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 in opioid-binding assays. 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 during the past year are shown in the following Table. Also shown are dates of Reports to the Biological Coordinator, Dr. Coop.

<table>
<thead>
<tr>
<th>NIH #</th>
<th>Date Submitted to Biological Coordinator</th>
<th>NIH #</th>
<th>Date Submitted to Biological Coordinator</th>
<th>NIH #</th>
<th>Date Submitted to Biological Coordinator</th>
</tr>
</thead>
<tbody>
<tr>
<td>11031</td>
<td>31 July 2003</td>
<td>11073</td>
<td>14 March 2002</td>
<td>11163</td>
<td>10 April 2003</td>
</tr>
<tr>
<td>11041</td>
<td>04 August 2003</td>
<td>11074</td>
<td>14 March 2002</td>
<td>11164</td>
<td>10 April 2003</td>
</tr>
<tr>
<td>11045</td>
<td>04 August 2003</td>
<td>11076</td>
<td>14 March 2002</td>
<td>11177</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11050</td>
<td>09 September 2003</td>
<td>11077</td>
<td>14 March 2002</td>
<td>11178</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11053</td>
<td>24 October 2001</td>
<td>11078</td>
<td>23 October 2001</td>
<td>11179</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11054</td>
<td>24 October 2001</td>
<td>11079</td>
<td>23 October 2001</td>
<td>11180</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11055</td>
<td>24 October 2001</td>
<td>11081</td>
<td>04 August 2003</td>
<td>11181</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11057</td>
<td>01 November 2001</td>
<td>11082</td>
<td>01 August 2003</td>
<td>11182</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11058</td>
<td>01 November 2001</td>
<td>11088</td>
<td>01 August 2003</td>
<td>11183</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11059</td>
<td>20 November 2001</td>
<td>11093</td>
<td>04 August 2003</td>
<td>11185</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11060</td>
<td>20 November 2001</td>
<td>11095</td>
<td>04 August 2003</td>
<td>11186</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11061</td>
<td>20 November 2001</td>
<td>11096</td>
<td>09 September 2003</td>
<td>11187</td>
<td>31 July 2003</td>
</tr>
<tr>
<td>11062</td>
<td>05 December 2001</td>
<td>11097</td>
<td>04 August 2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11063</td>
<td>25 November 2001</td>
<td>11098</td>
<td>09 September 2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11065</td>
<td>03 December 2001</td>
<td>11100</td>
<td>31 July 2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11066</td>
<td>03 December 2001</td>
<td>11101</td>
<td>04 August 2003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

METHODS

Opioid Receptor Binding and In Vitro Efficacy Assessment

Details of the binding assay have been described previously (Lee et al., 1999). Briefly, aliquots of a membrane preparation are incubated with [3H]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 μM 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 C6 rat glioma cells expressing recombinant \(\mu\) (rat; Emmerson et al., 1994) or \(\delta\) (rat; Clark et al., 1997) and CHO cells expressing the recombinant \(\kappa\) (human, Zhu et al., 1997). The affinity (Kd) values of \([3H]\)diprenorphine at the receptors are: \(\mu\) (0.15 nM); \(\delta\) (0.45 nM); \(\kappa\) (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 \([3H]\)diprenorphine as radioligand are: \(\mu\) (DAMGO, 7.6 nM; morphine, 11.2 nM), \(\delta\) (SNC80, 0.8 nM) and \(\kappa\) (U69593, 0.3 nM). If less than 50% displacement of \([3H]\)diprenorphine is seen at 10 μM, it is reported as > 10 μM and the percent displacement given in parentheses.

\([35S]\)GTP\(\gamma\)S assays are carried out using membranes from C6 cells expressing either \(\mu\) (Emmerson et al., 1996) or \(\delta\) (Clark et al., 1997) receptors or CHO cells expressing \(\kappa\) 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. EC\(_{50}\) values (nM) for standard compounds are as follows: mu receptor (morphine, 65 nM; DAMGO, 34 nM; fentanyl, 13 nM), delta receptor (SNC80, 9 nM; DPDPE 8.3 nM), and kappa 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 \([35S]\)GTP\(\gamma\)S binding stimulated by an ED\(_{80}\) concentration of appropriate agonist (DAMGO, \(\mu\); DPDPE, \(\delta\); U69593, \(\kappa\)) 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.

**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 was 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 produce 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).
NIH 10945  
(+)-(5S,8S,9R)-8-Amino-3-hydroxy-5,9-methano-9-(methoxymethyl)-5-methylbenzocyclooctene

![Chemical Structure](image)

**OPIOID RECEPTOR BINDING (nM) †**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Affinity (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>δ-receptor</td>
<td>156.0 ± 25.0</td>
</tr>
<tr>
<td>κ-receptor</td>
<td>6.3 ± 0.4</td>
</tr>
</tbody>
</table>

[³⁵S]GTPγS ASSAY

**Agonist Activity**

µ-receptor: maximal stimulation = 59.6 ± 5.9% with EC₅₀ = 151 ± 49 nM  
κ-receptor: maximal stimulation = 74.4 ± 1.9% with EC₅₀ = 66.1 ± 10.1 nM

**SUMMARY**

NIH 10945 has high affinity for both µ and κ opioid receptors. Affinity at δ receptors is over 20-fold less. NIH 10945 is also a partial agonist at µ and κ receptors that likely explains its activity in the PPQ assay in the mouse and its ability to partially substitute for morphine in the morphine-dependent monkey. ††

† Binding data previously reported in NIDA Monograph 182:141, 2002.  
†† PPQ data reported previously in NIDA Monograph 182:168, 2002.

* * *

NIH 11001  
4-(3-Hydroxyphenyl)-4-(1-oxopropyl)-1-(4-trifluoromethylbenzyl)piperidine.HCl

![Chemical Structure](image)

**OPIOID RECEPTOR BINDING (nM) †**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Affinity (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor</td>
<td>32.9 ± 1.1</td>
</tr>
<tr>
<td>δ-receptor</td>
<td>291 ± 83</td>
</tr>
<tr>
<td>κ-receptor</td>
<td>118 ± 28</td>
</tr>
</tbody>
</table>

[³⁵S]GTPγS ASSAY

**Agonist Activity**

No significant stimulation of [³⁵S]GTPγS binding in C6 cells expressing the rat µ (C6µ) cells.

**Antagonist Activity**

Ke (µ) = 516 ± 121 nM
NIH 11001 (continued)

SUMMARY

NIH 11001 has affinity for \(\mu > \kappa = \delta\), but showed no activity \textit{in vivo} or \textit{in vitro} as an agonist or \(\mu\) antagonist in the mouse or monkey. The present findings show that the compound has only very weak \(\mu\) antagonist activity in spite of a reasonably high binding affinity. Note: repeat of the binding results in a buffer containing guanine nucleotides and Na\(^+\) ions afforded a \(K_i\) at the \(\mu\) receptor of 221 \(\pm\) 71 nM, in line with the functional affinity measure.

† Binding data previously reported in NIDA Monograph 181:151, 2001
‡‡ NIDA Monograph 181:197, 2001

* * *

NIH 11027 (-)-(1\(R\),5\(R\),9\(R\))-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

\[
\begin{align*}
\text{OPIOID RECEPTOR BINDING (nM)} & \\
\mu\text{-receptor:} & 25.0 \pm 9.9 \\
\delta\text{-receptor:} & 1362 \pm 53 \\
\kappa\text{-receptor:} & 11.1 \pm 2.3
\end{align*}
\]

\([^{35}\text{S}]GTP\gamma S\) ASSAY

Agonist Activity

No stimulation of \([^{35}\text{S}]GTP\gamma S\) binding was observed.

Antagonist Activity

\(Ke (\mu) \quad 34.5 \pm 17.5 \text{ nM}\)
\(Ke (\kappa) \quad 23.2 \pm 6.2 \text{ nM}\)

SUMMARY

NIH 11027 has affinity for \(\kappa\) and \(\mu\) receptors with high selectivity (\(\delta/\kappa = 123; \delta/\mu = 55\)) for both of these over \(\delta\) receptors. However, no activity as agonist or antagonist was seen in the mouse, although a non-dose-dependent exacerbation of withdrawal was observed in morphine-dependent monkeys. The present findings show that the compound is an antagonist at both \(\mu\) and \(\kappa\) receptors. However, the affinity (\(Ke\)) at \(\mu\) receptors is approximately 10-fold less than that of naloxone. This may explain the \textit{in vivo} results. Alternatively, the lack of \textit{in vivo} activity may relate to the pharmacokinetic profile of this compound.

† Binding data previously reported in NIDA Monograph 183:175, 2003
NIH 11031 17-Cyclopropylmethyl-[5β,7β,3',5']-pyrrolidino-2'-[5]-phenyl-7α-methyl-6,14-endo-ethenomorphinan.HCl

[35S]GTPγS ASSAY

μ-receptor: <5% up to 10 μM
δ-receptor: maximal stimulation = 35.0 ± 5.7% with EC50 = 1.8 ± 0.5 nM
κ-receptor: maximal stimulation = 76.3 ± 11.0 with EC50 = 0.36 ± 0.03 nM

SUMMARY

The binding affinity (Ki) of NIH 11031 is very high at all three receptors. The opioid effects in the mouse and monkey†† may be explained by the highly potent agonist activity at 6 receptors.

† Binding data previously reported in NIDA Monograph 194:155, 2004
†† NIDA Monograph 184:181-183, 2004

NIH 11041 (-)-(1R,5R,9R)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl

[35S]GTPγS ASSAY

No significant stimulation of [35S]GTPγS binding was observed up to a concentration of 10 μM.

SUMMARY

NIH 11041 has affinity for κ receptors and has 5-times lesser affinity at μ receptors and 26 times lesser at δ receptors. However, it has no activity in vivo or in vitro as an agonist or μ antagonist in the mouse or monkey. †† The present findings show that the compound has no agonist action and is likely to be a κ/μ antagonist. The affinity values suggest that it will be approximately 20-fold less potent as a : antagonist than naloxone. This may explain the lack of observed antagonist activity in vivo.

† Binding data previously reported in NIDA Monograph 183:177, 2003
†† Monkey data previously reported in NIDA Monograph 183:211, 2003
NIH 11044  
(-)-(1R,5R,9R)-2’-Acetoxy-2-(3-cis-chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan.oxalate

**OPIOID RECEPTOR BINDING (nM)** †

\[
\begin{align*}
\mu\text{-receptor:} & \quad 14.9 \pm 2.5 \\
\delta\text{-receptor:} & \quad 17.4 \pm 2.3 \\
\kappa\text{-receptor:} & \quad 3.0 \pm 0.1
\end{align*}
\]

[^1]GTPγS ASSAY

\[
\begin{align*}
\mu\text{-receptor:} & \quad \text{no stimulation up to 10 µM} \\
\delta\text{-receptor:} & \quad 5\% \text{ stimulation at 10 µM} \\
\kappa\text{-receptor:} & \quad \text{maximal stimulation} = 56.1 \pm 10.0\% \text{ with EC}_{50} = 22.7 \pm 7.3 \text{ nM}
\end{align*}
\]

**SUMMARY**

NIH 11044 has high affinity for κ opioid receptors > µ = δ receptors, with a selectivity of 5-fold for κ receptors over the other types. It acts as a partial agonist at κ opioid receptors. Its binding affinity (Ki) is high at all three receptors (see above), suggesting that it is also a potent µ and δ antagonist. This agrees with its in vivo profile in the mouse that it acts as a µ antagonist activity but is antinociceptive in the PPQ†† test and that it has µ antagonist activity with some κ agonist properties in the monkey.

† Binding data previously reported in NIDA Monograph 183:178, 2003
†† NIDA Monograph 183:214, 2003

* * *

NIH 11045  
(-)-(1R,5R,9R)-2’-Acetoxy-5,9-dimethyl-2-(propenyl)-6,7-benzomorphan.oxalate

**OPIOID RECEPTOR BINDING (nM)** †

\[
\begin{align*}
\mu\text{-receptor:} & \quad 136 \pm 34 \\
\delta\text{-receptor:} & \quad 96.2 \pm 8.1 \\
\kappa\text{-receptor:} & \quad 29.2 \pm 1.6
\end{align*}
\]

[^1]GTPγS ASSAY

\[
\begin{align*}
\mu\text{-receptor:} & \quad \text{no stimulation up to 10 µM} \\
\delta\text{-receptor:} & \quad \text{no stimulation up to 10 µM} \\
\kappa\text{-receptor:} & \quad \text{maximal stimulation} = 45.5 \pm 5.6\% \text{ with EC}_{50} = 127 \pm 2.3 \text{ nM}
\end{align*}
\]
NIH 11045 (continued)

SUMMARY

NIH 11045 has affinity for opioid receptors but is only 3-4-fold selective for the κ over δ and μ receptors. In vivo, the compound is a μ and κ antagonist (versus morphine and enadoline, respectively) in the mouse but in the monkey is a μ antagonist with signs of κ agonism.†† The present findings show that the compound has partial agonist action at 6 receptors, which would explain the in vivo observation.

† Binding data previously reported in NIDA 183:179, 2003

NIH 11050 17-Methyl-6,7-didehydro-3,14-dihydroxy-4,5α-epoxy-(2-methyl)-pyrazolo-[6,7]morphan.2HCl

OPIOID RECEPTOR BINDING (nM)⊥

\[
\begin{align*}
\text{μ-receptor:} & & 23.9 \pm 10.1 \\
\text{δ-receptor:} & & 22.7 \pm 3.3 \\
\text{κ-receptor:} & & 157 \pm 53
\end{align*}
\]

[^35S]GTP(S ASSAY

\[
\begin{align*}
\text{μ-receptor:} & & \text{maximal stimulation} = 89 \pm 3\% \text{ with } EC_{50} = 154 \pm 58 \text{ nM} \\
\text{δ-receptor:} & & \text{maximal stimulation} = 27 \pm 2\% \text{ with } EC_{50} = 302 \pm 78 \text{ nM} \\
\text{κ-receptor:} & & \text{maximal stimulation} = 19 \pm 7\% \text{ with } EC_{50} = 245 \pm 54 \text{ nM}
\end{align*}
\]

SUMMARY

NIH 11050 has the same affinity for μ and δ receptors, but with no selectivity. It is approximately 7 times weaker at κ receptors. It is a relatively high efficacy agonist at μ receptors but has only low efficacy at δ and κ receptors. There is little selectivity in potency across the three receptors.

† Binding data previously reported in NIDA Monograph 183:179, 2003.

NIH 11052 (-)-(1R,5R,9R)-5,9-Dimethyl-2-(propenyl)-2′-prorionoxy-6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM)⊥

\[
\begin{align*}
\text{μ-receptor:} & & 107 \pm 42 \\
\text{δ-receptor:} & & 90.7 \pm 15.4 \\
\text{κ-receptor:} & & 7.9 \pm 0.7
\end{align*}
\]
NIH 11052 has high affinity for κ opioid receptors and is 12 times more selective for κ over µ or δ receptors. In the mouse and monkey, NIH 11052 was a µ antagonist, with weak antinociceptive properties in the mouse.†† The present findings show that the compound is likely to be a µ and δ antagonist with a partial agonist action at κ receptors, which would explain the weak antinociceptive properties observed in the mouse.

† Binding data previously reported in NIDA Monograph 183:180, 2003
†† NIDA Monograph 183:217, 2003

NIH 11053

17-Propyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

**OPIOID RECEPTOR BINDING (nM)**

µ-receptor: 0.09 ± 0.05
δ-receptor: 0.93 ± 0.18
κ-receptor: 0.08 ± 0.02

NIH 11054

17-[(2R,S-Tetrahydrofuranyl)methyl]-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

**OPIOID RECEPTOR BINDING (nM)**

µ-receptor: 0.20 ± 0.04
δ-receptor: 0.09 ± 0.02
κ-receptor: 0.08 ± 0.02

NIH 11052 (continued)

[^S]GTPγS ASSAY

**Agonist Activity**

µ-receptor: no stimulation up to 10 µM
δ-receptor: no stimulation up to 10 µM
κ-receptor: maximal stimulation = 37.3 ± 3.1% with EC₅₀ = 147 ± 67nM

**SUMMARY**

NIH 11052 has high affinity for κ opioid receptors and is 12 times more selective for κ over µ or δ receptors. In the mouse and monkey, NIH 11052 was a µ antagonist, with weak antinociceptive properties in the mouse.†† The present findings show that the compound is likely to be a µ and δ antagonist with a partial agonist action at κ receptors, which would explain the weak antinociceptive properties observed in the mouse.

† Binding data previously reported in NIDA Monograph 183:180, 2003
†† NIDA Monograph 183:217, 2003
NIH 11055 17-Phenethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

**OPIOID RECEPTOR BINDING (nM)**

- µ-receptor: 1.1 ± 0.4
- δ-receptor: 1.25 ± 0.5
- κ-receptor: 0.60 ± 0.2

**SUMMARY**

NIH 11055 has high affinity for all opioid receptors, but with no selectivity.

* * *

NIH 11057 17-Cyclobutylmethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

**OPIOID RECEPTOR BINDING (nM)**

- µ-receptor: 0.25 ± 0.07
- δ-receptor: 0.46 ± 0.16
- κ-receptor: 0.49 ± 0.25

**SUMMARY**

NIH 11057 has very high affinity for all three opioid receptors.

* * *

NIH 11058 17-Cyclobutylmethyl-4,5α-epoxy-3-hydroxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

**OPIOID RECEPTOR BINDING (nM)**

- µ-receptor: 0.20 ± 0.01
- δ-receptor: 0.26 ± 0.07
- κ-receptor: 0.11 ± 0.05

**SUMMARY**

NIH 11058 has very high affinity for all three opioid receptors, but with no selectivity.
NIH 11059 17-[(2R,S-Tetrahydrofuranyl)methyl]-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1.9 ± 0.38
δ-receptor: 5.4 ± 1.2
κ-receptor: 1.4 ± 0.67

SUMMARY

NIH 11059 has high affinity for all three opioid receptors.

* * *

NIH 11060 4,5α-Epoxy-3-methoxy-17-(2-phenylethyl)-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3.8 ± 1.3
δ-receptor: 6.2 ± 0.2
κ-receptor: 61.4 ± 1.9

SUMMARY

NIH 11060 has high affinity for μ and δ receptors with 10- to 16-fold lower affinity for κ receptors.

* * *

NIH 11061 17-Allyl-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1.7 ± 0.9
δ-receptor: 16.4 ± 5.2
κ-receptor: 4.1 ± 0.6

SUMMARY

NIH 11061 has high affinity for the three opioid receptors in the order μ > κ > δ.
NIH 11062 17-Allyl-4,5α-epoxy-3-methoxy-14β-(3-phenylpropyloxy)morphinan-6-one.HCl

[![Chemical Structure for NIH 11062]  

**OPIOID RECEPTOR BINDING (nM)**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Binding (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>δ-receptor</td>
<td>69.8 ± 21.2</td>
</tr>
<tr>
<td>κ-receptor</td>
<td>6.13 ± 1.9</td>
</tr>
</tbody>
</table>

**SUMMARY**

NIH 11062 has high affinity for µ > κ receptors and δ receptor affinity. Its selectivity for κ receptors is 4-fold over κ and 44-fold over δ.

* * *

NIH 11063 4,5α-Epoxy-14β-ethoxy-3-hydroxy-17-(propyl)morphinan-6-one.HCl

[![Chemical Structure for NIH 11063]  

**OPIOID RECEPTOR BINDING (nM)⊥**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Binding (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor</td>
<td>270 ± 20.3</td>
</tr>
<tr>
<td>δ-receptor</td>
<td>1.07 ± 0.18</td>
</tr>
<tr>
<td>κ-receptor</td>
<td>108 ± 5.3</td>
</tr>
</tbody>
</table>

**[^135]GTPγS ASSAY**

**Agonist Activity**

No stimulation of [^135]GTPγS binding was observed up to 10 µM.

**Antagonist Activity**

Ke (δ) = 0.24 ±0.05 nM

**SUMMARY**

NIH 11063 is a high affinity δ-antagonist. It is 100-fold selective for δ over κ and 250-fold selective for δ over µ in binding assays.

† Binding data previously reported in NIDA Monograph 183:180, 2003.
NIH 11065  5,6-Didehydro-14β-hydroxy-3,4-dimethoxy-17-methylmorphinan-6-carbonitrile

**OPIOID RECEPTOR BINDING (nM)**

- μ-receptor: 11.7 ± 1.0
- δ-receptor: 342 ± 68
- κ-receptor: 383 ± 89

**SUMMARY**

NIH 11065 has affinity for μ opioid receptors. It is 30-fold selective for μ receptors over κ receptors and δ receptors.

* * *

NIH 11066  5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile

**OPIOID RECEPTOR BINDING (nM)**

- μ-receptor: 261 ± 30.4
- δ-receptor: 3386 ± 138
- κ-receptor: 4179 ± 629

**SUMMARY**

NIH 11066 has low affinity for the μ opioid receptor, but is 16-fold selective for μ over κ and 13-fold selective for μ over δ.

* * *

NIH 11067  5,6-Didehydro-4-hydroxy-3,14β-dimethoxy-17-methylmorphinan-6-carbonitrile

**OPIOID RECEPTOR BINDING (nM)**

- μ-receptor: 22.3 ± 8.5
- δ-receptor: 1006 ± 316
- κ-receptor: 1480 ± 369

**SUMMARY**

NIH 11067 has μ receptor affinity with > 40-fold selectivity for the μ receptor compared with δ and κ receptors.
NIH 11068  17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-3-hydroxy-5β-methymorphinan-6-one

**OPIOID RECEPTOR BINDING (nM)**

- µ-receptor: 0.47 ± 0.03
- δ-receptor: 31.3 ± 9.3
- κ-receptor: 6.1 ± 2.0

**SUMMARY**

NIH 11068 has very high µ receptor affinity with some (12-fold) selectivity over the κ receptor and 60-fold selectivity over the δ receptor.

* * *

NIH 11072  17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-4-methoxymorphinan-6-carbonitrile

**OPIOID RECEPTOR BINDING (nM)**

- µ-receptor: 68.7 ± 21.6
- δ-receptor: 2108 ± 434
- κ-receptor: 93 ± 20

**SUMMARY**

NIH 11072 has approximately equal affinity for µ and κ receptors and 20-fold lower affinity for the δ receptor.

* * *

NIH 11073  17-Cyclopropylmethyl-5,6-didehydro-4-hydroxy-3,14β-dimethoxymorphinan-6-carbonitrile

**OPIOID RECEPTOR BINDING (nM)**

- µ-receptor: 236 ± 14.6
- δ-receptor: 1613 ± 370
- κ-receptor: 411 ± 127

**SUMMARY**

NIH 11073 has low affinity for µ and κ receptors, with even lower affinity for δ receptors.
NIH 11074 17-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxy-3-methoxymorphinan-6-carbonitrile

OPIOID RECEPTOR BINDING (nM)

µ-receptor: 382 ± 25.5
δ-receptor: 4880 ± 881
κ-receptor: 368 ± 27

SUMMARY

NIH 11074 has low affinity for µ and κ receptors, with very low δ receptor affinity.

*   *   *

NIH 11075 17-Cyclopropylmethyl-5,6-didehydro-4,14β-dihydroxymorphinan-6-carbonitrile

OPIOID RECEPTOR BINDING (nM)

µ-receptor: 23.1 ± 6.1
δ-receptor: 405 ± 121
κ-receptor: 12.2 ± 5.5

SUMMARY

NIH 11075 has affinity for µ and κ receptors, with lower δ receptor affinity.

*   *   *

NIH 11076 17-Cyclopropylmethyl-5,6-didehydro-14β-hydroxy-3,4-dimethoxymorphinan-6-carbonitrile

OPIOID RECEPTOR BINDING (nM)

µ-receptor: 40.9 ± 11.4
δ-receptor: 1138 ± 138
κ-receptor: 49 ± 15

SUMMARY

NIH 11076 has affinity for µ and κ receptors with low δ receptor affinity.
**NIH 11077**
5,6-didehydro-4,14β-dihydroxy-17-methylmorphinan-6-carbonitrile

![Molecule Structure]

**OPIOID RECEPTOR BINDING (nM)**

- μ-receptor: 3.8 ± 1.1
- δ-receptor: 419 ± 92
- κ-receptor: 408 ± 30

**SUMMARY**

NIH 11077 has high μ receptor affinity with 100-fold selectivity over the κ- and δ-opioid receptors.

* * *

**NIH 11078**
7-Hydroxymethyl-8-methyl-6,7,8,9,10,10a-hexahydro-1H-2-oxa-8-aza-cycloocta[c,d]inden-3-ol

![Molecule Structure]

**OPIOID RECEPTOR BINDING (nM)**

- μ-receptor: 22.4 ± 4.3% inhibition at 10 µM
- δ-receptor: 22.6 ± 2.4% inhibition at 10 µM
- κ-receptor: 27.0 ± 6.4% inhibition at 10 µM

**SUMMARY**

NIH 11078 has no affinity for opioid receptors.

* * *

**NIH 11079**
8-Methyl-6,7,8,9,10,10a-hexahydro-1H-2-oxa-8-aza-cycloocta[c,d]inden-3-ol

![Molecule Structure]

**OPIOID RECEPTOR BINDING (nM)**

- μ-receptor: 25.0 ± 2.5% inhibition at 10 µM
- δ-receptor: 18.0 ± 9.0% inhibition at 10 µM
- κ-receptor: 12.0 ± 2.5% inhibition at 10 µM

**SUMMARY**

NIH 11079 has no affinity for opioid receptors.
NIH 11081  
\((-\text{I}R,5\text{R},9\text{R})\)-2-(2-bromobenzyl)-5,9-Dimethyl-2’-hydroxy-6,7-benzomorphan.HCl

**OPIOID RECEPTOR BINDING (nM)**

\[
\begin{align*}
\mu-\text{receptor: } & 40.2 \pm 4.4 \\
\delta-\text{receptor:} & 1227 \pm 138 \\
\kappa-\text{receptor:} & 13.5 \pm 2.0
\end{align*}
\]

\[^{35}\text{S}]\text{GTP} \gamma \text{S ASSAY}

**Agonist Activity**

No stimulation of \[^{35}\text{S}]\text{GTP} \gamma \text{S} binding was observed up to 10 µM.

**SUMMARY**

In binding assays, NIH 11081 has affinity for µ and κ receptors, but has no opioid effects in the mouse††. The present results suggest the compound to be a κ/µ antagonist with µ affinity 20-fold less than naloxone. This may explain the lack of observed in vivo activity.

† Binding data previously reported in NIDA Monograph 183:182, 2003.
†† NIDA Monograph 183:220, 2003

**NIH 11082**  
\((-\text{I}R,5\text{R},9\text{R})\)-5,9-Dimethyl-2’-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl

**OPIOID RECEPTOR BINDING (nM)**

\[
\begin{align*}
\mu-\text{receptor: } & 10.2 \pm 0.73 \\
\delta-\text{receptor:} & 140 \pm 15.8 \\
\kappa-\text{receptor:} & 28.6 \pm 4.5
\end{align*}
\]

\[^{35}\text{S}]\text{GTP} \gamma \text{S ASSAY}

**Agonist Activity**

\[
\begin{align*}
\mu-\text{receptor: } & \text{maximal stimulation} = 50.5 \pm 6.7\% \text{ with } \text{EC}_{50} = 303 \pm 57 \\
\delta-\text{receptor:} & \text{maximal stimulation} = 9.3 \pm 4.7\% \text{ with } \text{EC}_{50} = 555 \pm 149 \\
\kappa-\text{receptor:} & \text{maximal stimulation} = 21.7 \pm 4.1\% \text{ with } \text{EC}_{50} = 1346 \pm 514
\end{align*}
\]

**SUMMARY**

These data show that 11082 is a partial agonist at µ and κ receptors, but with low potency. It has almost no efficacy at δ receptors. These data help to explain why the compound is only active in the phenylquinone writing assay in mice††, but not in nociceptive tests using heat, even though the compound has high binding affinity.

† Binding data previously reported in NIDA Monograph 183:182, 2003
†† NIDA Monograph 183:221, 2003
NIH 11088  
(+)-(1S,5S,9S)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM) †

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Binding (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor</td>
<td>139 ± 33</td>
</tr>
<tr>
<td>δ-receptor</td>
<td>3565 ± 1191</td>
</tr>
<tr>
<td>κ-receptor</td>
<td>23.3 ± 2.4</td>
</tr>
</tbody>
</table>

[^35S]GTP\(\gamma\)S ASSAY

Agonist Activity

NIH 11088 has no agonist activity at µ, δ, or κ opioid receptors.

SUMMARY

NIH 11088 has binding affinity for κ > µ > δ, with selectivity for κ over µ of 12-fold, but with no effects in vivo in the mouse††. It shows no agonism in the[^35S]GTP\(\gamma\)S assay and may therefore be a κ antagonist with some selectivity.

† See NIDA Monograph 183:222, 2003
†† See NIDA Monograph 184:190, 2004

* * *

NIH 11093  
(-)-(1R,5R,9R)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy--6,7-benzomorphan.HCl

OPIOID RECEPTOR BINDING (nM) †

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Binding (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor</td>
<td>16.8 ± 2.1</td>
</tr>
<tr>
<td>δ-receptor</td>
<td>600 ± 93</td>
</tr>
<tr>
<td>κ-receptor</td>
<td>17.5 ± 5.4</td>
</tr>
</tbody>
</table>

[^35S]GTP\(\gamma\)S ASSAY

Agonist Activity

No significant stimulation of[^35S]GTP\(\gamma\)S binding was observed up to a concentration of 10 µM.

SUMMARY

In binding assays, NIH 11093 showed equal affinity for κ and µ, with low affinity for δ receptors. However, no activity as agonist or µ-antagonist was seen in the mouse or monkey. The present findings show that the compound has no agonist activity and is likely to be a µ/κ nonselective antagonist. However, the affinity values suggest that it will be approximately 10-fold less potent as a µ antagonist than naloxone. This may explain the lack of observed antagonist activity in vivo.

† Binding data previously reported in NIDA Monograph 183:184, 2003
†† NIDA Monograph 183:223, 2003
NIH 11095  

(+)-(1S,5S,9S)-5,9-Dimethyl-2-(2-fluorobenzyl)-2’-hydroxy-6,7-benzomorphan.Oxalate

![Chemical structure of NIH 11095]

**OPIOID RECEPTOR BINDING (nM)**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor</td>
<td>560 ± 92</td>
</tr>
<tr>
<td>δ-receptor</td>
<td>4129 ± 867</td>
</tr>
<tr>
<td>κ-receptor</td>
<td>47 ± 10.5</td>
</tr>
</tbody>
</table>

| isotopic GTPγS ASSAY |

**Agonist Activity**

No significant stimulation of [³⁵S]GTPγS binding was observed up to a concentration of 10 µM.

**SUMMARY**

In binding assays, NIH 11095 showed a 12-fold selectivity for κ over µ, with very low affinity for δ receptors. However, no activity as agonist or µ antagonist was seen in the mouse. †† The present findings show that the compound has no agonist activity and is likely to be an antagonist with a preference for the κ receptor. However, the affinity values suggest that it will be a weak antagonist.

† Binding data previously reported in NIDA Monograph 183:184, 2003.

NIH 11096  

(-)-(1R,5R,9R)-2’-Butyroxy-5,9-Dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl

![Chemical structure of NIH 11096]

**OPIOID RECEPTOR BINDING (nM)**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ receptor</td>
<td>30.2 ± 13.5</td>
</tr>
<tr>
<td>δ receptor</td>
<td>37.0 ± 1.7</td>
</tr>
<tr>
<td>κ receptor</td>
<td>0.9 ± 0.05</td>
</tr>
</tbody>
</table>

| isotopic GTPγS ASSAY |

**Agonist Activity**

µ-receptor: maximal stimulation = 11 ± 7% with EC₅₀ = 919 ± 685
κ-receptor: maximal stimulation = 74.4 ± 1.9% with EC₅₀ = 66.1 ± 10.1

**SUMMARY**

NIH 11096 is a partial κ agonist with no significant µ efficacy. The binding affinity at the µ receptor suggests the compound would be a µ antagonist. These results are in keeping with the in vivo findings†† that the compound has µ and κ antagonist properties against high efficacy agonists.

† Binding data previously reported in NIDA Monograph 183:185, 2003
†† NIDA Monograph 184:193-194, 2004
NIH 11097  
(-)-(1R,5R,9R)-5,9-Dimethyl-2-(2-fluorobenzyl)-2’-hydroxy-6,7-benzomorphan.Oxalate

**OPIOID RECEPTOR BINDING (nM)**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Binding (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor</td>
<td>23.3 ± 4.5</td>
</tr>
<tr>
<td>δ-receptor</td>
<td>326 ± 40</td>
</tr>
<tr>
<td>κ-receptor</td>
<td>2.1 ± 0.9</td>
</tr>
</tbody>
</table>

**[35S]GTPγS ASSAY**

**Agonist Activity**

No stimulation of [35S]GTPγS binding in C6 cells was observed.

**Antagonist Activity**

Ke (µ) 96.5 ± 17.4  
Ke (κ) 17.4 ± 3.3

**SUMMARY**

In binding assays, NIH 11097 showed a 10-fold selectivity for κ over µ. However, no activity as agonist or µ-antagonist was seen in the mouse. The present findings show that the compound is an antagonist at both µ and κ receptor with a small (~5-fold) preference for the κ receptor. However, the affinity (Ke) at µ receptors is approximately 10-fold less than that of naloxone, which may explain the previously reported lack of µ antagonist activity in vivo ††. Alternatively, the lack of in vivo activity may relate to the pharmacokinetic profiles of the compound.

† Binding data previously reported in NIDA Monograph 183:185, 2003  
†† NIDA Monograph 183:224, 2003

NIH 11098  
(+)-(1S,5S,9S)-2’-Butoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl

**OPIOID RECEPTOR BINDING (nM)†**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Binding (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor</td>
<td>601 ± 10.8</td>
</tr>
<tr>
<td>δ-receptor</td>
<td>3099 ± 405</td>
</tr>
<tr>
<td>κ-receptor</td>
<td>1712 ± 167</td>
</tr>
</tbody>
</table>

**[35S]GTPγS ASSAY**

**Agonist Activity**

µ-receptor: maximal stimulation = 17.8% with EC50 = 950 ± 307 nM  
κ-receptor: no stimulation up to 10 µM

NIH 11098 (continued)
SUMMARY

NIH 11098 is a weak, very low efficacy µ agonist with no agonist activity at the κ receptor. The weak action in the PPQ assay in the mouse†† may be due to this µ activity, but could also be non-opioid.

† Binding data previously reported in NIDA Monograph 183:185, 2003.
†† NIDA Monograph 183: 224, 2003

* * *

NIH 11100 18-(E)-benzylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan.oxalate

\[
\begin{align*}
\text{OPIOID RECEPTOR BINDING (nM)} \downarrow \\
\mu\text{-receptor:} & \quad 41.8 \pm 17.2 \\
\delta\text{-receptor:} & \quad 30.0 \pm 3.6 \\
\kappa\text{-receptor:} & \quad 60.0 \pm 9.3
\end{align*}
\]

Agonist Activity

\begin{align*}
\mu\text{-receptor:} & \quad \text{no stimulation up to 10 } \mu\text{M} \\
\delta\text{-receptor:} & \quad \text{maximal stimulation} = 40.6 \pm 6.2\% \text{ with } EC_{50} = 463 \pm 38 \text{ nM} \\
\kappa\text{-receptor:} & \quad \text{maximal stimulation} = 64.0 \pm 18.7\% \text{ with } EC_{50} = 2063 \pm 324 \text{ nM}
\end{align*}

SUMMARY

The binding affinity (Ki) of NIH 11100 is similar at all three receptors. However, its efficacy at the three receptors is different such that NIH 11100 is a partial agonist with low potency at δ receptors and very low potency at κ receptors. The results indicate that it would be a weak µ antagonist.

† See NIDA Monograph 184:156, 2004

* * *

NIH 11101 18-Isopropylidene-4-hydroxy-3-methoxy-17-methyl-[6,7:2',3']-indolomorphinan.oxalate

\[
\begin{align*}
\text{OPIOID RECEPTOR BINDING (nM)} \uparrow \\
\mu\text{-receptor:} & \quad 267 \pm 18 \\
\delta\text{-receptor:} & \quad 148 \pm 33 \\
\kappa\text{-receptor:} & \quad 158 \pm 51
\end{align*}
\]

NIH 11101 (continue)
[^35]S[GTPγS ASSAY

**Agonist Activity**

- **µ-receptor:** maximal stimulation = 63.6 ± 3.1 with $EC_{50} = 2126 ± 587$ nM (n=2)
- **δ-receptor:** no stimulation up to 10 µM
- **κ-receptor:** no stimulation up to 10 µM

**SUMMARY**

NIH 11101 is a weak partial agonist at µ receptors. From its binding profile, it is also likely to be a low affinity δ/κ antagonist.

† Binding data previously reported in NIDA Monograph 184:156, 2004

* * *

**NIH 11128**  (+)-(1S,5S,9S)-5,9-dimethyl-2'-Hydroxy-2-(7-hydroxyheptyl)-6,7-benzomorphan.HBr

![Chemical Structure](image)

**OPIOID RECEPTOR BINDING (nM)**

- **µ-receptor:** 907 ± 112
- **δ-receptor:** 5822 ± 3500
- **κ-receptor:** 1789 ± 379

**SUMMARY**

NIH 11128 has very low affinity for µ, δ, and κ receptors.

* * *

**NIH 11140**  (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(8-hydroxyoctyl)-6,7-benzomorphan.HCl

![Chemical Structure](image)

**OPIOID RECEPTOR BINDING (nM)**

- **µ-receptor:** 136 ± 13.5
- **δ-receptor:** 204 ± 33
- **κ-receptor:** 449 ± 104

**SUMMARY**

NIH 11140 has low affinity for µ, δ, and κ opioid receptors nor is there evidence of selectivity.
Four doses of NIH 11161 were evaluated in four rhesus monkeys. Each animal was tested at least twice per dose. This compound generated an inverted-U shaped dose-response curve (see rates in Table 1), and was self-administered by all four animals studied.

Table 1 shows absolute response rates (± SEM) for alfentanil and NIH 11161 self-administration, as well as their appropriate vehicles, aggregated across all four animals. Rates of response for NIH 11161 were high across a dose range approximately 30-fold higher than that required to engender contingent responding for alfentanil. The maximal rate of responding for NIH 11161 (at 0.01 mg/kg/inj) peaked at approximately 70% of alfentanil control, although rates for all doses tested were higher than those engendered by contingent saline or the NIH 11161 vehicle. By way of comparison, NIH 11161 is thus 30-fold less potent and 30% less effective than alfentanil in terms of reinforcing effects.

<table>
<thead>
<tr>
<th>Dose (mg/kg/inj)</th>
<th>0.00003</th>
<th>0.0001</th>
<th>0.0003</th>
<th>0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>0.27 ± 0.13</td>
<td>0.95 ± 0.22</td>
<td>2.23 ± 0.48</td>
<td>2.06 ± 0.61</td>
</tr>
<tr>
<td>Saline</td>
<td>0.21 ± 0.11</td>
<td>0.20 ± 0.09</td>
<td>0.22 ± 0.14</td>
<td>0.14 ± 0.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose (mg/kg/inj)</th>
<th>0.001</th>
<th>0.003</th>
<th>0.01</th>
<th>0.03</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH11161</td>
<td>0.58 ± 0.34</td>
<td>1.33 ± 0.54</td>
<td>1.69 ± 0.47</td>
<td>0.45 ± 0.12</td>
</tr>
<tr>
<td>Vehicle</td>
<td>0.08 ± 0.03</td>
<td>0.14 ± 0.06</td>
<td>0.11 ± 0.08</td>
<td>0.08 ± 0.05</td>
</tr>
</tbody>
</table>

Table 1 – Response rates (responses per second) for alfentanil, NIH11161, and their infusion volume control vehicles across four doses (in mg/kg/inj) and expressed as mean ± SEM. Data were aggregated across four experimental subjects, and each dose condition was studied at least twice.

*  *  *

NIH 11163  (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(5-hydroxypentyl)-6,7-benzomorphan.HCl

<table>
<thead>
<tr>
<th>OPIOID RECEPTOR BINDING (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ-receptor: 45 ± 2.0% displacement at 10 µM</td>
</tr>
<tr>
<td>δ-receptor: 10.3 ± 1.2% displacement at 10 µM</td>
</tr>
<tr>
<td>κ-receptor: 13.5 ± 6.5% displacement at 10 µM</td>
</tr>
</tbody>
</table>

SUMMARY

NIH 11163 has no affinity for opioid receptors.
**NIH 11164**  
(-)-(1R,5R,9R)-2-(5-Acetoxypentyl)-5,9-Dimethyl-2’-hydroxy-6,7-benzomorphan.HCl

**OPIOID RECEPTOR BINDING (nM)**
- **µ-receptor**: 7.3 ± 2.9
- **δ-receptor**: 140 ± 27
- **κ-receptor**: 55.3 ± 4.2

**SUMMARY**
NIH 11164 has high affinity for µ receptors and some selectivity for µ over κ (7-fold) and δ (20-fold) receptors.

**NIH 11176**  
(-)-(1R,5R,9R)-5,9-Dimethyl-2-(1,3-dioxalanylethyl)-2’-hydroxy-6,7-benzomorphan.HCl

**OPIOID RECEPTOR BINDING (nM)**
- **µ-receptor**: 26.6 ± 9.5
- **δ-receptor**: 53.4 ± 5.9
- **κ-receptor**: 41.9 ± 15.6

**SUMMARY**
NIH 11176 has affinity for all three opioid receptors with no selectivity.

**NIH 11177**  
(+)-(1S,5S,9S)-5,9-Dimethyl-2-(1,3-dioxalanylethyl)-2’-hydroxy-6,7-benzomorphan.HCl

**OPIOID RECEPTOR BINDING (nM)**
- **µ-receptor**: 673 ± 95
- **δ-receptor**: 8734 ± 2570
- **κ-receptor**: 642 ± 70

**SUMMARY**
NIH 11177 has low, but equivalent, affinity for µ and κ opioid receptors and very low affinity for δ opioid receptors.
NIH 11178  
(+)-(1S,5S,9S)- 5,9-Dimethyl-2’-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl

**OPIOID RECEPTOR BINDING (nM)**

- μ-receptor: 613 ± 163
- δ-receptor: 6072 ± 4320
- κ-receptor: 260 ± 83

**SUMMARY**

NIH 11178 has low affinity for μ and κ opioid receptors. It has very low affinity for δ opioid receptors.

***

NIH 11179  
(-)-(1R,5R,9R)- 5,9-Dimethyl-2’-hydroxy-2-(4-methylpentyl)-6,7-benzomorphan.HCl

**OPIOID RECEPTOR BINDING (nM)**

- μ-receptor: 6.0 ± 1.2
- δ-receptor: 59. ± 5.1
- κ-receptor: 7.3 ± 2.2

**SUMMARY**

NIH 11179 has high affinity for μ and κ opioid receptors, with 8- to 10-fold selectivity for these receptors over δ.

***

NIH 11180  
(-)-(1R,5R,9R)- 2-(3-Acetoxypropyl)-5,9-dimethyl-2’-hydroxy-6,7-benzomorphan.oxalate

**OPIOID RECEPTOR BINDING (nM)**

- μ-receptor: 33.7 ± 1.8
- δ-receptor: 285 ± 14
- κ-receptor: 24.9 ± 3.7

**SUMMARY**

NIH 11180 has similar affinity for μ and κ opioid receptors with approximately 10-fold selectivity for these receptors over δ.
NIH 11181  
(+)-(1S,5S,9S)-2-(3-Acetoxypropyl)-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan.oxalate

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 4478 ± 358  
δ-receptor: 5% inhibition at 10 µM  
κ-receptor: 4141 ± 778

**SUMMARY**

NIH 11181 has similar, very low affinity for μ and κ opioid receptors with no affinity for δ receptors.

* * *

NIH 11182  
(+)-(1S,5S,9S)-2-(3-Acetoxyethyl)-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan.oxalate

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 1951 ± 198  
δ-receptor: 22% inhibition at 10 µM  
κ-receptor: 1830 ± 269

**SUMMARY**

NIH 11182 has similar, very low affinity for μ and κ opioid receptors. It shows no appreciable binding to δ receptors.

* * *

NIH 11183  
(-)-(1R,5R,9R)-2-(3-Acetoxyethyl)-5,9-dimethyl-2′-hydroxy-6,7-benzomorphan.oxalate

**OPIOID RECEPTOR BINDING (nM)**

μ-receptor: 42.6 ± 6.9  
δ-receptor: 421 ± 41  
κ-receptor: 60.1 ± 17

**SUMMARY**

NIH 11183 has similar affinity for μ and κ opioid receptors, with low affinity for δ receptors.
NIH 11185  \((-)-(1R,5R,9R)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2’-hydroxy-6,7-benzomorphan.HCl\)

**OPIOID RECEPTOR BINDING (nM)**

- \(\mu\)-receptor: 4.3 ± 0.8
- \(\delta\)-receptor: 42.8 ± 5.1
- \(\kappa\)-receptor: 51.0 ± 15.5

**SUMMARY**

NIH 11185 has high affinity for \(\mu\) opioid receptors and is 10- to 12-fold selective over \(\delta\) and \(\kappa\) receptors.

* * *  

NIH 11186  \((+)-(1S,5S,9S)-2-(2-Cyclohexylethyl)-5,9-dimethyl-2’-hydroxy-6,7-benzomorphan.HCl\)

**OPIOID RECEPTOR BINDING (nM)**

- \(\mu\)-receptor: 142 ± 10.5
- \(\delta\)-receptor: 2793 ± 430
- \(\kappa\)-receptor: 215 ± 246

**SUMMARY**

NIH 11186 has similar, low affinity for \(\mu\) and \(\kappa\) opioid receptors and very low affinity for \(\delta\) receptors and very low affinity for \(\delta\) receptors.

* * *  

NIH 11187  \((-)-(1R,5R,9R)-2-(2-Ethylbutyl)-5,9-dimethyl-2’-hydroxy-6,7-benzomorphan.HCl\)

**OPIOID RECEPTOR BINDING (nM)**

- \(\mu\)-receptor: 9.2 ± 0.8
- \(\delta\)-receptor: 58.2 ± 4.7
- \(\kappa\)-receptor: 5.9 ± 0.3

**SUMMARY**

NIH 11187 has high affinity for \(\mu\) and \(\kappa\) opioid receptors and low affinity for \(\delta\) receptors. It has no selectivity between \(\mu\) and \(\kappa\).
REFERENCES


ACKNOWLEDGMENTS

This research was supported, in part, by the College on Problems of Drug Dependence and the USPHS Grant DA-00254.

***

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 \( \kappa \) agonist ethylketazocine (EKC); a second group discriminates the \( \mu \) 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 15 min and consists of an initial 10-min blackout 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 100 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 responding on the drug-appropriate 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 with each cycle. 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
The effects of test compounds on ventilatory function are studied in rhesus monkeys breathing air or 5% CO₂ in air (France and Woods, 1990; Howell et al., 1988). Monkeys are restrained at the neck and waist while seated in a primate chair. 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 naltrexone 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 °C, 50 °C, 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 different temperatures. The interinjection 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.
Plexiglas primate chair. Normal air or 5% CO₂ in air is delivered at a rate of 10 l/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 (VT) in ml/inspiration. Data are recorded continuously during 23-minute exposures to air alternating with 7-minute exposures to CO₂. The last 3 minutes of exposure to CO₂ 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).