

# Supporting Information

## Theoretical investigations and density functional theory based quantitative structure activity relationships model for novel cytotoxic Pt(IV) complexes

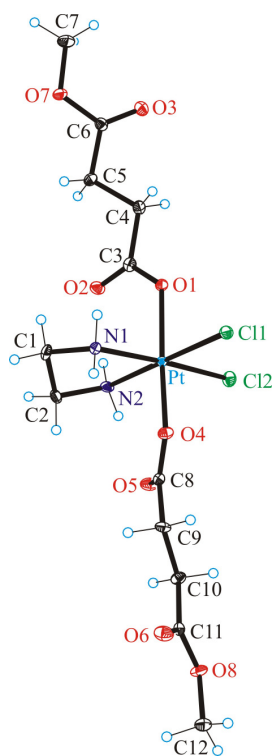
*Hristo Varbanov<sup>†</sup>, Michael A. Jakupec<sup>†</sup>, Alexander Roller<sup>†</sup>, Frank Jensen<sup>‡\*</sup>, Markus Galanski<sup>‡\*</sup>,  
and Bernhard K. Keppler<sup>†</sup>*

<sup>†</sup> University of Vienna, Institute of Inorganic Chemistry, Währinger Strasse 42, A-1090 Vienna,  
Austria

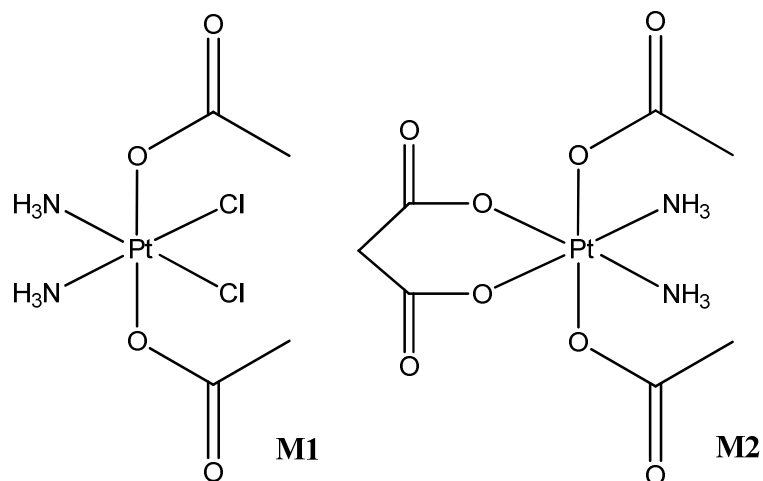
<sup>‡</sup> University of Aarhus, Department of Chemistry, Langelandgade 140, 8000 Aarhus C, Denmark

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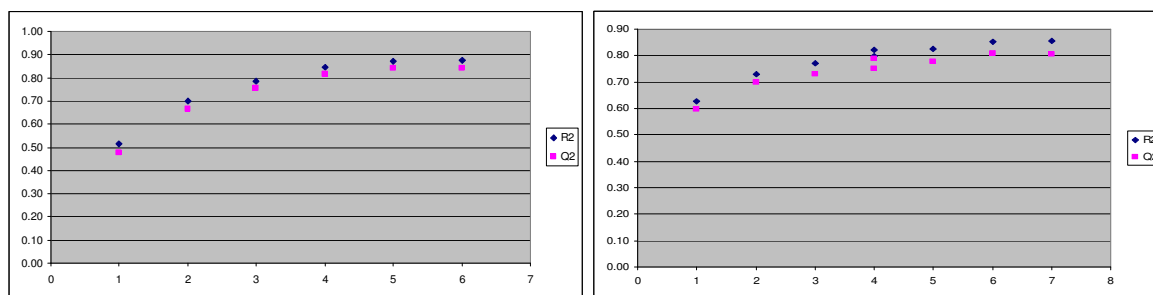
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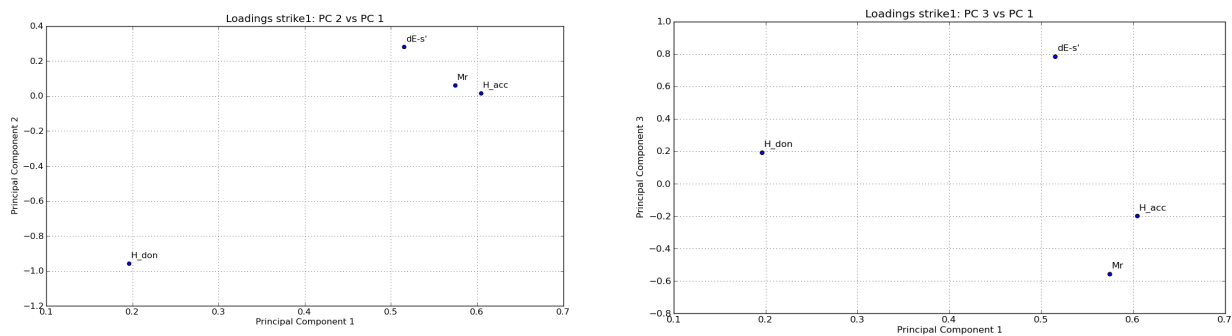
**Figure S1.** ORTEP view of **7** with atom labeling scheme. The thermal ellipsoids have been drawn at 50% probability level.



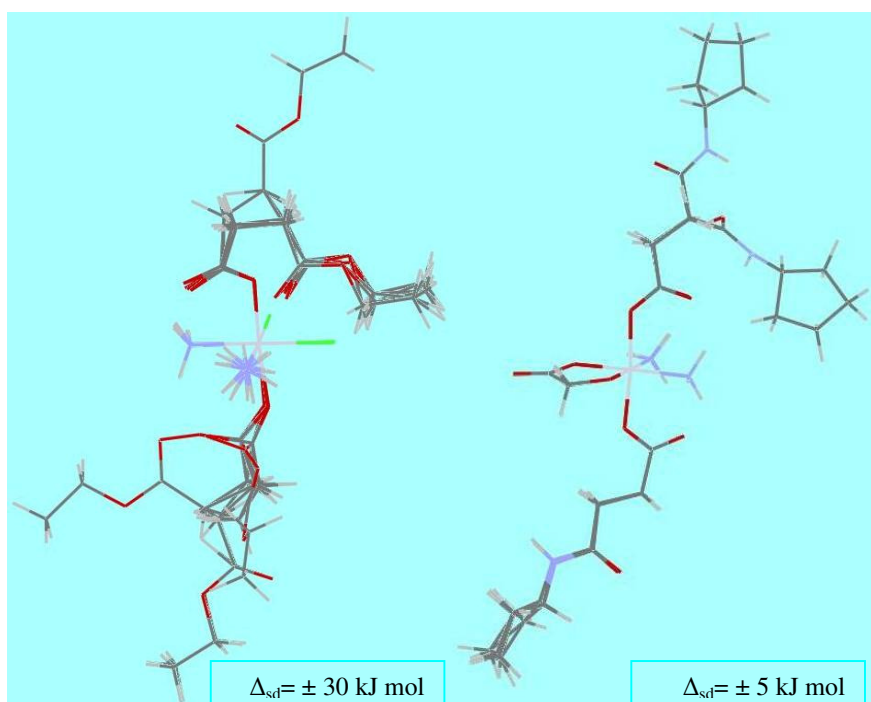
**Figure S2.** Chemical structure of model systems **M1** and **M2**



**Figure S3.** Dependency of the linear fit ( $R^2$ ) and predictability ( $Q^2$ ) of the QSAR models from the number of descriptors used for CH1 (left) and for SW480 (right) cells.



**Figure S4.** Loading plots derived from PCA on the four descriptors ( $MW$ ,  $E_{eas'}$ ,  $H_{don}$  and  $H_{acc}$ ), used in the proposed model for cytotoxicity in CH1 cells.



**Figure S5.** Superposition of the optimized four conformers of complex **2** (left) and two conformers of complex **50** (right).

**Table S1.** Comparison of crystal structure and wb97x optimized geometries in the gas phase and in a solvent model for **1**, **6**, **7**, **22** and **38**.

bond lengths(Å), angles(°)		<b>1</b>	<b>6</b>	<b>7</b>	<b>22</b>	<b>38</b>
Pt-N	X-ray	2.050, 2.066	2.054, 2.054	2.050, 2.036	2.063, 2.068	2.050, 2.050
	DFT/gas	2.074, 2.085	2.085, 2.085	2.088, 2.076	2.107, 2.100	2.073, 2.073
	DFT/solv	2.062, 2.055	2.058, 2.058	2.060, 2.053	2.076, 2.080	2.050, 2.051
Pt-Cl/Pt-O <sub>eq</sub>	X-ray	2.311, 2.319	2.318, 2.318	2.338, 2.307	2.309, 2.324	2.005, 2.031
	DFT/gas	2.310, 2.321	2.307, 2.307	2.318, 2.297	2.319, 2.306	1.965, 1.966
	DFT/solv	2.340, 2.334	2.338, 2.338	2.328, 2.348	2.335, 2.343	1.988, 1.990
Pt-O <sub>ax</sub>	X-ray	1.993, 2.008	2.011, 2.011	2.000, 2.031	2.039, 2.039	1.997, 1.965
	DFT/gas	2.013, 2.018	2.016, 2.016	2.012, 2.018	1.998, 2.030	2.011, 2.017
	DFT/solv	2.013, 2.016	2.015, 2.015	2.017, 2.012	2.001, 2.025	2.011, 2.017
N-Pt-N	X-ray	90.2	83.7	83.3	92.7	93.1
	DFT/gas	91.0	83.1	83.5	95.9	93.2
	DFT/solv	90.1	83.4	83.4	93.9	91.3
Cl-Pt-Cl/ O <sub>eq</sub> -Pt-O <sub>eq</sub>	X-ray	94.4	91.2	89.6	92.2	95.1
	DFT/gas	95.1	94.7	94.1	94.4	97.7
	DFT/solv	93.7	93.0	92.4	93.8	95.4
O <sub>ax</sub> -Pt-O <sub>ax</sub>	X-ray	172.6	174.5	168.7	172.7	171.8

	DFT/gas	175.7	176.0	172.3	171.1	173.9
	DFT/solv	174.6	176.8	172.1	171.8	173.1
Pt-O <sub>ax</sub> -C	X-ray	123.0, 125.3	125.5, 125.5	125.2, 126.7	123.7, 127.5	123.3, 127.7
	DFT/gas	122.6, 122.4	126.5, 126.5	126.8, 126.0	126.3, 126.7	122.8, 122.2
	DFT/solv	123.0, 123.3	126.2, 126.2	126.4, 125.9	128.6, 126.8	122.9, 123.3
Pt-N-C	X-ray	-	108.2, 108.2	109.2, 109.5	120.2, 118.7	-
	DFT/gas	-	108.2, 108.3	109.0, 107.5	120.6, 118.1	-
	DFT/solv	-	108.8, 108.8	108.3, 109.9	118.5, 120.5	-

**Table S2.** Calculated descriptors for the investigated compounds: molecular weight (MW), molar volume (Vm), polarizability ( $\alpha$ ), solvent accessible surface area (SASA), dipole moment ( $\mu$ ), charge at the Pt atom (q(Pt)), vertical and adiabatic energy of hydration (Es and Es'), number of H-bond donors and acceptors ( $H_{don}$  and  $H_{acc}$ ), presence (1) or absence (0) of COOH group.

The coloring is based on the subtypes, exerting the same equatorial ligands (Figure 2)

complex	MW (g/mol)	Vm (cm <sup>3</sup> /mol)	$\alpha$ (bohr <sup>3</sup> )	SASA (bohr <sup>2</sup> )	$\mu$ (D)	q (Pt) (a.u.)	Es (kJ/mol)	Es' (kJ/mol)	$H_{don}$	$H_{acc}$	COOH
1	534.22	222.60	215.54	1121.38	5.217	0.913	86.035	89.785	4	8	1
2a	590.32	280.04	266.29	1105.02	4.895	0.919	78.408	82.114	2	8	0
2b	590.32	318.18	270.31	1034.83	4.996	0.917	92.614	96.406	2	8	0
2c	590.32	278.93	264.05	1143.75	6.813	0.917	71.440	75.377	2	8	0
2d	590.32	308.56	265.24	1232.36	6.339	0.918	70.790	74.999	2	8	0
3	620.35	295.30	284.66	1490.84	2.696	0.922	110.316	115.194	6	10	0
4	616.41	320.11	300.92	1240.14	3.139	0.923	90.276	95.023	4	8	0
5	668.49	351.10	340.09	1270.93	4.711	0.924	92.679	97.081	4	8	0
6	560.24	262.29	235.78	1249.41	10.038	0.883	111.868	119.697	4	8	1
7	588.30	279.03	263.82	1333.65	9.631	0.885	107.458	114.152	2	8	0
8	616.35	303.87	289.57	1465.76	9.456	0.885	107.375	114.120	2	8	0
9	644.40	350.94	314.84	1583.99	9.475	0.885	107.265	113.794	2	8	0
10	672.45	344.68	340.01	1866.04	9.426	0.885	107.383	113.902	2	8	0
11	646.38	313.16	308.55	1232.00	11.048	0.885	138.603	146.752	6	10	0
12	642.43	325.44	324.77	1368.51	9.604	0.885	122.957	130.222	4	8	0
13	694.51	357.09	364.41	1451.39	9.768	0.885	122.864	130.239	4	8	0
14	588.31	271.41	262.25	1272.38	5.813	0.884	105.143	110.849	4	8	1



15	644.42	320.71	312.35	1313.59	5.582	0.884	99.242	104.679	2	8	0
16	674.45	351.78	330.49	1229.71	4.147	0.885	129.568	135.961	6	10	0
17	670.50	340.28	339.25	1407.21	12.531	0.886	97.084	102.165	4	8	0
18	722.58	407.88	380.11	1339.52	9.977	0.886	104.990	110.228	4	8	0
19	644.40	321.27	311.74	1261.18	6.453	0.883	97.187	102.575	2	8	0
20	672.46	356.75	336.82	1203.31	6.300	0.884	97.318	102.509	2	8	0
21	590.32	277.70	269.56	1432.61	6.616	0.900	137.789	145.133	4	8	1
22	618.38	331.49	296.10	1714.83	9.048	0.899	111.916	118.178	2	8	0
23	646.43	296.25	321.51	1911.50	10.306	0.897	116.950	123.075	2	8	0
24	674.49	372.49	346.95	1425.27	10.418	0.897	116.643	123.350	2	8	0
25	674.49	371.93	345.56	1406.09	10.369	0.897	115.271	121.218	2	8	0
26	724.59	381.31	396.75	1879.12	5.916	0.899	124.879	131.664	4	8	0
27	605.42	298.95	264.44	1311.26	6.574	1.330	117.073	123.275	4	12	1
28	633.48	307.57	291.45	1320.90	9.854	1.330	109.316	115.441	2	12	0
29	661.53	338.83	316.66	1284.74	9.881	1.330	107.975	114.256	2	12	0
30	689.58	379.24	342.06	1310.12	9.949	1.330	107.649	114.011	2	12	0
31	689.58	371.64	340.04	1302.96	9.738	1.330	106.280	111.909	2	12	0
32	717.64	389.86	367.08	1219.40	9.938	1.330	107.711	114.122	2	12	0
33	719.69	396.75	360.53	1273.95	5.264	1.330	131.364	137.835	4	14	0
34	687.62	331.97	351.82	1665.79	6.335	1.330	121.395	127.642	4	12	0
35	739.69	402.95	391.02	1292.81	6.090	1.330	120.894	127.001	4	12	0
36	767.75	426.16	415.08	1864.06	6.278	1.330	119.904	126.080	4	12	0
37	785.67	450.17	427.26	2752.28	10.008	1.330	115.488	121.547	4	12	0
38	633.48	288.88	288.34	1311.57	10.410	1.330	128.700	137.113	4	12	1
39	661.53	340.69	312.80	1385.26	10.533	1.331	120.313	128.774	2	12	0
40	689.58	339.05	338.05	1399.50	10.027	1.330	118.948	127.480	2	12	0
41	715.67	424.16	370.92	1258.04	9.734	1.334	121.170	128.906	4	12	0

42	661.53	337.39	311.20	1426.34	9.210	1.326	126.238	132.477	4	12	1
43	689.58	359.24	335.02	1431.79	9.273	1.326	118.219	125.579	2	12	0
44	743.72	426.20	396.18	1425.48	12.598	1.331	112.826	120.966	4	12	0
45	689.58	361.41	334.48	1457.78	8.237	1.324	119.234	130.934	4	12	1
46	717.78	387.67	359.18	1613.85	8.780	1.324	111.339	120.691	2	12	0
47	771.78	495.12	420.93	1987.67	9.252	1.324	117.298	124.778	4	12	0
48	537.35	227.62	219.09	1063.21	6.278	1.331	108.407	113.363	4	11	1
49	621.51	343.68	296.51	1549.29	8.507	1.331	98.825	104.036	2	11	0
50a	671.62	341.22	345.91	1233.02	6.170	1.330	112.372	117.504	4	11	0
50b	671.62	362.46	340.48	1207.20	5.614	1.330	108.068	114.896	4	11	0
51	631.46	288.83	286.22	1354.69	12.809	1.318	153.353	164.242	4	12	1
52	687.57	355.00	337.82	1235.64	15.747	1.317	126.985	136.235	2	12	0
53	713.65	391.69	373.29	1457.55	11.945	1.317	137.753	146.294	4	12	0

**Table S3.** Calculated descriptors for the investigated compounds (all values are in eV): energies of HOMO ( $E_{\text{HOMO}}$ ), LUMO ( $E_{\text{LUMO}}$ ) and their gap (H/L gap)), vertical ionization energy ( $E_i$ ) in vacuum and in water ( $E_{iS}$ ), vertical electron affinity in vacuum ( $E_{\text{ca}}$ ) and in water ( $E_{\text{caS}}$ ), adiabatic electron affinity in water ( $E_{\text{caS}}$ ). The coloring is based on the subtypes, exerting the same equatorial ligands (Figure 2).

complex	$E_{\text{HOMO}}$	$E_{\text{LUMO}}$	H/L gap	$E_i$	$E_{iS}$	$E_{\text{ca}}$	$E_{\text{caS}}$	$E_{\text{caS}}$
1	-10.005	-0.487	9.517	9.805	8.400	1.025	2.938	4.225
2a	-9.977	-0.447	9.530	9.740	8.279	0.989	2.944	3.976
2b	-10.086	-0.608	9.477	9.899	8.402	1.118	2.976	3.988
2c	-9.670	-0.109	9.561	9.397	8.348	0.716	2.858	4.102
2d	-9.680	-0.133	9.547	9.435	8.216	0.670	2.864	3.898
3	-9.702	-0.331	9.372	9.494	7.428	0.897	2.879	3.915
4	-9.592	-0.316	9.275	9.346	7.299	0.872	2.785	4.124
5	-9.477	-0.249	9.228	9.138	7.211	0.830	2.884	3.920
6	-9.796	-0.465	9.330	9.548	8.243	1.023	2.989	3.841
7	-9.827	-0.504	9.323	9.577	8.325	1.093	2.968	3.997
8	-9.813	-0.491	9.323	9.562	8.252	1.084	2.965	3.996
9	-9.812	-0.489	9.323	9.558	8.253	1.084	2.965	3.995
10	-9.810	-0.486	9.323	9.555	8.251	1.083	2.964	3.997
11	-9.513	-0.420	9.093	9.287	7.323	1.016	2.951	3.982
12	-9.485	-0.430	9.055	9.250	7.277	1.030	2.953	3.986
13	-9.408	-0.421	8.987	9.074	7.184	1.023	2.950	3.981
14	-9.930	-0.573	9.357	9.674	8.228	1.143	2.954	4.060
15	-9.887	-0.524	9.363	9.622	8.224	1.103	2.943	3.971
16	-9.379	-0.512	8.867	9.166	7.236	1.092	2.933	4.058

17	-8.932	-1.103	7.829	8.564	7.157	1.781	3.056	4.281
18	-8.596	-0.916	7.680	8.187	7.043	1.583	3.035	4.137
19	-9.880	-0.518	9.362	9.608	8.225	1.107	2.942	3.967
20	-9.874	-0.512	9.362	9.598	8.225	1.104	2.941	3.965
21	-9.425	-0.657	8.769	9.088	7.672	1.265	2.969	3.976
22	-9.219	-0.479	8.741	8.857	7.659	1.096	2.961	3.965
23	-9.210	-0.492	8.719	8.839	7.650	1.112	2.969	3.980
24	-9.210	-0.494	8.716	8.834	7.650	1.117	2.972	3.975
25	-9.200	-0.488	8.712	8.820	7.644	1.113	2.971	3.976
26	-9.104	-0.401	8.703	8.730	7.607	1.034	2.946	3.949
27	-9.510	-0.518	8.992	9.237	7.988	1.305	2.648	4.170
28	-9.431	-0.438	8.992	9.153	7.979	1.234	2.632	4.142
29	-9.421	-0.422	8.999	9.140	7.979	1.224	2.630	4.142
30	-9.419	-0.417	9.002	9.135	7.981	1.223	2.629	4.143
31	-9.410	-0.405	9.004	9.126	7.977	1.211	2.625	4.140
32	-9.415	-0.413	9.002	9.130	7.980	1.222	2.629	4.142
33	-9.453	-0.396	9.057	9.167	7.959	1.205	2.600	4.122
34	-9.410	-0.348	9.061	9.124	7.955	1.159	2.595	4.115
35	-9.400	-0.340	9.060	9.111	7.954	1.153	2.595	4.115
36	-9.390	-0.333	9.057	9.099	7.954	1.148	2.597	4.118
37	-9.409	-0.446	8.963	9.120	7.044	1.262	2.637	4.148
38	-9.430	-0.443	8.986	9.153	7.959	1.244	2.576	4.091
39	-9.413	-0.399	9.014	9.128	7.952	1.208	2.562	4.081
40	-9.412	-0.396	9.016	9.123	7.962	1.210	2.578	4.093
41	-9.354	-0.333	9.021	9.050	7.301	1.145	2.531	4.125
42	-9.455	-0.441	9.014	9.167	7.968	1.262	2.571	4.100

43	-9.446	-0.405	9.041	9.150	7.962	1.236	2.561	4.076
44	-8.995	-0.500	8.494	8.598	7.168	1.325	2.616	4.099
45	-9.400	-0.374	9.026	9.107	7.968	1.216	2.587	4.098
46	-9.358	-0.318	9.040	9.062	7.963	1.168	2.579	4.128
47	-9.283	-0.209	9.074	8.979	7.947	1.066	2.545	4.052
48	-9.212	-0.089	9.123	8.877	7.136	0.801	2.351	3.872
49	-9.166	0.010	9.176	8.793	7.133	0.722	2.334	3.838
50a	-9.133	0.088	9.400	8.747	7.116	0.649	2.303	3.806
50b	-9.312	-0.092	9.041	8.887	7.148	0.849	2.358	3.898
51	-9.327	-0.480	8.847	9.033	7.878	1.290	2.735	4.094
52	-9.130	-0.277	8.853	8.828	7.870	1.100	2.718	4.076
53	-9.109	-0.213	8.896	8.802	7.858	1.044	2.692	4.056

**Table S4.** QSAR models for the cytotoxicity in the cell line CH1 with simulated annealing chosen combination of descriptors. ( $Q^2$ , AAR' and RMS' are the  $R^2$ , AAR and RMS values for cross validated predictions, using LOOP; the derived coefficients are for a model equation with auto scaled values of the descriptors).

Model	Number of variables	Used descriptors	$R^2$	$Q^2$	AAR	AAR'	RMS	RMS'	Coefficients
<b>1</b>	1	q(Pt)	0.4132	0.3920	0.6318	0.6431	0.8241	0.8389	-0.643
<b>2</b>	1	$H_{acc}$	0.5130	0.4953	0.5695	0.5795	0.7508	0.7643	-0.716
<b>3</b>	2	$H_{don}$ , $H_{acc}$	0.6978	0.6769	0.4707	0.4878	0.5914	0.6115	-0.435, -0.651
<b>4</b>	2	q(Pt), $H_{don}$	0.6847	0.6643	0.4698	0.4843	0.6041	0.6233	-0.633, -0.522
<b>5</b>	3	$H_{don}$ , $H_{acc}$ , COOH	0.7450	0.7226	0.4160	0.4355	0.5433	0.5666	-0.363, -0.647, -0.229
<b>6</b>	3	q(Pt), $E_{caS}$ , $H_{don}$	0.7867	0.7641	0.3794	0.4000	0.4968	0.5226	-0.516, -0.340, -0.513
<b>7</b>	3	q(Pt), $H_{don}$ , COOH	0.7130	0.6866	0.4415	0.4620	0.5763	0.6023	-0.617, -0.466, -0.178
<b>8</b>	3	MW, q(Pt), $H_{don}$	0.7122	0.6800	0.4271	0.4505	0.5769	0.6087	0.187, -0.716, -0.541
<b>9</b>	3	$\alpha$ , q(Pt), $H_{don}$	0.7285	0.6987	0.4088	0.4306	0.5603	0.5905	0.224, -0.710, -0.546
<b>10</b>	3	q(Pt), $dE_iS$ , $H_{don}$	0.7219	0.6910	0.4305	0.4529	0.5674	0.5980	-0.652, -0.227, -0.639
<b>11</b>	3	$E_{caS}$ , $H_{don}$ , $H_{acc}$	0.7768	0.7542	0.3998	0.4210	0.5083	0.5334	-0.308, -0.444,

									-0.525
<b>12</b>	4	MW, $E_{caS}$ , $H_{don}$ , $H_{acc}$	0.8459	0.8228	0.3434	0.3695	0.4223	0.4529	0.309, -0.359, -0.456, -0.656
<b>13</b>	4	MW, q(Pt), $E_{caS}$ , $H_{don}$	0.8458	0.8196	0.3324	0.3595	0.4225	0.4570	0.280, -0.621, -0.399, -0.539
<b>14</b>	4	q(Pt), $E_i$ , $E_{caS}$ , $H_{don}$	0.8137	0.7802	0.3611	0.3921	0.4643	0.5044	-0.584, -0.180, -0.336, -0.543
<b>15</b>	5	MW, $\alpha$ , q(Pt), $E_{caS}$ , $H_{don}$	0.8713	0.8471	0.3178	0.3484	0.3859	0.4207	-1.056, 1.268, -0.487, -0.316, -0.541
<b>16</b>	5	$\alpha$ , $E_{ca}$ , $E_{caS}$ , $H_{don}$ , $H_{acc}$	0.8505	0.8229	0.3393	0.3721	0.4160	0.4527	0.302, -0.051, -0.309, -0.462, -0.625

**Table S5.** External validation of the best models for cytotoxicity in CH1 cells, obtained with three, four or five descriptors:

Model N	Training set	Number of variables	Used descriptors	R <sup>2</sup>	Q <sup>2</sup>	Pred R <sup>2</sup>	pred AAR	pred RMS
<b>5</b>	a	3	H <sub>don</sub> , H <sub>acc</sub> , COOH	0.751	0.7197	<b>0.7210</b>	0.402	0.5394
	b			0.7278	0.6879	<b>0.7828</b>	0.5039	0.7049
	c			0.7728	0.7383	<b>0.6263</b>	0.5655	0.6976
	d			0.7239	0.6924	<b>0.808</b>	0.3738	0.4831
	e			0.7532	0.7263	<b>0.7139</b>	0.4734	0.5492
<b>6</b>	a	3	q(Pt), E <sub>caS'</sub> , H <sub>don</sub>	0.7931	0.7652	<b>0.7560</b>	0.3726	0.5044
	b			0.7699	0.7289	<b>0.8158</b>	0.4782	0.6492
	c			0.8085	0.7731	<b>0.7043</b>	0.4672	0.6206
	d			0.7778	0.7492	<b>0.8471</b>	0.3511	0.4311
	e			0.7868	0.7622	<b>0.7794</b>	0.3765	0.4822
<b>8</b>	a	3	MW, q(Pt), H <sub>don</sub>	0.7329	0.6872	<b>0.6390</b>	0.4236	0.6136
	b			0.6382	0.5864	<b>0.7908</b>	0.4658	0.692
	c			0.7249	0.6782	<b>0.5843</b>	0.6199	0.7358
	d			0.6898	0.6414	<b>0.7452</b>	0.4671	0.5565
	e			0.8358	0.8132	<b>0.0635</b>	0.7271	0.9935
<b>9</b>	a	3	α, q(Pt), H <sub>don</sub>	0.748	0.7056	<b>0.6593</b>	0.4084	0.596
	b			0.6512	0.6012	<b>0.8116</b>	0.443	0.6566
	c			0.7445	0.7029	<b>0.5970</b>	0.6029	0.7245
	d			0.7052	0.6587	<b>0.7662</b>	0.4502	0.5332
	e			0.8395	0.8176	<b>0.1942</b>	0.6843	0.9216
<b>11</b>	a	3	E <sub>caS'</sub> , H <sub>don</sub> , H <sub>acc</sub>	0.7804	0.7511	<b>0.7536</b>	0.3976	0.5068
	b			0.7606	0.7191	<b>0.8103</b>	0.4987	0.6589
	c			0.8018	0.7705	<b>0.7116</b>	0.4759	0.6129



	d			0.7652	0.7368	<b>0.8474</b>	0.3648	0.4307
	e			0.7649	0.7363	<b>0.8346</b>	0.3534	0.4176
<b>12</b>	a	4	MW, $E_{eaS'}$ , $H_{don}$ , $H_{acc}$	0.8614	0.8313	<b>0.7753</b>	0.4361	0.484
	b			0.8381	0.8027	<b>0.8546</b>	0.434	0.5767
	c			0.8736	0.8478	<b>0.754</b>	0.4838	0.566
	d			0.8303	0.7966	<b>0.9141</b>	0.2398	0.3232
	e			0.8459	0.8112	<b>0.842</b>	0.3824	0.4082
<b>13</b>	a	4	MW, q(Pt), $E_{eaS'}$ , $H_{don}$	0.8553	0.8199	<b>0.8023</b>	0.3662	0.454
	b			0.8422	0.8054	<b>0.8385</b>	0.4723	0.608
	c			0.8644	0.8285	<b>0.7494</b>	0.4912	0.5713
	d			0.8297	0.7913	<b>0.9199</b>	0.2564	0.3119
	e			0.8729	0.8435	<b>0.6236</b>	0.5156	0.6299
<b>14</b>	a	4	q(Pt), $E_i$ , $E_{eaS'}$ , $H_{don}$	0.8275	0.773	<b>0.7422</b>	0.4167	0.5185
	b			0.7723	0.7215	<b>0.8454</b>	0.4307	0.5949
	c			0.8524	0.8155	<b>0.6043</b>	0.598	0.7179
	d			0.8176	0.7766	<b>0.8157</b>	0.3818	0.4734
	e			0.8163	0.774	<b>0.8161</b>	0.3614	0.4403
<b>15</b>	a	5	$\alpha$ , $E_{ea}$ , $E_{eaS'}$ , $H_{don}$ , $H_{acc}$	0.8646	0.8154	<b>0.7701</b>	0.445	0.4896
	b			0.8486	0.8041	<b>0.8365</b>	0.4554	0.6117
	c			0.8785	0.8416	<b>0.7246</b>	0.5217	0.5989
	d			0.8352	0.7956	<b>0.9176</b>	0.2341	0.3165
	e			0.8494	0.8105	<b>0.8491</b>	0.3615	0.3989
<b>16</b>	a	5	MW, $\alpha$ , q(Pt), $E_{eaS'}$ , $H_{don}$	0.8769	0.8438	<b>0.8439</b>	0.34	0.4034
	b			0.8648	0.8296	<b>0.8802</b>	0.4132	0.5236
	c			0.8894	0.857	<b>0.8073</b>	0.4262	0.501
	d			0.8574	0.8216	<b>0.9352</b>	0.2446	0.2806
	e			0.8787	0.8455	<b>0.7716</b>	0.4136	0.4906

**Table S6.** QSAR models for cytotoxicity in the cell line SW480 with simulated annealing chosen combination of descriptors ( $Q^2$ , AAR' and RMS' are the  $R^2$ , AAR and RMS values for cross validated predictions, using LOOP; the derived coefficients are for a model equation with auto scaled values of the descriptors).

Model	Number of variables	Used descriptors	$R^2$	$Q^2$	AAR	AAR'	RMS	RMS'	Coefficients
<b>1</b>	1	q(Pt)	0.5453	0.5292	0.5847	0.5950	0.7388	0.7518	-0.738
<b>2</b>	2	$H_{don}$ , $H_{acc}$	0.7009	0.6785	0.4446	0.4620	0.5992	0.6212	-0.321, -0.727
<b>3</b>	2	q(Pt), $H_{don}$	0.7196	0.7010	0.4173	0.4315	0.5802	0.5991	-0.731, -0.418
<b>4</b>	3	q(Pt), $E_s'$ , $H_{don}$	0.7535	0.7247	0.4246	0.4495	0.5440	0.5749	-0.813, -0.220, -0.505
<b>5</b>	3	q(Pt), $E_i$ , $H_{don}$	0.7587	0.7259	0.4083	0.4337	0.5382	0.5736	-0.811, -0.217, -0.454
<b>6</b>	3	q(Pt), $E_{HOMO}$ , $H_{don}$	0.7552	0.7213	0.4121	0.4381	0.5422	0.5784	-0.812, 0.210, -0.461
<b>7</b>	3	$\alpha$ , q(Pt), $H_{don}$	0.7466	0.7208	0.4312	0.4539	0.5515	0.5789	0.176, -0.791, -0.436
<b>8</b>	3	$E_s'$ , $H_{don}$ , $H_{acc}$	0.7607	0.7282	0.4151	0.4419	0.5360	0.5712	-0.304, -0.423, -0.861
<b>9</b>	4	$E_s$ , $H_{don}$ , $H_{acc}$ , COOH	0.7893	0.7522	0.4084	0.4426	0.5030	0.5454	-0.334, -0.387, -0.867, -0.170
<b>10</b>	4	$E_s'$ , $H_{don}$ ,	0.7875	0.7507	0.4097	0.4438	0.5050	0.5470	-0.329, -0.377,

		$H_{acc}, COOH$								-0.869, -0.174
<b>11</b>	4	$q(Pt),$ $E_{LUMO}, E_i,$ $H_{don}$	0.7811	0.7486	0.4084	0.4395	0.5126	0.5494		-0.891, 0.167, -0.244, -0.457
<b>12</b>	4	$E_i, E_{ca}, E_{caS},$ $H_{don}$	0.8094	0.7834	0.3891	0.4167	0.4783	0.5099		-0.307, -0.412, 0.845, -0.431
<b>13</b>	4	$E_i, E_{caS},$ $E_{caS'}, H_{don}$	0.7965	0.7648	0.3900	0.4197	0.4943	0.5314		-0.185, 0.711, -0.365, -0.412
<b>14</b>	5	$E_i, E_{ca}, E_s,$ $E_{caS}, H_{don}$	0.8230	0.7912	0.3784	0.4141	0.4610	0.5007		-0.281, -0.459, -0.147, 0.871, -0.486
<b>15</b>	5	$q(Pt),$ $H/Lgap, E_i,$ $E_{caS}, H_{don}$	0.8145	0.7768	0.3798	0.4157	0.4719	0.5176		-0.329, 0.678, -0.818, 0.695, -0.409

**Table S7.** External validation of the best models for SW480 cells, obtained with three, four or five descriptors:

Model N	Training set	Number of variables	Used descriptors	R <sup>2</sup>	Q <sup>2</sup>	Pred R <sup>2</sup>	pred AAR	pred RMS
<b>4</b>	a	3	q(Pt), Es', H <sub>don</sub>	0.7655	0.7280	<b>0.6834</b>	0.4844	0.6029
	b			0.6899	0.6304	<b>0.7981</b>	0.6115	0.7160
	c			0.7905	0.7440	<b>0.4651</b>	0.7380	0.8212
	d			0.7467	0.7087	<b>0.7074</b>	0.5710	0.7321
	e			0.8262	0.8028	<b>0.3439</b>	0.7227	0.8329
<b>6</b>	a	3	q(Pt), E <sub>HOMO</sub> , H <sub>don</sub>	0.7519	0.7042	<b>0.7481</b>	0.4249	0.5379
	b			0.6644	0.6111	<b>0.8211</b>	0.5277	0.6740
	c			0.8147	0.7812	<b>0.3419</b>	0.7643	0.9109
	d			0.7409	0.6936	<b>0.7483</b>	0.4843	0.6790
	e			0.8288	0.7975	<b>0.3705</b>	0.6516	0.8159
<b>8</b>	a	3	Es, H <sub>don</sub> , H <sub>acc</sub>	0.7915	0.7538	<b>0.6227</b>	0.5458	0.6582
	b			0.7294	0.6824	<b>0.7667</b>	0.6592	0.7697
	c			0.8040	0.7485	<b>0.5766</b>	0.6131	0.7307
	d			0.7385	0.6908	<b>0.7976</b>	0.4893	0.6088
	e			0.7836	0.7450	<b>0.6809</b>	0.4268	0.5809
<b>9</b>	a	4	Es, H <sub>don</sub> , H <sub>acc</sub> , COOH	0.8119	0.7644	<b>0.6638</b>	0.5392	0.6213
	b			0.7482	0.6909	<b>0.7892</b>	0.6224	0.7316
	c			0.8270	0.7681	<b>0.5750</b>	<b>0.6405</b>	0.7320
	d			0.7843	0.7340	<b>0.7593</b>	0.5677	0.6640
	e			0.8241	0.7848	<b>0.5864</b>	0.5129	0.6613
<b>11</b>	a	4	q(Pt),	0.7684	0.6919	<b>0.8088</b>	0.4027	0.4686

	b		$E_{\text{LUMO}}, E_i,$ $H_{\text{don}}$	0.7034	0.6534	<b>0.8608</b>	0.5016	0.5945
	c			0.8178	0.7769	<b>0.4493</b>	0.7042	0.8333
	d			0.7571	0.7048	<b>0.8254</b>	0.4502	0.5656
	e			0.8439	0.8118	<b>0.5137</b>	0.5467	0.7171
<b>12</b>	a	4	$E_i, E_{\text{ca}},$ $E_{\text{caS}}, H_{\text{don}}$	0.8045	0.7716	<b>0.8003</b>	0.4235	0.4789
	b			0.7451	0.6966	<b>0.8799</b>	0.4801	0.5522
	c			0.8531	0.8138	<b>0.5918</b>	0.6445	0.7174
	d			0.8033	0.7667	<b>0.7904</b>	0.4678	0.6196
	e			0.8409	0.8116	<b>0.4570</b>	0.6464	0.7578
<b>13</b>	a	4	$E_i, E_{\text{caS}},$ $E_{\text{caS}'}, H_{\text{don}}$	0.8009	0.7550	<b>0.7445</b>	0.4786	0.5416
	b			0.7312	0.6669	<b>0.8705</b>	0.4677	0.5734
	c			0.8577	0.8208	<b>0.5174</b>	0.6361	0.7801
	d			0.7834	0.7379	<b>0.7856</b>	0.4471	0.6266
	e			0.8195	0.7797	<b>0.5191</b>	0.6080	0.7131
<b>14</b>	a	5	$E_i, E_{\text{ca}}, E_{\text{S}},$ $E_{\text{caS}}, H_{\text{don}}$	0.8274	0.7486	<b>0.7697</b>	0.4388	0.5142
	b			0.7466	0.6722	<b>0.9020</b>	0.4415	0.4988
	c			0.8761	0.8364	<b>0.5470</b>	0.6869	0.7557
	d			0.8222	0.7824	<b>0.7861</b>	0.4741	0.6260
	e			0.8527	0.8251	<b>0.4405</b>	0.6629	0.7692
<b>15</b>	a	5	$q(\text{Pt}),$ $H/L\text{gap},$ $E_i, E_{\text{caS}},$ $H_{\text{don}}$	0.8057	0.7410	<b>0.8381</b>	0.3838	0.4311
	b			0.7577	0.6872	<b>0.8924</b>	0.4661	0.5228
	c			0.8554	0.8006	<b>0.6248</b>	0.6118	0.6878
	d			0.8019	0.7461	<b>0.8268</b>	0.4338	0.5632
	e			0.8516	0.8181	<b>0.5809</b>	0.5569	0.6657

**Table S8.** Statistical parameters for the best four-variable models, using IC<sub>50</sub> = 600, 1000 or 2000 μM as input for the inactive compounds from **subset 2**.

input IC <sub>50</sub>	model 1			model 2			model 3		
	R <sup>2</sup>	Q <sup>2</sup> (LOOP)	AAR	R <sup>2</sup>	Q <sup>2</sup> (LOOP)	AAR	R <sup>2</sup>	Q <sup>2</sup> (LOOP)	AAR
600	0.79	0.75	0.41	0.80	0.77	0.39	0.81	0.78	0.39
1000	0.80	0.76	0.43	0.80	0.77	0.40	0.82	0.80	0.40
2000	0.80	0.77	0.47	0.81	0.78	0.43	0.83	0.80	0.42

**Table S9.** Elemental analysis data.

Compound	Formula	MW	Calculated (%)			Found (%)		
			C	H	N	C	H	N
<b>nedaplatin</b>	C <sub>2</sub> H <sub>8</sub> N <sub>2</sub> O <sub>3</sub> Pt	303.17	7.92	2.66	9.24	8.03	2.45	9.05
<b>48</b>	C <sub>10</sub> H <sub>18</sub> N <sub>2</sub> O <sub>11</sub> Pt	537.33	22.35	3.38	5.21	22.32	3.24	5.04
<b>49</b>	C <sub>16</sub> H <sub>30</sub> N <sub>2</sub> O <sub>11</sub> Pt·0.5H <sub>2</sub> O	630.50	30.48	4.96	4.44	30.41	4.59	4.39
<b>50</b>	C <sub>20</sub> H <sub>36</sub> N <sub>4</sub> O <sub>9</sub> Pt·0.5H <sub>2</sub> O	680.61	35.29	5.48	8.23	35.15	5.10	7.98

**Table S10.** Crystal data and details of data collection for **7**

Complex	7
empirical formula	C <sub>12</sub> H <sub>22</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>8</sub> Pt
fw	588.31
space group	P-1
<i>a</i> , Å	8.2185(3)
<i>b</i> , Å	10.0375(4)
<i>c</i> , Å	12.4165(5)
<i>V</i> , Å <sup>3</sup>	891.63(6)
<i>Z</i>	2
$\lambda$ , Å	0.71073
$\rho_{\text{calcd}}$ , g cm <sup>-3</sup>	2.191
crystal size, mm	0.10 x 0.08 x 0.02
<i>T</i> , K	100
$\mu$ , mm <sup>-1</sup>	8.211
R1 <sup>a</sup>	0.0234
wR2 <sup>b</sup>	0.0486
GOF <sup>c</sup>	0.998

<sup>a</sup>  $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$ , <sup>b</sup>  $wR2 = \{ \sum [w (F_o^2 - F_c^2)^2] / \sum [w(F_o^2)] \}^{1/2}$ . <sup>c</sup>  $GOF = \{ \sum [w(F_o^2 - F_c^2)^2] / (n - p) \}^{1/2}$ , where *n* is the number of reflections and *p* is the total number of parameters refined.