BIOLOGICAL EVALUATION OF OPIOIDS, STIMULANTS, AND DEPRESSANTS. I. AN OVERVIEW OF THE STUDIES PERFORMED BY THE DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2004)

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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, 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/images/dec.pdf) which contains archived DEC annual reports together with the DEC indices, a list of all compounds evaluated by DEC and reference to their year of publication. 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), and three 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), and UM (Drs. W. Fantegrossi, J. Woods). Drs. J. Winter (University of Buffalo) and K. Cunningham (University of Texas Medical Branch at Galveston) currently serve as special purpose members, and Drs. T. Cicero, A. Jacobson, and G. Winger act as emeritus members. DEC reports to the CPDD Liaison Committee for Drug Testing and Evaluation (Dr. F. I. Carroll, Chair). Members of both that CPDD committee and other CPDD committees as well as representatives from governmental agencies, attend DEC's meeting held during the Annual Scientific Meeting of the CPDD. One other DEC meeting was held in Michigan in May 2004 to discuss the work which has been accomplished and future plans. Separate meetings are held at VCU quarterly with the members of the VCU Analgesic Testing Group, as well as Drs. E. May and E. Bowman, Dr. A. Coop, and a NIDA representative (Dr. D. Thomas), to discuss the results obtained from the VCU testing and research program.

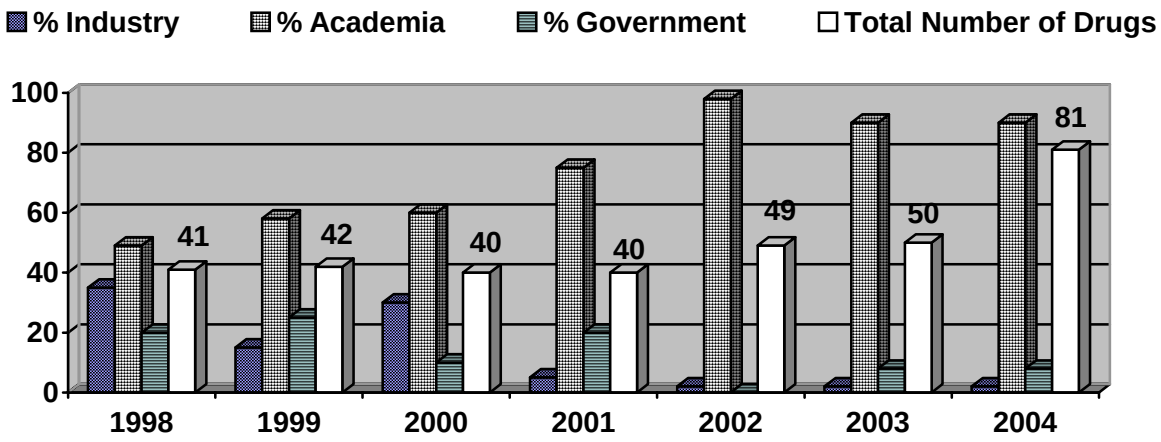
Data obtained under the auspices of DEC are held confidential for a maximum of three years, but can be released prior to the three-year limit with the permission of the submitter. Data were released for publication this year on 78 compounds evaluated by the Analgesic Testing Program (Figure 1). This figure is far larger than previous years, and it is anticipated that a similar number of compounds will be released next year. Of these 78 compounds, 51 were evaluated at VCU (antinociceptive assays in mice - tail flick, hot plate, and phenylquinone, and the tail-flick antagonist assay, as well as substitution for morphine and precipitated withdrawal assays in rhesus monkeys), and 57 at UM (56 for binding affinity to the μ, δ, and κ opioid receptors and GTPγS functional studies, and one for self-administration in monkeys). Compounds were submitted primarily from academia; one compound was submitted from the pharmaceutical industry. Figure 1 clearly shows that the percentage of compounds originating from academia has been steadily increasing over the past few years, with the percentage from other sources correspondingly decreasing. It is noteworthy that a number of new industrial submitters have submitted compounds over the past year, thereby increasing the diversity of sources for compounds to be released in future years. In addition, several new academic submitters are represented this year, and it is anticipated that submissions from these sources will continue. Three compounds were released this year from the Stimulant/Depressant program which, when coupled to the three compounds released last year, represents a significant increase in compounds over the historical 1-2 releases per year.

Two joint publications based on the data gathered under DEC auspices were published since the last annual report (E. Greiner et al., 2003; J. Schutz et al., 2003; Spetea et al., 2004).

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. Similar to previous years (Coop 2004), the examined compounds are classified according to their molecular structure: morphinans and 4,5-epoxymorphinans in Tables 2, 3 and 4; miscellaneous compounds in Table 5; 6,7-benzomorphans in Tables 6 and 7; esters and ethers of opioids in Table 8; opioid peptides in Table 9; compounds evaluated by the Stimulant/Depressant program are shown in Table 10. The more interesting compounds evaluated during the year 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 (1998-2004)



The 14-phenylpropyloxy morphinans **NIH 11053 – NIH 11061** (Table 2) represent a unique class of opioids. They possess extraordinary potency as antinociceptive agents (10,000 x morphine), and high affinity for all three opioid receptors. As such, they can be considered of similar potency to the orvinols (Lewis, 1985, Casey and Parfitt, 1986). **NIH 11053 – NIH 11058** are 3-phenolic, and therefore the most potent, but the most interesting aspect of these compounds is that they are all mu opioid agonists. This is demonstrated through the Straub tail which was noted in most rodent assays, and also the reversal of the agonist actions by mu opioid antagonists. **NIH 11055** would be expected to have mu agonist actions due to the presence of the *N*-phenethyl group, but **NIH 11053** (*N*-propyl), **NIH 11054** (*N*-tetrahydrofuranyl), **NIH 11056** (*N*-cyclopropylmethyl), **NIH 11057** (*N*-cyclobutylmethyl), and **NIH 11058** (*N*-allyl) would all be expected to have mu opioid antagonist activity (Greiner et al., 2003). Although still very potent, **NIH 11055** is the least potent of the six compounds. These results suggest that the presence of a phenylpropyloxy group on the 14-position of these opioids leads to mu agonists of high potency, regardless of the nature of the N-substituent. The corresponding 3-methyl ethers display approximately 50-fold lower potency and affinity, but again the *N*-tetrahydrofuranyl (**NIH 11059**) and *N*-allyl (**NIH 11061**) possess greater potency than the *N*-phenethyl substituted **NIH 11060**.

The 3-ethers and esters of naltrexone in Table 3 have been discussed previously (Coop, 2002, 2004). These compounds were designed to possess a longer duration of action than naltrexone through the requirement for metabolism. The 3-ether **NIH11028** and the 3-cinnamoyl ester **NIH 11037** are neither particularly potent nor of longer duration. The 3-butyrate ester **NIH 11109** is of note for its increased potency which is estimated to be 5 times greater than naloxone. It is assumed that the increased lipophilicy of the drug as compared to naltrexone promotes rapid access to the CNS.

Table 4 contains several different morphinans and 4,5-epoxymorphinans. **NIH 11062** (an epoxymorphinan with N-propyl and 14-ethoxyl groups) shows again that N-propyl substituted opioids do not always possess a profile of mu antagonism. Indeed, **NIH 11062** is a potent mu opioid agonist (100 x morphine), but it should be

remembered that the phenylpropyloxy derivative (NIH 11053, Table 2) is about 5000 times more potent than morphine. The corresponding 6,7-indole (**NIH 11063**, Table 4) is a derivative of naltrindole, the prototypical delta opioid antagonist (Portoghese et al., 1990). This compound exhibits delta selectivity in binding assays and delta antagonism in GTPγS functional assays. **NIH 11063** may find use as a pharmacological tool for the study of delta receptors. Morphinans with 4-phenolic groups (such as **NIH 11066** Table 4) rarely possess significant opioid activity (Coop et al., 1999), yet **NIH 11066** appears to possess similar potency as morphine in primates. The corresponding 4-methyl ether, **NIH 11065**, can be seen to possess the anticipated greater antinociceptive potency, being about 150 times more potent than morphine in rodents and 40 times more potent than morphine in primates. Interestingly, the corresponding *N*-cyclopropylmethyl substituted analog, **NIH 11076** Table 4, only possesses moderate morphine antagonism. Demonstrating again that traditional structure-activity relationships may not apply to this series, the *N*-methyl substituted 4-phenol with no 3-substituent, **NIH 11077** Table 4, possess excellent mu agonist potency, yet the corresponding *N*-cyclopropylmethyl substituted analog, **NIH 11075**, possesses 10-fold weaker antinociceptive activity, and no morphine antagonism.

NIH 10945 (Table 5) is similar to a benzomorphan, but with a nitrogen atom differently positioned. It was previously shown (Coop, 2002) that **NIH 10945** displayed weak antinociceptive activity in the anti-writing assay, yet possessed good affinity for both mu and kappa receptors. GTPγS functional assays have now shown this compound to be a partial agonist at both mu and kappa receptors of moderate potency. **NIH 11100** (Table 5) is a bridged indolomorphinan which was previously shown to possess moderate affinity for all three receptors. GTPγS assays have now shown this compound to have to no mu agonist activity – a very unusual finding for a morphinan with an *N*-methyl substituent. **NIH 11031** (Table 5) has a long duration of action, but its activity changes as time progresses. It is initially a kappa agonist and manifests as a mu and kappa antagonist after 24-48 hours (Coop, 2004). New data in GTPγS functional assays is consistent with these findings and shows that **NIH 11031** is a potent partial agonist at both kappa and delta receptors, and possesses no agonist activity at mu receptors.

NIH 11161 (Table 5) is an analog of the prototypical delta agonist SNC80 (Calderon et al., 1997), but lacking the benzamide group generally considered important for activity (Calderon and Coop, 2004). **NIH 11161** showed weak reinforcing effects in primates experienced with mu agonists, and was estimated to be 30-fold less potent than the mu agonist alfentanyl. The presence of a phenolic group has previously been shown to lead to increased mu agonist activity, typified by BW373U86 (Calderon and Coop, 2004), so the fact that phenolic **NIH 11161** shows mu agonist activity is as expected.

The *N*-benzyl substituted benzomorphans (Table 6a) have garnered attention due to their unusual pharmacology (May et al., 1998; May et al., 2003). The corresponding homologs (*N*-phenethyl) tends to be potent mu agonists, yet the *N*-benzyl derivatives show little, if any, activity *in vivo*. Most of the analogs also display low affinity at opioid receptors, yet several of the compounds clearly show good affinity at mu and kappa receptors. The three *ortho* halogen substituted analogs (**NIH 11097** (*o*-F), **NIH 11093** (*o*-Cl), and **NIH 11081** (*o*-Br) Table 6a) were chosen for further study as all three possess good affinity (K_i <40 nM) at mu and kappa receptors, and all were inactive in both rodents and primates. GTPγS functional assays showed all three compounds to possess no agonist activity at mu, kappa, and delta receptors. Antagonist GTPγS studies confirmed that **NIH 11097** is an antagonist at both mu and kappa receptors. This still leaves the question as to why **NIH 11097** (for example) shows no activity in the rodent tail flick versus morphine nor exacerbate withdrawal in monkeys. In addition, it was also shown that **NIH 11097** did not antagonize a kappa agonist in rodents when administered s.c. One possible explanation for these apparent contradictions is that *N*-benzyl substituted benzomorphans do not readily cross into the CNS. Studies using **NIH 11097** administered by the i.c.v. route lead to an ED_{50} of 15 μM/brain in the tail flick assay. Further studies are warranted to examine the actions of **NIH 11097**, **NIH 11081,** and **NIH 11093** as antagonists when administered i.c.v.. The (+)-isomer of **NIH 11097** (**NIH 11095**, Table 6b) also possesses significant affinity at kappa receptors. Again, GTPγS assays indicated no kappa agonist activity for this compound.

NIH 11082 (*N*-6-hydroxyhexyl substituted (-)-benzomorphan, Table 7a) possess an unusual profile. The compound possesses good affinity at mu and kappa receptors, and lower affinity at delta receptors. It has antinociceptive activity in the anti-writing assay, that is reversed by the delta selective antagonist naltrindole.

The *in vivo* studies indicate delta agonist actions which is not consistent with the low binding affinity at delta receptors. GTPγS functional assays complicate the matter further: **NIH 11082** acts as a weak partial mu agonist, a very weak kappa agonist of low efficacy, and at delta receptors very little stimulation is observed (9%) together with low potency. This would tend to suggest that the antinociceptive actions seen in PPQ are mu agonist actions. Why these actions were reversible with naltrindole remains to be determined.

The opioid ester **NIH 11044** (Table 8) was previously shown to possess a mixed agonist/antagonist profile in rodents (Coop, 2003), and overt signs in primates suggested a kappa agonist component. GTPγS functional assays have confirmed this profile, as **NIH 11044** is a kappa partial agonist and shows no stimulation in mu assays. The related analog lacking a terminal chlorine atom (**NIH 11045**, Table 8) possesses a similar profile of no stimulation in mu assays and kappa partial agonism, but with a weaker potency. In the case of **NIH 11045**, the kappa actions are so weak that they do not translate to activity in anti-writing assays.

Peptides **NIH 11086** and **NIH 11078** (Table 9) are analogs of the opioid peptide dynorphin. Severe convulsive effects were noted when these two compounds were administered i.c.v. The enkephalin analogs **NIH11089 - NIH11092** (Table 9) were also administered i.c.v. and exhibited varying degrees of antinociceptive activity in PPQ and TF. **NIH 11090** was notable for giving rise to convulsions and rigidity, but the other three peptides appear free from these undesired effects.

CPDD 0066 (5-Methoxy-N,N-diisopropyltryptamine) and **CPDD 0068** (2C-T-7) (Table 10) are hallucinogens of increasing concern to the Federal authorities, and they were shown to share discriminate stimulus effects with LSD. These compounds possesses a profile which would suggest LSD-like effects in humans. **CPDD 0067** (phenylpiperazine) (Table 10) shares structural similarities to TFMPP and BZP (Coop, 2004). This compound shows no evidence of LSD-like effects.

IN CONCLUSION, DEC evaluated numerous interesting compounds this year. The 14-phenylpropylethers (Table 2) are extremely potent and have unique structure-activity relationships. The indolomorphinan (**NIH 11063**, Table 4) could prove useful as a delta selective antagonist, and the 4-phenols in Table 4 are some of only a very few available potent 4-phenolic opioids. **NIH 10945** (Table 5) is an opioid with a unique carbon-nitrogen skeleton, and **NIH 11161** (Table 5) is an analog of SNC80 which display mu agonism. The *N*-benzyl benzomorphans (Table 6a) have been shown to possess mu and kappa antagonism, and it is suggested that access to the CNS is one possible reason for their low potency *in vivo*. The hydroxyalkyl benzomorphan (**NIH 11082**, Table 7a) appears to show delta agonism *in vivo* and delta antagonism *in vitro*. The purported hallucinogens **CPDD 0066** and **CPDD 0068** (Table 10) have been shown to possess a profile which predicts LSD-like activity in humans.

TABLE 1. EVALUATED COMPOUNDS

	COMPOUND NAME	TABLE #-Evaluator
NIH#	**ANALGESIC TESTING PROGRAM**	
10945	(±)-(5S,8S,9R)-8-Amino-3-hydroxy-5,9-methano-9-(methoxymethyl)-5-methylbenzocyclooctene	5-UM
11001	4-(3-Hydroxyphenyl)-4-(1-oxopropyl)-1-(4-trifluoromethylbenzyl)piperidine.HCl	5-UM
11027	(-)-(1*R*,5*R*,9*R*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-UM
11028	3-O-Methylnaltrexone.HCl	3-VCU
11031	17-Cyclopropylmethyl-7α-methyl-2'-[*S*]-phenyl-[5β,7β,3',5']-pyrrolidino-6,14-endo-ethenomorphinan.HCl	5-UM
11037	3-O-Cinnamoylnaltrexone.HCl	3-VCU
11041	(-)-(1*R*,5*R*,9*R*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-UM
11044	(-)-1*R*,5*R*,9*R*-2'-Acetoxy-2-(3-*cis*-chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan.oxalate	8-UM
11045	(-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-5,9-dimethyl-2-(propenyl)-6,7-benzomorphan.oxalate	8-UM
11050	6,7-Didehydro-3,14-dihydroxy-17-methyl-4,5α-epoxy-[(2-methyl)-pyrazolo-[6,7]]morphinan.2HCl	5-UM
11052	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(propenyl)-2'-proprionoxy-6,7-benzomorphan.HCl	8-UM
11053	4,5α-Epoxy-3-hydroxy-14β-(3-phenylpropyloxy)-17-propyl-morphinan-6-one.HCl	2-VCU/UM
11054	4,5α-Epoxy-3-hydroxy-14β-(3-phenylpropyloxy)-17-([2-*R*,*S*-tetrahydrofuranyl)methyl)-morphinan-6-one.HCl	2-VCU/UM
11055	4,5α-Epoxy-3-hydroxy-17-phenethyl-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU/UM
11056	17-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-14-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU
11057	17-Cyclobutylmethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU/UM
11058	17-Allyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-VCU/UM
11059	4,5α-Epoxy-3-methoxy-14β-(3-phenylpropyloxy)-17-[(2-*R*,*S*-tetrahydrofuranyl)methyl]-morphinan-6-one.HCl	2-VCU/UM
11060	4,5α-Epoxy-3-methoxy-17-(2-phenethyl)-14β-(3-phenylpropyloxy)-morphinan-6-one.HCl	2-VCU/UM
11061	17-Allyl-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl	2-UM
11062	4,5α-Epoxy-14β-ethoxy-3-methoxy-17-(propyl)morphinan-6-one.HCl	4-VCU/UM
11063	4,5α-Epoxy-3-hydroxy-14β-methoxy-17-(propyl)indolo[2',3':6,7]morphinan-3-ol.HCl	4-UM
11165	5,6-Didehydro-14β-hydroxy-3,4-dimethoxy-17-methylmorphinan-6-carbonitrile	4-VCU/UM
11066	5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile	4- VCU/UM

11067	5,6-Didehydro-4-hydroxy-3,14β-dimethoxy-17-methylmorphinan-6-carbonitrile	4-VCU/UM
11068	17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-3-hydroxy-5β-methymorphinan-6-one	4-VCU/UM
11072	17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-4-methoxymorphinan-6-carbonitrile	4-VCU/UM
11073	17-Cyclopropylmethyl-5,6-didehydro-4-hydroxy-3,14β-dimethoxymorphinan-6-carbonitrile	4-VCU/UM
11074	17-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxy-3-methoxymorphinan-6-carbonitrile	4-VCU/UM
11075	17-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxymorphinan-6-carbonitrile	4-VCU/UM
11076	17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-3,4-dimethoxymorphinan-6-carbonitrile	4-VCU/UM
11077	5,6-didehydro-4,14β-dihydroxy-17-methylmorphinan-6-carbonitrile	4-VCU/UM
11078	7-Hydroxymethyl-8-methyl-6,7,8,9,10,10a-hexahydro-1H-2-oxa-8-aza-cycloocta[c,d]inden-3-ol	5-UM
11079	7-Hydroxymethyl-8-methyl-6,7,8,9,10,10a-hexahydro-1H-2-oxa-8-aza-cycloocta[c,d]inden-3-ol	5-UM
11081	(-)-(1*R*,5*R*,9*R*)- 2-(2-bromobenzyl)-5,9-Dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-UM
11082	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl	7a-VCU/UM
11086	Dynorphin analog	9-VCU
11087	Dynorphin analog	9-VCU
11088	(+)-(1*S*,5*S*,9*S*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	6b-UM
11089	Enkephalin analog	9-VCU
11090	Enkephalin analog	9-VCU
11091	Enkephalin analog	9-VCU
11092	Enkephalin analog	9-VCU
11093	(-)-(1*R*,5*R*,9*R*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-UM
11095	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan. Oxalate	6b-UM
11096	(-)-(1*R*,5*R*,9*R*)-2'-Butyroxy-5,9-Dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	8-UM
11097	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.Oxalate	6a-VCU/UM
11098	(+)-(1*S*,5*S*,9*S*)-2'-Butryoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	8-VCU/UM
11100	18-(*E*)-Benzylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan.oxalate	5-UM
11101	18-Isopropylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan. oxalate	5-UM

11106	1'-Benzyloxymorphindole	5-VCU
11109	3-O-Butyrylnaltrexone.oxalate	3-VCU
11111	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanly)-6,7-benzomorphan.hemioxalate	6a-VCU
11112	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-1,3-dioxalanly)-6,7-benzomorphan.hemioxalate	6b-VCU
11113	(+)-(1*S*,5*S*,9*S*)-2-Cyclopentylmethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6b-VCU
11114	(-)-(1*R*,5*R*,9*R*)-2-Cyclopentylmethyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-VCU
11127	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(7-hydroxyheptyl)- 6,7-benzomorphan.HBr	7a-VCU
11128	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(7-hydroxyheptyl)-6,7-benzomorphan.HBr	7b-UM
11139	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl	7a-VCU
11140	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)6,7-benzomorphan.HCl	7b-VCU/UM
11161	(-)-3-{(*S*)-[(2*S*,5*R*)-4-Allyl-2,5-dimethyl-1-piperazinyl](3-thienyl)methyl}phenol	5-UM
11163	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(5-hydroxypentyl)-6,7-benzomorphan.HCl	7b-UM
11164	(-)-(1*R*,5*R*,9*R*)-2-(5-Acetoxypentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7a-VCU/UM
11165	(+)-(1*S*,5*S*,9*S*)-2-(5-Acetoxypentyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl	7b-VCU
11166	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(5-hydroxypentyl)-6,7-benzomorphan.HCl	7a-VCU
11167	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(1,3-dioxanylethyl)-2'-hydroxy-6,7-benzomorphan.HBr	6a-VCU
11168	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(1,3-dioxanylethyl)-2'-hydroxy-6,7-benzomorphan.HBr	6b-VCU
11176	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(1,3-dioxalanylethyl)-2'-hydroxy-6,7-benzomorphan. HCl	6a-VCU/UM
11177	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(1,3-dioxalanylethyl)-2'-hydroxy-6,7-benzomorphan. HCl	6b-UM
11178	(+)-(1*S*,5*S*,9*S*)- 5,9-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl	6b-UM
11179	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl	6a-VCU/UM
11180	(-)-(1*R*,5*R*,9*R*)-2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan. oxalate	7a-VCU/UM
11181	(+)-(1*S*,5*S*,9*S*)-2-(3-Acetoxypropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	7b-VCU/UM
11182	(+)-(1*S*,5*S*,9*S*)-2-(3-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	7b-VCU/UM
11183	(-)-(1*R*,5*R*,9*R*)-2-(3-Acetoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.oxalate	7a-VCU/UM

11185	(-)-(1*R*,5*R*,9*R*)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-VCU/UM
11186	(+)-(1*S*,5*S*,9*S*)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6b-VCU/UM
11187	(-)-(1*R*,5*R*,9*R*)-2-(2-Ethylbutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6a-VCU/UM

CPDD# STIMULANT DEPRESSANT PROGRAM

0066	5-Methoxy-N,N-diisopropyltryptamine.HCl	9-SD
0067	Phenylpiperazine oxalate	9-SD
0068	2,5-Dimethoxy-4-(n)-propyl-thiophenethylamine.HCl	9-SD

NOTES FOR TABLES 2 - 9

Salt forms are shown. Rounded numbers are used (2 significant figures); precise values and details of the procedures are given in the VCU, UM, and Stimulant Depressant reports (Aceto *et al.*, 2005; Woods et al., 2005; France et al., 2005). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained. NTI = naltrindole (delta antagonist); norBNI = norbinaltorphimine (kappa antagonist); β–FNA = β-funaltrexamine (mu antagonist).

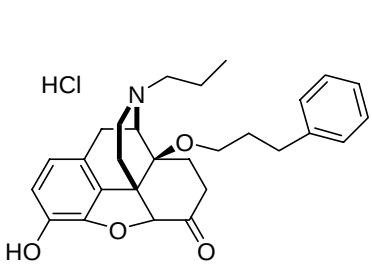
1) Antinociceptive reference data:
Morphine ED_{50} (mg/kg): Hot Plate = 0.8; Phenylquinone = 0.23; Tail-Flick = 5.8; Tail-Flick Antagonism vs. morphine (naltrexone AD_{50} = 0.007; naloxone AD_{50} = 0.035).

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

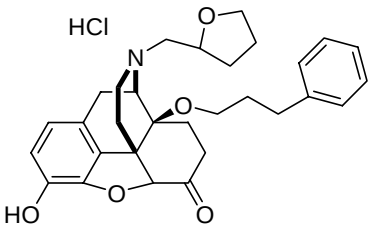
[^{35}S]GTPγS functional data were obtained with the recombinant receptors described above. Values are given as EC_{50} with % stimulation compared to the standard full agonist (DAMGO, SNC80, U69,593), or the maximum stimulation achieved: μ (ED_{50}) morphine = 65 nM (100% stimulation), DAMGO = 34 nM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

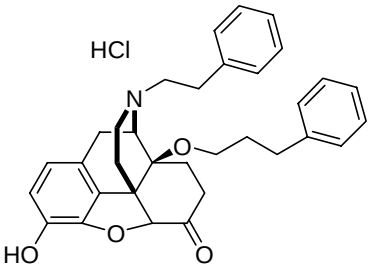
TABLE 2. 14-PHENYLPROPYL SUBSTITUTED MORPHINANS AND 4,5-EPOXYMORPHINANS



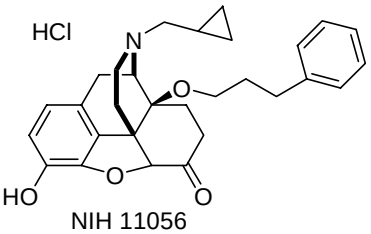
NIH 11053



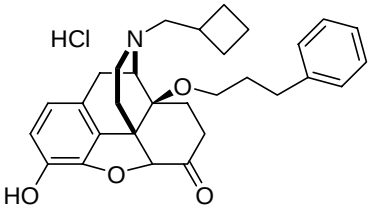
NIH 11054



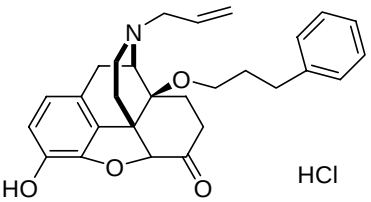
NIH 11055



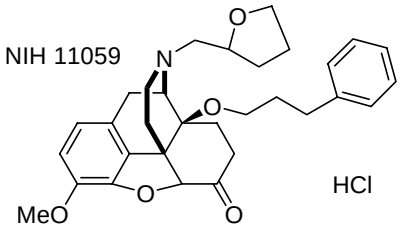
NIH 11056

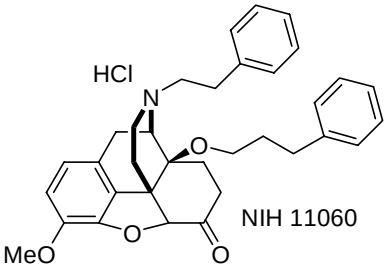


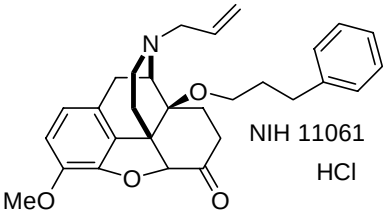
NIH 11057



NIH 11058







	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)
11053	0.0017	0.0009[a]	0.0016[b]	Inactive	μ=0.09, δ=0.93, κ=0.37	-
11054	0.0013	0.0017[c]	0.007[d]	Inactive	μ=0.20, δ=0.09, κ=0.08	-
11055	0.012	0.0094[e]	0.11	Inactive	μ=1.1, δ=1.25, κ=0.60	-
11056	0.0023	0.0062	0.0032	Inactive	–	Complete substitution for morphine at 0.04
11057	0.0037	0.0003[f]	0.0082	Inactive	μ=0.25, δ=0.46, κ=0.49	-
11058	0.0059	g	0.0056	Inactive	μ=0.20, δ=0.26, κ=0.11	-
11059	0.06[h]	0.0063[h]	0.084[h]	Inactive	μ=1.9, δ=5.4, κ=1.4	-
11060	0.68	i	0.76	Inactive	μ=3.8, δ=6.2, κ=61	-
11061	-	-	-	-	μ=1.7, δ=16, κ=4.1	-

a) Straub tail at 0.003 mg/kg. Subtype testing vs. ED_{80} of NIH 11053: β-FNA (mu) AD50 = 6.4 μg/brain; nor-BNI (kappa) 73% at 30 mg/kg; naltrindole (delta) inactive.

b) Clonic convulsions at 10 mg/kg (2/6 died); increased locomotor activity at 1 mg/kg.

c) Straub tail at 0.01 mg/kg.

d) Increased locomotor activity and clonic convulsions at 1 mg/kg. Naloxone vs. NIH 11054 in TF: AD_{50} = 0.14 mg/kg.

e) Straub tail, hyperactivity, and ataxia at 1 mg/kg.

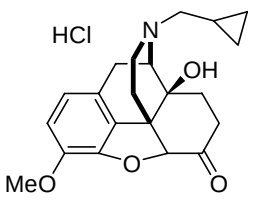
f) Straub tail, ataxia, and increased locomotion.

g) Non-dose related antinociception; Straub tail and increased locomotor activity at 1 mg/kg.

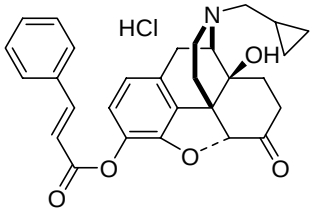
h) Straub tail in all rodent assays. Naloxone vs. NIH 11059 in TF: AD_{50} = 0.026 mg/kg.

i) Non-dose related antinociception; Straub tail noted.

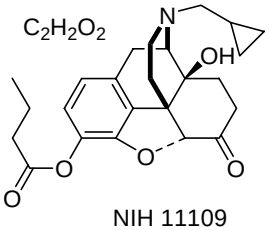
TABLE 3. NALTREXONE ANALOGS



NIH 11028



NIH 11037



NIH 11109

	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)
11028	Inactive[a]	-	Inactive[a]	0.47[a]	μ=31, δ=590, κ=95[a]	Exacerbated withdrawal at 4 and 16.[b]
11037	Inactive[c]	Inactive[c]	Inactive[c]	0.013[c,d]	μ=18, δ=385, κ=31[c]	Precipitated withdrawal at 0.03 and 0.15[c]
11109	Inactive[e]	Inactive[e]	Inactive[e]	0.0029[e,f]	μ=3.1, δ=63, κ=3.5[e]	Exacerbated withdrawal at 0.1.[f]

a) Reported previously (Coop, 2002, 2004). Tail flick: NIH 11028 vs. ED_{80} of: enadoline (kappa agonist) AD_{50} = 5.4 mg/kg; sufentanyl (mu agonist) AD_{50} = 0.12 mg/kg; DPDPE (delta agonist) AD_{50} = 1.8 mg/kg. NIH 11028 (p.o.) vs. ED_{80} of morphine in tail flick: AD_{50} = 2.3 mg/kg.

b) New data.

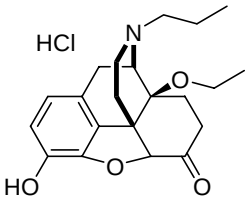
c) Reported previously (Coop, 2002). NIH 11037 vs. ED_{80} of enadoline (kappa) AD_{50} = 0.20 mg/kg; Four hour pretreatment study: Naloxone vs. morphine AD_{50} = 1.92 mg/kg; NIH 11037 vs. morphine AD_{50} = 2.69 mg/kg.

d) New data: NIH 11037 vs. ED_{80} of DPDPE (delta, i.c.v.) inactive. Time course of NIH 11037 vs. morphine in tail flick: 20 minutes pretreatment, 70% antagonism; 2 hour pretreatment, 63% antagonism; 4 hours pretreatment, 2% antagonism.

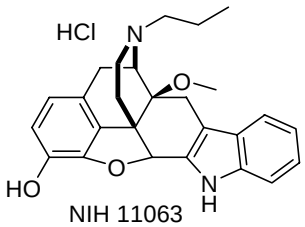
e) Reported previously (Coop, 2004).

f) New data: time course in tail flick vs. morphine, loss of activity after four hours.

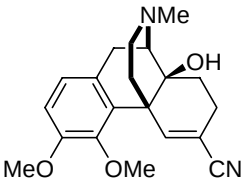
TABLE 4. MORPHINANS AND 4,5-EPOXYMORPHINANS



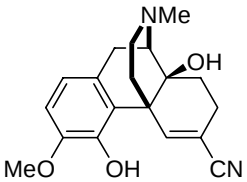
NIH 11062



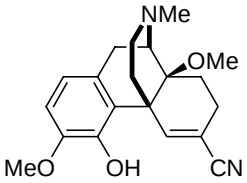
NIH 11063



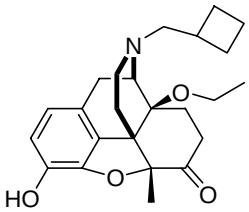
NIH 11065



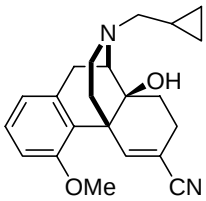
NIH 11066



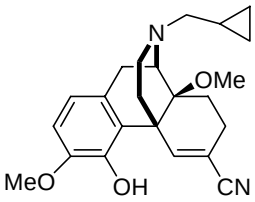
NIH 11067



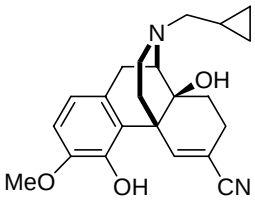
NIH 11068



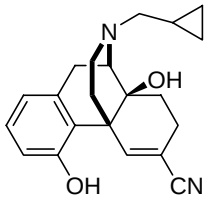
NIH 11072



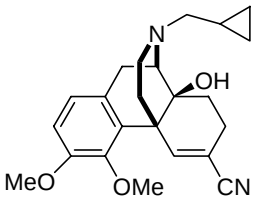
NIH 11073



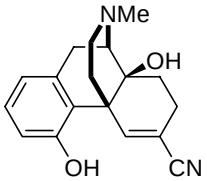
NIH 11074



NIH 11075



NIH 11076



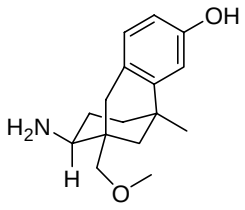
NIH 11077

	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)	GTPγS Functional Assays (EC_{50} and stimulation or K_e)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11062	0.062[a]	0.0022[a]	0.074[a]	Inactive	μ=1.6, δ=70, κ=6.1	-	-
11063	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=270, δ=1.1, κ=110[b]	μ,κ,δ: no agonist stimulation. Antagonism of SNC80 (δ): K_e=0.24 nM	-
11065	0.15	0.026	0.018	Inactive	μ=12, δ=240, κ=380	-	Complete substitution at 0.1
11066	0.50	0.18	1.88	Inactive	μ=261, δ=3400, κ=4200	-	Complete substitution at 3
11067	0.25	0.11	0.21	Inactive	μ=22, δ=1000, κ=1500	-	Complete substitution at 0.3 and 1.2
11068	0.20	0.091	0.19	Inactive	μ=0.47, δ=31, κ=6.1	-	-
11072	Inactive	Inactive	Inactive	2.8	μ=69, δ=2100, κ=93	-	-

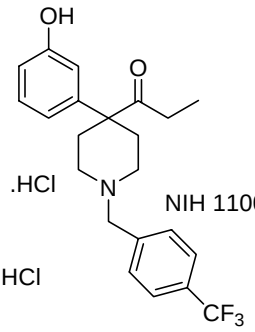
11073	Inactive	2.4	8.0	Inactive	μ=240, δ=1600, κ=410	-	-
11074	Inactive	5.8	14	Inactive	μ=380, δ=4900, κ=370	-	-
11075	Inactive[c]	1.5[c]	8.65	Inactive	μ=23, δ=410, κ=12	-	-
11076	Inactive	Inactive	Inactive	5.5	μ=41, δ=1100, κ=49	-	-
11077	0.38	0.13	0.43[d]	Inactive[e]	μ=3.8, δ=420, κ=410	-	-

a) Straub tail in all assays suggest mu agonism. Potency estimated to be 100 times greater than morphine.
b) Previously reported (Coop, 2003).
c) Rapid and heavy breathing; one convulsed and died in antiwrithing assay.
d) Straub tail noted. Naloxone vs. ED_{80} of NIH 11077 AD_{50} = 0.06 mg/kg; naltrindole (delta) vs. ED_{80} of NIH 11077 inactive.
e) Ataxia and increased locomotor activity at 30 mg/kg.

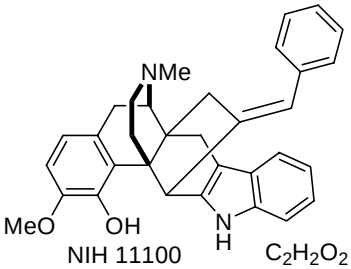
TABLE 5. MISCELLANEOUS DRUGS



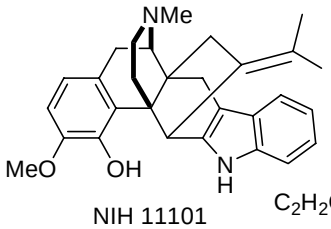
NIH 10945



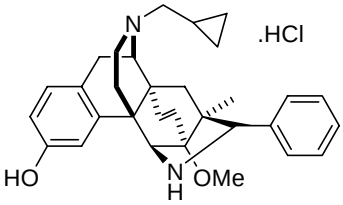
NIH 11001



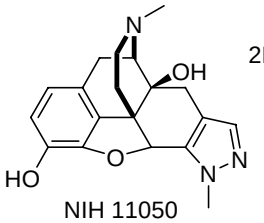
NIH 11100 $C_2H_2O_2$



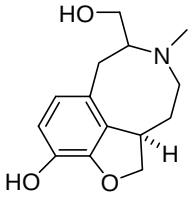
NIH 11101 $C_2H_2O_2$



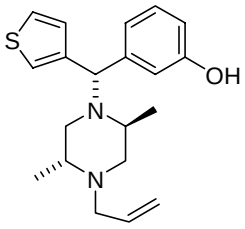
NIH 11031



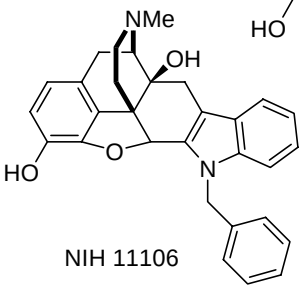
NIH 11050



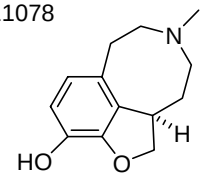
NIH 11078



NIH 11161



NIH 11106



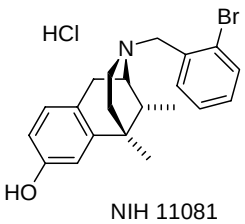
NIH 11079

	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)	GTPγS Functional Assays (EC_{50} and stimulation or K_e)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
10945	Inactive[a]	3.75[a]	Inactive[a]	Inactive[a]	μ=3.7, δ=160, κ=6.3[a]	μ EC_{50} = 151 nM (60%); κ EC_{50} = 66 nM (74%)	Partial suppression[a]
11001	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=33, δ=290, κ=120[b,c].	μ,κ,δ: no agonist stimulation. Antagonism of μ: K_e = 520 nM	No substitution[b]
11031	0.31[d]	0.018[d]	0.37[d]	Inactive[d]	μ=0.35, δ=0.95, κ=0.08[d]	μ: no stimulation; κ EC_{50} = 0.36 nM (76%); δ EC_{50} = 108 nM (35%)	Neither substitutes nor exacerbates withdrawal[d]
11050	-	-	-	-	μ=24, δ=23, κ=160[e]	μ EC_{50} = 150 nM (89%); κ EC_{50} = 250 nM (19%); δ EC_{50} = 300 nM (27%)	-
11078	-	-	-	-	μ, δ, κ>10,000		-
11079	-	-	-	-	μ, δ, κ>10,000		-

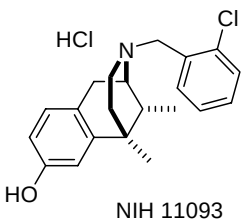
11100	-	-		-	μ=42, δ=30, κ=60[i]	μ: no stimulation; κ EC_{50} = 2100 nM (64%); δ EC_{50} = 460 nM (41%)	-
11101	-	-	-	-	μ=270, δ=150, κ=160[f]	μ EC_{50} = 2100 nM (64%); κ and δ no stimulation	-
11106	-	4.6[g]	-	-	–	-	-
11161	-	-	-	-	–	-	Reinforcing effects in primates: 30-fold less potent and 30% less effective than alfentanyl.

a) Previously reported (Coop, 2002).
b) Previously reported (2001)
c) Binding assays at mu performed in buffer with guanine nucleotides and sodium gave a K_i of 220 nM.
d) Previously reported (2004). Subtype testing in tail flick vs. ED_{80} of NIH 11031: β-FNA (mu) inactive; nor-BNI (kappa) AD_{50} = 8.5 mg/kg; naltrindole (delta) inactive. Timecourse: Delayed mu and kappa antagonism; peaks at 48 hours, dissipated at 72 hours. Long term signs of jaw sag, ptosis, and ataxia in primate.
e) Previously reported (Coop, 2003).
f) Previously reported (Coop, 2004).
g) Previously reported (Coop, 2003). Antagonism of ED_{80} of SNC80 in antiwrithing: inactive s.c. and i.c.v. New data: Naloxone vs. ED_{80} of NIH 11106 in antiwrithing AD_{50} = 0.02 mg/kg.

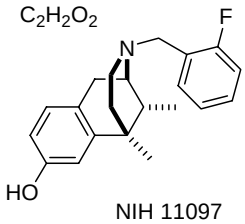
TABLE 6a. (-)-6,7-BENZOMORPHANS



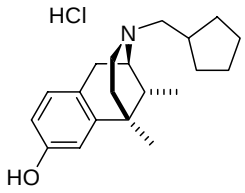
NIH 11081



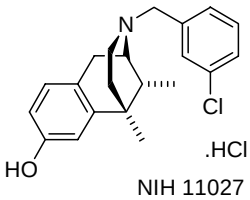
NIH 11093



NIH 11097



NIH 11114



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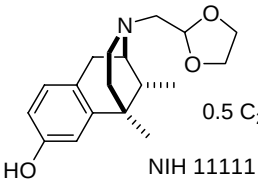
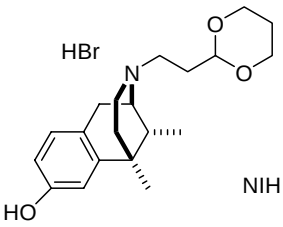
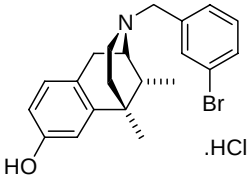


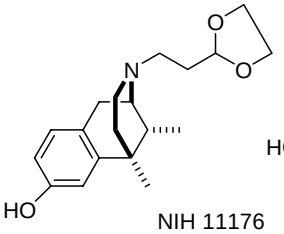
NIH 11111



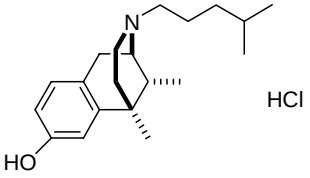
NIH 11167



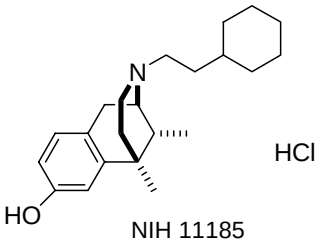
NIH 11041



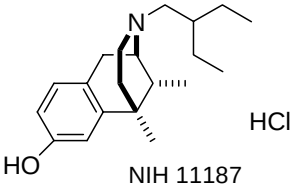
NIH 11176



NIH 11179



NIH 11185



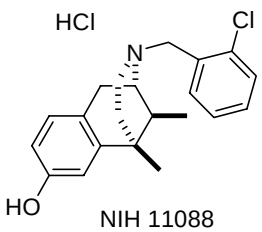
NIH 11187

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)	GTPγS Functional Assays (EC_{50} and stimulation or K_e)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11027	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=25, δ=1360, κ=11[a]	μ,κ,δ: no stimulation; Antagonist assays: μ K_e = 35 nM, κ K_e = 23 nM.	Non-dose related exacerbation of withdrawal[a]
11041	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=48, δ=1330, κ=10[a]	μ,κ,δ: no stimulation	Neither substituted nor exacerbated withdrawal at 4 and 16.[a]

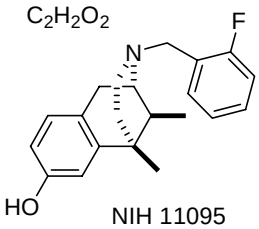
11081	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=40, δ=1200 κ=14[b]	μ,κ,δ: no stimulation	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[b]
11093	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	μ=17, δ=600, κ=18[b]	μ,κ,δ: no stimulation	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[b]
11097	Inactive[b]	Inactive[b]	Inactive[b,c]	Inactive[b]	μ=23, δ=330 κ=2.1[b]	μ,κ,δ: no stimulation; antagonist assays: μ K_e = 97 nM, κ K_e =17 nM	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[b]
11111	Inactive[b]	1.9[b,d]	Inactive[b,d]	0.2[b]	–	-	Neither substituted nor exacerbated withdrawal at 0.15 and 0.6
11114	Inactive[b]	7.0[b,e]	Inactive[b]	2.4[b]	μ=0.8, δ=8.3, κ=0.2[b,e]	μ: no stimulation; κ EC_{50} = 11 nM (50%); δ EC_{50} = 250 nM (18%); antagonist assays: μ K_e = 2.4 nM	-
11167	Inactive	5.5	Inactive	Inactive	μ=20, δ=58, κ=67[b]	-	-
11176	Inactive	Inactive	Inactive	Inactive	μ=27, δ=53, κ=42	-	Attenuated withdrawal signs at 3 and 12
11179	Inactive	2.7	10	Inactive	μ=6.0, δ=60, κ=7.3	-	Tremors and convulsions prevented assessment
11185	8.5[f]	1.2[f]	3.0[f]	Inactive	μ=4.3, δ=43, κ=51	-	Attenuated withdrawal signs at 1.5 and 6
11187	Inactive[g]	1.4[g]	2.2[g]	Inactive	μ=9.2, δ=58, κ=5.9	-	Substituted for morphine at 1 and 4.[g]

a) Previously reported (Coop, 2003).
b) Previously reported (Coop, 2004).
c) New data: tail flick (i.c.v.) ED_{50} = 15 μg/brain; NIH 11097 vs. ED80 of enadoline (kappa) in tail flick inactive.
d) New data: norBNI (kappa) vs. ED_{80} of NIH 11111 in antiwrithing inactive; ED_{80} of NIH 11111 vs. DPDPE in TF AD_{50} = 0.27 mg/kg.
e) New data: norBNI (kappa) vs. ED_{80} of NIH 11114 in antiwrithing inactive.
f) Straub tail and increased locomotor activity noted.
g) Straub tail and ataxia in rodents; Slowing, ataxia, eyelid ptosis, and jaw sag in monkeys.

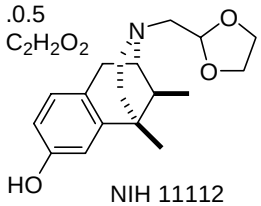
TABLE 6b. (+)-6,7-BENZOMORPHANS



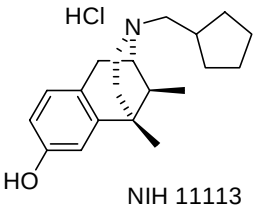
NIH 11088



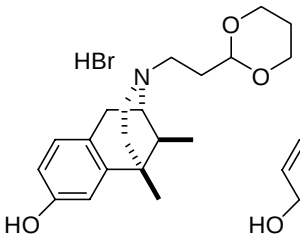
NIH 11095



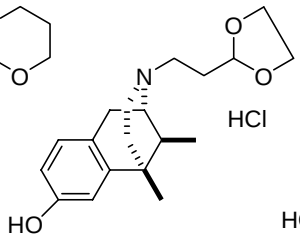
NIH 11112



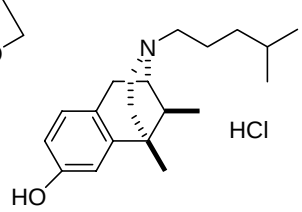
NIH 11113



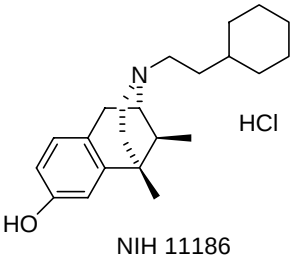
NIH 11168



NIH 11177



NIH 11178



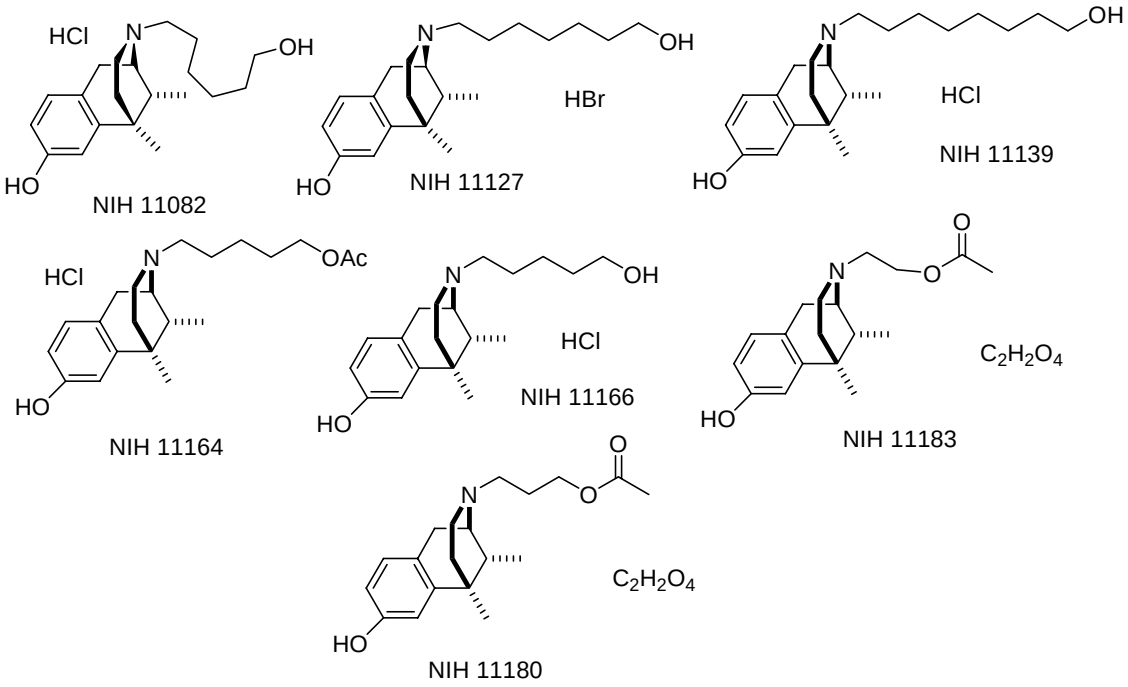
NIH 11186

	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)	GTPγS Functional Assays (EC_{50} and stimulation or K_e)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11088	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=140, δ=3600, κ=23[a]	μ,κ,δ: no stimulation	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[a]
11095	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=560, δ=4100, κ=47[a]	μ,κ,δ: no stimulation	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16[a]
11112	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=480, δ=1100, κ=190[a]	-	Neither substituted for morphine nor exacerbated withdrawal at 4 and 16
11113	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	μ=33, δ=610, κ=3.5[a]	-	-
11168	Inactive	Inactive	Inactive	Inactive	μ=1900, δ>10,000, κ=540[a]	-	-
11177	-	-	-	-	μ=670, δ=8700, κ=640	-	-
11178	-	-	-	-	μ=610, δ=6100, κ=260	-	-

11186	Inactive	18	Inactive	Inactive	μ=140, δ=2800, κ=220		No effects on withdrawal signs at 4. At 16, one monkey convulsed

a) Previously reported (Coop, 2004)

TABLE 7a. (-)-6,7-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)	GTPγS Functional Assays (EC_{50} and stimulation or K_e)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11082	Inactive[a]	1.93[a,b]	Inactive[a,b]	Inactive[a]	μ=10, δ=140, κ=29[a]	μ EC_{50} = 300 nM (51%); κ EC_{50} = 1300 nM (22%); δ EC_{50} = 560 nM (9%).	Brief attenuation of withdrawal at 16
11127	Inactive[c]	2.9[c]	20[c]	Inactive[c]	μ=4.6, δ=200, κ=36[c]		Non-dose related attenuation of withdrawal signs
11139	Inactive	4.4	Inactive	Inactive	μ=5.8, δ=35, κ=8.8[c]		Attenuated some withdrawal signs at 3 and 15[d]
11164	Inactive	8.4	Inactive	Inactive	μ=15, δ=140, κ=55		-
11166	Inactive	Inactive	Inactive	Inactive	μ=33, δ=300, κ=260[c]		-
11180	Inactive	Inactive	Inactive	Inactive	μ=34, δ=290, κ=25		Precipitated withdrawal at 2 and 8[e]
11183	Inactive	10	Inactive	8.8	μ=43, δ=420, κ=60		Exacerbated withdrawal at 4 and 16

a) Previously reported (Coop, 2003). Naltrindole (delta) vs. ED_{80} of NIH 11082 in antiwrithing AD_{50} = 0.75 mg/kg.

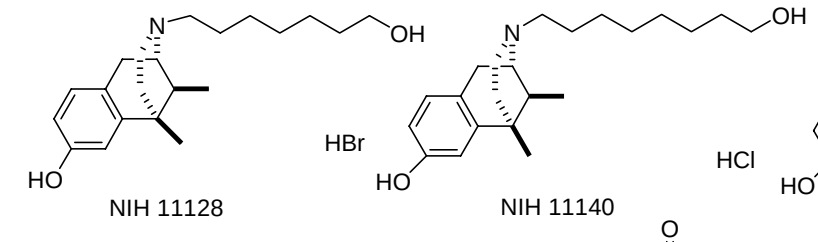
b) New data: norBNI (kappa) vs. ED_{80} of NIH 11082 in antiwrithing inactive; β-FNA (mu) vs. ED_{80} of NIH 11082 in antiwrithing inactive. Timecourse in antiwrithing 77% at 20 minutes, 26% at 1 hour. Effects additive with morphine in antiwrithing; no additive effects with morphine in tail flick.

c) Previously reported (Coop, 2004)

d) Did not block vocalization nor rigidity (mu effects).

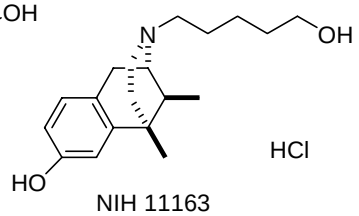
e) Eyelid ptosis, slowing, and ataxia noted.

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

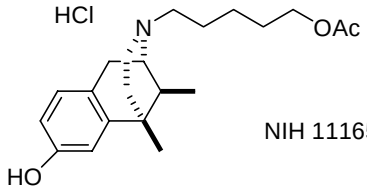


NIH 11128

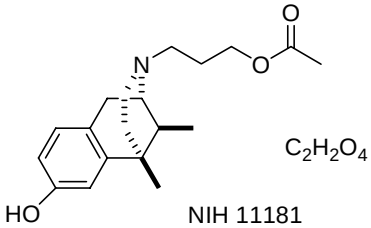
NIH 11140



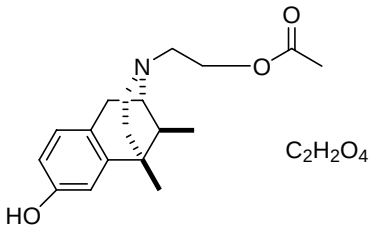
NIH 11163



NIH 11165



NIH 11181

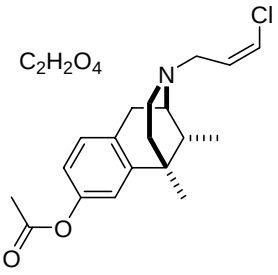


NIH 11182

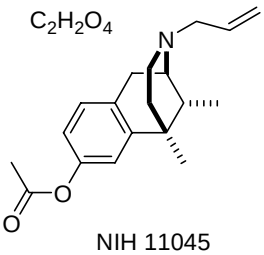
	MOUSE ANTINOCICEPTIVE ASSAYS				*IN VITRO*	MONKEY
NIH #	Hot Plate (ED_{50}, s.c., mg/kg)	Phenylquinone (ED_{50}, s.c., mg/kg)	Tail Flick (ED_{50}, s.c., mg/kg)	Tail Flick Antagonist (AD_{50}, s.c., mg/kg)	Binding Affinity, (K_i, nM)	Studies in Morphine Dependen Monkeys (s.c., mg/kg)
11128	-	-	-	-	μ=900, δ=5800, κ=1800	-
11140	Inactive	Inactive	Inactive	Inactive	μ=140, δ=200, κ=450	Neither substituted nor exacerbated withdrawal at 4 and 16
11163	-	-	-	-	μ,δ,κ>10,000	-
11165	Inactive	Inactive	Inactive	Inactive	μ=1400, δ=>10,000, κ=830[a]	-
11181	Inactive	Inactive	Inactive	Inactive	μ=4500, δ=>10,000, κ=4100	Attenuation of withdrawal at 4 and 16
11182	Inactive	4.7	Inactive	Inactive	μ=2000, δ=>10,000, κ=1800	No effects in SDS at doses up to 8

a) Previously reported (Coop, 2004)

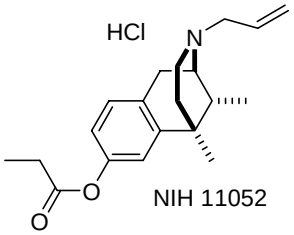
TABLE 8. OPIOID ESTERS



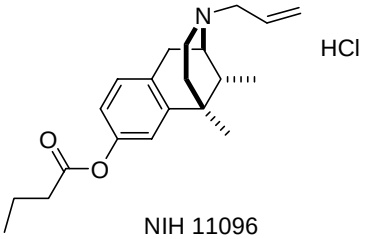
NIH 11044



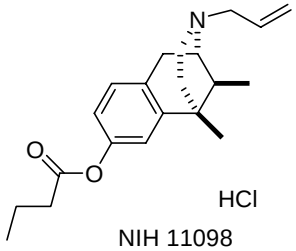
NIH 11045



NIH 11052



NIH 11096



NIH 11098

	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)	GTPγS Functional Assays (EC_{50} and stimulation or K_e)	Studies in Morphine Dependent Monkeys (s.c., mg/kg)
11044	Inactive[a]	10.5[a]	Inactive[a]	0.24[a]	μ=15, δ=17, κ=3.0[a]	μ,δ: no stimulation; κ EC_{50} = 23 nM (51%)	Slowing, eye-lid ptosis, jaw sag[a]
11045	Inactive[b]	Inactive[b]	Inactive[b]	1.35[b]	μ=136, δ=96, κ=29[b]	μ,δ: no stimulation; κ EC_{50} = 130 nM (46%)	Slowing, eye-lid ptosis, jaw sag[b]
11052	-	-	-	-	μ=110, δ=91, κ=8.0[a]	μ,κ: no stimulation; δ EC_{50} = 150 nM (37%)	-
11096	Inactive[c]	Inactive[c]	Inactive[c]	0.29[c]	μ=30, δ=37, κ=0.9[c]	μ EC_{50} = 920 nM (11%), κ EC_{50} = 66 nM (74%)	Precipitated withdrawal; potency equal to naloxone[c]
11098	Inactive[a]	9.6[a]	Inactive[a]	Inactive[a]	μ=600, δ=3100, κ=1700[a]	μ EC_{50} = 950 nM (17%), κ: no stimulation	Attenuated withdrawal at 2 and 8

a) Reported previously (Coop, 2003).

b) Reported previously (Coop, 2003). AD_{50} of NIH 11046 vs. ED80 of enadoline (kappa) = 2.7 mg/kg.

c) Reported previously (Coop, 2004). Antagonism testing in tail flick vs. morphine – non-selective.

TABLE 9. OPIOID PEPTIDES

AcTyr-Lys-Trp-Trp-Le-Arg-Arg-D-Ala-Arg-Pro-Lys-NH_2	NIH 11086
AcPhe-Phe-Phe-Arg-Leu-Arg-Arg-D-Ala-Arg-Pro-Lys-NH_2	NIH 11087
(D)-Phe-N-piperonyl-Gly-(D)Nle-(D)Arg-NH_2	NIH 11089
(D)-Phe-(D)Nal-(D)Nle-NLys-NH_2	NIH 11090
NhPhe-(D)Phe-(D)Nle-(D)Arg-NH_2	NIH 11091
N-Pentyl-Gly-(D)Phe-(D)Nle-(D)Arg-NH_2	NIH 11092

	MOUSE ANTINOCICEPTIVE ASSAYS (I.C.V.)				***IN VITRO***	**MONKEY**
NIH #	Hot Plate (ED_{50}, i.c.v., 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)
11086	Inactive[a]	Inactive[a]	Inactive[a]	Inactive[a]	–	-
11087	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	–	-
11089	Inactive[c]	Inactive[c]	2.5 μg/brain	Inactive	–	-
11090	Inactive	17 μg/brain[d]	0.29 μg/brain	Inactive[d]	–	-
11091	Inactive[e]	2.1 μg/brain[e]	Inactive[e]	Inactive	–	-
11092	Inactive	0.85 μg/brain	0.14 μg/brain	Inactive	–	-

a) Severe effects noted: hot plate (30 μg/brain) - tremors and whirling; antiwrithing unable to test higher doses; tail flick (30 μg/brain) tremors and sedation.

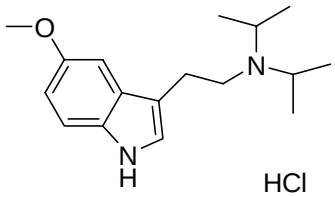
b) Severe CNS effects noted: hot plate (3 mg/kg) - convulsions/death/ immobile; antiwrithing unable to test higher doses due to convulsions at 3; tail flick (10 mg/kg) immobility and loss of righting reflex.

c) Insufficient drug for full analysis in hot plate and antiwrithing - highest dose was 3 μg/brain

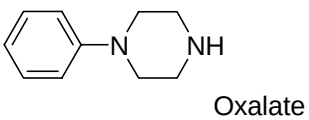
d) Antiwrithing: clonic extensions, hunched backs, convulsions, and rigidity; tail flick vs. morphine: convulsions, hunched back, rigidity.

e) Sedation in all mice at 10 μg/brain, 3/8 moved in circles.

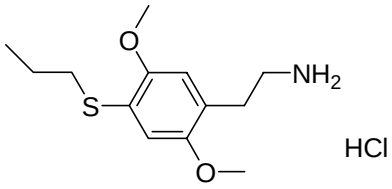
TABLE 10. COMPOUNDS EVALUATED BY STIMULANT DEPRESSANT PROGRAM



CPDD 0066



CPDD 0067



CPDD 0068

	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)
0066	Shares no discriminative stimulus effects with either flumazenil or midazolam	No self-administration up to 0.3 mg/kg/inj	No amphetamine discriminative stimulus effects up to 10 mg/kg. At 17 mg/kg seizures were evident	LSD-like responding at 3 mg/kg	5-HT_{1A} = 7.4 5-HT_{2A} = 5.3 5-HT_{2C} = 5.8
0067	Shares no discriminative stimulus effects with either flumazenil or midazolam	No self-administration up to 0.3 mg/kg/inj	-	No significant LSD-like responding	5-HT_{1A} = 6.5 5-HT_{2A} = 5.1 5-HT_{2C} = 5.6
0068	Shares no discriminative stimulus effects with either flumazenil or midazolam	No self-administration up to 0.3 mg/kg/inj[a]	No amphetamine discriminative stimulus effects up to 3 mg/kg[b]	LSD-like responding at 1 mg/kg	5-HT_{1A} = 5.9 5-HT_{2A} = 6.9 5-HT_{2C} = 7.4

a) In the drug elicited head twitch response, CPDD-0068 acts as an agonist at 5-HT_2 receptors in the mouse with similar potency and effectiveness as the phenylisopropylamine hallucinogens DOM and DOI.

b) A dose of 3 mg/kg was behaviorally active, with the subjects calm and staring

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