

BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XX. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (1996)

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PURPOSES OF THE DRUG EVALUATION COMMITTEE (DEC)

This Committee's purposes and activities were recently delineated (Jacobson 1997). In that review of the 67 year history of DEC, it was noted that DEC and CPDD were indistinguishable during their initial 43 years of existence. DEC was considered one of the essential programs or functions of CPDD, but the committee structure of CPDD did not exist. 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.

DEC members are now involved with methodological research and the testing of drugs with analgesic, stimulant, depressant, and/or hallucinogenic actions, and they provide information relating to the physical dependence potential and abuse liability of these drugs to the pharmaceutical industry, university researchers, and governmental organizations in the U.S. and abroad, and the WHO. For the membership of CPDD, as well as to researchers throughout the world, DEC offers to determine the physical dependence potential and abuse liability of your interesting new or old analgesics, stimulants and/or depressants. The Biological Coordinator can be reached by mail, fax (301-402-089), or e-mail (aej@helix.nih.gov) to answer any questions about the submission of compounds and about this free service. This free public service by the DEC sets the CPDD apart from all other scientific membership organizations. The data which are obtained by DEC, under the auspices of the CPDD, are published within three years and can be seen in this Monograph, and preceding Monograph issues (Aceto *et al.* 1996; English *et al.* 1996; Woods *et al.* 1996) as well as in various journals (Aceto *et al.* 1989; May *et al.* 1994).

MEMBERS OF THE DRUG EVALUATION COMMITTEE (DEC) AND THEIR RESPONSIBILITIES

The CPDD Board has assigned two of its members to DEC, Dr. J. Smith (Wake Forest University), the current Chair of DEC, and Dr. M. R. Johnson. Dr. T. Cicero (Washington University) is the Executive Secretary, and I serve as Biological Coordinator. Other members of DEC are directly involved with drug evaluation (Drs. L. Harris, M. Aceto, J. Woods, G. Winger, W. Woolverton, and C. France).

The Chair links the DEC and the CPDD, and reports to the CPDD Board. The Executive Secretary plans, organizes and is fiscally responsible for the annual DEC meetings, and for maintaining the link between the stimulant-depressant-hallucinogenic testing groups and their main funding organization, NIDA. The DEC Executive Secretary is also involved with the research of the stimulant-depressant-hallucinogenic testing groups.

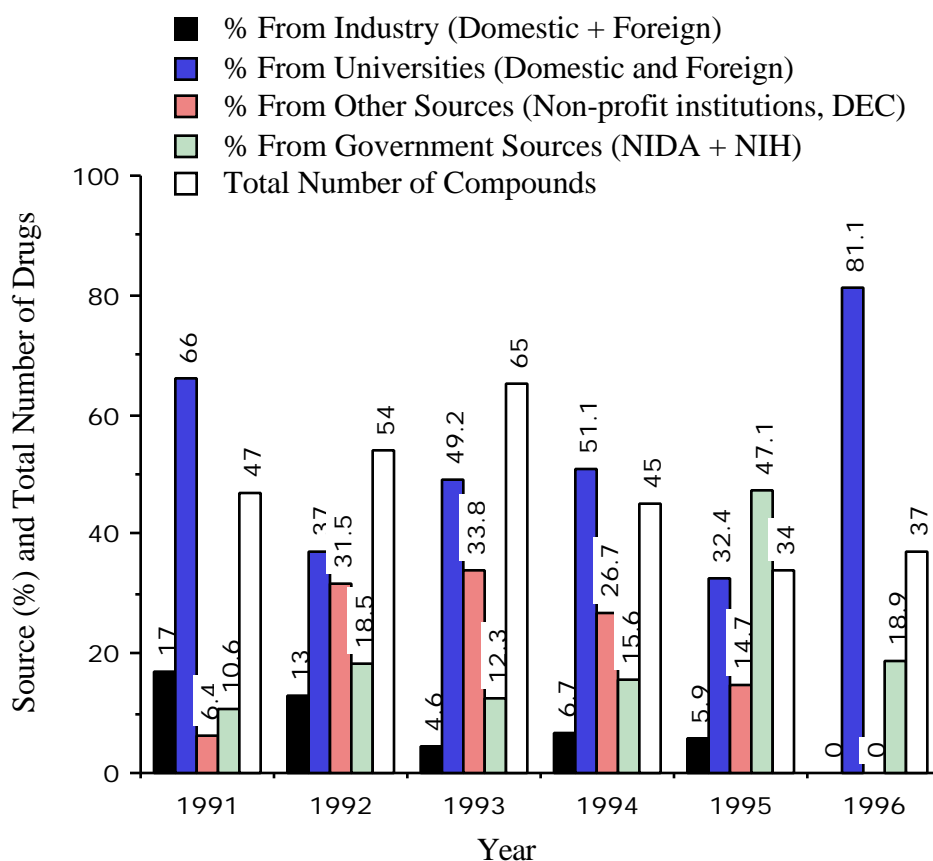
The Biological Coordinator has the responsibility for obtaining drugs from pharmaceutical industry, academia, and governmental organizations, assigning them code numbers, assessing the obtained spectroscopic and thin layer chromatographic data to validate drug structure and purity, and distributing the drugs to either or both the analgesic and the stimulant-depressant-hallucinogenic testing groups. The samples are sent with only a code number, molecular weight, solubility and, if known, toxicity data. The thin layer chromatographic data are repeated before and after biological testing by Dr. E. L. May at the Medical College of Virginia, Virginia Commonwealth University (MCV/VCU), to assure drug stability. Testing results from the DEC groups are sent to the Biological Coordinator who transmits them to the submitter of the drug, and occasionally aids the submitter with their interpretation. The data obtained from MCV/VCU are forwarded by the Biological Coordinator to the investigators at the University of Michigan (UM), and vice versa. Information on all of these drugs is maintained in a database by the Biological Coordinator, and, when requested, a report is given about DEC

work to the Chair or Executive Secretary, or directly to the Board. Requests for release of the obtained information are sent to the submitter of a drug by the Biological Coordinator. The released data are compiled annually and the code numbers are translated into drawn molecular structures and sent to the testing group, with the chemical name of the drug, for their publication of the data in the NIDA Research Monograph of the CPDD Annual Scientific Meeting. A compilation of these data from a molecular structure-biological activity viewpoint is also published in that Monograph by the Biological Coordinator. Further, the Biological Coordinator, with the help of May, compiles the annually published data and sends them to the UM to update their public database on DEC-evaluated drugs. The Biological Coordinator is also occasionally involved with some of the scientific work of DEC (Jacobson 1997).

STATISTICS

The sources and number of compounds released for publication from 1991 - 1996 can be seen in Fig. 1. In 1996, two sources accounted for all of the examined drugs, universities and governmental. The university sources (81%) were both domestic (64.9%) and foreign (16.2%), and NIH researchers were the governmental source. One compound, obtained from NIDA, was released for publication after testing by the stimulant/depressant testing groups. The total number of compounds released for publication this year was about 10% greater than the number released last year, but less than in the previous years shown in Fig. 1. No drugs from industrial sources, nor from non-profit institutions or governmental sources other than NIH were released this year. The sources will become more disparate next year when several drugs are automatically released for publication.

FIG. 1. DEC ANALGESIC PROGRAM. PERCENT, TOTAL NUMBER, AND SOURCE OF EXAMINED DRUGS (1991-1996)



GROUPS INVOLVED IN DEC RESEARCH AND TESTING

The analgesic testing groups are based in MCV/VCU (Drs. L. Harris, M. Aceto, E. Bowman, and E. May) and at UM (Drs. J. Woods, F. Medzihradsky, C. Smith, and G. Winger). The stimulant/ depressant testing groups are at UM (Dr. G. Winger), the University of Mississippi (Drs. W. Woolverton and J. Rowlett), and Louisiana State University (Dr. C. France).

The DEC is not a closed organization; its organizational structure serves to facilitate collaborative research on drugs of abuse by researchers in university groups with complementary techniques, and it is structured to allow its members to openly discuss ongoing work. The DEC welcomes those who can complement and extend existing expertise. However, the evaluation effort must be funded from sources outside of CPDD, and assurance must be given that the DEC testing will receive the highest priority.

EXPERIMENTAL OBSERVATIONS

Table 1 lists the names and assigned NIH 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 Aceto *et al.* (1997) , and Woods *et al.* (1997) , and Table 9 summarizes the work of the stimulant/depressant groups on CPDD 0044. The compounds in Tables 2 - 8 are grouped according to their molecular structure (e.g., 4,5-epoxymorphinans, endoethanooripavines, 6,7-benzomorphans, etc.) in order to facilitate recognition of the relationship between their molecular structure and biological activity.

Five epoxymorphinans in Tables 2 and 3 (NIH 10826, 10827, 10825, 10831, and 10832) have been included in a manuscript on potential SPECT ligands (Kayakiri *et al.* in review) . The C₆-iodo-substituted compounds were relatively μ -selective opioids, more potent in vitro and in vivo than their C₆-hydroxy relatives (10832 in Table 2 was estimated to be 300 times more potent than morphine in the SDS assay). Single-crystal x-ray analysis showed that the C₆ - (10832 in Table 3) and C₆ -iodine (10827 in Table 2) atoms were spatially closely located although the C-ring conformations of these compounds were quite different (twist-boat form vs. chair). The major epimeric conformational differences were not reflected in binding affinities to the μ -opioid receptor.

It is interesting to see the effect of a C₃-ether substituent in Table 3's 10844 and 10845. These drugs have identical substituents at C₁₄ and are both N-cyclopropylmethyl-substituted epoxymorphinans. In the SDS assay, the C₃-cyclopropylmethoxy-substituted compound (10844) is a potent long-acting antagonist with minimal agonist properties. The C₃-propargylmethoxy-substituted compound (10845) does not suppress abstinence; it initially acts as a potent agonist, and this is followed by its action as an apparently irreversible antagonist. The effect of the C₃-cyclopropylmethoxy-substituent is different in the endoethanooripavine series, as can be seen with 10806 and 10807 in Table 4. Like 10844, neither of these drugs have much antinociceptive activity; however, both are weak, non-selective antagonists.

The epoxymorphinan 10849 in Table 3 exhibits a profile of action which could enable it to be a clinically useful analgesic. In rodent assays it was found to have reasonable antinociceptive potency; it was essentially morphine-like. Unlike morphine, however, it did not suppress abstinence in SDS studies in the rhesus monkey and it displayed weak narcotic antagonist properties in a precipitated withdrawal study. It is, thus, unlikely to induce opioid-like physical dependence in man.

The effect of a haloperidol-like side-chain (on nitrogen) in N-desmethylketobemidone (10834, Table 4) is remarkable. The potent opioid ketobemidone is transformed to a non-selective narcotic antagonist (as shown in the vas deferens assay), and was observed to have cataleptic activity in the SDS assay. The same N-side-chain in the piperidine 10873 (Table 4) does not modify the expected agonist activity, nor does it do so in the benzomorphan 10835 (Table 5). Thus, the N-side-chain cannot represent the portion of these opioid-like molecule which dictates agonist vs. antagonist behavior. However, it is also unlikely that the ketobemidone-like portion of the 10834 structure could induce antagonist behavior. Structural considerations would suggest that 10834 would be unlikely to have narcotic antagonist activity. The results in the vas deferens preparation, then, may not realistically reflect the in vivo activity of the molecule.

In the 4,5-epoxymorphinan or 6,7-benzomorphan series, compounds with an N-allyl side-chain usually display narcotic antagonist activity. In order to explore the effect of that double-bond when situated further from the nitrogen atom, several longer-chain N-alkenyl normetazocines were synthesized at MCV/VCU. The enantiomeric N-butenyl, N-pentenyl, and N-hexenyl compounds serve to illustrate that effect. In the (-)-series, N-butenylnormetazocine (10847, Table 5) was essentially morphine-like antinociceptively and promiscuous in receptor binding assays, with high affinity for κ - and μ -opioid receptors. Its modest antagonist activity was seen in the TFA assay, and in SDS, where only partial suppression was observed. In contrast, the (-)-N-pentenyl analog (10852, Table 5) had only narcotic antagonist properties, and was somewhat weaker than 10847 in binding to κ - and μ -opioid receptors. Unpredictably, the (-)-hexenyl analog (10855, Table 6) was not found to have narcotic antagonist properties. It was morphine-like in antinociceptive assays and in the SDS assay. It is difficult to rationalize the activities of these normetazocines on structural grounds. That is, the (-)-N-allylnormetazocine (NIH 8773) (Aceto *et al.* 1990) is known to be a potent antagonist with minimal agonist activity. The (-)-N-butenylnormetazocine has now been found to be an agonist-antagonist, N-pentenyl a modest antagonist, and N-hexenyl a morphine-like agonist. The latter compound, with the largest side-chain, apparently cannot fit in an antagonist site in the various opioid receptors, or cannot convert an opioid receptor to an antagonist conformation.

Another (-)-normetazocine, 10864 (Table 7), with an N-hydroxyethyl side-chain, can interact with opioid receptors (especially μ) but displays no agonist activity in antinociceptive assays or in the SDS. Perhaps it is insufficiently lipophilic to pass through blood-brain barriers. Further work will be done with the drug to determine whether it could be clinically useful as a peripheral analgesic. When the amino alcohol side-chain is converted to an amino ether (10863, Table 7), morphine-like *in vivo* and *in vitro* activity appear. The amino ether 10863 is a potent and selective μ -receptor opioid (e.g., μ/κ ratio = 16, and μ/δ ratio = 44).

-Hydroxybutyric acid (CPDD 0044, Table 9) was sent to the stimulant/depressant groups from NIDA, at the request of the DEA. The data from self-administration and drug discrimination assays allowed the prediction that the drug would have little, if any, abuse liability in man.

ABBREVIATIONS USED IN TABLES 2 - 8

Rounded numbers are used in the tables; precise values and details of the procedures are given in the MCV (Aceto *et al.* 1997) and UM (Woods *et al.* 1997) reports.

1) MOUSE ED50/AD50: antinociceptive assays (sc injection); confidence limits are listed in the MCV report (Aceto *et al.* 1997).

HP = hot plate (morphine ED₅₀ = 0.8 (0.3-1.8))

PPQ = phenylquinone (morphine ED₅₀ = 0.23 (0.20-0.25))

TF = tail-flick (morphine ED₅₀ = 5.8 (5.7-5.9))

TFA = tail-flick antagonism vs. morphine (naltrexone AD₅₀ = 0.007 (0.002-0.02); naloxone AD₅₀ = 0.035 (0.01-0.093)).

I = inactive, without a reasonable dose-response relationship, or insufficiently active for statistical analysis.

2) IN VITRO (Data from UM) (Woods *et al.* 1997)

RBH = binding affinity in rat cerebrum membranes (displacement of 0.5 nM [³H] etorphine) in the presence of 150 mM NaCl (morphine EC₅₀ = 23.6).

NE = no effect.

NOTE: Contemporary EC₅₀ data cannot be directly compared with those from reports before 1985 (Jacobson 1986) which were obtained under "-NaCl" (without NaCl) conditions.

BIND = subtype selective binding affinity using monkey brain cortex membranes (data from UM) (Woods *et al.* 1997). Selectivity for μ , δ , and κ opioid receptors determined with [³H]-DAGO, [³H]-p-Cl-DPDPE and [³H]-U69,593, respectively.

VD = electrically stimulated mouse vas deferens EC₅₀ values. Partial agonist indicated by % inhibition of twitch in parenthesis; [A] = antagonism by naltrexone.

SE = slight effect on twitch.

NE = No significant agonist or antagonist effect.

ANT = Antagonist activity. Selective antagonist activity at μ , κ , and/or δ receptors is footnoted.

The antagonist effect may or may not be competitive. Compounds which suppress the twitch and are not antagonized by naltrexone or other narcotic antagonists are said to be non-opioid agonists (*e.g.*, clonidine, a non-opioid agonist, can suppress the twitch but is not antagonized by naltrexone). Compounds which bind with reasonable affinity in the RBH assay and do not suppress the twitch in the VD may have narcotic antagonist properties. The opioid receptor at which the drug exerts its antagonist effect is determined by testing various concentrations of the drug to induce a blockade (antagonism) of the suppression of the twitch in the VD preparation caused by sufentanil (μ), DSLET (κ), or U50,488 (δ) (Woods *et al.* 1997).

3) IN VIVO: in the rhesus monkey.

SDS = single-dose-suppression (Parenthesized numbers = dose range studied, in mg/kg) (from MCV (Aceto *et al.* 1997, or UM prior to 1988).

NS = no suppression

CS = complete suppression

PS = partial suppression

Other Studies (if noted in the footnotes to the tables)

A) In Rat: RI = rat continuous infusion (data from MCV) (Aceto *et al.* 1997)

1) SM = substitution for morphine

NS = no substitution for morphine

CS = complete substitution

PS = partial substitution

2) PPD = primary physical dependence

B) In Rhesus Monkey:

1) PPt-W = studies in non-withdrawn monkeys (data from MCV) (Aceto *et al.* 1997)

PW = precipitated-withdrawal at dose levels, in mg/kg, indicated in parentheses &/or comparison with naloxone [N].

SP = slight precipitation

NP = no precipitation

2) ND = studies using non-dependent monkeys (data from MCV) (Aceto *et al.* 1997)

M-like = morphine-like effect.

3) PPD = primary physical dependence (data from MCV) (Aceto *et al.* 1997)

4) SA or SI = self-administration or self-injection (data from UM) (Woods *et al.* 1997)

NE = no effect

High = codeine-like

IN = intermediate between saline and codeine

SE = slight effect

5) DD = drug discrimination (data from UM) (Woods *et al.* 1997)

NE = no effect

CS = complete substitution

6) MA = monkey analgesia (data from UM) (Woods *et al.* 1997)

7) RF = respiratory function (data from UM) (Woods *et al.* 1997)

Previous Reports

Previous work on a compound is noted using the year listed in the monograph title (*e.g.*, work cited as "1996" indicates that the work was included in "Problems of Drug Dependence 1996", which was published in 1997). Note that the monograph's publication date may be one year after the titled year of the monograph. Complete details of the original work on a compound can be found in the Annual Report from either UM or MCV.

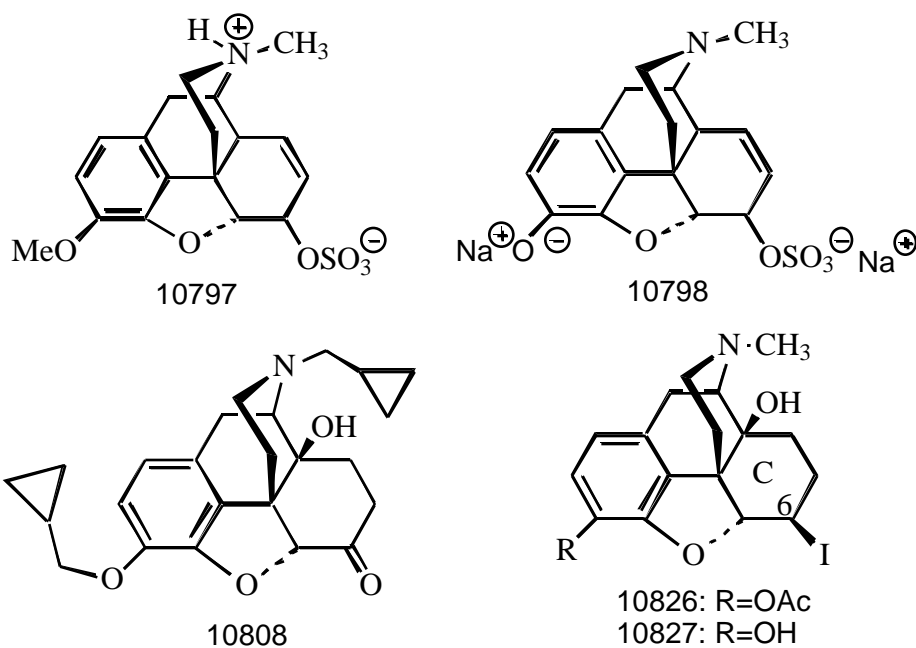
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TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

<u>NIH#</u>	<u>NAME</u>	<u>TABLE #- Evaluator</u>
10797	Codeine-6-O-sulfate zwitterion	2-MCV/UM
10798	Morphine-6-O-sulfate disodium salt	2-MCV/UM
10806	Buprenorphine-3-cyclopropylmethyl ether.HCl	4-MCV/UM
10807	Diprenorphine-3-cyclopropylmethyl ether.HCl	4-MCV/UM
10808	Naltrexone-3-cyclopropylmethyl ether.HCl	2-MCV/UM
10815	(+)-4-[(R)--(1 <i>S</i> ,5 <i>R</i>)-4-Allyl-2,5-dimethyl-1-piperazinyl]-3-methoxybenzyl]-N,N-diethylbenzamide (SNC 80)	8-UM
10825	3-Acetoxy-6 - trifluoromethanesulfonyloxy-14-hydroxy-17-methyl-4,5 - epoxymorphinan	3-MCV
10826	3-Acetoxy-14-hydroxy-6 -iodo-17-methyl-4,5 -epoxymorphinan	2-MCV/UM
10827	3,14-Dihydroxy-6 -iodo-17-methyl-4,5 -epoxymorphinan	2-MCV/UM
10831	3-Acetoxy-14-hydroxy-6 -iodo-17-methyl-4,5 -epoxymorphinan	3-UM
10832	3,14 -Dihydroxy-6 -iodo-17-methyl-4,5 -epoxymorphinan	3-MCV/UM
10834	1-[3-(4-Fluorobenzoyl)propyl]-4-(3-hydroxyphenyl)-4-(1-oxopropyl)piperidine.HCl	4-MCV/UM
10835	(-)-5,9 -Dimethyl-2-[3-(4-fluorobenzoyl)propyl]-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10836	(+)-5,9 -Dimethyl-2-[3-(4-fluorobenzoyl)propyl]-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10842	Oxymorphindole.HCl	3-MCV
10844	14 -(p-Chlorocinnamoylamino)-3-cyclopropylmethoxy-N-cyclopropylmethyl-7,8-dihydromorphinone	3-MCV
10845	14 -(p-Chlorocinnamoylamino)-N-cyclopropylmethyl-3-propargylmethoxy-7,8-dihydromorphinone	3-MCV
10847	(-)-2-(3-Butenyl)-5,9 -dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	5-MCV/UM
10848	(+)-2-(3-Butenyl)-5,9 -dimethyl-2'-hydroxy-6,7-benzomorphan HCl	5-MCV/UM
10849	N-Cyclopropylmethyl-7,8-dihydro-14 - [3'(methoxycarbonyl)propenamido]normorphinone.oxalate	3-MCV
10852	(-)-5,9 -Dimethyl-2'-hydroxy-2-(4-pentenyl)-6,7-benzomorphan.HCl	5-MCV/UM
10853	(+)-5,9 -Dimethyl-2'-hydroxy-2-(4-pentenyl)-6,7-benzomorphan.HCl	5-MCV/UM
10854	1-(2-Pyrimidinyl)piperazine.2HCl	8-MCV/UM
10855	(-)-5,9 -Dimethyl-2-(5-hexenyl)-2'-hydroxy-6,7-benzomorphan.HCl	6-MCV/UM
10856	(+)-5,9 -Dimethyl-2-(5-hexenyl)-2'-hydroxy-6,7-benzomorphan.HCl	6-MCV/UM
10857	(-)-2'-Acetoxy-5,9 -dimethyl-2-heptyl-6,7-benzomorphan.HCl	6-MCV/UM
10858	(-)-5,9 -Dimethyl-2-heptyl-2'-methoxy-6,7-benzomorphan.HCl	6-MCV
10860	(-)-5,9 -Dimethyl-2-heptyl-2-propionoxy-6,7-benzomorphan.HCl	6-UM
10862	(+)-2-(2-Cyanoethyl)-5,9 -dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	6-MCV/UM
10863	(-)-5,9 -Dimethyl-2-(2-ethoxyethyl)-2'-hydroxy-6,7-benzomorphan.oxalate	7-MCV/UM
10864	(-)-5,9 -Dimethyl-2'-hydroxy-2-(2-hydroxyethyl)-6,7-benzomorphan .oxalate	7-MCV/UM
10865	(+)-5,9 -Dimethyl-2'-hydroxy-2-(2-hydroxyethyl)-6,7-benzomorphan .oxalate	7-MCV
10866	(+)-5,9 -Dimethyl-2-(2-ethoxyethyl)-2'-hydroxy-6,7-benzomorphan .oxalate	7-MCV/UM
10868	Lofexidine [2-[1-(2,6-Dichlorophenoxy)ethyl]4,5-dihydro-1H-imidazole]	8-MCV
10869	(-)-2-Cyanomethyl-5,9 -dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-MCV
10872	(+)-2-(5-Chloropentyl)-5,9 -dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-MCV
10873	(+)-N-3-(p-Fluorobenzoyl)propyl-3 -methyl-4-phenyl-4-propionyloxypiperidine.fumarate	4-MCV
CPDD 0044	-Hydroxybutyric Acid	9-UM/UMs

TABLE 2. 4,5-EPOXYMORPHINANS^a



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10797	I	I	I	I	3092	3470(96%)[A]	NE
10798	0.4	0.3	1.4	I	60	269(80%)[A]	CS (0.5xM)
10808	I	I	I	0.2	553	ANT ^b	NS ^c
10826	0.03 ^d	0.02 ^d	0.02 ^d	I ^d	259 ^{d,e}	287(90%)[A] ^{d,f}	CS (20xM) ^d
10827	0.08	0.008	0.04	I	31 ^g	63(100%)[A]	CS (60xM)

a) See text for explanation of column headings and abbreviations.

b) Weak, non-selective, antagonist.

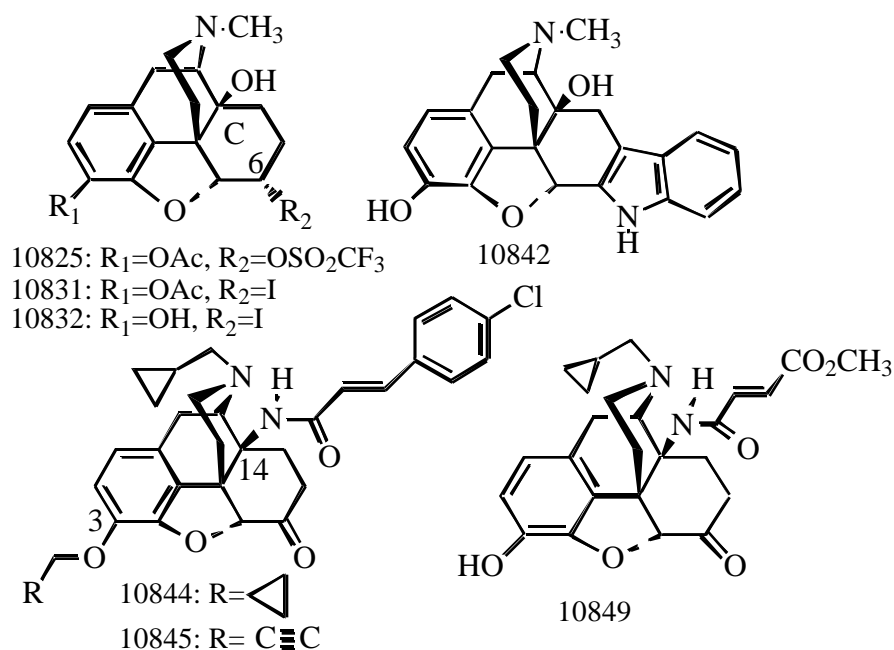
c) Weak μ -antagonist.

d) Previously reported - 1995.

e) BIND: $\mu=5.5$, $\kappa=319$, $\delta=103$ nM.

f) Partial μ -agonist, some δ -activity.

g) BIND: $\mu=0.9$, $\kappa=51$, $\delta=13$ nM.

TABLE 3 (CONTINUED). 4,5-EPOXYMORPHINANS^a

NIH #	MOUSE ED50/AD50 IN VITRO					MONKEY	
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10825	0.22	0.04	0.14	I	1590 ^b	276(91%)[A] ^b	CS (20xM)
10831	0.06 ^b	0.009 ^b	0.02 ^b	I ^b	242 ^{b,c}	6500(100%)[A] ^{b,d}	CS (75xM) ^b
10832	0.02 ^b	0.1 ^b	0.02 ^b	I ^b	40 ^{b,e}	82(100%)[A] ^b	CS (300xM) ^b
10842	I	I	I	I	BIND ^{b,f}	155 (78%)[A] ^{b,c,g}	NS ^h
10844	I	6.7	I	I			NS ⁱ
10845	0.26	0.26	1.2	I			CS (60xM) ^j
10849	1.8	1.5	1.2	I			NS, PW ^k

a) See text for explanation of column headings and abbreviations.

b) Previously reported - 1995.

c) BIND: $\mu=2.4$, $\sigma=238$, $\tau=71$ nM.

d) Weak μ - and κ -agonist.

e) BIND: $\mu=1.3$, $\sigma=79$, $\tau=14$ nM.

f) Previously reported - 1995; BIND: $\mu=157$, $\sigma=2.29$, $\tau=297$ nM.

g) Previously reported - 1995; selective μ -antagonist.

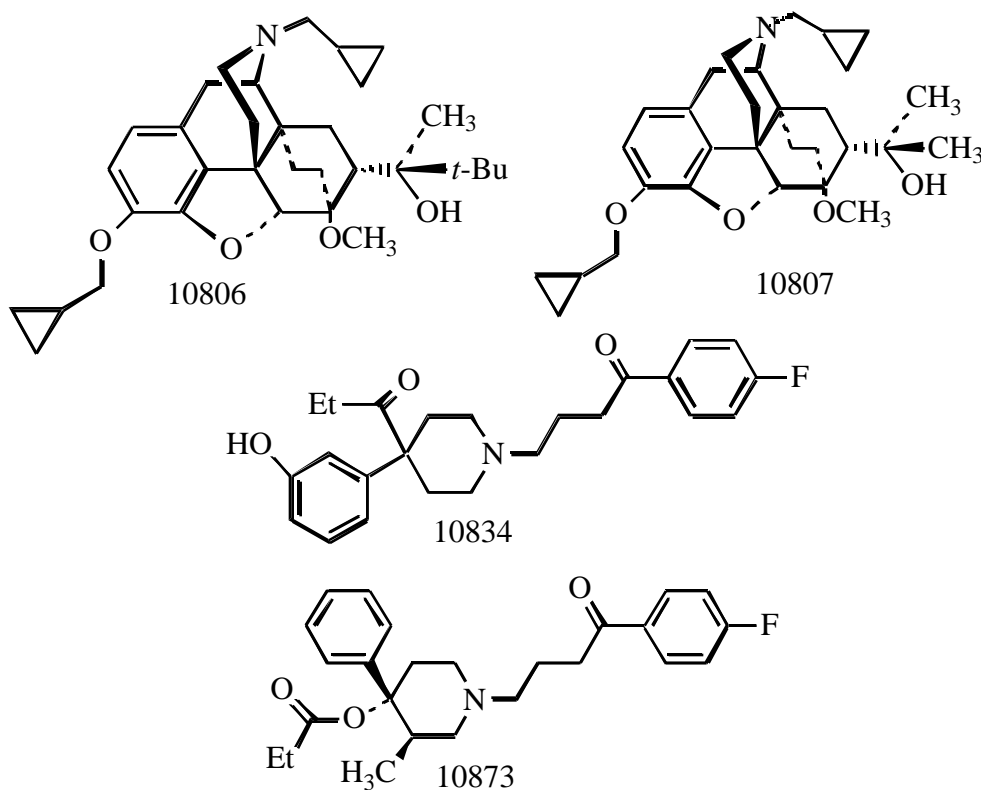
h) Some reduction in withdrawal signs at 5 mg/kg.

i) Potent, long-acting antagonist.

j) Initial μ -agonist, followed by irreversible antagonist activity.

k) In PW: 0.1xN; less intense withdrawal than N; duration > N.

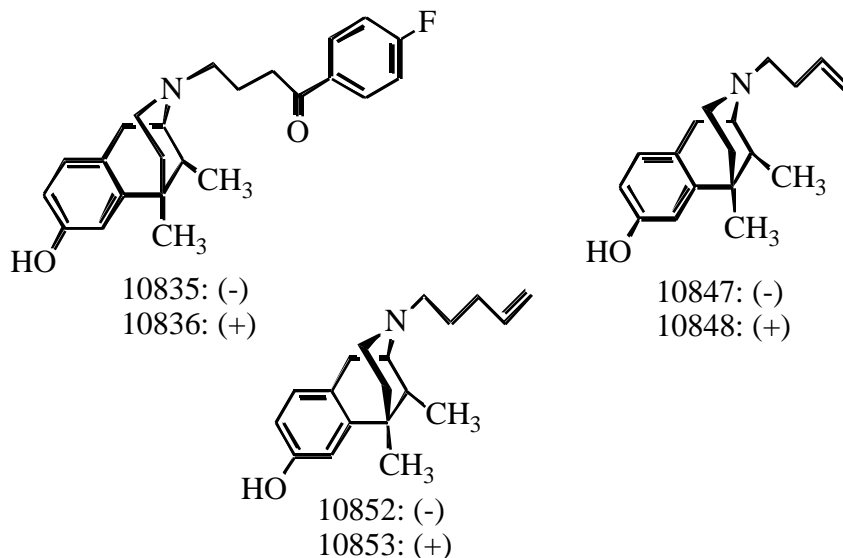
TABLE 4. ENDOETHANOORIPAVINES AND HALOPERIDOL-LIKE COMPOUNDS^a



NIH #	MOUSE ED50/AD50 IN VITRO				MONKEY		
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10806	I	8.3	I	I	1060	ANT ^b	PS ^c
10807	I	I	I	I	990	ANT ^d	NS ^e
10834	I	0.48	I	I	BIND ^f	9.8(31%)[NA] ^g	NS ^h
10873 ⁱ	0.5	0.09	0.5	I			PS ^j

- a) See text for explanation of column headings and abbreviations.
 b) Weak, non-selective, antagonist; insurmountable at .
 c) Weak, non-dose related suppression of withdrawal. Weak μ -activity.
 d) Very weak, non-selective, antagonist.
 e) Weak μ -antagonist with pronounced overt behavioral effects.
 f) BIND: μ =19, = 180, =449 nM.
 g) Weak, non-selective, antagonist.
 h) Attenuated withdrawal due to severe cataleptic activity.
 i) Racemate (NIH 10671) previously reported - 1991.
 j) Higher doses might cause complete suppression.

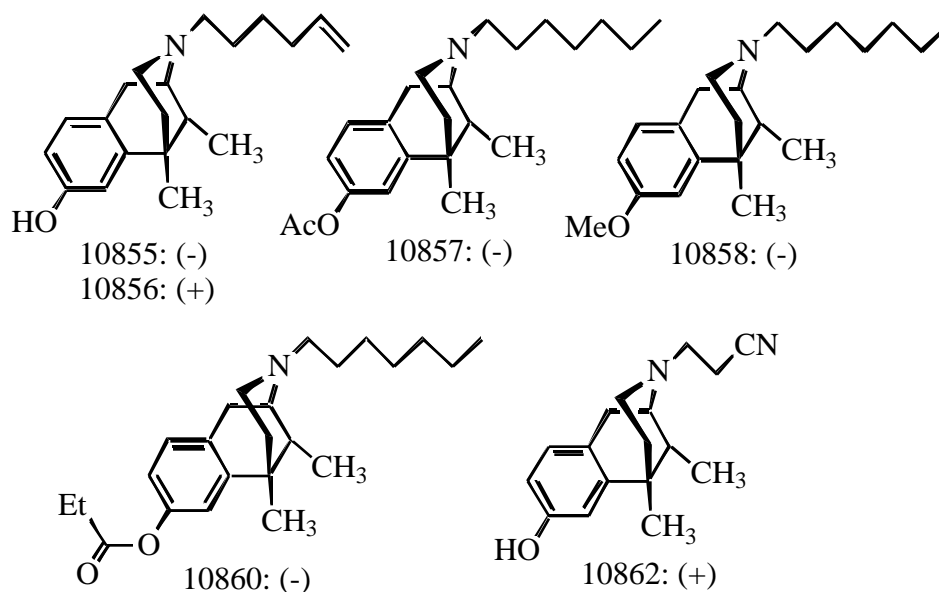
TABLE 5. 6,7-BENZOMORPHANS^a



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD (nM)	SDS
10835	I	2.8	10.1	I	BIND ^b	1.2(100%)[NA]	PS ^c
10836	I	0.08	4.7	I	BIND ^d	66(100%)[NA] ^e	NS ^f
10847	0.8	0.3	0.5	3.8	BIND ^g	103(84%)[A] ^h	PS ⁱ
10848	I	17	I	I	BIND ^j	48(30%)[NA]	NS
10852	I	I	I	6.1	BIND ^k	537(100%)[A] ^l	NS
10853	I	I	I	I	BIND ^m	308(16%)[NA]	NS

- a) See text for explanation of column headings and abbreviations.
- b) BIND: $\mu=161$, $\sigma=360$, $\tau=153$ nM.
- c) Behavioral signs in mice and monkeys suggest neuroleptic properties.
- d) BIND: $\mu=106$, $\sigma>6000$, $\tau=848$ nM.
- e) Very weak, non-selective antagonist.
- f) Reduction of withdrawal scores at 5 mg/kg; possible neuroleptic.
- g) BIND: $\mu=3$, $\sigma=34$, $\tau=1.5$ nM.
- h) Both μ - and κ -agonist.
- i) Dose-related reduction of withdrawal, and signs seen with antagonists.
- j) BIND: $\mu=1130$, $\sigma>6000$, $\tau=757$ nM.
- k) BIND: $\mu=12$, $\sigma=93$, $\tau=8$ nM.
- l) Both μ - and κ -agonist.
- m) BIND: $\mu>6000$, $\sigma=4177$, $\tau>6000$ nM.

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



NIH #	MOUSE ED50/AD50 IN VITRO				MONKEY		
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10855	0.6	0.3	0.8	I	BIND ^b	175(100%)[A] ^c	CS (1xM)
10856	I	I	I	I	BIND ^d	83(40%)[NA]	NS
10857	3	1.3	5.6	I	BIND ^e	246(93%)[NA]	NS ^f
10858	I	9.4	I	I			NS ^g
10860					BIND ^h	194(86%)[NA] ⁱ	
10862	I	I	I	I	BIND ^j	3960 (41%)[NA]	NS ^k

a) See text for explanation of column headings and abbreviations.

b) BIND: $\mu=18$, $\sigma=98$, $\tau=7$ nM. Possible μ -antagonist.

c) Both μ - and σ -agonist.

d) BIND: $\mu=816$, $\sigma=>6000$, $\tau=492$ nM.

e) BIND: $\mu=49$, $\sigma=93$, $\tau=60$ nM.

f) Convulsions 10 min after cumulative dose of 15 mg/kg.

g) Ataxia, convulsions; no μ -like activity.

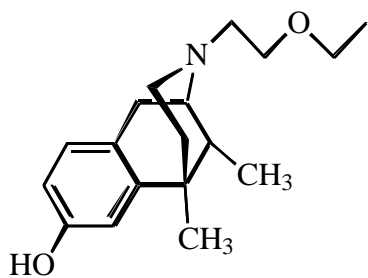
h) BIND: $\mu=28$, $\sigma=47$, $\tau=48$ nM.

i) Decreased magnitude, but did not suppress twitch at any concentration; unusual agonist.

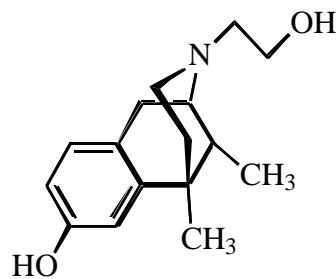
j) BIND: $\mu=>6000$, $\sigma=>6000$, $\tau=223$ nM.

k) Attenuated withdrawal; may have some antinociceptive activity.

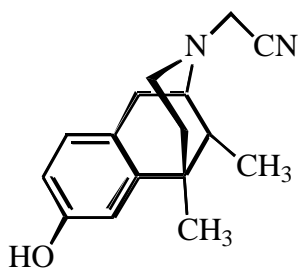
TABLE 7 (CONTINUED). 6,7-BENZOMORPHANS^a



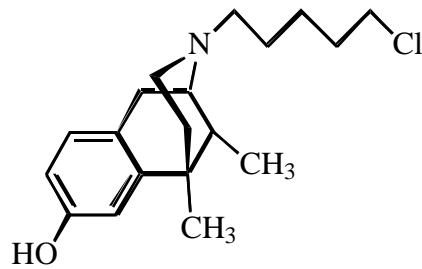
10863: (-)
10866: (+)



10864: (-)
10865: (+)



10869: (-)



10872: (+)

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10863	0.85	0.35	1.08	I	BIND ^b	210(91%)[A]	CS (1xM)
10864	I	I	I	I	BIND ^c	1290(68%)[SA] ^d	NS
10865	I	I	I	I			PS ^e
10866	I	I	I	I	BIND ^f	102(26%)[NA] ^g	NS
10869	8.5	1.5	11.6	I			CS (0.5xM)
10872	I	4.6	I	I			

a) See text for explanation of column headings and abbreviations.

b) BIND: $\mu=42$, $\sigma=115$, $\text{IC}_{50}=2.6$ nM.

c) BIND: $\mu=41$, $\sigma=316$, $\text{IC}_{50}=16$ nM.

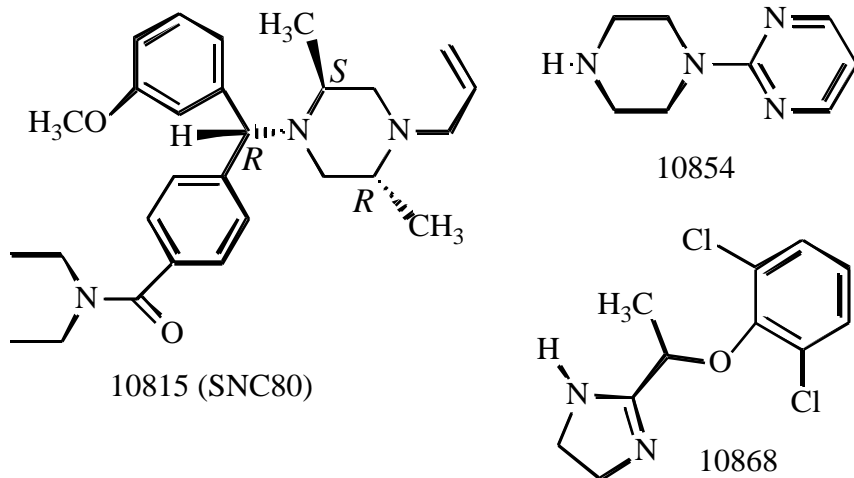
d) Weak μ -agonist.

e) Inverse dose-response; possible antinociceptive activity.

f) BIND: $\mu=956$, $\sigma=>6000$, $\text{IC}_{50}=629$ nM.

g) Weak antagonist at μ and κ .

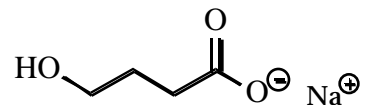
TABLE 8. MISCELLANEOUS^a



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10815	I ^b	3.8 ^b	I ^b	I ^b	>6000 ^{c,d}	6.4 (100%)[A] ^{c,e}	NS (3,15) ^{c,f}
10854	I	I	I	I	BIND ^g	515(46%)[NA]	NS
10868	I	0.01	0.4	I			PS ^h

- See text for explanation of column headings and abbreviations.
- Previously reported - 1995.
- Previously reported - 1994.
- BIND: $\mu=488$, $\sigma=0.9$, $KD=1170$ nM.
- Relatively selective μ -agonist.
- No exacerbation of withdrawal, ataxia, slowing; perhaps non-opioid.
- BIND: $\mu=>6000$, $\sigma=>6000$, $KD=>6000$ nM.
- Fewer behavioral effects observed than with clonidine.

TABLE 9. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



<u>CPDD#</u>	<u>SA</u> ^a	<u>DD</u> ^b
0044	Did not maintain behavior. No reinforcing effect.	PB-trained monkeys: No ^c AMPH-trained monkeys: 50% ^{d,e}

- a) Self-administration (monkey).
- b) Drug discrimination (intragastric administration, monkey).
- c) No drug-appropriate responding in PB-trained monkeys.
- d) Maximum of 50% drug-appropriate responding in AMPH-trained monkeys. The response was not dose-related.
- e) The drug may have weak AMPH-like subjective effects, but probably no PB-like subjective effects in humans.