

# Supplementary Materials: Three Birds, One Excipient: Development of an Improved pH, Isotonic, and Buffered Ketamine Formulation for Subcutaneous Injection

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**Table S1.** Results from Fehling's test for stability of Captisol®: Glucose sensitivity test. N = 3.

Sample	Result	Observation (20 minutes post-Fehling test)
Glucose (10 mg/mL)	Positive	Yellow solution, red precipitate
Glucose (5 mg/mL)	Positive	~Colorless solution, red precipitate
Glucose (2 mg/mL)	Positive	Mostly blue solution, red precipitate
Glucose (1 mg/mL)	Inconclusive	Blue solution, inconsistently produced a red precipitate
Glucose (0.75 mg/mL)	Inconclusive	Blue solution, inconsistently produced a red precipitate
Glucose (0.5 mg/mL)	Negative	Blue solution unchanged
40% Captisol® (Negative control)	Negative	Blue solution unchanged
HPLC H <sub>2</sub> O (Negative Control)	Negative	Blue solution unchanged

**Table S2.** Results from Fehling's test for stability of Captisol®: CapAcid prepared from 15% Captisol®. N = 3. Results were evaluated at 20 minutes after Fehling's test. CapAcid concentration from the column solution was determined to be  $11.4 \pm 0.2$  % off the column (mean  $\pm$  SEM, N = 3), several dilutions of the CapAcid solution were also prepared.

Sample	Result 0 hr	Result 24 hr	Result 48 hr	Result 72 hr
10 mg/mL Glucose (Positive control)	Positive	Positive	Positive	Positive
2% Glucose (Positive control)	Positive	Positive	Positive	Positive
40% Captisol® (Negative control)	Negative	Negative	Negative	Negative
HPLC H <sub>2</sub> O (Negative control)	Negative	Negative	Negative	Negative
CapAcid (11.4%)	Negative	Negative	Negative	Negative
CapAcid	Negative	Negative	Negative	Negative

(5.7%)

CapAcid  
(2.85%)

Negative

Negative

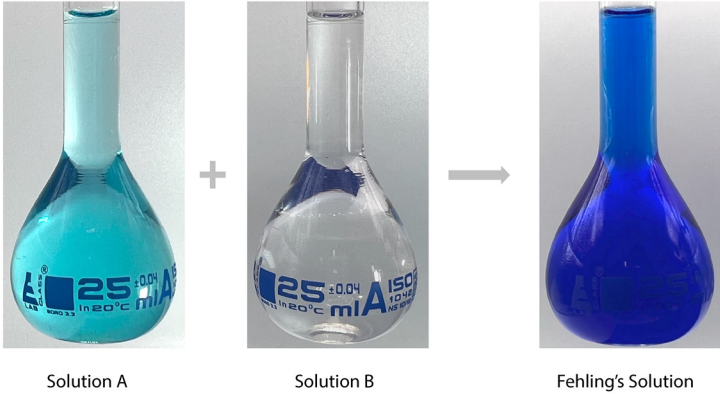
Negative

Negative

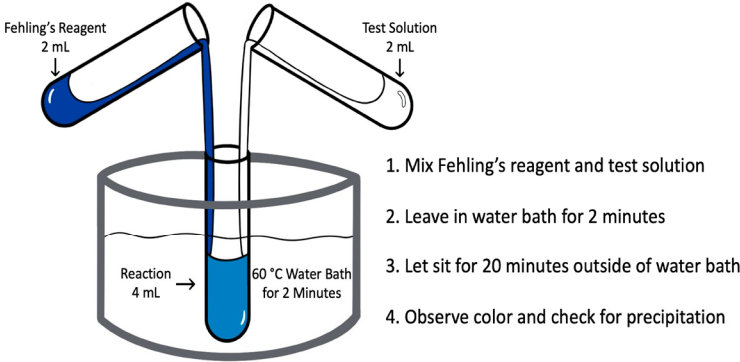
**Table S3.** Results from Fehling test for stability of Captisol®: CapAcid prepared from 20% Captisol®, N = 3. Results were 20 minutes after Fehling test. Mean concentration of CapAcid solution from the column was determined to be  $15.4 \pm 0.08$  % (mean  $\pm$  SEM, N = 3).

Sample	Result 0 hr	Result 24 hr	Result 48 hr	Result 168 hr
10 mg/mL Glucose (Positive control)	Positive	Positive	Positive	Positive
2% Glucose (Positive control)	Positive	Positive	Positive	Positive
40% Captisol® (Negative control)	Negative	Negative	Negative	Negative
HPLC H <sub>2</sub> O (Negative control)	Negative	Negative	Negative	Negative
CapAcid (15.4%)	Negative	Negative	Negative	Positive

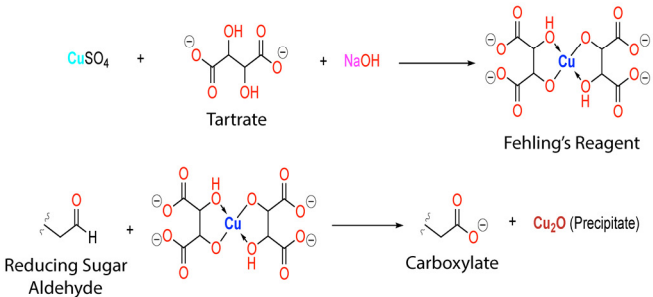
A. Fehling's Reagent Preparation



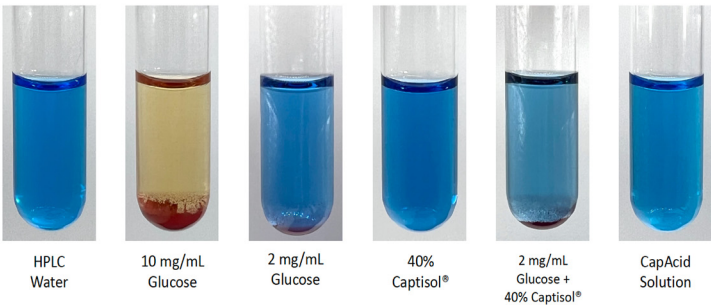
B. Fehling's Test Procedure



C. Reaction Scheme



D. Representative Reactions



**Figure S1.** Fehling's Test.

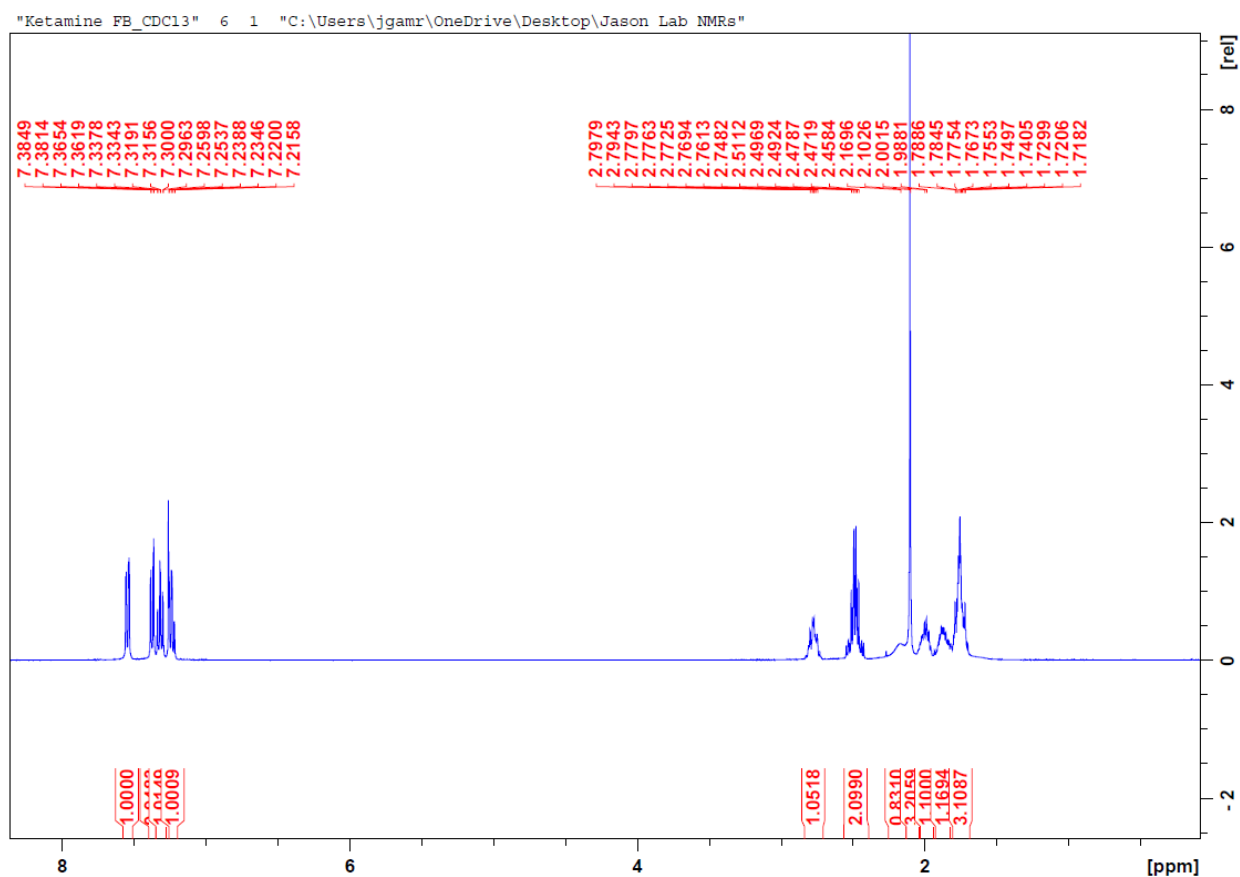
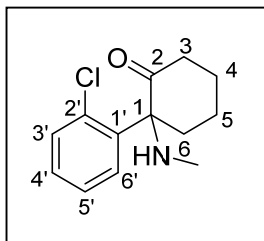
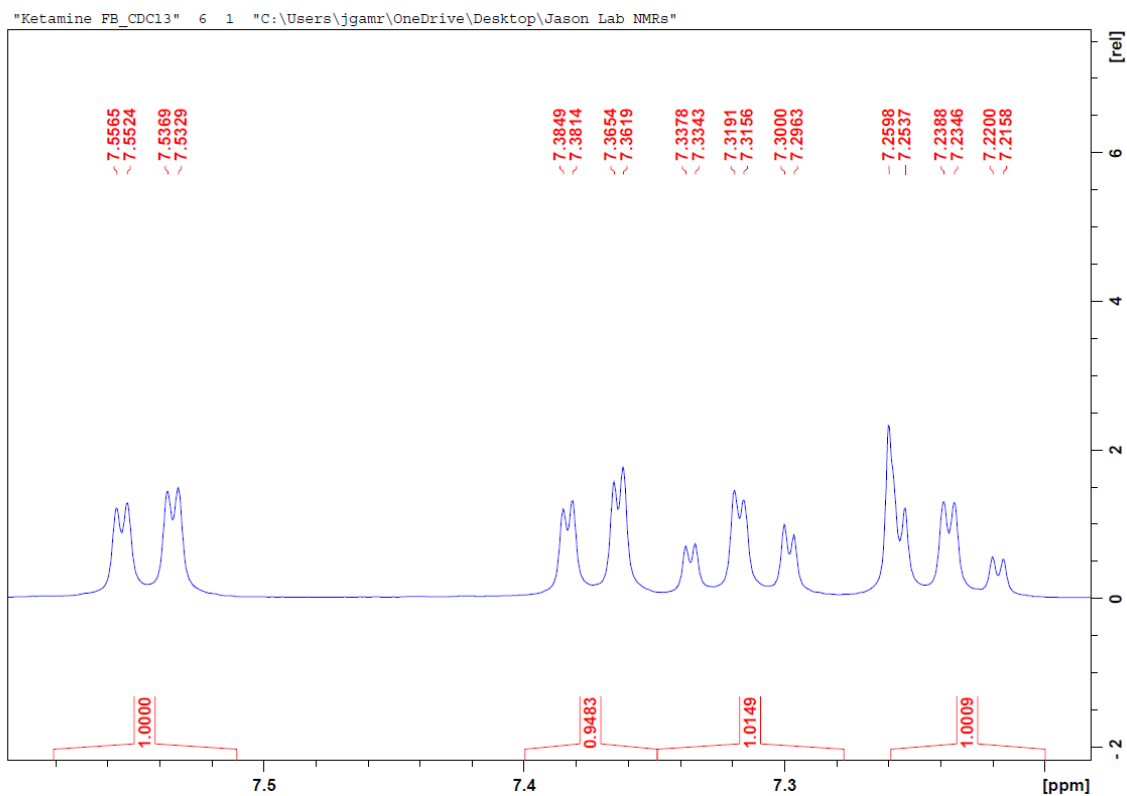
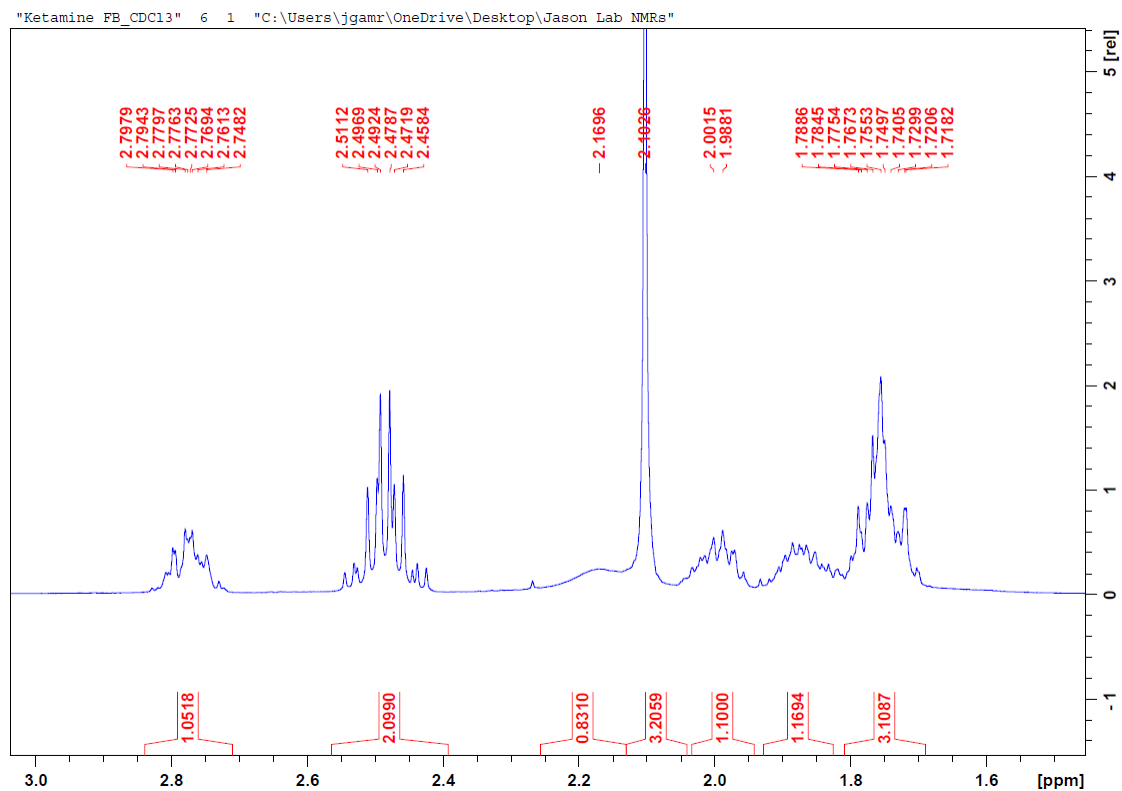


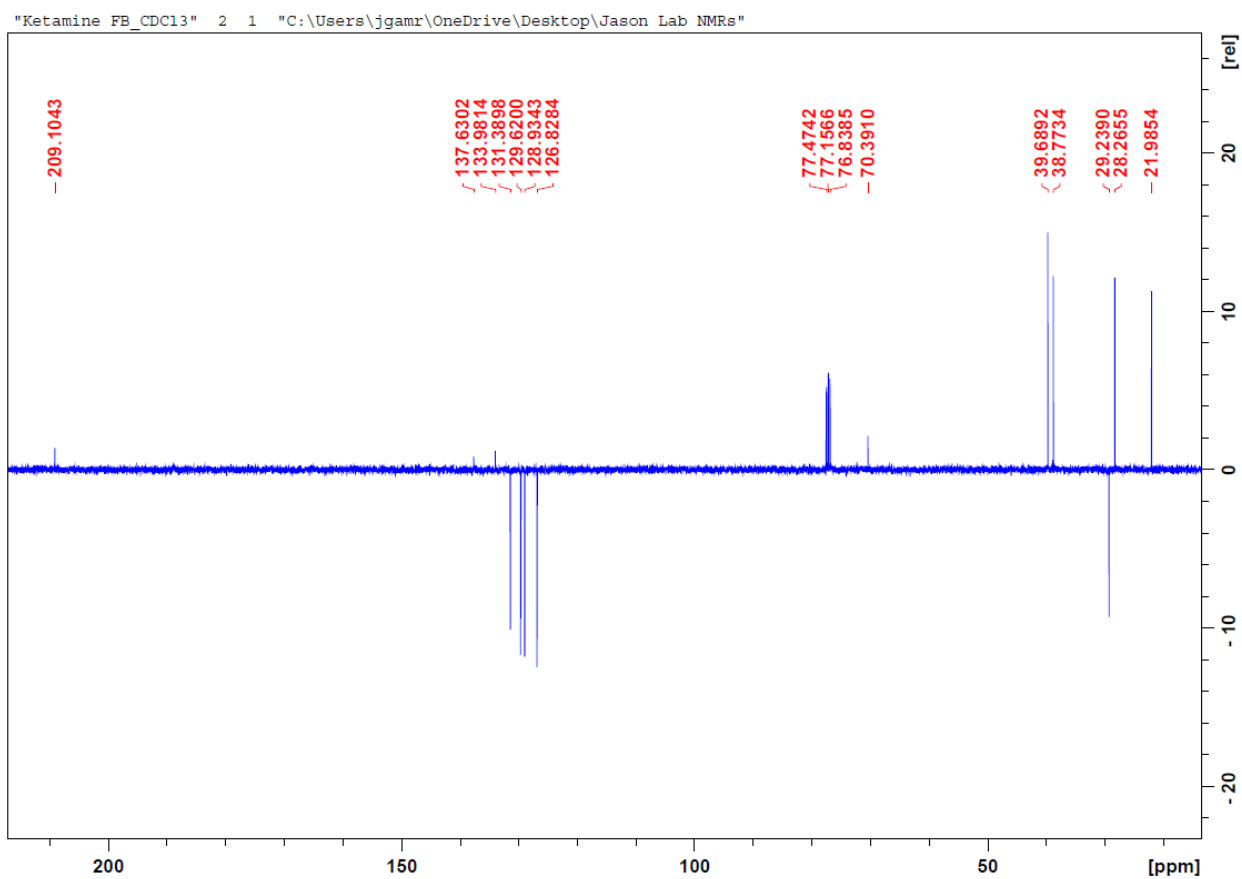
Figure S2a. <sup>1</sup>H NMR Spectrum of Ketamine Free Base. Compound dissolved at 20 mg/mL in CDCl<sub>3</sub>.



**Figure S2b.** Aromatic  $^1\text{H}$  NMR Spectrum of Ketamine Free Base. Compound dissolved at 20 mg/mL in  $\text{CDCl}_3$ .

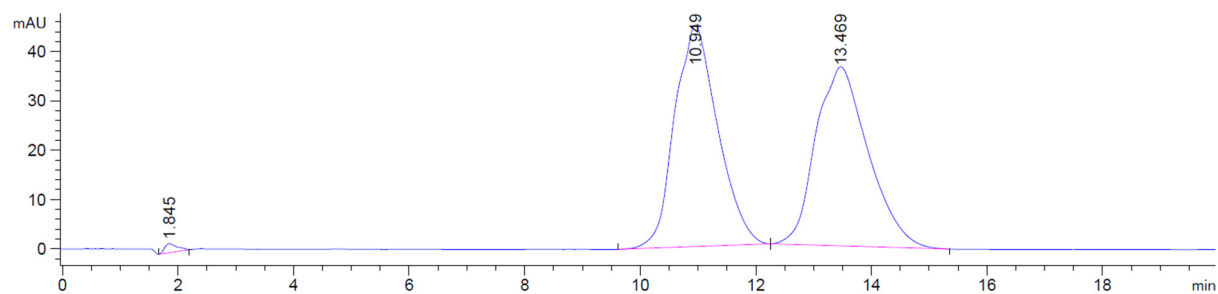


**Figure S2c.** Aliphatic  $^1\text{H}$  NMR Spectrum of Ketamine Free Base. Compound dissolved at 20 mg/mL in  $\text{CDCl}_3$ .

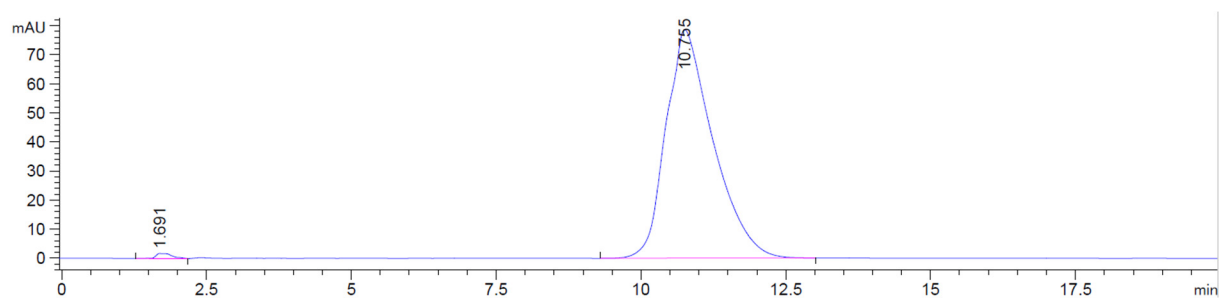


**Figure S3.**  $^{13}\text{C}$  NMR Spectrum of Ketamine Freebase. Compound dissolved at 20 mg/mL in  $\text{CDCl}_3$ .

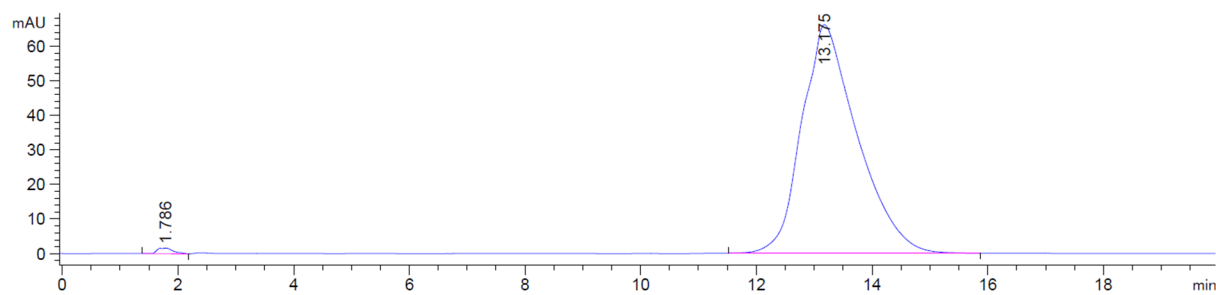
## HPLC analyses



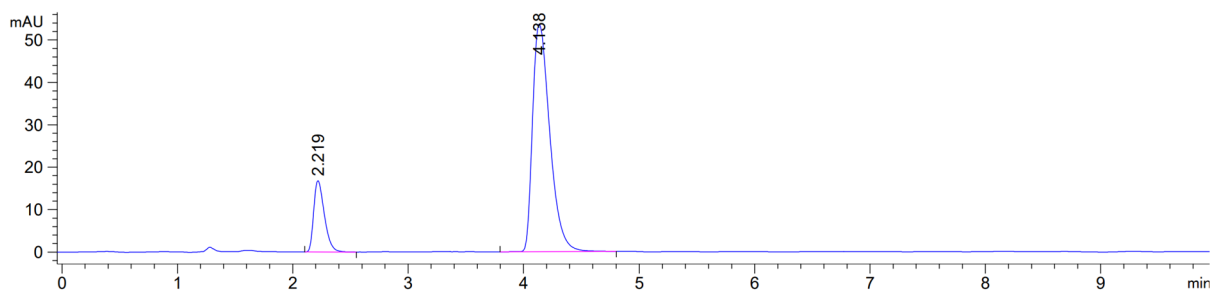
**Figure S4.** Chiral HPLC of Racemic Ketamine HCl (1 mg/mL).



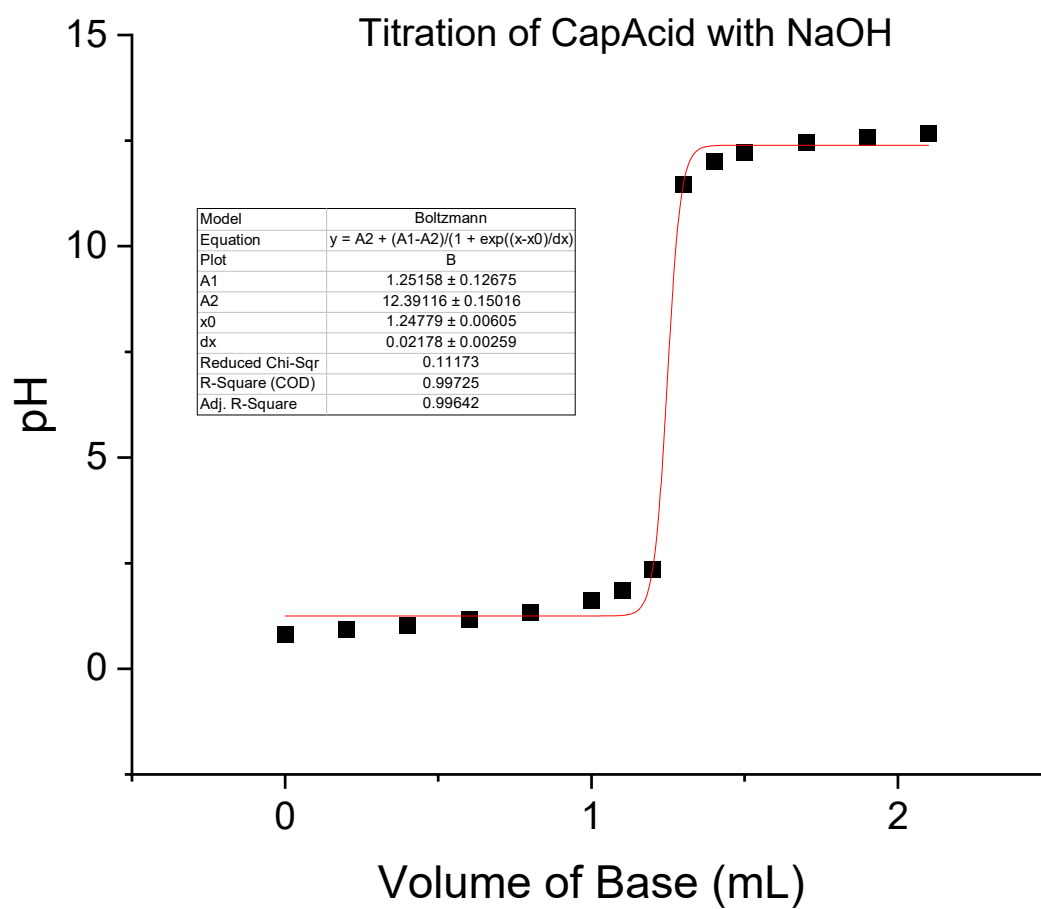
**Figure S5.** Chiral HPLC of S-Ketamine HCl (1 mg/mL).



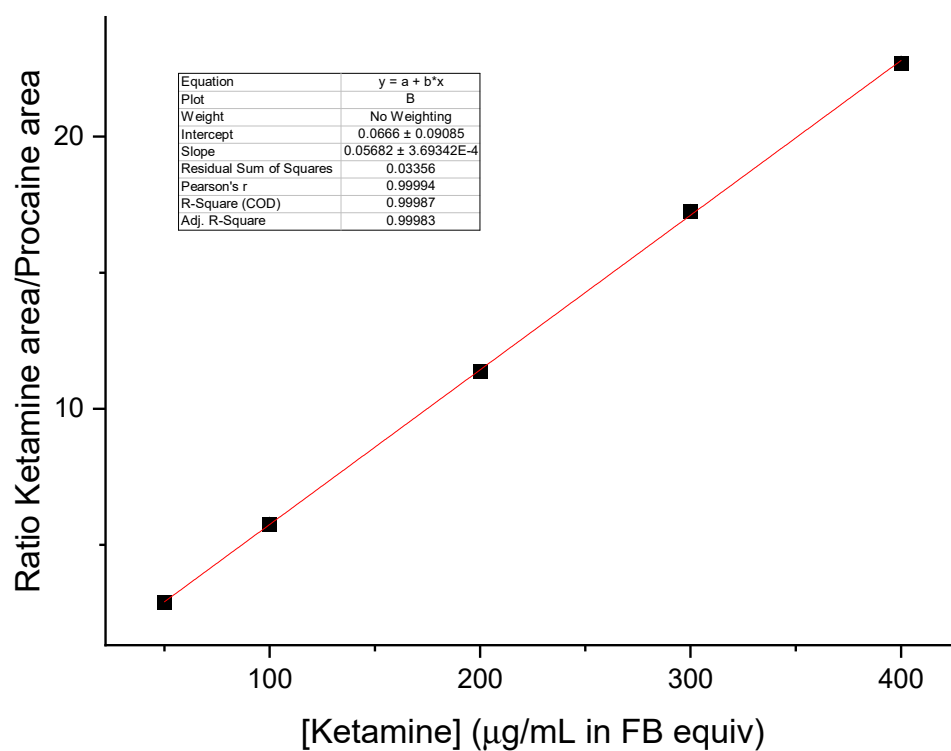
**Figure S6.** Chiral HPLC of R-Ketamine HCl (1 mg/mL).



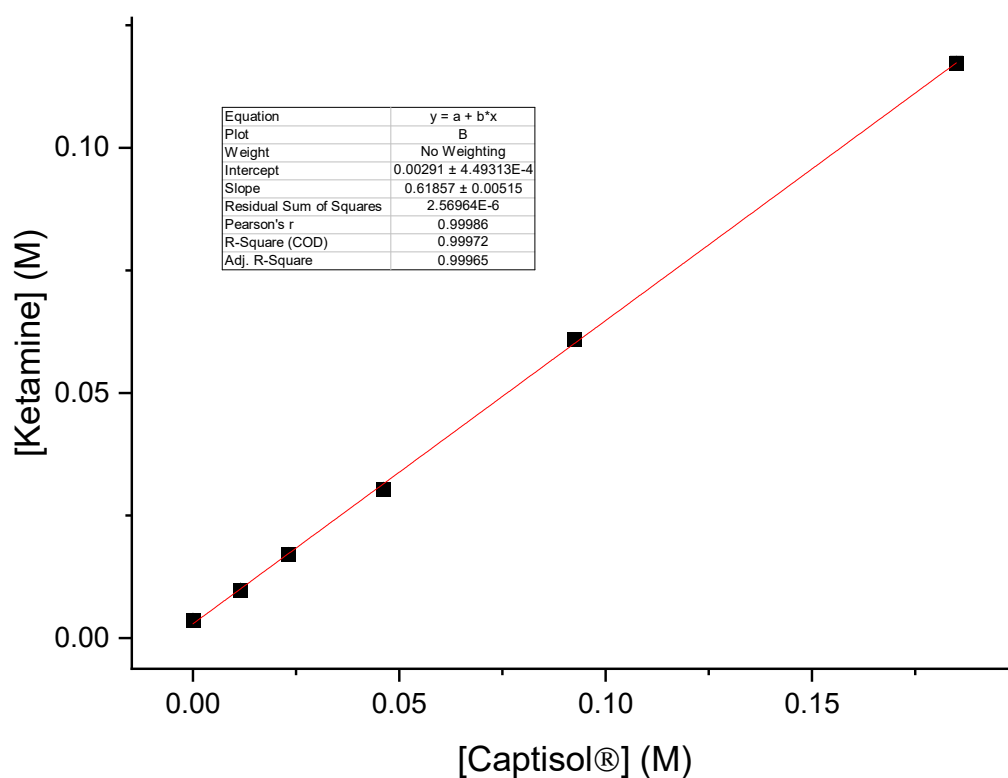
**Figure S7.** HPLC Trace of BB106; ketamine (4.138 min) with procaine HCl internal standard (2.219 min, 20 µg/mL).



**Figure S8.** Titration of CapAcid with sodium hydroxide.



**Figure S9.** Representative Ketamine HPLC calibration curve.



**Figure S10.** Ketamine Phase Solubility Curve with Captisol®.