

BIOLOGICAL EVALUATION OF COMPOUNDS FOR
THEIR PHYSICAL DEPENDENCE POTENTIAL AND
ABUSE LIABILITY. XV. ANIMAL TESTING COMMITTEE
OF THE COMMITTEE ON PROBLEMS OF DRUG
DEPENDENCE, INC. (1991)

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In: Harris, L.S., ed. Problems of Drug Dependence: 1991. National Institute on Drug Abuse Research Monograph. Washington, D.C.: Supt. of Docs., U.S. Govt. Print. Off., 1992, pp 490-512.

The Animal Testing Committee of the Committee on Problems of Drug Dependence (CPDD) is a subcommittee of the Drug Evaluation Committee (Dr. T. Cicero, Chairman). It is concerned with two programs: 1) the evaluation of analgesics, at both the Medical College of Virginia, Virginia Commonwealth University (MCV - Drs. M. Aceto, E. Bowman, L. Harris, and E. May) and the University of Michigan Medical School (UM - Drs. C. France, F. Medzihradsky, C. Smith, G. Winger, and J. Woods), and 2) the evaluation of stimulants and depressants, at the Medical College of Virginia, Virginia Commonwealth University (MCV - Drs. G. Patrick and L. Harris), the University of Chicago (UC - Drs. M. Nader, W. Woolverton), and the University of Michigan Medical School (UM - Dr. G. Winger). These programs are functioning well. The results which were obtained by the testing groups were discussed at a meeting of the Drug Evaluation Committee in May, 1991, in Richmond, VA.

ANALGESIC PROGRAM

The methodology used to evaluate potential analgesics remained essentially the same over the past year, with the addition of a new antinociceptive assay in mice at MCV, the hot plate assay. This assay was formerly run in NIDDK, NIH. Thus, the rodent assays now include the hot plate, phenylquinone, and tail-flick, as well as tail-flick antagonism vs. morphine.

New compounds are evaluated concurrently at MCV and UM. MCV also carries out single-dose-suppression studies, precipitated-withdrawal, and primary physical-dependence studies in monkeys. Data from substitution for morphine, and primary

physical-dependence studies by rat-infusion assays are also obtained from MCV.

The purity and identity of an examined compound is validated from submitted spectra (infrared or NMR), and thin layer chromatograms (TLC). The TLC are repeated by Dr. Everette L. May at MCV. When major differences are found between the TLC of Dr. May and that of the submitter, and this occurs perhaps two or three times/year, the sample is returned to the submitter for purification.

At UM, displacement assays are run, initially with [³H]etorphine as the radioligand, using a rat cerebrum membrane preparation. On request, μ , κ , and δ opioid assays are carried out using [³H]DAMGO (for μ), [³H]DPDPE for κ , and [³H]U-69,593 for δ opioid displacement assays. Monkey brain cortex membranes are used for this assay. The electrically stimulated mouse vas deferens preparation is also used to distinguish between the opioid receptor sites at which the various drugs interact. When requested, self-administration (SA) and drug discrimination (DD) experiments are carried out at UM, as well as antinociception and respiratory function in monkeys.

STIMULANTS AND DEPRESSANTS

The mouse inverted screen test and a spontaneous locomotor activity assay are carried out at MCV, as are primary physical dependence studies in nondependent rats, and substitution studies in pentobarbital dependent rats. Drug discrimination and self-administration assays are run in the rhesus monkey at UC and at UM, respectively.

STATISTICS

The statistical data on the number of compounds for which data were released, and their source, were in reasonable accord with the compilations obtained in the recent past (Jacobson 1991). I received 30 reports from UM and reports on 42 compounds from MCV (from 5/1/90 to 4/30/91).

About 20% of the compounds for which data were released this year came from domestic and foreign pharmaceutical industry, 65% from U.S. and foreign universities, and the remainder from U.S. governmental sources (NIDA, NIDDK, U.S. Army) or from the

deliberate introduction of older drugs for which contemporary data were desired. These percentages are comparable with the mean of the figures obtained over the past 8 years. Although these percentages have remained relatively invariant lately, it might be noted that between 1979 and 1981, 50-60% of our samples came from the pharmaceutical industry.

The 72 reports from UM and MCV which will be published in the NIDA monograph this year are a slightly higher number than those published last year, but somewhat less than the mean over the past 11 years. This may change dramatically next year if we obtain permission to release data on the compounds which have recently been submitted. We have seen a large increase in the number of compounds which have been sent for evaluation in our analgesic program.

COLLABORATION WITH NIDA

Drug Testing

A consortium of groups, including the CPDD's Animal Testing Committee, NIDA, and NIMH, are now involved in the testing of drugs which may have abuse potential, or which might be of value as medications for drug abuse. The Medications Development Division of NIDA has established two programs in which analgesics and stimulants are examined. In vitro assays are carried out at SRI International, Life Sciences Division, Menlo Park, CA, under the direction of Dr. Lawrence Toll. A poster presentation which describes this work will be presented during this Annual Scientific Meeting. Compounds of interest to NIDA are being evaluated in toxicological and other in vivo studies by groups with other NIDA contracts. Also, NIMH has a contract with NOVAScreen in Baltimore, MD, for general binding assays with a variety of radioligands. The NOVA/NIMH assays are intended to relate information about the interaction of a compound with just about any known receptor. At this time, the assays are conducted at only one or two concentrations (e.g., 10^{-5} M) of a drug. It is possible that K_i 's or IC_{50} 's can be obtained for compounds that possess substantial activity at particular binding sites.

A few of our compounds which need further evaluation will be examined through our collaboration with the NIDA/SRI program. There is some, but not a great deal of overlap between programs run under CPDD auspices and the NIDA/SRI program. Conversely,

NIDA compounds which appear to be of special interest in SRI's in vitro assays will be recommended to us by NIDA for in vivo evaluation under the auspices of the CPDD.

Computerization of Data

For the past year or two NIDA has been involved with the establishment of a database for medications development. NIDA has contracted out this effort to the Biometric Research Institute, Inc., in Arlington, VA, under the direction of Dr. Gene Barnett. A poster will be presented and the computerized database demonstrated at this Annual Scientific Meeting of the CPDD. Most, if not all, of the material which will be seen on the database consists of data gathered under the auspices of the Animal Testing Committee of the CPDD. Eventually, of course, the database will contain work from many other centers. As presently constituted, the database will be maintained on a microVAX 3300 computer at ERC BioServices Corp. (a subcontractor), in Gaithersburg, MD, and two software packages have been implemented for this purpose. These are the Oracle database program, and MACCS from Molecular Design Ltd. The gathered data are being placed in the database so that they will ultimately be accessible to scientists for their research studies from remote MS/DOS systems as well as Apple microcomputers. When the system becomes available as a research tool, answers could be obtained to questions which are difficult or, in some cases, impossible to answer now. For example, a list could be obtained of all of the compounds with an amide moiety embedded in its structure which effectively displace a radioligand from δ -opioid receptors, or a list could be obtained of all of the compounds which bind to μ , but not to δ opioid receptors and display diuretic activity. The questions which can be answered using a correctly established database is limited only by the imagination of the researcher.

ESPECIALLY INTERESTING COMPOUNDS

Several compounds shown in tables 1-10 are of great interest, and these are discussed below. For detailed information about the compounds which were examined this year, see Aceto et al. (1992) and Woods et al. (1992).

1-(2-Phenylethyl)-4-(N-(2-pyrazyl)-2-(furoylamido))piperidine hydrochloride - Mirfentanil -
NIH 10647 & 10669

NIH 10647 (or 10669), in table 4, has been given the generic name "mirfentanil". We found it to be from 3-14 times more potent than morphine as an antinociceptive in rodents, depending on the assay, and its actions were antagonized by naloxone. However, in the monkey analgesia assay, its analgesic action could not be blocked by naltrexone or quadazocine in doses sufficient to antagonize the effects of ordinary μ agonists. The relatively high doses required for analgesia in the monkey did not, thus, appear to be mediated by opioid receptors.

Mirfentanil did not substitute for morphine in the single-dose-suppression assay in monkeys. It was somewhat less potent than morphine in displacing [³H]etorphine from rat cerebrum membranes and displayed partial agonist action, which could be blocked by naltrexone, and relatively non-selective, competitive, opioid-antagonist action in the mouse vas deferens preparation. Its respiratory effects in the monkey were similar to those of buprenorphine and nalbuphine. That is, mirfentanil blocked the action of alfentanil in producing apnea.

As a discriminative stimulus, mirfentanil appeared to have μ opioid effects, substituting for a μ agonist but not a κ agonist. Its antagonist activity was shown by its ability to substitute for naltrexone in a drug discrimination assay. A similar pattern of discriminative stimulus effects has been observed with buprenorphine. In monkey self-administration, mirfentanil maintained rates of responding similar to that of codeine.

The mixture of results seen in the various assays, the different results in rodents and monkeys, and the antagonist activity observed, is very unusual for a fentanyl-like compound. The fentanyl series of drugs have not previously been noted to have narcotic antagonist activity. The ability of mirfentanil to block apnea caused by alfentanil in the monkey is especially noteworthy.

LAAM, norLAAM, and dinorLAAM (NIH 10679, 10652, 10655)

The acetylmethadols, LAAM and dinorLAAM were examined this year (NIH 10679 and 10655, table 6), and norLAAM was evaluated last year (Jacobson, 1991). LAAM was found to have morphine-like antinociceptive potency in rodents, and the N-nor metabolites were as potent as, or more potent than LAAM as antinociceptives. All three compounds completely suppressed withdrawal from morphine in the monkey single-dose-suppression assay, and they were all selective μ agonists in the mouse vas deferens assay. LAAM was unusual in displaying a biphasic concentration-effect curve in the vas deferens. LAAM was a potent and selective μ agonist in binding to the opioid receptors in monkey brain cortex. It was about 100 fold less potent at μ and δ opioid receptors.

The actions of these metabolites of LAAM, norLAAM and dinorLAAM, must be considered when appraising the in vivo activity of LAAM.

Naloxone benzoylhydrazone, BOZO, NIH 10656

Naloxone benzoylhydrazone, NIH 10656 (table 2), was found to have potent narcotic antagonist actions in the rodent assay. This compound has been given the acronym BOZO. It was noted by Pasternak and his colleagues (Paul et al. 1990) to "retain its ability to elicit analgesia through a novel and distinct supraspinal κ system". In our hands, NIH 10656 did not display agonist activity. It was equipotent with naloxone in the mouse vas deferens preparation and also acted as an antagonist in single-dose-suppression studies in the monkey. It was found to be essentially equipotent with naloxone in a precipitated-withdrawal study in monkeys. In drug discrimination BOZO substituted for naltrexone and its potency was similar to naltrexone in morphine-dependent rhesus monkeys. In monkey analgesia studies it antagonized the effects of both μ and δ agonists, and shifted the effects of alfentanil three-fold to the right in respiratory function studies.

BOZO was an effective antagonist against both μ and δ agonists and was more potent as a μ antagonist in the behavioral assay. We did not find it to be a particularly selective μ ligand.

(-)-[5 R-(5 ,7 ,8)]-N-Methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-4-benzofuranacetamide hydrochloride - NIH 10672

NIH 10672, a selective κ ligand, was extensively studied (table 9). This benzofuranacetamide was found to be several hundred times more potent than morphine in rodent antinociceptive assays. Its antinociceptive action in the tail-flick assay could only be antagonized by a high concentration of naloxone, suggesting κ rather than μ agonist activity. The antinociceptive activity of the drug in rodent assays could not be blocked by norbinaltorphimine. In monkey analgesia studies, the maximum effect was observed at a very low dose, 0.018 mg/kg, and this was antagonized with quadazocine.

NIH 10672 did not substitute for morphine or exacerbate withdrawal in the single-dose-suppression assay in monkeys or in the morphine-dependent rat studies. It was relatively free of physical dependence in rat primary physical dependence studies, but in the primary physical dependence study in monkeys dramatic agonist effects were seen to which tolerance developed, and a withdrawal syndrome was noted on abrupt withdrawal. This syndrome was completely suppressed by NIH 10672. The withdrawal syndrome was unlike that of μ opioids, and similar to that produced by κ opioids. However, naloxone did not precipitate withdrawal.

This drug was more potent in the vas deferens preparation than in binding experiments and appeared to be an opioid agonist selective for κ opioid receptors. Unlike most κ opioids, however, in the vas deferens the antagonism produced by norbinaltorphimine, a κ opioid antagonist, was surmountable. In drug discrimination, NIH 10672 substituted for ethylketocyclazocine (EKC), a prototypic κ opioid. It substituted for naltrexone in 2 out of 3 monkeys, but it did not antagonize the effects of morphine. It also failed to maintain self-injection responding in monkeys trained to administer alfentanil, a μ agonist. Respiratory function studies indicated that it would not produce apnea at a maximum dose of 0.032 mg/kg in monkeys.

This drug appears to have an unusual spectrum of action. It is, or will soon be in a clinical trial (Phase 2). From our studies, it is evident that the drug is unlikely to have abuse liability in

man. However, there remains the question of whether the subjective effects of the drug, like those of many other opioids, will be too adverse for its acceptability as an analgesic in people.

(-)-3-Acetyl-6-(acetylthio)-N-(cyclopropylmethyl)normorphine - NIH 10685

Structurally, NIH 10685 (table 2) is a 3-acetyl analog of N-cyclopropylmethylnormorphine, with a thioacetyl group at the C-6 position of the 4,5-epoxymorphinan. Undoubtedly, the 3-acetyl group is readily hydrolyzed in vivo to the phenolic compound, but the thioacetyl moiety may be relatively stable. NIH 10685 was about as potent as, or somewhat more potent than morphine in the rodent antinociceptive assays. A high dose of naloxone was needed to antagonize its effect in the tail-flick assay. Its analgesic action in the monkey was antagonized by quadazocine. NIH 10685 did not show appreciable narcotic antagonist activity in the tail-flick assay vs. morphine. However, it acted like an agonist-antagonist in the single-dose-suppression study in the monkey. It did not substitute for morphine in this study, and it exacerbated withdrawal. It appeared to have a dopaminergic component in its action. NIH 10685 had very high affinity for both κ and μ , and high affinity for the δ opioid receptor in membranes from monkey brain cortex. It showed antagonist activity in the vas deferens preparation against all three opioid receptor subtypes. NIH 10685 did not substitute for alfentanil in drug discrimination studies. It did substitute for, and was equipotent with, naltrexone, and it antagonized the reversal of withdrawal induced by alfentanil, a μ agonist, in these studies. NIH 10685 also substituted for EKC, a δ agonist, in these drug dependence studies. It antagonized the effect of alfentanil on respiratory function, and did not by itself produce apnea. The relatively small effect of NIH 10685 on respiratory function was not clearly antagonized by quadazocine. NIH 10685 apparently exerts its effects through its ability to act as a μ antagonist and a δ agonist.

It is of interest to note the effects of this thioacetyl group on the in vitro and in vivo action of N-cyclopropylmethylnormorphine (NIH 7952), the parent structure for NIH 10685. NIH 7952 was synthesized by Dr. Marshall Gates over 30 years ago. Drs. G. A. Deneau and M. H. Seevers reported

their work with the compound at UM in 1962. From single dose substitution studies in monkeys they concluded that N-cyclopropylmethylnormorphine was slightly less potent than nalorphine as an antagonist, but with a longer duration of action (24 hrs.). Apparently, the introduction of a thioacetyl group at C-6 and an acetyl moiety at C-3 into N-cyclopropylmethylnormorphine were causative factors for the increase in narcotic antagonist potency. In 1962, of course, methodology was not available for examining the interaction of ligands with opioid receptors. It might be of interest to examine the effect of NIH 7952 on subtypes of opioid receptors, to see whether introduction of the C-3 acetyl and the C-6 thioacetyl group alters its pattern of interaction with opioid receptors.

Other compounds examined

All of the seven 4,5-epoxymorphinans which are shown in Tables 1 and 2, are narcotic antagonists. NIH 10663, with a glucuronide moiety on C-3 of the aromatic ring, could represent a metabolic product of the parent 4,5-epoxymorphinan. It might act as a prodrug, where enzymatic hydrolysis of the glucuronide may provide the phenol in vivo, thus theoretically leading to a drug in situ with an overall slow onset and long duration of action. The compound showed little activity in vitro, and somewhat greater potency in vivo.

All of the N-alkyl substituted 6,7-benzomorphans in table 3, and those which have previously been discussed (Jacobson 1991), will be the subject of a paper by Dr. Everette May (MCV, Richmond, VA). The manuscript will include data from all of the analgesic testing groups and is presently in preparation for publication in J. Med. Chem.

Two of the phenylpiperidines in table 4, NIH 10651 and 10681, had some antagonist activity in vitro. None of the examined phenylpiperidines substituted for morphine in the single-dose-suppression assay. This is somewhat unusual for phenylpiperidines and fentanyl-like analogs.

As noted in table 5, haloperidol displays fairly potent antinociceptive activity, although it does not seem to interact with opioid receptors in vitro. The haloperidol analog, NIH 10671 is considerably more potent than haloperidol in the tail-flick assay. NIH 10671 also substitutes for morphine in the

single-dose-suppression assay, and the catalepsy induced in one monkey during that assay was reversed with naloxone.

A considerable number of miscellaneous types of compounds can be seen in tables 7 - 10. Etonitazene (NIH 10665), in table 9, was found to be, as expected, a very potent agonist in antinociceptive assays. It was noted to act as a partial, very potent, agonist in the vas deferens preparation.

ABBREVIATIONS USED IN TABLES 1 - 10

Rounded numbers are used in the tables. For precise values, and details of the procedures, see the MCV and UM reports in this volume (Aceto et al., 1992; Woods et al., 1992).

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

Confidence limits are listed in the MCV report (Aceto et al., 1992).

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., 1992)

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) in which
- Na values were quoted.

VD = electrically stimulated mouse vas deferens EC50 values, rounded to one significant figure.

Agonist activity is stated using "E" followed by a negative number: $E = 10^{-x}$ M, where x = the negative number, thus: $1E-3 = 1 \times 10^{-3}$ or 0.001 M (1 mM), $1E-6 = 1 \mu\text{M}$, and $1E-9 = 1 \text{ nM}$. Maximum percent inhibition was previously noted (Jacobson 1991) in parentheses following agonist activity.

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 can suppress the twitch, but is not antagonized by naltrexone. It is a non-opioid agonist). 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., 1992).

3) IN VIVO : in the rhesus monkey (from MCV, Aceto et al., 1992; 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 suppression

6) MA = monkey analgesia (data from UM)

7) RESP = respiratory function (data from UM)

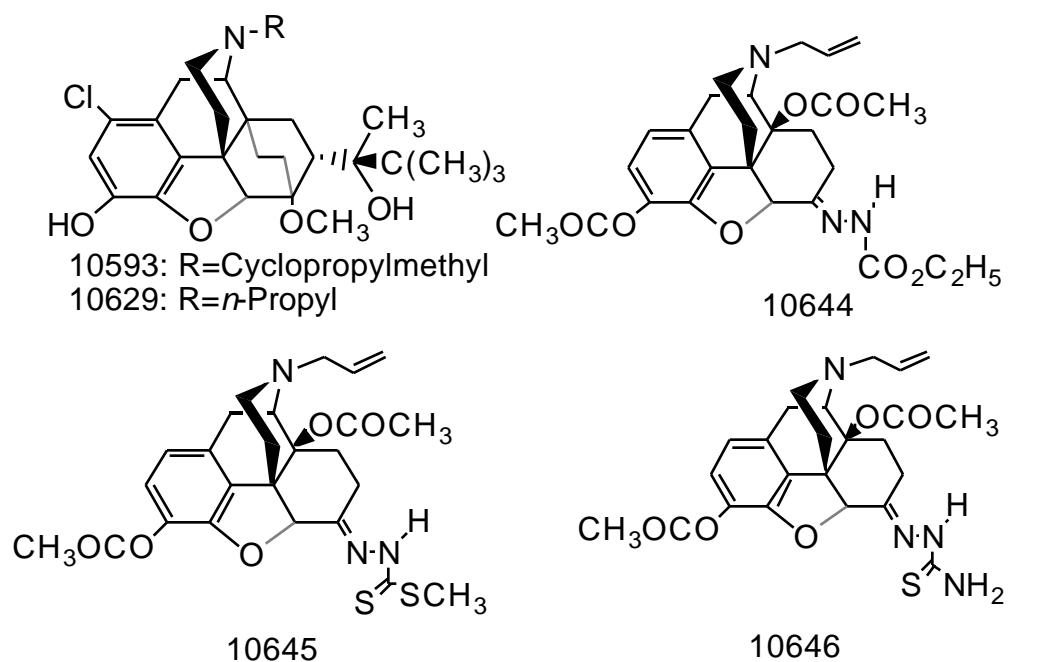
C) In Vitro

BIND - binding affinity using monkey brain cortex membranes (selectivity for μ , κ , and δ opioid receptors, using [³H]-sufentanil, -DPDPE and -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 "1983" indicates that the work was included in "Problems of Drug Dependence 1983", which was published in 1984). 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^a



NIH #	MOUSE ED50/AD50				IN VITRO VD	MONKEY SDS
	PPQ	TF	TFA	RBH		
10593	l	l	4.7 ^b	INSOL	INSOL	NS(0.06,0.25) c
10629	l	l	l ^d	INSOL	ANT(μ , ,) ^e	NS(0.5-10) ^f
10644	l	l	0.3	-	-	-
10645	l	l	0.8	18.3 nM	5.3E-7 ^g	-
10646	h	h	h	17.4 nM	ANT(μ , ,) ^{e,i}	-

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

b) Dependent on vehicle: AD50=4.7 in H₃PO₄/H₂O, and 10.4 in 10% Tween 80, lactic acid and H₂O.

c) PPT-W - severe withdrawal (0.125, 0.5); slow onset, prolonged duration of action.

d) No dose-response - 61% activity at 25 and 40 mg/kg, 74% at 30 mg/kg. However, 2-hr. pretreatment gave AD50=3.8 for naloxone.

e) Noncompetitive antagonist for μ , κ receptors.

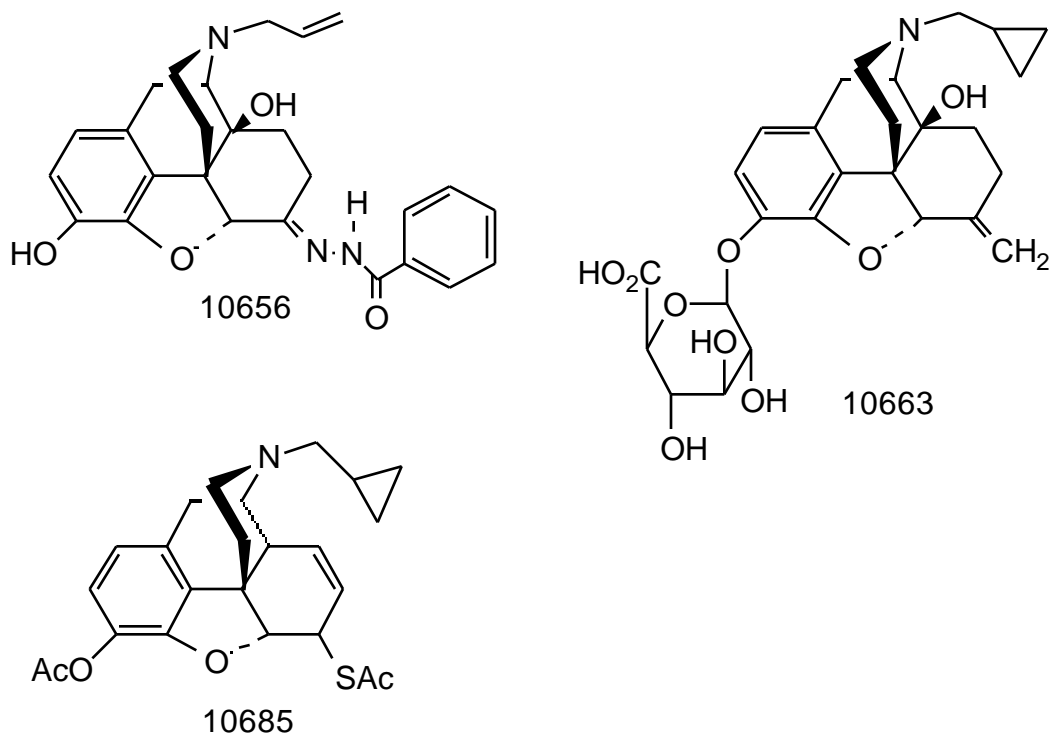
f) Exacerbated withdrawal. Duration of action > 2.5 hr.

g) Agonist activity not mediated by opioid receptors. Opioid antagonist at μ , κ receptors.

h) Thin layer chromatography indicated two spots. Sample not run.

i) Less potent than, but similar to norbinaltorphimine antagonism of κ receptors.

TABLE 2. 4,5-EPOXYMORPHINANS (CONTINUED)^a



NIH #	MOUSE ED50/AD50					IN VITRO VD	MONKEY SDS
	HP	PPQ	TF	TFA	RBH		
10656	-	I	I	0.05	6.1 nM	ANT(μ , δ) ^b	NS(0.01,0.04) ^c
10663	-	I	I	0.55	1.6 μ M	ANT(μ) ^d	-
10685	4.6	0.01	2.8	I ^f	-	-	NS(1.5,6) ^g

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

b) Similar to naltrexone in potency and selectivity.

c) PPt-W assay (1991) - PW (equipotent with naloxone).

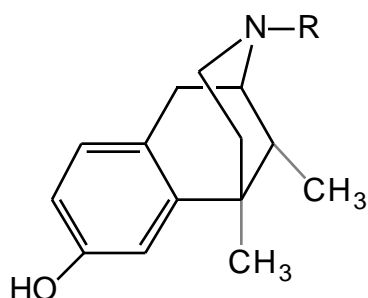
d) Weak selective μ antagonist.

e) High dose of naloxone needed for antagonism.

f) No dose-effect (50% at 30 and 80 mg/kg).

g) Agonist-antagonist (appeared to exacerbate withdrawal). Some dopaminergic activity.

TABLE 3. 6,7-BENZOMORPHANS^a



10650: R = BENZYL (+)
 10666: R = H (\pm)
 10667: R = METHYL (\pm)
 10673: R = *n*-HEPTYL (\pm)
 10674: R = *n*-HEPTYL (+)
 10675: R = *n*-HEPTYL (-)
 10686: R = *p*-METHOXYBENZYL (-)
 10691: R = *p*-METHOXYBENZYL (+)
 10694: R = *p*-HYDROXYBENZYL (+)

NIH #	MOUSE ED50/AD50			RBH	IN VITRO	MONKEY
	PPQ	TF	TFA		VD	SDS
10650	I	I	I	>10 μ M ^b	ANT ^{b,c}	-
10666	4.6	I	I	0.664 μ M	6.8E-6 ^d	NS(1.5,6)
10667 & 7410	0.6	1.5	I	119 nM	1.3E-6 ^e	NS(3,6), CS(24) ^f
10673	0.4	3.6	I	128 nM	4.4E-7 ^g	NS(2.5,10)
10674	3.5	12.9	I	4.7 μ M	1.1E-8 ^h	NS(2.5,10)
10675	0.13	1.7	I	89 nM	3.5E-7 ⁱ	NS(1.25,5)
10686	-	-	-	7.0 μ M	ANT ^j	-
10691	-	-	-	6.1 μ M	ANT ^k	-
10694	-	-	-	>6 μ M	ANT ^l	-

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

b) Previously reported - 1990.

c) Weak opioid antagonist, competitive at μ , non-competitive at δ .

d) Agonist at μ , δ , and κ opioid receptors.

e) μ agonist- μ , δ , and κ antagonist.

f) Previously reported - 1960, 1958

g) Agonist at μ opioid receptors.

h) Low efficacy (31% inhibition).

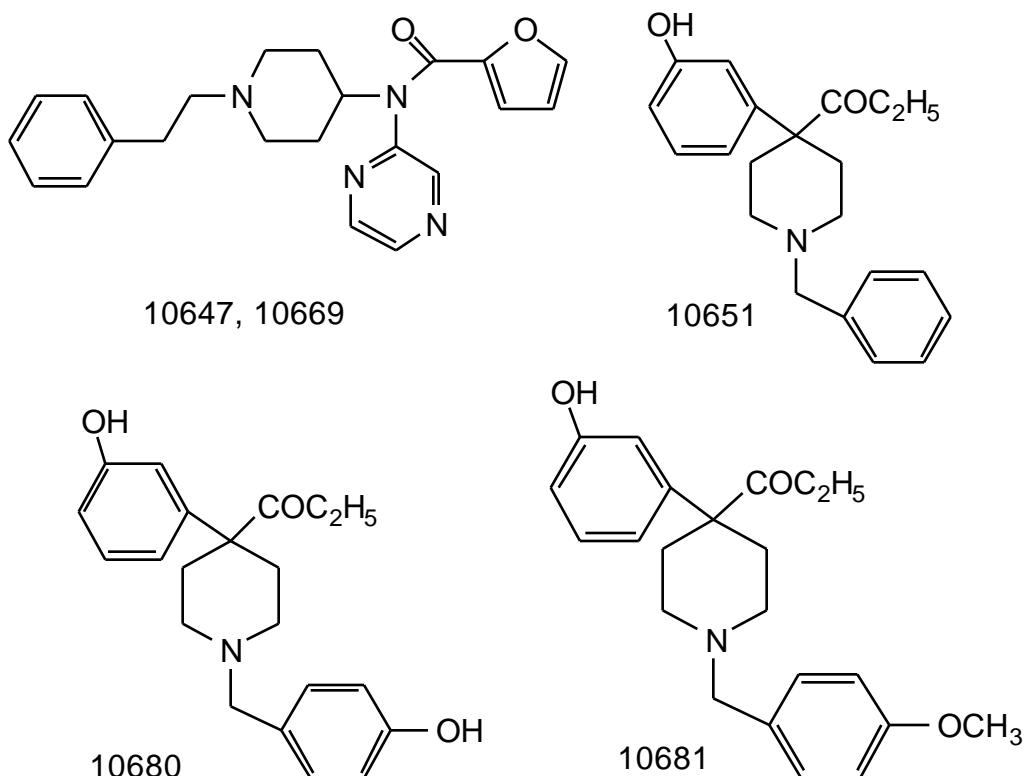
i) Agonist at μ and δ opioid receptors.

j) Very weak antagonist, with some δ selectivity.

k) μ , δ , and κ antagonist; insurmountable at δ , not simple competitive at μ , δ opioid receptors.

l) Antagonist only at high concentrations; slight non-opioid actions.

TABLE 4. PHENYLPIPERIDINES AND FENTANYL-LIKE COMPOUNDS^a



NIH #	MOUSE ED50/AD50				IN VITRO		MONKEY
	<u>HP</u>	<u>PPQ</u>	<u>TF</u>	<u>TFA</u>	<u>RBH</u>	<u>VD</u>	<u>SDS</u>
10647 & 10669	0.3	0.08 ^b	0.4 ^{b,c}	^b	91nM ^b	4.7E-8 ^{d,e,f}	NS(0.05-4) ^b
10651	-	7.5			1.0 μM ^b	ANT(μ, ,k) ^b	-
10680	-				-	-	NS(2,8)
10681	-				>6 μM	ANT ^g	NS(3,12) ^h

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

b) Previously reported - 1990.

c) Reversed by naloxone (before (AD50=0.06) or after ED80 of 10647 (AD50=0.03)).

d) Partial agonist; weak, non-selective, competitive antagonist.

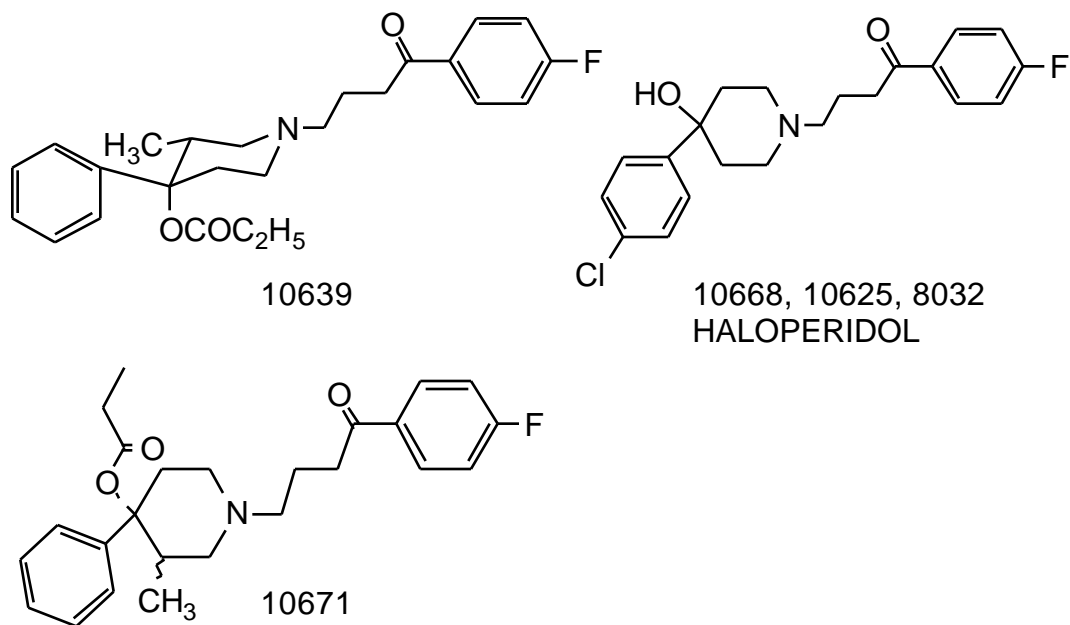
e) Other work (at UM - previously reported, 1990) - SA, DD, monkey analgesia, respiratory depression.

f) Previously reported as antagonist (μ, ,) - 1990.

g) Moderately selective antagonist.

h) Non-dose-related exacerbation of withdrawal.

TABLE 5. PHENYLPIPERIDINES RELATED TO HALOPERIDOL^a



NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY SDS
	PPQ	TF	TFA	RBH	VD	
10639	0.1 ^b	0.56 b	1 ^b	41.3 nM	5.6E- 8 ^c	CS(0.05, 0.25) ^b
10668 & 10625 & 8032	0.01 d	14.6 d	1 ^d	>10 μM ^d	SE ^{d,e}	NS ^d
10671	0.04	0.3	1	-	-	CS(0.006, .025) ^f

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

b) Previously reported - 1990.

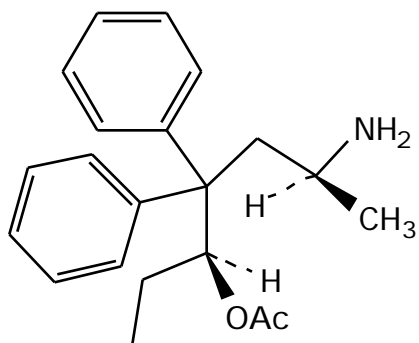
c) Agonist at μ opioid receptors.

d) Previously reported - 1990, 1989 and 1988 as NIH 10625, and in 1963 as NIH 8032. Other work - RI-SM (NS), RI-PPD.

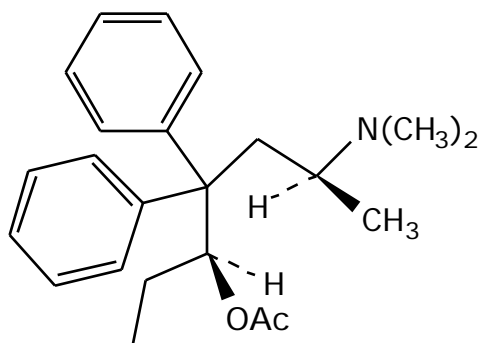
e) Inhibited twitch at 1E-5 concentration (1989), and partially inhibited at 6.1E-8 (1990). Opioid antagonist at μ and κ opioid receptors (1989), and devoid of antagonist activity (1990) in VD. No significant opioid activity in VD or RBH (1990).

f) At 0.5 mg/kg one monkey was cataleptic, unresponsive. Reversed with 0.05 mg/kg naloxone.

TABLE 6. METHADOLS^a



10655 (dinorLAAM)



10679 (LAAM)

<u>NIH #</u>	<u>MOUSE ED50/AD50</u>			<u>RBH</u>	<u>IN VITRO</u>	<u>MONKEY</u>
	<u>PPQ</u>	<u>TF</u>	<u>TFA</u>		<u>VD</u>	<u>SDS</u>
10655	0.14	5.4	I	22.3 ^b	3.4E-7 ^{b,c}	CS(4)
10679	0.4	7.2	I			CS(0.5,2) ^d

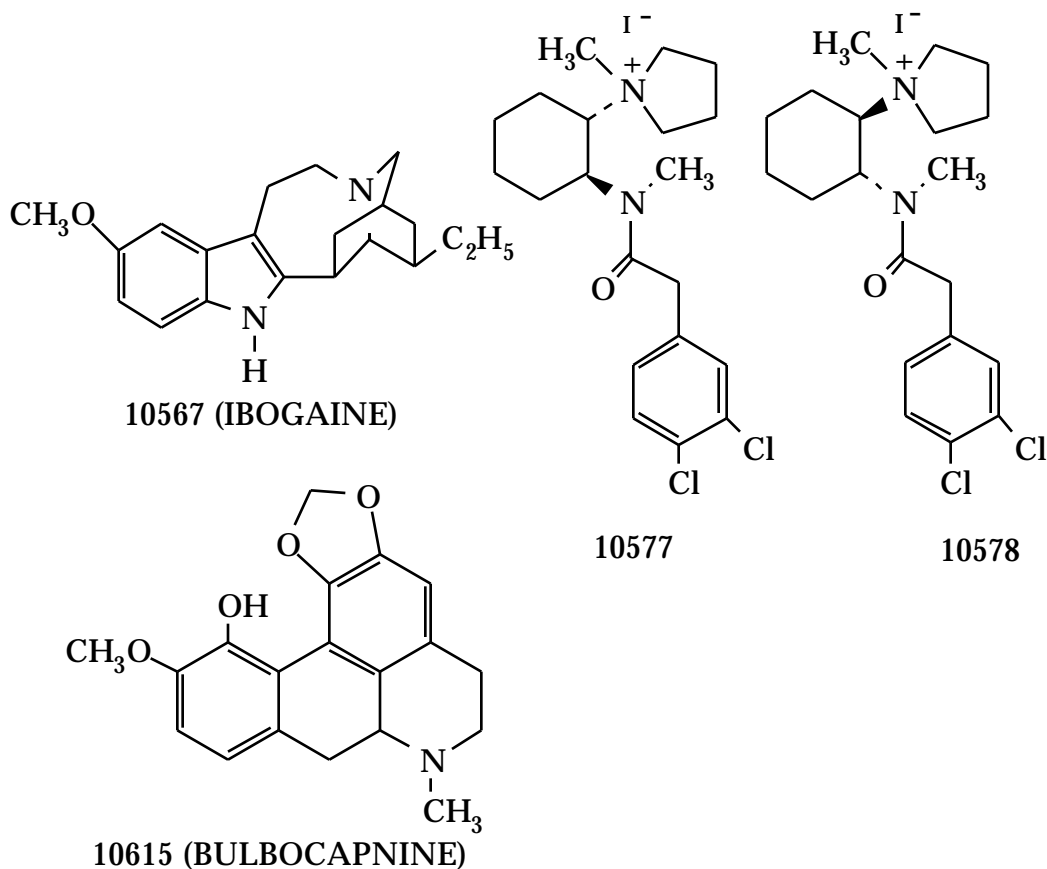
a) See text for explanation of column headings and abbreviations.

b) Previously reported - 1990.

c) μ Agonist; unusual response to naloxone.

d) Onset slower, duration longer than morphine, equivalent potency.

TABLE 7. MISCELLANEOUS^a



NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY SDS
	PPQ	TF	TFA	RBH	VD	
10567	9.7 ^b	^b	^b	6 μM	2.3E-5 ^{b,c}	PS(2,8) ^{b,d}
10577	4.2			76 μM ^e	SE ^e	NS(2.5,10)
10578	3.5			76 μM ^e	SE ^e	NS(3,12)
10615	4.5 ^f			-	-	NS(0.5,2)

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

b) Previously reported - 1989.

c) Not antagonized by naloxone.

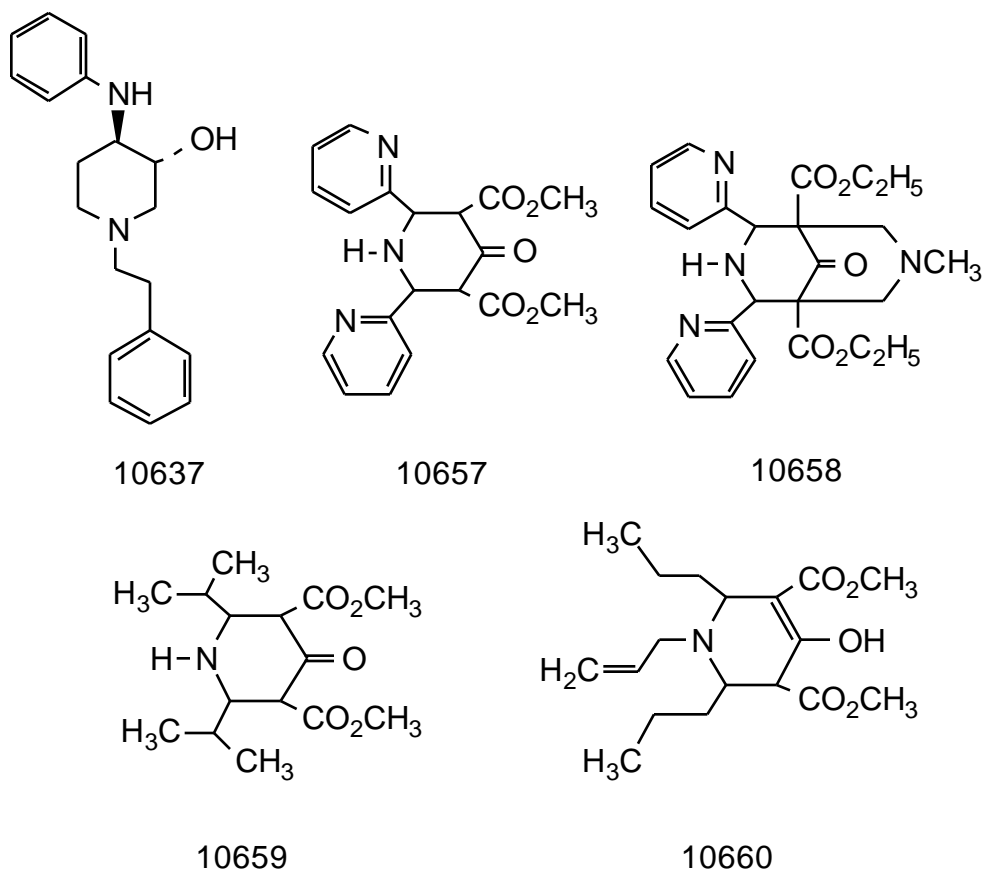
d) Rat infusion (1990): SM - NS(20), PS(80, possibly non-specific);

PPD - None.

e) Very low potency, probably non-opioid.

f) Not antagonized by naloxone (possible D₁ antagonist).

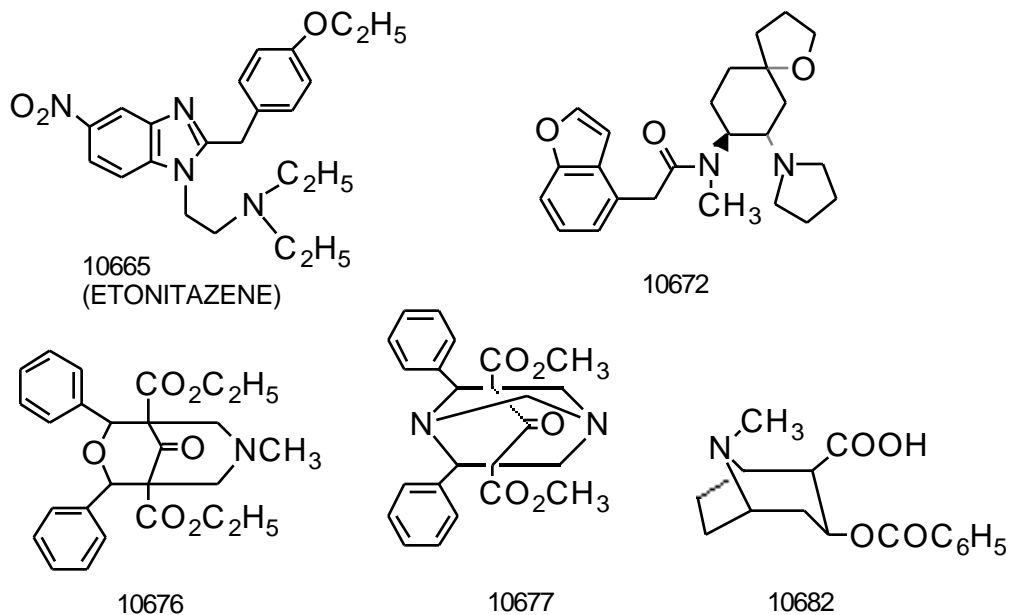
TABLE 8. MISCELLANEOUS (CONTINUED)^a



NIH #	MOUSE ED50/AD50				IN VITRO VD	MONKEY SDS
	PPQ	TF	TFA	RBH		
10637				>10 μ M	5.2E-8 ^b	NS(3,12)
10657				>6 μ M	NE	NS(2.5,10)
10658	0.6			>6 μ M	4.3E-7 ^c	CS(0.125-2)
10659				-	-	-
10660				-	-	-

- a) See text for explanation of column headings and abbreviations.
b) Partial inhibition, not mediated by opioid receptors; very weak antagonist at μ and κ opioid receptors.
c) Agonist selective for μ opioid receptors.

TABLE 9. MISCELLANEOUS (CONTINUED)^a



NIH #	MOUSE ED50/AD50				IN VITRO	MONKEY
	PPQ	TF	TFA	RBH	VD	SDS
10665	0.0017	0.005		0.51 nM	5.7E-	CS(0.0005,0.00
	b	b			10 ^c	2) ^d
10672	0.0015	0.015		1.18 μM	1.4E-9 ^f	NS(0.0002-
	e					0.0025)g,h
10676				>6 μM	4.5E-7 ^j	-
10677				>6 μM	2.9E-6 ^k	-
10682				-	-	NS(2,8,16) ⁱ

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

b) Blocked by naloxone.

c) Potent partial agonist at μ , κ , and δ opioid receptors.

d) Onset rapid, duration shorter and potency 1500 x morphine.

e) Naloxone prior to ED80 (AD50=0.3). Could not block with norbinaltorphimine in TF or PPQ.

f) Potent agonist, selective for δ . Antagonism produced by norbinaltorphimine is surmountable, unlike other δ agonists.

g) High doses of naloxone needed for antagonism. Potent agonist.

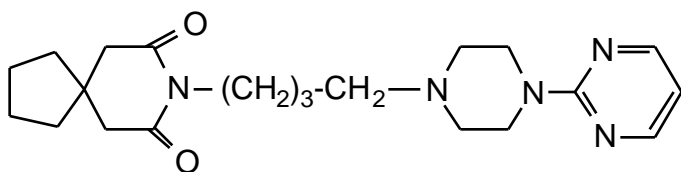
h) Rat SM - NS; Rat PPD - No dependence.

i) Intravenous administration.

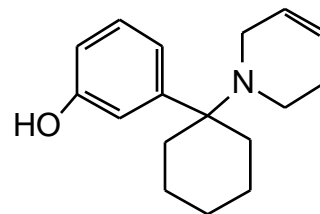
j) Agonist at μ and δ opioid receptors.

k) Weak partial agonist at μ , κ , and δ , weak antagonist at σ .

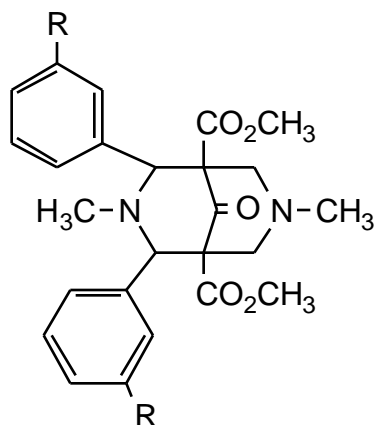
TABLE 10. MISCELLANEOUS (CONTINUED)^a



10687 (BUSPIRONE)



10700



10713: R=OCH₃
 10714: R=CH₃
 10715: R=NO₂

NIH #	MOUSE ED50/AD50			IN VITRO		MONKEY
	PPQ	TF	TFA	RBH	VD	
10687	14.6 ^b	l	l	-	-	PS(0.2-0.8) ^c
10700	0.3	4.8 ^{d,e}	l	-	-	-
10713	l	le	l	-	-	-
10714	l	le	l	-	-	-
10715	l	le	l	-	-	-

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

b) Not blocked by naloxone.

c) Precipitated withdrawal - NP.

d) Straub tail, ataxia, convulsions.

e) Hot plate assay - l.

STIMULANT/DEPRESSANT DRUG TESTING

Three new compounds were accepted for evaluation this year (5/1/90 to 4/30/91). The report by Winger et al., (this volume) will include the detailed evaluation of five compounds which have been released for publication, CPDD 0020, 0022, 0023, 0032 and 0033. With the exception of CPDD 0032, flunitrazepam, all of these compounds were obtained from pharmaceutical industry. The molecular structures of the compounds and a summary of the work which has been completed on them at UM, MCV, and UC, can be seen in table 11.

2,5-Dihydro-2-(4-methoxyphenyl)-3H-pyrazolo[4,3-c]quinolin-3-one (CPDD 0020)

This diazepam-like anxiolytic did not have discriminative stimulus effects in monkeys and therefore is unlikely to have pentobarbital-like subjective effects in humans.

6-Allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine dihydrochloride (CPDD 0022)

CPDD 0022 was developed to treat Parkinson's disease. It was not like pentobarbital or amphetamine in drug discrimination. It appeared to decrease cocaine-maintained response rates in the monkey, but further examination indicated that it did not have a selective effect on cocaine, as would be expected if it were acting as a cocaine antagonist.

4-Aminomethyl-1-benzyl-pyrrolidin-2-one fumarate (CPDD 0023)

The compound was indicated to be a nootropic agent (a cognitive enhancer). CPDD 0023 did not have pentobarbital-like or amphetamine-like discriminative stimulus effects in monkeys and therefore would not be expected to exhibit pentobarbital-like or amphetamine-like subjective effects in people.

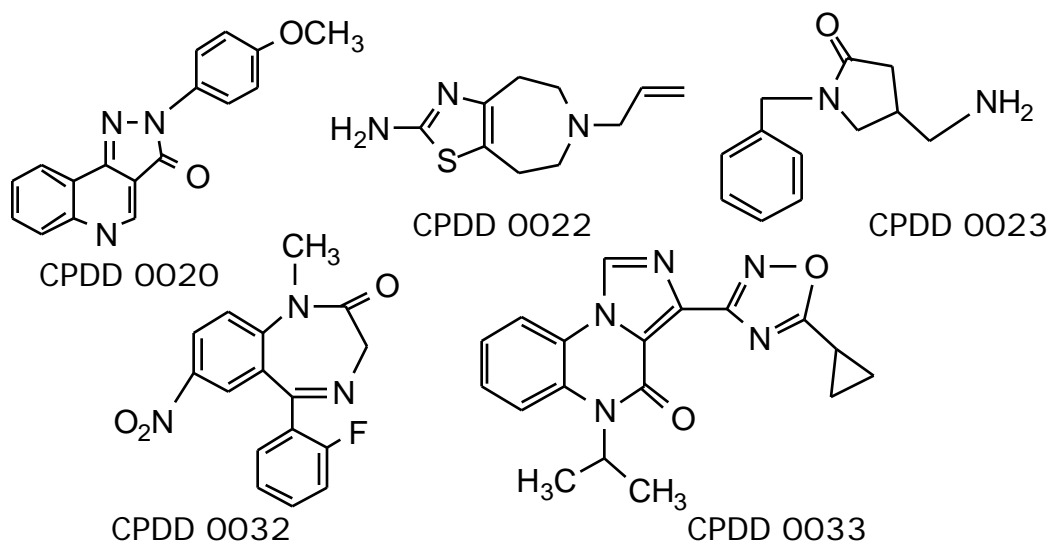
Flunitrazepam (CPDD 0032)

Flunitrazepam was evaluated at the request of the World Health Organization and our work on the drug was completed this year. It exhibited barbiturate-like effects in all of our assays, and would be expected to show pentobarbital-like subjective effects in people.

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-5-(1-methylethyl)imidazo[1,5-a]quinoxalin-4(5H)-one (CPDD 0033)

CPDD 0033 is under clinical evaluation as an anxiolytic. This compound did not act as a reinforcer nor did it exhibit pentobarbital-like discriminative stimulus effects in monkeys. From these studies we would not predict that it would have pentobarbital-like subjective effects in humans.

TABLE 11. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD#	SLA ^a	IS ^b	PD-S ^c	SA ^d	DDE ^e
0020	INCONS. ^f	SLIGHT ^g	- ^h	- ⁱ	NO ^j
0022	INCONS. ^f	SLIGHT ^k	NO ^l	NO ^m	NO ^{j,n}
0023	DEPRESS ^o	DEPRESS	NO ^p	NO ^m	NO ^{j,n}
0032	DEPRESS	DEPRESS	YES ^q	YES ^r	YES ^s
0033	DEPRESS ^t	DEPRESS ^u	- ⁱ	NO	NO ^j

- a) Spontaneous locomotor activity (mouse).
 b) Inverted screen assay (mouse).
 c) Physical dependence - substitution for pentobarbital (rat infusion).
 d) Self-administration (monkey).
 e) Drug discrimination (intra-gastric administration, monkey).
 f) Inconsistent - mild stimulatory and depressant effects, not dose-related.
 g) 20% effect at 300 mg/kg, a dose toxic to 1 out of 6 animals.
 h) Observed toxicity precluded procedure.
 i) Insufficient solubility for procedure.
 j) Discriminative stimulus effects not similar to pentobarbital.
 k) Effects not dose-related.
 l) Mild, transient sedative effects. No suppression of barbiturate abstinence.
 m) Lacks reinforcing effects in methohexital- or cocaine-trained monkeys.
 n) Does not share discriminative stimulus effects with amphetamine.
 o) Depression
 p) No substitution for pentobarbital in dependent animals - no effect on withdrawal signs.
 q) Capable of producing barbiturate-like physical dependence in the rat.
 r) Acted as a reinforcer in 1 out of 3 monkeys.
 s) Shares discriminative stimulus effects with pentobarbital.
 t) Erratic, not dose-related.
 u) Slightly less potent than pentobarbital, but longer acting.

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