

BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XXI. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (1997)

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PURPOSES OF THE DRUG EVALUATION COMMITTEE (DEC)

As previously noted (Jacobson 1997), the contemporary DEC is a direct descendent of the original analgesic testing program of the Committee on Drug Addiction of the National Research Council, National Academy of Sciences. It has only been within the past 20-25 years that the purposes and activities of DEC could be distinguished from those of CPDD. Within the past year DEC has reorganized to become an independent consortium of researchers which acts as the arm of the CPDD involved with drug testing and research. DEC activities are reported to the Chair of the the newly established Liaison Committee for Drug Evaluation and Testing.

DEC work now encompasses methodological research and physical dependence potential and abuse liability testing of drugs with analgesic, stimulant, and depressant actions. The work is done as a free public service to the pharmaceutical industry, university researchers, and governmental organizations in the U.S. and abroad, and the WHO. Researchers engaged in the work have grants or contracts from the National Institute on Drug Abuse, NIH, and some of DEC organizational expenses are paid by the CPDD. The DEC public service sets the CPDD apart from all other scientific membership organizations. Questions regarding this testing service can be addressed to the Biological Coordinator of DEC (fax: 301-402-0589, e-mail: aej@helix.nih.gov). Publication of the data gathered by DEC generally occurs within three years from receipt of sample, both in the NIDA Monograph (e.g., Aceto *et al.* 1997; English *et al.* 1996; Woods *et al.* 1997), as well as in various journals (Aceto *et al.* 1996; Aceto *et al.* 1989; May *et al.* 1994).

DEC MEMBERS

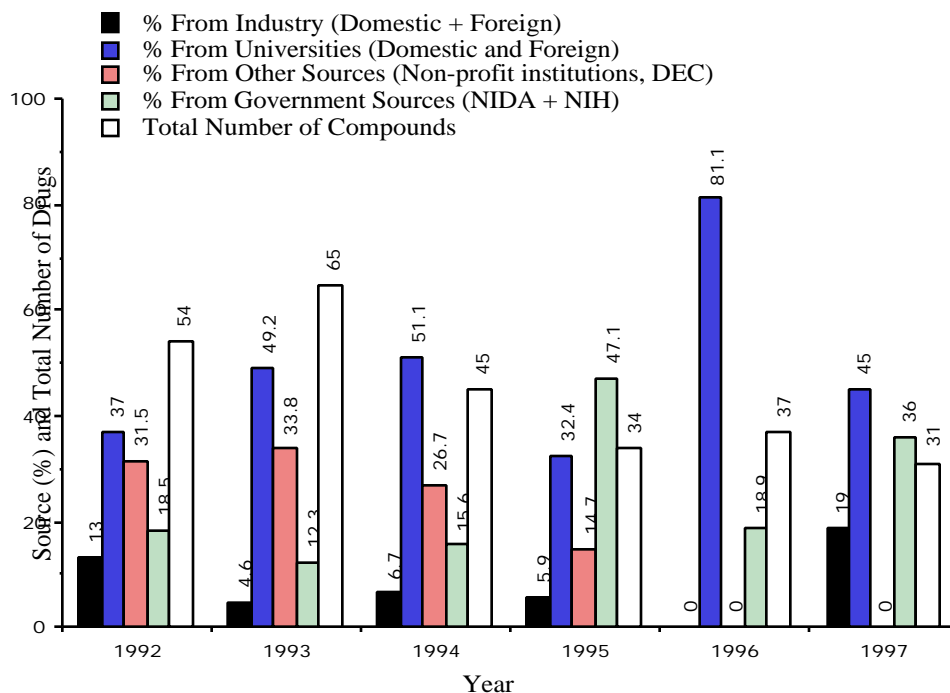
Members of DEC are those individuals who are presently associated with the Analgesic and Stimulant/Depressant Testing Programs. At this time, the DEC Members are: Drs. Mario Aceto and Louis Harris from the Medical College of Virginia, Virginia Commonwealth University, James Woods, Gail Winger, and John Traynor from the University of Michigan, Ted Cicero (DEC Chair) from Washington University, St. Louis, Arthur E. Jacobson (DEC Biological Coordinator) from NIDDK, NIH, Charles France from Louisiana State University, Bill Woolverton (DEC Recording Secretary) from the University of Mississippi, and the Chair of the CPDD Liaison Committee for Drug Testing and Evaluation (James Smith, Bowman Gray School of Medicine, *ex officio*).

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/contract. This drug testing must complement or extend existing drug testing programs, and the principal investigator must consider DEC drug testing as a priority for them. Their inclusion into DEC is gained by majority vote of the voting members of DEC.

STATISTICS

The sources and number of compounds released for publication from 1992 - 1997 can be seen in Fig. 1. In 1997, pharmaceutical industry once again became a major source of samples for evaluation (19%), and most of the industrial groups were foreign. The university sources (45%) were all domestic, and the governmental sources were, mostly, NIDA, with some drugs from NIDDK researchers. Additional data on four compounds were obtained by the stimulant/depressant testing groups. The total number of compounds released for publication this year was somewhat less than the number released last year, as shown in Fig. 1, but there are several very interesting drugs (see Experimental Observations section), one of which is in phase III clinical trials for intractable pain untreatable by morphine. The sources for the examined drugs are considerably more disparate than was observed last year, although no drugs came from non-profit institutions.

FIG. 1. DEC ANALGESIC PROGRAM. PERCENT, TOTAL NUMBER, AND SOURCE OF EXAMINED DRUGS (1992-1997)



EXPERIMENTAL OBSERVATIONS

Table 1 lists the names and assigned NIH and CPDD numbers of the compounds examined this year, and notes the specific table number where they appear. Tables 2 - 9 present the structures and a summary of the biological activities of compounds evaluated as analgesics, as obtained from work at the Medical College of Virginia, VCU, and the University of Michigan (Aceto *et al.* 1998; Woods *et al.* 1998), and additional work on CPDD 0007, 0032, 0042, and 0044 (France *et al.* 1998) from the Stimulant/Depressant group is summarized in Table 10. The compounds in Tables 2 - 9 are grouped according to their molecular structure (e.g., endoethano- and ethenooripavines, 4,5-epoxymorphinans, 6,7-benzomorphans, etc.) in order to facilitate recognition of the relationship between their molecular structure and biological activity.

In Table 2, the DEC work is shown on the very potent endoethenooripavine, etorphine (NIH 8068), and the even more potent endoethanooripavine, NIH 10846, dihydroetorphine, the latter having been sent to DEC by the NIDA Medications Development Division. Both drugs are many-fold more potent than morphine as antinociceptives. The dihydroetorphine has considerably greater affinity for the μ -opioid receptor than etorphine, and is more potent *in vivo*. Since both self-administration and drug discrimination indicate that 10846 is likely to show abuse liability in man, unless its clinical efficacy is considerably better than currently used analgesics it will probably not be clinically useful as an analgesic. NIH 10846 might have utility as medication for drug abuse; it will probably be well-liked by heroin addicts, and withdrawal from the drug might be physically easier than from methadone. It is not, however, a particularly long-acting drug.

Selective, potent, opioid agonists and antagonists would be useful both as therapeutic agents and as tools for the exploration of opioid receptor systems. Such drugs are known, if not well-utilized as yet, for the μ -, and perhaps δ -opioid receptors; less well known are drugs for the κ -opioid system. There is debate about whether the κ -opioid receptor acts independently, or interacts with the μ -receptor, or both, and whether an extremely selective κ -agonist would show physical dependence potential or abuse liability. Both a κ -agonist (NIH 10821) and antagonist (NIH 10822) were examined by DEC, and are shown in Table 3. It is interesting to note that neither drug displays an antinociceptive (or narcotic antagonist) effect in mice (sc administration), similar to our

findings for other known δ -ligands such as SNC 80 (NIH 10815 (Jacobson 1996)), nor do they suppress the morphine abstinence syndrome in monkey single-dose suppression assays, unlike μ -ligands. Even more interesting is their inability to displace [^3H]-etorphine from rat cerebral membrane preparations. However, the actual affinity and selectivity of the δ -antagonist was shown in specific opioid receptor assays. NIH 10822 was found to be high affinity for the δ -opioid receptor and the μ/δ ratio was found to be 37, and κ/δ was 88. Lastly, in Table 3, NIH 10875, was shown in 1930 to be a weak antinociceptive agent in the HP assay. Its binding affinity was determined, and it was found to be selective for μ -opioid receptors; its affinity is somewhat better than that of codeine, its isomer.

A series of N-substituted normetazocines were examined and the data are shown in Tables 4 and 5. It is surprising to note that the effect of various substituents on the nitrogen atom in this (or any other) class of analgesics is in large measure still quite unpredictable, although *in vivo* and *in vitro* data on many of them have been experimentally obtained (May *et al.* 1994). Of particular interest in Table 5 is the (+)-enantiomer, NIH 10898, which has weak antinociceptive activity and does not suppress morphine abstinence in the monkey single-dose suppression assay. Unfortunately, it appears to have convulsant actions. The (-)-normetazocine NIH 10884 is a fairly potent antinociceptive agent, also without much effect in the SDS assay. However, like many N-substituted normetazocines, it also has high affinity at the κ -receptor.

The remaining compounds examined, in Tables 6, 7, 8, and 9 have molecular structures which do not fit into well-known analgesic classes. (-)-Eseroline (NIH 10820, in Table 6) was reexamined for pharmaceutical industry and found to be a morphine-like antinociceptive which was fairly ineffective at displacing ^3H -etorphine from opioid receptors; interaction with selective receptor assays was not measured. Several compounds (NIH 10833, 10838, 10839, 10840, 10841, and 10867, in Tables 6 and 7) were examined for the NIDA Medications Development Division as potential treatment agents, and ω -conotoxin (NIH 10887, Table 8) was sent to us by pharmaceutical industry. That drug was noted by the submitter to be an extremely potent intrathecal analgesic. DEC found it to have a little antinociceptive activity sc or iv and it does not appear to have affinity for any of the opioid receptors, except weak affinity for the δ -receptor. It would not be predicted to have physical dependence potential or abuse liability of the opioid-type from our self-administration and drug discrimination tests. The conotoxin family of toxins come from the cone snail and it was recently noted that the disulfide links confer its rigidity and a characteristic shape allowing the toxin to nestle in a particular channel or portion of a specific CNS receptor (Ackerman 1997). The ω -conotoxin which DEC evaluated is a synthetic peptide which was developed as a potential treatment for intractable pain, for those unresponsive to morphine. It is in phase III clinical trials (Ackerman 1997).

In Table 10, new work is shown on four compounds which were previously evaluated by the Stimulant/Depressant Group (CPDD 0007, 0032, 0042, and 0044; methaqualone, flunitrazepam, zipeprol, and γ -hydroxybutyric acid, respectively). These data are from drug discrimination studies at Louisiana State University (France *et al.* 1998). Comparative data from previous work with these compounds are also listed in that Table. The procedures used, and the complete data, will be published this year in a separate Stimulant/Depressant Group report (France *et al.* 1998).

NOTES FOR TABLES 2 - 9

Rounded numbers are used; precise values and details of the procedures are given in the MCV (Aceto *et al.* 1998) and UM (Woods *et al.* 1998) reports.

1) Antinociceptive reference data:

Morphine ED_{50} (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 AD_{50} = 0.007 (0.002-0.02); naloxone AD_{50} = 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]-DAGO, [^3H]-*p*-Cl-DPDPE and [^3H]-U69,593, respectively.

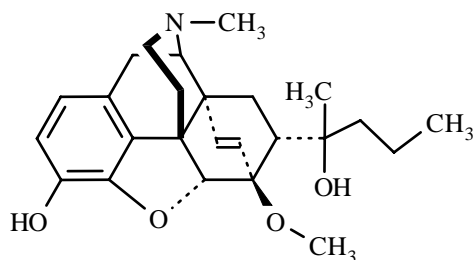
TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

<u>NIH#</u>	<u>NAME</u>	<u>TABLE #- Evaluator</u>
8068	Etorphine.HCl	2-MCV
10820	(-)-Eseroline (L)-ascorbate	6-MCV/UM
10821	3-O-Methyloxymorphindole hydrochloride	3-MCV/UM
10822	3-O-Methylnaltrindole fumarate	3-MCV/UM
10833	N-[(<i>R,S</i>)-2-Benzyl-3[(<i>S</i>)(2-amino-6-methylthio)butyldithiol]-1-oxopropyl]-L-phenylalanine benzyl ester methyl sulfite	6-MCV/UM
10838	2-Phenyl-1,3-propanediol dicarbamate (Felbamate)	6-MCV/UM
10839	3,5-Dimethyltricyclo[3.3.1.1 ^{3,7}]decan-1-amine (Memantine)	6-MCV/UM
10840	1-Aminocyclopropane carboxylic acid (ACPC)	7-MCV/UM
10841	D-Phenylalanine	7-MCV/UM
10846	Dihydroetorphine hydrochloride	2-MCV/UM
10860	(-)-5,9 α -Dimethyl-2-heptyl-2-propionoxy-6,7-benzomorphan hydrochloride	4-MCV/UM
10864	(-)-5,9 α -Dimethyl-2'-hydroxy-2-(2-hydroxyethyl)-6,7-benzomorphan oxalate	4-MCV/UM
10867	7-Nitroindazole	7-MCV/UM
10869	(-)-2-Cyanomethyl-5,9 α -dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride	4-MCV/UM
10870	(+)-2-Cyanomethyl-5,9 α -dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride	4-MCV/UM
10871	(-)-2-(5-Chloropentyl)-5,9 α -dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride	4-MCV
10874	7-Benzoyl-2-piperidinomethyl-1,6-benzodioxane hydrochloride	7-UM
10875	Pseudocodeine hydrochloride	3-UM
10884	2 <i>R</i> ,5 <i>R</i> ,9 <i>R</i> -(<i>-</i>)-2-(3-Cyanopropyl)-5,9 α -dimethyl-2'-hydroxy-6,7-benzomorphan	5-MCV/UM
10885	2 <i>S</i> ,5 <i>S</i> ,9 <i>S</i> -(<i>+</i>)-2-(3-Cyanopropyl)-5,9 α -dimethyl-2'-hydroxy-6,7-benzomorphan	5-MCV

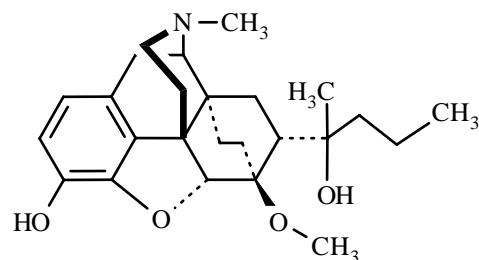
TABLE 1. CONTINUED - NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

<u>NIH#</u>	<u>NAME</u>	<u>TABLE #- Evaluator</u>
10886	(±)-Isonicotine oxalate	8-MCV/UM
10887	w-Conotoxin MVIIA (reduced, cyclic (1-16), (8-20), (15-25) - SNX-111)	8-MCV/UM
10895	(-)-Isonicotine oxalate	8-MCV/UM
10896	(+)-Isonicotine oxalate	8-MCV/UM
10897	2 <i>R</i> ,5 <i>R</i> ,9 <i>R</i> -(<i>-</i>)-2-(6-Chlorohexyl)-5,9 α -dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride	5-MCV
10898	2 <i>S</i> ,5 <i>S</i> ,9 <i>S</i> -(<i>+</i>)-2-(6-Chlorohexyl)-5,9 α -dimethyl-2'-hydroxy-6,7-benzomorphan hydrochloride	5-MCV
10899	2-Methyl-5-(3-pyridyl)morphan oxalate	9-UM
10900	11-[6-Hydroxy-6-(3-trifluoromethylphenyl)piperidin-1-yl]-2-methyl-6,11-dihydrodibenz[b,e]oxepine sulfuric acid	9-MCV
10901	11-(6-Hydroxy-6-phenylpiperidin-1-yl)-2-methyl-6,11-dihydrodibenz[b,e]oxepine fumaric acid	9-MCV
10902	11-[6-Hydroxy-6-(3-trifluoromethylphenyl)piperidin-1-yl]-2-hydroxymethyl-6,11-dihydrodibenz[b,e]oxepine fumaric acid	9-MCV
10903	11-(6-Hydroxy-6-phenylpiperidin-1-yl)-2-hydroxymethyl-6,11-dihydrodibenz[b,e]oxepine	9-MCV
CPDD 0007	Methaqualone	10-S/D:LSU
CPDD 0032	Flunitrazepam	10-S/D:LSU
CPDD 0042	Zipeprol dihydrochloride	10-S/D:LSU
CPDD 0044	γ -Hydroxybutyric acid, sodium salt	10-S/D:LSU

TABLE 2. ENDOETHENO- AND ENDOETHANORIPAVINES



8068 (Etorphine)



10846 (Dihydroetorphine)

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

IN VITRO

MONKEY

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC ₅₀ , nM (% twitch inhibition))	Substitution- for-Morphine (sc, mg/kg)
8068	0.00096 ^a	0.0004	0.002 ^b	Inactive	$\mu = 0.6; \delta = 1.13^c$	-	Complete substitution (~2000x morphine)
10846	0.0002	0.0002	0.00015 ^d	Inactive	$\mu = 0.088; \delta = 2.54; \kappa = 0.197$	0.34 (100) [antagonized by naltrexone]	Complete substitution (~20,000x morphine) ^e

a) Previously reported, with high physical dependence capacity noted in Substitution-for Morphine assay (Deneau and Seevers 1964).

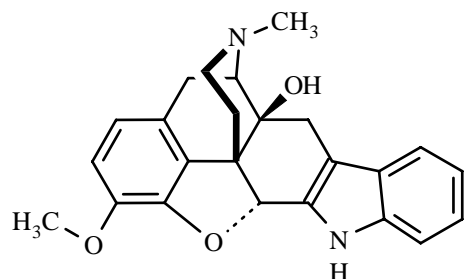
b) Tail flick assay with nor-BNI or naltrindole antagonism: μ -selective and devoid of δ or κ activity. Extended duration in morphine-dependent animals. Low pA₂ (0.09) suggests multiple drug properties.

c) Previously reported (displacement of ³H-sufentanil and ³H-DPDPE, [(Woods *et al.* 1997), see p 400]).

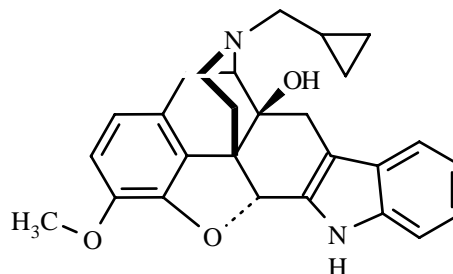
d) Naloxone AD₅₀ = 0.04

e) Rat Infusion (Substitution-for-Morphine): suppression less than with morphine; Rat Infusion (Primary Physical Dependence): withdrawal milder than morphine, but same behavioral signs; Monkey primary physical dependence: μ -like withdrawal syndrome, but body weight constant; Self-administration (monkey): >460x heroin, >20,000x codeine.

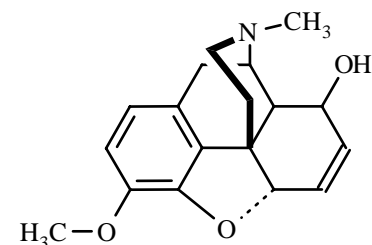
TABLE 3. 4,5-EPOXYMORPHINANS



10821
(3-O-Methyloxymorphindole fumarate)



10822
(3-O-Methylnaltrindole .HCl)



10875 (Pseudocodeine .HCl)

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

IN VITRO

MONKEY

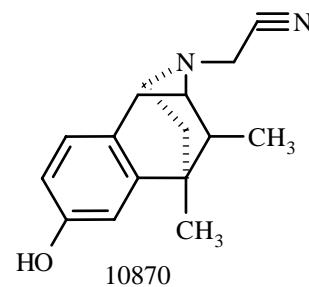
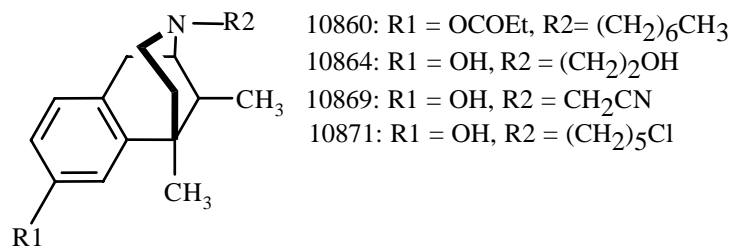
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC50, nM (% twitch inhibition))	Substitution- for-Morphine (sc, mg/kg)
10821	Inactive	Inactive	Inactive	Inactive	³ H-etorphine >6000	1300 (100) [antagonized by naltrexone] ^a	Partial substitution (20)
10822	Inactive	Inactive	Inactive	Inactive	³ H-etorphine >6000 $\mu = 66.4$; $\delta = 1.8$; $\kappa = 158$	-	No substitution, possible exacerbation of withdrawal (4,16)
10875 00003	431 ^b	-	-	-	$\mu = 427$; $\delta = >6000$; $\kappa = >6000$	14800 (63) ^c	-

a) Typical δ -agonist.

b) Determined in 1930 at NIDDK, NIH.

c) Very weak agonist with unusual activity at μ -opioid receptors (naltrexone decreased maximum response without shift in concentration-effect curve).

TABLE 4. 6,7-BENZOMORPHANS



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

IN VITRO

MONKEY

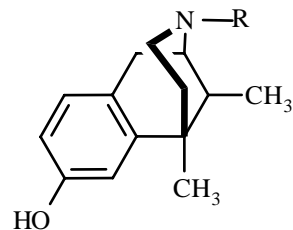
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC ₅₀ , nM (% twitch inhibition))	Substitution- for-Morphine (sc, mg/kg)
10860	5.5	0.31	3.13	Inactive	μ=28.2, δ=47, κ=47.5 ^a	No effect ^{a,b}	No substitution (2-12); convulsant, lethal
10864	Inactive	Inactive	Inactive (sc and icv)	Inactive	μ=41, δ=316, κ=16	1290 (68) Slight antagonism by naltrexone; weak δ-agonist	No substitution (3,12)
10869	8.5	1.52	11.6	Inactive	μ=166, δ=574, κ=69	1720 (83)	Complete substitution [0.25x morphine]
10870	Inactive	6.0	Inactive	Inactive	μ=4490, δ=>6000, κ=1310	7930 (35); not antagonized by naltrexone	Complete substitution (1) ^k
10871	3.6	0.5	0.84	Inactive	-	-	Complete substitution

a) Previously reported ((Woods *et al.* 1997) - see p 416).

b) Unusual agonist; decreased magnitude of twitch, but did not suppress it at any concentration. Very weak, non-selective, antagonist.

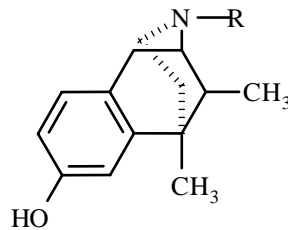
c) Severe ataxia; possible κ-opioid.

TABLE 5. 6,7-BENZOMORPHANS (CONTINUED)



10884 (-): R = (CH₂)₃CN

10897 (-): R = (CH₂)₆Cl



10885 (+): R = (CH₂)₃CN

10898 (+): R = (CH₂)₆Cl

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

IN VITRO

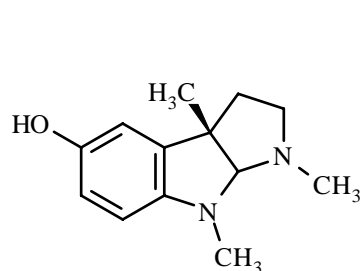
MONKEY

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC ₅₀ , nM (% twitch inhibition))	Substitution- for-Morphine (sc, mg/kg)
10884	1.1	0.1	0.36 ^a	Inactive	μ=6.5, δ= 21.6, κ=0.34	42.7 (100) [antagonized by naltrexone]	Non-dose-dependent
10885	Inactive	Inactive	Inactive	Inactive	-	-	Non-dose-dependent
10897	1.59	0.67	2.03	Inactive	-	-	Partial substitution (2,8) ^b
10898	Inactive	6.32	11.56	Inactive	-	-	No substitution (3,12); convulsions at 12 mg/kg.

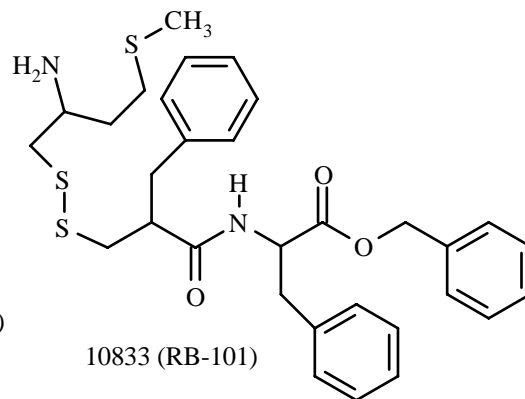
a) High naloxone AD₅₀ = 0.28, and effects in monkeys suggest heterogenous opioid properties.

b) Nearly suppresses morphine-withdrawal, potency >morphine; appears μ-opioid-like.

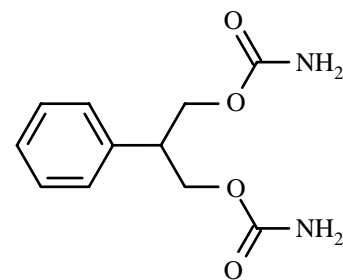
TABLE 6. MISCELLANEOUS



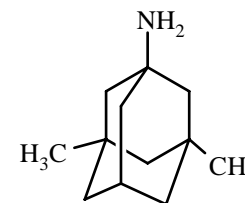
10820 ((-)-Eseroline (L)-ascorbate)
(10398^a)



10833 (RB-101)



10838 (Felbamate)



10839 (Memantine)

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

IN VITRO

MONKEY

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC ₅₀ , nM (% twitch inhibition))	Substitution- for-Morphine (sc, mg/kg)
10820	3	0.3	2.4 ^b	Inactive	1600 (³ H-etorphine)	3.9 (49) [Antagonized by naltrexone]	Complete substitution (2.5-10)
10833	-	-	39 (iv); ip inactive ^c	-	$\mu=2100$, $\delta=>6000$, $\kappa=>6000$	977 (23) [Not antagonized by naltrexone]	Solvent-like partial substitution (iv)
10838	Inactive	Inactive	Inactive	Inactive	$\mu=>6000$, $\delta=>6000$, $\kappa=>6000$	670 (29) [Not antagonized by naltrexone]	No substitution (3,15)
10839	Inactive	15.1	Inactive	Inactive	$\mu=>6000$, $\delta=>6000$, $\kappa=>6000$	47 (35) [Not antagonized by naltrexone]	No substitution (2,8) ^d

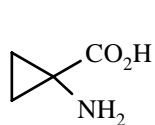
a) Previously reported (Aceto *et al.* 1987)

b) High naloxone AD₅₀= 0.16; pA₂: not typical opioid agonist, non-competitive or non-equilibrium steady state. No antagonism with norBNI.

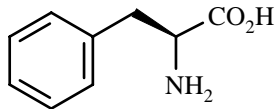
c) Drug has no acute or chronic effect on morphine's ED₅₀.

d) No exacerbation of withdrawal. Excitability seen in tail flick and phenylquinone assays; some signs suggest PCP-like behavior in monkeys.

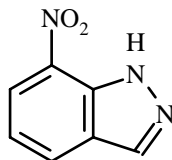
TABLE 7. MISCELLANEOUS (CONTINUED)



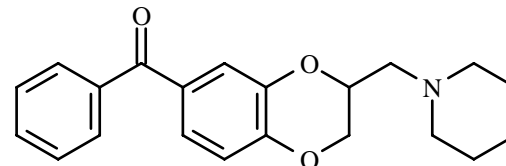
10840



10841



10867



10874

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

IN VITRO

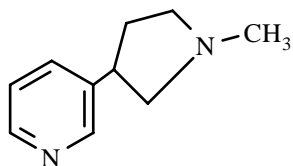
MONKEY

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC50, nM (% twitch inhibition))	Substitution- for-Morphine (sc, mg/kg)
10840	Inactive	Inactive	Inactive	Inactive	$\mu \Rightarrow >6000$, $\delta \Rightarrow >6000$, $\kappa \Rightarrow >6000$	3290 (34) [Not antagonized by naltrexone]	No substitution (5,25) ^a
10841	Inactive	Inactive	Inactive	Inactive	$\mu \Rightarrow >6000$, $\delta \Rightarrow >6000$, $\kappa \Rightarrow >6000$	185 (56) [Not antagonized by naltrexone]	No substitution (9,45) ^b
10867	Inactive	Inactive	Inactive	Inactive	$\mu \Rightarrow >6000$, $\delta \Rightarrow >6000$, $\kappa \Rightarrow >6000$	1500 (47) [Not antagonized by naltrexone]	-
10874	7.4	-	-	-	$\mu \Rightarrow >6000$, $\delta \Rightarrow >6000$, $\kappa \Rightarrow >6000$	21 (100) [Not antagonized by naltrexone]	No substitution (5,40)

a) A single (200 mg/kg) dose had no effect. When a 200 mg/kg sc was given for 4 days and the monkeys placed in withdrawal, followed by another 200 mg/kg sc dose, neither substitution nor exacerbated withdrawal was observed.

b) No exacerbation of withdrawal. Rat Infusion (Substitution-for-Morphine): no substitution. Heroin discrimination: no attenuation of heroin discriminative stimulus.

TABLE 8. MISCELLANEOUS (CONTINUED)



H-Cys-Lys-Gly-Lys-Gly-Ala-Lys-Cys-Ser-Arg-Leu-Met-Tyr-Asp-Cys-Cys-Thr-Gly-Ser-Cys-Arg-Ser-Gly-Lys-Cys-NH₂ cyclic (1-16), (8-20), (15-25)-tris(disulfide)

10887 [ω -Conotoxin MVIIA (reduced)]

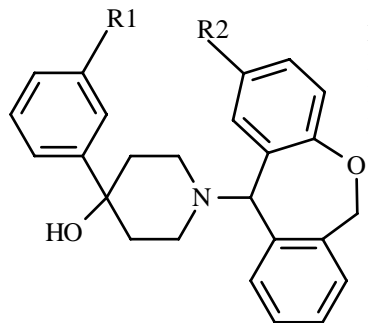
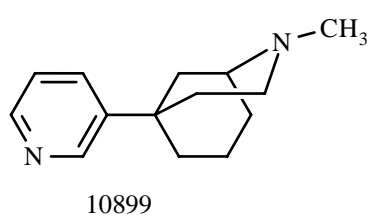
10886: (\pm)-Isonicotine oxalate

10895: (-)-Isonicotine oxalate

10896: (+)-Isonicotine oxalate

ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED ₅₀ /AD ₅₀ , sc, mg/kg)					IN VITRO	MONKEY	
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Mouse Vas Deferens (EC ₅₀ , nM (% twitch inhibition))	Substitution- for-Morphine (sc, mg/kg)
10886	Inactive	3.2	Inactive	Inactive	μ =>6000, δ =>6000, κ =>6000	Very weak antagonist at μ , and possibly δ	No substitution (3,12)
10887	-	3.16	17.7 (iv)	-	μ =>6000, δ =1190, κ =>6000	4.8 (100) [Not antagonized by naltrexone]	Partial substitution (0.25,1) ^a
10895	Inactive	3.8	Inactive	Inactive	-	-	Partial substitution (non-dose related)
10896	Inactive	1.63	Inactive	Inactive	-	-	No substitution (2.5,10)

a) Self-administration: no reinforcing effect; drug discrimination (naltrexone-saline): did not attenuate discrimination of morphine withdrawal.

TABLE 9. MISCELLANEOUS (CONTINUED)^a

10900: R1 = CF₃, R2 = CH₃
 10901: R1 = H, R2 = CH₃
 10902: R1 = CF₃, R2 = CH₂OH
 10903: R1 = H, R2 = CH₂OH

NIH #	ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED50/AD50, sc, mg/kg)				IN VITRO	MONKEY
	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, K _i , nM	Substitution- for-Morphine (sc, mg/kg)
10899	-	-	-	-	μ=>1175, δ=>10000, κ=>10000	-
10900	Inactive	Inactive	Inactive ^a	Inactive	-	Non-dose related suppression of withdrawal
10901	-	7.6	Inactive ^a	Inactive	-	Complete substitution (0.2x morphine)
10902	0.98	1.13	12.86 ^{b,c}	Inactive	-	Complete substitution (2,8)
10903	2.2	0.6	1.11 ^d	Inactive	-	Complete substitution - morphine-like μ-opioid agonist (3x morphine)

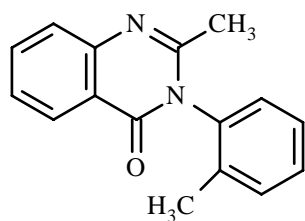
a) Also, orally with 20 or 40 min pretreatment: inactive

b) Possible pro-drug in mouse.

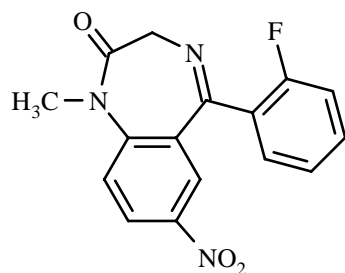
c) Naloxone AD50: 0.12 (high - suggests heterogenous activity)

d) Also, orally with 20 min pretreatment: 1.0 mg/kg; 40 min pretreatment: 0.98 mg/kg.

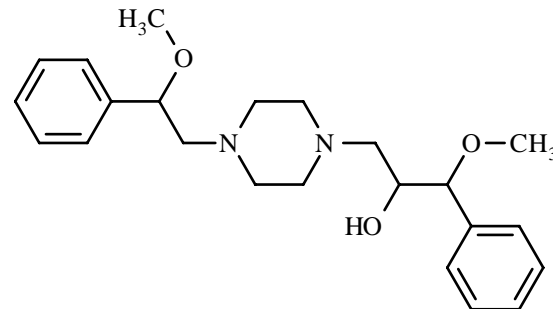
TABLE 10. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



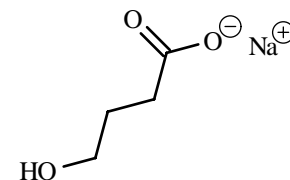
CPDD 0007 (Methaqualone)



CPDD 0032 (Flunitrazepam)



CPDD 0042 (Zipeprol)



CPDD 0044
(γ -Hydroxybutyric Acid)

CPDD#	Discriminative Stimulus Effects In Monkeys, Comparison To Flumazenil & Triazolam (sc) ^a	Monkey Self-Administration (iv)	Monkey Drug Discrimination (Intragastric)
0007	No benzodiazepine agonist or antagonist action	Reinforcer ^b	Substitutes for pentobarbital ^b
0032	Benzodiazepine-like agonist; potency similar to triazolam	Reinforcer in 1/3 monkeys ^c	<u>Pentobarbital-trained</u> : 100% Drug-appropriate responding at 0.3-1.0 mg/kg ^c
0042	No benzodiazepine agonist or antagonist action	Reinforcer in methohexital- and alfentanil-trained monkeys ^d	<u>Pentobarbital-trained</u> : No drug-appropriate responding <u>Amphetamine-trained</u> : No drug-appropriate responding ^d
0044	No benzodiazepine agonist or antagonist action	Did not maintain behavior. No reinforcing effect ^e	<u>Pentobarbital-trained</u> : No drug-appropriate responding <u>Amphetamine-trained</u> : Maximum of 50% drug-appropriate responding, probably not dose-related; may have weak amphetamine-like subjective effects ^e

a) See Stimulant/Depressant report (France *et al.* 1998)

b) Previously reported (Jacobson 1988a; Jacobson 1988b; Johanson 1986)

c) Previously reported (Jacobson 1991; Patrick *et al.* 1992; Winger *et al.* 1992)

d) Previously reported (English *et al.* 1996)

e) Previously reported (Jacobson 1997)

REFERENCES

- Aceto, M. D.; Bowman, E.; Butelman, E.; Harris, L.; Jacobson, A. E.; Mattson, M.; Medzihradsky, F.; Patrick, G.; Smith, C. B.; Winger, G. D.; Woods, J. H.; and Woolverton, W. Zipeprol: Assessment of Abuse Potential in Animals. Drug and Alcohol Dependence 42:93-104, 1996.
- Aceto, M. D.; Bowman, E. R.; Harris, L. S.; and May, E. L.: Dependence Studies of New Compounds in the Rhesus Monkey, Rat and Mouse (1986). In: L. S. Harris, ed. Problems of Drug Dependence 1986, pp. 392-447, NIDA Research Monograph 76, Washington, D.C., 1987.
- Aceto, M. D.; Bowman, E. R.; Harris, L. S.; and May, E. L.: Dependence Studies of New Compounds in the Rhesus Monkey, Rat and Mouse (1996). In: L. S. Harris, ed. Problems of Drug Dependence 1996, pp. 338-395, NIDA Research Monograph 174, Washington, D.C., 1997.
- Aceto, M. D.; Bowman, E. R.; Harris, L. S.; and May, E. L.: Dependence Studies of New Compounds in the Rhesus Monkey, Rat and Mouse (1997). In: L. S. Harris, ed. Problems of Drug Dependence 1997, NIDA Research Monograph, Washington, D.C., 1998, in press.
- Aceto, M. D.; Bowman, E. R.; May, E. L.; Harris, L. S.; Woods, J. H.; Smith, C. B.; Medzihradsky, F.; and Jacobson, A. E. Very Long-Acting Narcotic Antagonists: The 14 β -*p*-Substituted Cinnamoylaminomorphinones and their Partial Mu Agonist Codeinone Relatives. Arzneimittelforschung 39:570-575, 1989.
- Ackerman, S. J. Reform of the Killer Snails. National Center for Research Resources (NCRR) Reporter XXI:5-7, 1997.
- Deneau, G. A. and Seevers, M. H.: Evaluation of New Compounds for Morphine-like Physical Dependence in the Rhesus Monkey. Committee on Drug Addiction and Narcotics, Minutes of Twenty-Sixth Meeting, Feb., 1964; Addendum 1, pp. 1-14, National Academy of Sciences - National Research Council, Division of Medical Sciences, Washington, D.C., 1964, see p 3.
- English, J. A.; Rowlett, J. K.; Woolverton, W. L.; Patrick, G. A.; Hawkins, W. T.; Winger, G.; and Woods, J. H.: Progress Report From the Testing Program for Stimulant and Depressant Drugs (1995). In: L. S. Harris, ed. Problems of Drug Dependence 1995, pp. 452-468, NIDA Research Monograph 162, Washington, D.C., 1996.
- France, C. P.; Woolverton, W. L.; Winger, G.; and Woods, J. H.: Progress Report From the Testing Program for Stimulant and Depressant Drugs (1997). In: L. S. Harris, ed. Problems of Drug Dependence 1997, NIDA Research Monograph, Washington, D.C., 1998, in press.
- Jacobson, A. E.: Biological Evaluation of Compounds for their Physical Dependence Potential and Abuse Liability. XI. Drug Testing Program of the Committee on Problems of Drug Dependence, Inc. (1987). In: L. S. Harris, ed. Problems of Drug Dependence 1987, pp. 466-484, NIDA Research Monograph 81, Washington, D.C., 1988a.
- Jacobson, A. E.: Biological Evaluation of Compounds for their Physical Dependence Potential and Abuse Liability. XII. Drug Testing Program of the Committee on Problems of Drug Dependence, Inc. (1988). In: L. S. Harris, ed. Problems of Drug Dependence 1988, pp. 392-420, NIDA Research Monograph 90, Washington, D.C., 1988b.
- Jacobson, A. E.: Biological Evaluation of Compounds for their Physical Dependence Potential and Abuse Liability. XIV. Animal Testing Committee of the Committee on Problems of Drug Dependence, Inc. (1990). In: L. S. Harris, ed. Problems of Drug Dependence 1990, pp. 622-639, NIDA Research Monograph 105, Washington, D.C., 1991.
- Jacobson, A. E.: Biological Evaluation of Compounds for their Physical Dependence Potential and Abuse Liability. XIX. Drug Evaluation Committee of the College on Problems of Drug Dependence, Inc. (1995). In: L. S. Harris, ed. Problems of Drug Dependence 1995, pp. 363-376, NIDA Research Monograph 162, Washington, D.C., 1996.
- Jacobson, A. E.: Biological Evaluation of Compounds for their Physical Dependence Potential and Abuse Liability. XX. Drug Evaluation Committee of the College on Problems of Drug Dependence, Inc. (1996). In: L. S. Harris, ed. Problems of Drug Dependence 1996, pp. 323-337, NIDA Research Monograph 174, Washington, D.C., 1997.
- Johanson, C. E.: Stimulant Depressant Report. In: L. S. Harris, ed. Problems of Drug Dependence, 1985, pp. 98-104, NIDA Research Monograph 67, Washington, DC, 1986.
- May, E. L.; Aceto, M. D.; Bowman, E. R.; Bentley, C.; Martin, B. R.; Harris, L. S.; Medzihradsky, F.; Mattson, M. V.; and Jacobson, A. E. Antipodal α -N-Alkyl (Methyl-Decyl)-N-Normetazocines (2'-

- Hydroxy-5,9 α -methyl-6,7-benzomorphans): In Vitro and In Vivo Properties. J Med Chem 37:3408-3418, 1994.
- Patrick, G. A.; Harris, L. S.; Nader, M. A.; Woolverton, W. L.; Winger, G.; and Woods, J. H.: Progress Report From the Testing Program for Stimulant and Depressant Drugs (1990). In: L. S. Harris, ed. Problems of Drug Dependence 1991, pp. 604-624, NIDA Research Monograph 119, Washington, D.C., 1992.
- Winger, G.; Woods, J. H.; Patrick, G. A.; Powell, L. J.; Harris, L. S.; Nader, M. A.; and Woolverton, W. L.: Progress Report From the Testing Program for Stimulant and Depressant Drugs (1991). In: L. S. Harris, ed. Problems of Drug Dependence 1991, pp 625-639, NIDA Research Monograph 119, Washington, DC, 1992.
- Woods, J. H.; Medzihradsky, F.; Smith, C. B.; Butelman, E. R.; and Winger, G. D.: Evaluation of New Compounds for Opioid Activity (1996). In: L. S. Harris, ed. Problems of Drug Dependence 1996, pp. 396-420, NIDA Research Monograph 174, Washington, D.C., 1997.
- Woods, J. H.; Traynor, J.; Butelman, E. R.; and Winger, G. D.: Evaluation of New Compounds for Opioid Activity (1997). In: L. S. Harris, ed. Problems of Drug Dependence 1997, NIDA Research Monograph, Washington, D.C., 1998, in press.

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