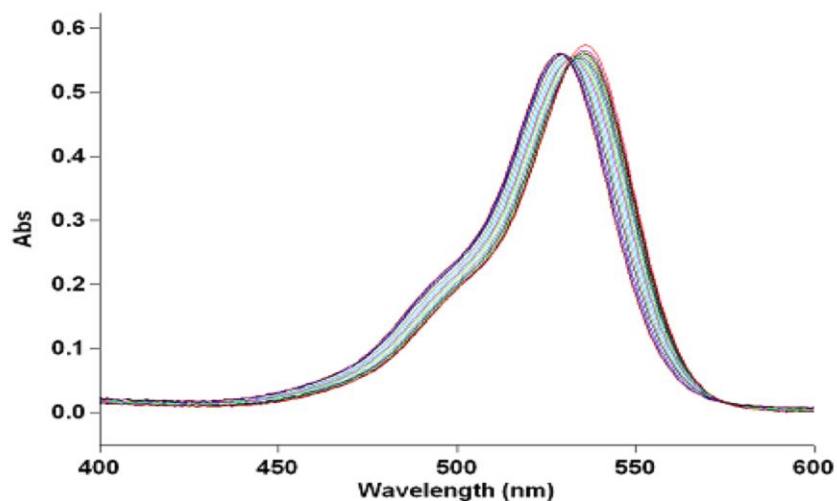


Supplemental Figures

a)



b)

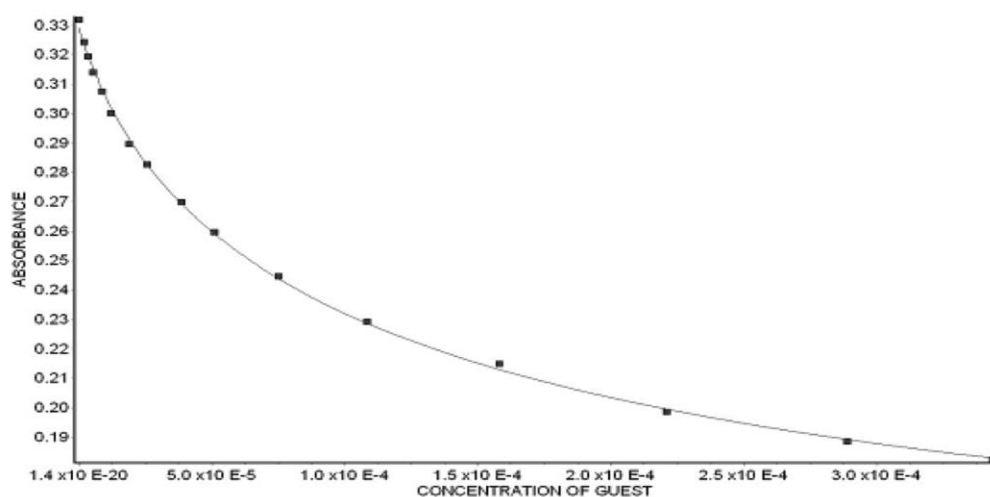
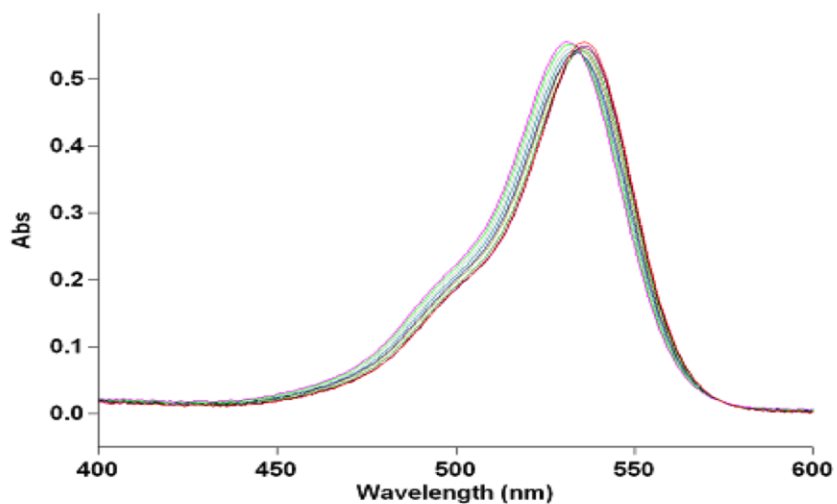


Fig. S1. Calabadiion 2 binds to ketamine. a) UV/Vis spectra from the titration of Calabadiion 2 (9.18 μM) and rhodamine 6G (10.00 μM) with ketamine (0 – 0.35 mM) in 20 mM NaH₂PO₄ buffer (pH = 7.4); b) plot of the A₅₅₀ as a function of the concentration of ketamine. The solid line represents the best non-linear fit of the data to a competitive binding model ($K_a = (1.8 \pm 0.1) \times 10^5 \text{ M}^{-1}$).

a)



b)

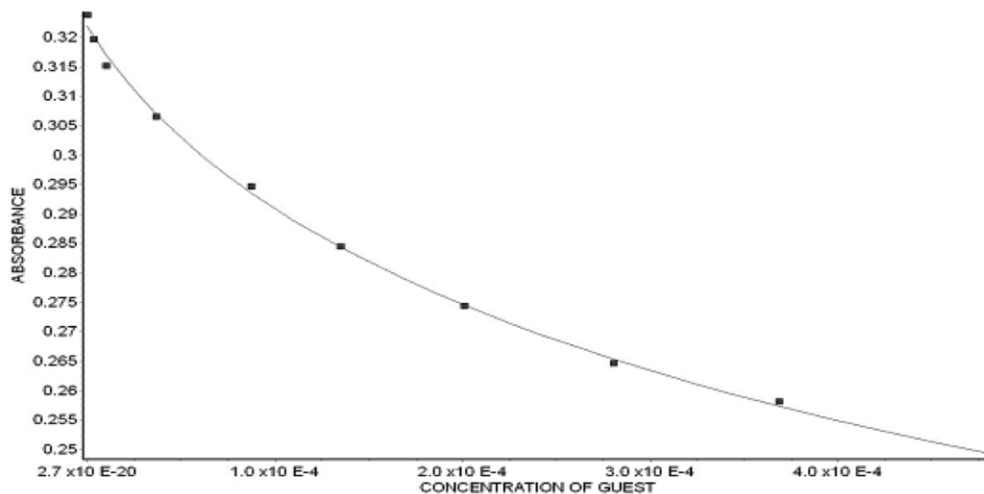


Fig. S2. Calabadiion 2 binds to etomidate. a) UV/Vis spectra from the titration of Calabadiion 2 ($9.18 \mu\text{M}$) and rhodamine 6G ($10.00 \mu\text{M}$) with etomidate (0 – 0.5 mM) in 20 mM NaH_2PO_4 buffer (pH = 7.4); b) plot of the A_{550} as a function of the concentration of etomidate. The solid line represents the best non-linear fit of the data to a competitive binding model ($K_a = (3.5 \pm 0.5) \times 10^4 \text{ M}^{-1}$).

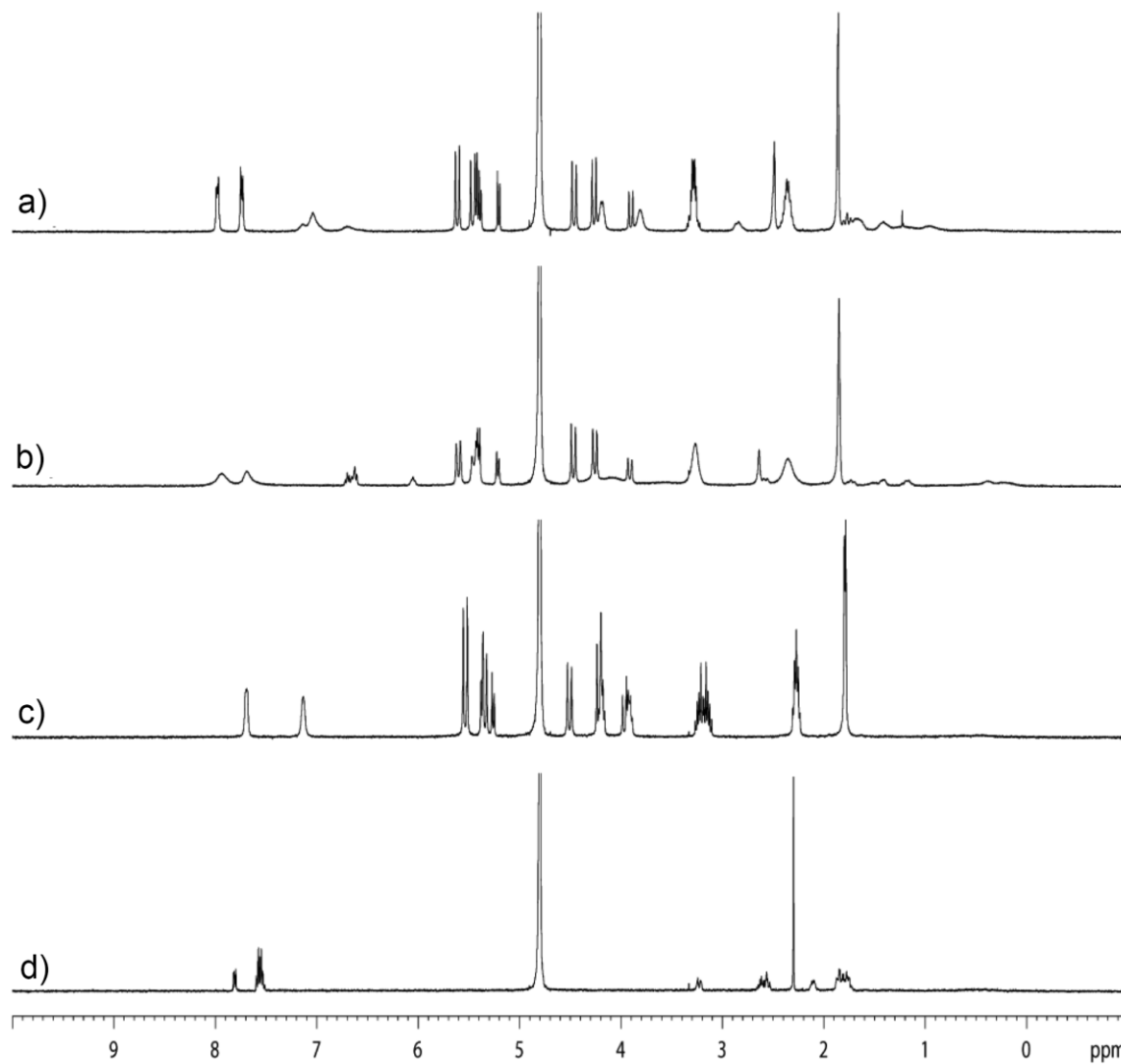


Fig. S3. Stoichiometry establishment of Calabadiol 2 and ketamine. ^1H NMR spectra recorded (400 MHz, RT, deuterated sodium phosphate buffer at pD = 7.4) for a) a 2:1 mixture of ketamine (2 mM) and Calabadiol 2 (1 mM), b) an equimolar mixture of ketamine and Calabadiol 2 (2 mM), c) Calabadiol 2 and d) ketamine.

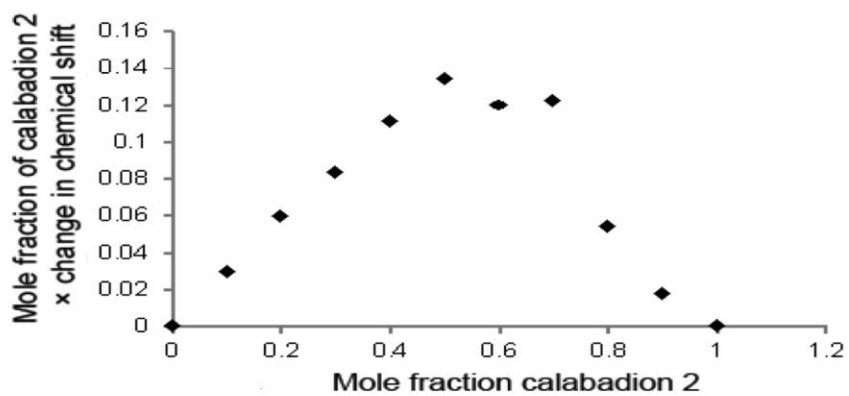
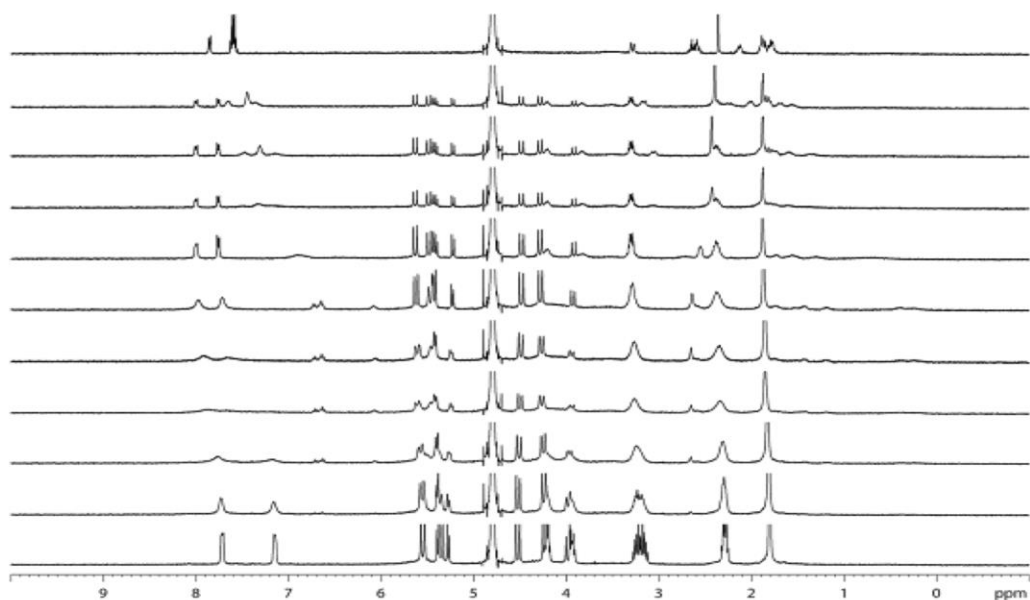


Fig. S4. Calabadiion 2 and ketamine bind 1:1. Job plot establishing 1:1 binding of calabadiion 2 (0-1 mM) with ketamine (0-1 mM) based on change in chemical shift at 7.73 ppm of calabadiion 2 measured by ^1H NMR (400 MHz, deuterated sodium phosphate buffer at pD = 7.4)

Table S1. Effect size of Fixed Effects – Calabadiion 2 during continuous anesthesia

a) Effect of treatment and dose on BSR during continuous etomidate				
Parameter	Effect size compared to baseline	P-Value	95% Confidence Interval	
			Lower Bound	Upper Bound
Calabadiion	-34.44	0.001	-51.32	-17.56
Placebo	0			
Dose, 0 mg / V_{eq} Placebo	-0.20	0.956	-7.32	6.92
Dose, 40 mg/ V_{eq} Placebo	2.69	0.458	-4.43	9.81
Dose, 60 mg/ V_{eq} Placebo	1.04	0.774	-6.08	8.16
Dose, 80 mg/ V_{eq} Placebo	1.45	0.690	-5.67	8.57
Dose, 100 mg/ V_{eq} Placebo	0			
reversal agent * dose				
Calabadiion 2, 0 mg	33.06	<0.001	24.93	41.19
Calabadiion 2, 40 mg	27.25	<0.001	19.12	35.38
Calabadiion 2, 60 mg	17.73	<0.001	9.60	25.85
Calabadiion 2, 80 mg	11.30	0.007	3.17	19.42
Calabadiion 2, 100 mg	0			

b) Effect of treatment and dose on EEG power during continuous ketamine

Parameter	Effect size compared to baseline	P-Value	95% Confidence Interval	
			Lower Bound	Upper Bound
Calabadion	-25.47	<0.001	-35.26	-15.69
Placebo	0			
Dose, 0 mg / V_{eq} Placebo	9.64	0.007	2.72	16.56
Dose, 20 mg/ V_{eq} Placebo	9.17	0.010	2.25	16.09
Dose, 40 mg/ V_{eq} Placebo	8.05	0.023	1.13	14.97
Dose, 60 mg/ V_{eq} Placebo	6.83	0.053	-0.09	13.75
Dose, 80 mg/ V_{eq} Placebo	0			
reversal agent * dose				
Calabadion 2, 0 mg	23.51	<0.001	15.63	31.40
Calabadion 2, 40 mg	23.30	<0.001	15.42	31.19
Calabadion 2, 60 mg	14.37	<0.001	6.49	22.26
Calabadion 2, 80 mg	4.53	0.258	-3.35	12.42
Calabadion 2, 100 mg	0			

BSR=Burst suppression ratio, EEG=electroencephalogram, V_{eq}= equivalent Volume

Table S2. Effect size of Fixed Effects – Calabadion 2 on balance after anesthesia

Parameter	Anesthetic	Effect size compared to placebo	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Calabadion 2	etomidate 4 mg/kg i.v.	4.85	0.013	1.09	8.60
	ketamine 30 mg/kg i.v.	3.90	0.002	1.51	6.30
	ketamine 50 mg/kg i.p.	15.71	<0.001	9.43	22.00

i.v. =intravenous, i.p.=intraperitoneal