DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (2004)

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When originally submitted by the Biological Coordinator, Dr. Andrew Coop of the University of Maryland, School of Pharmacy, the identity of all the compounds was unknown to us. These studies were conducted under the auspices of the Drug Evaluation Committee in association with the College on Problems of Drug Dependence. See summary of new data in Table l. All animals received care according to the "Guide for the Care and Use of Laboratory Animals" (1996). These facilities are certified by the American Association for the Accreditation of Laboratory Animal Care (AAALAC).

Dependence-Liability Studies in Rhesus Monkeys

Substitution-for-morphine (SDS) Test. Male and female rhesus monkeys (M. mulatta) weighing 2.5-7.5 kg were used, and they received 3 mg/kg, s.c., of morphine·SO_4 every 6 hr. All the animals had received morphine for at least 3 months and were maximally dependent on morphine (Seevers and Deneau 1963). A minimal 2-week recuperation period was allowed between tests. Unless otherwise noted, at least 3 monkeys/dose were used. The assay (Aceto and co-workers, 1977 and 1978) was initiated by a subcutaneous injection of the test drug or control substances (morphine and vehicle) into animals in a group that had not received morphine for 14-15 hr and showed definite signs of withdrawal. Each animal was randomly chosen to receive one of the following treatments: a) a dose of the compound under investigation; b) morphine control, 3.0 mg/kg; and c) vehicle control, 1 ml/kg. The animals were scored for suppression of withdrawal signs during a 2.5-hr observation period. The observer was "blind" regarding the assignment of treatments. The mean cumulative score ± SEM was calculated and the data illustrated in figure form. If indicated, the data were analyzed using the Kruskal-Wallis ANOVA and post hoc Mann-Whitney U-Tests.

Precipitated-Withdrawal (PPT-W) Test. This evaluation was done under the same conditions as described above, except that the animals were administered a test compound 2-3 hr after the last dose of morphine. These animals were not then in withdrawal. Naloxone·HCl (0.05 mg/kg, s.c.) served as the positive control.

Table 1. List of NIH compounds included in this report as well as an indication of the tests that were conducted on each compound.

NIH #.	CHEMICAL NAME OR GENERIC CLASS	MOUSE DATA				MONKEY DATA	
		TF	TF vs M	PPQ	HP	SDS	PPT-W
11028	3-O-methylnaltrexone	T [a,b]	T	T	T	T	T
11037	3-O-Cinnamoylnaltrexone	T [c,d]	T [e]	T	T		T
11053	4,5-Epoxymorphinan-6-one	T	T[f]	T	T		
11054	4,5-Epoxymorphinan-6-one	T[g]	T	T	T		
11055	4,5-Epoxmorphinan-6-one	T	T	T	T		
11056	4,5-Epoxmorphinan-6-one	T	T	T	T	T	
11057	4,5-Epoxymorphinan-6-one	T	T	T	T		
11058	4,5-Epoxymorphinan-6-one	T	T	T	T		
11059	4,5-Epoxymorphinan-6-one	T[g]	T	T	T		
11060	4,5-Epoxymorphinan-6-one	T	T	T	T		
11062	4,5-Epoxymorphinan-6-one	T	T	T	T		
11065	Morphinan-6-carbonitrile	T	T	T	T	T	
11066	Morphinan-6-carbonitrile	T	T	T	T	T	
11067	Morphinan-6-carbonitrile	T	T	T	T	T	
11068	4,5-Epoxymorphinan-6-one	T	T	T	T		
11072	Morphinan-6-carbonitrile	T	T	T	T		
11073	Morphinan-6-carbonitrile	T	T	T	T		
11074	Morphinan-6-carbonitrile	T	T	T	T		
11075	Morphinan-6-carbonitrile	T	T	T	T		
11076	Morphinan-6-carbonitrile	T	T	T	T		
11077	Morphinan-6-carbonitrile	T	T[h]	T	T		
11082	6,7-Benzomorphan	T[i]	T[j]	T	T	T	
11086	Dynorphan analog	T	T	T	T		
11087	Dynorphan analog	T	T	T	T		
11090	Enkephalin analog	T	T	T	T		
11091	Enkephalin analog	T	T	T	T		
11097	6,7-Benzomorphan	T[k]	T	T	T	T	
11098	6,7-Benzomorphan	T	T	T	T	T	
11106	N'-Benzyloxymorphindole	T	T[l]	T	T		
11109	O-Butyrylnaltrexone	T	T	T	T	T	
11111	6,7-Benzomorphan	T	T[m]	T	T	T	
11112	6,7-Benzomorphan	T	T	T	T	T	
11113	6,7-Benzomorphan	T	T	T	T		
11114	6,7-Benzomorphan	T	T[n]	T	T	T	
11127	6,7-Benzomorphan	T	T	T	T	T	
11139	6,7-Benzomorphan	T	T	T	T	T	
11140	6,7-Benzomorphan	T	T	T	T	T	
11164	6,7-Benzomorphan	T	T	T	T		
11165	6,7-Benzomorphan	T	T	T	T		
11166	6,7-Benzomorphan	T	T	T	T		
11167	6,7-Benzomorphan	T	T	T	T		
11168	6,7-Benzomorphan	T	T	T	T		
11176	6,7-Benzomorphan	T	T	T	T	T	
11179	6,7-Benzomorphan	T	T	T	T	T	

Table 1. (continued)

11180	6,7-Benzomorphan	T	T	T	T		T
11181	6,7-Benzomorphan	T	T	T	T		
11182	6,7-Benzomorphan	T	T	T	T	T	
11183	6,7-Benzomorphan	T	T	T	T	T	
11185	6,7-Benzomorphan	T	T	T	T	T	
11186	6,7-Benzomorphan	T	T	T	T	T	
11187	6,7-Benzomorphan	T	T	T	T	T	

T = Test Performed

[a]Special: NIH 11028 (p.o.) vs morphine in TF; naltrexone and NIH 11028 (6 hr pretreatment) vs ED80 of morphine in TF; [b]Special: Naloxone (p.o.) vs ED80 of NIH 11028 in TF; [c,d]Special: Naltrexone and NIH 11037 vs ED80 of morphine in TF, [e]AD50 of NIH 11037 vs ED80 of DPDPE in PPQ; [f]Special: NIH 11053 vs β-FNA, nor-BNI and naltrindole In PPQ; [g]Special: Naloxone vs NIH 11054 in TF; Naloxone vs NIH 11159 in TF. [h]Special: Naltrindole vs ED80 of NIH 11077 in PPQ. [i]Special time-course for NIH 11082 in PPQ, co-administration of NIH 11082 and morphine in PPQ. [j]Naltrindole, nor-BNI and β-FNA vs ED80 of NIH 11082 in PPQ; [k]Enadoline vs ED80 of NIH 11097 in TF; [l]Naloxone vs ED80 of NIH 11106 in PPQ; mNor-BNI vs ED80 of NIH 11111 in PPQ; nNor-BNI vs ED80 of NIH 11114 in PPQ.

Primary-Physical-Dependence (PPD) Study. Drug-naive monkeys were medicated with drug, using escalating dose regimens, periodically challenged with naloxone or placed in abrupt withdrawal. They were observed for overt behavioral signs during drug administration and when they were challenged with the antagonist, naloxone, or abruptly withdrawn from the drug.

Rat-Infusion Studies

The continuous-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with nylon sutures and attached to a flow-through swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 hr.

Substitution-for-Morphine (SM) Test. The rats received morphine·SO_4 (50 mg/kg/24 hr on the first day, 100 mg/kg/24 hr on the second day, and 200 mg/kg/24 hr from days 3 and 4). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of sterile water for injection. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 0.5 hr at 6, 24, 48, 72 and/or 96 hr after stopping the infusion of morphine.

Primary-Physical-Dependence (PPD) Study. The rats received test compound, as specified above, for 4-6 days and then, were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Male mice, weighing 20-30 g, were used. All drugs were dissolved in distilled water or in the vehicle indicated and injected subcutaneously (s.c.). At least three doses were tested, and 6-10 animals per dose were used. When applicable, ED50's or AD50's were calculated by using computerized probit analysis (Bliss, 1967). The results obtained with reference compounds are summarized in Table 2. Occasionally, when requested, drugs were given orally (p.o.) or intravenously (i.v.), intracerebroventricular (i.c.v) and the pretreatment times are indicated in the text.

Tail-Flick (TF) and (TF vs M) Assays. The procedure and modifications were described (D'Amour and Smith, 1941 and Dewey et al., 1970 and 1971) in the literature. Briefly, the mouse's tail was placed in a groove which contained a slit under which was located a photoelectric cell. When the heat source or noxious stimulus was turned on, it focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed though the slit and activated the photocell which, in turn, stopped the recording timer. The heat source was adjusted to produce tail flick of 2-4 sec under control conditions. Mice were injected with drug or vehicle and tested 20 min later. In the assays for antagonism of the antinociceptive effect, the potential antagonists were administered 10 min before the agonist, and evaluation occurred 20 min later.

Phenylquinone Abdominal-Stretching (PPQ) Assay. The procedure was reported previously (Pearl and Harris, 1966). The mice were injected with test drug and 10 min later received 2.0 mg/kg intraperitoneally (i.p.) of a freshly prepared paraphenylquinone (PPQ) solution. The mice were then placed in cages in groups of three each. Ten min after the PPQ injection, the total number of stretches per group were counted over 1-min periods. A stretch was characterized by an elongation of the mouse's body, development of tension in the abdominal muscles, and extension of the hindlimbs. The antinociceptive response was expressed as the percent inhibition of the PPQ-induced stretching response.

Hot-Plate (HP) Assay. The method was also reported previously (Eddy and Leimbach, 1953 and Atwell and Jacobson, 1978). The hot plate was held at 56°C. Mice were placed on the hot plate and activity was scored if the animal jumped, lifted its back feet, or licked its front paws.

Table 2

Comparative Data (ED50, mg/kg s.c.) [95% C.L.] of Selected Standards in 4 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick	Tail-Flick Antagonist	Phenylquinone	Hot-Plate
Pentazocine	15% at 10.0	18 (12 - 26)	1.7 (1.0 - 2.5)	13% at 30.0
Cyclazocine	17% at l.0[a]	0.03 (0.02 - 0.78)	0.01 (0.005 - 0.03)	25% at 9.0
Nalorphine·HCl	None at 10.0	2.6 (0.7-1.0)	0.6 (0.03 - 1.44)	13% at 30.0
Naloxone·HCl	None at 10.0	0.04 (0.0 - 0.09)	No Activity	- - - -
Naltrexone·HCl	None at 10.0	0.007 (.002 - 0.02)	No Activity	- - - -
Morphine·S0$_4$[b]	1.92 (0.89 - 4.14)	Inactive	0.4[b] (0.2-0.8)	0.85 (0.39 -1.86)
Codeine·P0	17.5 (15.4 - 19.9)	Inactive	8.2 (5.12 -13.29)	6.4 (2.4 -16.8)
Meperidine·HC1	8.4 (4.6 - 15.23)	Inactive	2.2 (1.7 - 2.9)	4.6 (1.2 - 11.7)

[a]Mice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time

[b]ICR - Harlan-Sprague-Dawley Inc.

Calculation of Apparent pA2 . Using the tail-flick or PPQ assay, the apparent pA$_2$ and 95% confidence limits were calculated using Schild and constrained plots as described in Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 2nd ed., Springer Verlag, NY, 1987).

Briefly, mice were pretreated with vehicle or various doses of antagonist followed 10 min later by an injection of agonist. The mice were tested 30 min after receiving the antagonist. Dose-response lines for antinociception were plotted using at least 3 doses of each opioid agonist in the presence of vehicle or one of the selected doses of antagonist. ED5Os were estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther., 96, 399, 1949). Each dose ratio (x) was calculated by dividing the ED50 of the opioid in the presence of a given dose of antagonist by that of the agonist alone. Log (x - 1) was plotted against the negative logarithm of the molar dose of the antagonist. At least 3 logs (x - l) were plotted. The pA$_2$ values for the antagonists were calculated from the point of intersection of the regression line with the abscissa. See Table 3 for summary of results.

Table 3. Apparent pA_2 values[a] using the mouse tail-flick assay

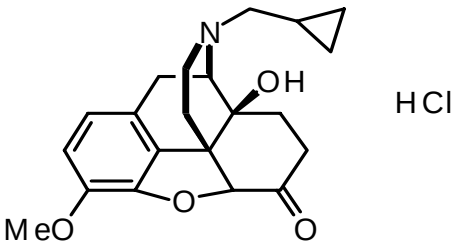
Treatment Antagonist/Agonist	Schild Plot pA_2 (95% C.L.) Slope	Constrained Plot pA_2(95% C.L.)
1) Naloxone/Morphine	7.2 (7.0-7.4)-1.2	7.3 (7.1 - 7.6)
2) Naloxone/Sufentanil	7.0 (6.5 - 7.5)-1.0	7.0 (6.8 - 7.1)
3) Naloxone/Mirfentanil	7.6 (7.3 - 8.0)-0.7	7.2 (6.9 - 7.5)
4) Naloxone/NIH 10672 (Enadoline) (selective kappa agonist)	6.1 (5.6 - 6.6)-1.2	6.6 (6.3 - 7.0)
5) Naloxone/U-50,488 (kappa agonist)	6.6 (6.3 - 6.9)-1.1	6.2 (5.9 - 7.3)
6) Naloxone/(-)-Nicotine	5.3 (5.3-5.3)-0.5	-
7) Nalmefene/Morphine	8.0 (7.6 - 8.3)-1.1	8.0 (7.7 - 7.6)
8) Naltrexone/Morphine	7.7 (4.9 - 10.5)-0.8	7.6 (7.1 - 8.3)
9) (-)-Quadazocine/Morphine	6.8 (6.7 - 7.0)-0.9	6.8 (6.1 - 7.6)
10) (-)-Quadazocine/Enadoline	6.2 (6.1 - 6.2)-1.7	6.7 (6.6 - 6.8)
11) nor BNI/Enadoline	6.5 (5.9 - 7.0)-1.3	6.6 (5.9 - 7.3)
12) Mecamylamine/(-)-Nicotine	6.6 (6.2 - 6.9)-0.9	-

[a]Negative logarithm of the molar concentrations of antagonist required to produce a two-fold shift of the agonist dose-response curve to the right. Competitive antagonism can be assumed when slope = -1. pA_2 provides a measure of the relative potency and affinity of the antagonist. When the slope differs significantly from unity, this may indicate non-equilibrium conditions, interactions with multireceptors, receptor sensitization, precoupling mechanisms, or multiple drug properties. With a constrained plot, the slope of the regression line is restricted to slope of - 1.

Special Intracerebroventricular (i.c.v.) Tail-Flick and PPQ Assays. In order to develop an in-vivo agonist and antagonist model to correlate with the in-vitro binding data of the various opioid receptor types (mu, kappa and delta), we chose the mouse Tail-Flick and PPQ tests and a variety of routes of administration. The intracerebroventricular (i.c.v.) route was chosen to test drugs that did not cross the blood-brain barrier.

Special in vivo opioid agonist and antagonist subtype testing. To further characterize an opioid, special subtype testing is conducted. Compounds are tested for mu, kappa and delta opioid agonist and antagonist properties using the opioid selective agonists sufentanil (mu), enadoline (kappa) and/or DPDPE (delta) and the selective opioid antagonists beta-funaltrexamine (mu), nor-binaltorphamine(kappa) and/or naltrindole(delta).

NIH 11028 3-O-Methylnaltrexone.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** -1% at 1, 0% at 3 and 3% at 30
2) **TF vs. M** - 0.47 (0.30 – 0.72)
3) **PPQ** – Not tested
4) **HP** - 13% at 1 and 10, 0% at 30

Special Tests: 1) NIH 11028 (p.o.) vs ED80 of morphine (s.c.) in TF: AD50 = 2.31 (1.73 –3.09)

Note: Naloxone (p.o.) AD50 vs ED80 of morphine (s.c.): 1.44 (0.51 – 4.03)

NIH 11028 (continued)

Table 1. Naltrexone (AD50) and NIH 11028 (ED50) versus ED80 mu-, kappa-, and delta-opioid agonists in TF test.

Naltrexone (AD 50) versus 80% response of Opioid Agonists						
	Enadoline	Enadoline	Sufentanil	Sufentanil	DPDPE	DPDPE
		(repeat)		(repeat)		(repeat)
AD_{50}	0.523	0.552	0.003	0.013	0.062	0.045
range	(0.162 -1.687)	(.265 - 1.028)	(0.001 - 0.009)	(0.004 - 0.039)	(0.023 - 0.171)	(0.033 - 0.062)
NIH 11028 (AD50) *vs* 80% Response of Opioid Agonists						
	Enadoline		Sufentanil		DPDPE	
AD_{50}	5.44		0.121		1.77	
range	(1.58 - 18.69)		(0.033 - 0.448)		(1.15 - 2.73)	

MONKEY DATA (SDS)

As shown in the figure below, at doses of 4 and 16 mg/kg, NIH 11028 neither attenuated withdrawal nor substituted for morphine in rhesus monkeys. Instead, it exacerbated withdrawal in a dose dependent manner.

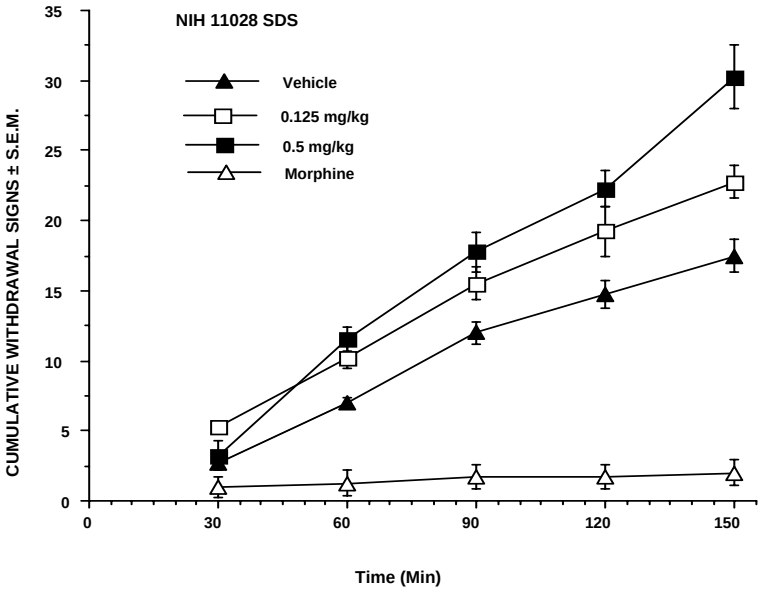


Fig NIH 11028-SDS. Results of study in which single doses of NIH 11028 were substituted for morphine in morphine-dependent monkeys in withdrawal.

NIH 11028 (continued)

MONKEY DATA (PPt-W)

NIH 11028 precipitated abstinence signs in monkeys dependent on morphine. Its action was dose related. However, the drug is much less potent than naloxone, The drug acted promptly and its duration of action was longer than that of naloxone. Potency estimate was about 1/20 that of naloxone, the reference standard.

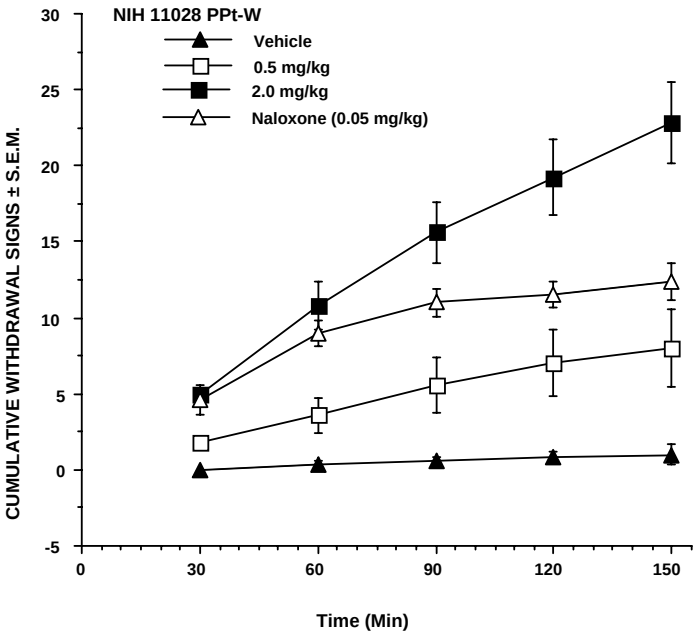
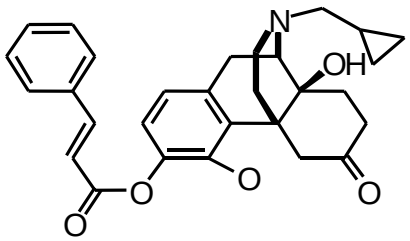


Fig. NIH 11028-PPt-Withdrawal. Results of study in which morphine-dependent monkeys were given single doses of NIH 11028 two hr after morphine.

Comment: The results show that NIH 11028 is a much weaker mu-, kappa- and delta-opioid receptor antagonist than naltrexone. Duration of action is waning at 6 hr.

NIH 11037 3-O-Cinnamoylnaltrexone.HCl



HCl

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30[a]
2) **TF vs. M** - 0.013 (0.003 - 0.04) 30 min
3) **PPQ** - Inactive at 30[a]
4) **HP** - 13% at 30[a]

Special 4-hr pretreatment study (s.c.): Naltrexone and NIH 11037 (AD50s) vs morphine.

Naltrexone	**NIH 11037**
AD50 = 1.92 (0.69 - 5.31)	2.69 (0.99 - 7.30)

NIH 11037 (continued)

Opioid subtype testing (kappa antagonist):

AD50 vs ED80 of enadoline, a kappa agonist = 0.196 (0.045 - 0.849).

<u>MONKEY DATA</u> (PPT-W)

NIH 11037 precipitated withdrawal in morphine-dependent monkeys at doses of 0.03 and 0.15 mg/kg. As shown in the accompanying figure, this drug appeared to be more potent than naloxone, the reference standard. Onset of action was rapid and offset seemed longer than that of naloxone.

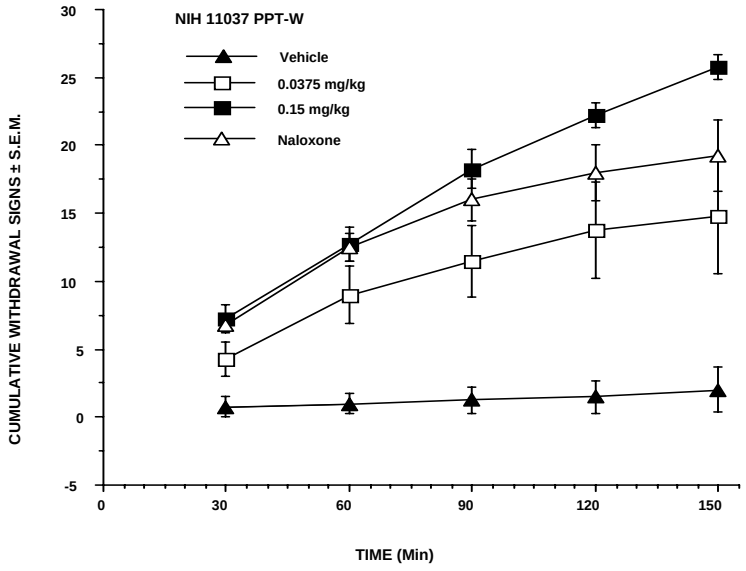
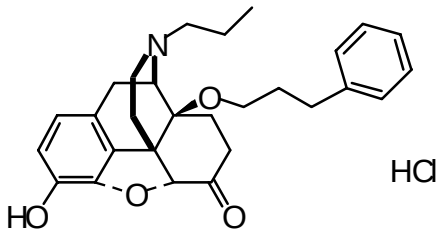


Fig. NIH 11037 Results of study in which NIH 11037 was administered to morphine-dependent monkeys (PPT-W).

Comment: Based on the results of studies in mice and morphine-dependent monkeys, we conclude that NIH 11037 is a potent mu- and kappa-opioid receptor antagonist. Whether or not this drug also has delta-opioid receptor antagonist activity remains to be determined.

NIH 11053 17-Propyl-4,5α-epoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.0016 (0.0009 - 0.0027)[a ,d]
2) **TF vs. M** - Inactive at 1[a ,b,d]
3) **PPQ** - 0.0009 (0.0005 - 0.0017)[a,d]
4) **HP** - 0.0017 (0.0008 - 0.0036)[a,b,c]

[a]Straub tail at 0.003 mg/kg.
[b]Increased locomotor activity.
[c]Clonic convulsions at 10 mg/kg, 2/6 died.
[d]Vehicle was 15% hydroxypropyl-β-cyclodextrin in water.

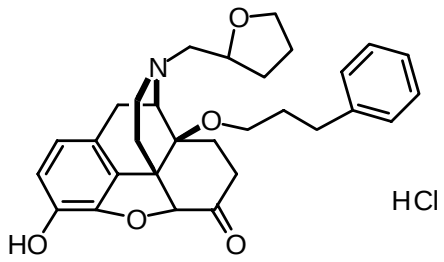
NIH 11053 (continued)

0pioid subtype testing:

a) β-FNA (i.c.v.) vs ED80 of NIH 11053 (s.c.,) in TF test: AD 50 = 6.48 (2.3 - 18) μg/brain.
b) nor-BNI (s.c.,) vs ED80 of NIH 11053) in TF test: Inactive at 1, 10 and 30.
c) Naltrindole (s.c.,) vs ED80 of NIH 11053,) in TF test: Inactive at 1, 10 and 30.

Comment: The results indicate that NIH 11053 is a very potent opioid with mu-receptor selective activity.

NIH 11054 17-([2-R,S-Tetrahydrofuranyl)methyl)-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

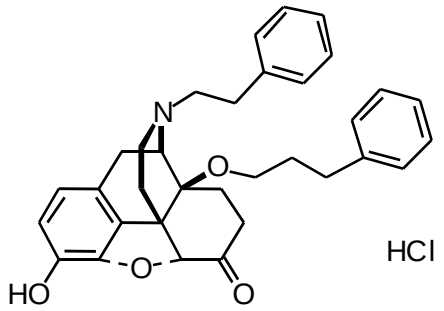
1) **TF** - 0.007 (0.004 - 0.014)d
2) **TF vs. M** - Inactive at 1 mg/kg[a,d]
3) **PPQ** - 0.0017 (0.0017 - 0.0041)[a,d]
4) **HP** - 0.0013 (0.0006 - 0.003)[a,b,c,d]

[a]Straub tail at 0.01.
[b]Clonic convulsions ,
[c]Straub tail and increased locomotor activity at 1 mg/kg
[d]Vehicle was 20% hydroxypropyl-β-cyclodextrin in aqueous solution.

Special Test: Naloxone vs ED80 NIH 11054 in TF: AD50 = 0.14 (0.06 - 0.30).

Comment: NIH 11054 is a very potent opioid with mu-receptor agonist properties. Onset of action was prompt.

NIH 11055 17-(2-Phenethyl)-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl



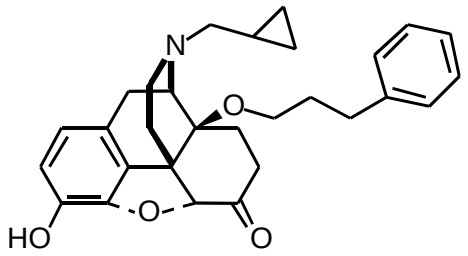
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.11 (0.06 - 0.20)[c]
2) **TF vs. M** – Inactive at 1[a,c]
3) **PPQ** - 0.0094 (0.0041 - 0.027)[a,b]
4) **HP** – 0.0117 (0.0049 - 0.0282)[b]

[a]Straub tail, ataxia and hyperactivity at 1 mg/kg.
[b]Vehicle - 20% DMSO in H_2O.
[c]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water.

Comment: NIH 11055 has potent opioid-agonist activity. Mu-receptor properties of rapid onset are indicated.

NIH 11056 17-2-cyclopropylmethyl-4,5α-epoxy-3-hydroxy-14β-(3- phenylpropyloxy)morphinan-6-one.HCl



MOUSE DATA - ED50 OR AD50 AD,
(95% C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.0032 (0.0016 - 0.0062).[a,]
2) **TF vs. M** - 14% at 1, 18% at 10 and 47% at 30.[a,b,c,d]
3) **PPQ** - 0.0062 (0.0031 -0.0125).[a,b,d]
4) **HP** - 0.0023 (0.0011 - 0.0047).[a,b]

[a]Vehicle was 1% lactic acid aqueous solution
[b]Straub tail and increased locomotor activity at 0.1
[c]Mild Straub tail at 0.01
[d]Mild Sedation at 10 and heavy sedation at 30

MONKEY DATA (SDS)

As depicted in the figure, NIH 11056 substituted completely for morphine at 0.04 mg/kg s.c. Potency estimate is approximately 100 times that of morphine sulfate. Jaw sag and scratching were noted in 1 monkey receiving 0.02 mg/kg s.c.

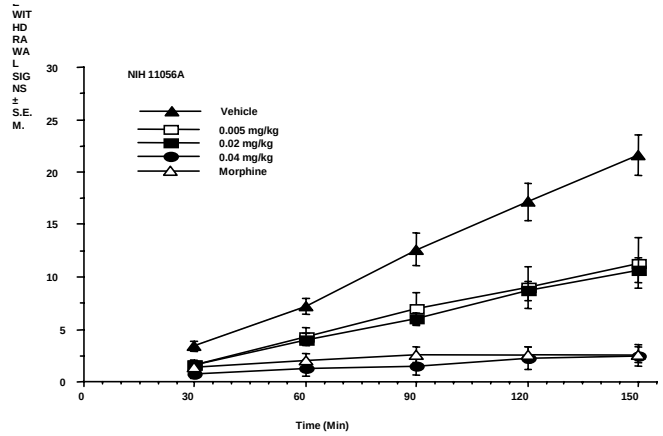
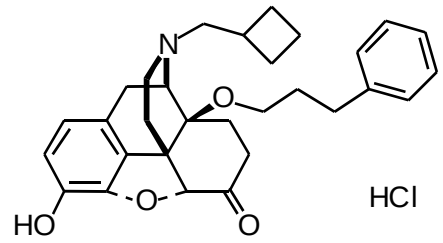


Fig NIH 11056 SDS. Results of study in which single doses of NIH 11056 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: The mouse data indicated that NIH 11056 is a potent opioid agonist with prominent mu-opioid receptor properties. Potency estimate is approximately 3000 times that of morphine sulfate. In the monkey, NIH 11056 substituted completely for morphine with a potency estimate of 100 times that of morphine sulfate.

NIH 11057 17-Cyclobutylmethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl



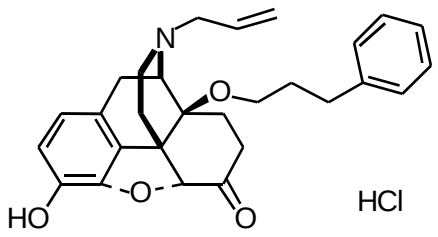
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.0082 (0.0034 - 0.02)[a,b]
2) **TF vs. M** - Inactive at 1[b]
3) **PPQ** - 0.0003 (0.00002 - 0.006)[a,b]
4) **HP** - 0.0037 (0.0008 - 0.0172)[b]

[a]Straub tail, ataxia and increased locomotor activity.
[b]Vehicle was 20% DMSO (dimethylsulfoxide) aqueous solution.

Comment: The results suggest that NIH 11057 has very potent opioid agonist activity with a mu-opioid component. The drug acts promptly.

NIH 11058 17-Allyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl



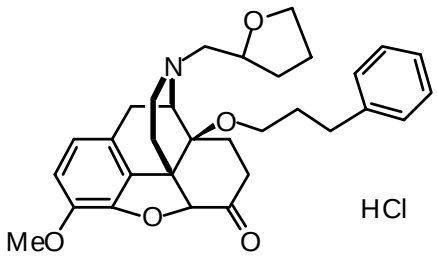
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.0056 (0.003 - 0.011)[a,b]
2) **TF vs. M** - Inactive at 1[b]
3) **PPQ** - 74% at 0.003, 42% at 0.005, 39% at 0.01, 95% at 0.02l and 100% at 0.03 and 1[a ,b]
4) **HP** - 0.0059 (0.0037 - 0.0094)[b]

[a]Straub tail and increased locomotor activity at 1 mg/kg
[b]Vehicle - 20% hydroxypropyl-β-cyclodextrin plus sonication

Comment: There was an erratic dose-response in the PPQ test. Overall, the results indicate that NIH 11058 has potent opioid agonist properties and that mu-opioid receptor system is involved.

NIH 11059 17,[(2-R,S-Tetrahydrofuranyl)methyl]-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

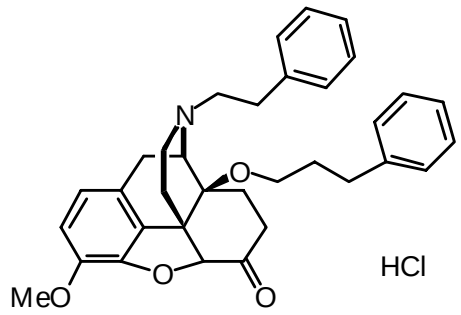
1) **TF** - 0.084 (0.05 - 0.14)[a,c]
2) **TF vs. M** - Inactive at 1[c]
3) **PPQ** - 0.0063 (0.0027 - 0.0144)[a ,c]
4) **HP** - 0.06 (0.02 - 0.17)[b,c]

[a]Straub tail and increased locomotor activity
[b]Straub tail at 1 mg/kg
[c]Vehicle - 20% hydroxypropyl-β-cyclodextrin plus sonication

Special Test: Naloxone vs NIH 11059 in TF: AD50 = 0.026 (0.009 - 0.076).

Comment: This compound has opioid agonist properties. Mu-opioid receptors seem to be involved.

NIH 11060 4,5 -Epoxy-3-methoxy-17-(2-phenylethyl)-14β -(3-phenylpropyloxy)morphinan-6-one.HCl

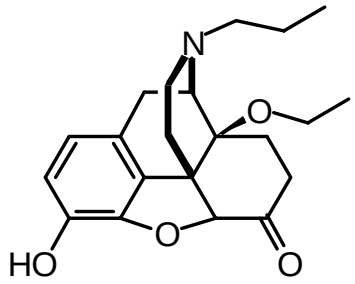


MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Not Requested - Limited Supplies
2) **TF vs. M** - Not Requested - Limited Supplies
3) **PPQ** - 29% at 0.001, 34% at 0.01, 3% at 0.03, 37% at 0.1, 24% at 0.3, 97% at 1 and 100% at 10[a,b]
4) **HP** - 0.68 (0.29 - 1.61)[b]

Comment: This compound produced an erratic dose-effect curve in the PPQ test. NIH 11060 has opioid agonist propertries of which the mu-opioid receptor subtype is involved.

NIH 11062 4,5-Epoxy-3-hydroxy -14-ethoxy-17-propylmorphinan-6-one.HCl



HCl

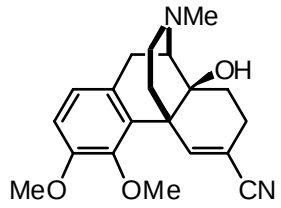
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** – 0.074 (0.027 - 0.182)[a]
2) **TF vs. M** – 18% at 1. [a,b]
3) **PPQ** – 0.0022 (0.0008 - 0.005)
4) **HP** - 0.062 (0.016 - 0.243)[a]

[a] Vehicle was 20% hydroxypropyl-β-cyclodextrin
[b] Straub tail at 1

Comment: The profile of activity is reminiscent of that of morphine. The potency estimate is 100 times that of morphine sulfate.

NIH 11065 5,6-Didehydro-14 beta -hydroxy-3,4-dimethoxy-17-methylmorphinan-6-carbonitrile



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** - 0.018 (0.061 - 0.226)[a,b]
2) **TF vs. M** - Inactive at1 and 10 [a,b]
3) **PPQ** - 0.026 (0.012 - 0.055)[a,b]
4) **HP** - 0.149 (0.054 - 0.41)[a,b]

[a] Straub tail and increased locomotor activity at 0.5 and 1 mg/kg.
[b] Vehicle was 20% hydroxypropyl-β-cyclodextrin and 1% lactic acid.

MONKEY DATA (SDS)

At doses of 0.07 and 0.35 mg/kg, NIH 11065 substituted completely for morphine in physically-dependent monkeys in withdrawal (see figure) The drug acted promptly; however, duration of action appeared to be waning after 60 min. Potency estimate at 1 hr was 40 times that of morphine sulfate.

NIH 11065 (continued)

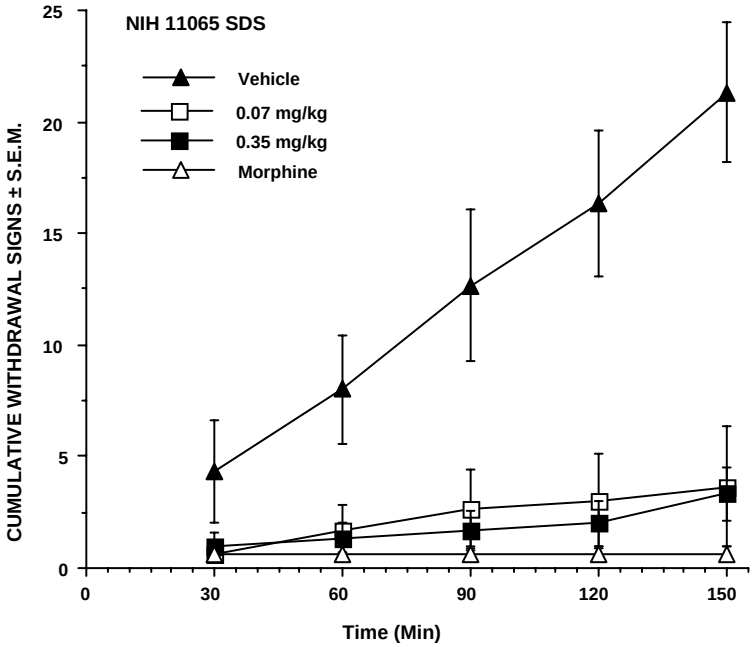
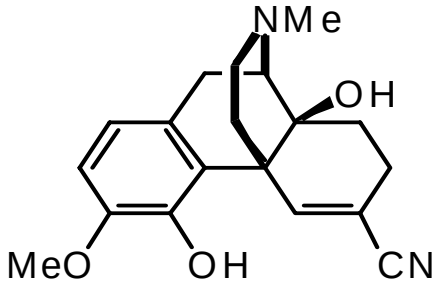


Fig NIH 11065 SDS. Results of study in which single doses of NIH 11065 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity suggests that NIH 11065 is a potent mu-opioid agonist. It is 100 to 150 times more potent than morphine sulfate in the mouse. In the monkey, its potency is about 40 times that of morphine sulfate.

NIH 11066 5,6-Didehydro-4,14 beta -dihydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 1.88 (1.25 - 2.83)[a,b]
2) **TF vs. M** - Inactive at 1 and 10[a,b]
3) **PPQ** - 0.178 (0.076 - 0.42)[a,b]
4) **HP** - 0.5 (0.12 - 2.02)[a,b]

[a]Straub tail at 3 and 10 mg/kg.
[b]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water and 1% lactic acid.

MONKEY DATA (SDS)

NIH 11066 substituted completely for morphine at 3 mg/kg (n = 2). Limited drug supply prevented a complete study. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

NIH 11066 (continued)

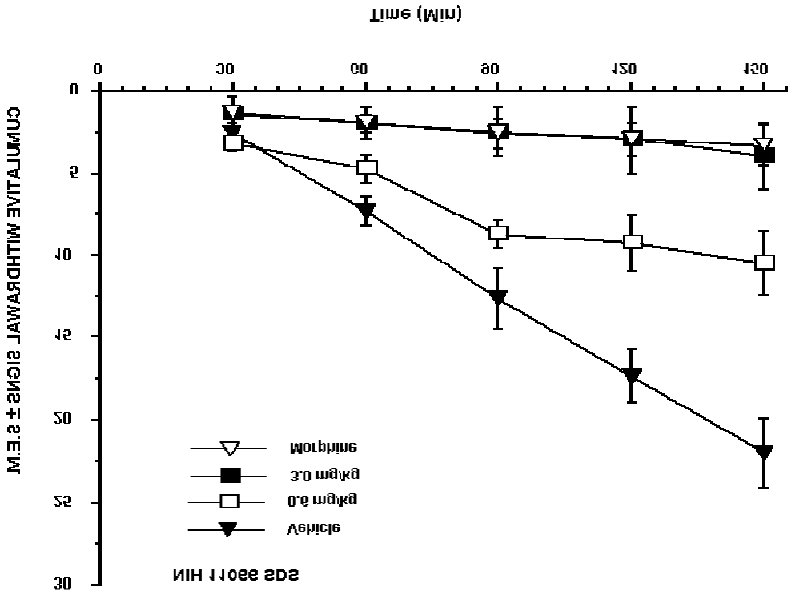
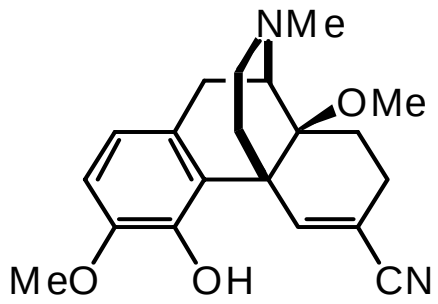


Fig NIH 11066 SDS. Results of study in which single doses of NIH11066 were substituted for morphine in morphine-dependent monkeys in withdrawal**.**

Comment: NIH 11066 exhibits a profile of activity not unlike that of morphine sulfate.

NIH 11067 5,6-Didehydro-4-hydroxy-3α,14β-dimethoxy-17-methylmorphinan-6-carbonitrile



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.209 (0.109 - 0.4)[a,b]
2) **TF vs. M** - Inactive at 1 and 10[a,b]
3) **PPQ** - 0.108 (0.072 - 1,64)[a,b]
4) **HP** - 0.253 (0.072 - 1.64)[a,b]

[a]Straub tails at 1 and 10 mg/kg.
[b]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water and 1% lactic acid

MONKEY DATA (SDS)

At doses of 0.3 and 1.2 mg/kg, NIH 11067 substituted completely for morphine sulfate in morphine-dependent monkeys in withdrawal (see accompanying figure). Onset was prompt and duration of action was at least as long as that of the reference standard.

NIH 11067 (continued)

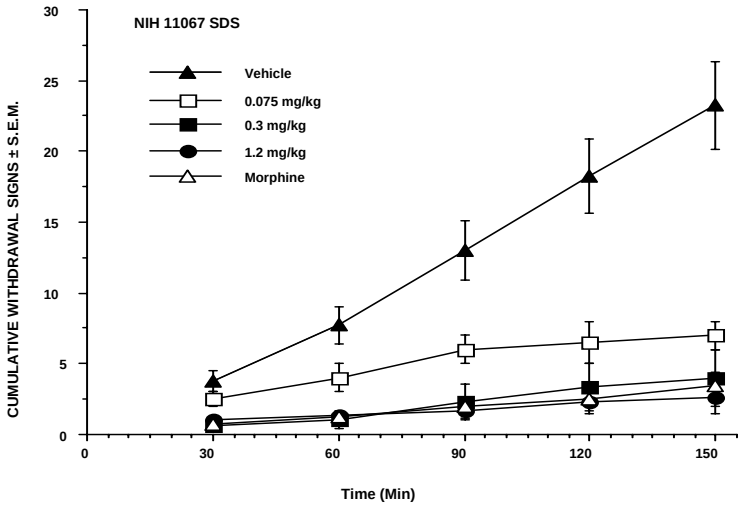
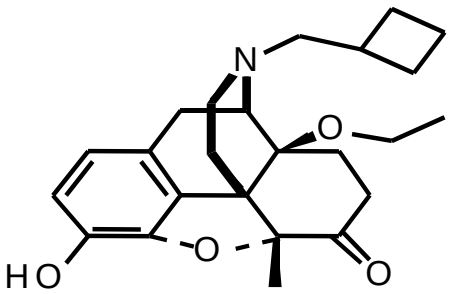


Fig NIH 11067 SDS. Results of study in which single doses of NIH 11067 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: This compound (NIH 11067) acts like a typical mu-opioid receptor agonist. Potency is about 10 times that of morphine sulfate.

NIH 11068 17-Cyclobutylmethyl-4,5α-epoxy-14β -ethoxy-3-hydroxy-5β-methymorphinan-6-one



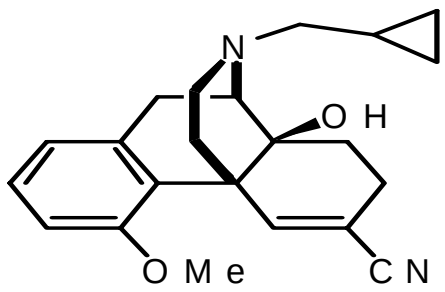
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg.s.c.

1) **TF** - 0.192 (0.071 - 0.515).[a]
2) **TF vs. M** - Inactive at 1 and 10.[a,b]
3) **PPQ** - 0.091 (0.062 - 0.134).[a]
4) **HP** - 0.198 (0.134 - 0.292).[a]

[a]Vehicle was 1% lactic acid in water.
[b] Insufficient drug for testing higher doses.

Comment: The results suggest a morphine-like profile of activity. It is 10 times more potent than morphine sulfate.

NIH 11072 17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-4-methoxymorphinan-6-carbonitrile



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

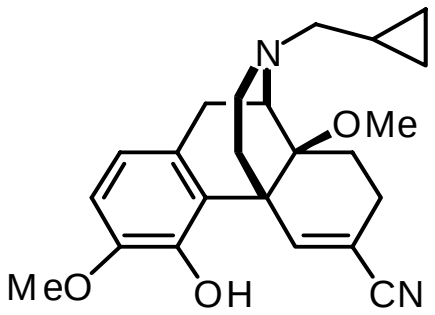
1) **TF** – Inactive at 1 and 10, 23% at 30.[a]
2) **TF vs. M** – 2.77 (1.23 - 6.25).[a]
3) **PPQ** – Inactive at 1 and 10, 7% at 30.[a]
4) **HP** - 13% at 1, 0% at 10 and 37% at 30.[a]

[a]Vehicle was 1% lactic acid aqueous solution.

NIH 11072 s.c. in TF versus ED80 of Enadoline: AD50 = 6.3 (2.62 - 15.17) mg/kg.

Comment: NIH 11072 has very weak mu-opioid antagonist activity. It is approximately 100 times less potent than naloxone. It also has kappa-opioid antagonist activity.

NIH 11073 17-Cyclopropylmethyl-5,6-didehydro-4-hydroxy-3,14β -dimethoxymorphinan-6-carbonitrile



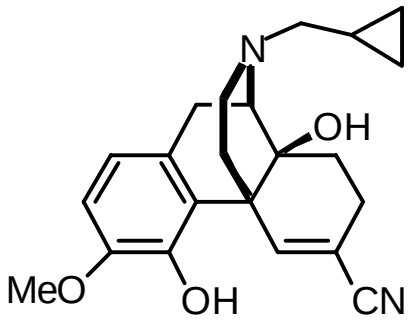
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 7.99 (2.78 - 22.84)[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 2.43 (0.89 - 6.62)[a]
4) **HP** - 13% at 1 , 25% at 10 and 13% at 30[a]

[a]Vehicle was 1% lactic acid aqueous solution.

Comment: NIH 11073 has weak analgesic properties. Whether or not it has opioid effects, would require further testing.

NIH 11074 7-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxy-3-methoxymorphinan-6-carbonitrile



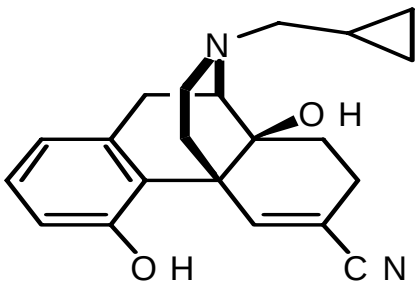
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 13.6 (6.7 - 27.5)
2) **TF vs. M** - 6% at 1, 0% at 10 and 11% at 30
3) **PPQ** - 5.84 (2.65 - 12.88)
4) **HP** - 13% at 1, 25% at 10 and 37% at 30

Vehicle was 1% lactic acid acid in water.

Comment: NIH 11074 is weakly active antinociceptively; however, additional testing would be required to characterize its mechanism of action.

NIH 11075 17-Cyclopropylmethyl-5,6-didehydro-4,14β -dihydroxymorphinan-6-carbonitrile



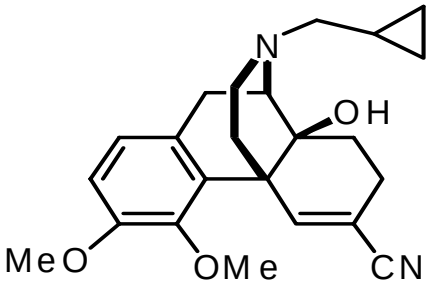
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** - 8.65 (2.16 - 34.64)[a]
2) **TF vs. M** - 0% at 1, 3% at 10 and 9% at 30
3) **PPQ** - 1.47 (1.15 - 1.89)[b]
4) **HP** - 0% at 1, 37% at 10 and 50% at 30[c]

[a]Slight ataxia.
[b]Rapid and heavy breathing; 1 convulsed and died at eight min.
[c]Labored breathing.
Vehicle was 1% lactic acid in water.

Comment: NIH 11075 has weak antinociceptive properties. Subtype testing might define its mechanism(s) of action.

NIH 11076 17-Cyclopropylmethyl-5,6-didehydro-14β -hydroxy-3,4-dimethoxymorphinan-6-carbonitrile



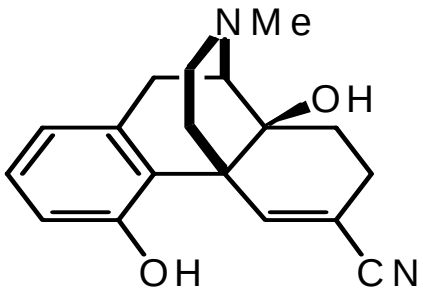
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** -7% at 1, 0% at 10 and 30
2) **TF vs. M** - 5.52 (2.01 - 15.16)
3) **PPQ** - 0% at 1, 50% at 2, 30% at 3, 40% at 5, 28% at 10, 53% at 20 and 74% at 30
4) **HP** - Inactive at 1[a]

[a] Insufficient drug for additional testing.
Vehicle was 1% lactic acid aqueous solution.

Comment: The evidence suggests that NIH 11076 is a weak mu-opioid receptor antagonist in the mouse. Drug supply was exhausted.

NIH 11077 5,6-didehydro-4,14β-dihydroxy-17-methylmorphinan-6-carbonitrile



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0.43 (0.33 - 0.56)[a,b]
2) **TF vs. M** - Inactive at 1, 10 and 30 [a,b,c]
3) **PPQ** - 0.13 (0.06 - 0.27)[a]
4) **HP** - 0.38 (0.15 - 1.0)[a]

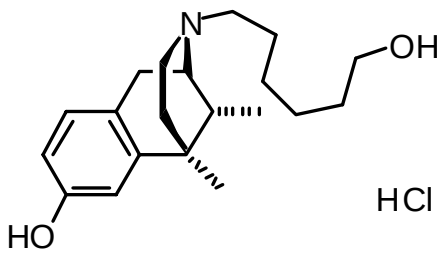
[a]Vehicle was 1% aqueous lactic acid.
[b]Straub tail.
[c]Increased locomotor activity at 10 and 30.

Opioid subtype testing:

Naltrindole (s.c.) vs ED80 of NIH 11077 in PPQ: 8% at 1, 8% at 3, 0% at 10 and 53% at 30.

Comment: The antinociceptive profile of activity and Straub tail suggest that NIH 11077 has mu-opioid receptor agonist activity. Potency is approximately 10 times that of morphine sulfate. It also has weak delta-opioid agonist properties.

NIH 11082 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1 and 10 and 20% at 30[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 1.93 (0.70 - 5.34)[a]
4) **HP** - Inactive at 1, 10, and 30[a]

[a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Opioid subtype testing:

a) Naltrindole (s.c.) vs ED80 of NIH 11082 in PPQ = 0.75 (0.26 - 2.20).

b) nor-BNI vs ED80 of NIH 11082 in PPQ = 0% at 9% at 10 and 26% at 30 mg/kg.

c) β-FNA vs ED80 of NIH 11082 in PPQ = 3% at 1, 9% at 3, 18% at 10 and 38% at 30 mg/kg.

Table 1. NIH 11082 ED80 time-course study in the PPQ assay

Dose (ED80) 10 mg/kg s.c.				
TIME	**20 min**	**1 hr**	**4 hr**	**6 hr**
% Inhibition	77	26	Inactive	Inactive

Table 2. Co-administration of ED50 of NIH 11082 and ED50 of morphine in the tail-flick assay

Treatment (ED50, mg/kg s.c.) in 10% hydoxypropyl β-cyclodextrin in water	**Percent Inhibition**
Morphine (4.0)	59
Morphine (4.0) + NIH 11082 (1)	54

Table 3. Co administration of ED50 of NIH 11082 and ED50 of morphine in the PPQ assay[a]

Treatment (ED50, mg/kg s.c.) in 10% hydoxypropyl β-cyclodextrin in water	**Percent Inhibition**
Morphine (0.35)	29
NIH 11082 (1.0)	43
Morphine (0.35) + NIH11082 (1.0)	89

[a] Preliminary

NIH 11082 (continued)

Table 4. Co-administration of ED25 of NIH 11082 and ED25 of morphine in the PPQ assay. (n = 12)

Treatment (ED 25, mg/kg sc) in 10% hydoxypropyl-β-cyclodextrin in water	Percent Inhibition
Morphine (0.3)	41
NIH 11082 (0.2)	13
Morphine (0.3) + NIH 11082 (0.2)	78

Table 5. Co-administration of ED50 of NIH 11082 and ED50 morphine in the PPQ assay. (n = 12)

Treatment (ED 50, mg/kg sc) in 10% hydoxypropyl-β-cyclodextrin in water	Percent Inhibition
Morphine (0.35)	49
NIH 11082 (6.0)	49
Morphine (0.35) + NIH 11082 (6.0)	87

MONKEY DATA (SDS)

As shown in the figure, NIH 11082 briefly attenuated withdrawal signs in morphine-dependent monkeys at a dose of 16 mg/kg.

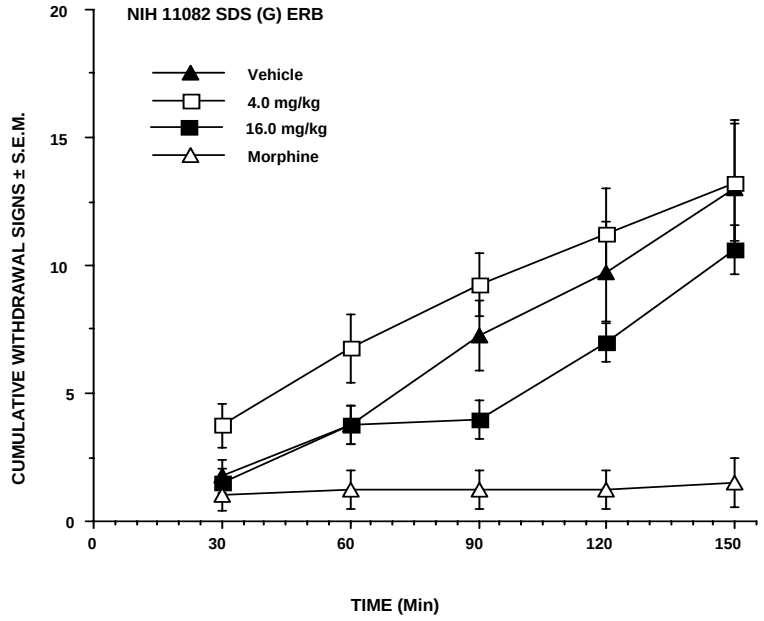


Fig NIH 11082 SDS. Results of study in which single doses of NIH 11082 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results indicate that NIH 11082 lacks significant mu-opioid properties in mice; and morphine-dependent monkeys. However, in mice, delta-opioid agonist activity is impressive. Unlike other delta-opioid agonists no convulsions were noted.

NIH 11086 Dynorphin analog

AcTyr-Lys-Trp-Trp-Le-Arg-Arg-D-Ala-Arg-Pro-Lys-NH2

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, µg/brain, i.c.v.

1) **TF** - 16% at 0.3, 42% at 1, 17% at 3, 29% at 10 and 8% at 30[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[b]
3) **PPQ** - 2% at 0.3, 36% at 1, 62% at 3 and 50% at10[c]
3) **HP** - Inactive at 1, 10 and

[a] At 30, 3/6 had slight tremors, 2/6 were heavily sedated.
[b]At 30, 2/6 were heavily sedated, 1/6 had slow righting reflex at 30.
[c]Insufficient drug to run higher doses.
[d]At 30, 1/6 had tremors, 2/6 whirled about on the hot-plate.

Comment: Although NIH 11086 showed some effects on the central nervous system in mice, antinociceptive activity was not evident. Insufficient drug supply precluded further testing.

NIH 11087 Dynorphin analog

AcPhe-Phe-Phe-Arg-Leu-Arg-Arg-D-Ala-Arg-Pro-Lys-NH2

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, µg/brain, i.c.v.

1) **TF** - 5% at 0.3, 27% at 1 and 24% at 3[a,d]
2) **TF vs. M** - Inactive at 1 and 10[b,d]
3) **PPQ** - 5% at 0.1, 45% at 0.3, 52% at 1 and 69% at 3[c,d]
4) **HP** - 25% at 1 and 2/8 were positive[e,d]

[a]At 3 ug/brain, tumbling in 5/6, immobility 1/6 and clonic convulsions in 2/6.
[b]At 10 ug/brain, loss of righting reflex and immobility in 2/6.
[c]At 3 ug/brain, immediate convulsion in 1/6 and intermittent convulsions thereafter.
[d]Insufficient drug for further testing.
[e]At 1 ug/brain, convulsion in 1/8, and tumbling in 2/8; At 3 ug/brain, 2/8 tested positive, 1/8 could not be tested, 1/8 died, 5/8 convulsed, 3/8 lost righting reflex and 2/8 were immobile.

Comment: Severe central nervous system effects precluded further testing of NIH 11087.

NIH 11090 Enkephalin analog

(D)-Phe-(D)Nal-(D)Nle-NLys-NH2

MOUSE DATA - ED50 OR AD50
(95 % C.L.) and % change, µg/brain, i.c.v.

1) **TF** - 0.29 (0.094 - 0.92) (i.c.v.)
2) **TF vs. M** -11% at 1 and inactive at 10 and 30 (i.c.v.)[a]
3) **PPQ** - 28% at 0.1, 59% at 0.3 and 1, 0% and 91% at 3, 47% at 10 and 91% at 30 (i.c.v.)[b]
4) **HP** - 13% at 1 and 3, 50% at 10 and 25% at 30 (i.c.v.)

[a]30 µg/brain, hunched backs in 4/6, rigidity in 2/6 and convulsions in 2/6.

[b]At 30 µg/brain, clonic extensions in 4/6, hunched backs and rigidity in 2/6 and convulsions in 1/6.

Comment: The evidence suggests that NIH 11090 is active antinociceptively. This drug might have mu- and/or delta-opioid receptor agonist activity. Because supply was exhausted, additional testing was not possible.

NIH 11091 Enkephalin analog

NhPhe-(D)Phe-(D)Nle-(D)Arg-NH2

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, □g/brain, i.c.v.

1) **TF** - 34% at 0.1, 59% at 0.3, 61% at 1, 55% at 3 and 68% at 10 (i.c.v.)[a]
2) **TF vs. M** - Inactive at 1 and10 (i.c.v.)[a,b]
3) **PPQ** - 2.14 (1.01 - 4.56) (i.c.v.)[a,c]
4) **HP** -13% at 1 and 38% at 10 (i.c.v.)[a,b,c]

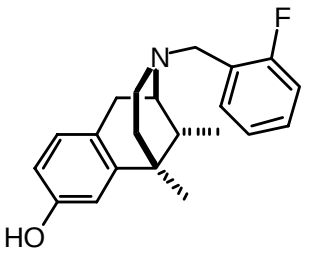
[a]At 10 µg/brain, 6/6 were sedated.

[b]At 10 µg/brain 1/6 convulsed.

[c]At 10 µg/brain, 3/8 moved in circles.

Comment: NIH 11091 is active antinociceptively in the PPQ test and has prominent central nervous system effects. Additional testing might provide insights regarding its mechanism of action.

NIH 11097 (-),(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate



$C_2H_2O_4$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, ug/brain,i.c.v.,or s.c.

1) **TF** - 14.8 (8.14 – 26.9) ug/brain,i.c.v.
   - Inactive at 1, 10 and 30, s.c.
2) **TF vs. M** - 0% at 1, 18% at 10 and 0% at 30
3) **PPQ** - 7% at 1, 10% at 10 and 27% at
4) **HP** - 13% at 1 and 10, 0% at 30

Vehicle was 20% hydroxypropyl-β-cyclodextrin in water

Opioid subtype testing:

Enadoline s.c. vs ED80 of NIH 11097 s.c. in TF; 20% at 1, 8% at 10 and 7% at 30 mg/kg.

NIH 11097 (continued)

MONKEY DATA (SDS)

Because of limited supplies, only 2 subjects per dose regimen were tested. These results suggest that NIH 11097 did not attenuate withdrawal or substitute for morphine and that it may have exacerbated withdrawal (see Fig).

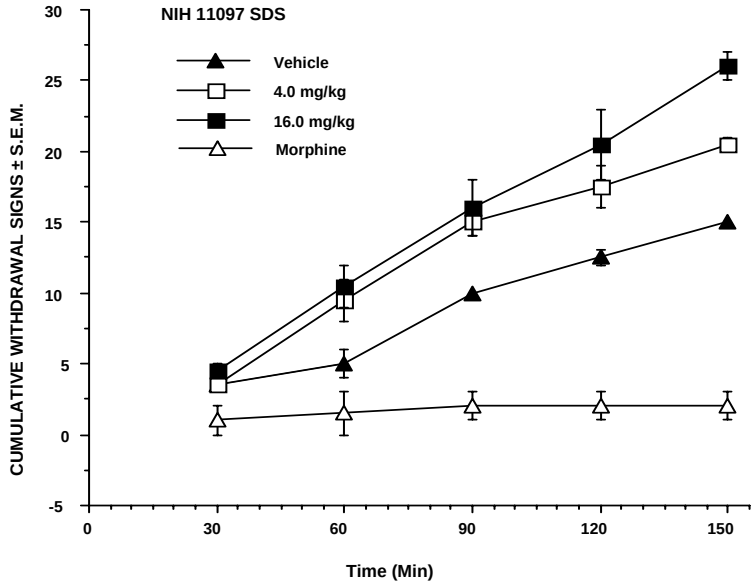
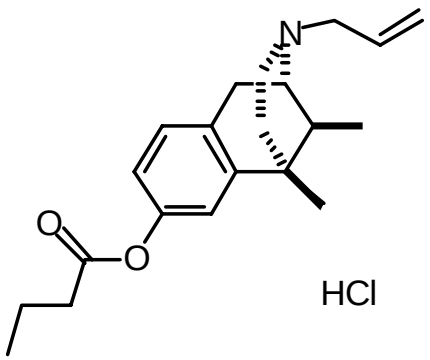


Fig NIH 11097-SDS. Results of study in which single doses of NIH 11097 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: This profile of activity is not indicative of significant mu-opioid receptor properties.

NIH 11098 (+),(1S,5S,9S)-2'-Butryoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30[a,d]
2) **TF vs. M** - Inactive at 1, 10 and 30[a,b,d]
3) **PPQ** - 9.6 (4.4 - 21.0)[a,c,d]
4) **HP** - Inactive at 1, 13% at 10 and inactive at 30[a,c,]

[a]At 30 mg/kg, ataxia and mild Straub tail.
[b]At 20 mg/kg, ataxia prior to morphine, Straub tail.
[c]Ataxia at 3, 10 and 30, increased respiration at 30.
[d]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water.

MONKEY DATA (SDS)

NIH 11098 attenuated withdrawal (see accompanying fig.). The response was dose related and delayed.

NIH 11098 (continued)

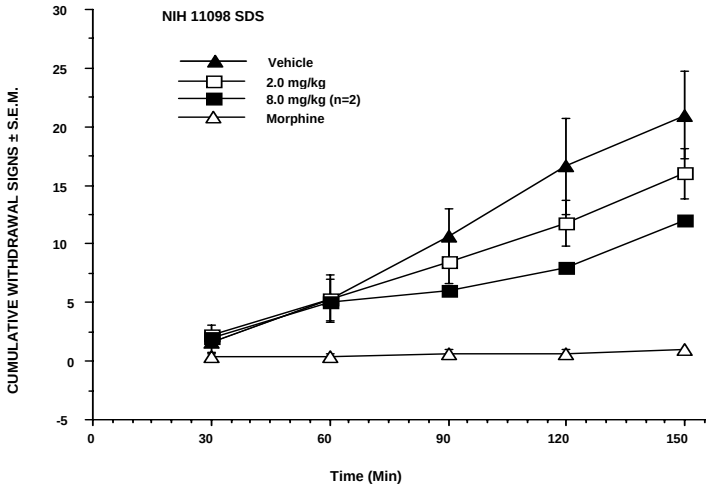
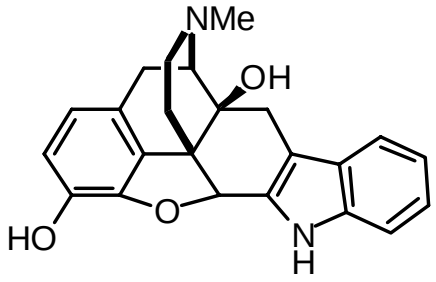


Fig NIH 11098-SDS. Results of study in which single doses of NIH 11098 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: This so-called Straub tail is probably associated with the ataxia. NIH 11098 does not display activity reminiscent of mu-opioid receptor agonists. However, it may have delta-opioid agonist activity.

NIH 11106 (BU 99041) N' -Benzyl-4,5,6,7-tetrahydrooxymorphindole



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,or μg/brain

1) **TF** - Not Tested
2) **TF vs. M** - Not tested
3) **PPQ** - 4.63 (1.55 – 13.8)
4) **PPQ - NIH 11106 vs NIH 10815 (SNC80)**
   a) - 0% at 10 and 30 mg/kg (s.c.)[a]
   b) Inactive at 1, 10 and 30 mg/kg (s.c.) [b]
   c) 21% at 1 and 53% at 10 μg/brain (i.c.v.)[b,c]
5) **HP** - Not Tested

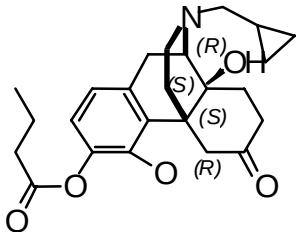
[a]30 min pretreatment and
[b] 24 hr pretreatment.
[c]At 30 μg /brain one mouse convulsed and another died.

Special Test:

Naloxone AD50 vs. ED80 of NIH 11106 in PPQ = 0.02 (0.031 - 0.047).

Comment: Initially, NIH 11106 had opioid agonist activity in the PPQ test. It exhibited delayed delta-opioid antagonist activity when given centrally.

NIH 11109 3-O-Butyrylnaltrexone.oxalate



$C_2H_2O_4$

MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30[a]
2) **TF vs. M** - 0.0029 (0.0013 - 0.0067)[a]
3) **PPQ** - Inactive at 1, 10 and 30[a]
4) **HP** - Inactive at 1, 10 and 30[a]

[a]Solubilized with sonification in 20% hydroxypropyl-β-cyclodextrin.

MONKEY DATA (SDS)

NIH 11109 did not substitute for morphine or attenuate withdrawal in morphine-dependent monkeys. Instead, it exacerbated withdrawal.

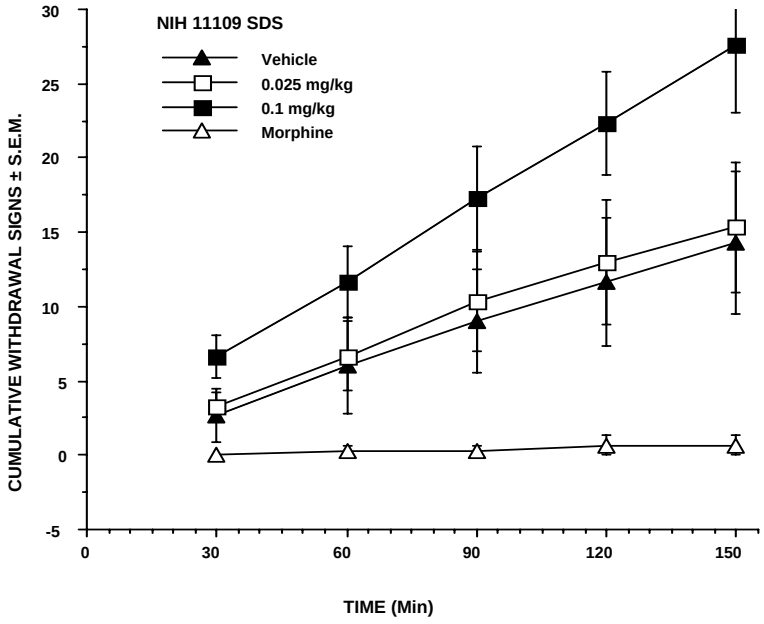
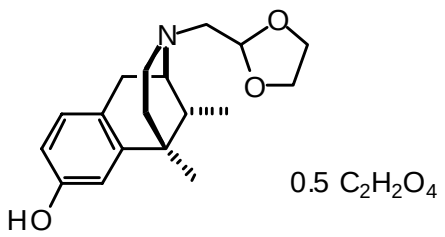


Fig NIH 11109-SDS. Results of study in which single doses of NIH 11109 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in mice and morphine-dependent monkeys indicate that NIH 11109 has potent mu-opioid antagonist properties.

NIH 11111 (-),(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanyl)-6,7-benzomorphan.hemioxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** -13% at 1, 12% at 10, and inactive at 30[a,c]
2) **TF vs. M** - 0.2 (0.06 - 0.65)[c]
3) **PPQ** - 1.85 (0.43 - 8.0)[a,c]
4) **HP** - Inactive at 2, 25% at 6 and inactive at 20 and 30[a,b,c]

[a]At 30 mg/kg, ataxia and sedation.
[b]At 20 mg./kg, slight ataxia and Straub tail.
[c]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Opioid subtype testing:

Nor-BNI (s.c.) vs ED80 of NIH 11111 in PPQ: 6% at 1, 22% at 3, 25% at 10 and 17% at 30.

<u>MONKEY DATA</u> (SDS)

At doses of 0.15 and 0.6 mg/kg, NIH 11111 neither substituted for morphine nor exacerbated withdrawal in morphine-dependent monkeys.

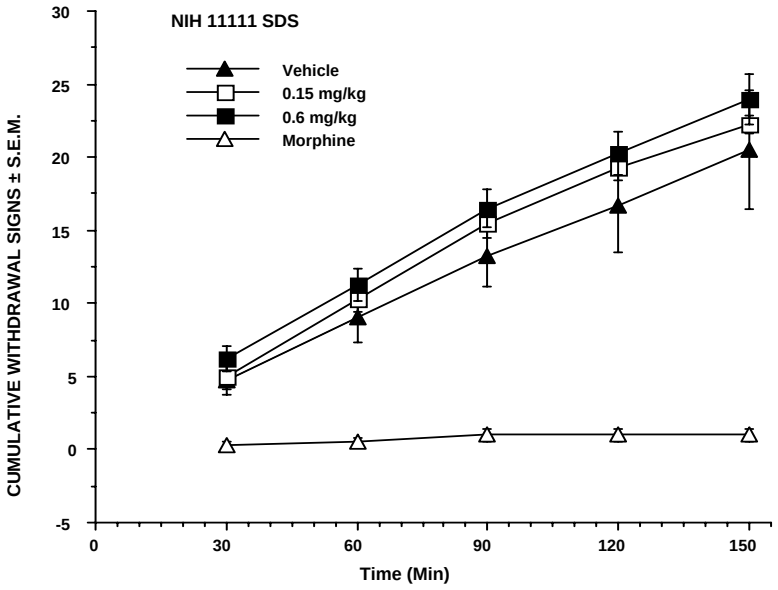
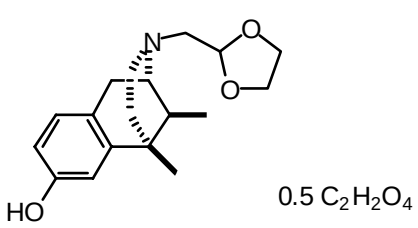


Fig NIH 11111-SDS. Results of a study in which single doses of NIH 11111 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11111 is active in the PPQ test and has mu-opioid antagonist effects in the mouse. This compound may also have delta opioid agonist activity.

NIH 11112 (+),(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanyl)-6,7-benzomorphan.hemioxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1 and 10, 4% at 30[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 23% at 1 and 10, 19% at 30[a]
4) **HP** - Inactive at 1, 10 and 30[a]

[a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water

<u>MONKEY DATA</u> (SDS)

Although the data illustrated in the figure seem provocative, no conclusion is possible because of insufficient supplies to test higher doses.

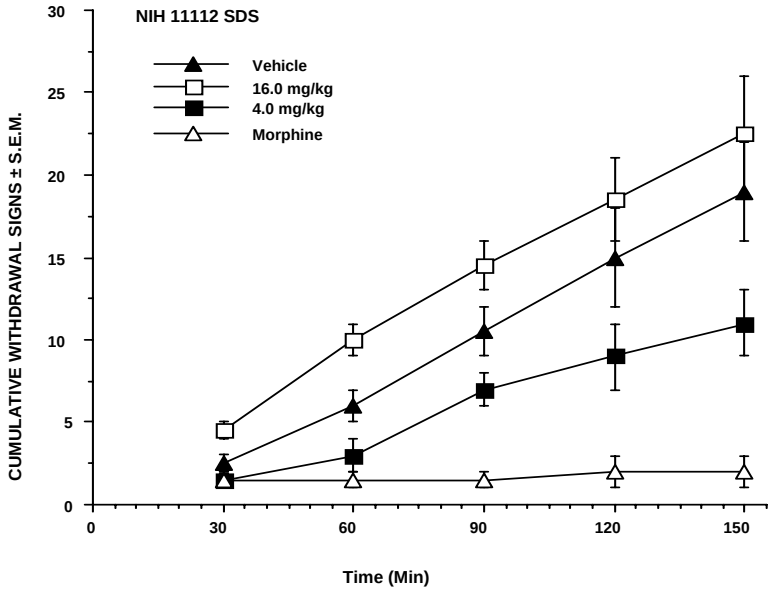
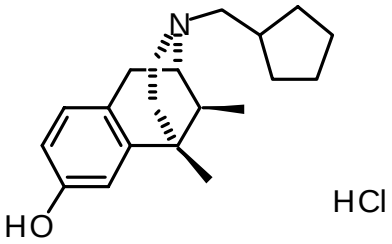


Fig NIH 11112-SDS. Results of study in which single doses of NIH 11112 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: As tested, NIH 11112 appears devoid of mu-opioid agonist/antagonist properties.

NIH 11113 (+),(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-cyclopentylmethyl-6,7-benzomorphan.HCl

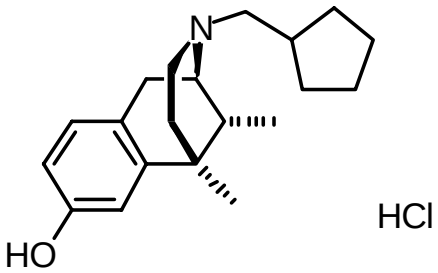


MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 7% at 1, 9% at 10 and 10% at 30
2) **TF vs. M** – Inactive at 1, 9% at 10 and 18% at 30
3) **PPQ** - 31% at 1, Inactive at 10 and 30
4) **HP** - Inactive at 1, 25% at 10 and inactive at 30

Comment: The profile of activity of NIH 11113 does not portend significant opioid agonist/antagonist activity.

NIH 11114 (-),(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-cyclopentylmethyl-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 16% at 1, 14% at 10 and 4% at 30[a,c]
2) **TF vs. M** - 2.44 (1.03 - 5.78)[a,c]
3) **PPQ** - 7.0 (2.73 - 18.56) [a,b,c]
4) **HP** - Inactive at 1, 3, 10 and 30[a,c]

[a]Vehicle was 20% hydroxypropyl-β-cyclodextrin in water.
[b]At 30 mg/kg, mild ataxia.
[c]This sample contained small black and brown particles.

Opioid subtype testing:

Nor-BNI (s.c.) vs ED80 of NIH 11114 in PPQ: 0% at 1, 12% at 3, 3% at 10 and 30.

MONKEY DATA (SDS)

As shown in the figure, NIH 11114 dose-dependently attenuated withdrawal in morphine-dependent monkeys at 1 and 4 mg/kg. However, at these doses it had little effect on two important withdrawal signs that are crucial for characterizing mu-opioid agonists in this test. It failed to block vocalization and abdominal muscle rigidity associated with abdominal palpation.

NIH 11114 (continued)

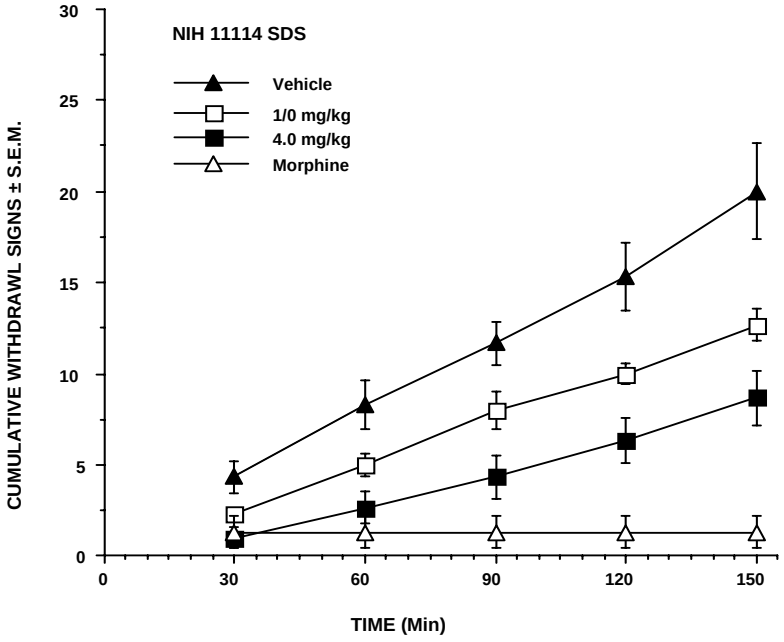
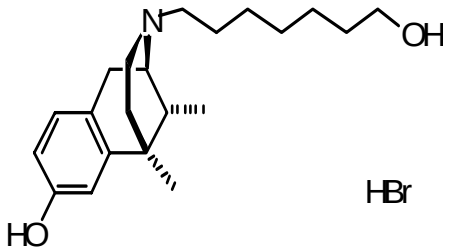


Fig NIH 11114-SDS. Results of study in which single doses of NIH 11114 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: In the mouse, NIH 11114 displayed agonist antinociceptive properties, lacking kappa-opioid agonist involvement. It also displayed weak mu-opioid antagonist effects. However, in morphine-dependent monkeys, neither agonist nor antagonist mu-opioid effects were evident because it failed to block vocalization when their abdomens were palpated and it failed to exacerbate withdrawal, respectively.

NIH 11127 (-),(1*R*,5*R*,9*R*)-5,9-dimethyl-2'-Hydroxy-2-(7-hydroxyheptyl)- 6,7-benzomorphan.HBr



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 20.0 (11.0 - 35.6)
2) **TF vs. M** - 16% at 1, 17% at 3 and inactive at 10 and 30
3) **PPQ** - 2.9 (1.37 - 6.25)
4) **HP** - Inactive at 1 and 10, 25% at 30

MONKEY DATA (SDS)

Although this compound lowered the incidence of withdrawal scores the results were not dose-related. In addition, the responses to abdominal palpation were not alleviated suggesting that NIH 11127 either lacked mu-opioid agonist properties or that a high enough dose was not tested.

NIH 11127 (continued)

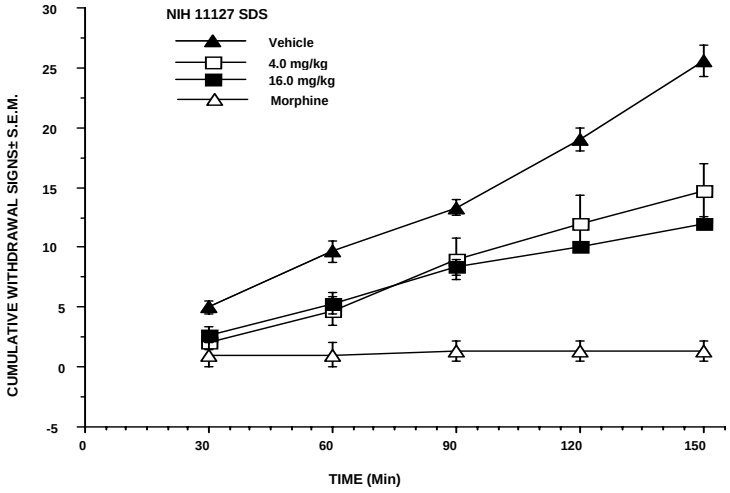
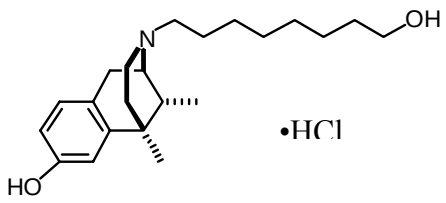


Fig NIH 11127-SDS. Results of study in which single doses of NIH 11127 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in mice and monkeys suggest that NIH 11127 does not have remarkable mu-opioid agonist or antagonist effects.

NIH 11139 (-),(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 4.4 (2.2 – 8.6)[a]
4) **HP** - 0% at 1 and 10, 13% at 30[a]

[a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water

<u>MONKEY DATA</u> (SDS)

Although NIH 11139 attenuated many withdrawal signs, it did not substitute completely for morphine because the monkeys had rigid abdominal muscles and vocalized when their abdomens were palpated.

NIH 11139 (continued)

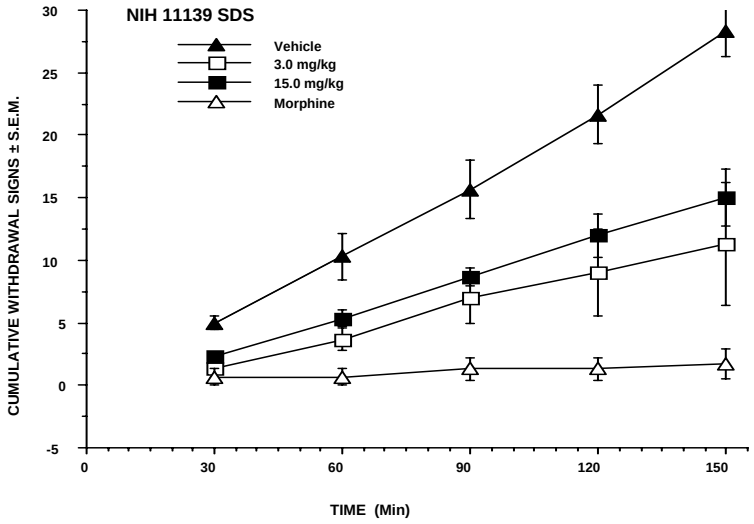
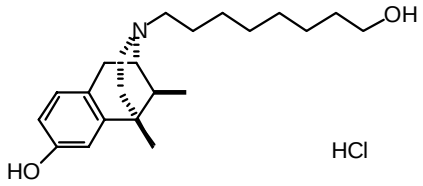


Fig NIH 11139-SDS. Results of study in which single doses of NIH 11139 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results do not portend remarkable mu-opioid agonist or antagonist properties. It may have delta-opioid agonist activity.

NIH 11140 (+),(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** – Inactive at 1, 10 and 30[a]
2) **TF vs. M** – Inactive at 1, 10 and 30[a]
3) **PPQ** – 41% at 1, 68% at 3, 38% at 10 and 30[a]
4) **HP** - Inactive at 1, 10 and 30[a]

[a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

MONKEY DATA (SDS)

As shown in the accompanying figure, at doses of 4 and 16 mg/kg, NIH 11140 neither substituted for morphine nor exacerbated withdrawal in withdrawn morphine-dependent monkeys.

NIH 11140 (continued)

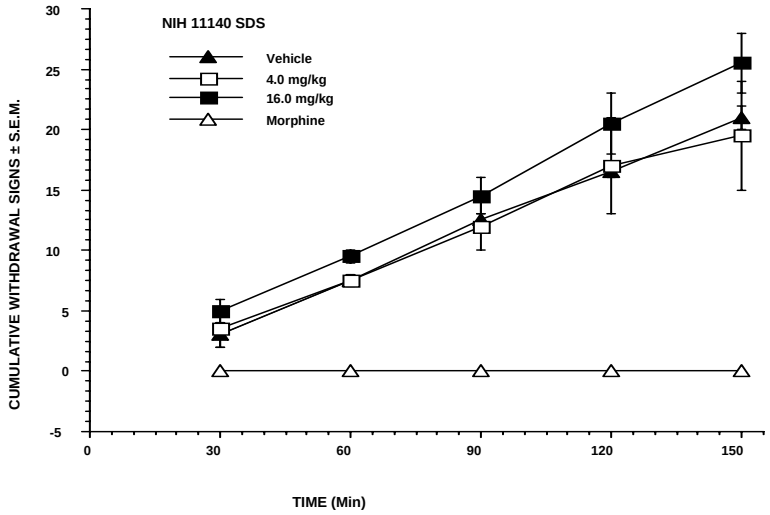
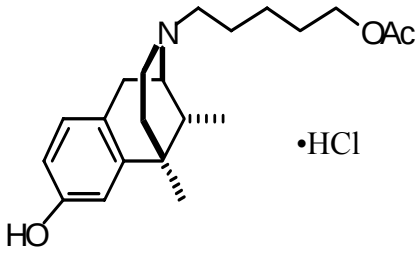


Fig NIH 11140-SDS. Results of study in which single doses of NIH 11140 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: This compound (NIH 11140) is essentially devoid of mu-opioid activity in both species.

NIH 11164 (-),(1R,5R,9R) -2-(5-Acetoxypentyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

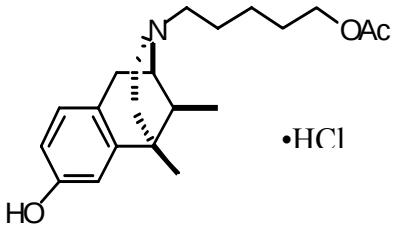


MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg.kg,s.c.

1) **TF** - 0% at 10, 16% at 10 and 48% at 30
2) **TF vs. M** - 16% at 1, 23% at 10 and 11% at 30
3) **PPQ** - 8.36 (3.02 - 23.1)
4) **HP** - 0% at 1 and 10, 13% at 30

Comment: These data suggest very weak, if any, mu-opioid properties. NIH 11164 may have delta-opioid agonist effects.

NIH 11165 (+),(1S,5S,9S)- 2-(5-Acetoxypentyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

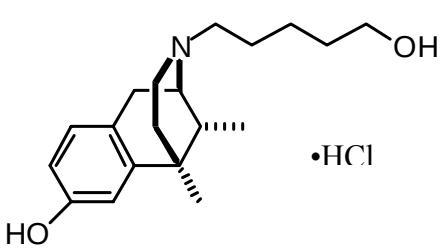


MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - 0% at 1 and 10, 14% at 30
4) **HP** - Inactive at 1, 10 and 30

Comment: Most likely, NIH 11165 is devoid of opioid properties.

NIH 11166 (-),(1R,5R,9R)- 5,9-Dimethyl-2'-hydroxy-2-(5-hydroxypentyl)-6,7-benzomorphan.HCl

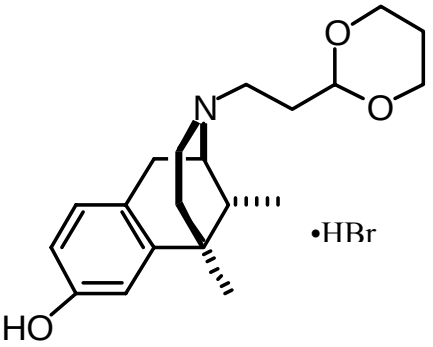


MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - 19% at 1, 11% at 10 and 8% at 30
4) **HP** - 0% at 1, 13% at 10 and 0% at 30

Comment: These results do not predict opioid activity for NIH 11166.

NIH 11167 (-),(1R,5R,9R)- 5,9-Dimethyl-2-(1,3-dioxanylethyl)- 2'-hydroxy-6,7-benzomorphan.HBr

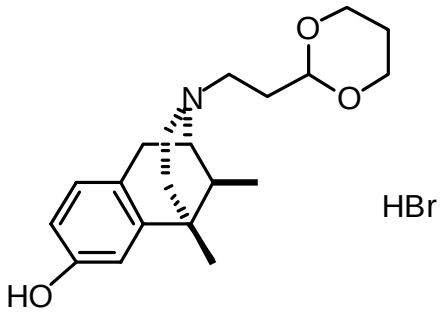


MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 0% at 1, 10% at 10 and 41% at 30
2) **TF vs. M** - 3% at 1, 16% at 10 and 9% at 30
3) **PPQ** - 5.48 (3.05 - 9.86)
4) **HP** - Inactive at 1, 10 and 30

Comment: These results do not indicate that NIH 11167 has mu-opioid properties; however delta-opioid effects have not been ruled out.

NIH 11168 (+),(1S,5S,9S)- 5,9-Dimethyl-2-(1,3-dioxanylethyl)- 2'-hydroxy-6,7-benzomorphan.HBr

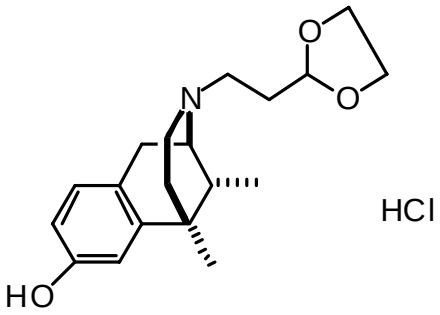


MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - 2% at 1, 8% at 10 and 0% at 30
3) **PPQ** - 21% at 1, 47% at 10 and 41% at 30
4) **HP** - 0% at 1 and 10, 13% at 30

Comment: Very weak, if any, opioid activity is apparent.

NIH 11176 (-),(1R,5R,9R)- 5,9-Dimethyl-2-(1,3-dioxalanylethyl)- 2'-hydroxy-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change. mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - Inactive at 1, 10 and 30
4) **HP** - Inactive at 1, 10 and 30

MONKEY DATA (SDS)

NIH 11176 dose dependently attenuated withdrawal in morphine-dependent monkeys at 3 and 12 mg/kg (see fig). Unfortunately, drug supply was exhausted and additional doses could not be tested.

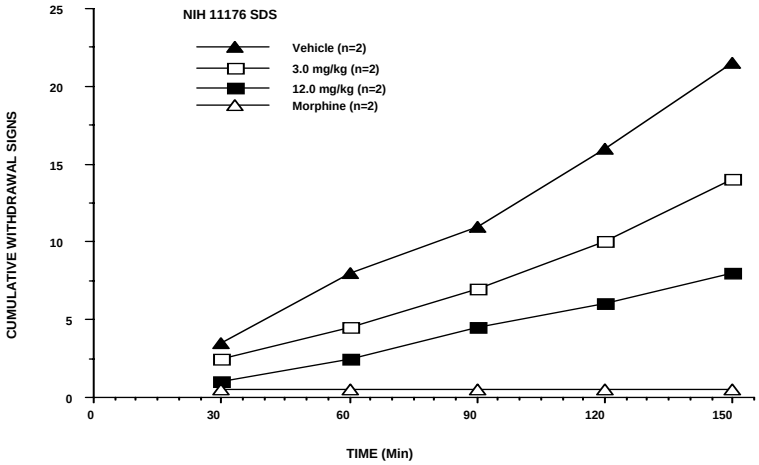
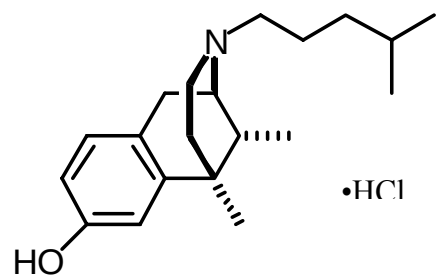


Fig NIH 11176-SDS. Results of study in which single doses of NIH 11176 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The drug appears inactive in the mouse and produces some attenuation of withdrawal signs in the monkey. However, insufficient supplies did not permit a full evaluation.

NIH 11179 (-),(1R,5R,9R)- 5,9-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** -10.25 (4.68 – 22.45)[a]
2) **TF vs. M** - Inactive at 1, 10 and 30[a]
3) **PPQ** - 2.70 (1.20 – 6.08)[a]
4) **HP** - 13% at 1, 10 and 30[a]

[a]Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

NIH 11179 (continued)

MONKEY DATA (SDS)

In the preliminary test, cumulative doses of 1, 2 and 4 mg/kg, spaced 15 min apart, respectively, NIH 11179 produced tremors and convulsions of short duration.

As depicted in the figure, some non dose-related attenuation of withdrawal signs was observed in the SDS assay. It should be noted that tremors were observed in 1 monkey and, brief convulsions, in another, receiving the high dose.

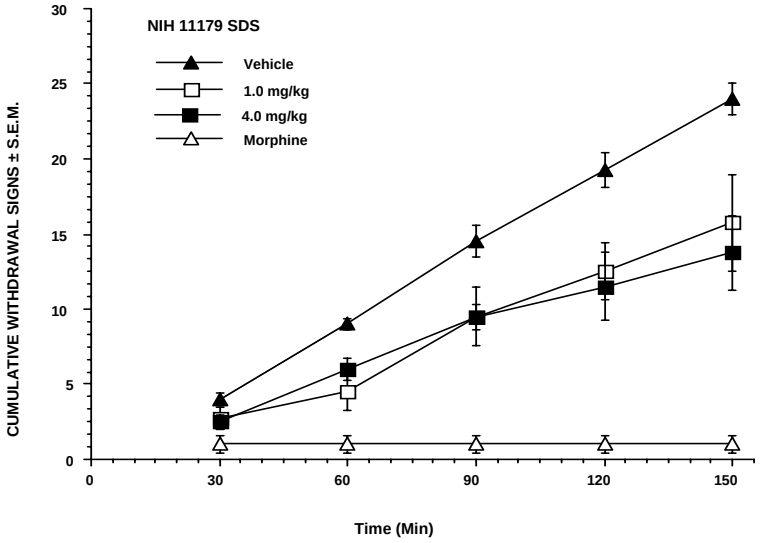
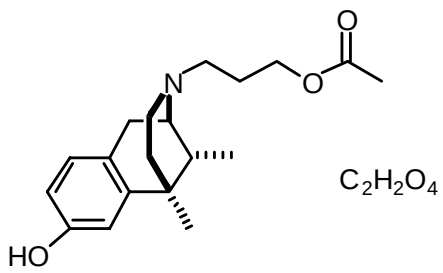


Fig NIH 11179-SDS. Results of study in which single doses of NIH 11179 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Further work would be required to characterize NIH 11179.

NIH 11180 (-),(1*R*,5*R*,9*R*)-2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - 4.83 (3.77 – 6.19)
2) **PPQ** - 2% at 1, 34% at 10 and 45% at 30
3) **HP** - 0% at 1 and 10, 13% at 30

MONKEY DATA (PPt-W)

As shown in the accompanying figure, a dose-related precipitated withdrawal was observed. Onset of action was prompt and duration of action was at least as long as that of naloxone, Eyelid ptosis, slowing and ataxia were observed at both doses. Potency estimate is 1/100 that of naloxone.

NIH 11180 (continued)

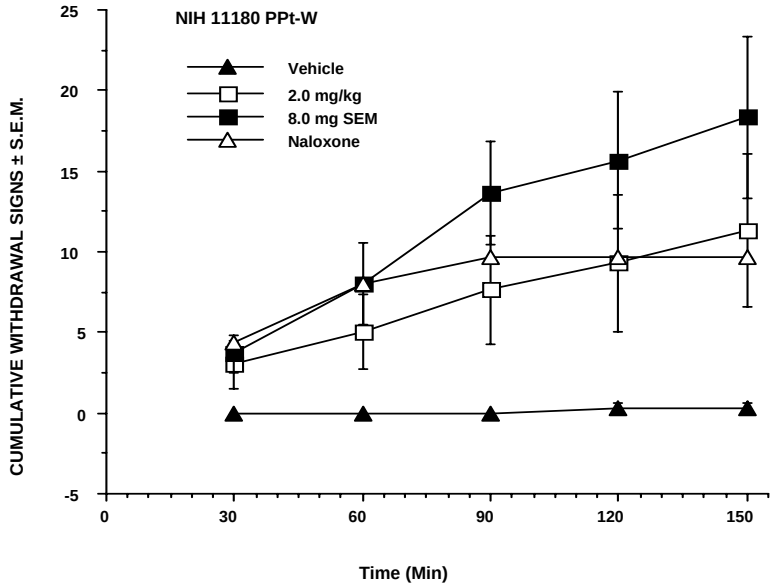
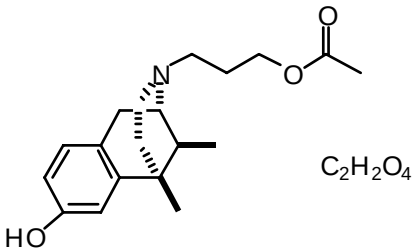


Fig. NIH 11180-PPt-Withdrawal. Results of study in which morphine-dependent monkeys were given single doses of NIH 11180 two hr after morphine.

Comment: The results in mice and monkeys suggest weak mu-opioid antagonist properties. It is possible that NIH11180 may also have some weak kappa- and delta-opioid antagonist effects.

NIH 11181 (+),(1*S*,5*S*,9*S*)-2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - 0% at 1, 7% at 10 and 0% at 30
4) **HP** - Inactive at 1, 10 and 30

<u>MONKEY DATA</u> (SDS)

Because of limited supplies, only 2 monkeys per dose regimen were tested. In spite of the large standard deviations, NIH 11181 appeared to attenuate withdrawal signs in rhesus monkeys in spontaneous withdrawal.

NIH 11181 (continued)

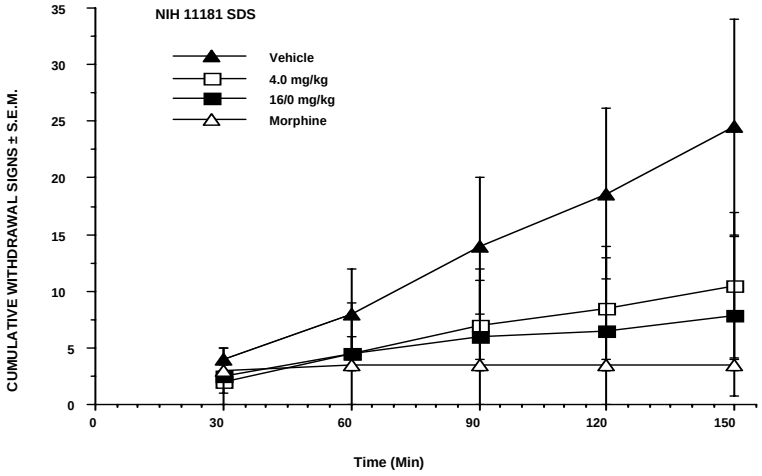
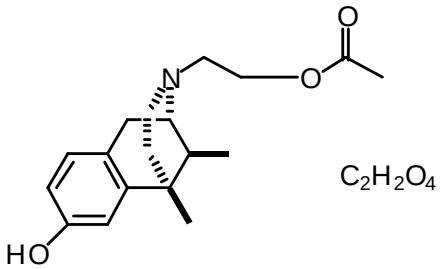


Fig NIH 11081 SDS. Results of study in which single doses of NIH 11081 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Overall, these results do not indicate that NIH 11181 has mu- opioid properties.

NIH 11182 (+),(1*S*,5*S*,9*S*)-2-(2-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

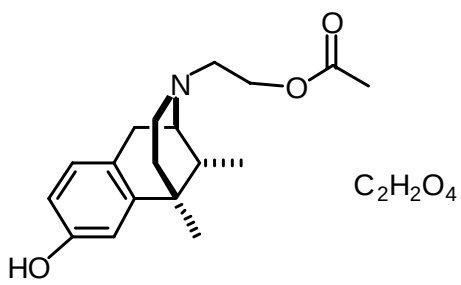
1) **TF** - Inactive at 1,10 and 30
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - 4.74 (3.22- 6.97)
4) **HP** - Inactive at 1,10 and 30

<u>MONKEY DATA</u> (SDS-Preliminary Study)

Limited supplies, permitted a preliminary study only. Over a period of 45 min, doses of 1, 2, 4, and 8 mg/kg, given at 15 min intervals respectively, produced no remarkable effects in morphine-dependent rhesus monkeys.

Comment: These results do not predict kappa- or mu-opioid agonist effects. However, they do not exclude delta-opioid properties. If warranted, subtype testing with naltrindole would settle the issue.

NIH 11183 (-),(1R,5R,9R)- 2-(2-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change. mg/kg,s.c.

1) **TF** - Inactive at 1, 10 and 30
2) **TF vs. M** - 8.76 (4.01 – 29.17
3) **PPQ** - 10.23 (0.57 – 186.5)
4) **HP** - 12.5% at 1, Inactive at 10 and 30

NIH 11183 (continued)

MONKEY DATA (SDS)

At doses of 4 and 16 mg/kg, NIH 11183 did not substitute for morphine. Instead, it exacerbated withdrawal. Due to limited supplies, only 2 monkeys were tested at the high dose regimen. Thus, the cumulative number of withdrawal signs in the figure was lower when compared to vehicle because the latter treatment group consisted of 5 subjects.

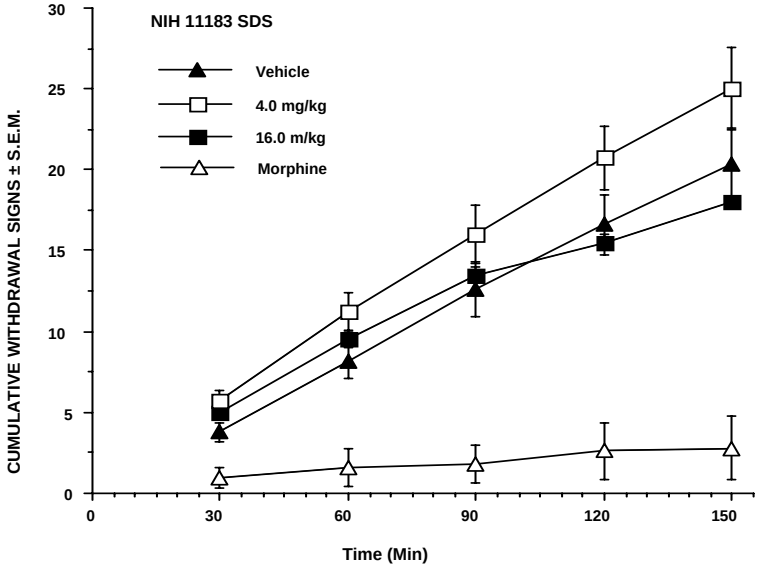
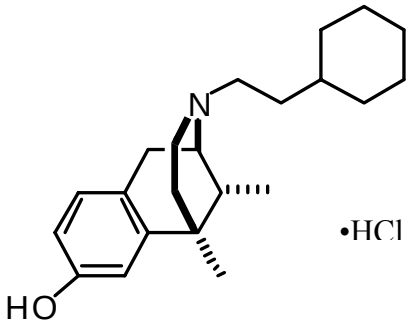


Fig NIH 11183-SDS. Results of study in which single doses of NIH 11183 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The evidence indicates that NIH 11183 has rather weak mu-opioid antagonist properties.

NIH 11185 (-),(1R,5R,9R)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 3.0 (2.4 - 3.8)[a,c]
2) **TF vs. M** - Inactive at 1, 10 and 30[a,c]
3) **PPQ** -1.21 (0.69 - 2.17)[a,c]
4) **HP** - 8.50 (1.18 - 61.37)[b,c]

[a]Vehicle was sterile water (with sonification).
[b]Vehicle was 0.1% HCl.
[c]Straub tail and increased locomotor activity.

MONKEY DATA (SDS)

As shown in the figure, NIH11185 attenuated withdrawal signs in monkeys in spontaneous withdrawal at doses of 1.5 and 6.0 mg/kg. Complete substitution was not seen.

NIH 11185 (continued)

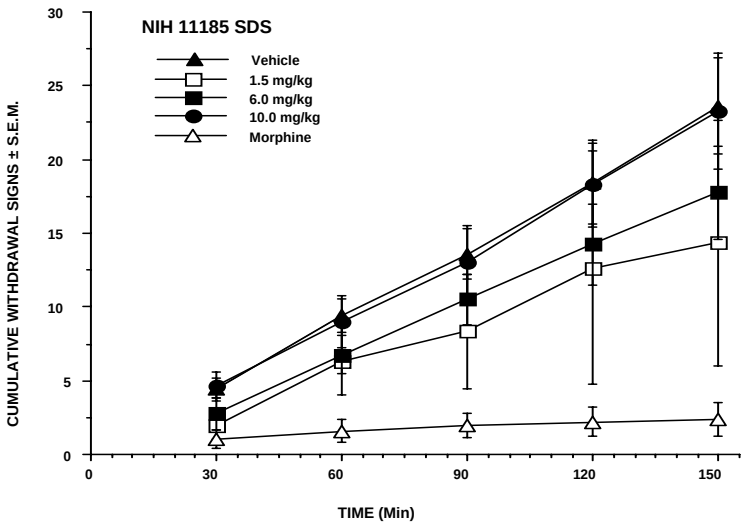
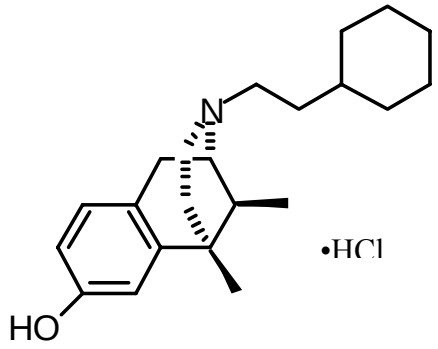


Fig NIH 11185-SDS. Results of study in which single doses of NIH 11185 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Overall, the results indicate that NIH 11185 has mu-opioid agonist properties.

NIH 11186 (+),(1S,5S,9S)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

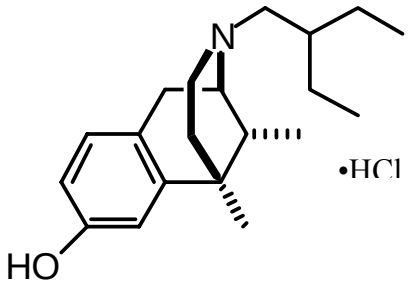
1) **TF** - 0% at 1, 2% at 10 and 17% at 30a
2) **TF vs. M** - Inactive at 1, 10 and 30
3) **PPQ** - 17.95 (2.08 – 154.85)
4) **HP** - 0% at 1, 12.5% at 10 and 0% at 30
   [a]Slightly ataxic at 30 mg/kg.

<u>MONKEY DATA</u> (SDS)

Only one experiment could be conducted because drug supply was exhausted. At 4 mg/kg, the monkey behaved essentially as the vehicle control. One-half hr after receiving 16 mg/kg, convulsions were noted in one monkey. The convulsions were quickly terminated following an injection of pentobarbital.

Comment: These results do not portend mu- and or kappa-opioid agonist or mu-opioid antagonist properties. Further testing in the mouse might reveal delta-opioid agonist effects.

NIH 11187 (-),(1R,5R,9R)-2-(2-Ethylbutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg,s.c.

1) **TF** - 2.21 (1.69 – 2.90)[a,b]
2) **TF vs. M** - 10% at 1, 0% at 10 and 30% at 30[a,c]
3) **PPQ** - Inactive at 0.3, 48% at 0.6. 50% at 1 and 98% at 3
4) **HP** - 12.5% at 1, 25% at 10 and 37.5% at 30[a,b,c]

[a]Straub tail at 10 and 30, [b]Increased locomotor activity at 10, and [c]Ataxia at 30.

MONKEY DATA (SDS)

At doses of 1 and 4 mg/kg, NIH 11187 substituted completely for morphine (see accompanying figure). Dose-related signs designated slowing, ataxia, jaw sag and eyelid ptosis were observed.

This cluster of side effects along with its ability to substitute for morphine usually heralds mu- and kappa-opioid agonist activity.

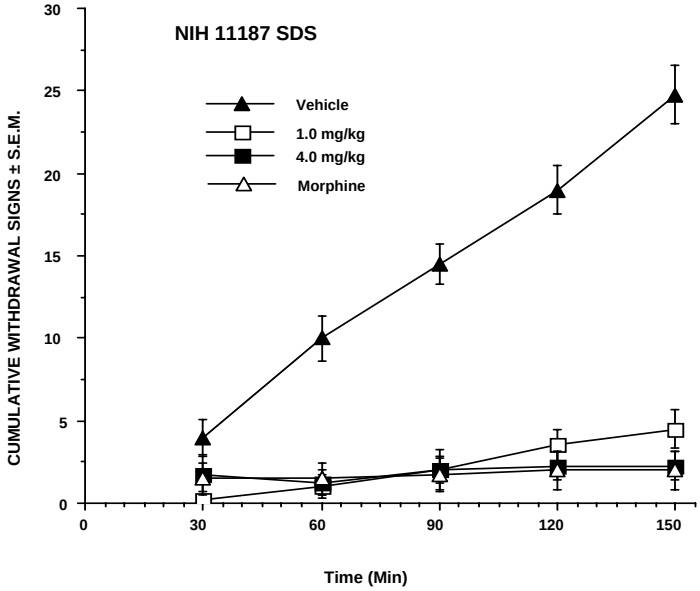


Fig NIH 11187-SDS. Results of study in which single doses of NIH 11187 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profiles of activity in mice and rhesus monkeys suggest that NIH 11187 has mixed opioid effects, probably mu- and kappa. Some weak mu opioid-antagonist effects were also observed at the highest dose in mice.

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