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Pain Research

Product Guide | Edition 1 | USD

Chili plant
Capsicum annuum
A source of Capsaicin

Contents by Research Area:

- Nociception
- Ion Channels
- G-Protein-Coupled Receptors
- Intracellular Signaling

Pain Research

Contents

Introduction

Pain is a major public health problem with studies suggesting one fifth of the general population in both the USA and Europe are affected by long term pain. The International Association for the Study of Pain (IASP) defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'.

Management of chronic pain in the clinic has seen only limited progress in recent decades. Treatment of pain has been reliant on, and is still dominated by two classical medications: opioids and non-steroidal anti-inflammatory drugs (NSAIDs). However, side effects such as dependence associated with opioids and gastric ulceration associated with NSAIDs demonstrates the need for new drug targets and novel compounds that will bring in a new era of pain therapeutics.

Pain has been classified into three major types: nociceptive pain, inflammatory pain and neuropathic or pathological pain. Nociceptive pain involves the transduction of painful stimuli by peripheral sensory nerve fibers called nociceptors. Neuropathic pain results from damage or disease affecting the sensory system, and inflammatory pain represents the immunological response to injury through inflammatory mediators that contribute to pain. Our latest pain research guide focuses on nociception and the transduction of pain to the spinal cord, examining some of the main classical targets as well as emerging pain targets.

It is hoped that a thorough understanding of nociceptive pain will lead to the identification of key interventions most likely to provide therapeutic benefit in the future. Tocris Bioscience provides a range of high performance life science reagents that enable researchers to target the mechanisms that underlie pain. A selection of our key products are highlighted within each section, and a full product listing can be found on pages 23-33.

Key Pain Research Products

Nociception

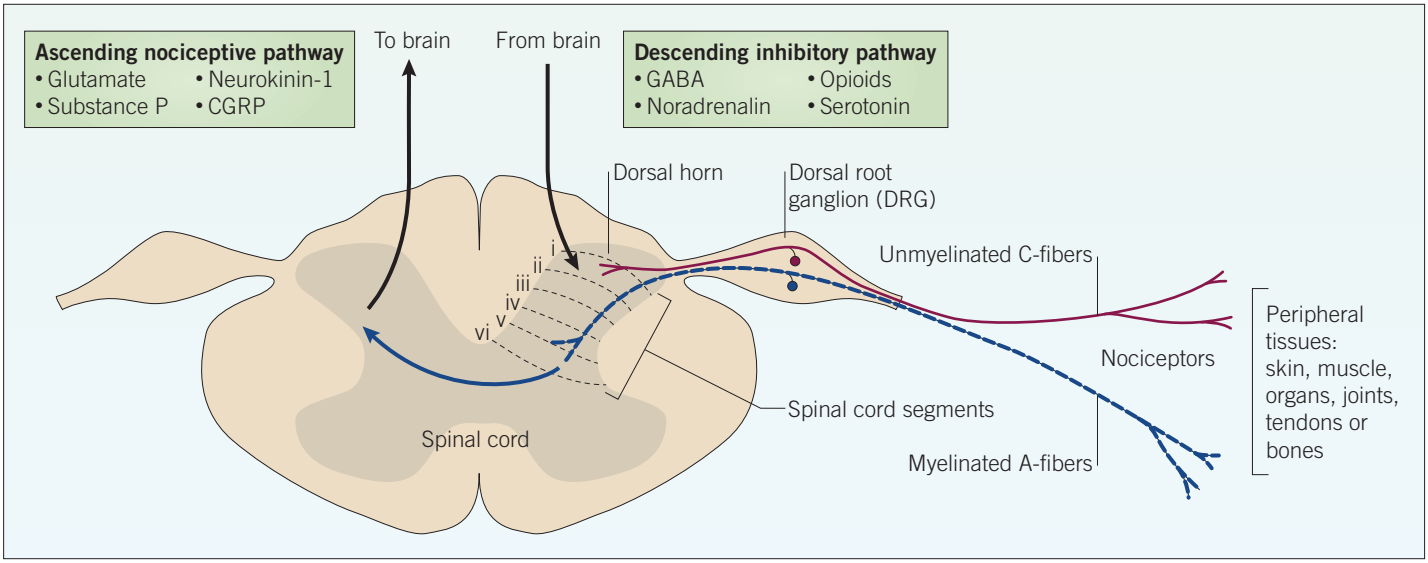
Nociception is a process involving transduction of intense thermal, chemical or mechanical stimuli that is detected by a subpopulation of peripheral nerve fibers called nociceptors (also called pain receptors). Whilst neuropathic pain results from damage or disease affecting the sensory system, nociceptive pain is the normal response to noxious insult or injury of tissues including: skin, muscle, organs, joints, tendons and bones. Inflammatory pain, while not discussed in this guide, is characterized by the mobilization of white blood cells and antibodies, leading to swelling and fluid accumulation. Noxious signals can be enhanced or sensitized by inflammatory mediators, during which pain fibers are activated by this lower intensity stimuli, and the pain generated can be more persistent. NSAIDs (such as aspirin (Cat. No. 4092), ibuprofen (Cat. No. 2796) and valdecoxib (Cat. No. 4206)) which inhibit cyclooxygenases, are one of the most popular drug types used to prevent inflammatory pain in humans, but are not without severe side effects, highlighting the need for new pain targets.

Nociceptors are activated by noxious stimuli such as tissue injury, exposure to an acid or irritant, or extreme temperatures. They generate electrophysiological activity that is transmitted to the spinal cord. Nociceptors can be divided functionally into three compartments: the peripheral terminal which detects painful stimuli; the axon which transduces the signal; and the presynaptic terminal which transmits the signal, using glutamate as a primary neurotransmitter, across the synapse to second order neurons. There are two major classes of nociceptor: myelinated A-fibers and unmyelinated C-fibers. The speed of transmission is correlated to the axon diameter of sensory neurons and whether or not they are myelinated. Most nociceptors are unmyelinated C-fibers that contribute to a poorly-localized sensation of secondary pain, whilst fast-onset, sharp pain is mediated by myelinated A-fibers.

The cell bodies of nociceptive neurons in the dorsal root ganglion (DRG) send two processes: one axon to the peripheral tissue, and a second axon that synapses on second order neurons in the dorsal horn of the spinal cord. The central axon of DRG neurons enters the spinal cord via the dorsal root and branches to innervate multiple spinal segments in the rostral and caudal direction (laminae I, II, IIA and V), from which the ascending nociceptive pathways originate (Figure 1). Within these laminae, DRG neurons may interact with both excitatory and inhibitory interneurons that help to fine-tune the incoming signals. Calcium channels play a key role in the transmission of the pain signal, by triggering release of neuropeptides such as substance P, neurokinin 1 and calcitonin gene-related peptide (CGRP), as well as neurotransmitters such as glutamate. The ascending relay neurons then project to the medulla, mesencephalon and thalamus in the brain, which in turn project to the somatosensory and anterior cingulate cortices to drive the cognitive aspects of pain. Both local GABA-releasing inhibitory interneurons in the dorsal horn and descending noradrenergic neurons originating in the brain can inhibit pain signaling.

Signals relayed from nociceptors may act in combination to produce changes that lead to hyperalgesia: an over-exaggerated response to normally painful mechanical or thermal stimuli, or allodynia: a pain from a stimulus that would not normally provoke pain.

Figure 1 | Nociceptive pain pathway



The cell bodies of nociceptors are located in the dorsal root ganglion (DRG) and terminate as free endings in peripheral tissues. Pain signals originating from the periphery pass through the dorsal root ganglion carried by C-fiber nerves (red) and myelinated A-fiber nerves (blue). Inputs directed to the dorsal horn synapse on interneurons that modulate the transmission of nociceptive signals to higher CNS centres. Signals are relayed to the brain via ascending pathways, and descending pathways from the brain send inhibitory signals. Highlighted in the boxes are key mediators and drug targets that play important roles in pain processing and transmission.

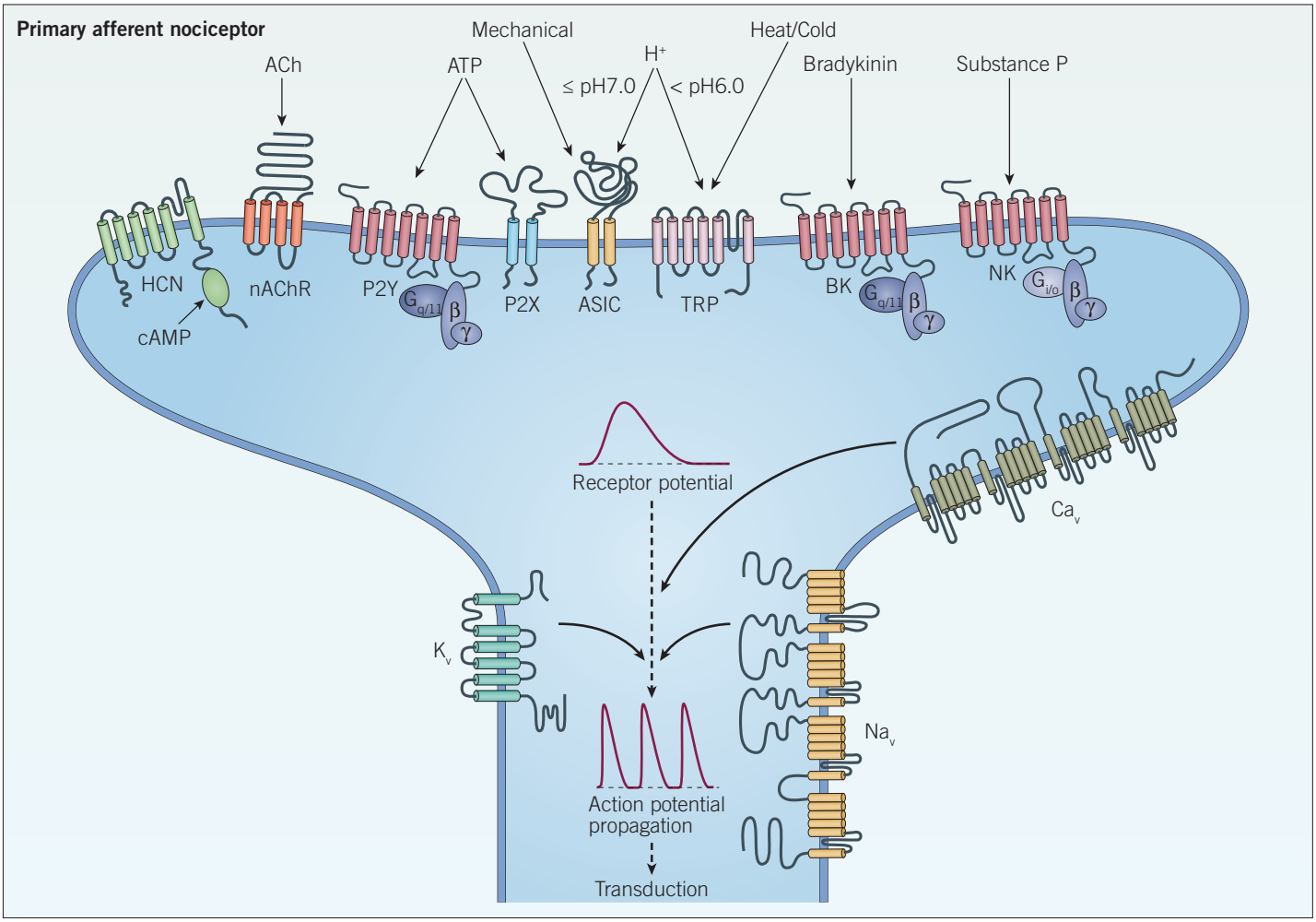
Ion Channels

Nociceptors express a wide variety of voltage-gated and ligand-gated ion channels that transduce receptor potential into either a single action potential or multiple action potentials. These signals encode the intensity of a noxious stimulus, leading to the transduction of pain signals (Figure 2). Recently, TRP (transient receptor potential) channels have been pursued as pain targets since they were identified at the genetic level and found to mediate the painful effects of capsaicin (via the TRPV1 channel), the chemical responsible for the pungency of chili. A more classical understanding of the ion channels involved in pain implicates the sodium channels, these determine excitability of the neurons alongside the calcium channels that influence membrane potential and neurotransmission. Potassium channels are important in repolarizing neurons back to a resting state, and could be important targets in the future, alongside the emerging roles that the ASIC, HCN and P2X receptor ion channels play in pain.

TRP Channels

Since the discovery of the role of TRP channels in pain, research has focused on identifying compounds that inhibit

Figure 2 | Peripheral sensitization and signal propagation in nociception



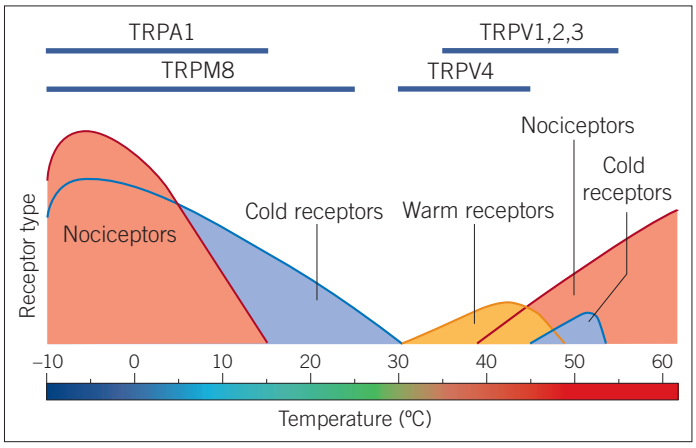
Peripheral terminals respond to noxious stimuli through ion channels such as TRP, ASIC, HCN and P2X receptors and GPCRs such as bradykinin (BK), neurokinin (NK) and P2Y receptors which indirectly modulate ion channels and intracellular signaling pathways. When a threshold depolarization is reached, voltage-gated sodium and calcium channels (Na_V and Ca_V respectively) are activated, which generates an action potential. At this point voltage-gated potassium channels (K_V) open and repolarize the membrane, inactivating Na_V channels and returning the neuron to a resting state. The action potential then propagates along the axon in a process called transduction.

their activity and can therefore bring about analgesia. TRP channels, named after the function they play in phototransduction in *Drosophila*, are classified into six subfamilies in mammals – TRPC, TRPM, TRPA1, TRPP, TRPML and TRPV. They assemble as six transmembrane domains and generate tetramers of cation-selective channels with varying degrees of calcium and sodium permeability. TRP channels respond to a range of stimuli including temperature (Figure 3), mechanical stress, changing osmolarity and intracellular and extracellular messengers, and are weakly sensitive to voltage. Upon opening, they depolarize cells from the resting membrane potential, raising intracellular sodium and calcium concentration, and exciting the cell.

The recent advancement of TRPV1 and TRPV3 channel blockers to clinical trials, and TRPA1 blockers to preclinical development for the treatment of pain, has highlighted the emerging importance of the TRP channel as a key target in pain. Whilst all six families have wide roles in many physiological and pathophysiological processes, the TRPV1, TRPM8 and TRPA1 channels are the most studied and are thought to play an integral role in pain via sensory nerve activation in the DRG.

The TRPV1 channel, formerly known as the vanilloid receptor, is the most extensively studied of the TRP channels and is activated by noxious heat, acidic pH and pungent extracts from chilies, garlic, black pepper and cinnamon. TRPV1 expression is increased in several chronic human pain states and knockout animal models that lack a functional TRPV1 gene do not show typical responses to painful stimuli. The recent generation of selective TRPV blockers, such as the TRPV1-selective blocker JNJ 17203212 (Cat. No. 3361) and the TRPV4-selective blocker RN 1734 (Cat. No. 3746), have demonstrated significant

Figure 3 | TRP channels as temperature sensors

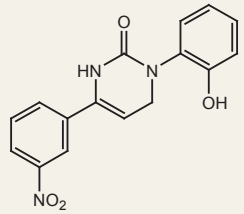


Thermal activation profile of temperature-sensitive TRP channels. Receptor type activated by particular temperatures is highlighted in the lower part of the figure, aligned to a temperature scale bar.

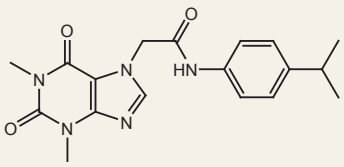
attenuation of painful symptoms in cancer models, underlying the importance of TRPV as a novel pain target. Other TRPV1 blockers including capsazepine (Cat. No. 0464) and A 784168 (Cat. No. 4319), have been shown to block acute pain induced by capsaicin and BCTC (Cat. No. 3875) (Box 1). The multimodal nature of TRPV1 channels offers the opportunity to design specific drugs that are modality-specific, therefore activation by distinct stimuli could be blocked whilst sparing TRPV1 channels' sensitivity to other stimuli. The design of channel blockers that inhibit TRPV1 activation by, for example, capsaicin but not acid (e.g. SB 366791 (Cat. No. 1615)), and others that do not differentiate between capsaicin and acid (e.g. AMG 9810 (Cat. No. 2316)), has demonstrated the feasibility of this approach.

Box 1: TRP Channel Products

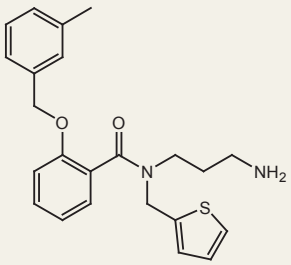
A full list of targets and related products are listed on pages 23-33



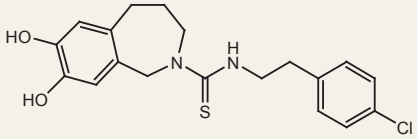
Icilin (1531)
Activates cold receptors, TRPM8 and TRPA1



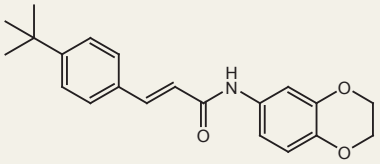
HC 030031 (2896)
Selective TRPA1 blocker



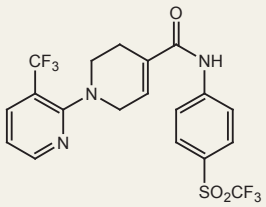
AMTB (3989)
TRPM8 blocker



Capsazepine (0464)
Vanilloid receptor antagonist



AMG 9810 (2316)
Competitive antagonist of TRPV1



A 784168 (4319)
Potent and selective TRPV1 antagonist

Although most attention focuses on blocking the TRPV1 channel in the treatment of pain, TRPV1 activators such as (*E*)-capsaicin (Cat. No. 0462) have also paradoxically been demonstrated to induce analgesia. Topical application of TRPV1 activators (e.g. capsaicin creams) have been used clinically for many years to alleviate chronic painful conditions such as diabetic neuropathy. It is thought that desensitization of the capsaicin receptor may mediate this analgesic effect. However, it has also been hypothesized that capsaicin may reversibly deplete substance P, one of the body's main neurotransmitters for pain and heat, from nerve endings, leading to a reduction in the sensation of pain. Indeed resiniferatoxin (Cat. No. 1137), a capsaicin analog, is being evaluated for long term analgesia in cancer patients who have chronic intractable pain.

The TRPA1 channel is the only member of the ankyrin family found in mammals and is predominantly expressed in C-afferent sensory nerve fibers. TRPA1 colocalizes with TRPV1 and is also thought to play an important role in nociception. TRPA1 is activated by sub-zero temperatures, mustard oil, cinnamon oil, raw garlic, onions and formalin, all of which elicit a painful burning or prickling sensation. A super-cooling agent that activates both cold receptors, TRPM8 and TRPA1, is icilin (Cat. No. 1531). Icilin produces extreme sensations of cold in both human and animals and is almost 200 times more potent than menthol.

Variation in TRPA1 gene expression can alter pain perception in humans, whilst the TRPM8 channel's role in cold hypersensitivity, analgesia (in neuropathic pain) and inflammation, suggest that it could represent a key therapeutic target. TRPA1 channel blockers such as HC 030031 (Cat. No. 2896) reduce neuropathic pain and cold hypersensitivity without altering normal cold sensation, suggesting that these are useful tools to understand nociception. A structurally related compound, TCS 5861528 (Cat. No. 3938), also prevents the development of mechanical hyperalgesia in animal models of diabetes-induced pain. The TRPM8 channel blocker AMTB (Cat. No. 3989) attenuates the bladder micturition reflex and nociceptive reflex responses in the rat, and hence could represent a new therapeutic avenue for overactive bladder and painful bladder syndrome.

It is apparent that a growing number of TRP channels are of potential therapeutic interest and may in the future result in novel clinical drugs for the treatment of pain.

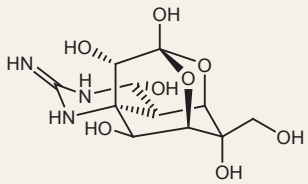
Sodium Channels

Excitability in neurons is dictated by the activity of voltage-gated sodium channels (Na_V). Na_V channels are activated by depolarization and allow the rapid influx of sodium ions, generating action potentials. Pain signals, in the form of action potentials are able to propagate along the axon of the nociceptor by activation of Na_V channels. There are nine known subtypes of Na_V channels, these are designated $Na_V1.1$-1.9. They are composed of an alpha subunit that forms four homologous domains (each with six-transmembrane helices) and two auxiliary beta subunits that are involved in regulation.

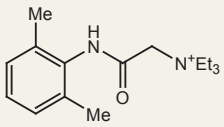
Na_V channels are largely blocked by nanomolar concentrations of tetrodotoxin (TTx) (Cat. No. 1078) (Figure 4), yet $Na_V1.5$, $Na_V1.8$ and $Na_V1.9$ are relatively resistant to TTx (also known as TTx-R). Gain-of-function mutations in Na_V channels have been shown to result in the hyperexcitability of nociceptors. Most sodium channels, excluding $Na_V1.4$ and $Na_V1.5$, have

Box 2: Sodium Channel Products

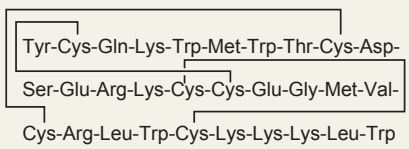
A full list of targets and related products are listed on pages 23-33



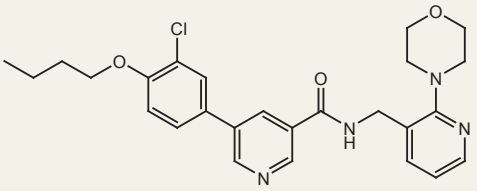
Tetrodotoxin (1078)
Sodium channel blocker



QX 314 bromide (1014)
Sodium channel blocker

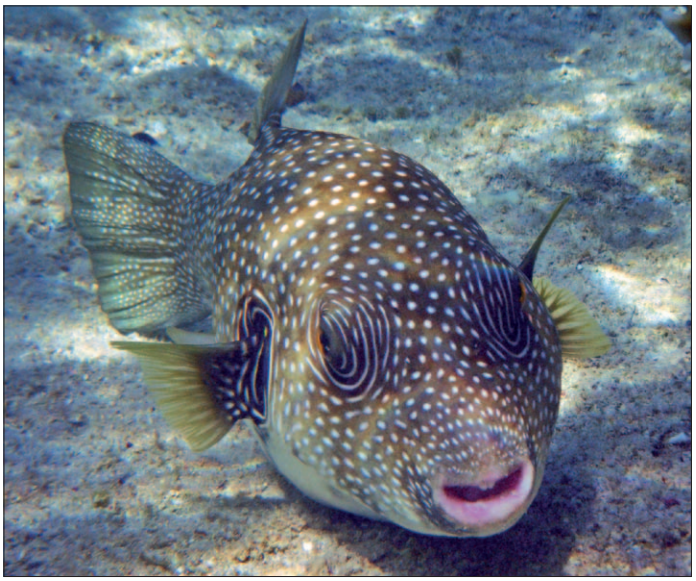


ProTx II (4023)
Potent and selective $Na_v1.7$ channel blocker



A 887826 (4249)
Potent voltage-dependent $Na_v1.8$ channel blocker

Figure 4 | *Tetraodontidae* – a source of tetrodotoxin



The pufferfish (*Tetraodontidae*) is a well known source of tetrodotoxin. Although tetrodotoxin was originally discovered in these fish, it is actually produced by symbiotic bacteria that reside within the liver and other organs of the pufferfish.

been identified in the adult DRG, though $Na_V1.7$ and $Na_V1.8$ channels display the greatest influence on nociception. In support of this, mice lacking $Na_V1.7$ and $Na_V1.8$ display deficits in mechanosensation. Mutations in the human *SCN9A* gene that encodes $Na_V1.7$ are associated with three known pain disorders in humans: channelopathy-associated insensitivity to pain, paroxysmal extreme pain disorder and primary erythermalgia.

The $Na_V1.7$-selective tarantula venom peptides, ProTx II (Cat. No. 4023) and Huwentoxin IV (Cat. No. 4718), have been useful tools for blocking action potential propagation and excitability in nociceptors. TC-N 1752 (Cat. No. 4435), an orally available blocker of TTx-sensitive sodium channels, also decreases pain sensitization in rat sensory neurons. $Na_V1.8$ channel mRNA and protein is increased in the DRG following injection of a painful inflammatory agent in rodents, whereas, genetic knockdown has been shown to reduce mechanical allodynia and impair thermal and mechanical pain hypersensitivity in rats. $Na_V1.8$ channel blockers such as A 803467 (Cat. No. 2976) and A 887826 (Cat. No. 4249) have both been shown to attenuate mechanical allodynia in rat neuropathic pain models (Box 2).

Most anesthetics block sodium channels and thereby the excitability of all sensory neurons. However, a charged lidocaine derivative that would otherwise be impermeant, QX 314 bromide (Cat. No. 1014), has been used to selectively target Na_V channels by passing through the open pore of a TRPV1 channel. By administering the TRPV1 agonist (*E*)-capsaicin (Cat. No. 0462) in combination with QX 314 bromide, researchers have been able to produce pain-specific local anesthesia in TRPV1-expressing nociceptors without affecting other sensory neurons. This represents an insightful strategy of how exploiting ion channels as drug delivery ports can create specificity.

Acid-sensing Ion Channels

Pain can be caused by extracellular tissue acidosis as a result of tissue injury. A drop in pH (increased acidity) is detected by acid-sensing ion channels (ASICs) in primary sensory neurons (≤pH 7.0) and by TRPV1 channels in more severe acidification (< pH 6.0). ASICs are linked to the sodium channel family and are primarily expressed in central and peripheral neurons, including nociceptors, where they regulate neuronal sensitivity to acidosis. The activity of ASICs is regulated by peptides such as neuropeptide SF (Cat. No. 3647), and can be blocked by the broad spectrum Na^+ channel blocker, amiloride (Cat. No. 0890). A potent novel ASIC3 specific channel blocker, APETx2 (Cat. No. 4804) that does not block ASIC1a, 1b or 2a channels, has demonstrated analgesic properties against acid-induced pain. Newly developed subtype selective inhibitors like this will be key to unlocking the role of ASICs in pain.

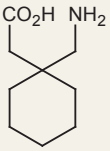
Calcium Channels

Voltage-gated calcium channels (Ca_V) increase intracellular calcium in response to depolarization; this in turn initiates the release of neurotransmitters such as substance P and CGRP, determines membrane excitability and regulates gene expression. These channels are important in the propagation and processing of pain signals, and a variety of calcium channels are expressed in nociceptors. Calcium channels are complex proteins composed of four or five distinct subunits that are encoded by multiple genes. The pore-forming alpha subunit is the largest domain, and like the sodium channel, is comprised of four homologous domains with six transmembrane helices in each. The alpha subunit is modulated by auxiliary β, $\alpha_2\delta$, and γ subunits that regulate the channel properties. There are five main types of calcium channel: L-, P/Q-, N-, R-, and T-type.

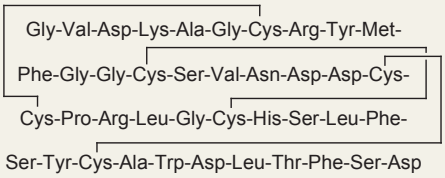
Studies of calcium currents in the DRG led to the functional discovery of the N-type ($Ca_V2.2$) calcium channel, with the greatest expression reported at the presynaptic terminal. Knockout studies with N-type ($Ca_V2.2$)-null mice showed that these mice had an increased threshold for pain, thereby demonstrating the involvement of these channels in pain. The ω-conotoxins, belong to a group of conotoxins which are neurotoxic peptides isolated from the venom of the marine cone snail (Figure 5). ω-conotoxins remain the most selective inhibitors of N-type calcium channels identified. Administration of the N-, P/Q-type calcium channel blocker, ω-conotoxin MVIIC (Cat. No. 1084), reduces pain behavior in rats for up to 24 hours. Key research tools such as the N-type selective ω-conotoxin GVIA (Cat. No. 1085), may help unlock the role of these channels in pain transmission. Studies of the R-type ($Ca_V2.3$) calcium

Box 3: Calcium Channel Products

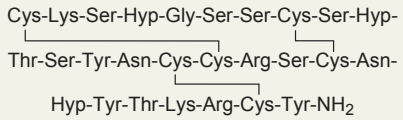
A full list of targets and related products are listed on pages 23-33



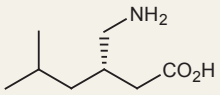
Gabapentin (0806)
Binds to $\alpha_2\delta$ subunit of calcium channel



SNX 482 (2945)
Potent and selective $Ca_V2.3$ channel blocker (R-type)



ω-Conotoxin GVIA (1085)
Ca^{2+} channel blocker (N-type)



Pregabalin (3775)
Selectively binds the $\alpha_2\delta$ subunit of Ca_V channel

Figure 5 | *Conus textile* – a source of conotoxins

The marine cone snail (*Conus textile*) is a source of the neurotoxic peptide known as conotoxin. Cone snails use a hypodermic-like tooth and a venom gland to attack and paralyze their prey before engulfing it.

channel using a selective antagonist SNX 482 (Cat. No. 2945) have also demonstrated a role for this channel in chronic neuropathic pain (Box 3). The T-type ($Ca_V3.1$-3.3) calcium channel is a low voltage-activated channel that is expressed in cell bodies and nerve endings of afferent fibers involved in the initiation of action potentials. T-type channels can lower the threshold for action potentials and promote bursting and excitation, both of which can enhance pain sensation. T-type channel blockers such as mibefradil (Cat. No. 2198) attenuate hyperalgesia and reverse experimental neuropathic pain.

Interestingly, gabapentin (Cat. No. 0806), a widely used drug for the treatment of neuropathic pain, and pregabalin (Cat. No. 3775) both interact with the calcium channel $\alpha_2\delta$ auxiliary subunit, reducing channel currents. Although the precise functions of these subunits are not clear, studies have implicated them in the enhancement of channel current. Peripheral nerve injury has been shown to upregulate $\alpha_2\delta$ in the dorsal horn, highlighting their importance as therapeutic targets for neuropathic pain.

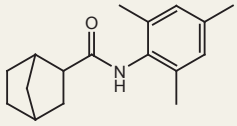
Potassium Channels

The principal function of potassium channels is to stabilize membrane potential by conducting hyperpolarizing outward potassium ion (K^+) currents, thereby decreasing cellular excitability. The ability to re-establish electrical neutrality through modulation of potassium channels makes them a potential target to decrease nociceptor excitability, although there have been limited studies in this field. There are four families of potassium channels: voltage-gated (K_V), inward rectifier (K_{ir}), calcium-activated (K_{Ca}) and two-pore (K_{2P}). The diversity in the structure and function of these channels allows them to fulfil a variety of roles in the membrane and for some, a role in antinociception. Peripheral nerve injury markedly reduces the densities of K_V channels, implicating them in the development of pain. The DRG neurons express three distinct classes of K^+ currents, based on their sensitivities to their respective antagonists, tetraethylammonium (TEA) (Cat. No. 3068) that block the slow-inactivating sustained K^+ current carried by $K_V7.2/7.3$ channels, 4-aminopyridine (4-AP) (Cat. No. 0940) that block the fast-inactivating transient A-current carried by the $K_V1.4$ channel and α-dendorotoxin (α-DTX) that blocks the slow-inactivating transient D-current carried by $K_V1.1/1.2$. channels. K_V channel openers, such as ML 213 (Cat. No. 4519), that display selectivity for a specific channel subtype ($K_V7.2$ and $K_V7.4$), may be useful for identifying the role of K^+ channel subtypes in pain sensation (Box 4). The ATP-sensitive (K_{ATP}) channel, a member of the K_{ir} family, is inhibited by glibenclamide (Cat. No. 0911) and has also been implicated in the pathophysiology of pain. Therefore K_{ir}-selective tools such as tertiapin-Q (Cat. No. 1316) may also be useful in the study of pain. Despite limited understanding of the roles that potassium channels play in pain modulation, they may become promising pain targets in the future.

Ion Channels – continued

Box 4: Potassium Channel Products

A full list of targets and related products are listed on pages 23-33



ML 213 (4519)
Selective $K_V7.2$ and $K_V7.4$ channel opener

Ala-Leu-Cys-Asn-Cys-Asn-Arg-Ile-Ile-Ile-Pro-
His-Gln-Cys-Trp-Lys-Lys-Cys-Gly-Lys-Lys-NH_2

Tertiapin-Q (1316)
Selective blocker of K_{ir} channels

HCN Channels

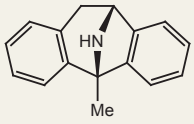
Hyperpolarization-activated cyclic nucleotide-modulated (HCN) channels are also prominent in peripheral sensory neurons and recently have been proposed as a target for the treatment of pain and nerve injury-associated allodynia. They carry an inward current which is unusual because they are activated by membrane hyperpolarization and are modulated by intracellular cAMP. Evidence suggests that HCN channels may have a role in initiation of neuropathic pain, though certain subtypes may also influence heart rate making them less suitable pain targets. The HCN blocker ZD 7288 (Cat. No. 1000) causes significant suppression of action potential firing in nociceptors, independent of changes in the speed of conduction.

Glutamate (Ionotropic) Receptors

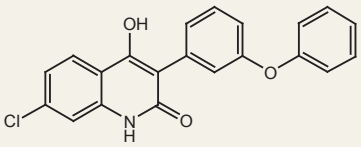
Glutamate is the most widely distributed excitatory neurotransmitter in the CNS. It is fundamental to excitatory transmission and emerging evidence supports the notion that modulation of glutamate receptors may be of therapeutic use in the treatment of pain. Glutamate acts at two main types of receptors: the ionotropic receptors, which are ligand-gated ion channels; and the metabotropic receptors, coupled to intracellular second messengers through a G-protein signaling cascade, which are discussed in the next section on GPCRs (Figure 7). NMDA, AMPA and kainate receptors are all members of the ionotropic class of glutamate receptors which are ligand-gated non-selective cation channels allowing the flow of K^+, Na^+ and Ca^{2+} in response to glutamate binding. Several pharmacological studies using animal models have identified the ionotropic receptors in persistent pain states. AMPA antagonists such as NBQX (Cat. No. 0373) and CNQX (Cat. No. 0190) have been shown to be effective in blocking the development of hyperalgesia in models of first degree burns. Blocking the ion channel pore of the NMDA receptor using antagonists such as (+)-MK 801 (Cat. No. 0924), is effective in alleviating pain in rats and humans (Box 5). However, selective targeting of different sites on the NMDA receptor can be achieved using specific compounds that then allow researchers to block particular aspects of channel activity. Targeting the alternate glycine modulatory site on the NMDA receptor using the antagonist, L-701,324 (Cat. No. 0907) has already proven effective in preclinical animal models for pain. Antagonizing one type of subunit from this receptor, such as the NR2B subunit using Ro 25-6981 (Cat. No. 1594), has also been useful in alleviating mechanical allodynia. Research such as this demonstrates the importance of the ionotropic glutamate receptors in pain, but also indicates that selectively targeting subtypes or binding sites within the same receptor, may lead to greater functional specificity in the treatment of pain.

Box 5: iGlu and $GABA_A$ Receptor Products

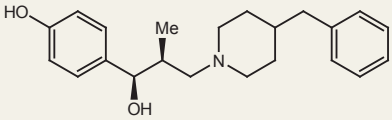
A full list of targets and related products are listed on pages 23-33



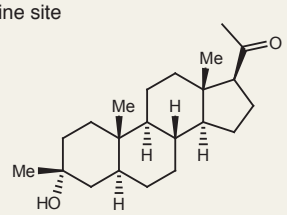
(+)-MK 801 (0924)
Non-competitive NMDA antagonist, acts at ion channel site



L-701,324 (0907)
NMDA antagonist, acts at glycine site



Ro 25-6981 (1594)
Subtype-selective NR2B antagonist



Ganaxolone (2531)
Potent, allosteric modulator of $GABA_A$ receptors

$GABA_A$ Receptors

Inhibitory control of nociceptive signals is attributed to γ-aminobutyric acid (GABA) (Cat. No. 0344). There are two classes of GABA receptors: $GABA_A$ and $GABA_B$. A third type of GABA receptor, insensitive to typical modulators of $GABA_A$ was designated as a $GABA_C$ receptor, however this has since been described to be a variant within the $GABA_A$ receptor family. $GABA_A$ receptors are ligand-gated ion channels, or ionotropic receptors, whereas $GABA_B$ receptors are G-protein-coupled receptors, or metabotropic receptors, and are discussed in the next section on GPCRs (Figure 7). The discovery that GABA receptor agonists, and inhibitors of GABA uptake or metabolism, could display antinociceptive properties provided an impetus for developing agents for this purpose. $GABA_A$ agonists such as THIP (Cat. No. 0807), and the positive allosteric modulator ganaxolone (Cat. No. 2531), have all evoked significant analgesia making $GABA_A$ receptors an interesting target for pain.

P2X Receptors

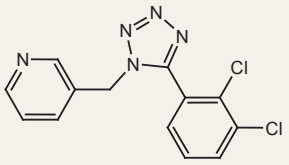
Purinergic receptors have been implicated in pain. There are two types of purinergic receptor: the adenosine receptor (also classed as a P1 receptor) and P2 (ATP) receptor, which is further divided into P2X and P2Y receptors (adenosine and P2Y receptors are discussed in the next section on GPCRs). However, it is the P2X receptor that plays a greater part in current research into pain. Recent investigations into the role of ATP in modulating nociception indicates that there are multiple P2X receptor-based mechanisms by which ATP can facilitate the generation of pain signals. P2X receptors are a family of cation-permeable ligand-gated ion channels of which seven subtypes (P2X1-P2X7) have been found in the central and peripheral mammalian nervous system.

Experimentally, P2X receptor agonists such as α,β-Methyleneadenosine 5'-triphosphate (Cat. No. 3209), elicit short-lasting nociceptive responses that are increased as a result of neuronal sensitization during inflammatory pain. The potent P2X3 receptor antagonist TNP-ATP (Cat. No. 2464) has been demonstrated to be a useful tool for understanding the role of the P2X3 receptor *in vitro*; however its rapid degradation makes it of limited use *in vivo*. Several novel small molecule antagonists that selectively block P2X3 and P2X2/3 receptors, such as RO-3 (Cat. No. 3052), Ro 51 (Cat. No. 4391) and TC-P 262 (Cat. No. 4386), have recently been reported to reduce nociceptive sensitivity in animal models of pain (Box 6).

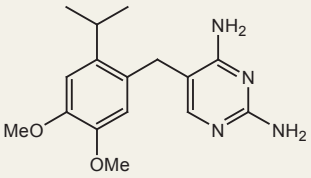
The P2X7 receptor is highly expressed in macrophages, microglia and certain lymphocytes. Studies with P2X7 selective antagonists have provided evidence for their role in animal models of persistent neuropathic and inflammatory pain. Direct support for the role of P2X7 receptors in pain modulation is provided by studies using selective antagonists such as A 438079 (Cat. No. 2972) and A 740003 (Cat. No. 3701) that demonstrate dose-dependent antinociceptive effects in models of neuropathic and inflammatory pain, suggesting that purinergic glial-neural interactions may be important modulators of noxious sensory neurotransmission.

Box 6: P2X Receptor Products

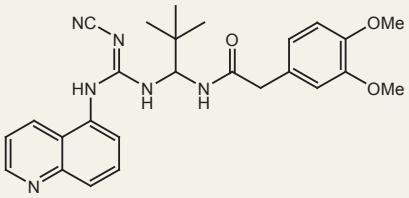
A full list of targets and related products are listed on pages 23-33



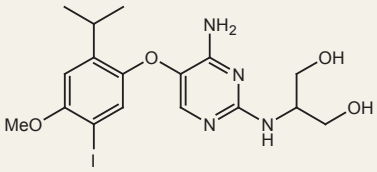
A 438079 (2972)
Competitve P2X7 antagonist



RO-3 (3052)
Selective P2X3 and P2X2/3 antagonist



A 740003 (3701)
Potent and selective P2X7 antagonist



Ro 51 (4391)
Potent P2X3, P2X2/3 antagonist

Nicotinic Acetylcholine Receptors

Nicotine has been known to have weak analgesic activity for many years. It produces its effects via nicotinic acetylcholine receptors (nAChRs) which are ligand-gated ion channels. They are assembled from a combination of one or more alpha subunits (α1-10), and one or more non-alpha subunits including β1-4, γ, δ, and ε subunits. Chronic injury leads to overexpression of key nAChR subunits such as α4, α5, and α7.

Activation of cholinergic pathways by nicotine and nicotinic agonists has been shown to elicit antinociceptive effects in a variety of species and pain tests. The nAChR agonist

Figure 6 | *Epipedobates tricolor* – a source of epibatidine

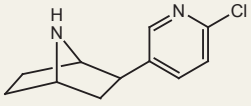
Epibatidine is an alkaloid found on the skin of the endangered Ecuadorian frog (*Epipedobates tricolor*). The frog uses the compound to protect itself from predators, as it can kill animals many times larger than itself.

(±)-epibatidine (Cat. No. 0684) is an alkaloid poison naturally found on the skin of the Ecuadorian frog (*Epipedobates tricolor*) (Figure 6), and is 100-200 times more potent than morphine as an analgesic. It has demonstrated potent antinociceptive effects in neuropathic pain models yet, despite its potency, there are intolerable toxic side effects due to non-selectivity that make it very unlikely to ever be of clinical use. The key to the development of safe and effective nicotinic agonists as analgesics is therefore to first understand which nAChR subtypes are involved in modulating nociceptive transmission and subsequently develop drugs with increased specificity for these nAChR subtypes. The effect of nicotine on inhibitory currents could be mimicked by the α4β2 nAChR agonist RJR 2403 (Cat. No. 1053), and also by choline, an α7 nAChR agonist. However, whilst the effect of nicotine could be completely blocked by the nAChR antagonist mecamylamine (Cat. No. 2843) and the α4β2 nAChR antagonist dihydro-β-erythroidine (Cat. No. 2349), they display differing effects on nAChR activity. α4β2 agonists such as sazetidine A (Cat. No. 2736), the partial agonist varenicline (Cat. No. 3754), and the α7 agonist LY 2087101 (Cat. No. 4141) will help to elucidate of the role different receptor subtypes play in pain sensation (Box 7).

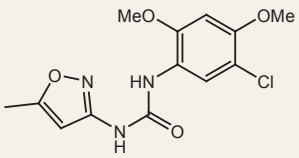
Modulators of the α7 receptor such as the antagonists, methyllycaconitine (Cat. No. 1029) and α-bungarotoxin (Cat. No. 2133), and the agonists, PNU 120596 (Cat. No. 2498), AR-R 17779 (Cat. No. 3964) and A 844606 (Cat. No. 4477), have been useful in studies investigating acute pain, suggesting that subtype specificity may hold the key to understanding the role of nicotinic receptors in pain.

Box 7: Nicotinic Receptor Products

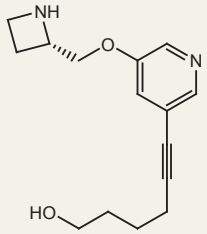
A full list of targets and related products are listed on pages 23-33



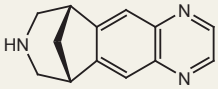
(±)-Epibatidine (0684)
Potent nicotinic agonist



PNU 120596 (2498)
Positive allosteric modulator of α7 nAChR



Sazetidine A (2736)
α4β2 receptor ligand



Varenicline (3754)
Subtype-selective α4β2 partial agonist

G-Protein-Coupled Receptors

A variety of G-Protein-Coupled Receptors (GPCRs) have important roles in nociception. They modulate the function of a wide variety of ion channels and signaling molecules in sensory neurons. The basic cycle of G-protein activation and inactivation involves agonist binding and receptor activation. This in turn induces a conformational change such that the α-subunit binds GTP in exchange for GDP, thereby causing it to dissociate into a GTP-bound α-subunit and a βγ dimer. There are many classes of Gα subunits such as, $G\alpha_s$ (G stimulatory), $G\alpha_i$ (G inhibitory), $G\alpha_o$ (G other), $G\alpha_{q/11}$, and $G\alpha_{12/13}$ which can signal to downstream targets to stimulate or inhibit cellular activity. Hydrolysis of GTP inactivates the G-protein, returning it to its heteromeric state. Cannabinoids have become a new and exciting area in pain research, building upon knowledge gained from studies into the more traditional targets such as the opioid, glutamate and GABA receptors, which has greatly expanded the field of GPCRs in nociception. Bradykinin and neurokinin receptors have also been shown to play a role in nociception, as well as mediating neurotransmission in pain pathways, making them useful targets for current research.

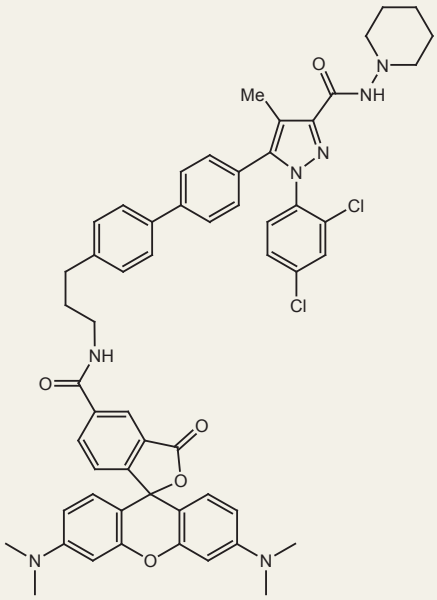
Cannabinoid Receptors

The analgesic properties of cannabinoids have been recognized for centuries. However it is only recently, since the characterization of the metabotropic cannabinoid receptors – CB_1 and CB_2 – that their mechanism of action has started to be understood. CB_1 and CB_2 receptors inhibit adenylyl cyclase by coupling $G\alpha_{i/o}$. The CB_1 receptor also modulates calcium and potassium conductances and activates mitogen-activated protein kinase (MAPK), leading to inhibition of cellular activity and suppression of neuronal excitability (Figure 7). In contrast, the CB_2 receptor appears not to gate ion channels but does activate MAPK. Additionally, an orphan G-protein-coupled receptor, GPR55, has been recently described to bind cannabinoids.

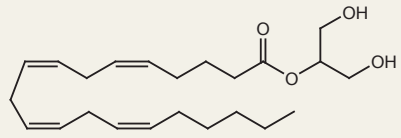
Two major classes of lipids activate cannabinoid receptors – *N*-acyl ethanolamines (NAE) and monoacylglycerols (MAGL). Anandamide (AEA) (Cat. No. 1339), an NAE, was the first endocannabinoid to be isolated from the brain. This was closely followed by the monoacylglycerol, 2-Arachidonylglycerol (2-AG) (Cat. No. 1298) (Box 8). AEA is synthesized from *N*-arachidonoyl phosphatidylethanolamine (NAPE) via multiple

Box 8: Cannabinoid Receptor Products

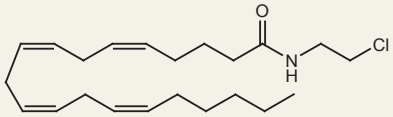
A full list of targets and related products are listed on pages 23-33



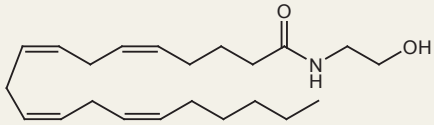
Tocrifluor T1117 (2540)
Novel fluorescent cannabinoid ligand



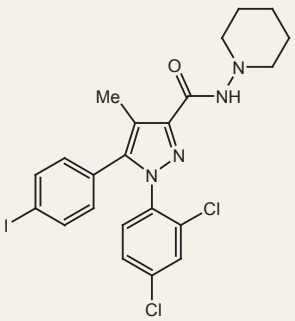
2-Arachidonylglycerol (1298)
Endogenous cannabinoid agonist



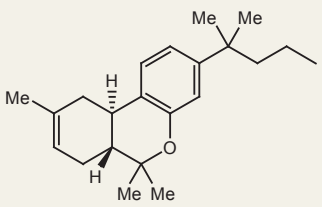
ACEA (1319)
Potent, highly selective CB_1 agonist



Anandamide (1339)
Endogenous CB receptor agonist

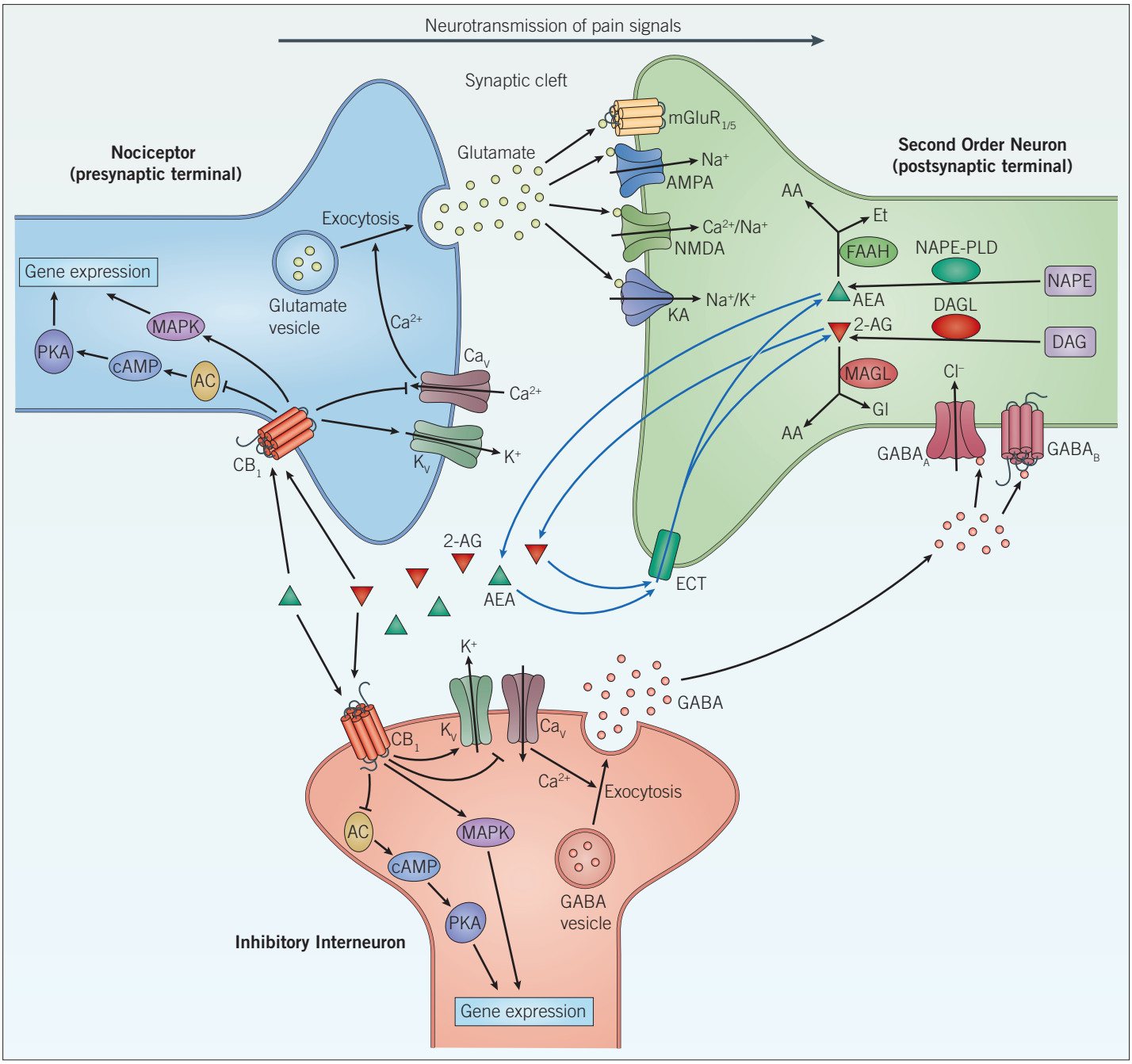


AM 251 (1117)
Potent CB_1 antagonist



JWH 133 (1343)
Potent CB_2 selective agonist

Figure 7 | Endocannabinoid signaling and neurotransmission

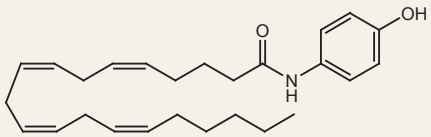


Pain signals from the nociceptor arrive at the presynaptic terminal where upon opening of voltage-gated calcium channels (Ca_V), elevates intracellular calcium and stimulates exocytosis so that glutamatergic signaling can occur. Glutamate acts on two different types of receptors on the postsynaptic neuron: ionotropic glutamate receptors (NMDA, AMPA and KA) and metabotropic glutamate receptors (mGluR). Activation of these channels and receptors initiate a receptor potential in the postsynaptic neuron. Endocannabinoids (such as, anandamide (AEA) and 2-arachidonoylglycerol (2-AG)) are synthesized in response to increased activity in the postsynaptic neuron. They exert their effects by binding to specific G-protein-coupled receptors located on the presynaptic neuron. The CB_1 receptor inhibits the AC-cAMP-PKA pathway and activates the mitogen-activated protein kinase (MAPK) cascade, both of which regulate gene expression. The CB_1 receptor modulates ion conductances, inhibiting voltage-sensitive Ca^{2+} channels, which blocks exocytosis and activates voltage-sensitive K^+ channels (K_V), leading to suppression of the signals coming from the nociceptor – this is called retrograde signaling. Endogenous cannabinoids in the synaptic cleft are taken up by endogenous cannabinoid transporters (ECT) into the cell whereby they are broken down by enzymes that include, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). Inactivation of AEA (by FAAH) and 2-AG (by MAGL) occurs via hydrolysis to arachidonic acid (AA) and ethanolamine (Et) or glycerol (Gl), respectively. GABAergic neurons also act on the postsynaptic cell to decrease excitability. $GABA_A$, a ligand-gated ion channel that conducts chloride ions and $GABA_B$, a G-protein-coupled receptor that is linked to K^+ channels and that inhibits the AC-cAMP-PKA pathway, leads to inhibition of the postsynaptic neuron and a dampening down of pain signals communicated to the brain.

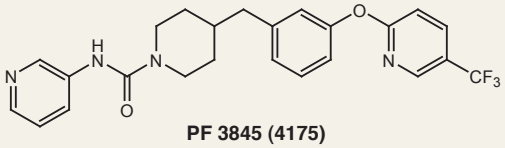
pathways which include enzymes such as phospholipase A_2, phospholipase C and NAPE-PLD. 2-AG is synthesized from arachidonic acid-containing diacylglycerol (DAG) by the action of diacylglycerol lipase (DAGL). Several other putative endocannabinoids have since been found including noladin ether (Cat. No. 1411), virodhamine (Cat. No. 1569) and NADA (Cat. No. 1568). The endocannabinoids are thought to be synthesized on demand by activity-dependent or receptor-stimulated cleavage of membrane lipid precursors, and are released from postsynaptic cells immediately following their production. The endocannabinoids can then regulate neurotransmitter release on the presynaptic neuron through CB receptors, which influences calcium influx driving exocytosis. Therefore they can control GABAergic or glutamatergic transmission by retrograde signaling (Figure 7).

Box 9: Cannabinoid Modulation Products

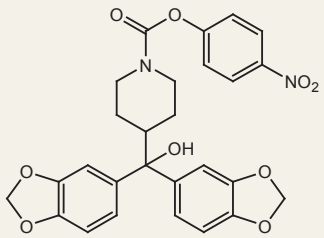
A full list of targets and related products are listed on pages 23-33



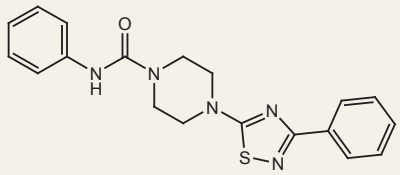
AM 404 (1116)
Anandamide transport inhibitor



PF 3845 (4175)
Selective FAAH inhibitor



JZL 184 (3836)
Monoacylglycerol lipase (MAGL) inhibitor



JNJ 1661010 (3262)
Selective, reversible FAAH inhibitor

The CB_1 receptor is found mainly in the CNS and has been identified at the peripheral and central terminals of primary afferents. In neuropathic pain states, the levels of CB_1 protein and mRNA are increased in DRG neurons projecting into the injured nerve. In contrast, CB_1 knockout studies have demonstrated that these mice are hypersensitive to mechanical stimulation. Agonists for the CB_1 receptor such as ACEA (Cat. No. 1319) and WIN 55,212-2 (Cat. No. 1038) have demonstrated success in alleviating mechanical allodynia, acute pain and hyperalgesia *in vivo*, through both peripheral and central mechanisms. In the spinal cord, the non-selective cannabinoid receptor agonist CP 55,940 (Cat. No. 0949) has shown antinociceptive effects, and application of the selective CB_1 agonist ACEA (Cat. No. 1319) inhibited spinal nociceptive transmission.

The main hurdle in activating CB_1 receptors in the CNS for the alleviation of pain is the association with psychotropic side effects, temporary memory impairment and dependence that arise as an effect on forebrain circuits. Therefore, the clinical exploitation of cannabinoids must first overcome their adverse side effects, without attenuating their analgesic properties.

The CB_2 receptor was originally thought to be localized solely to the immune system, but has now also been identified in the brain, DRG, spinal cord and sensory neurons. The CB_2 agonists HU 308 (Cat. No. 3088), JWH 133 (Cat. No. 1343) and GW 405833 (Cat. No. 2374) have provided direct support for the hypothesis that CB_2 produces antinociceptive effects in persistent pain states. Importantly, CB_2 selective agonists lack the centrally-mediated side effects on motility, body temperature or cognition typically observed with CB_1 agonists. Consequently, it has been proposed that CB_2 agonists would be unlikely to be psychoactive and therefore may be ideal candidates to provide analgesia independent of unwanted side effects.

Some biological effects reported for particular cannabinoids have been found to be independent of CB_1 or CB_2 receptor activity and have since been attributed to GPR55 such as (-)-cannabidiol (Cat. No. 1570). GPR55 is also activated by the cannabinoid ligand CP 55,940 (Cat. No. 0949) and a cannabidiol analog O-1602 (Cat. No. 2797). The GPR55 receptor antagonist O-1918 (Cat. No. 2288) blocks nociceptive firing in afferent C-fibers, suggesting that manipulation of GPR55 is a valid therapeutic target for pain. A useful tool developed to fluorescently label GPR55 receptors *in vitro* is Tocrifluor T1117 (Cat. No. 2540), a 5-TAMRA fluorescently-labeled form of AM 251 (Cat. No. 1117), that fluoresces at 543 nm excitation and can be used to help identify the neuronal expression of the GPR55 receptor (Figure 8).

Cannabinoid Modulation

In addition to treating pain states by targeting cannabinoid receptors, a new approach is to target endogenous cannabinoids

and their tonic influence over nociception in the CNS. Reuptake of endocannabinoids from the synaptic space, whereby they are broken down within the cell, is reported to be facilitated by a transporter that has yet to be identified (endogenous cannabinoid transporter – ECT). However, pharmacological inhibitors of this unidentified transporter have been developed, including AM 404 (Cat. No. 1116), OMDM-2 (Cat. No. 1797), UCM 707 (Cat. No. 1966) and VDM 11 (Cat. No. 1392). These have shown antinociceptive effects in neuropathic and inflammatory rodent pain models. Systemic administration of these putative transport inhibitors increases levels of naturally occurring endocannabinoids AEA and 2-AG in the brain, providing a novel mechanism for alleviating symptoms of pain.

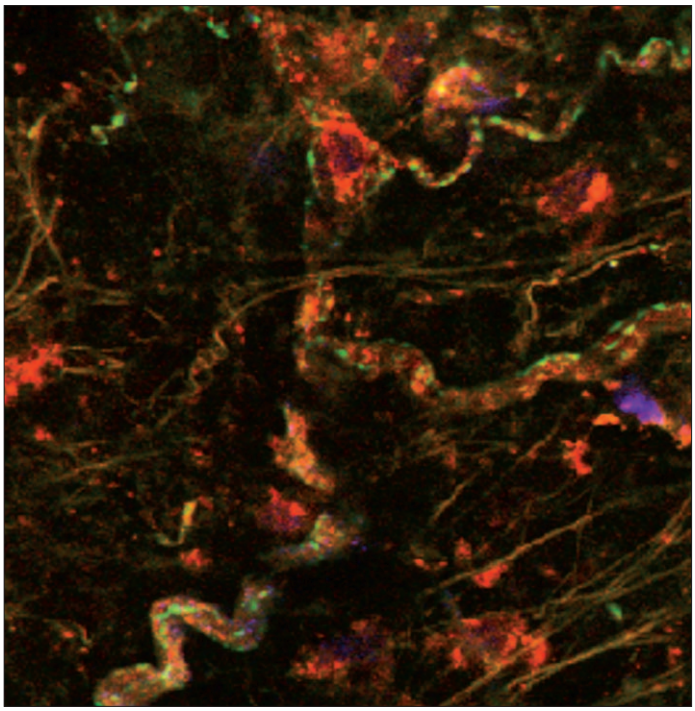
Within the cell, endocannabinoids are degraded by enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). FAAH hydrolyzes AEA to arachidonic acid (AA), whereas 2-AG is metabolized to AA by MAGL (Figure 7). Inhibitors for FAAH such as MAFP (Cat. No. 1421), PF 750 (Cat. No. 3307), arachidonyl serotonin (Cat. No. 2836) and JNJ 1661010 (Cat. No. 3262) (Box 9), have been shown to possess antinociceptive properties and are effective in reducing allodynia and hyperalgesia. Inhibitors for MAGL, such as JZL 184 (Cat. No. 3836) and *N*-arachidonyl maleimide (Cat. No. 3329), elevate levels of endocannabinoids in the body and therefore may have a beneficial effect in boosting natural pain relief mechanisms (Box 9). Inhibition of DAGL, an enzyme that catalyzes the conversion of 1,2-diacylglycerol (DAG) into 2-AG using the inhibitor, RHC 80267 (Cat. No. 1842) may also be useful for examining the role of endogenous cannabinoids.

The proposed tonic influence of endocannabinoids in the CNS could be targeted through inactivating FAAH, the enzyme responsible for cannabinoid breakdown. Indeed this has been demonstrated in FAAH knockout mice that have reduced hyperalgesia. Whilst endocannabinoids appear to exert a moderate influence on pain pathways, elevation of their endogenous levels by inhibition of FAAH or manipulation of endocannabinoid transporters may present a therapeutic strategy for modulating endocannabinoid tone. This could have significant effects on analgesia in pain models, without the side effects associated with CB_1 agonists, making endocannabinoids a potential target for modulating long term pain.

Opioids

Opioids are a well-established classical treatment for pain and remain one of the most effective targets in pain therapeutics to this day. Opioid receptors are found within the CNS, as well as throughout peripheral tissues. These G-protein-coupled receptors are stimulated by endogenous peptides such as endorphins, enkephalins and dynorphins, and are currently classified into four types: kappa (κ), delta (δ), mu (μ) and NOP receptors, with multiple subtypes within each group.

Figure 8 | Fluorescent ligand binding in the perivascular nerve



Fluorescent ligand, Tocrifluor T1117 (Cat. No. 2540), shows GPR55 receptor (red/orange) expression in perivascular nerve cells and blood vessels, additional staining illustrates expression of α_1-adrenoceptors (green). Image kindly provided by Dr Craig Daly, University of Glasgow (see Daly *et al* (2010), for further reference).

The term 'opioid' applies to any substance which produces morphine-like effects and can be blocked by antagonists such as naloxone (Cat. No. 0599). Opioids have an unmatched effectiveness in easing pain yet they have serious side effects including nausea, constipation, respiratory depression, sleepiness, depression, hallucinations and dependence due to their highly addictive properties.

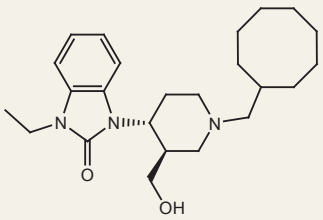
Opioids inhibit adenylyl cyclase by binding to inhibitory G-proteins ($G_{i/o}$), thereby reducing intracellular cAMP levels. They also exert an analgesic effect through direct coupling to ion channels, specifically by opening potassium channels and inhibiting calcium channel opening. The overall effect is a reduced neuronal excitability and a decrease in the release of pain neurotransmitters, resulting in analgesia.

Pure opioid agonists (e.g. morphine, hydromorphone, and fentanyl (Cat. No. 3247)) stimulate μ receptors and are the most potent analgesics. In contrast, partial agonists such as buprenorphine (Cat. No. 2808) or pentazocine exhibit a 'ceiling effect'; that is, they have no further effect on pain above a particular dosage.

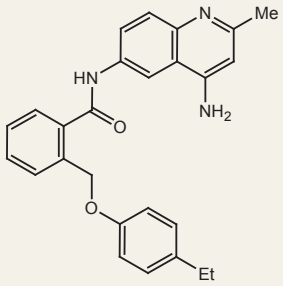
Analgesia can also be achieved by targeting specific subtypes of opioid receptors. The highly selective δ opioid receptor agonist SNC 80 (Cat. No. 0764) produces both antinociceptive

Box 10: Opioid Receptor Products

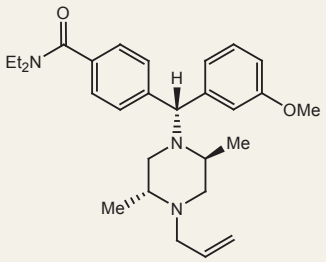
A full list of targets and related products are listed on pages 23-33



J-113397 (2598)
Potent and selective NOP antagonist



JTC 801 (2481)
Selective NOP antagonist



SNC 80 (0764)
Highly selective non-peptide δ agonist

Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln

Nociceptin (0910)
Endogenous NOP agonist

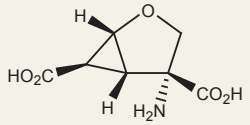
Tyr-D-Ala-Gly-NMe-Phe-Gly-ol

DAMGO (1171)
Selective μ agonist

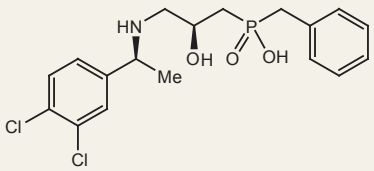
and antidepressant effects in rodents, whereas endomorphin-1 (Cat. No. 1055) and endomorphin-2 (Cat. No. 1056) are potent analgesic peptides that show the highest affinity and selectivity for the μ opioid receptor. Additionally, the μ opioid agonist DAMGO (Cat. No. 1171) produces long lasting antinociceptive effects in a rat model of neuropathic pain. The NOP novel opioid receptor-like 1 (ORL_1) receptor antagonists JTC 801 (Cat. No. 2481) and (±)-J 113397 (Cat. No. 2598), demonstrate potent antinociceptive effects in animal models of acute pain (Box 10).

Box 11: mGlu and $GABA_B$ Receptor Products

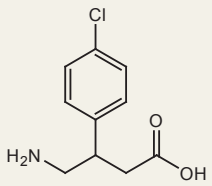
A full list of targets and related products are listed on pages 23-33



LY 379268 (2453)
Highly selective group II mGlu agonist



CGP 55845 (1248)
Potent, selective $GABA_B$ antagonist



(*RS*)-Baclofen (0417)
Selective $GABA_B$ agonist

Glutamate (Metabotropic) Receptors

Glutamate metabotropic receptors (mGluRs) have also been identified as a therapeutic targets in pain. They are G-protein-coupled receptors that are divided into three groups : mGlu Group I-III. Glutamate binding to the extracellular region of an mgluR activates G-proteins bound to the intracellular region of the receptor to be phosphorylated which then affects multiple intracellular pathways in the cell (Figure 7). Compounds that selectively target the mGluR subtypes have demonstrated an ability to block pain pathways. These include the selective $mGlu_{1a}$ receptor antagonist, LY 367385 (Cat. No. 1237) and highly potent group II antagonist LY 341495 (Cat. No. 1209). There is also evidence that mGluR agonists, such as the $mGlu_2$ receptor agonist LY 379268 (Cat. No. 2453) (Box 11) and $mGlu_3$ agonist L-AP4 (Cat. No. 0103), can reverse pain pathways that are locked in a sensitized state, demonstrating a different approach to targeting persistent pain. Advances in the identification of compounds that are subtype-selective and systemically active have allowed investigators to begin to determine the therapeutic potential of the glutamate receptor in persistent pain states along with the ionotropic glutamate receptors.

GABA

The $GABA_B$ receptor is a metabotropic receptor that is linked via G-proteins to potassium channels (Figure 7). Altering the potassium concentration in the cell leads to hyperpolarization thus preventing sodium channels opening and action potentials

from firing. Hence they are considered inhibitory receptors. The $GABA_B$ receptor agonist (*RS*)-Baclofen (Cat. No. 0417) has been shown to have analgesic properties whereas the $GABA_B$ antagonist CGP 55845 (Cat. No. 1248) blocks the antinociceptive actions of cholinergic agents (Box 11). Inhibition of GABA uptake by the GABA transporter GAT-1 is also a target with NNC 711 (Cat. No. 1779), a GAT-1 inhibitor, demonstrating an ability to induce analgesia in a rat model of sciatic nerve injury. The evidence suggests that stimulation of GABA receptors at certain sites to offset the sedative side effects could be beneficial in the management of pain.

Adenosine and P2Y Receptors

The adenosine receptor (also categorized as a purinergic P1 receptor) is a G-protein-coupled receptor that has recently been associated with research into pain. Several adenosine receptor agonists have progressed through clinical trials, demonstrating that adenosine is a potential target for new drug development in pain. There are four types of adenosine receptors, A_1, A_{2A}, A_{2B} and A_3, all of which couple to G-proteins. In functional studies, peripheral administration of A_1 and A_{2A} receptor agonists such as, N^6-Cyclopentyladenosine (Cat. No. 1702) and CGS 21680 (Cat.No. 1063) respectively, lead to antinociception against hyperalgesia. The role of A_{2B} and A_3 receptors seem to be largely associated with inflammatory pain. It has also recently become apparent that the metabotropic P2Y receptor can be found on sensory afferents and may have a role in modulating pain transmission. P2Y receptors are G-protein-coupled receptors that are in the same family as the ionotropic P2X receptor. *In vivo* studies have revealed that administration of the $P2Y_{2/4}$ agonist UTPγS (Cat.No. 3279) inhibits pain transmission and $P2Y_1$ agonist MRS 2500 (Cat. No. 2159) reduces hyperalgesia, suggesting that the P2Y receptor could also potentially be an important pain target.

Substance P and Tachykinin Receptors

The neuropeptide substance P (Cat. No. 1156) and its closely related neuropeptide, neurokinin A (Cat. No. 1152), are thought to play an important physiological role in the modulation of nociception. They are involved in relaying the intensity of noxious or painful stimuli, although can also be released from the peripheral terminals of sensory nerve fibers in the skin, muscle and joints to initiate pain. Substance P is a ligand for the tachykinin seven-transmembrane GPCR family and its endogenous receptors are called neurokinin 1 (NK_1) and NK_2. Substance P coexists with glutamate in primary afferents that respond to painful stimuli. Administration of NK_1 antagonists such as L-732,138 (Cat. No. 0868) and RP 67580 (Cat. No. 1635) (Box 12) have been shown to attenuate hyperalgesia in rats, although this has not been proven clinically.

Bradykinin Receptors

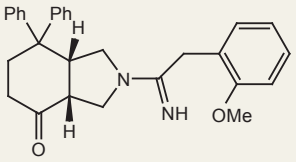
Bradykinin, although considered to be a peripherally acting inflammatory mediator, has also been proposed to play a role in pain transmission. Bradykinin is released from kininogen precursors at the site of tissue injury and inflammation and acts on G-protein-coupled bradykinin receptor subtypes in primary sensory neurons. The bradykinin 1 (B_1) receptor is activated by injury whilst the B_2 receptor is constitutively active. B_2 agonists including bradykinin (Cat. No. 3004), have been shown to induce thermal hyperalgesia, whilst B_2 antagonists such as HOE 140 (Cat. No. 3014) reduce pain sensation in the formalin test of pain hypersensitivity. The B_1 receptor, usually absent from non-inflamed tissue and with a low affinity for bradykinin, is thought to play a lesser role in pain transduction. However, as demonstrated with B_2 agonists, B_1 receptor agonists such as Lys-[Des-Arg^9]Bradykinin (Cat. No. 3225) also produce a nociceptive response and B_1 receptor antagonists such as R 715 (Cat. No. 3407) (Box 12) may be useful for investigating further the role of the B_1 receptor in nociception.

Box 12: Bradykinin and Tachykinin Receptor Products

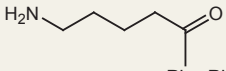
A full list of targets and related products are listed on pages 23-33

D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg

HOE 140 (3014)
Potent and selective B_2 antagonist



RP 67580 (1635)
Potent and selective NK_1 antagonist



Phe-Phe-Pro-(Me)Leu-Met-NH_2

GR 73632 (1669)
Potent and selective NK_1 agonist

Ac-Lys-Arg-Pro-Pro-Gly-Phe-Ser-DβNal-Ile

R 715 (3407)
Potent and selective B_1 antagonist

Intracellular Signaling

The transition between 'acute' and 'chronic' pain is largely arbitrary, with temporal cut-offs after which point acute pain is renamed chronic pain. Understanding the cellular mechanisms underlying chronic pain states will be crucial for the development of new long-term therapeutic strategies. Neuronal plasticity at multiple sites in the pain pathway is now widely accepted as critical in the maintenance of chronic pain. The cellular mechanisms that underlie this plasticity are not well known, although are likely to involve changes in gene expression and regulation of protein synthesis. In the nociceptor, changes in synaptic strength and efficacy can trigger increases in the transduction of pain signals. Plasticity can also occur at peripheral terminals of nociceptors, where changes in receptor and channel expression, distribution, and activation thresholds can generate hypersensitivity. It is through multiple intracellular pathways that these changes occur; for example, protein kinase A (PKA), PKC and PKG cascades can generate posttranslational modifications on target proteins that affect their activation and trafficking. The regulation of gene transcription and translation that controls expression of proteins has been suggested to occur primarily through the ERK and PI 3-K/mTOR signaling cascades (Figure 9) which have been highlighted as potential areas that will generate future therapeutic pain targets.

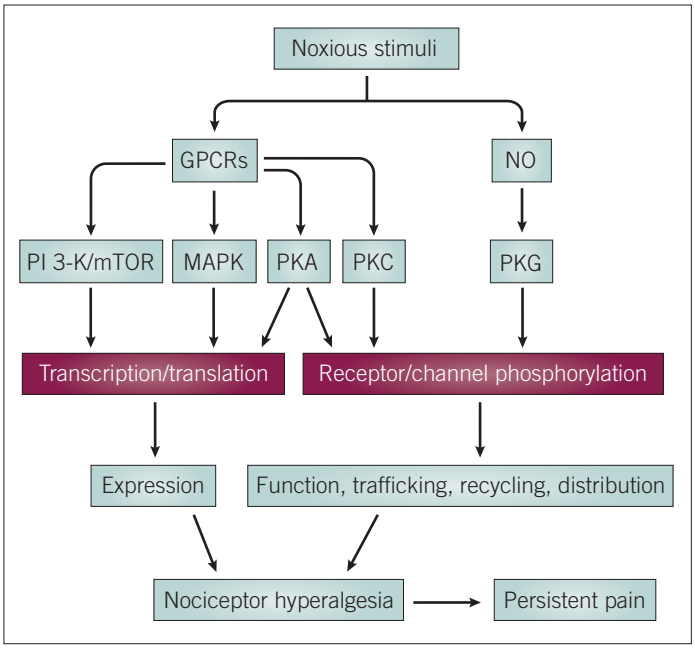
Protein Kinase A

PKA exerts a profound modulatory role on sensory nociceptor physiology. Activation of PKA by cAMP is sufficient to produce hyperalgesia in nociceptors. It may mediate some of these effects through direct phosphorylation of TTx-R sodium channels such as $Na_v1.8$ or TRPV1 channels, both of which have been shown to induce pain in a neuropathic pain model. PKA also interacts with MEK, a component of the MAPK pathway, leading to activation of further downstream targets. This can regulate gene expression, affecting neuronal plasticity. Opioid receptors, meanwhile, produce analgesia by inhibiting adenylyl cyclase, thereby blocking PKA activation, hence making it a key therapeutic pain target. Injection of a PKA inhibitor, cAMPS-Rp (Cat. No. 1337), before a painful stimulus was shown to inhibit hyperalgesia (Box 13). Furthermore, H 89 (Cat. No. 2910), also a PKA inhibitor, was able to block the nociceptive response to an inflammatory agent in sensory pain fibers. Activation of PKA signaling pathways implicated in pain can also be achieved using drugs such as 8-Bromo-cAMP (Cat. No. 1140) or cAMPS-Sp (Cat. No. 1333), which are membrane-permeable cAMP analogs that stimulate PKA phosphorylation.

Protein Kinase C

PKC consists of 15 isozymes that can be divided into three groups, conventional, novel and atypical. The conventional isozymes are activated by a process requiring phospholipase C (PLC), diacylglycerol (DAG) and calcium. In contrast, the novel forms do not require calcium and atypical forms do not require DAG or calcium. Activation of PKC has been shown to enhance the TTx-R sodium currents and TRPV1 channel currents. In particular, PKCε can translocate to the plasma membrane of nociceptors in response to inflammatory mediators such as bradykinin and substance P. PKCε activity has also been linked to maintaining the 'primed' state whereby nociceptors have increased sensitivity to noxious stimuli, characteristic of chronic pain. PKC inhibitors, GF 109203X (Cat. No. 0741) and chelerythrine (Cat. No. 1330) have demonstrated significant reductions in rat models of mechanical

Figure 9 | Intracellular signaling in chronic pain states



MAPK and PI 3-K/mTOR signaling pathways are thought to be the primary pathways involved in chronic pain and the regulation of gene transcription and translation in nociceptors. PKC, PKA and PKG pathways control posttranslational regulation of receptor and channel proteins, and also have influences on gene expression. Long term modulation of nociceptor plasticity in this way can lead to hyperalgesia and persistent pain states.

hyperalgesia, therefore it will be interesting to see how inhibitors of PKCε and other isoforms advance in the current research field.

Protein Kinase G and Nitric Oxide

In contrast, less is known about the role of cGMP/PKG signaling and nitric oxide (NO)-mediated modulation of pain. NO stimulates guanylyl cyclase which activates cGMP and PKG. Studies have shown that intracutaneous injections of NO precursors evoke pain, implicating it as a pronociceptive mediator. However, NO has been shown to mediate the analgesic effects of opioids and other analgesic substances, suggesting its role in nociception is complex and diverse. Classical inhibitors such as L-NAME (Cat. No. 0665) will help to define the role of NO in pain. Newer products such as the soluble guanylyl cyclase inhibitor, NS 2028 (Cat. No. 4517), may offer increased selectivity in targeting the cGMP/PKG pathway.

MAPK Signaling

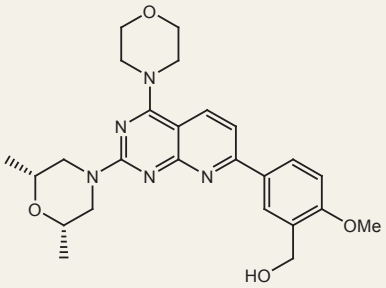
MAPK is a critical kinase in cell signaling pathways. It transduces extracellular stimuli into intracellular translational and transcriptional responses. Stimulation of nociceptive DRG neurons increases phosphorylation of various types of MAPK which initiate changes in short term acute pain or long term transcription. The three major MAPK family members – ERK, p38 and c-Jun N-terminal kinase (JNK) – represent three different MAPK signaling cascades. Whilst inhibition of all three MAPK pathways has been shown to attenuate persistent pain after nerve injury, increased ERK and / or p38 activity has been linked to pain plasticity upstream of ERK. The ERK pathway involves a sequential cascade including Ras, Raf, and MEK. MEK inhibitors such as PD 98059 (Cat. No. 1213) and U0126 (Cat. No. 1144) demonstrate an ability to block acute pain behavior after formalin injection, suggesting that ERK must play a role in short term nociception given the short-time involved. However, ERK produces not only short-term functional changes by non-transcriptional mechanisms but has also been suggested to generate long-term adaptive changes by modification of gene transcription and translation. Direct ERK inhibitors have been useful in blocking this pathway such as the selective ERK inhibitor, FR 180204 (Cat. No. 3706). p38 is typically activated by MKK4 protein kinases and can be inhibited by SB 203580 (Cat. No. 1202), demonstrating an ability to reduce mechanical allodynia and reverse the pain associated with arthritis. p38 MAPK activation has also been implicated in increasing TRPV1 channel expression at the plasma membrane and contributes to pain hypersensitivity and the early development of mechanical allodynia. Less is known about the role of JNK in pain, yet SP 600125 (Cat. No. 1496) a JNK inhibitor attenuates pain after repeated injection over several days, demonstrating an accumulated analgesic effect in a rat cancer-induced bone pain model (Box 13).

PI 3-K/Akt/mTOR Pathway

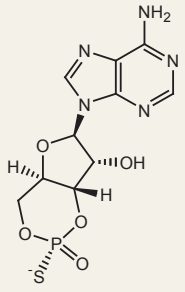
The PI 3-K/mTOR pathway appears to play a key role in plasticity. PI 3-kinase (PI 3-K) is a lipid kinase that generates PIP_3 from membrane phosphoinositides, thereby activating the serine/threonine kinases Akt and mTOR, which regulate gene

Box 13: Intracellular Signaling Products

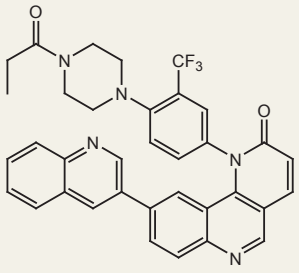
A full list of targets and related products are listed on pages 23-33



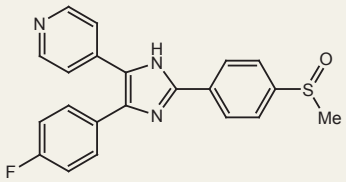
KU 0063794 (3725)
Selective mTOR inhibitor



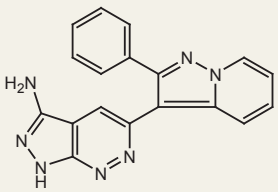
cAMPS-Rp (1337)
cAMP antagonist



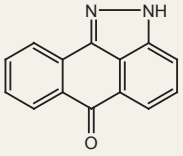
Torin 1 (4247)
Potent and selective mTOR inhibitor



SB 203580 (1202)
Selective inhibitor of p38 MAPK



FR 180204 (3706)
Selective ERK inhibitor



SP 600125 (1496)
Novel and selective JNK inhibitor

expression. Increased activation of Akt and mTOR is observed in DRG and dorsal horn neurons following nerve injury, therefore inhibition of this pathway is an important target in pain research. Selective PI 3-kinase inhibitors, such as LY 294002 (Cat. No. 1130) and 740 Y-P (Cat. No. 1983), have demonstrated an ability to block downstream phosphorylation of Akt and the initiation of hyperalgesia. Inhibition of mTOR activity in the spine by rapamycin (Cat. No. 1292) shows antinociceptive effects in animal models of pain. Systemic administration of Torin 1 (Cat. No. 4247), also an mTOR inhibitor, reduces the response to mechanical and cold stimuli in mice experiencing neuropathic pain (Box 13). KU 0063794 (Cat. No. 3725) is a selective mTOR inhibitor which shows no activity at PI 3-kinase and maybe be useful in investigating the physiological role of mTOR in nociception. mTOR has been shown to play a key role in phosphorylation of a protein, 4E-BP that controls the initiation of protein translation. Direct inhibition of protein translation can be achieved by targeting the downstream binding protein, eIF4E, with 4E1RCat (Cat. No. 4215), a small molecule inhibitor that prevents assembly of the regulatory protein complex. Therefore the multiple roles of mTOR in transcription, translation and posttranslational modifications make it an important target in pain research, provided specificity or direct targeting of peripheral nociceptors can be achieved.

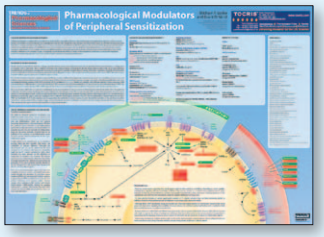
Investigations of these complex intracellular pathways using selective inhibitors and activators will help deepen our understanding of the genesis of both acute and long-term chronic pain, whilst also helping to identify new targets for pharmacological intervention.

List of Acronyms

Acronym	Definition
2-AG	2-arachidonoylglycerol
4-AP	4-aminopyridine
AA	Arachidonic acid
AA-5-HT	Arachidonyl serotonin
AC	Adenylyl cyclase
ACh	Acetylcholine
AEA	Anandamide
AMPA	2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid
ASIC	Acid-sensing ion channel
ATP	Adenosine triphosphate
BK	Bradykinin
Ca_V	Voltage-gated calcium channel
CB	Cannabinoid
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
COX	Cyclooxygenase
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
DAG	Diacylglycerol
DAGL	Diacylglycerol lipase
DRG	Dorsal root ganglion
ECT	Endocannabinoid transporter
ERK	Extracellular signal-regulated kinase
Et	Ethanolamine
FAAH	Fatty acid amide hydrolase
GABA	γ-aminobutyric acid
GDP	Guanosine diphosphate
GL	Glycerol
GPCRs	G-protein-coupled receptors
GTP	Guanosine triphosphate
H^+	Hydrogen
HCN	Hyperpolarization-activated cyclic nucleotide-modulated

Acronym	Definition
IASP	International Association for the Study of Pain
JNK	c-Jun N-terminal kinase
K_V	Voltage-gated potassium channel
KA	Kainate
MAG	Monoacylglycerol
MAGL	Monoacylglycerol lipase
MAPK	Mitogen-activated protein kinase
MEK	MAP/ERK kinase
mGluR	Metabotrophic glutamate receptor
mRNA	Messenger ribonucleic acid
mTOR	Mammalian target of rapamycin
Na_V	Voltage-gated sodium channel
nAChR	Nicotinic acetylcholine receptor
NAPE-PLD	N-acyl phosphatidylethanolamine phospholipase D
NADA	N-arachidonoyldopamine
NAE	N-acyl ethanolamine
NK	Neurokinin
NMDA	N-Methyl-D-aspartic acid
NO	Nitric oxide
NOS	Nitric oxide synthase
NSAIDs	Non-steroidal anti-inflammatory drugs
PI 3-K	Phosphoinositide 3-kinase
PIP_3	Phosphatidylinositol (3,4,5)-triphosphate
PKA	Protein kinase A
PKC	Protein kinase C
PKG	Protein kinase G
PLC	Phospholipase C
PNS	Peripheral nervous system
TRP	Transient receptor potential
TTx	Tetrodotoxin
TTx-R	Tetrodotoxin-resistant
TEA	Tetraethylammonium

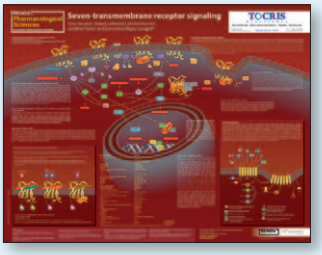
Related literature from Tocris that you may be interested in:



Pharmacological Modulators of Peripheral Sensitization

Michael R. Vasko and Grant D. Nicol, Indiana University

Peripheral sensitization is defined as a reduction in the threshold of excitability of sensory neurons that results in an augmented response to a given external stimulus. This poster summarizes the key receptors, channels and pathways in peripheral sensitization.



Seven-transmembrane Receptor Signaling

Terry Kenakin, Robert Lefkowitz, Michel Bouvier, Jonathan Violin and Genevieve Oligny-Longpré, GlaxoSmithKline, Durham University, Université de Montréal

7-transmembrane (7-TM) receptors are complex processors of information that can bind molecules and cytosolic interactants at the cell membrane, resulting in various signaling events and cellular responses. This poster summarizes the intracellular pathways involved in 7-TM signaling.

Cannabinoid Receptor Ligands

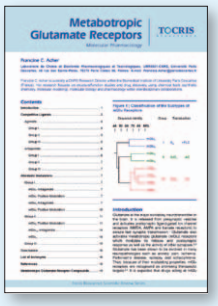
Roger G. Pertwee, University of Aberdeen

Cannabinoid receptors are composed of two types: CB_1 and CB_2. This review discusses the modulation of cannabinoid receptors

P2X and P2Y Receptors

Kenneth A. Jacobson, National Institutes of Health, Maryland

Purinergic receptors are made up of P2X and P2Y receptors. This review discusses the structure and function of P2X and P2Y receptors and key pharmacological modulators for each subtype.



Metabotropic Glutamate Receptors

Francine C. Acher, Universite Paris Descartes

Glutamate is the major excitatory neurotransmitter in the brain. It acts on ionotropic receptors (NMDA, AMPA and KA receptors) as well as metabotropic glutamate receptors (mGluR). This review provides an overview of the metabotropic glutamate receptors.

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Pain Research Products from Tocris

Category	Cat. No.	Product Name	Description	Unit Size	USD
Adenosine Receptors					
Agonists	1063	CGS 21680	A_{2A} agonist	10 mg 50 mg	265 1115
	1705	2-Chloro-N^6-cyclopentyladenosine	Potent, selective A_1 agonist	10 mg 50 mg	135 569
	1104	2-Cl-IB-MECA	Highly selective A_3 agonist	10 mg 50 mg	339 1425
	1710	CV 1808	Non-selective A_2 receptor agonist	10 mg	95
	1702	N^6-Cyclopentyladenosine	Potent, selective A_1 agonist	50 mg	115
	1066	IB-MECA	A_3 selective agonist	5 mg 25 mg	195 819
Antagonists	0439	DPCPX	A_1 selective antagonist	100 mg	169
	2752	MRS 1754	Selective A_{2B} antagonist	10 mg 50 mg	195 819
	2403	MRS 3777	High affinity, selective A_3 antagonist	10 mg	155
	2270	SCH 58261	Potent, highly selective A_{2A} antagonist	10 mg 50 mg	185 779
	1036	ZM 241385	Potent, highly selective A_{2A} antagonist	10 mg 50 mg	155 655
ASIC Channels					
Blockers	0890	Amiloride	Non-selective ASIC blocker	100 mg	59
	4804	APETx2	ASIC3 channel blocker	100 µg	315
Modulators	3647	Neuropeptide SF (mouse, rat)	Modulates ASIC3 currents. Also NPFF agonist	1 mg	195
Bradykinin Receptors					
Agonists	3004	Bradykinin	Endogenous agonist at bradykinin receptors ($B_2 > B_1$)	5 mg	79
	3225	Lys-[Des-Arg^9]Bradykinin	Selective B_1 agonist	1 mg	75
Antagonists	3014	HOE 140	Potent and selective B_2 antagonist	500 µg	195
	3407	R 715	Potent and selective B_1 antagonist	1 mg	205
Calcium Channels					
Activators	1544	(±)-Bay K 8644	Ca^{2+} channel activator (L-type)	10 mg 50 mg	165 695
	1403	FPL 64176	Potent activator of Ca^{2+} channels (L-type)	10 mg 50 mg	125 525
Blockers	2799	ω-Agatoxin IVA	Ca^{2+} channel blocker (P-type)	10 µg	195
	2802	ω-Agatoxin TK	Ca^{2+} channel blocker (P/Q-type)	10 µg	195
	1085	ω-Conotoxin GVIA	Ca^{2+} channel blocker (N-type)	250 µg	325
	1084	ω-Conotoxin MVIIC	Ca^{2+} channel blocker (N-, P- and Q-type)	100 µg	235
	0806	Gabapentin	Selectively binds the $\alpha_2\delta$ subunit of Ca_V channels. Anticonvulsant	10 mg 50 mg	125 495
	2198	Mibefradil	Ca^{2+} channel blocker (T-type)	10 mg 50 mg	195 819
	1075	Nifedipine	Ca^{2+} channel blocker (L-type)	100 mg	75
	0600	Nimodipine	Ca^{2+} channel blocker (L-type)	100 mg	105
	2268	NNC 55-0396	Highly selective Ca^{2+} channel blocker (T-type)	10 mg	255
	3552	PD 173212	Potent N-type Ca^{2+} channel blocker	10 mg	265
	3775	Pregabalin	Selectively binds the $\alpha_2\delta$ subunit of Ca_V channels. Anticonvulsant	10 mg 50 mg	169 715
	2945	SNX 482	Potent and selective $Ca_V2.3$ blocker (R-type)	10 µg	169

Category	Cat. No.	Product Name	Description	Unit Size	USD
Cannabinoid CB_1 Receptors					
Agonists	1319	ACEA	Potent, highly selective CB_1 agonist	5 mg 25 mg	69 295
	1121	(*R*)-(+)-Methanandamide	Potent and selective CB_1 agonist	5 mg	95
	1568	NADA	Endogenous CB_1 agonist. Also inhibitor of FAAH and AMT	5 mg 25 mg	109 459
Antagonists	1117	AM 251	Potent CB_1 antagonist. Also GPR55 agonist	1 mg 10 mg 50 mg	75 155 655
	1115	AM 281	Potent, selective CB_1 antagonist/inverse agonist	10 mg 50 mg	195 819
	4236	CP 945598	CB_1 receptor antagonist	10 mg 50 mg	219 925
	4063	MJ 15	Potent and selective CB_1 antagonist	10 mg 50 mg	189 795
	3676	PF 514273	Potent and selective CB_1 antagonist	10 mg 50 mg	195 819
Cannabinoid CB_2 Receptors					
Agonists	2764	GP 1a	Highly selective CB_2 agonist	10 mg 50 mg	219 925
	2374	GW 405833	Selective, high affinity CB_2 receptor partial agonist	10 mg	185
	3088	HU 308	Potent and selective CB_2 agonist	10 mg 50 mg	249 1049
	1343	JWH 133	Potent, selective CB_2 agonist	10 mg	245
	4205	MDA 19	CB_2 agonist	10 mg 50 mg	169 715
Antagonists	1120	AM 630	CB_2 selective antagonist/inverse agonist	10 mg 50 mg	195 819
	2479	JTE 907	Selective CB_2 receptor antagonist/inverse agonist	10 mg 50 mg	195 819
Cannabinoid GPR55 Receptors					
Agonists	1411	Noladin ether	Endogenous GPR55 and CB_1 receptor agonist	5 mg 25 mg	139 585
	2797	O-1602	Potent GPR55 receptor agonist	10 mg	195
	1484	Oleylethanolamide	GPR55 agonist	10 mg 50 mg	89 365
	0879	Palmitoylethanolamide	Selective GPR55 agonist; FAAH and PAA substrate	10 mg 50 mg	89 375
Cannabinoid Receptors (Non-selective)					
Agonists	1339	Anandamide	Endogenous cannabinoid receptor agonist	5 mg 25 mg	79 289
	1298	2-Arachidonylglycerol	Endogenous cannabinoid agonist	10 mg	185
	2928	CB 13	Potent dual CB_1/CB_2 agonist	10 mg 50 mg	125 525
	0949	CP 55,940	Potent, non-selective cannabinoid receptor agonist	10 mg 50 mg	239 1005
	0966	HU 210	Highly potent cannabinoid agonist	5 mg 25 mg	185 779
	2540	Tocrifluor T1117	Novel fluorescent cannabinoid ligand. Fluorescent form of AM 251 (Cat. No. 1117)	100 µg	265
	1038	WIN 55,212-2	Highly potent cannabinoid agonist	10 mg 50 mg	89 375
Antagonists	1570	(-)-Cannabidiol	Natural cannabinoid; GPR55 antagonist, weak CB_1 antagonist, CB_2 inverse agonist	10 mg 50 mg	149 629
	1655	O-2050	Putative CB_1 silent antagonist; displays mixed activity at CB receptors	10 mg	265

Pain Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size	USD
Cannabinoid Modulation					
Inhibitors	2836	Arachidonyl serotonin	Dual FAAH inhibitor/TRPV1 antagonist	10 mg	105
	3262	JNJ 1661010	Selective, reversible FAAH inhibitor	10 mg 50 mg	155 655
	3836	JZL 184	Monoacylglycerol lipase (MAGL) inhibitor	10 mg 50 mg	125 445
	1815	Palmitoylisopropylamide	FAAH inhibitor	10 mg 50 mg	89 365
	4175	PF 3845	Selective FAAH inhibitor	10 mg 50 mg	245 1029
	3307	PF 750	Selective FAAH inhibitor	10 mg 50 mg	195 819
	3731	Pristimerin	Potent, reversible MAGL inhibitor	10 mg 50 mg	195 819
	1842	RHC 80267	Diacylglycerol lipase inhibitor	10 mg 50 mg	139 585
	4355	TC-F 2	Potent, reversible and selective FAAH inhibitor	10 mg 50 mg	205 865
Cannabinoid Transport					
Inhibitors	3381	AM 1172	Anandamide uptake inhibitor. Also FAAH inhibitor and CB receptor partial agonist	10 mg	195
	1116	AM 404	Anandamide transport inhibitor	10 mg 50 mg	89 369
	1354	Arvanil	Anandamide transport inhibitor Also potent CB_1 and TRPV1 agonist	5 mg 25 mg	69 239
	2452	LY 2183240	Novel, potent anandamide uptake inhibitor. Inhibits FAAH	1 mg 10 mg	115 239
	1797	OMDM-2	Potent inhibitor of anandamide uptake	5 mg 25 mg	89 375
	1966	UCM 707	Potent anandamide transport inhibitor	10 mg 50 mg	169 715
	1392	VDM 11	Potent, selective anandamide transport inhibitor	5 mg 25 mg	99 419
Cyclooxygenase					
Inhibitors	4092	Aspirin	Cyclooxygenase inhibitor; NSAID	50 mg	49
	3786	Celecoxib	Selective cyclooxygenase-2 (COX-2) inhibitor	10 mg 50 mg	155 655
	2796	(*S*)-(+)-Ibuprofen	Cyclooxygenase inhibitor (COX-1 > COX-2)	100 mg	75
	2655	Naproxen sodium	Cyclooxygenase inhibitor	50 mg	65
	4206	Valdecoxib	Selective and potent COX-2 inhibitor	10 mg 50 mg	155 655
$GABA_A$ Receptors					
Agonists	0344	GABA	Endogenous GABA receptor agonist	1 g	59
	2531	Ganaxolone	Potent, positive allosteric modulator of $GABA_A$ receptors	10 mg 50 mg	139 585
	0807	THIP	$GABA_A$ agonist; also $GABA_C$ antagonist	50 mg	139
Antagonists	2503	(-)-Bicuculline methiodide	Water-soluble $GABA_A$ antagonist	10 mg 50 mg	89 375
	1262	SR 95531	Selective, competitive $GABA_A$ receptor antagonist	10 mg 50 mg	125 495

Category	Cat. No.	Product Name	Description	Unit Size	USD
$GABA_B$ Receptors					
Agonists	0417	(*RS*)-Baclofen	Selective $GABA_B$ agonist	1 g	75
	0379	SKF 97541	Extremely potent $GABA_B$ agonist	10 mg 50 mg	169 715
Antagonists	1245	CGP 35348	Brain penetrant, selective $GABA_B$ antagonist	10 mg 50 mg	185 779
	1248	CGP 55845	Potent, selective $GABA_B$ antagonist	10 mg 50 mg	199 839
GABA Transport					
Inhibitors	1779	NNC 711	Selective inhibitor of GAT-1	10 mg 50 mg	185 779
	1561	(*S*)-SNAP 5114	GABA uptake inhibitor	10 mg 50 mg	185 779
Glutamate (Ionotropic) Receptors					
Agonists	1074	(*RS*)-AMPA hydrobromide	Selective AMPA agonist; more water soluble form of (*RS*)-AMPA (Cat. No. 0169)	1 mg 10 mg 50 mg	95 195 819
	0222	Kainic acid	Potent excitant and neurotoxin	1 mg 10 mg 50 mg	69 149 629
	0114	NMDA	Selective AMPA receptor agonist	50 mg 500 mg	89 355
	0188	L-Quisqualic acid	AMPA/group I mGlu agonist	1 mg 10 mg 50 mg	89 185 779
Antagonists	0190	CNQX	Potent AMPA/kainate antagonist	10 mg 50 mg	139 585
	0907	L-701,324	NMDA antagonist, acts at glycine site	10 mg 50 mg	139 585
	0924	(+)-MK 801	Non-competitive NMDA antagonist, acts at ion channel site	10 mg 50 mg	89 339
	0373	NBQX	Potent AMPA antagonist. More selective than CNQX (Cat. No. 0190)	10 mg 50 mg	195 819
	1594	Ro 25-6981	Subtype-selective NR2B antagonist	1 mg 10 mg 50 mg	79 165 695
Glutamate (Metabotropic) Receptors					
Agonists	0103	L-AP4	Selective group III mGlu agonist	1 mg 10 mg 50 mg	85 179 755
	0805	(*S*)-3,5-DHPG	Selective group I mGlu agonist. Active enantiomer of 3,5-DHPG (Cat. No. 0342)	5 mg 10 mg	139 259
	2453	LY 379268	Highly selective group II mGlu agonist	10 mg 50 mg	345 1449
Antagonists	0972	CPPG	Very potent group III mGlu antagonist	10 mg 50 mg	165 695
	1209	LY 341495	Highly potent, selective group II antagonist	1 mg 10 mg 50 mg	95 229 965
	1237	LY 367385	Selective $mGlu_{1a}$ antagonist	10 mg 50 mg	169 715

Pain Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size	USD
Guanylyl Cyclase					
Activators	4430	BAY 41-2272	Soluble guanylyl cyclase (sGC) activator	10 mg 50 mg	195 819
	0756	SIN-1 chloride	Guanylyl cyclase activator	50 mg	139
Inhibitors	4517	NS 2028	Potent soluble guanylyl cyclase (sGC) inhibitor	10 mg 50 mg	185 779
	0880	ODQ	Selective inhibitor of NO-sensitive guanylyl cyclase	10 mg 50 mg	99 405
HCN Channels					
Blockers	2202	Zatebradine	Bradycardic agent; blocks I_f pacemaker current	10 mg 50 mg	149 629
	1000	ZD 7288	Sino-atrial node function modulator (I_f inhibitor)	10 mg 50 mg	149 629
MAPK					
Activators	1290	Anisomycin	Activates JNK/SAPK/p38 MAPK	10 mg 50 mg	89 339
Inhibitors	3706	FR 180204	Selective ERK inhibitor	10 mg 50 mg	245 1029
	1264	SB 202190	Potent, selective inhibitor of p38 MAPK	10 mg 50 mg	169 715
	1202	SB 203580	Selective inhibitor of p38 MAPK	1 mg 10 mg 50 mg	105 215 905
	1496	SP 600125	Novel and selective JNK inhibitor	10 mg 50 mg	109 445
	4132	XMD 8-92	Selective ERK5/BMK1 inhibitor	10 mg 50 mg	219 925
MEK					
Inhibitors	1213	PD 98059	MEK inhibitor	1 mg 10 mg 50 mg	65 139 585
	1969	SL 327	Selective inhibitor of MEK1 and MEK2; brain penetrant	1 mg 10 mg 50 mg	95 199 839
	1144	U0126	Potent, selective inhibitor of MEK1 and 2	5 mg 25 mg	195 819
mTOR					
Inhibitors	3725	KU 0063794	Selective mTOR inhibitor	10 mg	239
	4257	PP 242	Dual mTORC1/mTORC2 inhibitor	10 mg 50 mg	219 925
	1292	Rapamycin	mTOR inhibitor	1 mg	255
	4247	Torin 1	Potent and selective mTOR inhibitor	10 mg 50 mg	245 1029
	4248	Torin 2	Potent and selective mTOR inhibitor	10 mg 50 mg	219 925
	4282	WYE 687	Potent and selective mTOR inhibitor	10 mg 50 mg	249 1049

Category	Cat. No.	Product Name	Description	Unit Size	USD
Nicotinic Receptors					
Agonists	4477	A 844606	Selective α7 nAChR agonist	10 mg 50 mg	169 715
	3964	AR-R 17779	α7-selective agonist	10 mg	195
	3549	3-Bromocytisine	Potent agonist of α4β4, α4β2 and α7 nACh receptors	10 mg 50 mg	195 819
	3328	Desformylflustrabromine	Positive allosteric modulator of α4β2	10 mg 50 mg	165 695
	0684	(±)-Epibatidine	Very potent nicotinic agonist	10 mg	255
	4141	LY 2087101	Potentiator of α7 nAChRs	10 mg 50 mg	169 715
	3546	(-)-Nicotine	Prototypical nAChR agonist	50 mg	65
	3092	PHA 543613	Potent and selective α7 nAChR agonist	10 mg	195
	2498	PNU 120596	Positive allosteric modulator of α7 nAChR; active *in vivo*	10 mg 50 mg	169 715
	1053	RJR 2403	α4β2 selective nicotinic agonist	10 mg 50 mg	129 545
	3855	RuBi-Nicotine	Caged nicotine; rapidly excitable by visible light	10 mg	425
	2736	Sazetidine A	α4β2 receptor ligand; may act as an agonist or a desensitizer	10 mg	185
	3754	Varenicline	Orally active, subtype-selective α4β2 partial agonist	10 mg 50 mg	205 865
Antagonists	2133	α-Bungarotoxin	α7 subtype-selective nAChR antagonist	1 mg	169
	3119	α-Conotoxin Iml	α7 and α9 selective nAChR antagonist	500 µg	235
	2349	Dihydro-β-erythroidine	Antagonist for neuronal α4-containing nicotinic receptors	10 mg 50 mg	175 735
	2843	Mecamylamine	Non-competitive nicotinic receptor antagonist	10 mg 50 mg	89 365
	1029	Methyllycaconitine citrate	α7 neuronal nicotinic receptor antagonist	5 mg 25 mg	89 375
Nitric Oxide Synthase					
Activators	0663	L-Arginine	Endogenous substrate for NOS	100 mg	59
Inhibitors	1415	1400W	Potent, highly selective iNOS inhibitor	10 mg 50 mg	125 525
	0871	AMT	Potent, selective iNOS inhibitor	10 mg 50 mg	115 485
	0735	3-Bromo-7-nitroindazole	Selective nNOS inhibitor	10 mg 50 mg	129 545
	0665	L-NAME	Non-selective NOS inhibitor	100 mg	75
	0771	L-NMMA	Non-selective NOS inhibitor	10 mg 50 mg	69 249
	1200	N^{ω}-Propyl-L-arginine	Highly selective inhibitor of nNOS	10 mg 50 mg	169 715
Opioid δ Receptor					
Agonists	4335	AR-M 1000390	Low-internalizing δ opioid receptor agonist	10 mg 50 mg	165 695
	0764	SNC 80	Highly selective non-peptide δ agonist	10 mg 50 mg	195 819
Antagonists	0740	Naltrindole	δ opioid selective non-peptide antagonist	10 mg 50 mg	135 559

Pain Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size	USD
Opioid μ Receptor					
Agonists	1171	DAMGO	Selective μ agonist	1 mg	75
	1055	Endomorphin-1	Potent and selective μ agonist	5 mg	115
	1056	Endomorphin-2	Potent and selective μ agonist	5 mg	115
	3247	Fentanyl	Potent and selective μ agonist	10 mg 50 mg	69 249
Antagonists	1560	CTAP	Selective and potent μ antagonist	1 mg	145
	1578	CTOP	Highly selective, potent μ antagonist	1 mg	169
	0926	β-Funaltrexamine	Irreversible μ-selective antagonist	10 mg 50 mg	195 819
Opioid NOP Receptor					
Agonists	0910	Nociceptin	Endogenous NOP agonist	1 mg	139
	3932	Orphanin FQ (1-11)	Potent NOP agonist; displays analgesic properties	1 mg	105
	3240	SCH 221510	Potent and selective NOP agonist	10 mg 50 mg	195 819
Antagonists	3661	BAN ORL 24	Potent and selective NOP antagonist	10 mg 50 mg	195 819
	2598	(±)-J 113397	Potent and selective NOP antagonist	10 mg 50 mg	259 1089
	2481	JTC 801	Selective NOP antagonist	10 mg 50 mg	145 609
	1118	Nocistatin (bovine)	Opposes action of nociceptin	1 mg	205
	3573	SB 612111	Selective NOP receptor antagonist	10 mg 50 mg	239 1005
	1552	UFP-101	Potent, selective silent antagonist for NOP	1 mg	305
Opioids (Miscellaneous)					
Agonists	2808	Buprenorphine	Opioid receptor ligand	10 mg 50 mg	59 219
	1886	Neuropeptide SF (human)	Implicated in pain modulation and opioid function	1 mg	205
Antagonists	0599	Naloxone	Broad spectrum opioid antagonist	100 mg	95
PI 3-K					
Activators	1983	740 Y-P	Cell-permeable PI 3-kinase activator	1 mg	259
Inhibitors	3578	AS 605240	Potent and selective PI 3-kinase γ (PI 3-Kγ) inhibitor	10 mg 50 mg	149 629
	4026	GSK 1059615	Potent PI 3-kinase inhibitor	10 mg 50 mg	195 819
	1130	LY 294002	Selective PI 3-kinase inhibitor	5 mg 25 mg	129 545
	2930	PI 103	Inhibitor of PI 3-kinase, mTOR and DNA-PK	1 mg 10 mg 50 mg	95 195 819
	2814	PI 828	PI 3-kinase inhibitor	1 mg 10 mg 50 mg	95 195 819
	1125	Quercetin	Non-selective PI 3-kinase inhibitor	100 mg	65
	4264	TG 100713	PI 3-kinase inhibitor	10 mg 50 mg	219 925
	1232	Wortmannin	Potent, irreversible inhibitor of PI 3-kinase	1 mg 5 mg	89 339

Category	Cat. No.	Product Name	Description	Unit Size	USD
PKA					
Activators	1140	8-Bromo-cAMP	Membrane permeable cAMP analog; activates PKA	10 mg 50 mg	69 245
	1333	cAMPS-Sp	Cell-permeable cAMP analog; activates PKA	1 mg	139
Inhibitors	1337	cAMPS-Rp	cAMP antagonist; inhibits PKA activation	1 mg	145
	2910	H 89	Protein kinase A inhibitor	1 mg 10 mg 50 mg	85 179 755
	1288	KT 5720	Selective protein kinase A inhibitor	100 µg	179
	1904	PKA inhibitor fragment (6-22) amide	Potent protein kinase A inhibitor	1 mg	169
PKC					
Activators	2383	Bryostatin 1	Protein kinase C activator	10 µg	159
	1201	Phorbol 12-myristate 13-acetate	Protein kinase C activator	1 mg 5 mg	75 245
Inhibitors	1626	Calphostin C	Potent, selective and photo-dependent PKC inhibitor	100 µg	179
	2442	CGP 53353	Selective inhibitor of PKCβII	10 mg	229
	1330	Chelerythrine	Potent protein kinase C inhibitor	5 mg	139
	0741	GF 109203X	Protein kinase C inhibitor	1 mg 10 mg	89 185
	2253	Go 6976	Potent protein kinase C inhibitor; selective for α and β isozymes	1 mg	215
	2285	Go 6983	Broad spectrum PKC inhibitor	1 mg 10 mg	105 219
	2992	PKC 412	Protein kinase C inhibitor	1 mg	169
PKG					
Inhibitors	1883	cGMP dependent kinase inhibitor peptide	Inhibitor of protein kinases G and A	1 mg	105
	1289	KT 5823	Selective protein kinase G inhibitor	100 µg	179
	3028	Rp-8-Br-PET-cGMPS	Protein kinase G inhibitor	560 µg	185
Potassium Channels					
Activators	1377	Cromakalin	$K_{ir}6$ channel opener	10 mg 50 mg	185 779
	4305	ICA 069673	$K_V7.2/K_V7.3$ channel opener	10 mg 50 mg	165 685
	1378	Levcromakalim	$K_{ir}6$ channel opener. Active enantiomer of cromakalim (Cat. No. 1377)	10 mg 50 mg	219 925
	4519	ML 213	$K_V7.2$ and $K_V7.4$ channel opener	10 mg 50 mg	155 655
	4166	NS 5806	$K_V4.3$ channel activator	10 mg 50 mg	205 865
	1355	P1075	Potent $K_{ir}6$ channel opener	10 mg 50 mg	185 779
Blockers	0940	4-Aminopyridine	Non-selective K_V channel blocker	100 mg	75
	0911	Glibenclamide	$K_{ir}6$ channel blocker	100 mg	65
	3564	Kaliotoxin	K_V and K_{Ca} blocker	100 µg	315
	1278	KN-93	K_V channel blocker	1 mg	185
	4231	Nateglinide	$K_{ir}6$ blocker; displays high affinity for SUR1/$K_{ir}6.2$ channels	10 mg 50 mg	109 459
	4367	Psora 4	Potent $K_V1.3$ channel blocker	10 mg 50 mg	185 779
	1316	Tertiapin-Q	Selective blocker of inward-rectifier K^+ channels	1 mg	389
	3068	Tetraethylammonium chloride	Non-selective K^+ channel blocker	50 mg	59

Pain Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size	USD
Protein Synthesis					
Inhibitors	4215	4E1RCat	Protein translation inhibitor; blocks eIF4F subunit interaction	10 mg 50 mg	195 819
	1290	Anisomycin	Protein synthesis inhibitor	10 mg 50 mg	89 339
	0970	Cycloheximide	Inhibitor of protein synthesis	100 mg	75
	4089	Puromycin	Protein synthesis inhibitor	50 mg	79
Purinergic P2X Receptors					
Agonists	1062	2-Methylthioadenosine triphosphate	P2 purinergic agonist	10 mg	245
	3245	ATP	P2 agonist	50 mg	75
	3312	BzATP	P2X7 agonist. Also P2X1 and $P2Y_1$ partial agonist	1 mg	65
	3209	α,β-Methyleneadenosine 5′-triphosphate	P2 agonist	10 mg	185
Antagonists	2972	A 438079	Competitve P2X7 antagonist	10 mg 50 mg	165 695
	3701	A 740003	Potent and selective P2X7 antagonist	10 mg 50 mg	165 695
	4473	A 804598	Potent and selective P2X7 antagonist	10 mg 50 mg	165 685
	4232	A 839977	Potent P2X7 antagonist	10 mg 50 mg	185 779
	0625	PPADS	P2 purinergic antagonist	10 mg 50 mg	75 315
	3052	RO-3	Selective P2X3 and P2X2/3 antagonist	10 mg	155
	4391	Ro 51	Potent P2X3, P2X2/3 antagonist	10 mg 50 mg	195 819
	1472	Suramin	Non-selective P2 antagonist	100 mg	89
	4386	TC-P 262	Selective P2X3, P2X2/3 antagonist	10 mg 50 mg	145 609
	2464	TNP-ATP	Potent, selective P2X antagonist	5 mg	255
Purinergic P2Y Receptors					
Agonists	2157	MRS 2365	Highly potent and selective $P2Y_1$ agonist	1 mg	335
	2715	PSB 0474	Potent and selective $P2Y_6$ agonist	1 mg	295
	3279	UTPγS	Selective $P2Y_{2/4}$ agonist	1 mg	205
Antagonists	3321	AR-C 66096	Potent and selective $P2Y_{12}$ antagonist	1 mg	315
	0900	MRS 2179	Selective $P2Y_1$ antagonist	10 mg 50 mg	209 879
	2159	MRS 2500	Potent and selective $P2Y_1$ antagonist	1 mg	319
Sodium Channels					
Activators	2918	Veratridine	Voltage-gated Na^+ channel opener	10 mg 50 mg	95 399
Blockers	2976	A 803467	Selective $Na_V1.8$ blocker	10 mg 50 mg	139 585
	4249	A 887826	Potent voltage-dependent $Na_V1.8$ channel blocker	10 mg 50 mg	185 779
	0890	Amiloride	Na^+ channel blocker. Also I_2 imidazoline ligand	100 mg	59
	4718	Huwentoxin IV	Selective $Na_V1.7$ channel blocker	100 µg	205
	3057	Lidocaine	Na^+ channel blocker	50 mg	59
	4023	ProTx II	Potent and selective $Na_V1.7$ channel blocker	100 µg	145
	1014	QX 314 bromide	Na^+ channel blocker	100 mg	115
	2313	QX 314 chloride	Na^+ channel blocker	50 mg	129
	4435	TC-N 1752	Selective $Na_V1.7$ blocker	10 mg 50 mg	219 925
	1078	Tetrodotoxin	Na^+ channel blocker	1 mg	199

Category	Cat. No.	Product Name	Description	Unit Size	USD
Tachykinin Receptors					
Agonists	1669	GR 73632	Potent, selective NK_1 agonist	1 mg	315
	3228	[Lys^5,$MeLeu^9$,Nle^{10}]-NKA(4-10)	Selective NK_2 agonist	1 mg	195
	1152	Neurokinin A (porcine)	Endogenous tachykinin peptide	1 mg	145
	1068	Senktide	Tachykinin NK_3 agonist	500 µg	115
Antagonists	3417	CP 99994	High affinity NK_1 antagonist	10 mg 50 mg	219 925
	1274	GR 159897	Non-peptide, potent NK_2 antagonist	10 mg 50 mg	195 819
	0868	L-732,138	Potent, selective NK_1 antagonist	10 mg 50 mg	89 339
	1145	L-733,060	Potent NK_1 antagonist	10 mg 50 mg	195 819
	1635	RP 67580	Potent and selective NK_1 antagonist	10 mg 50 mg	195 819
	1393	SB 222200	Potent, selective non-peptide NK_3 antagonist. Brain penetrant	10 mg 50 mg	185 779
	1156	Substance P	Sensory neuropeptide, inflammatory mediator	5 mg	139
TRPA1 Channels					
Activators	3197	Polygodial	TRPA1 channel activator; analgesic and antifungal	10 mg 50 mg	155 655
Blockers	4716	A 967079	Selective TRPA1 channel blocker	10 mg 50 mg	139 585
	3296	AP 18	Reversible TRPA1 channel blocker	10 mg 50 mg	125 499
	2896	HC 030031	Selective TRPA1 blocker	10 mg 50 mg	139 585
	3938	TCS 5861528	TRPA1 blocker	10 mg 50 mg	149 629
TRPM Channels					
Activators	1531	Icilin	TRPM8 and TRPA1 activator; cooling agent	10 mg 50 mg	125 525
	3040	WS 12	TRPM8 agonist; cooling agent	10 mg 50 mg	125 525
	2927	WS 3	TRPM8 agonist, cooling agent	10 mg 50 mg	89 375
Blockers	3989	AMTB	TRPM8 blocker	10 mg 50 mg	195 819
TRPV Channels					
Activators	0462	(*E*)-Capsaicin	Prototypic vanilloid receptor agonist	100 mg	119
	1641	OLDA	Potent, selective endogenous TRPV1 agonist	5 mg 25 mg	109 445
	0934	Olvanil	Potent vanilloid receptor agonist	10 mg 50 mg	119 505
	1137	Resiniferatoxin	Potent vanilloid receptor agonist	1 mg	145

Pain Research Products – continued

Category	Cat. No.	Product Name	Description	Unit Size	USD
Blockers	4319	A 784168	Potent and selective TRPV1 antagonist	10 mg 50 mg	185 779
	2316	AMG 9810	Potent and selective, competitive antagonist of TRPV1	10 mg 50 mg	169 715
	3875	BCTC	TRPV1 antagonist	10 mg 50 mg	155 655
	0464	Capsazepine	Vanilloid receptor antagonist. Also activator of ENaCδ	10 mg 50 mg	155 655
	4100	HC 067047	Potent and selective TRPV4 antagonist	10 mg 50 mg	185 779
	3361	JNJ 17203212	Reversible, competitive and potent TRPV1 antagonist	10 mg 50 mg	165 695
	3746	RN 1734	Selective TRPV4 antagonist	10 mg 50 mg	129 545
	1615	SB 366791	Potent, selective, competitive TRPV1 antagonist	10 mg 50 mg	149 629
	4729	α-Spinasterol	TRPV1 antagonist; displays *in vivo* activity	1 mg	105

Prices are correct for 2016. For a full product listing please visit www.tocris.com

Further Reading

Please refer to the list of recommended papers for more information.

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