

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)

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PURPOSES OF THE DRUG EVALUATION COMMITTEE (DEC)

The DEC was founded to ensure the continuation of the drug evaluation program, a major program of the CPDD which has been maintained as a public service from the CPDD's inception in 1928 as a committee of the National Research Council of the National Academy of Sciences. The DEC manages the evaluation carried out by a consortium of university-based groups. The researchers determine the physical dependence potential and abuse liability of drugs, and establish new, or improve older, methodology. The initial program was highly dependent on the interdisciplinary work of chemists, pharmacologists and clinicians, focusing on the synthesis and appraisal of potent analgesics which might lack the undesirable side-effects of morphine. The contemporary design of the DEC is somewhat different. The pharmacological techniques have expanded well beyond what was originally envisioned, and the new drugs which are examined are obtained from domestic and foreign universities, pharmaceutical industry, governmental units, the World Health Organization, and other sources. Our program now also includes testing and research on stimulants and depressants.

Data obtained from the various groups associated with the DEC have provided essential information for the regulation of these drugs by governmental agencies and the World Health Organization, and are invaluable for scientists involved with the chemistry, pharmacology and clinical utility of drugs with potential abuse problems, as well as those who seek to explain the function and interaction of these drugs with CNS receptors on the molecular level. The theoretical exploration of the interaction of opioids with their receptors, as well as experimentally in binding assays, has recently become possible due to the cloning of the cDNA's of all three opioid receptors and their sequencing.¹⁻⁸ The data obtained by DEC will play an important role in that research.

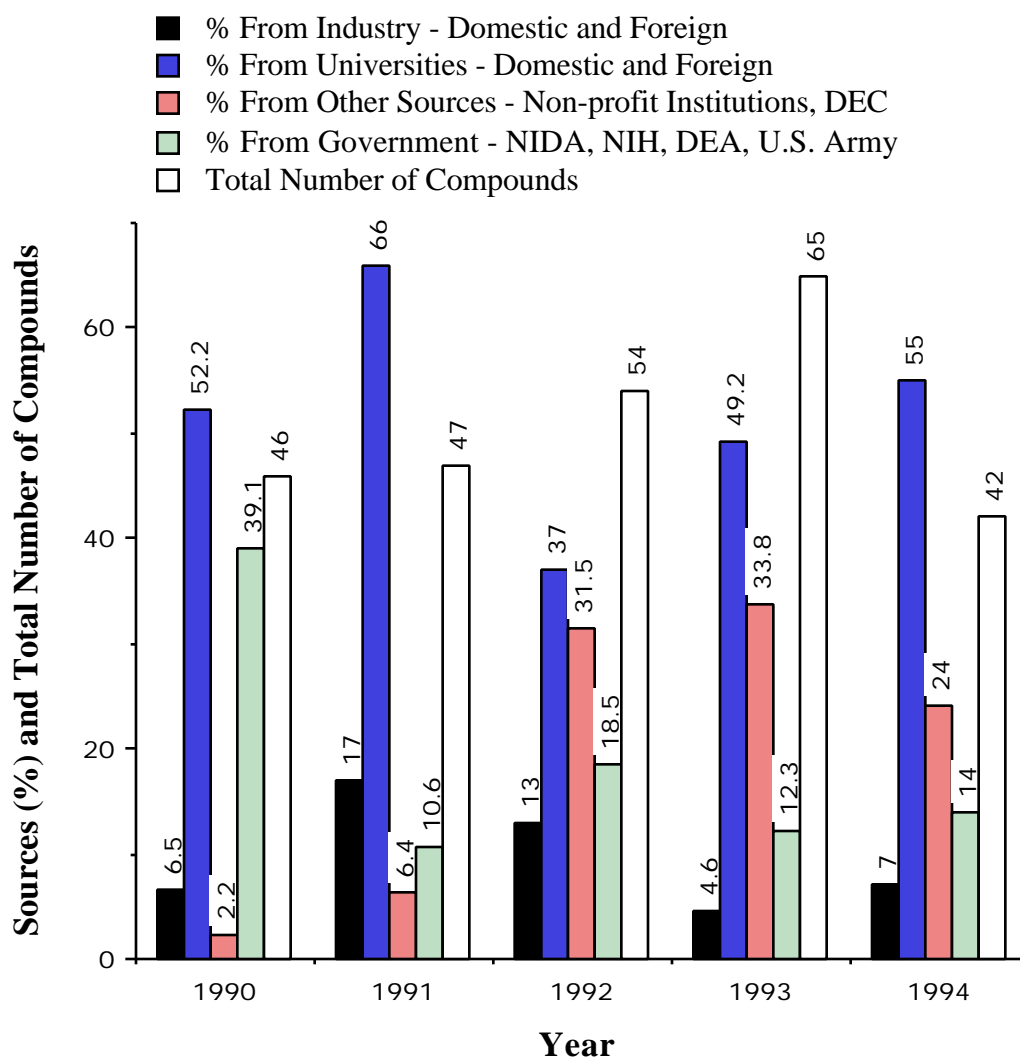
MEMBERS OF THE DEC

The DEC, under the chairmanship of Dr. T. Cicero (Washington University, St. Louis), has three representatives from the CPDD Board of Directors who are appointed by the President of the Board of the CPDD. These are Drs. L. Cook (DuPont Merck Pharmaceutical Co.), S. Holtzman (Emory University School of Medicine), and J. Smith (Bowman Gray School of Medicine). Each of the testing groups involved with the work of the DEC have one member on the DEC: Drs. L. Harris and P. Graham (Medical College of Virginia), G. Winger and J. Woods (University of Michigan), and W. Woolverton (University of Mississippi Medical Center). I serve as Biological Coordinator for the DEC, continuing the work of Drs. Everette May and Nathan Eddy, the latter having initiated the coordination of the program more than 40 years ago. From its inception, this program has been coordinated in the Laboratory of Medicinal Chemistry of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, although there have been several organizational name changes over the decades.

STATISTICS

Of the 42 drugs which were evaluated this year as analgesics by either or both Aceto et al.⁹ and Woods et al.,¹⁰ three came from the U.S. and foreign pharmaceutical industry (7%), 23 from U.S. and foreign universities (55%), 10 from a non-profit institute (24%), and six from NIH Intramural researchers (14%). Comparison of the sources and numbers of compounds over a five year period is shown graphically in Figure 1. The fluctuations in the source of compounds over the past five years can be seen in that figure. The total number of compounds annually evaluated show modest changes (from 42 to 65 - a mean of 51 (± 9)). For the last several years the major source of compounds has been from universities or from a combination of universities and non-profit institutions. It is likely that this trend will continue for the next several years.

FIGURE 1. DEC ANALGESIC PROGRAM. SOURCES AND NUMBER OF COMPOUNDS FROM 1990-1994



PROCEDURES FOR EVALUATION OF DRUGS

The various procedures which are used to determine the physical dependence potential and abuse liability of analgesics, depressants and stimulants have been noted heretofore,¹¹ and are summarized in the papers by Drs. Aceto et al.,¹² Woods et al.,¹³ and Patrick et al.¹⁴

SURVEY OF EVALUATED COMPOUNDS

1) Analgesics

The chemical names for all of the drugs which were evaluated this year can be found in table 1, and the group which evaluated the drug is also indicated therein. 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 tables 2-12 with a summarization of the DEC-derived biological data. More comprehensive data on the individual drugs can be obtained from the reports of the members of the DEC.^{9,10} The tables note the biological data obtained on these drugs in previous years and indicate where those data can be found.

Seven 4,5-epoxymorphinans are shown in tables 2 and 3. The four compounds in table 2 represent two pairs of epimers with different substituents at C-6 (NIH 10683 and 10684, and 10701 and 10702). The biological properties of the latter two are similar, but 10683 and 10684 are distinctly different. Depending on the assay, NIH 10683 might be considered a μ - or κ -agonist. It does not show antagonist properties in antinociceptive studies or in the monkey analgesia study. NIH 10683 does not substitute for morphine in the SDS assay; it does not act as a μ -agonist, but rather acts as a non-selective antagonist in the vas deferens preparation. In drug discrimination it acts as a κ -agonist and not as a μ -agonist or antagonist, and in self administration NIH 10683 substitutes for alfentanil, a μ -agonist. It suppresses respiration in the respiratory function assay in monkeys, like other μ -agonists. Its C-6 β -OH epimer, NIH 10684, appears to have μ -antagonist or perhaps μ -agonist properties, depending on the assay. It has agonist activity in the PPQ assay but not in other assays in mice or monkey. It is seen as a μ -selective antagonist in the vas deferens, precipitates withdrawal with a slow onset and long duration of action in SDS in monkeys, and shows antagonist properties in drug discrimination. NIH 10684 maintains self-injection in the monkey, but it was less efficacious than alfentanil, a μ -agonist. All four of the compounds have good affinity for the opioid receptors. The bulky iodine atom at C-6- and - for 10701 and 10702, respectively, appears to have little effect on its binding to μ , κ , and δ receptors.

NIH 10773 (table 3) bears a sulfate ester at C-6 and is morphine-like in antinociceptive potency in the mouse. However, it does not substitute for morphine in SDS, appears as a weak agonist in the vas deferens, and does not bind well to opioid receptors. The compound exists as a zwitterion, possessing structural characteristics reminiscent of an amino acid, yet appears to easily pass through the blood-brain barrier in vivo.

The substituents at C-1 and C-2 in NIH 10787 and 10814 (table 3) might have been expected (from the work of others) to interfere with biological activity. However, NIH 10787 was found to be a very potent antagonist and 10814, which had less affinity for the opioid receptors than 10787, was noted to have insurmountable antagonist actions at the δ receptor.

Table 4 lists the actions of 6 endoetheno- and endoethanooripavines. NIH 10805 has a chlorine atom at C-1, like NIH 10787 (table 3) and acts as a potent antagonist. NIH 10812, however, a 2-nitro-substituted buprenorphine, does not have opioid actions in vivo. NIH 10813 appears to be very similar to 10814 (table 3) in binding and in the vas deferens preparation. The in vivo work on most of the compounds in table 4 is scheduled for 1994.

Four rather inactive (+)-morphinans are listed in table 5, as is a (-)-morphinan (NIH 10802). Structurally similar molecules have affinity for sigma (σ) receptors

or PCP binding sites. SDS data on the phenylmorphans in table 5, NIH 10779, completes the data gathered previously on that essentially morphine-like compound.

Table 6 displays the actions of four (+)- and (-)-6,7-benzomorphans. These, and other N-*n*-alkyl-substituted 6,7-benzomorphans are among the compounds which were the subject of a paper which was recently submitted to J. Med. Chem.¹⁵ Several of the authors are DEC members. Some of the compounds in the series were found to be among the most potent known μ -receptor ligands. It is perhaps somewhat surprising to note that NIH 10675 and 10697, although they are in the (+)-benzomorphan series, have good (NIH 10675) or reasonable (NIH 10697) antinociceptive activity.

Three arylpiperidines which seem to exert antagonist activity in the vas deferens preparation are shown in table 7, and 10 compounds related to fentanyl are listed in tables 8 and 9. Most of the fentanyl-like compounds had activity in the SDS assay ranging between morphine-like to that of NIH 10792 (table 9) or 10741 (table 8), which were estimated to be 30,000 or 20,000-50,000 times more potent than morphine, respectively. These compounds are among the most potent known narcotic agonists.

The remaining tables 10 and 11 consider the miscellaneous compounds. NIH 10700 (table 11) is structurally similar to PCP, but has antinociceptive activity and some affinity for the opioid receptors. NIH 10815 (table 11) was seen to be relatively selective, and potent, for δ -receptors in the vas deferens preparation, but did not have much affinity for opioid receptors. Other workers have indicated that it is a potent and selective δ -ligand in vitro as well as in the vas deferens and guinea pig ileum preparations.

2) Stimulants and Depressants

Two compounds (stimulants) were released for publication this year (CPDD 0038 from pharmaceutical industry, and 0041, Etryptamine acetate, from NIDA).¹⁶ The molecular structures of these compounds and the summarization of the data collected on them by the Stimulant/Depressant testing groups of DEC are shown in table 12. Our data on Etryptamine and several other drugs will be used by the World Health Organization for scheduling purposes. Two or three compounds are being processed for testing in 1994-1995.

ABBREVIATIONS USED IN TABLES 2 - 13

Rounded numbers are used in the tables; M = morphine. Precise values and details of the procedures are given in the MCV⁹ and UM¹⁰ reports; NT = not tested.

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

1) MOUSE ED50/AD50: Antinociceptive Assays (sc injection)⁹

Confidence limits are listed in the MCV report.⁹

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) ¹⁰

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 reports before 1985¹⁷ 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 (δ), or U50,488 (κ).¹⁰

3) **IN VIVO**: in the rhesus monkey (from MCV⁹; from MCV or UM prior to 1988).

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)⁹

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)⁹

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)⁹
M-like = morphine-like effect.
 - 3) **PPD** = primary physical dependence (data from MCV)⁹
 - 4) **SA** or **SI** = self-administration or self-injection (data from UM)¹⁰
NE = no effect
High = codeine-like
IN = intermediate between saline and codeine
SE = slight effect
 - 5) **DD** = drug discrimination (data from UM)¹⁰
NE = no effect
CS = complete substitution
 - 6) **MA** = monkey analgesia (data from UM)¹⁰
 - 7) **RF** = respiratory function (data from UM)¹⁰
- C) In Vitro (data from UM)¹⁰
BIND - binding affinity using monkey brain cortex membranes
(selectivity for μ , κ , and δ opioid receptors determined with [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 from either UM or MCV.

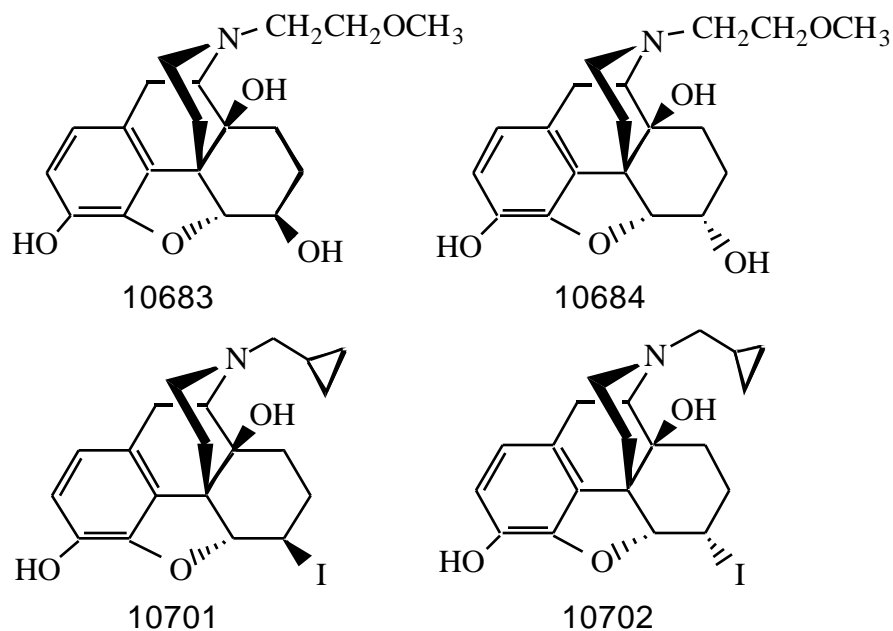
TABLE 1. NIH NUMBERS, CHEMICAL NAMES, TABLE NUMBER, AND EVALUATING GROUP

<u>NIH#</u>	<u>NAME</u>	<u>TABLE #-</u> <u>Evaluator^a</u>
04591	(+)-3-Hydroxy-N-methylmorphinan.HBr (Dextrorphan, Dromoran)	5-MCV ^a
10560	(-)-5,9 -Dimethyl-2-ethyl-2'-hydroxy-6,7- benzomorphan.HCl	6-MCV
10675	(-)-5,9 -Dimethyl-2- <i>n</i> -heptyl-2'-hydroxy-6,7- benzomorphan.HCl	6-MCV
10683	14-Hydroxy-N-(2-methoxyethyl)-7,8- dihydronormorphine	2-MCV/UM ^b
10684	14-Hydroxy-N-(2-methoxyethyl)-7,8- dihydronorisomorphine	2-MCV/UM
10697	(-)-5,9 -Dimethyl-2'-hydroxy-2- <i>n</i> -octyl-6,7- benzomorphan.HCl	6-UM
10698	(+)-5,9 -Dimethyl-2'-hydroxy-2- <i>n</i> -octyl-6,7- benzomorphan.HCl	6-UM
10700	1-[1-(2-Hydroxyphenyl)cyclohexyl]-3,4- dehydropiperidine.HCl	10-UM
10701	6 -Iodo-3,14-dihydroxy-17-cyclopropylmethyl-4,5 - epoxymorphinan.oxalate	2-UM
10702	6 -Iodo-3,14-dihydroxy-17-cyclopropylmethyl-4,5 - epoxymorphinan.oxalate	2-UM
10703	N-[(3,4-Dichlorophenyl)acetyl]-N,2-dimethyl-2- (N',N'-dimethylamino)ethylamine.oxalate	10-UM
10705	N-(<i>n</i> -Propyl)-N'-(3,4-dichlorophenylethyl) piperazine.2HBr	10-UM
10735	(+)-N-Benzyl-3-hydroxymorphinan.HCl	5-MCV
10738	4-(3-Hydroxyphenyl)-1-(4-nitrobenzyl)-4-(1- oxopropyl)piperidine .HCl	7-MCV
10739	1-(4-Fluorobenzyl)-4-(3-hydroxybenzyl)-4-(1- oxopropyl)piperidine .HCl	7-MCV
10741	(<i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-(+)- <i>cis</i> -N-[1-(2()-Hydroxy-2- phenylethyl)-3-methyl-4-piperidinyl]-N- phenylpropanamide.HCl	8-MCV
10749	(+)-3-Hydroxy-N-(4-nitrobenzyl)morphinan oxalate	5-MCV
10762	(±)- <i>cis</i> -N-[3-Methyl-1-[2-oxo-2-(2-thienyl)ethyl]-4- piperidinyl]-N-phenylpropanamide.HCl	8-UM
10765	(±)- <i>cis</i> -N-[1-(2-Hydroxy-1-phenylethyl)-3-methyl-4- piperidinyl]-N-phenylpropanamide.HCl	8-UM
10773	Morphine-3-acetate-6-sulfate (zwitterion)	3-MCV/UM
10779	2,3-Dimethyl-5-(3-hydroxyphenyl) morphan.HBr	5-MCV/UM
10782	Rifampin (Rifampicin)	10-MCV/UM
10784	(±)- <i>cis</i> -N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4- piperidinyl]-N-(3-fluorophenyl)propanamide.HCl	8-MCV
10785	(±)- <i>cis</i> -N-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4- piperidinyl]-N-(4-fluorophenyl)propanamide.HCl	8-MCV/UM
10786	(±)- <i>cis</i> -N-[1-[2-(4-Bromophenyl)ethyl-2-hydroxy]-3- methyl-4-piperidinyl]-N-phenylpropanamide.HCl	9-MCV/UM
10787	1-Chloronaltrexone.HCl	3-MCV/UM

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

10790	(±)-1-(2-Hydroxy-2-phenylethyl)-t-3-methyl-4-[(1-oxopropyl)phenylamino]-r-4-piperidinecarboxamide Methyl Ester.HCl	9-MCV/UM
10791	(±)-1-(2-Hydroxy-2-phenylethyl)-c-3-methyl-4-[(1-oxopropyl)phenylamino]-r-4-piperidinecarboxamide Methyl Ester.HCl	9-MCV/UM
10792	(±)-1-(2-Hydroxy-2-phenylethyl)-t-3-methyl-4-[(1-oxopropyl)phenylamino]-r-4-piperidinecarboxamide Ethyl Ester.HCl	9-MCV/UM
10793	(±)-N-[1-(2-Hydroxy-2-phenylethyl)-4-methoxymethyl-c-3-methyl-r-4-piperidinyl]-N-phenylpropanamide oxalate	9-MCV/UM
10794	Amitriptylene.HCl	11-MCV/UM
10795	4-(3-Hydroxyphenyl-4-(1-oxopropyl)-1-(2-methyl-2-butenyl) piperidine.HCl	7-MCV
10796	(+)-N-(2-Methylpropenyl)-3-hydroxymorphinan.HBr	5-MCV
10802	(-)-3-Hydroxy-N-(4-hydroxybenzyl)morphinan.HBr	5-MCV/UM
10803	(±)-N-Allylmecamylamine.HCl	11-MCV/UM
10805	1-Chlorodiprenorphine oxalate	4-MCV/UM
10809	N-Cyclopropylmethyl[7 ,8 ,2',3']cyclopentano-1'-[R]hydroxy-6,14-endoethenotetrahydronororipavine .HCl	4-MCV/UM
10810	N-Cyclopropylmethyl[7 ,8 ,2',3']cyclopentano-1'-[S]hydroxy-6,14-endoethenotetrahydronororipavine .HCl	4-UM
10811	N-Cyclopropylmethyl[7 ,8 ,2',3']cyclohexano-1'-[S]hydroxy-6,14-endoethenotetrahydronororipavine .HCl	4-UM
10812	2-Nitrobuprenorphine.HCl	4-UM
10813	2-Nitrodiprenorphine.HCl	4-UM
10814	2-Nitronaltrexone.HCl	3-UM
10815	(+)-4-[(R)- -(12S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl]-3-methoxybenzyl]-N,N-diethylbenzamide	11-UM
CPDD 0038	2-(7-Chloro-1,8-naphthyridin-2-yl)-3-[(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)carbonylmethyl]isoindolin-1-one	12-MCV/UM /UMSb
CPDD 0041	Etryptamine acetate	12-MCV/UM/UMSb

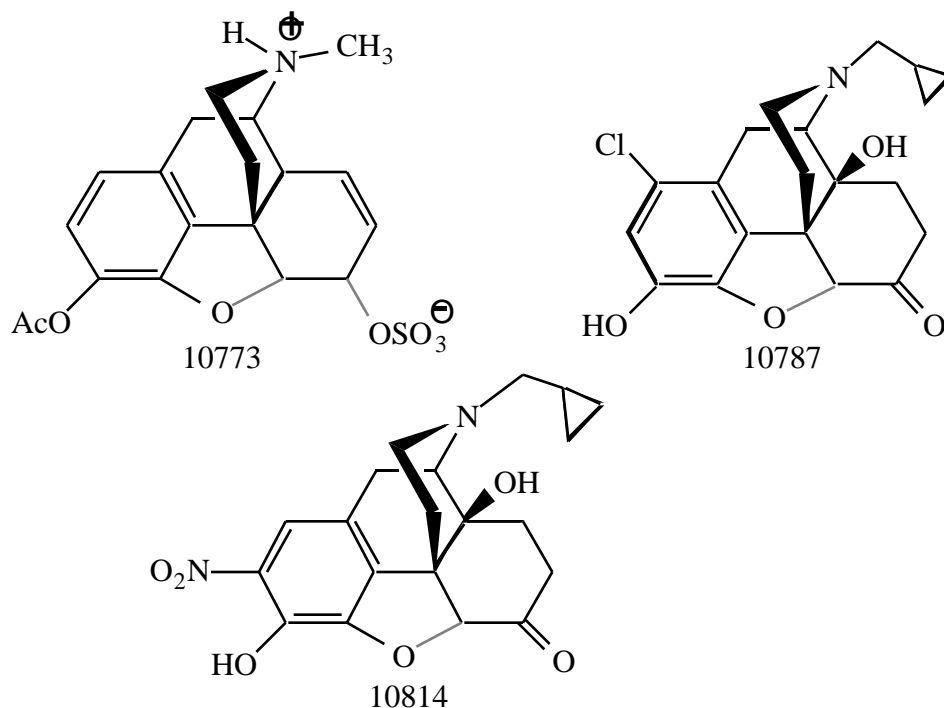
- a) For complete data from MCV, see reference 13, and see reference 14 for complete data from UM.
b) See reference 16 for complete data from MCV, UM, and UMS.

TABLE 2. 4,5-EPOXYMORPHINANS^a

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10683	0.3	0.03 ^b	0.2 ^b	I	8.2 nM	7E-6[NA] ^c	NS(0.5-6) ^d
10684	I	2.6	I	I	5.4 nM	4.9E-5[NA] ^e	NS(1,4) ^f
10701	I ^g	I ^g	I ^g	0.08 ^g	5.2 nM ^{g,h}	ANT ^{g,i}	NS ^{g,j}
10702	I ^g	I ^g	I ^g	0.04 ^g	2.1 nM ^{g,k}	ANT ^{g,l}	NS ^{g,m}

- a) See text for explanation of column headings and abbreviations.
- b) AD50 (naloxone vs ED80) - **PPQ**: 0.6; - **TF**: 0.03.
- c) Not μ -like agonist; μ , δ , κ -antagonist.
- d) Not μ -like in monkey; **MA**: analgesic[A]; **SA**: substitutes for alfentanil (0.03 mg/kg/inj); **DD**: μ -agonist, not μ -agonist or antagonist; **RF**: suppression[A].
- e) μ -Selective antagonist.
- f) **PPt-W**: agonist-antagonist with slow onset and long duration; **DD**: no agonist effects, substituted for naltrexone; **MA**: NE (antagonist); **RF**: NE; **SA**: maintained self-injection in 2/3 monkeys, less efficacious than alfentanil.
- g) Previously reported - 1992.
- h) **BIND**: μ =1.06 nM, δ =26 nM, κ =0.34 nM
- i) Non-selective.
- j) **PPt-W** - PW.
- k) **BIND**: μ =0.42 nM, δ =9.6 nM, κ =0.3 nM
- l) μ -Selective.
- m) Exacerbates withdrawal.

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



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10773	1.0	0.5	2.5	I	517 nM	139 nM(81)[A] ^b	NS (2.5,10)
10787	I	I	I ^c	4.8E-4	0.38 nM	ANT ^d	NS (0.0016) ^e
10814	-	-	-	-	196 nM	3.5E-9(23)[A] ^f	-

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

b) Weak partial agonist.

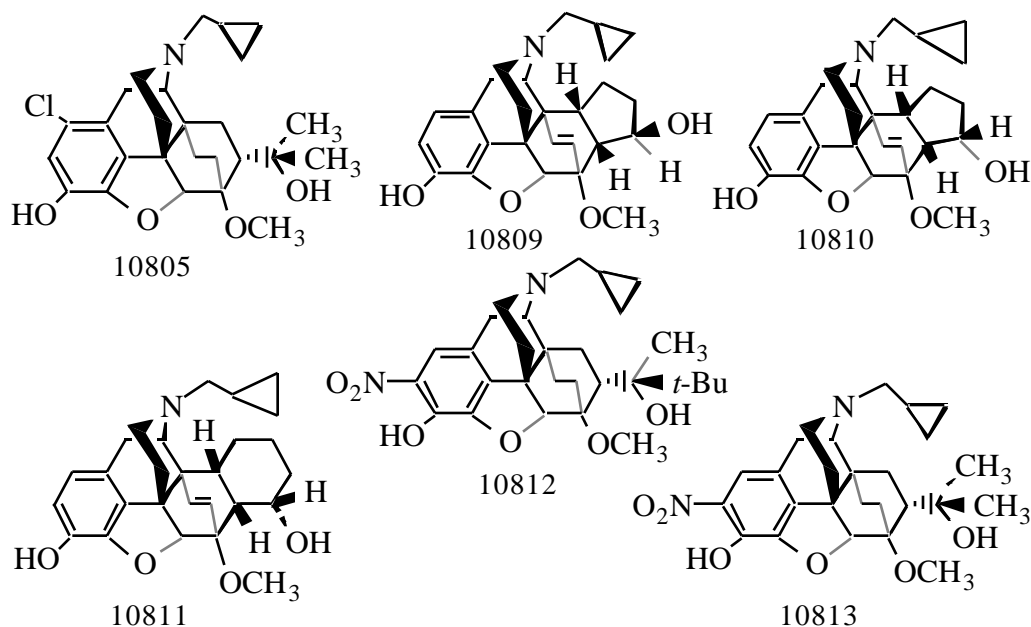
c) pA_2 vs M = 8.7, pA_2 vs 10672 () = complete antagonism.

d) Potent antagonist, slightly selective for μ -receptors.

e) **PPt-W**: PW [5 x naloxone].

f) Competitive antagonist at μ and , insurmountable antagonist at .

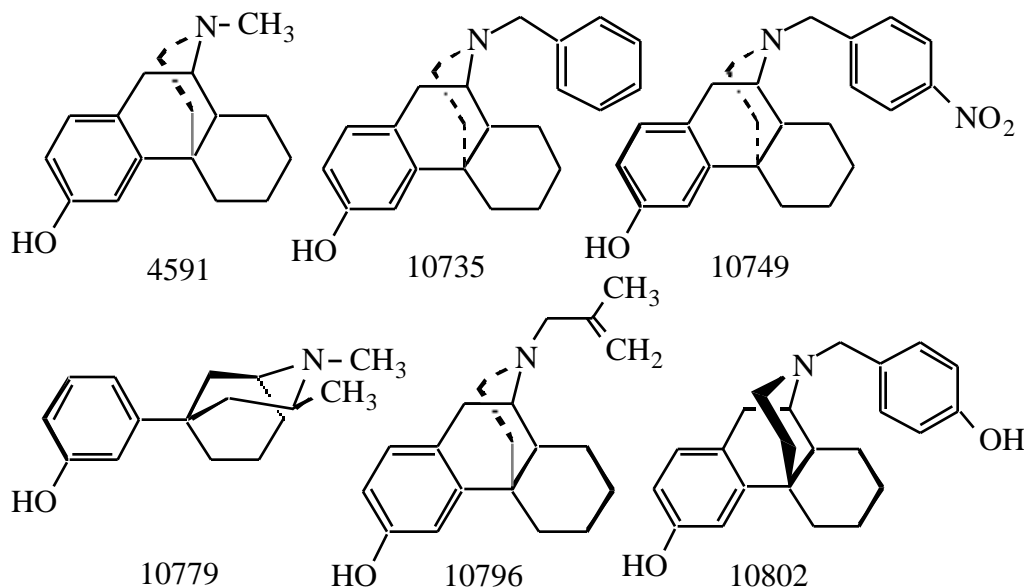
TABLE 4. ENDOETHENO- AND ENDOETHANOORIPAVINES^a



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10805	I	I	I	0.09 ^b	0.61 nM	ANT ^c	NS (0.01-0.02) ^d
10809	I	0.01	0.1	9.3	0.49 nM	2.2E-9(74)[A] ^e	NS (0.05-0.025) ^{d,f}
10810	-	-	-	-	0.91 nM	8.8E-9(78)[A] ^g	-
10811	-	-	-	-	0.59 nM	0.86E-9(99)[A] ^g	-
10812	-	-	-	-	3.81 μM	6.7E-9(56)[NA] ^h	-
10813	-	-	-	-	140 nM	4E-7(44)[A] ⁱ	-

- a) See text for explanation of column headings and abbreviations.
 b) pA_2 vs M = non-competitive antagonist; pA_2 vs 10672 () = 8.0 (high affinity for).
 c) Non-selective; insurmountable at .
 d) Exacerbates withdrawal; **PPt-W**: PW (like naloxone).
 e) Relatively selective -agonist.
 f) Longer-acting than naloxone. Partial μ -agonist; perhaps - and -actions.
 g) Relatively selective μ -agonist.
 h) Very weak mixed antagonist, slightly more potent at and .
 i) Competitive antagonist at μ and , insurmountable antagonist at .

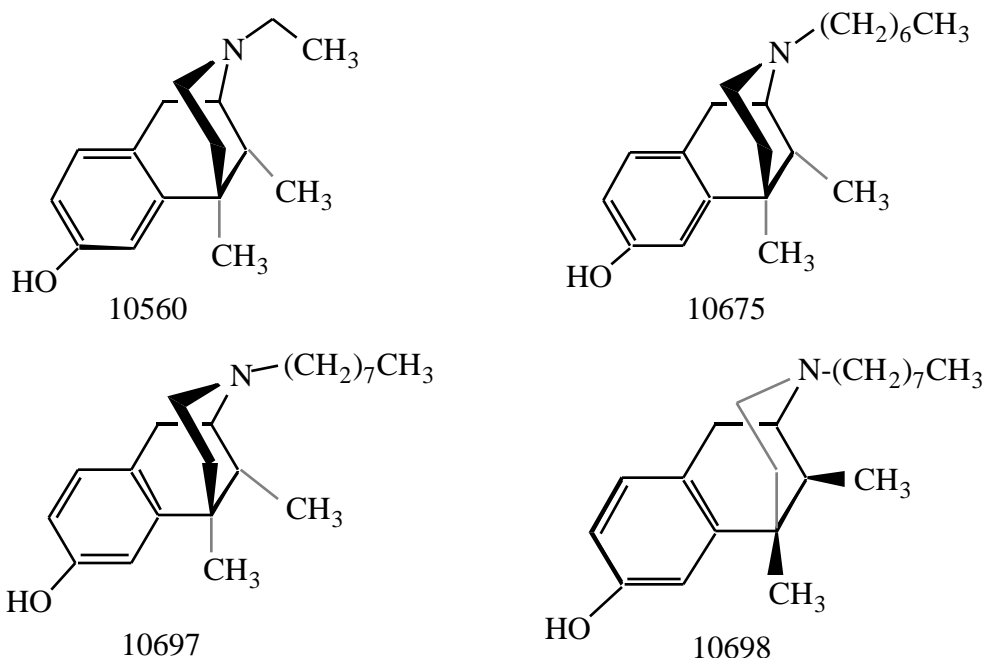
TABLE 5. MORPHINANS AND 5-PHENYLMORPHAN^a



NIH #	MOUSE ED ₅₀ /AD ₅₀				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
04591	58 ^b	24	I	I	1.4 μ	-	PS (4) ^c
10735	I	6.1	I	I	>6 μ ^d	ANT ^{d,e}	NS(1.8,7) ^f
10749	I	I	I	I	>6 μ ^d	Insoluble ^d	NS (4,16)
10779	4.8 ^d	0.3 ^d	1.3 ^d	I ^d	592 nM ^d	15.8 μ ^{d,g}	CS (0.75,3)
10796	I	11.4	I	I	>6 μM ^d	ANT ^{d,h}	PS (15) ⁱ
10802	I	I	I	I	2.1 μM	108 nM(23) [NA] ^j	NT

- See text for explanation of column headings and abbreviations.
- Previously reported - 1951.
- Ataxia; **Ppt-W**: - NE (1,4); **PPD**: Tolerance and withdrawal, exacerbated by naltrexone. Some M-like signs missing; **RI: SM** - withdrawal, no weight loss. Previously reported - **SDS**: NE, 1981.
- Previously reported - 1993.
- Low potency -antagonist activity (and some -antagonist activity).
- Convulsions noted.
- Low potency μ-partial agonist.
- Weak -antagonist.
- Not μ-opioid action; produces CNS excitation.
- No opioid agonist action; μ-antagonist (not simple competitive).

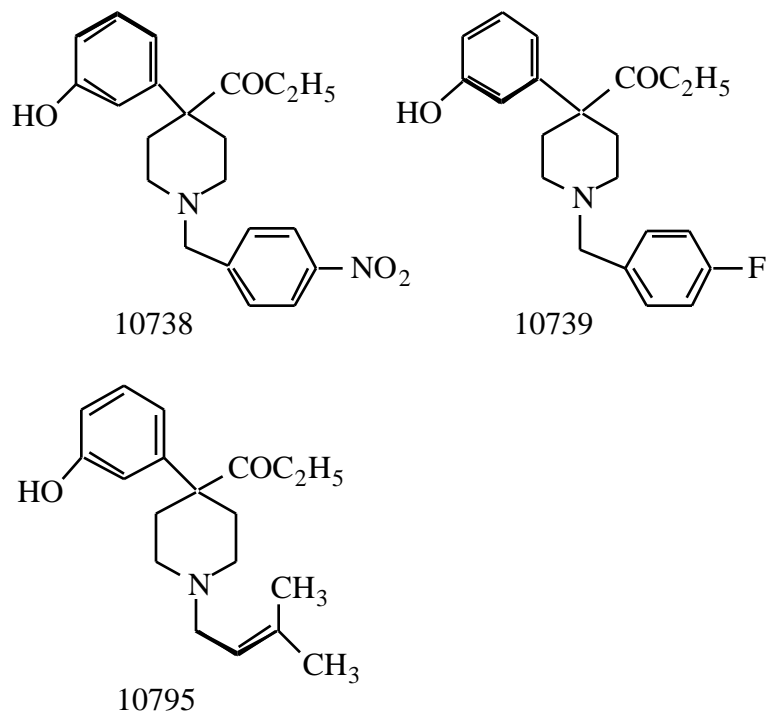
TABLE 6. 6,7-BENZOMORPHANS^a



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10560	1 ^b	1.4 ^b	1 ^b	3.7 ^b	144 nM ^b	ANTAG ^{b,c}	NS ^d
10675	2.4 ^e	0.13 ^f	1.7 ^f	I	89 nM	3.5E-7(100) ^g	NS (1.25, 5) ^h
10697	5.4 ⁱ	0.5 ⁱ	10.0 ⁱ	1 ⁱ	226 nM ^{i,j}	ANTI ^{i,k}	NS(1,4) ^l
10698	11.1 ⁱ	7.8 ⁱ	1 ⁱ	1 ⁱ	3.4 μ i,m	ANTI ^{i,n}	NS(4,16) ⁱ

- a) See text for explanation of column headings and abbreviations.
 b) Previously reported - 1988; **TF**: pA₂ vs M: 5.85, μ-competitive.
 c) Unusual, non-competitive, non-selective.
 d) Exacerbates withdrawal.
 e) Previously reported - 1992.
 f) Agonist at μ and receptors.
 g) Convulsions with cumulative dose of 11.5 mg/kg/hr; **RI**: SM - PS; **RI**: PPD - μ-like withdrawal.
 h) Previously reported - 1993.
 i) **BIND**: μ=150, =197, =115 nM (non-selective).
 j) Non-typical μ- and -agonist, weak μ-antagonist.
 k) May exacerbate withdrawal, possible -agonist properties.
 l) **BIND**: μ=763 nM, =21% at 6 μM, =2.8 μM (non-selective, low potency)
 n) Weak μ- and -antagonist.

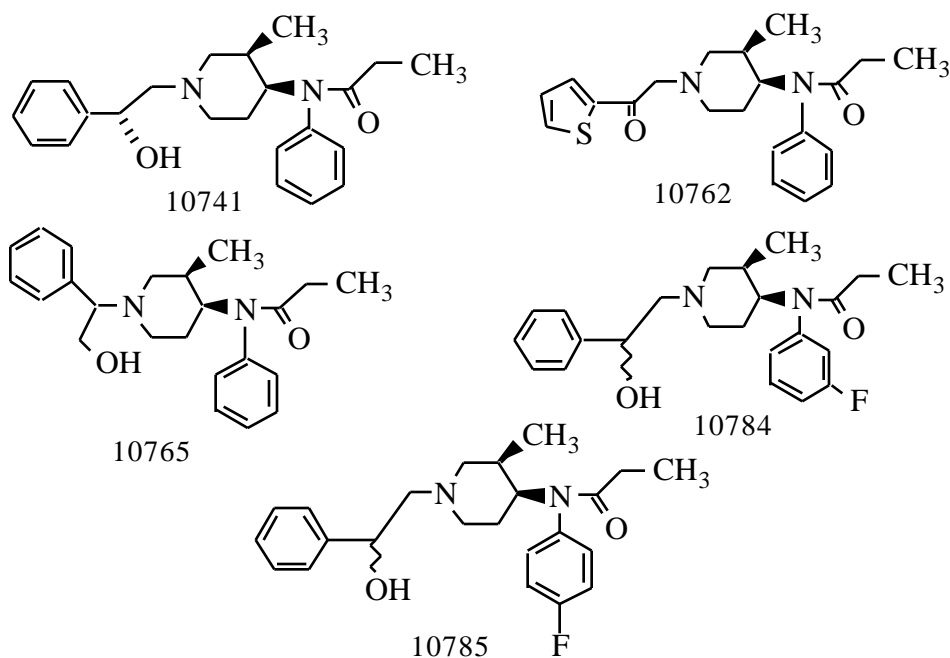
TABLE 7. ARYLPIPERIDINES^a



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	<u>HP</u>	<u>PPQ</u>	<u>TF</u>	<u>TF</u> <u>A</u>	<u>RBH</u>	<u>VD</u>	<u>SDS</u>
10738	I	7.3	I	I	3.4 μ ^b	ANT ^{b,c}	NS (3,12)
10739	I	18.3	I	I	1.3 μ ^b	ANT ^{b,d}	NS (2.5,10)
10795	8.3	2.2	9.7	I	507 nM ^b	ANT ^{b,e}	PS(2.5,10) ^f

- a) See text for explanation of column headings and abbreviations.
 b) Previously reported - 1993.
 c) Low potency - and -antagonist, not simple competitive-type.
 d) Low potency, mostly -antagonist (some -antagonism), not competitive.
 e) Weak non-opioid partial agonist; weak non-selective antagonist.
 f) Non-dose related suppression. Some observed signs seen from abrupt withdrawal are more typical from precipitated withdrawal.

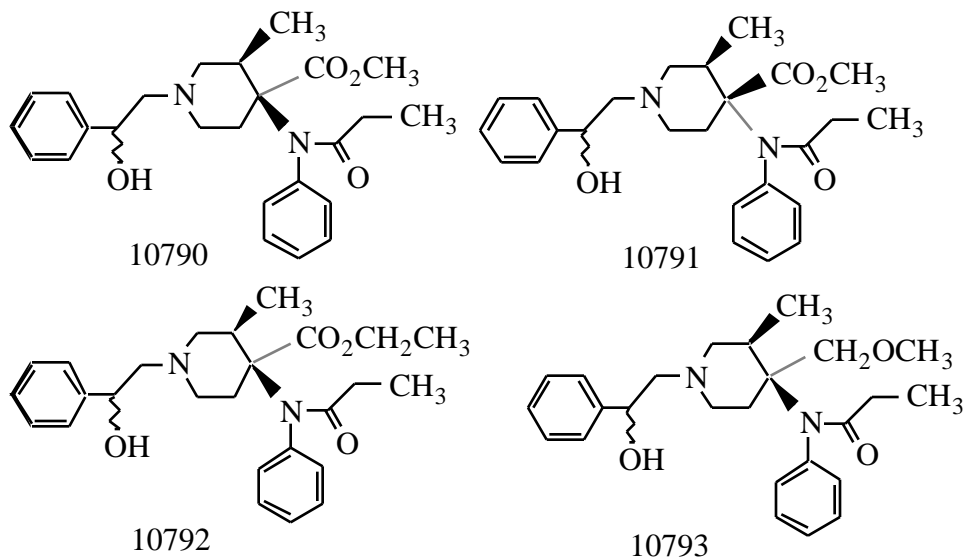
TABLE 8. FENTANYL-LIKE COMPOUNDS^a



NIH #	MOUSE ED ₅₀ /AD ₅₀				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10741	1E-4 ^b	9E-5 ^b	2E-4 ^{b,c}	I ^b	5.9 nM ^b	56 fM [A] ^{b,d}	CS ^{b,e} (1.5E-4 -3E-5)
10762	0.24 ^b	0.02 ^b	0.03 ^{b,f}	I ^b	569 nM	>3 μg	CS[60 x M] ^b
10765	3.4 ^b	0.1 ^b	3.0 ^b	I ^b	6 μM	ANT ^h	CS [1.5 x M] ^b
10784	0.005	0.001	0.004 ⁱ	I	6.5 nM ^b	7.6 nM [A] ^{b,j}	CS [6000 x M]
10785	0.001	3.4E-4	0.002 ^k	I	4.5 nM	2.8 nM (100)[A] ^l	CS [1000 x M]

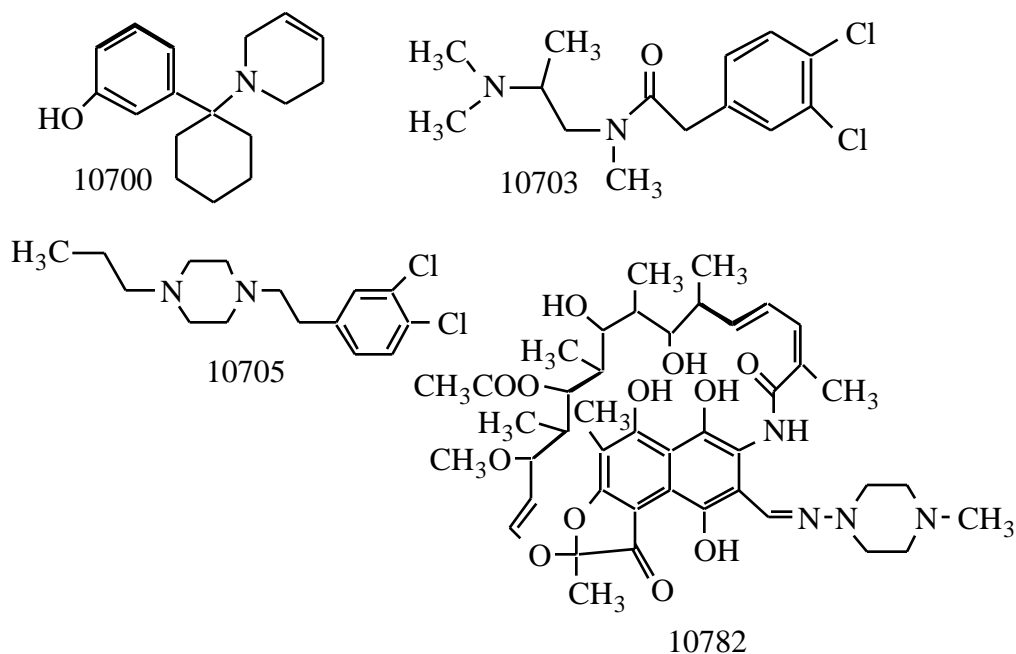
- See text for explanation of column headings and abbreviations.
- Previously reported - 1993.
- Naloxone (AD₅₀) vs ED₈₀ of 10741=0.008. pA₂ vs naloxone = 7.2, suggesting competitive interaction with μ-receptor.
- Biphasic (also, 4 nM[A]). Complex actions - -agonist activity.
- 20,000-50,000 x M.
- Naloxone (AD₅₀) vs ED₈₀ of 10762=0.03.
- Low potency μ-opioid agonist.
- Very low potency μ-opioid antagonist.
- Naloxone (AD₅₀) vs ED₈₀ of 10784=0.11.
- Potent μ-agonist.
- Naloxone (AD₅₀) vs ED₈₀ of 10785=0.04.
- Selective agonist.

TABLE 9 (CONTINUED). FENTANYL-LIKE COMPOUNDS^a



NIH #	MOUSE ED50/AD50			IN VITRO			MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10786	0.013	0.007	0.03 ^b	I	22.9 nM	1.4 μM ^c	CS [60 x M]
10790	6.1E-4	1E-4	4.4E-4 ^d	I	0.85 nM	0.77 nM[A] ^f	CS [6000 x M]
10791	0.001	8E-4	0.001 ^e	I	2.3 nM	1.3 nM[A] ^f	CS [6000 x M]
10792	0.003	1E-4	2.4E-4 ^g	I	1.2 nM	1.3 nM[A] ^f	CS [30,000 x M]
10793	3.1E-4	5E-4	0.0013 ^h	I	0.78 nM	0.84 nM[A] ^f	CS [10,000 x M]

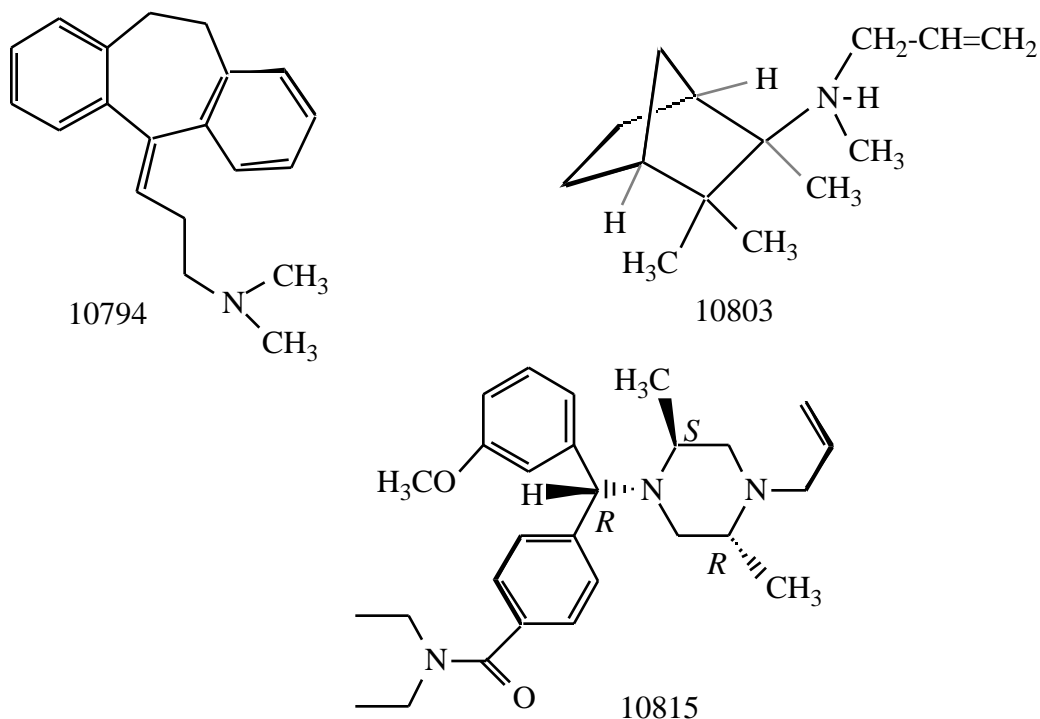
- a) See text for explanation of column headings and abbreviations.
 b) Naloxone (AD50) vs ED80 of 10786=0.04.
 c) Complex, multiphasic action, weak antagonist
 d) Naloxone (AD50) vs ED80 of 10790=0.02; pA₂ naloxone vs 10790 = 7.4.
 e) Naloxone (AD50) vs ED80 of 10791=0.02; pA₂ naloxone vs 10791 = 7.5.
 f) Potent, somewhat μ-selective agonist.
 g) Naloxone (AD50) vs ED80 of 10792=0.04.
 h) Naloxone (AD50) vs ED80 of 10793=0.04.

TABLE 10. MISCELLANEOUS^a

NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10700	I ^b	0.3 ^b	4.8 ^{b,c}	I	619 nM ^{d,e}	ANT ^{d,f}	NT
10703	I ^d	13.4 ^d	I ^d	I ^d	>6 μM ^{d,g}	49 μM(100)[A] ^{d,h}	NS ^{d,i}
10705	I ^d	10.6 ^d	I ^d	I ^d	>6 μM ^{d,j}	NE ^d	NS ^{d,k}
10782	I	I	I	I	>6 μM	3.7E-8(30[A]) ^l	NS ^m

- a) See text for explanation of column headings and abbreviations.
- b) Previously reported - 1991 (potent -ligand).
- c) Straub tail, ataxia, convulsions.
- d) Previously reported - 1992 (potent -ligand).
- e) **BIND**: μ=62 nM, =2370 nM, =2695 nM.
- f) Weak, non-selective narcotic antagonist.
- g) **BIND**: μ=1791 nM, =>6 μM, =287 nM.
- h) Possibly some , or mixed μ- activity.
- i) Disorientation noted.
- j) **BIND**: μ=5210 nM, =>6 μM, =3181 nM.
- k) Exacerbates withdrawal signs.
- l) Possible low potency agonist.
- m) Cumulative dose of 11 mg/kg.

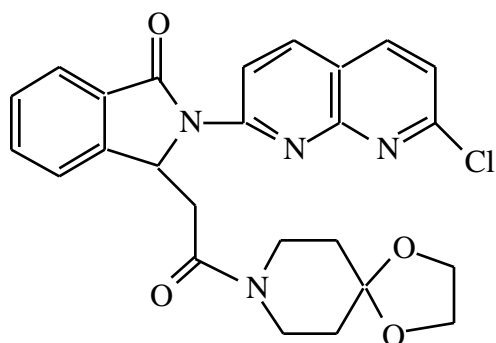
TABLE 11 (CONTINUED). MISCELLANEOUS^a



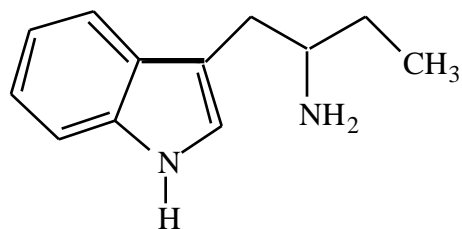
NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	HP	PPQ	TF	TFA	RBH	VD	SDS
10794	I	0.09	I	I	>6 μM	3E-9(39)[A] ^b	CS(2,8)[NA] ^c
10803	I	9.8	I	I	>6 μM	1.8E-9(23)[NA] ^d	NS ^e
10815	-	-	-	-	>6 μM	6.4E-9(100)[A] ^f	-

- See text for explanation of column headings and abbreviations.
- Low efficacy μ-agonist, low potency antagonist.
- Drug actions not opioid-like. In mice, naloxone did not prevent nor antagonize drug actions. In non-dependent monkeys, the overt neurological signs associated with withdrawal were not antagonized by naloxone.
- Naloxone decreased maximum response without shift in concentration-effect curve; weak partial agonist or non-opioid agonist.
- Non-μ-opioid properties.
- Relatively selective for κ-receptors.

TABLE 12. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD 0038



CPDD 0041

CPDD#	SLA ^a	IS ^b	PD-S ^c	PD-PPD ^d	SA ^e	DD ^f
0038	Stimulant ^g	Impaired ^h	NT	NT	Insoluble	NO ⁱ
0041	Stimulant	Impaired ^j	NT	NT	YES ^k	No ^l

- 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 (intragastric administration, monkey).
- g) Mild stimulation, not dose-related
- h) Non-specific toxicity: impairment not dose-related. Drug actions not typical of usual stimulants or depressants.
- i) Does not share discriminative stimulus effects with *d*-amphetamine or pentobarbital.
- j) Stimulant efficacy and potency greater than cocaine and less than *d*-amphetamine.
- k) Reinforcing effects in two out of three cocaine-trained monkeys. Unusually variable rates of responding.
- l) Does not share discriminative stimulus effects with pentobarbital; may have slight, but not full discriminative stimulus effects with *d*-amphetamine.

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