

# The Universal Hotness, Part 3: Capsaicin Family<sup>a</sup>

## Chemistry and application in flavor

Michael Zviely, CIC; mzviely@cathay-israel-chemistry.com

**C**apsaicin (8-methyl-N-vanillyl-*trans*-6-nonenamide; FEMA# 3404, CAS# 404-86-4) (**F-1**) occurs in the *Capsicum* species. It has a mild, warm-herbaceous odor, with very pungent taste, and it is applied for its pungent taste in meaty and spicy formulations.<sup>b</sup>

Capsaicin is at the head of a list of capsaicinoids, all having high Scoville heat unit values (**F-2**). As a comparison, piperine has only 100,000 Scoville heat units.

The capsaicin transient receptor potential (TRP) TRPV1 is the principal transduction channel for nociception. Excessive TRPV1 activation causes pathological pain.<sup>1</sup> Capsaicin selectively binds to a protein known as TRPV1, which resides on the membranes of pain- and heat-sensing neurons. TRPV1 is a heat-activated calcium channel, which opens between 37–45°C. When capsaicin binds to TRPV1, it causes the channel to open below 37°C, which is why capsaicin is linked to the sensation of heat. Prolonged activation of these neurons by capsaicin depletes presynaptic substance P, one of the body's neurotransmitters for pain and heat. Neurons that do not contain TRPV1 are unaffected.<sup>2</sup>

Capsaicin and the oleoresin capsicum are popularly used in both OTC and prescription topical analgesics. Used as a counterirritant, capsaicin is believed to have a desensitizing effect on nerves, thus providing substantial relief from the pain associated with osteoarthritis, rheumatoid arthritis, herpes zoster and diabetic neuropathy.<sup>c</sup>

Capsaicin can be synthesized in a three-stage process, starting from bromomethyl-heptene (3-heptene, 7-bromo-2-methyl-, (3E)-; CAS# 59721-83-4) and diethyl malonate (CAS# 105-53-3) to give, in the first stage, methylheptenyl diethyl malonate, which gives under reflux in presence of KOH methylnonenoic acid. Further reaction of methylnonenoic acid with aminomethyl methoxyphenol (CAS# 7149-10-2) yields capsaicin (**F-3**).<sup>3</sup>

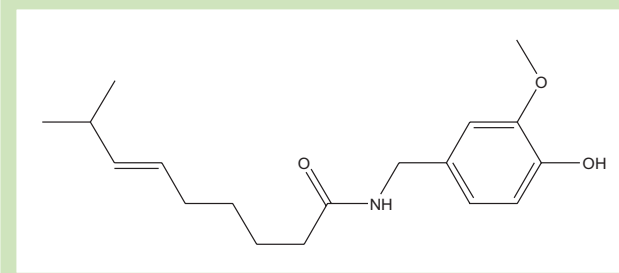
<sup>a</sup>Part 1 of this series, which ran in the October 2011 issue of *Perfumer & Flavorist* magazine, dealt with allyl isothiocyanate (The Universal Hotness, Part 1: Allyl Isothiocyanate, pp. 66–69); Part 2 on piperine (The Universal Hotness, Part 2: Piperine, pp. 46–49) ran in the November 2011 issue of *Perfumer & Flavorist* magazine.

<sup>b</sup>Some information on organoleptic properties and uses is taken from FRM 2001 Database of Perfumery Materials & Performance, Boelens Aroma Chemicals Information Services, The Netherlands.

<sup>c</sup>Information from The Good Scents Company.

Capsaicin (8-methyl-N-vanillyl-*trans*-6-nonenamide)

F-1



Additional groups of molecules that have structural and functional similarity exist in ginger. Ginger is the rhizome of the plant *Zingiber officinale* Rosc. The characteristic odor and flavor—bitter, aromatic, spicy, citrusy—of ginger is caused by a mixture of zingerone, shogaols and gingerols (**F-4**).

The last plant to be referred in this three-part series is Sichuan pepper. This is the outer pod of the tiny fruit of a number of species in the genus *Zanthoxylum*, mostly grown in Asia as a spice. This plant is not related to black pepper or to chili peppers. Sichuan pepper has a unique aroma and flavor that is not hot or pungent like black pepper or chili peppers. It has slight lemony flavor, which creates a tingly numbness in the mouth that sets the stage for hot spices.<sup>4</sup> According to the cited book, “Sichuan pepper produces a strange tingling, buzzing, numbing sensation that is something like the effect of carbonated drinks or of a mild electrical current (touching the terminals of a nine-volt battery to the tongue). The active ingredient (hydroxy- $\alpha$ -sanshool, (2E,6Z,8E,10E)-N-(2-hydroxy-2-methylpropyl)dodeca-2,6,8,10-tetraenamide; CAS# 83883-107 [**F-5**]) appears to act on several differ-

## Physical Data for Capsaicin

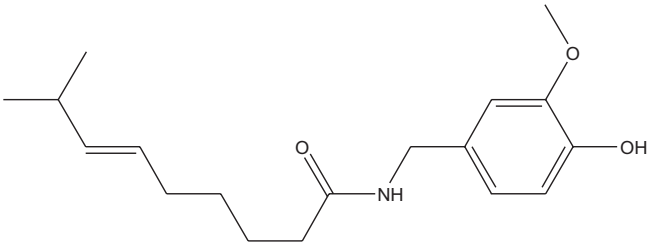
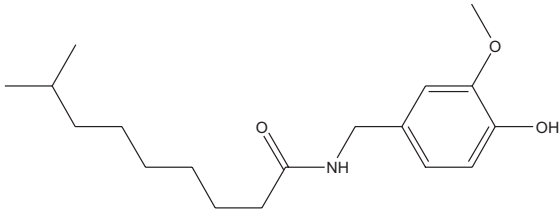
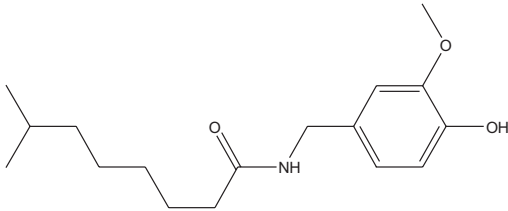
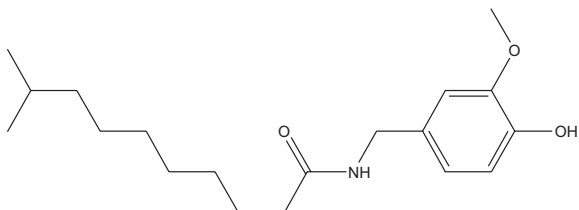
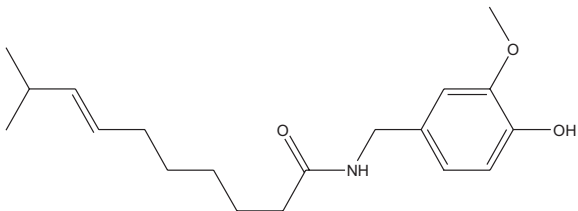
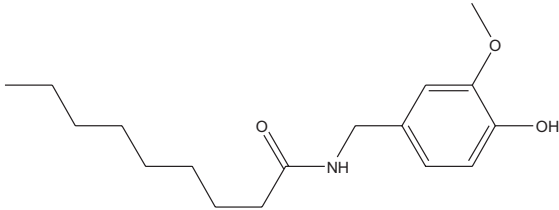
Appearance: White to pale yellow crystalline powder

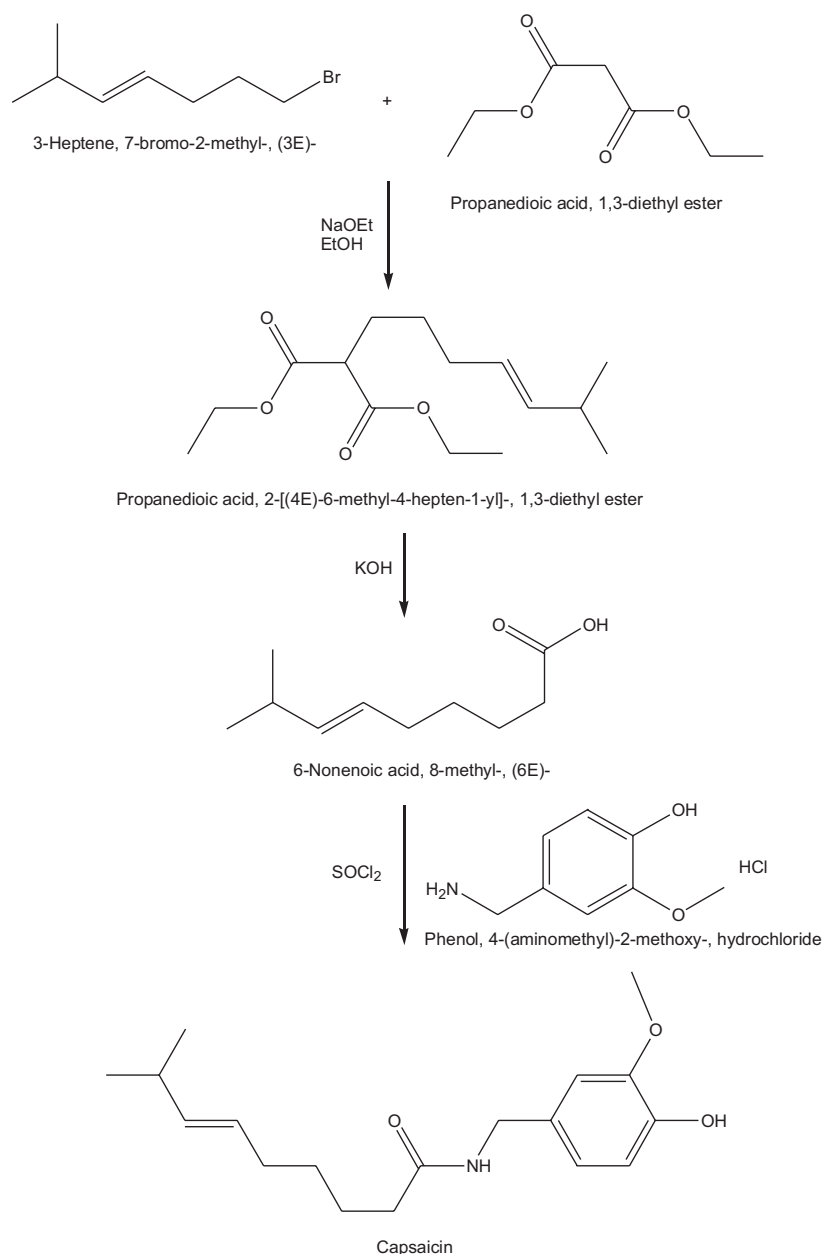
Molecular weight: 305.41

Molecular formula: C<sub>18</sub>H<sub>27</sub>NO<sub>3</sub>

Melting point: 62–65°C

Log P: 4.0

Structure	Name, FEMA# (where applicable), CAS#	Scoville heat units
	Capsaicin, FEMA# 3404, CAS# 404-86-4	$16 \times 10^6$
	Dihydrocapsaicin, CAS#19408-84-5	$15 \times 10^6$
	Nordihydrocapsaicin, CAS# 28789-35-7	$9.1 \times 10^6$
	Homdihydrocapsaicin, CAS# 279-06-5	$8.6 \times 10^6$
	Homocapsaicin, CAS# 58493-48-4	$8.6 \times 10^6$
	Nonivamide, CAS# 2444-46-4	$9 \times 10^6$



ent kinds of nerve endings at once to induce sensitivity to touch and cold in nerves that are ordinarily nonsensitive. So it theoretically may cause a kind of general neurological confusion.”

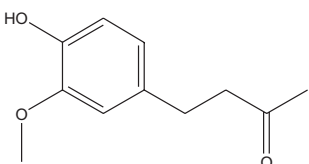
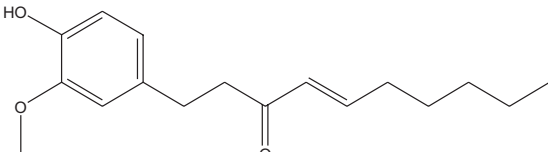
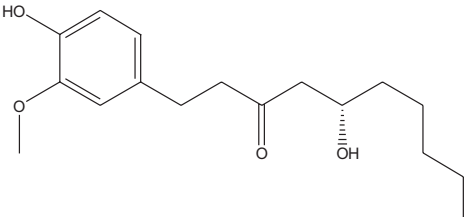
Hydroxy- $\alpha$ -sanshool activates a subset of sensory dorsal root ganglion neurons by inhibiting two-pore potassium channels. In research published this year, the authors investigated a tingle-evoking sanshool analog, isobutylalkenyl amide.<sup>5</sup> Thirty-four percent of dorsal root ganglion neurons tested responded to isobutylalkenyl amide, with 29% of them also responding to menthol, 29% to cinnamic aldehyde, 66% to capsaicin, and subsets responding to two or more TRP agonists.

#### References

1. H Li, S Wang, AY Chuang, BE Cohen and H-H Chuang, *Proc Natl Acad Sci USA*, **108**(20), 8497–8502 (2011).
2. MJ Caterina, MA Schumacher, M Tominaga, TA Rosen, JD Levine and D Julius, *Nature*, **389**(6653), 816–824 (1997).
3. S Zhou, CN Pat 101,717,346, Artificial synthesis method of capsaicin homologue. (2010).
4. H McGee, *On Food and Cooking: The Science and Lore of the Kitchen*, 2nd Edition, Scribner, New York (2004).
5. AH Klein, CM Sawyer, KLZanotto, MA Ivanov, A Margaret, SCheung, MI Carstens, S Furrer, CT Simons, JP Slack and E Carstens, *J Neurophys*, **105**(4), 1701–1710 (2011).

Molecules with functional and structural similarities to capsaicin

F-4

Structure	Name, FEMA# (if applicable), CAS#	Remarks
	Zingerone, FEMA# 3124, CAS# 122-48-5	Sweet aromatic and vanilla-like with a slightly spicy flavor.  Applied in vanilla and fruity flavorings, with ginger and aromatic nuances.
	Shogaol, CAS# 555-66-8	160,000 Scoville heat units
	Gingerol, CAS# 23513-14-6	60,000 Scoville heat units

Hydroxy- $\alpha$ -sanshool, (2E,6Z,8E,10E)-N-(2-hydroxy-2-methylpropyl)dodeca-2,6,8,10-tetraenamide

F-5

