Anticancer Ruthenium(II) Tris(pyrazolyl)methane Complexes with Bioactive Co-ligands

Alberto Gobbo, Sarah A. P. Pereira, Lorenzo Biancalana, Stefano Zacchini, M. Lúcia M. F. S. Saraiva, Paul J. Dyson, Fabio Marchetti

University of Pisa, Department of Chemistry and Industrial Chemistry, Via G. Moruzzi 13, I-56124 Pisa, Italy.

LAQV, REQUIMTE, Laboratório de Química Aplicada, Faculdade de Farmácia da Universidade do Porto, Portugal.

University of Bologna, Department of Industrial Chemistry "Toso Montanari", Viale Risorgimento 4, I-40136 Bologna, Italy.

Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), Switzerland.

Supporting Information

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IR spectra

Figure S1. Solid-state IR spectrum (650-4000 cm^{-1}) of **Py-EA.**

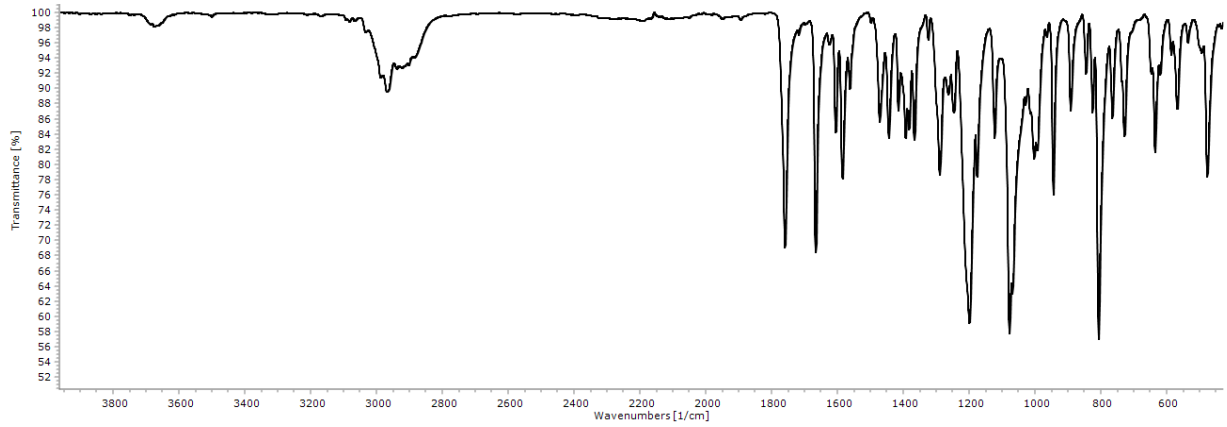


Figure S2. Solid-state IR spectrum (650-4000 cm^{-1}) of **Py-FLU.**

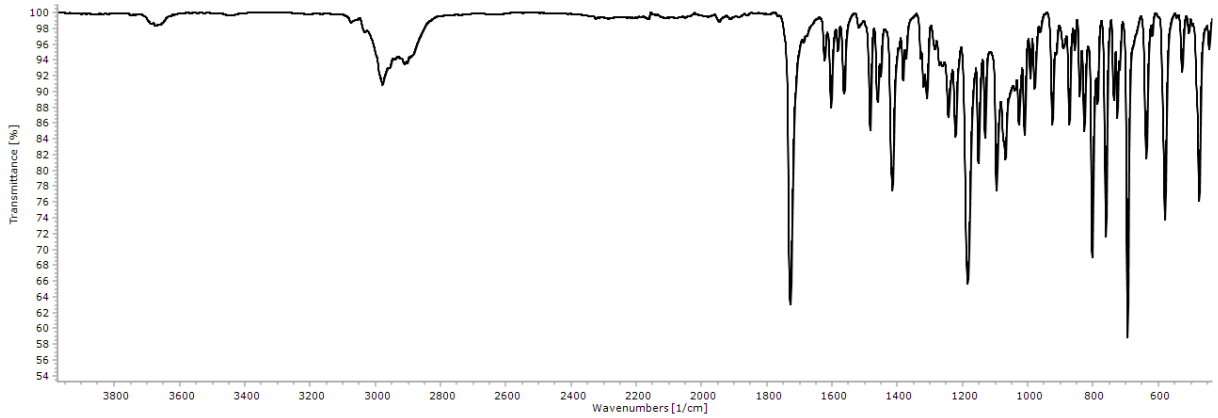


Figure S3. Solid-state IR spectrum (650-4000 cm^{-1}) of **Py-IBU.**

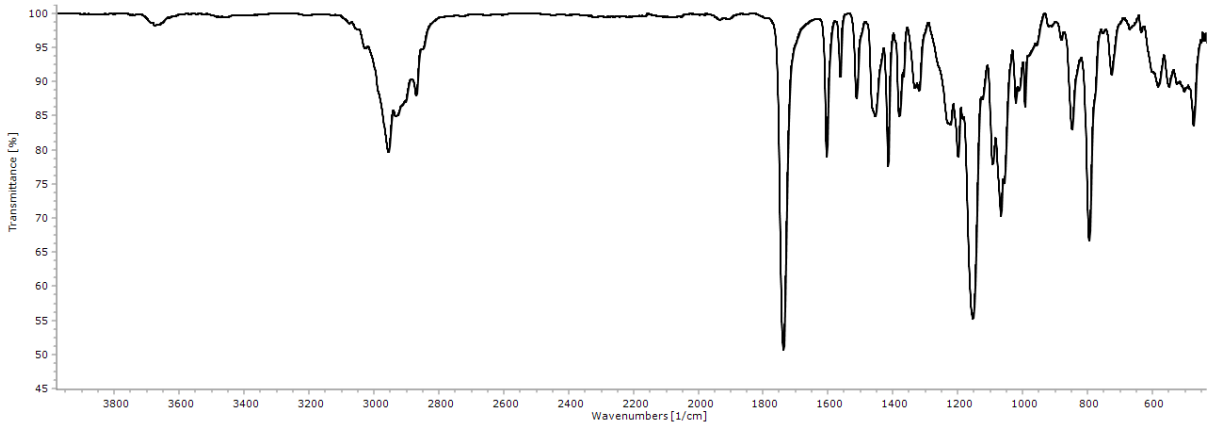


Figure S4. Solid-state IR spectrum (650-4000 cm^{-1}) of **Py-NAP.**

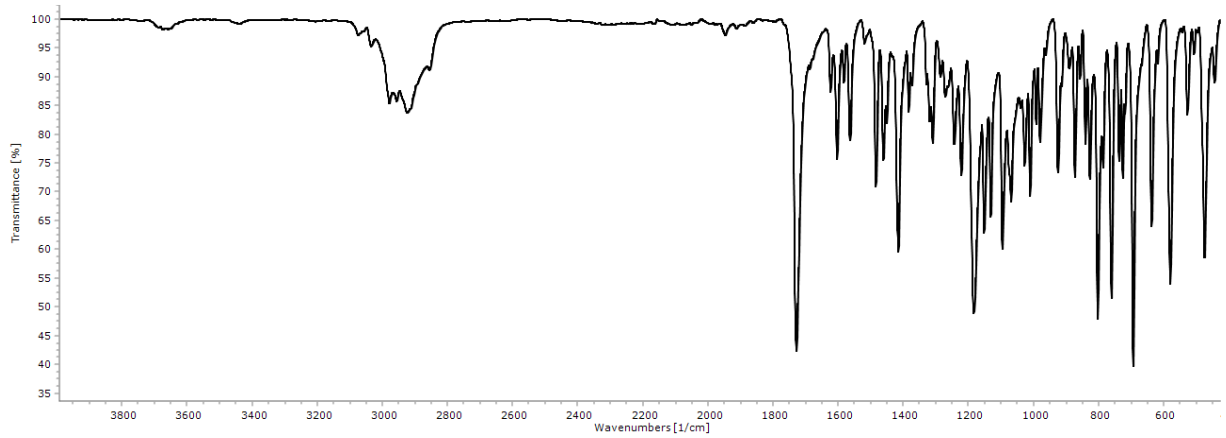


Figure S5. Solid-state IR spectrum (650-4000 cm^{-1}) of **2.**

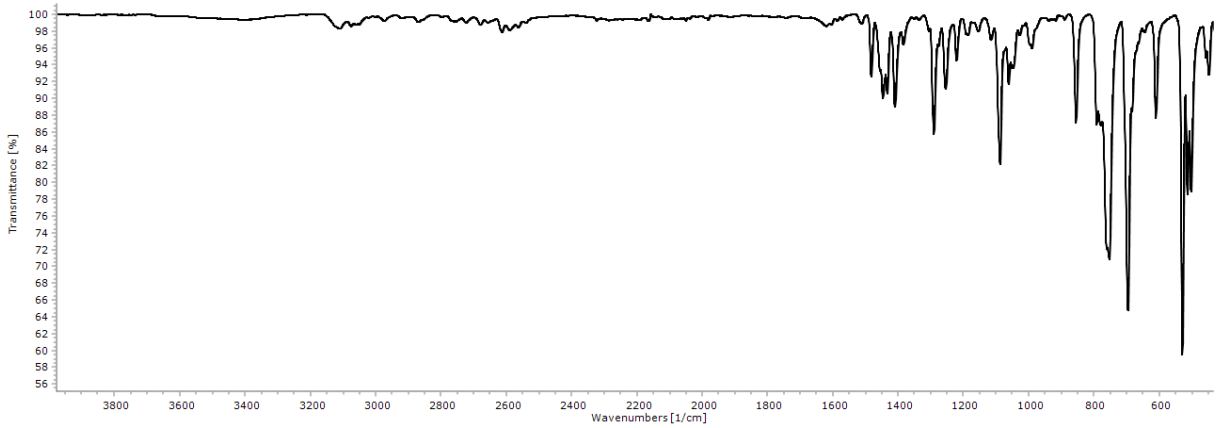


Figure S6. Solid-state IR spectrum (650-4000 cm^{-1}) of **3.**

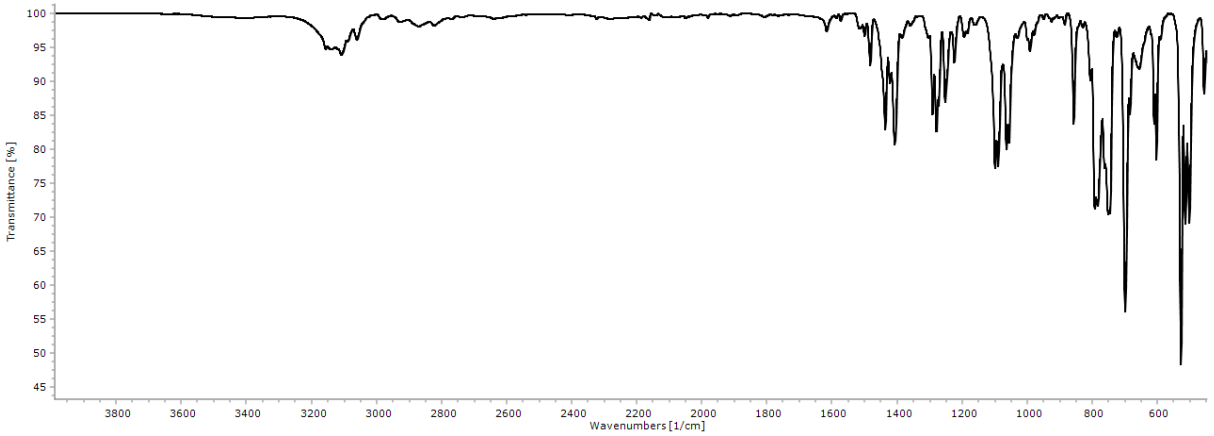


Figure S7. Solid-state IR spectrum (650-4000 cm^{-1}) of **4.**

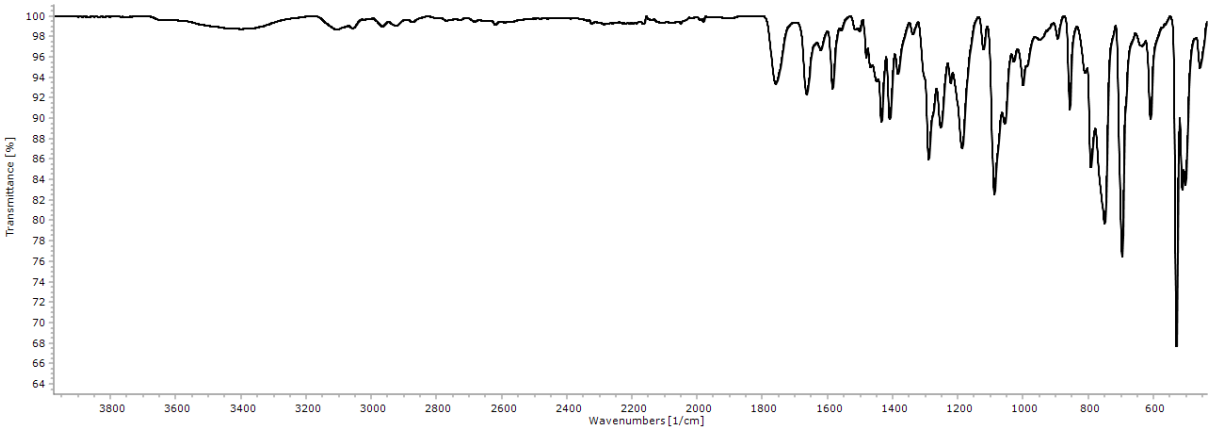


Figure S8. Solid-state IR spectrum (650-4000 cm^{-1}) of **5.**

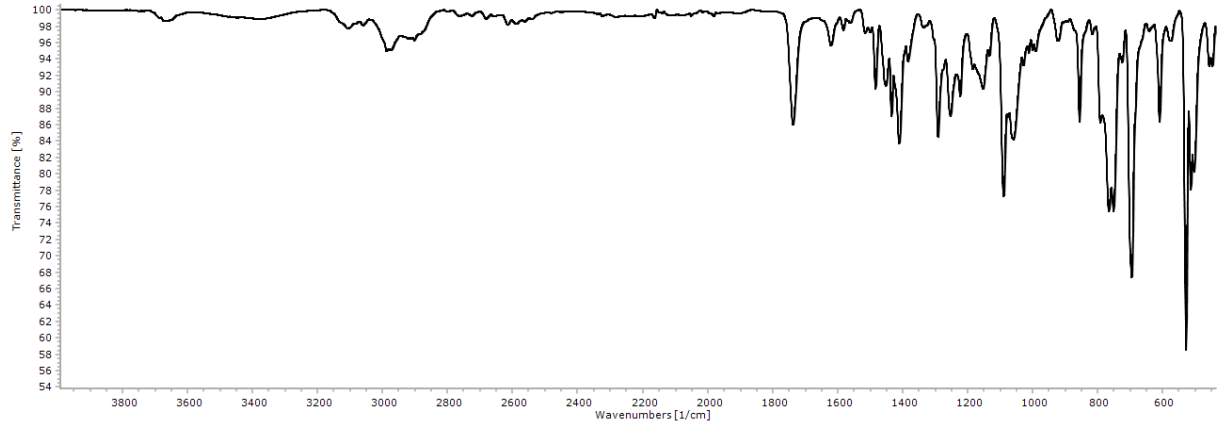


Figure S9. Solid-state IR spectrum (650-4000 cm^{-1}) of **6.**

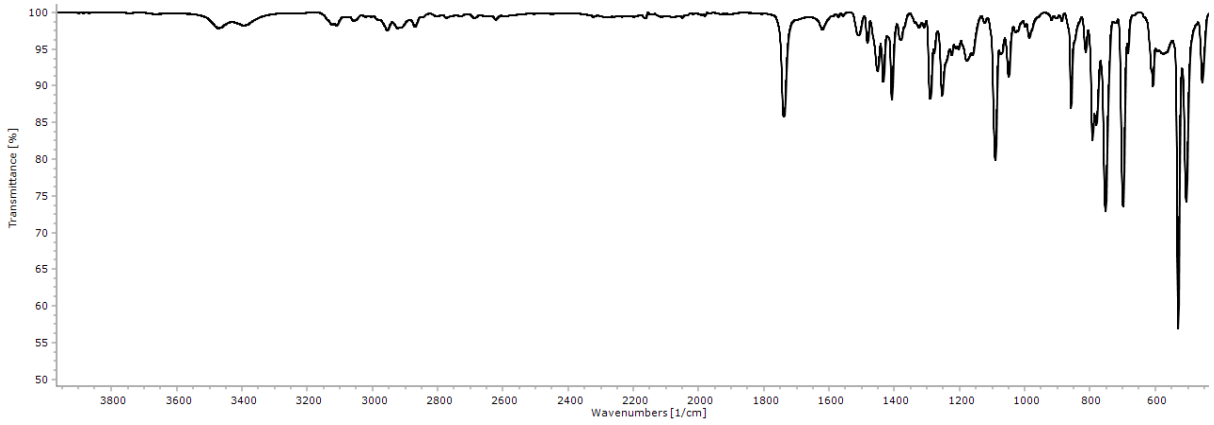
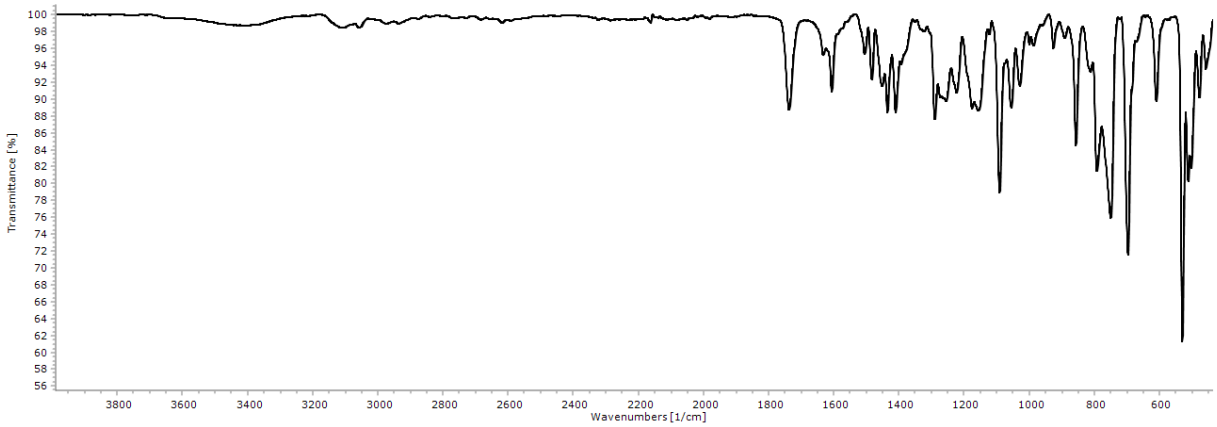


Figure S10. Solid-state IR spectrum (650-4000 cm^{-1}) of **7.**



NMR spectra

Figure S11. ^{1}H NMR spectrum (301 MHz, $CDCl_3$) of **Py-EA**

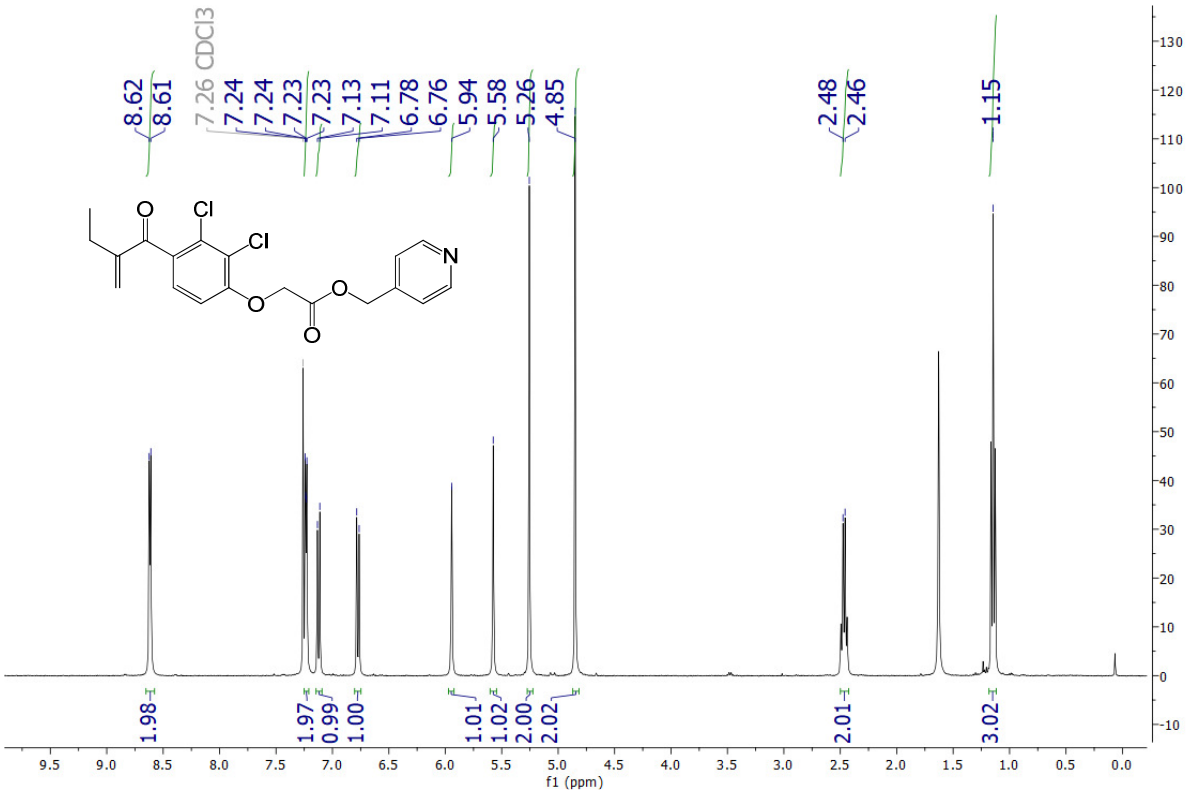


Figure S12. ^{1}H NMR spectrum (301 MHz, CD_2Cl_2) of **Py-FLU**

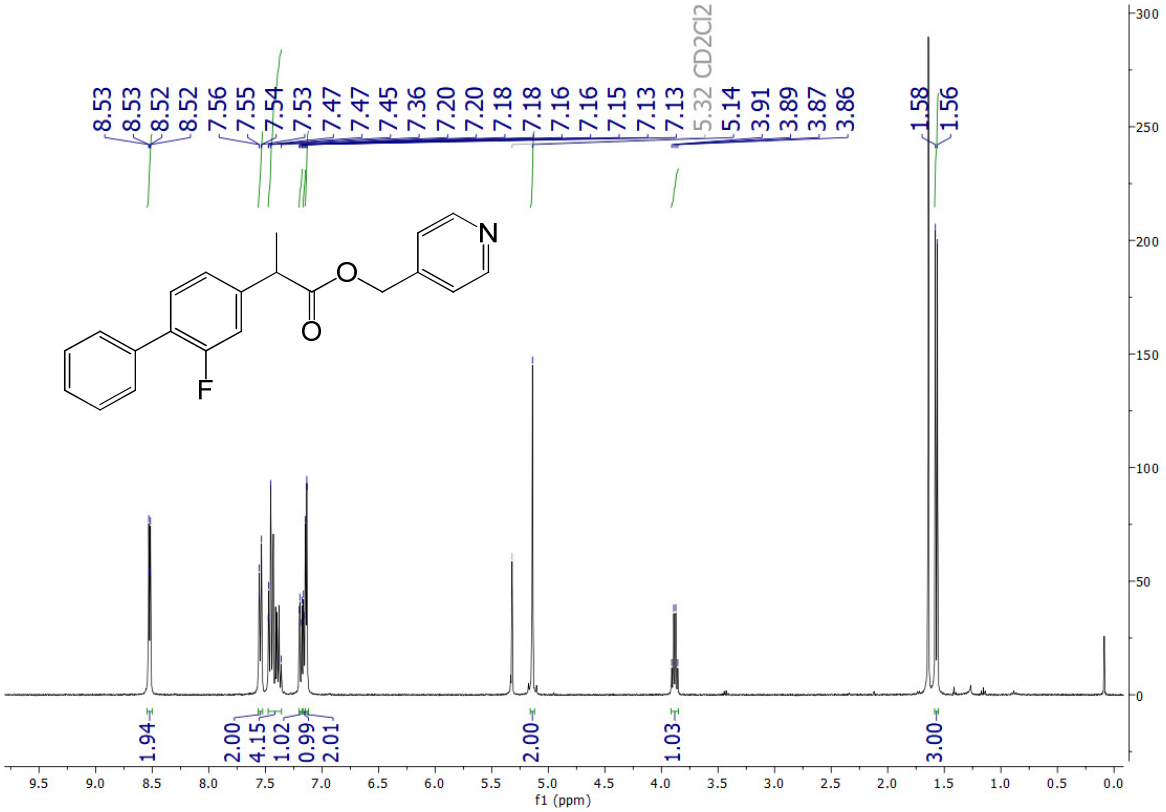


Figure S13. ^{13}C NMR spectrum (76 MHz, CD_2Cl_2) of **Py-FLU**

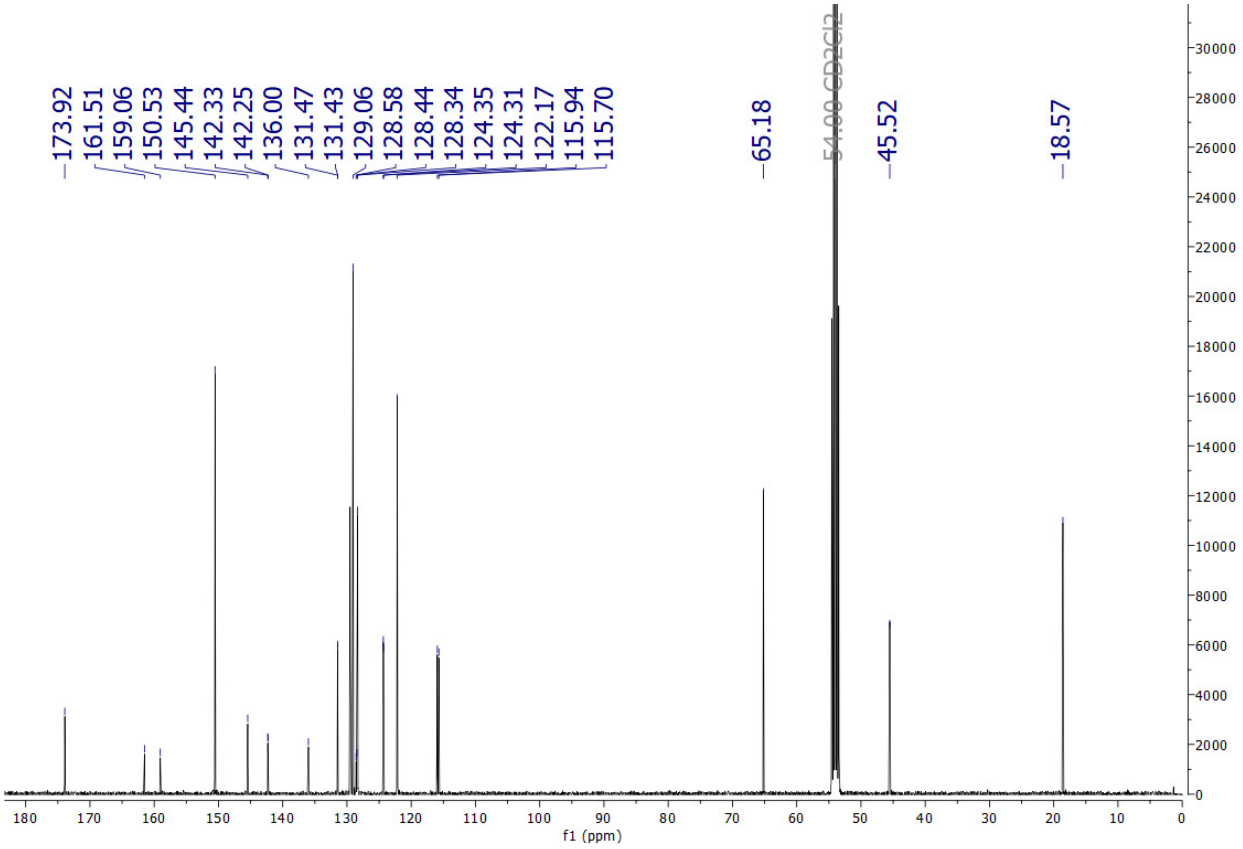


Figure S14. ^{19}F NMR spectrum (282 MHz, CD_2Cl_2) of **Py-FLU**

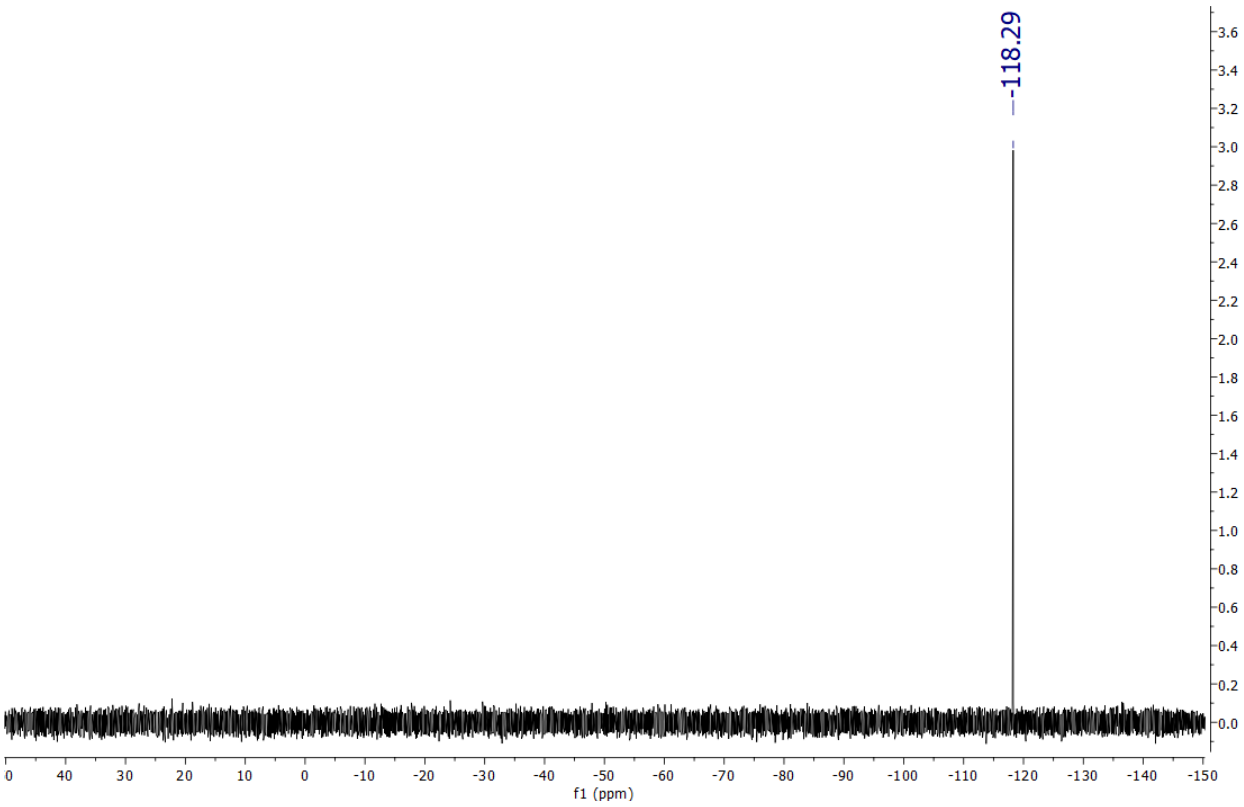


Figure S15. ^{1}H NMR spectrum (301 MHz, CD_2Cl_2) of **Py-IBU**

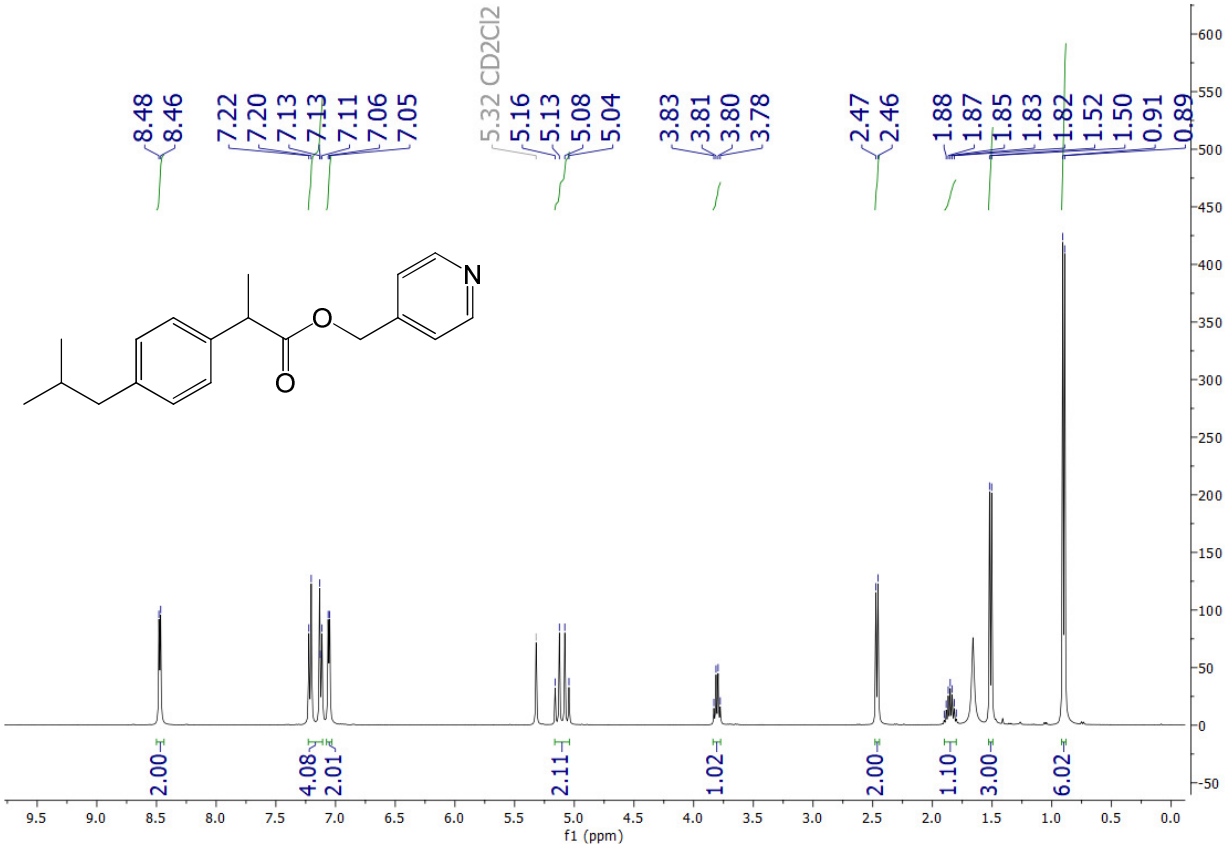


Figure S16. ^{13}C NMR spectrum (76 MHz, CD_2Cl_2) of **Py-IBU**

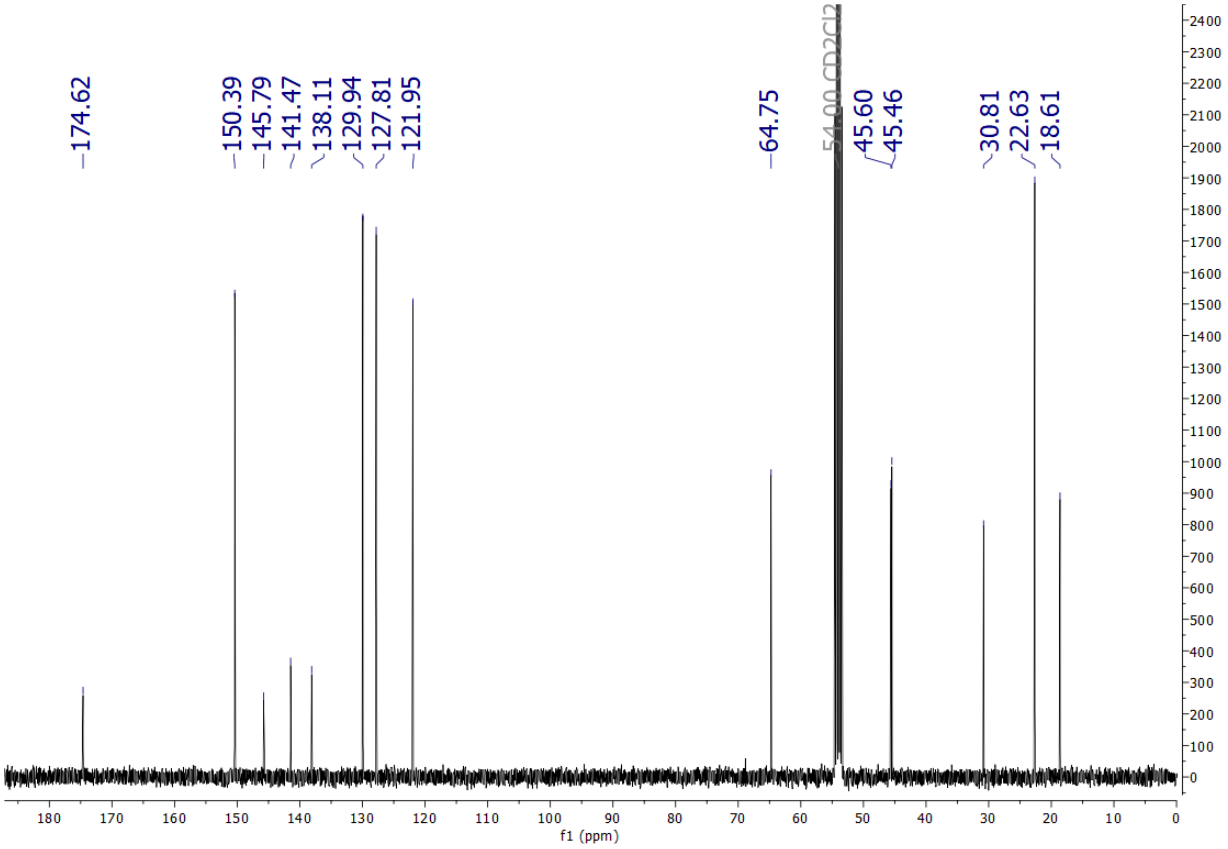


Figure S17. ^{1}H NMR spectrum (301 MHz, CD_2Cl_2) of **Py-NAP**

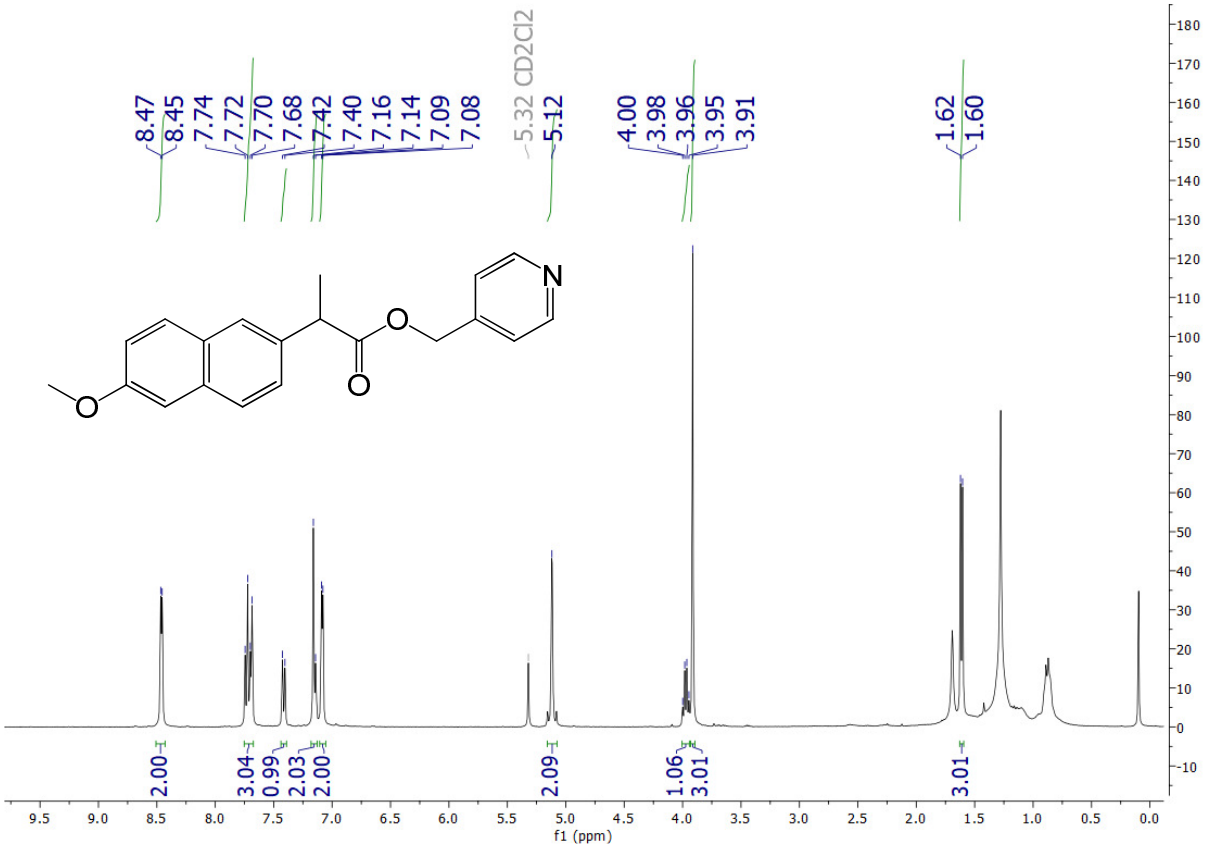


Figure S18. ^{13}C NMR spectrum (76 MHz, CD_2Cl_2) of **Py-NAP**

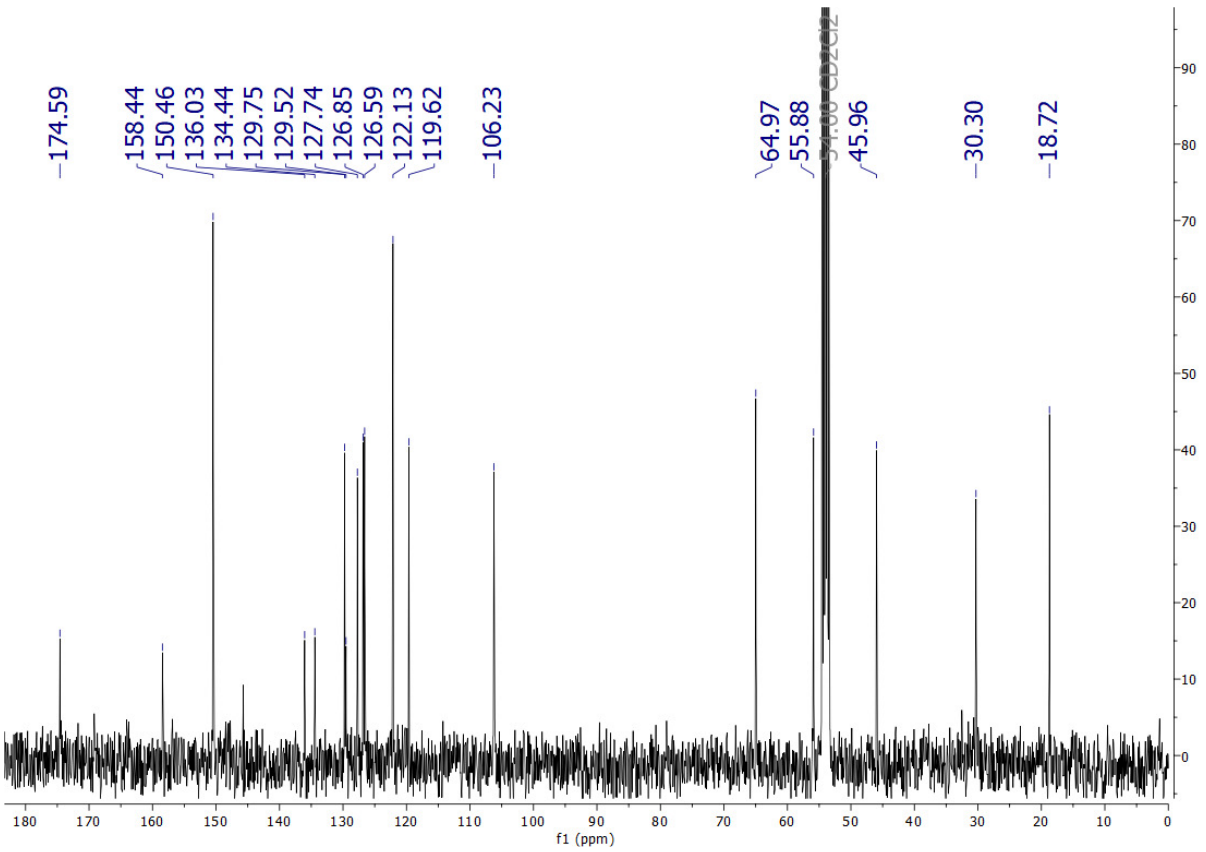


Figure S19. ^{1}H NMR spectrum (301 MHz, $CDCl_3$) of **2**

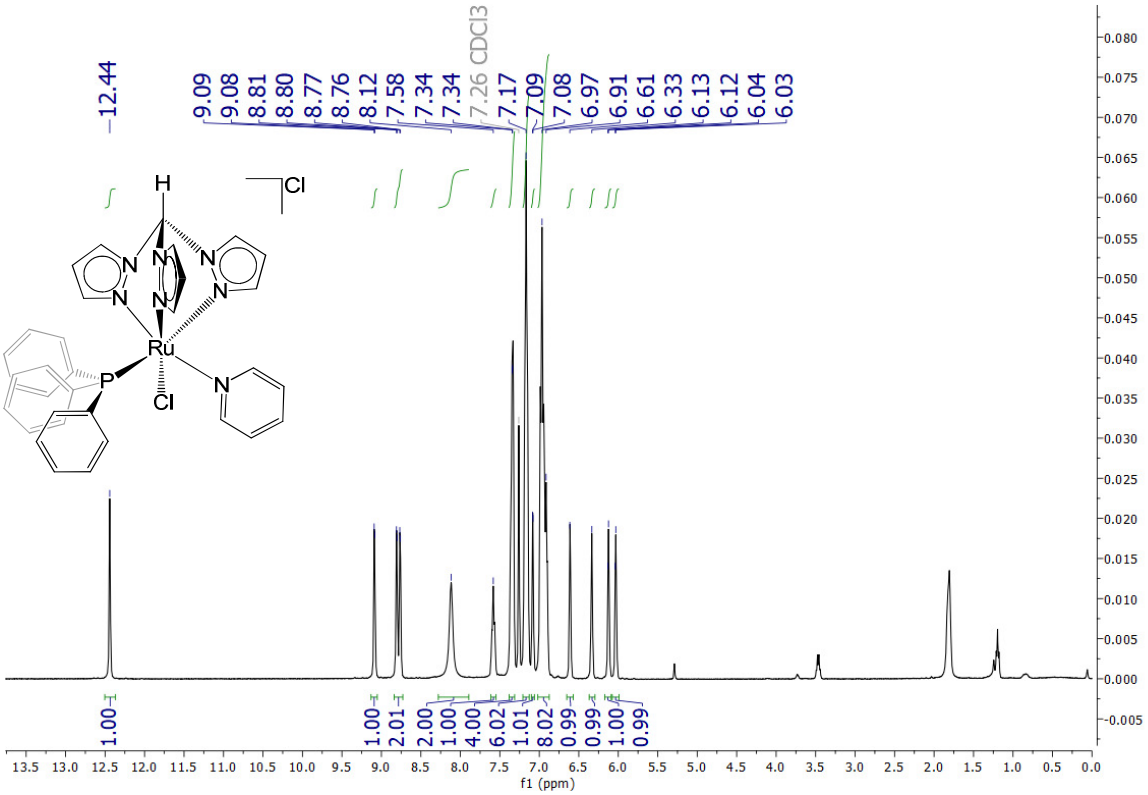


Figure S20. ^{13}C NMR spectrum (76 MHz, $CDCl_3$) of **2**

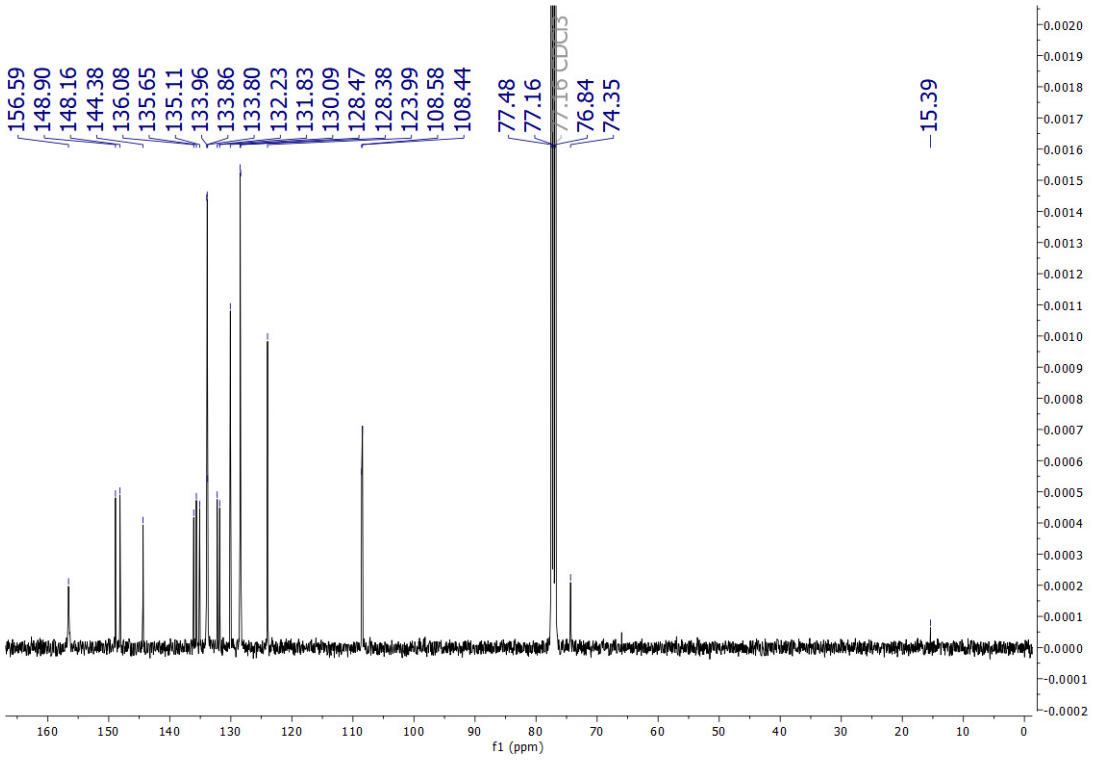


Figure S21. ^{31}P NMR spectrum (121 MHz, $CDCl_3$) of **2**

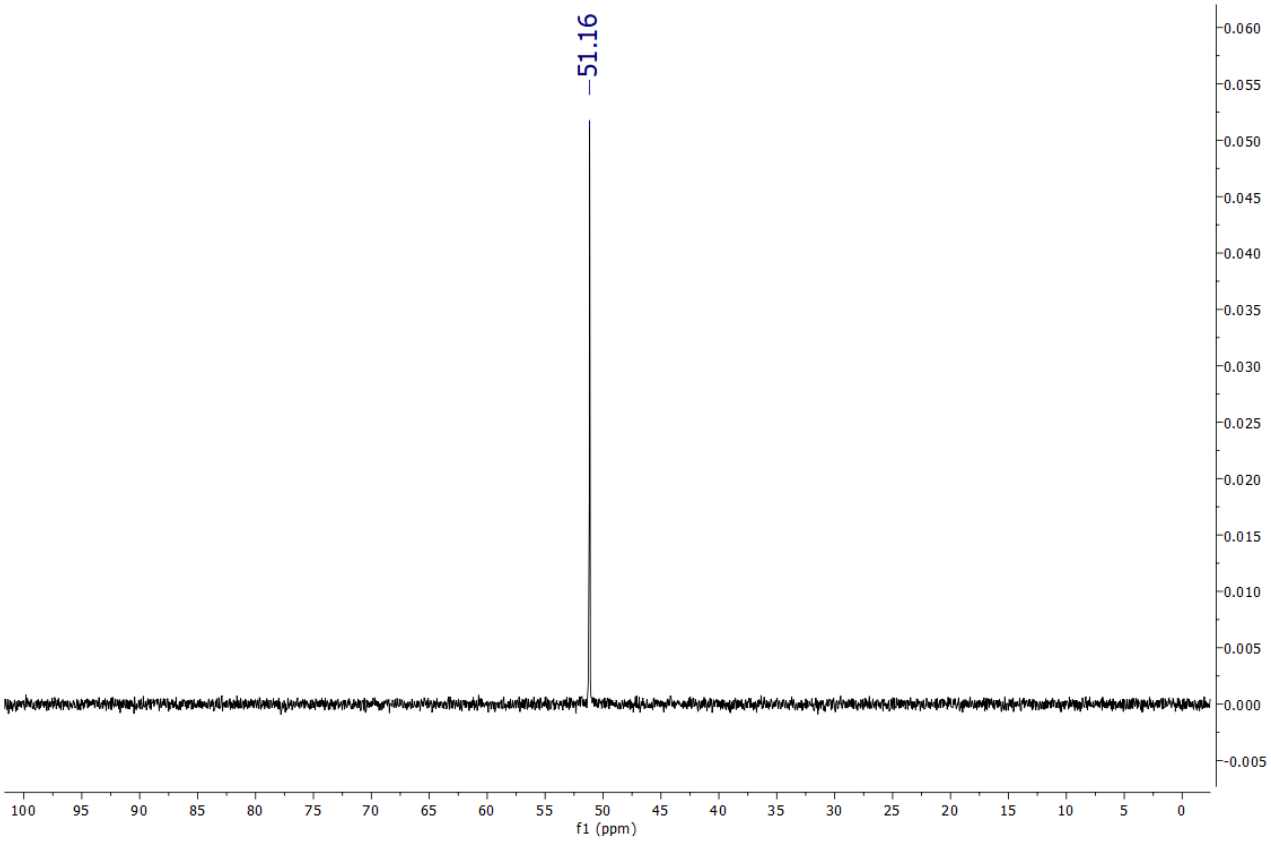


Figure S22. ^{1}H NMR spectrum (301 MHz, $CDCl_3$) of **3**

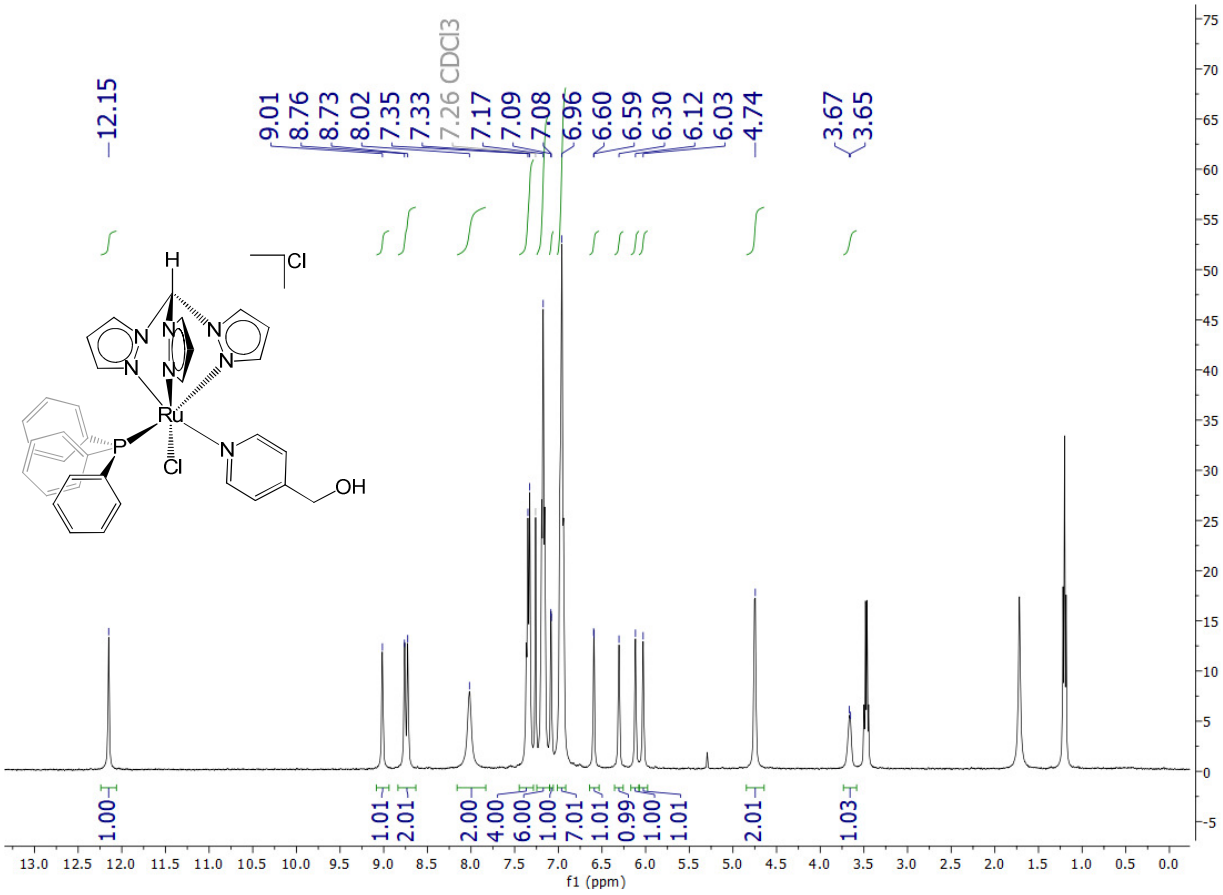


Figure S23. ^{31}P NMR spectrum (121 MHz, $CDCl_3$) of **3**

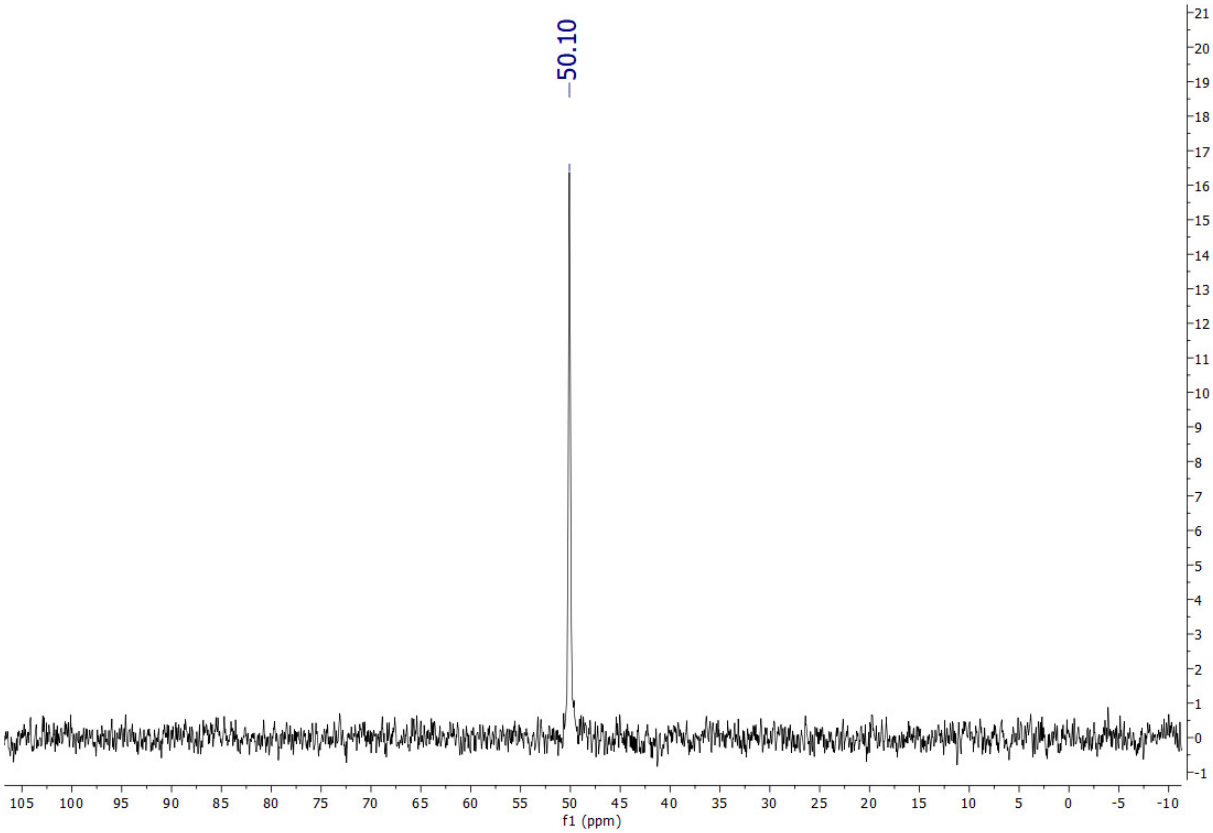


Figure S24. ^{1}H NMR spectrum (301 MHz, CD_3OD) of **3**

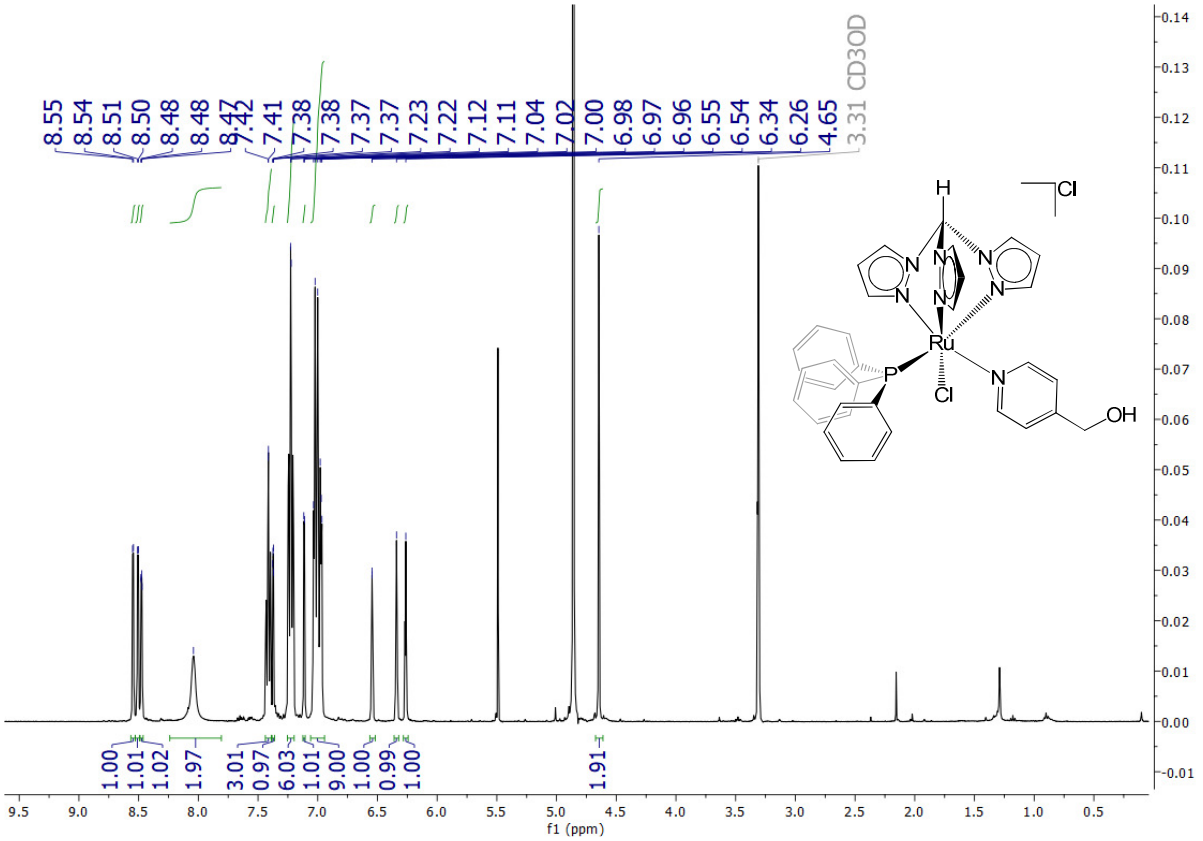


Figure S25. ^{13}C NMR spectrum (126 MHz, CD_3OD) of **3**

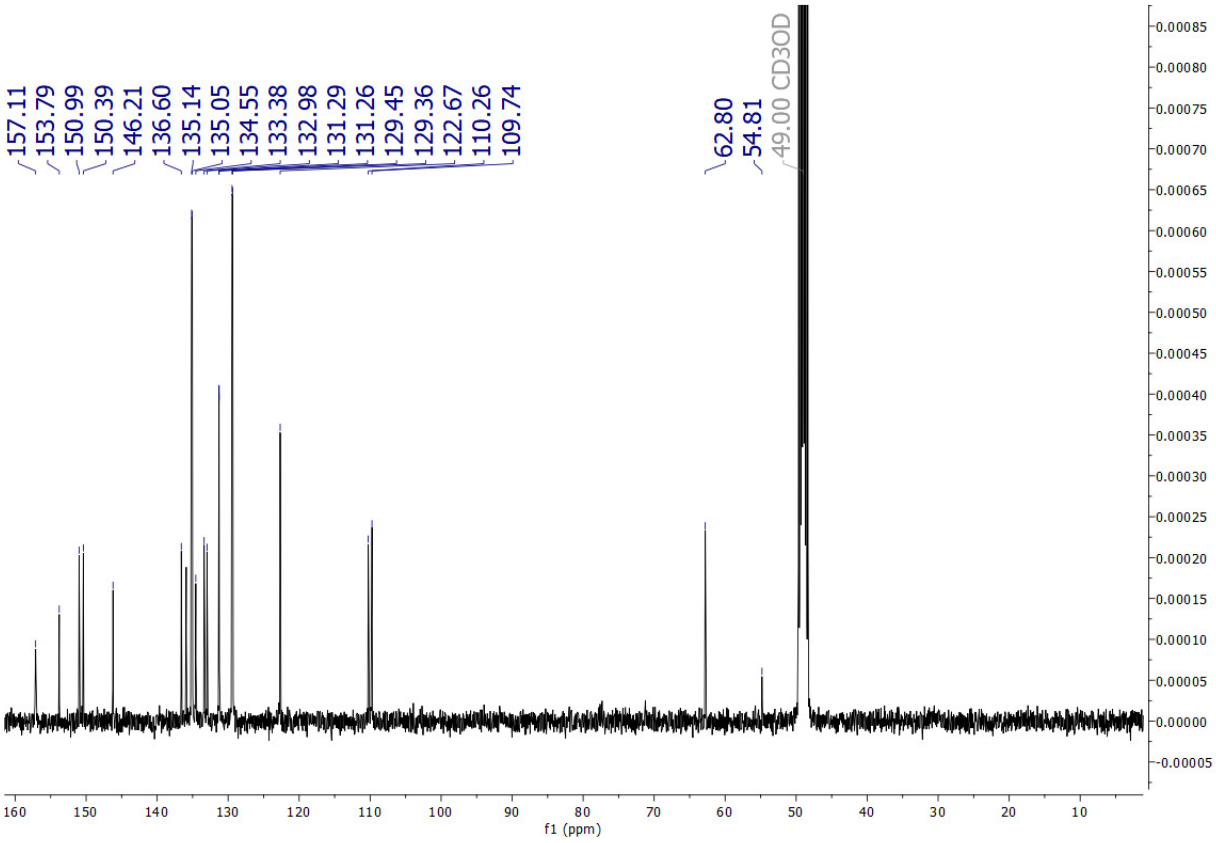


Figure S26. ^{31}P NMR spectrum (202 MHz, CD_3OD) of **3**

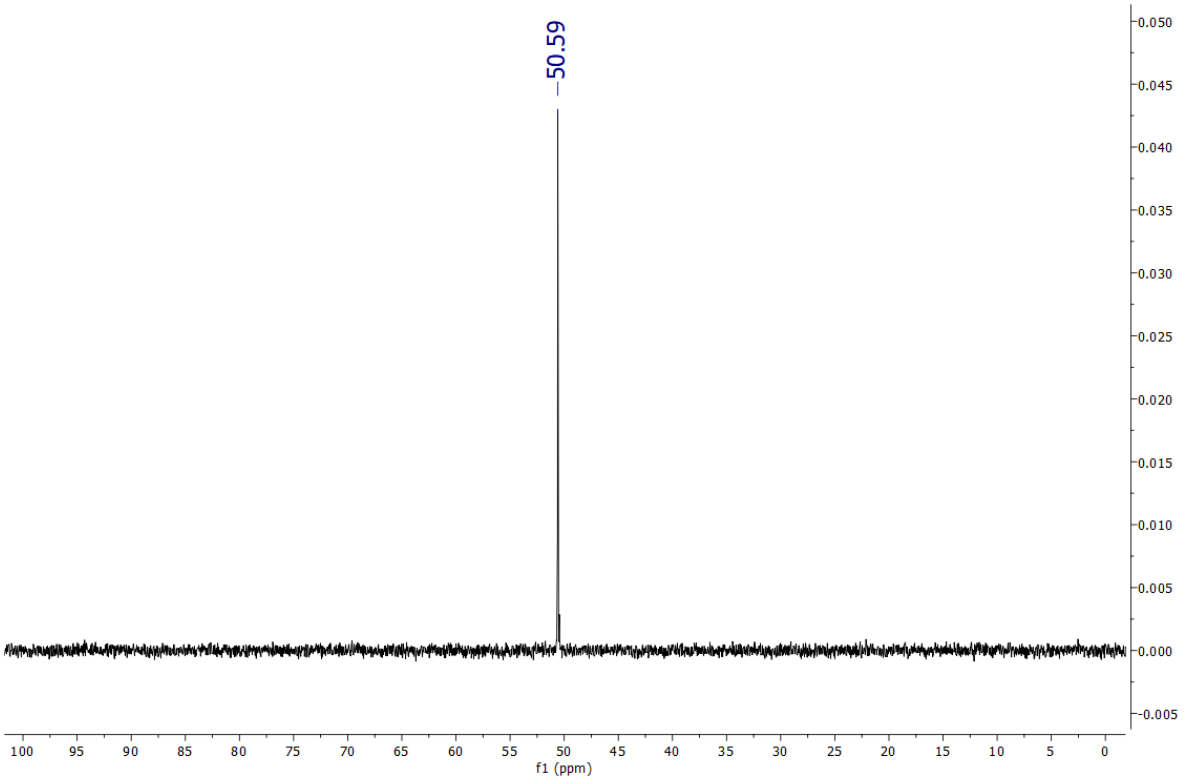


Figure S27. ^{1}H NMR spectrum (301 MHz, CD_2Cl_2) of **4**

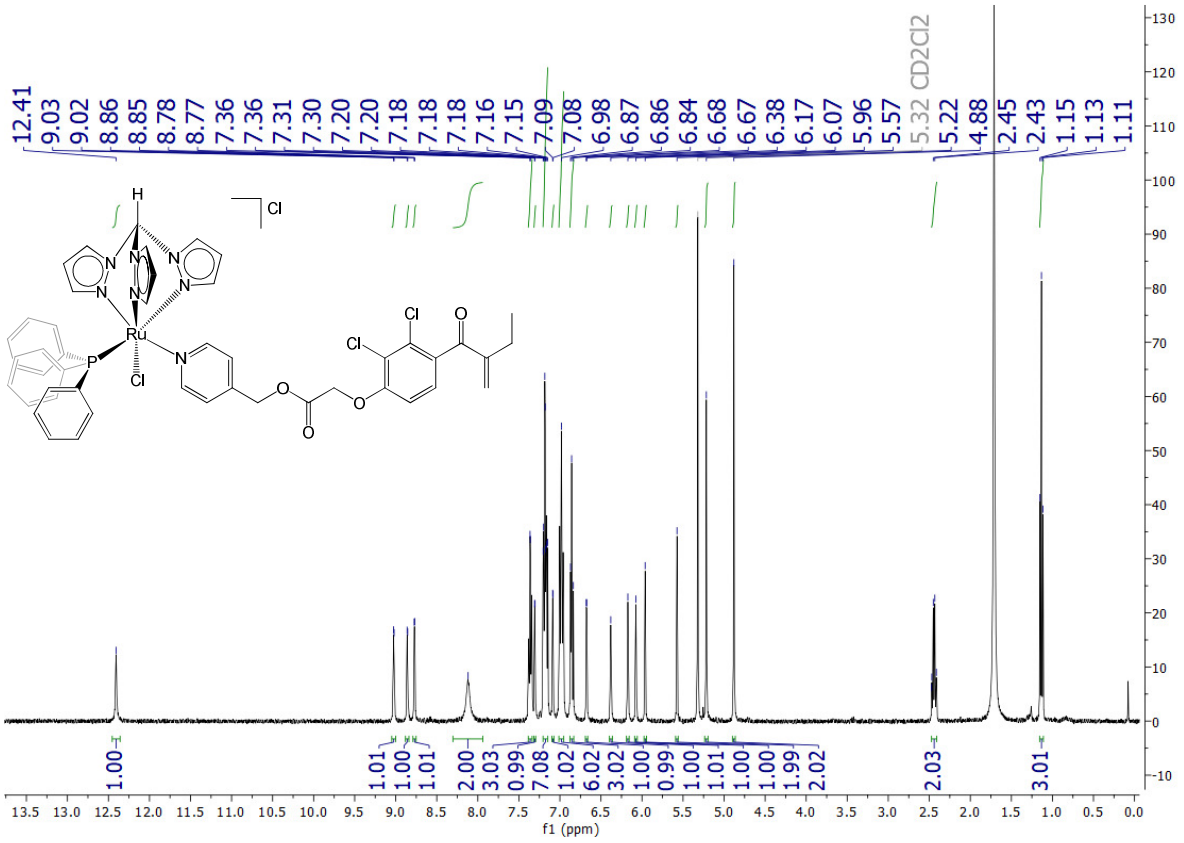


Figure S28. ^{13}C NMR spectrum (76 MHz, CD_2Cl_2) of **4**

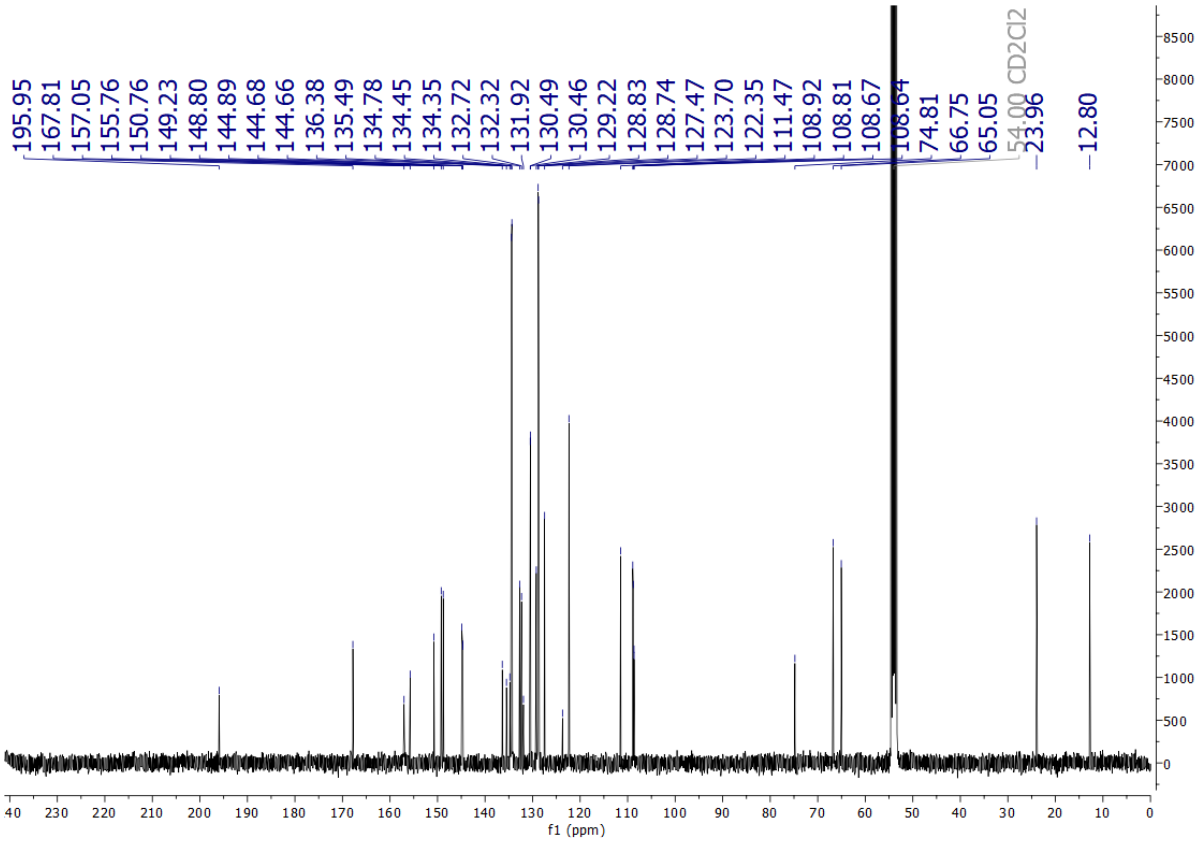


Figure S29. ^{31}P NMR spectrum (121 MHz, CD_2Cl_2) of **4**

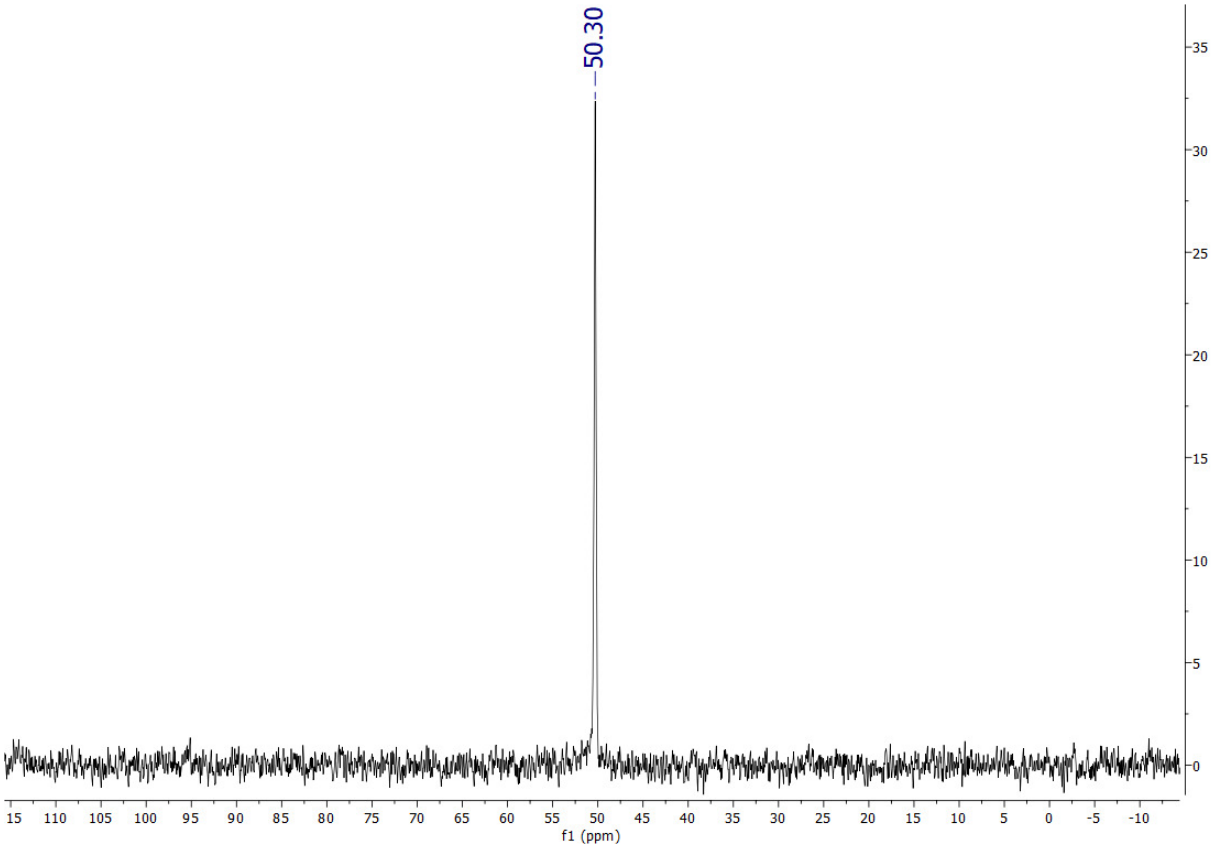


Figure S30. ^{1}H NMR spectrum (301 MHz, CD_2Cl_2) of **5**

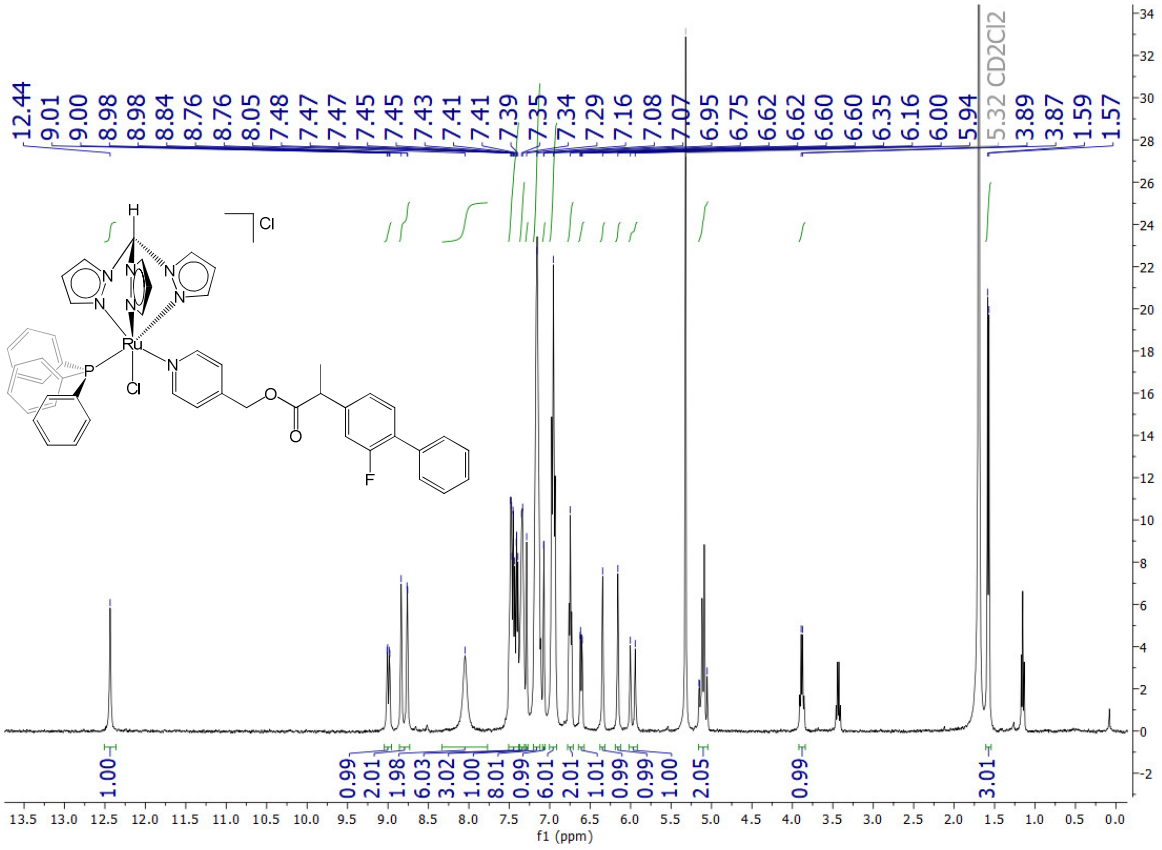


Figure S31. ^{13}C NMR spectrum (76 MHz, CD_2Cl_2) of **5**

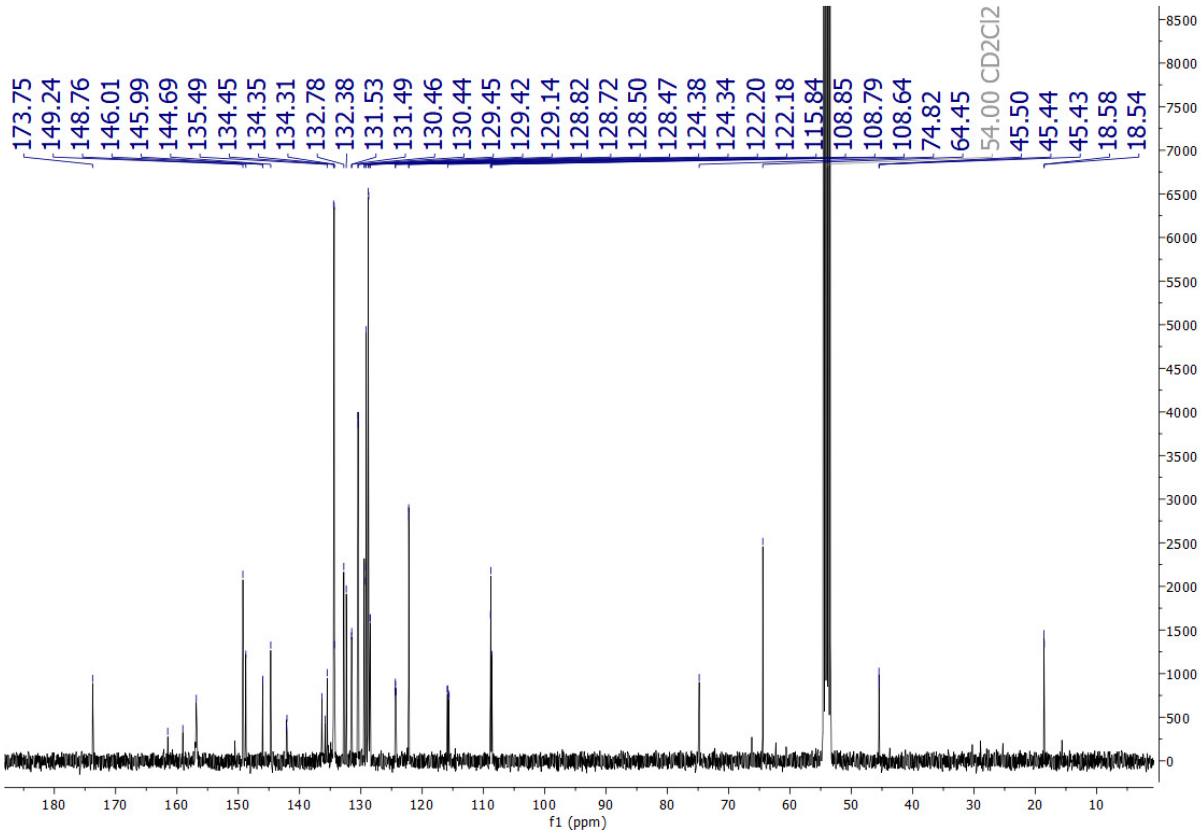


Figure S32. ^{31}P NMR spectrum (121 MHz, CD_2Cl_2) of **5**

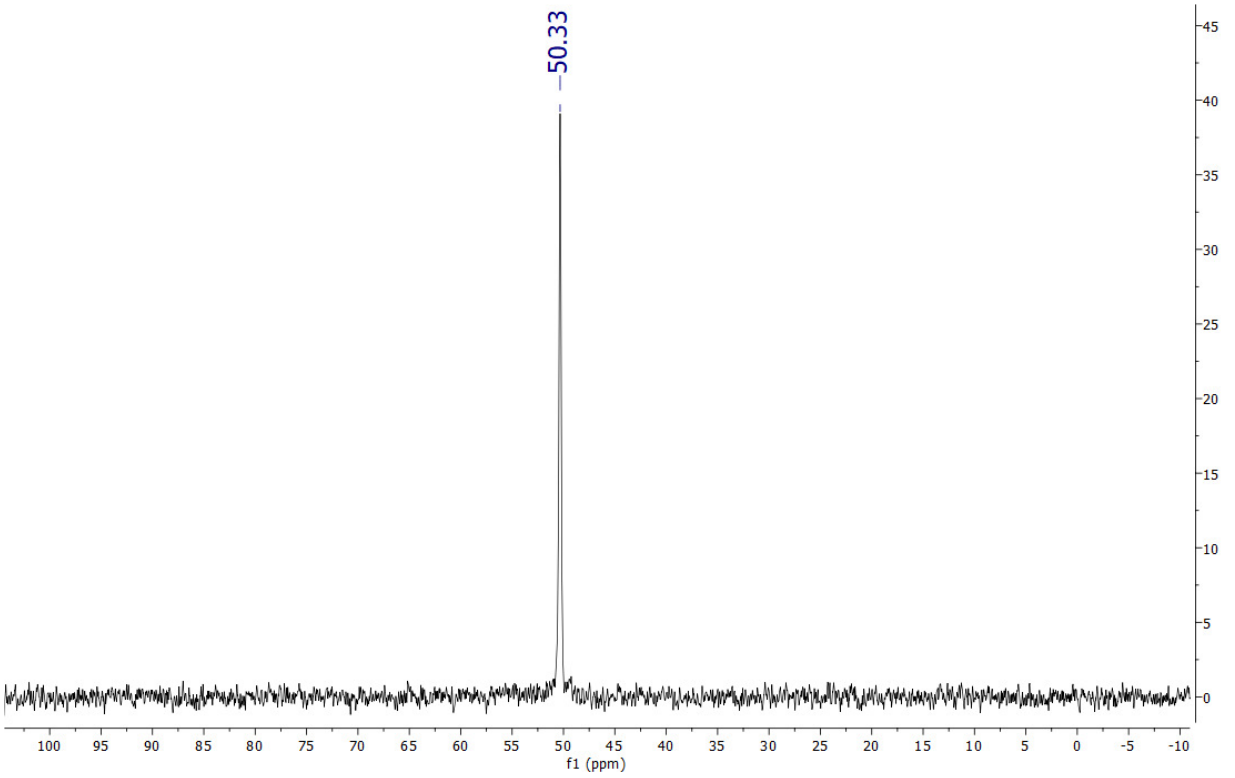


Figure S33. ^{19}F NMR spectrum (282 MHz, CD_2Cl_2) of **5**

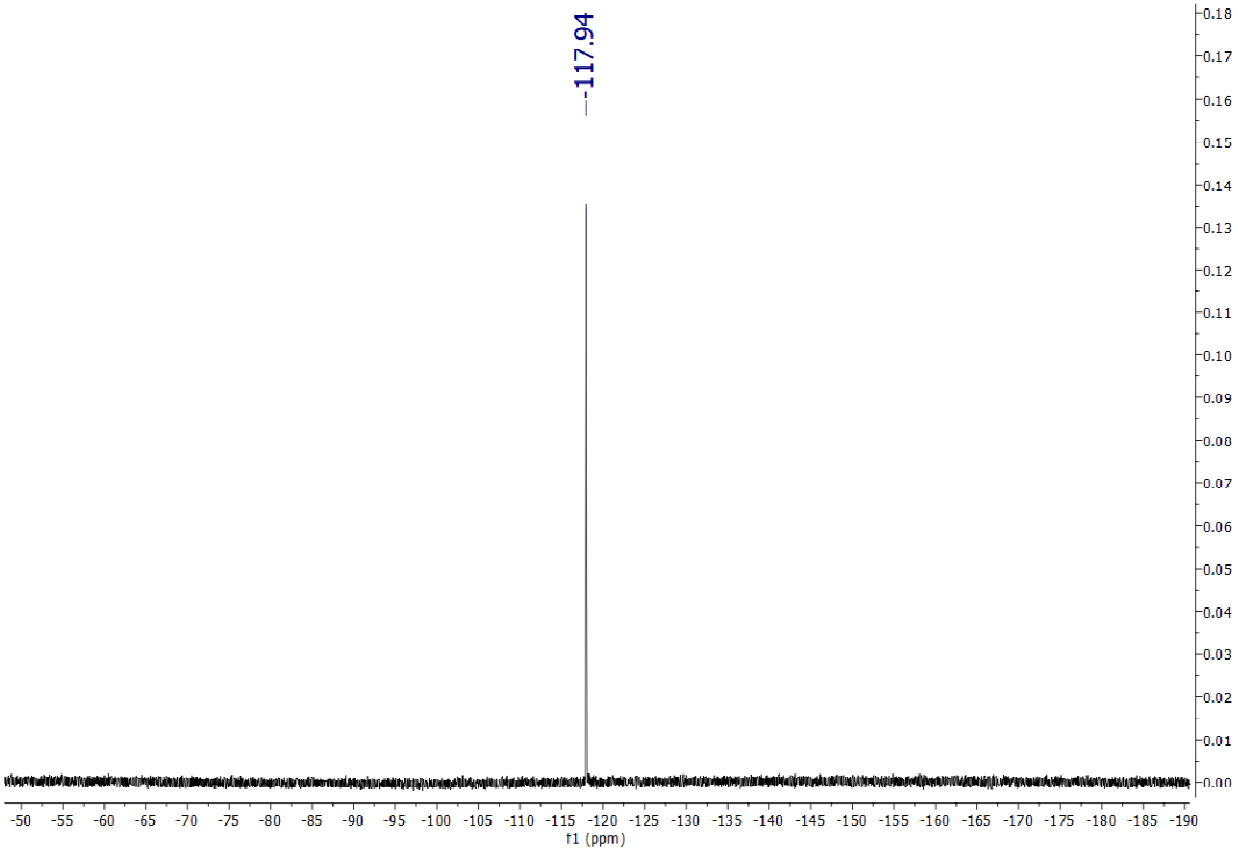


Figure S34. ^{1}H NMR spectrum (301 MHz, CD_2Cl_2) of **6**

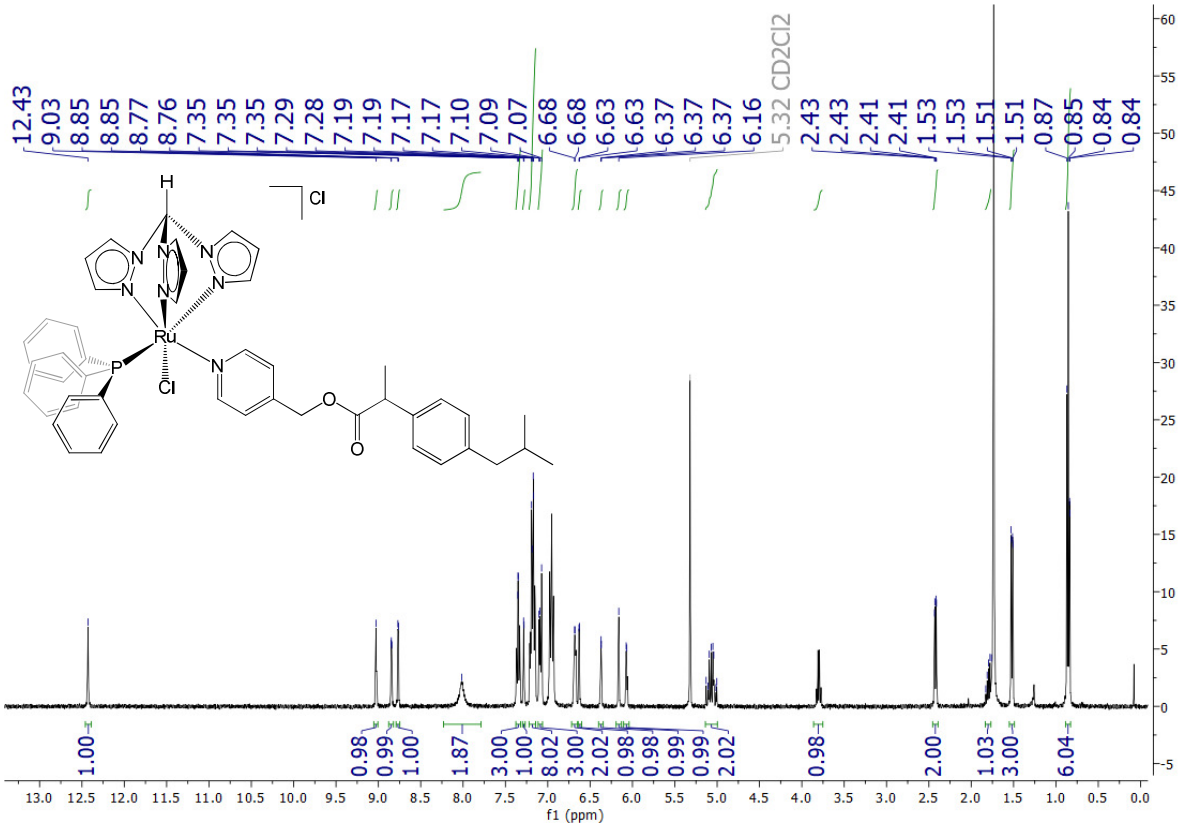


Figure S35. ^{13}C NMR spectrum (76 MHz, CD_2Cl_2) of **6**

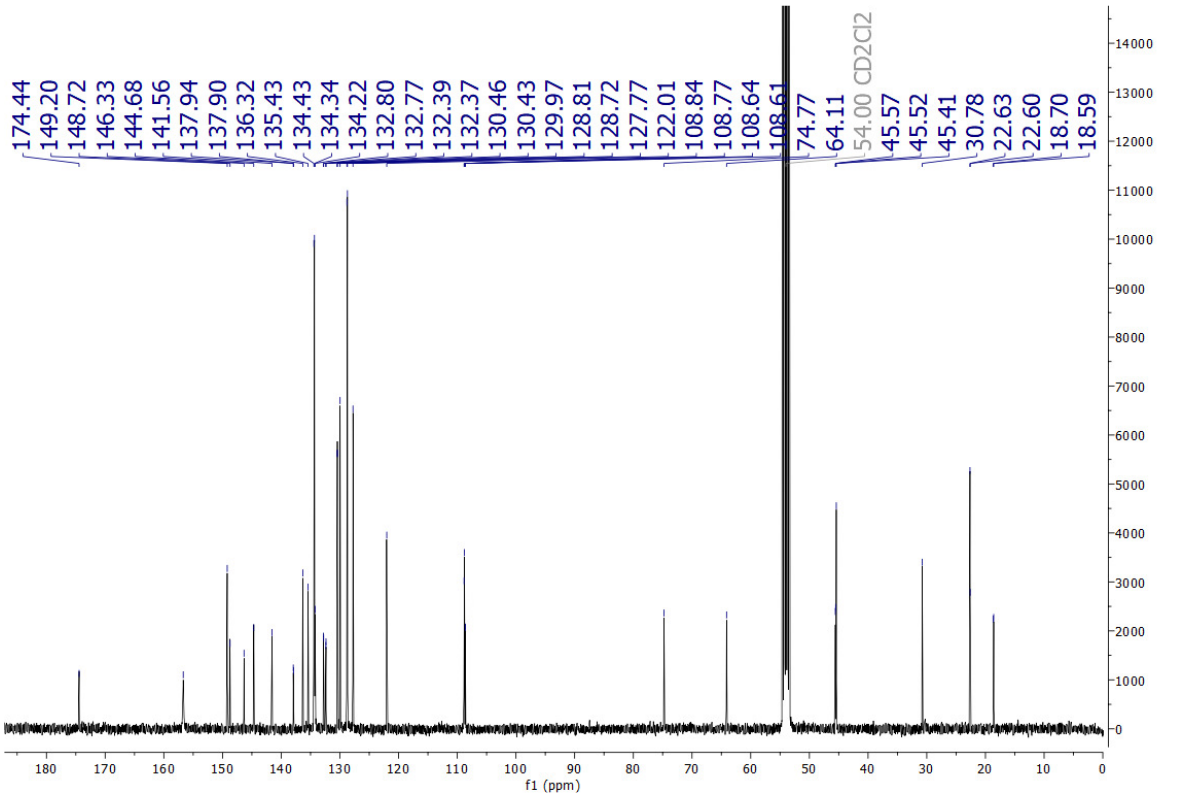


Figure S36. ^{31}P NMR spectrum (121 MHz, CD_2Cl_2) of **6**

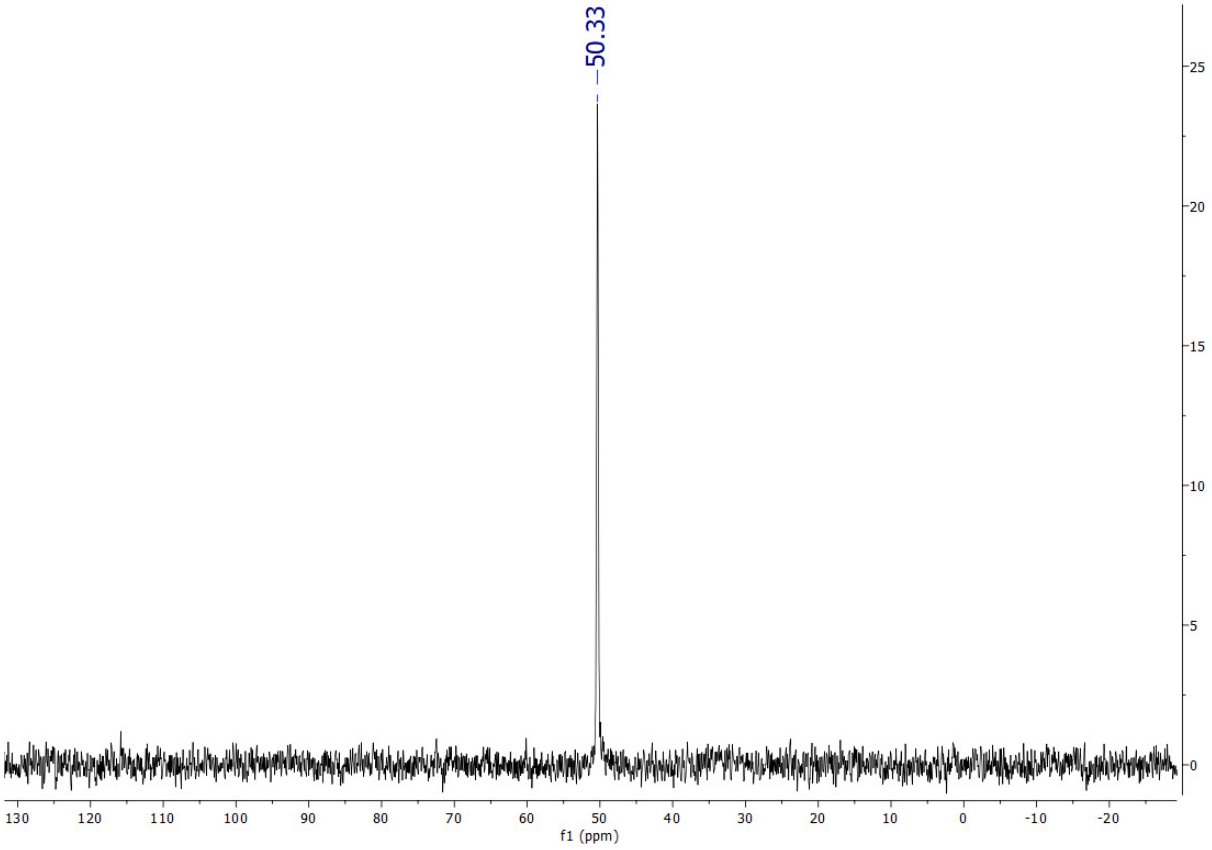


Figure S37. ^{1}H NMR spectrum (301 MHz, CD_2Cl_2) of **7**

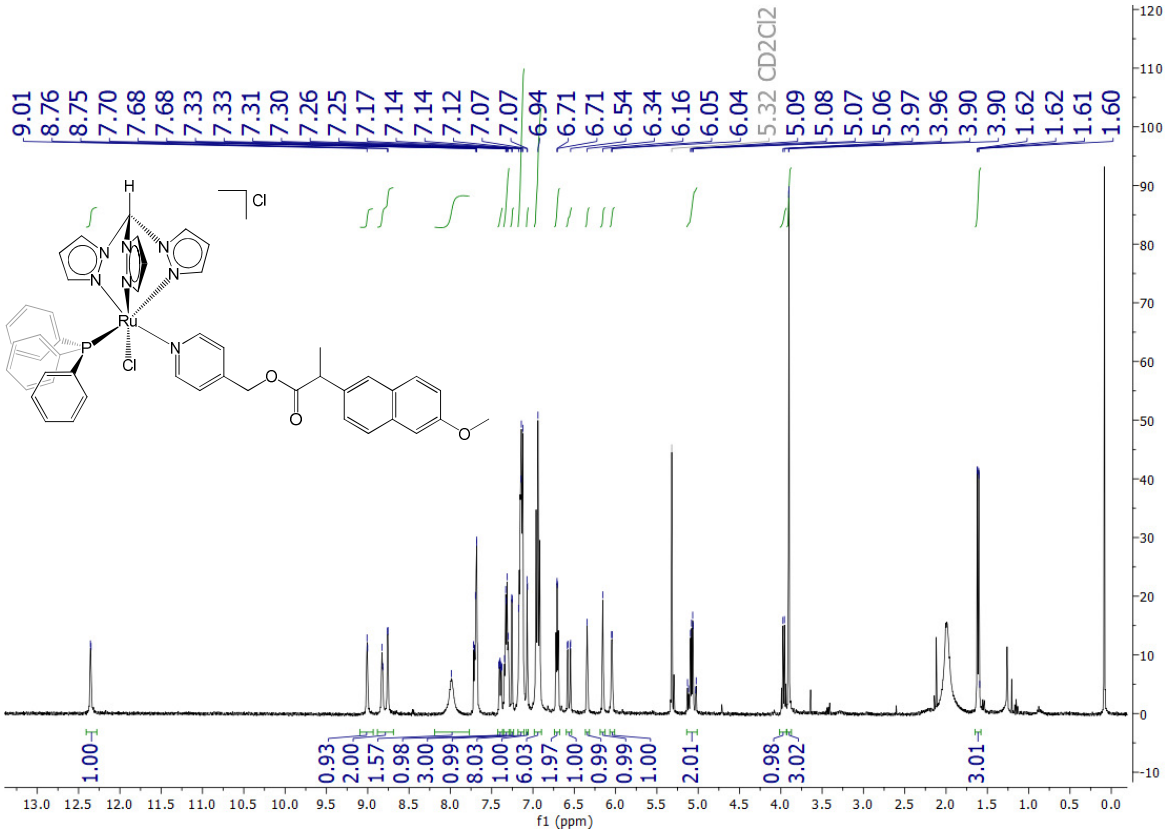


Figure S38. ^{13}C NMR spectrum (76 MHz, CD_2Cl_2) of **7**

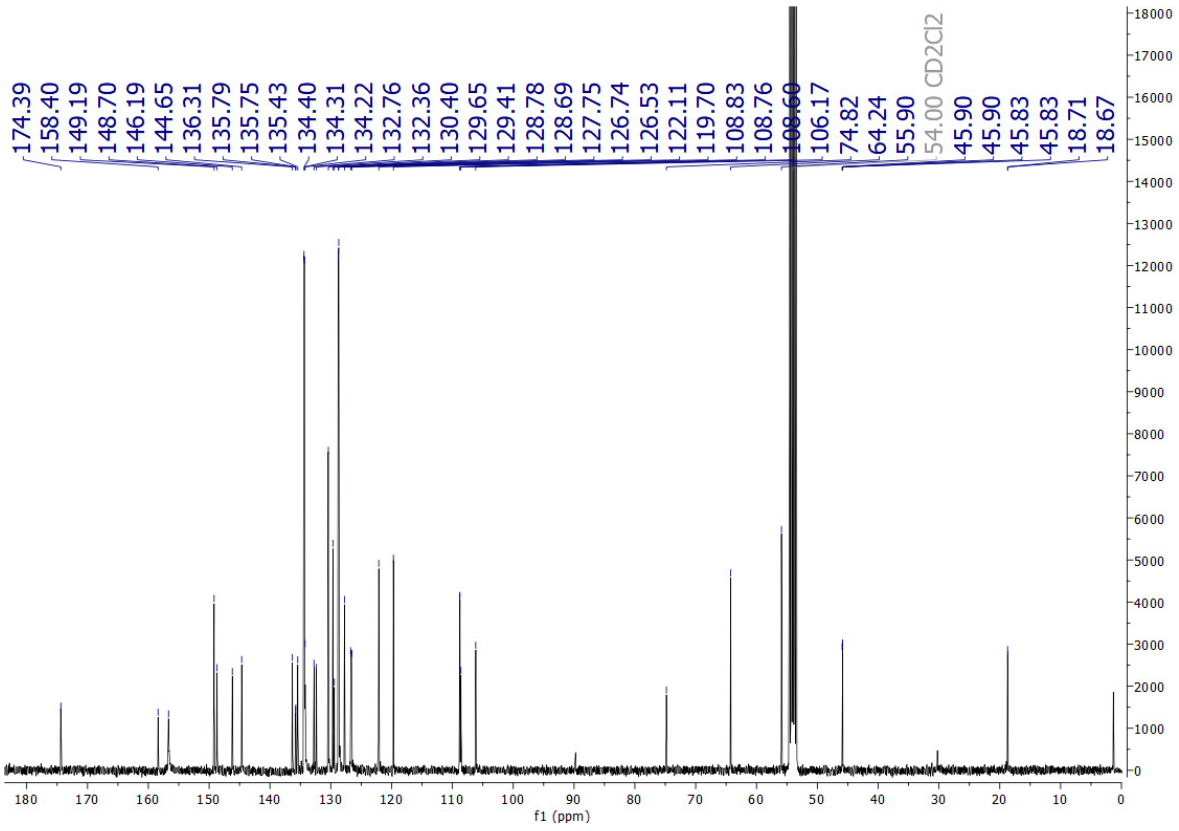


Figure S39. ^{31}P NMR spectrum (121 MHz, CD_2Cl_2) of **7**

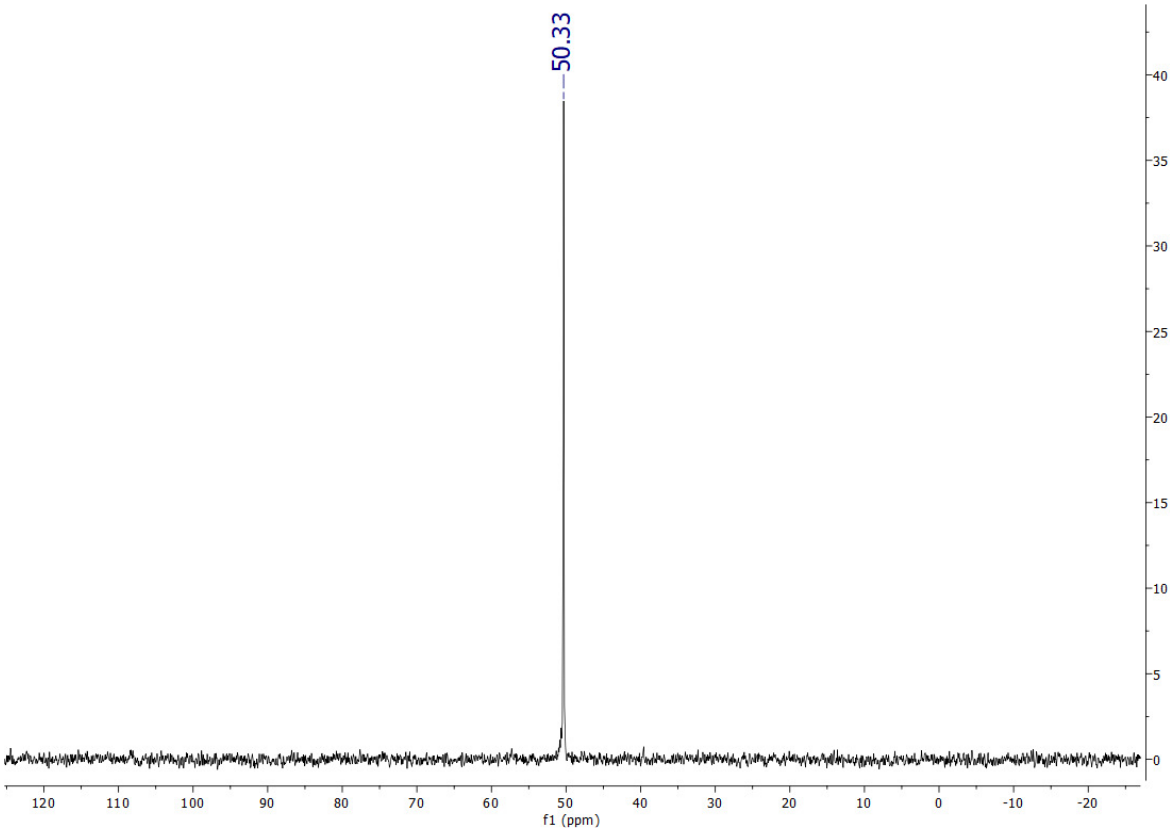


Table S1. Hydrogen bonds for **2**·CH_2Cl_2·$2H_2O$ [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(401)···Cl(2)#1	0.85(2)	2.33(3)	3.151(5)	165(7)
O(1)-H(402)···Cl(2)#2	0.85(2)	2.39(3)	3.212(5)	165(7)
O(2)-H(501)···Cl(2)#3	0.858(15)	2.389(16)	3.241(6)	172(7)
O(2)-H(502)···Cl(2)	0.859(15)	2.385(15)	3.245(6)	179(10)

Symmetry transformations used to generate equivalent atoms: #1 x, y+1, z; #2 -x+1, -y+1, -z+1; #3 -x, -y,-z+1.

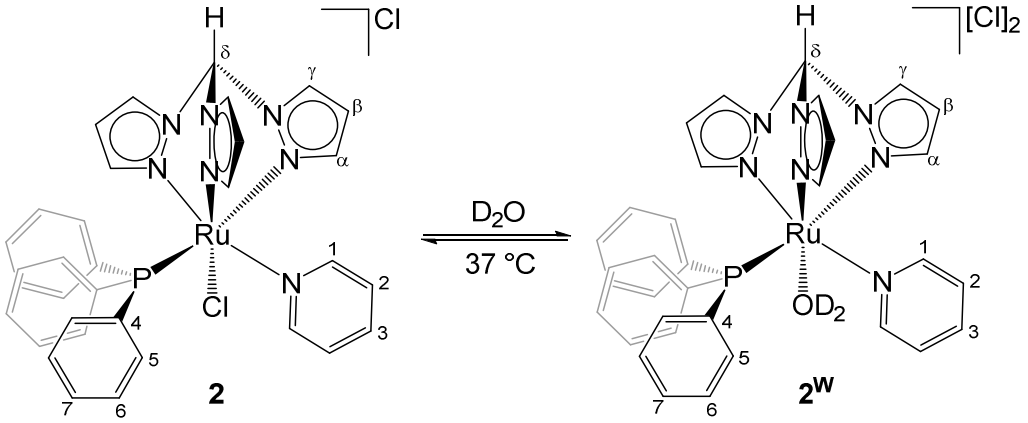
Table S2. Hydrogen bonds for **3**·$3CHCl_3$ [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1A)···Cl(3)	0.84	2.24	3.051(3)	163.8
O(11)-H(11)···Cl(4)#1	0.84	2.34	3.108(3)	151.7

Symmetry transformations used to generate equivalent atoms: #1 x+1, y, z+1.

NMR data of complexes in aqueous solutions

Figure S40. Chloride/water exchange equilibrium for **2** in D_2O solutions.



^{1}H NMR (D_2O). δ/ppm (**2**) = 8.42, 8.40, (d, 3H, $^3J_{HH}$ = 2.9 Hz, C$^{\gamma}$H); 8.09 (s-br, 2H, C^{1}H); 7.80 (t, 1H, $^3J_{HH}$ = 7.4 Hz, C^{3}H); 7.44 (t, 3H, $^3J_{HH}$ = 7.2 Hz, C^{7}H); 7.40, 7.10, 7.02 (d-br, 3H, C$^{\alpha}$H); 7.24 (t-br, 6H, $^3J_{HH}$ = 7.4 Hz, C^{6}H); 7.06 (t, 2H, $^3J_{HH}$ = 6.7 Hz, C^{2}H); 6.97 (t-br, 6H, C^{5}H); 6.54, 6.33, 6.18 (t-br, 3H, C$^{\beta}$H). δ/ppm (**2^{W}**) = 8.49, 8.45, 8.43 (d, 3H, $^3J_{HH}$ = 2.9 Hz, C$^{\gamma}$H); 7.97 (s-br, 2H, C^{1}H); 7.85 (t, 1H, $^3J_{HH}$ = 7.4 Hz, C^{3}H); 7.50 (t, 3H, $^3J_{HH}$ = 7.2 Hz, C^{7}H); 7.44, 7.02, 6.99 (d-br, 3H, C$^{\alpha}$H); 7.30 (t-br, 6H, C^{6}H); 7.17 (t, 2H, $^3J_{HH}$ = 6.7 Hz, C^{2}H); 6.93 (t-br, 6H, C^{5}H); 6.59, 6.37, 6.20 (t-br, 3H, C$^{\beta}$H). C$^{\delta}$H not observed. ^{31}P{^{1}H} NMR (D_2O). δ/ppm = 50.2 (**2^{W}**), 50.0 (**2**). **2^{W}/2** ratio (from ^{1}H NMR) = 0.1 (t_0), 33.3 (after 48h at 37 °C). In DMEM-d: **2^{W}/2** ratio (from ^{1}H NMR) = 0 (t_0), 1.3 (after 24h at 37 °C).

Figure S41. ^{1}H NMR spectrum (301 MHz, D_2O) of **2** + **2^{W}** at t_0 (blue) and after 48h (red) at 37 °C.

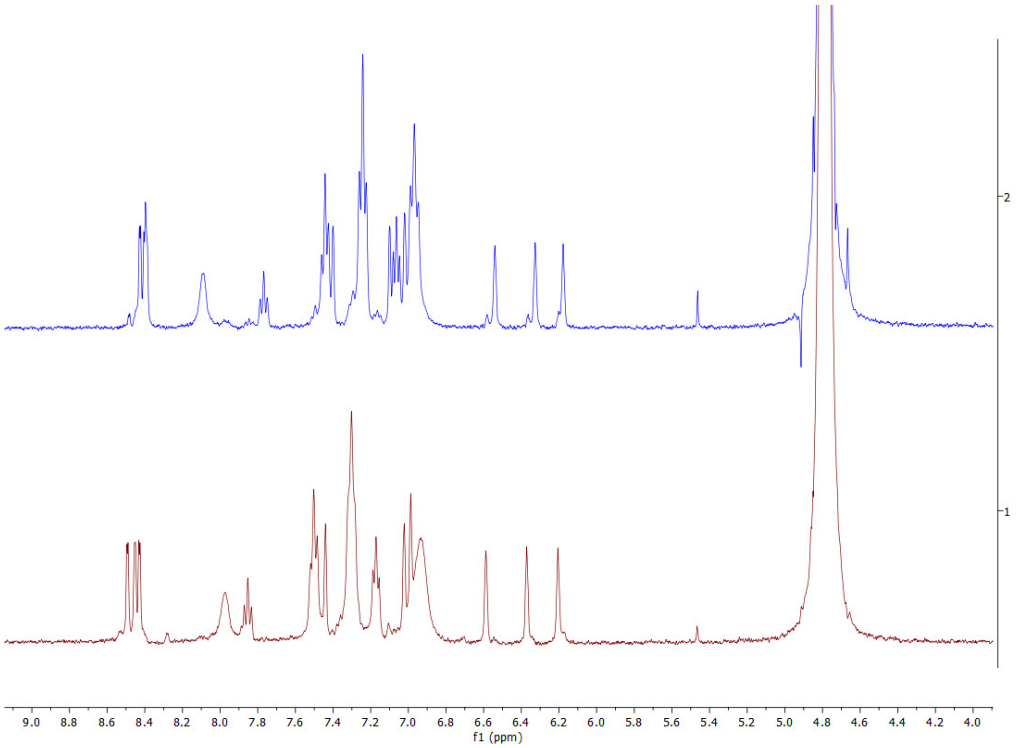


Figure S42. ^{31}P NMR spectrum (121 MHz, D_2O) of **2** + **2^{W}** at t_0 (blue) and after 48h (red) at 37 °C.

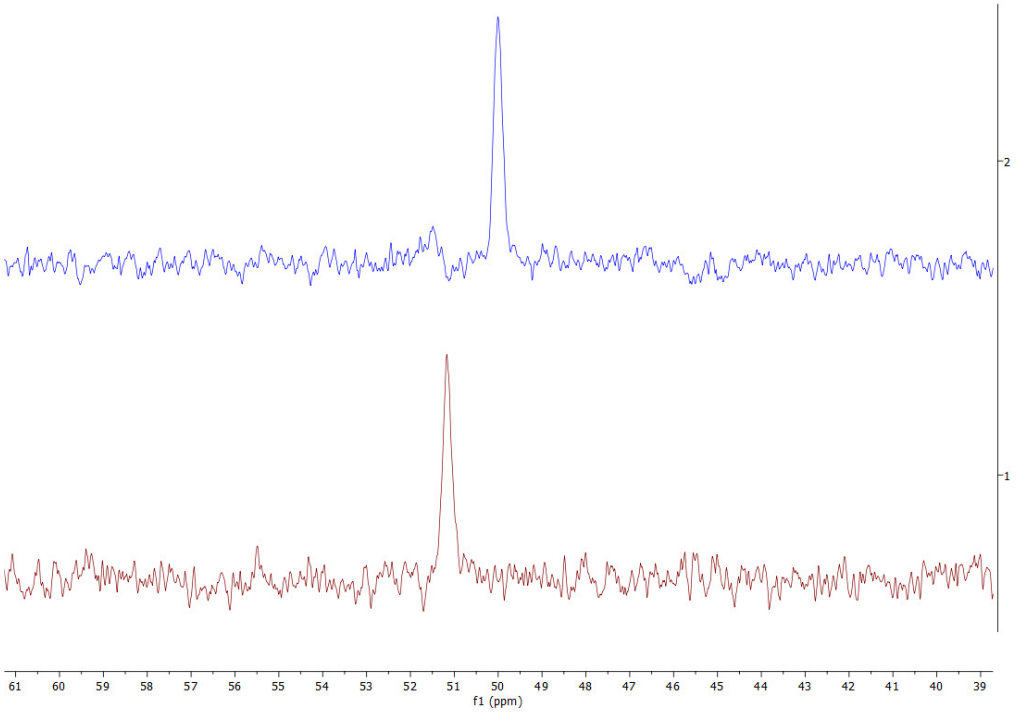
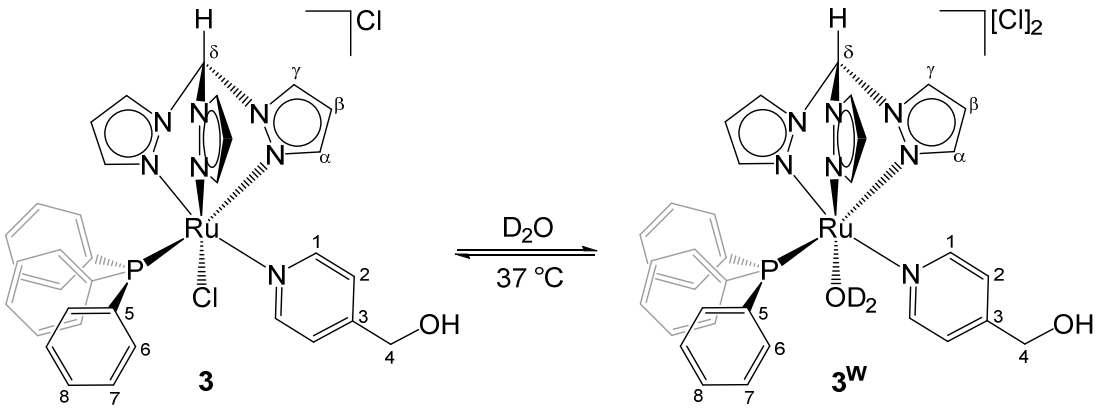


Figure S43. Chloride/water exchange equilibrium for **3** in D_2O solutions.



^{1}H NMR (D_2O). δ/ppm (**3**) = 8.44, 8.41 (m, 3H, $C^{\gamma}H$); 8.05 (s-br, 2H, C^1H); 7.48 (t-br, 3H, C^8H); 7.41 (m, 1H, $C^{\alpha}H$); 7.28 (m, 6H, C^7H); 7.13 (d, 2H, C^2H); 7.05-7.00 (m, 8H, C^6H + $C^{\alpha}H$); 6.56, 6.36, 6.20 (m, 3H, $C^{\beta}H$). $C^{\delta}H$, CH_2, OH not detected. δ/ppm (**3^W**) = 8.51, 8.46, 8.44 (m, 3H, $C^{\gamma}H$); 7.93 (s-br, 2H, C^1H); 7.51 (t-br, 3H, C^8H); 7.45, 7.05, 6.99 (m, 3H, $C^{\alpha}H$); 7.31 (t-br, 6H, C^7H); 7.14 (d-br 2H, C^2H); 6.96 (m, 8H, C^6H); 6.60, 6.39, 6.21 (m, 3H, $C^{\beta}H$). $C^{\delta}H$, CH_2, OH not detected. $^{31}P\{^1H\}$ NMR (D_2O): δ/ppm = 51.1 (**3^W**), 50.0 (**3**). **3^W/3** ratio (from ^{1}H NMR) = 1.4 (t_0), ∞ (after 48h at 37 °C). In DMEM-d: **3^W/3** ratio (from ^{1}H NMR) = 0 (t_0), 1.1 (after 24h at 37 °C).

Experiments on chloride/water exchange. Compound **3** was dissolved in H_2O and maintained at 37 °C for 24h. The solution was then cooled to room temperature, the solvent was evaporated, and the obtained solid was washed with diethyl ether (2 x 3 mL). The isolated yellow powder was dissolved in CD_3OD, then ^{1}H NMR and ^{31}P NMR spectra of the solution were recorded immediately after the preparation of the sample (red), and after 24h at room temperature (green). Both **3** and $\mathbf{3^W}$ were identified in the first recorded spectrum. After 24h, only **3** was detected.

Figure S44. ^{1}H NMR spectra (401 MHz) of $\mathbf{3/3^W}$ in CD_3OD solution. Red: from isolated solid following chloride/water exchange in H_2O at 37 °C; green: same sample maintained in CD_3OD solution at room temperature for 24h.

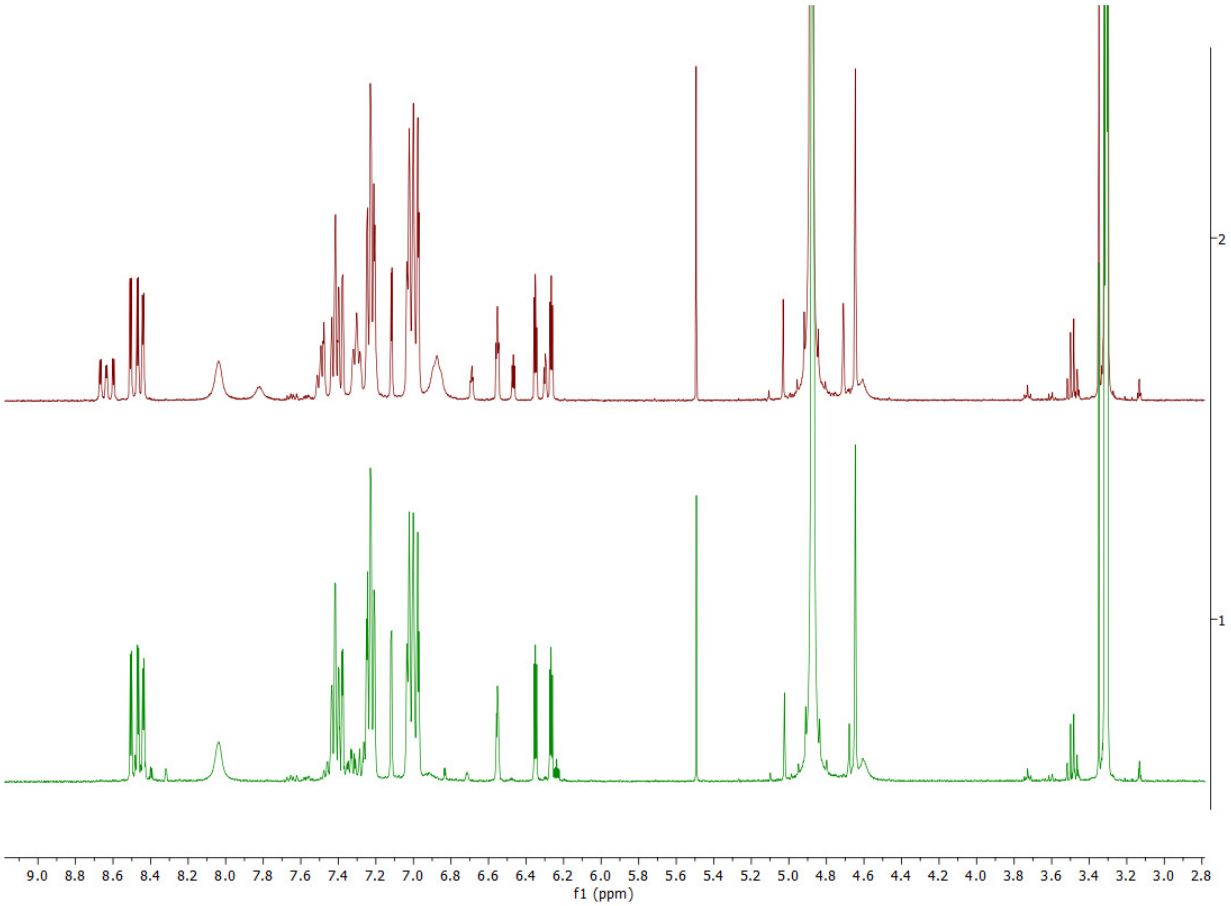


Figure S45. ^{31}P NMR spectra (162 MHz) of **3/3^{W}** in CD_3OD solution. Red: from isolated solid following chloride/water exchange in H_2O at 37 °C; green: same sample maintained in CD_3OD solution at room temperature for 24h.

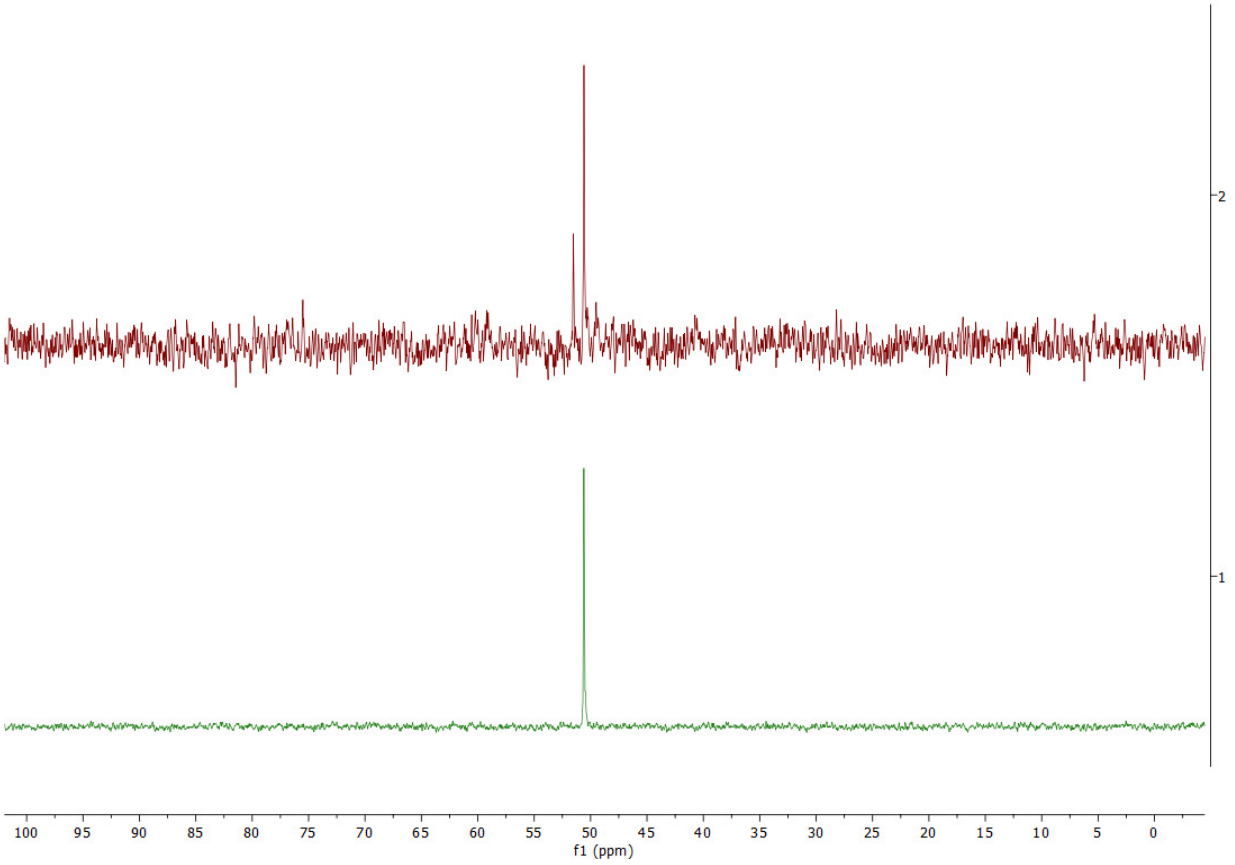


Figure S46. ^{1}H NMR spectrum (301 MHz, D_2O) of **3** + **3^{W}** at t_0 (blue) and after 48h (red) at 37 °C.

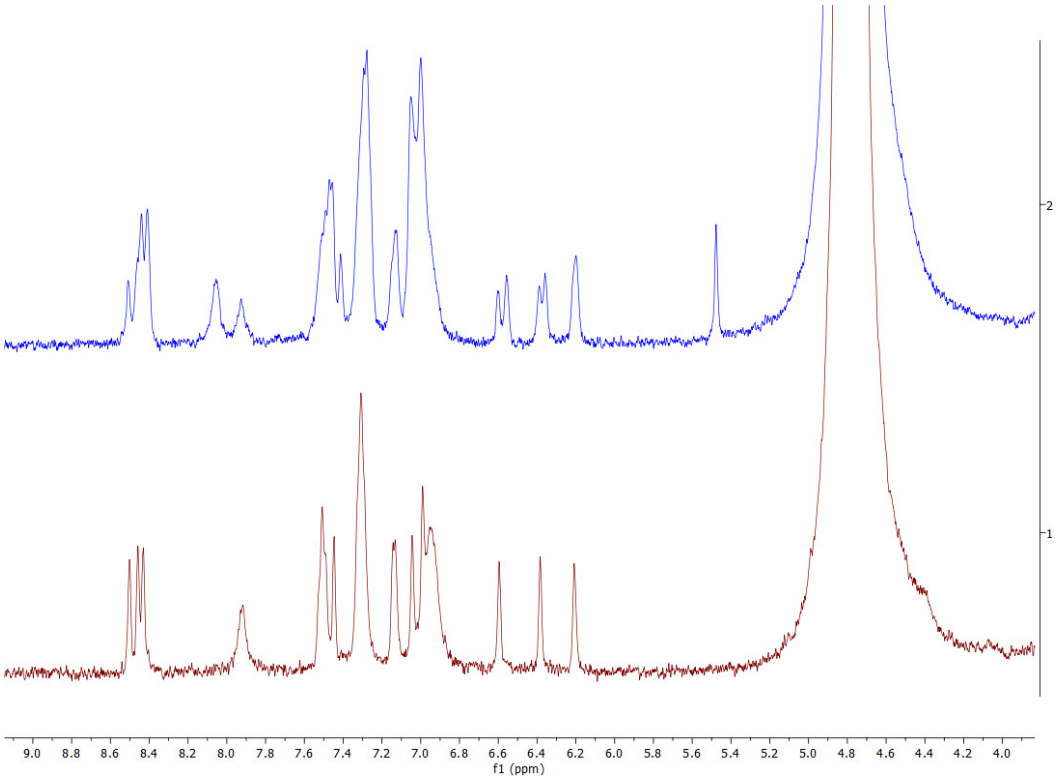


Figure S47. ^{31}P NMR spectrum (121 MHz, D_2O) of **3** + **3^{W}** at t_0 (blue) and after 48h (red) at 37 °C.

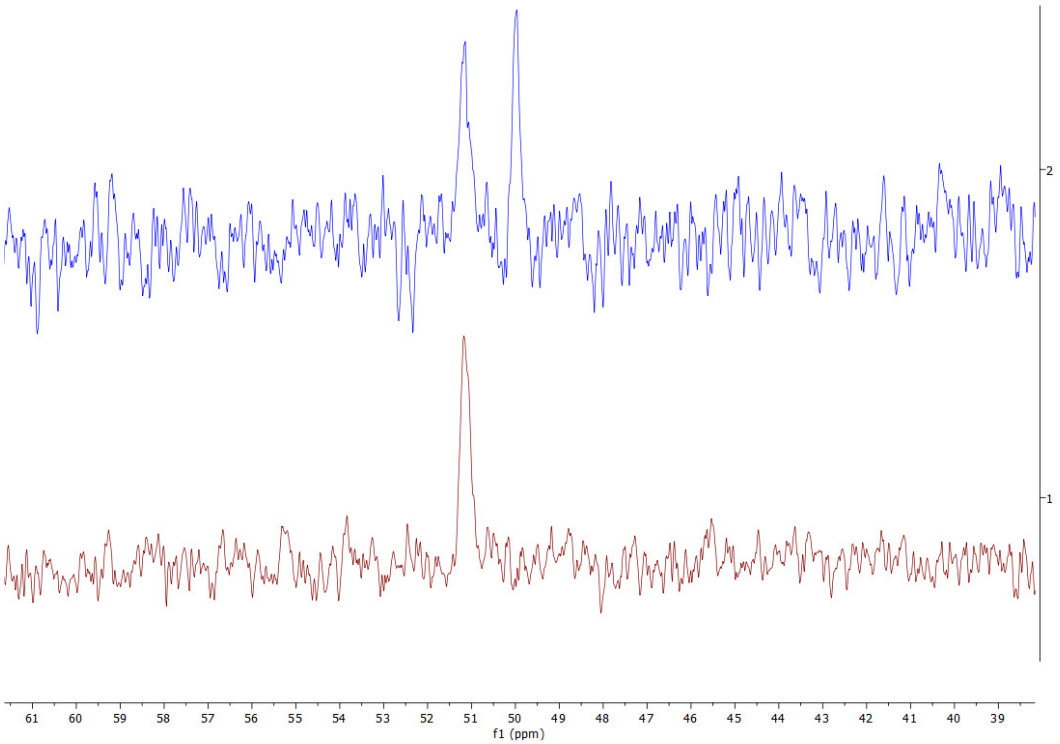
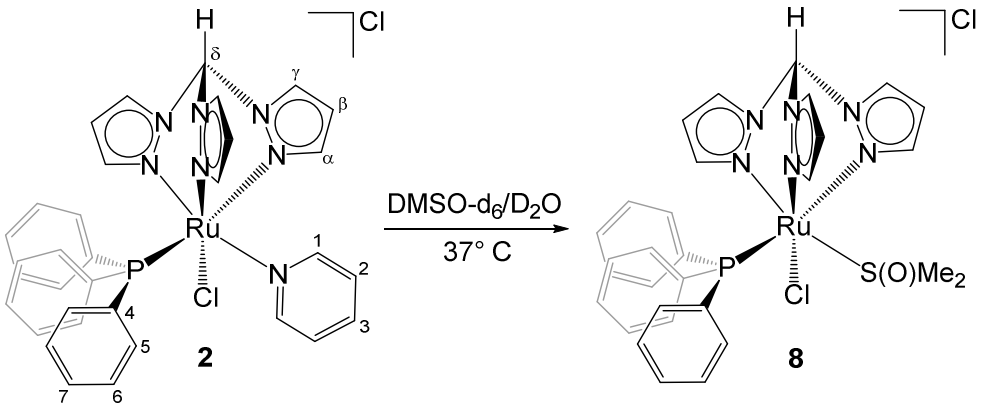
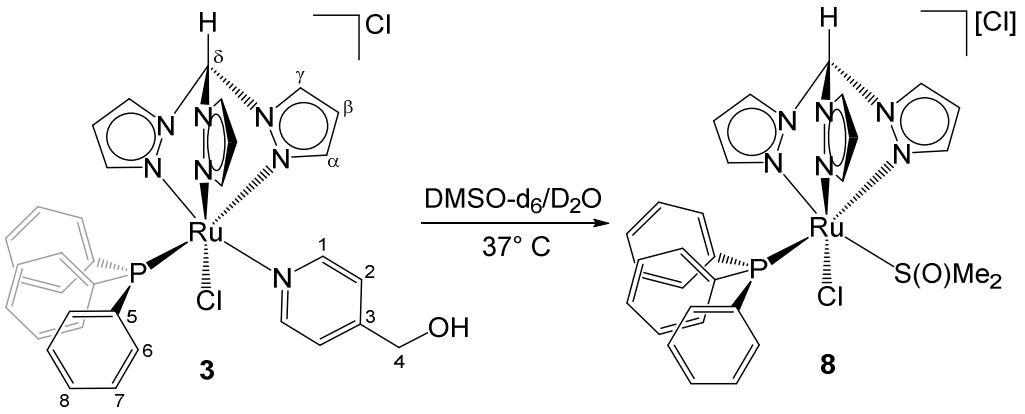


Figure S48. NMR data of **2** in DMSO-d_6/D_2O solution



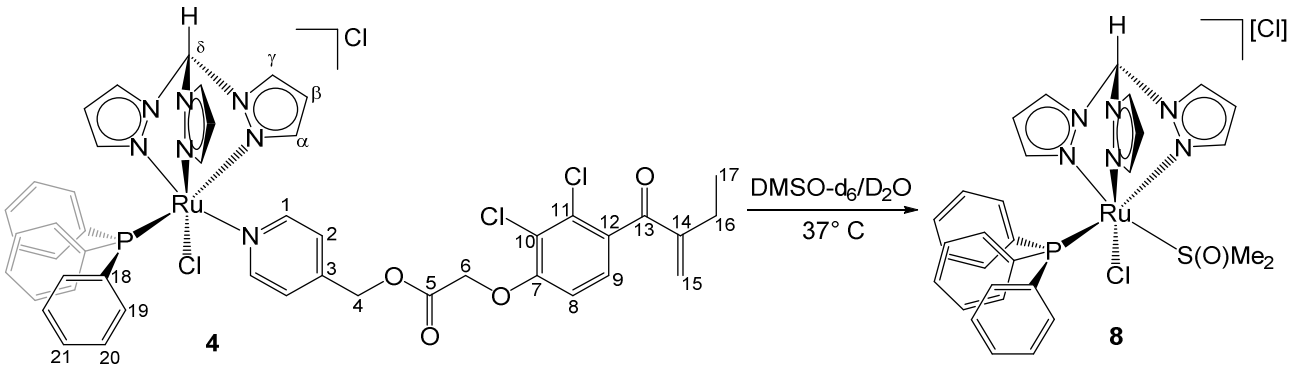
^{1}H NMR (DMSO-d_6/D_2O, 4:1 v/v ratio, **2**): δ/ppm = 9.80 (s, 1H, $C^{\delta}H$); 8.50, 8.56 (d, 3H, $^3J_{HH}$ = 2.8 Hz, $C^{\gamma}H$); 7.94 (s-br, 2H, C^1H); 7.70 (t, 1H, $^3J_{HH}$ = 7.5 Hz, C^3H); 7.39 (t, 3H, $^3J_{HH}$ = 7.5 Hz, C^7H); 7.19 (m, 7H, C^6H + $C^{\alpha}H$); 7.00 (t, 2H, $^3J_{HH}$ = 6.8 Hz, C^2H); 6.97, 6.88 (d, 2H, $^3J_{HH}$ = 2.1 Hz, $C^{\alpha}H$); 6.85 (t-br, 6H, C^5H); 6.55, 6.37, 6.24 (t-br, 3H, $^3J_{HH}$ = 2.6 Hz $C^{\beta}H$). $^{31}P\{^1H\}$ NMR (DMSO-d_6/D_2O, 4:1 v/v ratio, **2**): δ/ppm = 51.3. DMSO-d_6 as reference. **2**/**8** ratio (from ^{1}H NMR) = ∞ (t_0), 3.0 (after 48h at 37 °C).

Figure S49. NMR data of **3** in DMSO-d_6/D_2O solution



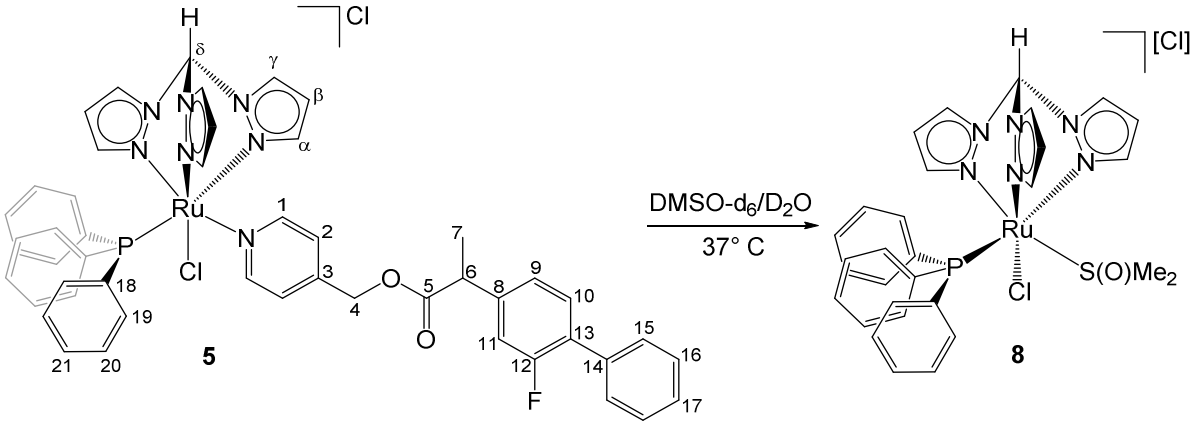
^{1}H NMR (DMSO-d_6/D_2O, 4:1 v/v ratio, **3**): δ/ppm = 9.78 (s, 1H, $C^{\delta}H$); 8.49, 8.45, (d, 3H, $^3J_{HH}$ = 2.8 Hz, $C^{\gamma}H$); 7.86 (s-br, 2H, C^1H); 7.38 (t, 3H, $^3J_{HH}$ = 7.5 Hz, C^8H); 7.24, 7.00, 6.84 (d, 3H, $^3J_{HH}$ = 2.2 Hz, $C^{\alpha}H$); 7.19 (t-br, 6H, $^3J_{HH}$ = 7.70 Hz, C^7H); 6.93 (d, 2H, $^3J_{HH}$ = 6.0 Hz, C^2H); 6.89 (t-br, 6H, C^6H); 6.55, 6.36, 6.24 (t, 3H, $^3J_{HH}$ = 2.5 Hz, $C^{\beta}H$), 4.49 (s, 2H, $^3J_{HH}$ = 4.8 Hz, C^4H). OH not observed. $^{31}P\{^1H\}$ NMR (DMSO-d_6/D_2O, 4:1 v/v ratio, **3**): δ/ppm = 51.2. DMSO-d_6 as reference. **3**/**8** ratio (from ^{1}H NMR) = ∞ (t_0), 6.7 (after 48h at 37 °C).

Figure S50. NMR data of **4** in DMSO-d_6/D_2O solution



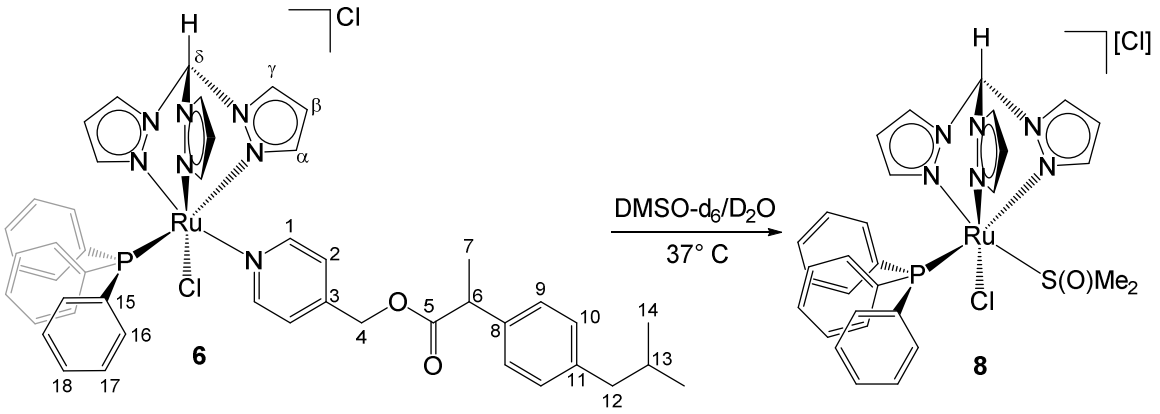
^{1}H NMR (DMSO-d_6/D_2O, 4:1 v/v ratio, **4**): δ/ppm = 8.49, 8.45 (m, 3H, $C^{\gamma}H$); 7.90 (s-br, 2H, C^1H); 7.36 (t, 3H, $^3J_{HH}$ = 7.5 Hz, $C^{21}H$); 7.24-7.12 (m, 9H, $C^{20}H$ + C^9H, $2C^{\alpha}H$); 6.99 (d, 3H, $^3J_{HH}$ = 2.2 Hz, $C^{\alpha}H$); 6.90 (d, 2H, $^3J_{HH}$ = 6.2 Hz, C^2H); 6.83 (t, 6H, $^3J_{HH}$ = 8.3 Hz, $C^{19}H$); 6.81 (m, 1H, C^8H); 6.54, 6.37, 6.22 (m, 3H, $C^{\beta}H$); 6.01, 5.46 (s, 2H, $C^{15}H$); 5.19 (s, 2H, C^4H); 5.11 (s, 2H, C^6H); 2.30 (q, 2H, $^3J_{HH}$ = 7.6 Hz, $C^{16}H$); 1.01 (t, 3H, $^3J_{HH}$ = 7.6 Hz, $C^{17}H$). $C^{\delta}H$ not observed. $^{31}P\{^1H\}$ NMR (DMSO-d_6/D_2O, 4:1 v/v ratio, **4**): δ/ppm = 50.3. DMSO-d_6 as reference. **4/8** ratio (from ^{1}H NMR) = ∞ (t_0), 3.2 (after 48h at 37 °C).

Figure S51. NMR data of **5** in DMSO-d_6/D_2O solution



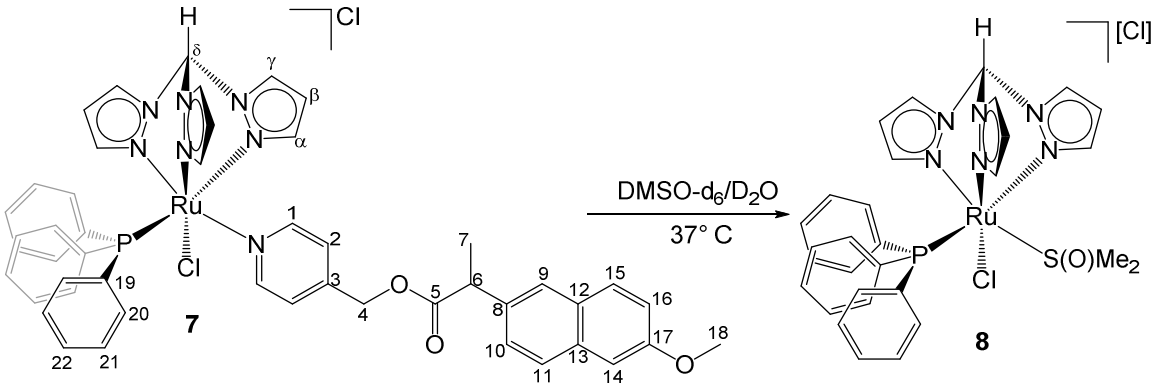
^{1}H NMR (DMSO-d_6/D_2O, 4:1 v/v ratio, **5**): δ/ppm = 8.47, 8.43, 8.41 (m, 3H, $C^{\gamma}H$); 7.80 (s-br, 2H, C^1H); 7.44-7.34 (m, 9H, $C^{15}H$ + $C^{17}H$ + $C^{10}H$ + $C^{16}H$+ C^9H + $C^{11}H$ + $C^{\alpha}H$); 7.21 (t-br, 3H, $C^{21}H$); 7.12 (t-br, 6H, $C^{20}H$); 6.96 (m, 1H, $C^{\alpha}H$); 6.78-6.72 (m, 7H, $C^{19}H$ + $C^{\alpha}H$); 6.65 (m, 2H, C^2H); 6.51, 6.36 (m, 2H, $C^{\beta}H$); 6.10, 6.04 (m, $1H_{A+B}$, $C^{\beta}H$); 5.23-5.00 (m, 2H, C^4H); 4.00 (m, 1H, C^6H); 1.45 (d, 3H, $^3J_{HH}$ = 7.1 Hz, C^7H). $C^{\delta}H$ not observed. $^{31}P\{^1H\}$ NMR (DMSO-d_6/D_2O, 4:1 v/v ratio, **5**): δ/ppm = 50.3. DMSO-d_6 as reference. **5/8** ratio (from ^{1}H NMR) = ∞ (t_0), 2.1 (after 48h at 37 °C).

Figure S52. NMR data of **6** in DMSO-d_6/D_2O and DMSO-d_6 solutions



^{1}H NMR (DMSO-d_6/D_2O, 4:1 v/v ratio): δ/ppm = 8.51, 8.48, 8.45 (m, 3H, $C^{\gamma}H$); 7.75 (s-br, 2H, C^1H); 7.37 (t, 3H, $^3J_{HP}$ = 7.1 Hz, $C^{18}H$); 7.20-7.12 (m, 9H, $C^{17}H$ + $C^{10}H$); 7.03-6.94 (m, 3H, C^9H + $C^{\alpha}H$); 6.79 (m, 7H, $C^{16}H$ + C^2H); 6.56, 6.45, 6.43, 6.42, 6.36, 6.28, 6.26 (m, 5H, $3C^{\beta}H$ + $2C^{\alpha}H$); 5.20, 4.94 (m, $2H_{A+B}$, C^4H); 3.85 (m, 1H, C^6H); 2.29 (m, 2H, $C^{12}H$); 1.57 (m, 1H, $C^{13}H$); 1.38 (m, 3H, C^7H); 0.72, 0.66 (d, $6H_{A+B}$, $^3J_{HH}$ = 6.6, Hz, $C^{14}H$). $C^{\delta}H$ not observed. $^{31}P\{^1H\}$ NMR (DMSO-d_6/D_2O, 4:1 v/v ratio): δ/ppm = 50.2. DMSO-d_6 as reference. **6/8** ratio (from ^{1}H NMR) = ∞ (t_0), 7.7 (after 48h at 37°C). ^{1}H NMR (DMSO-d_6, **6**): δ/ppm = 10.27 (s, 1H, $C^{\delta}H$); 8.65, 8.59 (m, 3H, $C^{\gamma}H$); 7.83 (s-br, 2H, C^1H); 7.40 (t-br, 3H, $C^{18}H$); 7.22 (m, 9H, $C^{17}H$ + $C^{10}H$); 7.07 (m, 2H, C^9H); 6.98 (m, 1H, $C^{\alpha}H$); 6.88 (m, 7H, $C^{16}H$ + C^2H); 6.65, 6.57, 6.44, 6.34, 6.31 (m, 5H, $3C^{\beta}H$ + $2C^{\alpha}H$); 5.22, 5.03 (m, 2H, C^4H); 3.90 (q-br, 1H, C^6H); 2.36 (m, 2H, $C^{12}H$); 1.68 (m, 1H, $C^{13}H$); 1.43 (m, 3H, C^7H); 0.77 (d, $6H_{A+B}$, $^3J_{HH}$ = 5.8, Hz, $C^{14}H$). $^{31}P\{^1H\}$ NMR (DMSO-d_6, **6**): δ/ppm = 50.7. **6/8** ratio (from ^{1}H NMR) = ∞ (t_0), 5.5 (after 48h at 37 °C).

Figure S53. NMR data of **7** in DMSO-d_6/D_2O solution



^{1}H NMR (DMSO-d_6/D_2O, 4:1 v/v ratio, **7**): δ/ppm = 8.47, 8.44, 8.43 (m, 3H, $C^{\gamma}H$); 7.72-7.66 (m, 5H, C^1H + $C^{11}H$ + C^9H + $C^{15}H$); 7.39-7.30 (m, 4H, $C^{22}H$ + $C^{10}H$); 7.21 (d, 1H, $^3J_{HH}$ = 6.7 Hz, $C^{16}H$); 7.17 (m, 1H, $C^{\alpha}H$); 7.13-7.07 (m, 7H, $C^{21}H$ + $C^{14}H$); 6.96 (m, 1H, $C^{\alpha}H$); 6.76 (t, 6H, $^3J_{HP}$ = 8.1 Hz, $C^{20}H$); 6.68, 6.65 (m, 3H, C^2H + $C^{\alpha}H$); 6.53, 6.36, 6.22 (m, 3H, $C^{\beta}H$); 5.19-4.96 (m, 2H, C^4H); 4.06 (m, 1H, C^6H); 3.80 (s, 3H, $C^{18}H$); 1.49 (m, 3H, C^7H). $C^{\delta}H$ not observed. $^{31}P\{^1H\}$ NMR (DMSO-d_6/D_2O 4:1 v/v ratio, **7**): δ/ppm = 50.2. DMSO-d_6 as reference. **7/8** ratio (from ^{1}H NMR) = ∞ (t_0), 10 (after 48h at 37 °C).

Figure S54. ^{31}P NMR spectrum (121 MHz) of **3** + **8** in DMSO-d_6/D_2O (4:1 v/v ratio) (blue) and DMSO-d_6 (red) after 24h at 37 °C.

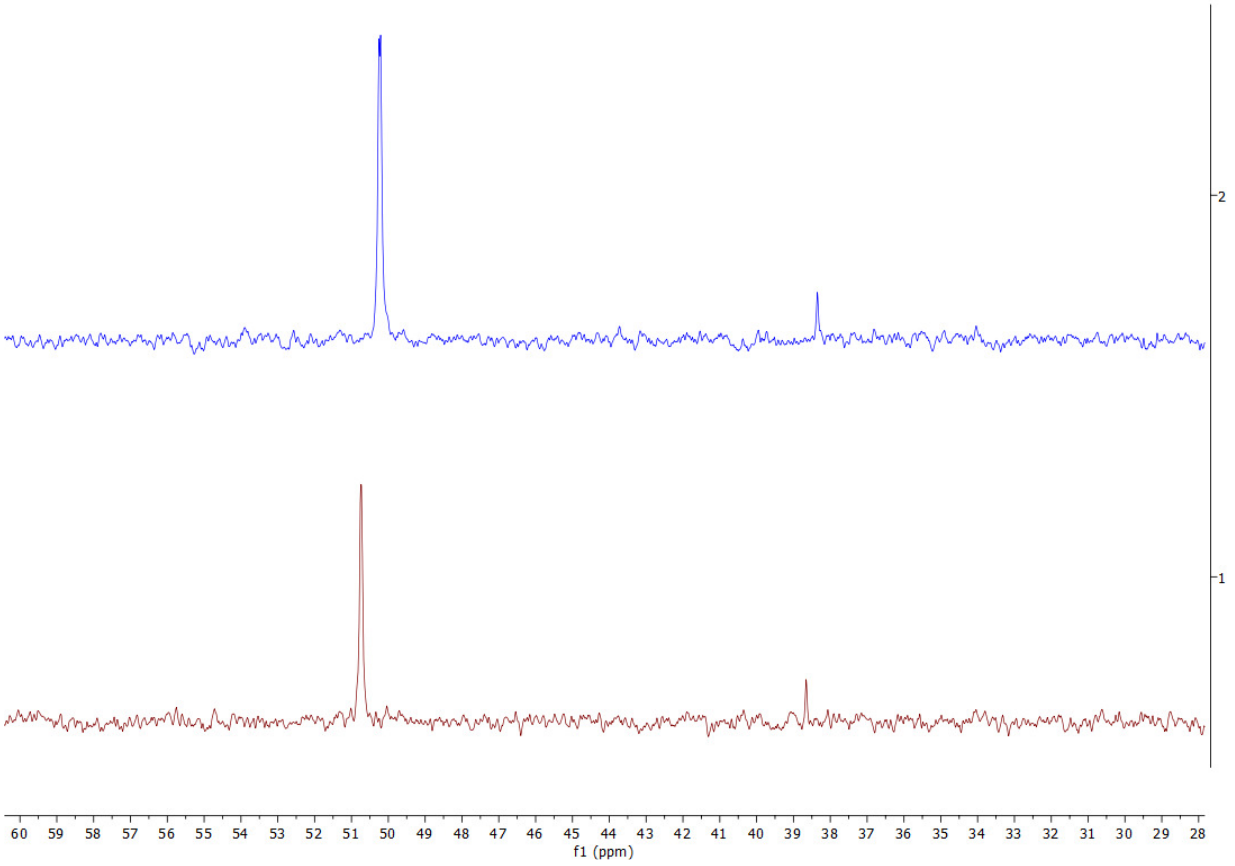


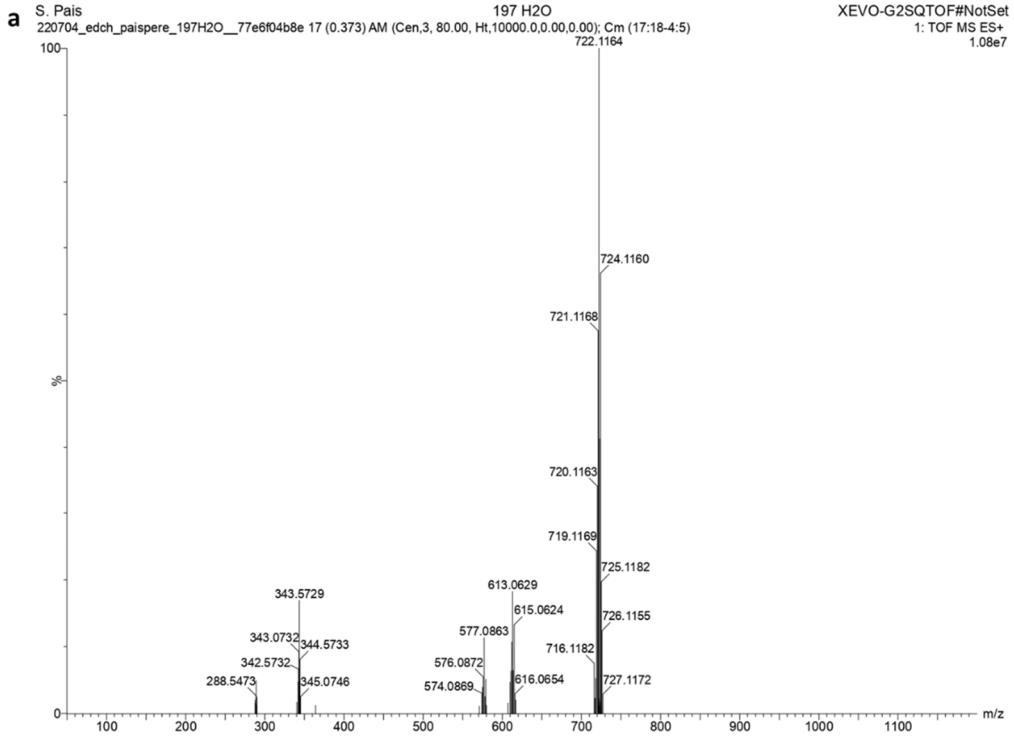
Table S3. Relative amounts of aquo-complexes in aqueous solutions after a variable time at 37 °C (calculated from ^{1}H NMR spectra).

Compound	Aquo species % in D_2O at t_0	Aquo species % in D_2O after 48h	Aquo species % in DMEM-d/DMSO-d_6 at t_0	Aquo species % in DMEM-d/DMSO-d_6 after 24h
2	13	97	0	77
3	42	93	0	87

Table S4. Relative amounts of residual starting material in aqueous solutions after a variable time at 37 °C (calculated from ^{1}H NMR spectra, Me_2SO_2 as internal standard); IC_{50} values on A2780 cancer cell line; Log P_{ow} values (see also Table 2).

Compound	Residual complex % in D_2O/DMSO-d_6 after 48h	Residual complex % in DMEM-d/DMSO-d_6 after 24h	IC_{50}	Log P_{ow}
2	77	-	8 ± 3	-0.04 ± 0.05
3	87	-	26 ± 10	-0.25 ± 0.04
4	77	89	12 ± 2	0.46 ± 0.02
5	81	90	4.5 ± 0.6	> 2
6	87	85	5 ± 1	> 2
7	86	89	6 ± 1	> 2

Figure S55. HR-ESI-MS spectra of **3** in H_2O. a) Recorded immediately after the preparation of the sample; b) recorded after 3h at RT.



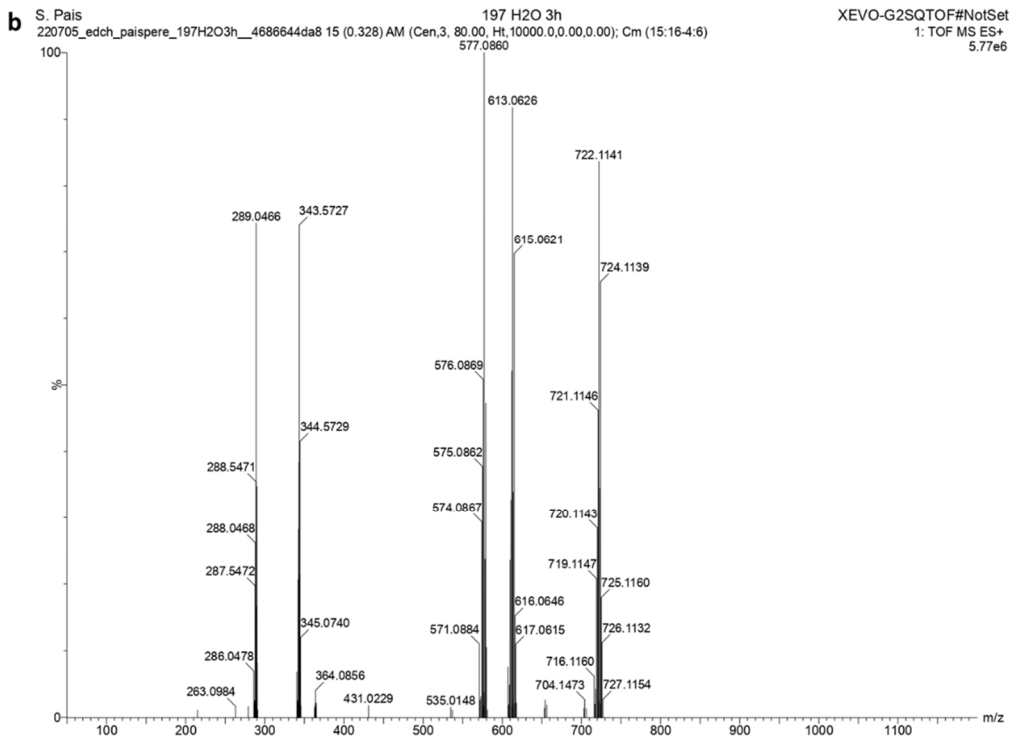


Figure S56. Graphical representation of IC_{50} values obtained for complexes **2-7** on three cell lines.