



# PHARMACOLOGICAL PROFILE OF A NOVEL SERIES OF CB2-SELECTIVE AGONISTS WITH EFFICACY IN VISCERAL, INFLAMMATORY, AND NEUROPATHIC PAIN

PW 056

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## Introduction

Non-selective cannabinoid (CB) agonists are known for their analgesic and anti-inflammatory effects. However, these therapeutic benefits are accompanied by undesirable side effects which restrict their development for broad clinical use. Since the side effects of cannabinoids are primarily CNS-related and attributed to activation of central CB1 receptors, our aim was to develop compounds with combined activity at CB1 and CB2 receptors but limited access to the CNS.

Our hypothesis is that this profile may present the therapeutic advantage of combining the putative anti-inflammatory properties of CB2 and the known analgesic effects of CB1 without the CNS-side effect liabilities.

The goal of this investigation was to characterize two of these peripherally-restricted mixed CB1/CB2 agonists (CR07 and CR08) in a series of *in vitro* and *in vivo* assays to assess their anti-inflammatory effects and their analgesic properties in models of somato-visceral, inflammatory and neuropathic pain.

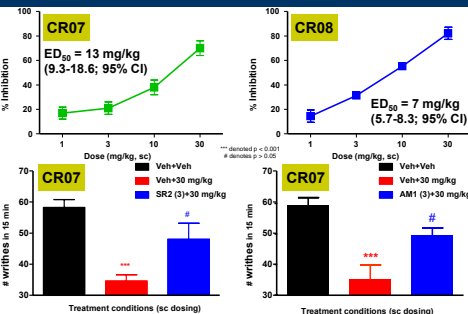
CR07 is a CB2 agonist with weak activity at CB1 receptors whereas CR08 is a true mixed CB1/CB2 agonist. The profile of these compounds is compared and the relevance of the combined CB1/CB2 properties investigated.

## In Vitro Profile of CR07 and CR08

| Compound | cAMP, EC <sub>50</sub> (nM) |      |                                |      |      |                                |
|----------|-----------------------------|------|--------------------------------|------|------|--------------------------------|
|          | hCB2                        | hCB1 | Fold Selectivity (hCB1 / hCB2) | rCB2 | rCB1 | Fold Selectivity (rCB1 / rCB2) |
| CR07     | 70                          | 1484 | 21                             | 48   | 1672 | 35                             |
| CR08     | 4                           | 25   | 6                              | 7    | 79   | 11                             |

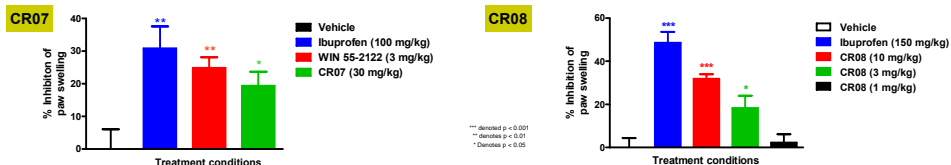
- ✓ Potent, full agonists at human and rodent CB receptors (cAMP assay)
- ✓ No off-target activity across series of 47 pain-related receptors, channels, enzymes and transporters including COX-2, FAAH and TRPV1

## CR07 and CR08 Attenuate Writting Behavior in Mice



- ✓ 0.6% acetic acid induced writhing in male CD-1 mice
- ✓ Activity of CR07 is attenuated following pretreatment with either a CB2 or a CB1 antagonist, SR144528 or AM251, respectively.

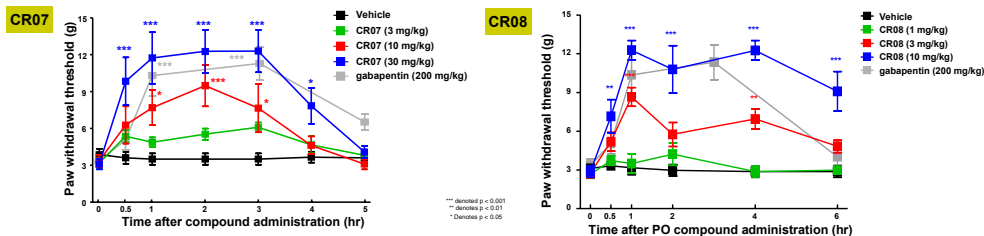
## CR07 and CR08 Inhibit Carrageenan-induced Hind Paw Edema in Rats



**Method:** 0.1 mL of 2% carrageenan intraplantar to male SD rats ; Hind paw volumes were obtained using a plethysmometer.

- ✓ Reversal with WIN 55-212 (3 mg/kg) slightly less than Ibuprofen
- ✓ CR07 MED = 30 mg/kg, SC
- ✓ CR08 efficacy compared to ibuprofen at 10 mg/kg is 65%
- ✓ Normalized to ibuprofen, relative CR08 ED<sub>50</sub> = 5.3 mg/kg, SC (3.6-7.7; 95% CI)

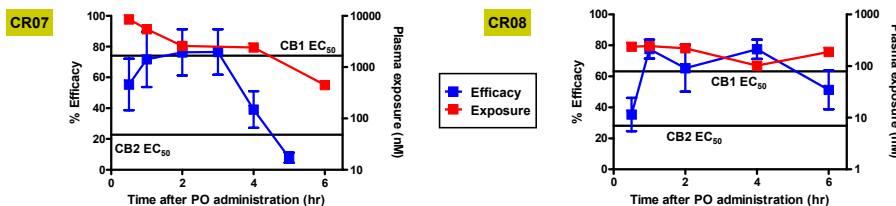
## CR07 and CR08 Reverse Tactile Hypersensitivity in a Rat Model of Neuropathic Pain



**Method:** L<sub>5</sub>/L<sub>6</sub> spinal nerve ligation (Chung model) in male SD rats ; Response to probing injured paw with Von Frey filaments.

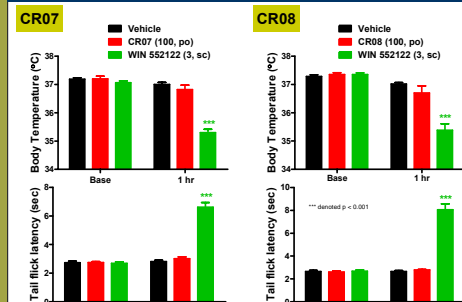
- ✓ ED<sub>50</sub> = 10 mg/kg @ 1 hr (6-18; 95% CI), Oral
- ✓ Duration of action > 3 hr
- ✓ No evidence of hypothermia at any dose
- ✓ ED<sub>50</sub> = 3.8 mg/kg @ 1 hr (3-5; 95% CI), Oral
- ✓ Duration of action > 4 hr
- ✓ No evidence of hypothermia at any dose

## Efficacy of CR07 and CR08 Against Tactile Hypersensitivity is Driven Predominantly by Activation of Peripheral CB1 Receptors



- ✓ Plasma concentrations for CR07 and CR08 are at least 30-fold higher than the cellular CB2 EC<sub>50</sub>.
- ✓ Anti-allodynic effect is maintained for CR07 and CR08 provided plasma concentrations remain above cellular CB1 EC<sub>50</sub>.

## Lack of Central Nervous System Side Effects for CR07 and CR08



|                   | Plasma (ng/mL) | Brain (ng/g) | Brain:Plasma Ratio |
|-------------------|----------------|--------------|--------------------|
| CR07 10 mg/kg, PO | 311            | 7            | 0.11               |
| CR08 30 mg/kg, PO | 918            | 14           | 0.01               |

- ✓ WIN 55-212 produces CB1-related CNS side effects including decreased body temperature, increased tail-flick latency and motor impairment (not shown).
- ✓ CR07 and CR08 do not produce these CNS effects at doses up to 100 mg/kg, oral, (i.e. 10x > than efficacious dose).
- ✓ Brain penetration of CR08 is 1%
- ✓ Data consistent with lack of central CB1 activity

## Conclusions

- CR07 and CR08 are peripherally-restricted cannabinoid agonists, with varying degrees of selectivity across CB1 and CB2 receptors.
- These compounds are efficacious in a variety of rodent models of pain and inflammation
  - ✓ Somato-Visceral pain (writting)
  - ✓ Acute Inflammation (carrageenan)
  - ✓ Neuropathic pain (Chung model)
- Good PK/ADME properties
  - ✓ Good oral bioavailability (F > 60% in rat) with plasma half-life of 1-2 hr.
- PK/PD analysis indicates that CB1 receptors are the major contributor to the efficacy observed *in vivo*.
- CB1 related CNS side-effects were not detected at doses significantly above levels required for efficacy in pain and inflammatory models.
  - ✓ Suggests therapeutic index ≥ 25 fold
- Analogues of CR08 are currently under development for inflammatory and neuropathic pain.