

**BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR
PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY.
XVII. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON
PROBLEMS OF DRUG DEPENDENCE, INC. (1993)**

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PURPOSES OF THE DRUG EVALUATION COMMITTEE

The Drug Evaluation Committee (DEC) of the CPDD (Dr. T. Cicero, Chairman) is charged with the responsibility of determining the physical dependence potential and abuse liability of potential analgesics, stimulants and depressants, and with associated methodological research. The drugs are obtained from investigators in universities, industrial groups, and the public sector. The testing function is carried out under the auspices of the CPDD as a public service and has provided information to pharmaceutical industry and governmental agencies for the appropriate scheduling of a drug with the potential for abuse. The information which DEC provides to university researchers, who frequently work under a NIDA grant, is useful for determining the desirability of structural modification of a drug and the DEC biological data are often needed for publication of their work in medicinal chemistry journals.

THE DRUG EVALUATION COMMITTEE'S PARTICIPATION IN THE MAIN FUNCTIONS OF CPDD

The dissemination of information on the physical dependence potential and abuse liability of drugs for the public welfare continues to serve one of the major purposes of the CPDD, as it has since the establishment of CPDD as a Committee of the National Academy of Sciences, National Research Council. The data obtained by the DEC have been requested this past year by U.S. governmental agencies, such as NIDA, the Drug Enforcement Agency (DEA), and the Food and Drug Administration (FDA). Examples of our continued cooperation with governmental agencies are as follows.

- 1) We were asked this year to examine a drug seized by the DEA, and its structural relative. These compounds (see NIH 10759 and 10760, in table 9) were not found to have opioid-like effects.
- 2) Data recently obtained on LAAM (levo-alpha-acetylmethadol) by the DEC were provided to the FDA in response to the request of one of their officials. These data were apparently required as part of the comprehensive information necessary for a scheduling decision on LAAM.
- 3) Some of our older data were also utilized by the FDA. In 1982 the analgesic testing groups reported on a drug which was recently found to be a minor contaminant in a commercially marketed product. These data were used to allow retention of the commercial product on the market. Toxicological studies on the contaminant will be requested from the supplier by the FDA.
- 4) Evaluation of NIH 10710 (table 8) and 10766 (table 9) by the analgesic testing groups, was requested by the NIDA Medications Development group. The testing of NIH 10710 by the stimulant/depressant groups was reported last year (as CPDD 0037, Woolverton et al. 1993).
- 5) Lastly, the stimulant/depressant groups evaluated two compounds at the request of NIDA, CPDD 0039 and 0040. The World Health Organization (WHO) asked NIDA to provide data on the latter compound, Mesocarb (CPDD 0040, table 10).

Thus, the DEC in this past year has provided data for NIDA, the FDA and DEA, and the WHO. The CPDD has then, through the DEC, fulfilled one of its main functions, providing essential dependence potential and abuse liability information on drugs with the potential for abuse to governmental agencies, pharmaceutical industry, and university researchers.

PUBLICATION OF DATA

The CPDD's evaluation of drugs began around 1951 and the data gathered on these drugs have been published since 1979 in a NIDA Monograph "Problems of Drug Dependence". The published data have always been archival, in the sense that they were declared to be reference material. In 1977 and 1978, the testing data were published by CPDD as part of the proceedings of the annual scientific meeting. From 1951 to 1976, however, the reports were published by the National Academy of Sciences. In those volumes the proceedings of the CPDD meeting were not archival and were not meant to be used as reference material, but rather to record research in progress. The drug testing results, however, were available for quotation. Thus, for more than 40 years, the results obtained from drug testing have been part of the open literature. Unfortunately the volumes published by the National Academy of Sciences are out of print and have been unavailable to all but the few individuals who have maintained a private library of such work. Fortunately, most of these data have now been included in a computerized database by the NIDA Medications Development group, and this database can be accessed and utilized by researchers.

GROUPS REPRESENTED IN THE DEC AND THEIR FUNDING

The testing function has evolved over the past 40 years. At this time two university groups, one at the Medical College of Virginia (MCV) of Virginia Commonwealth University (headed by Drs. M. Aceto and L. Harris) and the other at the University of Michigan (UM) Medical School (led by Dr. J. Woods), are involved with testing potential analgesics, and three groups, one at each of the above mentioned medical schools (Dr. G. Patrick at MCV, and G. Winger at UM) and the third at the University of Chicago Medical School, have been involved with work on stimulants and depressants. Dr. W. Woolverton, who is in charge of the latter group, will continue the work in the future at the University of Mississippi Medical Center. The stimulant/depressant work by the consortium of university groups is carried out through a NIDA grant to Washington University under the direction of Dr. T. Cicero, the Chairman of the Drug Evaluation Committee. The analgesic work at the Medical College of Virginia is carried out under a contract with NIDA, and the work at the University of Michigan Medical School is pursued with a NIDA grant. Each of these groups receives a supplemental grant from the CPDD for their research. There are eight members of the Drug Evaluation Committee, one from each of the five testing groups, Dr. Cicero, myself as Biological Coordinator, and Dr. Steve Holtzman, who is also a member of the Board of the CPDD. Three representatives from NIDA also attended the annual meeting of the Drug Evaluation Committee.

PROCEDURES FOR EVALUATION OF DRUGS

The analgesic testing program employs some or all of the following assays:

- 1) Antinociceptive and narcotic antagonist assessment in the mouse.
- 2) Substitution for morphine and primary physical dependence by rat infusion.

- 3) Single dose suppression and, if warranted, precipitated withdrawal, as well as primary physical dependence studies in the rhesus monkey.
- 4) Opioid receptor binding.
- 5) Electrical stimulation of the mouse vas deferens.
- 6) Self-administration in the rhesus monkey.
- 7) Drug discrimination in the rhesus monkey.
- 8) Analgesic studies in the rhesus monkey.
- 9) Respiratory function studies in the rhesus monkey.

The stimulant and depressant groups use the following methodology:

- 1) Inverted screen test and spontaneous locomotor activity, in mice.
- 2) Physical dependence potential by substitution in pentobarbital-dependent rats using continuous intraperitoneal infusion.
- 3) Primary physical dependence determination in rats, by infusion.
- 4) Self-administration studies in rhesus monkeys.
- 5) Drug discrimination studies in rhesus monkeys.

A complete description of each of the tests on potential analgesics can be obtained from the reports from the Medical College of Virginia (Aceto et al. 1994) and the University of Michigan (Woods et al. 1994). The procedures used for the evaluation of stimulants and depressants are described in the group report which will be written this year by Dr. Graham Patrick (Patrick et al. 1994). All of these testing procedures were summarized in a previous report (Jacobson 1993).

STATISTICS

About 62 compounds were evaluated as potential analgesics this year at either or both the Medical College of Virginia and the University of Michigan. Several others were explored as basic research topics (Aceto et al. 1994) and do not appear in the tables of this report. For example, researchers at the Medical College of Virginia investigated the effects of various dynorphins (2-17, 1-13, and a three amino acid peptide MIF), as well as (-)-nicotine). Of the compounds which were sent for testing, 5% came from industrial sources (domestic and foreign), 48% came from university groups (domestic and foreign), 14% were sent by government agencies, and the remaining 32% came from a non-profit institution. Except for the diminution of requests for examination of drugs from industrial sources, a downward trend observed over the last decade, and the large number from a single group, neither the sources of the drugs nor their number were particularly unusual.

SURVEY OF EVALUATED COMPOUNDS

1) Analgesics

In order to more easily discern the biological effect of structural changes in a basic molecular structure, the examined drugs were grouped in structural classes in the following 10 tables. More comprehensive data on the individual drugs can be obtained from the reports of the members of the DEC (Aceto et al. 1994, Woods et al. 1994).

Two 4,5-epoxymorphinans and two phenylmorphans are shown in table 1, and eight morphinans, divided between the (+)- and the (-)-enantiomeric series are listed in table 2. Table 3 displays eight N-substituted benzomorphans, also divided between the (+)- and the (-)-enantiomeric series. Three arylpiperidines are shown

in table 4, and 18 compounds related to fentanyl are listed in tables 5-7. The remaining two tables consider the miscellaneous compounds.

Remarkable differences in the activity of enantiomers can be seen among the fentanyl compounds. For example, there is about a 16,000-fold difference in the tail flick assay between the enantiomeric NIH 10743 and 10744 (table 5). They are 10,000-fold different in the vas deferens preparation and 10744 was noted to exhibit only partial agonist properties. NIH 10744 does not substitute for morphine in the SDS assay in monkeys. Similarly, the enantiomers NIH 10741 and 10742 in table 5 show even more extreme differences in the vas deferens preparation (4,000,000-fold different), and appear to be 10,000 to 20,000-fold different in the SDS assay. One of these fentanyl compounds, NIH 10741, was found to be 20,000 to 50,000 times more potent than morphine in the SDS assay. The potency of the other fentanyl compounds ranged from morphine-like to 12,000 times more potent than morphine in that assay. The extremely potent drugs are likely to be interesting research tools, especially if they are found to be opioid receptor subtype selective.

An additional compound of interest is NIH 10678 (table 8) which appears to have a novel profile of action, dissimilar to other opioid agonists and partial agonists. Structurally, as a two-dimensional drawing, the compound does not appear to have much resemblance to the usual opioid types.

2) Stimulants and Depressants

The number and origin of stimulants or depressants were not unusual this year. The NIDA grant for this work is mostly utilized for basic research by the individual investigators. Four compounds were released for publication this year. That number of compounds is around the maximum which we are able to examine with current available resources. Two new compounds were received for evaluation (5/1/92 to 4/30/93).

This Monograph contains the detailed report (Patrick *et al.* 1994) on the four compounds released for publication. These are CPDD 0027 (*cis*-4-phosphomethyl)-2-piperidinecarboxylic acid), 0035 (1.3.4.16b-tetrahydro-2-methyl-2*H*,10*H*-indolo[2,1-*c*]pyrazino[1,2-*a*][1,4] benzodiazepine-16-carboxylic acid methyl ester hydrochloride), 0039 (Aminorex hydrochloride [4,5-dihydro-5-phenyl-2-oxazolamine hydrochloride]), and 0040 (Mesocarb [3-(1-methyl-2-phenylethyl)-*N*-(phenylaminocarbonyl)sydnone imine]). The latter two compounds were submitted by NIDA. The molecular structures of these four compounds and the summarization of the data collected on them by the Stimulant/Depressant testing groups in the Drug Evaluation Committee are shown in table 10.

ABBREVIATIONS USED IN TABLES 1 - 9

Rounded numbers are used in the tables; M = morphine. For precise values and details of the procedures see Aceto *et al.* 1994 and Woods *et al.* 1994.

For "E" notation: 1E-3 = 1×10^{-3} or 0.001 M (1 mM), 1E-6 = 1 μ M, 1E-9 = 1 nM, 1E-12 = 1 pM (picomole), and 1E-15 = 1 fM (femtomole).

- 1) **MOUSE ED50/AD50:** Antinociceptive Assays (sc injection)
Confidence limits are listed in the MCV report (Aceto *et al.* 1994).

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.* 1994)

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

NE = no effect.

NOTE: Contemporary EC₅₀ data cannot be directly compared with those from some previous reports (Jacobson 1984, and preceding years) which were obtained under "-NaCl" (without NaCl) conditions.

VD = electrically stimulated mouse vas deferens EC₅₀ values, rounded to one significant figure. 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 noted in parentheses. 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) (for these data see Woods *et al.* 1994).

- 3) **IN VIVO:** in the rhesus monkey (from MCV, Aceto *et al.* 1994; prior to 1988 from MCV or UM).

SDS = single-dose-suppression

NS = no suppression

CS = complete suppression

PS = partial suppression

(Parenthesized numbers = dose range studied, in mg/kg)

Other Studies (noted in the footnotes to the tables)

A) In Rat:

RI = rat continuous infusion (data from MCV)

- 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:

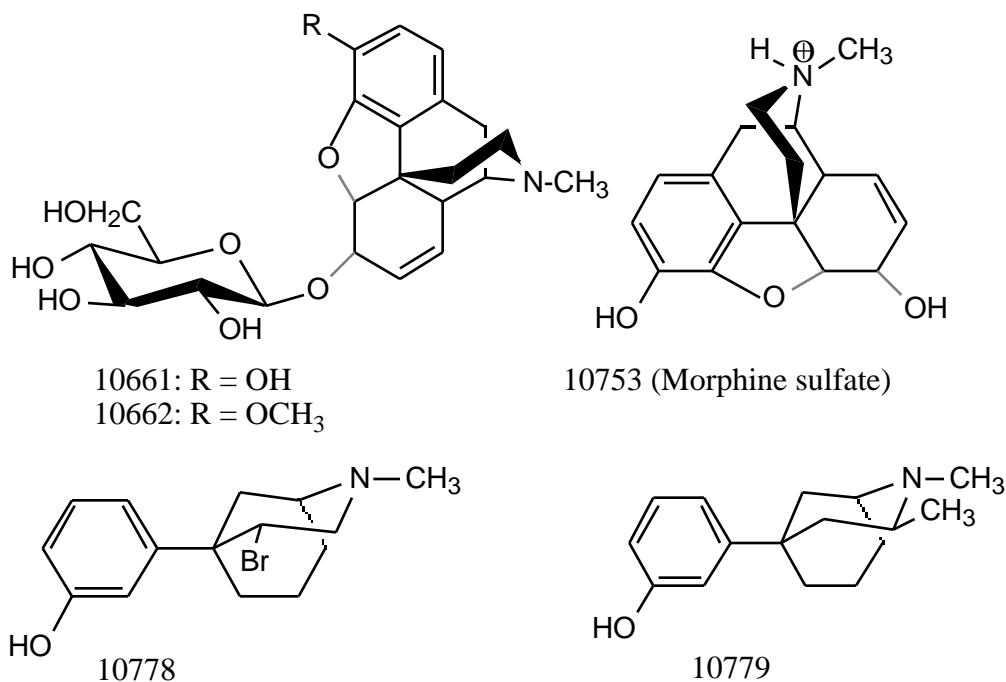
- 1) **PPt-W** = studies in non-withdrawn monkeys (data from MCV)
 - PW = precipitated-withdrawal at dose levels, in mg/kg, indicated in parentheses &/or comparison with naloxone [N].
 - SP = slight precipitation
 - NP = no precipitation
- 2) **ND** = studies using non-dependent monkeys (data from MCV)
 - M-like = morphine-like effect.
- 3) **PPD** = primary physical dependence (data from MCV)
- 4) **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
- 5) **DD** = drug discrimination (data from UM)
 - NE = no effect
 - CS = complete substitution
- 6) **MA** = monkey analgesia (data from UM)
- 7) **RF** = respiratory function (data from UM)

C) In Vitro (data from UM)

BIND - binding affinity using monkey brain cortex membranes (selectivity for μ , κ , and δ opioid receptors using [³H]-sufentanil, [³H]-DPDPE and [³H]-U69,593, respectively).

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 of either Aceto *et al.* or Woods *et al.*

TABLE 1. 4,5-EPOXYMORPHINANS AND 5-PHENYLMORPHANS^a

NIH #	MOUSE ED ₅₀ /AD ₅₀				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10661	-	0.4	0.7		40.4 nM	167 nM ^b	CS (0.5,2) ^c
10662	-				6.4 μM	12 μM(80) ^d	PS (3,12) ^e
10753	3.1	0.4	0.73		74.5 nM	544 nM[A] ^f	CS(2.0)[1 x M] ^g
10778					753 nM	ANT ^h	-
10779	4.8	0.3	1.3		592 nM	15.8 μM ⁱ	-

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

b) Selective μ-agonist.

c) Prompt action, long duration.

d) Weak -agonist.

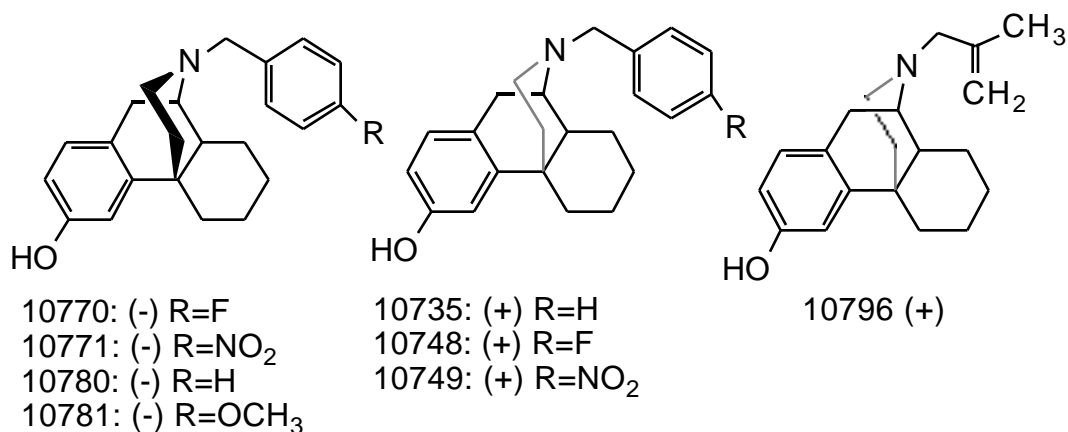
e) Does not completely substitute for M or exacerbate withdrawal.

f) μ- and -agonist.

g) Prompt action, 2.5 hr. duration.

h) Weak, non-selective antagonist, no agonist activity.

i) Low potency μ-partial agonist.

TABLE 2. MORPHINANS ^a

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10735	-	-	-	-	>6 μM	ANT ^b	-
10748		12			>6 μM	NE	NS (4,16)
10749	-	-	-	-	>6 μM	Insoluble	-
10770					1.3 μM	ANT ^c	-
10771					2.1 μM	7 nM(20) ^d	-
10780					260 nM	ANT ^e	-
10781					>6 μM	5 nM(18) ^f	-
10796	-	-	-	-	>6 μM	ANT ^c	-

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

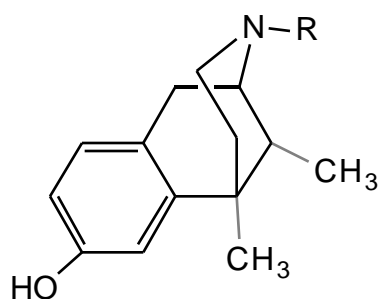
b) Low potency -antagonist activity (and some -antagonist activity).

c) No agonist activity, very weak -antagonist with limited selectivity.

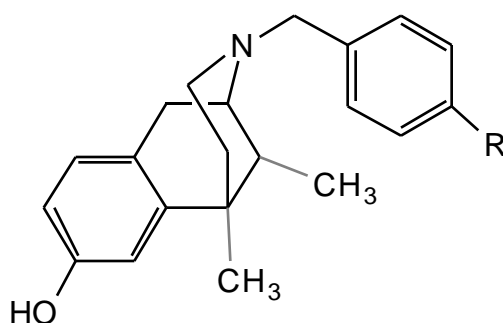
d) Partial agonist, weak non-selective antagonist.

e) Weak non-selective antagonist.

f) Very weak partial agonist only slightly antagonized by naltrexone, very weak non-selective antagonist.

TABLE 3. 6,7-BENZOMORPHANS^a

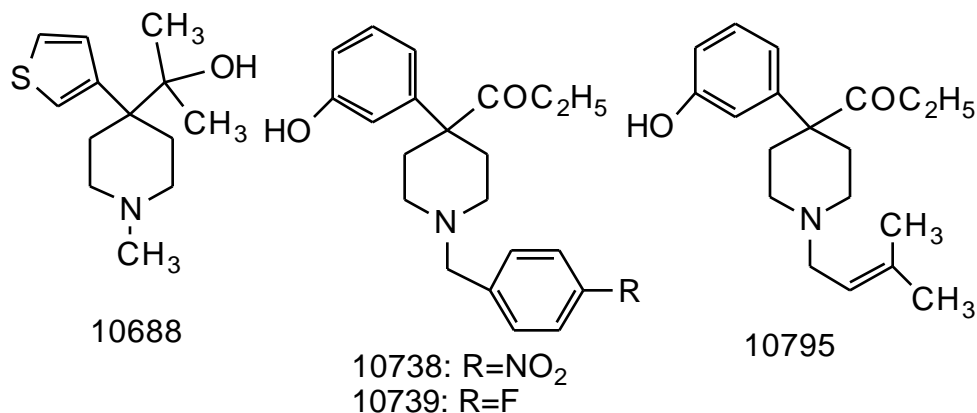
10697: (-) R=(CH₂)₇CH₃
 10698: (+) R=(CH₂)₇CH₃
 10768: (-) R=(CH₂)₉CH₃
 10769: (+) R=(CH₂)₉CH₃



10750: (-) R=NO₂
 10751: (+) R=F
 10752: (-) R=F
 10772: (+) R=NO₂

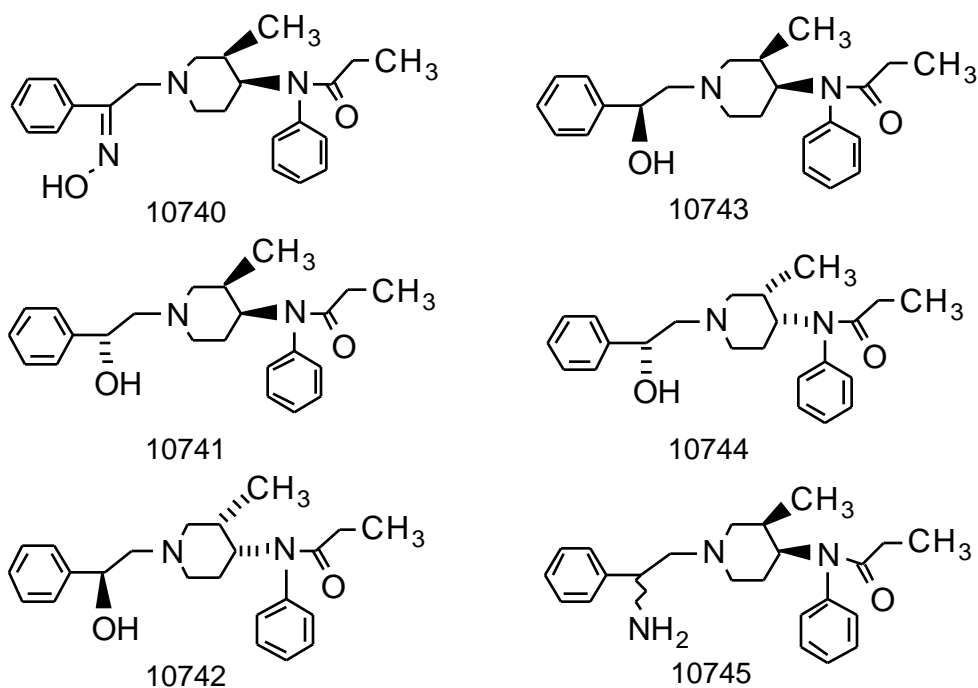
NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10697	5.4 ^b	0.5 ^b	10.0 ^b	^b	226 nM ^b	ANT ^{b,c}	NS(1,4) ^d
10698	11.1 ^b	7.8 ^b	^b	^b	3.4 μM ^b	ANT ^{b,e}	NS(4,16)
10750					>6 μM	1.9 nM(37)[A] ^f	NS(4,16)
10751					>6 μM	ANT ^g	NS(4,16)
10752					>6 μM	Insoluble	NS(4,16)
10768					>6 μM	SE ^h	NS(2.5,10) ⁱ
10769					>6 μM	13 nM(20) ^j	NS(4,16)
10772					>6 μM	ANT ^k	NS(3,12)

- a) See text for explanation of column headings and abbreviations.
 b) Previously reported - 1993.
 c) Non-typical μ- and δ-agonist, weak μ-antagonist.
 d) May exacerbate withdrawal, possible δ-agonist properties.
 e) Weak μ- and δ-antagonist.
 f) Partial agonist, weak non-selective μ- and δ-antagonist
 g) Weak non-competitive δ-antagonist with limited selectivity.
 h) Weak low efficacy partial agonist, antagonized by naloxone at lower concentrations; non-opioid action at higher concentrations.
 i) May exacerbate withdrawal at 10 mg/kg.
 j) Low efficacy partial agonist or non-opioid.
 k) Weak non-selective antagonist.

TABLE 4. ARYLPIPERIDINES^a

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10688	μ ^b	5.4 ^b	μ ^b	μ ^b	10.3 μM ^b	SE ^{b,c}	PS(4,24) ^{b,d,e,f}
10738	-	-	-	-	3.4 μM	ANT ^g	-
10739	-	-	-	-	1.3 μM	ANT ^h	-
10795	-	-	-	-	507 nM	ANT ⁱ	-

- a) See text for explanation of column headings and abbreviations.
- b) Previously reported - 1992.
- c) Unusual partial agonist with doubtful opioid action.
- d) **RI (SM: NS**, but behavioral suppression; and **PPD: PS**): Doubtful μ-like dependence potential
DD - agonist effects (>5.6 mg/kg), no μ agonist or antagonist activity;
MA - 100% effect (10 mg/kg, 50^o, attenuated by quadazocine);
RF - decreased function (attenuated by quadazocine);
SA - limited reinforcing capacity.
- f) New data - **PPD** (monkeys) - produced physical dependence, probably μ-related and, possibly, and/or dopaminergic.
- g) Low potency - and -antagonist; not simple competitive-type.
- h) Low potency, mostly -antagonist (some -antagonism); not competitive.
- i) Weak, partial agonist, non-opioid; weak non-selective antagonist.

TABLE 5. FENTANYL-LIKE COMPOUNDS^a

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10740	1.8	0.8	0.9	l	3 μ M	2 μ M(47)[A] ^b	CS(0.3-3.6)
10741	0.0001	9E-5	2E-4 ^c	l	5.9 nM	56 fM[A] ^d	CS (1.5E-4 -3E-5) ^e
10742	0.08	0.03	0.06 ^c	l	102 nM	1.4 μ M[A] ^f	CS[30 x M]
10743	0.0013	1.2E-4	8E-4 ^c	l	6.8 nM	96 fM[A] ^g	CS[1500 x M]
10744	2.1	0.6	13.0	l	380 nM	1 nM(28)[A] ^h	NS(0.6,12) ⁱ
10745	0.7	0.09	0.6 ^c	l	410 nM	7.6 nM[A]	CS[4-6 x M]

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

b) No significant agonist or antagonist activity.

c) Naloxone (AD₅₀) vs ED₈₀ of 10741=0.008, of 10742 and 10745=0.03, of 10743=0.035.

d) Biphasic (also, 4 nM[A]).

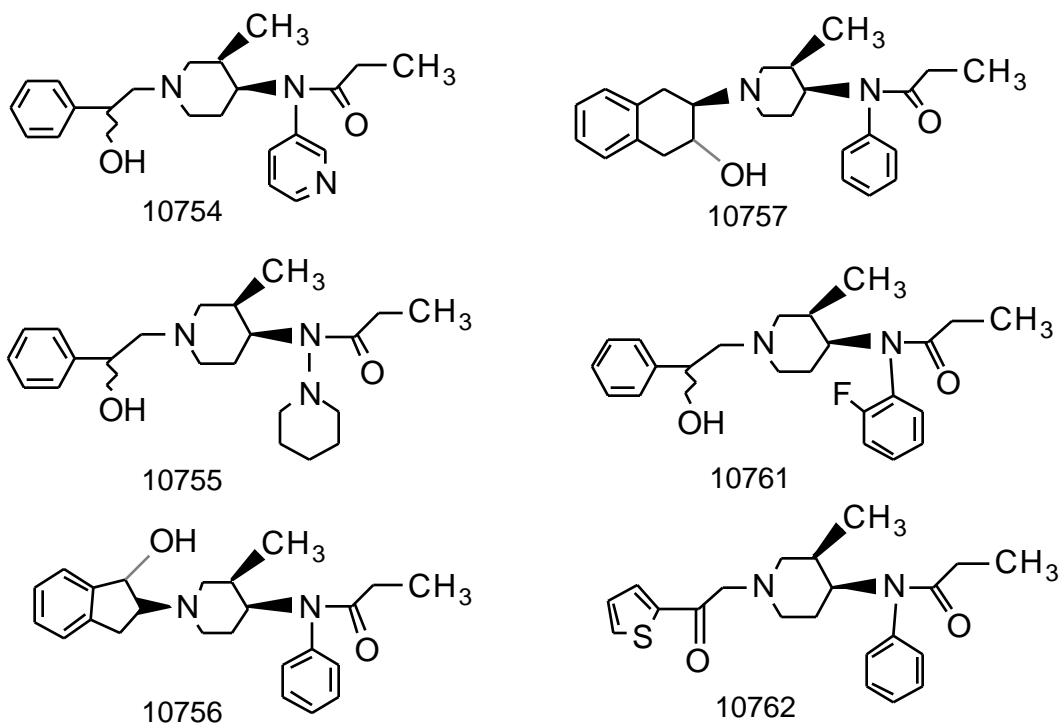
e) 20,000-50,000 x M.

f) Biphasic.

g) Biphasic (also, 6.7E-9[A]).

h) Weak partial μ -agonist, and weak μ -antagonist.

i) Biphasic (weak antagonist at lower doses; no effect at highest dose).

TABLE 6. FENTANYL-LIKE COMPOUNDS (CONTINUED)^a

NIH #	MOUSE ED ₅₀ /AD ₅₀				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10754	0.004	4E-4	0.001		28.4 nM	32 nM[A] ^b	CS[2000 x M]
10755	0.16	0.07	0.12 ^c		377 nM	90 nM(85)[A]	CS[10 x M]
10756	0.18	0.03	0.14 ^c		1037 nM	310nM(91)[A] ^d	CS[6 x M]
10757	0.006	1E-3	3.6E-3		48.2 nM	Agonist ^e	CS[300 x M]
10761	4E-4	1E-4	4E-4 ^c		1.02 nM	33 nM ^f	CS[6000 x M]
10762	0.24	0.02	0.03 ^c		-	-	CS[60 x M]

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

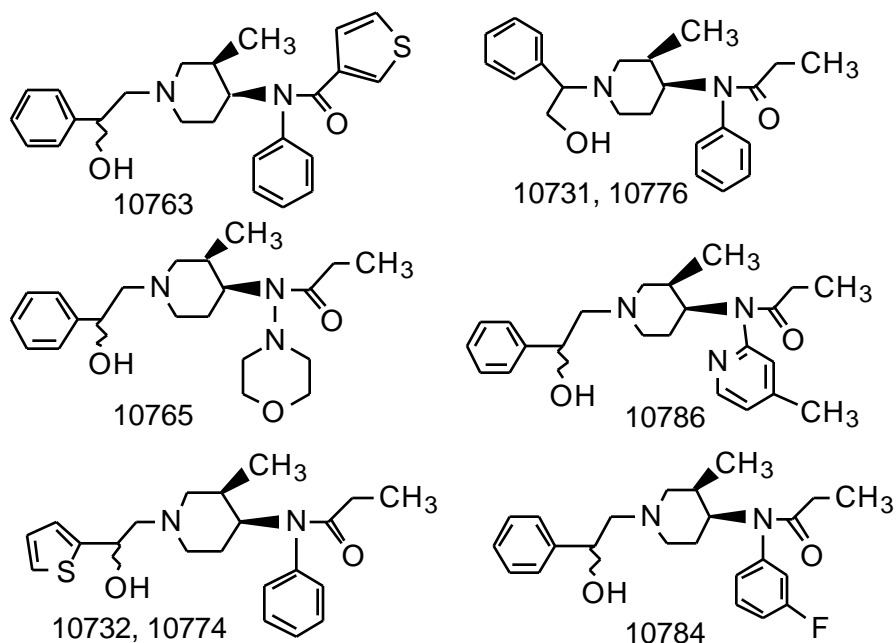
b) Actions at μ - and κ -opioid receptors.

c) Naloxone (AD₅₀) vs ED₈₀ of 10755=0.04, of 10756=0.11, of 10761=0.04, and of 10762=0.03.

d) Partial agonist, μ -selective.

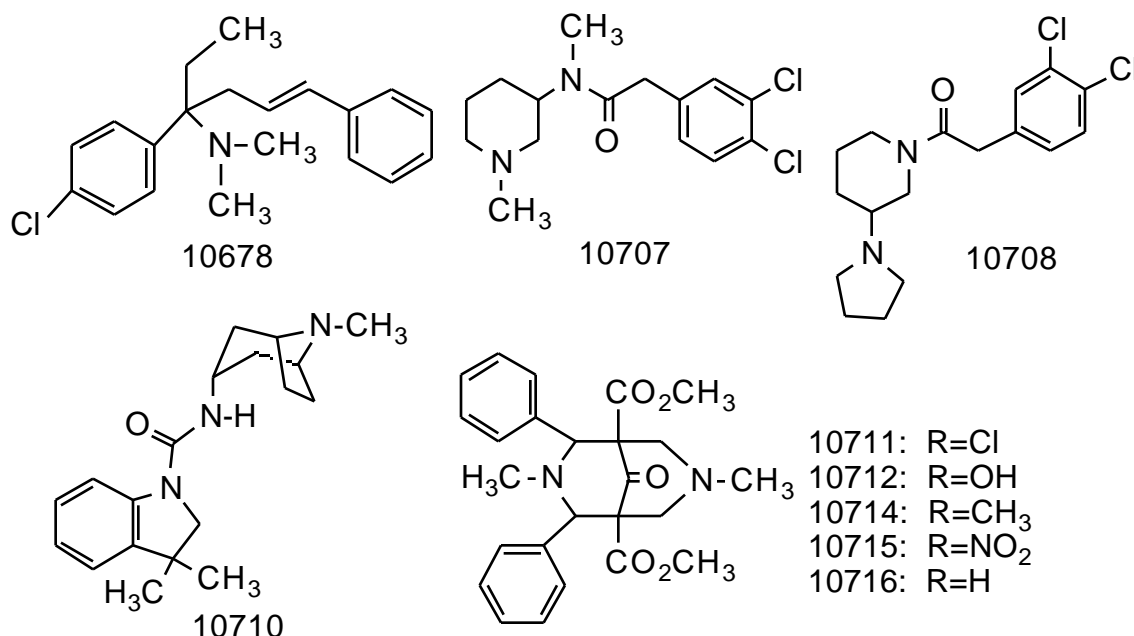
e) Fairly potent, multiphasic action.

f) Only slightly antagonized by μ -, κ -, or δ -antagonists; possible δ -agonist and μ -antagonist activity.

TABLE 7. FENTANYL-LIKE COMPOUNDS (CONTINUED)^a

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10763	2E-3	1E-4	1E-3 ^b	I	5.6 nM	113 nM ^c	CS [1500 x M]
10765	3.4	0.1	3.0	I	-	-	CS[1.5 x M]
10732; 10774	0.6 ^d	0.3 ^d	0.7 ^d	I ^d	3 μM ^d 5.3 μM	15.7 μM ^{d,e} 1.6 μM(85)[A] ^f	CS[12 x M] ^d
10731; 10776	4E-3 ^d	1E-3 ^d	3E-3 ^d	I ^d	7.3 nM ^d 2.8 nM	300nM [NA] ^{d,g} 3 nM [A] ^h	CS[750 x M] ^d
10783	9E-3	3E-4	2E-3	I	19 nM	7 nM [A] ⁱ	CS [12,000xM]
10784	-	-	-	-	6.5 nM	7.6 nM[A] ⁱ	-

- a) See text for explanation of column headings and abbreviations.
 b) Naloxone (AD₅₀) vs ED₈₀ = 0.02.
 c) Slight antagonism by μ- and -antagonists.
 d) Published in 1992.
 e) Slight shift by μ- and -antagonists; actions possibly non-opioid.
 f) μ-selective agonist.
 g) Non-opioid action.
 h) Potent agonist primarily at - and, possibly, μ-receptors.
 i) Potent μ-agonist.

TABLE 8. MISCELLANEOUS^a

NIH #	MOUSE ED50/AD50					IN VITRO	MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10678	-	0.9	13.7		216 nM ^b	734 nM(90)[A]	CS [0.5 x M] ^c
10707		5.6			>6 μM	NE	NS(2.5,10)
10708	-	-	-	-	>6 μM	58 nM(22)	-
10710					-	-	NS (2,8) ^{d,e}
10711	^f	^f	^f		5.6 μM	1.7 μM [A] ^g	PS(2,10)
10712	-	-	-	-	>6 μM	91 μM[A] ^h	-
10714					>6 μM	ANT ⁱ	-
10715					>6 μM	10 nM(33)	-
10716					>6 μM	ANT ^j	NS(1.8-6.4)

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

b) **BIND**: μ=40 nM, =727 nM, =86 nM.

c) **PPD**: produced physical dependence. Study terminated because of skin ulcers; **DD**: No discriminative effect; **RF**: non-opioid, similar to competitive NMDA antagonists and ketamine-like drugs; **MA**: inactive, but augments effect of μ- or -agonists; **SA**: Maintained rates of responding slightly below alfentanil at one dose only.

d) May exacerbate withdrawal.

e) **PPt-W**: NP(3,12); **RI (PPD)**: low or no physical dependence.

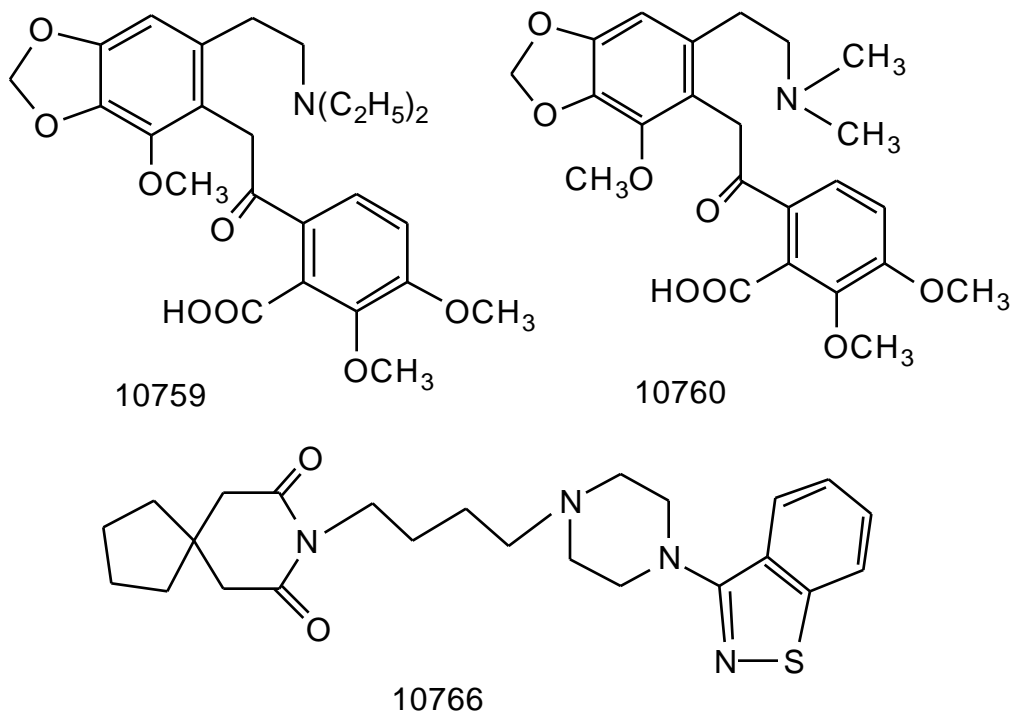
f) Delayed effects or delayed absorption due to vehicle (gum tragacanth).

g) Unusual agonist with μ-, -, and -effects.

h) -, or μ- agonist actions.

i) μ-, -antagonist at high concentrations.

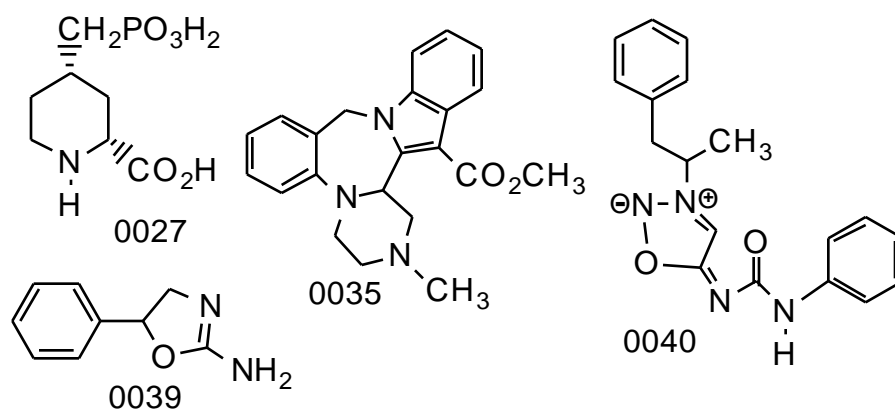
j) Competitive μ -antagonist.

TABLE 9. MISCELLANEOUS (CONTINUED)^a

NIH #	MOUSE ED50/AD50					IN VITRO	MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10759					>6 μM	NE	NS(2-24) ^b
10760					>6 μM	3.9 nM(41) ^c	NS(2-12) ^d
10766	5.3	0.07			>6 μM	4.1 μM ^c	PS(0.25,1.0)

- a) See text for explanation of column headings and abbreviations.
 b) **SA**: Reinforcing properties (like alfentanil) in only one out of four monkeys.
 c) Non-opioid or partial low efficacy agonist, μ-selective.
 d) **SA**: No reinforcing properties.

TABLE 10. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD#	SLA ^a	IS ^b	PD-Sc	PD-PPD ^d	SA ^e	DD ^f
0027	DEPRESS. ^g	DEPRESS.	NO ^h	MILD ⁱ	NO ^j	NO ^k
0035	DEPRESS. ^l	DEPRESS. ^l	NO ^m	-	NO	NO ⁿ
0039	STIMULANT	NO ^o	YES ^p	-	YES ^q	YES ^r
0040	STIMULANT ^s	NO	.t	-	YES ^u	YES ^r

- Spontaneous locomotor activity (mouse).
- Inverted screen assay (mouse).
- Physical dependence - substitution for pentobarbital (rat infusion).
- Physical dependence - primary (rat infusion).
- Self-administration (monkey).
- Drug discrimination (intra-gastric administration, monkey).
- Depression: ED₅₀ = 3 mg/kg (5 to 8 x more potent than pentobarbital).
- Did not substitute for pentobarbital to prevent weight loss on withdrawal.
- Mild abstinence on abrupt withdrawal; unlike pentobarbital or benzodiazepines.
- Reinforcing effects in one out of three monkeys; ataxic at 1.0 mg/kg/inj.
- Does not share discriminative stimulus effects with *d*-amphetamine or pentobarbital after intravenous, intramuscular, or intra-gastric administration.
- Slightly more potent than pentobarbital.
- Lack of suppression may be due low doses necessitated by drug insolubility.
- Does not share discriminative stimulus effects with *d*-amphetamine or pentobarbital.
- Impairment observed at highest dose (20 mg/kg) due to toxicity.
- Exacerbation of withdrawal in pentobarbital-treated rats; potency and duration of action greater than cocaine in cocaine-infused rats.
- Variability within animals.
- Discriminative stimulus effects similar to *d*-amphetamine, but not to pentobarbital.
- Stimulant efficacy and potency slightly greater than cocaine.
- Insufficient solubility for assay.

u) Reinforcing effects; limited by solubility of compound.

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