The Potential of Transient Receptor Potential Vanilloid Type 1 Channel Modulators for the Treatment of Pain

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Introduction

Since it was first cloned by Caterina and co-workers in 1997,[1] the nonselective, ligand gated ion channel vanilloid receptor 1 (VR1[a]) has attracted a huge amount of attention from both the pharma industry and academia for its potential exploitation in a number of therapeutic areas, particularly the alleviation of chronic pain states. The receptor is now known as TRPV1, transient receptor potential vanilloid type 1 channel.[2]

TRPV1 is predominantly expressed on the peripheral and central terminals of primary sensory neurons (nociceptors) located in the dorsal root, trigeminal, and nodose ganglia[3] where it plays a key role in the detection of noxious stimuli that may result in tissue damage. Activation of the channel leads to an influx of cations (such as Na^+ and Ca^{2+}) into the cell, resulting in depolarization, neuronal hyperexcitability, and ultimately the sensation of pain. A wide range of stimuli are responsible for activation of TRPV1 including noxious heat (T > 42 °C), low extracellular pH, and a variety of chemical mediators.[3] Probably the most well-known of the exogenous chemical agonists of TRPV1 is capsaicin (**1**, Figure 1), the principle pungent component of hot chilli peppers. Many other plant-derived chemicals have also demonstrated agonist activity at this channel, for example, the highly potent diterpene, resiniferatoxin (**2**). Among the numerous endogenous substances that either directly activate and/or potentiate the activity of TRPV1 are the cannabinoid anandamide (**3**), *N*-arachidonoyldopamine (NADA), and arachidonic acid metabolites from the lipoxygenase pathway. The various different stimuli may act independently or cooperatively in opening the channel. For example, many of the inflammatory activators are only weak agonists in their own right but at the site of tissue injury these compounds work synergistically with increased levels of protons, resulting in a decrease in the heat activation threshold of the channel such that activation and the consequent sensation of pain occur at body temperature.[4]

Modulation of TRPV1 sensitivity by other inflammatory mediators such as prostaglandins, nerve growth factor, and bradykinin is also thought to occur indirectly through protein kinase A (PKA), protein kinase C (PKC), and Ca^{2+}/calmodulin dependent kinase (CaMKII) mediated phosphorylation of the channel.[5] As well as increasing its sensitivity to other mediators, phosphorylation of the channel by PKC can also result in direct activation of TRPV1 at body temperature.

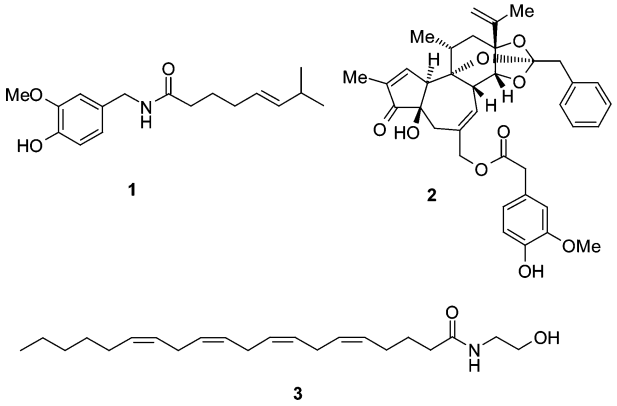

Figure 1. TRPV1 agonists capsaicin (**1**), resiniferatoxin (RTX, **2**), and anandamide (**3**).

The release of neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) from central and peripheral ends of primary spinal afferent neurons is also mediated through activation of TRPV1.[4,6] The initial response to noxious stimuli and the peripheral neurogenic inflammation and sensitization of the central nervous system (CNS) caused by release of these neuropeptides contribute to the establishment of persistent pain states.

Role of TRPV1 in Pain States

Extensive studies with TRPV1 agonists have enabled clear definition of the role of this receptor in human pain pathways. Topical application of capsaicin initially induces a painful sensation due to activation of the receptor. Then, on prolonged contact (days or weeks depending on the concentration of capsaicin applied), an analgesic response is achieved.[7] The constant activation of the channel results in high intracellular levels of calcium, ultimately leading to desensitization to a variety of noxious stimuli through functional and morphological alterations to the peripheral ends of nerve fibers. In the clinic, treatment with topical capsaicin has been shown to be of some benefit in a number of painful conditions such as postherpetic neuralgia[8] and diabetic neuropathy.[9]

Several studies using animal models have shown altered levels of expression of TRPV1 in pain states. In models of neuropathic pain,[10−13] there is evidence that TRPV1 expression is decreased in the injured nerve fibers but increased in those proximal to the site of damage. Furthermore, TRPV1 expression has been shown to increase to a larger extent in the thinly myelinated Aδ-fibers than in the unmyelinated C-fibers where the channel is predominantly expressed under normal physiological conditions. In models of inflammatory pain, increases in transport of TRPV1 mRNA from neuronal cell bodies to central and

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[a] Abbreviations: BCTC, *N*-(4-*tert*-butylphenyl)-4-(3-chloropyridin-2-yl)-tetrahydropyrazine-1(2*H*)-carboxamide; CaMKII, Ca^{2+}/calmodulin dependent kinase; CGRP, calcitonin gene-related peptide; CHO, Chinese hamster ovary; DRG, dorsal root ganglion; FCA, Freund's complete adjuvant; FLIPR, fluorescence imaging plate reader; HEK, human embryonic kidney; KO, knockout; NADA, *N*-arachidonoyldopamine; PKA, protein kinase A; PKC, protein kinase C; RTX, resiniferatoxin; TM3/4, transmembrane domains 3 and 4; TRPV1, transient receptor potential receptor vanilloid type 1; VR1, vanilloid receptor 1; WT, wild-type.

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Table 1. Reported Activity of Antagonists (**4**−**14**) vs Capsaicin (cap) and Acid (H^+) at Human (h) and Rat (r) TRPV1 in Recombinant Cell Lines

		IC_{50} (nM)					
antagonist	cell line	hTRPV1 (cap)	hTRPV1 (H^+)	rTRPV1 (cap)	rTRPV1 (H^+)	assay	ref
4	CHO	39	320	220	>30000	aequorin	16a
	CHO	53	69	887	>40000	$^{45}Ca^{2+}$ uptake	20
5	HEK293	NR[a]	NR[a]	35	6	FLIPR	19
	HEK293	5	0.6	1.9	0.6	FLIPR	21
	CHO	0.6	0.7	0.5	0.7	$^{45}Ca^{2+}$ uptake	20
6	CHO	25	93	86	294	$^{45}Ca^{2+}$ uptake	20
7	HEK293	5	2	9[b]	NR[a]	FLIPR	22
8	CHO	NR[a]	50	NR[a]	105	FLIPR	23
9	CHO	NR[a]	NR[a]	0.9	0.9	$^{45}Ca^{2+}$ uptake	24
10	HEK293	65	16	102	16	FLIPR	25
11	HEK293	103	226	NR[a]	NR[a]	FLIPR	26
12	HEK293	90	104	NR[a]	NR[a]	FLIPR	27
13	HEK293	70	597	NR[a]	NR[a]	FLIPR	27
14	HEK293	32	1778	NR[a]	NR[a]	FLIPR	27

[a] NR: not reported. [b] Data from electrophysiology study on DRG preparation.

peripheral axon terminals and an overall up-regulation of TRPV1 expression in unmyelinated axons have been observed.[14]

Over recent years several publications have appeared describing the effects of TRPV1 antagonists in animal models of pain. The capsaicin analogue, capsazepine (**4**), was the first competitive antagonist to be disclosed by researchers at Novartis back in 1992, and it was later shown to reverse capsaicin-evoked mechanical hyperalgesia in rat, mouse, and guinea pig.[15] However, species differences became apparent when studies using the partial sciatic nerve ligation model of neuropathic pain showed that capsazepine was efficacious in reversing mechanical hyperalgesia in the guinea pig (statistically significant effects observed at 1, 10, and 30 mg/kg sc with maximum reversal of 80%) but not in the rat or mouse. Furthermore, capsazepine was again only efficacious in the guinea pig in inflammatory pain models of Freund's complete adjuvant (FCA) induced mechanical hyperalgesia (3−30 mg/kg sc with maximum reversal of 44%) and carageenan-induced thermal hyperalgesia (30 mg/kg sc with maximum reversal of 54%). These results have been attributed to the differential activity across species in blocking the various modes of activation of TRPV1.[15] Capsazepine blocks the responses of human, rat, and guinea pig TRPV1 to capsaicin in recombinant TRPV1 systems, although the level of activity appears to be species-dependent with the potency at the human receptor being approximately 5 times higher than at the rat (Table 1). Blockade of the acid-induced activation is also claimed to be species-dependent, since investigations utilizing both native tissues and recombinant receptors have demonstrated that capsazepine possesses antagonist activity against acid at the guinea pig and human receptors but is not efficacious at rat TRPV1.[15,16]

The in vitro potency data for a selection of TRPV1 antagonists **5**−**10** with published in vivo pain model data are summarized in Table 1. From the data available in the literature, it is apparent that many of these compounds exhibit species differences and there is often a discrepancy between the potencies for antagonism of the different modes of activation tested (capsaicin vs low pH). The binding and function of agonists and antagonists at TRPV1 have been the subject of much research, which has resulted in identification of key molecular determinants for activity in the TM3/4 region and proposal of a vanilloid binding site.[17] More recently, the results from investigations into the binding mode leading to blockade of acid activation have been published.[18] Two types of antagonist were used in these experiments: those that block both capsaicin and acid mediated activation (group A) and those that block only the capsaicin response (group B). Initially, both groups of compounds were shown to bind in a competitive manner to the capsaicin binding site at rat TRPV1 and in further experiments the group B compounds were shown to compete with and block group A antagonism of acid activation. Therefore, it has been proposed that the differential activity is not due to conformational changes at this binding site induced by acid activation. In addition, both groups of antagonists did not affect the activity of the nonselective pore blocker ruthenium red, leading to the proposal that the group A compounds are able to block the acid-induced opening of TRPV1 through interactions in the capsaicin binding pocket. This results in stabilization or locking of the channel in a nonconducting state, even at low pH, and as such, these compounds can be described as allosteric inhibitors of acid-induced activation. The key interactions in the capsaicin binding site required for this effect have yet to be determined. From analysis of the structural subtypes that show this differentiation, it is not immediately apparent as to which features may result in either reduced or enhanced antagonism against the acid-induced activation of TRPV1 (Table 1, Figures 2 and 3). Most compounds contain either an amide or urea core (or a heterocyclic isostere thereof) flanked by two relatively lipophilic groups; thus, the features that result in the differences in activity against the two modes of action are potentially quite subtle. For example, the piperazine-derived urea, BCTC (**5**), discovered by researchers at Purdue[19] and the close analogue **10**, from Johnson & Johnson,[24] possess the same core and are more potent against acid-induced activation than capsaicin-induced activation when assayed under similar experimental conditions (FLIPR using TRPV1 expressing HEK293 cells). However, the related compound, **11**, a "second generation BCTC analogue" (also from Purdue) shows a reversal of this trend when assayed under similar conditions.[25] Compounds **12**−**14**, wherein the piperazinyl-2-benzimidazole isostere replaces the piperazine-derived urea moiety, possess higher potency against capsaicin than against acid-induced activation of the channel.[26] It is also noteworthy that within this latter set of compounds **12**−**14**, changes in the nature of the pyridyl substituent have quite marked effects on the level of TRPV1 antagonism. For instance, replacement of chlorine with methyl or trifluoromethyl results in increased potency against capsaicin but a quite significant decrease in potency against acid-induced activation. Quinazolone **8** from Novartis does possess a different substructure in that the lipophilic flanking groups are in a different spatial arrangement with respect to the core group, but only data against acid-induced activation are currently published for this compound.[22] Analysis of structure−activity relationships based on current literature data is also further complicated by the use of different

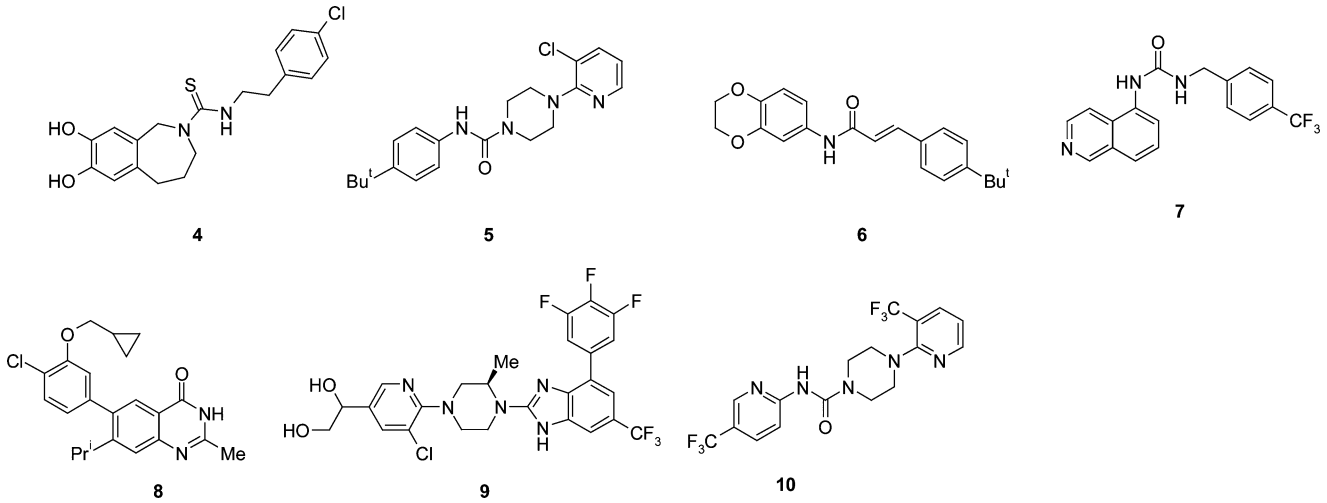

Figure 2. Selected TRPV1 antagonists with reported activity in in vivo pain models.

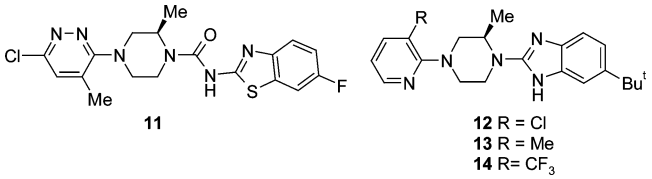

Figure 3. Selected TRPV1 antagonists with reported in vitro activity against capsaicin and protons.

assay formats and conditions by different research groups; for example, see Table 1, compound **5**.

Following the appearance of pain model data for capsazepine, the importance of the ability of antagonists to block the response of TRPV1 to multiple stimuli was further emphasized by the publication of results from pain models with the piperazine-derived urea BCTC (**5**).[28] As shown in Table 2, **5** produced significant reduction of thermal and mechanical hyperalgesia in models of inflammatory pain in the rat. In addition, **5** was also active in neuropathic pain models of mechanical hyperalgesia and tactile allodynia. These results are consistent with the ability of **5** to block the response of rat TRPV1 to both capsaicin and acid (Table 1).

Selected pain model data for other antagonists in the rat are also shown in Table 2. From these examples, it would appear that at this stage, the prediction of in vivo efficacy based on in vitro potency and pharmacokinetics is not straightforward, particularly across different chemical series. Cinnamide **6** (AMG-9810) from Amgen possesses low oral bioavailability but on intraperitoneal (ip) dosing was effective at reducing FCA-induced thermal and mechanical hyperalgesia.[20] Researchers from Abbott Laboratories have reported that isoquinolinylurea **7** (A-425619) also shows efficacy in models of FCA- and carrageenan-induced inflammatory pain and of postoperative pain in the rat.[22b] However, in two models of neuropathic pain, only low levels of activity were observed on oral dosing that has been attributed in part to the low CNS penetration of **7** (spinal cord to plasma ratio of ~0.05:1). More recently, the activity of the brain-penetrant quinazolone **8** (brain to blood ratio of ~0.9:1) from Novartis in models of both inflammatory and neuropathic pain has also been reported.[23] The piperazinylbenzimidazole **9** from Amgen also shows activity in a rat model of FCA-induced thermal hyperalgesia, although data for only one relatively high dose are reported (30 mg/kg po), which may reflect the relatively modest level of oral bioavailability of **9**.[24] Certainly, compounds such as **7** and **8**, which possess improved oral bioavailability, show statistically significant activity at doses as low as 3 mg/kg po in models of inflammatory thermal and mechanical hyperalgesia. However in comparison, compound **5** possesses only 10% oral bioavailability, is approximately equipotent with **9** at rat TRPV1 against acid when tested under the same assay format,[20] and yet shows efficacy at 3 mg/kg po in vivo. From the somewhat limited cross-species and cross-modality data available for compounds **4**−**9**, it is apparent that activity against multiple modes of activation of TRPV1 is an important contributory factor to in vivo efficacy. In comparison to capsazepine **4**, compounds **5**−**9** show much improved activity against acid-induced activation of rat TRPV1 as does compound **10**, which shows activity in NADA- and capsaicin-induced models of hyperalgesia and allodynia.[25]

Studies with "knockout" (KO) mice in which the TRPV1 gene has been deleted have provided further insight into the role of TRPV1 in pain.[29,30] In early experiments, no difference was observed between wild type (WT) and KO mice with respect to noxious heat sensitivity. However, the KO mice did not exhibit thermal hyperalgesia in models of inflammatory pain induced by either carageenan or FCA, indicating a key role of TRPV1 in the development of pain sensation to noxious heat in inflamed tissue. In contrast, results from an initial neuropathic pain study with the KO mice indicated that TRPV1 does not contribute to thermal or mechanical hyperalgesia after nerve injury. More recently, findings from further investigations with KO mice have been reported.[31] In carrageenan-induced inflammatory and partial sciatic nerve lesion induced neuropathic pain models of mechanical hyperalgesia, both WT and KO mice gave similar responses whereas the KO mice showed reduced thermal and mechanical hyperalgesia on mild heat injury. On examination of the response of the WT and KO mice in models of diabetic and toxic polyneuropathy, a somewhat surprising effect was observed: mechanical hyperalgesia was evoked at an earlier time point and to a greater level in the KO mice compared to the WT animals. In this case, the authors postulate that this effect is due to activation of TRPV1 causing an antinociceptive effect due to a counter-regulatory mechanism in which somatostatin is released from the sensory neurons.

Clearly, the combination of data from testing of various TRPV1 antagonist tool compounds in animal models of pain, clinical data on the efficacy of agonists such as capsaicin, and the results obtained from studies with TRPV1 KO mice suggests that the role of TRPV1 in the development and maintenance of various different pain states is highly complex and has yet to

Table 2. Activity of Selected TRPV1 Antagonists (**4**−**9**) in Rat Models of Inflammatory and Neuropathic Pain[a]

		inflammatory pain FCA-induced		neuropathic pain		
antagonist	rat *F* po (%)	thermal hyperalgesia	mechanical hyperalgesia	mechanical hyperalgesia	tactile allodynia	ref
5	10	3 mg/kg po	3 mg/kg po	10 mg/kg po[b]	10 mg/kg po[b]	28
6	3	30 mg/kg ip	100 mg/kg ip			20
7	46	10 μmol/kg po (∼3 mg/kg po)			100 μmol/kg ip[b,c] (∼30 mg/kg ip)	22b
8	75		3 mg/kg po	3 mg/kg po[b]		23
9	17	30 mg/kg po				24

[a] Doses shown are the minimum reported dose where statistically significant effects are observed. [b] Partial sciatic nerve injury. [c] Spinal nerve injury.

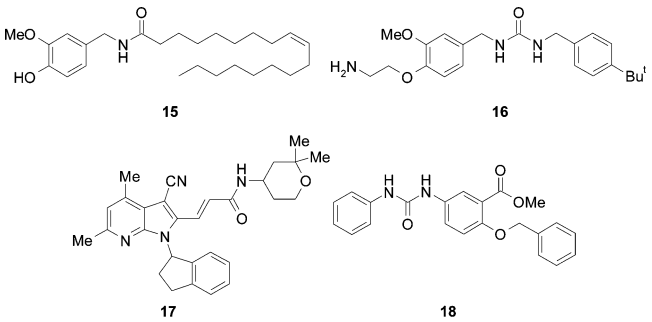

Figure 4. TRPV1 agonists **15** (olvanil), **16** (SDZ 249-665), and exemplars **17** and **18** from Takeda patents WO2004007495 and WO2003029199, respectively.

be fully elucidated. Furthermore, from the results with the KO mice in models of diabetic and toxic polyneuropathy, it is possible that different modes of action (agonism vs antagonism) may be more beneficial in some disease conditions than in others.

TRPV1 Agonist Approaches to Pain Relief

As previously mentioned, from clinical studies, there is a wealth of evidence on the efficacy of topical capsaicin in treating a number of painful conditions. The main disadvantage of this approach is the pain and discomfort experienced by the patient on initial application, which often leads to noncompliance. Therefore, a key focus in the agonist-based approach has been on the development of less pungent alternatives to capsaicin. Clinical development of resiniferatoxin **2** has thus far focused on treatment of bladder disorders with trials in interstitial cystitis and urinary incontinence.[7] However, preclinical evaluation of **2** against various pain states is also underway. Rat models of inflammatory hyperalgesia and neurogenic inflammation together with veterinary dog studies on cancer-induced and arthritic pain have shown very promising results.[32]

Research by Proctor & Gamble and Novartis led to the identification of olvanil **15**[33] and urea **16** (SDZ 249-665),[34] respectively (Figure 4), both of which possess lower pungency when compared to capsaicin. Also to their advantage is their lack of acute toxicity at analgesic doses (e.g., bronchoconstriction, blood pressure changes). Despite the promise of published data, no significant later stage development of these compounds has been reported.

Further patents[35] and papers[36] have appeared describing new TRPV1 agonists. Many of these contain vanilloid derivatives, but of particular note are two patents from Takeda claiming the series of pyrrolopyridines[35b] and phenylureas,[35c] as exemplified by **17** and **18**. It is of interest to see how compounds from these classes will compare with more traditional vanilloid agonists in terms of their efficacy and pungency.

Current development efforts in this area appear to be focused on alternative formulations of capsaicin. NeurogesX is developing a topical application of high-concentration capsaicin via dermal patches (NGX-4010) for the treatment of pain associated with postherpetic neuralgia and HIV associated neuralgia (www.neurogesX.com). Corgentech (formerly AlgoRX Pharmaceuticals) is developing an injectable formulation (ALGRX-4975) for neuropathic, musculoskeletal, and postoperative pain (www.corgentech.com). Civamide (or zucapsaicin) is the orally active cis isomer of capsaicin[37] and is under development by Winston Laboratories as a topical cream for osteoarthritic pain and as an intranasal spray for migraine and cluster headaches (www.winstonlabs.com or www.clinicaltrials.gov).

TRPV1 Antagonist Approaches to Pain Relief

Since the cloning of TRPV1 in 1997, the interest in the discovery of antagonists of TRPV1 as potential therapeutic agents, particularly for pain, has been phenomenal. There is a high unmet medical need in pain therapy as a whole because not all mechanisms of pain relief are suitable for all types of pain and the side effect profiles of existing medications (e.g., opioids, NSAIDs, and more recently COX-2 inhibitors) are often far from ideal. The development of TRPV1 antagonists offers the potential for a new mechanism to treat various pain states with the potential for an improved safety profile. Published data on the efficacy of various TRPV1 antagonists in a variety of models of neuropathic and inflammatory pain have already been described. However, in terms of the number of TRPV1 antagonists disclosed in patents and papers, these data represent the tip of a potentially very large iceberg. At the time of writing at least 150 publications have appeared disclosing new chemical entities, the majority of which are patents from the pharmaceutical industry.[38]

Some representative examples of the structural subtypes claimed in patents are shown in Figure 5. Many of the publications focus on thiourea, urea, and amide containing structures. These include dibenzylthioureas **19** from Pacific Corporation, ureas **20**−**24** from Neurogen, GlaxoSmithKline, Bayer, Janssen, and Merck, and amides **25**−**28** from GlaxoSmithKline, Janssen, AstraZeneca, and Pfizer.

A wide variety of patents disclosing heterocyclic bioisosteres of these groups have also appeared. Examples include piperazinylbenzimidazoles **29** and aryloxypyrimidines **30** from Amgen, aminophthalazines **31** from Merck, pyridopyridinamines **32** from Renovis, and quinazolines **33** from Neurogen. Further bicyclic structures are exemplified by quinazolones **34** and chromones **35** from Novartis.

The first compound to enter clinical development was the pyrrolidinyl urea **21** (SB-705498) from GlaxoSmithKline.[39] Having completed phase 1, including demonstration of analgesic activity, **21** has now progressed to a phase II trial for acute migraine (www.gsk.com) and a further phase I trial for dental pain (www.clinicaltrials.gov). Amgen announced that one of their compounds (AMG-517) (structure not in public domain) has entered phase I trials in 2004 (www.amgen.com), and the Neurogen/Merck collaboration have recently announced that

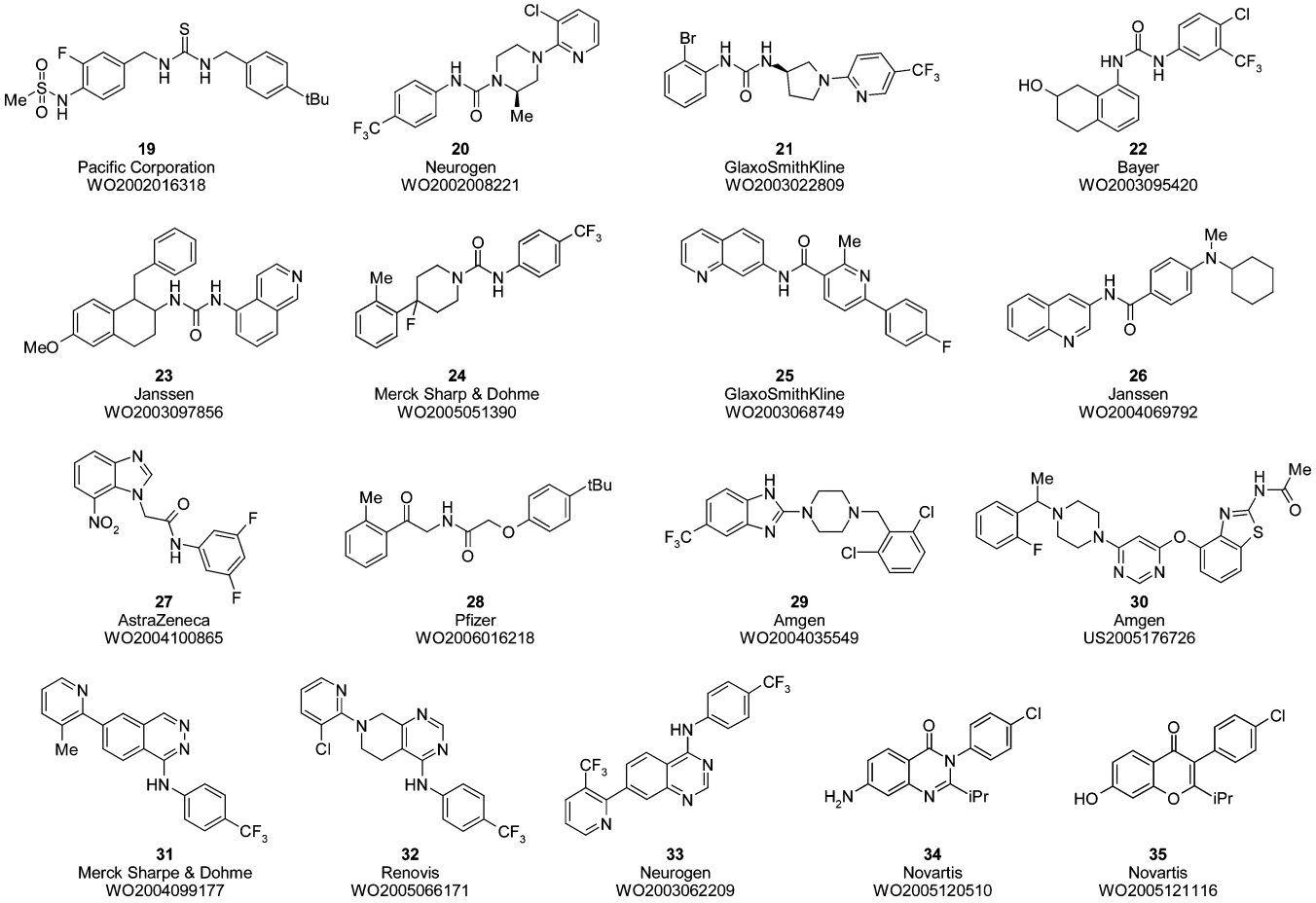

Figure 5. Representative TRPV1 antagonist structural types from the patent literature including **21** (SB-705498) from GlaxoSmithKline, which is currently in phase II clinical trials, and **33** (NGD8243) from Neurogen/Merck, which is in phase I trials.

33 (NGD8243) has commenced phase 1 trials (www.neurogen.com).

Although this is clearly a highly competitive area, the three compounds described above represent a comparatively small number in relation to the large number of patent cases that have appeared over the past 4 years. Many of the structures disclosed are relatively lipophilic, and it is likely they possess poor aqueous solubility. This in turn may lead to issues in their development with respect to absorption and pharmacokinetic profiles, thus hampering progression in the clinic. It will therefore be fascinating to see the final number and identity of compounds that progress to clinical trials in the coming months and years.

Other Functions of TRPV1

It has long been known that the expression of TRPV1 occurs predominantly in primary afferent sensory neurons where it plays a key role in the integration of responses to noxious stimuli. However, over recent years, evidence has been accumulating on the distribution of TRPV1 in other neuronal and non-neuronal tissues, although the elucidation of the function of the receptor in these tissues is far from complete. Furthermore, many studies have been carried out with nonselective agonists such as anandamide and capsaicin and the nonselective antagonist capsazepine **4**. Therefore, investigations using more selective agents would be beneficial in aiding the understanding of the role of TRPV1 in other tissues.

TRPV1 is expressed in many areas of the brain[40] where it appears to be involved in a variety of functions, many of which are not related to pain processing, such as neuroprotection[41] and gastric acid secretion.[42] There is evidence that a CNS penetrant TRPV1 antagonist may provide relief of a wider spectrum of pain states than a peripherally restricted compound.[43] However, because of the presence of functional TRPV1 receptors in the brain that are involved in other processes,[44] further investigations are required in order to determine the side effect profile of such an agent.

In the GI tract, TRPV1 is located on primary afferents and in epithelial cells of the stomach where it plays an important role in gastric protection. Activation of TRPV1 has also been implicated in the development of inflammation and hypermotility/hyperreflexia in the GI tract as well as abdominal pain associated with irritable bowel syndrome, functional dyspepsia, and inflammatory bowel disease.[45,46]

Activation of TRPV1 expressing superficial afferents terminating in the mucosa of the respiratory tract results in release of neuropeptides (e.g., substance P, CGRP, and neuropeptide A), which in turn contribute to increased mucosal secretion, bronchoconstriction, cough, and neurogenic inflammation. Neurogenic inflammation caused by activation of TRPV1 is recognized as an important factor in the development of asthma and chronic obstructive pulmonary disease.[46,47]

TRPV1 is expressed on the primary afferents and in the urothelial cells of the bladder, and its role in bladder dysfunction (urge incontinence) through studies with capsaicin and resiniferatoxin is well documented.[48] TRPV1 activation also potentially plays a role in the pathophysiology of migraine through stimulation of CGRP release from trigeminal sensory nerve fibers and the consequent dilation of dural blood vessels. However, despite the modest activity of capsazepine in blocking

capsaicin-induced vasodilation[49] and the relatively low levels of expression (estimated to be ~16% of total neuronal cell bodies in human trigeminal ganglia),[50] TRPV1 antagonists are currently of interest for the potential treatment of migraine.

In summary, further to their potential to treat inflammatory and neuropathic pain, TRPV1 modulators may also find utility in the treatment of a range of conditions including visceral pain, irritable bowel syndrome, cough, asthma, chronic obstructive pulmonary disease, urinary incontinence, and migraine. As mentioned earlier, trials for migraine are already underway and it also remains to be seen which additional indications/diseases will be targeted by industry in phase II clinical trials and beyond. The potential disadvantages arising from the wide distribution of this channel must also be recognized. There is mounting evidence that activation of TRPV1 has beneficial effects in the body, and therefore, the deactivation of the receptor through the use of systemically available agonists (desensitisation/denervation) or antagonists (blockade) may result in a detrimental side effect profile.

Conclusions

Research into the mechanism of the pain-inducing and -relieving properties of capsaicin stretches back over 100 years. However, since the identification and cloning of the "capsaicin" receptor (now known as TRPV1) in the 1990s, interest in this area has exploded. In particular, TRPV1 antagonism has the potential to provide a new mechanism for the treatment of a variety of pain states (such as neuropathic pain), many of which have a high unmet medical need. From the results of early research into the expression of TRPV1 it was thought that these receptors were almost solely located on primary sensory neurons; hence, this approach held the promise of delivering agents with side effect profiles far superior to those of existing pain medications. However, there is now a wealth of evidence showing that TRPV1 is expressed in many neuronal and non-neuronal tissues where it has potentially beneficial roles. Consequently, blockade of the receptor through systemic administration of an antagonist may result in a less favorable risk/benefit profile than perhaps was initially anticipated. However, until the results of extensive clinical trials are published, this will remain an area of conjecture. The fact that a TRPV1 antagonist has entered phase II trials is an encouraging development and the results of pivotal proof of concept (POC) studies are eagerly anticipated to see whether TRPV1 antagonism does indeed fulfill its promise as a beneficial new mechanism for the treatment of wide range of painful conditions.

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Biography

Susan M. Westaway received her B.Sc. (Hons) degree in Chemistry and her Ph.D. degree in Organic Chemistry from the University of Bristol, U.K., working in the laboratories of Prof. T. J. Simpson and Prof C. L. Willis. Following a postdoctoral teaching fellowship with Prof. N. S. Simpkins at the University of Nottingham, U.K., she joined Rhone-Poulenc Agro in 1997 before moving to GlaxoSmithKline in 2001. Currently, she is a Team Leader in the Department of Medicinal Chemistry, Neurology & GI CEDD, working in the areas of pain and gastrointestinal disorders.

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