Supplementary Information

Increasing the Cytotoxicity of Ru(II) Polypyridyl Complexes by tuning the Electronic Structure of Dioxo Ligands

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1) **Table S1.** UV/Vis/NIR absorptions of the complexes in their native and electrochemically generated states in DMF.

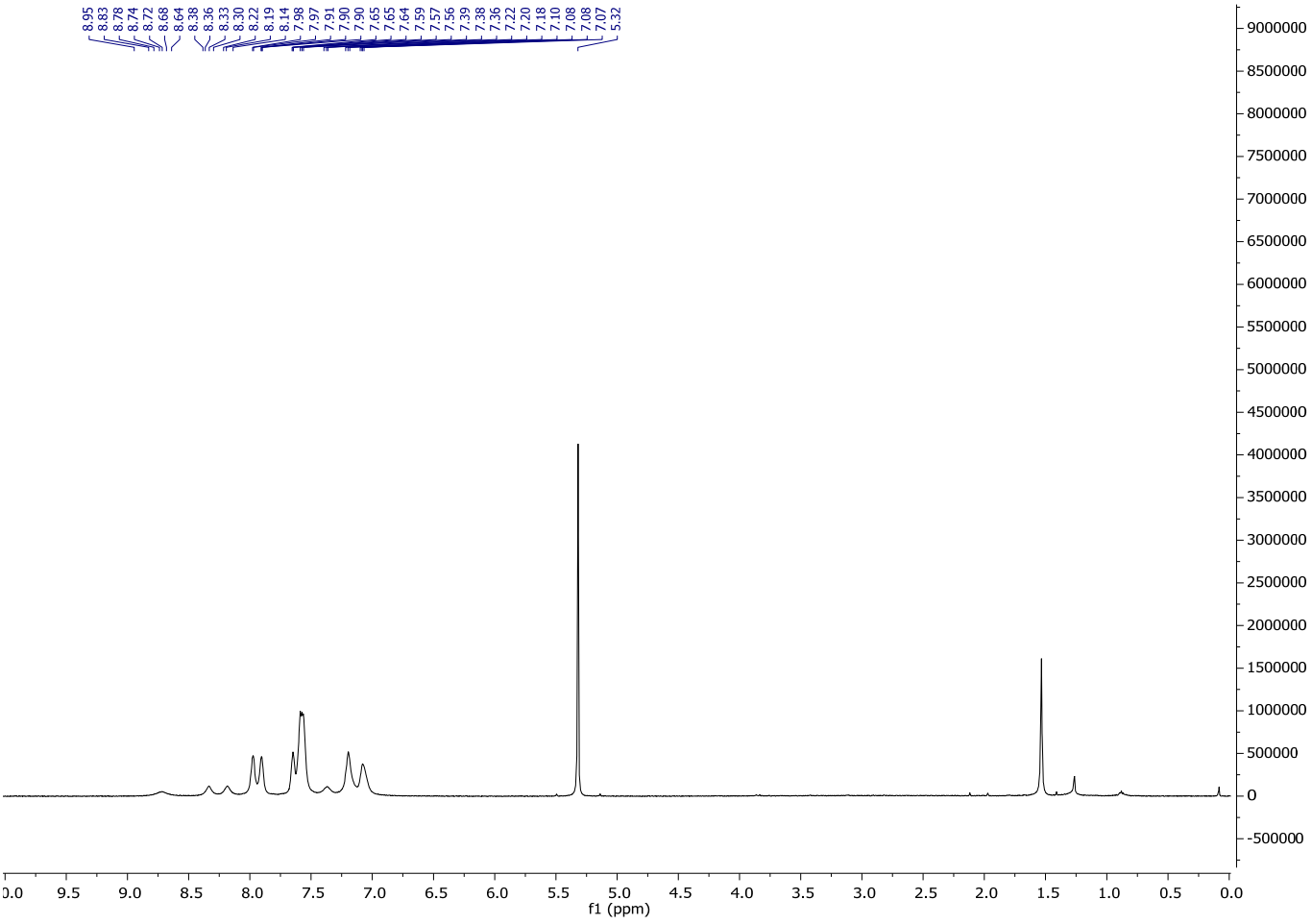
compound	oxidation state	λ_{max}
1	0	810(br) 650 535
	1+	885 510, 470
	2+	675 405(sh) 350(sh)
2	0	810(br) 655 535
	1+	890 520, 470
	2+	675 405(sh) 350(sh)
3	1+	900 525, 490
4	1+	895 525, 480
5	0	675(sh) 600, 505 345(sh)
	1+	985-845 465, 410
	2+[a]	430 (sh), 390
6	0	675(sh) 590, 510(sh) 375

Electrochemically generated species in DMF / 0.1M NBu_4PF_6,

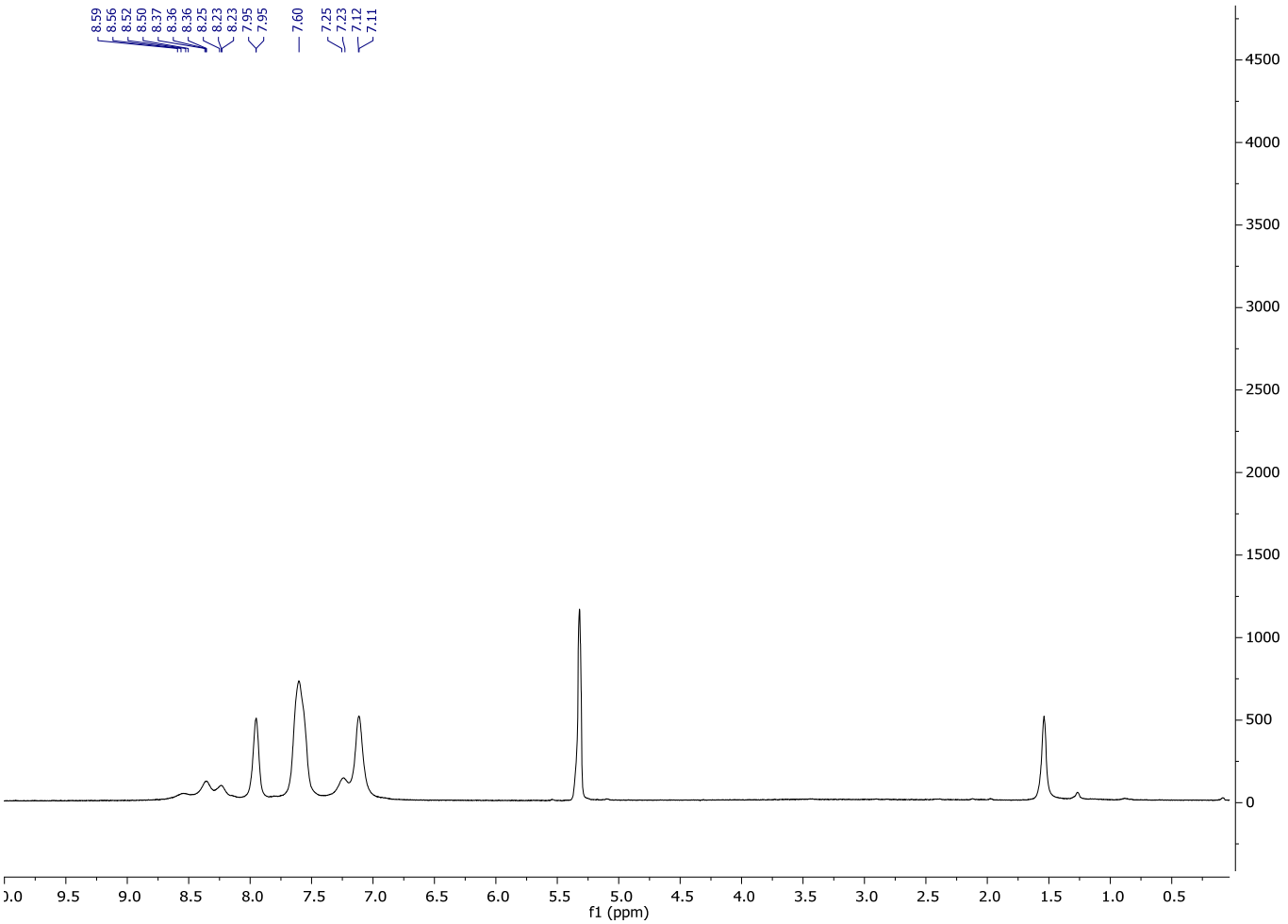
[a] irreversible

2) Figure S1. NMR spectra of complexes **1-6**.

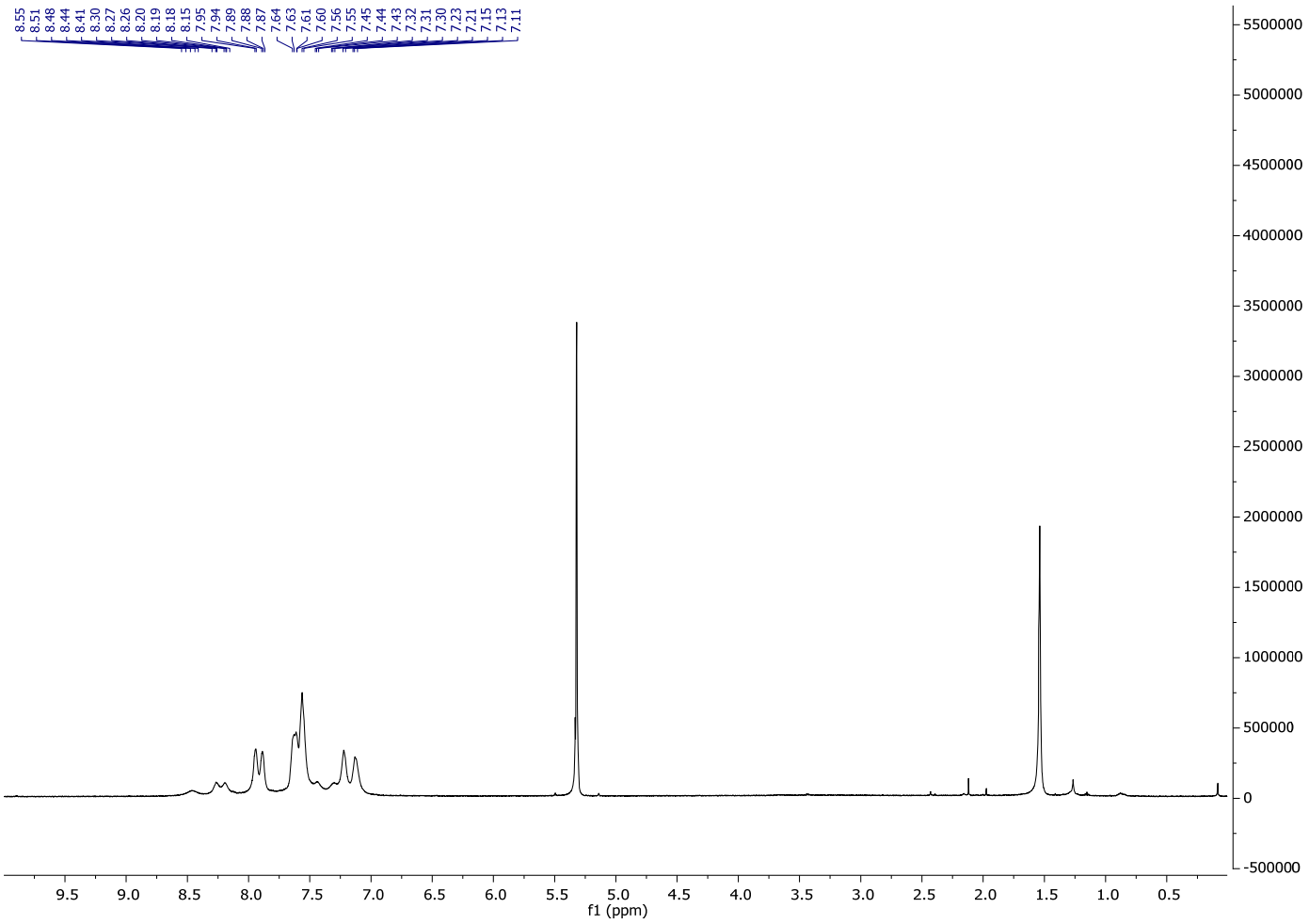
(**1**), ^{1}H, CD_2Cl_2, 500 MHz



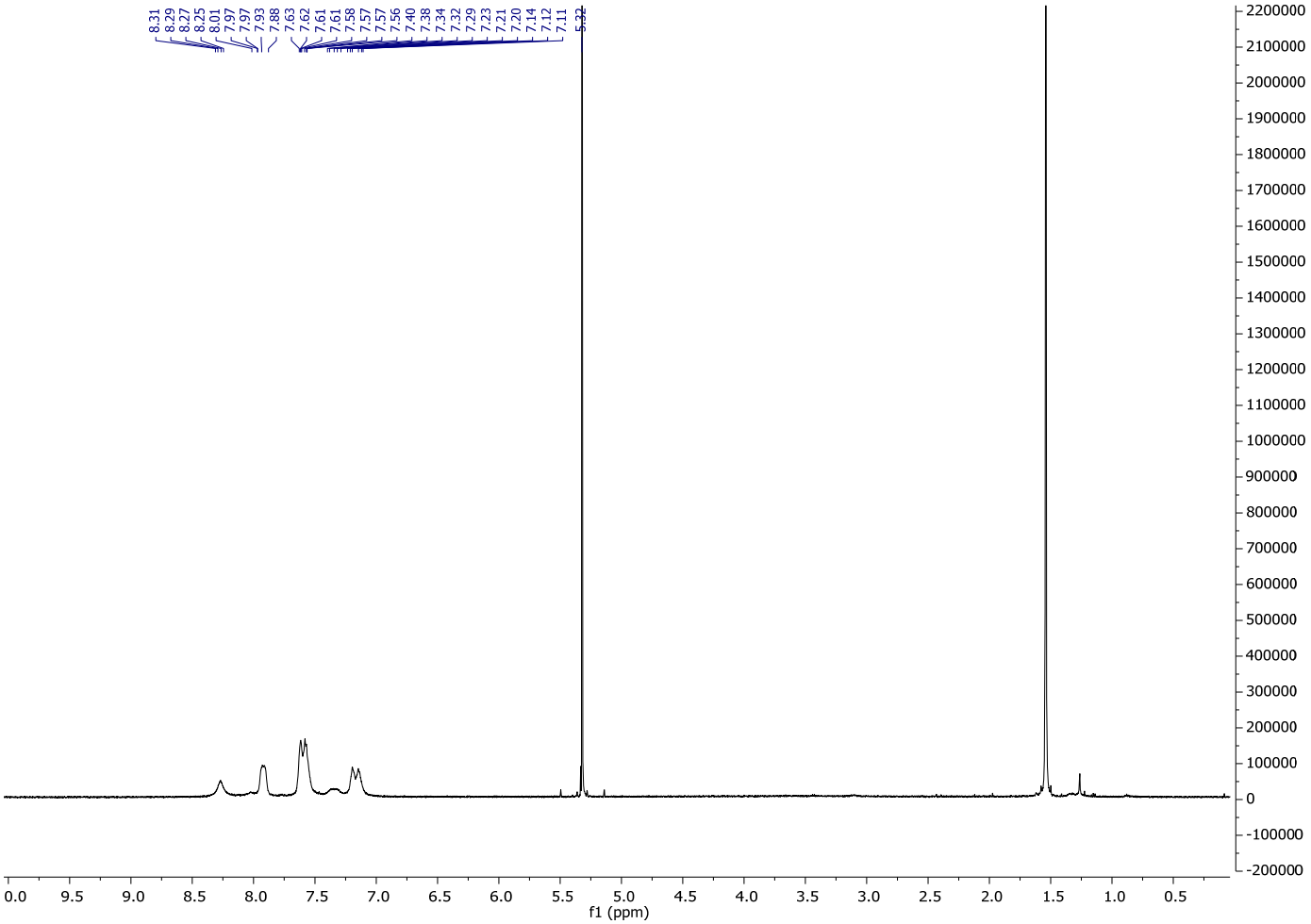
(**2**), ^{1}H, CD_2Cl_2, 400 MHz



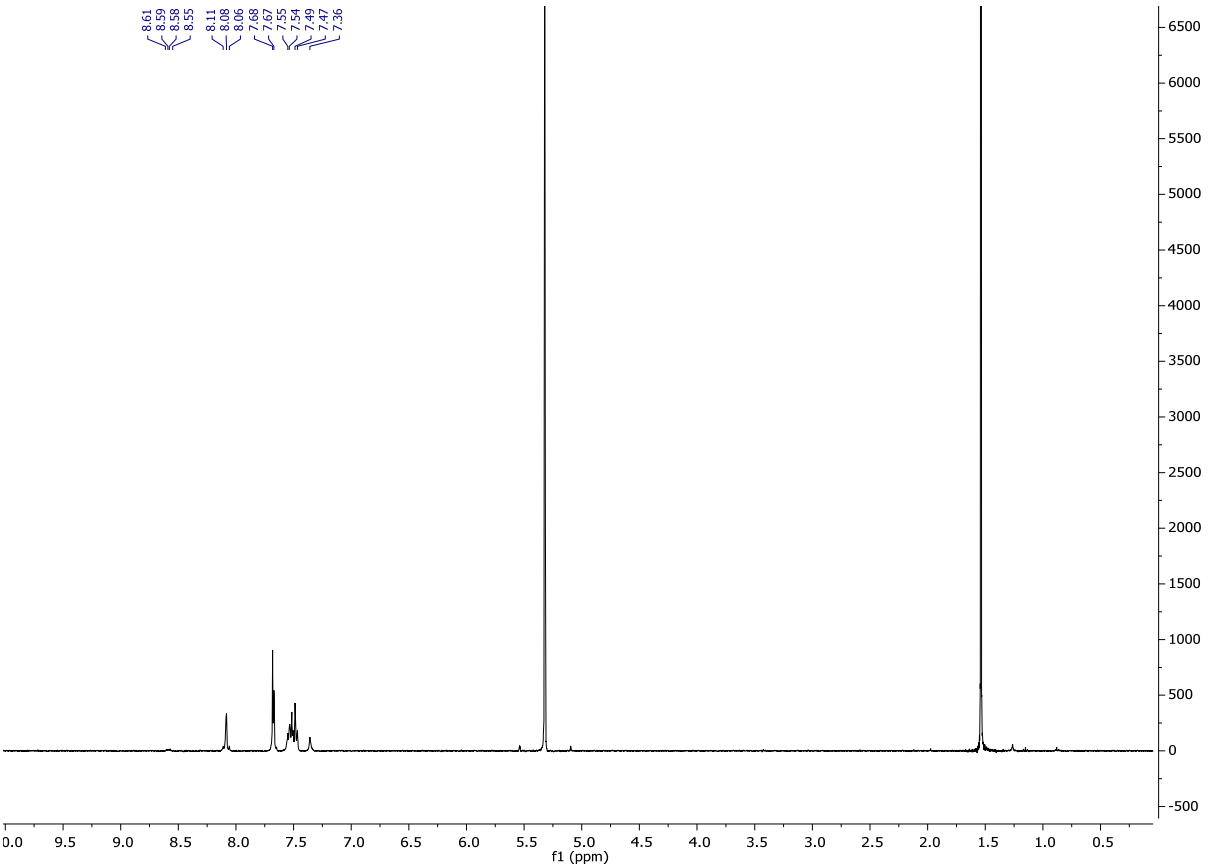
(**3**), ^{1}H, CD_2Cl_2, 500 MHz



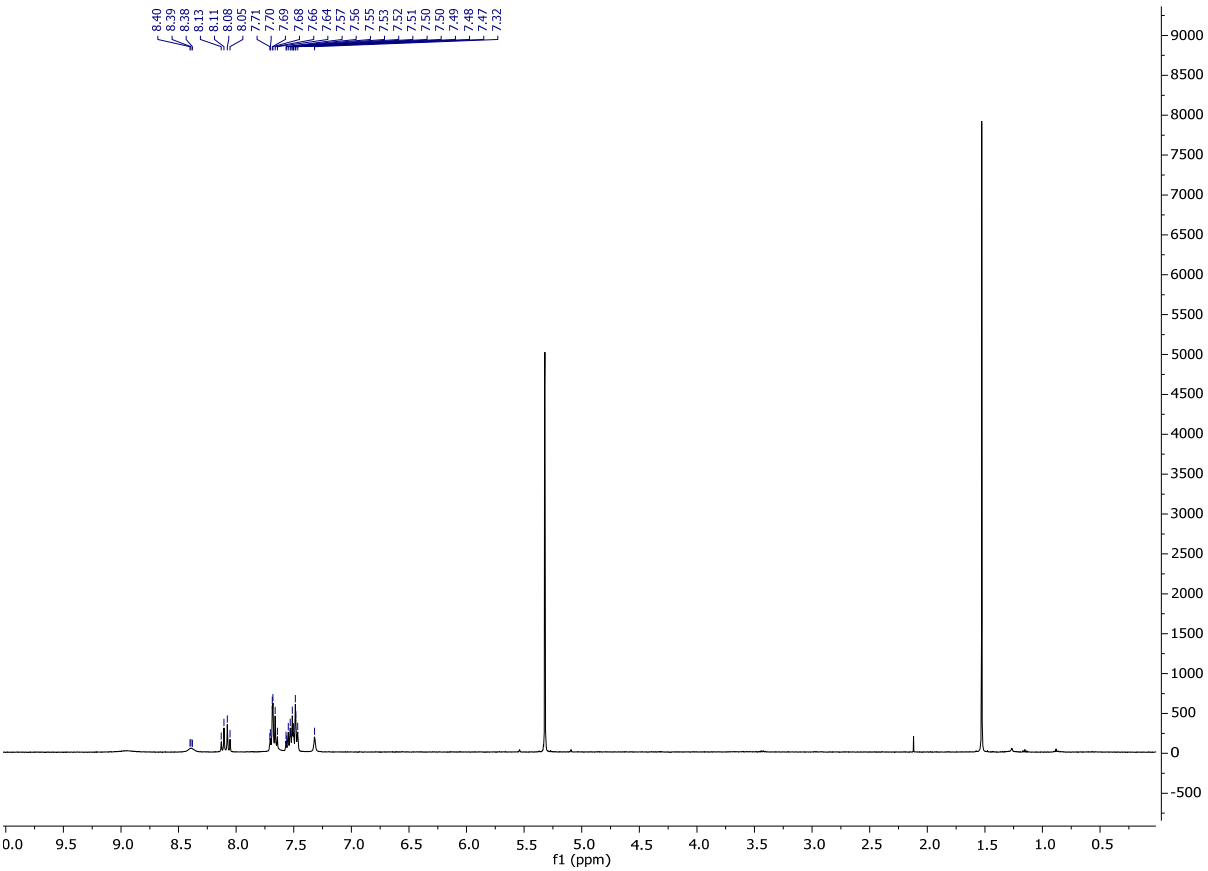
(**4**), ^{1}H, CD_2Cl_2, 500 MHz



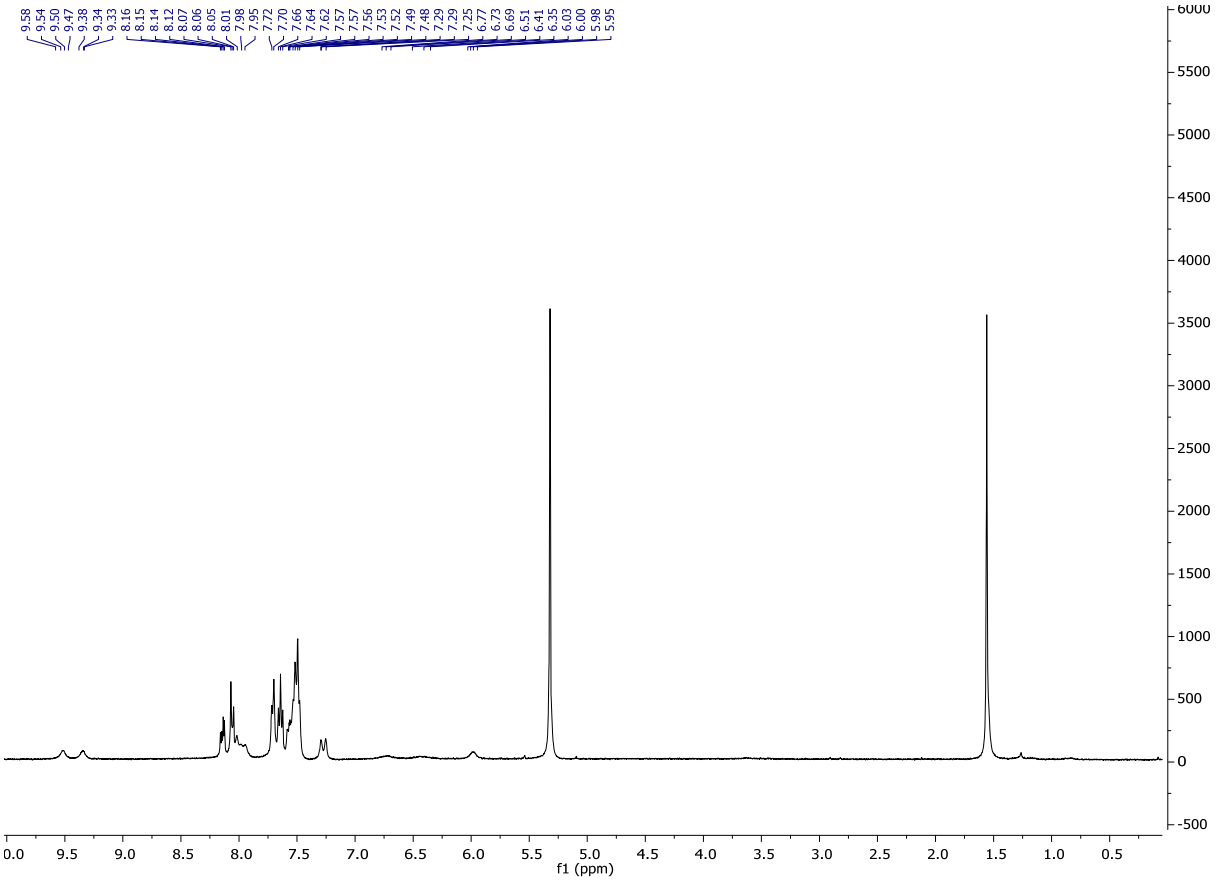
(**5**), ^{1}H, CD_2Cl_2, 400 MHz



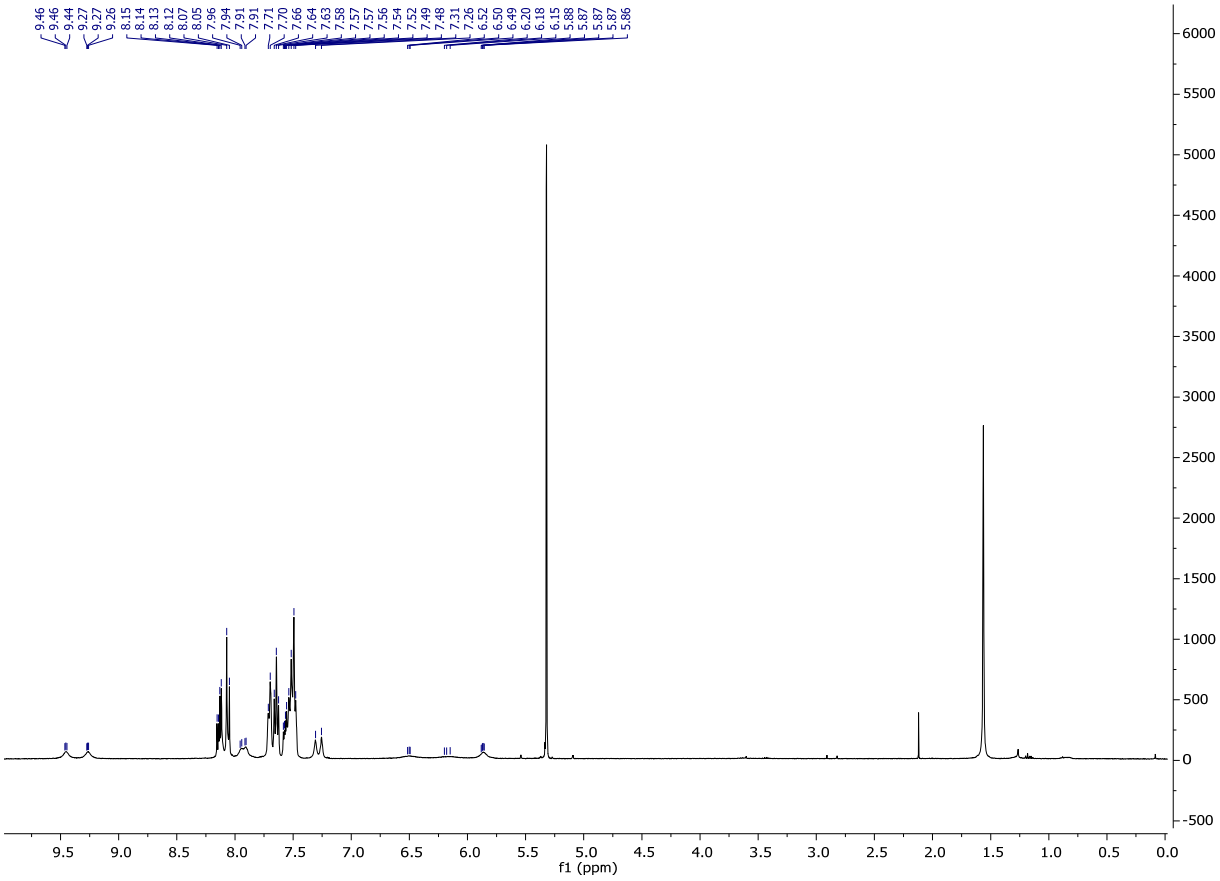
^{1}H, CD_2Cl_2, 400 MHz containing elemental Zinc



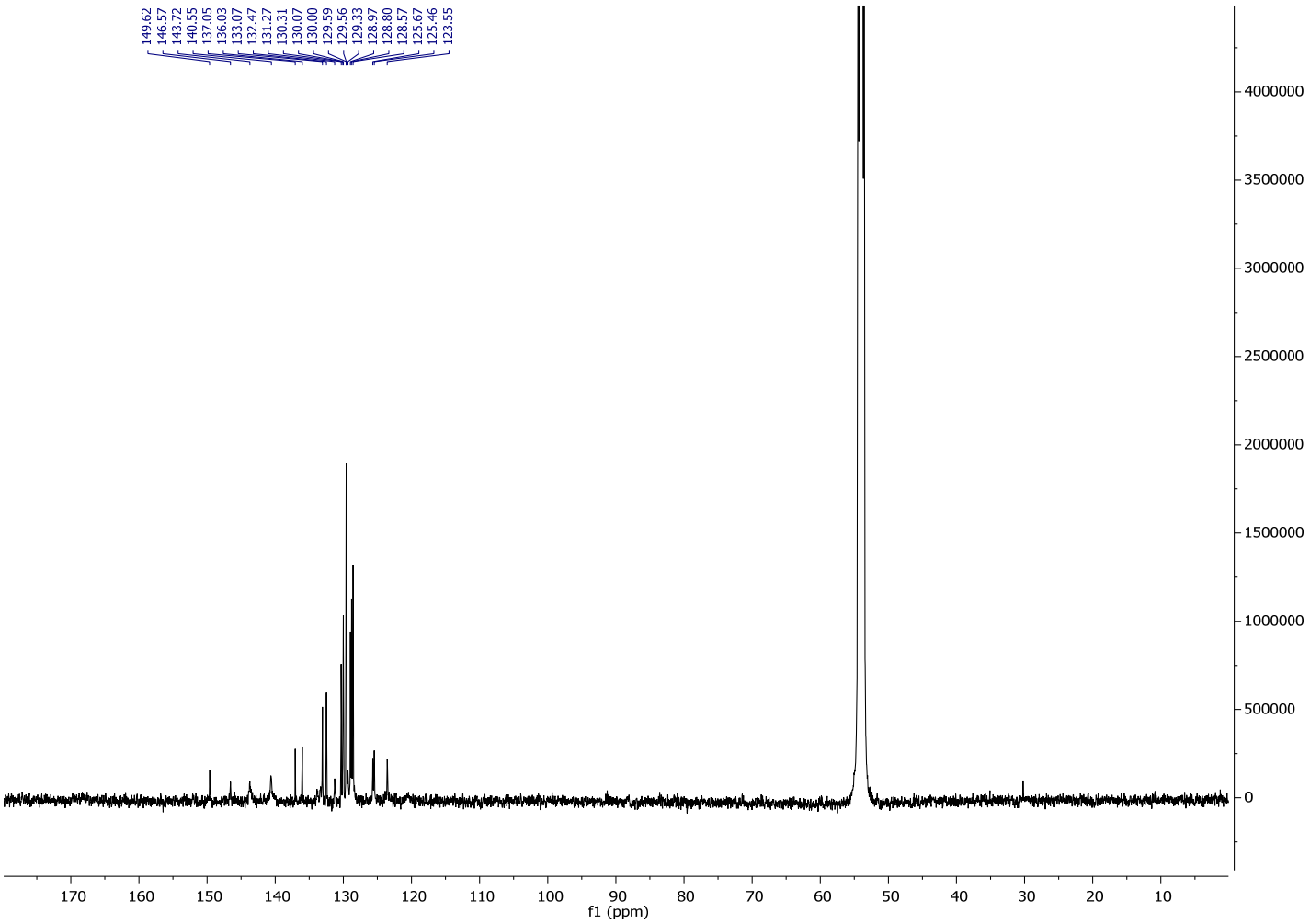
(**6**), ^{1}H, CD_2Cl_2, 400 MHz



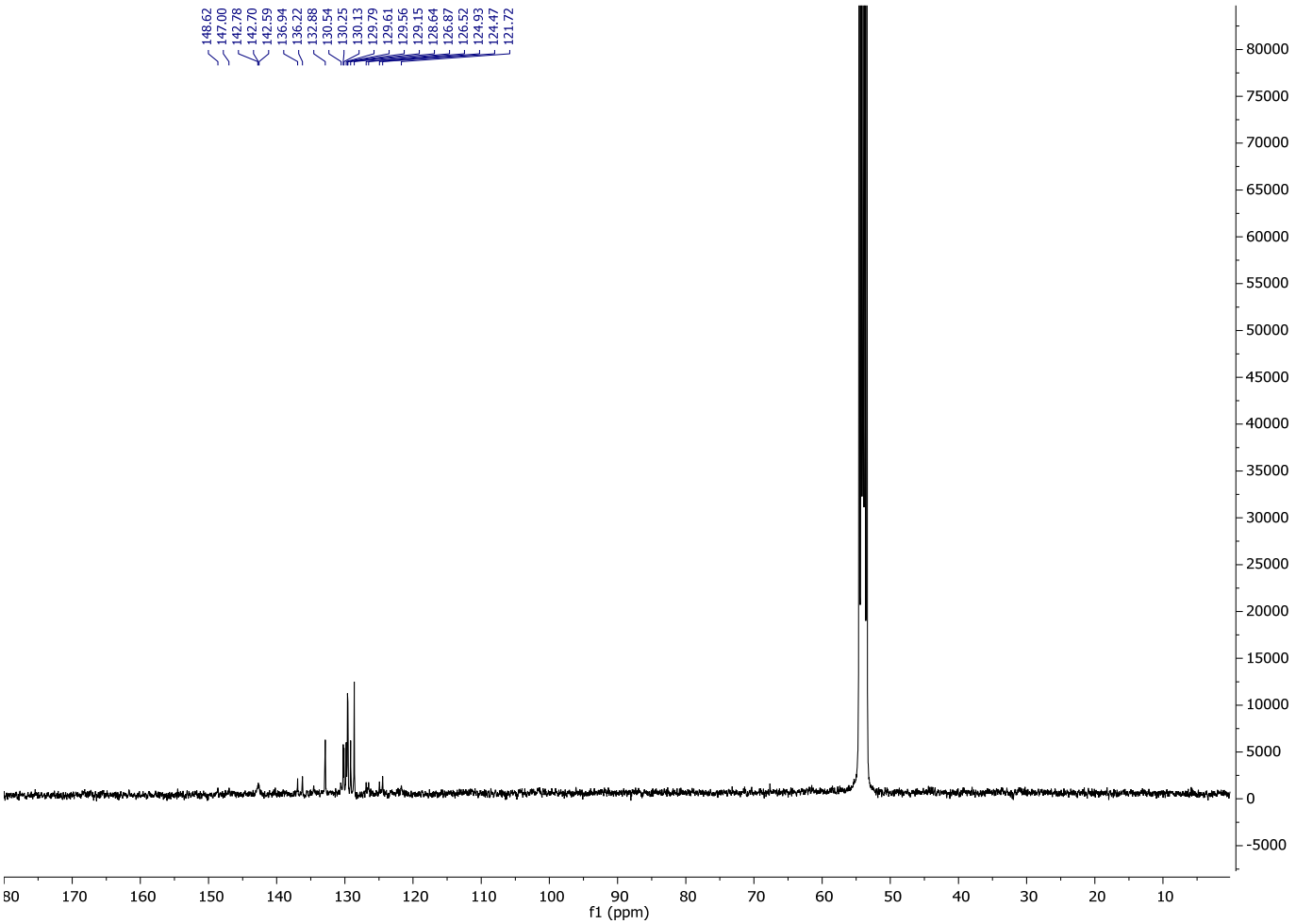
^{1}H, CD_2Cl_2, 400 MHz containing elemental Zinc



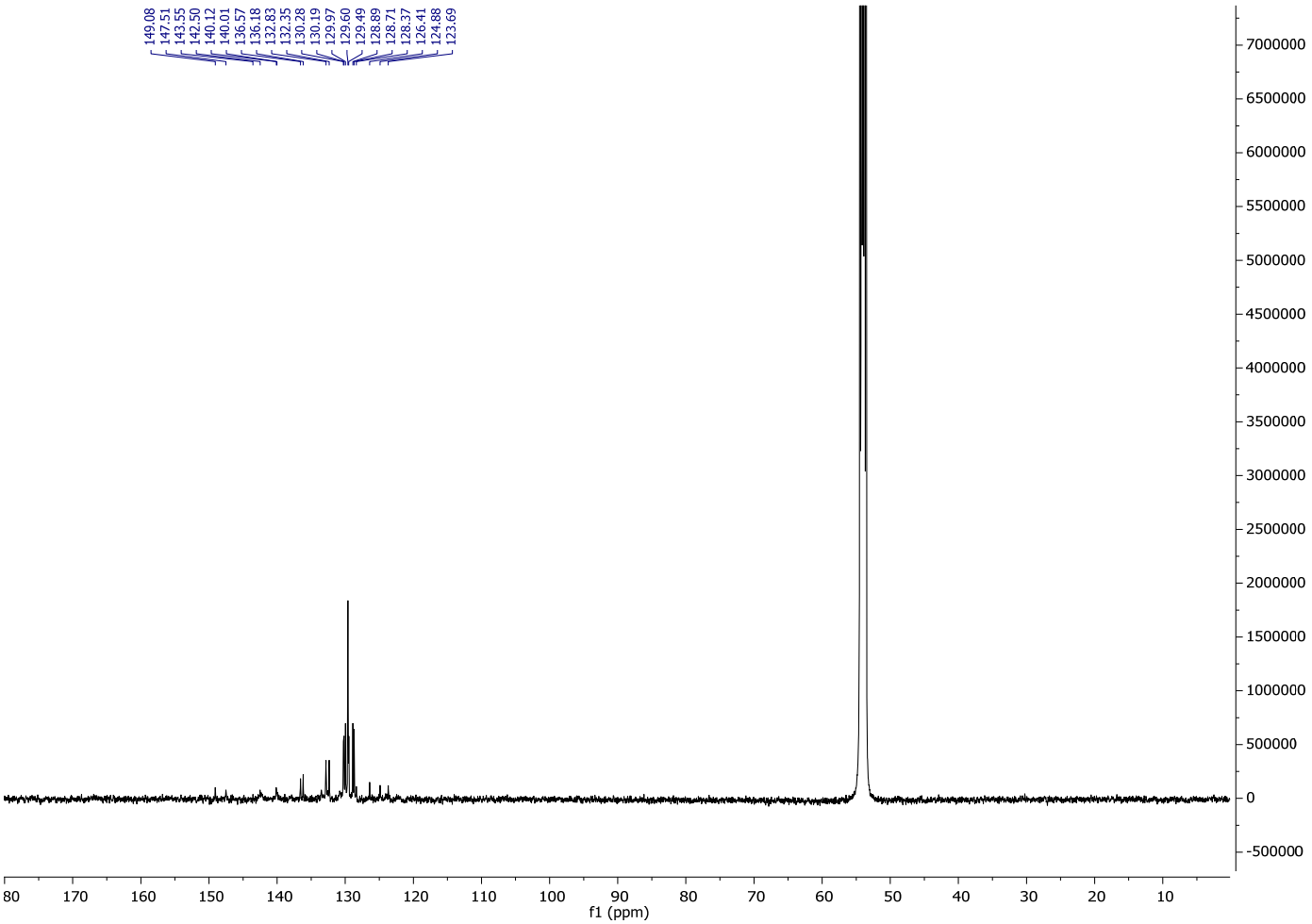
(**1**), ^{13}C, CD_2Cl_2, 125 MHz



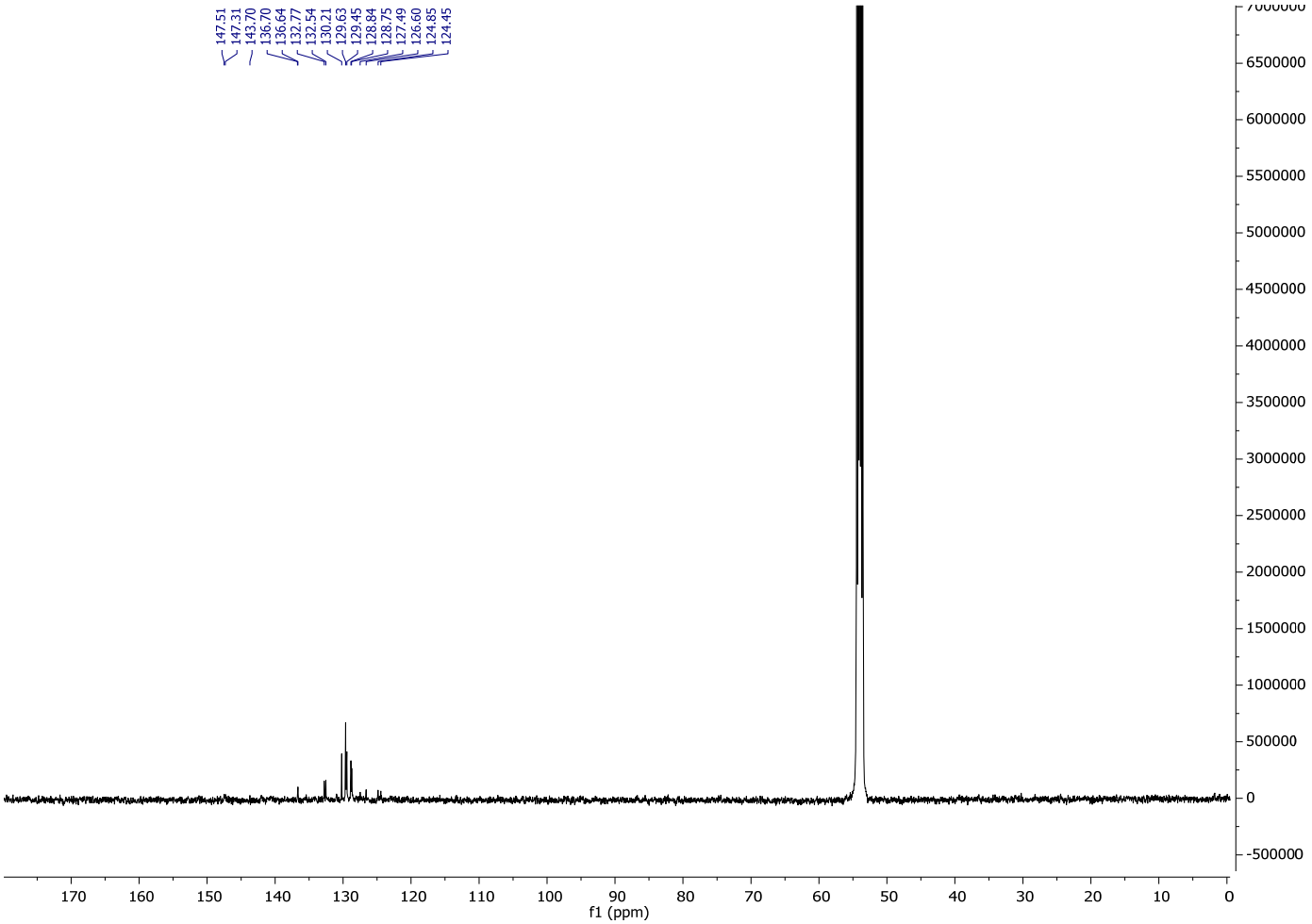
(**2**), ^{13}C, CD_2Cl_2, 125 MHz



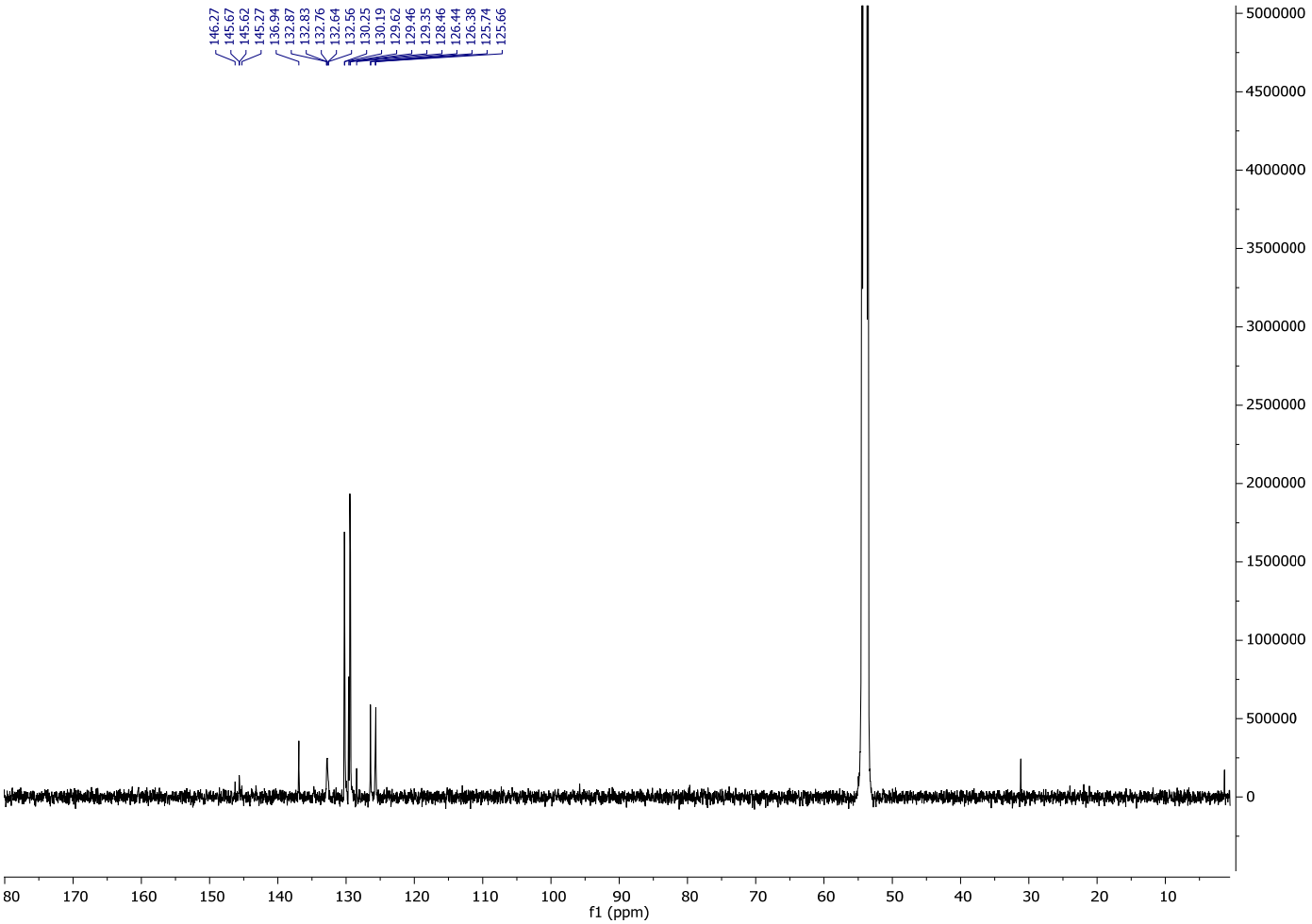
(**3**), ^{13}C, CD_2Cl_2, 125 MHz



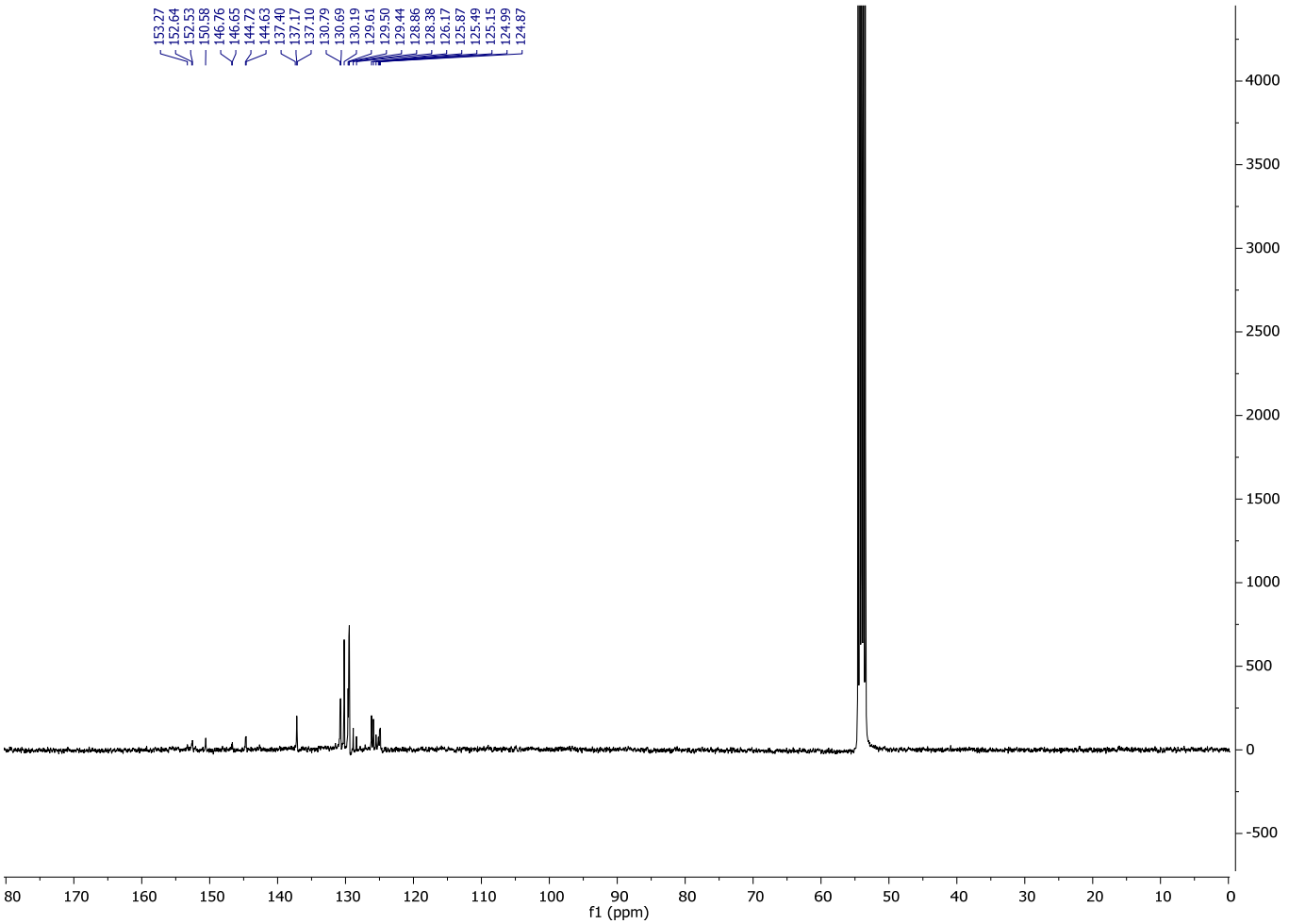
(**4**), ^{13}C, CD_2Cl_2, 125 MHz



(**5**), ^{13}C, CD_2Cl_2, 125 MHz

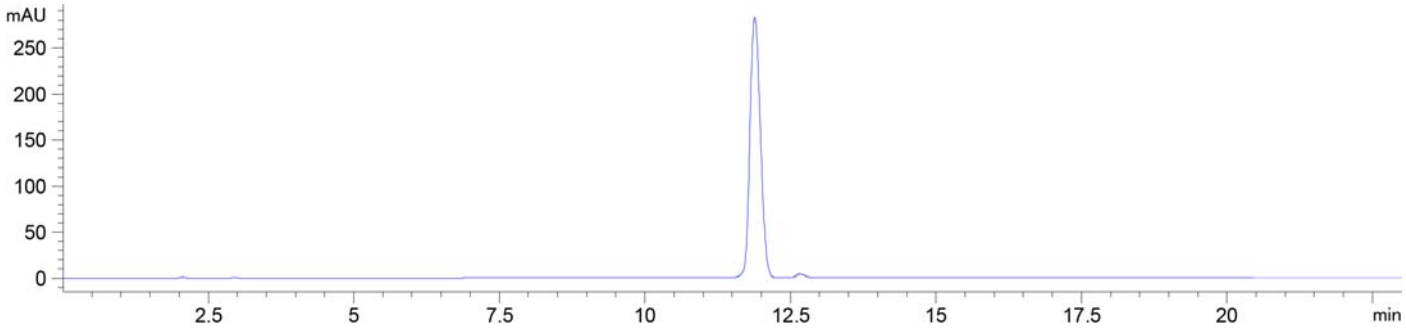


(**6**), ^{13}C, CD_2Cl_2, 100 MHz

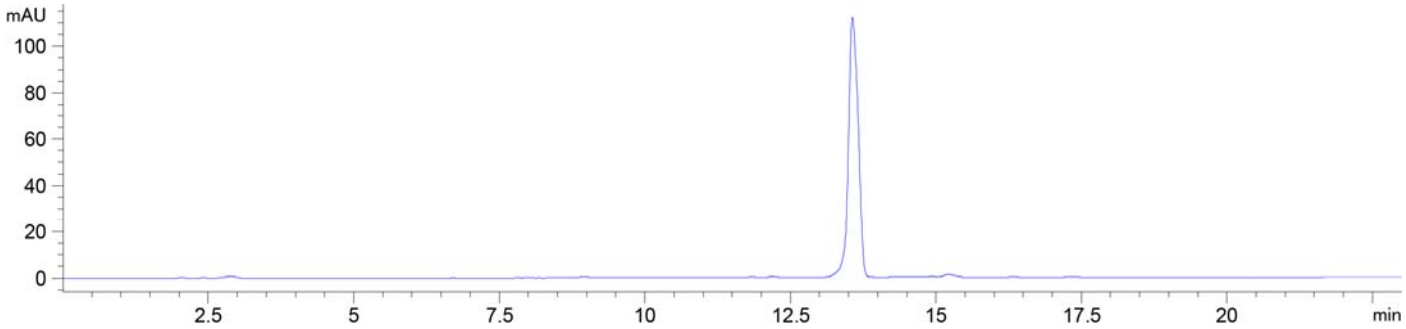


3) **Figure S2.** HPLC traces at 450 nm of complexes **1-6**.

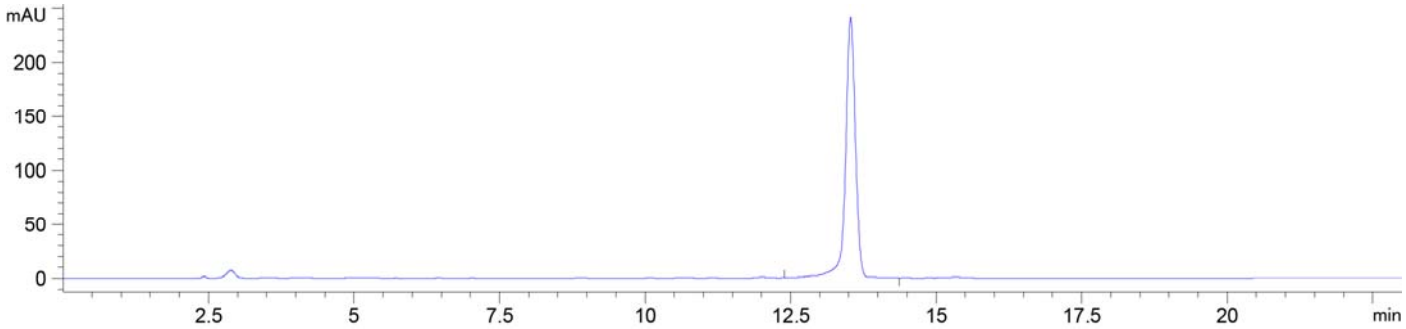
(**1**), HPLC trace 450 nm.



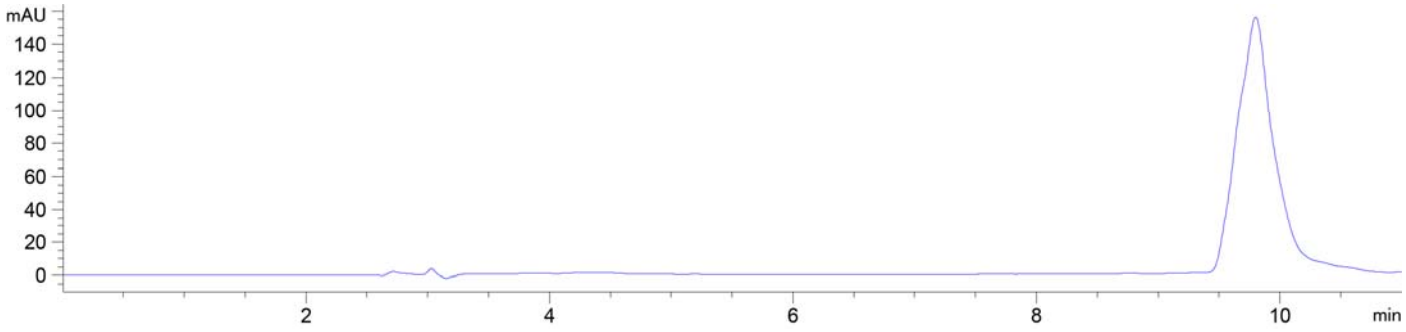
(**2**), HPLC trace 450 nm.



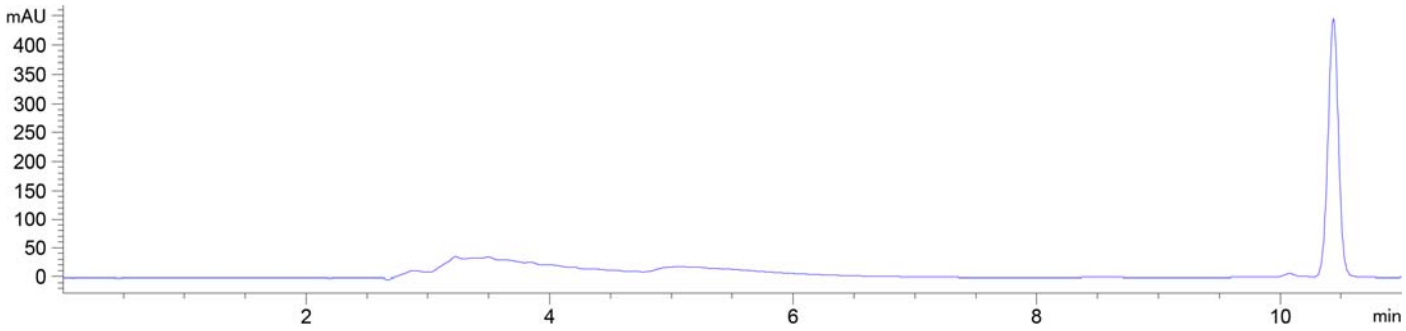
(**3**), HPLC trace 450 nm.



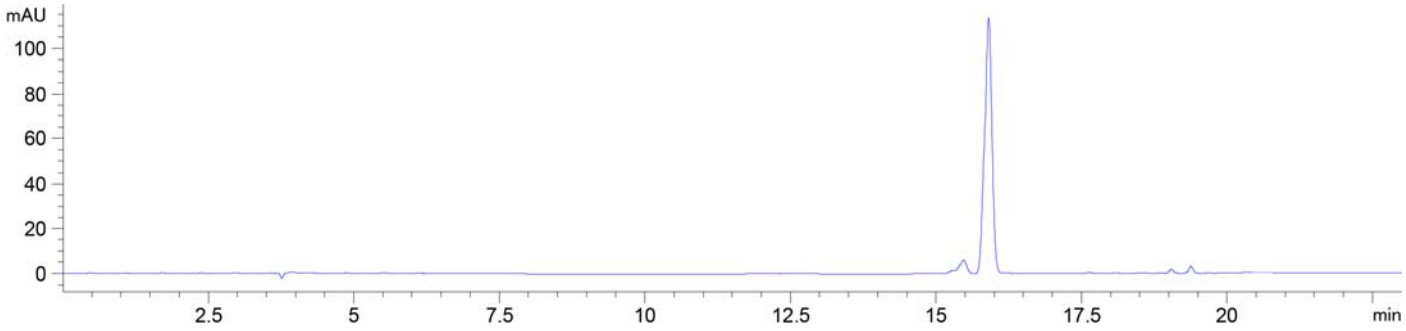
(**4**), HPLC trace 450 nm.



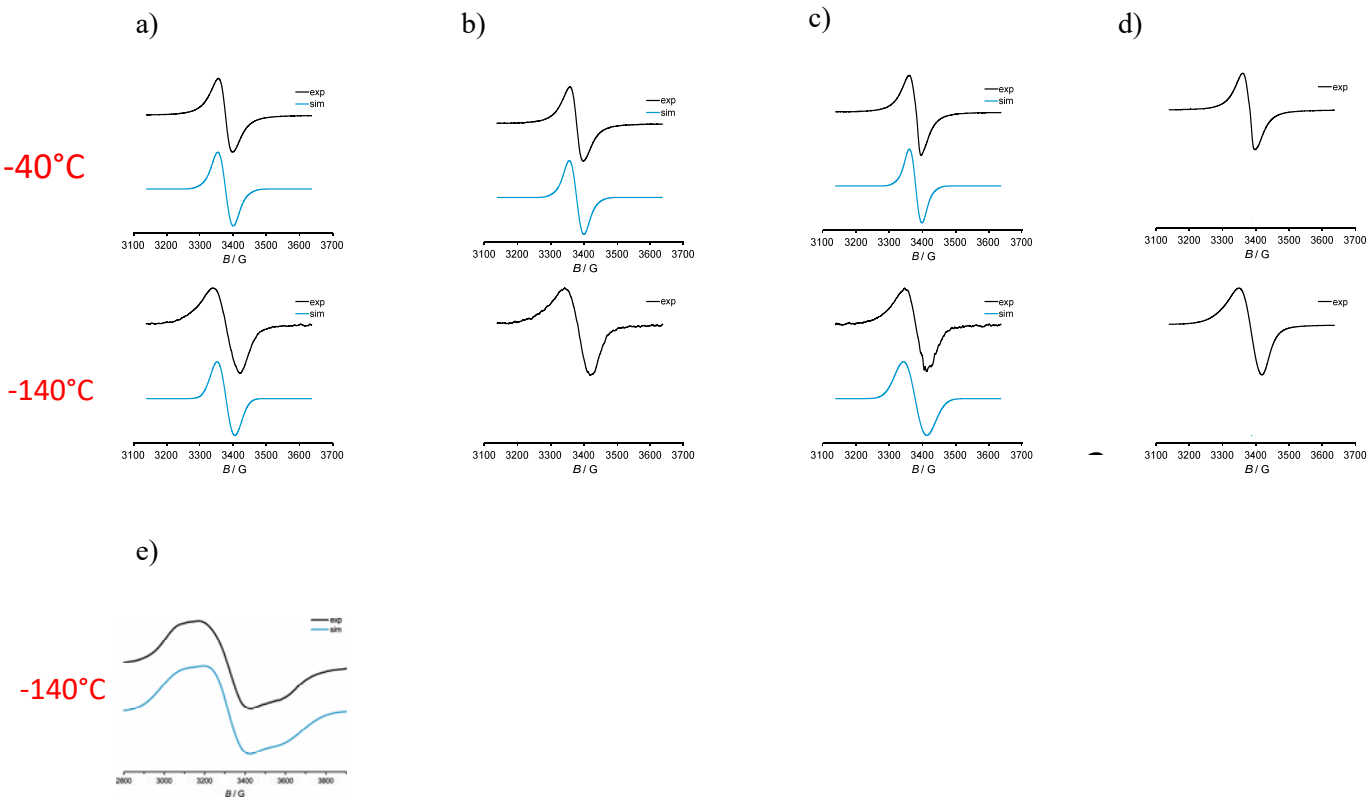
(**5**), HPLC trace 450 nm.



(**6**), HPLC trace 450 nm.



4) **Figure S3**. EPR spectra of a) **1**, b) **2**, c) **3** and d) **4** at -40 °C and -140 °C and e) **6ox** at -140 °C.

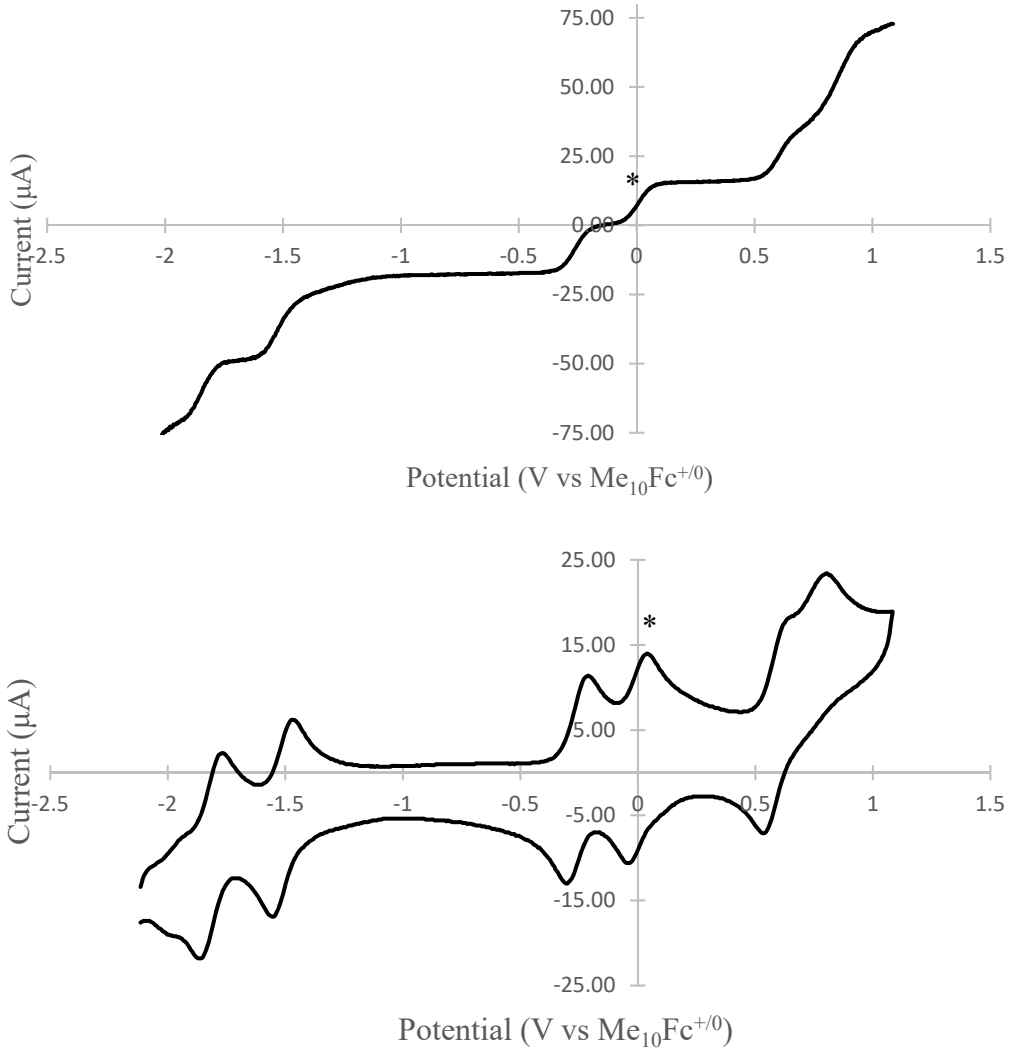


5) **Table S2**. Computed and Experimental *g*-Tensors (absolute g-values with *g*-shifts in ppt in parentheses). $< S^2 >$ values correspond to the expectation values of the Kohn-Sham determinant.

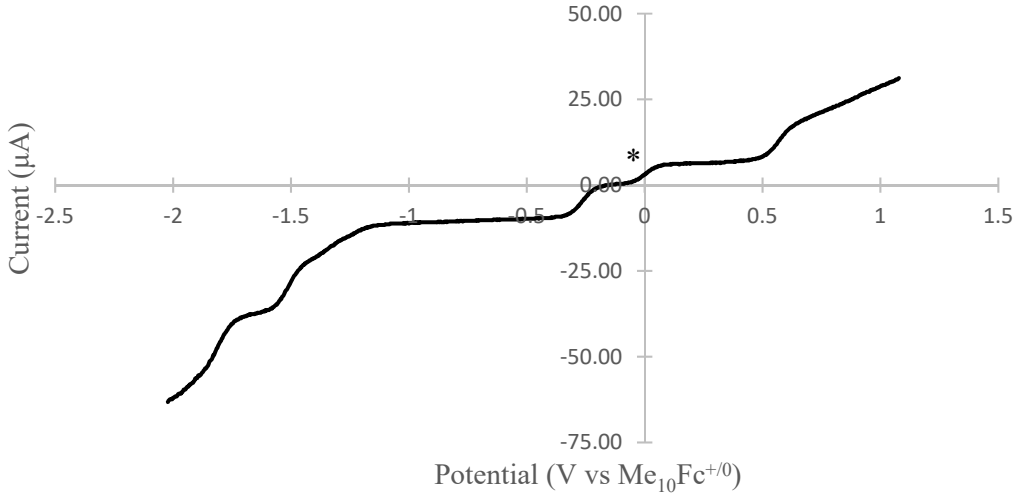
		B3LYP	exp.
(**1**)	g_{iso}	2.0055 (3.2)	1.9893 (-13.0)
	g_{11}	2.0020 (-0.3)	
	g_{22}	2.0070 (4.7)	
	g_{33}	2.0074 (5.0)	
	g_{33}-g_{11}	0.0054	
	$< S^2 >$	0.759	
(**3**)	g_{iso}	2.0054 (3.1)	1.9872 (-15.1)
	g_{11}	2.0020 (-0.3)	
	g_{22}	2.0070 (4.7)	
	g_{33}	2.0071 (4.9)	
	g_{33}-g_{11}	0.0051	
	$< S^2 >$	0.759	
(**5ox**)	g_{iso}	2.0089 (6.6)	2.019 (16.7)
	g_{11}	2.0019 (-0.4)	
	g_{22}	2.0090 (6.6)	
	g_{33}	2.0159 (13.6)	
	g_{33}-g_{11}	0.0140	
	$< S^2 >$	0.759	
(**6ox**)	g_{iso}	2.0076 (5.3)	2.032 (29.7)
	g_{11}	2.0038 (1.5)	1.870 (-132.3)
	g_{22}	2.0076 (5.3)	2.025 (22.7)
	g_{33}	2.0076 (8.9)	2.190 (187.7)
	g_{33}-g_{11}	0.0074	0.32
	$< S^2 >$	0.760	

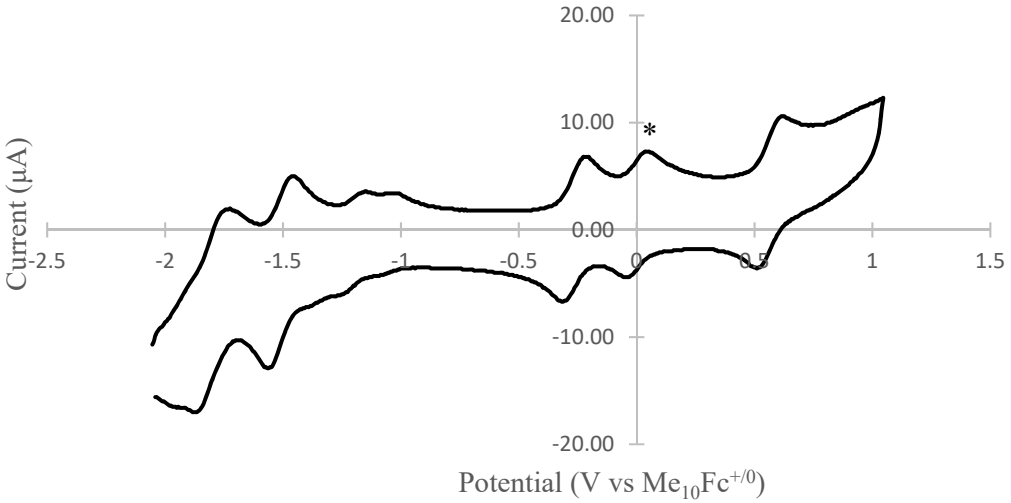
6) **Figure S4.** Voltammograms recorded by CV and with the use of RDE of complexes **2-6**.

(**2**) (from -2.1 to +1 V) at a glassy carbon electrode in DMF (1 mM) containing Bu_4NPF_6 (100 mM) as supporting electrolyte and decamethylferrocene as an internal standard (0.25 mM). Data were recorded versus saturated calomel electrode at scan rate of 100 mV/s and recalculated versus $Me_{10}Fc^{0/+}$ potential value (-0.09 V and -0.09 V for RDE and CV respectively).

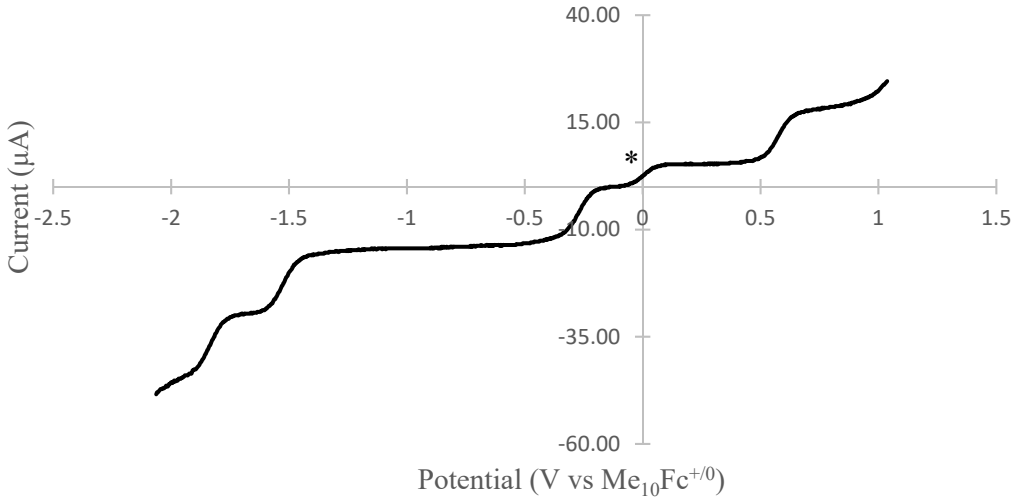


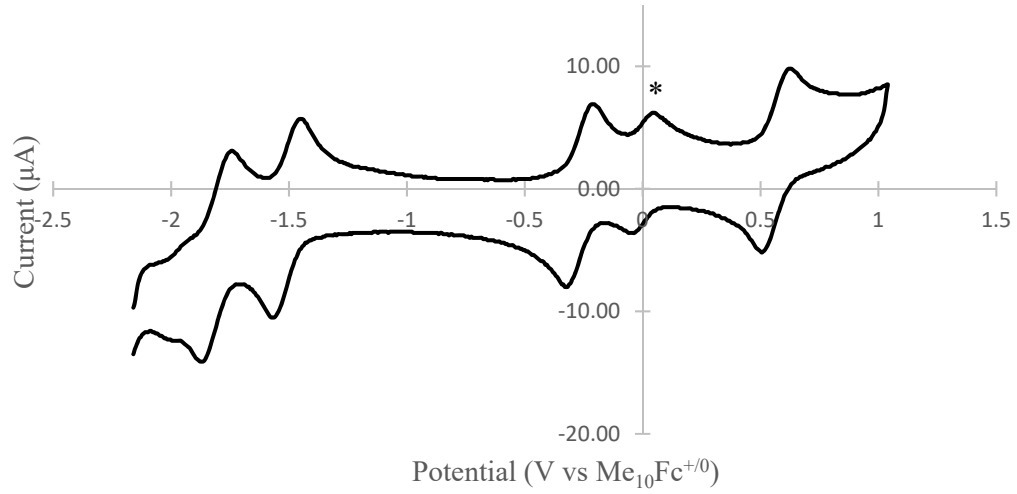
(**3**) (from -2.1 to +1 V) at a glassy carbon electrode in DMF (1 mM) containing Bu_4NPF_6 (100 mM) as supporting electrolyte and decamethylferrocene as an internal standard (0.25 mM). Data were recorded versus saturated calomel electrode at scan rate of 100 mV/s and recalculated versus $Me_{10}Fc^{0/+}$ potential value (-0.07 V and -0.05 V for RDE and CV respectively).



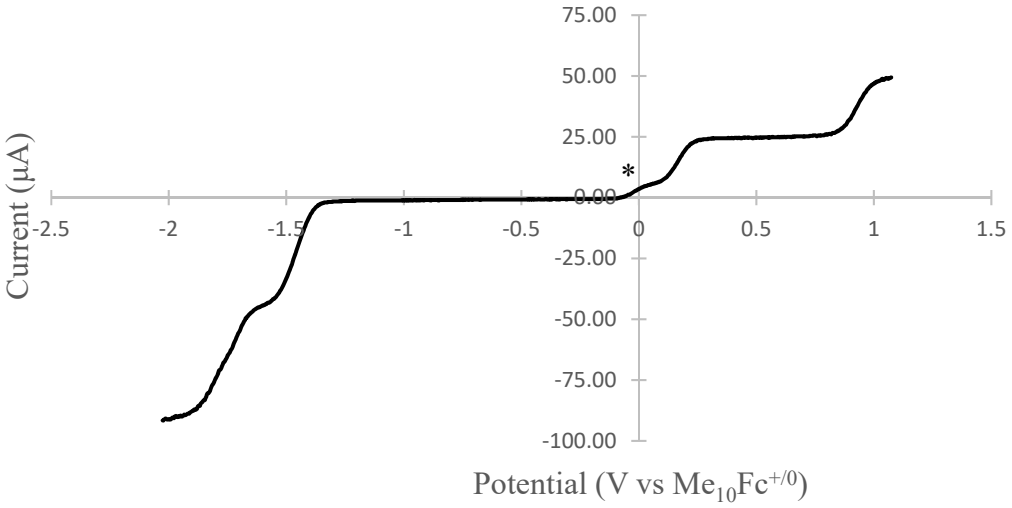


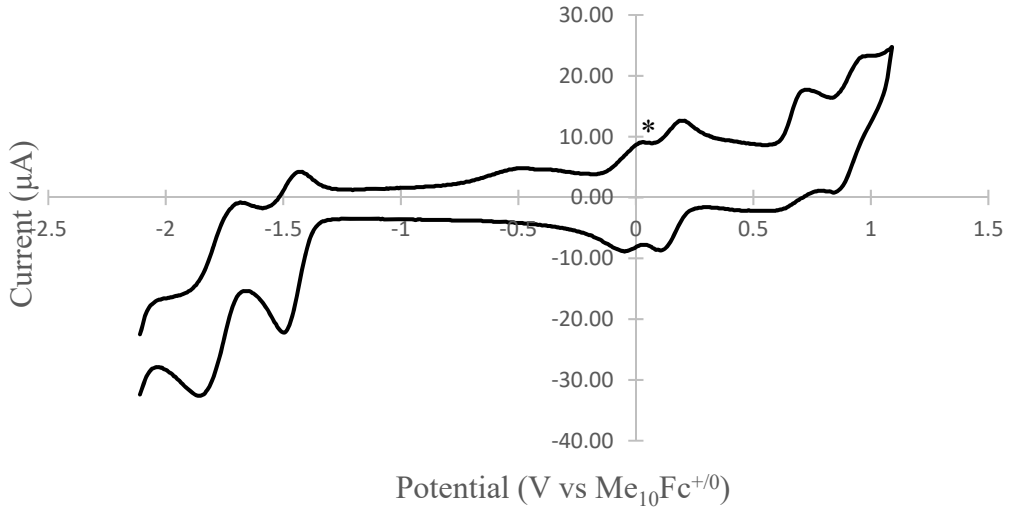
(**4**) (from -2.1 to +1 V) at a glassy carbon electrode in DMF (1 mM) containing Bu_4NPF_6 (100 mM) as supporting electrolyte and decamethylferrocene as an internal standard (0.25 mM). Data were recorded versus saturated calomel electrode at scan rate of 100 mV/s and recalculated versus $Me_{10}Fc^{0/+}$ potential value (-0.04 V and -0.04 V for RDE and CV respectively).



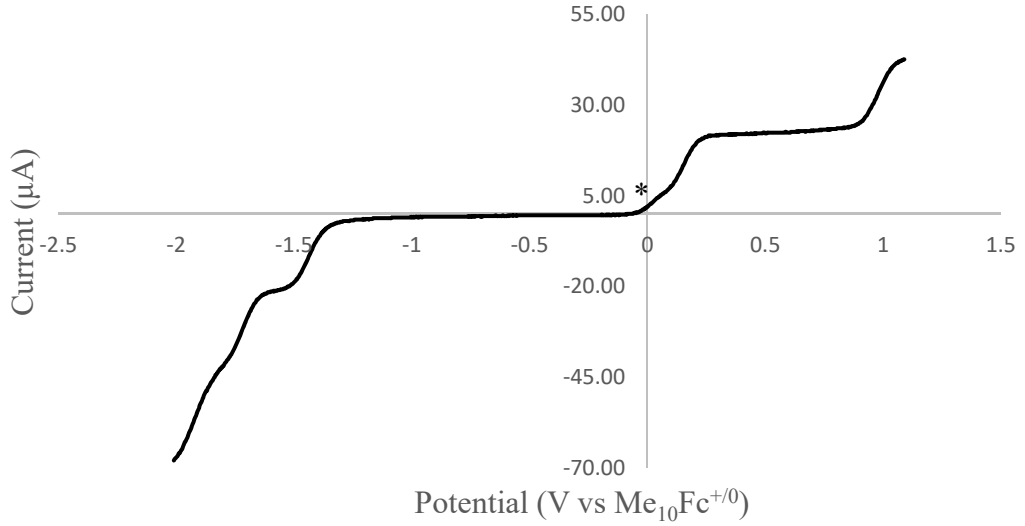


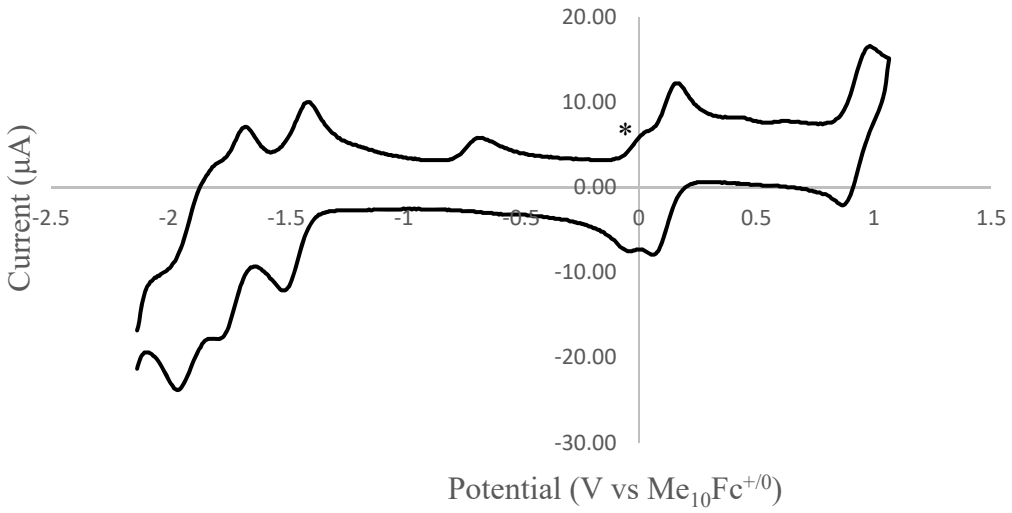
(**5**) (from -2.1 to +1 V) at a glassy carbon electrode in DMF (1 mM) containing Bu_4NPF_6 (100 mM) as supporting electrolyte and decamethylferrocene as an internal standard (0.25 mM). Data were recorded versus saturated calomel electrode at scan rate of 100 mV/s and recalculated versus $Me_{10}Fc^{0/+}$ potential value (-0.07 V and -0.09 V for RDE and CV respectively).





(**6**) (from -2.1 to +1 V) at a glassy carbon electrode in DMF (1 mM) containing Bu_4NPF_6 (100 mM) as supporting electrolyte and decamethylferrocene as an internal standard (0.25 mM). Data were recorded versus saturated calomel electrode at scan rate of 100 mV/s and recalculated versus $Me_{10}Fc^{0/+}$ potential value (-0.07 V and -0.09 V for RDE and CV respectively).



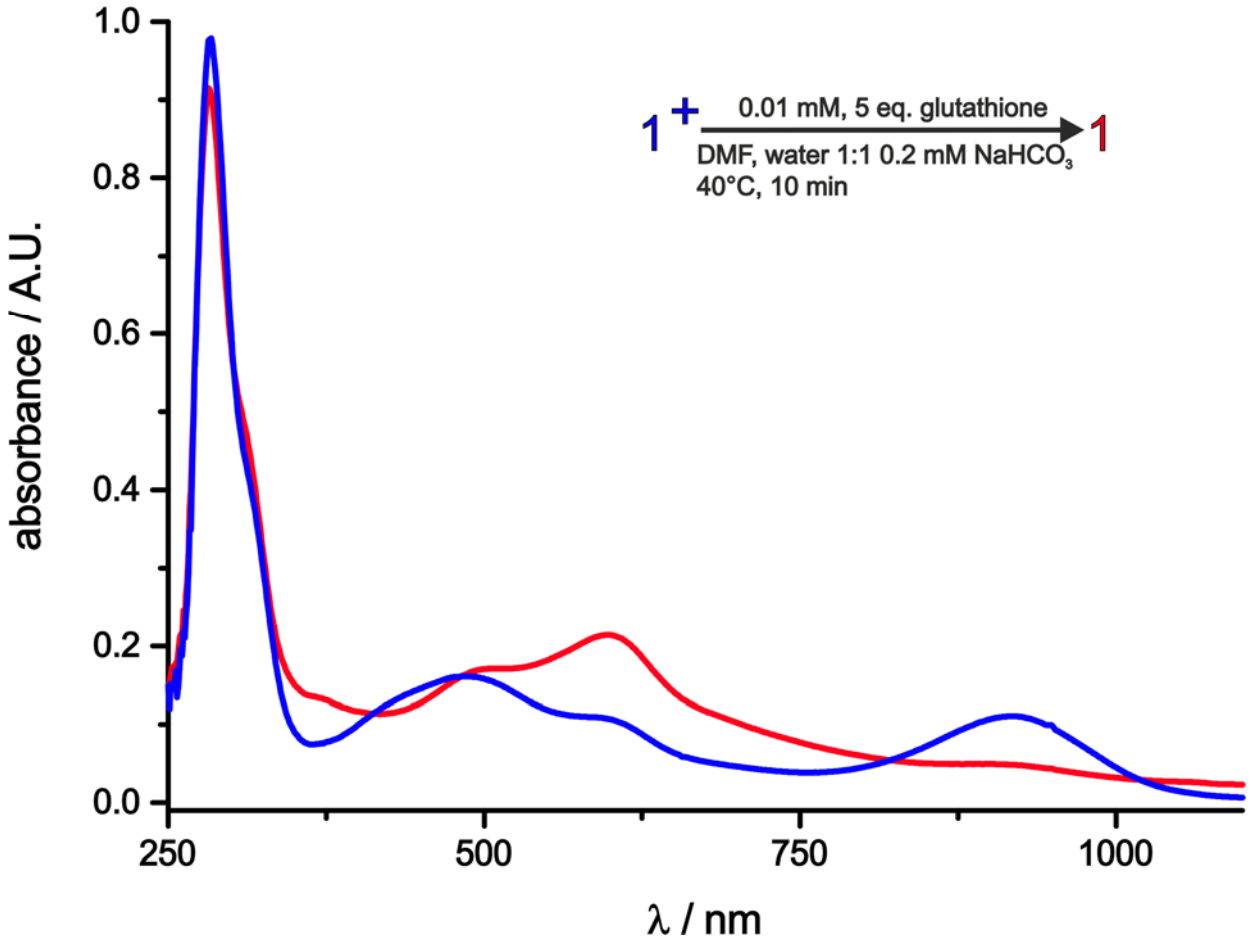


7) **Table S3.** Electrochemical data for complexes **1-4**

		$Ph_2Phen^{0/-}$	**$Ph_2Phen^{0/-}$**	**sq/cat**	**$Ru^{II/III}$**
Ru-sq*	**$E_{1/2}$[a] [V] (RDE)**	-1.876 ± 0.039	-1.578 ± 0.035	-0.249 ± 0.010	0.647 ± 0.018
	$E_{1/2}$[b] [V] (CV)	-1.816 ± 0.015	-1.507 ± 0.007	-0.209 ± 0.002	0.623 ± 0.005
1	**$E_{1/2}$[a] [V] (RDE)**	-1.848 ± 0.015	-1.537 ± 0.008	-0.284 ± 0.005	0.595 ± 0.011
	$E_{1/2}$[b] [V] (CV)	-1.798 ± 0.001	-1.503 ± 0.002	-0.251 ± 0.001	0.602 ± 0.002
2	**$E_{1/2}$[a] [V] (RDE)**	-1.833 ± 0.007	-1.497 ± 0.012	-0.252 ± 0.011	0.615 ± 0.003
	$E_{1/2}$[b] [V] (CV)	-1.813 ± 0.002	-1.510 ± 0.002	-0.256 ± 0.001	0.592 ± 0.004
3	**$E_{1/2}$[a] [V] (RDE)**	-1.836 ± 0.028	-1.472 ± 0.070	-0.265 ± 0.019	0.636 ± 0.011
	$E_{1/2}$[b] [V] (CV)	-1.797 ± 0.002	-1.511 ± 0.001	-0.264 ± 0.002	0.569 ± 0.003
4	**$E_{1/2}$[a] [V] (RDE)**	-1.839 ± 0.017	-1.515 ± 0.005	-0.271 ± 0.008	0.574 ± 0.001
	$E_{1/2}$[b] [V] (CV)	-1.807 ± 0.006	-1.506 ± 0.003	-0.265 ± 0.002	0.567 ± 0.004

* Values taken from[2] We however note that these experiments were performed on the same days.
[a] $E_{1/2}$ = half-wave potential in Volts.
[b] $E_{1/2} = (E_{Pa} + E_{Pc})/2$ in Volts.

8) **Figure S5.** UV/Vis/NIR-spectroelectrochemistry data for complex 1 in the presence of the reducing agent glutathione.



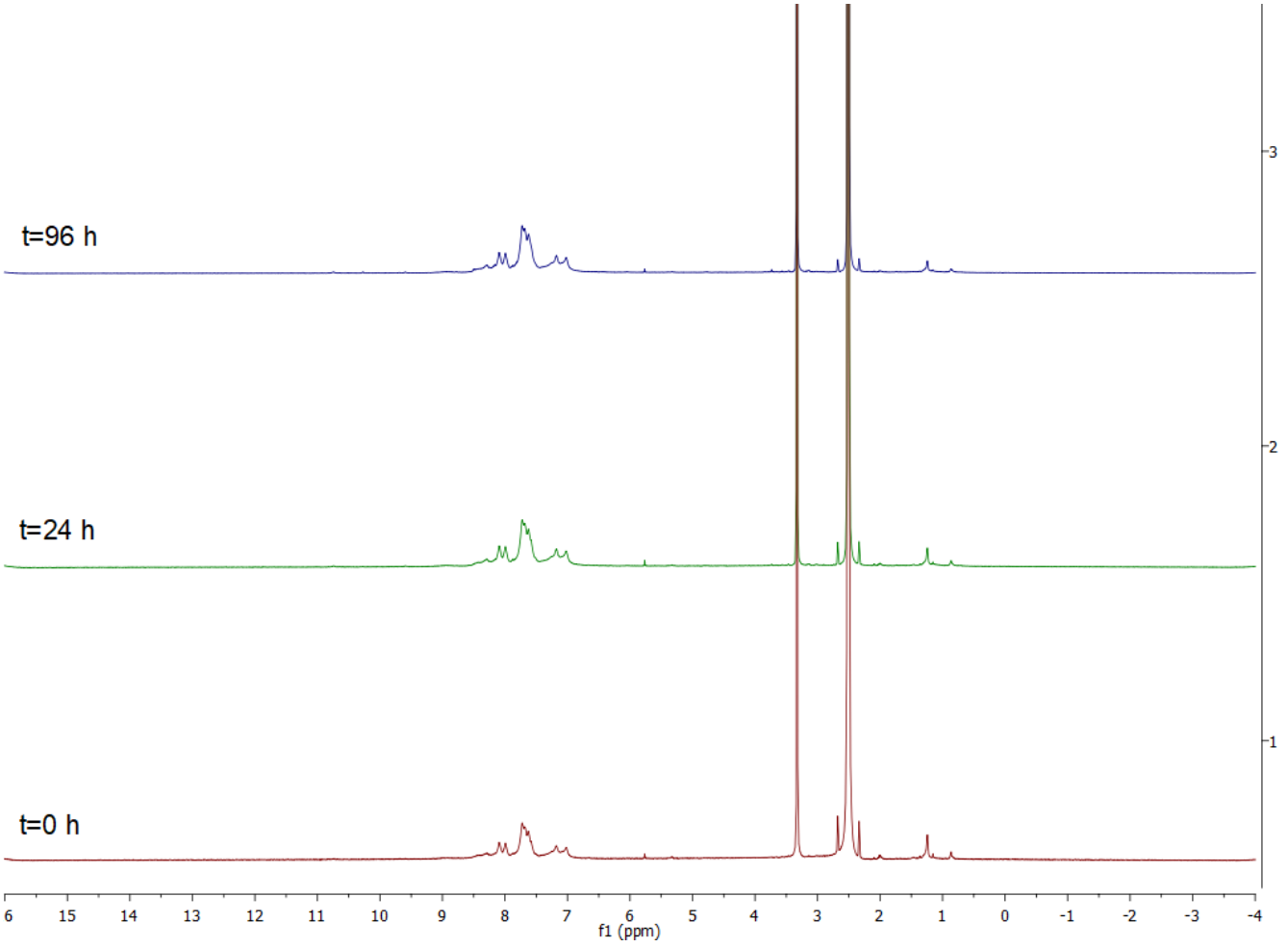
9) Table S4. Electrochemical data for complexes **5** and **6**.

		$Ph_2Phen^{0/-}$	$Ph_2Phen^{0/-}$	Ox1	Ox2
5	**$E_{1/2}$[a] [V] (RDE)**	-1.746 ± 0.003	-1.423 ± 0.002	0.182 ± 0.005	0.927 ± 0.008
	$E_{1/2}$[b] [V] (CV)	-1.764 ± 0.011	-1.456 ± 0.003	0.162 ± 0.001	0.910 ± 0.003
6	**$E_{1/2}$[a] [V] (RDE)**	-1.737 ± 0.009	-1.440 ± 0.009	0.164 ± 0.013	0.970 ± 0.009
	$E_{1/2}$[b] [V] (CV)	-1.734 ± 0.006	-1.456 ± 0.003	0.114 ± 0.004	0.929 ± 0.007

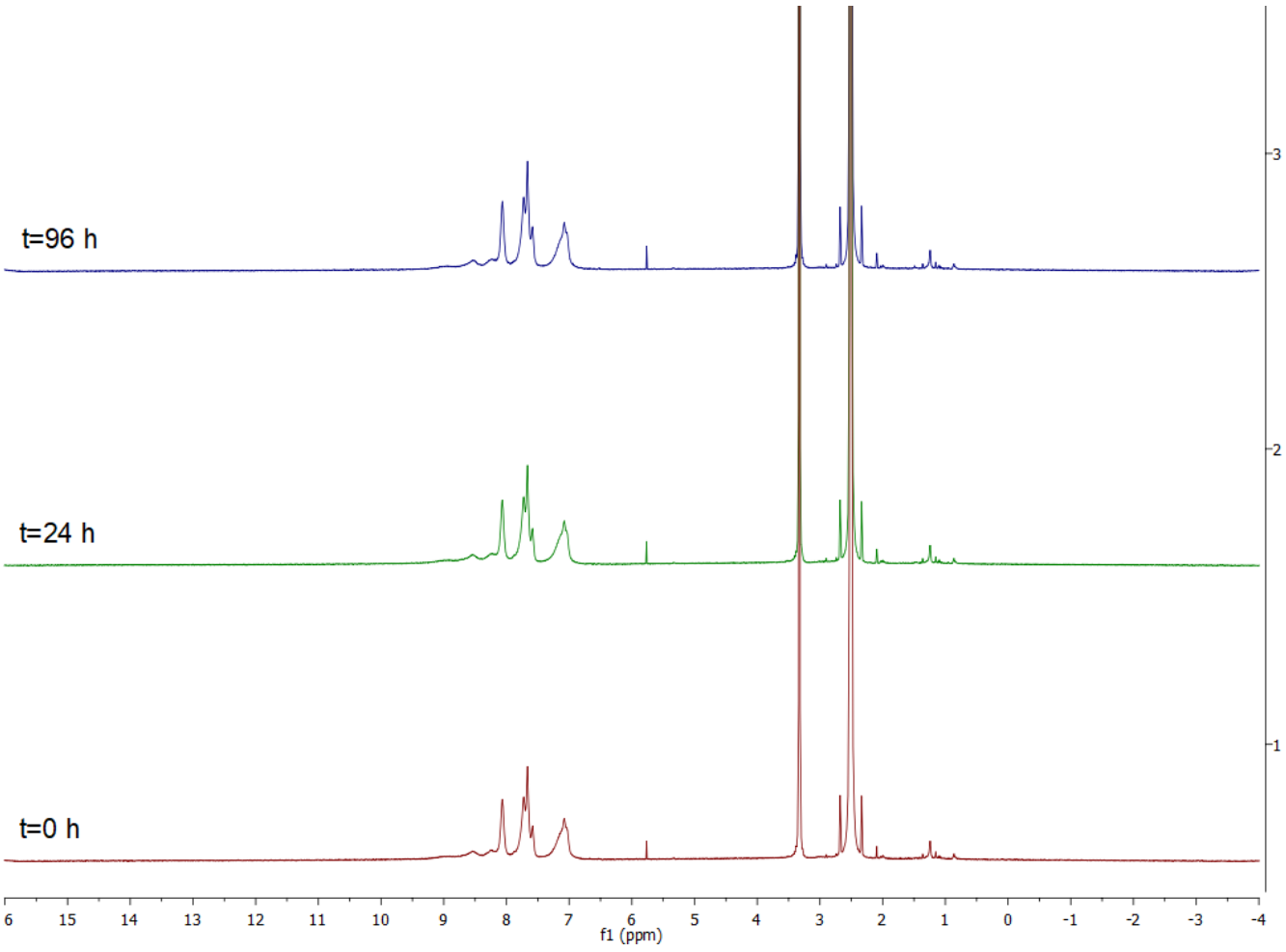
[a] $E_{1/2}$ = half-wave potential in Volts.
[b] $E_{1/2} = (E_{Pa} + E_{Pc})/2$ in Volts.

10) Figure S6. Overlap of ^{1}H spectra of complexes **1-6** in DMSO over 96 h**.**

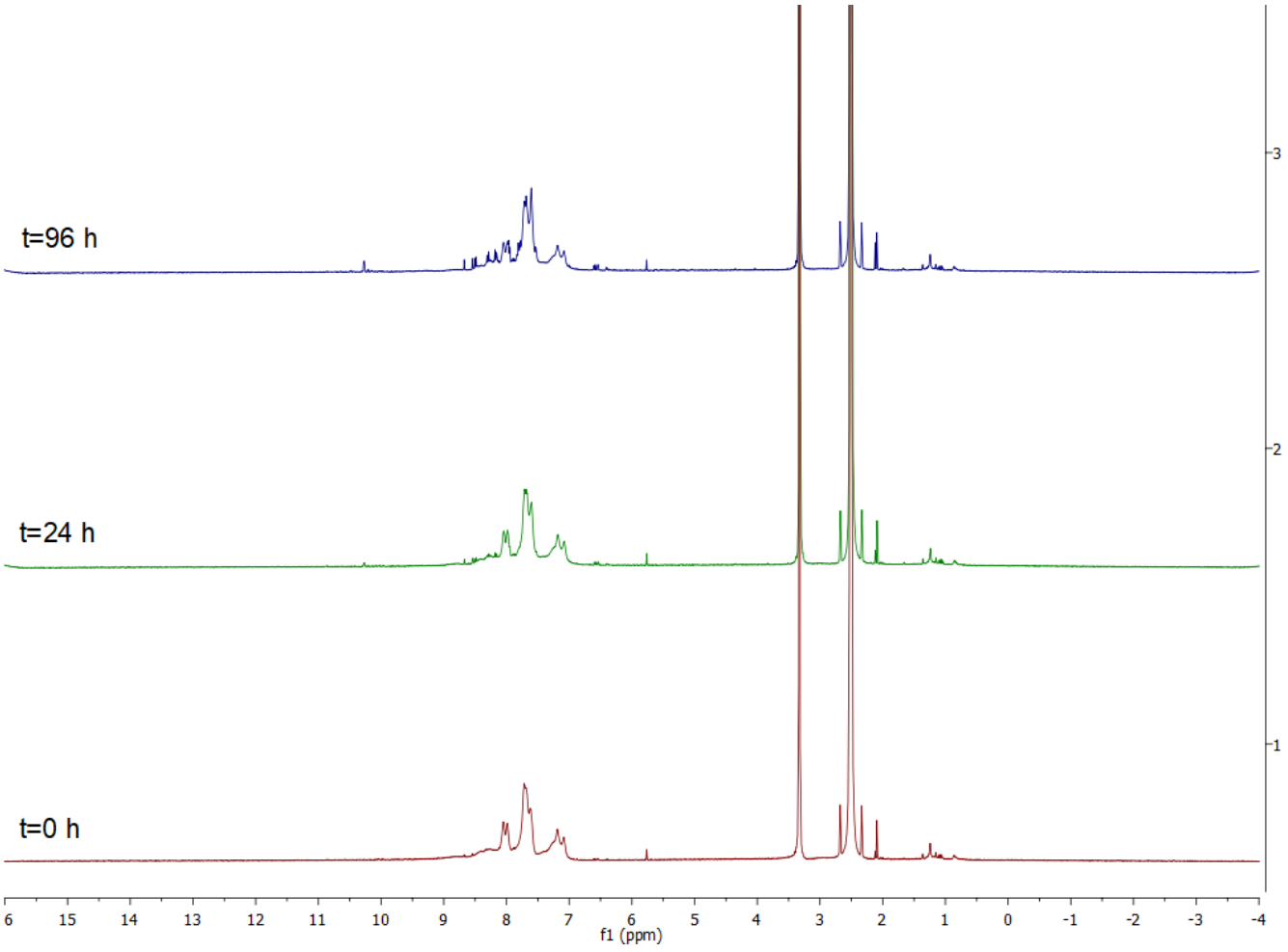
(1)



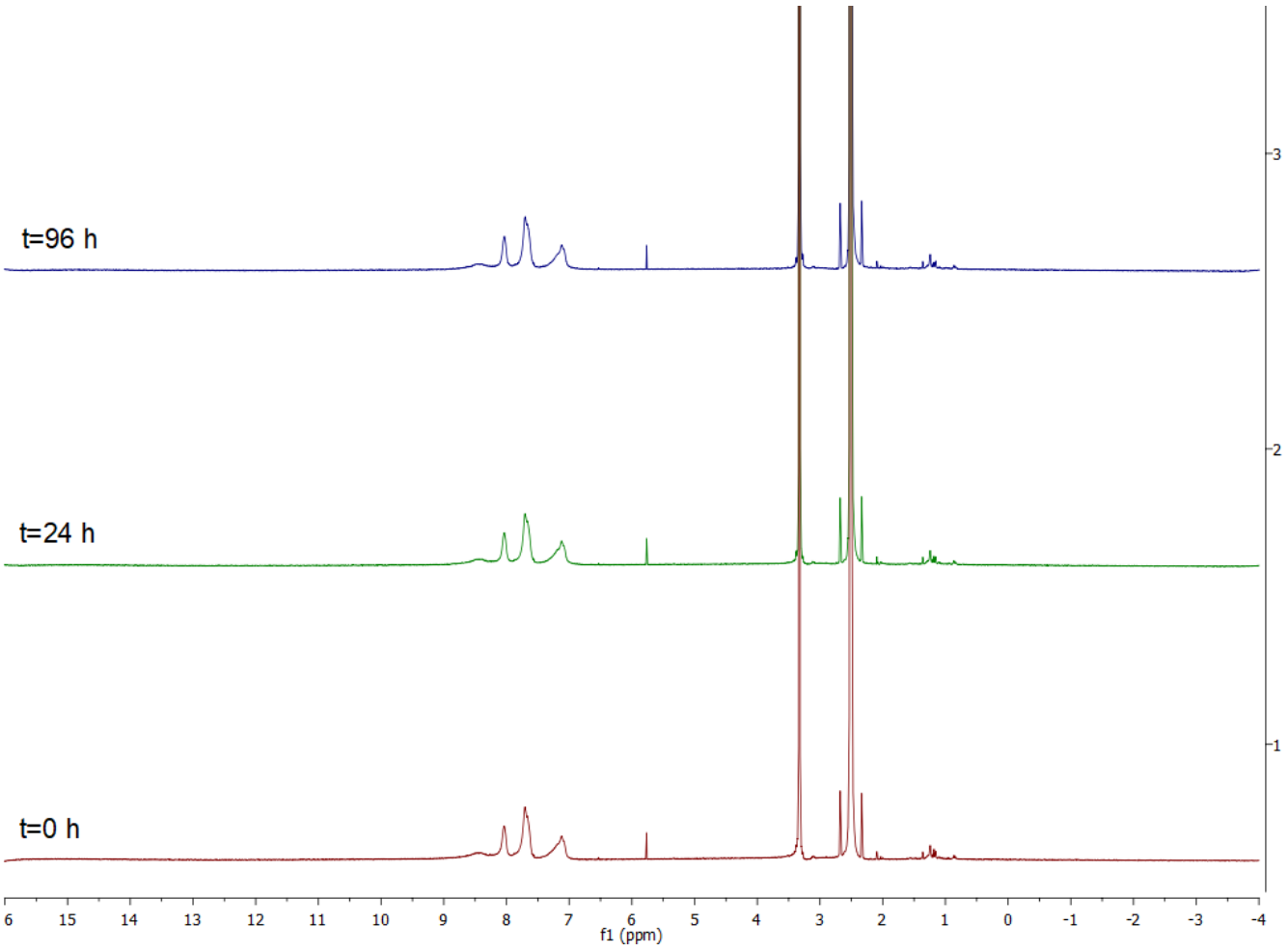
(**2**)



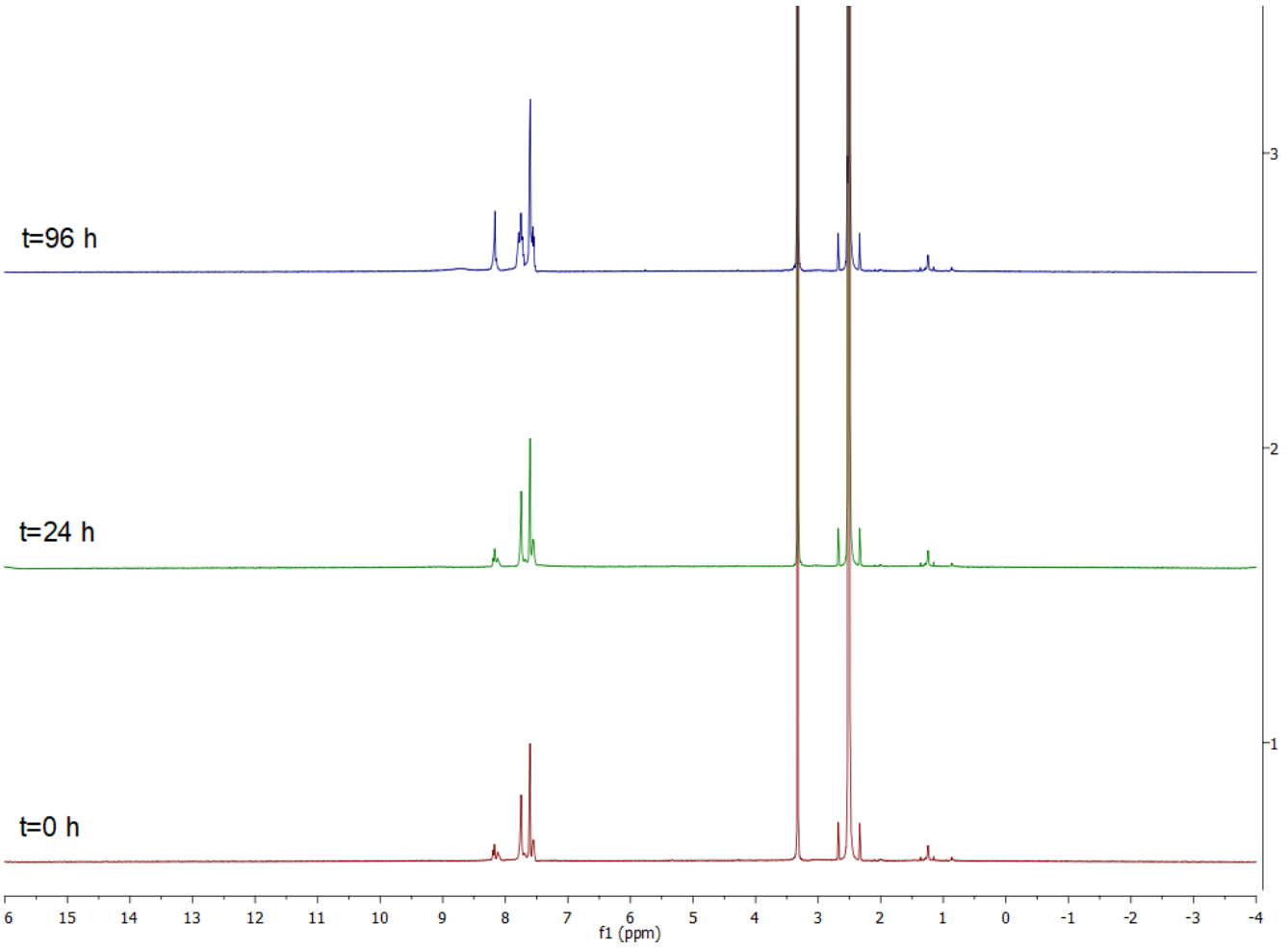
(**3**)



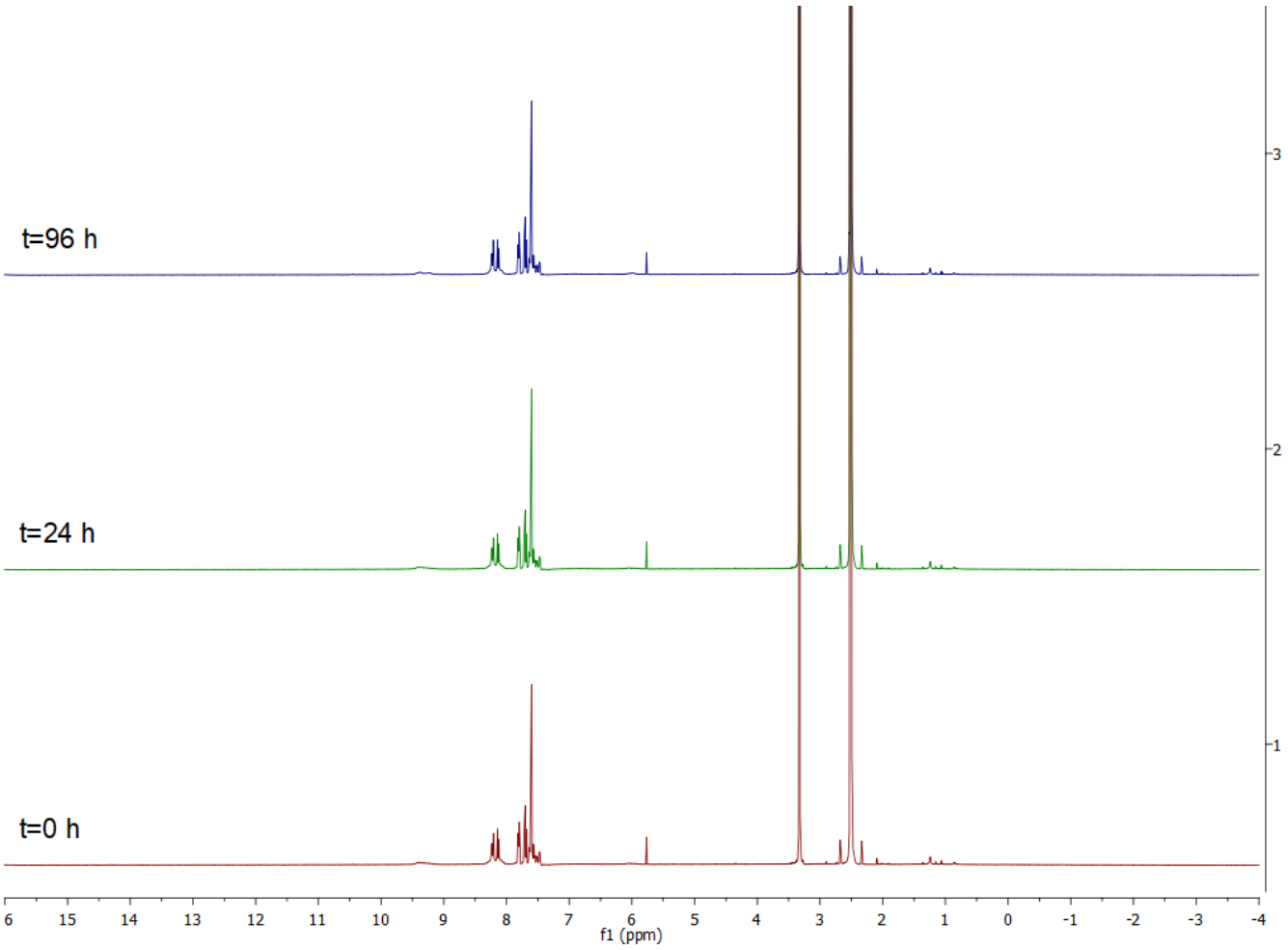
(4)



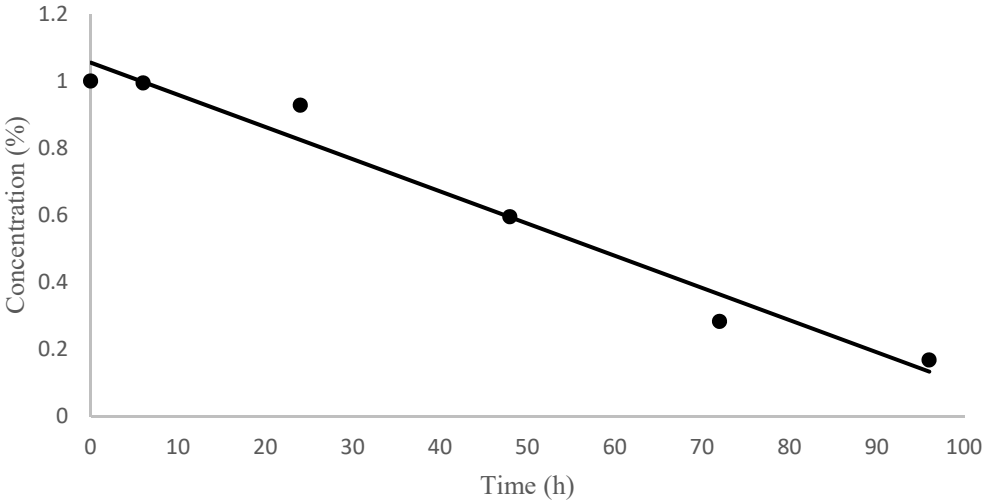
(**5**)



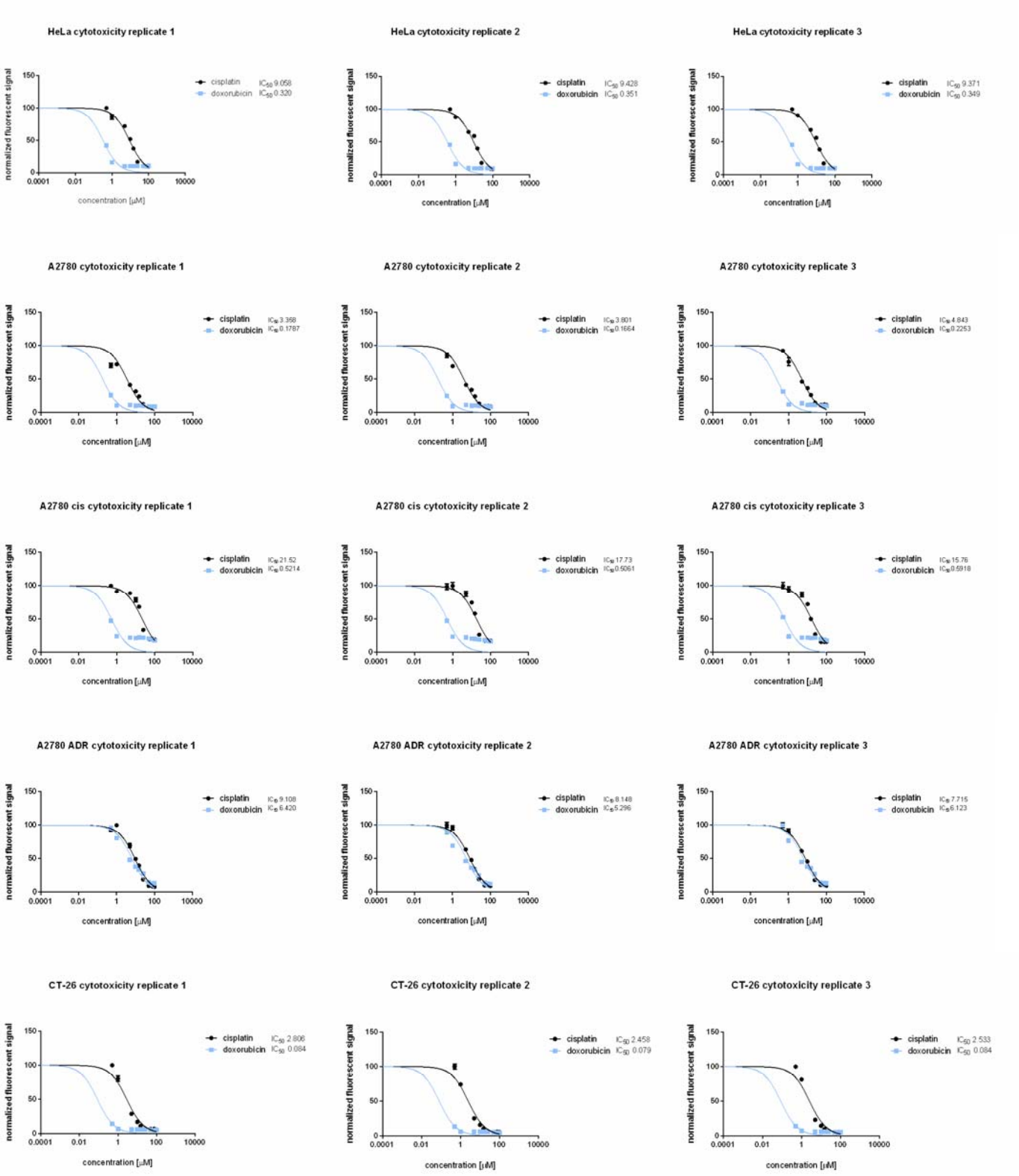
(6)



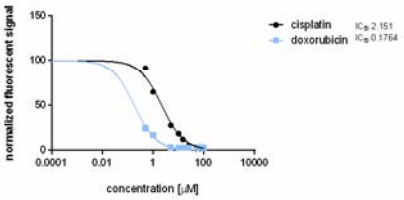
11) **Figure S7.** Percentage concentration of complex **1** in human plasma, normalized with respect to the internal standard (caffeine) and plotted against time.



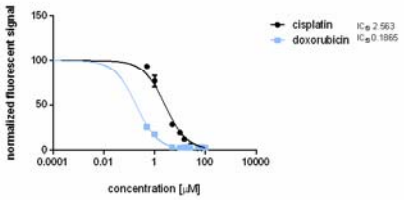
12) Figure S8. Fluorometric cell viability assay.



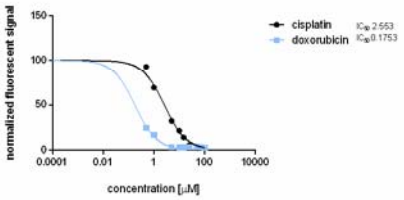
CT-26 LUC cytotoxicity replicate 1



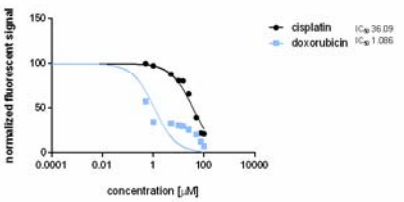
CT-26 LUC cytotoxicity replicate 2



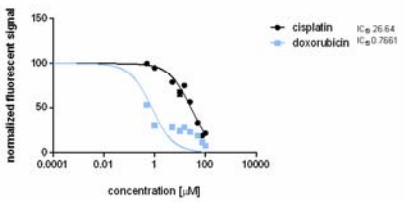
CT-26 LUC cytotoxicity replicate 3



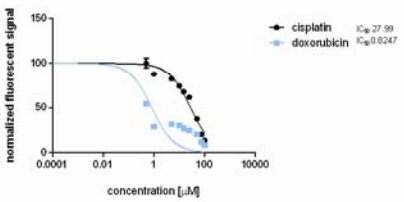
RPE-1 cytotoxicity replicate 1



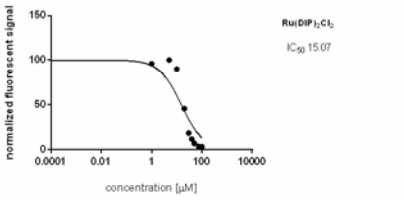
RPE-1 cytotoxicity replicate 2



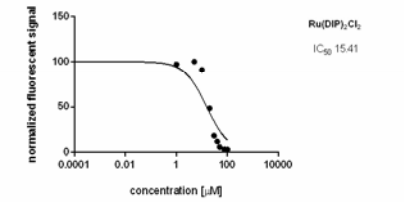
RPE-1 cytotoxicity replicate 3



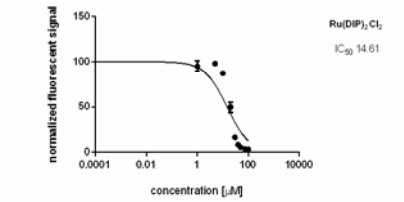
HeLa cytotoxicity replicate 1



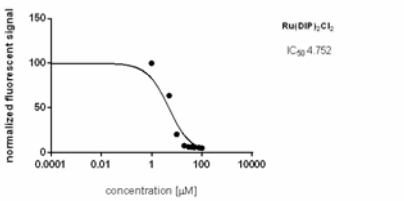
HeLa cytotoxicity replicate 2



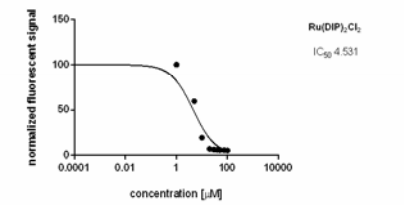
HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



A2780 cytotoxicity replicate 2



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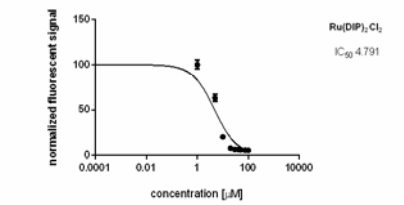
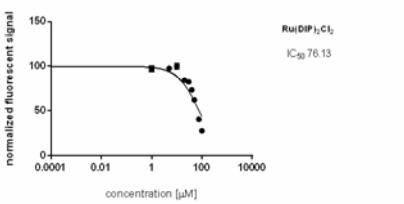


A2780 ADR cytotoxicity replicate 1



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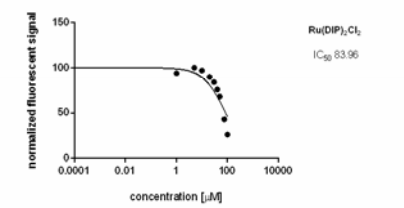
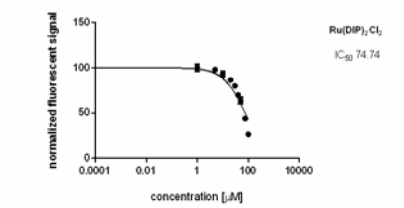
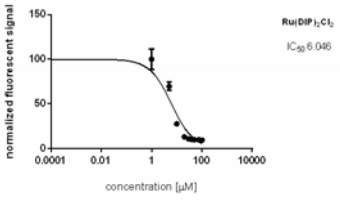


A2780 ADR cytotoxicity replicate 3



A2780 cis cytotoxicity replicate 1



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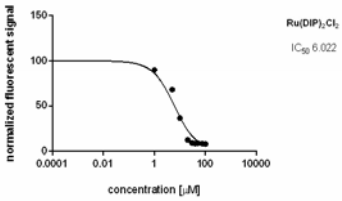
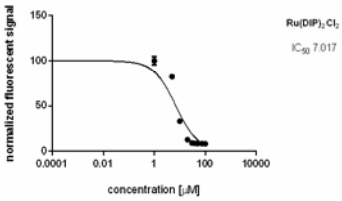
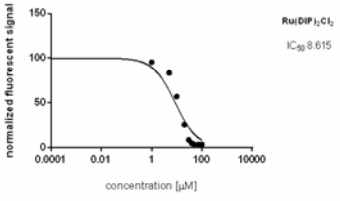


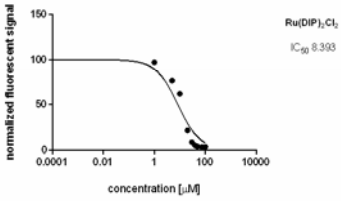
A2780 cis cytotoxicity replicate 3



CT-26 cytotoxicity replicate 1



CT-26 cytotoxicity replicate 2



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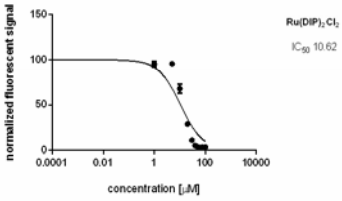
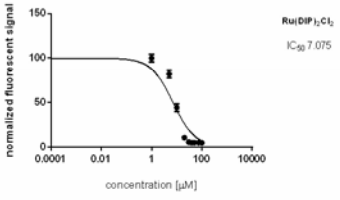


CT-26 LUC cytotoxicity replicate 1



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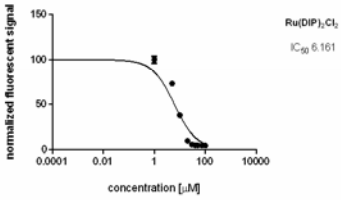
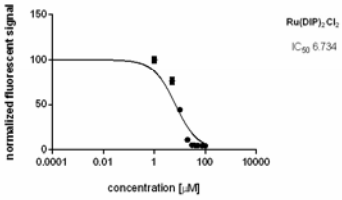
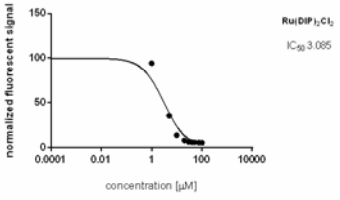


CT-26 LUC cytotoxicity replicate 3



RPE-1 cytotoxicity replicate 1



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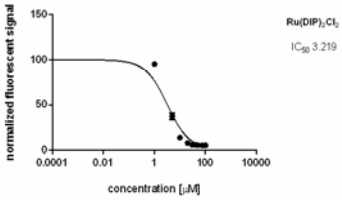

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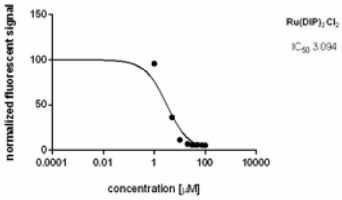
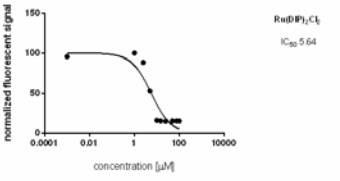


MRC-5 cytotoxicity replicate 1



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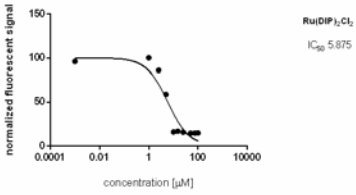

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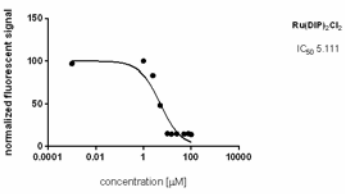
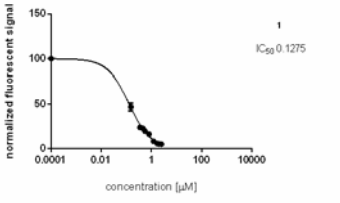
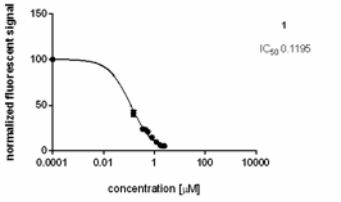


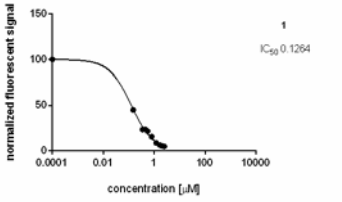
HeLa cytotoxicity replicate 1



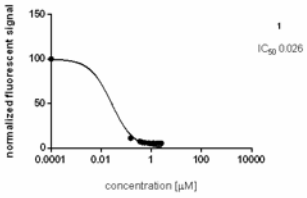
HeLa cytotoxicity replicate 2



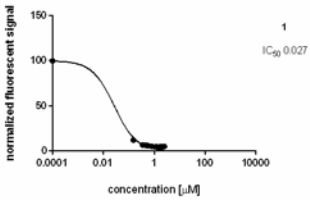
HeLa cytotoxicity replicate 3



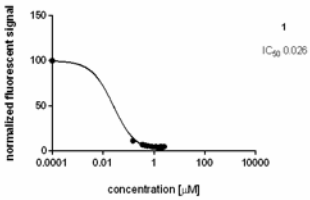
A2780 cytotoxicity replicate 1



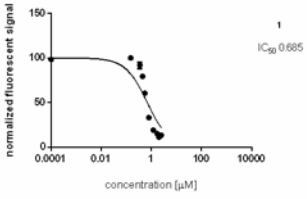
A2780 cytotoxicity replicate 2



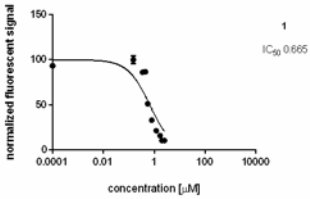
A2780 cytotoxicity replicate 3



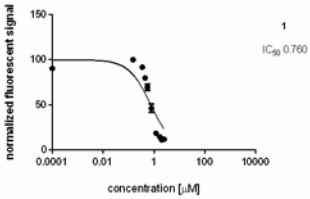
A2780 ADR cytotoxicity replicate 1



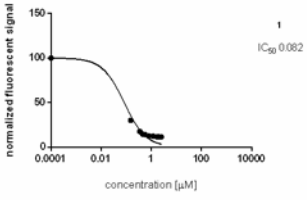
A2780 ADR cytotoxicity replicate 2



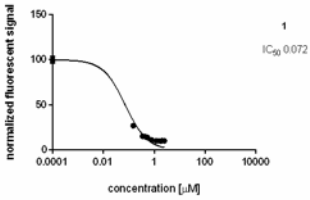
A2780 ADR cytotoxicity replicate 3



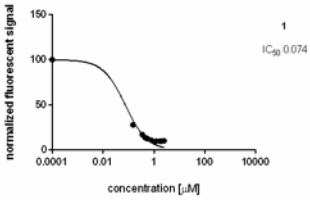
A2780 cis cytotoxicity replicate 1



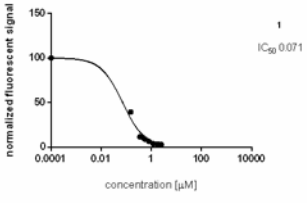
A2780 cis cytotoxicity replicate 2



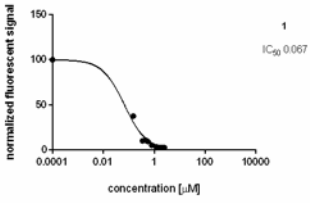
A2780 cis cytotoxicity replicate 3



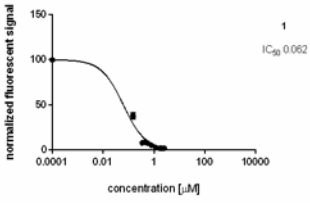
CT-26 cytotoxicity replicate 1



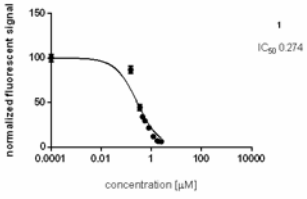
CT-26 cytotoxicity replicate 2



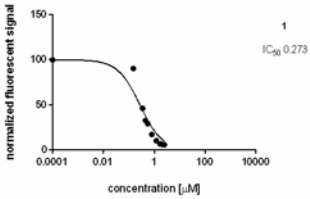
CT-26 cytotoxicity replicate 3



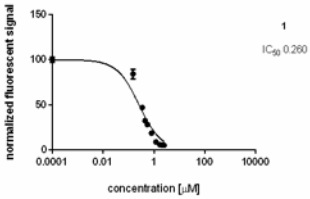
CT-26 LUC cytotoxicity replicate 1



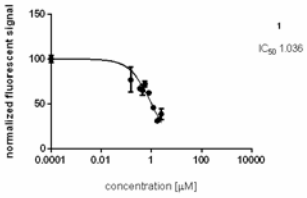
CT-26 LUC cytotoxicity replicate 2



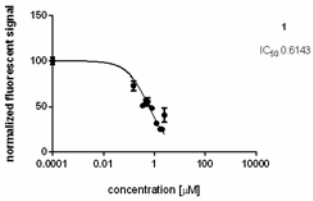
CT-26 LUC cytotoxicity replicate 3



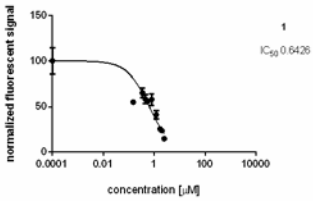
RPE-1 cytotoxicity replicate 1



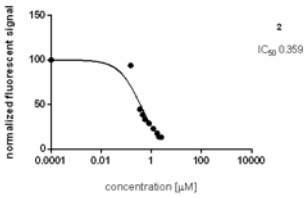
RPE-1 cytotoxicity replicate 2



RPE-1 cytotoxicity replicate 3



HeLa cytotoxicity replicate 1



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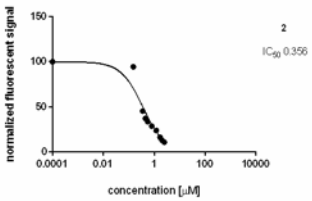
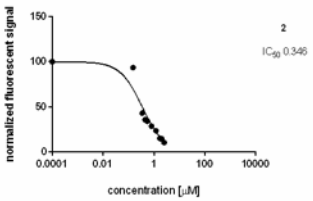
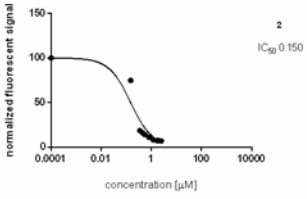


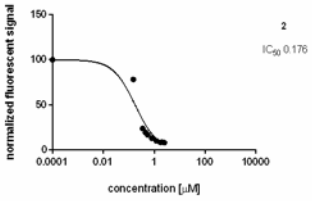
HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



A2780 cytotoxicity replicate 2



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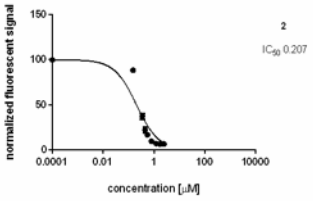
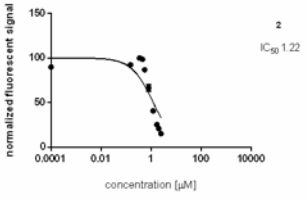


A2780 ADR cytotoxicity replicate 1



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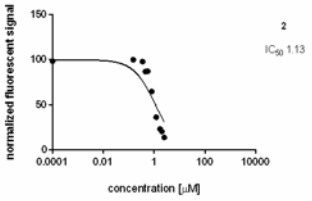

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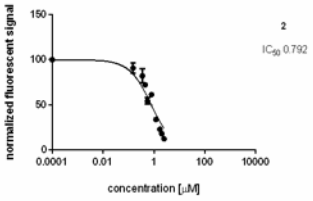
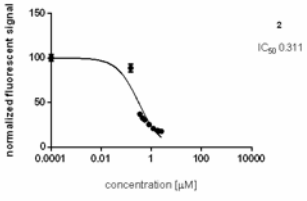


A2780 cis cytotoxicity replicate 1



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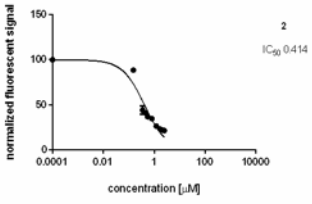

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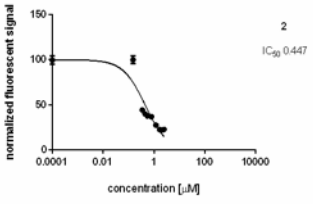
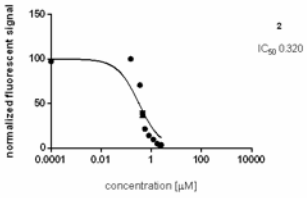
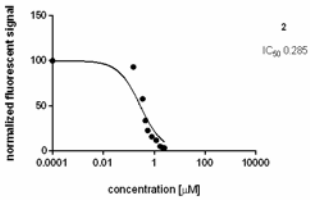


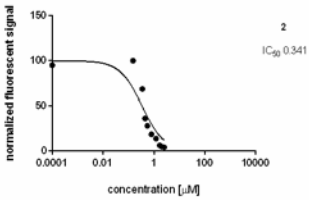
CT-26 cytotoxicity replicate 1



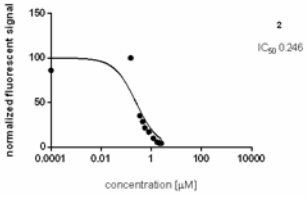
CT-26 cytotoxicity replicate 2



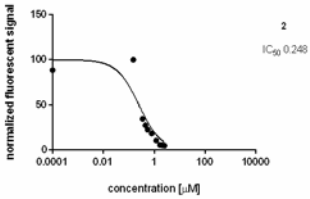
CT-26 cytotoxicity replicate 3



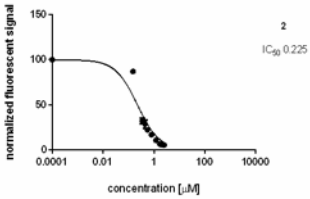
CT-26 LUC cytotoxicity replicate 1



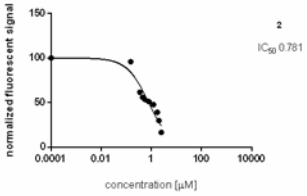
CT-26 LUC cytotoxicity replicate 2



CT-26 LUC cytotoxicity replicate 3



RPE-1 cytotoxicity replicate 1



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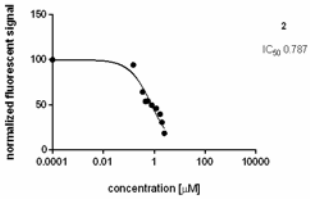
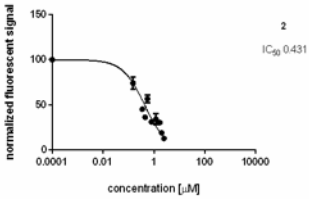
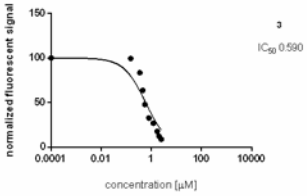


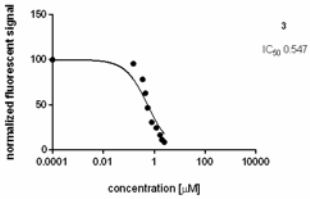
RPE-1 cytotoxicity replicate 3



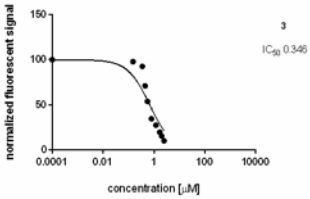
HeLa cytotoxicity replicate 1



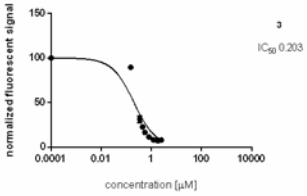
HeLa cytotoxicity replicate 2



HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



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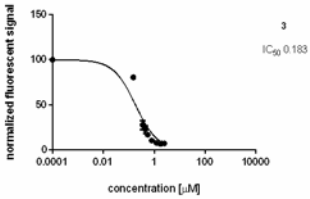

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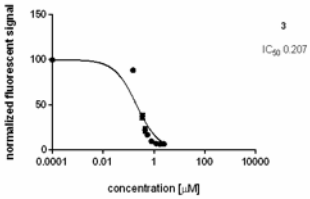

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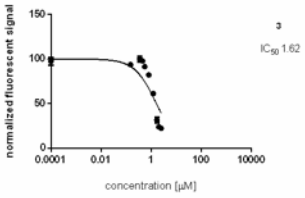

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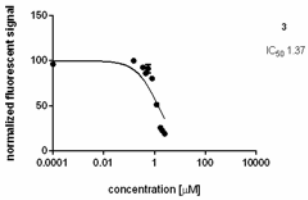

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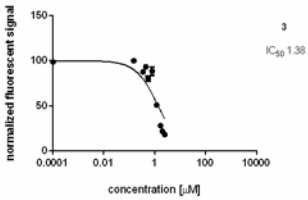

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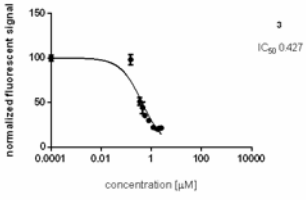

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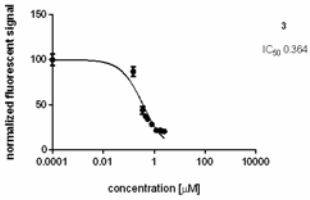

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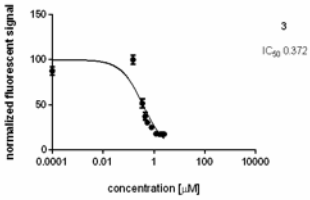
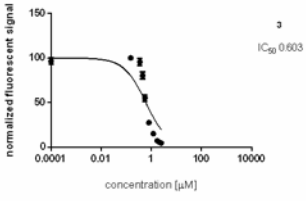
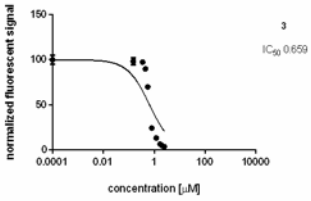


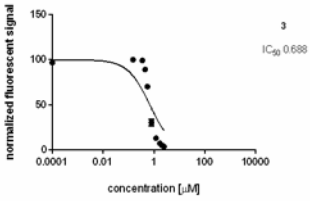
CT-26 cytotoxicity replicate 1



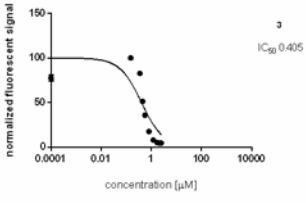
CT-26 cytotoxicity replicate 2



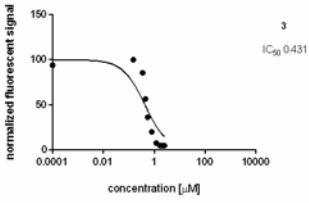
CT-26 cytotoxicity replicate 3



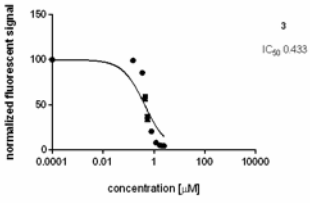
CT-26 LUC cytotoxicity replicate 1



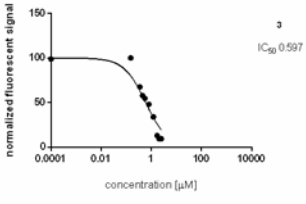
CT-26 LUC cytotoxicity replicate 2



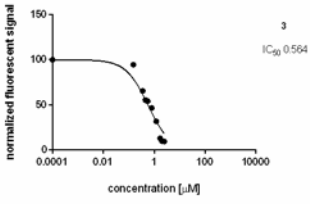
CT-26 LUC cytotoxicity replicate 3



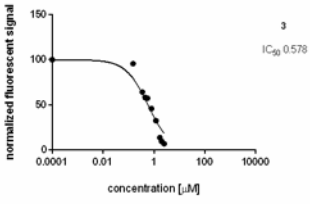
RPE-1 cytotoxicity replicate 1



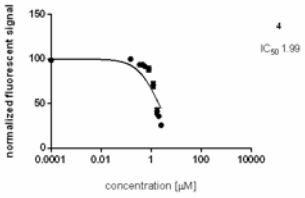
RPE-1 cytotoxicity replicate 2



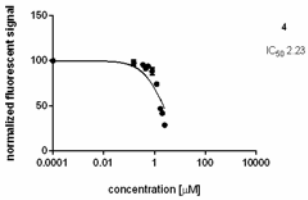
RPE-1 cytotoxicity replicate 3



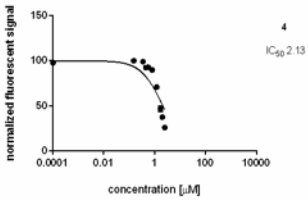
HeLa cytotoxicity replicate 1



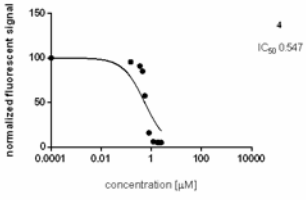
HeLa cytotoxicity replicate 2



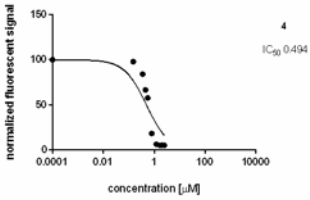
HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



A2780 cytotoxicity replicate 2



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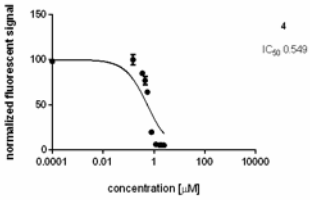
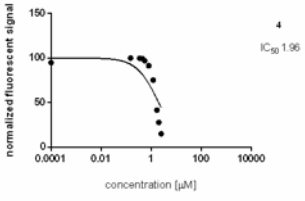


A2780 ADR cytotoxicity replicate 1



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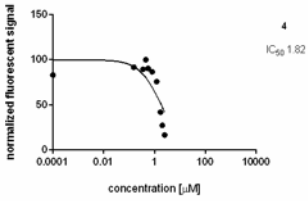
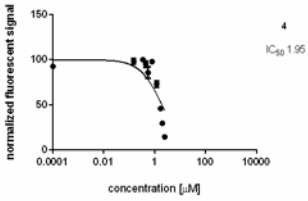


A2780 ADR cytotoxicity replicate 3



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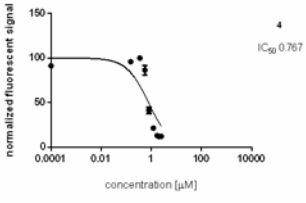
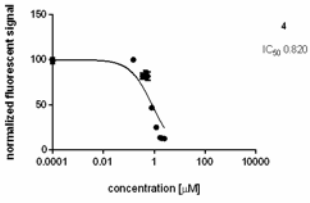


A2780 cis cytotoxicity replicate 2



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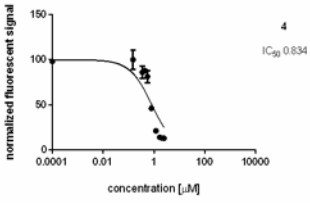
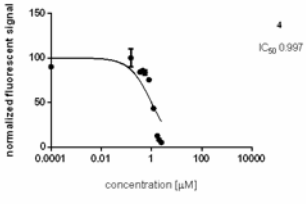
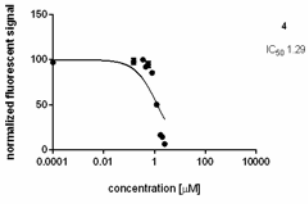


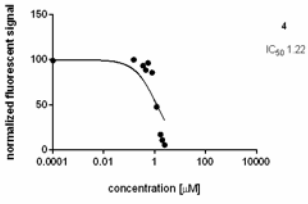
CT-26 cytotoxicity replicate 1



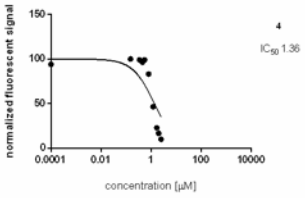
CT-26 cytotoxicity replicate 2



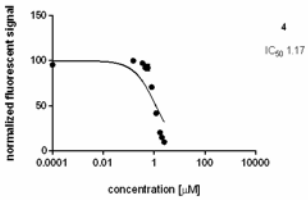
CT-26 cytotoxicity replicate 3



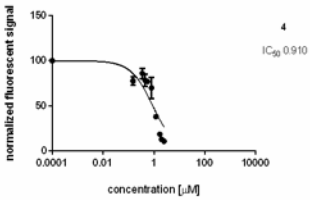
CT-26 LUC cytotoxicity replicate 1



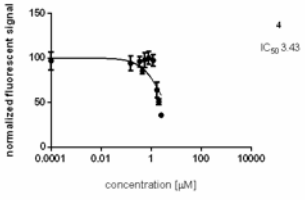
CT-26 LUC cytotoxicity replicate 2



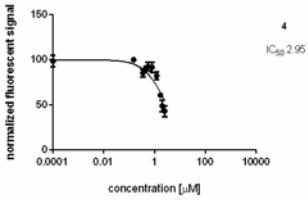
CT-26 LUC cytotoxicity replicate 3



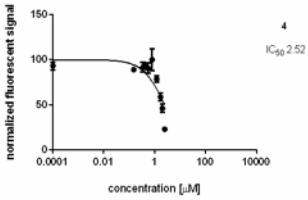
RPE-1 cytotoxicity replicate 1



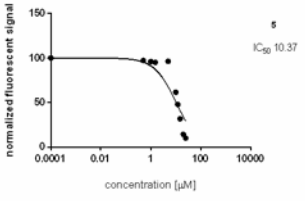
RPE-1 cytotoxicity replicate 2



RPE-1 cytotoxicity replicate 3



HeLa cytotoxicity replicate 1



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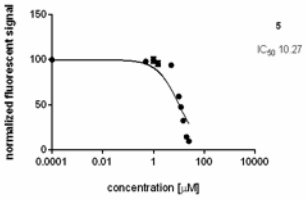
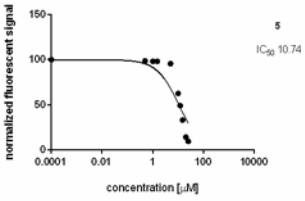
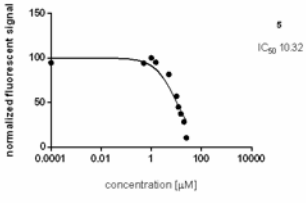


HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



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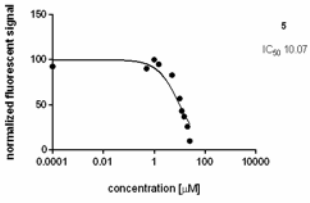

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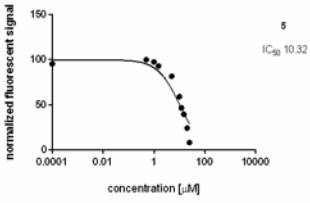

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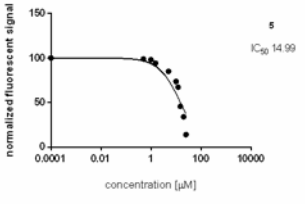

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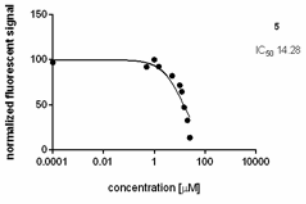

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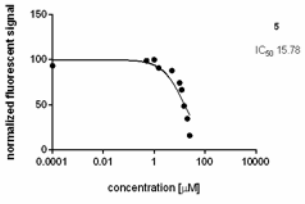

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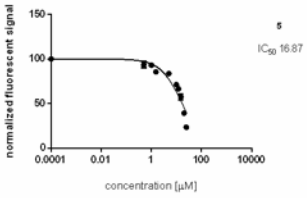

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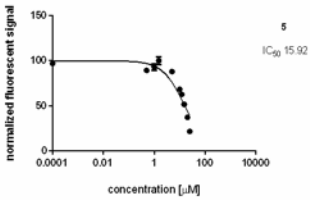
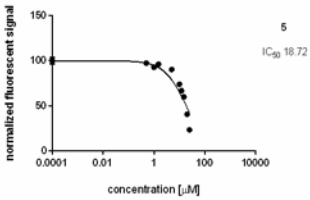
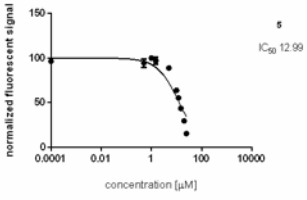


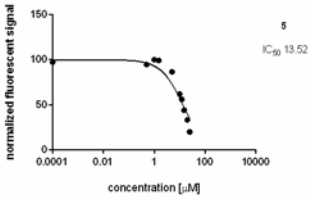
A2780 cis cytotoxicity replicate 3



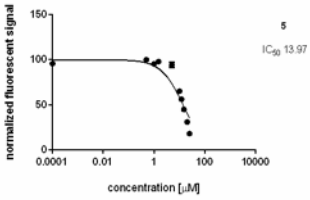
CT-26 cytotoxicity replicate 1



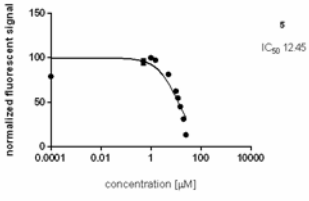
CT-26 cytotoxicity replicate 2



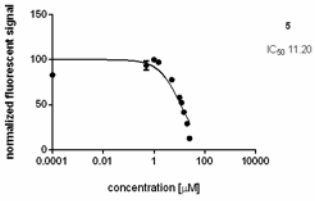
CT-26 cytotoxicity replicate 3



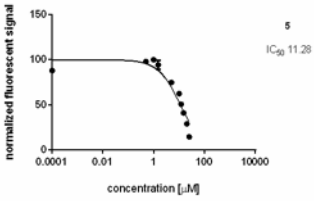
CT-26 LUC cytotoxicity replicate 1



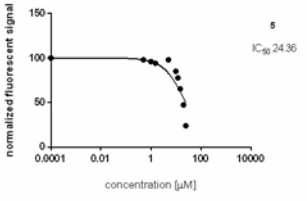
CT-26 LUC cytotoxicity replicate 2



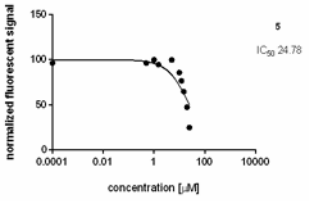
CT-26 LUC cytotoxicity replicate 3



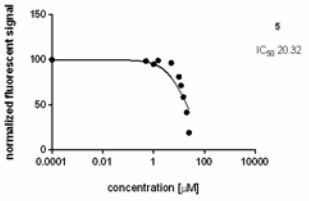
RPE-1 cytotoxicity replicate 1



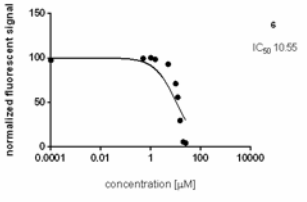
RPE-1 cytotoxicity replicate 2



RPE-1 cytotoxicity replicate 3



HeLa cytotoxicity replicate 1



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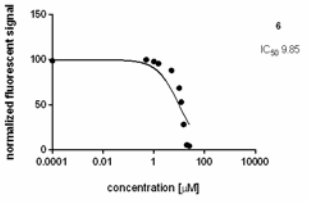
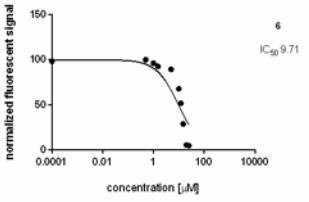
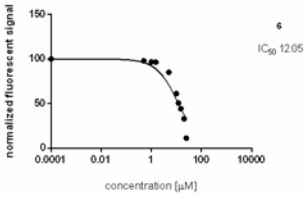


HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



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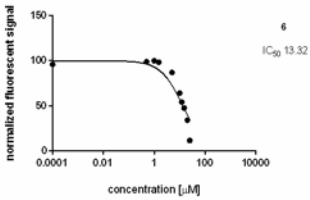

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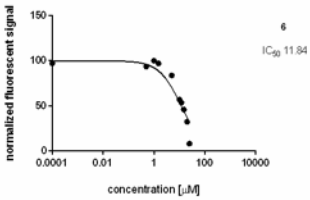
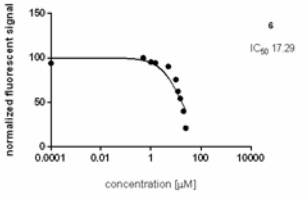


A2780 ADR cytotoxicity replicate 1



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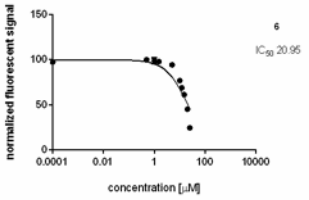

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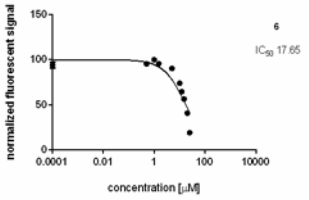

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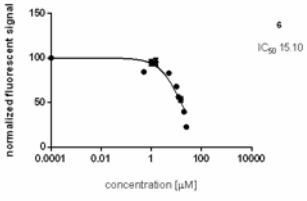

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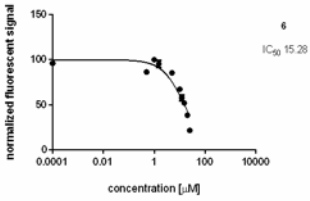

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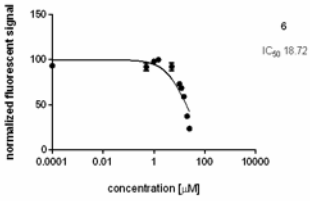
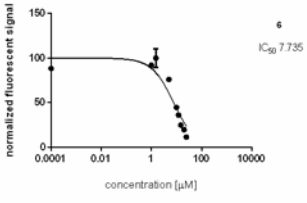
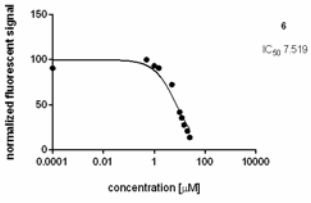


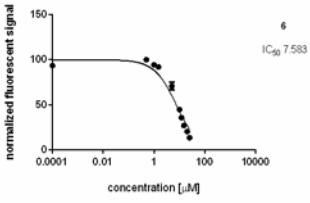
CT-26 cytotoxicity replicate 1



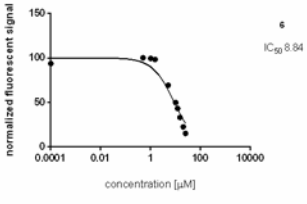
CT-26 cytotoxicity replicate 2



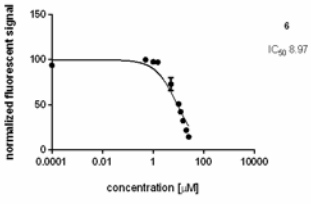
CT-26 cytotoxicity replicate 3



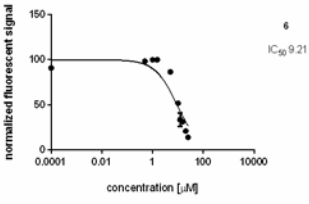
CT-26 LUC cytotoxicity replicate 1



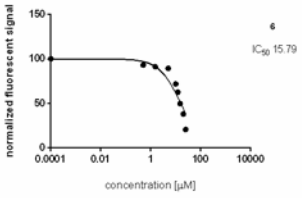
CT-26 LUC cytotoxicity replicate 2



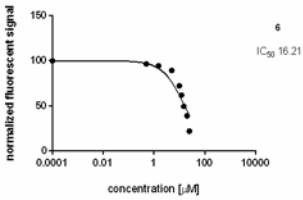
CT-26 LUC cytotoxicity replicate 3



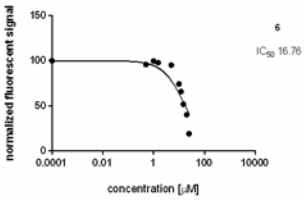
RPE-1 cytotoxicity replicate 1



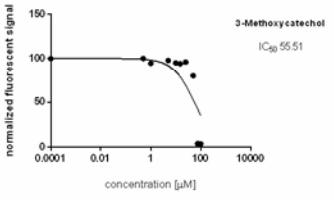
RPE-1 cytotoxicity replicate 2



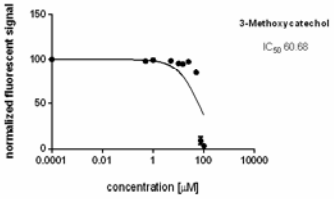
RPE-1 cytotoxicity replicate 3



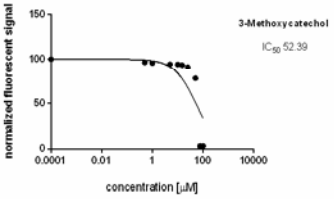
HeLa cytotoxicity replicate 1



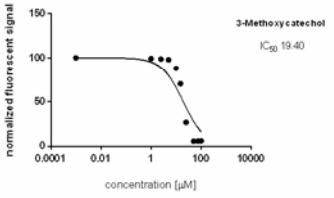
HeLa cytotoxicity replicate 2



HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



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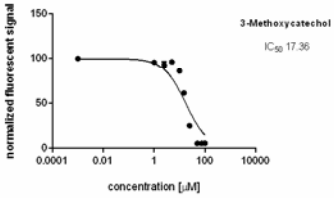

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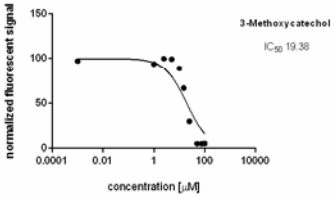
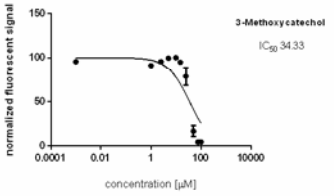


A2780 ADR cytotoxicity replicate 1



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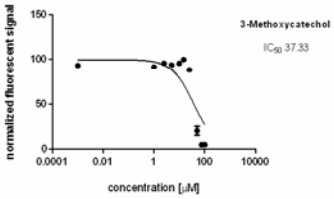

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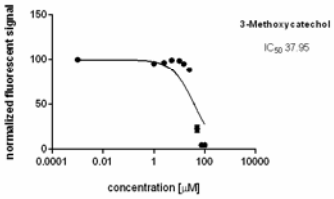

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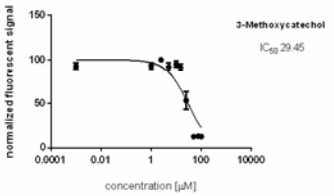
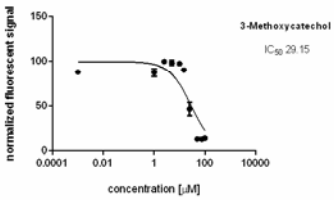
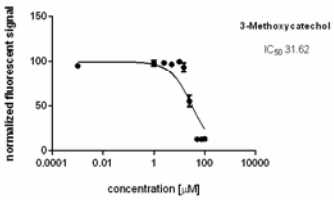


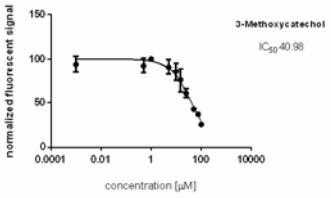
A2780 cis cytotoxicity replicate 2



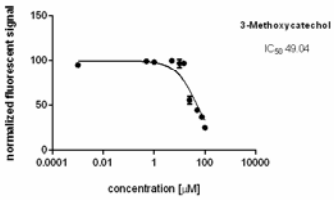
A2780 cis cytotoxicity replicate 3



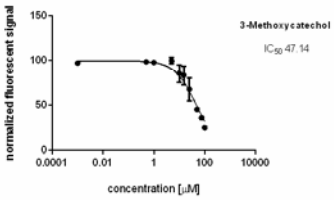
CT-26 cytotoxicity replicate 1



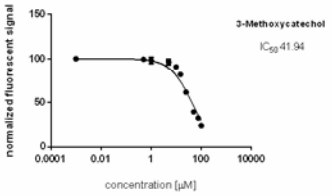
CT-26 cytotoxicity replicate 2



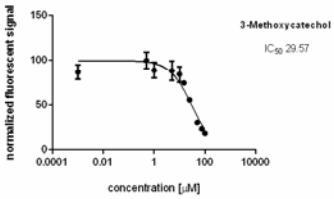
CT-26 cytotoxicity replicate 3



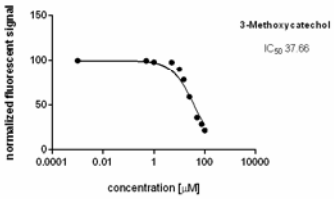
CT-26 LUC cytotoxicity replicate 1



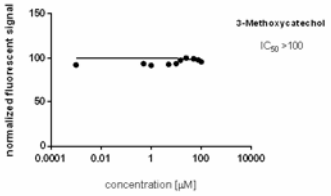
CT-26 LUC cytotoxicity replicate 2



CT-26 LUC cytotoxicity replicate 3



RPE-1 cytotoxicity replicate 1



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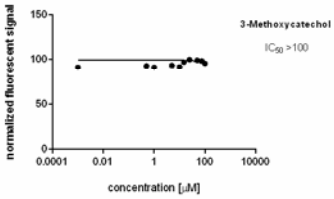

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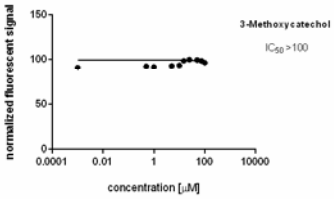
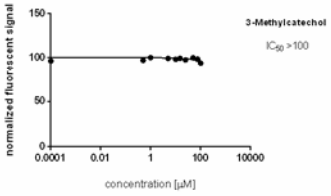
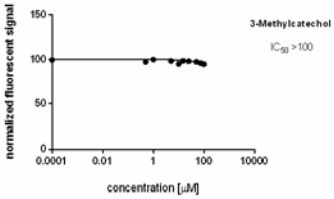


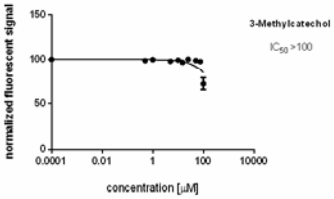
HeLa cytotoxicity replicate 1



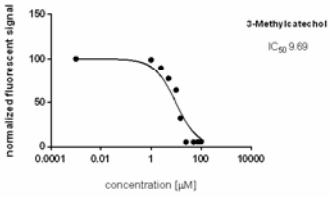
HeLa cytotoxicity replicate 2



HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



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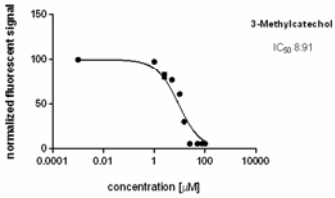

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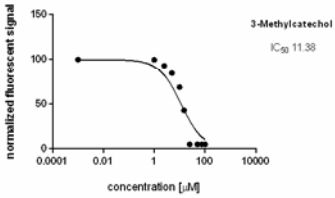

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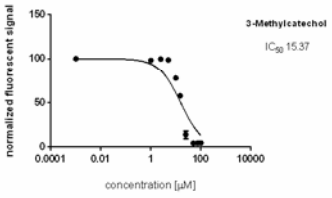

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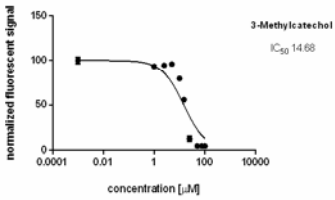

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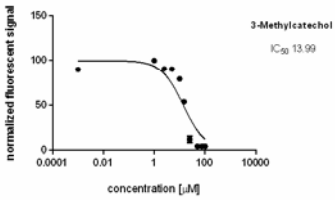

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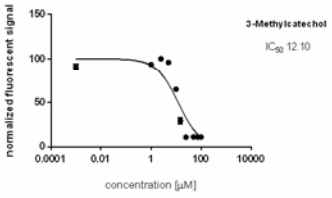

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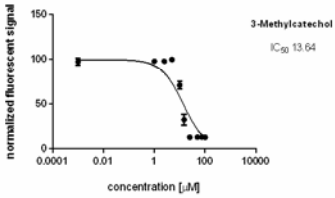
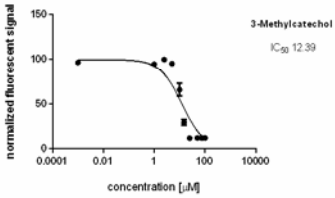
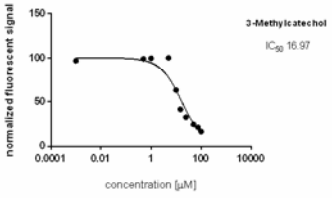


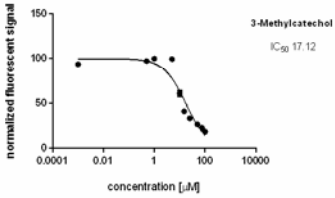
A2780 cis cytotoxicity replicate 3



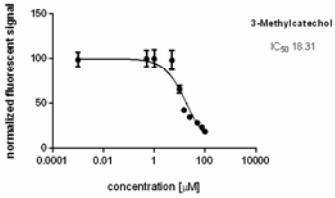
CT-26 cytotoxicity replicate 1



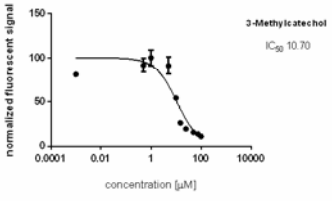
CT-26 cytotoxicity replicate 2



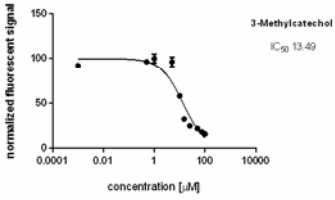
CT-26 cytotoxicity replicate 3



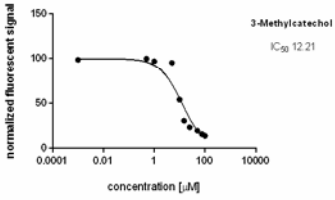
CT-26 LUC cytotoxicity replicate 1



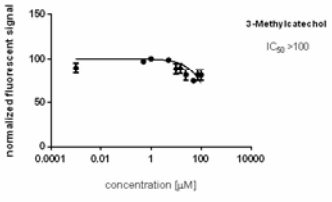
CT-26 LUC cytotoxicity replicate 2



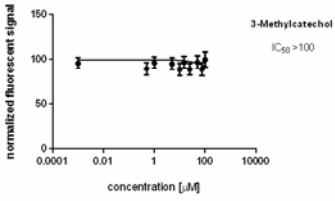
CT-26 LUC cytotoxicity replicate 3



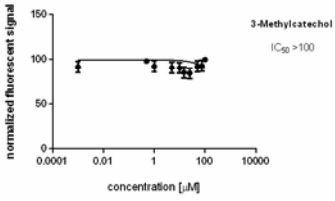
RPE-1 cytotoxicity replicate 1



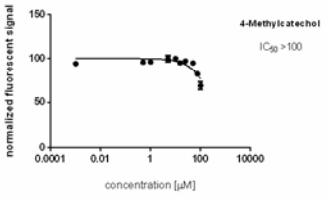
RPE-1 cytotoxicity replicate 2



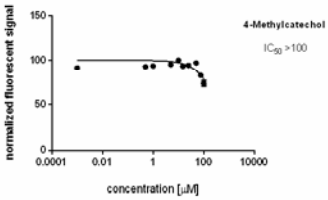
RPE-1 cytotoxicity replicate 3



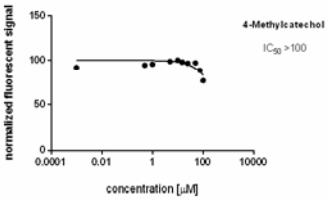
HeLa cytotoxicity replicate 1



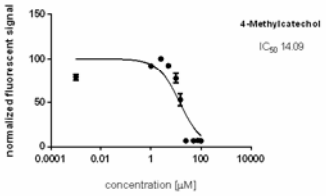
HeLa cytotoxicity replicate 2



HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



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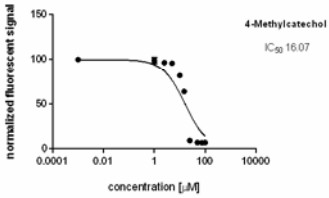

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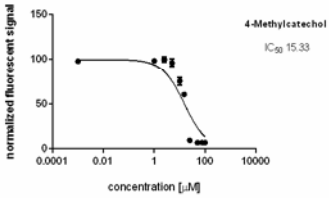
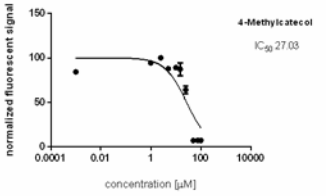
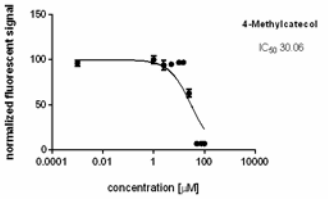


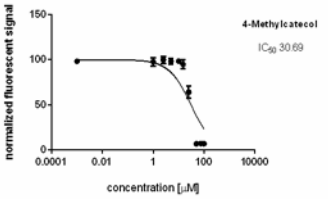
A2780 ADR cytotoxicity replicate 1



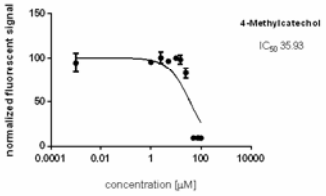
A2780 ADR cytotoxicity replicate 2



A2780 ADR cytotoxicity replicate 3



A2780 cis cytotoxicity replicate 1



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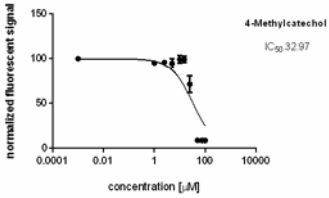

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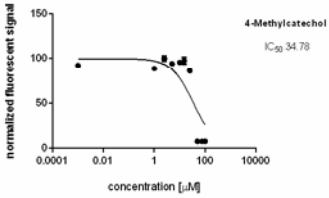
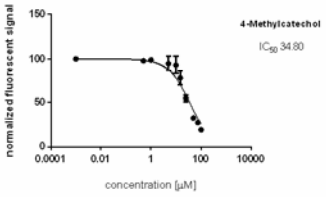
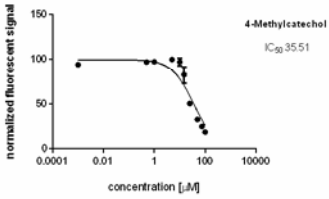


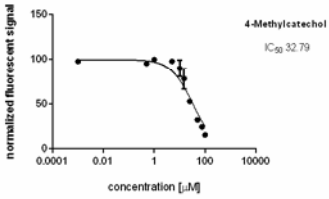
CT-26 cytotoxicity replicate 1



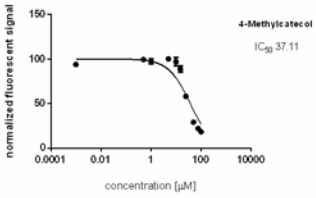
CT-26 cytotoxicity replicate 2



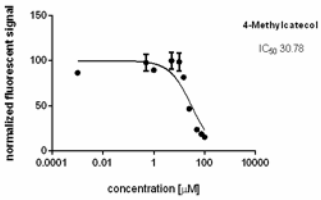
CT-26 cytotoxicity replicate 3



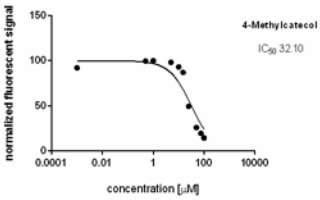
CT-26 LUC cytotoxicity replicate 1



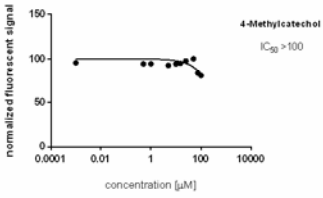
CT-26 LUC cytotoxicity replicate 2



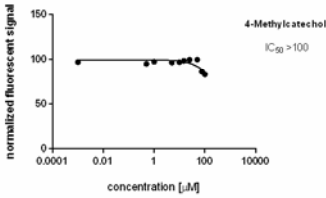
CT-26 LUC cytotoxicity replicate 3



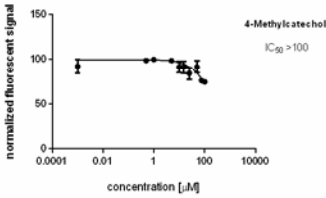
RPE-1 cytotoxicity replicate 1



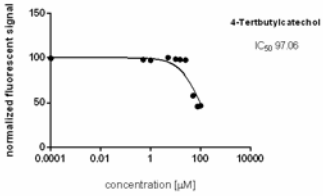
RPE-1 cytotoxicity replicate 2



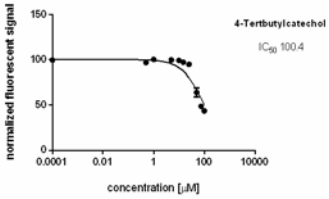
RPE-1 cytotoxicity replicate 3



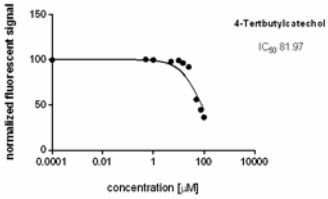
HeLa cytotoxicity replicate 1



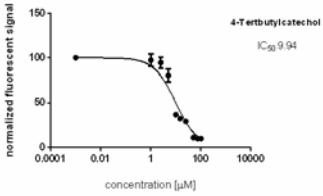
HeLa cytotoxicity replicate 2



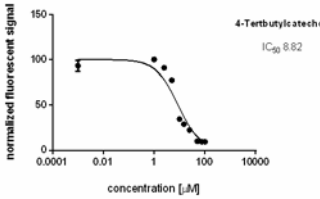
HeLa cytotoxicity replicate 3



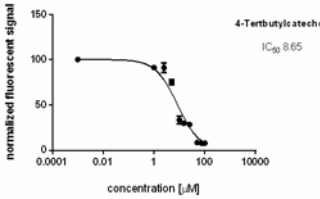
A2780 cytotoxicity replicate 1



A2780 cytotoxicity replicate 2



A2780 cytotoxicity replicate 3



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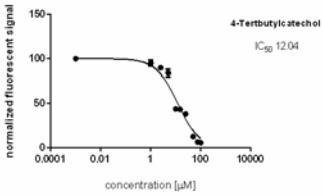

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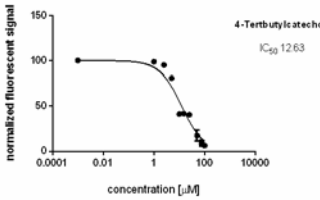
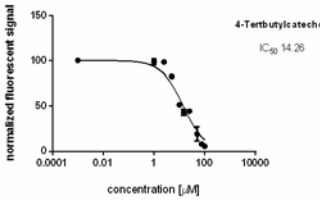


A2780 ADR cytotoxicity replicate 3



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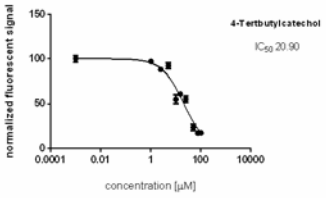

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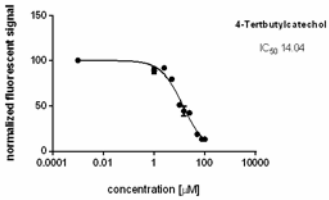

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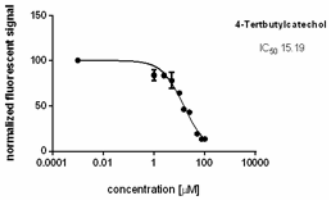
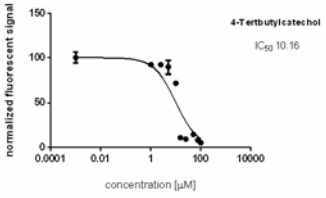
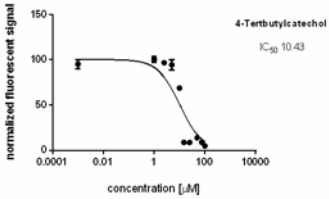


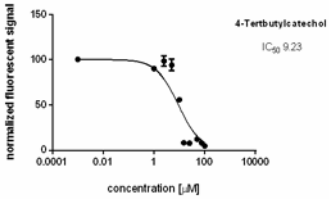
CT-26 cytotoxicity replicate 1



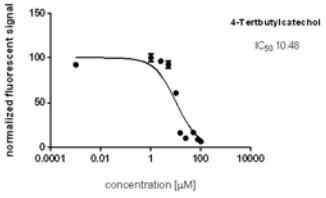
CT-26 cytotoxicity replicate 2



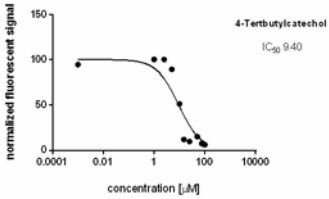
CT-26 cytotoxicity replicate 3



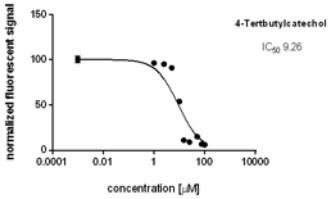
CT-26 LUC cytotoxicity replicate 1



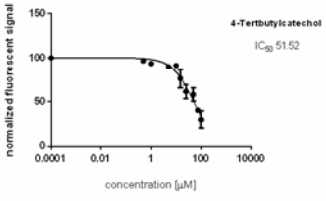
CT-26 LUC cytotoxicity replicate 2



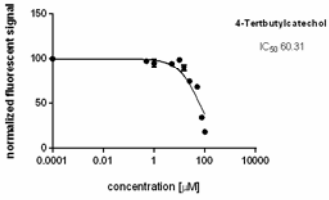
CT-26 LUC cytotoxicity replicate 3



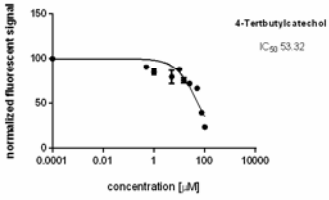
RPE-1 cytotoxicity replicate 1



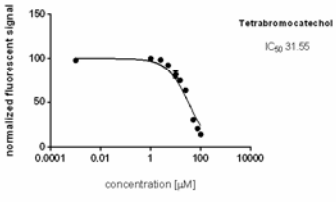
RPE-1 cytotoxicity replicate 2



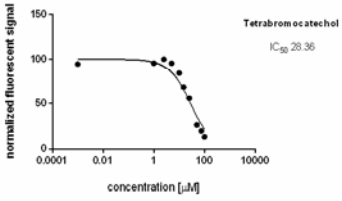
RPE-1 cytotoxicity replicate 3



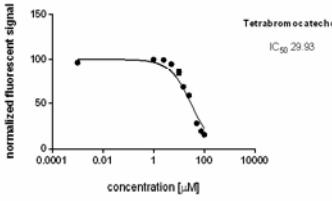
HeLa cytotoxicity replicate 1



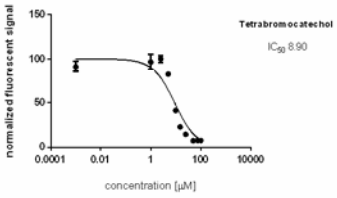
HeLa cytotoxicity replicate 2



HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



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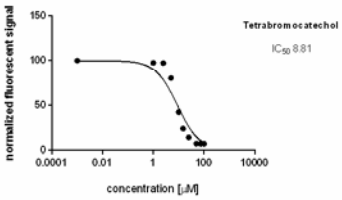

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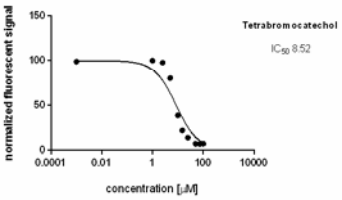

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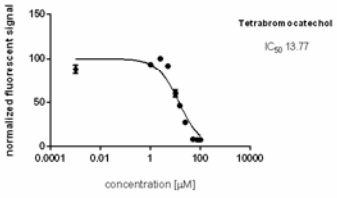

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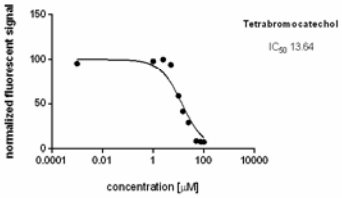

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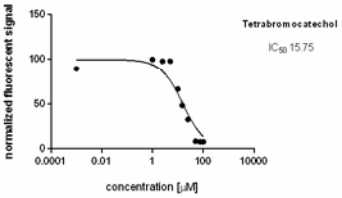
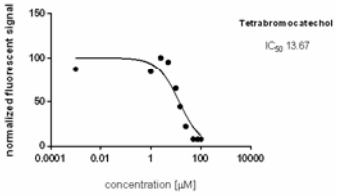


A2780 cis cytotoxicity replicate 1



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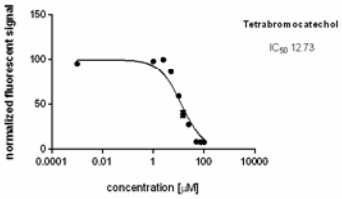

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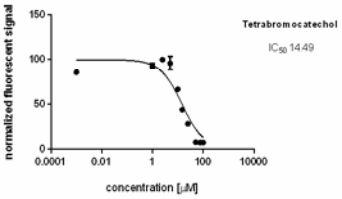
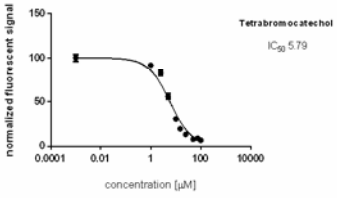
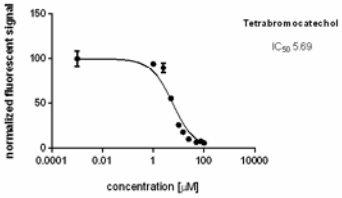


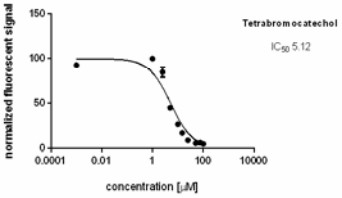
CT-26 cytotoxicity replicate 1



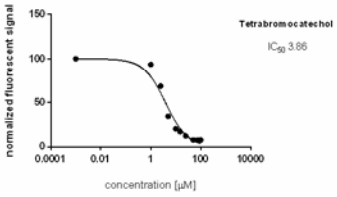
CT-26 cytotoxicity replicate 2



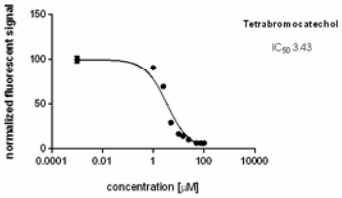
CT-26 cytotoxicity replicate 3



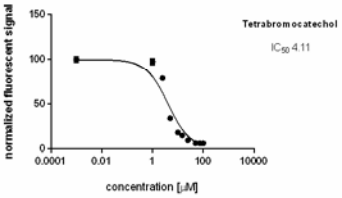
CT-26 LUC cytotoxicity replicate 1



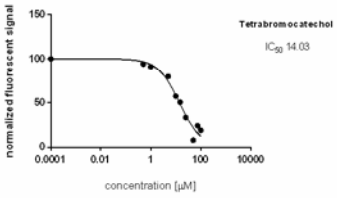
CT-26 LUC cytotoxicity replicate 2



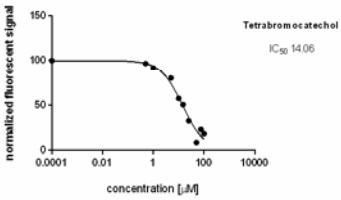
CT-26 LUC cytotoxicity replicate 3



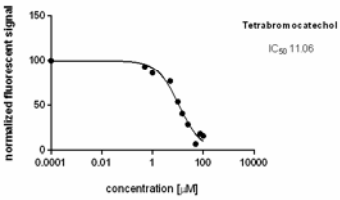
RPE-1 cytotoxicity replicate 1



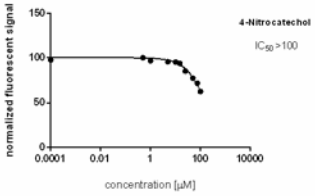
RPE-1 cytotoxicity replicate 2



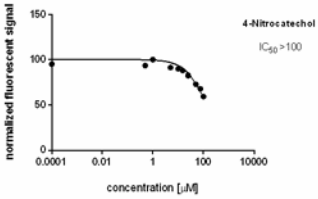
RPE-1 cytotoxicity replicate 3



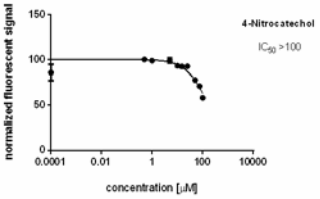
HeLa cytotoxicity replicate 1



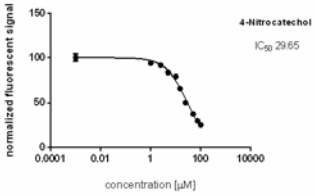
HeLa cytotoxicity replicate 2



HeLa cytotoxicity replicate 3



A2780 cytotoxicity replicate 1



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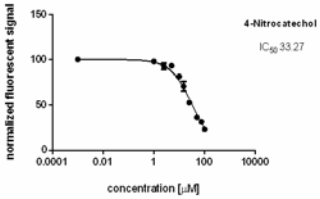

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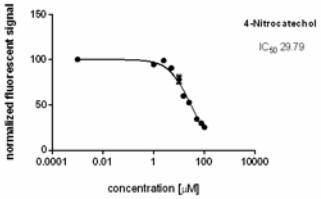
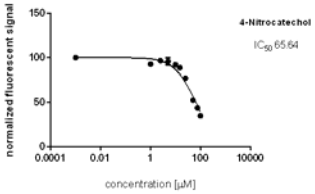
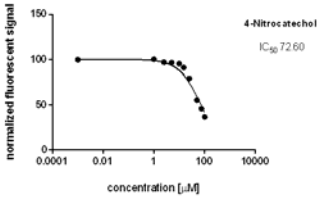


A2780 ADR cytotoxicity replicate 1



A2780 ADR cytotoxicity replicate 2



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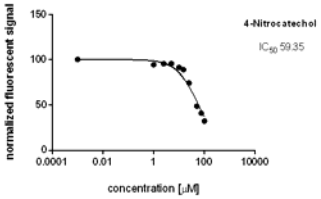
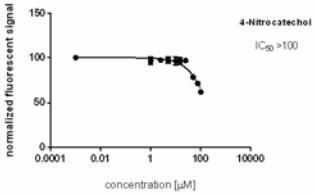
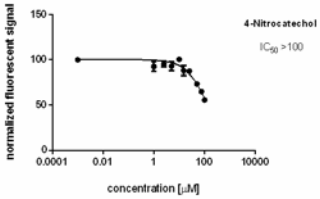


A2780 cis cytotoxicity replicate 1



A2780 cis cytotoxicity replicate 2



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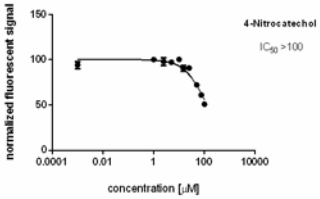
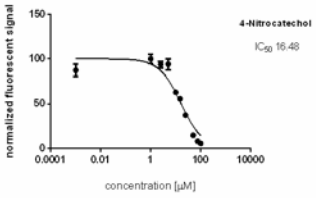
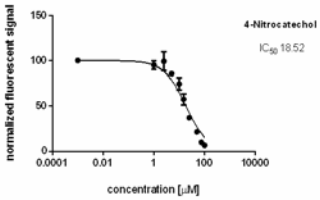


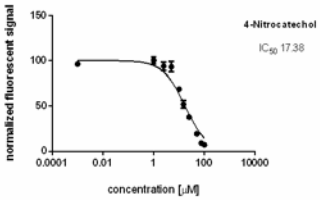
CT-26 cytotoxicity replicate 1



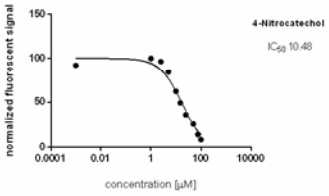
CT-26 cytotoxicity replicate 2



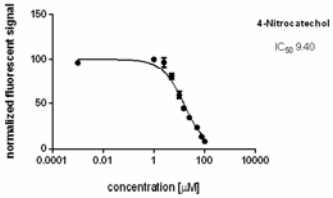
CT-26 cytotoxicity replicate 3



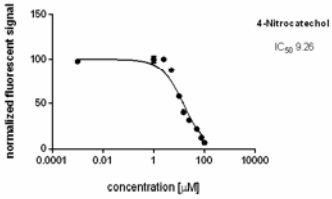
CT-26 LUC cytotoxicity replicate 1



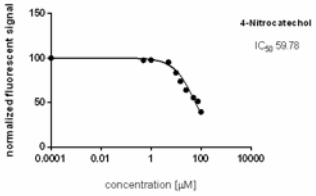
CT-26 LUC cytotoxicity replicate 2



CT-26 LUC cytotoxicity replicate 3



RPE-1 cytotoxicity replicate 1



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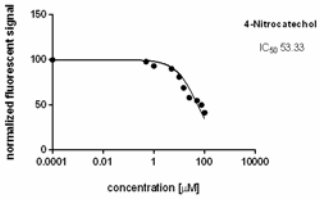

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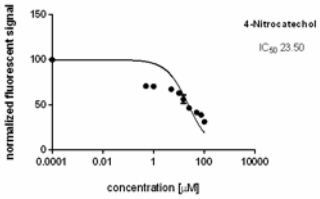
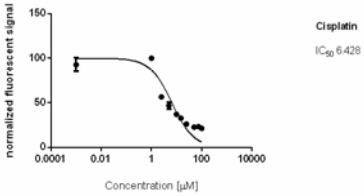
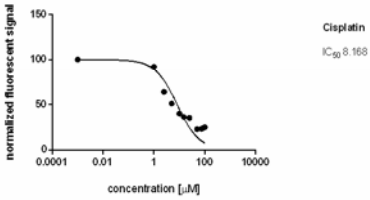


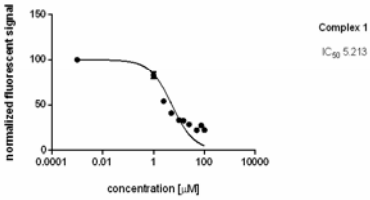
HEK293 cytotoxicity replicate 1



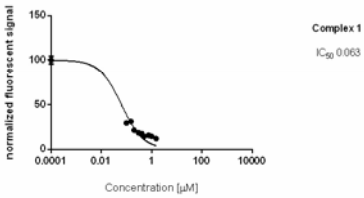
HEK293 cytotoxicity replicate 2



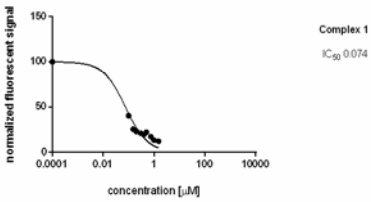
HEK293 cytotoxicity replicate 3



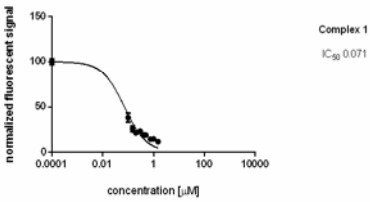
HEK293 cytotoxicity replicate 1



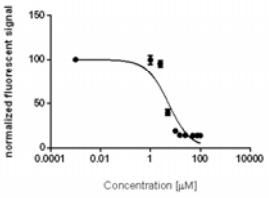
HEK293 cytotoxicity replicate 2



HEK293 cytotoxicity replicate 3



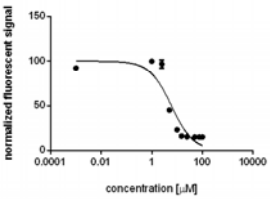
HEK293 cytotoxicity replicate 1



$Ru(DIP)_3Cl_2$

IC_{50} 5.31

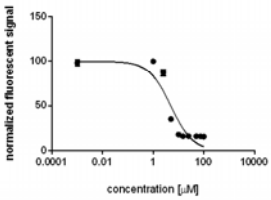
HEK293 cytotoxicity replicate 2



$Ru(DIP)_3Cl_2$

IC_{50} 5.98

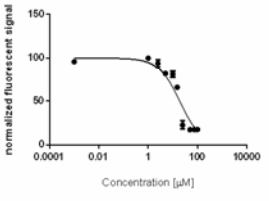
HEK293 cytotoxicity replicate 3



$Ru(DIP)_3Cl_2$

IC_{50} 4.97

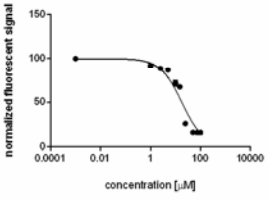
HEK293 cytotoxicity replicate 1



3-methoxycatechol

IC_{50} 19.01

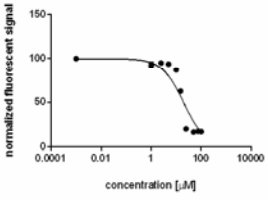
HEK293 cytotoxicity replicate 2



3-methoxycatechol

IC_{50} 18.06

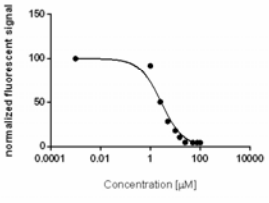
HEK293 cytotoxicity replicate 3



3-methoxycatechol

IC_{50} 19.81

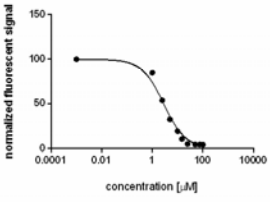
HEK293 cytotoxicity replicate 1



Cisplatin

IC_{50} 2.76

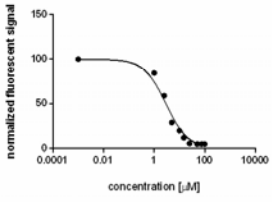
HEK293 cytotoxicity replicate 2



Cisplatin

IC_{50} 2.82

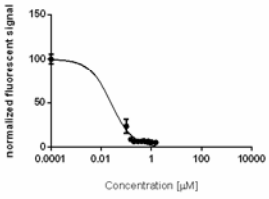
HEK293 cytotoxicity replicate 3



Cisplatin

IC_{50} 2.92

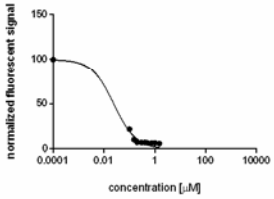
HEK293 cytotoxicity replicate 1



Complex 1

IC_{50} 0.0243

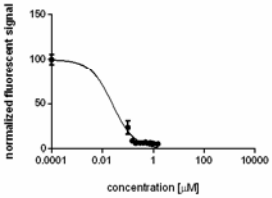
HEK293 cytotoxicity replicate 2



Complex 1

IC_{50} 0.0242

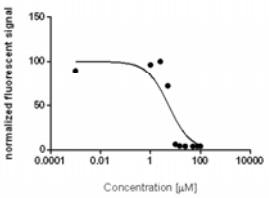
HEK293 cytotoxicity replicate 3



Complex 1

IC_{50} 0.0243

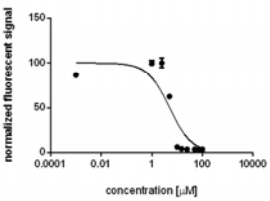
HEK293 cytotoxicity replicate 1



$Ru(DIP)_3Cl_2$

IC_{50} 5.38

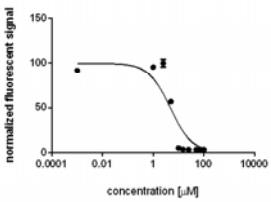
HEK293 cytotoxicity replicate 2



$Ru(DIP)_3Cl_2$

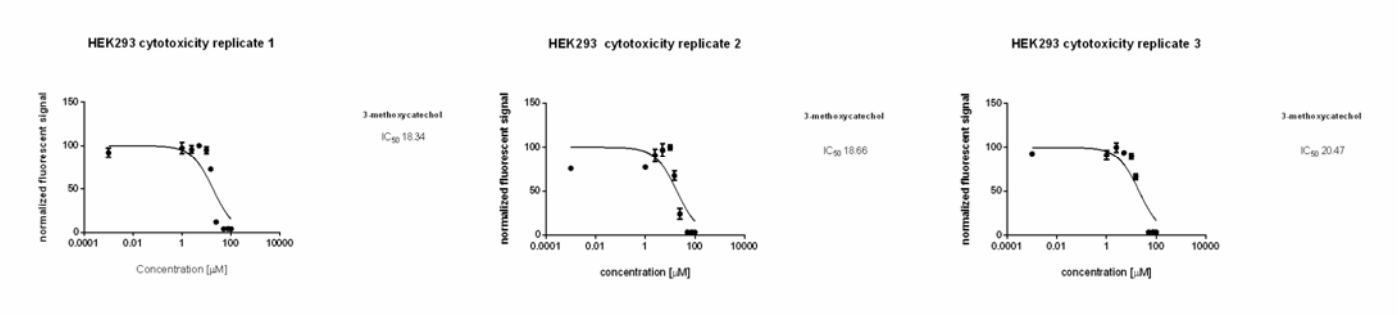
IC_{50} 5.07

HEK293 cytotoxicity replicate 3



$Ru(DIP)_3Cl_2$

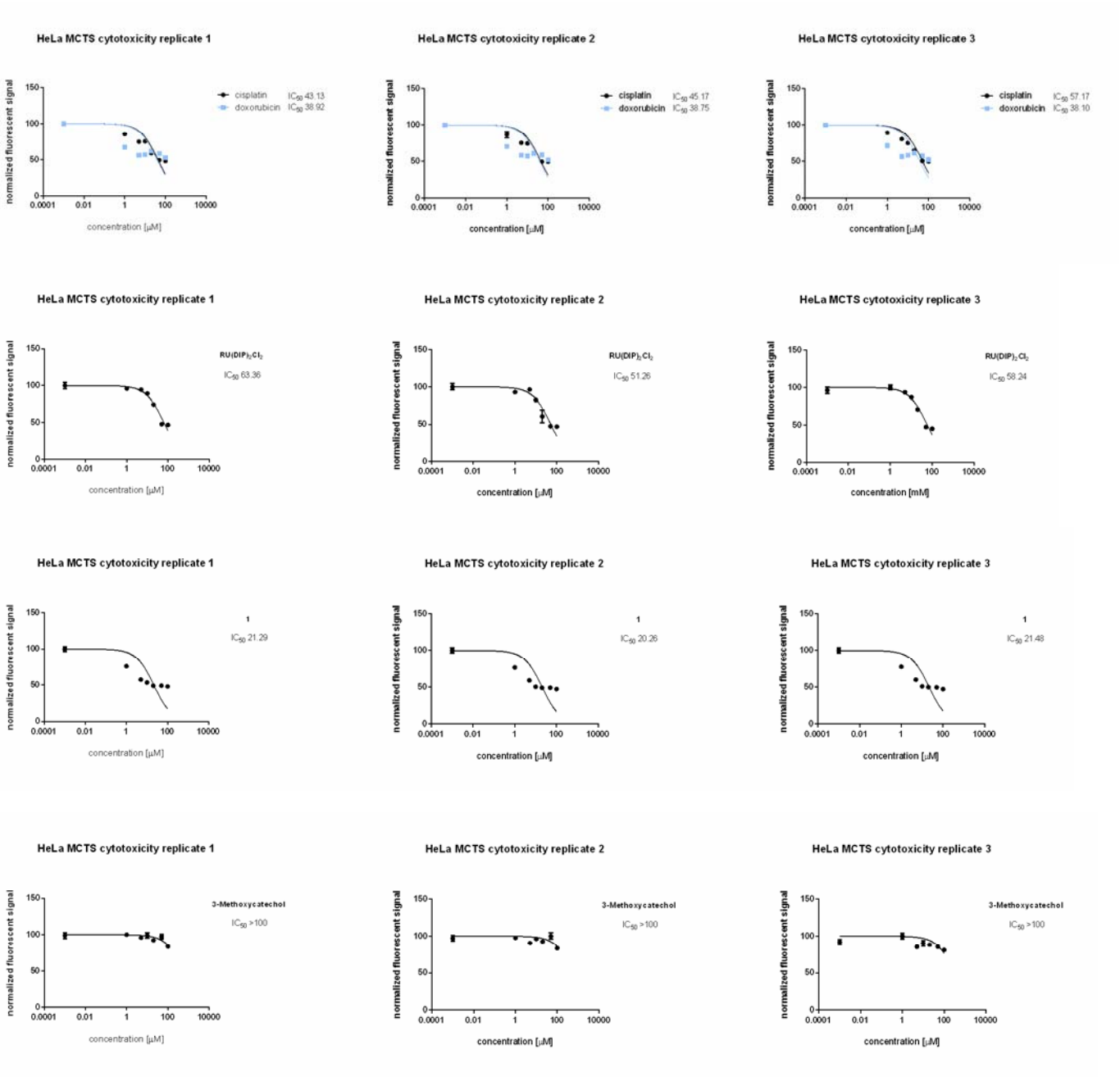
IC_{50} 4.75


HEK293 cytotoxicity replicate 1
normalized fluorescent signal
150
100
50
0
0.0001
0.01
1
100
10000
Concentration [µM]
3-methoxycatechol
IC50 18.34
HEK293 cytotoxicity replicate 2
normalized fluorescent signal
150
100
50
0
0.0001
0.01
1
100
10000
concentration [µM]
3-methoxycatechol
IC50 18.66
HEK293 cytotoxicity replicate 3
normalized fluorescent signal
150
100
50
0
0.0001
0.01
1
100
10000
concentration [µM]
3-methoxycatechol
IC50 20.47

13) **Table S5.** IC_{50} values for 3-methoxycatechol, 3-methylcatechol, 4-methylcatechol, 4-tertbutylcatechol, tetrabromocatechol and 4-nitrocatechol.

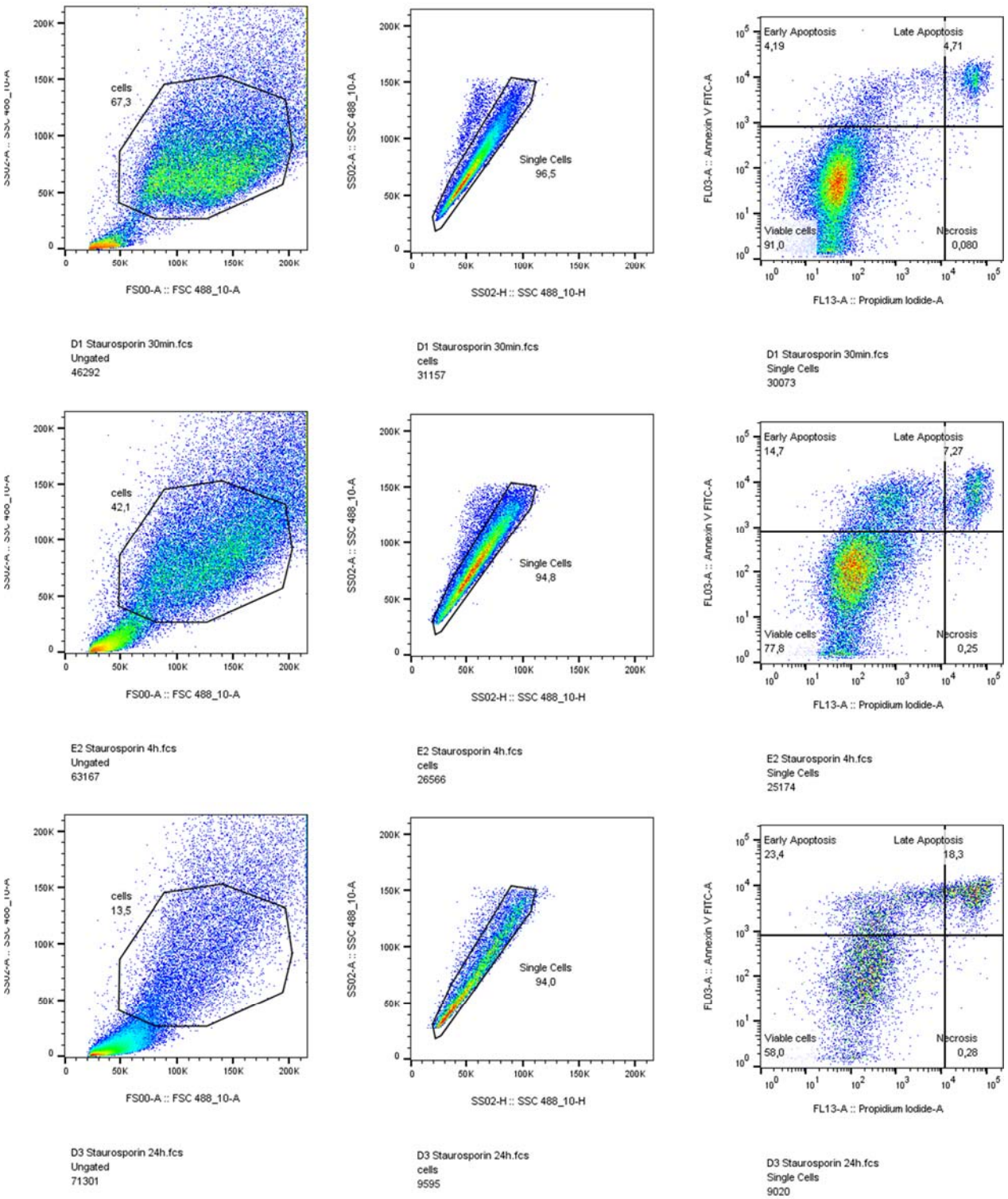
IC_{50} (μM)	HeLa	A2780	A2780 ADR	A2780 cis	CT-26	CT-26 LUC	RPE-1
3-methoxycatechol	56.19 ± 4.18	18.71 ± 1.17	36.54 ± 1.94	30.07 ± 1.35	45.72 ± 4.21	36.39 ± 6.28	>100
3-methylcatechol	>100	9.99 ± 1.26	14.68 ± 0.69	12.71 ± 0.82	17.47 ± 0.73	12.13 ± 1.40	>100
4-methylcatechol	>100	15.16 ± 1.0	29.27 ± 1.96	34.56 ± 1.49	34.37 ± 1.41	33.33 ± 3.4	>100
4-tertbutylcatechol	93.14 ± 9.8	9.14 ± 0.7	12.89 ± 1.20	16.71 ± 3.67	9.94 ± 0.63	9.72 ± 0.67	55.05 ± 4.64
Tetrabromocatechol	29.95 ± 1.60	8.75 ± 0.20	14.39 ± 1.18	13.63 ± 0.88	5.53 ± 0.37	3.80 ± 0.34	13.5 ± 1.7
4-nitrocatechol	>100	30.90 ± 2.05	65.86 ± 6.62	>100	17.46 ± 1.02	15.31 ± 1.0	45 ± 19

14) **Figure S9.** CellTiter Glo® viability Test

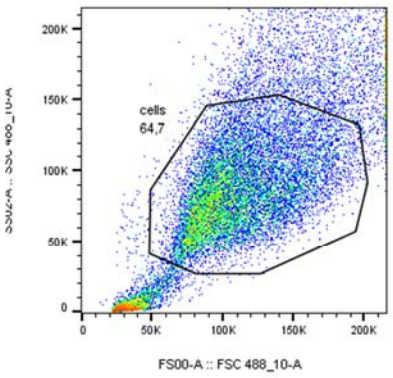


15) **Figure S10.** Cell Death Mechanism: Dot plots of staurosporin (a) and complex **1** (b) after 30 min, 4 h and 24 h treatment.

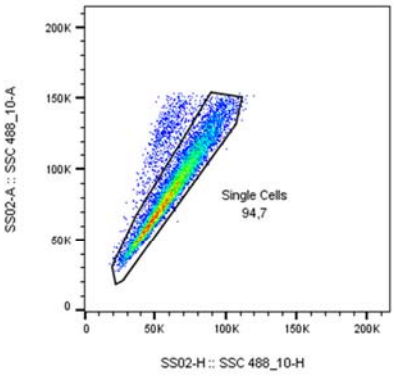
a)



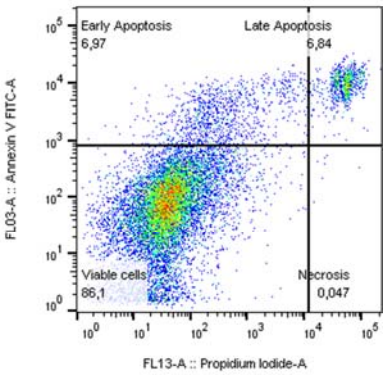
b)



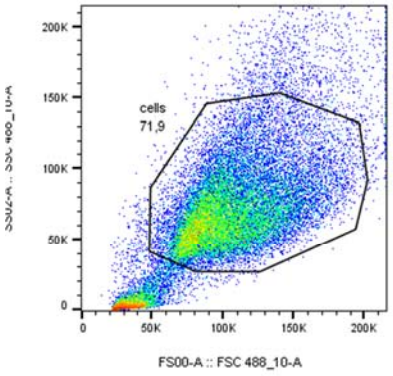
C2 Complex1 30min 2.fcs
Ungated
24331



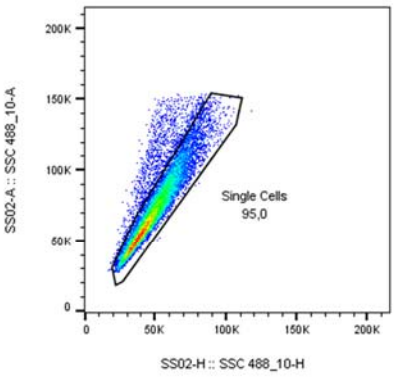
C2 Complex1 30min 2.fcs
cells
15744



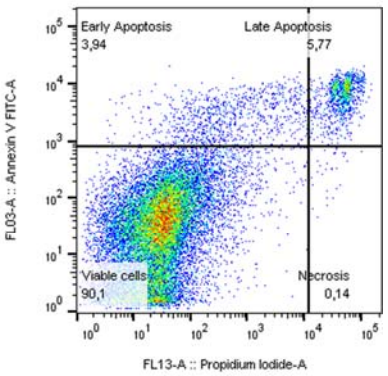
C2 Complex1 30min 2.fcs
Single Cells
14911



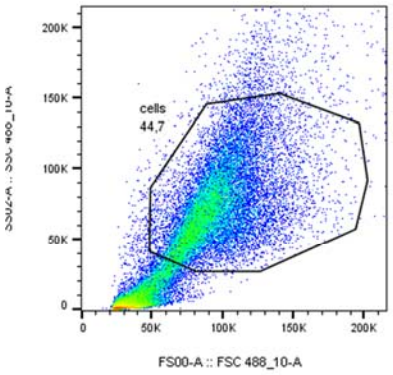
C4 Complex1 4h 2.fcs
Ungated
35597



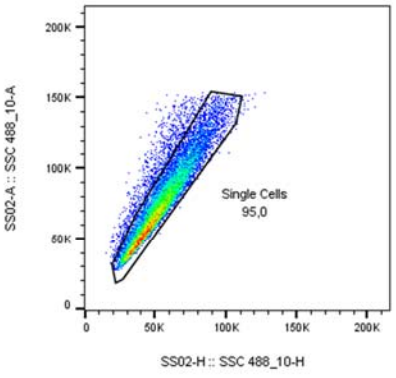
C4 Complex1 4h 2.fcs
cells
25597



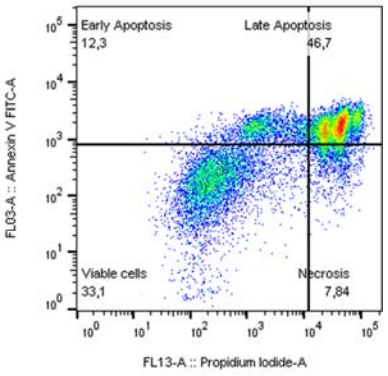
C4 Complex1 4h 2.fcs
Single Cells
24312



C6 Complex1 24h 2.fcs
Ungated
45617

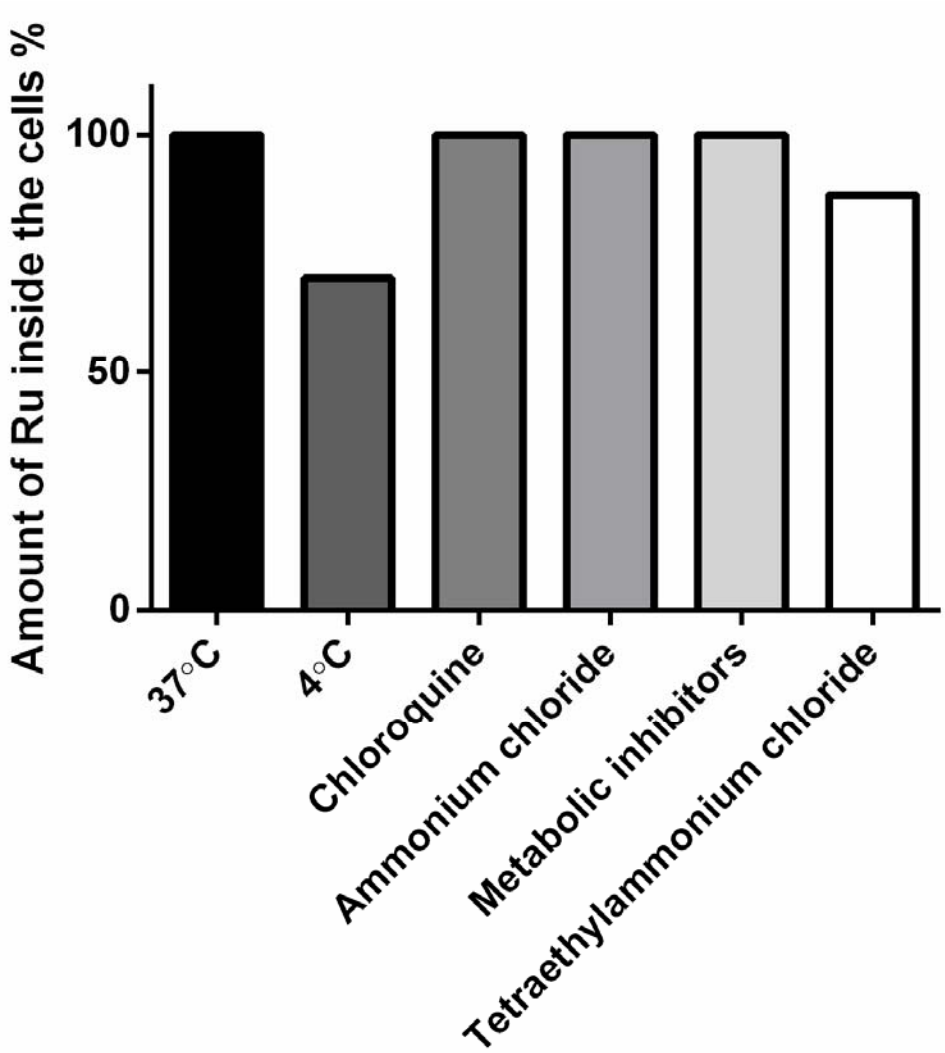


C6 Complex1 24h 2.fcs
cells
20390

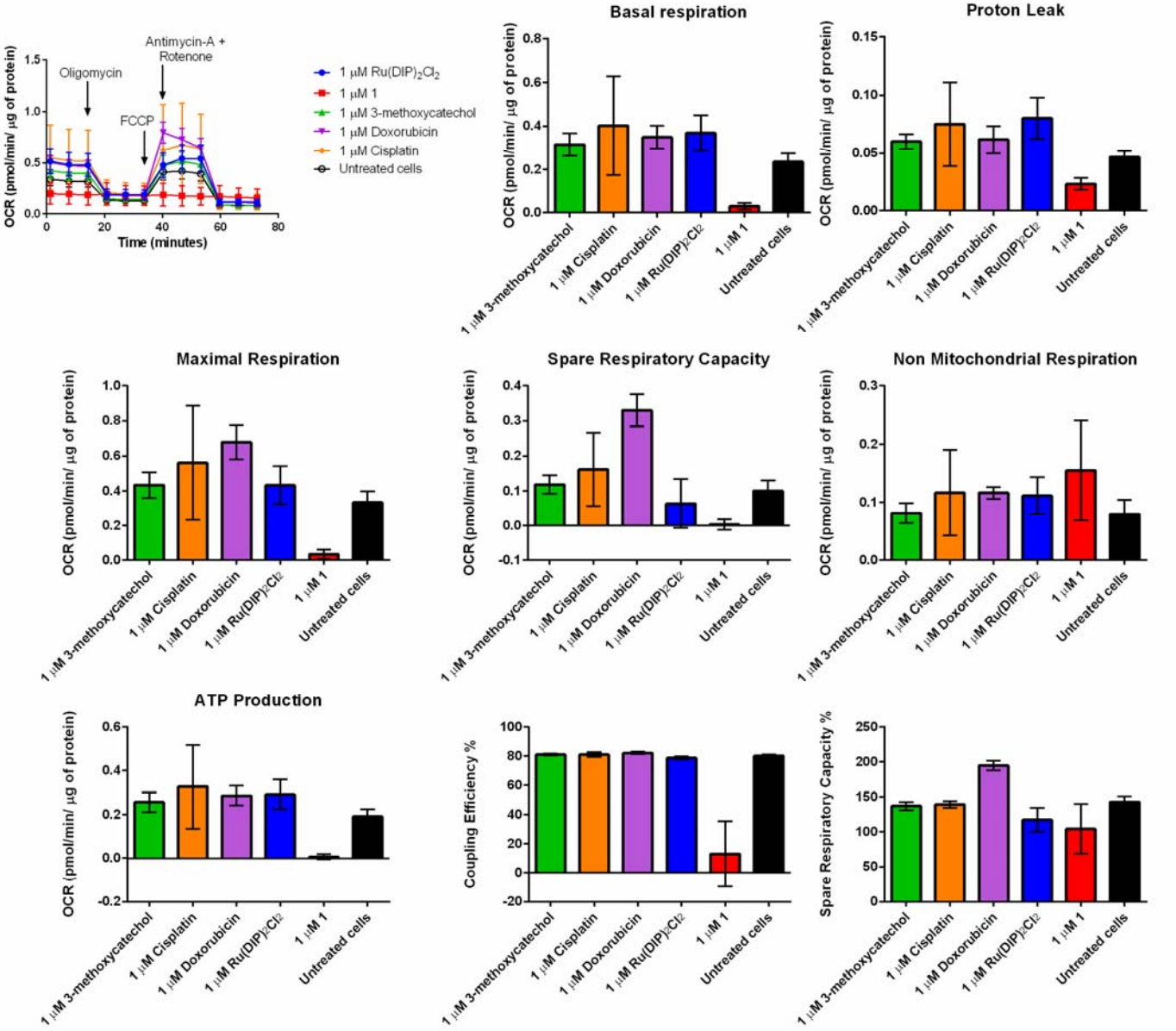


C6 Complex1 24h 2.fcs
Single Cells
19366

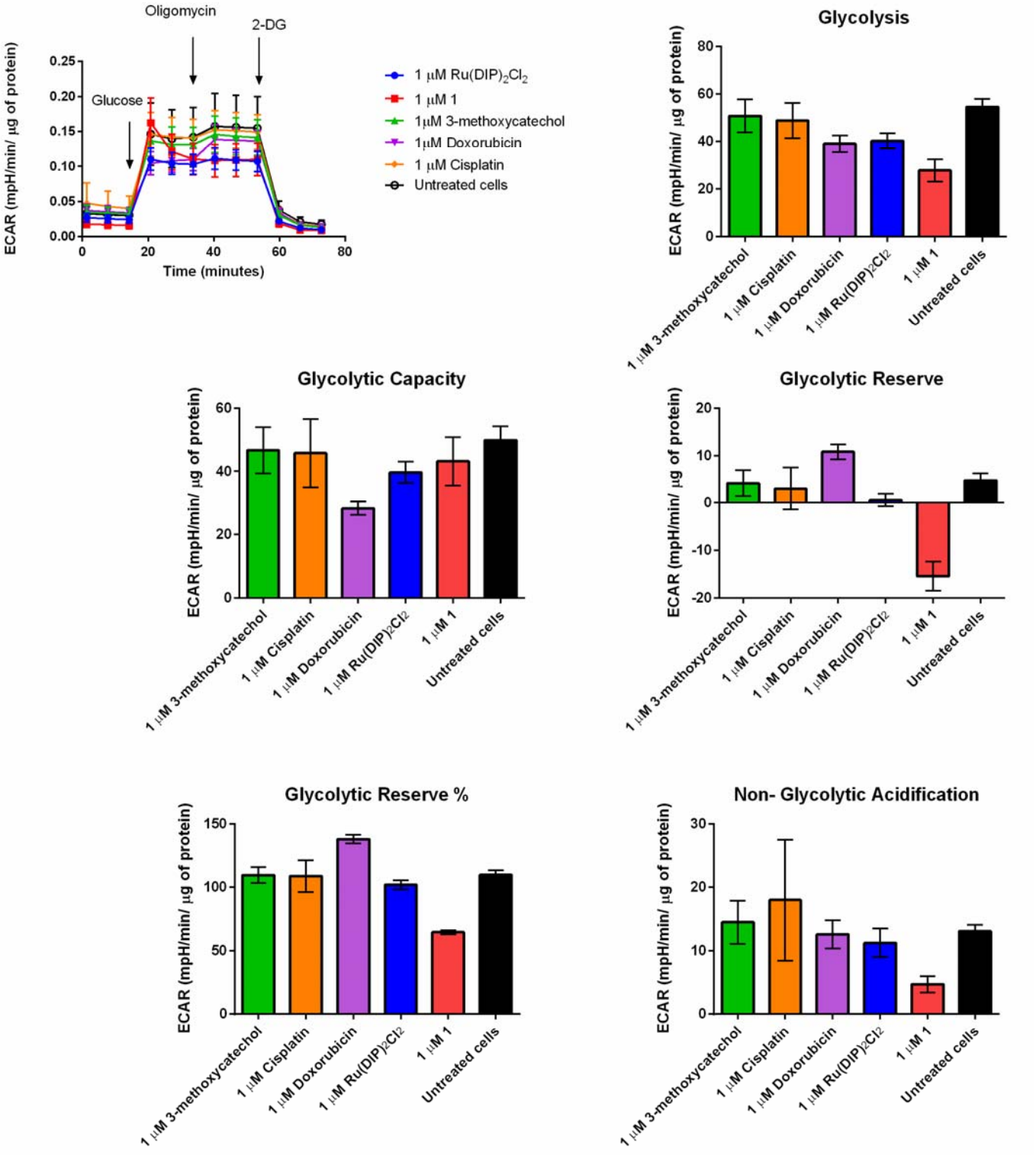
16) **Figure S11.** Cellular uptake mechanism of complex **1**. Accumulation of ruthenium in HeLa cells in presence of different inhibitors and conditions: low temperature (4ºC), blocked cellular metabolism (2-Deoxy-D-glucose, oligomycin), blocked endocytic pathways (chloroquine or ammonium chloride), blocked cation transporters (tetraethylammonium chloride). Cells were pre-treated with uptake inhibitors and then incubated with 1 (2 h, 5 μM). Amounts of ruthenium were measured using ICP-MS.



17) **Figure S12.** Oxygen consumption rates and different respiration parameters in HeLa cells alone or after treatment with various test compounds.



18) **Figure S13.** Extracellular acidification rate and different parameters of glycolysis in HeLa cells alone or after treatment with various test compounds.



19) **Figure S14.** Fuel flex assay in HeLa cells. Dependency studies were performed by adding the inhibitor for the target pathway in port A and inhibitors for the other two pathways in port B while capacity studies were done using the reverse sequence. UK-5099 (20 μM), BPTES (30 μM) and etomoxir (40 μM) were used as the inhibitors for the fuela pathways run by glucose, glutamine and fatty acids.