

Communication

N-(((1*S*,5*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-3-dodecan/tetradecanamido-N,N-dimethylpropan-1-aminium Bromide

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Abstract: The syntheses of the title compounds were performed using lauric and myristic acids. The compounds obtained were characterized using ¹H-, ¹³C-NMR and 2D ¹H-¹³C COSY, ¹H-¹³C HSQC NMR, IR, and high-resolution mass spectrometry. Both compounds exhibited bactericidal activity on *S. aureus* comparable to that of a reference drug (miramistin). Compound **10**, with lauric acid fragment, had a 16-fold higher activity on *P. aeruginosa* compared to compound **11**, which in turn contains myristic acid fragment (with minimum inhibitory concentrations of 32 and 512 µg/mL, respectively). Compound **11** exhibited a pronounced activity against all types of fungi (higher than the activity of miramistin), while the activity of compound **10** was considerably lower. Thus, compound **11** can serve as a promising antimicrobial agent for the treatment of various fungal and staphylococcal infections, while compound **10** is of interest to treat *P. aeruginosa*-associated infections.

Keywords: lauric acid; myristic acid; myrtenol

1. Introduction

For many years, antibiotics have played an important role in the treatment and prevention of infections. However, their extensive use has led to the quick development and spread of antimicrobial resistance (AMR) in pathogenic bacteria and fungi. Therefore, the creation of either new antimicrobials or alternative options to fight bacteria is urgently required [1,2]. Terpenes and their derivatives, commonly found in essential oils, have been reported to exhibit moderate bacteriostatic properties while facilitating the penetration of other compounds into the cell [3–5].

In our previous work, several compounds in which fragments of miramistin **1**, myrten (an) one acids, and myrtenol fragments were fused into one molecule were synthesized (Figure 1) [6]. Despite the presence of a quaternary ammonium moiety, both compounds

2, **3** had moderate antimicrobial activity with a MIC of 128 µg/mL on *S. aureus* and 512 µg/mL on *E. coli*. The antifungal activity was also low on *Candida* isolates, while comparable to conventional antimycotic (Fluconazole) on filamentous fungi. These data suggest that two bulky bicyclic terpene fragments both increase lipophilicity and close the quaternary ammonium moiety located in the center of molecules, drastically decreasing the antimicrobial potential of biparmacophore.

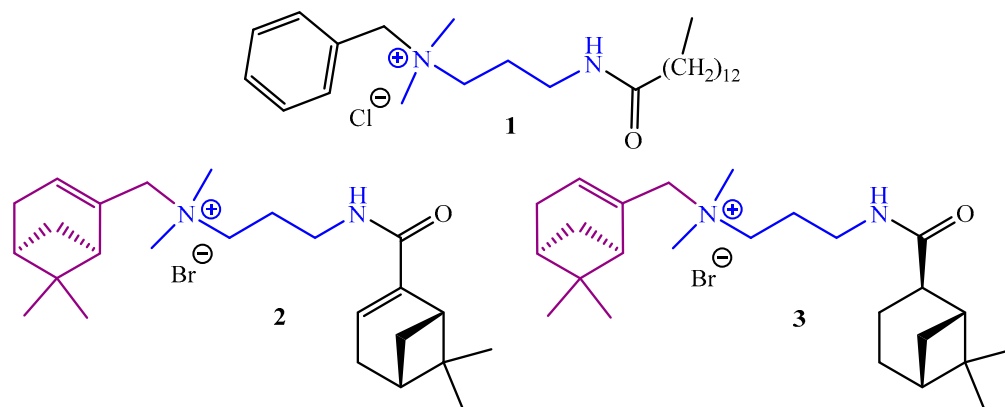


Figure 1. Structures of miramistin **1** and previously synthesized compounds **2**, **3**.

The present work is aimed at synthesizing novel antimicrobial agents by combining fragments of myristic and lauric acids, myrtenol, and Miramistin®. For this purpose, we used (+)-myrtenol **8** (ee 91), which is a terpene that exhibits biological activity by itself. (+)-Myrtenol is a bicyclic alcohol monoterpene found in the essential oils of several plants, such as *Cyperus rotundus* L., *Rhodiola rosea* L., *Tanacetum vulgare* L., and *Paeonia lactiflora* Pall. Myrtenol-containing plant extracts are used in folk medicine to treat gastrointestinal pain, anxiety symptoms, inflammation, and infection. The acute anti-inflammatory, antinociceptive, and antifungal effects of myrtenol have been reported. Moreover, the anxiolytic and anti-proliferative effects on human cancer cells have also been shown [7–9]. We assumed that the replacement of one of the bulky fragments of compounds **2**, **3** with a fatty acid residue would increase the activity of the compounds obtained. Fragments of myristic and lauric acids were chosen as agents with established antimicrobial properties [10].

2. Results and Discussion

The presence of a strained four-membered ring in myrtenol **8** determines isomerization processes as the main direction of reactions with various reagents [11]. In particular, our attempts to brominate myrtenol **8** with phosphorus tribromide were unsuccessful due to the formation of an inseparable mixture of products and the gumming of the reaction mixture. Previously, we described the bromination of myrtenol **8** using *N*-bromosuccinimide with triphenylphosphine [12]. The yield of target product **9** was only 56%. In this article, another reaction has been used, namely the Appel reaction. The use of this method made it possible to significantly increase the yield of (+)-myrtenyl bromide **9** (90%).

The syntheses of compounds **10** and **11** were performed, as shown in Figure 2.

Reactions of lauric **4** or myristic **5** acids with dimethylaminopropylamine (DMAPA) at 140 °C using the Dean–Stark receiver and *p*-toluenesulfonic acid as a catalyst were carried out for 20 h (10 h on the first day and 10 h on the second day). As a result of the reactions of amides **6** or **7** with an excess of bromide **9**, followed by washing with hexane, target compounds **10** and **11** were obtained in 91% and 90% yields, respectively.

The structures of compounds **10** and **11** were confirmed by spectroscopic methods (¹H-, ¹³C-NMR and 2D ¹H-¹H COSY, ¹H-¹³C HSQC NMR, IR, and high-resolution mass spectrometry; see Supplementary Materials).

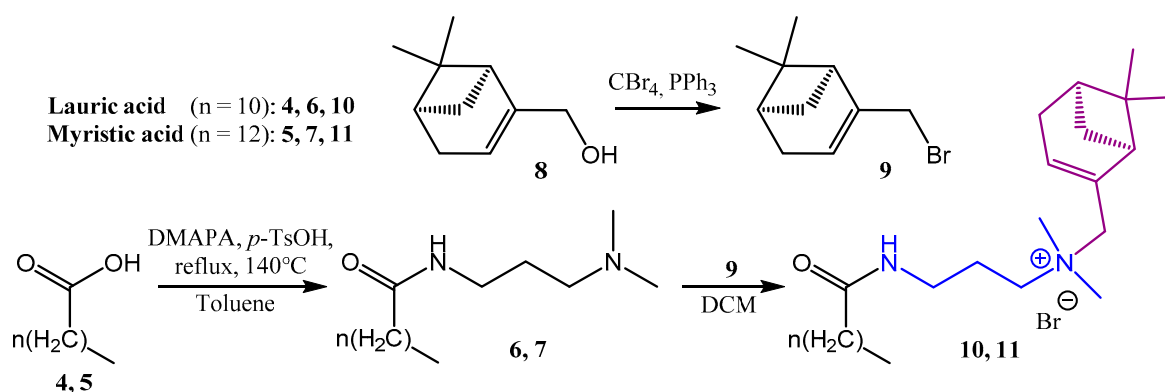


Figure 2. Syntheses of compounds **10** and **11**.

Compounds **10** and **11** exhibited bactericidal activity on *S. aureus* cells comparable with miramistin, with **11** being significantly more active than **10**, suggesting that a longer hydrophobic tail increases activity (Table 1). By contrast, compound **10** had a 16-fold higher activity than compound **11** on *P. aeruginosa* cells with minimum inhibitory concentrations of 32 and 512 µg/mL, respectively (Table 1). Of note, miramistin, an antiseptic approved for clinical practice, was not active against *P. aeruginosa* under the conditions tested. An analysis of the antifungal activity of compounds **10** and **11** against microscopic fungi revealed significant differences. Thus, compound **10** did not exhibit fungicidal activity against all types of fungi. The maximum MIC values of compound **10** for *Candida* yeasts were 512 µg/mL, and for filamentous fungi (*Aspergillus niger*, *Rhizopus nigricans*, and *Fusarium oxysporum*), 128 µg/mL. On the contrary, compound **11** showed a pronounced activity against all types of fungi, higher than the activity of compound **10** and miramistin. Thus, compound **11** can serve as a promising antimicrobial for the treatment of fungal and staphylococcal infections, while compound **10** is active against *P. aeruginosa* cells.

Table 1. Antibacterial and antifungal activities of **10** and **11**.

Strains	MIC, µg/mL		
	10	11	Miramistin
<i>S. aureus</i> ATCC29213	8	2	4
<i>P. aeruginosa</i> ATCC27853	32	512	>1024
<i>Candida albicans</i> NCTC- 885-653	128	32	>1500
<i>Candida tropicalis</i> Y-1513/784	512	64	>1500
<i>Aspergillus niger</i> F-1119	128	32	>1500
<i>Rhizopus nigricans</i> F-1537/1722	128	64	>1500
<i>Fusarium oxysporum</i> (clinical isolate)	128	32	>1500

3. Materials and Methods

3.1. General

Toluene, dichloromethane (DCM), *p*-toluenesulfonic acid, and hexane were reagent-grade and used without purification. Lauric and myristic acids, DMAPA, tetrabromomethane, and triphenylphosphine were purchased from Sigma-Aldrich (St. Louis, MO, USA). The preparation of (+)-myrtenol **8** and (+)-myrtenyl bromide **9** was performed according to [13].

The reaction progress and purity of compounds were monitored by TLC on Sorbfil PTLT-AF-A-UF plates (developer—anisaldehyde and sulfuric acid in ethanol, 5:5:90).

The IR spectra were recorded on a Spectrum Two PerkinElmer FT-IR spectrometer with the UATR (Single Reflection Diamond) attachment. Samples were applied to the attachment and pressed with a hand press until maximum absorption was obtained. For analyzing optical rotation, a digital polarimeter P8000-T (A. KRUS Optronic GmbH, Hamburg, Germany) was used.

The NMR spectra were recorded on a Bruker AVANCE-II-500 spectrometer with operating frequencies of 500 MHz (for ^1H) and 125 MHz (for ^{13}C) in a CDCl_3 solvent using standard Bruker pulse programs. The internal standard is the solvent residual peak (CDCl_3). The numbering of atoms in the description of the NMR spectra differs from the numbering in the names of compounds.

HPLC-HRMS experiment. Samples were analyzed using an Impact II mass spectrometer with an Elute UHPLC system (Bruker Daltonik GmbH, Bremen, Germany). The column used was a YMC-Triart C18 (50×2.0 mm; $3 \mu\text{m}$). The temperature of the column thermostat was set at 40°C and the temperature of the autosampler at 12°C . The elution solvents used were Milli-Q water + 0.1% FA (A) and HPLC-grade acetonitrile + 0.1% FA (B), and the elution gradient was as follows: 0 min at 50% B, 2 min at 95% B, 4 min at 95% B, 4.1 min at 50% B, 6 min at 50% B, with a flow rate of 0.3 mL/min. The injection volume was 2 μL . Analytes were ionized by electrospray (ESI) in positive polarity. The ESI conditions were set with the capillary temperature at 220°C , the capillary voltage at 4.5 kV, and a nitrogen drying gas flow rate of 6 L/min. Measurements were made in the range m/z 50–1300. The solution of analyte (1 mg/mL, HPLC methanol) was diluted in an acetonitrile:water (50%:50%) solvent mixture to a concentration of 0.005 mg/mL. The solution of sodium iodide in Milli-Q water was used as a calibrant. The relative error in determining the masses was no more than 3.0 ppm. For instrument control and data acquisition, the otofControl software (Bruker Daltonik GmbH, Version 5.2) was used. Data processing was performed by DataAnalysis software (Bruker Daltonik GmbH, Version 5.3).

3.2. General Procedure for Synthesis of *N*-(3-(Dimethylamino)propyl)dodecan/tetradecanamide **6**, **7**

To a round-bottom flask containing lauric **4** (0.5 mmol) or myristic **5** acids (0.44 mmol) in toluene (50 mL), an equimolar amount of DMAPA and *p*-toluenesulfonic acid (0.02 g) were added and stirred for 20 h (10 h on the first day and 10 h on the second day) at 140°C using a Dean–Stark receiver. After the evaporation of the reaction mixture in vacuo, compounds **3** and **4** were washed with water and dried under low pressure.

N-(3-(dimethylamino)propyl)dodecanamide (**6**). Whitish amorphous solid. Yield: 95%. IR, ν , cm^{-1} : 3309 (N–H), 1636 (C=O), 1542 (N–C=O).

NMR ^1H (CDCl_3) δ , ppm: 0.79 (t, 3H, CH_3 -17, $J = 6.7$), 1.17 (s, 16H, CH_2 -9-16), 1.52 (m, 2H, CH_2 -8), 1.59 (m, 2H, CH_2 -4), 2.07 (t, 2H, CH_2 -7, $J = 7.4$), 2.16 (s, 6H, CH_3 -1,2), 2.31 (t, 2H, CH_2 -3, $J = 6.7$), 3.22 (m, 2H, CH_2 -5), 7.10 (s, 1H, NH-6).

NMR ^{13}C (^1H) (CDCl_3) δ , ppm: 14.0 (CH_3 -17), 22.6 (CH_2 -16), 25.7 (CH_2 -8), 26.2 (CH_2 -4), 29.3 (CH_2 -9,10), 29.5 (CH_2 -11-14), 31.8 (CH_2 -15), 36.8 (CH_2 -7), 38.7 (CH_2 -5), 45.0 (CH_3 -1,2), 58.1 (CH_2 -3), 173.2 (C=O-6).

HRMS (ESI), m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{37}\text{N}_2\text{O}^+$ 285.2900, found 285.2905.

N-(3-(dimethylamino)propyl)tetradecanamide (**7**). Pale yellow amorphous solid. Yield: 93%. IR, ν , cm^{-1} : 3303 (N–H), 1639 (C=O), 1551 (N–C=O).

NMR ^1H (CDCl_3) δ , ppm: 0.80 (t, 3H, CH_3 -19, $J = 6.7$), 1.18 (s, 20H, CH_2 -9-18), 1.52 (m, 2H, CH_2 -8), 1.61 (m, 2H, CH_2 -4), 2.07 (t, 2H, CH_2 -7, $J = 7.4$), 2.19 (s, 6H, CH_3 -1,2), 2.34 (t, 2H, CH_2 -3, $J = 6.7$), 3.22 (m, 2H, CH_2 -5), 7.00 (s, 1H, NH-6).

NMR ^{13}C (^1H) (CDCl_3) δ , ppm: 14.0 (CH_3 -19), 22.6 (CH_2 -18), 25.7 (CH_2 -8), 26.0 (CH_2 -4), 26.0 (CH_2 -9,10), 29.4 (CH_2 -11-16), 31.8 (CH_2 -17), 36.7 (CH_2 -7), 38.6 (CH_2 -5), 44.9 (CH_3 -1,2), 57.8 (CH_2 -3), 173.2 (C=O-6).

HRMS (ESI), m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{41}\text{N}_2\text{O}^+$ 313.3213, found 313.3215.

3.3. General Procedure for Synthesis of *N*-(((1*S*,5*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-3-dodecan/tetradecanamido-*N,N*-dimethylpropan-1-aminium bromide **10**, **11**

An excess of compound **9** (3 eq) was added to the solution of amide **6** (0.35 mmol, 1 eq) or **7** (0.32 mmol, 1 eq) in DCM (20 mL). The reaction mixture was left at room temperature for 1 h. After the solvent had evaporated in vacuo, the products were washed with hexane, filtrated, and then dried under low pressure to provide the target compounds **10**, **11**.

N-(((1*S*,5*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-3-dodecanamido-*N,N*-dimethylpropan-1-aminium bromide (**10**). Yellow amorphous solid. Yield: 91%. IR, ν , cm^{-1} : 3416, 3259 (N–H), 1650 (C=O), 1541 (N–C=O). $[\alpha]_D^{26} = +8.8^\circ$ (1.06 c; MeOH).

NMR ^1H (CDCl_3) δ , ppm: 0.86 (s, 6H, CH_3 -1,2), 0.88 (t, 3H, CH_3 -25, $J = 6.7$), 1.18 (d, 2H, CH_2 -16, $J = 9.4$), 1.25 (s, 16H, CH_2 -17–24), 1.61 (s, 1H, CH -4), 2.13 (m, 2H, CH_2 -12), 2.19 (m, 1H, CH -3), 2.30 (m, 2H, CH_2 -5), 2.42 (m, 2H, CH_2 -6), 2.54 (m, 2H, CH_2 -15), 3.16 (s, 3H, CH_3 -9), 3.18 (s, 3H, CH_3 -10), 3.37 (m, 2H, CH_2 -11), 3.82 (m, 2H, CH_2 -13), 4.15 and 3.90 (AB pattern, 2H, CH_2 -8, $J = 12.6$), 6.16 (s, 1H, CH -7), 7.86 (s, 1H, NH -14).

NMR ^{13}C (^1H) (CDCl_3) δ , ppm: 14.1 (CH_3 -25), 21.3 (CH_3 -1,2), 22.7 (CH_2 -16), 25.9 (CH -4), 29.6 (CH_2 -17–24), 31.9 (CH_2 -15,11), 32.1 (CH_2 -5), 36.2 (CH -3,7), 36.5 (C -26), 38.1 (C -26), 39.7 (CH_2 -12), 47.1 (CH_2 -6), 50.2 (CH_3 -9,10), 63.1 (CH_2 -13), 69.9 (CH_2 -8), 135.9 (CH -7), 136.6 (C -27), 174.7 (CO -14).

HRMS (ESI), m/z : $[\text{M} - \text{Br}]^+$ calcd for $\text{C}_{27}\text{H}_{51}\text{N}_2\text{O}^+$ 419.3996, found 419.3998; $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{37}\text{N}_2\text{O}^+$ 285.2900, found 285.2901.

N-(((1*S*,5*R*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-3-tetradecanamido-*N,N*-dimethylpropan-1-aminium bromide (**11**). Yellow amorphous solid. Yield: 90%. IR, ν , cm^{-1} : 3413, 3261 (N–H), 1663 (C=O), 1540 (N–C=O). $[\alpha]_D^{26} = +8.5^\circ$ (0.74 c; MeOH).

NMR ^1H (CDCl_3) δ , ppm: 0.85 (s, 6H, CH_3 -1,2), 0.88 (t, 3H, CH_3 -27, $J = 6.7$), 1.18 (d, 2H, CH_2 -16, $J = 9.4$), 1.25 (s, 20H, CH_2 -17–26), 1.61 (m, 1H, CH -4), 2.14 (m, 2H, CH_2 -12), 2.29 (m, 1H, CH -3), 2.31 (m, 2H, CH_2 -5), 2.41 (m, 2H, CH_2 -6), 2.54 (m, 2H, CH_2 -15), 3.17 (s, 3H, CH_3 -9), 3.18 (s, 3H, CH_3 -10), 3.37 (m, 2H, CH_2 -11), 3.82 (m, 2H, CH_2 -13), 4.15 and 3.90 (AB pattern, 2H, CH_2 -8, $J = 12.6$), 6.16 (s, 1H, CH -7), 7.83 (s, 1H, NH -14).

NMR ^{13}C (^1H) (CDCl_3) δ , ppm: 14.1 (CH_3 -27), 21.3 (CH_3 -1,2), 22.7 (CH -4), 23.0 (CH_2 -18), 25.9 (CH_2 -12), 29.7 (CH_2 -17–26), 31.9 (CH_2 -6), 36.2 (CH_2 -15,16), 36.5 (C -28), 38.1 (CH_2 -11), 39.7 (CH -3), 47.1 (CH_2 -5), 50.1 (CH_3 -9,10), 63.0 (CH_2 -13), 69.8 (CH_2 -8), 135.9 (CH -7), 136.6 (C -29), 174.7 (CO -14).

HRMS (ESI), m/z : $[\text{M} - \text{Br}]^+$ calcd for $\text{C}_{29}\text{H}_{55}\text{N}_2\text{O}^+$ 447.4309, found 447.4309; $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{41}\text{N}_2\text{O}^+$ 313.3213, found 313.3216.

3.4. Antibacterial and Antifungal Activities

Staphylococcus aureus ATCC[®] 29213TM and *Pseudomonas aeruginosa* ATCC[®] 27853TM were grown on Mueller–Hinton broth (MH, BD Difco) and used for antibacterial activity testing. The fungal strains *Candida albicans* NCTC-885-653, *Candida tropicalis* Y-1513/784, *Aspergillus niger* F-1119, and *Rhizopus nigricans* F-1537/1722 were obtained from an all-Russian collection of microorganisms (Moscow, Russia). *Fusarium oxysporum* C2611-17 (a clinical isolate from the skin) was obtained from the Kazan Institute of Microbiology and Epidemiology (Kazan, Russia). All strains were grown in RPMI or Sabouraud broth.

The minimum inhibitory concentrations (MICs) of the compounds were determined using the broth microdilution method in 96-well plates (Eppendorf) in MH broth (for bacteria) or in tubes with RPMI (for yeast fungi) and Sabouraud broth (for filamentous fungi) in accordance with EUCAST guidelines for antimicrobial susceptibility testing [14]. Bacteria were incubated at 37 °C for 24 h. Yeasts and filamentous fungi were incubated at 30 °C for 2 and 5 days, respectively. The MIC was defined as the lowest concentration of the compound at which no visible growth could be seen.

Supplementary Materials: The following supporting information can be downloaded online. Figures S1 and S2: ^1H - and ^{13}C -NMR spectra of *N*-(3-(dimethylamino)propyl)dodecanamide (**6**) in CDCl_3 - d_1 ; Figure S3: the fragment of ^1H - ^1H COSY NMR spectrum of **6** in CDCl_3 - d_1 ; Figure S4: the fragment of ^1H - ^{13}C HSQC NMR spectrum of **6** in CDCl_3 - d_1 ; Figure S5: the IR spectrum of **6**; Figures S6 and S7: ^1H - and ^{13}C -NMR spectra of *N*-(3-(dimethylamino)propyl)tetradecanamide (**7**) in CDCl_3 - d_1 ; Figure S8: the fragment of ^1H - ^1H COSY NMR spectrum of **7** in CDCl_3 - d_1 ; Figure S9: the fragment of ^1H - ^{13}C HSQC NMR spectrum of **7** in CDCl_3 - d_1 ; Figure S10: the IR spectrum of **7**; Figures S11 and S12: ^1H - and ^{13}C -NMR spectra of *N*-(((1*S*,5*R*)-6,6-dimethylbicyclo [3.1.1]hept-2-en-2-yl)methyl)-3-dodecanamido-*N,N*-dimethylpropan-1-aminium bromide (**10**) in CDCl_3 - d_1 ; Figure S13: the fragment of ^1H - ^1H COSY NMR spectrum of **10** in CDCl_3 - d_1 ; Figure S14: the fragment of ^1H - ^{13}C

HSQC NMR spectrum of **10** in CDCl₃-d₁; Figure S15: the IR spectrum of **10**; Figures S16 and S17: ¹H- and ¹³C-NMR spectra of *N*-(((1*S*,5*R*)-6,6-dimethylbicyclo [3.1.1]hept-2-en-2-yl)methyl)-3-tetradecanamido-*N,N*-dimethylpropan-1-aminium bromide (**11**) in CDCl₃-d₁; Figure S18: the fragment of ¹H-¹H COSY NMR spectrum of **11** in CDCl₃-d₁; Figure S19: the fragment of ¹H-¹³C HSQC NMR spectrum of **11** in CDCl₃-d₁; Figure S20: the IR spectrum of **11**; copies of HRMS reports; raw 1D ¹H- and ¹³C-NMR files.

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are not available from the authors.

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