# DRUG EVALUATION COMMITTEE REPORT ON: EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (2005)

*John R. Traynor and James H. Woods*

Departments of Pharmacology and Psychology, University of Michigan, Ann Arbor, MI

This report contains information on compounds that have been submitted to the Drug Evaluation Committee of the College and released for publication by the submitters. The information obtained usually involves *in vitro* evaluation for opioid activity. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. These behavioral assessments are conducted in rhesus monkeys.

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia is currently administered by the Biological Coordinator, Dr. A. Coop, University of Maryland. The compounds come originally from pharmaceutical companies, universities, government laboratories, or international organizations.

At the UM and MCV laboratories, drug samples arrive from the Biological Coordinator with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information. After the evaluation is complete and the report sent to Dr. Coop, the submitter of the compound(s) is requested to release the chemical structure to include with the evaluation data in the ANNUAL REPORT. The submitter can withhold the structure for up to three years. When the structure is released all of the data on the compound are reported herein.

**SUMMARY OF TESTS PERFORMED**

The compounds that were evaluated at the University of Michigan and available for release during the past year are shown in the following Table. Also shown are dates of Reports to the Biological Coordinator.

| NIH # | Date Submitted to Biological Coordinator | NIH # | Date Submitted to Biological Coordinator |
|---|---|---|---|
| 10820 | 10 November 2004 | 11154 | 26 April 2003 |
| 11116 | 9 September 2002 | 11188 | 31 July 2003 |
| 11117 | 9 September 2002 | 11189 | 16 September 2003 |
| 11118 | 10 February 2003 | 11190 | 16 September 2003 |
| 11119 | 12 February 2003 | 11191 | 16 September 2003 |
| 11120 | 9 September 2002 | 11192 | 16 September 2003 |
| 11121 | 26 April 2003 | 11194 | 21 November 2003 |
| 11127 | 14 March 2003 | 11195 | 21 November 2003 |
| 11130 | 14 March 2003 | 11196 | 21 November 2003 |
| 11131 | 10 February 2003 | 11197 | 21 November 2003 |
| 11132 | 26 April 2003 | 11209 | 24 December 2003 |
| 11133 | 10 February 2003 | 11210 | 24 December 2003 |
| 11134 | 10 February 2003 | 11212 | 24 December 2003 |
| 11135 | 26 April 2003 | 11213 | 10 November 2004 |
| 11136 | 26 April 2003 | 11214 | 10 November 2004 |
| 11137 | 26 April 2003 | 11220 | 10 November 2004 |
| 11144 | 10 February 2003 | 11228 | 10 November 2004 |
| 11146 | 10 February 2003 | 11231 | 10 November 2004 |
| 11149 | 26 April 2003 | 11232 | 10 November 2004 |
| 11150 | 10 February 2003 | 11233 | 10 November 2004 |
| 11151 | 17 March 2003 | 11234 | 10 November 2004 |
| 11152 | 17 March 2003 | 11235 | 10 November 2004 |
| 11153 | 17 March 2003 | 11247 | 3 January 2005 |
| | | 11248 | 3 January 2005 |

## METHODS

### Opioid Receptor Binding and In Vitro Efficacy Assessment

Details of the binding assay been described previously (Lee et al., 1999). Briefly, aliquots of a membrane preparation are incubated with [$^3$H]diprenorphine (0.3 nM) in the presence of different concentrations of the drug under investigation at 25° C for 1 hr. Specific, *i.e.*, opioid-receptor-related binding is determined as the difference in binding obtained in the absence and presence of 10:M naloxone. The potency of the drugs in displacing the specific binding of [$^3$H]-ligand is determined from data using Graphpad Prism (GraphPAD, San Diego, CA) and converted to Ki values by the method of Cheng and Prussoff (1973). Opioid binding is performed in membranes from $C_6$ rat glioma cells expressing recombinant μ (rat; Emmerson et al., 1994) or δ (rat; Clark et al., 1997) and CHO cells expressing the recombinant κ (human, Zhu et al., 1997). The affinity (Kd) values of [$^3$H]diprenorphine at the receptors are: μ (0.15 nM); δ (0.45 nM); κ (0.25 nM).

The results of the selective binding assays are given as means ± SEM from three separate experiments, each performed in duplicate. Ki values for standard compounds using recombinant receptors and [$^3$H]diprenorphine as radioligand are: μ (DAMGO, 7.6 nM; morphine, 11.2 nM), δ (SNC80, 0.8 nM) and κ (U69593, 0.3 nM). If less than 50% displacement of [$^3$H]diprenorphine is seen at 10 μM, it is reported as > 10 μM and the percent displacement given in parentheses.

*[$^{35}$S]GTPγS assays* are carried out using membranes from C6 cells expressing either μ (Emmerson et al., 1996) or δ (Clark et al., 1997) receptors or CHO cells expressing κ receptors (Zhu et al., 1997). Assays are performed as described by Traynor and Nahorski (1995). Values are given as $EC_{50}$ with % effect compared to a standard agonist (DAMGO, SNC80, or U69593) or as maximal stimulation achieved at 10 μM concentration. $EC_{50}$ values (nM) for standard compounds are as follows: μ receptor (morphine, 65 nM; DAMGO, 34 nM; fentanyl, 13 nM), δ receptor (SNC80, 9 nM; DPDPE 8.3 nM), and κ receptor (U69593, 31.0 nM; bremazocine, 0.5 nM)

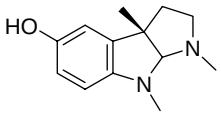
DPDPE (60%) and bremazocine (86%) are partial agonists compared with the standards SNC80 and U69593. Morphine and DAMGO give equivalent responses.

Antagonist activity is given as $AD_{50}$ values or as $pK_B$ values. $AD_{50}$ refers to the concentration of test compound that reduces [$^{35}$S]GTPγS binding stimulated by an $ED_{80}$ concentration of appropriate agonist (DAMGO,μ; DPDPE,δ; U69593,κ) by 50%. $pK_B$ is the concentration of antagonist required to shift the dose-effect curve for appropriate agonist by 2-fold. It is a measure of the affinity of the antagonist for a receptor.

### Behavioral Assessments in Rhesus Monkeys.

No compounds assessed in rhesus monkeys were made available for release this year. A description of the assays available to submitters is included in the appendix.

**NIH 10820 Eseroline.ascorbate**




ascorbate

**OPIOID RECEPTOR BINDING (nM) †**

μ-receptor: 128 ± 39
δ-receptor: 1961 ± 648
κ-receptor: 876 ± 395

**SUMMARY**

NIH 10820 has low affinity for μ opioid receptors > κ opioid receptors and very low affinity for δ opioid receptors.

† Rat brain binding data ($EC_{50}$ = 1604 nM vs. [$^3$H]etorphine) published in Woods, J.H., Medzihradsky, F., Smith, C.B., Winger, G., and Traynor, J.R. Evaluation of new compounds for opioid activity (1997). In: Harris, L.S. (ed.), Problems of Drug Dependence, National Institute on Drug Abuse Monograph 178, U.S. Government Printing Office, Washington, D.C., 1998, pp. 408-428

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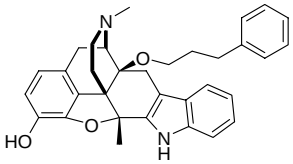
**NIH 11116 4,5α-Epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]indolo[2',3':6,7]morphinan-3-ol**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor**:** 80 ± 5.8
δ-receptor: 3.3 ± 1.2
κ-receptor: 76 ± 3.8

**SUMMARY**

NIH 11116 has high affinity for the δ opioid receptor and is 24-times selective for δ over the other opioid receptors.

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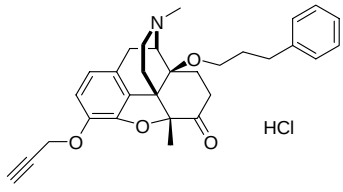
**NIH 11117 4,5α-Epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]-3-[(prop-2-inyl)oxy]morphinan-6-one.HCl**



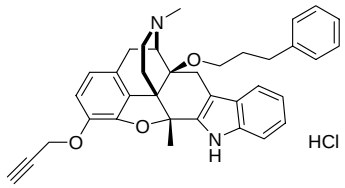

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 1.1 ± 0.5
δ-receptor: 8.9 ± 1.7
κ-receptor: 6.4 ± 1.2

**SUMMARY**

NIH 11117 has high affinity for all three receptors with 6- and 8-fold selectivity for μ over κ and δ receptors respectively.

**NIH 11118** **4,5α-Epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]-3-[(prop-2-inyl)oxy]indolo[2',3':6,7] morphinan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor = 82.6 ± 27
δ-receptor = 31.9 ± 3.3
κ-receptor = 178 ± 44

**SUMMARY**

NIH 11118 has affinity for opioid receptors, but little selectivity for the different types.

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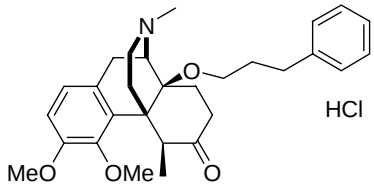
**NIH 11119** **3,4-Dimethoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy] morphinan-6-one.HCl**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor = 0.015 ± 0.01
δ-receptor = 0.13 ± 0.13
κ-receptor = 0.27 ± 0.14

**SUMMARY**

NIH 11119 has very high affinity for all three opioid receptors in the order μ > δ = κ

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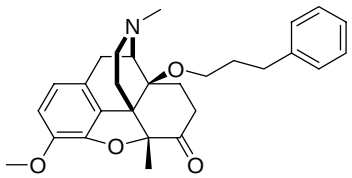
**NIH 11120** **4,5α-Epoxy-3-methoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one**



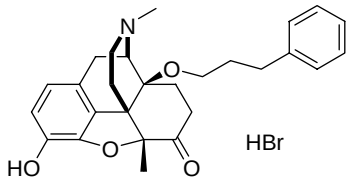

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor = 0.8 ± 0.2
δ-receptor = 0.3 ± 3.8
κ-receptor = 0.2 ± 0.07

**SUMMARY**

NIH 11120 has very high affinity for κ > μ receptors and high affinity for δ receptors.

**NIH 11121 4,5α-Epoxy-3-hydroxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one.HBr**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor = 0.02 ± 0.004
δ-receptor = 0.55 ± 0.22
κ-receptor = 0.09 ± 0.05

**SUMMARY**

NIH 11121 has extremely high affinity for μ > κ receptors with very high affinity for δ receptors.

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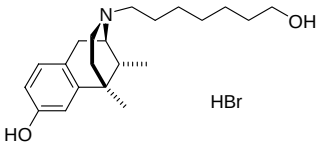
**NIH 11127 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-Hydroxy-2-(7-hydroxyheptyl)-6,7-benzomorphan.HBr**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 4.6 ± 0.2
δ-receptor: 202 ± 73
κ-receptor: 36.1 ± 11.2

**SUMMARY**

NIH 11127 has high affinity for μ receptors. It is 9-fold selective for μ over κ and 44-fold selective for μ over δ receptors.

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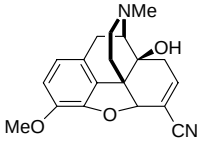
**NIH 11130 6,7-Didehydro-4,5α-epoxy-14β-hydroxy-3-methxoy-17-methylmorphinan-6-carbonitrile**



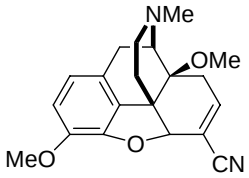

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 45.9 ± 8.1
δ-receptor: 837 ± 137
κ-receptor: 1118 ± 289

**SUMMARY**

NIH 11130 has affinity for the μ opioid receptor and is 18- and 24-fold selective for the μ receptor over κ and δ, respectively.

**NIH 11131** **6,7-Didehydro-4,5α-epoxy-3,14β-dimethxoy-17-methylmorphinan-6-carbonitrile**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 8.7 ± 2.9
δ-receptor: 224 ± 40
κ-receptor: 512 ± 43

**SUMMARY**

NIH 11131 has high affinity for the μ opioid receptor and has 25-fold selectivity for this receptor over the δ receptor and 58-fold selectivity over the κ receptor.

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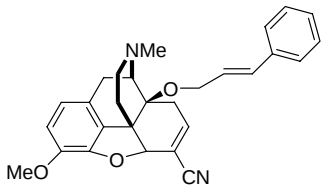
**NIH 11132** **6,7-Didehydro-4,5α-epoxy-3-methxoy-17-methyl-14β-{[(*E*)-3-phenylprop-2-nyl]oxy}morphinan-6-carbonitrile**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 0.06 ± 0.03
δ-receptor: 0.08 ± 0.02
κ-receptor: 0.35 ± 0.05

**SUMMARY**

NIH 11132 has extremely high affinity for μ = δ with very high affinity for κ receptors.

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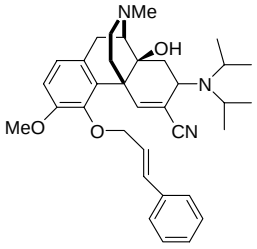
**NIH 11133** **6,7-Didehydro-7-{{(*N*,*N*)-diisopropyl]amino}-14β-hydroxy-3-methoxy-17-methyl-4-{[(*E*)-3-phenylprop-2-enyl]oxy}morphinan-6-carbonitrile**



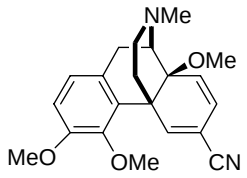

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor**:** 144 ± 32
δ-receptor: 1515 ± 432
κ-receptor: 1322 ± 130

**SUMMARY**

NIH 11133 has some affinity for the μ opioid receptor and is approximately 10-fold selective for the μ receptor over δ and κ receptors.

**NIH 11134** **5,6,7,8-Tetradehydro-3,4,14β-trimethoxy-17-methylmorphinan-6-carbonitrile**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 0.7 ± 0.1
δ-receptor: 56.1 ± 14.6
κ-receptor: 229 ± 25.5

**SUMMARY**

NIH 11134 has high affinity for the μ opioid receptor. It is 80-fold selective for this receptor over the δ receptor and 320-fold over the κ receptor.

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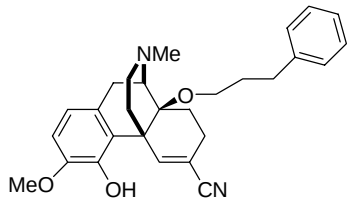
**NIH 11135** **5,6-Didehydro-4-hydroxy-3-methoxy-17-methyl-14β-{[3-phenylpropyl]oxy}morphinan-6-Carbonitrile**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 0.10 ± 0.04
δ-receptor: 0.94 ± 0.6
κ-receptor: 1.49 ± 0.7

**SUMMARY**

NIH 11135 has very high affinity for μ receptors with high affinity for δ ≥ κ receptors.

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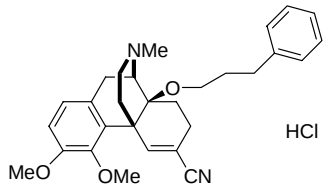
**NIH 11136** **5,6-Didehydro-3,4-dimethoxy-17-methyl-14β-{[3-phenylpropyl]oxy}morphinan-6-carbonitrile.HCl**



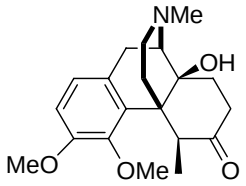

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 0.02 ± 0.01
δ-receptor: 0.45 ± 0.13
κ-receptor: 1.0 ± 0.3

**SUMMARY**

NIH 11136 has extremely high affinity for μ receptors with high affinity for δ and κ receptors.

**NIH 11137 14β-Hydroxy-3,4-dimethoxy-5β,17-dimethylmorphinan-6-one**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 5.3 ± 2.7
δ-receptor: 262 ± 51
κ-receptor: 2040 ± 568

**SUMMARY**

NIH 11137 has high affinity for μ receptors and is 50-times selective for μ over δ and 380-fold selective for μ over κ receptors.

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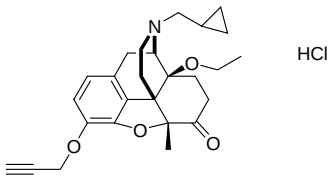
**NIH 11144 17-Cyclopropylmethyl-4,5α-epoxy-14β-ethoxy-5β-methyl-3-[(prop-2-inyl)oxy]morphinan-6-one.HCl**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 75.7 ± 8.3
δ-receptor: 2477 ± 480
κ-receptor: 533 ± 82.3

**SUMMARY**

NIH 11144 has affinity for the μ opioid receptor > κ opioid receptor (7-fold preference for the μ receptor). It is 30-fold selective for the μ receptor compared with the δ receptor.

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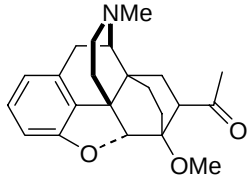
**NIH 11146 3-Desmethoxy-18,19-dihydrothevinone**



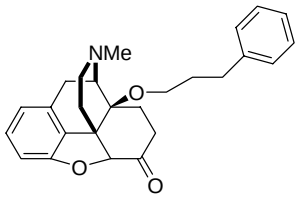

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 14.7 ± 4.4
δ-receptor: 143 ± 40.3
κ-receptor: 2208 ± 187

**SUMMARY**

NIH 11146 has high affinity for the μ opioid receptor > δ opioid receptor (10-fold higher at μ), but very low affinity for the κ opioid receptor.

**NIH 11149 4,5α-Epoxy-17-methyl-14β-{[3-phenylpropyl]oxy}morphinan-6-one**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 0.03 ± 0.01
δ-receptor: 0.96 ± 0.38
κ-receptor: 3.9 ± 1.2

**SUMMARY**

NIH 11149 has extremely high affinity for μ receptors and is 30-times selective for μ over δ and > 100-fold selective for μ over κ receptors.

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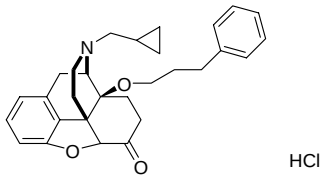
**NIH 11150 17-Cyclopropylmethyl-4,5α-epoxy-14β-{[3-phenylpropyl]oxy}morphinan-6-one.HCl**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 0.2 ± 0.07
δ-receptor: 9.7 ± 2.3
κ-receptor: 5.3 ± 1.4

**SUMMARY**

NIH 11150 has very high affinity for the μ opioid receptor and is approximately 25- and 50-fold selective for the μ receptor over κ and δ, respectively.

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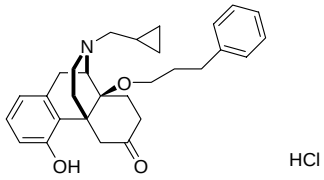
**NIH 11151 17-Cyclopropylmethyl-4-hydroxy-14β-{[3-phenylpropyl]oxy}morphinan-6-one.HCl**



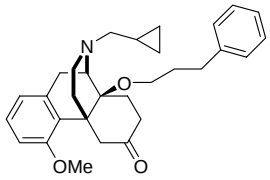

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 0.03 ± 0.01
δ-receptor: 1.12 ± 0.28
κ-receptor: 1.01 ± 0.40

**SUMMARY**

NIH 11151 has extremely high affinity for the μ opioid receptor and very high affinity for δ and κ receptors. The selectivity for μ receptors is approximately 35-fold over δ and κ receptors.

**NIH 11152 17-Cyclopropylmethyl-4-methoxy-14β-{[3-phenylpropyl]oxy}morphinan-6-one.HCl**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 0.07 ± 0.02
δ-receptor: 6.2 ± 2.0
κ-receptor: 2.1 ± 0.3

**SUMMARY**

NIH 11152 has extremely high affinity for the μ opioid receptor and high affinity for δ and κ receptors. The selectivity for μ receptors is 80-fold over δ receptors and 30-fold over κ receptors.

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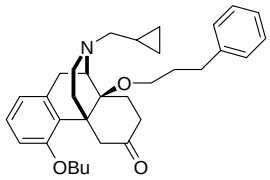
**NIH 11153 4-Butyloxy-17-cyclopropylmethyl-14β-{[3-phenylpropyl]oxy}morphinan-6-one.HCl**




**OPIOID RECEPTOR BINDING (nM)**

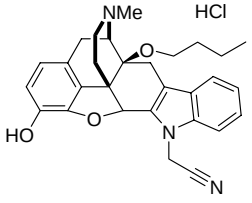
μ-receptor: 1.14 ± 0.3
δ-receptor: 24.3 ± 6.6
κ-receptor: 6.6 ± 2.6

**SUMMARY**

NIH 11153 has very high affinity for the μ opioid receptor and affinity for δ and κ receptors. The selectivity for μ receptors is 21-fold over δ receptors but only 6-fold over κ receptors.

* * *

**NIH 11154 β-Butyloxy-6,7-didehydro-4,5α-epoxy-3-hydroxy-17-methylindolo[2',3':6,7]morphinan]-1'-acetonitrile.HCl**



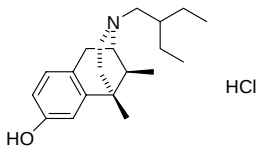

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 1.5 ± 0.3
δ-receptor: 0.24 ± 0.18
κ-receptor: 13.6 ± 0.6

**SUMMARY**

NIH 11154 has high affinity for δ receptors > μ receptors and also has affinity for κ receptors.

**NIH 11188 (+)-(1*S*,5*S*,9*S*)-2-(2-Ethylbutyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

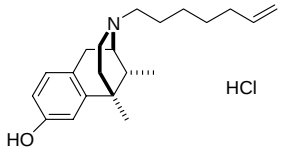
μ-receptor: 1552 ± 120
δ-receptor: 20% inhibition at 10 μM
κ-receptor: 82.6 ± 19

**SUMMARY**

NIH 11188 has affinity for κ opioid receptor and is selective for this receptor over μ (19-fold) and δ (>100-fold) receptors.

* * *

**NIH 11189 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(7-heptenyl)-2'-hydroxy--6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

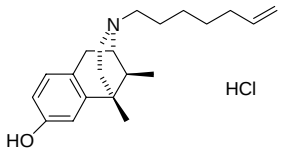
μ-receptor: 4.3 ± 0.7
δ-receptor: 24.7 ± 3.6
κ-receptor: 13.5 ± 1.7

**SUMMARY**

NIH 11189 has high affinity for μ opioid receptors, but is less than 10-fold selective for μ over δ or κ receptors.

* * *

**NIH 11190 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(7-heptenyl)-2'-hydroxy--6,7-benzomorphan.HCl**



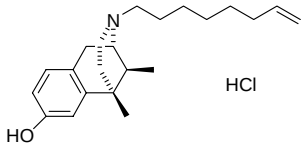

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 354 ± 23
δ-receptor: 4049 ± 271
κ-receptor: 142 ± 4.6

**SUMMARY**

NIH 11190 has low affinity for κ ≥ μ opioid receptors with very low affinity at δ receptors.

**NIH 11191 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(8-octenyl)-2'-hydroxy--6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

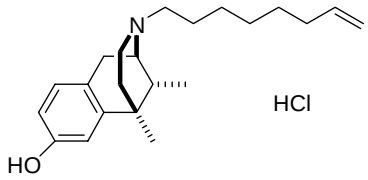
μ-receptor: 183 ± 9.4
δ-receptor: 4621 ± 240
κ-receptor: 291 ± 21

**SUMMARY**

NIH 11191 has low affinity for μ ≥ κ opioids with very low affinity at δ receptors.

* * *

**NIH 11192 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(8-octenyl)-2'-hydroxy--6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

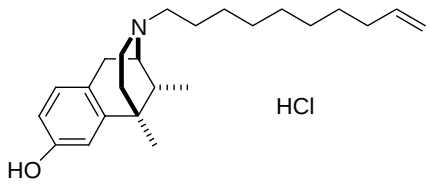
μ-receptor: 3.2 ± 0.2
δ-receptor: 28.6 ± 3.4
κ-receptor: 27.0 ± 0.9

**SUMMARY**

NIH 11192 has high affinity for μ receptors and is approximately 9-fold selective for μ over δ = κ opioid receptors.

* * *

**NIH 11194 (-)-(1*R*,5*R*,9*R*)- 2-(10-Decenyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl**



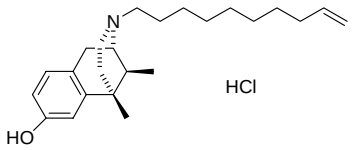

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 36.5 ± 4.2
δ-receptor: 468 ± 93
κ-receptor: 62.8 ± 7.8

**SUMMARY**

NIH 11194 has affinity for μ and κ opioid receptors and low affinity for the δ opioid receptor.

**NIH 11195 (+)-(1*S*,5*S*,9*S*)- 2-(10-Decenyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

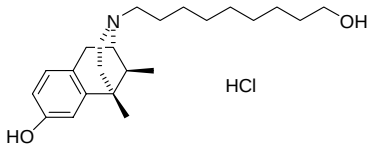
μ-receptor: 150 ± 18
δ-receptor: 4246 ± 843
κ-receptor: 964 ± 129

**SUMMARY**

NIH 11195 has low affinity for μ > κ opioid receptors and very low affinity for the δ opioid receptor.

* * *

**NIH 11196 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(9-hydroxynonyl)-6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

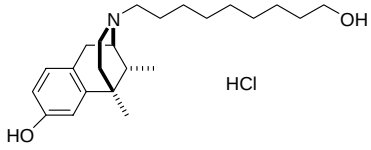
μ-receptor: 868 ± 215
δ-receptor: 37 ± 5.5 % inhibition at 10μM
κ-receptor: 1011 ± 32.2

**SUMMARY**

NIH 11196 has very low affinity for μ = κ opioid receptors and no measurable affinity for the δ opioid receptor.

* * *

**NIH 11197 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(9-hydroxynonyl) -6,7-benzomorphan.HCl**



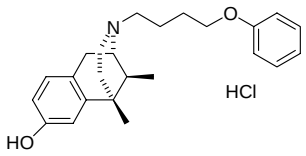

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 32.7 ± 4.6
δ-receptor: 197 ± 12.2
κ-receptor: 33.6 ± 3.7

**SUMMARY**

NIH 11197 has equal affinity for μ and κ opioid receptors and low affinity for the δ receptor.

**NIH 11209 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

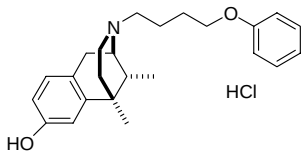
μ-receptor: 70.1 ± 6.4
δ-receptor: 3243 ± 184
κ-receptor: 303 ± 27.7

**SUMMARY**

NIH 11209 has affinity for the μ receptor > κ receptor with very low affinity for the δ receptor.

* * *

**NIH 11210 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

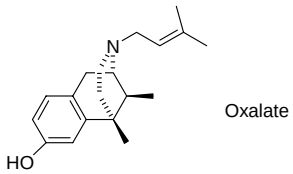
μ-receptor: 6.3 ± 0.6
δ-receptor: 42.8 ± 0.7
κ-receptor: 43.5 ± 3.8

**SUMMARY**

NIH 11210 has high affinity for the μ receptor and approximately 7-fold selectivity for μ over δ = κ receptors.

* * *

**NIH 11212 (+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-6,7-benzomorphan.Oxala**



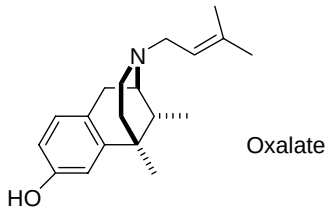

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 519 ± 145
δ-receptor: 5300 ± 390
κ-receptor: 80.2 ± 22.1

**SUMMARY**

NIH 11212 has affinity for κ > μ > δ receptors.

**NIH 11213 (-)-(1*R*,5*R*,9*R*)-5,9-dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-6,7-benzomorphan.oxalate**




**OPIOID RECEPTOR BINDING (nM)**

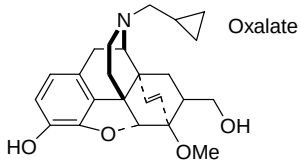
μ-receptor: 6.8 ± 1.0
δ-receptor: 117 ± 32.9
κ-receptor: 8.1 ± 2.0

**SUMMARY**

NIH 11213 has high affinity for μ = κ receptors and approximately 15-fold less affinity for δ receptors.

* * *

**NIH 11214 17-Cyclopropylmethyl-7α-hydroxymethylorvinol.oxalate**




**OPIOID RECEPTOR BINDING (nM)**

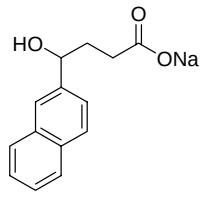
μ-receptor: 0.09 ± 0.001
δ-receptor: 0.79 ± 0.14
κ-receptor: 0.17 ± 0.01

**SUMMARY**

NIH 11214 has very high affinity for all three opioid receptors in the order of μ > κ > δ.

* * *

**NIH 11220 4-Hydroxy-4-napthylbutyric acid, sodium salt**



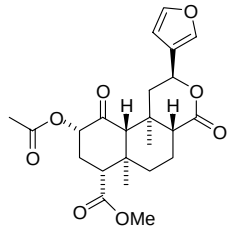

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 22 ± 4% inhibition at 10 :M
δ-receptor: 16 ± 7% inhibition at 10 :M
κ-receptor: 0% inhibition at 10 :M

**SUMMARY**

NIH 11220 has no affinity for opioid receptors.

**NIH 11228 Salvinorin A**



**OPIOID RECEPTOR BINDING (nM)**

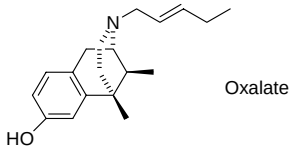
μ-receptor: 38 ± 7% inhibition at 10 μM
δ-receptor: 21 ± 17% inhibition at 10 μM
κ-receptor: 42.1± 11.1

**SUMMARY**

NIH 11228 has affinity for κ opioid receptors but no affinity at μ or δ opioid receptors.

* * *

**NIH 11231 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate**




**OPIOID RECEPTOR BINDING (nM)**

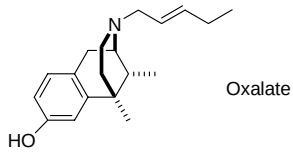
μ-receptor: 235 ± 15
δ-receptor: 3070 ± 272
κ-receptor: 89.2 ± 5.2

**SUMMARY**

NIH 11231 has affinity for κ > μ > δ opioid receptors.

* * *

**NIH 11232 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-pentenyl)-6,7-benzomorphan.oxalate**



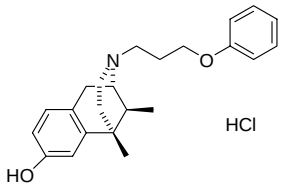

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 4.1 ± 0.26
δ-receptor: 128 ± 22
κ-receptor: 7.20 ± 2.51

**SUMMARY**

NIH 11232 has high affinity for κ and μ opioid receptors with at least 17-fold selectivity over δ opioid receptors.

**NIH 11233 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

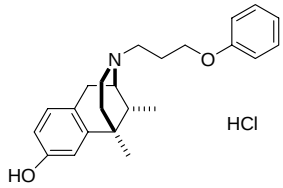
μ-receptor: 77.3 ± 11.3
δ-receptor: 3140 ± 96
κ-receptor: 598 ± 57

**SUMMARY**

NIH 11233 has affinity for μ > κ > δ opioid receptors

* * *

**NIH 11234 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(3-phenoxypropyl)-6,7-benzomorphan.HCl**




**OPIOID RECEPTOR BINDING (nM)**

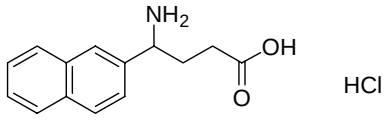
μ-receptor: 1.17 ± 0.15
δ-receptor: 5.17 ± 1.33
κ-receptor: 9.95 ± 1.69

**SUMMARY**

NIH 11234 has high affinity for μ, δ, and κ opioid receptors.

* * *

**NIH 11235 4-Amino-4-(2-napthyl)butyric acid.HCl**




**OPIOID RECEPTOR BINDING (nM)**

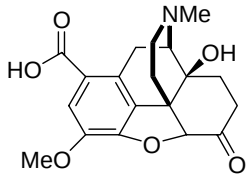
μ-receptor: 2990 ± 470
δ-receptor: 27 ± 3% inhibition at 10 μM
κ-receptor: 31 ± 9% inhibition at 10 μM

**SUMMARY**

NIH 11235 has very low affinity for μ opioid receptors and no affinity for δ or κ opioid receptors.

* * *

**NIH 11247 1-Carboxyoxycodone**




**OPIOID RECEPTOR BINDING (nM)**

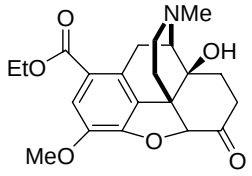
μ-receptor: 0.5 ± 0.5% inhibition at 10 μM
δ-receptor: 9 ± 6% inhibition at 10 μM
κ-receptor: 14 ± 14% inhibition at 10 μM

**SUMMARY**

NIH 11247 has no affinity for μ, δ, or κ opioid receptors.

* * *

**NIH 11248 1-Carboxyoxycodone ethyl ether**




**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 25 ± 1.5% inhibition at 10 μM
δ-receptor: 10 ± 2% inhibition at 10 μM
κ-receptor: 21 ± 18% inhibition at 10 μM

**SUMMARY**

NIH 11248 has no affinity for opioid receptors.

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***

**AFFILIATION**

The Drug Abuse Basic Research Program, Departments of Pharmacology and Psychology, University of Michigan, Ann Arbor, MI 48109-0632

APPENDIX

The University of Michigan laboratories also offer the following tests under the auspices of the Drug Evaluation Committee:

**DRUG DISCRIMINATION IN RHESUS MONKEYS**

We currently use three groups of monkeys to test the discriminative stimulus effects of submitted drugs: one of these groups discriminates the administration of the κ agonist ethylketazocine (EKC); a second group discriminates the μ agonist alfentanil or fentanyl; a third group is treated daily with morphine and discriminates the opioid antagonist naltrexone.

The procedures used with the EKC-trained monkeys have been described by Bertalmio et al. (1982). The monkeys are removed from their home cages each day and seated in primate restraining chairs. These chairs are placed in chambers equipped with two response levers, several stimulus lights and a cup to receive Noyes, banana-flavored pellets. These monkeys are required to make 100 consecutive responses on the correct one of the two levers and receive ten 300-mg food pellets. The right lever is correct if they were given a subcutaneous injection of 0.0032 mg/kg EKC immediately prior to the start of the cycle. The left lever is designated correct if they were given a sham injection before the start of the cycle. Each cycle lasts l5-min and consists of an initial l0-min black out period followed by a period of as long as 5 min, during which a blue light is illuminated in the chamber and the monkey can respond for food. If the food pellets are delivered before the 5 min period is completed, the lights are extinguished for the remainder of this time. Typically, a daily session consists of several 15 min cycles. During a training session, if EKC is given, it is given on the penultimate cycle of that session. Responding on the drug-appropriate lever is reinforced during that cycle and on the subsequent, final cycle of the day. These last two cycles may be preceded by from zero to four sham cycles on a training day. A training session of six sham cycles is also scheduled from time to time.

With this type of multiple, discrete-cycle training, the animals can be tested with a cumulative dosing procedure. On a test session, the first cycle is preceded by an injection of saline, and prior to subsequent cycles, increasing, cumulative doses of the test drug are administered. One hundred consecutive responses on either lever are reinforced throughout the test session. The test drug is administered in increasing doses until the monkey either responds on the drug-appropriate lever, the response rate falls to less than half of the saline-control rate, or six cycles are given. In the latter situation, it is assumed that the selected dose range is too low, and the test is continued at higher doses on the next test session. Each test session is preceded and followed by a training session. The criterion for satisfactory performance must be met on each training session that is followed by a test session. This criterion is that at least 90% of the responses during each cycle of a training session must be on the injection-appropriate lever, either sham or EKC.

The procedure for the alfentanil-trained monkeys is similar, but not identical. These animals are also trained and tested in a discrete, multiple-cycle procedure. The main difference between the alfentanil procedure and the EKC procedure is that the alfentanil monkeys are required to make 20 rather than l00 responses, and they receive a single pellet for correct responses. They can receive as many as 10 pellets during the 5-min, food-availability period of each cycle, but each pellet is delivered after 20 responses. Because in this procedure, monkeys can switch from one lever to another following the delivery of food, an additional criterion is added for satisfactory performance. In addition to making 90% or more of their responses on the correct lever, the monkeys must make fewer than 20 responses on the incorrect lever prior to delivery of the first food pellet of each cycle. Tests of the discriminative stimulus effects of submitted drugs in the alfentanil-trained monkeys are also done using a cumulative dosing procedure with dosing criteria identical to those used in the EKC-trained monkeys.

The procedure for studying discriminative stimulus effects in morphine-treated monkeys has been described previously (France and Woods, 1989). Daily sessions are comprised of a 10-min time out during which lever presses have no programmed consequence and a 5-min response period during which green stimulus lights are illuminated and signal the activation of a schedule of stimulus-shock termination. Sessions consist of between two and six discrete, 15-min cycles . Under these experimental conditions electric shock is scheduled to be delivered to the subject's feet every 15 seconds; monkeys can terminate the lights and postpone scheduled shocks for 30 seconds by pressing five times consecutively

(*i.e.*, fixed-ratio 5) the lever appropriate for the solution administered during the first minute of the time out (left lever, saline; right lever, naltrexone). Monkeys receive an injection of saline (0.1 ml/kg) or drug (0.01 mg/kg naltrexone) during the first minute of each time out. On drug training days a single injection of naltrexone is administered during one time out and for that one training cycle, and all subsequent cycles on that day only responding on the right lever postpones shocks. A variable number of saline cycles (0-5) precede the naltrexone cycle and on some days saline is administered during the time out of all cycles. Under these conditions monkeys switch their response choice from the saline lever to the naltrexone lever with complete generalization usually occurring in all three subjects at a dose of 0.01 mg/kg. Responding on the naltrexone lever is accompanied by other behavioral effects indicative of opioid withdrawal (*e.g.*, irritability, miosis, salivation). Moreover, when saline is substituted for the daily injection of 3.2 mg/kg of morphine monkeys respond predominantly on the naltrexone lever and show directly observable signs of withdrawal; the discriminative stimulus and other effects produced by morphine abstinence are reversed by some opioid agonists (*e.g.*, alfentanil; France and Woods, 1989; France et al., 1990).

For test sessions increasing doses of drug are administered during the first minute of consecutive time outs and five consecutive responses on either lever postpone shocks. In monkeys that receive 3.2 mg/kg of morphine 3 hours earlier, increasing doses of a test compound are administered up to doses that produce an average of at least 80% responding on the naltrexone lever or to doses that disrupt responding and result in the delivery of electric shock. Drugs that do not substitute for naltrexone (*i.e.*, precipitate withdrawal) are also studied for their ability to reverse responding on the naltrexone lever in morphine-abstinent (*i.e.*, withdrawn) subjects. Test compounds are studied using a cumulative-dosing procedure in morphine-abstinent monkeys up to doses that reverse completely responding on the naltrexone lever (<20%) or to doses that disrupt responding. Some compounds that substitute for naltrexone also are studied for their capacity to prevent the effects of cumulative doses of opioid agonists. Monkeys that receive saline three hours earlier, rather than the daily injection of morphine, receive saline (control) or a single injection of test compound during the first cycle and increasing doses of agonist (alfentanil or morphine) during subsequent cycles. Agonists are administered up to doses that produce a switch from the naltrexone lever to the saline lever or to doses that disrupt responding and result in the delivery of electric shock.

**THERMAL ANALGESIA IN RHESUS MONKEYS**

The tail withdrawal procedure used to study analgesic effects of test compounds in rhesus monkeys has been described previously (Dykstra and Woods, 1986). Monkeys are restrained loosely at the neck and arms while seated in Plexiglas primate chairs. For tests of tail withdrawal latency, the lower 10-12 cm of the shaved tail is immersed in a thermos containing water at 40°, 50°, or 55° C and the latency until the tail is withdrawn from the thermos is recorded for each monkey at each temperature. When the tail is not withdrawn within 20 seconds (cut-off latency) the experimenter removes the thermos and a latency of 20 seconds is recorded. Experimental sessions begin with several exposures to 40°C water. Four or five monkeys are tested consecutively and the time between tail immersions for individual monkeys is 5 minutes. Generally, 40° C water does not produce tail withdrawal in rhesus monkeys (Dykstra and Woods, 1986); however, if a monkey fails to keep its tail in 40° C water for 20 seconds on at least 3 of 4 immersions, that animal is not tested further for that particular session. In a subsequent pre-test component, tails are immersed in 40°, 50°, and 55° C water. The order in which the three temperatures are presented is varied among subjects. If the latencies for tail withdrawal in the pre-test component are at or near 20 seconds for 40° C water and less than 5 seconds for 55° C water, monkeys receive the test compound. The test is identical to the pre-test, except that monkeys receive s.c. injections of drug 10 minutes prior to tail immersion. The time between immersions for individual subjects is 5 minutes or less and the order in which temperatures are presented varies among subjects and across cycles. The inter-injection interval typically is 30 minutes and between four and six doses are studied in a single experiment using the cumulative dosing procedure. For some studies a single dose of an opioid antagonist is administered prior to the test compound and for other studies a single dose of test compound is administered prior to increasing doses of a μ (*e.g.*, alfentanil) or κ (*e.*g., U-50,488) opioid agonist.

**SELF-ADMINISTRATION BY MONKEYS**

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject alfentanil. Each of at least three monkeys is studied with saline as a negative control and a number of doses of the test

compound until a maximum rate of responding is obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior are produced by the compound.

The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response produces an intravenous drug injection accompanied by another light that is illuminated during drug delivery. After each injection, a 45 sec timeout period occurs. A component of the session ends after 20 injections have been received or 25 min have passed, whichever occurs first. Different doses of the drug are available during each of four components of a session. Other procedural details are given in Winger *et al*. (1989 and 1992). Procedures in which a single dose point is available as a comparison compound can be customized to accommodate drugs that may have pharmacokinetics different from alfentanil.

**RESPIRATORY STUDIES IN RHESUS MONKEYS**

The effects of test compounds on ventilatory function are studied in rhesus monkeys breathing air or 5% $CO_2$ in air (France and Woods, 1990; Howell et al., 1988). Monkeys are restrained at the neck and waist while seated in a Plexiglas primate chair. Normal air or 5% $CO_2$ in air is delivered at a rate of 10 1/min into a sealed helmet placed over the subject's head. Changes in pressure within the helmet are measured and recorded by a transducer and a microprocessor, and are transformed according to known standards to frequency of respiration (f) in breaths/minute and to tidal volume ($V_T$) in ml/inspiration. Data are recorded continuously during 23-minute exposures to air alternating with 7-minute exposures to $CO_2$. The last 3 minutes of exposure to $CO_2$ are used for data analyses and are compared to the last 3 minutes of exposure to air only. Increasing doses of drug are administered during the first minute of consecutive time outs so that the interinjection interval is 30 minutes. For some studies a single injection of an opioid antagonist is administered prior to increasing doses of a test compound and for other studies a single injection of test compound is administered prior to cumulative doses of a standard compound (*e.g*., alfentanil).