

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)

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THE DRUG EVALUATION COMMITTEE (DEC)

The analgesic testing program of DEC originated with the appointment of Dr. Nathan Eddy to direct the pharmacology program in the University of Michigan in 1930, a year after the CPDD was formed as the Committee on Drug Addiction of the National Research Council, NAS (Eddy, 1973; May and Jacobson, 1989). A CPDD Preclinical Testing Program was established in 1983 to initiate the evaluation of stimulants and depressants and incorporate the on-going analgesic testing program. The Program eventually became known as the CPDD's Animal Testing Committee and in 1989 the name changed to the CPDD Drug Evaluation Committee (DEC). This CPDD committee is responsible for gathering in vivo and in vitro information on potentially abusable drugs.

The DEC currently examines, and/or does methodological research on drugs with analgesic, stimulant, depressant, and/or hallucinogenic actions, and provides information relating to the physical dependence potential and abuse liability of these drugs to pharmaceutical industry, university researchers, and governmental organizations in the U.S. and abroad, as well as to the World Health Organization. The DEC data have been used by NIDA, the DEA, and the FDA for the determination of the scheduling of these drugs, and have been recently used by researchers in their search for medications to treat drug abuse. DEC is one of the few organizations able to provide such information using predetermined, established, published methodology in a completely independent and unbiased manner. 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.*, 1995b; Jacobson, 1995; Winger *et al.*, 1995; Woods *et al.*, 1995), as well as in various journals (Aceto *et al.*, 1989; May *et al.*, 1994).

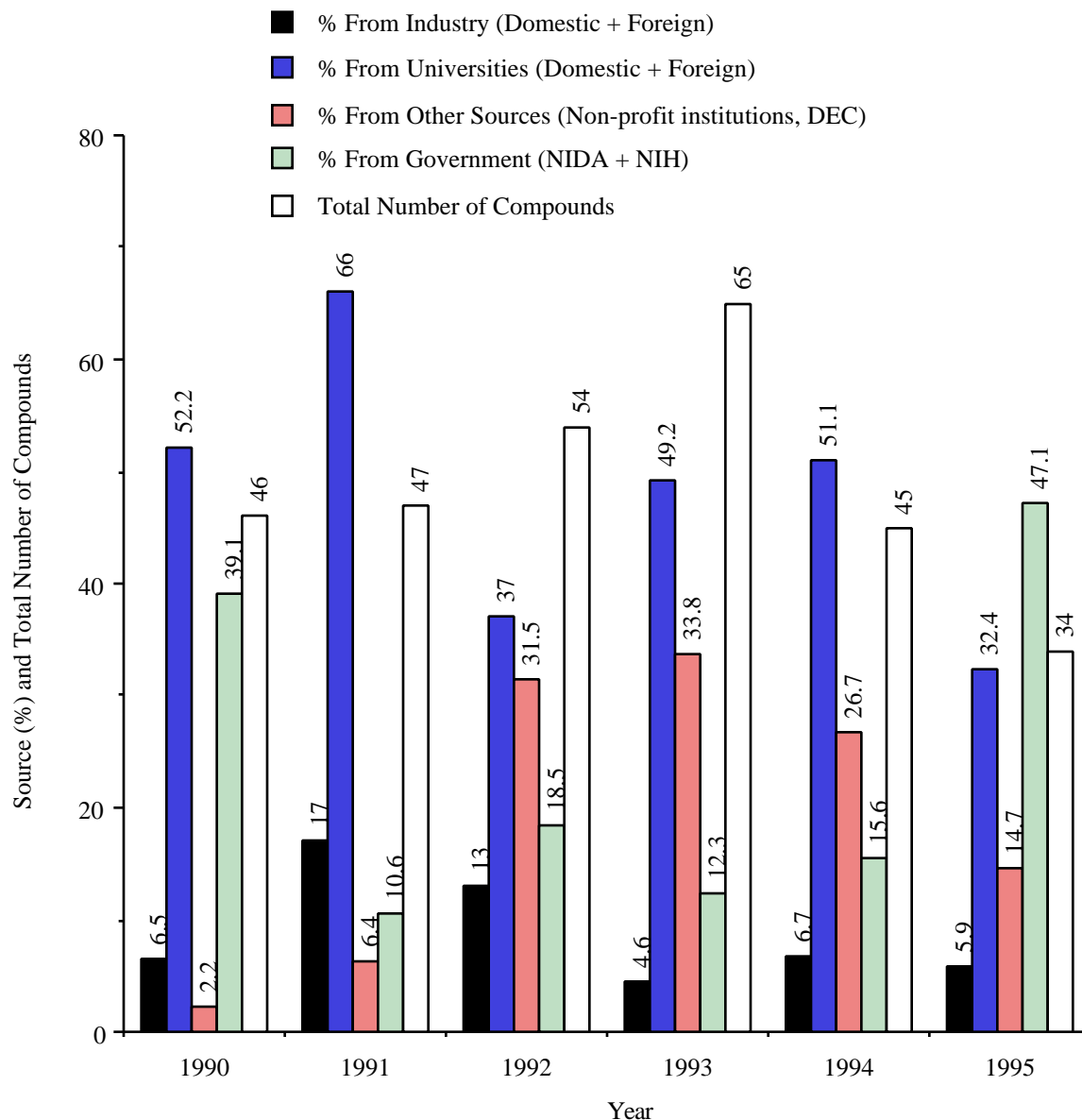
MEMBERS OF THE DRUG EVALUATION COMMITTEE (DEC)

The analgesic testing groups are based in the Medical College of Virginia (MCV; Drs. Harris, Aceto, Bowman, and May) and at the University of Michigan (UM, Drs. Woods, Medzihradsky, Smith, and Winger). The stimulant/ depressant testing groups were at MCV (Drs. Patrick and Harris), UM (Dr. Winger), and the University of Mississippi (Dr. Woolverton). In August, Louisiana State University (Dr. France) will initiate its testing program. Dr. T. Cicero (Washington University) is the chairman of the DEC.

STATISTICS

The sources, and total number of compounds, released for publication during the past six years (1990 - 1995) can be seen in Fig. 1. Except for 1991-1992, the percentage of drugs received from pharmaceutical industry has remained about the same (ca. 6% during this time period). A much larger percentage of our drugs come from chemists in universities, domestic and foreign, and this percentage can be seen to be variable (e.g., 66% of the released compounds originated in universities in 1991, contrasted with 32% this year). The number of compounds which come from non-profit institutions (14.7%) have appreciably lessened since 1992-1993. This year almost half of our compounds came from various government groups (NIDA and NIH). The two compounds released for publication after testing by the stimulant/depressant testing groups came from the WHO, and NIDA. The WHO-submitted drug, zipeprol, is the subject of a recent paper submitted to Drug and Alcohol Dependence by the involved DEC scientists (Aceto *et al.*, 1995a).

FIG. 1. DEC ANALGESIC PROGRAM: SOURCES AND NUMBER OF COMPOUNDS TESTED (1990-1995)



EXPERIMENTAL OBSERVATIONS

Table 1 lists the names and assigned NIH numbers of the compounds examined this year, and notes the Tables in which they are shown. Tables 2 - 8 present the structures and a summary of the biological activities of compounds evaluated as analgesics, as obtained from Aceto *et al.* (1996), and Woods *et al.* (1996), and Table 9 summarizes the work of the stimulant/depressant groups. The compounds in Tables 2 - 8 are grouped according to their molecular structure (e.g., 4,5-epoxymorphinans, morphinans, fentanyl-like compounds, etc.) in order to facilitate the comparison of their molecular structure and biological activity. As seen in Tables 2 - 4, the 4,5-epoxymorphinan class of compounds are still being explored, and are the source of new, interesting, and potent agonists (e.g., NIH 10801, Table 2) and antagonists (e.g., NIH 10805, Table 2). The 4,5-epoxymorphinans, exemplified by morphine, codeine, and heroin, were initially described over a century ago - yet the properties of compounds in this class still fascinates both chemists and pharmacologists. Another 4,5-epoxymorphinan, the

zwitterion NIH 10775 (Table 2) displays reasonably potent antinociceptive activity, yet does not substitute for morphine in the SDS assay in monkeys; it is possible that it is metabolized differently in the various animal species used for these assays, exemplifying the importance of using several assays in different animal species. This compound has little affinity for opioid receptors in the binding assay (as expected for phenolic esters) and in the vas deferens preparation. NIH 10842 (Table 2, oxymorphindole) appears to be a selective agonist-antagonist in the vas deferens preparation, and is potent and selective in the binding assays. Subtype-selective opioids are valuable and are the subject of considerable contemporary research. The endoethano and endoetheno derivatives of the 4,5-epoxymorphinans have been explored for some time (buprenorphine is one of the useful relatives in this class); new members of this class are shown in Table 3. NIH 10811 (Table 3) is an especially potent antagonist. The compounds listed in Table 4 come from a series of 4,5-epoxymorphinans explored at LMC, NIDDK, to find a suitable SPECT imaging ligand. The ¹²³I labelled NIH 10826 has been noted to be a highly selective μ -agonist and is being explored for SPECT imaging purposes.

Data on α -levomethadol (NIH 10837, Table 5), a probable metabolite of LAAM, were needed for toxicity studies. Although NIH 10837 was first synthesized in 1950 by Dr. E. L. May at NIH (as NIH 4552), it was not tested at UM at that time. It is interesting to note that although it is reasonably potent in antinociceptive assays and in a binding assay (where it shows selectivity for the μ -opioid receptor), it does not display the typical opioid-like property of suppressing abstinence in the SDS assay in monkeys.

Except for NIH 10789, the fentanyl-like compounds in Table 6 are atypically impotent as antinociceptives. Most interesting for theoretical chemists, only one of the two compounds (NIH 10788 and 10789), which differ at one chiral center, appears to behave as an opioid. This is very common in the structurally rigid classes of opioids where stereochemistry is known to be important for opioid activity (e.g., in the 4,5-epoxymorphinan class, (-)- but not (+)-morphine has opioid activity).

Among the miscellaneous compounds, those with structures uncharacteristic of the known classes of opioids, NIH 10815 (Table 7), has been noted to be a selective, potent, δ -receptor agonist by others (Calderon *et al.*, 1994). In our hands it displayed only weak antinociceptive activity. The vas deferens preparation gave data in general accord with the previously published work. Zipeprol (NIH 10843, CPDD 0042; Table 8) was examined by both the analgesic and stimulant/depressant groups. Although it showed weak antinociceptive activity in one (PPQ) assay, it completely suppressed abstinence in morphine-dependent monkeys in the SDS assay.

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.*, 1996) and UM (Aceto *et al.*, 1996) reports.

1) MOUSE ED₅₀/AD₅₀: antinociceptive assays (sc injection); confidence limits are listed in the MCV report (Aceto *et al.*, 1996).

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.*, 1996)

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, 1996) which were obtained under "-NaCl" (without NaCl) conditions.

BIND = subtype selective binding affinity using monkey brain cortex membranes (data from UM) (Woods *et al.*, 1996) . Selectivity for μ , κ , and δ 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.*, 1996) .

3) IN VIVO: in the rhesus monkey (from MCV (Aceto *et al.*, 1996) ; from MCV or UM prior to 1988).

SDS = single-dose-suppression (Parenthesized numbers = dose range studied, in mg/kg)

NS = no suppression

CS = complete suppression

PS = partial suppression

Other Studies (noted in the footnotes to the tables)

A) In Rat: RI = rat continuous infusion (data from MCV) (Aceto *et al.*, 1996)

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.*, 1996)

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.*, 1996)

M-like = morphine-like effect.

3) PPD = primary physical dependence (data from MCV) (Aceto *et al.*, 1996)

4) SA or SI = self-administration or self-injection (data from UM) (Woods *et al.*, 1996)

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.*, 1996)

NE = no effect

CS = complete substitution

6) MA = monkey analgesia (data from UM) (Woods *et al.*, 1996)

7) RF = respiratory function (data from UM) (Woods *et al.*, 1996)

Previous Reports

Previous work on a compound is noted using the year listed in the monograph title (*e.g.*, work cited as "1992" indicates that the work was included in "Problems of Drug Dependence 1992", which was published in 1993). 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.

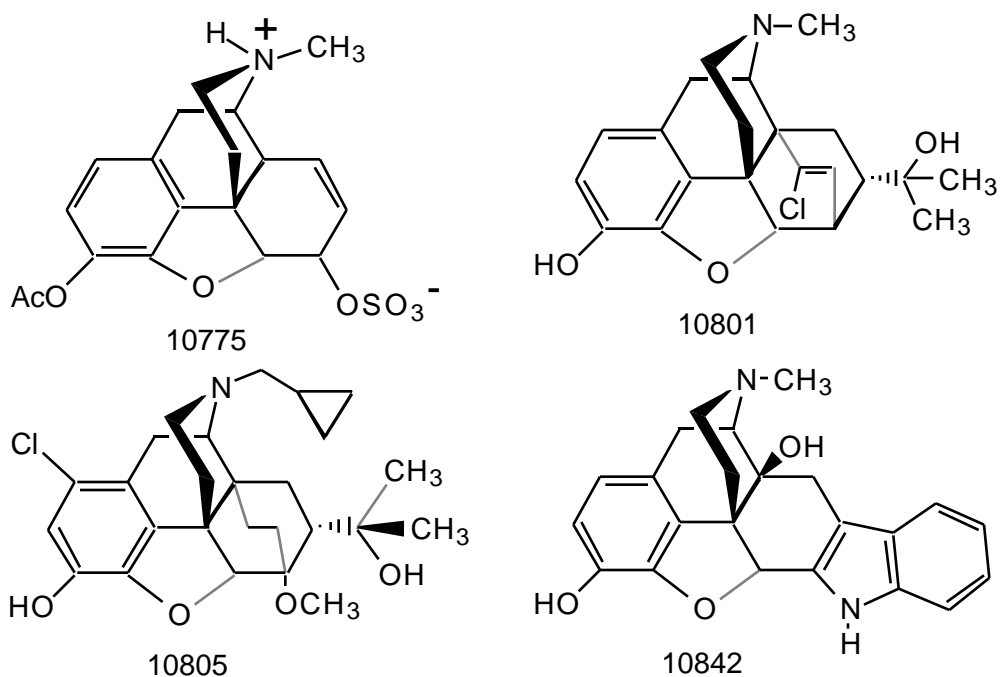
REFERENCES

- 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, 1995a, in review.
- 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 (1994). *In* Problems of Drug Dependence 1994, ed. by L. S. Harris, vol. I, pp. 162-212, NIDA Research Monograph 152, Washington, DC., 1995b.
- 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 (1995). *In* Problems of Drug Dependence 1995, ed. by L. S. Harris, NIDA Research Monograph, Washington, DC., 1996, 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 *p*-substituted cinnamoylaminomorphinones and their partial mu agonist codeinone relatives. Arzneimittelforschung 39:570-575, 1989.
- Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; and Rice, K. C. Probes for narcotic receptor mediated phenomena .19. Synthesis of (+)-4-[(R)-((2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC 80): A highly selective, nonpeptide delta opioid receptor agonist. J Med Chem 37:2125-2128, 1994.
- Eddy, N. B.: The National Research Council Involvement in the Opiate Problem, 1928-1971, National Academy of Sciences, Washington, DC., 1973.
- Jacobson, A. E.: Biological evaluation of compounds for their physical dependence potential and abuse liability. XVIII. Drug Evaluation Committee of the College on Problems of Drug Dependence, Inc. (1994). *In* Problems of Drug Dependence 1994, ed. by L. S. Harris, vol. I, pp. 84-104, NIDA Research Monograph 152, Washington, DC, 1995.
- 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* Problems of Drug Dependence 1995, ed. by L. S. Harris, NIDA Research Monograph, Washington, DC, 1996, in press.
- 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 *n*-alkyl (methyl-decyl)-*n*-normetazocines (2'-hydroxy-5,9 -methyl-6,7-benzomorphans): in vitro and in vivo properties. J Med Chem 37:3408-3418, 1994.
- May, E. L. and Jacobson, A. E. The Committee on Problems of Drug Dependence: a legacy of the National Academy of Sciences. A historical account. Drug Alcohol Depend 23:183-218, 1989.
- Winger, G.; Woolverton, W. L.; Rowlett, J. K.; English, J. A.; Patrick, G. A.; Nader, M. A.; McDaniel, R. E.; Hawkins, W. T.; Massey, B. W.; Harris, L. S.; and Woods, J. H.: Progress report from the testing program for stimulant and depressant drugs (1994). *In* Problems of Drug Dependence 1994, ed. by L. S. Harris, vol. I, pp. 105-116, NIDA Research Monograph 152, Washington, DC., 1995.
- Woods, J. H.; France, C. P.; Medzihradsky, F.; Smith, C. B.; and Winger, G. D.: Evaluation of new compounds for opioid activity. Annual report (1995). *In* Problems of Drug Dependence 1995, ed. by L. S. Harris, NIDA Research Monograph, Washington, DC., 1996, in press.
- Woods, J. H.; Medzihradsky, F.; Smith, C. B.; France, C. P.; and Winger, G. D.: Evaluation of new compounds for opioid activity. 1994. *In* Problems of Drug Dependence 1994, ed. by L. S. Harris, vol. I, pp. 117-161, NIDA Research Monograph 152, Washington, DC., 1995.

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

<u>NIH#</u>	<u>NAME</u>	<u>TABLE #- Evaluator^a</u>
10747	3-(4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino] piperidine)-propanoic acid, methyl ester. HCl	6-MCV/UM
10764	N-(Phenyl)-N-[1-(2-(1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7H-purin-7-yl)ethyl)-4-methoxycarbonyl-4-piperidinyl]propanamide oxalate	6-MCV/UM
10767	<i>R</i> -(+)-3-Amino-1-hydroxy-2-pyrrolidone	7-MCV/UM
10775	Dihydromorphine 3-acetate 6-sulfate	2-MCV/UM
10788	(±)-8-(2-Hydroxy-2-phenylethyl)-2-ethyl-t-6-methyl-1-phenyl-1, 3, 8-triazaspiro[4.5]dec-2-ene-r-4-one .2HCl	6-MCV/UM
10789	(±)-8-(2-Hydroxy-2-phenylethyl)-2-ethyl-c-6-methyl-1-phenyl-1, 3, 8-triazaspiro[4.5]dec-2-ene-r-4-one .2HCl	6-MCV/UM
10801	18-Chloro-4,5 -epoxy-3-hydroxy- , ,N-trimethyl-6 ,14 -ethenoisomorphinan-7 -methanol.HCl	2-MCV/UM
10804	Metathebainone.HCl	5-MCV/UM
10805	1-Chlorodiprenorphine oxalate	2-MCV/UM
10810	N-Cyclopropylmethyl[7 ,8 ,2',3']cyclopentano-1'-[S]hydroxy-6,14-endoethenotetrahydronororipavine.HCl	3-MCV/UM
10811	N-Cyclopropylmethyl[7 ,8 ,2',3']cyclohexano-1'-[S]hydroxy-6,14-endoethenotetrahydronororipavine.HCl	3-MCV/UM
10812	2-Nitrobuprenorphine.HCl	3-MCV/UM
10813	2-Nitrodiprenorphine.HCl	3-MCV/UM
10814	2-Nitronaltrexone.HCl	3-MCV/UM
10815	(+)-4-[(<i>R</i>)- -(1 <i>S</i> ,5 <i>R</i>)-4-Allyl-2,5-dimethyl-1-piperazinyl]-3-methoxybenzyl]-N,N-diethylbenzamide	7-MCV/UM
10816	(±)-2,4-Dimethyl-5-(3-hydroxyphenyl)morphane .HBr	5-MCV/UM
10817	7-Chloro-7-cyano-1,2,3,4,6,7,8,8a-octahydro-6-methoxy-2-methyl-6,8a-ethanoisoquinoline	7-MCV/UM
10818	N -Nitro-L-arginine methyl ester	7-MCV/UM
10819	N -Nitro-L-arginine	7-MCV/UM
10823	3,6 ,14-Trihydroxy-17-methyl-4,5 -epoxymorphinan	4-MCV/UM
10824	3-Acetoxy-6 ,14-dihydroxy-17-methyl-4,5 -epoxymorphinan	4-MCV/UM
10825	3-Acetoxy-6 -trifluoromethanesulfonyloxy-14-hydroxy-17-methyl-4,5 -epoxymorphinan	4-UM
10826	3-Acetoxy-14-hydroxy-6 -iodo-17-methyl-4,5 -epoxymorphinan	4-MCV/UM
10827	3,14-Dihydroxy-6 -iodo-17-methyl-4,5 -epoxymorphinan	4-MCV/UM
10828	3,6 ,14-Trihydroxy-17-methyl-4,5 -epoxymorphinan	4-MCV/UM
10829	3-Acetoxy-6 ,14-dihydroxy-17-methyl-4,5 -epoxymorphinan	4-MCV/UM
10830	3-Acetoxy-6 -trifluoromethanesulfonyloxy-14-hydroxy-17-methyl-4,5 -epoxymorphinan	4-MCV/UM
10831	3-Acetoxy-14-hydroxy-6 -iodo-17-methyl-4,5 -epoxymorphinan	4-MCV/UM
10832	3,14 -Dihydroxy-6 -iodo-17-methyl-4,5 -epoxymorphinan	4-MCV/UM
10837	-(-)-6-Dimethylamino-4,4-diphenyl-3-heptanol .HCl (-levomethadol, -l-methadol)	5-MCV/UM
10842	Oxymorphindole .HCl	2-UM
10843	Zipeprol [4-(2-methoxy-2-phenylethyl)- -(methoxyphenylmethyl)-1-piperazineethanol .2HCl]	8-MCV/UM
10850	(+)-Epibatidine hemioxalate (= natural base)	8-MCV
10851	(-)-Epibatidine hemioxalate (= unnatural base)	8-MCV
CPDD 0042	Zipeprol [4-(2-methoxy-2-phenylethyl)- -(methoxyphenylmethyl)-1-piperazineethanol .2HCl]	9-MCV, UM, UMS
CPDD 0043	4-Bromo-2,5-dimethoxy- -phenethylamine .HCl	9-MCV, UM, UMS

TABLE 2. 4,5-EPOXYMORPHINANS^a



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10775	5.0 ^b	0.7	4.2	I ^b	2500	2405 (85%)[A] ^c	NS (3,16) ^d
10801	0.03	0.01	0.03	I	3.7	26.8 (99%)[A] ^e	CS (150xM)
10805	I ^f	I ^f	I ^{f,g}	0.09 ^f	0.61 ^f	ANT ^{f,h}	NS (0.01-0.02) ^{f,i}
10842	-	-	-	-	BIND ^j	155 (78%)[A] ^k	-

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

b) Toxic.

c) Weak, partial μ -opioid agonist.

d) Inconsistent dose-response; attenuation of withdrawal. Lack of effect, compared with mice antinociceptive data, may reflect metabolic differences.

e) Relatively selective μ -agonist.

f) Previously reported - 1993.

g) Apparent pA_2 vs. M: non-competitive antagonist; apparent pA_2 vs. NIH 10672 (-agonist): 8.0; time course study - acts promptly, duration of action >4 h.

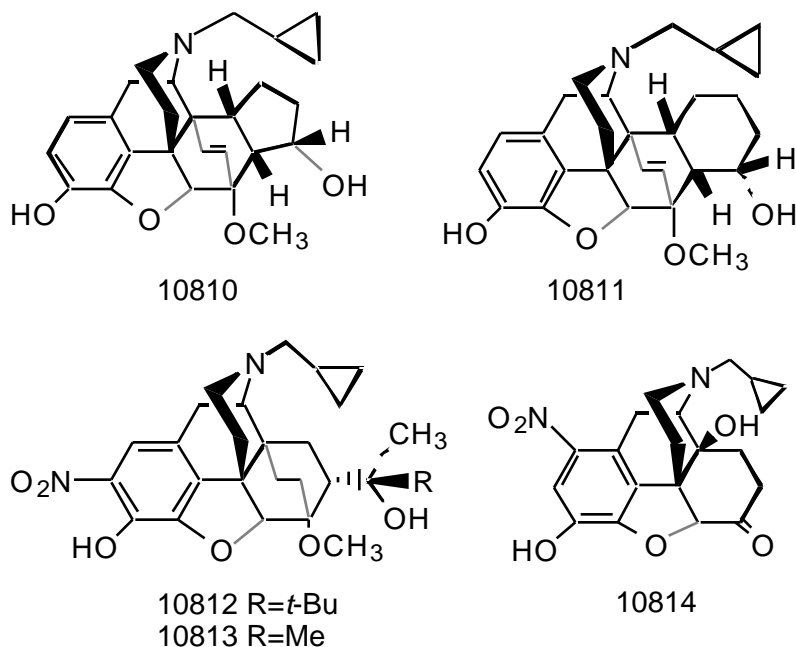
h) Non-selective; insurmountable at .

i) Exacerbates withdrawal; PPt-W: PW (like naloxone).

j) BIND: μ : 157 nM; κ : 2.29 nM; δ : 297 nM.

k) Selective δ -antagonist.

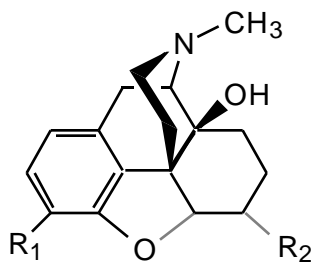
TABLE 3 (CONTINUED). 4,5-EPOXYMORPHINANS^a



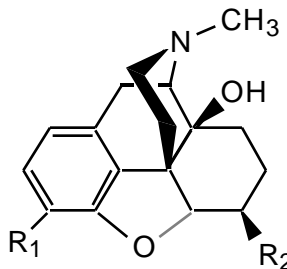
NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10810	I	I	I	0.4	0.91 ^b	8.7 (78%)[A] ^{b,c}	NS ^d
10811	I	I	I	0.02	0.59 ^b	0.86 (99%)[A] ^{b,c}	NS ^e
10812	I	I	I	I	3.81 ^b	6.6 (56%)[NA] ^{b,f}	NS ^g
10813	I	I	I	I	140 ^b	410 (44%)[A] ^{b,h}	NS ⁱ
10814	I	1.2	4.3	3.8	196 ^b	3.4 (23%)[A] ^{b,j}	NS ^k

- a) See text for explanation of column headings and abbreviations.
- b) Previously reported - 1993.
- c) Relatively selective μ -agonist.
- d) Exacerbated withdrawal ($\sim 0.1xN$); longer duration of action than N.
- e) Exacerbated withdrawal; Ppt-W: PW (5xN).
- f) Very weak mixed antagonist, slightly more potent at μ and κ .
- g) Did not exacerbate withdrawal.
- h) Competitive antagonist at μ and κ , insurmountable antagonist at σ .
- i) May have exacerbated withdrawal.
- j) Competitive antagonist at μ and κ , insurmountable antagonist at σ .
- k) Exacerbated withdrawal; strong convulsant (monkey died).

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



10823 R₁=OH, R₂=OH
 10824 R₁=OAc, R₂=OH
 10825 R₁=OAc, R₂=OSO₂CF₃
 10831 R₁=OAc, R₂=I
 10832 R₁=OH, R₂=I



10826 R₁=OAc, R₂=I
 10827 R₁=OH, R₂=I
 10828 R₁=OH, R₂=OH
 10829 R₁=OAc, R₂=OH
 10830 R₁=OAc, R₂=OSO₂CF₃

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10823, 7472 ^b	1.2	0.11	0.4	I	94	1000 (97%)[A]	CS (3xM)
10824	0.61	0.14	0.3	I	517	642 (94%)[A] ^c	CS (10xM)
10825	-	-	-	-	1590	276 (91%)[A] ^d	-
10826	0.03	0.02	0.02	I	259	287 (90%)[A] ^c	CS (20xM) ^e
10827	0.08	0.008	0.04	I	31	472 (98%)[A] ^c	CS (60xM)
10828	2.73	0.36	1.37	I	304	472 (98%)[A] ^c	CS (M-like)
10829	3.83	0.24	2.49	I	478	261 (86%)[A] ^c	CS (M-like)
10830	0.22	0.04	0.09	I	634	295 (100%)[A] ^c	CS (10xM)
10831	0.06	0.009	0.02	I	242	6500 (100%)[A] ^f	CS (75xM)
10832	0.02	0.1	0.02	I	40	92 (100%)[A] ^g	CS (300xM)

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

b) Previously published - 1962.

c) Relatively selective μ -agonist.

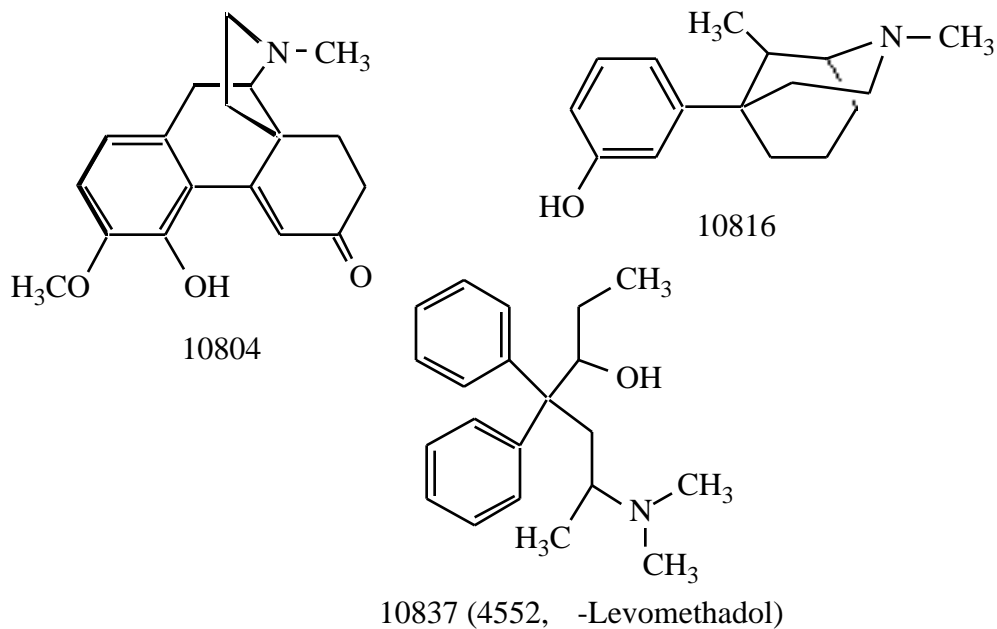
d) Partial μ -agonist.

e) Typical μ -agonist.

f) Weak μ - and κ -agonist

g) μ - and κ -agonist.

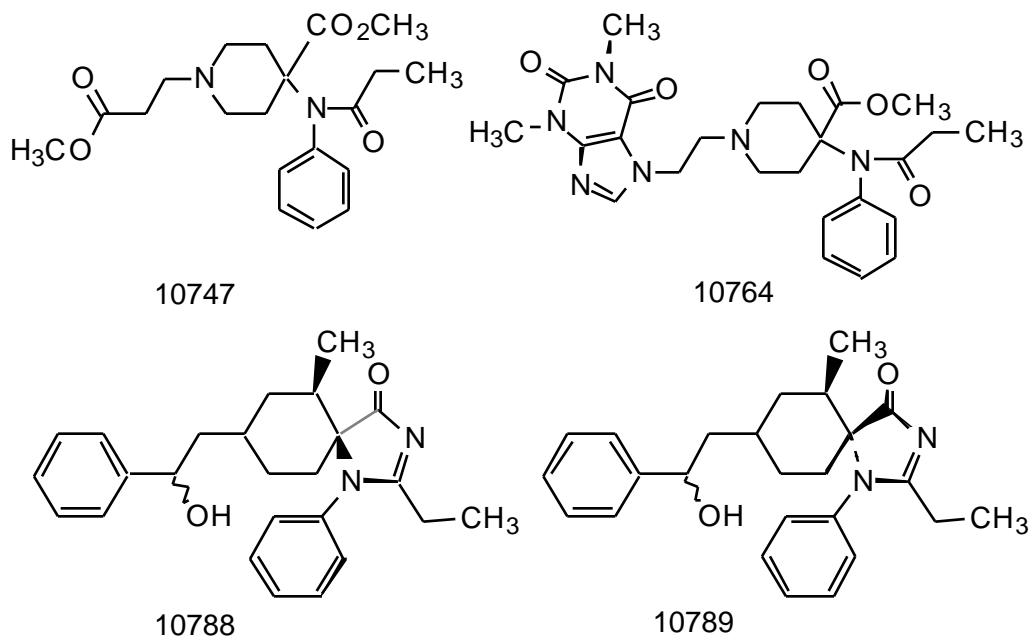
TABLE 5. MORPHINAN, METHADOL, PHENYLMORPHAN^a



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD (nM)	SDS
10804	I	I	I	I	>6 μ M	104 (30%)[SA] ^b	NS ^c
10816	I	15.8	I	I	-	-	NS ^d
10837 (4552)	4.9	1.9	13.9	I	BIND ^e	134 (31%)[NA] ^f	NS ^g

- See text for explanation of column headings and abbreviations.
- Low potency partial agonist, or non-opioid.
- Perhaps D₂ blockade - near catalepsy.
- Observed tremors, chewing, increased respiratory rate.
- BIND: $\mu = 248$ nM, and $\kappa = >6$ μ M
- Weak μ antagonist.
- Effects not dose-related; delayed, questionable suppression observed.

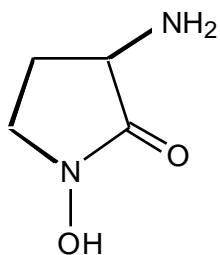
TABLE 6. FENTANYL-LIKE COMPOUNDS^a



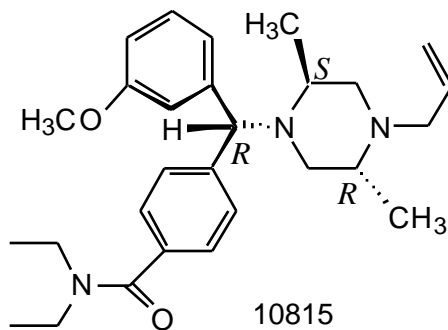
NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10747	I	I	I ^b	I	117	110 (100%)[A] ^c	PS (3000xM) ^d
10764	I	I	I	I	>6000	220 (31%)[NA] ^e	PS (6.25)
10788	I	I	I	I	2500	3.3 (71%)[NA] ^f	NS (3-12)
10789	0.05	0.003	0.011	I	6.25	4.96 (99%)[A] ^g	CS (60xM)

- a) See text for explanation of column headings and abbreviations.
 b) Straub tail at 30 mg/kg; μ -agonist for 10 min, no action after 20 min; increased locomotion blocked by N in all antinociceptive tests.
 c) μ -agonist.
 d) Atypical attenuation of withdrawal, but μ -like overall.
 e) Low efficacy agonist, no antagonist activity.
 f) No significant agonist or antagonist activity.
 g) Potent μ -agonist.

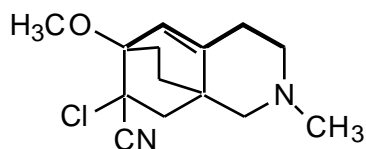
TABLE 7. MISCELLANEOUS^a



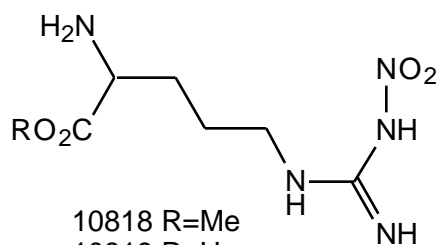
10767



10815



10817



10818 R=Me

10819 R=H

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH (nM)	VD (nM)	SDS
10767	I	1.8 ^b	I	I	>6000	I ^c	NS (2.5,10)
10815	I	3.8	I	I	>6000	6.4 (100%)[A] ^d	NS (3,15) ^e
10817	I	I	I	I	>6000	1.3 (33%)[NA] ^f	PS(4); NS(16) ^g
10818	I	I	I	I	>6000	2800 (80%)[A] ^h	NS(4,16) ⁱ
10819	I	I	I	I	>6000	66 (63%)[NA] ^j	NS (3,15) ^k

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

b) Naloxone AD₅₀: 14% @ 1 mg/kg.

c) No significant activity as agonist or antagonist.

d) Relatively selective μ -agonist.

e) No exacerbation of withdrawal, ataxia, slowing; perhaps non-opioid.

f) Minimal antagonist activity at highest concentration.

g) Possible stimulant at higher dose.

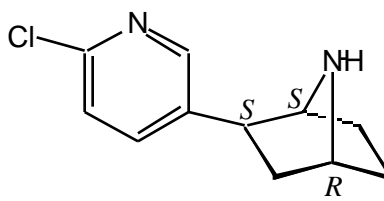
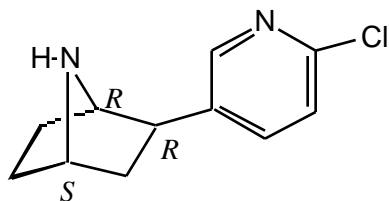
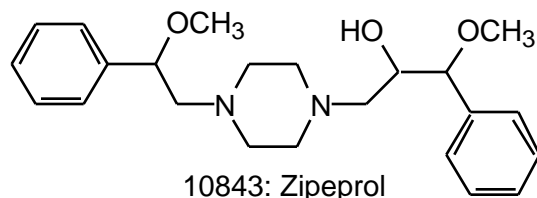
h) Weak, selective μ -agonist.

i) Observed depressed respiration, confusion.

j) Devoid of significant opioid activity.

k) Possible μ -antagonist activity, may exacerbate withdrawal.

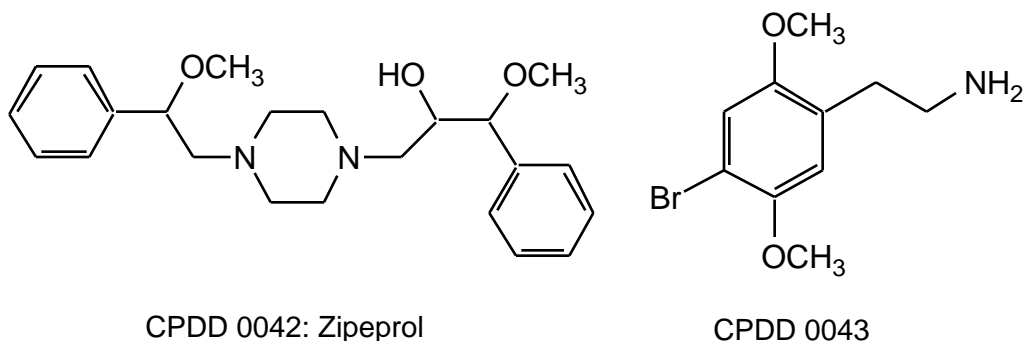
TABLE 8 (CONTINUED). MISCELLANEOUS^a



NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY	
	HP	PPQ	TF	TFA	RBH	VD (nM)	SDS
10843	I	8.7	I	I	BIND ^b	148 (31)[NA]	CS (0.25xM) ^c
10850	-	1.6 ^d	12.5 ^e	-	-	-	-
10851		0.8 ^f	8.6 ^g	-	-	-	-

- a) See text for explanation of column headings and abbreviations.
 b) BIND: $\mu = 369$ nM, $= 67$ μ M, $= 60$ μ M.
 c) Rapid onset, short duration of action; depressant actions.
 d) Naloxone vs NIH 10850 ED₅₀ - inactive; mecamylamine pA₂ = 6.2.
 e) Naloxone vs NIH 10850 ED₈₀ - no dose-response (51% @ 10).
 f) Naloxone vs NIH 10851 ED₅₀ = 0.02 mg/kg.
 g) Naloxone vs NIH 10851 ED₈₀ = 0.1 mg/kg.

TABLE 9. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD#	<u>SLA</u> ^a	<u>IS</u> ^b	<u>PD-S</u> ^c	<u>SA</u> ^e	<u>DD</u> ^f
0042 (NIH 10843)	Stimulant/ Depressant ^g	Impaired ^h	NS ⁱ	Reinforcer ^j	No ^k
0043	Erratic ^l	Impaired ^m	NS ⁿ	Possible ^o	No ^p

- a) Spontaneous locomotor activity (mouse).
- b) Inverted screen assay (mouse).
- c) Physical dependence - substitution for pentobarbital (rat infusion).
- d) Physical dependence - primary (rat infusion).
- e) Self-administration (monkey).
- f) Drug discrimination (intra-gastric administration, monkey).
- g) Mild stimulation @ 40 mg/kg, profound depression @ 100, 175 mg/kg followed by mild excitation.
- h) @ 40 mg/kg and up. Mild effects on central excitability at nontoxic doses; greatest effect is dose-related depression persisting 60 min, followed by mild stimulation. Not a classical stimulant or depressant.
- i) Slight, not significant, reduction of behavioral signs.
- j) In methohexital- and alfentanil-trained monkeys (quadazocine reduced reinforcing potency in latter, suggesting opioid effect).
- k) No drug-appropriate responding in either amphetamine (AMPH)- or pentobarbital (PB)-trained monkeys. Unlikely to have AMPH- or PB-like effects in humans. Low therapeutic index.
- l) Mild depressant @ 6 mg/kg, mild stimulant @ 50 mg/kg, followed by mild depression.
- m) Dose-related impairment (5-6 x pentobarbital); not clearly depressant.
- n) Appears to promote sedative and muscle-relaxant effects without promoting barbiturate-type dependence.
- o) Served as reinforcer in some monkeys at some doses; at larger or smaller doses, only saline-like behavior.
- p) Not predicted to have AMPH- or PB-like effects in humans.