AN OVERVIEW OF THE STUDIES PERFORMED BY THE DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2007)

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THE DRUG EVALUATION COMMITTEE

The Drug Evaluation Committee (DEC) evaluates compounds 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 Biological Coordinator of DEC (Dr. A. Coop) receives samples for evaluation and distributes 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 and 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) 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.

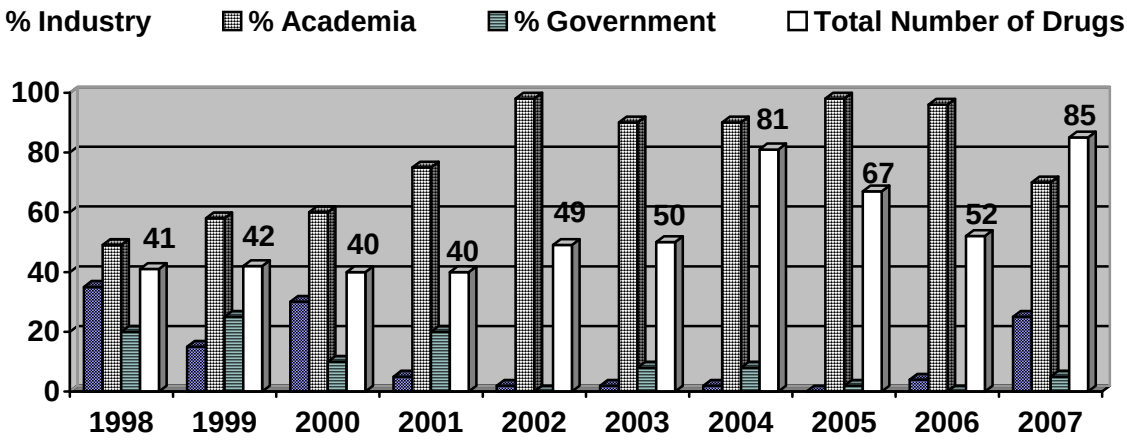
DEC reports to the CPDD Committee on Abuse Liability Testing (CALT; formerly the DEC Liaison Committee; Dr. S. Negus, Chair). Members of both that CPDD committee and other CPDD committees, as well as representatives from governmental agencies, attend DEC's meeting held during the Annual Scientific Meeting of the CPDD. One other DEC meeting was held in Richmond in May 2007 to discuss the work which has been accomplished and future plans for DEC. Separate meetings have been 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., 2008; Traynor and Woods, 2008). 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 84 compounds evaluated by the Analgesic Testing Program (Figure 1). This figure remains high by historical standards. Of these 83 compounds, 59 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 74 at UM (warm water tail withdrawal in rhesus monkeys, binding affinity to the μ, δ, and κ opioid receptors, and GTPγS functional studies) Compounds were submitted primarily from academia, but a significant number of compounds (25%) came from industrial submitters this year. Two compounds were also released from the Stimulant/Depressant program this year and evaluated for amphetamine, benzodiazepine, and PCP discriminative stimulus effects and also self administration effects in cocaine-maintained monkeys. The two programs give a total of 85 releases. Three publications based on the data gathered under DEC auspices were published since the last annual report (Li et al., 2007, Cheng et al., 2007, Aceto et al., 2007)

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 13. As in previous years (Coop, 2007), the compounds are classified according to their molecular structure: 4,5-epoxymorphinans in Table 2; Prodrugs of oxycodone in Table 3; 6,7-benzomorphans in Tables 4-7; analogs of potent opioids in Table 8; analogs of oxymorphindole in Table 9; peptides in Table 10; small molecules in Table 11; compounds with miscellaneous structures in Table 12. Compounds evaluated by the stimulant/depressant group are shown in Table 13. 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 (1998-2007)



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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 11121** (Table 2) was evaluated for its efficacy at mu and delta receptors, and shown to be an extremely potent full mu agonist, and a potent delta partial agonist. This is consistent with previous animal assays where antinociceptive effects of NIH 11121 were reversed by the mu antagonist β–FNA, but not the delta antagonist NTI.

NIH 11333, NIH 11334, and **NIH 11335** (Table 2) are analogs of morphine lacking hydroxyl groups. As anticipated, NIH 11334 containing a 3-hydroxyl group had the greatest affinity for opioid receptors, but it was interesting that losing the 6-hydroxyl between NIH 11333 and 11335 led to an increase in opioid receptor affinity.

NIH 11227 (Table 3), a peptidic prodrug of hydrocodone, displayed only modest antinociceptive activity in mice, and was inactive in the 50°C warm water tail withdrawal assay in monkeys, indicating that the putative active metabolite, hydrocodone, may not be forming. Table 3 contains numerous peptidic prodrugs of oxycodone. As a class, these compounds have low affinity at opioid receptors and very weak partial agonist activity in GTPγS functional assays. An interesting compound in this series is NIH 11243, which displays modest delta affinity and selectivity. Unfortunately, GTPγS assays indicate the compound to be a very weak partial delta agonist.

Table 4 contains (-)-N-alkyl benzomorphans which contain oxygen functions 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).

Interestingly, a separation of activities in vitro and in vivo was observed with **NIH 11210**, where high affinity at mu receptors does not translate to activity in neither mice nor monkeys. The *N*-ethoxyethyl analog (**NIH 11288**) shows high affinity at mu and kappa opioid receptors, a corresponding antinociceptive activity in mice, and fully substitutes for morphine in monkeys. Thus, NIH 11288 has properties typical of a mu agonist. Adding a hydroxyl group to the terminal carbon on the N-substituent of NIH 11288 gives **NIH 11347**, and a great decrease in affinity at opioid receptors. Reducing the size of the N-substituent of NIH 11288 by one carbon gives methoxyethyl analog **NIH 11352** which has very high affinity for all three opioid receptors. This indicates that alkoxyethyl N-substituents are well tolerated in the benzomorphan series, and should receive study in other opioid classes for the preparation of high affinity ligands. Benzomorphans in Table 4 with ketone groups as part of the N-substituent were generally less well tolerated, yielding low affinity ligands at opioid receptors. The corresponding (+)-benzomorphans are shown in Table 5 and are, as anticipated, generally less active as opioids. The exception being the *N*-ethoxyethyl analog **NIH 11287** which has a high affinity and selectivity for mu opioid receptors (mu K_i = 2 nM, kappa/mu=100). Interestingly, NIH 11287 has no antinociceptive nor morphine antagonist activity in mice, indicating additional separation of activities in this series.

NIH 11116 (Table 8) was previously reported to be an antinociceptive agent and also delta opioid selective. Studies were performed to determine the origin of the antinociceptive activity to determine if the compound was displaying delta-opioid mediated antinociception. This was shown not to be the case with GTPγS assays, as NIH 11116 is a full agonist at mu receptors and has low efficacy (37% stimulation) at delta receptors. This is consistent with in vivo data showing that NTI did not reverse the antinociception of NIH 11116. 4-phenolic morphinans are generally of low opioid activity, yet **NIH 11221-11223** (Table 8) with an additional long alkyl group at position 7 show good opioid binding affinity, although this does not translate to antinociceptive activity in mice. Thienorphine (**NIH 11310**, Table 8) was reported to display a profile of mu agonism, but this did not appear consistent with previous SAR patterns (Li et al., 2007). GTPgS functional assays showed that NIH 11310 is actually a kappa agonist/mu antagonist, and any antinociceptive activity of NIH 11310 is almost certainly mediated through kappa opioid receptors.

Oxymorphindole (**NIH 11319**, Table 9) is a selective delta opioid. Studies into the effect of halogen substitution on the indole ring led to the finding that **NIH 11318** (dichloro) possesses similar affinity for mu and delta receptors and acts as an antinociceptive agent. This is an excellent lead for the development of mu agonist/delta antagonist ligands which have the potential to yield analgesic agents to which tolerance does not develop (Ananthan, 2006). The peptides in Table 10 were evaluated for opioid activity and were shown to be generally lacking in such activity.

NIH 11296 (Table 11) is an analog of meperidine in which the nitrogen has been replaced by an oxygen. The lack of opioid activity suggests that the basic nitrogen is essential for opioid activity in this series. The other small amines shown in Table 11 all possess no significant opioid activity, and important finding for their development into medications acting selectively at neurotransmitters.

NIH 11211 (Table 12) is an analog of the delta selective agonist SNC80, and was shown to be inactive in animal antinociceptive assays. The phenylmorphans, **NIH 11289** and **NIH 11290** (Table 12) are potent antinociceptive agents in mice, and their substitution for morphine in monkeys strongly suggests the activity occurs through mu opioid receptors. These two compounds are representative examples from an extremely interesting series of high efficacy mu agonists (Cheng et al., 2007).

Salvinorin A (**NIH 11228**, Table 12) has been reported as a naturally occurring non-nitrogenous kappa opioid agonist with hallucinogenic activity (Harding et al., 2005). These studies confirm the selectivity for kappa opioid receptors and antinociceptive activity in mice. Salvinorin A was also evaluated by the Stimulant/Depressant group as **CPDD0070** (Table 13). CPDD0070 was not recognized as PCP, amphetamine, nor benzodiazepines in discriminative stimulus assays. The amphetamine prodrug, **CPDD 0069** (Table 13) was recognized in amphetamine discriminative stimulus assays and was self-administered in cocaine-maintained monkeys. This compound would be predicted to possess stimulant-like properties in humans.

TABLE 1. EVALUATED COMPOUNDS

	COMPOUND NAME	TABLE #-Evaluator
NIH#	**ANALGESIC TESTING PROGRAM**	
11107	Oxycodone.HCl	3-UM
11116	4,5α-epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]indolo[2',3':6,7]morphinan-3-ol	8-UM
11121	4,5α-epoxy-3-hydroxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one.HBr	2-UM
11199	Acetyl-Arg-Phe(4-COOH)-Tyr-Arg-Trp-Arg-NH_2	10-VCU/UM
11200	Acetyl-Arg-Phe(4-F)-Tyr-Arg-Trp-Arg-NH_2	10-VCU/UM
11201	Acetyl-Arg-Phe(4-OCH_3)-Tyr-Arg-Trp-Arg-NH_2	10-VCU/UM
11202	Acetyl-Arg-Phe(4-CN)-Tyr-Arg-Trp-Arg-NH_2	10-VCU/UM
11203	Acetyl-Arg-Tyr-Tyr-Arg-Trp(5-CN)-Arg-NH_2	10-VCU/UM
11204	Acetyl-Arg-Tyr-Phe(4-F)-Arg-Trp-Arg-NH_2	10-VCU/UM
11205	Acetyl-Arg-Tyr-Phe(4-NHAc)-Arg-Trp-Arg-NH_2	10-VCU/UM
11206	Acetyl-Arg-Tyr(3-Cl)-Tyr-Arg-Trp-Arg-NH_2	10-VCU/UM
11207	Acetyl-Arg-Tyr-Phe(4-benzyl)-Arg-Trp-Arg-NH_2	10-VCU/UM
11208	Heptanoyl-Arg-Tyr-Phe-Arg-Trp-Arg-NH_2	10-VCU/UM
11209	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl	5-VCU/UM
11210	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl	4-VCU/UM
11211	9(8-Azabicyclo[3.2.1]oct-3-ylidene)-15,5*R*-9*H*-xanthene-3-carboxylic acid diethylamide.HCl	12-VCU/UM
11213	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-6,7-benzomorphan.oxalate	6-UM
11221	5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(4-phenylbutyl)morphinan-6-carbonitrile	8-VCU/UM
11222	5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(5-phenylpentyl)morphinan-6-carbonitrile	8-VCU/UM
11223	5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(6-phenylhexyl)morphinan-6-carbonitrile	8-VCU/UM
11224	7β-Benzyl-5,6-didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-morphinan-6-carbonitrile	8-VCU/UM
11225	6,7-Didehydro-4,5-epoxy-6-idimazolyl-3-methoxy-17-methyl-14-(3-phenylpropyloxy)morphinan	8-VCU/UM
11226	4-Cinnamyloxy-5,6,7,8-tetradehydro-14β-hydroxy-3-methoxy-17-methyl-morphinan-6-carbonitrile	8-VCU/UM

11227	Tyr-Tyr-Phe-Phe-Ile-(6-O)-hydrocodone.HCl	3-VCU/UM
11228	Salvinorin A	12-VCU
11238	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11239	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11240	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11241	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11242	Oxycodone-enol ether prodrug. .2Trifluroacetate	3-UM
11243	Oxycodone-enol ether/valine prodrug. .Trifluroacetate	3-UM
11244	6-O-(2,2,2-trimethylacetyl)oxycodone-enol ether. HCl	3-UM
11245	Oxycodone-enol ether prodrug. .Trifluroacetate	3-UM
11285	(+)-(1S,5S,9S)- 2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	7-VCU
11286	(-)-(1R,5R,9R)- 2-(6-Cyano-6,6-dimethylhexyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	6-VCU
11287	(+)-(1S,5S,9S)- 2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.Oxalate	5-VCU
11288	(-)-(1R,5R,9R)- 2-Ethoxyethyl-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.Oxalate	4-VCU
11289	(1R,5R,9R)-5-(3-Hydroxyphenyl)-2-phenethyl-2-aza-bicyclo[3.3.1]nonan-9-ol.HCl	12-VCU
11290	(1R,5R)-3-(9-Methylene-2-phenethyl-2-aza-bicyclo[3.3.1]nonan-5-yl.]-phenol.Oxalate	12-VCU
11292	4-Phenyltetrahydro-2*H*-pyran-4-ol	11-VCU/UM
11293	*N*,*N*-Dimethyl-2-(3-phenylpropoxy)ethylamine	11-VCU/UM
11294	1-(2-[3-phenylpropoxy]ethyl)pyrrolidine	11-UM
11296	4-Phenyltetrahydro-2*H*-pyran-4-yl propionate	11-VCU/UM
11304	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl	5-VCU/UM
11305	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl	4-VCU/UM
11306	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl	5-VCU/UM
11307	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl	4-VCU/UM
11308	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl	5-VCU/UM
11309	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl	4-VCU/UM

11310	Thienorphine.HCl	8-UM
11312	5’-Fluorooxymorphindole.HCl	9-VCU/UM
11313	5’-Chlorooxymorphindole.HCl	9-VCU/UM
11314	5’-Brorooxymorphindole.HCl	9-VCU/UM
11315	5’-Iodooxymorphindole.HCl	9-VCU/UM
11316	7’-Fluorooxymorphindole.HCl	9-VCU/UM
11317	5’,7’-Difluorooxymorphindole.HCl	9-VCU/UM
11318	5’,7’-Dichlorooxymorphindole.HCl	9-VCU/UM
11319	Oxymorphindole.HCl	9-VCU/UM
11320	7α-(o-Methylcinnamoylaminomethyl)-6,14-endoethanotetrahydrooripavine.HCl	8-VCU
11321	7α-(*p*-Methylcinnamoylaminomethyl)-6,14-endoethanotetrahydrooripavine.HCl	8-VCU
11322	6β-*o*-Nitrocinnamoylnaltrexamine.Oxalate	8-VCU
11323	(+)-(1S,5S,9S)-5,9-Dimethyl-2-(5-hexynyl)-2’-hydroxy-6,7-benzomorphan	7-VCU/UM
11324	(-)-(1R,5R,9R)-5,9-Dimethyl-2-(5-hexynyl)-2’-hydroxy-6,7-benzomorphan.	6-VCU/UM
11325	(-)-(1R,5R,9R)-5,9-Dimethyl-2-(5-cyanopentyl)-2’-hydroxy-6,7-benzomorphan.	6-VCU/UM
11326	(+)-(1S,5S,9S)-5,9-Dimethyl-2-(5-cyanopentyl)-2’-hydroxy-6,7-benzomorphan.	7-VCU/UM
11327	*N*-(4-Phenylbutyl)-4-phenylpiperidine-4-nitrile. Oxalate	11-UM
11328	*N*-(Benzyl)-4-phenylpiperidine-4-nitrile. Oxalate	11-UM
11329	*N*-Allyl-4-phenylpiperidine-4-nitrile. HCl	11-UM
11330	*N*-Crotyl-4-phenylpiperidine-4-nitrile. HCl	11-UM
11331	*N*-(2-Methylallyl)-4-phenylpiperidine-4-nitrile. HCl	11-UM
11332	*N*-Methyl-4-phenylpiperidine-4-nitrile. HCl	11-UM
11333	3-Desoxy-7,8-dihydromorphine.Oxalate	2-UM
11334	6-Desoxymorphine.Oxalate	2-VCU/UM
11335	3,6-Didesoxydihydromorphine.HCl	2-UM
11345	(-)-(1R,5R,9R)-5,9-Dimethyl-2’-hydroxy-2-(2-oxo-3,3-dimethylbutyl)-6,7-benzomorphan.Oxalate	4-VCU/UM

11346	(+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-oxo-3,3-dimethylbutyl)-6,7-benzomorphan.HBr	5-VCU/UM
11347	(-)-(1R,5R,9R)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl	4-VCU/UM
11348	(+)-(1S,5S,9S)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl	5-VCU/UM
11349	(-)-(1R,5R,9R)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6-VCU/UM
11350	(+)-(1S,5S,9S)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11351	(+)-(1R,5R,9R)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-VCU/UM
11352	(-)-(1S,5S,9S)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	4-UM
11353	3-Isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine	12-VCU/UM
CPDD#	**Stimulant/Depressant Program**	
0069	(2*S*,2'*S*)-2,6-Diamine-*N*-(1-phenylpropan-2-yl)hexanamide.dimesylate	13-SD
0070	Salvinorin A	13-SD

NOTES FOR TABLES 2 - 10

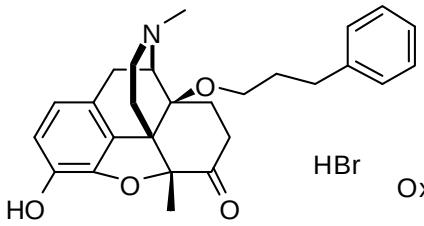
Salt forms are shown. Rounded numbers are used (2 significant figures); precise values and details of the procedures are given in the VCU and UM reports (Aceto et al., 2008; Traynor and Woods, 2008). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained at 30 mg/kg. NTI = naltrindole (delta 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).

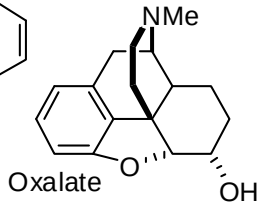
2) *In Vitro*:
Subtype selective binding affinity using recombinant receptors: μ (C_6 rat glioma cells expressing rat μ receptor), κ (CHO cells expressing human κ receptor), and δ (C_6 rat glioma cells expressing rat δ receptor). Affinity was assessed through the displacement of [^{3}H]-diprenorphine.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

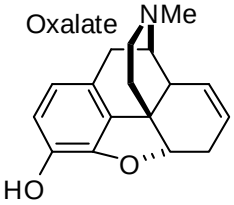
TABLE 2. 4.5-EPOXYMORPHINANS



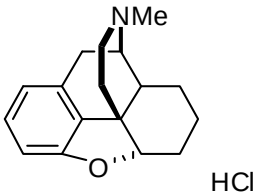
NIH 11121



NIH 11333



NIH 11334

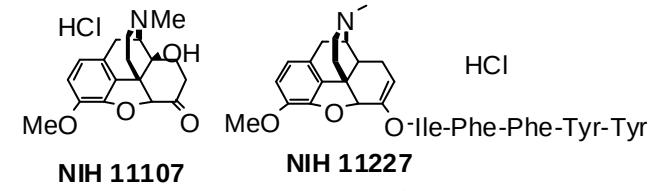


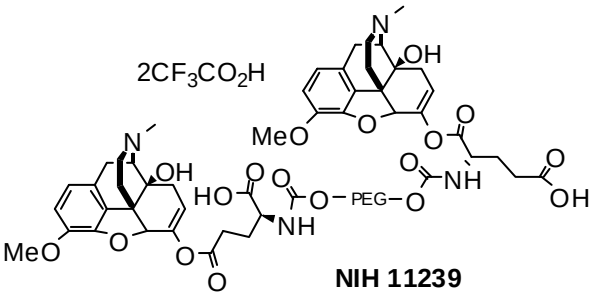
NIH 11335

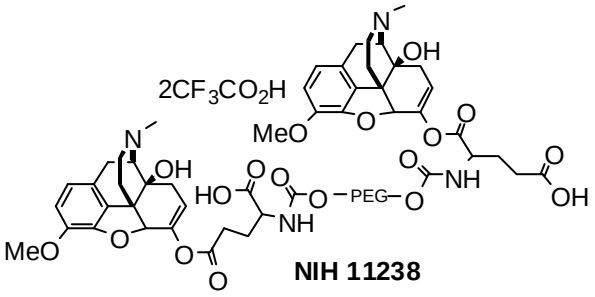
	MOUSE ANTINOCICEPTIVE ASSAYS				***IN VITRO***	**MONKEY**
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM) and GTPγS (EC_{50}, nM and % stimulation)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11121	0.0001[a]	0.00016[a]	0.00008[a] Naltrexone vs. ED_{80}: AD_{50}=0.05 βFNA vs. ED80: AD50=3.59. NTI and norBNI: inactive[a]	Inactive[a]	μ=0.02, δ=0.55, κ=0.09[a] New data: GTPγS: μ EC_{50}=0.06 nM, 104% stimulation δ EC_{50}=2.6 nM, 52% stimulation	Substitution for morphine at 0.04[a]
11333	-	-	-	-	μ=120, δ=4900, κ=5300	-
11334	0.33	0.03	0.2	Inactive	μ=2.9, δ=46, κ=12	-
11335	-	-	-	-	μ=23, δ=590, κ=240	-

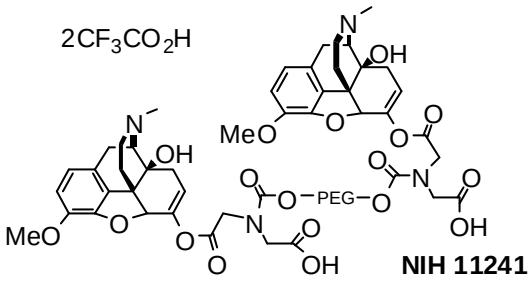
a) Previously reported (Coop, 2005)

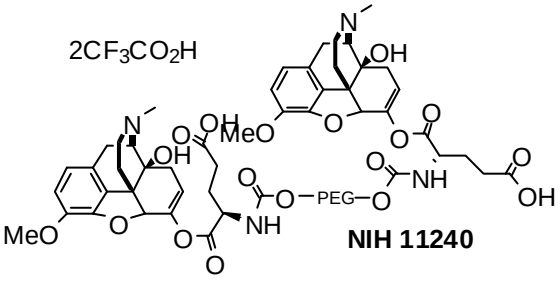
TABLE 3. PRODRUGS OF OXYCODONE

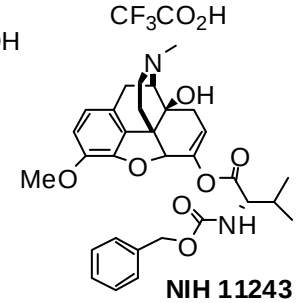


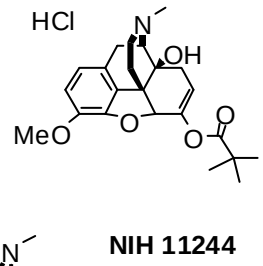


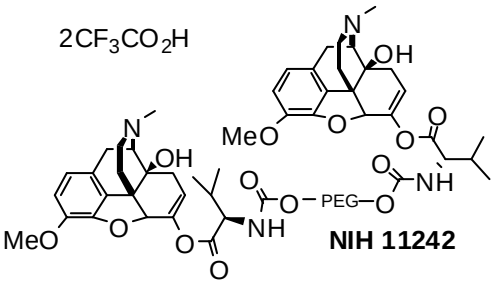


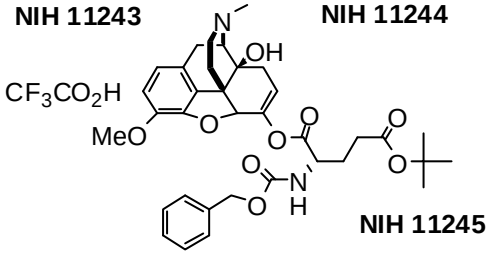










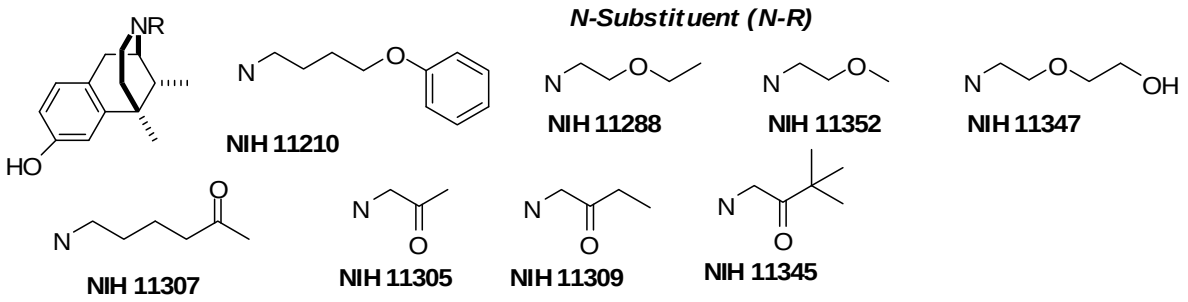


	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenyl-quinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM) and GTPγS (EC_{50}, nM and % stimulation)	Studies in Monkeys (s.c., mg/kg)
11107	1.4[a]	0.38[a]	0.94[a]	Inactive[a]	[b]μ=210,δ, κ>10,000 (Phosphate buffer) GTPγS: μ EC_{50}=850 nM, 97% stimulation	Complete substitution for morphine at 0.75[a]

11227	Inactive	3.4	Inactive	Inactive	μ=52, δ=80, κ=350	Neither attenuated nor precipitated withdrawal in morphine dependant monkeys at 1,10 Inactive in 50°C warm water ta withdrawal assay at 10
11238	-	-	-	-	μ=460, δ=7400, κ=7100 GTPγS: μ 12% stimulation	-
11239	-	-	-	-	μ=440, δ=6500, κ=7800 GTPγS: μ <5% stimulation	-
11240	-	-	-	-	μ=510, δ=7500, κ=6400 GTPγS: μ <5% stimulation	-
11241	-	-	-	-	μ=380, δ=5500, κ>10,000 GTPγS: μ <5% stimulation	-
11242					μ=1300, δ=1100, κ=6800	
11243					μ=170, δ=26, κ=4300 GTPγS: μ <10% stimulation; δ EC_{50}=1600 nM, 38% stimulation	
11244					μ=52, δ=160, κ=7900 GTPγS: μ EC_{50}=1800 nM, 56% stimulation; δ EC_{50}=2900 nM, 30% stimulation	
11245					μ=240, δ=190, κ=1700 GTPγS: μ <10% stimulation; δ 17% stimulation	

a) Previously published (Coop, 2003)
b) New data

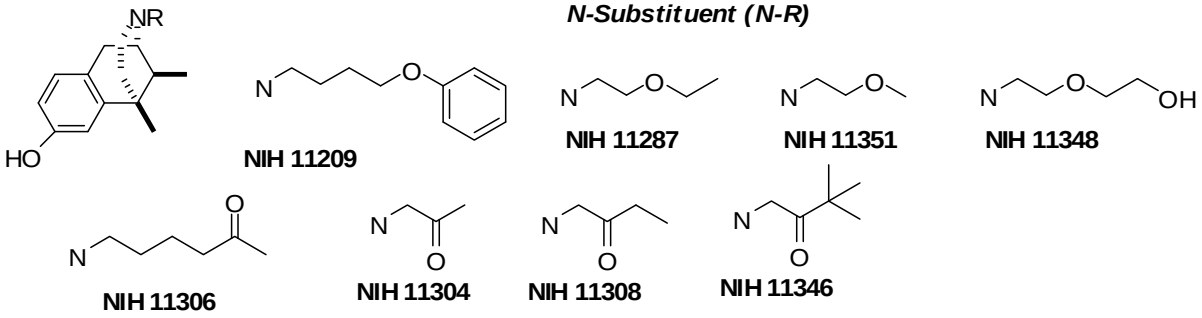
TABLE 4. (-)-*N*-OXO- AND HYDROXY-ALKYL BENZOMORPHANS



	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)
11210	Inactive	6.3	Inactive	Inactive	μ=6.3, δ=43, κ=44	Neither substituted for morphine nor exacerbated withdrawal at 10
11288	0.3	0.18	0.86	Inactive	μ=1.2, δ=30, κ=2.0[a]	Substitution for morphine at 3. Slowing and Salivation noted
11305	Inactive	8.0	Inactive	1.3	μ=77, δ=890, κ=120	Precipitated withdrawal at 1.5 and 6
11307	Inactive	13	Inactive	Inactive	μ=21, δ=370, κ=140	-
11309	Inactive	Inactive	Inactive	5.3	μ=72, δ=850, κ=71	Neither substituted for morphine nor exacerbated withdrawal at 10
11345	Inactive	7.9	Inactive	Inactive	μ=300, δ=2100, κ=200	-
11347	Inactive	Inactive	Inactive	Inactive	μ=230, δ=1100, κ=64	-
11352	-	-	-	-	μ=0.32, δ=2.1, κ=0.24	-

a) Previously reported (Coop, 2007)

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

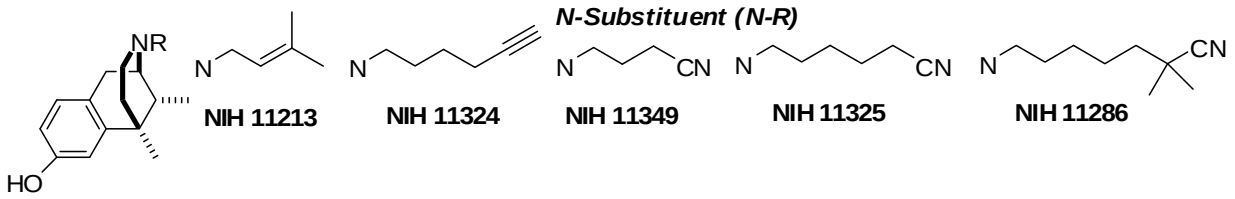


N-Substituent (N-R)

	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)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11209	Inactive	13	Inactive	Inactive	μ=70, δ=3200, κ=300	Neither attenuated nor exacerbated withdrawal at 2 and 8
11287	Inactive	Inactive	Inactive	Inactive	μ=2.1 δ=2600, κ=220[a]	-
11304	Inactive	3.4	Inactive	Inactive	μ=6300, δ,κ>10,000	-
11306	Inactive	Inactive	Inactive	Inactive	μ=3400, δ>10,000, κ=5100	-
11308	Inactive	Inactive	Inactive	Inactive	μ,δ>10,000, κ=9500	-
11346	Inactive	Inactive	Inactive	Inactive	μ,δ>10,000, κ=4900	-
11348	Inactive	Inactive	Inactive	Inactive	μ=1200, δ>10,000, κ=580	-
11351	Inactive	2.6	Inactive	Inactive	μ=250, δ=1800, κ=120	-

a) Previously reported (Coop, 2007)

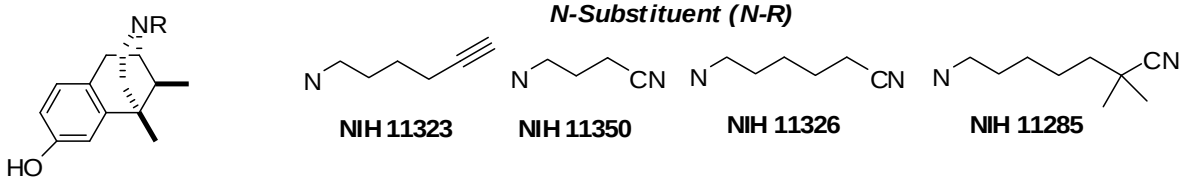
TABLE 6. (-)-N-ALKYL-BENZOMORPHANS



	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) and GTPγS (% stimulation and $EC_{50,}$ nM)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11213	Inactive[a]	1.2[a]	Inactive[a]	Inactive[a]	μ=6.8, δ=120, κ=8.1[a] New data: GTPγS: μ 4% stimulation; δ 9% stimulation	-
11286	Inactive	Inactive	Inactive	Inactive	μ=9.4, δ=39, κ=77[a]	-
11324	1.5	0.76	4.6	Inactive	μ=4.3, δ=55, κ=7.5	Attenuated withdrawal at 2.5
11325	Inactive	2.8	8.7	Inactive	μ=17, δ=210, κ=8.1	Attenuated withdrawal at 2.5
11349	5.1	0.14	0.3	Inactive	μ=3.1, δ=9.9, κ=0.32	-

a) Previously reported (Coop, 2007)

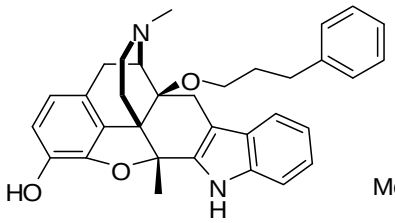
TABLE 7. (+)-N-ALKYL-BENZOMORPHANS



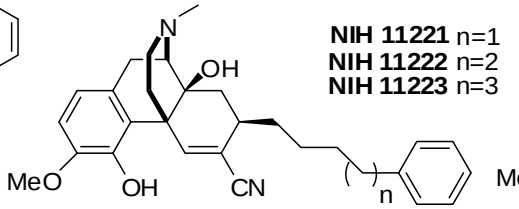
	MOUSE ANTINOCICEPTIVE ASSAYS			*IN VITRO*	
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)
11285	Inactive	Inactive	Inactive	Inactive	μ=380, δ=3100, κ=530[a]
11323	Inactive	15	Inactive	Inactive	μ=630, δ>10,000, κ=240
11326	Inactive	Inactive	Inactive	Inactive	μ=2200, δ>10,000, κ=300
11350	Inactive	Inactive	Inactive	Inactive	μ=1900, δ=7100, κ=180

a) Previously reported (Coop, 2007)

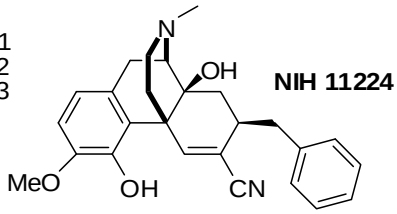
TABLE 8. ANALOGS OF POTENT OPIOIDS



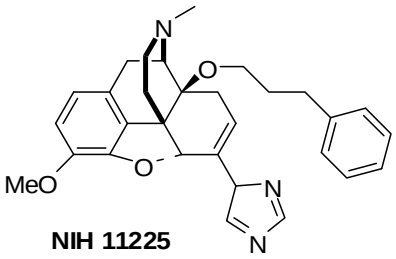
NIH 11116



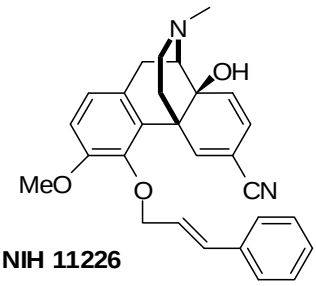
NIH 11221 n=1
NIH 11222 n=2
NIH 11223 n=3



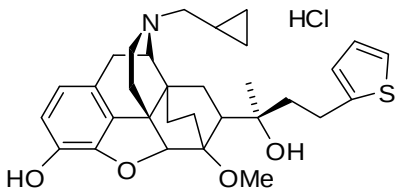
NIH 11224



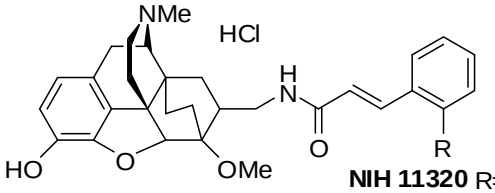
NIH 11225



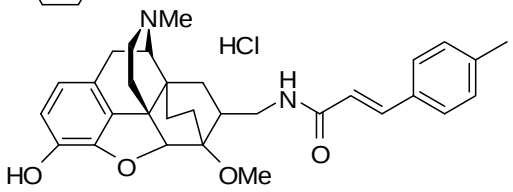
NIH 11226



NIH 11310



NIH 11320 R=Me
NIH 11322 R=NO_2



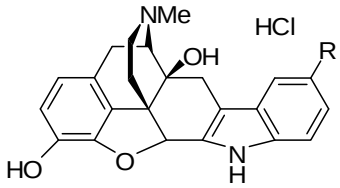
NIH 11321

MOUSE ANTINOCICEPTIVE ASSAYS ***IN VITRO***

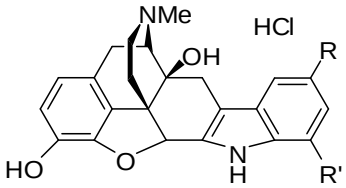
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM) and GTPγS (% stimulation and EC_{50}, nM)
11116	8.8[a]	6.5[a]	10[a] NTI vs. ED_{80}: Inactive[a]	Inactive[a]	μ=80, δ=3.3, κ=76[a] New data: GTPγS: μ EC_{50}=230 nM, 86% stimulation; δ EC_{50}=3.5 nM, 37% stimulation
11221	Inactive	4.0	Inactive	Inactive	μ=7.0, δ=120, κ=1500
11222	Inactive	3.0	Inactive	Inactive	μ=0.63, δ=78, κ=510
11223	Inactive	Inactive	Inactive	Inactive	μ=0.32, δ=140, κ=570
11224	Inactive	Inactive	Inactive	Inactive	μ=1500, δ=87, κ=2000
11225	2.7	0.66	Inactive	Inactive	μ=0.96, δ=1.3, κ=0.42
11226	Inactive	2.8	12	Inactive	μ=0.83, δ=460, κ=1200
11310					μ=0.22, δ=0.69, κ=0.14 GTPγS: μ EC_{50}=1.9 nM, 19% stimulation; δ no stimulation κ EC_{50}=0.3 nM, 75% stimulation
11320	1.0	0.63	1.8	Inactive	–
11321	2.3	2.7	6.4	Inactive	–
11322	-	19	-	-	–

a) previously reported (Coop, 2006)

TABLE 9. ANALOGS OF OXYMORPHINDOLE



NIH 11312 R=F
NIH 11313 R=Cl
NIH 11314 R=Br
NIH 11315 R=I
NIH 11319 R=H



NIH 11316 R=H, R'=F
NIH 11317 R=F, R'=F
NIH 11318 R=Cl, R'=Cl

	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) and GTPγS (% stimulation and $EC_{50,}$ nM)
11312	Inactive	Inactive	Inactive	Inactive	μ=21, δ=2.3, κ=310 GTPγS: μ EC50=1100 nM 24% stimulation δ EC50=16 nM 16% stimulation
11313	Inactive	Inactive	Inactive	Inactive	μ=47, δ=5.1, κ=360
11314	Inactive	Inactive	Inactive	Inactive	μ=71, δ=8.6, κ=250
11315	Inactive	Inactive	Inactive	Inactive	μ=66, δ=3.8, κ=160
11316	Inactive	Inactive	Inactive	Inactive	μ=65, δ=0.5, κ=270
11317	Inactive	Inactive	Inactive	Inactive	μ=59, δ=1.1, κ=210
11318	Inactive	2.4	Inactive	Inactive	μ=29, δ=6.7, κ=380
11319	Inactive	Inactive	Inactive	Inactive	μ=110, δ=0.9, κ=520

TABLE 10. PEPTIDES

NIH 11199: Acetyl-Arg-Phe(4-COOH)-Tyr-Arg-Trp-Arg-NH_2

NIH 11200: Acetyl-Arg-Phe(4-F)-Tyr-Arg-Trp-Arg-NH_2

NIH 11201: Acetyl-Arg-Phe(4-OCH_3)-Tyr-Arg-Trp-Arg-NH_2

NIH 11202: Acetyl-Arg-Phe(4-CN)-Tyr-Arg-Trp-Arg-NH_2

NIH 11203: Acetyl-Arg-Tyr-Tyr-Arg-Trp(5-CN)-Arg-NH_2

NIH 11204: Acetyl-Arg-Tyr-Phe(4-F)-Arg-Trp-Arg-NH_2

NIH 11205: Acetyl-Arg-Tyr-Phe(4-NHAc)-Arg-Trp-Arg-NH_2

NIH 11206: Acetyl-Arg-Tyr(3-Cl)-Tyr-Arg-Trp-Arg-NH_2

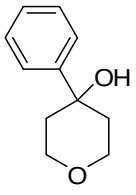
NIH 11207: Acetyl-Arg-Tyr-Phe(4-benzyl)-Arg-Trp-Arg-NH_2

NIH 11208: Heptanoyl-Arg-Tyr-Phe-Arg-Trp-Arg-NH_2

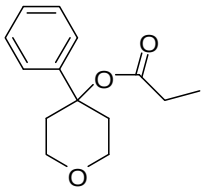
	MOUSE ANTINOCICEPTIVE ASSAYS				***IN VITRO***
NIH #	Hot Plate (ED_{50}, i.c.v. μg/brain)	Phenylquinone (ED_{50}, i.c.v. μg/brain)	Tail Flick (ED_{50}, i.c.v. μg/brain)	Tail Flick Antagonist (AD_{50}, i.c.v. μg/brain)	Binding Affinity, (K_i, nM)
11199	Inactive	1.8	Inactive	Inactive	μ=2800, δ=2000, κ>10,000
11200	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=740, δ>10,000, κ=720
11201	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=670, δ>10,000, κ=1000
11202	Inactive	Inactive	Inactive	Inactive	μ=1500, δ>10,000, κ=990
11203	-	Inactive	Inactive	-	μ=270, δ>10,000, κ=1400
11204	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=190, δ=5900, κ=780
11205	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=470, δ>10,000, κ=1200
11206	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=600, δ>10,000, κ=2700
11207	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=220, δ=5900, κ=570
11208	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=110, δ=3300, κ=130

a) Also inactive S.C.

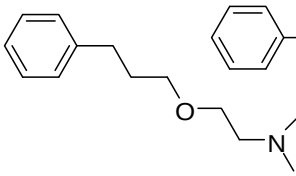
TABLE 11. SMALL MOLECULES



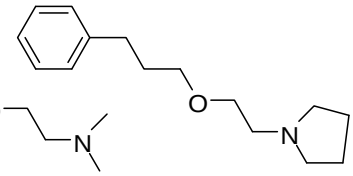
NIH 11292



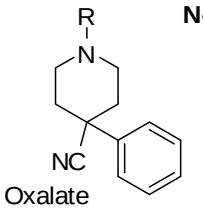
NIH 11296



NIH 11293

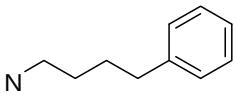


NIH 11294

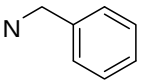


Oxalate

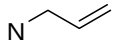
N-Substituent (N-R)



NIH 11327



NIH 11328



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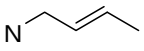
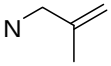


NIH 11330



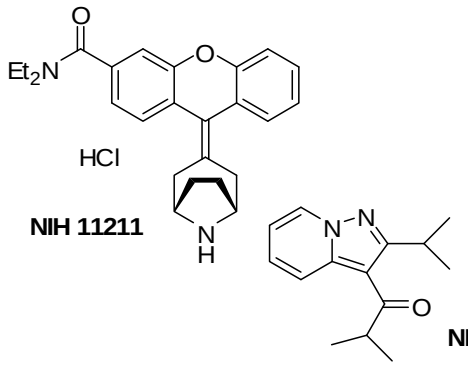
NIH 11331

NIH 11332 NMe

MOUSE ANTINOCICEPTIVE ASSAYS ***IN VITRO***

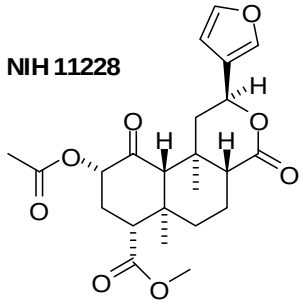
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)
11292	Inactive	Inactive	Inactive	Inactive	μ,δ,κ>10,000
11293	Inactive	Inactive	Inactive	Inactive	μ,δ,κ>10,000
11294	-	-	-	-	μ=3100, δ,κ>10,000
11296	Inactive	Inactive	Inactive	Inactive	μ,δ,κ>10,000
11327	-	-	-	-	μ=9800,δ,κ>10,000
11328	-	-	-	-	μ=5900,δ,κ>10,000
11329	-	-	-	-	μ,δ,κ>10,000
11330	-	-	-	-	μ,δ,κ>10,000
11331	-	-	-	-	μ,δ>10,000, κ=5000
11332	-	-	-	-	μ,δ,κ>10,000

TABLE 12. COMPOUNDS WITH MISCELANEOUS STRUCTURES



NIH 11211

NIH 11353



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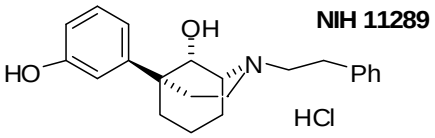
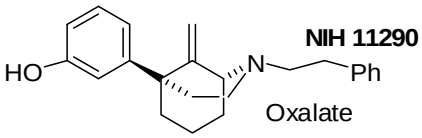


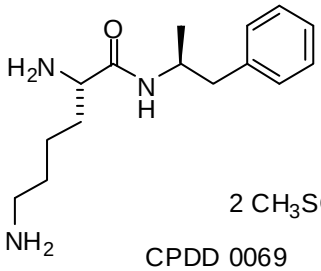
NIH 11289



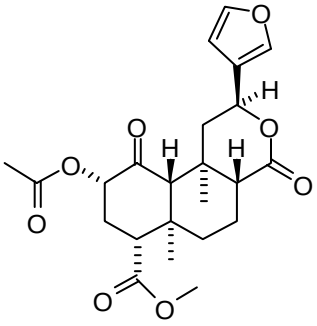
NIH 11290

	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 Monkeys (s.c., mg/kg)
11211	Inactive	Inactive	Inactive	Inactive	–	Inactive in 50°C tail withdrawal at doses between 0.01 and 3
11228	Inactive	0.59	2.0	Inactive	κ=42; μ, δ, >10,000	-
11289	0.0018	0.0023	0.0043	-	-	Complete substitution for morphine at 0.005 and 0.03
11290	0.017	0.023	0.03	-	-	Complete substitution for morphine at 1
11353	23	3.1	Inactive	Inactive	μ, δ, κ>10,000	Neither substituted for morphine nor precipitated withdrawal at 2.5 and 10

TABLE 13. COMPOUNDS EVALUATED BY STIMULANT DEPRESSANT PROGRAM



CPDD 0069



CPDD 0070

	Discriminative Stimulus Effects in Benzodiazepine-Trained Monkeys	Self-Administration in Cocaine-Maintained Monkeys	Drug Discrimination in Amphetamine-Trained Monkeys	Discriminative Stimulus Effects in PCP-Trained Rats
0069	Shares no discriminative stimulus effects with either flumazenil or midazolam at doses up to 5.6 mg/kg	Reinforcing effects at 0.03 and 0.1 mg/kg/inj	Full appropriate responding at 3 mg/kg s.c.	-
0070	Shares no discriminative stimulus effects with either flumazenil or midazolam at doses up to 0.56 mg/kg	-	No amphetamine discriminative stimulus effects in doses up to 1 mg/kg i.g.	No significant PCP-like responding

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