

**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).**

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One of the main purposes of the Committee on Problems of Drug Dependence (CPDD) continues to be the evaluation of drugs for their physical dependence potential and abuse liability (May and Jacobson 1989). These drugs are obtained from U.S. and foreign sources in pharmaceutical industries, universities, and governmental organizations. The Animal Testing Committee is responsible for methodological research and testing of drugs in the analgesic as well as the stimulant and depressant classes of compounds. The analgesic class of drugs was examined by researchers in the Department of Pharmacology and Toxicology of the Medical College of Virginia, Virginia Commonwealth University, Richmond, VA (under the direction of Drs. M. Aceto and L. Harris), and the Department of Pharmacology of the University of Michigan, Ann Arbor, MI (under the direction of Dr. J. Woods). The stimulants and depressants were examined in the Department of Psychiatry of the University of Chicago (UC), Chicago, IL (under the direction of Dr. W. Woolverton), the Department of Pharmacology of the University of Michigan (UM), Ann Arbor, MI (under the direction of Dr. G. Winger and C. France), and the Department of Pharmacology and Toxicology of the Medical College of Virginia (MCV), Virginia Commonwealth University, Richmond, VA (under the direction of Drs. G. Patrick and L. Harris).

The CPDD's Drug Evaluation Committee (Dr. T. Cicero, Chairman) is responsible for guiding the Animal Testing Committee (Dr. A. E. Jacobson, Chairman), and Human Testing Committee (Drs. N. K. Mello and M. W. Fischman, Cochairmen) and, at its annual meeting in April, in Chicago, the accomplishments of these Committees were discussed.

**ANIMAL TESTING COMMITTEE - ANALGESICS**

**Statistics**

Most of the 44 compounds which were released this year (5/1/89 - 4/30/90) were obtained from universities, domestic and foreign (33% and 22% of the total), and from governmental organizations (NIH and NIDA

- 29%, and 9%, respectively). Remarkably few compounds (ca. 5% and 2% of the total) were obtained from pharmaceutical industry (domestic and foreign, respectively). The percentage of compounds from industry is as low, or lower, than at any time since 1981-1982. One consequence of the major source change of compounds from industry to the university and governmental institutions, is that compounds are obtained, generally, in lesser quantity; less than might be considered desirable. Several of the researchers from universities, unlike industrial groups, are interested only in our initial rodent studies and, perhaps, *in vitro* work.

Last year only 25 compounds were examined in one of the primary screens, the single dose suppression assay in monkeys (Aceto et al. 1989). This year, 30 compounds were evaluated in that assay. In the separate reports from UM (Woods et al. 1991) and MCV (Aceto et al. 1991), work is described on 28 compounds at UM, and 38 compounds at MCV. Twenty-one of these compounds were examined at both UM and MCV this year. The total number of compounds (45 [one compound was reexamined under a different NIH number]) is considerably lower than that of last year, when UM reported their work on 40 compounds and MCV on 51 compounds (with 26 compounds in common), for a total number of 65 compounds.

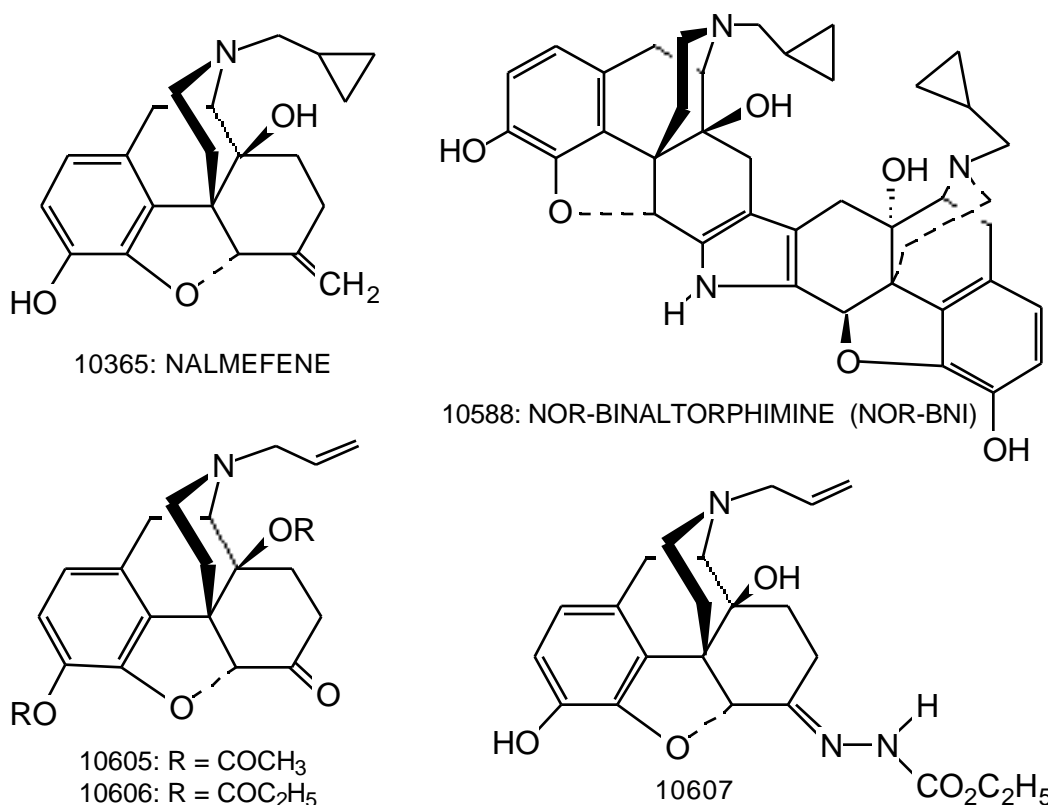
The announcements of the work of the testing facilities under the auspices of the CPDD to medicinal chemists, initiated by Dr. K. Rice (Chief, Laboratory of Medicinal Chemistry, NIDDK, NIH) through the American Chemical Society, resulted in inquiries from several groups in disparate places of which we were previously unaware (Italy, Yugoslavia, France, Canada, Australia, and universities in various states in this country, Georgia, Alabama, Pennsylvania, and Hawaii). The Drug Evaluation Committee, during its Chicago meeting in April, recommended that a brochure should be prepared with an outline of the work done by the Animal Testing Committee of the CPDD, and that the brochure should be widely circulated.

### **Types of Analgesics Evaluated**

The evaluated analgesics have been categorized in six main groups, the 4,5-epoxymorphinans (fourteen compounds, listed in tables 1 - 3), 6,7-benzomorphans (table 4, seven compounds), phenylpiperidines and fentanyl-like compounds in table 5 (four compounds), phenylpiperidines related to haloperidol (table 6, four compounds), methadols (four compounds, table 7), and a group (eleven compounds) of miscellaneous structures (tables 8 and 9). The work which was accomplished with these compounds, both this year and during previous years at MCV and

UM, is summarized in the various tables, and their molecular structures are depicted.

TABLE 1. 4,5-EPOXYMORPHINANS<sup>a</sup>



NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY SDS/PPTW
	PPQ	TF	TFA	RBH (nM)	VD	
10365	1 <sup>b</sup>	1 <sup>b,c</sup>	0.001 <sup>b</sup>	-	ANT(μ)	NS <sup>b</sup> , PW <sup>b,d</sup>
10588	I	I	I	70.0	ANT( )	NS (2,8) <sup>e</sup>
10605	I	I	0.11	11.8g	ANT(μ, , )g	-
10606	I	I	0.8	59.2g	ANT(μ)g	-
10607	I	I	0.12	7.2g	1E-6(32)[A]g,h	PW(0.5,2)[0.1N]

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

b) Previously reported - 1986, 1985.

c) Tail flick assay - study of nalmefene antagonism of buprenorphine (1990).

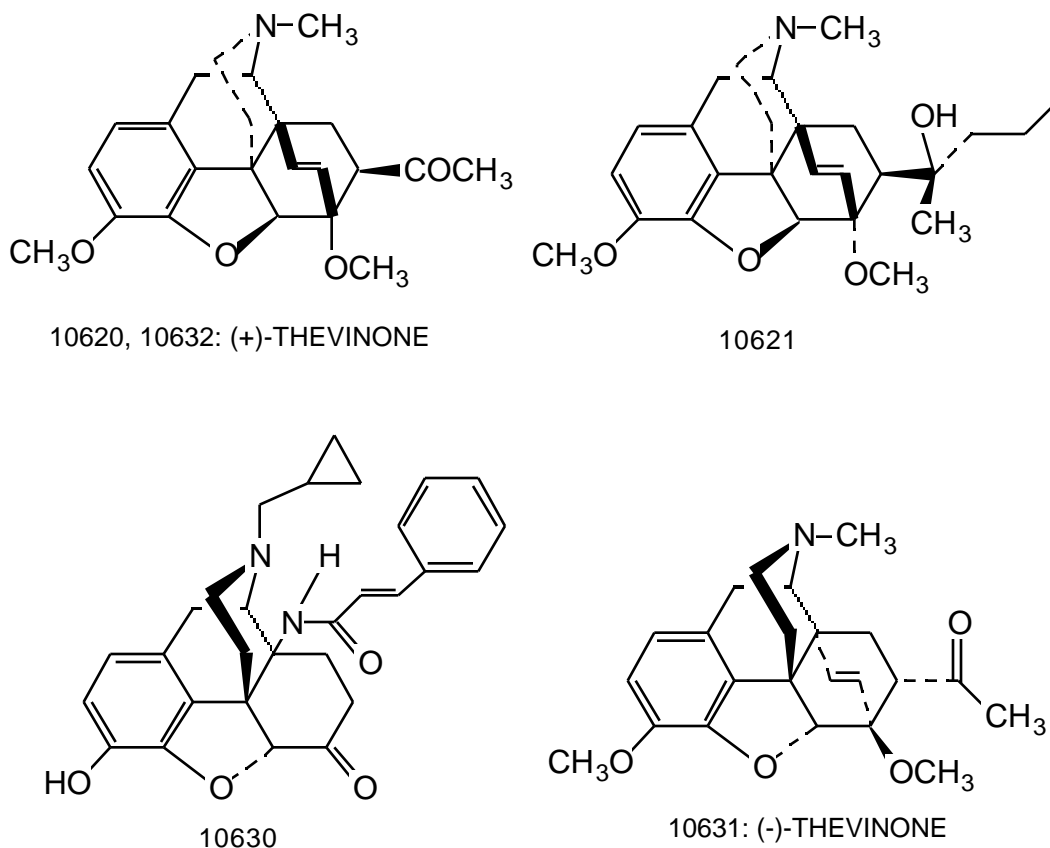
d) Other assays - SA (NE), PPD (NE).

e) Exacerbates withdrawal at highest dose.

g) Previously reported - 1989.

h) Partial opioid agonist with significant μ, , antagonist activity.

TABLE 2. 4,5-EPOXYMORPHINANS (CONTINUED)<sup>a</sup>



NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY
	<u>PPQ</u>	<u>TF</u>	<u>TFA</u>	<u>RBH</u>	<u>VD</u>	<u>SDS</u>
10620 (10632)	I	I	I	>10 $\mu\text{M}^{\text{b}}$	ANT( $\mu$ , , )	NS (1,4,16)
10621	I	I	I	>10 $\mu\text{M}^{\text{b}}$	NE <sup>b</sup>	NS (4,16)
10630	I	I	1.3	0.73	ANT( $\mu$ , , )	NS (1,5) <sup>c</sup>
10631	2.0	8.3	I	1186	1.7E-8 <sup>d</sup>	CS (8)

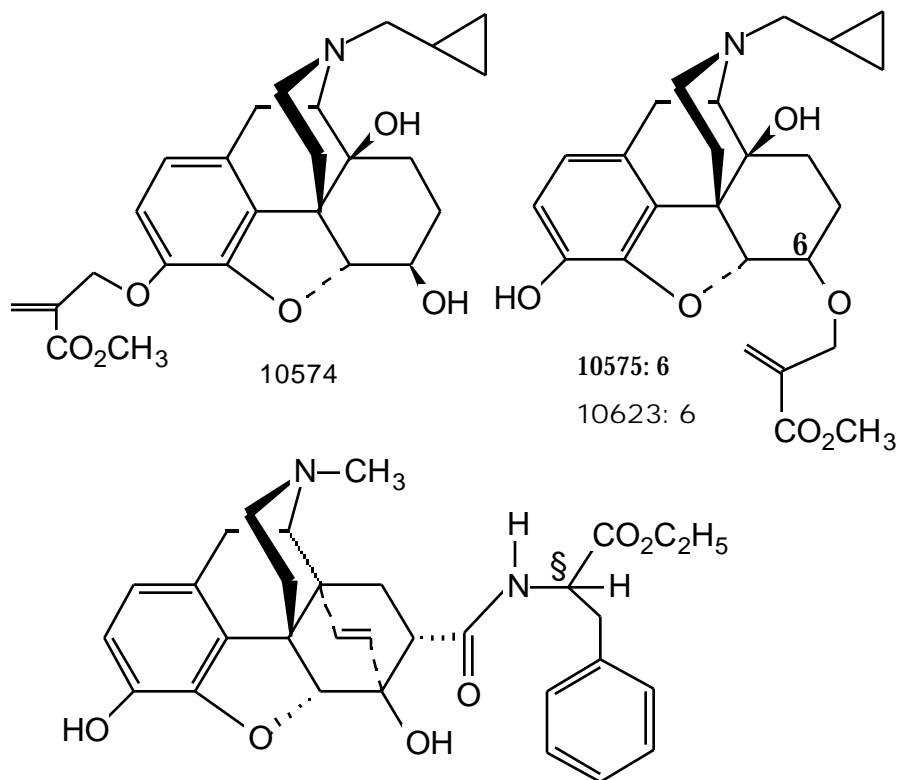
a) See text for explanation of column headings and abbreviations.

b) Previously reported - 1989.

c) Slow onset, long duration of action.

d) Not antagonized by  $\mu$ , , antagonists (non-opioid agonist or antagonist.).

TABLE 3. 4,5-EPOXYMORPHINANS (CONTINUED)<sup>a</sup>



10635: § = L-PHENYLALANYL ETHYL ESTER

10636: § = D-PHENYLALANYL ETHYL ESTER

NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY SDS
	PPQ	TF	TFA	RBH (nM)	VD	
10574	I	I	3.1	29.8	ANT( ) <sup>b</sup>	NS (0.0075-0.03)
10575	I	I	0.07	3.1	ANT( $\mu$ , )	NS (0.019,0.15) <sup>c</sup>
10623	I	I	0.03	4.4	ANT( $\mu$ , ) <sup>d</sup>	NS (0.02-0.16)
10635	0.01	0.3	I	1.5	4.5E-9 <sup>e</sup>	-
10636	0.4	0.9	I	1.4	2.1E-9 <sup>e</sup>	-

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

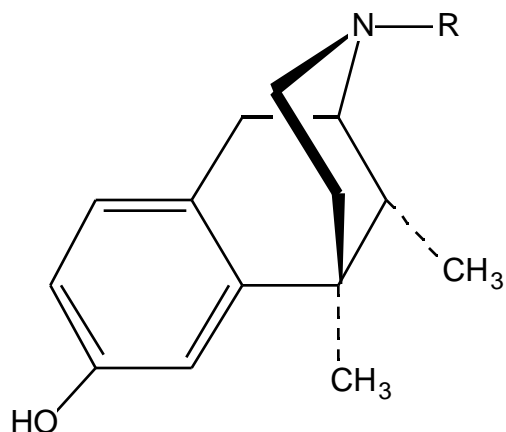
b) Insurmountable antagonist at  $\mu$  and  $\delta$ -opioid receptors.

c) PPt-W - Precipitated withdrawal [5 x naloxone].

d) Insurmountable antagonist at  $\delta$ -opioid receptors.

e) Potent, selective agonist at  $\mu$  receptors.

TABLE 4. 6,7-BENZOMORPHANS<sup>a</sup>



7589: R = *n*-BUTYL (±)

8209: R = *n*-HEXYL (±)

10626: R = *n*-HEXYL (+)

10627: R = *n*-HEXYL (-)

10648: R = BENZYL (±)

10649: R = BENZYL (-)

10650: R = BENZYL (+)

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY SDS
	HP	PPQ	TF	TFA	RBH	VD	
7589	1 <sup>b</sup>	9.7	I	1.4	101 <sup>c</sup>	ANT(μ, ) <sup>c,d</sup>	NS <sup>e</sup> (1,4)
8209	1.4 <sup>f</sup>	0.07	2.1	I	358	5.4E-7 <sup>g</sup>	PS (2,8)
10626	-	1.0	20.4	I	>10 μM	ANT( )	NS (3,12)
10627	-	0.3	1.1	I	166	3E-7 <sup>h</sup>	PS (1,5)
10648	-	I	I	26	-	-	NS (3,12) <sup>e</sup>
10649	-	13.4	I	20.3	485	ANT(μ, ) <sup>i</sup>	NS <sup>e</sup>
10650	-	j	j	j	>10 μM	ANT(μ) <sup>k</sup>	-

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

b) Previously reported - 1972.

c) Previously reported - 1989.

d) May not be simple, competitive antagonist.

e) Exacerbated withdrawal.

f) Previously reported - 1977.

g) Agonist at μ and receptors.

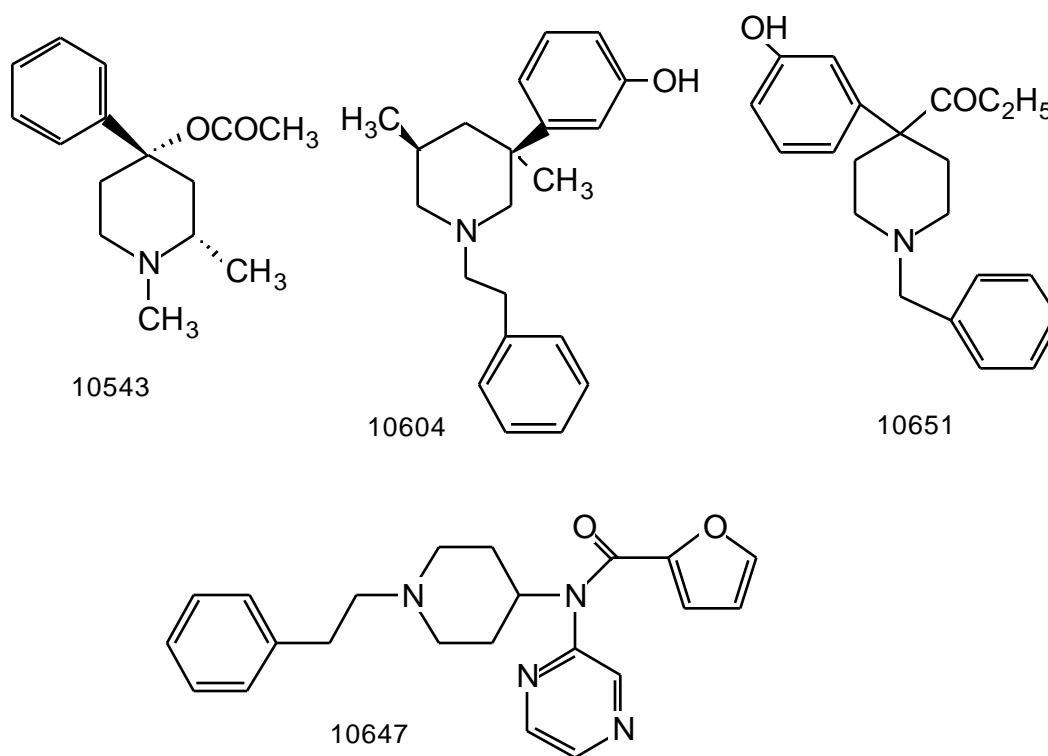
h) Partial agonist at μ and receptors.

i) Non-competitive from Schild plots.

j) Preliminary data appear to be in accord with binding data.

k) Non-competitive at receptors.

TABLE 5. PHENYLPYPERIDINES AND FENTANYL-LIKE COMPOUNDS<sup>a</sup>



NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY
	<u>PPQ</u>	<u>TF</u>	<u>TFA</u>	<u>RBH</u>	<u>VD</u>	<u>SDS</u>
10543	0.9 <sup>b</sup>	15.2 <sup>b</sup>	1 <sup>b</sup>	76 $\mu$ M	SE <sup>c</sup>	-
10604	4.7 <sup>d</sup>	1 <sup>d</sup>	1 <sup>d</sup>	444	1.4E-7 <sup>e</sup>	-
10647	0.08	0.4 <sup>f</sup>	I	91	ANT( $\mu$ , , ) g	NS (0.05-4)
10651	.h	.h	.h	1017	ANT( $\mu$ , , )	-

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

b) Previously reported - 1988.

c) EC50 not determinable. Effect blocked by naltrexone.

d) Previously reported - 1989.

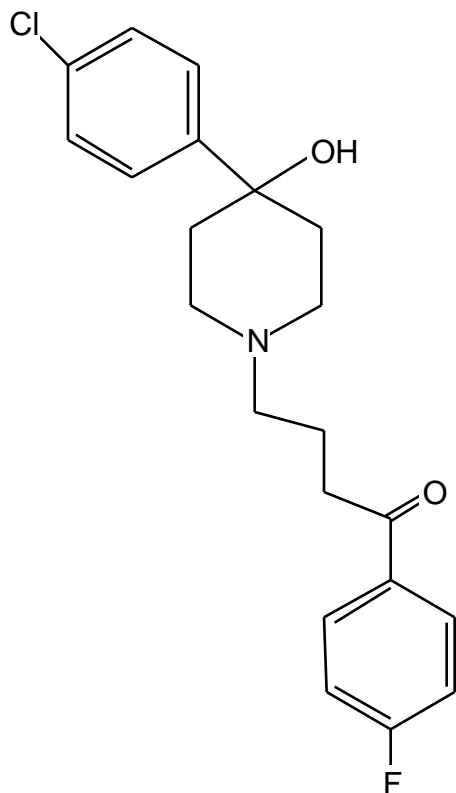
e) Non-opioid (not antagonized by naltrexone).

f) Reversed by naloxone.

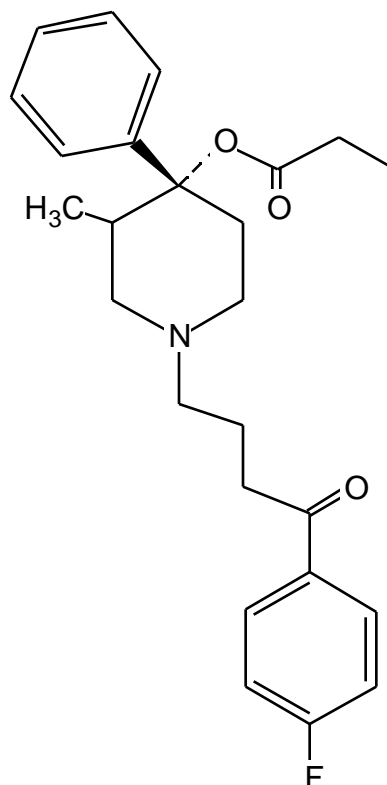
g) Other work (at UM, 1990) - SA, DD, analgesia and respiratory effects in monkeys.

h) Preliminary data appear to be in accord with binding data.

TABLE 6. PHENYLPIPERIDINES RELATED TO HALOPERIDOL<sup>a</sup>



10625: HALOPERIDOL



10639: 3*R*,4*S* (+)  
10640: 3*S*,4*R* (-)  
10641: (±)

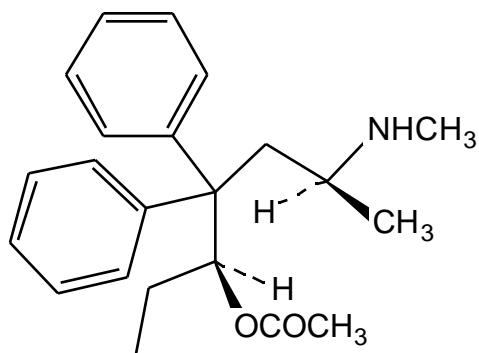
NIH #	MOUSE ED50/AD50				IN VITRO	MONKEY
	<u>PPQ</u>	<u>TF</u>	<u>TFA</u>	<u>RBH</u>	<u>VD</u>	<u>SDS</u>
10625 (8032)	0.01 <sup>b</sup>	14.6 <sup>b</sup>	I <sup>b</sup>	>10 μM	ANT(μ,k) <sup>c</sup>	NS <sup>b</sup>
10639	0.1	0.56	I	-	-	CS (0.05, 0.25)
10640	1.5	I	I	-	-	NS (0.5, 0.25)
10641	0.11	0.77	I	-	-	CS (0.5, 0.25)

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

b) Previously reported - 1989, 1988, 1963. Other Work - RI-SM (NS), RI-PPD; DD (at UM, 1990).

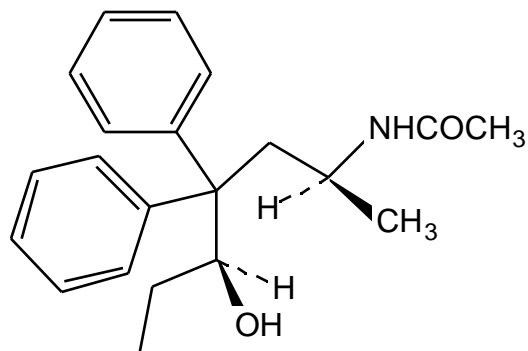
c) Agonist at 10<sup>-5</sup> M, not reversed by naloxone.

TABLE 7. METHADOLS<sup>a</sup>



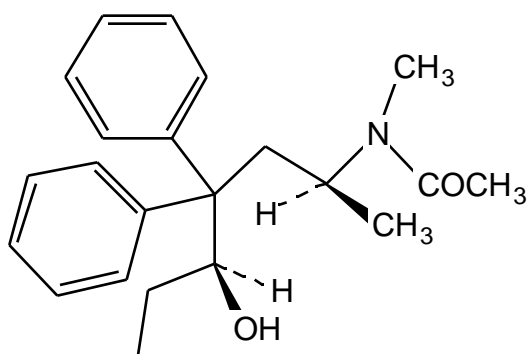
10652

(-)-N-ACETYL-N-NORMETHADOL



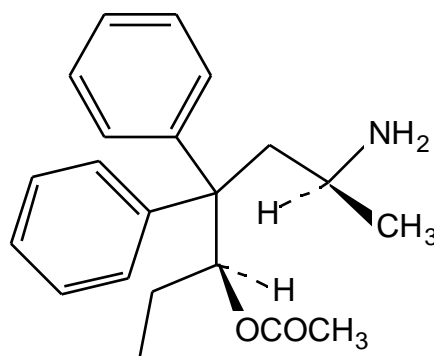
10653

(-)-N-ACETYL-N,N-DINORMETHADOL



10654

(-)-N-ACETYL-N-NORMETHADOL



10655

(-)-ACETYL-N,N-DINORMETHADOL

NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY
	PPQ	TF	TFA	RBH	VD	SDS
10652	0.07	0.5	I	13.4	8.2E-8 <sup>b</sup>	CS (0.5)
10653	I	I	I	>6 μM	SE <sup>c</sup>	NS (3,12)
10654	I	I	I	>6 μM	SE <sup>c</sup>	NS (3,12)
10655	.d	.d	.d	22.3	3.4E-7 <sup>e</sup>	.d

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

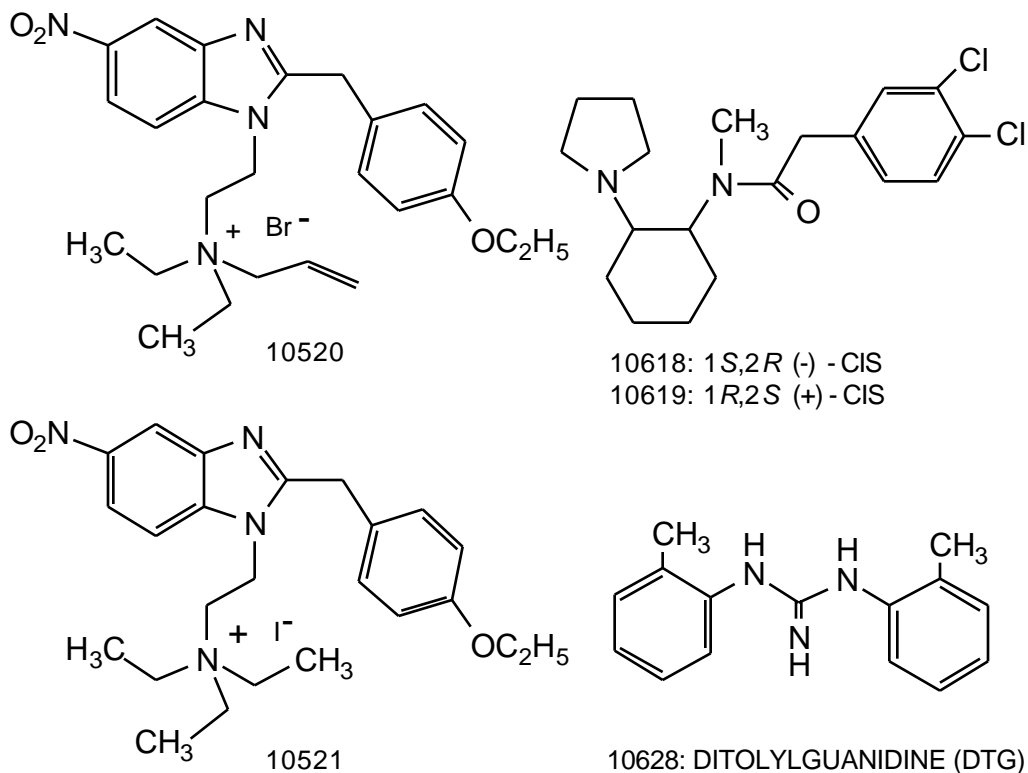
b) Potent, selective μ agonist.

c) Little or no opioid activity.

d) Preliminary data appear to be in accord with binding data.

e) μ Agonist; unusual response to naltrexone.

TABLE 8. MISCELLANEOUS<sup>a</sup>



NIH #	MOUSE ED50/AD50				IN VITRO VD	MONKEY SDS
	PPQ	TF	TFA	RBH		
10520	0.6	0.4	I	175	1.6E-7	CS (0.25, 1)
10521	5.0	I	I	2800	5.8E-6	-
10618	9.7	I	I	>10 $\mu$ M	ANT( $\mu$ , )	NS (3.75, 15)
10619	7.0	I	I	>10 $\mu$ M	ANT( $\mu$ , )	NS <sup>b</sup> (5, 20)
10628	-	I	I	-	-	NS <sup>c</sup> , PWD

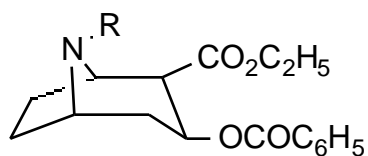
a) See text for explanation of column headings and abbreviations.

b) May have exacerbated withdrawal.

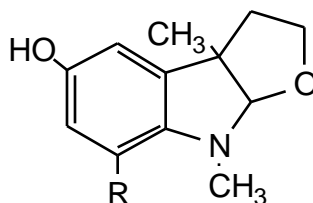
c) Appeared to exacerbate withdrawal (8 mg/kg).

d) Did not precipitate complete withdrawal syndrome.

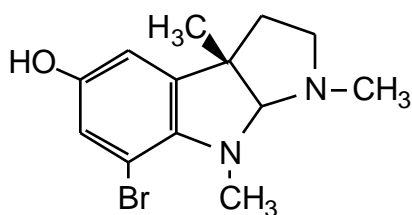
TABLE 9. MISCELLANEOUS (CONTINUED)<sup>a</sup>



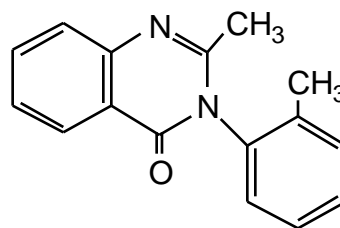
8211: R = CH<sub>3</sub> (COCAINE)  
10664: R = H (NORCOCAINE)



10633: R = H  
10634: R = Br



10642: (-)



10643: METHAQUALONE

NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY
	PPQ	TF	TFA	RBH (nM)	VD	
08211	2.83 <sup>b</sup>	1 <sup>b</sup>	1 <sup>b</sup>	-	-	PS <sup>c</sup>
10633	I	I	I	-	-	-
10634	I	I	I	-	-	-
10642	0.18	0.54	I	29.4	2.5E-8 <sup>d</sup>	PS (0.5,2,8)
10643	-	-	-	-	-	NS (0.75-12)
10664	1.65	I	I	-	-	PS <sup>e</sup> (1, 2)

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

b) Previously reported - 1986 (RI-PPD), 1987.

c) Morphine (0.6 mg/kg (s.c.) - no effect, alone) with cocaine (2 mg/kg i.v.) significantly suppressed morphine withdrawal.

d) Weak antagonist at  $\mu$ ,  $\kappa$ , receptors.

e) Attenuates abrupt morphine withdrawal.

## ABBREVIATIONS USED IN TABLES 1 - 9.

### 1) MOUSE ED50 OR AD50: Antinociceptive Assays (sc injection)

Confidence limits for the ED50 and AD50 are listed in the MCV report (Aceto et al. 1991).

HP = hot plate; N = Nilsen; PPQ = phenylquinone; TF = tail flick; TFA = tail flick antagonism vs. morphine. These assays are performed at MCV, except for the HP and N (carried out at NIDDK, NIH).

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

For comparison: in mg/kg, sc in mice, morphine ED50 = 5.8 (5.7-5.9) in TF, 0.23 (0.20-0.25) in PPQ. Naltrexone AD50 = 0.007 (0.002-0.02) in TFA; Naloxone AD50 = 0.035 (0.01-0.093) in TFA.

### 2) In Vitro Determinations (Data from UM, Woods et al. 1991))

A) RBH = binding affinity, in the presence of 150mM NaCl, to rat or monkey cerebrum membrane preparations, in nM (parenthesized number, noted in previous reports, is the +sodium/-sodium [+Na/-Na] ratio). EC50 was determined by displacement of 0.5 nM [<sup>3</sup>H]etorphine.

For comparison: morphine EC50 (from RBH) = 23.6 (1.69).

NE = no effect.

NOTE: The present EC50 data cannot be directly compared with those from some previous reports (Jacobson 1984, and preceding years) in which -Na values were quoted. However, the former numbers can be recalculated for comparison with those which are currently utilized through the use of the +Na/-Na ratio.

B) VD = electrically stimulated mouse vas deferens EC50 values, rounded to one significant figure. Agonist activity is stated using "E" followed by a negative number: E = 10<sup>-x</sup> M, where x = the negative number, thus: 1E-3 = 0.001 M (1 mM), 1E-6 = 1 μM, and 1E-9 = 1 nM (parenthesized numbers are maximum percent inhibition at EC50); [bracketed letters: A = antagonized by 10<sup>-7</sup> M naltrexone; NA = not antagonized by naltrexone; SA = slight antagonism by naltrexone].

SE = slight effect on twitch.

NE = No significant agonist or antagonist effect.

ANT = Antagonist activity. Parenthesized letters indicate μ, , and/or receptor antagonism. The antagonist effect may or may not be competitive (see the UM report (Woods et al. 1991) for these data).

Compounds which suppress the twitch and are not antagonized by naltrexone or UM 979 [NIH 8859, (-)-5,9 -dimethyl-2-(3-furylmethyl)-2'-hydroxy-6,7-benzomorphan] are said to be non-opioid agonists (e.g., clonidine can suppress the twitch, but is not antagonized by naltrexone. It is a non-opioid agonist). (The effect of UM 979 is not noted in this report, but see the UM report (Woods et al. 1991) for these data). Compounds which bind with reasonable affinity in the rat brain homogenate 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 ( $\mu$ ), DSLET ( ), or U50,488 ( ) (for these data see Woods et al. 1991).

3) Monkey Colony Data (from MCV, Aceto et al. 1991; prior to 1988 from MCV or UM).

A) SDS = single dose suppression  
NS = no suppression.  
CS = complete suppression  
PS = partial suppression. (Parenthesized numbers = dose range studied, in mg/kg; if CS, then dose at which CS was observed is noted in the parentheses). Potency comparison with morphine [M] may be stated, in brackets.

B) NW or PPt-W = studies in non-withdrawn monkeys  
PW = precipitated withdrawal at dose levels, in mg/kg, indicated in parentheses &/or comparison with naloxone [N], in brackets  
NP = no precipitation  
SP = slight precipitation.

4) Other Studies (OTHER):

A) RI = rat continuous infusion (data from MCV)

a) SM = substitution for morphine  
NS = no substitution for morphine.  
CS = complete substitution.  
PS = partial substitution.

b) PPD = primary physical dependence, in rats.

B) ND = non-dependent monkeys  
M-like = morphine-like effect.

- C) PPD = primary physical dependence (in the rhesus monkey).
- D) SA or SI = self-administration or self-injection (data from UM)  
NE = no effect.  
High = codeine-like.  
IN = intermediate between saline and codeine.  
SE = slight effect.
- E) DD = drug discrimination (data from UM)  
NE = no effect.  
CS = complete suppression.

## Previous Reports

Previous work on a compound is noted by year, the year listed in the monograph title (e.g. Problems of Drug Dependence 1986). Note that the monograph's publication date may be one year after the titled year of the monograph. Previously published data are listed in the tables in the appropriate column, and the year in which the original work can be found is cited in the footnotes to the tables ("previously reported" work cited as "1983" indicates that the work was included in "Problems of Drug Dependence 1983", which was published in 1984. The complete, original, work can be found in the Annual Report of either Aceto et al., or Woods et al.).

NOTE: Rounded numbers are used in the tables. For precise values, and details of the procedures, see the MCV and UM reports in the NIDA Monograph (Aceto et al. 1991; Woods et al. 1991).

## **Observations About The Analgesics**

The well-known nor-BNI (NIH 10588, table 1) was found to be a potent, noncompetitive, selective  $\mu$ -opioid antagonist *in vitro*. It antagonized  $\mu$  and  $\delta$  receptors at much higher concentrations than were necessary for antagonism. Nor-BNI also displays narcotic antagonist activity *in vivo*.

It was interesting to note that NIH 10575 and 10623 (table 3) had fairly similar *in vitro* and *in vivo* activity, although they are stereochemically quite different at the C-6 position of the 4,5-epoxymorphinan structure. Both compounds are potent, non-selective, opioid antagonists. The effect of the stereochemical difference was observable in the *in vitro* work. NIH 10623, the C-6 compound, appeared to have insurmountable antagonist activity at the  $\delta$ -receptor.

The effect of D vs. L amino acids at C-7 of the 4,5-epoxymorphinan structure can be seen with NIH 10635 and 10636 in table 3, the former having an L-phenylalanyl residue and the latter the D-moiety. The L-amino acid containing compound, NIH 10635, was found to be somewhat more potent *in vivo*, especially in the PPQ assay for antinociceptive activity, and about the same or slightly less potent *in vitro*. In the electrically stimulated mouse vas deferens preparation, both compounds were potent selective agonists at the  $\mu$  receptor.

Only three of the fourteen 4,5-epoxymorphinans seen in tables 1 - 3 appear to have agonist activity. Eight of the fourteen compounds had

more, or less, opioid antagonist activity, *in vivo*, and the nor-BNI compound showed its antagonist activity *in vitro* and *in vivo*. Two compounds, NIH 10620 (or 10632) and 10621 (table 2) had, as expected, no *in vivo* or *in vitro* activity. These compounds are being synthesized and examined at NIH by Dr. K. Rice and colleagues, and are the inactive enantiomers of the natural, (-), series of the 4,5-epoxymorphinans.

The N-substituted 6,7-benzomorphans (table 4) are being synthesized and examined by Dr. E. L. May at MCV, and will be the subject of a joint paper by MCV, UM, and NIH, next year. The (+) and (-) series from N-H to N-heptyl, at least, will be explored. The (+)-6,7-benzomorphans are of contemporary interest due to the discovery, in the past several years, that some of these compounds have PCP-like activity (Goldman et al. 1985), and (+)-pentazocine has been reported to be one of the most potent (non-opioid, non-dopaminergic binding sites distinct from PCP-binding sites) ligands (de Costa et al. 1989). NIH 10626, the (+)-N-hexyl derivative has, as would be predicted, much weaker activity as an antinociceptive *in vivo* than the (-)-relative (NIH 10627), but, surprisingly, the (+)-compound appears to have opioid antagonist activity, relatively selective for  $\mu$  receptors, in the MVD assay. Also noteworthy is the N-benzyl compound in the (-)-series (NIH 10649) which displays narcotic antagonist activity *in vivo* and *in vitro*, and is a very weak antinociceptive in the PPQ assay.

A fentanyl-like compound, NIH 10647 in table 5, is of considerable interest. It is a potent agonist which does not suppress withdrawal in morphine-dependent monkeys (in the SDS assay), and appears to have antagonist activity *in vitro*. If this antagonist activity is substantiated, the NIH 10647 will be the first antagonist found in the fentanyl series. The compound appears to display  $\mu$  opioid effects in drug discrimination, comparable to buprenorphine; its analgesic effects in the monkey appear, however, to be non-opioid.

Three new phenylpiperidines related to haloperidol were examined this year *in vivo*, continuing our investigation of potential neuroleptic-analgesics (table 6). The methadols in table 7 were examined for the National Institute on Drug Abuse. The methadol-like secondary amines (NIH 10652 and 10655) were potent *in vivo* and *in vitro*, and the two amides (NIH 10653 and 10654) were essentially inactive.

The etonitazene-derived quaternary amines, NIH 10520 and 10521 (table 8) were quite different *in vivo*, although they are structurally similar. One of them, the NIH 10520, does appear to cross the blood-brain barrier, which is unusual for quaternary amines. The two

enantiomers in table 8, NIH 10618 and 10619, have little *in vivo* potency but appear to have  $\mu$  and  $\kappa$  opioid antagonist activity *in vitro*, although they do not bind to opioid receptors. These compounds are known to have moderate, and selective, affinity for  $\sigma$  binding sites. In that regard, it is interesting to note that another  $\sigma$  ligand, DTG (table 9, NIH 10628), also appears to act as an opioid antagonist (SDS assay). The (-)-bromo eseroline (table 9, NIH 10642), like (-)-eseroline itself, was found to have good antinociceptive activity. NIH 10642 appeared to show some narcotic antagonist activity.

## STIMULANTS AND DEPRESSANTS

Eight compounds were received for examination as stimulants or depressants this year. Several of these were examined at the request of the World Health Organization (WHO), and the work which was completed on four of them, CPDD 0028, 0030, 0031, and 0032, has been forwarded to the WHO and to the submitter of the drug, after perusal by the Drug Testing Committee of the CPDD. Work on at least one of the remaining drugs has been completed, but will not be released this year.

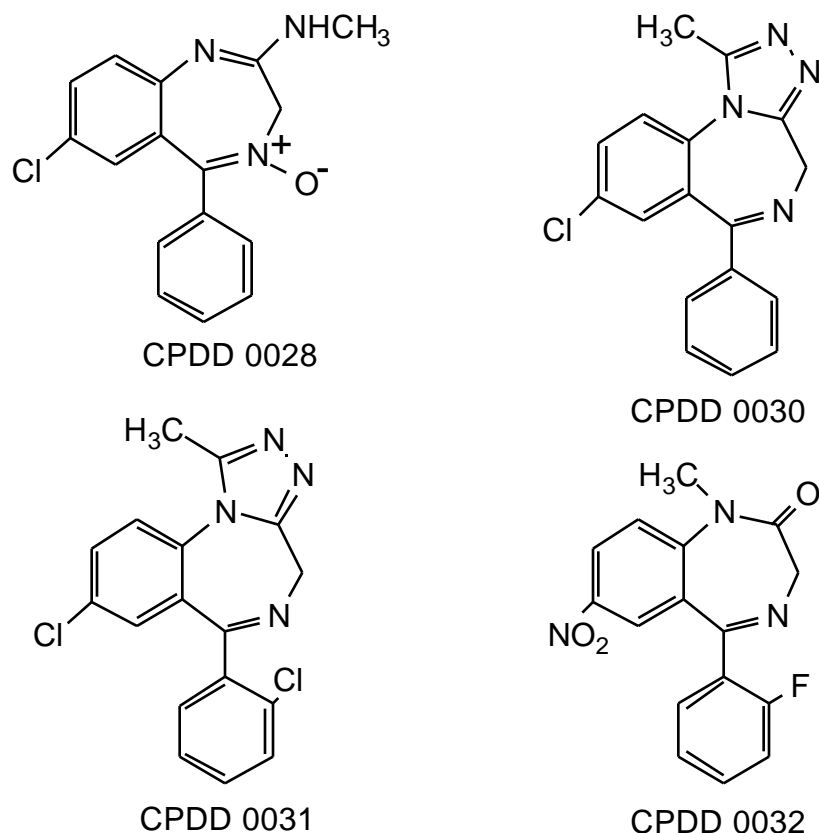


FIGURE 1. Structures of examined depressants

### Chlordiazepoxide hydrochloride (CPDD 0028, Figure 1)

Chlordiazepoxide was found to produce pentobarbital-like effects on motor coordination and locomotor activity, and substituted partially for pentobarbital in dependent rats. Withdrawal from CPDD 0028 appeared to be mild. The rates of self-administration were greater than saline and slightly less than sodium methohexital. Orally-administered, the compound produced discriminative stimulus effects similar to those of pentobarbital in monkeys, and thus would be predicted from these experiments to have pentobarbital-like subjective effects in humans.

### **Alprazolam (CPDD 0030, Figure 1)**

Alprazolam was found to produce dose-related effects that are characteristic of CNS depressant drugs. Its potency appeared to be at least 30 times that of pentobarbital and slightly greater than diazepam. Substitution of alprazolam suppresses signs of abstinence in pentobarbital-dependent rats, and mild signs of abstinence appeared following cessation of drug. Alprazolam appeared to be capable of causing barbiturate-like physical dependence. It also induced discriminative stimulus effects similar to those of pentobarbital in monkeys, and thus would be predicted from these experiments to have pentobarbital-like subjective effects in humans.

### **Triazolam (CPDD 0031, Figure 1)**

Triazolam was found to induce discriminative stimulus effects similar to those of pentobarbital in monkeys, and thus would be predicted from these experiments to have pentobarbital-like subjective effects in humans.

### **Flunitrazepam (CPDD 0032, Figure 1)**

Flunitrazepam was found to induce discriminative stimulus effects similar to those of pentobarbital in monkeys, and thus would be predicted from these experiments to have pentobarbital-like subjective effects in humans.

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