

DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (2002)

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All of the compounds submitted by the Biological Coordinator, Dr. Andrew Coop of the University of Maryland, School of Pharmacy were unknown to us except oxycodone and naltrindole, which were obtained elsewhere. 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.

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. 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 choice of treatments. At the end of the study, the data were grouped according to dose and drug. 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 in withdrawal. Naloxone·HCl (0.05 mg/kg, s.c.) served as the positive control.

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behavioral signs during drug administration and when they were challenged with the antagonist, naloxone, or abruptly withdrawn from the drug.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 silk 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·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 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 were calculated by using computerized probit analysis. The results obtained with reference compounds are summarized in Table 2. Occasionally, when requested, drugs were given orally (p.o.) or intravenously (i.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 of noxious stimulus was turned on, the heat 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 three 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 parphenylquinone (PPQ) solution. The mice were then placed in cages in groups of two each. Ten min after the PPQ injection, the total number of stretches per group were counted over a 1-min period. A stretch was characterized by an elongation of the mouse's body, development of tension in the abdominal muscles, and extension of the forelimbs. 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 55°C. Mice were placed on the hot plate and activity was scored if the animal jumped or licked its paws after a delay of 5 sec or more, but no more than 30 sec beyond the control time.

Table 2

Comparative Data (ED50 or AD50, 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) (1.0-2.5) | 1.7 | 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 |
| 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·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 ₄ | ---- | Inactive | 8.25 (5.12-13.29) | 6.4 (2.4-16.8) |
| Meperidine·HCl | 8.37 (4.59-15.27) | Inactive | ---- | 4.6 (1.18-11.7) |

^aMice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time

^bICR - 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.

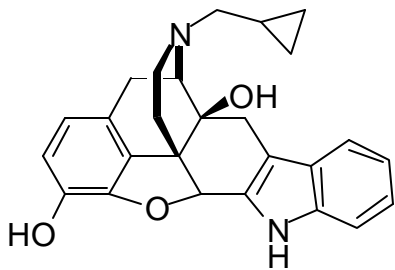
Table 3. Apparent pA₂ values^a using the mouse tail-flick assay

| <u>Treatment</u> Antagonist/Agonist | <u>Schild Plot</u> pA ₂ (95% C.L.) Slope | <u>Constrained Plot</u> 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 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 accommodate the fact that no delta agonist is available which is active by peripheral routes of administration.

NIH 10589 Naltrindole•HCl



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

- 1) TF - Inactive at 1, 10 and 30^a
- 2) TF vs. M - Inactive at 1, 20 and 30^a
- 3) PPQ - 0% at 1, and 10 and 28% at 30^a
- 4) HP - Not tested

^aPreviously reported, see NIDA Res. Monog. 95, 614, 1989

NIH 10589 (continued)

NEW DATA

Table 1. The interaction of opioid-agonist subtypes and naltrindole in the mouse PPQ test.

| Antagonist | Antagonist Pretreatment Time (min) | Agonist ED ₈₀ | Agonist Pretreatment Time (min) | AD ₅₀ (95% Confidence Limits) |
|--------------------|------------------------------------|--|---------------------------------|---|
| Naltrindole (s.c.) | 30 | Morphine Sulfate (mu agonist) (s.c.) | 20 | 30.0 mg/kg: 7% antagonism 10.0 mg/kg: 7% antagonism 1.0 mg/kg: 7% antagonism |
| Naltrindole (s.c.) | 30 | NIH 10672 (Enadoline) (kappa agonist) (s.c.) | 20 | 30.0 mg/kg: 0% antagonism 10.0 mg/kg: 0% antagonism 1.0 mg/kg: 0% antagonism |
| Naltrindole (s.c.) | 30 | U-50,488 ED ₈₀ (kappa agonist) (s.c.) | 20 | 30.0 mg/kg: 29% antagonism 10.0 mg/kg: 8% antagonism 1.0 mg/kg: 0% antagonism |
| Naltrindole (s.c.) | 30 | DPDPE delta agonist (i.c.v.) | 10 | AD ₅₀ = 0.12 mg/kg (0.1 - 0.27) Slope - 3.63 |

MONKEY DATA (Previously reported, see NIDA Res. Monog. 95, 615, 1989)
(SDS)

This compound did not substitute for morphine. It exacerbated withdrawal at 3 and 12 mg/kg (see fig NIH 10589).

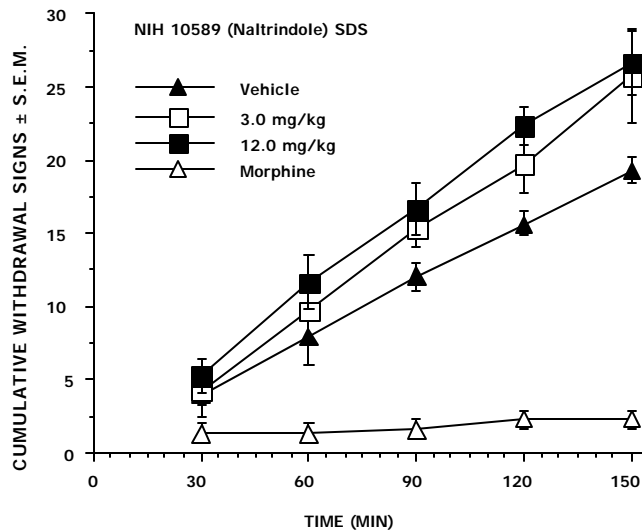
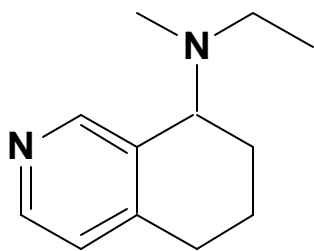


Fig NIH 10589 Results of study in which single doses of NIH 10589 (Naltrindole) were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Naltrindole is a selective delta opioid antagonist in the PPQ test. Note however, that the drug also acts as a mu antagonist in the morphine-dependent monkey or perhaps reveals a delta component of withdrawal.

NIH 10967 8-(Ethylmethylamino)-5,6,7,8-tetrahydroisoquinoline



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

- 1) TF – 0.8 (0.64 – 1.01)^a
- 2) TF vs. M – Inactive at 1, 10 and 30^b
- 3) PPQ – 0.37 (0.13 – 1.06)
- 4) HP – 0.8 (0.3 – 2.1)^c

^a2 of 6 convulsed and died at 1 mg/kg and 1 of 6 convulsed but did not die at 1 mg/kg.

^bAll convulsed and died at 10 and 30 mg/kg

^cAll convulsed and died at 10 mg/kg and 4 of 8 died at 3 mg/kg.

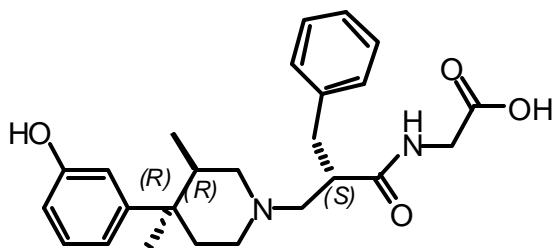
Special: Naloxone vs NIH 10967 ED₈₀ in PPQ test = 0% antagonism.

MONKEY DATA
(SDS)

Not tested.

Comment: The compound displayed potent antinociceptive effects. However, the drug also produced convulsions and was lethal. The profile of activity does not indicate opioid properties.

NIH 10996 (+)-2-[2(*S*)-Benzyl-3-[4(*R*)-(3-hydroxyphenyl)-3(*R*),4-dimethylpiperidin-1-yl]propionamido]acetic acid



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

- 1) a) TF (s.c.) – Inactive at 1, 10 and 30^a
b) TF (oral) - 3% at 1, 0% at 10 and 1% at 30^{a,b}
c) TF (oral) - 0% at 1, 1% at 10 and 12% at 30^{a,c}

(Repeat)

- 1) ^aTF (s.c.) - Inactive at 1, 10 and 30 (in 50% DMSO)^d
^bTF vs. M – Inactive at 1, 10 and 30^a
^cTF vs M – 26 % at 1, 0% at 10 and 21% at 30 (in 50% DMSO)^d
- 2) PPQ – 0% at 1, 3% at 10, 43% at 30 and 69% at 60^a
- 3) HP – Inactive at 1, 10 and 30^a

^aVehicle was 30% hydroxypropyl-β-cyclodextrin in water.

^aTwenty min pretreatment.

^cSixty min pretreatment.

^dDMSO is dimethyl sulfoxide.

Special test: Naloxone (s.c.) vs 69% activity at 60 mg/kg of NIH 10996 (s.c.) in the PPQ test: Inactive at 1 and 10 mg/kg.

NIH 10996 (Continued)

MONKEY DATA

(SDS)

At 5 and 20 mg/kg, NIH 10996 neither substituted for morphine nor exacerbated withdrawal. Vehicle was 10% hydroxypropyl- β -cyclodextrin in water.

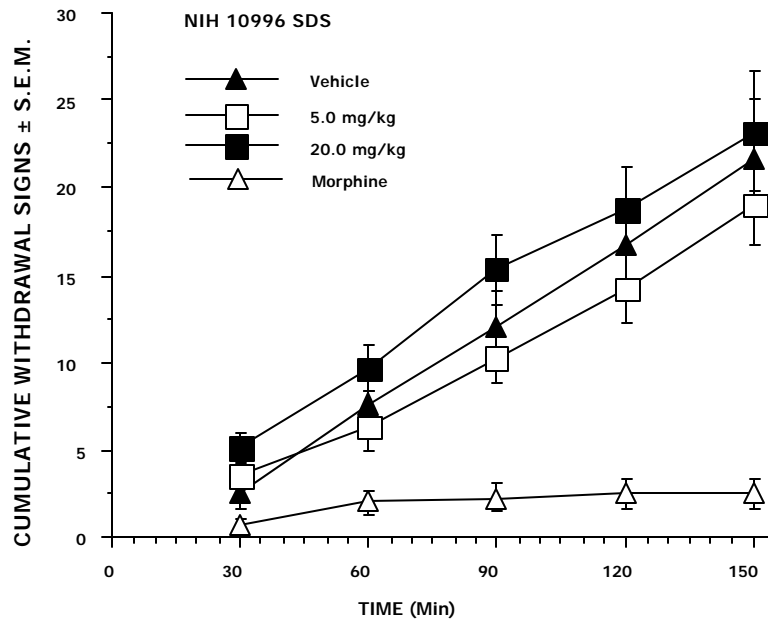
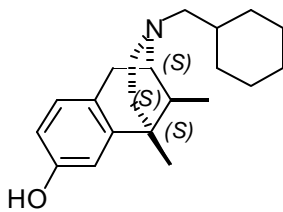


Fig NIH 10996-SDS. Results of study in which single doses of NIH 10996 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: When given subcutaneously or orally, NIH 10996 did not display remarkable antinociceptive properties in a variety of tests when given in different vehicles (30% hydroxypropyl- β -cyclodextrin in water or 50% dimethylsulfoxide aqueous solution). The effects in mice or monkeys were not indicative of mu-opioid activity.

NIH 11011 (+)-(1S,5S,9S)-2-(Cyclohexylmethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



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

- 1) TF – Inactive at 1, 10 and 30
- 2) TF vs. M – 20% at 1, 1% at 10 and 7% at 30
- 3) PPQ – 17.57 (5.91 – 52.26)
- 4) HP – 0% at 1 and 10, 13% at 30

NIH 11011 (continued)

Special Test:

Natrindole vs NIH 11011, 60 mg/kg, in PPQ Test: Antagonism = 23% at 1, 33% at 3, 11% at 10 and 0% at 30.

MONKEY DATA

(SDS)

Attenuation of withdrawal signs at 16 mg/kg was accompanied by jaw sag and ataxia. These behavioral signs and salivation were also noted at the lower dose.

Drug supply was exhausted. Thus, a complete evaluation of NIH 11011 was precluded.

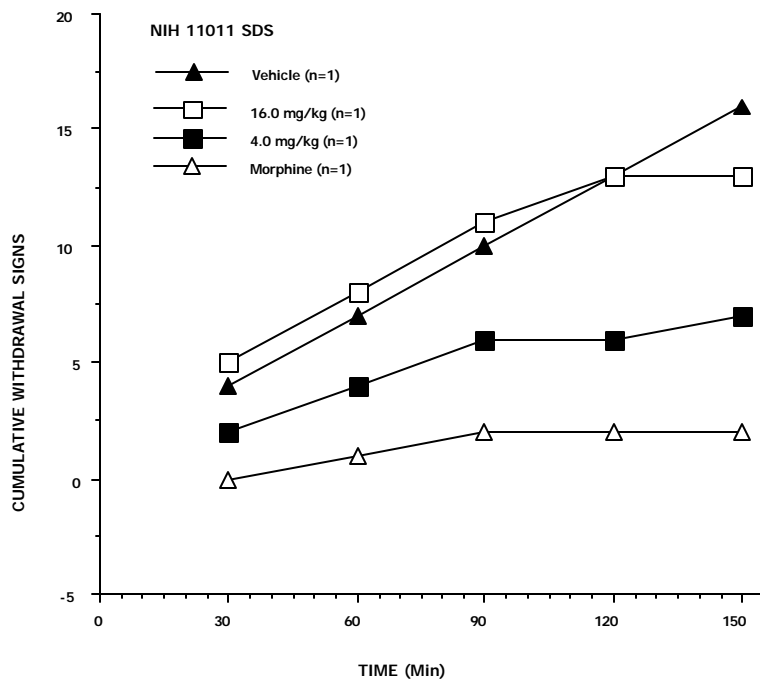
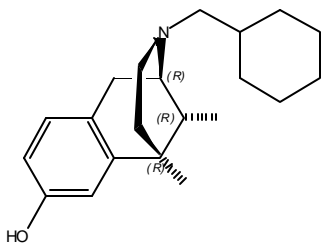


Fig NIH 11011-SDS. Results of study in which single doses of NIH 11011 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity does not suggest mu opioid-receptor interactions.

NIH 11012 (-)-(1R,5RS,9R-2-(Cyclohexylmethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



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

- 1) TF – 3% at 1 and 10, 0% at 30^a
- 2) TF vs. M – 3.70 (1.02 – 13.45)^a
- 3) PPQ – 14.62 (3.12 – 68.3)^{a,b}
- 4) HP – 0% at 1 and 10, 13% at 30^a

^aVehicle was 4% Tween 80 in water.

^bOne mouse at 60 mg/kg was very lethargic and one mouse had convulsions that lasted to end of experiment.

Special Test:

5) Naltrindole (s.c.), (30 min pretreatment) vs NIH 11012 ED80 in the PPQ test: 15% at 1, and 13% at 10 and 30^c mg/kg.

^cVehicle was 5% hydroxypropyl- β -cyclodextrin in water.

MONKEY DATA

(SDS)

At doses of 0.75 and 3.0 mg/kg, NIH 11012 did not substitute for morphine or exacerbate withdrawal. Jaw sag was noted at 3 mg/kg. One monkey who received 12 mg/kg had tremors followed by convulsions. Pentobarbital (30 mg/kg, i.p.) effectively terminated the convulsions.

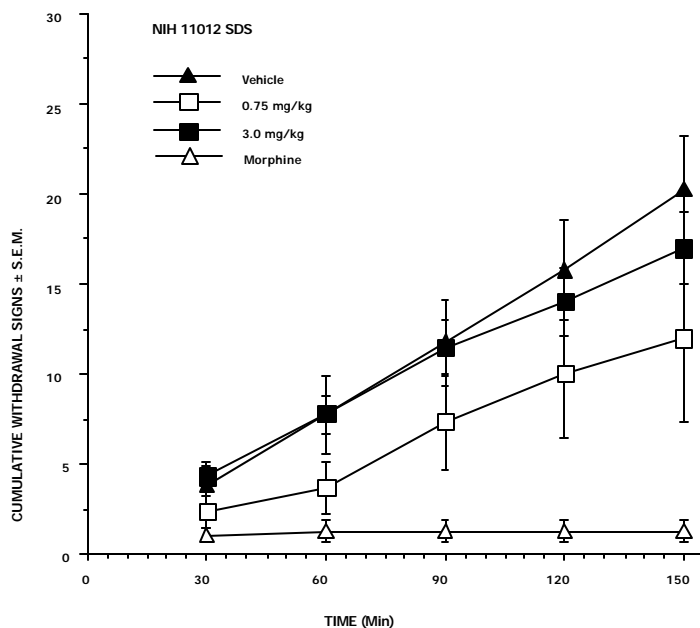
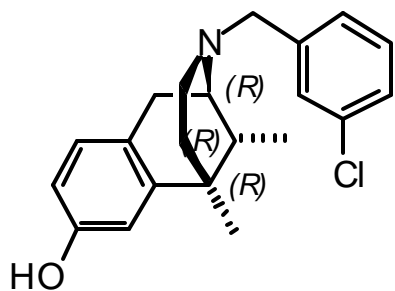


Fig NIH 11012-SDS. Results of study in which single doses of NIH 11012 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results suggest that NIH 11012 has weak mu-opioid antagonist properties. Some antinociception was noted in the PPQ test which was not delta-opioid receptor related. The drug also produced convulsions in both species.

NIH 11027 (-)-(1R,5R,9R)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy -6,7-benzomorphan Hydrochloride



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

- 1) TF – Inactive at 1, 10 and 30^a
- 2) TF vs. M – 2% at 1, 0% at 10 and 21% at 30^a
- 3) PPQ – 15% at 1 and 0% at 10 and 30^a
- 4) HP – 0% at 1 and 10, 25% at 30^a

^aVehicle was dilute lactic acid + heat.

MONKEY DATA
(SDS)

Doses of 4 and 16 mg/kg of NIH 11027 exacerbated withdrawal in morphine-dependent monkeys (see figure). The effect was not dose related and duration was at least 2 1/2 hr. Vehicle was 10% hydroxypropyl- β -cyclodextrin in water.

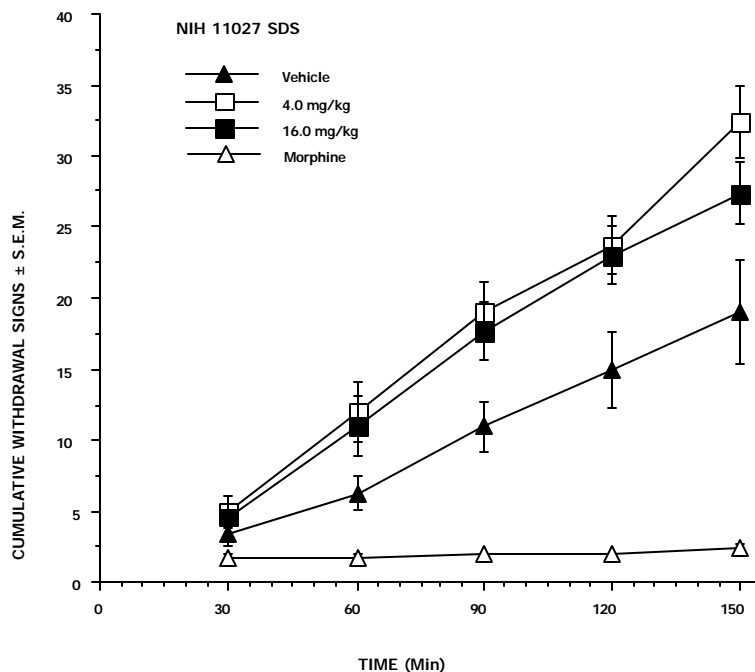
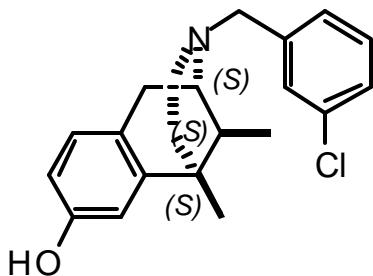


Fig NIH 11027-SDS. Results of study in which single doses of NIH 11027 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11027 may have weak mu-opioid receptor antagonist properties.

NIH 11029 (+)-(1*S*,5*S*,9*S*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



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

- 1) TF – 2.1% at 1, 0% at 10 and 21.5% at 30^a
- 2) TF vs. M – Inactive at 1 and 10, 6% at 30^a
- 3) PPQ – Inactive at 1 and 10, 44% at 30^a
- 4) HP – 13% at 1, Inactive at 10 and 30^a

^aVehicle was dilute lactic acid in water.

MONKEY DATA
(SDS)

At 4 and 16 mg/kg, some partial attenuation of withdrawal signs was observed (see figure). The effect was not dose related. Jaw sag was noted in one monkey at the high dose. The drug acted promptly. Duration of action was 2 1/2 hr. Vehicle was 10% hydroxypropyl- β -cyclodextrin in water.

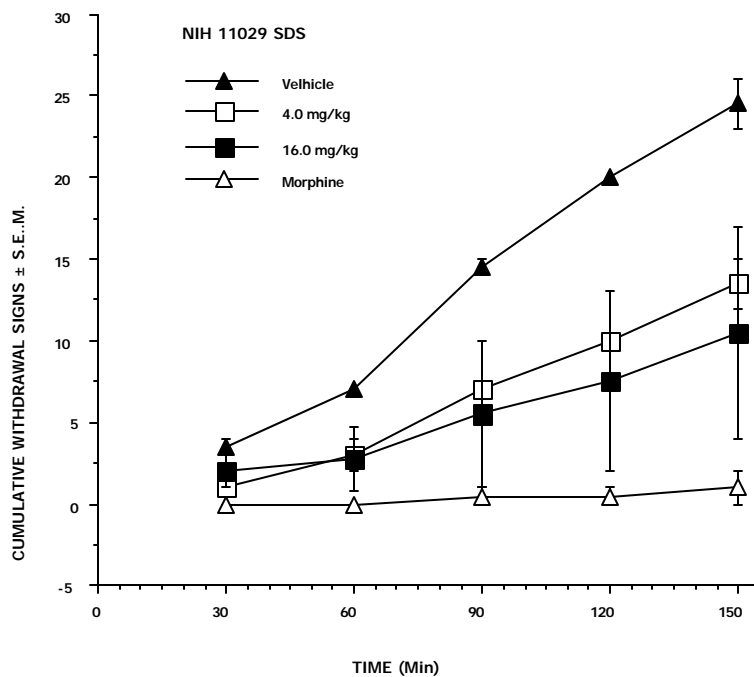
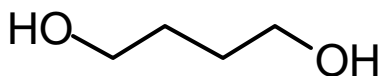


Fig NIH 11029-SDS. Results of study in which single doses of NIH 11029 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity does not indicate significant opioid effects.

NIH 11030 1,4-Butanediol (Purported precursor of γ -hydroxybutyrate)



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

- 1)a TF – Inactive at 1, 10% at 10 and 45% at 30^a
- b TF – Inactive at 1, 3% at 10 and 6% at 30^b
- 2)a TF vs. M – Inactive at 1 and 10, 20% at 30^b
- b TF vs. M – 5% at 1, 11% at 10 and 6% at 30^b
- 3)a PPQ – 8% at 1, 10% at 10 and 40% at 30^b
- b PPQ – Inactive at 1, 17% at 10 and 23% at 30^b
- 4)a HP – Inactive at 1, 10 and 30^a
- b HP – 13% at 1, Inactive at 10 and 30^b

^aPretreatment time 20 min.

^bPretreatment time 60 min.

MONKEY DATA
(SDS)

NIH 11030 neither substituted for morphine nor exacerbated withdrawal in the dose range of 4.5 to 18 mg/kg. Curiously, it attenuated withdrawal signs at the low dose but not at the higher dose.

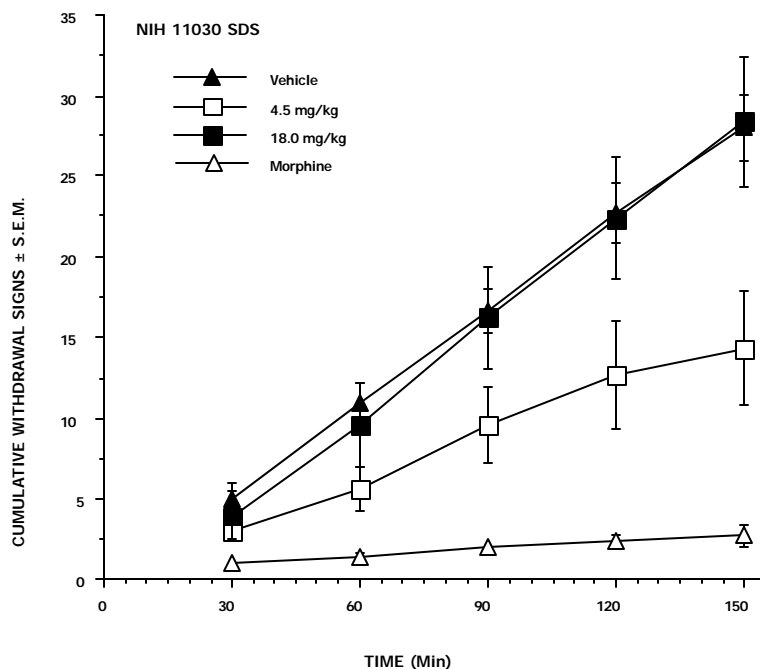
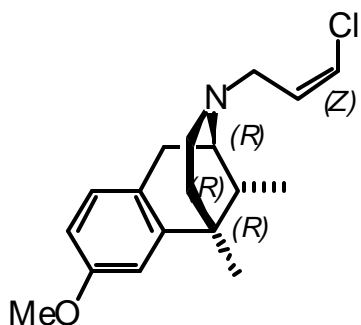


Fig NIH 11030-SDS. Results of study in which single doses of NIH 11030 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Apparently, this compound is free of opioid effects.

NIH 11032 (-)-(1*R*,5*R*,9*R*)-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan Oxalate



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

- 1) TF – 3% at 1, 13% at 10 and 14% at 30
- 2) TF vs. M – 1.08 (0.31 - 3.73)
- 3) PPQ – 17.43 (10.26 - 29.62)
- 4) HP - 25% at 1, 0% at 10 and 30

Vehicle was water aided by warming.

MONKEY DATA
(SDS)

NIH 11032 did not substitute for morphine and may have exacerbated withdrawal. Because the vehicle controls showed fewer than the usual number of withdrawal signs, the exacerbation of withdrawal depicted in the figure may be exaggerated. The drug does produce some jaw sag and slowing in 1/3 at 1.25 mg/kg and jaw sag in 2/3, slowing in 2/3 and body sag in 1/3 monkeys at 5 mg/kg. Vehicle was 10% aqueous hydroxypropyl- β -cyclodextrin solution.

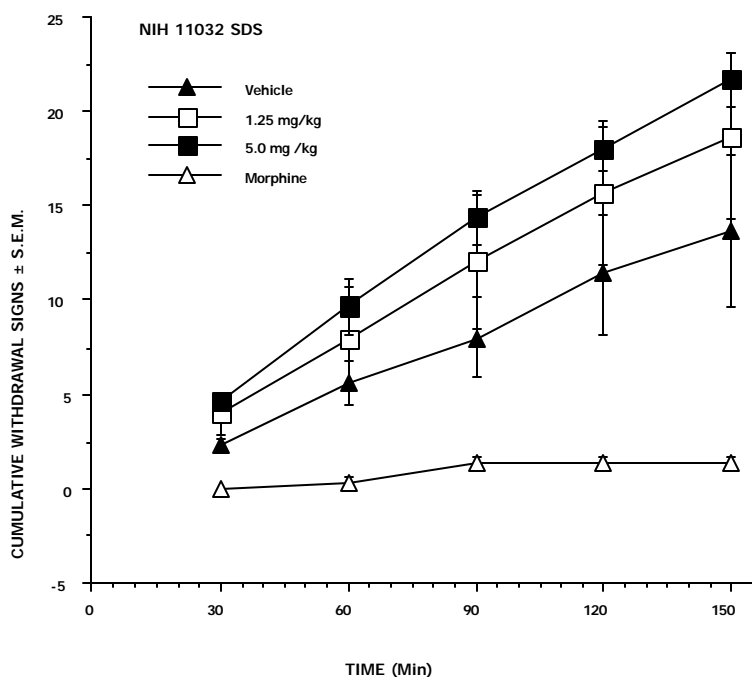
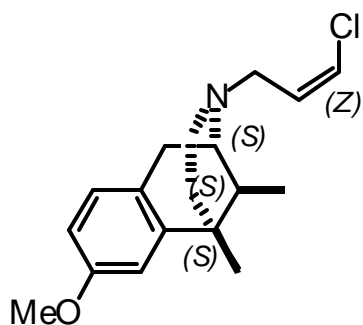


Fig NIH 11032 SDS. Results of study in which single doses of NIH 11032 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: NIH 11032 has very weak mu-opioid receptor antagonist activity as well as some antinociceptive action.

NIH 11033 (+)-(1*S*,5*S*,9*S*)-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan oxalate



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

- 1) TF – Inactive at 1, 10 and 30
- 2) TF vs. M – 32% at 1, 15% at 10 and 47% at 30
- 3) PPQ – Inactive at 1 and 10, 16% at 30
- 4) HP – 25% at 1, 0% at 10 and 13% at 30

MONKEY DATA
(SDS)

As shown in the accompanying figure, NIH 11033 did not produce a remarkable attenuation of withdrawal signs. At the high dose slowing, ataxia and jaw sag were noted.

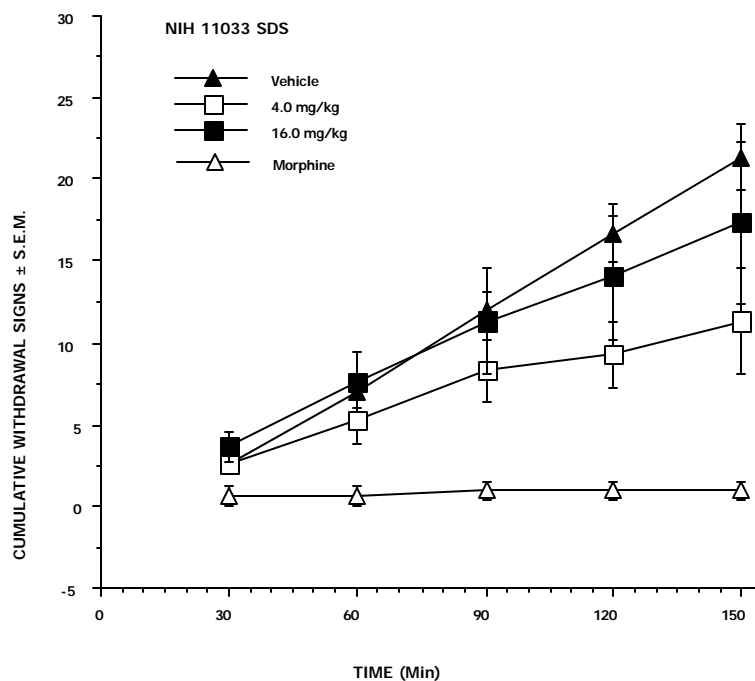
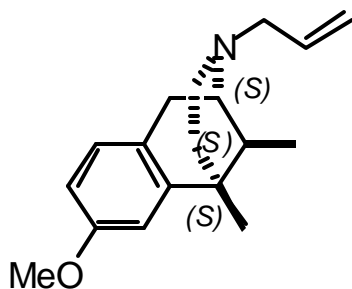


Fig NIH 11033-SDS. Results of study in which single doses of NIH 11033 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Very weak biological activity in the mouse as well as non dose-related attenuation of withdrawal signs in the monkey, suggest that NIH 11033 does not have remarkable mu-opioid properties.

NIH 11036 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan Oxalate



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

- 1) TF – 4% at 1, 5% at 10 and 0% at 30
- 2) TF vs. M – Inactive at 1, 10 and 30
- 3) PPQ – 21.6 (12.7 - 36.5)
- 4) HP - Inactive at 1, 10 and 30
- 5) TF -5% at 1 and 5, 25% and 31% at 10 and 12% at 30^c
(Intravenously)

^cTremors at 10 mg/kg and clonic convulsions, rapid respiration at 30. 1/6 Straub tail and 1/6 died at 30.

MONKEY DATA
(SDS)

At doses of 4.5 and 18 mg/kg, NIH 11036 neither substituted for morphine nor exacerbated withdrawal (see figure). At the low dose, overt behavioral signs designated as slowing (1/3) and ataxia (2/3) were noted. At the higher dose, slowing (2/3), ataxia (2/3), jaw sag 1/3, eyelid ptosis (2/3) and glassy eyes (1/3) were observed.

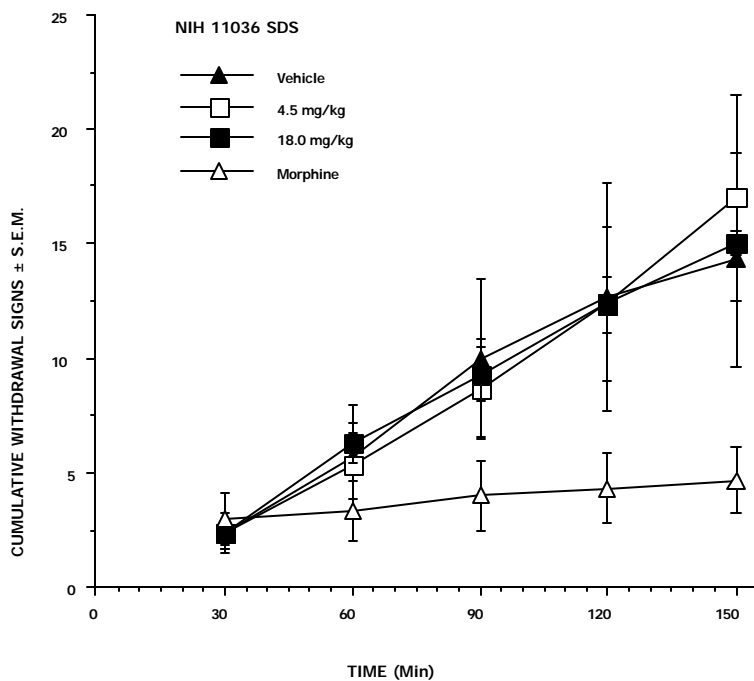
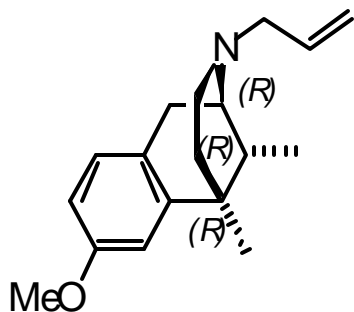


Fig NIH 11036-SDS. Results of study in which single doses of NIH 11036 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity in mice and monkeys is not indicative of mu-opioid agonist activity. However, the drug has significant central nervous system depressant activity.

NIH 11038 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan Oxalate



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

- 1) TF – Inactive at 1, 10 and 30
- 2) TF vs. M – 3.25 (1.05 - 10.04)^a
TF vs. M – 9.09 (1.97 - 41.98)^b
- 3) PPQ – Inactive at 3, 24% at 10, 3% at 20 and 8% at 30
- 4) HP – Inactive at 30
^a30-min pretreatment time.
^b4-hr pretreatment time.

MONKEY DATA
(SDS)

At 2 mg/kg, NIH 11038 exacerbated withdrawal (see figure). Onset was prompt and duration of action was at least 2 1/2 hr. Also noted, at 2 mg/kg was slowing in 3/4 and ataxia in 2/4 of the subjects. At 8 mg/kg, the signs slowing in 3/4, ataxia in 3/4, jaw sag in 2/4 and eyelid ptosis in 1/4 of the monkeys were observed during the first 90 min of the study.

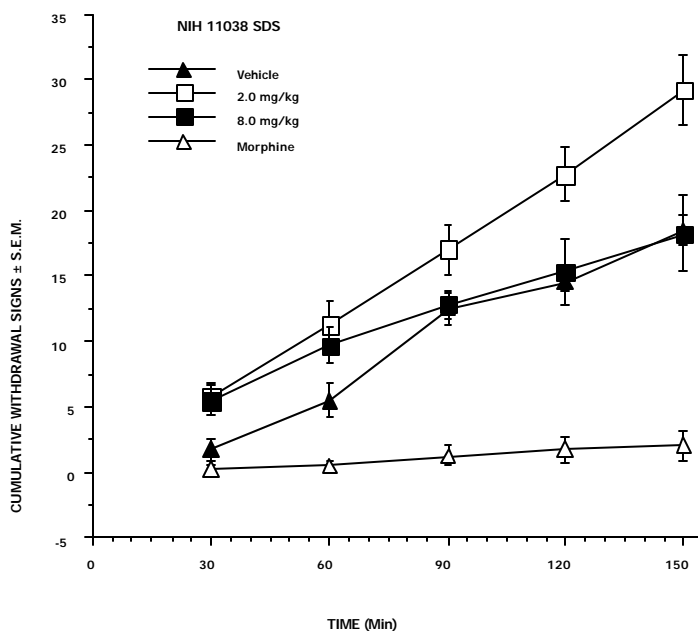
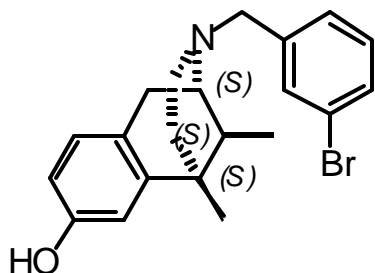


Fig NIH 11038-SDS. Results of study in which single doses of NIH 11038 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results indicate that NIH 11038 is a weak mu-opioid receptor antagonist. Some of the behavioral signs noted suggest other CNS effects.

NIH 11039 (+)-(1*S*,5*S*,9*S*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy -6,7-benzomorphan Hydrochloride



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

- 1) TF – 12% at 1, 1% at 10 and 5% at 30
- 2) TF vs. M – 6% at 1, 21% at 10 and 19% at 30
- 3) PPQ – 30% at 1, 37% at 10 and 47% at 30
- 4) HP – Inactive at 1 and 10, 13% at 30

MONKEY DATA
(SDS)

At doses of 4 and 16 mg/kg, NIH 11039 did not display mu-opioid agonist or antagonist action in morphine-dependent rhesus monkeys.

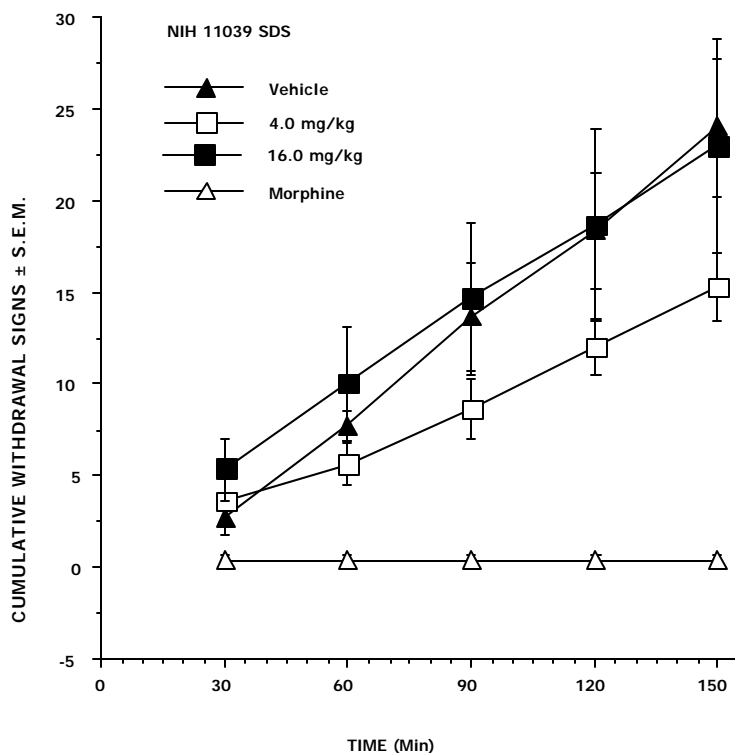
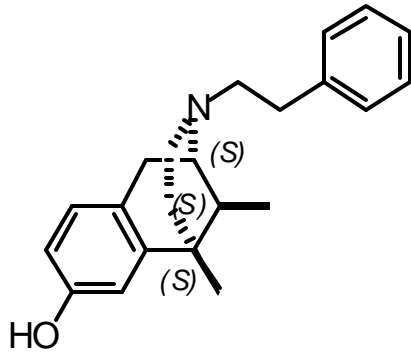


Fig NIH 11039-SDS. Results of study in which single doses of NIH 11039 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11039 does not display activity typical of mu-opioid agonists or antagonists.

NIH 11040 (+)-Phenazocine Hydrobromide (NIH 7614)



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

- 1) TF - 0% at 1, 24% at 10 and 15% at 30.
- 2) TF vs. M - 2% at 1, 0% at 10 and 13% at 30.
- 3) PPQ - 3.4 (1.4 - 8.2).
- 4) HP - 0% at 1, 25% at 10 and 38% at 30.^{a,b}

^aVehicle was 5% hydroxypropyl- β -cyclodextrin in H₂O.

^bLightly sedated at 30 mg/kg.

MONKEY DATA
(SDS)

At doses of 1, 4 and 16 mg/kg, NIH 11041 neither substituted for morphine nor exacerbated withdrawal in morphine-dependent monkeys (see figure). Jaw sag was observed at the lowest dose in one monkey, slowing and eyelid ptosis were noted in 1/3 at the next higher dose, and jaw sag, ataxia, slowing, vomiting and convulsions were noticed in one of two monkeys at the highest dose. Pentobarbital, 30 mg i.p., promptly terminated the convulsions. Drug supply was exhausted. Vehicle was 10% hydroxypropyl- β -cyclodextrin in water.

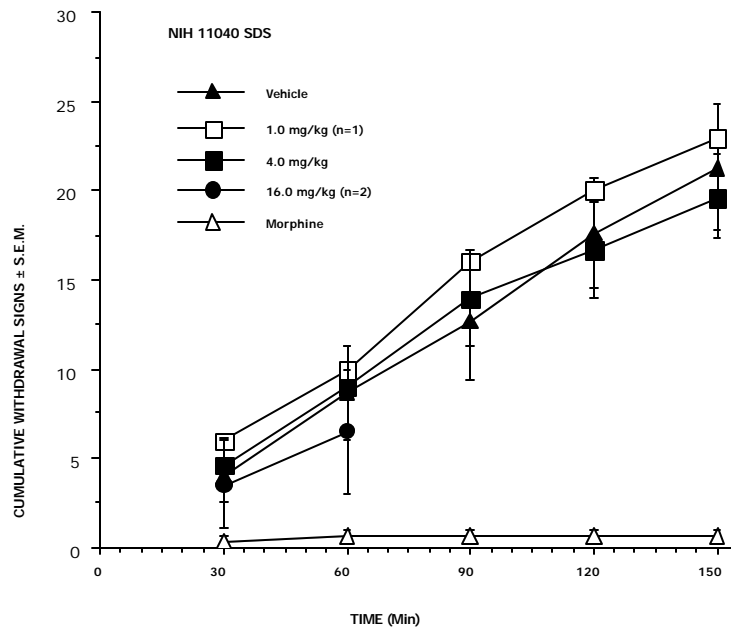
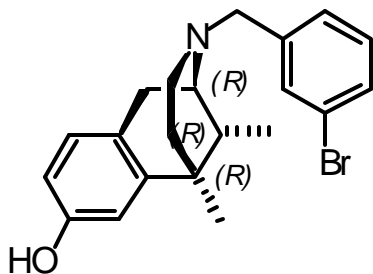


Fig NIH 11040 SDS. Results of study in which single doses of NIH 11040 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity exhibited by NIH 11040 does not portend remarkable mu-opioid properties. Antinociceptive activity in the PPQ test coupled with convulsions in the SDS study hint at delta-opioid activity.

NIH 11041 (-)-(1*R*,5*R*,9*R*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy -6,7-benzomorphan Hydrochloride



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

- 1) TF – 3% at 1 and inactive at 10 and 30.^a
- 2) TF vs. M – Inactive at 1, 10 and 30.^a
- 3) PPQ – 18% at 1, 0% at 10 and 18% at 30.^a
- 4) HP - Inactive at 1, 10 and 30.^a

^aVehicle was 10% hydroxypropyl- β -cyclodextrin in H₂O.

MONKEY DATA
(SDS)

At doses of 4 and 16 mg/kg NIH 11041 was without apparent effect in withdrawn morphine-dependent rhesus monkeys. The results are depicted in the accompanying figure.

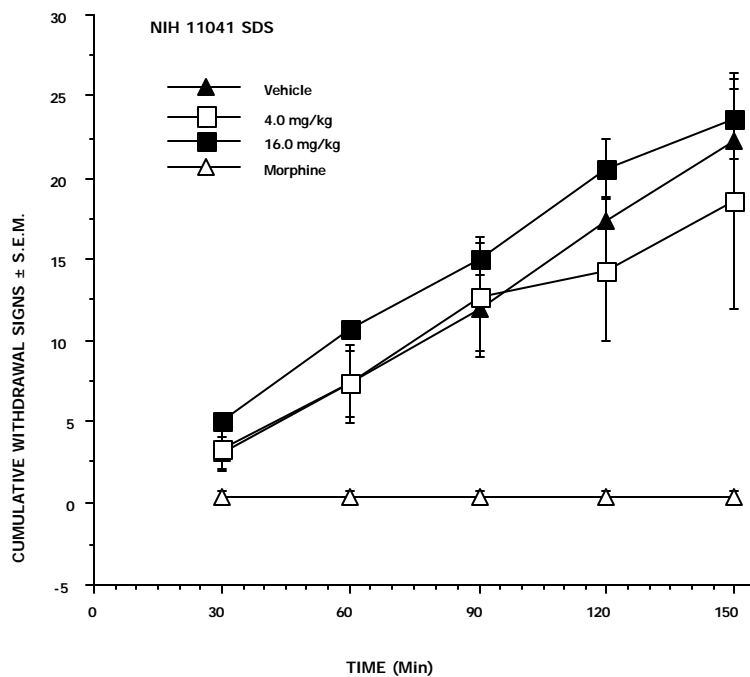
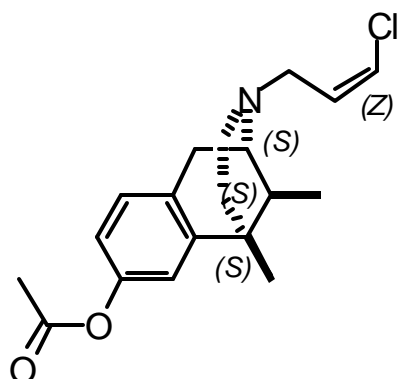


Fig NIH 11041 SDS. Results of study in which single doses of NIH 11041 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: NIH 11041 appeared devoid of opioid activity in mice and morphine-dependent monkeys.

NIH 11042 (+)-(1*S*,5*S*,9*S*)-2'-Acetoxy-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan Oxalate



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

- 1) TF – 0% at 1, 6% at 10 and 0% at 30.
 - 2) TF vs. M – 22.0 (13.6 - 35.6).
 - 3) PPQ – 3% at 1, 26% at 10 and 35% at 30^{a,b,c}
 - 4) HP - 13% at 1 and 0% at 10 and 30.^{a,c}
- ^aAtaxic at 30.
^bSlightly ataxic at 20.
^cHyperactivity at 30.

MONKEY DATA
(SDS)

NIH 11042 did not substitute for morphine or exacerbate withdrawal (see figure). Attenuation of withdrawal signs was probably associated with the side effects of the drug which were: ataxia in 3/4, slowing in 4/4, jaw sag in 1/4 at 1 mg/kg; body sag in 1/4 and eyelid ptosis in 1/4 at 4 mg/kg; and, ataxia in 2/2 and slowing in 2/2 at highest dose.

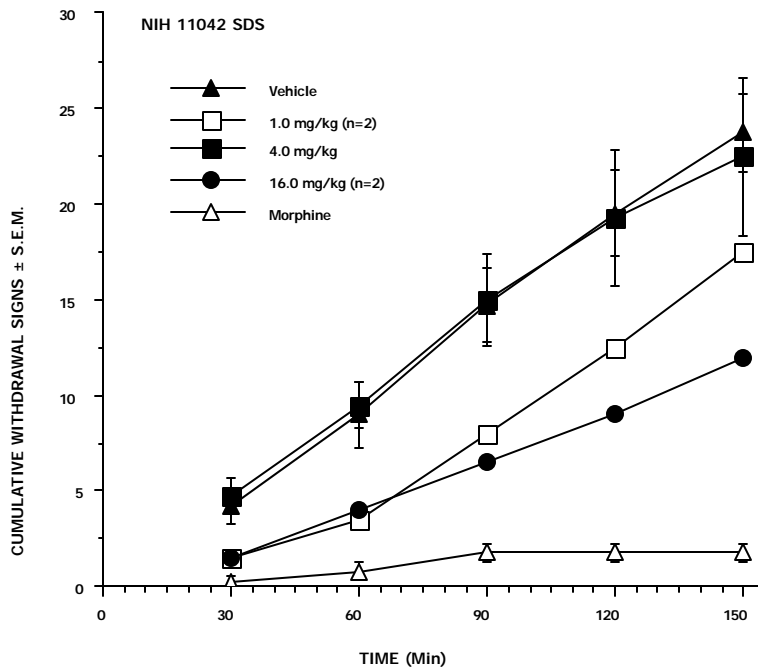
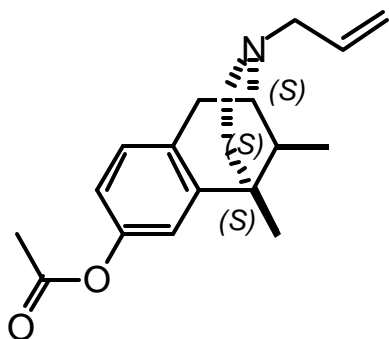


Fig NIH 11042 SDS. Results of study in which single doses of NIH 11042 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: The results in mice indicate that NIH 11042 has very weak mu-antagonist properties and potent CNS effects.

NIH 11043 (+)-(1*S*,5*S*,9*S*)-2'-Acetoxy -5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan Oxalate



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

- 1) TF – Inactive at 1, 10 and 30.^{a,b}
- 2) TF vs. M – Inactive at 1, 10 and 30.
- 3) PPQ – 8.90 (5.08 - 15.60).
- 4) HP - 13% at 1 and 0% at 10 and 30.^b

^aJumpy when handled.

^bAtaxia at 30.

MONKEY DATA
(SDS)

Although NIH 11043 appeared to attenuate withdrawal signs in rhesus monkeys in a dose-related manner (see accompanying figure), the reduction in signs was probably associated with the severe side effects of the drug. At the high dose, 4/4 were severely ataxic, 4/4 were slow, 3/4 had jaw sag, 2/4 had eyelid ptosis and 1/4 developed body sag. The drug acted promptly and its effects lasted for approximately 90 min.

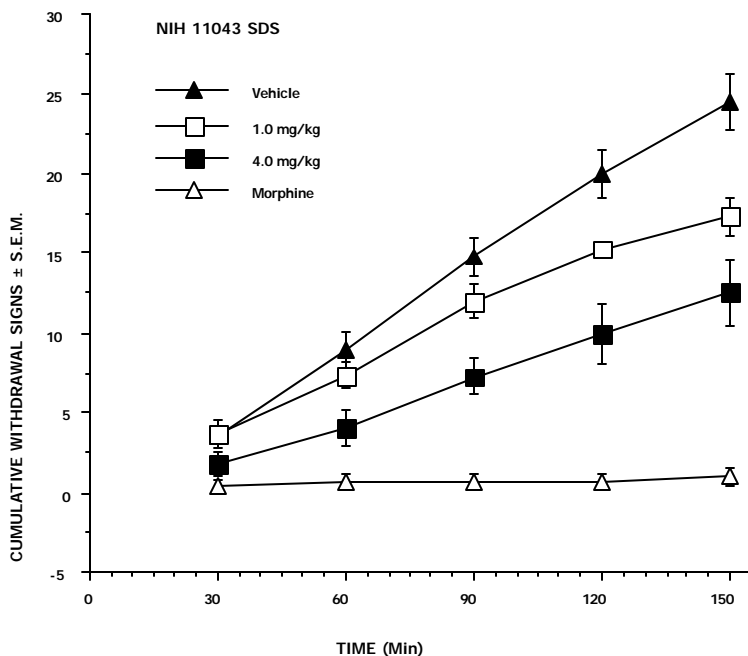
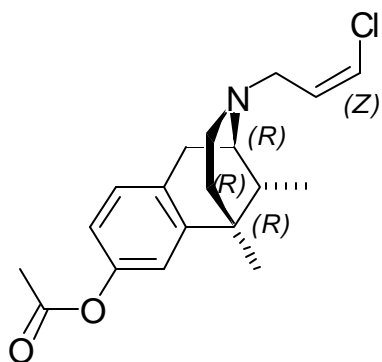


Fig NIH 11043 SDS. Results of study in which single doses of NIH 11043 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: In the mouse and rhesus monkey, NIH 11043 did not display mu-opioid receptor agonist or antagonist properties. Prominent CNS effects were noted.

NIH 11044 (-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan Oxalate



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

- 5) TF – Inactive at 1, 10 and 30^{a,b}
- 6) TF vs. M - 0.24 (0.01 - 0.60)
- 3) PPQ – 10.50 (2.42 - 45.60)^a
- 7) HP - 25% at 1, 0% at 10 and 30^a

^aAtaxia at 10 and 30.

^bIncreased locomotor activity at 10.

MONKEY DATA
(SDS)

The behavioral signs exhibited by NIH 11044 suggested multiple opioid properties. The signs designated jaw sag, slowing, eyelid ptosis, vomiting and, especially salivation, suggested kappa-opioid agonist properties. Also observed, were the signs designated retching, vomiting, tremors, and rigid abdominal muscles accompanied by vocalization when palpated, indicative of mu-opioid receptor antagonist activity. It should be noted that vomiting is noted infrequently in abruptly withdrawn morphine-dependent monkeys. This sign is usually associated with precipitated withdrawal. These effects were dose-related, of rapid onset and were diminished after 90 min. At 1 mg/kg, the drug appeared to exacerbate withdrawal. At the highest dose (10 mg/kg), the results depicted in the accompanying figure suggest that this compound was attenuating withdrawal. However, this interpretation is probably not correct because all the monkeys receiving this dose refused to leave the pen to have their abdomens palpated during the 30-min check. Two would not leave the pen during the 60-min examination and 1 declined the 90-min check. The end result was a lower than normal cumulative withdrawal score.

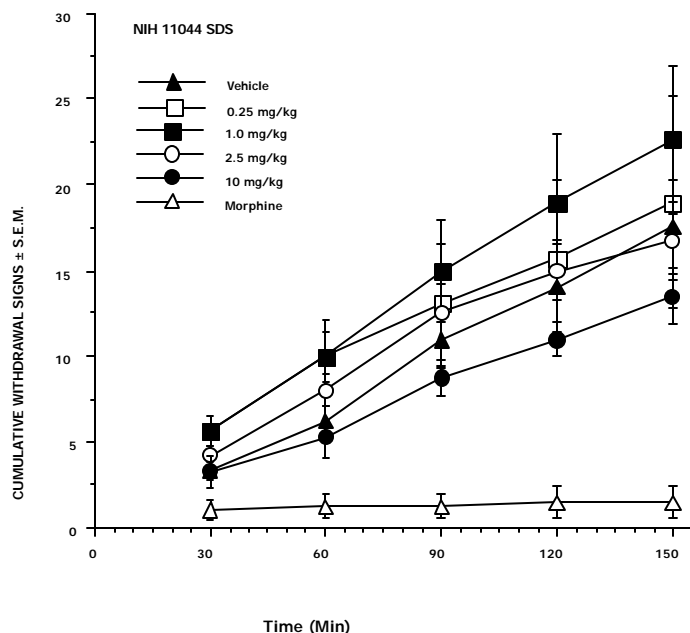
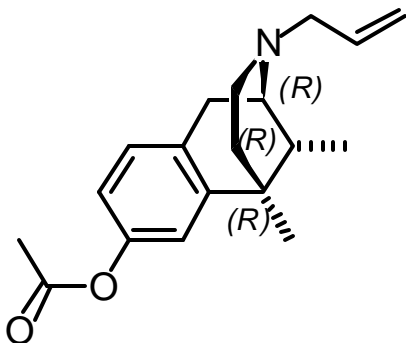


Fig NIH 11044 SDS. Results of study in which single doses of NIH 11044 were substituted for morphine in morphine-dependent monkeys in withdrawal

NIH 11044 (continued)

Comment: The results in the mouse indicate some weak analgesic and mu-opioid receptor antagonist properties. In the monkey, NIH 11044 appeared to be a mu-opioid receptor antagonist and kappa-opioid receptor agonist. A complete opioid subtype profiling in the mouse might be more revealing.

NIH 11045 (-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan Oxalate



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

- 1) TF – 0% at 1 and 10, 5% at 30^{a,b}
- 2) TF vs. M - 1.35 (0.76 - 2.39)
- 2) PPQ – 3% at 1, 8% at 10 and 13% at 30^a
- 3) HP - Inactive at 1, 10 and 30^a

^aIncreased locomotor activity at 30.

^bAtaxia at 10 and 30.

Special Test: AD50 of NIH 11046 vs ED80 of enadoline, a selective kappa agonist, (0.3 mg/kg, s.c.) = 2.73 (1.43 - 5.22).

MONKEY DATA
(SDS)

With NIH 11045 there is evidence for heterogeneous opioid subtype activity in the morphine-dependent monkey in abrupt withdrawal. This compound displayed a behavioral profile not unlike that of NIH 11044. The signs designated jaw sag, ataxia, slowing, eyelid ptosis, tremors and salivation were noted. The effects appeared dose-related. The drug acted promptly and the duration of action was 90 to 120 min. In addition, 3 monkeys refused to leave their pen during the 30-min abdominal muscles check; 2 would not leave their pen during the 60-min examination; and, 1 would not leave its pen until the 120-min interval.

NIH 11045 (continued)

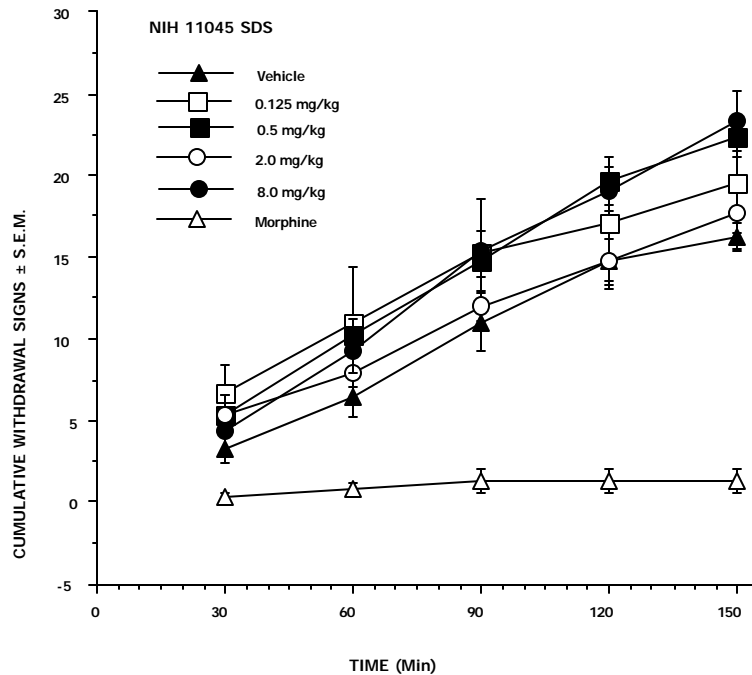
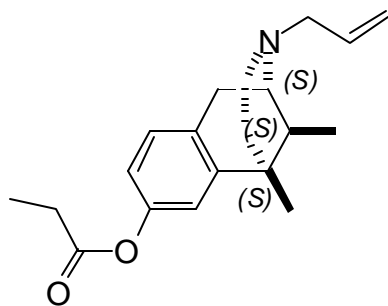


Fig NIH 11045 SDS. Results of study in which single doses of NIH 11045 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: In the mouse, NIH 11045 displayed mu- and kappa-opioid receptor antagonist activity. Its potency as a mu-opioid receptor antagonist was very weak or approximately 1/100 that of the reference standard, naloxone. Potency as a kappa-opioid receptor antagonist was about equivalent to that of norbinaltorphimine (nBNI). However, onset of action was much faster (30 min) than that of nBNI (2 hr). The behavioral profile in the withdrawn morphine-dependent monkey suggested mu- antagonist and kappa agonist properties.

NIH 11051 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-propenyl)-2'-propionyloxy-6,7-benzomorphan Hydrochlorides



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

- 1) TF – Inactive at 1 and 10, 10% at 30^{a,d}
- 2) TF vs. M – Inactive at 1, 10 and 30^{a,b,d}
- 3) PPQ – 3.57 (3.05 - 4.17)^{a,d}
- 4) HP - Inactive at 1 and 10, 13% at 30^{a,c,d}

^aAtaxia, increased locomotor activity and Straub tail at 10 and 30.

^bAt 10 and 30, ataxia which was diminished in intensity after morphine.

^cSlight ataxia at 6 mg/kg.

^dVehicle was 10% hydroxypropyl-β-cyclodextrin in water.

NIH 11051 (continued)

MONKEY DATA (SDS)

NIH 11051 attenuated withdrawal signs (see figure). However, severe dose-related CNS depressant properties were noted. Slowing, ataxia and salivation were seen. One monkey fell from its perch but was fully recovered after 90 min.

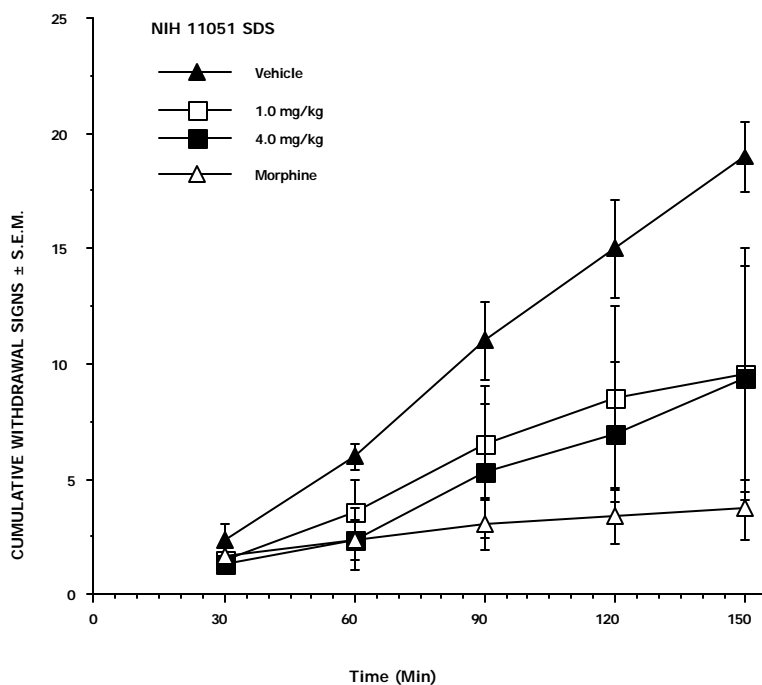
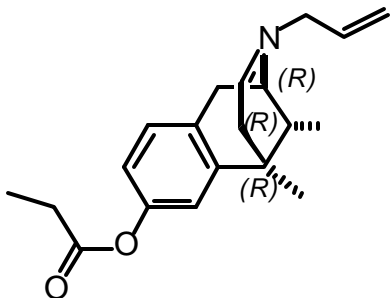


Fig NIH 11051 SDS. Results of study in which single doses of NIH 11051 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The mice and monkeys showed behavioral signs consistent with those produced by CNS depressants. Limited supplies precluded a full evaluation.

NIH 11052 (-)-(1R,5R,9R)-5,9-Dimethyl-2-(2-propenyl)-2'-propionyloxy-6,7-benzomorphan.HCl



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

- 1) TF – Inactive at 1, 10 and 30a,b
- 2) TF vs. M – 0.30 (0.09 - 0.99)a,b
- 3) PPQ – 10.30 (3.76 - 28.27)a,b
- 4) HP - Inactive at 1, 10 and 30a,b

aAtaxia at 10 and 30.

bVehicle was 10% hydroxypropyl- β -cyclodextrin in water.

NIH 11052 (continued)

MONKEY DATA
(SDS)

As shown in the figure, NIH 11052 did not substitute for morphine, instead it exacerbated withdrawal at 1.0 mg/kg. Potency estimate is 1/20 that of naloxone, the reference standard.

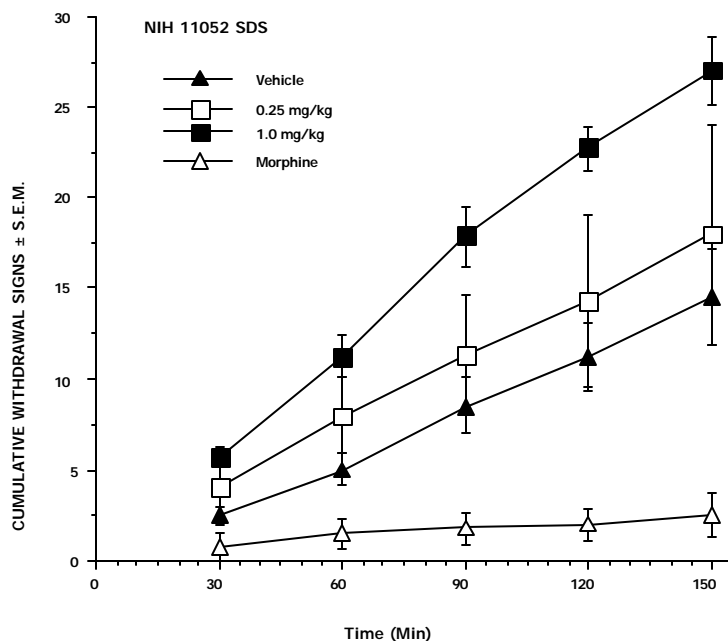
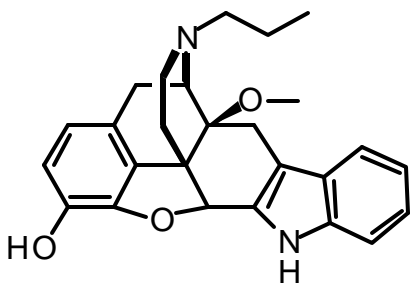


Fig NIH 11052 SDS. Results of study in which single doses of NIH 11052 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: In the mouse, NIH 11052 displayed weak antinociceptive properties and low order opioid-receptor antagonism. In morphine-dependent rhesus monkeys, it demonstrated antagonist activity.

NIH 11063 4,5 α -Epoxy-14 β -methoxy-17-(propyl)indolo[2',3':6,7]morphinan-3-ol



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

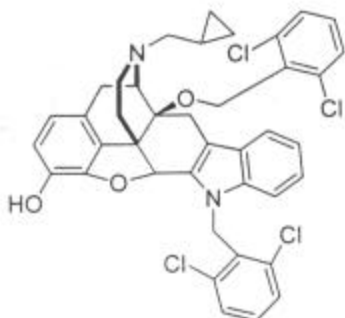
- 1) TF – Inactive at 1 and 10.^{a,b}
- 2) TF vs. M – 7% at 1, 4% at 10 and 0% at 30.^{a,b}
- 3) PPQ – Inactive at 1.^{a,b}
- 4) HP - 13% at 1.^{a,b}

^aVehicle was 1% lactic acid in water.

^bDrug supply exhausted.

Comment: In the dose range tested, NIH 11063 does not display remarkable opioid agonist or antagonist activity.

NIH 11069 1'-(2,6-Dichlorobenzyl)-14β-[(2,6-dichlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo[2',3':6,7]morphinan-3-ol· HCl

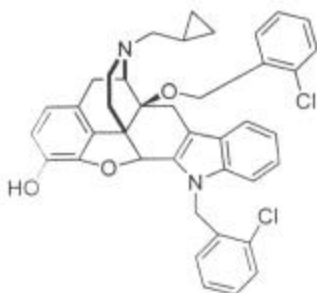


MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

- 1) TF – 0% at 1, 11% at 3, 63% at 10 and 39% at 20.^{a,b}
 - 2) TF vs. M – 0% at 1, 11% at 3, 63% at 10 and 39% at 20.^{a,b}
 - 3) PPQ – Inactive at 3.^{a,b}
 - 4) HP - 13% at 1 and 37% at 10.^{a,b}
- ^aDrug was dissolved in 100% DMSO. When attempts were made to dilute this stock solution with water, particles formed and adhered to sides of container. Therefore, dilutions were made using 100% DMSO. Vehicle alone, 100% DMSO, produced 9% effect at 0.1 ml and 24% effect at 0.3 ml. .
- ^bInactivity, eyelid ptosis, arched backs and large wheals at sites of injection.

Comment: This drug could not be reliably tested because of problems with solubility. Apparently DMSO, per se, accounts for the activity noted.

NIH 11070 1'-(3-Chlorobenzyl)-14β-[(3-chlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo[2',3':6,7]-morphinan-3-ol.

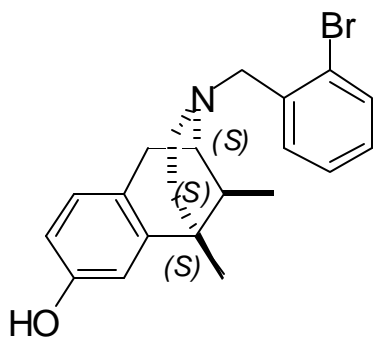


MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

- 1) TF – 0% at 1, 63% at 10 and 11% 30.^{a,b}
 - 2) TF vs. M – Inactive at 1, 10 and 30. ^{a,b}
 - 3) PPQ – 17% at 1, 0% 10 and 34 % at 30.^{a,b}
 - 4) HP - 0% at 1, 25% at 10 and 37% at 30.^{a,b}
- ^aDrug was dissolved in 100% DMSO. When attempts were made to dilute this stock solution with water, particles formed and adhered to sides of container. Therefore dilutions were made using 100% DMSO. Vehicle alone, 100% DMSO, produced 11% effect at 0.1 ml and 12 to 86% effect at 0.3 ml.
- ^bInactivity, eyelid ptosis and large wheals at sites of injection.

Comment: This drug could not be reliably tested because of problems with solubility. Apparently DMSO per se, accounts for the activity noted.

NIH 11080 (+)-(1*S*,5*S*,9*S*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



MOUSE DATA - ED50 OR AD50
(mg/kg or % change)

- 1) TF – Inactive at 1, 10 and 30^a
 - 2) TF vs. M - Inactive at 1, 4% at 10 and 21% at 30^a
 - 3) PPQ – Inactive at 1, 10 and 30^a
 - 4) HP - Inactive at 1, 13% at 10 and 30^a
- ^aVehicle - 0.4% lactic acid in water.

NIH 11080 (continued)

MONKEY DATA
(SDS)

As shown in the figure, NIH 11080 did not substitute for morphine. Instead, it may have exacerbated withdrawal. Because of inadequate supplies, only 2 monkeys could be tested at the high dose (16.0 mg/kg).

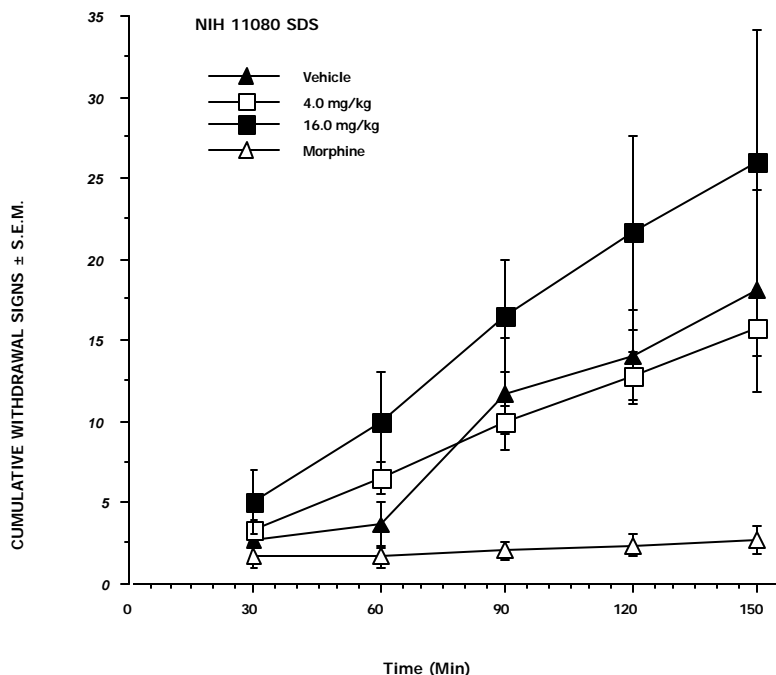
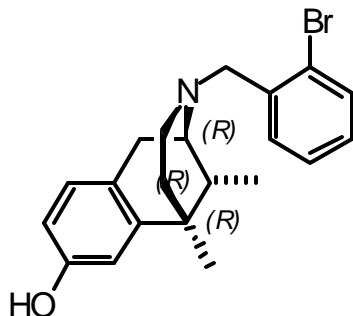


Fig NIH 11080 SDS. Results of study in which single doses of NIH 11080 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: The results in mice and monkeys suggest that NIH 11080 has weak mu-opioid antagonist properties. Drug supply was exhausted.

NIH 11081 (-)-(1*R*,5*R*,9*R*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride

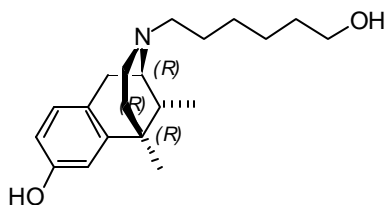


MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

- 1) TF – 2% at 1, 4% at 10 and 8% at 30^a
 - 2) TF vs. M - 24% at 1, 35% at 10 and 24% at 30^a
 - 3) PPQ – 15% at 1 and inactive at 10 and 17% at 30^a
 - 4) HP - 13% at 1 and inactive at 10 and 13% at 30^a
- ^aVehicle was 0.4% lactic acid in water.

Comment: As tested, NIH 11081 was devoid of opioid properties in mice.

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



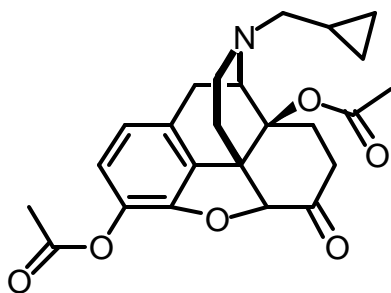
MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

- 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

^aVehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: Apparently, NIH 11082 lacks mu -opioid properties in mice.

NIH 11083 3,14-Diacetoxynaltrexone Oxalate



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

- 1) TF – 12% at 1 and inactive at 10 and 30^a
- 2) TF vs. M - 0.0037 (0.0016 - 0.0086)^a
- 3) PPQ – Inactive at 1 and 10, 3% at 30^a
- 4) HP - Inactive at 1, 10 and 30^a

^aVehicle was 10% hydroxypropyl-β-cyclodextrin in water.

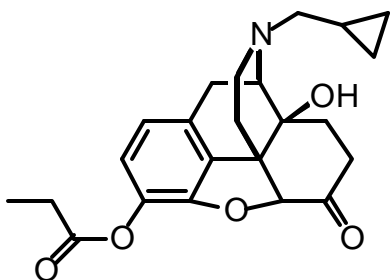
Time Course Study

| NIH 11083, (AD80 = 0.03 mg/kg, s.c.) Pretreatment:Time | | |
|--|----------------|---------------|
| 30 min | 2 hr | 24 hr |
| 88% Antagonism | 19% Antagonism | 0% Antagonism |

Morphine ED50 (5 mg/kg, s.c.) given 20 min before testing.

Comment: Although NIH 11083 is very potent mu -opioid receptor antagonist, its duration of action is not remarkable. Potency estimate is 10 times that of naloxone.

NIH 11084 3-Propionylnaltrexone Oxalate



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

- 1) TF – Inactive at 1, 10 and 30^a
- 2) TF vs. M - 0.01 (0.0034 - 0.034)^a
- 3) PPQ – Inactive at 1 and 10, 3% at 30^a
- 4) HP - Inactive at 1, 10 and 30^a

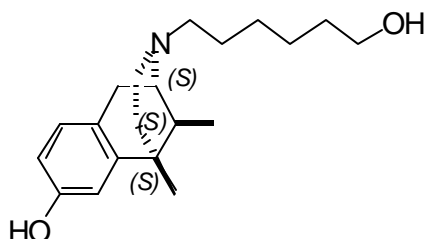
^aVehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Time Course Study

| NIH 11083, AD80 = 0.04 mg/kg, s.c.) Pretreatment Time | | |
|---|----------------|----------|
| 30 min | 2 hr | 24 hr |
| 93% Antagonism | 24% Antagonism | Inactive |

Comment: NIH 11084 is a potent mu-opioid receptor antagonist. However, its duration of action is short. Its potency is approximately equal to that of naloxone, the reference standard.

NIH 11085 (+)-(1S,5S,9S)-5,9-dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan Hydrochloride



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

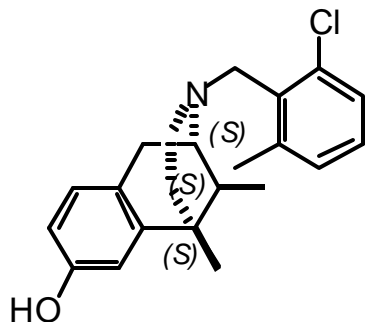
- 1) TF – Inactive at 1 and 10, 9% at 30^a
- 2) TF vs. M – Inactive at 1, 10 and 30^a
- 3) PPQ – 18% at 1, 8% at 3, 0% and 70% at 10 (tested twice at 10) and 40% and 16% at 30 (tested twice at 30)^a
- 4) HP - 25% at 1, 13% at 10 and 0% at 30

^aVehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: NIH 11085 displays a rather erratic dose-response in the PPQ test. This drug probably lacks mu-opioid receptor activity in mice.

^aVehicle was 10% hydroxypropyl-β-cyclodextrin in water.

NIH 11088 (+)-(1S,5S,9S)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



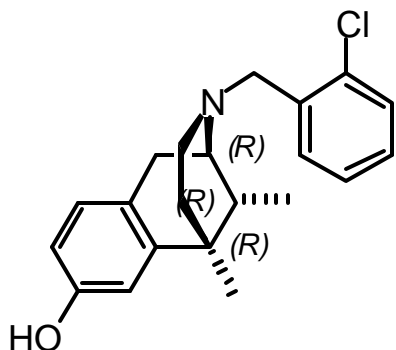
MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

- 1) TF – Inactive at 1, 10 and 30^a
- 2) TF vs. M – 10% at 1, Inactive at 10 and 30^a
- 3) PPQ – 18% at 1, 20% at 10 and Inactive at 30^a
- 4) HP - 25% at 1, 13% at 3, Inactive at 10 and 30^a

^aVehicle - 10% hydroxypropyl-β-cyclodextrin in water.

Comment: According to the results, NIH 11088 is inactive

NIH 11093 (-)-(1*R*,5*R*,9*R*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy -6,7-benzomorphan Hydrochloride

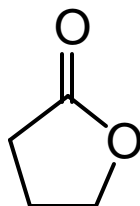


MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

- 1) TF – Inactive at 1, 10 and 30^a
 - 2) TF vs. M – Inactive at 1, 10 and 30^a
 - 3) PPQ – Inactive at 1, 16% at 10 and 14% at 30^a
 - 4) HP - 25% at 1, 13% at 10 and 30% at 30^a
- ^aVehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: Antinociceptively speaking, the drug is essentially inactive.

NIH 11094 gamma-Butyrolactone, Also, NIH 10540

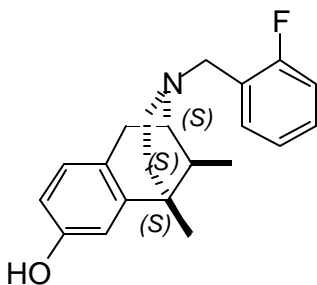


MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

- 1) TF – Inactive at 1, 10 and 30
- 2) TF vs. M – Inactive at 1, 13% at 10 and inactive at 30
- 3) PPQ – Inactive at 1, 3% at 10 and 53% at 30
- 4) HP - 25 % at 1, Inactive at 10 and 30

Comment: NIH 11094 appears to be devoid of opioid activity. Studies in mice and morphine-dependent monkeys were reported previously (NIDA Monograph 81, 1988, pp541-542). This drug was reported to be inactive in the TF test and active in the PPQ test. It neither substituted for morphine nor exacerbated withdrawal in morphine-dependent rhesus monkeys.

NIH 11095 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy -6,7-benzomorphan Oxalate

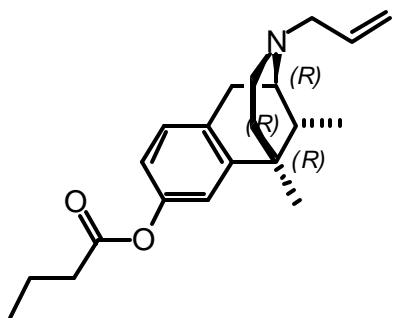


MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

- 1) TF – Inactive at 1, 10 and 30
- 2) TF vs. M – Inactive at 1, 10 and 30
- 3) PPQ – 14% at 1, Inactive at 10 and 39% at 30
- 4) HP - Inactive at 1 and 30, 13% at 10

Comment: As tested, NIH 11095 is unremarkable, antinociceptively

NIH 11096 (-)-(1*R*,5*R*,9*R*)-2'-Butyryloxy -5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan Hydrochloride



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

- 1) TF – Inactive at 1, 10 and 30^{a,c}
- 2) TF vs. M – 0.29 (0.09 - 0.93)^c
- 3) PPQ – Inactive at 1 and 10, 27% at 30^{a,c}
- 4) HP - 13% at 1, Inactive at 10 and 13% at 30^{a,b,c}

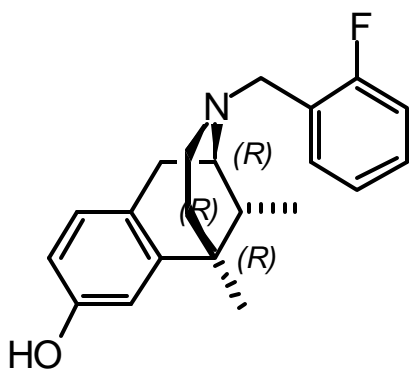
^aAt 30 mg/kg, mild ataxia.

^bAt 30 mg/kg, hyperactivity.

^cVehicle was 20% hydroxypropyl- β -cyclodextrin in water.

Comment: Apparently, NIH 11096 has mu -opioid antagonist effects. Potency estimate is approximately 1/10 that of naloxone, the reference standard.

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



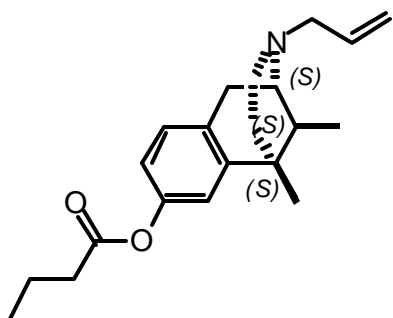
MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

- 1) TF – Inactive at 1, 9% at 10 and 13% at 30^a
- 2) TF vs. M – Inactive at 1 and 30, 18% at 10^a
- 3) PPQ – 7% at 1, 10% at 10 and 27% at 30^a
- 4) HP - 13% at 1 and 10, Inactive at 30^a

^aVehicle was 20% hydroxypropyl- β -cyclodextrin in water.

Comment: As tested, this compound is not remarkable as an opioid.

NIH 11098 (+)-(1*S*,5*S*,9*S*)-2'-Butyryloxy -5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan Hydrochloride



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

- 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,d}

^aAt 30 mg/kg, ataxia and mild Straub tail.

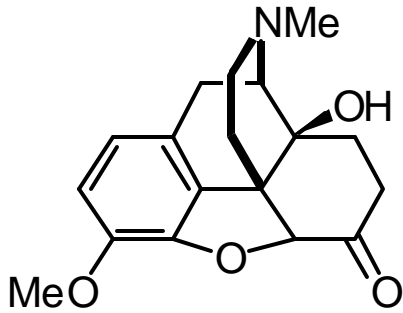
^bAt 20 mg/kg, ataxia prior to morphine, Straub tail.

^cAtaxia at 3, 10 and 30, increased respiration at 30.

^dVehicle was 20% hydroxypropyl- β -cyclodextrin in water.

Comment: This drug does not display activity reminiscent of mu -opioid receptor agonists or antagonists.

NIH 11107 Oxycodone Hydrochloride



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

- 1) TF – 0.94 (0.4 - 2.2)^a
 - 2) TF vs. M - Inactive at 1, 10 and 30 ^{a,b}
 - 3) PPQ – 0.38 (0.19 - 0.75)
 - 4) HP - 1.37 (0.48 - 3.92)^a
- ^aStraub tail and increased locomotor activity.
^bOnset within 5 min prior to morphine. Paws were arched.

Special Tests:

- 1) Opioid subtype testing
 - a) Naltrindole (s.c.) vs ED80 of NIH 11107 in TF: 0% at 1 and 10, 15% at 30.
 - b) Nor-BNI (s.c., 120 min pretreatment time) vs ED80 of NIH 11107 (s.c.) in TF: Inactive at 1, 10 and 30).
 - c) β -FNA (i.c.v., 240 min pretreatment time) vs ED80 of NIH 11107 (s.c.) in TF: AD50 = 1.23 (0.27 - 5.56) μ g/brain.

MONKEY DATA
(SDS)

NIH 11107 substituted completely for morphine in morphine-dependent monkeys in withdrawal. Onset and offset of actions were equivalent to those of morphine.

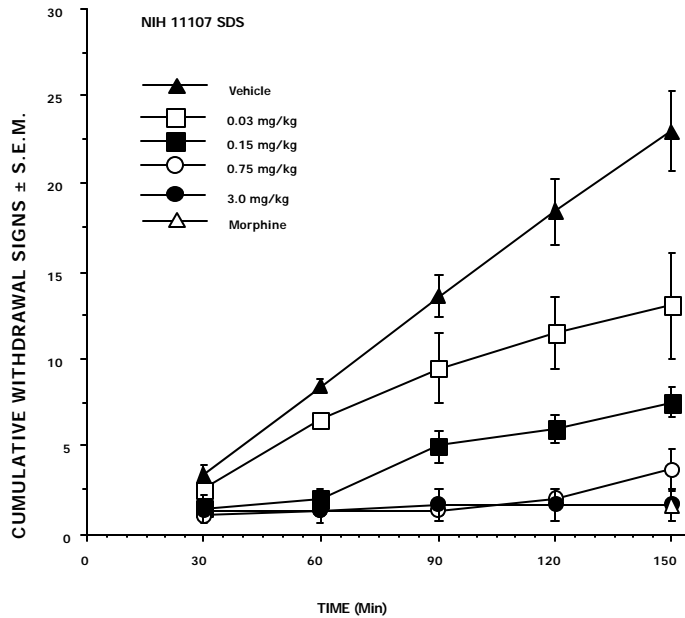


Fig NIH 11107 SDS. Results of study in which single doses of NIH 11107 were substituted for morphine in morphine-dependent monkeys in withdrawal

NIH 11107 (continued)

Comment: Oxycodone was classified as an opioid in 1957. The growing incidence of OxyContin abuse by humans prompted us to scrutinize in more detail its opioid properties. Oxycodone hydrochloride was found to be more active than morphine sulfate, antinociceptively speaking, in mice. It was without activity, as an antagonist, versus morphine. In addition, beta-funaltrexamine antagonized the ED80 of oxycodone indicating it was a potent mu-opioid receptor agonist. We did not find evidence that oxycodone had kappa-opioid agonist properties as reported by (Ross and Smith, 1997). In our hands, nor-BNI, a kappa antagonist, was inactive up to 30 mg/kg. In vivo studies by Spetea and coworkers (1998), indicated high affinity binding at delta-opioid sites and lesser potency for mu- and kappa-opioid sites. In our evaluation, naltrindole, a delta opioid antagonist, was inactive up to 30 mg/kg. In morphine-dependent rhesus monkeys in withdrawal, oxycodone dose-dependently substituted completely for morphine. Onset and duration of actions were equivalent to those of morphine; however, oxycodone was approximately 2 to 3 times more potent than morphine. We conclude that oxycodone is a selective mu-opioid receptor agonist.

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