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The Vanilloid Receptor TRPV1

& Other TRP Channels

highlight

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The Vanilloid Receptor TRPV1 & Other TRP Channels

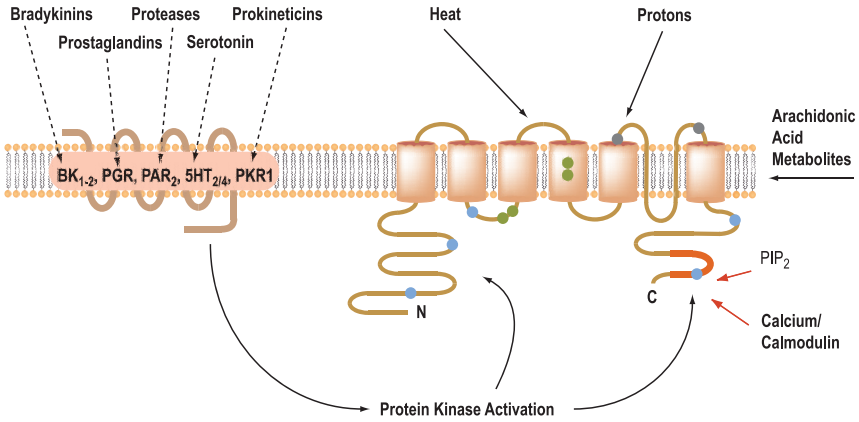

FIGURE 1: Schematic summary of TRPV1 signal integration in the peripheral nociceptor terminal. Solid arrows indicate transient receptor potential cation channel subfamily member 1 (TRPV1)-sensitizing stimuli. The red arrows indicate negative regulation by phosphatidylinositol 4,5-bisphosphate (PIP_2), calcium and calmodulin. Receptors and cognate ligands known to mediate the sensitization of TRPV1 are shown on the left. These largely sensitize TRPV1 through protein kinase activation, although increased arachidonic acid metabolite production and PIP_2 hydrolysis are also important. Coloured circles represent amino acid residues that have been identified to be important in particular functions: green: vanilloid binding (Y511, S512, L547, T550); blue: protein kinase phosphorylation sites (S116, T370, S502, T704, S800); grey: low-pH activation (E600, E646). The red line indicates the carboxy-terminal domain of TRPV1, which has been shown to interact with both PIP_2 and calmodulin. *Adapted from: The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept: A. Szallasi, et al.; Nat. Rev. Drug. Discov.* ***6****, 357 (2007)*

Transient Receptor Potential (TRP) channels constitute a family of cation-permeable channels with members across the phylogenetic tree, from yeast to humans. Most of the proteins in this family display a putative topology of six transmembrane domains with a pore forming loop between the fifth and sixth segment. Based on amino acid sequence homology, the mammalian members of the TRP family have been classified into six subfamilies; TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), and TRPA (ankyrin) [1-3].TRP channels gate in response to a myriad of stimuli such as mechanical stimuli, natural compounds, temperature, or changes in the lipid bilayer. They are crucially involved in physiological processes such as pain perception, photoreception, thermal and mechanical nociception, perception of pungent compounds, osmosensation, smooth muscle tone and blood pressure regulation [4-6].

TRPV1

Six vanilloid receptors have been characterized so far (see Table 1). They are all sensory transducers, highly conservative in their transmembrane regions, but heterogenous in their N-terminal amino acid sequences and widely different in their gating mechanism and regulation. The archetypal vanilloid receptor is the transient receptor potential cation channel subfamily V member 1 [TRPV1; vanilloid receptor 1 (VR1); OSM9-like TRP channel 1 (OTRPC1); capsaicin receptor]. TRPV1 was first identified due to its responsiveness to the pungent compound capsaicin isolated from hot chilli peppers and has been cloned in 1997 [7, 8]. Because TRPV1 has also been shown to be activated by another vanilloid called resiniferatoxin (RTX), as well as temperatures in the noxious range (>43°C) and low pH (<5.9) [7-9], it has been

CONTINUED ON PAGE 2

Introduction *continued*

suggested to mediate both thermal and chemical pain. Since then, TRPV1 has been reported to be activated by multiple stimuli such as allicin [10, 11], camphor [12], nitric oxide [13], and venoms from jellyfish and spider [14, 15]. As a transducer for thermal, chemical and mechanical stimuli TRPV1 is expressed in primary afferent nociceptors but can also be found in higher brain centers, as well as various non-neuronal tissues [8, 16]. TRPV1 knockout-animals exhibit normal responses to noxious mechanical stimuli but exhibit a lack of behavioural responses to capsaicin and diminished responses to acute thermal stimuli [17, 18]. In addition, they show reduced thermal hypersensitivity in inflammatory pain models with no significant reduction in the thermal hyperalgesia induced by nerve-injury models. These findings present TRPV1 as a polymodal receptor responding predominately under inflammatory conditions and during tissue damages.

Sensitization and Modulation

Recently, different inflammatory mediators such as bradykinin [19], prostaglandins [20], prokineticin [21], proteases [22, 23] and serotonin [24] (see cover figure), as well as nerve growth factor (NGF) [19] and ATP [25] have been shown to indirectly sensitize TRPV1. The mechanism by which TRPV1 sensitization is modulated is not yet fully understood. TRPV1 is under the inhibitory control of phosphatidylinositol biphosphate (PIP2) and can be cleaved by phospholipase C (PLC), which is coupled to important pain receptors such as bradykinin B2 receptor [19]. Other mechanisms involve different signalling pathways leading to the phosphorylation of TRPV1 by kinases such as protein kinase A (PKA) [26] and C (PKC) [27, 28]. Dephosphorylation by protein phosphatases such as calcineurin are thought to promote desensitization [29, 30].

Endovanilloids (TRPV1 Agonists)

Endovanilloids are defined as endogenous ligands and activators of TRPV1. The search for such ligands has led to candidate molecular classes including endocannabinoids, N-arachidonoyldopamine, lipoxygenase metabolites of arachidonic acid, and polyamines. Anandamide (AEA), a known agonist of cannabinoid receptors, has been also identified as the first endogenous ligand of TRPV1 [31, 32]. Later, N-arachidonoyl-dopamine (NADA) was found to activate TRPV1 in the hippocampus [33], N-oleoyldopamine (OLDA) has been shown to induced hyperalgesic effects [34], and several products of lipoxygenases such as 12-(S)-hydroperoxyeicosatetraenoic acid (12-(S)-HPETE), 15-(S)-hydroperoxyeicosatetraenoic acid (15-(S)-HPETE), and leukotriene B_4 (LTB_4) were found to activate the capsaicin-activated channel in isolated membrane patches of sensory neurons [35].

TRPV1 Antagonists

The area of vanilloid antagonism has been the most active area in medicinal chemistry of vanilloids carried out in industry. The first generation TRPV1 antagonist capsazepine, a weak and only moderately selective agent [36], has long been the only vanilloid antagonist available, whereas the dye ruthenium red is a relatively unspecific pore-blocker for TRP channels and a powerful convulsant *in vivo*. Serendipity played a key role in the discovery of capsazepine, as it did in the discovery of the first ultrapotent antagonist, 5'-iodoresiniferatoxin (I-RXT). While the first antagonists were based on natural products, newer leads structurally unrelated to agonists are starting to emerge. The field of vanilloid antagonists would greatly benefit from a direct comparison between the various classes of these new agents, whose inhibitory activity was evaluated under different conditions and using TRPV1 versions from different animal species. In this context, it is important to note that the mouse version of TRPV1 shows considerable differences from human TRPV1 in terms of affinity and activity of antagonists. Several chemically novel and potent antagonists have been identified in recent years; many of them are in preclinical studies or clinical trials.

New Name	Old Name(s)	Activation
TRPV1	Vanilloid Receptor 1 (VR1) OSM9-like Transient Receptor Potential Channel 1 (OTRPC1)	T>43°C; Protons; Capsaicin; Resiniferatoxin; Anandamide
TRPV2	Vanilloid Receptor Like 1 (VRL-1) Growth Factor-regulated Channel (GRC) OSM9-like Transient Receptor Potential Channel 2 (OTRPC2)	T>53°C; Insulin Growth Factor 1
TRPV3	Vanilloid Receptor Like 3 (VRL-3)	T>31°C
TRPV4	Vanilloid Receptor Like 2 (VRL-2) OSM9-like Transient Receptor Potential Channel 4 (OTRPC4) Vanilloid Receptor-mediated-osmotically Activated Channel (VR-OAC) Transient Receptor Potential 12 (TRP12)	T>24°C; Hypo-osmolarity; Phorbol esters; Anandamide; Arachidonic acid
TRPV5	Epithelial Calcium Channel (ECAC) Epithelial Calcium Channel 1 (ECAC1) Calcium Transporter Type 2 (CaT2) OSM9-like Transient Receptor Potential Channel 3 (OTRPC3)	Constitutive
TRPV6	Epithelial Calcium Channel 2 (ECAC2) Calcium Transporter (CaT) Calcium Transporter Type 1 (CaT1) Calcium Transporter-like (CaT-like)	Constitutive

TABLE 1: TRPV nomenclature, synonyms of the vanilloid receptors and their mode of activation.

LIT: [1] A unified nomenclature for the superfamily of TRP cation channels: C. Montell, et al.; Mol. Cell **9,** 229 (2002) ▪ **[2]** The TRP channels, a remarkably functional family: C. Montell, et al.; Cell **108,** 595 (2002) ▪ **[3]** An introduction to TRP channels: I. S. Ramsey, et al.; Annu. Rev. Physiol. **68,** 619 (2006) ▪ **[4]** Transient receptor potential cation channels in disease: B. Nilius, et al.; Physiol. Rev. **87,** 165 (2007) ▪ **[5]** Sensing with TRP channels: T. Voets, et al.; Nat. Chem. Biol. **1,** 85 (2005) ▪ **[6]** TRP channels as cellular sensors: D. E. Clapham; Nature **426,** 517 (2003) ▪ **[7]** Vanilloid (Capsaicin) receptors and mechanisms: A. Szallasi & P. M. Blumberg; Pharmacol. Rev. **51,** 159 (1999) ▪ **[8]** The capsaicin receptor: a heat-activated ion channel in the pain pathway: M. J. Caterina, et al.; Nature **389,** 816 (1997) ▪ **[9]** The cloned capsaicin receptor integrates multiple pain-producing stimuli: M. Tominaga, et al.; Neuron **21,** 531 (1998) ▪ **[10]** More than cool: promiscuous relationships of menthol and other sensory compounds: L. J. Macpherson, et al.; Mol. Cell. Neurosci. **32,** 335 (2006) ▪ **[11]** The pungency of garlic: activation of TRPA1 and TRPV1 in response to allicin: L. J. Macpherson, et al.; Curr. Biol. **15,** 929 (2005) ▪ **[12]** Camphor activates and strongly desensitizes the transient receptor potential vanilloid subtype 1 channel in a vanilloid-independent mechanism: H. Xu, et al.; J. Neurosci. **25,** 8924 (2005) ▪ **[13]** Nitric oxide activates TRP channels by cysteine S-nitrosylation: T. Yoshida, et al.; Nat. Chem. Biol. **2,** 596 (2006) ▪ **[14]** Jellyfish and other cnidarian envenomations cause pain by affecting TRPV1 channels: E. Cuypers, et al.; FEBS Lett. **580,** 5728 (2006) ▪ **[15]** Spider toxins activate the capsaicin receptor to produce inflammatory pain: J. Siemens, et al.; Nature **444,** 208 (2006) ▪ **[16]** Distribution of mRNA for vanilloid receptor subtype 1 (VR1), and VR1-like immunoreactivity, in the central nervous system of the rat and human: E. Mezey, et al.; PNAS **97,** 3655 (2000) ▪ **[17]** Impaired nociception and pain sensation in mice lacking the capsaicin receptor: M. J. Caterina, et al.; Science **288,** 306 (2000) ▪ **[18]** Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia: J. B. Davis, et al.; Nature **405,** 183 (2000) ▪ **[19]** Bradykinin and nerve growth factor release the capsaicin receptor from PtdIns(4,5)P2-mediated inhibition: H. H. Chuang, et al.; Nature **411,** 957 (2001) ▪ **[20]** Sensitization of TRPV1 by EP1 and IP reveals peripheral nociceptive mechanism of prostaglandins: T. Moriyama, et al.; Mol. Pain **1,** 3 (2005) ▪ **[21]** 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: L. Negri, et al.; J. Neurosci. **26,** 6716 (2006) ▪ **[22]** Protease-activated receptor 2 sensitizes the capsaicin receptor transient receptor potential vanilloid receptor 1 to induce hyperalgesia: S. Amadesi, et al.; J. Neurosci. **24,** 4300 (2004) ▪ **[23]** Proteinase-activated receptor 2-mediated potentiation of transient receptor potential vanilloid subfamily 1 activity reveals a mechanism for proteinase-induced inflammatory pain: Y. Dai, et al.; J. Neurosci. **24,** 4293 (2004) ▪ **[24]** TRPV1 function in mouse colon sensory neurons is enhanced by metabotropic 5-hydroxytryptamine receptor activation: T. Sugiuar, et al.; J. Neurosci. **24,** 9521 (2004) ▪ **[25]** Potentiation of capsaicin receptor activity by metabotropic ATP receptors as a possible mechanism for ATP-evoked pain and hyperalgesia: M. Tominaga, et al.; PNAS **98,** 6951 (2001) ▪ **[26]** cAMP-dependent protein kinase regulates desensitization of the capsaicin receptor (VR1) by direct phosphorylation: G. Bhave, et al.; Neuron **35,** 721 (2002) ▪ **[27]** Direct phosphorylation of capsaicin receptor VR1 by protein kinase Cepsilon and identification of two target serine residues: M. Numazaki, et al.; J. Biol. Chem. **277,** 13375 (2002) ▪ **[28]** Induction of vanilloid receptor channel activity by protein kinase C: L. S. Premkumar & G. P. Ahern; Nature **408,** 985 (2000) ▪ **[29]** Phosphorylation of vanilloid receptor 1 by Ca2+/calmodulin-dependent kinase II regulates its vanilloid binding: J. Jung, et al.; J. Biol. Chem. **279,** 7048 (2004) ▪ **[30]** Regulation of Ca2+-dependent desensitization in the vanilloid receptor TRPV1 by calcineurin and cAMP-dependent protein kinase: D. P. Mohapatra & C. Nau; J. Biol. Chem. **280,** 13424 (2005) ▪ **[31]** Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide: P. M. Zygmunt, et al.; Nature **400,** 452 (1999) ▪ **[32]** The endogenous lipid anandamide is a full agonist at the human vanilloid receptor (hVR1): D. Smart, et al.; Br. J. Pharmacol. **129,** 227 (2000) ▪ **[33]** An endogenous capsaicin-like substance with high potency at recombinant and native vanilloid VR1 receptors: S. M. Huang, et al.; PNAS **99,** 8400 (2002) ▪ **[34]** N-oleoyldopamine, a novel endogenous capsaicin-like lipid that produces hyperalgesia: C. J. Chu, et al.; J. Biol. Chem. **278,** 13633 (2003) ▪ **[35]** Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances: S. W. Hwang, et al.; PNAS **97,** 6155 (2000) ▪ **[36]** Capsazepine: a competitive antagonist of the sensory neurone excitant capsaicin: S. Bevan, et al.; Br. J. Pharmacol. **107,** 544 (1992)

Selected Review Articles

The Vanilloid Receptor TRPV1

Biochemical pharmacology of the vanilloid receptor TRPV1: D.N. Cortright & A. Szallasi; Eur. J. Biochem. **271,** 1814 (2004) ▪ Endovanilloids: M. Van Der Stelt & V. Di Marzo; Eur. J. Biochem. **271,** 1827 (2004) ▪ The TRPV1 receptor and nociception: D. C. Immke & N. R. Gavva; Semin. Cell Dev. Biol. **17,** 582 (2006) ▪ TRPV1: a therapeutic target for novel analgesic drugs?: A. Szallasi, et al.; Trends Mol. Med. **12,** 545 (2006) ▪ TRP channels: Targets for the relief of pain: J. D. Levine & N. Alessandri-Haber; Biochim. Biophys. Acta, in press (2007) ▪ Biochemistry and pharmacology of endovanilloids: K. Starowicz, et al.; Pharmacol. Ther. **114,** 13 (2007) ▪ Transient receptor potential channels as drug targets: D. Y. Okuhara, et al.; Expert Opin. Ther. Targets **11,** 391 (2007) ▪ Transient receptor potential cation channels in disease: B. Nilius, et al.; Physiol. Rev. **87,** 165 (2007)

TRPV1 Antagonists

Vanilloid receptor TRPV1 antagonists as the next generation of painkillers. Are we putting the cart before the horse?: A. Szallasi & G. Appendino; J. Med. Chem. **47,** 2717 (2004) ▪ Clinically useful vanilloid receptor TRPV1 antagonists: just around the corner (or too early to tell)?: G. Appendino and A. Szallasi; Prog. Med. Chem. **44,** 145 (2006) ▪ The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept: A. Szallasi, et al.; Nat. Rev. Drug Discov. **6,** 357 (2007)

Endovanilloids, TRPV1 Agonists & Related Products

Allicin

[2-Propene-1-sulfinothioic acid S-2-propenyl ester; Diallyl thiosulfinate]

ALX-350-329-M001 **1 mg**
ALX-350-329-M005 **5 mg**

Activator of TRPV1.

LIT: More than cool: promiscuous relationships of menthol and other sensory compounds: L. J. Macpherson, et al.; Mol. Cell. Neurosci. **32,** 335 (2006)

Anandamide

[AEA; N-Arachidonoylethanolamine; (all-Z)-N-(2-Hydroxyethyl)-5,8,11,14-eicosatetraenamide]

ALX-340-029-M005 **5 mg**

Endogenous ligand for the CB_1 receptor (CB_1: K_i=52nm; CB_2: K_i=1930nm) and TRPV1 (K_i=5.78µM).

LIT: Isolation and structure of a brain constituent that binds to the cannabinoid receptor: W.A. Devane, et al.; Science **258,** 1946 (1992) ▪ The MAP kinase signal transduction pathway is activated by the endogenous cannabinoid anandamide: M. Wartmann, et al.; FEBS Lett. **359,** 133 (1995) ▪ Biochemistry and pharmacology of arachidonylethanolamide, a putative endogenous cannabinoid: C.J. Hillard & W.B. Campbell; J. Lipid Res. **38,** 2383 (1997) ▪ Cannabinoid receptors and their endogenous agonist, anandamide: J. Axelrod & C.C. Felder; Neurochem. Res. **23,** 575 (1998) ▪ Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide: P. M. Zygmunt, et al.; Nature **400,** 452 (1999) ▪ The endogenous lipid anandamide is a full agonist at the human vanilloid receptor (hVR1): D. Smart, et al.; Br. J. Pharmacol. **129,** 227 (2000) ▪ **For a comprehensive bibliography please visit our website.**

N-Arachidonoyldopamine

[N-Arachidonoyl-3-hydroxytyramine; NADA; AA-DA]

ALX-340-049-M001 **1 mg**
ALX-340-049-M005 **5 mg**

Endogenous, specific ligand for the CB_1 receptor (CB_1: K_i=250nM; CB_2: K_i=12µM) and TRPV1 (EC_{50}=50nM) found in nervous tissues.

LIT: N-acyl-dopamines: novel synthetic CB(1) cannabinoid-receptor ligands and inhibitors of anandamide inactivation with cannabimimetic activity in vitro and in vivo: T. Bisogno, et al.; Biochem. J. **351,** 817 (2000) ▪ Synthesis and biological evaluation of novel amides of polyunsaturated fatty acids with dopamine: V. Bezuglov, et al.; Bioorg. Med. Chem. Lett. **11,** 447 (2001) ▪ An endogenous capsaicin-like substance with high potency at recombinant and native vanilloid VR1 receptors: S.M. Huang, et al.; PNAS **99,** 8400 (2002) ▪ Arachidonyl dopamine as a ligand for the vanilloid receptor VR1 of the rat: A. Toth, et al.; Life Sci. **73,** 487 (2003) ▪ Characterisation of the vasorelaxant properties of the novel endocannabinoid N-arachidonoyl-dopamine (NADA): S.E. O'Sullivan, et al.; Br. J. Pharmacol. **141,** 803 (2004) ▪ Modulation of trigeminal sensory neuron activity by the dual cannabinoid-vanilloid agonists anandamide, N-arachidonoyl-dopamine and arachidonyl-2-chloroethylamide: T.J. Price, et al.; Br. J. Pharmacol. **141,** 1118 (2004) ▪ Actions of two naturally occurring saturated N-acyldopamines on transient receptor potential vanilloid 1 (TRPV1) channels: L. De Petrocellis, et al.; Br. J. Pharmacol. **143,** 251 (2004) ▪ **For a comprehensive bibliography please visit our website.**

N-Arachidonoyl-L-serine

[N-[(5Z,8Z,11Z,14Z)-1-Oxo-(5,8,11,14-eicosatetraenyl)]-L-serine; ARA-S]

ALX-340-063-M010 **10 mg**

Endocannabinoid-like brain constituent with similar biological profile like abnormal cannabidiol. Binds weakly to CB_1 and CB_2 receptors and TRPV1.

LIT: N-arachidonoyl L-serine, an endocannabinoid-like brain constituent with vasodilatory properties: G. Milman, et al.; PNAS **103,** 2428 (2006)

Arvanil

[N-[(4-Hydroxy-3-methoxyphenyl)methyl]-5Z,8Z,11Z,14Z-eicosatetraenamide]

ALX-340-042-M005 **5 mg**

„Hybrid" activator of CB_1 receptor (CB_1: K_i=0.5µM; CB_2: K_i=>15µM) and TRPV1 (K_i=0.3µM). Also inhibits anandamide uptake (IC_{50}=3.6µM) and fatty acid amide hydrolase (FAAH) (IC_{50}=3µM).

LIT: Unsaturated long-chain N-acyl-vanillyl-amides (N-AVAMs): vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to CB1 cannabinoid receptors: D. Melck, et al.; BBRC **262,** 275 (1999) ▪ A structure/activity relationship study on arvanil, an endocannabinoid and vanilloid hybrid: V. Di Marzo, et al.; J. Pharmacol. Exp. Ther. **300,** 984 (2002) ▪ Arvanil, a hybrid endocannabinoid and vanilloid compound, behaves as an antihyperkinetic agent in a rat model of Huntington's disease: E. de Lago, et al.; Brain Res. **1050,** 210 (2005) ▪ **For a comprehensive bibliography please visit our website.**

(E)-Capsaicin

[(E)-N-([4-Hydroxy-3-methoxyphenyl]methyl)-8-methyl-6-nonenamide; *trans*-8-Methyl-N-vanillyl-6-nonenamide]

ALX-550-066-M100 **100 mg**

Isolated from *Capsicum* fruit. Constituent of cayenne pepper. Powerful excitant of peripheral sensory nerve endings, specifically unmyelinated afferent neurons (C-fibers).

LIT: Capsaicin: identification, nomenclature, and pharmacotherapy: G.A. Cordell & O.E. Araujo; Ann. Pharmacother. **27,** 330 (1993)

Dihydrocapsaicin

[8-Methyl-N-vanillylnonenamide]

ALX-350-052-M010 **10 mg**
ALX-350-052-M050 **50 mg**

Isolated from *Capsicum* fruit. Dihydro-analog and congener of capsaicin (Prod. No. ALX-550-066) in chili peppers *(Capsicum)*. Dihydrocapsaicin accounts for about 22% of the total capsaicinoids mixture and has about the same pungency as capsaicin.

LIT: Dihydrocapsaicin treatment depletes peptidergic nerve fibers of substance P and alters mast cell density in the respiratory tract of neonatal sheep: R. Ramirez-Romero, et al.; Regul. Pept. **91,** 97 (2000) ▪ Determination of capsaicin and dihydrocapsaicin in capsicum fruits by liquid chromatography-electrospray/time-of-flight mass spectrometry: A. Garces-Claver, et al.; J. Agric. Food Chem. **54,** 9303 (2006)

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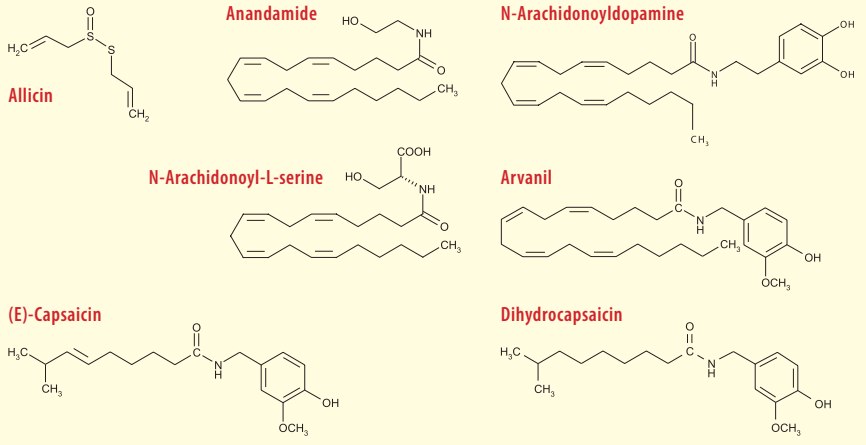


Anandamide – Crosstalk between TRPV1 and Cannabinoid Receptors

In 1999, it was reported that anandamide can activate rat TRPV1 receptors in mesenteric arteries as well as both rat and human TRPV1 in heterologous expression systems. This made this compound the first endogenous ligand for TRPV1 [1,2]. It is widely recognized that anandamide is not stored in vesicles like other mediators but by analogy with other eicosanoids, is produced 'on demand' in a Ca^{2+}- dependent manner [3]. This is the result of a biosynthetic mechanism relying on the existence of a phospholipid precursor for anandamide, and of a Ca^{2+}-sensitive phosphodiesterase for the conversion of this precursor into anandamide.

Although the biosynthetic route underlying the formation of anandamide has been extensively studied, the phospholipase D (PLD) responsible for release of anandamide from its precursor *N*-arachidonoylphosphatidylethanolamine has only been purified recently, cloned and characterized [4]. The discovery of crosstalk between TRPV1 ligands and cannabinoids has added a further layer of complexity to the field of cannabinoids and vanilloids [5]. The endocannabinoid anandamide shows affinity for the cannabinoid receptor (CB1) and TRPV1. The two receptors are co-expressed in dorsal root ganglia and several areas of the CNS. Furthermore, there is also a partial overlapping between the ligand recognition properties of TRPV1 and the anandamide transporter. Clearly, the endocannabinoid and the vanilloid systems are closely related and these discoveries have sparked a heated debate regarding the physiological relevance of this relationship. Although anandamide can activate TRPV1, there are still doubts about whether this compound should be considered a true endovanilloid, since the concentrations required for TRPV1 activation are higher than those needed for CB1 activation. On the other hand, the activity of anandamide is increased *in vivo* by the phosphorylation of TRPV1 by PKA and further potentiated by the entourage effect of various inactive ethanolamides. These are synthesized on demand along with anandamide and inhibit its metabolic degradation by the enzyme fatty acid amide hydrolase (FAAH).

The cannabinoid-vanilloid crosstalk can provide new opportunities for clinical exploitation, since cannabinoid-vanilloid hybrids could overcome some of the drawbacks of the systemic administration of compounds with pure vanilloid activity. Recently, first such cannabinoid-vanilloid hybrids have been synthesized [6].

LIT: [1] Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide: P.M. Zygmunt, et al.; Nature **400,** 452 (1999) ▪ **[2]** The endogenous lipid anandamide is a full agonist at the human vanilloid receptor (hVR1): D. Smart, et al.; Br. J. Pharmacol. **129,** 227 (2000) ▪ **[3]** Formation and inactivation of endogenous cannabinoid anandamide in central neurons: V. Di Marzo, et al.; Nature **372,** 686 (1994) ▪ **[4]** Molecular characterization of a phospholipase D generating anandamide and its congeners: Y. Okamoto, et al.; J. Biol. Chem. **279,** 5298 (2004) ▪ **[5]** Endovanilloid signaling in pain: V. Di Marzo, et al.; Curr. Opin. Neurobiol. **12,** 372 (2002) ▪ **[6]** First „hybrid" ligands of vanilloid TRPV1 and cannabinoid CB2 receptors and non-polyunsaturated fatty acid-derived CB2-selective ligands: G. Appendino, et al.; FEBS Lett. **580,** 568 (2006)

Endovanilloids, TRPV1 Agonists & Related Products *continued*

Docosatetraenylethanolamide

[N-(2-Hydroxyethyl)-7Z,10Z,13Z,16Z-docosatetraenamide; DEA]

ALX-300-148-M005 **5 mg**

Endocannabinoid. Also inhibits adenylate cyclase (IC_{50}=117nM). Does also bind to TRPV1 (K_i=5.63µM).

LIT: Two new unsaturated fatty acid ethanolamides in brain that bind to the cannabinoid receptor: L. Hanus, et al.; J. Med. Chem. **36,** 3032 (1993) ▪ Anandamide, an endogenous cannabimimetic eicosanoid, binds to the cloned human cannabinoid receptor and stimulates receptor-mediated signal transduction: C.C. Felder, et al.; PNAS **90,** 7656 (1993) ▪ Cannabinomimetic behavioral effects of and adenylate cyclase inhibition by two new endogenous anandamides: J. Barg, et al.; Eur. J. Pharmacol. **287,** 145 (1995) ▪ Structure-activity relationship for the endogenous cannabinoid, anandamide, and certain of its analogues at vanilloid receptors in transfected cells and vas deferens: R.A. Ross, et al.; Br. J. Pharmacol. **132,** 631 (2001) ▪ **For a comprehensive bibliography please visit our website.**

Eugenol (high purity)

[2-Methoxy-4-(2-propenyl)phenol]

ALX-350-123-G001 **1 g**

Isolated from clove oil, nutmeg, cinnamon and bay leaf. TRPV1 agonist. Analgesic.

LIT: Activation of vanilloid receptor 1 (VR1) by eugenol: B.H. Yang, et al.; J. Dent. Res. **82,** 781 (2003) ▪ Study of anticandidal activity of carvacrol and eugenol in vitro and in vivo: N. Chami, et al.; Oral. Microbiol. Immunol. **20,** 106 (2005)

Evodiamine

ALX-350-330-M010 **10 mg**

ALX-350-330-M050 **50 mg**

A non-pungent vanilloid receptor agonist isolated from *Evodia rutaecarpa.*

LIT: Capsaicin-like anti-obese activities of evodiamine from fruits of Evodia rutaecarpa, a vanilloid receptor agonist: Y. Kobayashi, et al.; Planta Med. **67,** 628 (2001) ▪ Evodiamine functions as an agonist for the vanilloid receptor TRPV1: L.V. Pearce, et al.; Org. Biomol. Chem. **2,** 2281 (2004)

12(S)-HpETE

[12-(S)-Hydroperoxy-5Z,8Z,10E,14Z-eicosatetraenoic acid]

ALX-340-057-C025 **25 µg**

ALX-340-057-C050 **50 µg**

Endogenous TRPV1 agonist.

LIT: Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances: S.W. Hwang, et al.; PNAS **97,** 6155 (2000) ▪ Bradykinin-12-lipoxygenase-VR1 signaling pathway for inflammatory hyperalgesia: J. Shin, et al.; PNAS **99,** 10150 (2002)

15(S)-HpETE

[15-(S)-Hydroperoxy-5Z,8Z,11Z,13E-eicosatetraenoic acid]

ALX-340-058-C025 **25 µg**

ALX-340-058-C050 **50 µg**

Endogenous TRPV1 agonist.

LIT: Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances: S.W. Hwang, et al.; PNAS **97,** 6155 (2000)

Leukotriene B_4

[LTB_4]

ALX-340-038-C025 **25 µg**

Linoleylethanolamide

[N-(2-Hydroxyethyl)-9Z,12Z-octadecadienamide; LEA]

ALX-300-149-M005 **5 mg**

Endocannabinoid. Does also bind to TRPV1 (K_i=5.60µM).

LIT: Two new unsaturated fatty acid ethanolamides in brain that bind to the cannabinoid receptor: L. Hanus, et al.; J. Med. Chem. **36,** 3032 (1993) ▪ Structure-activity relationship for the endogenous cannabinoid, anandamide, and certain of its analogues at vanilloid receptors in transfected cells and vas deferens: R.A. Ross, et al.; Br. J. Pharmacol. **132,** 631 (2001) ▪ **For a comprehensive bibliography please visit our website.**

Linvanil

ALX-340-044-M005 **5 mg**

Ligand of TRPV1 with low affinity to CB_1 receptor (K_i=3.4µM). Also inhibits anandamide uptake (IC_{50}=8.0µM).

LIT: Unsaturated long-chain N-acyl-vanillyl-amides (N-AVAMs): vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to CB1 cannabinoid receptors: D. Melck, et al.; BBRC **262,** 275 (1999) ▪ Anandamide uptake by human endothelial cells and its regulation by nitric oxide: M. Maccarrone, et al.; J. Biol. Chem. **275,** 13484 (2000) ▪ Overlap between the ligand recognition properties of the anandamide transporter and the VR1 vanilloid receptor: inhibitors of anandamide uptake with negligible capsaicin-like activity: L. De Petrocellis, et al.; FEBS Lett. **483,** 52 (2000) ▪ **For a comprehensive bibliography please visit our website.**

R-1 Methanandamide

[(R)-(+)-Arachidonyl-1'-hydroxy-2'-propylamide; AM 356; N-(2-Hydroxy-1R-methylethyl)-5Z,8Z,11Z,14Z-eicosatetraenamide]

ALX-340-030-M005 **5 mg**

Amidase resistant cannabinoid receptor (CB) agonist (CB_1: K_i=20nM; CB_2: K_i=815nM). The most potent of the series of methyl-anandamides. About 4-fold higher binding affinity for cannabinoid receptor CB_1 than anandamide (Prod. No. ALX-340-029) in the presence of PMSF. Does also bind to TRPV1 (K_i=4.67µM).

LIT: (R)-methanandamide: a chiral novel anandamide possessing higher potency and metabolic stability: V. Abadji, et al.; J. Med. Chem. **37,** 1889 (1994) ▪ Head group analogs of arachidonylethanolamide, the endogenous cannabinoid ligand: A.D. Khanolkar, et al.; J. Med. Chem. **39,** 4515 (1996) ▪ Extrapyramidal effects of methanandamide, an analog of anandamide, the endogenous CB1 receptor ligand: J. Romero, et al.; Life Sci. **58,** 1249 (1996) ▪ Substrate specificity and stereoselectivity of rat brain microsomal anandamide amidohydrolase: W. Lang, et al.; J. Med. Chem. **42,** 896 (1999) ▪ Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide: P.M. Zygmunt, et al.; Nature **400,** 452 (1999) ▪ Structure-activity relationship for the endogenous cannabinoid, anandamide, and certain of its analogues at vanilloid receptors in transfected cells and vas deferens: R.A. Ross, et al.; Br. J. Pharmacol. **132,** 631 (2001) ▪ **For a comprehensive bibliography please visit our website.**

Nonivamide

[Nonylic vanillylamide; N-[4-Hydroxy-3-methoxy-benzyl] nonanamide; N-Vanillylnonamide; Pelargonic acid vanillylamide; Vanillyl pelargonic amide; Pseudocapsaicin]

ALX-550-239-M025 **25 mg**

ALX-550-239-M100 **100 mg**

Synthetic. Minor constituent of hot pepper *(Capsicum oleoresin)*.

LIT: Comparison of nonivamide and capsaicin with regard to their pharmacokinetics and effects on sensory neurons: G. Skofitsch, et al.; Arzneimittel-Forschung **34,** 154 (1984) ▪ The effects of a series of capsaicin analogues on nociception and body temperature in the rat: A.G. Hayes, et al.; Life Sci. **34,** 1241 (1984) ▪ Hypotensive and antinociceptive effect of ether-linked and relatively non-pungent analogues of N-nonanoyl vanillylamide: J. Chen, et al.; Eur. J. Med. Chem. **27,** 187 (1992) ▪ **For a comprehensive bibliography please visit our website.**

N-Oleoyldopamine

[OLDA; N-[2-(3,4-Dihydroxyphenyl)ethyl]-9Z-octadecenamide]

ALX-550-398-M005 **5 mg**

Endogenous TRPV1 agonist (K_i=36nM, EC_{50}=36nM) with weak affinity for rat CB_1 receptor (K_i=1.6µM). Potent inhibitor of 5-lipoxygenase (IC_{50}=7.5nM) and of early and late events in TCR mediated T cell activation.

LIT: Inhibition of arachidonate 5-lipoxygenase by phenolic compounds: S. Iwakami, et al.; Chem. Pharm. Bull. **34,** 3960 (1986) ▪ Inhibition of in vitro prostaglandin and leukotriene biosyntheses by cinnamoyl-beta-phenethylamine and N-acyldopamine derivatives: C.F. Tseng, et al.; Chem. Pharm. Bull. **40,** 396 (1992) ▪ N-oleoyldopamine, a novel endogenous capsaicin-like lipid that produces hyperalgesia: C.J. Chu, et al.; J. Biol. Chem. **278,** 13633 (2003) ▪ Direct evidence for activation and desensitization of the capsaicin receptor by N-oleoyldopamine on TRPV1-transfected cell, line in gene deleted mice and in the rat: J. Szolcsanyi, et al.; Neurosci. Lett. **361,** 155 (2004) ▪ **For a comprehensive bibliography please visit our website.**

Oleoylethanolamide

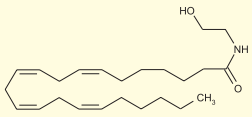
[N-(2-Hydroxyethyl)-9Z-octadecenamide; OEA]

ALX-300-150-M005 **5 mg**

Activates TRPV1. Does not activate cannabinoid receptors (CB) but is a PPARα agonist (EC_{50}=120nM) *in vitro* and *in vivo*; induces satiety through activation of PPARα. Inhibits ceramidase.

LIT: Two new unsaturated fatty acid ethanolamides in brain that bind to the cannabinoid receptor: L. Hanus, et al.; J. Med. Chem. **36,** 3032 (1993) ▪ Cannabinomimetic behavioral effects of and adenylate cyclase inhibition by two new endogenous anandamides: J. Barg, et al.; Eur. J. Pharmacol. **287,** 145 (1995) ▪ Differential regulation of sphingomyelinase and ceramidase activities by growth factors and cytokines. Implications for cellular proliferation and differentiation: E. Coroneos, et al.; J. Biol. Chem. **270,** 23305 (1995) ▪ A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding: R. Gomez, et al.; J. Neurosci. **22,** 9612 (2002) ▪ Activation of TRPV1 by the satiety factor oleoylethanolamide: G.P. Ahern; J. Biol. Chem. **278,** 30429 (2003) ▪ **For a comprehensive bibliography please visit our website.**

CONTINUED ON PAGE 5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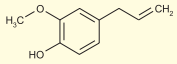
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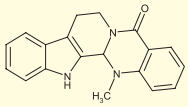
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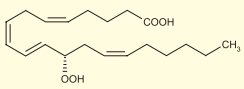
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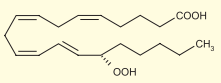
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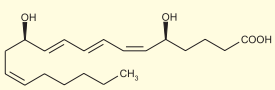
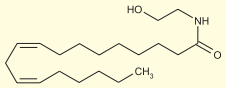
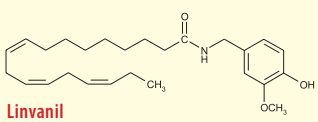
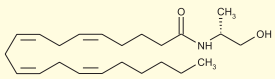
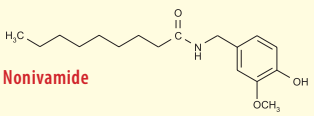

Leukotriene B_4


Linoleylethanolamide


Linvanil


R-1 Methanandamide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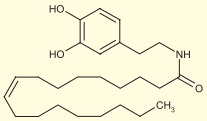
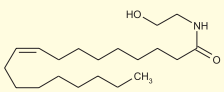

N-Oleoyldopamine


Oleoylethanolamide

Endovanilloids, TRPV1 Agonists & Related Products *cont.*

Olvanil

[NE-19550; N-Vanillyloleoylamide]

ALX-340-041-M005 5 mg
ALX-340-041-M010 10 mg

„Hybrid" activator of CB_1 receptor (CB_1: K_i=1.6µM; CB_2: K_i=15µM) and TRPV1 (K_i=0.4µM; EC_{50}=33nM (human); EC_{50}=6.71nM (rat)). Also inhibits anandamide uptake (IC_{50}=9µM, K_i=14.1µM) and fatty acid amide hydrolase (FAAH) (IC_{50}=20µM).

LIT: NE-19550: a novel, orally active anti-inflammatory analgesic: L. Brand, et al.; Drugs Exp. Clin. Res. **13,** 259 (1987) ▪ The antinociceptive effect and pharmacokinetics of olvanil following oral and subcutaneous dosing in the mouse: W.K. Sietsema, et al.; Life Sci. **43,** 1385 (1988) ▪ Olvanil: more potent than capsaicin at stimulating the efferent function of sensory nerves: S.R. Hughes, et al.; Eur. J. Pharmacol. **219,** 481 (1992) ▪ Interactions between synthetic vanilloids and the endogenous cannabinoid system: V. Di Marzo, et al.; FEBS Lett. **436,** 449 (1998) ▪ Unsaturated long-chain N-acyl-vanillyl-amides (N-AVAMs): vanilloid receptor ligands that inhibit anandamide-facilitated transport and bind to CB1 cannabinoid receptors: D. Melck, et al.; BBRC **262,** 275 (1999) ▪ Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide: P.M. Zygmunt, et al.; Nature **400,** 452 (1999) ▪ Anandamide transport inhibition by the vanilloid agonist olvanil: M. Beltramo & D. Piomelli; Eur. J. Pharmacol. **364,** 75 (1999) ▪ **For a comprehensive bibliography please visit our website.**

ROPA

[Resiniferonol 9,13,14-ortho-phenylacetate]

ALX-350-074-M005 5 mg

20-Deacylated derivative of resiniferatoxin (Prod. No. ALX-550-179) and tinyatoxin. Not active as a capsaicin analog. Useful as starting material for synthesis of resiniferatoxin analogs.

For Bulk inquire!

The Resiniferatoxin Source™

ALEXIS® BIOCHEMICALS **High Purity High Activity Low Price** *Step up to the Source™*

Resiniferatoxin (high purity)

[RTX]

ALX-550-179-M001 1 mg
ALX-550-179-M005 5 mg

Isolated from *Euphorbia poisonii*. Ultrapotent capsaicin analog.

LIT: For a comprehensive bibliography please visit our website.

For Bulk inquire!

Resiniferatoxin-type Phorboid Vanilloids

PDDHV

[Phorbol 12,13-didecanoate 20-homovanillate]

ALX-550-371-M001 1 mg
ALX-550-371-M005 5 mg

Resiniferatoxin-type phorboid vanilloid with capsaicin-like selectivity for TRPV1 (K_i=60nM).

LIT: Resiniferatoxin-type phorboid vanilloids display capsaicin-like selectivity at native vanilloid receptors on rat DRG neurons and at the cloned vanilloid receptor VR1: A. Szallasi, et al.; Br. J. Pharmacol. **128,** 428 (1999) ▪ **For a comprehensive bibliography please visit our website.**

PDNHV

[Phorbol 12,13-dinonanoate 20-homovanillate]

ALX-550-372-M001 1 mg
ALX-550-372-M005 5 mg

Resiniferatoxin-type phorboid vanilloid with capsaicin-like selectivity for TRPV1.

LIT: Resiniferatoxin-type phorboid vanilloids display capsaicin-like selectivity at native vanilloid receptors on rat DRG neurons and at the cloned vanilloid receptor VR1: A. Szallasi, et al.; Br. J. Pharmacol. **128,** 428 (1999) ▪ Phorboid 20-homovanillates induce apoptosis through a VR1-independent mechanism: A. Macho, et al.; Chem. Biol. **7,** 483 (2000) ▪ **For a comprehensive bibliography please visit our website.**

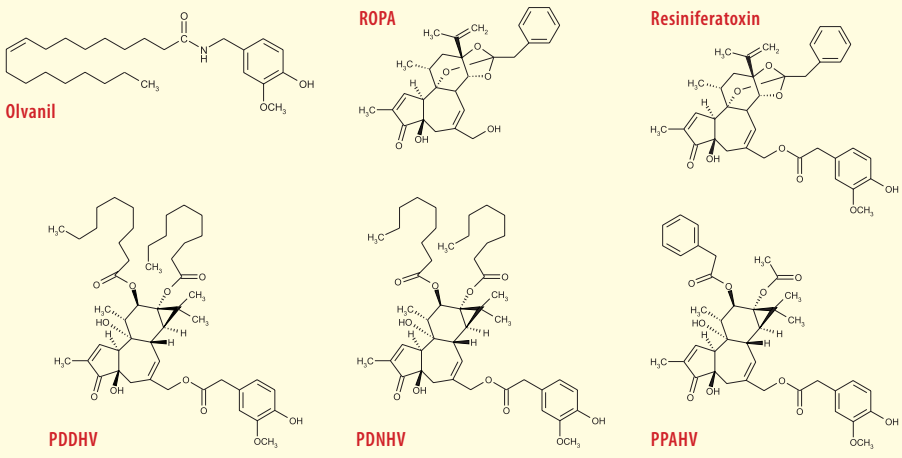
PPAHV

[Phorbol 12-phenylacetate 13-acetate 20-homovanillate]

ALX-550-355-M001 1 mg
ALX-550-355-M005 5 mg

Non-pungent resiniferatoxin-type phorboid vanilloid. Agonist at rat TRPV1 (EC_{50} between 3 and 10µM) but virtually inactive at human TRPV1 (EC_{50}>10µM). Induces apoptosis through a TRPV-independent mechanism.

LIT: Synthesis and evaluation of phorboid 20-homovanillates: discovery of a class of ligands binding to the vanilloid (capsaicin) receptor with different degrees of cooperativity: G. Appendino, et al.; J. Med. Chem. **39,** 3123 (1996) ▪ A novel agonist, phorbol 12-phenylacetate 13-acetate 20-homovanillate, abolishes positive cooperativity of binding by the vanilloid receptor: A. Szallasi, et al.; Eur. J. Pharmacol. **299,** 221 (1996) ▪ A non-pungent resiniferatoxin analogue, phorbol 12-phenylacetate 13 acetate 20-homovanillate, reveals vanilloid receptor subtypes on rat trigeminal ganglion neurons: L. Liu, et al.; Neuroscience **84,** 569 (1998) ▪ Functional and desensitizing effects of the novel synthetic vanilloid- like agent 12-phenylacetate 13-acetate 20-homovanillate (PPAHV) in the perfused rat hindlimb: C.D. Griffiths, et al.; Br. J. Pharmacol. **131,** 1408 (2000) ▪ Phorboid 20-homovanillates induce apoptosis through a VR1-independent mechanism: A. Macho, et al.; Chem. Biol. **7,** 483 (2000) ▪ Pharmacological differences between the human and rat vanilloid receptor 1 (VR1): P. McIntyre, et al.; Br. J. Pharmacol. **132,** 1084 (2001) ▪ **For a comprehensive bibliography please visit our website.**



PAb to TRPV1

PAb to TRPV1 (human)

ALX-210-417-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 7-21 (T^7DLGAAADPLQKDTC^{21}) of human TRPV1. **SPECIFICITY:** Recognizes human TRPV1. **APPLICATION:** IHC (FS), ICC. **BP:** ALX-170-005.

LIT: Deletion of vanilloid receptor 1-expressing primary afferent neurons for pain control: L. Karai, et al.; J. Clin. Invest. **113,** 1344 (2004)

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Latest Insight

TRCP3 and TRCP6 promote neuronal survival

Transient receptor potential (TRP) channels constitute a family of cation-permeable channels with variety of physiological functions. One subfamily is formed by TRPC (canonical) members. In a recent report, TRPC3 and TRPC6 have been shown to promote survival of cerebellar granule neurons (CGNs), by a mechanism which triggers cAMP/Ca^{2+}-response element binding protein (CREB).

LIT: TRPC channels promote cerebellar granule neuron survival: Y. Jia, et al.; Nat. Neurosci. **10,** 559 (2007)

PAb to TRPC3 (CT)

PSC-3905-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to 14 aa near the C-terminus of human TRPC3 (short transient receptor potential channel 3). **SPECIFICITY:** Recognizes human, mouse and rat TRPC3. **APPLICATION:** WB. **BP:** PSC-3905P.

PAb to TRPC3 (NT)

PSC-3895-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to 14 aa near the N-terminus of human TRPC3 (short transient receptor potential channel 3). **SPECIFICITY:** Recognizes human and mouse TRPC3. **APPLICATION:** WB. **BP:** PSC-3895P.

PAb to TRPC6 (CT)

PSC-3897-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to 14 aa near the C-terminus of human TRPC6 (short transient receptor potential channel 6). **SPECIFICITY:** Recognizes human, mouse and rat TRPC6. **APPLICATION:** WB. **BP:** PSC-3897P.

PAb to TRPC6 (NT)

PSC-3899-C100 100 µg

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to 14 aa near the N-terminus of human TRPC6 (short transient receptor potential channel 6). **SPECIFICITY:** Recognizes human and mouse TRPC6. **APPLICATION:** WB. **BP:** PSC-3899P.

TRPV1 Antagonists & Related Products

Capsazepine

ALX-550-145-M005 5 mg
ALX-550-145-M025 25 mg

Analog of capsaicin (Prod. No. ALX-550-066) that acts as a specific capsaicin antagonist.

LIT: Capsazepine, a novel capsaicin antagonist, selectively antagonises the effects of capsaicin in the mouse spinal cord in vitro: L. Urban & A. Dray; Neurosci. Lett. **134,** 9 (1991) ▪ For a comprehensive bibliography please visit our website.

6′-Iodononivamide

ALX-350-122-M005 5 mg
ALX-350-122-M010 10 mg

Potent competitive TRPV1 antagonist (IC_{50}=10nM against 100nM capsaicin; Prod. No. ALX-550-066). Convenient replacement for capsazepine (Prod. No. ALX-550-145) in most of the *in vitro* preparations currently used to assess the activity of putative vanilloid receptor agonists.

LIT: Halogenation of a capsaicin analogue leads to novel vanilloid TRPV1 receptor antagonists: G. Appendino, et al.; Br. J. Pharmacol. **139,** 1417 (2003) ▪ The taming of capsaicin. Reversal of the vanilloid activity of N-acylvanillamines by aromatic iodination: G. Appendino, et al.; J. Med. Chem. **48,** 4663 (2005)

Technical Note
Isomer-free, Pure I-RTX

5′-Iodoresiniferatoxin (I-RTX) is an ultra-potent inhibitor of TRPV1 activation [1-5]. To use this molecular probe it is key essential to use isomer-free and pure I-RTX since 6′-iodo-resiniferatoxin shows agonistic activity [6]. G. Appendino's group has developed a convenient synthesis of high purity I-RTX [7].

LIT: [1] Iodo-resiniferatoxin, a new potent vanilloid receptor antagonist: P. Wahl, et al.; Mol. Pharmacol. **59,** 9 (2001) ▪ **[2]** Functional properties of the high-affinity TRPV1 (VR1) vanilloid receptor antagonist (4-hydroxy-5-iodo-3-methoxyphenylacetate ester) iodo-resiniferatoxin: G.R. Seabrook, et al.; J. Pharmacol. Exp. Ther. **303,** 1052 (2002) ▪ **[3]** Neurogenic responses mediated by vanilloid receptor-1 (TRPV1) are blocked by the high affinity antagonist, iodo-resiniferatoxin: M. Rigoni, et al.; Br. J. Pharmacol. **138,** 977 (2003) ▪ **[4]** Antitussive activity of iodo-resiniferatoxin in guinea pigs: M. Trevisani, et al.; Thorax **59,** 769 (2004) ▪ **[5]** Kinetics of penetration influence the apparent potency of vanilloids on TRPV1: J. Lazar, et al.; Mol. Pharmacol. **69,** 1166 (2006) ▪ **[6]** Synthesis and in vitro evaluation of a novel iodinated resiniferatoxin derivative that is an agonist at the human vanilloid VR1 receptor: M.E. McDonnell, et al.; Bioorg. Med. Chem. Lett. **12,** 1189 (2002) ▪ **[7]** A convenient synthesis of 5′-iodoresiniferatoxin (I-RTX): A. Ech-Chahad, et al.; Nat. Prod. Commun. **1,** 1147 (2006)

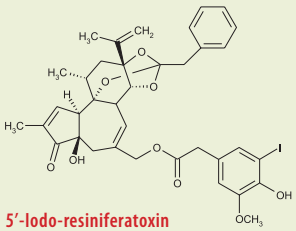
5′-Iodo-resiniferatoxin

[I-RTX]

ALX-550-389-M001 1 mg

Binds to TRPV1 receptors expressed in HEK293 cells (K_i=5.8nM) and to native rat TRPV1 receptors (K_i=4.8nM). At least 40-fold more potent than capsazepine (Prod. No. ALX-550-145). Blocks capsaicin-induced currents in oozytes expressing TRPV1 (IC_{50}=3.9nM). Potently blocks pain responses elicited by capsaicin (Prod. No. ALX-550-066) *in vivo*.

LIT: For a comprehensive bibliography please visit our website.



IBTU

[N-(4-Chlorobenzyl)-N′-(4-hydroxy-3-iodo-5-methoxybenzyl) thiourea]

ALX-550-384-M001 1 mg
ALX-550-384-M005 5 mg

Potent TRPV1 antagonist with marked selectivity for the calcium entry-linked receptor subpopulation of TRPV1.

LIT: For a comprehensive bibliography please visit our website.

Isovelleral

ALX-550-356-M001 1 mg
ALX-550-356-M005 5 mg

TRPV1 antagonist.

LIT: Comparison of the antimicrobial and cytotoxic activities of twenty unsaturated sesquiterpene dialdehydes from plants and mushrooms: H. Anke & O. Sterner; Planta Med. **57,** 344 (1991) ▪ The stimulation of capsaicin-sensitive neurones in a vanilloid receptor-mediated fashion by pungent terpenoids possessing an unsaturated 1,4-dialdehyde moiety: A. Szallasi, et al.; Br. J. Pharmacol. **119,** 283 (1996) ▪ The preparation and bioactivities of (-)-isovelleral: M. Jonassohn, et al.; Bioorg. Med. Chem. **5,** 1363 (1997)

JYL-79

ALX-550-296-M001 1 mg
ALX-550-296-M005 5 mg

Potent TRPV1 agonist (K_i=19nM). About 300-fold more potent than capsaicin (Prod. No. ALX-550-066). *For product details and chemical structure see page 7.*

LIT: For a comprehensive bibliography please visit our website.

JYL-273

ALX-550-390-M001 1 mg
ALX-550-390-M005 5 mg

Potent TRPV1 agonist (K_i=11nM). About 500-fold more potent than capsaicin (Prod. No. ALX-550-066). *For product details and chemical structure see page 7.*

LIT: For a comprehensive bibliography please visit our website.

JYL-827

ALX-550-391-M001 1 mg
ALX-550-391-M005 5 mg

Potent TRPV1 agonist. *For product details and chemical structure see page 7.*

LIT: For a comprehensive bibliography please visit our website.

JYL-1413

ALX-550-392-M001 1 mg
ALX-550-392-M005 5 mg

Potent TRPV1 antagonist which blocks TRPV1 on the membrane more selectively rather than in internal stores. *For product details and chemical structure see page 7.*

LIT: For a comprehensive bibliography please visit our website.

JYL-1433

ALX-550-393-M001 1 mg
ALX-550-393-M005 5 mg

Full and potent TRPV1 antagonist. *For product details and chemical structure see page 7.*

LIT: For a comprehensive bibliography please visit our website.

JYL-1511

ALX-550-394-M001 1 mg
ALX-550-394-M005 5 mg

Potent TRPV1 antagonist. RTX binding affinity (K_i=50.4nM), agonism (calcium influx; EC_{50}=32.4nM) and antagonism (IC_{50}=3.37nM). *For product details and chemical structure see page 7.*

LIT: For a comprehensive bibliography please visit our website.

MSK-195

ALX-550-396-M001 1 mg
ALX-550-396-M005 5 mg

Potent analgesic with EC_{50}=0.96µg/kg in the acetic acid-induced writhing test. *For product details and chemical structure see page 7.*

LIT: For a comprehensive bibliography please visit our website.

PSY-279

ALX-550-397-M001 1 mg
ALX-550-397-M005 5 mg

TRPV1 agonist. *For product details and chemical structure see page 7.*

LIT: For a comprehensive bibliography please visit our website.

Ruthenium red

ALX-550-295-M500 500 mg
ALX-550-295-G001 1 g

Blocks TRPV1. Capsaicin and calcium antagonist. Inhibitor of Ca^{2+}/Mg^{2+}-ATPase.

LIT: Ruthenium red as a stain for electron microscopy. Some new aspects of its application and mode of action: R. Dierichs; Histochemistry **64,** 171 (1979) ▪ The effects of ruthenium red on the response of guinea-pig ileum to capsaicin: L.A. Chahl; Eur. J. Pharmacol. **169,** 241 (1989) ▪ Capsaicin desensitization in vivo is inhibited by ruthenium red: R. Amann, et al.; Eur. J. Pharmacol. **186,** 169 (1990) ▪ Ruthenium red as a capsaicin antagonist: R. Amann & C.A. Maggi; Life Sci. **49,** 849 (1991) ▪ For a comprehensive bibliography please visit our website.

SB366791

[N-(3-Methoxyphenyl)-4-chlorocinnamide]

ALX-550-388-M001 1 mg
ALX-550-388-M005 5 mg
ALX-550-388-M025 25 mg

Potent and selective TRPV1 antagonist.

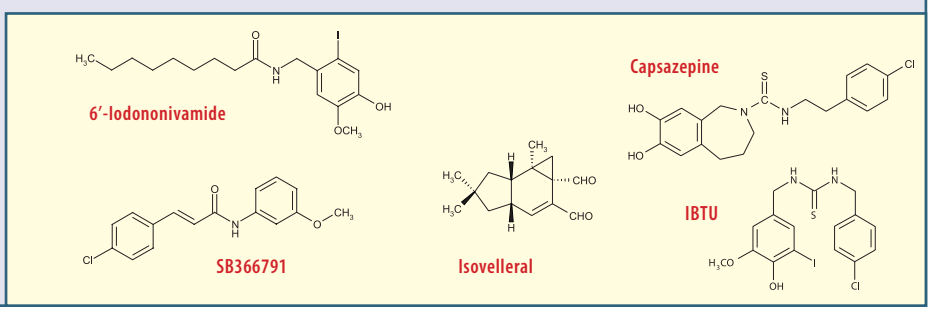
LIT: Identification of SB-366791, a potent and selective antagonist of vanilloid receptor-1: H.K. Rami, et al.; Drugs Fut. **27 (Supply A),** 411 (2002) ▪ Identification and charakterisation of SB-366791, a potent and selective vanilloid receptor (VR1/TRPV1) antagonist: M.J. Gunthorpe, et al.; Neuropharmacology **46,** 133 (2004) ▪ Effects of the novel TRPV1 receptor antagonist SB366791 in vitro and in vivo in the rat: A. Varga, et al.; Neurosci. Lett. **385,** 137 (2005) ▪ Vanilloid receptor agonists and antagonists are mitochondrial inhibitors: how vanilloids cause non-vanilloid receptor mediated cell death: A. Athanasiou, et al.; BBRC **354,** 50 (2007)

SU-154

ALX-550-395-M001 1 mg
ALX-550-395-M005 5 mg

TRPV1 antagonist. Nc-hydroxy thiourea analog with high analgesic potency in the acetic writhing assay.

LIT: For a comprehensive bibliography please visit our website.



TRPV1 Antagonists & Related Products

After the identification of resiniferatoxin (RTX) as a archetypal vanilloid receptor TRPV1 agonist with a binding potency approximately 4 orders of magnitude greater than that of capsaicin (CAP) (RTX: K_i=0.13nM, CAP: K_i=1,700nM in CHO/TRPV1 [1]), and on the basis of previously published SAR studies on RTX [2] Jeewoo Lee, et al. proposed a hypothetical pharmacophore model for the interaction with the capsaicin binding site of TRPV1 in which four groups, 4-hydroxy-3-methoxyphenyl (A-region), C_{20}-ester (B-region), orthophenyl (C1-region) and C_3-keto (C2-region) represent principal pharmacophores (see Figure 2). On the basis of this model, two ultrapotent TRPV1 agonists, JYL-79 and JYL-273, with K_i values of 19nM and 11nM, respectively, in a [^{3}H]RTX binding assay, have been synthesized and characterized [3, 4]. Relative to capsaicin these compounds appear to be approximately 300 and 500 times more potent.

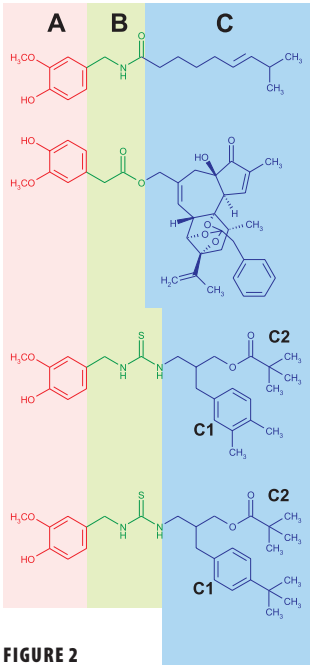
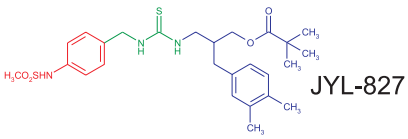
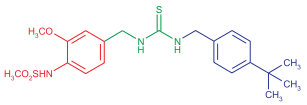


FIGURE 2

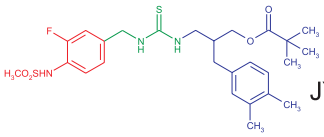
The isosteric replacement of the phenolic hydroxyl groups in the potent TRPV1 agonists JYL-79 and JYL-273 with the alkylsulfonamido group provided a series of compounds which are effective antagonists to the action of capsaicin on rat TRPV1 [5]. As a prototype, *N*-[2-(3,4-dimethylbenzyl)-3-pivaloyloxypropyl]-*N'*-[4-(methylsulfonylamino)benzyl]thiourea (JYL-827) showed a high binding affinity with a Ki value of 29.3nM for the inhibition of [^{3}H]RTX binding and potent antagoism with an IC_{50} value of 67nM for the inhibition of Ca^{2+} uptake in response to capsaicin, displaying partial agonism [6]. The SAR of the prototype has been examined extensively based on the pharmacophoric regions represented in Figure 2 [5, 7].



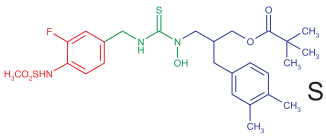
A similar compound is *N*-(4-*tert*-butylbenzyl)-*N'*-[3-methoxy-4-(methylsulfonylamino)benzyl]-thiourea (JYL-1511) [6].



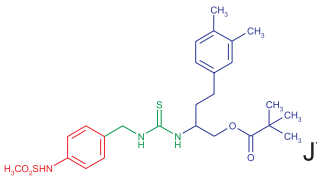
In the SAR of the A-region, JYL-1433 (the 3-fluoro analog of JYL-827) was a full and potent TRPV1 antagonist with an IC_{50}=7.8nM [5].



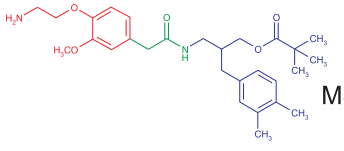
In the SAR of the B-region, compounds with potent analgesic activity were found. Despite its relatively week *in vitro* potency, SU-154, an Nc-hydroxy thiourea analog, exhibited high analgesic potency in the acetic writhing assay [7].



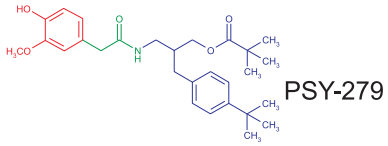
Among a series of derivatives in which the distances between the proposed four pharmacophores in the lead compound JYL-827 have been varied, the JYL-1413 has shown to be a better TRPV1 antagonist than the lead compound (although the binding affinity is lower) [8]. It is assumed that JYL-1413 blocks TRPV1 on the membrane more selectively rather than in internal stores.



The related compound *N*-[2-(3,4-dimethylbenzyl)-3-(pivaloyloxy)propyl]-2-[4-(2-aminoethoxy)-3-methoxyphenyl]acetamide (MSK-195) is a potent analgesic with an EC_{50}=0.96µg/kg in the acetic acid-induced writhing test [4].



Another amide based RTX analog, *N*-[2-(4-*tert*-butylbenzyl)-3-(pivaloyloxy)propyl]-2-[4-hydroxy-3-methoxyphenyl]acetamide (PSY-279) approaches the high agonism of RTX in the CHO/TRPV1 cells (RTX: EC_{50}=0.27nM, PSY-279: EC_{50}=0.29nM) [4, 9].



Finally two other high affinity TRPV1 receptor antagonists were synthesized and characterized by the group including Jeewoo Lee, MK056 (KJM-429) and SC0030 (JYL-1421) [10-12].

Literature References

LIT: [1] The cloned rat vanilloid receptor VR1 mediates both R-type binding and C-type calcium response in dorsal root ganglion neurons: A. Szallasi, et al.; Mol. Pharmacol. **56,** 581 (1999) ▪ **[2]** Similarities and differences in the structure-activity relationships of capsaicin and resiniferatoxin analogues: C.S. Walpole, et al.; J. Med. Chem. **39,** 2939 (1996) ▪ **[3]** N-(3-Acyloxy-2-benzylpropyl)-N'-(4-hydroxy-3-methoxybenzyl) thiourea derivatives as potent vanilloid receptor agonists and analgesics: J. Lee, et al.; Bioorg. Med. Chem. **9,** 19 (2001) ▪ **[4]** Phenolic modification as an approach to improve the pharmacology of the 3-acyloxy-2-benzylpropyl homovanillic amides and thioureas, a promising class of vanilloid receptor agonists and analgesics: J. Lee, et al.; Bioorg. Med. Chem. **10,** 1171 (2002) ▪ **[5]** N-(3-acyloxy-2-benzylpropyl)-N'-[4-(methylsulfonylamino)benzyl]thiourea analogues: novel potent and high affinity antagonists and partial antagonists of the vanilloid receptor: J. Lee, et al.; J. Med. Chem. **46,** 3116 (2003) ▪ **[6]** High-affinity partial agonists of the vanilloid receptor: Y. Wang, et al.; Mol. Pharmacol. **64,** 325 (2003) ▪ **[7]** Analysis of structure-activity relationships for the 'B-region' of N-(3-acyloxy-2-benzylpropyl)-N(')-[4-(methylsulfonylamino) benzyl]thiourea analogues as vanilloid receptor antagonists: discovery of an N-hydroxythiourea analogue with potent analgesic activity: J. Lee, et al.; Bioorg. Med. Chem. Lett. **14,** 2291 (2004) ▪ **[8]** Analysis of structure–activity relationships with the N-(3-acyloxy-2-benzylpropyl)-N'-[4-(methylsulfonylamino)benzyl]-thioureatemplate for vanilloid receptor 1 antagonism: J. Lee, et al.; Bioorg. Med. Chem. **12,** 3411 (2004) ▪ **[9]** Structure-activity relationships of simplified resiniferatoxin analogues with potent VR1 agonism elucidates an active conformation of RTX for VR1 binding: J. Lee, et al.; Bioorg. Med. Chem. **12,** 1055 (2004) ▪ **[10]** High affinity antagonists of the vanilloid receptor: Y. Wang, et al.; Mol. Pharmacol. **62,** 947 (2002) ▪ **[11]** Novel non-vanilloid VR1 antagonist of high analgesic effects and its structural requirement for VR1 antagonistic effects: Y.G. Suh, et al.; Bioorg. Med. Chem. Lett. **13,** 4389 (2003) ▪ **[12]** N-4-Substituted-benzyl-N'-tert-butylbenzyl thioureas as vanilloid receptor ligands: investigation on the role of methanesulfonamido group in antagonistic activity: H.G. Park, et al.; Bioorg. Med. Chem. Lett. **14,** 787 (2004)

Compound	RTX Binding Affinity (K_i: nM)	Antagonism (Calcium Influx; EC_{50}: nM)	Antagonism (IC50: nM)	Lit.
Capsaicin	1800	44.8	NE	
Capsazephine	1300	NE	520	
JYL-79	17.4	1.97	NE	[3, 4]
JYL-273	6.35	2.83	NE	[3, 4]
JYL-827	29.3	weak	67	[5, 7]
JYL-1413	390	weak	33.7	[8]
JYL-1433	54	NE	7.8	[5]
JYL-1511	50.4	17.4% (32.4 nM)	84.1% (3.37 nM)	[6]
MSK-195	603	240	NE	[4]
PSY-279	15	0.29	NE	[4, 9]
SU-154	212	NE	94	[7]
SC0030	53.5	NE	9,2	[10-12]
MK056	62.6	NE	54	[10-12]

TABLE 3: Summary of the pharmacological activity of compounds characterized by J. Lee, et al. Data from Rat TRV1 in CHO cells.

TRPV1 Modulation

Adenosine 5'-triphosphate . 2Na
[ATP . 2Na]

ALX-480-021-G001	1 g
ALX-480-021-G005	5 g

Bradykinin

ALX-152-006-M005	5 mg
ALX-152-006-M025	25 mg

LIT: For a comprehensive bibliography please visit our website.

MAb to Bradykinin (MBK3)

ALX-804-647-R100 100 µl

CLONE: MBK3. **ISOTYPE:** Mouse IgG1. **IMMUNOGEN:** Bradykinin. **SPECIFICITY:** Recognizes bradykinin from various species. **APPLICATION:** WB.

LIT: For a comprehensive bibliography please visit our website.

PAb to Bradykinin B_2 Receptor

ALX-210-872-R200 200 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to aa 356-391 of human B_2R (bradykinin B_2 receptor). **SPECIFICITY:** Recognizes human, mouse and rat B_2R. **APPLICATION:** IP, WB.

LIT: For a comprehensive bibliography please visit our website.

PAb to Prokineticin Receptor 1 (human) (NT)

CVL-PAB0192-1 200 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to the N-terminus of human prokineticin receptor 1. **SPECIFICITY:** Recognizes human prokineticin receptor 1 (45kDa). **APPLICATION:** IHC (PS), WB, FACS.

PAb to Prokineticin 1 (human) (NT)

CVL-PAB0190-1 200 µl

From rabbit. **IMMUNOGEN:** Synthetic peptide corresponding to the N-terminus of human prokineticin 1 (PK1; EG-VEGF). **SPECIFICITY:** Recognizes human prokineticin 1. **APPLICATION:** IHC (PS), WB, FACS.

MAb to TRK Receptor (human) (MGR12)

ALX-804-575-C100 100 µg

CLONE: MGR12. **ISOTYPE:**Mouse IgG1. **IMMUNOGEN:** SKNBE neuroblastoma cell line transfected with TrkA (TRK receptor). **SPECIFICITY:** Recognizes an epitope present in the extracellular domain of human TrkA. Detects a band of ~140kDa by IP. **APPLICATION:** FC, IHC (FS), IP.

LIT: For a comprehensive bibliography please visit our website.

Prostaglandin E_2
[Dinoprostone]

ALX-340-028-M001	1 mg
ALX-340-028-M005	5 mg
ALX-340-028-M010	10 mg

Serotonin . HCl

ALX-550-328-M050	50 mg
ALX-550-328-M250	250 mg
ALX-550-328-G001	1 g

LIT: For a comprehensive bibliography please visit our website.

The TRP (Transient Receptor Potential) Superfamily

TRPV4 & Related Products

The relevance of anandamide as an endovanilloid is further highlighted by its identification as an endogenous activator of TRPV4 (OTRPC4; VRL-2; VR-OAC; TRP12) [1-4], an observation which adds to the growing receptor promiscuity of this important endogenous lipid. The activation of TRPV4 by anandamide is indirect and mediated by oxidative metabolites of arachidonic acid. TRPV4 was originally characterised as an osmotically regulated ion channel sensing changes in cell volume, but was later discovered to be activated not only by physical stimuli, such as cell swelling or heat. It is basically a thermosensor similar to TRPV1 but insensitive to capsaicin. TRPV4 is activated under physiological conditions by the non-tumor promoter phorboid 4α-phorbol didecanoate (4α-PDD) [2]. 4α-PDD does not activate TRPV1 like phorbol 12,13-didecanoate 20-homovanillate (PDDHV), another resiniferatoxin-type phorboid vanilloid. TRPV4 is an interesting new pharmacological target whose potential is just beginning to surface.

LIT: [1] Anandamide and arachidonic acid use epoxyeicosatrienoic acids to activate TRPV4 channels: H. Watanabe, et al.; Nature **424,** 434 (2003) ▪ **[2]** Activation of TRPV4 channels (hVRL-2/mTRP12) by phorbol derivatives: H. Watanabe, et al.; J. Biol. Chem. **277,** 13569 (2002) ▪ **[3]** The TRPV4 channel: structure-function relationship and promiscuous gating behaviour: B. Nilius, et al.; Pflugers Arch. **446,** 298 (2003) ▪ **[4]** TRPV4 calcium entry channel: a paradigm for gating diversity: B. Nilius, et al.; Am. J. Physiol. Cell Physiol. **286,** C195 (2004)

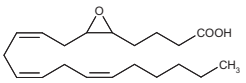
TRPV4 Agonist

5',6'-Epoxyeicosatrienoic acid

ALX-340-059-C025	25 µg
ALX-340-059-C050	50 µg

Endogenous TRPV4 agonist (K_i=150nM).

LIT: Anandamide and arachidonic acid use epoxyeicosatrienoic acids to activate TRPV4 channels: H. Watanabe, et al.; Nature **424,** 434 (2003)



TRPV4 Activator

4α-Phorbol 12,13-didecanoate BULK
[4α-PDD]

ALX-445-006-M001	1 mg
ALX-445-006-M005	5 mg

Activator of TRPV4. Negative control for phorbol 12,13-didecanoate (PDD) (Prod. No. ALX-445-002).

LIT: Activation of TRPV4 channels (hVRL-2/mTRP12) by phorbol derivatives: H. Watanabe, et al.; J. Biol. Chem. **277,** 13569 (2002) ▪ TRPV4 calcium entry channel: a paradigm for gating diversity: B. Nilius, et al.; Am. J. Physiol. Cell Physiol. **286,** C195 (2004) ▪ Antidipsogenic effects of a TRPV4 agonist, 4alpha-phorbol 12,13-didecanoate, injected into the cerebroventricle: H. Tsushima and M. Mori; Am. J. Physiol. Regul. Integr. Comp. Physiol. **290,** R1736 (2006) ▪ Determinants of 4 alpha-phorbol sensitivity in transmembrane domains 3 and 4 of the cation channel TRPV4: J. Vriens, et al.; J. Biol. Chem. **282,** 12796 (2007) ▪ For a comprehensive bibliography please visit our website.

Activator of TRPV1, V2 & V3

2-Aminoethoxydiphenyl borate

ALX-400-045-M100 100 mg

Cell permeable modulator of Ins(1,4,5)-P_3-induced Ca^{2+} release. A prototype drug for a group of structurally related calcium channel blockers in human platelets. Has been shown, in the absence of other stimuli, to activate TRPV1, V2 and V3, but not TRPV4, V5 and V6 expressed in HEK293 cells.

LIT: 2APB, 2-aminoethoxydiphenyl borate, a membrane-penetrable modulator of Ins(1,4,5)P3-induced Ca2+ release: T. Maruyama, et al.; J. Biochem. **122,** 498 (1997) ▪ For a comprehensive bibliography please visit our website.

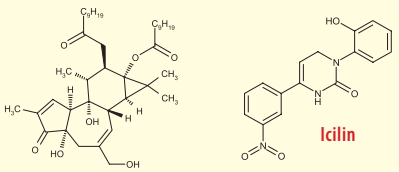
TRPM8 [CMR1]/TRPA1 Activator

NEW Icilin BULK

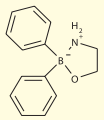
ALX-420-037-M001	1 mg
ALX-420-037-M005	5 mg
ALX-420-037-M025	25 mg

Cooling agent. Strongly activates TRPM8 (cold menthol receptor 1 (CMR1)) and TRPA1 (at 10- to 100-fold higher concentration). Induces currents in TRPM8 expressing HEK 293 cells (EC_{50}=0.36mM) more potently than menthol or low temperatures.

LIT: AG-3-5: a chemical producing sensations of cold: E.T. Wei and D.A. Seid; J. Pharm. Pharmacol. **35,** 110 (1983) ▪ TRPM8 activation by menthol, icilin, and cold is differentially modulated by intracellular pH: D.A. Andersson, et al.; J. Neurosci. **24,** 5364 (2004)



4α-Phorbol 12,13-didecanoate



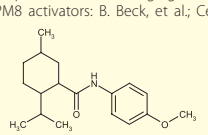
2-Aminoethoxydiphenyl borate

Coming Soon!

WS-12 – An Ultra Potent TRPM8 Agonist

B. Beck, et al. recently described the new compound WS-12 as the highest-affinity TRPM8 (transient receptor potential melastatin B) ligand known to date, with an EC_{50} value about 2000 times lower than that of menthol.

LIT: Prospects for prostate cancer imaging and therapy using high-affinity TRPM8 activators: B. Beck, et al.; Cell Calcium **41,** 285 (2007)



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