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Wilkinson Sword Cooling Compounds: From the Beginning to Now

A chronological review of research into the cooling and therapeutic effects of these types of materials.

John Leffingwell, Leffingwell & Associates, and David Rowsell, Chromatography Resources

Wilkinson Sword was founded in 1772, and its origins began with the manufacture of swords and, later, guns and shears. In 1898, the company branched out to manufacture safety razors and became a U.K.-leader in shaving products. In the 1960s, it introduced stainless steel razor blades coated with PTFE (polytetrafluoroethylene), which in 1967 brought one of the present authors (David Rowsell) to the company. With a background in fluorine chemistry, the author's project at the time was to investigate PTFE alternatives.

Late 1960s to the 1980s: Pursuing New Compounds

However, around 1969–1970, Wilkinson Sword management wanted to expand/diversify and proposed products in the toiletries/cosmetics area, and thus the R&D focus shifted. This proposal was developed further (mostly by Wilkinson Sword researcher Hugh Watson) into pursuing compounds with a menthol-like cooling effect, no odor and low volatility. This idea was attractive because one of the major negatives of menthol-containing shaving creams and after-shave lotions was the propensity for eye and mucus membrane irritation. A literature search indicated that these compounds were likely to be novel. The only cooling compounds other than menthol known at that time seemed to owe their properties to hydrolysis to menthol.

It appeared from published physiological studies that the interaction of menthol with "cold receptors" in the skin could be interpreted as a drug-receptor type of interaction. A structure-activity relationship (SAR) approach using the methodology introduced by Hansch et al. in the mid-1960s was applied.[1–7] General principles that were developed based on correlations observed in work on acetylcholine drug-receptor interactions were applied in addition to SAR methods.[8]

As a result of preparing a few compounds (early WS numbers, e.g. WS-3), it seemed likely that compounds with cooling properties and low volatility could be prepared. More staff was recruited, and the project began. The work expanded from 1971 onwards, with about 1,200 cooling compounds being synthesized.[9–40]

In the course of the work, it was found that four important criteria needed to be satisfied for a compound to possess effective cooling activity:[9]

- a hydrogen bonding group
- a compact hydrocarbon skeleton
- a correct hydrophilic/hydrophobic balance (LogP between 1.5–5.0)
- a molecular weight in the range of 150–350

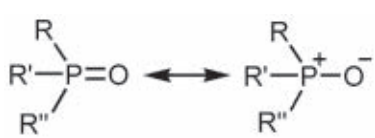
A hydrogen-bonding function appears essential for cooling action. This is an electron-donating oxygen atom capable of acting as a hydrogen bond acceptor. The best H-bonding groups found were those of the oxygen groups of hydroxy, N-alkyl carboxamides, sulfoxides and phosphine oxides.

For cooling activity, the hydrocarbon portion (or portions) of the molecule must provide a compact hydrophobic region near the site of hydrogen bonding. At the time of this early work, researchers did not have access to the numerous LogP calculators available today in programs such as Chemsketch, ChemAxon, ChemDraw or EpiSuite or, on the internet, via ChemSpider or the Virtual Computational Chemistry Laboratory websites. At the time of the research discussed here, the logP values of cooling compounds were all hand-calculated using the published tables of Hansch for the substituent π values.[5]

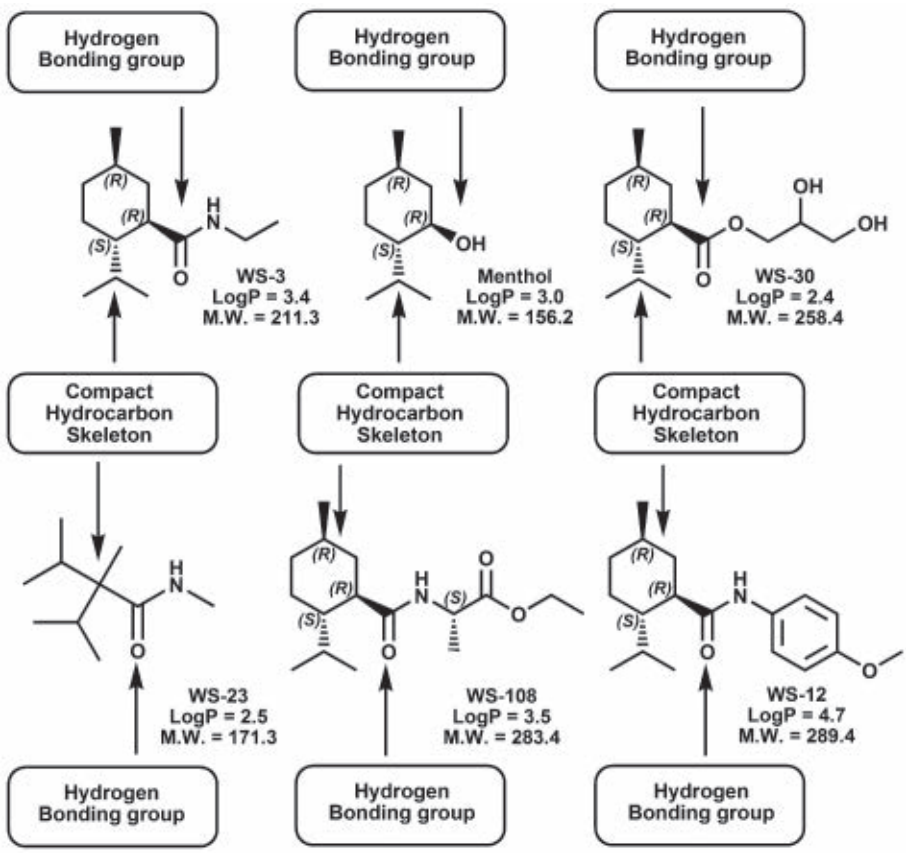
Generally, strong cooling compounds had logP values in the relatively narrow range of 1.5–4.0, and values for nearly all cooling compounds lay in the range of 1.0–5.0. The calculated logP value of (-)-menthol is 3.0±0.35, while experimental values are 3.2–3.4.

Problems were encountered in deciding on a value for the phosphine oxide group. At that time, there were very few measurements of logP of phosphine oxides. It was concluded that the phosphine oxide group should be "balanced" by ~14–15 carbon atoms (compared to 10–11 in menthol and 12–13 with amides). This was born out as a number of phosphine oxides were found to be about three times cooler than (-)-menthol, based on cooling threshold tests—e.g., isobutyl-sec-butyl-n-heptylphosphine

F-1. The phosphine oxide group is capable of strong H-bonding (via oxygen); the usual resonance description of this bond is shown here



F-2. Cooling criteria



oxide (WS-46), sec-butyl-n-heptyl-isopropyl phosphine oxide (WS-51) and sec-butyl-n-octyl-isopropyl phosphine oxide (WS-52).[9]

The above indicates that the phosphine oxide group is capable of strong H-bonding (via oxygen). The usual resonance description of this bond is shown in **F-1**.

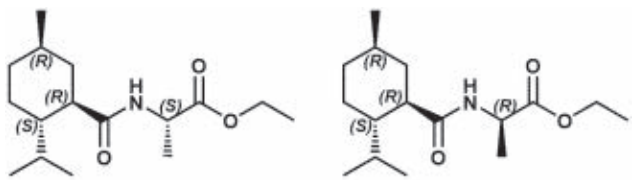
A more detailed description in molecular orbital terms remains elusive (see, for example, references 41–44).

Initial work was concentrated on compounds containing the p-menthane structure. A number of compounds containing polar groups capable of H-bonding were tried and found to be active as cooling agents, provided the polar groups were attached directly to the p-menthane group (**F-2**). Separation by a -CH2- group reduced activity, and separation by -CH2CH2- resulted in almost complete loss of cooling activity.

The next stage in determining the range of structures that might produce cooling was to investigate the hydrocarbon (low polarity) group. By analogy from the work on the acetylcholine receptor, it seemed reasonable to try acyclic structures. It was found that structures containing "elements" of the p-menthane structure, e.g. WS-23, were active, provided there was an appropriate logP value.

Stereochemistry was found to play an important role in the coolant properties. In the case of p-menthane-based coolants, the stereochemistry having the (1R,2S,5R)- configuration, like (-)-menthol, is important. Although not previously reported, it was found that the stereochemistry of side chain groups for

F-3. L-Alanine ethyl ester and D-alanine ethyl ester



menthyl carboxamides may also be important. This is apparent in the cooling activity of the N-(p-menthane-3-carbonyl)-alanine ethyl esters, as substantial differences in the cooling properties of the D-alanine ethyl ester are found versus the L-alanine ester (**F-3**), where the L-alanine ester is significantly cooler (David Rowsell, unpublished data). Such differences have subsequently been found in non-carboxamide coolants such as Takasago's trademarked Coolant 10 [3-(L-menthoxy)propane-1,2-diol], in which the side chain hydroxyl having the (2S) configuration has about twice the cooling power versus the racemic (R,S) configuration.[45]

Similarly, Kazuma et al. have shown that L-menthyl (3S)-3-hydroxybutyrate is both more cooling and lacking in the bitterness exhibited by the racemate.[96] Further, Erman and Snow indicated that the menthyl lactate enantiomer with the

(2S) hydroxyl side chain configuration "is particularly preferred" for its cooling properties.[87]

An example of how a "slight" structural change can dramatically change the sensory perception is the case of the Wilkinson Sword compound (1R,2S,5R)-N-cyclopropyl-p-menthanecarboxamide (FEMA# 4693; FEMA name: N-cyclopropyl-5-methyl-2-isopropylcyclohexanecarboxamide) vs. the racemic proprietary Symrise compound N-((1SR,2SR,5RS)-2-isopropyl-5-methylcyclohexyl)cyclopropanecarboxamide (FEMA# 4558) (**F-4**).[46]

Throughout this paper, all mentions of the various p-menthane-3-carboxamides infer the same (1R,2S,5R) configuration as is found in (-)-menthol.

In 1975, the first of the Wilkinson Sword coolants, WS-3 (N-ethyl-p-menthane-3-carboxamide), was granted FEMA GRAS status for use in beverages, frozen desserts, confections, puddings, gelatins, jams and chewing gum.[47] However, for quite a few years, commercial implementation by consumer companies was extremely slow.

In 1974–1975, R.J. Reynolds examined WS-14, WS-10, WS-23, WS-123, WS-125 and WS-3 for the cooling effect in menthol cigarettes. WS-14 (N-tert-butyl-p-menthane-3-carboxamide) was found to be as acceptable as menthol as a cooling agent for cigarettes. Consumer testing was conducted with excellent results. However, R.J. Reynolds decided not to pursue commercialization.[48] In the late 1970s, Philip Morris also found WS-14 to be the optimum WS-cooling agent for cigarettes. In July 1981, Philip Morris introduced the *Northwind* cigarette into test market with a "Cool without Menthol" advertising theme. This test market was not successful.[49–50]

Around 1978, Sterling Organics became the manufacturer and distributor for the Wilkinson Sword coolants. This allowed for the beginning of a broader commercial exposure than the previous approach of directly licensing the products to consumer product companies. However, it wasn't until the 1990s that major companies began to take a serious interest in WS-3, WS-23 and other non-menthol coolants. In 1996, WS-23 (2-isopropyl-N,2,3-trimethylbutyramide) received FEMA GRAS status.[51]

1990s: Great Leaps Forward

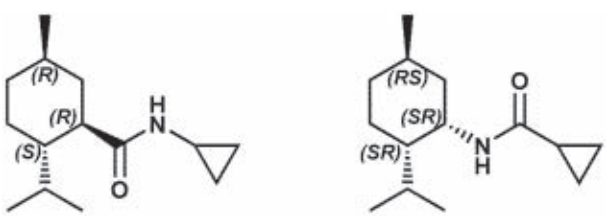
By the late 1990s, there was an explosion in growth of the use of WS-3 alone or in combination with WS-23 and other coolants recently introduced at that time, including Haarmann & Reimer's (now Symrise's) Frescolat MGA (menthone glyceryl ketal) and Frescolat ML (menthyl lactate), and Takasago's Coolant 10 (3-L-menthoxypropane-1,2-diol). As consumer product companies sought well-balanced, increased-cooling-impact materials, a number of flavor and fragrance suppliers responded with more research. Because menthol alone can cause burning, irritation and pain at higher concentrations, these new cooling materials have become increasingly important for high-cooling-impact oral care, breath fresheners, confections and chewing gums. This has led to a number of additions to the FEMA GRAS list over the years (**T-1**).

The importance of the Wilkinson Sword work on coolants is attested to by the fact that it originally developed 20% of the materials in **T-1**.

In the late 1990s, the discovery of the class of thermoreceptors began a transformation in how chemical agonists (i.e., activators) could be screened. The major thermoreceptors are shown in **T-2** with the types of agonists that activate the receptors.

Thermoreceptors belong to the class of transient receptor potential (TRP) ion channels, of which seven subfamilies exist (TRPC, TRPV, TRPM, TRPA, TRPP, TRPML and TRPN). Six members of three TRP subfamilies are involved in mammalian temperature-sensitive thermoreception. The TRPV receptors are activated by heat, TRPV1 (≥42°C), TRPV2 (≥52°C), TRPV3 (32°–39°C) and TRPV4 (27°–34°C), while TRPM8 (25°–34°C) and TRPA1 (<~18°C) are activated by cold. Certain types of chemical agonists activate these same thermo-TRP channels. TRPV1 (transient receptor potential cation channel subfamily V member 1) was the first thermoreceptor characterized, and is referred to as a vanilloid receptor, as it is activated by capsaicin and noxious heat. TRPV2 is activated by temperatures above 52°C. Alternatively, it can be activated at lower temperatures by chemicals, such as the plant cannabinoid cannabidiol, which is not psychoactive in healthy individuals and is considered to have a wide scope of medical applications including anti-inflammation. The TRPV3 channel is directly activated by moderate temperatures and various natural compounds like carvacrol, thymol and eugenol. TRPV4 is perhaps the least-understood TRPV receptor but is known to be activated by 4-α-phorbol 12,13-didecanoate. TRPA1 is activated by cold temperatures, pain and chemical irritants such as isothiocyanates. TRPM8 is the receptor that is primarily activated by coolants such as menthol, WS-3 and other familiar coolants. Among the excellent reviews on thermo receptors are those of Voets et al., Jordt et al., Vay et al. and Dhaka et al.[53–56]

F-4. Wilkinson Sword compound (1R,2S,5R)-N-cyclopropyl-p-menthanecarboxamide (FEMA# 4693; FEMA name: N-cyclopropyl-5-methyl-2-isopropylcyclohexanecarboxamide) and the racemic proprietary Symrise compound N-((1SR,2SR,5RS)-2-isopropyl-5-methylcyclohexyl) cyclopropanecarboxamide (FEMA# 4558)[46]



2000 to Present: Advances in Cooling and Therapeutic Properties

In 1951, Hensel and Zotterman hypothesized that menthol exerted its actions on "an enzyme" that was involved in the activation of cold receptors.[57] Confirmation of Hensel and Zotterman's original hypothesis for the action of menthol finally came in the March 7, 2002, issue of *Nature*. McKemy et al. characterized and cloned a menthol receptor from trigeminal sensory neurons that is also activated by thermal stimuli in the cool to cold range. This cold- and menthol-sensitive receptor, called CMR1 (or TRMP8), is a member of the TRP family of excitatory ion channels, and it functions as a transducer of

T-1. Important cooling compounds added to the FEMA GRAS lists (by year)

CAS	WS #	Flavis #	FEMA #	MATERIAL	YEAR
89-79-2	NA[a]	02.067	2962	Coolact P; isopulegol; (-)-isopulegol[b]	1965
39711-79-0	**WS-3**	**16.013**	**3455**	N-Ethyl-p-menthane-3-carboxamide	**1975**
59259-38-0	NA	09.551	3748	Frescolat ML; L-menthyl lactate[c]	1985
87061-04-9	NA	02.224	3784	Coolact 10; Coolant 10; 3-(L-menthoxy)propane-1,2-diol	1993
51115-67-4	**WS-23**	**16.053**	**3804**	2-Isopropyl-N,2,3-trimethylbutyramide	**1996**
156324-78-6	NA	09.842	3805	Frescolat MGC; L-menthol ethylene glycol carbonate	1996
30304-82-6	NA	09.843	3806	Frescolat MPC; L-menthol 1&2-propylene glycol carbonate	1996
563187-91-7	NA	06.133	3807	Frescolat MGA; L-menthone 1,2-glycerol ketal	1996
63187-91-7	NA	06.120	3806	Frescolat MGA (racemic); DL-menthone 1,2-glycerol ketal	1996
77341-67-4	NA	09.616	3810	Monomenthyl succinate	1996
195863-84-4	NA	02.254	3849	3-(L-Menthoxy)-2-methylpropan-1,2-diol	1998
156324-82-2	NA	-	3992	Frescolat Type MPC (racemic); DL-menthol propylene glycol carbonate	2001
220621-22-7	NA	09.929	4006	(-)-Menthyl glutarate	2001
42822-86-6	NA	02.246	4053	Coolact 38D; PMD 38; (+)-*cis* & (-)-*trans* p-menthane-3,8-diol	2003
38618-23-4	NA	02.247	4154	Coolact 5; 2-(L-menthoxy)ethanol	2005
68127-22-0	NA	-	4155	Questice;[d] (-)-menthyl pyrrolidone carboxylate	2005
544714-08-1	NA	16.092	4230	(±)-N,N-Dimethyl menthyl succinamide[e]	2005
115869-76-6	NA	09.949	4308	L-Menthyl (S)-3-hydroxybutyrate[f]	2007
68489-14-5	**WS-5**	**16.111**	4309	(1R,2S,5R)-N-((Ethoxycarbonyl)methyl)-p-menthane-3-carboxamide	**2007**
59557-05-0	NA	-	4327	Ultracool 7; (-)-menthyl acetoacetate[g]	2007
852379-28-3	NA	16.117	4496	G-180; N-(4-cyanomethylphenyl)-p-menthanecarboxamide	2009
23445-02-5	NA	-	4497	(-)-Cubebol	2009
51115-77-6	**WS-116**	**-**	**4603**	2,2-Diethyl-N-(2-hydroxy-1,1-dimethylethyl)butanamide	**2009**
406179-71-3	NA	09.935	4604	Dimenthyl glutarate	2009
51115-70-9	**WS-27**	**-**	**4557**	N-Ethyl-2,2-diisopropylbutanamide	**2009**
883215-02-9	NA	-	4602	N-(2-Hydroxyethyl)-2,3-dimethyl-2-isopropylbutanamide	2009
847565-09-7	NA	16.118	4549	G-190; (IR,2S,5R)-N-(2-pyridin-2-ylethyl)menthylcarboxamide	2009
1119711-29-3	NA	16.125	4684	(2S,5R)-N-[4-(2-Amino-2-oxoethyl)phenyl]-p-menthanecarboxamide	2011
73435-61-7	**WS-NA**	**16.124**	4693	(1R,2S,5R)-N-Cyclopropyl-p-menthanecarboxamide	**2011**
28804-53-7	NA	-	4718	2-[(2-p-Menthoxy)ethoxy]ethanol	2011
68489-09-8	**WS-12**	**16.123**	**4681**	(1R,2S,5R)-N-(4-Methoxyphenyl)-p-menthanecarboxamide	**2011**
917750-72-2	NA	-	4742	(1R,2R,4R)-1-(2-Hydroxy-4-methylcyclohexyl)ethanone	2013

[a]WS-NA = a Wilkinson Sword compound not assigned a WS-number
[b]Coolact is a trademark of Takasago; only in 1996 was it disclosed that (-)-isopulegol with >99.7% enantiomeric purity possessed a clean refreshing cooling sensation[52]
[c]Frescolat is a trade name of Symrise (formerly Haarmann & Reimer)
[d]Questice is a trademark of Givaudan (formerly Quest International)
[e]The Flavor and Extract Manufacturers Association specifies (±)-N,N-dimethyl menthyl succinamide, while the 2012 E.U. list of flavorings authorized for use in foods in the European Union specifies the (1R,2S,5R)-isomer
[f]The Flavor and Extract Manufacturers Association specifies L-menthyl (R,S)-3-hydroxybutyrate, while the 2012 E.U. list of flavorings authorized for use in foods in the European Union specifies L-menthyl (S)-3-hydroxybutyrate
[g]Ultracool is a former trademark of P&G; no longer used

cold stimuli in the somatosensory system.[58] Simultaneously, Andrea Peier and coworkers also identified the TRPM8 receptor channel that senses cold stimuli and menthol.[59]

In 2004, H-J. Behrendt et. al. published a study on the effects of 70 odorants and menthol-related substances on recombinant cold-menthol receptor TRPM8 expressed in HEK293 cells.[60] These were examined using a fluorometric imaging plate reader (FLIPR) assay.[a] In all, 10 substances were found to be agonists: linalool, geraniol, hydroxycitronellal, WS-3, WS-23, Frescolat MGA, Frescolat ML, PMD 38, Coolact P and Coolant 10. This procedure measures the EC_{50} values, which is the half maximal effective concentration of a compound that induces a response halfway between the baseline and maximum after a specified exposure time (**F-5**). A cautionary statement on the use of EC_{50} values: such results, while providing efficacy values on the ligand binding to the cold receptors, which are strongly indicative, do not always directly correlate directly to sensory cooling tests.

[a]FLIPR is a trademark of Molecular Devices

T-2. Thermoreceptors and agonists

Chemical agonist (botanical source)	Thermo TRP receptor*
Capsaicin (hot chili peppers, e.g., Tabasco)	TRPV1
Piperine (black pepper)	TRPV1
[8] & [6]-Gingerol (ginger)	TRPV1
α-Hydroxysanshool (Sichuan pepper)	TRPV1, TRPA1
[6]-Shogaol (dried ginger)	TRPV1, TRPA1
Allicin (fresh garlic)	TRPV1, TRPA1
Polygodial (*Persicaria odorata*, *Tasmannia lanceolat*a)	TRPA1, TRPV1
Cannabichromene (*Cannabis sativa*)	TRPA1
Allyl isothiocyanate (mustard, horseradish)	TRPA1
Benzyl isothiocyanate (mustard, horseradish)	TRPA1
Phenethyl isothiocyanate (mustard, horseradish)	TRPA1
Cannabidiol (*Cannabis sativa*)	TRPV2
D-9-Tetrahydrocannabinol (*Cannabis sativa*)	TRPV2, TRPA1
Carvacrol (oregano)	TRPV3
Thymol (thyme)	TRPV3
Camphor (*Cinnamomum camphora*)	TRPV3, TRPV1
Cinnamaldehyde (cinnamon, cassia)	TRPA1, TRPV3
Eugenol (clove)	TRPV3, TRPA1,TRPV1
Bisandrographolide A (*Andrographis paniculata*)	TRPV4
1,4-Cineole (lime)	TRPA1, TRPM8
1,8-Cineole, eucalyptol (eucalyptus)	TRPM8, TRPV3
Icilin [AG-3-5] (synthetic)	TRPM8, TRPA1
(-)-Menthol (peppermint)	TRMP8, TRPV3
WS-3 (synthetic)	TRPM8
WS-12 (synthetic)	TRPM8
WS-109 = CPS- 369 (synthetic)	TRPM8

*Primary TRP receptors activated

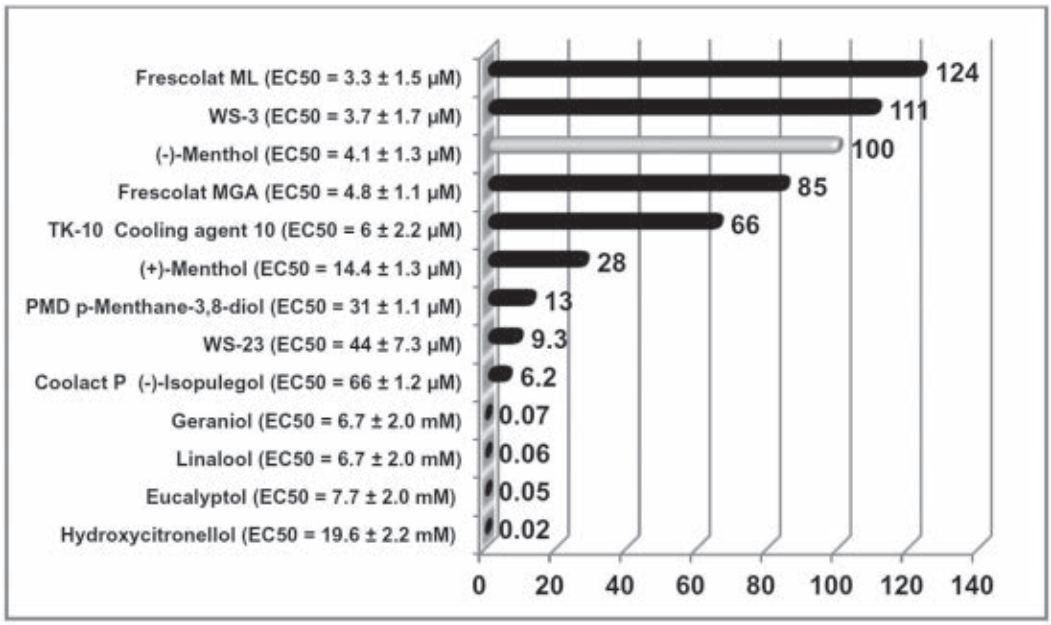
The chemistry and receptor mechanisms of cold and coolants have been reviewed by McKemy, Bharate and Bharate, Galopin, Furrer et al. and Leffingwell.[61–66]

To place the relative cooling strengths of various cooling agents in perspective, **F-6** compares a number of important cooling compounds.

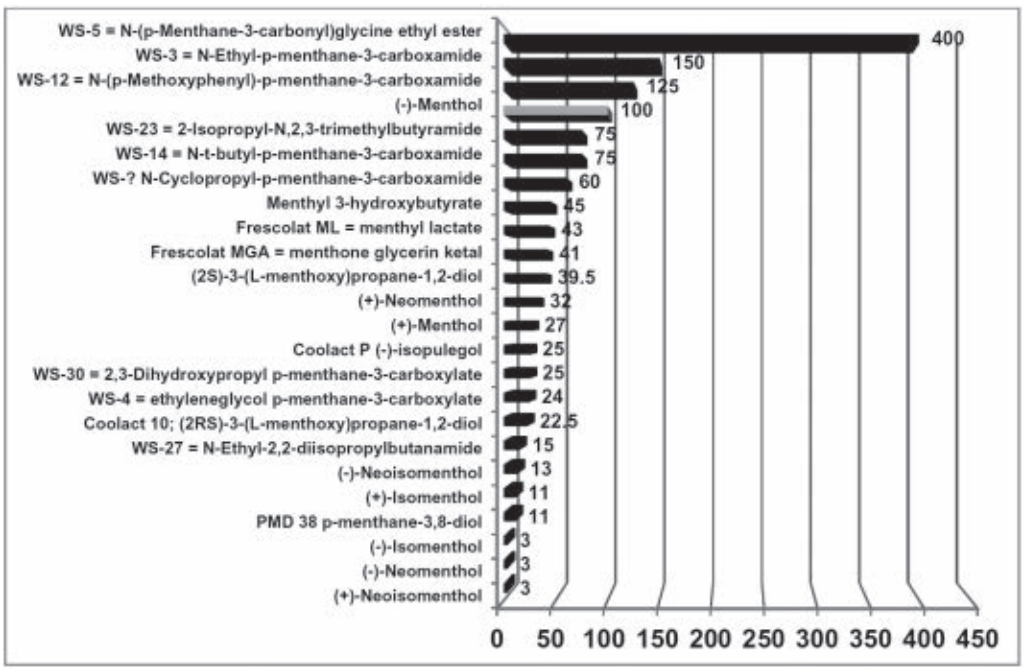
Starting in 2005, a series of highly relevant patents and patent applications by Edward Wei began to appear.[67–78] He has modeled a series of therapeutic analgesic substances consisting of Wilkinson Sword coolants and close analogs as topical anti-nociceptive (pain-suppressant) compounds for the treatment of non-keratinized stratified epithelium (NKSE) around the eyes, larynx, trachea and/or bronchi, and oral cavity. In particular, Wei sought long-lasting coolants. As shown in the **F-7**, N-(p-menthane-3-carbonyl)-D-alanine ethyl ester (WS-109) was a preferred compound due to its very long-lasting cooling effect.[68] As long-lasting coolants are of interest for both flavors and cosmetic products, these findings are of great interest. In addition, Wei found that the 4-ethoxy-substituted (CPS-128) analog of WS-12 was qualitatively more cooling than cold (as compared to WS-12), and had a longer duration of action, averaging about 2.5 hours.[67]

In addition to the work of Wei, an active focus of basic pharmaceutical research has been the study of TRPM8 agonists relative to cancer. TRPM8 is upregulated (i.e., increased) in a number of cancerous cells including melanoma, colorectal cancer, breast cancer, lung cancer and prostate cancer cells. TRPM8 contains a binding site for p53, a gene that functions as a tumor suppressor involved in preventing cancer. Much of the seminal work in this area has shown that several of the WS coolants specifically activate the TRMP8 channel receptor and could be leads for both diagnostic and therapeutic ligands. Among the important compounds that have been studied are WS-12 = CPS-112 (reputedly the most specific TRPM8 ligand), WS-5, WS-109 = CPS-369 (N-(p-menthane-3-carbonyl)-D-alanine ethyl ester), WS-30 (2,3-dihydroxypropyl p-menthane-3-carboxylate) and WS-148 = CPS-148 (di-sec-butyl-n-heptylphosphine oxide).[78–83]

F-5. Relative potency of TRPM8 agonists based on EC_{50} values (mean) with (-)-menthol = 100



F-6. Approximate relative cooling strengths vs. menthol (as 100)



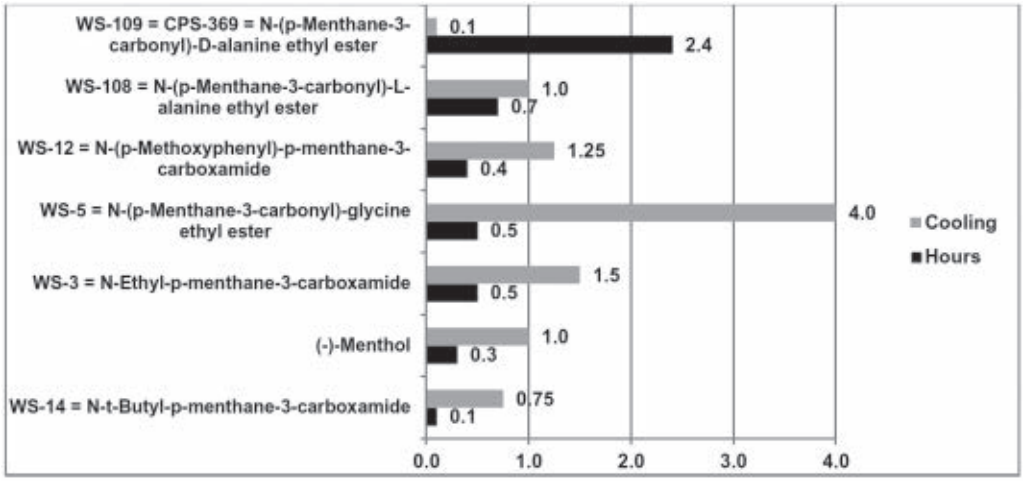
Future Opportunities

Among the many Wilkinson Sword materials not yet commercially used as coolants, several promising compounds warrant more extensive investigation. In fact, based on prior work, the authors are particularly surprised that WS-14 is not one of the approved materials. **T-3** provides a list of potential candidates.

Acknowledgements

The authors wish to thank Mark Erman for his interest in providing the F&F industry with much of the information on the commercial aspects of the Wilkinson Sword materials. Without his publications, patents and presentations—from which the authors derived considerable insight, especially on relative cooling intensities—this article might not have been possible.[84–95]

F-7. Relative cooling vs. menthol as 1.0, and duration of cooling (topical) in hours on skin



T-3. Potential non-GRAS (generally recognized as safe) Wilkinson Sword coolants' approximate cooling strength vs. (-)-menthol (as 100)*

WS-63	N-(3-Hydroxy-4-methylphenyl)-p-menthane-3-carboxamide	300
WS-61	N-(3,4-Dimethylphenyl)-p-menthane-3-carboxamide	300
CPS-128	N-(4-Ethoxyphenyl)-p-menthane-3-carboxamide	300
WS-35	N-(4-Methylphenyl)-p-menthane-3-carboxamide	100
WS-22	N-(p-Menthane-3-carbonyl)glycine propyl ester	100
WS-84	N-tert-Butyl-2-isopropylcycloheptanecarboxamide	100
CPS-113	N-(3-Fluoro-4-methoxyphenyl)-p-menthane-3-carboxamide	100
WS-108	N-(p-Menthane-3-carbonyl)-L-alanine ethyl ester	100
WS-26	N-(p-Menthane-3-carbonyl)-DL-alanine ethyl ester	75
WS-14	N-tert-Butyl-p-menthane-3-carboxamide	75
WS-11	N-(1,1-Dimethyl-2-hydroxyethyl)-p-menthane-3-carboxamide	67
WS-10	N-Isopropyl-p-menthane-3-carboxamide	67
WS-138	N-(3-Pyridyl)-p-menthane-3-carboxamide	60
CPS-124**	N-(4-Fluorophenyl)-p-menthane-3-carboxamide	60
WS-82	N,1-Diisopropyl-2-methylcyclopentanecarboxamide	60
WS-157	N,2-Diisopropyl-3-methylpentanamide	60
WS-134	N-Cyclopentyl-p-menthane-3-carboxamide	60
WS-56	N-(5-Hydroxy-n-pentyl)-p-menthane-3-carboxamide	60
WS-31	N-(p-Menthane-3-carbonyl)glycine methyl ester	50
WS-34	N-sec-Butyl-p-menthane-3-carboxamide	43
WS-33	N-n-Propyl-p-menthane-3-carboxamide	38
WS-139	N-(p-Menthane-3-carbonyl)3-aminobutyric acid ethyl ester	38
WS-55	N-Ethyl-2-sec-butyl-3-methylpentanamide	33
WS-24	N-Ethyl-2,3-dimethyl-2-isopropylbutanamide	33
WS-78	N-Cyclohexyl-p-menthane-3-carboxamide	30
WS-30	2,3-Dihydroxypropyl p-menthane-3-carboxylate	25
WS-4	2-Hydroxyethyl p-menthane-3-carboxylate	24
WS-109 = CPS-369	N-(p-Menthane-3-carbonyl)-D-alanine ethyl ester	10

*calculated from relative oral threshold cooling values (including unpublished data of David Rowsell)
**note that CPS-124 is incorrectly referred to as CPS-113 by several groups[61,80]

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