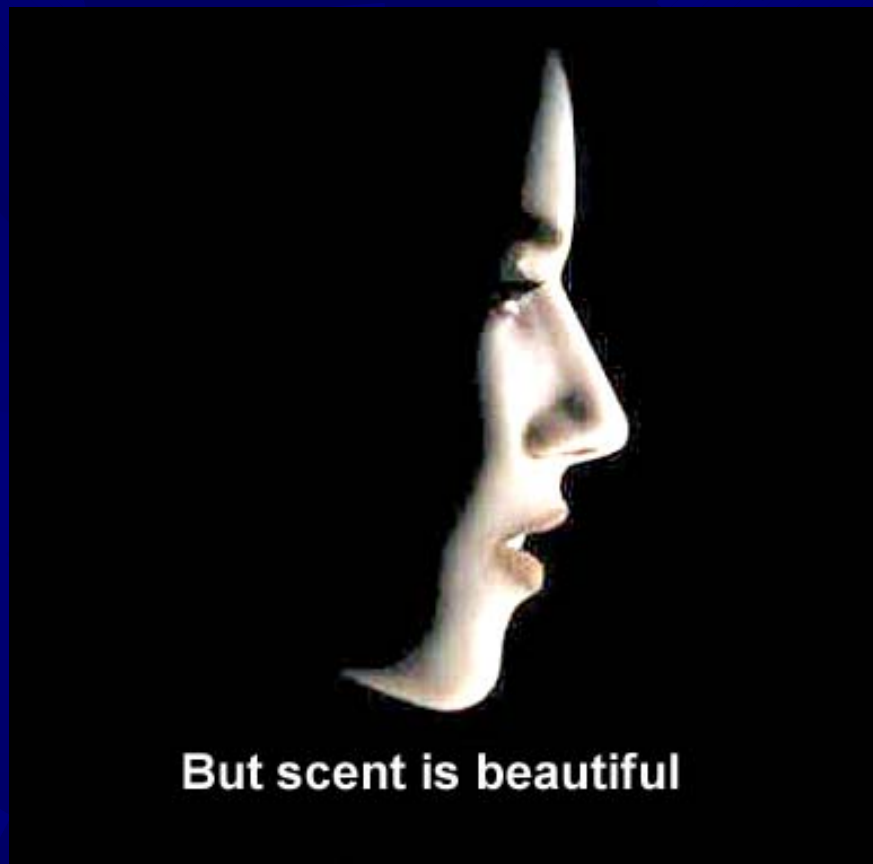


New Cooling Related Compounds



Society of Flavor Chemist's

November 20, 2008

Revised Jan. 20, 2009

World Production of Menthol

Table 1 Worldwide Sources of Menthol (2007)

Source	Metric ton
India (natural)	9,700
China (natural)	2,120
Symrise (synthetic)	3,600
Takasago (synthetic)	1,500
Other synthetic ^a	1,200
Brazil (natural) ^b	450
Taiwan (natural) ^b	300
Japan (natural) ^b	300
Total ^c	19,170

^aOther synthetic includes menthol produced from menthone as well as racemic menthol.

^bPrimarily from *Mentha arvensis* oil or crude menthol ex India (or China).

^cTotal menthol volume based on Clark's estimate (4).

Leffingwell, Handbook of Cosmetic Science and Technology, 3d edition (2009), In Press

World Uses of Menthol

Table 2 2007 Estimated Worldwide Consumption of Menthol % by Product Category

Product category	Menthol %
Oral hygiene	28.00
Pharmaceuticals	26.60
Tobacco	25.30
Confectionaries	11.00
Shaving products	7.00
Miscellaneous	2.10

Source: From Ref. 4.

Leffingwell, Handbook of Cosmetic Science and Technology, 3d edition (2009), In Press

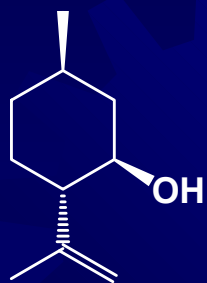
Thermo TRP Receptors & Agonists

Table 4 Thermoreceptor Agonists

Chemical agonist (botanical source)	ThermoTRP
Capsaicin (hot chilli peppers, e.g., Tabasco)	TRPV1
Piperine (black pepper corns)	TRPV1
Allicin (fresh garlic)	TRPV1, TRPA1
Camphor (Cinnamomum camphora)	TRPV3, TRPV1
D-9-Tetrahydrocannabinol (Cannabis sativa)	TRPV2, TRPA1
2-Aminoethoxydiphenyl borate (synthetic)	TRPV1, TRPV2, TRPV3
4-a-phorbol 12,13-didecanoate (synthetic)	TRPV4
(-)-Menthol (peppermint)	TRMP8, TRPV3
1,8-Cineole, eucalyptol (eucalyptus)	TRPM8
WS-3 (synthetic)	TRPM8
Icilin (synthetic)	TRPM8, TRPA1
Cinnamaldehyde (cinnamon, cassia)	TRPA1, TRPV3
Allyl isothiocyanate (mustard, horseradish)	TRPA1
Benzyl isothiocyanate (mustard, horseradish)	TRPA1
Phenethyl isothiocyanate (mustard, horseradish)	TRPA1

Leffingwell, Handbook of Cosmetic Science and Technology, 3d edition (2009), In Press

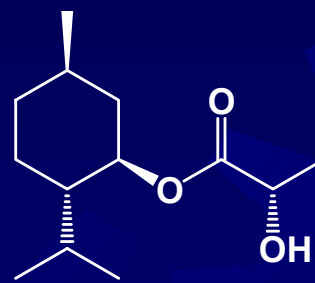
Menthoxy Cooling Agents Thru GRAS 23



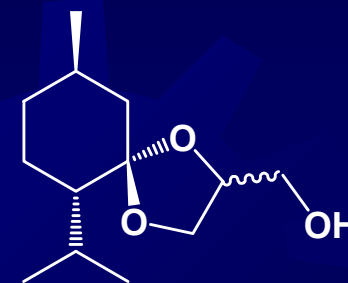
(-)- Isopulegol
FEMA 2962
0.25 X Menthol



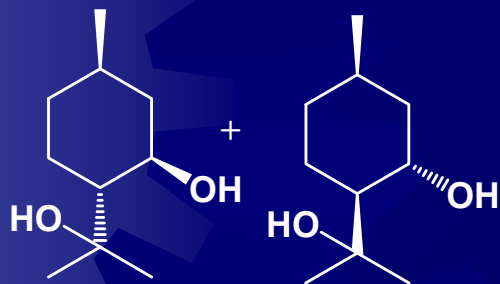
Coolact-10
FEMA 3784
0.2-0.4 X Menthol



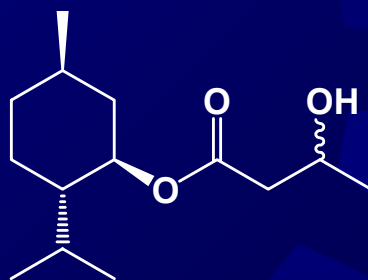
Frescolat ML
FEMA 3748
0.43 X Menthol



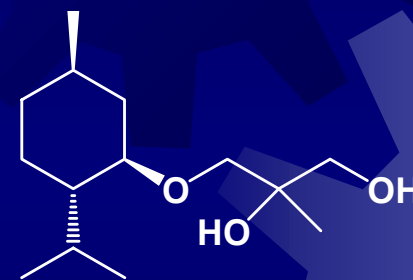
Frescolat MGA
FEMA 3807
0.41 X Menthol



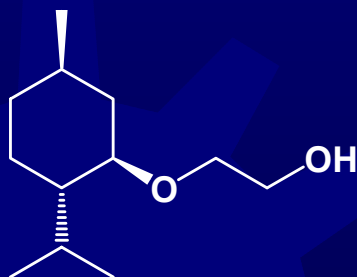
Coolact 38D
FEMA 4053
0.11 X Menthol



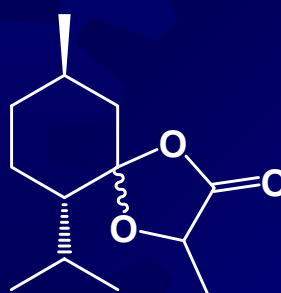
MHB
FEMA 4308
~0.45 X Menthol



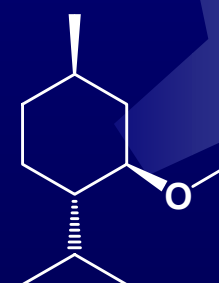
MMPD
FEMA 3849



Coolact 5
FEMA 4154

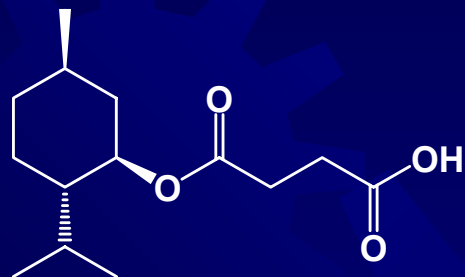


Menthone lactic acid ketal
FEMA 4285

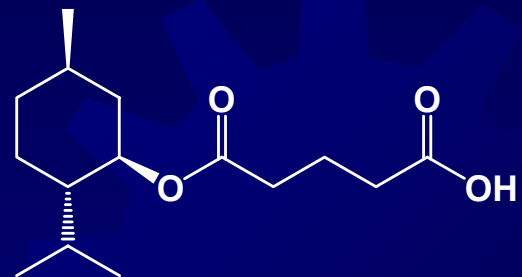


Menthyl methyl ether
FEMA 4054

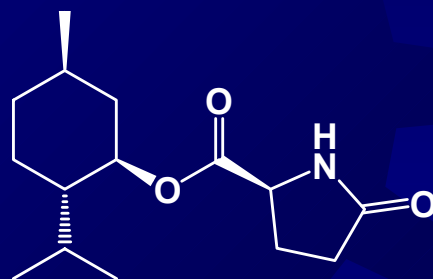
More Menthoxy Cooling Agents Thru GRAS 23



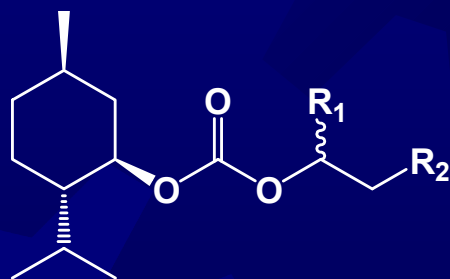
Monomenthyl succinate
FEMA 3810
~0.2-0.3 X Menthol



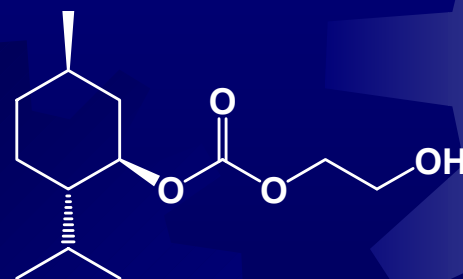
Monomenthyl glutarate
FEMA 4006
~0.1-0.15 Menthol



Questice
FEMA 4155

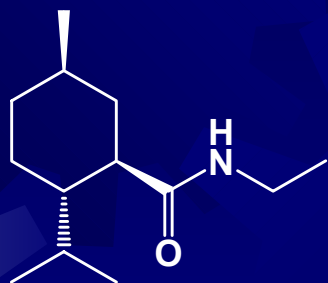


Menthol propylene glycol carbonate
FEMA 3806
Isomer 1 – R₁=OH, R₂=CH₃
Isomer 1 – R₁=CH₃, R₂=OH

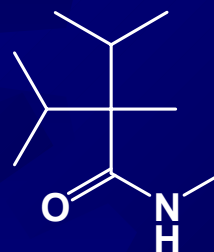


Menthol ethylene glycol carbonate
Frescolat MGC
FEMA 3805

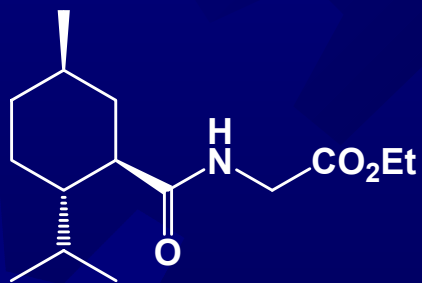
Amide GRAS Cooling Agents Thru GRAS 23



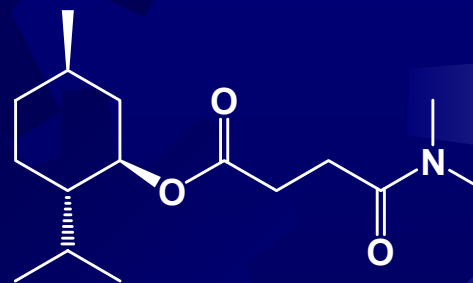
WS-3
FEMA 3455
1.5 X Menthol



WS-23
FEMA 3804
0.75 X Menthol



WS-5
FEMA 4309
4 X Menthol



Menthyl N,N-dimethylsuccinamide
FEMA 4230

Givaudan's New Powerful GRAS Cooling Agents

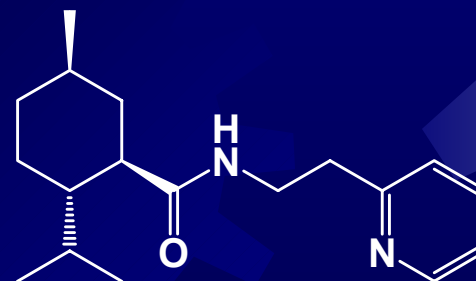
Table 1 Comparison of data for the TRPM8 activation, expressed as EC₅₀ and iso-intensity to menthol of selected menthane carboxamides

Cpd.	R ₁	R ₂	EC ₅₀ (μM)	Isointensity (ppm)	CAS no.
2a	CH ₃	CH ₃	25.6	2.0	39668-77-4
2b	C ₂ H ₅	H	3.6	1.5	68489-00-9
2c	CH ₂ C ₆ H ₅	H	3.5	2.0	73435-72-0
2d	4-C ₆ H ₄ SO ₂ NH ₂	H	0.7	0.5	852379-29-4
2e	C ₆ H ₅	H	0.6	1.0	824947-52-6
2f	2-C ₆ H ₄ CONH ₂	H	0.6	0.5	915962-26-4
2g	4-C ₆ H ₄ OCH ₃	H	0.5	2.0	68489-09-8
2h	4-C ₆ H ₄ CONH ₂	H	0.4	0.15	847564-94-7
2i	4-C ₆ H ₄ CH ₂ OH	H	0.4	1.0	847564-90-3
2j	4-C ₆ H ₄ CH ₂ CN	H	0.2	0.2	852379-28-3
2k	CH ₂ CH ₂ (2-C ₅ H ₄ N)	H	0.1	0.05	926913-58-8
2l	2-C ₆ H ₅ OCH ₃	H	5.1	2.0	824947-60-6
2m	CH ₂ CH ₂ CH ₂ OCH(CH ₃) ₂	H	0.9	0.7	663218-92-6

Furrer et al., Chem. Percept. (June 2008) 1:119–126; Galopin et al., US Patent 7,414,152 (August 19, 2008); Bell et al., WO2007019719 (Feb. 22, 2007)

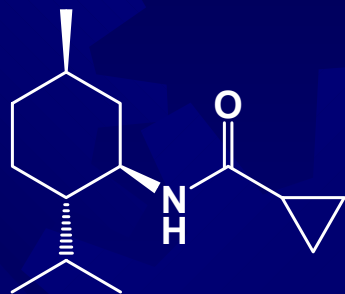


2j = FEMA 4496
10 X Menthol



2k = FEMA 4549
40-100 X Menthol

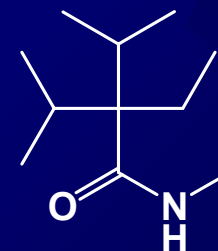
New GRAS 24 Related Cooling Agents



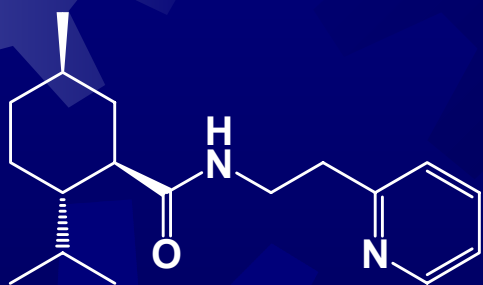
**Menthyl
cyclopropanecarboxamide**
FEMA 4558

Not Cooling – Umami-like

U.S. Patent Application 20080292763



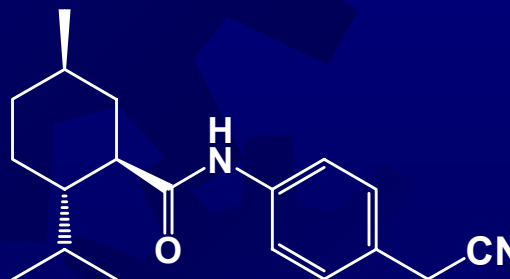
**N-Ethyl-2,2-diisopropyl-
butanamide**
FEMA 4557



**N-(2-(Pyridin-2-yl)ethyl)-3-p-
menthanecarboxamide**

FEMA 4549

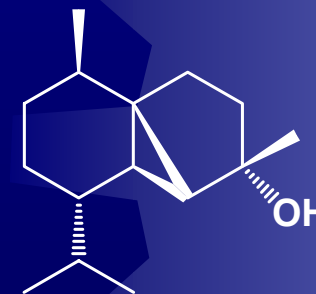
40-100 X Menthol



**N-p-Benzeneacetonitrile-
menthanecarboxamide**

FEMA 4496

10 X Menthol



Cubebol
FEMA 4497

Fig. 11
EFFICACY OF COOLANTS ON THE TRPM8 RECEPTOR
(BY Ca^{++} FLUOROMETRIC ASSAY)
Adapted from : Refs. 73,74,88

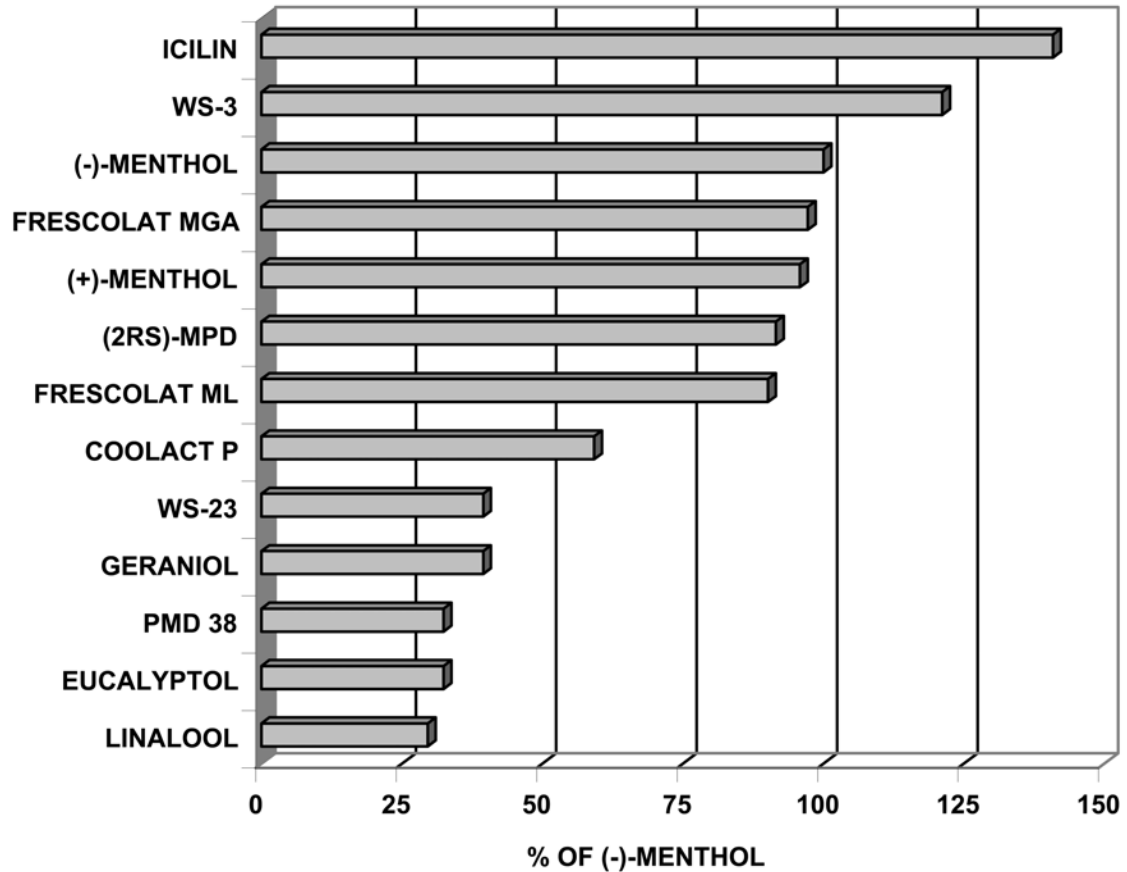
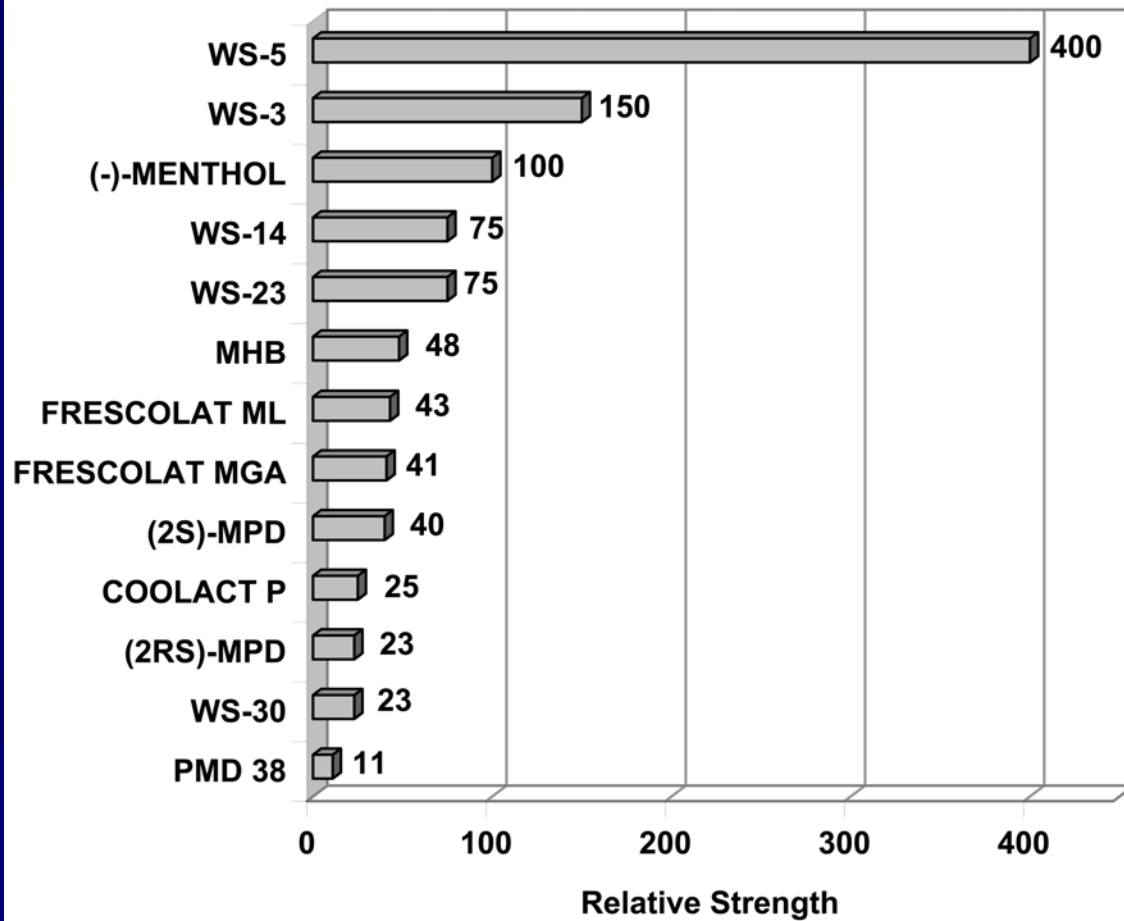


Fig. 8
APPROXIMATE "ACCEPTED" COOLING
STRENGTHS vs. MENTHOL (as 100)
Adapted from : Ref. 73,74



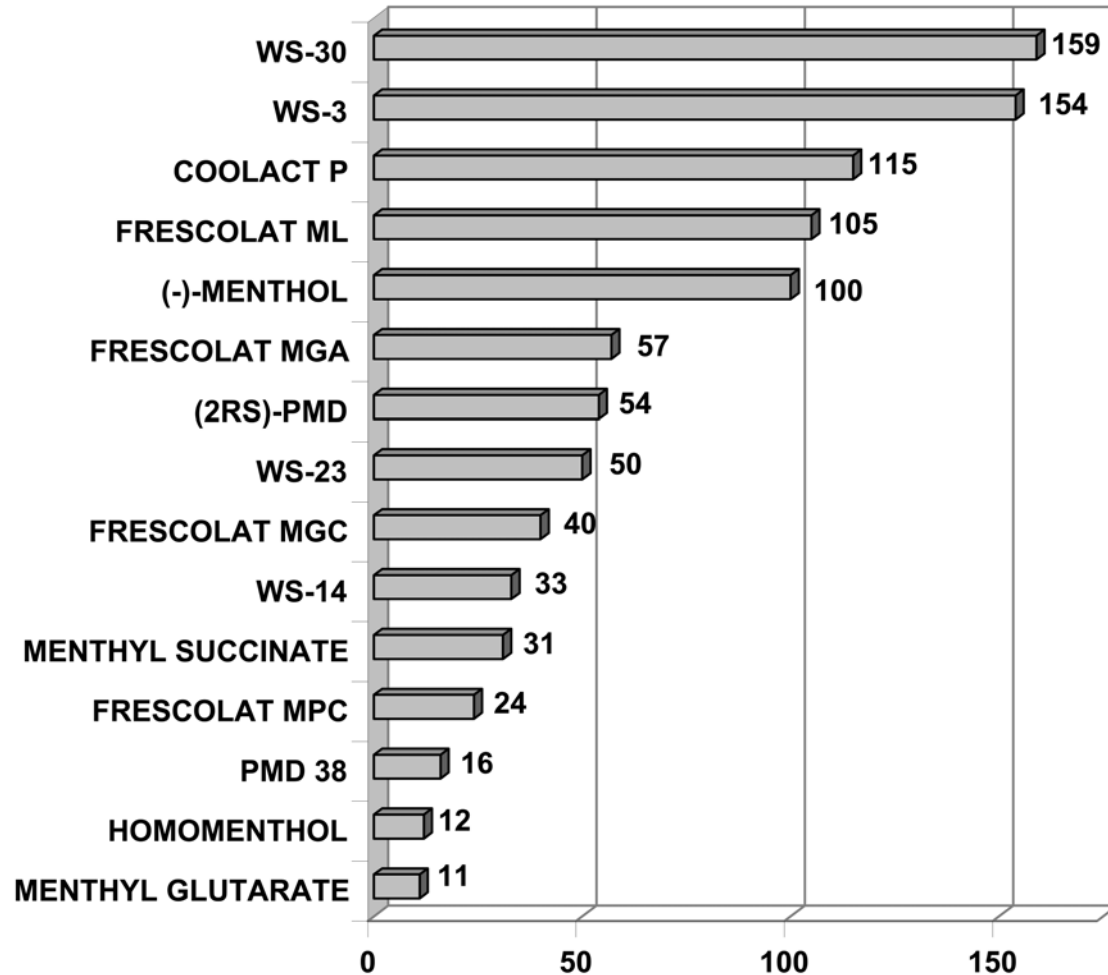
Relative Cooling & Bitterness in 5% sucrose

TABLE 1

COOLANT OR MIXTURE	COOLING INTENSITY PPM	COOLING INTENSITY MOLAR	BITTERNESS PPM
WS-30	63 PPM	2.44×10^{-4} M	30 PPM
WS-3	65 PPM	3.08×10^{-4} M	330 PPM
I-ISOPULEGOL	87 PPM	5.65×10^{-4} M	81 PPM
MENTHYL LACTATE	95 PPM	4.17×10^{-4} M	78 PPM
I-MENTHOL	100 PPM	6.41×10^{-4} M	100 PPM
MENTHONE GLYCEROL KETAL	175 PPM	7.87×10^{-4} M	140 PPM
TCA	185 PPM	8.04×10^{-4} M	160 PPM
WS-23	200 PPM	1.17×10^{-3} M	320 PPM
MENTHOL EG CARBONATE	250 PPM	1.02×10^{-3} M	155 PPM
WS-14	300 PPM	1.26×10^{-3} M	400 PPM
MENTHYL SUCCINATE	325 PPM	1.27×10^{-3} M	275 PPM
MENTHOL PG CARBONATE	410 PPM	1.59×10^{-3} M	90 PPM
MENTHANEDIOL	640 PPM	3.72×10^{-3} M	200 PPM
HOMOMENTHOL	825 PPM	5.81×10^{-3} M	250 PPM
MENTHYL GLUTARATE	950 PPM	3.52×10^{-3} M	>500 PPM

Johnson SS, Stawski BZ, Sheldon GT. Confections Containing a Blend of Physiological Cooling Agents. U.S. Patent Application 20070248717, 2007, Oct. 25. (Wrigley)

Fig. 9
RELATIVE ORAL COOLING IN 5% SUCROSE
SOLUTIONS vs. 100 PPM MENTHOL
Adapted from : Ref. 72



Adapted from Johnson SS, Stawski BZ, Sheldon GT. Confections Containing a Blend of Physiological Cooling Agents. U.S. Patent Application 20070248717, 2007, Oct. 25. (Wrigley)

Other Potential Cooling Agents

NEW p-MENTHANE CARBOXYAMIDE COOLANTS

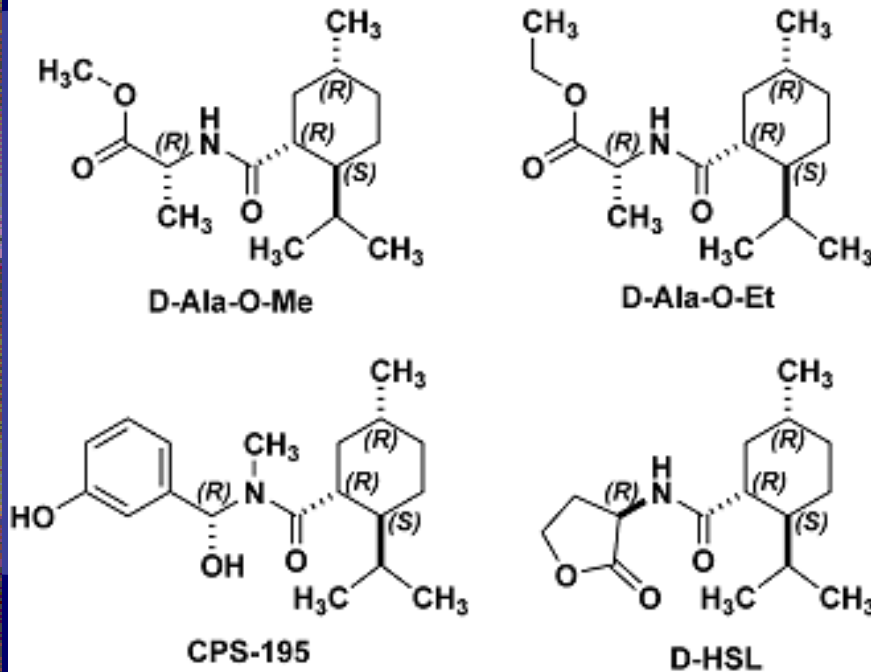
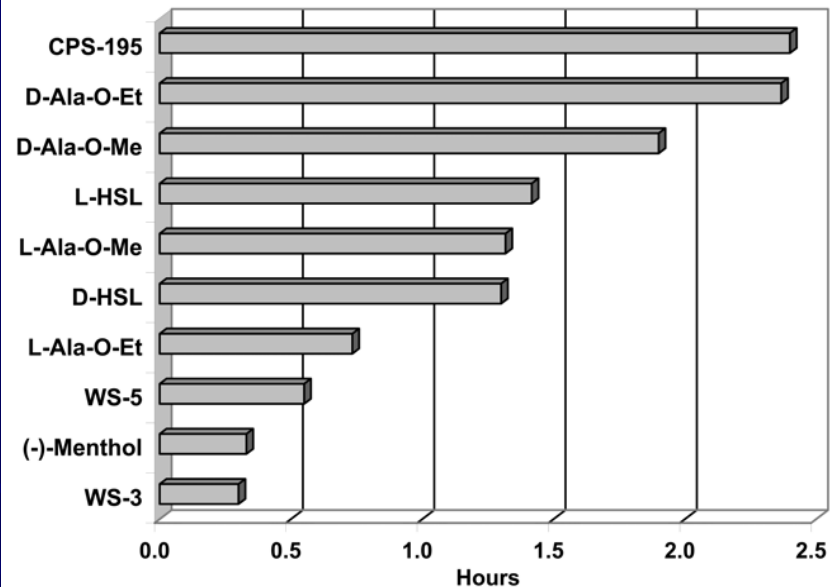
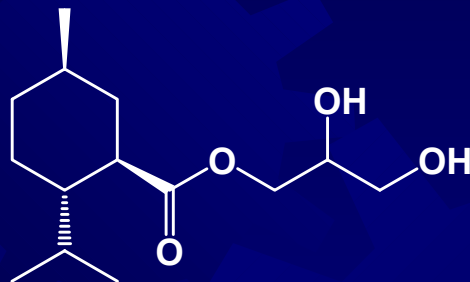


Fig. 7
TOPICAL COOLING DURATION
1% IN OINTMENT
Adapted from : Refs. 69,70

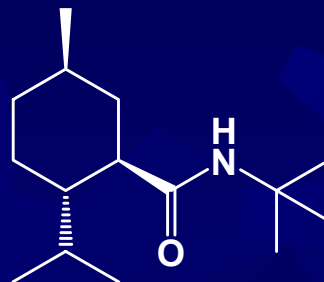


Leffingwell, Handbook of Cosmetic Science and Technology, 3d edition (2009), In Press;
From WO 2006103401 (2006) & US20070155755 (2007)

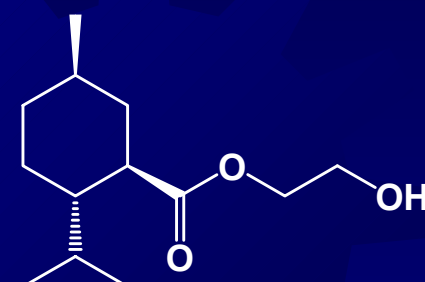
Other Potential Cooling Agents



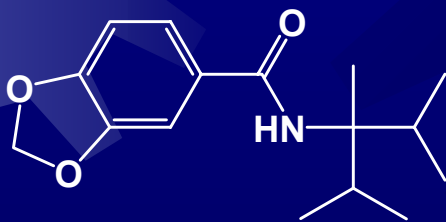
WS-30
0.2-0.25 X Menthol



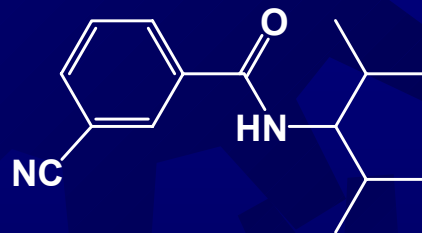
WS-14
0.75 X Menthol



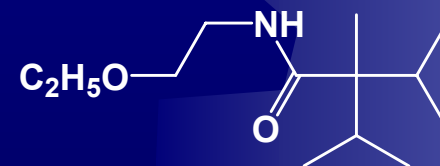
WS-4
0.16-0.33 X Menthol



~2.2 X Menthol
WO 2006/099762 (2006)

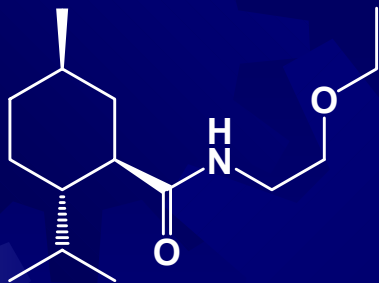


~10 X Menthol
WO 2006/099762 (2006)



~0.75 X Menthol
US Patent 7030273 (2007)

Other Potential Cooling Agents



Hase-1
Cooling, No bitterness
JP2004059474 (2004)



**N-benzo[1,3]dioxol-5-yl-
3-p-menthanecarboxamide**
~100 X Menthol
WO 2006/092074 (2006)