Table S1

Procedure/Treatment group (n)	Week 1	Week 2	Week 3
20% alcohol DID (intake in g/kg/4 hours):			
TSA (n = 9)	4.31±0.24	4.28±0.21	4.49±0.40
SAHA (n = 15)	5.61±0.22	5.93±0.26	6.57±0.16
MS275 (n = 10)	4.91±0.26	5.69±0.30	5.62±0.55
Saccharin DID (intake in ml/kg/4 hours):			
TSA/MS275 (n = 8)	51.4±4.8	56.2±6.2	-
SAHA (n = 9)	52.9±1.9	54.3±3.0	-

Table S1 Basal level of 20% alcohol or 0.03% saccharin intake in the DID procedure before testing HDAC inhibitors. Data are expressed as mean ± SEM.

Table S2

Session Schedule (session duration)	Active lever presses	Inactive lever presses	Alcohol deliveries
FR1 (overnight/12 hours)	122.38±12.84	43.90±54.87	101.85±10.0
FR1 (1 hour)	31.96±3.00	2.50±0.50	29.0±2.56
FR3 (1 hour)			
Week 1	59.54±4.82	3.67±0.53	19.65±1.66
Week 2	67.0±6.83	3.38±0.87	22.17±2.26
FR3 (30 minutes)			
Week 1	60.40±7.79	2.03±0.49	19.05±2.09
Week 2	58.03±6.67	1.38±0.21	17.98±1.95
Week 3	66.22±8.39	2.21±0.65	20.95±2.15
Week 4	67.35±8.33	1.96±0.46	21.70±2.42
Week 5	73.64±9.67	2.03±0.52	20.95±2.36
Week 6	66.59±6.82	2.05±0.52	23.7±2.04
Week 7	71.03±9.32	2.9±0.77	22.58±2.66
Week 8	67.27±8.17	2.25±0.54	21.60±2.40
Week 9	69.44±9.03	1.83±0.44	22.08±2.79
Week 10	71.68±8.66	1.25±0.39	23.48±2.85

Table S2 Characteristics of the acquisition of operant alcohol self-administration of a 20% alcohol solution in rats. Data are expressed as mean ± SEM. n = 12.

Table S3

Session Schedule (session duration) Sucrose Concentration		Active lever presses	Inactive lever presses	Sucrose deliveries
FR1 (overnight/12 hours) Sucrose 8%		120.00±13.88	62.35±8.28	97.94±12.03
FR1 (1 hour) Sucrose 8%		78.98±10.90	9.16±2.07	73.64±10.58
FR3 (1 hour) Sucrose 8%		236±49.37	14.79±1.37	80.71±14.23
FR3 (1 hour) Sucrose 6%		125.71±19.03	10.12±1.81	41.25±6.26
FR3 (30 minutes) Sucrose 6%		103.92±18.50	3.28±0.96	37.14±7.13
FR3 (30 minutes) Sucrose 3%		95.04±13.20	6.66±1.25	31.16±4.38
FR3 (30 minutes) Sucrose 2.5%		91.08±9.97	5.16±1.16	30.00±3.33
FR3 (30 minutes) Sucrose 2.0%		88.19±9.56	6.11±1.05	28.92±3.15
FR3 (30 minutes) Sucrose 1.5%				
	Week 1	93.78±10.50	7.08±1.27	30.72±3.41
	Week 2	82.25±9.42	5.23±1.21	26.95±3.09
	Week 3	75.44±8.58	3.97±0.71	24.80±2.84
	Week 4	113.81±10.86	5.47±0.73	39.52±4.41
	Week 5	92.85±11.57	5.77±1.33	30.52±3.65
	Week 6	82.06±11.28	2.57±0.59	26.95±3.74
	Week 7	88.54±12.06	3.37±1.08	29.16±4.03

Table S3 Characteristics of the acquisition of operant self-administration of a 1.5% sucrose solution in rats. Data are expressed as mean ± SEM. n = 12.

Figure S1

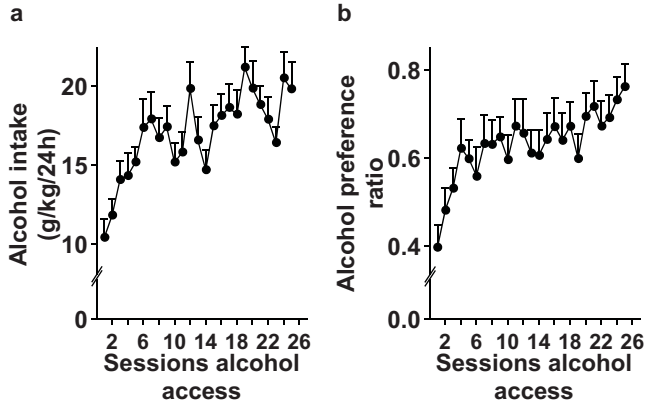

Figure S1 Intermittent access to 20% alcohol induces excessive drinking in mice. Mice were housed in the reverse cycle (lights turn off at 10:00 AM) and had access to one bottle of 20% alcohol and one bottle of water for 24 hours, starting at 12:00 PM (i.e., 2 hours after lights turn off) on Mondays, Wednesdays, and Fridays for a period of 8 weeks. (**a**) Amount of alcohol (g/kg) consumed during the 24 hours of 20% alcohol access. (**b**) Preference for alcohol is calculated as the ratio of the volume of alcohol solution intake/volume of total fluid intake during the 24 hours of 20% alcohol access. Results are expressed as mean ± SEM. n = 10.

Figure S2

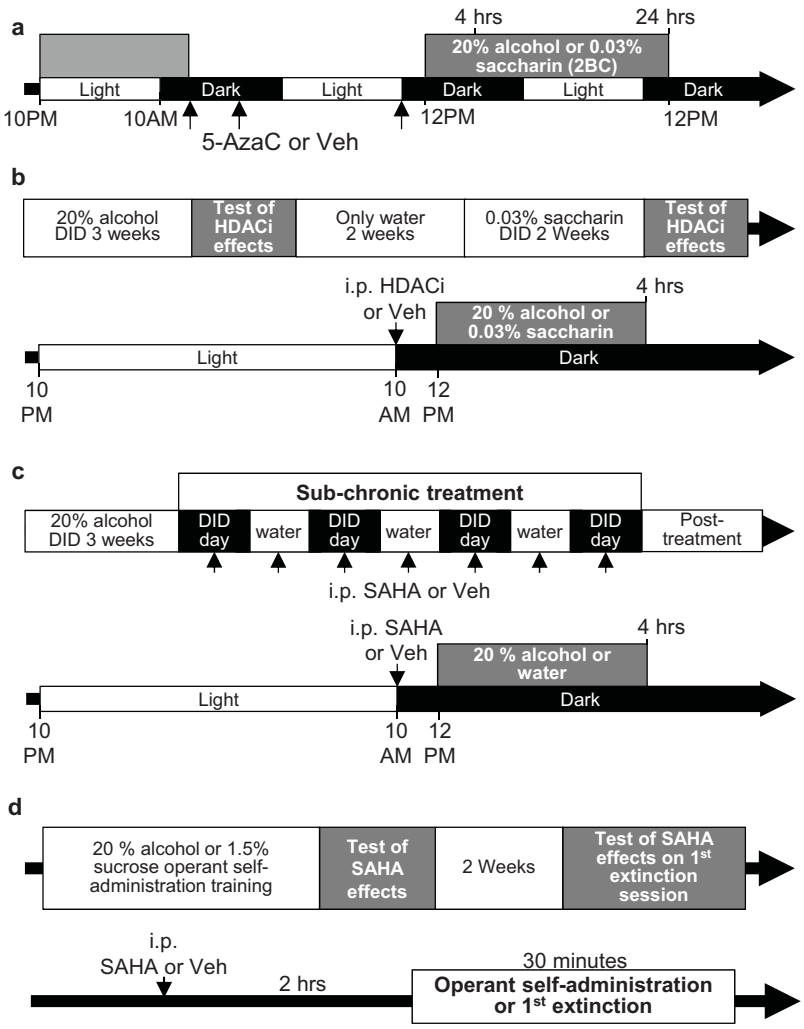

Figure S2 Timeline of treatments and consumption measurements in the procedures used. (**a**) Timeline of 5-AzaC or Vehicle (Veh) treatments and consumption measurements during the intermittent access to 20% alcohol or 0.03% saccharin in mice. (**b**) The top represents the timeline of the DID procedures to test the effects of acute administration of HDAC inhibitors (HDACi) in mice. The bottom is the timeline of HDACi or Veh treatments and consumption measurements of 20% alcohol or 0.03% saccharin during the test days. (**c**) The top represents the timeline of the sub-chronic of SAHA or Veh treatments during the 20% alcohol DID procedure. The bottom emphasizes the timeline of treatments and consumption measurements on test days. (**d**) The top is the timeline of measurements of SAHA or Veh effects on operant self-administration behaviors. The bottom emphasizes the timeline of treatments and measurements on the test days.

Figure S3

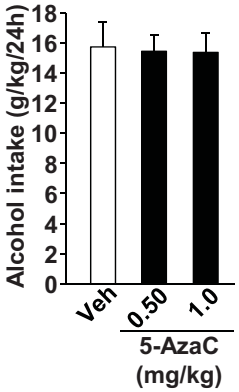

Figure S3 5-AzaC does not have a long-lasting effect on 20% alcohol drinking in mice. A representation of the level of alcohol (g/kg/24 hours) consumed during the first session of 20% alcohol access post-5-AzaC treatment (i.e., 50 hours after the last i.p. administration). One-way RM-ANOVA reveals that there was no long-lasting effect of 5-AzaC treatment on alcohol drinking ($F_{(2,18)}$ = 0.04, P =0.96). Results are expressed as mean ± SEM. n = 10.

Figure S4

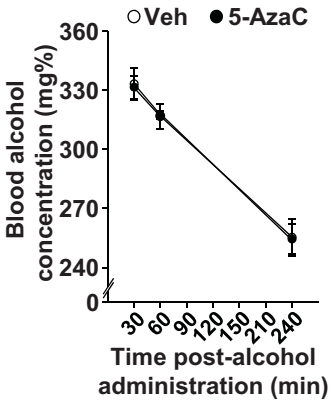

Figure S4 5-AzaC does not affect blood alcohol clearance in mice. Mice were systemically administered (i.p.) with 5-AzaC (1.0 mg/kg) or its vehicle (Veh) 24, 18, and 2 hours before they received an i.p. administration of 4.0 g/kg of alcohol. Trunk blood was collected 30, 60, and 240 minutes after alcohol administration. Systemic administration of 5-AzaC does not change the kinetics of blood alcohol clearance in mice [two-way RM-ANOVA, main effects of time ($F_{(2,16)}$ = 135.40, P < 0.001), no effect of treatment ($F_{(1,8)}$ = 0.06 , P = 0.81), no interaction ($F_{(2,16)}$ = 0.34 , P = 0.71)]. Results are expressed as mean ± SEM. n = 5.

Figure S5

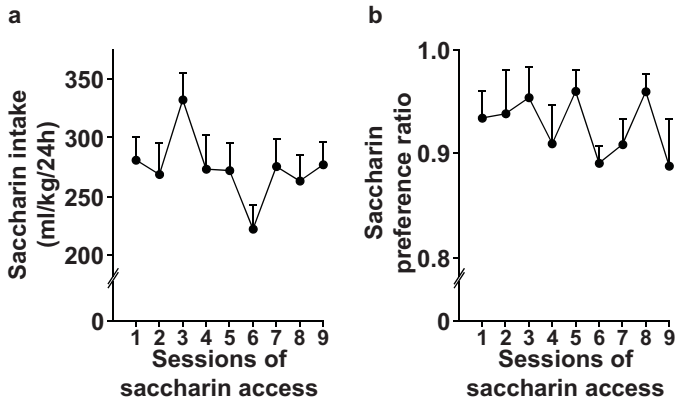

Figure S5 Intermittent access to 0.03% saccharin solution in mice. Mice were housed in the reverse cycle (lights turn off at 10:00 AM) and had access to one bottle of 0.03% saccharin solution and one bottle of water for 24 hours, starting at 12:00 PM (i.e., 2 hours after lights turn off) on Mondays, Wednesdays, and Fridays for 3 weeks. (**a**) Volume of 0.03% saccharin solution (ml/kg) consumed during the 24 hours of access. (**b**) Preference for saccharin is calculated as the ratio of the volume of 0.03% saccharin solution consumed/volume of total fluid intake during the 24 hours of access. Results are expressed as mean ± SEM. n = 10.

Figure S6

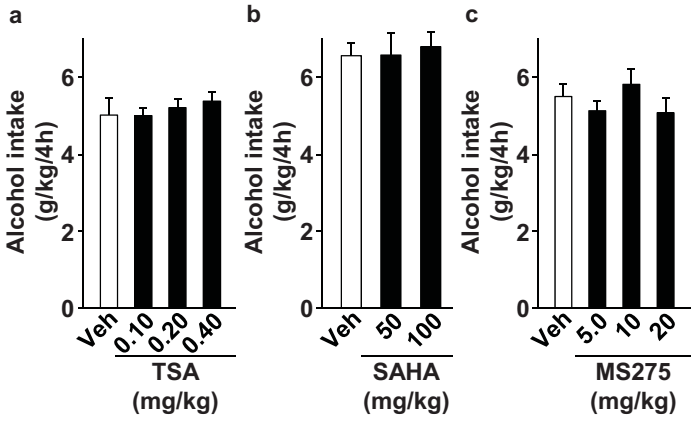

Figure S6 Acute administration of HDAC inhibitors does not have a long-lasting effect on binge-like alcohol drinking in mice. (**a-c**) Amount of alcohol (g/kg/4 hours) consumed during the first session of DID post-HDAC inhibitors treatment (i.e., 50 hours after the last i.p. administration). No long-term effects are observed on binge-like alcohol drinking after TSA treatment [one-way RM-ANOVA: $F_{(3,23)}$ = 0.29 , P = 0.82; (**a**)], SAHA [one-way RM-ANOVA: $F_{(2,28)}$ = 0.08, P = 0.92; (**b**)], or MS275 [one-way RM-ANOVA: $F_{(3,27)}$ = 1.24, P = 0.31; (**c**)]. Results are expressed as mean ± SEM. (**a**) n = 9, (**b**) n = 15, (**c**) n = 10.

Figure S7

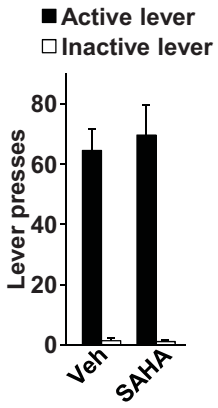

Figure S7 Acute SAHA administration does not have a long-lasting effect on alcohol operant administration in rats. A representation of the number of lever presses during the first session of self-administration after 50 mg/kg SAHA treatment (i.e., 26 hours after the last i.p. administration). Two-way RM-ANOVA showed that there was no long-lasting effect of the SAHA treatment ($F_{(1,8)}$ = 0.036, P =0.57). Results are expressed as mean ± SEM. n = 9.

Figure S8

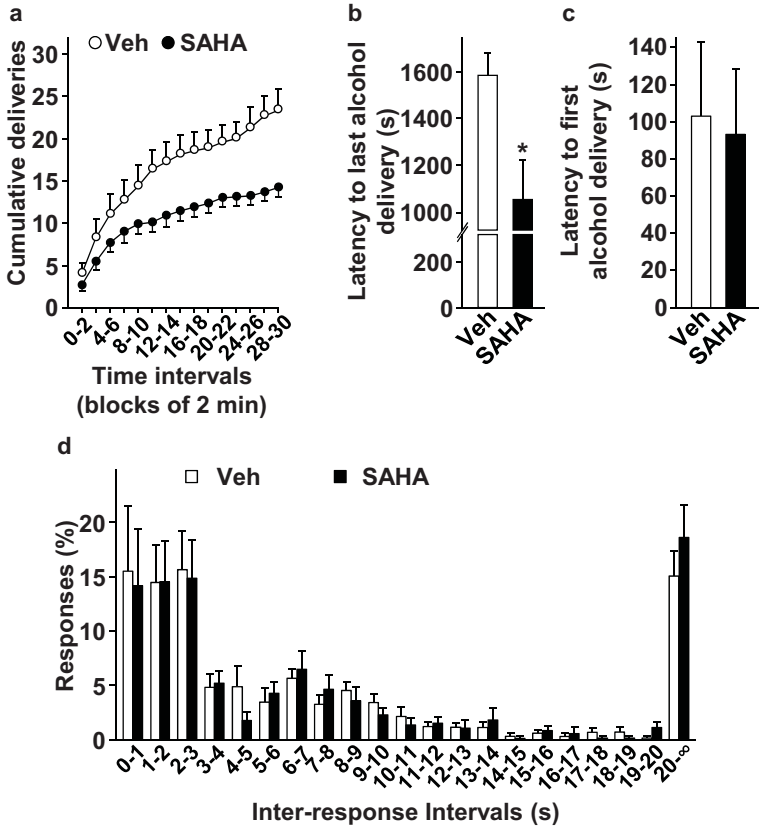

Figure S8 Systemic administration of SAHA alters operant responding for alcohol in rats. (**a**) Mean cumulative deliveries in bins of 2 minutes, indicative of the rate of alcohol drinking during a 30-minute session. (**b**) Latency to the last 20% alcohol delivery. (**c**) Latency to the first 20% alcohol delivery. (**d**) Distribution of inter-response intervals. Results are expressed as mean ± SEM. n = 9.