BIOLOGICAL EVALUATION OF OPIOIDS, STIMULANTS, AND DEPRESSANTS. II. AN OVERVIEW OF THE STUDIES PERFORMED BY THE DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2005)

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THE DRUG EVALUATION COMMITTEE

The Drug Evaluation Committee (DEC) evaluates analgesics, stimulants, and depressants for preclinical physical dependence potential as a public health service. DEC works with researchers from academia, industry, and also governmental organizations (FDA, DEA, NIDA, WHO) to characterize the pharmacological profile of compounds in order to facilitate decisions on matters ranging from medication development to drug scheduling. The duties of the Biological Coordinator of DEC (Dr. A. Coop) involve receiving samples for evaluation and distributing them blind to the relevant pharmacological groups within DEC. All data are collated by the Biological Coordinator, who maintains a confidential database and corresponds with the submitters. The Biological Coordinator also maintains the DEC website (http://www.cpdd.vcu.edu/DEC_ARCHIVES/dec.pdf) which contains archived DEC annual reports together with the DEC indices (http://www.pharmacy.umaryland.edu/faculty/acoop/dec%20folder/DEC%20indices2003web.xls), a list of all compounds evaluated by DEC and reference to their year of publication. In order to improve access to information, the Biological Coordinator is currently updating the indices with the goal of including links to original data in the on-line DEC annual reports. The other members of DEC are in the two analgesic testing groups, at Virginia Commonwealth University (VCU, Drs. L. Harris, M. Aceto, P. Beardsley, C. Cook) and the University of Michigan (UM, Drs. J. Woods [DEC Chair], J. Traynor, H. Ko), and four stimulant/depressant testing groups, at the University of Mississippi Medical Center (UMMC, Dr. W. Woolverton), University of Texas Health Science Center at San Antonio (UTHSCSA, Drs. C. France, L. McMahon), University of Michigan (UM, Drs. G. Winger, J. Woods), and Yerkes National Primate Research Center, Emory University (Dr. W. Fantegrossi). Drs. T. Cicero and A. Jacobson act as emeritus members.

DEC reports to the CPDD Committee on Abuse Liability Testing (CALT; formerly the DEC Liaison Committee; Dr. S. Negus, 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 in Atlanta in May 2005 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. McCann), to discuss the results obtained from the VCU testing and research program. The Chair and Biological Coordinator of DEC, together with the Chair of CALT, also met with representatives from DEA, FDA, and NIDA in Washington DC in November 2004 in order to facilitate the evaluation of compounds from governmental organizations.

This report provides an overview of the results obtained by all groups within DEC; precise values and details of the procedures are given in the VCU, UM, and Stimulant Depressant reports (Aceto et al., 2006; Woods and Traynor, 2006; Woolverton et al., 2006). Data obtained under the auspices of DEC are held confidential for a maximum of three years, but can be released prior to the three-year limit with the permission of the submitter. Data were released for publication this year on 65 compounds evaluated by the Analgesic Testing Program (Figure 1). This figure remains high by historical standards. Of these 65 compounds, 61 were evaluated at VCU (antinociceptive assays in mice: tail flick, hot plate, and phenylquinone antiwrithing, and the tail-flick antagonist assay; as well as substitution for morphine and precipitated withdrawal assays in rhesus monkeys and rats), and 47 at UM (binding affinity to the μ, δ, and κ opioid receptors and GTPγS functional studies). Compounds were submitted primarily from academia; one compound was submitted from a governmental source. Figure 1 shows the continuing trend that the percentage of compounds originating from academia has been steadily increasing over the past few years, with the percentage from other sources decreasing. Several new pharmaceutical

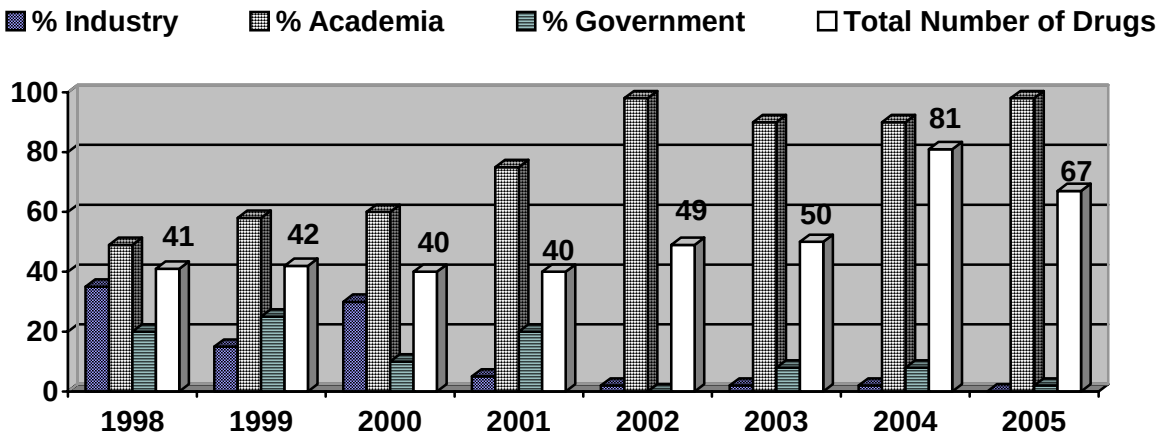
companies have submitted a large number of compounds over the past 2-3 years, thereby increasing the diversity of sources for compounds to be released starting in 2006. In addition, two new academic submitters are represented this year, and it is anticipated that submissions from these sources will continue. Two compounds originating from academia were released this year from the Stimulant/Depressant program, and submissions to this program continue to increase.

Three publications based on the data gathered under DEC auspices were published or are under review since the last annual report (Fantegrossi et al., 2005; Fantegrossi et al., (in review); Harding et al., (in review)).

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 10. As in previous years (Coop, 2005), the compounds are classified according to their molecular structure: morphinans and 4,5-epoxymorphinans in Tables 2, 3 and 4; orvinol analogs in Table 5; indolomorphinans in Table 6; 6,7-benzomorphans in Tables 7 and 8; atypical opioid and other compounds in Table 9; compounds evaluated by the Stimulant/Depressant program are shown in Table 10. Numerous interesting compounds were released this year, and they are discussed below. For compounds that have been evaluated previously, the new data are discussed in relation to the published data.

FIGURE 1. DEC TESTING PROGRAMS: PERCENT AND SOURCE OF EXAMINED DRUGS AND TOTAL NUMBER OF COMPOUNDS (1998-2005)



NIH 11247 and **NIH 11248** (Table 2) are two analogs of hydrocodone (**NIH 11230**, Table 2) with carboxylate substituents in the 1-position, and no activity was seen in antinociceptive assays in mice. The zwitterionic nature of NIH 11247 led to the hypothesis that entry to the central nervous system may be limited, thereby resulting in the lack of activity when administered s.c. However, the compounds were also inactive when administered i.c.v. The lack of opioid activity s.c. is probably due to their low binding affinity to opioid receptors, rather than limited access to the central nervous system.

As reported last year (Coop, 2005), the 14-phenylpropyloxy morphinans (Table 3) represent a unique class of opioids with extraordinary potency as antinociceptive agents (10,000 x morphine), and high affinity for all three opioid receptors (Greiner et al., 2003, Spetea et al., 2004). As such, they can be considered of similar potency to the orvinols (Lewis, 1985, Casey and Parfitt, 1986). The compounds follow standard opioid structure-activity relationships in that 3-phenols (such as **NIH 11121**) were found to possess greater antinociceptive potency and greater opioid receptor affinity than the corresponding 3-methyl ethers (**NIH 11120**). NIH 11121 was confirmed to be a mu agonist through antagonism of the antinociceptive effects in the mouse tail flick assay with selective antagonists, and was shown to fully substitute for morphine in monkeys as a dose of 0.0004 mg/kg. Thus, NIH 11121 was shown to be approximately 7500 times the potency of morphine in monkeys and

approximately 25,000 times the potency of morphine in mice. One interesting aspect of this class of compounds is that both the *N*-methyl and *N*-cyclopropylmethyl analogs are mu agonists, whereas *N*-cyclopropylmethyl substitution generally leads to mu antagonists. Thus, both the *N*-methyl **NIH 11149** and its *N*-cyclopropylmethyl analog, **NIH 11150**, were active as antinociceptive agents, albeit with the *N*-cyclopropylmethyl NIH 11150 possessing lower potency and ten-fold lower affinity at all three opioid receptors. Traditional structure-activity relationships predict that opioids containing 4-phenolic groups will have low mu activity (Coop et al., 1999), but this is again not followed in the 14-phenylpropyloxy series. 4-Phenolic **NIH 11151** was shown to have excellent affinity at all three opioid receptors, and was 5-10-fold more potent than the corresponding 4-methyl ether **NIH 11152** in mouse antinociceptive assays (Spetea et al., 2004). A similar relationship was seen for **NIH 11135** and **NIH 11136**, with the 4-phenolic NIH 11135 having the greater potency in mice, although both had the same affinity at opioid receptors.

Table 4 contains morphinans and 4,5-epoxymorphinans with unusual substituents. **NIH 11132** (Table 4) has a 14-O-cinnamyl group, and is closely related to the 14-phenylpropyloxy morphinans in Table 3. The presence of the corresponding 14-unsubstituted hydroxyl derivative (**NIH 11130**) allowed an assessment of the potency increase on adding the cinnamyl group – a 44,000-fold increase in potency in the anti-writhing assay. Although this is an important finding, it should be noted that **NIH 11131**, the 14-methoxy analog, also had potent antinociceptive activity. **NIH 11134** and **NIH 11137** both contain a 3,4-dimethoxy substitution pattern, which is predicted to result in relatively low mu opioid receptor affinity and antinociceptive potency. This was indeed the case for NIH 11137, but NIH 11134 was shown to have high mu affinity and far greater potency in antinociceptive assays than morphine. **NIH 11144**, a 3-ether derivative of naltrexone, was shown to has weak morphine antagonist activity.

The products of Diels-Alder adducts of thebaine (thevinols and orvinols) continue to receive considerable attention (Lewis and Husbands, 2004). 3-Desoxythevinone (**NIH 11146**, Table 5) was shown to retain reasonable mu opioid receptor affinity and antinociceptive potentcy, even though the 3-phenol is generally required for high affinity mu opioids. The four analogs of thevinone, **NIH 11172** – **NIH 11175** (Table 5), have an additional hydroxyl group in either the 18- or 19-position, positions which have received little attention in terms of substituents. Table 5 shows that all four compounds had weak (if any) antinociceptive activity, and therefore the introduction of hydroxyl substituents into these positions appears to result in low activity compounds. The related compounds, **NIH 11215** and **NIH 11219** (Table 5), possess additional lipophilic substituents at the 18-position, but neither showed any appreciable activity in any assay except for anti-writhing. The known orvinol **NIH 11214** (Table 5) (Lewis and Husbands, 2004) was investigated for its potential to act as a very potent pure opioid antagonist. Potent morphine antagonism was seen in the tail flick assay, and NIH 11214 precipitated withdrawal in morphine dependent primates. As with other orvinols, little selectivity was observed in binding assays, with NIH 11214 showing sub-nanomolar affinity at all three opioid receptors. Antinociceptive activity was observed in the anti-writhing assay in mice and, based on previous knowledge of the pharmacology of orvinols (Husbands and Lewis, 2004), it is proposed that this activity may be due to kappa agonism. A duration of action study of the mu antagonism of NIH 11214 showed that antagonist activity was reduced to 32% of starting potency after 2 hours, indicating that NIH 11214 does not share the extremely long duration of action seen with other orvinols, such as buprenorphine (Lewis, 1985).

The 6,7-indoles (**NIH 11116** and **NIH 11118**, Table 6) are hybrids of naltrindole, the prototypical delta opioid antagonist (Portoghese et al., 1990) and the potent phenylpropyloxy morphinans seen in Table 2. The propargyl ether (NIH 11118) showed modest binding affinity, and no activity in antinociceptive assays. The corresponding phenol had the expected greater affinity and was weakly active in mouse antinociceptive assays. The delta opioid selectivity of NIH 11118 in binding assays led to the consideration that NIH 11118 may be acting as a delta agonist in vivo, but this was shown not to be the case as the activity in the tail flick assay was not reversed with naltrindole. The 3,4-dimethoxy analogs of the indolomorphinans and benzylidenenaltrexone (**NIH 11216**-**NIH 11218**, Table 6) were shown to be inactive in antinociceptive assays, and further studies are required to determine their profiles.

The *N*-substituted benzomorphans (Table 7) continue to be studied to determine the effects of the N-substituent in opioids (May et al., 1998; May et al., 2003). Many of these compounds displayed good affinity at opioid

receptors, yet are weakly active, or inactive, in antinociceptive assays. For example **NIH 11139** (*N*-8-hydroxyoctyl) had good affinity at all three receptors, but was only active in the antiwrithing assay in mice. This was demonstrated not to be delta agonist mediated through the lack of antagonism with naltrindole.

Table 9 contains four opioids with atypical structures, together with two known cannabinoid ligands. Eseroline (**NIH 10820**, Table 8) is known to be an acetylcholine esterase inhibitor (Furst et al., 1982), but also has unusual opioid activity (Jacobson, 1988). Receptor binding assays showed that NIH 10820 had relatively low affinity for mu opioid receptors, and very low affinity for kappa and delta receptors. **NIH 11220** is an analog of gamma-hydroxybutyrate (GHB) which was designed to possess greater affinity for GHB receptors than GHB itself. In the course of testing NIH 11220 at large doses in rodents, weak opioid activity became apparent (Carter et al., 2005), and the compound was assessed through DEC to determine the potency of this compound as an opioid. NIH 11220 was shown to have an affinity at opioid receptors of >10,000 nM and no activity was seen in mice at doses up to 100 mg/kg, indicating that any opioid component in its profile is small. The lack of activity of NIH 11220 led to the consideration of **NIH 11235**, which has a basic nitrogen generally considered essential for mu opioid activity (Casy and Parfitt, 1986). Little improvement in opioid activity was observed in binding and antinociceptive assays.

Salvinorin A (**NIH 11228**, Table 9) has been reported as a naturally occurring non-nitrogenous kappa opioid agonist with hallucinogenic activity (Harding et al., 2005). Although many assays have shown it to possess many of the characteristics of the traditional basic nitrogen-containing kappa opioid agonists, its antinociceptive activity has received little attention. Table 9 confirms that NIH 11228 is indeed a selective kappa opioid, and that it acts as an antinociceptive agent in the antiwrithing and tail flick assays. NIH 11228 therefore appears to be the first systemically active kappa opioid agonist lacking a basic nitrogen, and has the potential to aid in the understanding of the interaction of agonists with the kappa opioid receptor. Its development into a pharmacological tool and potential medication has interesting implications, but the problems of poor solubility and ease of metabolic hydrolysis require addressing.

Mounting evidence suggests that cannabinoid CB1 receptor antagonists have the potential to be useful pharmacoptherapies for the abuse of various drugs of abuse (Le Foll and Goldberg, 2004). Table 9 shows that neither the CB1 receptor antagonist, SR141716A (**NIH 11251**) nor the cannabinoid agonist, cannabindiol (**NIH 11252**) had any effect on withdrawal signs in morphine dependant monkeys at doses up to 10 mg/kg.

The readily available **CPDD 0067** (phenylpiperazine) (Table 10) shares structural similarities to TFMPP and BZP, small molecules of increasing concern to the Federal authorities (Fantegrossi et al., 2005; Coop, 2004; Coop, 2005). A full investigation of CPDD 0067 showed no activity in any of the stimulant and depressant assays, and was not recognized as LSD in discriminative stimulus assays. **CPDD 0072** (Table 10) is a readily available *meta*-methoxyl substituted analog of BZP (Fantegrossi et al., 2005), and was investigated to assess its potential for abuse as an alternative to BZP. As shown in Table 10, CPDD 0072 had no discriminative stimulus effects in benzodiazepine or amphetamine trained monkeys, but may have activity as a reinforcer in cocaine maintained monkeys. Unfortunately, the poor aqueous solubility of the drug prevented a full assessment at doses above 0.3 mg/kg/inj.

IN CONCLUSION, DEC evaluated numerous interesting compounds this year. The 14-phenylpropylethers (**NIH 11121**) were extremely potent and had unique structure-activity relationships, including mu agonist activity for *N*-cyclopropylmethyl derivatives and the high potency of the 4-phenolic derivatives. Simply adding a cinnamyl ether to the 14-hydroxyl of **NIH 11130** gave **NIH 11132** with an increase in potency of over 40,000-fold. **NIH 11214** was shown to be a potent mu opioid antagonist, but is limited by apparent agonist effects in antiwrithing assays in mice. Salvinorin A (**NIH 11228**) has been confirmed as a selective kappa ligand in binding assays, and antinociceptive activity was demonstrated in mice. Hydrocodone (**NIH 11230**) was shown to act as a typical mu opioid agonist, whereas the 1-substituted analogs were devoid of activity. The analogs of known drugs of abuse, **CPDD 0067** and **CPDD 0072,** showed no activity in the stimulant and depressant assays, and CPDD 0067 was not recognized as LSD.

TABLE 1. EVALUATED COMPOUNDS

	COMPOUND NAME	TABLE #-Evaluator
NIH#	**ANALGESIC TESTING PROGRAM**	
10820	Eseroline.ascorbate	9-UM
11111	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanly)-6,7-benzomorphan.hemioxalate	7-VCU
11116	4,5α-Epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]indolo[2',3':6,7]morphinan-3-ol	6-VCU/UM
11117	4,5α-Epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]-3-[(prop-2-inyl)oxy]-morphinan-6-one.HCl	3-VCU/UM
11118	4,5α-Epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]-3-[(prop-2-inyl)oxy]indolo-[2',3':6,7]morphinan.HCl	6-VCU/UM
11119	3,4-Dimethoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one.HCl	3-VCU/UM
11120	4,5α-Epoxy-3-methoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one.	3-VCU/UM
11121	4,5α-Epoxy-3-hydroxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one.HBr	3-VCU/UM
11127	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(7-hydroxyheptyl)-6,7-benzomorphan.HBr	7-UM
11130	6,7-Didehydro-4,5α-epoxy-14β-hydroxy-3-methxoy-17-methylmorphinan-6-carbonitrile	4-VCU/UM
11131	6,7-Didehydro-4,5α-epoxy-3,14β-dimethoxy-17-methylmorphinan-6-carbonitrile	4-VCU/UM
11132	6,7-Didehydro-4,5α-epoxy-3-methxoy-17-methyl-14β-{[(*E*)-3-phenylprop-2-enyl]oxy}morphinan-6-carbonitrile	4-VCU/UM
11133	6,7-Didehydro-7-{[(*N*,*N*)-di*iso*propyl]amino}-14β-hydroxy-3-methoxy-17-methyl-4-{[(*E*)-3-phenylprop-2-enyl]oxy}morphinan-6-carbonitrile	4-VCU/UM
11134	5,6,7,8-Tetradehydro-3,4,14β-trimethoxy-17-methylmorphinan-6-carbonitrile	4-VCU/UM
11135	5,6-Didehydro-4-hydroxy-3-methoxy-17-methyl-14β-{[3-phenylpropyl]oxy}morphinan-6-carbonitrile	3-VCU/UM
11136	5,6-Didehydro-3,4-dimethoxy-17-methyl-14β-{[3-phenylpropyl]oxy}morphinan-6-carbonitrile.HCl	3-VCU/UM
11137	14β-Hydroxy-3,4-dimethoxy-5β,17-dimethylmorphinan-6-one	4-VCU/UM
11139	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl	7-VCU
11144	17-Cyclopropylmethyl-4,5α-epoxy-14β-ethoxy-5β-methyl-3-[(prop-2-inyl)oxy]-morphinan-6-one.HCl	4-VCU/UM
11146	3-Desmethoxy-18,19-dihydrothevinone	5-VCU/UM
11149	4,5α-Epoxy-17-methyl-14β-{[3-phenylpropyl]oxy}morphinan-6-one	3-VCU/UM
11150	17-Cyclopropylmethyl-4,5α-epoxy-14β-{[3-phenylpropyl]oxy}morphinan-6-one.HCl	3-VCU/UM
11151	17-Cyclopropylmethyl-4-hydroxy-14β-{[3-phenylpropyl]oxy}morphinan-6-one.HCl	3-VCU/UM
11152	17-Cyclopropylmethyl-4-methoxy-14β-{[3-phenylpropyl]oxy}morphinan-6-one.HCl	3-VCU/UM

11153	4-Butyloxy-17-cyclopropylmethyl-14β-{[3-phenylpropyl]oxy}morphinan-6-one.HCl	3-VCU/UM
11154	[14β-Butyloxy-6,7-didehydro-4,5α-epoxy-3-hydroxy-17-methylindolo[2',3':6,7] morphinan]-1'-acetonitrile.HCl	6-VCU/UM
11164	(-)-(1*R*,5*R*,9*R*)-2-(5-Acetoxypentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU
11167	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(1,3-dioxanylethyl)-2'-hydroxy-6,7-benzomorphan.HBr	7-VCU
11172	18-(*R*)-Hydroxy-20-(*R*)-orvinol.oxalate	5-VCU
11173	18-(*R*)-Hydroxy-20-(*S*)-orvinol.oxalate	5-VCU
11174	19-(*S*)-Hydroxy-20-(*S*)-orvinol.oxalate	5-VCU
11175	19-(*S*)-Hydroxy-20-(*R*)-orvinol.oxalate	5-VCU
11185	(-)-(1*R*,5*R*,9*R*)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU
11186	(+)-(1*S*,5*S*,9*S*)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	8-VCU
11188	(+)-(1*S*,5*S*,9*S*)-2-(2-Ethylbutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	8-VCU/UM
11189	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(7-heptenyl)-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11190	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(7-heptenyl)-2'-hydroxy-6,7-benzomorphan.HCl	8-VCU/UM
11191	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(8-octenyl)-2'-hydroxy-6,7-benzomorphan.HCl	8-VCU/UM
11192	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(8-octenyl)-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11194	(-)-(1*R*,5*R*,9*R*)-2-(10-Decenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11195	(+)-(1*S*,5*S*,9*S*)-2-(10-Decenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	8-VCU/UM
11196	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(9-hydroxynonyl)-6,7-benzomorphan.HCl	8-VCU/UM
11197	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(9-hydroxynonyl)-6,7-benzomorphan.HCl	7-VCU/UM
11209	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl	8-VCU/UM
11210	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl	7-VCU/UM
11212	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11213	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-6,7-benzomorphan.oxalate	7-VCU/UM
11214	17-Cyclopropylmethyl-7α-hydroxymethylorvinol.oxalate	5-VCU/UM
11215	7-Benzyl-7-hydroxy-6β,14β-butenyl-5,6,7,8-tetrahydrooripavine	5-VCU
11216	17-Cyclopropylmethyl-3,4-dimethoxy-14β-hydroxy-[6,7:2',3']indolomorphinan	6-VCU

11217	3,4-Dimethoxy-14β-hydroxy-17-methyl-[6,7:2',3']indolomorphinan	6-VCU
11218	7-(*E*)-Benzylidene-3,4-dimethoxy-14β-hydroxy-17-methylmorphinan-6-one	6-VCU
11219	18-(*R*)-Benzyloxy-4,5α-epoxy-3-hydroxy-7α-hydroxymethyl-17-methyl-6α,14α-ethano-isomorphinan	5-VCU
11220	4-Hydroxy-4-napthylbutyric acid, sodium salt	9-VCU/UM
11228	Salvinorin A	9-VCU/UM
11230	Hydrocodone	2-VCU
11231	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11232	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate	7-VCU/UM
11233	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan.HCl	8-UM
11234	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan.HCl	7-UM
11235	4-Amino-4-(2-napthyl)butyric acid.HCl	9-VCU/UM
11247	1-Carboxyoxycodone	2-VCU/UM
11248	1-Carboxyoxycodone ethyl ester	2-VCU/UM
11251	SR141716; Rimonabant	9-VCU
11252	Cannabidiol	9-VCU

CPDD#	**STIMULANT DEPRESSANT PROGRAM**	
0067	Phenylpiperazine oxalate	10-SD
0072	1-(3-Methoxybenzyl)piperazine.dioxalate	10-SD

NOTES FOR TABLES 2 - 10

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., 2006; Woods and Traynor, 2006; Woolverton et al., 2006). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained at 30 mg/kg. NTI = naltrindole (delta antagonist); norBNI = norbinaltorphimine (kappa antagonist); β–FNA = β-funaltrexamine (mu antagonist administered i.c.v as μg/brain).

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

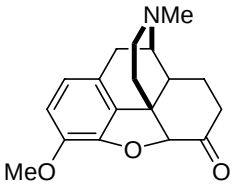
2) *In Vitro*:
Subtype selective binding affinity using recombinant receptors: μ (C_6 rat glioma cells expressing rat μ receptor), κ (CHO cells expressing human κ receptor), and δ (C_6 rat glioma cells expressing rat δ receptor). Affinity was

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)

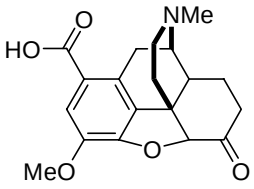
[^{35}S]GTPγS functional data were obtained with the recombinant receptors described above. Values are given as EC_{50} with % stimulation compared to the standard full agonist (DAMGO, SNC80, U69,593), or the maximum stimulation achieved: μ (ED_{50}) morphine = 65 nM (100% stimulation), DAMGO = 34 nM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

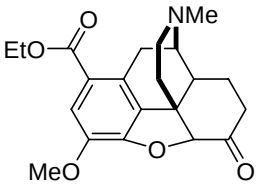
TABLE 2. HYDROCODONE AND ANALOGS OF HYDROCODONE



NIH 11230



NIH 11247



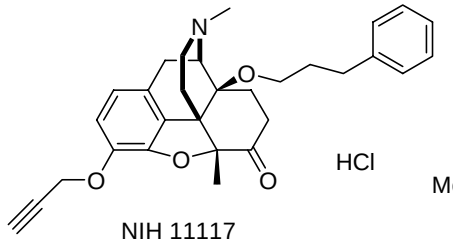
NIH 11248

	MOUSE ANTINOCICEPTIVE ASSAYS				***IN VITRO***	**MONKEY**
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11230[a]	2.4	0.14	1.5 Antagonism vs. ED_{80}: β–FNA: AD_{50}=1.6 NorBNI and NTI: Inactive	Inactive	-	Substitution for morphine at 0.75
11247[b]	Inactive s.c. and i.c.v.	Inactive s.c. and i.c.v.	Inactive s.c. and i.c.v.	Inactive s.c. and i.c.v.	μ, δ, κ> 10,000	-
11248	Inactive s.c. and i.c.v.	Inactive s.c. and i.c.v.	Inactive s.c. and i.c.v.	Inactive s.c. and i.c.v.	μ=9000, δ, κ> 10,000	-

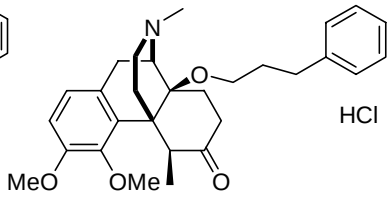
a) Previously reported as NIH 00154: Mouse; Hotplate ED_{50}=3.2; LD_{50}=129. Monkey: Intermediate physical dependence (1955, 1956).

b) Convulsions and lethality seen via i.c.v route.

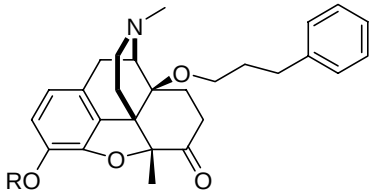
TABLE 3. 14-(3-PHENYLPROPYL)OXYMORPHINANS



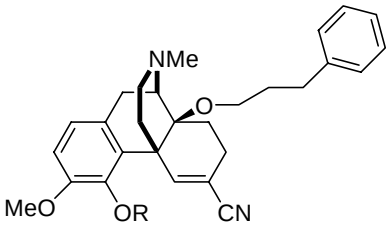
NIH 11117



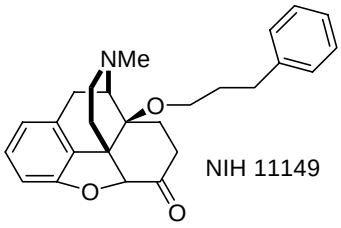
NIH 11119



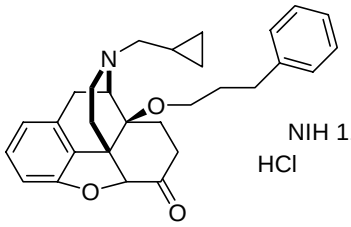
NIH 11120 R=Me
NIH 11121 R=H HBr salt



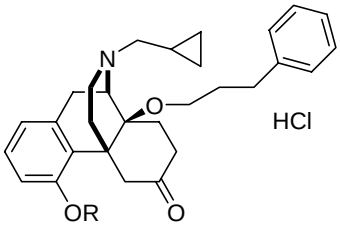
NIH 11135 R=H
NIH 11136 R=Me HCl salt



NIH 11149



NIH 11150
HCl



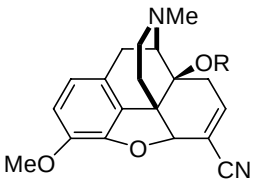
NIH 11151 R=H
NIH 11152 R=Me
NIH 11153 R=n-Bu

	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenyl-quinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11117[a]	0.14	0.01	0.02 Naloxone vs. ED_{80}: AD_{50}=0.036	Inactive	μ=1.1, δ=8.9, κ=6.4	-
11119[a]	0.022	0.0023	0.014 Naloxone vs. ED_{80}: AD_{50}=0.16	Inactive	μ=0.015, δ=0.13, κ=0.27	-
11120[a]	0.0026	0.0017	0.044	Inactive[b]	μ=0.8, δ=8.3, κ=0.20	-
11121[a]	0.0001	0.00016	0.00008 Antagonism vs. ED_{80}: β–FNA: AD_{50}=3.6 Naltrexone: AD_{50}=0.05 NorBNI and NTI: Inactive	Inactive[b]	μ=0.02, δ=0.55, κ=0.09	Complete substitution for morphine at 0.0004
11135[a]	0.004	0.0004	0.01	Inactive	μ=0.10, δ=0.94, κ=1.5	-
11136[a]	0.01	0.021	0.024	Inactive	μ=0.02, δ=0.45, κ=1.0	-

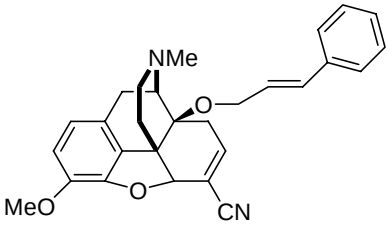
11149[a]	0.003	0.000065	0.0004	Inactive	μ=0.03, δ=0.96, κ=3.9	-
11150[a]	0.68	0.0094	0.19	Inactive	μ=0.2, δ=9.7, κ=5.3	-
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenyl-quinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11151[a]	0.04	0.0014	0.05	Inactive	μ=0.03, δ=1.1, κ=1.0	-
11152[a]	0.3	0.06	0.28	Inactive	μ=0.07, δ=6.2, κ=2.1	-
11153[a]	Inactive	1.9	4.5	Inactive	μ=1.1, δ=24, κ=6.6	-

a) Straub tail and increased locomotor activity in all mouse assays.
b) All mice died at 30.

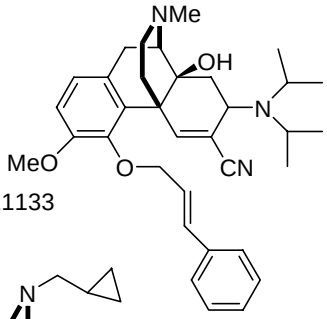
TABLE 4. MORPHINANS AND 4,5-EPOXYMORPHINANS



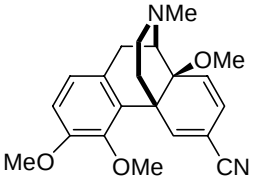
NIH 11130 R=H
NIH 11131 R=Me



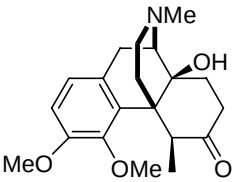
NIH 11132



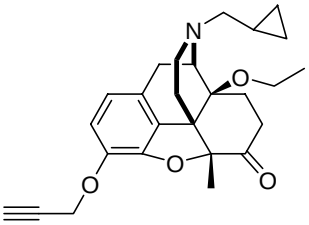
NIH 11133



NIH 11134



NIH 11137



HCl

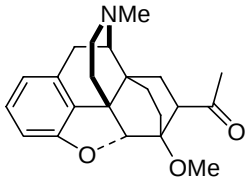
NIH 11144

MOUSE ANTINOCICEPTIVE ASSAYS ***IN VITRO***

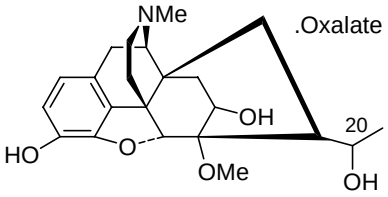
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenyl-quinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)
11130	Inactive	4.4	Inactive	Inactive	μ=46, δ=840, κ=1100
11131	0.089	0.0003	0.12	Inactive	μ=8.7, δ=220, κ=510
11132[a]	0.0006	0.0001	0.0014	Inactive	μ=0.06, δ=0.08, κ=0.35
11133	Inactive	1.7	7.7	Inactive	μ=140, δ=1500, κ=1300
11134[a]	0.08	0.0023	0.04	Inactive	μ=0.7, δ=56, κ=230
11137	6.2	0.59	1.9	Inactive	μ=5.3, δ=260, κ=2000
11144	Inactive	Inactive	Inactive	3.8	μ=76, δ=2400, κ=530

a) Straub tail in mouse assays.

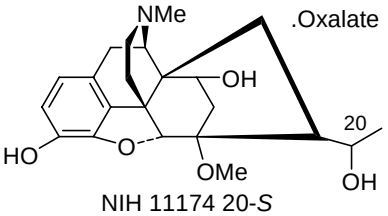
TABLE 5. ORVINOL ANALOGS



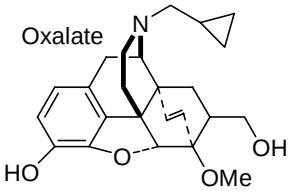
NIH 11146



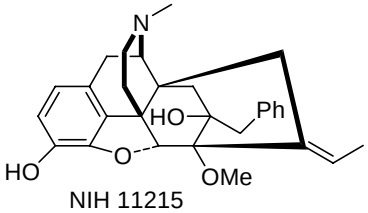
NIH 11172 20-*R*
NIH 11173 20-*S*



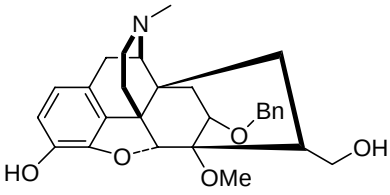
NIH 11174 20-*S*
NIH 11175 20-*R*



NIH 11214



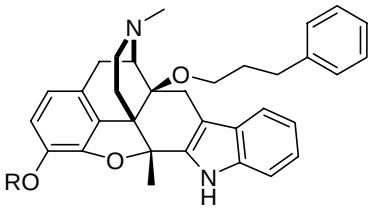
NIH 11215



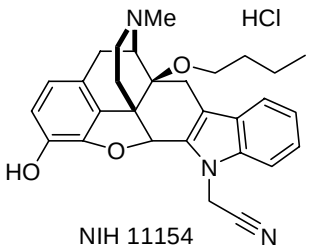
NIH 11219

	MOUSE ANTINOCICEPTIVE ASSAYS				***IN VITRO***	**MONKEY**
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11146	1.7	0.32	1.6	Inactive	μ=15, δ=140, κ=2200	-
11172	Inactive at 10	4.1	Inactive at 10	Inactive	-	-
11173	Inactive	4.7	Inactive	Inactive	-	-
11174	Inactive at 10	Inactive at 10	Inactive at 10	Inactive at 10	-	-
11175	Inactive at 10	4.6	Inactive at 10	Inactive at 10	-	-
11214	Inactive	0.11	Inactive	0.0098 Duration of action: 73% at 20 mins; 32% at 2h, 16% at 24h	μ=0.09, δ=0.79, κ=0.17	Precipitated withdrawal at 0.005 and 0.02
11215	Inactive	Inactive	Inactive	Inactive	-	-
11219	Inactive	0.79	Inactive	Inactive	-	-

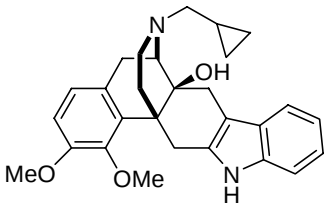
TABLE 6. INDOLOMORPHINANS



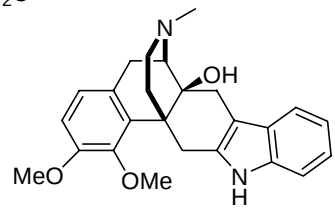
NIH 11116 R=H
NIH 11118 R= H_2C—≡



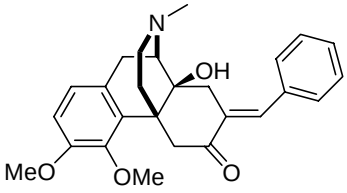
NIH 11154



NIH 11216



NIH 11217



NIH 11218

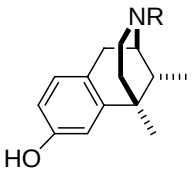
MOUSE ANTINOCICEPTIVE ASSAYS ***IN VITRO***

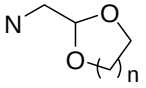
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)
11116[a]	8.8	6.5	10 NTI vs. ED_{80}: Inactive	Inactive	μ=80, δ=3.3, κ=76
11118	Inactive	Inactive	Inactive	Inactive	μ=83, δ=32, κ=180
11154	Inactive	2.5	Inactive	Inactive	μ=1.5, δ=0.24, κ=14
11216	Inactive	Inactive	Inactive	Inactive	-
11217	Inactive	Inactive	Inactive[b]	Inactive	-
11218	Inactive	Inactive	Inactive[b]	Inactive	-

a) Straub tail in rodent assays.
b) Administration i.c.v. gave erratic behavior (spinning, convulsions).

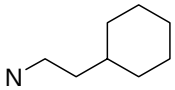
TABLE 7. (-)-6,7-BENZOMORPHANS

N-Substituent (N-R)



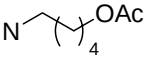


NIH 11111 n=1
NIH 11167 n=2

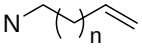


NIH 11185

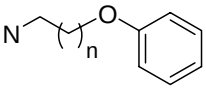
NIH 11127 n=6
NIH 11139 n=7
NIH 11197 n=8



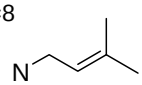
NIH 11164



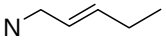
NIH 11189 n=4
NIH 11192 n=5
NIH 11194 n=7



NIH 11234 n=2
NIH 11210 n=3



NIH 11213



NIH 11232

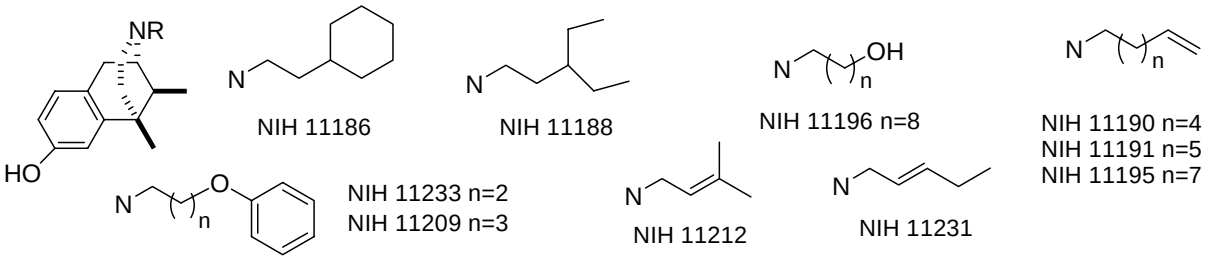
	MOUSE ANTINOCICEPTIVE ASSAYS				***IN VITRO***	**MONKEY**
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM) and GTPγS (% stimulation or K_e)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11111	Inactive[a]	1.9[a] [a]NorBNI vs. ED_{80}: Inactive [b]NTI vs. ED_{80}: Inactive	Inactive[a] [a]ED_{80} of NIH 11111 vs. DPDPE: AD_{50}=0.27	0.2[a]	-	Neither substituted for morphine nor exacerbated withdrawal at 0.6[a]
11127	Inactive[a]	2.9[a] [b]NTI vs. ED_{80}: Inactive	20[a]	Inactive[a]	μ=4.6, δ=200, κ=36[a]	Non-dose related attenuation of withdrawal signs[a]
11139	Inactive[a]	4.4[a] [b]NTI vs. ED_{80}: Inactive	Inactive[a]	Inactive[a]	μ=5.8, δ=35, κ=8.8[a]	Attenuated some withdrawal signs at 15[a]
11164	Inactive[a]	8.4[a] [b]NTI vs. ED_{80}: Inactive	Inactive[a]	Inactive[a]	μ=15, δ=140, κ=55[a]	-
11167	Inactive[a]	5.5[a] [b]NTI vs. ED_{80}: Inactive	Inactive[a]	Inactive[a]	μ=20, δ=58, κ=67[a]	-
11185	8.5[a]	1.2[a]	3.0[a] [b]NTI, β-FNA, NorBNI vs. ED_{80}: all inactive	Inactive[a]	μ=4.3, δ=43, κ=51[a]	Attenuated withdrawal signs at 6
11189	Inactive	0.50 NTI vs. ED_{80}: Inactive	2.8	Inactive	μ=4.3, δ=25, κ=14	Neither substituted for morphine nor exacerbated withdrawal at 5

NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM) and GTPγS (% stimulation or K_e)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11192	Inactive	0.46	11	Inactive	μ=3.2, δ=29, κ=27	Neither substituted for morphine nor exacerbated withdrawal at 10
11194	Inactive	Inactive	Inactive	Inactive	μ=37, δ=470, κ=63	Partial attenuation of withdrawal at 10
11197	Inactive	Inactive	Inactive	Inactive	μ=33, δ=200, κ=34	Partial attenuation of withdrawal at 6
11210	Inactive	6.3	Inactive	Inactive	μ=6.3, δ=43, κ=44	Neither substituted for morphine nor exacerbated withdrawal at 10
11213	Inactive	1.2 NTI vs. ED_{80}: Inactive	Inactive	Inactive	μ=6.8, δ=120, κ=8.1	-
11232	Inactive	0.74	Inactive	1.9	μ=4.1, δ=130, κ=7.2	-
11234	-	-	-	-	μ=1.2, δ=5.2, κ=10	-

a) Previously reported (Coop, 2004; Coop, 2005).
b) New data.

TABLE 8. (+)-6,7-BENZOMORPHANS

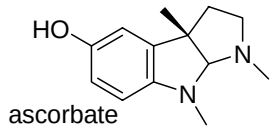
N-Substituent (N-R)



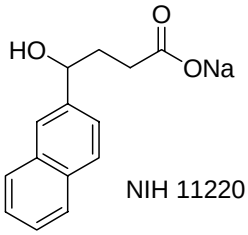
	MOUSE ANTINOCICEPTIVE ASSAYS				***IN VITRO***	**MONKEY**
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM) and GTPγS (% stimulation or K_e)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11186	Inactive[a]	18[a] [b]NTI vs. ED_{80}: Inactive	Inactive[a]	Inactive[a]	μ=140, δ=2800, κ=220[a]	No attenuation of withdrawal at 4; convulsions at 16[a]
11188	Inactive	Inactive	Inactive	Inactive	μ=1600, δ>10,000, κ=83	-
11190	Inactive	Inactive	Inactive	Inactive	μ=350, δ=4000, κ=140	Neither substituted for morphine nor exacerbated withdrawal at 10
11191	Inactive	Inactive	Inactive	Inactive	μ=180, δ=4600, κ=290	Neither substituted for morphine nor exacerbated withdrawal at 10
11195	Inactive	Inactive	Inactive	Inactive	μ=150, δ=4200, κ=960	Neither substituted for morphine nor exacerbated withdrawal at 10
11196	Inactive	Inactive	Inactive	Inactive	μ=870, δ>10,000, κ=1000	Neither substituted for morphine nor exacerbated withdrawal at 10
11209	Inactive	13	Inactive	Inactive	μ=70, δ=3200, κ=300	Neither substituted for morphine nor exacerbated withdrawal at 8
11212	Inactive	Inactive	Inactive	Inactive	μ=520, δ=5300, κ=80	Neither substituted for morphine nor exacerbated withdrawal at 10
11231	Inactive	1.6	Inactive	Inactive	μ=240, δ=3100, κ=89	-
11233	-	-	-	-	μ=77, δ=3100, κ=600	-

a) Previously reported (Coop, 2005).
b) New data.

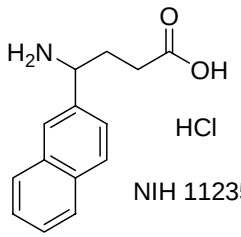
TABLE 9. ATYPICAL OPIOID AND OTHER COMPOUNDS



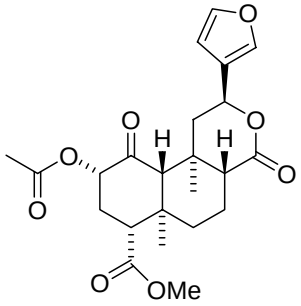
NIH 10820



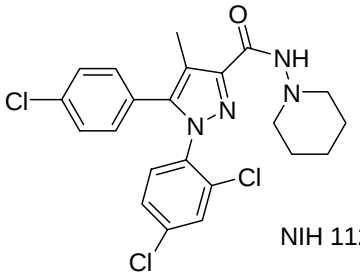
NIH 11220



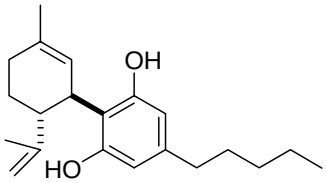
NIH 11235



NIH 11228



NIH 11251

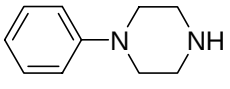


NIH 11252

	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
10820	3.0[a]	0.3[a]	2.4[a] Non-typical antagonism with naloxone[a]	Inactive[a]	1600 nM vs. [^{3}H]etorphine[a] [b]μ=130, δ=2000, κ=880	Complete substitution at 2.5[a]
11220	Inactive	Inactive at 100	Inactive	Inactive	μ, δ, κ>10,000	-
11228	Inactive	0.59	2.0	Inactive	κ=42; μ, δ, >10,000	-
11235	Inactive s.c. and i.c.v.	5.5 (s.c.) Inactive (i.c.v.)	Inactive s.c. and i.c.v.	Inactive s.c. and i.c.v.	μ=3000 κ, δ, >10,000	-
11251	-	-	-	-	-	Neither substituted for morphine nor exacerbated withdrawal at 10
11252	-	-	-	-	-	Neither substituted for morphine nor exacerbated withdrawal at 10

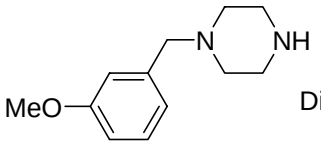
a) Previously reported (Jacobson, 1998).
b) New data.

TABLE 10. COMPOUNDS EVALUATED BY STIMULANT DEPRESSANT PROGRAM



Oxalate

CPDD 0067



Dioxalate

CPDD 0072

	Discriminative Stimulus Effects in Benzodiazepine-Trained Monkeys	Self-Administration in Cocaine-Maintained Monkeys	Drug Discrimination in Amphetamine-Trained Monkeys	Discriminative Stimulus Effects in LSD-Trained Rats	Binding affinity at 5HT receptors (pK_i)
0067	Shares no discriminative stimulus effects with either flumazenil or midazolam at doses up to 10 mg/kg[a]	No self-administration up to 0.3 mg/kg/inj[a]	[b]No amphetamine discriminative stimulus effects in doses up to 3 mg/kg i.g.	No significant LSD-like responding[a]	5-HT_{1A} = 6.5[a] 5-HT_{2A} = 5.1[a] 5-HT_{2C} = 5.6[a]
0072	Shares no discriminative stimulus effects with either flumazenil or midazolam at doses up to 10 mg/kg	Marginal self-administration at 0.3 mg/kg/in	No amphetamine discriminative stimulus effects in doses up to 30 mg/kg i.g.	-	-

a) Previously reported (Coop, 2005).
b) New data.

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