Supporting Information

A Dynamic Intramolecular Cap for Preserving Metallodrug Integrity – a Case of Catalytic Fluoroquinolones

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I. Supplementary figures, tables and schemes (pages S2-S12)

**Figure S1.** Differential plot of potentiometric titrations of 11-Cu(II) vs. 4-Cu(II). Annotated with UV-vis (pH 6-10) and EPR (pH 7-10) data. A comparison of 11-Cu(II) to its parent complex 4-Cu(II), demonstrates that neither the UV-vis d-d transition band or the EPR hyperfine coupling constant \( A_{iso} \) are significantly perturbed for 11-Cu(II) at pH 10 vs pH 7, strongly suggesting that the buffering region defined by the differential titration plot represents the protonation of the amine and **not** amine-metal coordination.

**Figure S2.** 13C NMR of 9, 9-Co(III)(H_2O)(OH) and 9-Co(III)(H_2O). Strong downfield shift observed in C-N region in going from 9 to 9-Co(III)(H_2O)(OH), and then again in going from 9-Co(III)(H_2O)(OH) to 9-Co(III)(H_2O).
Figure S3. Potentiometric titration of 7-Co(III) before (A→B) and after (C→D) activation.

Figure S4. 13C NMR for 11 and 11-Co(III)(H₂O). Strong downfield shift observed in C-N region in going from 11 to 11-Co(III)(H₂O).
**Figure S5.** UV-vis for 11-Co(III) vs. 11-Co(II). 11-Co(II) was prepared from 11-Co(III) by the addition of 5 equivalents of DTT at rt, which induced an immediate colour change from deep red to orange. The DTT was then removed by extensive washing of the (dry) product with chloroform before recording the UV-vis spectrum in water solution.

**Figure S6.** UV-vis for 11-Co(III)(H₂O) (pH 4-12).
Figure S7. DNase assay in absence of adjuvants for 7-10 and their Cu(II) and Co(III) complexes. Comparative concentration dependent cleavage of (+) supercoiled pHOT-1 plasmid (0.007 μg μL$^{-1}$ for metal-free compounds and corresponding Cu(II) complexes; 0.021 μg μL$^{-1}$ for Co(III) complexes) in HEPES buffer (50 mM, pH 7.4) over 5 h (metal-free compounds and Cu(II)) or 10 h (Co(III)). Compounds include 2-Cu(II) as positive control.
Figure S8. DNase assay in absence of adjuvants for 11-14 and their Cu(II) complexes. Comparative concentration dependent cleavage of (+) supercoiled pHOT-1 plasmid (0.014 μg μL\(^{-1}\)) in HEPES buffer (50 mM, pH 7.4) over 10 h. Compounds include 2-Cu(II) as positive control.

Figure S9. DNase assay in absence of adjuvants for Co(III) complexes of 11-14. Comparative concentration dependent cleavage of (+) supercoiled pHOT-1 plasmid (0.021 μg μL\(^{-1}\)) in HEPES buffer (50 mM, pH 7.4) over 10 h. Compounds include 2-Cu(II) as positive control. Standard deviations of three independent experiments are shown as error bars. The agarose gel images show one representative experiment.
**Figure S10.** DNase assay in absence of adjuvants for 11-Co(III) alone or with a series of scavenging compounds (10 mM). Comparative concentration dependent cleavage of (+) supercoiled pHOT-1 plasmid (0.021 µg µL^{-1}) in HEPES buffer (50 mM, pH 7.4) over 10 h. The graphical representation only shows the percentage of Form II DNA produced at the highest tested concentration of 11-Co(III) (i.e.; 80 µM). Compounds include 2-Cu(II) as positive control. Standard deviations of three independent experiments are shown as error bars. The agarose gel images show one representative experiment.

**Figure S11.** Cleavage of (+) supercoiled pHOT-1 plasmid (0.021 µg µL^{-1}) in TRIS buffer (50 mM, pH 7.4) with 11-Co(III) alone, or with ATP (1.8 mM) over 10 h.
Figure S12. DNase assay in the presence of ascorbic acid (0.32 mM) for the Cu(II) and Co(III) complexes of 7-14. Comparative concentration dependent cleavage of (+) supercoiled pHOT-1 plasmid (0.014 μg μL⁻¹) in HEPES buffer (50 mM, pH 7.4) and ascorbic acid (0.32 mM) over 2 h.

Figure S13. DNase assay in the presence of DTT (0.3 mM) for the Cu(II) and Co(III) complexes of 11. Comparative concentration dependent cleavage of (+) supercoiled pHOT-1 plasmid (0.014 μg μL⁻¹) in HEPES buffer (50 mM, pH 7.4) and ascorbic acid (0.32 mM) over 2 h.
**Figure S14.** Gels show experiments for Cipro and 11-Co(III) (A), and for 11 and 11-Cu(II) (B) incubated for 1.5 h with (+) supercoiled DNA (0.009 μg μL⁻¹) in the presence of E. coli DNA gyrase, and with Proteinase K (PK) or EDTA in the second incubation. Graphical representation of the exemplar data in parts A and B for experiments treated with proteinase K (PK) in the second incubation (C). Standard deviations of three independent experiments are shown as error bars for cipro and 11-Co(III).
**Figure S15.** DNase assay for the metal-free compounds 7 and 10-13. Comparative concentration dependent cleavage of (+) supercoiled pHOT-1 plasmid (0.014 μg μL⁻¹) in HEPES buffer (50 mM, pH 7.4) over 10 h, in the presence or absence of 1 mM EDTA. Compound 2-Cu(II) is included as a positive control.
Figure S16. The structures of stereoisomers of 11-Co(III) and its relative free energies in kcal/mol. For clarity, the ciprofloxacin scaffold is not shown.
**Table S1.** ‘Effective’ guanidine $pK_a$ values derived from potentiometric titration, UV-vis data and EPR data (as detailed in main paper).

| Compound | Guanidine-Metal $pK_a$ |
|----------|-----------------------|
| 7-Cu(II) | 8.6                   |
| 8-Cu(II) | 8.3                   |
| 9-Cu(II) | 8.8                   |
| 10-Cu(II)| 8.8                   |

**Scheme S1.** Synthesis of bromide derivative 15d. Reagents and Conditions: (a) 3-butyn-1-ol, PdCl$_2$(PPh$_3$)$_2$, CuI, Et$_3$N, DMF, RT, 51%; (b) TBDMSCl, imidazole, DMF, RT, 91%; (c) H$_2$(g) 1 atm, Pd/C 10%, EtOAc, 94%; (d) HBr, AcOH, 100°C, 96%, (e) Ciprofloxacin methyl-ester$^1$, DIPEA, CH$_3$CN, 0 °C to RT, 58%.

**Scheme S2.** Synthesis of common intermediate 16. Reagents and Conditions: (a) EtOH, diethyl oxalate, rt, 97% (see ref.$^2$); (b) CH$_3$CN, N-(2-bromoethyl) phthalimide$^3$, 60°C, 33%.
II. Synthetic and analytical data for compounds 15d, 16a, 16b-d, 18a-d, 19a-c and 19 (pages S13-S18)

Compound 15d. A suspension of ciprofloxacin methyl ester$^1$ (9.5 g, 24.8 mmol) and DIPEA (17 mL, 4 eq.) in dry CH$_3$CN (250 mL) was set stirring in an ice bath, and then the dibromo compound 19 was added (9.08 g, 1.2 equiv.) under an atmosphere of argon. The ice-bath was maintained for the duration of the reaction. TLC analysis (DCM/MeOH 9:1) indicated complete consumption of ciprofloxacin methyl ester after 10 h. The solvent was evaporated, and the residue was dried in vacuo overnight. The crude product was then loaded onto a DCM-packed silica column as a DCM solution; the desired product was eluted in 1% MeOH/DCM to yield 15d as a white solid (8.22 g, 14.4 mmol, 58%); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$H 8.43 (s, 1H, QH-2), 7.88 (d, $J_{HF} = 13.4$ Hz, 1H, QH-5), 7.25 (d, $J = 8.0$ Hz, 2H, linker Ar), 7.20 (d, $J_{HF} = 7.1$ Hz, 1H, QH-8), 7.13 (d, $J = 8.0$ Hz, 2H, linker Ar), 3.86 (s, 3H, OCH$_3$), 3.54 (s, 2H, linker CH$_2$-piperazine), 3.43-3.35 (m, 3H, linker CH$_2$-Br, cyclopropane CH), 3.30-3.16 (m, 4H, piperazine 2×CH$_2$), 2.70-2.55 (m, 6H, piperazine 2×CH$_2$, linker CH$_2$(CH$_2$)$_3$-Br), 1.87 (quint, $J = 6.8$ Hz, 2H, linker CH$_2$CH$_2$-Br), 1.74 (quint, $J = 7.5$ Hz, 2H, linker CH$_2$(CH$_2$)$_2$-Br), 1.29-1.24 (m, 2H, cyclopropane CH$_2$), 1.13-1.06 (m, 2H, cyclopropane CH$_2$), $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$C 173.00 (d, $J_{CF} = 2.1$ Hz, C=O), 166.22 (s, C=O), 153.34 (d, $J_{CF} = 248.4$ Hz, cipro), 148.30 (s, C-H cipro), 144.62 (d, $J_{CF} = 10.6$ Hz, cipro), 140.86 (s, linker Ar), 137.93 (d, $J_{CF} = 1.2$ Hz, cipro), 135.17 (s, linker Ar), 129.34 (s, C-H linker Ar), 128.36 (s, C-H linker Ar), 122.71 (d, $J_{CF} = 7.2$ Hz, cipro), 112.95 (d, $J_{CF} = 23.1$ Hz, C-H cipro), 109.76 (s, cipro), 104.85 (d, $J_{CF} = 3.1$ Hz, C-H cipro), 62.69 (s, linker CH$_2$-piperazine), 52.78 (s, piperazine CH$_2$), 51.98 (s, OCH$_3$), 49.92 (d, $J_{CF} = 4.4$ Hz, piperazine CH$_2$), 34.64 (s, linker CH$_2$(CH$_2$)$_3$-Br), 34.55 (s, cyclopropane CH), 33.75 (s, linker CH$_2$-Br), 32.24 (s, linker CH$_2$CH$_2$-Br), 29.88 (s, linker CH$_2$(CH$_2$)$_2$-Br), 8.11 (s, cyclopropane CH$_2$). MS (ESI+ QTOFMS) calculated for C$_{29}$H$_{33}$BrF$_3$N$_3$O$_3$ ([M+H]$^+$) m/e 570.18; measured m/e 570.18.

Compound 16a. Compound 16a was prepared according to a previously reported procedure with some modifications$^2$. Cyclen$^4$ (5.0 g, 29 mmol) was dissolved in absolute EtOH (100 mL) and diethyl oxalate (4.24 g, 29 mmol) was added dropwise at room temperature. TLC analysis (CHCl$_3$/MeOH/MeNH$_2$ (33% MeNH$_2$ in EtOH), 80:15:5) indicated complete consumption of cyclen after 48 h. The solvent was removed in vacuo and the crude product then purified with silica chromatography using an CHCl$_3$/MeOH elution system, to yield 21a as a yellow oil (6.40 g, 28.3 mmol, 97%); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 4.33-4.14 (m, 2H), 3.54-3.38 (m, 4H), 2.99-2.79 (m, 4H), 2.70-2.55 (m, 4H), 2.55-2.40 (m, 2H); $^{13}$C NMR (75 MHz, CD$_3$OD) $\delta$C 161.31 (s, C=O), 48.64, 48.31, 45.79, 43.77 (s, CH$_2$N); MS (ESI+QTOFMS) calculated for C$_{10}$H$_{18}$N$_4$O$_2$Na ([M+Na]$^+$) m/e 249.14; measured m/e 249.14.

Compound 16. Compound 16 was prepared according to a previously reported procedure with some modifications$^3$. A stirred solution of 16a (6.4 g, 28 mmol), N-(2-bromoethyl) phthalimide$^3$ (10.7 g, 43 mmol), and Cs$_2$CO$_3$ (10.1 g, 1.1 eq.) in CH$_3$CN (185 mL) was heated at 60°C. The reaction was monitored by TLC using two systems: 1) CHCl$_3$/MeOH/MeNH$_2$ (33% MeNH$_2$ in EtOH), 85:14:1; 2) EtOAc/Hexane, 3:7, which indicated complete consumption of starting material after 6 days. The reaction mixture was filtered, the solvent removed in vacuo, and the residue purified by silica chromatography using an CHCl$_3$/MeOH elution system to yield compound 16 (2.71 g, 6.78 mmol, 24%); $^1$H NMR (600 MHz, CD$_3$OD) $\delta$H 7.82 (dd, $J = 5.4$ Hz, 3.0 Hz, 2H,
Some of the intermediate compounds (17c-d and 18b-d) exhibit duplicated or proton peaks in specific areas of the molecular structure, which are indicative of conformational isomers and/or tautomers exchanging on the NMR time scale.

**Compound 17b.** Following the general procedure, compound 16 (2.0 g, 5.01 mmol) and 15b (2.72 g, 5.01 mmol), yielded 22% over two steps (801 mg, 1.10 mmol); 1H NMR (600 MHz, CDCl3) δH 8.96 (q, J = 4.9 Hz, 1H, CH3-NH-CO), 8.77 (s, 1H, QH-2), 7.96 (dd, J = 13.2 Hz, 1.6 Hz, 1H, QH-5), 7.31-7.26 (m, 2H, linker Ar), 7.23 (d, JCF = 7.9 Hz, 1H, QH-8), 7.21-7.15 (m, 2H, linker Ar), 5.41-5.45 (bs, 2H, NH2), 4.39-3.95 (m, 3H, CH2N), 3.64-3.58 (m, 1H, CH2N), 3.58-3.49 (m, 4H, Ph-CH2-piperazine (2H), CH2N (2H)), 3.49-3.41 (m, 2H, cyclopropane CH (1H), CH2N (1H)), 3.41-3.31 (m, 1H, CH2N), 3.31-3.21 (m, 4H, piperezine), 3.02-2.85 (m, 7H, CH2-NH-CO (3H), CH2N (4H)), 2.85-2.75 (m, 3H, CH2N), 2.75-2.58 (m, 10H, cycler-CH2CH2-Ph (2H), piperezine (4H), CH2N (4H)), 2.58-2.50 (m, 2H, CH2N), 2.43-2.29 (m, 1H, CH2N), 1.38-1.24 (m, 2H, cyclopropane CH2), 1.15-1.05 (m, 2H, cyclopropane CH2); 13C NMR (150 MHz, CDCl3) δc 175.51 (s, cipro C=O), 165.71 (s, cipro C=O), 161.05 (s, oxaly C=O), 153.47 (d, JCF = 249.0 Hz, cipro), 146.60 (s, C-H cipro), 145.16-144.87 (m, cipro), 139.40 (s, linker Ar), 138.56 (s, cipro), 135.42 (s, linker Ar), 129.75-129.38 (m, C-H linker Ar), 128.91 (s, C-H linker Ar), 128.85 (s, C-H linker Ar), 121.87-121.67 (m, cipro), 112.51 (d, JCF = 23.3 Hz, C-H cipro), 111.39 (s, cipro), 104.86 (s, C-H cipro), 62.69, 62.62 (s, Ph-CH2-piperazine), 56.59 (bs, CH2N), 55.14 (bs, CH2N), 54.63 (bs, CH2N), 54.17 (bs, CH2N), 53.43 (bs, CH2N), 52.84, 52.79 (s, piperezine), 51.15 (s, CH2N), 50.06 (s, piperezine), 48.65 (s, CH2N), 48.48 (s, CH2N), 46.54 (s, CH2N), 45.22 (s, CH2N), 38.07 (s, CH2-NH2), 34.77 (s, cyclopropane CH), 30.89 (s, cycler-CH2CH2-Ph), 25.90 (s, CH3-NHCO), 8.26 (s, cyclopropane CH2). MS (ESI-QTOFMS) calculated for C39H35N8O4Na ([M+Na]+) m/e 730.41; measured m/e 730.42.

**Compound 17c.** Following the general procedure, compound 16 (1.10 g, 2.76 mmol) and 15c (3.06 g, 5.51 mmol), yielded 44% over two steps (908 mg, 1.22 mmol); 1H NMR (600 MHz, CDCl3) δH 8.96 (q, J = 4.9 Hz, 1H, CH3-NH-CO), 8.77 (s, 1H, QH-2), 8.00-7.91 (m, 1H, QH-5), 7.32-7.27 (m, 1H, QH-8), 7.24 (d, J = 8.2 Hz, 2H, linker Ar), 7.16 (d, J = 8.2 Hz, 1.3H, linker Ar), 7.13 (d, J = 8.2 Hz, 0.7H, linker Ar), 4.44-4.00 (m, 2H, CH2N), 3.86-3.58 (m, 3H, CH2N), 3.54 (s, 2H, Ph-CH2-piperazine), 3.50-3.40 (m, 2H, cyclopropane CH (1H), CH2N (1H)), 3.32-3.21 (m, 4H, piperezine), 3.11-2.71 (m, 10H, CH2-NH-CO (3H), CH2N (7H)), 2.71-2.36 (m, 14H, piperezine (4H), cycler-(CH2)3CH2-Ph (2H), cycler-CH2-CH2-Ph (2H), CH2N (6H)), 2.36-2.23 (m, 2H, linker Ar), 1.88-1.75 (m, 2H, linker Ar), 0.84-0.76 (m, 6H, linker Ar).
Compound 17d. Following the general procedure, compound 16 (1.9 g, 4.75 mmol) and 15d (5.4 g, 9.5 mmol), yielded 22% over two steps (0.797 g, 1.05 mmol): 1H NMR (600 MHz, CDCl3) δH 9.87 (q, J = 4.6 Hz, 0.3H, CH3-NH-CO), 8.80 (s, 1H, QH-2), 7.99 (d, JCF = 13.2 Hz, 1H, QH-5), 7.30 (d, JCF = 7.2 Hz, 1H, QH-8), 7.26-7.23 (m, 2H, linker Ar), 7.16-7.10 (m, 2H, linker Ar), 4.33-3.62 (m, 5H, cyclen), 3.60-3.56 (m, 1H, cyclen), 3.55 (s, 2H, Ph-CH2-piperazine), 3.48-3.36 (m, 3H, cyclopropane CH (1H), cyclen (2H)), 3.31-3.25 (m, 4H, piperazine), 2.98 (q, J = 4.6 Hz, 1H, CH3-NH-CO), 2.92-2.87 (m, 1H, cyclen), 2.87-2.81 (m, 2H, CH2-NH2), 2.81-2.68 (m, 3H, cyclen), 2.68-2.57 (m, 8H, piperazine (4H), cyclen-(CH2)2CH2(Ph) (2H), cyclen-CH2(2H)3-Ph (1H), CH2-CH2-NH2 (1H)), 2.57-2.32 (m, 6H, cyclen-CH2(2H)3-Ph (1H), CH2-CH2-NH2 (1H)), cyclen (4H)), 1.75-1.36 (m, 4H, cyclen-CH2CH2(2H)3-Ph (2H), cyclen-(CH2)2CH2CH2(Ph) (2H)), 1.33-1.27 (m, 2H, cyclopropane CH2), 1.16-1.08 (m, 2H, cyclopropane CH2); 13C NMR (150 MHz, CDCl3) δC 175.59 (s, cyclopropane C=O), 165.71 (d, JCF = 14.9 Hz, cyclopropane C=O), 160.14 (s, oxalyl C=O), 158.97 (s, oxalyl C=O), 153.56 (d, JCF = 249.4 Hz, cyclopropane), 146.66 (s, C-H cyclopropane), 145.13 (s, cipro), 141.48, 141.03 (s, linker Ar), 138.61 (s, cipro), 135.45, 135.22 (s, linker Ar), 129.41 (s, C-H linker Ar), 128.46 (s, C-H linker Ar), 121.88 (s, cipro), 112.64 (d, JCF = 22.8 Hz, C-H cyclopropane), 111.49 (s, cipro), 104.83 (s, C-H cyclopropane), 62.81 (s, Ph-CH2-piperazine), 56.27 (s, CH2N), 55.79 (s, CH2N), 53.61 (s, CH2N), 52.88 (s, piperazine), 52.07 (s, CH2N), 50.14 (s, piperazine), 49.46 (s, CH2N), 48.98 (s, CH2N), 48.77 (s, CH2N), 46.86 (s, CH2N), 46.06 (s, CH2N), 39.03 (s, CH2-NH2), 35.62, 35.19 (s, cyclen-(CH2)3CH2-Ph), 34.77 (s, cyclopropane CH), 29.51 (s, non-terminal linker CH2), 28.82 (s, non-terminal linker CH2), 25.90 (d, JCF = 18.6 Hz, CH3-NHCO), 8.31 (s, cyclopropane CH2). MS (ESI+QTOFMS) calculated for C40H55FN9O4 ([M+H]+) m/e 758.45; measured m/e 758.45.

Compound 18a. Following the general procedure, compound 17a (631 mg, 0.88mmol) yielded 82% (692 mg, 0.72 mmol): 1H NMR (600 MHz, CDCl3) δH 11.46 (s, 1H, Boc-NH2-guanidine), 9.83 (q, J = 4.9 Hz, 1H, CH3-NH-CO), 8.75 (s, 1H, QH-2), 8.28 (s, 1H, QH-8), 7.94 (d, JCF = 13.3 Hz, 1H, QH-5), 7.30-7.23 (m, 3H, linker Ar (2H), QH-8 (1H)), 7.23-7.16 (m, 2H, linker Ar), 4.36-4.03 (m, 4H, cyclen), 3.71 (d, J = 13.4 Hz, 1H, cyclen-CH2-Ph (1H)), 3.58-3.48 (m, 3H, Ph-CH2-piperazine (2H), cyclen (1H)), 3.48-3.36 (m, 4H, cyclen-CH2-Ph (1H), CH2-guanidine (1H), cyclopropane CH (1H), cyclen (1H)), 3.36-3.28 (m, 1H, CH2-guanidine (1H), 3.28-3.19 (m, 4H, piperazine), 2.93 (d, J = 4.9 Hz, 3H, CH2-NH-CO), 2.91-2.85 (m, 1H, cyclen), 2.09-2.00 (m, 1H, phenyl) 1.88-1.70 (m, 1H, phenyl) 1.58-1.45 (m, 1H, phenyl) 1.36-1.26 (m, 1H, phenyl), 1.19-1.17 (m, 1H, phenyl), 1.06-1.03 (m, 1H, phenyl), 0.99-0.86 (m, 2H, methylene, 0.85-0.66 (m, 2H, methylene, 0.85-0.66 (m, 2H, methylene), 0.64-0.58 (m, 2H, methylene), 0.58-0.46 (m, 2H, methylene, 0.46-0.41 (m, 2H, methylene), 0.41-0.36 (m, 2H, methylene), 0.36-0.32 (m, 2H, methylene).
2.85-2.76 (m, 2H, cyclen), 2.66-2.59 (m, 4H, piperazine), 2.59-2.51 (m, 3H, CH of cyclen-CH$_2$-CH$_2$-guanidine (1H), cyclen (2H)), 2.51-2.43 (m, 3H, CH of cyclen-CH$_2$-CH$_2$-guanidine (1H), cyclen (2H)), 2.40-2.28 (m, 2H, cyclen), 2.26-2.18 (m, 1H, cyclen), 1.45 (s, 9H, Boc), 1.41 (s, 9H, Boc), 1.30-1.24 (m, 2H, cyclopropane CH$_2$), 1.13-1.05 (m, 2H, cyclopropane CH$_2$); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$C 175.41 (d, $J_{CF}$ = 2.2 Hz, cipro C=O), 165.58 (s, cipro C=O), 163.44 (s, guanidine C), 159.82 (s, oxalyl C=O), 159.66 (s, oxalyl C=O), 156.06 (s, Boc C=O), 153.41 (d, $J_{CF}$ = 249.9 Hz, cipro Ar), 153.26 (s, Boc C=O), 146.49 (s, cipro C-H Ar), 144.94 (d, $J_{CF}$ = 10.8 Hz, cipro Ar), 138.47 (s, cipro Ar), 137.26 (s, linker Ar), 136.85 (s, linker Ar), 129.71 (s, C-H linker Ar), 129.12 (s, C-H linker Ar), 121.71 (d, $J_{CF}$ = 7.2 Hz, cipro Ar), 112.46 (d, $J_{CF}$ = 23.1 Hz, C-H cipro Ar), 111.36 (s, cipro Ar), 104.69 (d, $J_{CF}$ = 2.6 Hz, C-H cipro Ar), 83.28 (s, Boc quaternary C), 79.26 (s, Boc quaternary C), 62.56 (s, Ph-CH$_2$-piperazine), 58.65 (s, cyclen-CH$_2$-Ph), 56.65 (s, CH$_2$N), 56.26 (s, CH$_2$N), 52.78 (s, piperazine), 52.55 (s, CH$_2$N), 52.28 (s, CH$_2$N), 49.98 (d, $J_{CF}$ = 3.7 Hz, piperazine), 49.74 (s, CH$_2$N), 49.11 (s, CH$_2$N), 47.44-47.03 (m, CH$_2$N), 38.57 (s, CH$_2$-guanidine), 34.63 (s, cyclopropane CH), 28.26 (s, Boc CH$_3$), 28.08 (s, Boc CH$_3$), 25.80 (s, CH$_3$-NHCOCO), 8.17 (s, cyclopropane CH$_2$). MS (ESI+ QTOFMS) calculated for C$_{60}$H$_{69}$FN$_{11}$O$_8$ ([M+H]$^+$) m/e 958.53; measured m/e 958.57.

**Compound 18b.** Following the general procedure, compound 17b (801 mg, 1.10 mmol) yielded 52% (570 mg, 0.573 mmol); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$H 11.57-11.39 (m, 1H, Boc-NH- guanidine), 9.87 (q, $J$ = 4.8 Hz, 1H, CH$_3$-NH-CO), 8.80 (s, 1H, QH-2), 8.39 (t, $J$ = 5.4 Hz, 0.3 H, guanidine NH), 8.36-8.27 (m, 0.5 H, guanidine NH), 7.99 (d, $J_{CF}$ = 13.3 Hz, 1H, QH-5), 7.32-7.27 (m, 2H, QH-8 (1H), linker Ar (1H)), 7.25 (d, $J$ = 8.1 Hz, 1H, linker Ar), 7.23-7.15 (m, 1H, linker Ar), 7.13 (d, $J$ = 8.1 Hz, 1H, linker Ar), 4.45-3.77 (m, 4H, cyclen), 3.62-3.21 (m, 14H, Ph-CH$_2$-piperazine (2H), CH$_2$-guanidine (2H), cyclopropane CH (1H), CH$_2$N (5H), piperazine (4H)), 3.02-2.89 (m, 6H, CH$_2$-NH-CO (3H), CH$_2$N (3H)), 2.89-2.76 (m, 2H, CH$_2$N), 2.76-2.69 (m, 2H, cyclen-CH$_2$CH$_2$-Ph), 2.69-2.24 (m, 10H, piperazine (4H), cyclen-CH$_2$CH$_2$-guanidine (2H), CH$_2$N (4H)), 1.49-1.45 (m, 14.6 H, 2 x Boc (11.2 H), 1 x Boc (3.4 H)), 1.42 (s, 3.4 H, 1 x Boc), 1.34-1.28 (m, 2H, cyclopropane CH$_2$), 1.15-1.09 (m, 2H, cyclopropane CH$_2$); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$C 175.57 (s, cipro C=O), 165.71 (s, cipro C=O), 163.58, 163.55 (s, guanidine C), 159.90 (s, oxalyl C=O), 159.69 (s, oxalyl C=O), 156.19, 156.10 (s, Boc C=O), 155.52 (d, $J_{CF}$ = 248.8 Hz, cipro), 153.33 (s, Boc C=O), 146.62 (s, C-H cipro), 145.19-144.92 (m, cipro), 139.34 (s, linker Ar), 138.59 (s, cipro), 135.52 (s, linker Ar), 129.75-129.40 (m, C-H linker Ar), 128.89 (s, C-H linker Ar), 128.81 (s, C-H linker Ar), 121.95-121.77 (m, cipro), 112.63 (d, $J_{CF}$ = 23.0 Hz, C-H cipro), 111.49 (d, $J_{CF}$ = 2.8 Hz, cipro), 104.78 (d, $J_{CF}$ = 7.8 Hz, C-H cipro), 83.27 (s, Boc quaternary C), 79.42 (s, Boc quaternary C), 62.70 (s, Ph-CH$_2$-piperazine), 57.83 (s, CH$_2$N), 57.01 (s, CH$_2$N), 55.74 (s, CH$_2$N), 55.50 (s, CH$_2$N), 52.88 (s, piperazine), 52.83 (s, piperazine), 52.73 (s, CH$_2$N), 51.50 (s, CH$_2$N), 50.11 (s, piperazine), 49.83 (s, CH$_2$N), 49.38 (s, CH$_2$N), 47.68 (s, CH$_2$N), 46.93 (s, CH$_2$N), 38.73 (s, CH$_2$-guanidine), 34.84-34.67 (m, cyclopropane CH), 31.75 (s, cyclen-CH$_2$CH$_2$-Ph), 28.38 (s, Boc CH$_3$), 28.20 (s, Boc CH$_3$), 28.11 (s, Boc CH$_3$), 25.91 (s, CH$_3$-NHCOCO), 8.27 (s, cyclopropane CH$_2$). MS (ESI+QTOFMS) calculated for C$_{51}$H$_{73}$FN$_{11}$O$_8$ ([M+Na]$^+$) m/e 994.54; measured m/e 994.62.

**Compound 18c.** Following the general procedure, compound 17c (687 mg, 0.924 mmol) yielded 59% (540 mg, 0.55 mmol); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$H 11.57-11.35 (m, 1H, Boc-NH- guanidine), 9.85 (q, $J$ = 4.8 Hz, 1H, CH$_3$-NH-CO), 8.77 (s, 1H, QH-
2), 8.36 (t, J = 5.2 Hz, 1H, guanidine NH), 7.96 (d, J_CF = 13.6 Hz, 1H, QH-5), 7.30-7.27 (m, 1H, QH-8), 7.26-7.21 (m, 2H, linker Ar), 7.12 (d, J = 7.9 Hz, 2H, linker Ar), 4.50-3.92 (m, 4H, cyclen), 3.58-3.37 (m, 7H, Ph-CH_2-piperazine (2H), CH_2-guanidine (1H), cyclopropane CH (1H), cyclen (3H)), 3.37-3.29 (m, 1H, CH_2-guanidine), 3.29-3.23 (m, 4H, piperazine), 2.95 (d, J = 4.8 Hz, 3H, CH_3-NH-CO), 2.95-2.85 (m, 1H, cyclen), 2.84-2.74 (m, 2H, cyclen), 2.74-2.67 (m, 1H, cyclen), 2.67-2.62 (m, 4H, piperazine), 2.62-2.34 (m, 9H, cyclen-CH_2-CH_2-guanidine (2H), cyclen-(CH_2)_2CH_2-Ph (2H), cyclen-CH_2(CH_2)_2-Ph (2H), cyclen (3H)), 2.31-2.22 (m, 1H, cyclen), 2.22-2.13 (m, 1H, cyclen), 2.08-1.86 (m, 0.3 H, cyclen-CH_2CH_2CH_2-Ph), 1.82-1.63 (m, 1.4H, cyclen-CH_2CH_2CH_2-Ph), 1.49-1.42 (m, 18H, Boc × 2), 1.32-1.25 (m, 2H, cyclopropane CH_2), 1.14-1.08 (m, 2H, cyclopropane CH_2); ^13C NMR (150 MHz, CDCl_3) δ 175.45 (s, cipro C=O), 165.60 (s, cipro C=O), 163.46 (s, guanidine C), 159.73 (s, oxalyl C=O), 159.57 (s, oxalyl C=O), 156.09, 155.98 (s, Boc C=O), 153.41 (d, J_CF = 249.1 Hz, cipro), 153.27, 153.21 (s, Boc C=O), 146.51 (s, C-H cipro), 144.99 (d, J_CF = 10.9 Hz, cipro), 140.98, 140.07 (s, linker Ar), 138.46 (s, cipro), 135.47, 135.23 (s, linker Ar), 129.40, 129.33, 128.31, 128.27 (s, C-H linker Ar), 121.70 (d, J_CF = 7.0 Hz, cipro), 112.48 (d, J_CF = 22.7 Hz, C-H cipro), 111.34 (s, cipro), 104.68 (s, C-H cipro), 83.19 (s, Boc quaternary C), 79.32 (s, Boc quaternary C), 62.65 (s, Ph-CH_2-piperazine), 56.71 (s, CH_2N), 55.93 (s, CH_3N), 53.31 (s, CH_2N), 53.21 (s, CH_2N), 52.74 (s, piperazine), 52.48 (s, CH_2N), 51.86 (s, CH_2N), 49.99 (d, J_CF = 3.7 Hz, piperazine), 49.78 (s, CH_2N), 49.69 (s, CH_2N), 47.59 (s, CH_2N), 47.31 (s, CH_2N), 38.70 (s, CH_2-guanidine), 34.63 (s, cyclopropane CH), 33.51 (s, cyclen-(CH_2)_2CH_2-Ph), 28.29 (s, Boc CH_3), 28.08 (s, Boc CH_3), 27.59 (s, cyclen-CH_2CH_2CH_2-Ph), 25.83 (s, CH_3-NHCO), 8.18 (s, cyclopropane CH_2). MS (ESI+QTOFMS) calculated for C_{51}H_{75}F_{11}O_{8} ([M+H]^+) m/e 986.56; measured m/e 986.57.

**Compound 18d.** Following the general procedure, compound 17d (0.757 g, 0.99 mmol) yielded 78% (0.776 g, 0.77 mmol); ^1H NMR (600 MHz, CDCl_3) δ 11.50 (s, 1H, Boc-NH-guanidine), 9.86 (q, J = 4.8 Hz, 1H, CH_3-NH-CO), 8.78 (s, 1H, QH-2), 8.36 (t, J = 5.0 Hz, 1H, guanidine NH), 7.97 (d, J_CF = 12.9 Hz, 1H, QH-5), 7.29 (d, J_CF = 7.0 Hz, 1H, QH-8), 7.23 (d, J = 7.8 Hz, 2H, linker Ar), 7.11 (d, J = 7.8 Hz, 2H, linker Ar), 4.41-3.95 (m, 4H, cyclen), 3.58-3.49 (m, 5H, Ph-CH_2-piperazine (2H), CH_2-guanidine (1H), cyclen (2H)), 3.48-3.40 (m, 2H, cyclen (1H), cyclopropane CH (1H)), 3.40-3.30 (m, 1H, CH_2-guanidine), 3.30-3.20 (m, 5H, piperazine (4H), cyclen (1H)), 2.96 (d, J = 4.8 Hz, 3H, CH_3-NH-CO), 2.95-2.86 (m, 1H, cyclen), 2.85-2.71 (m, 2H, cyclen), 2.70-2.55 (m, 10H, piperazine (4H), cyclen-CH_2-CH_2-guanidine (2H), cyclen-(CH_2)_2CH_2-Ph (2H), cyclen (2H)), 2.55-2.35 (m, 5H, cyclen-(CH_2)_2CH_2-Ph (2H), cyclen (3H)), 1.61-1.50 (m, 2H, cyclen-(CH_2)_2CH_2CH_2-Ph), 1.48-1.45 (m, 20H, cyclen-(CH_2)_2CH_2CH_2-Ph), 1.13-1.26 (m, 2H, cyclopropane CH_2), 1.14-1.09 (m, 2H, cyclopropane CH_2); ^13C NMR (150 MHz, CDCl_3) δ 175.52 (s, cipro C=O), 165.69 (s, cipro C=O), 163.53, 163.49 (s, guanidine C), 159.78 (s, oxalyl C=O), 159.65 (s, oxalyl C=O), 156.33, 156.14 (s, Boc C=O), 153.48 (d, J_CF = 249.1 Hz, cipro), 153.38, 153.29 (s, Boc C=O), 146.58 (s, C-H cipro), 145.19-144.96 (m, cipro), 141.41 (s, linker Ar), 138.53 (s, cipro), 135.11 (s, linker Ar), 129.33 (s, C-H linker Ar), 128.40 (s, C-H linker Ar), 121.78 (d, J_CF = 5.0 Hz, cipro), 112.53 (d, J_CF = 23.1 Hz, C-H cipro), 111.40 (s, cipro), 104.76 (s, C-H cipro), 83.75-83.34 (m, Boc quaternary C), 83.27, 79.69, 79.39 (s, Boc quaternary C), 62.76 (s, Ph-CH_2-piperazine), 56.99 (s, CH_2N), 56.03 (s, CH_2N), 53.73 (s, CH_2N), 53.30 (s, CH_2N), 52.81 (s, piperazine), 52.58 (s, CH_2N), 51.86 (s, CH_2N), 50.04 (s, piperazine), 49.89 (s, CH_2N), 49.70 (s, CH_2N), 47.65 (s, CH_2N), 47.31 (s, CH_2N), 38.80 (s, CH_2-guanidine), 35.52 (s, cyclen-(CH_2)_2CH_2-Ph),
34.72 (s, cyclopropane CH), 29.75 (s, non-terminal linker CH₂), 29.45 (s, non-terminal linker CH₂), 28.35, 28.34, 28.14, 28.12 (s, Boc CH₃), 25.89 (s, CH₃-NHCO), 8.25 (s, cyclopropane CH₂). MS (ESI+QTOFMS) calculated for C₅₂H₇₅FN₁₁O₈ ([M+H]⁺) m/z 1000.59; measured m/z 1000.58.

**Compound 19a.** The compound was synthesized according to a previously reported (general) procedure for Sonogashira coupling of propargyl alcohol to benzyl halide derivatives. Yield 51% (3.78 g, 23.3 mmol); ¹H NMR (400 MHz, CDCl₃) δH 7.39 (d, J = 8.1 Hz, 2H, Ar), 7.30 (d, J = 8.1 Hz, 2H, Ar), 4.59 (s, 2H, Ph-CH₂OH), 3.74 (t, J = 6.8 Hz, 2H, CH₂OH), 2.63 (t, J = 6.8 Hz, 2H, HOCH₂CH₂H₂); ¹³C NMR (100 MHz, CDCl₃) δC 142.36 (Ar), 132.51 (Ar), 127.76 (Ar), 123.94 (Ar), 87.62 (alkyne carbon), 82.30 (alkyne carbon), 64.73 (CH₂OH), 61.68 (CH₂OH), 24.16 (HOCH₂CH₂H₂).

**Compound 19b.** The compound was prepared from 19a using the same conditions as previously published by us. Yield 91% (13 g, 32.1 mmol); ¹H NMR (300 MHz, CDCl₃) δH 7.74 (d, J = 8.3 Hz, 2H, Ar), 7.21 (d, J = 8.3 Hz, 2H, Ar), 4.69 (s, 2H, Ph-CH₂OTBDMS), 3.80 (t, J = 7.1 Hz, 2H, CH₂OTBDMS), 2.60 (t, J = 7.1 Hz, 2H, TBDMSOCH₂CH₂H₂), 0.91 (s, 9H, Si-C(CH₃)₃), 0.89 (s, 9H, Si-C(CH₃)₃), 0.08 (s, 6H, 2 × Si-CH₃), 0.07 (s, 6H, 2 × Si-CH₃).

**Compound 19c.** The compound was prepared from 19b using the same conditions as previously published by us. Yield 94% (6.67 g, 16.3 mmol); ¹H NMR (300 MHz, CDCl₃) δH 7.27-7.21 (m, 2H, Ar), 7.19-7.11 (m, 2H, Ar), 4.73 (s, 2H, Ph-CH₂-OTBDMS), 3.64 (t, J = 6.2 Hz, Ph-(CH₂)₂-CH₂-OTBDMS), 2.63 (t, J = 7.5 Hz, 2H, Ph-CH₂-(CH₂)₂-OTBDMS), 1.73-1.62 (m, 2H, non-terminal CH₂), 1.59-1.48 (m, 2H, non-terminal CH₂), 0.96 (s, 9H, Si-C(CH₃)₃), 0.91 (s, 9H, Si-C(CH₃)₃), 0.11 (s, 6H, 2 × Si-CH₃), 0.06 (s, 6H, 2 × Si-CH₃).

**Compound 19.** The compound was prepared from 19c using the same conditions as previously published by us. Yield 96% (4.8 g, 15.7 mmol); ¹H NMR (500 MHz, CDCl₃) δH 7.32 (d, J = 7.9 Hz, 2H, Ar), 7.17 (d, J = 7.9 Hz, 2H, Ar), 4.50 (s, 2H, Ph-CH₂-Br), 3.42 (t, J = 6.8 Hz, 2H, Ph-(CH₂)₂-CH₂-Br), 2.64 (t, J = 7.5 Hz, 2H, Ph-CH₂-(CH₂)₂-Br), 1.93-1.85 (m, 2H, non-terminal CH₂), 1.81-1.74 (m, 2H, non-terminal CH₂); ¹³C NMR (126 MHz, CDCl₃) δC 142.30 (Ar), 135.45 (Ar), 129.18 (C-H Ar), 128.88 (C-H Ar), 34.73 (Ph-CH₂-(CH₂)₂-Br), 33.73 (CH₂-Br), 33.66 (CH₂-Br), 32.23 (non-terminal CH₂), 29.73 (non-terminal CH₂).
III. $^1$H and $^{13}$C NMR spectra of compounds 7-14 (pages S19-S26)
IV. Synthetic and/or analytical data for Cu(II) and Co(III) complexes of 7-14 (pages S27-S30)

Analytical data for Cu(II)-complexes (7-14)

UV-vis and HRMS:

7-[Cu(II)(H₂O)](ClO₄)₂: UV-vis (H₂O): λmax = 633 (pH 6), 642 (pH 8), 669 (pH 10); HRMS (ESI QTOFMS) calculated for C₃₆H₅₀CuFN₁₀O₃ ([M-H]+) 752.3342 m/e; measured 752.3346 m/e.

8-[Cu(II)(H₂O)](ClO₄)₂: UV-vis (H₂O): λmax = 623 (pH 6), 648 (pH 8), 666 (pH 10); HRMS (ESI QTOFMS) calculated for C₃₇H₅₂CuFN₁₀O₃ ([M-H]+) 766.3498 m/e; measured 766.3513 m/e.

9-[Cu(II)(H₂O)](ClO₄)₂: UV-vis (H₂O): λmax = 618 (pH 6), 630 (pH 8), 660 (pH 10); HRMS (ESI QTOFMS) calculated for C₃₈H₅₄CuFN₁₀O₃ ([M-H]+) 780.3657 m/e; measured 780.3657 m/e.

10-[Cu(II)(H₂O)](ClO₄)₂: UV-vis (H₂O): λmax = 617 (pH 6), 628 (pH 8), 661 (pH 10); HRMS (ESI QTOFMS) calculated for C₃₉H₅₆CuFN₁₀O₃ ([M-H]+) 794.3816 m/e; measured 794.3816 m/e.

11-[Cu(II)(H₂O)](ClO₄)₂: UV-vis (H₂O): λmax = 625 (pH 6), 630 (pH 8), 626 (pH 10); HRMS (ESI QTOFMS) calculated for C₃₅H₄₈CuFN₈O₃ ([M-H]+) 710.3124 m/e; measured 710.3124 m/e.

12-[Cu(II)(H₂O)](ClO₄)₂: UV-vis (H₂O): λmax = 610 (pH 6), 610 (pH 8), 610 (pH 10); HRMS (ESI QTOFMS) calculated for C₃₆H₅₀CuFN₈O₃ ([M-H]+) 724.3280 m/e; measured 724.3289 m/e.

13-[Cu(II)(H₂O)](ClO₄)₂: UV-vis (H₂O): λmax = 608 (pH 6), 608 (pH 8), 608 (pH 10); HRMS (ESI QTOFMS) calculated for C₃₇H₅₂CuFN₈O₃ ([M-H]+) 738.3428 m/e; measured 738.3428 m/e.

14-[Cu(II)(H₂O)](ClO₄)₂: UV-vis (H₂O): λmax = 620 (pH 6), 619 (pH 8), 621 (pH 10); HRMS (ESI QTOFMS) calculated for C₃₈H₅₄CuFN₈O₃ ([M-H]+) 752.3599 m/e; measured 752.3599 m/e.

EPR Spectra:
EPR spectra were recorded for Cu(II) complexes of the ligands 4, 6, 9, and 11. The spectra shown below are water solutions at 350K (giso = 2.131), and are annotated with the recorded hyperfine coupling constant values (Aiso⁹⁵⁶⁵Cu)) and the pH of the water solution.

9-Cu(II) 6-Cu(II) 11-Cu(II) 4-Cu(II)
**Potentiometric titration:**
Titrations were performed in the pH range 12 to 4 for Cu(II) complexes of all the new compounds 7-14, and for all the parents compounds that we had previously synthesized (i.e.; compounds 4-Cu(II), 5-Cu(II) and 6-Cu(II)). One representative plot is shown below for the guanidine series (i.e.; 9-Cu(II) vs. 6-Cu(II)) and one plot is shown for the amine series (i.e.; 11-Cu(II) vs. 4-Cu(II)).
**Synthetic and analytical data for Co(III)-complexes (7-14)**

**Introductory note:** The Co(III) chloride salts are not necessarily stable under the ionizing conditions of mass spectrometry, and the major metal ion detected can be Co(II) ion for some types of complexes but Co(III) for others. Consequently, some of the cobalt complexes are reported as [M-H]^2+ (i.e., 7-10-[Co(III)(H2O)]Cl2 and 12-[Co(III)(H2O)(NO3)]2 and some as [M-H]^+ (i.e., 7-10-[Co(III)(OH)(H2O)]Cl2 and 11, 13 and 14-[Co(III)(H2O)]Cl2). It is important to note however that UV-vis spectroscopy confirms that all prepared complexes are in-fact Co(III), either by comparison with the literature (for 7-10-[Co(III)(OH)(H2O)]Cl2; see reference 38 in main paper) or by comparison to the UV-vis spectra of the prepared Co(II) complexes (for 11, 13 and 14-[Co(III)(H2O)]Cl2; see Fig. S5).

7-[Co(III)(OH)(H2O)]Cl2: Following the general procedure, compound 7 (0.049 g, 0.054 mmol) and Na3[Co(CO3)3]·3H2O (0.020 g, 0.054 mmol) were heated for 16 h, and yielded the corresponding Co(III)(OH)(H2O) complex as a dark, pink powder (43 mg, 89%). UV-vis (H2O): λmax = 536 (pH 6.0); MS (ESI+ QTOFMS) calculated for C36H50CoFNO10O3 ([M-H]^+) 748.34 m/e; measured 748.37 m/e.

8-[Co(III)(OH)(H2O)]Cl2: Following the general procedure, compound 8 (0.049 g, 0.053 mmol) and Na3[Co(CO3)3]·3H2O (0.019 g, 0.053 mmol) were heated for 16 h, and yielded the corresponding Co(III)(OH)(H2O) complex as a dark, pink powder (42 mg, 87%). UV-vis (H2O): λmax = 528 (pH 7.9); MS (ESI+ QTOFMS) calculated for C37H52CoFNO10O3 ([M-H]^+) 762.35 m/e; measured 762.39 m/e.

9-[Co(III)(OH)(H2O)]Cl2: Following the general procedure, compound 9 (0.052 g, 0.057 mmol) and Na3[Co(CO3)3]·3H2O (0.021 g, 0.057 mmol) were heated for 16 h, and yielded the corresponding Co(III)(OH)(H2O) complex as a dark, pink powder (33 mg, 65%). UV-vis (H2O): λmax = 528 (pH 7.6); MS (ESI+ QTOFMS) calculated for C38H54CoFNO10O3 ([M-H]^+) 776.37 m/e; measured 776.35 m/e.

10-[Co(III)(OH)(H2O)]Cl2: Following the general procedure, compound 9 (0.052 g, 0.055 mmol) and Na3[Co(CO3)3]·3H2O (0.020 g, 0.055 mmol) were heated for 16 h, and yielded the corresponding Co(III)(OH)(H2O) complex as a dark, pink powder (52 mg, 100%). UV-vis (H2O): λmax = 530 (pH 7.0); MS (ESI+ QTOFMS) calculated for C39H56CoFNO10O3 ([M-H]^+) 790.38 m/e; measured 790.45 m/e.

7-[Co(III)(H2O)]Cl2: Following the general procedure, the aqua-hydroxo complex was activated with base treatment as shown by the immediate colour change from dark pink to bright violet; UV-vis (H2O): λmax = 556 (pH 6), 560 (pH 8), 560 (pH 10); HRMS (ESI+ QTOFMS) calculated for C36H50CoFNO10O3 ([M-H]^2+) 374.1686 m/e; measured 374.1694 m/e.

8-[Co(III)(H2O)]Cl2: Following the general procedure, the aqua-hydroxo complex was activated with base treatment as shown by the immediate colour change from dark pink to bright violet; UV-vis (H2O): λmax = 540 (pH 6), 538 (pH 8), 536 (pH 10); HRMS (ESI+ QTOFMS) calculated for C37H52CoFNO10O3 ([M-H]^2+) 381.1764 m/e; measured 381.1769 m/e.
9-[Co(III)(H₂O)]Cl₂: Following the general procedure, the aqua-hydroxocomplex was activated with base treatment as shown by the immediate colour change from dark pink to bright violet; UV-vis (H₂O): $\lambda_{\text{max}} = 542$ (pH 6), 547 (pH 8), 548 (pH 10); HRMS (ESI+ QTOFMS) calculated for C₃₈H₄CoFN₁₀O₃ $([M-H]^{2+})$ 388.1843 m/e; measured 388.1870 m/e.

10-[Co(III)(H₂O)]Cl₂: Following the general procedure, the aqua-hydroxocomplex was activated with base treatment as shown by the immediate colour change from dark pink to bright violet; UV-vis (H₂O): $\lambda_{\text{max}} = 533$ (pH 6), 535 (pH 8), 537 (pH 10); HRMS (ESI+ QTOFMS) calculated for C₃₉H₅₆CoFN₁₀O₃ $([M-H]^{2+})$ 395.1921 m/e; measured 395.1927 m/e.

11-[Co(III)(H₂O)]Cl₂: Following the general procedure, compound 11 (0.050 g, 0.058 mmol) and Na₃[Co(CO₃)₃]-3H₂O (0.021 g, 0.058 mmol) were heated for 16 h, and yielded the corresponding Co(III)(H₂O) complex as a red powder (39 mg, 78%). UV-vis (H₂O): $\lambda_{\text{max}} = 501$ (pH 6), 499 (pH 8), 498 (pH 10); HRMS (MALDI) calculated for C₃₅H₄₈CoFN₈O₃ $([M-H]^{2+})$ 706.316 m/e; measured 706.316 m/e.

12-[Co(III)(H₂O)](NO₃)₂: UV-vis (H₂O): $\lambda_{\text{max}} = 478$ (pH 6), 478 (pH 8), 478 (pH 10); HRMS (ESI+ QTOFMS) calculated for C₃₆H₅₀CoFN₈O₃ $([M-H]^{2+})$ 360.1655 m/e; measured 360.1654 m/e.

13-[Co(III)(H₂O)]Cl₂: Following the general procedure, compound 13 (0.028 g, 0.032 mmol) and Na₃[Co(CO₃)₃]-3H₂O (0.012 g, 0.032 mmol) were heated for 16 h, and yielded the corresponding Co(III)(H₂O) complex as a red powder (28 mg, 100%). UV-vis (H₂O): $\lambda_{\text{max}} = 498$ (pH 6), 494 (pH 8), 496 (pH 10); HRMS (MALDI) calculated for C₃₇H₅₂CoFN₈O₃ $([M-H]^{2+})$ 734.347 m/e; measured 734.347 m/e.

14-[Co(III)(H₂O)]Cl₂: Following the general procedure, compound 14 (0.051 g, 0.057 mmol) and Na₃[Co(CO₃)₃]-3H₂O (0.021 g, 0.057 mmol) were heated for 16 h, and yielded the corresponding Co(III)(H₂O) complex as a red powder (30 mg, 60%). UV-vis (H₂O): $\lambda_{\text{max}} = 496$ (pH 6), 499 (pH 8), 499 (pH 10); HRMS (MALDI) calculated for C₃₈H₅₄CoFN₈O₃ $([M-H]^{2+})$ 748.363 m/e; measured 748.362 m/e.
V. HRMS figures for Cu(II) and Co(III) complexes (pages S31-S34)
VI. HPLC analysis for the purity determination of compounds 7-14 (S35-S45)

| Compound | Retention time (min) | % Purity |
|----------|----------------------|----------|
| 7        | 17.19                | 95.4     |
| 8        | 17.47                | 97.4     |
| 9        | 18.19                | 96.7     |
| 10       | 18.58                | 95.2     |
| 11*      | Conformational isomer 1: 12.01 (Peak 1) | 95.2     |
|          | Conformational isomer 2: 14.68 (Peak 2) |          |
|          | Conformational isomer 3: 16.78 (Peak 4) |          |
| 12       | 17.23                | 95.0     |
| 13**     | 17.75                | 95.5     |
| 14       | 18.31                | 95.3     |

Method: Column Phenomenex® C18, flow 1.2 mL/min; buffer A, water 0.1% TFA; buffer B, MeCN 0.1% TFA; gradient 0-60% buffer B over 30 mins; run time, 20-30 min; injection, 200 μL of 0.1 mg/mL in water; UV detection at 271 nm.

*Mass spectrometry analyses of the HPLC-isolated peaks of compound 11 demonstrate that the three major peaks have identical mass (see below). Thus, these three peaks correspond to conformational isomers that are resolved under the conditions of the HPLC experiment.

**Two conformational isomers of 13 are partially resolved under the conditions of the HPLC experiment.
Compound 7

| Peak No. | Peak Name | Ret. Time min | Amount m.a. | Rel.Area % | Area mAU*min | Height mAU | Type | Width (50%) min | Asym. EP | Resol. EP | Plates EP |
|----------|-----------|---------------|-------------|------------|--------------|------------|------|-----------------|----------|-----------|-----------|
| 1        |           | 16.675        | n.a.        | 4.58       | 7.2623      | 74.77      | BMG* | 0.090           | 1.34     | 2.71      | 185292    |
| 2        |           | 17.191        | n.a.        | 95.42      | 151.3509    | 850.13     | BMG* | 0.135           | 2.61     | n.a.      | 89912     |
| Maximum  |           | 0.0000        | 95.42       | 151.3509   | 850.13      | 0.135      | 2.61 | 2.71            | 185292   | 89912     |
| Minimum  |           | 0.0000        | 4.58        | 7.2623     | 74.77       | 0.090      | 1.34 | 2.71            | 185292   | 89912     |
| Sum      |           | 0.0000        | 100.00      | 158.6232   | 934.90      |            |      |                 |          |           |

S36
| Peak No. | Peak Name | Ret.Time (min) | Amount (n.a.) | Rel.Area (%) | Area (mAU*min) | Height (mAU) | Type | Width (50%) (min) | Asym. (EP) | Resol. (EP) | Plates (EP) |
|---------|-----------|----------------|---------------|--------------|----------------|--------------|------|----------------|------------|------------|-------------|
| 1       |           | 17.241         | n.a.          | 2.66         | 67277         | 5220         | BM*  | 0.116          | n.a.       | 0.96       | 121771      |
| 2       |           | 17.476         | n.a.          | 97.44        | 2556375       | 119794       | MB*  | 0.173          | 2.55       | n.a.       | 56559       |
| Maximum |           | 0.0000         | 97.44         | 2556375      | 119794        |              |      | 0.173          | 2.55       | 0.96       | 121771      |
| Minimum |           | 0.0000         | 2.56          | 67277        | 5220          |              |      | 0.116          | 2.55       | 0.96       | 56559       |
| Sum     |           | 0.0000         | 100.00        | 2623652      | 125014        |              |      |                |            |            |             |
| Peak No. | Ret. Time min | Amount % | Rel. Area mAU | Area mAU*min | Height mAU | Type | Width (50%) min | Asym. EP | Resol. EP | Plates EP |
|---------|---------------|----------|---------------|--------------|------------|------|----------------|---------|-----------|-----------|
| 1       | 17.911        | n.a.     | 3.32          | 7.2400       | 77.97      | BM3* | 0.089          | 1.13    | 1.36      | 224040    |
| 2       | 18.193        | n.a.     | 96.68         | 210.7235     | 1057.25    | BM3* | 0.156          | 2.54    | n.a.      | 75242     |
| Maximum |               |          | 96.68         | 210.7235     | 1057.25    |      | 0.156          | 2.54    | 1.35      | 224040    |
| Minimum |               |          | 3.32          | 7.2400       | 77.97      |      | 0.089          | 1.13    | 1.36      | 75242     |
| Sum     | 0.0000        | 100.00   | 217.9635      | 1175.22      |            |      |                |         |           |           |
Compound 10

| Peak No. | Peak Name | Ret.Time (min) | Amount n.a. | Rel.Area % | Area mAU*min | Height mAU | Type | Width (50%) min | Asym. EP | Resol. EP | Plates EP |
|----------|-----------|----------------|-------------|------------|--------------|------------|------|----------------|----------|-----------|-----------|
| 1        |           | 14.293         | n.a.        | 0.36       | 0.8302       | 12.02      | BMB* | 0.065          | 1.32     | 17.15     | 257947    |
| 2        |           | 16.695         | n.a.        | 4.43       | 10.1964      | 62.52      | BMB* | 0.102          | 1.96     | 8.45      | 147174    |
| 3        |           | 18.590         | n.a.        | 93.21      | 2189.9003    | 959.97     | BMB* | 0.161          | 2.83     | n.a.      | 73995     |
| Maximum  |           |                |             | 95.21      | 2189.9003    | 959.97     |      | 0.161          | 2.83     | 17.15     | 257947    |
| Minimum  |           |                |             | 0.36       | 0.8302       | 12.02      |      | 0.065          | 1.32     | 8.45      | 73995     |
| Sum      |           |                |             | 100.00     | 2299.5208    | 1035.31    |      |                |          |           |           |
Main peaks MS analysis: Mass spectrometry analyses (ESI+ QTOFMS) of the HPLC-isolated peaks of compound 11 are shown below.
Peak 4:
Compound 12
### Compound 14

![Chemical structure of Compound 14](image)

| No. | Peak Name | Ret.Time | Amount | Rel.Area | Area mAU | Height mAU | Type  | Width (50%) min | Asym. | Resol. | Plates |
|-----|-----------|----------|--------|----------|----------|------------|-------|----------------|-------|--------|--------|
| 1   |           | 16.428   | n.a.   | 2.16     | 65938    | 51.69      | BMB² | 0.085          | 2.17  | 11.24  | 209124 |
| 2   |           | 18.056   | n.a.   | 1.58     | 50951    | 57.70      | BMB² | 0.085          | 1.05  | 1.07   | 242111 |
| 3   |           | 18.398   | n.a.   | 95.28    | 3067007  | 1343.69    | BMB² | 0.191          | 2.58  | 0.39   | 506952 |
| 4   |           | 19.780   | n.a.   | 0.98     | 31685    | 39.79      | BMB² | 0.081          | 1.15  | n.a.   | 334019 |
| **Maximum** |          | 0.0000  | 95.28 | 3067007  | 1343.69 | 0.191      | 2.58  | 11.24 | 334019 |
| **Minimum** |          | 0.0000  | 0.56  | 51055    | 39.79   | 0.081      | 1.05  | 1.07  | 506952 |
| **Sum**   |          | 0.0000  | 100.00| 3215042  | 1452.35 |            |       |       |        |
VII. *In Silico* Methods (S46-S50)

**Stability of 11-Co(III) stereoisomers**
The starting geometry of 11-Co(III) in the capped state was built based on two crystal structures – of ciprofloxacin⁹ and of cyclen derivative complexed with Co(III)¹⁰. The initial structures of stereoisomers of 11-Co(III) were constructed using Maestro¹¹. To find the most favorable conformation of each stereoisomer, we performed conformational analysis using the iMTD-sMTD algorithm¹² implemented in the CREST 2.11 software¹³. The energy of the conformers was calculated with the semiempirical potential GFN2-xTB¹⁴ and ALPB solvation model¹⁵ as an aqueous phase. Subsequently, we optimized the lowest-energy conformers with the DFT functional B3LYP and D3BJ dispersion correction¹⁶ in the SMD implicit solvation model¹⁷. We applied SDD on the cobalt ion and 6-31+G(d) basis set on the remaining atoms. We evaluated thermochemical properties of the compounds at the same level of theory under standard conditions (298.15 K, 1 atm). No imaginary frequencies were detected, which proves that the conformers correspond to the true energy minima on the potential energy surface. To improve the accuracy of the obtained free energies, we calculated single-point energies at the respective optimized geometries with 6-311++G(d,p)/SDD basis set. The final Gibbs free energies were computed as sums of the single-point energies at B3LYP-D3BJ/SMD/6-311++G(d,p)/SDD and respective thermal corrections at B3LYP-D3BJ/SMD/6-31+G(d)/SDD. All the DFT calculations were performed using Gaussian 09 package¹⁸.

**Parametrization of the force field for 11-Co(III)**

**Non-bonded terms**
In the AMBER force field, atomic charges are derived canonically with the RESP procedure which uses electrostatic potential (ESP) calculated around a molecule on the quantum chemical level (Hartree-Fock method) in gas phase¹⁹. Since 11-Co(III) is zwitterionic, we could not apply RESP directly on the entire molecule because the charge is artificially transferred from ciprofloxacin to cyclen-Co(III) complex. To alleviate this problem, the conjugate was partitioned into three parts – a ciprofloxacin scaffold, aryl linker and cyclen-Co(III) complex, each of which was parametrized independently. Each part was appropriately appended to mimic the potential of adjacent segments, as illustrated below.

![Segments of 11-Co(III)](image)

Segments of 11-Co(III) – ciprofloxacin (A), linker (B), cyclen-Co(III) complex in the capped (C) and uncapped (D) states, and the total charges of the un-appendaged residues. The caps are highlighted in grey.
To account for the effect of multiple conformations of each segment on its charge distribution, we applied the following protocol:

I. Calculation of the initial RESP charges
   a. The initial geometry of the capped segment was optimized at the B3LYP/6-31G(d) level of theory in Gaussian 09\textsuperscript{18}.
   b. The single-point energy calculation at the optimized geometry was performed at the HF/6-31G(d) level of theory and the corresponding ESP was produced in Gaussian 09\textsuperscript{18}.
   c. The RESP charges of the residue were computed using antechamber (AmberTools 21\textsuperscript{20}).

II. Generation of the multiple residue conformations using classical molecular dynamics (MD)
   a. The residue was neutralized with K\textsuperscript{+}/Cl\textsuperscript{−} ions and solvated in a rectangular box with a 20 Å layer of explicit OPC3 water molecules\textsuperscript{21} and 150 mM of KCl\textsuperscript{22} in leap (AmberTools 21\textsuperscript{20}).
   b. The system was energy minimized with the steepest descent method (500 steps) followed by the conjugate gradient method (500 steps) using sander (AmberTools 21\textsuperscript{20}).
   c. The system in 5 independent copies was thermalized to 310.15 K for 1 ns of Langevin dynamics implemented in pmemd.cuda (Amber 20\textsuperscript{20}).
   d. The system replicas were equilibrated for 1 ns under pressure of 1 atm maintained by Monte Carlo barostat.
   e. For all the system replicas, the production runs were performed for 100 ns each.
   f. The residue conformations obtained in MD were clustered in the dihedral angles space using cpptraj (AmberTools 21\textsuperscript{20}) and k-means algorithm. 500 representative structures of the residue were selected for the next steps.

III. Calculation of the RESP charges averaged over the ensemble of residue conformers
   a. The representative conformations of the residue were optimized with the selected dihedral angles frozen at the B3LYP/6-31G(d) level of theory in Gaussian 09\textsuperscript{18}.
   b. The single-point energy calculations at the optimized geometries of the conformers were performed at the HF/6-31G(d) level of theory and the corresponding ESP data were produced in Gaussian 09\textsuperscript{18}.
   c. The RESP charges of the residue conformers were computed using antechamber (AmberTools 21\textsuperscript{20}) and averaged. Charge constraints were used to keep the total charge of the uncapped residues as shown in Figure S1.

Calculating the RESP charges for 11-Co(III) in the uncapped state required an additional step. To enable a direct interaction between the cobalt ion in 11-Co(III) and DNA phosphate, it was necessary to create a vacant site on the cobalt ion. Thus, the hydroxyl ion was removed from the optimized geometry of cyclen-Co(III) complex in the uncapped state. Furthermore, we performed a single-point energy calculation at the HF/6-31G(d) level of theory to produce the corresponding ESP in Gaussian 09\textsuperscript{18} and calculated the RESP charges using antechamber (AmberTools 21\textsuperscript{20}).
The atom types and corresponding van der Waals parameters (epsilon and radii) were assigned according to the GAFF2 force field.

**Bonded terms**

The bonding parameters for ciprofloxacin and linker were assigned using parmchk2 (AmberTools 21) in accord with the GAFF2 force field. Cyclen-Co(III) complex was built in the bonded model approach, in which the cobalt ion is covalently bound to the rest of the molecule. We applied the Metal Center Parameter Builder method implemented in MCPB.py (AmberTools 21), in which the metal-involving bond and angle terms are derived from quantum chemical calculations of the force constants from the submatrices of the cartesian Hessian matrix, and the dihedral terms are neglected.

**Building the DNA-topoisomerase IV system**

The model of the DNA-topoisomerase IV complex with fluoroquinolone binding sites was prepared based on the 2XKK crystal structure. Any missing amino acids were inserted and modelled with Modeller 9.17. Protonation states of the protein titratable groups were established and hydrogens added with Propka 3.0 using the PDB2PQR server. Moxifloxacin molecules were removed, and magnesium ions were preserved as in the crystal structure. 11-Co(III) was docked to the fluoroquinolone binding sites (for details see below). The system was neutralized with ions and solvated in a truncated octahedron box with a 12 Å layer of explicit OPC3 water molecules and 150 mM of KCl in leap (AmberTools 21). The entire system consisted of about 147 000 atoms.

For visualization of the system, we used the VMD 1.9.4 software. The standard AMBER force field was used for parametrization of the protein (ff14SBonlysc), and DNA (OL15). The non-standard AMBER force field parameters for 11-Co(III) were developed by us (see above).

The ribbon model of the DNA-topoisomerase IV complex with 11-Co(III) in the capped state. For clarity, explicit water and ions are not shown.
**Molecular docking**

\(\text{II}-\text{Co(III)}\) was docked in the capped and uncapped states to the fluoroquinolone binding sites within the DNA-topoisomerase IV complex using the DOCK 6.9 suite of programs\(^{31}\) as it is fully compatible with the AMBER force field. The structures used for the docking were prepared as in the procedures described above.

Initially, the molecular surface of the DNA-protein complex with hydrogens removed was produced by the DMS module implemented in Chimera 1.15\(^{32}\). It was further used by the sphgen program to generate spheres within the binding sites. The spheres located within 12 Å of the starting position of two \(\text{II}-\text{Co(III)}\) molecules, aligned to the crystallographic structures of moxifloxacin, were selected for docking. Subsequently, the box was constructed around the spheres with an addition of a 4 Å margin in all directions by using the showbox program. Then, energy interactions between a dummy atom and all the atoms of the DNA-protein complex were calculated on a 0.2 Å resolution grid within the box by using the grid program. For the energy evaluation, we used Lennard-Jones potential with 6 for attractive and 12 for repulsive exponents, and Coulomb potential with a distance-dependent dielectric constant of \(\varepsilon=4r\).

In all the docking experiments, the fixed-anchor protocol with the single grid energy score was used to generate and score the docking poses. The ciprofloxacin scaffold was anchored to its starting geometry aligned to the crystallographic structure of moxifloxacin, while the remaining part of \(\text{II}-\text{Co(III)}\) was free to move. The internal energy of the ligand during its growth was described by van der Waals potential with a repulsive exponent of 12. In each step of the growth, a cycle of energy minimization using simplex minimizer was performed with a convergence threshold of 0.1 kcal/mol. Conformers with a score greater than 100.0 kcal/mol were rejected. Finally, one hundred of the best-score conformations were clustered with a 2.0 Å RMSD threshold.

To increase the conformational sampling, we repeated the docking 500 times with a different seed in the simplex minimization.

The interactions formed between the DNA and \(\text{II}-\text{Co(III)}\) were analyzed with the cpptraj program (AmberTools 21\(^{20}\)). To detect the interactions the distance of 4.0 Å was used as the sole criterion.

**Classical molecular dynamics**

The DNA-topoisomerase IV system with \(\text{II}-\text{Co(III)}\) was energy minimized with the steepest descent method (1000 steps) followed by the conjugate gradient method (500 steps) using the sander program (AmberTools 21\(^{20}\)). All the subsequent steps were simulated using the pmemd.cuda program (AmberTools 21\(^{20}\)). The solute was restrained with a harmonic constant of 10 kcal/mol/Å\(^2\) imposed on the non-hydrogen atoms, and the entire system was thermalized from 10.15 to 310.15 K, in 30 K increments of 10 ps length. The temperature was controlled by Langevin thermostat with a damping coefficient of 1.0 ps\(^{-1}\), and the pressure of 1 atm was maintained isotropically by Monte Carlo barostat (NpT ensemble). During equilibration, the restraints were released over twenty rounds of 100 ps each. The production run was continued for 50 ns. In the system containing \(\text{II}-\text{Co(III)}\) in the uncapped state, the distance between the cobalt ion and DNA phosphate’s oxygen after energy minimization was restrained harmonically with a force constant of 65 kcal/mol/Å\(^2\) for all the subsequent steps.

In all the simulations, periodic boundary conditions and Particle Mesh Ewald method with a grid spacing of 1.0 Å were used. The bonds involving hydrogens were
constrained using the SHAKE algorithm, which allowed to use the integration time step of 2 fs. The cutoff for short-range non-bonded interactions was set to 9 Å. Data were collected every 5 ps.

Hybrid QM-MM dynamics
Representative structures of the DNA-topoisomerase IV system with 11-Co(III) extracted from the classical MD simulations were simulated using the QM-MM method implemented in NAMD 2.1433,34 interfaced to Orca 5.0335 and xtb 6.5.014.

In the system, two independent QM regions corresponding to the two binding sites were selected. In each, the QM atoms comprised of 11-Co(III) and the three closest DNA nucleobases (195 atoms in the first, and 197 atoms in the second QM part). The charge of each QM segment was 0 for 11-Co(III) in the uncapped state, and -1 for the capped state. The QM parts were modelled with the GFN2-xTB semiempirical potential14. To account for interactions between the QM and MM atoms, electrostatic embedding was applied. The atoms linking the QM and MM regions were treated by the charge shift scheme.

The simulations were carried out in the NpT ensemble. The temperature of 310.15 K was maintained by Langevin thermostat (with a damping coefficient of 50 ps⁻¹), and the pressure of 1 atm was balanced by Langevin Piston barostat. The system was equilibrated for 100 ps. The production run was conducted for 500 ps.

In the QM-MM-CVSMD36 simulations, the distance between the hydroxyl ion of 11-Co(III) and the phosphorus atom of the DNA phosphate was steered using a harmonic potential with a force constant of 200 kcal/mol/Å² for 200 ps.

The simulations were carried out under periodic boundary conditions. The Particle Mesh Ewald method with a grid spacing of 1.0 Å was used for long-range electrostatics. Only the bonds within water were constrained using the SETTLE algorithm. The integration time step of 0.5 fs was used. The cutoff for short-range non-bonded interactions was set to 12 Å. Data were saved every 10 fs.
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