Supporting Information

The effect of halogenation of salicylaldehyde on antiproliferative activities of {Δ/Λ-[Ru(bpy)$_2$(X,Y-sal)]BF$_4$} complexes

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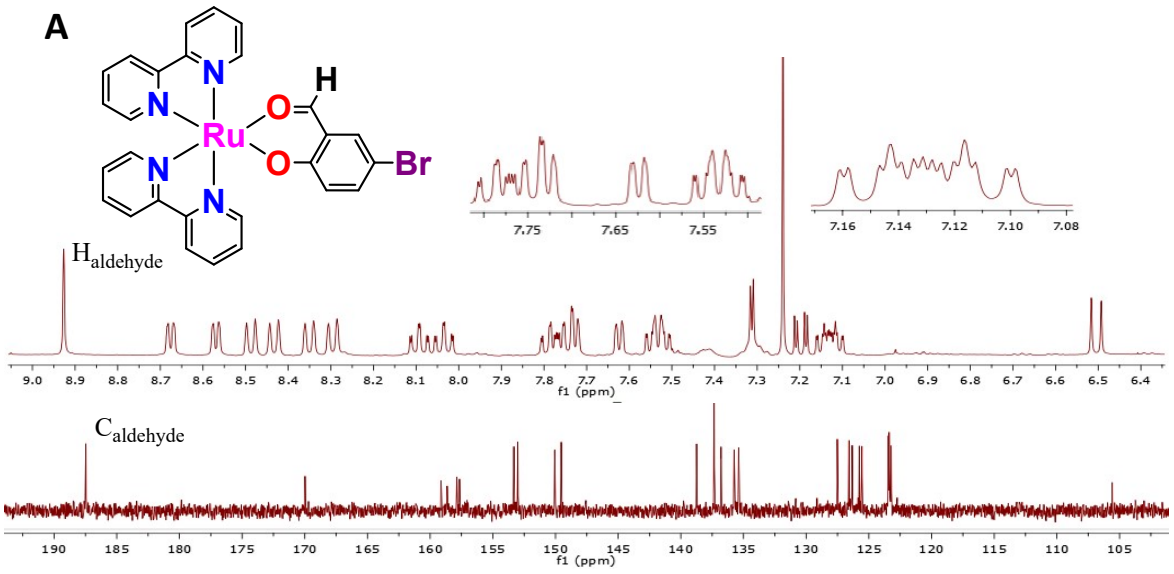

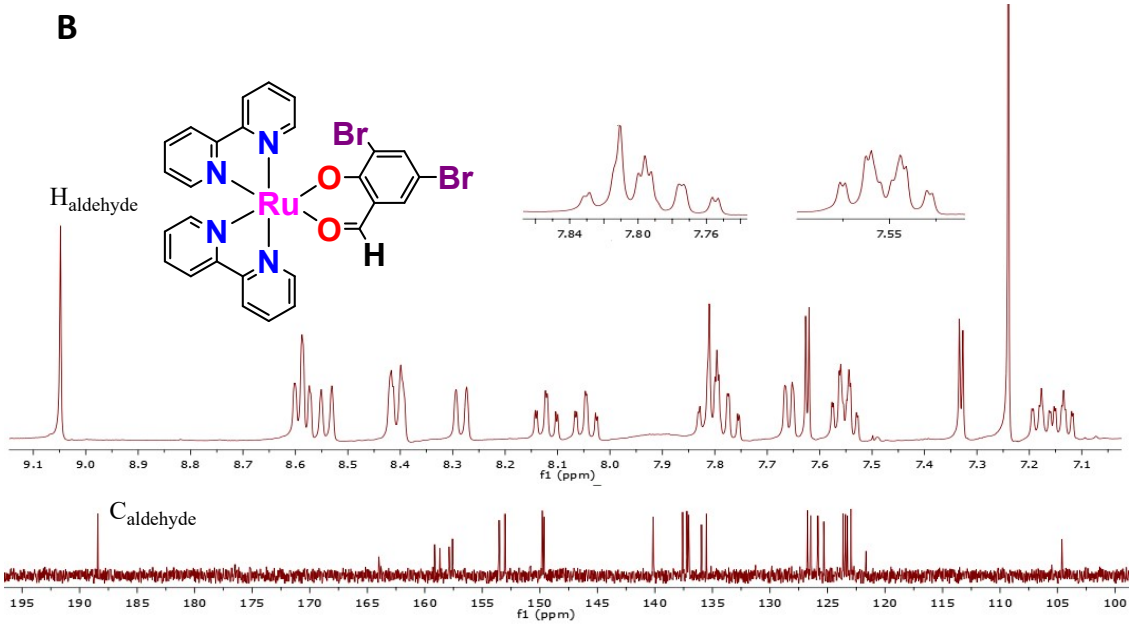
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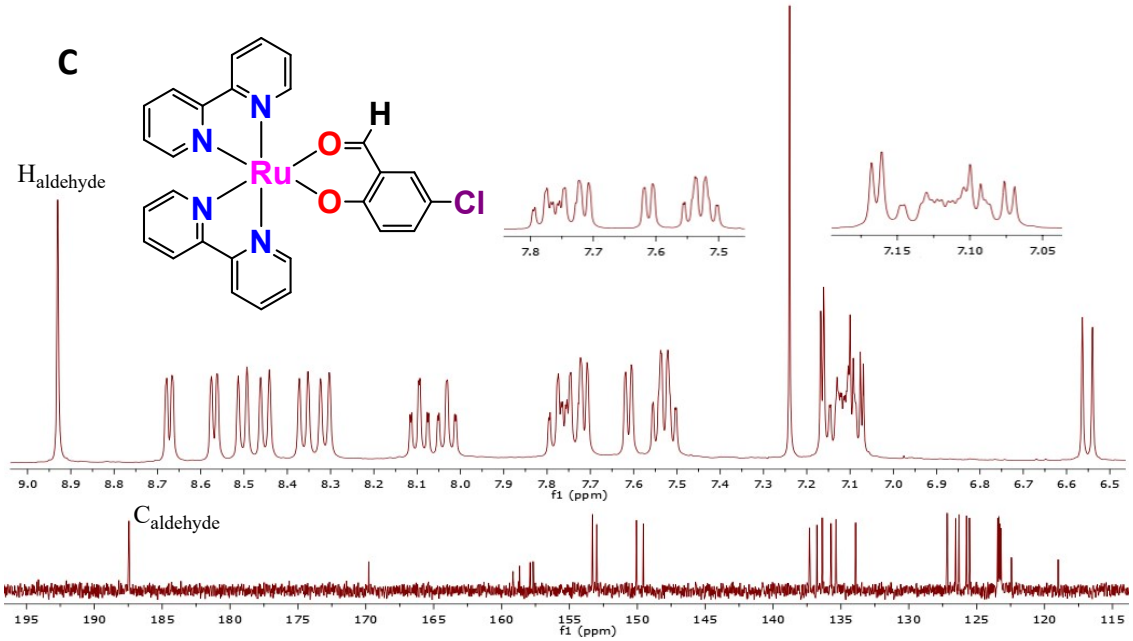
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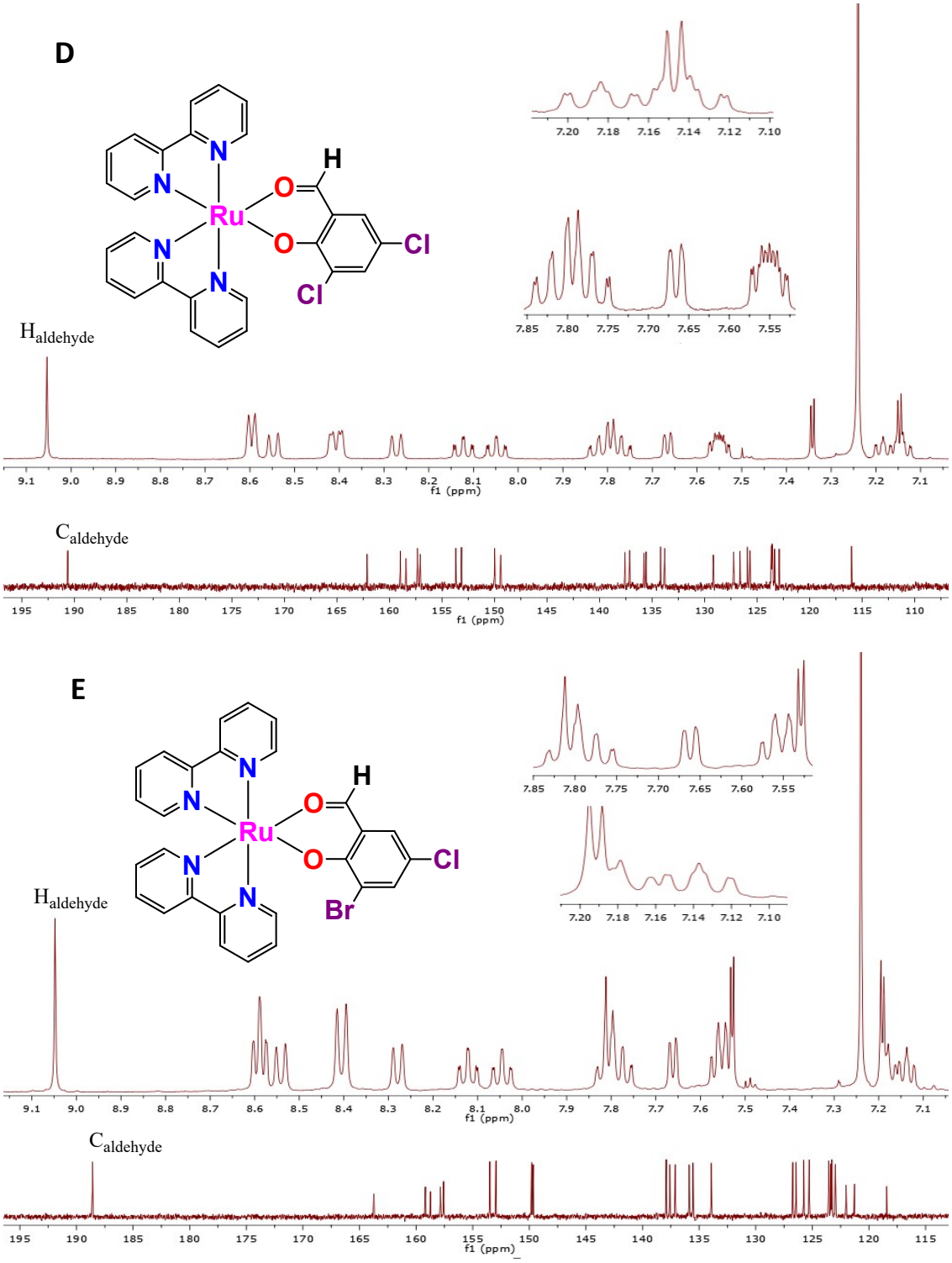
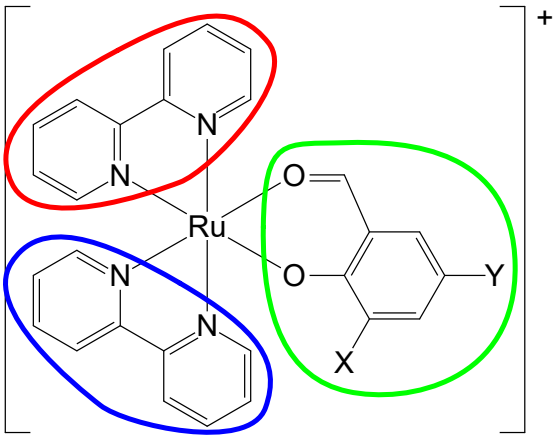


Figure S1. A) ^{1}H-/^{13}C-NMR spectra of complex **1** in $CDCl_3$, **B)** ^{1}H-/^{13}C-NMR spectra of complex **2** in $CDCl_3$, **C)** ^{1}H-/^{13}C-NMR spectra of complex **3** in $CDCl_3$, **D)** ^{1}H-/^{13}C-NMR spectra of complex **4** in $CDCl_3$ and DMSO respectively **, E)** ^{1}H-/^{13}C-NMR spectra of complex **5** in $CDCl_3$

Table S1. Calculated composition of the molecular orbitals with the participation of the metal center and the ligands.



Bipy_1 red, Bipy_2 blue, Sal green

1	H-5	H-4	H-3	H-2	H-1	H	L	L+1	L+2	L+3	L+4	L+5
Ru	0,86	0,39	35,62	78,88	74,63	50,73	4,51	6,37	4,37	3,12	4,73	1,16
Bipy_1	51,73	47,04	3,48	8,51	6,67	5,33	60,30	28,74	8,19	49,14	47,01	57,67
Bipy_2	46,86	51,87	5,42	5,79	8,08	4,64	33,25	58,53	6,42	46,89	47,55	40,79
Sal	0,55	0,69	55,48	6,82	10,62	39,29	1,94	6,36	81,02	0,85	0,71	0,39
2	H-5	H-4	H-3	H-2	H-1	H	L	L+1	L+2	L+3	L+4	L+5
Ru	0,73	0,28	35,46	78,36	74,12	48,27	4,42	5,84	5,12	3,07	4,63	1,55
Bipy_1	54,72	32,66	3,38	8,64	6,92	5,08	74,93	6,42	15,17	51,00	45,59	71,15
Bipy_2	39,39	56,84	5,46	5,51	7,78	4,67	11,36	78,03	7,94	44,92	49,08	26,72
Sal	5,16	10,22	55,70	7,49	11,18	41,98	9,28	9,71	71,77	1,01	0,70	0,58
3	H-5	H-4	H-3	H-2	H-1	H	L	L+1	L+2	L+3	L+4	L+5
Ru	0,87	0,43	36,66	78,87	74,71	50,94	4,52	6,39	4,35	3,12	4,74	1,16
Bipy_1	51,45	47,33	3,66	8,49	6,66	5,37	60,13	29,10	8,03	49,19	47,00	58,07
Bipy_2	47,16	51,59	5,70	5,79	8,09	4,67	33,49	58,34	6,38	46,84	47,53	40,39
Sal	0,53	0,65	53,98	6,85	10,54	39,02	1,86	6,17	81,24	0,85	0,73	0,38
4	H-5	H-4	H-3	H-2	H-1	H	L	L+1	L+2	L+3	L+4	L+5
Ru	0,83	0,39	36,49	78,49	74,34	48,52	4,55	5,96	4,96	0,87	4,59	1,47
Bipy_1	61,24	36,60	3,68	8,62	6,87	5,30	75,03	8,08	13,58	51,45	46,51	66,75
Bipy_2	37,14	61,14	5,72	5,54	7,90	4,65	12,82	77,13	7,43	47,16	48,17	31,24
Sal	0,79	1,86	54,10	7,35	10,90	41,53	7,60	8,84	74,02	0,53	0,73	0,53
5	H-5	H-4	H-3	H-2	H-1	H	L	L+1	L+2	L+3	L+4	L+5
Ru	2,78	0,91	1,61	78,65	74,18	48,22	4,49	5,93	5,02	3,06	4,64	1,55
Bipy_1	6,75	59,14	32,03	8,53	6,96	5,10	75,27	7,04	14,25	51,03	45,55	70,92
Bipy_2	2,33	37,48	57,58	5,43	7,75	4,73	11,75	78,02	7,61	44,90	49,09	26,97
Sal	88,14	2,47	8,78	7,39	11,11	41,95	8,49	9,01	73,11	1,01	0,72	0,56

Table S2. Lowest Singlet and Triplet Excited States Calculated at the TDDFT B3LYP/(def2-SVP+LANL2DZ) Level for Complexes **2-5** in Water Solution[a]

Complex	Estate	Energy (eV)	λ (nm)	f.osc.	Monoexcitacions	Nature	Description
2	S_1	2.247	551.7	0.0008	HOMO-1 → LUMO+2 (94)	$d_\pi(Ru) \rightarrow \pi^*_{sal}$	^{1}MLCT
	S_2	2.264	547.5	0.0019	HOMO-1 → LUMO (78)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$	^{1}MLCT
	S_3	2.282	543.3	0.0017	HOMO → LUMO (22) HOMO → LUMO+1 (47)	$d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{1}MLCT/^{1}LLCT ^{1}MLCT/^{1}LLCT
	S_8	**2.816**	**445.5**	**0.1209**	HOMO-2 → LUMO (70) HOMO-2 → LUMO+1 (17)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) \rightarrow \pi^*_{bpy}$	^{1}MLCT ^{1}MLCT
	S_{21}	**3.618**	**342.7**	**0.1067**	HOMO-2 → LUMO+3 (55) HOMO-1 → LUMO+5 (28)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) \rightarrow \pi^*_{bpy}$	^{1}MLCT ^{1}MLCT
	T_1	1.750	708.7		HOMO-1 → LUMO+2 (89)	$d_\pi(Ru) \rightarrow \pi^*_{sal}$	^{3}MLCT
	T_2	1.853	669.2		HOMO-1 → LUMO (34) HOMO → LUMO (41)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{3}MLCT ^{3}MLCT/^{3}LLCT
	T_3	1.896	653.9		HOMO-1 → LUMO (34) HOMO → LUMO (23) HOMO → LUMO+1 (31)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{3}MLCT ^{3}MLCT/^{3}LLCT ^{3}MLCT/^{3}LLCT
	T_4	1.902	652.0		HOMO → LUMO (17) HOMO → LUMO+2 (69)	$d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{sal}$	^{3}MLCT/^{3}LLCT ^{3}MLCT/^{3}LC
	T_5	1.991	622.7		HOMO-1 → LUMO (25) HOMO-1 → LUMO+1 (47)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) \rightarrow \pi^*_{bpy}$	^{3}MLCT ^{3}MLCT
3	S_1	2.082	595.4	0.0069	HOMO → LUMO (76)	$d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{1}MLCT/^{1}LLCT
	S_2	2.113	586.7	0.0024	HOMO → LUMO+1 (66)	$d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{1}MLCT/^{1}LLCT
	S_3	2.205	562.4	0.0140	HOMO-1 → LUMO (72) HOMO-1 → LUMO+1 (19)	$d_\pi(Ru) + \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) + \rightarrow \pi^*_{bpy}$	^{1}MLCT ^{1}MLCT
	S_8	**2.792**	**444.1**	**0.0997**	HOMO-2 → LUMO (34) HOMO-2 → LUMO+1 (49)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) \rightarrow \pi^*_{bpy}$	^{1}MLCT ^{1}MLCT
	S_{20}	**3.578**	**346.6**	**0.0906**	HOMO-2 → LUMO+3 (45) HOMO-1 → LUMO+5 (45)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) \rightarrow \pi^*_{bpy}$	^{1}MLCT ^{1}MLCT
	T_1	1.715	723.0		HOMO → LUMO (20) HOMO → LUMO+1 (66)	$d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{3}MLCT/^{3}LLCT ^{3}MLCT/^{3}LLCT
	T_2	1.769	700.9		HOMO-1 → LUMO (91) HOMO → LUMO (20)	$d_\pi(Ru) + \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{3}MLCT ^{3}MLCT/^{3}LLCT
	T_3	1.774	699.0		HOMO-1 → LUMO+2 (93)	$d_\pi(Ru) + \rightarrow \pi^*_{sal}$	^{3}MLCT
	T_4	1.934	641.2		HOMO → LUMO+1 (76)	$d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{3}MLCT/^{3}LLCT
	T_5	1.945	637.4		HOMO-1 → LUMO+1 (57) HOMO → LUMO (26)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{3}MLCT ^{3}MLCT/^{3}LLCT
4	S_1	2.246	552.0	0.0084	HOMO-1 → LUMO+2 (93)	$d_\pi(Ru) \rightarrow \pi^*_{sal}$	^{1}MLCT
	S_2	2.249	551.2	0.0194	HOMO-1 → LUMO (81)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$	^{1}MLCT
	S_3	2.266	547.3	0.0038	HOMO → LUMO+1 (58)	$d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$	^{1}MLCT /^{1}LLCT
	S_8	**2.808**	**441.6**	**0.1138**	HOMO-2 → LUMO (66) HOMO-2 → LUMO+1 (20)	$d_\pi(Ru) \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) \rightarrow \pi^*_{bpy}$	^{1}MLCT ^{1}MLCT
	S_{21}	**3.671**	**337.8**	**0.1436**	HOMO-3 → LUMO+2 (31) HOMO-2 → LUMO+3 (33)	$d_\pi(Ru) + \pi_{sal} \rightarrow \pi^*_{bpy}$ $d_\pi(Ru) \rightarrow \pi^*_{bpy}$	^{1}MLCT/^{1}LLCT ^{1}MLCT

					HOMO-1 → LUMO+5 (26)	d_π(Ru) → π^*_{bpy}	^{1}MLCT
	T_1	1.731	716.3		HOMO-1 → LUMO+2 (91)	d_π(Ru) → π^*_{sal}	^{3}MLCT
	T_2	1.836	675.2		HOMO-1 → LUMO (40) HOMO → LUMO (36)	d_π(Ru) → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{bpy}	^{3}MLCT ^{3}MLCT/^{3}LLCT
	T_3	1.888	656.6		HOMO → LUMO (15) HOMO → LUMO+2 (75)	d_π(Ru) + π_{sal} → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{sal}	^{3}MLCT/^{3}LLCT ^{3}MLCT/^{3}LC
	T_4	1.925	644.2		HOMO-1 → LUMO+1 (39) HOMO → LUMO (27) HOMO → LUMO+1 (20)	d_π(Ru) → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{bpy}	^{3}MLCT ^{3}MLCT/^{3}LLCT ^{3}MLCT/^{3}LLCT
	T_5	1.958	633.2		HOMO-1 → LUMO (22) HOMO → LUMO+1 (58)	d_π(Ru) → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{bpy}	^{3}MLCT ^{3}MLCT/^{3}LLCT
5	S_1	2.245	552.3	0.0079	HOMO-1 → LUMO+2 (95)	d_π(Ru) → π^*_{sal}	^{1}MLCT
	S_2	2.259	548.9	0.0200	HOMO-1 → LUMO (79)	d_π(Ru) → π^*_{bpy}	^{1}MLCT
	S_3	2.265	547.4	0.0036	HOMO → LUMO (16) HOMO → LUMO+1 (58)	d_π(Ru) + π_{sal} → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{bpy}	^{1}MLCT/^{1}LLCT ^{1}MLCT/^{1}LLCT
	S_8	**2.814**	**440.6**	**0.1168**	HOMO-2 → LUMO (69) HOMO-2 → LUMO+1 (18)	d_π(Ru) → π^*_{bpy} d_π(Ru) → π^*_{bpy}	^{1}MLCT ^{1}MLCT
	S_{21}	**3.624**	**342.1**	**0.1179**	HOMO-2 → LUMO+3 (53) HOMO-1 → LUMO+5 (29)	d_π(Ru) → π^*_{bpy} d_π(Ru) → π^*_{bpy}	^{1}MLCT ^{1}MLCT
	T_1	1.742	711.9		HOMO-1 → LUMO+2 (90)	d_π(Ru) → π^*_{sal}	^{3}MLCT
	T_2	1.858	667.2		HOMO-1 → LUMO (35) HOMO → LUMO (40)	d_π(Ru) → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{bpy}	^{3}MLCT ^{3}MLCT/^{3}LLCT
	T_3	1.894	654.5		HOMO → LUMO (16) HOMO → LUMO+2 (71)	d_π(Ru) + π_{sal} → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{sal}	^{3}MLCT/^{3}LLCT ^{3}MLCT/^{3}LC
	T_4	1.914	647.7		HOMO-1 → LUMO+1 (38) HOMO → LUMO (25) HOMO → LUMO+1 (24)	d_π(Ru) → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{bpy}	^{3}MLCT ^{3}MLCT/^{3}LLCT ^{3}MLCT/^{3}LLCT
	T_5	1.980	626.3		HOMO-1 → LUMO (24) HOMO → LUMO+1 (53)	d_π(Ru) → π^*_{bpy} d_π(Ru) + π_{sal} → π^*_{bpy}	^{3}MLCT ^{3}MLCT/^{3}LLCT

[a]Vertical excitation energies (E), dominant monoexcitations with contributions (within parentheses) of >15%, the nature of the electronic transition, and the description of the excited state are summarized.

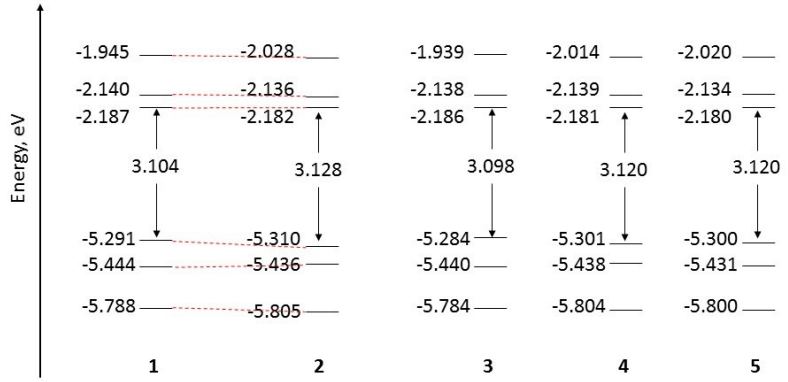


Figure S2. Calculated energy levels of the FMOs for complexes **1-5**.

Compound 2.

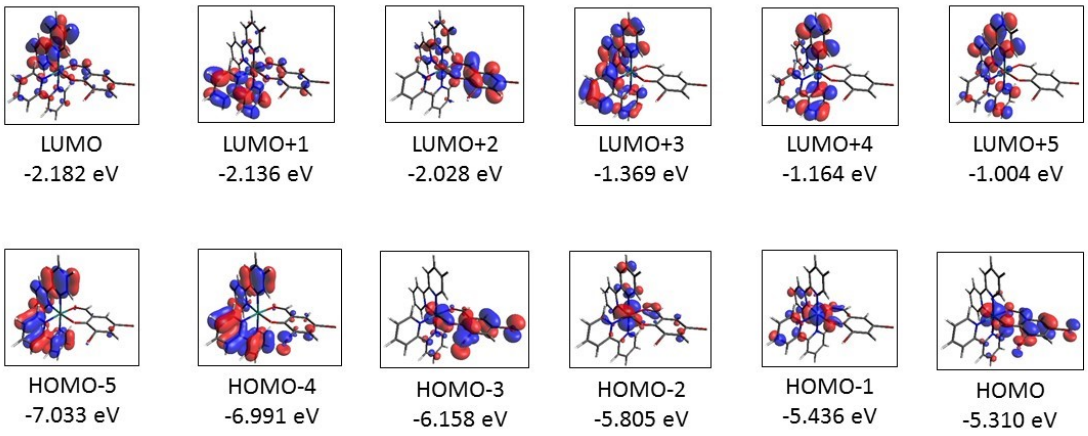


Figure S3. FMOs for complex **2**.

Compound 3.

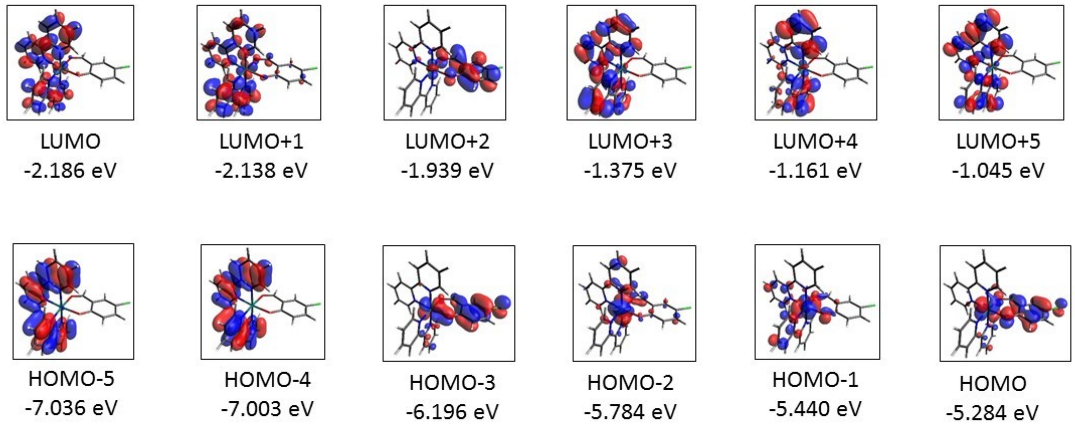


Figure S4. FMOs for complex **3**.

Compound 4.

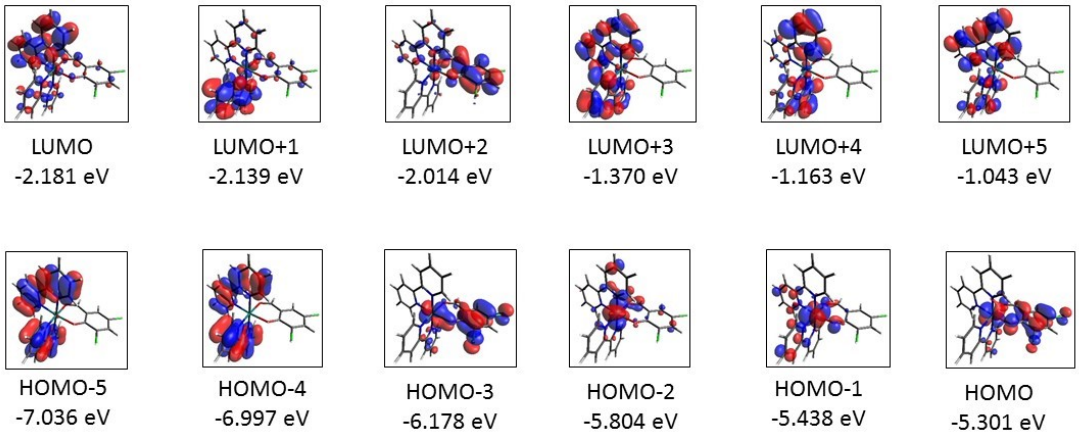


Figure S5. FMOs for complex **4**.

Compound 5.

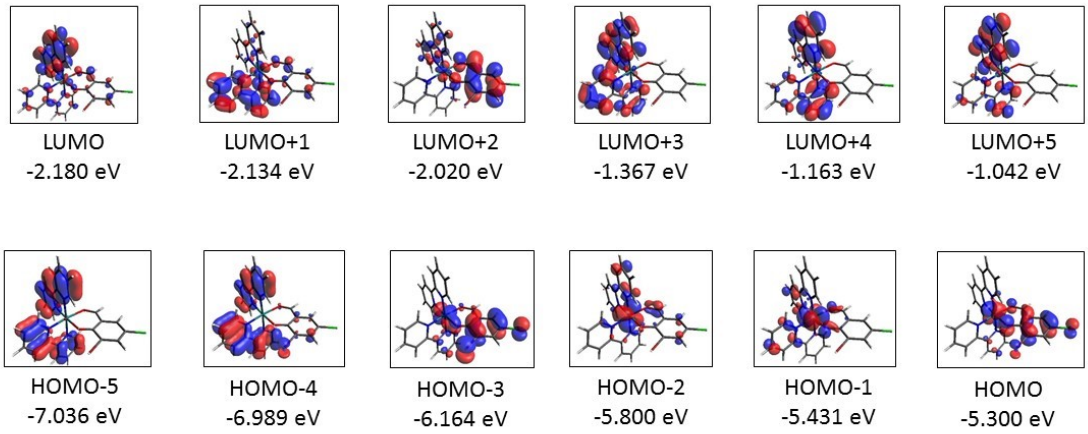


Figure S6. FMOs for complex **5**.

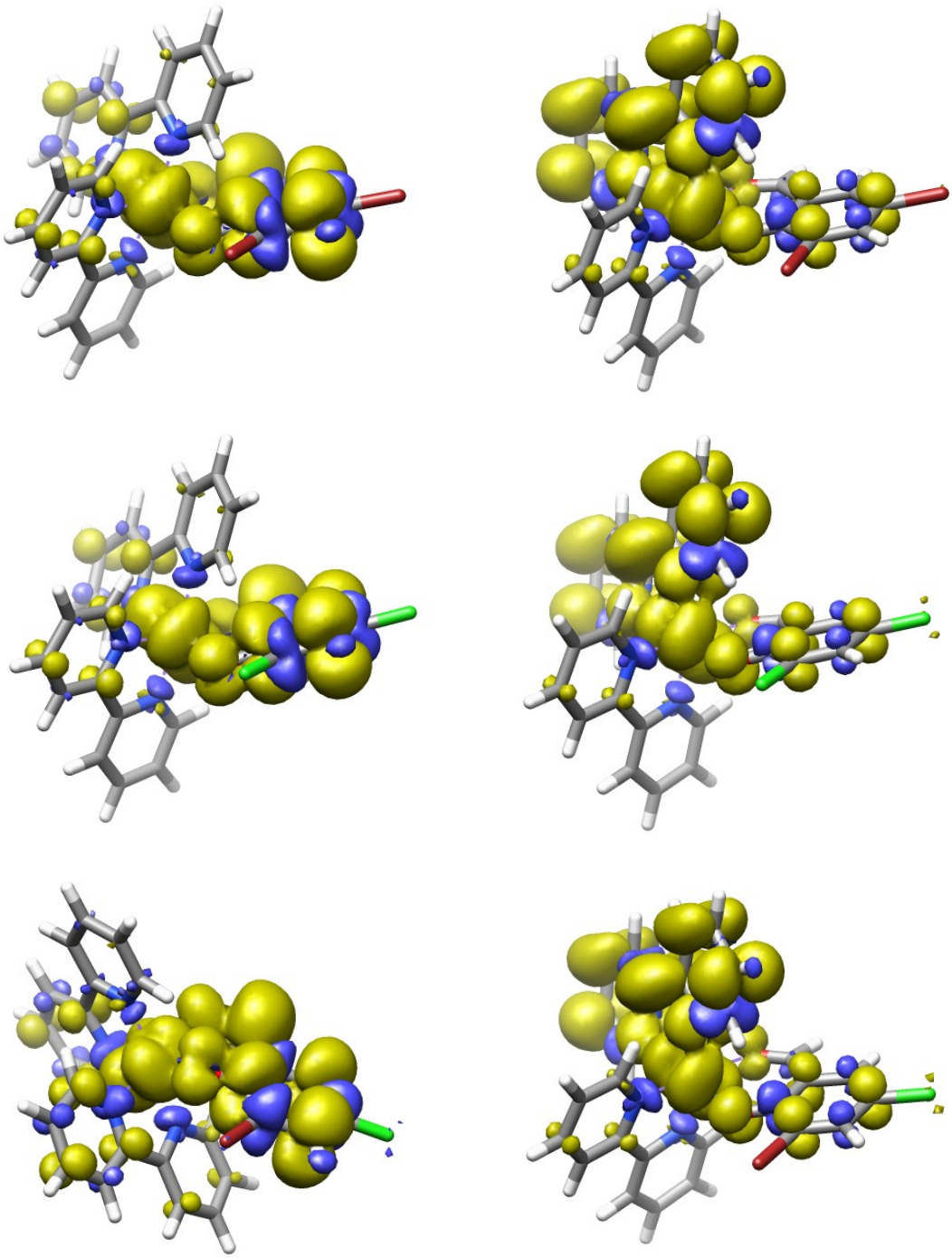
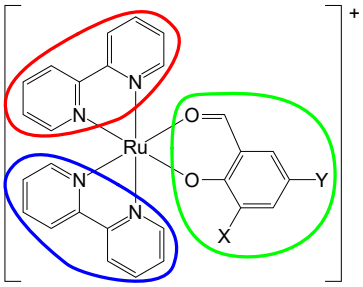


Figure S7. Spin-density contours calculated for fully relaxed T_1 (left) and T_2 (right) states of complex **2** (up), **4** (middle) and **5** (down).

Table S3. Calculated spin-density values for the optimized triplet states



	1	2	3	4	5
Triplets T_1					
Ru	0,77266	0,788774	0,770134	0,787451	0,837568
bpy1 (red)	0,014564	0,016658	0,014433	0,016112	0,010139
bpy2 (blue)	0,009992	0,005802	0,00972	0,007144	0,021477
Sal (Green)	1,202782	1,188764	1,205711	1,189293	1,130817
Triplets T_2					
Ru	0,83879	0,843156	0,835579	0,836799	0,839924
bpy1 (red)	1,014541	1,017636	1,013825	1,013483	1,016898
bpy2 (blue)	-0,004531	-0,003939	-0,004794	-0,003682	-0,004125
Sal (Green)	0,151199	0,143148	0,155391	0,153403	0,147306

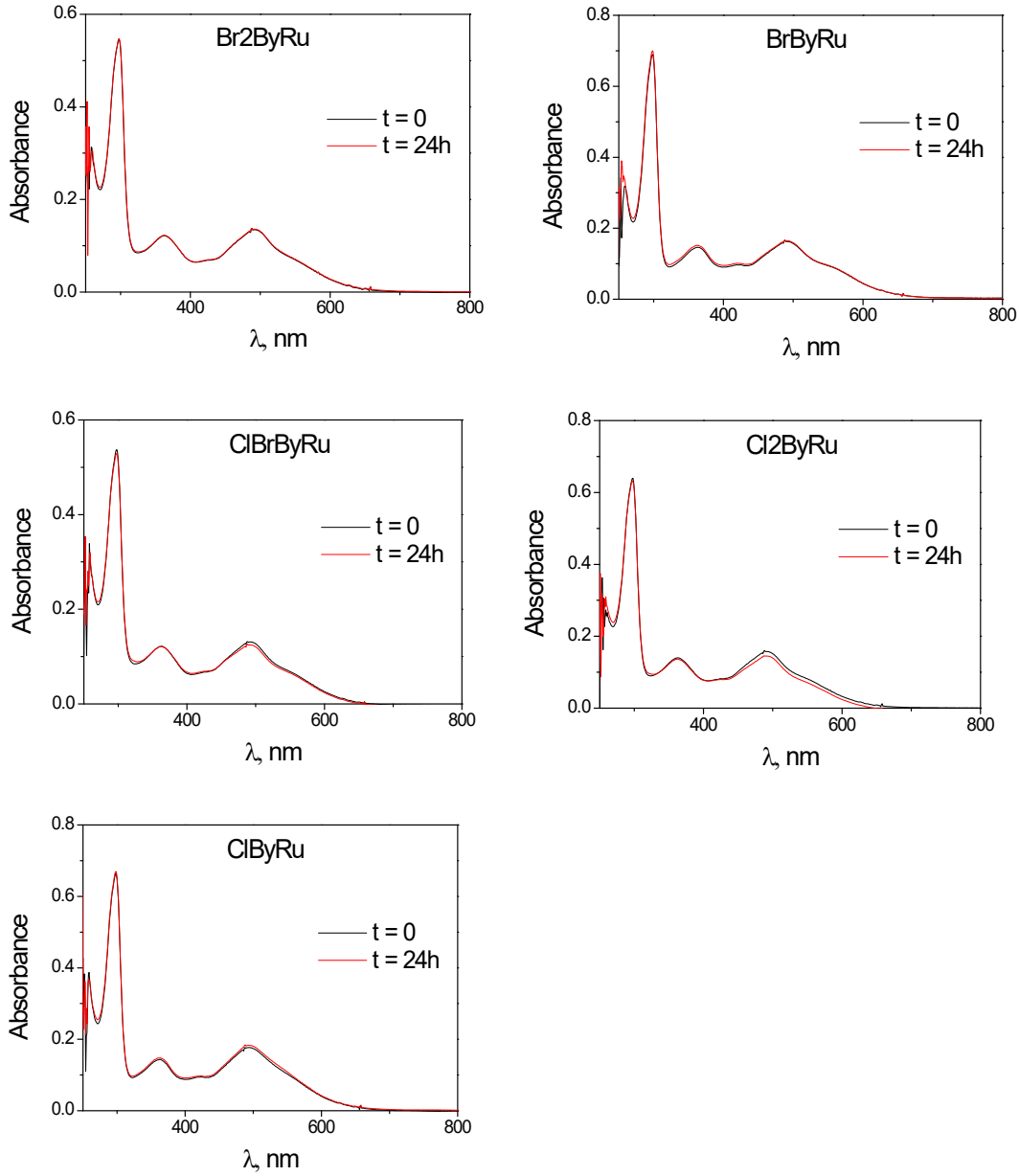
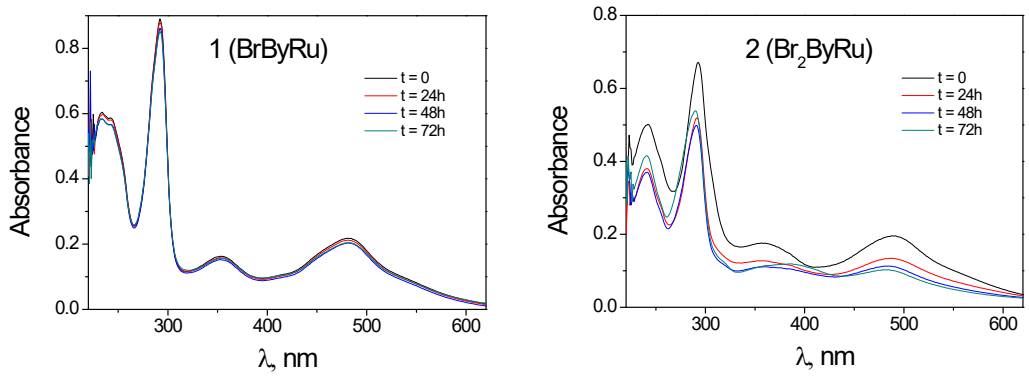


Figure S8 Absorbance spectra of 20 µM of the compounds under study recorded in DMSO just after being dissolved and after 24 h.



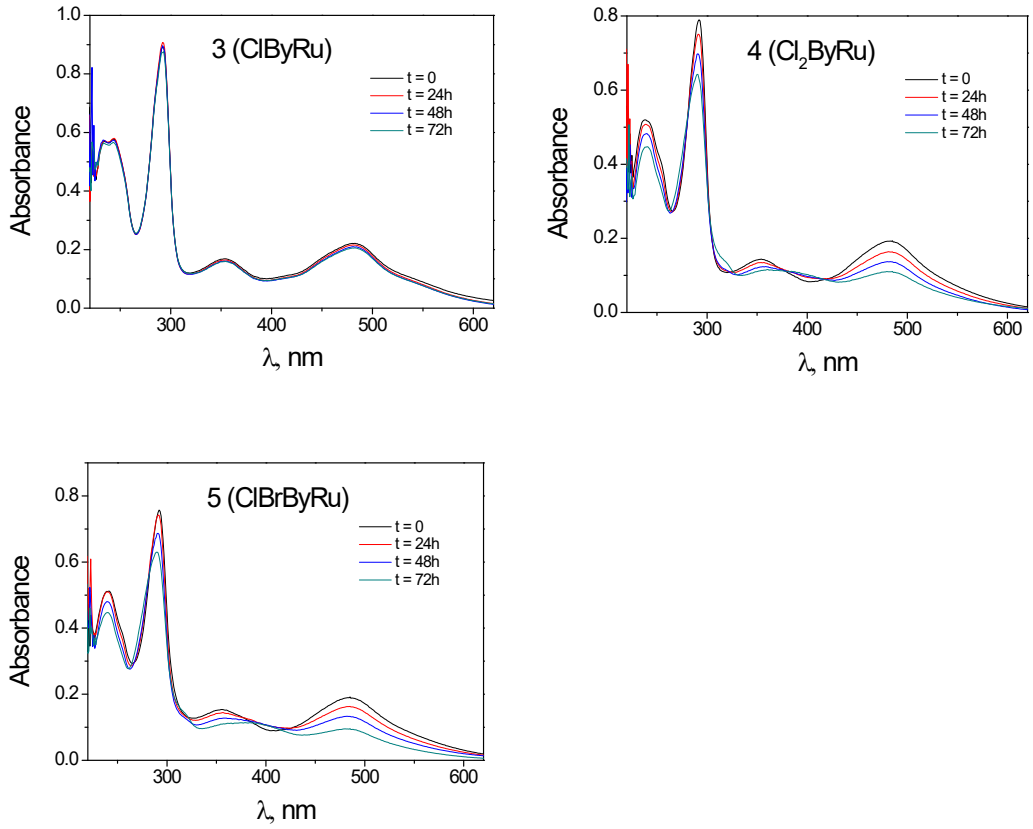
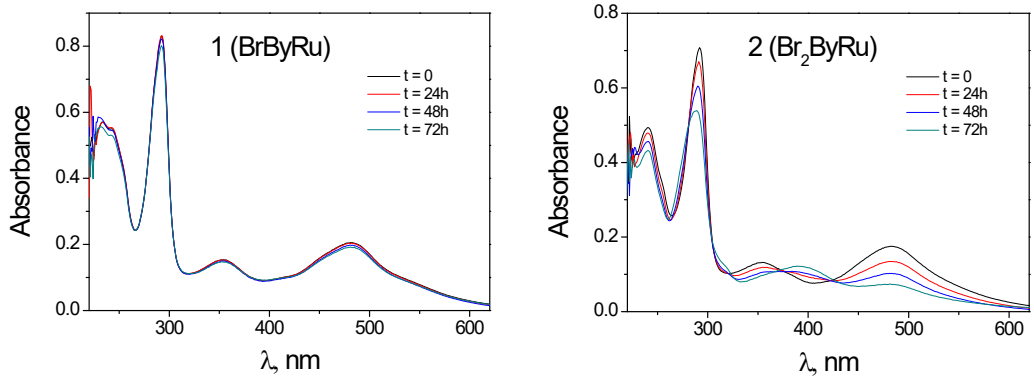


Figure S9. Absorbance spectra of the Ru(II) complexes (25 µM) as a function of time recorded in buffer (2.5 mM NaCaC), pH = 7, 0.1 %DMSO and T = 25°C.



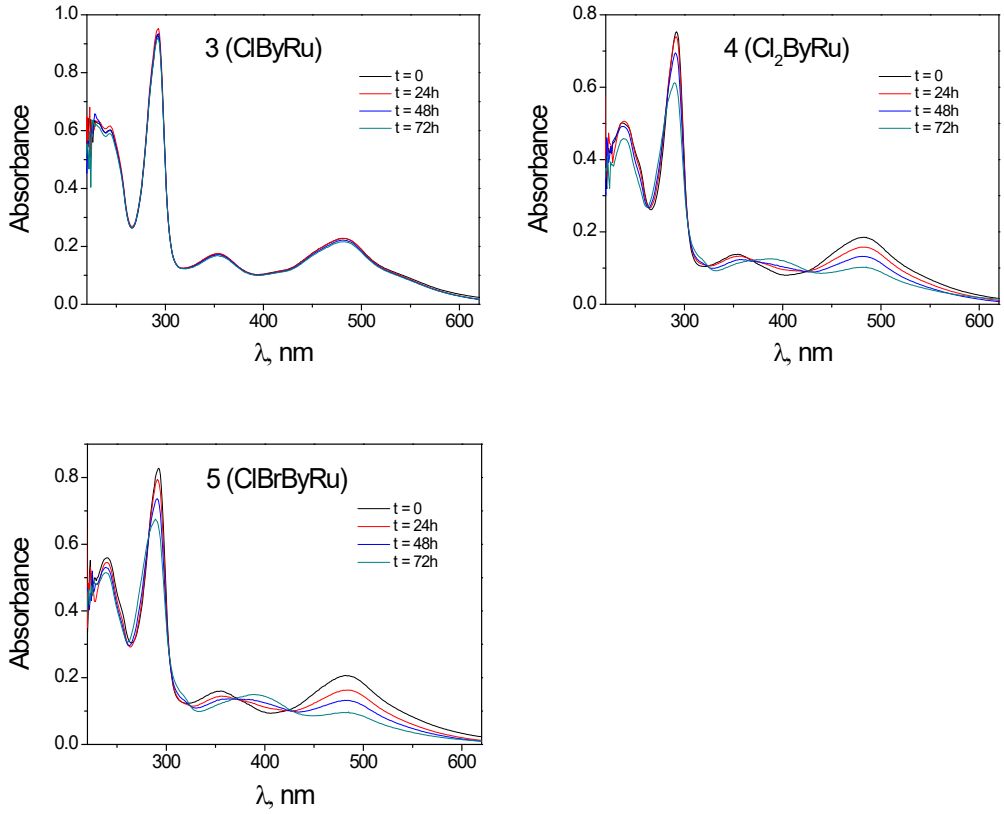
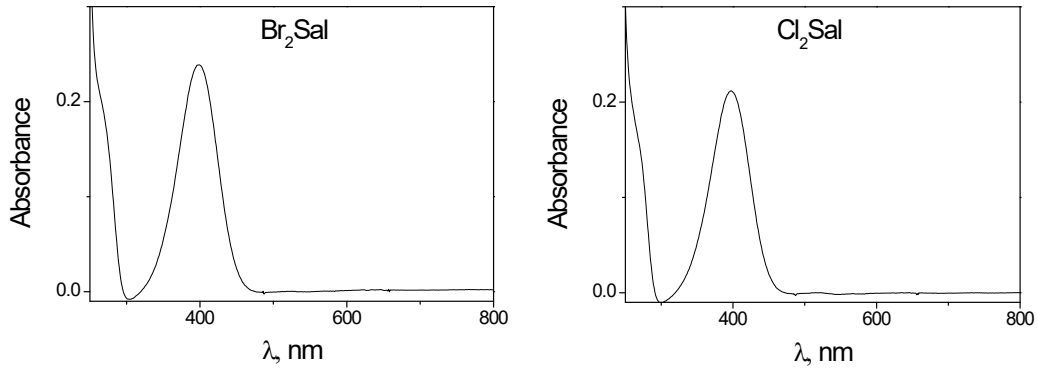


Figure S10. Absorbance spectra of the Ru(II) complexes (25 µM) as a function of time recorded in buffer (2.5 mM NaCaC, 0.1M NaCl), pH = 7, 0.1 %DMSO and T = 25°C.



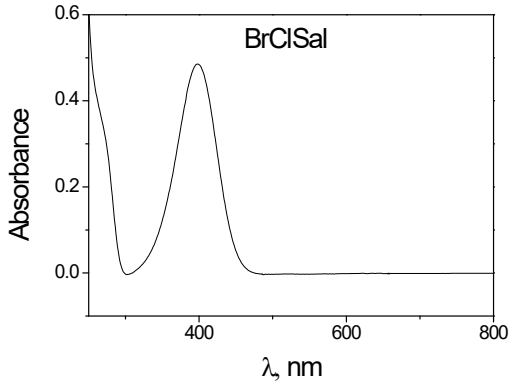
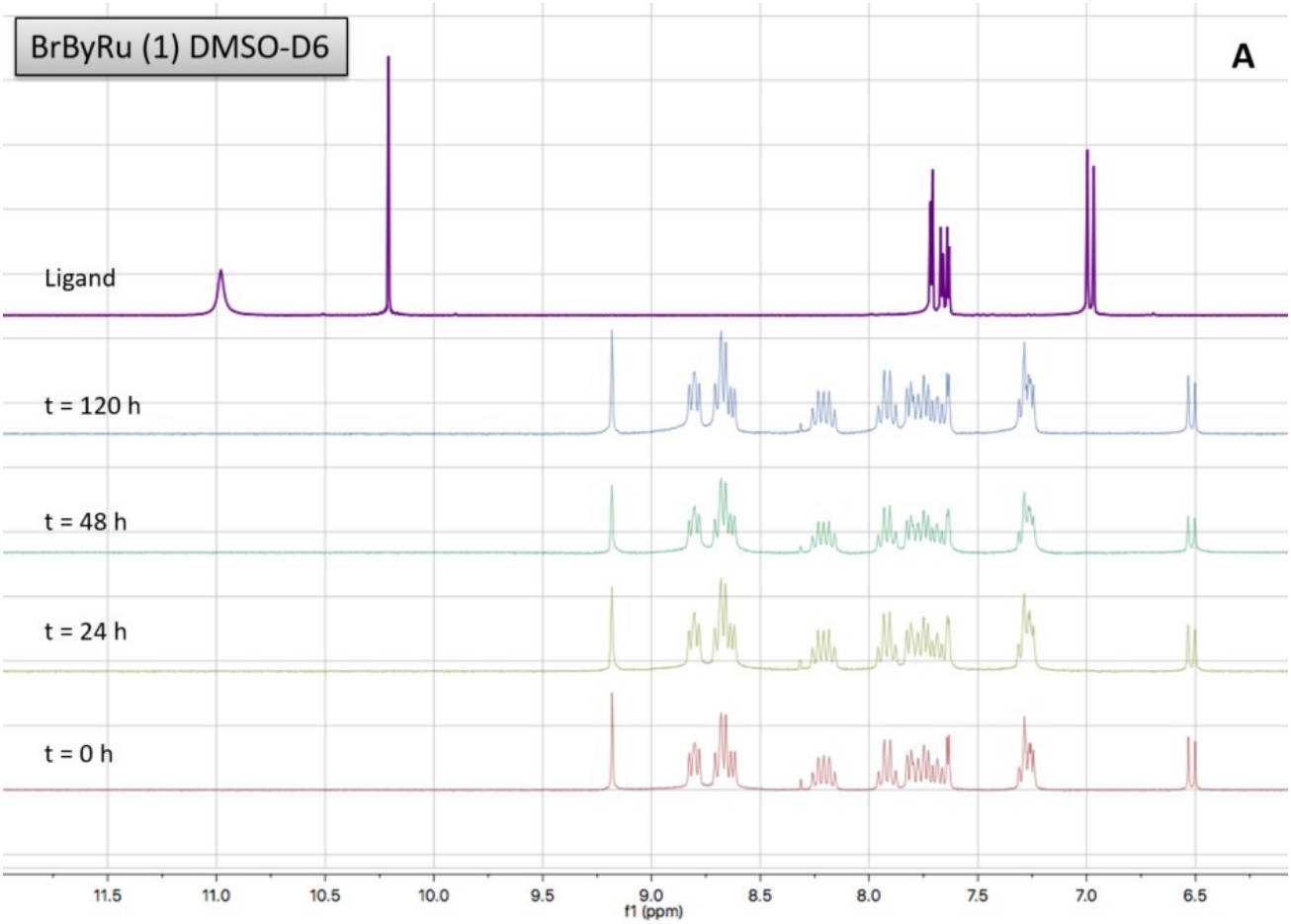
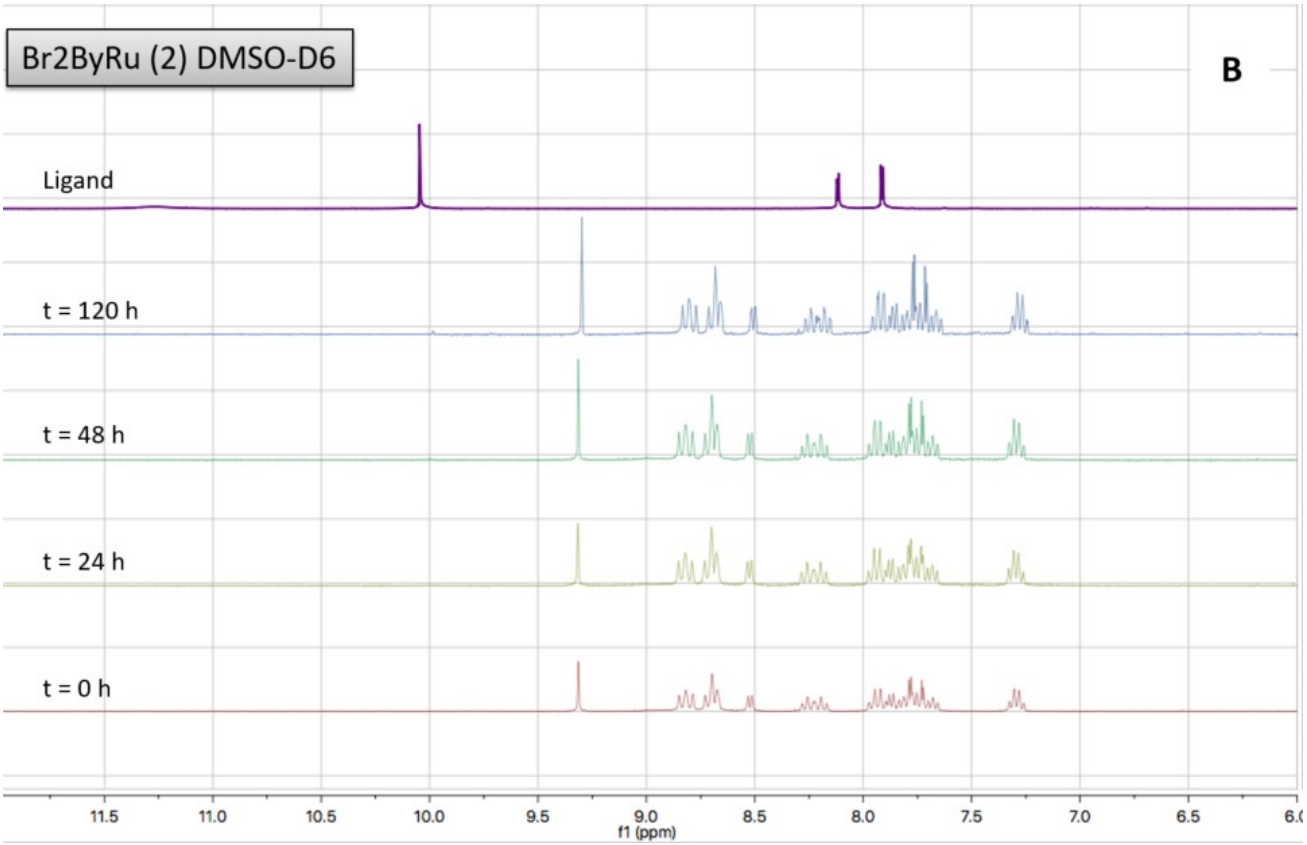
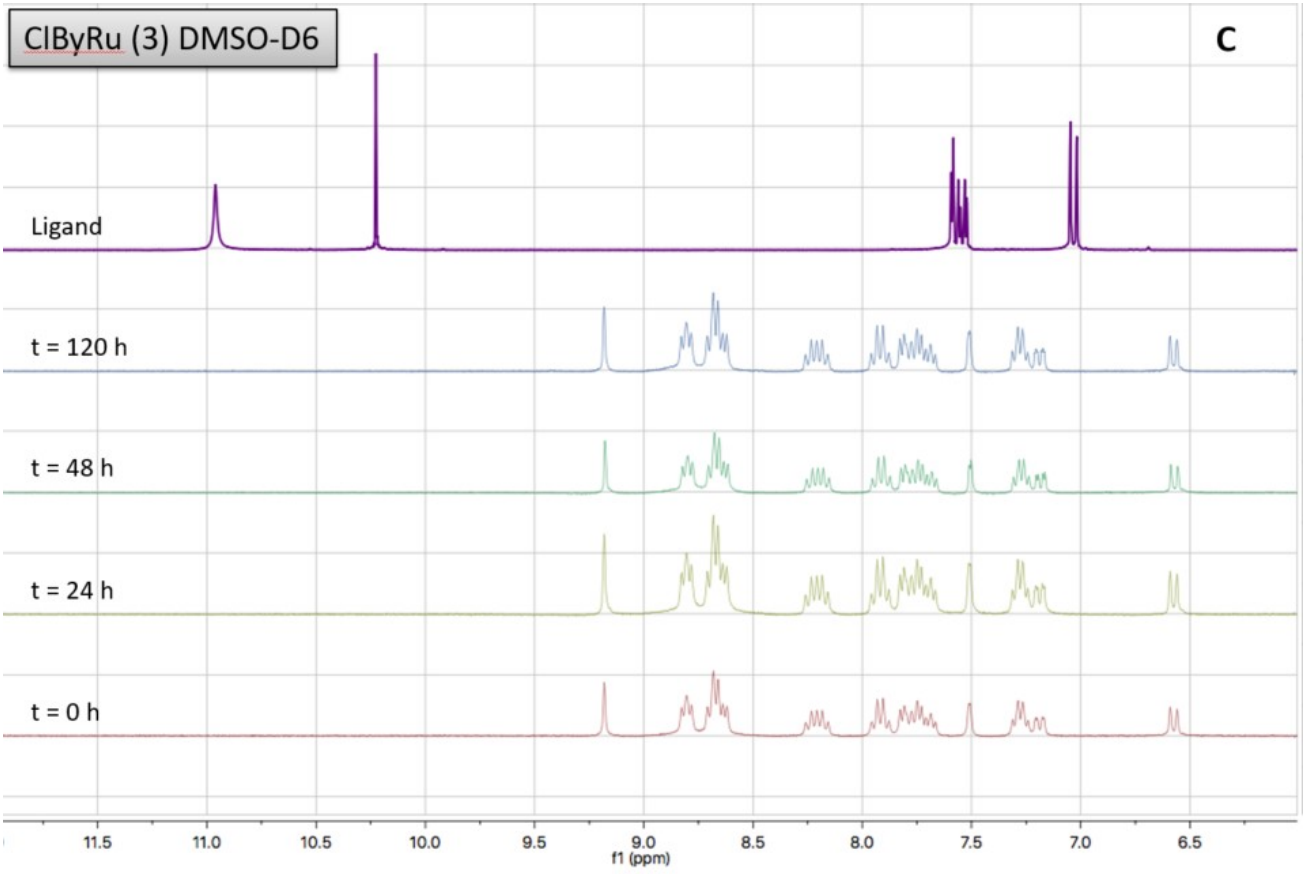


Figure S11. Absorbance spectra of 20 µM of the dihalogenated ligands in buffer (2.5 mM NaCaC), pH = 7, 0.1 %DMSO and T = 25°C.




Br2ByRu (2) DMSO-D6
B
Ligand
t = 120 h
t = 48 h
t = 24 h
t = 0 h
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
f1 (ppm)


ClByRu (3) DMSO-D6
C
Ligand
t = 120 h
t = 48 h
t = 24 h
t = 0 h
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
f1 (ppm)

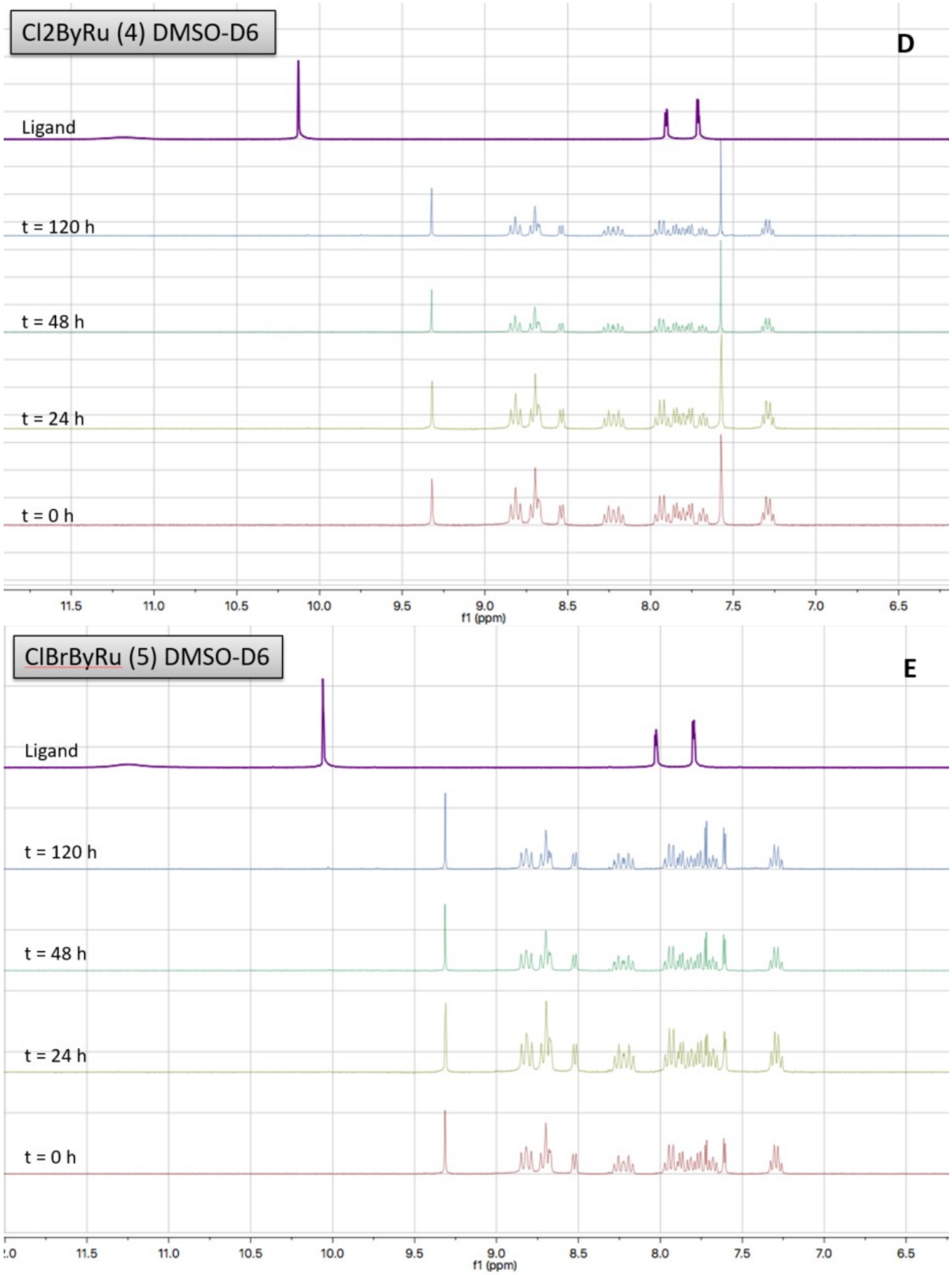
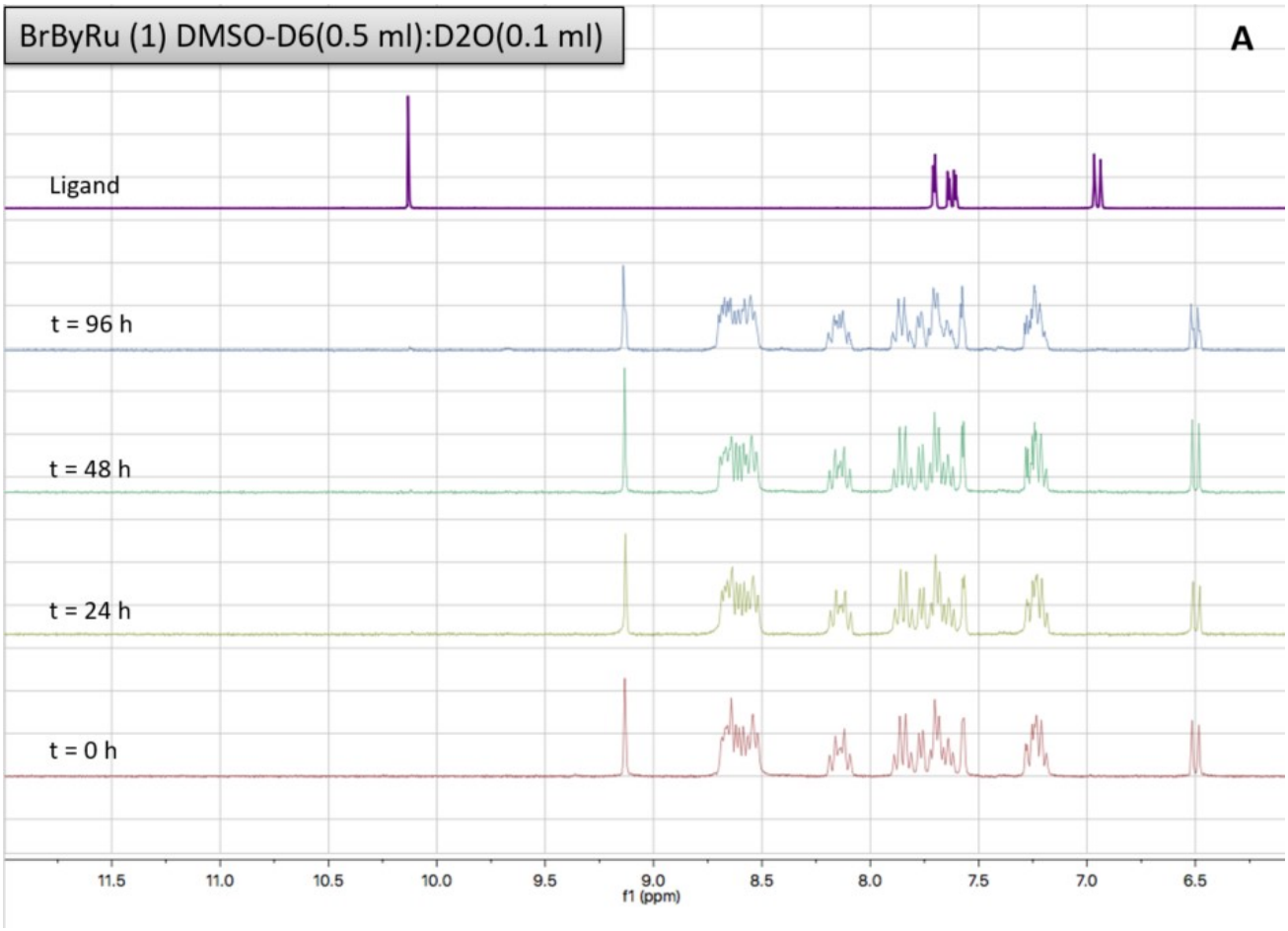
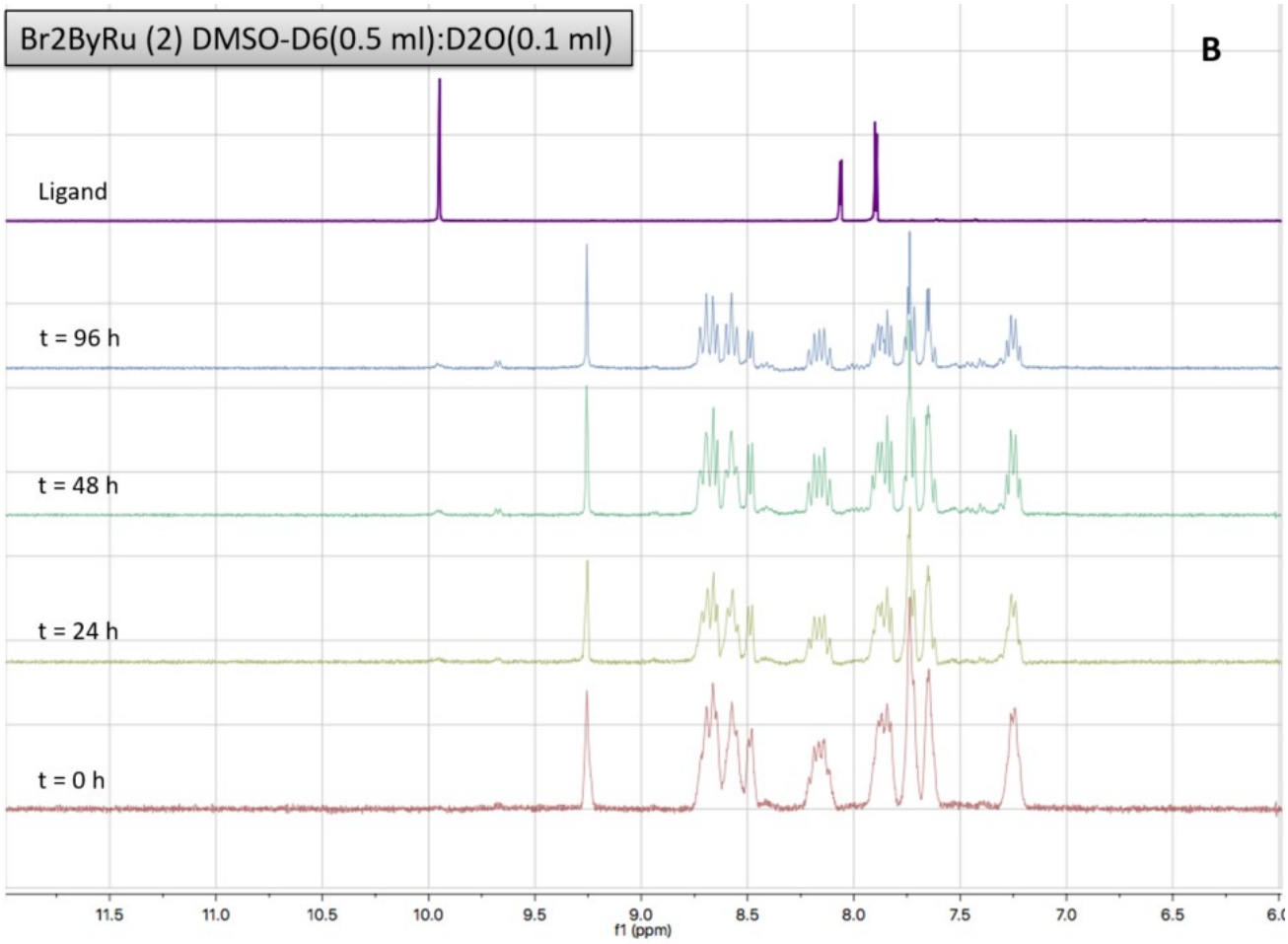
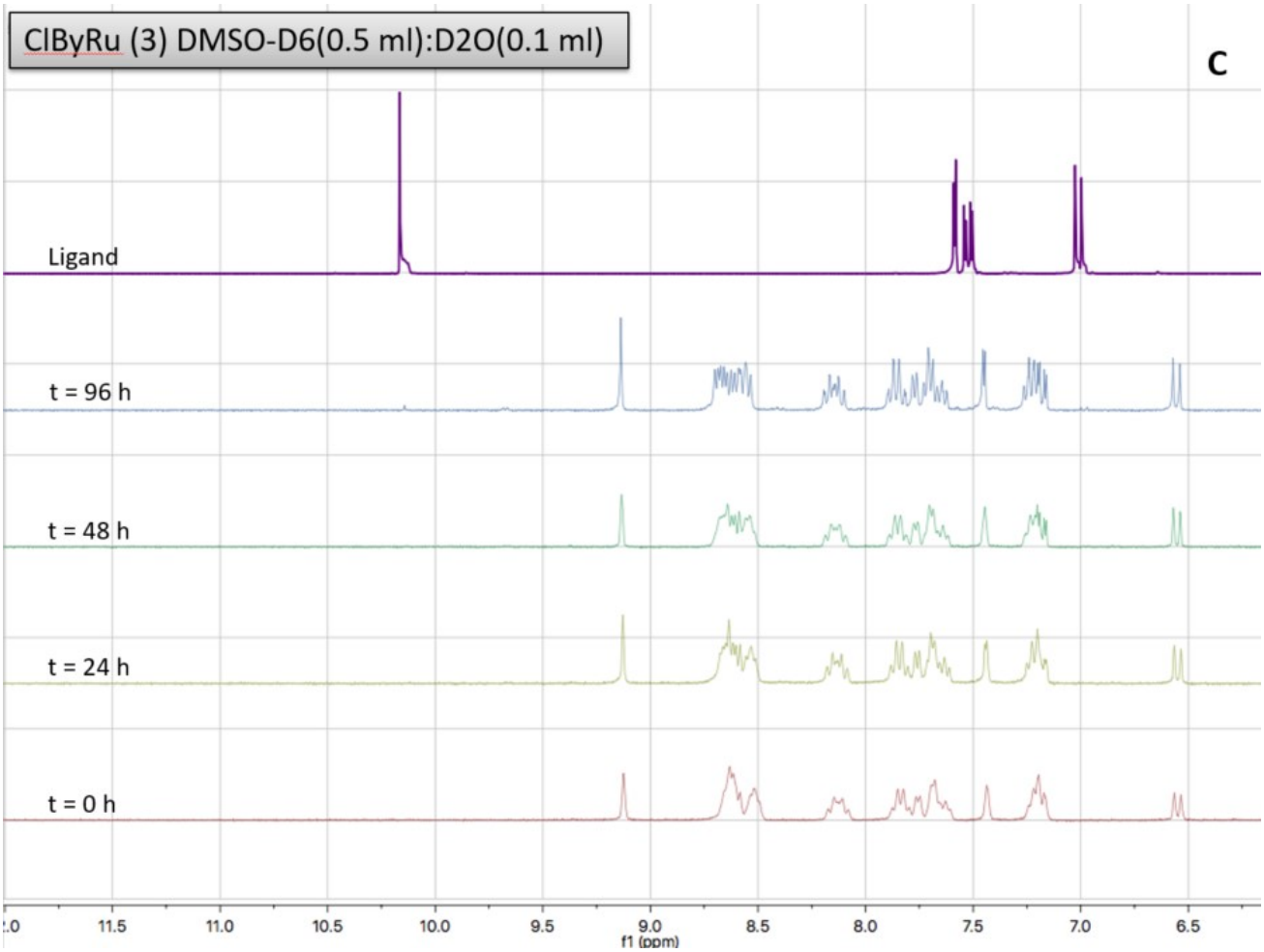
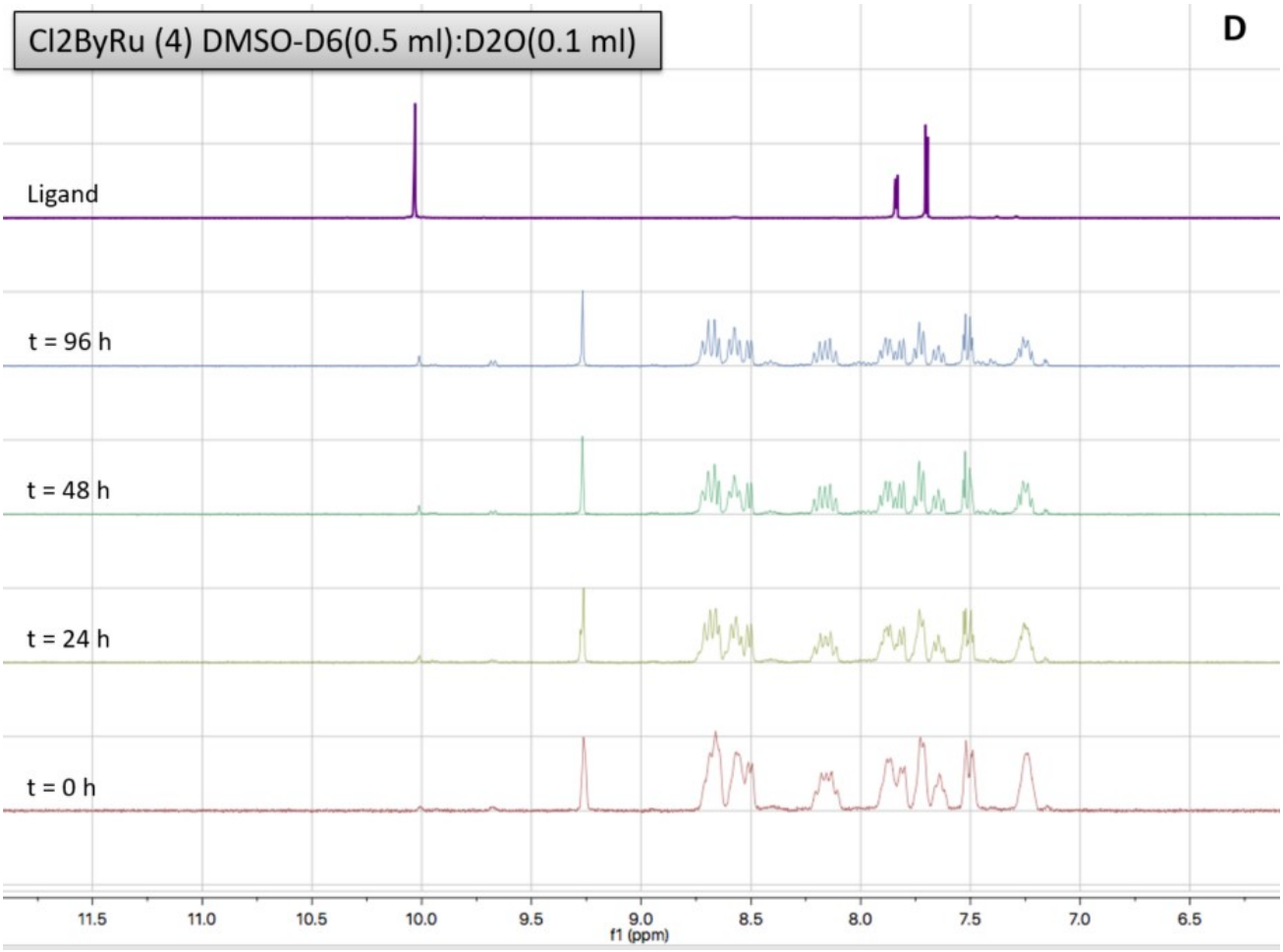


Figure S12. ^{1}H NMR spectra for the Ru(II) complexes in DMSO-d6 recorded at different incubation times.


BrByRu (1) DMSO-D6(0.5 ml):D2O(0.1 ml)
A
Ligand
t = 96 h
t = 48 h
t = 24 h
t = 0 h
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
f1 (ppm)


Br2ByRu (2) DMSO-D6(0.5 ml):D2O(0.1 ml)
B
Ligand
t = 96 h
t = 48 h
t = 24 h
t = 0 h
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
f1 (ppm)


ClByRu (3) DMSO-D6(0.5 ml):D2O(0.1 ml)
C
Ligand
t = 96 h
t = 48 h
t = 24 h
t = 0 h
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
f1 (ppm)


Cl2ByRu (4) DMSO-D6(0.5 ml):D2O(0.1 ml)
D
Ligand
t = 96 h
t = 48 h
t = 24 h
t = 0 h
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
f1 (ppm)

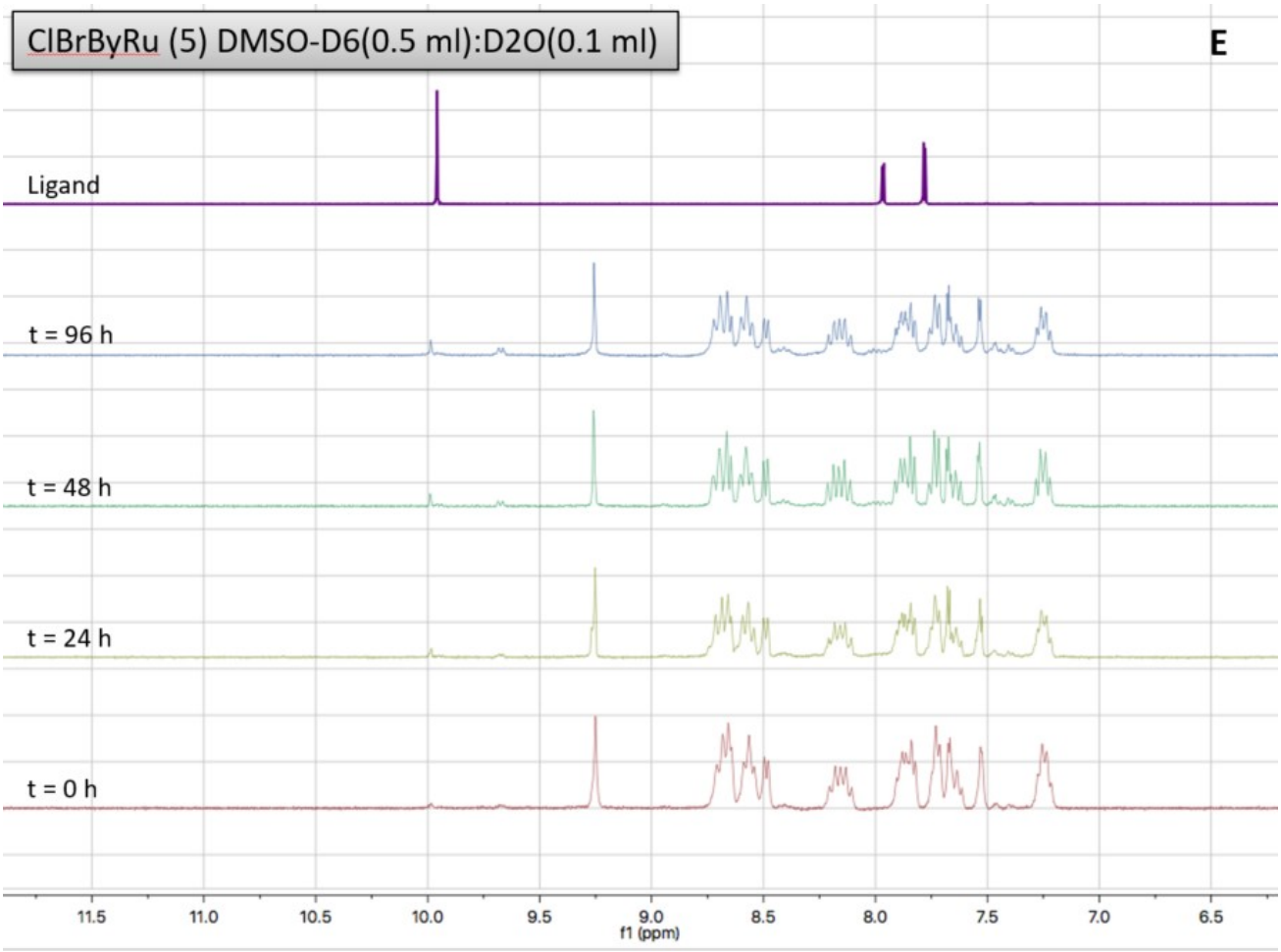


Figure S13. ^{1}H NMR spectra for the Ru(II) complexes in DMSO-d_6:D_2O recorded at different incubation times.

Table S4. MIC values of the studied compounds. Norfloxacin is included as positive control.

	MIC, µM			
	VR *E. faecium*	MRSA *S. aureus*	*A. baumanii*	*P. aeruginosa*
Norfloxacin	6.2	6.2	20	3.1
Cl-Sal	> 100	> 100	> 100	> 100
Br-Sal	> 100	> 100	> 100	> 100
Cl_2-Sal	100	100	> 100	> 100
BrCl-Sal	> 100	100	> 100	> 100
Br_2-Sal	100	50	> 100	> 100
ByRu	> 100	> 100	> 100	> 100
1	40	25	> 100	> 100
2	25	12.5	100	> 100
3	100	100	> 100	> 100
4	25	12.5	> 100	> 100
5	25	12.5	> 100	> 100

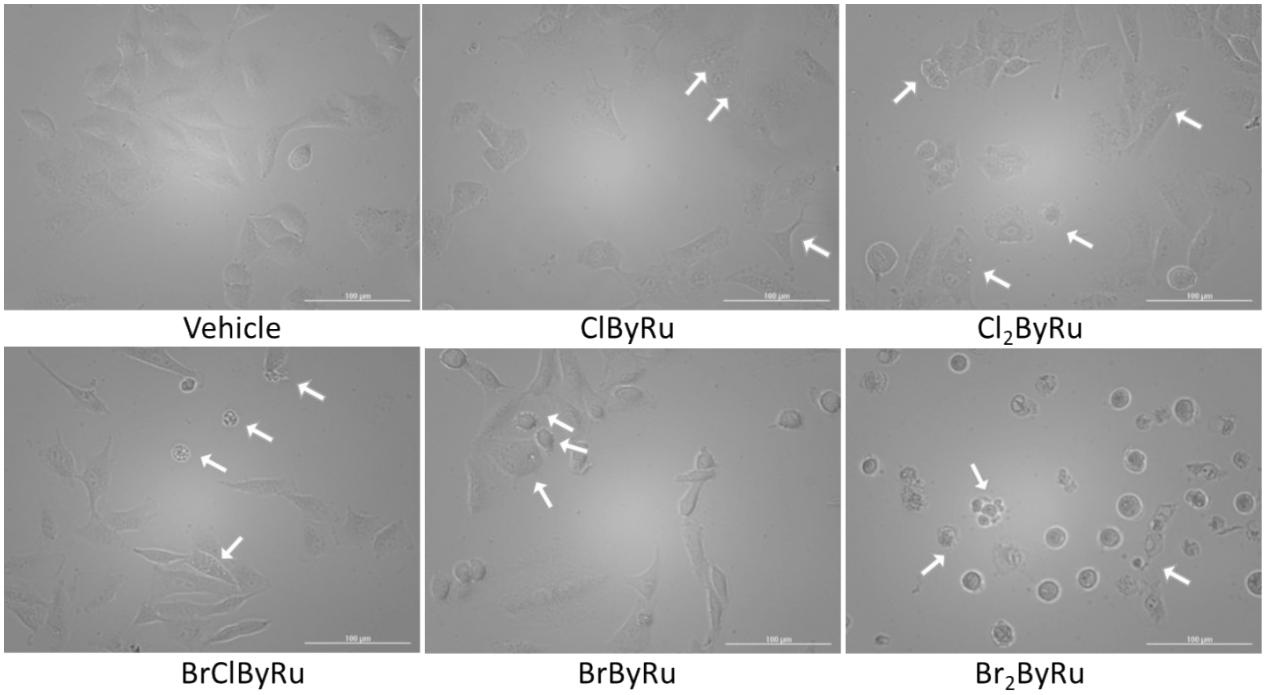


Figure S14. Bright Field Images of A549 cells treated with 10 µM of the Ru(II) complexes during 17h (20 × magnification). White arrows highlight apoptotic morphology.