DRUG EVALUATION COMMITTEE REPORT ON: EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (2007)

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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 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**
11107	21 November 2003	11296	2 March 2006
11116	4 August 2006	11303	29 November 2005
11121	4 August 2006	11304	2 March 2006
11199	2 April 2004	11305	2 March 2006
11200	2 April 2004	11306	2 March 2006
11201	2 April 2004	11307	15 August 2006
11202	2 April 2004	11308	15 August 2006
11203	2 April 2004	11309	15 August 2006
11204	2 April 2004	11312	15 August 2006
11205	2 April 2004	11313	15 August 2006
11206	2 April 2004	11314	15 August 2006
11207	2 April 2004	11315	15 August 2006
11208	2 April 2004	11316	15 August 2006
11209	24 December 2003	11317	15 August 2006
11210	24 December 2003	11318	15 August 2006
11211	19 September 2005	11319	15 August 2006
11213	4 August 2006	11325	15 August 2006
11221	10 November 2004	11326	15 August 2006
11222	10 November 2004	11327	15 August 2006
11223	10 November 2004	11328	15 August 2006
11224	10 November 2004	11329	15 August 2006
11225	10 November 2004	11330	15 August 2006
11226	10 November 2004	11331	15 August 2006

NIH #	DATE SUBMITTED TO BIOLOGICAL COORDINATOR	NIH #	DATE SUBMITTED TO BIOLOGICAL COORDINATOR
11227	10 November 2004	11332	15 August 2006
11238	10 November 2004	11333	15 August 2006
11239	8 March 2005	11334	15 August 2006
11240	8 March 2005	11335	18 October 2006
11241	8 March 2005	11345	18 October 2006
11242	8 March 2005	11346	18 October 2006
11243	8 March 2005	11347	15 December 2006
11244	8 March 2005	11348	15 December 2006
11245	8 March 2005	11349	15 December 2006
11292	2 March 2006	11350	15 December 2006
11293	2 March 2006	11352	15 December 2006
11294	2 March 2006	11353	15 December 2006
11295	2 March 2006		

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 10μM 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)

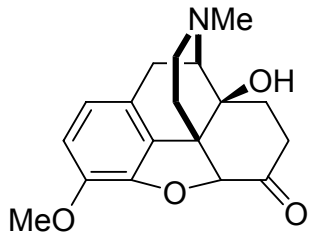
DPDPE (60%) and bremazocine (86%) are partial agonists compared with the standards SNC80 and U69593. Morphine and DAMGO give equivalent responses.

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.

One compound assessed in rhesus monkeys was made available for release this year (NIH 11211). It appears at the end of this report. A detailed description of this and other assays available to submitters is included in the reference list.

NIH 11107 Oxycodone.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 485 ± 134
δ-receptor: >3000
κ-receptor: > 3000

OPIOID RECEPTOR BINDING (nM): Phosphate buffer*

μ-receptor: 207 ± 12.8
δ-receptor: 45 ± 3% inhibition at 10 μM
κ-receptor: 19 ± 5 % inhibition at 10 μM

*These studies were performed in phosphate buffered solutions (pH 7.4) as requested by the submitter.
[NOTE: These studies were performed in parallel with studies on NIH 11198 as requested by the submitter.]

GTPγS ASSAY:
μ-receptor: 88.2 + 3.3 % maximal stimulation; EC_{50} = 605 ± 82.6

GTPγS ASSAY: Phosphate buffer*

μ-receptor: 97.0 ± 1.9 % maximal stimulation; EC_{50} = 854 ± 147
δ-receptor: Not done
κ-receptor: Not done

*These studies were performed in phosphate buffer at pH 7.4 as requested by the submitter.

SUMMARY

NIH 11107 has low affinity for μ opioid receptors in the phosphate buffer. It has no appreciable affinity for the δ or κ receptor. NIH 11107 is an efficacious μ agonist of low potency.

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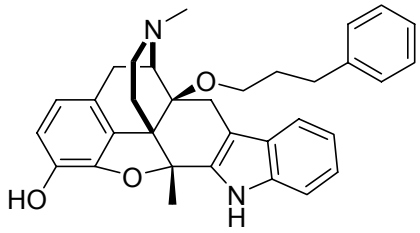
NIH 11116 4,5α-epoxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]indolo[2',3':6,7]-morphinan-3-ol



GTPγS ASSAY (nM)

μ-receptor: 86 ± 2 % of maximal stimulation EC_{50} = 229 ± 78
δ-receptor: 37 ± 3 % of maximal stimulation: EC_{50} = 3.5 ± 1.3
κ-receptor: 42 ± 3 % of maximal stimulation; EC_{50} = 39 ± 8

SUMMARY

NIH 11116 is a full agonist with low potency at the μ opioid receptor, a low efficacy partial agonist with high potency at the δ opioid receptor, and a partial agonist with potency at the κ opioid receptor. Binding and behavioral data on this compound are available in the 2005 Annual Report (NIDA Monograph 186).

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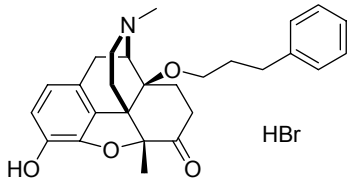
NIH 11121 4,5α-epoxy-3-hydroxy-5β,17-dimethyl-14β-[(3-phenylpropyl)oxy]morphinan-6-one.HBr



OPIOID RECEPTOR BINDING (nM)

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

GTPγS ASSAY (nM)

μ-receptor: 104 ± 2 % of max; EC_{50} = 0.06 ± 0.02
δ-receptor: 52 ± 5 % of max; EC_{50} = 2.6 ± 0.9
κ-receptor: not requested

SUMMARY

NIH 11121 has extremely high affinity for μ and κ receptors with very high affinity for δ receptors. It is a full agonist with extremely high potency at the μ opioid receptor and a partial agonist with high potency at the δ opioid receptor. Behavioral data on this compound are in the 2005 Annual Report (NIDA Monograph 186)

[Note: This compound is extremely "sticky" and difficult to work with.]

* * *

NIH 11199 Acetyl-Arg-Phe(4-COOH)-Tyr-Arg-Trp-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 2770 ± 281
δ-receptor: 2024 ± 374
κ-receptor: 30 ± 7.5% inhibition at 10 μM

SUMMARY

NIH 11199 has very low affinity for opioid receptors.

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

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NIH 11200 Acetyl-Arg-Phe(4-F)-Tyr-Arg-Trp-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 744 ± 106
δ-receptor: 41 ± 1.0% inhibition at 10 μM
κ-receptor: 715 ± 324

SUMMARY

NIH 11200 has low affinity for μ and κ opioid receptors and no appreciable affinity for δ receptors.

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

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NIH 11201 Acetyl-Arg-Phe(4-OCH_3)-Tyr-Arg-Trp-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 674 ± 80
δ-receptor: 42 ± 6.0 inhibition at 10 μM
κ-receptor: 1037 ± 485

SUMMARY

NIH 11201 has low affinity for μ and κ opioid receptors and no appreciable affinity for δ receptors.

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

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NIH 11202 Acetyl-Arg-Phe(4-CN)-Tyr-Arg-Trp-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1472 ± 484
δ-receptor: 32 ± 3.5% inhibition at 10 μM
κ-receptor: 986 ± 499

SUMMARY

NIH 11202 has low affinity for μ and κ opioid receptors and no appreciably affinity for δ receptors.

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

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NIH 11203 Acetyl-Arg-Tyr-Tyr-Arg-Trp(5-CN)-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 266 ± 115
δ-receptor: 41 ± 4.5% inhibition at 10 μM
κ-receptor: 1446 ± 657

SUMMARY

NIH 11203 has low affinity for μ, very low affinity for κ and no appreciable affinity for δ receptors.

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

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NIH 11204 Acetyl-Arg-Tyr-Phe(4-F)-Arg-Trp-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 189 ± 87
δ-receptor: 5898 ± 845
κ-receptor: 773 ± 38

SUMMARY

NIH 11204 has low affinity for μ and κ receptors and very low affinity for δ receptors.

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM and captopril (10 μM).]

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NIH 11205 Acetyl-Arg-Tyr-Phe(4-NHAc)-Arg-Trp-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 467 ± 109
δ-receptor: 49 ± 1.0% inhibition at 10 μM
κ-receptor: 1215 ± 560

SUMMARY

NIH 11205 has low affinity for μ, very low affinity for κ and no appreciable affinity for δ receptors.,

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM and captopril (10 μM).]

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NIH 11206 Acetyl-Arg-Tyr(3-Cl)-Tyr-Arg-Trp-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 597 ± 121
δ-receptor: 45 ± 6.0% inhibition at 10 μM
κ-receptor: 2745 ± 1633

SUMMARY

NIH 11206 has low affinity for μ, very low affinity for κ and no appreciable affinity for δ receptors.

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM and captopril (10 μM).]

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NIH 11207 Acetyl-Arg-Tyr-Phe(4-benzyl)-Arg-Trp-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 223 ± 19
δ-receptor: 5901 ± 540
κ-receptor: 570 ± 36

SUMMARY

NIH 11207 has low affinity for μ and κ receptors with very low affinity for δ receptors.

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM and captopril (10 μM).]

NIH 11208 Heptanoyl-Arg-Tyr-Phe-Arg-Trp-Arg-NH_2

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 107 ± 36
δ-receptor: 3349 ± 214
κ-receptor: 127 ± 7

SUMMARY

NIH 11208 has equivalent affinity for μ and κ receptors with very low affinity for δ receptors.

[Note: These assays were performed in the presence of a peptidase inhibitor cocktail of bestatin (10 μM), thiorphan (0.3 μM) and captopril (10 μM).]

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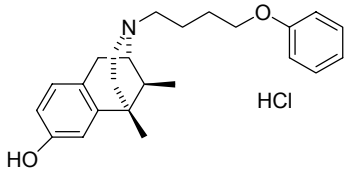
NIH 11209 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl



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.

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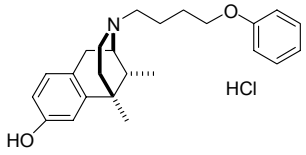
NIH 11210 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(4-phenoxybutyl)-6,7-benzomorphan.HCl



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.

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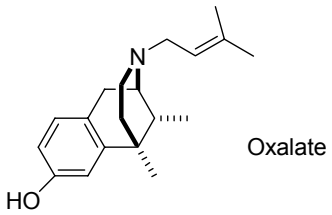
NIH 11213 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-methyl-2-butenyl)-6,7-benzomorphan .oxalate



OPIOID RECEPTOR BINDING (nM)

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

GTPγS ASSAY (nM)

μ-receptor: 4.4 ± 0.9 % of max; EC_{50} = not available
δ-receptor: 8.7 ± 3.3 % of max; EC_{50} = not available
κ-receptor: 37 ± 6 % of max; EC_{50} = 34 ± 10

SUMMARY

NIH 11213 has high affinity for μ = κ receptors and has approximately 15-fold less affinity for δ receptors. It is a low efficacy partial agonist with potency at the κ opioid receptor and has no effect at the μ and δ opioid receptors, suggesting
μ and δ antagonism. Behavioral data on this compound are available in the 2005 Annual Report (NIDA Monograph 186).

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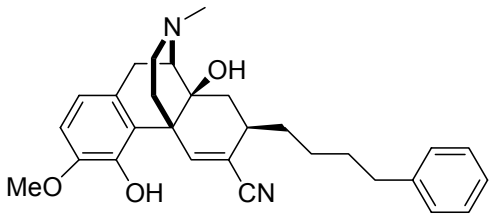
NIH 11221 5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(4-phenylbutyl)-morphinan-6-carbonitrile



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 7.0 ± 3.1
δ-receptor: 120 ± 30
κ-receptor: 1461 ± 390

SUMMARY

NIH 11211 has high affinity for μ opioid receptors > δ opioid receptors with approximately 15-fold selectivity. It has very low affinity for κ opioid receptors.

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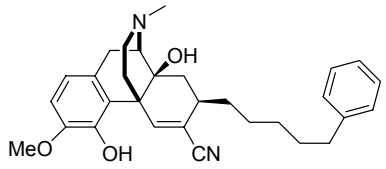
NIH 11222 5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(5-phenylpentyl)-morphinan-6-carbonitrile



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.63 ± 0.12
δ-receptor: 77.8 ± 17.0
κ-receptor: 506 ± 109

SUMMARY

NIH 11222 has very high affinity for μ opioid receptors. It is 120-fold selective for μ over δ receptors and 800-fold selective for μ over κ receptors.

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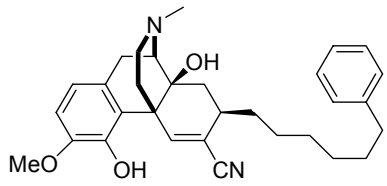
NIH 11223 5,6-Didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-7β-(6-phenylhexyl)-morphinan-6-carbonitrile



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.32 ± 0.11
δ-receptor: 135 ± 22
κ-receptor: 566 ± 192

SUMMARY

NIH 11223 has very high affinity for μ opioid receptors. It is 120-fold selective for μ over δ receptors and 800-fold selective for μ over κ receptors.

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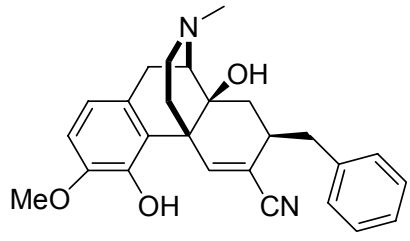
NIH 11224 7β-Benzyl-5,6-didehydro-4,14β-dihydroxy-3-methoxy-17-methyl-morphinan-6-carbonitrile



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1515 ± 240
δ-receptor: 86.8 ± 6.6
κ-receptor: 2015 ± 289

NIH 11224 (continued)

SUMMARY

NIH 11224 has affinity for δ opioid receptors with 17-fold selectivity over μ. It has very low affinity for μ and κ opioid receptors.

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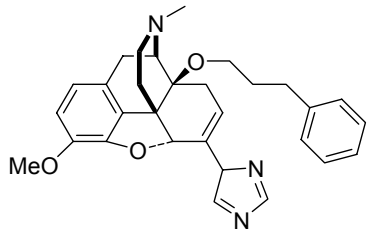
NIH 11225 6,7-Didehydro-4,5-epoxy-6-idimazolyl-3-methoxy-17-methyl-14-(3-phenylpropyloxy)morphinan



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.96 ± 0.41
δ-receptor: 1.34 ± 0.34
κ-receptor: 0.42 ± 0.09

SUMMARY

NIH 11225 has very high affinity for μ, δ, and κ opioid receptors.

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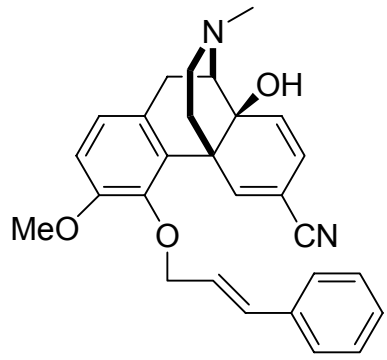
NIH 11226 4-Cinnamyloxy-5,6,7,8-tetradehydro-14β-hydroxy-3-methoxy-17-methylmorphinan-6-carbonitrile



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.83 ± 0.24
δ-receptor: 462 ± 154
κ-receptor: 1150 ± 257

NIH 11226 (continued)

SUMMARY

NIH 11226 has very high affinity for μ and low affinity for δ and κ opioid receptors with over 500-fold selectivity for μ over δ or κ opioid receptors.

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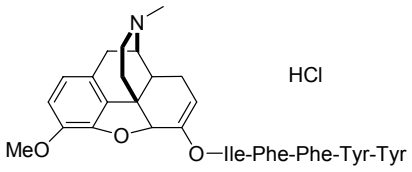
NIH 11227 Tyr-Tyr-Phe-Phe-Ile-(6-O)-hydrocodone.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor:	51.9 ± 3.6
δ-receptor:	80.2 ± 25.4
κ-receptor:	351 ± 114

SUMMARY

NIH 11227 has affinity for μ ≥ δ > κ opioid receptors.

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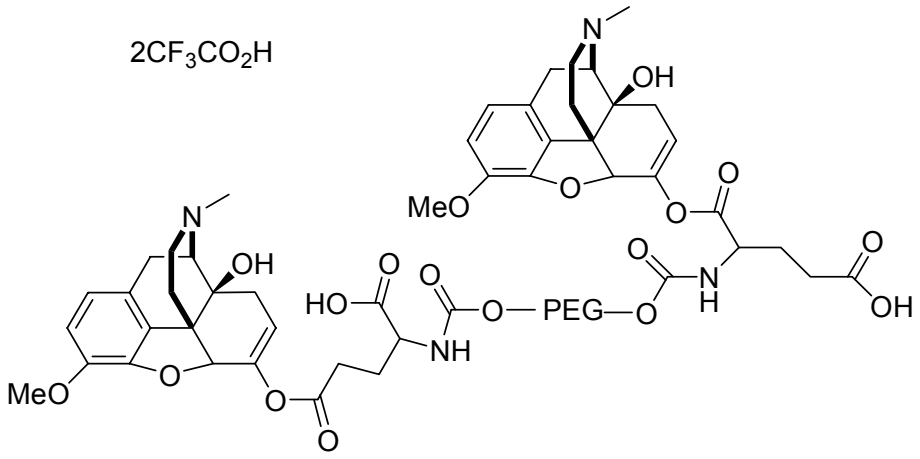
NIH 11238 Oxycodone-enol ether prodrug. .2Trifluroacetate



NIH 11238 (continued)

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 456 ± 187
δ-receptor: 7410 ± 590 (n=2)
κ-receptor: 7100 ± 890 (n=2)

GTPγS ASSAY

μ-receptor: 12 ± 6% of maximal stimulation; EC_{50} not available
δ-receptor: not done
κ-receptor: not done

SUMMARY

NIH 11238 has low affinity for μ opioid receptors and very low affinity for δ and κ opioid receptors. It has very little measurable agonist effect at the μ opioid receptor.

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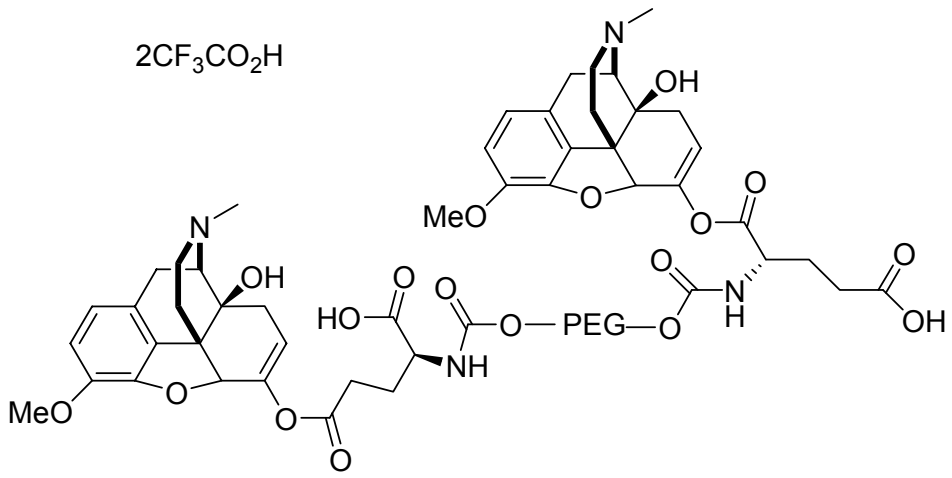
NIH 11239 Oxycodone-enol ether prodrug. .2Trifluroacetate



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 443 ± 56
δ-receptor: 6530 ± 710
κ-receptor: 7760 ± 770 (n=2)

GTPγS ASSAY (nM)

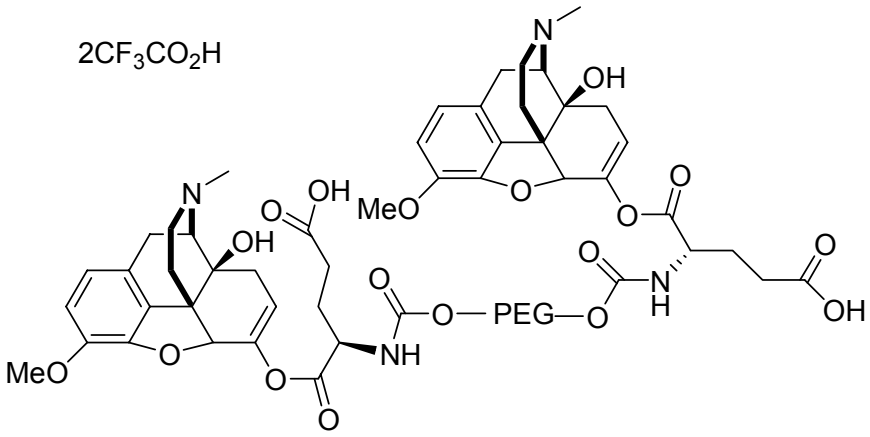
μ-receptor: <5% of maximal stimulation; EC_{50} not available
δ-receptor: not done
κ-receptor: not done

SUMMARY

NIH 11239 has no measurable agonist effect at the μ opioid receptor. It has low affinity for μ opioid receptors and very low affinity for δ and κ opioid receptors.

* * *

NIH 11240 Oxycodone-enol ether prodrug. .2Trifluroacetate



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 512 ± 92
δ-receptor: 7500 ± 20 (n=2)
κ-receptor: 6420 ± 750 (n=2)

GTPγS ASSAY (nM)

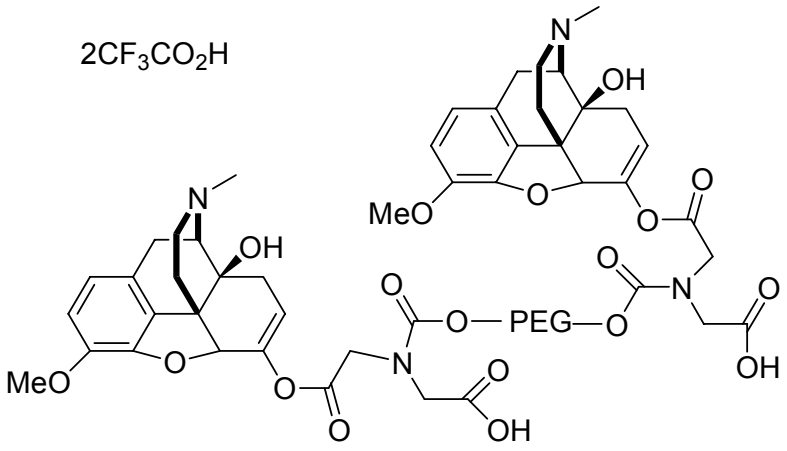
μ-receptor: <5% of maximal stimulation; EC_{50} not available
δ-receptor: not done
κ-receptor: not done

SUMMARY

NIH 11240 has no measurable agonist effect at the μ opioid receptor. It has low affinity for μ opioid receptors and very low affinity for δ and κ opioid receptors.

* * *

NIH 11241 Oxycodone-enol ether prodrug. .2Trifluroacetate



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 381 ± 32
δ-receptor: 5470 ± 300 (n=2)
κ-receptor: 25 ± 8% inhibition at 10 μM

GTPγS ASSAY (nM)

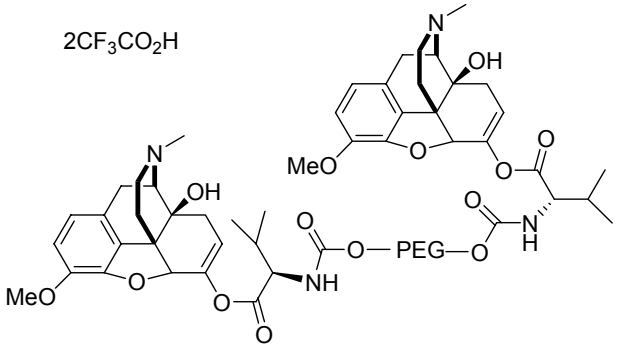
μ-receptor: <5% of maximal stimulation; EC_{50} not available
δ-receptor: not done due to very low binding
κ-receptor: not done due to very low binding

SUMMARY

NIH 11240 has no measurable agonist effect at the μ opioid receptor. It has low affinity for μ opioid receptors, very low affinity for δ opioid receptors and no affinity for κ opioid receptors.

* * *

NIH 11242 Oxycodone-enol ether prodrug. .2Trifluroacetate



NIH 11242 (continued)

OPIOID RECEPTOR BINDING (nM)

μ-receptor: 1290 ± 200
δ-receptor: 1110 ± 160
κ-receptor: 6820 ± 2140 (n=2)

GTPγS ASSAY (nM)

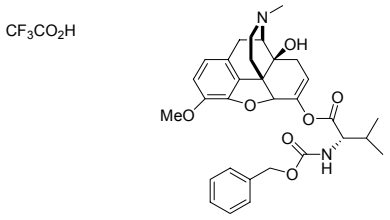
μ-receptor: not done due to very low binding affinity
δ-receptor: not done due to very low binding affinity
κ-receptor: not done due to very low binding affinity

SUMMARY

NIH 11242 was not evaluated for agonist activity due to very low receptor binding affinity at each of the opioid receptors. It had very low affinity for μ, δ, and κ opioid receptors.

* * *

NIH 11243 Oxycodone-enol ether/valine prodrug. .Trifluroacetate



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 169 ± 11
δ-receptor: 25.8 ± 6.1
κ-receptor: 4260 ± 550

GTPγS ASSAY (nM)

μ-receptor: <10% of maximal stimulation; EC_{50} not available
δ-receptor: 37 ± 8% of maximal stimulation; EC_{50} = 1620 ± 540
κ-receptor: not done

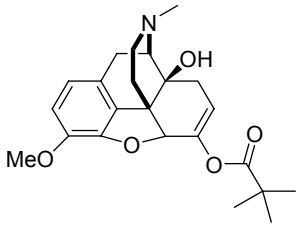
SUMMARY

NIH 11243 has an affinity for δ opioid receptors with 6.5-fold selectivity over μ opioid receptors, and 165-fold selectivity over κ opioid receptors. It has no measurable effect at the μ opioid receptor and is a weak partial agonist with very low potency at the δ opioid receptor. Activity at the κ opioid receptor was not evaluated.

* * *

NIH 11244 6-O-(2,2,2-trimethylacetyl)oxycodone-enol ether. HCl

HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 51.6 ± 6.7
δ-receptor: 163 ± 33
κ-receptor: 7930 ± 870

GTPS ASSAY (nM)

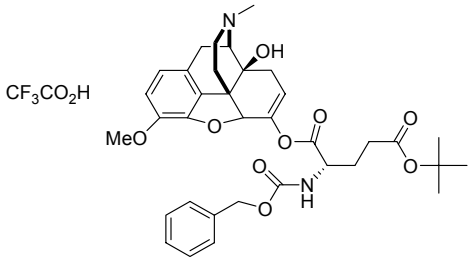
μ-receptor: 56 ± 10% of maximal stimulation: EC_{50} = 1820 140
δ-receptor: 30 ± 5% of maximal stimulation: EC_{50} = 2900 1300
κ-receptor: not done due to very low binding affinity

SUMMARY

NIH 11244 It has affinity for μ > δ >> κ opioid receptors. It is a partial agonist with very low potency at the μ opioid receptor and a weak partial agonist with very low potency at the δ opioid receptor. Activity at the κ opioid receptor was not evaluated.

* * *

NIH 11245 Oxycodone-enol ether prodrug. .Trifluroacetate



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 238 ± 28
δ-receptor: 190 ± 25
κ-receptor: 1720 ± 280

GTPγS ASSAY (nM)

μ-receptor: <10% of maximal stimulation: EC_{50} not available
δ-receptor: 17 ± 7% of maximal stimulation: EC_{50} not available
κ-receptor: not done

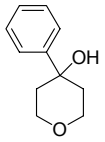
NIH 11245 (continued)

SUMMARY

NIH 11245 has low affinity for μ and δ receptors and very low affinity for κ opioid receptors. It is a very weak partial agonist at the δ opioid receptor and has no measurable agonist effect at the μ opioid receptor. Activity at the κ opioid receptor was not evaluated.

* * *

NIH 11292 4-Phenyltetrahydro-2*H*-pyran-4-ol



OPIOID RECEPTOR BINDING (nM)

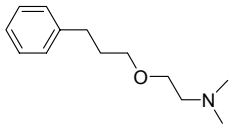
μ-receptor: 11% inhibition at 10 μM
δ-receptor: 26% inhibition at 10 μM
κ-receptor: 15% inhibition at 10 μM

SUMMARY

NIH 11292 has no affinity for μ, δ, or κ opioid receptors.

* * *

NIH 11293 *N,N*-Dimethyl-2-(3-phenylpropoxy)ethylamine



OPIOID RECEPTOR BINDING (nM)

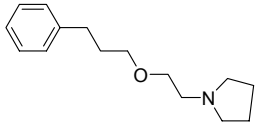
μ-receptor: 23% inhibition at 10 μM
δ-receptor: 25% inhibition at 10 μM
κ-receptor: 18% inhibition at 10 μM

SUMMARY

NIH 11293 has no affinity for μ, δ, or κ opioid receptors.

* * *

NIH 11294 1-(2-[3-phenylpropoxy]ethyl)pyrrolidine



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3120 ± 430
δ-receptor: 29% inhibition at 10 μM
κ-receptor: 13% inhibition at 10 μM

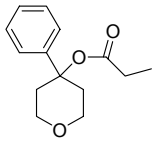
NIH 11294 (continued)

SUMMARY

NIH 11294 has very low affinity at the μ opioid receptor and no affinity at δ or κ opioid receptors.

* * *

NIH 11296 4-Phenyltetrahydro-2*H*-pyran-4-yl propionate



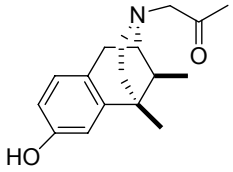
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 14% inhibition at 10 μM
δ-receptor: 24% inhibition at 10 μM
κ-receptor: 3% inhibition at 10 μM

SUMMARY

NIH 11296 has no affinity at μ, δ, or κ opioid receptors.

NIH 11304 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

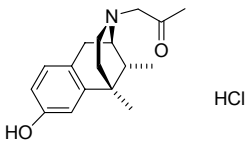
μ-receptor: 6300 ± 980
δ-receptor: 24% inhibition at 10 μM
κ-receptor: 21% inhibition at 10 μM

SUMMARY

NIH 11304 has very low affinity at the μ opioid receptor and no affinity at δ or κ opioid receptors.

* * *

NIH 11305 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxopropyl)-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 77.2 ± 30.7
δ-receptor: 893 ± 151
κ-receptor: 121 ± 9

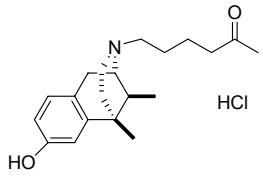
NIH 11305 (continued)

SUMMARY

NIH 11305 has affinity at the μ opioid receptor, with similar affinity at the κ opioid receptor but and low affinity at the δ opioid receptor.

* * *

NIH 11306 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

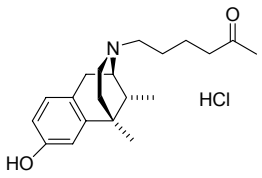
μ-receptor: 3360 ± 760
δ-receptor: 14% inhibition at 10 μM
κ-receptor: 5110 ± 1390

SUMMARY

NIH 11306 has very low affinity at the μ and κ opioid receptors and no affinity at the δ opioid receptor.

* * *

NIH 11307 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(5-oxohexyl)-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

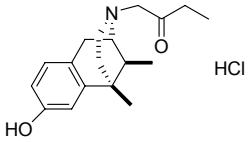
μ-receptor: 21.0 ± 1.5
δ-receptor: 372 ± 24
κ-receptor: 140 ± 40

SUMMARY

NIH 11307 has affinity at μ opioid receptors and low affinity at the δ and κ opioid receptors. The compound is 7 fold selective for μ over δ and 18-fold selective for μ over δ

* * *

NIH 11308 (+)-(1*S*,9*S*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

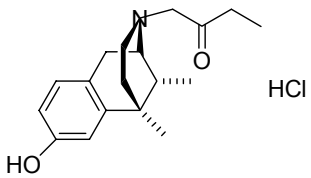
μ-receptor: 15% inhibition at 10 μM
δ-receptor: 28% inhibition at 10 μM
κ-receptor: 9490 ± 3900

SUMMARY

NIH 11308 has very low affinity at the κ opioid receptor and no affinity at δ or μ opioid receptors.

* * *

NIH 11309 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(2-oxobutyl)-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

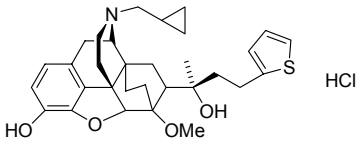
μ-receptor: 71.5 ± 11
δ-receptor: 848 ± 56
κ-receptor: 71.1 ± 10

SUMMARY

NIH 11309 has equal affinity at the μ and κ opioid receptors and low affinity at δ opioid receptors.

* * *

NIH 11310 Thienorphine.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 0.22 ± 0.07
δ-receptor: 0.69 ± 0.03
κ-receptor: 0.14 ± 0.06

GTPγS ASSAY (nM)

μ-receptor 19 ± 4 % of maximal stimulation; EC_{50} = 1.9 ± 0.4
δ-receptor: 2 ± 2 % of maximal stimulation; EC_{50} = not available
κ-receptor: 75 ± 5 % of maximal stimulation; EC_{50} = 0.3 ± 0.2

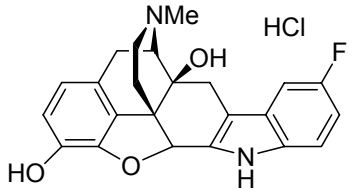
NIH 11310 (continued)

SUMMARY

NIH 11310 has very high affinity at μ, δ and κ opioid receptors. It is a partial agonist with very high potency at the κ opioid receptor and a very low efficacy partial agonist with high potency at the μ opioid receptor. NIH 11310 has no effect at the δ opioid receptor.

* * *

NIH 11312 5'-Fluorooxymorphindole.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 21.4 ± 4.7
δ-receptor: 2.3 ± 0.1
κ-receptor: 307 ± 43

GTPγS ASSAY (nM)

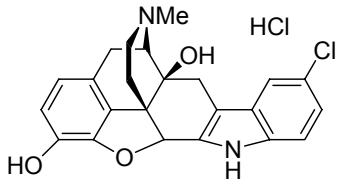
μ-receptor 24 ± 4 % of maximal stimulation; EC_{50} = 1730 ± 1080
δ-receptor: 16 ± 1 % of maximal stimulation; EC_{50} = 16 ± 10
κ-receptor: not determined

SUMMARY

NIH 11312 has high affinity at the δ opioid receptor with 9-fold selectivity over μ and 130-fold selectivity over κ opioid receptors. NIH 11312 is a low efficacy partial agonist with very low potency at the μ opioid receptor, and a very low efficacy partial agonist with potency at the δ opioid receptor (100x more potent at δ than μ).

* * *

NIH 11313 5'-Chlorooxymorphindole.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 46.6 ± 9.9
δ-receptor: 5.1 ± 1.2
κ-receptor: 361 ± 36

GTPγS ASSAY (nM)

μ-receptor: 25 ± 1 % of maximal stimulation; EC_{50} = 630 ± 120
δ-receptor: 9 ± 2 % of maximal stimulation; EC_{50} = 20 ± 4

κ-receptor: not determined

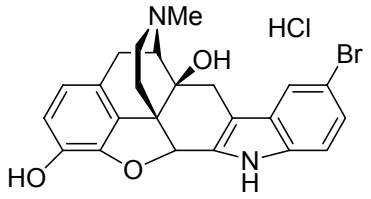
NIH 11313 (continued)

SUMMARY

NIH 11313 has high affinity at the δ opioid receptor with 9-fold selectivity over μ and 70-fold selectivity over κ opioid receptors. It is a low efficacy partial agonist at the μ opioid receptor and a very low efficacy partial agonist at the δ opioid receptor and is 30 times more potent at the δ opioid receptor than at the μ opioid receptor.

* * *

NIH 11314 5'-Brorooxymorphindole.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 71.2 ± 22.6
δ-receptor: 8.6 ± 0.4
κ-receptor: 253 ± 45

GTPγS ASSAY

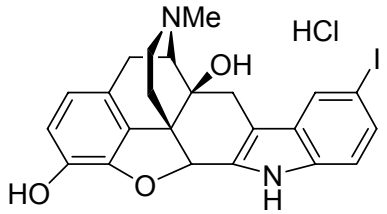
μ-receptor: 25 ± 1 % of maximal stimulation; EC_{50} = 770 ± 200
δ-receptor: 12 ± 2 % of maximal stimulation: EC_{50} = 13 ± 6
κ-receptor: not done

SUMMARY

NIH 11314 has high affinity at the δ opioid receptor with 8-fold selectivity over μ and 29-fold selectivity over the κ opioid receptor. The compound is a low efficacy partial agonist at the μ opioid receptor and a very low efficacy partial agonist at the δ opioid receptor and is 60 times more potent at the δ opioid receptor than at the μ opioid receptor.

* * *

NIH 11315 5'-Iodooxymorphindole.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 65.5 ± 12.6
δ-receptor: 3.8 ± 0.3
κ-receptor: 161 ± 46

NIH 11315 (continued)

GTPγS ASSAY (nM)

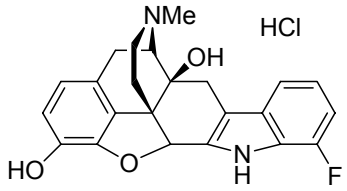
μ-receptor: 25 ± 2 % of maximal stimulation: EC_{50} = 430 ± 180
δ-receptor: 14 ± 2 % of maximal stimulation: EC_{50} = 19 ± 1
κ-receptor: not determined

SUMMARY

NIH 11315 has high affinity at the δ opioid receptor with at least 17-fold selectivity over μ and κ opioid receptors. It is a low efficacy partial agonist at the μ opioid receptor and a very low efficacy partial agonist at the δ opioid receptor and is 20 times more potent at the δ opioid receptor than at the μ opioid receptor.

* * *

NIH 11316 7'-Fluorooxymorphindole.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 65.0 ± 13.1
δ-receptor: 0.5 ± 0.2
κ-receptor: 271 ± 50

GTPγS ASSAY (nM)

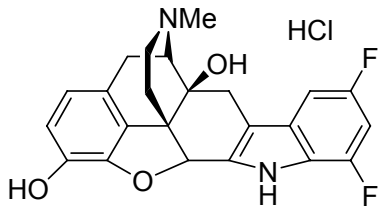
μ-receptor: 11 ± 3 % of maximal stimulation: EC_{50} = 560 ± 200
δ-receptor: 10 ± 5 % of maximal stimulation: EC_{50} = not determined
κ-receptor: not determined

SUMMARY

NIH 11316 has very high affinity at the δ opioid receptor with at least 130-fold selectivity over μ and κ opioid receptors. NIH 11316 is likely to be a high affinity selective δ-antagonist.

* * *

NIH 11317 5',7'-Difluorooxymorphindole.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 58.5 ± 3.8
δ-receptor: 1.1 ± 0.3
κ-receptor: 207 ± 44

NIH 11317 (continued)

GTPγS ASSAY (nM)

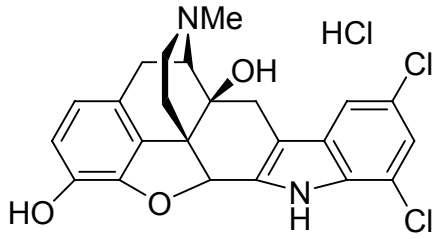
μ-receptor: 24 ± 4 % of maximal stimulation: EC_{50} = 440 ± 100
δ-receptor: 13 ± 3 % of maximal stimulation: EC_{50} = 19 ± 7
κ-receptor: not determined

SUMMARY

NIH 11317 has high affinity at the δ opioid receptor with at least 53 fold selectivity over μ and κ opioid receptors. The compound is a low efficacy partial agonist at the μ opioid receptor and a very low efficacy partial agonist at the δ opioid receptor and is 20 times more potent at the δ opioid receptor than at the μ opioid receptor.

* * *

NIH 11318 5',7'-Dichlorooxymorphindole.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 28.9 ± 4.6
δ-receptor: 6.7 ± 1.1
κ-receptor: 380 ± 45

GTPγS ASSAY (nM)

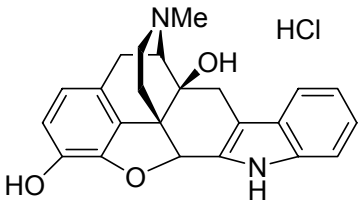
μ-receptor 67 ± 8 % of maximal stimulation; EC_{50} = 416 ± 106
δ-receptor: 24 ± 6 % of maximal stimulation; EC_{50} = 29 ± 14
κ-receptor: not determined

SUMMARY

NIH 11318 has high affinity at the δ opioid receptor with 4 fold selectivity over μ and 57 fold selectivity over κ opioid receptors. The compound is a partial agonist with low potency at the μ opioid receptor and a low efficacy partial agonist with potency at the δ opioid receptor (14x more potent at δ than μ).

* * *

NIH 11319 Oxymorphindole.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 105 ± 23
δ-receptor: 0.9 ± 0.2
κ-receptor: 515 ± 35

GTPγS ASSAY (nM)

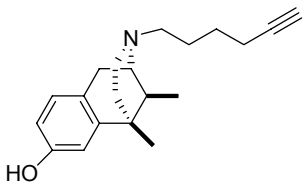
μ-receptor: 19 ± 1 % of maximal stimulation: EC_{50} = 560 ± 100
δ-receptor: 17 ± 3 % of maximal stimulation: EC_{50} = 16 ± 6
κ-receptor: not determined

SUMMARY

NIH 11319 has very high affinity at the delta opioid receptor with at least 117 fold selectivity over mu and kappa opioid receptors. NIH 11319 is a very low efficacy partial agonist at the mu and delta opioid receptors and is 35 times more potent at the delta opioid receptor than at the mu opioid receptor.

* * *

NIH 11323 (+)-(1S,5S,9S)-5,9-Dimethyl-2-(5-hexynyl)-2'-hydroxy-6,7-benzomorphan



OPIOID RECEPTOR BINDING (nM)

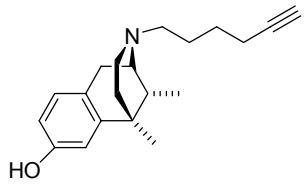
μ-receptor: 632 ± 40
δ-receptor: 13200 ± 4600
κ-receptor: 239 ± 2

SUMMARY

NIH 11323 has low affinity at the μ and κ opioid receptors and very low affinity at the δ opioid receptor.

* * *

NIH 11324 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(5-hexynyl)-2'-hydroxy-6,7-benzomorphan



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 4.3 ± 1.1
δ-receptor: 54.5 ± 16.9
κ-receptor: 7.5 ± 0.4

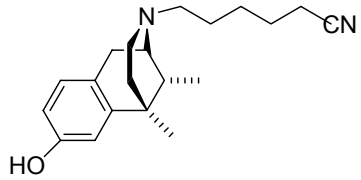
SUMMARY

NIH 11324 has high affinity at the mu and kappa opioid receptors and affinity at the delta opioid receptor.

* * *

NIH 11325 (-)-(1R,5R,9R)-5,9-Dimethyl-2-(5-cyanopentyl)-2'-hydroxy-6,7-benzomorphan

OPIOID RECEPTOR BINDING (nM)

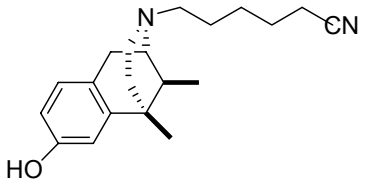


μ-receptor: 16.8 ± 2.2
δ-receptor: 212 ± 60
κ-receptor: 8.1 ± 2.1

SUMMARY

NIH 11325 has high affinity at the κ opioid receptor, affinity at the μ opioid receptor and low affinity at the δ opioid receptor.

NIH 11326 (+)-(1S,5S,9S)-5,9-Dimethyl-2-(5-cyanopentyl)-2'-hydroxy-6,7-benzomorphan



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 2240 ± 430
δ-receptor: 22% inhibition at 10 μM
κ-receptor: 302 ± 42

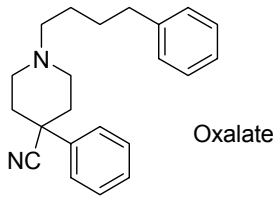
NIH 11326 (continued)

SUMMARY

NIH 11326 has low affinity at the κ opioid receptor, very low affinity at the μ opioid receptor and no affinity at the δ opioid receptor.

* * *

NIH 11327 *N*-(4-Phenylbutyl)-4-phenylpiperidine-4-nitrile.oxalate



OPIOID RECEPTOR BINDING (nM)

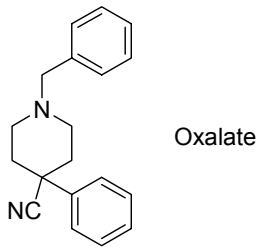
μ-receptor: 9760 ± 680
δ-receptor: 25% inhibition at 10 μM
κ-receptor: 27% inhibition at 10 μM

SUMMARY

NIH 11327 has very low affinity at the μ opioid receptor and no affinity at the δ and κ opioid receptors.

* * *

NIH 11328 *N*-(Benzyl)-4-phenylpiperidine-4-nitrile.oxalate



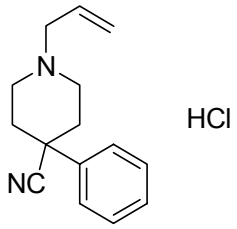
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 5850 ± 90
δ-receptor: 19 % inhibition at 10 μM
κ-receptor: 10,900 ± 2800

SUMMARY

NIH 11328 has very low affinity at the μ and κ opioid receptors and no affinity at the δ opioid receptor.

NIH 11329 *N*-Allyl-4-phenylpiperidine-4-nitrile.HCl



OPIOID RECEPTOR BINDING (nM)

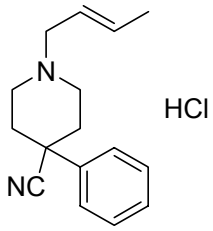
μ-receptor: 12% inhibition at 10 μM
δ-receptor: 10% inhibition at 10 μM
κ-receptor: 10% inhibition at 10 μM

SUMMARY

NIH 11329 has no affinity at μ, δ, or κ opioid receptors.

* * *

NIH 11330 *N*-Crotyl-4-phenylpiperidine-4-nitrile.HCl



OPIOID RECEPTOR BINDING (nM)

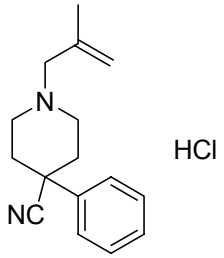
μ-receptor: 32% inhibition at 10 μM
δ-receptor: 26% inhibition at 10 μM
κ-receptor: 25% inhibition at 10 μM

SUMMARY

NIH 11330 has no affinity at μ, δ, or κ opioid receptors.

* * *

NIH 11331 *N*-(2-Methylallyl)-4-phenylpiperidine-4-nitrile.HCl



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 19% inhibition at 10 μM
δ-receptor: 25% inhibition at 10 μM
κ-receptor: 5040 ± 1310

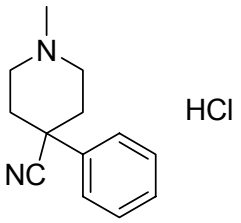
NIH 11331 (continued)

SUMMARY

NIH 11331 has very low affinity at the κ opioid receptor and no affinity at μ and δ opioid receptors.

* * *

NIH 11332 *N*-Methyl-4-phenylpiperidine-4-nitrile. HCl



OPIOID RECEPTOR BINDING (nM)

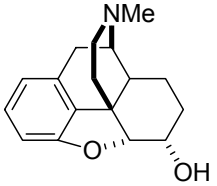
μ-receptor: 23% inhibition at 10 μM
δ-receptor: 16% inhibition at 10 μM
κ-receptor: 14%inhibition at 10 μM

SUMMARY

NIH 11332 has no affinity at μ, δ, or κ opioid receptors.

* * *

NIH 11333 3-Desoxy-7,8-dihydromorphine.oxalate



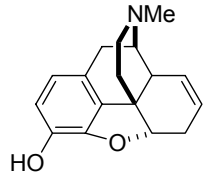
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 122 ± 37
δ-receptor: 4910 ± 320
κ-receptor: 5250 ± 2450

SUMMARY

NIH 11333 has low affinity at μ opioid receptor with very low affinity for δ and κ opioid receptors.

NIH 11334 6-Desoxymorphine.oxalate



Oxalate

OPIOID RECEPTOR BINDING (nM)

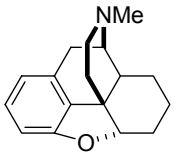
μ-receptor: 2.9 ± 1.1
δ-receptor: 45.5 ± 3.1
κ-receptor: 11.8 ± 3.1

SUMMARY

NIH 11334 has high affinity at the μ opioid receptor and affinity at δ and κ opioid receptors. It is 4 fold selective for μ over κ and 16-fold selective for μ over δ.

* * *

NIH 11335 3,6-Didesoxydihydromorphine.HCl



HCl

OPIOID RECEPTOR BINDING (nM)

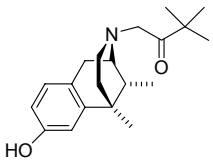
μ-receptor: 22.9 ± 2.9
δ-receptor: 589 ± 64
κ-receptor: 241 ± 27

SUMMARY

NIH 11335 has affinity at the μ opioid receptor with at least 10-fold selectivity over the δ and κ opioid receptors.

* * *

NIH 11345 (-)-(1R,5R,9R)-5,9-Dimethyl-2'-hydroxy-2-(2-oxo-3,3-dimethylbutyl)-6,7-benzomorphan.oxalate



Oxalate

OPIOID RECEPTOR BINDING (nM)

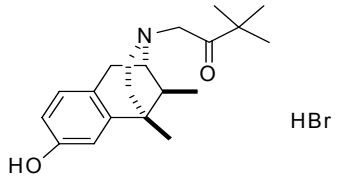
μ-receptor: 297 ± 95
δ-receptor: 2050 ± 210
κ-receptor: 200 ± 31

SUMMARY

NIH 11345 has low affinity at the μ and κ opioid receptors and very low affinity at the δ opioid receptor.

* * *

NIH 11346 (+)-(1S,5S,9S)-5,9-Dimethyl-2'-hydroxy-2-(2-oxo-3,3-dimethylbutyl)-6,7-benzomorphan.HBr



OPIOID RECEPTOR BINDING (nM)

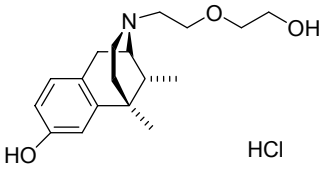
μ-receptor: 24% inhibition at 10 μM
δ-receptor: 26% inhibition at 10 μM
κ-receptor: 4900 ± 530

SUMMARY

NIH 11346 has very low affinity at the δ opioid receptor and no affinity for the μ and κ opioid receptors.

* * *

NIH 11347 (-)-(1R,5R,9R)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

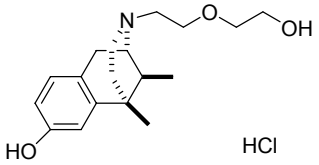
μ-receptor: 231 ± 40
δ-receptor: 1080 ± 47
κ-receptor: 64 ± 7

SUMMARY

NIH 11347 has affinity at the κ opioid receptor, low affinity at the μ opioid receptor, and very low affinity at the δ opioid receptor.

* * *

NIH 11348 (+)-(1S,5S,9S)-5,9-Dimethyl-2-(2-(2-hydroxyethoxy)ethyl)-2'-hydroxy-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

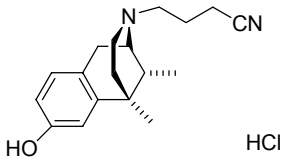
μ-receptor: 1240 ± 245
δ-receptor: 39% inhibition at 10 μM
κ-receptor: 582 ± 12

SUMMARY

NIH 11348 has low affinity at the κ opioid receptor, very low affinity at μ opioid receptor, and no affinity at the δ opioid receptor.

* * *

NIH 11349 (-)-(1R,5R,9R)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HC



OPIOID RECEPTOR BINDING (nM)

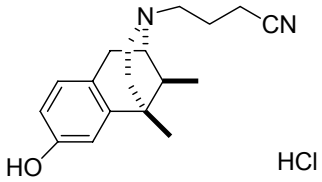
μ-receptor: 3.1 ± 1.3
δ-receptor: 9.9 ± 2.7
κ-receptor: 0.32 ± 0.03

SUMMARY

NIH 11349 has very high affinity at the κ opioid receptor and high affinity at μ and δ opioid receptors. It is 10-fold selective for κ over μ and 31-fold selective for κ over δ.

* * *

NIH 11350 (+)-(1S,5S,9S)-2-(3-Cyanopropyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

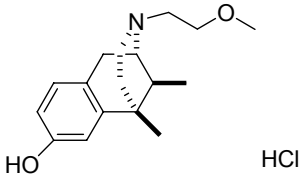
μ-receptor: 1890 ± 580
δ-receptor: 7090 ± 720
κ-receptor: 181 ± 17

SUMMARY

NIH 11350 has low affinity for the κ opioid receptor with 10-fold selectivity for κ over μ and 39-fold selectivity for κ over δ.

* * *

NIH 11351 (+)-(1R,5R,9R)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

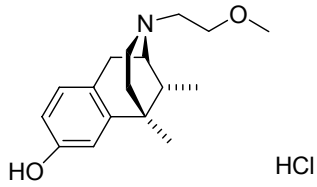
μ-receptor: 246 ± 62
δ-receptor: 1780 ± 140
κ-receptor: 123 ± 24

SUMMARY

NIH 11351 has low affinity at the κ and μ opioid receptors and very low affinity at the δ opioid receptor.

* * *

NIH 11352 (-)-(1S,5S,9S)-2-(2-Methoxyethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

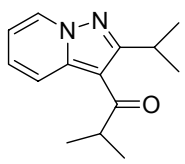
μ-receptor: 0.32 ± 0.10
δ-receptor: 2.1 ± 0.4
κ-receptor: 0.24 ± 0.04

SUMMARY

NIH 11352 has very high affinity at the κ and μ opioid receptors and high affinity at the δ opioid receptor.

* * *

NIH 11353 3-Isobutyryl-2-isopropylpyrazolo[1,5-a]pyridine



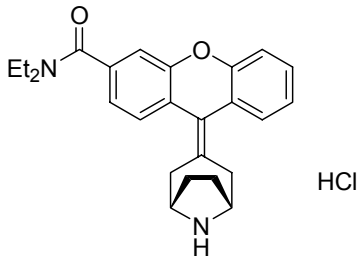
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3% inhibition at 10 μM
δ-receptor: 4% inhibition at 10 μM
κ-receptor: 1% inhibition at 10 μM

SUMMARY

NIH 11353 has no affinity at the μ, δ, or κ opioid receptors.

NIH 11211 9-(8-Azabicyclo[3.2.1]oct-3-ylidene)-15,5*R*-9*H*-xanthene-3-carboxylic acid diethylamide.HCl



THE REINFORCING EFFECTS OF NIH 11211 IN RHESUS MONKEYS

The reinforcing effects of NIH 11211 were evaluated in three monkeys that were experienced with intravenous self-administration of alfentanil and saline. The subjects were given the opportunity to respond and receive alfentanil or saline infusions through intravenously implanted catheters during two 130 min sessions each day. At the beginning of each session, a red light was illuminated over one of two levers in the monkeys' cages. When the light was illuminated, 30 responses (for Biff) or 10 responses (for Hilda and Bonzo) on that lever resulted in an intravenous infusion of drug or saline. Each infusion was followed by a 45 sec timeout; during the infusion and the timeout, the red light was extinguished. There was a centrally located green light that was illuminated during the infusions. After each timeout, the red light was turned on again, and the fixed ratio schedule was again in effect.

Each session was divided into four components of 25 min or 20 injections, whichever came first. The components were separated from each other by 10 min blackout periods, during which time all stimulus lights were extinguished and lever responses had no programmed consequences. The duration of the intravenous infusion that served to reinforce behavior was different in each of the four components. This resulted in four different doses of alfentanil or the test drug being available to the monkeys during different components of each session. When saline was available, different infusion durations of saline were delivered as a consequence of responding.

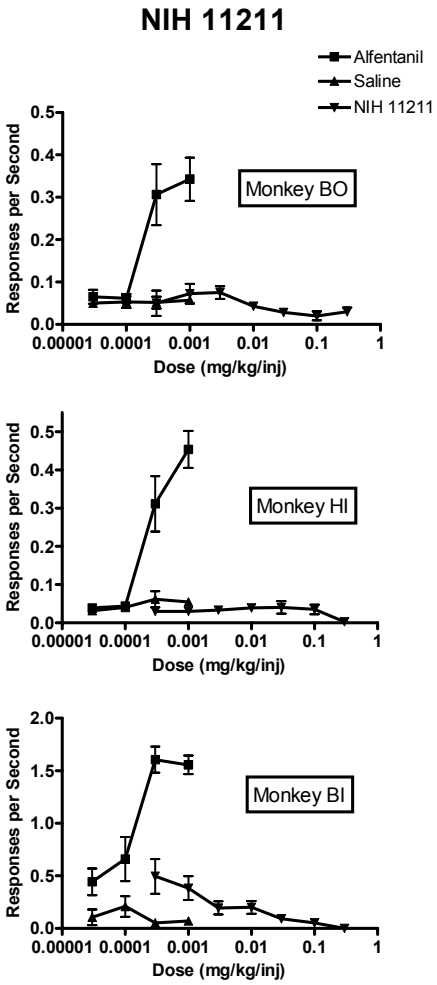
On approximately half of the sessions, alfentanil was used to maintain behavior; response-contingent saline was available on the other baseline sessions. The doses of alfentanil that were available during single sessions were 0.00003, 0.0001, 0.0003, and 0.001 mg/kg/inj. These doses were presented in one of four orders: ascending, descending, and two mixed orders.

These doses were associated with infusion durations of 0.5, 1.7, 5, and 16.7 sec. When saline was available, these infusion durations were also used to deliver saline during a session. Prior to substitution of NIH 11211, each monkey was required to demonstrate a dose-related increase in behavior maintained by alfentanil, and consistently low rates of responding when saline was response-contingent.

A wide range of doses of NIH 11211 was tested in each monkey using this procedure. Because only four doses could be evaluated in a single session, a wider range of doses were evaluated by using different concentrations of NIH 11211 solutions. In these three monkeys, 0.0003, 0.001, 0.003, and 0.01 mg/kg/inj NIH 11211 were substituted for alfentanil on each of two sessions; 0.001, 0.003, 0.01, and 0.03 mg/kg/inj NIH 11211 were substituted on each of two sessions; 0.003, 0.01, 0.03, and 0.1 mg/kg/inj NIH 11211 were substituted on each of two sessions; and 0.01, 0.03, 0.1, and 0.3 mg/kg/inj NIH 11211 were substituted on each of two sessions. An ascending dose order was consistently used during substitution of NIH 11211. These data were averaged across doses per injection, and the mean and standard deviation are included on the accompanying graph.

The graph demonstrates that, for each monkey, increasing doses of alfentanil (squares) led to increasing rates of

responding. Hilda and Bonzo responded at considerably lower rates than did Biff, perhaps because these monkeys were new to the procedure. Saline (triangles) did not maintain behavior in any monkey. Note: The abscissae [dose(mg/kg/inj)] does not refer to saline. NIH 11211 (inverted triangles) maintained rates of responding that were usually as low as those maintained by saline or by small doses of alfentanil. NIH 11211 did not appear to have reinforcing effects in these monkeys under these conditions.



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