Synthesis of Menthol Glycinates and Their Potential as Cooling Agents

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ABSTRACT: A convenient method of synthesis has been developed for a new class of potential cooling agents, menthol glycinates. These compounds are prepared in two synthetic steps, starting from bromoacetyl bromide and (−)-menthol. The resulting brominated menthol ester readily undergoes substitution reactions with NH$_3$ and 1° or 2° amines to provide menthol glycinates. For most of the prepared compounds, the two-step synthetic procedure requires no aqueous phase extractions.

INTRODUCTION

Menthol is a major commodity chemical which is derived from both natural and semisynthetic sources. The worldwide usage of purified menthol is estimated to be over 20,000 metric tons annually. Its usage includes numerous flavor applications as a cooling component and as a local anesthetic in medicinal formulations and skin products. Among the several known stereoisomers of (−)-menthol, these have been shown to be less effective cooling agents than (−)-menthol. In taste dilution tests, (−)-isomenthol exhibits a cooling threshold at 30.0 ppm, whereas (−)-menthol has a cooling threshold of just 0.8 ppm. Nevertheless, there has been ongoing interest in the development of agents having even more potent cooling effects. This includes (−)-menthol derivatives such as the esters of (−)-menthol, (−)-menthol ethers, menthol-related amides, and other varied structures (Figure 1). Depending on the assay used, WS-3 and WS-5 are both shown to have stronger cooling effects than (−)-menthol, whereas 4-methyl-3-(1-pyrrolidinyl)-2[5H]-furanone is estimated to have 35 times more cooling effects than (−)-menthol.

No one has examined the use of menthol glycinates (1) among the derivatives of (−)-menthol that show cooling effects. Glycine itself has been used as a flavor-enhancing component; so, we reasoned that glycine esters with (−)-menthol could have potential as cooling agents. In the following note, we describe an efficient synthetic route to a diverse set of menthol glycinates (Scheme 1).

RESULTS AND DISCUSSION

Initial efforts to prepare menthol glycinates were sought to couple glycine and related derivatives with (−)-menthol. However, these reactions were less than satisfactory; so, an alternative route was devised. We hypothesized that the menthol glycinates could be built stepwise by a sequence involving acyl transfer chemistry followed by nucleophilic substitution. Thus, an optimized procedure coupled (−)-menthol with bromoacetyl bromide in dichloromethane (DCM) with excess anhydrous sodium carbonate (Scheme 2). The

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Figure 1. Known cooling agents.
conversion is quantitative, and product 2 is sufficiently pure that no purification steps are generally required. The acyl transfer chemistry is complete within 3 h, after which the product is isolated by simple filtration and removal of the DCM solvent. If nuclear magnetic resonance (NMR) or gas chromatography (GC) analysis of 2 shows any remaining (−)-menthol, product 2 is readily purified by vacuum distillation. Compound 2 has been previously synthesized by various methods, including coupling menthol with bromoacetic acid, bromoacetyl chloride, and bromoacetyl bromide. In addition to the quantitative yield, our procedure has the advantage of avoiding an aqueous workup of the product mixture. Similar coupling reactions are known for chloroacetyl chloride; however, in our hands, these conversions were not as clean as the synthesis of derivative 2. Compound 2 is the ideal scaffold for building menthol glycinites as it is expected to be highly reactive toward nucleophilic substitution.5a An optimized substitution reaction was developed by reacting compound 2 with amines in ethyl acetate (Table 1). For example, dimethylamine is added to a solution of bromide 2 with added NaOH and anhydrous Na2SO4 (Scheme 3). With vacuum distillation, menthol glycinate 3 is isolated in 90% yield. In order to achieve substitution with ammonia, the chemical reaction performed by adding an ethyl acetate

Table 1. Products and Yields from the Substitution Reactions of Bromide 2 with Amines or Ammonia

| Product | Yield | Product | Yield |
|---------|-------|---------|-------|
| ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 90% | ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 90% |
| ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 92% | ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 90% |
| ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 81% | ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 81% |
| ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 81% | ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 81% |
| ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 61% | ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 75% |
| ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 74% | ![Menthol Glycinate 3](https://example.com/menthol-glycinate-3.png) | 75% |
solution of bromide 2 directly into a flask containing liquid ammonia at −78 °C. This provides the glycine ester of menthol (4) in good yield. A variety of secondary amines provided the corresponding menthol glycines. This includes the dialkylamines to give products 5–7, 13, and 15–16. Heterocyclic systems, such as pyrrolidine and piperidine, were also found to give the substitution products (8 and 9, respectively) in good yields. Primary amines also give the diamine reacts twice with bromide times cooler than menthol.3 In addition to monosubstitution, (FEMA 4549, Scheme 4), which is estimated to be about 100 compound is modeled after the known cooling agent, amide (−nucleophiles to give menthol glycinates. This includes some of these derivatives should have strong affinities for the TRMP8 receptor site which provides the physiological sensation of cooling, as well as other biological or medicinal effects.8 Preliminary screening of the new menthol glycinates has shown that several derivatives possess intense oral cooling sensations,9 including delayed onset cooling and prolonged cooling. Further testing of their potential as new cooling agents is currently in progress.

■ EXPERIMENTAL SECTION

Preparation of (1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-Bromoacetate (2).10 To 100 mL of CH3Cl (1)-menthol (7.2 g, 0.046 mmol) is dissolved and anhydrous Na2CO3 is added. The resulting solution is cooled to 0 °C and the flask is fitted with a CaCl2 drying tube. Bromoacetyl bromide (4.0 mL, 0.046 mol) is then added, the cooling bath is removed, and the solution is stirred for a minimum of 4 h. Following the reaction period, the solution is filtered through a glass wool and the solvent is removed by a vacuum. The product is isolated as a clear colorless oil (12.2 g, 0.044 mol, 96%). The analysis of the crude product by GC-flame ionization detector (FID) and NMR shows an extremely high purity of the product; however, the oil may be further refined by distillation (ca. 120 °C, 2 mm). With repeated runs, the yields of the crude product vary from 95 to 100%.

General Procedure for the Synthesis of Menthol Glycinates (1° Amines). The amine (0.02 mmol) is dissolved in 25 mL of EtOAc, after which is added NaOH (0.6 g, 15 mmol) and anhydrous sodium sulfate (0.5 g, 3.5 mmol). To this solution, (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (1.68 g, 6.06 mmol) is slowly added. The mixture is stirred for 6 h or until the GC-FID analysis shows no remaining bromoester (2). The solution is then filtered through a plug of glass wool and the solvent is removed by reduced pressure. For low-boiling amines, the excess amine is removed during this step. For less-volatile amines, fractional distillation may be necessary. The final purification of the menthol glycinate is achieved by vacuum distillation.

General Procedure for the Synthesis of Menthol Glycinates (2° Amines). (1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (1.68 g, 6.06 mmol) is dissolved in 25 mL of EtOAc. To this solution, the amine (9 mmol) is added, followed by NaOH (0.6 g, 15 mmol) and anhydrous sodium sulfate (0.5 g, 3.5 mmol). The mixture is stirred for 6 h or until the GC-FID analysis shows no remaining bromoester (2). The solution is then filtered through a plug of glass wool, and the solvent is removed by reduced pressure. For low-boiling amines, the excess amine is removed during this step. For less-volatile amines, fractional distillation may be necessary. The final purification of the menthol glycinate is achieved by vacuum distillation.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(Dimethylamino)acetate (3).11 Using the general procedure for 2° amines, (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (2) is reacted with dimethylamine (2.0 M solution in tetrahydrofuran) to provide methyl glycinate 3 in 86% yield as a clear oil (bp, ca. 140 °C at 1 mm).1H NMR (300 MHz, CDCl3): δ 0.36–0.42 (m, 2H), 0.42–0.48 (m, 2H), 0.78 (d, 3H, J = 7.0 Hz), 0.85–0.90 (m, 6H), 0.96–1.13 (m, 2H), 1.34–1.44 (m, 1H), 1.46–1.57 (m, 1H), 1.67–1.73

Scheme 4. Structure of the Cooling Agent FEMA 4549

Scheme 5. Double-Substitution Products Prepared

For most of the substitution reactions described above, the optimized procedure involves using an excess of the amine nucleophile. The menthol glycinate products are isolated in pure form by removing the ethyl acetate solvent and excess amine by reduced pressure. Then, menthol glycinate is typically distilled at 150–220 °C @ 1 mm Hg. Optimization studies revealed that the excess amine allows the substitution chemistry to go to completion within a relatively short period of time. For example, dibutylamine was reacted with bromide 2 to provide compound 7, and with 1.1 equiv of the amine, the substitution reaction is only 79% complete after 3 h. If the amount of dibutylamine is increased to 1.6 equiv (0.13 M in ethyl acetate), then the substitution reaction is 100% complete in less than 3 h.

■ CONCLUSIONS

In summary, we have developed a simple methodology to prepare a series of menthol glycimates. Starting from bromoacetyl bromide, bromoester 2 is prepared quantitatively. This substrate undergoes substitution reactions with a series of N-nucleophiles to give menthol glycimates 3–21 in generally good yields. The procedure avoids the need for extractions or aqueous workup. The products menthol glycimates are considered potential cooling agents, similar to other derivatives of menthol. As variants of (−)-menthol, it is expected that some of these derivatives should have strong affinities for the TRMP8 receptor site which provides the physiological sensation of cooling, as well as other biological or medicinal effects.
(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-Aminoacetate (4). Into a cooled (−78 °C) round-bottom flask, ammonia (ca. 2 mL, 80 mmol) is condensed and NaOH (0.5 g, 12.5 mmol) is added to the flask. To this flask, an addition funnel is connected. Menthol bromoacetate (1, 1.4 g, 5.0 mmol) is dissolved in 10 mL of ethyl acetate, and this solution is placed in the addition funnel. The solution of I is then added slowly to liquid ammonia. The resulting mixture is stirred at −30 °C and monitored by periodically taking samples and subjecting these samples to GC-mass spectrometry (MS) analysis. Typically, the conversion is complete within 6 h. If it is only partially complete, additional ammonia is condensed into the cooled flask. Following the completion of the reaction, the mixture is allowed to warm to room temperature and the excess ammonia boils off. To the reaction mixture, anhydrous sodium sulfate is added and the mixture is filtered through a plug of silica gel. The reaction flask is rinsed with 10 mL of ethyl acetate, and the solution is passed through silica gel. The solvent is removed by a vacuum to provide a clear oil. Further purification is accomplished by vacuum distillation at 150 °C (1 mm) and 0.467 g (2.2 mmol, 42%).

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-Diethylaminoacetate (5). Using the general procedure for 2° amines, (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (2) is reacted with diethylamine to provide methyl glycinate in 92% yield as a clear oil (bp, ca. 160 °C at 1 mm). 1H NMR (300 MHz, CDCl3): 0.73 (d, 3H, J = 7.0 Hz), 0.82−0.91 (m, 7H), 0.92−1.2 (m, 1H), 1.05 (t, 6H, J = 7.2 Hz), 1.31−1.40 (m, 1H), 1.40−1.54 (m, 1H), 1.60−1.73 (m, 2H), 1.79−1.89 (m, 1H), 1.94−2.04 (m, 1H), 2.66 (q, 4H, J = 7.2 Hz), 3.30 (s, 2H), 4.67−4.76 (m, 1H). 13C NMR (75 MHz, CDCl3): δ 9.1, 11.2, 16.0, 20.7, 21.8, 23.1, 26.1, 31.4, 33.8, 40.4, 42.6, 46.5, 56.9, 58.4, 77.8, 164.4. Low-resolution MS (electron impact ionization): 269 (M+), 132, 130, 116, 102.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-Dipropylaminoacetate (6). Using the general procedure for 2° amines, (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (2) is reacted with dipropylamine to provide methyl 2-isopropyl-5-methylcyclohexyl glycinamide in 81% yield as a clear oil (bp, ca. 140 °C at 1 mm). 1H NMR (300 MHz, CDCl3): 0.36−0.42 (m, 2H), 0.42−0.48 (m, 2H), 0.78 (d, 3H, J = 7.0 Hz), 0.85−0.90 (m, 6H), 0.96−1.13 (m, 2H), 1.34−1.44 (m, 1H), 1.46−1.57 (m, 1H), 1.67−1.73 (m, 2H), 1.82−1.90 (m, 1H), 1.97−2.04 (m, 1H), 2.20−2.26 (m, 1H), 2.40 (br s, 1H), 3.34−3.42 (m, 2H), 4.71−4.76 (m, 1H). 13C NMR (75 MHz, CDCl3): δ 6.2, 6.3, 16.4, 20.7, 22.0, 23.5, 26.3, 29.9, 31.4, 40.9, 47.0, 50.8, 74.7, 172.2. Low-resolution MS (electron impact ionization): 253 (M+), 224, 138, 116, 102. High-resolution MS (ESI): calc for C18H31NO2, 254.2120; found, 254.2083.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(Bis(2-methoxyethyl)amino)acetate (11). Using the general procedure for 2° amines, (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-bromoacetate (2) is reacted with bis(2-methoxyethyl)amine to provide methyl glycinate in 68% yield as a clear oil (bp, ca. 200 °C at 1 mm). 1H NMR (300 MHz, CDCl3): 0.69 (d, 3H, J = 7.0), 0.75−0.86 (m, 7H), 0.88−1.07 (m, 2H), 1.25−1.35 (m, 1H), 1.35−1.48 (m, 1H), 1.54−1.66 (m, 2H), 1.73−1.85 (m, 1H), 1.87−1.96 (m, 1H), 2.83−2.90 (m, 4H), 3.24−3.28 (m, 6H), 3.37−3.45 (m, 6H), 4.59−4.71 (m, 1H). 13C NMR (75 MHz, CDCl3): δ 16.2, 20.7, 23.2, 26.2, 29.6, 31.3, 34.2, 40.9, 47.0, 54.2, 55.2, 74.1, 171.2. Low-resolution MS (electron impact ionization): 325 (M+), 282, 144, 143, 142, 100. High resolution MS (ESI): calc for C28H39NO12, 326.3059; found, 326.3038.
22.0, 23.3, 26.2, 31.3, 34.2, 41.0, 46.9, 53.9, 55.9, 58.7, 71.4, 74.1, 171.1. Low-resolution MS (electron impact ionization): 297 (M⁺), 284, 190, 160, 146. High-resolution MS (ESI): calcd for C₁₅H₂₆NO₂, 256.2277; found, 256.2262.

(1R,2S,5R)-2-Isopropyl-5-methylocyclohexyl 2-(Isopentylamino)acetate (12). Using the general procedure for 1° amines, (1R,2S,5R)-2-isopropyl-5-methylocyclohexyl 2-bromoacetate (2) is reacted with isopentylamine to provide methyl glycinate 12 in 90% yield as a clear oil (bp, ca. 180 °C at 1 mm). ¹H NMR (300 MHz, CDCl₃): δ 0.75 (d, 3H, J = 7.0 Hz), 0.87–0.92 (m, 13H), 0.95–1.01 (m, 1H), 1.03–1.13 (m, 1H), 1.35–1.43 (m, 3H), 1.43–1.59 (m, 1H), 1.61–1.74 (m, 3H), 1.77–1.89 (m, 1H), 1.95–2.03 (m, 1H), 2.10 (s, 1H), 2.59–2.64 (m, 2H), 3.38 (s, 2H), 4.70–4.79 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 16.3, 20.7, 21.9, 23.4, 26.0, 26.3, 31.4, 34.2, 38.9, 40.9, 47.0, 74.7, 75.1, 74.7, 171.9. Low-resolution MS (electron impact ionization): 283 (M⁺), 226, 255 (M⁺), 240, 138, 123, 100. High-resolution MS (ESI): calcd for C₁₆H₃₀NO₂, 326.0359; found, 326.0299.

(1R,2S,5R)-2-Isopropyl-5-methylocyclohexyl 2-(tert-Butylamino)acetate (17). Using the general procedure for 1° amines, (1R,2S,5R)-2-isopropyl-5-methylocyclohexyl 2-bromoacetate (2) is reacted with tert-butylamine to provide methyl glycinate 17 in 78% yield as a clear oil (bp, ca. 180 °C at 1 mm). ¹H NMR (300 MHz, CDCl₃): δ 0.73 (d, 3H, J = 7.0 Hz), 0.86–0.90 (m, 7H), 0.90–1.04 (m, 1H), 1.09 (s, 9H), 1.29–1.37 (m, 1H), 1.38–1.54 (m, 1H), 1.57–1.72 (m, 3H), 1.79–1.92 (m, 1H), 1.94–2.07 (m, 1H), 3.35 (s, 2H), 4.65–4.77 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 16.3, 20.7, 21.9, 23.4, 26.2, 28.7, 31.3, 34.2, 40.8, 44.9, 47.0, 50.2, 74.6, 172.7. Low-resolution MS (electron impact ionization): 269 (M⁺), 254, 130, 116. High-resolution MS (ESI): calcd for C₁₉H₂₆NO₂, 270.2433; found, 270.2416.

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to vacuum distillation (160 °C at 1 mm for 20 min) to remove excess bromoester 2. The distillate is a clear oil (ca. 0.5 g) which is identified as a mixture of bromoester 2 and the desired product 20. The residue oil is taken up in 20 mL of EtOAc and passed through a plug of SiO2. Following the removal of the solvent, a clear oil is obtained, which is methyl glycinate 20 (0.425 g, 0.94 mmol, 32%).\(^1\)\(^\text{H}\) NMR (300 MHz, CDCl\(_3\)): δ 0.76 (d, 6H, J = 6.9 Hz), 0.85–0.95 (m, 14H), 0.94–1.04 (m, 2H), 1.04–1.10 (m, 4H), 1.33–1.42 (m, 2H), 1.42–1.55 (m, 2H), 1.64–1.73 (m, 4H), 1.80–1.93 (m, 2H), 1.96–2.04 (m, 2H), 3.04–3.13 (sep, 1H, J = 6.5 Hz), 3.54 (s, 4H), 4.68–4.77 (m, 2H).\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 16.3, 20.3, 20.7, 22.0, 23.4, 26.3, 31.4, 34.3, 40.9, 47.0, 52.7, 74.2, 171.8. High-resolution MS (ESI): calcld for C\(_{21}\)H\(_{35}\)NO\(_4\): 452.3740; found, 452.3701.

**Bis(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (22) \(^{-}\) (Ethane-1,2-diybis(methylazanediyl))diacetate (21). \(^{-}\) (1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate (2, 2.13 g, 7.7 mmol) is dissolved in 50 mL of EtOAc, and to this solution is added NaOH (1.2 g, 0.03 mol) and anhydrous Na\(_2\)SO\(_4\) (0.5 g). N,N-Dimethylhexylenediamine (0.3 mL, 2.79 mmol) is added to the solution, and the mixture is stirred at room temperature for 5 h or until the GC-FID analysis shows no remaining bromoester 2. The solution is then filtered through a glass wool and the solvent is removed under reduced pressure. The resulting oil is subjected to vacuum distillation (170–190 °C at 1 mm for 30 min) to remove excess bromoester 2. The residue yellow oil is taken up in 20 mL of EtOAc and passed through a plug of SiO2. Following the removal of the solvent, a clear oil is obtained, which is methyl glycinate 21 (0.84 g, 1.75 mmol, 43%).\(^1\)\(^\text{H}\) NMR (500 MHz, CDCl\(_3\)): δ 0.78 (d, 6H, J = 6.7 Hz), 0.82–0.95 (m, 14H), 0.96–1.13 (m, 4H), 1.37–1.42 (m, 2H), 1.43–1.55 (br s, 2H), 1.70 (d, 4H, J = 2.4 Hz), 1.80–1.90 (m, 2H), 2.00 (d, 2H, J = 6.9 Hz), 2.48 (s, 6H), 2.82 (s, 4H), 3.42 (s, 4H), 4.74–4.78 (m, 2H).\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): δ 16.3, 20.7, 22.0, 23.4, 26.3, 31.4, 34.2, 41.0, 42.2, 46.9, 53.9, 58.2, 74.6, 170.0. High-resolution MS (ESI): calcld for C\(_{23}\)H\(_{38}\)NO\(_4\): 481.4005; found, 481.3941.

**ASSOCIATED CONTENT**

1. Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b03624.

\(^1\)H and \(^{13}\)C NMR of new compounds (PDF)

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**Notes**

The authors declare no competing financial interest.

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**REFERENCES**

(1) Eccles, R. Menthol and Related Cooling Compounds. J. Pharm. Pharmacol. 1994, 46, 618–630.

(2) Update on Menthol Production & Use. http://www.leffingwell.com/menthol1/menthol1.htm, downloaded Dec 31, 2018.

(3) Leffingwell, J. C. Cool without Menthol & Cooler than Menthol and Cooling Compounds as Insect Repellents. http://www.leffingwell.com/cooler_than_menthol.htm, downloaded Dec 31, 2018.

(4) Bauer, K.; Garbe, D.; Surburg, H. Common Fragrance and Flavor Materials: Preparation, Properties and Uses, 4th ed.; Wiley-VHC: Weinheim, Germany, 2001.

(5) (a) Hettstedt, C.; Betzl, W.; Karaghiosoff, K. Synthesis and Characterization of (-)-Menthyl Containing N-Alkyl Cyclicmonium Salts. Z. Anorg. Allg. Chem. 2012, 638, 377–382. For alternative routes leading to compound 2, see: (b) Shankar, S. P.; Jagodzinka, M.; Malpezzic, L.; Lazzari, P.; Manca, I.; Geireg, R. I.; Sani, M.; Zanda, M. Synthesis and structure-activity relationship studies of novel tubulysin U analogues - effect on cytotoxicity of structural variations in the tubulysine fragment. Org. Biomol. Chem. 2013, 11, 2273–2287.

(6) Singh, R.; Ghosh, S. K. Diastereoselective synthesis of a highly functionalized cyclohexene embedded with a quaternary stereogenic centre by self Diels–Alder dimerization of a [3]endralene attached to a (–)-menthol auxiliary. Tetrahedron: Asymmetry 2014, 25, 57–62.

(7) (a) Mammen, M.; Choi, S.-K.; Whitesides, G. M. Polyvalent Interactions in Biological Systems: Implications for Design and Use of Multivalent Ligands and Inhibitors. Angew. Chem., Int. Ed. 1998, 37, 2754–2794. (b) Jahromi, A. H.; Fu, Y.; Miller, K. A.; Nguyen, L.; Loo, L. M.; Baranger, A. M.; Zimmerman, S. C. Developing Bivalent Ligands to Target CUG Triplet Repeats, the Causative Agent of Myotonic Dystrophy Type 1. J. MedChem. 2013, 56, 9471–9481. (c) Journé, A-S.; Habib, S. A. M.; Dodda, B. R.; Morcos, M. N. F.; Sadek, M. S.; Tadros, S. A. A.; Witt-Endery, P. A.; Jockers, R.; Zlotos, D. N1-Linked Melatonin Dimers as Bivalent Ligands Targeting Dimeric Melatonin Receptors. MedChemComm 2014, 5, 792–796. (d) Peng, X.; Neumeyer, J. Kappa Receptor Bivalent Ligands. Curr. Top. Med. Chem. 2007, 7, 363–373.

(8) (a) Yin, Y.; Wu, M.; Zubcevic, L.; Borschel, W. F.; Lander, G. C.; Lee, S-Y. Structure of the cold- and menthol-sensing ion channel TRPM8. Science 2018, 359, 237–241. (b) Shairi, T.; Kumihashi, K.; Sakase, M.; Kusuo, H.; Shibuya, Y.; Ohuchi, A. Identification of a
Novel TRPM8 Agonist from Nutmeg: A Promising Cooling Compound. ACS Med. Chem. Lett. 2017, 8, 715–719.

(9) The menthol glycinate compounds were subjected to preliminary safety evaluation using toxicology prediction databases. Organoleptic evaluations were then done using sip and spit testing methodology of aqueous solutions containing 100 ppm of the compounds.

(10) Ma, X.-P.; Zhu, J.-F.; Wu, S.-Y.; Chen, C.-H.; Zou, N.; Liang, C.; Su, G.-F.; Mo, D.-L. Cycloaddition of Fluorenone N-Aryl Nitrones with Methylenecyclopropanes and Sequential 1,3-Rearrangement: An Entry to Synthesis of Spirofluorenypiperidin-4-ones. J. Org. Chem. 2017, 82, 502−511.

(11) Narayan, A. R. H.; Jiménez-Oses, G.; Liu, P.; Negretti, S.; Zhao, W.; Gilbert, M. M.; Ramabhadran, R. O.; Yang, Y.-F.; Furan, L. R.; Li, Z.; Podust, L. M.; Montgomery, J.; Houk, K. N.; Sherman, D. H. Enzymatic hydroxylation of an unactivated methylene C-H bond guided by molecular dynamics simulations. Nat. Chem. 2015, 7, 653−660.

(12) Franchini, M. C.; Bonini, B. F.; Boschi, F.; Fochi, M.; Fini, F.; Mazzanti, A.; Ricci, A. First 1,3-dipolar cycloaddition of azomethine ylides with (E)-ethyl 3-fluoroacrylate: regio- and stereoselective synthesis of enantiopure fluorinated prolines. Synlett 2006, 0543−0546.

(13) Siemieniuk, A.; Szalkowska-Pagowska, H.; Lochynski, S.; Piatkowski, K.; Filipek, B.; Krupinska, J.; Czarnecki, R.; Librowski, T.; Zebala, K. Synthesis and local anesthetic and circulatory actions of aminosteres and hydroxamine monoterpene derivatives. Pol. J. Pharmacol. Pharm. 1992, 44, 407−420.