# Pain Research

The development of novel pain therapeutics relies on understanding the highly complex nociceptive signaling pathways. Cayman offers a select group of tools to study transient receptor potential (TRP) ion channels, ligand- and voltage-gated ion channels, and various G protein-coupled receptors (GPCRs) that are known to have roles in nociceptive, inflammatory, and/or neuropathic pain.

## *Pain Transmission*

Primary nociceptor afferents release neurotransmitters such as glutamate and prostaglandins, which bind to specific receptors on the postsynaptic membrane to transmit a pain signal.

The antinociceptive response includes inhibitory interneurons that signal *via* GABA receptors.

Inhibitory pathways descending from the brainstem release neurotransmitters such as serotonin (5-HT) or activate small opioid-containing interneurons in the spinal dorsal horn to release opioid peptides.

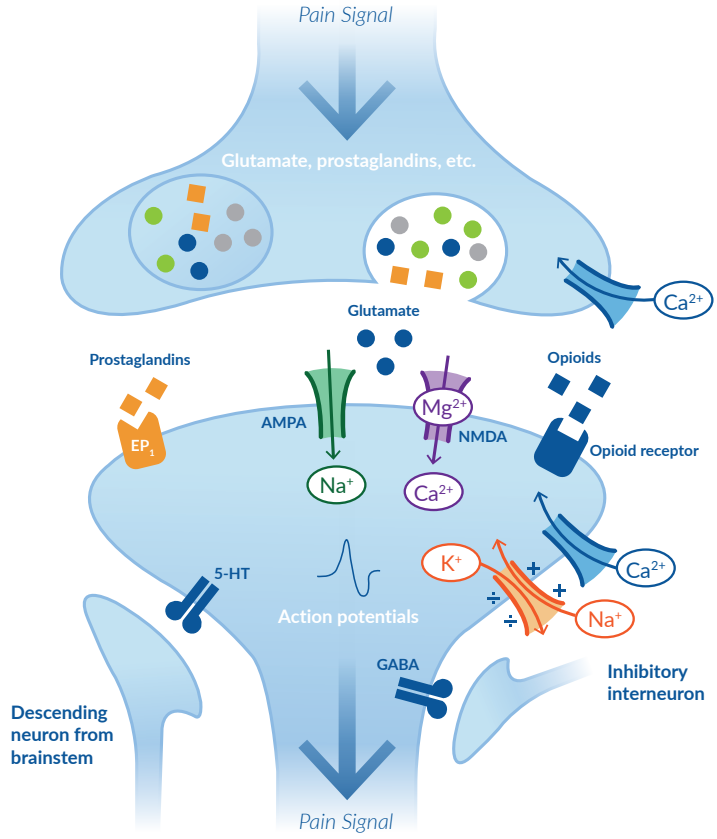



***Image adapted from:*** Olesen, A.E., Andresen, T., Staahl, C., *et al. Pharmacol. Rev.* **64(3)**, 722-779 (2012).

# TRP Ion Channels

## TRP Ion Channel Modulators

| Item No. | Product Name | Summary |
|---|---|---|
| 14715 | AMG 9810 | A TRPV1 antagonist; reverses thermal and mechanical hyperalgesia in a rat model of inflammatory pain |
| 31122 | ASP7663 | A TRPA1 agonist; reduces the number of abdominal contractions induced by colorectal distension in mice |
| 92350 | Capsaicin | A TRPV1 activator ($EC_{50}$ = 0.64 µM at neutral pH) that has been found in *Capsicum* |
| 10007518 | Capsazepine | A competitive TRPV1 antagonist that blocks the capsaicin-induced uptake of $Ca^{2+}$ ($IC_{50}$ = 0.42 µM in neonatal rat dorsal root ganglia) |
| 11923 | HC-030031 | A selective TRPA1 channel blocker that antagonizes TRPA1-mediated calcium influx induced by AITC and formalin ($IC_{50}$s = 6.2 and 5.3 µM, respectively) |
| 10137 | Icilin | A CMR1/TRPM8 super agonist that serves as the reference cold nociceptive agonist for TRP-type ion channels |
| 14979 | Polygodial | A TRPA1 activator ($EC_{50}$ = 59 nM) with antinociceptive effects |
| 11019 | SB-366791 | A selective TRPV1 antagonist that reduces capsaicin-induced nociceptive responses in mouse paw |

*View all TRP ion channel modulators at www.caymanchem.com*

# Ligand-Gated Ion Channels

## Ionotropic Glutamate Receptor Antagonists

| Item No. | Product Name | Summary |
|---|---|---|
| 14539 | D-AP5 | A selective NMDA receptor antagonist ($K_d$ = 1.4 µM) |
| 14618 | CNQX | A non-NMDA glutamate receptor antagonist ($IC_{50}$s = 0.3, 1.5, and 25 µM for AMPA, kainate, and NMDA receptors, respectively) |
| 23884 | (+)-CP 101,606 | An antagonist of NR2B subunit-containing NMDA receptors ($K_d$ = 4.2 nM) |
| 10009019 | (+)-MK-801 (hydrogen maleate) | A selective, non-competitive NMDA receptor antagonist ($K_i$ = 30.5 nM) |
| 14914 | NBQX (sodium salt) | An AMPA and kainate receptor antagonist ($IC_{50}$s = 0.15 and 4.8 µM, respectively) |

## P2X Receptor Antagonists

| Item No. | Product Name | Summary |
|---|---|---|
| 14580 | A-438079 (hydrochloride) | A competitive antagonist of the $P2X_7$ receptor ($pIC_{50}$ = 6.9) |
| 23034 | AF-353 (hydrochloride) | A dual $P2X_3$ and $P2X_{2/3}$ receptor antagonist ($IC_{50}$s = 10 and 79.4 nM, respectively) |
| 20902 | TNP-ATP (triethylammonium salt) | An antagonist of $P2X_1$, $P2X_3$, and $P2X_{2/3}$ receptors ($IC_{50}$s = 6, 0.9, and 7 nM, respectively) |

## Nicotinic Acetylcholine Receptor Modulators

| Item No. | Product Name | Summary |
|---|---|---|
| 31193 | (±)-Epibatidine (hydrochloride) | An agonist of α4β2 subunit-containing nAChRs ($K_i$ = 43 pM) |
| 21570 | GTS-21 (hydrochloride) | An agonist of α7 subunit-containing nAChRs |
| 15030 | Varenicline (tartrate) | A partial agonist of α4β2 subunit-containing nAChRs and full agonist of α7 subunit-containing nAChRs ($EC_{50}$s = 2.3 and 18 µM, respectively) |

# Voltage-Gated Ion Channels

## Sodium Channel Blockers

| Item No. | Product Name | Summary |
|---|---|---|
| 16618 | Bupivacaine | A sodium channel blocker and local anesthetic |
| 10011032 | QX-314 (bromide) | A selective blocker of sodium channels on nociceptive neurons |
| 21422 | (–)-Ropivacaine (hydrochloride hydrate) | A reversible blocker of sodium channels in nerve fibers |
| 14964 | Tetrodotoxin (citrate) | A neurotoxic blocker of $Na_v$ channels |

## Calcium Channel Ligands

| Item No. | Product Name | Summary |
|---|---|---|
| 10008346 | Gabapentin | Penetrates the central nervous system and binds to $\alpha_2\delta$-type voltage-gated calcium channels |
| 22475 | Mirogabalin | A calcium channel blocker that binds to $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits |
| 24114 | ω-Conotoxin GVIA (trifluoroacetate salt) | An N-type calcium channel blocker |

## Potassium Channel Modulators

| Item No. | Product Name | Summary |
|---|---|---|
| 16674 | Flupirtine (maleate) | An activator of KCNQ channels |
| 15185 | ML-213 | A selective activator of KCNQ2 and KCNQ4 channels ($EC_{50}$s = 230 and 510 nM, respectively) |
| 15193 | ML-277 | An activator of KCNQ1 channels ($EC_{50}$ = 260 nM) |
| 14582 | XE 991 (hydrochloride) | A blocker of KCNQ channels |

*Additional modulators of ligand- and voltage-gated ion channels available at www.caymanchem.com*

# GPCR Signaling

## Prostanoid Signaling

Cayman offers a variety of compounds that target the inflammatory mediators of the arachidonic acid cascade, including selective cyclooxygenase (COX) inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), blockers of microsomal prostaglandin E synthase-1 (mPGES-1), and antagonists of prostaglandin $E_2$ ($PGE_2$) receptors.

### COX Inhibitors

| Item No. | Product Name | Summary |
|---|---|---|
| 10008672 | Celecoxib | An NSAID and selective COX-2 inhibitor ($IC_{50}$ = 50 nM) |
| 70680 | Diclofenac (sodium salt) | An NSAID and COX inhibitor ($IC_{50}$s = 0.9-2.7 and 1.5-20 µM for COX-1 and COX-2, respectively) |
| 70280 | (±)-Ibuprofen | An NSAID and non-selective COX inhibitor ($IC_{50}$s = 2.6 and 1.3 µM for COX-1 and COX-2, respectively) |
| 70690 | Ketorolac (tromethamine salt) | An NSAID and non-selective COX inhibitor ($IC_{50}$ = 20 nM for both COX-1 and COX-2) |
| 70290 | (+)-Naproxen | An NSAID and COX inhibitor ($IC_{50}$s = 4.8 and 28.4 µM for COX-1 and COX-2, respectively) |

*A wide range of selective and non-selective COX-1 and -2 inhibitors available at www.caymanchem.com*

### mPGES-1 Inhibitors

| Item No. | Product Name | Summary |
|---|---|---|
| 13164 | CAY10589 | A dual mPGES-1 and 5-lipoxygenase inhibitor ($IC_{50}$s = 1.3 and 1.0 µM, respectively) |
| 18905 | CAY10700 | An orally bioavailable inhibitor of mPGES-1 ($IC_{50}$ = 0.24 µM) |
| 13217 | MF63 | A selective, orally active inhibitor of human mPGES-1 ($IC_{50}$ = 1.3 nM) |

*Additional mPGES-1 inhibitors as well as dual mPGES-1/lipoxygenase inhibitors available at www.caymanchem.com*

### $PGE_2$ Receptor Subtype $EP_1$ and $EP_4$ Antagonists

| Item No. | Product Name | Summary |
|---|---|---|
| 10010355 | CJ-023423 | An $EP_4$ antagonist ($K_i$ = 13 nM for human $EP_4$) that reduces acute and chronic inflammatory pain in different mouse models |
| 15973 | MF498 | A selective $EP_4$ antagonist ($K_i$ = 0.7 nM) |
| 10011561 | SC-51089 | An $EP_1$ antagonist ($K_i$ = 1.332 µM) that reduces phenylbenzoquinone-induced writhing in mice |
| 19118 | ONO-8130 | An orally bioavailable $EP_1$ antagonist ($K_i$ = 1.9 nM) that suppresses pain associated with cyclophosphamide-induced cystitis in mice |

*View additional $PGE_2$ receptor antagonists at www.caymanchem.com*

## Cannabinoid Receptors

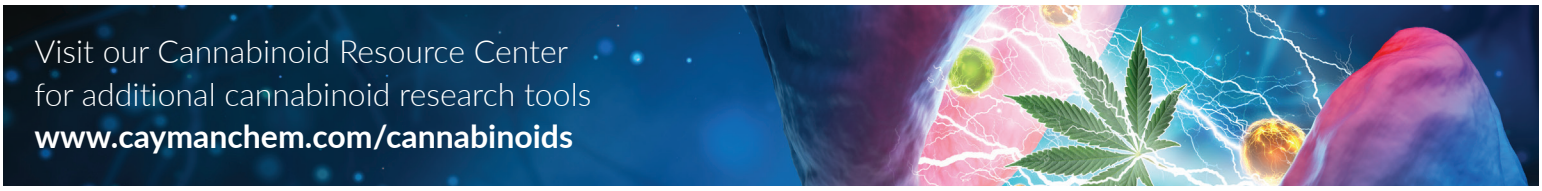
The cannabinoid receptors $CB_1$ and $CB_2$ can be activated by endogenous, plant, and synthetic cannabinoids to modulate pain perception. Cayman offers a collection of cannabinoid receptor ligands, as well as inhibitors of endocannabinoid transport and enzymatic degradation by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).

### Cannabinoid Receptor Agonists

| Item No. | Product Name | Summary |
|---|---|---|
| 91054 | Arachidonoyl 2'-Chloroethylamide | A potent, selective $CB_1$ receptor agonist ($K_i$ = 1.4 nM) |
| 90057 | N-Arachidonoyl Dopamine | An arachidonoyl amino acid and $CB_1$ receptor agonist ($K_i$ = 250 nM in rat brain membranes) |
| 90050 | Arachidonoyl Ethanolamide | An endogenous cannabinoid that binds to $CB_1$ and $CB_2$ receptors ($K_i$s = 61-543 and 279-1,940 nM, respectively) |
| 62160 | 2-Arachidonoyl Glycerol | An endogenous agonist of $CB_1$ and $CB_2$ receptors ($K_i$s = 25.3-472 and 145-1,400 nM, respectively) |
| 26791 | LY2828360 | A selective $CB_2$ receptor agonist ($K_i$ = 40.3 nM) |
| 10009023 | (+)-WIN 55,212-2 (mesylate) | A potent $CB_1$ and $CB_2$ receptor agonist ($K_i$s = 62.3 and 3.3 nM, respectively) |

### Endocannabinoid Reuptake and Degradation Inhibitors

| Item No. | Product Name | Summary |
|---|---|---|
| 90060 | AM404 | A blocker of arachidonoyl ethanolamide (AEA) reuptake with an $IC_{50}$ of 1 µM in rat neurons |
| 13158 | JZL 184 | A selective MAGL inhibitor ($IC_{50}$s = 8 nM and 4 µM for MAGL and FAAH in mouse brain membranes, respectively) |
| 17583 | MJN110 | A selective MAGL inhibitor ($IC_{50}$ = 9.1 nM) |
| 13279 | PF-3845 | An inhibitor of FAAH ($K_i$ = 0.23 µM) |
| 10046 | URB597 | An inhibitor of FAAH ($IC_{50}$s = 4.6 and 0.5 nM in brain membranes and intact neurons, respectively) |




## Opioid Signaling

Cayman offers modulators of the µ-, κ-, and δ-opioid receptors, as well as the nociceptin receptor.

### Opioid Receptor Modulators

| Item No. | Product Name | Summary |
|---|---|---|
| 28928 | DADLE | A peptide agonist of δ-opioid receptors ($K_i$ = 2.06 nM) |
| 34542 | Difelikefalin (trifluoroacetate salt) | A κ-opioid receptor agonist ($EC_{50}$ = 0.16 nM) |
| 21553 | DAMGO (trifluoroacetate salt) | A selective peptide agonist of the µ-opioid receptor ($K_i$ = 1.18 nM for human µ-opioid receptors) |
| 18169 | Dynorphin A (trifluoroacetate salt) | A κ-, µ-, and δ-opioid receptor agonist ($K_i$s = 0.5-1 nM); activates human nociceptin receptor ($K_i$ = 386 nM) |
| 21254 | JTC 801 | An antagonist of the nociceptin receptor ($K_i$ = 44.5 nM; $IC_{50}$ = 94 nM) |
| 15070 | Nociceptin (trifluoroacetate salt) | A nociceptin receptor ligand ($K_i$ = 88 µM in CHO cells) |
| 20576 | PZM21 | A µ-opioid receptor agonist ($K_i$ = 1.1 nM) |
| 15599 | SNC 80 | A nonpeptide δ-opioid receptor agonist ($K_i$ = 0.18 nM; $IC_{50}$ = 2.73 nM) |

*Additional opioid receptor agonists available at www.caymanchem.com*

## Additional GPCRs

Cayman offers agonists and antagonists of additional GPCRs with roles in pain signaling, including neurokinin-1 ($NK_1$) receptors, serotonin (5-HT) receptors, metabotropic glutamate receptors (mGluRs), and $GABA_B$ receptors.

### Additional GPCR Modulators

| Item No. | Product Name | Summary |
|---|---|---|
| 31595 | (+)-Baclofen (hydrochloride) | A $GABA_B$ receptor agonist; increases latency to paw withdrawal in the hot-plate test in mice |
| 18599 | CGP 35348 | $GABA_B$ receptor antagonist ($IC_{50}$ = 34 µM) that prevents baclofen-induced antinociception in mice and rats |
| 34362 | CPPG | An antagonist of group II and group III mGluRs that reduces formalin-induced flinching in a rat model of inflammatory pain |
| 30894 | L-732,138 | An $NK_1$ receptor antagonist ($IC_{50}$ = 1.6 nM) that attenuates mechanical allodynia and cold hyperalgesia in a rat model of neuropathic pain |
| 27658 | Methysergide (maleate) | A 5-$HT_1$ receptor agonist and 5-$HT_2$ receptor antagonist; has antinociceptive activity in mouse models of pain |
| 24035 | Substance P (trifluoroacetate salt) | A tachykinin neuropeptide that binds to and induces pain through $NK_1$ receptors |
| 14600 | Sumatriptan (succinate) | An agonist of 5-$HT_{1B}$ and 5-$HT_{1D}$ receptors ($IC_{50}$s = 9.3 and 7.3 nM, respectively); reduces acute, but not chronic, mechanical hyperalgesia in a mouse model of pain induced by nitroglycerin |

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