(4-(4-(3-(dimethylamino)propoxy)phenyl)pyridine-2,6-diyl)bis(4,1-phenylene))diethane-1,2-diamine (13)**



**14** (75 mg, 0.17 mmol), 2-bromoethylamine•HCl (140 mg, 0.68 mmol) and sodium iodide (20 mg, catalyst) were refluxed overnight with triethylamine (1 mL) and MeOH (5 mL). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 80% MeCN over 22 min, $R_t$=15.5 min) afforded **13** as a bright yellow oil (63.4 mg, 71%). **$^1$H-NMR (500 MHz, MeOD):** 8.04 (*s*, 2H); 8.03 (*d*, 2H, *J*=9.0 Hz); 7.87 (*d*, 4H, *J*=8.8 Hz); 7.18 (*d*, 2H, *J*=9.0); 6.92 (*d*, 4H, *J*=8.8 Hz); 4.22 (*t*, 2H, *J*=5.5 Hz); 3.55 (*t*, 4H, *J*=6.0 Hz); 3.38 (*t*, 2H, *J*=7.5 Hz); 3.18 (*t*, 4H, *J*=6.0 Hz); 2.38-2.23 (*m*, 6H); 2.27 (*s*, 2H) **$^{13}$C-NMR (125 MHz, MeOD):** 155.5, 153.4, 151.4, 129.7, 129.3, 128.3, 120.4, 116.7, 115.1, 112.8, 112.8, 64.8, 55.2, 44.4, 42.2, 40.1, 24.3. **IR (Neat):** 3040*w*, 1676*vs*, 1609*m*, 1516*m*, 1432*w*, 1207*s*, 1136*s*, 844*w*, 801*w*, 725*w*. **HRMS (ESI):** Calculated for $C_{32}H_{41}N_6O$ ($[M+H]^+$): 525.3342. Found: 525.3362.

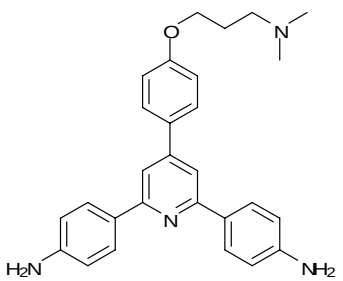
**3-(4-(2,6-Bis(4-nitrophenyl)pyridin-4-yl)phenoxy)-N,N-dimethylpropan-1-amine**

**(14a)**



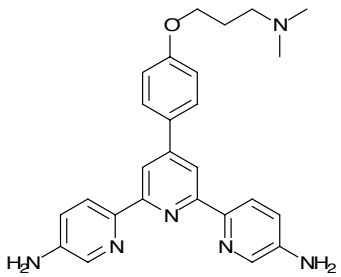
4-(3-(dimethylamino)propoxyl)benzaldehyde (1.53 mL, 1.57 g, 7.6 mmol) and 4-nitroacetophenone (2.5 g, 15.2 mmol) were refluxed in AcOH (10 mL) and ammonium acetate (10 g, excess) for 2 hrs. The cooled gloopy solid was dissolved in MeOH and adsorbed onto silica. FC (DCM/MeOH, 10:1) afforded **14a** (3.8 g, 50%) as a deep red oil. **$^{1}$H-NMR (400 MHz, MeOD):** 8.33 (*d*, 4H, *J*=9.0 Hz); 8.23 (*d*, 4H, *J*=9.0 Hz); 8.03 (*s*, 2H); 7.76 (*d*, 2H, *J*=9.0 Hz); 7.03 (*d*, 2H, *J*=9.0 Hz); 4.16 (*t*, 2H, *J*=6.0 Hz); 3.39 (*t*, 2H, *J*=8.0 Hz); 3.00 (*s*, 6H); 2.38-2.23 (*m*, 2H). **$^{13}$C-NMR (100 MHz, MeOD):** 162.1, 161.8, 156.8, 152.1, 150.1, 146.6, 130.2, 129.6, 125.4, 119.6, 116.7, 66.7, 57.4, 44.3, 26.3. **IR (Neat):** 3391*w*, 2949*w*, 1673*s*, 1593*s*, 1547*m*, 1517*s*, 1444*m*, 1432*m*, 1391*m*, *1335vs*, 1255*m*, 1236*m*, 1179*s*, 1128*s*, 1026*m*, 1011*m*, 855*m*, 820*s*, 799*s*, 763*m*, 732*m*, 721*s*, 690*m*. **HRMS (ESI):** Calculated for $C_{28}H_{27}O_5N_4$ ($[M+H]^+$): 499.1976. Found: 499.1972.

**4,4'-(4-(4-(3-(Dimethylamino)propoxy)phenyl)pyridine-2,6-diyl)dianiline (14)**



**14a** (3.0 g, 0.6 mmol) and Pd (10% on Carbon, 100 mg) were stirred in MeOH in a $H_2$-atmosphere overnight. The solution was filtered through Celite® and the solvent removed *in vacuo* to afford **14** (2.4 g, 92%) as a deep red viscous oil. **$^1$H-NMR (400 MHz, MeOD):** 8.05 (*s*, 2H); 7.98-7.96 (*m*, 6H); 7.16-7.14 (*m*, 6H); 4.19 (*t*, 2H, *J*=5.6 Hz); 3.37 (*t*, 2H, *J*=6.4 Hz); 2.95 (*s*, 6H); 2.30-2.25 (*m*, 2H). **$^{13}$C-NMR (100 MHz, MeOD):** 160.6, 154.1, 152.9, 146.9, 128.9, 128.6, 127.7, 123.1, 116.2, 116.1, 116.0, 114.5, 64.2, 54.6, 41.6, 23.7. **IR (Neat):** 3331*w*, 3213*w*, 2931*w,* 1706*w*, 1666*vs*, 1600*s*, 1592*vs*, 1540*s*, 1511*vs*, 1437*m*, 1390*s*, 1291*m*, 1251*s*, 1179*s*, 1095*m*, 1056*m*, 1011*m*, 832*s*. **HRMS (ESI):** Calculated for $C_{28}H_{31}N_4O$ ($[M+H]^+$): 439.2492. Found: 439.2492.

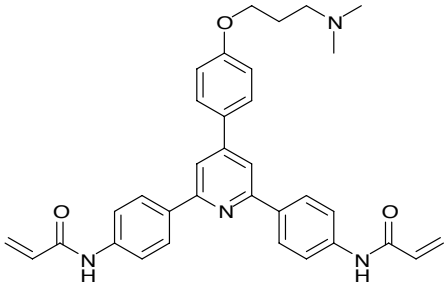
***N*-[4'-[4-(3-dimethylamino-propoxy)-phenyl]-5''-(3-amino)-[2,2';6',2'']terpyridin-5-yl]-3-amine (15)**




According to **route 1** with **7a** (1.12 g, 8.25 mmol), sodium hydroxide (0.17 g, 4.125 mmol) and benzaldehyde (0.85 g, 0.55 mL, 4.125 mmol), refluxed in MeOH and ammonium acetate (1.9 g, 24 mmol). **15** was recovered as a maroon solid (0.98 g, 63%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 70% MeCN over 22 min, $R_t$=16.0 min). **$^1$H-NMR (400 MHz, MeOD):** 8.50 (*br d*, 2H, *J*=9.2 Hz); 8.40 (*s*, 2H); 8.24 (*d*, 2H, *J*=2.8 Hz); 7.98 (*d*, 2H, *J*=8.8 Hz); 7.62 (*br d*, 2H, *J*=9.2 Hz); 7.15 (*d*, 2H, *J*=8.8 Hz), 4.22 (*t*, 2H, *J*=6.00 Hz), 3.33 (*t*, 2H, *J*=4.8 Hz), 2.98 (*s*, 6H), 2.31-2.24 (*m*,

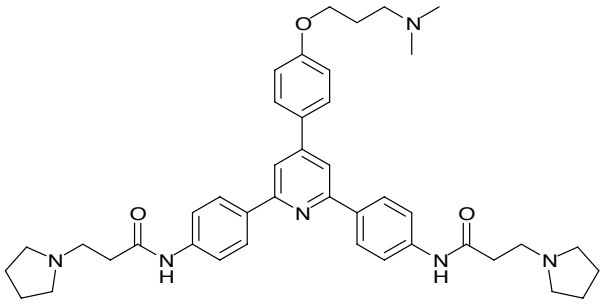
2H). **$^{13}$C-NMR (100 MHz, MeOD):** 160.2, 148.3, 147.1, 133.1, 124.2, 123.6, 120.6, 117.7, 115.6, 115.6, 114.8, 114.4.0, 64.3, 54.8, 41.8, 23.9. **IR (Neat):** 3334*w*, 3199*w*, 1670*s,* 1619*w*, 1590*s*, 1561*s*, 1537*m*, 1520*s*, 1484*w*, 1434*m*, 1408*m*, 1318*m*, 1242*m*, 1175*s*, 1056*m*, 995*m*, 952*w*, 830*s*, 798*s*, 719*s*. **HRMS (ESI):** Calculated for $C_{26}H_{29}N_6O$ ($[M+H]^+$): 441.2397. Found: 441.2396.

***N,N'*-(4,4'-(4-(4-(3-(dimethylamino)propoxy)phenyl)pyridine-2,6-diyl)bis(4,1-phenylene))diacrylamide (16a)**



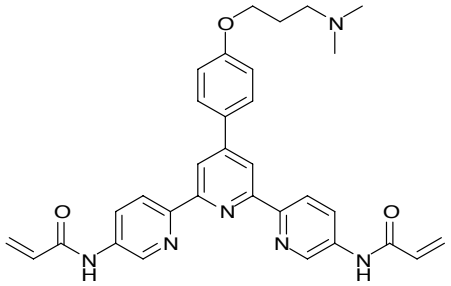
According to **route 2** with **14** (35 mg, 0.10 mmol) and 3-chloropropionyl chloride (1 mL, 5.9 mmol, solvent and reagent, great excess). **16a** was recovered as a cream white solid (48.9 mg, >99%). **$^{1}$H-NMR (400 MHz, MeOD):** 8.10 (*s*, 2H); 8.07 (*d*, 4H, *J*=8.8 Hz); 7.96 (*d*, 2H, *J*=8.8 Hz); 7.88 (*d*, 4H, *J*=8.8); 7.14 (*d*, 2H, *J*=8.8 Hz); 6.51-6.38 (*m,* 4H); 5.80 (*dd,* 2H, *J*=8.8 and 2.4 Hz); 4.20 (*t*, 2H, *J*=5.6 Hz); 3.38 (*t*, 2H, *J*=6.4 Hz, ); 2.95 (*s*, 6H); 2.29-2.24 (*m*, 2H). **$^{13}$C-NMR (125 MHz, MeOD):** 164.8, 160.2, 155.6, 151.8, 140.2, 132.8, 130.9, 130.1, 128.6, 127.9, 126.8, 119.8, 116.6, 114.9, 65.7, 55.3, 42.2, 24.3. **IR (Neat):** 3050*w*, 1663*s*, 1600*s*, 1530*m*, 1513*m*, 1432*m*, 1237*w*, 1183*vs*, 1133*s*, 1057*w*, 982*w*, 827*m*, 800*m*, 723*m*. **HRMS (ESI):** Calculated for $C_{34}H_{35}N_4O_3$ ($[M+H]^+$): 547.2709. Found: 547.2722.

***N*-(4-{4-[4-(3-dimethylamino-propoxy)-phenyl]-6-[4-(3-pyrrolidin-1-yl-propionylamino)-phenyl]-pyridin-2-yl}-phenyl)-3-pyrrolidin-1-yl-propionamide (16)**



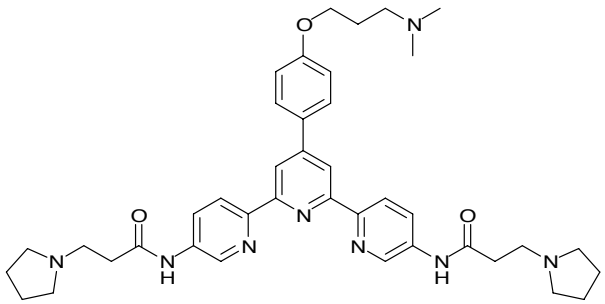
According to **route 3** with **16a** (43 mg, 0.08 mmol) and pyrrolidine (1 mL, 12 mmol, solvent and reagent, excess) to afford **16** as a yellow oil (33 mg, 60%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 70% MeCN over 42 min, $R_t$=27.5 min). **$^1$H-NMR (400 MHz, MeOD):** 8.23 (*d*, 4H, *J*=8.6 Hz); 8.02 (*s*, 2H); 7.90 (*d*, 2H, *J*=8.6 Hz); 7.77 (*d*, 4H, *J*=8.6); 7.16 (*d*, 2H, *J*=8.6 Hz); 4.20 (*t*, 2H, *J*=5.5 Hz); 3.78-3.68 (*m*, 4H); 3.59 (*t*, 4H, *J*=6.6 Hz); 3.39 (*t*, 2H, *J*=8.0 Hz); 3.23-3.13 (*m*, 4H); 3.05-3.00 (*m*, 4H); 2.96 (*s*, 6H); 2.32-2.24 (*m*, 2H); 2.24-2.12 (*m*, 4H); 2.12-2.02 (*m*, 4H). **$^{13}$C-NMR (125 MHz, MeOD):** 170.0, 161.5, 138.7, 157.4, 141.3, 134.8, 131.8, 129.9, 129.3, 121.0, 117.9, 116.3, 66.1, 56.7, 55.5, 52.2, 43.6, 32.9, 25.8, 24.0. **IR (Neat):** 3417*w*, 3040*w*, 1673*vs*, 1602*m*, 1515*m*, 1431*m*, 1185*s*, 1132*s*, 836*m*, 801*m*, 723*m*. **HRMS (ESI):** Calculated for $C_{42}H_{53}N_6O_3$ ($[M+H]^+$): 689.4198. Found: 689.4173.

***N*-[4'-[4-(3-Dimethylamino-propoxy)-phenyl]-5''-(3-acrylamido)-[2,2';6',2'']terpyridin-5-yl]-3-acrylamide (17a)**



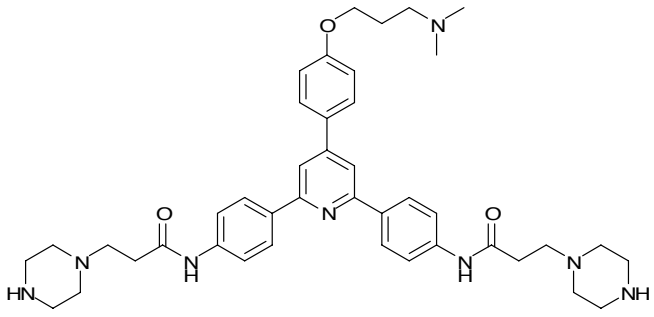
According to **route 2** with **15** (30 mg, 0.069 mmol) and 3-chloropropionyl chloride (1 mL, 5.9 mmol, solvent and reagent, great excess). **17a** was recovered as a cream white solid (37 mg, >99%). **$^{1}$H-NMR (400 MHz, MeOH):** 8.90 (*s*, 2H); 8.50 (*br m*, 2H ); 8.41 (*s*, 2H); 8.22 (*br m*, 2H); 7.78 (*d*, 2H, *J*=6.8 Hz); 7.02 (*d*, 2H, *J*=6.8 Hz); 6.52-6.39 (*m,* 4H); 5.83 (*d,* 2H, *J*=9.6 Hz); 4.07 (*t*, 2H, *J*=6.0 Hz); 2.54 (*t*, 2H, *J*=7.6 Hz); 2.25 (*s*, 6H); 2.02-1.97 (*m*, 2H). **$^{13}$C-NMR (100 MHz, $CDCl_3$):** 223.5, 170.1, 168.8, 163.9, 159.0, 143.8, 139.8, 134.5, 134.0, 131.5, 131.3, 131.0, 125.3, 120.5, 118.5, 71.7, 59.8, 47.8, 30.6. **IR (Neat):** 2951*w*, 1633*s*, 1567*s*, 1516*m*, 1465*m*, 1429*m*, 1404*m*, 1378*m*, 1315*m*, 1255*m*, 1187*m*, 1099*m*, 1088*m*, 826*m*. **HRMS (ESI):** Calculated for $C_{32}H_{33}N_6O_3$ ($[M+H]^+$): 549.2614. Found: 549.2618.

***N*-[4'-[4-(3-dimethylamino-propoxy)-phenyl]-5''-(3-pyrrolidin-1-yl-propionylamino)-[2,2';6',2'']terpyridin-5-yl]-3-pyrrolidin-1-yl-propionamide (17)**



According to **route 3** with **17a** (36 mg, 0.069 mmol) and pyrrolidine (1 mL, 12 mmol, solvent and reagent, excess) to afford **17** as a yellow oil (38 mg, 79%). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 40% MeCN over 42 min, $R_t$=24.8 min). **$^1$H-NMR (400 MHz, MeOD):** 9.11 (*d*, 2H, *J*=2.4 Hz); 8.71 (*d*, 2H, *J*=8.8 Hz); 8.66 (*s*, 2H); 8.40 (*dd*, 2H, *J*=8.8, 2.4); 8.00 (*d*, 2H, *J*=8.8 Hz); 7.17 (*d*, 2H, *J*=8.8 Hz); 4.22 (*t*, 2H, *J*=5.7 Hz); 3.72 (*m*, 4H); 3.59 (*t*, 4H, *J*=6.6 Hz); 3.39 (*t*, 2H, *J*=7.9 Hz); 3.16 (*m*, 4H); 3.01 (*t*, 4H, *J*=6.6 Hz); 2.95 (*s*, 6H); 2.35-2.27 (*m*, 2H); 2.22-2.14 (*m*, 4H); 2.10-2.02 (*m*, 4H). **$^{13}$C-NMR (125 MHz, MeOD):** 170.7, 153.5, 140.3, 138.7, 131.0, 130.3, 130.1, 124.1, 121.1, 119.4, 118.8, 116.5, 114.2, 66.2, 56.7, 55.6, 51.9, 43.6, 32.9, 25.7, 24.0. **IR (Neat):** 3386*w*, 3040*w*, 1670*s*, 1603*m*, 1537*m*, 1432*m*, 1184*s*, 1129*s*, 835*m*, 800*m*, 722*m*. **HRMS (ESI):** Calculated for $C_{40}H_{51}N_8O_3$ ($[M+H]^+$): 691.4107. Found: 691.4079.

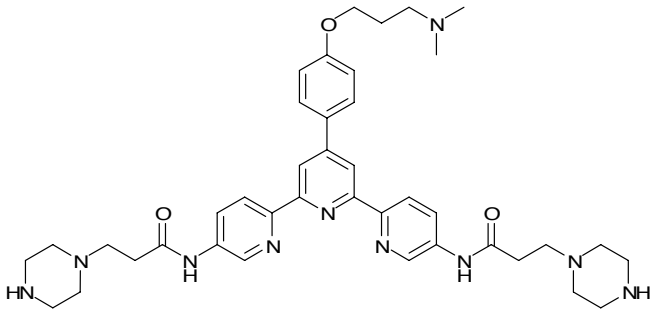
***N*,*N*'-(4,4'-(4-(4-(3-(dimethylamino)propoxy)phenyl)pyridine-2,6-diyl)bis(4,1-phenylene))bis(3-(piperazin-1-yl)propanamide) (18)**



According to **route 3** with **16a** (40 mg, 0.07 mmol) and piperazine HCl (60 mg, 1.83 mmol) in THF (1 mL) and triethylamine (1 mL). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 70% MeCN over 22 min, $R_t$=12.9 min) afforded **18** as a yellow oil (21 mg, 42%). **$^1$H-NMR (400 MHz, MeOD):** 8.24 (*s*, 2H); 8.08-8.03 (*m*, 6H); 7.88 (*d*,

4H, *J*=8.8 Hz); 7.18 (*d*, 2H, *J*=8.8 Hz); 4.22 (*t*, 2H, *J*=5.6 Hz); 3.56-3.51 (*m*, 20H); 3.38 (*t*, 2H, *J*=6.4 Hz); 2.99 (*t*, 4H, *J*=6.4 Hz); 2.94 (*s*, 6H); 2.31-2.26 (*m*, 2H). **$^{13}$C-NMR (125 MHz, MeOD):** 170.5, 162.8, 156.9, 155.2, 143.0, 130.9, 130.4, 130.0, 129.6, 121.1, 120.1(CH) 116.6, 66.2, 56.6, 54.2, 50.2, 43.2, 42.4, 32.2, 25.9. **IR (Neat):** 3026*w*, 1676*vs*, 1603*m*, 1534*m*, 1513*m*, 1431*w*, 1392*w*, 1202*s*, 1182*s*, 1132*s*, 834*w*, 800*w*, 722*w*. **HRMS (ESI):** Calculated for $C_{42}H_{55}N_8O_3$ ($[M+H]^+$): 719.4397. Found: 719.4401.

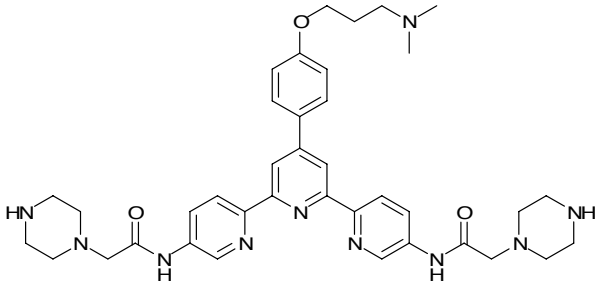
**_N_-[4'-[4-(3-dimethylamino-propoxy)-phenyl]-5''-(3-(piperazin-1-yl)propanamido)-[2,2';6',2'']terpyridin-5-yl]- 3-(piperazin-1-yl)propanamide (19)**



According to **route 3** with **17a** (37 mg, 0.06 mmol) and piperazine•HCl (130 mg, 1.50 mmol) in THF (1 mL) and triethylamine (1 mL). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 70% MeCN over 22 min, $R_t$=14.0 min) afforded **18** as a pale orange oil (22 mg, 51%). **$^{1}$H-NMR (500 MHz, MeOD):** 9.14 (*d*, 2H, *J*=2.1 Hz); 8.74 (*d*, 2H, *J*=7.8 Hz); 8.68 (*s*, 2H); 8.44 (*dd*, 2H, *J*=7.8, 2.4); 8.03 (*d*, 2H, *J*=8.9 Hz); 7.18 (*d*, 2H, *J*=8.9 Hz); 4.23 (*t*, 2H, *J*=5.8 Hz); 3.59 (*t*, 8H, *J*=4.9 Hz); 3.39 (*t*, 2H, *J*=7.9 Hz); 3.32-3.20 (*m*, 12H); 2.96 (*s*, 6H); 2.92 (*t*, 4H, *J*=6.6 Hz); 2.31-2.26 (*m*, 2H, $CH_2C\underline{H}_2CH_2$). **$^{13}$C-NMR (125 MHz, MeOD):** 170.4, 160.6, 138.4, 137.7, 129.3, 128.8, 122.9, 119.6, 118.2, 117.3, 116.7, 115.0, 112.7, 64.8, 55.3, 52.8, 42.2, 41.9, 40.3, 29.2, 24.3. **IR (Neat):** 2985*w*, 1676*vs*, 1603*m*, 1536*w*, 1435*w*, 1205*s*, 1134*s*, 1056*w*, 841*w*,

800*w*, 724*m*. **HRMS (ESI):** Calculated for $C_{40}H_{53}N_{10}O_3$ ($[M+H]^+$): 721.4334. Found: 721.4323.

***N*-[4'-[4-(3-dimethylamino-propoxy)-phenyl]-5''-(2-(piperazin-1-yl)acetamido)-[2,2';6',2'']terpyridin-5-yl]- 2-(piperazin-1-yl)acetamide (20)**



According to **route 1** with **15** (34 mg, 0.08 mmol) and chloroacetylchloride (1 mL, 12.5 mmol, excess reagent and solvent) gave a cream coloured solid (44 mg, >99%, 0.08 mmol) that was used as crude according to **route 3** with piperazine•HCl (130 mg, 1.50 mmol) in THF (1 mL) and triethylamine (1 mL). HPLC (gradient: starting from Solvent A:Solvent B 90:10 to 70% MeCN over 22 min, $R_t$=12.8 min) afforded **20** as a pale pink oil (39 mg, 73%). **$^1$H-NMR (500 MHz, MeOD):** 9.04 (*s*, 2H); 8.85 (*d*, 2H, *J*=9.0 Hz); 8.44-8.43 (*m*, 4H); 8.27 (*d*, 2H, *J*=8.8); 7.28 (*d*, 2H, *J*=8.8 Hz); 4.24 (*t*, 2H, *J*=5.7 Hz); 3.42 (*t*, 2H); 3.37 (*s*, 4H); 3.20-3.13 (*m*, 8H); 2.98 (*s*, 6H); 2.73-2.65 (*m*, 8H); 2.42-2.35 (*m*, 2H). **$^{13}$C-NMR (125 MHz, MeOD):** 169.6, 156.1, 149.5, 142.9, 138.8, 138.2, 129.4, 123.3, 120.0, 117.7, 115.4, 115.2, 113.1, 64.9, 60.4, 55.2, 50.8, 43.0, 42.2, 22.8. **IR (Neat):** 3004*w*, 1673*vs*, 1542*m*, 1206*s*, 1137*m*, 1068*w*, 839*w*, 799*w*, 726*w*. **HRMS (ESI):** Calculated for $C_{38}H_{49}N_{10}O_3$ ($[M+H]^+$): 693.3989. Found: 693.4001.

## 3.0 Surface Plasmon Resonance

Surface plasmon resonance measurements were performed on a four-channel BIAcore 3000 optical biosensor system (Biacore Inc.) using a streptavidin-coated sensor chip (Biacore SA-chip). In a typical experiment, biotinylated *ds-DNA* comprising the oligonucleotide d(biotin-[$G_2CATAGTGCGTG_3CGT_2AGC$]) hybridized with its complementary sequence, biotinylated *hTelo* d(biotin-[$GT_2A(G_3T_2A)_4G_2$]) and biotinylated *c-kit* d(biotin-[$C_3G_3CG_3CGCGAG_3AG_4AG_2$]) were thermally annealed in filtered and degassed running buffer (Tris-HCl 50 mM pH 7.4, 100 mM KCl; 95 °C for 5 min then cooled to room temperature overnight) and immobilized (600 RU) in flow cells 2, 3 and 4, leaving the first flow cell empty as a blank. DNA binding experiments were carried out with running buffer at a flow rate of 20 μL $min^{-1}$. Ligand solutions (between 0.0125, 0.025, 0.05, 0.10, 0.19, 0.39, 0.78, 1.56, 3.125, 6.25, 12.5 and 25 μM) were prepared with running buffer by serial dilutions from stock solutions. These solutions were injected using the KINJECT command (Biacore 3000 Control Software version 3.0.1) for 2 min followed by a 30 s 1 M KCl injection and a 30 s running buffer injection for chip regeneration. Each injection was performed in duplicate and the average response at equilibrium taken for analysis.

The response at equilibrium ($R_{eq}$) was plotted against concentration of analyte to generate a hyperbolic binding curve. The final graphs were obtained by subtracting blank sensorgrams from the duplex or quadruplex sensorgrams. For all compounds dissociation constants were determined by fitting the binding curve (from at least 5 concentrations) using the steady state affinity algorithm (Biaevaluation 3.0.2). Each experiment was repeated in duplicate and the average of the two taken.

## 4.0 Fluorescence Resonance Energy Transfer (FRET) Assay

All the oligonucleotides and their fluorescent conjugates (Eurogentec, Southampton, UK) were initially dissolved as a 100 μM stock solution in purified water; further dilutions were carried out in the appropriate buffer. The ability of the compounds to stabilize G-quadruplex DNA was investigated using a fluorescence resonance energy transfer (FRET) assay modified to be used as a high-throughput screen in a 96-well format. The labelled oligonucleotides hTelo: 5'-FAM-d(GGG[TTAGGG]3)-TAMRA-3', c-kit: 5'-FAM-d(GGG CGG GCG CGA GGG AGG GG)-TAMRA-3', DNA duplex: 5'-FAM-d(TAT AGC TAT A-HEG-TAT AGC TAT A)-TAMRA-3'; donor fluorophore FAM is 6-carboxyfluorescein; acceptor fluorophore TAMRA is 6-carboxytetramethyl-rhodamine] were prepared as a 400 nM solution in a 60 mM potassium cacodylate buffer (pH 7.4) and then annealed by heating to 90°C for 2 min, followed by cooling to room temprature. Compounds were stored at -80°C and dilutions were done with 60 mM potassium cacodylate buffer (pH 7.4) (1 mM stock solution of the TAP ligands were made up in water). The 96-well plates (MJ Research, Waltham, MA) were prepared by aliquoting 50 μL of the annealed DNA into each well, followed by 50 μL of the compound solutions using Beckman Coulter liquid-handling robot. For each compound, a minimum of 10 different concentrations were tested. Fluorescence melting curves were determined in a Roche light cycler 480, using a total reaction volume of 100 μL. Measurements were made in duplicate with excitation at 483 nm and detection at 533 nm. Final analysis of the data was carried out using Origin 7.5 (OriginLab Corp., Northampton, MA).