

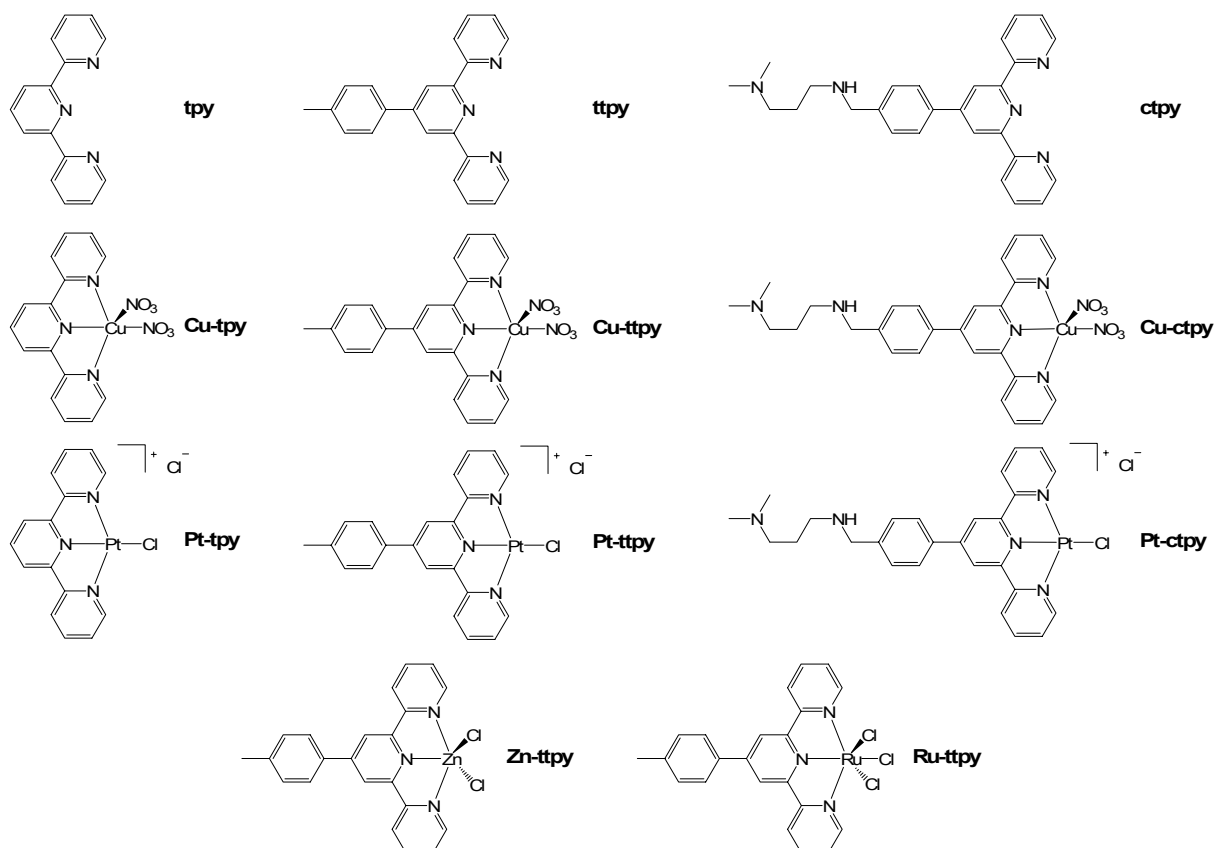
The importance of the metal geometry in the recognition of G-quadruplex-DNA by metal terpyridine complexes.

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Supplementary data

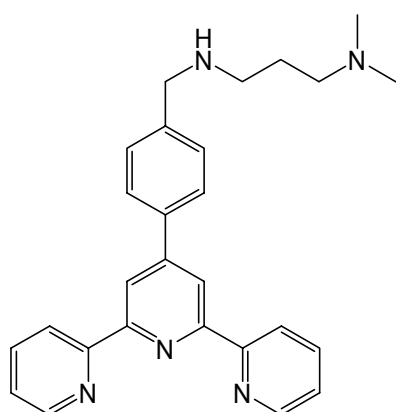
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Structures of terpyridines **tpy**, **ttpty** and **ctpy**, and of their related metallo-organic complexes with Cu(II), Pt(II), Zn(II) and Ru(III).

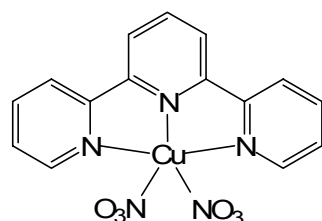
Chemistry. ^1H and ^{13}C spectra were recorded on a Bruker Avance 300 using TMS as internal standard. Deuterated solvents (CDCl_3 , D_2O , MeOD, DMSO-d_6) were purchased from SDS. The following abbreviations are used: singlet (s), doublet (d), doubled doublet (dd), triplet (t), doubled triplet (td) and multiplet (m). Mass spectrometry services were provided by the I.C.S.N. (Institut de Chimie des Substances Naturelles, Gif-sur-Yvette). The following abbreviations are used: chemical ionization (CI), electro spray (ES), time of flight (TOF). Reagents and chemicals were purchased from Sigma-Aldrich unless otherwise stated. Solvents were purchased from SDS. Dichloromethane (CH_2Cl_2 or DCM), methanol (MeOH) were distilled from calcium hydride, diethyl ether (Et_2O) was distilled from sodium.

The compounds **Pt-tpy** and **Ru-tpy** were synthesized following literature procedures (G. Annibale et al. *Polyhedron* **1995**, *14*, 451-453 and G.R. Newkome et al. *Chem. Eur. J.* **2002**, *8*, 13, 2946-2954 respectively).



4'-(4-[3-dimethylamino-1-propyl]amino-methyl-phenyl)-2,2':6',2''-terpyridine ctpy:

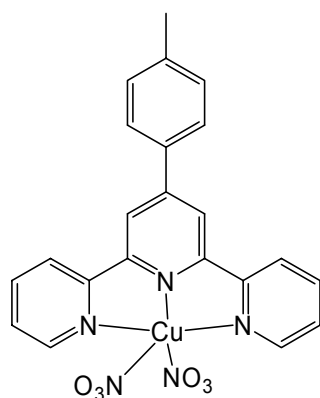
In an argon purged flask containing anhydrous CCl_4 (7mL) are introduced 4'-(4-methylphenyl)-2,2':6',2''-terpyridine (300mg, 0.93mmol, 1.0equiv.), N-bromosuccinimide (165mg, 0.93mmol, 1.0equiv.) and azobisisobutyronitrile (AIBN, 4.5mg, 0.028mmol, 0.03equiv.). The mixture is refluxed under nitrogen for 6hrs then cooled to RT. The obtained precipitate is filtered, washed and dried with diisopropylether to afford 4'-(4-bromo-methyl-phenyl)-2,2':6',2''-terpyridine (205mg, 55% chemical yield) as a white solid. $^1\text{H-NMR}$ (300MHz, CDCl_3): δ (ppm) 8.80 (m, 4H), 8.72 (d, $J=8.1\text{Hz}$, 2H), 7.96-7.90 (m, 4H), 7.58 (d, $J=8.4\text{Hz}$, 2H), 7.40 (ddd, $J=7.5\text{Hz}$, 6Hz, 1.2Hz, 2H), 4.61 (s, 2H) $^{13}\text{C-NMR}$ (75MHz, DMSO-d_6): δ (ppm) 155.7, 149.4, 148.9, 138.7, 138.3, 137.1, 129.6, 127.6, 124.0, 121.2, 118.7, 33.0. A solution of 4'-(4-bromo-methyl-phenyl)-2,2':6',2''-terpyridine (151.5mg, 0.38mmol, 1.0equiv.) and Et_3N (53 μL , 0.38mmol, 1.0equiv.) in *N,N*-dimethyl-amino-propylamine (10mL, large excess) is stirred at 90°C under nitrogen for 4 days. After concentration to dryness, the residue is dissolved in DCM (20mL) and washed with a 5% NaHCO_3 solution (1x20mL) and H_2O (2x20mL). The organic phase is dried over MgSO_4 , filtered and concentrated. The residue is taken up in a minimal amount of MeOH/HCl (prepared with acetyl chloride in dry MeOH) and precipitated with Et_2O . The precipitate is dissolved in H_2O , the pH is adjusted to 8 by addition of NaOH 5% and the aqueous phase is extracted with toluene (5x20mL). The organic layer is dried over MgSO_4 , filtered and concentrated to afford **ctpy** as yellow sticky oil (81.2mg, 51% chemical yield). $^1\text{H-NMR}$ (300MHz, CDCl_3): δ (ppm) 8.76 (m, 4H), 8.70 (d, $J=7.8\text{Hz}$, 2H), 7.90 (m, 4H), 7.49 (d, $J=8.1\text{Hz}$, 2H), 7.37 (m, 2H), 3.9 (s, 2H), 2.74 (t, $J=7.2\text{Hz}$, 2H), 2.37 (t, $J=7.2\text{Hz}$, 2H), 2.26 (s, 6H), 2.04 (s broad, 1H), 1.75 (q, $J=7.2\text{Hz}$, 2H). $^{13}\text{C-NMR}$ (75MHz, CDCl_3): δ (ppm) 156.4, 155.94, 150.1, 149.15, 141.65, 137.0, 136.85, 128.6, 127.3, 123.8, 121.4, 118.8, 58.15, 53.7, 48.0, 45.6, 28.1 **LRMS** (CI^+): m/z 424 ($[\text{M}+\text{H}^+]$, 100%)



[Cu-(2,2':6',2''-terpyridine)(NO₃)₂] Cu-tpy:

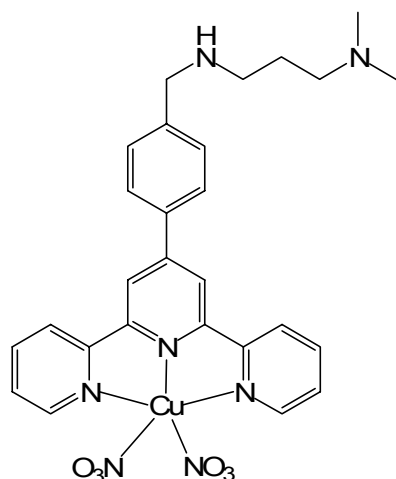
A solution of $\text{Cu}(\text{NO}_3)_2$ (16.1mg, 0.086mmol, 1.0equiv.) in anhydrous acetonitrile (2mL) is layered onto a solution of 2,2':6',2''-terpyridine (20mg, 0.086mmol, 1.0equiv.) in anhydrous DCM (2mL) and the solution is put in the fridge. After 3 days, **Cu-tpy** is obtained as blue needles (15.2mg, 49.2% chemical yield).

LRMS (TOF ES⁺) (MeOH): *m/z* 296.0 ([Cu(tpy)(NO₃)]⁺-(NO₃), fragmentation, 100%), 358.0 ([Cu(tpy)(NO₃)]⁺, 58%); **HRMS (TOF ES⁺)** (MeOH) Calcd for : 358.0127
Found : 358.0122 C₁₅H₁₁N₄O₃⁶³Cu⁺; **UV Data** : λ_{max} (nm) [ε_{max} (M⁻¹ cm⁻¹): 264 nm [15530], 275 [15300], 297 [17980], 325 [18090]



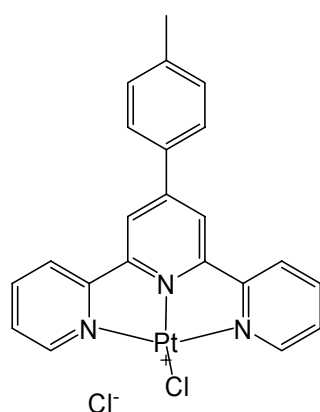
[Cu(4'-(4-methylphenyl)-2,2':6',2''-terpyridine)(NO₃)₂] Cu-tpty:

A solution of Cu(NO₃)₂ (11.6mg, 0.062mmol, 1.0equiv.) in anhydrous acetonitrile (1.5mL) is layered onto a solution of 4'-(4-methylphenyl)-2,2':6',2''-terpyridine (20mg, 0.062mmol, 1.0equiv.) in anhydrous DCM (1.5mL) and the solution is put in the fridge. After 4 days, **Cu-tpty** is obtained as blue needles (11.2mg, 35.3% chemical yield). **LRMS (TOF ES⁺)** (MeOH): *m/z* 386 (fragmentation, 100%), 448 ([Cu(tpy)(NO₃)]⁺, 45%); **HRMS (TOF ES⁺)** (MeOH) Calcd for : 448.0597 Found : 448.0646 C₂₂H₁₇N₄O₃⁶³Cu⁺; **UV Data** : λ_{max} (nm) [ε_{max} (M⁻¹ cm⁻¹): 267 nm [18400], 279 [23940], 287 [34660], 329 [21980], 344 [17710]



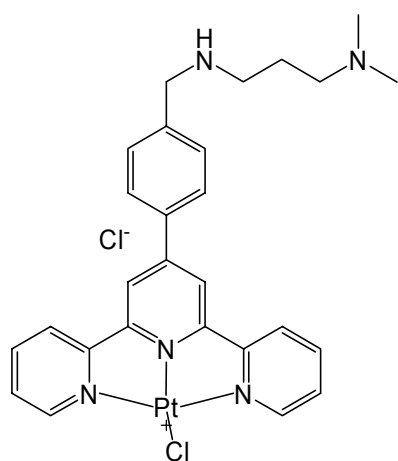
[Cu(4'-(4-[3-dimethylamino-1-propyl]amino-methyl-phenyl)-2,2':6',2''-terpyridine)(NO₃)₂] Cu-ctpy:

A solution of Cu(NO₃)₂ (9.4mg, 0.05mmol, 1.0equiv.) in anhydrous acetonitrile (1.2mL) is layered onto a solution of 4'-(4-[3-dimethylamino-1-propyl]amino-methyl-phenyl)-2,2':6',2''-terpyridine **ctpy** (21.1mg, 0.05mmol, 1.0equiv.) in anhydrous DCM (1.2mL) and the solution is put in the fridge. After 2 days, **Cu-ctpy** has precipitated as a green solid (10.1mg, 36.7% chemical yield). **LRMS (TOF ES⁺)** (MeOH+H₂O) *m/z* 521.1 (fragmentation, 100%), 386 (fragmentation, 100%), 548.1 ([Cu-ctpy-(NO₃)]⁺, 81%); **HRMS (TOF ES⁺)** (MeOH-H₂O) Calcd for: 548.1597 Found: 548.1557 C₂₇H₂₉N₆O₃⁶⁴Cu⁺; **UV Data** : λ_{max} (nm) [ε_{max} (M⁻¹ cm⁻¹): 268 nm [16250], 280 [21480], 288 [28910], 327 [10940], 346 [9220]



[Pt(4'-(4-methylphenyl)-2,2':6',2''-terpyridine)Cl]Cl Pt-tpty:

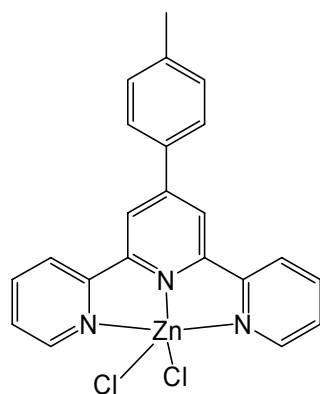
To a suspension of Pt(COD)Cl₂ (57.8mg, 0.155mmol, 1equiv.) in dry MeOH (4mL), heated to 50°C under nitrogen, is added 4'-(4-methylphenyl)-2,2':6',2''-terpyridine (50mg, 0.155mmol, 1 equiv.). The mixture is stirred at 50°C under nitrogen and protected from light for 3h30. The obtained suspension is filtered on membrane (Schleicher & Schuell, 1μm), the resulting yellow solid is washed with EtOH and Et₂O to afford pure **Pt-tpty** (84mg, 92% chemical yield). ¹H-NMR (300MHz, DMSO-d₆): δ (ppm) 8.98 (s, 2H), 8.93 (d, J=4.8Hz, 2H), 8.87 (d, J=7.8Hz, 2H), 8.54 (t, J=7.8Hz, 2H), 8.14 (d, J=8.4Hz, 2H), 7.96 (t, J=6.3Hz, 2H), 7.5 (d, J=8.4Hz, 2H), 2.45 (s, 3H) **LRMS (ES⁺)**: *m/z* 554 ([M-Cl]⁺, 100%); **HRMS (TOF ES⁺)** (MeOH) Calcd for : 553.0759 Found : 553.0763 C₂₂H₁₇N₃³⁵Cl¹⁹⁵Pt⁺; **UV Data** : λ_{max} (nm) [ε_{max} (M⁻¹ cm⁻¹): 262 nm [25690], 279 [23250], 334 [17000], 403 [5150]



[Pt(4'-(4-[3-dimethylamino-1-propyl]amino-methyl-phenyl)-2,2':6',2''-terpyridine)Cl]Cl Pt-ctpy:

To a suspension of Pt(COD)Cl₂ (23.6mg, 0.063mmol, 1.0equiv.) in dry MeOH (1.5mL), heated to 50°C under nitrogen, is added 4'-(4-[3-dimethylamino-1-propyl]amino-methyl-phenyl)-2,2':6',2''-terpyridine **ctpy** (26.7mg, 0.063mmol, 1.0equiv.) in dry MeOH (1.5mL). The mixture is stirred at 50°C under nitrogen and protected from light for 16hrs. Some drops of Et₂O are added to the resulting solution and upon diffusion **Pt-ctpy** precipitates as thin orange needles (15mg, 35% chemical yield). ¹H-NMR (300MHz, DMSO-*d*₆): δ (ppm) 8.68 (d, J=6.3Hz, 2H), 8.56 (m, 4H), 8.28 (t, J=7.5Hz, 2H), 8.20 (d, J=7.8Hz, 2H), 7.98 (m, 2H),

7.63 (6.3Hz, 2H), 3.8 (s, 2H), 3.51-3.31 (m broad, 8H), 2.30 (s broad, 2H), 1.59 (s broad, 2H); **LRMS (ES⁺):** *m/z* 653 ([M=C₂₇H₂₉N₅Cl₂Pt)-Cl]⁺, 100%), 310 ([M-2Cl]²⁺, 93.2%), 568 ([C₂₂H₁₈N₄ClPt]⁺ fragmentation, 81%); **HRMS (TOF ES⁺)** (MeOH) Calcd for: 653.1759 Found: 653.1758 C₂₇H₂₉N₅³⁵Cl¹⁹⁵Pt⁺ and Calcd for: 654.1761 Found: 654.1763 C₂₇H₂₉N₅³⁵Cl¹⁹⁶Pt⁺; **UV Data :** λ_{max} (nm) [ε_{max} (M⁻¹ cm⁻¹): 258 nm [19860], 283 [21050], 334 [10660], 392 [2960]



[Zn(4'-(4-methylphenyl)-2,2':6',2''-terpyridine)Cl₂] Zn-ttpy:

To a solution of 4'-(4-methylphenyl)-2,2':6',2''-terpyridine (20mg, 0.062mmol, 1.0equiv.) in dry DCM (10mL) is added drop wise a solution of ZnCl₂ (8.4mg, 0.062mmol, 1.0equiv.) in anhydrous acetonitrile (10mL). The mixture is stirred under nitrogen for 24hrs. The resulting white precipitate is filtered and dried with Et₂O to afford **Zn-ttpy** as a white solid (16.2mg, 56.8% chemical yield). ¹H-NMR (300MHz, CDCl₃): δ (ppm) 9.22 (d, J=4.5Hz, 2H), 8.4 (s, 2H), 8.3 (d, J=7.8Hz, 2H), 8.1 (t, J=7.8Hz, 2H), 7.73 (m, 4H), 7.46 (d, J=7.8Hz, 2H), 2.54 (s, 3H) **LRMS (TOF ES⁺)** (MeOH): *m/z* 355 ([Zn(tpy)₂]²⁺, 100%), 422 ([Zn(tpy)Cl]⁺, 10.6%); **UV Data :** λ_{max} (nm) [ε_{max} (M⁻¹ cm⁻¹): 279 [26370], 286

nm [31010], 323 [21150], 337 [16770]

Oligonucleotides used in comparative G4-FID and competitive FRET-melting assays:

The sequence of the 17bp duplex-DNA matrix is [5'-C₂AGT₂CGTAGTA₂C₃-3']/[5'-G₃T₂ACTACGA₂CTG₂-3'] and the one of the 26bp duplex-DNA competitor is [5'-CA₂TCG₂ATCGA₂T₂CGAT-C₂GAT₂G-3'] (self complementary sequence).

G4-FID protocol:

Fluorescence measurements are performed on a FluoroMax-3 spectrophotometer (Jobin-Yvon). The G4-FID assay is designed as follows: onto a mixture of pre-folded 22AG-quadruplex (0,25μM) or duplex-DNA (17bp or ds26, 0,25μM) and TO (0,50μM for 22AG and 17bp, 0,75μM for ds26), in a 10mM sodium cacodylate pH 7.3, 100mM K⁺ buffer, addition of increasing concentration of ligand (from 0.5 to 10 equiv.) is followed by a 3 min equilibration period before the fluorescence spectrum is recorded. The fluorescence area (FA, 510-750nm), converted in percentage displacement (PD, with PD = 100-[(FA/FA₀)×100], FA₀ being FA before addition of ligand), is then plotted vs the concentration of added ligand.

G4-FID results for ds26 and 17bp:

G4-FID results are presented as follows: **Cu-tpy** (■), **Cu-ttpty** (●), **Cu-ctpy** (◆), **Pt-tpy** (■), **Pt-ttpty** (●) and **Pt-ctpy** (◆), for experiments carried out with 17bp (S1) or ds26 (S2).

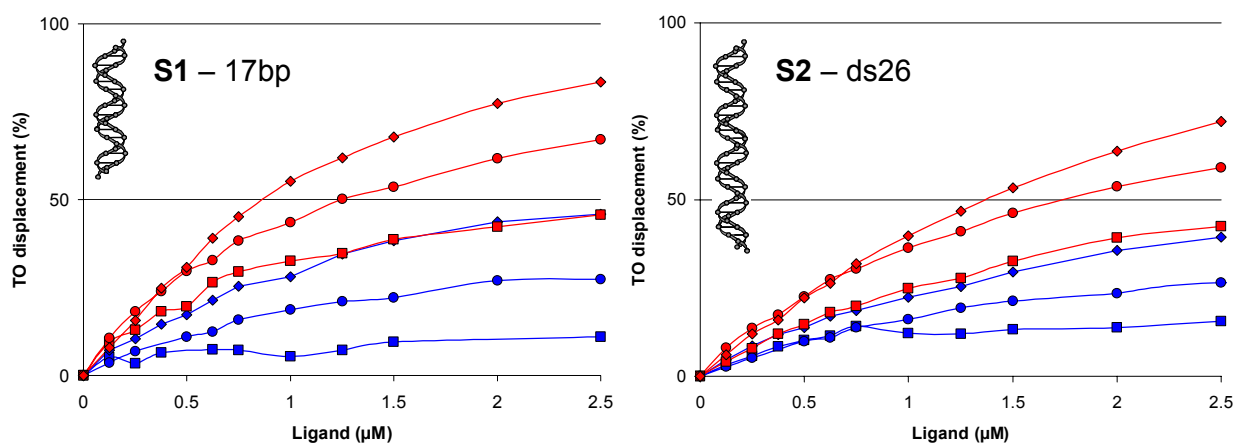


Table S1 Comparative G4-FID of metallo-organic complexes **Cu-tpy**, **Cu-ttpty**, **Cu-ctpy**, **Pt-tpy**, **Pt-ttpty** and **Pt-ctpy**, performed with 22AG, ds26 and 17bp.

Ligand	22AG	ds26	G4-FID	17bp	G4-FID
	^{G4} DC ₅₀ (μM)	^{ds} DC ₅₀ (μM)	Sel. ^a 22AG vs ds26	^{ds} DC ₅₀ (μM)	Sel. ^a 22AG vs 17bp
Cu-tpy	>2.5	>2.5	-	>2.5	-
Cu-ttpty	0.30	>2.5	22 ^b	>2.5	22 ^b
Cu-ctpy	0.19	>2.5	19 ^b	>2.5	15 ^b
Pt-tpy	1.46	>2.5	2 ^b	>2.5	2 ^b
Pt-ttpty	0.18	1.74	10	1.26	7
Pt-ctpy	0.25	1.37	5	0.86	3

^(a) G4-FID selectivity is defined as ^{ds}DC₅₀/^{G4}DC₅₀ ratio; ^(b) in the case of ^{ds}DC₅₀>2.5μM, the selectivity is estimated on the basis of TO displacement (%) obtained with 2.5μM of ligand with 17bp or ds26 and the concentration required with 22AG to reach the same displacement (^{G4}C): Sel. = 2.5/^{G4}C. Experimental errors are estimated at ±5%.

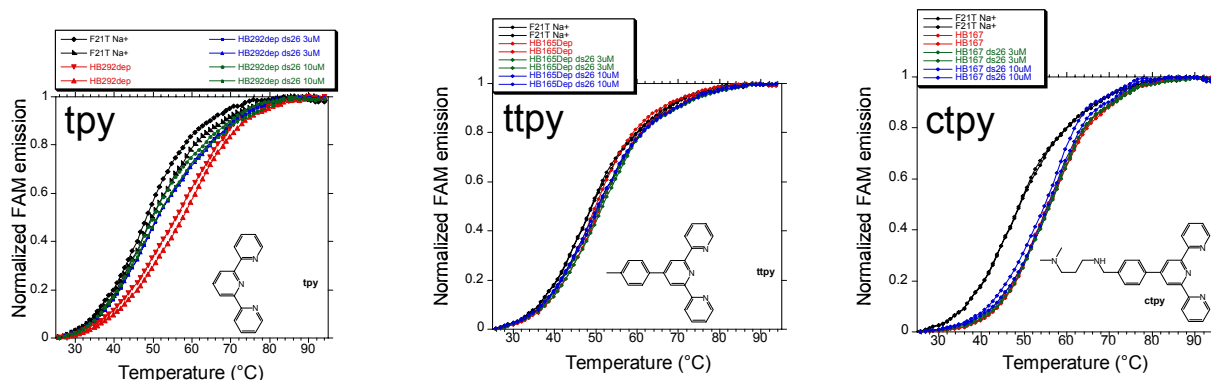
FRET-melting protocol:

Labelled oligonucleotide is purchased from Eurogentec (Belgium); after an initial dilution at 100μM concentration in purified water, further dilutions are carried out in the relevant buffer. FRET assay is performed as a high-throughput screen in a 96-well format, with F21T (*FAM*-G₃[T₂AG₃T]₃-*Tamra*, with *FAM*: 6-carboxyfluorescein and *Tamra*: 6-carboxytetramethylrhodamine). Fluorescence melting curves were determined with a Stratagene Mx3000P real-time PCR machine, using a total reaction volume of 25μL, with 0.2μM of tagged oligonucleotide in a buffer containing 10mM lithium cacodylate pH 7.2 and 100mM NaCl. After a first equilibration step at 25°C during 5 minutes, a stepwise increase of 1°C every minute for 71 cycles to reach 95°C was performed and measurements were made after each “cycle” with excitation at 492nm and detection at 516nm. The melting of the G-quadruplex was monitored alone or in the presence of various concentrations of compounds and/or of double-stranded competitor ds26 (⁵-CAATCGGATCGAATTCGATCCGATTG-³). Final analysis of the data was carried out using Excel and Kaleida graph software. Emission of FAM was normalized between 0 and 1, and *T*_{1/2} was defined as the temperature for which the normalized emission is 0.5. Δ*T*_{1/2} values are mean of 2 to 4 experiments ± standard deviation.

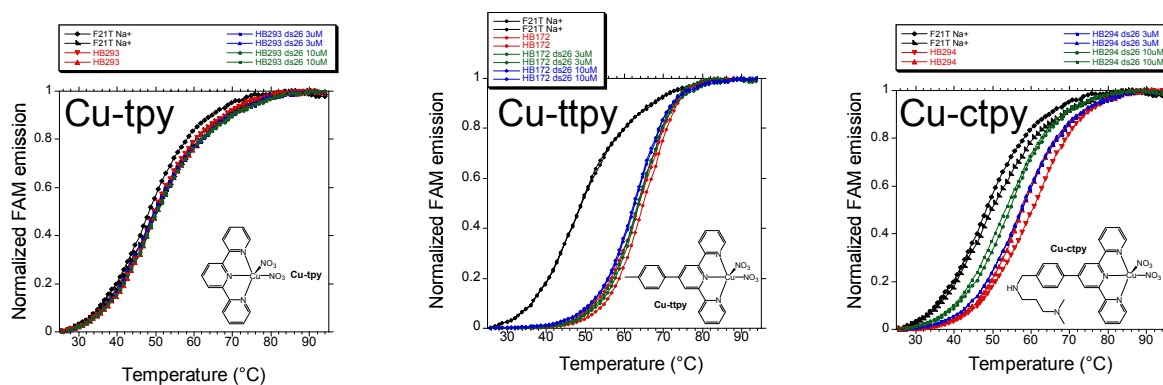
FRET-melting results:

FRET-melting results are presented as follows: F21T (0.2 μ M, black curves), F21T + ligand (1 μ M, red curves), F21T + ligand + 3 μ M ds26 (green curves) and F21T + ligand + 3 μ M ds26 (blue curves)

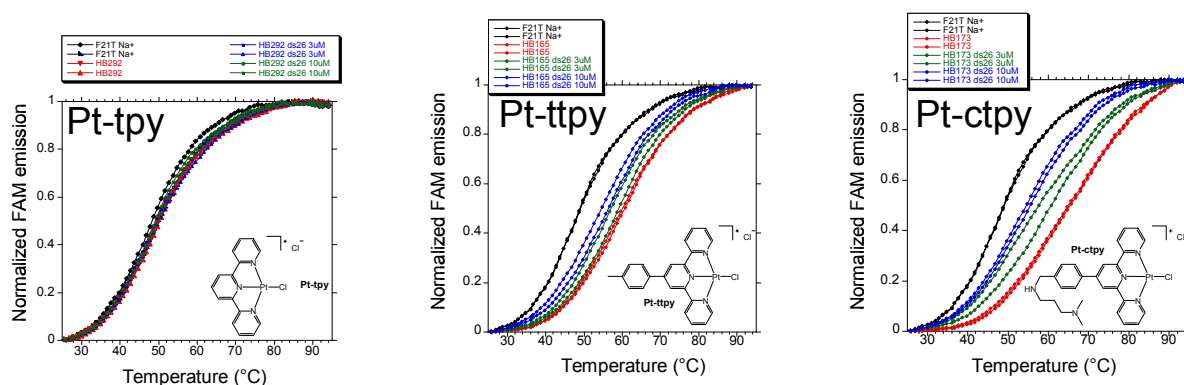
- Free terpyridines:



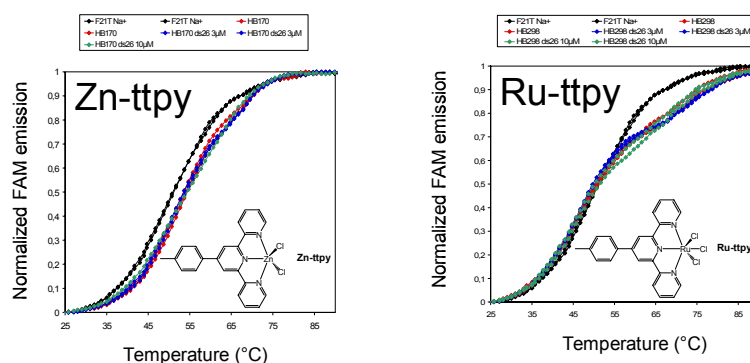
- Cu-complexes:



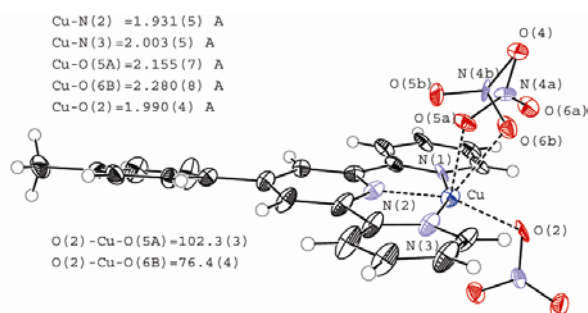
- Pt-complexes:



- Zn- and Ru-complexes:



X-ray diffraction of Cu-ttpy: data were collected by using a Kappa X8 APPEX II Bruker



diffractometer with graphite-monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The temperature of the crystal was maintained at the selected value (100K) by means of a 700 series Cryostream cooling device to within an accuracy of $\pm 1 \text{ K}$. The data were corrected for Lorentz, polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97 (G. M.

Sheldrick, SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Göttingen, Germany, 1997) and refined against F^2 by full-matrix least-squares techniques using SHELXL-97 (G. M. Sheldrick, SHELXL-97, Program for the refinement of crystal structures from diffraction data, University of Göttingen, Göttingen, Germany, 1997) with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located on a difference Fourier map and introduced into the calculations as a riding model with isotropic thermal parameters. All calculations were performed by using the Crystal Structure crystallographic software package WINGX (L.J. Farrugia, *J. Appl. Cryst.* **1999**, *32*, 837-838). The geometry of the methyl H atoms of C22 has been further investigated using a HFIX 137 refinement, but its orientation does not influence the principal molecular geometry.

One NO_3^- anion of structure **Cu-ttpy** appeared to be disordered. The occupancy factors were fixed in the ratio 50:50 for the N4 atom and two O atoms (O(6) and O(5)), the other O(4) atom being refined with an occupancy factor of 1.0.