**ROS-mediated Carbon Monoxide and Drug Release from Drug-conjugated Carboxyboranes**

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# Supporting Information

## General Information

All reagents were purchased from Acros Organics, Alfa Aesar, ThermoFisher, and Sigma-Aldrich unless noted otherwise. All NMR solvents were purchased from Cambridge Isotope Laboratories. Cell cultures and media were obtained from ATCC. $^{1}H$, $^{11}B$, and $^{13}C$ NMR spectra were recorded on Bruker 300 MHz Avance III spectrometer. Mass spectrometry was performed on Electrospray Ionization Micromass QTOF by Waters. IR spectra were recorded on Thermo Scientific Nicolet iS50 FT-IR. CO gas concentration measurements in ppm were recorded using Honeywell ToxiPro Single Gas Detector. Cell viability assay and ELISA measurements were done using a SpectraMax M2 plate reader from Molecular Devices.

## Synthetic Procedures

**Synthesis of hexamethylenetetramine carboxyborane (CORCB-1).** CORCB-1 or HMTA-CB was prepared by amine exchange reaction using trimethylamine carboxyborane as described previously.[1]

**Synthesis of pyridine carboxyborane (CORCB-2).** Pyridine carboxyborane (CORCB-2) was previously reported to have prepared from cyanoborane.[2] In this report, pyridine carboxyborane was prepared from CORCB-3 through amine exchange reaction. Trimethylamine carboxyborane (60 mg, 0.50 mmol) was dissolved in pyridine (1.5 mL), protected from the atmosphere by purging with $N_2$ gas, and maintained at 40 – 70 °C for 24 hours. The solution was purged with $N_2$ gas for 5 minutes and concentrated by vacuum distillation leaving white solid crude product (70 mg). The residue was purified by recrystallization in dichloromethane and hexane to yield a white solid (40 mg, 59%): $^{1}H$ NMR ($D_2O$) δ 2.19 – 3.58 (br. m, $BH_2$), δ 7.77 – 7.91 (m, 2H, CH), δ 8.24 – 8.38 (m, 1H, CH), δ 8.52 – 8.65 (m, 2H, CH); $^{13}C$ NMR ($D_2O$) δ 126.44, 142.01, 148.02; $^{11}B$ NMR ($D_2O$) δ -11.44 (t, 1B); FT-IR (solid, ATR) 1645 $cm^{-1}$ (C=O), 2396 $cm^{-1}$ ($BH_2$), 2465-3330 $cm^{-1}$ (C-H and O-H).

**Synthesis of trimethylamine carboxyborane (CORCB-3).** Trimethylamine carboxyborane (CORCB-3) was prepared with a few modifications on the procedures from literature described by Spievogel et al.,[3] in which $NaBH_3CN$ was reacted under reflux with trimethylammonium hydrochloride. The resulting product was first reacted with $Et_3OBF_4$ in methylene chloride under reflux followed by sodium hydroxide and then acidified with hydrochloric acid. This literature procedure yields 61 – 83% of CORCB-3. A higher purity product was obtained by recrystallization in chloroform and acetone to yield white solid with 86 – 92 % recovery: $^{1}H$ NMR (DMSO) δ 1.38 – 2.72 (br. m, $BH_2$), δ 2.86 (s, 3H, $CH_3$); $^{13}C$ NMR (DMSO) δ 51.78; $^{11}B$ NMR (DMSO) δ -10.29 (t, 1B); FT-IR (solid, ATR) 1645 $cm^{-1}$ (C=O), 2382 $cm^{-1}$ ($BH_2$), 2649-3350 $cm^{-1}$ (C-H and O-H).

**Synthesis of memantine carboxyborane (CORCB-4).** Memantine carboxyborane (CORCB-4) was prepared as follows. Trimethylamine carboxyborane (CORCB-3) (117 mg, 1.0 mmol) and memantine (780 mg, 4.4 mmol) were dissolved in THF (8.0 mL), protected from the atmosphere by purging with $N_2$ gas, and maintained at 67 °C for 24 hours. The solution was concentrated by vacuum distillation leaving white solid crude product (208 mg). The residue was purified by recrystallization in dichloromethane and hexane to yield a white solid (15 mg, 6.3%): HRMS (pos. ion ESI) m/z: $[M]^+$ Calcd for $C_{13}H_{24}BNO_2$ 237.2009; Found 237.2004; $^{1}H$ NMR ($CDCl_3$) δ 0.89 (s, 6H, $CH_3$), δ 1.08 – 2.64 (br. m, 15H, memantine and $BH_2$), δ 3.67 – 4.15 (br. m, 2H, $NH_2$), δ 8.46 (br. s, 1H, $CO_2H$); $^{13}C$ NMR ($CDCl_3$) δ 29.91, δ 30.03, δ 32.78, δ 40.00, δ 42.24, δ 47.33, δ 50.22, δ 55.32; $^{11}B$ NMR ($CDCl_3$) δ -21.60 (br. s, 1B); FT-IR (solid, ATR) 1624 $cm^{-1}$ (C=O), 2429 $cm^{-1}$ ($BH_2$), 2839-2947 $cm^{-1}$ (C-H), 3094-3300 $cm^{-1}$ (O-H).

**Synthesis of the sodium salt of memantine carboxyborane (Na-CORCB-4).** Memantine carboxyborane sodium salt (Na-CORCB-4) was prepared as follows. Memantine carboxyborane (CORCB-4) (420 mg, 1.8 mmol) was dissolved in dichloromethane (10 mL). A mixture of sodium

hydroxide (116 μL, 15.21 M) and water (25 mL) was added to CORCB-4 solution and stirred for 10 minutes. The aqueous layer was separated from the mixture and the organic layer was washed with water (3 x 5 mL). Combine aqueous layer was dried under vacuum distillation to yield white solid (300 mg, 65%): HRMS (neg. ion ESI) m/z: [M]- Calcd for $C_{13}H_{23}BNO_2$ 236.1827; Found 236.1829; $^{1}H$ NMR ($D_2O$) δ 0.85 (s, 6H, $CH_3$), δ1.05 – 2.38 (br. m, 15H, memantine and $BH_2$); $^{13}C$ NMR ($D_2O$) δ 29.27, δ 29.68, δ 31.71, δ 38.83, δ 41.70, δ 46.29, δ 49.57, δ 53.77; $^{11}B$ NMR ($D_2O$) δ -21.52 (br. s, 1B); FT-IR (solid, ATR) 1600 $cm^{-1}$ (C=O), 2360 $cm^{-1}$ ($BH_2$), 2740-2990 $cm^{-1}$ (C-H).

**Experimental Methods and Procedures**

**Decomposition measurement by NMR.** CORCBs in $D_2O$ at concentrations range from 6.0 – 12.0 mg/mL was incubated at 37 °C in the standard NMR tube. $^{1}H$, $^{11}B$, and $^{13}C$ NMR spectra were recorded at the times indicated. For decomposition mediated by $H_2O_2$, said amounts of $H_2O_2$ were mixed with the samples before incubation starts.

**CO measurement by Meter.** CORCBs at the concentration range from 30 – 60 mM were incubated at 37 °C in a sealed vessel with 50 mL gas space. At specified time points, liberated CO gas in ppm was measured using a CO gas detector and the moles calculated based on 50 mL volume. For samples with ROS, said amounts of $H_2O_2$ were added into the samples before incubation starts. Fenton reagent was prepared in aqueous solution using 1 equivalent of $FeSO_4$ and 1.5 equivalents of $H_2O_2$. In one minute, CORCB solution was added into the Fenton reagent and incubated for 5 minutes before measuring the concentration of CO in the head space.

**TNF-α assay.** Murine macrophage cell line (RAW264.7) was used to test for LPS-induced TNF-α production and inhibition of that by CORCB. $2x10^4$ cells per well were seeded into a 96-well plate in DMEM with 10% FBS. Cells were treated with varying concentrations of HMTA-CB and incubated at 37 °C under humidified condition with 5% $CO_2$ for 24 hours. LPS was then added to a final concentration of 100 ng/mL and incubated for 4 additional hours. The media containing secreted inflammatory cytokines were collected and TNF-α concentration in each sample was measured using the ELISA assay (Invitrogen).

**Cell viability assay.** After LPS containing media was removed, regular media along with CellTiter-Blue reagent (Promega) was added to the culture and incubated for 4 more hours at 37 °C in 5% $CO_2$ under a humidified atmosphere. Fluorescence signals (560Ex/590Em) were measured using a 96-well plate reader.

**Additional note.** Due to low solubility in aqueous medium, a more soluble sodium salt of CORCB-4 was used for all the experiments.

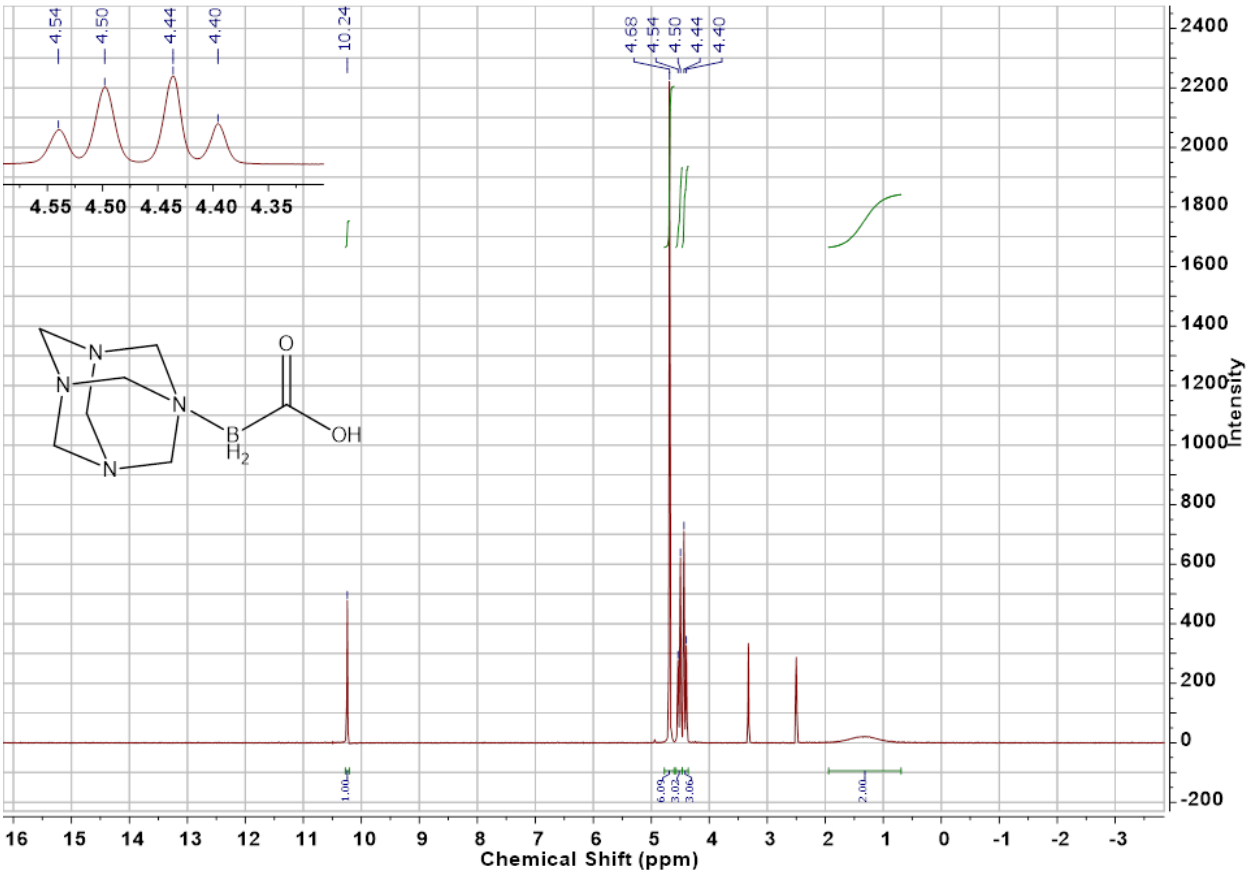


**Figure S1.** $^{1}$H NMR spectrum of CORCB-1 in DMSO.

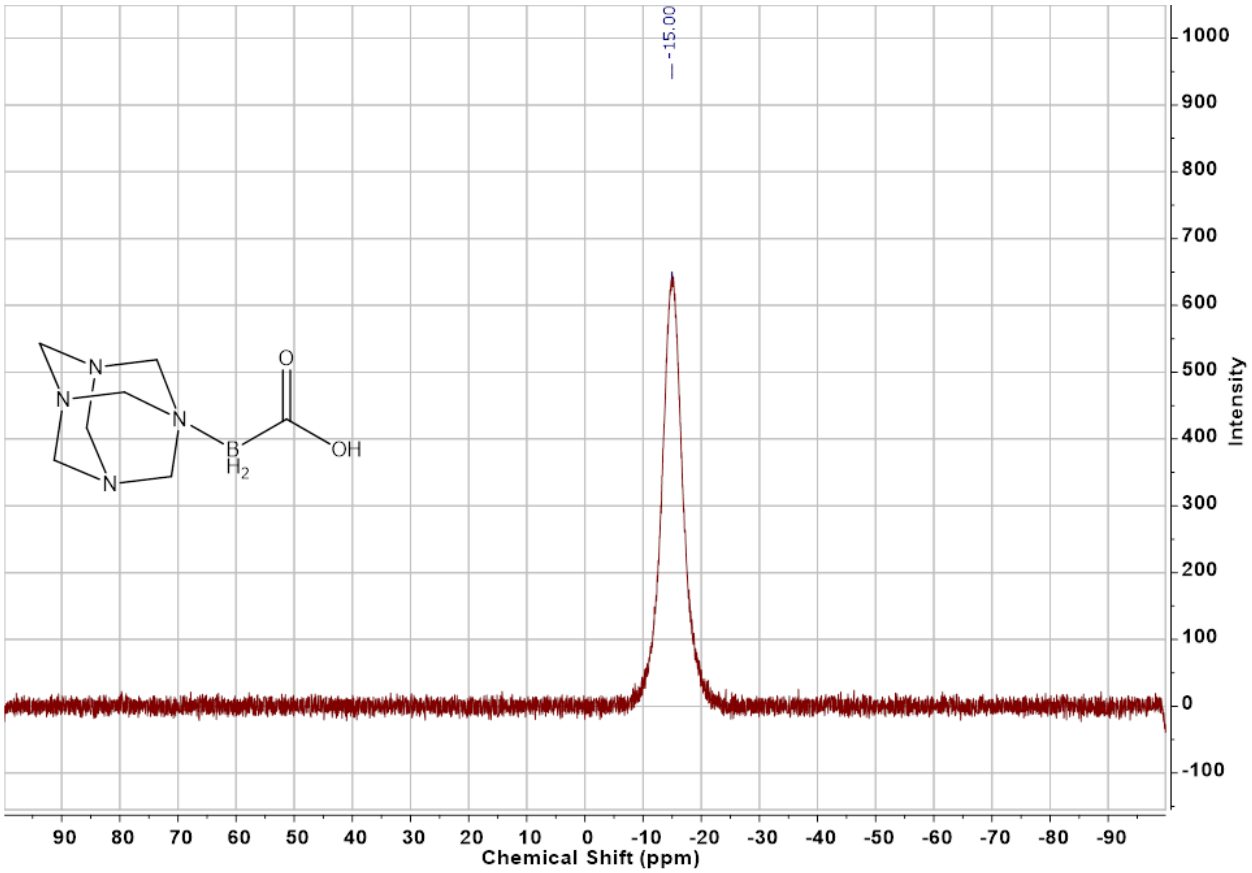


**Figure S2.** $^{11}$B NMR spectrum of CORCB-1 in DMSO.

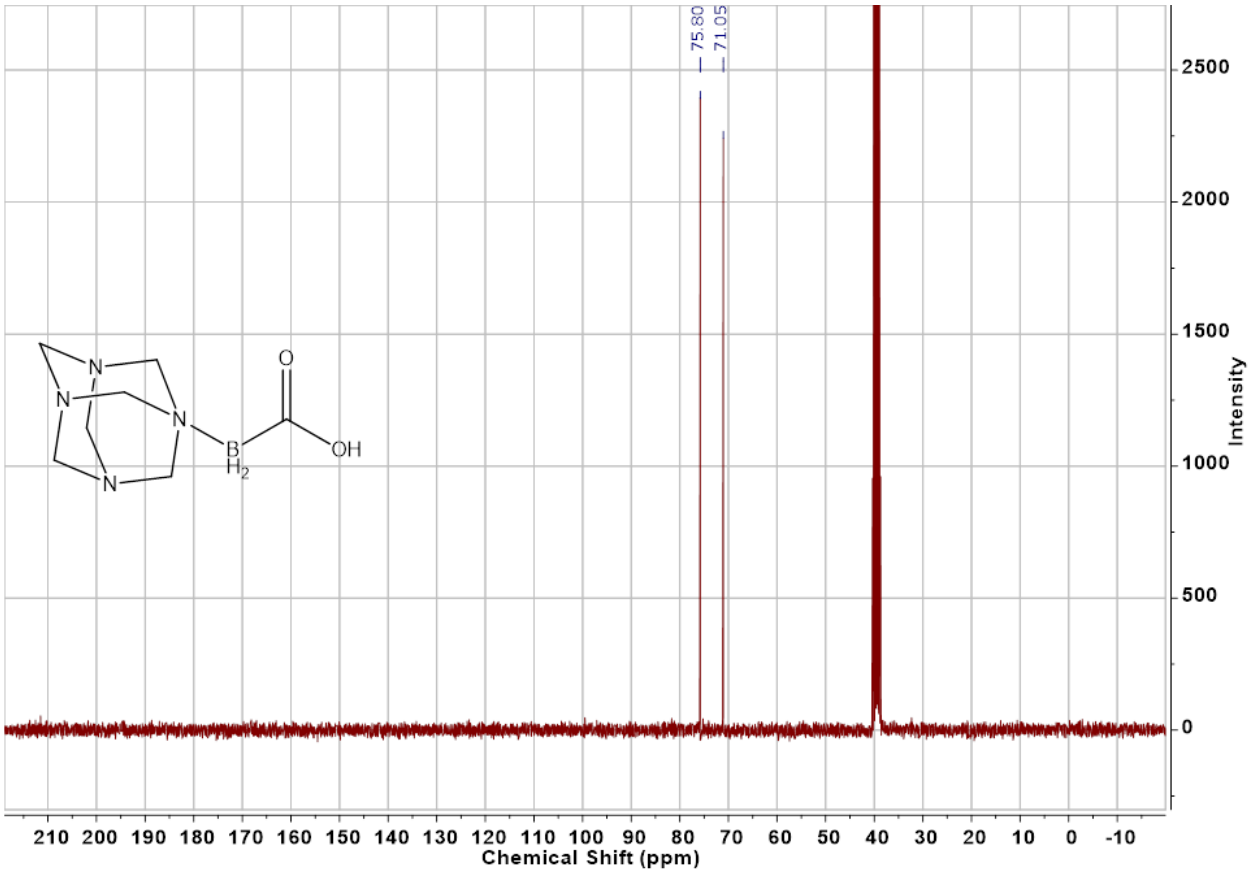


**Figure S3.** $^{13}$C NMR spectrum of CORCB-1 in DMSO.

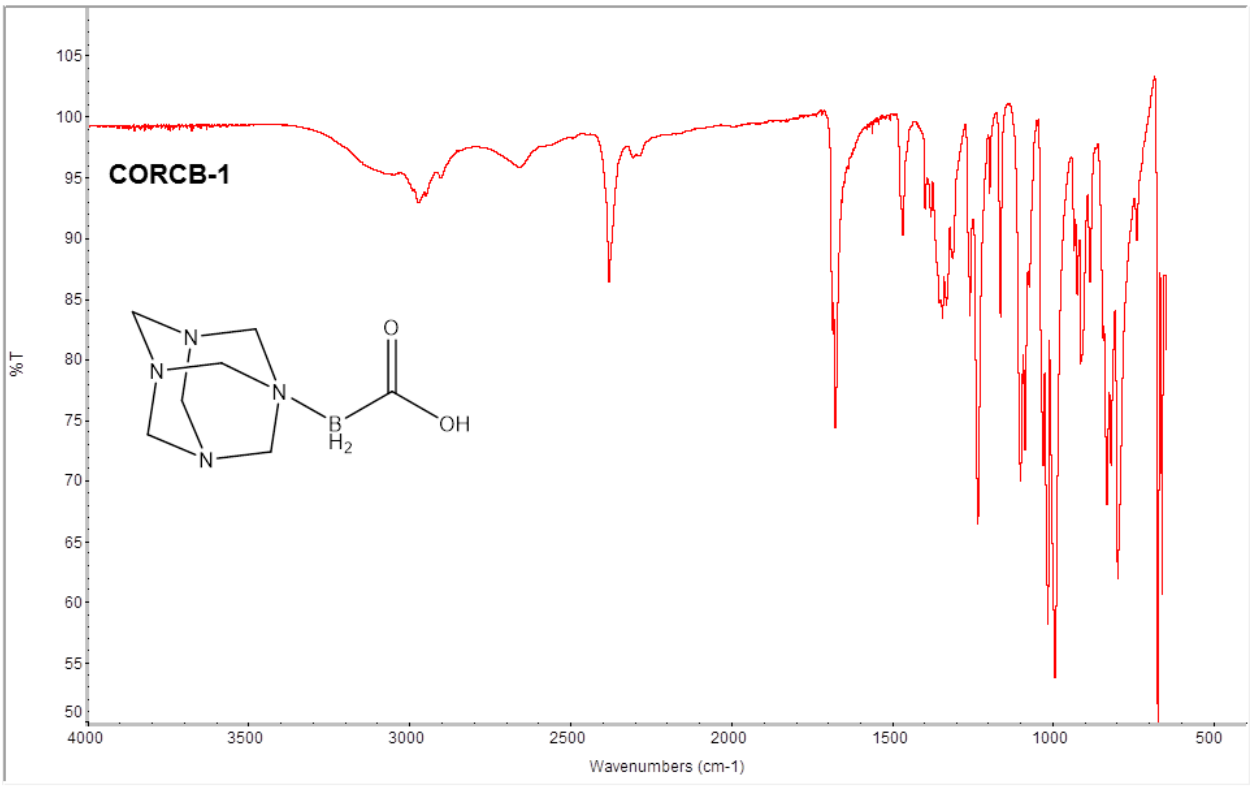


**Figure S4.** IR spectrum of CORCB-1.

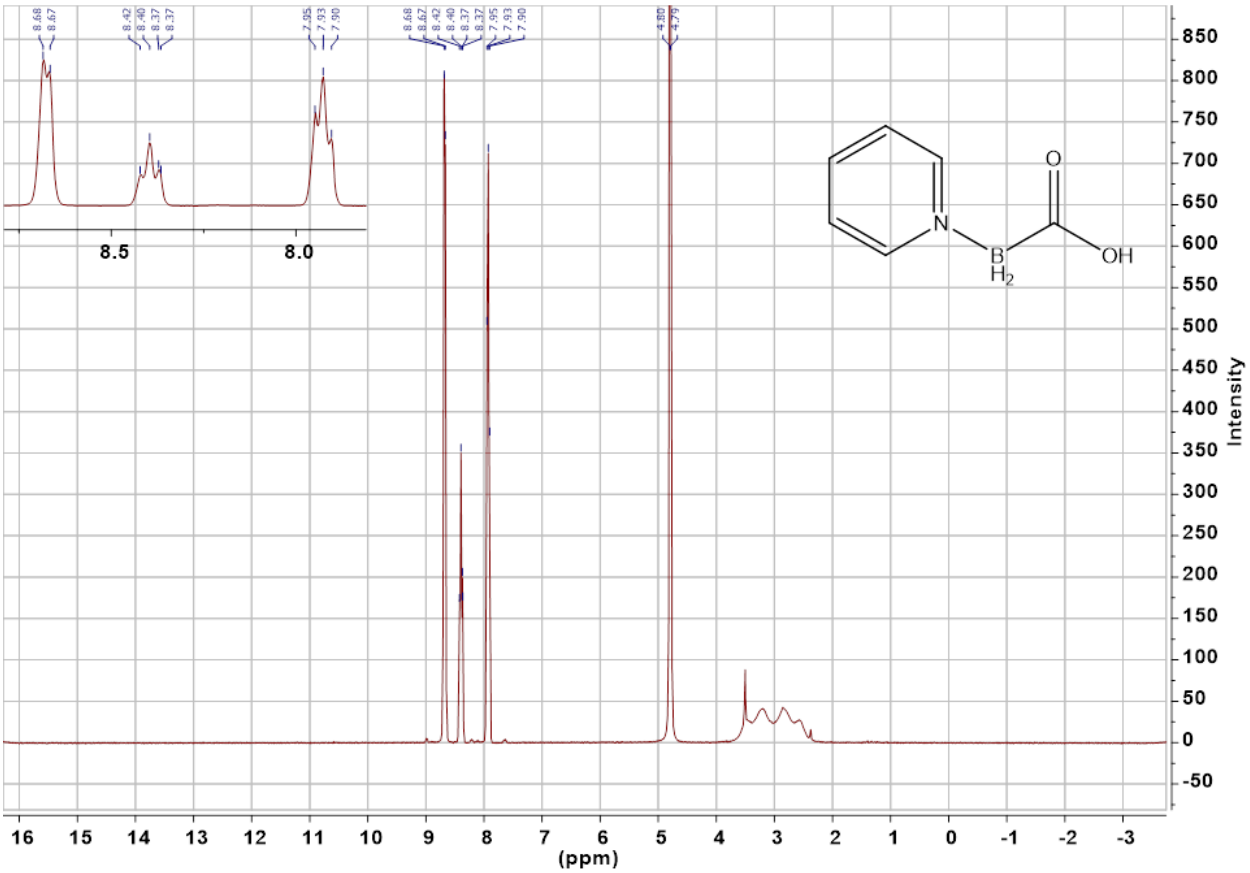


**Figure S5.** $^{1}$H NMR spectrum of CORCB-2 in $D_2O$.

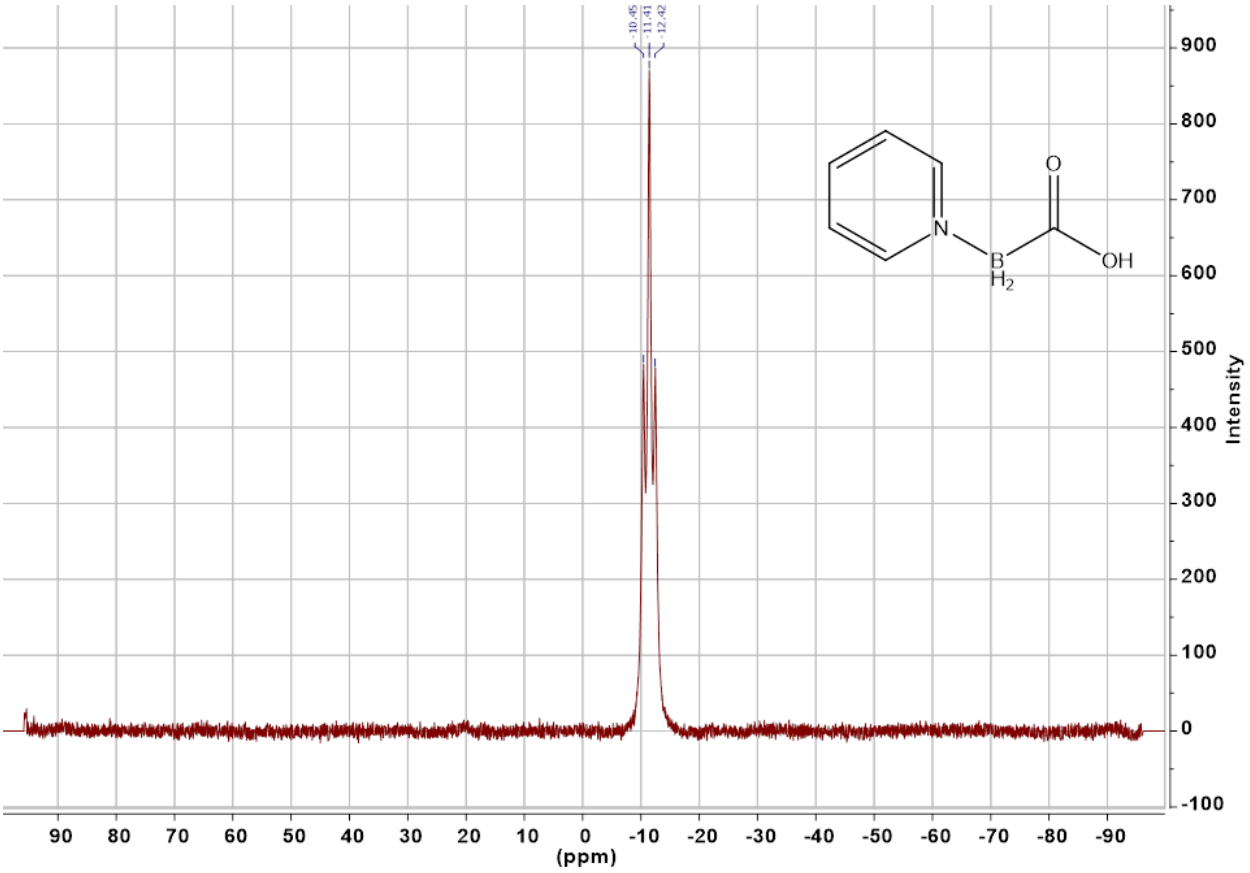


**Figure S6.** $^{11}B$ NMR spectrum of CORCB-2 in $D_2O$.

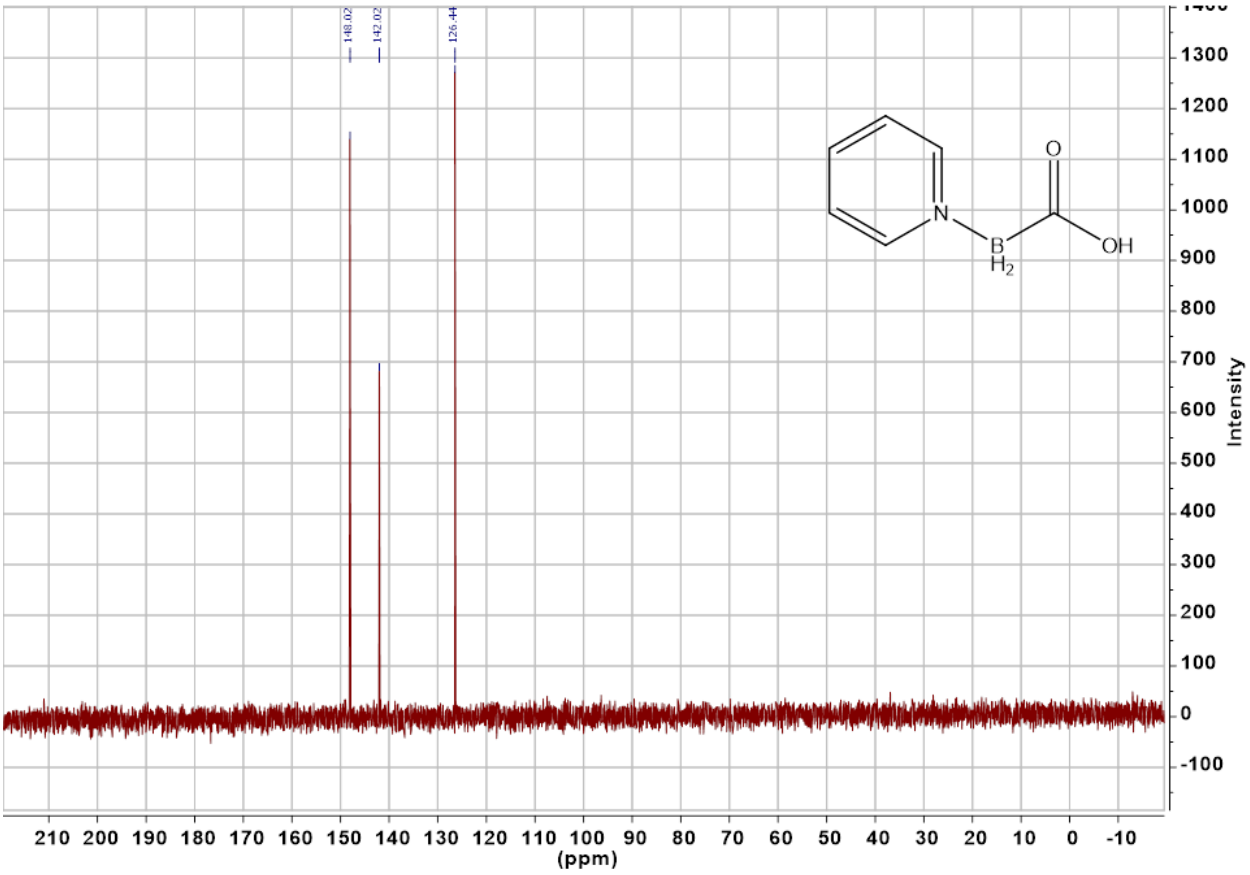


**Figure S7.** $^{13}C$ NMR spectrum of CORCB-2 in $D_2O$.

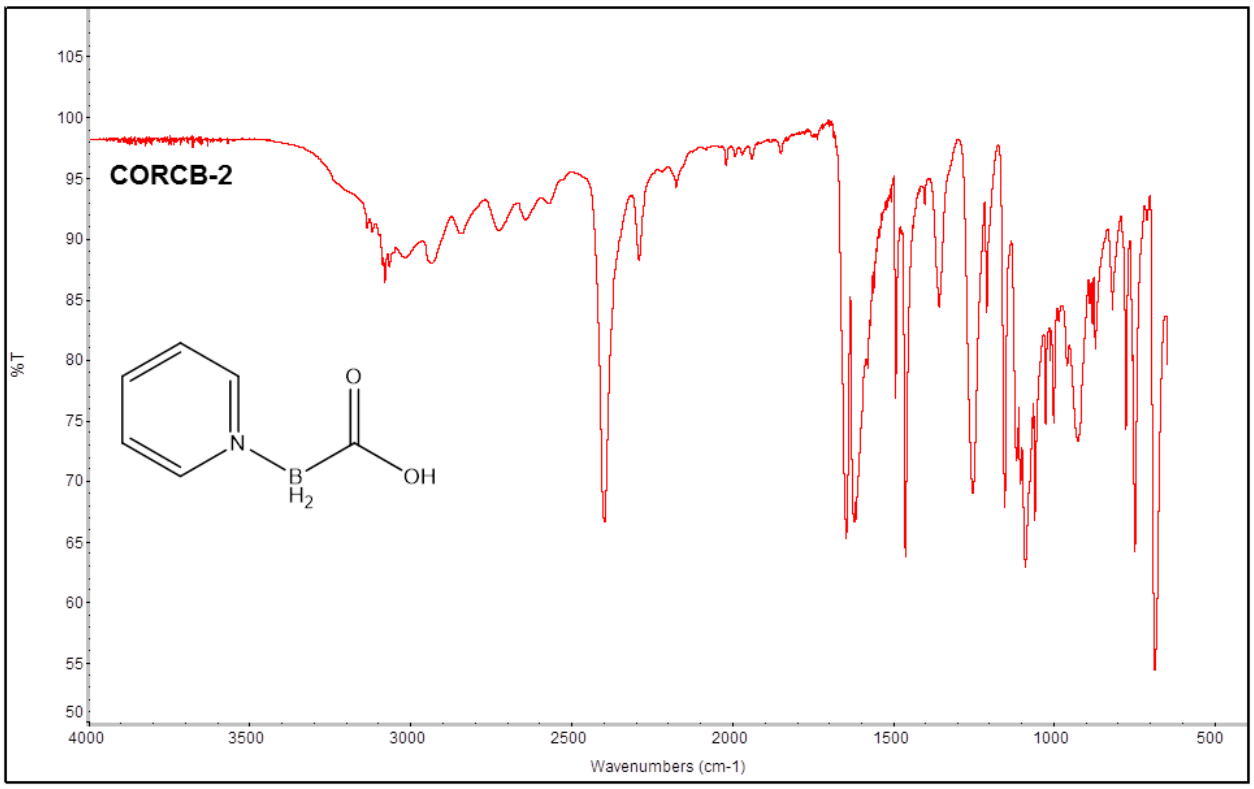


**Figure S8.** IR spectrum of CORCB-2.

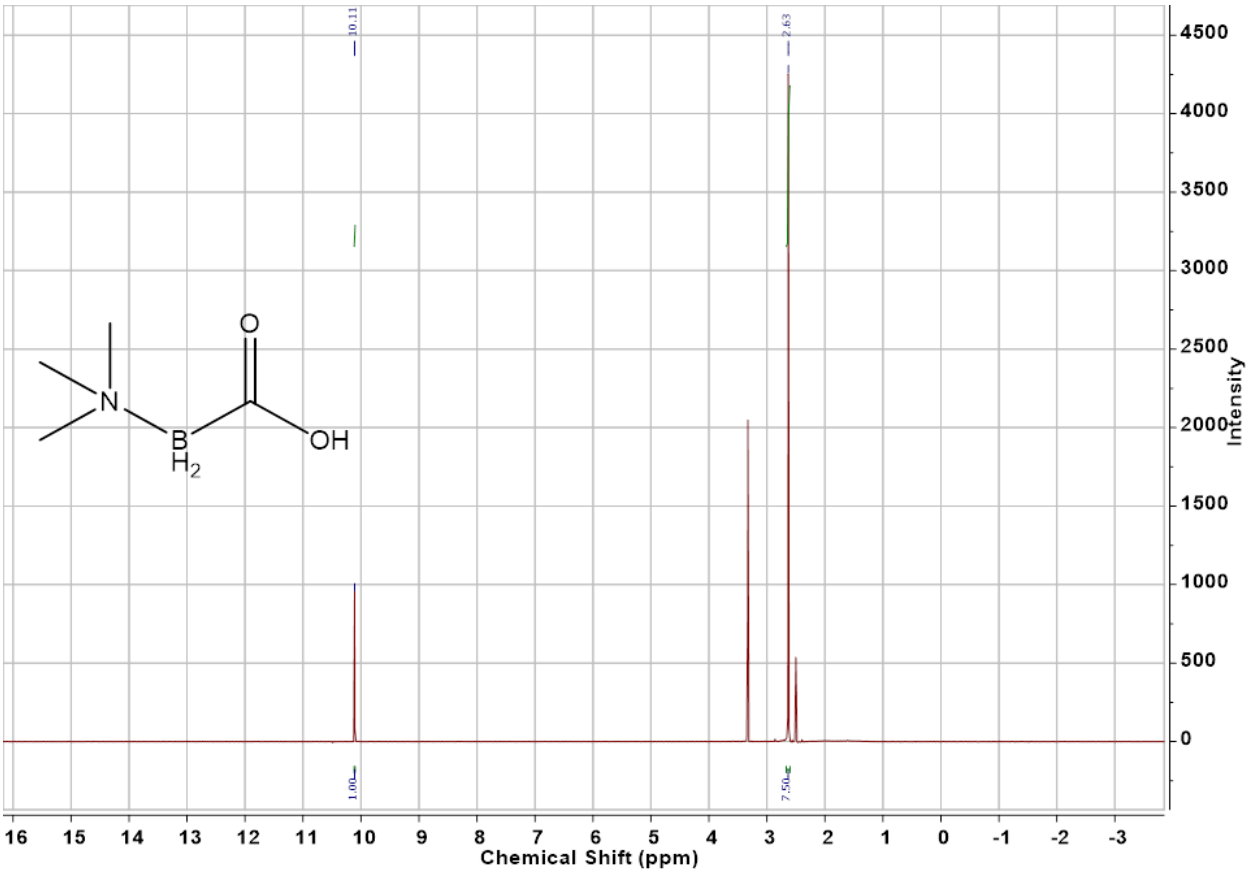


**Figure S9.** $^{1}$H NMR spectrum of CORCB-3 in DMSO.

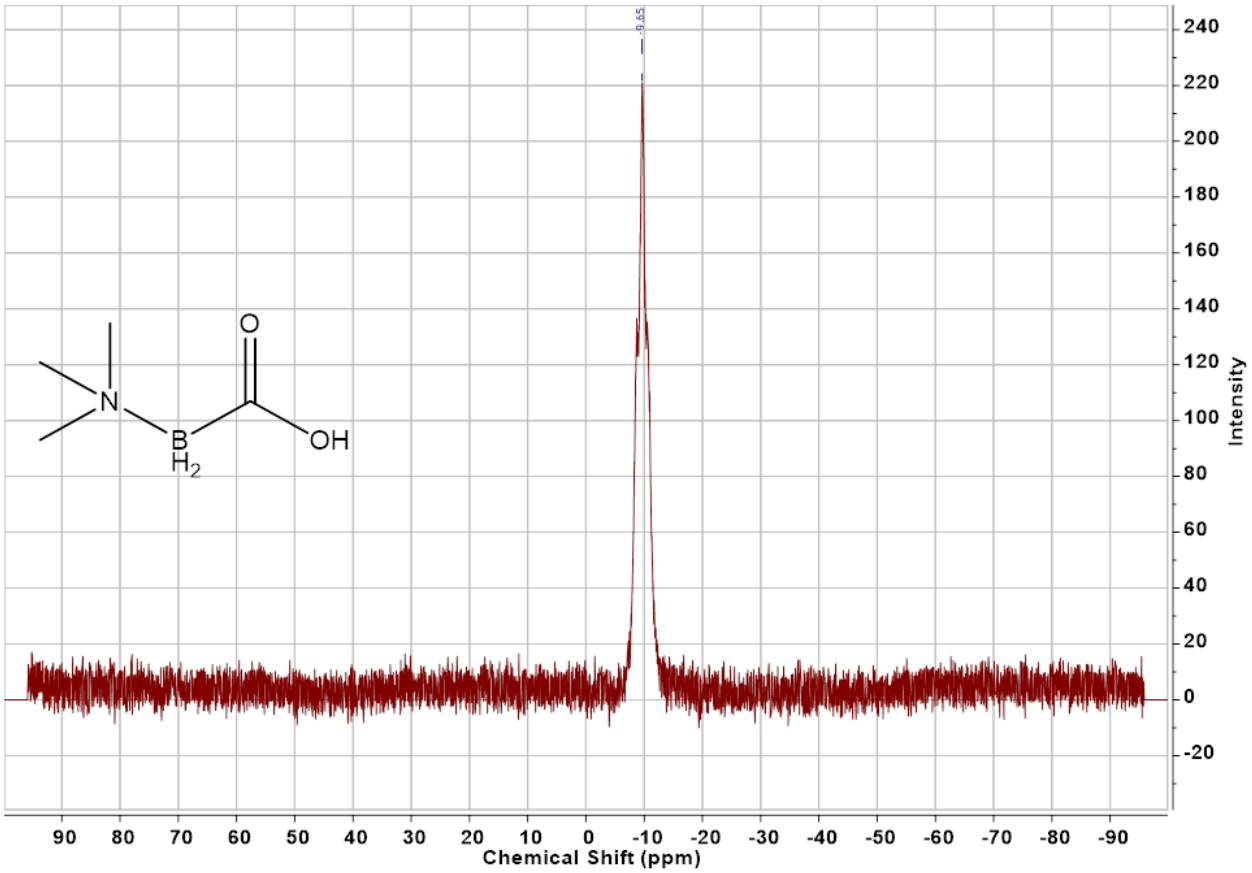


**Figure S10.** $^{11}$B NMR spectrum of CORCB-3 in DMSO.

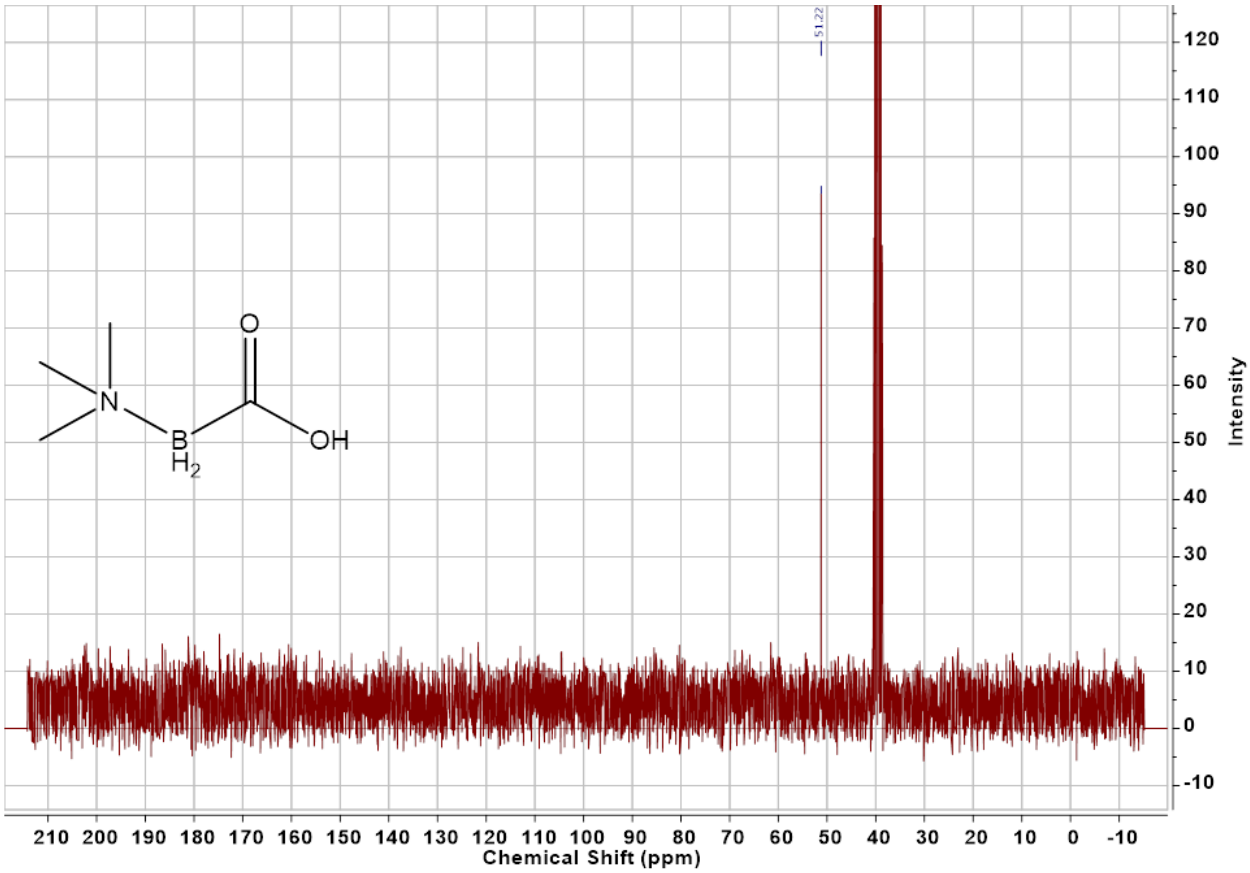


**Figure S11.** $^{13}$C NMR spectrum of CORCB-3 in DMSO.

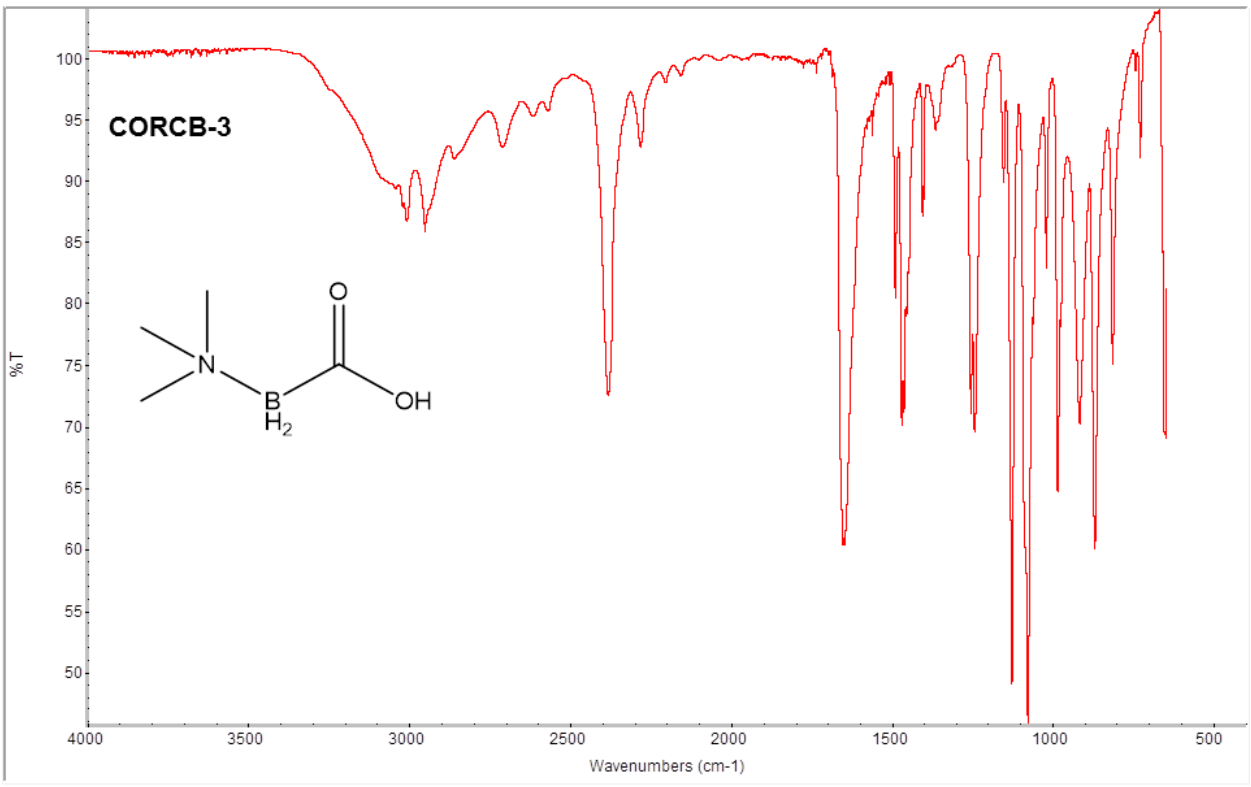


**Figure S12.** IR spectrum of CORCB-3.

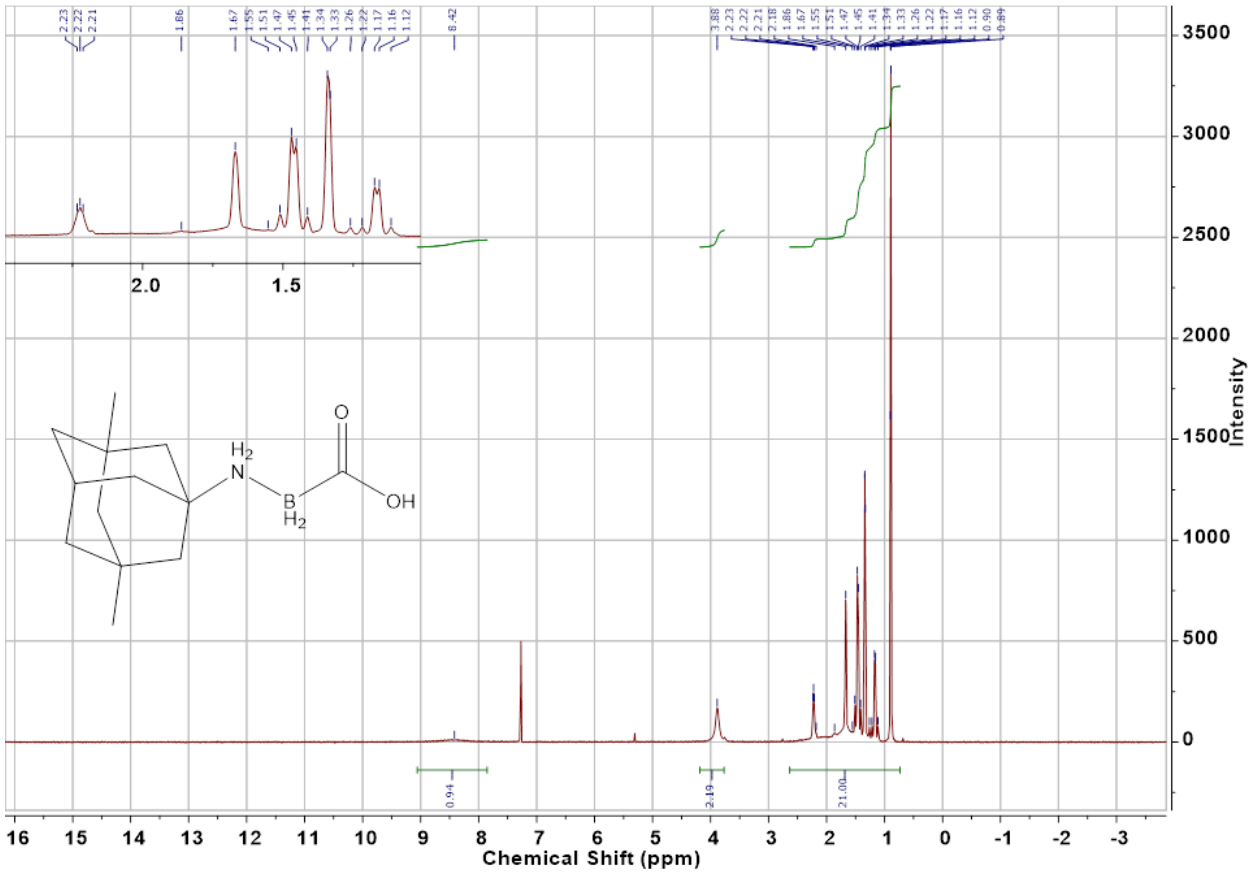


**Figure S13.** $^{1}H$ NMR spectrum of CORCB-4 in $CDCl_3$.

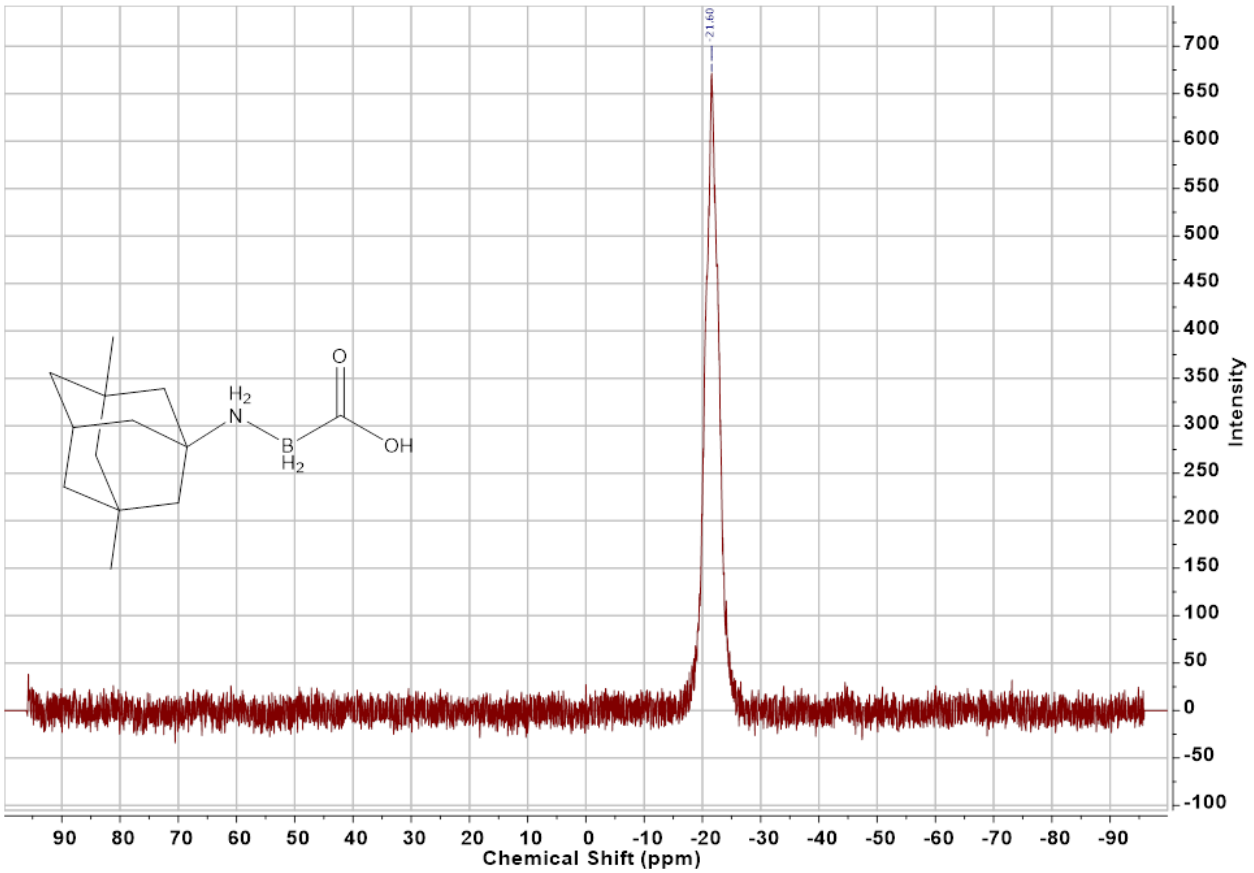


**Figure S14.** $^{11}B$ NMR spectrum of CORCB-4 in $CDCl_3$.

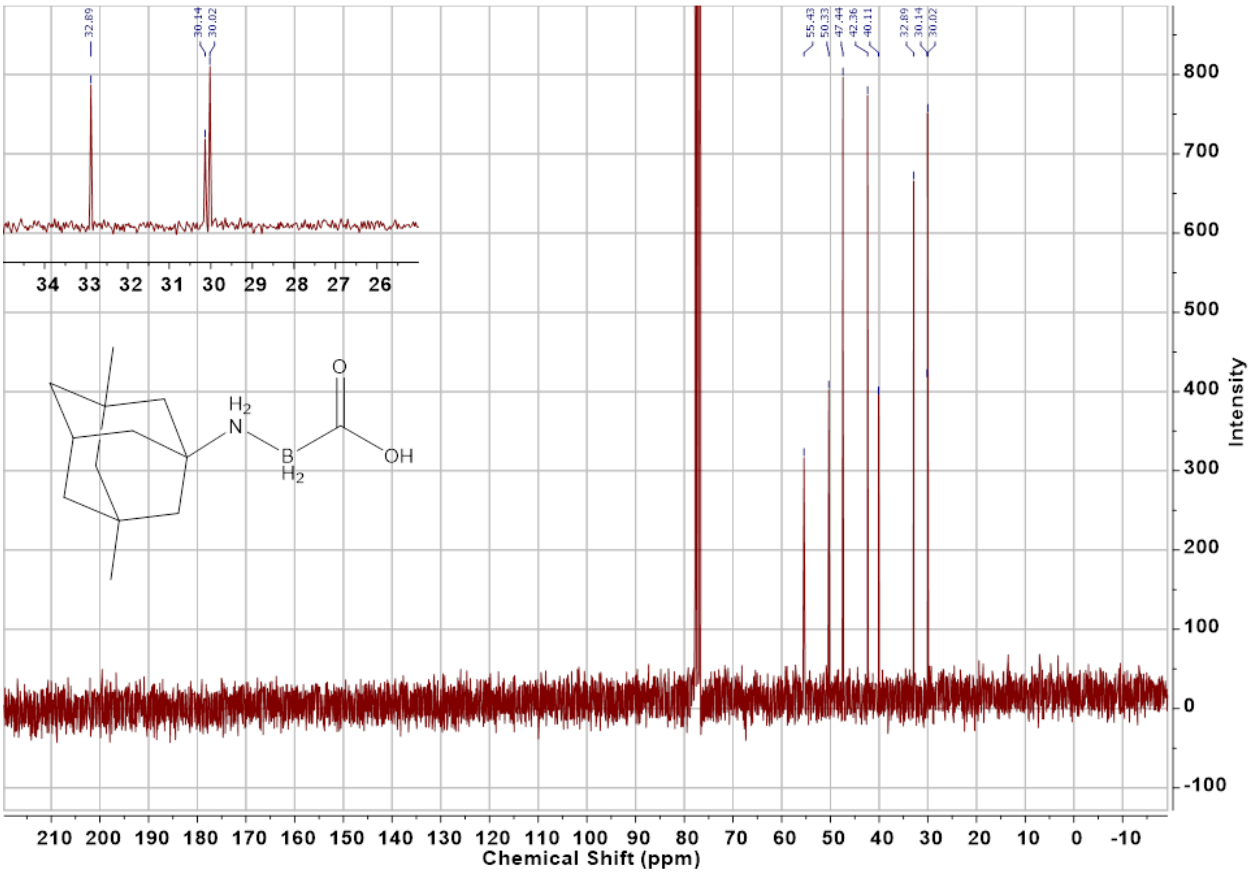


**Figure S15.** $^{13}C$ NMR spectrum of CORCB-4 in $CDCl_3$.

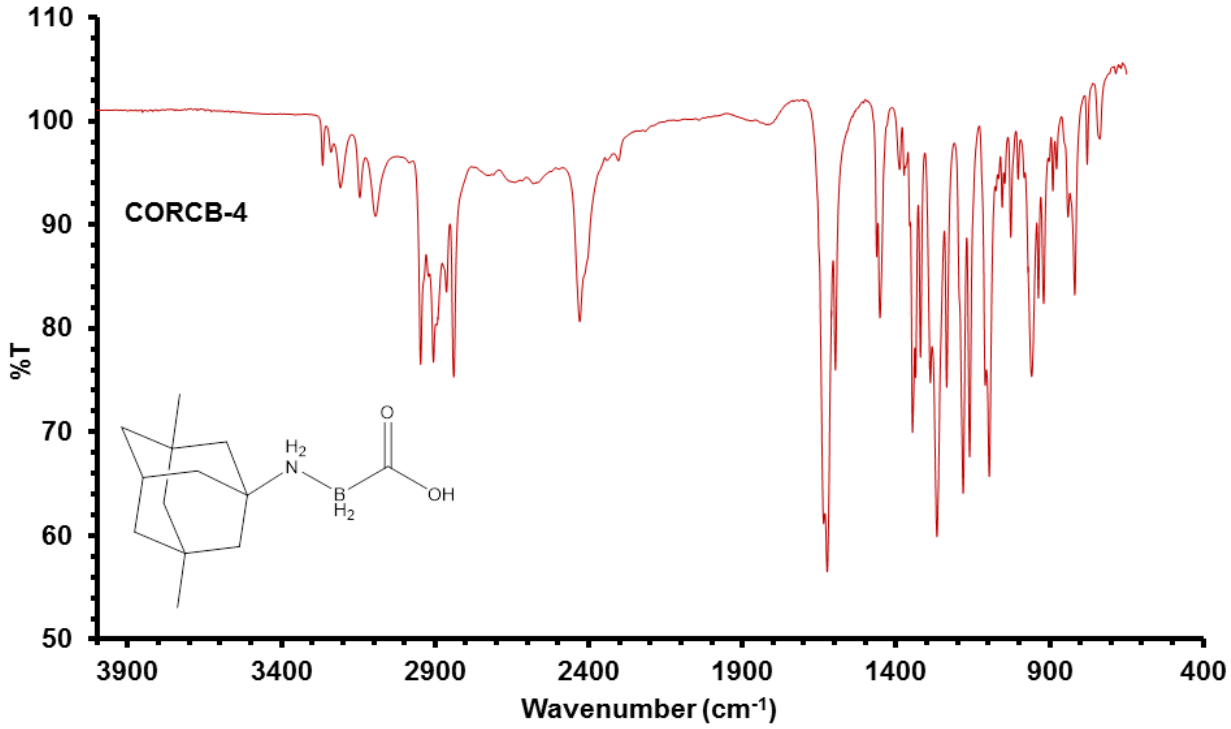


**Figure S16.** IR spectrum of CORCB-4.

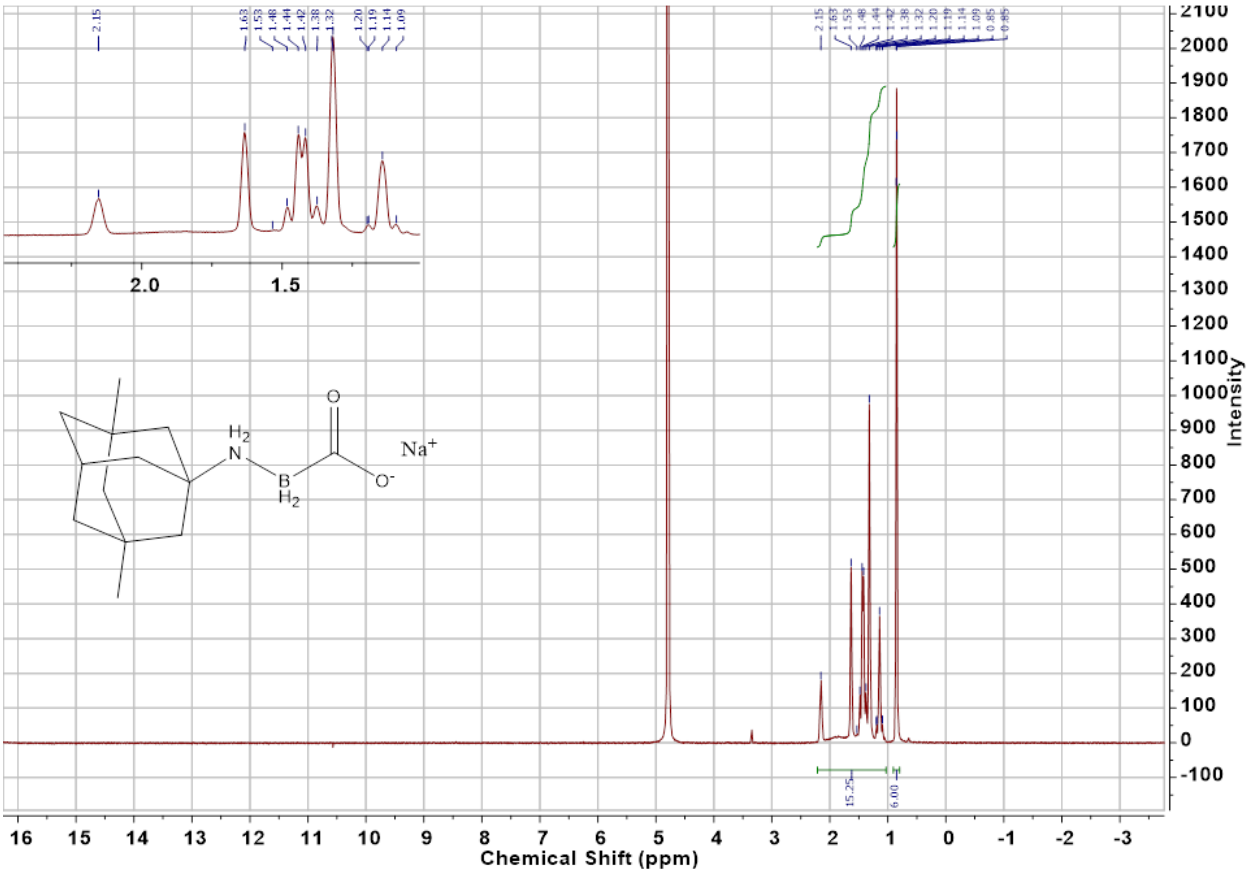


**Figure S17.** $^{1}H$ NMR spectrum of CORCB-4 sodium salt in $D_2O$.

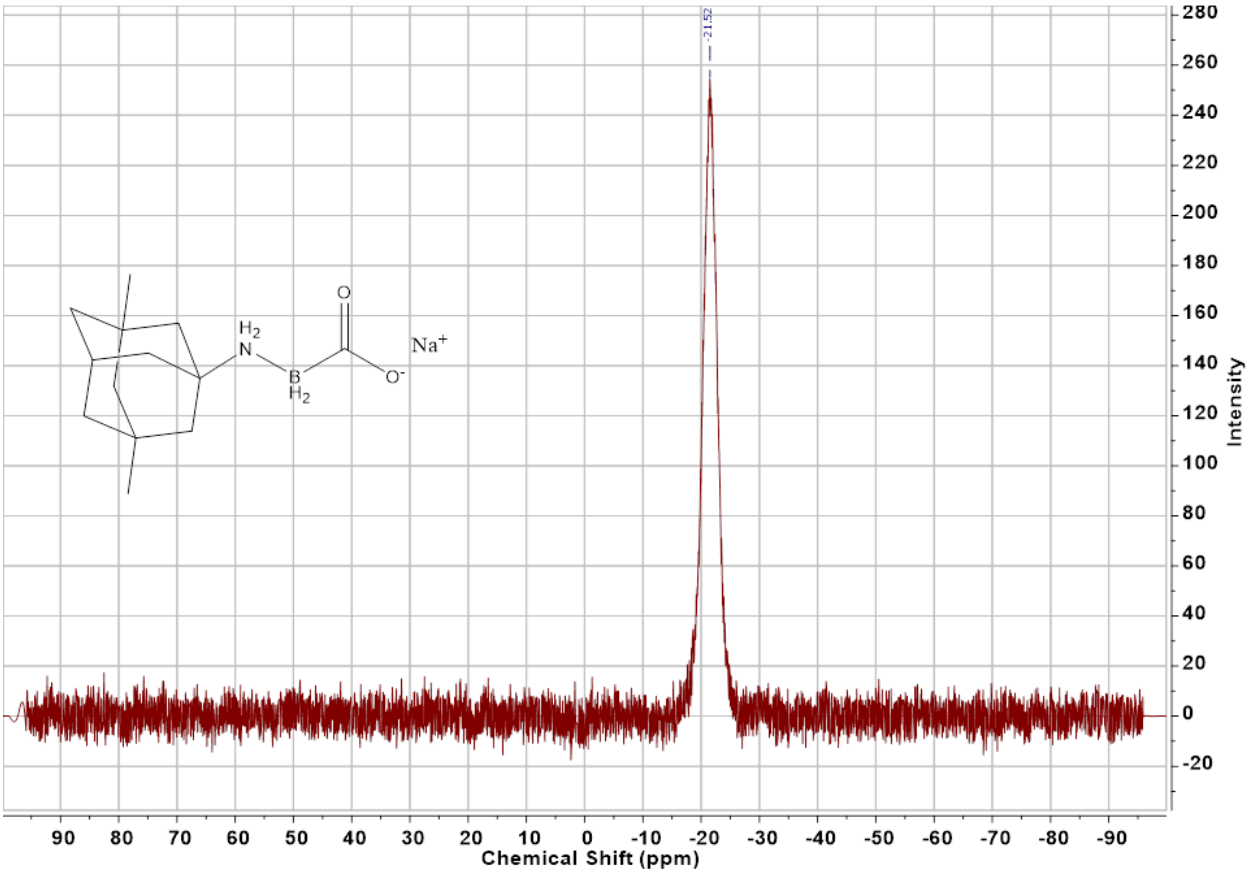


**Figure S18.** $^{11}B$ NMR spectrum of CORCB-4 sodium salt in $D_2O$.

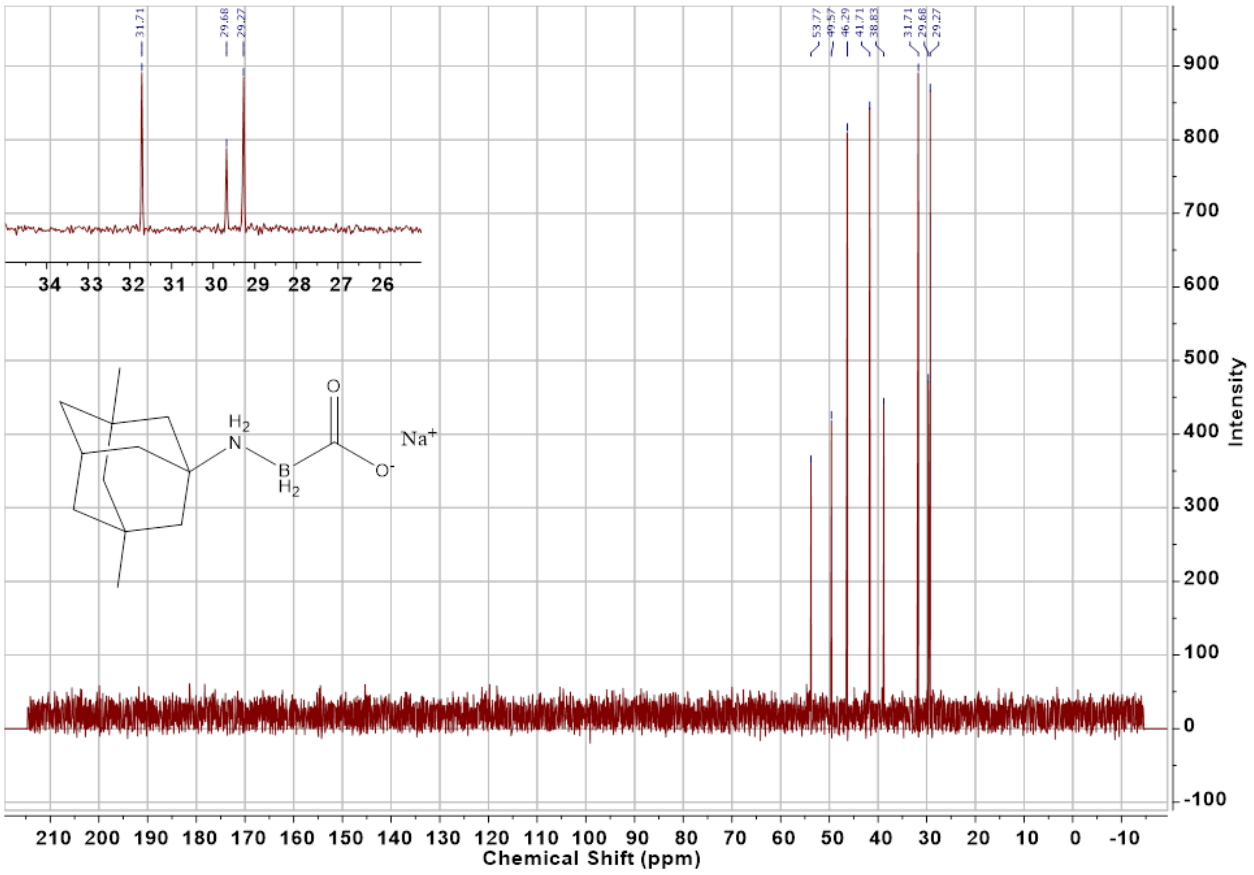


**Figure S19.** $^{13}C$ NMR spectrum of CORCB-4 sodium salt in $D_2O$.

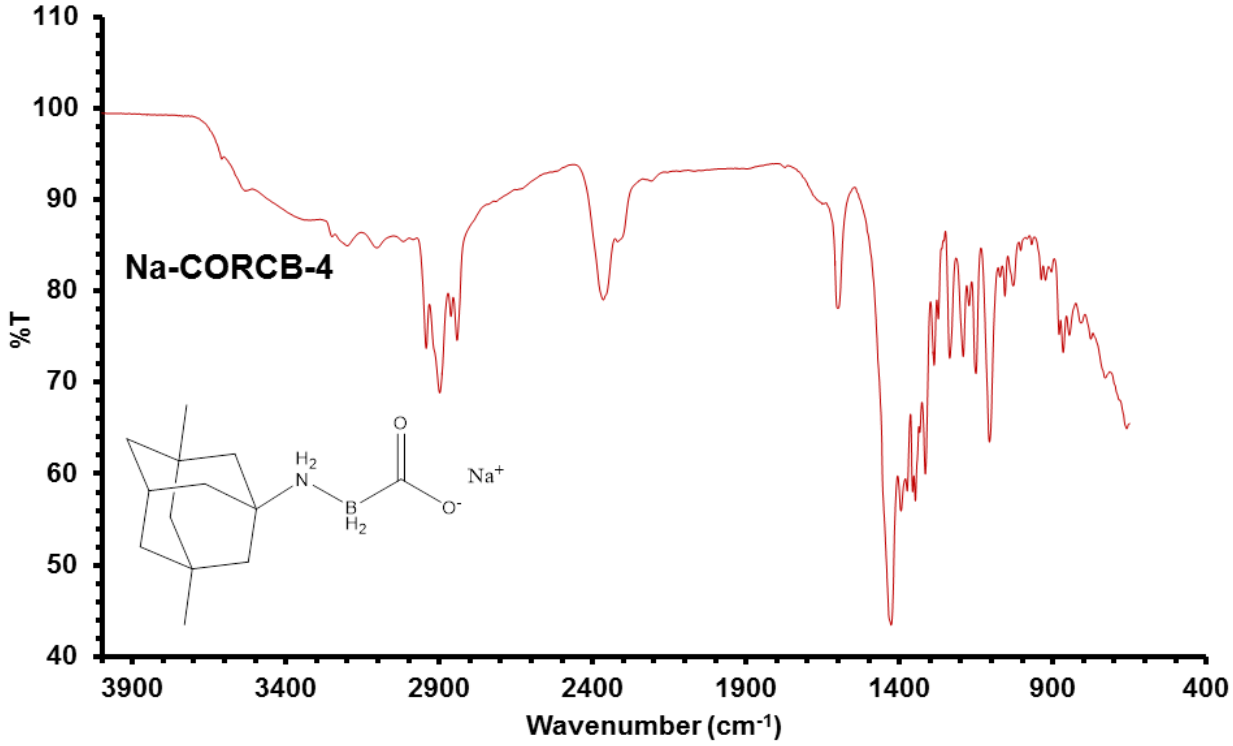


**Figure S20.** IR spectrum of CORCB-4 sodium salt.

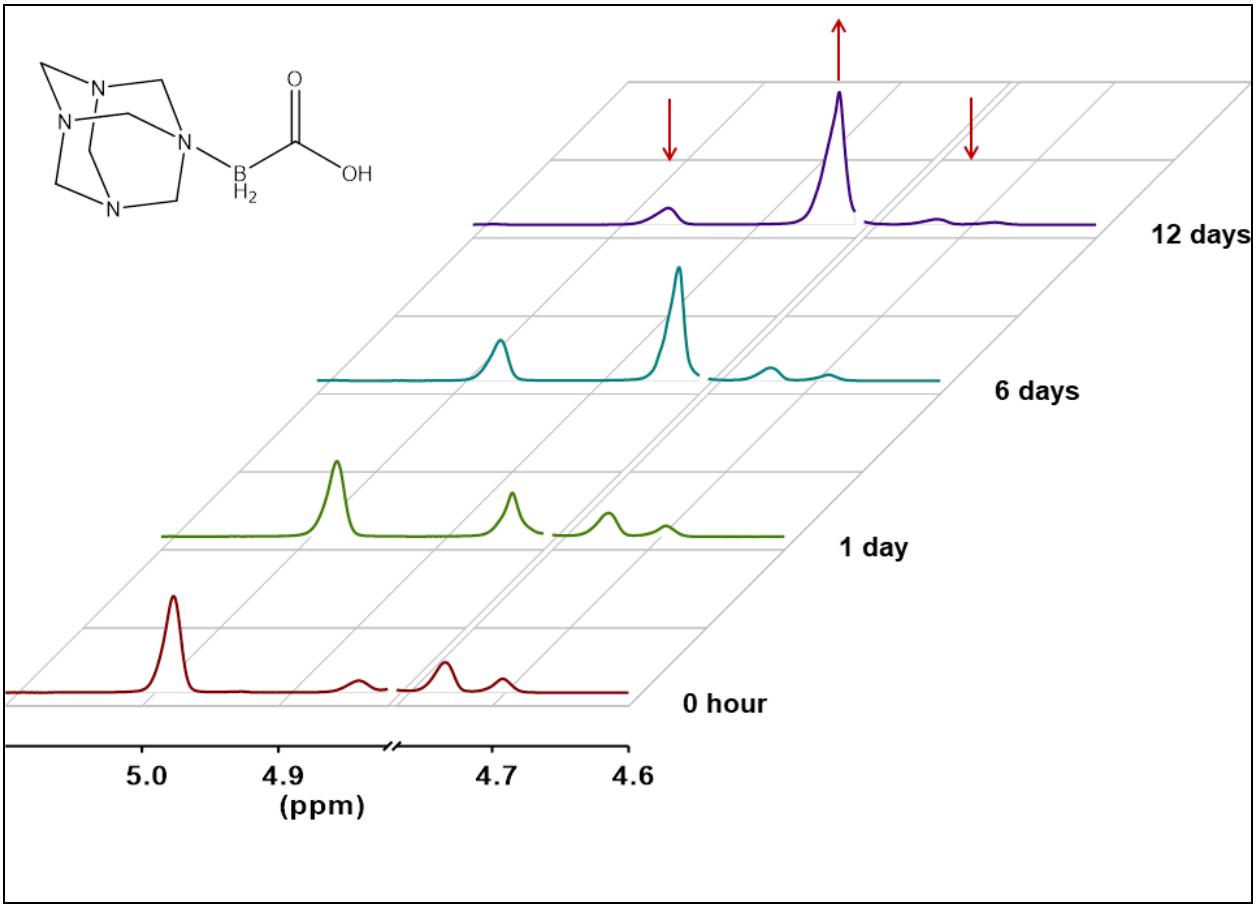


**Figure S21.** Decomposition of CORCB-1 monitored by $^{1}$H NMR. CORCB-1 was dissolved in $D_2O$ at the concentration of 60 mM and incubated at 37 °C. Spectra were recorded at 0, 1, 6, and 12 days. Disappearance of HMTA-CB peaks at δ 4.97, 4.73, and 4.69 ppm is compared with the appearance of free HMTA peak at δ 4.84 ppm. Note: HDO peak at δ 4.79 ppm is removed from stacked spectra for clearer view of the peaks. For accurate estimation of the ratio, a small peak area from the far right is subtracted from the new peak.

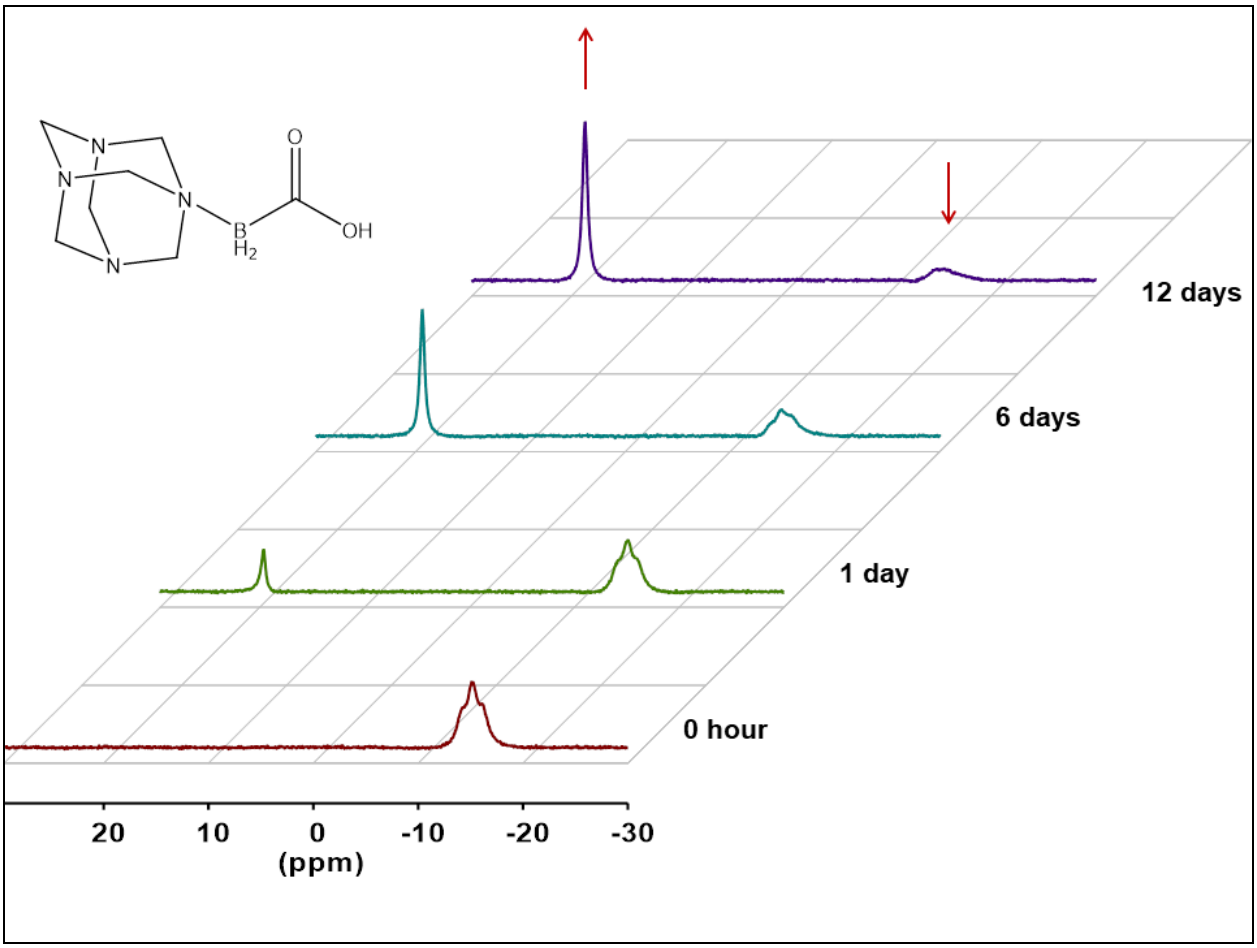


**Figure S22.** Decomposition of CORCB-1 monitored by $^{11}$B NMR. CORCB-1 was dissolved in $D_2O$ at the concentration of 60 mM and incubated at 37 °C. Spectra were recorded at 0, 1, 6, and 12 days. Boron atom on CORCB-1 is a triplet at δ ─15.16 ppm in $D_2O$ while the product of decomposition, boric acid, shows a singlet at δ 19.63 ppm.

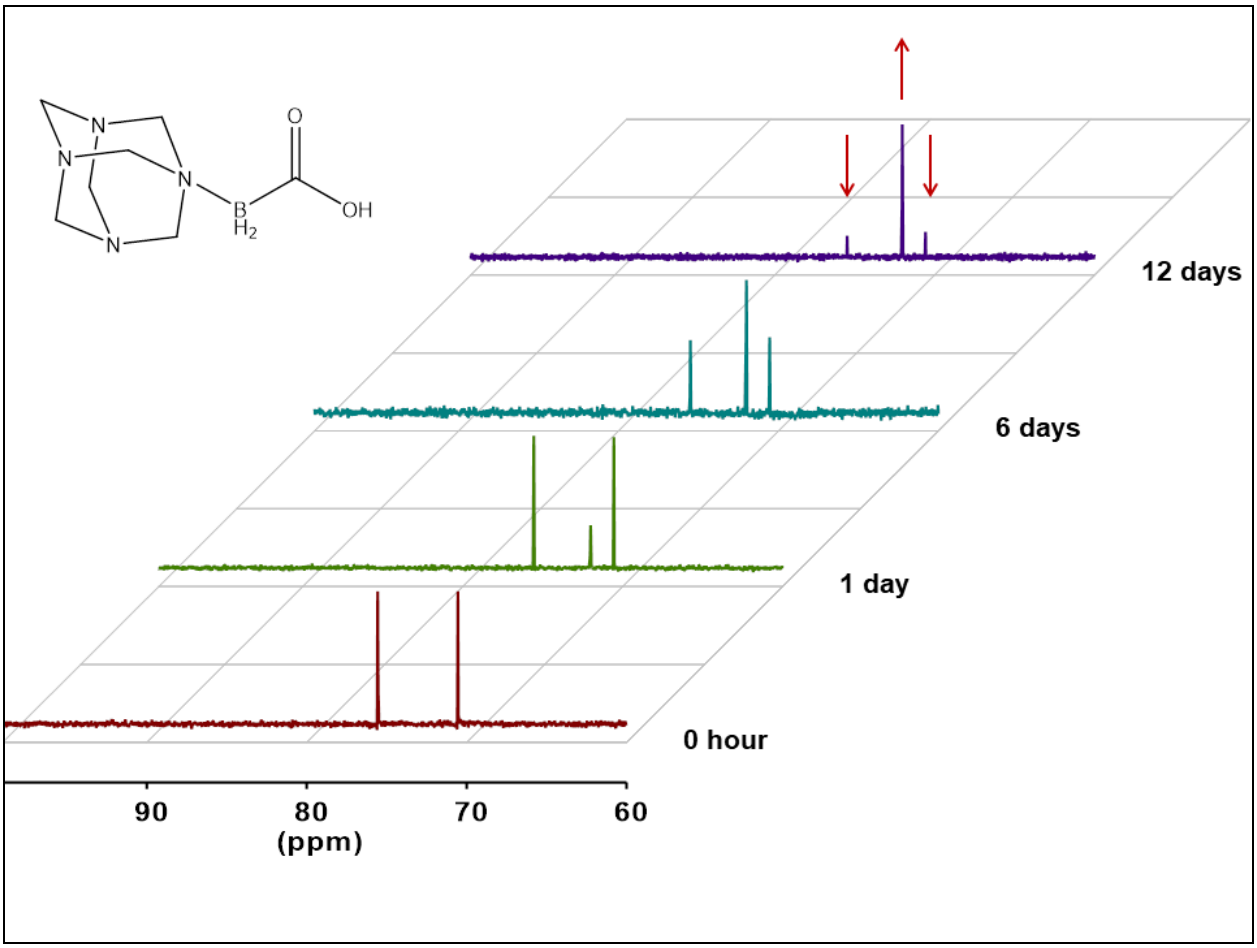


**Figure S23.** Decomposition of CORCB-1 monitored by $^{13}C$ NMR (normalized). CORCB-1 was dissolved in $D_2O$ at the concentration of 60 mM and incubated at 37 °C. Spectra were recorded at 0, 1, 6, and 12 days. Generation of free HMTA molecule, a product of decomposition, was determined by the appearance of a singlet peak at δ 72.00 ppm.

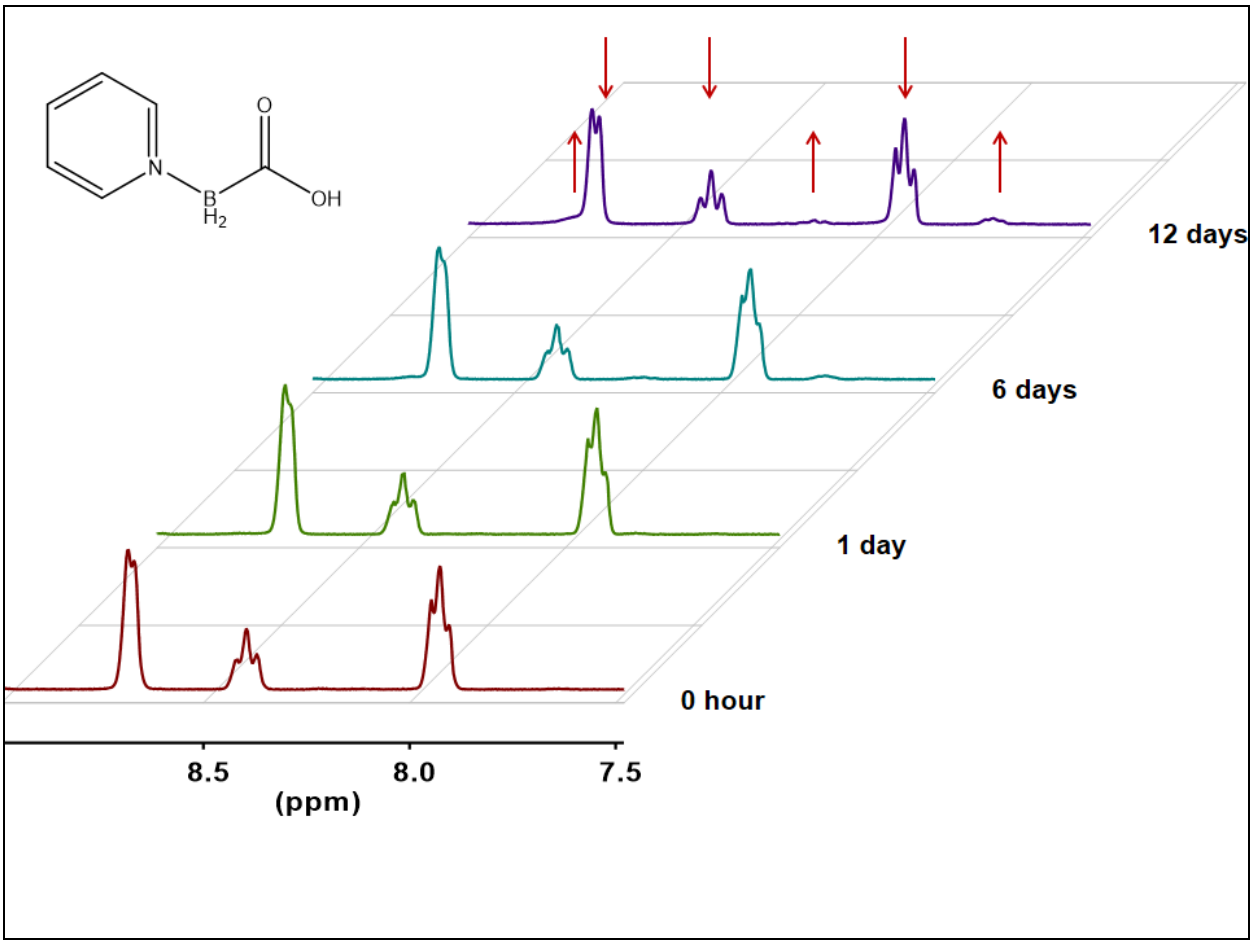


**Figure S24.** Decomposition of CORCB-2 monitored by $^{1}$H NMR. CORCB-2 was dissolved in $D_2O$ at the concentration of 30 mM and incubated at 37 °C. NMR spectra were recorded at 0, 1, 6, and 12 days. A new set of peaks for aromatic hydrogens of the free pyridine group at δ 8.75 ppm, δ 8.19 ppm, and δ 7.75 ppm is observed on 6 and 12 days.

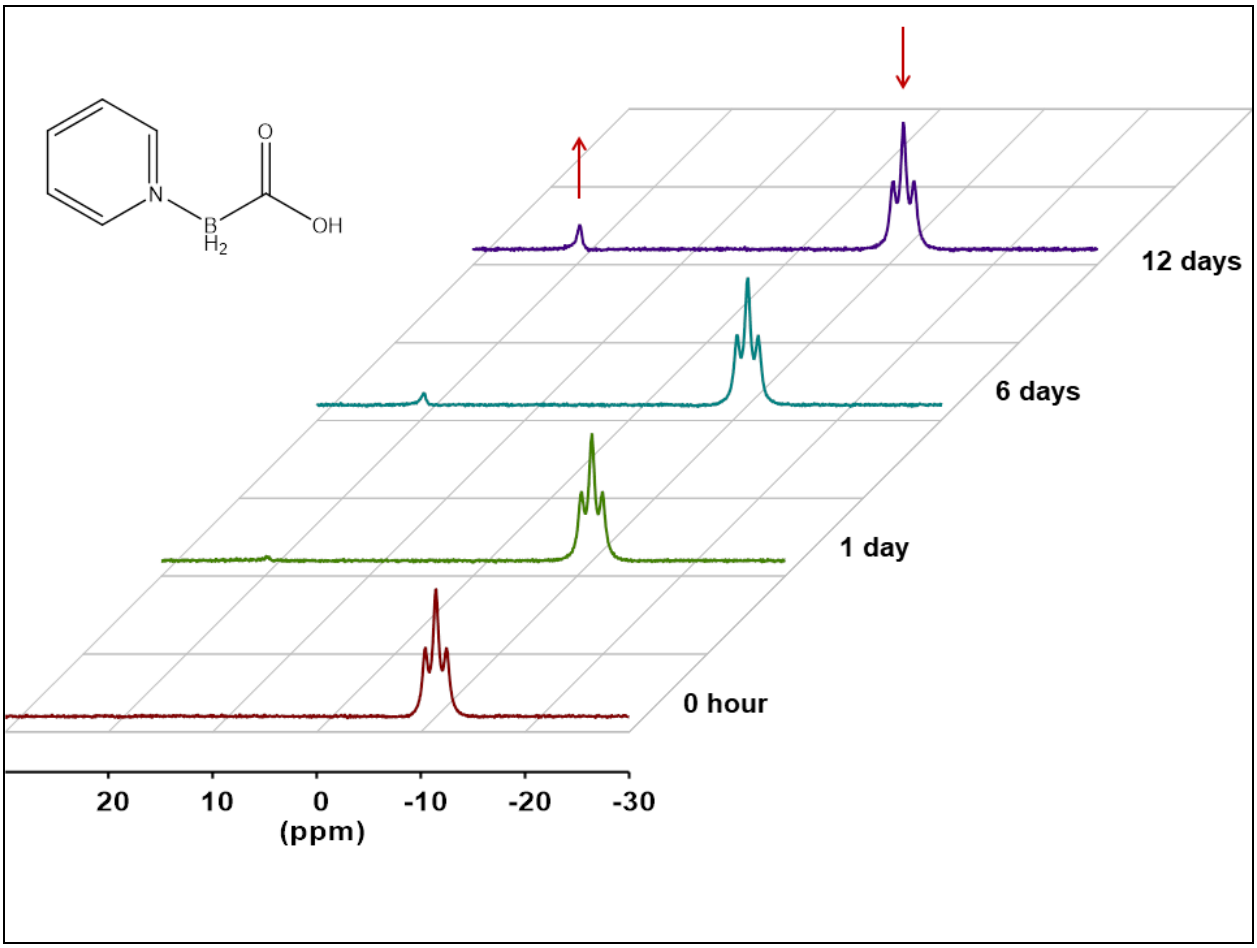


**Figure S25.** Decomposition of CORCB-2 monitored by $^{11}B$ NMR (normalized). A solution of 30 mM concentration was prepared in $D_2O$ and incubated at 37 °C. NMR spectra were recorded at 0, 1, 6, and 12 days. Boron atom on CORCB-2 is a triplet at δ -11.38 ppm in $D_2O$ while the product of decomposition, boric acid, shows a singlet at δ 19.72 ppm.

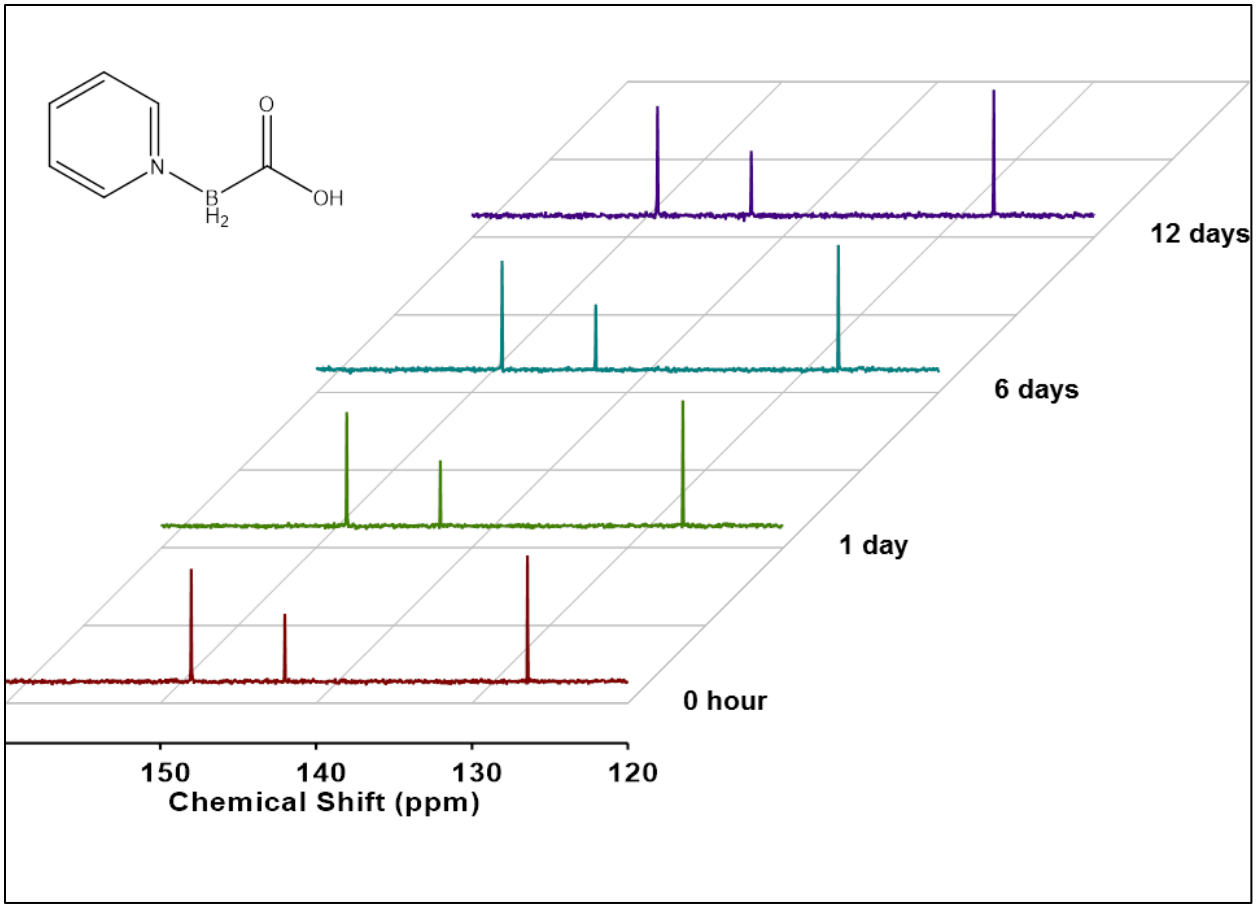


**Figure S26.** Decomposition of CORCB-2 monitored by $^{13}C$ NMR (normalized). A solution of 30 mM concentration was prepared in $D_2O$ and incubated at 37 °C. NMR spectra were recorded at 0, 1, 6, and 12 days. Decomposition rate is too slow to observe any changes in $^{13}C$ NMR.

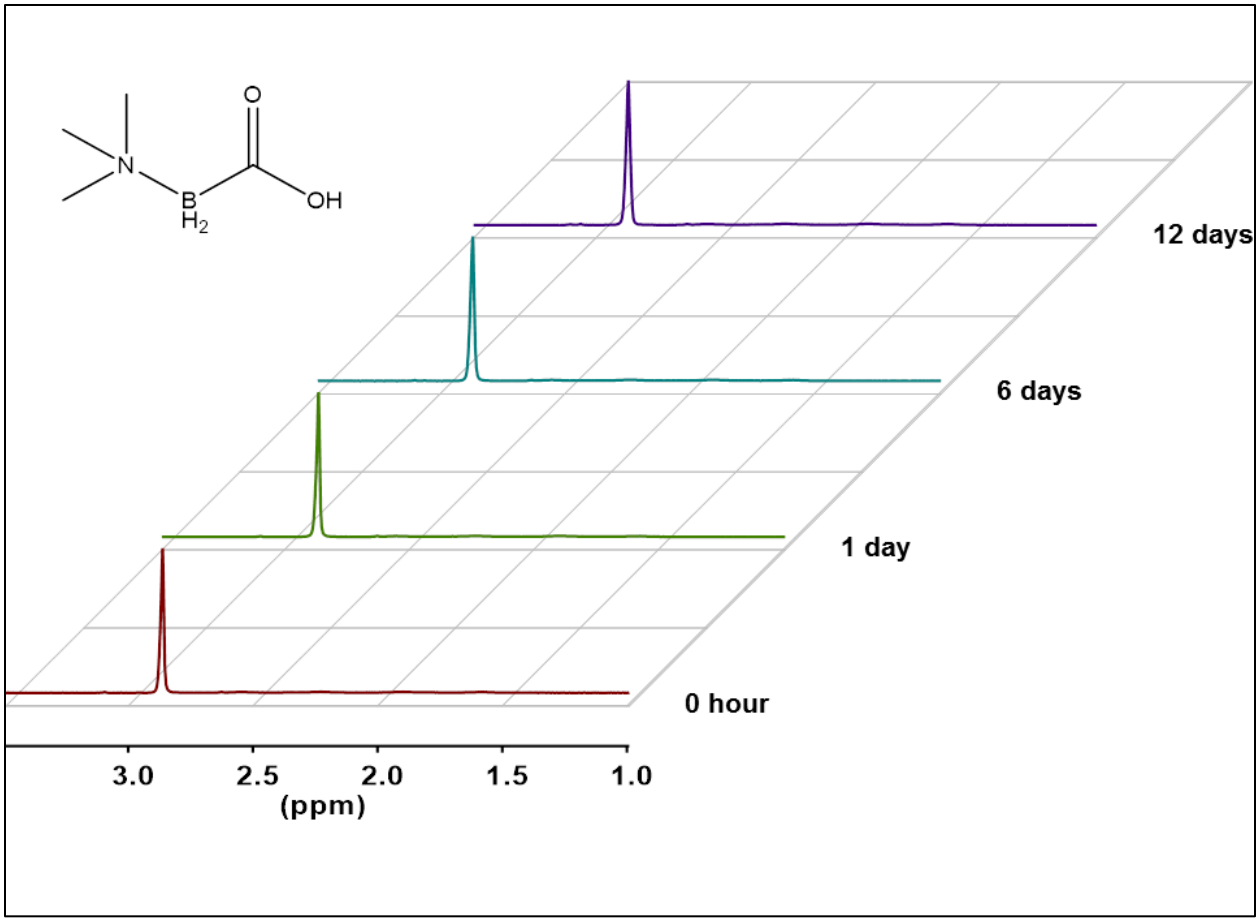


**Figure S27.** Decomposition of CORCB-3 monitored by $^{1}H$ NMR. A solution of 60 mM concentration was prepared in $D_2O$ and incubated at 37 °C. NMR spectra were recorded at 0, 1, 6, and 12 days. A new peak is observed at δ 3.05 ppm.

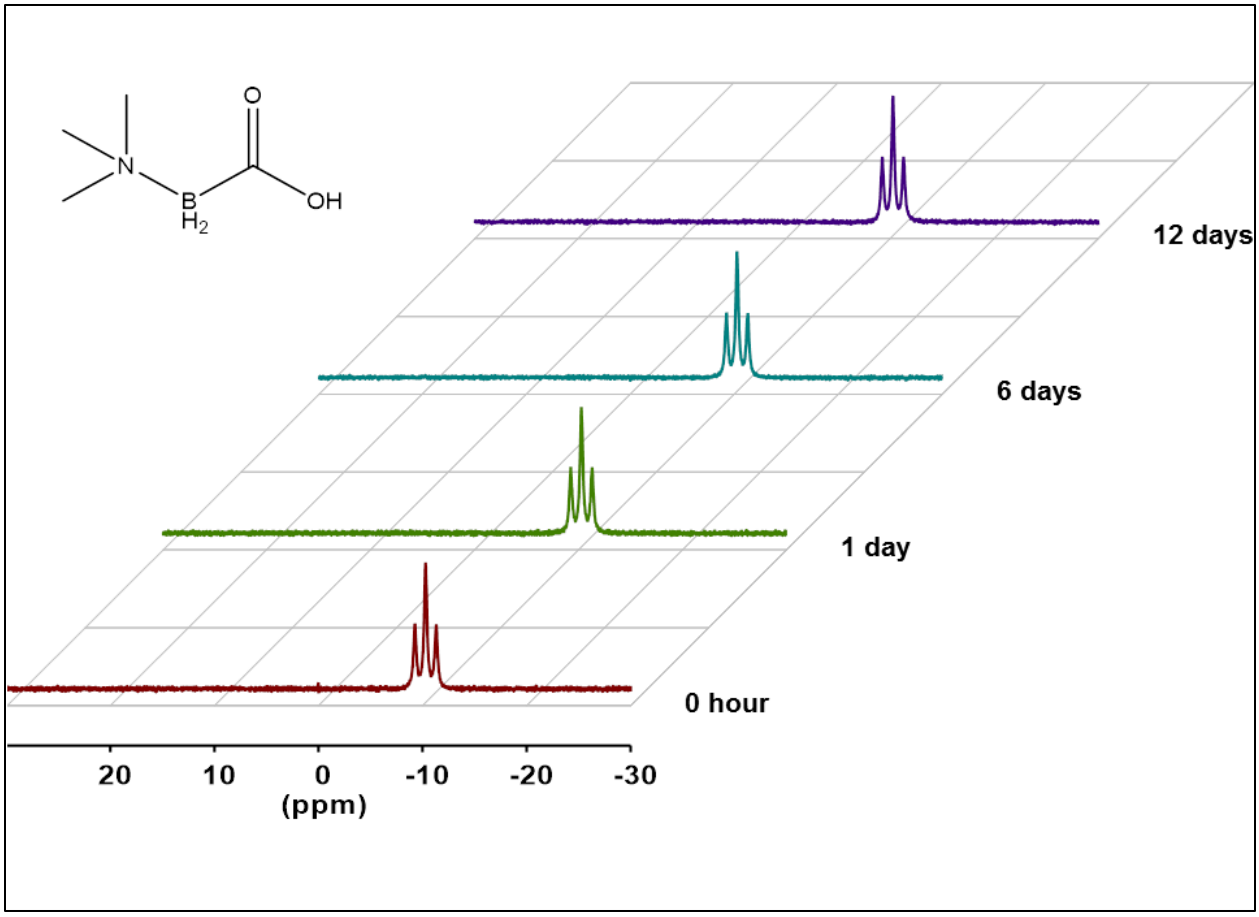


**Figure S28.** Decomposition of CORCB-3 monitored by $^{11}B$ NMR (normalized). A solution of 30 mM concentration was prepared in $D_2O$ and incubated at 37 °C. NMR spectra were recorded at 0, 1, 6, and 12 days. Boron atom on CORCB-3 is a triplet at δ -10.28 ppm in $D_2O$ while the product of decomposition, boric acid, is not visible up to 12 days.

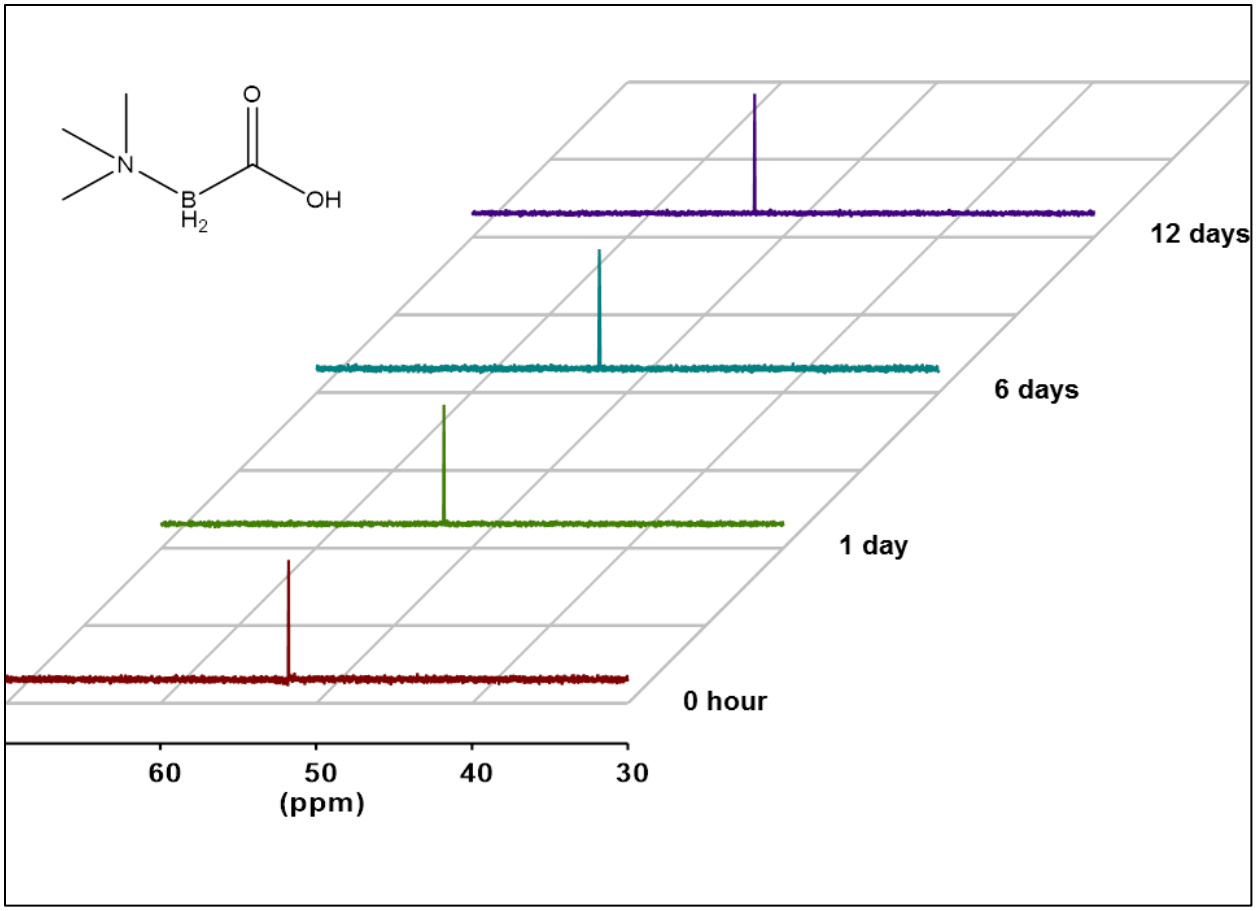


**Figure S29.** Decomposition of CORCB-3 monitored by $^{13}C$ NMR (normalized). A solution of 60 mM concentration was prepared in $D_2O$ and incubated at 37 °C. NMR spectra were recorded at 0, 1, 6, and 12 days. No changes observed for new carbon species.

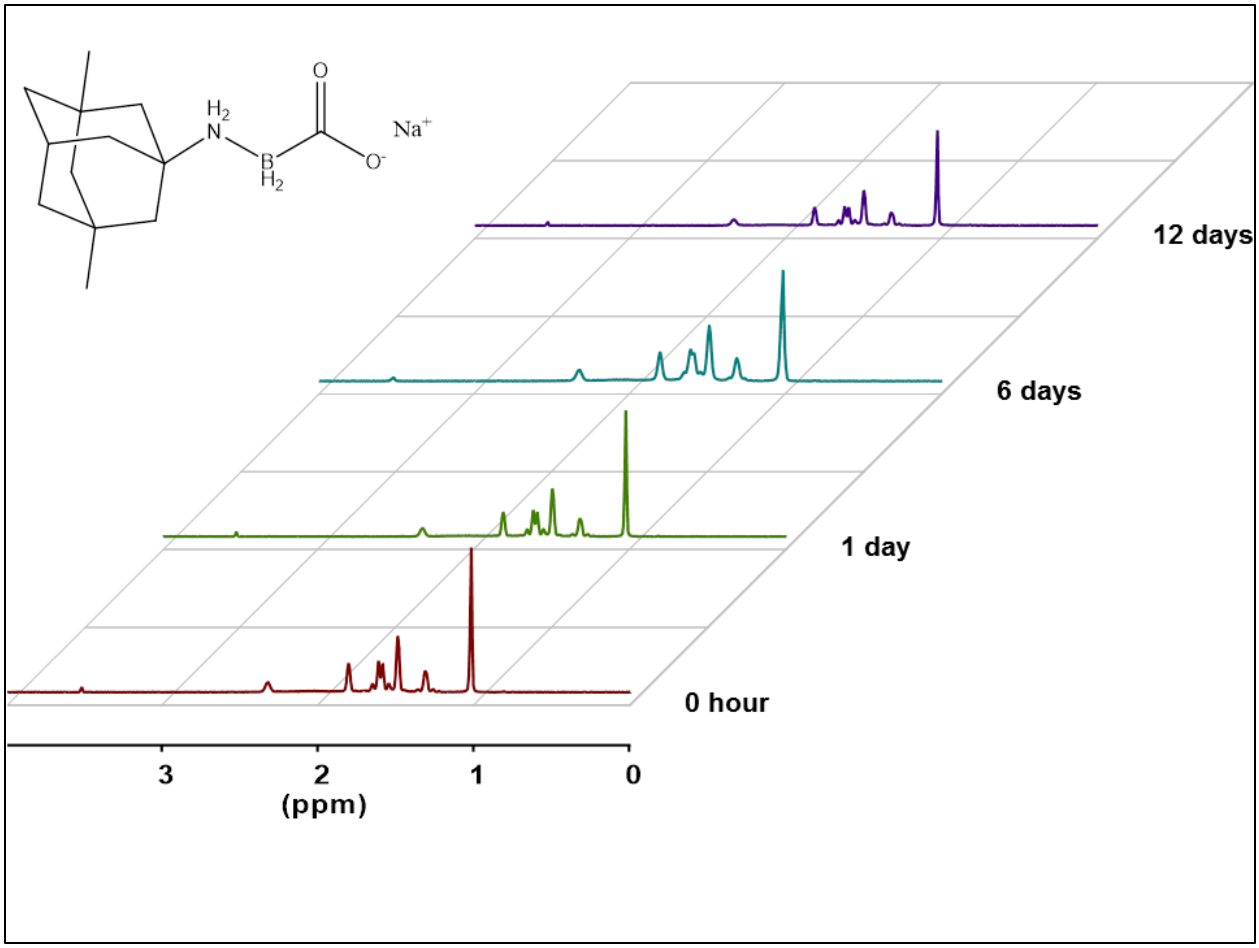


**Figure S30.** Decomposition of CORCB-4 sodium salt monitored by $^{1}$H NMR. A solution of 30 mM concentration was prepared in $D_2O$ and incubated at 37 °C. NMR spectra were recorded at 0, 1, 6, and 12 days. No visible changes observed.

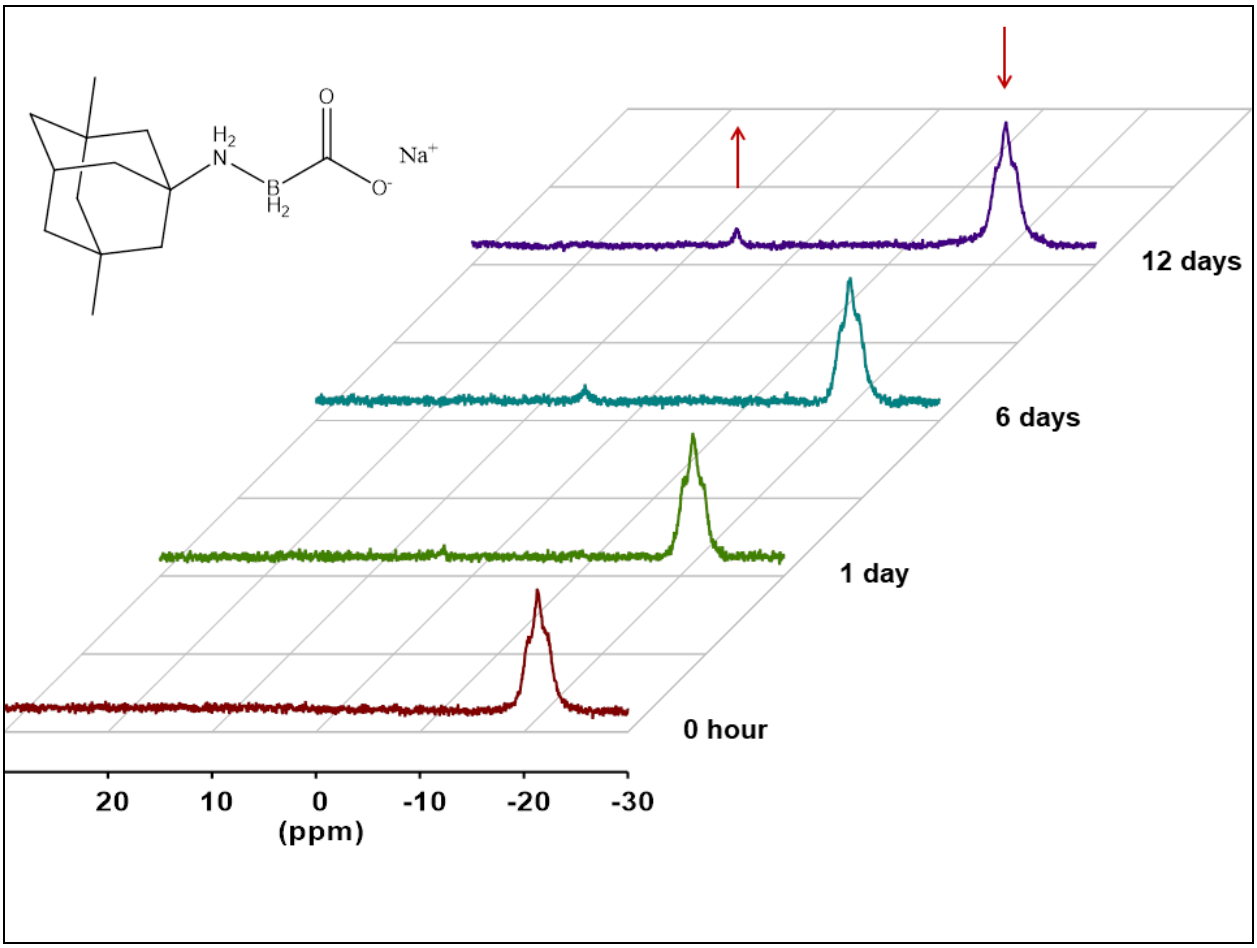


**Figure S31.** Decomposition of CORCB-4 sodium salt monitored by $^{11}B$ NMR (normalized). A solution of 30 mM concentration was prepared in $D_2O$ and incubated at 37 °C. NMR spectra were recorded at 0, 1, 6, and 12 days. A triplet at δ –21.52 ppm represents boron atom on CORCB-4 in $D_2O$ while the product of decomposition, borate, is a singlet at δ 4.50 ppm.

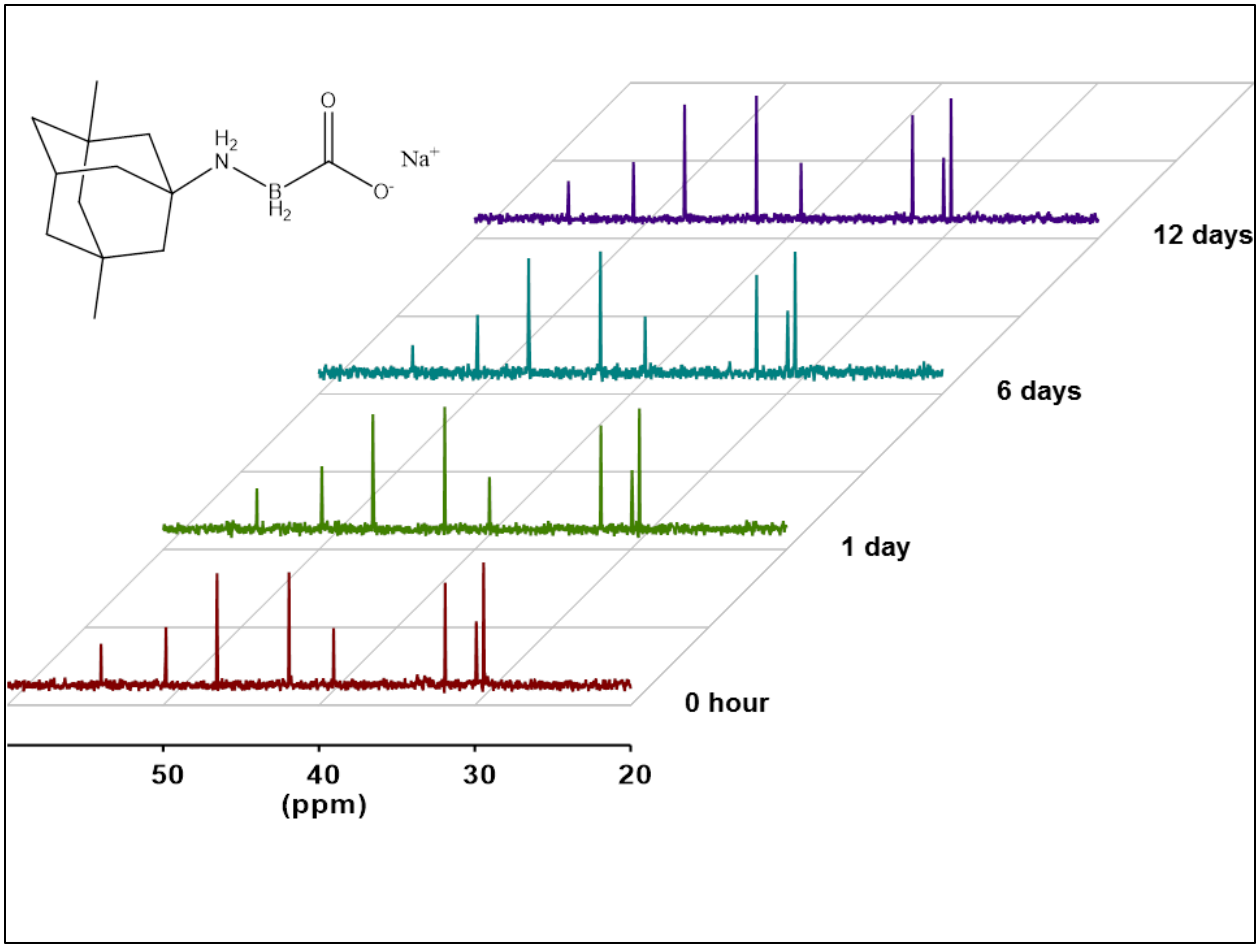


**Figure S32.** Decomposition of CORCB-4 sodium salt monitored by $^{13}C$ NMR (normalized). A solution of 30 mM concentration was prepared in $D_2O$ and incubated at 37 °C. NMR spectra were recorded at 0, 1, 6, and 12 days. No visible changes observed on $^{13}C$ NMR.

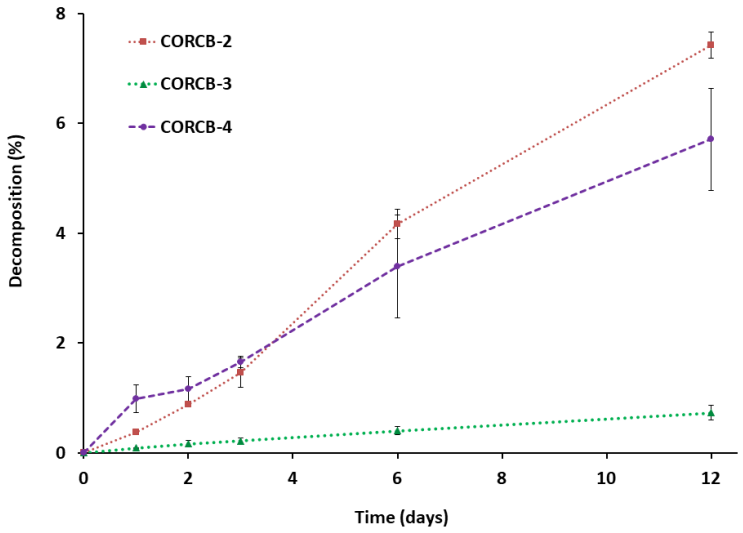


**Figure S33.** Decarbonylation of CORCBs under physiological pH and temperature. Percent decomposition in $D_2O$ was monitored by using NMR spectroscopy for 12 days. The percentages of amine group released are calculated from $^1H$ NMR integration.

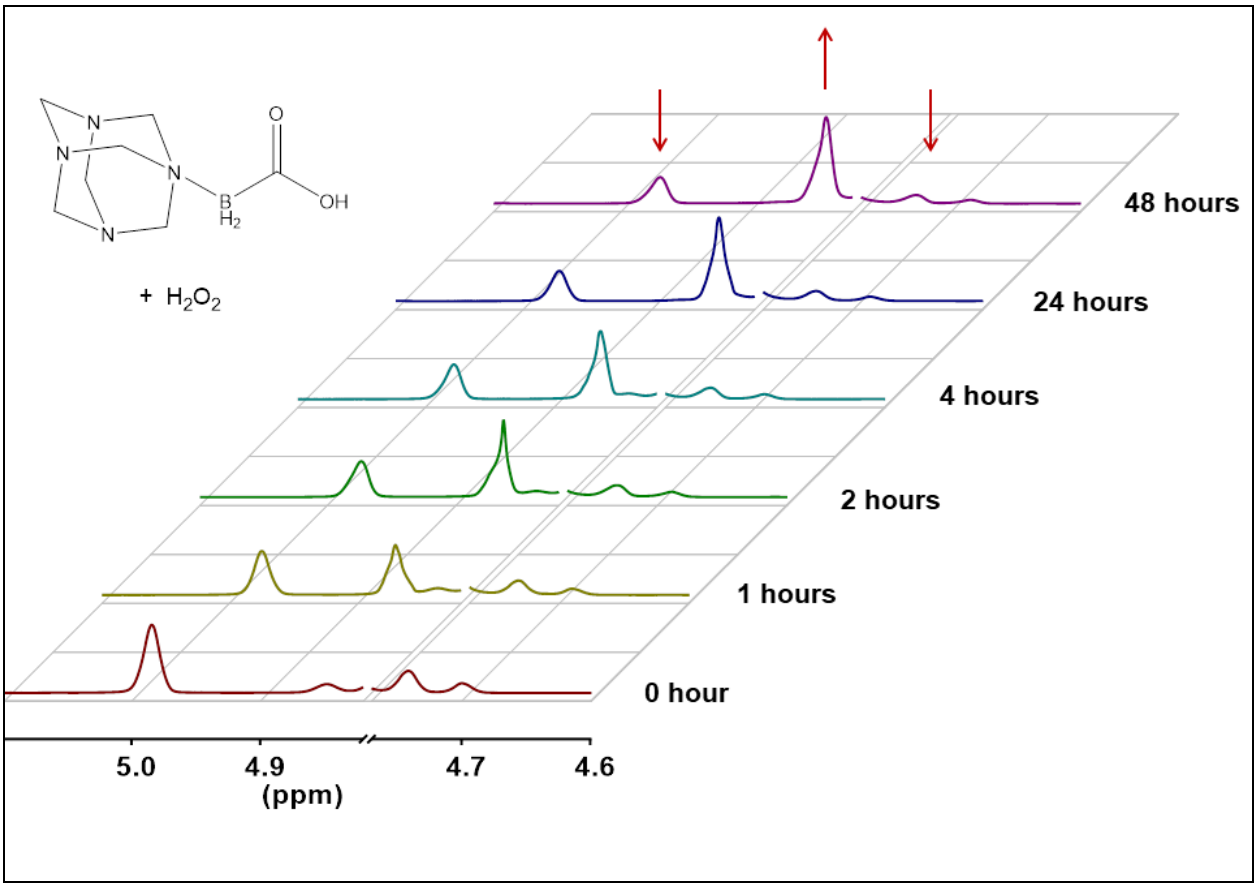


**Figure S34.** Decomposition of CORCB-1 in the presence of $H_2O_2$ monitored by $^1H$ NMR. A solution at the concentration of 60 mM was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, 24 and 48 hours. Fast decomposition is evident within 1 hour with the appearance of free HMTA peak at 4.84 ppm.

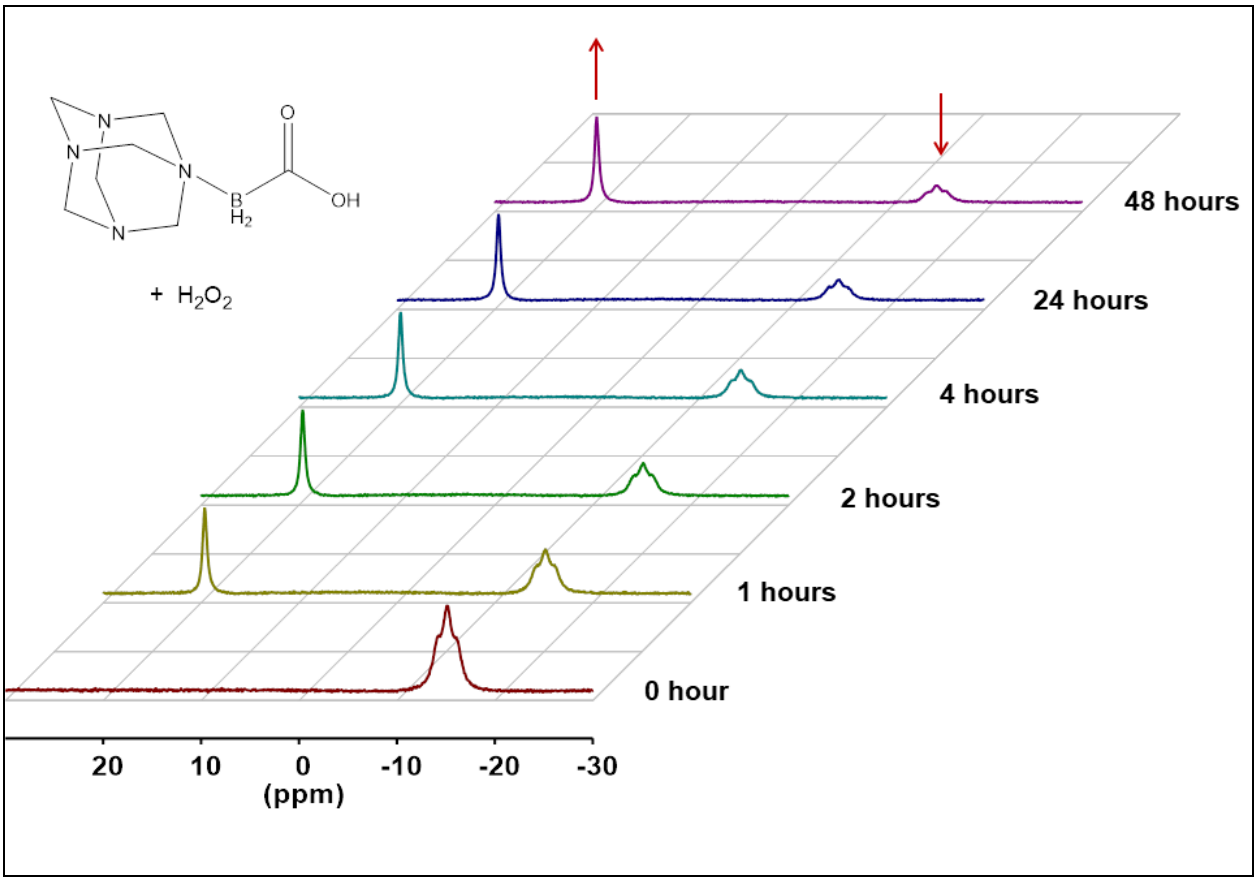


**Figure S35.** Decomposition of CORCB-1 in the presence of $H_2O_2$ monitored by $^{11}B$ NMR. A solution at the concentration of 60 mM was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, 24 and 48 hours. A triplet representing boron atom on CORCB-1 at -15.16 ppm disappears while the product of decomposition, boric acid, a singlet at 19.63 ppm is greatly noticeable by 1 hour.

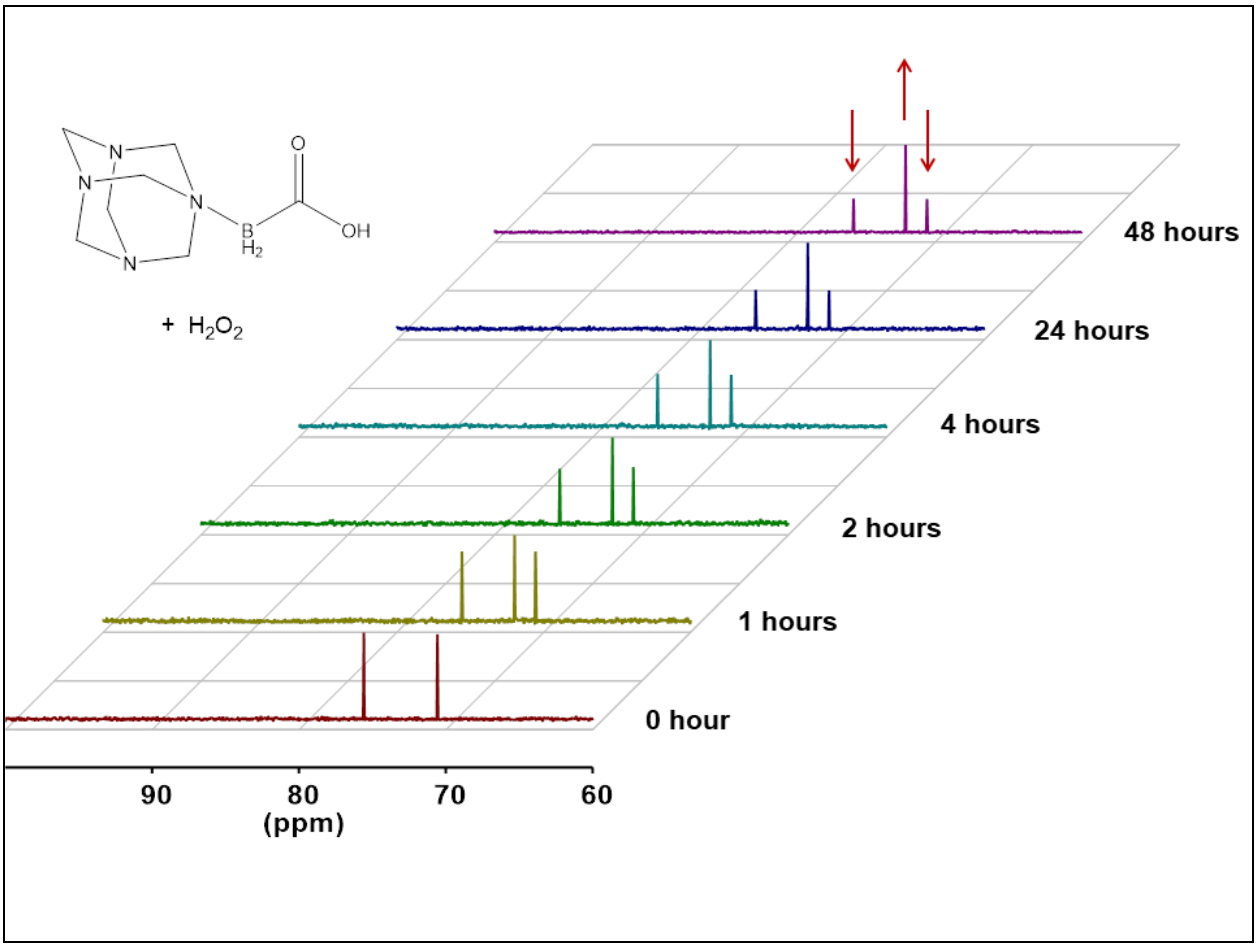


**Figure S36.** Decomposition of CORCB-1 in the presence of $H_2O_2$ monitored by $^{13}C$ NMR (normalized). A solution at the concentration of 60 mM was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, 24 and 48 hours. A singlet peak at 72.00 ppm representing free HMTA molecule appears within 1 hour.

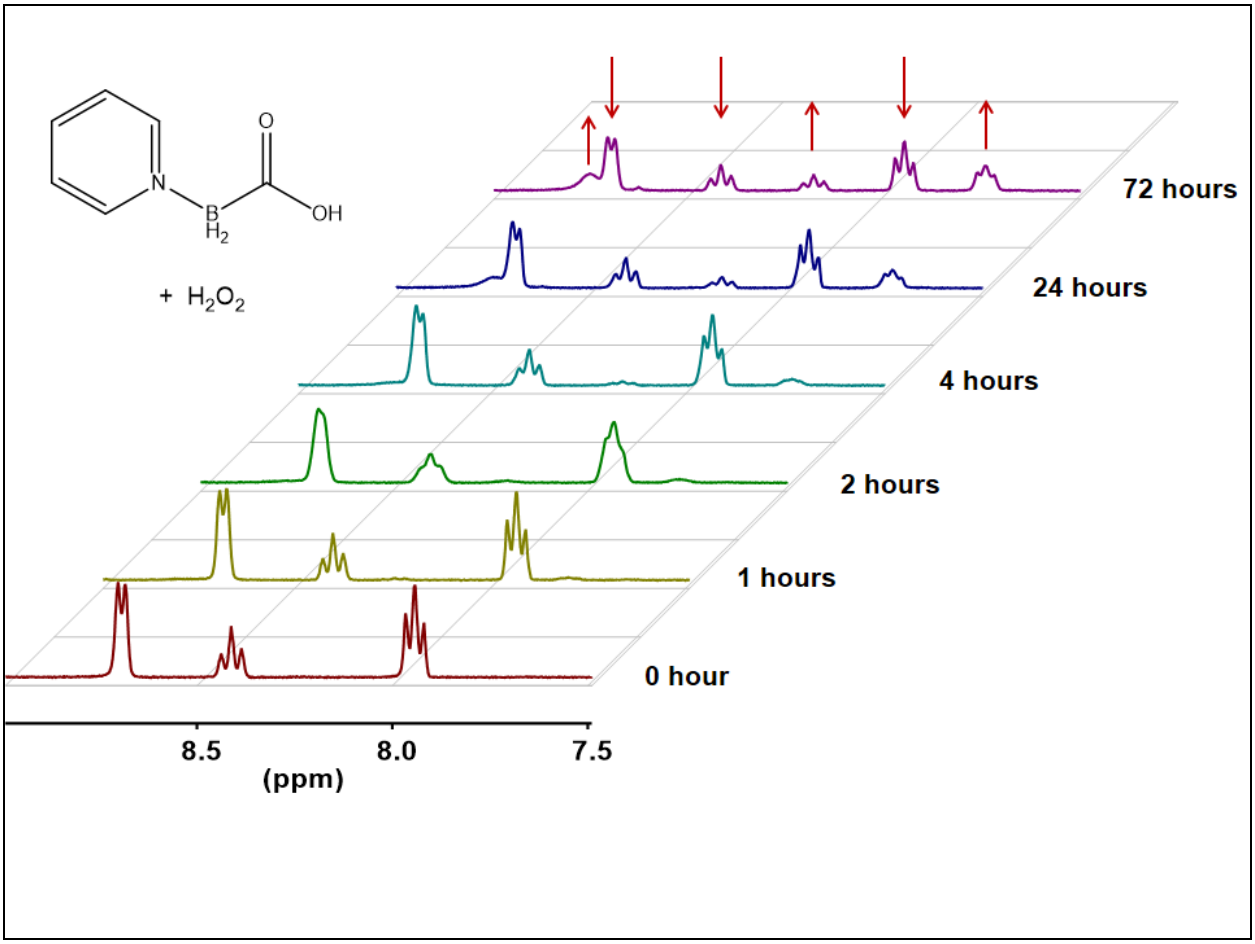


**Figure S37.** Decomposition of CORCB-2 in the presence of $H_2O_2$ monitored by $^1H$ NMR. A solution at the concentration of 30 mM was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, 24 and 72 hours. A new set of peaks for aromatic hydrogens of the free pyridine at δ 8.75 ppm, δ 8.17 ppm, and δ 7.73 ppm starts to emerge in 2 hours and apparent by 24 hours.

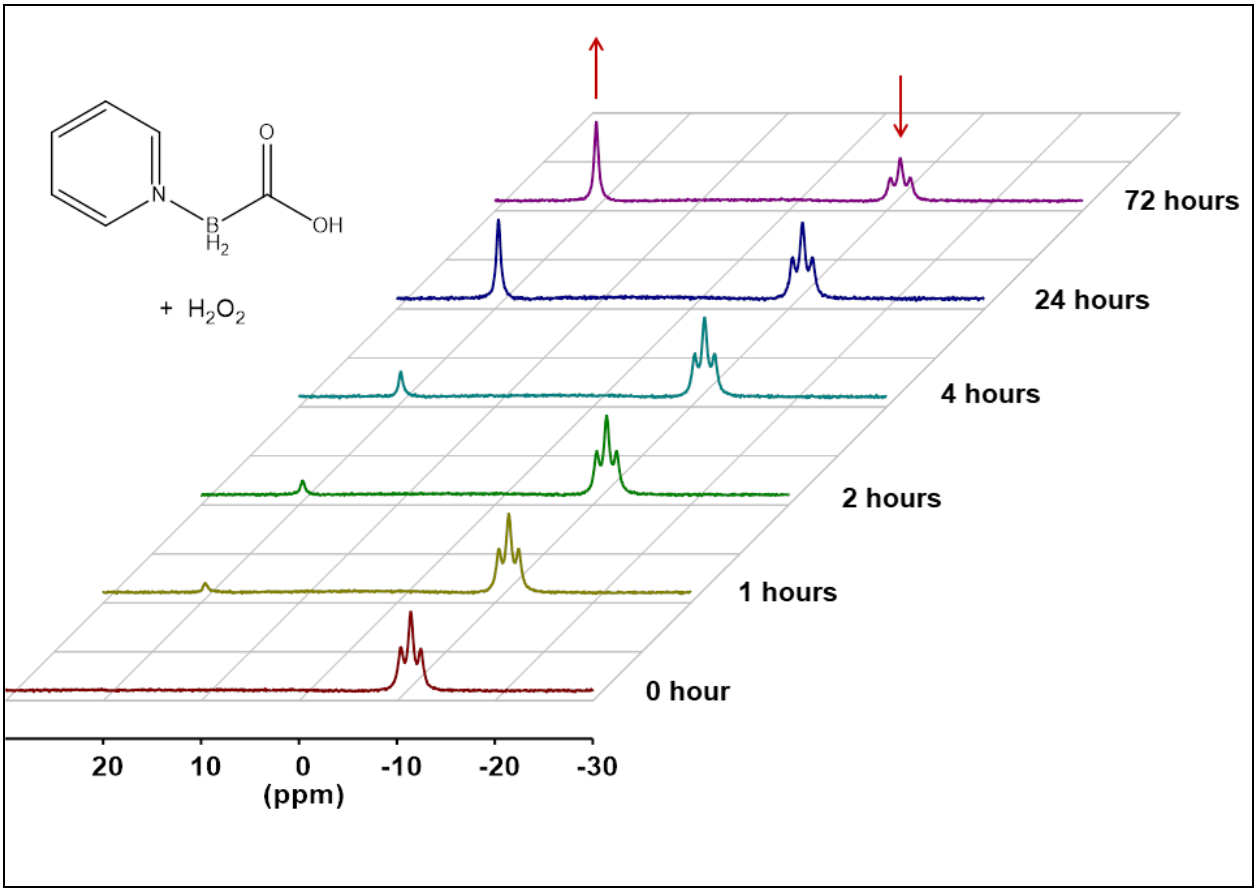


**Figure S38.** Decomposition of CORCB-2 in the presence of $H_2O_2$ monitored by $^{11}B$ NMR (normalized). A solution of 30 mM concentration was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, 24 and 72 hours. Boric acid, a decomposition product emerges as a singlet at 19.64 ppm within 1 hour.

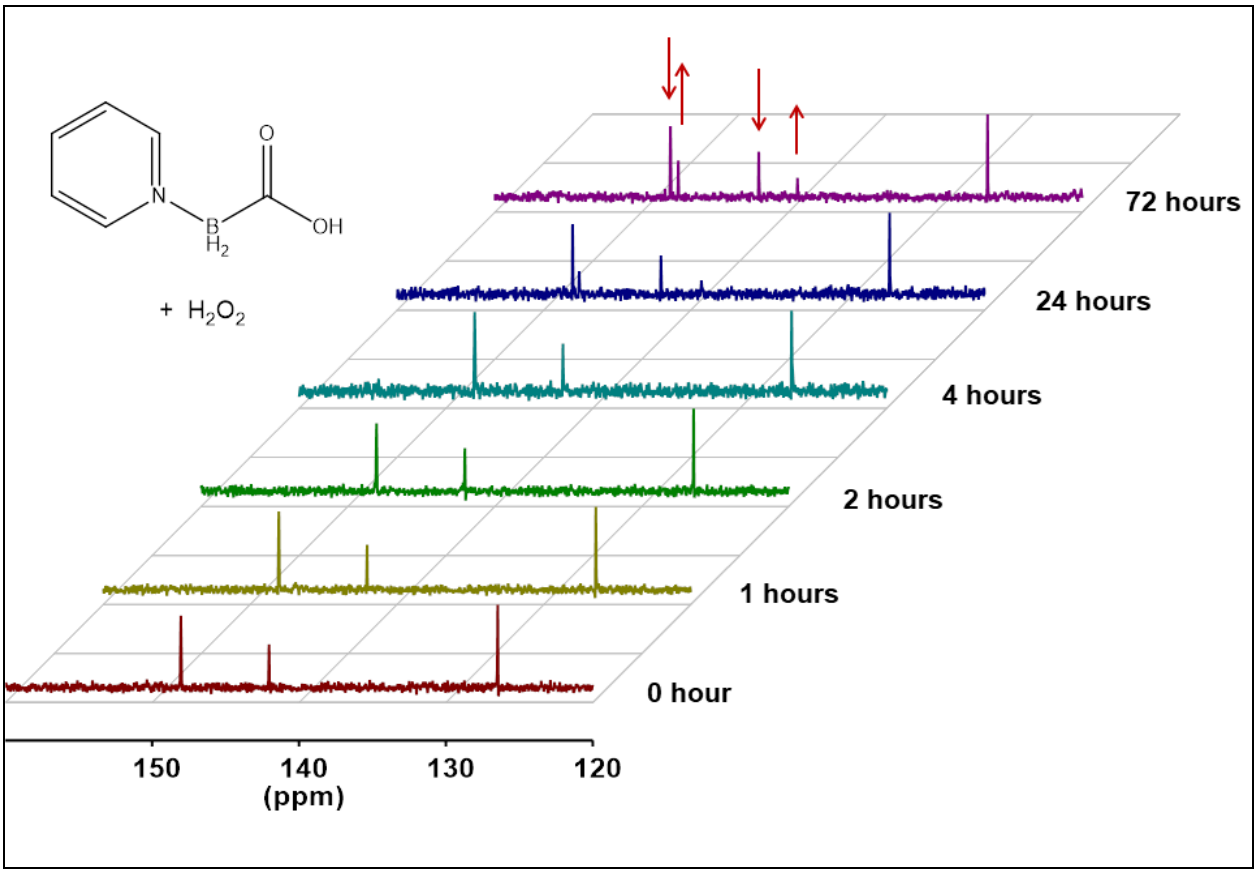


**Figure S39.** Decomposition of CORCB-2 in the presence of $H_2O_2$ monitored by $^{13}C$ NMR (normalized). A solution of 30 mM concentration was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, 24 and 72 hours. Changes in $^{13}C$ NMR are visible within 24 hours.

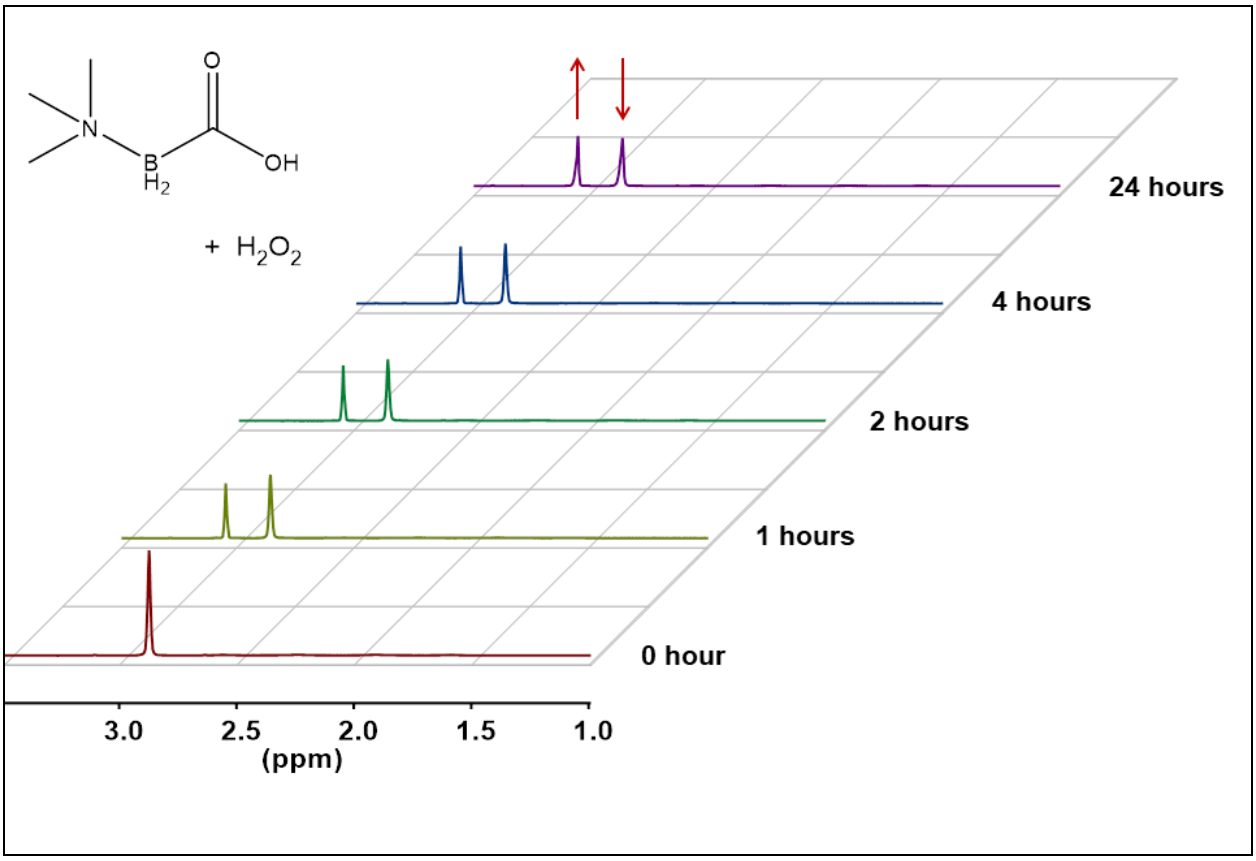


**Figure S40.** Decomposition of CORCB-3 in the presence of $H_2O_2$ monitored by $^1H$ NMR. A solution at the concentration of 60 mM was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, and 24 hours. A new peak at δ 3.05 ppm emerges within 1 hour as an evidence of decomposition.

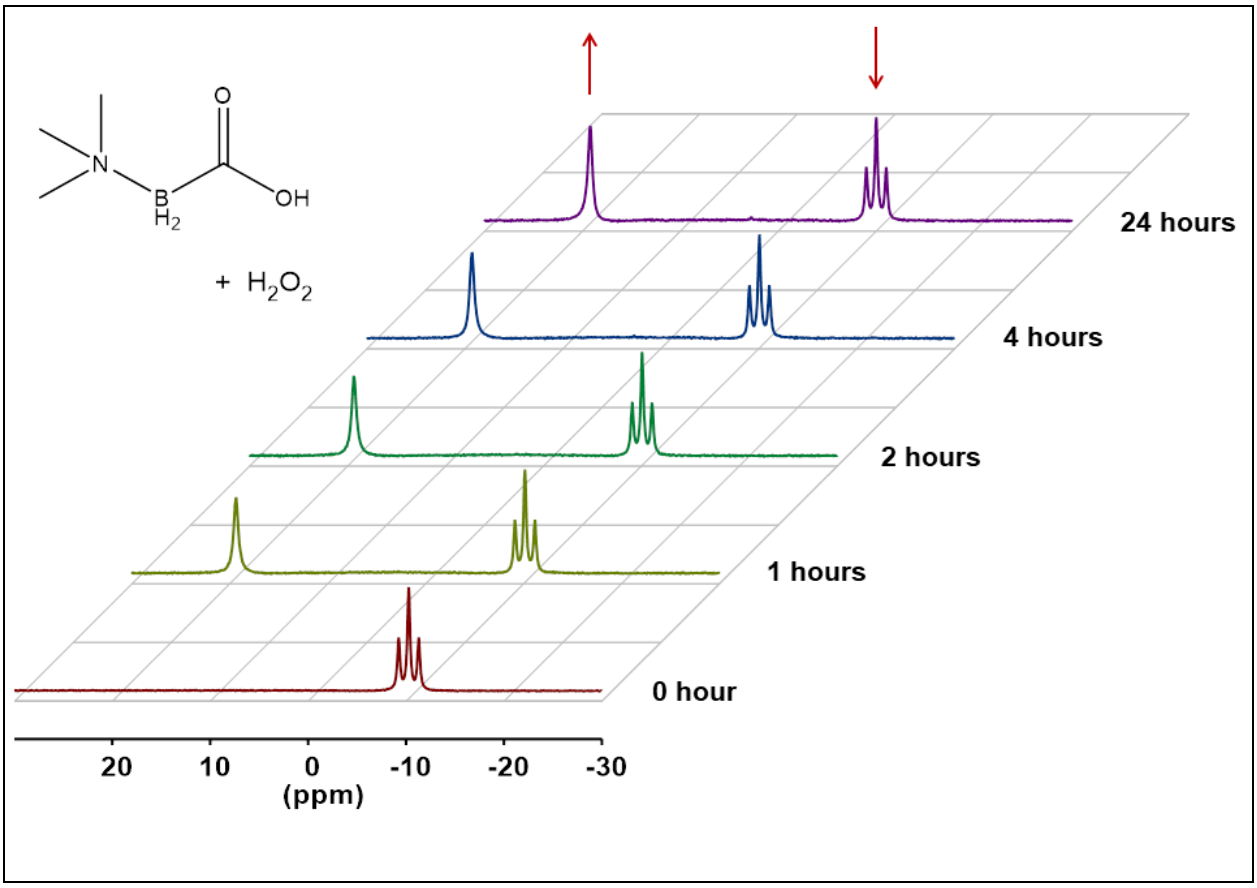


**Figure S41.** Decomposition of CORCB-3 in the presence of $H_2O_2$ monitored by $^{11}B$ NMR (normalized). A solution of 60 mM concentration was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, and 24 hours. Boric acid, a singlet at δ 19.99 ppm is clearly detectable by 1 hour.

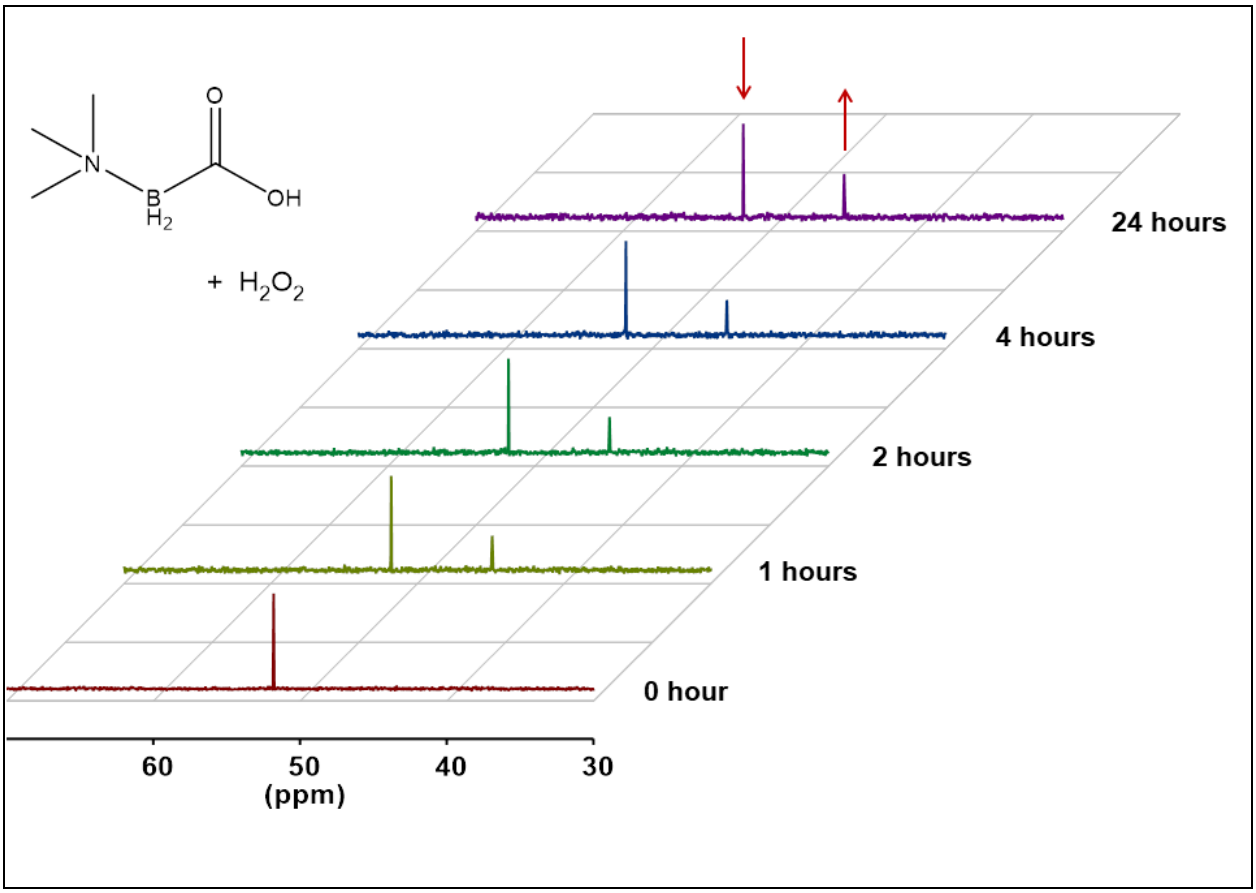


**Figure S42.** Decomposition of CORCB-3 in the presence of $H_2O_2$ monitored by $^{13}C$ NMR (normalized). A solution of 60 mM concentration was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, and 24 hours. Changes in $^{13}C$ NMR are visible within 1 hour with a new peak emerging at δ 44.91 ppm for the free trimethylamine.

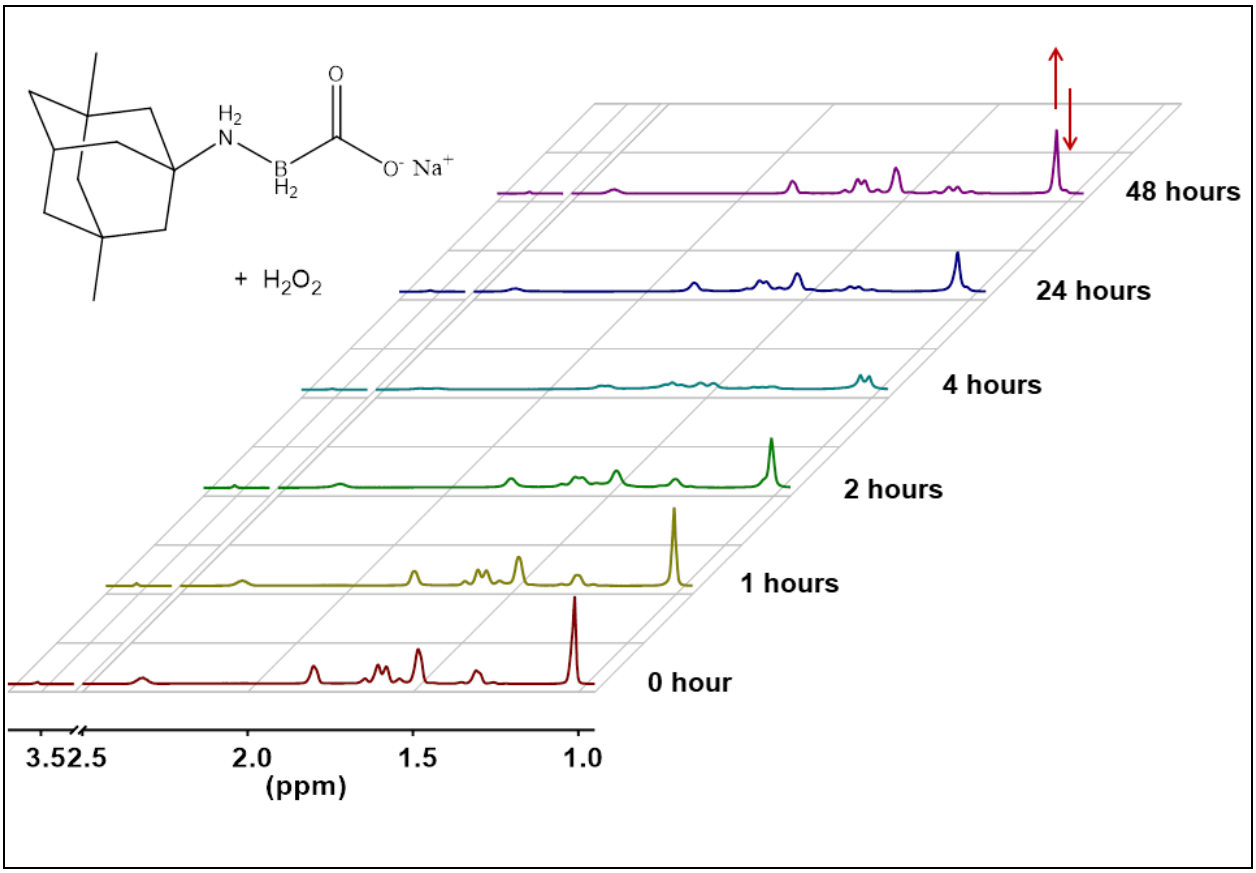


**Figure S43.** Decomposition of CORCB-4 sodium salt in the presence of $H_2O_2$ monitored by $^1H$ NMR. A solution at the concentration of 30 mM was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, 24 and 48 hours. A new peak of methyl groups at δ 1.03 ppm is visible on 4-hour spectrum as an evidence of decomposition.

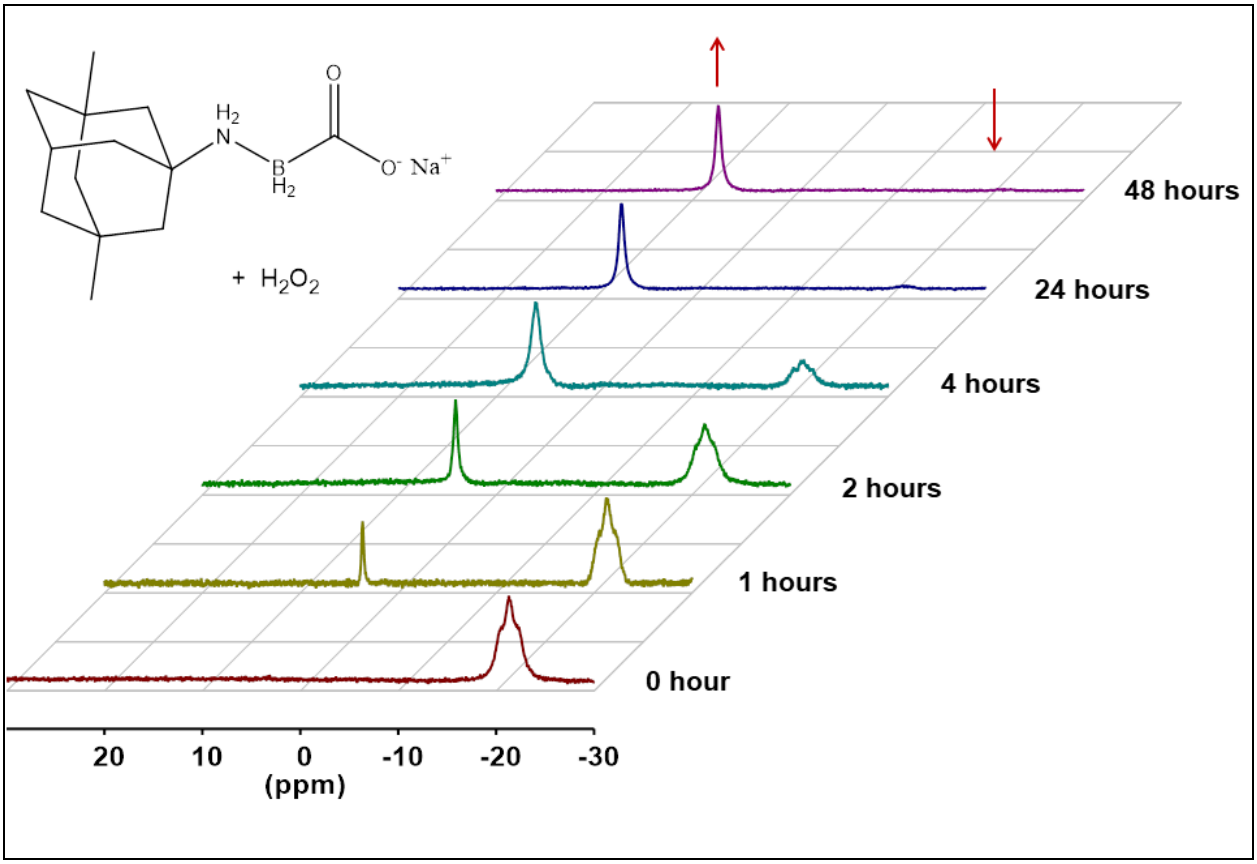


**Figure S44.** Decomposition of CORCB-4 sodium salt in the presence of $H_2O_2$ monitored by $^{11}B$ NMR (normalized). A solution of 30 mM concentration was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, 2, 4, 24 and 48 hours. Borate, a singlet at δ 7.35 ppm can be seen by 1 hour.

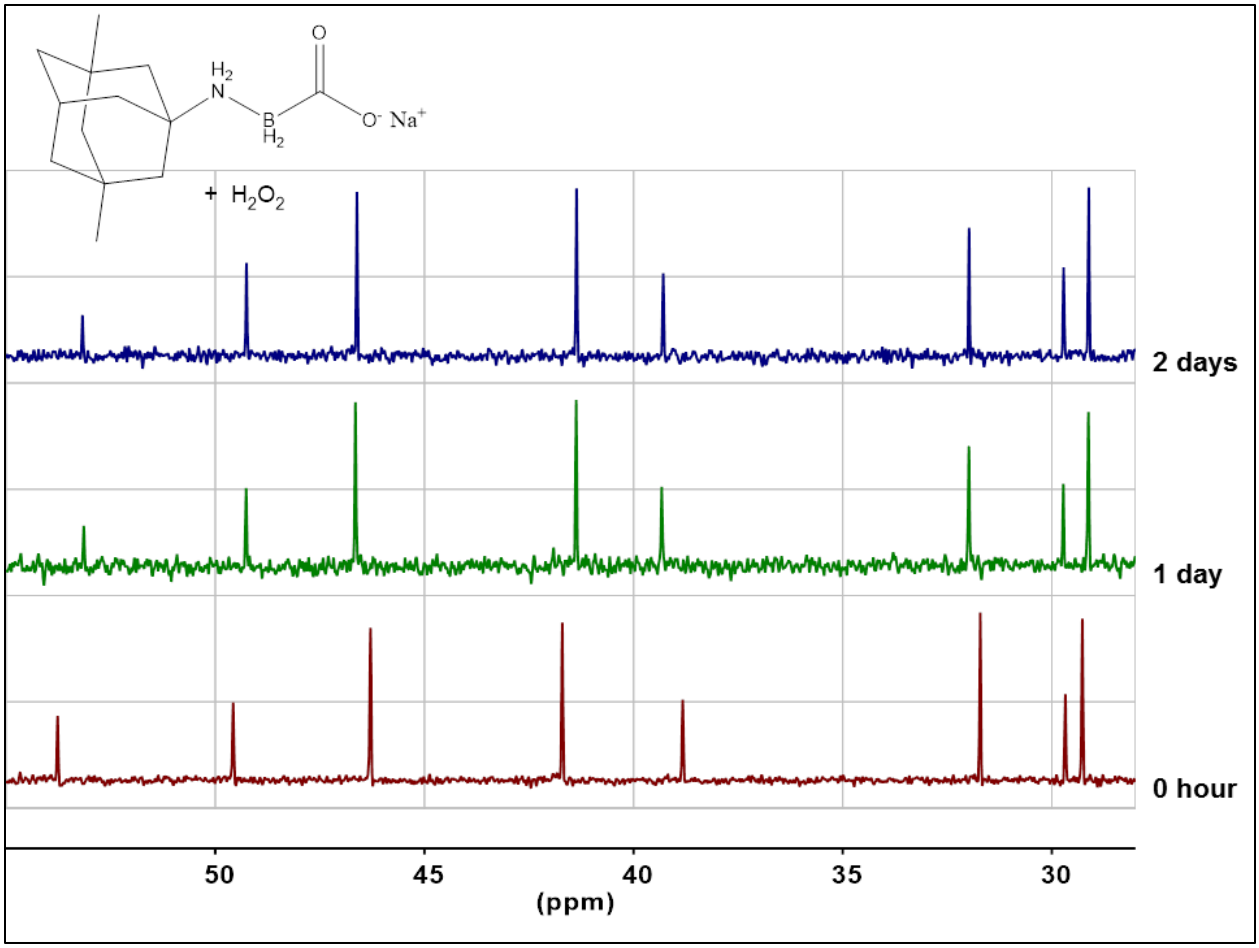


**Figure S45.** Decomposition of CORCB-4 sodium salt in the presence of $H_2O_2$ monitored by $^{13}C$ NMR (normalized). A solution of 30 mM concentration was prepared in $D_2O$ and incubated with 1.5 equivalent of $H_2O_2$ at 37 °C. NMR spectra were recorded at 0, 1, and 2 days. Shifting of the peaks is observed in 1 day.

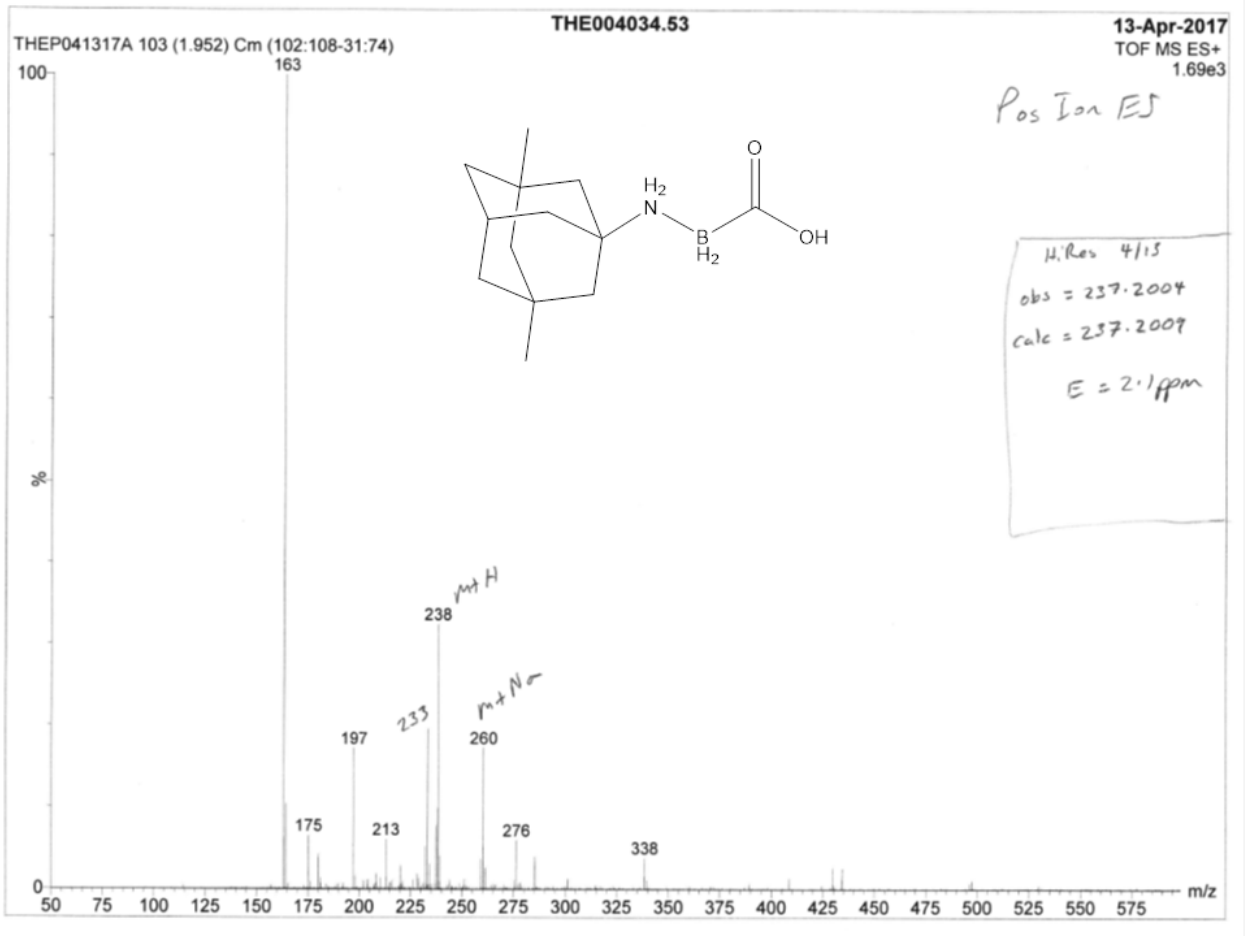


**Figure S46.** ESI mass spectrum of CORCB-4.

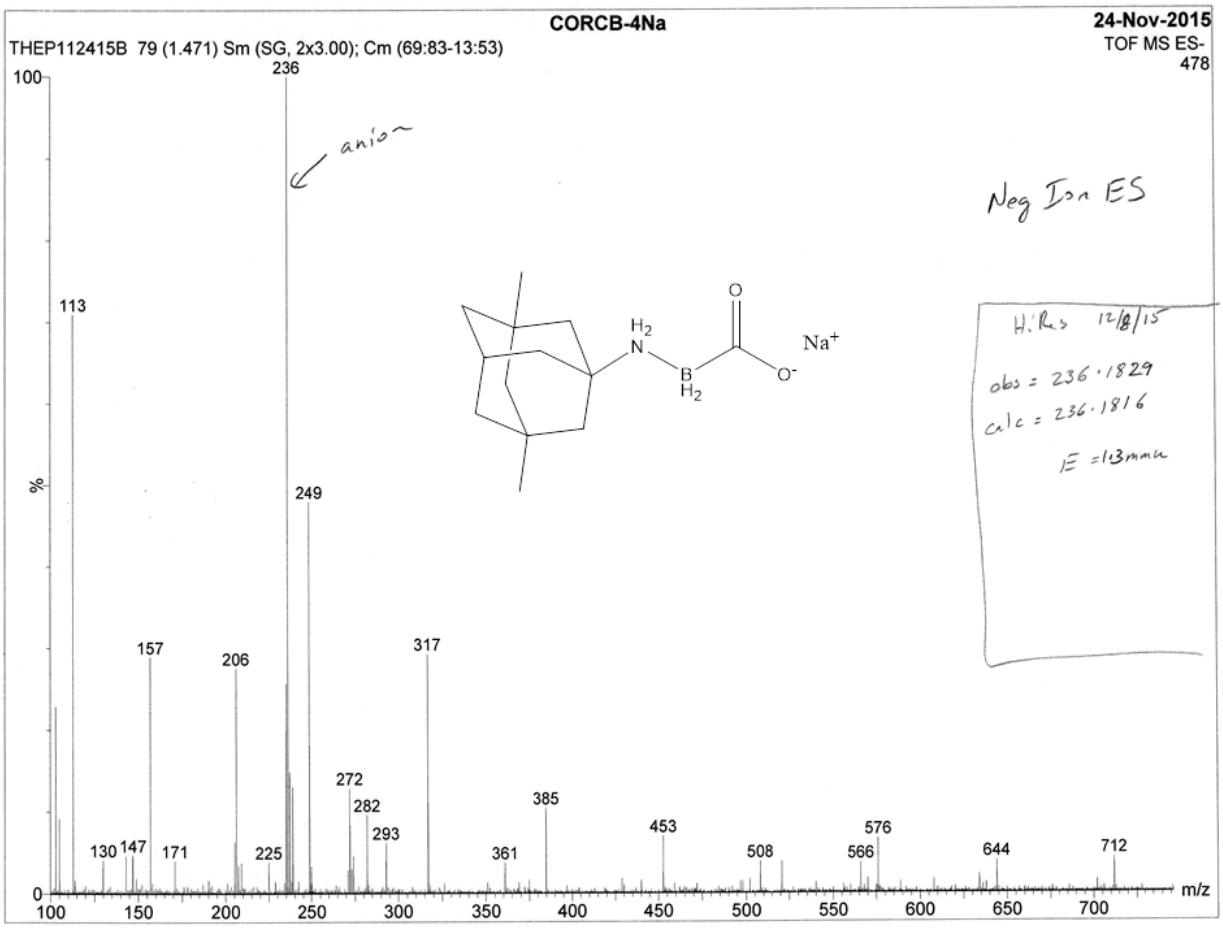


**Figure S47.** ESI mass spectrum of CORCB-4 sodium salt.

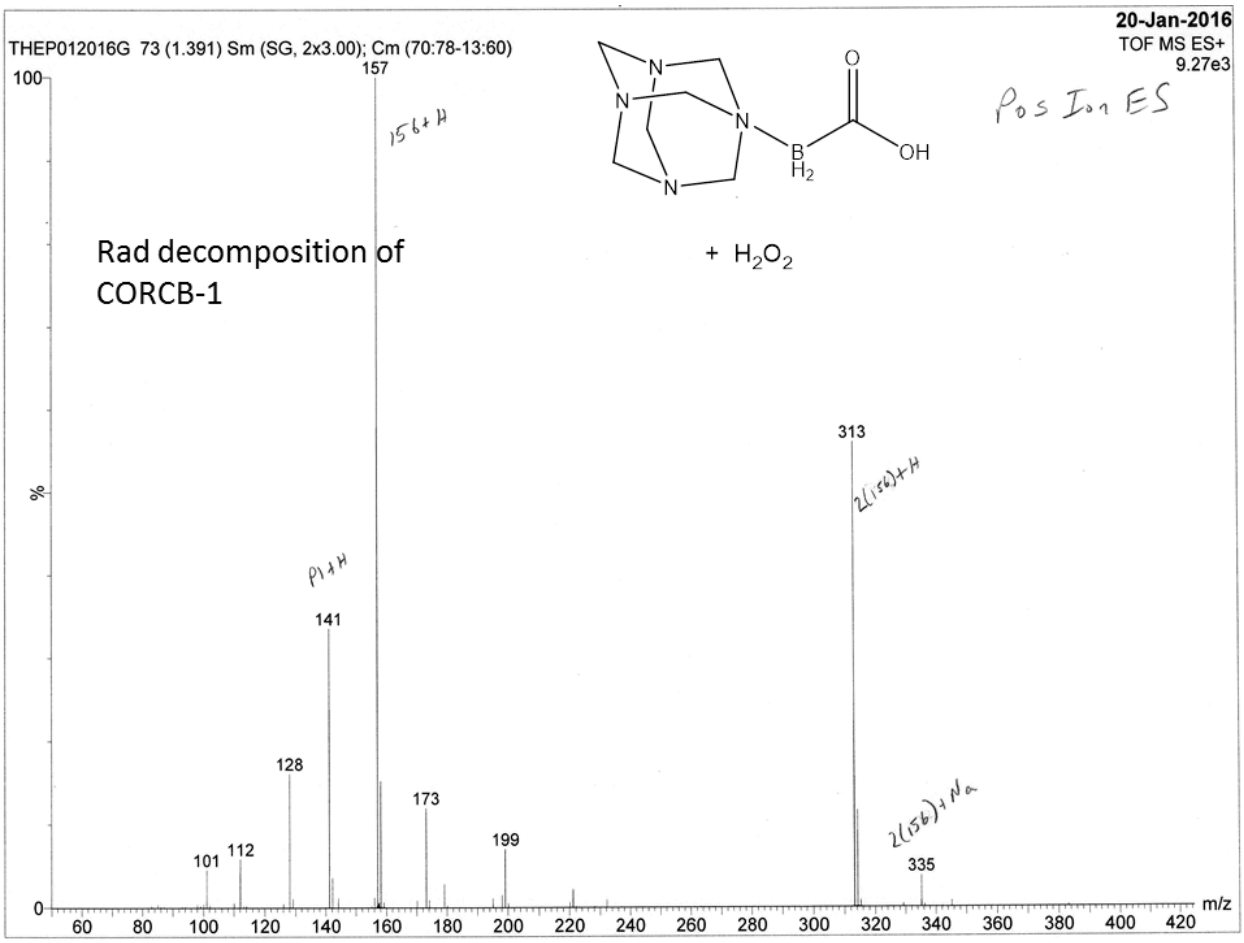


**Figure S48.** ESI mass spectrum of CORCB-1 after decomposition by $H_2O_2$.

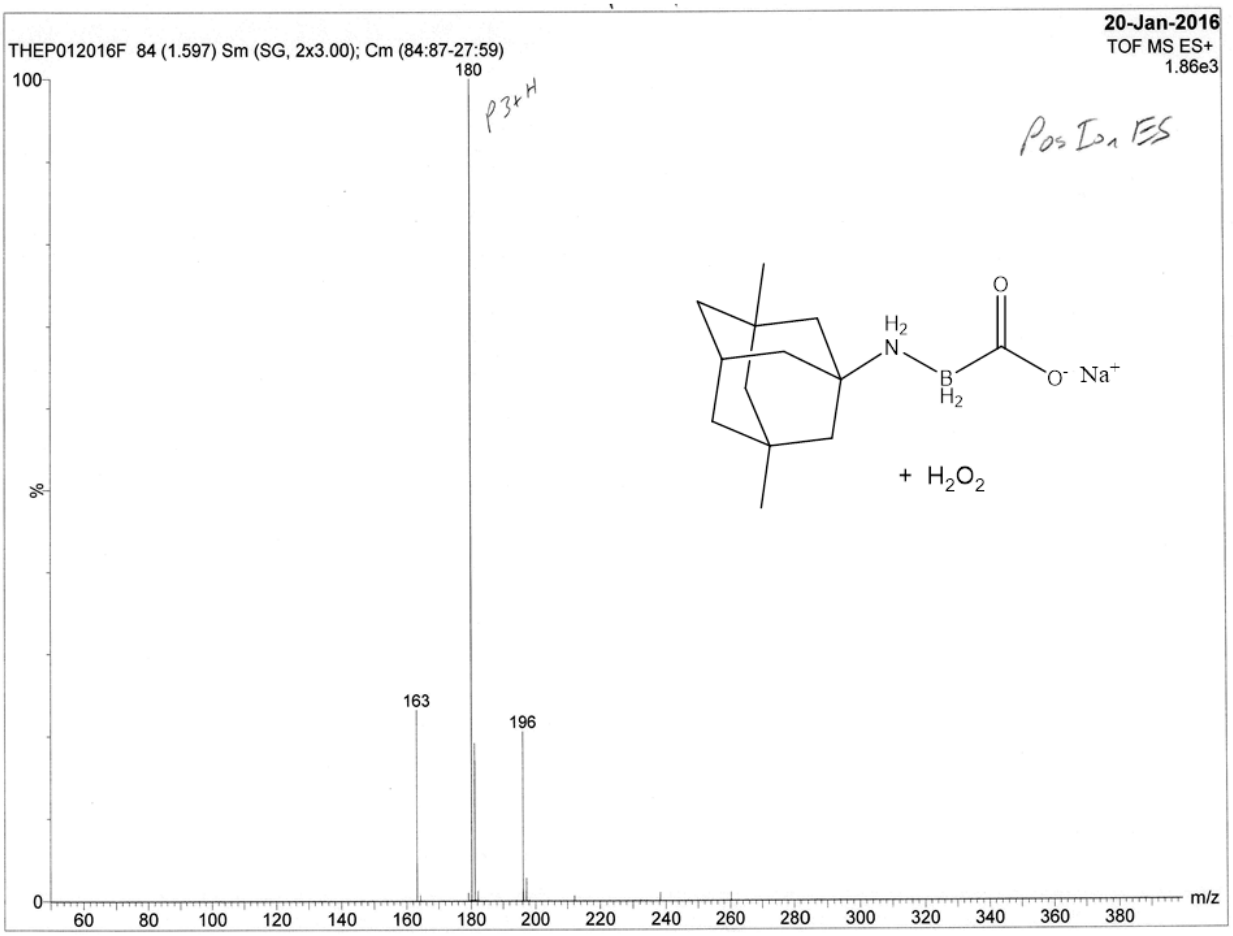


**Figure S49.** ESI mass spectrum of CORCB-4 sodium salt after decomposition by $H_2O_2$.

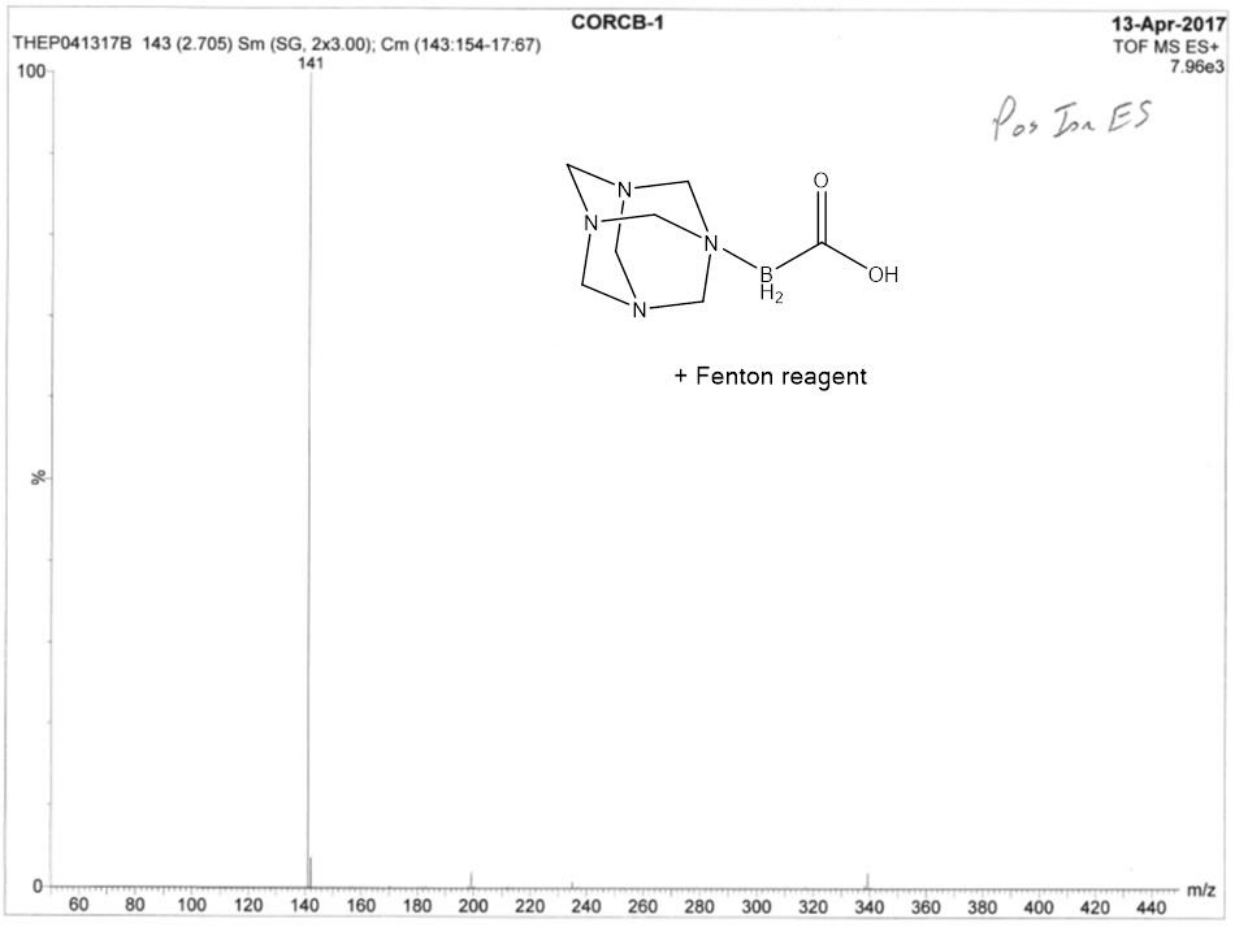


**Figure S50.** ESI mass spectrum of CORCB-1 after decomposition by Fenton reagent.

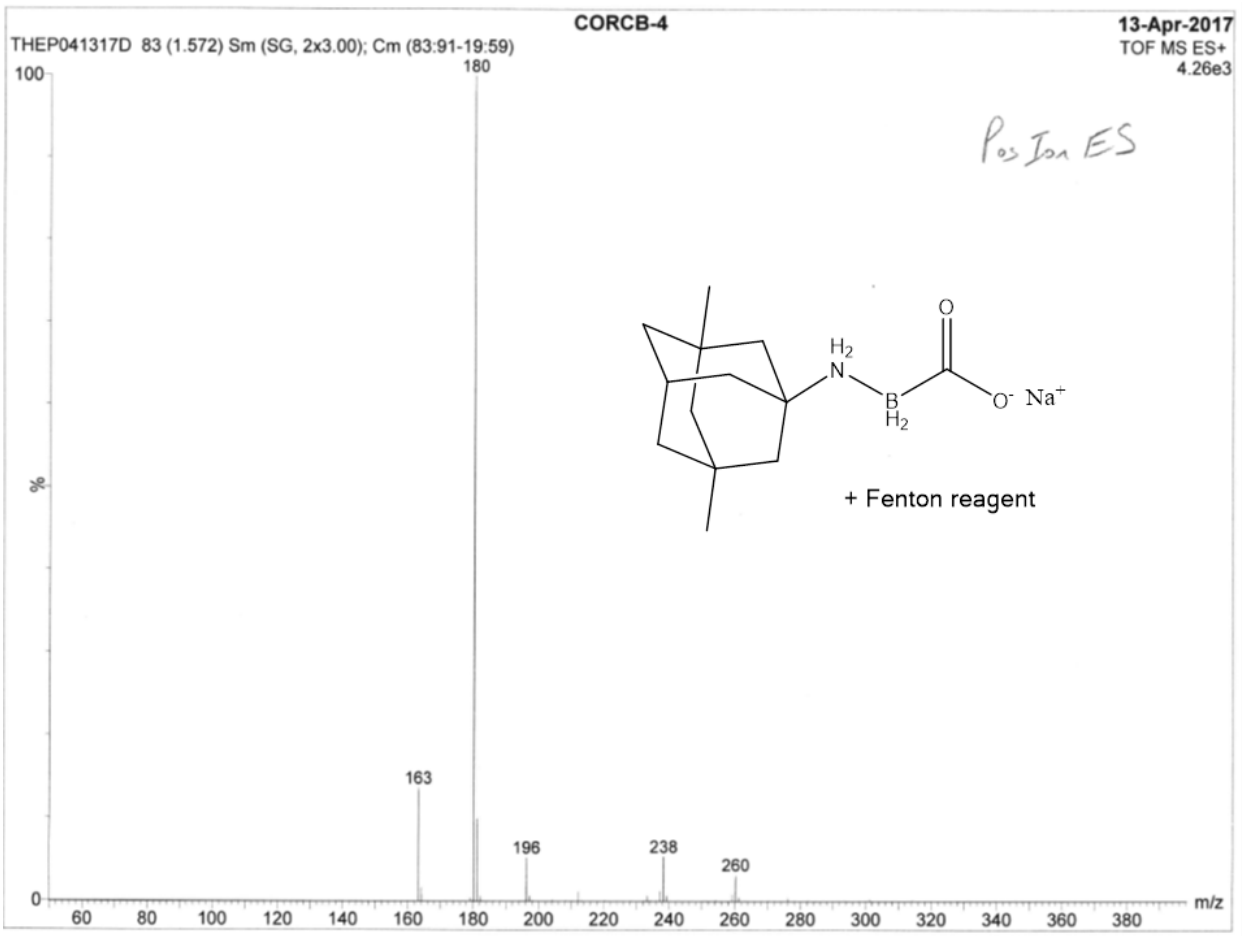


**Figure S51.** ESI mass spectrum of CORCB-4 sodium salt after decomposition by Fenton reagent.

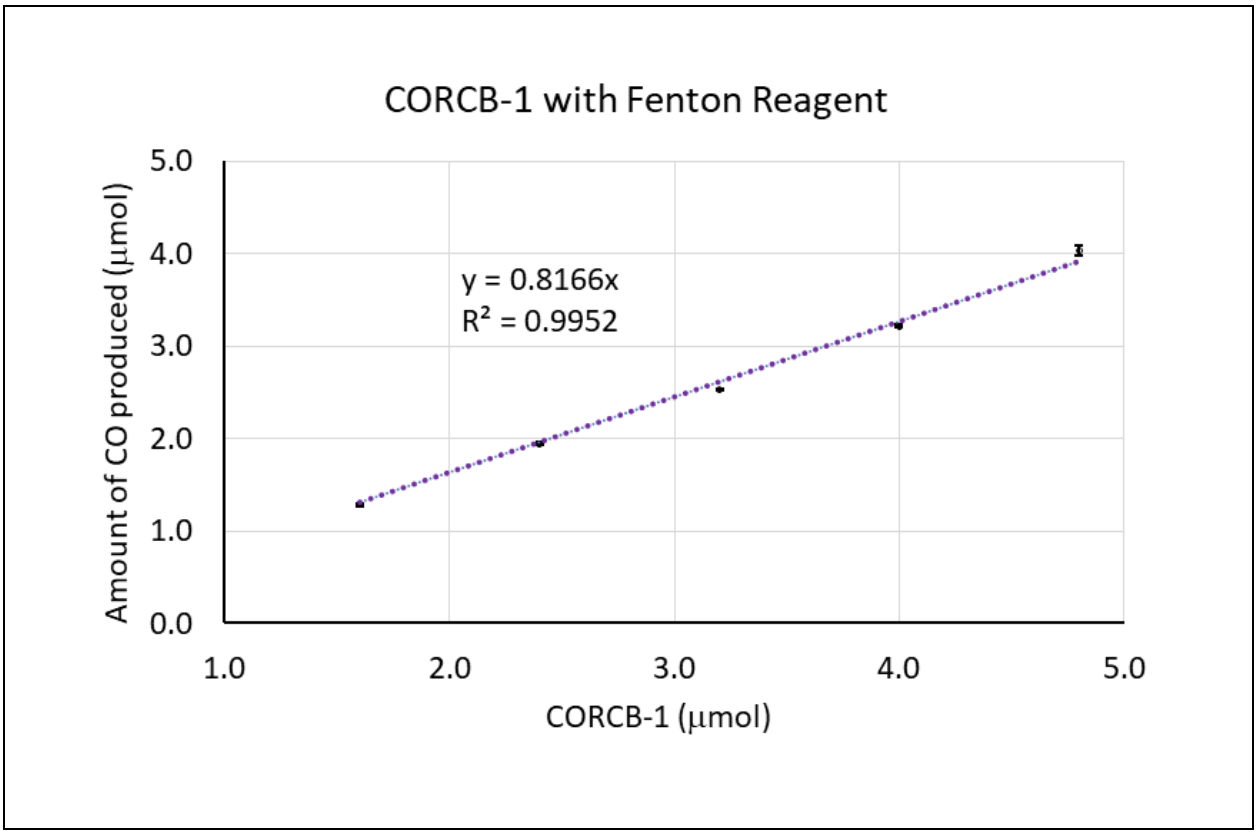


**Figure S52.** CO release process of CORCB-1 in the presence of radical ROS. Hydroxyl radical is produced from Fenton reagent and CORCB-1 added into the solution. Various amounts of CORCB-1 ranging from 1.6 µmol to 4.8 µmol were mixed with Fenton reagent for 5 minutes and CO concentration in ppm in the 50 mL head space was measured using CO meter. CO in µmol amount is calculated from concentration.

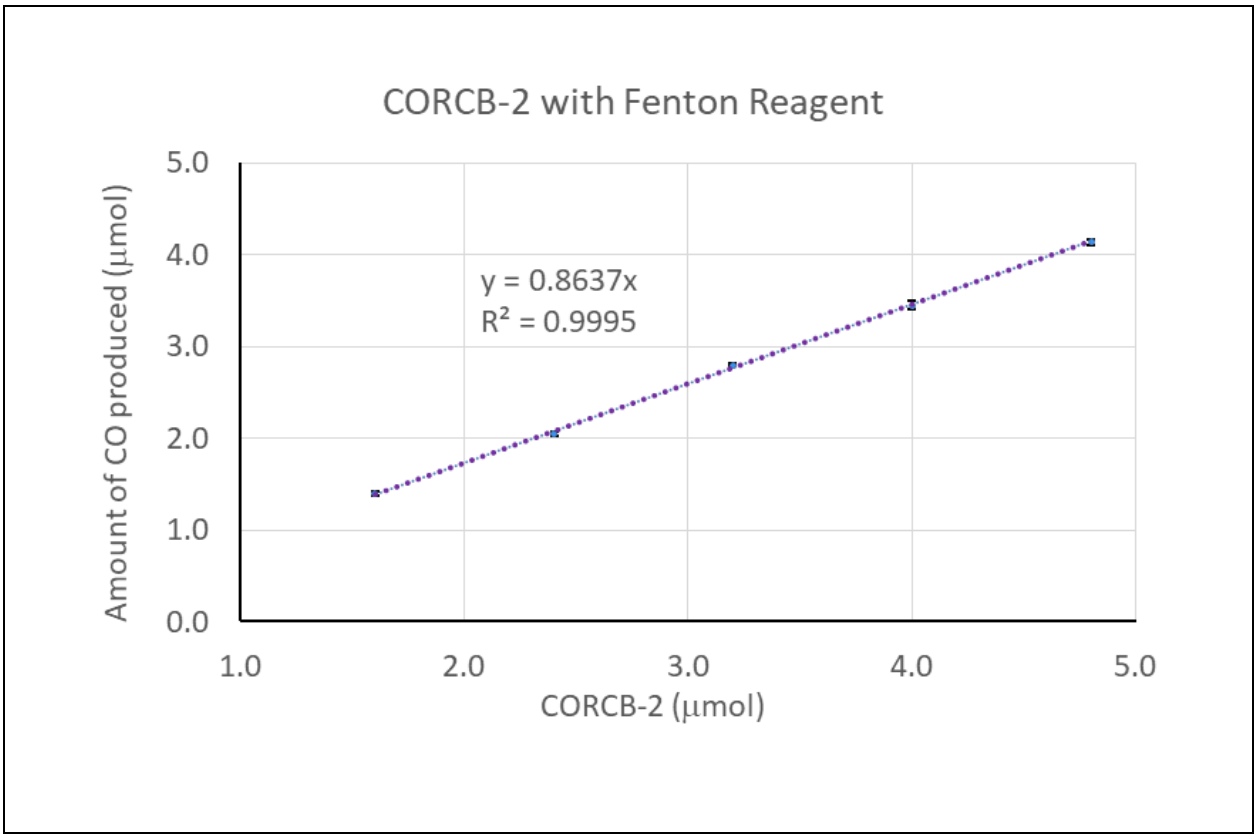


**Figure S53.** CO release process of CORCB-2 in the presence of radical ROS. Hydroxyl radical is produced from Fenton reagent and CORCB-2 added into the solution. Various amounts of CORCB-2 ranging from 1.6 µmol to 4.8 µmol were mixed with Fenton reagent for 5 minutes and CO concentration in ppm in the 50 mL head space was measured using CO meter. CO in µmol amount is calculated from concentration.

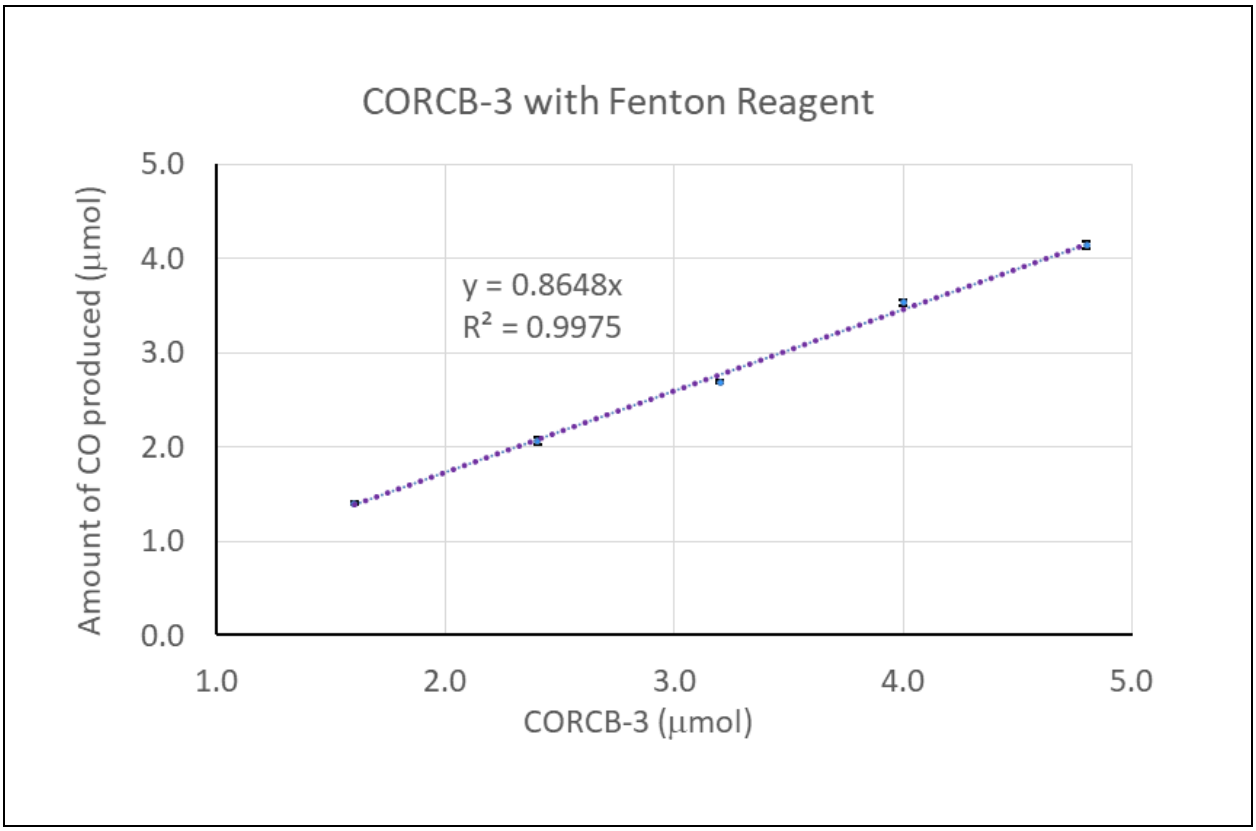


**Figure S54.** CO release process of CORCB-3 in the presence of radical ROS. Hydroxyl radical is produced from Fenton reagent and CORCB-3 added into the solution. Various amounts of CORCB-3 ranging from 1.6 µmol to 4.8 µmol were mixed with Fenton reagent for 5 minutes and CO concentration in ppm in the 50 mL head space was measured using CO meter. CO in µmol amount is calculated from concentration.

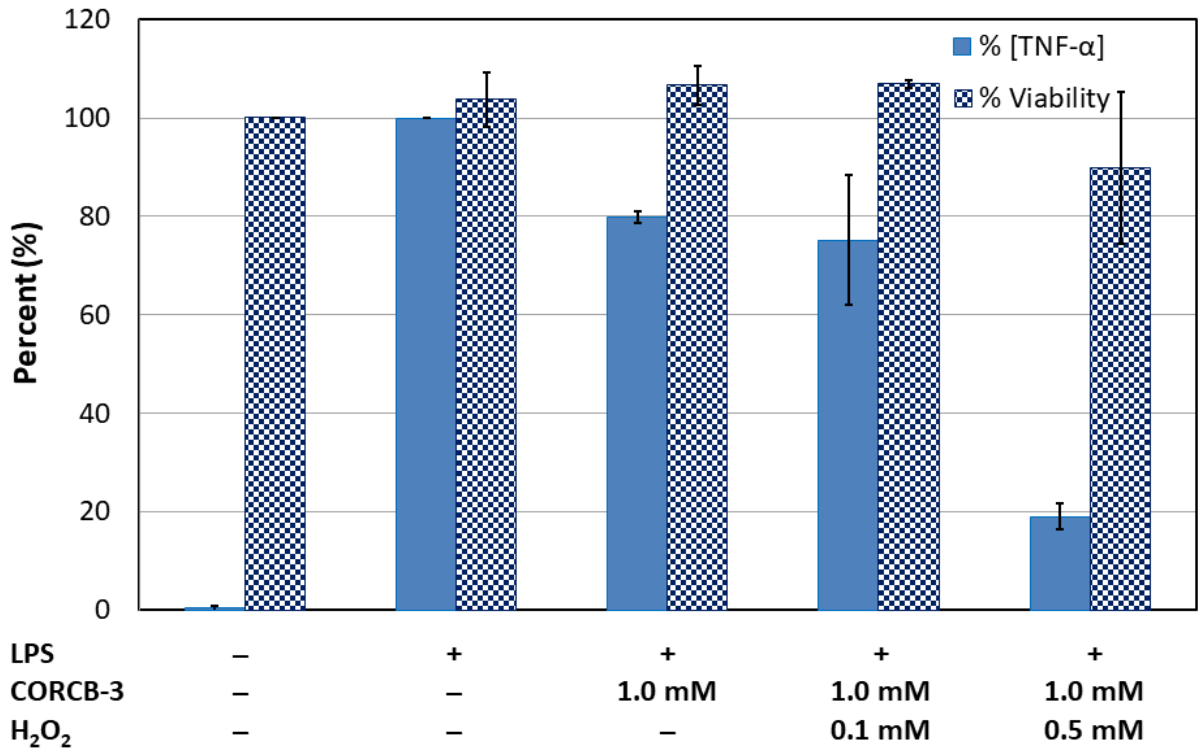


**Figure S55.** Anti-inflammatory and cell toxicity effect of CORCB-3 in the presence of $H_2O_2$ tested on mouse macrophages. LPS induced TNF-α production was tested first and cell viability assay performed on the same cells. Untreated cells sample was set at 100% for calculating % viability and LPS only sample was normalized to 100% for calculating TNF-α percentage.

## References


(1) Ayudhya, T. I.; Raymond, C. C.; Dingra, N. N. *Dalton Trans* **2017**, *46*, 882.

(2) Wisian-Neilson, P.; Das, M. K.; Spielvogel, B. F. *Inorganic chemistry* **1978**, *17*, 2327.

(3) Spielvogel, B. F.; Wojnowich, L.; Das, M. K.; McPhail, A. T.; Hargrave, K. D. *Journal of American Chemical Society* **1976**, *98 (18)*: 5702.