CHAPTER 2

Recent Advances Toward Pain Therapeutics

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Contents

1. INTRODUCTION

Chronic pain includes a variety of indications, all of which share a common feature that sufferers experience long-term periods of pain interfering with normal life. The treatment of all forms of chronic pain remains a huge unmet medical need. It is estimated that there are over 160 million people suffering from chronic pain conditions in the G7 countries, with

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Annual Reports in Medicinal Chemistry, Volume 46
ISSN: 0065-7743, DOI: 10.1016/B978-0-12-386009-5.00025-4

those numbers increasing as the population ages. Unfortunately, none of the currently available treatments appear to be able to help even half of patients achieve at least a 50% reversal of their pain without significant adverse events. Thus, although pain sufferers annually spend over $20 billion, many seek new therapies that have both better efficacy and tolerability than existing treatments.

The dominant types of chronic pain include osteoarthritis (OA), chronic lower back pain (CLBP), fibromyalgia, and neuropathic pain. These various forms are believed to have complex and overlapping mechanisms of action. For example, inflammatory cytokines in degenerating OA joints activate nociceptive nerve endings in the periphery. However, the central pain pathways receiving input from the OA joint are also likely to be sensitized in ways similar to that which occurs during various types of neuropathic pain. Conversely, neuropathic pain may involve long-term increases in the spontaneous activity of peripheral nerves that drive central pain pathways sensitized by the chronic excitatory drive [1]. In either case, the signals that are transmitted ultimately to the brain are persistent and strongly activate areas of the brain involved in pain perception. Thus the potential list of mechanisms to target for novel pain therapies is very diverse [2]. Targets in the periphery include those involved in sensory transduction and central nervous system (CNS) transmission. In the CNS, potential targets are involved in signal processing and setting the relative excitability in the pain processing pathways.

Two of the most promising novel targets actively pursued for chronic pain are the voltage-gated sodium (Nav) channels, in particular Nav 1.3, 1.7, and 1.8, and nerve growth factor (NGF/tropomyosin-related kinase receptor A (TrkA). Both of these targets are predominantly localized in the periphery. They are believed to play key roles in the sensitization and excitability of the nociceptors that takes place during chronic pain. The achievement of good target selectivity with small molecules is also a common challenge of both pathways. This review will provide a summary of recent drug development for these two pathways, highlighting recent developments and progress made toward finding truly selective inhibitors.

A third target, fatty acid amide hydrolase (FAAH), has been the focus of much work in the past several years. FAAH is an enzyme that catabolizes a family of molecules called fatty acid amides (FAAs). A subset of FAAs is known to have agonist activity at cannabinoid receptors. Therefore, inhibition of FAAH is predicted to raise the levels of the endocannabinoids and provide analgesic relief. In contrast to sodium channels and NGF/TrkA, FAAH is believed to play a role in both the periphery and the CNS. This review will cover some recently disclosed novel noncovalent inhibitors as well as some recent clinical data that raise questions about the validity of the target.

2. SODIUM CHANNEL BLOCKERS

The use of sodium channel blockers for the treatment of pain has been extensively reviewed in the past 5 years [3–13]. This chapter will very briefly summarize background and key findings from this period and then focus on recent developments.

2.1. Nav subtypes as pain targets

Even before their molecular target was known, nonselective sodium channel blockers were used as analgesics. Voltage-gated sodium (Nav) channels are formed by a pore forming alpha subunit and an auxiliary beta subunit. Cloning studies have resulted in the identification of nine alpha subtypes of the sodium channel (Nav1.1–9) sharing $>50\%$ sequence identity in the extracellular loops and membrane domains. Of these subtypes, Nav1.3, 1.7, 1.8, and 1.9 are expressed in peripheral nerves and have been considered as potential targets to develop novel analgesics. Further interest by the pharmaceutical industry to identify selective Nav1.7 inhibitors has arisen from the recent discovery that Nav1.7 mutations associated with loss-of-function are linked to congenital indifference to pain [14], while gain-of-function mutations [15] result in primary erythermalgia. However, in order to achieve a robust therapeutic window when treating chronic pain, blockade of the following subtypes must be avoided: Nav1.2 (CNS side effects), Nav1.4 (paralysis), Nav1.5 (cardiac side effects), and Nav1.6 (neuromuscular side effects) [6]. Although structurally diverse, the known Nav inhibitors are able to bind all Nav subtypes. Furthermore, mutagenesis studies have demonstrated that a diverse set of known Nav blockers appears to bind to a common binding site which is unfortunately highly conserved across various Nav subtypes [3]. The high subtype homology displayed within the known anesthetic binding site suggests that other chemotypes, binding to an alternate site, would have to be discovered to achieve significant binding selectivity.

2.2. Pharmacological versus functional selectivity *via* state-dependent inhibition

Despite being able to block all Nav subtypes *in vitro*, a variety of Nav blockers such as lidocaine and mexilitine can be used systemically in the clinic with appropriate monitoring. The presence of a therapeutic margin is believed to arise from an interaction between state-dependent binding of these inhibitors, variations in the rate- and voltage-dependence of the transitions between channel states, and tissue-specific expression of Nav subtypes [3,5]. State-dependent blockers are most potent while cells are

strongly depolarized when Nav channels are predominantly in the inactivated state. These state-dependent blockers have also been referred to as ''use dependent'' since the Nav blockade preferentially takes place on cells firing action potentials at nominally high rates. Thus, during high activity states such as those evoked in pain pathways relevant to chronic pain (>10 Hz), Nav channels accumulate in the inactivated state and allow state-dependent inhibitors to bind. In comparison, the cardiac activity rate is much lower (1–2 Hz), cells rest at more negative resting potentials, resulting in Nav1.5 channels not accumulating in the inactivated state and experiencing very little inhibition. The overall state dependency of each of the nonselective blockers is directly related to their *in vivo* efficacy and safety. State-dependent inhibitors that can provide functional selectivity with minimal CNS and cardiac effects are still actively pursued.

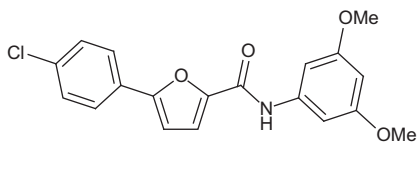
In contrast to state-dependent selectivity, achieving pharmacological selectivity across Nav subtypes has remained an elusive goal. Pharmacological selectivity can be defined as the relative potency of a compound to inhibit various Nav subtypes under a common relative activation state of the channels. A typical approach is to use electrophysiological protocols specific to each Nav subtype to cause ~50% of channels to be in the inactivated state and then determine the relative IC_{50}s [16–18]. To date, there are very few compounds that have been demonstrated to have any true pharmacological selectivity for subtypes in pain over those critical for cardiac function (see below).

2.3. Subtype-selective inhibitors

The quest for pharmacologically selective Nav blockers has been greatly hampered by the limited throughput techniques necessary to control for channel activation states. However, efforts to find leads with increased subtype selectivity have recently been catalyzed by improvements in electrophysiological screening technologies. IonWorks and PatchXpress are current examples of automated patch clamp systems. In the recent past, a large number of inhibitors with improved potency have been disclosed, but selectivity is usually lacking or not documented appropriately [4,7,8]. Unfortunately, definitions of selectivity have not been standardized and have mostly been based solely on state-dependent properties. In the absence of a standardized approach, IC_{50}s for state-dependent selectivity should be accompanied by a suitable description of the assay to allow more informed comparisons across structural series. Following are the examples of inhibitors with demonstrated subtype selectivity against one of the Nav subtypes targeted for pain.

A-803467 (**1**) has been described as a 100- to 1000-fold pharmacologically selective Nav1.8 state-dependent blocker displaying analgesia in a

variety of pain models. However, clinical development has been hampered by poor bioavailability [16,17]. Mutation studies suggest a binding site that partially overlaps with nonselective Nav blockers [19]. Further studies led to inhibitors with improved oral bioavailability [20,21]. A-887826 (**2**) is a representative example with ~30-fold pharmacological selectivity against the Nav1.5 channel [22].



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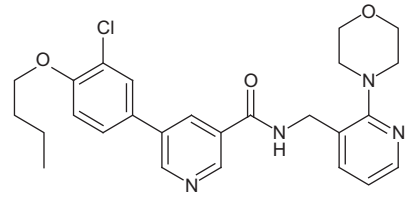

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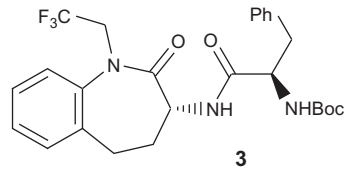
The search for selective Nav1.7 blockers has experienced a recent surge in activity. Benzazepinone **3** has been reported to be a 90/680 nM state-dependent inhibitor of the Nav1.7/Nav1.8 channels while maintaining ~10-fold use-dependent selectivity against Nav1.5 [23]. Although compounds from this series are efficacious in animal models, their moderate bioavailability limits their potential for clinical development. Binding experiments suggested that these inhibitors bind to or very close to the original local anesthetic binding site.



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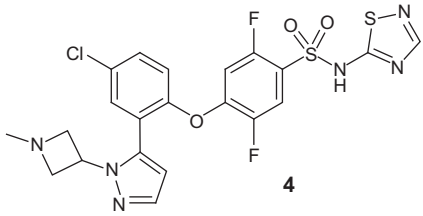
In 2010, a patent application disclosed a series of potent Nav1.7 blockers. The most preferred examples were claimed to display up to 100-fold pharmacological selectivity against the Nav1.5 channel and unspecified pharmacological selectivity against the Nav1.3 channel [18]. Estimated IC_{50} values for Nav1.7 using a PatchXpress platform were reported in the single nanomolar to picomolar range for a number of examples. Two examples, among those that were prepared in multigram quantities, are represented below (**4** and **5**). Interestingly, shortly after the publication of this patent, the originating corporations, Icagen and Pfizer, announced their engagement in human clinical studies with potent and selective Nav1.7 blockers [24]. The original microdosing pharmacokinetics study (July 2010) included four compounds and concluded with the selection of one, PF-05089771, that is now the subject of further clinical studies (December 2010). Consultation of the NIH clinical trials website will direct the reader to two clinical trials that could correspond to the Icagen press releases mentioned above [25].



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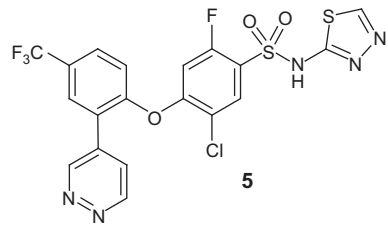

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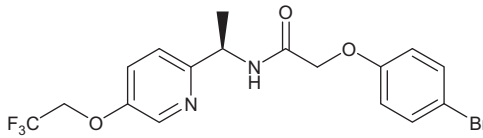
Another recent patent application has disclosed a series of aryl substituted carboxamides as blockers of T-type calcium channels or sodium channels [26]. Preferred compounds are claimed to bind potently to Nav1.7 and Nav1.3 and to be selective against the Nav1.5 channel. A representative example is illustrated below (**6**). A more recent application from the same group has claimed picolinamides **7** as potent blockers of Nav1.7 and Nav1.3 with selectivity against the Nav1.5 channel [27].



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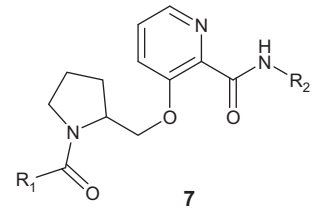

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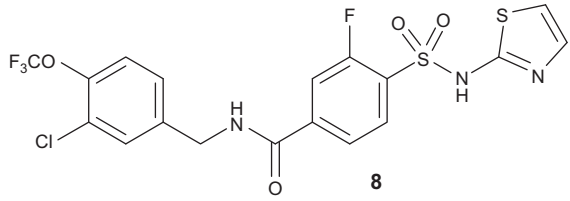
A series of benzamides related to **4** and **5** have been claimed as pharmacologically selective Nav1.3 blockers over Nav1.5 [28]. For example, **8** is a 15-nM inhibitor of Nav1.3 with >1000-fold selectivity over Nav1.5.



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3. NGF/TrkA PATHWAY INTERFERENCE

Strategies targeting blockade of NGF activation of the TrkA receptor for the treatment of inflammatory and neuropathic pain have been recently reviewed [29]. This chapter will very briefly summarize various approaches and then focus on the most recent developments.

3.1. NGF sequestration

The NGF/TrkA pathway is one of the few new targets with clinical proof of concept against chronic pain [30]. The recent reports of positive PhII and PhIII trials against OA, chronic low back pain, and interstitial cystitis using neutralizing anti-NGF antibodies (Tanezumab [30], REGN475 [31]) have all demonstrated good efficacy and tolerability and have driven an increased focus on developing novel therapeutics in this pathway. However, it is important to note that the FDA has imposed a clinical hold on all active anti-NGF programs in the USA to explore concerns related to potential acceleration and exacerbation of joint degeneration. The release of the actual clinical findings driving these concerns will be necessary to understand the impact of NGF sequestration with antibodies on safety and efficacy. It is important to note that all the companies with anti-NGF mAbs in late stage clinical programs are purported to be working with the FDA to resolve the concerns and proceed with development.

Other preclinical efforts at NGF sequestration include using a variety of engineered peptide fragments including those derived from the extracellular NGF-binding domain of the TrkA receptor to bind and sequester NGF. These efforts have been recently reviewed [29]. These peptide approaches have largely been discontinued in favor of the anti-NGF antibody approaches due to concerns about neoepitope-induced immunogenicity which is a risk of the engineered peptides of these classes.

3.2. Inhibition of NGF/TrkA interaction

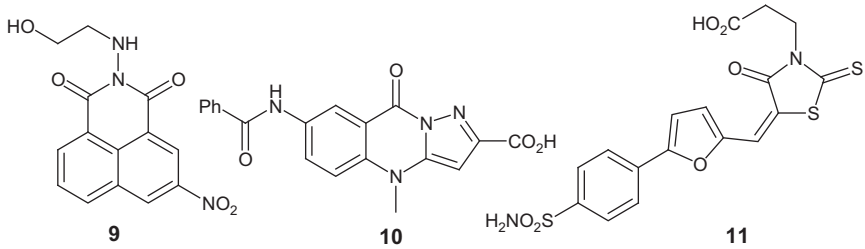
MNAC-13, also known later as BXL-1H5 or GBR-900, is a specific TrkA monoclonal antibody that has shown improvements in various pain models [32]. It has recently been in-licensed by Glenmark Pharmaceuticals to be advanced toward clinical development.

Small peptide mimetics of NGF are capable of functionally blocking the NGF–TrkA interaction. One such peptide, IPTRK3, has recently been demonstrated to suppress both thermal and mechanical hyperalgesia induced by CFA upon local injection [33]. Other peptides, NL1L4 and L1L4, have been shown to reduce neuropathic behavior and restore neuronal function in a rat model of pain [34].

Triazine-diketopiperazine-based peptidomimetics have recently been studied as antagonists of the TrkA [35] and TrkC [36] receptors.

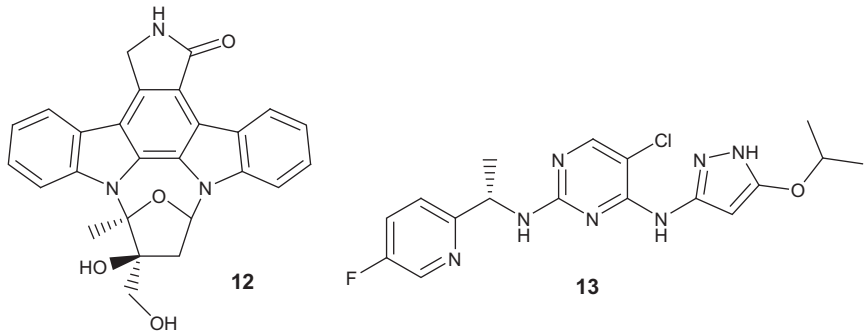
Selectively disrupting the interaction between NGF and TrkA using a small molecule as opposed to an antibody or peptide remains an attractive goal from a drug discovery standpoint. ALE-0540 (**9**) was one of the first nonpeptidic molecules to specifically inhibit the binding of NGF to TrkA and had some limited efficacy in models of neuropathic and inflammatory pain [37]. In 2009, Painceptor Pharma claimed derivatives of

ALE-0540 to be efficient in animal models of chronic pain, with the compound PPC-1807 being the closest to clinical development [38]. PD90780 (**10**) represents another class of antagonists of the NGF–TrkA interaction [39,40]. More recent contributions by the same group of scientists are illustrated by thioxothiazolidine Y1036 (**11**) which prevents neurotrophin-mediated differentiation of dorsal-root ganglion sensory neurons [41].



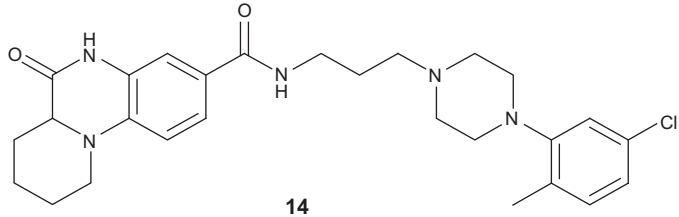
3.3. TrkA kinase inhibitors

Numerous small-molecule inhibitors of Trk receptor kinases have been described or claimed, mostly for the treatment of cancer. They have recently been reviewed and very few of these are Trk selective [42]. Lestaurtinib (CEP-701, **12**), an indolocarbazole staurosporine derivative inhibitor of multiple kinases including TrkA, and CEP-751, a pan-Trk inhibitor, have entered clinical development for various cancers. Another example, AZ-23 (**13**) has been characterized as a 2/8 nM inhibitor of TrkA/B with anticancer potential but still retains significant activity against a number of other kinases such as Flt3 and FGFR1 [43,44].



A recent patent application disclosed a series of isoform-selective TrkA kinase inhibitors with activities in the 10–100 nM range against TrkA and >10 μM against other kinases including TrkB and C [45].

One example (compound B, structure not identified) was claimed to reduce mechanical allodynia in the chronic-constriction injury rat neuropathic pain model in a dose-dependent and more significantly efficacious manner than gabapentin. The examples illustrated in the application are quite structurally diverse. Compound **14**, corresponding to example 201 or compound A, is claimed to be an 85-nM inhibitor of TrkA.



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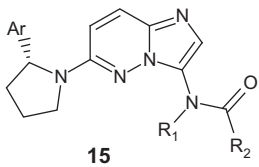
In the past 3 years, scientists from Array Biopharma have delivered several presentations related to small-molecule Trk inhibitors that are efficacious in various preclinical models of pain [46]. While they have indicated that they are pursuing TrkA selective inhibitors [47], thus far they have only disclosed data related to pan-Trk inhibitors. AR00457470 (formerly designated AR-872, structure not disclosed) has been characterized as a ''first in class'' pan-Trk inhibitor, with activities in the 10 nM range against TrkA,B,C. It exhibits >100-fold selectivity against a very diverse panel of kinases, and >1000-fold selectivity versus a diverse panel of receptors and ion channels. AR00457470 is claimed to have drug-like physical properties (MW < 450, cLogP < 3, PSA < 100, >1 mg/mL solubility at pH 1.2–7.4) and to present low potential for drug–drug interactions. This compound achieves good oral exposures in rats and is restricted to the periphery (high PgP efflux). AR00457470 has been described to be efficacious in various pain models. It inhibits thermal hyperalgesia under acute or prophylactic dosing paradigms in the rat CFA or CIA models, inhibits CFA-induced mechanical allodynia, and is superior to Naproxen, Valdecoxib, or Rofecoxib in a CFA-induced model of monoarthritis, as measured by guarding index and difference in weight bearing. AR00457470 has also been demonstrated to have no effect on normal thermal responses or normal nociceptive behaviors in preclinical species. AR00457470 reduces nonmalignant skeletal pain in the adult mouse without interfering with sensory and sympathetic nerve fibers or early fracture healing [48]. Recent patent applications from the same group of scientists claim Trk kinase inhibitors to be useful for treating pain [49–51]. Representative structures of such amides Trk kinase inhibitors are illustrated below (**15–17**).



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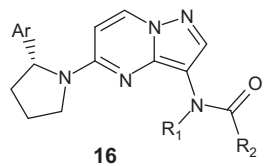

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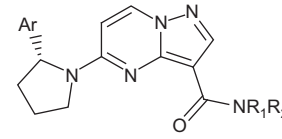

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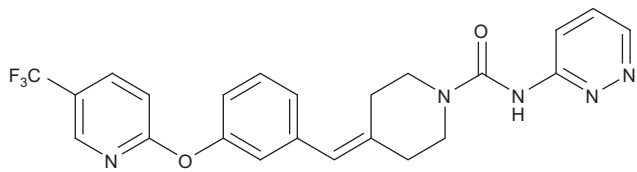
4. FAAH INHIBITORS

The role of endocannabinoids in pain relief and the potential value of FAAH inhibitors have been reviewed [52–54]. This chapter will focus on recent developments including both new chemical series and recent clinical data.

4.1. Covalent FAAH inhibitors

The majority of compounds pursued as FAAH inhibitors have been of the irreversible covalent type. An irreversibly inhibited enzyme would not show any subsequent competition for binding by accumulated endogenous substrates. This has been proposed to be a necessary feature of FAAH inhibitors to enable and maintain the essentially complete inhibition of the enzyme that appears to be required for analgesic efficacy in preclinical pain models. The most advanced covalent compound, PF-4457845 (**18**), is reported to have a k_{inact}/K_i of 40,200 M^{-1} s^{-1} against human FAAH [55]. This compound is effective in preclinical models of pain as long as near maximum FAAH inhibition is achieved. PF-4457845 was recently taken into a PhII clinical study for OA. Although the compound achieved good peripheral target engagement, it failed to show any analgesic efficacy versus a placebo group [56]. A number of other irreversible covalent compounds of unknown structure are also in clinical development including IPI-940, IW-6118, and V-158866.



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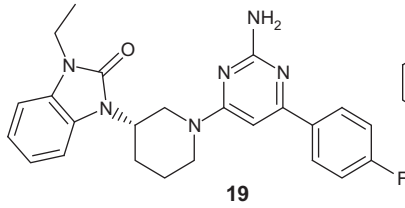
4.2. Noncovalent FAAH inhibitors

Recently, a few novel scaffolds have been disclosed as the root for potent, reversible noncovalent inhibitors of the FAAH enzyme. Aminopyrimidine **19** is reported to have an IC_{50} against recombinant human FAAH of ~14 nM with reasonable CNS penetration [57]. Sulfonamide **20** has been described as a 19-nM reversible and selective FAAH inhibitor that might act as a transition-state analogue [58]. A series of patent applications have claimed FAAH inhibitors based on oxazole, imidazole, and pyrazole templates as illustrated by generic structures **21**–**23** [59–62]. In no case has the *in vivo* analgesic efficacy been reported for these compounds. However, assuming these compounds are indeed active *in vivo*, they would provide an alternative approach to irreversible covalent inhibitors that might eliminate potential safety concerns over the creation of long-lived covalent adducts between compounds and the FAAH enzyme.



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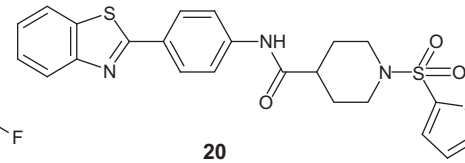

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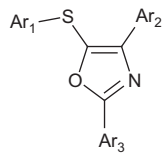

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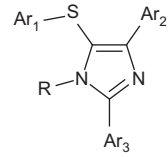

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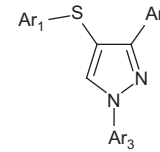

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5. CONCLUSIONS

The treatment of chronic pain is potentially on the cusp of entering a new era with a number of novel mechanistic approaches in clinical development. Many of these novel mechanisms present unique medicinal chemistry challenges in developing safe and effective medicines. This review has touched on three of the leading targets being actively pursued across the pharmaceutical industry. For the Nav inhibitor approach, the recent identification of compounds with true pharmacological selectivity for Nav1.7 versus Nav 1.5 has provided evidence that alternatives to state-dependent selective inhibition are possible. The next step will be to see

if these frontrunner Nav compounds can demonstrate the necessary efficacy and safety in the clinic against chronic pain. For the NGF/TrkA pathway, thus far selective inhibition has only been achieved with antibodies. It remains to be seen whether small-molecule TrkA kinase or NGF-binding inhibitors with adequate selectivity and potency can be discovered and developed. Finally, in contrast to Nav and TrkA, FAAH is one of the few targets that appears to impact pain processing both in the periphery and in the CNS. Despite this, the FAAH inhibitor approach has failed its first attempt to establish clinical proof of concept to treat OA pain. However, sufficient questions remain unanswered in this trial, such as whether there was adequate CNS target engagement or whether OA pain is the most relevant clinical pain population. The remaining active programs will be watched closely to see how they inform on the clinical relevance of this target.

Taken as a group, these three targets demonstrate both the opportunity and challenges faced in developing novel analgesics and the next few years will be very interesting to watch how these programs evolve. Finally, it will be interesting to see what additional novel targets will be brought forward and the medicinal chemistry challenges they will present.

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