

## Supporting Information

### Shooting for Selective Drug-Like G-Quadruplex Binders: Evidence for Telomeric DNA Damage and Tumor Cell Death

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**Table S1.** Vendor codes and suppliers for each tested compound.

<b>Cpd</b>	<b>Supplier Code</b>	<b>Supplier</b>
<b>1a</b>	F1190-0101	Life Chemicals <sup>1</sup>
<b>1b</b>	F1190-0088	Life Chemicals <sup>1</sup>
<b>1c</b>	PBMRNS000346	PBMR LABS <sup>2</sup>
<b>1d</b>	PBMRNS034963	PBMR LABS <sup>2</sup>
<b>1e</b>	PBMR NS036540	PBMR LABS <sup>2</sup>
<b>1f</b>	PBMR NS037637	PBMR LABS <sup>2</sup>
<b>2a</b>	BAS 42149	Asinex <sup>3</sup>
<b>2b</b>	IBS 3S 85040	InterBioScreen <sup>4</sup>
<b>2c</b>	IBS 3S 75443	InterBioScreen <sup>4</sup>
<b>2d</b>	PBMR 106449	PBMR LABS <sup>2</sup>
<b>2e</b>	IBS 3S 79280	InterBioScreen <sup>4</sup>
<b>2f</b>	IBS 1S 78280	InterBioScreen <sup>4</sup>
<b>2g</b>	IBS 1S 70945	InterBioScreen <sup>4</sup>
<b>2h</b>	IBS 3S 90408	InterBioScreen <sup>4</sup>
<b>2i</b>	IBS3S 88091	InterBioScreen <sup>4</sup>
<b>2j</b>	IBS3S76091	InterBioScreen <sup>4</sup>
<b>2k</b>	IBS 3S 81487	InterBioScreen <sup>4</sup>
<b>2l</b>	IBS 3S 45984	InterBioScreen <sup>4</sup>
<b>2m</b>	IBS 3S 49344	InterBioScreen <sup>4</sup>
<b>2n</b>	IBS 3S 45929	InterBioScreen <sup>4</sup>
<b>2o</b>	IBS 3S 46190	InterBioScreen <sup>4</sup>
<b>2p</b>	F3139-0342	Life Chemicals <sup>1</sup>
<b>2q</b>	PBMR 033647	PBMR LABS <sup>2</sup>
<b>2r</b>	PBMR 106390	PBMR LABS <sup>2</sup>
<b>2s</b>	F0821-0227	Life Chemicals <sup>1</sup>
<b>2t</b>	IBS 1N 28824	InterBioScreen <sup>4</sup>

<sup>1</sup>**Life Chemicals** Life Chemicals Inc. conducts regular quality control of all compounds. The analytical data including NMR spectra and/or LC MS spectra for each delivered compound are provided on demand of a customer.

<http://www.lifechemicals.com/ordering/9325>

<sup>2</sup>**PBMR LABS** quality assurance: all compounds are accompanied with <sup>1</sup>H NMR and /or LC/MS trace and Mass Spectra to verify purity. The purity for compound collection is +90% and building blocks +97%.

<http://www.princetonbio.com/pages16.html>

<sup>3</sup>**Asinex** quality control: all Asinex compounds have a minimum purity of +90% which is verified by NMR and LCMS.

<http://www.asinex.com/Libraries.html>

<sup>4</sup>**InterBioScreen** quality control: all compounds are put to quality control on two NMR spectrometers (Brucker-300/500 MHz) and a Finnigan mass spectrometer. ALL compounds have passed NMR/MS control (purity 92-98%).

<http://www.ibscreen.com/products.shtml>

**Table S2.** Differences in chemical shifts ( $\Delta\delta$ ) of selected signals of DNA upon binding of derivatives **1b-1d**, **2b**, **2c**, **2e-2k**, **2l-2o** (complexed DNA minus free DNA). For each compound, two series of  $\Delta\delta$  values are reported concerning the titrations with the ligand dissolved in H<sub>2</sub>O and DMSO respectively.

	NH 1	NH 2	NH 3	NH 4	H8G2	H8G4	H8G3	H8G5	H6T1	H6T6	MeT6	MeT1
<b>1a</b> H <sub>2</sub> O	-0.36	-0.24	-0.20	-0.40	-0.10	-0.13	-0.12	-0.05	-0.02	0.32	0.21	-0.12
<b>1a</b> DMSO	-0.35	-0.24	-0.17	-0.34	-0.08	-0.11	-0.09	-0.04	-0.01	0.33	0.23	-0.13
<b>1b</b> H <sub>2</sub> O	-0.41	-0.26	-0.22	-0.41	-0.11	-0.13	-0.11	-0.07	-0.02	0.33	0.23	-0.14
<b>1b</b> DMSO	-0.37	-0.21	-0.19	-0.34	-0.09	-0.07	-0.09	-0.05	0.01	0.28	0.20	-0.13
<b>1c</b> H <sub>2</sub> O	-0.21	-0.45	-0.13	-0.30	-0.05	-0.09	-0.05	-0.01	0.00	0.28	0.17	-0.06
<b>1c</b> DMSO	-0.19	-0.37	-0.15	-0.22	0.00	-0.03	-0.03	0.01	0.06	0.19	0.12	-0.01
<b>1d</b> H <sub>2</sub> O	-0.47	-0.29	-0.25	-0.41	-0.16	-0.19	-0.16	-0.08	-0.07	0.30	0.21	-0.17
<b>1d</b> DMSO	-0.33	-0.23	-0.20	-0.32	-0.11	-0.13	-0.12	-0.06	-0.05	0.15	0.18	-0.13
<b>2b</b> H <sub>2</sub> O	-0.18	-0.11	-0.12	-0.24	-0.05	-0.07	-0.06	-0.01	0.00	0.27	0.18	-0.06
<b>2b</b> DMSO	-0.23	-0.18	-0.13	-0.24	-0.05	-0.10	-0.05	-0.01	0.03	0.32	0.23	-0.08
<b>2c</b> H <sub>2</sub> O	-0.32	-0.20	-0.17	-0.36	-0.10	-0.12	-0.10	-0.02	0.00	0.34	0.24	-0.09
<b>2c</b> DMSO	-0.25	-0.17	-0.13	-0.25	-0.05	-0.08	-0.06	-0.02	0.03	0.36	0.25	-0.08
<b>2e</b> H <sub>2</sub> O	-0.16	-0.12	-0.11	-0.24	-0.04	-0.07	-0.06	-0.01	0.00	0.30	0.20	-0.06
<b>2e</b> DMSO	-0.22	-0.15	-0.11	-0.24	-0.03	-0.07	-0.05	0.00	0.04	0.32	0.23	-0.07
<b>2f</b> H <sub>2</sub> O	-0.25	-0.21	-0.11	-0.20	-0.07	-0.07	-0.07	0.00	0.02	0.28	0.23	-0.09
<b>2f</b> DMSO	-0.23	-0.20	-0.10	-0.20	-0.05	-0.07	-0.05	0.00	0.03	0.26	0.24	-0.08
<b>2g</b> H <sub>2</sub> O	-0.16	-0.11	-0.11	-0.25	-0.04	-0.07	-0.06	-0.02	0.00	0.27	0.19	-0.05
<b>2g</b> DMSO	-0.09	-0.14	-0.12	-0.24	-0.04	-0.07	-0.05	-0.02	0.02	0.30	0.21	-0.06
<b>2h</b> H <sub>2</sub> O	-0.25	-0.21	-0.14	-0.27	-0.07	-0.09	-0.07	0.00	0.00	0.35	0.21	-0.01
<b>2h</b> DMSO	-0.24	-0.18	-0.13	-0.25	-0.05	-0.08	-0.06	-0.01	0.04	0.36	0.25	-0.08
<b>2i</b> H <sub>2</sub> O	-0.16	-0.13	-0.12	-0.29	-0.05	-0.08	-0.06	-0.01	0.00	0.29	0.20	-0.05
<b>2i</b> DMSO	-0.25	-0.18	-0.13	-0.25	-0.05	-0.08	-0.06	-0.02	0.03	0.35	0.25	-0.09
<b>2j</b> H <sub>2</sub> O	-0.14	-0.10	-0.09	-0.22	-0.04	-0.18	-0.05	0.00	0.00	0.31	0.20	-0.05
<b>2j</b> DMSO	-0.25	-0.18	-0.13	-0.25	-0.05	-0.08	-0.06	-0.02	0.03	0.35	0.24	-0.09
<b>2k</b> H <sub>2</sub> O	-0.05	-0.10	-0.09	-0.22	-0.04	-0.07	-0.06	0.00	0.00	0.31	0.20	-0.03
<b>2k</b> DMSO	-0.17	-0.14	-0.10	-0.21	-0.03	-0.07	-0.05	0.01	0.05	0.35	0.24	-0.04
<b>2l</b> H <sub>2</sub> O	-0.22	-0.15	-0.13	-0.23	-0.06	-0.10	-0.07	-0.06	-0.02	0.28	0.17	-0.07
<b>2l</b> DMSO	-0.27	-0.19	-0.13	-0.23	-0.06	-0.09	-0.07	-0.06	0.00	0.34	0.23	-0.07
<b>2m</b> H <sub>2</sub> O	-0.24	-0.18	-0.13	-0.25	-0.08	-0.10	-0.08	-0.08	-0.02	0.29	0.18	0.00
<b>2m</b> DMSO	-0.24	-0.08	-0.12	-0.22	-0.05	-0.08	-0.06	-0.04	0.00	0.32	0.22	-0.08
<b>2n</b> H <sub>2</sub> O	-0.18	-0.13	-0.12	-0.22	-0.05	-0.10	-0.07	-0.05	-0.02	0.27	0.18	-0.05
<b>2n</b> DMSO	-0.21	-0.15	-0.11	-0.21	-0.04	-0.07	-0.05	-0.04	0.03	0.34	0.23	-0.06
<b>2o</b> H <sub>2</sub> O	-0.25	-0.18	-0.15	-0.30	-0.02	-0.11	-0.09	-0.06	-0.03	0.31	0.21	-0.08
<b>2o</b> DMSO	-0.17	-0.07	-0.10	-0.19	-0.03	-0.07	-0.04	-0.02	0.04	0.31	0.21	-0.05

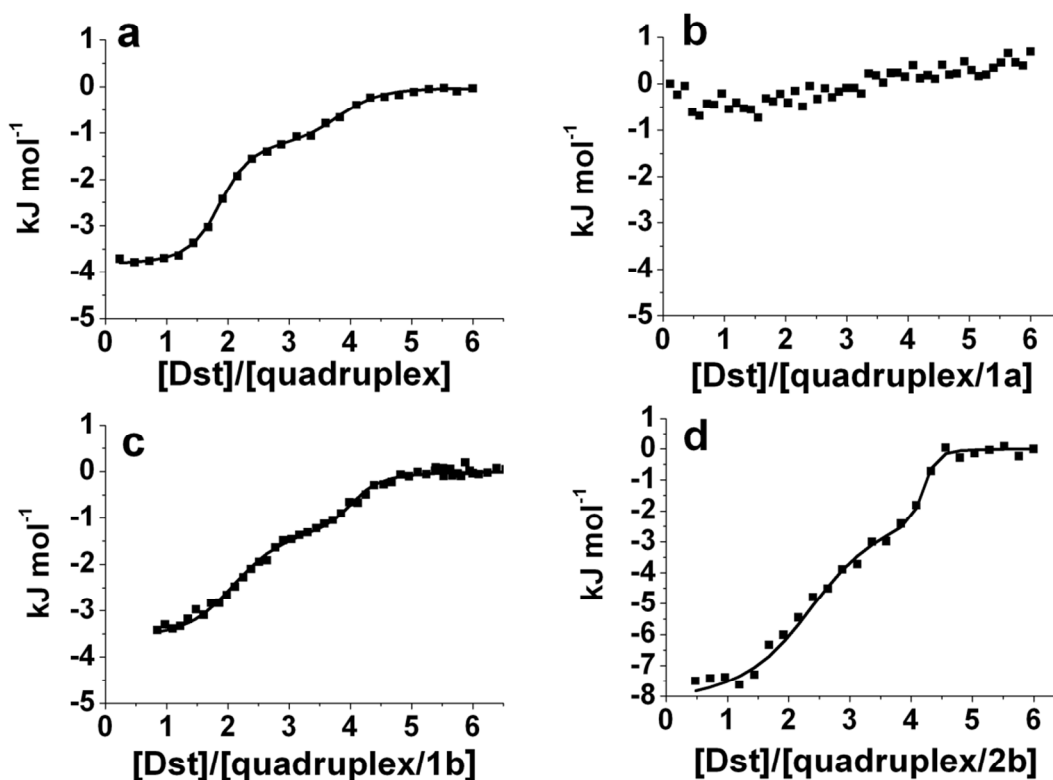
### Isothermal titration calorimetry

To investigate the binding affinity of the selected compounds for the [d(TGGGGT)]<sub>4</sub> G-quadruplex, isothermal titration calorimetry (ITC) experiments were performed. Because of solubility issues regarding the ligands at the rather high concentrations required for canonical measurements, we performed displacement ITC experiments, in which the binding of distamycin A (Dst) to the DNA previously saturated with a compound was analyzed. Indeed, despite the solubility issues, mixtures of G-quadruplex with each compound were successfully prepared by dissolving the compounds in DMSO and diluting them in the aqueous buffer solution containing the DNA (see methods).

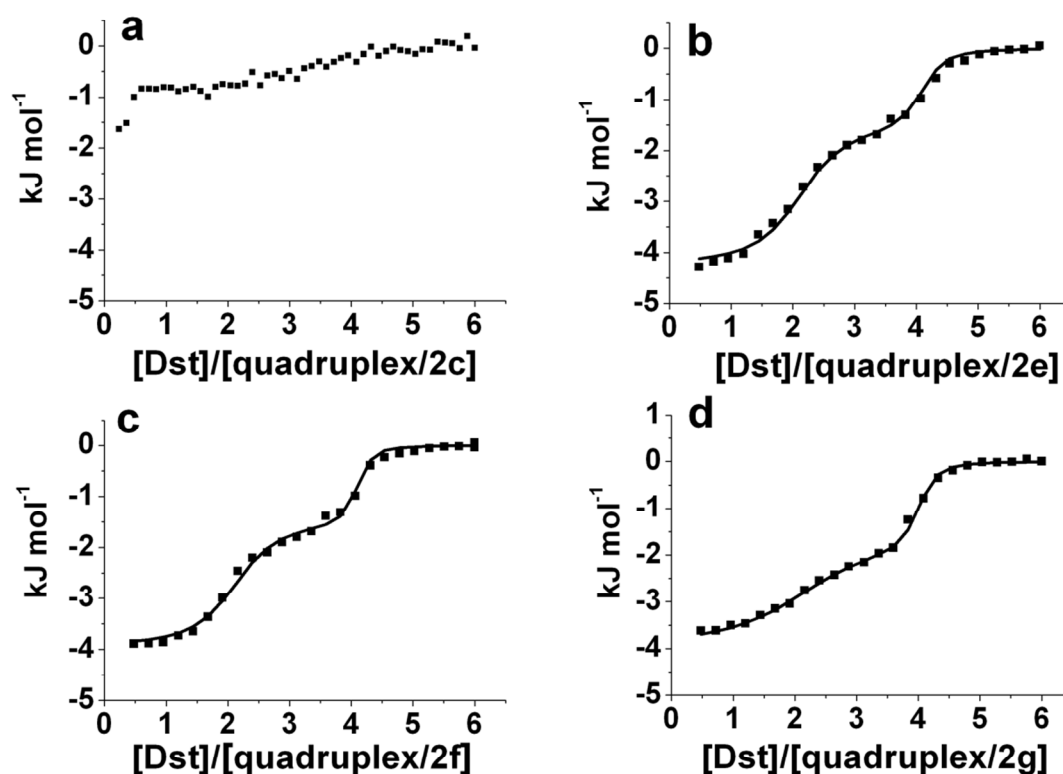
Supplementary figures S1, S2 and S3 show examples of the integrated heat for the ITC titration of [d(TGGGGT)]<sub>4</sub> G-quadruplex solution (Figure S1a) and of the G-quadruplex/ligand mixtures (Figures S1b-d, S2 and S3) with Dst. In most cases, the ITC profile for the titration of ligand-saturated G-quadruplex is similar to the one obtained for the binding of Dst to the G-quadruplex alone, thus indicating that the presence of the compound does not affect the interaction. On the contrary, the titrations of the G-quadruplex/**1a**, /**2c**, /**2l** and /**2m** mixtures with Dst (Figure S1b, S2a, 1b (main text) and S3c, respectively) give completely different results. In these cases, the ITC data show an almost constant heat release after each injection of Dst (only due to Dst dilution), proving that it is no longer able to interact with the G-quadruplex.

The ligands that have been shown to bind the G-quadruplex more tightly than Dst (**1a**, **2c**, **2l** and **2m**) were evaluated for their selectivity for the G-quadruplex over duplex. Therefore, identical ITC displacement experiments were performed by titrating with Dst the DNA duplex d(CGCGAATTCGCG)<sub>2</sub> saturated with such ligands.

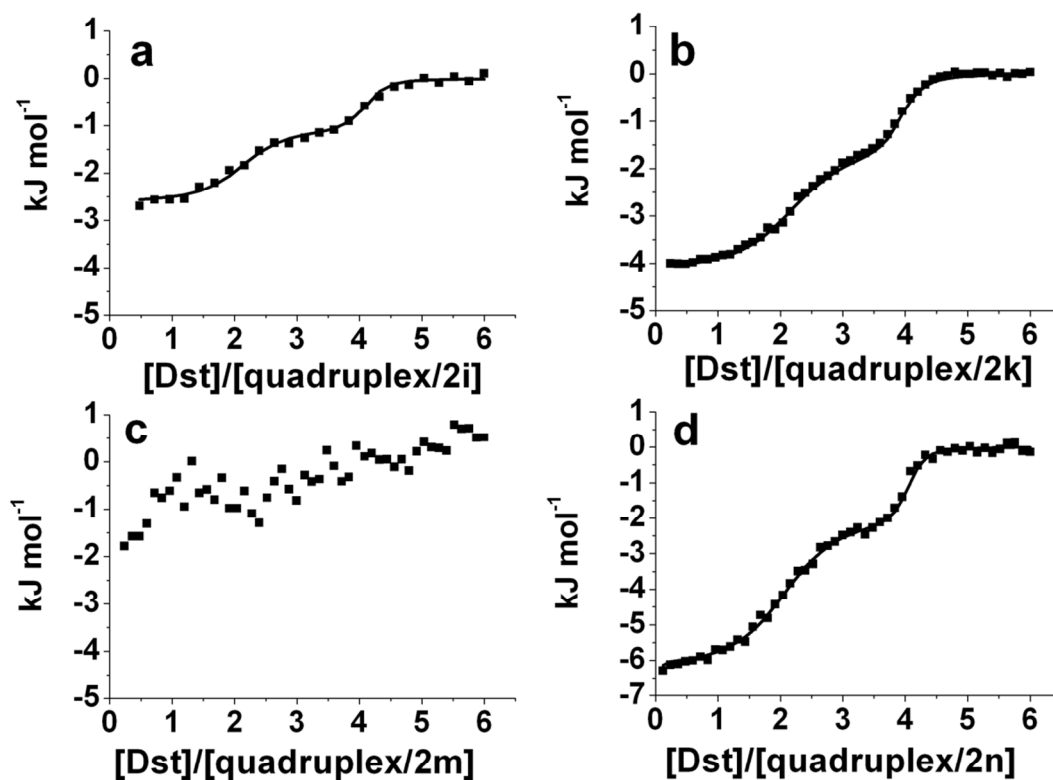
Supplementary figure S4 shows examples of the integrated heat for the ITC titration of d(CGCGAATTCGCG)<sub>2</sub> duplex solution (Figure S4a) and of the duplex/**1a**, /**2c** and /**2m** mixtures (Figure S4b-d) with Dst. In the case of duplex/**2c** and duplex/**2m** mixtures (Figure S4c and d, respectively), the resulting binding isotherms show a typical sigmoidal binding curve and clearly suggest that the presence of the compounds in the mixture has no effect on the interaction of Dst with the duplex. Similar results were obtained for **2l** (see Figure 1c, main text). On the other hand, the integrated heat for the titration of the duplex/**1a** mixture (Figure S4b) clearly indicate that the presence of **1a** affects the interaction of Dst with the duplex, thus suggesting a tight interaction resulting in a poor selectivity for the G-quadruplex.



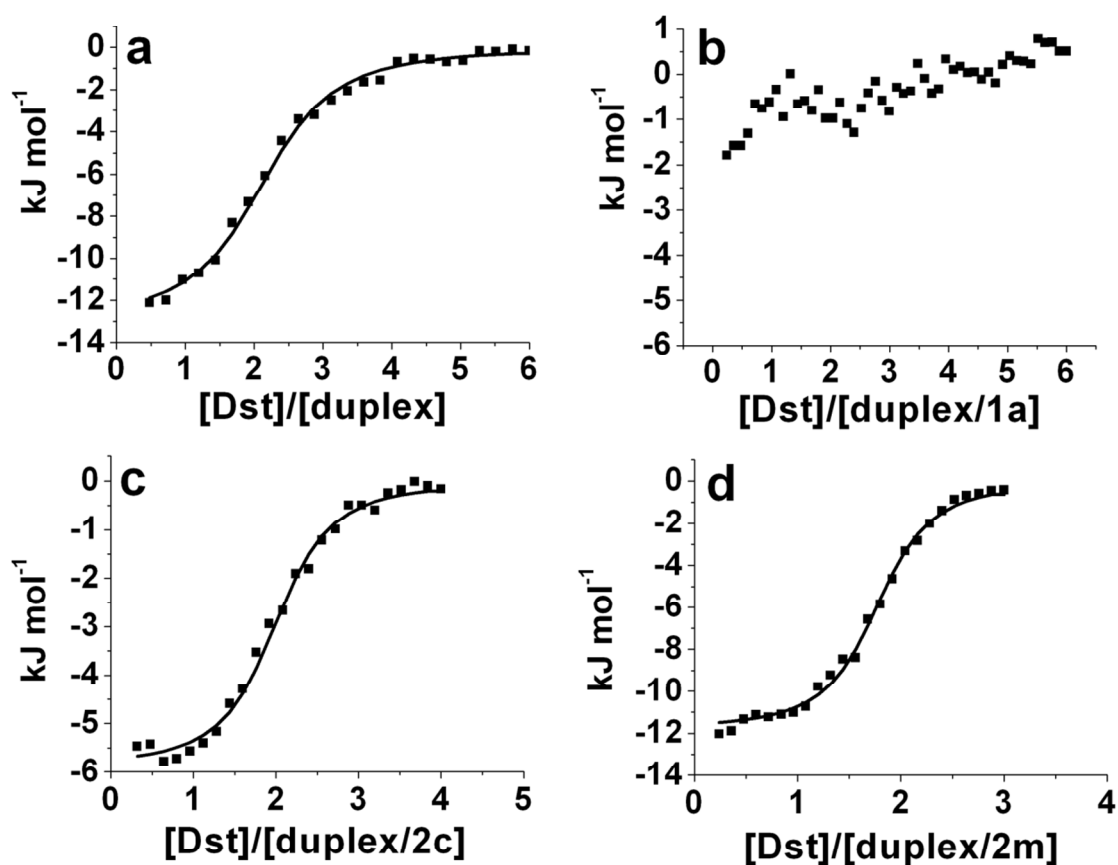
**Figure S1.** Integrated heat for ITC titration of [d(TGGGGT)]<sub>4</sub> G-quadruplex (a), [d(TGGGGT)]<sub>4</sub>/1a (b), [d(TGGGGT)]<sub>4</sub>/1b (c) and [d(TGGGGT)]<sub>4</sub>/2b (d) mixtures with Dst at 25 °C. The integrated heat for the titrations (squares) was obtained by integrating the raw data and subtracting the heat of the Dst dilution. The lines represent nonlinear least squares fit of the data to the appropriate binding model.



**Figure S2.** Integrated heat for ITC titration of [d(TGGGGT)]<sub>4</sub>/2c (a), [d(TGGGGT)]<sub>4</sub>/2e (b), [d(TGGGGT)]<sub>4</sub>/2f (c) and [d(TGGGGT)]<sub>4</sub>/2g (d) mixtures with Dst at 25 °C. The integrated heat for the titrations (squares) was obtained by integrating the raw data and subtracting the heat of the Dst dilution. The lines represent nonlinear least squares fit of the data to the appropriate binding model.



**Figure S3.** Integrated heat for ITC titration of [d(TGGGGT)]<sub>4</sub>/2*i* (a), [d(TGGGGT)]<sub>4</sub>/2*k* (b), [d(TGGGGT)]<sub>4</sub>/2*m* (c) and [d(TGGGGT)]<sub>4</sub>/2*n* (d) mixtures with Dst at 25 °C. The integrated heat for the titrations (squares) was obtained by integrating the raw data and subtracting the heat of the Dst dilution. The lines represent nonlinear least squares fit of the data to the appropriate binding model.

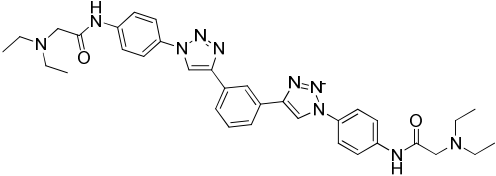
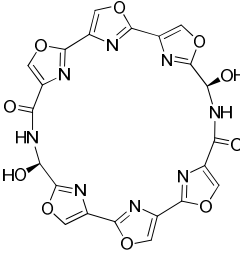
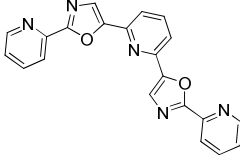
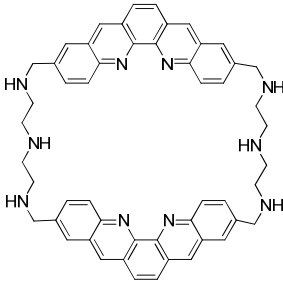
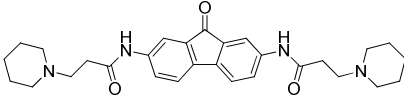
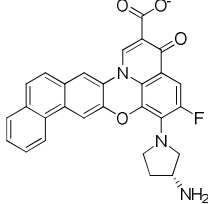
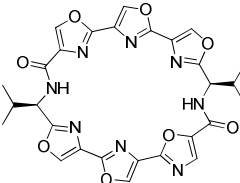
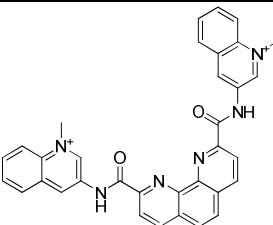


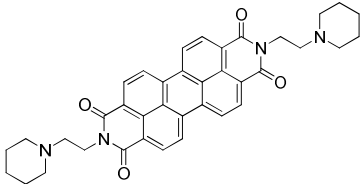
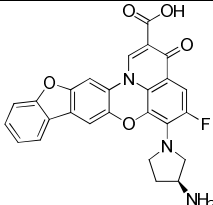
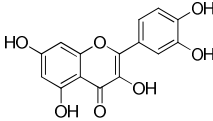
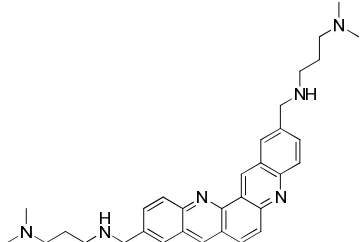
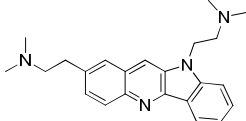
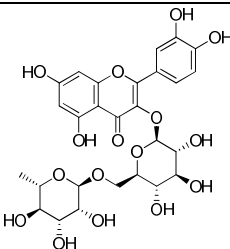
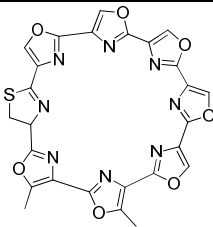
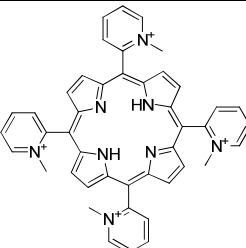
**Figure S4.** Integrated heat for ITC titration of d(CGCGAATTCGCG)<sub>2</sub> duplex (a), d(CGCGAATTCGCG)<sub>2</sub>/1a (b), d(CGCGAATTCGCG)<sub>2</sub>/2c (c) and d(CGCGAATTCGCG)<sub>2</sub>/2m (d) mixtures with Dst at 25 °C. The integrated heat for the titrations (squares) was obtained by integrating the raw data and subtracting the heat of the Dst dilution. The lines represent nonlinear least squares fit of the data to the appropriate binding model.

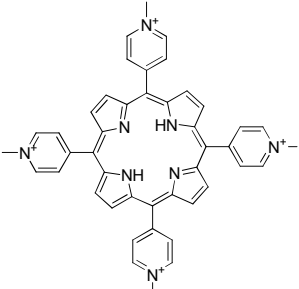
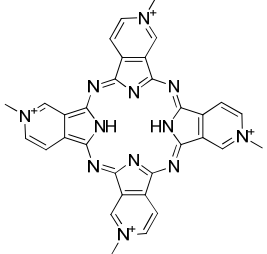
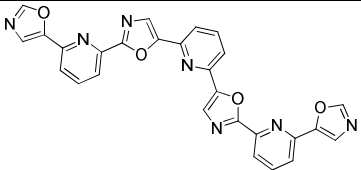
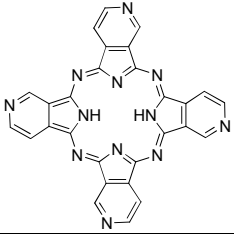
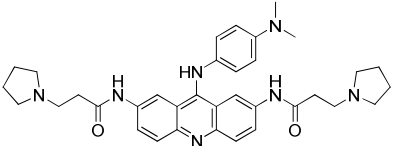


**Table S3.** Structure of the G-quadplex ligands considered in the QikProp calculations.

Name	Structure	Ref.
115405		1
12459		1
1a		
2c		
2l		
2m		
307A		1
Acridine		1
Anthraquinone		1
Benzofuroquinoline		1
Bipyridine		1

<b>Bistriazole</b>		1
<b>Bistrioxazole</b>		1
<b>BOxaPy</b>		2
<b>Cyclo-bis-quinacridine</b>		1
<b>Fluorenones</b>		1
<b>FQA-T</b>		1
<b>HXDV</b>		1
<b>Phenanthroline</b>		1

<b>Piper</b>		1
<b>QQ58</b>		1
<b>Quercetin</b>		1
<b>Quinacridine</b>		1
<b>Quindoline</b>		1
<b>Rutin</b>		1
<b>Telomestatin</b>		1
<b>TMPyP2</b>		1

<b>TMPyP4</b>		1
<b>TMPyPz</b>		1
<b>TOxaPy</b>		2
<b>TPyPz</b>		1
<b>Trisamidoacridine</b>		1

**Table S4.** QikProp properties and descriptors. Range is for 95% of known drugs.

Property or Descriptor	Description	Range or recommended values
#stars	Number of property or descriptor values that fall outside the 95% range of similar values for known drugs.	0 – 5
#rotor	Number of non-trivial (not CX3), non-hindered (not alkene, amide, small ring) rotatable bonds.	0 – 15
#rtvFG	Number of reactive functional groups. The presence of these groups can lead to false positives in HTS assays and to decomposition, reactivity, or toxicity problems <i>in vivo</i>	0 – 2
mol_MW	Molecular weight of the molecule.	130.0 – 725.0
dipole	Computed dipole moment of the molecule.	1.0 – 12.5
SASA	Total solvent accessible surface area (SASA) in square angstroms using a probe with a 1.4 Å radius.	300.0 – 1000.0
FISA	Hydrophilic component of the SASA (SASA on N, O, and H on heteroatoms).	7.0 – 330.0
PISA	$\pi$ (carbon and attached hydrogen) component of the SASA.	0.0 – 450.0
volume	Total solvent-accessible volume in cubic angstroms using a probe with a 1.4 Å radius.	500.0 – 2000.0
donorHB	Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution. Values are averages taken over a number of configurations, so they can be non-integer.	0.0 – 6.0
acceptHB	Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution. Values are averages taken over a number of configurations, so they can be non-integer.	2.0 – 20.0
dip <sup>2</sup> /V	Square of the dipole moment divided by the molecular volume. This is the key term in the Kirkwood-Onsager equation for the free energy of solvation of a dipole with volume V.	0.0 – 0.13
ACxDN <sup>5</sup> /SA	Index of cohesive interaction in solids.	0.0 – 0.05
glob	Globularity descriptor, $(4\pi^2)/SASA$ , where $r$ is the radius of a sphere with a volume equal to the molecular volume. Globularity is 1.0 for a spherical molecule.	0.75 – 0.95
QPpolrz	Predicted polarizability in cubic angstrom.	13.0 – 70.0
QPlogPC16	Predicted hexadecane/gas partition coefficient.	4.0 – 18.0
QPlogPoct	Predicted octanol/gas partition coefficient.	8.0 – 35.0
QPlogPo/w	Predicted octanol/water partition coefficient.	–2.0 – 6.5
QPlogS	Predicted aqueous solubility, log S. S in mol/dm <sup>3</sup> is the concentration of the solute in a saturated solution that is in equilibrium with the crystalline solid.	–6.5 – 0.5
CIQPlogS	Conformation-independent predicted aqueous solubility, log S. S in mol/dm <sup>3</sup> is the concentration of the solute in a saturated solution that is in equilibrium with the crystalline solid.	–6.5 – 0.5
QPPCaco	Predicted apparent Caco-2 cell permeability in nm/sec. Caco-2 cells are a model for the gut blood barrier. QikProp predictions are for non-active transport.	<25 poor, >500 great
QPlogBB	Predicted brain/blood partition coefficient. Note: QikProp predictions are for orally delivered drugs so, for example, dopamine and serotonin are CNS negative because they are too polar to cross the blood-brain barrier	–3.0 – 1.2
QPPMDCK	Predicted apparent MDCK cell permeability in nm/sec. MDCK cells are considered to be a good mimic for the blood-brain barrier. QikProp predictions are for non-active transport.	<25 poor, >500 great
QPlogKp	Predicted skin permeability, log K <sub>p</sub> .	–8.0 – –1.0
IP(ev)	PM3calculatedionizationpotential.	7.9 – 10.5
EA(eV)	PM3calculated electron affinity.	–0.9 – 1.7
#metab	Number of likely metabolic reactions.	1 – 8
QPlogKhsa	Prediction of binding to human serum albumin.	–1.5 – 1.5
%Human-OralAbsorption	Predicted human oral absorption on 0 to 100% scale. The prediction is based on a quantitative multiple linear regression model.	>80% is high, <25% is poor
PSA	Van der Waals surface area of polar nitrogen and oxygen atoms.	7.0 – 200.0
#NandO	Number of nitrogen and oxygen atoms.	2 – 15
RuleOfFive	Number of violations of Lipinski's rule of five. The rules are: mol_MW < 500, QPlogPo/w < 5, donorHB ≤ 5, acceptHB ≤ 10. Compounds that satisfy these rules are considered drug-like.	maximum is 4
RuleOfThree	Number of violations of Jorgensen's rule of three. The three rules are: QPlogS > –5.7, QPPCaco > 22 nm/s, # Primary Metabolites < 7. Compounds with fewer (and preferably no) violations of these rules are more likely to be orally available.	maximum is 3

**Table S5.** Calculated ADME and physical properties and descriptors for 32 G-quadruplex ligands. Values that fall outside the 95% range of similar values for known drugs (for recommended ranges see Table S4) are colored in red.

Compound	#stars	#rotor	#rtvFG	mol MW	dipole	SASA	FISA	PISA	volume	donorHB	accptHB	dip^2/V	ACxDN^5/SA
1a	0	5	0	423.49	6.05	711.30	153.34	312.35	1268.11	2	10.45	0.03	0.02
2c	0	5	0	380.46	3.29	672.92	96.77	309.77	1194.71	1	6.75	0.01	0.01
2l	0	4	0	435.54	5.03	706.79	122.63	280.49	1299.10	3	7.25	0.02	0.02
2m	0	4	0	421.51	5.24	694.42	135.77	278.62	1269.02	3	7.25	0.02	0.02
Quindoline	0	6	0	360.50	2.76	722.13	25.43	297.29	1282.49	0	5	0.01	0.00
QQ58	0	2	0	471.44	10.86	703.26	202.64	343.20	1282.46	2	6.5	0.09	0.01
Quercetin	0	5	0	302.24	6.03	531.68	281.86	249.82	882.97	4	5.25	0.04	0.02
115405	1	7	0	525.67	3.84	891.01	84.06	269.71	1637.98	2	8	0.01	0.01
Acridine	1	12	0	463.62	4.87	925.20	107.40	270.73	1628.42	2	10	0.01	0.02
Benzofuroquinoline	1	4	0	347.42	0.46	619.33	36.41	357.17	1100.34	1	6.2	0.00	0.01
BOxaPy	1	0	0	367.37	4.71	680.96	88.70	592.26	1165.56	0	7	0.02	0.00
FQA-T	1	2	0	481.48	10.98	736.33	205.64	374.08	1345.31	2	6	0.09	0.01
Fluorenones	1	8	0	488.63	10.48	933.67	152.40	220.31	1650.75	2	11	0.07	0.02
HXDV	1	8	0	600.55	0.82	835.79	136.88	385.19	1620.76	2	17	0.00	0.03
Telomestatin	1	0	0	582.51	3.93	783.49	94.77	397.15	1487.87	0	15.5	0.01	0.00
Anthraquinone	2	8	0	516.64	4.28	958.93	187.41	210.56	1703.16	2	13	0.01	0.02
Bistrioxazole	2	8	0	548.38	3.76	734.80	290.59	403.21	1368.17	2	18.4	0.01	0.04
Quinacridine	3	12	0	508.71	1.43	1014.26	57.70	384.34	1799.91	2	9	0.00	0.01
TOxaPy	3	0	0	501.46	4.73	838.26	137.00	701.26	1479.33	0	11	0.02	0.00
12459	4	5	0	410.48	2.43	744.59	124.20	464.80	1296.56	4	5.5	0.00	0.01
307A	4	4	0	449.51	11.21	810.93	104.32	551.11	1430.15	2	7	0.09	0.01
Piper	4	6	0	612.73	0.49	968.45	147.36	291.14	1819.04	0	10	0.00	0.00
Phenanthroline	5	4	0	550.62	6.37	832.53	110.80	612.98	1595.53	2	8	0.03	0.01
TPyPz	5	8	0	518.50	0.00	752.46	159.69	592.77	1398.95	2	13	0.00	0.02
Trisamidoacridine	5	11	0	593.77	6.35	1100.11	124.36	313.40	1978.14	3	11.5	0.02	0.02
Bipyridine	6	5	0	526.60	14.83	848.43	109.23	605.96	1601.45	2	8	0.14	0.01
TMPyPz	7	8	0	578.64	0.04	899.93	55.70	494.63	1671.85	2	9	0.00	0.01
Bistriazole	9	10	0	620.76	13.50	1143.59	167.44	476.71	2050.27	2	13	0.09	0.02
Rutin	9	15	2	610.52	5.61	773.30	410.65	158.35	1523.72	9	20.55	0.02	0.08
TMPyP2	10	12	0	678.84	9.27	1017.07	21.94	754.20	1999.23	2	5	0.04	0.01
Cyclo-bis-quinacridine	11	20	0	815.03	4.07	1354.24	100.46	777.70	2546.13	6	13	0.01	0.02
TMPyP4	14	12	0	678.84	41.98	1080.29	23.87	706.15	2064.20	2	5	0.85	0.01

**Table S6.** Calculated ADME and physical properties and descriptors for 32 G-quadruplex ligands. Values that fall outside the 95% range of similar values for known drugs (for recommended ranges see Table S4) are coloured in red.

Compound	glob	QPpolrz	QPlogPC16	QPlogPoct	QPlogPo/w	QPlogS	CIQPlogS	QPPCaco	QPlogBB	QPPMDCK	QPlogKp
1a	0.79	44.37	14.04	23.95	1.19	-2.40	-2.40	121.66	-0.47	115.20	-6.89
2c	0.81	41.41	12.70	18.96	3.29	-4.18	-4.18	298.62	-0.23	247.11	-3.79
2l	0.81	45.95	14.08	24.03	3.22	-4.68	-4.68	169.79	-0.42	129.40	-4.47
2m	0.81	44.72	13.89	23.69	2.95	-4.48	-4.48	127.42	-0.54	96.02	-4.72
Quindoline	0.79	44.16	12.48	16.82	4.35	-3.87	-3.33	353.65	0.73	196.87	-4.49
QQ58	0.81	47.16	14.27	24.09	1.70	-5.88	-6.57	7.50	-1.14	4.97	-5.92
Quercetin	0.84	28.36	10.96	19.03	0.52	-3.10	-4.04	21.04	-2.42	7.62	-5.35
115405	0.75	57.48	17.03	26.42	5.96	-8.44	-8.20	1580.40	-0.73	1440.62	-1.45
Acridine	0.72	53.90	17.14	25.85	3.65	-4.85	-3.36	59.05	-0.73	28.44	-5.52
Benzofuroquinoline	0.83	38.72	11.43	17.28	3.24	-3.44	-3.88	1115.67	0.37	616.04	-2.61
BOxaPy	0.79	46.15	13.88	19.72	3.57	-5.46	-5.31	1428.25	-0.39	727.23	-1.07
FQA-T	0.80	49.97	15.12	24.81	2.30	-6.62	-7.03	7.02	-1.23	4.66	-5.86
Fluorenones	0.72	56.88	17.31	28.43	3.00	-5.27	-3.47	22.10	-1.06	9.83	-6.91
HXDV	0.80	57.25	17.38	31.51	1.77	-3.92	-6.31	498.76	-1.35	233.24	-1.92
Telomestatin	0.80	57.18	15.81	28.16	1.42	-3.13	-6.52	1250.71	-0.31	1071.31	-1.87
Anthraquinone	0.72	58.88	18.05	29.60	2.22	-4.95	-3.29	10.29	-1.54	4.30	-7.59
Bistrioxazole	0.81	47.31	16.28	29.67	-1.31	-1.94	-4.74	17.39	-2.86	6.20	-4.69
Quinacridine	0.71	61.84	19.49	27.78	4.55	-4.35	-3.03	43.60	-0.14	22.67	-4.20
TOxaPy	0.75	59.75	18.23	26.90	3.46	-6.34	-6.90	497.44	-1.06	232.58	-1.57
12459	0.77	46.96	15.47	24.58	4.22	-6.50	-6.63	657.83	-1.13	314.60	-1.69
307A	0.76	53.78	16.86	26.05	5.08	-7.69	-7.06	1015.35	-0.89	502.92	-1.12
Piper	0.74	65.57	18.62	27.47	4.56	-5.92	-6.98	24.68	-0.78	11.08	-6.76
Phenanthroline	0.79	60.99	18.62	28.64	5.76	-7.71	-9.19	881.34	-0.85	431.58	-1.02
TPyPz	0.80	50.36	17.00	27.31	2.16	-4.01	-6.67	303.10	-1.57	136.14	-1.61
Trisamidoacridine	0.69	68.94	21.61	33.54	4.96	-7.42	-5.74	40.78	-1.03	19.06	-5.78
Bipyridine	0.78	60.51	18.70	29.88	5.79	-7.82	-8.58	912.17	-0.93	447.92	-0.92
TMPyPz	0.76	60.34	18.38	27.83	6.04	-7.87	-9.47	2935.82	-0.57	1584.57	-0.04
Bistriazole	0.68	74.03	23.74	36.07	4.80	-7.82	-6.12	15.92	-1.64	6.90	-6.09
Rutin	0.83	46.71	18.31	41.04	-2.59	-2.02	-4.16	1.26	-4.33	0.36	-7.09
TMPyP2	0.75	73.35	22.90	31.06	10.34	-10.81	-13.65	6134.82	-0.42	3514.55	1.89
Cyclo-bis-quinacridine	0.67	90.33	31.31	46.31	5.87	-4.44	-6.42	17.14	-1.36	8.26	-2.84
TMPyP4	0.73	75.49	23.60	42.68	10.68	-11.97	-13.65	5882.77	-0.46	3358.74	1.68

**Table S7.** Calculated ADME and physical properties and descriptors for 32 G-quadruplex ligands. Values that fall outside the 95% range of similar values for known drugs (for recommended ranges see Table S4) are coloured in red.

Compound	IP(eV)	EA(eV)	#metab	QPlogKhsa	%HumanOralAbsorption	PSA	#NandO	RuleOfFive	RuleOfThree
1a	8.94	1.38	6.00	-0.18	67.816	100.048	7	0	0
2c	9.02	0.97	4.00	0.32	90.485	70.153	5	0	0
2l	8.64	0.81	4.00	0.50	85.736	88.201	6	0	0
2m	8.79	0.72	4.00	0.42	81.911	94.89	6	0	0
Quindoline	8.00	0.98	4.00	0.75	100	25.293	4	0	0
QQ58	8.37	1.35	2.00	0.55	52.529	123.114	8	0	2
Quercetin	8.64	0.75	5.00	-0.32	53.652	140.082	7	0	1
115405	8.35	1.03	4.00	1.12	93.157	79.704	9	2	1
Acridine	8.19	1.55	4.00	0.45	80	93.293	7	0	0
Benzofuroquinoline	8.47	1.17	5.00	0.23	100	48.101	5	0	0
BOxaPy	8.94	1.22	4.00	0.13	100	74.632	7	0	0
FQA-T	8.20	1.25	1.00	0.80	55.549	113.796	7	0	2
Fluorenones	8.56	1.25	4.00	0.48	68.551	113.714	7	0	1
HXDV	9.36	0.82	8.00	-0.69	59.679	198.128	16	2	1
Telomestatin	8.90	0.70	10.00	-1.21	64.795	158.389	15	2	1
Anthraquinone	9.15	1.54	4.00	0.21	45.118	137.281	8	1	1
Bistrioxazole	9.47	0.90	8.00	-1.51	15.57	248.449	18	2	2
Quinacridine	8.30	1.49	6.00	1.10	69.997	60.188	6	1	0
TOxaPy	9.04	1.39	4.00	-0.03	69.568	117.58	11	2	1
12459	4.56	3.44	3.00	0.60	100	84.821	8	0	1
307A	4.07	2.96	3.00	0.89	100	87.626	7	1	1
Piper	8.63	2.66	2.00	0.97	65.604	117.29	8	1	1
Phenanthroline	4.46	2.28	3.00	1.16	87.481	96.768	8	2	1
TPyPz	7.86	3.23	9.00	-0.45	58.114	126.996	12	2	1
Trisamidoacridine	7.43	1.53	7.00	1.05	71.827	108.151	9	1	2
Bipyridine	3.52	3.06	3.00	1.12	87.924	96.58	8	2	1
TMPyPz	4.72	2.01	9.00	0.97	85.505	88.123	12	3	2
Bistriazole	8.68	1.02	4.00	1.00	50.639	138.55	12	2	2
Rutin	8.85	0.76	10.00	-1.30	0	260.554	16	3	2
TMPyP2	3.07	2.68	13.00	2.51	100	47.526	8	2	2
Cyclo-bis-quinacridine	8.13	1.34	10.00	1.59	44.538	124.263	10	3	2
TMPyP4	6.24	5.68	13.00	2.68	100	47.681	8	2	2



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