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Ion channel therapeutics for pain

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Pain is a complex disease which can progress into a debilitating condition. The effective treatment of pain remains a challenge as current therapies often lack the desired level of efficacy or tolerability. One therapeutic avenue, the modulation of ion channel signaling by small molecules, has shown the ability to treat pain. However, of the 215 ion channels that exist in the human genome, with 85 ion channels having a strong literature link to pain, only a small number of these channels have been successfully drugged for pain. The focus of future research will be to fully explore the possibilities surrounding these unexplored ion channels. Toward this end, a greater understanding of ion channel modulation will be the greatest tool we have in developing the next generation of drugs for the treatment of pain.

Introduction

The effective and safe treatment of pain remains an immense clinical challenge. Current therapies often lack the desired level of efficacy or tolerability to offer optimal pain management. This unmet medical need has driven huge research efforts toward the improved understanding of the physiology and pathophysiology of pain mechanisms, with the aim of providing more effective treatment options.

Modulation of ion channel signaling has the potential to effectively treat pain. Ion channel modulators such as Lidocaine (1)[1] and Carbamazepine (2)[2] (**Fig. 1**) act on voltage-gated sodium channels and are known to reduce pain in both the clinical and pre-clinical setting. However, modulators such as these identified early in the era of modern drug discovery, generally lack ion channel selectivity which makes firm conclusions about the roles of individual ion channels difficult to draw. More recently, evidence for the role of ion channels in pain has come from the study of monogenic pain related diseases caused by mutations that affect the function of specific ion channels. These include studies into both loss and gain of function mutations in the voltage gated sodium channel Nav1.7 mutations, which cause profound pain insensitivity[3] and sensitivity[4,5] respectively, in individuals with such mutations.

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Ion channels are integral membrane proteins with a gated, water-filled pore that regulates voltage potential across cell membranes *via* control of ion flow between the intracellular and extracellular environments. Ion flow results in the production of an electrical signal, causing adjacent voltage-sensitive channels to open in a chain-reaction fashion, thereby creating a self-propagating electrical signal that can traverse the entire length of a human nerve cell, a distance of as much as one meter, within milliseconds. Ion channels are broadly classified into voltage or ligand gated families, depending on the primary factors that lead to channel opening and closing. Within family types, ion channels are further categorized into sub-types, based on various factors that include the location and function of the specific channel. This review focuses on the current status of ion channel modulators and their application toward pain relief. It also discusses some of the drawbacks of current therapies and potential directions for improved treatment of the human pain condition.

Current Ion Channel Modulators for Pain Therapy

Of the 215 ion channels that exist in the human genome, 85 ion channels have strong literature links with pain, many of which are linked to multiple pain types.[6] Some common ion channel-targeting drugs for pain are highlighted in **Table 1**. The number of discrete channels that have been successfully drugged for pain is very small compared to the number of ion channels that could have therapeutic potential.

Most of the currently available ion channel pain therapeutics were discovered more than a decade ago and some are over 50 y old. For example, Carbamazepine (2) is a first generation anticonvulsant developed in the 1950s for the treatment of trigeminal neuralgia, epilepsy, and mania.[2] Drugs of this era were often discovered using "phenotypic" methods such as *in vivo* efficacy models or isolated tissue preparations designed to mimic a component of the clinical condition. In this way, a definitive characterization of which protein target(s) the ligand engaged with often came much later on. Carbamazepine is now known to inhibit sustained repetitive firing by blocking sodium channels in a use-dependent fashion with pain relief resulting from synaptic transmission blockade in the trigeminal nucleus. Carbamazepine also blocks calcium channels and GABA receptors at high micromolar levels of potency. This pan-ion channel inhibition profile likely drives Carbamazepines' broad list of indications (including antiarrhythmic, antidepressant, neuromuscular blocking, and sedative effects). Additional older drugs in this class are local anesthetics exemplified by lidocaine (1), which have been used in surgical

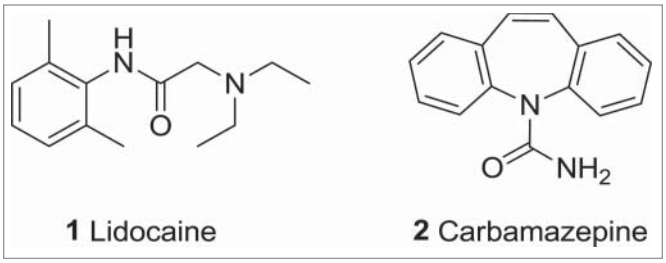

Figure 1. Lidocaine (1) and Carbamazepine (2) are known ion channel modulators.

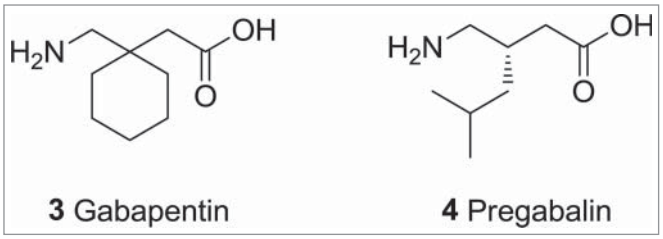

Figure 2. Gabapentin and Pregabalin.

procedures carried out on peripheral tissues, to reverse acute pain, or to treat chronic pain.[1] These anesthetics are administered at relatively high doses to primarily block voltage gated sodium channels, but also block potassium and calcium channels.[7] As with many compounds possessing polypharmacology, safety side effects of non-selective agents limit their chronic usage.[8]

A commercially successful compound, Gabapentin (3)[9] (**Fig. 2**), was discovered using this "phenotypic" method. Gabapentin was originally developed to treat epilepsy and is currently also used in the treatment of neuropathic pain. As a lipophilic analog of GABA, Gabapentin was originally thought to increase GABA levels by activating glutamate decarboxylase and was found to be efficacious as an anti-convulsant. It was not until much later that Gabapentin's true mechanism of action was discovered, namely an interaction with the α2δ subunit of voltage gated calcium channels.[10] A follow up drug discovery effort from Pfizer[8] has since delivered Pregabalin (4), a compound with improved pharmacokinetics over Gabapentin that has become the gold standard for the treatment of chronic pain associated with diabetic neuropathy.

The relative lack of success in bringing new ion channel pain therapies to market in recent years is notable. The reasons for this include failure to deliver clear efficacy and/or safety differentiation over the current standard of care therapies. This lack of return upon investment has driven new approaches in pain research. The strategy to select and validate pain targets is moving away from those supported by preclinical pain models (which are largely unsuccessful in predicting clinical efficacy for novel pain medicines) to an approach in which human data, including genetic data and human *in vitro* pharmacology data from patient-derived cells, define confidence in mechanism. These human data are coupled with an increased focus on the delivery of translatable biomarkers to enable effective clinical dose-setting. In addition to assessing the efficacy of new mechanisms, it is hoped that such human cell platforms will enable a more phenotypic approach to the identification of new pain targets. The increased investment in human biology, human-relevant *in vitro* screening platforms, and translational biomarkers is hoped to lead to greater success in Phase 2 and 3 clinical trials.

Ion Channel Modulators for Pain Therapy in Clinical Development

As described above, non-selective sodium channel blockers have been used for many years in the treatment of acute pain, but their utility is limited due to the functional consequences of inhibiting sodium channels other than those expressed in nociceptors, *e.g.* in the heart and CNS. A more recent understanding of which sodium channels are expressed in nociceptors and the generation of experimental and/or genetic data linking specific Nav receptors to a pain phenotype, has spurred the pain research community to deliver selective sodium inhibitors for clinical characterization. Advances in automated *in vitro* electrophysiology screening platforms[8] have greatly facilitated these research efforts, enabling high quality Nav isoform data to be generated in a high through-put fashion.

In 2006, a seminal publication by Cox *et al.*[3] demonstrated that congenital insensitivity to pain (CIP) could be conferred by missense mutations in Nav1.7. In addition to this, gain-of-function Nav1.7 mutations have been described in the rare, extreme pain conditions of inherited primary erythromelalgia (IEM)[5] and paroxysmal extreme pain disorder (PEPD).[4] These findings initiated a huge pharmaceutical investment that has delivered a range

Table 1. Common Ion Channel Drugs for Pain Indications

Drug	Target Channel	Disease Target	Year of First Clinical Usage
Gabapentin	Cav (α2δ)	Pain	1994
Pregabalin	Cav (α2δ)	Pain	2004
Ziconotide	Cav 2.2	Severe Pain	2004
Lidocaine	Nav	Local Anesthetic	1949
Bupivacaine	Nav	Local Anesthetic	1987
Lamotrigine	Nav	Off label neuropathic pain	1994
Lacosamide	Nav	Seizures and Pain	2008
Carbamazepine	Nav	Epilepsy and off label for pain	1963
Eslicarbazepine	Nav	Epilepsy	2009

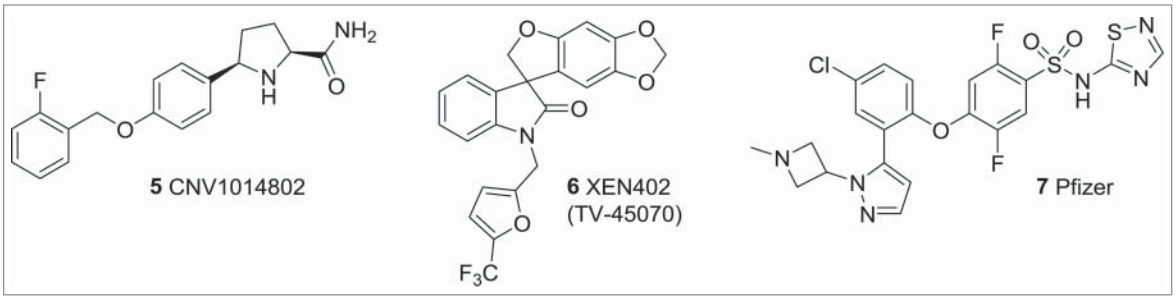

Figure 3. Nav1.7 compounds.

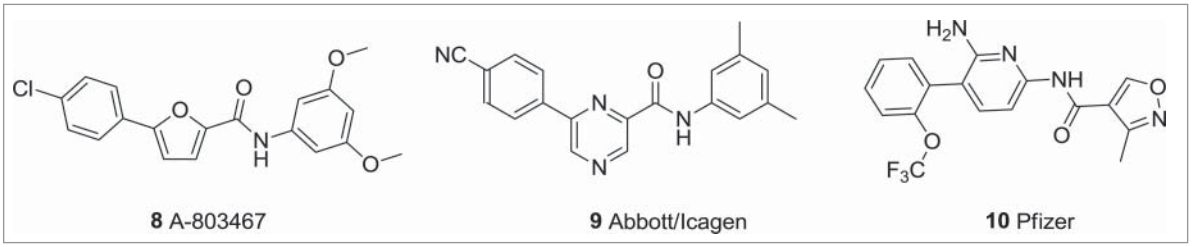

Figure 4. Nav1.8 compounds.

of reportedly selective Nav 1.7 blockers. A number of these compounds have now entered clinical trials for pain (**Fig. 3**), including the proline derivative 5 from GSK/Convergence,[11] a spiro-oxindole compound from Xenon (series exemplified by 6 XEN402, now known as TV-45070)[12] and an aminoheterocycle sulphonamide series from a Pfizer-Icagen collaboration (series exemplified by 7).[13] To-date, Xenon have reported efficacy treating pain in patients with congenital erythromelalgia, but no efficacy was seen in a study of postherpatic neuralgia. Also, Convergence has reported positive data from an open-label phase of a trigeminal neuralgia study as well as statistically significant differences in the reduction of pain in a lumbosacral radiculopathy (sciatica) trial.[50]

In addition to Nav 1.7, a lot of interest has been generated in Nav1.8 as a target for both inflammatory and neuropathic pain. Abbott, in collaboration with Icagen, reported the discovery of a number of biaryl Nav1.8 inhibitors (**Fig. 4**), exemplified by 8 (A-803467)[14] and 9,[15] of which A-803467 has been used extensively in preclinical target validation. Pfizer has also disclosed a series of Nav1.8 selective compounds, exemplified by 6,6-biaryl amide 10,[16] and progressed an example into the clinic. Unfortunately, in the one result published so far, amide 10 showed no efficacy in a post-surgical dental pain clinical trial.

The TRP channels constitute a family of mammalian cation channels with biological functions that include pain perception and thermosensation.[17] TRPV1 is activated by numerous stimuli including heat (>42°C), vanilloids, lipids, and protons/cations. Several highly selective TRPV1 antagonists have advanced into clinical development for the treatment of pain including 11 AMG517,[18] 12 SB-705498,[19] 13 ABT-102,[20] and 14 MK-2295[21] (**Fig. 5**). Unfortunately, reports from many of the clinical studies have shown TRPV1 blockade to have effects on core body

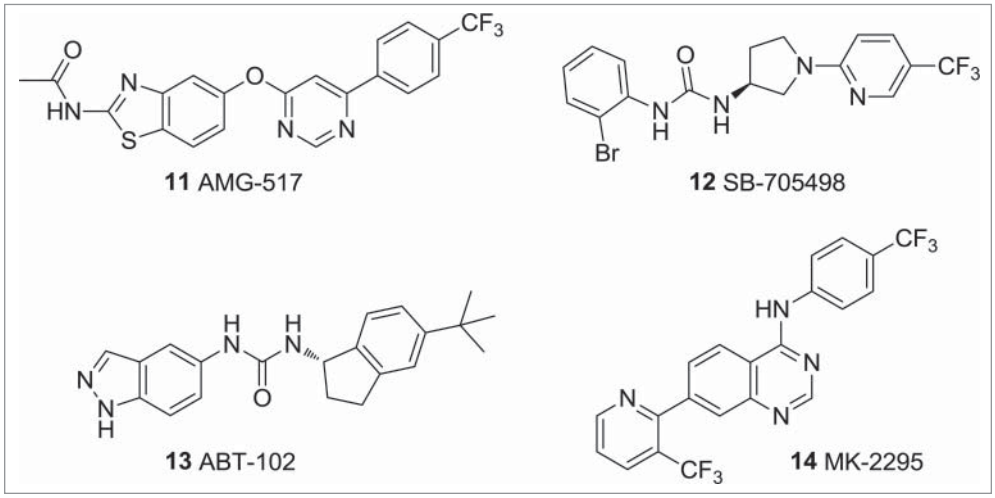

Figure 5. TRPV1 ligands.

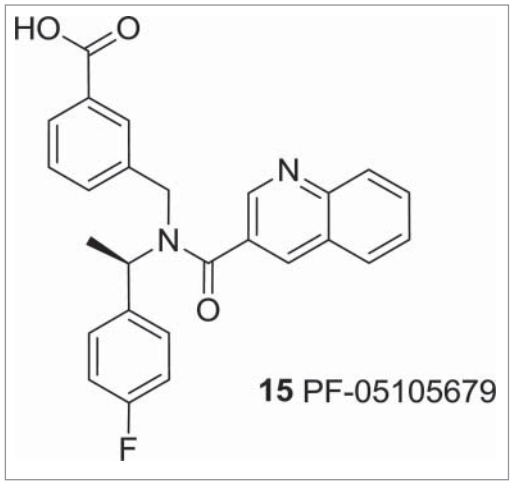

Figure 6. TRPM8 modulator PF-05105679.

temperature, which has halted much of the drug development activity targeting this channel. The use of desensitising TRPV1 agonists has also been shown to reduce pain sensitivity.[22,23] This has found clinical application with a topical approach (e.g., Astella's Qutenza® patch, 8% capsaicin) in which a local anesthetic is applied to the painful area prior to topical capsaicin, preventing the initial painful flare that occurs with agonist-induced nociceptor excitation prior to desensitisation.

TRPM8 is activated *in vitro* by cool temperatures (10−23°C) and cooling agents such as icilin and menthol. Researchers at Pfizer have recently disclosed that TRPM8 antagonist 15 (PF-05105679), **Figure 6**, is analgesic in an experimental model of cold pain (the Cold Pressor Test) in humans, without affecting core body temperature.[24]

TRPA1 is activated by a variety of ligands including exogenous electrophiles such as cinnamaldehyde, allyl isothiocyanate, and the endogenous ligand 4-hydroxynonenal (4-HNE).[9] Recombinant TRPA1 is activated by noxious cold (<17°C).[17] The TRPA1 channel has been directly linked to pain in humans by a gain-of-function mutation that causes familial episodic pain syndrome.[25] The most advanced TRPA1 antagonist is Glenmark's GRC17536, which has shown a statistically significant and clinically relevant response in a Phase 2a clinical trial for treating diabetic peripheral neuropathy. The structure of GRC17536 has not been disclosed, but an exemplar from one of Glenmark Pharmaceutical's patent applications is shown in **Figure 7** (compound 16,[26] TRPA1 IC50 2.5nM). Another TRPA1 compound comes from a Hydra Biosciences/Cubist Pharmaceuticals partnership. They have taken TRPA1 antagonist CB-625, presumed to be from a series that includes 17 HC-030031[27] and 18 HC-068559,[28] to the clinic for the potential oral treatment of pain and inflammatory conditions. Hydra/Cubist have reported completion of a single ascending-dose Phase 1 study with CB-625, but efficacy data is not yet available.

TRPV3 is activated by natural products such as camphor, 2-APB, and warm temperatures (>32°C). Several classes of selective TRPV3 antagonists have to-date been disclosed (**Fig. 8**) that have enabled research into the role of TRPV3 in pain signaling. These include the benzothiazole 19[29] and the quinazolin-4-one 20 from Hydra[30] and Glenmark's GRC15300 (structure not disclosed), Glenmark reported the completion of a Phase 1 study with GRC 15300 in 2011 and, following a deal with Sanofi-Aventis, opened a Phase 2 trial in neuropathic pain in 2012.[51] Unfortunately, Sanofi discontinued the trial in 2014 when the compound failed the Phase 2 proof of concept trial. Glenmark has filed a number TRPV3 patent applications, examples from which include pyridopyrimidine 21[31] and benzimidazole 22.[32]

TRPV4 is activated by a number of small molecules that include anandamide, 5,6-epoxyeicosatrienoic acid, and GSK1016790A, and by heat (27−34°C). A number of selective TRPV4 antagonists have been disclosed over recent years (**Fig. 9**). These include RN-1734[33] from Renovis, Hydra's HC-067047; a compound reported to be efficacious in preclinical models of bladder cystitis,[34] and sulphonamide 25 from Pfizer.[35] To date, the only TRPV4 ligand to have entered clinical trials is GSK 2798745, a compound of undisclosed structure that has entered a Phase 1 study. This ligand is hoped to be effective in treating pulmonary edema.

There is interest in the pain research field in delivering small molecule *N*-type Cav2.2 selective compounds. This is driven by the established clinical link of this subtype to neuropathic pain[36] and the fact that specific knockdown of Cav2.2 ameliorates pain in chemically induced and neuropathic pain models.[37] The only marketed *N*-type Cav2.2 selective compound is the analgesic peptide Ziconotide, derived from the toxin of the cone snail *Conus magus*. Ziconotide requires intrathecal administration to be efficacious and is associated with significant side effects. Progress has been made in developing orally acting small molecule *N*-type inhibitors to overcome these limitations. *N*-type Cav2.2 chemotypes have now been disclosed from several research groups (**Fig. 10**) including CNV2197944 from Convergence

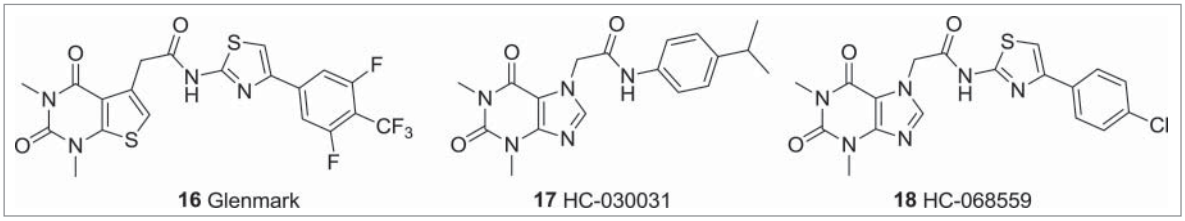

Figure 7. TRPA1 ligands.

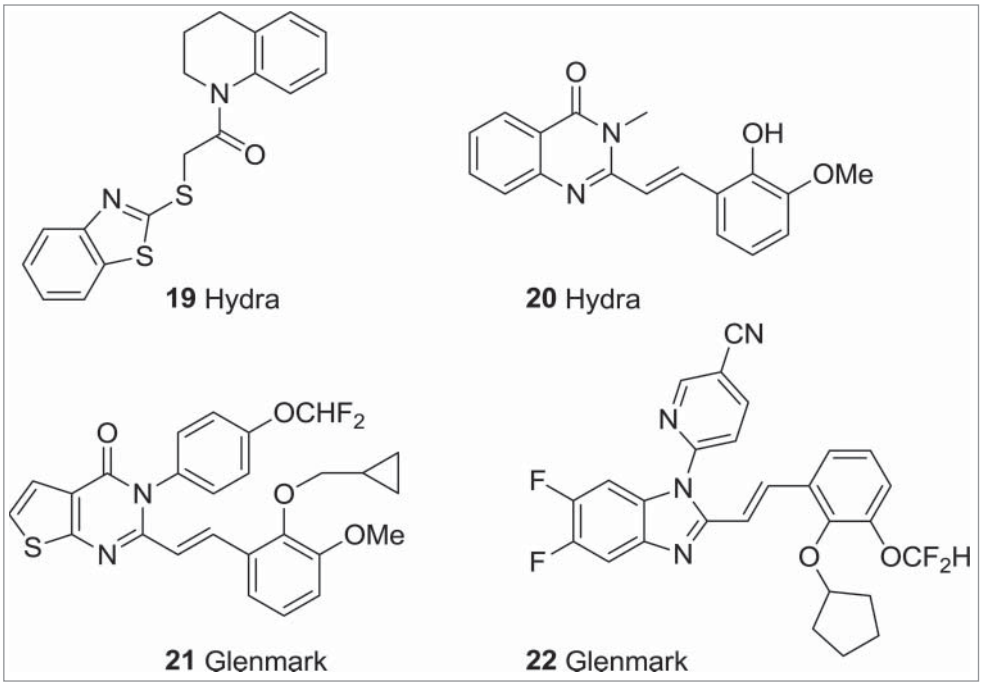

Figure 8. TRPV3 ligands.

(likely to be from the same family as compound 26)[38] and Z-160 from Zalicus (now Epirus Biopharma),[39] both of which have been progressed into Phase 2 studies. The Convergence compound has now completed a pair of Phase 2 studies, in postherpetic neuralgia and diabetic peripheral neuropathy. While the resulting efficacy data is not yet available, it is expected to be revealed at the end of 2015. The Zalicus compound has also finished a pair of Phase 2 studies, in lumbosacral radiculopathy and postherpetic neuralgia. Compound 27 did not meet the primary endpoint for either of these studies.

T-type calcium channels are low-voltage activated calcium channels that act as modulators of action potential threshold by increasing the calcium current, leading to further depolarization of the cell and activation of other calcium channels, and ultimately, sodium and potassium channels. They are present within cardiac and smooth muscle, and many neuronal cells within the central nervous system. *T*-type calcium channel blockade can reduce pain in neuropathic, inflammatory, and visceral pain models. Z944, is a novel, oral, state-dependent, selective T-type calcium channel blocker (structure not disclosed). This blocker has >150-fold selectivity vs. non-T-type voltage-gated ion channels. A Phase 1 study to determine the safety, tolerability, and pharmacokinetics of oral Z944 showed it was safe and well tolerated. A Phase 1b clinical study measuring Laser-Evoked Potentials (LEP) from skin irritated following topical application of capsaicin or exposure to UV light demonstrated that Z944 reduced peak-to-peak amplitudes of LEPs from both capsaicin and UV irritated skin models and reduced subjective Visual Analog Scale (VAS) pain scores in both skin types. On the basis of these findings, Z944 is currently being tcgq.[53]

Kv7 ion channels are widely expressed in neurons and a genetic association exists between channel mutations in Kv7.2 and Kv7.3 and neuronal hyperexcitability.[40] A number of preclinical pain models have been used to examine the effects of activation of Kv7 channels[41,42] which support the role of Kv7 channels in pain signaling and the potential opportunities for Kv7 openers in pain therapy. Retigabine was approved in 2011 for use in partial-onset seizures and then later taken on to a Phase 2 proof-of-concept clinical trial for pain from postherpetic neuralgia. Unfortunately Retigabine was non-superior to placebo in this study with respect to reducing pain scores. A structurally similar analog of Retigabine, Flupirtine, is approved for treatment of lower back pain in Europe.

Ionotropic glutamate receptors (iGluRs) are ligand gated ion channels that mediate excitatory neurotransmission.[43] Subtype-selective GluN2B receptor antagonists in particular have attracted attention from the pharmaceutical research community for targeting CNS disorders including stroke and Parkinson disease.[44] Examples of GluN2B receptor antagonists include Ifenprodil[45] and the more selective derivative Traxoprodil[46] (**Fig. 11**). Traxoprodil has progressed into clinical trials for a number of indications including stroke and neuropathic pain.

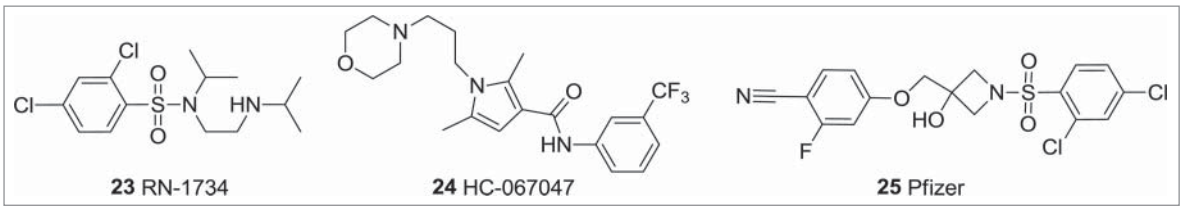

Figure 9. TRPV4 ligands.

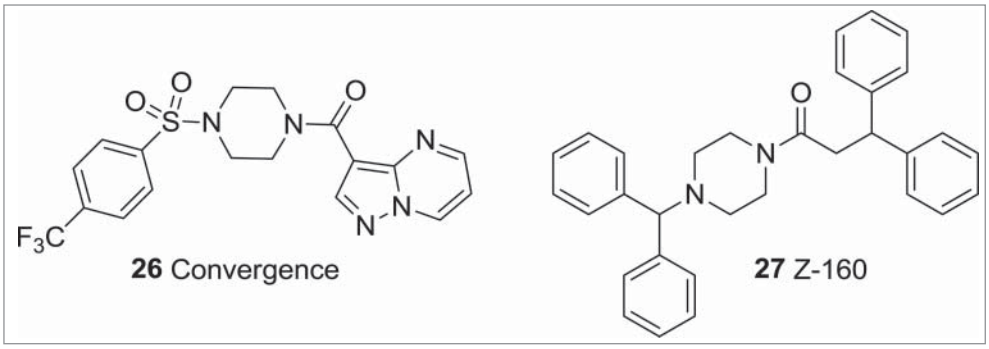

Figure 10. N-type Cav2.2 compounds.

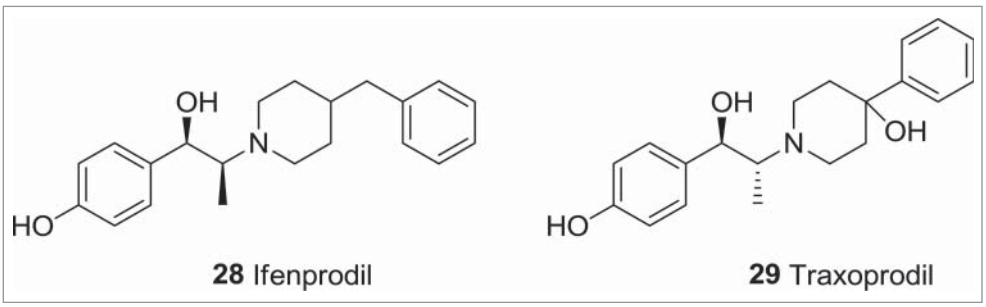

Figure 11. Ionotropic glutamate receptor ligands.

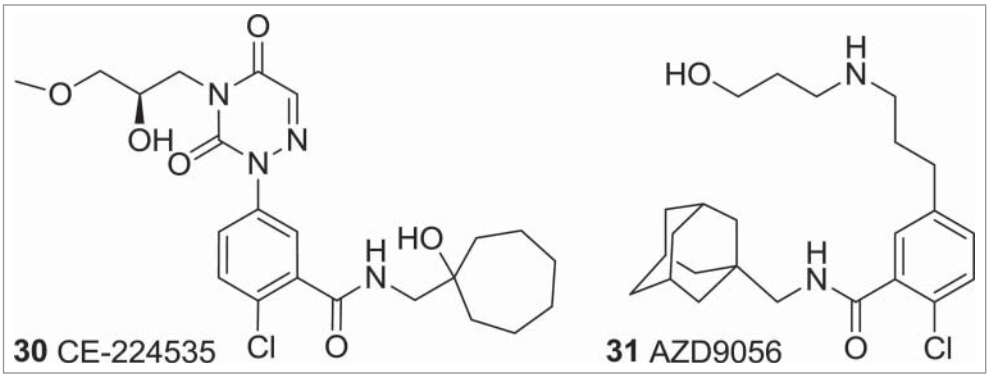

Figure 12. P2 × 7 ligands.

P2X receptors are purinergic cell surface ion channels gated by extracellular ATP.[47] P2 × 3, P2 × 2/3, P2 × 4, and P2 × 7 receptors have received much attention over the last few years as potential targets to treat a variety of conditions that include chronic pain and arthritis.[48] Evotec, Pfizer, and AstraZeneca have progressed P2 × 7 receptor antagonists to the clinic. Unfortunately, CE-224535 and AZD9056 (**Fig. 12**) did not demonstrate clinical efficacy in rheumatoid arthritis, although it is not yet known whether compounds such as these may be useful in pain indications.[49]

Conclusion and outlook

The modulation of ion channel signaling by small molecules has shown the ability to treat pain. However, current therapies often lack the desired level of efficacy or tolerability to offer optimal pain management. The focus for future research will inevitably be to provide safer and more effective treatments for pain. This future research will include advances in ion channel cloning and screening capabilities, increased knowledge regarding subtype selective molecules, and

additional screening against ion channels known to elicit CNS and cardiovascular side effects. Finally, discovery of strong genetic linkages between specific ion channels and their related diseases will help to determine the most beneficial targets. In the end, a greater understanding of ion channel modulation will be the greatest tool we have in developing the next generation of drugs for the modulation of pain in the human disease state.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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