BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XXVII. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2003)

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THE DRUG EVALUATION COMMITTEE

Dr. A. Coop has held the position of the Biological Coordinator of the Drug Evaluation Committee (DEC) since 1999. The duties of the Biological Coordinator involve receiving samples for evaluation, and distributing them blind to the relevant pharmacological groups within DEC. All data are received by the Biological Coordinator who maintains a confidential database, and forwards data to the submitters. Dr. Coop (UMB) is the fourth DEC Biological Coordinator (the others were Drs. N. Eddy, E. May, and A. Jacobson). The other members of DEC are in the two analgesic testing groups, at Virginia Commonwealth University (VCU, Drs. L. Harris, M. Aceto, P. Beardsley) and the University of Michigan (UM, Drs. J. Woods [DEC Chair], J. Traynor), and three stimulant/depressant testing groups, at the University of Mississippi (UMS, Dr. W. Woolverton), University of Texas Health Science Center San Antonio (UTHSCSA, Drs. C. France, L. McMahon), and UM (Drs. W. Fantegrossi, J. Woods). Drs. L. Winter (University of Buffalo) and K. Cunningham (University of Texas, Galveston) are also collaborating with DEC to determine the pharmacological profile of emerging drugs of abuse. Drs. T. Cicero, A. Jacobson, and G. Winger act as emeritus members. DEC reports to the CPDD's Liaison Committee for Drug Testing and Evaluation (Dr. F. I. Carroll, Chair). Members of both that CPDD committee and other CPDD committees as well as representatives from governmental agencies, attend DEC's meeting held during the Annual Scientific Meeting of the CPDD. One other DEC meeting was held with representatives from NIDA, and the DEA in Baltimore in May 2003 to discuss the work which has been accomplished, and future plans. Separate meetings are held at VCU quarterly with the members of the VCU Analgesic Testing Group, as well as Drs. E. May and E. Bowman, Dr. A. Coop, and a NIDA representative (Dr. D. Thomas), to discuss the results obtained from the VCU testing and research program.

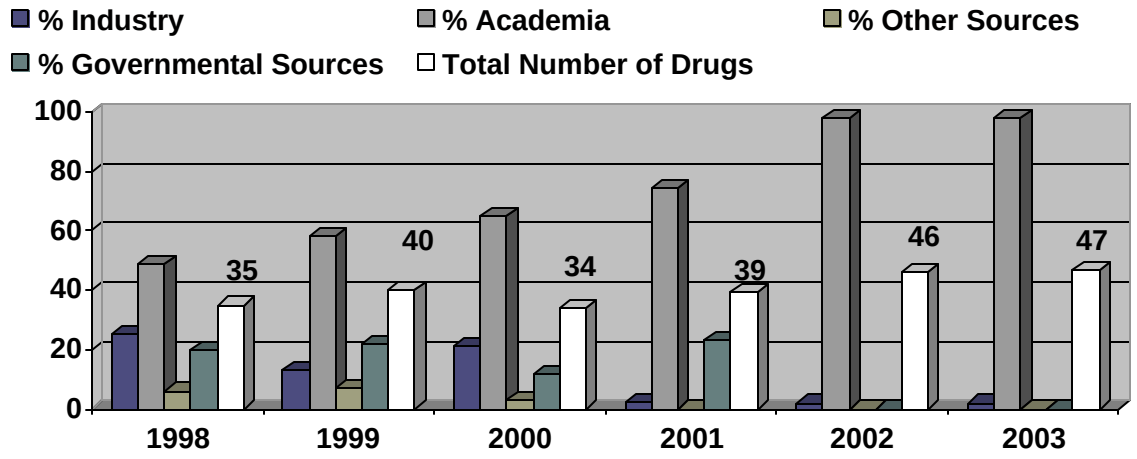
Data were released for publication this year on 47 different compounds evaluated by DEC's Analgesic Testing Program (Figure 1). Of these, 31 compounds were evaluated at VCU (antinociceptive assays in mice - tail flick, hot plate, and phenylquinone, and the tail-flick antagonist assay, as well as substitution for morphine and precipitated withdrawal assays in rhesus monkeys), and 29 at UM (28 for binding affinity to the μ, δ, and κ opioid receptors and GTPγS functional studies, and one for self-administration studies in monkeys). Compounds came primarily from academia; the remaining compound came from pharmaceutical industry. Figure 1 clearly shows that the percentage of compounds originating from academia has been steadily increasing over the past few years, with the percentage from other sources correspondingly decreasing. Three compounds were also released this year from the Stimulant/Depressant program.

Two joint publications based on the data gathered under DEC auspices were published in 2003 (May et al., 2003; Greiner et al., 2003). A manuscript based on the data gathered by the stimulant/depressant group (UMS, UM, and UTHSCSA) concerning GHB and its precursors was also published (McMahon et al., 2003).

EXPERIMENTAL OBSERVATIONS

Compounds released for publication this year are listed in Table 1; their molecular structures and a summary of their *in vivo* and *in vitro* data are in Tables 2 to 9. Similar to previous years (Coop 2003), the examined compounds are classified according to their molecular structure: morphinans and 4,5-epoxymorphinans in Tables 2 and 3; esters and ethers of opioids in Tables 4 and 5; 6,7-benzomorphans in Tables 6 and 7; miscellaneous compounds in Table 8; compounds evaluated by the Stimulant/Depressant program are shown in Table 9. The more interesting compounds evaluated during the year are discussed below. For compounds that have been previously evaluated, the new data are discussed in relation to the published data.

FIGURE 1. DEC ANALGESIC TESTING PROGRAM: PERCENT AND SOURCE OF EXAMINED DRUGS AND TOTAL NUMBER OF COMPOUNDS (1998-2003)



The bridged morphinan **NIH 11031** (Table 2) possesses very high affinity for all three opioid receptors, but it should be noted that it binds to kappa receptors with a K_i of 0.08 nM. This makes NIH 11031 one of the highest affinity kappa ligands known. Its antinociceptive effects are reversed by the kappa selective antagonist, nor-BNI, but not by a mu selective antagonist (β-FNA) nor a delta selective antagonist (naltrindole), indicating that NIH 11031 acts a kappa agonist *in vivo*. Interestingly, NIH 11031 has a long duration of action, but its activity changes as time progresses. It is initially a kappa agonist (as described above), but manifests as a mu and kappa antagonist after 24-48 hours. One possible reason for the delayed antagonist profile may be attributed to the slow receptor pharmacokinetics of NIH 11031, making it a pseudo-irreversible ligand.

NIH 11099, NIH 11100, NIH 11101, and NIH 11102 (Table 2) can be viewed as analogs of the 4-phenolic indolomorphinans (Coop *et al.*, 1999), which contain a bridging ring like buprenorphine (Lewis, 1985). It is interesting to see that such compounds are non-selective in binding assays, and this is in contrast to the current theory that the presence of an indole group leads to delta selectivity (Portoghese *et al.*, 1990).

The analogs of clocinnamox (C-CAM) shown in Table 2 include NIH 11122, NIH 11123, NIH 11124, and NIH 11125. **NIH11122** shows high affinity binding to the receptors and potent activity as an antinociceptive agent, yet the corresponding 3-phenol (**NIH 11123**) shows only weak activity as an opioid in both agonist and antagonist assays. As the structure activity relationships of opioids generally follow the pattern that 3-phenols are more potent than 3-methyl ethers, this is obviously an interesting class of compounds. The 3-ether substituted **NIH 11124** and **NIH 11125** also demonstrate excellent antinociceptive activity. The straub tail noted in the assays strongly suggests that the antinociception is mu receptor mediated.

The three indolomorphinans in Table 3 (**NIH 11142**, **NIH 11143**, and **NIH 11145**) would be expected to display delta selective antagonist activity due the presence of the indole group (Portoghese *et al.*, 1990). NIH 11145 does indeed display delta selectivity in binding assays, and all three appear free of any opioid agonist or mu antagonist effects.

The esters of naltrexone (**NIH 11083** and **NIH 11084**, Table 4) were reported last year (Coop, 2003) to possess potent mu antagonism. Both contain esters at the 3-position which can be rapidly metabolized to give the active phenol. Further studies have investigated whether the effect of the ester group extends the duration of action of the antagonism. The antagonist activity of both compounds was evident at 30 minutes, but had waned after 2 hours. At a time point of 24 hours, no activity remained indicating that these two compounds are probably not candidates for long acting mu antagonists. The related naltrexone-3-methyl ether (**NIH 11028**, Table 5), was

previously shown to possess mu opioid antagonist activity (Coop, 2003). The current studies indicate that NIH 11028 possess potent antagonism at all three opioid types. The unusual 3-chloropropenyl substituted benzomorphan (**NIH 11032**, Table 5) displays a profile of mu antagonism, but importantly it also displays a profile of delta antagonism – one of the few non-indolic delta opioid antagonists.

A series of halogen substituted *N*-benzyl and *N*-cycloalkylalkyl benzomorphans is shown in Tables 6a and 6b. It has been previously reported that the (+)-isomers of benzomorphans can display moderate to good opioid activity (Aceto and Zenk, 1986). **NIH 11113** (Table 6b) is an excellent example of this, as it possess an affinity of 3.5 nM at kappa receptors. The (-) isomers (Table 6a) have generally greater activity than the (+)-isomers (Table 6b). Indeed, the cyclopentylmethyl derivative (**NIH 11114**) has sub-nanomolar affinity for mu and kappa receptors and appears to possess the profile of a mixed agonist/antagonist. **NIH 11097** (Table 6b) possesses an affinity of 2.1 nM at kappa and 23 nM at mu receptors, yet fails to exert antinociceptive effects or morphine antagonism *in vivo*. Data from current studies indicate that the lack of activity of NIH 11097 is not confined to rodents, as no activity was seen in monkeys. As many researchers in the opioid field initially utilize *in vitro* assays for screening novel compounds, further study into the reason for the inconsistencies between *in vitro* and *in vivo* assays for this class may yield important information for the opioid drug design and discovery process.

A series of *N*-hydroxyalkyl substituted benzomorphans are shown in Tables 7a and 7b. The (+)-isomers in Table 7b display the expected low affinity for opioid receptors. **NIH11139** (Table 7b) has an 8-hydroxyoctyl N-substituent, and possesses the highest affinity of the hydroxyalkyl compounds so far studied. The presence of an hydroxyl group in this position on the benzomorphan skeleton opens up the possibility that further functionalization of the N-substituent is possible, leading to many new analogs of the benzomorphans.

NIH 10997 (Table 8) is an analog of the kappa selective agonists, U50,588 and U69,593. In vitro assays indicate high affinity for kappa receptors, and kappa agonism in GTPγS assays. The lack of activity of this compound *in vivo* is probably due to it being peripherally restricted (Kumar *et al*., 2000). As kappa agonists can exert analgesic effects through the peripheral system, such restricted agonists have garnered interest as they would lack the severe CNS effects often encountered with centrally acting kappa agonists. The increased occurrences of CNS effects at higher doses are probably due to incomplete peripheral restriction.

CPDD 0063 (1-benzylpiperazine, BZP) (Table 9) is readily self-administered in monkeys maintained on cocaine, and is active in the amphetamine discriminative stimulus assay. This profile suggests that this compound is a stimulant which has the potential to be abused. The related **CPDD 0064** (1-(3-trifluoromethyl)piperazine, TFMPP) (Table 9) appeared inactive in discriminative stimulus assays, and was not a reinforcer in cocaine maintained monkeys. **CPDD 0065** (1-phenthylpiperidine) (Table 9) is a ligand with affinity for sigma receptors, and it has been suggested that CPDD 0065 may have the potential to be an anti-cocaine agent. CPDD 0065 is only a very weak reinforcer in cocaine maintained animals, and inactive in the amphetamine discriminative stimulus assay.

TABLE 1. EVALUATED COMPOUNDS - ANALGESIC TESTING PROGRAM

NIH#	COMPOUND NAME	TABLE # - Evaluator
9929	Morphine Sulfate	8-UM
10650	(+)-(1*S*,5*S*,9*S*)-2-Benzyl-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HBr	6-UM
10997	*N*-Methyl-*N*-[(1*S*)-(1-phenyl-2-pyrrolidinyl)ethyl]-2-methanesulfonamidylphenyl-acetamide. methanesulfonate.	8-VCU/UM
11023	(-)-(1*R*,5*R*,9*R*)-2-(3-Methylbutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxa late	7-VCU
11028	3-O-Methylnaltrexone.HCl	5-VCU
11031	17-Cyclopropylmethyl-[5β,7β,3',5']-pyrrolidino-2'-[*S*]-phenyl-7α-methyl-6,14-endo-ethenomorphinan.HCl	2-VCU/UM
11032	(-)-1R,5R,9R-2-(3-*cis*-chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan. oxalate	5-VCU
11081	(-)-(1*R*,5*R*,9*R*)-2-(2-bromobenzyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6-VCU
11083	3,14-Diacetoxynaltrexone.oxalate	4-VCU
11084	3-Propionylnaltrexone.oxalate	4-VCU
11085	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyethyl)-6,7-benzomorphan.HCl	7-VCU
11088	(+)-(1*S*,5*S*,9*S*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	6-VCU
11093	(-)-(1*R*,5*R*,9*R*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	6-VCU
11095	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy--6,7-benzomorphan. oxalate	6-VCU
11096	(-)-(1*R*,5*R*,9*R*)-2'-Butyroxy-5,9-Dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	4-VCU
11097	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate	6-VCU
11099	18-(1-Methyl-(*E*)-benzylidene)-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan.oxalate	2-UM
11100	18-(*E*)-benzylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan. oxalate	2-UM
11101	18-Isopropylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan. oxalate	2-UM
11102	18-(*E*)-Ethylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan. oxalate	2-UM
11108	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenylbutyl)-6,7-benzomorphan.oxalate	6-VCU
11109	3-O-Butyrylnaltrexone.oxalate	4-VCU/UM
11110	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenylbutyl)-6,7-benzomorphan.oxalate	6-VCU/UM
11111	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanly)-6,7-benzomorphan.hemioxalate	6-VCU
11112	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanly)-6,7-benzomorphan.hemioxalate	6-VCU/UM

11113	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-cyclopentylmethyl-6,7-benzomorphan.HCl	6-VCU/UM
11114	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-cyclopentylmethyl-6,7-benzomorphan.HCl	6-VCU/UM
11122	17-Cyclopropylmethyl-14β-(2-methylcinnamido)-7,8-dihydrocodeinone.oxalate	2-VCU/UM
11123	17-Cyclopropylmethyl-14β-(2-methylcinnamido)-7,8-dihydromorphinone.oxalate	2-VCU
11124	14β-(4-Chlorocinnamido)-7,8-dihydrocodeinone.oxalate	2-VCU
11125	14β-(4-Methylcinnamido)-7,8-dihydrocodeinone.oxalate	2-VCU/UM
11126	(-)-(1*R*,5*R*,9*R*)-2'-Chloroacetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	4-VCU/UM
11127	(-)-(1*R*,5*R*,9*R*)-5,9-dimethyl-2'-Hydroxy-2-(7-hydroxyheptyl)-6,7-benzomorphan.HBr	7-VCU/UM
11129	(+)-(1*S*,5*S*,9*S*)-2'-Chloroacetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	4-VCU/UM
11139	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl	7-UM
11142	4,5α-Epoxy-14β-ethoxy-5b-methyl-17-propylindolo[2',3':6,7]morphinan-3-ol.HCl	3-VCU
11143	17-Cyclopropylmethyl-4,5α-epoxy-14β-ethoxy-5β-methyl-3-[(prop-2-inyl)oxy]lindolo [2',3':6,7]morphinan-3-ol.HCl	3-VCU
11145	17-Allyl-4,5α-epoxy-5β-methyl-3-[(prop-2-inyl)oxy]-14β-propoxyindolo[2',3':6,7] morphinan-3-ol.HCl	3-VCU/UM
11155	(+)-(1*S*,5*S*,9*S*)-2-(4-Acetoxybutyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	7-UM
11156	(+)-(1*S*,5*S*,9*S*)-2-(4-Hydroxybutyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HBr	7-UM
11157	(-)-(1*R*,5*R*,9*R*)-2-(4-Acetoxybutyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	7-UM
11158	(-)-(1*R*,5*R*,9*R*)-2-(4-Hydroxybutyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HBr	7-UM
11162	Neurotensin analog	8-UM
11165	(+)-(1*S*,5*S*,9*S*)-2-(5-Acetoxypentyl)-5,9-Dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	7-UM
11166	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(5-hydroxypentyl)-6,7-benzomorphan.HCl	7-UM
11167	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(1,3-dioxanylethyl)-2'-hydroxy-6,7-benzomorphan.HBr	6-UM
11168	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(1,3-dioxanylethyl)-2'-hydroxy-6,7-benzomorphan.HBr	6-UM

CPDD# TABLE 1. EVALUATED COMPOUNDS - STIMULANT DEPRESSANT PROGRAM

0063	1-Benzylpiperazine difumarate	9-SD
0064	1-(3-Trifluoromethylphenyl)piperazine.HCl	9-SD
0065	*N*-Phenethylpipridine.oxalate	9-SD

NOTES FOR TABLES 2 - 9

Salt forms are shown. Rounded numbers are used (2 significant figures); precise values and details of the procedures are given in the VCU, UM, and Stimulant Depressant reports (Aceto *et al*., 2004; Woods et al., 2004; Fantegrossi et al., 2004). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained. HP = hot plate assay; PPQ = phenylquinone antiwrithing assay; TF = tail flick assay; NTI = naltrindole (delta antagonist); norBNI = norbinaltorphimine (kappa antagonist); β–FNA = β-funaltrexamine (mu antagonist).

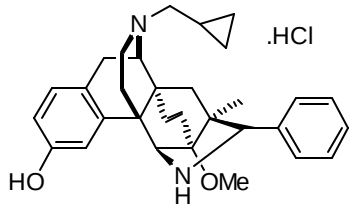
1) Antinociceptive reference data:
Morphine ED_{50} (mg/kg): Hot Plate = 0.8; Phenylquinone = 0.23; Tail-Flick = 5.8; Tail-Flick Antagonism vs. morphine (naltrexone AD_{50} = 0.007; naloxone AD_{50} = 0.035).

2) *In Vitro*:
Subtype selective binding affinity using recombinant receptors: μ (C_6 rat glioma cells expressing rat μ receptor), κ (CHO cells expressing human κ receptor), and δ (C_6 rat glioma cells expressing rat δ receptor). Affinity was assessed through the displacement of [^{3}H]-Diprenorphine. K_i values for standard ligands: μ (DAMGO 7.6 nM, morphine 11.2 nM); δ (SNC80 0.8 nM); κ (U69593 0.3 nM)

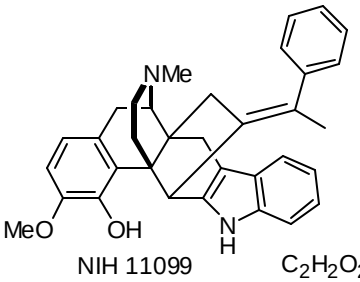
[^{35}S]GTPγS functional data were obtained employing recombinant receptors as described above. Values are given as EC_{50} with % stimulation compared to the standard full agonist (DAMGO, SNC80, U69,593), or the maximum stimulation achieved. μ (ED_{50}) morphine = 65 nM (100% stimulation), DAMGO = 34 nM (100% stimulation); δ (ED_{50}) SNC80 = 9 nM (100% stimulation), DPDPE = 8.3 nM (60% stimulation); κ (ED_{50}) U69,593 = 31 nM (100% stimulation), bremazocine = 0.5 nM (86% stimulation).

References to previous Drug Evaluation Committee annual reports are shown in parentheses, and refer to the actual year of publication.

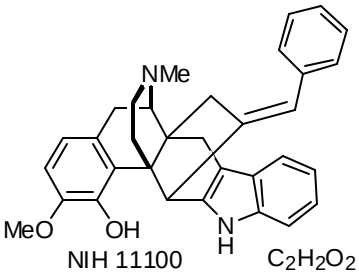
TABLE 2. MORPHINANS AND 4,5-EPOXYMORPHINANS



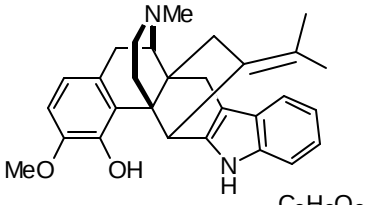
NIH 11031



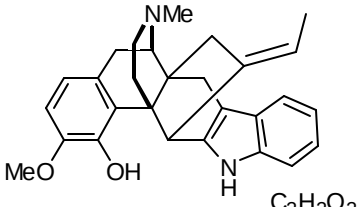
NIH 11099 $C_2H_2O_2$



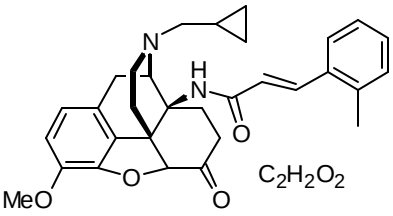
NIH 11100 $C_2H_2O_2$



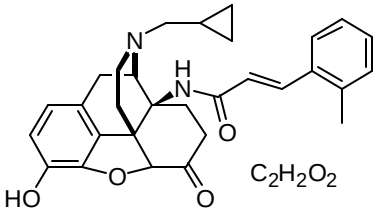
NIH 11101 $C_2H_2O_2$



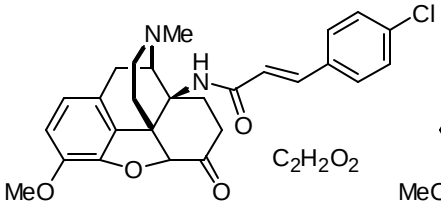
NIH 11102 $C_2H_2O_2$



NIH 11122 $C_2H_2O_2$



NIH 11123 $C_2H_2O_2$



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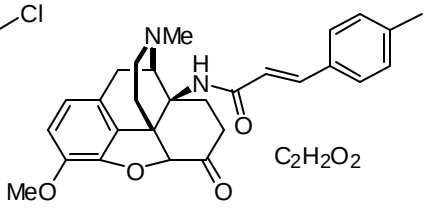


NIH 11125 $C_2H_2O_2$

ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg) **IN VITRO** **MONKEY**

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11031	0.31	0.018	0.37[a]	Inactive	μ=0.35, δ=0.95, κ=0.08	Neither substitutes nor exacerbates withdrawal[b]
11099	-	-	-	-	μ=46, δ=31, κ=21	-
11100	-	-	-	-	μ=42, δ=30, κ=60	-
11101	-	-	-	-	μ=270, δ=150, κ=160	-
11102	-	-	-	-	μ=230, δ=100, κ=280	-
11122	0.034	0.03	0.03[c]	Inactive	μ=0.54, δ=5.8, κ=0.69	-
11123	Inactive	3.17	Inactive	Inactive	–	-
11124	0.06[d]	0.02	0.04	Inactive[d]	–	-
11125	0.14[e]	0.40	0.06	Inactive[e]	μ=0.62, δ=17, κ=34	-

a) Subtype testing vs. ED_{80} of NIH 11031: β-FNA (mu) inactive; nor-BNI (kappa) AD_{50} = 8.5; naltrindole (delta) inactive. Timecourse: Delayed mu and kappa antagonism; peaks at 48h; dissipated at 72h.

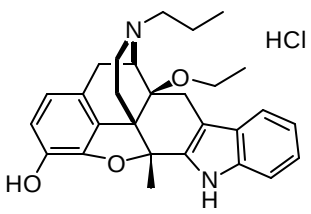
b) Long term signs of jaw sag, slowing, ptosis, and ataxia.

c) Straub tail at 1 mg/kg. Potency approx. 70 x morphine.

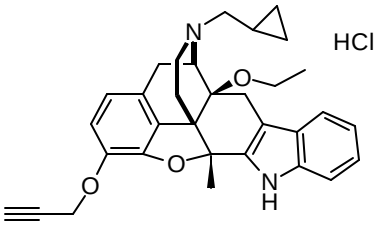
d) Straub tail observed. Potency in HP approx. 50 x morphine.

e) Straub tail observed. Potency in HP approx. 30 x morphine.

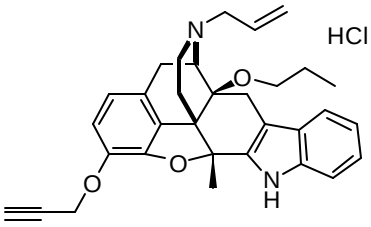
TABLE 3. 4,5-EPOXYMORPHINANS



NIH 11142



NIH 11143

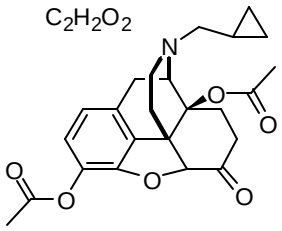


NIH 11145

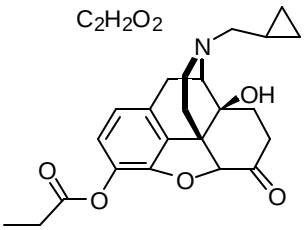
	ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg)				IN VITRO	MONKEY
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11142	Inactive[a]	Inactive[b]	Inactive	Inactive	-	-
11143	Inactive	Inactive	Inactive	Inactive	-	-
11145	Inactive	Inactive[c]	Inactive	Inactive	μ=1600, δ=37, κ=4100	-

a) 50% response at 30 mg/kg
b) 58% response at 30 mg/kg
c) 65% response at 30 mg/kg

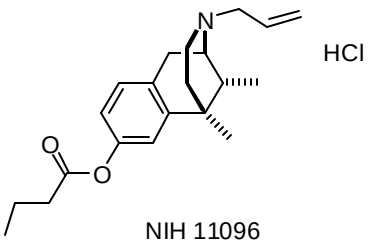
TABLE 4. OPIOID ESTERS



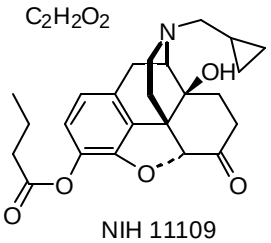
NIH 11083



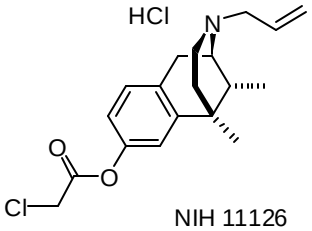
NIH 11084



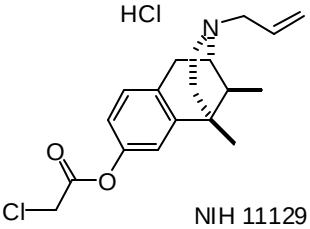
NIH 11096



NIH 11109



NIH 11126



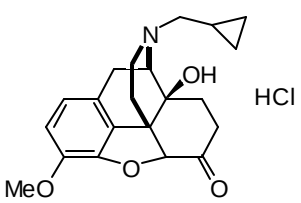
NIH 11129

ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg) **IN VITRO** **MONKEY**

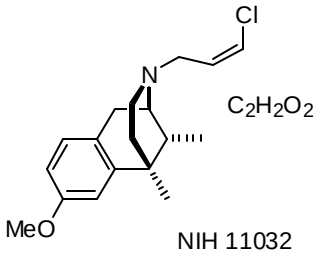
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11083	Inactive[a]	Inactive[a]	Inactive[a]	0.0037[a,b]	μ=2.7, δ=130, κ=6.7[a]	Precipitated withdrawal[c]
11084	Inactive[a]	Inactive[a]	Inactive[a]	0.01[a,d]	μ=1.8, δ=82, κ=9.7[a]	Precipitated withdrawal[c]
11096	Inactive[a]	Inactive[a]	Inactive[a]	0.29[a]	μ=30, δ=37, κ=0.9[a]	Precipitated withdrawal[c]
11109	Inactive	Inactive	Inactive	0.0029	μ=3.1, δ=63, κ=3.5	-
11126	Inactive	Inactive	Inactive	0.035[e]	μ=2.0, δ=31, κ=0.74	-
11129	Inactive	15	Inactive	Inactive[f]	μ=1200, δ=6700, κ=350	-

a) Previously reported (2003).
b) New data: Timecourse - percent antagonism after administration of 0.03 mg/kg of NIH 11083: 30 mins (88%); 2 h (19%); 24 h (0%).
c) Potency equal to naloxone.
d) New data: Timecourse - percent antagonism after administration of 0.03 mg/kg of NIH 11084: 30 mins (93%); 2 h (24%); 24 h (0%).
e) Timecourse vs. ED_{80} of morphine: 71% at 20 mins; 52% at 2 h; 2% at 4 h.
f) 79% response at 30 mg/kg. Ataxia and straub tail noted at the higher doses.

TABLE 5. OPIOID ETHERS



NIH 11028



NIH 11032

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED_{50}/AD_{50}, s.c., mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11028	Inactive[a]	-	Inactive[a]	0.47[a,b]	μ=31, δ=590, κ=95[a]	-
11032	Inactive[c]	17[c]	Inactive[c,d]	1.1	μ=48, δ=110, κ=9.4[c]	Neither substituted for morphine nor exacerbated withdrawal[c]

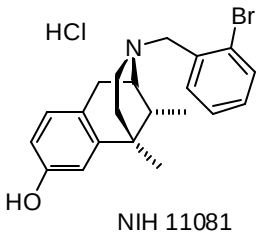
a) Previously reported (2002).

b) New Data: NIH 11028 vs. ED_{80} of: enadoline (kappa agonist) AD_{50} = 5.4 mg/kg; sufentanyl (mu agonist) AD_{50} = 0.12 mg/kg; DPDPE (delta agonist) AD_{50} = 1.8 mg/kg.

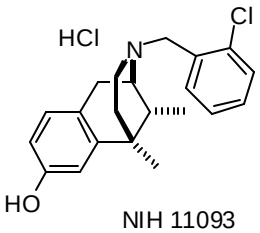
c) Previously reported (2003)

d) Antagonist activity of NIH 11032 vs. ED_{80} of enadoline (kappa agonist) 62% at 30 mg/kg; vs. ED_{80} of DPDPE (delta agonist) AD_{50} = 2 mg/kg.

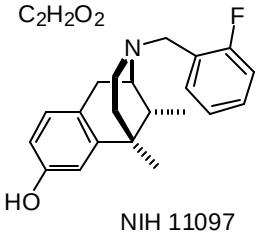
TABLE 6a. (-)-6,7-BENZOMORPHANS



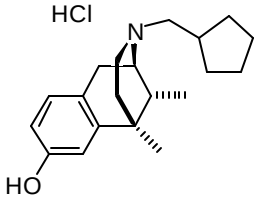
NIH 11081



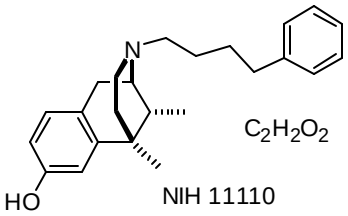
NIH 11093



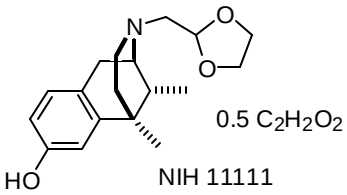
NIH 11097



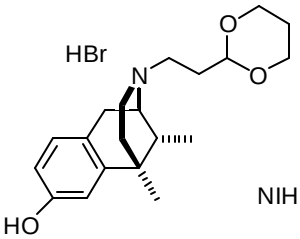
NIH 11114



NIH 11110



NIH 11111



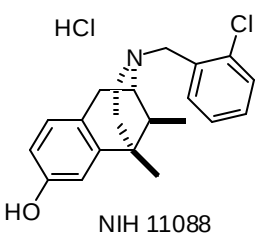
NIH 11167

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED_{50}/AD_{50}, s.c., mg/kg)

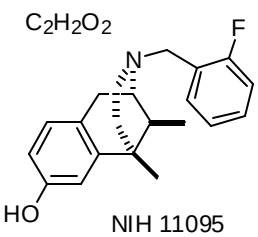
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11081	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=40, δ=1200 κ=14[a]	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16
11093	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=17, δ=600, κ=18[a]	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16
11097	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=23, δ=330 κ=2.1[a]	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16
11110	3.6	3.0	Erratic	Erratic	-	-
11111	Inactive	1.9[b]	Inactive	0.2[b]	–	-
11114	Inactive	7.0	Inactive	2.4[c]	μ=0.8, δ=8.3, κ=0.2	-
11167	-	-	-	-	μ=20, δ=58, κ=67	-

a) Previously reported (2003).
b) Ataxia and sedation seen at 30 mg/kg.
c) Mild ataxia at 30 mg/kg.

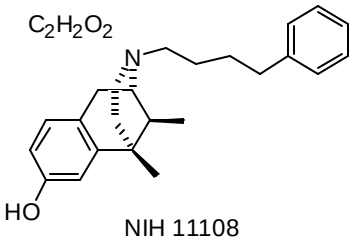
TABLE 6b. (+)-6,7-BENZOMORPHANS



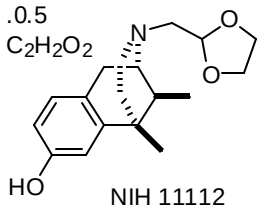
NIH 11088



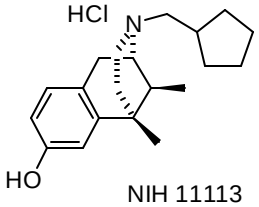
NIH 11095



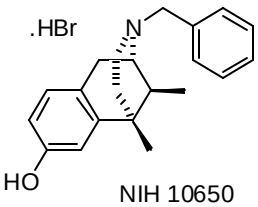
NIH 11108



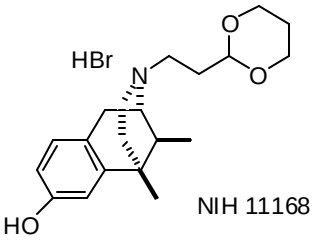
NIH 11112



NIH 11113



NIH 10650



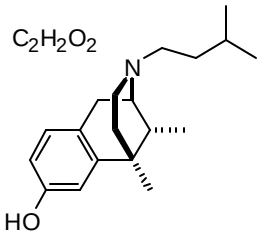
NIH 11168

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED_{50}/AD_{50}, s.c., mg/kg)

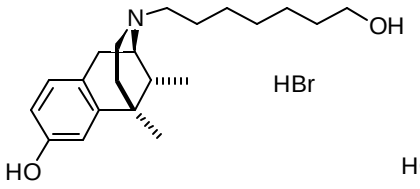
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
10650	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=590, δ=4000, κ=76	-
11088	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=140, δ=3600, κ=23[b]	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16
11095	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=560, δ=4100, κ=47[b]	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16
11108	Inactive	7.6	Inactive	Inactive	–	-
11112	Inactive	Inactive	Inactive	Inactive	μ=480, δ=1100, κ=190	-
11113	Inactive	Inactive	Inactive	Inactive	μ=33, δ=610, κ=3.5	-
11168	-	-	-	-	μ=1900, δ>10,000, κ=540	-

a) Previously reported (1990) (May et al., 1998; May et al., 2003)
b) Previously reported (2003).

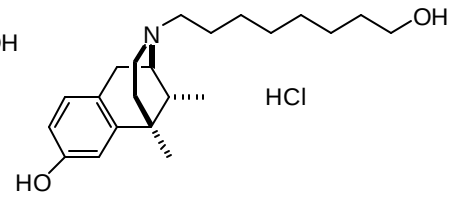
TABLE 7a. (-)-6,7-BENZOMORPHANS



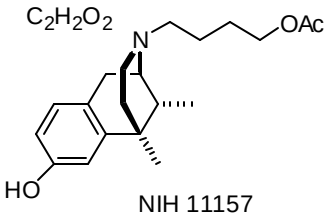
NIH 11023



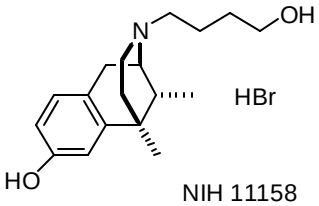
NIH 11127



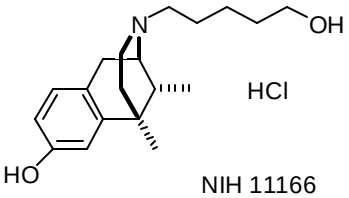
NIH 11139



NIH 11157



NIH 11158



NIH 11166

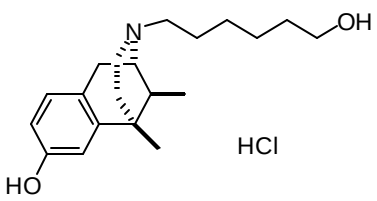
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED_{50}/AD_{50}, s.c., mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11023	Inactive[a]	0.39[a]	2.5[a,b]	Inactive[a]	μ=17, δ=37, κ=7.3[a]	Reduction in withdrawal signs at 2 and 8, but did not fully substitute[a]
11127	Inactive	2.9	20	Inactive	μ=4.6, δ=200, κ=36	-
11139	-	-	-	-	μ=5.8, δ=35, κ=8.8	-
11157	-	-	-	-	μ=8.6, δ=37, κ=48	-
11158	-	-	-	-	μ=34, δ=270, κ=100	-
11166	-	-	-	-	μ=33, δ=300, κ=260	-

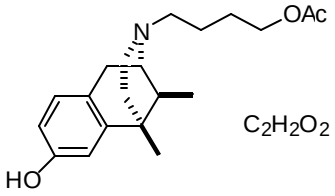
a) Previously reported (2002).

b) New data: pretreatment with β-FNA i.c.v. in TF: AD_{50} = 1.5 μg/brain.

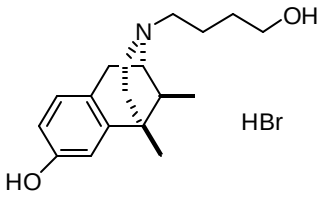
TABLE 7b. (+)-6,7-BENZOMORPHANS



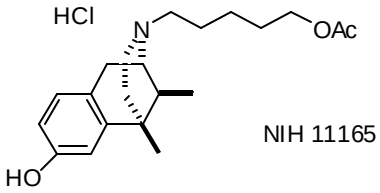
NIH 11085



NIH 11155



NIH 11156



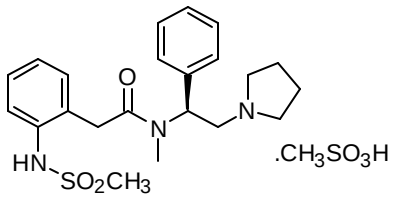
NIH 11165

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED_{50}/AD_{50}, s.c., mg/kg)

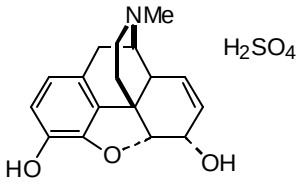
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11085	Inactive[a]	Non-dose related response[a]	Inactive[a]	Inactive[a]	μ=600, δ=>10,000, κ=1500[a]	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16
11155	-	-	-	-	μ=>10,000, δ=>10,000, κ=2600	-
11156	-	-	-	-	μ=>10,000, δ=>10,000, κ=3000	-
11165	-	-	-	-	μ=1400, δ=>10,000, κ=830	-

a) Previously reported (2003)

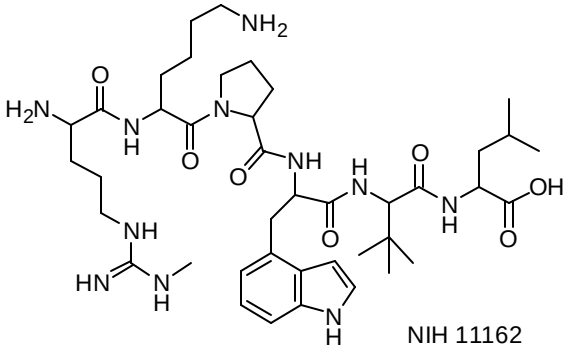
TABLE 8. MISCELLANEOUS COMPOUNDS



NIH 10997



NIH 9929



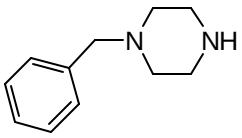
NIH 11162

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED_{50}/AD_{50}, s.c., mg/kg)

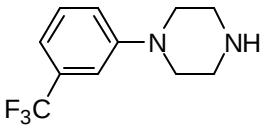
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
9929[a,b]						
10997	Inactive	11	Inactive	Inactive	μ=1900, δ=2600, κ=12[c]	Inverse dose-related attenuation of withdrawal[d]
11162[e]	-	-	-	-	-	-

a) Reported previously (1982, 1984). See previous reports for full data.
b) New data: Binding affinity to opioid receptors: K_i: mu 13 nM; delta 170 nM; kappa 61 nM.
c) [^{35}S]GTPγS agonist assay: kappa EC_{50} = 76 nM; mu - no stimulation.
d) Increased aggressiveness as well as cataleptic-like behavior noted at higher doses.
e) Assayed for reinforcing effects in monkeys. No reinforcing behavior observed.

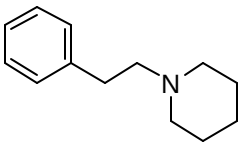
TABLE 9. COMPOUNDS EVALUATED BY STIMULANT DEPRESSANT PROGRAM



CPDD 0063



CPDD 0064



CPDD 0065

	Discriminative Stimulus Effects in Benzodiazepine-Trained Monkeys	Self-Administration in Cocaine-Maintained Monkeys, and Effect on Core Temperature	Drug Discrimination in Amphetamine-Trained Monkeys	Discriminative Stimulus Effects in LSD-Trained Rats	MDMA-like Discriminative Stimulus Effects, and Locomotor Effects
0063	No benzodiazepine discriminative stimulus effects	Readily self-administered at 0.1 and 0.3 mg/kg/inj. No significant effect on core temperature	Complete substitution at 17 mg/kg	No significant LSD-like responding	No effect on locomotor activity
0064	No benzodiazepine discriminative stimulus effects	No self-administration up to 1 mg/kg/inj. Mild hypothermia at 32 mg/kg	No amphetamine discriminative stimulus effects	No significant LSD-like responding	Decrease in locomotor activity at 1.6 and 3.2 mg/kg
0065	-	Weak reinforcer	No amphetamine discriminative stimulus effects	-	-

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