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Supplementary Information for

Halogenated Non-Innocent Vanadium(V) Schiff base complexes: chemical and anti-proliferative properties

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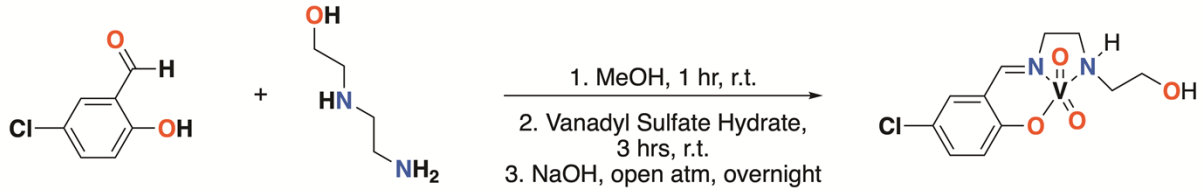
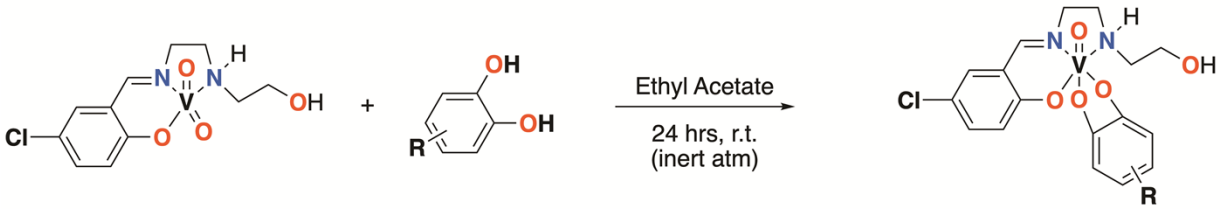
1. General Experimental Information

a. Schemes 1&2 Showing Synthesis of [VO_2(Cl-Hshed)] and [VO_2(Cl-Hshed)(R)]





b. Optimization Table of Reaction Conditions

Number	mmol cat.	mmol V Precursor	Temp (^{o}C)	Time (hrs.)	Yield
1	1	1	rt	3	55%
2	1	1	30	6	52%
3	1	1	rt	24	60%
4	1	1	30	24	50%
5	1	1	0	24	45%
6	1	1	-78	24	14.8%
7	1	1	rt	24	53%
8	1	1	rt	48	28%
9	1	1.2	rt	24	50%
10	1.2	1	rt	24	17%
11	1.5	1	rt	24	2%

Table SI 1.b. Optimization of Reaction Conditions on [VO(Cl-Hshed)(dtb)] before solvent optimization. Optimized conditions were then tested on all other compounds and shown to be best conditions.

c. Optimization Table of Reaction Conditions

Number	Solvent	Time (hrs.)	Yield
1	Acetone	24	70%
2	DCM	24	68%
3	EtOAc	24	90%
4	DMP	24	0%
5	DME	24	25%
6	Et_2O	24	30%
7	DMF	24	61%
8	DMSO	24	0%
9	EtOH	24	0%
10	MeOH	24	69%
11	MeCN	24	35%

Table SI 1.c. Optimization of Solvent of Reaction on [VO(Cl-Hshed)(dtb)]. Optimized conditions were then tested on all other compounds and shown to be best conditions.

2. NMR Spectra

a. Full Proton Spectra of [VO(Cl-Hshed)(R)] in CD_3CN and DMSO

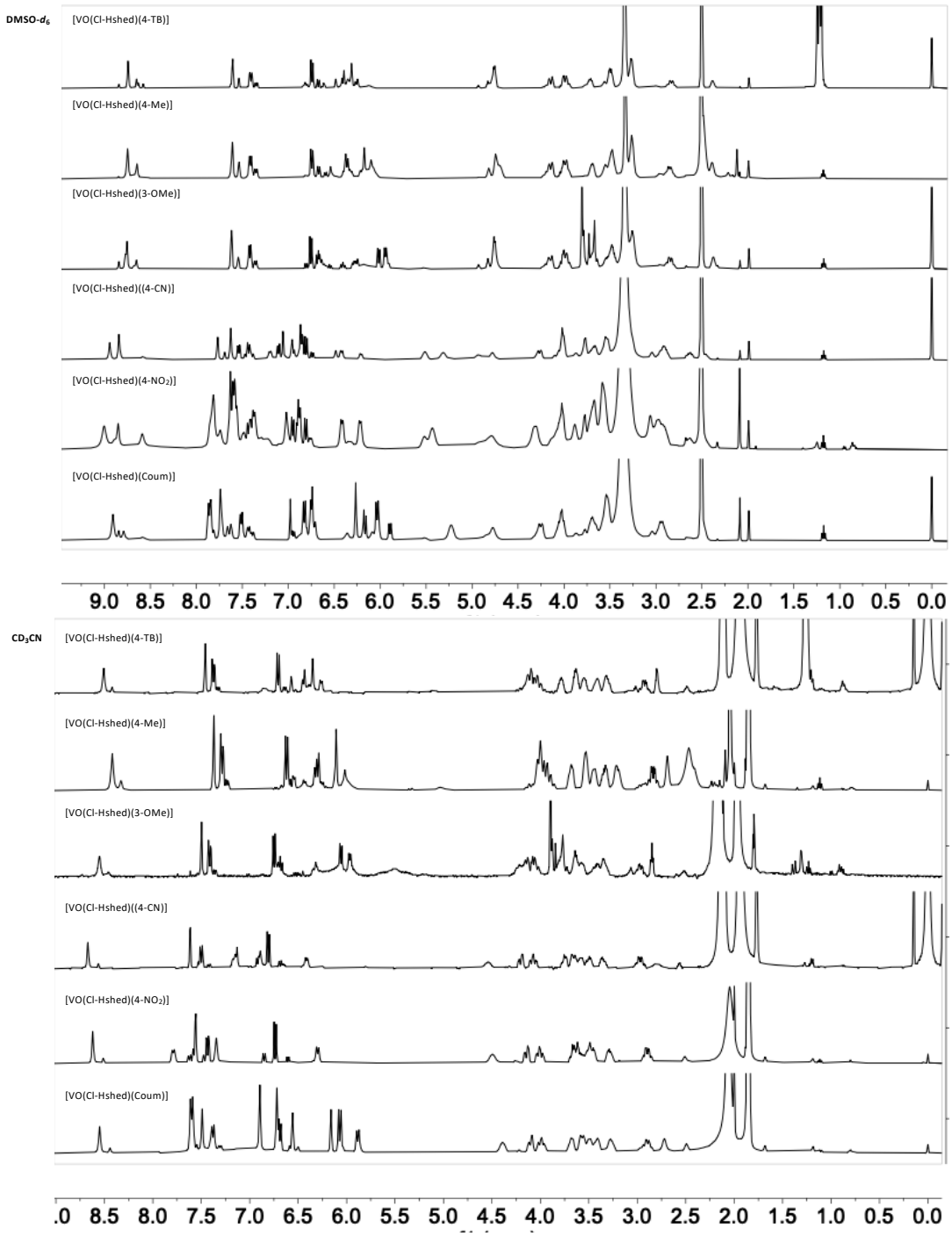


Figure SI 2.a. ^{1}H NMR (400mHz) of 10mM [VO(Cl-Hshed)(R)] complexes in DMSO (top) and CD_3CN (bottom) at 4 or 10mM. Compounds in 4mM concentration are [VO(Cl-Hshed)(4-tBu)], [VO(Cl-Hshed)(4-CN)], [VO(Cl-Hshed)(4-NO_2)] and [VO(Cl-Hshed)(Coum)].

b. Vanadium NMR Spectra of [VO(Cl-Hshed)(R)] in CD_3CN and DMSO

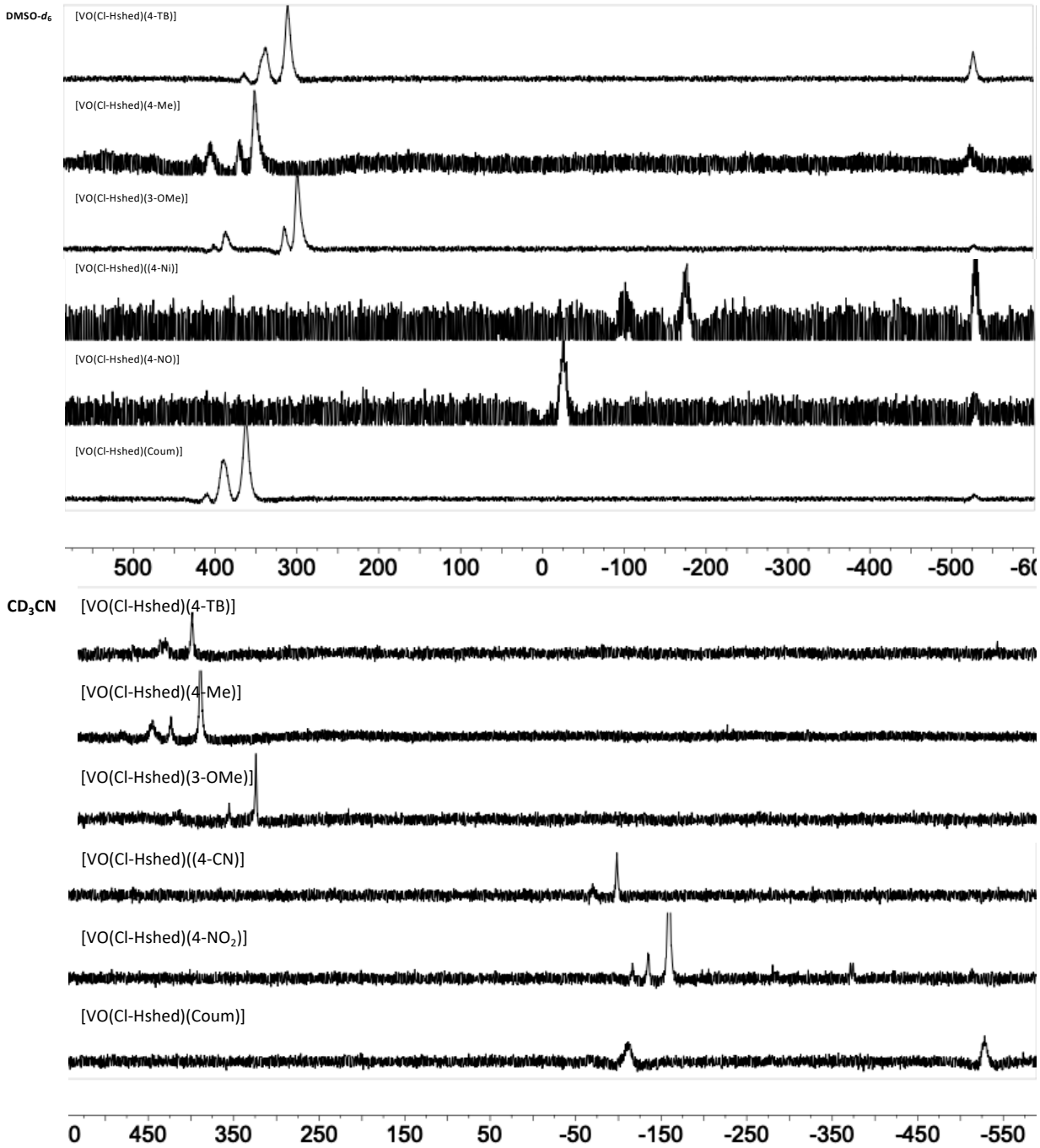


Figure SI 2.b. ^{51}V NMR (400mHz) of 10mM [VO(Cl-Hshed)(R)] complexes in DMSO (top) and CD_3CN (bottom)

c. Full Proton Spectra of [VO(Cl-Hshed)(4-tBu)] in CD_3OD

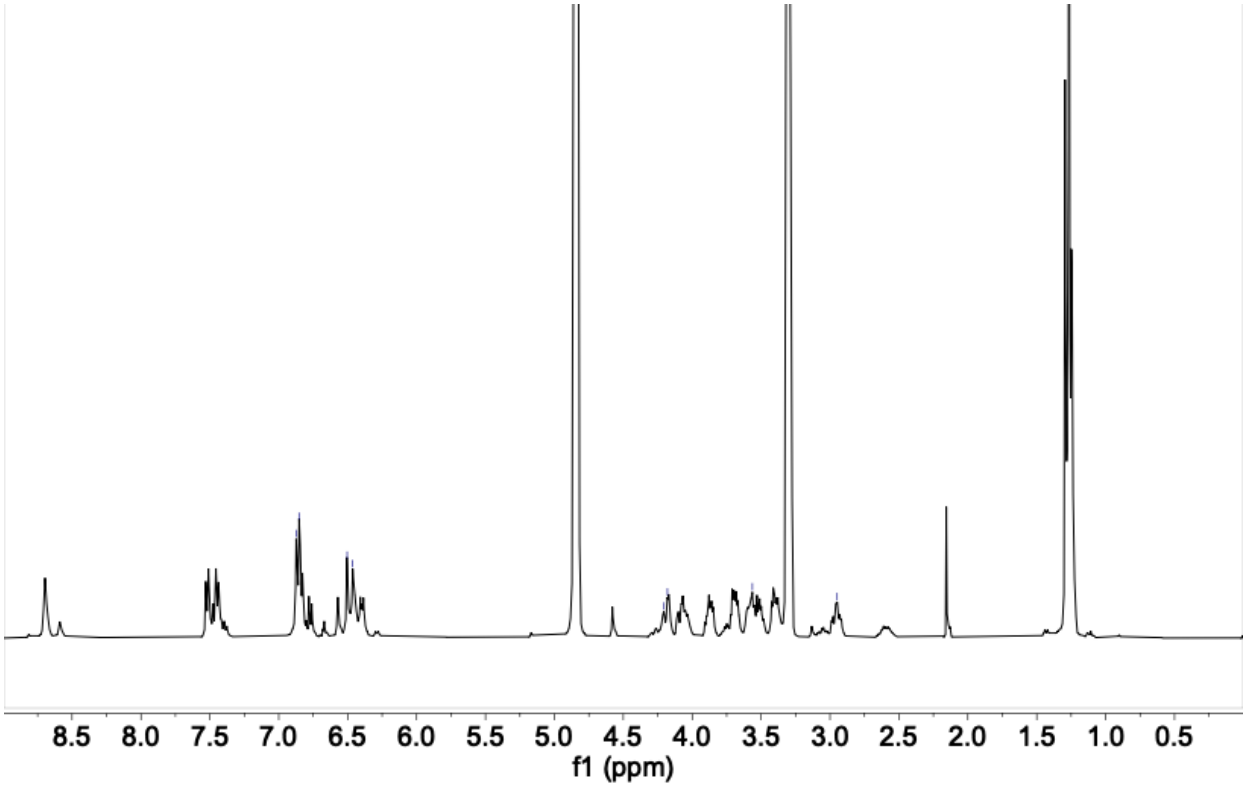


Figure SI 2.c. ^1H NMR (400mHz) of [VO(Cl-Hshed)(4-tBu) in 10mM CD_3OD

d. Vanadium NMR Spectra of [VO(Cl-Hshed)(4-tBu)] in CD_3OD

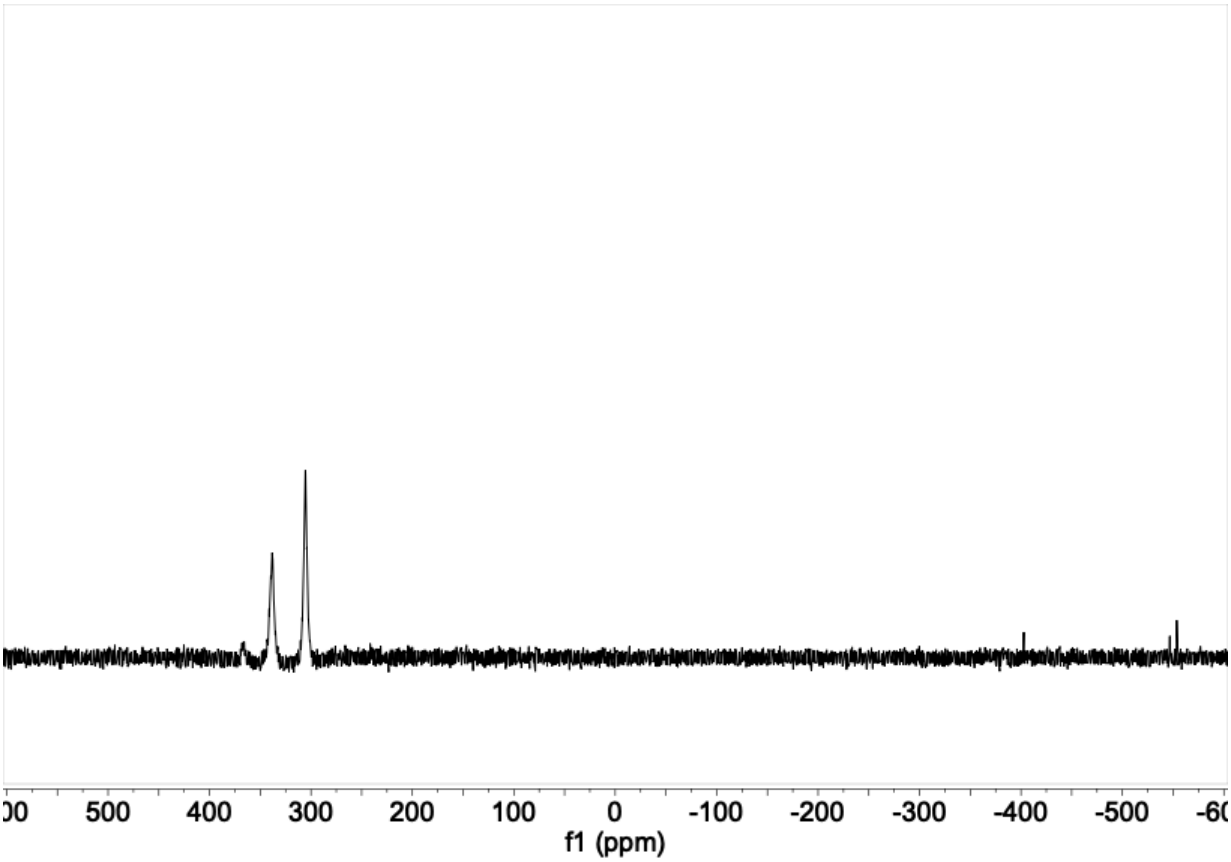


Figure SI 2.d. ^{51}V NMR (400mHz) of [VO(Cl-Hshed)(4-tBu) in 10mM CD_3OD

e. 2D NMR of [VO(Cl-Hshed)(4-tBu)] in DMSO

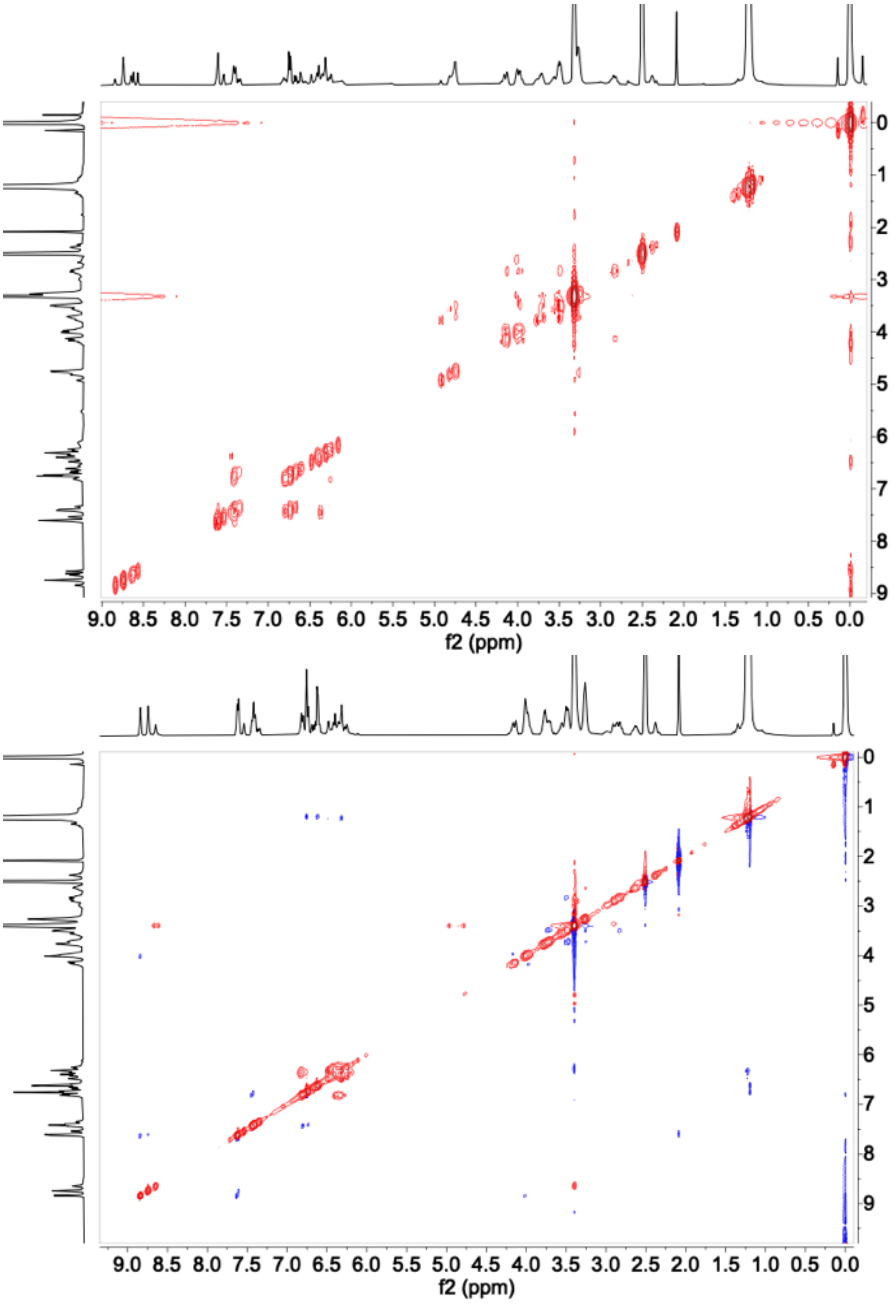


Figure SI 2.e. ^{1}H-^{1}H COSY and ^{1}H-^{1}H NOESY NMR (400MHz) spectra of 10mM [VO(Cl-Hshed)(4-tBu)] in DMSO. Full ^{1}H-^{1}H COSY (top) and full ^{1}H-^{1}H NOESY (bottom).

f. 2D NMR of [VO(Cl-Hshed)(4-tBu)] in CD_3CN

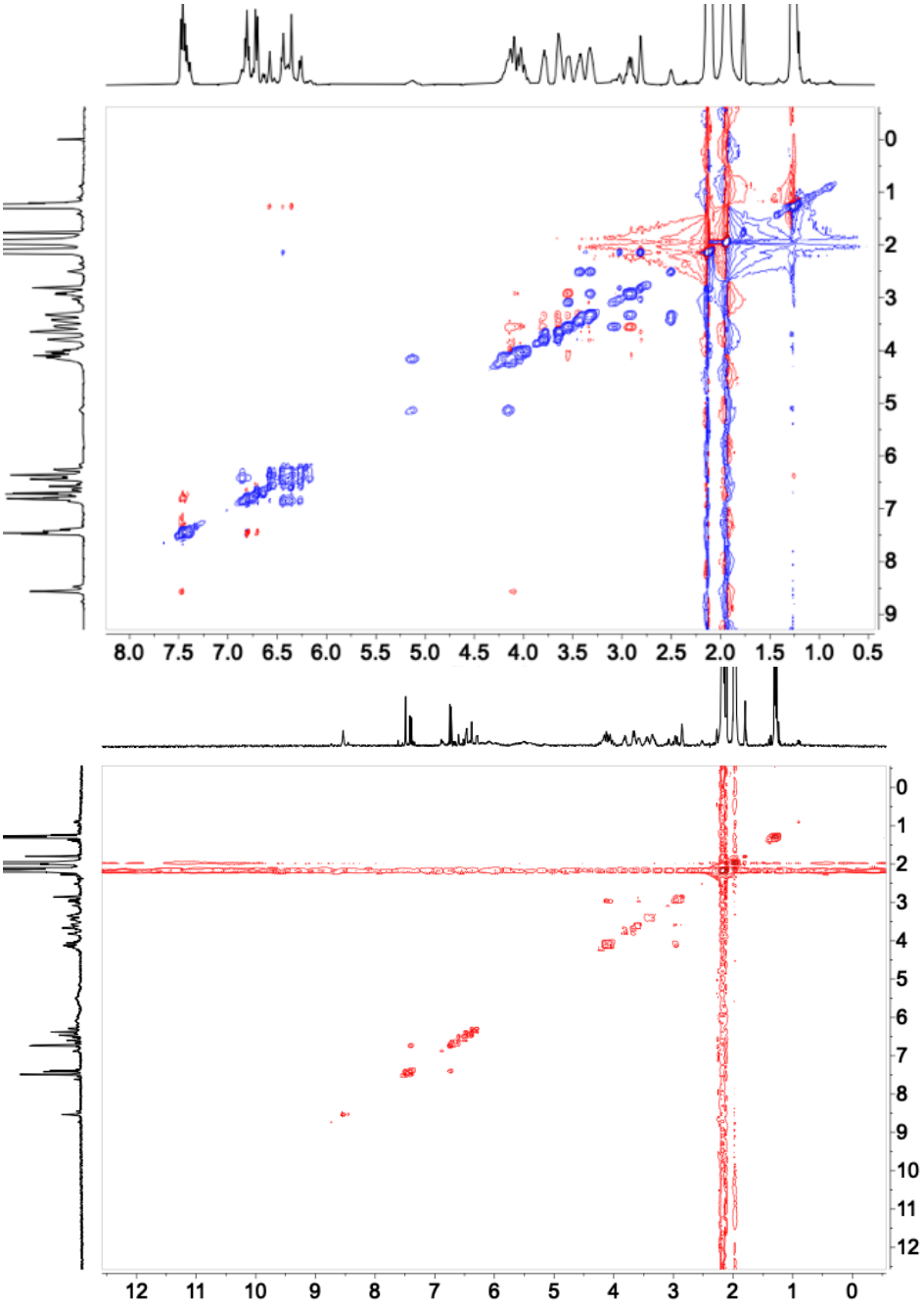


Figure SI 2.f. ^1H-^1H COSY and ^1H-^1H NOESY NMR (400MHz) spectra of 4mM [VO(Cl-Hshed)(4-tBu)] in CD_3CN. Full ^1H-^1H COSY (top) and full ^1H-^1H NOESY (bottom).

3. Mass Spectra

a. High Resolution ESI Mass Spectrometry of [VO(Cl-Hshed) Compounds

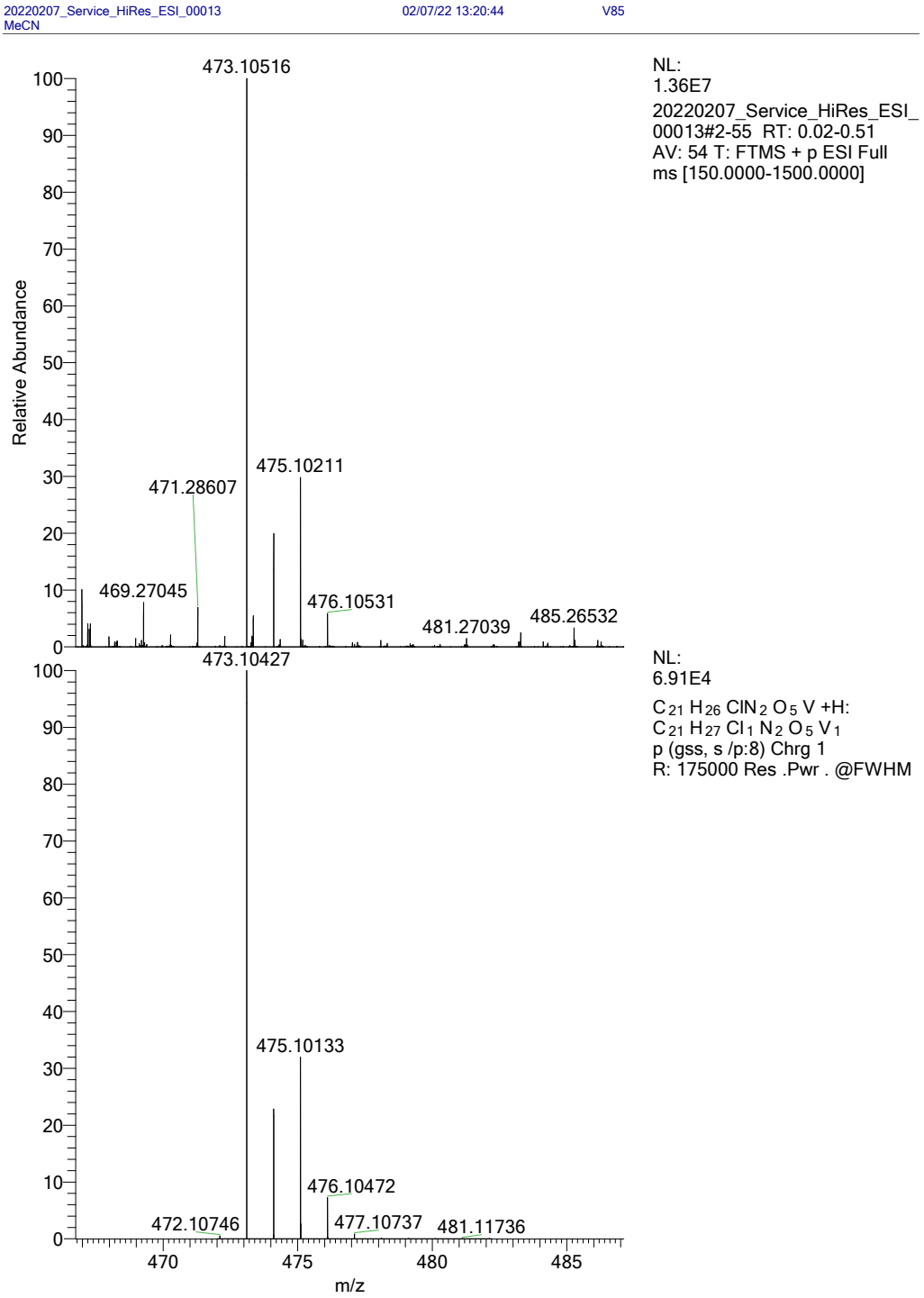


Figure SI 3.a.1. Experimental (top) and theoretical (bottom) spectra of [VO(Cl-Hshed)(4-tBu)]

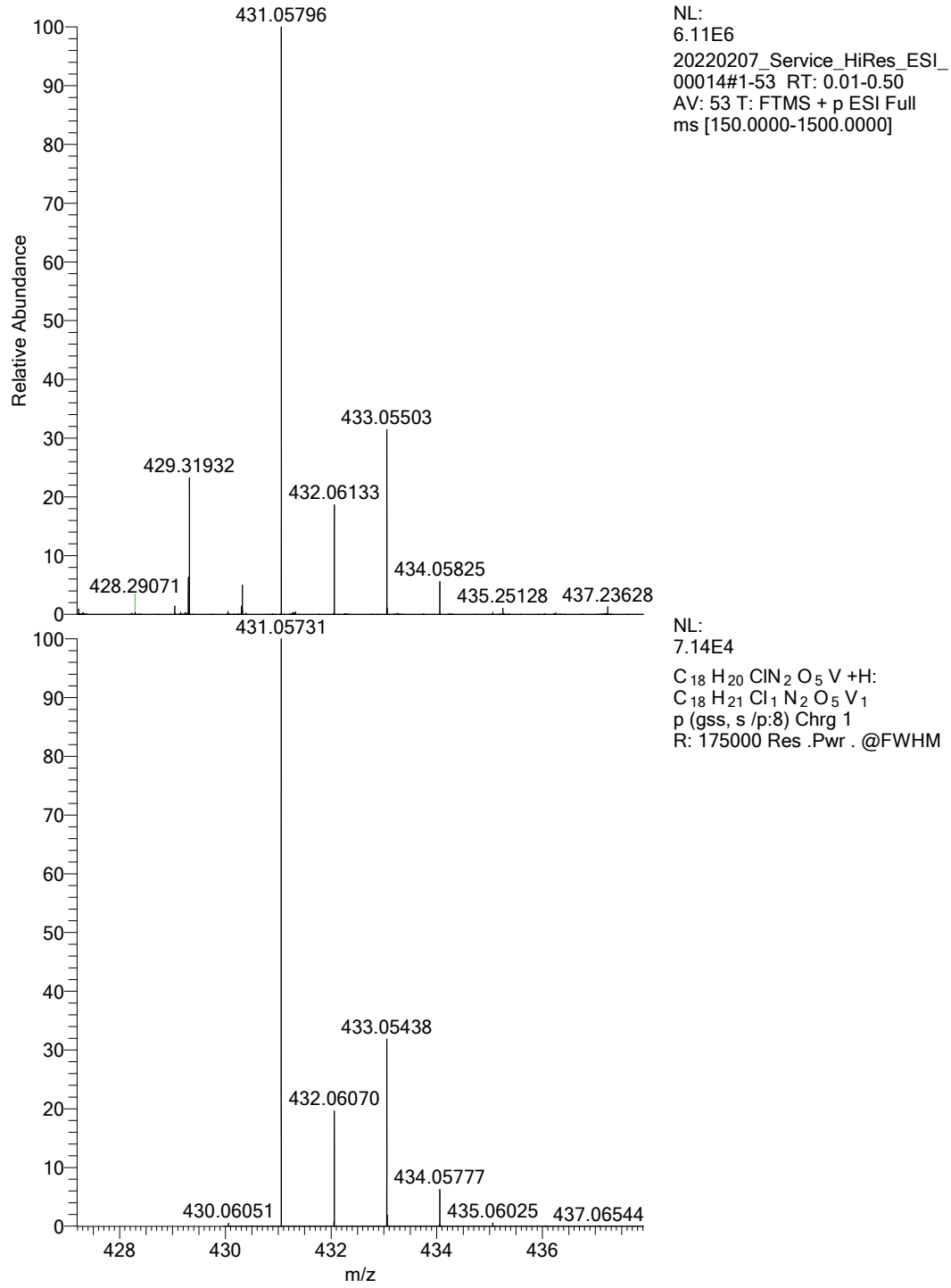


Figure SI 3.a.2. Experimental (top) and theoretical (bottom) spectra of [VO(Cl-Hshed)(4-Me)]

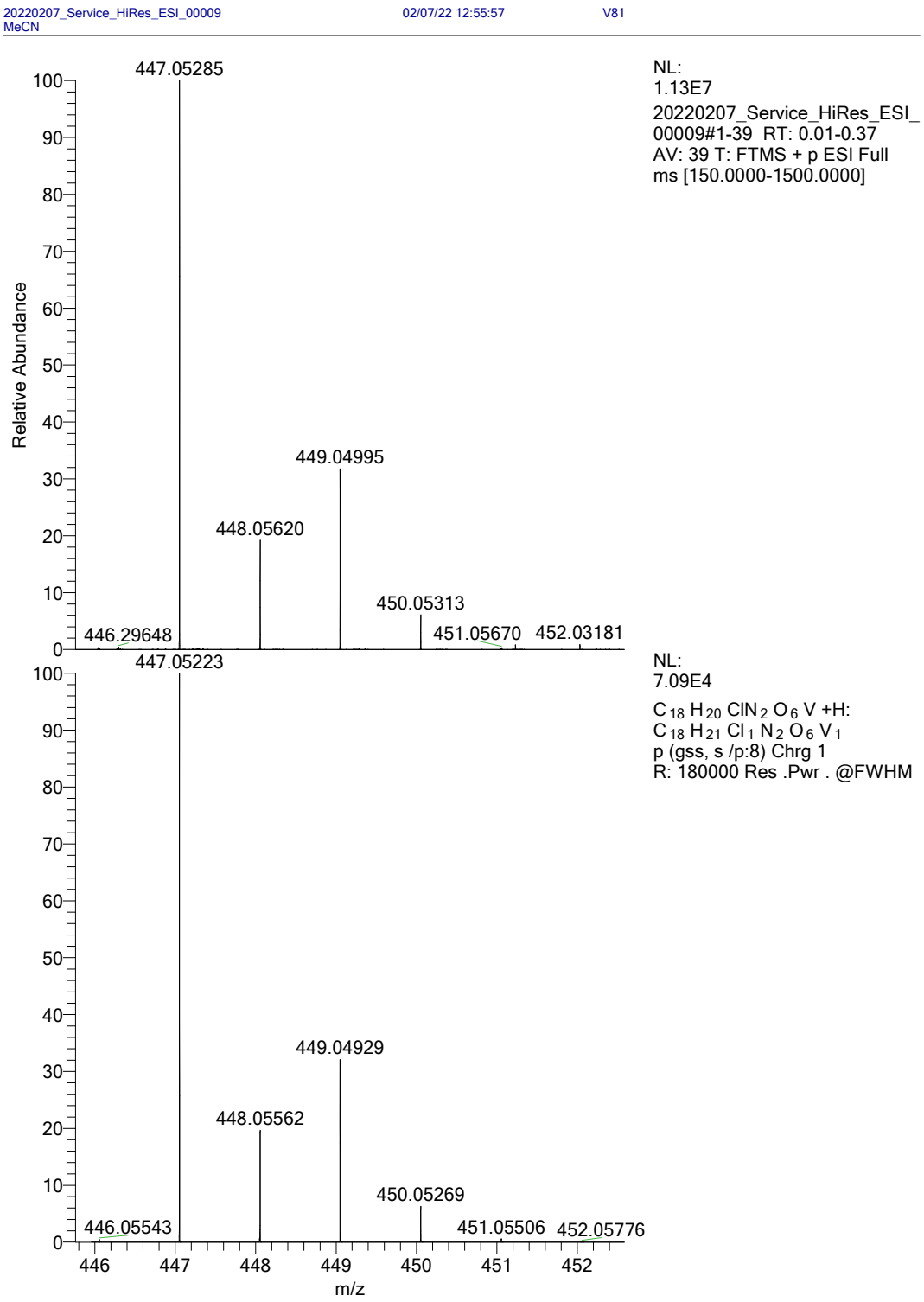


Figure SI 3.a.3. Experimental (top) and theoretical (bottom) spectra of [VO(Cl-Hshed)(3-OMe)]

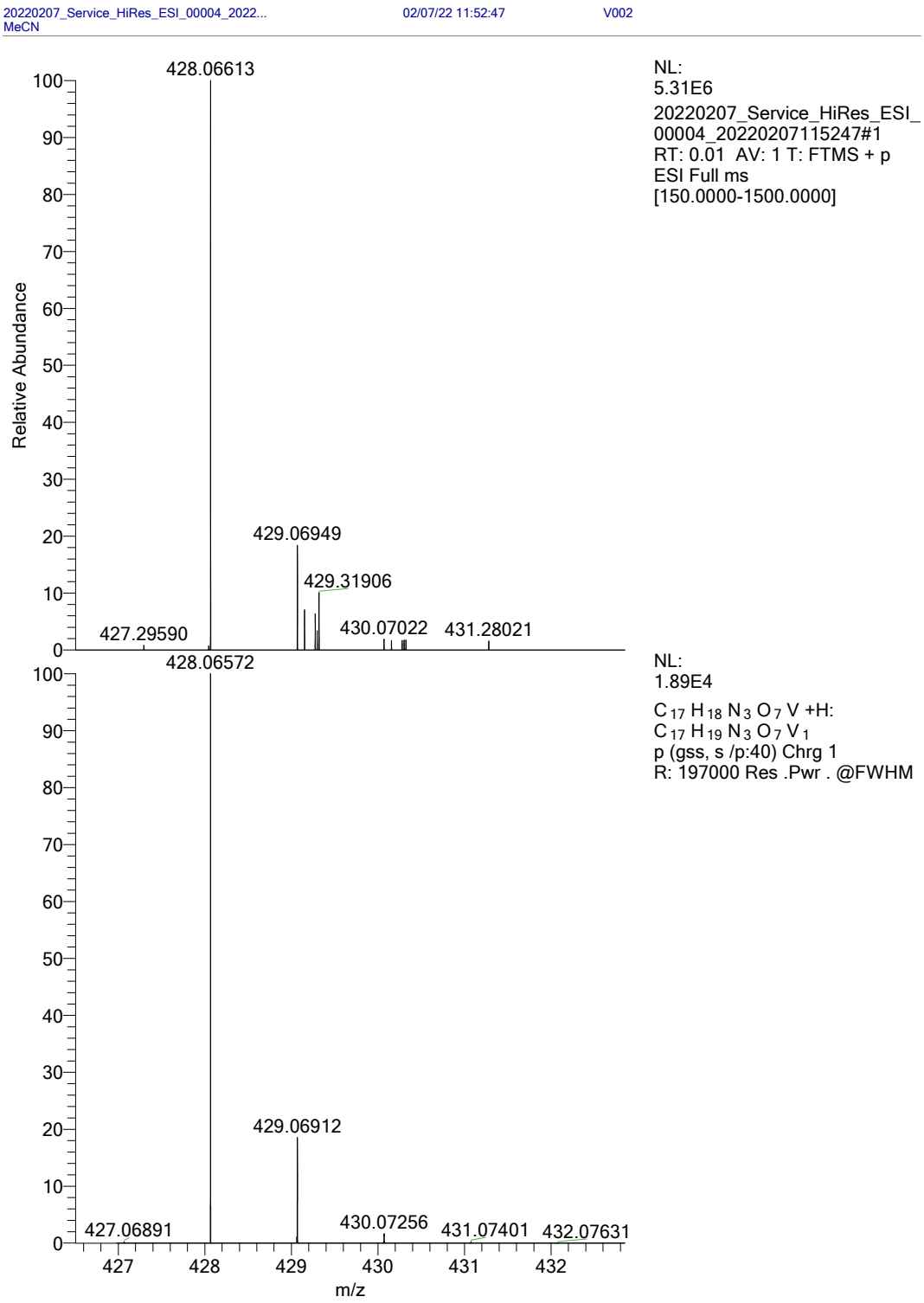


Figure SI 3.a.4. Experimental (top) and theoretical (bottom) spectra of [VO(Cl-Hshed)(4-NO_2)]

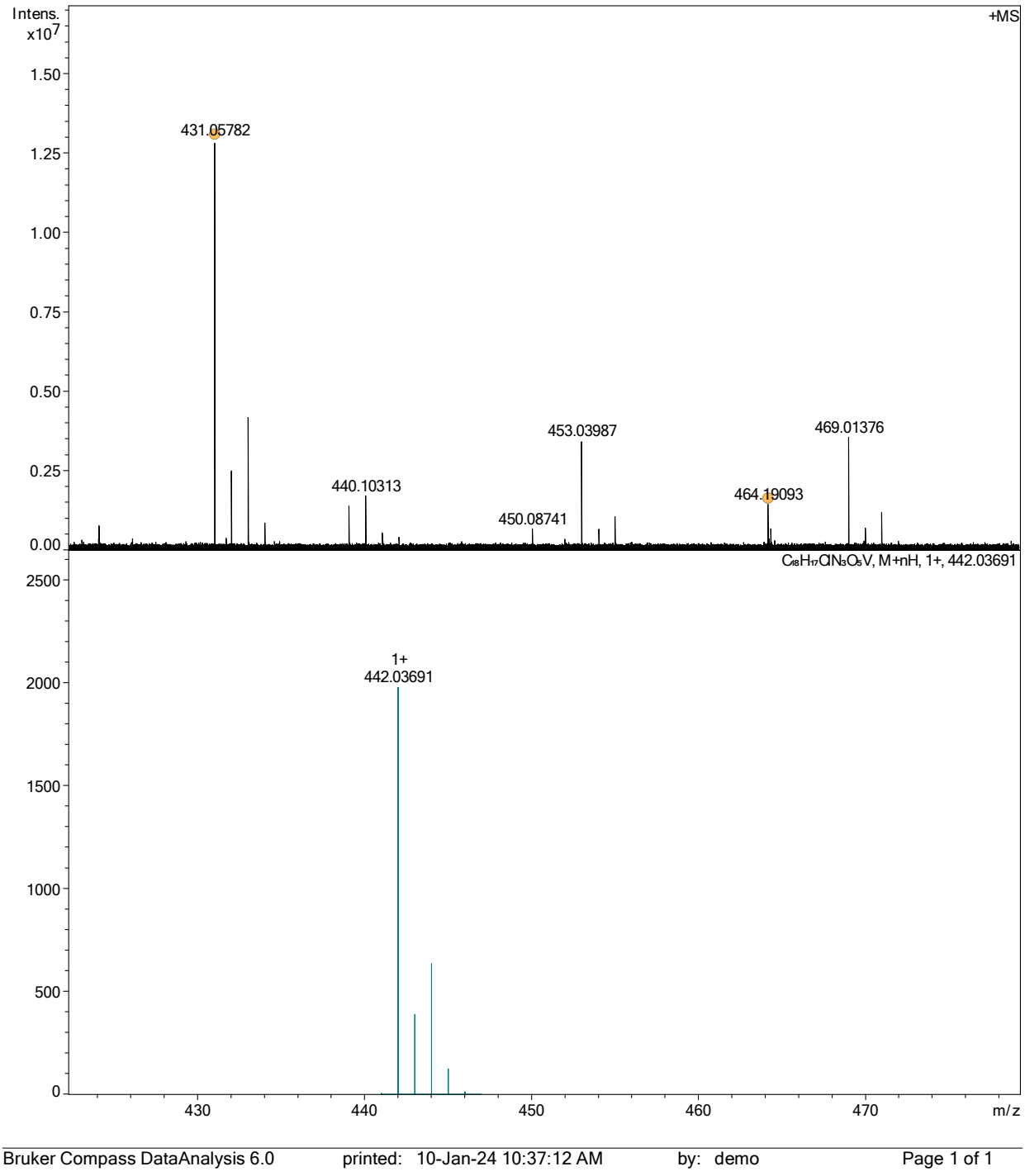


Figure SI 3.a.5. Experimental (top) and theoretical (bottom) spectra of [VO(Cl-Hshed)(4-CN)]

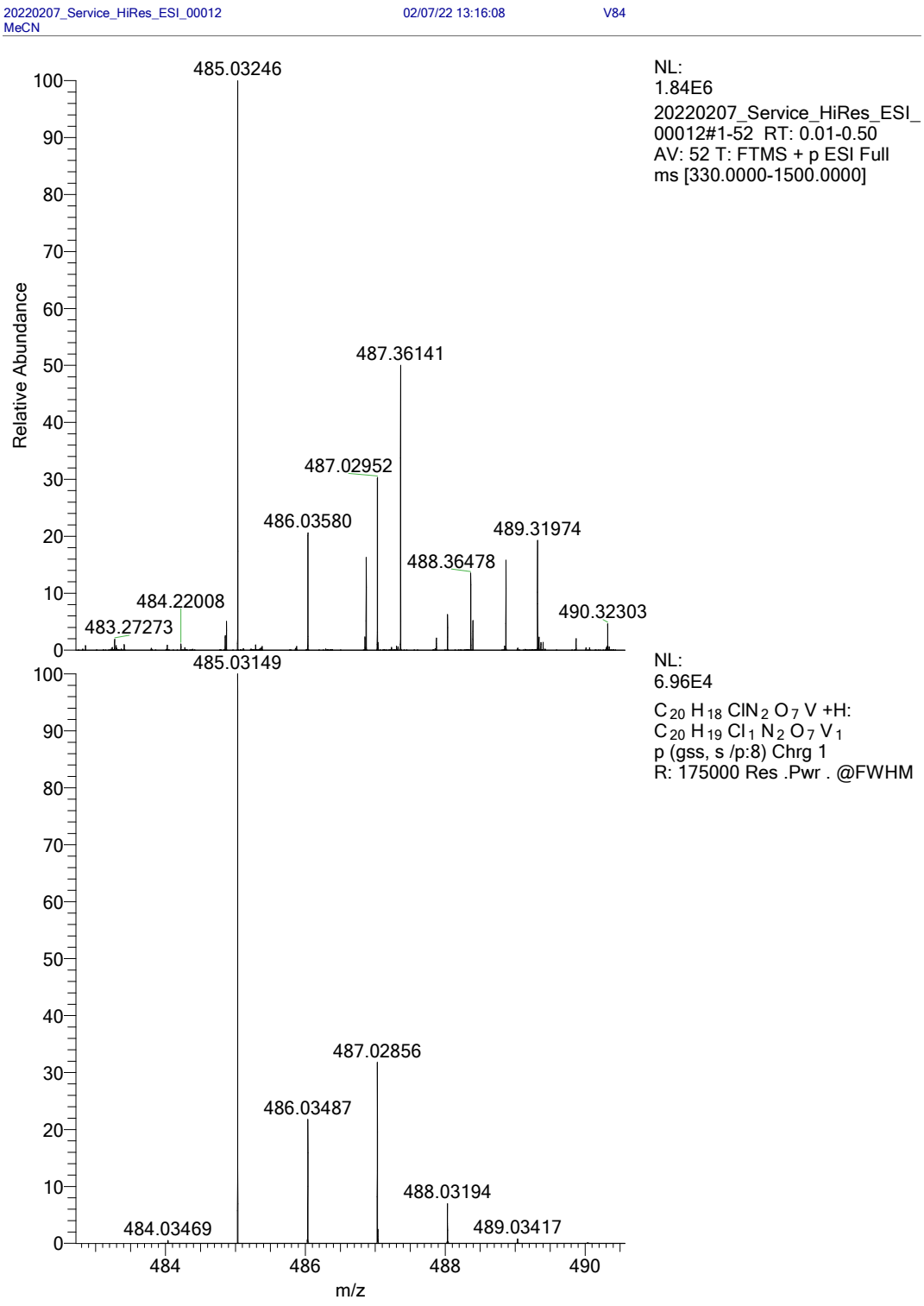


Figure SI 3.a.6. Experimental (top) and theoretical (bottom) spectra of [VO(Cl-Hshed)(coum)]

4. Electrochemistry

a. Full Cyclic Voltammograms of [VO(Cl-Hshed)(R)] tested

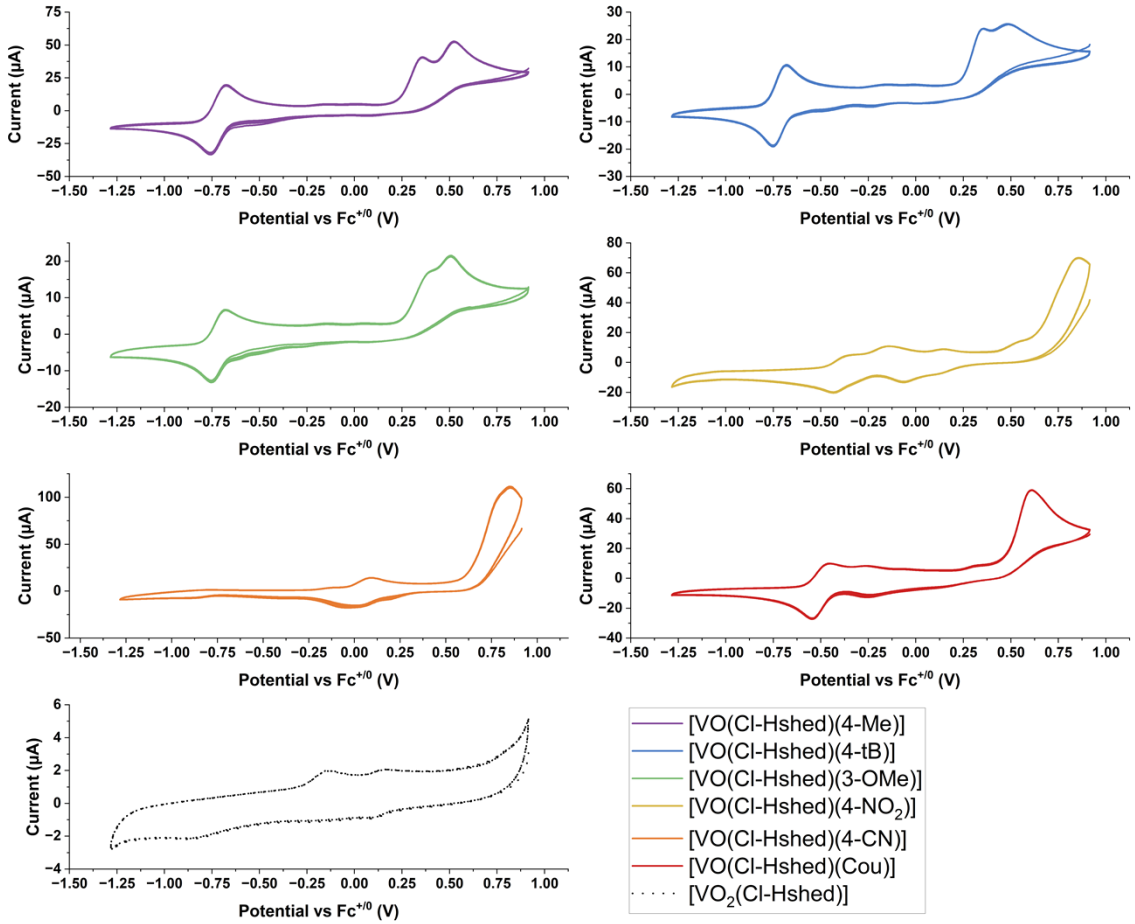


Figure SI 4.a.1. Cyclic voltammograms of tested compounds at 2 mM in CH_3CN in the presence of 0.1 M TBAP as the supporting electrolyte. Scans were cycled at 100 mV s^{-1} from approx. 1 V vs Fc+/0 to -1.5 V and back 5 times using a glassy carbon working electrode. Figure includes the $[VO_2(Cl\text{-}Hshed)]$ precursor at 2mM.

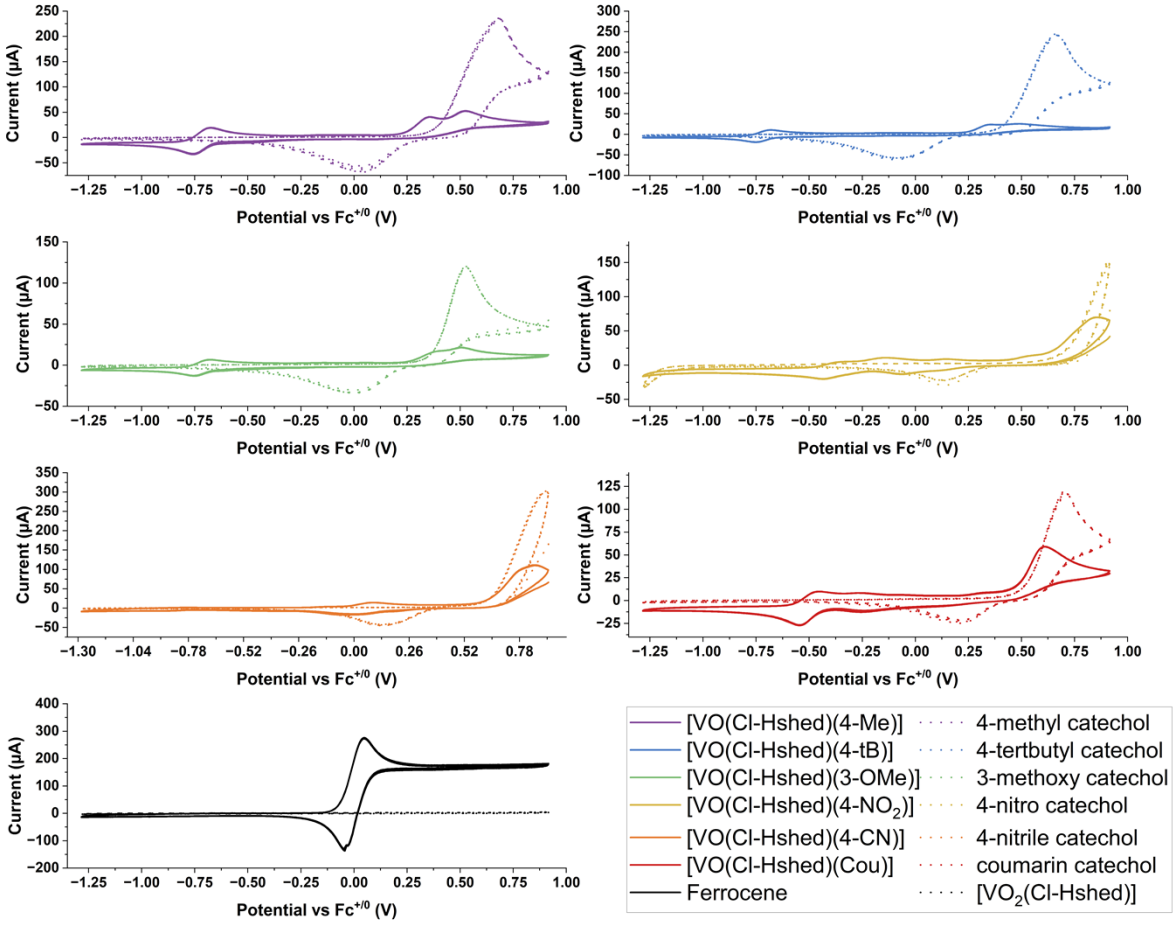


Figure SI 4.a.2. Cyclic voltammograms of tested compounds at 2 mM in CH_3CN in the presence of 0.1 M TBAP as the supporting electrolyte. Scans were cycled at 100 mV s^{-1} from approx. 1 V vs Fc+/0 to -1.5 V and back 5 times using a glassy carbon working electrode. Figure includes the $[VO_2(Cl\text{-}Hshed)]$ precursor and ferrocene at 2mM , while the free catecholate ligands were tested at 5mM.

b. Negative Cyclic Voltammograms of [VO(Cl-Hshed)(R)] tested

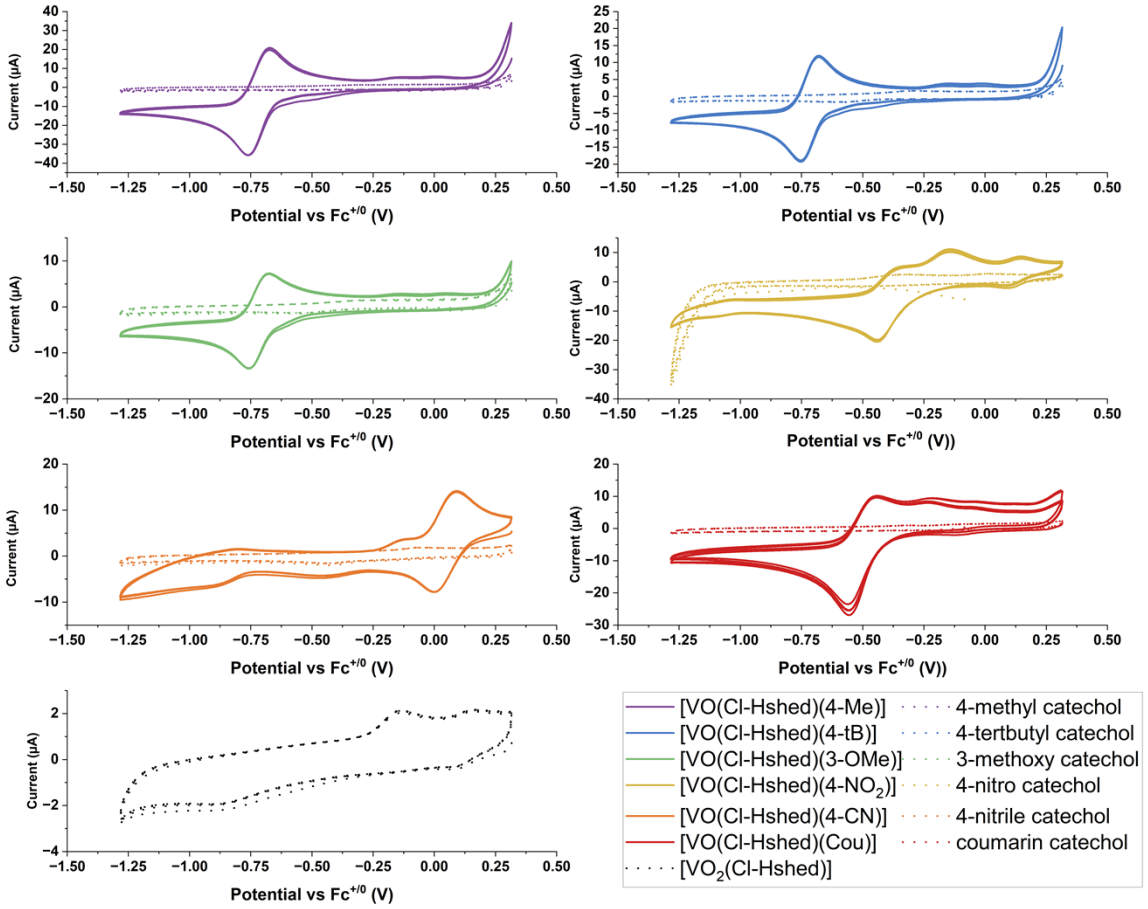


Figure SI 4.b.1. Cyclic voltammograms of tested compounds at 2 mM in CH_3CN in the presence of 0.1 M TBAP as the supporting electrolyte. Scans were cycled at 100 mV s^{-1} from approx. 0 V vs Fc+/0 to -1.1 V and back 5 times using a glassy carbon working electrode. Figure includes the $[VO_2(Cl\text{-}Hshed)]$ precursor at 2mM while the free catecholate ligands were tested at 5mM.

c. Positive Cyclic Voltammograms of [VO(Cl-Hshed)(R)] tested

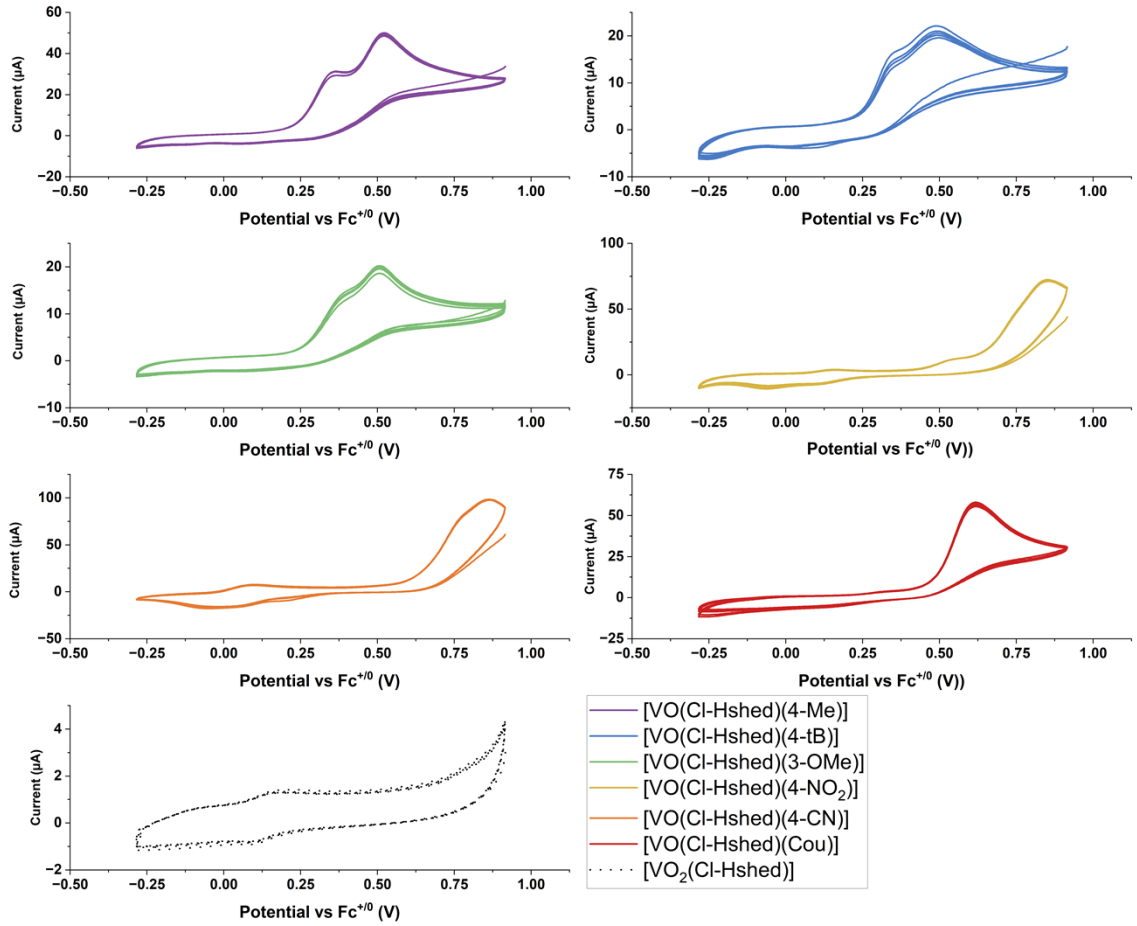


Figure SI 4.c.1. Cyclic voltammograms of tested compounds at 2 mM in CH_3CN in the presence of 0.1 M TBAP as the supporting electrolyte. Scans were cycled at 100 mV s^{-1} from approx. 1 V vs Fc+/0 to -0.25 V and back 5 times using a glassy carbon working electrode. Figure includes the [VO_2(Cl-Hshed)] precursor at 2mM.

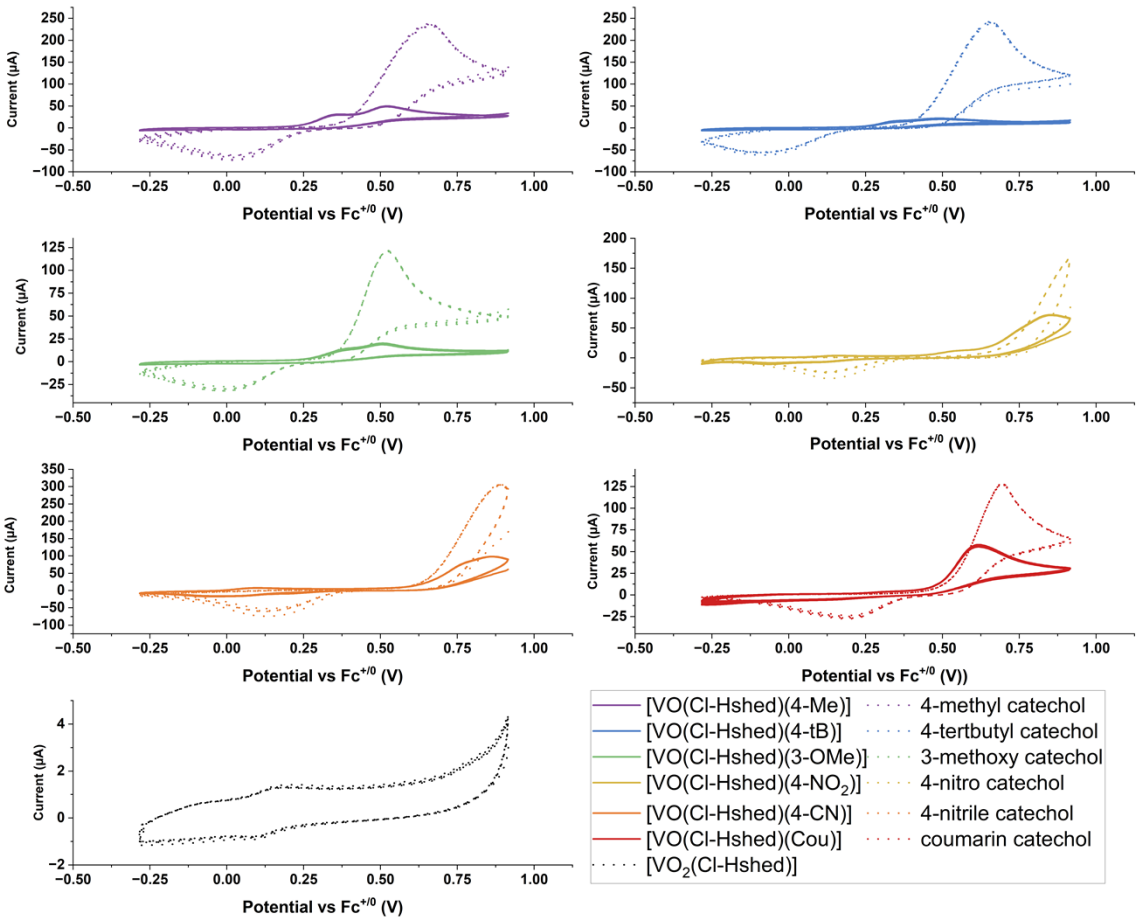


Figure SI 4.c.2. Cyclic voltammograms of tested compounds at 2 mM in CH_3CN in the presence of 0.1 M TBAP as the supporting electrolyte. Scans were cycled at 100 mV s^{-1} from approx. 1 V vs Fc+/0 to -0.25 V and back 5 times using a glassy carbon working electrode. Figure includes the [VO_2(Cl-Hshed)] precursor at 2mM while the free catecholate ligands were tested at 5mM.

d. Comparative Graphs of [VO(Cl-Hshed)(R)] Stability and half wave potentials

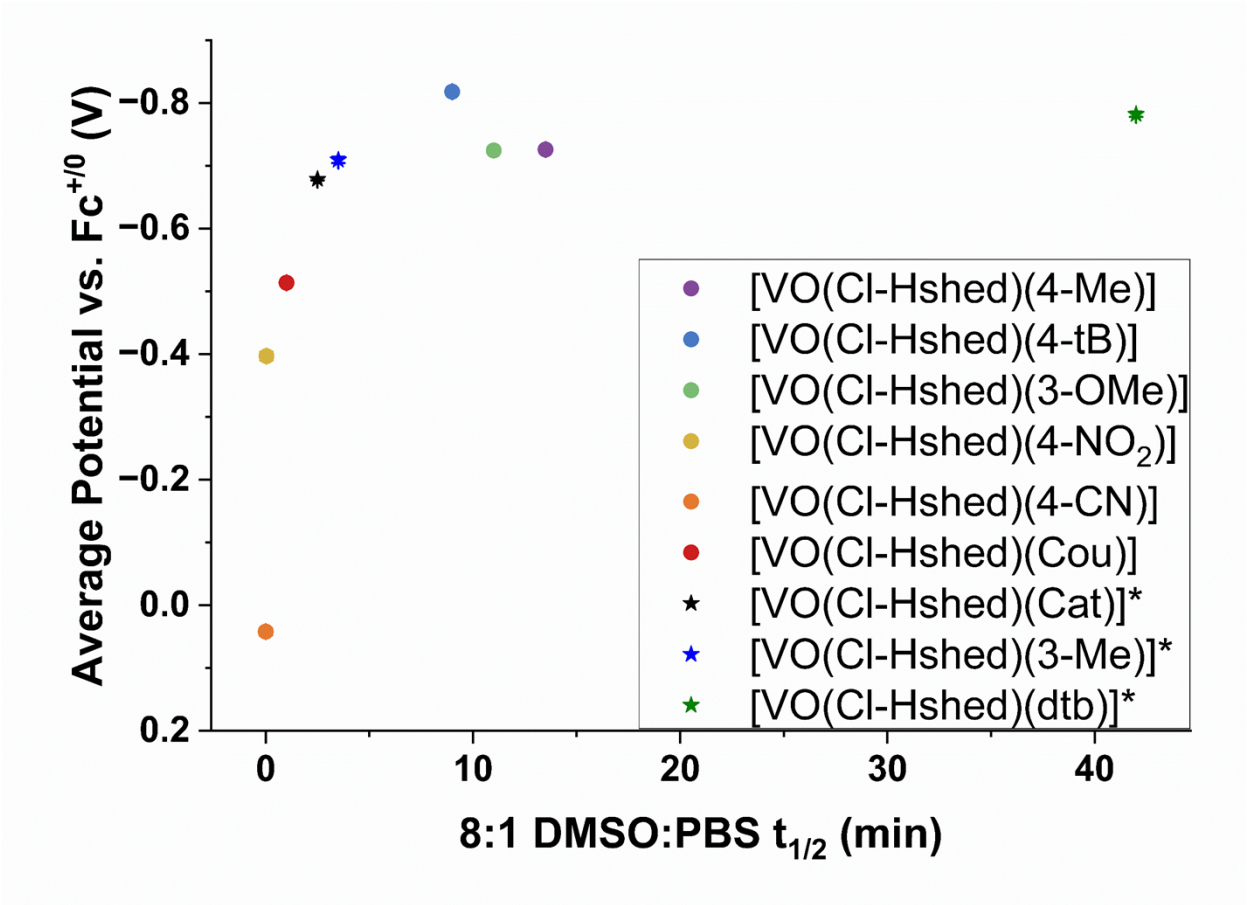


Figure SI 4.d.1. Half wave potentials of tested compounds at 2 mM in CH_3CN in the presence of 0.1 M TBAP as the supporting electrolyte vs the half life of the compounds in an 8:1 DMSO:PBS mix. In general, there is a trend of more compound with more negative half wave potentials being more stable when exposed to water.

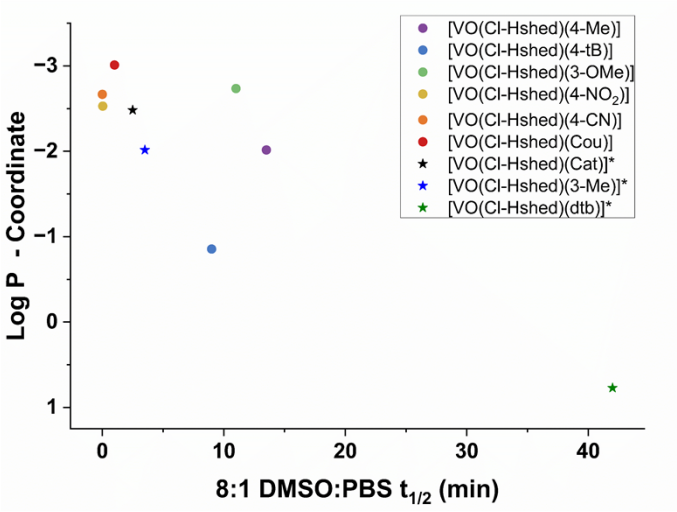


Figure SI 4.d.2. Computed log P values of tested compounds vs the half-life of the compounds in an 8:1 DMSO:PBS mix. There is no visible correlation between the two, other than the more water-soluble compounds seem to be less stable.

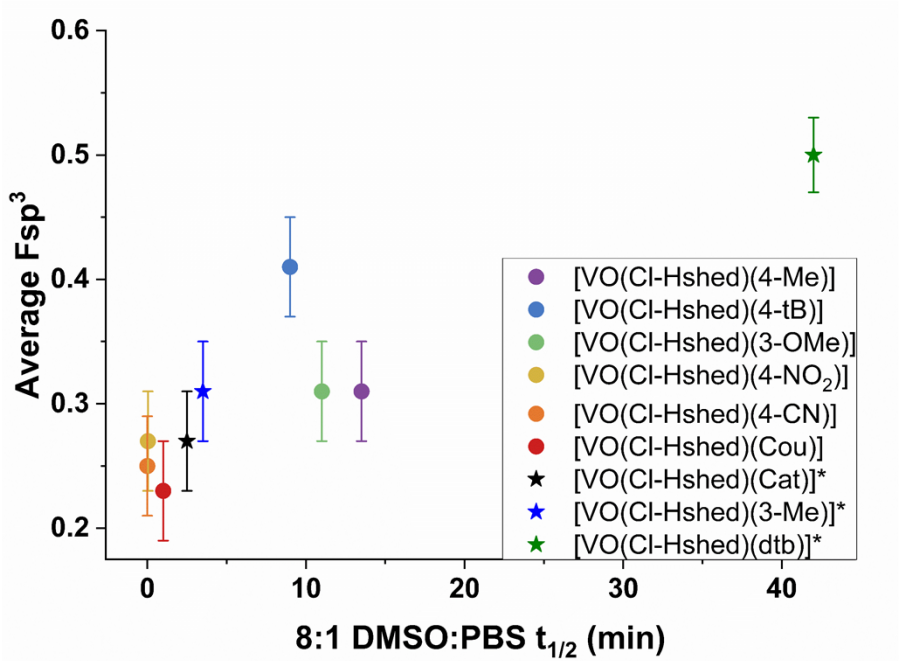


Figure SI 4.d.3. Average Fsp^3, the fraction ofsp3 hybridized carbona in the molecule divided by total amount of carbon vs the half-life of the compounds in an 8:1 DMSO:PBS mix. In general, when there is more sp^3 hybridized carbons on the molecule, it tends to degrade less when exposed to aqueous conditions.

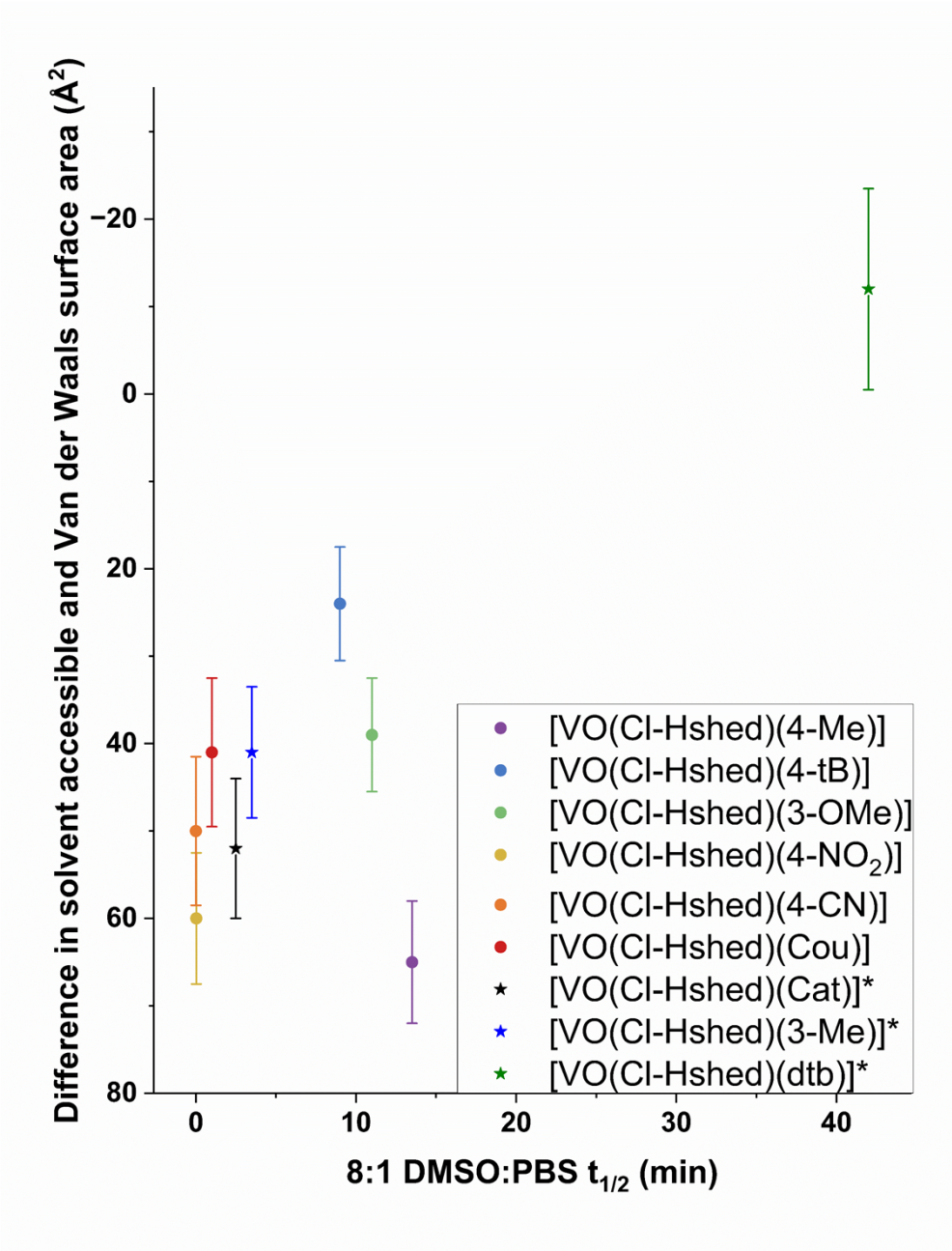


Figure SI 4.d.4. The difference in the solvent accessible surface area and the Van der Waals surface areas computed via Chemicalize vs the half-life of the compounds in an 8:1 DMSO:PBS mix. It is interesting to note that the most stable compound in this series is the only one with a larger Van der Waals surface area than a solvent accessible surface area. Future designed compounds should be computed for this property along with identifying stability before cell studies should be done.

5. Biological Data of Vanadium Schiff Base Catecholates

a. Concentration Dependencies of Cell Viability

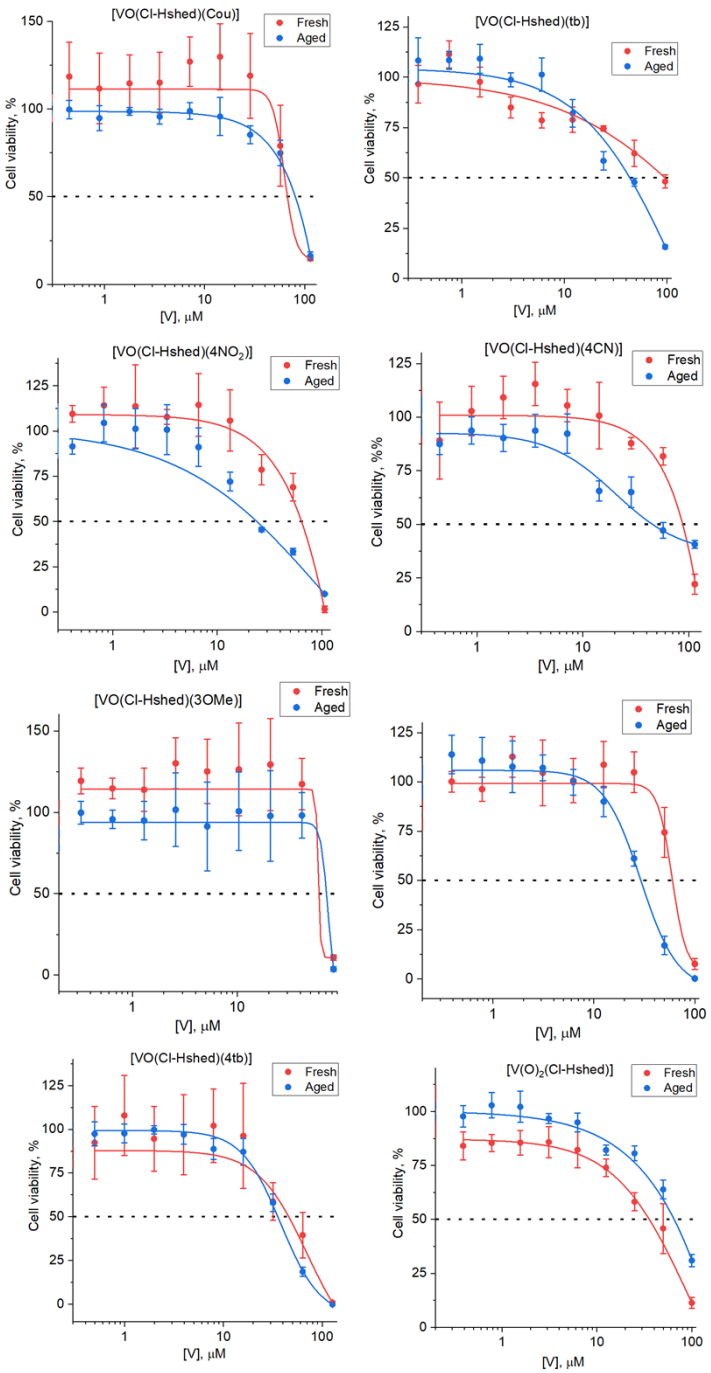


Figure SI 5.a. Typical concentration dependencies of T98g cell viabilities after 72 h treatments with fresh or aged (24 h) solutions of V(V)-Cl-Hshed complexes. Points are the experimental values (mean values and standard deviations of six replicate wells), and curves are sigmoidal fits of the experimental data.

6. Calculated Properties of compounds

a. Computed Physical Properties of the Catechol Ligands

Parameter	cat*	3-Me*	dtb*	4-Me	4-tB	3-OMe	4-NO_2	4-CN	Cou
Fsp^3	0	0.14	0.57	0.14	0.4	0.14	0	0	0
Polarizability ($Å^3$)	11.54	13.3	26.12	13.3	18.82	14.08	13.54	13.39	16.89
Molar refractivity (cm^3/mol)	30.02	35.06	67.35	35.06	48.69	36.48	37.34	35.74	45.51
Strongest acidic pKa	9.34	9.59	9.69	9.55	9.47	9.56	7.17	7.85	7.91
Secondary pKa	12.79	13.04	13.39	13.01	12.91	13.13	11.18	11.4	12.27
Log P	1.366	1.88	4.456	1.88	2.911	1.208	1.306	1.222	1.176
HLB	9.689	8.928	5.281	8.928	7.126	11.738	12.718	10.449	11.699
Intrinsic solubility (mg/mL)	-0.52	-0.832	-3.69	-1.06	-2.244	-0.59	-1.003	-0.839	-1.801
Van der Waals volume ($Å^3$)	99.01	115.85	236.12	115.78	167.41	125.09	121.01	115.56	143.05
Van der Waals surface area ($Å^2$)	158.06	189.84	412.86	190.09	285.83	205.83	198.73	175.12	208.24
Solvent accessible surface area ($Å^2$)	256.64	289.73	443.36	296.51	348.51	313.49	301.21	267.09	293.37
Topological polar surface area ($Å^2$)	40.46	40.46	40.46	40.46	40.46	49.69	86.28	64.25	66.76
Minimum projection area ($Å^2$)	22.52	25.38	43.04	22.96	33.23	27.64	24.44	24.05	24.11
Maximum projection area ($Å^2$)	38.17	43.79	69.4	43.92	54.38	46.15	43.63	44.41	55.21
Minimum projection radius (Å)	3.58	3.83	4.69	3.56	3.88	3.73	3.54	3.87	3.61
Maximum projection radius (Å)	3.95	4.21	5.61	4.44	5.17	4.67	4.61	4.85	5.31

Table SI 6.a. Computed physical properties of the catechol ligands.

b. Computed physical properties of the complex where a nitrogen is coordinately bonded to the vanadium center.

Coordinate Properties	cat*	3-Me*	dtb*	4-Me	4-tB	3-OMe	4-NO_2	4-CN	Cou
Fsp^3	0.24	0.28	0.48	0.28	0.38	0.28	0.24	0.22	0.2
Polarizability ($Å^3$)	38.62	40.37	53.09	40.37	45.84	41.18	40.65	40.48	44
Molar refractivity (cm^3/mol)	105.85	110.89	143.18	110.89	124.51	112.31	113.17	111.57	121.34
Strongest acidic pKa	14.64	14.64	14.64	14.64	14.64	14.64	14.64	14.64	14.64
Log P	-2.482	-2.015	0.772	-2.015	-0.855	-2.735	-2.529	-2.667	-3.011
HLB	14.439	13.98	11.026	13.98	12.665	15.345	16.183	14.607	15.718
Intrinsic solubility (mg/mL)	-4.447	-4.691	-7.078	-4.919	-5.901	-4.372	-4.714	-4.646	-5.401
Van der Waals volume ($Å^3$)	328.68	345.71	465.91	345.54	397.41	354.84	350.88	345.32	372.88
Van der Waals surface area ($Å^2$)	515.35	546.68	769.3	547.62	642.41	566.03	556.44	532.44	566.72
Solvent accessible surface area ($Å^2$)	578.76	592.82	758.91	623.03	674.05	614.33	626.71	594.44	610.8
Topological polar surface area ($Å^2$)	88.64	88.64	88.64	88.64	88.64	97.87	134.46	112.43	114.94
Minimum projection area ($Å^2$)	60.41	61.51	77.74	64.07	69.99	62.44	65.66	66.05	68.82
Maximum projection area ($Å^2$)	94.01	98.25	126.99	99.01	110.07	101.15	99.63	100.14	110.57
Minimum projection radius (Å)	5.68	5.96	6.55	5.7	6	5.77	5.72	6.55	6.61
Maximum projection radius (Å)	7.29	7.33	8.1	7.82	8.57	7.55	7.95	7.7	8.7

Table SI 6.b. Computed physical properties of the complex where a nitrogen is coordinately bonded to the vanadium center.

c. Computed physical properties of the complex where a nitrogen is covalently bonded to the vanadium center, but a hydrogen was lost from the nitrogen.

Covalent - Properties	**cat***	**3-Me***	**dtb***	**4-Me**	**4-tB**	**3-OMe**	**4-NO_2**	**4-CN**	**Cou**
Fsp^3	0.29	0.33	0.52	0.33	0.43	0.33	0.29	0.28	0.25
Polarizability ($Å^3$)	38.36	40.11	52.82	40.11	45.58	40.92	40.4	40.22	43.74
Molar refractivity (cm^3/mol)	91.33	96.37	128.66	96.37	109.99	97.79	98.65	97.05	106.82
Strongest acidic pKa	15.61	15.61	15.61	15.61	15.61	15.61	15.61	15.61	15.61
Log P	2.126	2.593	5.38	2.593	3.753	1.873	2.079	1.941	1.597
HLB	14.439	13.98	11.026	13.98	12.665	15.345	16.183	14.607	15.718
Intrinsic solubility (mg/mL)	-4.811	-5.055	-7.442	-5.284	-6.265	-4.736	-5.078	-5.01	-5.765
Van der Waals volume ($Å^3$)	331.47	348.53	469.17	348.61	400.46	357.66	353.79	348.48	375.86
Van der Waals surface area ($Å^2$)	531.13	562.62	786.32	563.65	659.69	579.39	572.24	548.53	582.02
Solvent accessible surface area ($Å^2$)	571.22	598.96	773.87	619.22	674.96	610.33	621.51	586.11	619.23
Topological polar surface area ($Å^2$)	71.47	71.47	71.47	71.47	71.47	80.7	117.29	95.26	97.77
Minimum projection area ($Å^2$)	55.7	59.87	78.18	57.58	63.22	59.63	57.72	57.54	58.24
Maximum projection area ($Å^2$)	102.91	104.09	130.78	107.93	118.42	104.57	109.91	107.59	115.76
Minimum projection radius (Å)	4.95	4.94	5.88	5.88	5.44	5.09	5.88	5.02	5.89
Maximum projection radius (Å)	7.85	7.78	9.01	8.02	8.99	7.76	8.16	8.57	8.75

Table SI 4.c. Computed physical properties of the complex where a nitrogen is covalently bonded to the vanadium center, but a hydrogen was lost from the nitrogen.

d. Average computed physical properties of the vanadium complex using both coordinate and covalent bonding methods.

Average	cat*	3-Me*	dtb*	4-Me	4-tB	3-OMe	4-NO_2	4-CN	Cou
Fsp^3	0.27 ± 0.04	0.31 ± 0.04	0.50 ±0.03	0.31 ±0.04	0.41 ±0.04	0.31 ±0.04	0.27 ±0.04	0.25 ±0.04	0.23 ±0.04
Polarizability ($Å^3$)	38.5 ± 0.2	40.2± 0.2	53.0 ± 0.2	40.2 ± 0.2	45.7 ± 0.2	41.1 ± 0.2	40.5 ± 0.2	40.4 ± 0.2	43.9 ± 0.2
Molar refractivity (cm^3/mol)	99 ± 10	104 ± 10	136 ± 10	104 ± 10	117 ± 10	105 ± 10	106 ± 10	104 ± 10	114 ± 10
Strongest acidic pKa	15.1 ±0.7	15.1 ±0.7	15.1 ±0.7	15.1 ±0.7	15.1 ±0.7	15.1 ±0.7	15.1 ±0.7	15.1 ±0.7	15.1 ±0.7
HLB	14.44	13.98	11.03	13.98	12.67	15.35	16.18	14.61	15.72
Intrinsic solubility (mg/mL)	-4.6 ±0.3	-4.9 ±0.3	-7.3 ±0.3	-5.1 ±0.3	-6.1 ±0.3	-4.6 ±0.3	-4.9 ±0.3	-4.8 ±0.3	-5.6 ±0.3
Van der Waals volume ($Å^3$)	330 ± 2	347 ± 2	468 ± 2	347 ± 2	399 ± 2	356 ± 2	352 ± 2	347 ± 2	374 ± 2
Van der Waals surface area ($Å^2$)	523 ± 11	555 ± 11	778 ± 12	556 ± 11	651 ± 12	573 ± 10	564 ± 11	540 ± 11	574 ± 11
Solvent accessible surface area ($Å^2$)	575 ± 5	596 ± 4	766 ± 11	621 ± 3	675 ± 1	612 ± 3	624 ± 4	590 ± 6	615 ± 6
Topological polar surface area ($Å^2$)	80 ± 12	80 ± 12	80 ± 12	80 ± 12	80 ± 12	89 ± 12	126 ± 12	104 ± 12	106 ± 12
Minimum projection area ($Å^2$)	58 ±3	61 ±1	78.0 ± 0.3	61 ± 5	67 ± 5	61 ± 2	62 ± 6	62 ± 6	64 ± 7
Maximum projection area ($Å^2$)	98 ± 6	101 ± 4	129 ± 3	103 ± 6	114 ± 6	103 ± 2	105 ± 7	104 ± 5	113 ± 4
Minimum projection radius (Å)	5.3 ± 0.5	5.5 ± 0.7	6.2 ± 0.5	5.8 ± 0.1	5.7 ± 0.4	5.4 ± 0.5	5.0 ± 0.1	6 ± 1	6.3 ± 0.5
Maximum projection radius (Å)	7.6 ± 0.4	7.6 ± 0.3	8.6 ± 0.6	7.9 ± 0.1	8. 8 ± 0.3	7.7 ± 0.2	8.1 ± 0.2	8.1 ± 0.6	8.7 ± 0.1

Table SI 4.d. Average computed physical properties of the vanadium complex using both coordinate and covalent bonding methods.