Nickel(II)-naproxen mixed-ligand complexes: Synthesis, structure, antioxidant activity and interaction with albumins and calf-thymus DNA

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Supplementary material

S1. Interaction with serum albumins

The extent of the inner-filter effect can be roughly estimated with the following formula:

$$I_{corr} = I_{meas} \times 10^{\frac{\varepsilon(\lambda_{exc})cd}{2}} \times 10^{\frac{\varepsilon(\lambda_{em})cd}{2}} \qquad \text{(eq. S1)}$$

where I_{corr} = corrected intensity, I_{meas} = the measured intensity, c = the concentration of the quencher, d = the cuvette (1 cm), $\varepsilon(\lambda_{exc})$ and $\varepsilon(\lambda_{em})$ = the ε of the quencher at the excitation and the emission wavelength, respectively, as calculated from the UV-vis spectra of the complexes.[1]

The Stern-Volmer and Scatchard graphs are used in order to study the interaction of a quencher with serum albumins. According to Stern-Volmer quenching equation:[2]

$$\frac{Io}{I} = 1 + k_q\tau_0[Q] = 1 + K_{SV}[Q] \qquad \text{(eq. S2)}$$

where Io = the initial tryptophan fluorescence intensity of SA, I = the tryptophan fluorescence intensity of SA after the addition of the quencher (i.e. complexes **1-5**), k_q = the quenching constant, K_{SV} = the Stern-Volmer constant, τ_o = the average lifetime of SA without the quencher, [Q] = the concentration of the quencher) K_{SV} (M^{-1}) can be obtained by the slope of the diagram Io/I versus [Q], and subsequently the quenching constant (k_q, $M^{-1}s^{-1}$) is calculated from eq. S3, with $\tau_o = 10^{-8}$ s as fluorescence lifetime of tryptophan in SA,

$$K_{SV} = k_q\tau_o \qquad \text{(eq. S3)}$$

From the Scatchard equation:[3]

$$\frac{\Delta I / Io}{[Q]} = nK - K\frac{\Delta I}{Io} \qquad \text{(eq. S4)}$$

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where n is the number of binding sites per albumin and K is the SA-binding constant, K (in M^{-1}) is calculated from the slope in plots (ΔI/Io)/[Q] versus ΔI/Io and n is given by the ratio of y intercept to the slope.[3]

S2. Interaction with CT DNA

The DNA-binding constant (K_b in M^{-1}) can be obtained by monitoring the changes in the absorbance at the corresponding λ_{max} with increasing concentrations of CT DNA and it is given by the ratio of slope to the y intercept in plots [DNA]/(ε_A-ε_f) versus [DNA], according to the Wolfe-Shimer equation:[4]

$$\frac{[DNA]}{(\varepsilon_A - \varepsilon_f)} = \frac{[DNA]}{(\varepsilon_b - \varepsilon_f)} + \frac{1}{K_b(\varepsilon_b - \varepsilon_f)} \qquad \text{(eq. S5)}$$

where [DNA] is the concentration of DNA in base pairs, $\varepsilon_A = A_{obsd}/[compound]$, ε_f = the extinction coefficient for the free compound and ε_b = the extinction coefficient for the compound in the fully bound form.

Cyclic voltammetry can be also used in order to calculate the corresponding equilibrium constant for the redox process. The oxidized and reduced forms are associated with a third species (DNA) in the solution using the following equation: [5]

$$\Delta E^o = E^o_{(b)} - E^o_{(f)} = 0.059 \times \log \frac{K_r}{K_{ox}} \qquad \text{(eq. S6)}$$

where $E^o_{(b)}$ and $E^o_{(f)}$ are the formal potentials of M(II)/M(I) couple in the fully bound and free complexes, respectively. K_{ox} and K_r are the binding constants for the binding of the oxidized and reduced species to DNA, respectively.

S3. Competitive studies with EB

The Stern-Volmer constant ($K_{SV,}$ in M^{-1}) is used to evaluate the quenching efficiency for each compound according to the Stern–Volmer equation (eq. S2),[2] where Io and I are the emission intensities of the EB-DNA solution in the absence and the presence of the quencher, respectively, [Q] is the concentration of the quencher (i.e. complexes **1**-**5**), τ_o = the average lifetime of the emitting system without the quencher and k_q = the quenching constant. K_{SV} may be obtained from the Stern-Volmer plots by the slope of the diagram Io/I versus [Q]. Taking τ_o = 23 ns as the fluorescence lifetime of the EB-DNA system,[6] the quenching constants (k_q, in $M^{-1}s^{-1}$) of the compounds can be determined according to eq. (S3).

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Table S1. The BSA and HSA binding constants and parameters (K_{sv}, k_q, K, n) for Hnap and its Ni(II) complexes **1-6**.

Compound	**K_{sv}(M^{-1})**	**k_q ($M^{-1}s^{-1}$)**	**K(M^{-1})**	**n**
BSA				
Hnap [1]	$1.18(\pm0.06)\times10^4$	$1.18(\pm0.06)\times10^{12}$	$5.35(\pm0.42)\times10^3$	2.03
$[Ni(nap)_2(MeOH)_4]$, **1**	$2.46(\pm0.12)\times10^4$	$2.46(\pm0.12)\times10^{12}$	$4.51(\pm0.34)\times10^4$	0.68
$[Ni(nap)_2(bipy)(CH_3OH)]$, **2**	$2.42(\pm0.24)\times10^4$	$2.42(\pm0.24)\times10^{12}$	$3.25(\pm0.31)\times10^5$	0.52
$[Ni(nap)_2(phen)(H_2O)]$, **3**	$5.90(\pm0.32)\times10^4$	$5.90(\pm0.32)\times10^{12}$	$4.18(\pm0.34)\times10^5$	0.46
$[Ni(nap)_2(bipyam)]$, **4**	$8.28(\pm0.22)\times10^4$	$8.28(\pm0.22)\times10^{12}$	$4.59(\pm0.35)\times10^4$	1.27
$[Ni(nap)_2(Hpko)_2]$, **5**	$4.50(\pm0.28)\times10^4$	$4.50(\pm0.28)\times10^{12}$	$1.08(\pm0.07)\times10^5$	0.67
$[Ni(nap)_2(py)_2(H_2O)_2]$, **6**	$9.52(\pm0.43)\times10^3$	$9.52(\pm0.43)\times10^{11}$	$7.44(\pm0.55)\times10^3$	1.09
HSA				
Hnap [1]	$1.24(\pm0.09)\times10^4$	$1.24(\pm0.09)\times10^{12}$	$3.27(\pm0.30)\times10^4$	0.43
$[Ni(nap)_2(MeOH)_4]$, **1**	$6.54(\pm0.37)\times10^4$	$6.57(\pm0.37)\times10^{12}$	$1.35(\pm0.11)\times10^4$	1.10
$[Ni(nap)_2(bipy)(CH_3OH)]$, **2**	$2.38(\pm0.29)\times10^4$	$2.37(\pm0.29)\times10^{12}$	$1.93(\pm0.03)\times10^5$	0.41
$[Ni(nap)_2(phen)(H_2O)]$, **3**	$1.13(\pm0.06)\times10^5$	$1.13(\pm0.06)\times10^{13}$	$2.73(\pm0.25)\times10^4$	1.00
$[Ni(nap)_2(bipyam)]$, **4**	$1.59(\pm0.05)\times10^5$	$1.59(\pm0.05)\times10^{13}$	$1.88(\pm0.26)\times10^5$	0.96
$[Ni(nap)_2(Hpko)_2]$, **5**	$4.71(\pm0.13)\times10^4$	$4.71(\pm0.13)\times10^{12}$	$3.02(\pm0.41)\times10^4$	0.95
$[Ni(nap)_2(py)_2(H_2O)_2]$, **6**	$1.61(\pm0.08)\times10^5$	$1.61(\pm0.08)\times10^{13}$	$4.05(\pm0.23)\times10^4$	0.94

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Table S2. Antioxidant activity (% DPPH scavenging ability (RA%) in 60 min, % superoxide radical scavenging activity (ABTS%), competition % with DMSO for hydroxyl radical ($^{\bullet}$OH%), and *in vitro* inhibition of soybean lipoxygenase (LOX) (IC_{50}, in μM)) of the reported metal-naproxen complexes (metal = copper(II), nickel(II), cobalt(II)) and Ni-NSAID complexes (NSAID = tolfenamato, mefenamato, flufenamato, naproxen, diflunisal).

Compound	**RA%**	**$^{\bullet}$OH %**	**ABTS%**	**LOX, IC_{50} (μM)**	**Ref.**
Hnap (naproxen)	8.43±0.20	89.55±0.44	87.51±0.17	56.61±0.71	1
$[Ni(nap)_2(MeOH)_4]$, **1**	16.53±0.41	96.53±0.32	96.03±0.43	22.62±0.41	2
$[Ni(nap)_2(bipy)(CH_3OH)]$, **2**	13.61±0.23	90.65±0.82	88.82±0.60	48.56±0.08	2
$[Ni(nap)_2(phen)(H_2O)]$, **3**	14.48±0.34	80.12±0.75	85.74±0.21	45.77±0.67	2
$[Ni(nap)_2(bipyam)]$, **4**	10.21±0.63	76.39±0.20	84.59±0.92	34.63±0.78	2
$[Ni(nap)_2(Hpko)_2]$, **5**	13.45±0.46	92.69±0.22	97.73±0.27	34.67±0.28	2
$[Ni(nap)_2(py)_2(H_2O)_2]$, **6**	15.91±0.45	96.78±0.45	87.72±0.54	37.22±0.23	2
$[Co(nap)_2(MeOH)_4]$	20.37±0.23	96.75±0.30	82.46±0.35	not tested	1
$[Co(nap)_2(py)_2(H_2O)_2]$	18.90±0.22	84.98±0.35	90.22±0.28	not tested	1
$[Co(nap)_2(phen)(H_2O)_2]$	42.42±0.13	92.46±0.22	87.32±0.17	not tested	1
$[Co(nap)_2(bipy)(H_2O)_2]$	26.98±0.41	90.21±0.19	84.54±0.29	not tested	1
$[Cu_2(nap)_4(H_2O)_2]$	20.16±0.23	72.84±0.05	77.74±0.39	not tested	1
$[Cu(nap)_2(py)_2(H_2O)]$	18.66±0.29	93.40±0.22	92.12±0.13	not tested	1
$[Cu(nap)_2(phen)]$	18.76±0.13	93.26±0.36	82.39±0.25	not tested	1
$[Cu(nap)_2(bipy)]$	19.48±0.12	80.11±0.17	76.44±0.20	not tested	1
Hmef (=mefenamic acid)	11.74±0.20	66.32±0.38	92.51±0.44	48.52±0.88	3
$[Ni(mef)_2(bipy)(MeOH)_2]$	10.34±0.67	76.09±0.14	89.92±0.92	46.71±0.48	4
$[Ni(mef)_2(phen)(MeOH)_2]$	10.92±0.54	83.18±0.27	90.03±0.33	33.48±0.24	4
$[Ni(mef)_2(bipyam)]$	12.42±0.24	85.57±0.80	93.56±0.83	25.64±0.38	4
$[Ni(mef)_2(Hpko)_2]$	12.49±0.12	85.56±0.42	97.23±0.76	35.18±0.92	4
$[Ni(mef)_2(py)_2(H_2O)_2]$	13.03±0.68	75.28±0.64	94.76±0.12	35.41±0.36	4
$[Ni(mef)_2(MeOH)_4]$	12.38±0.52	78.12±0.89	89.61±0.68	37.67±0.05	4
Htolf (=tolfenamic acid)	17.86±0.54	75.46±0.44	59.43±0.33	44.23±0.88	5
$[Ni(tolf)_2(H_2O)_4]$	22.32±0.31	88.94±0.44	82.08±0.42	25.16±0.65	6
$[Ni(tolf)_2(bipy)(MeOH)_2]$	17.46±0.62	79.62±0.76	69.75±0.07	39.41±0.61	6
$[Ni(tolf)_2(phen)(MeOH)_2]$	18.35±0.43	65.67±0.62	63.36±0.53	33.52±0.82	6
$[Ni(tolf)_2(bipyam)]$	21.93±0.78	86.68±0.74	83.05±0.78	33.78±0.63	6
$[Ni(tolf)_2(Hpko)_2]$	14.54±0.63	68.03±0.89	75.23±0.59	31.68±0.43	6

$[Ni(tolf)_2(py)_2(MeOH)_2]$	21.23±0.34	83.51±0.22	72.46±0.41	32.45±0.27	6
Hdifl (=diflunisal)	14.31±0.45	86.06±0.38	76.58±0.74	not tested	7
$[Ni(difl)_2(MeOH)_4]$	23.63±0.71	97.47±0.65	89.72±0.27	not tested	7
$[Ni(difl)_2(Hpko)_2]$	20.01±0.36	92.87±0.59	81.97±0.34	not tested	7
$[Ni(difl)_2(phen)(MeOH)_2]$	22.18±0.57	96.82±0.42	84.12±0.38	not tested	7
$[Ni(difl)_2(bipy)(MeOH)_2]$	19.70±0.14	96.17±0.28	90.35±0.88	not tested	7
$[Ni(difl)_2(bipyam)]$	19.78±0.77	93.62±0.49	92.16±0.49	not tested	7
NDGA	82.60±0.17	not tested	not tested	not tested	
BHT	60.00±0.38	not tested	not tested	not tested	
Trolox	not tested	82.80±0.13	91.80±0.17	not tested	
Caffeic acid	not tested	not tested	not tested	600±0.3	

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Table S3. DNA-, BSA- and HSA-binding constants for the reported metal-naproxen complexes (metal = copper(II), nickel(II), cobalt(II)) and Ni-NSAID complexes (NSAID = tolfenamato, mefenamato, flufenamato, naproxen, diflunisal).

Compound	**K_b (M^{-1})**	**$K_{(BSA)}$ (M^{-1})**	**$K_{(HSA)}$ (M^{-1})**	**Reference**
Hnap (=naproxen)	2.67×10^4	$5.35x10^3$	3.27×10^4	1
$[Ni(nap)_2(MeOH)_4]$, **1**	1.47×10^5	4.51×10^4	1.35×10^4	2
$[Ni(nap)_2(bipy)(CH_3OH)]$, **2**	5.96×10^5	$3.25)\times10^5$	1.93×10^5	2
$[Ni(nap)_2(phen)(H_2O)]$, **3**	1.54×10^5	4.18×10^5	2.73×10^4	2
$[Ni(nap)_2(bipyam)]$, **4**	2.91×10^5	4.59×10^4	1.88×10^5	2
$[Ni(nap)_2(Hpko)_2]$, **5**	8.01×10^5	1.08×10^5	3.02×10^4	2
$[Ni(nap)_2(py)_2(H_2O)_2]$, **6**	6.14×10^5	7.44×10^3	4.05×10^4	2
$[Cu(nap)_2(bipy)]$	3.86×10^4	1.20×10^4	3.20×10^4	1
$[Cu(nap)_2(phen)]$	9.20×10^3	1.90×10^4	7.69×10^4	1
$[Cu_2(nap)_4(H_2O)_2]$	2.27×10^4	6.61×10^4	7.83×10^4	1
$[Cu(nap)_2(py)_2(H_2O)]$	8.97×10^3	2.55×10^4	9.55×10^3	1
$[Co(nap)_2(MeOH)_4]$	3.15×10^4	1.25×10^5	3.20×10^4	1
$[Co(nap)_2(py)_2(H_2O)_2]$	2.29×10^4	2.64×10^4	2.69×10^4	1
$[Co(nap)_2(phen)(H_2O)_2]$	2.76×10^4	1.07×10^5	1.58×10^4	1
$[Co(nap)_2(bipy)(H_2O)_2]$	3.58×10^4	3.06×10^4	2.19×10^4	1
Hmef (=mefenamic acid)	1.05×10^5	1.35×10^5	1.32×10^5	3
$[Ni(mef)_2(bipy)(MeOH)_2]$	1.20×10^5	3.23×10^5	2.44×10^5	4
$[Ni(mef)_2(phen)(MeOH)_2]$	8.26×10^4	3.10×10^5	2.23×10^5	4
$[Ni(mef)_2(bipyam)]$	1.46×10^5	2.33×10^5	2.03×10^5	4
$[Ni(mef)_2(Hpko)_2]$	1.15×10^6	1.35×10^5	3.42×10^5	4
$[Ni(mef)_2(py)_2(H_2O)_2]$	1.19×10^5	3.22×10^5	3.85×10^5	4
$[Ni(mef)_2(MeOH)_4]$	2.62×10^5	2.11×10^5	3.00×10^5	4
Htolf (=tolfenamic acid)	5.00×10^4	1.60×10^5	3.12×10^5	5
$[Ni(tolf)_2(H_2O)_4]$	9.50×10^4	3.76×10^5	1.59×10^5	6
$[Ni(tolf)_2(bipy)(MeOH)_2]$	2.35×10^5	3.73×10^5	2.23×10^5	6
$[Ni(tolf)_2(phen)(MeOH)_2]$	1.11×10^6	4.92×10^5	1.46×10^6	6
$[Ni(tolf)_2(bipyam)]$	8.87×10^5	4.86×10^5	1.32×10^5	6
$[Ni(tolf)_2(Hpko)_2]$	2.80×10^5	3.12×10^5	2.08×10^6	6
$[Ni(tolf)_2(py)_2(MeOH)_2]$	2.01×10^6	1.57×10^5	1.44×10^5	6

Hfluf (=flufenamic acid)	2.70×10^{5}	1.06×10^{6}	1.79×10^{5}	7
$[Ni(fluf)_2(MeOH)_4]$	6.68×10^{4}	2.75×10^{6}	3.48×10^{5}	8
$[Ni(fluf)_2(bipyam)]$	7.18×10^{5}	2.32×10^{6}	1.16×10^{6}	8
$[Ni(fluf)_2(phen)(MeOH)_2]$	3.09×10^{4}	1.29×10^{6}	5.86×10^{5}	8
$[Ni(fluf)_2(bipy)(MeOH)_2]$	6.98×10^{4}	1.50×10^{6}	8.41×10^{5}	8
Hdifl (=diflunisal)	3.08×10^{3}	1.93×10^{5}	1.22×10^{5}	9
$[Ni(difl)_2(MeOH)_4]$	2.00×10^{5}	1.69×10^{5}	1.41×10^{5}	10
$[Ni(difl)_2(Hpko)_2]$	8.57×10^{5}	9.78×10^{4}	1.25×10^{5}	10
$[Ni(difl)_2(phen)(MeOH)_2]$	8.35×10^{4}	9.70×10^{4}	2.68×10^{5}	10
$[Ni(difl)_2(bipy)(MeOH)_2]$	1.06×10^{6}	7.33×10^{4}	2.66×10^{5}	10
$[Ni(difl)_2(bipyam)]$	2.00×10^{5}	1.04×10^{5}	1.60×10^{5}	10

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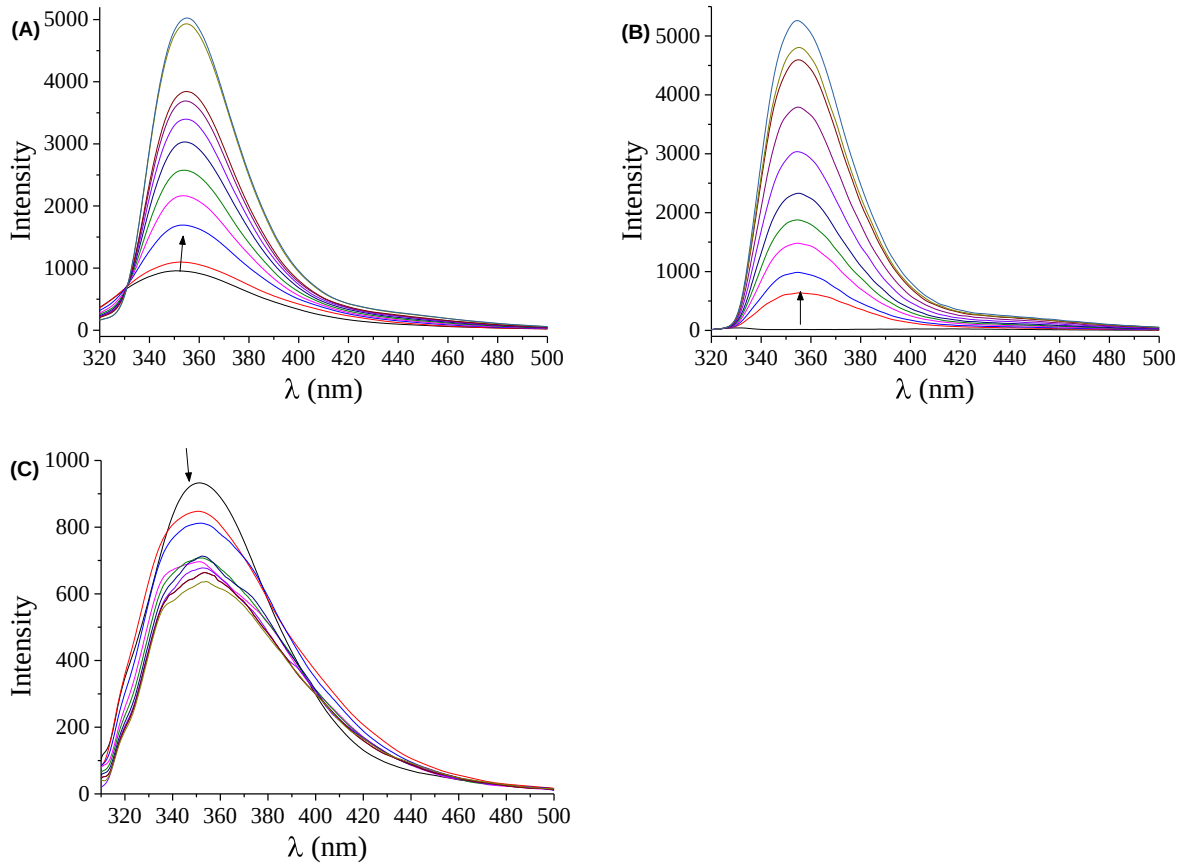

Figure S1. Fluorescence emission spectra (λ_{ex} = 295 nm) of (A) of HSA (3 μM) in buffer solution (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0) in the presence of increasing amounts of complex **2,** (B) of buffer solution (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0) in the presence of increasing amounts of complex **2** and (C) of HSA (A) after subtraction of (B) in the presence of increasing amounts of complex **2.** The arrows show the changes upon increasing amounts of the complex.

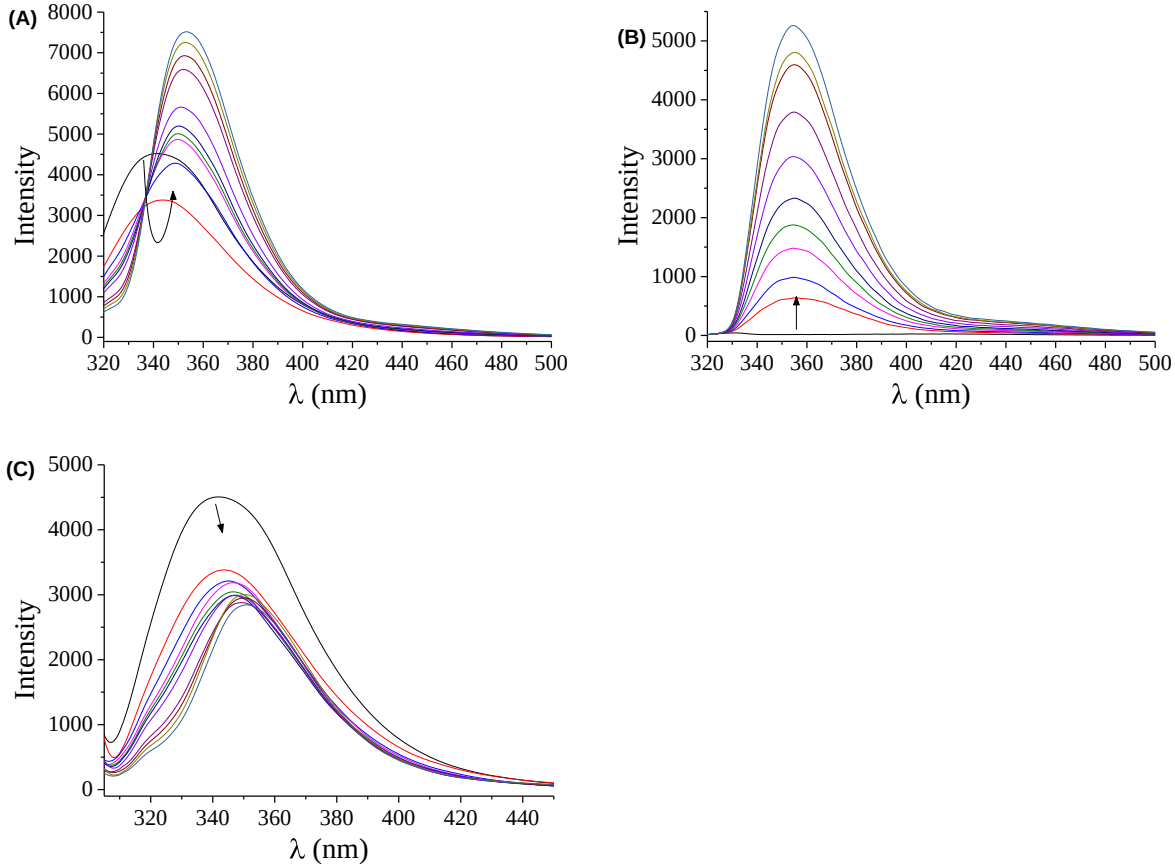

Figure S2. Fluorescence emission spectra (λ_{ex} = 295 nm) of (A) of BSA (3 μM) in buffer solution (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0) in the presence of increasing amounts of complex **2,** (B) of buffer solution (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0) in the presence of increasing amounts of complex **2** and (C) of BSA (A) after subtraction of (B) in the presence of increasing amounts of complex **2.** The arrows show the changes upon increasing amounts of the complex.

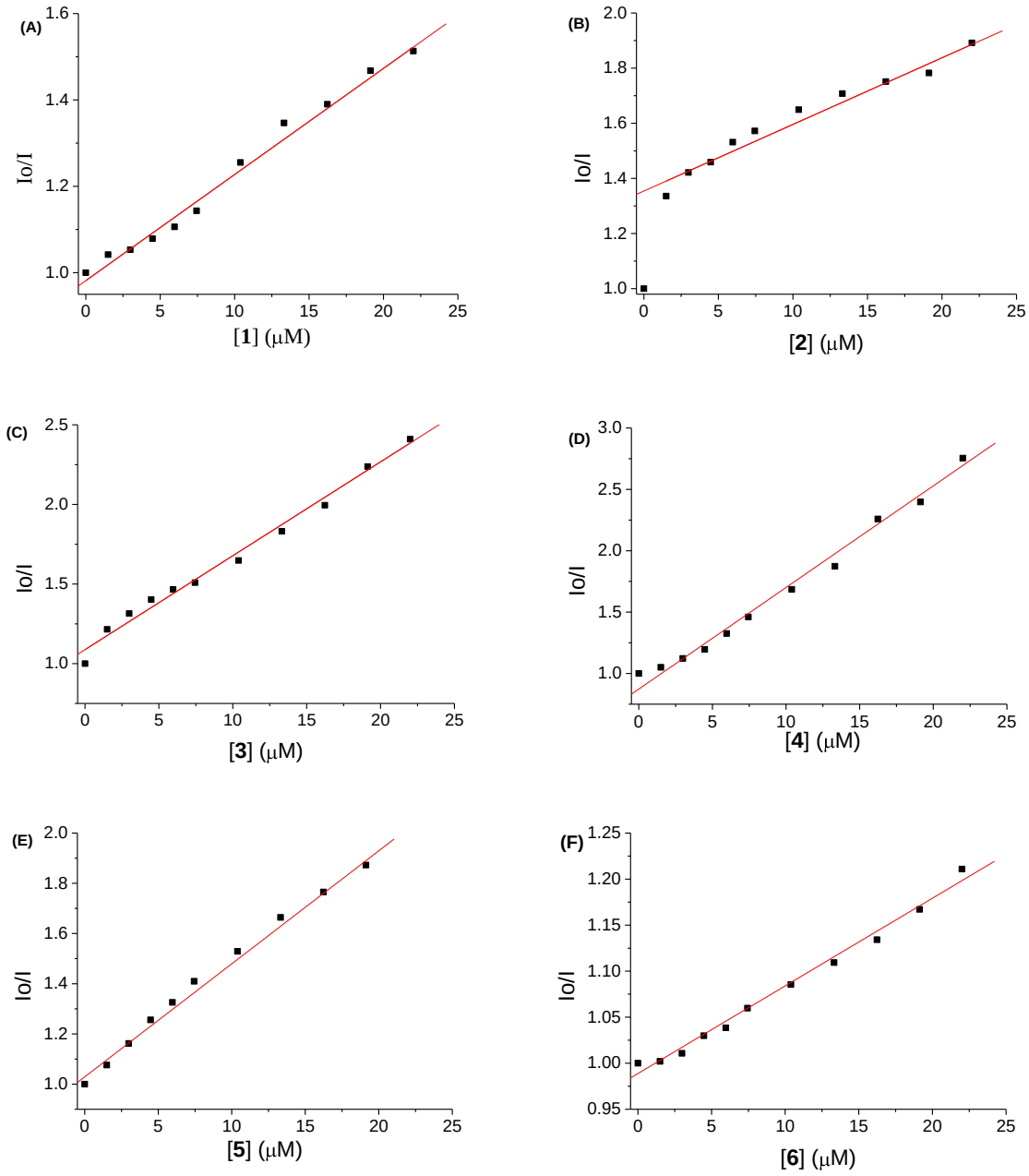

Figure S3. Stern-Volmer quenching plot of BSA for complexes (A)-(F) **1**-**6**, respectively.

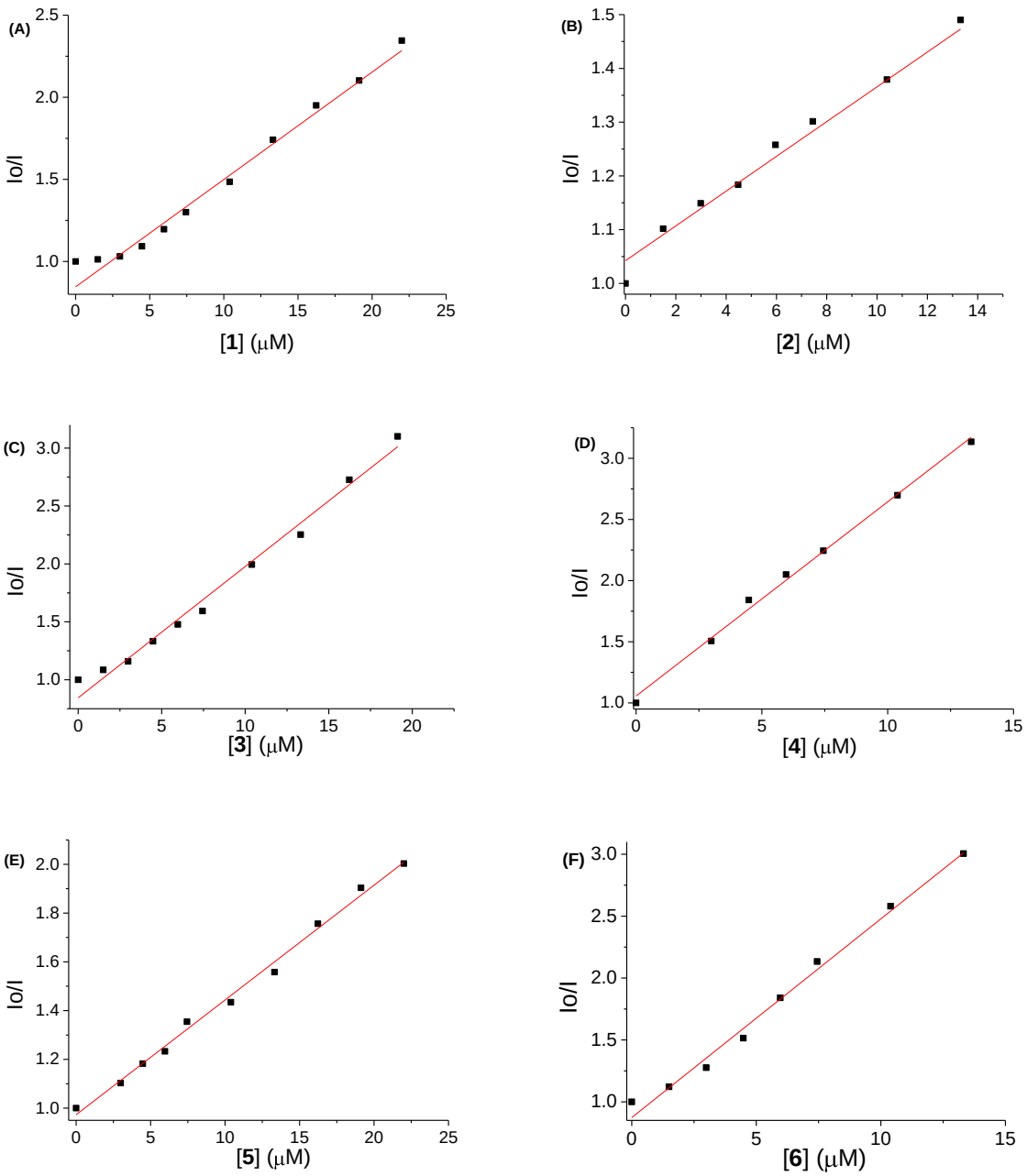

Figure S4. Stern-Volmer quenching plot of HSA for complexes (A)-(F) **1**-**6**, respectively.

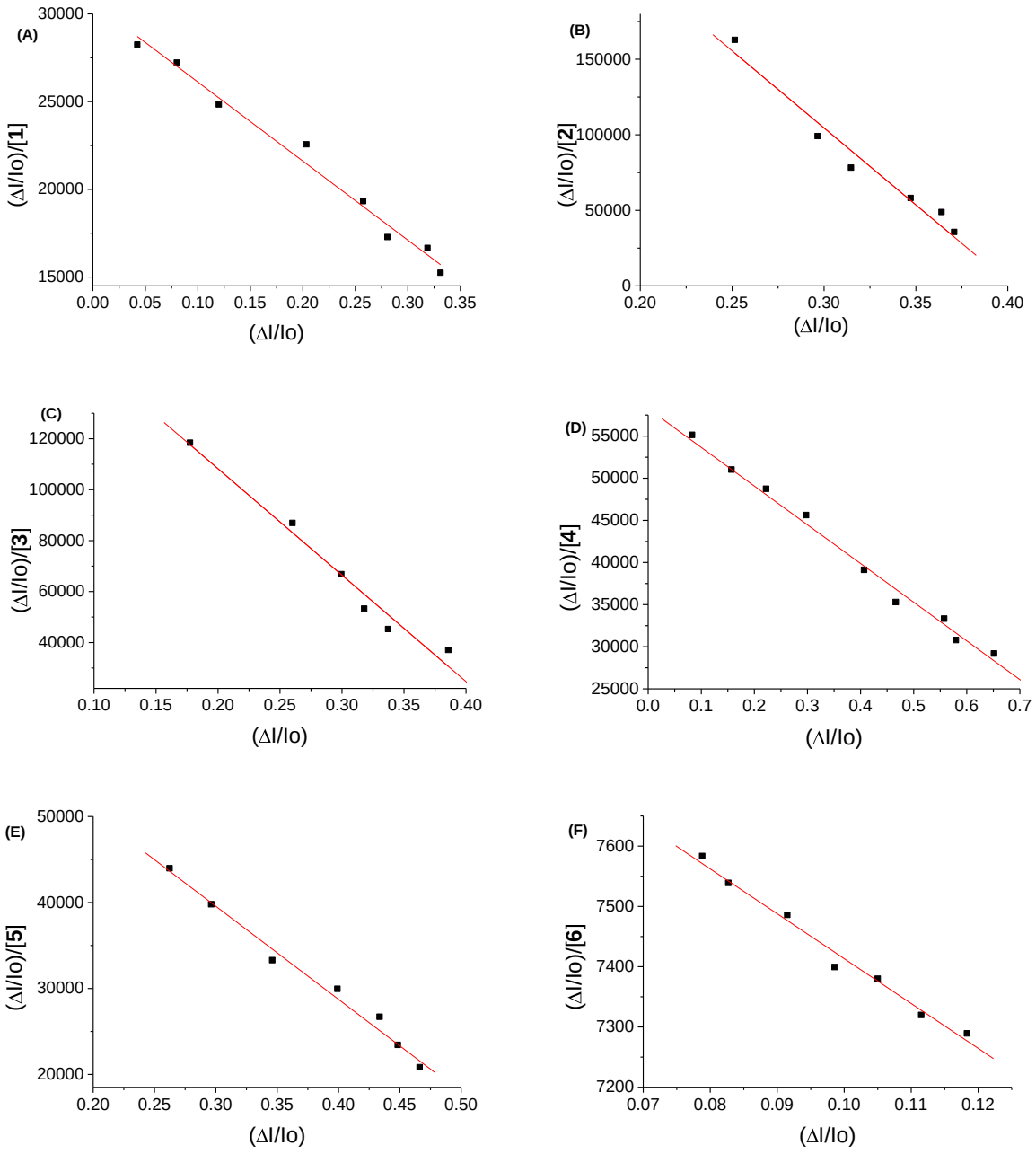

Figure S5. Scatchard plot of BSA for complexes (A)-(F) **1-6**, respectively.

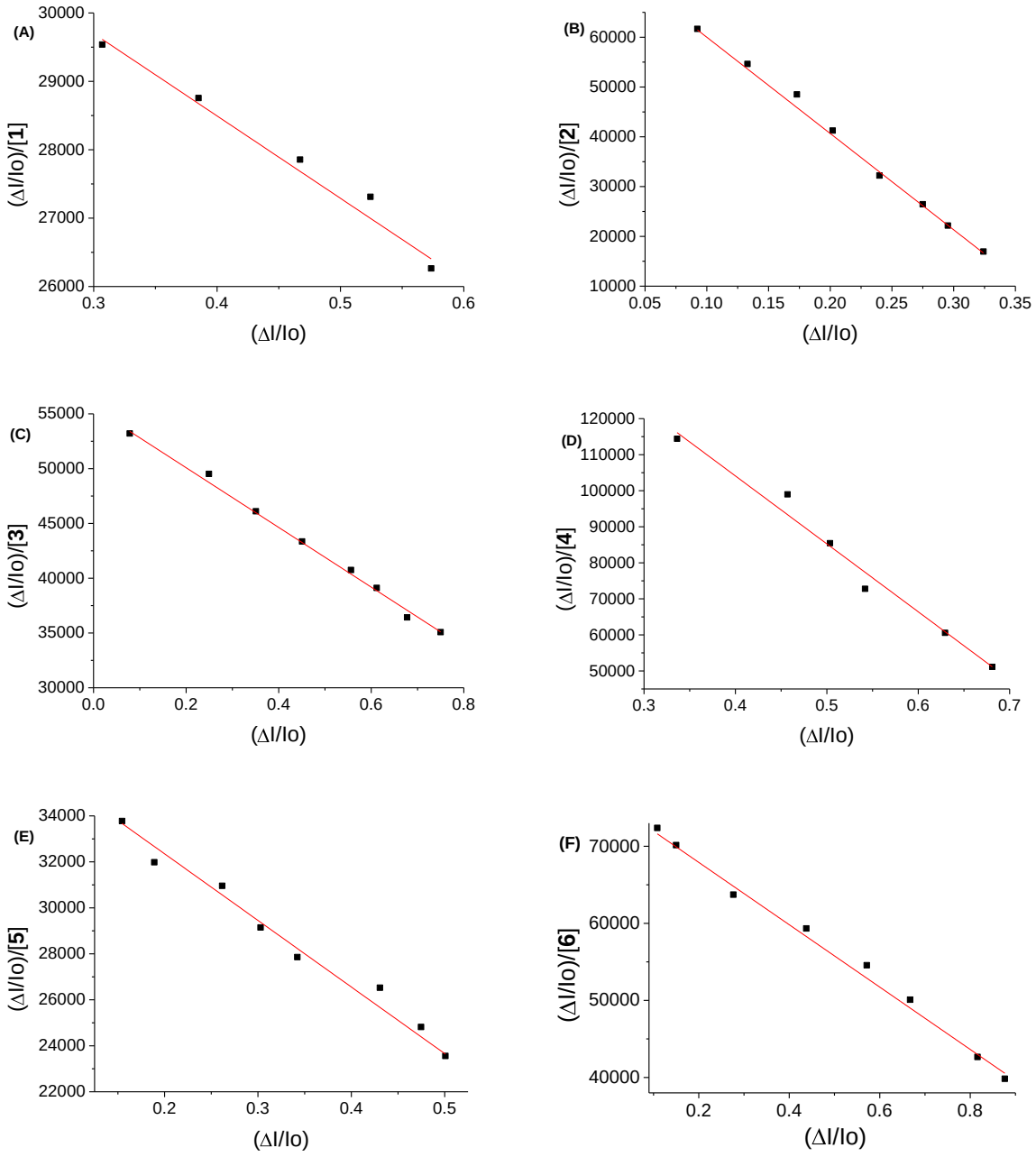

Figure S6. Scatchard plot of HSA for complexes (A)-(F) **1**-**6**, respectively.

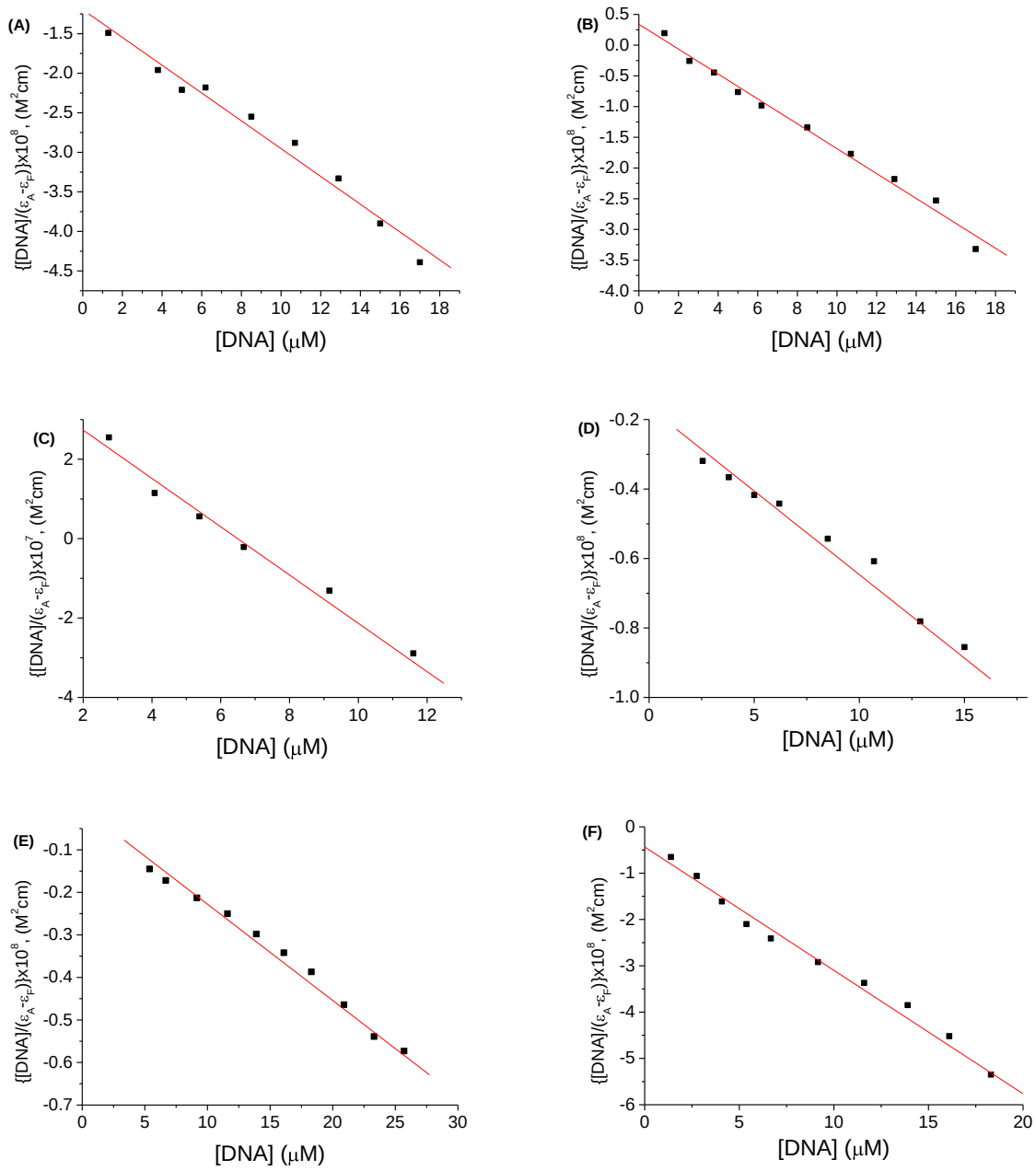

Figure S7. Plot of [DNA]/(ε_A-ε_f) vs [DNA] for complexes (A)-(F) **1-6**, respectively.

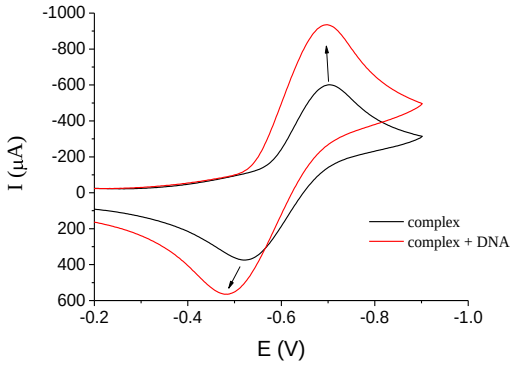

Figure S8. Cyclic voltammogram of 0.33 mM 1/2 dmso/buffer (containing 150 mM NaCl and 15 mM trisodium citrate at pH 7.0) solution of $[Ni(nap)_2(MeOH)_4]$, **1**in the absence or presence of CT DNA. Scan rate = 100 mV s^{-1}. Supporting electrolyte = buffer solution.

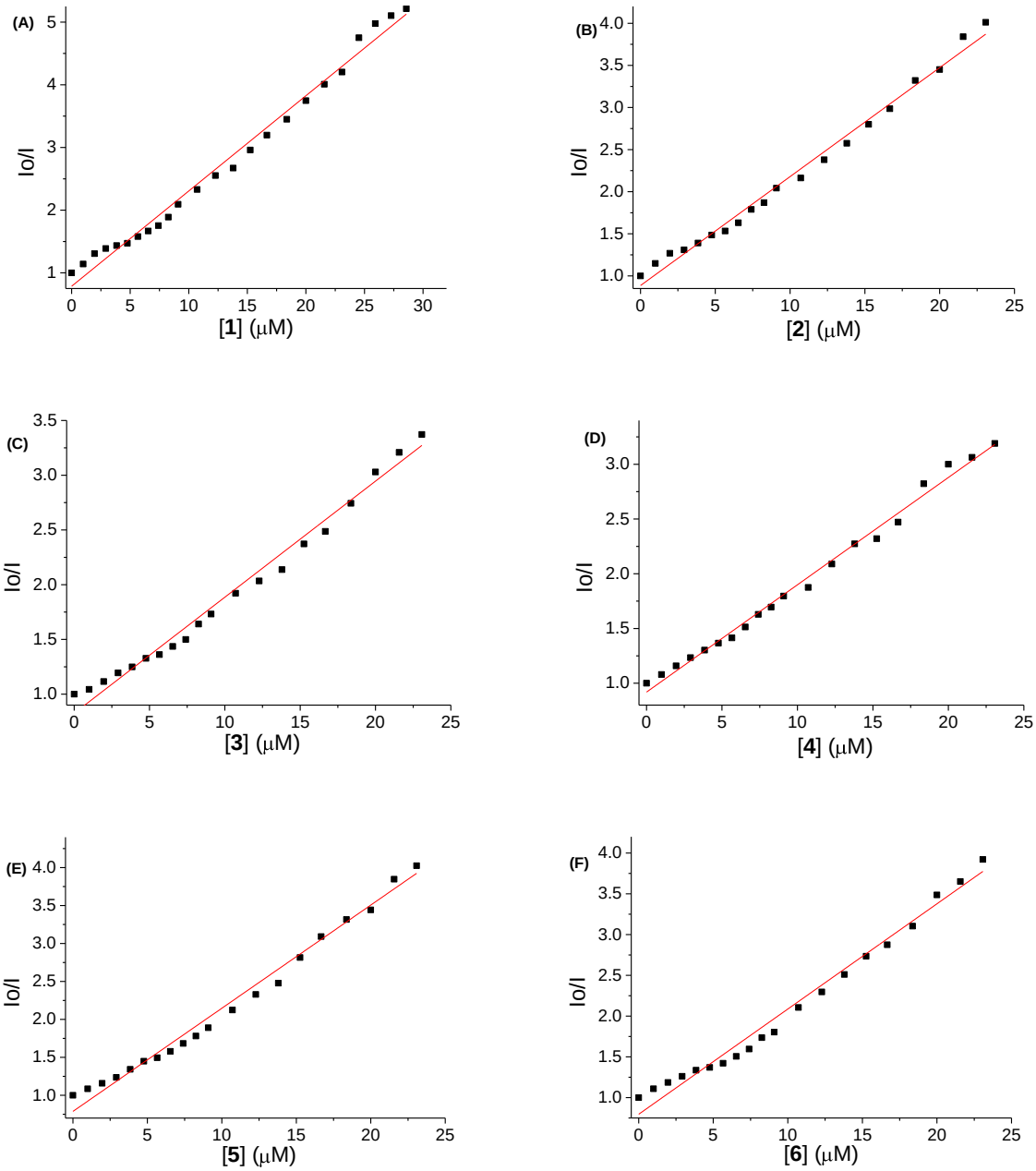

Figure S9. Stern-Volmer quenching plot of EB-DNA fluorescence for complexes (A)-(F) **1**-**6**, respectively.