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Contents

1. Supplementary Table 1: Relevant statistical analyses

Figure 1		**Sample size (figure order)**		**Treatment effect**	
a	1 hour post-injection FST	*n = 10/group*	one-way ANOVA	$F_{[7, 72]} = 2.60$	*p < 0.05*
	24 hours post-injection FST	*n = 10,9,10,10,9,9,10,9*	one-way ANOVA	$F_{[7, 68]} = 3.08$	*p < 0.01*
b	1 hour post-injection FST	*n = 10,10,10,10,10,10,9,9,9*	one-way ANOVA	$F_{[8, 78]} = 8.02$	*p < 0.001*
	• (S)-KET 1 mg/kg *vs* (R)-KET 1 mg/kg				*p > 0.05*
	• (S)-KET 3 mg/kg *vs* (R)-KET 3 mg/kg				*p > 0.05*
	• (S)-KET 10 mg/kg *vs* (R)-KET 10 mg/kg				*p < 0.05*
	• (S)-KET 30 mg/kg *vs* (R)-KET 30 mg/kg				*p < 0.05*
	24 hours post-injection FST	*n = 10,10,9,10,9,10,10,9,9*	one-way ANOVA	$F_{[8, 77]} = 2.39$	*p < 0.05*
	• (S)-KET 1 mg/kg *vs* (R)-KET 1 mg/kg				*p > 0.05*
	• (S)-KET 3 mg/kg *vs* (R)-KET 3 mg/kg				*p > 0.05*
	• (S)-KET 10 mg/kg *vs* (R)-KET 10 mg/kg				*p < 0.05*
	• (S)-KET 30 mg/kg *vs* (R)-KET 30 mg/kg				*p > 0.05*
c	Novelty-suppressed feeding	*n = 10,10,9,10,9,10,10*	Mantel-Cox test	C2 = 43.77; Df = 6	*p < 0.001*
	• (S)-KET 3 mg/kg *vs* (R)-KET 3 mg/kg				*p < 0.05*
	• (S)-KET 10 mg/kg *vs* (R)-KET 10 mg/kg				*p > 0.05*
	• (S)-KET 30 mg/kg *vs* (R)-KET 30 mg/kg				*p < 0.001*
d	Learned helplessness	*n = 8,7,8,8,8,8,8*	one-way ANOVA	$F_{[6, 48]} = 11.91$	*p < 0.001*
	• (S)-KET 1 mg/kg *vs* (R)-KET 1 mg/kg				*p > 0.05*
	• (S)-KET 5 mg/kg *vs* (R)-KET 5 mg/kg				*p < 0.001*
	• (S)-KET 25 mg/kg *vs* (R)-KET 25 mg/kg				*p > 0.05*
e	1 hour post-injection FST	*n = 10,9,10,9*	one-way ANOVA	$F_{[3, 34]} = 13.70$	*p < 0.001*
	24 hours post-injection FST	*n = 10,9,10,9*	one-way ANOVA	$F_{[3, 34]} = 9.47$	*p < 0.001*
g	Social defeats – Social interaction ratio	*n=10,10,9,15,14,14*	Kruskal-Wallis one-way ANOVA	H = 73.55; Df = 11	*p < 0.001*
	• Susceptible: SAL *vs* MK-801				*p > 0.05*
	• Susceptible: SAL *vs* (R,S)-KET				*p < 0.05*
	• Susceptible: MK-801 *vs* (R,S)-KET				*p < 0.05*
Figure 2				**Treatment effect**	
b	24 hours post-injection FST - males	*n = 10/group*	one-way ANOVA	$F_{[3, 36]} = 3.52$	*p < 0.05*
	24 hours post-injection FST - females	*n = 10/group*	one-way ANOVA	$F_{[3, 36]} = 8.67$	*p < 0.001*
	• males 1 mg/kg *vs* females 1 mg/kg				*p > 0.05*
	• males 3 mg/kg vs females 3 mg/kg				*p < 0.05*
	• males 10 mg/kg vs females 10 mg/kg				*p > 0.05*
c	Pharmacokinetics – males *vs* females: KET	*males: n=3,4,4,4,4* *females: n=4/time point*	No stats (n<5)		
d	Pharmacokinetics – males *vs* females: norKET	*males: n=4/time point* *females: n=4/time point*	No stats (n<5)		
e	Pharmacokinetics – males *vs* females: HNK	*males: n=4/time point* *females: n=4/time point*	No stats (n<5)		
f	Pharmacokinetics – (R,S)-KET *vs* (R,S)-d_2-KET: KET	*(R,S)-KET: n=4/time point* *(R,S)-d_2-KET: n=4/time point*	No stats (n<5)		
g	Pharmacokinetics – (R,S)-KET *vs* (R,S)-d_2-KET: norKET	*(R,S)-KET: n=4/time point* *(R,S)-d_2-KET: n=4/time point*	No stats (n<5)		
h	Pharmacokinetics – (R,S)-KET *vs* (R,S)-d_2-KET: HNK	*(R,S)-KET: n=4/time point* *(R,S)-d_2-KET: n=4/time point*	No stats (n<5)		

i	1 hour post-injection FST	*n = 10/group*	one-way ANOVA	$F_{[2, 27]} = 6.95$	*p < 0.01*				
	24 hours post-injection FST	*n = 10,9,10*	one-way ANOVA	$F_{[2, 26]} = 8.97$	*p < 0.01*				
j	Learned helplessness	*n = 9,9,9,10,9*	one-way ANOVA	$F_{[4,41]} = 4.57$	*p < 0.01*				
	• (R,S)-KET 3 mg/kg *vs* (R,S)-d_2-KET 3 mg/kg				*p > 0.05*				
	• (R,S)-KET 10 mg/kg *vs* (R,S)-d_2-KET 10 mg/kg				*p < 0.05*				
k	24 hours post-injection FST	*n = 8,7,8,7,8,7*	one-way ANOVA	$F_{[5, 39]} = 4.37$	*p < 0.01*				
	• (2S,6S)-HNK 3 mg/kg *vs* (2R,6R)-HNK 3 mg/kg				*p > 0.05*				
	• (2S,6S)-HNK 10 mg/kg *vs* (2R,6R)-HNK 10 mg/kg				*p < 0.05*				
l	Learned helplessness	*n = 8/group*	one-way ANOVA	$F_{[3, 28]} = 11.45$	*p < 0.001*				
m	Social defeats – Social interaction ratio	*n = 7,7,7,7,6,6,8,8*	Kruskal-Wallis one-way ANOVA	H = 29.46; Df = 7	*p < 0.001*				
Figure 3									
a	[3H]-MK-801 binding	*n=22,24,24,27,24*							
c	INMDA (% control)	*n=3/group*	No stats (n<5)						
				Drug effect		**Phase effect**		**Interaction**	
d	SC pathway – FP slope (10 last min *vs* baseline)	*n= 6/group*	two-way RM ANOVA	$F_{[1, 10]} = 11.38$	*p < 0.01*	$F_{[1, 10]} = 17.41$	*p < 0.001*	$F_{[1, 10]} = 10.83$	*p < 0.01*
e	SC pathway – FP amplitude (10 last min *vs* baseline)	*n= 6/group*	two-way RM ANOVA	$F_{[1, 10]} = 6.69$	*p < 0.05*	$F_{[1, 10]} = 12.65$	*p < 0.01*	$F_{[1, 10]} = 6.79$	*p < 0.01*
				Treatment effect		**Pre-treatment**		**Interaction**	
g	1 hour post-injection FST	*n = 8,8,9,9,6,6,9,9*	two-way ANOVA	$F_{[3, 56]} = 3.00$	*p < 0.05*	$F_{[1, 56]} = 73.44$	*p < 0.001*	$F_{[3, 56]} = 13.70$	*p < 0.001*
h	24 hours post-injection FST	*n = 8,8,8,9,8,9*	two-way ANOVA	$F_{[2, 44]} = 8.86$	*p < 0.001*	$F_{[1, 44]} = 8.00$	*p < 0.01*	$F_{[2, 44]} = 5.10$	*p < 0.05*
				Treatment effect					
j	Gamma power (% baseline): SAL	*n = 5*	Friedman one-way RM ANOVA	C2 = 6.08; Df = 6	*p > 0.05*				
	Gamma power (% baseline): (R,S)-KET	*n = 5*	Friedman one-way RM ANOVA	C2 = 19.45; Df = 6	*p < 0.01*				
	Gamma power (% baseline): (2R,6R)-HNK	*n = 6*	Friedman one-way RM ANOVA	C2 = 23.00; Df = 6	*p < 0.001*				
Figure 4				**Treatment effect**					
a	Hippocampus: 1 hour post-injection: eEF2	*n = 10,10,12*	one-way ANOVA	$F_{[2, 29]} = 0.72$	*p > 0.05*				
	Hippocampus: 1 hour post-injection: p-eEF2	*n = 10,10,11*	one-way ANOVA	$F_{[2, 28]} = 4.59$	*p < 0.05*				
b	Hippocampus: 24 hours post-injection: eEF2	*n = 10,11,11*	one-way ANOVA	$F_{[2, 29]} = 3.54$	*p < 0.05*				
	Hippocampus: 24 hours post-injection: p-eEf2	*n = 10,11,11*	one-way ANOVA	$F_{[2, 29]} = 3.65$	*p < 0.05*				
c	Hippocampus: 1 hour post-injection: proBDNF	*n = 12/group*	one-way ANOVA	$F_{[2, 33]} = 2.78$	*p > 0.05*				
	Hippocampus: 1 hour post-injection: mBDNF	*n = 11,12,12*	one-way ANOVA	$F_{[2, 32]} = 0.53$	*p > 0.05*				
d	Hippocampus: 24 hours post-injection: proBDNF	*n = 11,10,10*	one-way ANOVA	$F_{[2, 28]} = 0.52$	*p > 0.05*				
	Hippocampus: 24 hours post-injection: mBDNF	*n = 11/group*	one-way ANOVA	$F_{[2, 30]} = 4.07$	*p < 0.05*				
e	Hippocampus: 1 hour post-injection: GluA1	*n = 10,11,12*	one-way ANOVA	$F_{[2, 30]} = 1.52$	*p > 0.05*				
	Hippocampus: 1 hour post-injection: GluA2	*n = 10,11,12*	one-way ANOVA	$F_{[2, 30]} = 0.49$	*p > 0.05*				
f	Hippocampus: 24 hours post-injection: GluA1	*n = 11,11,12*	one-way ANOVA	$F_{[2, 31]} = 5.24$	*p < 0.05*				
	Hippocampus: 24 hours post-injection: GluA2	*n = 10,11,12*	one-way ANOVA	$F_{[2, 30]} = 8.25$	*p < 0.01*				
				Treatment effect		**Pre-treatment effect**		**Interaction**	
h	24-hour post-injection FST	*n = 9,10,10,9,9,10*	two-way ANOVA	$F_{[2, 51]} = 9.89$	*p < 0.001*	$F_{[1, 51]} = 11.00$	*p < 0.01*	$F_{[2, 51]} = 6.56$	*p < 0.01*
Figure 5				**Treatment effect**					
a	Locomotion - (2S,6S)-HNK	*n = 11,9,9,10,10,9*	Kruskal-Wallis one-way ANOVA	H = 16.09; Df = 5	*p < 0.01*				
b	Locomotion - (2R,6R)-HNK	*n = 11,9,9,9,10,10*	one-way ANOVA	$F_{[5, 52]} = 1.45$	*p > 0.05*				
				Treatment effect		**Trial effect**		**Interaction**	
c	Rotarod - (2S,6S)-HNK	*n = 7/group*	two-way RM ANOVA	$F_{[2, 18]} = 31.96$	*p < 0.001*	$F_{[5, 90]} = 9.43$	*p < 0.001*	$F_{[10, 90]} = 5.28$	*p < 0.001*
d	Rotarod - (2R,6R)-HNK	*n = 10,10,9,10*	two-way RM ANOVA	$F_{[3, 35]} = 9.38$	*p < 0.001*	$F_{[5, 175]} = 8.31$	*p < 0.001*	$F_{[15, 175]} = 13.00$	*p < 0.001*
				Treatment effect		**dB effect**		**Interaction**	
e	Pre-pulse inhibition	*n = 6,6,6,5,5*	two-way RM ANOVA	$F_{[4, 23]} = 5.37$	*p < 0.01*	$F_{[1, 23]} = 20.08$	*p < 0.001*	$F_{[4, 23]} = 0.67$	*p > 0.05*

				Treatment effect					
f	Drug discrimination - (2R,6R)-HNK	*n = 8,8,7,7*	Kruskal-Wallis one-way ANOVA	H = 20.95; Df = 6	*p < 0.001*				
g	Drug discrimination - PCP	*n = 6,8,7*	one-way ANOVA	$F_{[2, 19]}$ = 21.82	*p < 0.001*				
				Dose effect					
h	Self-administration - lever presses: (R,S)-KET	*n = 8*	one-way RM ANOVA	$F_{[1.44, 10.05]}$ = 2.13	*p > 0.05*				
	Self-administration - lever presses: (2R,6R)-HNK	*n = 6*	one-way RM ANOVA	$F_{[1.74, 8.72]}$ = 0.71	*p > 0.05*				
Extended Data Figure 2									
a	Pharmacokinetics - plasma	*n=4/time point*	No stats (n<5)						
b	Pharmacokinetics - brain	*n=4/time point*	No stats (n<5)						
c	Pharmacokinetics – (S)- *vs* (R)-KET: KET	*(S)-KET: n=4/time point* *(R)-KET: n=4/time point*	No stats (n<5)						
d	Pharmacokinetics – (S)- *vs* (R)-KET: norKET	*(S)-KET: n=4/time point* *(R)-KET: n=4/time point*	No stats (n<5)						
e	Pharmacokinetics – (S)- *vs* (R)-KET: HNK	*(S)-KET: n=4/time point* *(R)-KET: n=4/time point*	No stats (n<5)						
g	[3H]-MK-801 binding	*n=18,15,15*							
Extended Data Figure 3				**Treatment/group effect**					
b	Social defeats - Locomotion	*n=10,9,9,14,14,14*	one-way ANOVA	$F_{[5, 64]}$ = 0.78	*p > 0.05*				
c	Social defeats – Total compartmental crosses	*n=10,10,9,14,14,13*	one-way ANOVA	$F_{[5, 64]}$ = 0.	*p > 0.05*				
Extended Data Figure 4				**Treatment effect**		**Sex effect**		**Interaction**	
b	Locomotion- Males *vs* females	*n = 10,9,9,10,9,8*	two-way ANOVA	$F_{[2, 49]}$ = 13.08	*p < 0.01*	$F_{[1, 49]}$ =0.00001	*p > 0.05*	$F_{[2, 49]}$ = 0.27	*p > 0.05*
d	Locomotion - (R,S)-KET *vs* d-(R,S)-KET	*n = 9,10*	unpaired *t*-test		*p > 0.05*				
Extended Data Figure 5				**Treatment effect**					
a	Learned Helplessness: (2R,6R)-HNK	*n = 8,9,7,8,9,9,7*	one-way ANOVA	$F_{[6, 50]}$ = 17.53	*p < 0.001*				
b	Learned Helplessness: (2S,6S)-HNK	*n = 9,9,8,9,7*	one-way ANOVA	$F_{[4, 37]}$ = 8.09	*p < 0.001*				
c	1 hour post-injection FST: (2R,6R)-HNK	*n = 10,9,9,10,9,10,10*	Kruskal-Wallis one-way ANOVA	H = 25.69; Df = 6	*p < 0.001*				
	24 hours post-injection FST: (2R,6R)-HNK	*n = 10,9,10,9,9,10,9*	one-way ANOVA	$F_{[6, 59]}$ = 5.80	*p < 0.001*				
d	1 hour post-injection FST: (2S,6S)-HNK	*n = 17,17,16*	one-way ANOVA	$F_{[2, 47]}$ = 18.43	*p < 0.001*				
	24 hours post-injection FST: (2S,6S)-HNK	*n = 19,17,16*	one-way ANOVA	$F_{[2, 49]}$ = 4.96	*p < 0.05*				
e	Pharmacokinetics – (2S,6S)- *vs* (2R,6R)HNK	*(2S,6S)-HNK: n=4/time point* *(2R,6R)-HNK: n=4/time point*	No stats (n<5)						
f	Novelty-suppressed feeding	*n= 10/group*	Mantel-Cox test	C2 = 12.76; Df = 3	*p < 0.01*				
g	3-day FST	*n = 10/group*	one-way ANOVA	$F_{[2, 27]}$ = 4.23	*p < 0.05*				
				Treatment effect		**Phase effect (repeated)**		**Interaction**	
h	Sucrose preference	*n = 11,8*	two-way RM ANOVA	$F_{[1, 17]}$ = 0.89	*p > 0.05*	$F_{[2, 34]}$ = 24.42	*p < 0.001*	$F_{[2, 34]}$ = 5.96	*p < 0.01*
	• Baseline (SAL) vs Baseline ((2R,6R)-HNK)				*p > 0.05*				
	• CORT (SAL) vs CORT ((2R,6R)-HNK)				*p > 0.05*				
	• Treatment (SAL) vs Treatment ((2R,6R)-HNK)				*p < 0.01*				
i	Female urine sniffing test	*n = 8,8,8,8,8,8,7,7*	two-way RM ANOVA	$F_{[3, 27]}$ = 18.04	*p < 0.001*	$F_{[1, 27]}$ = 1.43	*p > 0.05*	$F_{[3, 27]}$ = 4.88	*p < 0.01*
j	Social defeats – locomotor activity	*n= 7,7,6,8*	one-way ANOVA	$F_{[3, 24]}$ = 0.61	*p > 0.05*				
k	Social defeats – total compartmental crosses	*n= 7,6,6,7*	one-way ANOVA	$F_{[3, 22]}$ = 0.71	*p > 0.05*				
Extended Data Figure 6				**Treatment effect**					
	AMPA sEPSCs frequency: (R,S)-KET	*n = 4*	No stats (n<5)						
f	AMPA sEPSCs frequency: (2S,6S)-HNK	*n = 4*	No stats (n<5)						
	AMPA sEPSCs frequency: (2R,6R)-HNK	*n = 6*	one sample *t*-test		*p < 0.01*				
j	AMPA sEPSCs amplitude: (R,S)-KET	*n = 4*	No stats (n<5)						
	AMPA sEPSCs amplitude: (2S,6S)-HNK	*n = 4*	No stats (n<5)						

	AMPA sEPSCs amplitude: (2R,6R)-HNK	*n = 6*	one sample *t*-test		*p < 0.01*
Extended Data Figure 7				**Treatment effect**	
a	Locomotor activity	*n = 4 (program malfunction)*	No stats (n<5)		
b	Alpha power (% baseline): SAL	*n = 5*	one-way RM ANOVA	$F_{[2.49, 9.97]} = 1.05$	*p > 0.05*
	Alpha power (% baseline): (R,S)-KET	*n = 5*	one-way RM ANOVA	$F_{[2.27, 9.07]} = 1.04$	*p > 0.05*
	Alpha power (% baseline): (2R,6R)-HNK	*n = 6*	Friedman one-way RM ANOVA	C2 = 2.10; Df = 8	*p > 0.05*
c	Beta power (% baseline): SAL	*n = 5*	Friedman one-way RM ANOVA	C2 = 15.93; Df = 8	*p < 0.05*
	Beta power (% baseline): (R,S)-KET	*n = 5*	one-way RM ANOVA	$F_{[2.35, 9.39]} = 1.01$	*p > 0.05*
	Beta power (% baseline): (2R,6R)-HNK	*n = 6*	Friedman one-way RM ANOVA	C2 = 5.94; Df = 8	*p > 0.05*
d	Delta power (% baseline): SAL	*n = 5*	one-way RM ANOVA	$F_{[2.47, 9.89]} = 0.88$	*p > 0.05*
	Delta power (% baseline): (R,S)-KET	*n = 5*	Friedman one-way RM ANOVA	C2 = 3.56; Df = 8	*p > 0.05*
	Delta power (% baseline): (2R,6R)-HNK	*n = 6*	one-way RM ANOVA	$F_{[1.45, 7.26]} = 0.65$	*p > 0.05*
e	Theta power (% baseline): SAL	*n = 5*	one-way RM ANOVA	$F_{[2.23, 8.91]} = 2.05$	*p > 0.05*
	Theta power (% baseline): (R,S)-KET	*n = 5*	one-way RM ANOVA	$F_{[1.27, 5.08]} = 1.02$	*p > 0.05*
	Theta power (% baseline): (2R,6R)-HNK	*n = 6*	Friedman one-way RM ANOVA	C2 = 8.69; Df = 8	*p > 0.05*
f	Locomotor activity: SAL/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 13.69; Df = 11	*p > 0.05*
	Locomotor activity: NBQX/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 9.02; Df = 11	*p > 0.05*
g	Alpha power (% baseline): SAL/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 20.92; Df = 11	*p < 0.05*
	Alpha power (% baseline): NBQX/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 12.94; Df = 11	*p > 0.05*
h	Beta power (% baseline): SAL/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 27.22; Df = 11	*p < 0.01*
	Beta power (% baseline): NBQX/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 17.07; Df = 11	*p > 0.05*
i	Gamma power (% baseline): SAL/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 29.36; Df = 11	*p < 0.01*
	Gamma power (% baseline): NBQX/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 28.89; Df = 11	*p < 0.01*
j	Delta power (% baseline): SAL/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 27.97; Df = 11	*p < 0.01*
	Delta power (% baseline): NBQX/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 18.71; Df = 11	*p > 0.05*
k	Theta power (% baseline): SAL/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 22.96; Df = 11	*p < 0.05*
	Theta power (% baseline): NBQX/(2R,6R)-HNK	*n= 11*	Friedman one-way RM ANOVA	C2 = 22.33; Df = 11	*p < 0.05*

Extended Data Figure 8				**Treatment effect**	
a	Hippocampus: 1 hour post-injection: mTOR	*n = 11,11,12*	one-way ANOVA	$F_{[2, 31]} = 0.0002$	*p > 0.05*
	Hippocampus: 1 hour post-injection: p-mTOR	*n = 10,11,11*	one-way ANOVA	$F_{[2, 29]} = 0.48$	*p > 0.05*
b	Hippocampus: 24 hours post-injection: mTOR	*n = 10,11,11*	one-way ANOVA	$F_{[2, 29]} = 1.37$	*p > 0.05*
	Hippocampus: 24 hours post-injection: p-mTOR	*n = 11,10,12*	one-way ANOVA	$F_{[2, 30]} = 0.08$	*p > 0.05*
c	Prefrontal cortex: 1 hour post-injection: mTOR	*n = 12/group*	one-way ANOVA	$F_{[2, 33]} = 0.11$	*p > 0.05*
	Prefrontal cortex: 1 hour post-injection: p-mTOR	*n = 12,11,12*	one-way ANOVA	$F_{[2, 32]} = 1.36$	*p > 0.05*
d	Prefrontal cortex: 24 hours post-injection: mTOR	*n = 11,10,12*	one-way ANOVA	$F_{[2, 30]} = 0.35$	*p > 0.05*
	Prefrontal cortex: 24 hours post-injection: p-mTOR	*n = 11,9,11*	one-way ANOVA	$F_{[2, 28]} = 1.91$	*p > 0.05*
e	Prefrontal cortex: 1 hour post-injection: eEF2	*n = 12/group*	one-way ANOVA	$F_{[2, 33]} = 0.83$	*p > 0.05*
	Prefrontal cortex: 1 hour post-injection: p-eEF2	*n = 11,12,12*	one-way ANOVA	$F_{[2, 32]} = 0.45$	*p > 0.05*
f	Prefrontal cortex: 24 hours post-injection: eEF2	*n = 10,10,12*	one-way ANOVA	$F_{[2, 29]} = 0.03$	*p > 0.05*
	Prefrontal cortex: 24 hours post-injection: p-eEF2	*n = 10,10,12*	one-way ANOVA	$F_{[2, 29]} = 0.59$	*p > 0.05*
g	Prefrontal cortex: 1 hour post-injection: proBDNF	*n = 11,11,12*	one-way ANOVA	$F_{[2, 31]} = 0.54$	*p > 0.05*
	Prefrontal cortex: 1 hour post-injection: mBDNF	*n = 12,12,11*	one-way ANOVA	$F_{[2, 32]} = 1.83$	*p > 0.05*
h	Prefrontal cortex: 24 hour post-injection: proBDNF	*n = 11,11,12*	one-way ANOVA	$F_{[2, 31]} = 0.46$	*p > 0.05*
	Prefrontal cortex: 24 hour post-injection: mBDNF	*n = 10,11,12*	one-way ANOVA	$F_{[2, 30]} = 2.07$	*p > 0.05*
i	Prefrontal cortex: 1 hour post-injection: GluA1	*n = 12/group*	one-way ANOVA	$F_{[2, 33]} = 1.43$	*p > 0.05*
	Prefrontal cortex: 1 hour post-injection: GluA2	*n = 12/group*	one-way ANOVA	$F_{[2, 33]} = 1.45$	*p > 0.05*

j	Prefrontal cortex: 24 hours post-injection: GluA1	*n = 11,11,12*	one-way ANOVA	$F_{[2, 31]} = 0.67$	*p > 0.05*
	Prefrontal cortex: 24 hours post-injection: GluA2	*n = 11,10,12*	one-way ANOVA	$F_{[2, 30]} = 0.55$	*p > 0.05*
Extended Data Figure 9				**Treatment effect**	
a	Startle amplitude	*n = 6,6,6,5,5*	one-way ANOVA	$F_{[4, 23]} = 0.64$	*p > 0.05*
b	Response rate: (2R,6R)-HNK	*n = 8,8,7,8*	one-way ANOVA	$F_{[3, 28]} = 0.85$	*p > 0.05*
c	Response rate: PCP	*n = 7,8,7*	one-way ANOVA	$F_{[2, 19]} = 1.10$	*p > 0.05*
d	Self-administration - drug intake: (R,S)-KET	*n = 8*	Friedman one-way RM ANOVA	$F_{[1.06, 7.41]} = 5.27$	*p = 0.05*
	Self-administration - drug intake: (2R,6R)-HNK	*n = 6*	Friedman one-way RM ANOVA	C2 = 1.33; Df = 2	*p > 0.01*

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; C2, chi-square; Df, degrees of freedom; eEF2, eukaryotic translation elongation factor 2; EPSCs, excitatory post-synaptic currents; FP, field potentials; FST, forced-swim test; HNK, hydroxynorketamine; KET, ketamine; mBDNF, mature brain-derived neurotrophic factor; mTOR, mammalian target of rapamycin; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione; NMDA, *N*-methyl-*D*-aspartate; PCP, phencyclidine; proBDNF, pro-brain-derived neurotrophic factor; RM, repeated measures; SAL, saline.

2. Supplementary Figure 1: Uncropped scans with size marker indications

Figure 4a

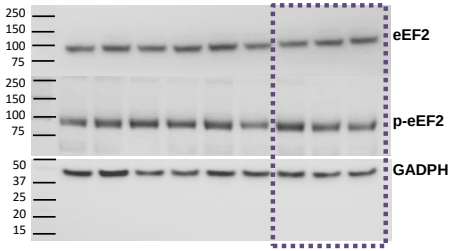


Figure 4b

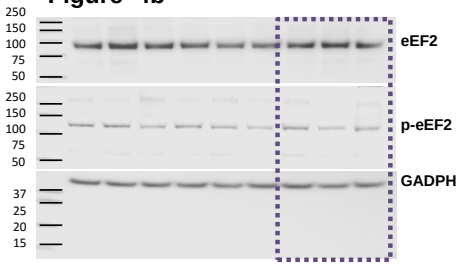


Figure 4c

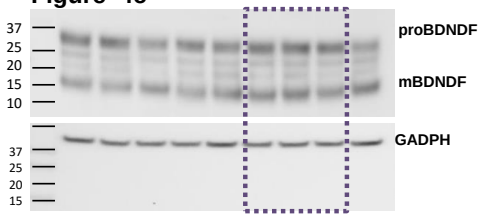


Figure 4d

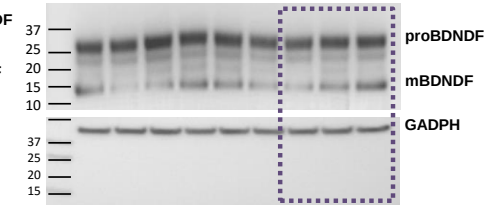


Figure 4e

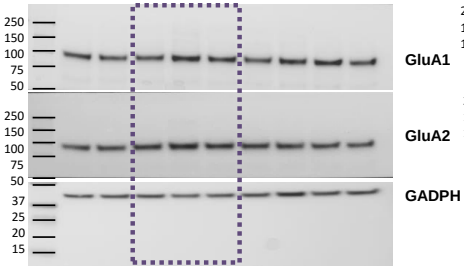
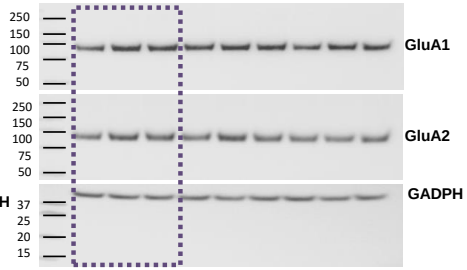
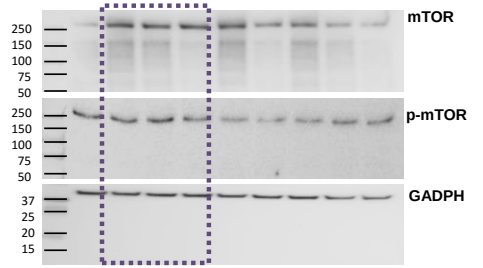


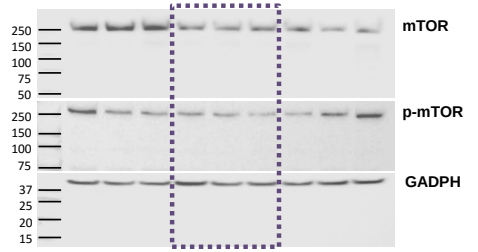
Figure 4f



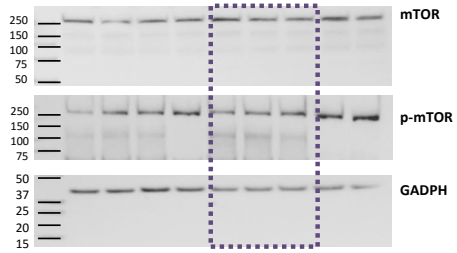
Extended Data Figure 8a



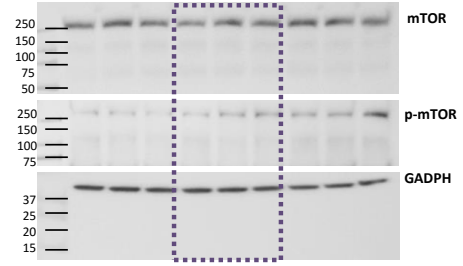
Extended Data Figure 8b



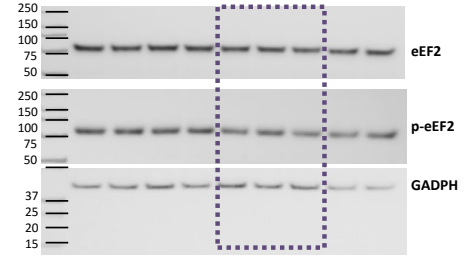
Extended Data Figure 8c



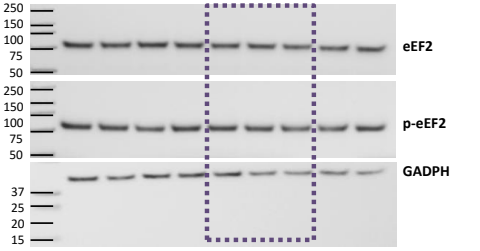
Extended Data Figure 8d



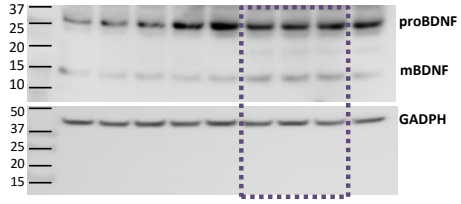
Extended Data Figure 8e



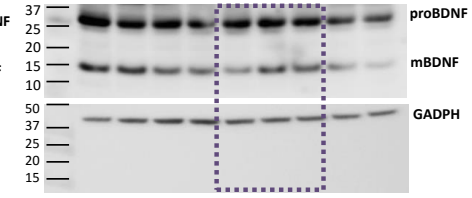
Extended Data Figure 8f



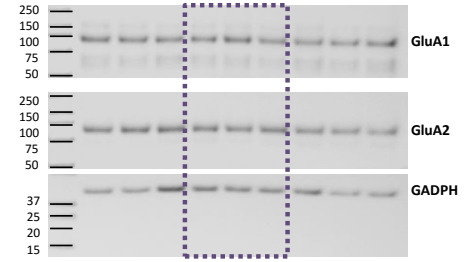
Extended Data Figure 8g



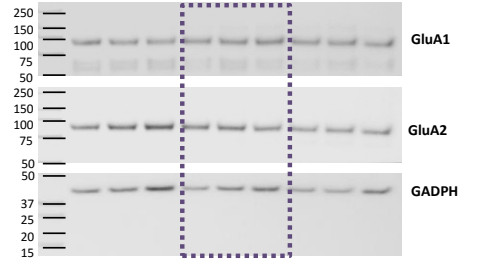
Extended Data Figure 8h



Extended Data Figure 8i



Extended Data Figure 8j



3. General Information

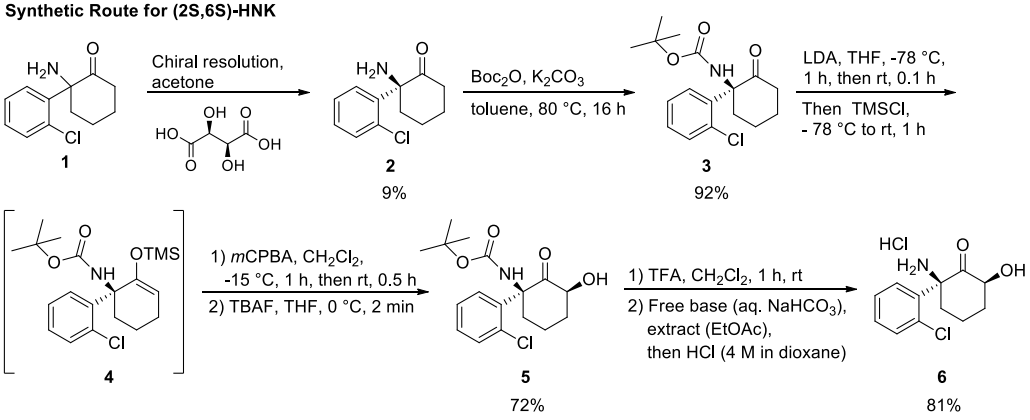
All commercially available reagents and solvents were purchased and used without further purification. All microwave reactions were carried out in a sealed microwave vial equipped with a magnetic stir bar and heated in a Biotage Initiator Microwave Synthesizer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz or Varian 600 MHz spectrometers in CD_3OD or $CDCl_3$ as indicated. For spectra recorded in CD_3OD, chemical shifts are reported in ppm with CD_3OD (3.31 ppm) as reference for ^{1}H NMR spectra and CD_3OD (49.0 ppm) for ^{13}C NMR spectra. Alternatively for spectra recorded in $CDCl_3$, chemical shifts are reported in ppm relative to $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.23 ppm for ^{13}C NMR). The coupling constants (*J* value) are reported as Hertz (Hz). The splitting patterns of the peaks were described as: singlet (s); doublet (d); triplet (t); quartet (q); multiplet (m) and septet (septet). Samples were analyzed for purity on an Agilent 1200 series LC/MS equipped with a Luna C18 (3 mm x 75 mm, 3 µm) reversed-phase column with UV detection at λ=220 nm and λ=254 nm. The mobile phase consisted of water containing 0.05% trifluoroacetic acid as component A and acetonitrile containing 0.025% trifluoroacetic acid as component B. A linear gradient was run as follows: 0 min 4% B; 7 min 100% B; 8 min 100% B at a flow rate of 0.8 mL/min. High resolution mass spectrometry (HRMS) was recorded on Agilent 6210 Time-of-Flight (TOF) LC/MS system. Optical rotations were measured on a PerkinElmer model 341 polarimeter using a 10 cm cell, at 589 nM and room temperature.

Chiral analysis was carried out with an Agilent 1200 series HPLC using an analytical Chiralpak AD or OJ column (4.6 mm x 250 mm; 5 µm). The mobile phase consisted of ethanol containing 0.1% diethylamine as component A and hexanes containing 0.1% diethylamine as component B. An isocratic gradient was run at 0.4 mL/min with 60% A.

(*2R,6R*)-hydroxynorketamine hydrochloride and (*2S,6S*)-hydroxynorketamine are previously described by Wainer *et. al.* [1] Spectral data matches those previously reported. Single crystal X-ray crystallography was performed in order to confirm absolute stereochemistry. X-ray crystallography and analysis was performed at the University of California, San Diego.

4. Synthetic Schemes

Synthetic Route for (2S,6S)-HNK



1

2

9%

3

92%

4

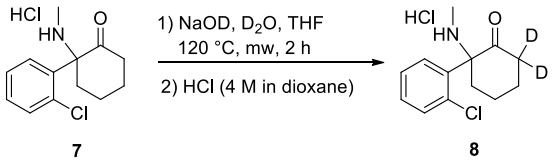
5

72%

6

81%

Synthetic route for 6,6-dideuteroketamine hydrochloride

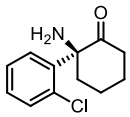


7

8

5. Synthetic Methods and Analytical Data

5.1. (S)-(+)-Norketamine (2) (NCGC00479288)

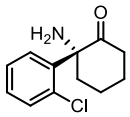


In an analogous procedure to that of Hong and Davisson [2], racemic norketamine (**1**)[2] (23 grams, 100 mmol) was dissolved in methanol (58 mL) and (*2S,3S*)-(D)-(-)-tartaric acid (17.1 grams) in methanol (230 mL) was added. The reaction was stirred at room temperature for 16 hours. The solvent was partially removed by rotary evaporation. 2-Butanone was added (100 mL) and the solvent was further removed by rotary evaporation to give the solid norketamine D-tartrate. The solid material was dissolved in 6.0 L of refluxing acetone. The reaction mixture was filtered, and allowed to cool to room temperature without stirring for two days. Fine needle-like low density crystals were collected to give 6.0 grams of (*S*)-(+)-norketamine D-tartrate. The filtrate was saved for later isolation of the other enantiomer. The (*S*)-(+)-norketamine D-tartrate was recrystallized from hot acetone a further three times to improve the enantiopurity, resulting in 3.2 grams of the (*S*)-(+)-norketamine D-tartrate. The optical rotation was measured and compared to that of Hojahmat, *et. al.* [3] to confirm the absolute stereochemistry, while enantiomeric excess was determined to be >97% by chiral HPLC. S-(+)-Norketamine D-tartrate was then converted into the free base by treatment with aqueous 1M sodium hydroxide and extraction with ethyl acetate. The organic phase was taken and the solvent removed by rotary evaporation to give (*S*)-(+)-norketamine as a white crystalline solid (1.9 grams, 8.6 % yield). ^{1}H NMR spectra matched the reported spectra.

Chiral HPLC: 97% ee. (Chiralpak AD, 60% ethanol in hexanes, 1 mL/min, rt: 5.01 min.)

$[\alpha]_D^{20}$: +55° (*c* 1.0, H_2O, D-tartrate salt) compared to (+)-57° (*c* 2.0, H_2O, D-tartrate salt) [3].

5.2. (R)-(-)-Norketamine (NCGC00421876)

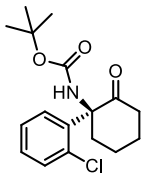


(*R*)-(-)-Norketamine was produced in an analogous fashion to that of (S)-(+)-norketamine, except that (*2R,3R*)-(L)-(+)-tartaric acid was used as a chiral resolution agent instead of (2S,3S)-(D)-(-)-tartaric acid.

Chiral HPLC: 98% ee. (Chiralpak AD, 60% ethanol in hexanes, 1 mL/min, rt: 6.83 min.)

$[\alpha]_D^{20}$: -53° (*c* 1.0, H_2O, L-tartrate salt)

5.3. (S)-tert-Butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate (3) (NCGC00390042)



To a solution of (*S*)-(+)-norketamine (1.85 g, 8.27 mmol) in toluene (100 mL), potassium carbonate (3.43 g, 24.8 mmol) and BOC-anhydride (2.71 g, 12.4 mmol) were added. The reaction was heated to 80 °C and stirred for 16 hours. The reaction was then cooled, extracted with ethyl acetate and washed with water. The organic layer was taken and the solvent removed *in vacuo* to give the crude product. Purification by silica gel chromatography (0% to 60% ethyl acetate in hexanes) gave the final product as a white solid (2.46 g, 92% yield).

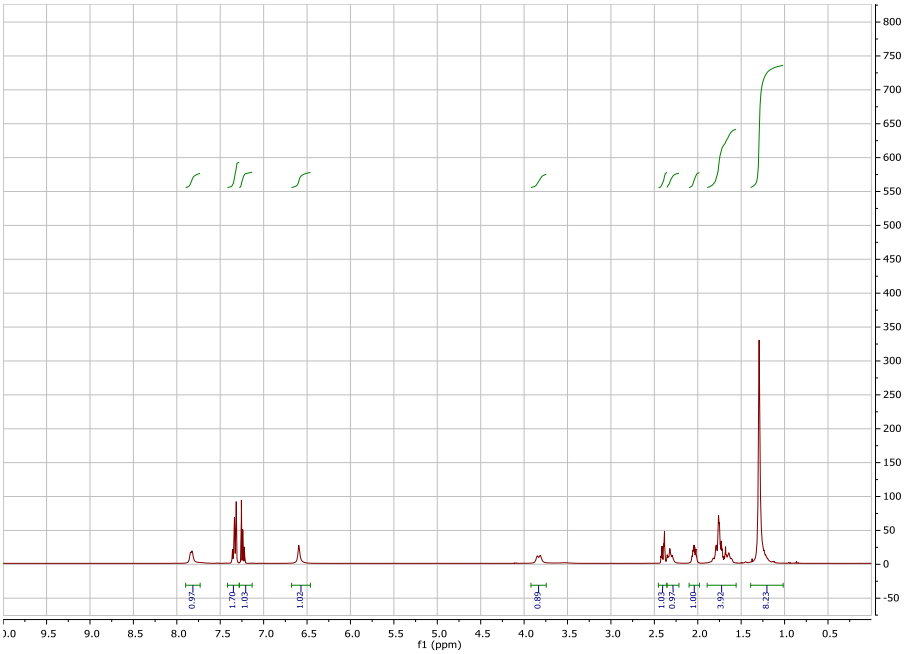
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.28 (m, 2H), 7.28 – 7.13 (m, 1H), 6.59 (s, 1H), 3.83 (d, *J* = 14.3 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.36 – 2.25 (m, 1H), 2.04 (ddq, *J* = 11.5, 5.5, 3.0 Hz, 1H), 1.89 – 1.56 (m, 4H), 1.29 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 153.4, 135.1, 133.7, 131.5, 130.9, 129.2, 126.2, 79.0, 67.1, 39.4, 38.4, 30.8, 28.2, 22.3.

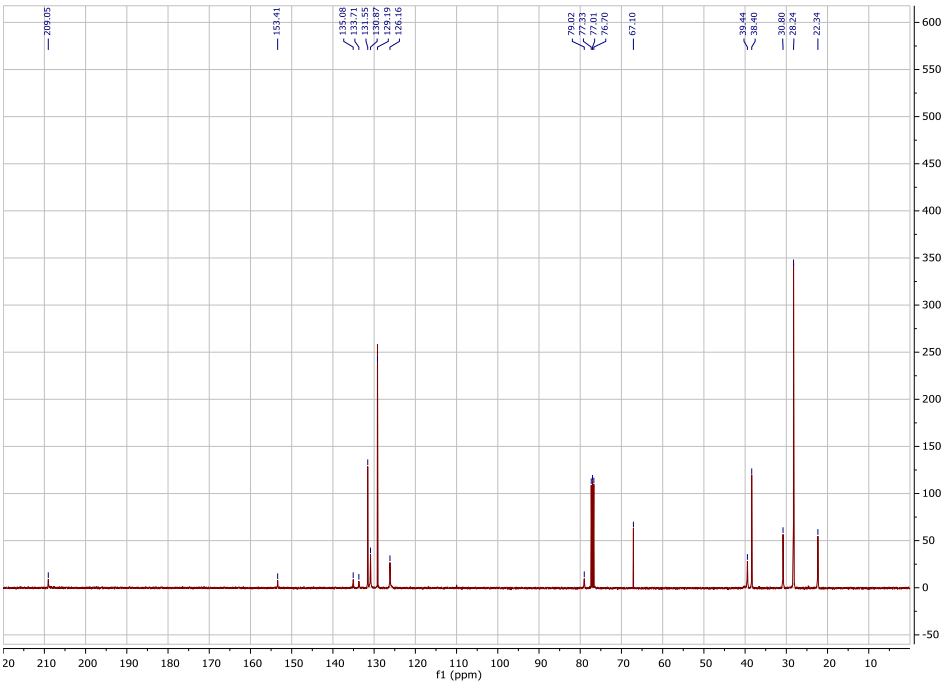
HRMS (ESI+): Expected 346.1186 [M+Na] ($C_{17}H_{22}ClNO_3Na$). Observed 346.1180.

$[\alpha]_D^{20}$: (+)-55.7° (*c* 1.0, $CHCl_3$).

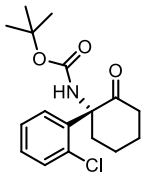
^{1}H NMR spectra of (*S*)-*tert*-butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate



^{13}C NMR spectra of (*S*)-*tert*-butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate



5.4. (R)-tert-Butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate (NCGC00479290)



The title compound was prepared in an analogous fashion to (*S*)-*tert*-butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate, utilizing (*R*)-(-)-norketamine instead of (*S*)-(+)-norketamine.

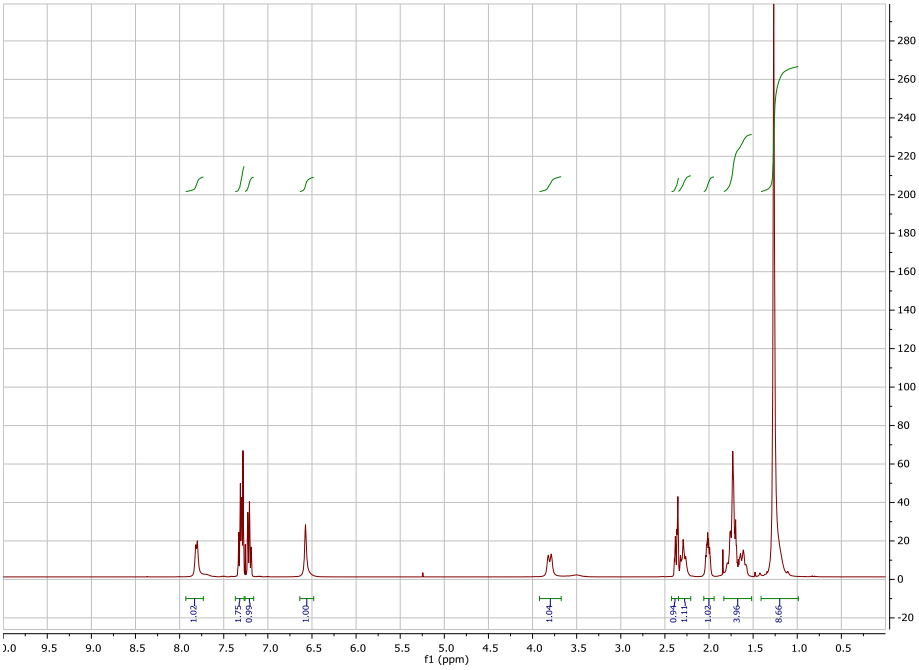
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.30 – 7.21 (m, 1H), 6.61 (s, 1H), 3.84 (d, *J* = 14.4 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.38 – 2.29 (m, 1H), 2.09 – 2.02 (m, 1H), 1.86 – 1.62 (m, 4H), 1.31 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 153.4, 135.0, 133.7, 131.5, 130.8, 129.2, 126.2, 79.0, 67.1, 39.4, 38.4, 30.8, 28.2, 22.3.

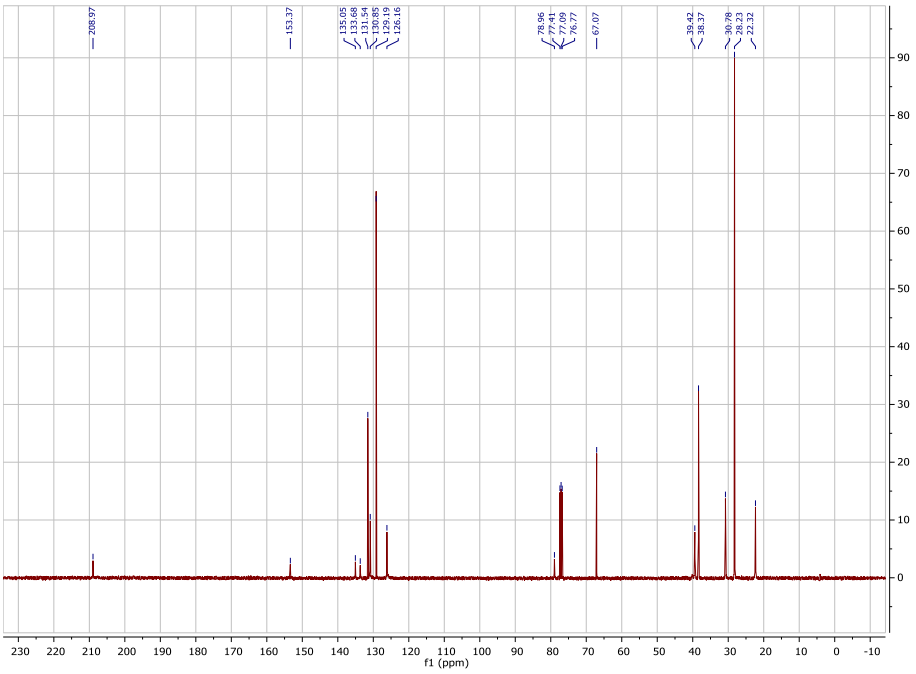
HRMS (ESI+): Expected 346.1186 [M+Na] ($C_{17}H_{22}ClNO_3Na$). Observed 346.1188.

$[\alpha]_D^{20}$: -50.7° (*c* 1.0, $CHCl_3$).

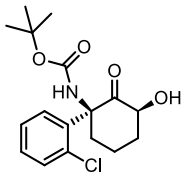
^{1}H NMR spectra of (*R*)-*tert*-butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate



^{13}C NMR spectra of (*R*)-*tert*-butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate



5.5. tert-Butyl ((1S,3S)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (5) (NCGC00414990)



A solution of (*S*)-*tert*-butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate (**3)** (6.5 grams, 20 mmol) in tetrahydrofuran (THF) (100 mL), was cooled to -78 °C under a nitrogen atmosphere. Lithium diisopropylamide (2.0 M in THF/heptane/ethylbenzene, 26 mL, 52 mmol, 2.6 eq.) was added by syringe. The reaction was stirred for 1 hour at -78 °C, then allowed to warm to room temperature for 5 minutes. The reaction was cooled to -78 °C, and chlorotrimethylsilane (5.7 grams, 52 mmol, 2.6 eq.) was added as a neat liquid by syringe. The reaction was stirred for 30 minutes at -78 °C, and then allowed to warm to room temperature over 30 minutes. The reaction

was then quenched by being poured into aqueous saturated ammonium chloride. Ethyl acetate was added to the resulting mixture, the organic phase was separated and the solvent was removed by rotary evaporation to give the crude enol ether **4** as a solid which was immediately used without further purification. The enol ether **4** (7.8 grams) was dissolved in dichloromethane (100 mL) and cooled to -15 °C (ice-lithium chloride), under a nitrogen atmosphere. 3-Chloroperbenzoic acid (5.0 grams, 1.1 eq.) was then added as a solid. The reaction was stirred for one hour at -15 °C, then the temperature was raised to room temperature and an additional 100 mL of dichloromethane was added. The reaction was stirred a further 0.5 hours. The reaction was then quenched by being poured into a 50/50 mixture of saturated aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate. The reaction was extracted into dichloromethane and the solvent removed by rotary evaporation. Then THF (100 mL) was added to the crude material. The reaction was cooled to -5 °C, and tetrabutylbutyl ammonium fluoride (1.0 M in THF, 25 mL, 1.2 eq. was added). The reaction was stirred for 2 minutes, before being quenched by addition to saturated aqueous sodium bicarbonate. Extraction into ethyl acetate, followed by removal of the solvent by rotary evaporation gave the crude final product **5**. Purification by silica gel chromatography (0% to 70% ethyl acetate in hexanes), gave the purified final product as a solid (4.9 g, 72% yield).

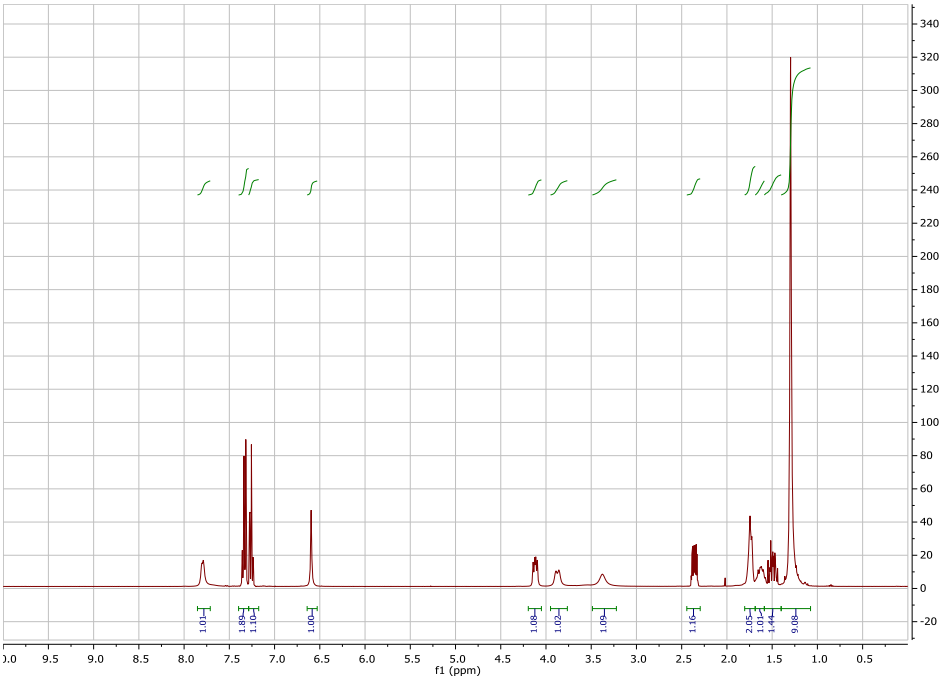
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 1H), 7.34 (ddd, *J* = 8.8, 7.1, 1.4 Hz, 2H), 7.29 – 7.18 (m, 1H), 6.60 (s, 1H), 4.12 (dd, *J* = 11.8, 6.7 Hz, 1H), 3.87 (d, *J* = 14.3 Hz, 1H), 3.38 (s, 1H), 2.36 (ddq, *J* = 13.1, 6.5, 3.2 Hz, 1H), 1.74 (ddt, *J* = 7.8, 5.7, 2.8 Hz, 2H), 1.69 – 1.59 (m, 1H), 1.59 – 1.40 (m, 1H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 153.3, 134.1, 133.8, 131.4, 131.0, 129.7, 126.3, 79.4, 72.4, 66.7, 40.4, 38.8, 28.2, 19.6.

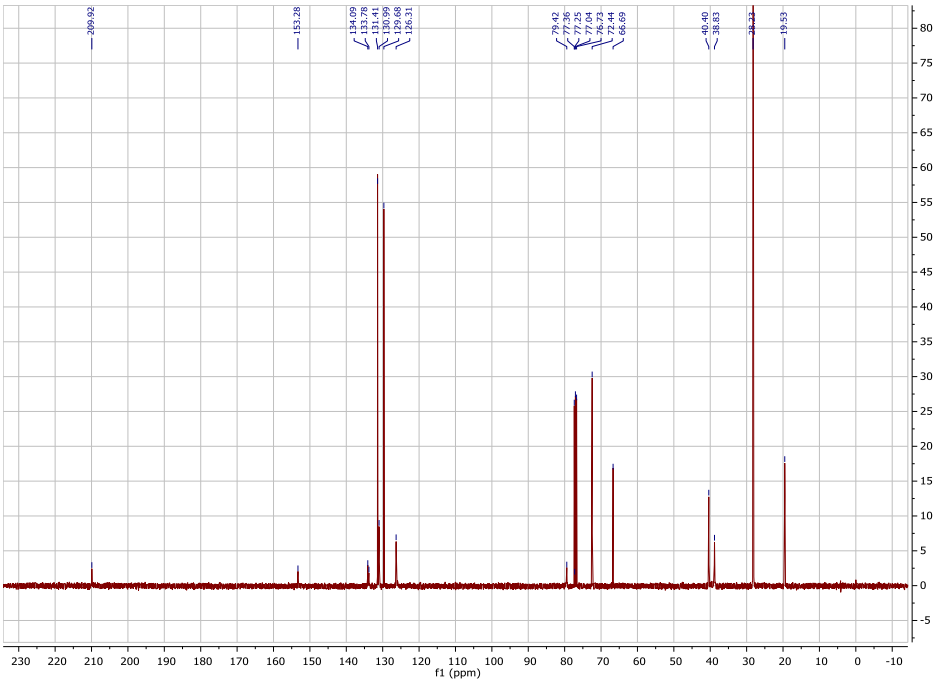
HRMS (ESI+): Expected 362.1135 [M+Na] ($C_{17}H_{22}ClNO_4Na$). Observed 362.1134.

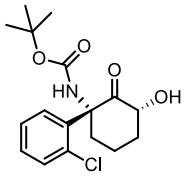
$[\alpha]_D^{20}$: +60.7° (*c* 1.0, $CHCl_3$).

^{1}H NMR spectra of tert-butyl ((*1S*,*3S*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate



^{13}C NMR spectra of tert-butyl ((*1S*,*3S*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate





5.6. tert-Butyl ((1R,3R)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (NCGC00402227)

The title compound was prepared in an analogous fashion to (*tert*-butyl ((*1S*,*3S*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate **(5)** by utilizing (*R*)-tert-butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate instead of the S-enantiomer.

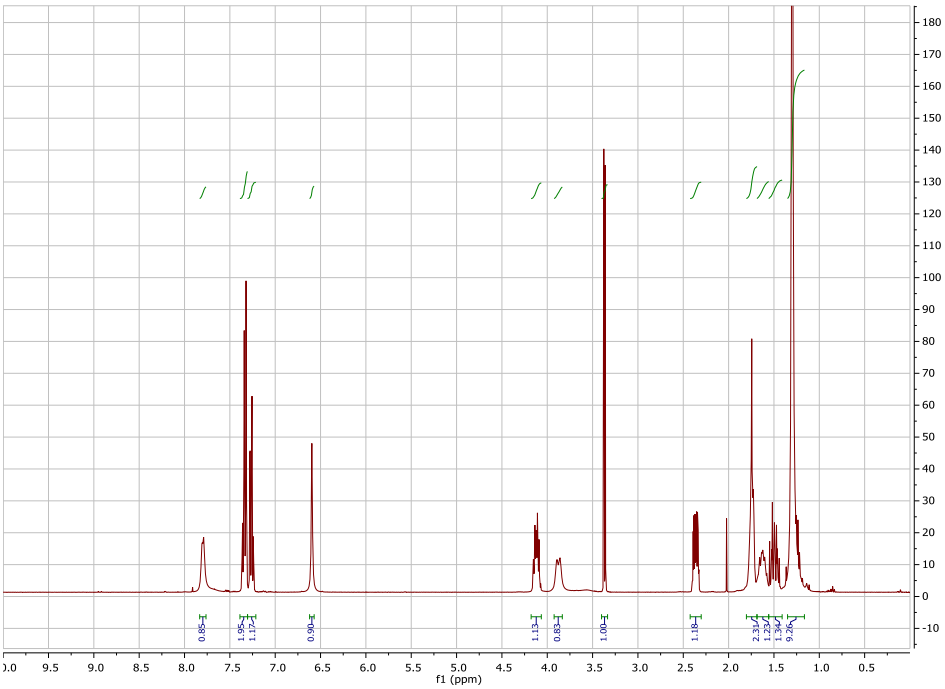
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 1H), 7.34 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.32 – 7.21 (m, 1H), 6.60 (s, 1H), 4.12 (ddd, *J* = 11.5, 8.9, 6.3 Hz, 1H), 3.92 – 3.83 (m, 1H), 3.37 (d, *J* = 6.5 Hz, 1H), 2.36 (ddq, *J* = 13.0, 6.5, 3.2 Hz, 1H), 1.74 (dq, *J* = 6.4, 3.2, 2.5 Hz, 2H), 1.63 (dq, *J* = 16.8, 9.2, 8.2 Hz, 1H), 1.59 – 1.40 (m, 1H), 1.30 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 153.3, 134.1, 133.8, 131.4, 131.0, 129.7, 126.3, 79.4, 72.4, 66.7, 40.4, 38.8, 28.2, 19.5.

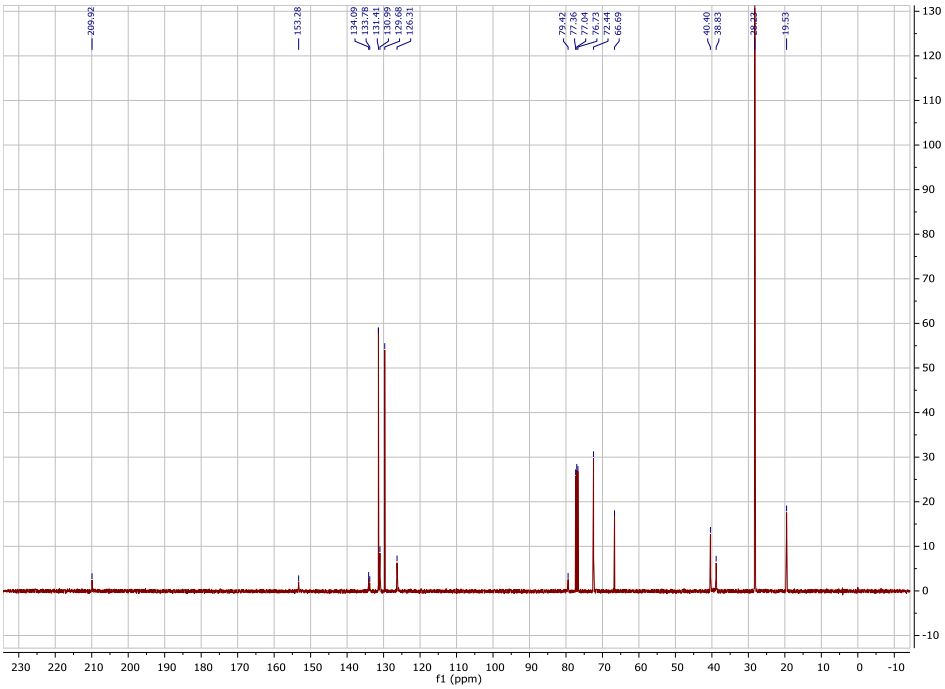
HRMS (ESI+): Expected 362.1135 [M+Na] ($C_{17}H_{22}ClNO_4Na$). Observed 362.1134.

$[\alpha]_D^{20}$: -63.7° (*c* 1.0, $CHCl_3$).

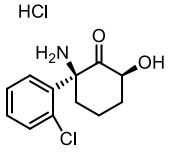
^{1}H NMR spectra of tert-butyl ((*1R,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate



^{13}C NMR spectra of tert-butyl ((*1R*,*3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate



5.7. (2S,6S)-(+)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexanone hydrochloride (6) ((2S,6S)-(+)-hydroxynorketamine hydrochloride) (NCGC00373033)



To a solution of *tert*-butyl ((*1S*,*3S*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate **5** (4.85 grams, 14.3 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (TFA; 11.0 mL, 143 mmol, 10 eq.). The reaction was stirred at room temperature for 1 hour. The solvent TFA were then removed by rotary evaporation. The resulting TFA salt was dissolved in water, washed with a 1:1 mixture of saturated aqueous sodium bicarbonate and saturated aqueous potassium carbonate solution, and extracted with ethyl acetate (2X) to give the free base. The

ethyl acetate was removed by rotary evaporation. Ethyl acetate (4 mL) was added and HCl in dioxane (4.0 M, 6.0 mL) was added. A white solid immediately precipitated. The suspension was agitated for 30 seconds and then the solid was filtered off and dried under vacuum to give the desired final product (3.05 g, 77% yield).

^{1}H NMR (400 MHz, MeOD) δ 7.92 – 7.81 (m, 1H), 7.66 – 7.50 (m, 3H), 4.28 (dd, *J* = 11.7, 6.6 Hz, 1H), 3.19 (dd, *J* = 14.0, 3.0 Hz, 1H), 2.30 (dddd, *J* = 12.2, 6.6, 4.1, 2.3 Hz, 1H), 1.80 – 1.70 (m, 2H), 1.68 – 1.52 (m, 2H).

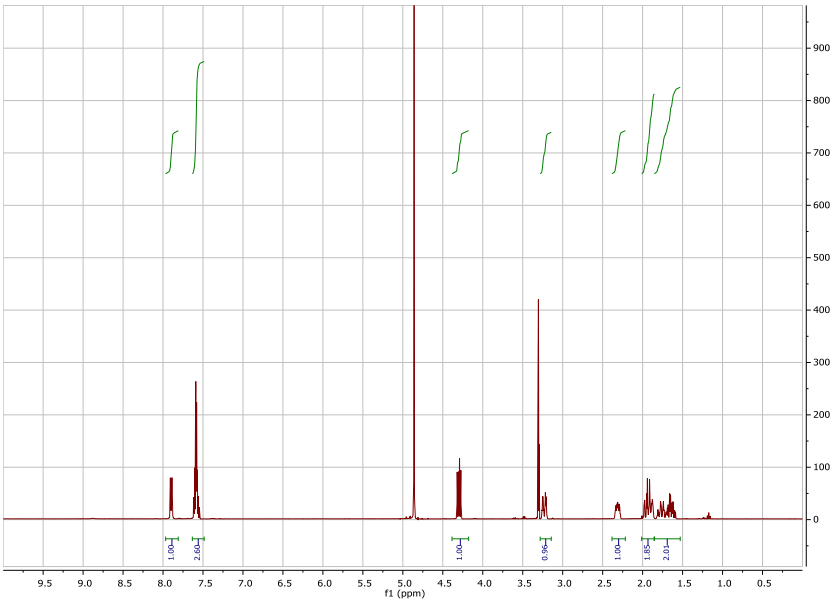
^{13}C NMR (101 MHz, MeOD): δ 206.8, 134.0, 132.1, 131.6, 130.5, 130.0, 128.3, 73.0, 67.0, 38.4, 37.1, 18.7.

Chiral HPLC: 98.3% ee (Chiralpak AD column, 60% ethanol in hexanes, 1.0 mL/min, rt = 6.0 min.)

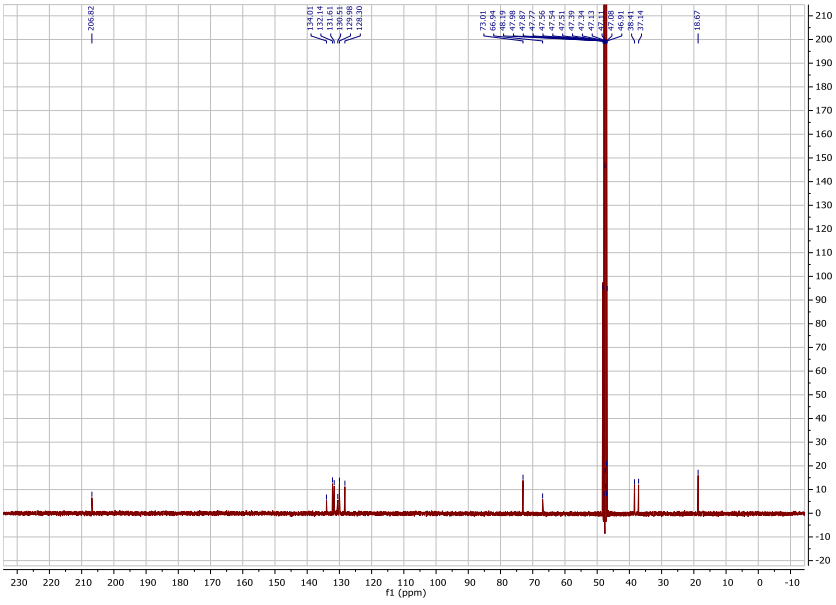
HRMS (ESI+): Expected 240.0786 [M+H] ($C_{12}H_{15}ClNO_2$). Observed 240.0782.

$[\alpha]_D^{20}$: +95° (*c* 1.0, H_2O).

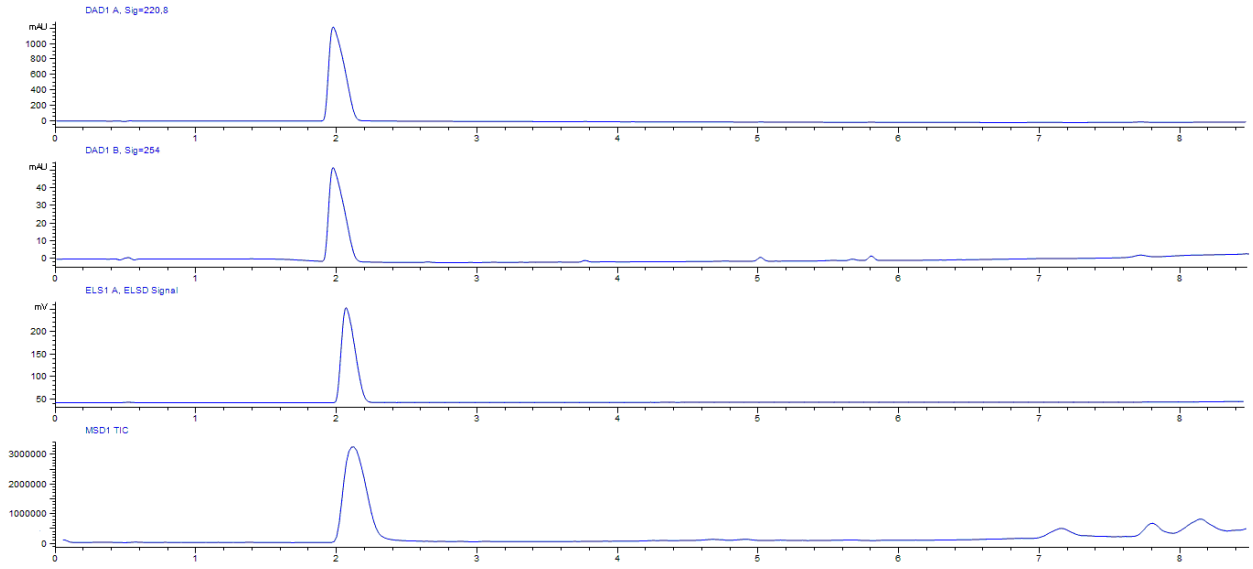
[1]H NMR spectra of (*2S,6S*)-(+)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexanone hydrochloride



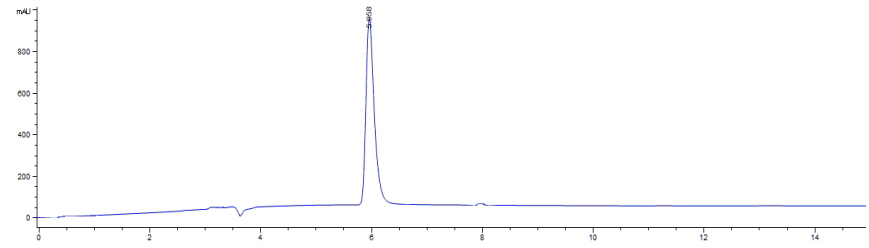
[13]C NMR spectra of (*2S,6S*)-(+)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexanone hydrochloride



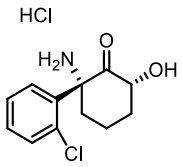
High pressure liquid chromatography trace of (*2S,6S*)-(+)-hydroxynorketamine



Chiral HPLC Trace (*2S,6S*)-(+)-hydroxynorketamine



5.8. (2R,6R)-(-)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexanone hydrochloride ((2R,6R)-(-)-hydroxynorketamine hydrochloride) (NCGC00378227)



The title compound was prepared in an analogous fashion to that of (*2S,6S*)-(+)-hydroxynorketamine hydrochloride by utilizing *tert*-butyl ((*1R,3R*)-1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate instead of the *S,S*-enantiomer.

^{1}H NMR (400 MHz, MeOD): δ 7.94 – 7.83 (m, 1H), 7.62 – 7.53 (m, 3H), 4.29 (dd, *J* = 11.6, 6.7 Hz, 1H), 3.19 (dd, J = 14.0, 3.0 Hz, 1H), 2.30 (dddd, J = 12.2, 6.6, 4.1, 2.3 Hz, 1H), 1.99 – 1.82 (m, 2H), 1.82 – 1.56 (m, 2H).

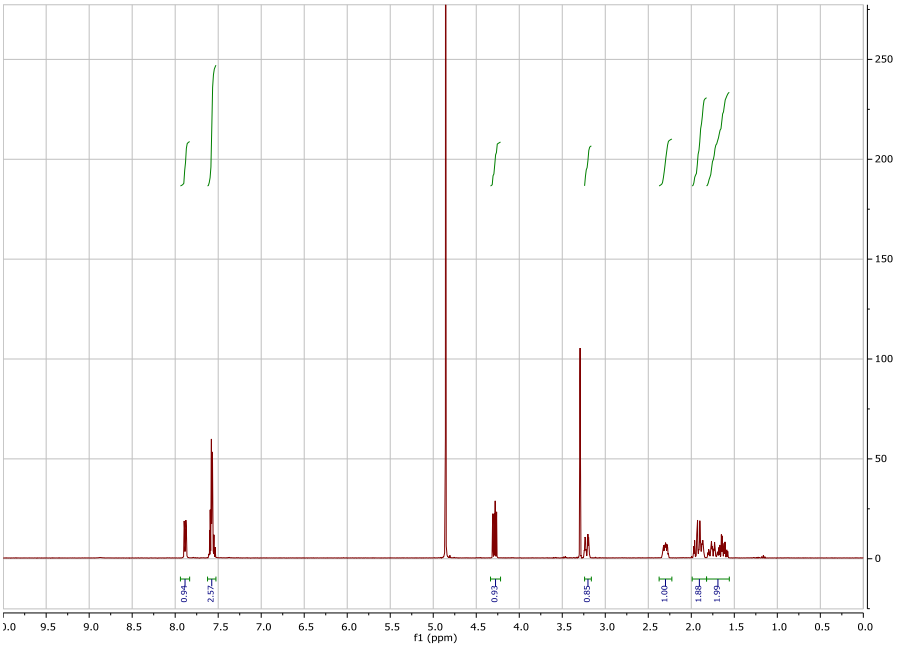
^{13}C NMR (101 MHz, MeOD): δ 206.8, 134.0, 132.1, 131.6, 130.5, 130.1, 128.3, 73.3, 67.0, 38.4, 37.2, 18.7.

Chiral HPLC: 98.3% ee (Chiralpak AD column, 60% ethanol in hexanes, 1.0 mL/min, rt = 7.9 min)

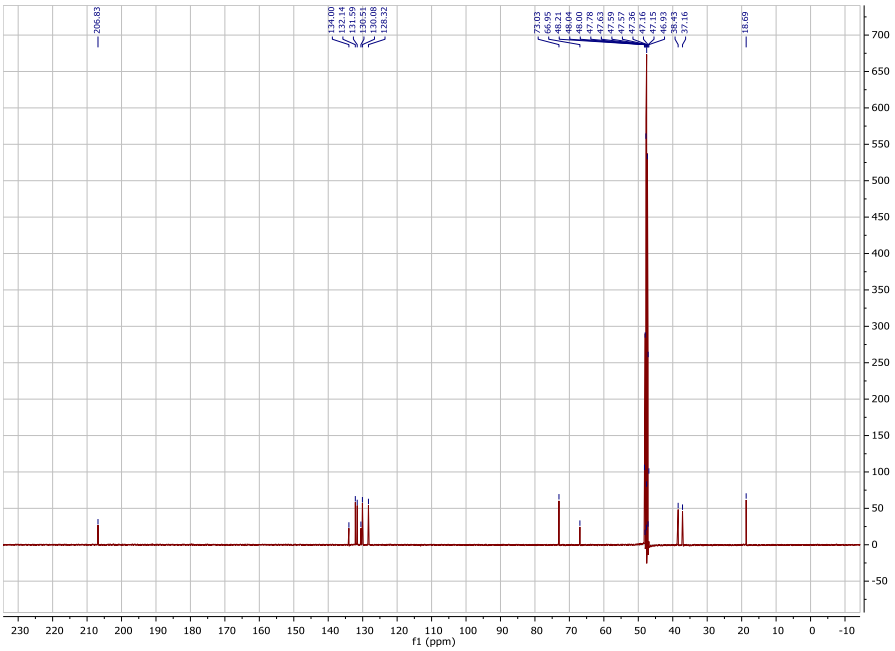
HRMS (ESI+): Expected 262.0605 [M+Na] ($C_{12}H_{14}ClNO_2Na$). Observed 262.0605

$[\alpha]_D^{20}$: -92° (*c* 1.0, H_2O).

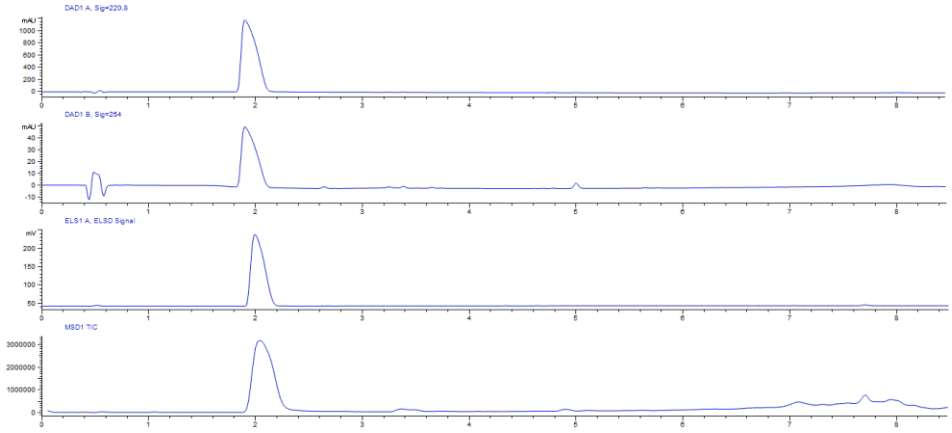
<u>^{1}H NMR spectra of (*2R,6R*)-(+)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexanone hydrochloride</u>



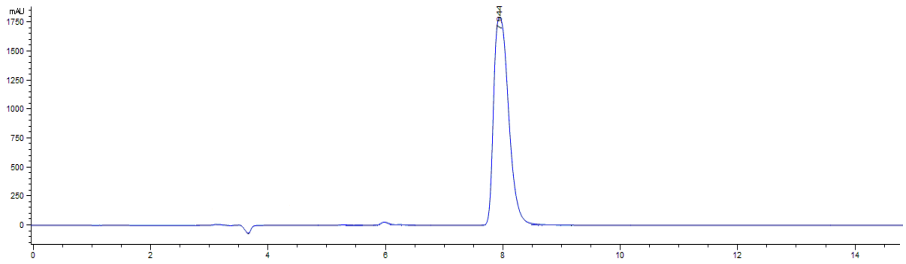
^{13}C NMR spectra of (*2R*,*6R*)-(+)-2-amino-2-(2-chlorophenyl)-6-hydroxycyclohexanone hydrochloride



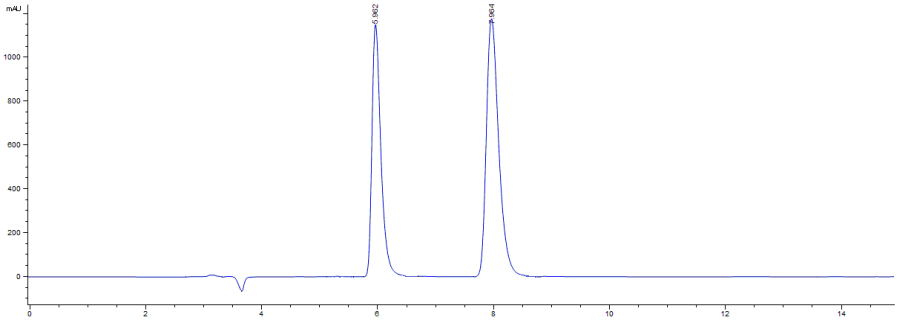
High pressure liquid chomatography trace of (*2R*,*6R*)-(-)-hydroxynorketamine



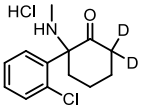
Chiral HPLC Trace (*2R,6R*)-(-)-hydroxynorketamine



Chiral trace: Racemate for (*2R,6R*)-(-)-hydroxynorketamine and (*2S,6S*)-(+)-hydroxynorketamine



5.9. 2-(2-Chlorophenyl)-6,6-dideutero-2-(methylamino)cyclohexanone hydrochloride (6,6-dideuteroketamine hydrochloride) (8) (NCGC00387722)



Sodium deuteroxide (30% in deuterium oxide, 3.0 mL) was added to a solution of racemic ketamine hydrochloride (0.80 grams, 2.9 mmol) in a mixture of THF (8.0 mL) and deuterium oxide (3.0 mL). The reaction was heated by microwave irradiation in a sealed vial to 120 °C for 2 hours. The reaction was cooled, extracted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The organic phase was taken and the solvent removed by rotary evaporation to give the crude product. Purification by reverse phase liquid chromatography (5% to 95% acetontrile in water with 0.1% TFA) gave the purified TFA salt. The free base was

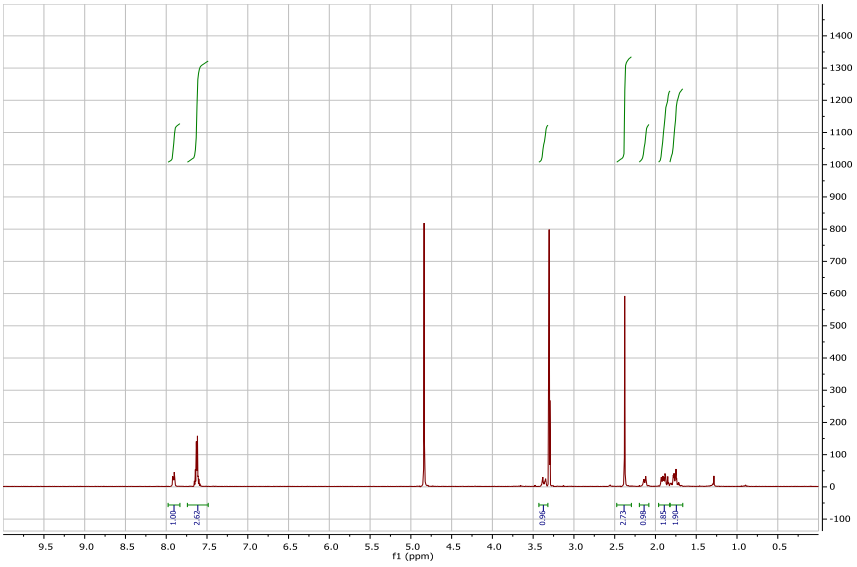
formed and isolated by washing the TFA salt with saturated aqueous sodium bicarbonate and extraction with ethyl acetate. The HCl salt was formed by the addition of HCl (4.0 M in dioxane), and filtration of the resulting white solid, to provide the title compound in 49% yield (0.45 grams) as a white solid.

^{1}H NMR (400 MHz, MeOD): δ 7.94-7.88 (m, 1H), 7.66-7.57 (m, 3H), 3.41-3.34 (m, 1H), 2.38 (s, 3H), 2.27-2.20 (m, 1H), 1.93-1.83 (m, 2H), 1.83-1.69 (m, 2H).

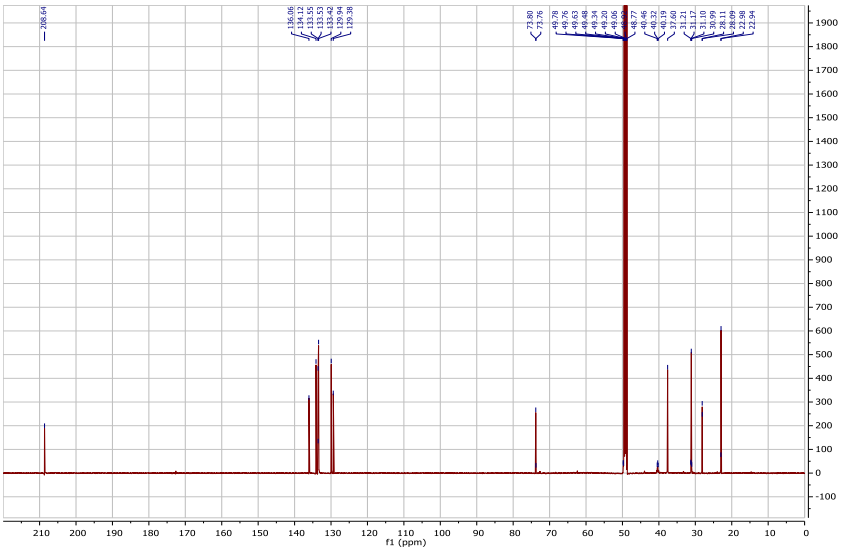
^{13}C NMR (151 MHz, MeOD): δ 208.6, 136.1, 134.1, 133.6, 133.5, 129.9, 129.4, 73.8, 40.3 (septet, $J_{C\text{-}D}$ = 21 Hz, 1C), 37.6, 31.2, 28.1, 23.0.

HRMS (ESI+): Expected 240.1119 [M+H], ($C_{13}H_{15}D_2ClNO$). Observed 240.1120.

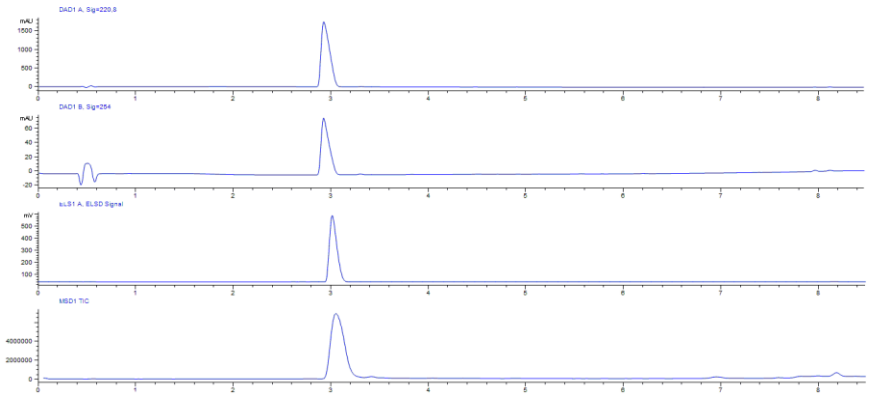
<u>^{1}H NMR spectra of 2-(2-chlorophenyl)-6,6-dideutero-2-(methylamino)cyclohexanone hydrochloride</u>



^{13}C NMR spectra of 2-(2-chlorophenyl)-6,6-dideutero-2-(methylamino)cyclohexanone hydrochloride



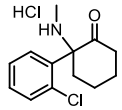
High pressure liquid chromatography trace of 2-(2-chlorophenyl)-6,6-diduetero-2-(methylamino)cyclohexanone hydrochloride



The regioplacement of the deuterium atoms in 6,6-dideuteroketamine hydrochloride was confirmed by comparison to the ^{1}H NMR and ^{13}C NMR spectra of ketamine hydrochloride. ^{1}H-^{13}C HMBC and ^{1}H-^{13}C HSQC experiments were performed in order to definitively assign the α-keto protons and carbon. The spectra for 6,6-dideuteroketamine hydrochloride clearly lack these

α-keto protons (at 2.64-2.46 ppm) and the corresponding carbon (at 41.2 ppm) is clearly split by the deuterium atoms. For reference, these spectra for ketamine hydrochloride are replicated here.

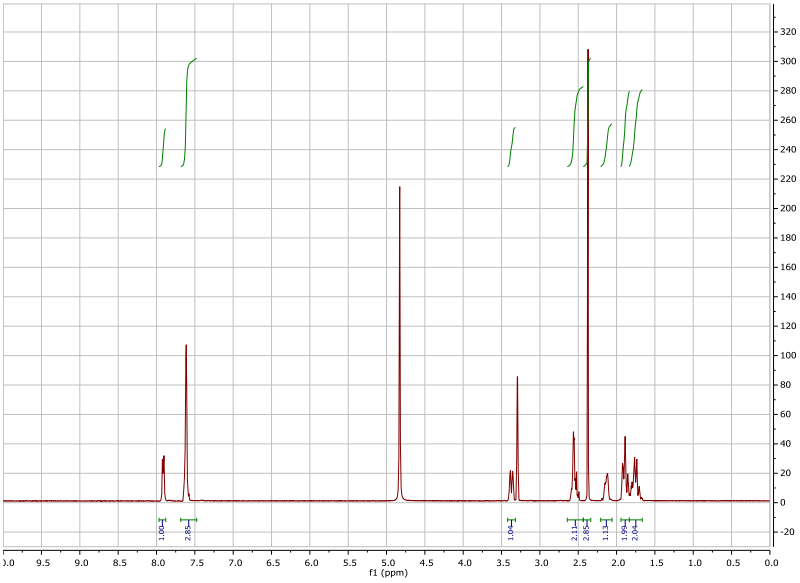
5.10. Ketamine hydrochloride (NCGC00159480)



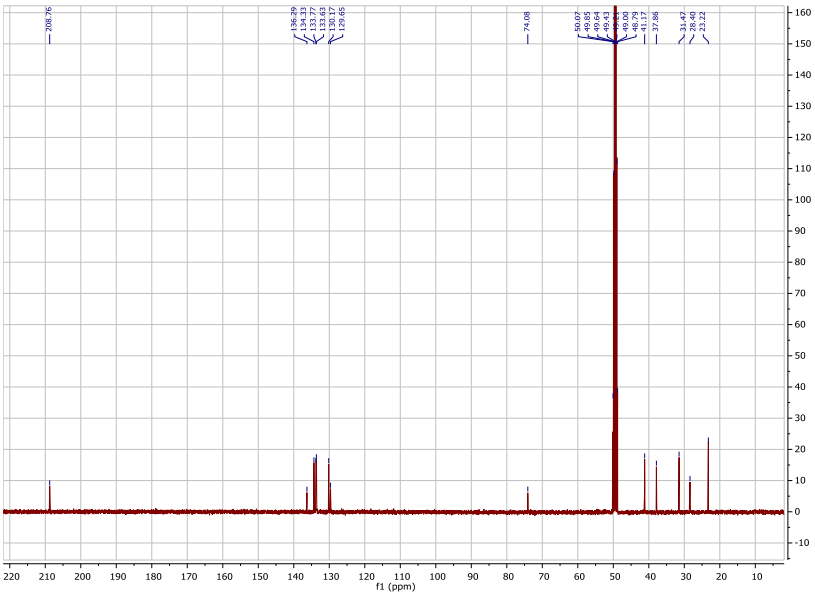
^{1}H NMR (400 MHz, MeOD): δ 7.94-7.88 (m, 1H), 7.66-7.57 (m, 3H), 3.41-3.34 (m, 1H), 2.64-2.46 (m, 2H), 2.38 (s, 3H), 2.27-2.20 (m, 1H), 1.93-1.83 (m, 2H), 1.83-1.69 (m, 2H).

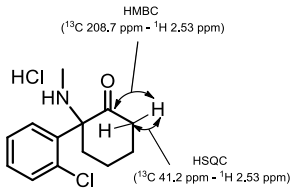
^{13}C NMR (101 MHz, MeOD) δ 208.8, 136.3, 134.3, 133.8, 133.6, 130.2, 129.6, 74.1, 41.2, 37.9, 31.5, 28.4, 23.2.

^{1}H NMR spectra of ketamine hydrochloride

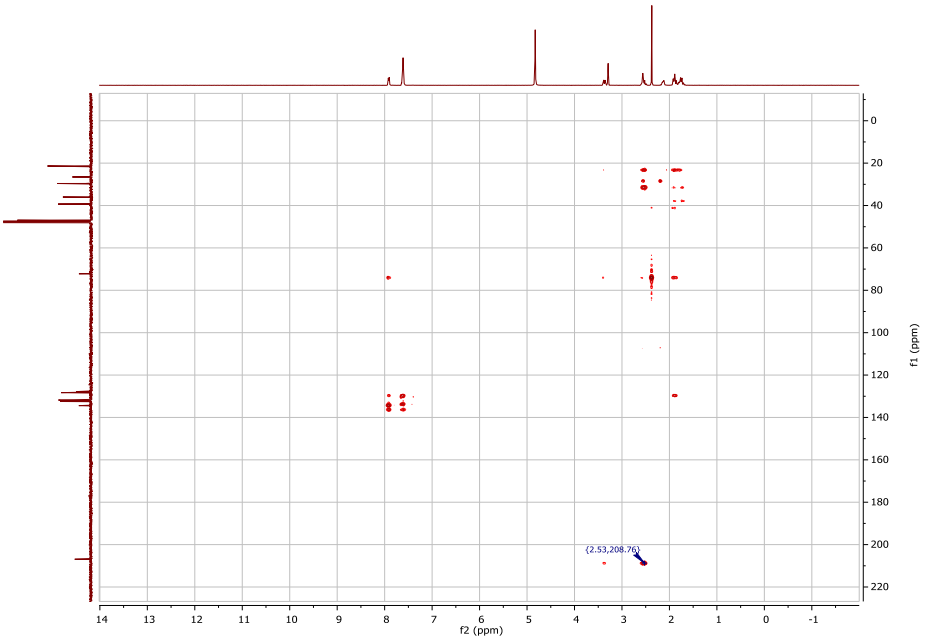


^{13}C NMR spectra of Ketamine hydrochloride

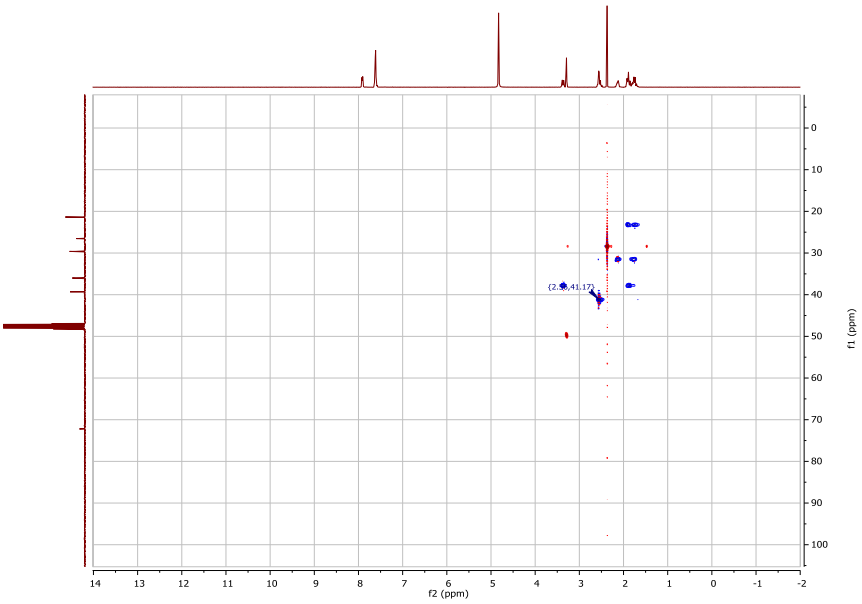




^{1}H-^{13}C HMBC spectra of ketamine hydrochloride



^{1}H-^{13}C HSQC spectra of ketamine hydrochloride



6. X-Ray Crystallography Data: (2S,6S)-(+)-hydroxynorketamine hydrochloride

CCDC number 1443735 [NCGC00373033]

Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Mo K_α radiation (λ = 0.71073 Å). Crystals of the subject compound were grown by slow evaporation of a 50/50 Dichloroethane/Methanol solution. A 0.227 x 0.215 x 0.106 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖscans. Crystal-to-detector distance was 40 mm and exposure time was 5 seconds per frame using a scan width of 2.0°. Data collection was 100% complete to 25.00° in θ. A total of 9466 reflections were collected covering the indices, -9<=h<=9, -9<=k<=9, -14<=l<=14. 2949 reflections were found to be symmetry independent, with a R_{int} of 0.0376. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_1$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. The absolute stereochemistry of the molecule was established by anomalous dispersion using the

Parson's method with a Flack parameter of -0.001(24). Crystallographic data are summarized in Table 1. Small molecule X-ray crystallographic coordinates and structure factor files have been deposited in the Cambridge Structural Database (Accession number 1443735, http://www.ccdc.cam.ac.uk/)

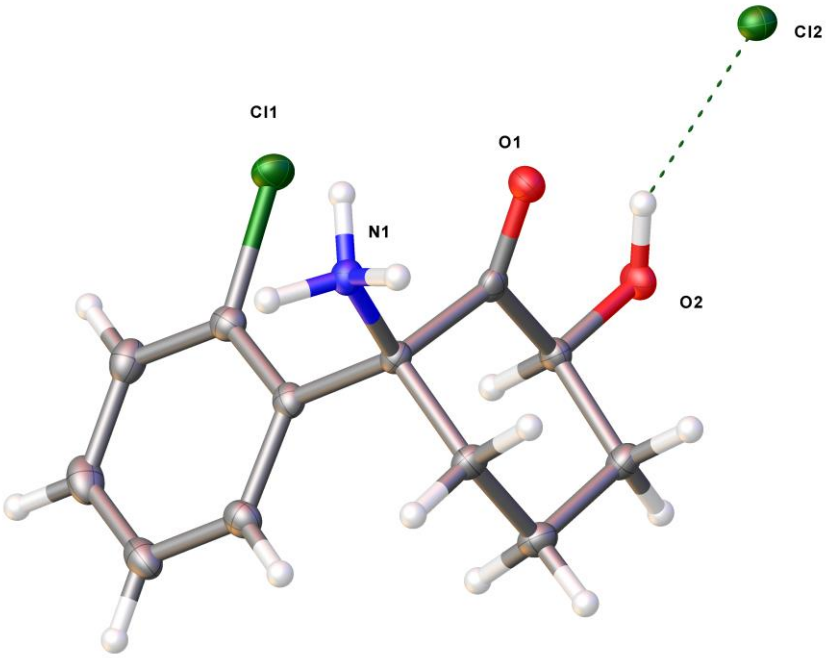


Table 1. Crystal data and structure refinement for NCGC00373033.

Report date	2015-12-11	
Identification code	NCGC00373033-14	
Empirical formula	$C_{12}H_{15}Cl_2NO_2$	
Molecular formula	$C_{12}H_{15}ClNO_2$, Cl	
Formula weight	276.15	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 7.3493(8) Å	α= 90°
	b = 7.4846(8) Å	β= 96.866(3)°
	c = 11.3404(12) Å	γ = 90°
Volume	619.32(12) $Å^3$	
Z	2	
Density (calculated)	1.481 Mg/m^3	
Absorption coefficient	0.513 mm^{-1}	

F(000)	288
Crystal size	0.227 x 0.215 x 0.106 mm^3
Crystal color, habit	Colorless Block
Theta range for data collection	1.809 to 28.411°
Index ranges	-9<=h<=9, -9<=k<=9, -14<=l<=14
Reflections collected	9466
Independent reflections	2949 [R(int) = 0.0376]
Completeness to theta = 25.000°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.0962 and 0.0677
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2949 / 5 / 170
Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0239, wR2 = 0.0624
R indices (all data)	R1 = 0.0245, wR2 = 0.0629
Absolute structure parameter	0.00(2)
Extinction coefficient	n/a
Largest diff. peak and hole	0.287 and -0.204 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for NCGC00373033. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	6563(1)	1930(1)	1363(1)	22(1)
O(1)	5226(2)	2952(2)	3850(1)	19(1)
O(2)	1922(2)	4022(2)	2743(1)	19(1)
N(1)	8564(2)	4290(2)	3690(2)	16(1)
C(1)	5225(2)	4235(3)	3197(2)	15(1)
C(2)	3480(2)	5092(2)	2626(2)	16(1)
C(3)	3299(3)	6901(3)	3233(2)	18(1)
C(4)	4997(3)	8055(3)	3174(2)	19(1)
C(5)	6740(2)	7066(3)	3678(2)	17(1)
C(6)	6981(2)	5272(3)	3034(2)	14(1)
C(7)	7326(2)	5480(3)	1734(2)	15(1)
C(8)	7195(3)	4052(3)	939(2)	17(1)
C(9)	7583(3)	4231(3)	-224(2)	21(1)
C(10)	8130(3)	5875(3)	-621(2)	24(1)
C(11)	8284(3)	7311(3)	146(2)	23(1)
C(12)	7907(3)	7117(3)	1311(2)	19(1)
Cl(2)	376(1)	481(1)	3708(1)	18(1)

Table 3. Bond lengths [Å] and angles [°] for NCGC00373033.

Cl(1)-C(8)	1.739(2)	C(1)-C(6)	1.536(2)
O(1)-C(1)	1.213(3)	C(2)-H(2A)	1.0000
O(2)-H(2)	0.90(2)	C(2)-C(3)	1.532(3)
O(2)-C(2)	1.417(2)	C(3)-H(3A)	0.9900
N(1)-H(1A)	0.937(19)	C(3)-H(3B)	0.9900
N(1)-H(1B)	0.93(2)	C(3)-C(4)	1.526(3)
N(1)-H(1C)	0.94(2)	C(4)-H(4A)	0.9900
N(1)-C(6)	1.496(2)	C(4)-H(4B)	0.9900
C(1)-C(2)	1.509(3)	C(4)-C(5)	1.529(3)

C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(5)-C(6)	1.548(3)
C(6)-C(7)	1.534(3)
C(7)-C(8)	1.394(3)
C(7)-C(12)	1.401(3)
C(8)-C(9)	1.389(3)
C(9)-H(9)	0.9500
C(9)-C(10)	1.386(3)
C(10)-H(10)	0.9500
C(10)-C(11)	1.379(3)
C(11)-H(11)	0.9500
C(11)-C(12)	1.389(3)
C(12)-H(12)	0.9500
C(2)-O(2)-H(2)	113(2)
H(1A)-N(1)-H(1B)	105(2)
H(1A)-N(1)-H(1C)	109(2)
H(1B)-N(1)-H(1C)	103(2)
C(6)-N(1)-H(1A)	110.7(17)
C(6)-N(1)-H(1B)	115.3(16)
C(6)-N(1)-H(1C)	112.4(16)
O(1)-C(1)-C(2)	122.48(16)
O(1)-C(1)-C(6)	122.31(18)
C(2)-C(1)-C(6)	114.63(16)
O(2)-C(2)-C(1)	112.02(15)
O(2)-C(2)-H(2A)	109.1
O(2)-C(2)-C(3)	110.04(15)
C(1)-C(2)-H(2A)	109.1
C(1)-C(2)-C(3)	107.38(16)
C(3)-C(2)-H(2A)	109.1
C(2)-C(3)-H(3A)	109.3
C(2)-C(3)-H(3B)	109.3
H(3A)-C(3)-H(3B)	108.0
C(4)-C(3)-C(2)	111.40(15)
C(4)-C(3)-H(3A)	109.3
C(4)-C(3)-H(3B)	109.3
C(3)-C(4)-H(4A)	109.4
C(3)-C(4)-H(4B)	109.4
C(3)-C(4)-C(5)	111.26(16)
H(4A)-C(4)-H(4B)	108.0
C(5)-C(4)-H(4A)	109.4
C(5)-C(4)-H(4B)	109.4
C(4)-C(5)-H(5A)	109.1
C(4)-C(5)-H(5B)	109.1
C(4)-C(5)-C(6)	112.43(16)
H(5A)-C(5)-H(5B)	107.8
C(6)-C(5)-H(5A)	109.1
C(6)-C(5)-H(5B)	109.1
N(1)-C(6)-C(1)	107.84(15)
N(1)-C(6)-C(5)	108.54(15)
N(1)-C(6)-C(7)	108.62(14)
C(1)-C(6)-C(5)	103.68(14)
C(7)-C(6)-C(1)	113.84(15)
C(7)-C(6)-C(5)	114.01(16)
C(8)-C(7)-C(6)	122.52(18)
C(8)-C(7)-C(12)	116.72(18)
C(12)-C(7)-C(6)	120.65(18)
C(7)-C(8)-Cl(1)	121.42(15)
C(9)-C(8)-Cl(1)	116.29(17)
C(9)-C(8)-C(7)	122.29(19)
C(8)-C(9)-H(9)	120.2
C(10)-C(9)-C(8)	119.6(2)
C(10)-C(9)-H(9)	120.2
C(9)-C(10)-H(10)	120.3
C(11)-C(10)-C(9)	119.47(19)
C(11)-C(10)-H(10)	120.3
C(10)-C(11)-H(11)	119.7
C(10)-C(11)-C(12)	120.5(2)
C(12)-C(11)-H(11)	119.7
C(7)-C(12)-H(12)	119.3
C(11)-C(12)-C(7)	121.4(2)
C(11)-C(12)-H(12)	119.3

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for NCGC00373033. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	27(1)	16(1)	22(1)	-3(1)	3(1)	-2(1)
O(1)	19(1)	18(1)	21(1)	3(1)	5(1)	0(1)
O(2)	13(1)	20(1)	23(1)	2(1)	3(1)	-1(1)
N(1)	14(1)	18(1)	15(1)	0(1)	2(1)	1(1)
C(1)	16(1)	15(1)	14(1)	-4(1)	4(1)	1(1)
C(2)	14(1)	16(1)	18(1)	1(1)	3(1)	-1(1)
C(3)	17(1)	17(1)	21(1)	-2(1)	3(1)	4(1)
C(4)	20(1)	15(1)	22(1)	-1(1)	2(1)	1(1)
C(5)	18(1)	15(1)	18(1)	-2(1)	1(1)	1(1)
C(6)	13(1)	14(1)	15(1)	-1(1)	2(1)	1(1)
C(7)	12(1)	18(1)	16(1)	2(1)	1(1)	2(1)
C(8)	15(1)	18(1)	18(1)	1(1)	1(1)	1(1)
C(9)	19(1)	28(1)	16(1)	-2(1)	1(1)	4(1)
C(10)	21(1)	35(1)	17(1)	7(1)	3(1)	5(1)
C(11)	18(1)	27(1)	24(1)	8(1)	4(1)	1(1)
C(12)	16(1)	20(1)	21(1)	2(1)	2(1)	-2(1)
Cl(2)	20(1)	16(1)	18(1)	0(1)	1(1)	1(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for NCGC00373033.

	x	y	z	U(eq)
H(2)	2200(40)	3010(30)	3160(30)	40(9)
H(1A)	9650(30)	4530(40)	3360(20)	23(6)
H(1B)	8460(30)	3060(30)	3690(20)	19(6)
H(1C)	8730(40)	4570(40)	4506(19)	23(6)
H(2A)	3575	5291	1764	19
H(3A)	2209	7535	2840	22
H(3B)	3116	6706	4074	22
H(4A)	4882	9168	3631	23
H(4B)	5086	8387	2338	23
H(5A)	6695	6831	4533	20
H(5B)	7815	7836	3604	20
H(9)	7474	3232	-745	25
H(10)	8397	6012	-1416	29
H(11)	8650	8442	-124	27
H(12)	8047	8115	1832	23

Table 6. Hydrogen bonds for NCGC00373033 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...Cl(2)	0.90(2)	2.44(3)	3.1317(16)	133(3)
N(1)-H(1A)...O(2)#1	0.937(19)	1.92(2)	2.814(2)	158(2)

N(1)-H(1B)...Cl(2)#1	0.93(2)	2.39(2)	3.1460(19)	139(2)
N(1)-H(1C)...Cl(2)#2	0.94(2)	2.16(2)	3.0925(18)	168(2)

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

7. X-Ray Crystallography Data: (2R,6R)-(-)-hydroxynorketamine hydrochloride

CCDC number 14437347 [NCGC00378227]

Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Mo K_α radiation (λ = 0.71073 Å). Crystals of the subject compound were grown by slow evaporation of an isopropanol solution. A 0.157 x 0.131 x 0.098 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using A 0.157 x 0.131 x 0.098 mm piece of a colorless block was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ϖ scans. Crystal-to-detector distance was 40 mm and exposure time was 3 seconds per frame using a scan width of 2.0°. Data collection was 100% complete to 25.00° in *θ*. A total of 7618 reflections were collected covering the indices, -9<=h<=9, -9<=k<=9, -14<=l<=14. 2927 reflections were found to be symmetry independent, with an R_{int} of 0.0350. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be $P2_1$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. The

absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson's method with a Flack parameter of 0.023(32). Crystallographic data are summarized in Table 7. Small molecule X-ray crystallographic coordinates and structure factor files have been deposited in the Cambridge Structural Database (Accession number 14437347, http://www.ccdc.cam.ac.uk/)

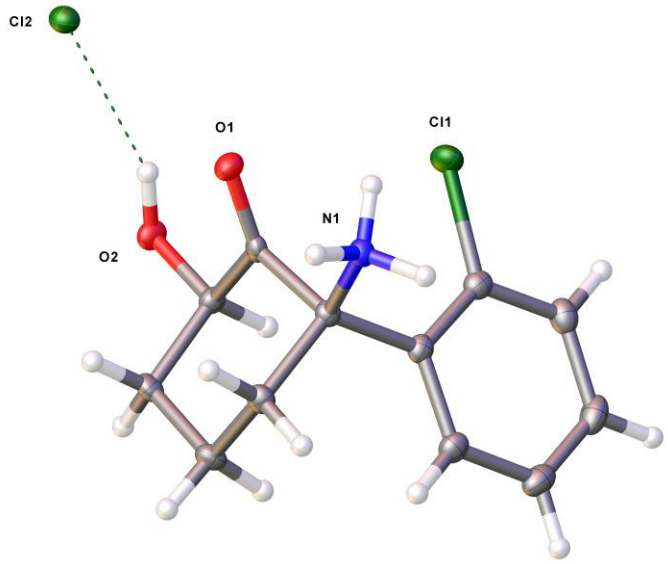


Table 7. Crystal data and structure refinement for NCGC00378227

Report date	2015-12-14	
Identification code	NCGC00378227-02	
Empirical formula	$C_{12}H_{15}Cl_2NO_2$	
Molecular formula	$C_{12}H_{15}ClNO_2$, Cl	
Formula weight	276.15	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 7.3549(6) Å	α= 90°
	b = 7.4932(5) Å	β= 96.868(2)°
	c = 11.3498(8) Å	γ = 90°
Volume	621.02(8) $Å^3$	
Z	2	
Density (calculated)	1.477 Mg/m^3	
Absorption coefficient	0.511 mm^{-1}	
F(000)	288	
Crystal size	0.157 x 0.131 x 0.098 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	1.807 to 28.290°.	
Index ranges	-9<=h<=9, -9<=k<=9, -14<=l<=14	

Reflections collected	7618
Independent reflections	2927 [R(int) = 0.0350]
Completeness to theta = 25.000°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.0962 and 0.0687
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2927 / 5 / 170
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0265, wR2 = 0.0659
R indices (all data)	R1 = 0.0280, wR2 = 0.0669
Absolute structure parameter	0.02(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.283 and -0.201 e.Å^{-3}

Table 8. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for NCGC00378227. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	3437(1)	8068(1)	8636(1)	20(1)
O(1)	4777(2)	7045(2)	6149(1)	18(1)
O(2)	8078(2)	5975(2)	7255(2)	18(1)
N(1)	1437(2)	5707(3)	6311(2)	14(1)
C(1)	4777(3)	5763(3)	6802(2)	13(1)
C(2)	6518(3)	4905(3)	7374(2)	14(1)
C(3)	6698(3)	3100(4)	6768(2)	16(1)
C(4)	5001(3)	1942(3)	6824(2)	17(1)
C(5)	3260(3)	2934(3)	6323(2)	16(1)
C(6)	3023(3)	4721(3)	6968(2)	13(1)
C(7)	2670(3)	4523(3)	8268(2)	14(1)
C(8)	2804(3)	5944(3)	9065(2)	16(1)
C(9)	2415(3)	5767(4)	10223(2)	20(1)
C(10)	1875(3)	4126(4)	10622(2)	23(1)
C(11)	1718(3)	2687(3)	9853(2)	21(1)
C(12)	2095(3)	2883(4)	8689(2)	18(1)
Cl(2)	9623(1)	9516(1)	6291(1)	17(1)

Table 9. Bond lengths [Å] and angles [°] for NCGC00378227

Cl(1)-C(8)	1.743(2)	C(4)-H(4A)	0.9900
O(1)-C(1)	1.214(3)	C(4)-H(4B)	0.9900
O(2)-H(2)	0.90(2)	C(4)-C(5)	1.531(3)
O(2)-C(2)	1.419(3)	C(5)-H(5A)	0.9900
N(1)-H(1A)	0.92(2)	C(5)-H(5B)	0.9900
N(1)-H(1B)	0.94(2)	C(5)-C(6)	1.546(3)
N(1)-H(1C)	0.95(2)	C(6)-C(7)	1.535(3)
N(1)-C(6)	1.502(3)	C(7)-C(8)	1.393(3)
C(1)-C(2)	1.508(3)	C(7)-C(12)	1.401(3)
C(1)-C(6)	1.539(3)	C(8)-C(9)	1.385(3)
C(2)-H(2A)	1.0000	C(9)-H(9)	0.9500
C(2)-C(3)	1.530(3)	C(9)-C(10)	1.385(4)
C(3)-H(3A)	0.9900	C(10)-H(10)	0.9500
C(3)-H(3B)	0.9900	C(10)-C(11)	1.383(4)
C(3)-C(4)	1.528(3)	C(11)-H(11)	0.9500

C(11)-C(12)	1.390(3)
C(12)-H(12)	0.9500
C(2)-O(2)-H(2)	114(2)
H(1A)-N(1)-H(1B)	105(3)
H(1A)-N(1)-H(1C)	105(3)
H(1B)-N(1)-H(1C)	109(3)
C(6)-N(1)-H(1A)	115.0(18)
C(6)-N(1)-H(1B)	111.9(18)
C(6)-N(1)-H(1C)	110.2(17)
O(1)-C(1)-C(2)	122.56(19)
O(1)-C(1)-C(6)	122.52(19)
C(2)-C(1)-C(6)	114.35(19)
O(2)-C(2)-C(1)	111.90(18)
O(2)-C(2)-H(2A)	109.2
O(2)-C(2)-C(3)	109.99(17)
C(1)-C(2)-H(2A)	109.2
C(1)-C(2)-C(3)	107.32(18)
C(3)-C(2)-H(2A)	109.2
C(2)-C(3)-H(3A)	109.3
C(2)-C(3)-H(3B)	109.3
H(3A)-C(3)-H(3B)	108.0
C(4)-C(3)-C(2)	111.61(18)
C(4)-C(3)-H(3A)	109.3
C(4)-C(3)-H(3B)	109.3
C(3)-C(4)-H(4A)	109.4
C(3)-C(4)-H(4B)	109.4
C(3)-C(4)-C(5)	111.11(19)
H(4A)-C(4)-H(4B)	108.0
C(5)-C(4)-H(4A)	109.4
C(5)-C(4)-H(4B)	109.4
C(4)-C(5)-H(5A)	109.1
C(4)-C(5)-H(5B)	109.1
C(4)-C(5)-C(6)	112.40(18)
H(5A)-C(5)-H(5B)	107.9
C(6)-C(5)-H(5A)	109.1
C(6)-C(5)-H(5B)	109.1
N(1)-C(6)-C(1)	107.57(18)
N(1)-C(6)-C(5)	108.39(17)
N(1)-C(6)-C(7)	108.37(17)
C(1)-C(6)-C(5)	103.73(16)
C(7)-C(6)-C(1)	114.02(17)
C(7)-C(6)-C(5)	114.42(19)
C(8)-C(7)-C(6)	122.9(2)
C(8)-C(7)-C(12)	116.8(2)
C(12)-C(7)-C(6)	120.3(2)
C(7)-C(8)-Cl(1)	121.18(17)
C(9)-C(8)-Cl(1)	116.4(2)
C(9)-C(8)-C(7)	122.4(2)
C(8)-C(9)-H(9)	120.1
C(8)-C(9)-C(10)	119.7(2)
C(10)-C(9)-H(9)	120.1
C(9)-C(10)-H(10)	120.3
C(11)-C(10)-C(9)	119.4(2)
C(11)-C(10)-H(10)	120.3
C(10)-C(11)-H(11)	119.8
C(10)-C(11)-C(12)	120.4(2)
C(12)-C(11)-H(11)	119.8
C(7)-C(12)-H(12)	119.4
C(11)-C(12)-C(7)	121.3(2)
C(11)-C(12)-H(12)	119.4

Table 10. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for NCGC00378227. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	26(1)	15(1)	20(1)	-3(1)	3(1)	-2(1)
O(1)	18(1)	17(1)	19(1)	4(1)	5(1)	0(1)
O(2)	12(1)	19(1)	22(1)	3(1)	2(1)	-1(1)
N(1)	13(1)	16(1)	14(1)	-1(1)	2(1)	1(1)
C(1)	13(1)	14(1)	13(1)	-3(1)	4(1)	0(1)
C(2)	13(1)	15(1)	16(1)	1(1)	2(1)	-1(1)
C(3)	15(1)	15(1)	19(1)	-1(1)	2(1)	5(1)
C(4)	18(1)	12(1)	21(1)	-2(1)	1(1)	1(1)
C(5)	16(1)	16(1)	16(1)	-3(1)	1(1)	0(1)
C(6)	11(1)	14(1)	14(1)	0(1)	1(1)	1(1)
C(7)	12(1)	18(1)	14(1)	2(1)	1(1)	1(1)
C(8)	14(1)	18(1)	18(1)	2(1)	1(1)	1(1)
C(9)	18(1)	26(1)	16(1)	-2(1)	1(1)	4(1)
C(10)	18(1)	34(2)	16(1)	6(1)	4(1)	3(1)
C(11)	17(1)	24(1)	23(1)	8(1)	2(1)	0(1)
C(12)	15(1)	20(1)	19(1)	1(1)	2(1)	-2(1)
Cl(2)	19(1)	15(1)	16(1)	1(1)	1(1)	1(1)

Table 11. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for NCGC00378227.

	x	y	z	U(eq)
H(2)	7830(50)	7000(40)	6860(30)	41(10)
H(1A)	1540(40)	6930(30)	6330(20)	22(8)
H(1B)	1270(40)	5410(40)	5500(20)	23(7)
H(1C)	340(30)	5450(40)	6650(20)	20(7)
H(2A)	6423	4708	8236	17
H(3A)	6881	3297	5928	20
H(3B)	7788	2467	7160	20
H(4A)	4913	1604	7659	21
H(4B)	5117	834	6364	21
H(5A)	2184	2166	6396	19
H(5B)	3304	3172	5468	19
H(9)	2518	6766	10741	24
H(10)	1614	3989	11417	27
H(11)	1351	1557	10123	26
H(12)	1960	1887	8168	21

Table 12. Hydrogen bonds for NCGC00378227 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...Cl(2)	0.90(2)	2.43(3)	3.1348(18)	135(3)
N(1)-H(1A)...Cl(2)#1	0.92(2)	2.39(3)	3.149(2)	140(2)
N(1)-H(1B)...Cl(2)#2	0.94(2)	2.16(2)	3.095(2)	169(2)
N(1)-H(1C)...O(2)#1	0.95(2)	1.92(2)	2.816(2)	156(3)

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

8. References

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