

BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XXII. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (1998)

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PURPOSES OF THE DRUG EVALUATION COMMITTEE (DEC)

The organizational structure and functions of DEC evolved as the College on Problems of Drug Dependence (CPDD) developed over the past ca. 70 years. The CPDD traces its origin to a 1929 Committee on Drug Addiction in the National Research Council of the National Academy of Sciences (NAS) (Acker 1995; Eddy 1973; May and Jacobson 1989). The precursor of the contemporary Drug Evaluation Committee (DEC) might be considered the pharmacology research component of that early NAS committee. Dr. Nathan Eddy was initially assigned, by the 1929 NAS Committee, to direct that pharmacology component at the University of Michigan (UM). Eddy moved to the National Institutes of Health (NIH) in about 1940; over the next several decades he held many positions in the CPDD. In fact, if not in name, he acted as the Biological Coordinator for the various university and governmental groups involved in the testing programs and research on analgesics until 1967, when Dr. Everette May at the NIH assumed the role of coordinator (Jacobson 1997). I have been the Biological Coordinator from late 1976 to date; during which time the CPDD became the College on Problems of Drug Dependence. The separation of the activities of DEC from those of CPDD occurred slowly, and DEC is now an independent group of researchers under the sponsorship of the CPDD, involved with the research and testing of analgesic, stimulant and depressant classes of drugs for their physical dependence potential and abuse liability.

The history of the CPDD and DEC have been placed online in the CPDD's home page by Dr. Ronald Wood (New York University Medical Center) and the Electronic Communications Subcommittee of the CPDD (<http://views.vcu.edu/cpdd/>; click on the "Drug Evaluation Committee"), as are my Annual Reports from 1990-1997, and the Analgesic, Stimulant, and Depressant Drug Indices. These Indices are a compilation of the NIH numbers, common names, and some part of the chemical names of all of the drugs which have been evaluated in monkeys at Virginia Commonwealth University (Medical College of Virginia Campus, VCU-MCV) and at UM, as well as those which have been examined by the Stimulant/Depressant groups, and relates the NIH or CPDD numbers assigned to the drugs to the year of the publication of the data obtained with those compounds. Early data (up to 1977) are in NAS published volumes of the CPDD Annual Scientific Meetings and are, unfortunately, out of print, as are many of the NIDA Monographs (from 1978) which contain the later work of the DEC. The CPDD itself published volumes containing the 1977 and 1978 DEC Annual Reports, and these are also not likely to be easily found. Sets of all of these volumes are owned by a few individuals; we are now considering how older DEC data can be made more generally available.

DEC MEMBERS

In order to evaluate the various classes of drugs, the DEC is divided into an Analgesic Testing Group and a Stimulant/Depressant Testing Group. Researchers in two universities are involved with the former and three universities with the latter. The Analgesic Testing Groups are at VCU-MCV in Richmond (Drs. Mario Aceto, Louis Harris, Everette May, and Ed Bowman), and at the University of Michigan Medical School in Ann Arbor (Drs. James Woods, John Traynor, and Gail Winger). The Stimulant/Depressant Testing Groups are at the University of Mississippi Medical School (Dr. William Woolverton), the University of Michigan Medical School (Drs. Gail Winger and James Woods), and at the Louisiana State University Medical Center (Dr. Charles France).

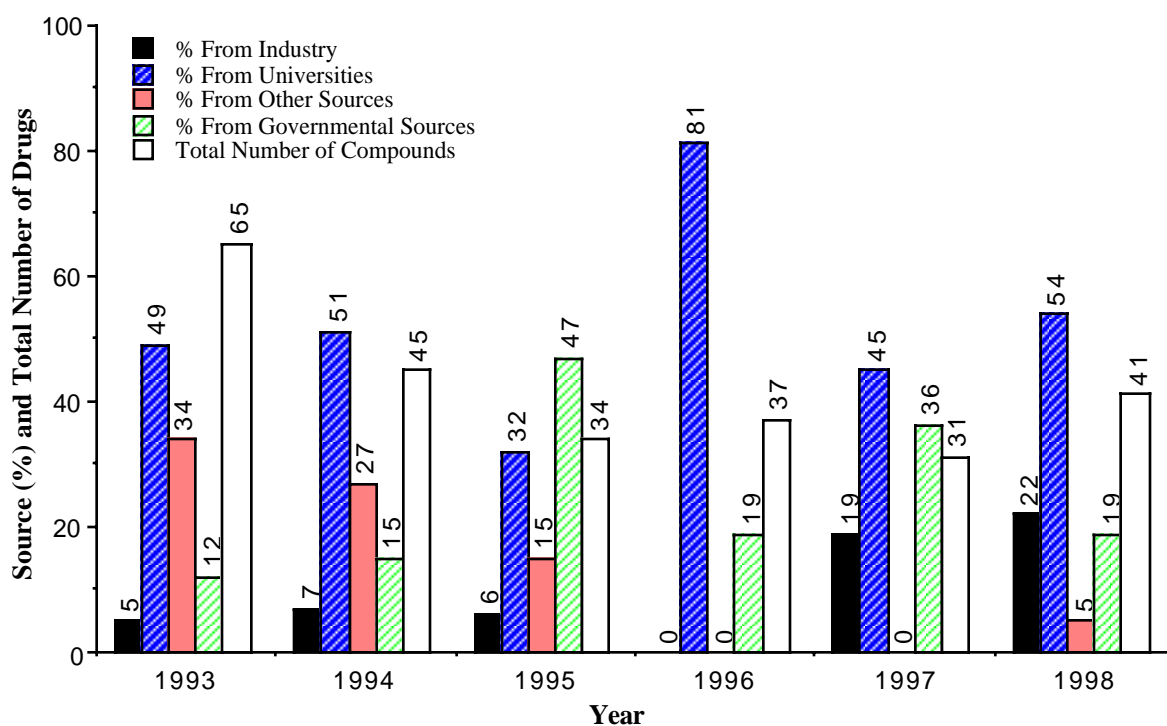
As formerly noted (Jacobson 1998), membership in DEC is available to anyone who has the expertise and resources to carry out drug testing, and who is the principal investigator on a grant or contract. This drug testing must complement or extend existing drug testing programs, and the principal investigator should consider DEC drug testing as a priority for them. Inclusion into DEC is gained by majority vote of the voting members of DEC.

STATISTICS

The source and number of the evaluated analgesics released for publication from 1993 - 1998 can be seen in Fig. 1. In 1998 as in 1997, but unlike the previous several years, pharmaceutical industry was one of the major suppliers of analgesic drugs (22%). Most of the evaluated compounds came from universities (54%); others from governmental sources and a non-profit institute. Data on five (CPDD 0046-0050) of the six compounds examined by the Stimulant/Depressant Testing Groups were requested by the World Health Organization (WHO, a governmental source), and the sixth compound (CPDD 0045) was obtained from pharmaceutical industry.

The total number of compounds evaluated as analgesics which were released for publication this year was considerably greater than the number released for the last several years, as shown in Fig. 1, and there are some interesting drugs among them (see Experimental Observations section).

FIG. 1. DEC ANALGESIC PROGRAM. PERCENT, TOTAL NUMBER, AND SOURCE OF EXAMINED DRUGS (1993-1998)



EXPERIMENTAL OBSERVATIONS

Table 1 relates the chemical or common names and assigned NIH or CPDD numbers of the compounds released this year, and the table in which their molecular structure and their *in vitro* and/or *in vivo* data appear. Tables 2 - 8 present the molecular structures and a summary of the biological activities of compounds evaluated as analgesics, as obtained from work at VCU-MCV, and at UM (Aceto *et al.* 1999; Woods *et al.* 1999), and the work of the Stimulant/Depressant group (Winger *et al.* 1999) is summarized in Table 9. The compounds in Tables 2 - 8 are grouped according to their molecular structure) in order to facilitate recognition of the relationship between their molecular structure and biological activity (e.g., 4,5-epoxymorphinans, morphinans, 6,7-benzomorphans, methadols, and a miscellaneous set of drugs).

In Tables 2 and 3, the DEC work is shown on the 4,5-epoxymorphinans. (-)-Thebaine and (-)-oripavine (NIH 00088 and 09821) were examined for comparison with data which will be obtained with a series of (+)-4,5-

epoxymorphinans. This will be eventually be published as a joint DEC Analgesic Group and NIDDK, NIH, paper.

The structurally interesting thiazalomorphinan, NIH 10888 in Table 2, binds with remarkably high affinity but with little selectivity to opioid receptors; in contrast, the indolomorphinan NIH 10889 (Table 3), a naltrindole-like compound with a C₁₄ alkyl substituent, binds with high affinity and good selectivity to the δ -opioid receptor. The N-benzylmorphine, NIH 10921, was found to be one of the few N-benzyl analogs, of the many which were synthesized in the morphinan, 6,7-benzomorphan, and ketobemidone series, to show agonist or antagonist activity. The complete study of these compounds will be published as a joint DEC Analgesic Group and NIDDK, NIH, paper (May *et al.* 1998). It remains uncertain why N-benzyl substituted compounds are generally inactive when molecularly similar substituents have shown good *in vivo* and *in vitro* activity.

Our binding data [Woods *et al.* 1999] on the well-known BNTX (NIH 10923, Table 2) are in good agreement with that of Nelson's group (Palmer *et al.* 1997; Portoghese *et al.* 1994). Naltriben (NIH 10924, Table 3) (Ohkawa *et al.* 1997; Takemori *et al.* 1992) was also evaluated. We found [Woods *et al.* 1999] that both BNTX and naltriben have good affinity for the δ -opioid receptor, as determined by displacement of [³H]p-CI-DPDPE; BNTX was relatively non-selective, and naltriben was found to have higher affinity and better selectivity ($\mu/\delta = 34$) than BNTX for the δ -opioid receptor. Portoghese *et al.* have reported that naltriben binds with considerably higher affinity to a δ_2 -opioid receptor subtype than to the δ_1 -opioid receptor. Naltriben has agonist activity in the PPQ assay, and both it and BNTX show antagonist activity in the tail flick vs morphine assay; BNTX displays considerably greater potency as an antagonist than naltriben (Aceto *et al.* 1999; Woods *et al.* 1999).

Three azamorphinans were evaluated (Table 4, 10910-10912). The (+)-3-azamorphinan, 10912, had far higher affinity for the μ -receptor than either of the two enantiomeric 2-azamorphinans. The classical morphinans have an hydroxyl group attached to the C₃ position, thus they, like the (+)-3-azamorphinan and unlike the 2-azamorphinans, can be considered electron-rich in that molecular area. The (+)- and (-)-optical rotations for morphinans relate to their absolute configuration such that, with few exceptions, the (-)-opioid enantiomer in the morphinan family is almost always the enantiomer which interacts with opioid receptors, and is the natural product. The absolute configurations of 10910-10912 are not known, insofar as I am aware. Thus, there is no way of knowing which represents the natural or unnatural opioid series. Generally, the (+)-morphinans represent the unnatural series and are relatively inactive as analgesics, compared with their (-)-enantiomers.

The N-cyanoalkyl-substituted 6,7-benzomorphan in Table 5 have, in common with many benzomorphan, high affinity for μ and κ opioid receptors. However, NIH 10861 (Table 5) interacts with δ and κ opioid receptors, not with μ and κ receptors. These compounds will be more fully discussed in a future joint article from researchers at VCU-MCV, UM, and NIDDK. The methadols in Table 6 are, with the exception of 10905 (β -(-)-methadol), good agonists in one or another antinociceptive assay, and all completely substitute for morphine in monkeys. These were examined as potential narcotic treatment medication agents, among other reasons, but their advantage over methadone or LAAM, if any, is not known at this time.

Two of the piperidines in Table 7, 10900-10901, may be pro-drugs for 10902-10903. The latter displayed morphine-like agonist activity. SNC80 (NIH 10815 in Table 7) was further examined for its antinociceptive activity in the mouse tail-flick assay using an icv route of administration. It was found to be inactive up to a dose of 5 μ g/brain. Thus, although it was shown to have high affinity and selectivity for the δ -opioid receptor ($\mu/\delta = 542$), in our hands only the PPQ assay showed its agonist action *in vivo*, and in that assay it was a very weak antinociceptive (ca. one-tenth the activity of morphine).

In Table 9, new work is shown on six compounds evaluated by the Stimulant/Depressant Group (CPDD 0045, 0046, 0047, 0048, 0049, 0050). The procedures used, and the complete data on these compounds, will be published this year in a separate Stimulant/Depressant Group report (Winger *et al.* 1999). Five of these compounds, CPDD 0046-0050, may be subject to critical review for scheduling purposes at an upcoming WHO meeting in Geneva.

Monkeys self-administered the ephedrine enantiomers (CPDD 0047 and 0048), the racemic mixture (CPDD 0046), and (+)-pseudoephedrine (CPDD 0050), but not (-)-pseudoephedrine (CPDD 0049). The latter was tested up to a dose of less than 1.0 mg/kg/inj; larger doses could not be tested because of the insolubility of (-)-pseudoephedrine in water. All of the drugs (CPDD 0046 - 0050) were at least partially amphetamine-like as discriminative stimuli; the racemate and (-)-ephedrine (CPDD 0046 and 0047, respectively) more so than the others. The data indicate that all

of these compounds (CPDD 0046 - 0050) may have some abuse potential, with the possible exception of (-)-pseudoephedrine (CPDD 0049).

There was no drug-appropriate responding in amphetamine or pentobarbital discrimination and rate of lever pressing was not affected by the imidazole CPDD 0045 in Table 9, nor were there benzodiazepine agonist or antagonist effects. However, variable effects were seen in self-administration with methohexital-trained monkeys. It is unlikely that CPDD 0045 will have stimulant or benzodiazepine-like abuse potential, nor as much potential for abuse as methohexital.

TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

NIH#	NAME	TABLE #- Evaluator
00088	(-)-Thebaine hydrochloride	2-MCV
09821	(-)-Oripavine hydrochloride	2-MCV
10815	SNC80	7-MCV
10820	(-)-Eseroline (L)-ascorbate	7-MCV
10861	(-)-2-(2-Cyanoethyl)-5,9 α -dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride	5-MCV/UM
10888	2'-Amino-17-cyclopropylmethyl-6,7-dehydro-3,14-dihydroxy-4,5 α -epoxy-6,7:4',5'-thiazolomorphinan dihydrochloride	2-UM
10889	3-Hydroxy-6,7-didehydro-4,5 α -epoxy-17-methyl-14 β -(3-methyl)butyl-6,7,2',3'-indolomorphinan hydrochloride	3-MCV/UM
10900	11-[4-Hydroxy-4-(3-trifluoromethylphenyl)piperidin-1-yl]-2-methyl-6,11-dihydrodibenz[b,e]oxepine sulfuric acid	7-UM
10901	11-(4-Hydroxy-4-phenylpiperidin-1-yl)-2-methyl -6,11-dihydrodibenz[b,e]oxepine fumaric acid	7-UM
10902	11-[4-Hydroxy-4-(3-trifluoromethylphenyl)piperidin-1-yl]-2-hydroxymethyl-6,11-dihydrodibenz[b,e]oxepine fumaric acid	7-UM
10903	11-(4-Hydroxy-4-phenylpiperidin-1-yl)-2- hydroxymethyl -6,11-dihydrodibenz[b,e]oxepine	7-UM
10904	α -(+)-Acetylmethadol hydrochloride	6-MCV
10905	β -(-)-Methadol hydrochloride	6-MCV
10906	β -(-)-Acetylmethadol hydrochloride	6-MCV
10907	β -(+)-Acetylmethadol hydrochloride	6-MCV
10909	(+)-N-[3-(4'-Fluorobenzoyl)propyl]-3-hydroxymorphinan hydrochloride	4-MCV/UM
10910	(+)-N-Methyl-2-azamorphinan dihydrobromide	4-MCV/UM
10911	(-)-N-Methyl-2-azamorphinan dihydrobromide	4-MCV/UM
10912	(+)-N-Methyl-3-azamorphinan dihydrobromide	4-MCV/UM
10915	(+)-(2 <i>S</i> ,5 <i>S</i> ,9 <i>S</i>)-2-(4-Cyanobutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10916	(-)-(2 <i>R</i> ,5 <i>R</i> ,9 <i>R</i>)-2-(4-Cyanobutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10920	(\pm)-N-Propyl-N-norisonicotine dioxalate	8-MCV/UM
10921	7-Benzylnoroxymorphone hydrochloride	2-MCV/UM
10922	17-Benzylnoroxymorphindole hydrochloride	3-MCV/UM
10923	7- Benzylidene-7-dehydronaltrexone (BNTX) hydrochloride	2-MCV/UM
10924	Naltriben (NTB) methanesulfonate	3-MCV/UM
10925	3-Deoxy-3-methylnaltrindole hydrochloride	3-MCV/UM
10926	(+)-(2 <i>S</i> ,5 <i>S</i> ,9 <i>S</i>)-2-(5-Cyanopentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10927	(-)-(2 <i>R</i> ,5 <i>R</i> ,9 <i>R</i>)-2-(5-Cyanopentyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10928	(-)-N-[3-(4'-Fluorobenzoyl)propyl]-3-hydroxymorphinan hydrochloride	4-MCV/UM

TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP
(CONTINUED)

NIH#	NAME	TABLE #- Evaluator
10929	Anandamide	8-MCV/UM
10930	Hydroxyzine	8-MCV/UM
10934	(-)-(2R,5R,9R)-2-(6-Cyanoethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10935	(+)-(2S,5S,9S)-2-(6-Cyanoethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10937	17-Cyclohexylmethylnoroxymorphone hydrochloride	2-MCV/UM
10938	17-Cyclohexylmethylnoroxymorphindole hydrochloride	3-MCV/UM
10939	(+)-Dihydromorphine hydrochloride	2-MCV/UM
10941	3-Deoxy-3-methyloxymorphindole hydrochloride	3-MCV/UM
10946	Melatonin	8-MCV/UM
10948	Mianserin hydrochloride	8-MCV/UM
CPDD 0045	2-Phenyl-4(5)-[4-((2-pyrimidinyl)-piperazin-1-yl)-methyl]-imidazole dimaleate	9-SD
CPDD 0046	(±)-Ephedrine hydrochloride	9-SD
CPDD 0047	1R,2S(-)-Ephedrine hydrochloride	9-SD
CPDD 0048	1S,2R(+)-Ephedrine hydrochloride	9-SD
CPDD 0049	1R,2R(-)-Pseudoephedrine	9-SD
CPDD 0050	1S,2S(+)-Pseudoephedrine hydrochloride	9-SD

NOTES FOR TABLES 2 - 9

Rounded numbers are used; precise values and details of the procedures are given in the VCU-MCV (Aceto *et al.* 1999) and UM (Woods *et al.* 1999) reports.

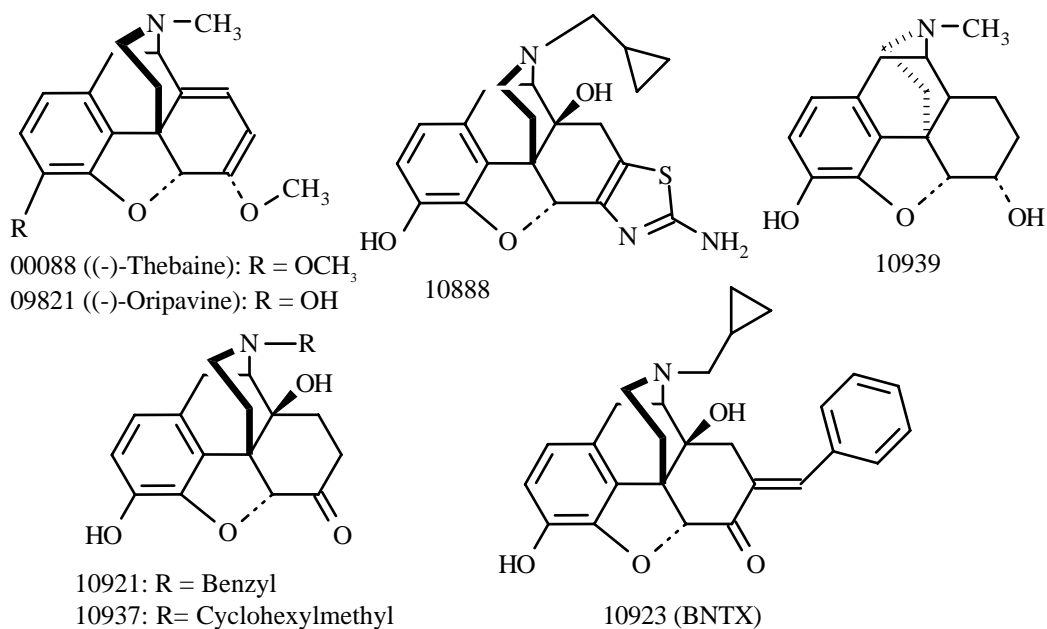
1) Antinociceptive reference data:

Morphine ED₅₀ (confidence limits): Hot Plate = 0.8 (0.3-1.8); Phenylquinone = 0.23 (0.20-0.25); Tail-Flick = 5.8 (5.7-5.9)

Tail-Flick Antagonism vs. morphine (naltrexone AD₅₀ = 0.007 (0.002-0.02); naloxone AD₅₀ = 0.035 (0.01-0.093)).

2) In Vitro - Subtype selective binding affinity using monkey brain cortex membranes. Selectivity for μ , δ , and κ -opioid receptors determined with [³H]-DAMGO, [³H]-*p*-Cl-DPDPE and [³H]-U69,593, respectively. Affinities of labeled ligands: [³H]DAMGO 0.57 nM, [³H]*p*-Cl-DPDPE 1.2 nM, [³H]U69,593 0.95 nM.

TABLE 2. 4,5-EPOXYMORPHINANS



ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED₅₀/AD₅₀, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
00088	-	-	Inactive ^a	-	-	-
09821	1.5 ^b	1.7 ^b	3.0 ^b	Inactive ^b	-	No substitution (0.5-2.0) ^b
10888	-	-	-	-	$\mu=0.16$, $\delta=0.67$, $\kappa=0.61$ ^c	-
10921	Inactive	Inactive	Inactive	0.52	$\mu=138$, $\delta=529$, $\kappa=134$	Exacerbates withdrawal. Dose-dependently precipitates withdrawal in PptW assay
10923	Inactive	Inactive	Inactive ^d	0.05	$\mu=9.1$, $\delta=6.8$, $\kappa=30$	-
10937	Inactive	Inactive	Inactive	11.3	$\mu=13$, $\delta=310$, $\kappa=795$	Partial suppression at relatively high dose ^e
10939	Inactive	Inactive	Inactive	45% @ 3	-	-

a) Convulsions, lethal @ 20, 30 mg/kg. Pretreatment with naloxone or naltrindole does not prevent lethality.

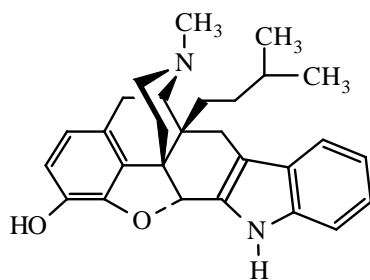
b) Previously reported, 1981. β -FNA (icv) and naltrindole pretreatment indicate μ - δ activity, and lethality not due to μ - δ interaction. Naltrindole AD₅₀ = 4.6.

c) Potent non-selective antagonist in mouse vas deferens assay; highest affinity at μ .

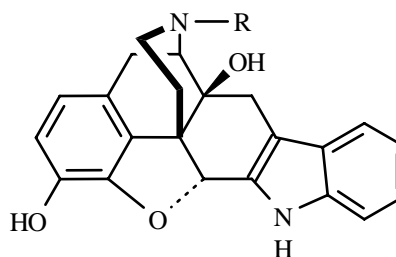
d) Naloxone AD₅₀ = 1.1, DPDPE (icv) AD₅₀ = 0.04, sufentanil (icv) AD₅₀ = 4.0, U69593 AD₅₀ = 27% @ 10 mg/kg.

e) One experiment, supply exhausted.

TABLE 3. 4,5-EPOXYMORPHINANS (CONTINUED)

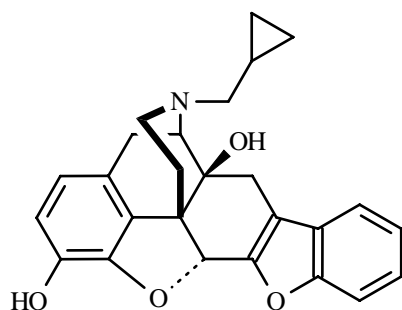


10889

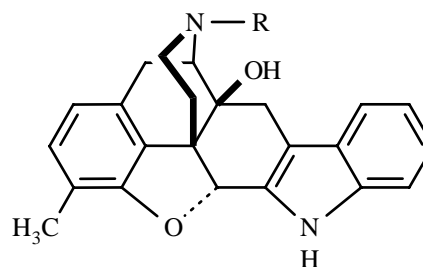


10922: R = Benzyl

10938: R = Cyclohexylmethyl



10924 (Naltriben)



10925: R = Cyclopropylmethyl

10941: R = Methyl

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED₅₀/AD₅₀, sc, mg/kg)

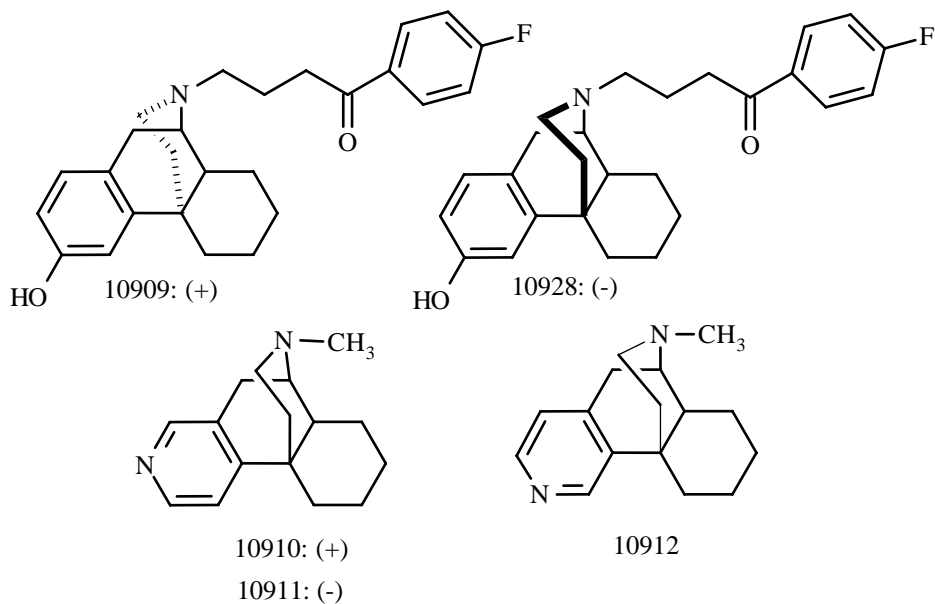
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10889	Inactive	6.7	Inactive	Inactive	$\mu=186$, $\delta=1.4$, $\kappa=204$	-
10922	Inactive	Inactive	Inactive	Inactive	$\mu=5330$, $\delta=115$, $\kappa=1537$	-
10924	Inactive	4.2	Inactive ^{a,b}	0.99	$\mu=12.4$, $\delta=0.36$, $\kappa=17.5$	-
10925	Inactive	Inactive	Inactive	58% @ 30	$\mu=3536$, $\delta=106$, $\kappa=6634$	-
10938	Inactive	Inactive	Inactive	Inactive	$\mu=1925$, $\delta=95$, $\kappa=1115$	Partial suppression ^c
10941	-	-	-	-	$\mu>10000$, $\delta=315$, $\kappa>10000$	-

a) Naltrindole pretreatment did not abolish lethal effects.

b) Convulsions, lethal @ 30 mg/kg.

c) Dose-dependently attenuated withdrawal, but major withdrawal signs persist in 2/3 monkeys.

TABLE 4. MORPHINANS



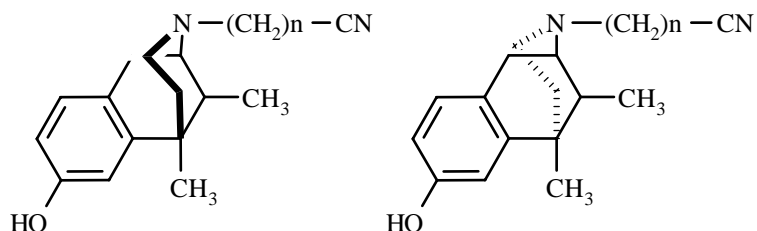
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED₅₀/AD₅₀, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10909	Inactive	0.25	Inactive ^a	Inactive	$\mu=59$, $\delta=>10000$, $\kappa=1227$	Non-dose related attenuation of withdrawal ^b
10910	-	-	-	-	$\mu=2870$, $\delta=>10000$, $\kappa=>10000$	-
10911	-	-	-	-	$\mu=1310$, $\delta=>10000$, $\kappa=>10000$	-
10912	-	-	-	-	$\mu=14.1$, $\delta=971$, $\kappa=344$	-
10928	Inactive	4.5	Inactive	Inactive	-	-

a) sc and iv.

b) Profile does not suggest opioid properties; appears to have CNS depressant effects.

TABLE 5. 6,7-BENZOMORPHANS



10861: n = 2
 10916: n = 4
 10927: n = 5
 10934: n = 6

10915: n = 4
 10926: n = 5
 10935: n = 6

ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED₅₀/AD₅₀, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10861	0.12	0.05	0.3 ^a	Inactive	$\mu=24.5$, $\delta=0.9$, $\kappa=2$	Partial suppression (0.3-3) ^b
10915	Inactive	Inactive	Inactive	Inactive	$\mu=4760$, $\delta=10000$, $\kappa=1260$	Non-dose-related attenuation of withdrawal
10916	Inactive	303	14.6 ^c	Inactive	$\mu=18$, $\delta=160$, $\kappa=6.9$	Complete suppression (3-12), ca. 0.5x morphine
10926	Inactive	Inactive	Inactive	Inactive	$\mu=1167$, $\delta=10000$, $\kappa=512$	-
10927	-	-	-	-	$\mu=91$, $\delta=216$, $\kappa=11$	-
10934	Inactive	9.4	Inactive	Inactive	$\mu=15$, $\delta=350$, $\kappa=38$	Brief substitution @ 3 ^d
10935	Inactive	Inactive	Inactive	Inactive	$\mu=694$, $\delta=10000$, $\kappa=1296$	Non-dose-related attenuation of withdrawal

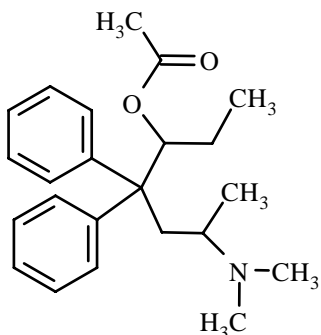
a) TF (icv) = 2.1 μ g/brain (not antagonized); TF (intrathecal, 5 min pretreatment) = 0.09; TF (intrathecal, 20 min pretreatment) = 3.7. Antagonized by nor-BNI and naloxone.

b) Positive reinforcer; abuse liability probably less than heroin.

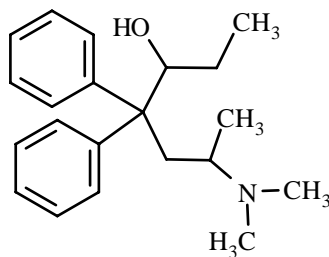
c) Naloxone AD₅₀ = 0.009.

d) Robust, non-significant elevation of cumulative withdrawal score at high dose (12 mg/kg).

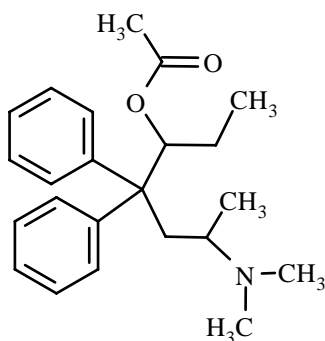
TABLE 6. METHADOLS



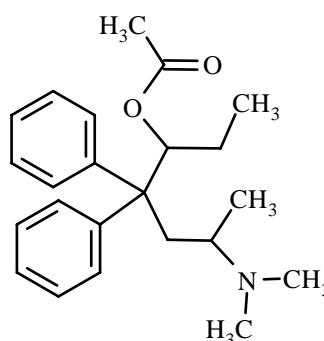
10904: (α-(+)-Acetylmethadol



10905: β-(-)-Methadol



10906: β-(-)-Acetylmethadol



10907: β-(+)-Acetylmethadol

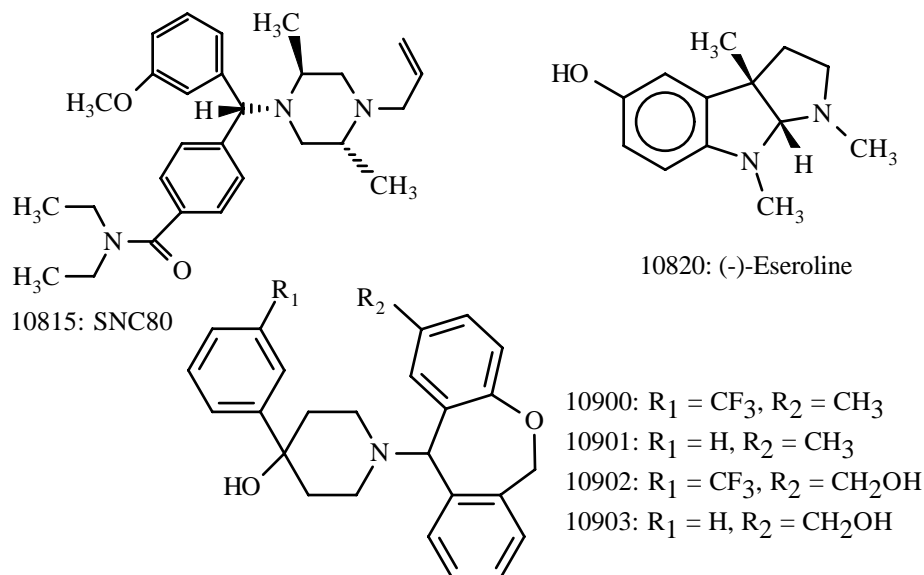
ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED50/AD50, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10904	0.58	0.29	0.59	Inactive	-	CS, ca. 6x morphine
10905	Inactive	Inactive	Inactive	Inactive	-	CS. ca. 0.2x morphine ^a
10906	6.0	1.5	4.3	Inactive	-	CS, morphine-like
10907	0.56	0.11	0.29	Inactive	-	CS, 3-4x morphine ^b

a) Short duration of action.

b) Duration of action at least as long as morphine.

TABLE 7. MISCELLANEOUS



ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED₅₀/AD₅₀, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10815	Inactive ^a	3.8 ^a	Inactive ^{a,b}	Inactive ^a	$\mu=488$, $\delta=0.9$, $\kappa=1170^a$	NS; no exacerbation of withdrawal ^a
10820	3 ^c	0.3 ^c	2.4 ^{c,d}	Inactive ^c	1600 ^{c,e}	CS, ca. morphine-like ^c
10900	Inactive ^f	Inactive ^f	Inactive ^f	Inactive ^f	$\mu=29$, $\delta=967$, $\kappa=935$	Non-dose-related suppression of withdrawal. Possible pro-drug ^f
10901	-	7.6 ^f	Inactive ^f	Inactive ^f	$\mu=69$, $\delta=1292$, $\kappa=327$	CS, 0.2x morphine. Possible pro-drug ^f
10902	0.98 ^f	1.1 ^f	12.9 ^{f,g}	Inactive ^f	$\mu=9.6$, $\delta=1162$, $\kappa=1110$	CS (2,8). Rapid onset, duration of action >2.5 hr
10903	2.2 ^f	0.6 ^f	1.1 ^{f,h}	Inactive ^f	$\mu=11.7$, $\delta=111$, $\kappa=242$	CS, 3x morphine

a) Previously reported, 1995, 1996.

b) TF, iv and icv = inactive (0.1-10 mg/kg, and 5 μ g/brain, respectively).

c) Previously reported in 1986, 1997.

d) Naloxone AD₅₀ = 0.16 (high)^c; atropine vs ED₈₀ in TF: inactive.

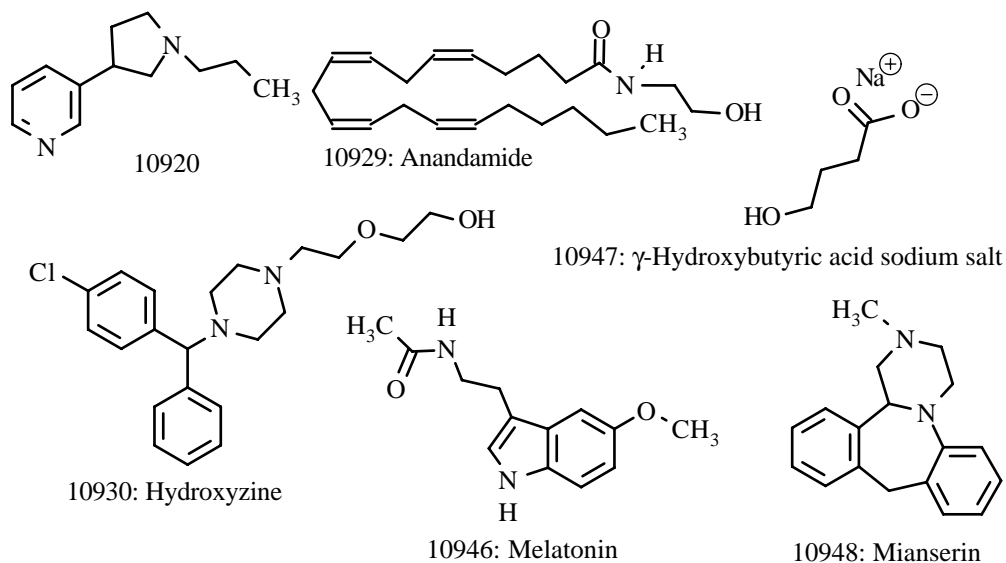
e) Radioligand: [³H]-etorphine, using rat brain homogenates.

f) Previously reported, 1997.

g) Naloxone AD₅₀ = 0.12 (high, suggesting heterogeneous opioid properties).^f

h) Naloxone AD₅₀ = 0.06.^f

TABLE 8. MISCELLANEOUS (CONTINUED)



ANTINOCICEPTIVE/ANTAGONIST ASSAYS IN VITRO MONKEY
(MOUSE ED₅₀/AD₅₀, sc, mg/kg)

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (sc, mg/kg)
10920	11.0	4.7	Inactive	Inactive	$\mu, \delta, \kappa = >10000$	NS (2.5,10)
10929	-	-	23.3 ^a	-	-	-
10930	Inactive	8.6 ^b	Inactive	Inactive	-	-
10946	Inactive	Inactive	Inactive	Inactive	-	NS (0.75,3)
10947 ^d	-	iv: 30.9	Inactive ^c	-	-	-
10948	50% @10	0.09 ^f	Inactive	Inactive	-	-

a) SKF 141716A AD₅₀ vs ED₈₀ 10929: 12.8 (after 15 min pretreatment with SKF 141716A, sc, and 5 min pretreatment with 10929, iv: antagonism of antinociceptive effect.

b) Naloxone AD₅₀: 7% antagonism at 1, 10 mg/kg. Weak antinociceptive effect not involving opioid system.

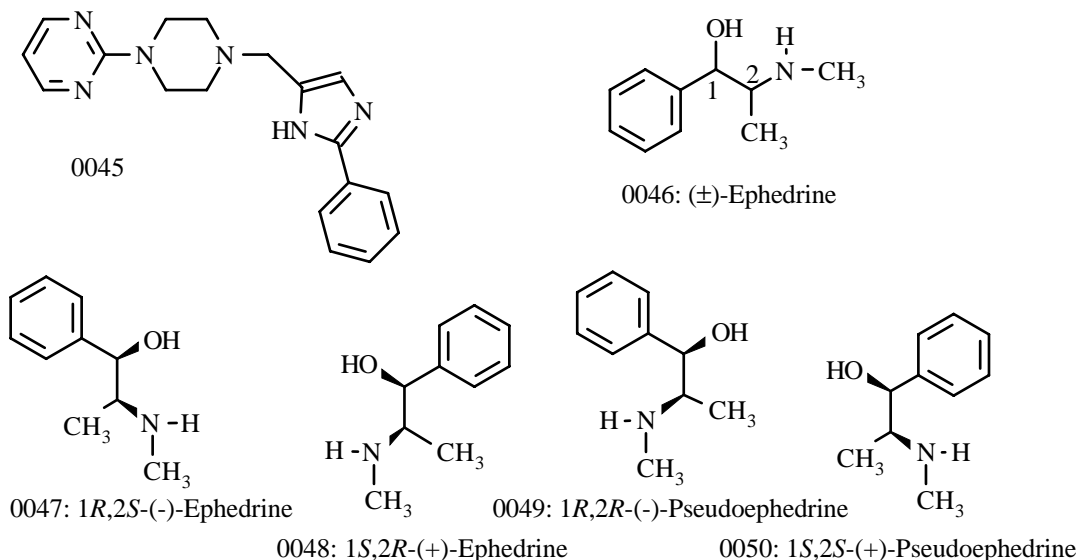
c) Mild convulsions at cumulative 9 mg/kg dose.

d) Previously published as CPDD 0044 (examined by Stimulant/Depressant group), 1996.

e) Inactive sc, iv (20 min pretreatment), or po (pretreat). Coadministration with ED₂₅ of morphine sulfate (MS) gave dose-related synergism. In mice tolerant to MS, 10947 in combination with MS partially restored antinociception; naloxone nearly abolished this effect.

f) Naloxone AD₅₀ = 1.07. NIH 10948, a serotonin antagonist, has antinociceptive activity which can be antagonized by naloxone.

TABLE 9. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD#	Discriminative Stimulus Effects In Monkeys. Comparison To Flumazenil & Triazolam (sc)	Monkey Self-Administration (iv)	Monkey Drug Discrimination (intra-gastric)
0045	No benzodiazepine agonist or antagonist action	Variable, perhaps slight, reinforcing effect in methohexital-trained monkeys	Pentobarbital-trained: No drug-appropriate responding Amphetamine-trained: No drug-appropriate responding
0046	No benzodiazepine agonist or antagonist action	Reinforcer in cocaine-trained monkeys	Amphetamine-like ^{a,b}
0047	No benzodiazepine agonist or antagonist action	Reinforcer in cocaine-trained monkeys	Amphetamine-like ^{a,b}
0048	-	Reinforcer in cocaine-trained monkeys	Amphetamine-like ^{b,c,d}
0049	-	No reinforcing effects in cocaine-trained monkeys	Amphetamine-like ^{b,c}
0050	-	Reinforcer in cocaine-trained monkeys	Some amphetamine-like properties ^{b,e}

a) In 2 out of 3 monkeys.

b) No drug-appropriate responding in pentobarbital-trained monkeys.

c) In 1 out of 3 monkeys.

d) At the highest dose (30 mg/kg), a maximum selection of 45% was obtained in a second monkey, and that monkey was visibly stimulated.

e) Considerable variability was observed.

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