



Delta Receptor Based New Drug Development - the Pharmacology and Clinical Applications

Dr. Kwen-Jen (Ken) Chang, Ph.D.

Chief Scientific Officer &
President-Asia Pacific Operations

Enhance Biotech, Inc.
631 United Drive, Suite 200
Durham, North Carolina, 27713

Enhance Biotech

Enhancing Quality of Life





Safe Harbour Statement

Certain statements contained herein are "forward-looking" statements (as such term is defined in the Private Securities Litigation Reform Act of 1995). Because these statements include risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Specifically, factors that could cause actual results to differ materially from those expressed or implied by such forward-looking statements include, but are not limited to: risks associated with preclinical and clinical developments in the biopharmaceutical industry in general and in Enhance Biotech's compounds under development in particular; the potential failure of Enhance Biotech's compounds under development to prove safe and effective for treatment of disease; uncertainties inherent in the early stage of Enhance Biotech' compounds under development; failure to successfully implement or complete clinical trials; failure to receive marketing clearance from regulatory agencies for our compounds under development; acquisitions, divestitures, mergers, licenses or strategic initiatives that change Enhance Biotech' business, structure or projections; the development of competing products; uncertainties related to Enhance Biotech' dependence on third parties and partners; and those risks described in the filings with the SEC.

The Company and Enhance Biotech disclaim any obligation to update these forward-looking statements.

Endorphins: Endogenous Morphine-like Peptides



1. β -Endorphin
2. Enkephalins
3. Dynorphins

Opioid Receptor Subtypes

1. Mu opioid receptors:

morphine, oxycodone, fentanyl

2. Delta receptors: BW373U86, SNC 80

3. Kappa receptors: U69593



Therapeutic Indications for Opioid Receptors

- Mu opioid receptors: analgesia, anti-diarrhea, anti-cough
 - Unwanted side effects: respiratory depression, addiction and dependence, emesis and nausea, constipation etc.
- Delta Receptors : unknown
 - Potential unwanted side effects seizure-like convulsion
- Kappa Receptors : Unknown
 - Unwanted sides: dysphoria and hallucination

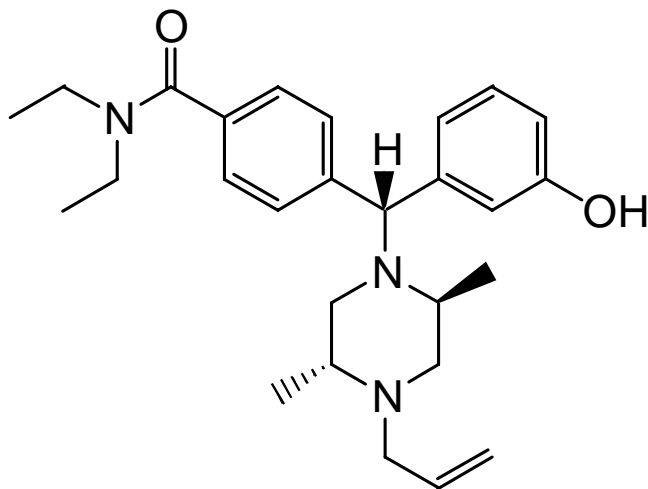




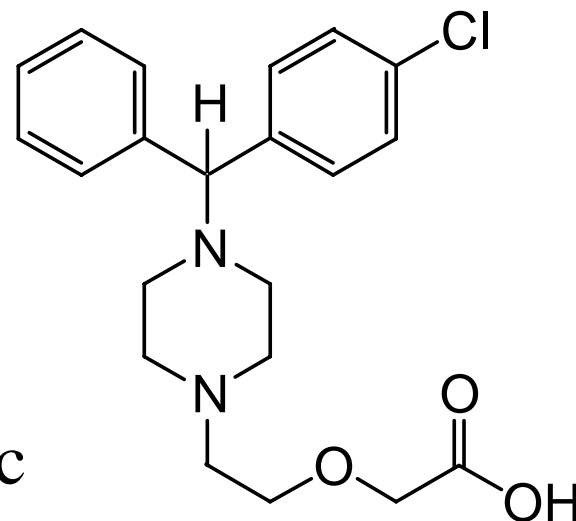
Delta Receptor Based New Drug Development – the Pharmacology and Clinical Applications

Non-peptide Delta Receptor Compounds : drugable molecules

- BW373U86 : first non-peptide mimic for delta receptors
- Chemical Structure – derivative of cyclizine, an old anti-histamine drug



BW373U86



Zyrtec

Delta Receptors: Potential Therapeutic Indications for Unmet Medical Needs

1. Analgesia with a compound with mixed delta/mu agonist activity
2. Urinary incontinence or overactive bladder
3. Parkinson's disease
4. Depression
5. Cardioprotection
6. Premature ejaculation



Delta Receptors: Potential Therapeutic Indications for Unmet Medical Needs

1. Analgesia with a compound with mixed delta/mu agonist activity : DPI-125
2. Urinary incontinence or overactive bladder: DPI-221
3. Parkinson's disease : DPI-290
4. Depression : DPI-289
5. Cardioprotection : ARD-353
6. Premature ejaculation : ARD-822



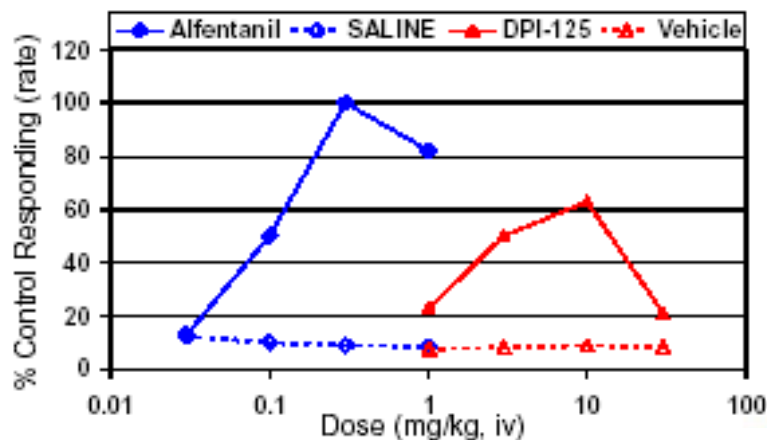
Analgesic, DPI-125 with Reduced Side Effects

DPI-125 has a Wide Therapeutic Window in Rat			
Compound	Analgesic ED ₅₀ Tail Pinch Assay	Respiratory Depression ED ₅₀ *	Therapeutic Ratio**
Morphine	2.01 mg/kg	4.23 mg/kg	2.1
Fentanyl	0.0034 mg/kg	0.0127 mg/kg	3.7
DPI-125	0.050 mg/kg	0.72 mg/kg	14.5

*Dose producing a 50% increase in blood PCO₂ as determined by arterial blood gas measurement

**Respiratory depression ED₅₀ divided by the analgesic ED₅₀

Less Abuse Potential Shown for DPI-125 than with Mu-opioids in Monkeys

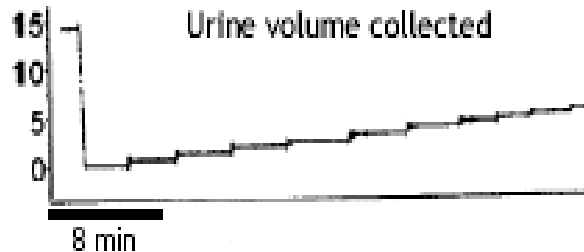
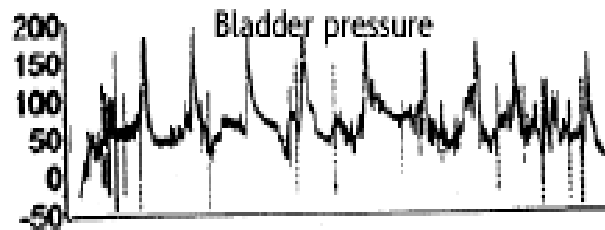


Urinary Incontinence/Overactive Bladder: DPI-221, Non Anti-muscarinic Mechanism

DPI-221 Reduces Hyperactivity in a Rat Model of Overactive Bladder

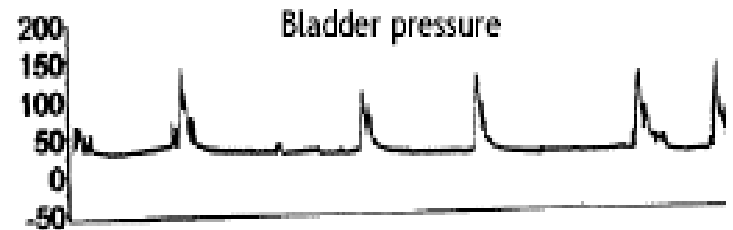


Before Treatment



- Erratic bladder pressure and activity
- Frequent, ineffective bladder emptying

30 Minutes After 10mg/kg DPI-221 p.o.



- Improved bladder pressure and activity
- More effective bladder emptying

Anti-parkinsonian Syndrome of Delta Agonists: Non-dopamine Based Therapy

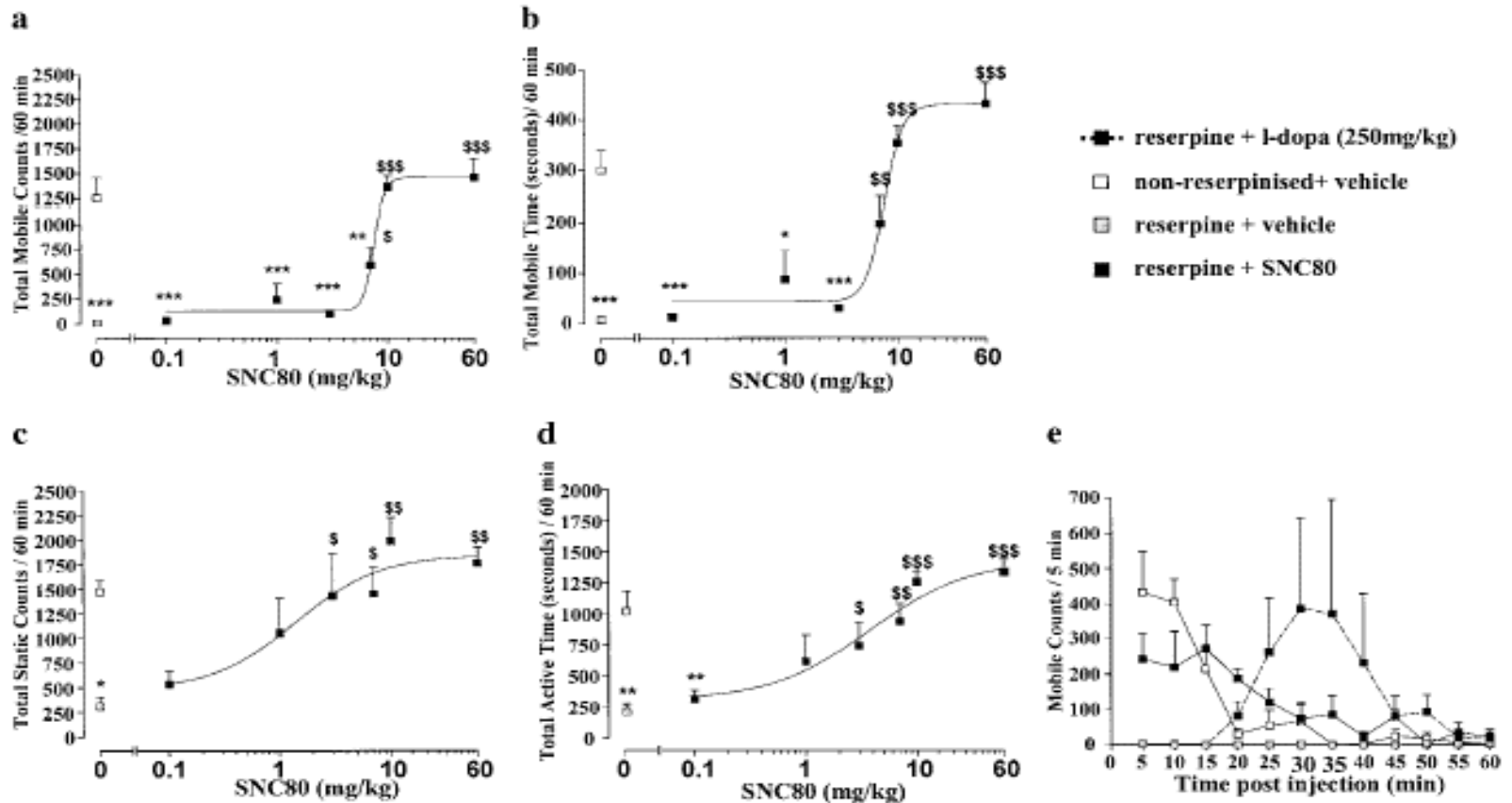
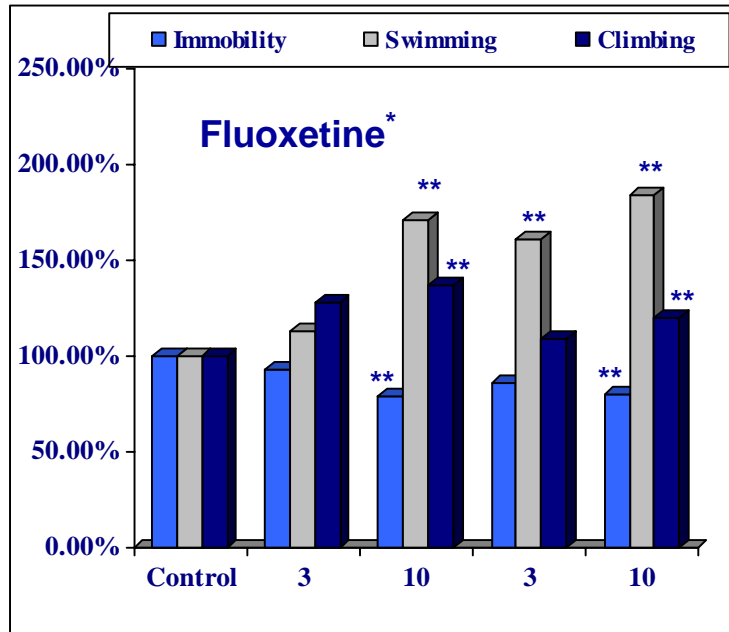


FIG. 1. Locomotor effect of SNC80 in reserpine-treated rats. Data are expressed as the means (\pm SE) of the total activity over the 60-min observation period following the injection of vehicle, or SNC80 (a–d) or as mean (\pm SE) mobile counts in 5-min time bins measured over the 60-min observation period following the injection of vehicle, l-dopa, or SNC80 (e). $***P < 0.001$, $**P < 0.01$, $*P < 0.05$ compared to vehicle-treated, nonreserpinized rats; $***P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ compared to reserpinized, vehicle-treated rats (Tukey–Kramer multiple comparisons test).

Fast Onset of Action of Delta Agonist in FST

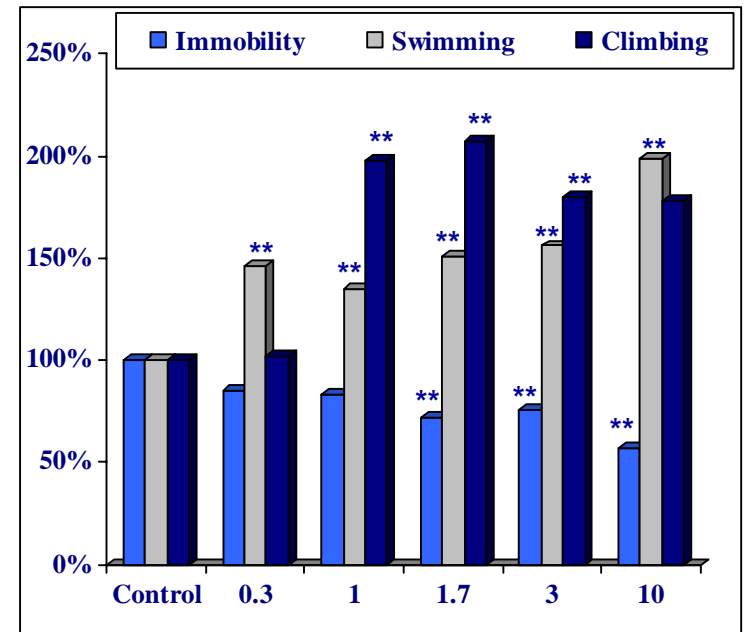
Rat Forced Swimming Test



(mg/kg, p.o.; 14 daily doses)

* Prozac[®] ^ Wellbutrin[®]

** P < 0.05



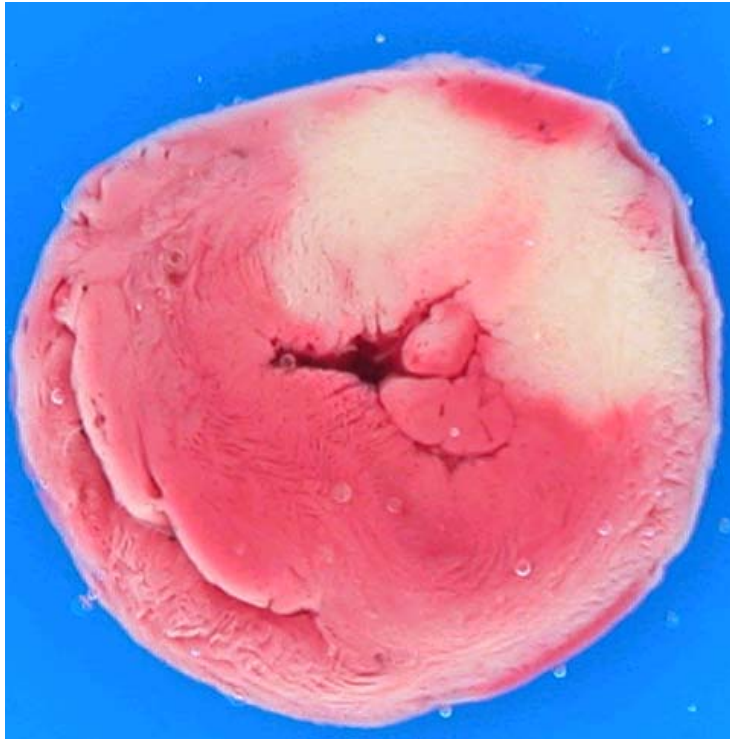
DPI-289 (mg/kg p.o.)

(Single dose)

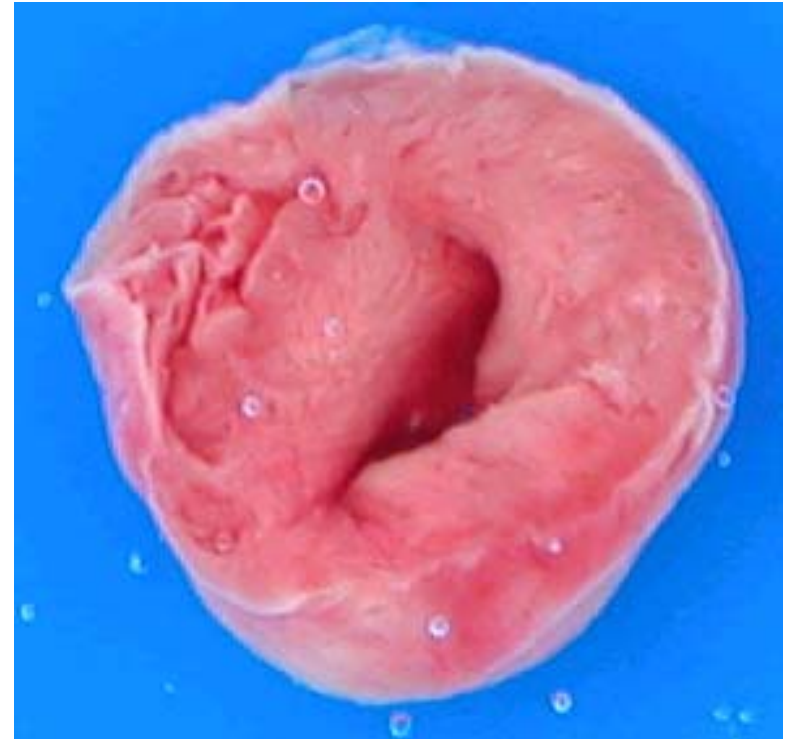
** P < 0.05

ARD-353 Reduces Infarct Size in a Rat Model of Myocardial Infarction

Occlusion-reperfusion control

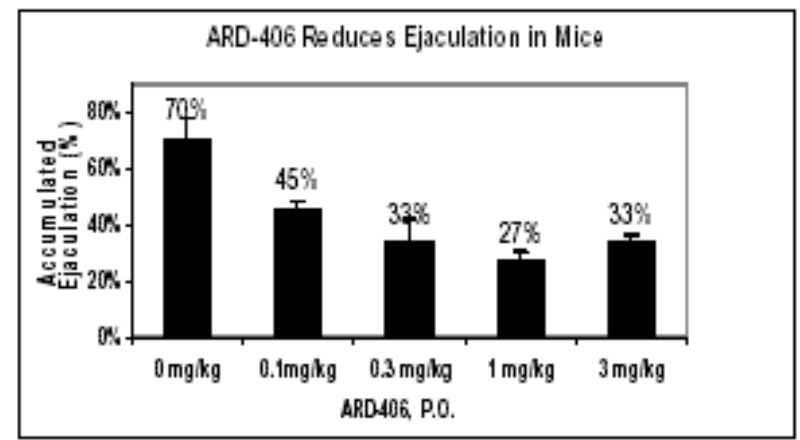
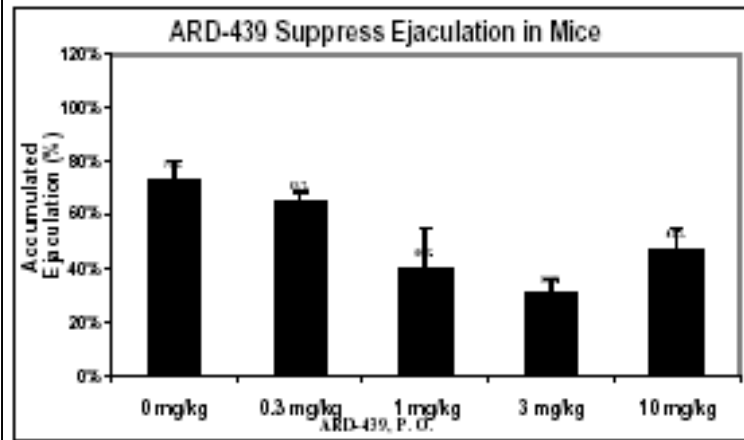
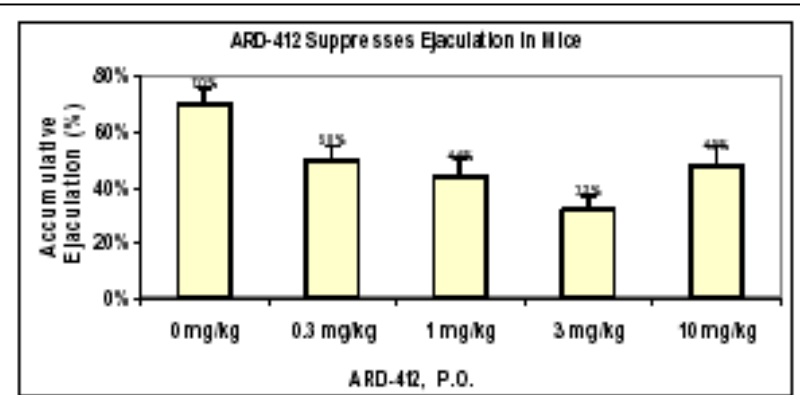
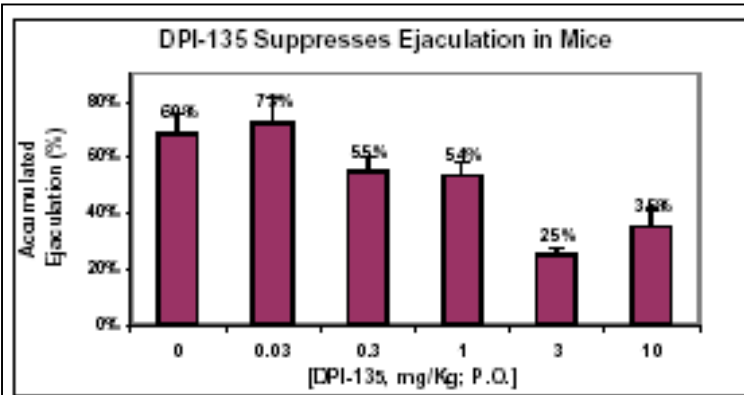


Occlusion-reperfusion after pre-treatment with ARD-353



Delta Agonists for Treating Premature Ejaculation

A number of delta receptor agonists from our library are effective against electro-ejaculation in mouse.



Delta Receptors: Potential Therapeutic Indications for Unmet Medical Needs

1. Analgesia with a compound with mixed delta/mu agonist activity : DPI-125, **reduced side effects**
2. Urinary incontinence or overactive bladder: DPI-221, **non-anti-muscarinic mechanism**
3. Parkinson's disease : DPI-290, **non-dopamine based therapy**
4. Depression : DPI-289, **fast onset of action**
5. Cardioprotection : ARD-353, **safe and effective therapy**
6. Premature ejaculation : ARD-822, **novel application**

