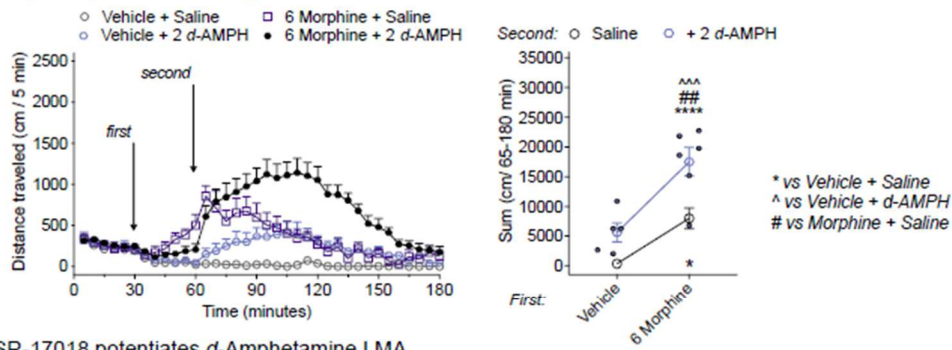


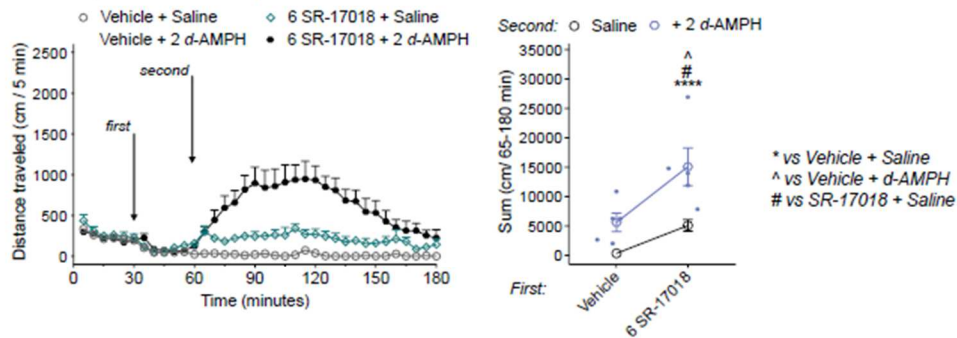
MOR-KO drug vs vehicle		Two-way RM ANOVA								
Figure	Drug vs vehicle	Time (min)	F (DFn, DFd) Time x Drug	p-Value	F (DFn, DFd) Drug v Vehicle	p-Value	Difference	SE	Drug treatment n	
SF1A	1 Fentanyl	35-120	F (17, 204) = 1.284	P=0.2055	F (1, 12) = 0.02158	P=0.8857	4.46	30.36	7	
	24 Morphine	35-120	F (17, 272) = 1.151	P=0.3055	F (1, 16) = 8.927	P=0.0087	-66.85	22.37	7	
	6 Oliceridine	35-120	F (17, 221) = 2.231	P=0.0044	F (1, 13) = 2.472	P=0.1399	-46.65	29.67	4	
	24 SR-15099	35-60	F (17, 340) = 1.281	P=0.2016	F (1, 20) = 13.60	P=0.0015	-68.43	18.56	11	
	24 SR-17018	35-120	F (17, 221) = 0.8418	P=0.6436	F (1, 13) = 1.856	P=0.1962	-40.36	29.63	4	
vehicle: n=11										

Figure S1. A lack of opioid-induced hyperactivity in MOR-KO mice. Male MOR-KO (n = 4–11) were IP treated with vehicle or the highest dose of each opioid tested after a 30-minute habituation period. Distance traveled (cm/5-minute bins) for 90 minutes was recorded and no locomotor stimulation was observed in the MOR-KO. Data are presented as mean \pm SEM.

A. Morphine potentiates *d*-Amphetamine LMA



B. SR-17018 potentiates *d*-Amphetamine LMA

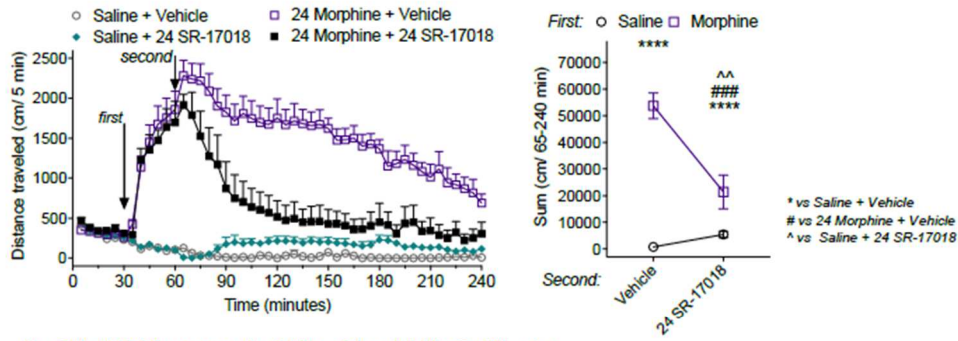


Locomotor Activity

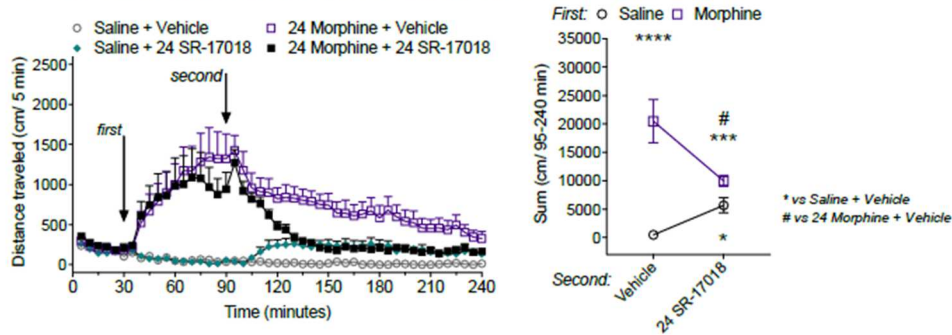
TIMECOURSE		Two-way RM ANOVA					
Figure	Treatment	Compared to	Time	F (DFn, DFd) time x drug	p-Value	F (DFn, DFd) drug effect	p-Value
SF2A	Vehicle + d-Amphetamine	Vehicle + Saline	65-180	F (29, 281) = 7.383	<0.0001	F (1, 9) = 12.34	0.0066
	6 Morphine + Saline	Vehicle + Saline	65-180	F (29, 232) = 10.67	<0.0001	F (1, 8) = 30.45	0.0006
	6 Morphine + d-Amphetamine	Vehicle + Saline	65-180	F (29, 290) = 20.05	<0.0001	F (1, 10) = 50.83	<0.0001
	Vehicle + d-Amphetamine	6 Morphine + d-Amphetamine	65-180	F (29, 281) = 6.634	<0.0001	F (1, 9) = 15.35	0.0035
	6 Morphine + Saline	6 Morphine + d-Amphetamine	65-180	F (29, 232) = 7.194	<0.0001	F (1, 8) = 6.193	0.0376
SF2B	Vehicle + d-Amphetamine	Vehicle + Saline	65-180	F (29, 281) = 7.383	<0.0001	F (1, 9) = 12.34	0.0066
	6 SR-17018 + Saline	Vehicle + Saline	65-180	F (29, 232) = 4.234	<0.0001	F (1, 8) = 44.02	0.0002
	6 SR-17018 + d-Amphetamine	Vehicle + Saline	65-180	F (29, 281) = 14.73	<0.0001	F (1, 9) = 27.44	0.0005
	Vehicle + d-Amphetamine	6 SR-17018 + d-Amphetamine	65-180	F (29, 232) = 3.882	<0.0001	F (1, 8) = 7.116	0.0285
	6 SR-17018 + Saline	6 SR-17018 + d-Amphetamine	65-180	F (29, 203) = 5.484	<0.0001	F (1, 7) = 7.291	0.0306
Figure	Treatment	Compared to	Time	p-Value	treatment n		
SF2A	Vehicle + d-Amphetamine	Vehicle + Saline	65-180	0.1825	5	ns	
	6 Morphine + Saline	Vehicle + Saline	65-180	0.0375	4	*	
	6 Morphine + d-Amphetamine	Vehicle + Saline	65-180	<0.0001	5	****	
	Vehicle + d-Amphetamine	6 Morphine + d-Amphetamine	65-180	0.0005	5	***	
	6 Morphine + Saline	6 Morphine + d-Amphetamine	65-180	0.0075	5	##	
SF2B	Vehicle + d-Amphetamine	Vehicle + Saline	65-180	0.2198	8	ns	
	6 SR-17018 + Saline	Vehicle + Saline	65-180	0.3739	4	ns	
	6 SR-17018 + d-Amphetamine	Vehicle + Saline	65-180	<0.0001	7	****	
	Vehicle + d-Amphetamine	6 SR-17018 + d-Amphetamine	65-180	0.0102	4	^	
	6 SR-17018 + Saline	6 SR-17018 + d-Amphetamine	65-180	0.0107	5	#	

Figure S2. SR-17018, like, morphine, increases *d*-amphetamine-induced locomotor activity. (A,B). Pretreatment with the vehicle, morphine (6 mg/kg, i.p.), or SR-17018 (6 mg/kg, i.p.) for 30 minutes followed by challenge with saline or *d*-amphetamine (2 mg/kg, i.p.) in male C57BL6 mice (n=4-6). Effects over time (left) and sum of the distance traveled (cm) from 65-180 minutes for individual mice (right) are shown in (A,B). Comparison of sums are indicated in the figure. Data are presented as mean \pm SEM of the total distance (cm).

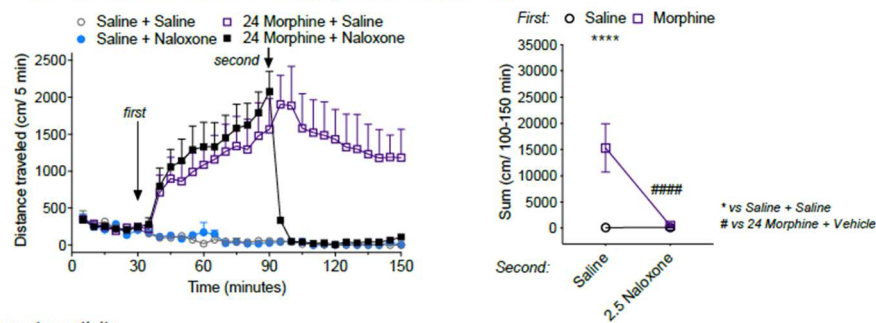
A. SR-17018 reversal of Morphine LMA @ 30 min



B. SR-17018 reversal of Morphine LMA @ 60 min



C. Naloxone reversal of Morphine LMA @ 60 min



Locomotor activity

Figure	Treatment	Compared to	Time	F (DFn, DFd)	p-Value	F (DFn, DFd)	p-Value	treatment n
Two-way RM ANOVA								
SF3A	24 Morphine + Vehicle	Saline + Vehicle	65-240	F (35, 350) = 7.374	<0.0001	F (1, 10) = 83.36	<0.0001	7
	Saline + 24 SR-17018	Saline + Vehicle	65-240	F (35, 350) = 2.886	<0.0001	F (1, 10) = 11.04	0.0077	7
	24 Morphine + Vehicle	24 Morphine + 24 SR-17018	65-240	F (35, 280) = 12.94	<0.0001	F (1, 8) = 10.67	0.0114	5
	24 Morphine + Vehicle	24 Morphine + 24 SR-17018	65-240	F (35, 350) = 2.192	0.0002	F (1, 10) = 17.14	0.002	7
SF3B	24 Morphine + 24 SR-17018	Saline + 24 SR-17018	65-240	F (35, 350) = 20.51	<0.0001	F (1, 10) = 8.687	0.0146	5
	24 Morphine + Vehicle	Saline + Vehicle	95-240	F (29, 290) = 4.476	<0.0001	F (1, 10) = 13.19	0.0046	7
	Saline + 24 SR-17018	Saline + Vehicle	95-240	F (29, 174) = 3.693	<0.0001	F (1, 6) = 15.24	0.0079	7
	24 Morphine + Vehicle	24 Morphine + 24 SR-17018	95-240	F (29, 290) = 13.26	<0.0001	F (1, 10) = 48.75	<0.0001	5
SF3C	24 Morphine + 24 SR-17018	Saline + 24 SR-17018	95-240	F (29, 406) = 1.924	0.0032	F (1, 14) = 7.235	0.0176	7
	24 Morphine + 24 SR-17018	Saline + 24 SR-17018	95-240	F (29, 290) = 17.39	<0.0001	F (1, 10) = 7.040	0.0242	5
	Saline + 2.5 Naloxone	Saline + Saline	100-150	F (10, 60) = 0.6125	0.7971	F (1, 6) = 0.3596	0.5706	4
	24 morphine + Saline	Saline + Saline	100-150	F (10, 80) = 2.870	0.0042	F (1, 8) = 6.920	0.0302	6
SUMS	Saline + Saline	24 morphine + 2.5 naloxone	100-150	F (10, 80) = 1.639	0.1106	F (1, 8) = 6.970	0.0297	4
	24 morphine + 2.5 naloxone	24 morphine + Saline	100-150	F (10, 100) = 5.270	<0.0001	F (1, 10) = 10.28	0.0094	6
	24 morphine + 2.5 naloxone	Saline + 2.5 Naloxone	100-150	F (10, 80) = 1.101	0.3717	F (1, 8) = 5.600	0.0455	6
	24 morphine + 2.5 naloxone	Saline + 2.5 Naloxone	100-150	F (10, 80) = 1.101	0.3717	F (1, 8) = 5.600	0.0455	6
Ordinary one-way ANOVA, Šidák's multiple comparison post-hoc								
Figure	Treatment	Compared to	Time	p-Value	treatment n			
SF3A	24 Morphine + Vehicle	Saline + Vehicle	65-240	0.9313	7	ns		
	Saline + 24 SR-17018	Saline + Vehicle	65-240	<0.0001	7	****		
	24 Morphine + Vehicle	24 Morphine + 24 SR-17018	65-240	0.014	5	*		
	24 Morphine + Vehicle	24 Morphine + 24 SR-17018	65-240	0.0491	7	*		
SF3B	24 Morphine + 24 SR-17018	Saline + 24 SR-17018	65-240	<0.0001	5	****		
	24 Morphine + Vehicle	Saline + Vehicle	95-240	0.0004	7	***		
	Saline + 24 SR-17018	Saline + Vehicle	95-240	0.8083	7	ns		
	24 Morphine + Vehicle	24 Morphine + 24 SR-17018	95-240	0.1414	5	ns		
SF3C	24 Morphine + Vehicle	24 Morphine + 24 SR-17018	95-240	0.0235	7	*		
	24 Morphine + 24 SR-17018	Saline + 24 SR-17018	95-240	0.8354	5	ns		
	Saline + 2.5 Naloxone	Saline + Saline	100-150	>0.9999	4	ns		
	24 morphine + Saline	Saline + Saline	100-150	0.0093	6	**		
SUMS	Saline + Saline	24 morphine + 2.5 naloxone	100-150	>0.9999	4	ns		
	24 morphine + 2.5 naloxone	24 morphine + Saline	100-150	0.0046	6	**		
	24 morphine + 2.5 naloxone	Saline + 2.5 Naloxone	100-150	>0.9999	6	ns		
	24 morphine + 2.5 naloxone	Saline + 2.5 Naloxone	100-150	>0.9999	6	ns		

Figure S3. SR-17018 reversal of morphine-induced locomotor activity. The basal activity was recorded for 30 minutes followed by 30- (A) or 60-minute (B) treatment with saline or morphine (24 mg/kg, i.p.) before vehicle

or SR-17018 (24 mg/kg, i.p.) challenge in male C57BL6 mice (n = 4–8). Effects over time (*left*) and sum or the distance traveled (cm) from 65–240 minutes for individual mice (*right*) are shown in (A–B). C. Naloxone (2.5 mg/kg, i.p.) reversal after 60 minutes of morphine locomotor activity is shown for reference (n = 4–6). Comparison of sums are indicated in the figure. Sums figures have different Y-axis scales based on the maximal stimulation per treatment combination and we are showing individual sums per mouse. D. Table showing least square mean differences Tukey HSD analysis for pretreatment x second treatment interactions after saline or morphine + vehicle, SR-17018, or naloxone challenge. Data are presented as mean \pm SEM of the total distance (cm).

A. Locomotor Activity: SR-15099 + Morphine

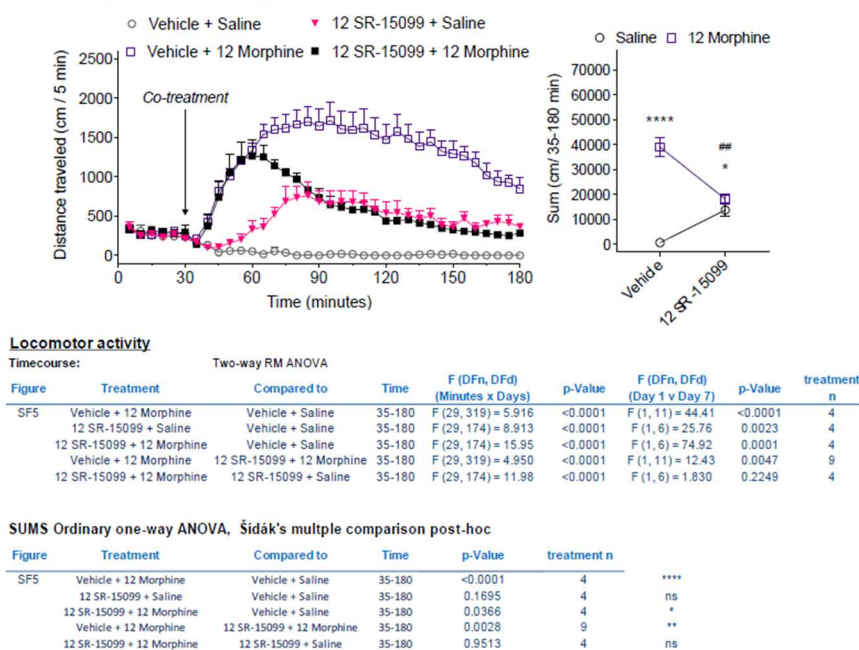
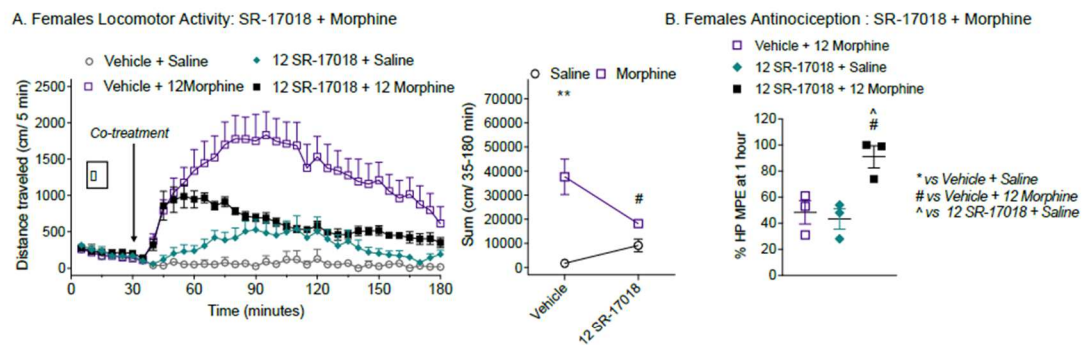


Figure S4. Co-treatment of morphine with SR-15099 attenuates morphine-induced hyperactivity. *In vivo* drug interactions in the open field locomotor activity assay showing total distance traveled (cm/ 5-minutes) (*left*) with total distance sums after co-treatment (cm/ 35-180 minutes) (*right*) in male C57BL/6 (n = 4–7). Locomotor activity after cotreatment with vehicle or SR-15099 (12 mg/kg, i.p.) and saline or morphine (12 mg/kg, i.p.). SR-15099 and morphine drug combination attenuate morphine's hyperactivity to the level of SR-15099. Comparison of sums are shown in the figure. Data are presented as mean \pm SEM.



Locomotor Activity

TIMECOURSE		Two-way RM ANOVA						
Figure	Treatment	Compared to	Time	F (DFn, DFd) time x drug	p-Value	F (DFn, DFd) drug effect	p-Value	treatment n
SF4a	Vehicle + 12 Morphine	Vehicle + Saline	35-180	F (29, 203) = 6.199	P<0.0001	F (1, 7) = 11.12	P=0.0125	6
	12 SR-17018 + Saline	Vehicle + Saline	35-180	F (29, 145) = 2.521	P=0.0002	F (1, 5) = 5.285	P=0.0699	4
	12 SR-17018 + 12 Morphine	Vehicle + Saline	35-180	F (29, 290) = 7.029	P<0.0001	F (1, 10) = 6.869	P=0.0256	6
	Vehicle + 12 Morphine	12 SR-17018 + 12 Morphine	35-180	F (29, 290) = 7.029	P<0.0001	F (1, 10) = 6.869	P=0.0256	6
	12 SR-17018 + 12 Morphine	12 SR-17018 + Saline	35-180	F (29, 232) = 4.238	P<0.0001	F (1, 8) = 13.14	P=0.0067	6

Sums Ordinary one-way ANOVA, Šidák's multiple comparison post-hoc

Figure	Treatment	Compared to	Time	p-Value	treatment n
SF4a	Vehicle + 12 Morphine	Vehicle + Saline	35-180	0.0014	6
	12 SR-17018 + Saline	Vehicle + Saline	35-180	0.9099	4
	12 SR-17018 + 12 Morphine	Vehicle + Saline	35-180	0.216	6
	Vehicle + 12 Morphine	12 SR-17018 + 12 Morphine	35-180	0.0342	6
	12 SR-17018 + 12 Morphine	12 SR-17018 + Saline	35-180	0.699	6

vehicle+saline n=3

Hot Plate Latency

Ordinary one-way ANOVA, Šidák's multiple comparison post-hoc

	Treatment	Compared to	Time	p-Value	treatment n
SF4b	Vehicle + 12 Morphine	12 SR-17018 + Saline	1h	0.90960	3
	12 SR-17018 + 12 Morphine	Vehicle + 12 Morphine	1h	0.0274	3
	12 SR-17018 + 12 Morphine	12 SR-17018 + Saline	1h	0.017	3

Figure S5. In female mice, co-treatment of morphine with SR-17018 decreases morphine-induced hyperactivity without attenuating antinociception. Results recapitulate in female C57BL6 mice testing for SR-17018 + morphine locomotor (n = 3–6) and antinociception (n = 3) Doses are indicated as mg/kg, i.p. in the figure legends. Data are presented as mean ± SEM. .