Supplementary Information (SI) for Inorganic Chemistry Frontiers.
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Supporting Information

Heavy Atom engineeringof Ru(II) Complex based Sonosensitizers for Enhancing Antifungal Therapy

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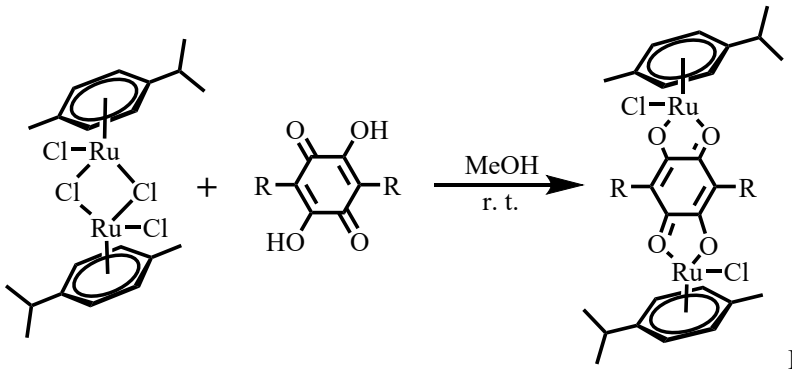
The Synthesis of complexes **RuH**, **RuCl** and **RuBr**.



R=H, Cl and Br

RuH: Under a nitrogen atmosphere, dissolve dichloro(p-cymene)ruthenium(II) dimer (612.0 mg, 1 mmol, 1 equiv) and 2,5-dihydroxy-1,4-benzoquinone (140.0 mg, 1 mmol, 1 equiv) in 20 mL of anhydrous methanol in a 50 mL round-bottom flask. Stir the reaction mixture at room temperature for 12 h. Afterward, separate the resulting solid using vacuum filtration, and wash the product sequentially with methanol (3 × 30 mL) and diethyl ether (3 × 30 mL). Dry the solid under vacuum to collect the red solid **RuH** (610.5 mg, 90.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 2H), 5.74 (d, J = 5.7 Hz, 4H), 5.49 (d, J = 5.6 Hz, 4H), 3.07 – 2.98 (m, 2H), 2.41 (s, 6H), 1.44 (d, J = 6.9 Hz, 12H). ^{13}C NMR (100 MHz, MeOD) δ 184.82, 121.89, 118.83, 101.09, 97.37, 80.81, 78.86, 31.35, 20.93, 17.22. HR-MS is shown in **Fig. S3**: m/z = 650.334 for $[M\text{-}Cl]^+$.

RuCl: Under a nitrogen atmosphere, dissolve dichloro(p-cymene)ruthenium(II) dimer (612.0 mg, 1 mmol, 1 equiv) and chloranilic acid (208.9 mg, 1 mmol, 1 equiv) in 20 mL of anhydrous methanol in a 50 mL round-bottom flask. Stir the reaction mixture at room temperature for 12 hours. Afterward, separate the resulting solid using vacuum filtration, and wash the product sequentially with methanol (3 × 30 mL) and diethyl ether (3 × 30 mL). Dry the solid under vacuum to collect the reddish-brown solid **RuCl** (693.7 mg, 93.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (d, J = 6.1 Hz, 4H), 5.51 (d, J = 6.0 Hz, 4H), 3.08–2.88 (m, 2H), 2.37 (s, 6H), 1.40 (d, J = 6.9 Hz, 12H).^{13}C NMR (100 MHz, MeOD) δ 178.26, 122.42, 118.88, 101.74, 98.17, 81.13, 79.29, 31.68, 21.11, 16.96. HR-MS is shown in **Fig. S7**: m/z = 718.256 for $[M\text{-}Cl]^+$.

RuBr: Under a nitrogen atmosphere, dissolve dichloro-bis(4-methylisopropylbenzene)ruthenium(II) (612.0 mg, 1 mmol, 1 equiv) and bromanilic acid (297.8 mg, 1 mmol, 1 equiv) in 20 mL of anhydrous methanol in a 50 mL round-bottom flask. Stir the reaction mixture at room temperature for 12 h. Afterward, separate the resulting solid using vacuum

filtration, and wash the product sequentially with methanol (3 × 30 mL) and diethyl ether (3 × 30 mL). Dry the solid under vacuum to collect the reddish-brown solid **RuBr** (792.3 mg, 95.1%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (d, J = 5.8 Hz, 4H), 5.51 (d, J = 5.7 Hz, 4H), 3.05 – 2.87 (m, 2H), 2.39 (s, 6H), 1.43 (d, J = 6.8 Hz, 12H). ^{13}C NMR(100 MHz, MeOD) δ 179.24, 121.98, 118.91, 101.89, 97.45, 80.76, 79.29, 31.54, 21.16, 17.24. HR-MS is shown in **Fig. S9**: m/z = 802.812 for $[M-Cl]^+$.

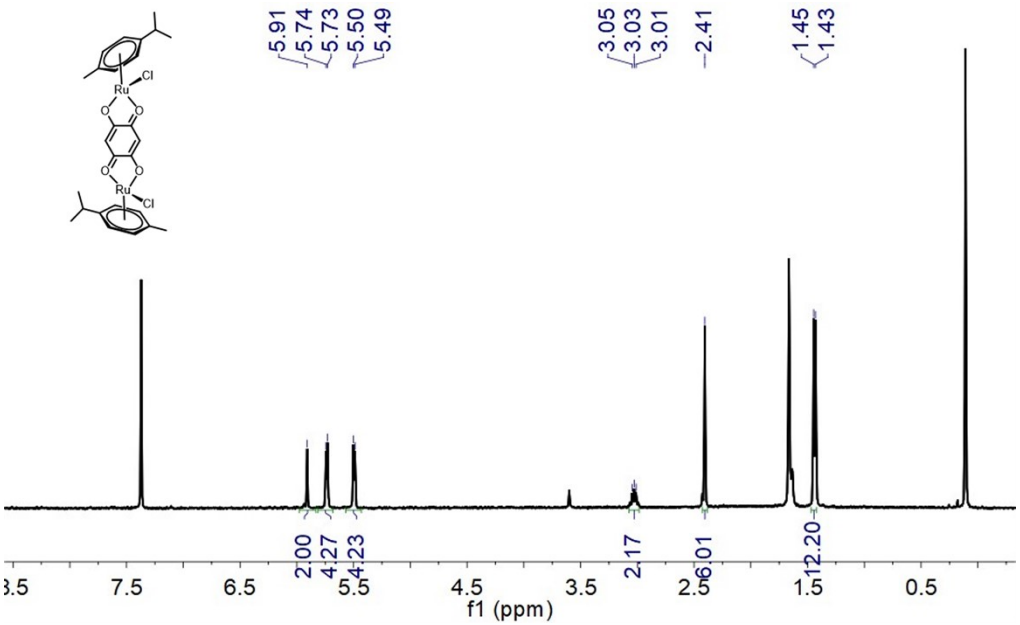


Fig. S1 ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of **RuH**.

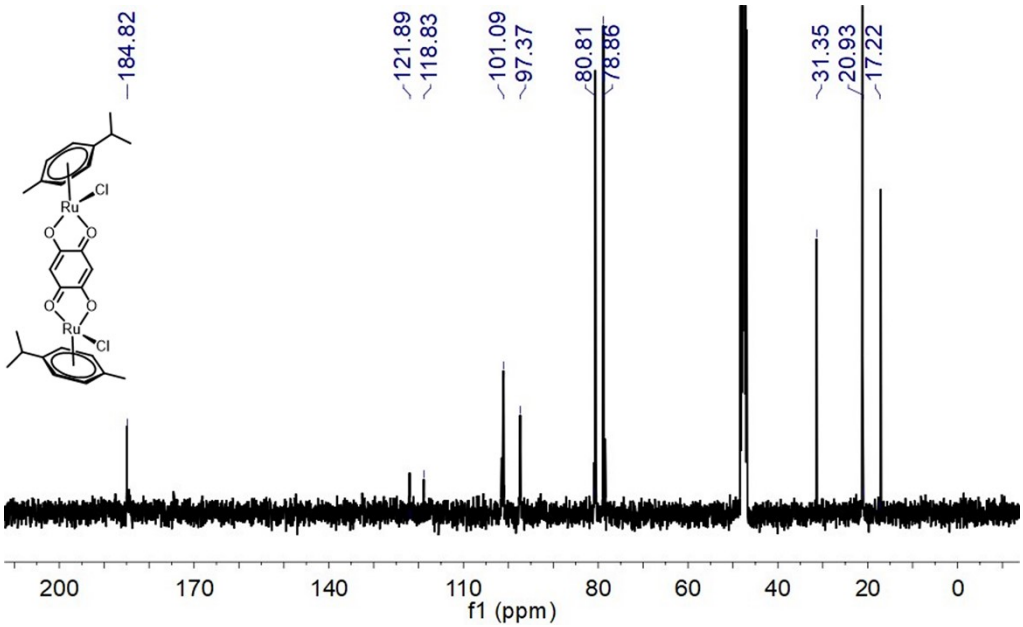


Fig. S2 ^{13}C NMR spectrum (100 MHz, MeOD, 298 K) of **RuH**.

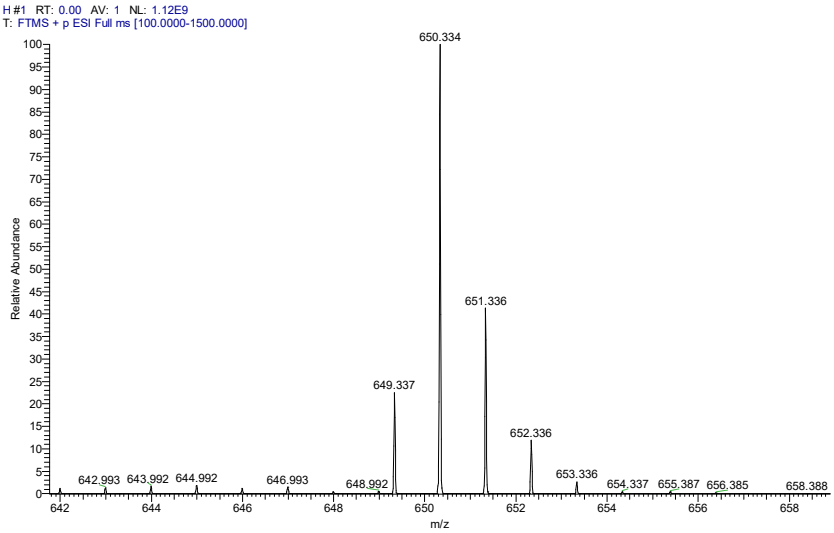


Fig. S3 High-Resolution Mass Spectrometry **(**HR-MS) spectrum of **RuH**.

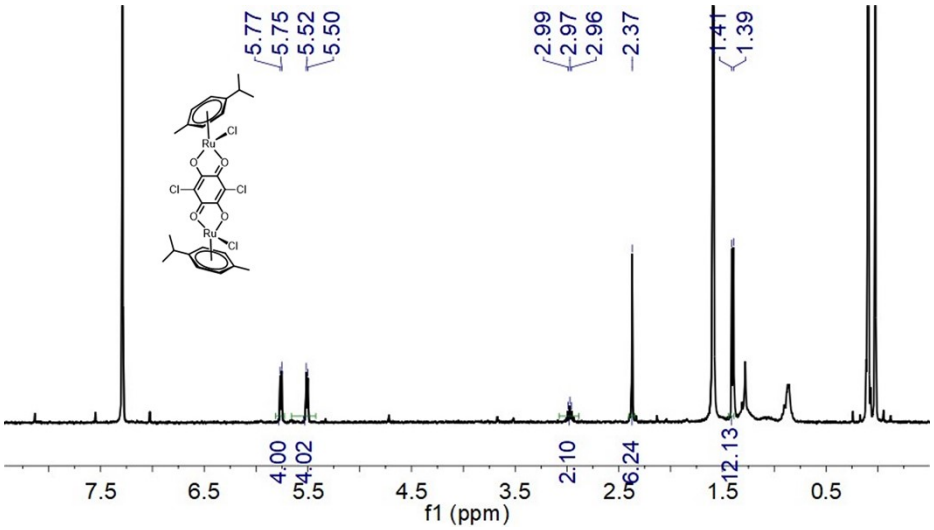


Fig. S4 ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of **RuCl**.

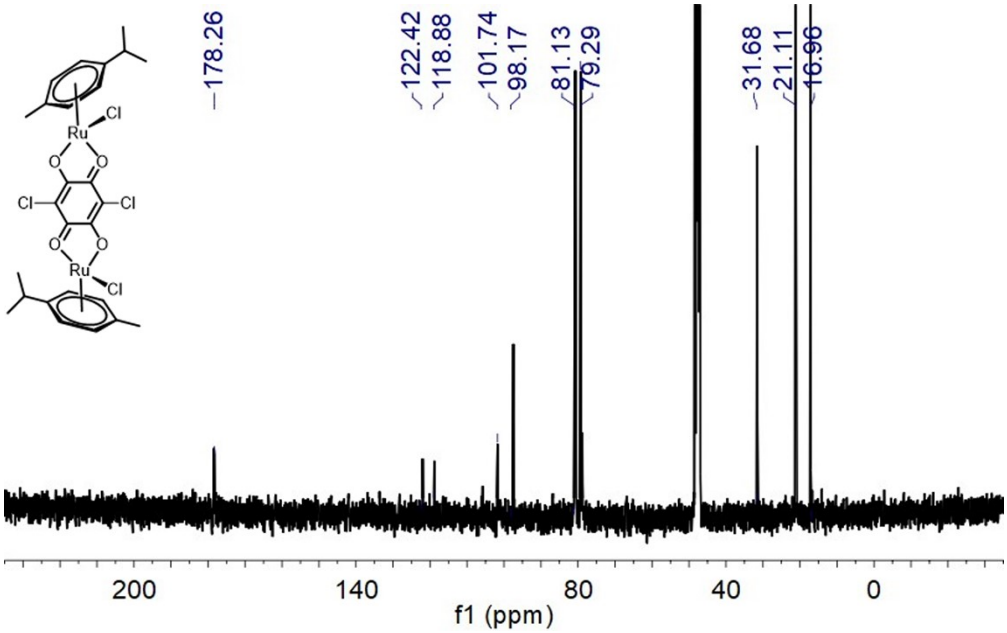


Fig. S5 ^{13}C NMR spectrum (100 MHz, MeOD, 298 K) of **RuCl**.

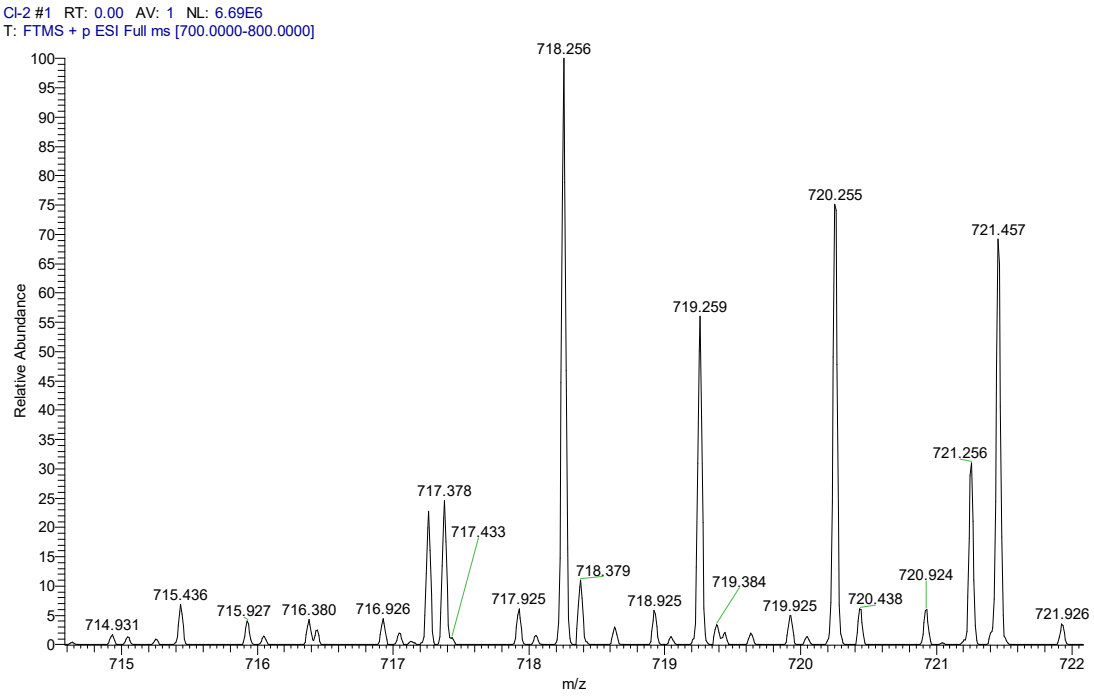


Fig. S6 HR-MS spectrum of **RuCl**.

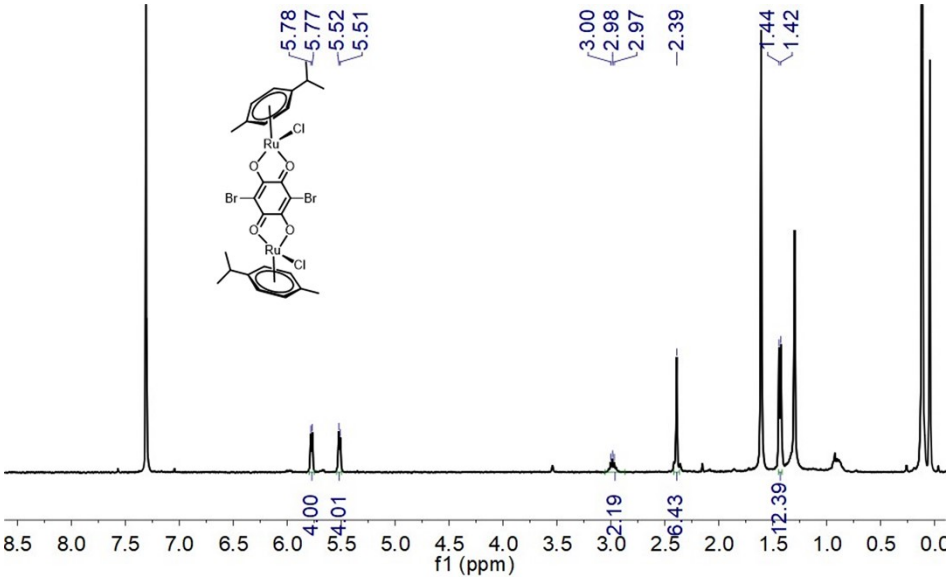


Fig. S7 ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of **RuBr**.

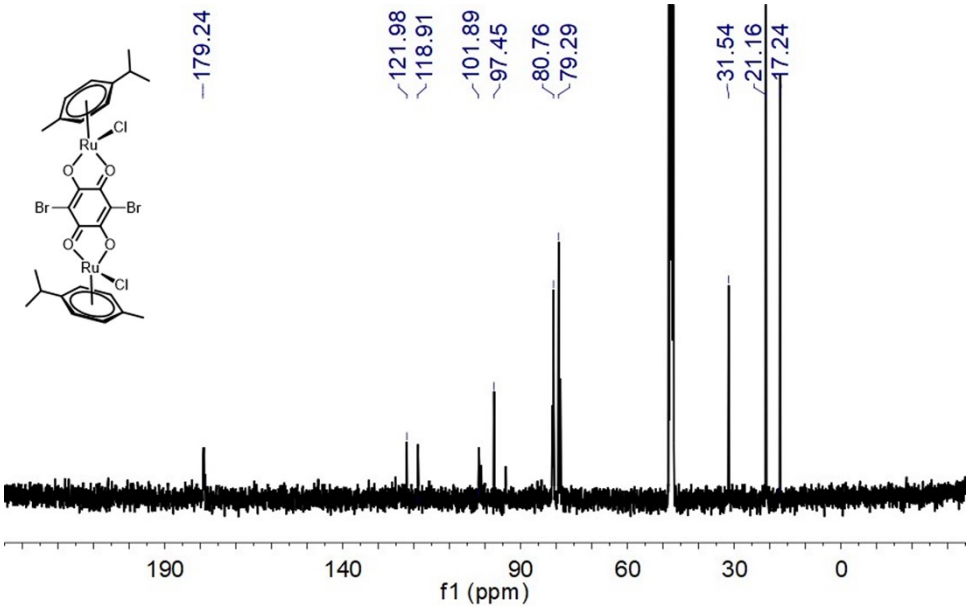


Fig. S8 ^{13}C NMR spectrum (100 MHz, MeOD, 298 K) of **RuBr**.

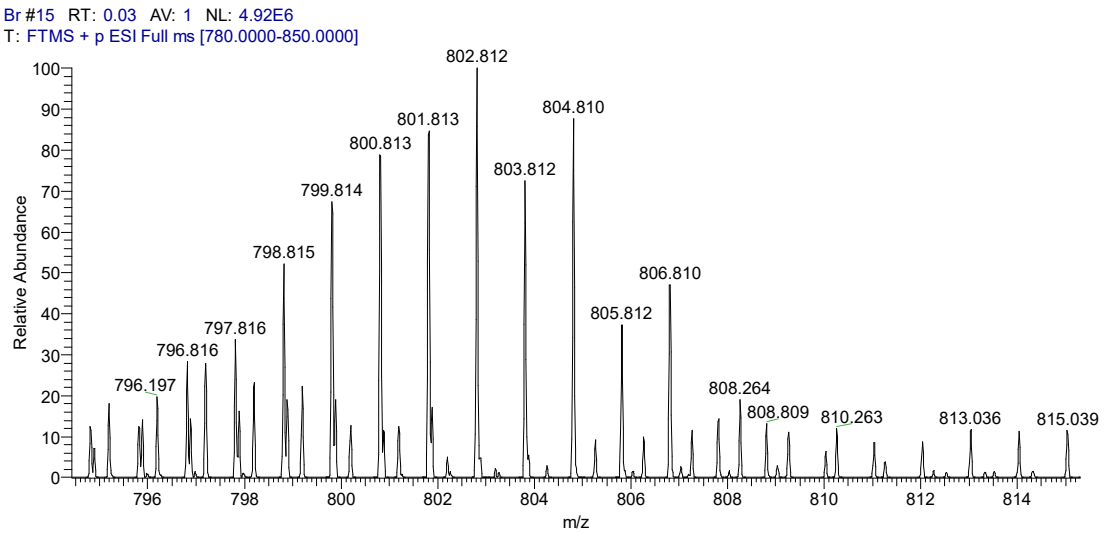


Fig. S9 HR-MS spectrum of **RuBr**

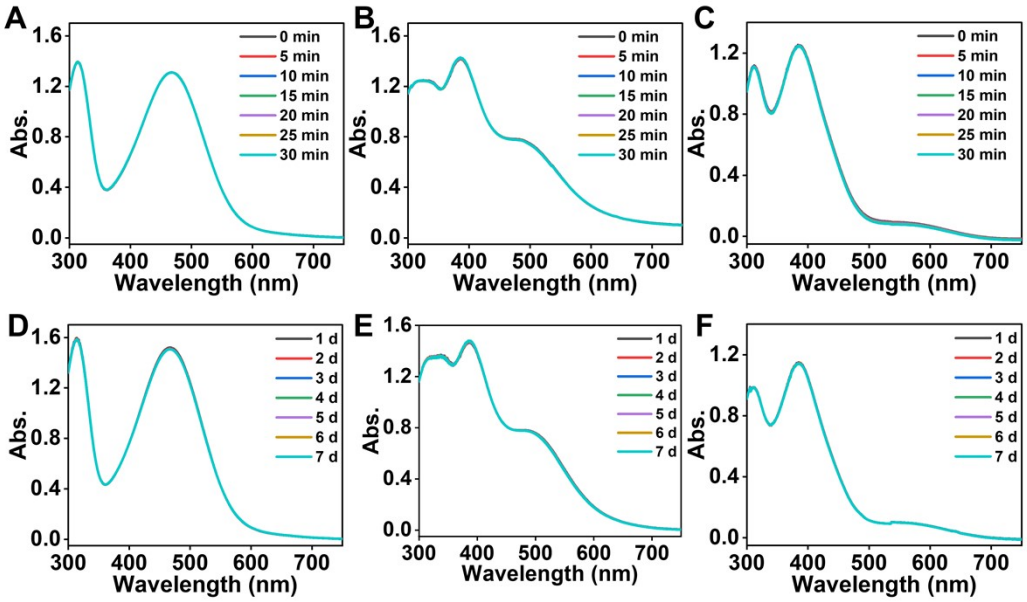


Fig. S10 The stability of **RuH**, **RuCl** and **RuBr** under US irradiation(1 MHz, 50% duty cycle, 1 W/cm^2) for 30 min (A) and 7 days in PBS (B).

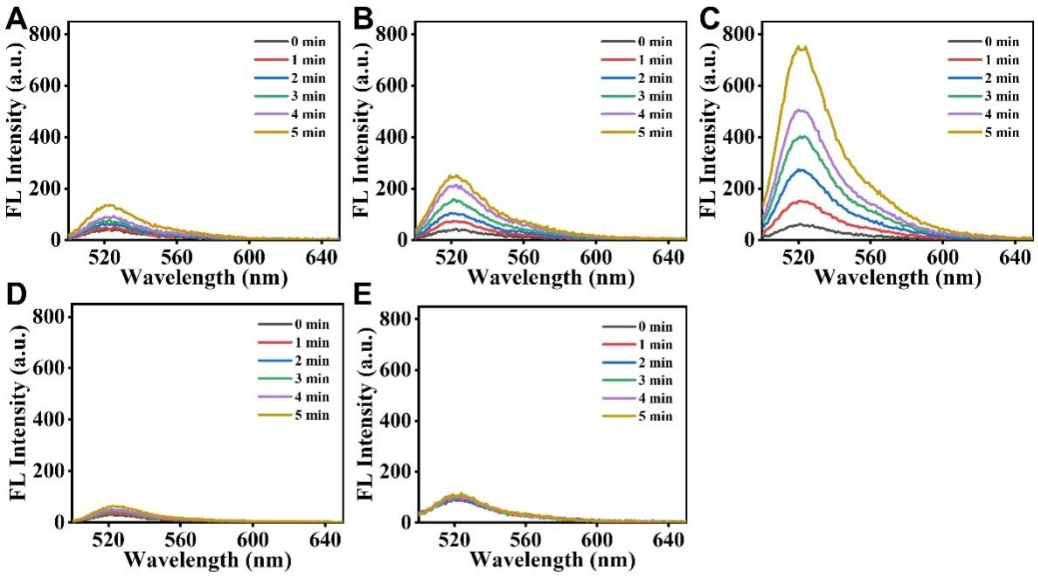


Fig. S11 FL intensity of DCFH by US-activity with **RuH**(A), **RuCl** (B), **RuBr** (C), $Ru(bpy)_3Cl_2$ (D) and H_2O (E) for 5 min.

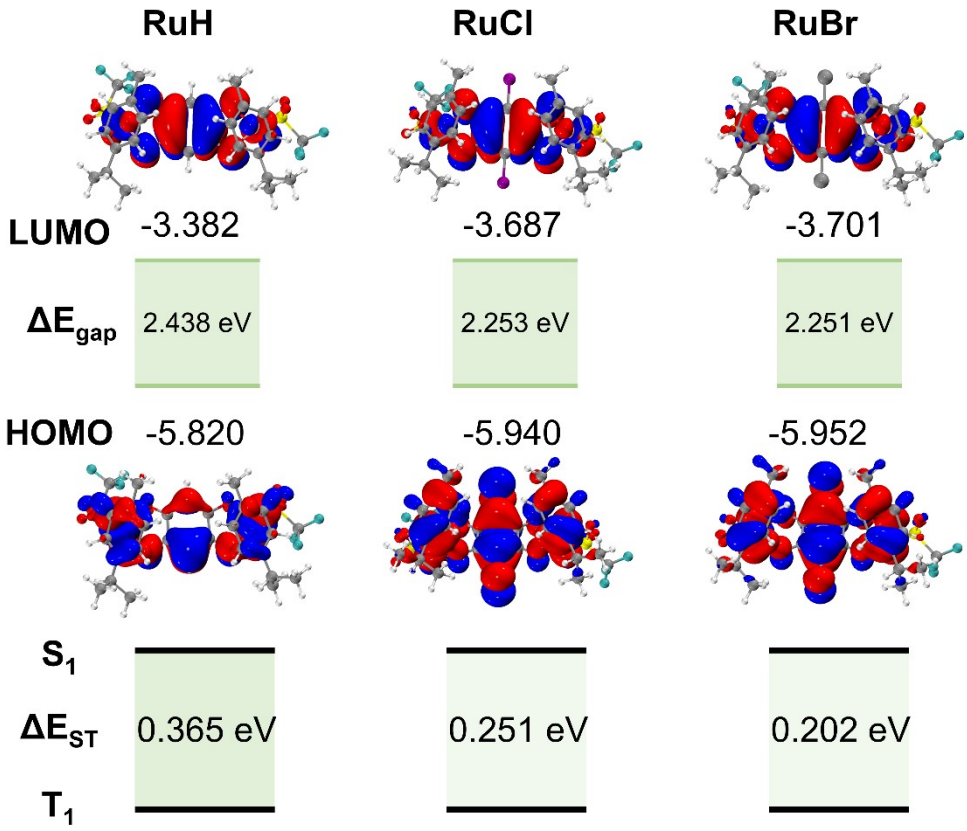


Fig. S12 LUMO, HOMO, E_{gap} and ΔE_{ST} of **RuH**, **RuCl**, **RuBr**.

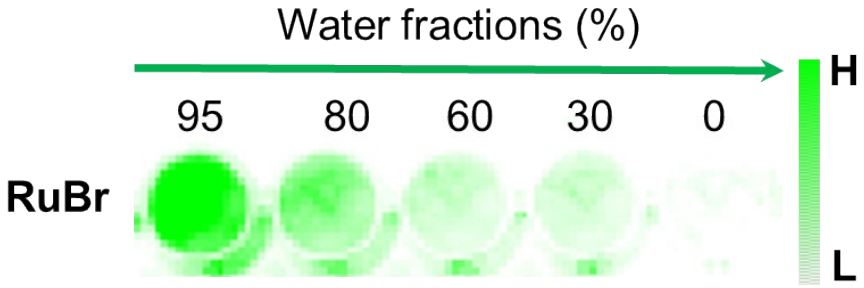


Fig. S13 FL images of DCFH under US irradiation (1 MHz, 50% duty cycle, 1 W/cm^2, 1 min) with **RuBr** with different water fractions.

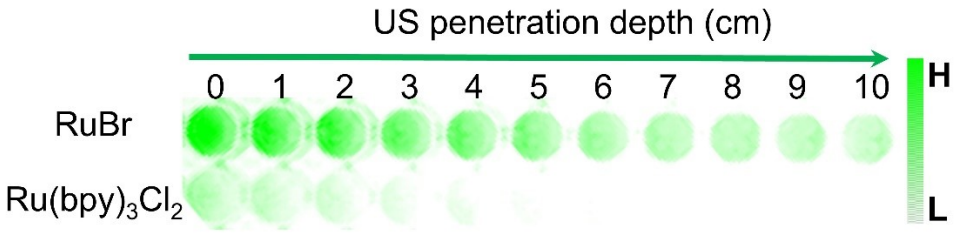


Fig. S14 FL images of DCFH under ultrasound irradiation (1 MHz, 50% duty cycle, 1 W/cm^2, 1 min) with **RuBr** and **Ru(bpy)$_3$Cl$_2$** with different depth of agarose blocks (containing 1% intralipid and 1% agarose).

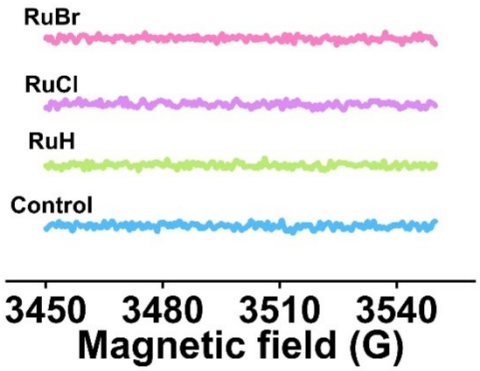


Fig. S15 ESR spectra of **RuH**, **RuCl** and **RuBr** under US irradiation (1 MHz, 50% duty cycle, 1 W/cm^2, 1 min) with DMPO as capture agent.

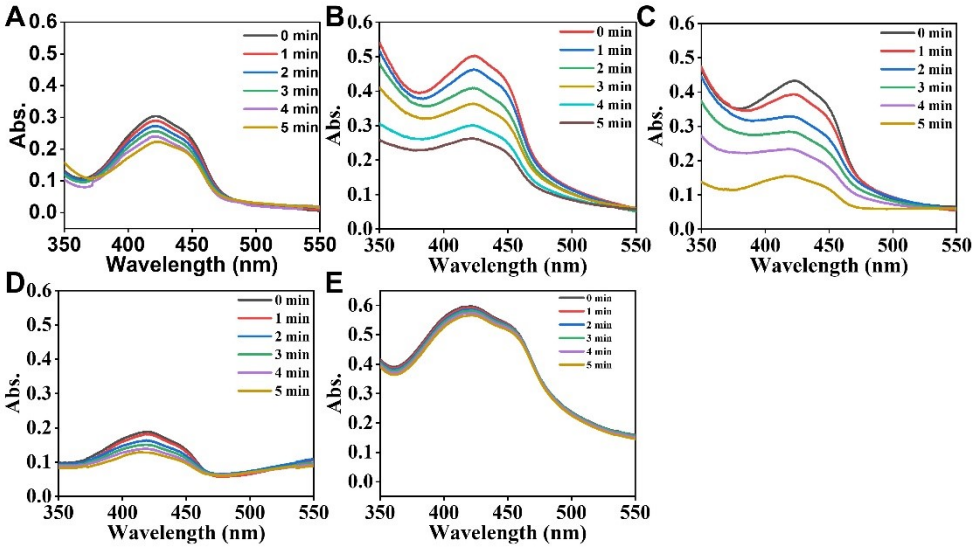


Fig. S16 UV-vis spectrum of DPBF by US-activity (1 MHz, 50% duty cycle, 1 W/cm^2) with **RuH** (A), **RuCl** (B), **RuBr** (C), $Ru(bpy)_3Cl_2$(D) and H_2O (E) for 5 min.

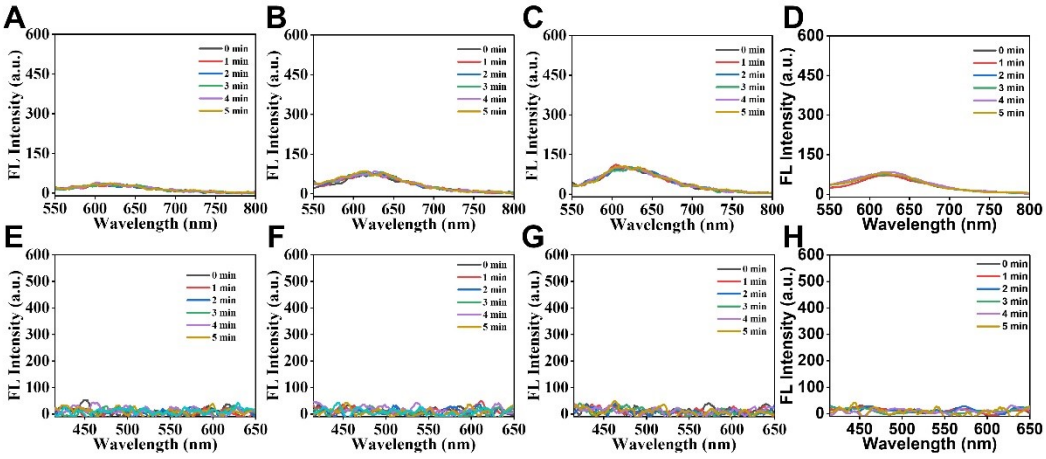


Fig. S17 The detection of O_2^- in **RuH** (A),**RuCl** (B),**RuBr** (C) and H_2O (D) solution by using DHE (5 μM) after US irradiation (1 MHz, 50% duty cycle, 1 W/cm^2, 5 min), λex = 488 nm. The detection of •OH in **RuH** (E),**RuCl** (F), **RuBr** (G) and H_2O (H) solution using 3-CCA (5 μM) after US irradiation (1 MHz, 50% duty cycle, 1 W/cm^2, 5 min), λ_{ex} = 405 nm.

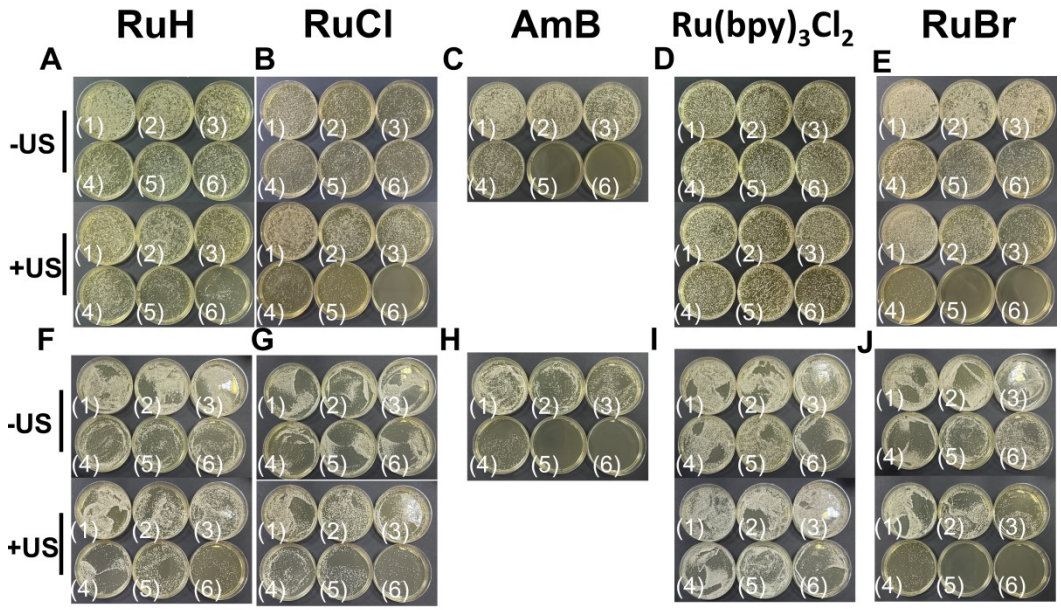


Fig. S18 PA images of C. albicans (A-E) and C. glabrata (F-J) after incubated with different concentration of **RuH**, **RuCl**, **RuBr**, $Ru(bpy)_3Cl_2$ and AmB with/without US irradiation (1 MHz, 50% duty cycle, 1 W/cm2) : 0 μM (1), 2.5 μM (2), 5 μM (3), 10 μM (4), 20 μM (5), 40 μM (6).

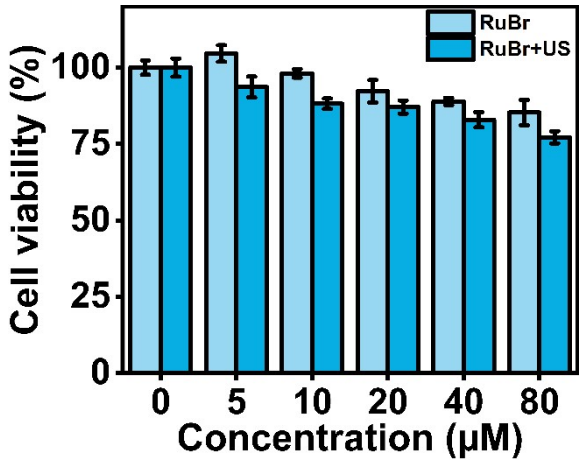


Fig. S19 The relative cellular viability of L929 cells treated with various concentrations of **RuBr** (2.5-40 μM) with/without US irradiation (1 MHz, 50% duty cycle, 1 W/cm^2, 5 min) (n = 3 independent experiments).

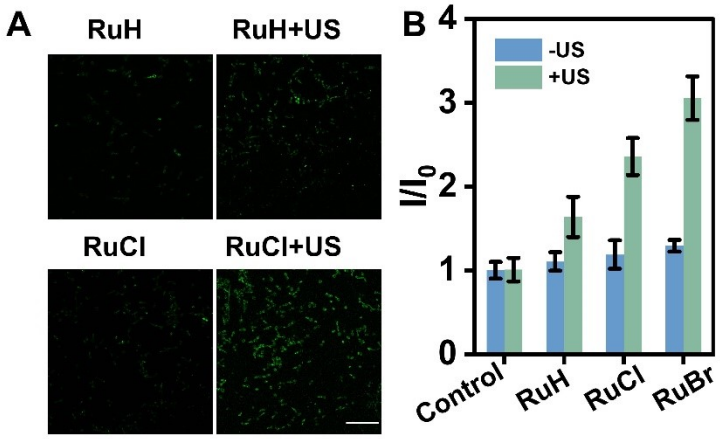


Fig. S20 Fluorescence images (A) and semiquantitative statistics of ROS fluorescence intensity (B) of *C. albicans* stained by DCFH after incubation with **RuH**, **RuCl** and **RuBr**, with or without US irradiation (1 W/cm^2, 5 min). Scale bar: 20 μm.

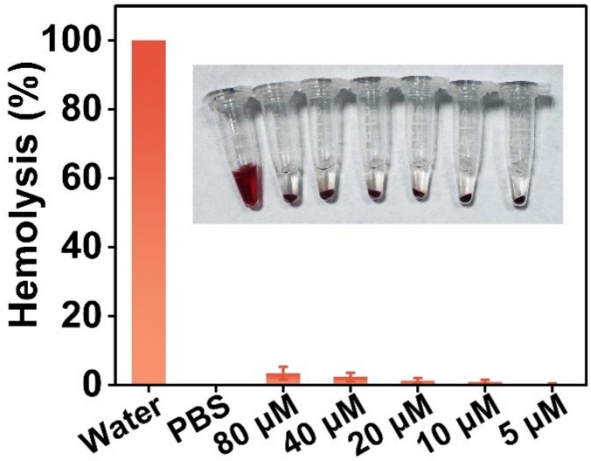


Fig. S21 The hemolysis rate of red blood cells after incubation with different concentrations of **RuBr** (n = 3 independent experiments).

Fig. S22 Schematic of in vivo ultrasound.

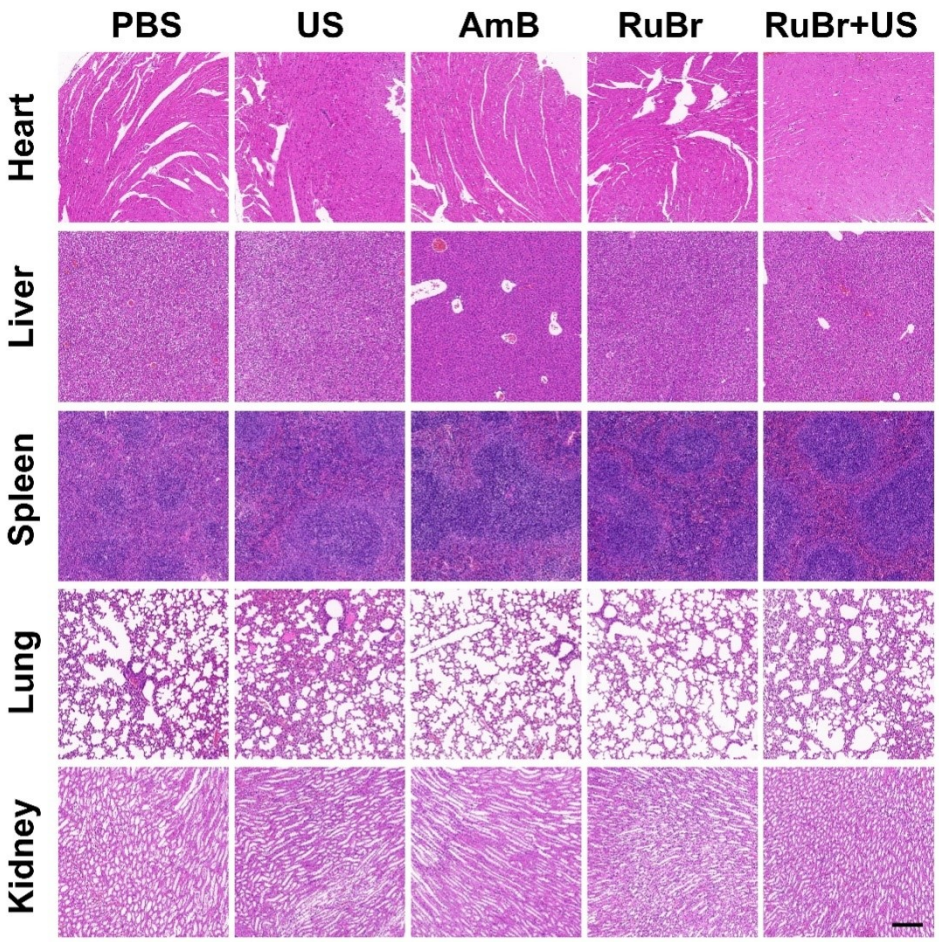


Fig. S23 H&E staining of different organ slices collected from fungi infections mice models at 6 days. Scale bar, 100 μm.