BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XXV. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2001)

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THE DRUG EVALUATION COMMITTEE (DEC) AND ITS MEMBERSIHP

Dr. A. Coop replaced Dr. A. E. Jacobson as the sole Biological Coordinator of DEC, CPDD in 2000. Dr. Jacobson and Dr. Coop worked closely together during 1999 and 2000, and Dr. Jacobson is to be congratulated on his efforts to ensure a smooth transition. Dr Coop (UMB) is the fourth DEC Biological Coordinator (the initial two were Drs. N. Eddy and E. May). The other members of DEC remained unchanged this year; they are in DEC's two analgesic testing groups, at Virginia Commonwealth University (VCU, Drs. L. Harris, M. Aceto, P. Beardsley) and the University of Michigan (UM, J. Woods (DEC Chair), J. Traynor), and three stimulant/depressant testing groups, at the University of Mississippi (UMS, W. Woolverton), University of Texas Health Science Center San Antonio (UTHSCSA, C. France), and UM (G. Winger, J. Woods). Drs. T Cicero and A. E. Jacobson act as emeritus members. The DEC reports to the CPDD's Liaison Committee for Drug Testing and Evaluation (N. Ator, Chair). Members of both that CPDD Committee, and the Industry Relations Committee (W. Schmidt, Chair), as well as NIDA, attend DEC's meeting held during the Annual Scientific Meeting of the CPDD. One or two other DEC meetings are held during the year 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, the DEC Biological Coordinator, and a NIDA representative, to discuss the results obtained from the VCU testing and research program.

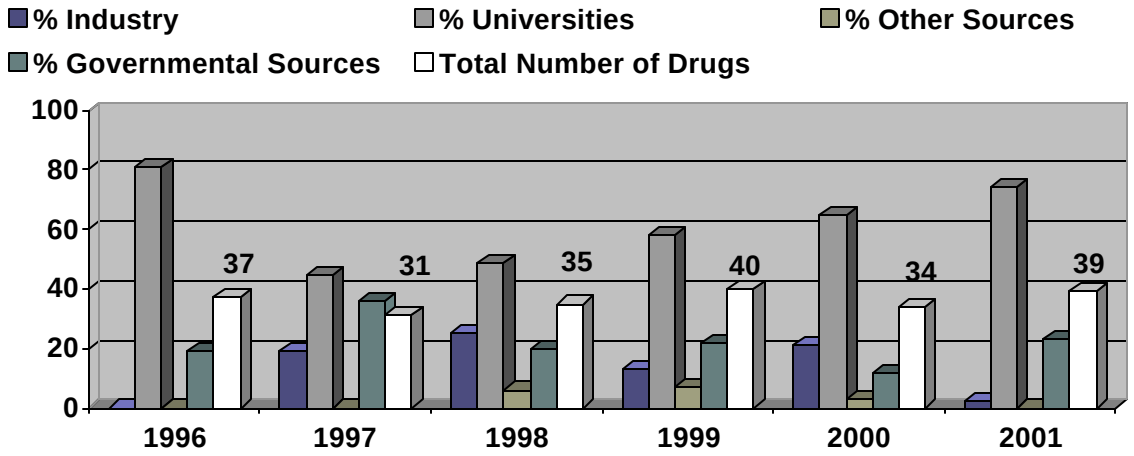
Data were released for publication this year on 39 different compounds evaluated by DEC's Analgesic Testing Program (Figure 1). Of these, 33 compounds were evaluated at VCU (antinociceptive assays in mice - tail flick, hot plate, and phenylquinone, and the tail-flick antagonist assay, as well as substitution for morphine and precipitated withdrawal assays in rhesus monkeys), and 33 at UM (binding affinity to the μ, δ, and κ opioid receptors, and GTPγS functional studies). The compounds came from two main sources: 74% from universities and 23% from governmental sources. The remaining compounds (3%) came from pharmaceutical industry, a figure lower than previous years. One compound was released for publication this year by the groups in the Stimulant/Depressant Testing Program.

Joint publications based on the data gathered under DEC auspices from VCU, UM, UMB, and NIH, have been published (Coop et al., 2000; May et al., 2000a; May et al., 2000b). In addition, a poster based on the data gathered by DEC was presented at the 63rd Annual Meeting of the College on Problems of Drug Dependence (Coop et al., 2001). A DEC report on CPDD 0056, a sulfur containing derivative of amphetamine, was communicated to the World Health Organization.

EXPERIMENTAL OBSERVATIONS

The names of the compounds that were released for publication this year are listed in Table 1, and 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 and Jacobson, 2001), the examined compounds are classified according to their molecular structure: 4,5-epoxymorphinans in Tables 2 and 3; 3-O-substituted 4,5-epoxymorphinans in Table 4; miscellaneous opioids in Table 5; 6,7-benzomorphans in Table 6; miscellaneous compounds (those which do not fall into the usual opioid classes) are listed in Tables 7 and 8. Compounds evaluated by the Stimulant/Depressant testing groups 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 PROGRAM: PERCENT, TOTAL NUMBER, AND SOURCE OF EXAMINED DRUGS (1996-2001)



NIH 10497 (Table 2) possesses an unusual *N*-1*R*-1-cyclopropylethyl substituent, similar to the μ-antagonist conferring *N*-cyclopropylmethyl. Previous reports (1989, 2001) showed that NIH 10497 is not active as a morphine antagonist in the mouse, and can completely substitute for morphine in monkeys, indicating a μ-agonist profile. Side-effects seen in the monkeys (e.g. salivation) also suggested κ-agonist activity, consistent with the high affinity seen for both μ and κ receptors. However, in contrast, GTPγS functional data show that NIH 10497 has low μ efficacy, which is not consistent with the *in vivo* substitution data. This is consistent with the fact that NIH 10497 appears to be relatively free of μ-opioid dependence liability in the rat. Table 2 shows that opioid subtype testing in the tail-flick assay demonstrates predominantly κ agonist effects. It thus appears that the activity of NIH 10497 is due to a profile of κ agonism.

NIH 10978 in Table 2, is an analog of the δ-opioid selective antagonist naltrindole (NIH 10990, Table 2) possessing a 2-methylallyl N-substituent. The introduction of this N-substituent gives rise to an extremely δ selective ligand in binding assays, and δ-antagonism in GTPγS functional assays. These data suggest that a 2-methylallyl substituent may be superior to the traditional cyclopropylmethyl group in morphinan-based δ selective ligands. In contrast, **NIH 10979** (Table 2), with an unusual *N*-cyclohexylethyl substituent, actually displays preference for μ receptors over δ. This demonstrates that the nature of the N-substituent is an extremely important factor in the binding profile of analogs of naltrindole (Coop et al., 2000; McLamore et al, 2001).

NIH 10986 and **NIH 10989** (Table 3) are both well known μ antagonists - their activity in GTPγS assays was consistent with this profile. **NIH 10985** and **NIH 10990** are both considered δ selective antagonists but, as can be seen from Table 3, they both display potent μ antagonism (only 4-5 fold less potent than naltrexone). These data are consistent with the previous findings that NIH 10990 effectively exacerbates withdrawal in the morphine dependent monkey. **NIH 10987** (buprenorphine) (Table 3) is a potent μ receptor mediated analgesic which is employed clinically (Lewis, 1985). Its partial μ agonist activity can be seen *in vitro*, in that it efficiently acts as an antagonist of the μ agonist DAMGO, but only reverses 67% of the response of DAMGO.

Table 4 contains three compounds which do not have the 3-phenolic substituent usually required for high potency at the opioid system. The cinnamoyl ester of **NIH 11037** will hydrolyze rapidly *in vivo* to give naltrexone, and indeed was shown to be a potent μ and κ antagonist *in vivo*. **NIH 11028** contains a 3-methyl ether which undergoes metabolism more slowly to naltrexone, and was shown to possess lower morphine antagonist potency than NIH 11037 in the mouse. **NIH 11015** (Table 4) displayed the expected μ agonism, and is probably O-demethylated to the more active phenol *in vivo*.

NIH 10945 (Table 5) possesses a benzomorphan-like structure, but with the basic nitrogen in a unique position. It displays high affinity for μ and κ receptors, yet has only feeble opioid activity *in vivo*. It is possible that NIH 10945 has problems with transport into the CNS, or is conjugated rapidly on the nitrogen to an inactive species. **NIH 11026** (Table 5) is the unnatural enantiomer of the minor opium alkaloid oripavine. The natural isomer is known to be an antinociceptive agent (Gomez-Serranillos et al., 1998), but interest in the unnatural enantiomers was kindled after the finding that (+)-thebaine (the 3-O-methyl ether of (+)-oripavine) also displayed opioid mediated antinociceptive properties (Aceto et al., 1999). As 3-phenols in the natural series tend to possess greater potency than the 3-methyl ethers, it was of interest to investigate if similar SAR was present for the unnatural isomers. As can be seen from Table 5, NIH 11026 showed only weak opioid agonist activity. This suggests that the unnatural thebaines may possess a very different SAR to the natural isomers.

A series of benzomorphans is shown in Tables 6a and 6b. It has been previously reported that *N*-benzyl substituted benzomorphans display poor *in vivo* and *in vitro* opioid activity (Coop and Jacobson, 2001), and **NIH 10994, NIH 10995, NIH 11003, NIH 11004,** and **NIH 11021** follow the same trend. **NIH 11020** (Table 6a) has, however, an unusual profile. NIH 11020 possesses high affinity for μ and κ receptors, yet is completely inactive *in vivo* as an antinociceptive agent or as a morphine antagonist. The reason for this profile is not obvious, but underscores the need for *in vivo* assays together with *in vitro* assays. **NIH 11013** and **NIH 11014** are the (-) and (+) enantiomers of a benzomorphan with an *N*-phenylpropyl substituent. As expected, NIH 11013 displays higher affinity for opioid receptors, and greater potency in most *in vivo* assays, yet the (+)-isomer NIH 11014 is of greater potency in the antiwrithing assay (PPQ). Indeed, NIH 11014 is unusually active for a (+)-isomer in all assays. Interestingly, side-effects noted in the monkey assays tend to suggest that the agonism may be mediated through κ receptors. **NIH 11006** (Table 6a) possesses a cyclobutylmethyl N-substituent - a substituent generally regarded as being associated with μ antagonism, and the GTPγS assays show low μ efficacy. The side effects noted in the monkey (e.g. salivation) tend to suggest a strong κ-opioid component to the antinociceptive activity of NIH 11006. **NIH 11023** (Table 6a), with a 3-methylbutyl N-substituent, was about ten-fold less potent than NIH 11006 in the rodent antinociceptive assays, but side-effects again suggest a strong κ-mediated component from the monkey assays.

The notorious γ-hydroxybutyrate (GHB, **NIH 10947**) (Table 7) has been widely studied by DEC. It has previously been reported (Coop and Jacobson, 2001) that NIH 10947 has little opioid-like activity alone, but acts synergistically with morphine in PPQ. In withdrawn morphine dependent monkeys, NIH 10947 attenuated withdrawal at low doses, but exacerbated withdrawal at higher doses. In addition, when NIH 10947 was given with morphine to morphine tolerant mice, antinociception was partially restored (Aceto and Bowman, 2000). These data suggested potential therapeutic uses for GHB in the treatment of pain in morphine tolerant patients, and potential safety issues for opioid abusers if they also administer GHB. It has now been shown that synergism may occur between NIH 10947 and ethanol - an extremely important finding as NIH 10947 is often placed into alcoholic drinks. Indeed, in combination with ethanol, mice became ataxic at relatively low doses compared to doses required of GHB alone. The interaction of GHB with the opioid system, led to the study of the effects of the putative GHB antagonist **NIH 11016** (NCS-382 Maitre et al., 1990) (Table 7) on the opioid system. With the exception of feeble, non-dose related attenuation of withdrawal in the monkey, no effects were seen. These data indicate that NCS-382 can be employed as a GHB antagonist when investigating the effects of GHB on the opioid system, without the antagonist having direct effects on the opioid system itself.

NIH 11018 ((-)-nicotine, Table 8) demonstrated antinociception in mice and appeared to exacerbate withdrawal signs in the monkey. Convulsions were noted in all rodent assays, and the apparent exacerbation of withdrawal (increased retching and vocalization were noted) are probably due to the stimulant effects of nicotine. The (+)-isomer of nicotine (**NIH 11017**) showed lower potency as an antinociceptive agent, and a lower incidence of CNS effects. Agmatine (**NIH 11035** Table 8) has been reported to attenuate morphine withdrawal signs in rats (Reis and Regumathan, 2000). Consistent with this report, it is shown in Table 8 that a suggestion of attenuation of withdrawal is seen in the monkey, but is not significant at 6 mg/kg.

Racemic mecamylamine **CPDD 0059** (Table 9) was previously reported by the analgesic group as NIH 11010 (Coop and Jacobson, 2001). As with the resolved enantiomers (CPDD 0057 and CPDD 0058), no reinforcing effects were observed in methohexital trained monkeys.

TABLE 1. EVALUATED COMPOUNDS

NIH#	COMPOUND NAME	TABLE #-Evaluator
10497	*N*-(1*R*-1-Cyclopropyl)ethylnormorphine hydrochloride	2-VCU
10945	(+/-)-(5*S*,8*S*,9*R*)-8-Amino-3-hydroxy-5,9-methano-9-(methoxymethyl)-5-methylbenzocyclooctene	5-VCU/UM
10947	γ-Hydroxybutyric Acid, sodium salt	7-VCU
10978	*N*-(3-Methylallyl)noroxymorphindole	2-VCU/UM
10979	*N*-Cyclohexylethylnoroxymorphindole.HCl	2-VCU/UM
10985	7-Benzylidene-7-dehydronaltrexone.HCl (BNTX)	3-UM
10986	Naltrexone.HCl	3-UM
10987	Buprenorphine.HCl	3-UM
10988	Norbinaltorphimine.HCl (norBNI)	3-UM
10989	14β-(*p*-Chlorocinnamoylamino)-7,8-dihydro-*N*-cyclopropylmethylnormorphinone mesylate (Clocinnamox)	3-UM
10990	Naltrindole.HCl	2-UM
10992	(+)-(1*S*,5*S*,9*S*)-2-Acetamido-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan	6-VCU/UM
10994	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-trifluoromethylbenzyl)-6,7-benzomorphan .oxalate	6-VCU/UM
10995	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(4-trifluoromethylbenzyl)-6,7-benzomorphan .oxalate	6-VCU/UM
11003	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-trifluoromethylbenzyl)-6,7-benzomorphan . HCl	6-VCU/UM
11004	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-trifluoromethylbenzyl)-6,7-benzomorphan . HCl	6-VCU/UM
11005	4-(3-hydroxyphenyl)-4-(1-oxo-propyl)-1-(2-trifluoromethylbenzyl)piperidine.HCl	5-VCU/UM
11006	(-)-(1*R*,5*R*,9*R*)-2-Cyclobutylmethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan. HCl	6-VCU/UM
11007	(+)-(1*S*,5*S*,9*S*)-2-Cyclobutylmethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan. HCl	6-VCU/UM
11011	(+)-(1*S*,5*S*,9*S*)-2-Cyclohexylmethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan. HCl	6-VCU/UM
11012	(-)-(1*R*,5*R*,9*R*)-2-Cyclohexylmethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan. HCl	6-VCU/UM
11013	(-)-(1*R*,5*R*,9*R*)-2-(3-Phenylpropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan. HCl	6-VCU/UM
11014	(+)-(1*S*,5*S*,9*S*)-2-(3-Phenylpropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan. HCl	6-VCU/UM
11015	Thevinone.oxalate	4-VCU/UM
11016	NCS-382, sodium salt	7-VCU/UM
11017	(*R*)-(+)-Nicotine di-*d*-tartrate	8-VCU/UM

11018	(*S*)-(-)-Nicotine di-*l*-tartrate	8-VCU/UM
11019	Caffeine tartrate	8-VCU
11020	(-)-(1*R*,5*R*,9*R*)-5,9-dimethyl-2-(3-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate	6-VCU/UM
11021	(+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2-(3-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate	6-VCU/UM
11022	(+)-(1*S*,5*S*,9*S*)-2-(3-Methylbutyl)- 5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	6-VCU/UM
11023	(-)-(1*R*,5*R*,9*R*)-2-(3-Methylbutyl)- 5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	6-VCU/UM
11024	Metanicotine.oxalate	8-VCU
11025	2-(2-phenethyl)-1,2,3,4-tetrahydroisoquinoline.oxalate	8-VCU/UM
11026	(+)-Oripavine.oxalate	5-VCU/UM
11028	3-O-Methylnaltrexone.HCl	4-VCU/UM
11034	L-Lobeline	8-VCU
11035	Agmatine.sulfate	8-VCU
11037	3-O-Cinnamoylnaltrexone.HCl	4-VCU/UM
CPDD 0059	(+/-)-Mecamylamine.HCl	9-S/D Group

NOTES FOR TABLES 2 - 9

Rounded numbers are used; precise values and details of the procedures are given in the VCU and UM reports (Aceto et al., 2002; Woods et al., 2002). "Inactive" is stated when an ED_{50} or AD_{50} is not reached. 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).

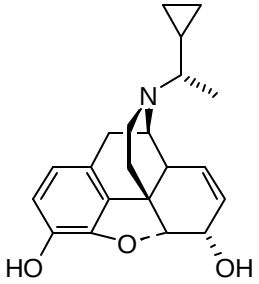
1) Antinociceptive reference data:
Morphine ED_{50} (mg/kg): Hot Plate = 0.8; Phenylquinone = 0.23; Tail-Flick = 5.8; Tail-Flick Antagonism vs. morphine (naltrexone AD_{50} = 0.007; naloxone AD_{50} = 0.035).

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)

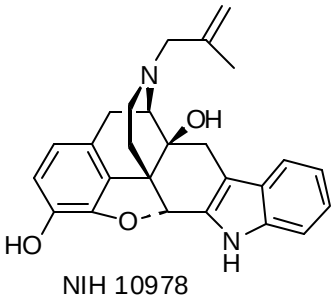
[^{35}S]GTPγS functional data were obtained employing recombinant receptors as described above. Values are given as EC_{50} with % stimulation compared to the standard full agonist (DAMGO, SNC80, U69,593), or the maximum stimulation achieved. μ (ED_{50}) morphine = 65 nM (100% stimulation), DAMGO = 34 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 refer to the year of publication.

TABLE 2. 4,5-EPOXYMORPHINANS



NIH 10497



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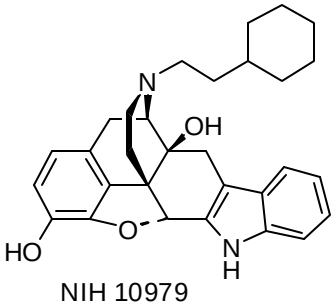

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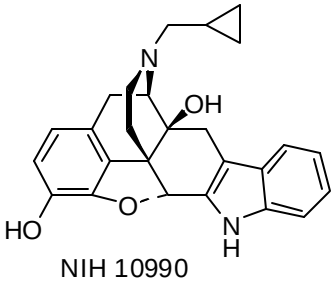


NIH 10990

	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)
10497[b]	-	0.03[a]	2.0[a]	Inactive[a]	μ=0.1, δ=29, κ=1.3[a]	Complete substitution[a]
10978[c]	Inactive	Inactive	Inactive	Inactive	μ=430, δ=0.68, κ=355	No substitution or exacerbation of withdrawal
10979	2.42	0.39	3.86[d]	-	μ=7.3,[e] δ=181, κ=378	-
10990[f,g]	-	-	-	-		

a) Previously reported (2001). [^{35}S]GTPγS assay: μ EC_{50} = 2191 nM (18.7% stimulation); δ EC_{50} = 72.2 nM (11.7% stimulation); κ EC_{50} = 18.3 nM (78.4% stimulation). Monkey self-administration: maintained rates between saline and codeine; monkey drug discrimination: codeine like; thermal analgesia: μ + κ, more effective @ 50 than 55 °C; rat primary physical dependence: relatively free of μ-opioid dependence liability; naloxone AD_{50} (TF): 2.98; vas deferens: κ-profile; rat brain homogenate binding: 2.1 nM.

b) New data: Opioid subtype testing against ED_{80} of NIH 10497 in TF demonstrated weak κ-agonist effects, and no μ-agonist effects. Activity of three different samples of NIH 10497 in TF: ED_{50} = 4.47 (0.51-39.08); 2.52 (0.67-9.47); 1.67 (0.31-8.96).

c) [^{35}S]GTPγS assay: μ: <5% stimulation at 10 μM; δ: no stimulation at 10 μM; κ: no stimulation at 10 μM. Antagonism of SNC80 (δ agonist) pK_B = 8.93.

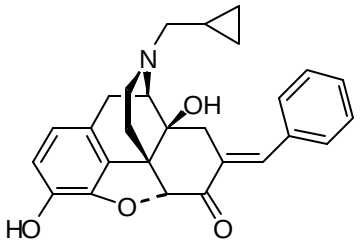
d) Naloxone AD_{50} = 0.1; β-FNA (μg/brain) AD_{50} = 1.25; norBNI inactive; NTI inactive.

e) [^{35}S]GTPγS assay: μ: EC_{50} = 105 nM (52% stimulation).

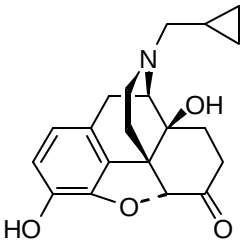
f) Previously reported as NIH 10589 (1999, 2000) (See Table 3)

g) New data: [^{35}S]GTPγS assay: AD_{50} vs. DAMGO = 7.9 nM.

TABLE 3. 4,5-EPOXYMORPHINANS



NIH 10985



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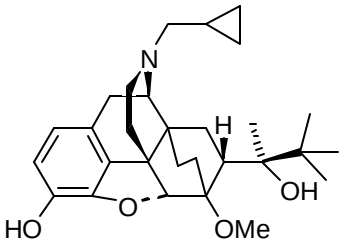

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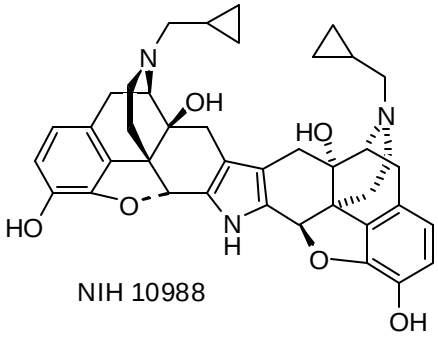
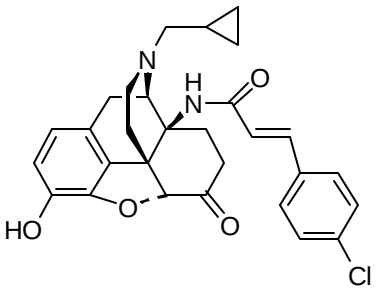


NIH 10988



NIH 10989

[^{35}S]GTPgS FUNCTIONAL ASSAYS (AD_{50} nM ± SEM)

NIH #	Antagonism of DAMGO (μ)
10985[a]	4.1 ± 1.1
10986[b]	1.4 ± 0.3
10987[c]	1.3 ± 0.3 (67% reduction of stimulation)
10988[d]	-
10989[e]	1.2 ± 0.2
10990[f]	7.9 ± 2.2

a) Previously reported as NIH 10923 (1998): Inactive in HP, TF, and PPQ. Antagonism of morphine in TF AD_{50} = 0.05 mg/kg. Antagonism of : DPDPE in TF AD_{50} = 0.04 mg/kg; sufentanyl in TF AD_{50} = 4.0 mg/kg; U69,593 in TF inactive.

b) Previously reported as NIH 8503 (1971) and NIH 9930 (1983, 1984, 1986): Inactive in HP, PPQ, and TF. Antagonism of morphine in TF AD_{50} = 0.007 mg/kg. Precipitation of withdrawal in morphine dependent monkeys (potency 10x naloxone)

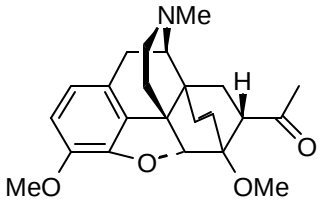
c) Previously reported as NIH 8805 (1974) and NIH 10276 (1985, 1986): ED_{50} (mg/kg) HP = 0.035, PPQ = 0.016, TF = 0.14. Antagonism of morphine in TF AD_{50} = 1.0 mg/kg. Precipitates withdrawal in morphine dependent monkeys at 0.32 mg/kg. No substitution for morphine observed.

d) Previously reported as NIH 10588 (1991): Inactive in PPQ, TF, and as an antagonist of morphine in TF. Exacerbated withdrawal in morphine dependent monkeys. Binding against [^{3}H]-etorphine in rat brain homogenates K_i = 70 nM; Functional assays (vas deferens) indicated κ-antagonism.

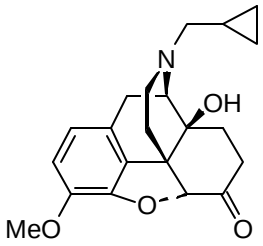
e) Previously reported as NIH 10443 (1988, 1989, 1990): Inactive in HP, PPQ, and TF. Antagonism of morphine in TF AD_{50} = 0.12 (long duration of action). Binding against [^{3}H]-etorphine in rat brain homogenates K_i = 0.65 nM; Functional assays (vas deferens) indicated irreversible antagonism. Severe withdrawal in morphine dependent monkeys, which could not be reversed.

f) Structure in Table 2. Previously reported as NIH 10589 (1990, 2000): Inactive in PPQ, TF, and as an antagonist of morphine in TF. Exacerbates withdrawal in morphine dependent monkeys. Binding (K_i, nM, monkey brain cortex) μ = 9.5, δ = 0.21, κ = 20.5. pA_2 vs. DSLET = 9.44, pA_2 vs. sufentanyl = 7.71.

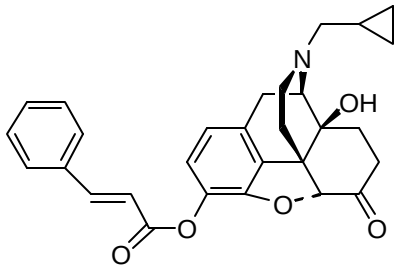
TABLE 4. 3-O-SUBSTITUTED 4,5-EPOXYMORPHINANS



NIH 11015



NIH 11028



NIH 11037

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)
11015[a]	4.49	2.36	5.56[b]	-	μ=211, δ=2102, κ=6311	Complete substitution at 2 and 8 mg/kg
11028	Inactive	-	Inactive	0.47[c]	μ=30.8, δ=589, κ=95.2	-
11037	Inactive	Inactive	Inactive	0.013[d]	μ=18.4, δ=385, κ=30.7	Precipitated withdrawal at 0.03 and 0.15 mg/kg.[e]

a) Previously reported as NIH 10631 (1991): ED_{50} (mg/kg) - PPQ = 2.0; TF = 8.3. Mouse vas deferens functional assay EC_{50} = 1.7 nM (Max. 63% inhibition). Complete suppression of withdrawal signs in withdrawn morphine dependent monkeys.

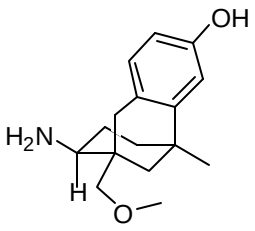
b) Naloxone vs. ED_{80} NIH 11015 in TF: AD_{50} = 0.02.

c) Antagonism of morphine ED_{80} (p.o.) in TF: AD_{50} = 2.31. Six hour pretreatment with NIH 11028 - Antagonism of morphine ED_{80} (p.o.) in TF: Inactive.

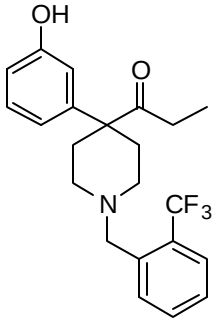
d) At 30 min. pretreatment. With 4h pretreatment, AD_{50} = 2.69. AD_{50} vs. ED_{80} enadoline = 0.196.

e) Slightly more potent and longer acting than naloxone.

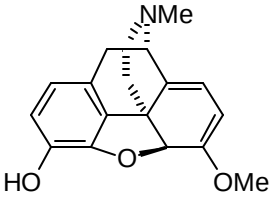
TABLE 5. MISCELLANEOUS OPIOIDS



NIH 10945



NIH 11005



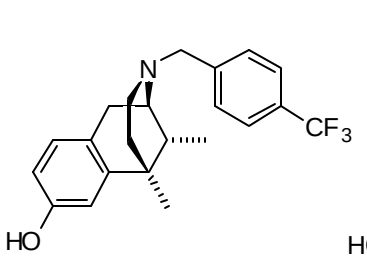
NIH 11026

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

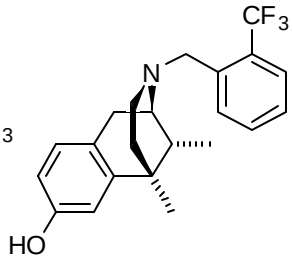
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
10945	Inactive	3.75[a]	Inactive	Inactive	μ=3.7, δ=156, κ=6.3	Partial suppression[b]
11005	Inactive	Inactive[c]	Inactive	Inactive	μ=546, δ=119, κ=836	No suppression at 15 mg/kg
11026	Inactive	0.58[d]	Inactive	Inactive	μ=806, δ=>10,000 κ=>10,000	Partial attenuation of withdrawal signs at 4 and 16 mg/kg

a) Naloxone AD_{50} vs. ED_{80} NIH 10945 = 2.63.
b) Lower dose (4 mg/kg) appeared more effective than higher dose (16 mg/kg).
c) 49% inhibition at 30; 51% at 60.
d) Antagonism of ED_{80} in PPQ: β-FNA= 46% at 10μg (i.c.v.); norBNI = 60% at 10 mg/kg; NTI inactive.

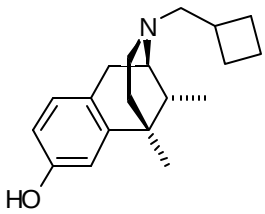
TABLE 6a. (-)-6,7-BENZOMORPHANS



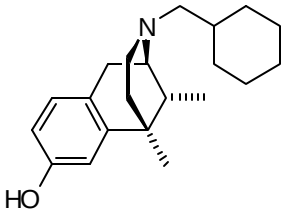
NIH 10994



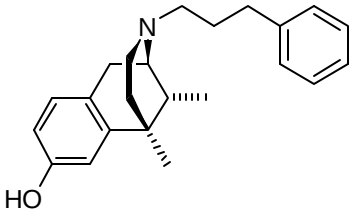
NIH 11004



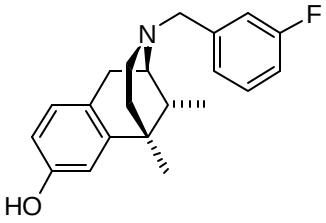
NIH 11006



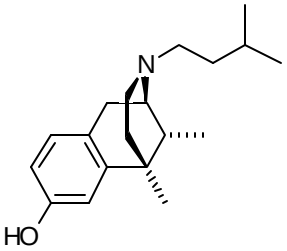
NIH 11012



NIH 11013



NIH 11020



NIH 11023

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)
10994	Inactive	27.4	Inactive	Inactive	μ=1435, δ=>10,000, κ=>1872	Neither substituted nor exacerbated withdrawal at 4 and 16 mg/kg
11004	Inactive	Inactive	Inactive	Inactive	μ=335, δ=1091 κ=149	Neither substituted nor exacerbated withdrawal at 4 and 16 mg/kg
11006	0.12	0.04	0.26[a]	-	μ=2.9, δ=11.3 κ=0.74[b]	Complete substitution at 0.25 mg/kg[c]
11012	Inactive	14.62	Inactive	3.7	μ=26, δ=315, κ=13	Neither substituted nor exacerbated withdrawal at 0.75 and 3 mg/kg[d]
11013	9.63	4.59	8.86	-	μ=11, δ=47, κ=34	Partial substitution at 3.5 mg/kg[e]
11020	Inactive	Inactive	Inactive	Inactive	μ=16.3, δ=351, κ=7.9	Neither substituted nor exacerbated withdrawal at 4 and 16 mg/kg
11023	Inactive	0.39	2.5	-	μ=16.4, δ=36.7, κ=7.3	At 2 and 8 mg/kg, reduced withdrawal signs, but did not substitute for morphine[f]

a) Antagonism of NIH 11006 in TF: Naloxone vs. ED80 - AD50 = 0.84; NTI vs. ED_{80} 19% at 30; norBNI vs. ED_{80} 16% at 30; β-FNA vs. ED_{80} - AD_{50} = 0.49.

b) [^{35}S]GTPγS assay: μ EC_{50} = 2.0 nM (25.5% stimulation); δ EC_{50} = 54.3 nM (22.3% stimulation); κ EC_{50} = 3.1 nM (57.9% stimulation).

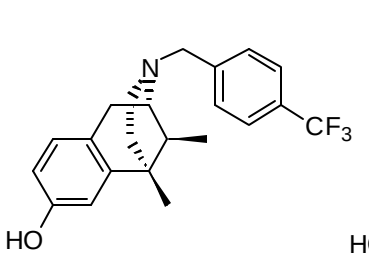
c) Other effects included ataxia, jaw sag, salivation, tremor, eyelid ptosis.

d) Jaw sag was noted at 3 mg/kg, and tremors were noted at 12 mg/kg which prevented assessment.

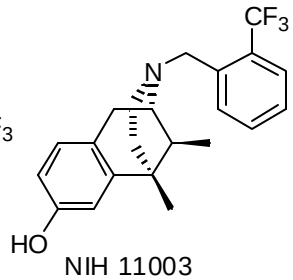
e) Other effects included ataxia, jaw sag, eyelid ptosis. Prompt onset of action, and duration of action less than morphine.

f) Other effects included ataxia, jaw sag, eyelid ptosis.

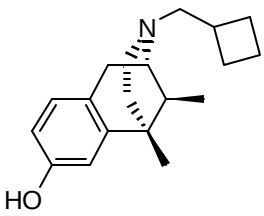
TABLE 6b. (+)-6,7-BENZOMORPHANS



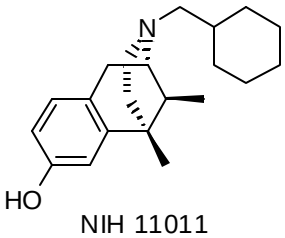
NIH 10995



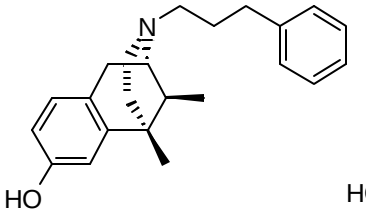
NIH 11003



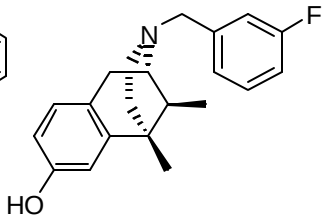
NIH 11007



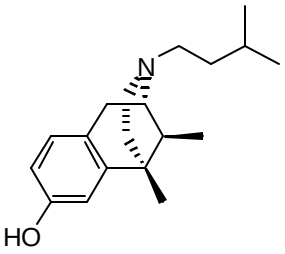
NIH 11011



NIH 11014



NIH 11021



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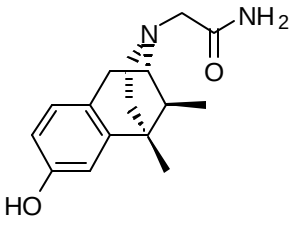


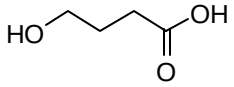
NIH 10992

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

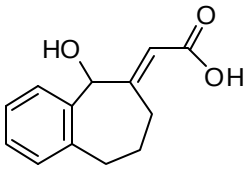
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
10992	Inactive	4.05	Inactive	Inactive	μ=>10,000, δ=>10,000, κ=>10,000	Neither substituted nor exacerbated withdrawal at 4 and 16 mg/kg
10995	Inactive	32.8	Inactive	Inactive	μ=279, δ=2217, κ=564	Weak inverse dose response
11003	Inactive	Inactive	Inactive	Inactive	μ=867, δ=3538, κ=645	Neither substituted nor exacerbated withdrawal at 4 and 16 mg/kg
11007	Inactive	Inactive	Inactive	Inactive	μ=352, δ=1496, κ=97	Possible slight attenuation of withdrawal at 4 and 16 mg/kg[a]
11011	Inactive	17.6	Inactive	Inactive	μ=568, δ=5806, κ=83	Slight attenuation of withdrawal at 16 mg/kg[b]
11014	22.1[c]	1.42[c]	19.1[c]	-	μ=187, δ=2273, κ=283	Weak, non dose-related attenuation of withdrawal[d]
11021	Inactive	Inactive	Inactive	Inactive	μ=2087, δ=>10,000, κ=864	Neither substituted nor exacerbated withdrawal at 4 and 16 mg/kg
11022	Inactive	19.4	Inactive	Inactive	μ=1850, δ=>10,000, κ=175	Neither substituted nor exacerbated withdrawal

a) Behavior at high dose: ataxia, slowing, walking in circles, staggering, spinning while sitting.
b) Other effects at 16 mg/kg: ataxia and jaw sag.
c) Eyelid ptosis and immobility at 30 mg/kg.
d) At high doses, jaw sag, salivation, eyelid ptosis were noted.

TABLE 7. MISCELLANEOUS COMPOUNDS



NIH 10947



NIH 11016

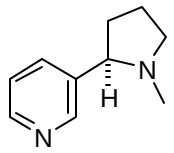
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY (MOUSE ED_{50}/AD_{50}, s.c., mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
10947[b]	-	iv: 31[a]	Inactive[a]	-	–	Inverse dose response[a]
11016	Inactive	Inactive	Inactive	Inactive	μ=>10,000 δ=>10,000 κ=>10,000	Feeble attenuation of withdrawal at 16 mg/kg; no attenuation at 32 mg/kg. No precipitation of withdrawal at 32 mg/kg

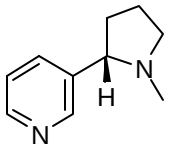
a) Previously reported (Coop and Jacobson, 2001). Attenuation of withdrawal at low dose, exacerbation of withdrawal at higher doses. PPQ: Co-administration with ED_{25} morphine led to dose-related synergism. Morphine tolerant mice: NIH 10947 + morphine partially restored antinociception.

b) New Data: In combination with alcohol (GHB in a 12% EtOH solution) (p.o.) mice were ataxic at 30 and 100 mg/kg. Rat Continuous Infusion assays: the animals showed no signs of physical dependence to NIH 10947, nor did NIH 10947 substitute for morphine in morphine dependent rats.

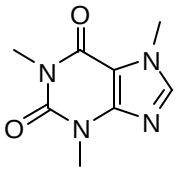
TABLE 8. MISCELLANEOUS (CONTINUED)



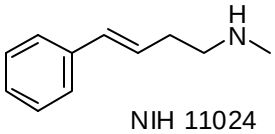
NIH 11017



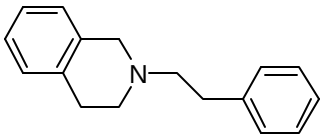
NIH 11018



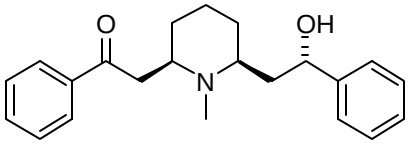
NIH 11019



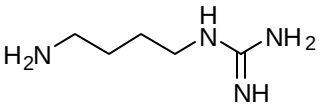
NIH 11024



NIH 11025



NIH 11034



NIH 11035

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)
11017[a]	Inactive	10.23[b]	Inactive	Inactive	μ=>10,000 δ=>10,000 κ=>10,000	Reduced withdrawal signs at 1.5 mg/kg, intensified at 6 mg/kg
11018[c]	16.92[d]	1.42[d]	8.91[d]	Inactive[d]	μ=>10,000 δ=>10,000 κ=>10,000	Exacerbated withdrawal signs at 0.75 and 3 mg/kg
11019[e]	Inactive	Inactive	Inactive	Inactive	-	Neither substituted or exacerbated withdrawal
11024[f]	Inactive	Inactive	Inactive[g]	Inactive	-	Neither substituted or exacerbated withdrawal
11025	Inactive	10.5	Inactive	Inactive	μ=>10,000 δ=>10,000 κ=>10,000	Displayed delayed attenuation of withdrawal signs at 4 and 16 mg/kg (after 60 mins)
11034	Inactive[h]	3.01	Inactive[h]	Inactive	-	No attenuation of withdrawal at 1 and 4 mg/kg[j]
11035	Inactive	Inactive[j]	Inactive	Inactive	-	A suggestion of attenuation of withdrawal at 6 mg/kg

a) Previously studied as NIH 9801 (1983): ED_{50} HP = 23.2 mg/kg. Inactive in PPQ, TF, and as an antagonist of morphine in TF. Partial suppression of withdrawal signs in withdrawn monkeys.

b) NTI vs. ED_{80} gave erratic antagonism.

c) Previously studied as NIH 9733 (1984): ED_{50} (mg/kg) HP = 2.2; TF = 5.2, PPQ = 1.3. Primary physical dependence in monkey - no withdrawal signs after abrupt withdrawal.

d) Convulsions were seen in all mouse assays, and were reduced by administration of NTI in TF. NTI had no effect on antinociception in TF

e) Previously studied as NIH 10613 (1990): Inactive in PPQ and TF.

f) Previously studied as NIH 10936 (1999): Affinity >10,000 nM for μ, κ, and δ receptors.

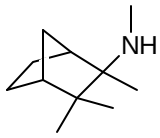
g) TF (i.v.) Inactive at 30 mg/kg, but 6/6 mice had clonic convulsions, 3/6 died).

h) HP: At 30 mg/kg all mice convulsed, and 4/8 died. TF: At 10 mg/kg 5/6 mice convulsed and died

i) Muscle relaxation and retching was observed

j) 40% inhibition at 10 mg/kg (s.c.); 50% at 3, 41% at 10, and 53% at 30 μg/brain (i.c.v.).

TABLE 9. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD 0059

CPDD#	Discriminative Stimulus Effects in Monkeys. Comparison to Flumazenil & Midazolam (s.c.)	Monkey Self-Administration (iv)	Monkey Drug Discrimination (i.g.)
0059[a]	-	No reinforcing effects in methohexital trained monkeys	-

a) Previously reported as NIH 11010 (Coop and Jacobson, 2001): Inactive in TF. PPQ ED_{50} = 4.2 mg/kg; neither mecamylamine nor naloxone antagonized NIH 11010 ED_{80} in PPQ; 6/6 mice died at 30 mg/kg.

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ACKNOWLEDGEMENT

We gratefully acknowledge CPDD for the financial support of the Biological Coordinator.