BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XXVI. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2002)

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THE DRUG EVALUATION COMMITTEE (DEC)

Dr. A. Coop has held the position of Biological Coordinator of DEC since 1999. The duties of the Biological Coordinator involve receiving samples for evaluation, and distributing them blind to the relevant pharmacological groups within DEC. All data are received by the Biological Coordinator who maintains a confidential database, and forwards data to the submitters. Dr. Coop (UMB) is the fourth DEC Biological Coordinator (the other were Drs. N. Eddy, E. May, and A. Jacobson). 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), and three stimulant/depressant testing groups, at the University of Mississippi (UMS, Dr. W. Woolverton), University of Texas Health Science Center San Antonio (UTHSCSA, Drs. C. France, L. McMahon), and UM (Drs. G. Winger, J. Woods). Drs. T. Cicero and A. Jacobson act as emeritus members. DEC reports to the CPDD's 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 NIDA staff, attend DEC's meeting held during the Annual Scientific Meeting of the CPDD. One other DEC meeting was held in Baltimore in May 2002 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, to discuss the results obtained from the VCU testing and research program.

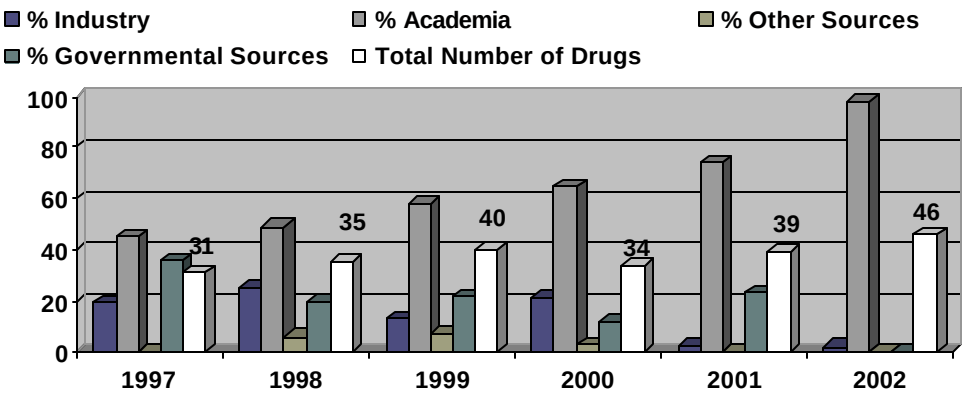
Data were released for publication this year on 46 different compounds evaluated by DEC's Analgesic Testing Program (Figure 1). Of these, 41 compounds were evaluated at VCU (antinociceptive assays in mice - tail flick, hot plate, and phenylquinone, and the tail-flick antagonist assay, as well as substitution for morphine and precipitated withdrawal assays in rhesus monkeys), and 37 at UM (binding affinity to the μ, δ, and κ opioid receptors, and GTPγS functional studies). Compounds came primarily from academia. The remaining compound came from 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 industry and governmental sources correspondingly decreasing. Four new submitters from academic institutions have provided compounds this year. Discussions between the Chair of DEC and governmental agencies have led to the anticipation that compounds from governmental sources will increase in future years as well. Two compounds which are metabolic precursors to gamma-hydroxybutyric acid (GHB) were released for publication this year by the groups in the Stimulant/Depressant Testing Program.

A joint publication based on the data gathered under DEC auspices from VCU, UM, and UMB, is currently in preparation (May *et al.*, 2002).

EXPERIMENTAL OBSERVATIONS

The names of the compounds that were released for publication this year are listed in Tables 1 and 2, and their molecular structures and a summary of their *in vivo* and *in vitro* data are in Tables 3 to 11. Similar to previous years (Coop 2002), the examined compounds are classified according to their molecular structure: indolomorphinans in Tables 3, 4, and 5; miscellaneous opioids in Table 6; 6,7-benzomorphans in Tables 7 and 8; esters of naltrexone in Table 9; analogs of gamma-hydroxybutyrate in Table 10. Compounds evaluated by the Stimulant/Depressant Testing Program are shown in Table 11. The more interesting compounds evaluated during the year are discussed below. For compounds that have been previously evaluated, the new data are discussed in relation to the published data.

FIGURE 1. DEC ANALGESIC TESTING PROGRAM: PERCENT AND SOURCE OF EXAMINED DRUGS AND TOTAL NUMBER OF COMPOUNDS (1997-2002)



The delta opioid selectivity (K_i ratio: mu/delta = 45) of the standard delta antagonist naltrindole (**NIH 10589**) in Table 3, is thought to be due to the indolic group (Portoghese *et al.*, 1990), and indeed the pyrazolo derivative **NIH 11050** (Table 3) shows no delta selectivity. Interestingly, **NIH 11063** (Table 3), a naltrindole derivative containing a 14-methoxyl group and an *N*-propyl group, shows enhanced selectivity (K_i ratio: mu/delta = 250). This compound may find great use as a delta selective ligand in pharmacological assays. The related NIH **11064** (Table 3), with an *N*-cyclobutylmethyl group together with a 14-ethoxy and 5-methyl group, possesses equal selectivity as naltrindole, but has ten-fold reduced affinity at delta receptors.

NIH 11069 and **NIH 11070** (Table 4) are also analogs of naltrindole, but containing additional chlorinated aromatic rings. Both compounds proved to possess limited aqueous solubility, and a reliable *in vivo* assessment was not achieved. *In vitro* assays indicated that delta affinity and selectivity has been lost. Thus, the poor aqueous solubility, coupled with the low affinity, implies that such compounds will not find wide pharmacological use.

Table 5 shows *N*'-benzyl analogs of naltrindole. **NIH 11103** has previously been reported to be a long-acting delta antagonist (Korlipara *et al.*, 1994), but with the exception of **NIH 11104**, Table 5 shows that all derivatives display no delta antagonist activity after only 30 minutes, and no compound showed activity at 24 hours. These data show that there is no extended delta antagonism for these compounds, and indeed show little, if any, delta antagonism at all. It should be noted, however, that **NIH 11103** and **NIH 11104** showed toxic actions when administered i.c.v.

NIH 10967 (Table 6) is an amino substituted tetrahydroisoquinoline, which shows potent antinociceptive effects in mice. The lack of opioid receptor binding, coupled with the fact that naloxone did not reverse the antinociception, indicates that these effects are not opioid.

The phenylpiperidine, **NIH 10996** (Table 6) demonstrates high affinity for mu opioid receptors and potent mu antagonism *in vitro*, yet is completely inactive as an opioid agonist or antagonist *in vivo*. This can be attributed to the presence of the acidic function on the *N*-substituent giving a zwitterionic species, thereby limiting transport into the CNS. NIH 10996 is thus an important lead for the development of peripherally restricted morphine antagonists (Schmidt, 2001). Peripherally restricted antagonists are of great interest as they are able to attenuate the severe consipatory effects of morphine in patients treated chronically with morphine, yet will not antagonize the desired analgesic effect.

Oxycodone (**NIH 11107** in Table 6) has been receiving a great deal of interest in both the scientific and non-scientific media, as Oxycontin®, a delayed release formulation containing large dose of oxycodone, has become a drug of choice for opiate abusers because a large dose of oxycodone can be extracted and diverted for illicit purposes (Passik, 2001). NIH 11107 was previously studied by a previous incarnation of this committee in 1958 as NIH 5710, and found to be morphine-like. The current study corroborates these data, showing that NIH 11107 completely substitutes for morphine, and is a selective mu agonist. Therefore, it is not surprising that oxycodone has found favor among opiate abusers.

A series of halogen substituted *N*-benzyl benzomorphans is shown in Tables 7a and 7b. It has been previously reported that *N*-benzyl substituted benzomorphans display poor *in vivo* and *in vitro* opioid activity (May *et al.*, 1998), and the (+)-isomers tend to follow the same trend. It should be noted, however, that **NIH 11088** (Table 7b) has an unusually high affinity at kappa receptors (23 nM) for a (+)-opioid. The (-)-isomers in Table 7a are further examples of opioids possessing high affinity at mu and kappa receptors, yet no activity *in vivo*. **NIH 11097**, for example, possesses an affinity of 2.1 nM at kappa and 23.3 nM at mu receptors, yet fails to exert antinociceptive effects or morphine antagonism *in vivo*. The lack of kappa activity could be explained by the compound possessing low kappa efficacy, but the lack of *in vivo* mu activity is puzzling. As with NIH 10996, the *N*-benzyl substituted benzomorphans may be peripherally restricted, but there is no group in NIH 11097 which would be anticipated to prevent transport into the CNS. Further studies are required to investigate this intriguing profile.

(+)-Phenazocine (**NIH 11040**, Table 7b) is one of the few opioid (+)-isomers that is known to possess significant antinociceptive activity *in vivo*. A re-evaluation of NIH 11040 confirms a profile of antinociceptive activity in the mouse, but it does not substitute for morphine in dependent monkeys. The side-effects of slowing and jaw sag may suggest kappa agonist activity, which is consistent with NIH 11040 displaying higher affinity to kappa, than mu and delta receptors.

A series of *N*-allyl substituted benzomorphans are shown in Tables 8a and 8b. As expected the (+)-isomers in Table 8b display low affinity for opioid receptors, and little opioid activity in *in vivo* assays. The attenuation of withdrawal seen with **NIH 11043** and **NIH 11051** is probably a consequence of the non-opioid effects of these compounds masking withdrawal signs. **NIH 11032** and **NIH 11038** (Table 8a) both possess a methyl ether which can be metabolized to the more active phenol. NIH 11032 is active as a morphine antagonist in the mouse, but not in the monkey, whereas NIH 11038 is a weak morphine antagonist in the monkey, but is less active than NIH 11032 in the mouse. **NIH 11045** and **NIH 11096** (Table 8a) are esters corresponding to the methyl ether NIH 11038, and will be rapidly metabolized to the active phenol. As expected, morphine antagonism was observed in the mouse, but the assessment of NIH 11045 in the monkey was complicated by non-opioid CNS effects.

The esters of naltrexone (**NIH 11083** and **NIH 11084**, Table 9) would be expected to be rapidly metabolized to the active 3-phenols. NIH 11084 only contains a 3-ester, and the active metabolite would be naltrexone. NIH 11083 contains an additional ester group at the 14-position which would undergo metabolism far more slowly, making the active metabolite 14-acetoxynaltrexone which would be expected to possess greater lipophilicity than naltrexone. Thus, the greater morphine antagonist activity of NIH 11084 as compared to NIH 11083 can be rationalized in terms of it producing an active metabolite of greater lipophilicity and, therefore, greater CNS penetration.

The rise in recreational use and abuse of gamma-hydroxybutyrate (GHB) has led DEC to fully study the activity of this compound in previous years (1998, 2001). The scheduling of GHB has led to an increase in the use of metabolic precursors of GHB such as 1,4-butanediol (1,4-BDL) and gamma-butyrolactone (GBL) (Bernasconi *et al.*, 1999), and DEC has taken the lead in evaluating the activity of the precursors. 1,4-BDL has been evaluated by the analgesic group as **NIH 11030** (Table 10) and by the stimulant depressant group as **CPDD 0060** (Table 11). GBL has been reevaluated by the analgesic group as **NIH 11094** (Table 10) and by the stimulant depressant group as **CPDD 0061** (Table 11).

The activity of both compounds were very similar, with no activity in the analgesic assays, and little activity in the stimulant and depressant assays. It shoul d be noted that in the pentobarbital discrimination assay severe sedation was observed at 300 mg/kg. These data reinforce the hypothesis that GHB acts through a yet to be determined mechanism of action, and underscores the need for the development of new and robust assays for evaluating the behavioral effects of GHB-like compounds.

TABLE 1. EVALUATED COMPOUNDS - ANALGESIC TESTING PROGRAM

NIH#	COMPOUND NAME	TABLE #-Evaluator
10589	Naltrindole.HCl	3-VCU
10967	8-(Ethylmethylamino)-5,6,7,8-tetrahydroisoquinoline.Oxalate	6-VCU/UM
10979	*N*-Cyclohexylethylnoroxymorphindole.HCl	3-UM
10996	(+)-2-[2(*S*)-Benzyl-3-[4(*R*)-(3-hydroxphenyl)-3(*R*),4-dimethylpiperidin-1-yl]propion-amido]acetic acid	6-VCU/UM
11011	(+)-(1*S*,5*S*,9*S*)-2-(Cyclohexylmethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU
11012	(-)-(1*R*,5*R*,9*R*)-2-(Cyclohexylmethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU
11027	(-)-(1*R*,5*R*,9*R*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11029	(+)-(1*S*,5*S*,9*S*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11030	1,4-Butanediol (1,4-BDL)	10-VCU/SD
11032	(-)-(1*R*,5*R*,9*R*)-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan.oxalate	8-VCU/UM
11033	(+)-(1*S*,5*S*,9*S*)-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan.oxalate	8-VCU/UM
11036	(+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11038	(-)-(1*R*,5*R*,9*R*)-5,9-dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11039	(+)-(1*S*,5*S*,9*S*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11040	(+)-Phenazocine.HBr	7-VCU/UM
11041	(-)-(1*R*,5*R*,9*R*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11042	(+)-(1*S*,5*S*,9*S*)-2'-Acetoxy-2-(3-*cis*-chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan.oxalate	8-VCU/UM
11043	(+)-(1*S*,5*S*,9*S*)-2'-Acetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11044	(-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-2-(3-*cis*-chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan.oxalate	8-VCU/UM
11045	(-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11050	17-Methyl-6,7-didehydro-3,14-dihydroxy-4,5α-epoxy-[(2-methyl)-pyrazolo-[6,7]]-morphinan.2HCl	3-UM
11051	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-propenyl)-2'-propionoxy-6,7-benzomorphan.HCl	8-VCU/UM
11052	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-propenyl)-2'-propionoxy-6,7-benzomorphan.HCl	8-UM

11063	4,5α-Epoxy-14β-methoxy-17-(propyl)indolo[2',3':6,7]morphinan-3-ol.HCl	3-VCU/UM
11064	17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-5β-methylindolo[2',3':6,7]morphinan-3-ol.HCl	3-UM
11069	1'-(2,6-Dichlorobenzyl)-14β-[(2,6-dichlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo[2',3':6,7]morphinan-3-ol.HCl	4-VCU/UM
11070	1'-(3-Chlorobenzyl)-14β-[(3-chlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo[2',3':6,7]morphinan-3-ol.HCl	4-VCU/UM
11080	(+)-(1*S*,5*S*,9*S*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11081	(-)-(1*R*,5*R*,9*R*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11082	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphanHCl	8-VCU/UM
11083	3,14-Diacetoxynaltrexone.oxalate	9-VCU/UM
11084	3-Propionylnaltrexone.oxalate	9-VCU/UM
11085	(+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl	8-VCU/UM
11088	(+)-(1*S*,5*S*,9*S*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11093	(-)-(1*R*,5*R*,9*R*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11094	gamma-Butyrolactone (GBL)	10-VCU
11095	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate	7-VCU/UM
11096	(-)-(1*R*,5*R*,9*R*)-2'-Butyroxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	8-VCU/UM
11097	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate	7-VCU/UM
11098	(+)-(1*S*,5*S*,9*S*)-2'-Butyroxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	8-VCU/UM
11103	1'-Benzylnaltrindole	5-VCU
11104	1'-Benzy-17-cyclopropylmethyl-14-hydroxy-4'-phenyl-[2',3':6,7]-pyrrolomorphinan	5-VCU
11105	1'-Benzyl-4,5,6,7-tetrahydronaltrindole	5-VCU
11106	1'-Benzyl-4,5,6,7-tetrahydrooxymorphindole	5-VCU
11107	Oxycodone.HCl	6-VCU/UM
11148	Oxymorphone.HCl	6-UM

TABLE 2. EVALUATED COMPOUNDS - STIMULANT/DEPRESSANT TESTING PROGRAM

CPDD#	COMPOUND NAME	TABLE #-Evaluator
0060	1,4-Butanediol (1,4-BDL)	11-S/D Group
0061	gamma-Butyrolactone (GBL)	11-S/D Group
0062	Melatonin	11-S/D Group

NOTES FOR TABLES 3 - 9

Salt forms are not shown. Rounded numbers are used; precise values and details of the procedures are given in the VCU, UM, and stimulant depressant reports (Aceto *et al.*, 2003; Woods and Traynor, 2003, McMahon and France, 2003). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained. HP = hot plate assay; PPQ = phenylquinone antiwrithing assay; TF = tail flick assay; NTI = naltrindole (delta antagonist); norBNI = norbinaltorphimine (kappa antagonist); β–FNA = β-funaltrexamine (mu antagonist).

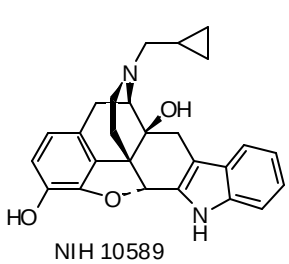
1) Antinociceptive reference data:
Morphine ED_{50} (mg/kg): Hot Plate = 0.8; Phenylquinone = 0.23; Tail-Flick = 5.8; Tail-Flick Antagonism vs. morphine (naltrexone AD_{50} = 0.007; naloxone AD_{50} = 0.035).

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

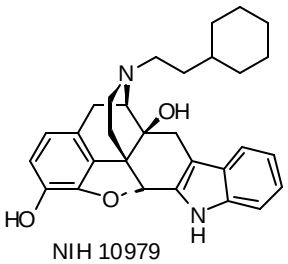
[^{35}S]GTPγS functional data were obtained employing recombinant receptors as described above. Values are given as EC_{50} with % stimulation compared to the standard full agonist (DAMGO, SNC80, U69,593), or the maximum stimulation achieved. μ (ED_{50}) morphine = 65 nM (100% stimulation), DAMGO = 34 nM (100% stimulation); δ (ED_{50}) SNC80 = 9 nM (100% stimulation), DPDPE = 8.3 nM (60% stimulation); κ (ED_{50}) U69,593 = 31 nM (100% stimulation), bremazocine = 0.5 nM (86% stimulation).

References to previous Drug Evaluation Committee annual reports are shown in parentheses, and refer to the actual year of publication.

TABLE 3. INDOLOMORPHINANS



NIH 10589



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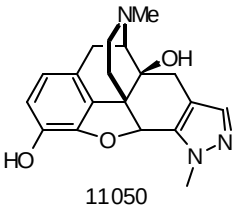

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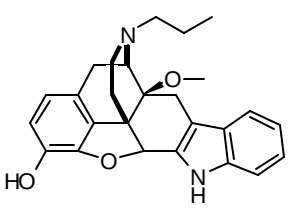
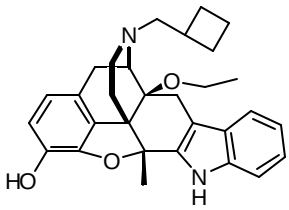


11063



11064

	ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg)				IN VITRO	MONKEY
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
10589[a,b]	-	Inactive[a]	Inactive[a]	Inactive[a]	μ=9.5, δ=0.21, κ=20.4[a]	Exacerbates withdrawal[a]
10979[d]	2.42[c]	0.39[c]	3.86[c]	-	μ=7.3, δ=181, κ=378[c]	-
11050	-	-	-	-	μ=23.9, δ=22.7, κ=157	-
11063	Inactive	Inactive	Inactive	Inactive	μ=270, δ=1.07, κ=108	-
11064	-	-	-	-	μ=182, δ=3.6, κ=128	-

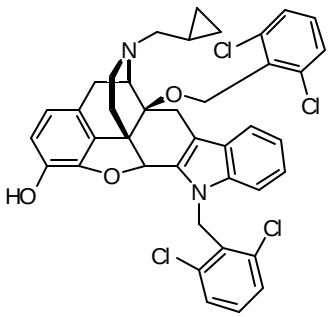
a) Previously reported as NIH 10589 (1990, 2000): pA_2 vs. DSLET = 9.44, pA_2 vs. sufentanyl = 7.71. Previously reported as NIH 10990 (2002) [^{35}S]GTPγS assay: AD_{50} vs. DAMGO = 7.9 nM.

b) New data: NIH 10589 vs. ED_{80} of SNC80 in PPQ: 30 min pretreatment AD_{50} = 1.69; 24 h. pretreatment inactive (s.c. and i.c.v.).

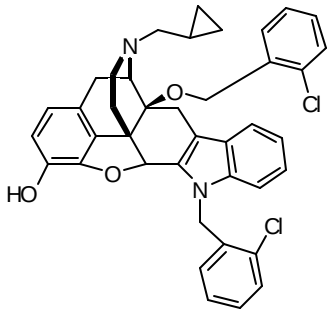
c) Previously reported (2002).

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

TABLE 4. INDOLOMORPHINANS



11069

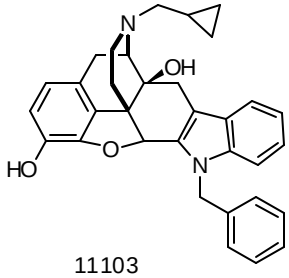


11070

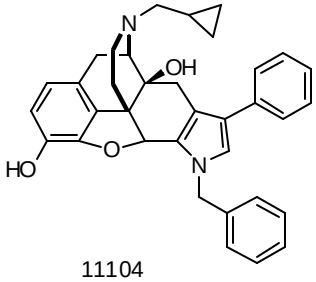
ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg)					IN VITRO	MONKEY
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11069[a]	-	-	-	-	μ=25.2, δ=62.7, κ=254	-
11070[b]	-	-	-	-	μ=192, δ=46.3, κ=627	-

a) Compound is not soluble enough for consistent results *in vivo*.
b) Compound is not soluble enough for consistent results *in vivo*.

TABLE 5. INDOLOMORPHINANS



11103



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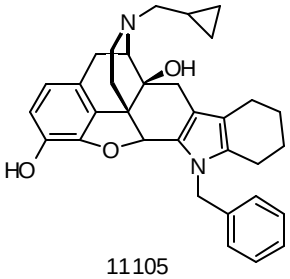

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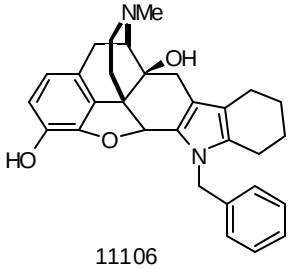


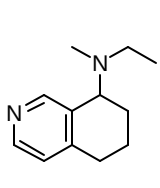
11106

DELTA OPIOID ANTAGONIST ASSAYS
(MOUSE AD_{50}: s.c., mg/kg or i.c.v. mg/brain)

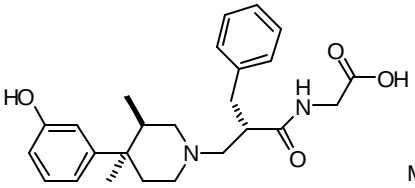
NIH #	Antagonism of SNC80 ED_{80} in PPQ		
	30 min. pretreatment	24 h pretreatment	24 h pretreatment, i.c.v.
11103	Inactive[a]	Inactive	Inactive[b]
11104	4.34	Inactive	Inactive[c]
11105	Inactive	Inactive	Inactive
11106	Inactive	Inactive	Inactive

a) One mouse convulsed at 30 mg/kg (s.c.).
b) Lethal when given i.c.v. prior to SNC80.
c) One mouse died at 10 µg/brain.

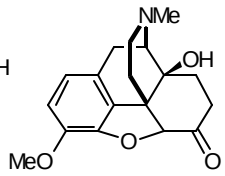
TABLE 6. MISCELLANEOUS OPIOIDS



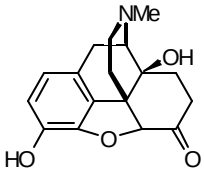
10967



10996



11107



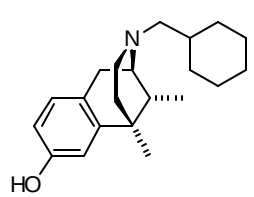
11148

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

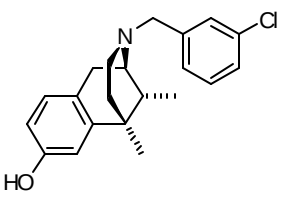
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
10967[a]	0.8	0.37[b]	0.8	Inactive	μ,δ,κ > 10,000	-
10996	Inactive	Inactive[c]	Inactive[d]	Inactive	μ=0.41, δ=235, κ=48.3[e]	No substitution or exacerbation up to 20
11107[f]	1.37	0.38	0.94	Inactive	μ=485, δ>3,000, κ>3,000[g]	Complete substitution for morphine at 0.3[h,i]
11148[j]	-	-	-	-	μ=8.6, δ=50.5, κ=93.5[k]	See footnote[l]

a) Caused lethal convulsions in some mice.
b) Naloxone AD_{50} vs. ED_{80} of NIH 10967 in PPQ: Inactive.
c) 43% inhibition at 30 mg/kg; 69% at 60 mg/kg. Naloxone vs. ED_{69} of NIH 10996 in PPQ: inactive.
d) Inactive both s.c. and oral.
e) [^{35}S]GTPγS assay: no agonist activity at mu, kappa, and delta. Antagonism: mu: AD_{50} = 0.34 nM; kappa AD_{50} = 9.3 nM.
f) Previously published as NIH 5710 (1957) TF = 1.41 mg/kg; LD_{50} = 446.3 mg/kg. Complete substitution for morphine in monkeys. Potential for physical dependence: 1 mg/kg for 31 days followed by abrupt withdrawal gave rise to abstinence syndrome similar to that of morphine.
g) [^{35}S]GTPγS assay: mu EC_{50} = 605 nM (88% stimulation).
h) Timecourse similar to morphine. Partial attenuation of withdrawal signs at 0.03 mg/kg.
i) Respiratory depressant and a strong reinforcer in the monkey.
j) Previously evaluated as NIH 5501 (1956): TF = 0.17 mg/kg; LD_{50} = 182.7 mg/kg.
k) [^{35}S]GTPγS assay: mu EC_{50} = 32.2 nM (91% stimulation).
l) Respiratory depressant and a strong reinforcer in the monkey.

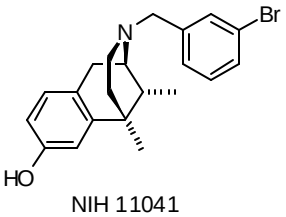
TABLE 7a. (-)-*N*-BENZYL-6,7-BENZOMORPHANS



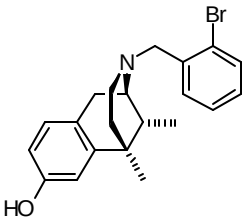
NIH 11012



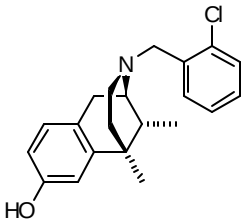
NIH 11027



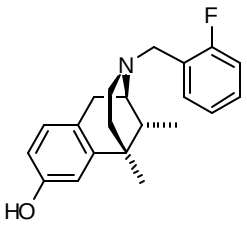
NIH 11041



NIH 11081



NIH 11093



NIH 11097

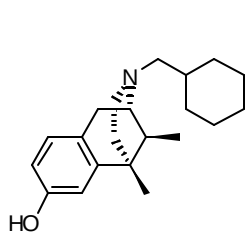
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED_{50}/AD_{50}, s.c., mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11012[a,b]	Inactive[a]	14.62[a]	Inactive[a]	3.7[a]	μ=26, δ=315 κ=13[a]	Neither substituted nor exacerbated withdrawal at 0.75 and 3[a]
11027	Inactive	Inactive	Inactive	Inactive	μ=25.0, δ=1362, κ=11.1	Non-dose related exacerbation of withdrawal
11041	Inactive	Inactive	Inactive	Inactive	μ=47.7, δ=1326 κ=9.9	Neither substituted nor exacerbated withdrawal at 4 and 16
11081	Inactive	Inactive	Inactive	Inactive	μ=40.2, δ=1227 κ=13.5	-
11093	Inactive	Inactive	Inactive	Inactive	μ=16.8, δ=600, κ=17.5	-
11097	Inactive	Inactive	Inactive	Inactive	μ=23.3, δ=326, κ=2.1	-

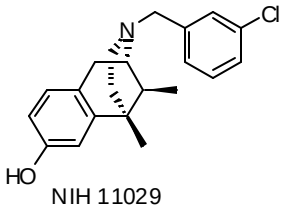
a) Previously reported (2002). Jaw sag noted in the monkey at 3 mg/kg; tremors noted at 12 mg/kg.

b) New data: Antagonism of ED_{80} in PPQ by naltrindole - inactive.

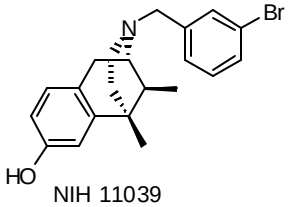
TABLE 7b. (+)-*N*-BENZYL-6,7-BENZOMORPHANS



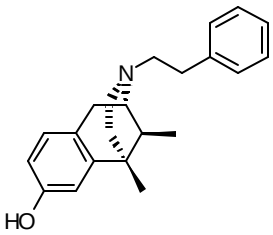
NIH 11011



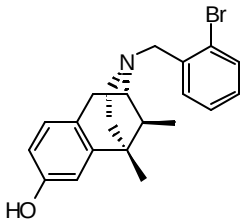
NIH 11029



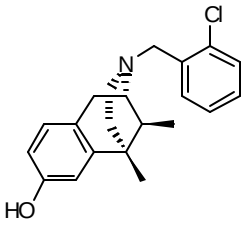
NIH 11039



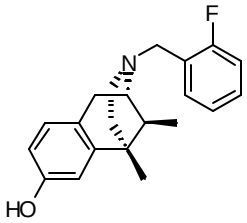
NIH 11040



NIH 11080



NIH 11088



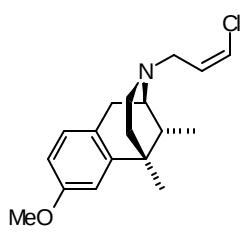
NIH 11095

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

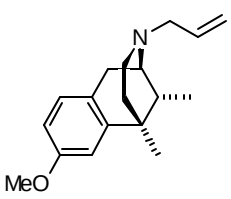
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11011[a,b]	Inactive[a]	17.57[a]	Inactive[a]	Inactive[a]	μ=568, δ=5806, κ=83[a]	Slight attenuation of withdrawal at 4 and 16. Salivation at 4; jaw sag at 16[a]
11029	Inactive	Inactive	Inactive	Inactive	μ=1223, δ=6732, κ=347	Partial attenuation of withdrawal at 4 and 16
11039	Inactive	Inactive	Inactive	Inactive	μ=745, δ=3479, κ=255	Neither substituted nor exacerbated withdrawal at 4 and 16
11040[c]	Inactive	3.4	8.75	Inactive	μ=126, δ=875, κ=61	Neither substituted nor exacerbated withdrawal at 1, 4, and 16.[d]
11080	Inactive	Inactive	Inactive	Inactive	μ=409, δ=1853, κ=52.1	Exacerbation of withdrawal at 16.
11088	Inactive	Inactive	Inactive	Inactive	μ=139, δ=3565, κ=23.3	-
11095	Inactive	Inactive	Inactive	Inactive	μ=560, δ=4129, κ=47	-

a) Previously reported (2002).
b) New data: Antagonism of ED_{80} in PPQ by naltrindole - inactive.
c) Previously reported as NIH 7614 (1961). TF = 6.63 mg/kg; LD_{50} = 200.7 mg/kg.
d) Jaw sag and slowing noted. One monkey convulsed at 1 and 4 mg/kg.

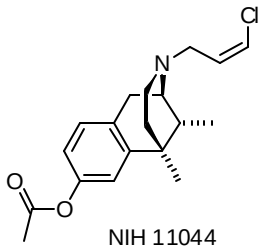
TABLE 8a. (-)-*N*-ALLYL-6,7-BENZOMORPHANS



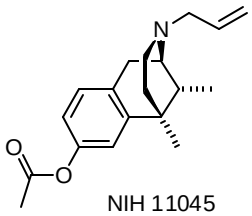
NIH 11032



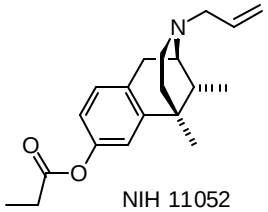
NIH 11038



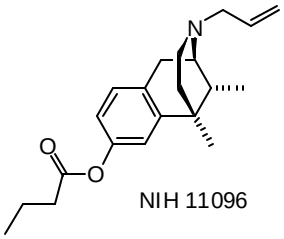
NIH 11044



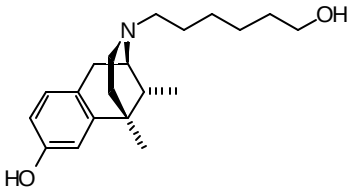
NIH 11045



NIH 11052



NIH 11096



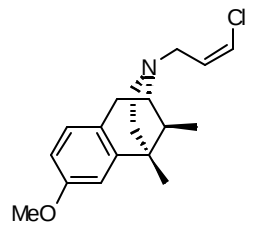
NIH 11082

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

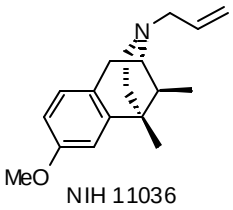
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11032	Inactive	17.43	Inactive	1.08	μ=47.5, δ=105, κ=9.4	Neither substituted for morphine nor exacerbated withdrawal. Some jaw sag and slowing at 5
11038	Inactive	Inactive	Inactive	3.25[a]	μ=417, δ=763, κ=71.9	Exacerbation of withdrawal at 2[b,c]
11044	Inactive	10.50	Inactive	0.24	μ=14.9, δ=17.4, κ=3.0	Appeared to exacerbate withdrawal[c]
11045	Inactive	Inactive	Inactive	1.35	μ=136, δ=96.2, κ=29.2	Appeared to exacerbate withdrawal[c]
11052	-	-	-	-	μ=107, δ=90.7, κ=7.9	-
11082	Inactive	1.93	Inactive	Inactive	μ=10.2, δ=140, κ=28.6	-
11096	Inactive	Inactive	Inactive	0.29[d]	μ=30.2, δ=37.0, κ=0.9	-

a) Data with 30 minute pretreatment. With 4 h pretreatment, AD_{50} = 9.09 mg/kg.
b) Prompt onset of action, with a duration of 2.5h.
c) CNS effects made assessment difficult (slowing, eyelid ptosis, jaw sag).
d) Antagonist potency approx. 0.1x naloxone. Mild ataxia and hyperactivity seen at 30 mg/kg.

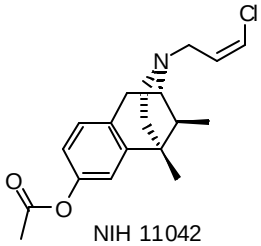
TABLE 8b. (+)-*N*-ALLYL-6,7-BENZOMORPHANS



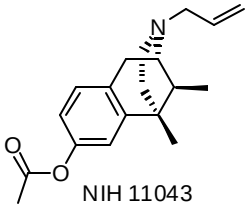
NIH 11033



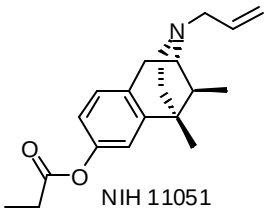
NIH 11036



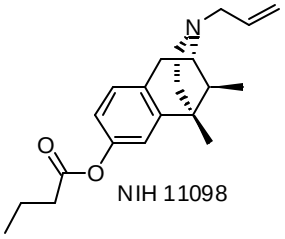
NIH 11042



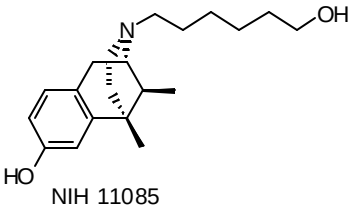
NIH 11043



NIH 11051



NIH 11098



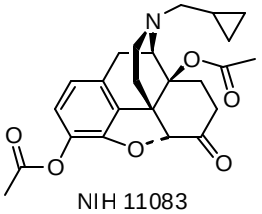
NIH 11085

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

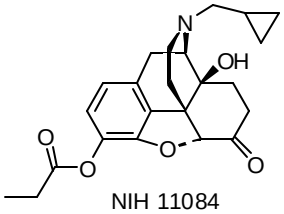
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11033	Inactive	Inactive	Inactive	Inactive	μ=852, δ=1347, κ=296	No significant attenuation at 4 and 16[a]
11036	Inactive	21.6	Inactive	Inactive	μ=>10,000, δ=>10,000, κ=>10,000	Neither substituted nor exacerbated withdrawal at 4 and 16[a]
11042	Inactive	Inactive	Inactive	Inactive	μ=880, δ=1285, κ=196	Neither substituted nor exacerbated withdrawal at 4 and 16[a]
11043	Inactive	8.9	Inactive	Inactive	μ=2727, δ=>10,000, κ=>10,000	Attenuation of withdrawal at 16[a]
11051	Inactive	3.57	Inactive	Inactive	μ=3623, δ=>10,000, κ=4687	Attenuation of withdrawal at 16[a]
11085	Inactive	b	Inactive	Inactive	μ=598, δ=>10,000, κ=1476	-
11098	Inactive	9.6	Inactive	Inactive	μ=601, δ=3099, κ=1712	-

a) Jaw sag and ataxia noted at 16 mg/kg.
b) Erratic dose response

TABLE 9. ESTERS OF NALTREXONE



NIH 11083



NIH 11084

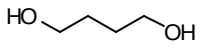
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED_{50}/AD_{50}, s.c., mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11083	Inactive	Inactive	Inactive	0.0037[a]	μ=2.66, δ=134, κ=6.7	-
11084	Inactive	Inactive	Inactive	0.01[b]	μ=1.83, δ=82.3, κ=9.7	-

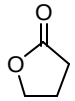
a) Short duration of action: % antagonism of morphine after administration of 0.03 mg NIH 11083: 30 min (88%), 2h (19%), 24h (0%). Potency approx. 10x naloxone.

b) Short duration of action: % antagonism of morphine after administration of 0.04 mg NIH 11084: 30 min (93%), 2h (24%), 24h (0%). Potency approx. equal to naloxone.

TABLE 10. ANALOGS OF GAMMA-HYDROXYBUTYRATE



NIH 11030



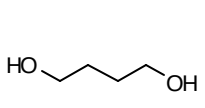
NIH 11094

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

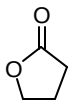
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11030[a]	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	–	Neither substitutes for morphine nor exacerbates withdrawal at 4.5 and 18
11094[c]	Inactive	Inactive	Inactive	Inactive	–	-

a) Also evaluated by stimulant depressant group as CPDD0060.
b) NIH 11030 administered 20 and 60 minutes prior to testing.
c) Also evaluated by stimulant depressant group as CPDD0061. Previously reported as NIH 10540 (1988). TF: Inactive at 96 mg/kg; PPQ: ED_{50} = 7.9 mg/kg. Monkey: Neither substituted for morphine nor exacerbated withdrawal.

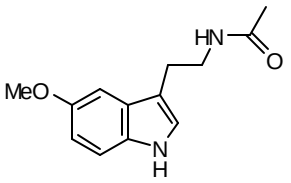
TABLE 11. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD 0060



CPDD 0061



CPDD 0062

CPDD#	Discriminative Stimulus Effects in Monkeys. Comparison to Flumazenil & Midazolam (s.c.)	Monkey Self-Administration (iv)	Monkey Drug Discrimination (i.g.)
0060[a]	No benzodiazepine discriminative stimulus effects	No reinforcing effects in methohexital trained monkeys up to 3.2 mg/kg/inj	No substitution for pentobarbital up to 300 mg/kg. Monkeys sedated and ataxic at 300 mg/kg
0061[b]	No benzodiazepine discriminative stimulus effects	No reinforcing effects in methohexital trained monkeys up to 3.2 mg/kg/inj	No substitution for pentobarbital up to 300 mg/kg. Monkeys sedated and ataxic at 300 mg/kg
0062[c]	No benzodiazepine discriminative stimulus effects	No reinforcing effects in methohexital trained monkeys up to 3.2 mg/kg/inj	-

a) Also evaluated as NIH 11030 (See Table 10).

b) Also evaluated as NIH 11094 (See Table 10). Previously reported as NIH 10540 (1988).

c) Previously evaluated as NIH 10946 by the analgesic testing group (1999): Inactive in rodent and primate assays.

REFERENCES

M. D. Aceto, E.R. Bowman, L.S. Harris, and E.L. May: Dependence studies of new compounds in the rhesus monkey, rat and mouse (2002), in: Problems of Drug Dependence 2002, ed. W. L. Dewey (NIDA Research Monograph, Washington, D.C.), 2003, in press.

R. Bernasconi, P. Mathivet, S. Bischoff, C. marescaux: Gamma-hydroxybutyric acid: an endogenous neuromodulator with abuse potential?. Trends. Pharmacol. Sci., 20: 135-141, 1999.

A. Coop: Biological evaluation of compounds for their physical dependence potential and abuse liability. XXV. Drug Evaluation Committee of the College on Problems of Drug Dependence, Inc. (2001), in: Problems of Drug Dependence 2001, ed. L. S. Harris (NIDA Research Monograph, Washington, D.C), 182: 124-138, 2002.

V. L. Korlipara, A. E. Takemori, and P. S. Portoghese: N-Benzylnaltrindoles as long-acting delta-opioid receptor antagonists. J. Med. Chem., 37: 188-1885, 1994.

E. L. May, A.E. Jacobson, M.V. Mattson, A. Coop, M.D. Aceto, E.R. Bowman J.R. Traynor, J.H. Woods, and L.S. Harris: Synthesis, *in vitro*, and *in vivo* activity of *N*-*p*-substituted-benzyl- (-)- and (+)-*N*-normetazocines, (-)- and (+)-*N*-normorphinans, *N*-norketobemidones, and (-)-*N*-nor-4,5-epoxymorphinans, Med. Chem. Res., 8: 311-321, 1998

E. L. May, A. Coop, J. R. Traynor, J. H. Woods, M. D. Aceto, E. R. Bowman, L. S. Harris: *N*-(Trifluoromethyl)benzyl Substituted *N*-Normetazocines and *N*-Norketobemidones, 2002 (in preparation).

L. R. McMahon, C. P. France, G. Winger, and W. L. Woolverton: Progress report from th e testing program for stimulant and depressant drugs (2002), in: Problems of Drug Dependence 2002, ed. W. L. Dewey (NIDA Research Monograph, Washington, D.C.), 2003, in press.

S. D. Passik: Responding rationally to recent reports of abuse/diversion of Ox ycontin®. 21: 359-360, 2001.

P. S. Portoghese, M. Sultana, and A. E. Takemori: Design of peptidomimetic delta opioid receptor antagonist using the message-address concept. J. Med. Chem., 33: 1714-1720, 1990.

W. K. Schmidt: Alvimpan (ADL-8-2698) is a perip heral opioid antagonist, Am. J. Surg., 182: S27-S38, 2001.

J. H. Woods, M. -C. Ko, G. Winger, C. P. France, and J. Traynor: Evaluation of new compounds for opioid activity (2002), in: Problems of Drug Dependence 2002, ed. W. L. Dewey (NIDA Research Monogr aph, Washington, D.C.), 2003, in press.

ACKNOWLEDGEMENT

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