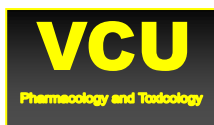


**EVALUATION OF NEW COMPOUNDS IN THE
RHESUS MONKEY, RAT AND MOUSE
(2005)**

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**Supported by NIDA Contract DA 1-7725
Conducted under the auspices of the
Drug Evaluation Committee (DEC)
in association with
The College on Problems of Drug Dependence (CPDD)**

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EVALUATION OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (2005)

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The identity of compounds submitted by the Biological Coordinator, Dr. Andrew Coop of the University of Maryland 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 1. 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·SO₄ 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. Withdrawal signs were scored, absent or present, once during each of five consecutive, 30 min observation periods. Withdrawal signs included: slowing of movement, drowsiness (sitting with eyes closed and lethargic or being indifferent to surroundings), fighting, vocalizing, rigidity of abdominal muscles, vocalization during palpation of abdominal muscles, restlessness (pacing), tremors, coughing, retching, vomiting, wet-dog shakes and masturbation. The observer was "blind" regarding the assignment of treatments. The mean cumulative score \pm SEM was calculated for each observation period 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
11111	6,7-Benzomorphan	T	T	T	T ^a	T	
11116	4,5-Epoxyomorphan	T _b	T	T	T		
11117	4,5-Epoxyomorphan	T ^c	T	T	T		
11118	4,5-Epoxyomorphan	T	T	T	T		
11119	Morphinan-6-one	T _d	T	T	T		
11120	4,5-Epoxyomorphan	T	T	T	T		
11121	4,5-Epoxyomorphan	T _e	T	T	T	T	
11127	6,7-Benzomorphan	T	T	T	T	T	
11130	4,5-Epoxyomorphan	T	T	T	T		
11131	4,5-Epoxyomorphan	T	T	T	T		
11132	4,5-Epoxyomorphan	T	T	T	T		
11133	3-Methoxyomorphan	T	T	T	T		
11134	Trimethoxyomorphan	T	T	T	T		
11135	3-Methoxyomorphan	T	T	T	T		
11136	3,4-Dimethoxyomorphan	T	T	T	T		
11137	Morphinan-6-one	T	T	T	T		
11139	6,7-Benzomorphan	T	T	T ^f	T	T	
11144	4,5-Epoxyomorphan	T	T	T	T		
11146	Dihydrothevinone	T	T	T	T		
11149	4,5-Epoxyomorphan	T	T	T	T		
11150	4,5-Epoxyomorphan	T	T	T	T		
11151	Morphinan-6-one	T	T	T	T		
11152	Morphinan-6-one	T	T	T	T		
11153	Morphinan-6-one	T	T	T	T		
11154	4,5-Epoxyomorphan	T	T	T	T		
11164	6,7-Benzomorphan	T	T	T ^g	T	T	
11167	6,7-Benzomorphan	T	T	T ^h	T		
11172	Hydroxyorvinol	T	T	T	T		
11173	Hydroxyorvinol	T	T	T	T		
11174	Hydroxyorvinol	T	T	T	T		
11175	Hydroxyorvinol	T	T	T	T		
11185	6,7-Benzomorphan	T	T	T	T	T	

11186	6,7-Benzomorphan	T	T	T ⁱ	T	T	
11188	6,7-Benzomorphan	T	T	T	T	T	
11189	6,7-Benzomorphan	T	T	T ^j	T	T	
11190	6,7-Benzomorphan	T	T	T	T	T	
11191	6,7-Benzomorphan	T	T	T	T	T	
11192	6,7-Benzomorphan	T	T	T	T	T	
11194	6,7-Benzomorphan	T	T	T	T	T	
11195	6,7-Benzomorphan	T	T	T	T	T	
11196	6,7-Benzomorphan	T	T	T	T	T	
11197	6,7-Benzomorphan	T	T	T	T	T	
11209	6,7-Benzomorphan	T	T	T	T	T	
11210	6,7-Benzomorphan	T	T	T	T	T	
11212	6,7-Benzomorphan	T	T	T	T	T	
11213	6,7-Benzomorphan	T	T	T	T		
11214	Methylorvinol	T ^k	T	T	T		
11215	Tetrahydrooripavine	T	T	T	T		
11216	Indolomorphinan	T	T	T	T		
11217	Indolomorphinan	T	T	T	T		
11218	Morphinan-6-one	T	T	T	T		
11219	4,5-Epoxyisomorphinan	T	T	T	T		
11220	Naphthylbutyric acid	T	T	T	T		
11228	Salvinorin A	T	T	T	T		
11230	Hydrocodone	T	T	T	T	T	
11231	6,7-Benzomorphan	T	T	T	T		
11235	Naphthylbutyric acid	T	T	T	T		
11247	Carboxyoxycodone	T	T	T	T		
11248	Carboxyoxycodone ethylether						
11251	SR 141716 Rimonabant					T	
11252	Cannabidiol					T	

T = Test Performed

^aSpecial: NIH 11111 vs norBNI and naltrindole in PPQ.; ^bSpecial: NIH 11116 vs naltrindole in TF; ^cSpecial: NIH 11117 vs naloxone in TF; ^dSpecial: NIH 11119 vs □□□□□□□□□□T□; ^eNIH 11121 vs naltrexone, b-FNA, nor-BNI and naltrindole in TF; ^fSpecial: NIH 11139 vs naltrindole in PPQ; ^gSpecial: NIH 11164 vs naltrindole in PPQ; ^hSpecial: NIH 11167 vs naltrindole in PPQ; ⁱSpecial: NIH 11186 vs naltrindole in PPQ; ^jSpecial: NIH 11189 vs naltrindole in PPQ; ^kSpecial duration of action study: NIH 11214 vs morphine in TF; ^kNIH 11214 vs morphine in TF.

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 that allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe that was attached to a syringe pump. The animals received 7-10 ml of solution every 24 hr. During withdrawal, the following signs were noted: irritability; front-paw shakes; wet-dog shakes; facial rubbings with front paws; eyelid ptosis and immobility.

Substitution-for-Morphine (SM) Test. The rats received morphine-SO₄ (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 ICR mice, weighing 20-30 g, were used. All drugs were dissolved in sterile water or in a suitable vehicle and usually injected by the subcutaneous (s.c.) route of administration. Other routes when employed were so indicated in the report. 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 light stimulus was turned on, it focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed through 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 1.0 ^a	0.03 (0.02 - 0.78)	0.01 (0.005 - 0.03)	25% at 9.0
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·SO ₄ ^b	1.92 (0.89 - 4.14)	Inactive	0.4 ^b (0.2-0.8)	0.85 (0.39 -1.86)
Codeine·PO	17.5 (15.4 - 19.9)	Inactive	8.25 (5.12 -13.29)	6.4 (2.4 -16.8)
Enadoline ·HCl (NIH 10672)	0.015 (0.003 – 0.059)	Inactive	0.0015 (0.0004 – 0.006)	0.01 (0.004 – 0.04)

^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 pA₂ 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. ED₅₀s 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 - 1) were plotted. The pA₂ 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 pA₂ values^a using the mouse tail-flick assay

<u>Treatment</u>	<u>Schild Plot</u>	<u>Constrained Plot</u>
Antagonist/Agonist	pA ₂ (95% C.L.) Slope	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	-

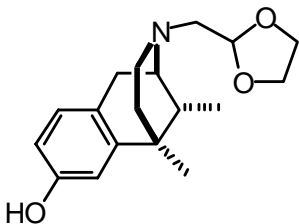
^aNegative logarithm of the molar concentrations of antagonist required to produce a two-fold shift of the agonist dose-response curve to the right. Competitive antagonism can be assumed when slope = -1. pA₂ provides a measure of the relative potency and affinity of the antagonist. When the slope differs 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 test 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 11111, (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxolanlyl)-6,7-benzomorphan.hemioxalate



MOUSE DATA - ED50 OR AD50

(95 % C.L.) or % change, mg/kg s.c.

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

At 10 and 30 mg/kg ataxia and sedation were noted and at 10 mg/kg ataxia and Straub tail were observed. Vehicle was 10% hydroxypropyl-beta-cyclodextrin in water.

Opioid subtype testing:

AD50 or %Antagonism by opiate subtype antagonist (s.c.) vs ED80 of NIH 11111 (s.c.) in PPQ	
Antagonist	Results- mg/kg/s.c.
norBNI (kappa)	6% at 1, 22% at 3. 25% at 10 and 17% at 30
Naltrindole (delta)	Inactive at 1, 10 and 30

MONKEY DATA – SDS

As shown in the accompanying figure, at doses of 0.15 and 0.6 mg/kg, NIH 11111 neither substituted for morphine nor exacerbated withdrawal in morphine-dependent monkeys.

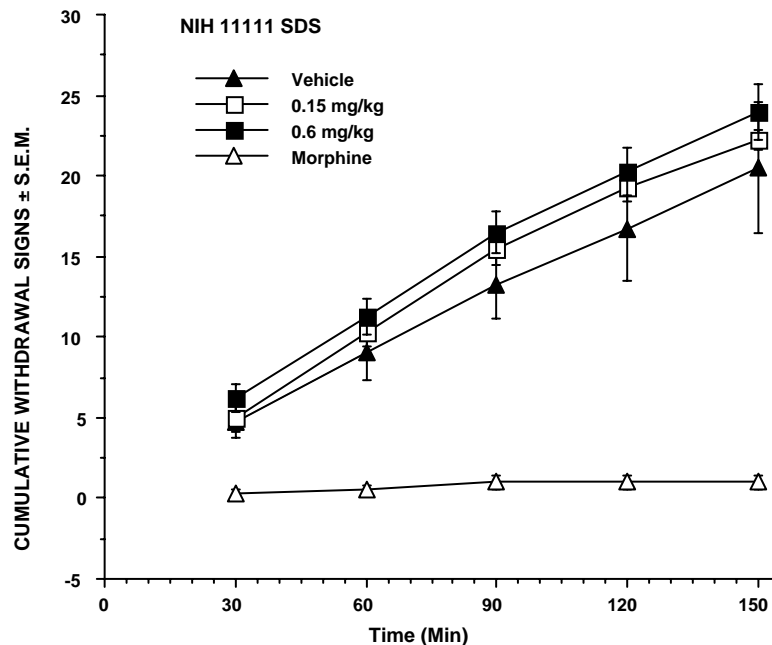
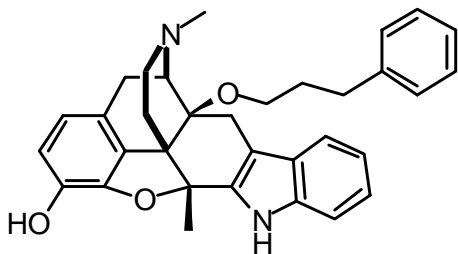


Fig NIH11111-SDS. Results of study in which single doses of NIH 11111 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11111 is active in the PPQ test and has some opioid antagonist effects in the tail-flick test. Kappa-and delta-opioid receptor agonist properties are not remarkable. Antagonist potency is about 1/10 that of naloxone, the reference standard. The Straub tail is probably an artifact associated with CNS effects. In the monkey, evidence regarding antagonist activity is not supported statistically. Perhaps higher doses or a precipitated withdrawal test might have produced a more robust withdrawal syndrome.

NIN 11116, 4,5 α -Epoxy-5 β ,17-dimethyl-14 β -[(3- phenylpropyl)oxy]-indolo-[2',3':6,7]morphinan-3-ol



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

- 1) **TF** – 10.36 (4.13 - 26.01)
- 2) **TF vs. M** – 29% at 0.01, 8% at 0.1, 12% at 1 and inactive at 10 and 30
- 3) **PPQ** – 6.45 (3.26 - 12.78)
- 4) **HP** – 8.78 (4.35 - 17.75)

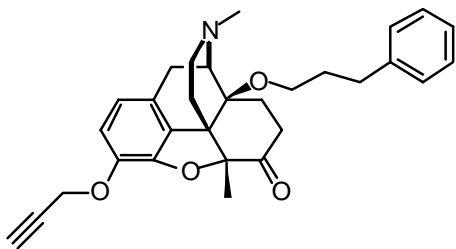
At 30 mg/kg sedation was noted in TF test. In the TF vs M, PPQ and HP tests, Straub tail and increased locomotor activity were evident. Vehicle was 1% lactic acid in water.

Opioid subtype testing:

AD50 or %Antagonism by an opiate subtype antagonist (s.c.) vs ED80 of NIH 11116 (s.c.) in TF	
Antagonist	Results-mg/kg/s.c.
Naltrindole (delta)	Inactive at 1, 10 and 30

Comment: This profile suggests mu-opioid agonist activity.

NIH 11117, 4,5 α -Epoxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy]-3-[(prop-2-ynyl)oxy]morphinan-6-one.HCl



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

- 1) **TF** – 0.02 (0.01 - 0.04)
- 2) **TF vs. M** – Inactive at 0.1, 1, 10 and 30
- 3) **PPQ** - 0.009 (0.0045 – 0.012)
- 4) **HP** – 0.038 (0.016- 0.09)

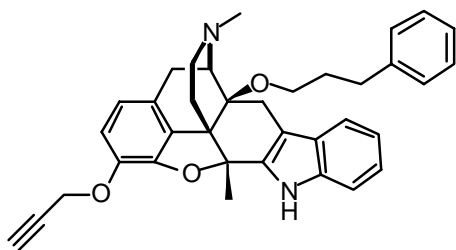
In the dose range 0.01 to 1 mg/kg, Straub tail was evident. Increased locomotor activity and ataxia were observed at 1 mg/kg. Vehicle was 1% lactic acid in water.

Special Test:

AD50 or %Antagonism by an opiate antagonist (s.c.) vs ED80 of NIH 11117 (s.c.) in TF assay	
Antagonist	Results-mg/kg/s.c.
Naloxone	0.036 (0.013 – 0.10)

Comment: This profile of activity is typical of mu-opioid receptor agonists. Potency is about 100 times that of morphine sulfate.

NIH 11118, 4,5 α -Epoxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy]-3-[(prop-2-ynyl)oxy]indolo[2',3':6,7]morphinan.HCl



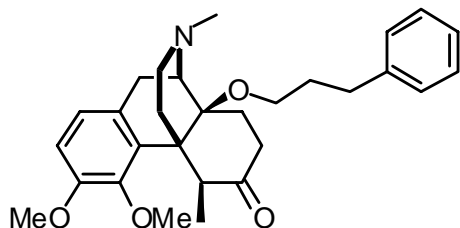
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 4% at 0.1, 0% at 1, 45% at 10 and 59% at 30
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0% at 1, 11% at 10 and 48% at 30
- 4) **HP** - 13% at 1

Vehicle was 25% hydroxypropyl-beta-cyclodextrin in water. There was insufficient drug for additional testing.

Comment: NIH 11118 has relatively weak antinociceptive properties. Remarkable opioid activity was not evident.

NIH 11119, 3,4-Dimethoxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy] morphinan-6-one.HCl



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

- 1) **TF** – 0.014 (0.0005 - 0.04)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.0023 (0.001 - 0.005)
- 4) **HP** – 0.022 (0.009 - 0.054)

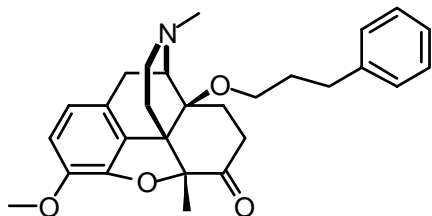
Straub tail and increased locomotor activity were observed and varying degrees of sedation were noted at 1, 10 and 30.

Special Test:

AD50 or %Antagonism by an opiate antagonist (s.c.) vs ED80 of NIH 11119 (s.c.) in TF	
Antagonist	Results- mg/kg/s.c.
Naloxone	0.16 (0.11 –0.25)

Comment: The results indicate that NIH 11119 is a potent (about 150 x morphine sulfate) mu-opioid receptor agonist. Other opioid -subtype agonist activity is suggested by the relatively high naloxone AD50

NIH 11120, 4,5 α -Epoxy-3-methoxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy]-morphinan-6-one.



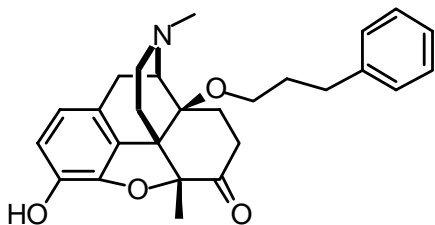
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.044 (0.021 - 0.0094)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.0017 (0.001 - 0.003)
- 4) **HP** - 0.0026 (0.0007 - 0.0095)

Straub tail and increased locomotor activity were noted in all tests and all the animals died at 30 mg/kg. Vehicle was dilute HCl in sterile water.

Comment: This profile of activity is reminiscent of that of a potent mu-opioid receptor agonist (approximately 50 x morphine sulfate).

NIH 11121, 4,5 α -Epoxy-3-hydroxy-5 β ,17-dimethyl-14 β -[(3-phenylpropyl)oxy]-morphinan-6-one.HBr



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

- 1) **TF** – 0.0009 (0.0003 - 0.0027)
- 2) **TF vs. M** – Inactive at 1
- 3) **PPQ** – 0.00016 ((0.00007 - 0.0004)
- 4) **HP** - 0.0001 (0.00005 - 0.00045)

Straub tail and increased locomotor activity were noted in the dose range 0.001 to 1.0 mg/kg. All animals receiving the 10 mg/kg dose died. Vehicle was 5% hydroxypropyl-beta-cyclodextrin in water

Opioid subtype testing:

AD50 or %Antagonism by opioid antagonists vs ED80 of NIH 11121 (s.c.) in TF	
Antagonist	Results- mg/kg/s.c. or ug/brain
Naltrexone, s.c.	0.05 (0.023 – 0.114)
Beta-FNA (mu) i.c.v.	3.59 (1.71 – 758) ug/brain
Nor-BNI, (kappa) s.c.	2% at 1, 19% at 10 and 10% at 30
Naltrindole (delta) s.c.	Inactive at 1,10 and 30

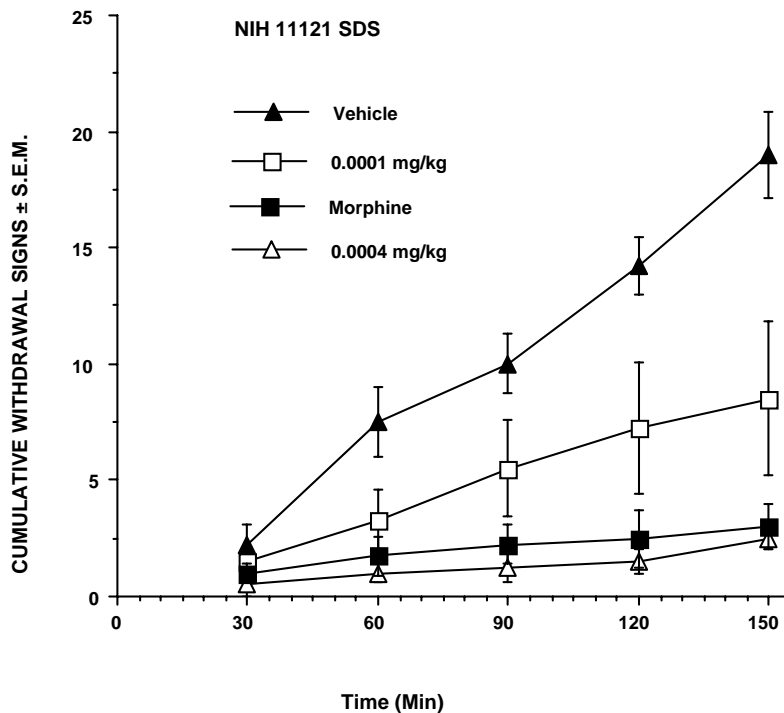


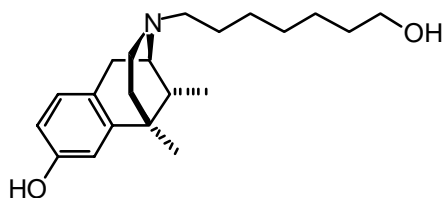
Fig NIH 11121-SDS. Results of study in which single doses of NIH 11121 were substituted for morphine in morphine-dependent monkeys in withdrawal

MONKEY DATA - SDS

NIH 11121 substituted completely for morphine in monkeys in spontaneous withdrawal (see Fig above). Onset and offset were not unlike that of morphine. Potency estimate is approximately 7,500 times that of morphine sulfate.

Comment: The results suggest that NIH 11121 is a very potent (about 25,000 x morphine sulfate) mu-opioid receptor agonist.

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 withdrawal scores it was not dose-related. In addition, the responses to abdominal palpation were not alleviated suggesting that NIH 11127 lacked mu-opioid agonist properties or that a high enough dose was not tested.

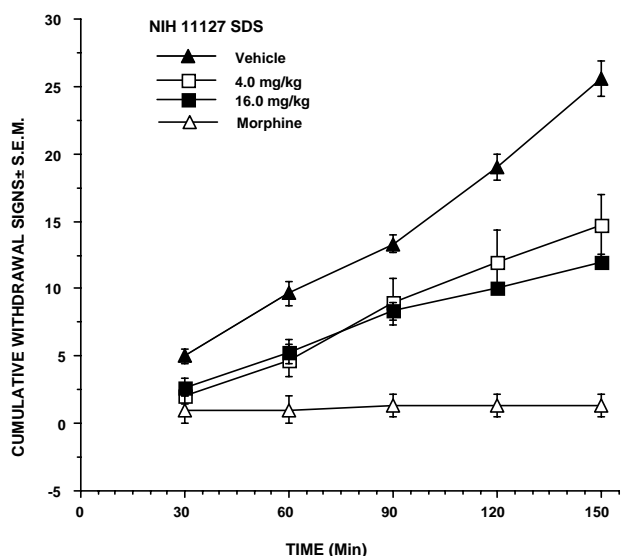
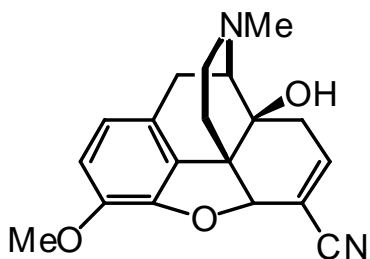


Fig NIH 11127-SDS. Results of study in which single doses of NIH 11127 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in mice and monkeys suggest that NIH 11127 does not have remarkable mu-opioid agonist effects. Perhaps the drug does not distribute well.

NIH 11130, 6,7-Didehydro-4,5 α -epoxy-14 α -hydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile



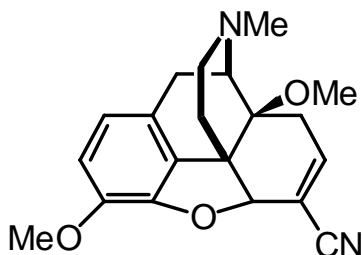
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – Inactive at 1, 10 and 30
- 2) **TF vs. M** – Inactive at 0.0001, 0.001, 0.1, 1, 10 and 30
- 3) **PPQ** – 4.4 (21.2 - 8.6)
- 4) **HP** - Inactive at 1, 10 and 30

Vehicle was 0.01 N HCl in sterile water.

Comment: Apparently, NIH 11130 is devoid of mu- and kappa- opioid agonist activity. Delta-opioid agonist activity has not been ruled out. Also, it is unlikely to have remarkable mu-,kappa- or delta-opioid antagonist effects

NIH 11131 6,7-Didehydro-4,5 α -epoxy-3,14 -dimethoxy-17-methylmorphinan-6-carbonitrile



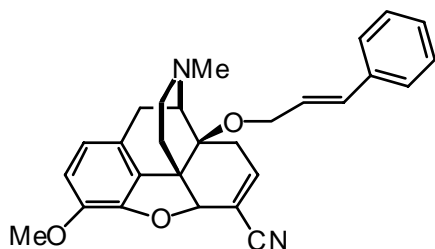
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.12 (0.07 - 0.20)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.0003 (6.6 x 10⁻⁴ - 0.012)
- 4) **HP** – 0.089 (0.037 - 0.212)

Straub tails, increased locomotor activity were seen. Vehicle was 0.01N HCl.

Comment: NIH 11131's profile of activity is that of a mu-opioid receptor agonist. Potency is approximately 40 times that of morphine sulfate.

NIH 11132. 6,7-Didehydro-4,5 α -epoxy-3-methoxy-17-methyl-14- β -{[(E)-3-phenylprop-2-enyl]oxy}morphinan-6-carbonitrile



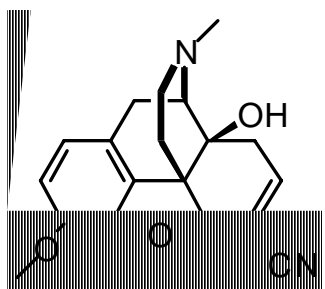
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.0014 (0.0007 - 0.0029)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.001 (0.00036 – 0.00047)
- 4) **HP** – 0.00061 (0.0002 – 0.0016)

Straub tail and increased locomotor activity were observed in the TF and HP tests. Sedation also occurred at 1, 10 and 30 mg/kg in the TF vs M test. Vehicle was 0.01 N HCl in sterile water.

Comment: The results indicate that NIH 11132 is a potent mu-opioid receptor agonist with a potency of about 1,400 times that of morphine sulfate.

NIH 11133, 6,7-Didehydro-7-{{(N,N)-diisopropyl]amino}}-14 β -hydroxy-3-methoxy-17-methyl-4-{{(E)-3-phenylprop-2-enyl]oxy}morphinan-6-carbonitrile



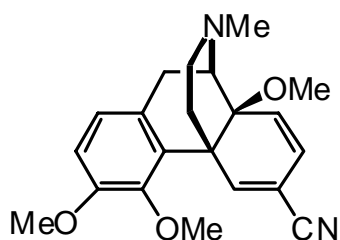
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 7.72 (2.73 - 21.80)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 1.68 (1.18 - 2.40)
- 4) **HP** – Inactive at 1 and 10, 100% at 30

Straub tails were observed at 10 and 30 mg/kg. The number of subjects was 4 in the PPQ test because drug supply was exhausted. Vehicle was 0.05 N HCl in water.

Comment: The results (Straub tail and antinociceptive profile), suggest weak mu-opioid agonist receptor activity.

NIH 11134, 5,6,7,8-Tetrahydro-3,4,14 α -trimethoxy-17-methylmorphinan-6-carbonitrile



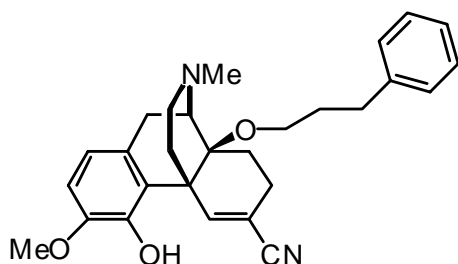
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.04 (0.02 - 0.09)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.0023 (0.0009 - 0.006)
- 3) **HP** – 0.08 (0.011 - 0.606)

Straub tail was noted at 0.1 mg/kg. Vehicle was 0.01 N HCl.

Comment: NIH 11134 is a potent mu-opioid receptor agonist. Potency estimate is 100times that of morphine sulfate.

NIH 11135, 5,6-Didehydro-4-hydroxy-3-methoxy-17-methyl-14 β -{[3- morphinan-6-carbonitrile



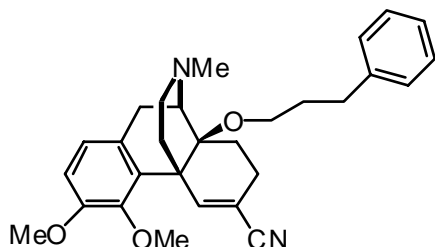
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.01 (0.004 - 0.026)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.0004 (0.0002 - 0.0008)
- 4) **HP** - 0.004 (0.0013 - 0.0127)

Straub tails and increased locomotor activity were noted at 0.02 and 0.1 mg/kg, Vehicle was 0.01 N HCl in sterile water.

Comment: NIH 11135 displays a mu-opioid receptor agonist profile in the mouse. It is 200 times more potent than the reference standard, morphine sulfate.

NIH 11136, 5,6-Didehydro-3,4-dimethoxy-17-methyl-14 β -{[3-phenylpropyl]oxy}-morphinan-6-carbonitrile.HCl



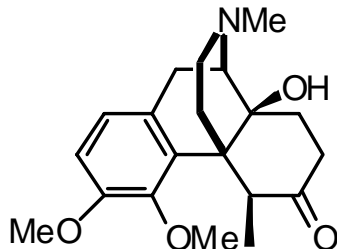
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.024 (0.014 - 0.042)
- 2) **TF vs. M** – Inactive at 1 and 10
- 3) **PPQ** – 0.021 (0.012 - 0.034)
- 4) **HP** – 0.01 (0.0036 - 0.03)

Straub tails and increased locomotor activity were noted at 1.0 and 10 mg/kg. Vehicle was 0.1 N HCl in sterile water.

Comment: This profile of activity for NIH 11136 is typically generated by a mu-opioid receptor agonist. Potency estimate is about 100 times that of morphine sulfate.

NIH 11137, 14β-Hydroxy-3,4-dimethoxy-5β,17-dimethylmorphinan-6-one



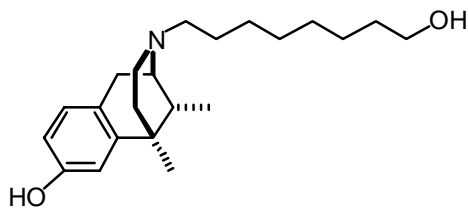
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 1.94 (0.95 - 3.93)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.59 (0.27 - 1.25)
- 4) **HP** – 3.80 (1.83 - 7.93)

Straub tail and increased locomotor activity were observed. Vehicle was 0.01N HCl.

Comment: This drug's profile of activity and potency are not unlike those of morphine sulfate.

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

Vehicle was 10% hydroxypropyl-beta-cyclodextrin in sterile water.

Opioid subtype testing:

AD50 or %Antagonism by an opiate subtype antagonist (s.c.) vs ED80 of NIH 11116 (s.c.) in PPQ test	
Antagonist	Results-mg/kg/s.c.
Naltrindole (delta)	Inactive at 1, 10 and 30

MONKEY DATA - SDS

Although NIH 11139 attenuated many withdrawal signs, it did not substitute completely for morphine. The monkeys still had rigid abdominal muscles and vocalized when their abdomens were palpated. These two withdrawal signs are not present when a drug substitutes completely for morphine.

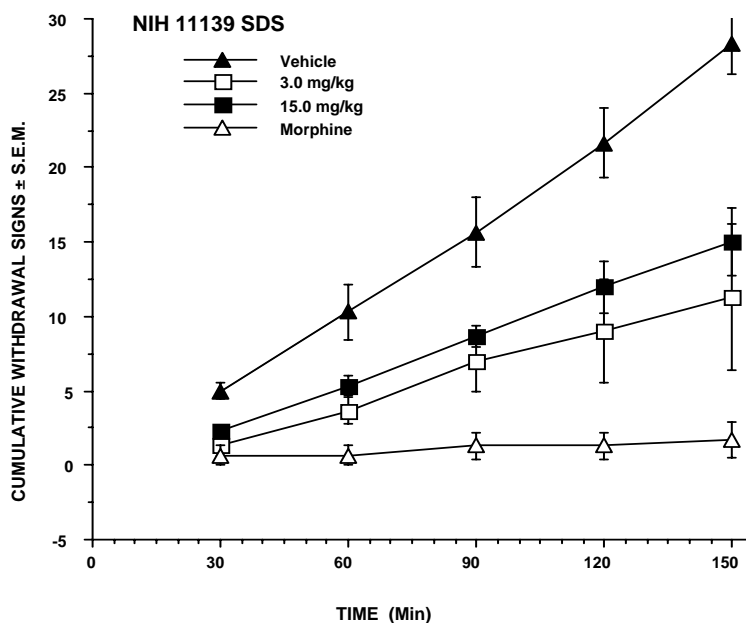
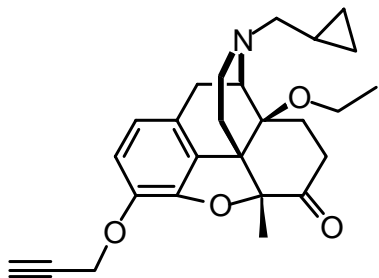


Fig NIH11139-SDS. Results of study in which single doses of NIH 11139 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: The results do not signify remarkable mu-opioid agonist or antagonist properties or delta-opioid agonist activity for NIH 11139.

NIH 11144, 17-Cyclopropylmethyl-4,5 α -epoxy-14 β -ethoxy-5 β -methyl-3-[(prop-2-ynyl)oxy]morphinan-6-one.HCl



MOUSE DATA - ED50 OR AD50

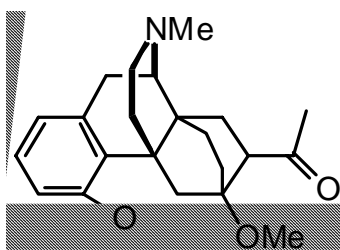
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – Inactive at 1, 10 and 30
- 2) **TF vs. M** – 3.8 (1.33 - 10.88)
- 3) **PPQ** – Inactive
- 4) **HP** - Inactive at 1 and 10

Vehicle was 10% hydroxypropyl-beta-cyclodextrin in sterile water

Comment: NIH 11144 displays some very weak mu-opioid antagonist activity. It probably is not a potent mu-opioid antagonist.

NIH 11146, 3-desmethoxy-18,19-dihydrothevinone



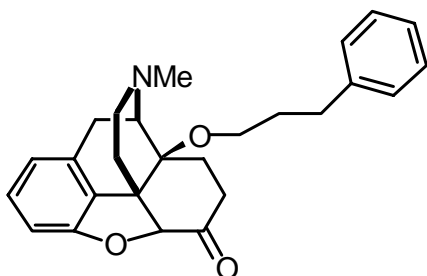
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 1.63 ((0.95 - 2.77)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.32 (0.143 - 0.718)
- 4) **HP** – 1.68 (0.83 - 3.41)

Straub tails and increased locomotor activity were noted. Vehicle was hydroxypropyl-beta-cyclodextrin in water.

Comment NIH11146's profile of activity is similar to that of morphine sulfate.

NIH 11149, 4,5 α -Epoxy-17-methyl-14 β -{[3-phenylpropyl]oxy}morphinan-6-one



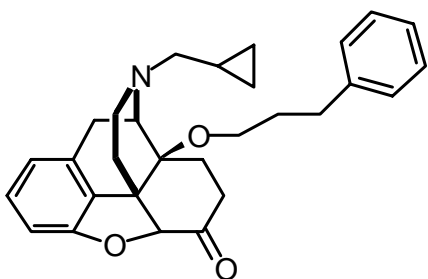
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.0004 (0.0002 – 0.0008)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.000065 (0.0000.46 – 0.000092)
- 4) **HP** – 0.003 (0.00061 – 0.014)

Straub tails, increased locomotor activity, and loss of righting reflex were seen. Vehicle was 0.05 N HCl in sterile water.

Comment: This profile of activity is typical of mu-opioid receptor agonists. Potency estimate is 5000 times that of morphine sulfate.

NIH 11150, 17-Cyclopropylmethyl-4,5 α -epoxy-14 β -{[3-phenylpropyl]oxy}morphinan-6-one.HCl



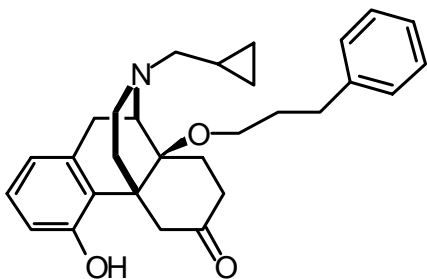
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.187 (0.054 – 0.640)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.0094 (0.003 - 0.028)
- 4) **HP** - 0.68 (0.29 - 1.6)

Straub tail and increased locomotor activity were noted. Vehicle was 20%hydroxypropyl-beta-cyclodextrin in sterile water.

Comment: The results are consistent with those observed with traditional mu-opioid receptor agonists. Potency is about 10 times that of morphine sulfate.

NIH 11151, 17-Cyclopropylmethyl-4-hydroxy-14 β -{[3-phenylpropyl]oxy}morphinan-6-one.HCl



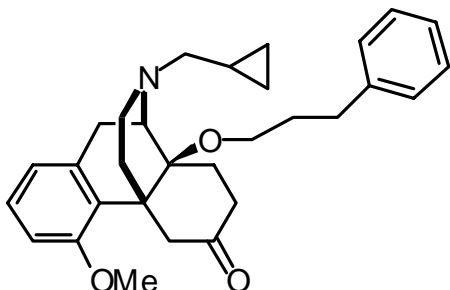
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.05 (0.015 - 0.17)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.0014 (0.0004 - 0.005)
- 4) **HP** – 0.04 (0.013 - 0.143)

Straub tail and increased locomotor activity were observed at 0.3 and 1 mg/kg. Sedation occurred at 30 mg/kg, Vehicle was 20% hydroxypropyl-beta-cyclodextrin in sterile water.

Comment: NIH 11151 appears to be a typical mu-opioid receptor agonist with a potency that is 40 times that of morphine sulfate.

NIH 11152, 17-Cyclopropylmethyl-4-methoxy-14β- {[3-phenylpropyl]oxy} morphinan-6-one.HCl



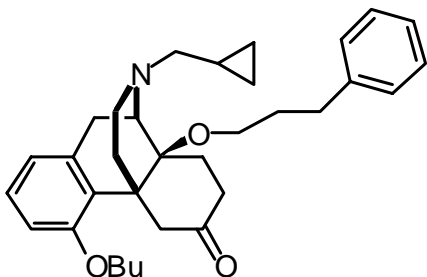
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0.28 (0.15 - 0.5)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.06 (0.019 - 0,197)
- 4) **HP** – 0.3 (0.094 - 0.96)

Straub tail noted at 0.3, 0.6 and 1 mg/kg. Increased locomotor activity was evident at 1, 10 and 30 mg/kg. Vehicle was 0.01 N HCl in water.

Comment: NIH 11152 is about 7 times more potent than the reference standard, morphine sulfate. It appears to be a typical mu-opioid receptor agonist.

NIH 11153, 4-Butyloxy-17-cyclopropylmethyl-14β- {[3-phenylpropyl]oxy} morphinan-6-one.HCl



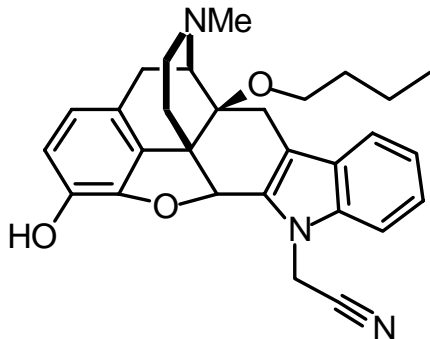
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 4.47 (2.0 - 10.0)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 1.94 (1.02 - 3.70)
- 4) **HP** – 1% at 1, 38% at 10 and 50% at 30

Straub tail was evident at 3, 10 and 30 mg/kg. Vehicle was 20% hydroxypropyl-beta-cyclodextrin in water.

Comment: This profile indicates that NIH 11153 is a mu-opioid receptor agonist.

NIH 11154, [14 β -Butyloxy-6,7-didehydro-4,5 α -epoxy-3-hydroxy-17- morphinan]-1'-acetonitrile.HCl



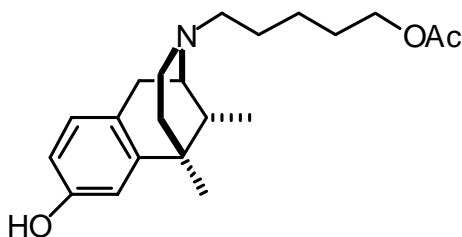
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – Inactive at 1, 18% at 10
- 2) **TF vs. M** – Inactive at 1 and 10
- 3) **PPQ** – 2.49 (1.14 - 5.47)
- 4) **HP** – 13% at 1 and 5% at 10

Vehicle was 5% hydroxypropyl-beta-cyclodextrin in sterile water. Drug supply was exhausted.

Comment: These data indicate very weak, if any, in vivo mu- and kappa-opioid effects. Delta-opioid receptor agonist activity has not been ruled out.

NIH 11164, (-)-(1*R*,5*R*,9*R*) -2-(5-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



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

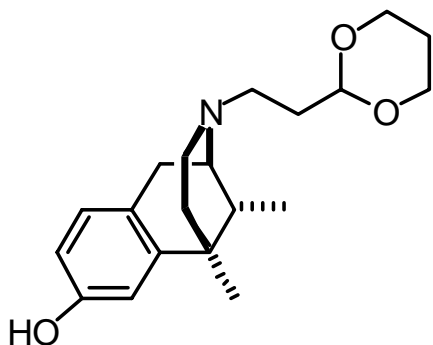
- 1) **TF** – 0% at 10, 16% at 10 and 48% at 30
- 2) **TF vs. M** – 16% at 1, 23% at 10 and 11% at 30
- 3) **PPQ** – 8.36 (3.02 - 23.1)
- 4) **HP** – 0% at 1 and 10, 13% at 30

Opioid subtype testing:

AD50 or %Antagonism by an opiate subtype antagonist (s.c.) vs ED80 of NIH 11164 (s.c.) in PPQ test	
Antagonist	Results-mg/kg/s.c.
Naltrindole (delta)	Inactive at 1 and 21% at 10 and 30

Comment: Very weak, if any, opioid-receptor effects were evident.

NIH 11167, (-)-(1*R*,5*R*,9*R*)-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.

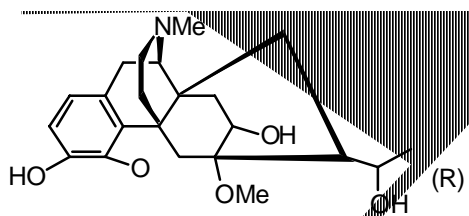
- 1) **TF** – 0% at 1, 10% at 10 and 41% at 30
- 2) **TF vs. M** – 3% at 1, 16% at 10 and 9% at 30
- 3) **PPQ** – 5.48 (3.05 - 9.86)
- 4) **HP** – Inactive at 1, 10 and 30

Opioid subtype testing:

AD50 or %Antagonism by an opiate subtype antagonist (s.c.) vs ED80 of NIH 11167 (s.c.) in PPQ test	
Antagonist	Results-mg/kg/s.c.
Naltrindole (delta)	14% at 1, 31% at 10 and 22% at 30

Comment: Very weak, if any, opioid activity was evident.

NIH 11172, 18-(*R*)-Hydroxy-20-(*R*)-orvinol.oxalate



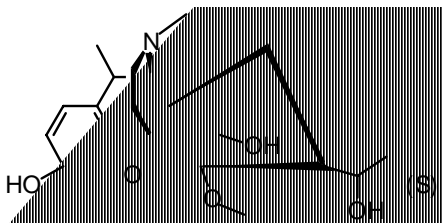
MOUSE DATA - ED50 OR AD50
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 0% at 1, 15% at 10
- 2) **TF vs. M** – 0% at 1, 15% at 10 and 6% at 30
- 3) **PPQ** – 4.06 (1.58 – 10.46)
- 5) **HP** – 0% at 1, 15% at 10

Insufficient drug for testing of higher doses.

Comment: It is unlikely that NIH 11172 has remarkable mu- and/or kappa- opioid agonist or antagonist activity. Delta-opioid agonist properties have not been ruled out.

NIH 11173, 18-(*R*)-Hydroxy-20-(*S*)-orvinol.oxalate



MOUSE DATA - ED50 OR AD50

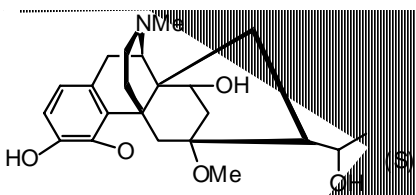
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 2% at 1 and 10, 33% at 30
- 2) **TF vs. M** – 6% at 1, 9% at 10 and 0% at 30
- 3) **PPQ** – 4.73 (2.02 – 11.1)
- 4) **HP** – Inactive at 1, 10 and 30

Vehicle was 20% hydroxypropyl-beta-cyclodextrin in sterile water.

Comment: Noteworthy mu- and/or kappa-opioid agonist or antagonist properties are not evident with this compound. Delta-opioid receptor agonist activity has not been ruled out.

NIH 11174, 19-(*S*)-Hydroxy-20-(*S*)-orvinol.oxalate



MOUSE DATA - ED50 OR AD50

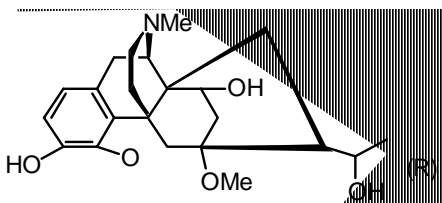
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 5% at 1, 7% at 10
- 2) **TF vs. M** – 0% at 1, 6% at 10
- 3) **PPQ** – 0% at 1, 54% at 10
- 4) **HP** – 13% at 1, 0% at 10

Drug supply was exhausted. N = 3 at 10 mg/kg. Vehicle was 20% hydroxypropyl-beta-cyclodextrin in sterile water.

Comment: At the doses tested, NIH 11174 did not exhibit opioid activity.

NIH 11175, 19-(*S*)-Hydroxy-20-(*R*)-orvinol.oxalate



MOUSE DATA - ED50 OR AD50

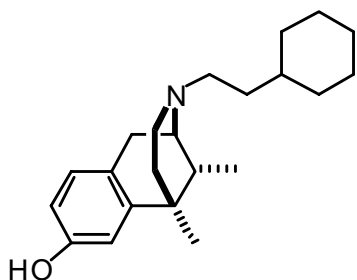
(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 5% at 1 and 41% at 10 (n = 4 at 10)
- 2) **TF vs. M** – Inactive at 1 and 10
- 3) **PPQ** – 30% at 1 and 100% at 10
- 4) **HP** – Inactive at 1 and 25% at 10 (n = 4 at 10)

Vehicle was 20% hydroxypropyl-beta-cyclodextrin in sterile water. Drug supply was exhausted.

Comment: Limited supplies precluded a characterization of NIH11175. It may have remarkable delta opioid properties. Subtype testing using naltrindole might resolve this issue.

NIH 11185, (-)-(1*R*,5*R*,9*R*)-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)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 1.21 (0.69 - 2.17)
- 4) **HP** – 8.50 (1.18 - 61.37)

Straub tail and increased locomotor activity were evident. Vehicle was sterile water plus a few drops of 0.1% HCl, followed by sonification.

MONKEY DATA – SDS

As shown in the figure, NIH 11185 attenuated withdrawal signs in monkeys in spontaneous withdrawal at doses of 1.5 and 6.0 mg/kg.

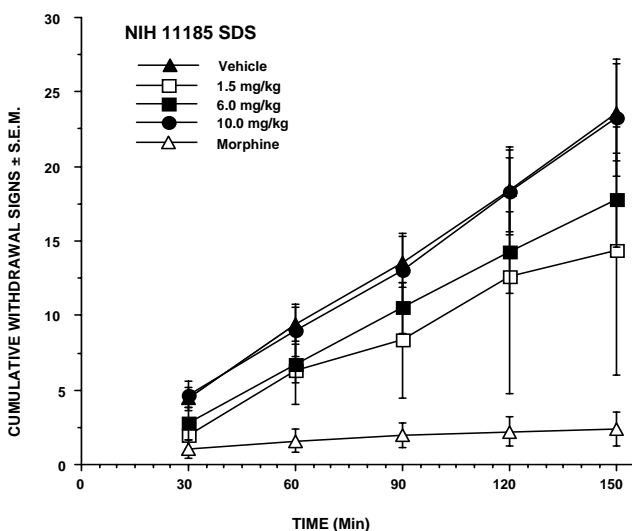
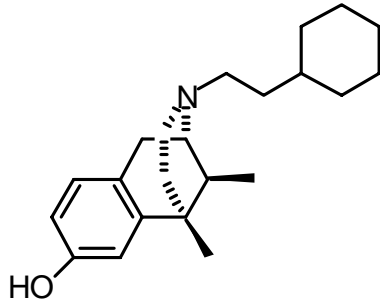


Fig NIH 11185-SDS. Results of study in which single doses of NIH 11185 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Overall, for NIH 11185, the results in mice including Straub tail and those in monkeys point toward mu-opioid agonist properties.

NIH 11186, (+)-(1*S*,5*S*,9*S*)-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 30
- 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

The mice were slightly ataxic at 30 mg/kg.

Opioid subtype testing:

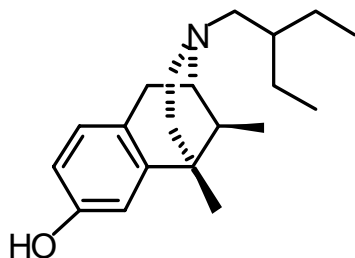
AD50 or %Antagonism by an opiate subtype antagonist (s.c.) vs ED80 of NIH 11186 (s.c.) in PPQ test	
Antagonist	Results-mg/kg/s.c.
Naltrindole (delta)	Inactive at 1, 10 and 30

MONKEY DATA – SDS

Only one experiment could be conducted because drug supply was limited. 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: For NIH11186, there is no indication regarding opioid effects.

NIH 11188, (+)-(1*S*,5*S*,9*S*)-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.

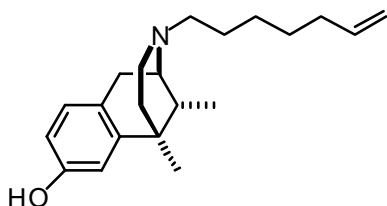
- 1) **TF** - Inactive at 1, 10 and 30
- 2) **TF vs. M** - 19% at 1, 0% at 10 and 23% at 30
- 3) **PPQ** - 23% at 0.3, 50% at 1, 38% at 10 and 65% at 30
- 4) **HP** - Inactive at 1, 10 and 30

MONKEY DATA – SDS

There was insufficient drug to conduct a complete evaluation. At doses of 4 and 16 mg/kg, using one subject per dose, NIH 11188 had no effect on morphine-dependent monkeys in withdrawal.

Comment: NIH 11188 produced erratic responses in the TF vs M and PPQ tests. Additional supplies required for further testing.

NIH 11189, (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(7-heptenyl)-2'-hydroxy--6,7-benzomorphan.HCl



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

- 1) **TF** – 2.8 (1.98 – 3.96)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.50 (0.27 – 0.90)
- 4) **HP** – Inactive at 1, 12.5% at 3, 37.5% at 10 and 25% at 30

Straub tail was noted. Vehicle was 20% hydroxypropyl-beta-cyclodextrin in sterile water.

Opioid subtype testing:

AD50 or %Antagonism by an opiate subtype antagonist (s.c.) vs ED80 of NIH 11189 (s.c.) in PPQ test	
Antagonist	Results-mg/kg/s.c.
Naltrindole (delta)	Inactive at 1, 10 and 30

MONKEY DATA – (SDS)

At doses of 1.25 and 5 mg/kg, NIH 11189 did not substitute for morphine or attenuate or exacerbate withdrawal. However. The signs ataxia, slowing and tremors were noted at the high dose. Hydroxypropyl-beta-cyclodextrin was used as vehicle,

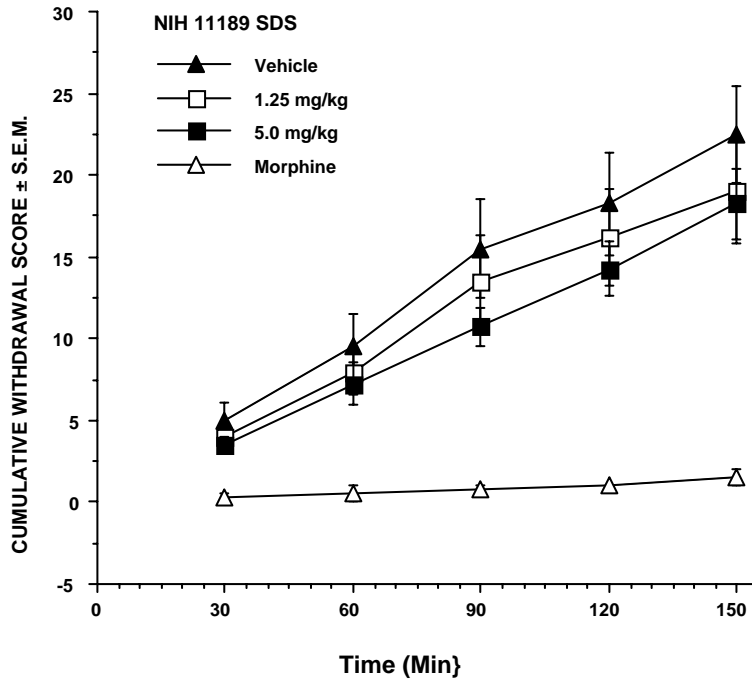
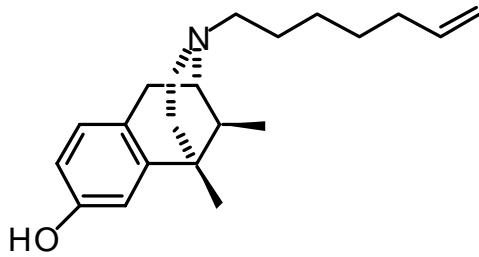


Fig NIH11189-SDS. Results of study in which single doses of NIH 11189 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in mice are suggestive of mu- and/or kappa-opioid agonist properties; however, in the dose range tested in monkeys, the results are not supportive. Delta-opioid agonist activity is not apparent.

NIH 11190, (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(7-heptenyl)-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** – 33% at 0.3, 45% at 1, 58% at 10 and 68% at 30
- 4) **HP** – 25% at 1 and inactive at 10 and 30

Straub tail was seen at 10 and 30 mg/kg. Vehicle was 20% hydroxypropyl-beta-cyclodextrin in sterile water.

MONKEY DATA – SDS

The results illustrated in the accompanying figure indicate that, at doses of 1 and 4 mg/kg, NIH 11190 did not substitute for morphine. Neither did it attenuate or exacerbate withdrawal. One monkey receiving the high dose convulsed. Pentobarbital was given to control the convulsions. Also, noted at this dose the signs designated as ataxia and slowing. Vehicle was 5% hydroxypropyl-beta-cyclodextrin in sterile water.

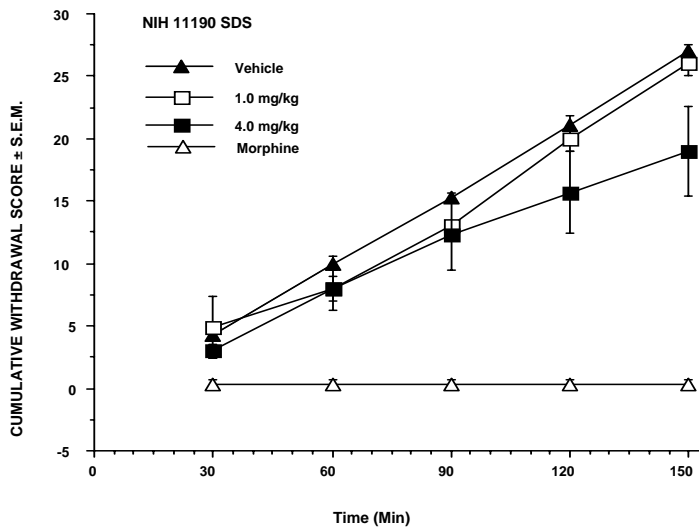
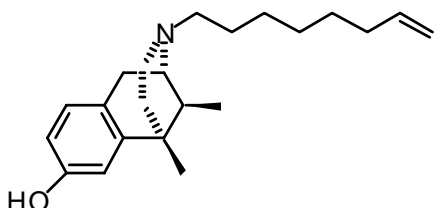


Fig NIH 11190-SDS. Results of study in which single doses of NIH 11190 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Although CNS signs were observed, the profile of activity of NIH 11190 does not implicate remarkable mu- and/or kappa-opioid agonist or antagonist properties. Delta-opioid agonist activity was not tested.

NIH 11191, (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(8-octenyl)-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** – 39% at 1, 23% at 10 and 32% at 30
- 4) **HP** – Inactive at 1, 10, and 30

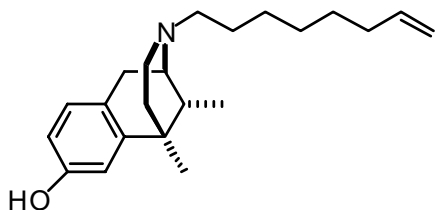
Vehicle was 20% hydroxypropyl-beta-cyclodextrin in sterile water

MONKEY DATA -(SDS)

Because of limited supplies, only 2 monkeys per treatment regimen could be tested. Nevertheless, there was no indication that NIH 11191 substituted for morphine, attenuated withdrawal signs or exacerbated withdrawal at doses of 2 and 10 mg/kg. At the high dose, ataxia and slowing were noted. Vehicle was 10% hydroxypropyl-beta-cyclodextrin in sterile water.

Comment: Apparently, NIH 11190 is not an opioid compound.

NIH 11192, (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(8-octenyl)-2'-hydroxy-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50

(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 10.92 (6.62 – 16.1)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.46 (0.134 – 1.16)
- 4) **HP** – 0% at 1, 12.5% at 10 and 37.5% at 30

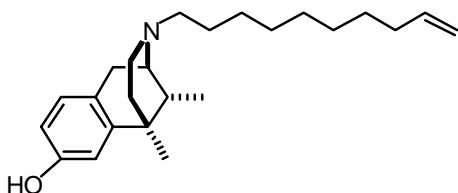
Vehicle was 20% hydroxypropyl-beta-cyclodextrin in sterile water.

MONKEY DATA - (SDS)

Limited supplies precluded a full evaluation of NIH 11192. However, at doses of 2.5 and 10 mg/kg (N = 2) there was no indication that this compound substituted for morphine, attenuated or exacerbated withdrawal. Vehicle was 10% solution of hydroxypropyl-beta-cyclodextrin in sterile water.

Comment: These data are not indicative of remarkable mu-opioid receptor agonist or antagonist activity or kappa-opioid receptor effects. Possibly, NIH11192 may have delta-opioid agonist properties.

NIH 11194, (-)-(1*R*,5*R*,9*R*)-2-(10-Decenyl)-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** – Inactive at 1, 21% at 10 and 66% 30
- 4) **HP** – Inactive at 1 and 10, 50% at 30

Vehicle was 10% hydroxypropyl-beta-cyclodextrin in sterile water.

MONKEY DATA – SDS

As illustrated in the accompanying figure, some attenuation of withdrawal signs occurred at the high dose (10 mg/kg). However, at this dose the sign slowing was noted in one monkey. Vehicle was hydroxypropyl-β-cyclodextrin in sterile water.

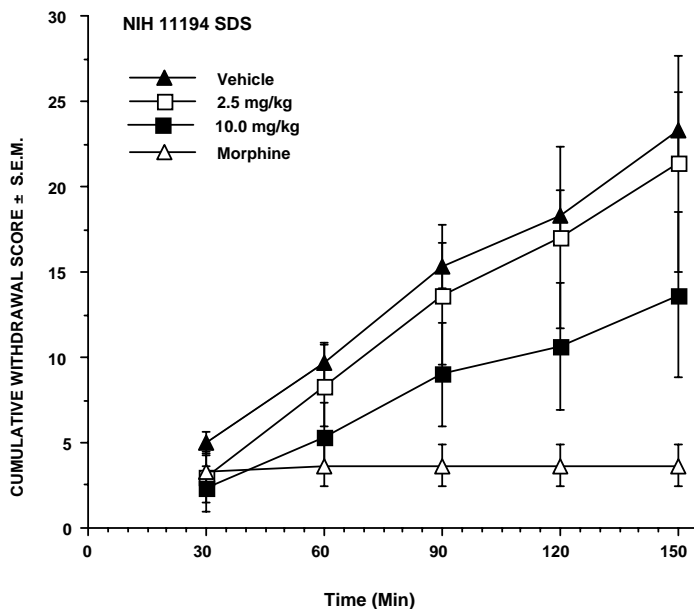
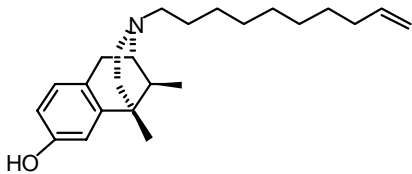


Fig NIH 11194-SDS. Results of study in which single doses of NIH11194 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Remarkable opioid activity was not evident.

NIH 11195, (+)-(1*S*,5*S*,9*S*)-2-(10-Decenyl)-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** – Inactive at 1, 15% at 19 and 32% at 30
- 4) **HP** – Inactive at 1, 10 and 30

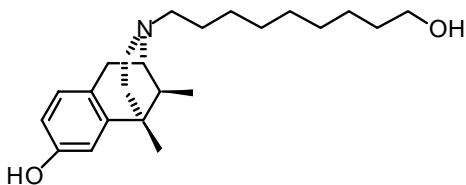
Vehicle was 10% hydroxypropyl-beta-cyclodextrin in water.

MONKEY DATA - SDS

The supply of NIH 11195 limited testing to 2 monkeys per dose (2.5 and 10 mg/kg). At both doses, some attenuation of withdrawal signs was noted. However, two especially important withdrawal signs, designated as rigid abdominal muscles and vocalization, associated with abdominal palpation were not abolished.

Comment: Noteworthy opioid properties were not manifested in these experiments with NIH 11195

NIH 11196, (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(9-hydroxynonyl)-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** – 25% at 1, 45% at 3, 32% at 10 and 36% at 30
- 3) **PPQ** – 25 at 1, 17% at 10 and 22% at 30
- 4) **HP** – Inactive at 1,10 and 30

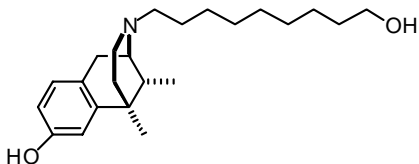
Vehicle was 10% hydroxypropyl-beta-cyclodextrin in sterile water.

MONKEY DATA – SDS

Limited supplies precluded a full evaluation. Using 2 monkeys per treatment regimen and doses of 2.5 and 10 mg/kg, the results suggested that NIH 11196 neither substituted for morphine nor alleviated or exacerbated withdrawal. Vehicle was 10% hydroxypropyl-beta-cyclodextrin in sterile water.

Comment: Notable opioid agonist and mu-opioid antagonist properties were not demonstrated in these experiments.

NIH 11197, (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(9-hydroxynonyl)-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 and 10, 19% at 30
- 2) **PPQ** - Inactive at 1, 59% at 10 and inactive at 30
- 3) **HP** - Inactive at 1, 12.5% at 10 and inactive at 30

Vehicle was 5% hydroxypropyl-beta-cyclodextrin in sterile water.

MONKEY DATA - SDS

As shown in the accompanying figure, some attenuation of withdrawal signs was evident at 2 hr at 6 mg/kg and it was more pronounced at 21/2 hr. The attenuation involved a reduction in the number of all withdrawal signs.

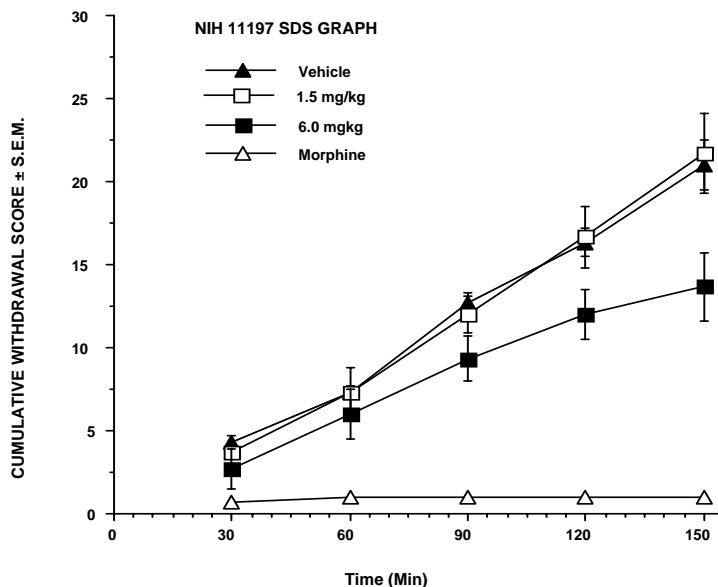
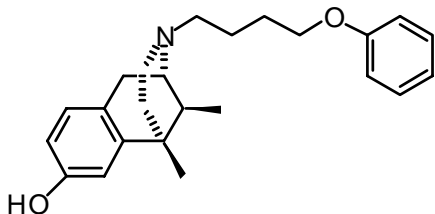


Fig NIH 11197-SDS. Results of a study in which single doses of NIH 11197 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The data suggests that NIH 11197 may have a delayed onset of action. Additional studies using longer pretreatment times in the mouse and monkey assays could resolve this issue.

NIH 11209, (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl



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

- 1) **TF** – 3% at 1, 0% at 10 and 9% at 30
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 12.61 (4.88 – 32.6)
- 4) **HP** – Inactive at 1 and 10, 12.5% at 30

Vehicle was 20% hydroxypropyl-beta-cyclodextrin in water.

MONKEY DATA -(SDS) As illustrated in the accompanying figure, at doses of 2 and 8 mg/kg, NIH 11209 is without effect in morphine-dependent monkeys in withdrawal

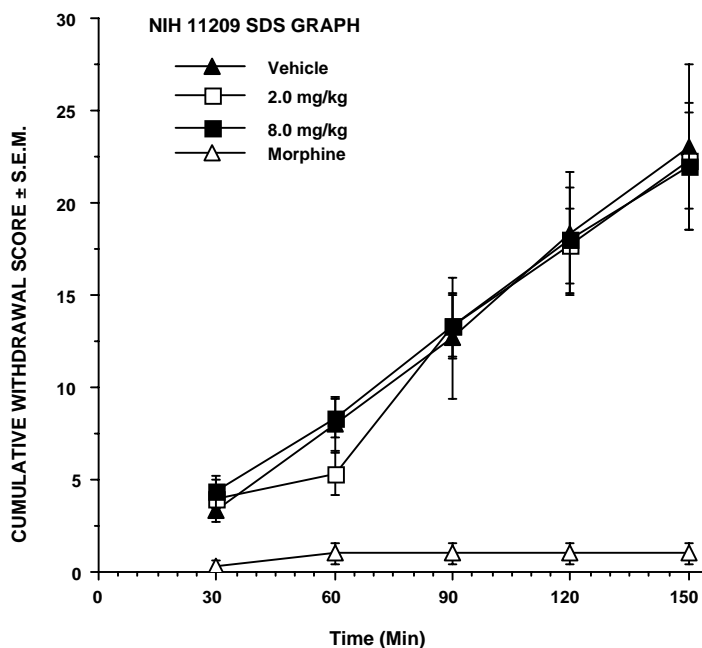
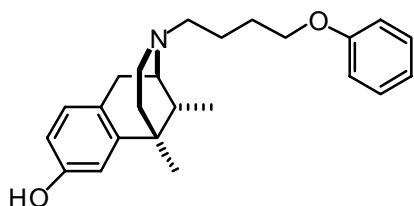


Fig NIH 11209-SDS. Results of a study in which single doses of NIH 11209 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: All the data indicates that NIH 11209 is devoid of mu- and/or kappa- opioid properties. Additional subtype testing might reveal delta-opioid agonist activity.

NIH 11210 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50

(95 % C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 5% at 1, 24% at 19 and inactive at 30
- 2) **TF vs. M** – 8% at 1, 20% at 10 and 8% at 30
- 3) **PPQ** – 6.28 (2.14 – 18.4)
- 4) **HP** – 12.5% at 1, inactive at 10 and 25% at 30

Vehicle was 20% hydroxypropyl-beta-cyclodextrin in warm sterile water

MONKEY DATA - (SDS)

The results in the accompanying figure clearly illustrate that NIH 11210 neither substituted for morphine nor attenuated or exacerbated withdrawal signs at doses of 2.5 and 10 mg/kg..

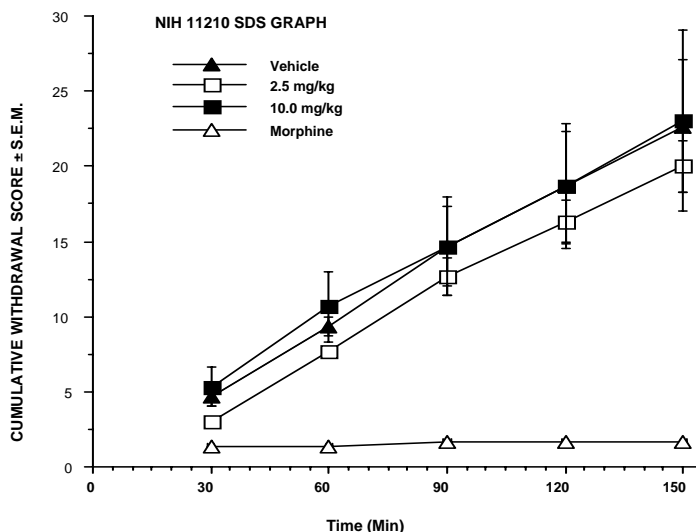
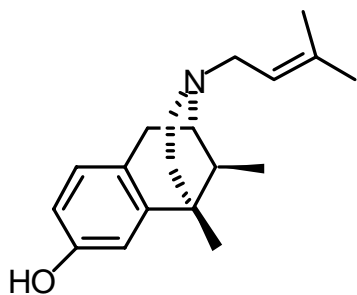


Fig NIH 11210-SDS. Results of a study in which single doses of NIH 11210 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results in two species indicate that NIH 11210 is unlikely to have mu- and/or kappa-opioid agonist or antagonist activity. Opioid subtype testing with naltrindole might reveal delta-opioid properties.

NIH 11212, (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-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, 33% at 10 and 55% at 30
- 3) **PPQ** – Inactive at 1, 10 and 30
- 4) **HP** – Inactive at 1, 10 and 30

MONKEY DATA – SDS

The data are illustrated in the accompanying figure. At the low dose, NIH 11212 seemed to attenuate withdrawal especially during the latter part of the experiment. However, it may have exacerbated withdrawal at the high dose. These data are inconclusive and additional studies are indicated.

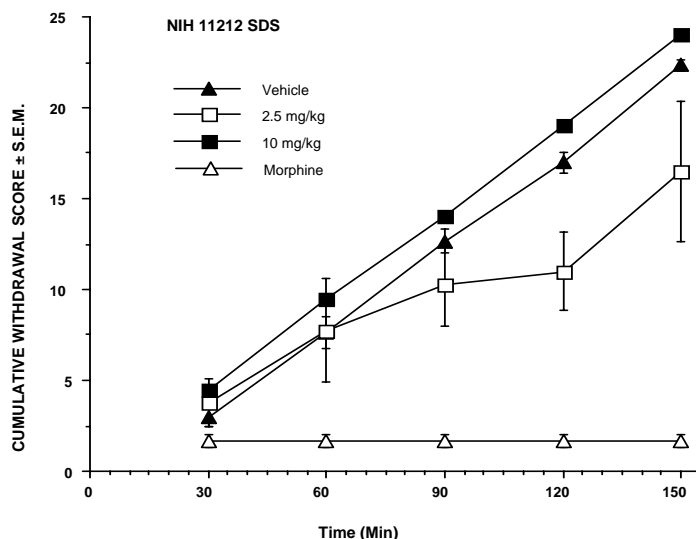
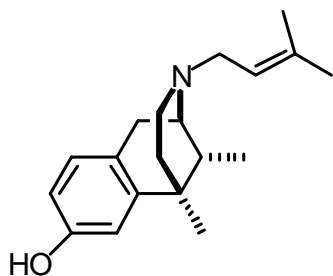


Fig NIH 11212-SDS. Results of study in which single doses of NIH 11212 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: In the mouse, NIH 11212 displayed very weak opioid antagonist properties. The monkey studies suggest opioid antagonist activity at the high dose. In view of the marginal activity, in both species, additional studies are not recommended,

NIH 11213, (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-6,7-benzomorphan.oxalate



MOUSE DATA - ED50 OR AD50

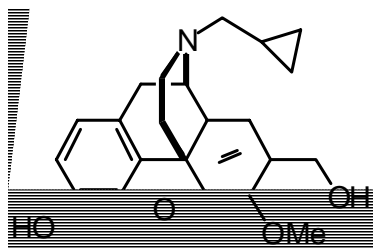
(95% C.L.) or % change, mg/kg/s.c.

- 1) **TF** - Inactive at 1, 10 and 30
- 2) **TF vs. M** – Inactive at 1, 8% at 3, 51% at 10 and 30
- 3) **PPQ** - 1.2 (0.72 – 2.02)
- 4) **HP** –14% at 1, 33% at 10 and 25% at 30

Opioid Subtype Testing: Naltrindole antagonism of ED80 of NIH 11213 in the PPQ test: Inactive at 1, 10 and 30

Comment: NIH 11213 has some weak mu-opioid antagonist properties. Although it produces antinociception in the PPQ test, delta-opioid agonist activity is not involved.

NIH 11214, 17-Cyclopropylmethyl-7 α -hydroxymethylorvinol.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** - 0.0098 (0.0039 – 0.0249)
- 3) **PPQ** - 0.1 (0.0081 – 1.482)
- 4) **HP** - Inactive at 1 and 30 and 21% at 10

Duration of Action Study: NIH 11214 antagonist activity vs ED80 Morphine Sulfate in the TF test

TIME	20 min	2hr	4 hr	6hr	24hr
Per Cent Antagonism	73	32	26	36	16

MONKEY DATA – PPt-W

The data are illustrated in the figure below. At the high dose (0.02 mg/kg) the onset of action was rapid and lasted more than 2 hr. With the low dose(0.005 mg/kg) duration of action was similar to that of naloxone, the reference standard. Potency estimate is approximately 10 times that of naloxone.

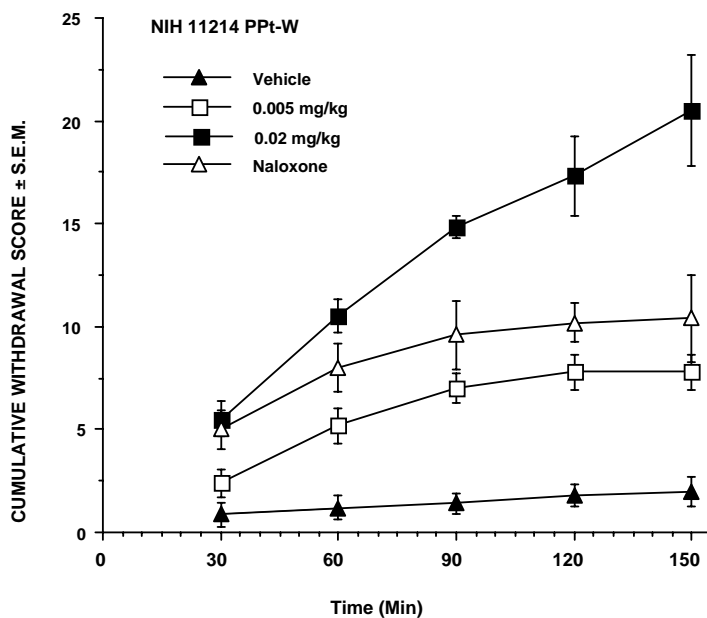
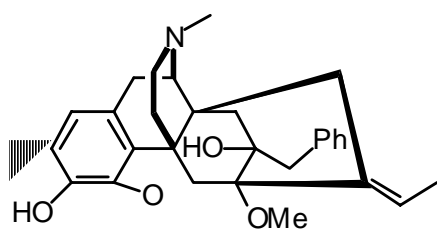


Fig. NIH 11214- PPT-W. Results of study in which NIH 11214 was administered to morphine dependent monkeys.

Comment: NIH 11214 is a powerful mu-opioid antagonist of longer duration of action than naloxone in the mouse and monkey. It is also quite active in the PPQ test. PPQ activity is sometimes indicative of delta-opioid agonist effect.

NIH 11215. 7-Benzyl-7-hydroxy-6 β ,14 β -butenyl-5,6,7,8-tetrahydrooripavine

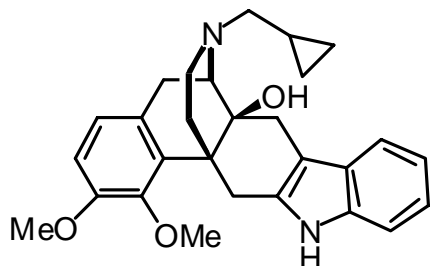


MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

- 1) **TF** - Inactive at 1 and 10
- 2) **TF vs. M** - 21% at 1 and inactive at 10
- 3) **PPQ** - 29% at 1 and inactive at 10
- 4) **HP** - Inactive at 1 and 16% at 10

Comment: Remarkable opioid activity is not evident.

NIH 11216 17-Cyclopropylmethyl-3,4-dimethoxy-14 β -hydroxy[6,7:2',3']-indolomorphinan

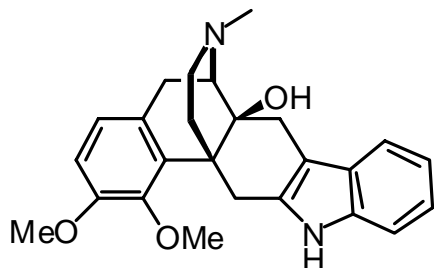


MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

- 1) **TF** - Inactive at 1 and 10
- 2) **TF vs. M** - Inactive at 1 and 10
- 3) **PPQ** - Inactive at 1 and 10
- 4) **HP** - Sixteen % at 1 and 23% at 10

Note: Limited quantities precluded testing at higher doses. Vehicle was 0.05N HCl in 20% hydroxypropyl-beta-cyclodextrin. Solution was cloudy and was shaken before each injection.

NIH 11217, 3,4-Dimethoxy-14 β -hydroxy-17-methyl-[6,7:2',3']indolomorphinan



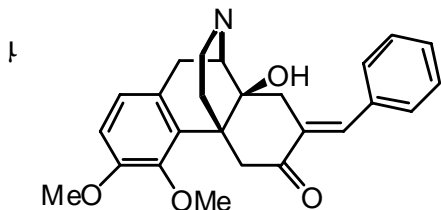
MOUSE DATA - ED50 OR AD50
95% C.L.) or % change, mg/kg/s.c. and i.c.v.

- 1) **TF** - **s.c.:** Inactive at 1, 10 and 30
i.c.v.: Inactive at 1 and 10, 18% at 30 μ g/brain
- 2) **TF vs. M** - **s.c.:** 28% at 1, 20% at 10 and 37% at 30
i.c.v.: Inactive at 1, 10 and 30 μ g/brain
- 3) **PPQ** - **s.c.:** Inactive at 1, 10 and 30
i.c.v.: 23% at 30 μ g/brain
- 4) **HP** - **s.c.:** 24% at 1 and 4% at 10
i.c.v.: Inactive at 1 and 10, 10% at 30 μ g/brain

At 30 μ g/brain, CNS effects predominated including spinning, walking in circles, limb extensions and/or convulsions. Vehicle was 10% hydroxypropyl-beta-cyclodextrin in 0.05N HCl.

Comment.: When given centrally, severe CNS effects were noted. However, antinociceptive agonist and antagonist activity was very weak and erratic after peripheral or central administration.

NIH 11218, 7-(*E*)-Benzylidene-3,4-dimethoxy-14 β -hydroxy-17-methylmorphinan-6-one



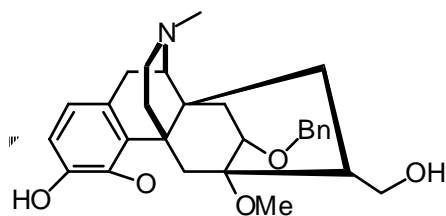
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.and

- 1) **TF** – **s.c.:** Inactive at 1, 10 and 30
i.c.v.: Inactive at 1, 23% at 10 and 34% at 30 μ g/brain
- 2) **TF vs. M** – **s.c.:** Inactive at 1, 18% at 10 and inactive at 30
i.c.v.: Inactive at 1 10 and 30 μ g/brain
- 3) **PPQ** – **s.c.:** Inactive at 1, 10 and 30
i.c.v.: 23% at 1, inactive at 10 and 26% at 30 μ g/brain
- 4) **HP** – **s.c.:** Inactive at 1, 10 and 30
i.c.v.: Inactive at 1 10, and 30 μ g/brain

1/6 Convulsed (i.c.v.) 30 min after testing in the TF vs M and HP tests and ataxia was observed in the PPQ test. Vehicle was 0.05N HCl in sterile water plus sonication. The solution was cloudy.

Comment.: Erratic agonist and antagonist peripheral and central activity characterized NIH 11218. Perhaps solubility or vehicle is a confounding factor.

NIH 11219 18-(*R*)-Benzyloxy-4,5 \square -epoxy-3-hydroxy-7 \square -hydroxymethyl-17-methyl-6 \square ,14 \square -ethano-isomorphinan

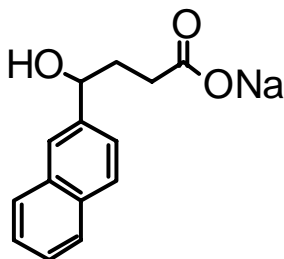


MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

- 1) **TF** - Inactive at 1 and 10
- 2) **TF vs. M** – Twenty-five % at 1 and inactive at 10
- 3) **PPQ** - 0.79 (0.08 – 7.74)
- 4) **HP** – Thirty one % at 1 and inactive 10

Supply was exhausted. Vehicle composition was 0.01N HCl in 20% hydroxypropyl-beta-cyclodextrin plus sonication.

NIH 11220, 4-Hydroxy-4-(2-naphthyl)butyric acid, sodium salt



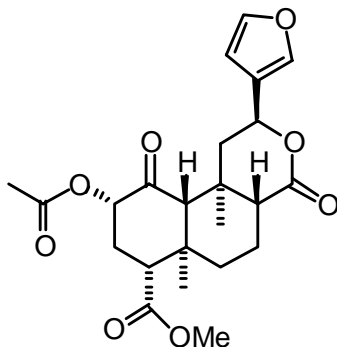
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

- 1) **TF** – Inactive at 1, 10 and 30
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ**- 21% at 1, 5% at 10, 32% at 30 and 24% at 100
- 4) **HP** – 19% at 1, 3% at 10 and 19% at 30

Vehicle was 5% hydroxypropyl-beta-cyclodextrin in sterile water.

Comment: Even when tested at 100 mg/kg in the PPQ test, little antinociceptive activity was evident. This compound has little, if any opioid activity.

NIH 11228 Salvinorin A



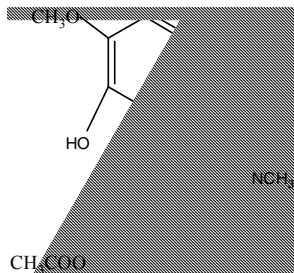
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 1.98 (1.02 – 3.82)
- 2) **TF vs. M** – Inactive at 1, 10 and 30
- 3) **PPQ** – 0.59 (0.024 – 1.43)
- 5) **HP** – Inactive at 1, 28% at 10 and inactive at 30

Straub tail noted in the HP test at 30 mg/kg. Vehicle was 50% hydroxypropyl-beta-cyclodextrin in 0.05N HCl. Very poor solubility. At times it was seen as a suspension.

Comment: In the TF and PPQ tests potent opioid agonist activity was evident. Curiously, significant HP activity was not manifested, The HP test was run twice and two technicians ran the tests.

NIH 11230, NIH 00154 Dihydrocodeinone, Hydrocodone



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

- 1) **TF**- 1.47 (0.59 – 3.67)
- 2) **TF vs. M** - Inactive at 1 and 30 and 22% at 10
- 3) **PPQ** - 0.14 (0.06 – 0.32)
- 4) **HP** - 2.4 (1.57 – 3.65)

Straub tail and increased locomotor activity were noted in the TF, TF vs M and HP tests. Vehicle was 20% hydroxypropyl-beta-cyclodextrin sterile water.

Opioid subtype testing:

AD50 or %Antagonism by opioid antagonists vs ED80 of NIH 11130 (s.c.) in the TF test	
Antagonist	Results- mg/kg/s.c. or ug/brain
Beta-FNA (mu) i.c.v.	0.16 (0.08 – 0.29) ug/brain
Nor-BNI, (kappa) s.c.	Inactive at 1, 10 and 30
Naltrindole (delta) s.c.	Inactive at 1,10 and 30

MONKEY DATA – SDS

As shown in the accompanying figure, dihydrocodeinone dose-dependently substituted completely for morphine in withdrawn morphine-dependent monkeys. Onset of action was prompt and offset was at least as long as that of the reference standard, morphine sulfate. Potency is estimated as equivalent to morphine sulfate

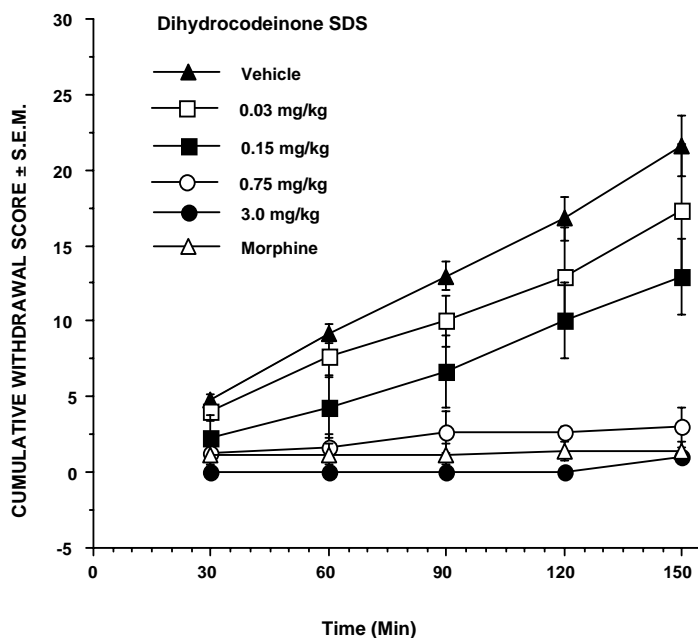
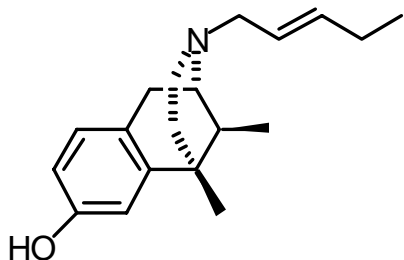


Fig NIH 11230-SDS. Results of a study in which single doses of dihydrocodeinone were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: These data indicate that dihydrocodeinone is a selective mu-opioid agonist.

NIH 11231, (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate



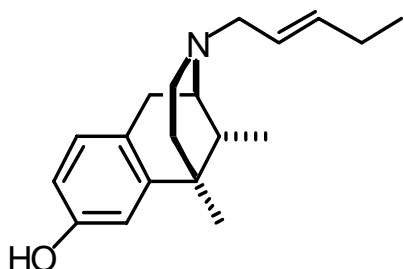
MOUSE DATA - ED50 OR AD50

(95% C.L.) or % change, mg/kg/s.c.

- 1) **TF** – Inactive at 1, 10 and 30
- 2) **TF vs. M** – 7% at 1, 15% at 10 and 53% at 30
- 3) **PPQ** – 1.63 (0.49 – 5.45)
- 6) **HP** – 26% at 1, 36% at 10 and inactive at 30

Vehicle was 15% hydroxypropyl-beta-cyclodextrin in sterile water. **Comment:** These tests indicate that NIH 11231 has very weak mu- and/or kappa-opioid antagonist effects. Testing with naltrindole might reveal delta-opioid agonist activity.

NIH 11232, (-)-(1*R*5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate



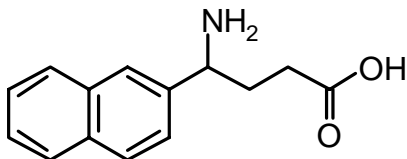
MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

- 1) **TF** – Inactive at 1, 10 and 30
- 2) **TF vs. M** – 1.87 (0.65 – 5.34)
- 3) **PPQ** – 0.74 (0.34 – 1.61)
- 4) **HP** – 6% at 1, 48% at 1 33% at 3, inactive at at10 and 30

Vehicle was 15% hydroxypropyl-beta-cyclodextrin in sterile water.

Comment: NIH 11232 has weak opioid-antagonist and perhaps delta-opioid agonist activity. Subtype testing would better characterize this compound.

NIH 11235, 4-Amino-4-(2-naphthyl)butyric acid.HCl

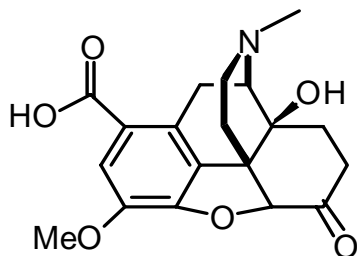


MOUSE DATA - ED50 OR AD50
(95% C.L.) or % change, mg/kg/s.c.

- 1) **TF** – 13% at 1, 7% at 10 and 13% at 30
- 2) **TF vs. M** – Inactive at 1, 9% at 10 and 38% at 30
- 3) **PPQ** – 48% at 1, 8% at 10 and 38% at 30
- 3) **HP** – Inactive at 1, 10 and 30

Comment: Some very weak opioid activity and antinociceptive properties were suggested by this data.

NIH 11247, 1-Carboxyoxycodone



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

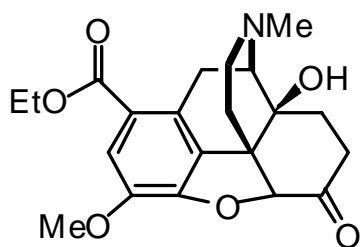
- 1) **TF** – (s.c.) Inactive at 1, 10 and 30
(i.c.v.) 8% at 1, 54% at 10 and 55% at 30
- 2) **TF vs. M** – (s.c.) Inactive at 1, 10 and 30

- 3) **PPQ** – (s.c.) 16% at 1, 0% at 10, and 16% at 30
 (i.c.v.) 24% at 1, 29% at 10 and 47% at 30
- 4) **HP** – (s.c.) 8% at 1, 3% at 10 and 7% at 30
 (i.c.v.) Inactive at 1, 19% at 10 and 69% at 30

Convulsions and death were noted at the highest dose when given i.c.v.

Comment: NIH 11247 showed little, if any, activity when given s.c.; it displayed some antinociceptive activity when given directly into the brain. However, convulsions and death occurred at the highest dose when it was given centrally.

NIH 11248, 1-Carboxyoxycodone ethyl ether



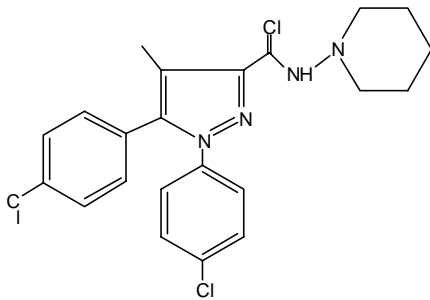
MOUSE DATA - ED50 OR AD50

(95% C.L.) or % change, mg/kg/s.c. and $\mu\text{g}/\text{brain}$

- 1) **TF** – (s.c.) Inactive at 1 and 3, 10% at 10
 (i.c.v.) 27% at 1, 8% at 10 and 7% at 30
- 2) **TF vs. M** – (s.c.) 7% at 1 and inactive at 10 and 30
 (i.c.v.) Inactive at 1, 10 and 30
- 3) **PPQ** – (s.c.) 34% at 1, 0% at 10 and 38% at 30
 (i.c.v.) Inactive at 1, 10% at 10 and 26% at 30
- 4) **HP** – (s.c.) 22% at 1, 31% at 10 and 19% at 30
 (i.c.v.) Inactive at 1, 10, and 30

Comment: These data are not indicative of remarkable activity when NIH 11248 is given either s.c. or i.c.v.

NIH 11251, SR141716, Rimonabant



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

Not tested in the mouse

MONKEY DATA – SDS

The data shown in the figure below were analyzed using Kruskal-Wallis one-way analysis of variance. The results indicated that rimonabant was without effect.

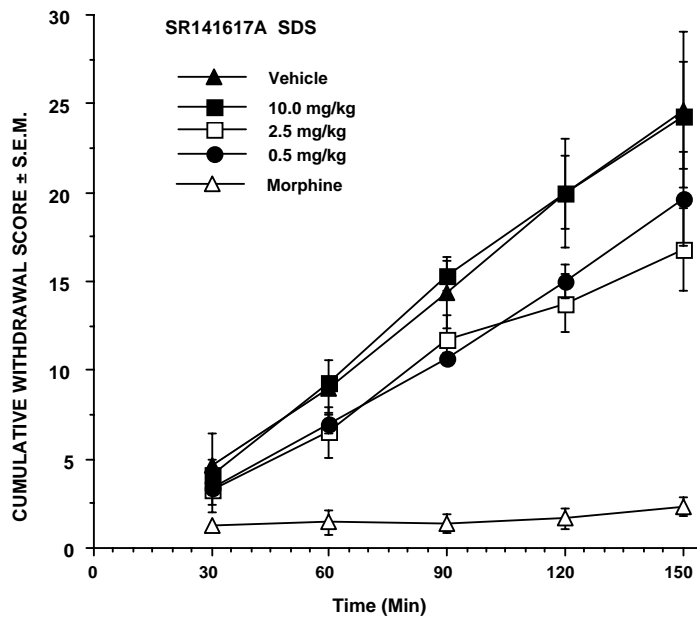
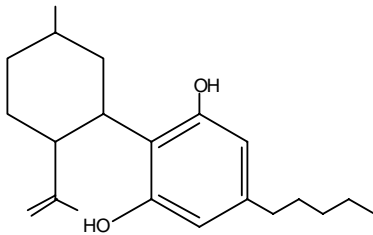


Fig NIH 11251-SDS. Results of a study in which single doses of rimonabant were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Evidence suggests that cannabinoid antagonists might be useful in the treatment of certain determinants of compulsive abuse of delta-9-tetrahydrocannabinol, nicotine, psychostimulants, alcohol and opiates (Reviewed by Le Foll and Goldberg, J. Pharmacol. Exp. Ther., 2004). However, the effects of rimonabant on an important

determinant of opiate abuse namely, physical dependence, have not been studied. Our objective was to provide preclinical support for the use of rimonabant in the treatment of this aspect of opiate abuse. We used an animal model that most closely mimics the withdrawal syndrome observed in humans. Apparently, rimonabant's purported benefits do not apply as regards opiate-induced physical dependence.

NIH 11252 Cannabidiol



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

Not tested in the mouse

MONKEY DATA – SDS

As illustrated in the accompanying figure, at doses of 2.5 and 10 mg/kg cannabidiol did not substitute for morphine or, for that matter, attenuate or exacerbate withdrawal. Vehicle was emulphor; ethanol: saline 1: 1:

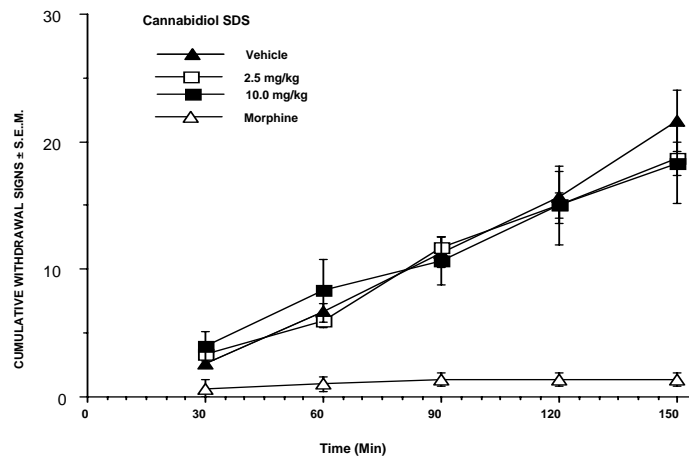


Fig NIH 11252-SDS. Results of a study in which single doses of cannabidiol were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: Cannabidiol is a substance that occurs naturally in *Cannabis sativa* and is devoid of CB1 receptor (cannabinomimetic) properties. However, behavioral studies indicate that it does produce anticonvulsant, hypnotic and anxiolytic effects. It was reported to block the block the psychotomimetic and anxiogenic effects of delta-9-THC in humans (Karniol, I.G. et al., 1974) and inhibited apomorphine-induced stereotyped behavior in rats ((Zuardi, A.W. et al., 1995). Accordingly, it was of interest to determine cannabidiol's effects on withdrawal in morphine-dependent monkeys. Apparently, it does not alleviate any of the behaviors associated with opioid withdrawal.

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