N-(4-Tertiarybutylphenyl)-4-(3-chlorophyridin-2-yl)tetrahydropyrazine-1(2H)-carbox-amide (BCTC), a Novel, Orally Effective Vanilloid Receptor 1 Antagonist with Analgesic Properties: II. In Vivo Characterization in Rat Models of Inflammatory and Neuropathic Pain

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ABSTRACT
The vanilloid receptor 1 (VR1) is a cation channel expressed predominantly by nociceptive sensory neurons and is activated by a wide array of pain-producing stimuli, including capsaicin, noxious heat, and low pH. Although the behavioral effects of injected capsaicin and the VR1 antagonist capsazepine have indicated a potential role for VR1 in the generation and maintenance of persistent pain states, species differences in the molecular pharmacology of VR1 and a limited number of selective ligands have made VR1 difficult to study in vivo. N-(4-Tertiarybutylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2H)-carbox-amide (BCTC) is a recently described inhibitor of capsaicin- and acid-mediated currents at rat VR1. Here, we report the effects of BCTC on acute, inflammatory, and neuropathic pain in rats. Administration of BCTC (30 mg/kg p.o.) significantly reduced both mechanical and thermal hyperalgesia induced by intraplantar injection of 30 μg of capsaicin. In rats with Freund’s complete adjuvant-induced inflammation, BCTC significantly reduced the accompanying thermal and mechanical hyperalgesia (3 mg/kg and 10 mg/kg p.o., respectively). BCTC also reduced mechanical hyperalgesia and tactile allodynia 2 weeks after partial sciatic nerve injury (10 and 30 mg/kg p.o.). BCTC did not affect motor performance on the rotarod after administration of doses up to 50 mg/kg p.o. These data suggest a role for VR1 in persistent and chronic pain arising from inflammation or nerve injury.

The vanilloid receptor type 1 (VR1) is a pivotal molecular integrator of noxious stimuli that is expressed on somatic and autonomic primary afferent neurons. VR1 has been confirmed as a ligand-gated ion channel after its cloning from rat and human tissues, and has been shown to be highly expressed in small-diameter primary afferent neurons (Caterina et al., 1997; Hayes et al., 2000; McIntyre et al., 2001). In vitro studies have shown that, like the native vanilloid receptor, recombinant VR1 can be activated by a variety of chemical as well as physical stimuli. In vitro, VR1 responds to plant-derived compounds, including capsaicin, a pungent component of chili peppers, lipid mediators such as anandamide (Smart et al., 2000), the lipooxygenase product 12-(S)-hydroperoxyeicosatetraenoic acid (Hwang et al., 2000), as well as noxious heat (Caterina et al., 1997) and low pH (Tominaa et al., 1998).

A potential role for VR1 in nociception has been evident for some time because injection of the VR1 agonist capsaicin induces nocifensive and hyperalgesic behaviors in rodents and pain in humans (Szolcsanyi, 1977; Carpenter and Lynn, 1981; Simone et al., 1987, 1989; Gilchrist et al., 1996). Further support for VR1 as a therapeutic target arose from experiments involving capsaizine. Capsazepine is a VR1 antagonist that has been shown to competitively inhibit capsaicin-mediated responses in isolated dorsal root ganglion (DRG) neurons (Bevan et al., 1992a) and tissues from rat (Bevan et al., 1992b; Cholewinski et al., 1993; Maggi et al., 1993; Santicioli et al., 1993; Jerman et al., 2000), mouse (Urban and Dray, 1991), and guinea pig (Ellis and Undem, 1994; Fox et al., 1995; Auberson et al., 2000). In vivo, capsaizepine has been shown to inhibit nocifensive and hyperalgesic responses to capsaicin in mice, rats, and guinea pigs.
(Santos and Calixto, 1997; Walker et al., 2003). However, both in vitro and in vivo studies have indicated that capsaicin also has species-dependent activity. In vitro, capsaicin has been shown to block low pH mediated activation of human or guinea pig, but not rat VR1 (Lou and Lundberg, 1992; Satoh et al., 1993; Fox et al., 1995; McIntyre et al., 2001; Savidge et al., 2002). These in vitro results correlate with the finding that capsaicin reverses inflammatory and neuropathic hyperalgesia in the guinea pig, but not in the rat (Walker et al., 2003).

Together, these data suggest that blockade of low pH induced VR1 activation may be predictive of antihyperalgesic efficacy in vivo. If this hypothesis is valid, then molecules that inhibit pH induced activation of rat VR1, in vitro, would also produce a reduction in hyperalgesia in rat models of chronic pain. In the accompanying report, Valenzano et al. (2003) describe N-(4-tERTarylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2H)-carbox-amide (BCTC) as a potent, selective, and orally bioavailable antagonist of rat VR1. In contrast to capsaicin, BCTC not only blocks the activation of rat VR1 by capsaicin but also by low pH at the native rat VR1 in a skin-nerve preparation. Thus, BCTC has provided us with an opportunity to test our hypothesis that the inhibition of low pH induced activation of VR1 confers in vivo efficacy in models of chronic pain. This report describes the effects of BCTC in models of inflammatory, neuropathic, and capsaicin-induced pain in the rat. The efficacy and side effect profile of BCTC in these models were compared with those of nonsteroidal anti-inflammatory drugs and antiepileptic drugs currently used for the clinical therapy of inflammatory and neuropathic pain, respectively.

Materials and Methods

Compounds and Administration Procedures. BCTC was synthesized according to known methods and was used in all experiments as its free base (molecular weight 372.89). Indomethacin (Sigma-Aldrich, St. Louis, MO) and BCTC were administered orally in 2% β-cyclodextrin (Sigma-Aldrich) by gastric gavage in a dose volume of 10 ml/kg b.wt. Gabapentin (Kemprote, Middlesborough, UK) was dissolved in saline and administered via i.p. injection in a dose volume of 2 ml/kg. Capsaicin (Sigma-Aldrich) was used in all experiments as its free base. The procedure of Gilchrist et al. (1996) was used to dissolve the capsaicin. Briefly, 6 mg of capsaicin was first dissolved in 0.14 ml of polyoxyethylene (20) sorbitan mono-oleate (Tween 80) by gently heating the solution to approximately 70°C. The solution was then diluted with 1.86 ml of 0.9% sodium chloride using an ultrasonic bath, and passed through a 0.20-μm filter. The final concentration of the capsaicin solution was 3 μg/μl. Intraplantar injections of the capsaicin solution were given in a 10-μl volume using a 100-μl Hamilton syringe fitted with a 27-gauge needle. The Tween 80/saline vehicle was used for control injections.

Animals. The Purdue Institutional Animal Care and Use Committee approved all animal procedures according to the guidelines of the Office of Laboratory Animal Welfare. Male Sprague-Dawley rats (Taconic Farms, Germantown, NY), weighing 180 to 200 g at the start of acute and inflammatory experiments or 90 to 110 g at the start of nerve ligation experiments, were used. Animals were group-housed and had free access to food and water at all times, except before oral administration of drugs when food was removed for 16 h before dosing. For comparison with compound-treated groups, animals treated with the appropriate drug vehicle were included in each experiment. The volume of administration was identical for vehicle- and compound-treated rats, and rats were identical with respect to all other experimental procedures.

Capsaicin-Induced Hyperalgesia. Intraplantar injection of capsaicin (30 μg) was used to induce mechanical and thermal hyperalgesia, as described previously (Gilchrist et al., 1996). The paw pressure assay was used to assess capsaicin-induced mechanical hyperalgesia. For this assay, hind paw withdrawal thresholds (PWTs) to a noxious mechanical stimulus were determined using an algosyngestor (model 7200; Ugo Basile, Varese, Italy) (Walker et al., 2001). Cut-off was set at 250 g and the endpoint was taken as complete paw withdrawal. PWTs were determined once for each rat at each time point. All rats were tested for baseline PWT and 1 h later, animals received a single dose of 1, 3, 10, or 30 mg/kg BCTC or vehicle (p.o., volume = 10 ml/kg, n = 10/group). Thirty minutes later, under isofluorane/oxygen anesthesia, rats received a single intraplantar injection of 30 μg of capsaicin or vehicle in a 10-μl volume. Ninety minutes after the intraplantar injection of capsaicin, PWTs were determined again.

The plantar test was used to assess capsaicin-induced thermal hyperalgesia (n = 8/group). For this test, hind paw withdrawal latencies (PWLs) to a noxious thermal stimulus were determined using the technique described by Hargreaves et al. (1988) using a plantar test apparatus (model 7370-371; Ugo Basile). Cut-off was set at 32 s, and any directed paw withdrawal from the heat source was taken as the endpoint. To assess the effects of BCTC on the development of capsaicin-induced thermal hyperalgesia rats were treated as described above for capsaicin-induced mechanical hyperalgesia, but PWLs were measured 30 min after capsaicin injection.

Inflammatory Hyperalgesia. The efficacy of BCTC against hyperalgesia associated with inflammation was investigated using the Freund’s complete adjuvant (FCA) model (Walker et al., 2001). Mechanical and thermal hyperalgesia were measured in separate groups of rats (n = 8–20/group) according to the procedure described above. Baseline PWTs or PWLs were determined, and rats were then anesthetized with isofluorane/oxygen and received an intraplantar injection of 100% FCA (50 μl). Twenty-four hours after FCA treatment, predrug PWT or PWL measurements were taken and then rats received a single dose of 1, 3, 10, or 30 mg/kg BCTC, 30 mg/kg indomethacin, or vehicle (p.o., volume = 10 ml/kg). PWTs or PWLs were determined again 2, 4, 6, and 24 h postdrug administration.

Hyperalgesia and Allodynia after Nerve Injury. The partial sciatic nerve ligation model was used as a model of nerve injury-related pain in rats, as described previously by Seltzer et al. (1990). Partial ligation of the left sciatic nerve was performed under isofluorane/O2 inhalation anesthesia. After induction of anesthesia, the left thigh was shaved and cleaned. The sciatic nerve was exposed at high thigh level through a small incision and was carefully cleared of surrounding connective tissues at a site near the trocanther just distal to the point at which the posterior biceps semitendinosus nerve branches off the common sciatic nerve. A 7-0 silk suture was inserted into the nerve with a 3/8 curved, reversed-cutting mini-needle, and tightly ligated so that the dorsal one-third to one-half of the nerve thickness was held within the ligature and the wound was closed in two layers. Sham-operated control rats underwent an identical dissection on the left hind limb, but the sciatic nerve was not dissected away from the surrounding muscle nor ligated. After surgery, animals were weighed and placed on a warm pad until they recovered from anesthesia.

The effects of BCTC on mechanical hyperalgesia and tactile allodynia were measured 14 to 17 days postsurgery (n = 8–10/group). Mechanical hyperalgesia was assessed using the paw pressure technique before, 2, 4, 6, and 24 h after drug administration. To assess tactile allodynia, rats (n = 10/group) were placed in clear Plexiglas compartments with a wire mesh floor and were allowed to habituate for a period of at least 15 min. After habituation, a series of von Frey monofilaments were presented to the plantar surface of the left (operated) foot of each rat. The series consisted of six monofilaments of increasing diameter, with the smallest diameter fiber presented first. Five trials were conducted with each filament, with each trial separated by approximately 2 min. Each presentation lasted for a
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Results

Capsaicin-Induced Hyperalgesia. Injection of 30 μg of capsaicin into the plantar surface of the left hindpaw induced a profound, but short-lasting decrease in PWL to thermal stimulation. Initial experiments revealed that this thermal hyperalgesia was present from 15 to 45 min after injection, and was most robust 30 min postinjection (data not shown). We therefore tested whether pretreatment of rats with BCTC would prevent the development of capsaicin-mediated thermal hyperalgesia. Injection of 30 μg of capsaicin resulted in a significant decrease in PWL (27.1 ± 1.0 versus 9.5 ± 2.25 s for vehicle- or capsaicin-treated rats, respectively). Pretreatment with BCTC (30 mg/kg p.o.) before capsaicin injection significantly inhibited the development of capsaicin-induced thermal hyperalgesia (18.3 ± 2.34 s; p < 0.01), compared with rats treated with capsaicin alone.

As reported previously (Gilchrist et al., 1996) intraplantar injection of capsaicin (30 μg) also induced mechanical hyperalgesia that lasted longer than the coincident thermal hyperalgesia. Our preliminary experiments indicated that maximal decreases in PWT occurred 90 min postcapsaicin injection (data not shown). There was a significant main effect of treatment on PWT, indicating a dose-dependent reversal of capsaicin-induced mechanical hyperalgesia by BCTC [F(5.41) = 4.008; p < 0.01]. Pretreatment with BCTC (30 mg/kg) 30 min before capsaicin injection significantly inhibited capsaicin-induced mechanical hyperalgesia relative to rats treated with capsaicin alone (p < 0.05; Fig. 1).

BCTC Reduces Thermal and Mechanical Hyperalgesia Associated with Inflammation. Intraplantar injection of 50 μl of FCA resulted in the development of thermal hyperalgesia as indicated by decreased PWL to a noxious thermal stimulus (Fig. 2). Oral administration of BCTC produced a dose-dependent reduction in thermal hyperalgesia 2 [F(5.42) = 8.892; p < 0.001] and 4 h postadministration [F(5.42) = 6.306; p < 0.001]. BCTC (3 and 10 mg/kg p.o.) produced significant antihyperalgesia 2 h after administration (p < 0.05). These effects were comparable both in terms of efficacy and duration of action to the nonsteroidal anti-inflammatory drug indomethacin (30 mg/kg p.o.; p < 0.05; Fig. 2). The effects of BCTC were restricted to the hyperalgesia associated with inflammation or injury and do not reflect an acute analgesic activity because PWTs from the noninjured hind paw were not affected by systemic BCTC administration (data not shown).

Intraplantar injection of 50 μl of FCA also resulted in the development of mechanical hyperalgesia, determined using the paw pressure assay (Fig. 3). BCTC (1–30 mg/kg p.o.) produced a dose-dependent reversal of FCA-induced mechanical hyperalgesia at 2, 4, and 6 h postadministration (p < 0.001 at each time point). BCTC significantly reduced FCA-induced mechanical hyperalgesia after oral administration at doses as low as 3 mg/kg (4 h) and at higher doses (10 and 30 mg/kg p.o.) were effective for up to 6 h (Fig. 3). The effects of BCTC were similar to indomethacin (30 mg/kg p.o.) in terms of efficacy, but indomethacin was only effective at 2 and 4 h after administration.

BCTC Reduces Mechanical Hyperalgesia Associated with Nerve Injury. Partial ligation of the sciatic nerve resulted in the development of mechanical hyperalgesia within 2 weeks of surgery. Administration of BCTC to rats 14 to 18 days after partial ligation of the sciatic nerve resulted in a significant and dose-dependent reversal of this mechanical hyperalgesia [F(5.42) = 10.675; p < 0.001; Fig. 4]. Oral administration of BCTC (1–30 mg/kg) produced a significant reversal of mechanical hyperalgesia in the partially denervated rat hind paw for at least 6 h after administration (p < 0.01). The effects of administration of BCTC (10 mg/kg p.o.) were similar to those seen after administration of gabapentin (100 mg/kg i.p.), but with a longer duration of action (6 versus 4 h; Fig. 4).

BCTC Reduces Tactile Alldynia Associated with Nerve Injury. Partial ligation of the sciatic nerve also resulted in the development of tactile allodynia that was evident within 14 days of surgery (Fig. 5A). Administration of 10 mg/kg BCTC to rats 14 to 18 days after partial ligation of the sciatic nerve resulted in the development of tactile allodynia as determined by a significant decrease in the median fiber weight, or the fiber weight required to evoke a hindpaw...
withdrawal with a 50% frequency relative to vehicle-treated controls. Administration of 10 mg/kg BCTC significantly increased the log FW50 at 2 h postadministration (p < 0.01; Fig. 5B). Administration of 100 mg/kg gabapentin (i.p.) also significantly increased the log FW50 in nerve-injured rats 2 h postadministration (p < 0.01; Fig. 5B).

**Side Effect Profiling: Ataxia.** A common side effect of compounds used to treat neuropathic pain is ataxia, which can confound the interpretation of behavioral assays. A role for VR1 in motor function has not been described; however, we tested rats for motor function using the rotarod assay. BCTC did not affect rotarod performance at 2 or 4 h after administration at doses up to 50 mg/kg, whereas gabapentin (100 mg/kg i.p.) produced in a significant decrease in rotarod performance 2 h postadministration (p < 0.05; Fig. 6).

**Discussion**

VR1 has been extensively investigated as an intriguing target for the pharmacotherapy of pain. Its expression is predominantly restricted to nociceptive neurons, and it is activated by pathological rather than physiological stimuli, including well known nociceptive stimuli such as acid, temperatures above 48°C, and the pungent spice capsaicin. Here, we report that systemic administration of the novel VR1 antagonist BCTC significantly reversed mechanical and thermal hyperalgesia associated with injection of capsaicin, with FCA-induced inflammation, or after nerve injury. These effects were seen in the absence of ataxia that is commonly associated with antiepileptic drugs used to treat neuropathic pain.

The VR1 antagonist capsazepine has also been used in many studies to investigate the role of VR1 in acute and chronic nociception. However, recent studies have revealed species-specific pharmacological actions of capsazepine that may limit its applicability in some animal models (Lou and Lundberg, 1992; Satoh et al., 1993; Fox et al., 1995; McIntyre et al., 2001; Savidge et al., 2002; Walker et al., 2003). Although capsazepine can inhibit activation of rat VR1 by capsaicin, Valenzano et al. (2003) found it to be ineffective at blocking acid-mediated VR1 currents, and is similarly ineffective at reversing pain behaviors associated with inflammation in rats (Walker et al., 2003). However, the pharmacological profile of capsazepine is markedly different in guinea pigs compared with rats. Capsazepine is effective at inhibiting both the acid- and capsaicin-induced VR1 currents at guinea pig VR1 (Savidge et al., 2002) and has been shown to reduce inflammatory and nerve injury-related pain in guinea pigs (Walker et al., 2003). Thus, the species-dependent activity of capsazepine to inhibit low pH induced currents at VR1 correlates with its ability to reduce hyperalgesia in models of chronic pain.

In contrast to capsazepine, BCTC inhibits the activation of rat VR1 by either capsaicin or low pH (Valenzano et al., 2003). The unique pharmacological profile of BCTC at the rat VR1 provided us with an opportunity to test the hypothesis that the effects of VR1 blockers in chronic pain models may be predicted by their ability to inhibit low pH induced activation of VR1. We found that pretreatment with BCTC effectively inhibits the VR1 agonist effects of capsaicin in the rat in vivo (Fig. 1). These results were consistent with the find-
ings of Valenzano et al. (2003) who demonstrated using an ex vivo rat skin-nerve preparation that BCTC completely inhibited the activation of nociceptors by capsaicin.

However, the most striking findings of this study were those indicating that BCTC is effective in reversing established thermal and mechanical hyperalgesia associated with inflammation (Figs. 2 and 3) or nerve injury (Figs. 4 and 5). The effects of BCTC were restricted to the hyperalgesia associated with inflammation or injury and do not reflect an acute analgesic activity because PWTs from the noninjured hind paw were not affected by systemic BCTC administration (data not shown). Likewise, BCTC did not produce any impairment of locomotor activity over and above the dose range that produced antihyperalgesic effects (Fig. 6). These findings are interesting in light of the recent study by Walker et al. (2002) indicating that systemic administration of the VR1 antagonist capsazepine effectively reverses mechanical hyperalgesia associated with inflammation or nerve injury in the guinea pig but was ineffective in rat models of chronic pain. These differences reflect the different molecular pharmacological profiles of capsazepine versus BCTC at rat VR1, in vitro. Valenzano et al. (2003) have demonstrated that unlike capsazepine, BCTC potently antagonizes low pH induced activation of recombinant or native rat VR1. This suggests that the in vivo efficacy of VR1 antagonists in models of chronic pain may be predicted by their ability to inhibit pH induced activation of VR1. Because both capsazepine and BCTC antagonize capsaicin-induced activation of VR1, in vitro and in vivo, this action seems to be less predictive of a VR1 antagonist’s efficacy in chronic pain states.

We have found that the VR1 antagonist BCTC (3–30 mg/kg p.o.) effectively reverses both thermal and mechanical hyper-

![Figure 4](image-url) BCTC dose dependently reverses mechanical hyperalgesia associated with nerve injury. Rats underwent surgery involving partial ligation of the sciatic nerve. Fourteen to 17 days postsurgery, rats received oral administration of vehicle or BCTC, or intraperitoneal administration of gabapentin (100 mg/kg; open circles). Asterisks denote significance (p < 0.05) from vehicle-treated control group according to Fisher’s PLSD test; error bars represent S.E.M. (n = 10–20 rats/group).

![Figure 5](image-url) BCTC significantly reduces tactile alldynia associated with nerve injury. Rats underwent surgery involving partial ligation of the sciatic nerve. Rats were tested for tactile alldynia 14 to 17 days postsurgery by application of von Frey monofilaments before (A) and 2 h (B) postadministration of vehicle BCTC, or intraperitoneal administration of gabapentin (100 mg/kg; open circles) (n = 10 rats/group).
algesia associated with inflammation in the rat (Figs. 2 and 3). However, whereas Walker et al. (2003) reported that capsazepine was weakly active against thermal hyperalgesia associated with inflammation in the guinea pig, we found that VR1 blockade via BCTC provided effective reversal of inflammatory hyperalgesia in the rat. Although this may indicate further differences in the molecular pharmacology of BCTC versus capsazepine at VR1, we cannot rule out the possibility that different behavioral phenotypes make the measurement of thermal hyperalgesia more robust in the rat as opposed to the guinea pig. Regardless the explanation, we know that the hyperalgesic effects of heat cannot be explained by the action of VR1 alone, because mice lacking VR1 retain the sensation of noxious heat (Caterina et al., 2000; Davis et al., 2000) and two VR1 homologs, VRL-1 (TRPV2) and TRPV3, have been reported to be insensitive to capsaicin or protons but respond to either high or low threshold heat stimulation (Caterina et al., 1999; Peier et al., 2002).

We have found that BCTC effectively reversed hypersensitivity to mechanical stimuli after inflammation or nerve injury. Stimuli that activate VR1 have been shown to induce mechanical hypersensitivity. To this end, intraplantar injection of either capsaicin (Simone et al., 1987, 1989; Gilchrist et al., 1996) or hyaluronic acid (Hamamoto et al., 1998) results in the development of mechanical hyperalgesia. In fact, the mechanical hyperalgesia observed after capsaicin injection is more robust than the thermal hyperalgesia both in terms of duration of action and the size of the area of secondary hyperalgesia (Gilchrist et al., 1996). There is also evidence that the mechanisms underlying the thermal and mechanical hyperalgesia after capsaicin injection differ. Thermal hyperalgesia is thought to be due to sensitization of nociceptors because it is restricted to the immediate area of injection, whereas central mechanisms may underlie the mechanical hyperalgesia because the sensitivity is seen in a larger area surrounding the site of injection (Simone et al., 1987, 1989; LaMotte et al., 1991). It has been shown that intradermal capsaicin injection facilitates the responses of dorsal horn neurons due to input of low threshold mechanoreceptors and nociceptors (LaMotte et al., 1991; Simone et al., 1991). In inflamed tissue, local pH decreases may ultimately activate VR1, sensitizing nociceptors and low threshold mechanoreceptors, decreasing the threshold at which mechanical stimuli result in the detection of noxious stimuli.

The ability of BCTC to reduce tactile allodynia and mechanical hyperalgesia after partial ligation of the sciatic nerve may be attributed, in part, to altered expression of VR1 in this nerve injury model. Hudson et al. (2001) recently demonstrated that partial ligation of the sciatic nerve results in decreased VR1 immunoreactivity in damaged (ligated) neurons, but increased VR1 immunoreactivity in undamaged neurons. In another rat model of neuropathy, tight ligation of the L5 spinal nerve resulted in a significant decrease of VR1-immunoreactivity in the injured L5 DRG neurons, with a concomitant increase in VR1-immunoreactivity in the uninjured L4 DRG neurons. Interestingly, the increased VR1-immunoreactivity was present not only in C-fibers, but also in myelinated A-fibers, as well, which could also explain the ability of BCTC to block mechanical sensitivity after nerve injury (Hudson et al., 2002). The increased levels of VR1 may then also prime the sensory neurons to respond to other physiological consequences of nerve damage that occur post injury, such as the release of inflammatory mediators from macrophages during Wallerian degeneration (Tracey and Walker, 1995).

The findings reported here provide strong support for a role for VR1 in the pathology of chronic pain, both of inflammatory and neuropathic origin. Moreover, the in vitro characterization of BCTC (Valenzano et al., 2003) indicates that the ability of VR1 antagonists to block low pH induced channel opening may be a key component in predicting the in vivo efficacy of VR1 antagonists in models of chronic pain.

Acknowledgments

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References


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