AN OVERVIEW OF THE STUDIES PERFORMED BY THE DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2006)

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THE DRUG EVALUATION COMMITTEE

The Drug Evaluation Committee (DEC) evaluates a variety of compounds with CNS activity for preclinical physical dependence potential and abuse liability 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 and 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 are 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 Michigan in May 2006 to discuss the work which has been accomplished and future plans. Separate meetings are held at VCU 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.

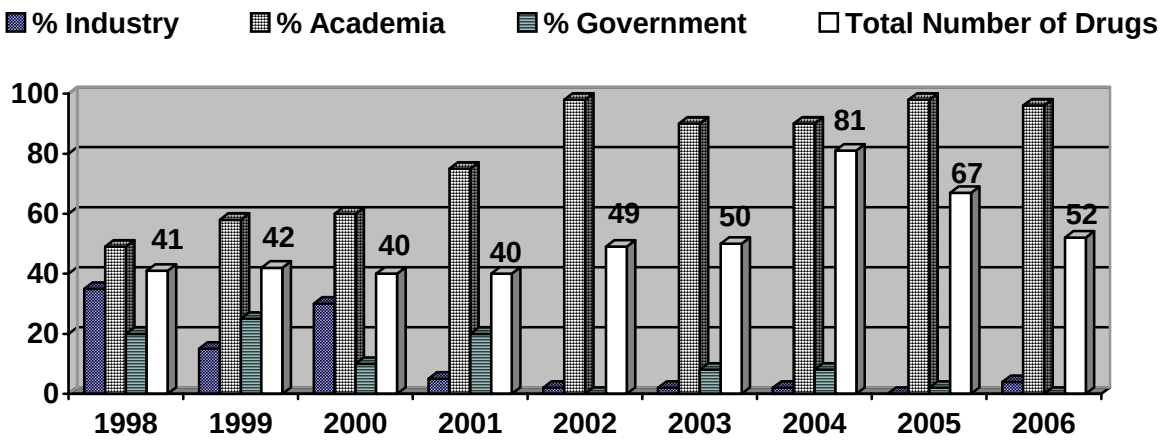
This report provides an overview of the results obtained by all groups within DEC; precise values and details of the procedures are given in the VCU and UM reports (Aceto et al., 2007; Traynor and Woods, 2007). Data obtained under the auspices of DEC are held confidential for a maximum of three years, but can be released prior to the three-year limit with the permission of the submitter. Data were released for publication this year on 52 compounds evaluated by the Analgesic Testing Program (Figure 1). This figure remains high by historical standards, but has dropped from recent unusually high numbers. Of these 52 compounds, 35 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 43 at UM (binding affinity to the μ, δ, and κ opioid receptors and GTPγS functional studies). Compounds were submitted primarily from academia; two compounds came from industrial submitters. 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 2007. No compounds were released from the Stimulant/Depressant program this year.

Four publications based on the data gathered under DEC auspices were published since the last annual report (Fantegrossi et al., (2005); Fantegrossi et al., (2006); Harding et al., (2005); Spetea et al., (2005)).

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, 2006), the compounds are classified according to their molecular structure: morphinans and 4,5-epoxymorphinans in Table 2; phenylmorphans and neodihydrothebaines in Table 3; 6,7-benzomorphans in Tables 4-7; small amines in Table 8; natural products in Table 9; cannabinoids 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 (1998-2006)



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As reported previously (Coop, 2005, 2006), the 14-phenylpropyloxy morphinans 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). One member of this class, **NIH 11056** (Table 2) was evaluated for its duration of antinociceptive action in the tail flick assay. An extended duration of action was noted (15 hours), raising the possibility of development into a long duration analgesic or pharmacotherapy for opiate dependence.

NIH 11198 (Table 2) is an ester prodrug of oxycodone (NIH 11107, Coop, 2003). The affinity of NIH 11198 for mu receptors is 2-3-fold lower than oxycodone (K_i = 1200 nM vs. 485 nM for oxycodone). In GTPγS functional assays, this compound was shown to be a full mu agonist, albeit of very low potency. Thus, there appears little difference between the *in vitro* profiles of oxycodone and NIH 11107.

The phenylmorphans, **NIH 8508** and **NIH 8509** (Table 3) have previously been shown to possess antinociceptive activity (Jacobson, 1981). The two isomers were evaluated in order to determine the receptor through which the activity is derived: NIH 8509 was reversed with β-FNA indicating mu agonist activity, whereas NIH 8508 could not be reversed by any of the selective antagonists. Further studies on NIH 8508 are warranted to determine the origin of its antinociceptive activity. **NIH 11261**, **NIH 11262**, and **NIH 11263** (Table 3) are (+)-neodihydrothebaine, (+)-bractazonine, and a substituted (+)-bractazonine, respectively. Novel syntheses of these compounds were reported recently (Chen et al., 2005), allowing evaluation showing no opioid activity.

Table 4 contains (-)-N-alkyl and N-alkynyl benzomorphans as a continuation of our previous studies to determine the effects of N-substituents in this series (May et al., 2003; May et al., 1998). The N-alkynyl derivatives (**NIH 11254**, **NIH 11256**, and **NIH 11258**) show high affinity at opioid receptors, weak antinociceptive activity, but potent morphine antagonism. This suggests that the compounds are mu antagonists and kappa agonists, but further sub-type testing is required to confirm such a profile. The corresponding (+)-isomers are shown in Table 5 and, as expected, show lower affinity for opioid receptors. Unexpectedly, **NIH 11255** shows increased morphine antagonist potency than its corresponding (-)-isomer (**NIH 11256**). Tables 6 and 7 show benzomorphan isomers with ether N-substituents. The phenoxyethyl derivatives ((-) **NIH 11236** and (+) **NIH 11237**) show moderate to good binding affinity, but are noteworthy due to their inverse agonism at kappa receptors. Both isomers reduce basal activity in the GTPγS assays by about 40%, and represent excellent lead compounds for the development of high affinity inverse kappa agonists.

The tertiary amines (**NIH 11169** to **NIH 11171**) in Table 8 are phenylethylamines which can be superimposed on the morphinan skeleton. Surprisingly for such simple achiral compounds, moderate affinity for opioid receptors is seen, with **NIH 11169** showing excellent affinity and selectivity for kappa receptors. The substituted piperidine (**NIH 11273**) and piperazines (**NIH 11274** and **NIH 11275**) in Table 8 were assayed for their opioid binding affinity for similar reasons. All compounds showed low affinity.

Salvinorin A (NIH 11228) has been reported as a naturally occurring non-nitrogenous kappa opioid agonist with hallucinogenic activity (Harding et al., 2005, Coop, 2006). A analysis of structurally similar compounds isolated from common sage (**NIH 11297-11303**, Table 9) indicated no binding affinity to opioid receptors. Such analyses aid in delineating the structural requirements for binding to kappa opioid receptors, with the aim of understanding ligand-receptor complexes at the molecular level.

The two cannabinoid agonists CP 55940 (**NIH 11276**) and Win 55,212-2 (**NIH 11277**) are shown in Table 10. These studies show that the mouse antiwrithing assay is useful for evaluating CB1 agonists as antinociceptive agents, and that the effects of CB1 agonism can be effectively reversed by a selective CB1 antagonist, but are unaffected by a CB2 antagonist.

TABLE 1. EVALUATED COMPOUNDS

	COMPOUND NAME	**TABLE #-Evaluator**
NIH#	**ANALGESIC TESTING PROGRAM**	
8508	(-)-5-(*m*-Hydroxyphenyl)-2-methylmorphan.HCl	3-VCU
8509	(+)-5-(*m*-Hydroxyphenyl)-2-methylmorphan.HCl	3-VCU
11056	17-Cyclopropylmethyl-4,5α-epoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU
11169	*N*-[(3-Hydroxy)-2-phenethyl]-*N*-cyclobutylmethyl-2-phenylethylamine.HCl	8-UM
11170	*N*-[(3-Hydroxy)-2-phenethyl]-*N*-cyclopropylmethyl-2-phenylethylamine.HCl	8-UM
11171	*N*-[(4-Hydroxy)-2-phenethyl]-*N*-cyclopropylmethyl-2-phenylethylamine.HCl	8-UM
11184	5,6-Didehydro-3,4,14β-trimethoxy-17-methylmorphinan-6-carboxamide	2-VCU/UM
11193	Substance P-opioid hybrid	2-VCU/UM
11198	2-(Benzyloxycarbonylamino)dl-pentanedioic acid-1-(3-methoxy-14-hydroxy-6,7-disehydro-4,5α-epoxy-17-methylmorpinan-6-yl)ester	2-UM
11231	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate	5-VCU

11232	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate	4-VCU
11233	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan.HCl	7-VCU
11234	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan.HCl	6-VCU
11236	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxyethyl)-6,7-benzomorphan.HCl	6-VCU/UM
11237	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxyethyl)-6,7-benzomorphan.HCl	7-VCU/UM
11249	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-methylpropyl)-6,7-benzomorphan.HBr	5-VCU/UM
11250	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-methylpropyl)-6,7-benzomorphan.HBr	4-VCU/UM
11253	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-propynyl)-6,7-benzomorphan.HCl	5-VCU/UM
11254	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-propynyl)-6,7-benzomorphan.HCl	4-VCU/UM
11255	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-pentynyl)-6,7-benzomorphan.oxalate	5-VCU/UM
11256	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-pentynyl)-6,7-benzomorphan.oxalate	4-VCU/UM
11257	(+)-(1S,5S,9S)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	5-VCU/UM
11258	(-)-(1R,5R,9R)-2-(2-Butynyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	4-VCU/UM
11259	(+)-(1S,5S,9S)-2-(2-Butenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	5-VCU/UM
11260	(-)-(1R,5R,9R)-2-(2-Butenyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	4-VCU/UM
11261	(+)-Neodihydrothebaine.HCl	3-VCU/UM
11262	(+)-Bractazonine.HCl	3-VCU/UM
11263	(+)-(3-Oxobutyl)bractazonine.HCl	3-VCU/UM
11265	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(4-methyl-3-pentenyl)-6,7-benzomorphan.HCl	5-VCU/UM
11266	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(5-methylheptyl)-6,7-benzomorphan.oxalate	4-VCU/UM
11267	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(5-methylheptyl)-6,7-benzomorphan.oxalate	5-UM
11268	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(3-methyl-2-butenyl)-6,7-benzomorphan.oxalate	4-UM
11269	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(3-methyl-2-butenyl)-6,7-benzomorphan.oxalate	5-VCU/UM
11270	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-[(S)-2-methylbutyl]-6,7-benzomorphan.HCl	4-VCU/UM
11271	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-[(S)-2-methylbutyl]-6,7-benzomorphan.HCl	5-UM
11272	(-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(4-methyl-3-pentenyl)-6,7-benzomorphan.HCl	4-VCU/UM
11273	3-Methyl-1-(3-phenylpropyl)piperidine.oxalate	8-VCU/UM

11274	1-(2-phenethyl)-4-(2-pyridyl)piperazine.oxalate	8-UM
11275	1-(3-Phenylpropyl)-4-(2-pyridyl)piperazine.oxalate	8-VCU/UM
11276	(1R,3R,4R)-3-[2Hydroxy-4-(1,1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)-cyclohexan-1-ol	10-VCU
11277	(R)-(+)-[2,3-Dihydro-5-methyl-3-[(4-morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl](1-napthalenyl)methanone	10-VCU
11285	(+)-(1S,5S,9S)-2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11286	(-)-(1R,5R,9R)- 2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6-VCU/UM
11287	(+)-(1S,5S,9S)-2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.Oxalate	7-VCU/UM
11288	(-)-(1R,5R,9R)-2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.Oxalate	6-UM
11297	Sage extract	9-UM
11298	Sage extract	9-UM
11299	Sage Extract	9-UM
11300	Sage Extract	9-UM
11301	Sage Extract	9-UM
11302	Sage Extract	9-UM
11303	Sage Extract	9-UM

NOTES FOR TABLES 2 - 10

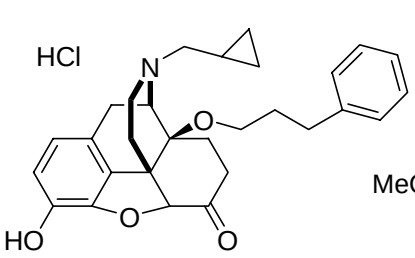
Salt forms are shown. Rounded numbers are used (2 significant figures); precise values and details of the procedures are given in the VCU and UM reports (Aceto et al., 2007; Traynor and Woods, 2007). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained at 30 mg/kg. NTI = naltrindole (delta 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).

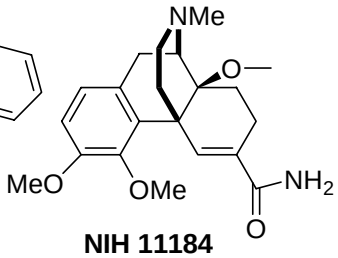
2) *In Vitro*:
Subtype selective binding affinity using recombinant receptors: μ (C_6 rat glioma cells expressing rat μ receptor), κ (CHO cells expressing human κ receptor), and δ (C_6 rat glioma cells expressing rat δ receptor). Affinity was assessed through the displacement of [^{3}H]-diprenorphine. 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.

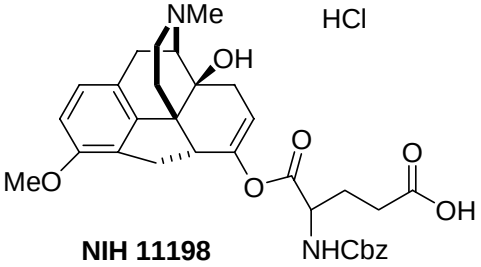
TABLE 2. 4.5-EPOXYMORPHINANS AND MORPHINANS



NIH 11056



NIH 11184



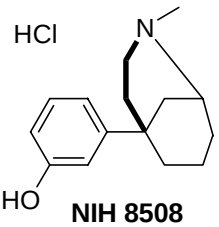
NIH 11198

	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 (EC_{50}, nM and % stimulation)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11056[a]	0.0023[a]	0.0062[a]	0.0032[a] Duration of action: 15 hours[b]	Inactive[a]	μ=0.06, δ=0.38, κ=0.11[a]	Substitution for morphine at 0.04[a]
11184	Inactive	0.18	Inactive	Inactive	μ=6.1, δ=96, κ=300	-
11193	Inactive	Inactive	Inactive	Inactive	μ=80, δ=300, κ=970	Neither substituted for morphine nor exacerbated withdrawal at 2.5 and 10
11198	-	-	-	-	μ=1200, δ=420, κ> 10,000 GTPγS: μ EC_{50}=3800, 96% stimulation; δ 0% stimulation	-

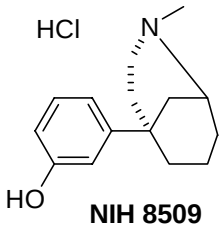
a) Previously reported (Coop, 2005)

b) New data.

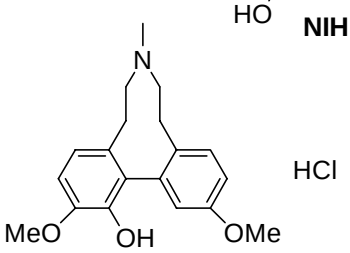
TABLE 3. PHENYLMORPHANS AND NEODIHYDROTHEBAINES



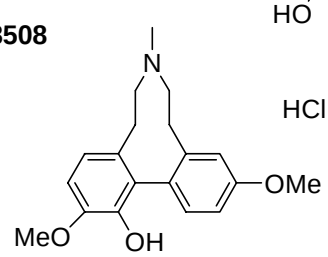
NIH 8508



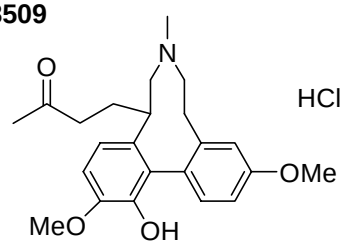
NIH 8509



NIH 11261



NIH 11262

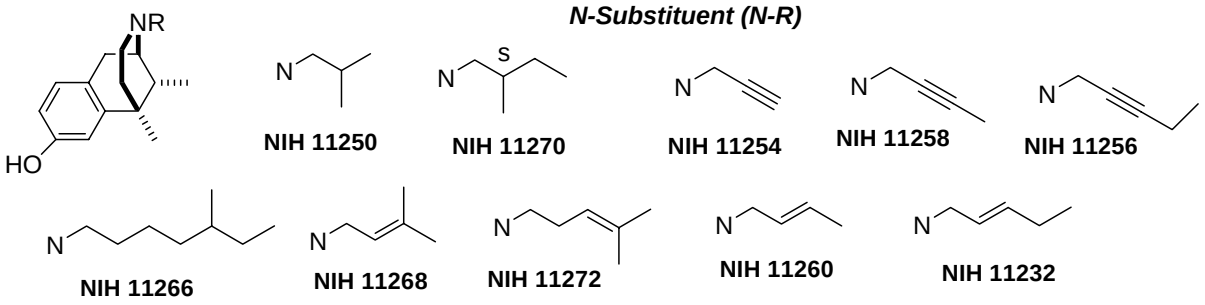


NIH 11263

	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)
8508[a]	1.7[a] Antagonism by selective antagonists: norBNI, NTI, β-FNA: Inactive	-	-	-	-	Partial suppression of withdrawal signs at 5; inactive at 10.
8509	0.35	0.5	4.8 Antagonism by selective antagonists: norBNI, NTI: Inactive β-FNA: AD_{50}=0.28	Inactive	-	Dose related suppression of withdrawal signs
11261	Inactive	4.6	Inactive	Inactive	μ, δ, κ>10,000	-
11262	Inactive	Inactive	Inactive	Inactive	μ=5300, δ>10,000, κ=5300	-
11263	Inactive	Inactive	Inactive	Inactive	μ=1800, δ=1700, κ>10,000	-

a) Previously published (1981)

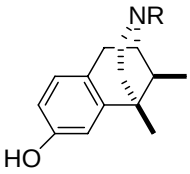
TABLE 4. (-)-*N*-ALKYL-BENZOMORPHANS



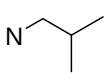
	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11232	Inactive[a]	0.74[a] Antagonism of ED_{80}: NTI - Inactive[b]	Inactive[a]	Inactive[a]	μ=4.1, δ=130, κ=7.2[a]	-
11250	Inactive	0.83	Inactive	Inactive	μ=2.8, δ=29, κ=0.9	Dose related attenuation of withdrawal signs at 0.05 and 0.2. Slowing and ataxia noted.
11254	Inactive	2.1	Inactive	0.18	μ=2.1, δ=4.5, κ=0.8	Precipitated withdrawal at 1 and 4
11256	Inactive	0.57	Inactive	4.7	μ=2.1, δ=130, κ=3.6	-
11258	Inactive	0.21	Inactive	0.65	μ=1.9, δ=39, κ=2.0	-
11260	Inactive	Inactive	Inactive	0.32	μ=3.2, δ=29, κ=2.2	Precipitated withdrawal at 1 and 4
11266	Inactive	6.3	24	Inactive	μ=4.0, δ=42, κ=26	Neither attenuated nor exacerbated withdrawal at 4.5 and 18.
11268	-	-	-	-	μ=5.6, δ=110, κ=13	-
11270	-	-	-	-	μ=5.3, δ=22, κ=2.8	-
11272	-	-	-	-	μ=0.97, δ=6.0, κ=6.6	-

a) Previously published (Coop, 2006)
b) New data

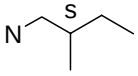
TABLE 5. (+)-N-ALKYL-BENZOMORPHANS



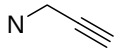
N-Substituent (N-R)



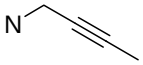
NIH 11249



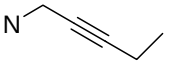
NIH 11271



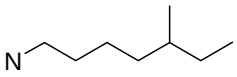
NIH 11253



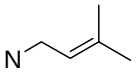
NIH 11257



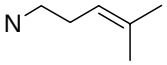
NIH 11255



NIH 11267



NIH 11269



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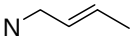
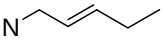


NIH 11259

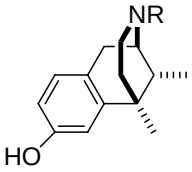


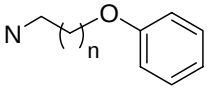
NIH 11231

	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)
11231	Inactive	1.6	Inactive	Inactive	μ=240, δ=3100, κ=89	Neither attenuated nor exacerbated withdrawal at 2.5 and 10.
11249	Inactive	Inactive	Inactive	Inactive	μ, δ>10,000, κ=83	-
11253	Inactive	6.7	Inactive	8.9	μ=500, δ=1500, κ=160	-
11255	Inactive	Inactive	Inactive	1.7	μ=250, δ=3300, κ=70	-
11257	Inactive	Inactive	Inactive	13	μ=270, δ=4000, κ=98	-
11259	Inactive	Inactive	Inactive	Inactive	μ=210, δ=6100, κ=120	-
11265	-	-	-	-	μ=130, δ=1000, κ=270	-
11267	-	-	-	-	μ=310, δ=2900, κ=94	-
11269	Inactive	Inactive	Inactive	Inactive	μ=310, δ=4600, κ=65	-
11271	-	-	-	-	μ=560, δ=2900, κ=48	-

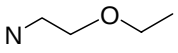
TABLE 6. (-)-N-ALKOXY-BENZOMORPHANS

N-Substituent (N-R)

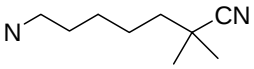




NIH 11234 n=2
NIH 11236 n=1



NIH 11288

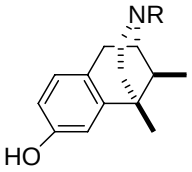


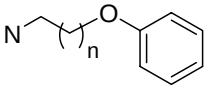
NIH 11286

	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 and $EC_{50,}$ nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11234	0.64	0.42	2.1	Inactive	μ=1.2, δ=5.2, κ=10	Substitution for morphine at 2.5; convulsions at 10.
11236	-	4.8	9.6	-	μ=10, δ=92, κ=75 GTPγS: μ 28% stimulation; δ <5% stimulation; κ -41% of basal (EC_{50}=775)	Attenuated withdrawal signs at 10.
11286	-	-	-	-	μ=9.4, δ=39, κ=77	-
11288	-	-	-	-	μ=1.2, δ=30, κ=2.0	-

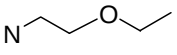
TABLE 7. (+)-N-ALKOXY-BENZOMORPHANS

N-Substituent (N-R)

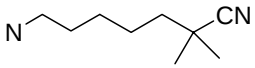




NIH 11233 n=2
NIH 11237 n=1



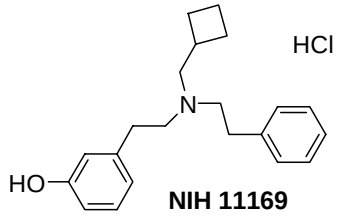
NIH 11287



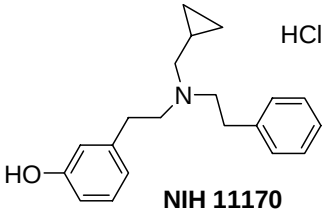
NIH 11285

	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 and $EC_{50,}$ nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11233	Inactive	2.8	Inactive	Inactive	μ=77, δ=3100, κ=600	Complete substitution for morphine at 2 and 10.
11237	14	6.8	Inactive	Inactive	μ=85, δ=2100, κ=110 GTPγS: μ <5% stimulation; κ -40% of basal (EC_{50}=300)	Neither substituted for morphine nor exacerbated withdrawal at 10
11285	-	-	-	-	μ=380, δ=3100, κ=530	-
11287	-	-	-	-	μ=2.1, δ=2600, κ=220	-

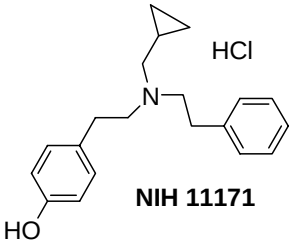
TABLE 8. SMALL AMINES



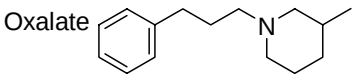
NIH 11169



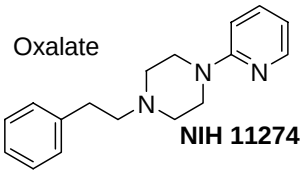
NIH 11170



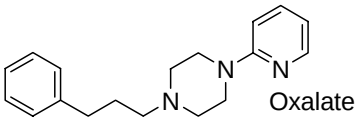
NIH 11171



NIH 11273



NIH 11274

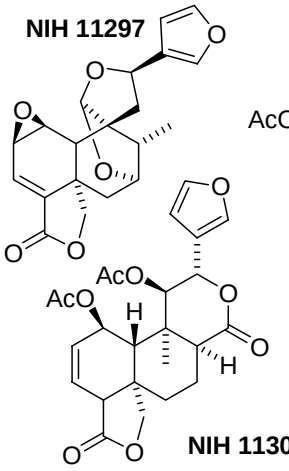


NIH 11275

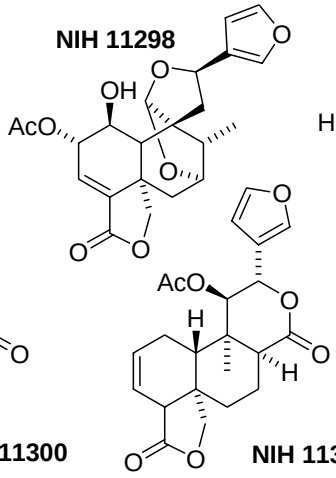
IN VITRO

NIH #	Binding Affinity, (K_i, nM)
11169	μ=85, δ=620, κ=3.4
11170	μ=170, δ=1500, κ=60
11171	μ=100, δ=930, κ=300
11273	μ, κ, δ >10,000
11274	μ=1100, δ, κ >10,000
11275	μ=450, δ > 10,000, κ=6000

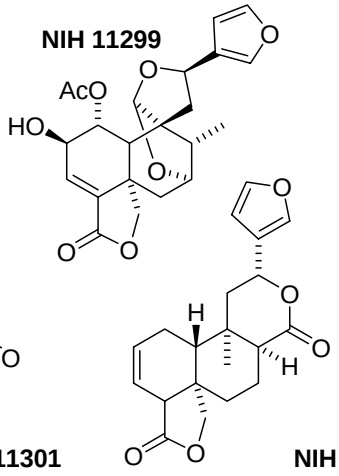
TABLE 9. NATURAL PRODUCTS



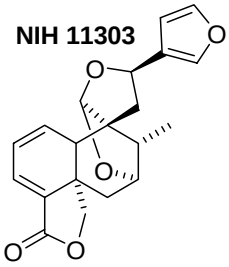
NIH 11297



NIH 11298



NIH 11299

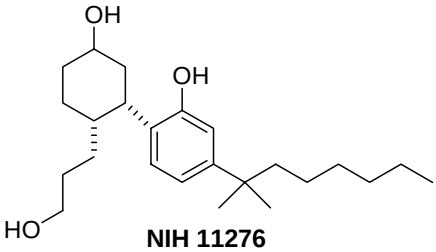


NIH 11303

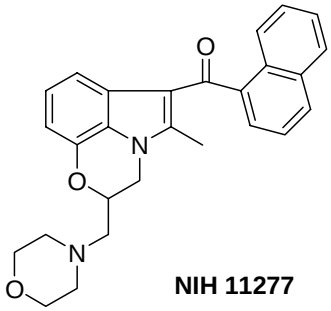
IN VITRO

NIH #	Binding Affinity, (K_i, nM)
11297	μ, δ, κ >10,000
11298	μ, δ, κ >10,000
11299	μ, δ, κ >10,000
11300	μ, δ, κ >10,000
11301	μ, δ, κ >10,000
11302	μ, δ, κ >10,000
11303	μ, δ, κ >10,000

TABLE 10. CANNABINOIDS



NIH 11276



NIH 11277

MOUSE ANTINOCICEPTIVE ASSAYS

NIH #	Phenylquinone (ED_{50}, s.c., mg/kg)	Antagonism of PPQ ED_{80} with SR 141716A (CB1) (AD_{50}, s.c., mg/kg)	Antagonism of PPQ ED_{80} with SR 144528 (CB2) (AD_{50}, s.c., mg/kg)
11276	0.0095	1.04	Inactive at 1 and 10
11277	0.17	0.1	Inactive at 1 and 10

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