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Research Article

Medicinal Chemistry of the Vanilloid (Capsaicin) TRPV1 Receptor: Current Knowledge and Future Perspectives

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ABSTRACT In peripheral sensory neurons, the vanilloid receptor TRPV1 (transient receptor potential vanilloid subfamily, member 1) functions as a molecular integrator of painful stimuli, including those mediated by capsaicin, acid, and heat. Antagonist blockade of TRPV1 activation is under investigation by several pharmaceutical companies in an effort to identify novel agents for pain management. TRPV1 is also expressed, albeit at lower levels, in the brain and in non-neuronal tissues, where its function(s) remains elusive. The contribution of TRPV1 receptor activity to physiological reflexes and disease states is complex and is only beginning to be understood. Consequently, the resultant effects of TRPV1 antagonists on the body may be unforeseen. Indeed, clinical trials with a number of TRPV1 antagonists were recently terminated due to their marked hyperthermic activity. In this review article, the medicinal chemistry of TRPV1 antagonists is discussed inasmuch as it relates to the efficacy, safety, tolerability and potential side effects of these compounds. In addition, the available information on the current status of the clinical trials with TRPV1 antagonists is summarized. Drug Dev Res 68:1–21, 2008. ©2008 Wiley-Liss, Inc.

INTRODUCTION AND HISTORICAL PERSPECTIVE

Capsaicin (1) (Fig. 1) is best recognized as the ingredient responsible for the piquancy of hot chili peppers eaten on a daily basis by an estimated one quarter of the world population. According to new fossil evidence, the cultivation of chili peppers in the Americas has a 6,000-year history [Perry and Flannery, 2007; Perry et al., 2007], with the rest of the World being rapidly conquered after Columbus introduced hot pepper to the Spanish royal court [Naj, 1992]. Connoisseurs of hot, spicy food know the predominant pharmacological actions of capsaicin from personal experience: it induces profuse perspiration (known as gustatory sweating) as well as a hot, burning sensation that dissipates upon repeated challenge [Buck and Burks, 1986; Szallasi and Blumberg, 1999; Malmberg and Bley, 2005]. Capsaicin is not only a spice, however, but an extremely versatile agent whose biological uses, covered by more than 900 patents, ranges from culinary applications (included to improve flavor and inhibit bacterial growth) through pain killers to chemical weapons and repellents [Buck and Burks, 1986; Szallasi and Blumberg, 1999; Malmberg and Bley, 2005]. The latter group encompasses such diverse applications as pepper spray [Forrester and Stanley, 2003], capsaicin-flavored bird seed to repel squirrels [Rouhi, 1996] and self-protectant lotions to keep away sharks. Apparently, there is little new under the sun: Native Americans burnt pepper plants as a chemical

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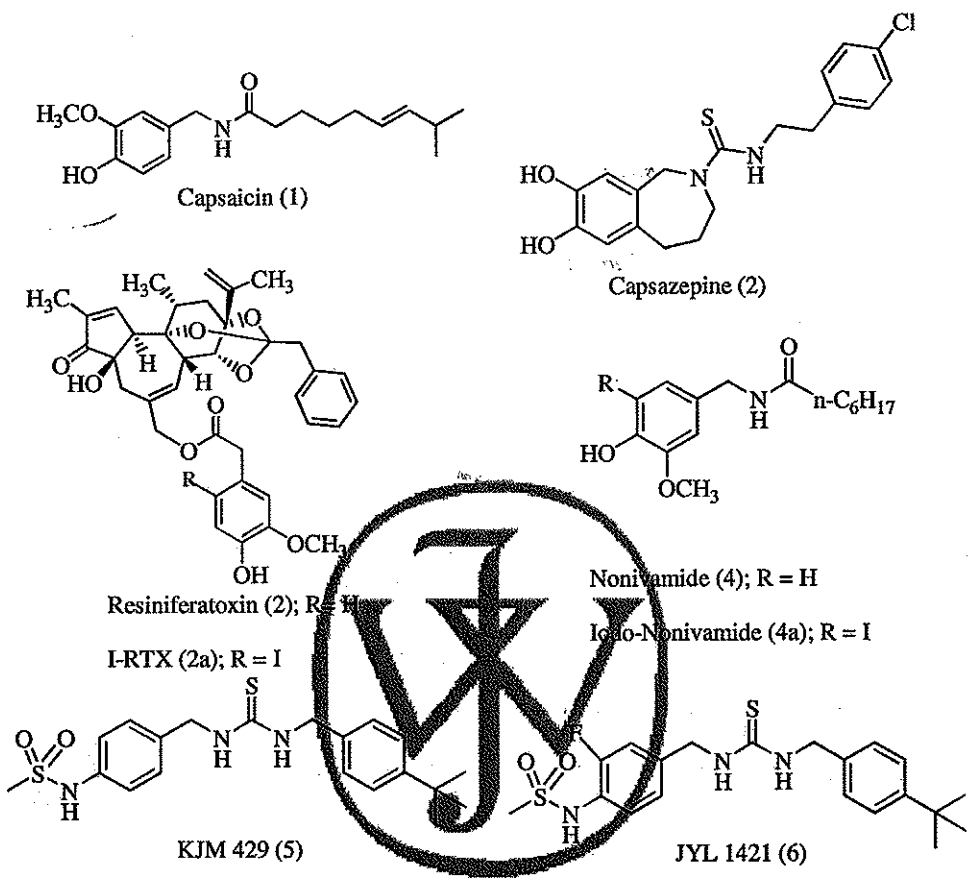

Fig. 1. Early synthetic and semi-synthetic TRPV1 antagonists.

weapon to fight the Conquistadors; they also used chili concoctions to relieve pain [Naj, 1992]. It is, however, still a mystery why the same pungency that repels squirrels or sharks is perceived as pleasurable by many human beings.

Capsaicin is unique among the naturally occurring irritants in that the initial neuronal excitation it causes is followed by a lasting refractory state, traditionally referred to as desensitization, in which the previously excited neuron is refractory to various unrelated stimuli [Buck and Burks, 1986; Szolcsányi, 1989; Szallasi and Blumberg, 1999; Malmberg and Bley, 2005]. Desensitization to capsaicin has a clear therapeutic potential. In fact, as reviewed recently, capsaicin-containing creams have been in clinical use for decades for indications, including diabetic neuropathy [Knotkova et al., 2007].

The concept of a specific capsaicin receptor was first postulated based on the distinct structure–activity relations shown by synthetic capsaicin analogues in their irritant activity [Szolcsányi and Jancsó-Gábor, 1975]. Biochemical proof for the existence of this receptor was furnished by the specific binding of resiniferatoxin (RTX), an ultrapotent capsaicin analogue isolated from the latex of the cactus-like plant, *Euphorbia resinifera* [Szallasi and Blumberg, 1990]. Since capsaicin and RTX share a (homo)vanillyl moiety essential for bioactivity but differ dramatically in the remainder of the molecule, their common membrane recognition site was termed the vanilloid receptor, VR1 [Szallasi and Blumberg, 1999]. Based on ion uptake and patch-clamp studies, it was postulated that the vanilloid receptor VR1 was a nonselective cation channel with limited selectivity for calcium [Wood et al., 1988]. Indeed, Julius and colleagues [Caterina et al., 1997] employed capsaicin-evoked Ca^{2+} uptake in a rat dorsal root ganglion (DRG) expression system to clone this receptor in 1997.

The past decade has witnessed unprecedented advances in the vanilloid field. The vanilloid VR1 receptor turned out to be the founding member of a now populous receptor family, the TRP (transient release potential) receptors, and, accordingly, was renamed as TRPV1 (transient release potential vanilloid subfamily 1) [Montell et al., 2002]. TRPV1 is no longer an orphan receptor anymore. In fact, activators

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of TRPV1 include noxious heat [Caterina et al., 1997] and pungent natural products (e.g., plant products as exemplified by capsaicin [Caterina et al., 1997], jellyfish [Cuypers et al., 2006], and spider toxins [Siemens et al., 2006) through low pH [Tominaga et al., 1998; Jordt et al., 2000] and agents in various "inflammatory soups" [Hwang et al., 2000; Chuang et al., 2001] to anandamide [Zygmunt et al., 1999] and other putative "endovanilloids" (endogenous TRPV1 ligands) [Di Marzo et al., 2002]. In other words, TRPV1 can be thought of as a molecular integrator of diverse noxious and pro-inflammatory stimuli rather than as a specific capsaicin (vanilloid) receptor [Tominaga et al., 1998; Caterina and Julius, 2001]. This observation provides a mechanistic explanation for the characteristic "hot" sensation evoked by capsaicin.

Other related channels (as of today, a total of seven) also turned out to be heat-sensitive, hot, or cold: these receptors, often referred to as "thermoTRPs," cover a wide temperature range with extremes falling between noxious cold (10°C, TRPA1) and noxious hot (53°C, TRPV2) and show significant overlap of the temperature range in which they are activated [Patapoutian et al., 2003; Dhaka et al., 2006].

Although all "thermoTRPs" represent attractive targets for drug development [Krause et al., 2005; Cortright et al., 2007], with a number of small-molecule antagonists already in clinical trials, TRPV1 is clearly in the most advanced stage [Szallasi et al., 2007]. These trials are exciting in that they represent the litmus test for the feasibility of a new pharmacological approach in pain relief, that is, the chronic blockade by an antagonist of a peripheral receptor where pain is generated [Szallasi et al., 2007]. If TRPV1 antagonists succeed in clinical practice, it will give further impetus to drug development efforts targeting other TRPV receptors. However, should TRPV1 antagonists fail to live up to expectations, it could also discourage these efforts. The goal of this review is to provide a comprehensive overview of the medicinal chemistry of TRPV1 ligands, both agonist and antagonists, with emphasis on the latter. We seek an answer to the question raised by Hicks [2006] in a recent editorial in *Gastroenterology and Motility*: is TRPV1 still hot or it is time to cool down? But in order to do so, first we have to briefly review the tissue distribution, function, and molecular pharmacology of TRPV1.

TISSUE DISTRIBUTION AND FUNCTION OF TRPV1 IN HEALTH AND DISEASE

TRPV1 s can be divided into three major tissue compartments: (1) capsaicin-sensitive sensory neurons in the peripheral nervous system (PNS) [Szallasi, 1996]; (2) neurons in the central nervous system (CNS) [Szallasi and Di Marzo, 2000; Steenland et al., 2006]; and (3) non-neuronal tissues [Gunthorpe and Szallasi, 2007]. The biological function of TRPV1 in the PNS is now well established and is reviewed further below. Despite extensive research, it is still unclear what biological roles TRPV1 may play in the CNS and non-neuronal cells.

TRPV is highly expressed in primary sensory neurons [Caterina et al., 1997; Guo et al., 1999; Sanchez et al., 2001]. Indeed, capsaicin was often referred to as "selective sensory neurotoxin," and capsaicin sensitivity was widely accepted as a "functional signature" of these cells [Szolcsányi, 1984; 2004]. Generally speaking, capsaicin-sensitive neurons are bipolar neurons with either unmyelinated (C-fibers) or thin myelinated axons (Aδ fibers) and cell bodies in sensory (dorsal root ganglion [DRG], and trigeminal) ganglia [Buck and Burks, 1986; Holzer, 1988]. The nodose ganglion also has a capsaicin-sensitive component: these fibers travel with the vagus nerve and are believed to play a pivotal role in visceral discomfort and pain [Wang et al., 2005]. The peripheral endings of capsaicin-sensitive neurons are sites of release for various pro-inflammatory neuropeptides, the most prominent examples of which are substance P (SP) and calcitonin gene-related peptide (CGRP) [Buck and Burks, 1986; Holzer, 1988]. Of note, spinal terminals also contain endogenous analgesic peptides like galanin [Skofitsch and Jacobowitz, 1985; Crawley et al., 2002]. Spinal galanin levels are upregulated following RTX treatment [Szallasi, 1996] and this effect was suggested to contribute to the cellular mechanism of RTX-evoked desensitization [Xu et al., 1997].

Sensory neuropeptides released from capsaicin-sensitive neurons have been implicated in a wide array of physiological responses and disease states. For instance, sustained release of CGRP plays a role in the physiological regulation of microvascular blood flow [Tam and Brain, 2004]. By contrast, deranged CGRP release was postulated to contribute to the pathomechanism of both migraine [Geppetti et al., 2005; Benemei et al., 2007] and hypertension [Marquez-Rodas et al., 2006]. In a rat model of hypertension, there is now good evidence that CGRP release is evoked by endovanilloids, and in particular methanandamide, acting on TRPV1 [Wang et al., 2007]. Slow SP release is believed to exert a trophic function on epithelial cells [Tanaka et al., 1988; Paus et al., 1995]. In keeping with this hypothesis, ablation of cutaneous peptidergic neurons by capsaicin administration at supratherapeutic doses interferes with wound healing [Smith and Liu, 2002] and leads to the formation of skin ulcers [Maggi et al., 1987]. Conversely,

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overproduction of SP has been suggested to play a role in the pathobiology of psoriasis [Naukkarinen et al., 1993; Raychaudhuri et al., 1998]. Indeed, topical capsaicin cream is beneficial in patients with psoriasis [Bernstein et al., 1986], although it is still unclear to what degree this beneficial action may be attributed to the anti-pruritic effect of capsaicin [Arck and Paus, 2006]. Nonetheless, there is anecdotal evidence that cutaneous nerve damage results in the clearance of psoriatic plaques [Farber et al., 1990]. Interestingly, psoriatic keratinocytes are known to produce large amount of nerve growth factor (NGF) [Raychaudhuri et al., 1998], a potent activator of TRPV1 [Chuang et al., 2001]. Last, deregulated CGRP and SP release from capsaicin-sensitive neurons has most recently been linked to both obesity and diabetes, implying therapeutic potential for TRPV1 ligands for weight control and blood glucose regulation [Gram, 2003; Suri and Szallasi, 2007; Tsui et al., 2007]. Indeed, the TRPV1 antagonist BCTC was reported by investigators at NovoNordisk to prevent aging-related weight gain and resultant type-2 diabetes in the rat [Gram et al., 2007].

When released en masse, sensory neuropeptides released from TRPV1-positive neurons initiate the biochemical cascade collectively known as neurogenic inflammation [Geppetti and Holzer, 1996]. At the same time, an impulse is generated and propagated into the CNS via the central fibers that enter the dorsal horn of the spinal cord. The pivotal role of TRPV1 in the initiation of the neurogenic inflammatory response and the transduction of pain is firmly established and forms the foundation for the use of TRPV1 antagonists as anti-inflammatory and analgesic drugs [Geppetti and Holzer, 1996; Szallasi et al., 2006, 2007]. Importantly, TRPV1 homozygous null mice (knockouts) are devoid of the thermal hypersensitivity that occurs in response to acute hind paw injection of pro-inflammatory agents (e.g., complete Freund's adjuvant [CFA]), predicting a clinical value for TRPV1 antagonists as novel analgesic drugs [Caterina et al., 2000; Davis et al., 2000]. This beneficial effect is mimicked by conditional knockdown of TRPV1 via siRNA in wild-type animals [Christoph et al., 2006; Kasama et al., 2007].

TRPV1 is also widely present in brain nuclei [Szallasi and Di Marzo, 2000; Steenland et al., 2006; Di Marzo and Maione, 2007] and non-neuronal tissues (Gunthorpe and Szallasi, 2007]. As to the biological roles of TRPV1 receptors in these tissues, speculations are abundant, but conclusive evidence is still absent. In the brain, recent behavioral studies imply a role for TRPV1 in fear and various cognitive functions [Marsch et al., 2007]. Furthermore, TRPV1 is co-localized with tyrosine hydroxylase in basal ganglia, identifying these neurons as dopaminergic [Mezey et al., 2000]. Indeed, there is preliminary evidence linking TRPV1-expressing basal ganglion neurons to a rat model of Parkinson's disease [Fernandez-Ruiz and Gonzalez, 2005; Di Marzo and Maione, 2007]. With regard to non-neuronal tissues, an exciting but very controversial area of research is the possible connection between TRPV1 and cancer [Gunthorpe and Szallasi, 2007; Prevarskaya et al., 2007]. TRPV1 is apparently expressed is various cancers but authors disagree whether TRPV1 ligands are tumorigenic or, conversely, anti-carcinogenic. Until this controversy is resolved, there are a few basic observations to keep in mind. First, bladder biopsies obtained from both experimental animals and patients undergoing chronic capsaicin or RTX treatment are unremarkable [Dasgupta et al., 1998; Avelino and Cruz, 2000; Apostolides et al., 2005]. Second, there is no published report of increased incidence of tumor formation in animals whose TRPV1 receptors have been ablated either chemically (e.g., neonatal capsaicin administration) or genetically (TRPV1 k.o. mice). These negative findings warrant caution in interpreting the biological significance of TRPV1 expression in cancers. Most studies employ high-dose capsaicin treatment in order to delineate the outcome of TRPV1 activation in tumor cells, which is usually apoptosis. Capsaicin is nonspecific, however, for TRPV1 at the high concentrations used in these studies [Szallasi and Blumberg, 1999]. Indeed, some investigators interpret their findings as a direct (TRPV1-independent) activation by capsaicin of apoptotic pathways [Athanasiou et al., 2007]. Of note, similar cautions apply to the putative CNS effects of TRPV1 activation: neither capsaicin, nor the first-generation TRPV1 antagonist, capsazepine, is selective for TRPV1. Clearly, these experiments need to be replicated using the new generation of more selective TRPV1 agonists and antagonists before a formal conclusion can be reached as to the role of TRPV1 in cancer and higher brain functions.

There is mounting evidence that TRPV1 expression may be altered during disease conditions [Szallasi et al., 2007]. Recognized patterns include (1) up- or downregulation of native TRPV1; (2) ectopic expression of TRPV1 in tissues where it is not normally present; and (3) epigenetic changes by enzymatic modification of the receptor protein (e.g., phosphorylation by kinases, in particular, protein kinase C). Representative examples are discussed below. Upfront, one needs to emphasize that it is unclear whether these alternations are pathogenic or represent adaptive/protective mechanisms.

TRPV1 expression is bidirectionally regulated in sensory neurons both at the transcriptional and

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posttranscriptional levels. A well-established example of upregulated TRPV1 expression is the presence of increased TRPV1 protein levels in animal models of inflammatory hyperalgesia [Wilson-Gerwing et al., 2005]. Importantly, this is in agreement with the increase in TRPV1-like immunoreactivity in a variety of painful human disease conditions that encompass such diverse conditions like caries [Morgan et al., 2005], reflux esophagitis [Matthews et al., 2004; Bhat and Bielefeldt, 2006], inflammatory bowel disease [Yiangou et al., 2001], fecal urgency/irritable bowel syndrome [Chan et al., 2003], vulvodynia [Tympanidis et al., 2004], mastalgia [Gopinath et al., 2005], and burning mouth syndrome [Yilmaz et al., 2007]. Conversely, a diffuse loss of TRPV1-positive axons was reported in patients with painful peripheral neuropathies [Lauria et al., 2006]: this loss may explain the less than satisfactory results obtained in many clinical trials using topical capsaicin for the indication of diabetic neuropathy [Hautkappe et al., 1995; Knotkova et al., 2007].

In animals, TRPV1 is downregulated via vanilloid (capsaicin or RTX) desensitization of sensory neurons [Szallasi and Blumberg, 1999]. This downregulation is both long lasting (up to 4 weeks following administration of a single RTX dose) and fully reversible [Szallasi and Blumberg, 1999]. It was suggested that agonist-induced TRPV1 downregulation is part of the phenotypic switch [Ueda, 2006], referred to as "vanilloid-induced messenger plasticity," that occurs following vanilloid treatment [Szallasi, 1996]. During this switch, the expression of pro-inflammatory neuropeptides (e.g., SP and CGRP) is suppressed, whereas the levels of endogenous analgesic peptides (e.g., galanin) are elevated [Buck and Burks, 1986; Szallasi and Blumberg, 1999]. The end-result of this phenotypic switch is a lasting refractory state.

Ectopic TRPV1 expression was described both in sensory neurons and non-neuronal tissues. For example, TRPV1 is ectopically expressed on Aδ fibers during nerve injury-induced thermal hyperalgesia [Hudson et al., 2001; Rashid et al., 2003] and in diabetic neuropathy [Rashid et al., 2003; Hong and Wiley, 2005]. As discussed above, in non-neuronal tissues, ectopic TRPV1 expression was detected in various cancers, the significance of which is yet to be delineated.

In feline interstitial cystitis, the phosphorylation state of TRPV1 appears to be disease-specific [Sculptoreanu et al., 2005]. If so, it may have important implications for drug development since the pharmacological activity of some agonist/partial antagonist compounds is affected by the phosphorylation state of TRPV1 [Wang et al., 2003; Lizanecz et al., 2006]. Theoretically, such TRPV1 antagonists can be synthesized that selectively target disease-specific (phosphorylated) TRPV1 but spare normal TRPV1 [Szallasi and Blumberg, 2006].

MOLECULAR PHARMACOLOGY OF TRPV1: IMPLICATIONS FOR ANALGESIA AND THERMOREGULATION

Similar to other members of the TRP superfamily, TRPV1 is a putative six-transmembrane spanning protein with a pore region localized between transmembrane segments 5 and 6 [Caterina et al., 1997]. The pore is thought to form a nonselective cation channel with a preference for Ca^{2+} that is directly activated by capsaicin and noxious temperatures with an activation threshold in vitro of about 43°C [Caterina et al., 1997]. These data suggest that TRPV1 is probably inactive at normal body temperature with one notable exception: TRPV1 involved in core temperature regulation seems to have an endogenous tone [Gavva et al., 2007a], as evidenced by the hyperthermic response to TRPV1 antagonists [Swanson et al., 2005].

The involvement of TRPV1 in heat sensation and body temperature regulation is an exciting, but still controversial, area of research [Caterina, 2007]. It was firmly established more than a half century ago that capsaicin administration results in a rapid drop in body temperature [Issekutz et al., 1950; Jancsó, 1955]. The hypothermic action of capsaicin was later linked to the preoptic area of the brain [Szolcsányi et al., 1975], and it may reflect the "cold seeking behavior" of the animal to counteract the acute, pro-inflammatory effects of capsaicin administration [Almeida et al., 2006]. Indeed, no hypothermia response is observed if capsaicin-treated animals are kept in ambient temperature environment [Jancsó, 1968]. Quite the contrary, animals suffer heat stress if they are transferred to a heated chamber [Jancsó, 1968; Szallasi and Blumberg, 1989]. These findings may be interpreted to imply a pivotal role for TRPV1 in regulation of body temperature. However, no difference in circadian body temperature regulation was described in TRPV1 knockout mice compared with controls [Iida et al., 2005].

The clinical significance of the hyperthermic response to TRPV1 antagonists remains to be delineated. In the rat, this hyperthermic response is modest (~1°C), transient (i.e., attenuates upon repeated TRPV1 antagonists administration), and can be easily managed by such common antipyretic drugs as acetaminophen [Gavva et al., 2007b]. Yet, Amgen effectively terminated the third molar extraction clinical trials with its lead compound after phase 1

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after the core temperature reached 40°C in one patient [Gavva, 2007]. The question awaiting answer is: "The capsaicin receptor TRPV1: Is it a pain transducer or a regulator of body temperature?" [Gavva, 2007].

The findings in animals are confusing and provide little guidance in patient management. If TRPV1 blockade is hyperthermic, it should exacerbate the febrile response to bacterial lipopolysaccharide (LPS). However, TRPV1 knockout mice not only show an attenuated fever in response to bacterial LPS [Iida et al., 2005] but also demonstrate enhanced hypothermia, hypotonia, and peritoneal exudates in a murine model of sepsis [Clark et al., 2007]. Based on these observations, pessimists may argue that TRPV1 antagonists can have deleterious effects in hospitalized patients by inducing fever and increasing vulnerability to septic shock. But this is not necessarily true. The relationship between LPS and TRPV1 is questionable. Indeed, it was suggested that LPS-induced fever is mediated by a capsaicin-sensitive mechanism that is independent of TRPV1 [Dogan et al., 2004]. In support of the hypothesis, capsaicin was shown to block the febrile response to LPS in the chicken [Mahmood et al., 2007] although chicken TRPV1 is insensitive to capsaicin because it lacks the capsaicin-recognition domain [Jordt and Julius, 2002]. Even more confusing, the effect of TRPV1 ablation on sepsis appears to be strikingly species-dependent. In the mouse, genetic deletion of TRPV1 exacerbates the harmful components of sepsis [Clark et al., 2007]. By contrast, in the rat chemical ablation of TRPV1 not only prevents mortality but also ameliorates sepsis-induced catabolic effects [Bryant et al., 2003]. Clearly, more research is needed to determine whether TRPV1 antagonists are beneficial or harmful in patients with sepsis.

TRPV1 functions as a polymodal nociceptor with a dynamic threshold of activation and is thought to mediate the phenomenon of peripheral sensitization [Julius and Basbaum, 2001; Messeguer et al., 2006]. Even considering the role of TRPV1 as a polymodal nociceptor, it is amazing how diverse agents can activate (or sensitize) TRPV1. An incomplete and ever-growing list of TRPV1 activators include (1) heat and protons [Caterina et al., 1997; Tominaga et al., 1998; Jordt et al., 2000]; (2) bradykinin and nerve growth factor [Chuang et al., 2001]; (3) arachidonic acid metabolites such as anandamide [Zygmunt et al., 1999; Mohaved, 2005], *N*-arachidonyl-dopamine and *N*-oleoyldopamine [Huang et al., 2002]; (4) lipoxygenase products (12- and 15-HPETE) [Hwang et al., 2000]; (5) leukotriene B_4 [Shin et al., 2002]; (6) prostaglandins [Moriyama et al., 2005]; (7) adenosine and ATP [Kwang et al., 2000]; (8) prokineticins [Negri et al., 2006]; (9) polyamines [Ahern et al., 2006]; (10) ethanol [Trevisani et al., 2002]; (11) plant natural products such as capsaicin [Caterina et al., 1997], RTX [Szallasi and Blumberg 1989], evodiamine [Pierce et al., 2004], camphor [Xu et al., 2005], and phorbol esters [Premkumar and Ahern, 2000]); (12) jellyfish [Cuypers et al., 2006] and spider venoms [Siemens et al., 2006]; (13) negatively charged air pollutants [Agopyan et al., 2004]; and (14) hydrogen sulfide [Trevisani et al., 2005]. Some of these agents activate TRPV1 directly by interacting at specific residues in the receptor protein, whereas others act indirectly via enzymatic modification of TRPV1 function.

The capsaicin-binding domain was first described by Julius and colleagues [2002]. This is in partial overlap with the residues that are responsible for the high-affinity [3 H]RTX binding [Johnson et al., 2006]. These ligand recognition sites are intracellular. A third intracellular domain was localized to the pore region: this is involved in capsaicin-gating but not heat and/or proton activation [Sutton et al., 2005; Johnson et al., 2006]. By contrast, the pH sensor in TRPV1 is extracellular [Tousova et al., 2005]. The N-terminus ankyrin repeats of TRPV1 contain a multiligand domain [Lishko et al., 2007] whereas the ATP binding site was localized to the C-terminus of TRPV1 [Grycova et al., 2007]. Given this complex structure of ligand activation, it is hardly surprising that TRPV1 antagonists show selectivity in their pharmacological profile. Indeed, it was postulated that TRPV1 antagonists fall into two broad categories: class A antagonists, which prevent TRPV1 activation both by capsaicin and protons, and class B antagonists, which are selective for capsaicin [Gavva et al., 2005].

The activation state of TRPV1 also depends on its phosphorylation state, which reflects a dynamic balance between phosphorylation by kinases and dephosphorylation by phosphatases [Cortright and Szallasi, 2004; Lee et al., 2005; Sugiura and Ohta, 2005]. Most studies agree that receptor protein phosphorylation by kinases (e.g., protein kinase C [Numazaki et al., 2002; Premkumar et al., 2004] and protein kinase A [Mohapatra and Nau, 2005]) of TRPV1 causes sensitization, whereas dephosphorylation by protein phosphatases (e.g., calcineurin [Mohapatra and Nau, 2005]) promotes TRPV1 desensitization. Notable exceptions include reports that (1) protein kinase C may directly activate TRPV1 [Premkumar and Ahern, 2000], and (2) both protein kinase A [Bhave et al., 2002] and C [Liu et al., 2004] may play a role in desensitization. Both pro-inflammatory/algesic and analgesic agents can affect these pathways. For instance, bradykinin [Lee et al., 2005] and nerve growth factor [Zhang et al., 2005] reduce the activation threshold of TRPV1 via protein kinase C-dependent phosphorylation. Conversely, morphine blocks TRPV1

sensitization by preventing its phosphorylation by protein kinase A [Vetter et al., 2006].

Of the protein kinase C isozymes, protein kinase Cε appears to be the most important: this isozyme has been linked to sensitization of TRPV1 to noxious heat [Cesare et al., 1999]. Compounds that selectively inhibit protein kinase Cε abolish heat hyperalgesia [Zhang et al., 2007], mimicking the phenotype of mice whose TRPV1 has been deleted by genetic recombination [Caterina et al., 2000; Davis et al., 2000].

The effect of phosphatidylinositol 4,5-biphosphate [abbreviated as PtdIns(4,5)P2 or PIP2] on TRPV1 is complex and less well understood [Brauchi et al., 2007; Qin, 2007]. Originally, Julius and colleagues suggested that TRPV1 is under the inhibitory control of PIP2 [Chuang et al., 2001; Prescott and Julius, 2003], which would be consistent with the lack of endogenous TRPV1 tone except for core temperature regulation. They also proposed that: (1) cleavage by phospholipase C of PIP2 may constitute a biochemical mechanism of TRPV1 activation [Chuang et al., 2001], and (2) functional recovery of TRPV1 from desensitization requires PIP2 resynthesis [Liu et al., 2005]. Subsequent studies, however, paint a far more complicated picture. In excised patches, PIP2 activates TRPV1 [Lukacs et al., 2007]. Furthermore, capsaicin activates phospholipase C in TRPV1-expressing cells, resulting in PIP2 depletion and subsequent desensitization. Importantly, the phospholipase C inhibitor, U73122 prevents capsaicin desensitization of TRPV1 [Lukacs et al., 2007]. How can one reconcile these conflicting findings? Rohacs and coworkers (Lukacs et al., 2007] believe the PIP2 may have both inhibitory and potentiating effects on TRPV1 depending on the cellular milieu. This biphasic behavior is hardly unprecedented: both some natural products (e.g., cinnamodial [Szallasi et al., 1998]) and synthetic compounds [Wang et al., 2003] activate or inhibit TRPV1, depending on their dose and/or the phosphorylation state of the receptor.

An emerging area of TRPV1 modulation is the heteromeric assembly of TRPV1 subunits [Garcia-Sanz et al., 2004; Hellwig et al., 2005] and the interaction of TRPV1 with its splice variants and other intracellular proteins that may play a role in the shuffling of TRPV1 among various subcellular compartments [Cortright and Szallasi, 2004; Szallasi and Blumberg, 2006; Szallasi et al., 2007]. As first predicted by its large radiation inactivation size inconsistent with a single protein [Szallasi and Blumberg, 1991], TRPV1 probably exists in a multimeric form, most likely as a tetramer [Garcia-Sanz et al., 2004]. This model is entirely consistent with the positive cooperative nature of the ligand binding properties of TRPV1 [Szallasi and Blumberg, 1999]. TRPV1 is actively transported between the cell membrane and intracytoplasmic compartments [Morenilla-Palao et al., 2004]: it was suggested that upon phosphorylation by protein kinase C, TRPV1 is directed to the membrane [Zhang et al., 2005] and then the dephosphorylated protein is reshuffled to the intracellular depots.

COMPETITIVE TRPV1 ANTAGONISTS OBTAINED BY CHEMICAL MODIFICATION OF AGONISTS

The very existence of TRPV1 predicted the existence of painful endogenous compounds, the so-called endovanilloids [Kwak et al., 1998; Szallasi and Blumberg, 1999; Di Marzo et al., 2002; Walker et al., 2003]. It can be argued that if endovanilloids are involved in the development of pathologic pain, competitive TRPV1 antagonists should be analgesic by blocking the access of pro-algesic endovanilloids to the receptor. This concept has gained strong experimental support by the absence of inflammatory thermal hyperalgesia in mice whose TRPV1 had been deleted by heterologous recombination (−/−) [Caterina et al., 2000; Davis et al., 2000].

The first competitive TRPV1 antagonists, as exemplified by capsazepine (2) (Fig. 1), were derived directly from structural modification of TRPV1 agonists by researchers at the Sandoz (now Novartis) Institute for Medical Research in an attempt to dissociate the intolerable irritant and pungent properties of capsaicin derivatives from their analgesic activity. [Walpole and Wrigglesworth, 1993]. Capsazepine is a conformationally constrained capsaicin analogue and extensive NMR and X-ray crystallographic studies gave rise to a proposal of different binding modes for agonist versus an antagonist [Walpole et al., 1994]: agonists bind to the TRPV1 receptor in an extended conformation, whereas the antagonists prefer an L-shaped orientation [Walpole and Wrigglesworth, 1993]. Capsazepine is still the most widely used pharmacological tool in studies involving TRPV1 despite its many unfavorable properties, including low potency, metabolic instability, and interaction at receptors other than TRPV1 (e.g., nicotinic acetylcholine receptors and voltage sensitive calcium channels) [Szallasi and Blumberg, 1999]. One must use caution when interpreting positive or negative results with capsazepine. Since capsazepine is a class B TRPV1 antagonist, that is, it does not inhibit all types of TRPV1 activators [Gavva et al., 2005], a lack of inhibition by capsazepine does not necessarily imply that TRPV1 was not involved in the response. Conversely, a block of response by capsazepine may be mediated by targets other than TRPV1.

It was with serendipity that it was discovered by investigators at NovoNordisk that halogenation, and

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more specifically iodination, of TRPV1 agonist may provide potent antagonists [Wahl et al., 2001]. For example, iodination of RTX [Wahl et al., 2001] and nonivamide [Appendino et al., 2003] in the homovanillyl moiety results in potent TRPV1 antagonists. Interestingly, the position of iodine is critical for determining the pharmacological activity of the molecule. For instance, introduction of iodine at C-5′ position in RTX (**3**) or at C-′ position in nonivamide (**4a**) (Fig. 1) resulted in complete reversal, whereas the converse produced either less potent antagonist or partial agonists [Appendino et al., 2005a,b,c]. It is unclear how halogenation works at the molecular level as iodination of vanillic- and dihydroferulic-RTX analogues has no impact on TRPV1 agonism [Appendino et al., 2007]. Halogenated TRPV1 antagonists are useful tool in in vitro assays, but not much is known about their in vivo efficacy, mostly because they are no considered as drug candidates.

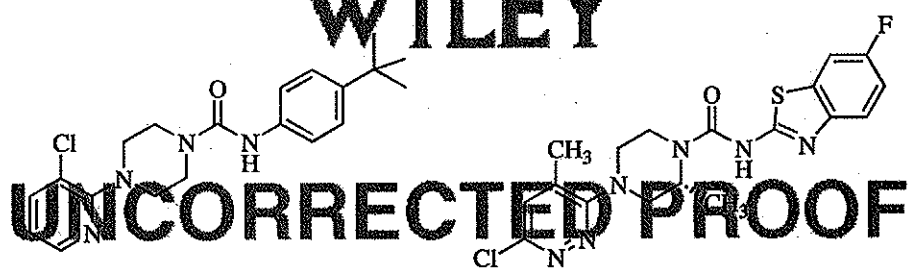
Other examples of TRPV1 antagonists obtained by chemical modification of existing TRPV1 agonists include the thiourea-based KJM 429 (**5**) and JYL 1421 (**6**) (Fig. 1) (also known as SC0030) [Wang et al., 2002; Lee et al., 2003; Kang et al., 2007]. These antagonists were obtained by specific substitution in the aromatic region of the corresponding agonist. KJM 429 was obtained via replacement by a methane sulfonamide group of the 3′ phenolic hydroxyl group in the terminal benzyl ring of the corresponding agonist. JYL 1421 is a result of an additional fluoro-substituent at C-2′ of KJM 429. JYL-1421 was assessed in various bioassays in the rat where it behaved as a TRPV1 antagonist, both more potent and more selective than capsazepine [Jakab et al., 2005].

POTENT, SMALL-MOLECULE TRPV1 ANTAGONISTS

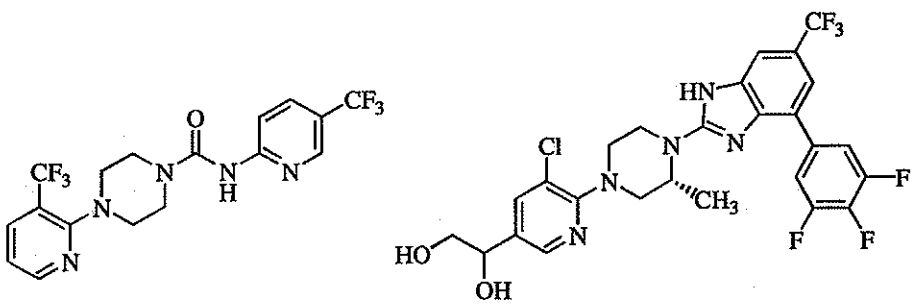
The molecular identification of TRPV1 in 1997 [Caterina et al., 1997] paved the way to the launching by pharmaceutical companies of high-throughput screening and combinatorial chemistry programs aimed at the identification of novel antagonists with better efficacy, safety, and pharmacokinetic profiles.

Pyridyl Piperazine Carboxamides

BCTC (N-(4-*tert*-butylphenyl)-4-(3-chloropyridin-2-yl) piperazine-1-carboxamide) (**7**) (Fig. 2) is the most studied member of the piperazine carboxamide class of TRPV1 antagonists [Bakthavatchalam, 2002; Dax et al., 2002; Yura et al., 2003; Rami et al., 2003; Lee et al., 2003; Sun et al., 2003; Tafesse et al., 2004]. In the patent literature, this class was first disclosed by Neurogen, followed by Johnson & Johnson, Bayer, GlaxoSmithKline (GSK), and Abbott and Purdue Pharma [Bakthavatchalam, 2002; Dax et al., 2002; Yura et al., 2003; Rami et al., 2003; Lee et al., 2003; Sun et al., 2003; Tafesse et al., 2004]. BCTC is a promising preclinical candidate molecule. It is a potent antagonist of rat TRPV1 (rTRPV1) activation by both acids



BCTC (7) (8)



(9) AMG 2674 (10)

Fig. 2. Piperazine carboxamides and benzimidazoles.

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(IC_{50} = 4.8 nM) and capsaicin (IC_{50} = 35 nM), that is, it is a class A antagonist. Moreover, it shows a much better selectivity profile as compared to capsazepine against a panel of ion channels, receptors, enzymes and transporters of clinical relevance. Importantly, BCTC is bioavailable per os (5–15%) with a plasma half-life of nearly 1.0 h and is active in rat models of acute inflammatory and neuropathic pain [Pomonis et al., 2003] with significant penetration into the CNS [Valenzano et al., 2003].

BCTC, however, showed significant shortcomings in preclinical studies, most importantly, it blocked (87% inhibition at 1 μM) hERG channels expressed in HEK-293 cells [Tafesse et al., 2004]. Inhibitors of hERG channels are known to produce potentially fatal cardiovascular effects such as prolongation of the cardiac QT interval causing ventricular arrhythmias and fibrillation [Roden et al., 1996].

Of note, Johnson & Johnson developed a 4-(3-trifluoromethylpyridin-2-yl)-1-(5-trifluoromethylpyridin-2-yl)piperazine-1-carboxamide (**9**) (Fig. 2) molecule as a close analogue of BCTC [Swanson et al., 2005]. This compound functioned as a potent human TRPV1 (hTRPV1) antagonist against capsaicin (IC_{50} = 6 nM) and other modes of activation such as low pH (IC_{50} = 16 nM) and also exhibited excellent oral bioavailability (100%) and plasma half-life (7–8 h) [Swanson et al., 2005]. The hyperthermia produced by this compound prevented its further development [Swanson et al., 2005].

In summary, the piperazine carboxamide class contains highly potent TRPV1 antagonists whose clinical potential is limited by a combination of complex pharmacokinetics, low aqueous solubility, metabolic stability, hyperthermia, and potential cardiovascular side effects (the latter mediated by hERG channels).

Piperazine Carboxamides and Piperazinyl-Benzimidazoles

AMG-2674 (**10**) (Fig. 2), a highly potent TRPV1 antagonist belonging to the series of 2-(4-pyridin-2-ylpiperazin-1-yl)-1H-benzo[d]imidazoles, was discovered at Amgen as a modified piperazine amide [Ognyanov et al., 2006]. The compounds in this class are modified BCTC analogues where the N1-carboxyanilide group of BCTC has been cyclized to form a benzimidazole moiety. The introduction of lipophilic groups such as 3,4,5-trifluorophenyl on the benzimidazole ring and polar head groups such as hydroxymethyls on the pyridine ring restores the high potency of these antagonists, implying the existence of a large hydrophobic pocket in the TRPV1 receptor. Similar to the BCTC series, introduction of a methyl group with R-configuration on the piperazine ring enhances the potency of these compounds. AMG-2674 was obtained by a stepwise modification of the BCTC scaffold. This compound demonstrated potent activity in vitro in capsaicin- and pH-induced activation of rTRPV1 (IC_{50} = 0.9 nM). In vivo, oral administration of AMG-2674 to rats blocked capsaicin-induced flinching (EC_{50} = 8.8 mg/kg) and thermal hyperalgesia by 46% following intraplantar application of complete Freund's adjuvant [Ognyanov et al., 2006].

Piperazine Carboxamides to Biaryl Carboxamides to Aminoquinazolines

A collaborative effort between Neurogen and Merck identified a series of biaryl carboxamides as TRPV1 antagonists with high potency and metabolic stability [Zheng et al., 2006]. This series featured bioisosteric replacement of the piperazine ring from the piperazine carboxamide series with a phenyl ring. Structure–activity relationships were similar to those of the piperazine carboxamide series. Compounds **11–14** (Fig. 3) showed excellent potency (IC_{50} values of 6–26 nM) for human as well as rat TRPV1. Compound **14** (Fig. 3) was the most potent compound in this class with an IC_{50} of 6 nM at hTRPV1 against capsaicin activation. However, these compounds still suffered from poor aqueous solubility and bioavailability. Introduction of a heteroatom such as nitrogen in the phenyl ring (see compounds **15–18**; Fig. 3), in an attempt to decrease the lipophilicity and, in turn, improve aqueous solubility of the compounds led to significant decrease in the potency.

By contrast, a dramatic increase in potency was observed upon cyclization of the carbonyl group to the central phenyl ring that yielded the aminoquinazoline derivative **19** (Fig. 4) [Zheng et al., 2006]. Combined, these studies indicate that co-planarity of the carboxamide group with the central phenyl ring is essential for high potency. Not only was compound **22** (Fig. 4) highly potent at hTRPV1 (IC_{50} = 1.1 nM) and rTRPV1 (IC_{50} = 1.4 nM) but also exhibited long half-life (8.1 h) and excellent oral bioavailability (99%) attributed to its low clearance (23 ml/min/kg) and may be to some extent to its conformational rigidity. A phase 2 clinical study was initiated in October 2006 to assess the safety, tolerability, and efficacy of NGD-8243/MK2295 (structure not disclosed) compared with ibuprofen in patients with postoperative dental pain.

d. 1,3-Disubstituted urea compounds

Several pharmaceutical companies (e.g., Abbott, GSK, Bayer) are actively investigating 1,3-disubstituted urea compounds. A series of 5-amino-isoquinoline urea derivatives was reported by Johnson & Johnson as potent TRPV1 antagonists [Jetter et al., 2004]. This

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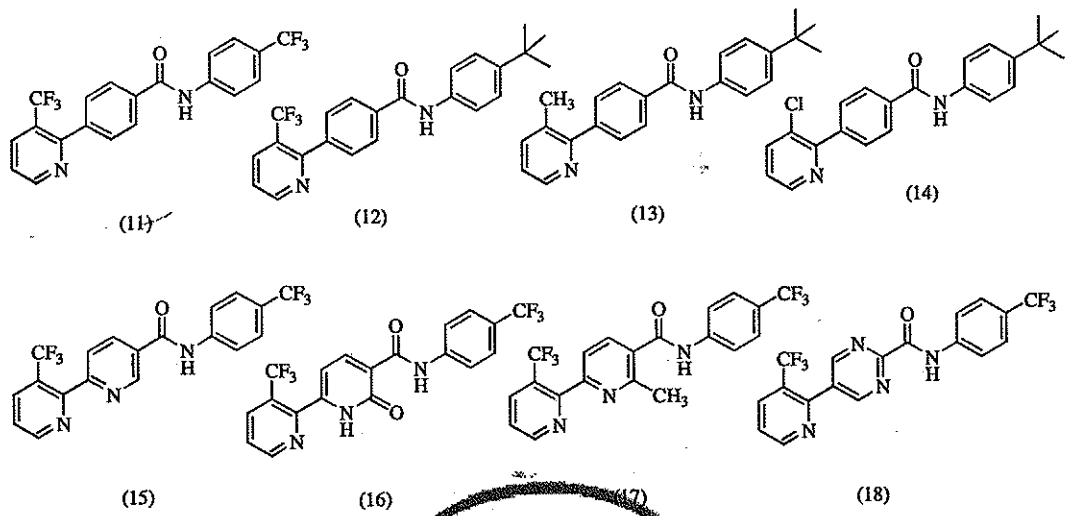

Fig. 3. Biaryl/biheteroaryl carboxamides.

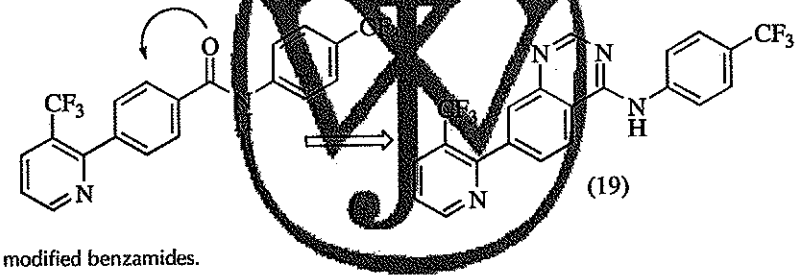

Fig. 4. Quinazolines as modified benzamides.

series resulted from a systematic modification and optimization of the TRPV1 agonist 4-pentyl-N-pyridin-3-yl-benzamide **20** (Fig. 5). Replacement of the pyridine group with isoquinoline led to a reversal of agonist activity to an antagonist activity in compound **21**. Further modification of the carboxamide (**21**) to a urea (**22**) (Fig. 5) and subsequent lead optimization of the urea resulted in a highly potent hTRPV1 antagonist, 1-(4-trifluoromethylbenzyl)-3-(isoquinolin-5-yl) urea (IC_{50} = 3.0 nM) (**23**) (Fig. 5). This urea derivative (**23**) was developed independently as an optimized lead compound, now known as A-425619 [Gomtsyan et al., 2005]. However, the lead for A-425619 was a hydroxynaphthalene urea derivative (**24**) (Fig. 5), coming from high-throughput screening of Abbott's compound library. Bioisosteric replacement of hydroxynaphthalene group was required since the hydroxy group, although essential for activity, was also a potential site for metabolism and hence a liability for pharmacokinetic properties. Several bicyclic heterocycles, based on their comparative charge distribution studies, were considered. Isoquinoline turned out to be the most suitable heterocycle for this series. A-425619 blocked capsaicin-evoked increases in intracellular Ca^{2+} concentrations in HEK293 cells expressing recombinant hTRPV1 receptors with a potent IC_{50} value of 5 nM [El Kouhen et al., 2005]. A-425619 showed similar potency (IC_{50} = 3–4 nM) in blocking TRPV1 receptor activation by anandamide and *N*-arachidonoyl-dopamine (El Kouhen et al., 2005]. In vivo, A-425619 reduced capsaicin-induced mechanical hyperalgesia dose-dependently with an ED_{50} of 45 μmol/kg when given p.o. A-425619 was effective in models of inflammatory pain and postoperative pain. For instance, A-425619 potently reduced CFA-induced chronic inflammatory pain orally [Honore et al., 2005].

Substituted Aminoethyl Ureas

This series of TRPV1 antagonists also belong to the 1,3-disubstituted urea class. Investigators at GSK described a substituted aminoethyl urea derivative, SB-452533 (**25**) (Fig. 6) that showed good potency as TRPV1 antagonist against capsaicin, heat and low pH-mediated activation [Rami et al., 2004]. This urea derivative, however, could not be developed further due to its high intrinsic clearance determined by in vitro rat and human liver microsomes. The high intrinsic clearance was attributed to the N-dealkylation of the N-ethyl group. To circumvent this problem, the N-ethyl group was cyclized on to the adjacent phenyl,

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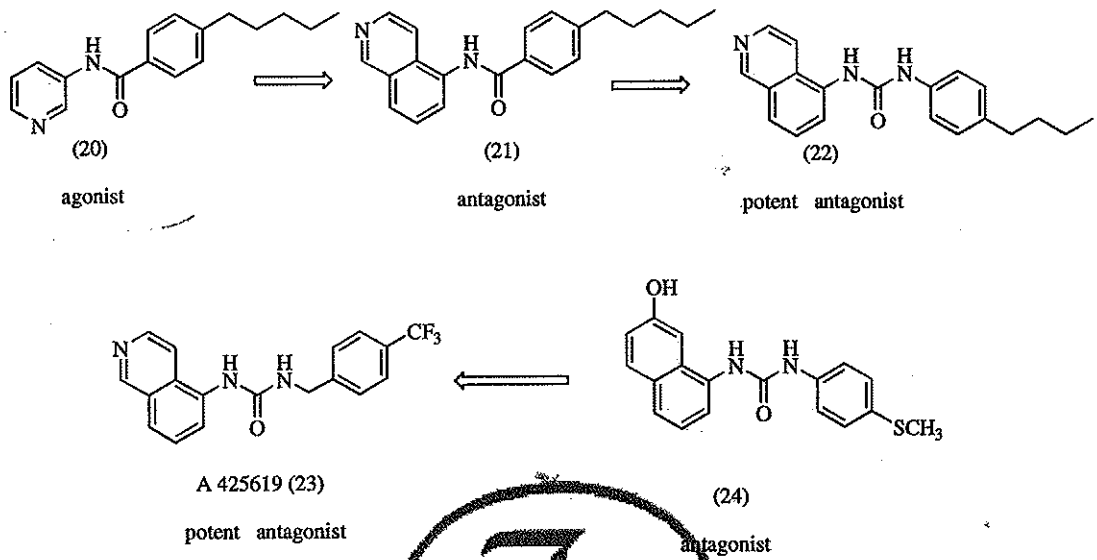

Fig. 5. 1,3-Disubstituted urea lead molecules.

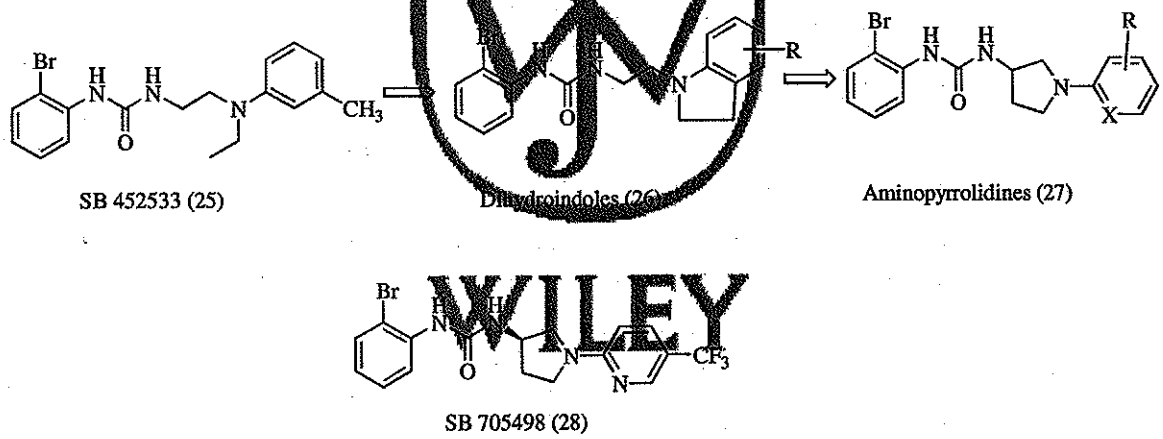

Fig. 6. Aminoethyl ureas and their cyclic analogues.

giving rise to a series of dihydroindole derivatives (**26**) (Fig. 6) that showed lower potency than SB-452533 and high intrinsic clearance rates. By contrast, cyclization of the N-ethyl group with the distant carbon of the ethylene linker produced 3-aminopyrrolidine ureas (**27**) (Fig. 6) with equivalent to or higher potency and lower intrinsic clearance than SB-452533. Further optimization of the 3-aminopyrrolidine derivative **27** led to the synthesis of SB-705498 (**28**) (Fig. 6) [Gomtsyan et al., 2005], a clinical candidate that was evaluated in phase 2 trials for migraine. These trials were discontinued due to a lack of efficacy.

Aryl Cinnamides

Researchers at GSK identified SB-366791 (**29**) (Fig. 7) by screening an in-house compound library as a potent competitive inhibitor of both hTRPV1 and rTRPV1, endowed with superior target selectivity compared to capsazepine [Gunthorpe et al., 2004]. Subsequently, investigators at Amgen described AMG-9810, (E)-3-(4-t-butylphenyl)-N-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl)acrylamide (**30**) (Fig. 7), as a potent TRPV1 antagonist by random screening of its synthetic compound library [Doherty et al., 2005]. AMG-9810 functions as a competitive antagonist of capsaicin activation ($IC_{50} = 17$ nM for hTRPV1) and blocked all known modes of TRPV1 activation, including protons, heat and endogenous ligands, such as anandamide, N-arachidonyl dopamine, and oleoyl-dopamine [Doherty et al., 2005]. In vivo, AMG-9810 was also effective at preventing capsaicin-induced eye wiping in a dose-dependent manner reversing

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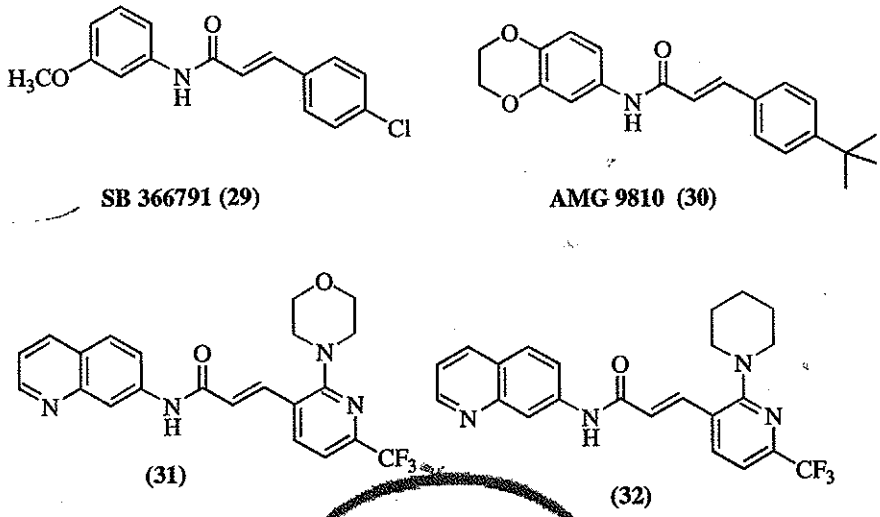

Fig. 7. Aryl cinnamides.

thermal and mechanical hyperalgesia in a model of inflammatory pain induced by intraplantar injection of CFA. However, it showed poor oral absorption and metabolic stability in rat. A stepwise optimization strategy was undertaken to come up with a clinical candidate having the desired efficacy, safety and pharmacokinetic profile. The lead structure was divided into three sections (benzodioxan-2-yl system, acrylamide core, aryl group) that were independently optimized to obtain analogues **31** and **32** (Fig. 7). In vitro, both analogues were highly potent (IC_{50} < 2 nM) in capsaicin as well as pH-mediated activation of hTRPV1. Their pharmacokinetic profile in Sprague-Dawley rats was also encouraging with compound **32** demonstrating low clearance (0.8 L/h/kg), high volume of distribution (2,800 ml/kg) and favorable half-life (2.9 h). While undoubtedly improved in terms of pharmacokinetic, compared to **30**, the bioactivity of both analogues awaits validation in vivo. 3D-QSAR models (CoMFA and CoMSIA) developed for the aryl cinnamides predict binding modes which are consistent with the previously developed models. It is predicted that these molecules also bind in the TM3/4 region of the TRPV1 channel [Vishwanadhan et al., 2007].

Additional TRPV1 Antagonists From Diverse Chemical Classes

The race for launching a clinically useful molecule in a broad therapeutic area such as pain for a novel therapeutic target has spurred tremendous research activity within the pharmaceutical industry. Although most of the molecules discovered can be broadly classified into the categories described above, a diverse class of chemical structures do not fit the classification. However, some common features such as the *tert*-butyl phenyl, the trifluoromethyl phenyl, quinoline, isoquinoline and their bioisosteres can still be found amongst these diverse classes with different set of linkers such as the pyrimidine, pyridazine, quinazoline, piperidine, indazolone and some others. Essentially, in most cases, the carbonyl or thiocarbonyl group, a key group for activity, has been incorporated as ring nitrogen in the above-mentioned linkers.

The chemical diversity in compounds **33–50** (Fig. 8) is evident from the structures listed above. A number of second generation TRPV1 antagonists such as AMG-517 (**51**) (Fig. 9) from Amgen [Doherty et al., 2007; Gavva et al., 2007; X. Wang et al., 2007; Y. Wang et al., 2007] and A-784168 from Abbott [Cui et al., 2006] belong to this chemical class. These compounds are under active investigation for pain management. AMG-517 demonstrates modification of the acrylamide group of AMG-9810 to a pyrimidine ring with an oxygen linked heterocycle. This modification has led to improvement in the overall pharmacokinetic profile of acrylamide class of TRPV1 antagonist. AMG-517 acts as a potent, competitive and orally available antagonist of TRPV1 in humans, monkeys, rats and mice (IC_{50} < 2 nM), with greater than 4,000-fold selectivity over other TRP channels, a panel of G-protein-coupled receptors, and various ion channels [Doherty et al., 2007; Gavva et al., 2007; X. Wang et al., 2007; Y. Wang et al., 2007]. AMG-517 demonstrated antihyperalgesic efficacy in animal models of inflammatory pain, including carrageenan- and CFA-induced thermal hyperalgesia. Like other TRPV1 antagonists, AMG-517 caused transient hyperthermia that attenuated after repeated dosing [Gavva et al., 2007]. Further

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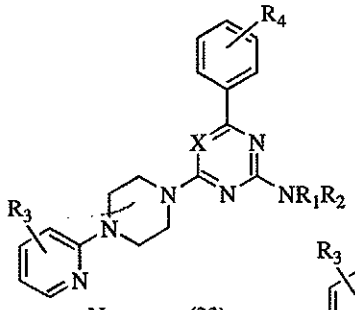

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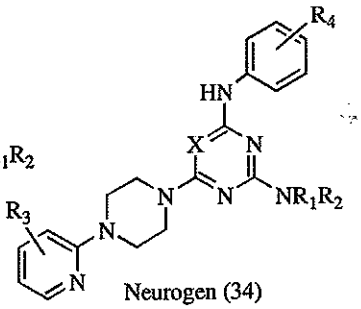

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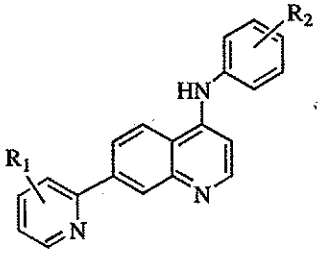

Neurogen (35)

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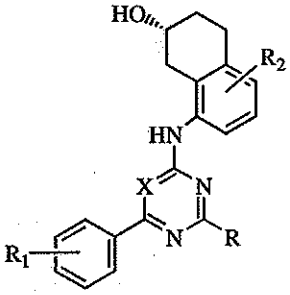

Amgen (36)

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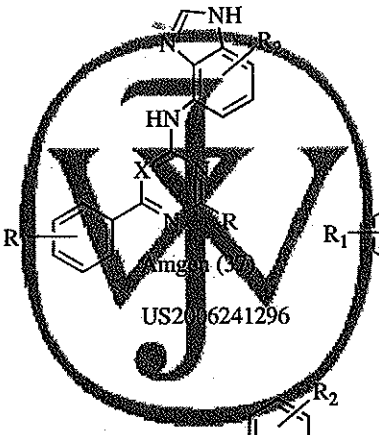

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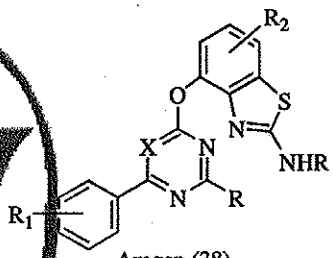

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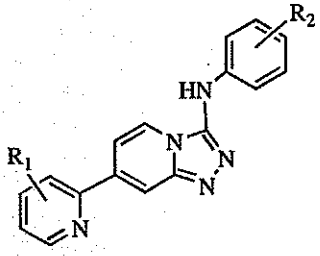

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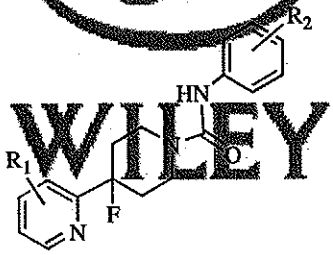
WO2004074290



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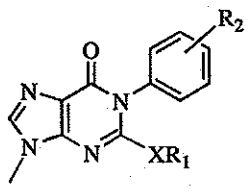

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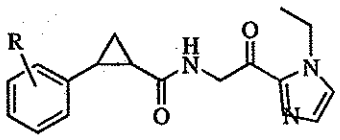
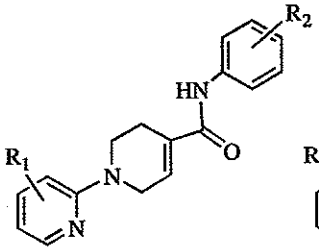


Pfizer Inc. (42)

WO2006103503



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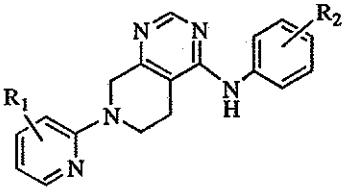

Renovis (44)

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Fig. 8. Chemical diversity of TRPV1 antagonists.

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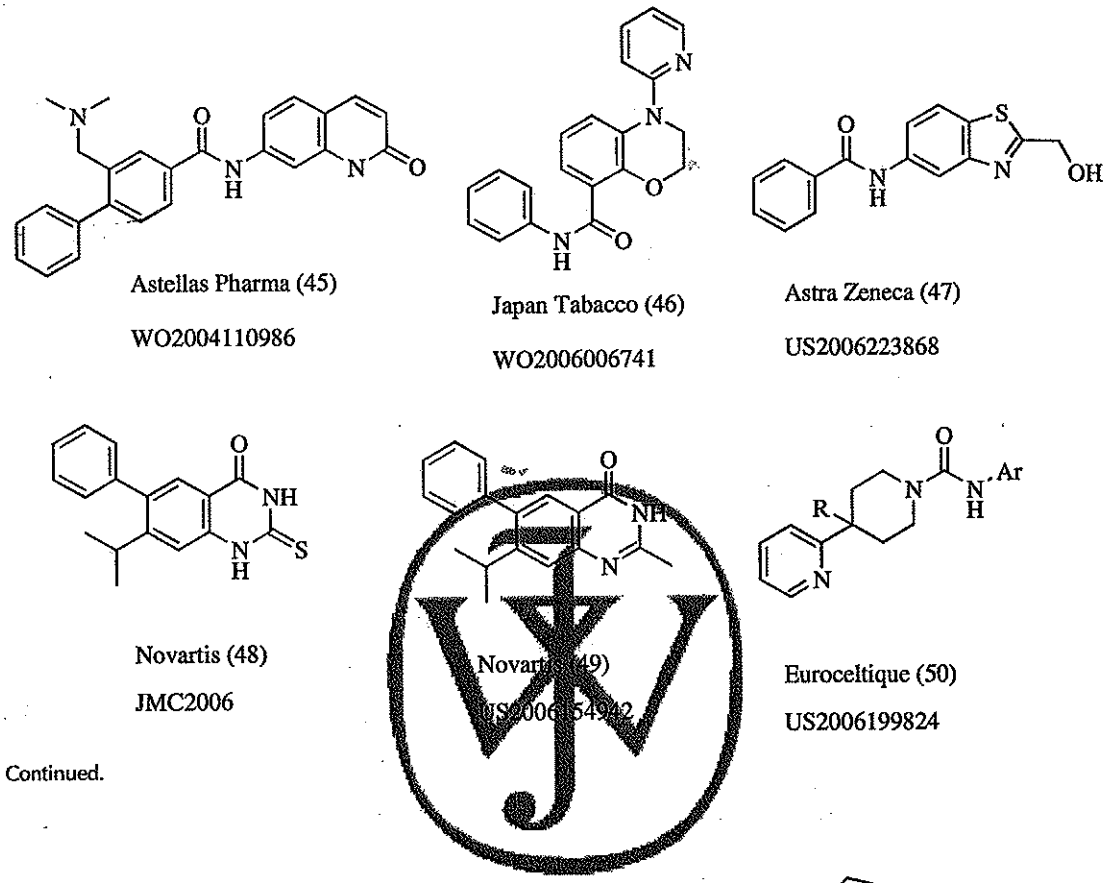

Fig. 8. Continued.

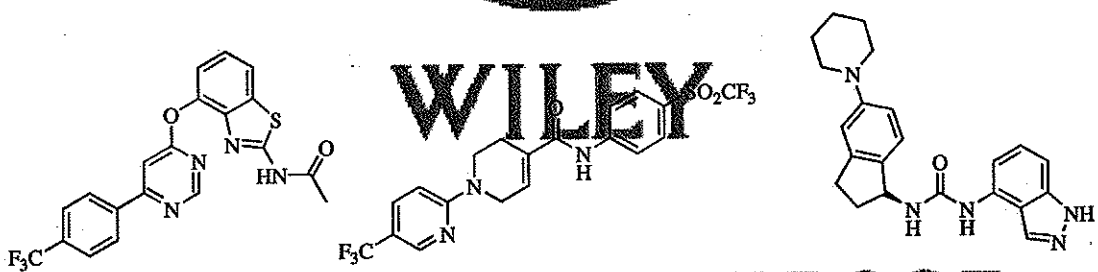

Fig. 9. Second-generation TRPV1 antagonists.

optimization of AMG-517 led to highly potent trisubstituted pyrimidines [Wang et al., 2007] with improved solubility profiles. A-784168 (**52**) (Fig. 9) is a modified piperazine-carboxamide analogue wherein the piperazine is replaced by tetrahydropyridine. This modification appears to conserve the desired conformation of the molecule to retain in vitro potency. A-784168 inhibited capsaicin induced activation of hTRPV1 with an IC_{50} value of 23 nM and also blocked capsaicin-induced acute nocifensive behavior in vivo. In the CFA model of chronic inflammatory pain, A-784168 inhibited both thermal hyperalgesia and mechanical allodynia following oral administration [Cui et al., 2006]. To asses the role of CNS in broad-spectrum analgesia, the efficacy of A-784168 was compared with another TRPV1 antagonist, A-795614 (**53**) (Fig. 9) in models, presumably mediated by central sensitization, including CFA- and capsaicin-induced mechanical allodynia and osteoarthritic pain [Cui et al., 2006]. In these models, the potency of the two compounds was similar after intrathecal administration. However, when administered p.o., A-784168, with good CNS penetration, was more potent than A-795614. These results demonstrate that TRPV1 receptors in the CNS play an important role in pain mediated by central sensitization. In addition, these results demonstrate that significant CNS penetration is necessary for a TRPV1 antagonist to produce broad-spectrum analgesia [Cui et al., 2006].

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CLINICAL DEVELOPMENT OF TRPV1 ANTAGONISTS: PAST, PRESENT, FUTURE

Several of the potent, small-molecule TRPV1 antagonists (at least six according to company press releases) are currently undergoing clinical trials, however, definitive information regarding their clinical efficacy and adverse effects are difficult to obtain. Companies with TRPV1 antagonists in phase 2 clinical trials include GSK (SB-705498), Merck-Neurogen (MK-2295/NGD-8243) and Glenmark/Lilly (GRC 6211). Companies with TRPV1 antagonists in phase 1 clinical trials include Amgen (AMG-517), Abbott (ABT102), and Pfizer.

According to the available information, the GSK lead compound SB-705498 has successfully completed phase 1 clinical trials [Chizh et al., 2007] and is now being evaluated in patients with postoperative dental pain and rectal hypersensitivity [http://clinicaltrials.gov/]. MK-2295/NGD-8243 and GRC-6211 are being tested in patients with dental pain (molar extraction). Further clinical indications for MK-2295/NGD-8243 are urinary incontinence and cough. Amgen terminated clinical trials with its lead compound for molar extraction due concerns over the hyperthermic response that reached 40°C in one patient [Gavva et al., 2007]. The status of the Abbott and Pfizer compounds remains unknown.

CONCLUSION

The worldwide analgesic drug market was estimated at US $38 billion in 2002 and is expected to nearly double by the year 2010. An estimated 50 million Americans suffer from chronic pain conditions, often requiring a combination of complex and expensive medical and surgical approaches to provide some relief. More than $100 billion is lost annually due to chronic pain (insurance claims, worker's compensation, and lost productivity), and this number is sure to rise. At the level of the individual, chronic pain adversely affects patient well-being, level of function, and quality of life. Chronic pain is often undertreated, and the unfilled needs are well recognized. Consequently, chronic pain is subject to intensive research and significant resources are devoted to the development of new analgesic drugs. TRPV1 antagonists represent a new paradigm in the development of analgesic drugs. Unlike traditional analgesic drugs that block the inflammatory response and the propagation and transmission of pain, TRPV1 antagonists prevent pain by silencing a nociceptor in the periphery where pain is generated [Szallasi et al., 2006, 2007]. In animals, there is strong evidence that TRPV1 antagonists can relieve inflammatory, cancer, and neuropathic pain [Krause et al., 2005; Immke and Gavva, 2006; Cortright et al., 2007]. Additionally, TRPV1 antagonists may be useful in the management of urinary incontinence, cough, pruritus, migraine, diabetes, and obesity [Anish and Szallasi, 2007; Gunthorpe and Szallasi, 2006; Szallasi et al., 2007].

In summary, TRPV1 antagonists are very promising drug candidates in animal models but their clinical future is unclear. Apparently, the hyperthermic response to TRPV1 antagonists that can be easily managed in experimental animals may reach dangerously high levels in patients. Another frequently voiced concern is the possibility of "silent myocardial infarction" in patients on TRPV1 antagonists for chronic pain due to long-QT syndrome. The widespread TRPV1 expression in the CNS and in non-neuronal tissues, where the biological functions of TRPV1 are essentially unknown, is also an area of concern. Yet, alone or in combination with other analgesic drugs, TRPV1 antagonists may prove clinically useful drugs to relieve chronic pain.

REFERENCES

Agopyan N, Head J, Yu S, Simon SA. 2004. TRPV1 receptors mediate particulate matter-induced apoptosis. Am J Physiol Lung Cell Mol Physiol 286:L563–L572.

Ahern GP, Wang X, Miyares RL. 2006. Polyamines are potent ligands for the capsaicin receptor TRPV1. J Biol Chem 281: 8991–8995.

Almeida MC, Steiner AA, Branco LG, Romanovsky AA. 2006. Cold-seeking behavior as a thermoregulatory strategy in systemic inflammation. Eur J Neurosci 23:3359–3367.

Apostolidis A, Brady CM, Yiangou Y, Davis J, Fowler CJ, Anand P. 2005. Capsaicin receptor TRPV1 in urothelium of neurogenic human bladders and effect of intravesical resiniferatoxin. Urology 65:400–405.

Appendino G, Harrison S, De Petrocellis L, Daddario N, Bianchi F, Morello AS, Trevesani M, Benvenuti F, Geppetti P, Di Marzo V. 2003. Halogenation of a capsaicin analogue leads to novel vanilloid TRPV1 receptor antagonists. Br J Pharmacol 139: 1417–1424.

Appendino G, De Petrocellis L, Trevisani M, Minassi A, Daddario N, Schiano-Morello A, Mazzieri D, Ligresti A, Campi B, Fontana G, Pinna C, Geppetti P, Di Marzo V. 2005a. Development of the first ultra-potent "capsaicinoid" agonist at transient receptor potential vanilloid type 1 (TRPV1) channels and its therapeutic potential. J Pharmacol Exp Ther 312:561–570.

Appendino G, Harrison S, De Petrocellis L, Daddario N, Bianchi F, Schiano-Morello A, Trevesani M, Benvenuti F, Geppetti P, Di Marzo V. 2005b. Halogenation of a capsaicin analogue leads to novel vanilloid TRPV1 receptor antagonists. Br J Pharmacol 139: 1417–1424.

Appendino G, Daddario N, Minassi A, Morello AS, De Petrocellis L, Di Marzo, V. 2005c. The taming of capsaicin. Reversal of the vanilloid activity of N-acylvanillamines by aromatic iodination. J Med Chem 48:4663–4669.

Journal: DDR ☑ Disk used Article : 7716 Pages: 21 Despatch Date: 3/1/2008

Appendino G, Ech-Chahad A, Minassi A, Bacchiega S, De Petrocellis L, Di Marzo V. 2007. Structure–activity relationships of the ultrapotent vanilloid resiniferatoxin (RTX): The homovanillyl moiety. Bioorg Med Chem Lett 17:132–135.

Arck P, Paus R. 2006. From the brain-skin connection: the neuroendocrine-immune misalliance of stress and itch. Neuroimmunomodul 13:347–356.

Athanasiou A, Smith PA, Vakilpour S, Kumaran NM, Turner AE, Bagiokou D, Layfield R, Ray DE, Westwell AD, Alexander SP, Kendall DA, Lobo DN, Watson SA, Lophatanon A, Muir KA, Guo DA, Bates TE. 2007. Vanilloid receptor agonists and antagonists are mitochondrial inhibitors: how vanilloids cause non-vanilloid receptor mediated cell death. Biochem Biophys Res Commun 354:50–55.

Avelino A, Cruz F. 2000. Peptide immunoreactivity and ultrastructure of the rat urinary bladder nerve fibers after topical desensitization by capsaicin or resiniferatoxin. Auton Neurosci 86:37–46.

Bakthavatchalam R. 2002. Capsaicin receptor ligands. Patent WO 0208221-A1.

Benemei S, Nicoletti P, Capone JA, Geppetti P. 2007. Pain pharmacology in migraine: focus on CGRP and CGRP receptors. Neurol Sci 2:S89–S93.

Bernstein JE, Parish LC, Rapaport M, Rosenbaum MM, Roenigk HH. 1986. Effects of topically applied capsaicin in moderate and severe psoriasis vulgaris. J Am Acad Dermatol 15:504–507.

Bhat YM, Bielefeldt K. 2006. Capsaicin receptor (TRPV1) and nonerosive reflux disease. Eur J Gastroenterol Hepatol 18:263–270.

Bhave G, Zhu W, Wang H, Brasier DJ, Oxford GS, Gereau RW IV. 2002. cAMP-dependent protein kinase regulates desensitization of the capsaicin receptor (VR1) by direct phosphorylation. Neuron 35:721–731.

Brauchi S, Orta G, Mascayano C, Salazar M, Raddatz N, Urrutia H, Rosenmann E, Gonzalez-Nilo F, Latorre R. 2007. Dissection of the components for PIP2 activation and thermosensation in TRP channels. Proc Natl Acad Sci USA 104:10246–10251.

Bryant P, Shumate M, Yumet G, Lang CH, Vary TC, Cooney RN. 2003. Capsaicin-sensitive nerves regulate the metabolic response to abdominal sepsis. J Surg Res 112:152–161.

Buck SH, Burks TF. 1986. The neuropharmacology of capsaicin: review of some recent observations. Pharmacol Rev 38:179–226.

Caterina MJ. 2007. Transient receptor potential ion channels as participants in thermosensation and thermoregulation. Am J Physiol Regul Integr Comp Physiol 292:R64–R76.

Caterina MJ, Julius D. 2001. The vanilloid receptor: a molecular gateway to the pain pathway. Annu Rev Neurosci 24:487–517.

Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. 1997. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 389:816–824.

Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Basbaum AI, Julius D. 2000. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 288:306–313.

Cesare P, Dekker LV, Sardini A, Parker PJ, McNaughton PA. 1999. Specific involvement of protein kinase C epsilon in sensitization of the neuronal response to painful heat. Neuron 23:617–624.

Chan CL, Facer P, Davis JB, Yiangou Y, Dyer HN, Anand P. 2003. Sensory nerve fibers expressing capsaicin receptor TRPV1 in patients with rectal hypersensitivity and fecal urgency. Lancet 361:385–391.

Chizh BA, O'Donnell MB, Napolitano A, Wang J, Brooke AC, Aylott MC, Bullman JN, Gray EJ, Lai RY, Williams PM, Appleby JM. 2007. The effects of the TRPV1 antagonist SB-705498 on TRPV1 receptor-mediated activity and inflammatory hyperalgesia in humans. Pain 132:132–141.

Christoph T, Grunweller A, Mika J, Schafer MK, Wade EJ, Weihe E, Erdmann VA, Frank R, Gillen C, Kurreck J. 2006. Silencing of vanilloid receptor TRPV1 by RNAi reduces neuropathic and visceral pain in vivo. Biochem Biophys Res Commun 350: 238–243.

Chuang HH, Prescott ED, Kong H, Shields S, Jordt SE, Basbaum AI, Chao MV, Julius D. 2001. Bradykinin and nerve growth factor release capsaicin receptor from PtdIns(4,5)P2-mediated inhibition. Nature 411:957–962.

Clark N, Keeble J, Fernandes ES, Starr A, Liang L, Sugden D, de Winter P, Brain SD. 2007. The transient receptor potential vanilloid-1 (TRPV1) receptor protects against the onset of sepsis after endotoxin. FASEB J 21:3747–3755.

Cortright DN, Szallasi A. 2004. The molecular pharmacology of TRPV1. Eur J Biochem 271:1814–1819.

Cortright DN, Krause JE, Broom DC. 2007. TRP channels and pain. Biochim Biophys Acta 1772:978–988.

Crawley JN, Mufson EJ, Hohmann JG, Teklemichael D, Steiner RA, Hohlberg K, Xu ZQ, Blakeman KH, Xu XJ, Wiesenfeld-Hallin Z, Bartfai T, Hokfelt T. 2002. Galanin overexpressing transgenic mice. Neuropeptides 36:145–156.

Cui M, Honore P, Zhong C, Gauvin D, Mikusa J, Hernandez G, Chandran P, Gomtsyan A, Brown B, Bayburt EK, Marsh K, Bianchi B, McDonald H, Niforatos W, Neelands TR, Moreland RB, Decker MW, Lee CH, Sullivan JP, Faltynek CR. 2006. TRPV1 receptors in the CNS play a key role in broad-spectrum analgesia of TRPV1 antagonists. J Neurosci 26:9385–9393.

Cuypers E, Yanagihara A, Karlson E, Tytgat J. 2006. Jellyfish and other cnidarian envenomations cause pain by affecting TRPV1 channels. FEBS Lett 580:5728–5732.

Dasgupta P, Chandiramani V, Parkinson MC, Beckett A, Fowler C. 1998. Treating the human bladder with capsaicin: is it safe? Eur J Urol 33:28–31.

Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P. 2000. Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. Nature 405:183–187.

Dax SL, Dubin AE, Jetter M, Nasser N, Shah C, Swanson DM, Carruthers NI. 2002. Drugs Future 27(suppl. A):93.

Dhaka A, Viswanath V, Patapoutian A. 2006. TRP ion channels and temperature sensation. Annu Rev Neurosci 29:135–161.

Di Marzo V, Maione S. 2007. TRPV1 receptors in the central nervous system: potential for previously unforeseen therapeutic applications. Curr Pharm Des (in press).

Di Marzo V, Blumberg PM, Szallasi A. 2002. Endovanilloid signaling in pain. Curr Opin Neurobiol 12:167–171.

Dogan MD, Patel S, Rudaya AY, Steiner AA, Szekely M, Romanovsky AA. 2004. Lipopolysaccharide fever is initiated via a capsaicin-sensitive mechanism independent of the subtype-1 vanilloid receptor. Br J Pharmacol 143:1023–1032.

Doherty EM, Fotsch C, Bo Y, Chakrabarti PP, Chen N, Gavva NR, Han N, Kelly G, Kincaid J, Klionsky L, Liu Q, Ognyanov VI, Tamir R, Wang X, Zhu J, Norman MH, Treanor JJS. 2005.

Journal: DDR ☑ Disk used Article : 7716 Pages: 21 Despatch Date: 3/1/2008

Discovery of potent, orally available vanilloid receptor-1 antagonists. Structure–activity relationship of N-aryl cinnamides. J Med Chem 48:71–90.

El Kouhen R, Surowy CS, Bianchi BR, Neelands TR, McDonald HA, Niforatos W, Gomtsyan A, Lee CH, Honore P, Sullivan JP, Jarvis MF, Faltynek CR. 2005. A-425619 [1-isoquinolin-5-yl-3-(4-trifluoromethyl-benzyl)-urea], a novel and selective transient receptor potential type V1 receptor antagonist, blocks channel activation by vanilloids, heat, and acid. J Pharmacol Exp Ther 314:400–409.

Farber EM, Lanigan SW, Boer J. 1990. The role of cutaneous sensory nerves in the maintenance of psoriasis. Int J Dermatol 29:418–420.

Fernandez-Ruiz J, Gonzales S. 2005. Cannabinoid control of motor function at the basal ganglia. Handb Exp Pharmacol 168: 479–507.

Gunthorpe MJ, Rami HK, Jerman JC, Smart D, Gill CH, Soffin EM, Luis Hannan S, Lappin SC, Egerton J, Smith GD, Worby A, Howett L, Owen D, Nasir S, Davies CH, Thompson M, Wyman PA, Randall AD, Davis JB. 2004. Identification and characterization of SB-366791, a potent and selective vanilloid receptor (VR1/TRPV1) antagonist. Neuropharmacology 46:133–149.

Garcia-Sanz N, Fernandez-Carvajal A, Morenilla-Palao C, Planells-Cases R, Fajardo-Sanchez E, Fernandez-Ballester G, Ferrer-Montiel A. 2004. Identification of a tetramerization domain in the C-terminus of the vanilloid receptor. J Neurosci 24:5307–5314.

Gavva N. 2007. The capsaicin receptor TRPV1: is it V pain transducer or a regulator of body temperature? Society for Neuroscience. San Diego, CA. Poster 400.9/OO22.

Gavva NR, Tamir R, Klionsky L, Norman MH, Louis JC, Wild KD, Treanor JJ. 2005. Proton activation does not alter antagonist interaction with the capsaicin binding pocket of TRPV1. Mol Pharmacol 68:1524–1533.

Gavva NR, Bannon AW, Surapaneni S, Hovland DN, Lehto SG, Gore A, Juan T, Deng H, Han B, Klionsky L, Kuang R, Le A, Tamir R, Wang J, Youngblood B, Zhu D, Norman MH, Magal E, Treanor JJ, Louis JC. 2007a. The vanilloid receptor TRPV1 is tonically activated in vivo and involved in body temperature regulation. J Neurosci 27:3366–3374.

Gavva NR, Bannon AW, Hovland DN, Lehto SG, Klionsky L, Surapaneni S, Immke DC, Henley C, Arik L, Bak A, Davis J, Ernst N, Hever G, Kuang R, Lehto E, Tamir R, Wang W, Zajic G, Zhu D, Norman MH, Louis JC, Treanor JJ. 2007b. Repeated administration of vanilloid receptor TRPV1 antagonists attenuates hyperthermia elicited by TRPV1 blockade. J Pharmacol Exp Ther 323:128–137.

Geppetti P, Holzer P. 1996. Neurogenic inflammation. Boca Raton, FL: CRC Press.

Geppetti P, Capone JG, Trevisani M, Nicoletti P, Zagli G, Tola MR. 2005. CGRP and migraine: neurogenic inflammation revisited. J Headache Pain 6:61–70.

Gomtsyan AR, Bayburt EK, Schmidt RG, Zheng GZ, Perner RJ, Didomenico S, Koenig JR, Turner S, Jinkerson T, Drizin I, Hannick SM, Macri BS, McDonald HA, Honore P, Wismer CT, Marsh KC, Wetter J, Steward KD, Oie T, Jarvis MF, Surrowy CS, Faltynek CR, Lee CH. 2005. Novel transient receptor potential vanilloid 1 receptor antagonists for the treatment of pain: structure–activity relationships for ureas with quinoline, isoquinoline, quinazoline, phthalazine, quinoxaline, and cinnoline moieties. J Med Chem 48:744–752.

Gopinath P, Wan E, Holdcroft, Anand P. 2005. Increased capsaicin receptor TRPV1 in skin nerve fibers and related vanilloid receptors TRPV3 and TRPV4 in keratinocytes in human breast pain. BMC Women's Health 5:2–6.

Gram DX. 2003. Capsaicin-sensitive nerves in experimental diabetes mellitus. PhD thesis. Royal Veterinary and Agricultural University, Copenhagen, Denmark.

Gram DX, Hansen AJ. 2007. The role of TRPV1 in impaired glucose tolerance in mice. Neuropeptides 2007: functions, dysfunctions, and therapeutic options. Abstract L116. Santorini, Greece.

Grycova L, Lansky Z, Friedlova E, Vlachova V, Kubala M, Obsilova V, Obsil T, Teisinger J. 2007. ATP binding site on the C-terminus of the vanilloid receptor. Arch Biochem Biophys 465:389–398.

Guo A, Vulchanova L, Wang J, Li X, Elde R. 1999. Immunocytochemical localization of the vanilloid receptor 1 (VR1): relationship to neuropeptides, the P2X3 purinoceptor and IB4 binding sites. Eur J Neurosci 11:946–958.

Gunthorpe MJ, Szallasi A. 2007. Peripheral TRPV1 receptors as targets for drug development: new molecules and mechanisms. Curr Pharm Des (in press).

Hautkappe M, Roizen MF, Toledano A, Roth S, Jeffries JA, Ostermeier AM. 1998. Review of the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction. Clin J Pain 14:97–106.

Hellwig N, Albrecht N, Harteneck C, Schultz G, Schaefer M. 2005. Homo- and heteromeric assembly of TRPV channel subunits. J Cell Sci 118:917–928.

Hicks GA. 2006. TRP channels as therapeutic targets: hot property, or time to cool down? Neurogastroenterol Motil 18:590–594.

Holzer P. 1988. Local effector functions of capsaicin-sensitive sensory nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. Neurosci 24:739–768.

Hong S, Wiley JW. 2005. Early painful diabetic neuropathy is associated with differential changes in the expression and function of vanilloid receptor 1. J Biol Chem 280:618–627.

Honore P, Wismer CT, Mikusa J, Zhu CZ, Zhong C, Gauvin DM, Gomtsyan A, El Kouhen R, Lee CH, Marsh K, Sullivan JP, Faltynek CR, Jarvis MF. 2005. A-425619 [1-isoquinolin-5-yl-3-(4-trifluoromethyl-benzyl)-urea], a novel transient receptor potential type V1 receptor antagonist, relieves pathophysiological pain associated with inflammation and tissue injury in rats. J Pharmacol Exp Ther 314:410–421.

Huang SM, Bisogno T, Trevisani M, Al-Hayani A, De Petrocellis L, Fezza F, Tognetto M, Petros TJ, Krey JF, Chu CJ, Miller JD, Davies SN, Geppetti P, Walker JM, Di Marzo V. 2002. An endogenous capsaicin-like substance with high potency at recombinant and native vanilloid VR1 receptors. Proc Natl Acad Sci USA 99:8400–8405.

Hudson LJ, Bevan S, Wotherspoon G, Gentry C, Fox A, Winter J. 2001. VR1 protein expression increases in undamaged DRG neurons after partial nerve injury. Eur J Neurosci 13:2105–2114.

Hwang SW, Cho H, Kwak J, Lee SY, Kang CJ, Jung J, Cho S, Min KH, Suh YG, Oh U. 2000. Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances. Proc Natl Acad Sci USA 97:6155–6160.

Iida T, Shimizu I, Nealen M, Campbell A, Caterina MJ. 2005. Attenuated fever response in mice lacking TRPV1. Neurosci Lett 378:28–33.

Journal: DDR ☑ Disk used Article : 7716 Pages: 21 Despatch Date: 3/1/2008

Issekutz B, Lichtneckert I, Nagy H. 1950. Effect of capsaicin and histamine on heat regulation. Arch Int Pharmacodyn Ther 81:35–46.

Jakab B, Helyes Z, Varga A, Bolcskei K, Szabo A, Sandor K, Elekes K, Borzsei R, Keszthelyi D, Pinter E, Petho G, Nemeth J, Szolcsanyi J. 2005. Pharmacological characterization of the TRPV1 receptor antagonist JYL1421 (SC0030) in vitro and in vivo in the rat. Eur J Pharmacol 517:35–44.

Jancsó N. 1955. Speicherung. Stoffanreicherung im Retikuloendothel und in der Niere. Budapest: Akademiai Kiado.

Jancsó N. 1968. Desensitization with capsaicin and related acylamides as a tool for studying the function of pain receptors. In: Lin K, Armstrong D, Pardo ED, editors. Pharmacology of pain. Oxford: Pergamon. p 33–55.

Jetter MC, Youngman MA, McNally JJ, Zhang S, Dubin AE, Shah C, Nasser N, Dax SL. 2004. Quinolin-5-yl-N′-aralkyl-urea and amide antagonists of human vanilloid receptor 1. Bioorg Med Chem Lett 14:3053–3056.

Johnson DM, Garrett EM, Rutter R, Bonnert TP, Gao YD, Middleton RE, Sutton KG. 2006. Functional mapping of the transient receptor potential vanilloid 1 intracellular binding site. Mol Pharmacol 70:1005–1012.

Jordt SE, Julius D. 2002. Molecular basis for species-specific sensitivity to "hot" chili peppers. Cell 108:421–430.

Jordt SE, Tominaga M, Julius D. 2000. Acid potentiation of the capsaicin receptor determined by a key extracellular residue. Proc Natl Acad Sci USA 97:8134–8139.

Julius D, Basbaum AI. 2001. Molecular mechanisms of nociception. Nature 413:203–210.

Kang DW, Ryu H, Lee J, Lang KA, Pavlyukovets VA, Pearce LV, Ikeda T, Lazar J, Blumberg PM. 2007. Halogenation of 4-hydroxy-3-methoxybenzyl thiourea TRPV1 agonists showed enhanced antagonism to capsaicin. Bioorg Med Chem Lett 17: 214–219.

Kasama S, Kawakubo M, Suzuki T, Nishizawa Y, Ishida A, Nakayama J. 2007. RNA interference-mediated knock-down of transient receptor potential vanilloid 1 prevents forepaw inflammatory hyperalgesia in rat. Eur J Neurosci 25:2956–2963.

Knotkova H, Pappagallo M, Szallasi A. 2007. Capsaicin (TRPV1 agonist) therapy for pain relief: farewell or revival? Clin J Pain (in press).

Krause JE, Chenard BL, Cortright DN. 2005. Transient receptor potential ion channels as targets for the discovery of pain therapeutics. Curr Opin Invest Drugs 6:48–57.

Kwak J, Jung JY, Hwang SW, Lee WT, Oh U. 1998. A capsaicin receptor antagonist, capsazepine, reduces inflammation-induced hyperalgesic responses in the rat: evidence for an endogenous capsaicin-like substance. Neuroscience 86:619–626.

Kwak J, Wang MH, Hwang SW, Kim TY, Lee SY, Oh U. 2000. Intracellular ATP increases capsaicin-activated channel activity by interacting with nucleotide-binding domains. J Neurosci 20:8298–8304.

Lauria G, Morbin M, Lombardi R, Geppetti P. 2006. Expression of capsaicin receptor immunoreactivity in human peripheral nervous system and painful neuropathies. J Periph Nerv Syst 11:262–271.

Lee CH, Bayburt EK, Didomenico S, Drizin I, Gomtsyan AR, Koenig JR, Perner RJ, Schmidt RG, Turner SC, White TK, Zheng GZ. 2003. Fused azabicyclic compounds that inhibit vanilloid receptor subtype 1(VR1) receptor. Patent WO 03070247.

Lee J, Kang M, Blumberg PM, Shin M, Kim JM, Kang SU, Lim JO, Choi HK, Suh YG, Park HG, Oh U, Kim HD, Park YH, Ha HJ, Kim YH, Toth A, Wang Y, Tran R, Pearce LV, Lundberg DJ, Blumberg PM. 2003. Acyloxy-2-benzylpropyl)-N′-[4-(methylsulfonylamino) benzyl] thiourea analogues: novel potent and high affinity antagonists and partial antagonists of the vanilloid receptor. J Med Chem 46:3116–3126.

Lee SY, Lee JH, Kang KK, Hwang SY, Choi KD, Oh U. 2005. Sensitization of vanilloid receptor involves an increase in the phosphorylated form of the channel. Arch Pharm Res 28:405–412.

Lishko PV, Procko E, Jin X, Phelps CB, Gaudet R. 2007. The ankyrin repeats of TRPV1 bind multiple ligands and modulate channel sensitivity. Neuron 54:905–918.

Liu B, Ma W, Ryu S, Qin F. 2004. Inhibitory modulation of distal C-terminal on protein kinase C-dependent phosphor-regulation of rat TRPV1 receptors. J Physiol 560:627–638.

Liu B, Zhang C, Qin F. 2005. Functional recovery from desensitization of vanilloid receptor TRPV1 requires resynthesis of phosphatidylinositol 4,5-bisphosphate. J Neurosci 25: 4835–4843.

Lizanecz E, Bagi Z, Pasztor ET, Papp Z, Edes I, Kedei N, Blumberg PM, Toth A. 2006. Phosphorylation-dependent desensitization by anandamide of vanilloid receptor 1 (TRPV1) function in rat skeletal muscle arterioles and in Chinese hamster ovary cells expressing TRPV1. Mol Pharmacol 69:1015–1023.

Lukacs V, Thyagarajan B, Varnai P, Balla A, Balla T, Rohacs T. 2007. Dual regulation of TRPV1 by phosphoinositides. J Neurosci 27:7070–7080.

Maggi CA, Borsini F, Santicioli P, Geppetti P, Abelli L, Evangelista S. 1987. Cutaneous lesions in capsaicin-pretreated rats. A trophic role of capsaicin-sensitive afferents? Naunyn-Schmiedebergs Arch Pharmacol 336:538–545.

Mahmoud ME, Shimizu Y, Shiina T, Nikami H, Dosoky RM, Ahmed NM, Takewaki T. 2007. Involvement of a capsaicin-sensitive TRPV1-independent mechanism in lipopolysaccharide-induced fever in chickens. Comp Biochem Physiol Mol Integr Physiol 148:578–583.

Malmberg AB, Bley KR. 2005. Turning up the heat on pain: TRPV1 receptors in pain and inflammation. Basel: Birkhauser AG.

Marquez-Rodas I, Longo F, Rothlin RP, Balfagon G. 2006. Pathophysiology and therapeutic possibilities of calcitonin gene-related peptide in hypertension. J Physiol Biochem 62: 45–56.

Marsch R, Foeller E, Rammes G, Bunck M, Kossi M, Holsboer F, Zieglgansberger W, Landgraf R, Lutz B, Wotjak CT. 2007. Reduced anxiety, conditioned fear, and hippocampal long-term potentiation in transient receptor potential vanilloid type 1 receptor-deficient mice. J Neurosci 27:832–839.

Matthews PJ, Aziz Q, Facer P, Davis JB, Thompson DG, Anand P. 2004. Increased capsaicin receptor TRPV1 nerve fibres in the inflamed human oesophagus. Eur J Gastroenterol Hepatol 16:897–902.

Messeguer A, Planells-Cases R, Ferrer-Montiel A. 2006. Physiology and pharmacology of the vanilloid receptor. Curr Neuropharmacol 4:1–15.

Mezey E, Toth Z, Cortright DN, Arzubi MK, Krause JE, Elde R, Guo A, Blumberg PM, Szallasi A. 2000. Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of rat and man. Proc Natl Acad Sci USA 97:3655–3660.

Journal: DDR ☑ Disk used Article : 7716 Pages: 21 Despatch Date: 3/1/2008

Mohapatra DP, Nau C. Regulation of calcium-dependent desensitization in the vanilloid receptor TRPV1 by calcineurin and cAMP-dependent protein kinase. J Biol Chem 280:13424–13432.

Mohaved P. 2005. Endogenous activators of the pain receptor TRPV1. From cell to man. PhD Thesis. Lund University.

Montell C, Birnbaumer L, Flokerzi V, Bindels RJ, Bruford EA, Caterina MJ, Clapham DE, Harteneck C, Heller S, Julius D, Kojima I, Mori Y, Penner R, Pawitt D, Scharenberg AM, Schultz G, Shimizu N, Zhu MX. 2002. A unified nomenclature for the superfamily of TRP cation channels. Mol Cell 9:229–231.

Morenilla-Palao C, Planells-Cases R, Garcia-Sanz N, Ferrer-Montiel A. 2004. Regulated exocytosis contributes to protein kinase C potentiation of vanilloid receptor activity. J Biol Chem 279:25665–25672.

Morgan CR, Rodd HD, Clayton N, Davis JB, Boissonade FM. 2005. Vanilloid receptor 1 expression in human tooth pulp in relation to caries and pain. J Orofac Pain 19:248–260.

Moriyama T, Higashi T, Togashi K, Iida T, Segi E, Sugimoto Y, Tominaga T, Naruyima S, Tominaga M. 2005. Sensitization of TRPV1 by EP1 and IP reveals peripheral nociceptive mechanism of prostaglandins. Mol Pain 1:3–9.

Naj A. 1992. Peppers. A Story of Hot Pursuits. New York: Alfred Knopf.

Naukkarinen A, Harvima I, Paukkonon K, Aalto ML, Horsmanheimo M. 1993. Immunohistochemical analysis of sensory nerves and neuropeptides, and their contacts with mast cells, in developing and mature psoriatic lesions. Arch Dermatol Res 285:341–346.

Negri L, Lattanzi R, Giannini E, Colucci M, Margheriti F, Melchiorri P, Vellani V, Tian H, De Felice M, Porreca F. 2006. Impaired nociception and inflammatory pain sensation in mice lacking the prokineticin receptor PKR1: focus on interaction between PKR1 and the capsaicin receptor TRPV1 in pain behavior. J Neurosci 26:6716–6727.

Numazaki M, Tominaga T, Toyooka H, Tominaga M. 2002. Direct phosphorylation of capsaicin receptor VR1 by protein kinase C epsilon and identification of two target serine residues. J Biol Chem 277:13375–13378.

Ognyanov VI, Balan C, Bannon AW, Bo Y, Dominguez C, Fotsch C, Gore VK, Klionsky L, Ma VV, Qian YX, Tamir R, Wang X, Xi N, Xu S, Zhu D, Gavva NR, Treanor JJ, Norman MH. 2006. Design of potent, orally available antagonists of the transient receptor potential vanilloid 1. Structure-activity relationships of 2-piperazin-1-yl-1H-benzimidazoles. J Med Chem 49:3719–3742.

Patapoutian A, Peier AM, Story GM, Viswanath V. 2003. ThermoTRP channels and beyond: mechanisms of temperature sensation. Nat Rev Neurosci 4:529–539.

Paus R, Heinzelmann T, Robicsek S, Czarnetzki BM, Maurer M. 1995. Substance P stimulates murine epidermal keratinocyte proliferation and dermal mast cell degranulation. Arch Dermatol Res 287:500–502.

Pearce LV, Petukhov PA, Szabo T, Kedei N, Bizik F, Kozikowski AP, Blumberg PM. 2004. Evodiamine functions as an agonist for the vanilloid receptor TRPV1. Org Biomol Chem 2:2281–2286.

Perry L, Flannery KV. 2007. Precolumbian use of chili peppers in the valley of Oaxaca, Mexico. Proc Natl Acad Sci USA 104:11905–11909.

Perry L, Dickau R, Zarrillo S, Holst I, Pearsall DM, Piperno DR, Berman MJ, Cooke RG, Rademaker K, Ranere AJ, Raymond JS, Sandweiss DH, Scaramelli F, Tarble K, Zeidler JA. 2007. Starch fossils and the domestication and dispersal of chili peppers (*Capsiocum* spp. L.) in the Americas. Science 315:986–988.

Pomonis JD, Harrison JE, Lilly M, Bristol DR, Valenzano KJ, Walker K. 2003. N-(4-Tertiarybutylphenyl)-4-(3-cholorphyridin-2-yl)tetrahydropyrazine-1(2 H) -carboxamide (BCTC), a novel, orally effective vanilloid receptor 1 antagonist with analgesic properties. II. In vivo characterization in rat models of inflammatory and neuropathic pain. J Pharmacol Exp Ther 306:387–393.

Premkumar LS, Ahern GP. 2000. Induction of vanilloid receptor channel activity by protein kinase C. Nature 408:985–990.

Premkumar LS, Qi ZH, Van Buren J, Raisinghani M. 2004. Enhancement of potency and efficacy of NADA by PKC-mediated phosphorylation of vanilloid receptor. J Neurophysiol 91:1442–1449.

Prevarskaya N, Zhang L, Barritt G. 2007. TRP channels in cancer. Biochim Biophys Acta 1772:937–946.

Qin F. 2007. Regulation of TRP ion channels by phosphatidylinositol-4,5-bisphosphate. Handb Exp Pharmacol 179:509–525.

Rami HK, Thompson M, Macdonald GJ, Westaway SM, Mitchell DJ. 2003. Vanilloid receptor modulators. Patent WO 03068749-A1.

Rami HK, Thompson M, Wyman P, Jerman JC, Egerton J, Brough S, Stevens AJ, Randall AD, Smart D, Gunthorpe MJ, Davis JB. 2004. Discovery of small molecule antagonists of TRPV1. Bioorg Med Chem Lett 14:3631–3634.

Rami HK, Thompson M, Wyman P, Stemp G, Fell S, Jerman JC, Stevens SJ, Smart D, Sargent B, Sanderson D, Randall AD, Gunthorpe MJ, Davis JB. 2006. Discovery of SB-705498: a potent, selective and orally bioavailable TRPV1 antagonist suitable for clinical development. Bioorg Med Chem Lett 16:3287–3291.

Rashid M, Inoue M, Bakoshi S, Ueda H. 2003. Increased expression of vanilloid receptor 1 on myelinated primary afferent neurons contributes to the antihyperalgesic effect of capsaicin cream in diabetic neuropathic pain in mice. J Pharmacol Exp Ther 306:709–717.

Raychaudhuri SP, Jiang WY, Farber EM. 1998. Psoriatic keratinocytes express high levels of nerve growth factor. Acta Derm Venereol 78:84–86.

Roden DM, Lazarra R, Rosen M, Schwartz PJ, Towbin J, Vincent GM. 1996. Multiple mechanisms in the long-QT syndrome. Current knowledge, gaps, and future directions. The SADS Foundation Task Force on LQTS. Circulation 94:1996–2012.

Rouhi MA. 1996. Chili pepper studies paying off with hot birdseed and better analgesics. Chem Eng News 74:30–31.

Sanchez JF, Krause JE, Cortright DN. 2001. The distribution and regulation of the vanilloid receptor VR1 and VR1 5'splice variant RNA expression in rat. Neurosci 107:373–381.

Sculptoreanu A, de Groat WC, Buffington CA, Birder LA. 2005. Protein kinase C contributes to abnormal capsaicin responses in DRG neurons from cats with feline interstitial cystitis. Neurosci Lett 381:42–46.

Shin J, Cho H, Hwang SW, Jung J, Shin CY, Lee SY, Kim SH, Lee MG, Choi YH, Kim J, Haber NA, Reichling DB, Khasar S, Levine JD, Oh U. 2002. Bradykinin-12-lipoxygenase-VR1 signaling pathway for inflammatory hyperalgesia. Proc Natl Acad Sci USA 99:10150–10155.

Siemens J, Zhou S, Piskorowski R, Nikai T, Lumpkin ES, Basbaum AI, King D, Julius D. 2006. Spider toxins activate the capsaicin receptor to produce inflammatory pain. Nature 444:208–212.

Journal: DDR ☑ Disk used Article : 7716 Pages: 21 Despatch Date: 3/1/2008

Skofitsch G, Jacobowitz DM. 1985. Galanin-like immunoreactivity in capsaicin sensitive sensory neurons and ganglia. Brain Res Bull 15:191–195.

Smith PG, Liu M. 2002. Impaired cutaneous wound healing after sensory denervation in developing rats: effects on cell proliferation and apoptosis. Cell Tissue Res 51:121–129.

Steenland HW, Ko SW, Zhuo M. 2006. Hot receptors in the brain. Mol Pain 2:34–43.

Suh YG, Oh U. 2005. Activation and activators of TRPV1 and their pharmacological implications. Curr Pharm Des 11:2687–2698.

Sun Q, Tafesse L, Islam K, Zhou X, Victory SF, Zhang C, Hachicha M, Schmidt LA, Patel A, Rotshteyn Y, Valenzano KJ, Kyle D. 2003. J. 4-(2-pyridyl)piperazine-1-carboxamides: potent vanilloid receptor 1 antagonists. Bioorg Med Chem Lett 13:3611–3616.

Suri A, Szallasi A. 2007. The emerging role of TRPV1 in diabetes and obesity. Trends Pharmacol Sci (in press).

Sutton KG, Rutter T, Bonnert L, Jarolinek W, Seabrook GR. 2005. Functional characterization of the S512Y mutant vanilloid human TRPV1 receptor. Br J Pharmacol 146:702–711.

Swanson DM, Dubin AE, Shah C, Nasser N, Chang L, Dax SL, Jetter MC, Breitenbucher JG, Liu C, Mazur C, Lord B, Gonzales L, Hoey K, Rizzolio M, Bogenstaetter M, Codd E, Lee D, Zhang SP, Chaplan SR, Carruthers NI. 2005. Identification and biological evaluation of 4-(3-trifluoromethylpyridin-2-yl)piperazine-1-carboxylic acid (5-trifluoromethyl pyridin-2-yl)amide, a high affinity TRPV1 (VR1) vanilloid receptor antagonist. J Med Chem 48:1857–1872.

Szallasi A. 1996. Vanilloid-sensitive neurons: a fundamental subdivision of the peripheral nervous system. J Periph Nerv Syst 1:6–18.

Szallasi A, Blumberg PM. 1989. Resiniferatoxin, a phorbol-related diterpene, acts as an ultrapotent analog of capsaicin, the irritant constituent in red pepper. Neuroscience 30:515–520.

Szallasi A, Blumberg PM. 1990. Specific binding of resiniferatoxin, an ultrapotent capsaicin analog, by dorsal root ganglion membranes. Brain Res 524:106–111.

Szallasi A, Blumberg PM. 1991. Molecular target size of the vanilloid (capsaicin) receptor in pig dorsal root ganglia. Life Sci 48:1863–1869.

Szallasi A, Blumberg PM. 1999. Vanilloid (capsaicin) receptors and mechanisms. Pharmacol Rev 51:159–211.

Szallasi A, Blumberg PM. 2003. Complex regulation of TRPV1 by vanilloids. In: Heller S, Liedtke W, editors. TRP ion channel function in sensory transduction and cellular signaling cascades. Boca Raton, FL: CRC Press. p 85–104.

Szallasi A, Di Marzo V. 2000. New perspectives on enigmatic vanilloid receptors. Trends Neurosci 23:491–497.

Szallasi A, Biro T, Modarres S, Garlascelli L, Petersen M, Klusch A, Vidari G, Jonassohn M, De Rosa S, Sterner O, Blumberg PM, Krause JE. 1998. Dialdehyde sesquiterpenes and other terpenoids as vanilloids. Eur J Pharmacol 356:81–89.

Szallasi A, Cruz F, Geppetti P. 2006. TRPV1: a therapeutic target for novel analgesic drugs? Trends Mol Med 12:545–554.

Szallasi A, Cortright DN, Blum CB, Eid S. 2007. The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. Nat Rev Drug Discov 6:357–372.

Szolcsányi J. 1989. Capsaicin, irritation and desensitization. Neurophysiological basis and future perspectives. In: Geen BG, Mason JR, Kare MR, editors. Chemical senses. Vol 2. Irritation. New York: Marcel Dekker. p 141–168.

Szolcsányi J. 2004. Forty years in capsaicin research for sensory pharmacology and physiology. Neuropeptides 38:377–384.

Szolcsányi J, Joó F, Jancsó-Gábor A. 1971. Mitochondrial changes in preoptic neurons after capsaicin desensitization of the hypothalamic thermodetectors in rats. Nature 299:116–117.

Szolcsányi J, Jancsó-Gábor A. 1975. Sensory effects of capsaicin congeners. I. Relationship between chemical structure and pain producing potency. Drug Res 25:1877–1881.

Tafesse L, Sun Q, Schmidt L, Valenzano KJ, Rotshteyn Y, Su X, Kyle DJ. 2004. Synthesis and evaluation of pyridazinylpiperazines as vanilloid receptor 1 antagonists. Bioorg Med Chem Lett 14:5513–5519.

Tam C, Brain SD. 2004. The assessment of vasoactive properties of CGRP and adrenomedullin in the microvasculature: a study using in vivo and in vitro assays in the mouse. J Mol Neurosci 22:117–124.

Tanaka T, Danno K, Ihai Imamura S. 1988. Effects os substance P on the growth of cultured keratinocytes. J Invest Dermatol 90:399–401.

Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D. 1998. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 21:531–543.

Tousova K, Vyklicky L, Susankova K, Benedikt J, Vlachova V. 2005. Gadolinium activates and sensitizes the vanilloid receptor TRPV1 through the external protonation sites. Mol Cell Neurosci 30:207–217.

Trevisani M, Smart D, Gunthorpe MJ, Tognetto M, Barbieri M, Campi B, Amadesi S, Gray J, Jerman JC, Brough SJ, Owen D, Smith GD, Randall AD, Harrison S, Bianchi A, Davis JB, Geppetti P. 2002. Ethanol elicits and potentiates nociceptor responses via the vanilloid receptor-1. Nat Neurosci 5:546–551.

Trevisani M, Patacchini R, Nicoletti P, Gatti R, Gazzieri D, Lissi N, Zagli G, Creminon C, Geppetti P, Harrison S. 2005. Hydrogen sulfide causes vanilloid receptor 1-mediated neurogenic inflammation in the airways. Br J Pharmacol 145:1123–1131.

Tsui H, Razavi R, Chan Y, Yantha J, Dosch HM. 2007. "Sensing" autoimmunity in type 1 diabetes. Trends Mol Med 13:405–413.

Tympanidis P, Casula MA, Yiangou Y, Anand P. 2004. Increased vanilloid receptor VR1 innervation of vulvodynia. Eur J Pain 8:129–133.

Woolf CJ, Ma Q. 2006. Molecular mechanisms of neuropathic pain-phenotypic switch and initiation mechanisms. Pharmacol Ther 109:57–77.

Valenzano KJ, Grant ER, Wu G, Hachicha M, Schmidt L, Tafesse L, Sun Q, Rotshteyn Y, Francis J, Limberis J, Malik S, Whittemore ER, Hodges D. 2003. N-(4-tertiarybutylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2 H)-carboxamide (BCTC), a novel, orally effective vanilloid receptor 1 antagonist with analgesic properties: I. in vitro characterization and pharmacokinetic properties. J Pharmacol Exp Ther 306:377–386.

Vetter I, Wyse BD, Monteith GR, Roberts-Thomson SJ, Cabot PJ. 2006. The μ opioid agonist morphine modulates potentiation of capsaicin-evoked TRPV1 responses through a cyclic AMP-dependent protein kinase A pathway. Mol Pain 2:22–26.

Viswanadhan VN, Sun Y, Norman MH. 2007. Three-dimensional quantitative structure—activity relationships and activity predictions of human TRPV1 channel antagonists: comparative molecular field analysis and comparative molecular similarity index analysis of cinnamides. J Med Chem. 50:5608–5619. Q4

Journal: DDR ☑ Disk used Article : 7716 Pages: 21 Despatch Date: 3/1/2008

Wahl P, Foged C, Tullin S, Thomsen C. 2001. Iodo-resiniferatoxin, a new potent vanilloid receptor antagonist. Mol Pharmacol 59:9–15.

Walker KM, Urban L, Medhurst SJ, Patel S, Panesar M; Fox AJ, McIntyre P. 2003. The VR1 antagonist capsazepine reverses mechanical hyperalgesia in models of inflammatory and neuropathic pain. J Pharmacol Exp Ther 304:56–62.

Walpole CSJ, Wrigglesworth R. 1993. Structural requirements for capsaicin agonists and antagonists. In: Wood JN, editor. Capsaicin in the study of pain. San Diego, CA: Academic Press. p 63–82.

Walpole CS, Bevan S, Bovermann G, Boelsterli JJ, Breckenridge R, Davies JW, Hughes GA, James I, Oberer L, Winter J, Wrigglesworth R. 1994. The discovery of capsazepine, the first competitive antagonist of the sensory neuron excitants capsaicin and resiniferatoxin. J Med Chem 37:1942–1954.

Wang X, Miyares RL, Ahern GP. 2005. Oleoylethanolamide excites vagal sensory neurons, induces visceral pain and reduces short-term food intake in mice via capsaicin receptor TRPV1. J Physiol 564:541–547.

Wang X, Chakrabarti PP, Ognyanov VI, Pettus LH, Tamir R, Tan H, Tang P, Treanor JS, Gavva NR, Norman MH. 2007. Trisubstituted pyrimidines as transient receptor potential vanilloid 1 (TRPV1) antagonists with improved solubility. Bioorg Med Chem Lett 17:6539–6545.

Wang Y, Toth A, Tran R, Szabo T, Welter JD, Blumberg PM, Lee J, Kang SU, Lim JQ, Lee J. 2003. High-affinity partial agonists of the vanilloid receptor. Mol Pharmacol 64:325–333.

Wang Y, Kaminski NE, Wang DH. 2007. Endocannabinoid regulates blood pressure via activation of the transient receptor potential vanilloid type 1 in Wistar rats fed a high-salt diet. J Pharmacol Exp Ther 321:763–769.

Wilson-Gerving TD, Dmyterko MV, Zochodne ZW, Johnston JM, Verge VM. 2005. Neurotropin-3 suppresses thermal hyperalgesia associated with neuropathic pain and attenuates transient receptor potential vanilloid receptor-1 expression in adult sensory neurons. J Neurosci 25:758–767.

Wood JN, Winter J, James IF, Rang HP, Yeats J, Bevan S. 1988. Capsaicin-induced ion fluxes in dorsal root ganglion cells in culture. J Neurosci 8:3208–3220.

Xu H, Blair NT, Clapham DE. 2005. Camphor activates and strongly desensitizes the transient receptor potential vanilloid subtype 1 channel in a vanilloid-independent mechanism. 25: 8924–8937.

Xu XJ, Farkas-Szallasi T, Lundberg JM, Hokfelt T, Wiesenfeld-Hallin Z, Szallasi A. 1997. Effects of the capsaicin analogue resiniferatoxin on spinal nociceptive mechanisms in the rat: behavioral, electrophysiological and in situ hybridization studies. Brain Res 752:52–60.

Yiangou Y, Facer P, Dyer NH, Fowler C, Anand P. 2001. Vanilloid receptor 1 immunoreactivity in inflamed human bowel. Lancet 357:1338–1339.

Yilmaz Z, Renton T, Yiangou Y, Zakrzewska J, Chessell IP, Bountra C, Anand P. 2007. Burning mouth syndrome as a trigeminal small fibre neuropathy: increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score. J Clin Neurosci 14:864–871

Yura S, Mogi M, Ikegami Y, Masuda T, Kokybo T, Urbahns K, Yoshida N, Marumo M, Shiroo M, Tajimi M, Takeshita K, Moriwaki T, Tsukumi Y. 2003. Piperazine carboxamide derivatives. Patent JP 2003192673-A2.

Zhang X, Huang J, McNaughton PA. 2005. NGF rapidly increases membrane expression of TRPV1 heat-gated ion channels. EMBO J 24:4211–4223.

Zhang H, Cang CL, Kawasaki Y, Liang LL, Zhang YQ, Ji RR, Zhao ZQ. 2007. Neurokinin-1 receptor enhances TRPV1 activity in primary sensory neurons via PKC epsilon: a novel pathway for heat hyperalgesia. J Neurosci 27:12067–12077.

Zheng X, Hodgetts KJ, Brielmann H, Hutchison A, Burkamp F, Brian-James A, Blurton P, Clarkson R, Chandrasekhar J, Bakthavatchalam R, De Lombaert S, Crandall M, Cortright D, Blum CA. 2006. From arylureas to biarylamides to aminoquinazolines: discovery of a novel, potent TRPV1 antagonist. Bioorg Med Chem Lett 16:5217–5221.

Zygmunt PM, Petersson J, Andersson DA, Chuang H, Sorgard M, Di Marzo V, Julius D, Hogestatt ED. 1999. Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature 400:452–457.