

Supporting Information

Density Functional Theory Characterization and Descriptive Analysis of Cisplatin and Related Compounds

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Table 1S. Chemical Formula, IUPAC and common/commercial names and anticancer activity for the 35 compounds characterized in this work.

Fig 1 Labeling	Compact chemical Formula	Chemical name	Commercial/ common name	Observations
[01]	<i>cis</i> -[Pt(NH ₃) ₂ Cl ₂]	<i>cis</i> -diamminedichloroplatinum(II)	Cisplatin, Platinol	FDA approval in 1978
[1t]	<i>trans</i> -[Pt(NH ₃) ₂ Cl ₂]	<i>trans</i> -[diamminedichloroplatinum(II)]	Transplatin	Inactive
[02]	<i>cis</i> -[Pd(NH ₃) ₂ Cl ₂]	<i>cis</i> -[diamminedichloropalladium(II)]		Pd analog of 01. Inactive
[2t]	<i>trans</i> -[Pd(NH ₃) ₂ Cl ₂]	<i>trans</i> -[diamminedichloropalladium(II)]		Pd analog of 1t. Inactive
[03]	<i>cis</i> -[Pt(1R,2R-Dach)Cl ₂], Dach = 1,2-diaminocyclohexane	<i>cis</i> -[(1R,2R-diaminocyclohexane)dichloroplatinum(II)]		Major metabolite of Pt(II) Oxaliplatin and of the Pt(IV) pro-drug Ormaplatin/Tetraplatin. Cytotoxic <i>in vitro</i> and <i>in vivo</i> .
[04]	<i>cis</i> -[Pt(1R,2S-Dach)Cl ₂]	<i>cis</i> -[(1R,2S-diaminocyclohexane)dichloroplatinum(II)]		Cytotoxic <i>in vitro</i>
[05]	<i>cis</i> -[Pt(1S,2S-Dach)Cl ₂]	<i>cis</i> -[(1S,2S-diaminocyclohexane)dichloroplatinum(II)]		Cytotoxic <i>in vitro</i> . More mutagenic than 03
[06]	<i>cis</i> -[Pt(1R,2R-Dach)(3-methyl-orotate)]	<i>cis</i> -[(1R,2R-diaminocyclohexane)methylorotatoplatinum(II)]		Inactive
[07]	<i>cis</i> -[Pd(1R,2R-Dach)(3-methyl-orotate)]	<i>cis</i> -[(1R,2R-diaminocyclohexane)methylorotatopalladium(II)]		Cytotoxic <i>in vitro</i>
[08]	<i>cis</i> -[Pt(1R,2R-Dach)(5-fluoro-orotate)]	<i>cis</i> -[(1R,2R-diaminocyclohexane)5-fluoro-orotatoplatinum(II)]		Inactive
[09]	<i>cis</i> -[Pd(1R,2R-Dach)(5-fluoro-orotate)]	<i>cis</i> -[(1R,2R-diaminocyclohexane)5-fluoro-orotatopalladium(II)]		Cytotoxic <i>in vitro</i>
[10]	<i>cis</i> -[Pt(NH ₃)(Py)Cl ₂]	<i>cis</i> -[amminedichloro(pyridine)platinum(II)]	JM494, AMD494	Cytotoxic <i>in vitro</i>
[10t]	<i>trans</i> -[Pt(NH ₃)(Py)Cl ₂]	<i>trans</i> -[amminedichloro(pyridine)platinum(II)]		Cytotoxic <i>in vitro</i>
[11]	<i>cis</i> -[Pt(NH ₃)(2-methylPy)Cl ₂], Py = pyridine	<i>cis</i> -[amminedichloro(2-methylpyridine)platinum(II)]	Picoplatin, ZD0473, AMD473	Cytotoxic <i>in vitro</i> and <i>in vivo</i> . Phase III clinical trials. FDA approval pending.
[11t]	<i>trans</i> -[Pt(NH ₃)(2-methylPy)Cl ₂]	<i>trans</i> -[amminedichloro(2-methylpyridine)platinum(II)]	AMD443	
[12]	<i>cis</i> -[Pt(NH ₃)(3-methylPy)Cl ₂]	<i>cis</i> -[amminedichloro(3-methylpyridine)platinum(II)]		
[12t]	<i>trans</i> -[Pt(NH ₃)(3-methylPy)Cl ₂]	<i>trans</i> -[amminedichloro(3-methylpyridine)platinum(II)]		
[13]	<i>cis</i> -[Pt(biPy)Cl ₂], biPy = 2,2'-bipyridine	[(2,2'-bipyridine)dichloroplatinum(II)]		Cytotoxic <i>in vitro</i>
[14]	<i>cis</i> -[Pd(biPy)Cl ₂]	[(2,2'-bipyridine)dichloropalladium(II)]		Cytotoxic <i>in vitro</i>
[15]	<i>cis</i> -[Pt(1R,2R-Dach)(oxalate)]	<i>cis</i> -[(1R,2R-diaminocyclohexane)oxalatoplatinum(II)]	Oxaliplatin, Eloxatin, L-OHP	FDA approval in 2002-2004
[16]	<i>cis</i> -[Pt(NH ₃) ₂ (1,1'-cyclobutanedicarboxylate)]	<i>cis</i> -diammine-(1,1'-cyclobutanedicarboxylato)platinum(II)	Carboplatin, Paraplatin	FDA approval in 1989
[17]	<i>cis</i> -[Pt(NH ₃)(aminocyclohexane)Cl ₂]	<i>cis</i> -[amminedichloro(cyclohexylamine)platinum(II)]	JM118	Metabolite of Pt(IV) Satraplatin (JM216). Cytotoxic <i>in vitro</i> and <i>in vivo</i> .
[17t]	<i>trans</i> -[Pt(NH ₃)(aminocyclohexane)Cl ₂]	<i>trans</i> -[amminedichloro(cyclohexylamine)platinum(II)]	JM334	Metabolite of Pt(IV) JM335.
[18]	<i>cis</i> -[Pt(1,4-Dach)Cl ₂]	<i>cis</i> -[(1,4-diaminocyclohexane)dichloroplatinum(II)]		Cytotoxic <i>in vitro</i>
[19]	<i>cis</i> -[Pd(1S,2S-Dach)Cl ₂]	<i>cis</i> -[(1S,2S-diaminocyclohexane)dichloropalladium(II)]		Pd analog of 05.
[20]	<i>cis</i> -[Pd(1R,2S-Dach)Cl ₂]	<i>cis</i> -[(1R,2S-diaminocyclohexane)dichloropalladium(II)]		Pd analog of 04.
[21]	<i>cis</i> -[Pd(1,4-Dach)Cl ₂]	<i>cis</i> -[1,4-diaminocyclohexane)dichloropalladium(II)]		Pd analog of 18.
[22]	<i>cis</i> -[Pt(1R,2S-di(aminomethyl)cyclobutane)(lactate)]	<i>cis</i> -[(1R,2S-diaminomethylcyclobutane)lactatoplatinum(II)]	Lobaplatin	Clinical use in Asian countries.
[23]	<i>cis</i> -[Pt(1R,2S-di(aminomethyl)cyclobutane)(glycolate)]	<i>cis</i> -[(1R,2S-diaminomethylcyclobutane)glycolatoplatinum(II)]		
[24]	<i>cis</i> -[Pt(NH ₃) ₂ (glycolate)]	<i>cis</i> -[diammine(glycolato)platinum(II)]	Nedaplatin, 254-S	Clinical use in Japan and Asian countries.Brabec, Kasparkova, 2005.
[25]	<i>cis</i> -[Pt(NH ₃) ₂ (lactate)]	<i>cis</i> -[diammine(lactato)platinum(II)]		
[26]	<i>cis</i> -[Pt(1R,2R-diaminocyclopropane)Cl ₂]	<i>cis</i> -[(1R,2R-diaminocyclopropane)dichloroplatinum(II)]		
[27]	<i>cis</i> -[Pt(1R,2R-diaminocyclobutane)Cl ₂]	<i>cis</i> -[(1R,2R-diaminocyclobutane)dichloroplatinum(II)]		
[28]	<i>cis</i> -[Pt(1R,2R-diaminocyclopentane)Cl ₂]	<i>cis</i> -[(1R,2R-diaminocyclopentane)dichloroplatinum(II)]		
[29]	<i>cis</i> -[Pt(NH ₃)(aminocyclopropane)Cl ₂]	<i>cis</i> -[amminedichloro(cyclopropylamine)platinum(II)]		

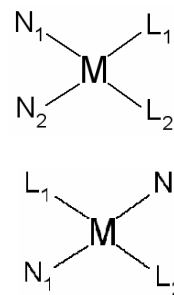
Table 2S. Biological and Pharmacological Activity Indices for several compounds in the set retrieved from literature.

Fig 1 Labeling	In vivo Assays				In vitro Assays							logP _{o/w} ⁱ
	%T/C ^a mouse	CD ^b rat (μmol/kg)	LD ₁₀ ^c mouse/rat (mg/m ³)	MTD ^c human (mg/m ³)	IC ₅₀ antitumoral activity			NCI-60 antitumoral screening (M) ^g		Neurotoxicity & reactivity ^h		
					5 HOC/A2780 (μM) ^d	A2780 (μM) ^e	20 cervical (μg/ml) ^f	GI ₅₀ (x10 ⁻⁵)	LC ₅₀ (x10 ⁻⁴)	GI ₅₀ DRG rat	t _{1/2} (h) rat	
[01] [1t] [02]	277 <i>163-200</i> <125	46.7 [17.6] ^j [26.0] ^j [30.8] ^j	33/41	100	3.5/0.33	1.37	0.730	1.05 9.77	0.90 1.00	256 94	3.43	-2.19 -1.35
[03] [04] [05]	242 <i>163-200</i> 185/229	[17.6] ^j [26.0] ^j [30.8] ^j				1.03		0.13 1.08 0.59	0.82 0.96 0.98		0.97 1.01 0.78	[-1.18] ^j [-1.17] ^j [-1.03] ^j
[06] [07] [08] [09]	<125 267 <125 270											
[10] [11] [15] [16]	<i>179</i>	15.0 302.0	50/115 495/312	200 440	16.9/4.6 14.7/3.8	0.48 7.66	18.600	0.29 9.96	0.91 1.00	Not inhib. 358	1.19 48.6	-1.65 -2.30
[17] [17t]		[2050] ^j	[648/930] ^j		[1.2/0.34] ^j [2.6/0.42] ^j						65	-0.87 / [-0.16] ^j
[18] [19] [22] [24]	203-242 <125		48/89	60			0.435					

- a- Toxicity and antitumor activity ratio expressed as percentage T/C%. Significant when ≥ 125 , where T and C respectively stand for the median survival time for drug treated and control animals (mice inoculated with Sarcoma 180 –data in normal fonts taken from Butour *et al.*,^{16a} data in italics taken from Vollano *et al.*²⁴ and Hoeschele *et al.*–).²⁵
- b- Cumulative Dose (CD) causing altered sensory nerve conduction velocity –SNVC– in female Wistar rats treated twice per week.²⁶
- c- Lethal single dose in 10% of treated mice/rats (LD₁₀) and maximally tolerated dose in humans (MTD) normalized in mg/m². Data taken from Clark *et al.*²⁸
- d- *In vitro* concentration inhibiting tumor cell growth by 50% (IC₅₀) evaluated on five human ovarian carcinoma cell lines (HOC). Values for A2780 HOC are provided in italics. Extracted from Holdford *et al.*^{13a}
- e- Mean IC₅₀ evaluated on A2780 HOC. Data from Monti *et al.*²⁵
- f- Median IC₅₀ evaluated on cervical carcinoma cells coming from 20 fresh untreated human solid tumors, in μg/ml. Data from Monk *et al.*³¹
- g- Mean GI₅₀ (concentration inhibiting tumor cell growth by 50%) and LC₅₀ (lethal concentration killing 50% of cells after treatment) evaluated on the National Cancer Institute (NCI, <http://dtp.nci.nih.gov/dtpstandard/cancerscreeningdata/index.jsp>) 60 human tumor cell lines.
- h- Neurotoxicity evaluated as GI₅₀ (50% inhibition of neurite outgrowth) in dorsal root ganglia –DRG– explants cultures from E-19 embryonic rats.²⁶ Reactivity measured as the half-life of complex binding to Wistar rats plasma proteins *in vitro*.²⁷
- i- log P_{octanol/water} taken from Platts *et al.*^{22b,f}
- j- Values reported in brackets actually correspond to the respective Pt(IV) parent drug. For the particular case of the pair JM216/JM118, Fokkema *et al.*^{29a} have recently shown that both compounds exhibit similar *in vitro* antitumoral response.

Table 3S. Quantum and non quantum calculated descriptors.

Fig 1 Labeling	NPA atomic charges (a.u.)						Frontier KS Orbitals Energy (eV)		Conceptual DFT Molecular Properties (eV)			Selected Bond lengths (Å) ^a				Molecular Size	
	M	L1	L2	N1	N2	H	ϵ_{HOMO}	ϵ_{LUMO}	Chemical potential (μ)	Chemical Hardness (η)	Electrophilicity (ω)	M-L1	M-L2	M-N1	M-N2	Volume ($\text{\AA}^3 \times 10^{-3}$)	Surface ($\text{\AA}^2 \times 10^{-3}$)
[1]	0.594	-0.581	-0.581	-1.059	-1.059	0.450	-0.23929	-0.06118	0.15024	0.08906	0.25345	2.349	2.349	2.117	2.117	0.175	0.172
[1t]	0.604	-0.597	-0.597	-1.049	-1.049	0.450	-0.22896	-0.06055	0.14476	0.08421	0.24885	2.379	2.379	2.070	2.070	0.175	0.173
[2]	0.667	-0.598	-0.598	-1.067	-1.067	0.445	-0.25003	-0.09404	0.17204	0.07800	0.37946	2.333	2.333	2.135	2.134	0.174	0.173
[2t]	0.671	-0.630	-0.630	-1.042	-1.042	0.447	-0.24142	-0.08826	0.16484	0.07658	0.35482	2.365	2.365	2.072	2.072	0.174	0.172
[3]	0.581	-0.603	-0.604	-0.845	-0.846	0.465	-0.23077	-0.05078	0.14078	0.09000	0.22021	2.346	2.345	2.099	2.102	0.253	0.279
[4]	0.581	-0.606	-0.607	-0.850	-0.845	0.466	-0.23074	-0.04958	0.14016	0.09058	0.21688	2.348	2.348	2.091	2.087	0.252	0.279
[5]	0.581	-0.604	-0.603	-0.846	-0.845	0.465	-0.23078	-0.05080	0.14079	0.08999	0.22027	2.346	2.345	2.099	2.102	0.253	0.279
[6]	0.780	-0.600	-0.736	-0.857	-0.849	0.469	-0.25247	-0.08196	0.16722	0.08526	0.32797	2.060	2.003	2.112	2.080	0.333	0.369
[7]	0.809	-0.601	-0.725	-0.856	-0.838	0.466	-0.25915	-0.08422	0.17169	0.08747	0.33700	2.074	1.982	2.122	2.083	0.333	0.368
[8]	0.782	-0.595	-0.738	-0.859	-0.847	0.469	-0.25268	-0.08265	0.16767	0.08502	0.33067	2.065	1.995	2.116	2.077	0.320	0.351
[9]	0.811	-0.597	-0.726	-0.858	-0.836	0.466	-0.25712	-0.08502	0.17107	0.08605	0.34009	2.081	1.975	2.127	2.080	0.319	0.351
[10]	0.613	-0.582	-0.577	-1.061	-0.479	0.452	-0.23915	-0.06061	0.14988	0.08927	0.25164	2.356	2.345	2.122	2.072	0.240	0.260
[10t]	0.626	-0.590	-0.589	-1.048	-0.481	0.451	-0.23230	-0.06533	0.14882	0.08349	0.26527	2.385	2.387	2.077	2.047	0.251	0.238
[11]	0.610	-0.586	-0.580	-1.059	-0.478	0.450	-0.23782	-0.05977	0.14880	0.08903	0.24869	2.358	2.350	2.121	2.082	0.259	0.289
[11t]	0.624	-0.595	-0.592	-1.050	-0.471	0.450	-0.22858	-0.06111	0.14485	0.08374	0.25055	2.381	2.390	2.079	2.048	0.289	0.256
[12]	0.612	-0.585	-0.578	-1.062	-0.474	0.450	-0.23846	-0.05980	0.14913	0.08933	0.24896	2.358	2.346	2.122	2.073	0.263	0.280
[12t]	0.625	-0.591	-0.590	-1.049	-0.475	0.451	-0.23159	-0.06456	0.14808	0.08352	0.26254	2.385	2.387	2.078	2.047	0.283	0.263
[13]	0.660	-0.575	-0.575	-0.469	-0.469	0.267	-0.24136	-0.09634	0.16885	0.07251	0.39319	2.351	2.351	2.053	2.053	0.285	0.327
[14]	0.691	-0.592	-0.592	-0.470	-0.470	0.268	-0.24920	-0.09666	0.17293	0.07627	0.39209	2.327	2.327	2.091	2.090	0.268	0.291
[15]	0.765	-0.749	-0.749	-0.864	-0.864	0.464	-0.23537	-0.03278	0.13408	0.10130	0.17746	2.000	2.000	2.118	2.118	0.263	0.275
[16]	0.785	-0.769	-0.769	-1.072	-1.072	0.449	-0.23600	-0.02857	0.13229	0.10372	0.16873	1.997	1.995	2.117	2.116	0.243	0.254
[17]	0.587	-0.592	-0.585	-1.059	-0.843	0.451	-0.23685	-0.05798	0.14742	0.08944	0.24298	2.359	2.352	2.115	2.116	0.274	0.304
[17t]	0.602	-0.599	-0.598	-1.054	-0.839	0.434	-0.22589	-0.05732	0.14161	0.08429	0.23791	2.380	2.381	2.082	2.073	0.306	0.273
[18]	0.574	-0.598	-0.599	-0.856	-0.856	0.457	-0.23324	-0.05345	0.14335	0.08990	0.22858	2.358	2.359	2.112	2.116	0.238	0.265
[19]	0.651	-0.627	-0.625	-0.844	-0.842	0.461	-0.24204	-0.08357	0.16281	0.07924	0.33452	2.328	2.327	2.112	2.117	0.278	0.253
[20]	0.649	-0.629	-0.629	-0.849	-0.843	0.463	-0.24226	-0.08274	0.16250	0.07976	0.33107	2.330	2.330	2.103	2.101	0.278	0.252
[21]	0.651	-0.622	-0.621	-0.858	-0.858	0.454	-0.24467	-0.08588	0.16528	0.07940	0.34405	2.342	2.341	2.131	2.128	0.264	0.238
[22]	0.726	-0.773	-0.828	-0.879	-0.860	0.451	-0.19760	-0.00875	0.10318	0.09443	0.11274	2.000	1.981	2.144	2.111	0.301	0.275
[23]	0.731	-0.777	-0.828	-0.879	-0.861	0.454	-0.19788	-0.00997	0.10393	0.09396	0.11495	2.002	1.983	2.141	2.111	0.272	0.246
[24]	0.740	-0.774	-0.825	-1.087	-1.074	0.446	-0.20245	-0.01467	0.10856	0.09389	0.12552	1.993	1.975	2.137	2.117	0.161	0.172
[25]	0.740	-0.770	-0.825	-1.088	-1.075	0.446	-0.20158	-0.01291	0.10725	0.09434	0.12192	1.992	1.973	2.140	2.118	0.190	0.197
[26]	0.574	-0.562	-0.563	-0.851	-0.851	0.459	-0.23252	-0.07355	0.15304	0.07949	0.29464	2.326	2.326	2.232	2.237	0.203	0.196
[27]	0.578	-0.583	-0.583	-0.849	-0.849	0.462	-0.23216	-0.06215	0.14716	0.08501	0.25474	2.337	2.338	2.157	2.157	0.230	0.216
[28]	0.582	-0.595	-0.595	-0.846	-0.846	0.464	-0.23124	-0.05577	0.14351	0.08774	0.23473	2.343	2.343	2.120	2.120	0.256	0.233
[29]	0.586	-0.590	-0.586	-1.057	-0.844	0.455	-0.23808	-0.05895	0.14852	0.08957	0.24626	2.355	2.352	2.111	2.118	0.230	0.224



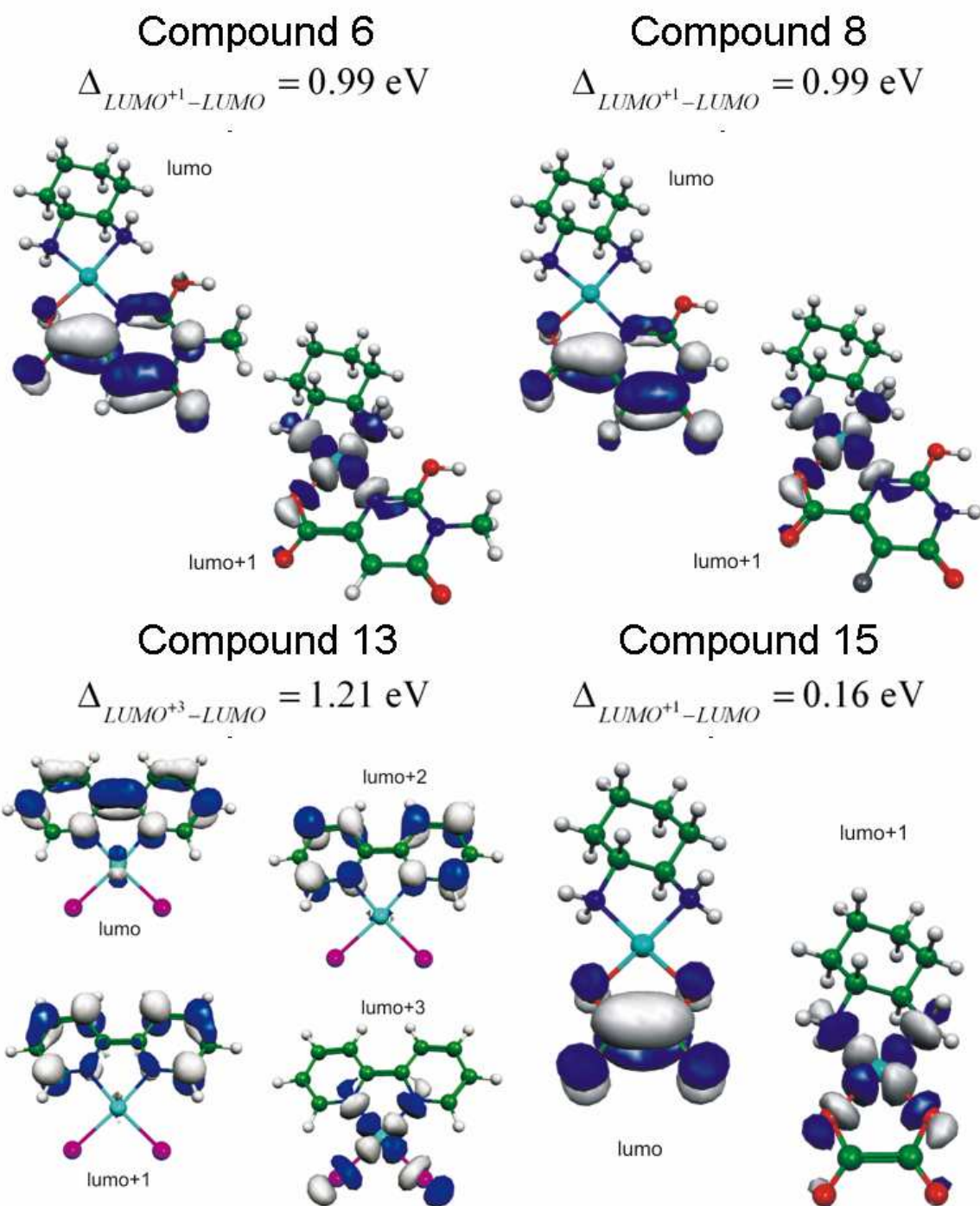


Figure 1S. Shape and relative stability of LUMO and LUMO+n calculated for compounds 6, 8, 13, and 15.